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Efficient aqueous-phase Suzuki coupling of activated aryl chlorides with arylboronic acids using D-glucosamine-based dicyclohexylarylphosphine

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Abstract—The synthesis of a new D-glucosamine-based dicyclohexylarylphosphine has been developed. The catalytic performance of this neutral ligand is demonstrated in the Suzuki–Miyaura cross-coupling reaction between several arylboronic acids and aryl or heteroaryl chlorides.

The palladium-catalyzed cross-coupling reaction of aryl halides with boronic acids, so-called Suzuki–Miyaura reaction, is recognized as one of the most attractive synthetic routes for the preparation of biaryl compounds.[1] These biaryls constitute important building blocks for the synthesis of pharmaceuticals, herbicides, polymers, materials, liquid crystals, and ligands. Some applications have been extended on industrial scale.[2] Suzuki–Miyaura cross-coupling reactions of aryl iodides and bromides have been extensively studied in the last decade. Due to their low cost and ready accessibility, aryl chlorides are more interesting from an industrial point of view.

Some examples of cross-coupling reactions of aryl chlorides with boronic acids have been described. Indolese[3] and Miyaura et al.[4] used successfully nickel catalysts, when the groups of Beller,[5] Buchwald,[6] Fu,[7] Fürstner,[8] Guram,[9] Herrmann,[10] Johannsen,[11] Nolan,[12] Richards,[13] Xiao,[14] Protasiewicz,[15] and Ozdemir[16] performed the same reactions in the presence of palladium catalysts. The key for the successful coupling was the use of electron-rich and sterically hindered phosphines (such as PCy_3, PCy_2Ar, aryl–MOPFs, $DmpPR_2$, etc.), carbene ligands, or imidazolium salts.

Due to the simplicity of catalyst–product separation, the economy, the safety and the environment impact, the use of water as a solvent in organic synthesis continues to attract considerable attention.[17] Only few examples have been reported concerning the cross-coupling reactions of chloroarenes with arylboronic acids in water or biphasic media. The use of water-soluble phosphines such as the trisodium salt of trisulfonated triphenylphosphine (TPPTS) in combination with $NiCl_2$ (dppe) in 1,4-dioxane–water has been described by Genêt and co-workers.[18] Oxime-derived palladacycles,[19] di-2-pyridylmethylamine-based palladium complexes,[20] and palladium *N*-heterocyclic carbene complexes[21] have also been reported in the cross-coupling of aryl chlorides with aryl or alkylboronic acids. However, the observed turnover numbers (TON) are generally lower for the coupling of aryl chlorides with phenylboronic acids than for aryl bromides, where TON up to 734,000 have been obtained using a more sterically water-soluble alkylphosphine as ligand.[22]

The use of carbohydrate-based ligands in this coupling reaction appeared recently in the literature, and this approach seems to have a great potential. Glycoside and gluconamide derivatives of triphenylphosphine have

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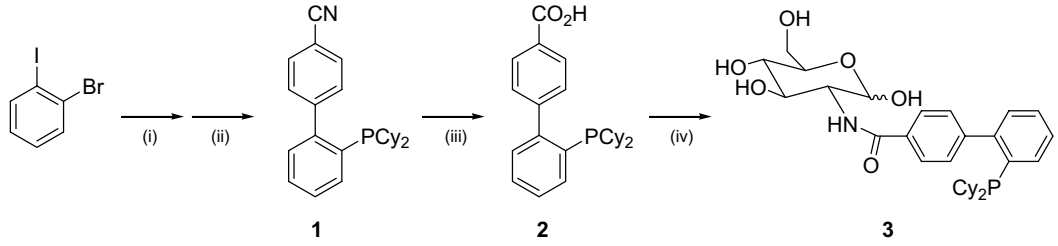
been prepared by the groups of Beller[23] and Miyaura,[24] respectively. In the case of glycoside derivative, only the coupling of aryl bromides has been performed with high TON (up to 9000). Despite the high TON obtained using as the catalyst $Pd(OAc)_2$ associated with the carbohydrate derivatives, the glycoside derivatives of triphenylphosphine suffered from their easy hydrolytic cleavage in the presence of water, prohibiting the efficient recycling of the catalyst. For the gluconamide derivatives, the coupling of bromo- and chloroarenes has although been developed. The screening of others ligands via the simple modification of the carbohydrate moiety, in order to improve the catalyst activity and recycling, seems difficult. Recently, we have presented some results concerning the synthesis of a new class of more stable carbohydrate-based triphenylphosphine derived from D-glucosamine.[25] These ligands have been successfully used in association with $Pd(OAc)_2$ in the aqueous-phase Suzuki cross-coupling reaction. However, these systems were limited to the coupling using aryl iodides and bromides.

