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Glucosamine-based phosphines. Efficient ligands in the Suzuki cross-coupling reaction in water

Sophie Parisot,[a] Robert Kolodziuk,[a] Catherine Goux-Henry,[a] Alexander Iourtchenko[a,b] and Denis Sinou[a,]*

[a]*Laboratoire de Synthèse Asymétrique, associé au CNRS, Université Claude Bernard Lyon 1, CPE Lyon, 43, boulevard du 11 novembre 1918, 69622 Villeurbanne cedex, France*

[b]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskya Str. 5, 02094 Kiev 94, Ukraine*

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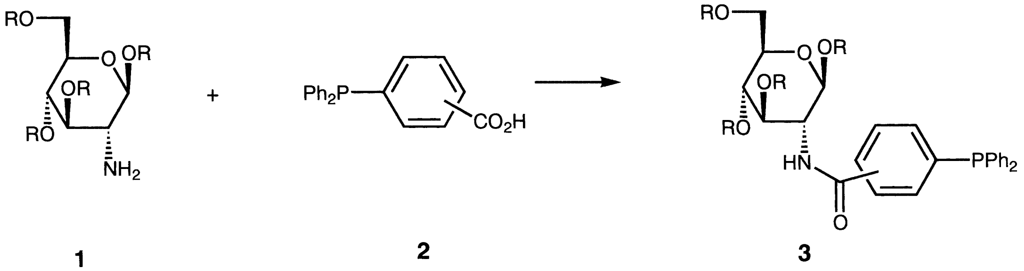
Abstract—Coupling of protected or non-protected D-glucosamine with *o*- or *p*-(diphenylphosphino)benzoic acid generates carbohydrate-substituted phosphines in quite good yields. The catalytic performance of these new neutral ligands is demonstrated in the Suzuki cross-coupling reaction. The polyhydroxy phosphines are more active than the peracetylated phosphines, and the process tolerates electron-rich as well as electron-poor substituents. Excellent turnovers are observed, and the catalyst can be recycled. © 2002 Elsevier Science Ltd. All rights reserved.

From both scientific and environmental points of view, development of easily separable organometallic catalysts from the organic products has attracted much attention. One way to solve this problem is the use of a two-phase catalysis water–organic solvent.[1] This implies the use of hydrophilic ligands such as phosphines in order to immobilize the catalyst in the aqueous phase. Most of the hydrosoluble phosphines used in recent years, such as the sodium salt of monosulfonated triphenylphosphine (TPPMS) or the trisodium salt of trisulfonated triphenyl phosphine (TPPTS), possessed ionic groups. Carbohydrate based phosphines, having neutral polar groups, appeared recently in the literature and seem to have a great potential; these ligands belong to an interesting class of neutral hydrophilic ligands derived from renewable materials.

Recently, glycosides of triphenylphosphines and gluconamide derivatives of triphenylphosphine were prepared by the groups of Beller[2] and Miyaura,[3] respectively. These ligands associated with $Pd(OAc)_2$ achieved higher efficiencies than that of TPPMS[4] and TPPTS[5] for Suzuki cross-coupling reaction of haloarenes with aryl boronic acids[6–9] in water or in a two-phase system. However, glycosides of triphenylphosphine probably suffered from their easy



1
a : R = $COCH_3$
b : R = H

2
a : *ortho*
b : *para*

3
a : R = $COCH_3$, *ortho*
b : R = H, *ortho*
c: R = $COCH_3$, *para*
d : R = H, *para*

Scheme 1. Synthesis of glucosamine-based phosphines **3a**–**d**.

Keywords: Suzuki coupling; carbohydrate; water-soluble; recycling.

* Corresponding author. Tel.: 33 (0)4 72448183; fax: 33 (0)4 78898914; e-mail: sinou@univ-lyon1.fr

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hydrolysis in the presence of water, precluding the possibility of an efficient recycling of the catalyst. In the case of the gluconamide derivative, although the modification of the phosphine is easy, the screening of other carbohydrate moieties, in order to improve the catalyst efficiency, seems more difficult. We present in this paper some results concerning the synthesis of a new class of more stable carbohydrate-based phosphines, whose modification is very easy both on the phosphine as well as on the carbohydrate moieties, and their application in Suzuki cross-coupling reactions.

