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Palladium-catalyzed biaryl-coupling reaction of arylboronic acids in water using hydrophilic phosphine ligands

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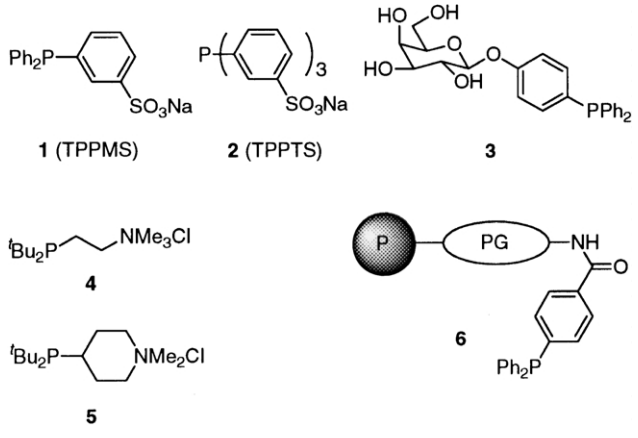
Abstract—Hydrophilic phosphine ligands possessing a carbohydrate side-chain, such as *N*-(4-diphenylphosphinophenyl)methyl gluconamide (**9**), *N*-[4-(2′-dicyclohexylphosphinobiphenyl)phenylmethyl] gluconamide (**10**), and *N*-[4-(2′-di-*t*-butylphosphinobiphenyl)]phenylmethyl gluconamide (**11**), were newly synthesized to carry out palladium-catalyzed biaryl coupling of arylboronic acids in a single aqueous medium. The catalyst prepared in situ from $Pd(OAc)_2$ and **10** exhibited a higher efficiency than that of **9**, **11**, $Ph_2P(m\text{-}C_6H_4SO_3Na)$ (TPPMS) or $P(m\text{-}C_6H_4SO_3Na)_3$ (TPPTS) for representative aryl bromides, chlorides, or triflates. The catalyst prepared in situ from $Pd(OAc)_2$ (0.001 mol%) and **10** (0.002 mol%) achieved 96,000 TON in the reaction of *p*-tolylboronic acid with 4-bromoacetophenone in water.

1. Introduction

Reactions in aqueous media are advantageous for large-scale industrial processes because of the simplicity of catalyst-product separation and the economy and safety of using water as a solvent.[1] Such reactions in aqueous media are also useful for the biaryl coupling of arylboronic acids.[2] A fine metallic palladium generated in situ from $Pd(OAc)_2$[3] or $Pd(OAc)_2/Bu_4NBr$[4] provided an excellent catalyst for the coupling of arylboronic acids with bromoarenes in water.[3] Although such catalysts containing no phosphine ligand are advantageous for eliminating the side-reaction giving a coupling product of phosphine-bound aryls,[5] complete conversion is not always possible under ligandless conditions, especially in slow reactions of electron-rich and sterically hindered bromo- and chloroarenes. Catalysts derived from water-soluble ligands such as TPPMS **1** and TPPTS **2** are alternatives for stabilizing the resting state of palladium intermediates in water[6] (Scheme 1).



Scheme 1. Ligands for water-soluble catalysts.

Glycosides of triphenylphosphine **3** are of the new class of ligands designed to solve the basic problems of homogeneous catalysts, namely, the separation and recycling of catalysts.[7] These ligands achieved higher turnover numbers than that of TPPTS in both biaryl coupling of arylboronic acids and Heck coupling in a two-phase, basic aqueous-organic medium. Quaternary ammonium salts derivatives of di-*t*-butylphosphines such as **4** and **5** were designed for reaction with chloroarenes because of their strong electron-donating ability to the palladium metal center.[8] Phosphine supported on a graft copolymer of styrene and ethylene glycol **6** is an efficient ligand in a single aqueous medium that can be recovered and reused with no decrease in activity.[9] Among such catalysts, $Pd(OAc)_2$,[3] $Pd(OAc)_2/Bu_4NBr$,[4] and $(\eta^3\text{-}C_3H_5)PdCl/\mathbf{6}$[9] have been utilized in a single, basic aqueous medium without employing organic co-solvents miscible to water.

We report here the synthesis of new hydrophilic phosphine ligands possessing a sugar side-chain (**9**–**11**) and their catalyst efficiency in the biaryl-coupling reaction of arylboronic acids in a single aqueous medium (Scheme 2).[10]

Keywords: cross-coupling; palladium; biaryls; aqueous medium; water-soluble hydrophilic phosphine; arylboronic acids.
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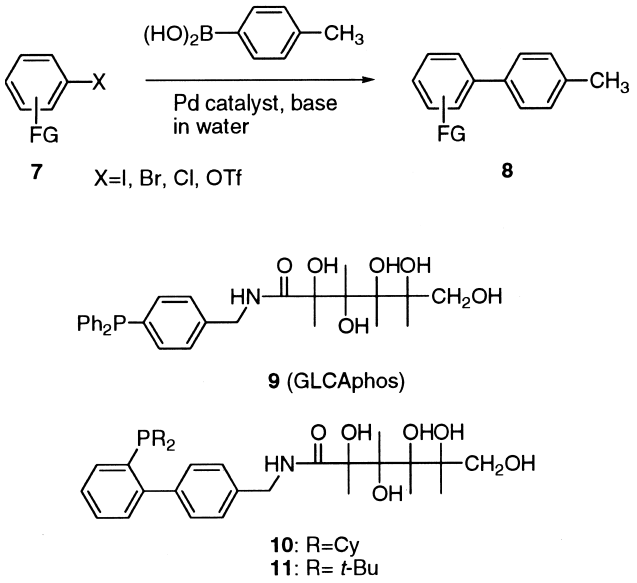


Scheme 2. Biaryl coupling in water.

