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A comparative Suzuki reaction of aryl halides using a new dimeric orthopalladated complex under conventional and microwave irradiation conditions

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The cross-coupling reaction between phenylboronic acid and various types of aryl halides (Suzuki reaction) was carried out using a catalytic amount of a new phosphine-based catalyst under microwave irradiation. The reaction conditions were optimized and results showed that, by application of this catalytic system, *N*-methyl-2-pyrrolidone as the solvent and potassium carbonate as the base, reactions could be completed in a short reaction time with high to excellent yields. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Suzuki cross-coupling reaction; catalyst; microwave irradiation

Introduction

Biaryl motifs are very useful organic compounds that have found many applications in different fields, including synthesis of pharmaceuticals, herbicides, conducting polymers, natural products and liquid crystalline materials.^[1,2] Therefore, in recent years, an extraordinary amount of effort has been spent in developing new straightforward and environment-friendly reactions for aryl–aryl coupling and this field of science has become a matter of wide interest.

In the history of organic chemistry, the formation of new bonds between two carbon atoms has always been one of the fundamental reactions,^[3] and therefore much research around the world has tried to broaden new methodologies that are able to improve the reaction conditions. Cross-coupling reactions catalyzed by palladium complexes, encouraged by the 2010 Nobel Laureates' discoveries, are powerful and suitable one-step tools for the construction of C-C bonds.^[4] Some of the well known reactions in this category are Stille,^[5,6] Suzuki^[7–13] and Kumada–Hiyama^[14] cross-coupling reactions. The Suzuki reaction is one of the most useful and applicable reactions that can be used on both laboratory and industrial scales.^[15] In this method an organic electrophile and a nucleophilic organoboron derivative couples with each other in the presence of a palladium catalyst^[8b] (Scheme 1).

The Suzuki cross-coupling reaction has more advantages than the other palladium-catalyzed processes, such as functional group tolerances, stability and availability of many boron derivatives, low toxicity of reagents and intermediates, high thermal stability and mild reaction conditions with high to excellent yield with a vast range of substrates.^[16] Also work-up of the reaction mixture is simple and inorganic products of the reaction easily removed with water.^[12b,17] However, for the success of coupling reactions, the catalyst should be chosen properly. During the past few years, very different types of palladium catalyst precursors have been developed that allow various aryl halides and pseudo halides (such as triflates) to be effectively coupled with boron reagents. First, some catalysts such as PdCl₂(PPh₃)₂ and Pd(OAc)₂/ PPh₃ were used for this purpose. However, although these types of catalysts were air stable and would be a good catalyst for the present reaction, their conversions, yields and chemoselectivities were not as good as this catalyst. In comparison to PdCl₂(PPh₃)₂ and Pd(OAc)₂/PPh₃, our catalyst has some advantages, e.g. the reactions perform in very shorter reaction times and also the catalyst is air stable and chemoselective. Furthermore, it does not decompose at high temperatures. Nowadays, many researchers have focused on preparing new types of palladium-based catalysts using different ligands with high efficiencies and yields to improve the efficiency of such types of reactions. Our catalyst excellent and therefore its application is preferable to other conventional catalysts.

Application of microwave heating in organic synthesis was developed about 50 years ago.^[18] Therefore, the use of this technique as an environmentally friendly green synergy source has grown and microwave irradiation has become a powerful technique by which the completion of the reaction can be decreased from hours to minutes.^[19–21] This technique was used also to improve the sluggish Suzuki coupling by various research groups.^[22–25]

Herein, in continuation of our previous investigations,^[26-32] we wish to report a new phosphine-based catalytic system for Suzuki cross-coupling reaction under microwave irradiation.

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X = halide or triflate or diazonium salt

Scheme 1. Suzuki cross-coupling reaction

Results and Discussion

The Suzuki cross-coupling reaction of different types of aryl halides using palladacycle complex $[Pd(\mu-CI)(C,C-[C_{e}H_{4}(PPh_{2}CHC$ $(O)C_6H_4-4-F_2]$], **2** (Scheme 2) was investigated under both traditional heating and microwave irradiation conditions. Initially, in order to optimize the reaction conditions, the Suzuki reaction of 4-bromobenzonitrile as the test substrate using phenylboronic acid as boron reagent was chosen and the effect of various parameters on the yields and conversions was examined. For this purpose, initially this reaction was performed using different solvents in the presence of 0.2 mol% palladacycle 2 as catalyst and K₂CO₃ as the base at 120°C under microwave irradiation. As can be seen in Table 1, the best results were obtained using *N*-methyl-2-pyrrolidone (NMP) as the solvent (Table 1, entries 1–5). We tried these conditions for finding a suitable base for this reaction and the results clearly showed that K₂CO₃ can apply as the best base (Table 1, entries 6-9).

For optimizing of catalyst concentration the above reaction was repeated using NMP as the solvent and K_2CO_3 as the base under microwave irradiation at $120^{\circ}C$ in the presence of various



Scheme 2. Synthetic procedure for preparation of palladacycle complex 2

amounts of catalyst. The results listed in Table 2 (entry 5) show that the best results were obtained using 0.1 mol% of catalyst **2**.

