Palladium-catalyzed Suzuki cross-coupling of aryl halides with aryl boronic acids in the presence of glucosamine-based phosphines

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Dedicated to Professor J.-P. Genêt on the occasion of his 60th birthday

Abstract

Carbohydrate-substituted phosphines are easily obtained in quite good yields by coupling of protected or non-protected D-glucosamine with the corresponding diphenylphosphino acid. These neutral ligands, in association with palladium acetate, are very active catalysts in the Suzuki cross-coupling reaction. The polyhydroxy phosphines are more active than the peracetylated phosphines. The process tolerates electron-rich as well as electron-poor substituents. Excellent turnovers, up to 97 000 are observed.
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1. Introduction

Palladium-catalyzed cross-coupling reaction of aryl halides with aryl boronic acids, the so-called Suzuki–Miyaura reaction, is one of the most versatile and powerful methods for carbon–carbon bond formation [1]. The versatility of this reaction is its wide applicability, the use of available reagents, the mild reaction conditions, the tolerance of a broad range of functional groups, as well as the use of aqueous organic solvent such as toluene–H_2O. It is also to be noticed that the inorganic by-products of this coupling reaction are non-toxic and easily removed from the reaction mixture. However, in most cases, phosphine ligands and high temperatures are usually required.

From both scientific and environmental points of view, development of very active and easily separable organometallic catalysts from the organic products has attracted much attention. One way to solve this problem is the use of a water-soluble organometallic catalyst, allowing the reaction to occur in water or better in a two-phase system organic solvent–water [2]. This approach would decrease the use of volatile and toxic organic solvents, and also simplify the catalyst recovery. With this aim in view, water-soluble phosphines, such as the sodium salt of monosulfonated triphenylphosphine (or TPPMS) or the trisodium salt of trisulfonated triphenylphosphine (or TPPTS), have been applied in this reaction; however the activity of these systems remains generally low [3]. So there is a need to find aqueous-phase catalyst systems exhibiting increased activities.

Carbohydrate based phosphines appeared recently in the literature and seemed to have a great potential in this coupling-reaction. Glycosides of triphenylphosphines [4] and gluconamide derivatives of triphenylphosphine [5] were prepared by the groups of Beller and Miyaura, respectively. The catalyst obtained by association of these ligands with $Pd(OAc)_2$ achieved higher turnover numbers (TON) than that obtained from TPPMS or TPPTS in Suzuki cross-coupling reaction of haloarenes with aryl boronic acids in water or even in a two-phase

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system. However, since glycosides of triphenylphosphine probably suffered from their easy hydrolytic cleavage in the presence of water, the recycling of the catalyst would be less efficient. For the gluconamide derivative, the screening of other carbohydrate moieties, in order to improve the catalyst activity and recycling, also seems difficult. Recently we presented preliminary results concerning the synthesis of a new class of more stable carbohydrate-based phosphines **1a**–**b** and **2a**–**b** [6], whose modification was very easy both on the phosphine as well as on the carbohydrate moieties. These ligands were very efficient in the palladium-catalyzed cross-coupling Suzuki reaction. We report herein a more detailed study concerning the synthesis of these ligands **1**–**3** (Fig. 1) having a carbohydrate side-chain and their catalytic efficiency in this coupling reaction between aryl halides and aryl boronic acids.

2. Results and discussion

The synthesis of the glucosamine-based phosphines is shown in Scheme 1. The reaction of 4-diphenylphosphinobenzoic acid with 2-amino-1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranose (**4a**) [7] in a CH_2Cl_2–THF mixture in the presence of EDC (or 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide) and HOBT (or 1-hydroxybenzotriazole) afforded the peracetylated phosphine **1a** in 50% yield. Deacetylation of **1a** with a catalytic amount of sodium methoxide in methanol gave the polyhydroxy phosphine **1b** in 80% yield, as a 87:13 mixture of the α- and β-anomers. This ligand could also be obtained directly by a simple condensation of D-glucosamine (**4b**) with 4-diphenylphosphinobenzoic acid in the presence of EDC, HOBT, and $NaHCO_3$ in a

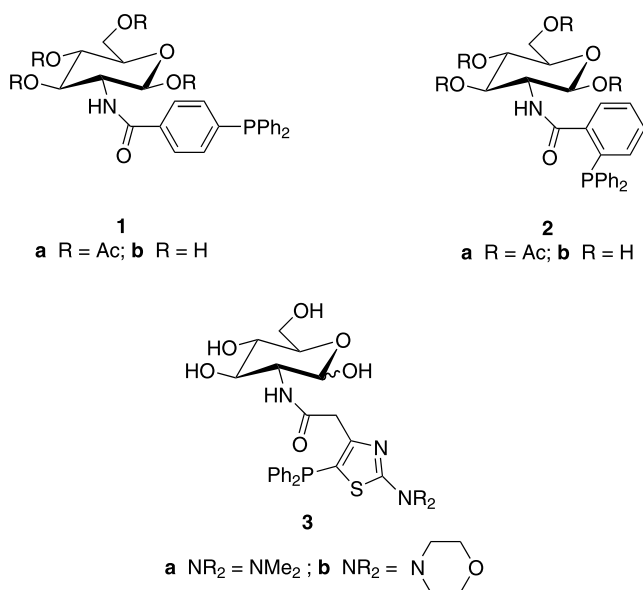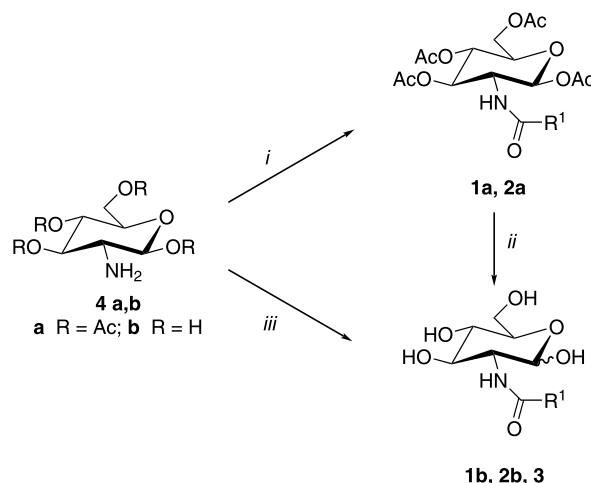Scheme 1. Synthesis of glucosamine-based phosphines **1**–**3**. (i) 4-$Ph_2PC_6H_4CO_2H$ for **1a** or 2-$Ph_2PC_6H_4CO_2H$ for **2a**, EDC, HOBT, CH_2Cl_2/THF, room temperature; (ii) CH_3ONa, CH_3OH, room temperature; (iii) 4-$Ph_2PC_6H_4CO_2H$ for **1b**, 2-$Ph_2PC_6H_4CO_2H$ for **2b**, **9a** for **3a**, **9b** for **3b**, EDC, HOBT, $NaHCO_3$, DMF, H_2O, room temperature.

