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Carbohydrate-based phosphines as supporting ligand for palladium-catalyzed Suzuki–Miyaura cross-coupling reaction

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ABSTRACT

Carbohydrate-based mono-phosphines (**1** and **2**) derived from glucose have been explored as supporting ligand for palladium-catalyzed Suzuki–Miyaura reaction. The combination of phosphine to palladium in a ratio of 2:1 resulted in a longer-living system than that in a ratio of 1:1. Using K_2CO_3 as base, aryl bromides as well as active aryl chlorides can be coupled nearly quantitatively by 0.1–0.2 mol % of **1**/$Pd(OAc)_2$ with 95–99% of isolated yields. The amount of the catalyst could be lowered to 0.01 mol % under the optimized condition with 80% yield at room temperature. The carbohydrate hydroxyl group in **1** was found to contribute to catalytic activity.

Metal-catalyzed cross-coupling methodology to form new carbon–carbon and carbon–heteroatom bonds has advanced organic synthesis significantly.[1] The palladium- and nickel-catalyzed coupling of aryl and alkenyl halides (or pseudo halides) with organoboronic acids, known as the Suzuki–Miyaura reaction,[2] is one of the most widely used methods[3] in the synthesis of pharmaceutical compounds,[4] natural products,[5] and polymers.[6] Thanks to the discovery and application of those ligands with electron-rich and sterically demanding characteristics, significant progresses have been witnessed in the last decade.[7–20]

The phosphine (**1**), (methyl 3-deoxy-4,6-*O*-phenylmethenyl-α-D-altropyranosido-3-)-diphenylphosphine, is easily prepared from glucose[21] and has shown interesting coordination mode to transition metals.[22–28] The two phenyl groups on phosphorus atom are chemically unequivalent shown by both of NMR and X-ray diffraction data,[21] indicating that the steric environment around phosphorus atom is crowed. The altropyrano-ring fusing with another six-member ring creates the highly sterically demanding around the 3-position phosphorus atom, leading to the chemical unequivalence of the two phenyl groups. Linking to an altropyrano-ring also makes the phosphorus atom electron-richer compared with triphenylphosphine. With the two features of electron-richer and sterically demanding, therefore it is attractive to explore the phosphine **1** as supporting ligand in the palladium-catalyzed Suzuki–Miyaura coupling reactions to enrich ligand library. The carbohydrate-based phosphine for cross-coupling reactions has been explored rarely.[29,30] Herein we report a highly efficient carbohydrate-based phosphine/palladium system for Suzuki–Miyaura coupling of aryl bromides and active aryl chlorides.

The carbohydrate phosphine **1** is easily accessed through 4 steps from cheap glucose (Scheme 1).[21] It had been found that the 2-hydroxyl group of altropyranoside in **1** coordinated to palladium(II) under basic condition in dichloromethane at room temperature to form phosphino- and alkoxo-palladium(II) chelate-complex **3** in 86% yield,[26] which had been isolated and fully characterized. Since Suzuki–Miyaura reaction is usually conducted under basic condition, the complex **3** can be expected to form especially as the ratio of phosphine to palladium is 2:1. In order to clarify the possible participation of species **3** in catalytic cycle, the 2-hydroxyl group in **1** was masked with methyl to form **2**, methyl 3-deoxy-2-*O*-2-methyl-4,6-*O*-phenylmethenyl-α-D-altropyranosido-3-)-diphenylphosphine.

In the initial experiments, the Suzuki–Miyaura reaction was performed between 4-bromotoluene and phenylboronic acid in different solvents with 0.2 mol % of $Pd(OAc)_2$ using K_2CO_3 as base. It was found that the reaction proceeded smoothly at room temperature in both of THF and 95% ethanol at beginning for the ratio of phosphine to palladium either 1:1 or 2:1. The catalyst system with a ratio of 1:1 stopped after 12 h with the conversion of 4-bromotoluene reaching 80% and 90% (Table 1, entries 1 and 3), respectively in THF

