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A facile and rapid access to resveratrol derivatives and their radioprotective activity

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ABSTRACT

A facile and rapid access to resveratrol derivatives has been achieved based on palladium-catalyzed oxidative Heck reaction of aryl boronic acids with styrenes followed by demethylation in moderate to good yields. A series of resveratrol derivatives with various functional groups has been synthesized easily. The radioprotective activity of synthesized compounds has also been evaluated using rat thymocytes. The results revealed that some resveratrol derivatives efficiently protected the thymocytes from radiation-induced apoptosis.

Recently, polyhydroxylated stilbenes and its congeners have attracted much attention due to the significance of their biological activity.[1] Among them, resveratrol [**1**, (*E*)-3,5,4′-trihydroxystilbene, Fig. 1], a naturally occurring phytoalexin present in grapevines, pines, and legumes but also in pomegranates, soy beans, and in peanuts,[2] is recognized to be a representative of *trans*-polyphenolic stilbenes. Resveratrol shows a plethora of remarkable biological properties such as antifungal,[3] antibacterial,[4] antiviral,[5] anti-cancer,[6,7] estrogenic,[8] platelet anti-aggregating,[9] and heart protecting activities.[10,11] For these reasons, many synthetic methods for polyhydroxylated stilbenes has been appeared which include Wittig reaction,[12] traditional Heck reaction,[13] cross-metathesis,[14] Perkin reaction,[15] and Hunsdiecker–Suzuki strategy.[16] However, the application of oxidative Heck reaction[17] using aryl boronic acids and styrenes as starting materials has not been appeared yet. It was assumed that such method would result in a facile access to polymethoxylated and polyhydroxylated stilbene derivatives due to the easy availability of boronic acid derivatives as commercial sources.

Recently, a triacetylated resveratrol derivative has reported to show an efficient protective effect against γ-irradiation-induced death of mice.[18] Radioprotectors are crucial for the cancer radiation therapy to protect the normal tissue around the target cancer.[19] Although a large number of chemical compounds with radioprotective effect in in vitro/vivo studies have so far reported,[20] only amifostine was authorized for clinical use by the FDA. However, due to the side effect such as vomiting,[21] amifostine has not been widely utilized. For these reason along with the Fukushima Daiichi nuclear disaster in Japan on 11 March 2011, it is an urgent necessity to develop effective radioprotectors. Thus we evaluated the effect of radioprotection of resveratrol derivatives synthesized in this study based on the method developed by our group.[22]

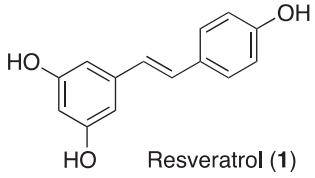

Figure 1. Structure of resveratrol (**1**).

We first examined the reaction of 3,5-dimethoxyphenylboronic acid **2a** with 4-acetoxystyrene **3a** to form (*E*)-4-(3,5-dimethoxystyryl)phenyl acetate **4a**[23] (Table 1). When the mixture of compounds **2a** and **3a** were treated with $Pd(OAc)_2$ (10 mol %) and sodium carbonate (2 equiv) under molecular oxygen in DMF at 50 °C for 3 h,[17] the desired stilbene **4a** was observed in a 80% isolated yield (Table 1, entry 1). Other palladium catalysts were proven to be less effective (entries 2–5) except for the case utilizing $(CH_3CN)_2PdCl_2$ (entry 6), which showed a slight better conversion (84%). For base variations, potassium carbonate was equally

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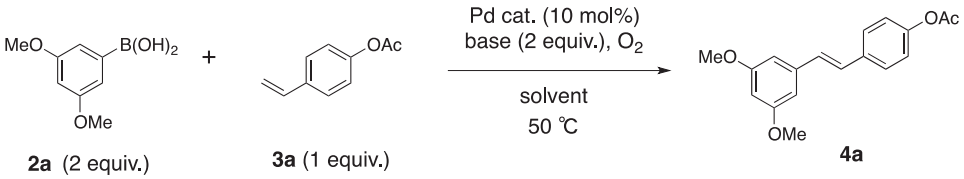
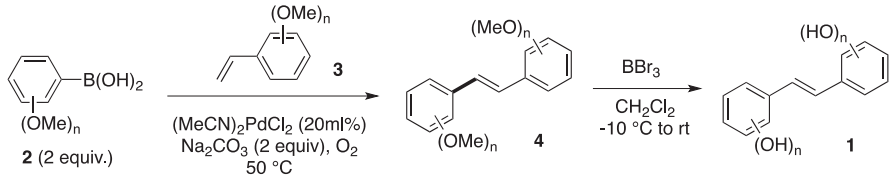
Table 1
Optimization studies for the couple of boronic acid **2a** with styrene **3a**[a]

