Highly efficient palladium-catalyzed Suzuki–Miyaura cross-coupling of aryl bromides using 2-(diphenylphosphino) benzaldoxime ligand

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Abstract

A highly effective method for palladium-catalyzed Suzuki–Miyaura coupling of aryl bromides and arylboronic acids using novel 2-(diphenylphosphino) benzaldoxime ligand was developed. The new catalytic system based on Pd(OAc)$_2$ and the readily prepared and air stable ligand afforded high turnover numbers (up to 10^4) for a variety of substrates.
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Keywords: Suzuki–Miyaura; Aryl bromides; Oxime-functionalized phosphine ligand

1. Introduction

Great efforts have been directed toward the development of efficient catalytic systems for Suzuki–Miyaura cross-coupling reaction in the past few years [1,2]. Recently, *N*-heterocyclic carbenes (NHCs) [3,4], biphenyl-type phosphines [5] and other electron-rich phosphine ligands [6–13] have been reported and showed high reactivity in the reaction. The representative ligands were depicted in Scheme 1. Nowadays, there were no problem for the transformations of a variety of arylchlorides, however, the utilization of large amounts of catalysts, expensive ligands and complex operation made the reaction not practical in some cases. Thus, cost-effective alternative methods with the use of cheap ligands and simple operation procedures were still needed.

The biphenyl-type ligands (**1**–**3**) reported by Buchwald showed high reactivity in Suzuki–Miyaura reactions. One of the major advantages of these ligands was that sterically demanding and electron-rich phosphines could facilitate both the oxidative addition and reductive elimination involved in this reaction. Furthermore, there was an η-arene coordination of arene to Pd, which was also an important factor for the high efficiency [5c,14]. Indeed, it was found that in **2**/Pd(dba),

there was a η^2-coordination of Pd to the C9 and C10 on the phenanthrene moiety. The C9–C10 bond of phenanthrene was a better π donor than a phenyl or naphthyl moiety, which partially satisfied the electron deficiency of palladium [5c,15]. Moreover, ligands **4** [7c], **5** [7d] and **6** [8a] might also support this view for the catalytic process. Very recently, phosphine-functionalized NHC **7** [4f] and bioxazoline-derived NHC **8** [4g] were reported. Recognizing these discoveries, we proposed that introducing σ-donors rather than potential π-donors (such as phenyl, nathphyl, etc.) onto the *ortho* position of phosphine on aryl might be also effective to enhance the electro-donating ability of phosphine ligands. This modification could possibly facilitate the oxide addition of aryl halides to palladium, which was usually the rate-determination step in cross-coupling reactions for aryl bromides or chlorides. Since oxime was a potential σ-donor [12], we designed and synthesized two novel oxime-functionalized phosphine ligands, namely, 2-(dicyclohexylphosphino) benzaldoxime (**10a**) and 2-(diphenylphosphino) benzaldoxime (**10b**). Preliminary results indicated that these two ligands were highly efficient for Suzuki–Miyaura coupling of aryl bromides.

2. Experimental

All reactions were carried out under an argon atmosphere condition and monitored by thin layer chromatog-

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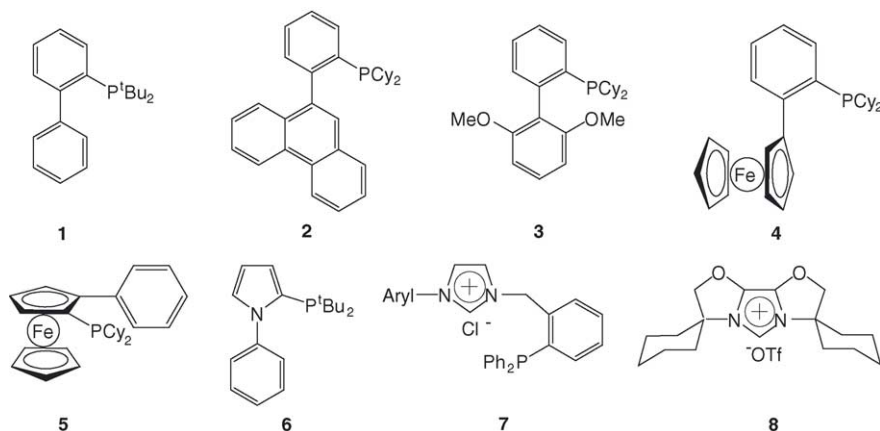
Scheme 1. Representative ligands.

raphy (TLC). Column chromatography purifications were performed using silica gel. All solvents were dried and degassed before use. NMR spectra were measured in CDCl$_3$ on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. High resolution mass spectra (HRMS) were recorded on a Mariner 5303 (Applied Biosystems, USA).