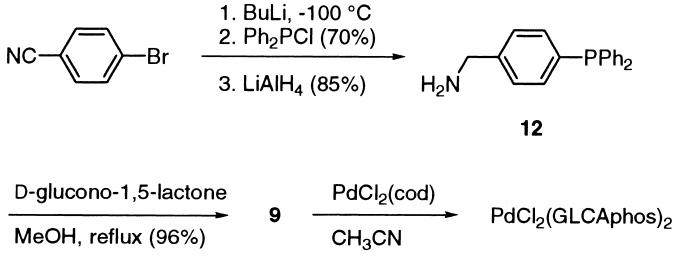
2. Results and discussions

2.1. Synthesis of ligands

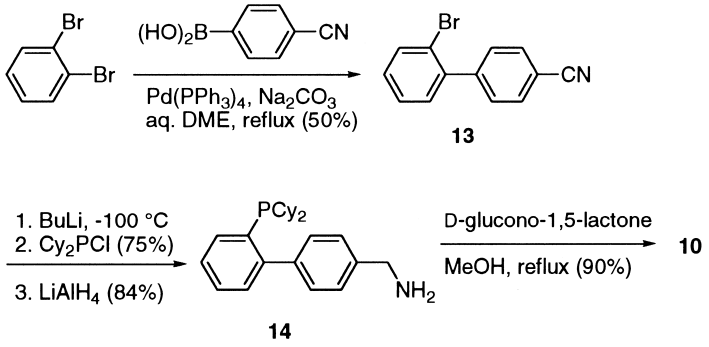
Various phosphine ligands are effective in stabilizing palladium(0) species, but the stoichiometry of phosphine to palladium and the bulkiness or donating ability of phosphine ligands change the reactivity of catalysts toward oxidative addition and transmetalation. Although triarylphosphines are excellent ligands for organic iodides, bromides, and triflates, their reaction with chlorides is very slow. Bulky and highly donating ligands overcome this limitation; for example, P(*t*-Bu)$_3$[11] and 2-(di-*t*-butylphosphino)biphenyl[12] provided highly active catalysts for chloroarenes even at room temperature. The high reactivity of these catalysts is attributable to a strong electron-donating ability to the metal center and the easy dissociation of the ligand to generate a coordinatively unsaturated species. It has also been noted that less bulky phosphines, such as P(Cy)$_3$,[11] (dicyclohexylphosphino)arylphosphines,[12] *N*-heterocyclic carbene,[13] and ^{t}Bu$_2$POH,[14] are more practical ligands yielding palladium catalysts stable at high temperature. From these previous observations, 2-(dicyclohexylphosphino)biphenyl (**10**) and 2-(di-*t*-butylphosphino)biphenyl (**11**) developed by Buchwald[12] together with triphenylphosphine (**9**) were functionalized with a gluconamide group to convert them into the corresponding hydrophilic ligands.

The synthesis of the gluconamide derivative of triphenylphosphine (GLCAphos: **9**) is shown in Scheme 3. The two-step procedure from 4-bromobenzonitrile afforded (4-diphenylphosphinophenyl)methylamine (**12**) in 60% yield. 4-Lithiobenzonitrile[15] thus generated in situ from 4-bromobenzonitrile and BuLi was unstable at the temperature higher than −78°C, but the subsequent reaction with Ph_2PCl was sufficiently fast to trap the intermediate in a yield of 70%. Treatment of **12** with D-glucono-1,5-lactone in refluxing methanol gave **9** in 96% yield.[16] The reaction of $PdCl_2$(cod) and GLCAphos (**9**, 2 equiv.) in MeCN at 100°C precipitated a red-brown solid, which was assigned to be $PdCl_2$(GLCAphos)$_2$.

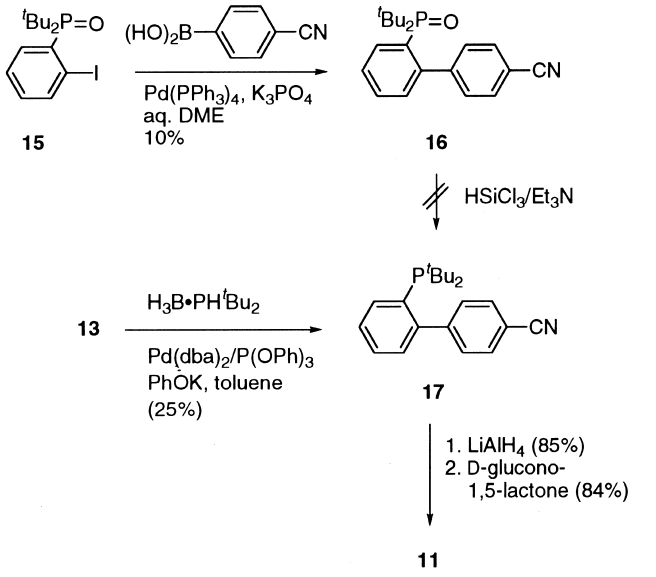
4-Cyanophenylboronic acid synthesized via lithiation–borylation of 4-bromobenzonitrile was coupled with 1,2-dibromobenzene to yield **13** in 50% yield. Phosphorylation of the C–Br bond (75%) was followed by reduction of the nitrile group with $LiAlH_4$ to furnish **14** (84%). The reaction of **14** with D-glucono-1,5-lactone gave **10** in 90% yield (Scheme 4).



Scheme 3.



Scheme 4.



Scheme 5.

Table 1. Reaction conditions

Entry	Catalyst/ligand (equiv.)	Base (equiv.)	Convn (%)	Yield (%)
1[a]	$PdCl_2$/GLCAphos (4)	Na_2CO_3 (2)	98	78
2[a]	$PdCl_2$/GLCAphos (4)	K_3PO_4 (2)	98	90
3[a]	$PdCl_2$/GLCAphos (4)	KOH (2)	94	75
4[a]	$PdCl_2$/GLCAphos (4)	CsF (4)	96	73
5[a]	$PdCl_2$/GLCAphos (4)	Et_3N (5)	98	92
6[a]	$PdCl_2$/GLCAphos (3)	K_3PO_4 (2)	94	84
7[a]	$PdCl_2$/GLCAphos (2)	K_3PO_4 (2)	89	71
8[b]	$Pd(OAc)_2$/**10** (1)	K_3PO_4 (2)	46	35
9[b]	$Pd(OAc)_2$/**10** (2)	K_3PO_4 (2)	95	90
10[b]	$Pd(OAc)_2$/**10** (4)	K_3PO_4 (2)	0	0
11[b]	$Pd(OAc)_2$/**11** (2)	K_3PO_4 (2)	75	62

[a] All reactions were carried out at 80°C for 16 h in water (3 mL) in the presence of 4-bromoanisole (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and a base (2–5 equiv.). The catalyst was prepared in situ from GLCAphos (**9**, 0–2 equiv.) and $PdCl_2$(GLCAphos)$_2$.