These reaction conditions were applied in the Suzuki crosscoupling reaction of different types of aryl halides using phenylboronic acid under both traditional heating and microwave irradiation conditions at 120°C.

As demonstrated in Table 3, this catalytic system can be used for Suzuki cross-coupling reaction of different types of aryl iodides, bromides and also less reactive aryl chlorides. However, in comparison to aryl bromides and aryl iodides, the Suzuki reaction using aryl chlorides as substrate needs longer reaction times for completion under both reaction conditions (Table 3, entries 3, 16 and 17). We also examined the electronic and steric effects on yields. For this purpose we used 2-, 3- and 4-bromoacetophenone under optimized reaction conditions (Table 3, entries 5-7). The Suzuki reaction of 4-bromoacetophenone was performed completely and its resulted yield was excellent. In the case of 3bromoacetophenone, although the reaction was carried out quantitatively, completion of the reaction required a longer reaction time than 4-substituted derivatives. However, the reaction of 2-bromoacetophenone, which has more steric effects, gave a moderate yield in a longer reaction time. On the other hand, the reaction of 1-bromonaphthalene performed faster with better yield than 9-bromophenantehrene, as the latter has more hindrance. Thus the greater the hindrance in the vicinity of the leaving group, the higher is the decrease in the reaction conversion. The Suzuki reaction was performed by aryl halides bearing both electron-donating and electron-withdrawing substituents and the results are comparable. Therefore, under the defined conditions, reactions did not show any sensitivity to electronic effects; for example, 4-bromomethoxybenzene (or 4-methoxyiodobenzene)

Table 1. Optimization of base and solvent for Suzuki cross-coupling reaction under microwave irradiation ^a								
NC NC NC NC NC NC NC NC NC NC NC NC NC N								
Entry	Base	Solvent	Conversion (%) ^b					
1	K ₂ CO ₃	DMF	83					
2	K ₂ CO ₃	NMP	91					
3	K ₂ CO ₃	Methanol	65					
4	K ₂ CO ₃	Toluene	22					
5	K ₂ CO ₃	DMSO	74					
6	Cs ₂ CO ₃	NMP	81					
7	Na ₂ CO ₃	NMP	78					
8	Et ₃ N	NMP	Trace					
9	NaOAc	NMP	57					

^aReaction conditions: 1 mmol aryl halide, 1.2 mmol phenylboronic acid, 1 mmol base, 3 ml solvent, 120°C and 0.2 mol% palladacycle **2**. ^bDetermined by gas chromatography.



^bDetermined by gas chromatography.

Table 3. Suzuki cross-coupling reaction of phenylboronic acid with various aryl halides under optimized reaction conditions under microwave irradiation and traditional heating conditions

		B(OH) ₂ X 0.001 mmol	Palladacycle 2			
		$\begin{array}{c} K_2CO_1\\ R & 12 \end{array}$,, NMP _ 0 ℃	_/ \X _R		
Entry	Ar-X	Product	Time (min)	Yield (%) ^c	Time (min)	Yield (%) ^c
			(MW) ^a		(heating) ^b	
1	Ph-I	Biphenyl	2	94	90	91
2	Ph-Br	Biphenyl	1	94	75	90
3	Ph-Cl	Biphenyl	6	84	210	91
4	1-Bromo-3-chlorobenzene	3-Chlorobiphenyl	2	91	180	89
5	4-Bromoacetophenone	4-Acetylbiphenyl	6	92	330	87
6	3-Bromoacetophenone	3-Acetylbiphenyl	11	90	510	75
7	2-Bromoacetophenone	2-Acetylbiphenyl	25	58	960	42
8	4-Bromobenzaldehyde	4-Formylbiphenyl	7	91	315	87
9	4-lodonitrobenzene	4-Nitrobiphenyl	10	89	960	64
10	2-Bromopyridine	2-Phenylpyridine	15	83	960	57
11	4-Methoxybromobenzene	4-Methoxybiphenyl	8	91	360	86
12	4-Methoxyiodobenzene	4-Methoxybiphenyl	9	92	360	88
13	4-Bromobenzonitrile	4-Cyanobiphenyl	5	95	300	85
14	1-Bromonaphtalene	1-Phenylnaphtalene	4	93	270	82
15	9-Bromophenanthrene	9-Phenylphenanhrene	6	89	405	79
16	4-Chloroacetophenone	4-Acetylbiphenyl	23	88	720	75
17	4-Chlorobenzaldehyde	4-Formylbiphenyl	22	86	720	71

^aReaction conditions: 1 mmol aryl halide, 1.2 mmol phenylboronic acid, 1 mmol K_2CO_3 , 3 ml NMP, 120°C and 0.1 mol% palladacycle **2**, 600 W. ^bReaction conditions: 1 mmol aryl halide, 1.2 mmol phenylboronic acid, 1 mmol K_2CO_3 , 3 ml NMP, 120°C and 0.1 mol% palladacycle **2**. ^cDetermined by gas chromatography.