2.1. Synthesis of ligands

Synthesis of **10a**: 2-(Dicyclohexylphosphino) benzaldehyde (**9a**) (1.0 g, 3.3 mmol) was dissolved in deoxygenated EtOH and the solution was transferred to a flask including 30 ml deoxygenated EtOH flushed by nitrogen. Hydroxylamine hydrochloride (1.39 mg, 20 mmol) was dissolved in deoxygenated H$_2$O (40 ml) and NaHCO$_3$ (2.5 g, 30 mmol) was added under stirring. The aqueous solution was added dropwise to the above flask, and the reaction mixture was stirred for 1 h. The resulting mixture was extracted with Et$_2$O and dried over Na$_2$SO$_4$, concentrated, and purified by flash chromatograph on a short silica gel column (100% petroleum ether) with N$_2$ pressure to give the product **10a** as a white solid (390.0 mg, 37%). mp: 116–118 °C. ^{1}H NMR δ 9.16–9.18 (m, 1H), 8.05 (s, 1H), 7.85–7.86 (m, 1H), 7.48–7.50 (m, 1H), 7.33–7.39 (m, 3H), 0.97–1.97 (m, 22H). ^{31}P NMR δ −15.9. ^{13}C NMR δ 150.7, 150.4, 135.1, 133.0, 128.9, 126.3, 77.5, 77.2, 76.8, 33.4, 33.3, 30.5, 30.3, 28.9, 27.4, 27.2, 27.1, 26.4. HRMS (APCI) calcd for C$_{19}$H$_{29}$NOP (M + H$^+$): 318.1981, found: 318.1988.

Synthesis of **10b**: An aqueous solution (50 ml) contain hydroxylamine hydrochloride (530.0 mg, 7.6 mmol) was prepared and NaHCO$_3$ (957.6 mg, 11.4 mmol) was added under stirring. 2-(Diphenylphosphino) benzaldehyde (**9b**) (1.83 g, 6.3 mmol) was dissolved in EtOH (50 ml) in reflux and the above aqueous solution was added dropwise. After the reaction mixture was refluxed continuously for 2 h, the flask was cooled to RT under stirring. The crude product was filtered and recrystallized from ethanol to give **10b** as a white solid (1.40 g, 73% yield). mp: 176–177 °C. ^{1}H NMR δ 8.81 (d,

1H, J = 4.4 Hz), 7.81–7.84 (m, 1H), 7.67(s, 1H), 7.23–7.38 (m, 12H), 6.90–6.93 (m, 1H). ^{31}P NMR δ −13.4. ^{13}C NMR δ 149.3, 149.1, 136.8, 136.6, 136.2, 136.0, 135.9, 134.2, 133.9, 133.9, 130.0, 129.2, 129.1, 128.9, 128.8, 126.7. HRMS (APCI) calcd for C$_{19}$H$_{17}$NOP (M + H$^+$): 306.1042, found: 306.1050.

2.2. General procedure for palladium-catalyzed Suzuki–Miyaura reaction

An oven dried Schlenk tube was charged with Cs$_2$CO$_3$ (685 mg, 2.1 mmol) and aryl boronic acid (1.5 mmol). The tube was evacuated and back filled with argon (three cycles). Aryl bromides (1.0 mmol), Pd(OAc)$_2$, **10b** and dioxane (3 ml) were added successively to the tube under an argon atmosphere. The tube was sealed and stirred in an oil bath (preheated to 90 °C) for the required time period. The reaction mixture was cooled to rt, ethyl acetate (2 ml), H$_2$O (2 ml) and *n*-hexadecane (100 μl, GC standard) were added. The organic layer was analyzed by GC and separated. The aqueous layer was further extracted by ethyl acetate (10 ml × 4). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$). Then the solution was concentrated to give a residue which was purified by column chromatograph on silica gel to afford the pure desired product.

3. Results and discussion

As shown in Scheme 2, ligand **10a** was prepared from 2-(dicyclohexylphosphino) benzaldehyde (**9a**) which was
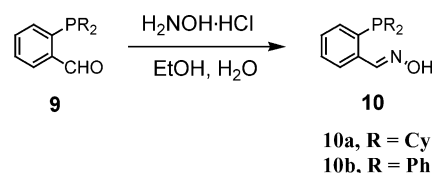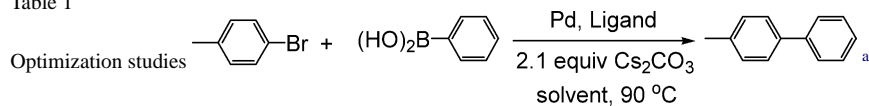

Scheme 2. Synthesis of ligands **10a** and **10b**.

Table 1

Optimization studies

Entry	Solvent	Pd	Ligand	[Pd] (mol%)	Time (h)	Conversion (%)[b]	Yield (%) [b]
1	Dioxane	Pd$_2$(dba)$_3$	**10a**	1	18	100	100
2	THF	Pd$_2$(dba)$_3$	**10a**	1	18	100	100
3	Toluene	Pd$_2$(dba)$_3$	**10a**	1	18	32	31
4	Dioxane	Pd$_2$(dba)$_3$	**10b**	1	12	100	100
5	Dioxane	Pd(OAc)$_2$	**10b**	1	9	100	100
6	Dioxane	Pd(OAc)$_2$	**10b**	0.01	9	100	100
7	Dioxane	Pd(OAc)$_2$	PPh$_3$	0.01	9	60[c]	59[c]

[a] Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenylboronic acid, Pd/ligand = 1/1. Solvent 3.0 ml, 90 °C.
[b] Determined by GC.
[c] Pd/ligand = 1/2.

made according to the reported literature [16]. Ligand **10b** was readily synthesized from commercially available 2-(diphenylphosphino)benzaldehyde (**9b**) in one step. Both **10a** and **10b** were stable for several weeks in air.

