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2-Arylhydroxytyrosol Derivatives via Suzuki−Miyaura Cross-Coupling

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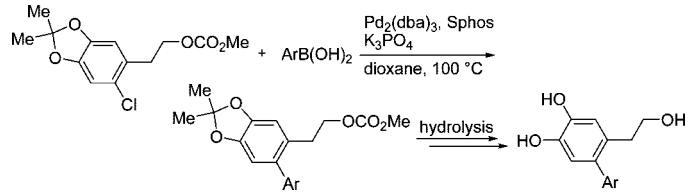
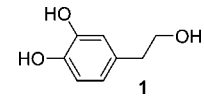
ABSTRACT



2-Arylhydroxytyrosol derivatives, a new class of hydroxytyrosol derivatives, have been prepared in high to excellent yields from the corresponding 2-chloro precursors via Suzuki−Miyaura cross-coupling with arylboronic acids containing electron-donating, electron-withdrawing, as well as ortho substituents. A remarkable halide effect has been observed. 2-Iodo- and 2-bromohydroxytyrosol derivatives have been found to be ineffective cross-coupling partners in many cases. The acetonide and carbonate protecting groups can be readily removed.

Hydroxytyrosol **1** is a naturally occurring bioactive molecule found in extra virgin olive oil[1] and agricultural wastewaters[2] which has been reported to exhibit antioxidant properties.[3] Because of this, it is widely used in food[4] and cosmetic[5] applications. Hydroxytyrosol has also been found to exert several pharmacological properties including prevention and treatment of cardiovascular, hepatic, and renal diseases and, most notably, prevention of cancer.[6]



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Given its importance, much effort has been directed toward the preparation of hydroxytyrosol derivatives. However, these derivatives are usually limited to the esterification of the

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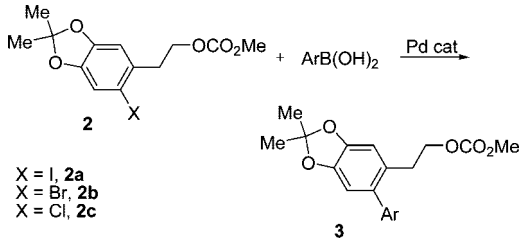
primary alcoholic group. Esters of lipophilic acids have been prepared to favor the utilization of hydroxytyrosol derivatives in nonaqueous media.[7–9] In addition, the synthesis of esters of polyphenolic acids such as caffeic acid[9] and gallic acid,[9] the latter exerting an HIV-1 reverse transcriptase inhibitor activity, have been described.

Surprisingly, despite the potential interest from a biological point of view of hydroxytyrosol derivatives bearing substituents on the aromatic ring, no examples of selective functionalization in this position have been reported. On the other hand, such a functionalization might provide a convenient access to new classes of bioactive molecules.

Thus, as part of a program devoted to the chemical valorization of widespread diffused molecules in renewable sources, we became interested in the preparation of arylated hydroxytyrosols via Suzuki−Miyaura cross-coupling. Clearly, Suzuki−Miyaura cross-coupling with this electron-rich hindered substrate is expected to be more difficult compared to electron-poor unhindered substrates.

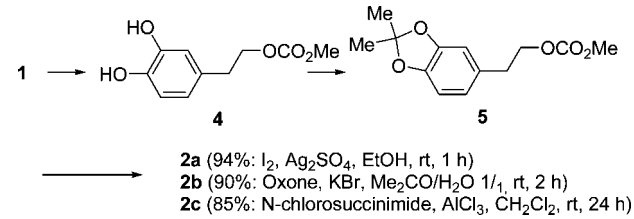
In the present paper, we report a general, high-yielding method for the palladium-catalyzed arylation of the 2-chlorohydroxytyrosol derivative **2c** with arylboronic acids (Scheme 1).

Scheme 1



Cross-coupling experiments were carried out with the 2-iodo, 2-bromo, and 2-chloro derivatives **2a**−**c**,[10] which were prepared in 94, 90, and 85% yields, respectively, via halogenation of **5** under the conditions shown in Scheme 2.

Scheme 2



Compound **5** was in turn prepared from hydroxytyrosol in 80% overall yield via selective protection with dimethyl carbonate/catalytic sulfuric acid[11] and 2,2-dimethoxypropane/catalytic camphorsulphonic acid.[12] Acetonide derivatives **2a**−**c** were chosen as substrates because our attempts to prepare the halogenated derivatives from the carbonate ester **4** met with failure. For example, treatment of **4** with I_2, Ag_2SO_4 in EtOH at room temperature[10a] for 24 h afforded an *o*-iodo monoethyl ether derivative (13% yield) as the sole isolable product.

