Efficient Diphosphane-Based Catalyst for the Palladium-Catalyzed Suzuki Cross-Coupling Reaction of 3-Pyridylboronic Acids

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A highly active catalyst system derived from $PdCl_2$ and 2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphanyl)-3,3'-bipyridine (P-Phos) has been developed for the Suzuki crosscoupling reaction of pyridylboronic acid with a variety of aryl halides in good to excellent yields, even in the presence of hindered and functional groups. In addition, P-Phos also exhibited high activity in the palladium-catalyzed Suzuki reac-

Introduction

The last several decades have seen growing attention placed on the synthesis of compounds containing heterobiaryl moieties, which are found in polymers,^[1] ligands,^[2] drugs,^[3] and various materials.^[4] Among the synthetic pathways, the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction between heteroaryl halides and arylboronic acids provided a general and applicable method for the preparation of heterobiaryls.^[5] In contrast, the reactions using aryl halides and heteroarylboronic acids^[6–8] have earned less attention, especially those pertaining to pyridylboronic acids.^[8]

Pyridine-derived boronic acids do not readily participate in Suzuki cross-coupling reactions as a result of their instability and slow rate of transmetalation, which can be attributed to the electron deficiency of the pyridine ring.^[8d,9] In the past 10 years, several ligands have been developed and great achievements were obtained in this challenging area. The group of Bryce reported that $Pd(PPh_3)_4$ and $Pd-(PPh_3)_2Cl_2$ catalyzed the reaction of substituted pyridylboronic acid and aryl bromides. This catalyst system could tolerate amine groups, and the cross-coupling reaction proceeded smoothly to give the desired products in moderate to good yields.^[10] Afterwards, dialkylbiarylphosphanes were developed and successfully applied to the Suzuki reaction of several pyridylboronic acids by Buchwald and coworkers. Both hindered and substituted chlorobenzene and

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tion of 2,6-dimethoxypyridylboronic acid in excellent yields with a fast rate. The steric and electronic effects of the P-Phos–palladium complex to this cross-coupling reaction were also discussed.

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heteroaryl chlorides could be transformed into the desired products in excellent yields, although these cross-coupling reactions were proven to be particularly difficult.^[8a,8b,8d,9] The success of this ligand was due to the large and electron-donating groups connected to the phosphorus atom.^[8b,11] Other ligands such as PCy₃,^[8c] Tedicyp,^[12] and fluorenyl-phosphanes^[13] were also used in this coupling reaction recently.

With the insight gained from the phosphanes mentioned above we noted that (a) alkylphosphanes exhibited higher activity than arylphosphanes by reason of the electron-donating properties and bulkiness of the alkyl groups, and at the same time they were more sensitive to moisture and air than arylphosphanes, although they could be tuned in structure (e.g., Buchwald's ligands) to adapt to the environment:^[11] (b) monophosphanes were proven to be efficient in the palladium-catalyzed cross-coupling reaction when the phosphorus atom was connected to an electron-donating group, but the instability of this unsaturated palladiumphosphanes complex was also noteworthy. Hence, we expected to discover an active and stable diphenylphosphane that could exhibit catalytic activity as high as that of alkylmonophosphanes in the Suzuki reaction of pyridine-derived boronic acids.

Results and Discussion

Considering the "pressure to coordinate" viewpoint that states that the greater the number of phosphanyl atoms the closer the phosphanes will be to the metal center, which can increase the stability of the catalyst,^[14] we decided to examine the catalytic activity of several diphosphane ligands in the palladium-catalyzed Suzuki reaction of 3-pyridylboronic acid with 4-methoxybromobenzene. According to the results illustrated in Scheme 1, we discovered that the use of ligands with either alkyl groups or phenyl groups con-



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Scheme 1. Several diphosphanes applied in the Suzuki cross-coupling reaction of 3-pyridylboronic acid with 1-bromo-4-methoxybenzene under the reaction conditions: $PdCl_2$ (1 mol-%), phosphane (2 mol-%), K_3PO_4 (2 equiv.), *n*BuOH, 80 °C, 5 h.

nected to the diphenylphosphane resulted in the desired product in low yields. It was observed that the yield was improved when bulky biphenyl groups were connected to the phosphanes. It is amazing that the reaction gave a yield as high as 90% when using the dipyridylphosphane ligand.