mixture of DMF–water as the solvent in 85% yield. The ligands **2a** and **2b** were obtained using the same procedure, **2a** as the anomer β only in 68% yield, **2b** as an α–β mixture (85/15) in 74% yield [8]. Heterocyclic ligands **3a** and **3b** were obtained by coupling of the corresponding heterocyclic acid **9a** and **9b** and D-glucosamine (**4b**) in a mixture of DMF–water in 90 and 94% yield, respectively. The heterocyclic acids **9a** and **9b** were obtained according to Scheme 2. 2-Dialkylaminothiazoles **7a**–**b** were obtained by condensation of an equimolecular amount of the corresponding N,N-dialkylthioureas with ethyl 4-chloro-3-oxobutanoate in alcohol. Phosphorylation of these esters with Ph_2PBr at 20 °C afforded the corresponding phosphines **8a**–**b** in 64 and 63% yield, respectively. Saponification of compounds **8a**–**b** gave the heterocyclic carboxylic phosphines **9a**–**b** in 70 and 73% yield.

The cross-coupling reaction of 4-nitroiodobenzene with phenylboronic acid was carried out in a 3/2/2 mixture toluene–EtOH–H_2O in the presence of the complex synthesized in situ from $Pd(OAc)_2$ and the different ligands (Table 1). All the catalysts were active. However, we noticed that the acetylated ligands **1a** and **2a** gave less active catalysts than the corresponding polyhydroxy ligands **1b** and **2b** (Table 1, compare entries 1 and 3, 2 and 4, 6 and 7). It is noteworthy that the use of ligand **1b** at 60 °C gave quantitatively the coupling-product after 5 min; comparison of the *ortho*- and the *para*-substituted polyhydroxyphosphine **1b** and **2b** showed that the *para*-substituted is more active than the *ortho* (Table 1, entries 4 and 7). The polyhydroxy heterocyclic ligands **3a** and particularly **3b** also gave

Fig. 1.
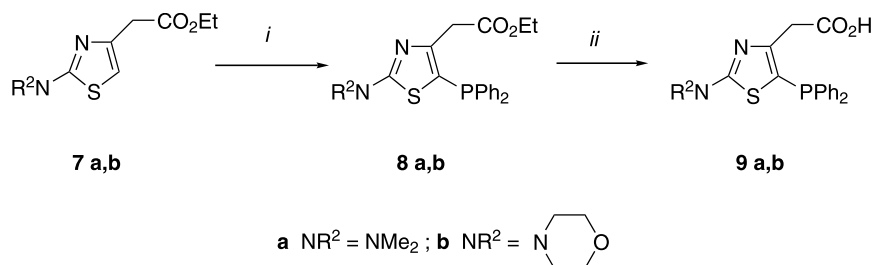
Scheme 2. Synthesis of heterocyclic carboxylic phosphines **9a** and **9b**. (i) PPh_2Br, C_5H_5N, Et_3N, 20 °C, 12 h; (ii) NaOH, CH_3CH_2OH, room temperature.

very active catalysts in this coupling reaction (Table 1, entries 10–14). It is to be noticed that no product resulting from the homo-coupling of phenylboronic acid (biphenyl) was observed under our conditions.

We then studied the influence of the solvent on the coupling reaction between 4-bromonitrobenzene and phenylboronic acid using 0.1% $Pd(OAc)_2$ and **1b** as the catalyst, and Na_2CO_3 as the base, at 60 °C (Table 2). We noticed that the highest conversions were obtained using toluene/EtOH/H_2O (Table 2, entry 1) or THF/H_2O (Table 2, entry 3) as the solvent. The use of water alone resulted in lower conversion (56%, Table 2, entry 4), while very low conversion was observed using toluene/H_2O or Et_2O as the solvent (Table 2, entries 2 and 5).

