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Synthesis of 8-arylated catechin and epicatechin derivatives via Suzuki cross-coupling

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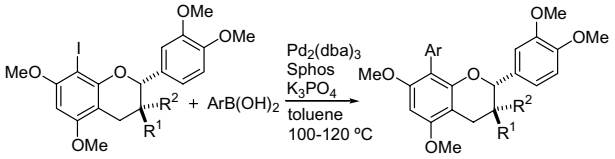
Abstract—8-Arylated catechin and epicatechin derivatives have been prepared in good to excellent yields via Suzuki cross-coupling in the presence of $Pd_2(dba)_3$ as the Pd(0) source and Sphos as the phosphine ligand.

Catechins, one of the major groups of flavanoids, are widely diffused in a variety of foods and beverages such as fruits, vegetables, chocolate, tea, and wine.[1] These bioactive compounds are also present in agricultural byproducts. For example, the grape pomace derived from the grapes processed by the wine industry is a rich source of catechins.[2] Catechins have been shown to be potentially beneficial to human health. Their biological activities include inhibition of platelet aggregation, anti-inflammatory action and, most notable, anticarcinogenic properties.[3] These activities have been mainly attributed to their antioxidant capacity.[4,5]

Because of these reasons, increasing attention has been dedicated to the preparation of catechin derivatives[6] and many of them have been compared to achieve structure-activity relationships.[7] Their oxidative modifications have also been described.[8] The synthesis of catechins, less soluble in water to improve absorption into living bodies, is a subject of great current interest.[9] In this last context, based on our interest in palladium-catalyzed coupling reactions[10] and as part of a program devoted to the chemical valorization of widespread diffused molecules in renewable sources, we became interested in the preparation of new arylated catechins via Suzuki cross-coupling.

Despite the remarkable versatility and efficiency of palladium catalysis in organic synthesis,[11,12] palladium-catalyzed reactions have been rarely mentioned in this area. Larock et al. recently described the annulation of 1,3-dienes by *o*-iodoacetoxyflavanoids to give dihydrofuroflavanoids.[13] 8-Flavoneboronic acids were subjected to Suzuki cross-coupling with 3′-iodonated flavones providing access to amentoflavone derivatives.[14] The Suzuki reaction was also applied to the synthesis of a *gem*-difluoromethylenated biflavanoid in moderate yield using a flavone 3′-boronate as the coupling partner.[15] However, no general method for the arylation at the C-8 position of catechins and epicatechins has been reported. Clearly, Suzuki cross-coupling is more difficult here compared to electron-poor unhindered substrates.

In the present Letter we describe just such a reaction where 8-iodocatechin-5,7,3′,4′-tetramethyl ether **1** and 8-iodoepicatechin-5,7,3′,4′-tetramethyl ether **3** react with boronic acids to give the corresponding 8-arylated derivatives **2** and **4** (Scheme 1).



1: R^1 = OH, R^2 = H
3: R^1 = H, R^2 = OH

2: R^1 = OH, R^2 = H
4: R^1 = H, R^2 = OH

Scheme 1.

Keywords: Catechins; Epicatechins; Suzuki arylation; Palladium Catalysis; Sphos.
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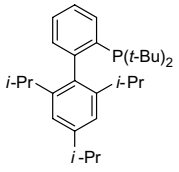
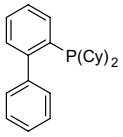
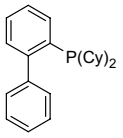
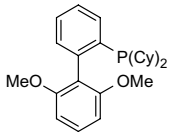
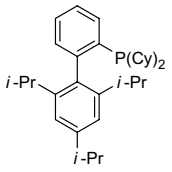
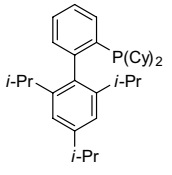
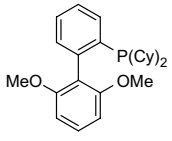
Iodo derivatives **1** and **3** were prepared from catechin and epicatechin in 74–77% overall yields via methylation with Me_2SO_4 in the presence of K_2CO_3 in acetone at room temperature (24 h) followed by iodination with NIS in acetone at room temperature (5 h) of the resultant tetramethyl ethers.[16]

Initial arylation attempts focused on the reaction of **1** with phenyl boronic acid, selected as the model system. Using K_3PO_4 as the base, the following reaction variables were examined: the nature of phosphine ligands, solvents, additives, and temperature. Some of the results of our screening study are summarized in Table 1.

Some of the most commonly used catalytic systems for this type of reaction met with failure (entries 1 and 2) or gave unsatisfactory results (entry 3). Even the use of P(*t*-Bu)$_3$ (added to the reaction mixture as the tetrafluoroborate salt)[17] (entry 4) and 2-(2′,4′,6′-triisopropylbiphenyl)di-*tert*-butylphosphine (entry 5), one of the biaryl monophosphine ligands introduced by Buchwald et al.,[18] failed to give the desired product.

