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Catalytic activity of 1-methylimidazole-based phosphine ligands in the palladium-catalyzed Suzuki coupling reaction

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The catalytic activities of three *N*-methylimidazole-based phosphine ligands in the Suzuki coupling reaction were tested using $PdCl_2$ as the catalyst. The results showed all three phosphine ligands exhibited excellent activity towards the Suzuki reaction, and the catalytic activity decreased with increasing number of imidazole groups. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: 1-methylimidazole; phosphine ligand; Suzuki coupling reaction

Introduction

The palladium-catalyzed Suzuki cross-coupling reaction of arylboronic acids and aryl halides is one of the most powerful and straightforward methods for the formation of C–C bonds in organic synthesis.[1–5] This method has been widely used for the synthesis of pharmaceuticals, bioactive compounds, natural products and optical materials, on both laboratory and industrial scales. Since the first discovery of the Suzuki cross-coupling reaction,[6] numerous efforts have been made to increase the reaction efficiency.[4,7,8] In general, the reaction is carried out in the presence of palladium–phosphine catalysts because they provide excellent catalytic activity for the coupling reaction.[2,9–13] In spite of these developments, there is still a need for readily available ligands which lead to highly active catalyst systems and are easily tunable and easy to scale up. 1-Substituted imidazole-based phosphines,[14] notably C_2 substituted phosphines, which can be synthesized in one or two reaction steps on multi-gram to kilogram scales and allow high tenability have attracted increasing interest in catalysis, such as alkene isomerizations,[15,16] Buchwald–Hartwig aminations,[17] Heck reactions,[18] hydrosilylation of alkenes,[19] Suzuki reactions,[17,20] C–H bond activation[21] and hydroxylation of aryl halides.[22] However, most research has focused on *N*-arylimidazole; just a few studies involving *N*-alkylimidazole[19,23] have been reported. As part of an ongoing project on palladium-catalyzed reactions,[24,25] we report herein an investigation of the catalytic activity of three 1-methylimidazole-based phosphines in the Suzuki reaction.

Experimental

General

All reactions were carried out under an atmosphere of highly purified nitrogen using standard Schlenk or vacuum-line techniques. All solvents were used after degassing with nitrogen. Phosphine ligands **1a–c**[26] (Fig. 1) were prepared according to literature procedures.

Product yields were calculated by GC, using a 6890N Network GC system (Agilent Technologies). ^{1}H NMR and ^{31}P NMR spectra were recorded with a Varian Mercury Plus 400 MHz spectrometer.

General Procedure for Suzuki Coupling Reaction

A mixture of aryl halide (2 mmol), phenylboronic acid (331.8 mg, 2.5 mmol), base (4 mmol), $PdCl_2$ (1.77 mg, 0.01 mmol), **1a** (532.57 mg, 0.02 mmol) and H_2O (3 ml) under nitrogen in a pressure tube was heated to given temperature and maintained for a given time. Then it was cooled and extracted with diethyl ether (4 × 5.0 ml) and dried with Na_2SO_4. After evaporation under reduced pressure, the residue was purified using silica gel to give the desired product.

Results and Discussion

The three 1-methylimidazole based-phosphines **1a–c** were synthesized according to literature procedures, and were characterized using ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectroscopy and melting point measurements. We then embarked on evaluating their activity in the Suzuki reaction. Bromobenzene and phenylboronic acid were selected as the model substrates to optimize the reaction conditions.

Our initial investigation was focused on the influence of various bases and various ligands at 80°C for 0.5 h (Table 1). The results show that K_3PO_4 is the most effective base (Table 1, entry 4), the other inorganic and organic bases being inferior. We also investigated the activities of ligands in the model reaction using K_3PO_4 as the base (Table 1, entries 4, 8 and 9). All three ligands exhibit good catalytic activity towards the reaction. Ligand **1a** gives the best yield (Table 1, entry 4), while ligands

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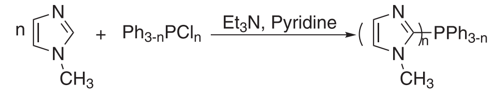


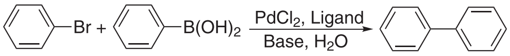
n=1, **1a**; n=2, **1b**; n=3, **1c**

Figure 1. 1-Methylimidazole-based phosphines.

1b and **1c** with two and three 1-methylimidazole substituents, respectively, give slightly lower yields (Table 1, entries 8 and 9). Probably the overcrowded steric hindrance prevents the oxidative addition. Then, we investigated the effect of solvent on the model reaction. It is evident from Table 2 that the reaction gives good yields in strong polar solvents (Table 2, entries 1, 7, 8 and 12), the best yield being obtained in ethanol (Table 2, entry 7), which is considered an eco-friendly and desirable solvent for organic synthesis.[27] In contrast, the commonly used DMF or 1,4-dioxane give poor yields (Table 2, entries 2 and 5). Thus the optimized reaction conditions are found to be 0.5 mol% of $PdCl_2$, 1 mol% of **1a**, 2 equiv. of K_3PO_4, in ethanol at 80°C.