The efficiencies of some bases were also studied in the coupling reaction between 4-bromonitrobenzene and phenylboronic acid, using $Pd(OAc)_2$ (0.1 mol.%) associated with ligand **1b** in a THF–H_2O mixture (Table 3). Sodium or potassium carbonate, potassium phosphate and even potassium hydroxide afforded quantitatively

Table 2
Effect of the solvent on the cross-coupling reaction

$$4\text{-}NO_2C_6H_4\text{–}Br + C_6H_5\text{–}B(OH)_2 \rightarrow 4\text{-}NO_2C_6H_4\text{–}C_6H_5$$
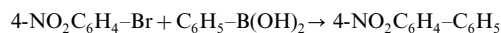
Entry	Solvent	Convn (%) (yield%) [a]
1	$C_6H_5CH_3$/EtOH/H_2O (3/2/2)	99 (99)
2	$C_6H_5CH_3$/H_2O (5/2)	11
3	THF/H_2O (5/2)	98
4	H_2O	56
5	Et_2O	5

All reactions were carried out in 14 ml of solvent in the presence of 4-nitrobromobenzene (0.7 mmol), phenylboronic acid (0.8 mmol), $Pd(OAc)_2$ 0.1 mol.%, ligand **1b** 0.3 mol.%, and Na_2CO_3 (2.1 mmol), at 60 °C for 1 h.
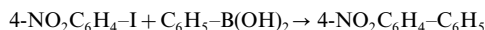[a] Conversion determined by GC; isolated chemical yield after column chromatography.

the expected coupling-product, while triethylamine is less efficient.

Finally the influence of the nature of the catalyst precursor was also studied, using **1b** as the ligand (Table

Table 1
Effect of ligands on the coupling reaction

$$4\text{-}NO_2C_6H_4\text{–}I + C_6H_5\text{–}B(OH)_2 \rightarrow 4\text{-}NO_2C_6H_4\text{–}C_6H_5$$

Entry	Ligand	T (°C)	Cat. (mol.%)	Time (h)	Convn (%) (yield%) [a]
1	**1a**	25	1	2	(89)
2	**1a**	60	1	2	(98)
3	**1b**	25	1	24	(90)
4	**1b**	60	1	0.08	(98)
5	**1b**	60	0.1	1	(97)
6	**2a**	60	1	3	32
7	**2b**	70	1	2	93
8	**2b**	60	0.1	3	(54)
9	**2b**	60	0.1	24	(99)
10	**3a**	25	1	18	(43)
11	**3a**	60	1	2	(98)
12	**3b**	25	1	1	(90)
13	**3b**	60	1	1	(99)
14	**3b**	60	0.1	1	(100)

All reactions were carried out in 14 ml of toluene/EtOH/H_2O (3/2/2) in the presence of 4-nitroiodobenzene (0.7 mmol), phenylboronic acid (0.8 mmol), a palladium catalyst, and Na_2CO_3 (2.1 mmol). The palladium catalyst was prepared in situ from $Pd(OAc)_2$ (one equivalent) and the ligand (three equivalents).
[a] Conversion determined by GC; isolated chemical yield after column chromatography.

Table 3
Effect of the base on the cross-coupling reaction

$4\text{-}NO_2C_6H_4\text{-}Br + C_6H_5\text{-}B(OH)_2 \rightarrow 4\text{-}NO_2C_6H_4\text{-}C_6H_5$

Entry	Base	Convn (%) (yield%) [a]
1	Na_2CO_3	99 (99)
2	K_2CO_3	99
3	K_3PO_4	99
4	KOH	97
5	NEt_3	35

All reactions were carried out in 14 ml of THF/H_2O (5/2) in the presence of 4-nitrobromobenzene (0.7 mmol), phenylboronic acid (0.8 mmol), $Pd(OAc)_2$ 0.1 mol.%, ligand **1b** 0.3 mol.%, and the base (2.1 mmol), at 60 °C for 1 h.

[a] Conversion determined by GC; isolated chemical yield after column chromatography.

Table 4
Effect of the catalyst precursor on the cross-coupling reaction

$4\text{-}NO_2C_6H_4\text{-}Br + C_6H_5\text{-}B(OH)_2 \rightarrow 4\text{-}NO_2C_6H_4\text{-}C_6H_5$

Entry	Catalyst/ligand **1b** (equivalent)	Convn (%) [a]
1	$Pd(OAc)_2$/**1b** (1/2)	99
2	$Pd(OAc)_2$/**1b** (1/3)	99
3	$Pd(OAc)_2$/**1b** (1/4)	99
4	$PdCl_2$/**1b** (1/2)	60
5	$PdCl_2$/**1b** (1/3)	99
6	$PdCl_2$/**1b** (1/4)	56

All reactions were carried out in 14 ml of THF/H_2O (5/2) in the presence of 4-nitrobromobenzene (0.7 mmol), phenylboronic acid (0.8 mmol), palladium catalyst 0.1 mol.%, and Na_2CO_3 (2.1 mmol), at 60 °C for 1 h.

[a] Conversion determined by GC; isolated chemical yield after column chromatography.

4). The coupling reaction between 4-bromonitrobenzene and phenylboronic acid in THF/H_2O in the presence of Na_2CO_3 occurred quantitatively starting from $Pd(OAc)_2$ as the palladium precursor, whatever the ratio Pd/ligand used (Table 4, entries 1–3). The use of $PdCl_2$ as the palladium precursor gave a less active catalyst, although the conversion was quantitative using a ratio Pd/**1b** = 1/3 (Table 4, entries 4–6).