[b] The reactions were carried out at 25°C for 16 h in water (3 mL) in the presence of 4-bromobenzoic acid (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol). The catalyst was prepared in situ by mixing $Pd(OAc)_2$ and **10** (1–4 equiv.) or **11** (2 equiv.).

The synthesis of **17** suffered from the difficulty of introducing a bulky di-*t*-butylphosphino group at the sterically hindered *ortho*-carbon. The procedure used for the synthesis of **10** failed due to instability of the lithium intermediate and its very slow reaction with *t*-Bu_2PCl. Alternatively, it was found that the phosphine oxide derivative **16** can be synthesized by cross-coupling reaction of **15**. Although the procedure is very convenient because **15**[17] is easy to obtain via *ortho*-lithiation and iodonation of di-*t*-butyl(phenyl)phosphine oxide, **15** and **16** had strong resistance to $HSiCl_3$/Et_3N or $LiAlH_4$. Reduction of **16** with a 5-fold excess of $HSiCl_3$ and Et_3N in a sealed ampule at 150°C failed. Finally, the cross-coupling reaction of **13** with di-*t*-butylphosphine–borane complex gave **17**.[18] Although the hydrogenolysis of a C–Br bond yielding 4-cyanobiphenyl (70%) predominated over the desired phosphorylation, the reaction directly provided a desired borane-free phosphine **17** in 25% yield. The reduction of the nitrile group was followed by amidation to furnish **11** (Scheme 5).

2.2. Reaction conditions

The cross-coupling reaction of *p*-tolylboronic acid with 4-bromoanisole was carried out in the presence of various catalysts and bases to optimize the reaction conditions (Table 1). In the presence of 0.1 mol% of $PdCl_2$/**9** in water, various bases were effective for completing the reaction within 16 h at 80°C (entries 1–5). Among them, K_3PO_4 and Et_3N provided yields of over 90%. The yield of 4-methylbiphenyl derived from the coupling of phosphine-bound phenyl[5] was a less than 0.5% when K_3PO_4 was used. The formation of a homo-coupling product[2a,f] of *p*-tolylboronic acid (bitolyl) varied depending on the base employed; e.g. NaOH (8%), Et_3N (8%), K_3PO_4 (0.5–3%), Na_2CO_3 (2%), and CsF (2%). The use of 4 equiv. of GLCAphos **9** to $PdCl_2$ gave the most efficient catalyst since the yields decreased by reducing the stoichiometry of the ligand (entries 2, 6 and 7).

The complex synthesized in situ from $Pd(OAc)_2$ and **10** catalyzed the reaction at room temperature (entries 8–10). The most active catalyst was obtained when 2 equiv. of **10** to $Pd(OAc)_2$ were used (entry 9), while further increase in the ligand reversely deactivated the catalyst (entry 10). The *t*-butyl derivative **11** resulted in a lower yield than that of the cyclohexyl derivative (entry 11).

Table 2. Effect of ligands

Entry	Catalyst/ligand (equiv.)	Yield (%)[a]			
		4-$MeOC_6H_4Br$ at 80°C	4-$C_6H_5C_6H_4Br$ at 60°C	4-$HO_2CC_6H_4Br$ at 25°C	4-$HO_2CC_6H_4Cl$ at 80°C
1	$Pd(OAc)_2$	63	<1	37	<1
2	$Pd(PPh_3)_4$	74	52	<1	<1
3	$Pd(OAc)_2$/TPPTS (3)	70	<1	<1	<1
4	$PdCl_2$/TPPMS (3)	69	38	15	<1
5	$PdCl_2$/GLCAphos (4)	90	68	43	<1
6	$Pd(OAc)_2$/**10** (2)	90	74	90	62
7	$Pd(OAc)_2$/**11** (2)	–	96	62	24

A mixture of a haloarene (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol) in water (3 mL) was stirred for 16 h at the temperature shown in this table.

[a] GC yields.

2.3. Effect of ligands

Four different types of haloarenes were coupled with *p*-tolylboronic acid in the presence of $Pd(OAc)_2$, $Pd(PPh_3)_4$, and a catalyst synthesized from TPPMS **1**, TPPTS **2**, GLCAphos **9**, **10**, or **11** (0.1 mol%) to investigate the efficiencies of the new ligands (Table 2).

The emulsion of 4-bromoanisole in water resulted in the slow conversion into a white suspension of 4-methoxy-4′-methylbiphenyl at 80°C (first column). All catalysts, including water-soluble and water-insoluble ligands, were effective for catalyzing such a liquid–liquid, two-phase system at 80°C. Among them, **9** and **10**, soluble in both organic and water phases, were found to be the most efficient ligands. Solid substrates, 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 a period of 16 h (second column). Palladium black in situ generated from $Pd(OAc)_2$ and the TPPTS complex were not effective for such a two-phase, liquid–solid system due to their low solubility in the solid phase. On the other hand, the palladium complexes of PPh_3, **9**, **10**, and **11** gave the coupling product. Among them, a bulky and highly electron-donating *t*-butyl derivative **11** exhibited the best efficiency (entry 7). The effect for water-soluble 4-bromobenzoic acid was examined at room temperature because the reactions catalyzed by the complexes of **9** and **10** were very fast at a high temperature (third column). The mixture initially yielded a clear solution followed by the precipitation of a white solid of potassium 4-tolylbenzoate. The order of yields was **10**>**11**>**9**>TPPMS **1**≫TPPTS **2**. Due to the electron-withdrawing property of the SO_3^- group (σ_m=0.30)[19] and strong electron-donating abilities of alkylphosphines, the observed relative efficiency is in the order of the donating abilities of the ligands, except for **11**, which unexpectedly resulted in a lower yield than that of **10**. On the other hand, the coupling reaction of 4-chlorobenzoic acid was significantly slow even at 80°C (fourth column). Alkylphosphine derivatives (**10** and **11**) limitedly catalyzed the reaction of chloroarenes.

The efficiencies of two ligands (GLCAphos **9** and **10**) were demonstrated by the turnover number of the catalyst (TON) (Table 3).[20] Both **9** and **10** exhibited an excellent catalyst activity, exceeding 90,000 TON, with a 0.001 mol% catalyst loading (entries 3 and 4). Further decrease in catalyst loading showed the superiority of **9**, presumably due to the greater air-sensitivity of alkylphosphines **10** than that of arylphosphines **9** (entries 5 and 6). On the other hand, both **10** and **9** resulted in 700–900 TON for 4-chloroacetophenone with a 0.1 mol% catalyst loading.