has a comparable result to 4-bromobenzonitrile or 4-bromobenzaldehyde (Table 3, entries 8, 11–13). Application of 1-bromo-3-chlorobenzene as aryl halide caused formation of 3-chlorobiphenyl as the only product. The result indicates that the reaction acts chemoselectively and only Br substitutes with the phenyl ring from phenylboronic acid (Table 3, entry 4). 2-Bromopyridine was used as a heterocyclic aryl halide in the Suzuki reaction and in this case full conversion to 2-phenylpyridine was achieved under microwave irradiation conditions, whereas the reaction under heating conditions occurred slowly and after 16 h only a moderate yield was obtained (Table 3, entry 10). The same results were achieved in the case of the Suzuki reaction of 4-iodonitrobenzene (Table 3, entry 9) and again only under microwave irradiation was full conversion to 4-nitrobiphenyl achieved, the reaction being performed quantitatively. The data in Table 3 clearly show that application of microwave irradiation can decrease the time of completion of the reactions and also in many cases improve conversion and yields. Reportedly, in almost all of the Suzuki coupling reactions, a small amount of biphenyl as byproduct of the reaction was formed as a result of the homocoupling reaction of phenylboronic acid precursor, which is a major drawback of the process. However, in this research, by application of microwave irradiation, the formation of this byproduct was reduced and under these conditions was hardly observed at all; this is another advantage of using microwave irradiation in organic synthesis.

Conclusion

In summary, a new catalytic system for Suzuki cross-coupling reaction was developed. The reactions were performed under both conventional heating and microwave irradiation as a green synergy source and these reaction conditions were compared. The results clearly show that using microwave irradiation conditions the required time for completion of the reactions could be minimized from hours to minutes in comparison to conventional heating conditions. The catalyst was not sensitive to oxygen and also any or a little amount of biphenyl as the byproduct of the reaction was formed in each case. The yields were very good to excellent, making this procedure a good synthetic route for biaryl synthesis.

Experimental

General

All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ¹H NMR spectra were recorded at 400 MHz in CDCl₃ solutions at room temperature (tetramethylsilane was used as an internal standard) on a Bruker Avance 500 instrument (Rheinstetten, Germany) and a Varian 400 NMR instrument. FT-IR spectra were recorded on a spectrophotometer (Jasco-680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported as wave number (cm⁻¹). We used a Milestone Microwave (Microwave Labstation-MLS GmbH ATC-FO 300) for synthesis. We also used a BEIFIN 3420 gas chromatograph equipped a Varian CP SIL 5CB column (30 m, 0.32 mm, 0.25 μ m) for examination of reaction completion and yields. Palladium acetate, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

Synthesis of palladacycle complex [Pd(μ -Cl){C, C-[C₆H₄(PPh₂CHC(O)C₆H₄-4-F)₂]}] (**2**)

The ligand [Ph₃PCHCOC₆H₄-4-F], **1** was synthesized according to published methods.^[30–35]

Palladium acetate (0.2 mmol) was added to a solution of **1** (0.2 mmol) in CH₂Cl₂ (15 ml) and the resulting mixture was refluxed for 24 h. The solvent was removed and the yellow solid residue was dissolved in MeOH (10 ml); anhydrous NaCl (0.6 mmol) was then added. A pale-yellow solid precipitated immediately. The reaction mixture was stirred for 12 h at room temperature and the resulting suspension was filtered off. The yellow solid was washed with H₂O (5 ml), MeOH (10 ml) and Et₂O (15 ml) and air dried to produce complex [Pd(μ -Cl){C, C-[C₆H₄(PPh₂CHC(O)C₆H₄-4-F)₂]}], **2** (Scheme 2).^[32]

General Procedure for the Suzuki Reaction of Aryl Halides

In a round-bottom flask equipped with a condenser for refluxing and a magnetic stirring bar, aryl halide (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (1 mmol), complex **2** (0.001 mmol) and NMP (3 ml) were added and heated at 120°C under air atmosphere. In the case of microwave-assisted reactions the mixture was irradiated in a microwave oven at 120°C and 600 W. The mixture was stirred under these reaction conditions and monitored by both TLC (EtOAc–*n*-hexane, 25:75) and gas chromatography. In each case after completion of the reaction, the mixture was diluted with *n*-hexane and water. The organic layer was washed with brine, dried over CaCl₂, and concentrated under reduced pressure using a rotary evaporator. The residue was purified by recrystallization from ethanol and water.

All of the compounds have been characterized by comparing melting point, ${}^{1}H$ and ${}^{13}C$ NMR with the values found in the literature:

4-Acetylbiphenyl (Table 3, entry 5)^[36a]
2-Phenylpyrdine (Table 3, entry 10)^[36b]
4-Methoxybiphenyl (Table 3, entry 11)^[36c]
4-Cyanobiphenyl (Table 3, entry 13)^[36a]
4-Phenylbenzaldehyde (Table 3, entry 17)^[36d]

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