Biaryl coupling of 4-nitroiodobenzene with various representative arylboronic acids in the presence of $Pd(OAc)_2$ as the palladium precursor, toluene/EtOH/H_2O as the solvent, and Na_2CO_3 as the base is summarized in Table 5. As previously noticed, the peracetylated ligands **1a** and **2a** associated with $Pd(OAc)_2$ gave less active catalysts than the analogues obtained using the polyhydroxyligands **1b**, **2b** and **3a**–**b** (Table 5, entries 1 and 8 vs entries 2 and 9–11). It is to be noticed that ligand **1b** showed the highest activity, total conversion of the 4-nitroiodobenzene being ob-

served after 5 min using 1 mol.% catalyst (Table 5, entry 2). The efficiency of this ligand **1b** was demonstrated by the TON of the catalyst; ligand **1b** exhibited effectively 86 000 and 97 000 TON, with a 0.001 mol.% catalyst loading, in the presence of Na_2CO_3 and K_3PO_4 as the base, respectively (Table 5, entries 6 and 7). Various aryl boronic acids such as 4-tolylboronic (Table 5, entry 12), 4-formylphenylboronic acid (Table 5, entries 16–18), and 4-methoxyphenylboronic acid (Table 5, entries 19–20) gave the coupling products in quite good yields, even using 0.1 mol.% catalyst. The sterically hindered 2,6-dimethylphenylboronic acid reacted also (Table 5, entries 13–15) affording the coupling product in 79% yield in the presence of 0.1 mol.% catalyst; this yield was increased to 96% using an increasing amount of aryl boronic acid.

Biaryl coupling of some bromoarenes with various arylboronic acids is also summarized in Table 6. 4- or 3-Nitrobromobenzene reacted efficiently with phenylboronic- or 4-tolylboronic acid to give quantitatively the corresponding biaryl compounds (Table 6, entries 1–5 and 24–26). Although peracetylated ligand **1a** gave quantitatively the coupling product after 2 h, the polyhydroxyphosphines **1b** and **2b** exhibited the highest activities; however the use of a mixture THF–H_2O as the solvent seemed detrimental for the conversion. It is to be noted that 2-nitrobromobenzene reacted with 4-tolylboronic acid using 0.1 mol.% $Pd(OAc)_2$ and ligand **1b** as the catalyst at 60 °C to give the coupling product in 78% conversion (Table 6, entry 27). 4-Formylbromobenzene reacted with benzeneboronic acid in high chemical yields in the presence of **1b** as the ligand, even using a 0.01 mol.% catalyst loading (Table 6, entries 6–9); we noticed again the detrimental effect of THF/H_2O as the solvent in this case (conversion < 9%). When the catalyst obtained from $Pd(OAc)_2$ and polyhydroxy ligand **2b** gave 92% conversion in this coupling reaction, no reaction occurred when the peracetylated ligand **2a** was used (Table 6, entries 10 and 11). 3-Acylbromobenzene, bearing a withdrawing group, reacted smoothly with benzeneboronic acid at 60 °C, even using 1 mol.% catalyst (Table 6, entries 12–14).

2-Bromochlorobenzene reacted quantitatively with benzeneboronic acid in the presence of $Pd(OAc)_2$ (1 mol.%) and ligand **1a** or **1b** (Table 6, entries 15 and 16), when 4-hydroxybromobenzene reacted smoothly using 0.1 mol.% catalyst (Table 6, entry 17). In the case of coupling of 4-methoxybromobenzene with benzeneboronic acid, the more active catalyst was the combination of $Pd(OAc)_2$ and ligand **2b** (Table 6, entries 18–21).

Finally when 2-bromonaphthalene and 4-vinylbromobenzene gave very low yields of coupling product with benzeneboronic acid (Table 6, entries 22 and 23), the condensation of the heterocyclic 2-bromopyridine with 4-tolylboronic acid occurred in quite good yields (Table 6, entries 29–30). We noticed again in the last example

Table 5
Synthesis of biaryls from 4-nitroiodobenzene and Ar–B(OH)$_2$

$4\text{-NO}_2\text{C}_6\text{H}_4\text{–I} + \text{Ar–B(OH)}_2 \rightarrow 4\text{-NO}_2\text{C}_6\text{H}_4\text{–Ar}$
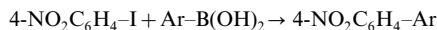
Entry	Ar–B(OH)$_2$ Ar=	Ligand	Pd(OAc)$_2$ (mol.%)	Time (h)	Convn (%) (yield%) [a]
1	C$_6$H$_5$	**1a**	1	2	(98)
2	C$_6$H$_5$	**1b**	1	0.08	(98)
3	C$_6$H$_5$	**1b**	0.1	1	(97)
4	C$_6$H$_5$	**1b**	0.1	1	(97)
5	C$_6$H$_5$	**1b**	0.01	1	(100)
6	C$_6$H$_5$	**1b**	0.001	18	(86)
7	C$_6$H$_5$	**1b**	0.001	18	(97) [b]
8	C$_6$H$_5$	**2a**	1	3	32
9	C$_6$H$_5$	**2b**	0.1	24	(99)
10	C$_6$H$_5$	**3a**	1	2	(98)
11	C$_6$H$_5$	**3b**	1	1	(99)
12	4-MeC$_6$H$_4$	**1b**	1	1	(98)
13	2,6-Me$_2$C$_6$H$_3$	**1b**	0.1	18	(79)
14	2,6-Me$_2$C$_6$H$_3$	**1b**	0.1	18	(96) [b]
15	2,6-Me$_2$C$_6$H$_3$	**2b**	0.1	24	(86)
16	4-CHOC$_6$H$_4$	**1b**	0.1	1	(99)
17	4-CHOC$_6$H$_4$	**1b**	0.01	24	(88)
18	4-CHOC$_6$H$_4$	**3b**	1	1	(98)
19	4-MeOC$_6$H$_4$	**1b**	1	18	(99)
20	4-MeOC$_6$H$_4$	**1b**	0.1	18	(90)

All reactions were carried out in 14 ml of toluene/EtOH/H$_2$O (3/2/2) in the presence of 4-nitroiodobenzene (0.7 mmol), Ar–B(OH)$_2$ (0.8 mmol), a palladium catalyst, and Na$_2$CO$_3$ (2.1 mmol) at 60 °C; the palladium catalyst was prepared in situ from Pd(OAc)$_2$ (one equivalent) and the ligand (three equivalents).