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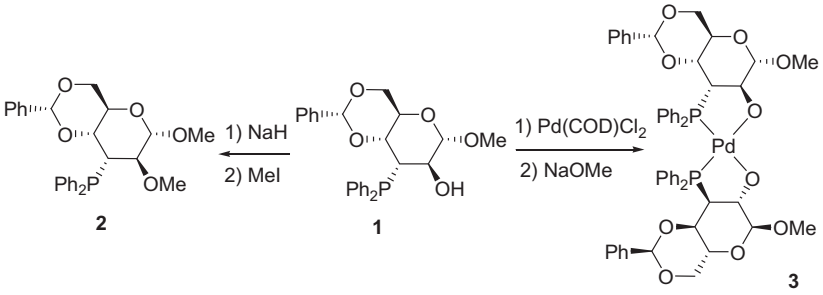


Scheme 1. Syntheses of carbohydrate-based phosphines and chelate-alkoxopalladium(II) complex.

Table 1
Effect of solvent and temperature on **1**/$Pd(OAc)_2$-catalyzed Suzuki–Miyaura reaction of 4-bromotoluene with phenylboronic acid[a]

Entry	Solvent	Pd/**1**	Temp (°C)	Time (h)	Yield[b] (%)
1	THF	1:1	rt[c]	12	70
				24	80 (75)
2	THF	1:2	rt	12	65
				24	89 (86)
3	95% Ethanol	1:1	rt	12	75
				24	90 (86)
4	95% Ethanol	1:2	rt	12	70
				24	97 (95)
5	Toluene	1:2	rt	12	40
				24	53
6	Acetonitrile	1:2	rt	12	5
				24	5
7	1,4-Dioxane	1:2	rt	12	15
				24	15
8	THF	1:2	73	3	99 (97)
9	95% Ethanol	1:2	88	12	95 (90)
10	Toluene	1:2	123	1	99 (96)
11	Acetonitrile	1:2	90	1	97 (95)
12	1,4-Dioxane	1:2	106	0.2	99 (99)
13	1,4-Dioxane	1:2	106	0.2	99 (99)[d]

[a] Reaction conditions: 4-bromotoluene (3.0 mmol), phenylboronic acid (4.5 mmol), $Pd(OAc)_2$ (0.006 mol), K_2CO_3 (6.0 mmol), solvent (9.0 mL).
[b] GLC yield calibrated via dodecane as an internal standard; isolated yields were given in parentheses (average of two runs).
[c] 22–32 °C.
[d] 0.003 mmol of $Pd(OAc)_2$.

and 95% ethanol, however the 2:1 ratio system showed a longer-living catalyst and can convert 4-bromotoluene to 97% level with 95% isolated yield of the desired biaryl (entry 4). Suzuki–Miyaura reaction is often needed in pharmaceutical industry, and the reaction carrying out in 95% ethanol at room temperature with mild base such as K_2CO_3 is highly desired.[29] These preliminary data showed that the carbohydrate-based phosphine **1** is much better than triphenylphosphine for palladium-catalyzed Suzuki–Miyaura reaction, with the latter as supporting ligand 3–5 mol % of palladium was usually employed.[31] Besides, with the carbohydrate-based phosphine **1** as supporting ligand the desired reaction condition for pharmaceutical industry upon 0.2 mol % of the palladium loading could be reached. The ratio of 2:1 was chosen and applied for the following exploration of the carbohydrate-based phosphine as supporting ligand for palladium-catalyzed Suzuki–Miyaura reaction. Other solvents such as toluene, acetonitrile, and 1,4-dioxane afforded low conversion of substrate at room temperature (entries 5–7). However, when the reactions were carried out under reflux conditions in the solvents other than 95% ethanol (entry 9), the reactions were completed in a much shorter time, and nearly quantitative conversion with excellent isolated yields was achieved (entries 8, 10–12). It is worthy of notification that the catalyst could be reduced to 0.1 mol % without affecting the reaction time and yield when the reaction was carried out in refluxing 1,4-dioxane (entry 13).