Table 3. Turnover number of catalysts

Entry	Catalyst/ligand (equiv.)	Mol%	Yield (%)[a]	TON
1	$PdCl_2$/GLCAphos (4)	0.01	95	9500
2	$Pd(OAc)_2$/**10** (2)	0.01	95	9500
3	$PdCl_2$/GLCAphos (4)	0.001	95	95,000
4	$Pd(OAc)_2$/**10** (2)	0.001	96	96,000
5	$PdCl_2$/GLCAphos (4)	0.0001	<50	<500,000
6	$Pd(OAc)_2$/**10** (2)	0.0001	<35	<350,000

All reactions were carried out at 80°C for 24 h in water (3 mL) in the presence of 4-bromoacetophenone (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol). $PdCl_2$/GLCAphos was prepared in situ by mixing $PdCl_2(GLCAphos)_2$ and GLCAphos (**9**, 2 equiv.), and $Pd(OAc)_2$/**10** from $Pd(OAc)_2$ and **10** (2 equiv.).
[a] GC yields.

Table 4. Synthesis of biaryls from bromoarenes

Entry	ArBr (**1**) R=	Yield (%)[a]	
		$PdCl_2$/**9**[b]	$Pd(OAc)_2$/**10**[c]
1	4-NO_2	96	
2	4-CN	94	
3	2-CN	85	
4	4-$COCH_3$	94	
5	4-CHO	99	
6	4-$CO_2C_2H_5$	99	
7	4-F	95	
8	4-Ph	99	
9	3-CH_3O	93	
10	4-CH_3O	89	
11	4-NH_2	90	
12	4-$N(CH_3)_2$	74	
13	1-Bromonaphthalene	99	
14	2-OH	44	
15[d]	4-OH	99	
16[e]	4-CO_2H	99	
17[f]	3-CO_2H–4-OH	77	87
18	2-CH=$CHCO_2H$	<40	90
19	4-CH=$CHCO_2H$	<40	90
20	2-Bromopyridine	18	42
21	3-Bromopyridine	89	
22	3-Bromoquinoline	99	

All reactions were carried out at 80°C for 16 h in water (3 mL) in the presence of a bromoarene (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol).
[a] Isolated yields by chromatography.
[b] $PdCl_2(GLCAphos)_2$ (0.1 mol%) and GLCAphos (**9**, 0.2 mol%).
[c] $Pd(OAc)_2$ (0.1 mol%) and **10** (0.2 mol%).
[d] The reaction completed within 2 h.
[e] The reaction completed within 30 min.
[f] The reaction was carried out at 20°C.

2.4. Scope and limitation

Biaryl coupling of 4-tolylboronic acid with representative bromoarenes at 80°C in the presence of $PdCl_2$/GLCAphos **9** or $Pd(OAc)_2$/**10** (0.1 mol%) is summarized in Table 4. $PdCl_2$/GLCAphos afforded high yields of biaryls for bromoarenes having an electron-withdrawing or -donating group (entries 1–13). Difficulties associated with the base were not encountered. No Cannizzaro reaction giving an acid and an alcohol was observed for 4-bromobenzaldehyde (entry 5). Functional group-sensitive bases such as ester and nitrile remained completely intact due to the insolubility of both substrates and products in water (entries 2, 3, and 6). In contrast to the slow reaction of a heterogeneous of a liquid–liquid or liquid–solid, two-phase system, the coupling reactions of bromophenols and bromobenzoic acids soluble in a basic water were significantly fast (entries 15–17). Although the Hammett constant[19] of the *p*-O^- group (σ_p=−0.81) is comparable to that of *p*-NMe_2 (σ_p=−0.83), the reaction of 4-bromophenol was completed within 2 h (entry 15). 4-Bromobenzoic acid was consumed completely within 30 min at 80°C (entry 16) and 3-carbohydroxy-4-hydroxybromobenzene coupled with the boronic acid at room temperature (entry 17). However, the ligand **10**

Table 5. Synthesis of biaryls from chloroarenes

Entry	ArCl (**1**) R=	Catalyst (mol%)	Yield (%)[a]	
			$PdCl_2$/**9**[b]	$Pd(OAc)_2$/**10**[c]
1	2-CN	0.1	<1	96
2	4-CN	0.1	46	90
3	4-CHO	0.1	–	93
4	4-$COCH_3$	0.1	71	95
5	2-$CO_2C_2H_5$	0.1	<1	66
6	4-$CO_2C_2H_5$	0.1	<1	98
7	4-OCH_3	2.0	<10	79
8[d]	2-CO_2H	1.0	0	0
9[d]	4-CO_2H	1.0	<1	73
10[d]	2-CH=$CHCO_2H$	1.0	<1	90
11[d]	4-CH=$CHCO_2H$	1.0	<30	88
12[d]	4-CO_2H–3-OH	3.0	<1	84
13[d]	3-CO_2H–4-OH	3.0	<1	45
14	2-Chloropyridine	0.1	43	88
15	3-Chloropyridine	1.0	–	96
17[d]	4-Chloropyridine	1.0	–	70
18	2-Chloroquinoline	0.1	–	97

All reactions were carried out at 80°C for 16 h in water (3 mL) in the presence of a chloroarene (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol).
[a] Isolated yields by chromatography.
[b] $PdCl_2$(GLCAphos)$_2$ and GLCAphos (**9**, 2 equiv.).
[c] $Pd(OAc)_2$ and **10** (2 equiv.).
[d] K_3PO_4 (3 mmol) was used.

was more effective than **9** for two coupling reactions of more electron-rich bromocinnamic acids (entries 18 and 19). Among these water-soluble substrates, the reaction of 2-bromophenol was strongly retarded, presumably due to the intramolecular chelation of a phenoxy anion to the palladium metal center (entry 14). The reactions of 2-bromopyridine resulted in 18 and 42% yields, respectively, for the two catalysts (entry 20), while the boronic acid readily coupled with 3-bromopyridine (entry 21), 3-bromoquinoline (entry 22), and presumably also 4-bromopyridine.