Here, we describe the synthesis of a new generation of sterically hindered dicyclohexylphosphine based on D-glucosamine, and its application in the cross-coupling reaction of aryl chlorides with arylboronic acids in an organic-aqueous medium.

The synthesis of glucosamine-based dicyclohexylarylphosphine **3** is shown in Scheme 1. Palladium-catalyzed coupling of 2-iodobromobenzene with 3-cyanophenylboronic acid, followed by lithiation–phosphorylation of the C–Br bond according to the procedure described in the literature from 1,2-dibromobenzene,[24] afforded 2′-(dicyclohexylphosphino)biphenyl-4-carbonitrile **1** in 60% yield. Acidic hydrolysis of compound **1** gave 2′-(dicyclohexylphosphino)biphenyl-4-carboxylic acid **2** in 45% yield after purification. Coupling of this acid **2** with D-glucosamine hydrochloride in a DMF–H_2O solution in the presence of 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide (EDC), 1-hydroxybenzotriazole (HOBT), and $NaHCO_3$, afforded 2-deoxy-2-{[[2′-(dicyclohexylphosphino)biphenyl-4-yl]carbonyl]amino}-D-glucopyranose **3** in 62% yield.[26]

Different cross-coupling reactions of various aryl chlorides with arylboronic acids were investigated, and the results are summarized in Table 1. The conditions of



Scheme 1. Synthesis of the glucosamine-based dicyclohexylphenylphosphine **3**. Reagents and conditions: (i) 4-cyanophenylboronic acid, $Pd(OAc)_2$/TPPTS, Et_3N, CH_3CN/H_2O, 45 °C, 48 h; (ii) *n*-BuLi at −100 °C during 1 h, then Cy_2PCl at rt during 10 h; (iii) HCl, 110 °C; (iv) D-glucosamine hydrochloride, $NaHCO_3$, EDC/HOBT, DMF/H_2O, rt, 24 h.

Table 1. Suzuki–Miyaura cross-coupling of aryl halides and boronic acids with $Pd(OAc)_2$/**3**[a] Ar–X + Ar′–$B(OH)_2$ → Ar–Ar′

Entry	Aryl halide Ar–X	Arylboronic acid Ar′–$B(OH)_2$	Temp (°C)	Conversion[b] (%)	Yield[c] (%)
1[d]	1-Bromo-4-nitrobenzene	Phenylboronic acid	60	98	97
2[d]	1-Chloro-4-nitrobenzene	Phenylboronic acid	60	53	50
3	1-Chloro-4-nitrobenzene	Phenylboronic acid	60	76	—
4	1-Chloro-4-nitrobenzene	Phenylboronic acid	80	100	98
5[e]	1-Chloro-4-nitrobenzene	Phenylboronic acid	80	100	99
6	4-Chlorobenzonitrile	Phenylboronic acid	80	96	96
7	4-Chlorobenzoic acid	Phenylboronic acid	80	100	97
8	4-Chlorobenzaldehyde	Phenylboronic acid	80	94	94
9	1-Chloro-4-methylbenzene	Phenylboronic acid	80	23	—
10	2-Chloro-1,3-dimethylbenzene	Phenylboronic acid	80	12	—
11	2-Chloropyridine	Phenylboronic acid	80	100	93
12	3-Chloropyridine	Phenylboronic acid	80	88	81
13	1-Chloro-4-nitrobenzene	4-Cyanophenylboronic acid	80	100	99
14	1-Chloro-4-nitrobenzene	4-Methoxyphenylboronic acid	80	100	95
15	1-Chloro-4-nitrobenzene	4-Acetylphenylboronic acid	80	100	98
16	1-Chloro-4-nitrobenzene	4-Formylphenylboronic acid	80	100	92
17	1-Chloro-4-nitrobenzene	4-Methylphenylboronic acid	80	100	99
18	1-Chloro-4-nitrobenzene	2,6-Dimethylphenylboronic acid	80	100	90