[a] Conversion determined by GC; isolated chemical yield after column chromatography.

[b] K$_3$PO$_4$ was used as the base.

the beneficial effect of K$_3$PO$_4$ on the coupling reaction; when the corresponding biaryl derivative was obtained in 81% yield using 0.01 mol.% catalyst after 18 h reaction in the presence of Na$_2$CO$_3$ as the base, this yield was increased to 95% after 10 h only in the presence of K$_3$PO$_4$.

We tried also some coupling reaction between various chloroarenes and benzeneboronic acid; however, whatever the conditions used, the formation of coupling products was never observed.

3. Conclusion

Palladium acetate associated with a carbohydrate-based phosphine has been shown to be efficient catalysts for the Suzuki cross-coupling reaction of a wide range or aryl iodides and bromides and boronic acids, very low catalyst loading being used. The polyhydroxylated ligands gave more active catalysts than the peracetylated ligands. Work is actually in progress in order to extend this methodology to hydroxylated polysaccharides based phosphines, in order to recycle efficiently the catalysts.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. All commercial available reagents were used as received. All reactions were monitored by TLC (TLC plates GF$_{254}$ Merck); detection was effected by UV absorbance. All manipulations involving palladium catalyst were performed under usual inert atmosphere techniques in Schlenk tube. Conversion was determined by GC using a Quadrex OV1 column (30 m × 0.25 mm). Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. NMR spectra were recorded with Bruker AC 300 spectrometer and referenced as following: ^{1}H (300 MHz), internal SiMe$_4$ at δ 0.00 ppm, ^{13}C (75 MHz), internal CDCl$_3$ at δ 77.23 ppm, and ^{31}P (121 MHz), external 85% H$_3$PO$_4$ at δ 0.00 ppm.

2-(Diphenylphosphino)benzoic acid and 4-(diphenylphosphino)benzoic acid are commercially available from Aldrich. 1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-β-D-glucopyranose (**4a**) was prepared according to the

Table 6
Synthesis of biaryls from bromoarenes Ar–Br and arylboronic acids Ar′–B(OH)$_2$

Ar–Br + Ar′–B(OH)$_2$ → Ar–Ar′

Entry	Ar–Br Ar =	Ar′B(OH)$_2$ Ar′ =	Ligand	% Pd	Solvent	T (°C)	Time (h)	Convn (%) (yield%) [a]
1	4-NO$_2$C$_6$H$_4$	C$_6$H$_5$	**1a**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	25	2	100
2	4-NO$_2$C$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	(95)
3	4-NO$_2$C$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	99 (99)
4	3-NO$_2$C$_6$H$_4$	C$_6$H$_5$	**2a**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	3	0
5	3-NO$_2$C$_6$H$_4$	C$_6$H$_5$	**2b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	2	99
6	4-CHOC$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	98 (95)
7	4-CHOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	99 (99)
8	4-CHOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.01	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	(88)
9	4-CHOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	THF/H$_2$O (5/2)	60	1	9
10	4-CHOC$_6$H$_4$	C$_6$H$_5$	**2a**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	3	0
11	4-CHOC$_6$H$_4$	C$_6$H$_5$	**2b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	2	92
12	3-MeCOC$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	44
13	3-MeCOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	44
14	3-MeCOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	THF/H$_2$O (5/2)	60	1	< 3
15	2-ClC$_6$H$_4$	C$_6$H$_5$	**1a**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	3	97
16	2-ClC$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	97
17	4-HOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	30
18	4-MeOC$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	32
19	4-MeOC$_6$H$_4$	C$_6$H$_5$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	32
20	4-MeOC$_6$H$_4$	C$_6$H$_5$	**2a**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	3	0
21	4-MeOC$_6$H$_4$	C$_6$H$_5$	**2b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	70	2	99
22	2-Bromonaphtalene	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	20
23	4-VinylC$_6$H$_4$	C$_6$H$_5$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	1	< 5
24	4-NO$_2$C$_6$H$_4$	4-MeC$_6$H$_4$	**1b**	0.01	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	(81)
25	4-NO$_2$C$_6$H$_4$	4-MeC$_6$H$_4$	**1b**	0.1	THF/H$_2$O (5/2)	60	1	46
26	4-NO$_2$C$_6$H$_4$	4-MeC$_6$H$_4$	**3b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	(77)
27	2-NO$_2$C$_6$H$_4$	4-MeC$_6$H$_4$	**1b**	0.1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	78
28	2-NO$_2$C$_6$H$_4$	4-MeC$_6$H$_4$	**1b**	1	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	> 99 [b]
29	2-Bromopyridine	4-MeC$_6$H$_4$	**1b**	0.01	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	18	(81)
30	2-Bromopyridine	4-MeC$_6$H$_4$	**1b**	0.01	C$_6$H$_5$CH$_3$/EtOH/H$_2$O (3/2/2)	60	10	(95) [b]

All reactions were carried out in 14 ml of solvent in the presence of bromoarene (0.7 mmol), Ar′–B(OH)$_2$ (0.8 mmol), a palladium catalyst, and Na$_2$CO$_3$ (2.1 mmol); the palladium catalyst was prepared in situ from Pd(OAc)$_2$ (one equivalent) and the ligand (three equivalents).