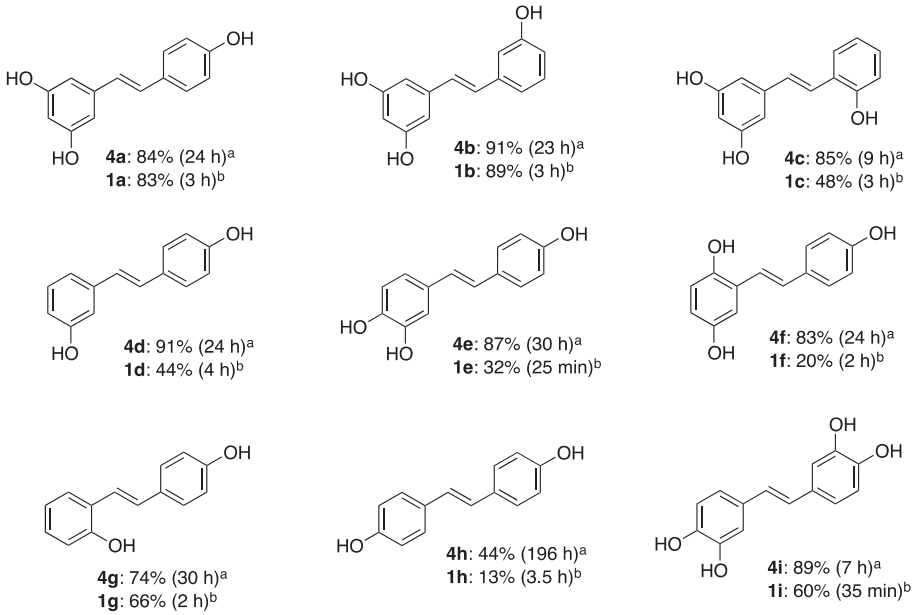


Entry	Pd catalyst	Base	Solvent	Time (h)	**4a** yield[b] %
1	$Pd(OAc)_2$	Na_2CO_3	DMF	3	80
2	$PdCl_2$	Na_2CO_3	DMF	3	70
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Na_2CO_3	DMF	24	58
4	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMF	24	38
5	$PdCl_2$(dppf)	Na_2CO_3	DMF	24	34
6	**$(CH_3CN)_2PdCl_2$**	**Na_2CO_3**	**DMF**	**3**	**84**[d]
7	$(CH_3CN)_2PdCl_2$	K_2CO_3	DMF	3	82
8	$(CH_3CN)_2PdCl_2$	Cs_2CO_3	DMF	24	22
9	$(CH_3CN)_2PdCl_2$	DBU	DMF	24	0
10	$(CH_3CN)_2PdCl_2$	Na_2CO_3	DMSO	24	50
11	$(CH_3CN)_2PdCl_2$	Na_2CO_3	Dioxane	24	8
12	$(CH_3CN)_2PdCl_2$	Na_2CO_3	MeCN	24	17
13[c]	$(CH_3CN)_2PdCl_2$	Na_2CO_3	DMF	18	68

[a] Reaction conditions: 3,5-Dimethoxyphenylboronic acid **2a** (0.50 mmol), *p*-acetoxystyrene **3a** (0.25 mmol), base (0.50 mmol), Pd catalyst (0.025 mmol), in solvent (1.3 ml) at 50 °C under oxygen atmosphere.
[b] Isolated yield.
[c] 5 mol % of $(CH_3CN)_2PdCl_2$ was introduced.
[d] Optimized conditions.

Table 2
Synthesis of polyhydroxylated stilbenes





[a] Reaction time for the synthesis of stilbenes.
[b] Reaction time for demethylation.