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Versatile palladium(II)-catalyzed Suzuki–Miyaura coupling in ethanol with a novel, stabilizing ligand

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ABSTRACT

Suzuki–Miyaura coupling reactions of arylboronic acids with aryl bromides were mediated by $PdCl_2$ and bdppmapy (*N*,*N*-bis-(diphenylphosphanylmethyl)-2-aminopyridine) that both stabilizes and solubilizes the catalyst in predominantly ethanol as a solvent. Excellent yields for a wide variety of substrates were obtained under relatively mild conditions in this 'green' solvent.

1. Introduction

Numerous modifications have been made to the reaction conditions of the Suzuki–Miyaura cross-coupling reaction and the carbonylative Suzuki–Miyaura reaction since their discoveries in 1979[1] and 1993,[2] respectively. Diaryl compounds are widespread structural motifs in natural products and pharmacologically active compounds.[3] The Suzuki–Miyaura reactions have provided highly efficient routes to otherwise challenging C_{sp2}–C_{sp2} bond formation.[4] Recent advances in this chemistry include ligand-free and/or 'green' reaction conditions with water or alcohol solubilizing ligands.[5,6] These include bulky or electron rich phosphines,[7] nitrogen-donors,[8] *N*-heterocyclic carbenes,[9] and other ligands[10] capable of increasing the electron density at palladium and thereby accelerating the oxidative addition step in the catalytic cycle.[11] Among these ligands, phosphines are the best known and still widely used because of their superior stabilization of the catalytically active Pd(0).[12]

One disadvantage of palladium catalysts is their cost and the potential for toxic contamination of pharmaceutical products. Many groups have therefore investigated Pd composites that can be easily separated and/or ultra-low loadings of catalyst.[13] For instance, a tetraphosphine ligand, *N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine (dppeda), was used in the coupling of aryl and heteroaryl bromides, which led to the yield of 98% with the $PdCl_2$ loading of 0.001 mol %.[13e] However, such a catalyst system sometimes involves ligands that are complicated and difficult to synthesize.[14]

The most frequently used solvents for these coupling reactions are acetone, toluene, THF, acetonitrile, and DMF,[15] which can be somewhat expensive, toxic, and difficult to recycle. Water-phase Suzuki–Miyaura reactions are an area of intensive investigation, but plagued with the low solubility of most substrates and catalysts.[10b,16–19]

Ethanol is an alternative renewable solvent, which is relatively cheap and nontoxic. Importantly, the range of organic substrates soluble in this solvent is much greater than those that are soluble in water. However, ethanol soluble palladium catalyst systems are not well studied.

P- and N-donor ligands bearing large groups are of interest because of their ability to stabilize transition metal catalysts.[6c] Additional N-donors in the ligand also accelerate certain reactions, even when there is no observable metal–nitrogen interaction in the pre-catalyst.[20] For example, a N-containing bis(phosphine) ligand displayed much higher activity in rhodium-catalyzed hydroformylation than did its all carbon analogue.[21] An amino-substituted *P*,*S*-phosphinite was also found to be more

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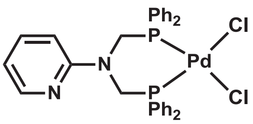
efficient in the palladium-catalyzed Heck reaction[22] and in a rhodium-catalyzed hydroformylation compared to the corresponding ligand without an amino group.[23]

A new complex [(bdppmapy)$PdCl_2$], constructed from $PdCl_2$ and a hybrid diphosphine-pyridine ligand bdppmapy (*N*,*N*-bis-(diphenylphosphanylmethyl)-2-aminopyridine) exhibits good catalytic performance in the decarboxylative C–C coupling of 4-piconic acid and aromatic bromides.[24] We herein report the extension of this investigation to the Suzuki–Miyaura cross-coupling reaction of arylboronic acids with aryl halides in predominantly ethanol as a solvent.



[(bdppmapy)$PdCl_2$]

2. Results and discussion

The coupling of 4′-bromoacetophenone (1 mmol) and 4-methoxyphenylboronic acid (1.5 mmol) was chosen as a model reaction. Because the amount of the catalyst loading was quite low (ranging 0.001–0.01 mol %) in this work, which related to the weighing of less than 0.067 mg, [(bdppmapy)$PdCl_2$] was used as a 0.01 M DMF solution to prevent large deviation (the solubility of [(bdppmapy)$PdCl_2$] is lower in ethanol and its 0.01 M ethanol solution could not be prepared). As we reported previously,[24] the solution of [(bdppmapy)$PdCl_2$] in DMF was the same as that made in situ from mixing $PdCl_2$ with equimolar bdppmapy in DMF. All reactions were performed by using 1–10 μL of such a $PdCl_2$/bdppmapy DMF solution and 4 mL of ethanol. The positive-ion ESI mass spectrum of this palladium/bdppmapy complex in DMF (2 μL) in ethanol (4 mL) was examined and provided an insight into its solution behavior (Fig. 1). A significant signal at m/z=716.08 could be assigned to the [(bdppmapy)Pd·DMF·CH_3CH_2O]$^+$ cation (Fig. 1). The detection of this cation implied that the ligand and Pd^{2+} were coordinated and stable in solution. Similar cations were observed in the corresponding ESI investigation of the more commonly used triphenylphosphine or diphosphines *N*,*N*-bis((diphenylphosphanyl)methyl)aniline (bdppma),[25] 1,1′-bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe) or 1,3-bis(diphenylphosphino)propane (dppp) (Fig. S1–S5, Supplementary data).