2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphanyl)-3,3'-bipyridine (P-Phos) was developed by the group of Chan in 2000.^[15] As is known, metal complexes of P-Phos are highly air stable.^[16] This advantage is important in industrial applications and also in tune with our notion to find a more stable phosphane that can be applied to the Suzuki reaction. After the selection of phosphanes, we further optimized the Suzuki reaction of 3-pyridylboronic acid with 1-bromo-4-methoxybenzene catalyzed by the P-Phospalladium complex. In early optimization studies, we observed that the best ratio of boronic acid/aryl halide was 2:1 and the catalyst exhibited better activity in polar solvents than in nonpolar solvents. Considering that the reaction should be carried out at high temperature, nBuOH was chosen as solvent to examine the effect of different bases such as Cs₂CO₃, K₃PO₄, Na₂CO₃, and KOH. Finally,

Table 1. Suzuki reaction of 3-pyridylboronic acid with different aryl halides.^[a]

		B(OH) ₂	+ aryl halide -	PdCl ₂ / P-Pho nBuOH, K ₃ P0 100°C, 3–20	$\frac{D_{4}}{h}$ $Aryl$		
Entry	Aryl halide	<i>t</i> [h]	Yield [%] ^[b]	Entry	Aryl halide	<i>t</i> [h]	Yield [%] ^[b]
1	Br-OCH3	20	94	12	Br	20	91
2	Br	6	99	13		20	85
3		6	99	14	B r	20	70
4	Br	10	88	15	⟨_SL _{Br}	20	99
5	Br	3	99 ^[c]	16	Br N	20	91
6	Br - NH ₂	20	99	17		20	99
7	Br	20	97	18		20	48
8	Br	20	99	19		20	83
9	Br	20	90	20		20	60
10	, Br ℃	20	55 ^[c]	21		20	84 ^[c]
11	Вг-СНО	20	90	22	сі————————————————————————————————————	20	91

[a] Reaction conditions: $PdCl_2$ (1 mol-%), P-Phos (2 mol-%), aryl bromide (1.0 equiv.), boronic acid (2.0 equiv.), K_3PO_4 (2.0 equiv.), *n*BuOH (2 mL), nitrogen protection, 100 °C. [b] Yield of isolated product based upon an the average of two runs. [c] Reaction was conducted with the use of P-Phos (1 mol-%).



 K_3PO_4 was adopted as the base for good results at 80 °C.

Under the optimum conditions of $PdCl_2/P$ -Phos/K₃PO₄/ *n*BuOH, we were pleased to find that the protocol could be applied to a wide range of different substituted aryl halides. As illustrated in Table 1, a variety of aryl bromide and chloride containing electron-donating or electron-withdrawing groups could be coupled with 3-pyridylboronic acid as expected.

There are several points to note in Table 1. Some unstable groups like NH₂ and CHO did not affect the activity of the catalyst (Table 1, Entries 6, 11, and 22). Furthermore, we also obtained the desired products in high yields when the bromides of thiophene, quinoline, and pyridine were used as reactants (Table 1, Entries 15-17). This revealed that the introduction of heteroatoms was not detrimental to the catalyst activity. The protocol could also be applied to some aryl chlorides with up to 91% yield (Table 1, Entries 18-22), although aryl chlorides were challenging substrates in the cross-coupling reaction. It is also notable that ortho-substituted aryl halides failed to couple with 3-pyridylboronic acid under the initial optimum condition. Considering that the steric hindrance of ortho-substituted groups might block the coordination of the P-Phos-palladium complex with the aryl halide, we tried to reduce the ratio of phosphane to facilitate the oxidative addition. Fortunately, we achieved success in the coupling of several ortho-substituted aryl bromides and chlorides by adjusting the amount of P-Phos to 1 mol-% (Table 1, Entries 5, 10, and 21). However, the activity of the catalyst under these conditions decreased remarkably when aryl halides substituted in the *meta* or *para* positions were used. It can be envisaged that the stability of the palladium-phosphane complex decreases with a decrease in the amount of phosphane used.

Heterobiaryl-containing pyridine rings are important building blocks for many biologically active molecules.^[17] It is evident that the Suzuki cross-coupling reaction of substituted pyridylboronic acid is valuable for the synthesis of these compounds.^[17a] We were delighted that P-Phos could be effectively applied to the Suzuki reaction of 2,6-dimethoxy-3-pyridylboronic acid to obtain functional heterobiaryls. Several aryl halides could be coupled with this morehindered pyridylboronic acid in excellent yield (Table 2). We were amazed that most substrates reacted completely within 2 or 3 h. To the best of our knowledge, this is the fastest rate that has been described for Suzuki reactions of pyridine-derived boronic acids. The reaction may profit from the electron-donating properties of the methoxy groups, which can compensate for the electron deficiency of the pyridine ring.