We expected that the carbohydrate side-chain could be introduced via the usual coupling between an aminosugar and a triphenylphosphine bearing a carboxylic function. In the first approach, we choose glucosamine as the aminosugar. The synthesis of the glucosamine derivatives of triphenylphosphine **3a**–**d** is shown in Scheme 1. Condensation of 2-amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**1a**) with *o*- or *p*-(diphenylphosphino)benzoic acid (**2a**) or (**2b**) in a mixture of CH_2Cl_2/THF in the presence of EDC (or 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide) and HOBT (or 1-hydroxybenzotriazole) afforded the corresponding carbohydrate based phosphines **3a** and **3c** in 50% and 68% yields, respectively. Deacetylation of these peracetylated phosphines with a catalytic amount of sodium methoxide in methanol gave the polyhydroxy phosphines **3b** and **3d** in 80% and 88% yields, respectively. These compounds could also be obtained directly by condensation of *N*-glucosamine (**1b**) with *o*- or *p*-(diphenylphosphino)benzoic acid (**2a**) and (**2b**) in the presence of EDC, HOBT, and $NaHCO_3$ in a mixture of DMF/water as the solvent in 85% and 74% yields, respectively.

The cross-coupling reaction was performed in a mixture of ethanol/water/toluene, using $Pd(OAc)_2$ in association with the *ortho*-substituted peracetylated ligand **3a**, or the polyhydroxy ligand **3b**, using a 1.1/1 ratio of aryl boronic acid/aryl halide. The results summarized in Table 1 show that the peracetylated ligand **3a** was surprisingly completely inefficient at 60°C in this coupling reaction, even using aryl iodides. On the other hand, the polyhydroxy phosphine ligand **3b** was found to catalyze efficiently the coupling of haloaryls and aryl boronic acids, the cross-coupling being efficient over a broad spectrum of *ortho* and *para*-substituted aryl iodides and bromides. A large number of functions are tolerated, and the reaction time for a total conversion is short (2 h), using 1% mol catalyst. Decreasing the amount of catalyst to 0.1% also allowed a total conversion by increasing the reaction time (compared entries 2 and 3).

The reaction is chemospecific for aryl bromide in the presence of aryl chloride (Table 1, entry 15). Even sterically hindered boronic acid such as 2,6-dimethylphenyl boronic acid reacted under these conditions with 4-iodonitrobenzene to give the coupling product in 86% yield after 24 h, using 0.1% mol catalyst (Table 1, entry 5). It is to be noticed that no formation of homo-coupling products was observed.

We then used $Pd(OAc)_2$ in association with *para*-substituted ligands **3c** or **3d** as the catalyst (Table 2). It is noteworthy that the coupling reaction occurred efficiently using the peracetylated ligand **3c** as well as the polyhydroxy ligand **3d**, and that the reaction could be performed even at room temperature (Table 2, entries 1, 3, and 17). However, the polyhydroxy ligand was more efficient than the peracetylated ligand. Again

Table 1. Suzuki cross-coupling of aryl halides and boronic acids with $Pd(OAc)_2$/**3a**–**b**[a]