After optimizing solvent and temperature, various bases were investigated in 95% ethanol. It looked that only K_2CO_3 matched with the solvent of 95% ethanol; other bases tried even such as KOH, Cs_2CO_3, and NaOH were not of choice (Table 2, entries 3, 6, and 8). Although the reason for such a big difference between K_2CO_3 and Cs_2CO_3 as base in 95% ethanol was unclear, that strong base such as NaOH and KOH did not work either might be a clue. On the other hand using 1,4-dioxane as solvent with 0.1 mol % of $Pd(OAc)_2$, a variety of bases including K_2CO_3, $K_3PO_4{\cdot}3H_2O$, KOH, Cs_2CO_3, and NaOH proved to be the choice within 1 h (Table 1, entry 13; Table 2, entries 1, 3, 5, and 7), but around 1% of diphenyl could be observed when using KOH or NaOH as base. The performance of NaOAc was also good although with a longer time (Table 2, entry 9), but the bases Na_2CO_3 and NaOBu-*t* resulted in low yields (entries 11–14).

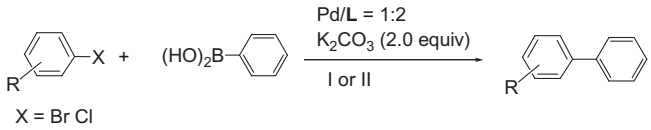
Since the phosphino- and alkoxo-palladium(II) chelate-complex **3** is easily formed,[26] we wondered the complex might participate in the catalytic reaction. Therefore, the hydroxyl-masked phosphine **2** was prepared and tested under the optimized condition to couple 4-bromotoluene with phenylboronic acid. Using **2** as supporting ligand it took 1 h to afford 96% of isolated yield in 1,4-dioxane (Table 3, entry 9), whereas by **1** only 0.2 h of time consumed. In 95% ethanol at room temperature, the difference is slight. These data suggest that the 2-hydroxyl group functions in the catalytic cycle and has the effect to increase the reaction rate. Although it

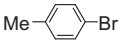
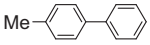
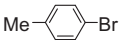
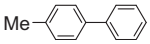
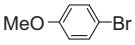
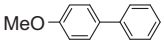
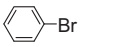
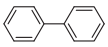
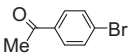
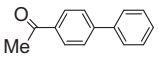
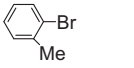
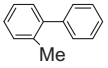
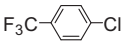
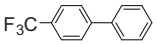
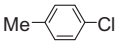
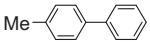
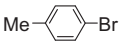
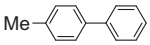
Table 2
Effect of base on **1**/$Pd(OAc)_2$-catalyzed Suzuki–Miyaura coupling 4-bromotoluene with phenylboronic acid

Entry	Base	React. Cond.[a]	Time (h)	Yield[b] (%)
1	$K_3PO_4{\cdot}3H_2O$	I	0.2	99 (99)
2	$K_3PO_4{\cdot}3H_2O$	II	24	10
3	KOH	I	0.2	99 (99)[c]
4	KOH	II	24	<5
5	Cs_2CO_3	I	0.2	98 (97)
6	Cs_2CO_3	II	24	13
7	NaOH	I	1	98 (97)[c]
8	NaOH	II	24	<5
9	NaOAc	I	6	94 (90)
10	NaOAc	II	24	10
11	Na_2CO_3	I	6	25
12	Na_2CO_3	II	24	<5
13	NaOBu-*t*	I	6	<5
14	NaOBu-*t*	II	24	<5

[a] Reaction conditions: aryl halide (3.0 mmol), phenylboronic acid (4.5 mmol), base (6.0 mmol), I or II (I: $Pd(OAc)_2$ (0.003 mmol), ligand (0.006 mmol), 1,4-dioxane (9 mL), oil bath 106 °C; II: $Pd(OAc)_2$ (0.006 mmol), ligand (0.012 mmol), 95% ethanol (9 mL), room temperature).
[b] GLC yield calibrated via internal standard, isolated yields were given in parentheses (average of two runs).
[c] Around 1% of biphenyl was observed.