[a] Conversion determined by GC; isolated chemical yield after column chromatography.

[b] K$_3$PO$_4$ was used as the base.

literature [7]. The preparation of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-{[4-(diphenylphosphino)benzoyl]amino}-β-D-glucopyranose (**1a**) and 2-deoxy-2-{[4-(diphenylphosphino) benzoyl]amino}-D-glucopyranose (**1b**) was described in another paper [8].

4.2. Synthesis of ethyl (2-dialkylamino-1,3-thiazol-4-yl)acetate (7)

A mixture of *N,N*-dialkylthiourea (0.3 mol) and ethyl 4-chloro-3-oxobutanoate (49.4 g, 0.3 mol) was refluxed in alcohol (150 ml) for 4 h. The solvent was removed under reduced pressure, and the residue was dissolved in the minimal amount of water. The pH of the solution was brought to 9 by addition of an aqueous solution of Na$_2$CO$_3$, and then extracted with CHCl$_3$. Evaporation

of the solvent gave a residue that was purified by distillation.

4.2.1. Ethyl [2-(dimethylamino)-1,3-thiazol-4-yl]acetate (7a)

Yield 64%; Eb$_{0.8}$ = 105–107 °C; ^{1}H-NMR (CDCl$_3$): δ 1.19 (t, J = 7.0 Hz, 3H, CH$_3$), 2.99 (s, 6H, NMe), 3.52 (s, 2H, CH$_2$CO$_2$), 4.06 (q, 2H, J = 7.0 Hz, CH$_2$), 6.49 (s, 1H, H-5). Anal. Calc. for C$_9$H$_{14}$N$_2$O$_2$S (214.28): N, 13.07; Found: N, 12.89%.

4.2.2. Ethyl (2-morpholin-4-yl-1,3-thiazol-4-yl)acetate (7b)

Yield 76%; Eb$_5$ = 155–162 °C; ^{1}H-NMR (CDCl$_3$): δ 1.27 (t, J = 7.2 Hz, 3H, CH$_3$), 3.43 (m, 4H, NCH$_2$), 3.60 (s, 2H, CH$_2$CO$_2$), 3.80 (m, 4H, OCH$_2$), 4.18 (q, 2H, J =

7.2 Hz, CH$_2$), 6.43 (s, 1H, H-5). Anal. Calc. for C$_{11}$H$_{16}$N$_2$O$_3$S (256.32): N, 10.93; Found: N, 10.87%.

4.3. Synthesis of ethyl [2-dialkylamino-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetate (8)

To a solution of the corresponding dialkylaminothiazole **7** (50 mmol) and Et$_3$N (50 mmol) in pyridine (50 ml) was added at 0 °C Ph$_2$PBr (13.2 mg, 50 mmol). After being stirred for 20 h at room temperature (r.t.), the solution was diluted with C$_6$H$_6$ (70 ml), filtered, and the solvent was evaporated under reduced pressure. The residue was recrystallized from methanol.

4.3.1. Ethyl [2-(dimethylamino)-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetate (8a)

Yield 64%; m.p. = 101–103 °C (methanol); ^{1}H-NMR (DMSO-d_6): δ 1.08 (t, $J = 7.2$ Hz, 3H, CH$_3$), 2.98 (s, 6H, NMe), 3.84 (s, 2H, CH$_2$CO$_2$), 4.01 (q, 2H, $J = 7.2$ Hz, CH$_2$), 7.36 (m, 10H, C$_6$H$_5$); ^{31}P-NMR (DMSO-d_6): δ −28.8. Anal. Calc. for C$_{21}$H$_{23}$N$_2$O$_2$PS (398.46): N, 7.03; P, 7.77; Found: N, 6.95; P, 7.82%.

4.3.2. Ethyl [5-(diphenylphosphino)-2-(morpholin-4-yl-1,3-thiazol-4-yl]acetate (8b)

Yield 63%; m.p. = 91–92 °C (methanol); ^{1}H-NMR (DMSO-d_6): δ 1.07 (t, $J = 7.0$ Hz, 3H, CH$_3$), 3.32 (m, 4H, NCH$_2$), 3.65 (m, 4H, OCH$_2$), 3.86 (s, 2H, CH$_2$CO$_2$), 4.02 (q, 2H, $J = 7.0$ Hz, CH$_2$), 7.36 (m, 10H, C$_6$H$_5$); ^{31}P-NMR (DMSO-d_6): δ −28.7. Anal. Calc. for C$_{23}$H$_{25}$N$_2$O$_3$PS (440.50): N, 6.36; P, 6.89; Found: N, 6.19; P, 7.03%.

4.4. Synthesis of [2-(dialkylamino)-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetic acid (9)

A solution of the ester **9** (10 mmol) and NaOH (800 mg, 20 mmol) in EtOH (25 ml) was refluxed for 2–3 h, until full consumption of the starting material (TLC control). After cooling to r.t., a 1 N HCl solution was added until pH 5–6. The solid was collected by filtration and recrystallized from MeOH.

4.4.1. [2-(Dimethylamino)-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetic acid (9a)

Yield 70%; m.p. = 107–108 °C (methanol); ^{1}H-NMR (DMSO-d_6): δ 3.07 (s, 6H, NMe), 3.83 (s, 2H, CH$_2$CO$_2$), 7.35 (m, 10H, C$_6$H$_5$), 9.25 (1H, s, OH); ^{31}P-NMR (DMSO-d_6): δ −28.6. Anal. Calc. for C$_{19}$H$_{19}$N$_2$O$_2$PS (370.41): N, 7.56; P, 8.36; Found: N, 7.43; P, 8.23%.