$Ar\text{-}X + Ar'\text{-}B(OH)_2 \rightarrow Ar\text{-}Ar'$

Entry	Aryl halide Ar-X	Aryl boronic acid $Ar'B(OH)_2$	Ligand	Mol Pd (%)	*T* (°C)/*t* (h)	Yield Ar-Ar′ (%)[b] (Conversion)[c]
1	4-Iodonitrobenzene	$C_6H_5B(OH)_2$	**3a**	1	60/3	(32)
2			**3b**	1	70/2	(93)
3			**3b**	0.1	60/24	>99
4	4-Iodonitrobenzene	$4\text{-MeC}_6H_4B(OH)_2$	**3b**	0.1	60/18	>98
5	4-Iodonitrobenzene	$2,6\text{-diMeC}_6H_3B(OH)_2$	**3b**	0.1	60/24	86
6	4-Bromonitrobenzene	$C_6H_5B(OH)_2$	**3a**	1	70/4	(8)
7			**3b**	1	70/2	(99)
8	4-Bromobenzaldehyde	$C_6H_5B(OH)_2$	**3a**	1	70/3	(0)
9			**3b**	1	70/2	(92)
10	4-Bromoanisole	$C_6H_5B(OH)_2$	**3a**	1	70/3	(0)
11			**3b**	1	70/2	(99)
12	3-Bromonitrobenzene	$C_6H_5B(OH)_2$	**3a**	1	70/3	(0)
13			**3b**	1	70/2	(99)
14	4-Bromochlorobenzene	$C_6H_5B(OH)_2$	**3a**	1	70/3	(0)
15			**3b**	1	70/2	(84)

[a] Reaction conditions: [aryl halide] = 0.05 M; [aryl halide]/[boronic acid]/[Na_2CO_3] = 1/1.1/3; [Pd]/[ligand] = 1/3; toluene/EtOH/H_2O = 3/2/2.

[b] Isolated chemical yield after column chromatography.

[c] Conversion determined by GC.

a large spectrum of aryl boronic acids, bearing substituents such as methyl (Table 2, entry 9), carbonyl (Table 2, entry 10), and methoxy (Table 2, entry 12), reacted with 4-iodonitrobenzene to give the corresponding biaryl derivative in excellent yields, even using 0.1% of catalyst (Table 2, entries 5, 10, 13, 19, and 26). Moreover, in the case of iodonitrobenzene and boronic acid, the coupling was quantitative at 60°C using 0.001% of catalyst in the presence of K_3PO_4 as the base (Table 2, entries 7 and 8).

The sterically hindered 2,6-dimethylphenyl boronic acid reacted also and gave the coupled product in 79% yield using 0.1% of catalyst. This yield was increased to 96% using an increasing amount of aryl boronic acid (Table 2, entries 14 and 15).

Condensation of 4-bromonitrobenzene and phenyl boronic acid occurred quantitatively in a short time using 0.1% catalyst (Table 2, entries 18 and 19). The beneficial effect of K_3PO_4 on the coupling was observed in the reaction of 2-bromopyridine with 4-methylphenyl boronic acid; when the corresponding biaryl derivative was obtained in 81% yield using 0.01% catalyst after 18 h reaction in the presence of Na_2CO_3, this yield was increased to 95% after only 10 h using K_3PO_4 as the base (Table 2, entries 28 and 29). The hindered 2-bromonitrobenzene reacted with 4-methylphenyl boronic acid in the presence of K_3PO_4 to give the coupling product in 99% yield using 1% catalyst (Table 2, entry 21). It is to be noted again that in all these experiments, the formation of homo-coupling products was never observed.

Finally it was possible to recycle the catalyst.[10] For example, the product resulting from the coupling of 4-iodonitrobenzene and phenyl boronic acid in the presence of 0.1% mol $Pd(OAc)_2$ and 0.3% mol ligand **3d** was obtained in 98% yield after 1 h reaction for the first cycle, 97% yield after 1 h for the second cycle, and 95% yield after 3 h for the third cycle. However using a low palladium loading (0.1% Pd), the degree of conversion decreases only for the second recycling; this decrease could be due to some accumulation of salts in the mixture.