The Suzuki reactions of a variety of aryl bromides and aryl chlorides with phenylboronic acid were studied under the optimized conditions. The results are summarized in Table 3. The reactions proceed well for all the substrates examined, and expected products are isolated in moderate to excellent yields. Alkyl-substituted bromobenzene reacts with phenylboronic acid to give the corresponding products in excellent yields (Table 3, entries 2–7), and an obvious decrease is observed in the case of *para*-$C_{12}H_{25}$-bromobenzene and *ortho*-methylbromobenzene (Table 3, entries 8 and 9). In the case of fluorine-containing substrates, the corresponding products are obtained in excellent yields (Table 3, entries 10–14). However, moderate yields are obtained for difluorine-substituted substrates (Table 3, entries 15 and 16). The reaction of 4-bromobiphenyl with phenylboronic acid gives the desired product in good yield (Table 3, entry 17). Less active aryl chlorides, such as 4-chloroacetophenone, also react with phenylboronic acid to give the desired product when the reaction time is prolonged to 24 h (Table 3, entry 18). However, a poor yield is obtained for chlorobenzene even after 24 h (Table 3, entry 19). These results also indicate that a variety of important functional groups can be tolerated under the reaction conditions.

Table 1. Effect of base and ligand on the Suzuki coupling reaction[a]



Entry	Base	Ligand	Yield (%)[b]
1	NaOH	**1a**	19
2	K_2CO_3	**1a**	13
3	Na_2CO_3	**1a**	46
4	K_3PO_4	**1a**	79
5	$NaHCO_3$	**1a**	50
6	Et_3N	**1a**	56
7	CH_3CH_2ONa	**1a**	55
8	K_3PO_4	**1b**	68
9	K_3PO_4	**1c**	56

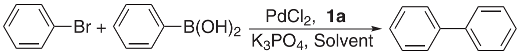
[a] Reaction conditions: bromobenzene (2 mmol), phenylboronic acid (2.5 mmol), base (4 mmol), $PdCl_2$ (0.01 mmol), ligand (0.02 mmol) and H_2O (3 ml) at 80°C for 0.5 h in a pressure tube.

[b] GC yields.

Conclusions

In summary, we investigated the activities of 1-methylimidazole-based phosphine ligands in the Suzuki reaction. The results showed that the ligand with one 1-methylimidazole substituent gave the best yield. Thus, ligand **1a** utilized in the Pd-catalyzed Suzuki

Table 2. Effect of solvent on the Suzuki coupling reaction[a]

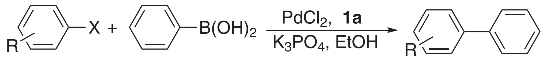


Entry	Solvent	Yield (%)[b]
1	H_2O	79
2	DMF	15
3	Toluene	26
4	Acetone	2
5	1,4-Dioxane	4
6	THF	20
7	EtOH	96
8	MeOH	91
9	Isopropanol	76
10	Ethyl acetate	2
11	Et_3N	18
12	Acetonitrile	90

[a] Reaction conditions: bromobenzene (2 mmol), phenylboronic acid (2.5 mmol), K_3PO_4 (4 mmol), $PdCl_2$ (0.01 mmol), **1a** (0.02 mmol) and solvent (3 ml) at 80°C for 0.5 h in a pressure tube.

[b] GC yields.

Table 3. Suzuki coupling reaction of aryl halides with phenylboronic acid[a]



Entry	R	X	Yield (%)[b]
1	H	Br	99
2	4-Methyl	Br	97
3	4-Propyl	Br	96
4	4-Butyl	Br	94
5	4-Pentyl	Br	95
6	4-Octyl	Br	94
7	4-Decyl	Br	93
8	4-Dodecyl	Br	80
9	2-Methyl	Br	85
10	4-Trifluoromethoxy	Br	96
11	4-Fluoro	Br	96
12	3-Fluoro	Br	94
13	2-Fluoro-4-methoxy	Br	90
14	2-Fluoro-4-formyl	Br	94
15	2,3-Difluoro	Br	46
16	3,5-Difluoro	Br	40
17	4-Phenyl	Br	72
18	4-Acetyl	Cl	85[c]
19	H	Cl	30[c]

[a] Reaction conditions: aryl halide (2 mmol), phenylboronic acid (2.5 mmol), K_3PO_4 (4 mmol), $PdCl_2$ (0.5 mol%), **1a** (1 mol%) and EtOH (3 ml) at 80°C for 3 h in a pressure tube.

[b] Isolated yields.

[c] $PdCl_2$ (1 mol%), **1a** (2 mol%), 80°C for 24 h.

reaction in ethanol provided moderate to excellent yields of the coupling products with excellent tolerance of various functional groups.

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