The reaction of 2-iododerivative **2a** with phenylboronic acid in toluene at 80 °C was initially examined as the model system. Good to excellent results were obtained using "classical" precatalyst systems such as $Pd(PPh_3)_4$ (Table 1, entry 1) or $Pd(OAc)_2/PPh_3$ (Table 1, entry 2). Utilization of $Pd_2(dba)_3$ in the presence of Xphos or Sphos[13,14] (Table 1, entries 3 and 4) did not afford yields significantly higher than those obtained with $Pd(OAc)_2$ and PPh_3.

Table 1. Palladium and Phosphine Ligands in the Suzuki−Miyaura Cross-Coupling of **2a** with Phenylboronic Acid[a]

entry	precatalyst system (equiv)	yield[b] (%) of **3a**
1	$Pd(PPh_3)_4$ (0.04)	75
2	$Pd(OAc)_2$ (0.04)/PPh_3 (0.16)	91
3	$Pd_2(dba)_3$ (0.02)/Xphos (0.04)	95
4	$Pd_2(dba)_3$ (0.02)/Sphos (0.04)	93

[a] Reactions were carried out on a 0.2 mmol scale, under argon, in 1.4 mL of toluene at 80 °C for 0.5 h using 1 equiv of **2a**, 1.5 equiv of phenylboronic acid, 3 equiv of K_3PO_4. [b] Yields are given for isolated products.

However, these conditions were quickly determined to be unsuitable for the development of a general arylation method. Indeed, when the procedure was extended to other arylboronic acids, only *p*-tolylboronic acid afforded the corresponding hydroxytyrosol derivative in 79% yield with

(7) For enzyme-catalyzed esterification, see: (a) Buisman, G. J. H.; Van Helteren, C. T. W.; Kramer, G. F. H.; Veldsink, J. W.; Derksen, J. T. P.; Cuperus, F. P. *Biotechnol. Lett.* **1998**, *20*, 131. (b) Torres de Pinedo, A.; Penalver, P.; Perez-Victoria, I.; Rondon, D.; Morales, J. C. *Tetrahedron* **2005**, *61*, 7654. (c) Trujillo, M.; Mateos, R.; Collantes De Teran, L.; Espartero, J. L.; Cert, R.; Jover, M.; Alcudia, F.; Bautista, J.; Cert, A.; Parrado, J. *J. Agric. Food Chem.* **2006**, *54*, 3779. (d) Grasso, S.; Siracusa, L.; Spatafora, C.; Renis, M.; Tringali, C. *Bioorg. Chem.* **2007**, *35*, 137. (e) Torres de Pinedo, A.; Penalver, P.; Morales, J. C. *Food Chem.* **2007**, *103*, 55. (f) Torres de Pinedo, A.; Penalver, P.; Perez-Victoria, I.; Rondon, D.; Morales, J. C. *Food Chem.* **2007**, *105*, 657.

(8) For Ce(III)-promoted esterification, see: Torregiani, E.; Seu, G.; Minassi, A.; Appendino, G. *Tetrahedron Lett.* **2005**, *46*, 2193.

(9) For esterification using the Mitsunobu reaction, see: Appendino, G.; Minassi, A.; Daddario, A.; Bianchi, F.; Tron, G. C. *Org. Lett.* **2002**, *4*, 3839.

(10) Compounds **2a**−**c** were prepared according to standard methods described in the literature. **2a**: (a) Wah, S. W. *Synth. Commun.* **1992**, *22*, 3215 **2b**: (b) Bovicelli, P.; Bernini, R.; Antonioletti, R.; Mincione, E. *Tetrahedron Lett.* **2002**, *43*, 5563 **2c**: (c) Yanhua, Z.; Kazutaka, S.; Hisashi, Y. *Synlett* **2005**, 2837.

(11) Bernini, R.; Mincione, E.; Crisante, F.; Fabrizi, G.; Gentili, P. *Tetrahedron Lett.* **2007**, *63*, 7000.

(12) Gambacorta, A.; Tofani, D.; Bernini, R.; Migliorini, A. *J. Agric. Food Chem.* **2007**, *55*, 3386.

(13) Sphos = 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine; Xphos = 2-(2′,4′,6′-triisopropylbiphenyl)dicyclohexylphosphine.

(14) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

$Pd(OAc)_2$ and PPh_3 in 0.5 h (but no reaction was observed with the $Pd_2(dba)_3$/Xphos combination). A variety of electron-rich and electron-poor arylboronic acids, including *p*-methoxyphenylboronic acid, *p*-bromophenylboronic acid, 3-methyl-4-fluoro-phenylboronic acid, and *p*-acetylphenylboronic acid, failed to give the desired cross-coupling products with $Pd(OAc)_2$/PPh_3, $Pd_2(dba)_3$/Sphos, and $Pd_2(dba)_3$/Xphos, even increasing the reaction temperature to 120 °C and/or using other solvents such as THF and dioxane. In general, **2a** was recovered in almost quantitative yields.

