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# A Palladium-Catalyzed Biaryl Coupling of Arylboronic Acids in Aqueous Media Using A Gluconamide-Substituted Triphenylphosphine (GLCAphos) Ligand

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**Abstract**: A water-soluble phosphine ligand, N-(4-diphenyl-phosphino)phenylmethyl gluconamide (GLCAphos), was newly synthesized to perform the palladium-catalyzed biaryl coupling of arylboronic acids in a single aqueous media. The catalyst prepared from GLCAphos revealed higher activity than that synthesized from $Ph_2P(m\text{-}C_6H_4SO_3Na)$ or $P(m\text{-}C_6H_4SO_3Na)_3$ for various haloarenes.

**Key words**: cross-coupling, palladium, biaryl, aqueous media, water-soluble ligand

The reaction in aqueous media offers advantages in large-scale industrial processes because of the simplicity of catalyst-product separation and the economy and safety of using water as the solvent.[1] Such reactions in aqueous media are also useful for the palladium-catalyzed biaryl coupling of arylboronic acids.[2] A fine metallic palladium generated *in situ* from $Pd(OAc)_2$ is an excellent catalyst for the cross-coupling of arylboronic acids with bromoarenes in water.[3] Although the use of such catalysts without a phosphine ligand is advantageous in as much as contamination by the phosphine ligand is avoided, complete conversion can not be always possible under “ligandless” conditions, especially in the slow reaction of electron-rich and sterically hindered haloarenes. The ligands soluble in water such as TPPMS **1**[5] and TPPTS **3**[6] have been alternatively used not only in the biaryl coupling of arylboronic acids but also in several industrial processes by using palladium or rhodium homogeneous catalysts[1] (Scheme 1). The glycosides of triphenylphosphine **2** are a new class of ligand designed to solve the basic problems of homogeneous catalysts, namely, the separation and recycling of the catalysts.[7] The ligand gave better results in the yields and the turnover number than TPPTS in both biaryl coupling of arylboronic acids and Heck coupling in a two-phase, basic aqueous-organic medium. The phosphine supported on a graft copolymer of styrene and ethylene glycol **4** provided a palladium catalyst efficient in a single aqueous media, which can be recovered from the reaction mixture and reused with no decrease in activity.[8]

We present here a new water-soluble ligand based on triphenyl-phosphine and gluconamide (GLCAphos, **5** in Scheme 2) to carry out the biaryl coupling of arylboronic acids in a single, basic aqueous phase (Scheme 3). The three-step procedure from 4-bromobenzonitrile afforded the required 4-(diphenylphosphino)benzylamine, which was then treated with D-glucono-1,5-lactone in refluxing benzene to give **5** in a quantitative yield (Scheme 3).[9] The reaction of $PdCl_2(cod)$ and **5** (2 equivs) in MeCN at 100 °C precipitated a red-brown solid, which was tentatively assigned to be $PdCl_2(GLCAphos)_2$ **6**. Both **5** and **6** are soluble in water and methanol, but they are highly insoluble in aprotic solvents such as toluene, $CH_2Cl_2$, $CHCl_3$, EtOAc, and DMSO.

Three different-type bromoarenes were reacted with 4-tolylboronic acid in the presence of a catalyst derived from GLCAphos, TPPMS, and TPPTS to reveal the efficiency of the new ligand (Table 1). The emulsion of 4-bromoanisole in water slowly converted into a white suspension of the biaryl at 80 °C (Entry 1).[10] The reaction completed within 8 h in the presence of a 1 mol% of catalyst, but a 0.1 mol% of catalyst also achieved high conversion exceeding 98% after 16 h. The 0.01 mol% catalyst resulted in 80% conversion of 4-bromoanisole and 76% yield of the biaryl which corresponds to a 7600 turnover number of the catalyst. The reaction was accompanied with small amounts of two by-products,[2a] a homo-coupling product of tolylboronic acid (bitolyl, 2%) and a coupling product between the phosphine-bound phenyl and tolylboronic acid (4-methylbiphenyl, 0.5%), along with the desired cross-coupling product (90%). On the other hand, the catalysts prepared from TPPMS and TPPTS yielded 69% and 70% of the biaryl at 80 °C (Entries 2 and 3). The solid aryl halides such as 4-bromobiphenyl suspended in water at 60 °C gradually changed to a fine suspension of another precipitate of 4-methyl-*p*-terphenyl over 16 h (Entry 4). The TPPMS ligand was less effective for such two-phase, liquid-solid system (Entry 5) and no coupling reaction was observed for the palladium-TPPTS catalyst (Entry 6). The reaction of water-soluble halides such as 4-bromobenzoic acid was carried out at room temperature because the reaction catalyzed by the GLCAphos complex was very fast at the elevated temperature (Entry 7). The mixture initially gave a clear solution and the white solid of potassium 4-tolylbenzoate then precipitated. Again, GLCAphos was recognized to be the better ligand than TPPMS and TPPTS (Entries 8 and 9). Thus, GLCAphos exhibited the best catalyst activity in a two-phase system of a liquid-liquid or a solid-liquid, and in a single liquid system. Due to the electron-withdrawing property of the $SO_3^-$ group ($\sigma_m$=0.30),[11] the observed relative efficiency (GLCAphos > TPPMS > TPPTS) is in the order of the electron-donating ability of the phosphine ligands, which will affect the oxidative addition of ArX to the palladium(0).[12]