[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] Conversion determined by GC.
[c] Isolated chemical yield after column chromatography.
[d] Reaction time 1 h.
[e] Catalyst concentration of 0.1% M.

the cross-coupling reaction were determined using 4-nitrobromobenzene and phenylboronic acid. As described before,[25b] the reaction was carried out in a 3/2/2 toluene/EtOH/H_2O mixture in the presence of the catalyst, formed in situ from 1% M of $Pd(OAc)_2$ and 3% M of ligand **3**, and in the presence of Na_2CO_3 (3 equiv) as the base.[27] After 1 h at 60 °C, the conversion and the yield were 98% and 97%, respectively (Table 1, entry 1). The same conditions of reactants and temperature were applied to the coupling of 4-nitrochlorobenzene with phenylboronic acid; however the conversion was only 53% after 1 h (Table 1, entry 2), and 76% after 20 h (Table 1, entry 3). When this cross-coupling reaction was performed at 80 °C, the conversion and the yield were 100% and 98%, respectively, after 20 h (Table 1, entry 4). Decreasing the amount of catalyst to 0.1% M gave the same results (Table 1, entry 5). Before testing other aryl chlorides and arylboronic acids, we compared these first results with those obtained using a 'ligandless' palladium catalyst.[1g,28] Under the conditions described above, but without ligand **3**, the conversion was 100% in the coupling of 4-nitrobromobenzene and phenylboronic acid, when no coupling reaction occurred using 4-nitrochlorobenzene and phenylboronic acid. It is known that in the case of aryl chloride, temperature higher than 80 °C or microwave are necessary in order to perform the coupling reaction.[29]

The biaryl coupling of various chloroarenes with phenylboronic acid was then investigated. Aryl chlorides bearing electron acceptor groups (Table 1, entries 6–8) reacted efficiently with phenylboronic acid affording quantitatively the corresponding biaryl compounds. Conversely, the aryl chlorides bearing electron donor groups gave very low conversion: 23% for 4-methylchlorobenzene (Table 1, entry 9), and 12% for 2,6-dimethylchlorobenzene (Table 1, entry10). It is known that in the case of *ortho*-substituted aryl chlorides, the catalytic efficiency depends on the bulkiness and/or electronic effects of the substituent. Generally, in order to obtain good yields starting from phenylboronic acid, a higher temperature ($\geqslant$100 °C) is necessary as shown by Beller and co-workers[5] and Buchwald and co-workers.[6] In our system, the use of the mixture of solvents toluene/EtOH/H_2O did not allowed to perform the reaction at a temperature higher than 85 °C.

Then, we studied the coupling of some heteroaryl chlorides with phenylboronic acid. The coupling reaction with 2-chloropyridine or 3-chloropyridine occurred in quite good yields, 93% and 81%, respectively (Table 1, entry 11 or 12).