To study the efficiency of these new ligands, 4-bromotoluene was selected as the prototypical substrate for the Suzuki–Miyaura reaction (Table 1). When ligand **10a** was used for Pd$_2$(dba)$_3$-catalyzed coupling reaction, high yields

Table 2

Suzuki–Miyaura cross-coupling of aryl bromides
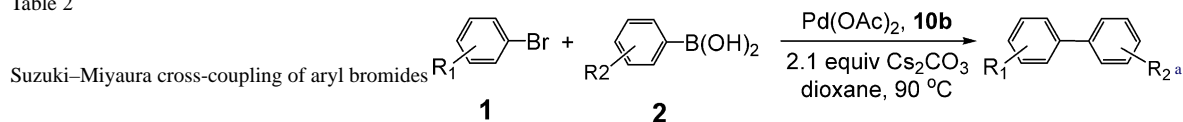
Entry	ArBr	ArB(OH)$_2$	Pd (mol%)	Time (h)	Yield (%) [b]	TON
1		**2a**	0.01	9	99	9900
2		**2a**	0.05	9	>99	2000
3		**2a**	0.05	6	98	1960
4		**2a**	0.05	6	>99	2000
5		**2a**	0.01	3	>99	10000
6		**2a**	0.05	9	99	1980
7		**2a**	0.05	9	99	1980
8		**2a**	0.5	9	72	144
9		**2b**	0.02	9	98	4900
10		**2b**	0.05	5	95	1900
11		**2b**	0.05	5	97	1940

[a] Reaction conditions: 1.0 mmol ArBr, 1.5 mmol ArB(OH)$_2$, Pd/**10b** = 1/1, 2.1 mmol Cs$_2$CO$_3$, 3.0 ml dioxane, 90 °C.
[b] Isolated yield.

of the desired product were observed using dioxane or THF as solvent (entries 1 and 2). However, bad yield was got while toluene was used (entry 3). When ligand **10b** was tested for the coupling reaction, the yields could also up to 100% using either $Pd_2(dba)_3$ or $Pd(OAc)_2$ as catalyst at 1 mol% loading (entries 4 and 5). Further study showed that the yield of the product was still quantitative while $Pd(OAc)_2$ catalyst loading was decreased to 0.01 mol% (entry 6). A control experiment using PPh_3 as ligand was conducted to confirm whether the oxime moiety was useful for the reaction. As expected, a remarkable decrease in activity was observed (entry 7). These results indicated that the oxime moiety on **10a** and **10b** played an important role. Although both **10a** and **10b** provided excellent yields for the model reaction, **10b** was chosen for further study since it was more economic than **10a**.

Preliminary results showed that Cs_2CO_3 was the best of choice among several bases that were screened [17]. Under the optimized reaction conditions, a variety of aryl bromides could react with arylboronic acid to provide the cross-coupling products in excellent yields at low loading levels of palladium (Table 2). It can be seen that unactivated 4-bromotoluene could be coupled with phenylboronic acid successfully (entry 1). Deactivated 4-bromoanisole worked also well using 0.05% palladium and gave nearly quantitative yield (entry 2). The reaction of activated aryl bromides with phenylboronic acid was very fast to afford the desired products completely, and the catalyst loading could be decreased to 0.01 mol% (entries 3–5). *ortho*-Substituted aryl bromides could also be translated to the desired product completely (entries 6 and 7). 2-Bromo-*m*-xylene bearing two *ortho*-substituted methyl could be coupled in a moderate yield (entry 8). Besides the phenylboronic acid, 4-methoxylphenyl boronic acid could also be used as substrates to provide the desired products with high yields (entries 9–11). Obviously, a combination of $Pd(OAc)_2$ and **10b** formed an excellent catalyst, which afforded high TONs for Suzuki–Miyaura cross-coupling of various arylbromides and arylboronic acids.

The excellent activity of **10b** suggested that introducing a σ-donor onto triphenylphosphine was successful for enhancing the effect of phosphine ligands. Though aryl chlorides were not suitable substrates for these reactions, this strategy might be quite valuable to find highly active catalytic systems else for more challenging substrates if other functionalized triarylphosphines instead of triphenylphosphine were used [18], since triarylphosphines could be readily prepared from relatively inexpensive chlorodiphenylphosphine using Grignard or organolithium reagents.

4. Conclusion

In summary, we have developed a highly effective method for $Pd(OAc)_2$-catalyzed Suzuki–Miyaura coupling of aryl bromides and arylboronic acids using novel 2-(diphenylphosphino) benzaldoxime ligand. The use of air

stable and readily available ligand, as well as the relatively high turnover numbers should made this protocol attractive for practical application. The utility of this method in other reactions are underway.

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