The biaryl coupling of 4-tolylboronic acid with the representative haloarenes at 80 °C in the presence of a $PdCl_2$/4GLCAphos catalyst is summarized in Table 2. Bromo-, iodo- and chloroarenes having an electron-withdrawing group afforded high yields of biaryls (Entries 1-9). The difficulties associated with the base are not observed here. No Cannizzaro reaction giving the acid and the alcohol was observed for 4-halobenzaldehydes (Entries 4 and 5). The ester and mesyl groups remained completely intact during the coupling at 80 °C, because both the starting halides and the biaryl products are insoluble in water (Entries 8 and 9). The presence of an electron-donating group such as *p*-$NMe_2$ slowed down the reaction (Entry 10), but the high solubility of halophenols and halobenzoic acids in basic water significantly accelerated the reaction (Entries 11 and 13). Thus, the coupling with 4-bromophenol completed within 2 h, though the Hammett constant[12] of the *p*-$O^-$ group ($\sigma_p$=-0.81) is comparable to that of *p*-$NMe_2$ ($\sigma_p$=-0.83) (Entries 10 and 11). The reaction of 4-bromobenzoic acid (*p*-$CO_2^-$, $\sigma_p$=0.00) completed after 0.5 h (Entry 13). However, a strong retarding effect of the neighboring groups was observed in two reactions, presumably due to their coordination to the palladium metal center. The coupling of 2-bromophenol resulted in 44% yield (Entry

12). The reactions of 2-chloro- and 2-bromopyridine are very slow, resulting in 43% and 18% yields (Entry 15), whereas the $Pd(PPh_3)_4$- or $PdCl_2$(dppp)-catalyzed reaction of 2-chloropyridine smoothly proceeds in an aqueous DME[13] or in a water/benzene, two-phase solution.[14] However, the boronic acid readily cross-coupled with 3-bromopyridine (Entry 16), 3-bromoquinoline (Entry 17), and probably also 4-bromopyridine.

Preliminary results for the cross-coupling of aryl triflates in an aqueous media are shown in Scheme 4. The trifluoromethanesulfoxy group is highly sensitive to the base, but the coupling reaction to yield biaryls was adequately faster than the saponification.

*Representative procedure*: $PdCl_2(GLCAphos)_2$ (0.001 mmol), GLCAphos (0.002 mmol) and arylboronic acid (1.3 mmol) were added to a 20 mL flask containing a magnetic stirring bar. The flask was flushed with argon and then charged with $H_2O$ (2 mL), $K_3PO_4$ (2 M solution, 1 mL, 2 mmol), and aryl halides (1.0 mmol) by using a syringe through the septum inlet. After being stirred for 16 h at 80 °C, the product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel gave a biaryl.

## References and Notes

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9. **5**: $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 3.62 (dd, $J$ = 5.8 and 11.0 Hz, 1H), 3.68-3.76 (m, 2H), 3.78 (dd, $J$ = 3.4 and 11.2 Hz, 1H), 4.15

(dd, *J* = 2.9 and 5.8 Hz, 1H), 4.28 (d, *J* = 3.4 Hz, 1H), 4.42 (d, *J* = 15.4 Hz, 1H), 4.49 (d, *J* = 15.4 Hz, 1H), 7.19-7.26 (m, 6H), 7.31-7.35 (m, 8H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 43.35, 64.72, 71.88, 72.97, 74.37, 75.56, 128.57 (d, *J* = 6.6 Hz), 129.59 (d, *J* = 7.4 Hz), 129.91, 134.64 (d, *J* = 19.7 Hz), 134.93 (d, *J* = 19.7 Hz), 137.16 (d, *J* = 10.7 Hz), 138.58 (d, *J* = 10.7 Hz), 140.84, 175.33; $^{31}$P NMR (161.7 MHz, $CD_3OD$) δ –4.05; HRMS (FAB), calcd for $C_{25}H_{28}NO_6P$ 469.1654, found 470.1750 (M+1). The procedures are reported in; Kobayashi, K.; Sumitomo, H.; Ina, Y. *Polym, J.* **1983**, *15*, 667.