4.4.2. [5-(Diphenylphosphino)-2-(morpholin-4-yl)-1,3-thiazol-4-yl]acetic acid (9b)

Yield 73%; m.p. = 176–177 °C (methanol); ^{1}H-NMR (DMSO-d_6): δ 3.43 (m, 4H, NCH$_2$), 3.65 (m, 4H,

OCH$_2$), 3.96 (s, 2H, CH$_2$CO$_2$), 7.34 (m, 10H, C$_6$H$_5$); ^{31}P-NMR (DMSO-d_6): δ −28.8. Anal. Calc. for C$_{21}$H$_{21}$N$_2$O$_3$PS (412.44): N, 6.79; P, 7.51; Found: N, 6.72; P, 7.44%.

4.5. 1,3,4,6-Tetra-O-acetyl-2-deoxy-2-{[4-(diphenylphosphino)benzoyl]amino}-β-D-glucopyranose (1a)

1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-β-D-glucopyranose (**4a**) (688 mg, 1.98 mmol), 4-diphenylphosphinobenzoic acid (1.8 mmol), EDC (0.4 g, 2.16 mmol), and HOBT (0.29 g, 2.16 mmol) were dissolved in a mixture of CH$_2$Cl$_2$ (10 ml) and THF (20 ml) in a Schlenk tube under argon. After being stirred for 5 h at r.t., the solvents were evaporated. The residue was washed with NaOH 5% (10 ml), and HCl 0.5 M (5 ml), then dried under vacuum to give phosphine **1a**. Yield 458 mg, (40%); m.p. 164–166 °C; $[\alpha]_D^{20} = +28.0$ (c 1, CHCl$_3$); ^{1}H-NMR (CDCl$_3$): δ 1.98 (s, 3H, CH$_3$), 2.05 (s, 6H, 2 × CH$_3$), 2.10 (s, 3H, CH$_3$), 3.86 (dm, $J = 9.6$ Hz, 1H, H-5), 4.15 (dd, $J = 12.4$, 2.1 Hz, 1H, H-6), 4.27 (dd, $J = 12.4$, 4.6 Hz, 1H, H-6), 4.57 (ddd, $J = 9.6$, 9.5, 8.7 Hz, 1H, H-2), 5.23 (dd, $J = 10.4$, 9.6 Hz, 1H, H-4), 5.35 (dd, $J = 10.4$, 9.5 Hz, 1H, H-3), 5.85 (d, $J = 8.7$ Hz, 1H, H-1), 6.75 (d, $J = 9.5$ Hz, 1H, NH), 7.25-8.00 (m, 14H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 20.6, 20.7, 20.8, 20.9, 53.4, 61.1, 67.9, 72.8, 73.0, 92.9, 126.8, 126.9, 128.7, 128.8, 129.2, 129.3, 129.4, 130.4, 133.0, 133.4, 133.7, 133.8, 134.2, 134.3, 136.3, 136.4, 143.1, 142.8, 167.3, 169.4, 169.6, 170.8, 171.4; ^{31}P-NMR (CDCl$_3$): δ −5.0. HRMS of C$_{33}$H$_{35}$O$_{10}$NP Calc. [M+H]$^+$ 636.1998, Found: 636.1984.

4.6. Synthesis of polyhydroxylated phosphines 1b, 2b, and 3

A solution of diphenylphosphino acid (0.5 mmol), EDC (112 mg, 0.6 mmol), and HOBT (81 mg, 0.6 mmol) in DMF (4 ml) was stirred in a Schlenk tube under argon at 0 °C for 1 h. A solution of D-glucosamine hydrochloride (215 mg, 1.0 mmol) in DMF (2 ml) was added, followed by the addition of a solution of NaHCO$_3$ (200 mg, 2.4 mmol) in H$_2$O (2 ml). After being stirred for 24 h at r.t., the solvents were evaporated under reduced pressure to give a solid that was purified by flash-chromatography on silica gel using CHCl$_3$/EtOH 3:1 as the eluent.

4.6.1. 2-Deoxy-2-{[4-(diphenylphosphino)benzoyl]amino}-D-glucopyranose (1b)

Yield 74%; m.p. 120–124 °C; $R_f = 0.59$ (CHCl$_3$/C$_2$H$_5$OH 3:1); $[\alpha]_D^{20} = +43.5$ (c 1, THF); ^{1}H-NMR (C$_5$D$_5$N): δ 4.01 (ddd, $J = 9.2$, 5.7, 2.1 Hz, 0.13H, H-5β), 4.23 (dd, $J = 9.2$, 9.0 Hz, 0.13H, H-4β), 4.32 (dd,

$J = 9.4$, 9.0 Hz, 0.87H, H-4α), 4.41 (dd, $J = 11.7$, 5.7 Hz, 0.87H, H-6α), 4.55 (dd, $J = 11.7$, 2.3 Hz, 0.87H, H-6α), 4.75–4.86 (m, 1.74H, H-3α, H-5α), 5.11 (ddd, $J = 10.4$, 8.5, 3.2 Hz, 0.87H, H-2α), 5.50 (bs, 4H, OH), 5.59 (d, $J = 8.3$ Hz, 0.13H, H-1β), 6.08 (d, $J = 3.2$ Hz, 0.87H, H-1α), 7.33–7.45 (m, 12H, H$_{arom}$), 8.15–8.22 (m, 2H, H$_{arom}$), 8.99 (d, $J = 8.5$, 0.87H, NH), 9.43 (d, $J = 8.7$, 0.13H, NH); ^{31}P-NMR (C$_5$D$_5$N): δ −4.4. HRMS of C$_{25}$H$_{27}$O$_6$NP Calc. [M+H]$^+$ 468.1576, Found: 468.1572.