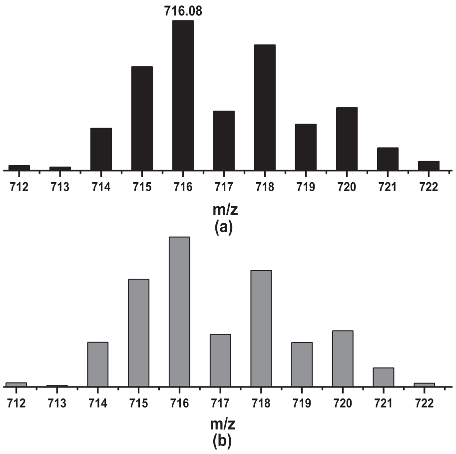
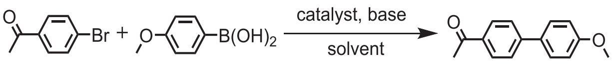


Fig. 1. The positive-ion ESI mass spectrum (top) and the calculated isotope pattern (below) of the [(bdppmapy)Pd·DMF·CH_3CH_2O]$^+$ in the catalyst system.

We initially evaluated the importance of different ligands (Table 1). Without ligand, the yield after 1.5 h was low relatively (13%, Table 1, entry 1). The utilization of bidentate ligands led to higher yields (Table 1, entries 4–6) than with monodentate triphenylphosphine and the backbone structure of the phosphines influenced the reaction rate (Table 1, entry 3). The highest yield was obtained with bdppmapy (Table 1, entry 2). Because the role of the pyridyl group in bdppmapy is unknown, a controlled experiment using its phenyl analogue, *N*,*N*-bis((diphenylphosphanyl)methyl) aniline (bdppma),[25] was performed. The yield (Table 1, entry 7) was the same as that using bdppmapy, implying that the pyridyl group in bdppmapy worked in the same manner as the phenyl group in bdppma, and could not coordinate to the Pd(II) center during the catalysis. Both groups only exhibited the steric hindrance effect, which is beneficial to the catalysis of the coupling reactions.[26]

We then investigated the lower limit of the catalyst loading (Table 2). The electron-poor substrate 4′-bromoacetophenone was almost completely converted into the desired product using 0.01 mol % $PdCl_2$ and 0.01 mol % bdppmapy for 0.5 h at 78 °C (Table 2, entry 1). When the catalyst loading was decreased to 0.005 mol %, 4′-bromoacetophenone could not be detected after 1 h (Table 2, entry 2). A yield of 99% was still achieved in the presence of 0.002 mol % catalyst after 1.5 h (Table 2, entry 3), but only 82% yield was observed after 1 h (Table 2, entry 4). Finally, a high yield was obtained with a catalyst loading as low as 0.001 mol % if the reaction time was prolonged to 4 h (Table 2, entry 5). These results indicated that the catalyst system has good longevity, which is attributed to the effective stabilization of the active palladium species by this bidentate phosphine. This lower catalyst loading was the same as the literature value using a tetraphosphine ligand (dppeda).[13e] However, the latter reaction reached 98% yield but was performed in dioxane in a longer time (20 h) and at a higher temperature (90 °C).

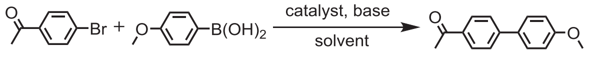
Table 1
The effect of different phosphine ligands on the Suzuki–Miyaura cross-coupling reaction



Entry	Ligand	Yield (%)
1	No ligand	13
2	bdppmapy	99
3	PPh_3	79
4	dppm	85
5	dppe	80
6	dppp	82
7	bdppma	99

Reaction conditions: 4′-bromoacetophenone 1 mmol, 4-methoxyphenylbor-onic acid 1.5 mmol, K_3PO_4 3 mmol, ethanol 4 mL, L/$PdCl_2$=1:1 (entries 2–7), catalyst 0.002 mol % Pd, 1.5 h, 78 °C, analyzed by GC, average of two runs.

Table 2
The effect of time and $PdCl_2$ loadings on the Suzuki–Miyaura cross-coupling reaction



Entry	Pd loading (mol %)	Time (h)	Yield (%)
1	0.01	0.5	99
2	0.005	1	99
3	0.002	1.5	99
4	0.002	1	82
5	0.001	4	99

Reaction conditions: 4′-bromoacetophenone 1 mmol, 4-methoxyphenylbor-onic acid 1.5 mmol, K_3PO_4 3 mmol, ethanol 4 mL, L/$PdCl_2$=1:1, 78 °C, analyzed by GC, average of two runs.