The success of P-Phos in the Suzuki reaction was stated previously. On the basis of these good results, we supposed that the bulkiness of the bipyridyl group might favor both the oxidative addition and the reductive elimination steps in the generally accepted catalytic cycle. Although the electron-withdrawing properties of the pyridine ring oppose the complexing ability of the lone electron pair of the phosphoTable 2. Suzuki reaction of 2,6-dimethoxy-3-pyridylboronic acid with different aryl halides. $\ensuremath{^{[a]}}$

H ₃ CO N OC	DH) ₂ + Aryl halide H ₃	PdCl ₂ / P-Phos <u>n</u> BuOH, K ₃ PO ₄ 100°C, 2–3h	H ₃ CO N OCH ₃
Entry	Aryl halide	<i>t</i> [h]	Yield [%] ^[b]
1	Br	2	99
2	Br	H ₃ 2	99
3	Br	3	99
4	Br	3	94
5	Br	l ₂ 3	99
6	Br	2	99
7	Br	3	80

[a] Reaction conditions: $PdCl_2$ (1 mol-%), P-Phos (2 mol-%), aryl bromide (1.0 equiv.), boronic acid (1.5 equiv.), K_3PO_4 (2.0 equiv.), *n*BuOH (2 mL), nitrogen protection, 100 °C. [b] Yield of isolated product based upon an the average of two runs.

rus atom,^[18] the electron-donating properties of the four methoxy groups will improve the electron density of the ring; this factor will provide the two phosphorus atoms with appropriate complexing ability. Moreover, the weak electron deficiency of the ligand is beneficial to the reductive elimination step (Figure 1).



Figure 1. Structural features of P-Phos and its impact on the efficacy of the catalyst.

Conclusions

In summary, we demonstrated that P-Phos as a highly stable diphenylphosphane exhibited excellent activity in the palladium-catalyzed Suzuki reaction of 3-pyridylboronic acid. The catalyst system could be applied to a wide range of substrates. It is not inhibited in the presence of some disubstituted groups. In addition, P-Phos also showed high catalytic activity in the Suzuki reaction of 2,6-dimethoxy-3-pyridylboronic acid. The structural specialties of P-Phos

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benefit this cross-coupling reaction. In comparison to other diphenylphosphanes reported in the Suzuki reaction of pyridine-derived boronic acids, P-Phos is more effective and applicable.

Experimental Section

General Procedure for the Cross-Coupling Reactions of 3-Pyridylboronic Acid: P-Phos (3.2 mg, 0.005 mmol) and PdCl₂ (0.4 mg, 0.0025 mmol) were added to a Schlenk tube equipped with a stir bar. The flask was evacuated and refilled with nitrogen three times. Under a nitrogen atmosphere, degassed nBuOH (1 mL) was added to dissolve the mixture, which was stirred for 5 min at room temperature. The aryl halide (0.25 mmol), pyridylboronic acid (48.6 mg, 0.5 mmol), and K₃PO₄ (106 mg, 0.5 mmol) were added to another Schlenk flask, which was then evacuated and refilled with nitrogen three times (if the halide was a liquid, it was added after the next step). The dissolved mixture of PdCl₂/P-Phos was transferred to the Schlenk flask of reactants by syringe. Then, nBuOH (1 mL) was added. The flask was sealed and heated in an oil bath at 100 °C for 6-20 h with vigorous stirring. After the reaction was complete, water (3 mL) was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc $(3\times)$. The combined extracts were concentrated. The residue was then purified by column chromatography on silica gel.

General Procedure for the Cross-Coupling Reactions of 2,6-Dimethoxy-3-pyridylboronic Acid: As for 3-pyridylboronic acid, but with the addition of 2,6-dimethoxy-3-pyridylboronic acid (68.1 mg, 0.375 mmol). The reaction mixture was stirred for 2–3 h.

Supporting Information (see footnote on the first page of this article): Detailed procedure and characterization data for the catalytic products illustrated in Tables 1 and 2.

Acknowledgments

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