Table 3
1/$Pd(OAc)_2$-catalyzed Suzuki–Miyaura reaction of aryl halides with phenylboronic acid



Entry	Ar-X	Product	Ligand	React. Cond.[a]	Time (h)	Yield[b] (%)
1			**1**	I II	0.2 24	98 95
2			**1**	I II	1 24	80[c] 78[c]
3			**1**	I II	0.2 12	99 97
4			**1**	I II	0.2 12	97 97
5			**1**	I II	0.2 12	99 98
6			**1**	I II	0.2 24	98 96
7			**1**	I II	1 24	98 25[d]
8			**1**	I II	6 24	45[d] 10[d]
9			**2**	I II	1 24	95 94

[a] Reaction conditions: aryl halide (3.0 mmol), phenylboronic acid (4.5 mmol), K_2CO_3 (6.0 mmol), I or II (I: $Pd(OAc)_2$ (0.003 mmol), ligand (0.006 mmol), 1,4-dioxane (9 mL), oil bath 106 °C; II: $Pd(OAc)_2$ (0.006 mmol), ligand (0.012 mmol), 95% ethanol (9 mL), room temperature).
[b] Isolated yield (average of two runs).
[c] 0.01 mol % catalyst.
[d] GLC yield.

is yet unclear how the 2-hydroxyl group participates in the reaction, some clues have been speculated: (a) taking part in producing Pd(0) species via reductive elimination with phenyl to form a phenyl ether; (b) the coordination of alkoxo anion enriching the election density of palladium center, therefore in favor of oxidative addition of aryl halide; (c) forming an alkoxo anion as intramolecular base to bind to boron atom to participate in transmetallation step. Further works are needed to clarify the functions of the 2-hydroxyl group and the principles found might be utilized in design of new catalyst system.

Since both of 95% ethanol as solvent and K_2CO_3 as base are very suitable for industrial application, the potential of **1** as supporting ligand was further explored. When 0.01 mol % of $Pd(OAc)_2$ was loaded with 0.02 mol % of **1**, 4-methylbiphenyl was obtained in respectable yields, 80% within 1 h in 1,4-dioxane at 106 °C of oil bath and 78% within 24 h in 95% ethanol at room temperature (Table 3, entry 2).

As expected the **1**/$Pd(OAc)_2$ catalyst system is very effective for the non-activated and activated aryl bromides (Table 3, entries 4 and 5). For the substrate with one-*ortho*-substituent 96–98% of yields were also achieved (entry 6). The catalyst system showed no influence as the deactivated substrate 4-bromoanisole as substrate (entry 3). These data promoted us to test chloroarenes as substrates. To our delight, using 1,4-dioxane as solvent 99% of isolated yield could be achieved for activated aryl chloride with 0.1 mol % catalyst loading within 1 h (entry 7), whereas in 95% ethanol 25% GLC yield was detected after 24 h. However, only 45% of the desired product was obtained when the nonactivated substrate was evaluated even in fluxing 1,4-dioxane (entry 8).

In summary, two carbohydrate-based phosphines have been found to be highly effective as supporting ligand for palladium-catalyzed Suzuki–Miyaura reaction of aryl bromides and activated aryl chlorides. The ratio 2:1 of phosphine to palladium afforded a longer-living catalyst system compared to that with the ratio 1:1. The base K_2CO_3 was the best choice for both 95% ethanol and 1,4-dioxane. With 95% ethanol and K_2CO_3 combination suitable for industrial application, the carbohydrate-based phosphine/palladium catalyst showed room temperature activities and the deactivated aryl bromide was converted nearly quantitatively by 0.1 mol % of palladium. Down to 0.01 mol % of palladium loading the desired biaryl still can be isolated in 80% yield. The 2-hydroxyl group in **1** has a positive effect for Suzuki–Miyaura coupling reaction, indicating that the carbohydrate hydroxy participated in the catalytic cycle in some way. To utilize deactivated chloroarenes as substrate and water as solvent, synthesis of those phosphines with two or even three altropyrano-rings is under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.011.

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