The synthesis of biaryls from chloroarenes is summarized in Table 5. Chloroarenes are economical substrates that are desirable for large-scale preparations; however, the reactions are very slow due to their slow oxidative addition to a palladium(0) complex.[11,12,21] Thus, ligand **10**, which has a greater donating ability, exhibited a higher catalyst activity than that of GLCAphos **9**. The coupling reaction of activated chloroarenes proceeded smoothly at 80°C with 0.1 mol% catalyst loading (entries 1–6), whereas 1–3 mol% of a catalyst was required for more electron-rich substrates (entries 7–13). Similar to the effect of an *o*-OH group (entry 14 in Table 4), the intramolecular chelation of a carboxylato anion strongly retarded the reaction of 2-chlorobenzoic acid (entry 8). Chloropyridines and chloroquinolines, including 2-chloro derivatives, gave the corresponding biaryls in high yields (entries 14–18).

Table 6. Synthesis of biaryls from aryl triflates

Entry	ArOTf (**1**) R=	Yield (%)[a]	
		$PdCl_2$/**9**[b]	$Pd(OAc)_2$/**10**[c]
1	4-CN	90	–
2	4-CO_2CH_3	88	–
3	4-OCH_3	46	93

All reactions were carried out at 80°C for 16 h in water (3 mL) in the presence of a triflate (1 mmol), *p*-tolylboronic acid (1.3 mmol), a palladium catalyst (0.1 mol%), and K_3PO_4 (2 mmol).
[a] Isolated yields by chromatography.
[b] $PdCl_2$(GLCAphos)$_2$ (0.1 mol%) and GLCAphos (**9**, 0.2 mol%).
[c] $Pd(OAc)_2$ (1 mol%) and **10** (2 mol%).

Preliminary results for cross-coupling reaction of aryl triflates in aqueous media are shown in Table 6. The trifluoromethanesulfoxy group is highly sensitive to the base, but the reaction was faster than the saponification of this group. Arylphosphine **9** can be used for electron-deficient substrates (entries 1 and 2), but **10** is recommended for more electron-rich triflates (entry 3).

3. Experimental

3.1. Reagents

p-Tolylboronic acid was purchased from Lancaster. P(*m*-$C_6H_5SO_3Na)_3$ (TPPTS), Ph_2P(*m*-$C_6H_5SO_3Na$) (TPPMS), $Pd(PPh_3)_4$, and $Pd(OAc)_2$ are available from Aldrich. Water was boiled and cooled under argon before use.

Other phosphine ligands were synthesized by the following methods.

3.1.1. 4-(Diphenylphosphino)benzonitrile. A solution of 4-bromobenzonitrile (1 g, 5.5 mmol) in THF (25 mL) and hexane (7 mL) was cooled to −100°C. BuLi in hexane (1.52 M, 3.6 mL, 5.5 mmol) was then added. After being stirred for 5 min, Ph_2PCl (0.99 mL, 5.5 mmol) was added. The bath temperature was gradually allowed to warm to room temperature over 3 h. The product was extracted with ether, washed with 1 M NaOH, and dried over $MgSO_4$. Chromatography over silica gel gave a pale yellow solid; yield 1.1 g (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.38 (m, 12H), 7.56 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.8, 118.7, 128.8 (d, J=7.4 Hz), 129.4, 131.6 (d, J=5.7 Hz), 133.4 (d, J=18.1 Hz), 134.0 (d, J=19.8 Hz), 135.3 (d, J=10.7 Hz), 145.1 (d, J=17.3 Hz); IR (Nujol) 2200 cm^{-1}; exact mass calcd for $C_{19}H_{14}NP$ 287.0942, found 288.0956 (M+1, FAB).

3.1.2. 4-(Diphenylphosphino)phenylmethylamine (12). A solution of 4-diphenylphosphinobenzonitrile (4.3 g, 15 mmol) was added to $LiAlH_4$ (0.68 g) in ether (30 mL). The resulting mixture was then refluxed for 1 h. Water (0.7 mL), 20% NaOH (0.5 mL), and water (2.5 mL) were added successively at 0°C to precipitate orange solid of the aluminum residue. The organic layer was separated by filtration through a celite pad and the solid was repeatedly washed with ether. Chromatography over silica gel with benzene/MeOH (8/1) gave a white solid; yield, 2.89 g (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 2H), 1.91 (s, 2H), 7.21–7.26 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.9, 127.0 (d, J=7.4 Hz), 128.3 (d, J=7.4 Hz), 128.5, 133.4 (d, J=19.9 Hz), 133.9 (d, J=19.9 Hz), 135.1 (d, J=9.9 Hz), 137.1 (d, J=10.8 Hz), 143.8; IR (Nujol) 3400 cm^{-1}; exact mass calcd for $C_{19}H_{18}NP$ 291.1255, found 292.1259 (M+1, FAB).

3.1.3. *N*-[(4-Diphenylphosphinophenyl)methyl] D-gluconamide (9). 4-Diphenylphosphinobenzylamine (2.89 g, 9.93 mmol) and D-glucono-1,5-lactone (1.78 g, 10 mmol) were dissolved in MeOH (75 mL) and the mixture was then refluxed for 1.5 h. The white solid precipitated was collected by filtration, washed with cold MeOH, and dried in vacuo to give a white solid; 4.46 g (96%); ^{1}H NMR(400 MHz, CD_3OD) δ 3.30 (dt, J=1.7, 3.2 Hz, 1H), 3.59–3.87 (m, 7H), 3.98 (d, J=9.5 Hz, 1H), 4.06 (m, 1H), 4.14 (dd, J=2.9, 5.6 Hz, 1H), 4.28 (d, J=3.2 Hz, 1H), 4.42 (d, J=15.4 Hz, 1H), 4.48 (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 43.36, 64.65, 71.83, 72.93, 74.31, 75.49, 128.54, 128.62, 129.57, 129.64, 129.94, 134.52, 134.72, 134.82, 135.02, 136.94, 138.52, 140.79, 175.33; ^{31}P NMR (161.7 MHz, CD_3OD) δ −4.05; IR (Nujol) 3300, 1650 cm^{-1}; exact mass calcd for $C_{25}H_{28}NO_6P$ 469.1733, found 470.1750 (M+1, FAB).

3.1.4. $PdCl_2$(GLCAphos)$_2$. A mixture of $PdCl_2$(1,5-cyclooctadiene) (0.172 g, 0.6 mmol) and **9** (0.62 g, 1.3 mmol) in CH_3CN (26 mL) was stirred for 1 h at 100°C. The brown solid precipitated was collected by filtration, washed with ether, and dried in vacuo.