We then attempted the utilization of the 2-bromo derivative **2b**. *p*-Methoxyphenylboronic acid, which failed to give the corresponding cross-coupling product with **2a**, afforded the desired derivative in 79% yield after 0.5 h in dioxane at 80 °C in the presence of $Pd_2(dba)_3$, K_3PO_4, and Sphos, one of the biaryl monophosphine ligands reported to generate more efficient palladium catalysts for the oxidative addition of C−Br and C−Cl bonds to Pd(0) species. Unfortunately, these conditions proved unsatisfactory when we investigated the reaction of **2b** with a variety of other aryl- and heteroarylboronic acids such as *p*-acetylphenylboronic acid, *p*-phenylphenylboronic acid, 3-methyl-4-fluorophenylboronic acid, and 3-thienylboronic acid. Even in these cases, **2b** was usually recovered in almost quantitative yields.

The utilization of potassium aryltrifluoroborates[15] was also briefly investigated. However, no evidence of cross-coupling product formation was attained upon treatment of potassium *p*-methoxyphenyltrifluoroborate with **2a** [$Pd(OAc)_2$, Sphos, K_2CO_3, MeOH, 50 °C, 24 h] or with **2b** [$Pd_2(dba)_3$, Sphos, K_3PO_4, dioxane, 80 °C, 9 h].

At this point, we decided to switch to the 2-chloro derivative **2c**. Representative optimization experiments carried out with *p*-acetylphenylboronic acid, which did not give the corresponding diaryl derivative with **2b**, are summarized in Table 2. As expected, utilization of $Pd(PPh_3)_4$ and $Pd(OAc)_2$/PPh_3 did not afford the coupling product **3f** (Table 2, entries 1 and 2). However, we were pleased to find that **3f** could be isolated in high yields using Xphos and, particularly, Sphos (Table 2, entries 3 and 4).

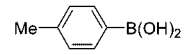
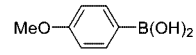
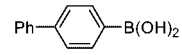
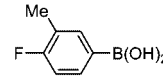
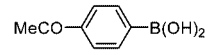
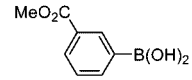
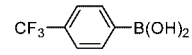
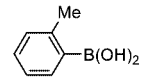
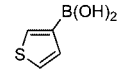
Table 2. Palladium and Phosphine Ligands in the Suzuki−Miyaura Cross-Coupling of **2c** with *p*-Acetylphenylboronic Acid[a]

entry	precatalyst system (equiv)	time (h)	yield[b] (%) of **3f**
1	$Pd(PPh_3)_4$ (0.04)	5	traces
2	$Pd(OAc)_2$ (0.04)/PPh_3 (0.16)	15	
3	$Pd_2(dba)_3$ (0.02)/Xphos (0.04)	5	76
4	$Pd_2(dba)_3$ (0.02)/Sphos (0.04)	5	83

[a] Reactions were carried out on a 0.3 mmol scale, under argon, in 2.5 mL of dioxane at 100 °C using 1 equiv of **2c**, 1.5 equiv of *p*-acetylphenylboronic acid, and 3 equiv of K_3PO_4. [b] Yields are given for isolated products.

Even more gratifying, the best conditions developed for *p*-acetylphenylboronic acid and **2c** (Table 2, entry 4) were found to be broadly applicable. When they were applied to a variety of neutral, electron-rich, and electron-poor arylboronic acids and heteroarylboronic acids to investigate the synthetic scope of the reaction, the corresponding 2-aryl and 2-heteroaryl hydroxytyrosol derivatives were isolated in high to excellent yields. Our preparative results are summarized in Table 3. *p*-Methoxyphenylboronic acid, which had given the cross-coupling product in 79% yield with **2b** under similar conditions, afforded the desired derivative in 98% yield (Table 3, entry 3). Notably, even electron-deficient arylboronic acids, which are known to be usually reluctant to give Suzuki−Miyaura products[14c] very likely because they are less nucleophilic than their electron-neutral analogues and consequently tend to transmetalate more slowly, gave the desired derivatives in excellent yields (Table 3, entries 6 and 7). Arylboronic acids bearing ortho substituents can also be used to prepare hindered cross-coupling products in high yield (Table 3, entry 9).