Table 2. Suzuki cross-coupling of aryl halides and boronic acids with $Pd(OAc)_2$/**3c–d**[a]

$\text{Ar-X} + \text{Ar}'\text{-B(OH)}_2 \rightarrow \text{Ar-Ar}'$

Entry	Aryl halide Ar-X	Aryl boronic acid $Ar'B(OH)_2$	Ligand	Mol Pd (%)	T (°C)/t (h)	Yield Ar-Ar′ (%)[b] (Conversion)[c]
1	4-Iodonitrobenzene	$C_6H_5B(OH)_2$	**3c**	1	25/2	89
2			**3c**	1	70/2	98
3			**3d**	1	25/24	90
4			**3d**	1	60/0.08	98
5			**3d**	0.1	60/1	97
6			**3d**	0.01	60/1	100
7			**3d**	0.001	60/18	86
8			**3d**	0.001[d]	60/18	97
9	4-Iodonitrobenzene	$4\text{-MeC}_6H_4B(OH)_2$	**3d**	1	60/1	98
10	4-Iodonitrobenzene	$4\text{-CHOC}_6H'B(OH)_2$	**3d**	0.1	60/1	>99
11			**3d**	0.01	60/24	88
12	4-Iodonitrobenzene	$4\text{-MeOC}_6H_4B(OH)_2$	**3d**	1	60/18	>99
13			**3d**	0.1	60/18	90
14	4-Iodonitrobenzene	$2,6\text{-diMeC}_6H_3B(OH)_2$	**3d**	0.1	60/18	79
15			**3d**	0.1[e]	60/18	96
16			**3d**	0.01	60/18	ε
17	4-Bromonitrobenzene	$C_6H_5B(OH)_2$	**3c**	1	25/2	(100)
18			**3d**	1	60/1	95
19			**3d**	0.1	60/2	97
20	4-Bromonitrobenzene	$4\text{-MeC}_6H_4B(OH)_2$	**3d**	0.01[d]	60/18	81
21	2-Bromonitrobenzene	$4\text{-MeC}_6H_4B(OH)_2$	**3d**	1[d]	60/18	>99
22			**3d**	0.1	60/18	78
23	2-Bromochlorobenzene	$C_6H_5B(OH)_2$	**3c**	1	70/3	(97)
24			**3d**	1	60/1	(97)
25	4-Bromobenzaldehyde	$C_6H_5B(OH)_2$	**3d**	1	60/18	95
26			**3d**	0.1	60/1	>99
27			**3d**	0.01	60/1	88
28	2-Bromopyridine	$4\text{-MeC}_6H_4B(OH)_2$	**3d**	0.01	60/18	81
29			**3d**	0.01[d]	60/10	95

[a] Reaction conditions: [aryl halide] = 0.05 M; [aryl halide]/[boronic acid]/$[Na_2CO_3]$ = 1/1.1/3; [Pd]/[ligand] = 1/3; toluene/EtOH/H_2O = 3/2/2.

[b] Isolated chemical yield after column chromatography.

[c] Conversion determined by GC.

[d] K_3PO_4 was used as the base.

[e] [aryl halide]/[boronic acid] = 1/2.3.

In conclusion, palladium associated with a carbohydrate-based phosphine has been shown to have very high efficiency for the Suzuki cross-coupling reaction of a wide range of aryl halides and boronic acids. The catalyst can be also recycled. Work is in progress to extend this methodology to other water-soluble carbohydrate-based phosphines, other aryl halides, as well as other palladium-catalyzed reactions.

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10. Typical procedure: $Pd(OAc)_2$ (1.5 mg, 7×10^{-3} mmol) and the ligand **3** (21×10^{-3} mmol) were placed in a flask under argon. Degassed water (1 mL) and ethanol (1 mL) were added and the solution was stirred for 30 min. A mixture of aryl halide (0.7 mmol) and boronic acid (0.8 mmol) in a mixture of toluene (6 mL) and ethanol (2 mL) was then added in the flask, followed by Na_2CO_3 (212 mg, 2 mmol) dissolved in water (3 mL). The resulting mixture was stirred at the desired temperature. After the indicated time, the mixture was cooled at room temperature, the two phases were separated, the ethanol/H_2O layer was washed twice with toluene. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by flash-chromatography on silica gel gave the coupling product. In the case of the recycling experiments, the water/ethanol layer was transferred under argon into a second flask containing the aryl halide, the boronic acid and the base, in a mixture water/toluene.