10. The presence of 4 equivalents of ligand to $PdCl_2$ gave better results in the turnover number of the catalyst. For example, a 0.1 mol% catalyst resulted in the following yields. $PdCl_2(GLCAphos)_2$ (71%), $PdCl_2(GLCAphos)_2$/GLCAphos (84%), and $PdCl_2(GLCAphos)_2$/ 2GLCAphos (90%).
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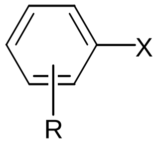
**Table 1**. Effect of Ligands[a]

| entry | ArX | catalyst | temp /°C | yield /%[b] |
|---|---|---|---|---|
| 1 | *p*-$MeOC_6H_4Br$ | $PdCl_2(GLCAphos)_2$/2GLCAphos | 80 | 90 |
| 2 | | $Na_2PdCl_4$/3TPPMS | 80 | 69 |
| 3 | | $Pd(OAc)_2$/3TPPTS | 80 | 70 |
| 4 | *p*-$PhC_6H_4Br$ | $PdCl_2(GLCAphos)_2$/2GLCAphos | 60 | 68 |
| 5 | | $Na_2PdCl_4$/3TPPMS | 60 | 38 |
| 6 | | $Pd(OAc)_2$/3TPPTS | 60 | trace |
| 7 | *p*-$HO_2CC_6H_4Br$ | $PdCl_2(GLCAphos)_2$/2GLCAphos | 25 | 43 |
| 8 | | $Na_2PdCl_4$/3TPPMS | 25 | 15 |
| 9 | | $Pd(OAc)_2$/3TPPTS | 25 | trace |

[a] A mixture of ArX (1 mmol), *p*-tolylboronic acid (1.3 mmol), $K_3PO_4$ (2 mmol), and a catalyst (0.001 mmol, 0.1 mol%) in water (3 ml) was stirred for 16 h at the temerature shown in Table.

[b] Isolated yields.

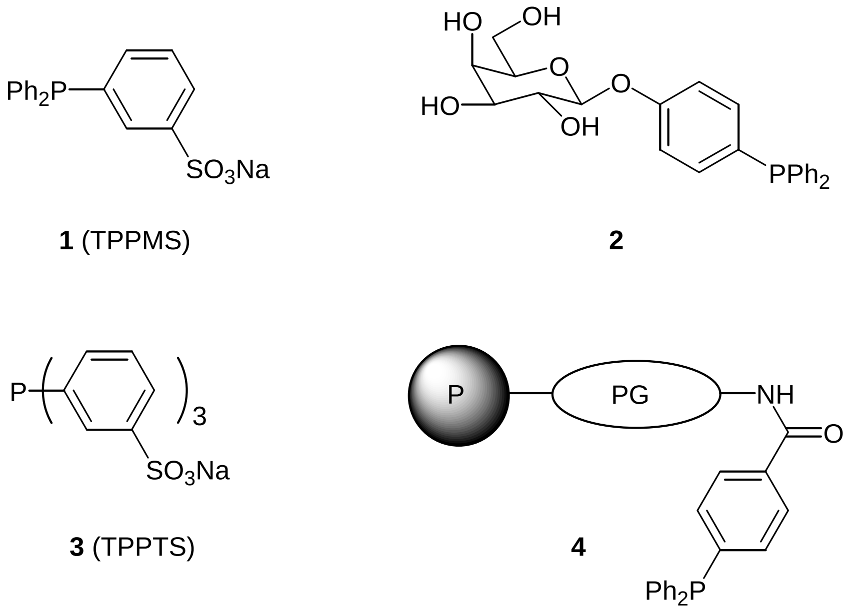
**Table 2**. Biaryl Coupling in Aqueous Media[a]

| entry | ArX | | | yield/%[b] |
|---|---|---|---|---|
| 1 |  | R= 4-$NO_2$ | X= Br | 96 |
| 2 | | 4-CN | Br | 94 |
| 3 | | 2-CN | Br | 85 |
| 4 | | 4-CHO | Br | 99 |
| 5 | | 4-CHO | Cl | 94 |
| 6 | | 4-$COCH_3$ | Br | 94 |
| 7 | | 4-$COCH_3$ | Cl | 71 |
| 8 | | 4-$CO_2Et$ | Br | 99 |
| 9 | | 4-$OSO_2CH_3$ | I | 99 |
| 10 | | 4-$NMe_2$ | Br | 74 |
| 11 | | 4-OH | Br | 99[c] |
| 12 | | 2-OH | Br | 44 |
| 13 | | 4-COOH | Br | 99[d] |
| 14 | 1-bromonaphthalene | | | 99 |
| 15 | 2-bromopyridine (2-chloropyridine) | | | 18 (43) |
| 16 | 3-bromopyridine | | | 89 |
| 17 | 3-bromoquinoline | | | 94 |