3.1.5. 2-Bromo-4′-cyanobiphenyl (13). To a solution of 4-bromobenzonitrile (6.66 g, 30 mmol) in ether (30 mL) was added BuLi (1.5 M in hexane, 20 mL) at −78°C. After being stirred for 1 h, a solution of B(O^{i}Pr)$_3$ (6.9 mL, 30 mmol) in ether (15 mL) was then added. The mixture was stirred for 1 h at −78°C, slowly warmed up to room temperature, and stand overnight. The resulting mixture was treated with 3 M HCl (20 mL), extracted with ether, and washed with brine. Evaporation of solvent followed by crystallization from hot water gave a white solid (65%).

A flask charged with Pd(PPh$_3$)$_4$ (6.6 g, 5.8 mmol, 5 mol%), 4-cyanophenylboronic acid (16.9 g, 115 mmol), Na_2CO_3 (69 g, 651 mmol) was flushed with argon. DME (160 mL), water (320 mL), and 1,2-diboromobenzene (27.1 g, 115 mmol) were added and the mixture was then refluxed for 24 h. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel with hexane/AcOEt (40/1) was followed by crystalization from hexane/CH_2Cl_2 to give a white solid; yield, 15.7 g, (53%); IR (Nujol) 2229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.30 (m, 2H), 7.40 (dd, J=7.9, 8.0 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 2H); MS m/z 151 (42), 177 (42), 178 (35), 257 (98), 259 (100); exact mass calcd for $C_{13}H_8NBr$ 256.9840, found 256.9826 (M, EI).

3.1.6. 2-Dicyclohexylphosphino-4′-cyanobiphenyl. A 100 mL flask charged with 2-bromo-4′-cyanobiphenyl (2.0 g, 7.8 mmol) in THF (20 mL) was cooled to −100°C. BuLi in hexane (2.6 M, 3 mL, 7.8 mmol) was added and the mixture was stirred for 1 h. A solution of dicyclohexylchlorophosphine (1.8 mL, 8.0 mmol) in THF (5 mL) was then added. After being stirred for 1 h at −100°C, the bath temperature was allowed to warm to room temperature over 3 h. The product was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and finally isolated by chromatography over neutral silica gel with hexane/AcOEt (30/1) to give a white solid; yield, 2.2 g (75%); IR (Nujol) 2226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.28 (m, 10H), 1.53–1.86 (m, 18H), 7.21–7.24 (m, 1H), 7.39–7.43 (m, 4H), 7.61–7.64 (m, 1H), 7.65 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.30, 27.02, 27.05, 27.09, 27.17, 29.10, 29.18, 30.27, 30.44, 34.44, 34.58, 110.48, 119.12, 127.42, 128.55, 129.72, 129.78, 131.19, 131.45, 131.50, 133.14, 133.18, 133.67, 133.89, 147.70, 147.77, 148.55, 148.83; ^{31}P NMR (161.7 MHz, $CDCl_3$) δ −13.09; MS m/z 154, 179, 209, 292, 376 (M$^+$, 100); exact mass calcd for $C_{25}H_{30}NP$ 375.2116, found 376.2172 (M+1, FAB).

3.1.7. 2-Dicyclohexylphosphino-4′-methylaminobiphenyl (14). To a solution of 2-dicyclohexylphosphino-4′-cyanobiphenyl (1 g, 2.6 mmol) in ether (10 mL) was added $LiAlH_4$ (0.11 g, 3.0 mmol) at 0°C and the mixture was then stirred for 2 h at room temperature. The mixture was treated with water at 0°C and the product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel with MeOH gave a white solid; yield, 0.81 g (84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0–1.27 (m, 10H), 1.55–1.85 (m, 14H), 3.92 (s, 2H), 7.24–7.38 (m, 7H), 7.58–7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.39, 27.14, 26.17, 27.22, 27.28, 29.16, 29.25, 30.30, 29.25, 30.30, 30.47, 34.60, 34.74, 46.31, 126.00, 126.39, 128.16, 130.24, 130.30, 130.74, 130.78, 132.84, 132.87, 133.83, 134.03, 141.47, 150.23, 150.51; ^{31}P NMR (161.7 MHz, $CDCl_3$) δ −13.04; exact mass calcd for $C_{25}H_{34}NP$ 379.2429, found 380.2503 (M+1, FAB).

3.1.8. *N*-[4-(2-Dicyclohexylphosphinophenyl)phenylmethyl] D-gluconamide (10). 2-Dicyclohexylphosphino-4′-methylaminobiphenyl (**14**) (0.81 g, 2.1 mmol) and D-glucono-1,5-lactone (0.38 g, 2.15 mmol) was dissolved in MeOH (15 mL) and the mixture was then refluxed for 3 h. Chromatography over silica gel with ethyl acetate/MeOH (10/1) gave a white solid; yield, 1.09 g (90%); ^{1}H NMR (400 MHz, CD_3OD): δ 0.96–1.28 (m, 10H), 1.51–1.87 (m, 12H), 3.61–3.81 (m, 5H), 4.18 (t, J=2.8 Hz, 1H), 4.31 (d, J=3.2 Hz, 1H), 4.50 (s, 2H), 7.18–7.22 (m, 3H), 7.31–7.36 (m, 4H), 7.59–7.62 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.53, 28.04, 28.07, 28.15, 30.56, 30.65, 31.81, 31.98, 36.03, 36.17, 43.53, 64.74, 71.90, 72.97, 74.34, 75.56, 127.51, 127.75, 129.59, 131.27, 131.33, 131.88, 131.92, 134.06, 134.09, 134.65, 134.84, 138.03, 143.09, 143.14, 151.49, 151.77, 175.19; ^{31}P NMR (161.7 MHz, CD_3OD) δ −13.28; IR (Nujol) 3349, 1648 cm^{-1}; MS m/z 392, 475, 558 (M$^+$); exact mass calcd for $C_{31}H_{44}NO_6P$ 557.2906, found 558.2964 (M+1, FAB).

