2-Arylhydroxytyrosol Derivatives via Suzuki-Miyaura Cross-Coupling

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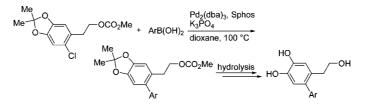
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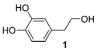




2-Arylhydroxytyrosol derivatives, a new class of hydroxytyrosol derivatives, have been prepared in high to excellent yields from the corresponding 2-chloro precursors via Suzuki-Miyaura cross-coupling with arylboronic acids containing electron-donating, electron-withdrawing, as well as ortho substituents. A remarkable halide effect has been observed. 2-lodo- 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 oil¹ and agricultural wastewaters² which has been reported to exhibit antioxidant properties.³ Because of this, it is widely used in food⁴ and cosmetic⁵ applications. Hydroxytyrosol has also been found to exert several pharmacological properties including prevention and

10.1021/ol8012292 CCC: \$40.75 © 2008 American Chemical Society Published on Web 07/10/2008 treatment of cardiovascular, hepatic, and renal diseases and, most notably, prevention of cancer.⁶



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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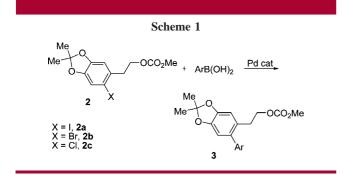
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primary alcoholic group. Esters of lipophilic acids have been prepared to favor the utilization of hydroxytyrosol derivatives in nonaqueous media.^{7–9} In addition, the synthesis of esters of polyphenolic acids such as caffeic acid⁹ and gallic acid,⁹ 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.

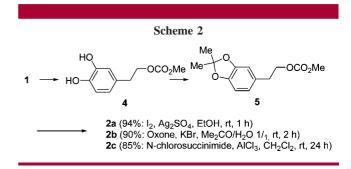
Thus, as part of a program devoted to the chemical valorization of widespread diffused molecules in renewable sources, we became interested in the preparation of arylated hydroxytyrosols via Suzuki–Miyaura cross-coupling. Clearly, Suzuki–Miyaura cross-coupling with this electron-rich hindered substrate 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).



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.

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Compound **5** was in turn prepared from hydroxytyrosol in 80% overall yield via selective protection with dimethyl carbonate/catalytic sulfuric acid¹¹ 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 I₂, Ag₂SO₄ 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(PPh₃)₄ (Table 1,

Table 1. Palladium and Phosphine Ligands in theSuzuki-Miyaura Cross-Coupling of 2a with PhenylboronicAcid^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.

entry 1) or Pd(OAc)₂/PPh₃ (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 .

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

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Pd(OAc)₂ and PPh₃ in 0.5 h (but no reaction was observed with the Pd₂(dba)₃/Xphos combination). A variety of electronrich 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/PPh₃, Pd₂(dba)₃/Sphos, and Pd₂(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 Pd₂(dba)₃, K₃PO₄, 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 heteroaryl-boronic acids such as *p*-acetylphenylboronic acid, *p*-phenylphenylboronic acid. Even in these cases, **2b** was usually recovered in almost quantitative yields.

The utilization of potassium aryltrifluoroborates¹⁵ 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, K₂CO₃, MeOH, 50 °C, 24 h] or with **2b** [Pd₂(dba)₃, Sphos, K₃PO₄, 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

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.

Pd(OAc)₂/PPh₃ 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).

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

Table 3. Pd-Catalyzed Arylation and Heteroarylation of the 2-Chlorohydroxytyrosol Derivative $2c^{a}$

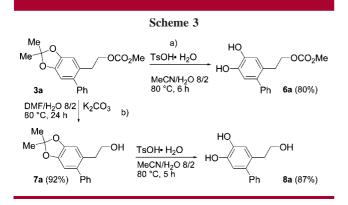
entry	boronic acid	time (h)	3 yield % ^b
	borome acid	time (ii)	5 yield 70
1	PhB(OH) ₂	5.5	94 3a
2	Me B(OH)2	5.5	80 3b
3	MeO-B(OH)2	5	98 3c
4	Ph-B(OH) ₂	17	96 3d
5	F-B(OH)2	6.5	85 3e
6	MeCO-B(OH)2	15	87 3f
7	MeO ₂ C B(OH) ₂	5	100 3g
8	CF ₃ -B(OH) ₂	5	89 3h
9	Me B(OH) ₂	5.5	81 3 i
10	S S	22	83 3 j

^{*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 Pd₂(dba)₃, 0.04 equiv of Sphos, and 3 equiv of K₃PO₄. ^{*b*} Yields are given for isolated products.

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).

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.



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

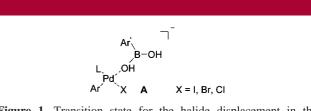


Figure 1. Transition state for the halide displacement in the transmetalation process.

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.

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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