Table 3. Pd-Catalyzed Arylation and Heteroarylation of the 2-Chlorohydroxytyrosol Derivative **2c**[a]

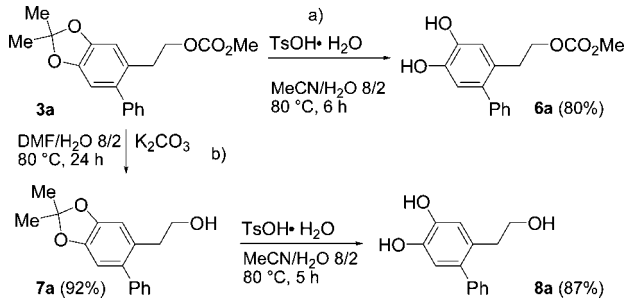
entry	boronic acid	time (h)	**3** yield %[b]
1	$PhB(OH)_2$	5.5	94 **3a**
2		5.5	80 **3b**
3		5	98 **3c**
4		17	96 **3d**
5		6.5	85 **3e**
6		15	87 **3f**
7		5	100 **3g**
8		5	89 **3h**
9		5.5	81 **3i**
10		22	83 **3j**

[a] Unless otherwise stated, reactions were carried out under argon on a 0.3 mmol scale in 2.5 mL of dioxane at 100 °C using 1 equiv of **2c**, 1.5 equiv of aryl- or heteroarylboronic 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.

The acetonide protecting group can be readily removed to give the free catechol substructure, which is crucial for the biological activity. As an example, subjecting **3a** to the conditions shown in Scheme 3a affords **6a** in 80% isolated yield. Completely deprotected *o*-phenylhydroxytyrosol **8a**, suitable for utilization as additive in cosmetic and food preparations, was also obtained in high yield (Scheme 3b).

(15) For a recent review on the reactivity of potassium aryltrifluoroborates, see: Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

Scheme 3



Our results point to the existence of a remarkable halide effect in this Suzuki−Miyaura cross-coupling, which is crucial for the success of the reaction. Although we have no direct evidence, we believe that the oxidative addition is not the step where the halide may exert its influence. In fact, the best results in term of applicability and yields have been obtained when the 2-chlorohydroxytyrosol derivative **2c** has been used as the coupling partner instead of the 2-iodo- and 2-bromohydroxytyrosol derivatives. Aryl iodides and bromides are known to be more prone to give oxidative addition intermediates than their chloride analogues. It seems also unlikely that the reductive elimination step, where the halide anion is most probably away from the coordination sphere of palladium, may be responsible for the different behavior of iodo, bromo, and chloro derivatives. It remains that the observed halide effect should operate on the transmetalation step which should be favored by the presence of the chloro atom. To the best of our knowledge, there are no precedents of such an influence on the transmetalation step of the Suzuki−Miyaura cross-coupling.[16,17] A working hypothesis to account for this influence might consider a stabilizing effect of the more electron-withdrawing halogen on the negative transition state **A** (Figure 1). A transition state of this type, which contains only one phosphine ligand in the presence of biaryl monophosphines, has been recently suggested to be involved in the Suzuki−Myiaura cross-coupling.[18] Clearly, further studies would be needed to shed some light on the mechanistic details of this step.

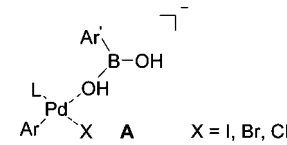


Figure 1. Transition state for the halide displacement in the transmetalation process.

In conclusion, we have developed a convenient, highly efficient method for the preparation of novel analogues of hydroxytyrosol. The reaction tolerates a variety of neutral, electron-rich, and electron-poor aryl groups. Arylboronic acids bearing ortho substituents can also be used to prepare hindered cross-coupling products. A remarkable halide effect has also been observed which makes the reaction strongly dependent on the nature of the starting 2-halohydroxytyrosol derivative, 2-iodo- and 2-bromohydroxytyrosol derivatives being ineffective cross-coupling partners.

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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Aryl chlorides have been shown to be more reactive than aryl triflates in the Suzuki−Miyaura cross-coupling: (a) Littke, F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. A mechanistic study on the Suzuki−Miyaura cross-coupling showed that the slow step of the reaction, using PPh_3 as ligand, depends on the identity of the halide. The slow step is the oxidative addition with an aryl bromide and the transmetalation with *p*-iodotoluene: (b) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151.

(17) A similar trend in the reactivity of aryl halides has been observed for the Stille reaction: Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

(18) For a recent interesting DFT study on the catalytic cycle of the Suzuki−Miyaura cross-coupling, see: (a) Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647. See also: (b) Sicre, C.; Braga, A. A. C.; Maseras, F.; Cid, M. M. *Tetrahedron* **2008**, *64*, 7437.