4.6.2. 2-Deoxy-2-({[2-(dimethylamino)-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetyl}amino)-D-glucopyranose (3a)

Yield 90%; m.p. 120–124 °C; $R_f = 0.53$ (CHCl$_3$/C$_2$H$_5$OH 4:1); $[\alpha]_D^{20} = +16.6$ (c 1, CHCl$_3$); ^{1}H-NMR (C$_5$D$_5$N): δ 2.78 (s, 6H, NMe$_2$), 3.95 (dm, $J = 9.5$ Hz, 0.2H, H-5β), 4.15 (dd, $J = 9.5$, 8.5 Hz, 0.2H, H-4β), 4.24 (dd, $J = 9.2$, 9.2 Hz, 0.8H, H-4α), 4.30–4.40 (m, 3H, H-6, COCH$_2$), 4.51 (dd, $J = 11.5$, 2.1 Hz 0.8H, H-6α), 4.66 (dd, $J = 10.5$, 9.2 Hz, 0.8H, H-3α), 4.74 (ddd, $J = 9.2$, 5.3, 2.1 Hz, 0.8H, H-5α), 4.85 (ddd, $J = 10.5$, 8.5, 3.0 Hz, 0.8H, H-2α), 4.97 (bs, 4H, OH), 5.36 (d, $J = 8.3$ Hz, 0.2H, H-1β), 5.86 (d, $J = 3.0$ Hz, 0.8H, H-1α), 7.26–7.39 (m, 6H, H$_{arom}$), 7.58–7.68 (m, 4H, H$_{arom}$), 9.04 (d, $J = 8.5$, 0.8H, NH), 9.24 (d, $J = 7.5$, 0.2H, NH); ^{31}P-NMR (C$_5$D$_5$N): δ −27.6. HRMS of C$_{25}$H$_{31}$O$_6$N$_3$PS Calc. [M+H]$^+$ 532.1671, Found: 532.1675.

4.6.3. 2-Deoxy-2-({[2-(morpholin-4-yl)-5-(diphenylphosphino)-1,3-thiazol-4-yl]acetyl}amino)-D-glucopyranose (3a)

Yield 94%; m.p. 102–105 °C; $R_f = 0.48$ (CHCl$_3$/C$_2$H$_5$OH 3:1); $[\alpha]_D^{20} = +14.2$ (c 1, CHCl$_3$); ^{1}H-NMR (C$_5$D$_5$N): δ 3.23–3.35 (m, 4H, NCH$_2$), 3.44–3.57 (m, 4H, OCH$_2$), 3.94 (dm, $J = 9.2$ Hz, 0.15H, H-5β), 4.15 (dd, $J = 9.2$, 8.7 Hz, 0.15H, H-4β), 4.24 (dd, $J = 9.2$, 9.2 Hz, 0.85H, H-4α), 4.30–4.40 (m, 3H, H-6, COCH$_2$), 4.50 (dd, $J = 11.7$, 2.0 Hz, 0.85H, H-6α), 4.65 (dd, $J = 10.7$, 9.2 Hz, 0.85H, H-3α), 4.71 (ddd, $J = 9.2$, 5.5, 2.0 Hz, 0.85H, H-5α), 4.85 (ddd, $J = 10.7$, 8.5, 3.4 Hz, 0.85H, H-2α), 5.36 (d, $J = 8.1$ Hz, 0.15H, H-1β), 5.86 (d, $J = 3.4$ Hz, 0.85H, H-1α), 6.10 (bs, 4H, OH), 7.29–7.41 (m, 6H, H$_{arom}$), 7.59–7.71 (m, 4H, H$_{arom}$), 9.01 (d, $J = 8.5$, 0.85H, NH), 9.25 (d, $J = 7.6$, 0.15H, NH); ^{31}P-NMR (C$_5$D$_5$N): δ −27.8. HRMS of C$_{27}$H$_{33}$O$_7$N$_3$PS Calc. [M+H]$^+$ 574.1777, Found: 574.1774.

4.7. Saponification of peracetylated phosphine 1a

To the acetylated phosphine **1a** (300 mg, 0.47 mmol) dissolved in THF (10 ml) under argon was slowly added a solution of Na (20 mg, 0.87 mmol) in CH$_3$OH (5 ml). After being stirred for 1 h at r.t., the solvent was evaporated to give a yellow solid that was purified by flash-chromatography on silica gel using CH$_2$Cl$_2$/

CH$_3$CO$_2$Et 90:10 as the eluent to give 193 mg of phosphine **1b** (yield = 88%).

4.8. Typical cross-coupling procedure

Pd(OAc)$_2$ (1.5 mg, 7 µmol) and the ligand (21 µmol) were placed in a flask under argon. Degassed water (1 ml) and ethanol (2 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$_2$CO$_3$ (212 mg, 2.0 mmol) dissolved in water (3 ml). The resulting mixture was stirred at the desired temperature. After the indicated time, the mixture was cooled at r.t., the two phases were separated, the ethanol/H$_2$O layer was washed twice with toluene. The combined organic phases were dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification of the crude product by flash-chromatography on silica gel gave the coupling product.

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