Finally, the biaryl coupling of 4-nitrochlorobenzene with different arylboronic acids was studied in the presence of our catalyst. The conversion was quantitative whatever the nature of the substituent of the arylboronic acids (Table 1, entries 13–18). It is noteworthy that the coupling of 4-methylphenylboronic acid and 2,6-dimethylphenylboronic acid with 4-nitrochlorobenzene occurred, the coupling products being obtained in 99% and 90% yield, respectively (Table 1, entries 17 and 18).

In conclusion, the synthesis of a new hydrosoluble glucosamine-based dicyclohexylarylphosphine has been described. This phosphine has been used as ligand in the palladium Suzuki cross-coupling reaction. The efficiency of this ligand has been demonstrated in a wide range of coupling between aryl or heteroaryl chlorides and arylboronic acids. The Suzuki reaction was carried out at 80 °C in a 3/2/2 mixture of toluene/EtOH/H_2O in the presence of 1.0% or 0.1% M catalyst prepared in situ from $Pd(OAc)_2$ and the carbohydrate derivative. With only 1.1 equiv of arylboronic acid in relation to aryl chloride, the conversions and the chemical yields are generally high. These results are quite similar to these published by Miyaura and co-workers[24] using the gluconamide derivative of triphenylphosphine, the same activities being observed using activated aryl chlorides. However, the screening of others ligands by the modification of the carbohydrate moiety, in order to improve the catalyst activity and recycling, seems more easy using our system. Work is in progress actually in order to prepare new ligands with higher hydrosolubility in order to perform this reaction in a true biphasic system water/organic solvent.

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26. Compound **3**: R_f = 0.65 ($CHCl_3$/EtOH 2.5/2); $[\alpha]_D^{20}$ +35.5 (*c* 0.2, $CHCl_3$); ^1H NMR (C_5D_5N): δ 9.43 (d, J = 8.3 Hz, 0.2H, NH_β), 9.02 (d, J = 8.5 Hz, 0.8H, NH_α), 8.34 (br d, J = 8.3 Hz, 2H, H_{arom}), 7.77–7.67 (m, 1H, H_{arom}), 7.55–7.30 (m, 5H, H_{arom}), 6.09 (d, J = 2.9 Hz, 0.8H, $H_{1\alpha}$), 5.61 (d, J = 8.3 Hz, 0.2H, $H_{1\beta}$), 5.16 (ddd, J = 3.4, 8.4, 10.8 Hz, 0.8H, $H_{2\alpha}$), 4.87–4.77 (m, 1.8H, $H_{2\beta}$, $H_{3\alpha}$, $H_{5\alpha}$), 4.65–4.50 (m, 1.2H, $H_{3\beta}$, H_6), 4.47–4.22 (m, 1.8H, $H_{4\alpha}$, $H_{6'}$), 4.10–4.00 (m, 0.2H, $H_{4\beta}$), 3.67–3.57 (m, 0.2H, $H_{5\beta}$), 2.00–1.80 (m, 2H, PCH), 1.97–1.42 (m, 10H, H_{Cy}), 1.32–0.90 (m, 10H, H_{Cy}); ^{31}P NMR (C_5D_5N): δ −12.6; HRMS of $[M+H]^+$ $C_{31}H_{43}NO_6P$ calcd 556.2828, found 556.2831.
27. Typical procedure: $Pd(OAc)_2$ (2.4 mg, 0.01 mmol) and ligand **3** (16.5 mg, 0.03 mmol) were placed in a flask under argon. Degassed water (2 mL) and ethanol (2 mL) were added, and the solution was stirred for 30 min at rt. A mixture of aryl chloride (1.0 mmol) and phenylboronic acid (130.0 mg, 1.1 mmol) in a mixture of toluene (8.5 mL) and ethanol (3.5 mL) was then added in the flask, followed by Na_2CO_3 (318 mg, 3.0 mmol) dissolved in water (3.5 mL). The resulting mixture was stirred at the desired temperature. After the indicated time, the mixture was cooled at rt, the two phases were separated, the ethanol–water layer was washed twice with toluene. The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by flash-chromatography on silica gel gave the coupling product.
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