Table 1. Ligands, palladium complexes, solvents and temperature in the reaction of phenylboronic acid with **1**[a]

Entry	Pd complex (equiv)	Phosphine ligand (equiv)	K_3PO_4 (equiv)	Additive (equiv)	Solvent	*T* (°C)	*t* (h)	**2a** yield[b] (%)	**1** (recovered) yield[b] (%)
1	$Pd_2(dba)_3$ (0.04)	PPh_3 (0.16)	3	—	Toluene	100	24	—	32
2	$Pd(PPh_3)_4$ (0.05)	—	1.5	—	Dioxane	80	24	—	80
3	$Pd(PPh_3)_4$ (0.05)	—	1.5	—	Toluene	120	24	35	40
4	$Pd_2(dba)_3$ (0.02)	[HP(Bu-*tert*)$_3$]BF_4 (0.1)	2	—	Dioxane	60	30	10	60
5	$Pd_2(dba)_3$ (0.025)	 (0.1)	1.5	—	Dioxane	80	24	—	84
6	$Pd_2(dba)_3$ (0.025)	 (0.1)	1.5	—	Dioxane	80	24	45	44
7	$Pd_2(dba)_3$ (0.025)	 (0.1)	2	—	Dioxane	100	24	31	42
8	$Pd_2(dba)_3$ (0.02)	 (0.04)	3	—	Dioxane	100	24	42	—
9	$Pd_2(dba)_3$ (0.025)	 (0.1)	1.5	—	Dioxane	80	24	23	—
10	$Pd_2(dba)_3$ (0.025)	 (0.1)	1.5	KF (3)	Dioxane	100	48	48	32
11	$Pd_2(dba)_3$ (0.02)	 (0.04)	3	—	Toluene	100	5	95	—

[a] Reactions were carried out under argon on a 0.1 mmol scale using 1 equiv of **1** and 1.5 equiv of phenyl boronic acid in 0.7 mL of solvent.
[b] Yields are given for isolated products.

Table 2. Preparation of arylated catechin and epicatechin derivatives **2** and **4** via palladium-catalyzed reaction of **1** and **3** with boronic acids[a]

Entry	Compounds **1** and **3**	Boronic acid	Time (h)	Arylated derivatives **2** and **4** yield[b] (%)
1	**1**	$PhB(OH)_2$	5	**2a** (95)
2	**3**	$PhB(OH)_2$	5	**4a** (95)
3	**1**	4-Me–C_6H_4–$B(OH)_2$	5	**2b** (75)
4	**3**	4-Me–C_6H_4–$B(OH)_2$	5	**4b** (85)
5	**1**	4-Me-3-FC_6H_4–$B(OH)_2$	8	**2c** (90)
6	**3**	4-Me-3-FC_6H_4–$B(OH)_2$	8	**4c** (72)
7	**1**	2-Me–C_6H_4–$B(OH)_2$	24	**2d** (65)
8	**3**	2-Me–C_6H_4–$B(OH)_2$	24	**4d** (60)
9	**1**	4-Ph–C_6H_4–$B(OH)_2$	24	—
10	**1**	4-Ph–C_6H_4–$B(OH)_2$	24[c]	**2e** (90)
11	**3**	4-Ph–C_6H_4–$B(OH)_2$	24[c]	**4e** (94)

[a] Unless otherwise stated, reactions were carried out on a 0.2 mmol scale at 100 °C in 1.4 mL of toluene, under an argon atmosphere, using 1 equiv of **1** or **3**, 1.5 equiv of aryl boronic acid, 0.02 equiv of $Pd_2(dba)_3$, 0.04 equiv of Sphos and 3 equiv of K_3PO_4.

[b] Yields are given for isolated products.

[c] In the presence of 0.04 equiv of $Pd_2(dba)_3$, 0.08 equiv of Sphos and 4 equiv of K_3PO_4 at 120 °C.

Switching to other biaryl monophosphine ligands such as 2-(biphenyl)dicyclohexylphosphine (entries 6 and 7), Sphos [2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine] (entry 8), and Xphos [2-(2′,4′,6′-triisopropylbiphenyl)dicyclohexylphosphine] (entries 9 and 10)—the latter with or without KF, a fluoride source reported to activate boronic acids in Suzuki cross-couplings[19] -afforded **2a** in low to moderate yields in dioxane. Eventually, compound **2a** was isolated in excellent yield when the reaction was carried out in the presence of Sphos in toluene[18c] (entry 11). The latter conditions were consequently utilized when the reaction was extended to epicatechin **3** and other aryl boronic acids.[20]

As apparent from Table 2, the reaction gave good to excellent results with the boronic acids examined. Even an *ortho*-substituted boronic acid was successfully used in this chemistry (Table 2, entries 7 and 8). With 4-(phenyl)phenyl boronic acid the reaction failed to give the desired product under standard conditions (Table 2, entry 9). However, increasing the temperature, the amount of $Pd_2(dba)_3$ and base led to the isolation of **2e** and **4e** in 90 and 94% yield, respectively (Table 2, entries 10 and 11).

In conclusion, we have described a simple and efficient method for the arylation at the C-8 position of catechin and epicatechin derivatives. Under the best conditions used [$Pd_2(dba)_3$, Sphos and K_3PO_4 in toluene] the arylated derivatives were isolated in good to excellent yields.

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20. Typical procedure for the preparation of **2** and **4**: To a stirred solution of **1a** (100 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), and Sphos (3.2 mg, 0.008 mmol) in 1.4 ml of deoxygenated toluene, K_3PO_4 (127.1 mg, 0.6 mmol), and phenylboronic acid (36.4 mg, 0.30 mmol) were added under Ar. The reaction mixture was heated at 100 °C for 5 h. After cooling, the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane/ethylacetate 50/50, v/v) to give 104 mg of **2a**: mp: 120–122 °C; IR (KBr) 3497, 2998, 2935, 2837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.21 (m, 5H), 6.87–6.80 (m, 3H), 6.26 (s, 1H), 4.73–4.71 (d, $J = 7.4$ Hz, 1H), 4.15–3.98 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.09–2.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.7, 156.7, 152.2, 149.2, 148.9, 134.0, 131.3, 130.9, 127.5, 126.4, 118.9, 111.8, 111.1, 109.5, 102.0, 88.9, 81.0, 68.3, 60.5, 56.2, 56.0, 55.8, 55.6, 31.6, 27.4. Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 71.15; H, 6.25.