3.1.9. 2-Di-*tert*-butylphosphino-4′-cyanobiphenyl (17). t-Bu_2PCl (1.9 mL, 10 mmol) in THF (10 mL) was added BH_3 in THF (1 M, 15 mL, 15 mmol) and $LiAlH_4$ (0.57 g, 15 mmol) at 0°C. After being stirred for 2 h at room temperature, the mixture was treated with water at 0°C. The product was extracted with ethyl acetate, dried over Na_2SO_4, chromatographed over silica gel, and finally crystallized from hexane to give a white solid of t-$Bu_2PH{\cdot}BH_3$; yield, 1.5 g (94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.51 (broad q, J=95.7, 3H), 1.31 (s, 9H), 1.34 (s, 9H), 4.11 (dq, J=6.4, 351 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.87, 28.89; ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 48.20 (q,

J=50.1 Hz, 1P); ^{11}B NMR (128 MHz, $CDCl_3$) δ −43.236 (d, 1B); MS *m/z* 57 (100), 90 (11), 91 (9), 146 (M^+-BH_3, 52).

A 50 mL flask charged with 2-bromo-4′-cyanobiphenyl (0.78 g, 3.0 mmol), *t*-$Bu_2PH{\cdot}BH_3$ (0.48 g, 3.0 mmol), $Pd(dba)_2$ (0.052 g, 3 mol%), PhOK (0.83 g, 6.0 mmol) was flashed with argon. Toluene (9 mL), $P(OPh)_3$ (0.047 mL, 6 mol%) were added and the mixture was then stirred at 100°C for 3 h. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. GC analysis indicated the formation of **17** in 25% yield. Thinlayer chromatography (Merck Silica gel 60 PF_{254}) gave a white solid; 0.013 g (13%); IR (Nujol) 2229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 9H), 1.15 (s, 9H), 7.19–7.22 (m, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.38–7.44 (m, 2H), 7.63 (d, J=8.1 Hz, 2H), 7.92 (d, J=7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.53, 30.68, 32.77, 33.01, 110.24, 119.23, 126.74, 128.74, 130.01, 130.07, 131.06, 131.36, 131.40, 135.51, 148.70, 149.17, 149.49; ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 15.42; exact mass calcd for $C_{21}H_{26}NP$ 323.1881, found 324.1910 (M+1, FAB).

3.1.10. 2-Di-*tert*-butylphosphino-4′-methylaminobiphenyl. 2-Di-*tert*-butylphosphino-4′-cyanobiphenyl (**17**) (0.07 g, 0.22 mmol) in ether (5 mL) was added $LiAlH_4$ (0.01 g, 0.26 mmol). After being stirred for 2 h at room temperature, the mixture was treated with water at 0°C. Chromatography over silica gel with ethyl acetate and MeOH gave a white solid; yield, 0.06 g (85%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.09 (s, 9H), 1.12 (s, 9H), 3.82 (s, 2H), 7.17–7.21 (m, 3H), 7.30 (d, J=8.08 Hz, 2H), 7.31–7.39 (m, 2H), 7.91 (d, J=7.08 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 31.13, 31.29, 33.41, 33.66, 46.47, 126.99, 127.34, 129.80, 131.64, 131.70, 131.84, 131.88, 136.19, 136.48, 136.51, 141.46, 143.81, 143.88, 152.26, 152.59; ^{31}P NMR (161.7 MHz, CD_3OD) δ 17.66; MS *m/z* 215, 270, 327 (M^+, 100); exact mass calcd for $C_{21}H_{30}NP$ 327.2116, found 327.2120 (M, EI).

3.1.11. *N*-[4-(Di-*t*-butylphosphinophenyl)phenylmethyl] D-gluconamide (11). 2-Di-*tert*-butylphosphino-4′-methylaminobiphenyl (0.06 g, 0.18 mmol) and D-glucono-1,5-lactone (0.034 g, 0.19 mmol) was dissolved in MeOH (3 mL). After being refluxed for 3 h, the solvent was evaporated in vacuo. Chromatography over silica gel with ethyl acetate and then MeOH gave a white solid; yield, 0.07 g (81%); IR (Nujol) 1510, 1347, 1650 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.10 (s, 9H), 1.13 (s, 9H), 3.61–3.80 (m, 5H), 4.18 (s, 1H), 4.31 (d, J=2.7 Hz, 1H), 4.51 (s, 2H), 7.16–7.18 (m, 3H), 7.30–7.39 (m, 4H), 7.92 (d, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 31.06, 31.21, 33.45, 33.69, 43.52, 64.76, 71.94, 72.99, 74.36, 75.56, 127.03, 127.34, 129.86, 131.68, 131.76, 131.80, 136.47, 136.49, 137.78, 144.01, 144.07, 152.15, 152.48; ^{31}P NMR (161.7 MHz, CD_3OD) δ 17.59; MS *m/z* 136, 154, 289, 307, 443, 460, 506 (M+1); exact mass calcd for $C_{27}H_{40}NO_6P$ 505.2672, found 506.2681 (M+1, FAB).

3.2. Reaction conditions (Table 1)

A 25 mL flask charged with $PdCl_2$(**9**)$_2$ (1.3 mg, 0.001 mmol, 0.1 mol%), **9** (1.2 mg, 0.002 mmol, 0.2 mol%), and a base (2.0 mmol) was flushed with nitrogen. Water (3 mL) and 4-bromoanisole (1.0 mmol) were then added. After being stirred for 16 h at 80°C, the product was extracted with benzene. The yield was estimated by GC analysis using tridecane as the internal standard. The $Pd(OAc)_2$/**10** and $Pd(OAc)_2$/**11** catalysts were prepared in situ by adding a solution of $Pd(OAc)_2$ in CH_3CN (0.01 M, 0.1 mL, 0.1 mmol) to **10** (0.1–0.4 mmol) or **11** (0.2 mmol).

3.3. Representative procedure for cross-coupling reaction of *p*-tolylboronic acid with haloarenes

$PdCl_2$(**9**)$_2$ (1.3 mg, 0.001 mmol, 0.1 mol%), **9** (1.2 mg, 0.002 mmol) and *p*-tolylboronic acid (0.177 g, 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, 1 mL, 2 mmol), and finally aryl halide (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.