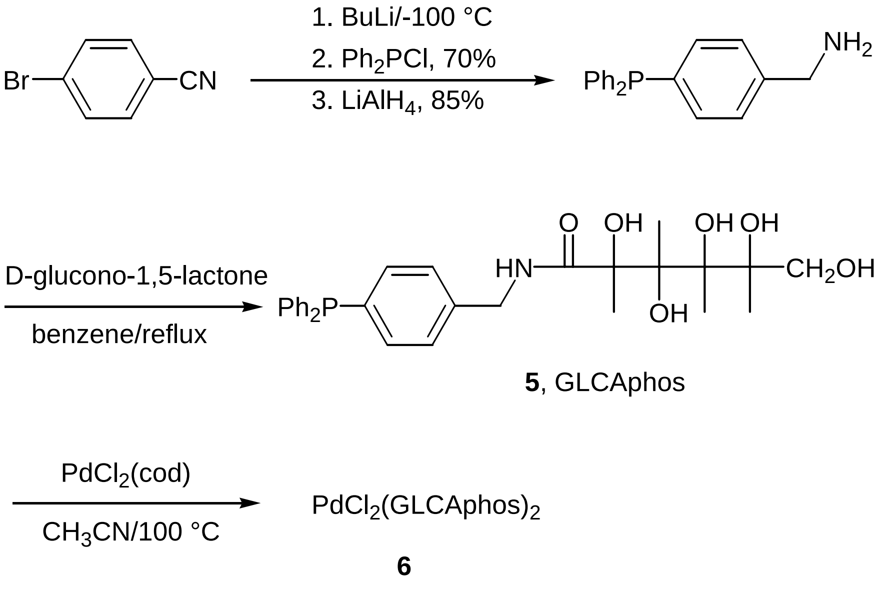
[a] A mixture of ArX (1 mmol), *p*-tolylboronic acid (1.3 mmol), $K_3PO_4$ (2 mmol), and a catalyst (0.001 mmol, 0.1 mol%) in water (3 ml) was stirred at 80 °C for 16 h, unless otherwise noted.

[b] Isolated yields by chromatography over silica gel.

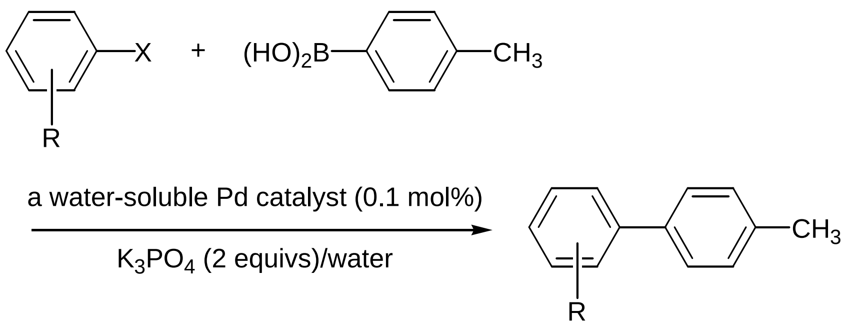
[c] At 80 °C for 2 h. [d] At 80 °C for 30 min.



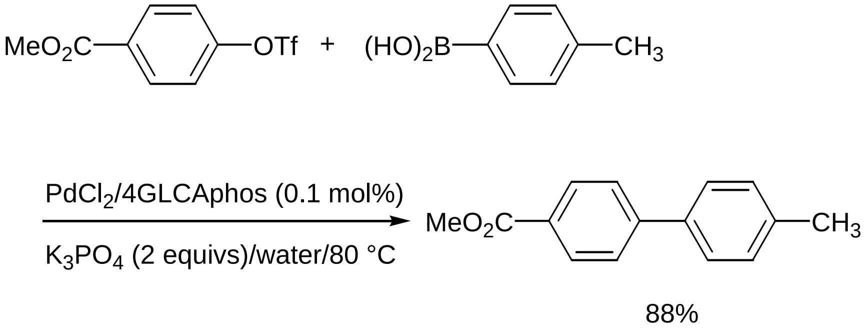
**Scheme 1**. Ligands for Water-Soluble Catalysts



**Scheme 2**. Synthesis of Ligand (GLCAphos)



**Scheme 3**. Biaryl Coupling in a Single Aqueous Media



**Scheme 4**. Biaryl Coupling with Aryl Triflates