The compounds in Tables 4 and 5 were synthesized by above general procedure. Among them, we previously reported the analytical data of 4-methyl-4′-nitrobiphenyl,[22] 4-cyano-4′-methylbiphenyl,[22] 2-cyano-4′-methylbiphenyl,[22] 4-acetyl-4′-methylbiphenyl,[23] 4-formyl-4′-methylbiphenyl,[24] 4-methyl-4′-methoxycarbonylbiphenyl,[23] 4-methyl-2′-methoxycarbonylbiphenyl,[23] 4-methyl-*p*-terphenyl,[23] 4-methyl-4′-methoxybiphenyl,[24] 4-methyl-3′-methoxybiphenyl,[24] 4-amino-4′-methylbiphenyl,[24] 4-*N*,*N*-dimethylamino-4′-methylbiphenyl,[24] 2-(4-methylphenyl)pyridine,[22] 3-(4-methylphenyl)pyridine,[22] 4-(4-methylphenyl)pyridine,[22] and 2-(4-methylphenyl)quinoline.[24]

3.3.1. 4-Fuluoro-4′-methylbiphenyl. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.08–7.12 (m, 2H), 7.24 (d, J=7.9 Hz, 2H), 7.43 (d, J=7.9 Hz, 2H), 7.48–7.53 (m, 2H); MS *m/z* 165 (40), 170 (12), 186 (M^+, 100); exact mass calcd for $C_{13}H_{11}F$ 186.0845, found 186.0866 (M, EI).

3.3.2. 1-(4-Methylphenyl)naphthalene. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.30 (d, J=7.8 Hz, 2H), 7.36–7.53 (m, 9H); MS *m/z* 202 (51), 203 (59), 218 (M^+, 100); exact mass calcd for $C_{16}H_{12}$ 218.1096, found 218.1084 (M, EI).

3.3.3. 2-Hydroxy-4′-methylbiphenyl. IR (Neat) 3540, 1290 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 5.22 (s, 1H), 6.96 (d, J=7.9 Hz, 1H), 6.95–6.99 (m, 2H), 7.21–7.26 (m, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H); MS *m/z* 115 (23), 128 (18), 141 (19), 152 (11), 155 (10), 169 (51), 184 (M^+, 100); exact mass calcd for $C_{13}H_{12}O$ 184.0888, found 184.0881 (M, EI).

3.3.4. 4-Hydroxy-4′-methylbiphenyl. IR (Nujol) 3400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 4.76 (s, 1H), 6.88 (d, J=8.5 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 7.43 (d, J=8.2 Hz, 2H), 7.46 (d, J=8.5 Hz, 2H); MS *m/z* 155 (11), 165 (14), 167 (7), 183 (35), 184 (M^+, 100); exact mass calcd for $C_{13}H_{12}O$ 184.0888, found 184.0892 (M, EI).

3.3.5. 4-Hydroxy-3-methoxycarbonyl-4′-methylbiphenyl. Before isolation, the product was treated with $BF_3{\cdot}OEt_2$ (2 mL) in MeOH (20 mL) at reflux over night to convert the acid into the corresponding ester derivative: IR (Neat) 3169, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.95 (d, J=0.5 Hz, 3H), 7.03 (d, J=8.8 Hz, 1H), 7.21 (d, J=8.8 Hz, 2H), 7.42, (d, J=8.1 Hz, 2H), 7.66 (dd, J=2.2, 6.4, 2.4 Hz, 1H), 8.03 (d, J=2.4 Hz, 1H), 10.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.01, 52.29, 112.41, 117.91, 119.50, 126.39, 127.80, 129.48, 132.23 (d, J=19.9 Hz), 134.21, 136.84 (d, J=19.8 Hz), 138.35: MS *m/z* 139 (12), 153 (20), 182 (16), 210 (100), 242 (M^+, 65); exact mass calcd for $C_{15}H_{14}O_3$ 242.0943, found 242.0942 (M, EI).

3.3.6. 3-Hydroxy-4-methoxycarbonyl-4′-methylbiphenyl. The product was treated with $BF_3{\cdot}OEt_2$ (2 mL) in MeOH (20 mL) at reflux over night to convert the acid into the corresponding ester: IR (Nujol) 3191, 1680, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.95 (s, 3H), 7.10 (dd, J=0.98, 7.3 Hz, 1H), 7.20 (s, 1H), 7.24, (d, J=7.8 Hz, 2H), 7.50 (d, J=8.1 Hz, 2H), 7.85 (d, J=8.3 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.15, 52.21, 110.86, 115.36, 117.93, 127.00, 129.58, 130.21, 136.66, 138.42, 148.42, 161.77, 170.49: MS *m/z* 153 (22), 182 (38), 195 (10), 210 (100), 242 (M^+, 57); exact mass calcd for $C_{15}H_{14}O_3$ 242.0943, found 242.0951 (M, EI).

3.3.7. Methyl 4-(4-methylphenyl)cinnamate. The product was isolated after conversion into the corresponding ester: IR (Nujol) 1710, 1632, 1463, 1314, 1196, 1175, 984, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.73 (s, 3H), 6.37 (d, J=16.1 Hz, 1H), 7.16 (d, J=7.6 Hz, 2H), 7.41 (d, J=7.8 Hz, 2H), 7.47–7.52 (m, 4H), 7.64 (d, J=16.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.10, 51.64, 117.34, 126.80, 127.22, 128.51, 129.58, 132.96, 137.15, 137.71, 142.94, 144.42, 167.44; MS *m/z* 149 (100), 185 (8), 205 (7), 221 (19), 252 (M^+, 30); exact mass calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1138 (M, EI).

3.3.8. Methyl 2-(4-methylphenyl)cinnamate. The product was converted into the corresponding ester before isolation: IR (Neat) 1713, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.74 (s, 3H), 6.39 (d, J=16.1 Hz, 1H), 7.19–7.25 (m, 4H), 7.33–7.43 (m, 3H), 7.67, (d, J=8.5 Hz, 1H), 7.75 (d, J=16.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.13, 51.53, 118.51, 126.75, 127.37, 129.00, 129.65, 129.80, 130.48, 132.53, 136.88, 137.28, 142.92, 144.15, 167.29: MS *m/z* 178, 193, 221, 252 (M^+); exact mass calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1155 (M, EI).

3.3.9. 3-(4-Methylphenyl)quinoline. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.33 (d, J=7.8 Hz, 2H), 7.56 (dd, J=8.1, 8.1 Hz, 1H), 7.61 (d, J=7.8 Hz, 2H), 7.68–7.72 (m, 1H), 7.86 (d, J=8.1 Hz, 1H), 8.13 (d, J=8.3 Hz, 1H), 8.27 (d, J=2.2 Hz, 1H), 9.17 (d, J=2.2 Hz, 1H); exact mass calcd for $C_{16}H_{13}N$ 219.1048, found 219.1049 (M, EI).

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