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Synthesis of Substituted Stilbenes via Direct Decarboxylative Coupling of Cinnamic Acids with Arylboronic Acids under Palladium Catalysis

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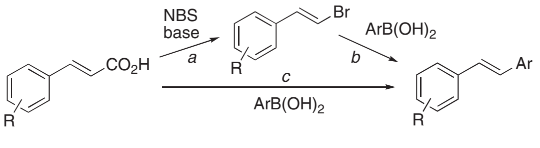
Readily available cinnamic acids possessing a hydroxy group including ferulic acid efficiently undergo direct decarboxylative arylation under palladium catalysis to form hydroxylated stilbenes. The reaction of related acids is also described.

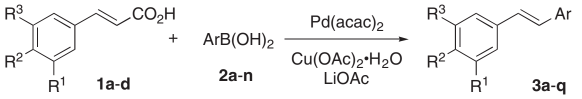
Hydroxylated cinnamic acids including ferulic acid are widely present in plants and are readily available from biomass as building blocks for high-volume manufacturing.[1] However, the derivatization methods of such sustainable starting marerials have been less explored and thus their development is strongly desired. Although decarboxylation and amidation reactions to form styrenes and cinnamamides have been described,[1b,1c] there are only a few examples of direct cross-coupling involving C–C bond formation.[2]

Meanwhile, we have continuously conducted research on developing new coupling methods for the synthesis of relatively complicated molecules from readily available, small molecules.[3] Recently we reported the couplings of simple benzoic and acrylic acids with alkynes under Rh-, Ir-, or Pd-catalysis to construct fused aromatic and heteroaromatic molecules.[4] During our further study of the catalytic reactions of organic acids, it has been revealed that the coupling of the hydroxylated cinnamic acids with arylboronic acids can smoothly proceed under Pd-catalysis accompanied by decarboxylation to form the corresponding hydroxylated stilbenes. Such stilbenes have been of considerable interest due to their interesting biological[5] and photophysical properties.[6] Compared with a conventional synthetic method involving the reaction sequence of the decarboxylative bromination of cinnamic acids (path *a* in Scheme 1) and the subsequent Suzuki–Miyaura coupling of the resulting bromostyrenes with arylboronic acids (path *b*),[7] the present halogen-free process is straightforward and atom-economical (path *c*).

In an initial attempt, the reaction of ferulic acid (**1a**) with phenylboronic acid (**2a**) was examined under various reaction conditions (see the Supporting Information). As a result, it was found that their decarboxylative coupling proceeded smoothly by using Pd(acac)$_2$ (acac = acetylacetonate; 5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), and LiOAc (4 equiv) as catalyst, oxidant, and additive, respectively, in DMF at 60 °C under N_2 to produce stilbene **3a** in 90% yield ($R^1 = OMe$, $R^2 = OH$, $R^3 = H$, Ar = Ph in eq 1; Entry 1 in Table 1).



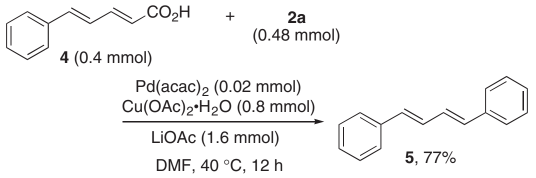
Scheme 1.



(1)

Table 1 also summarizes the results for the couplings of various cinnamic acids **1a**–**1d** with arylboronic acids **2a**–**2n**. A series of 4-substituted phenylboronic acids **2b**–**2l** reacted with **1a** to selectively produce the corresponding stilbenes **3b**–**3l** (Entries 2–12). 3-Methylphenylboronic acid (**2m**) and 2-naphthylboronic acid (**2n**) efficiently coupled with **1a** to give **3m** and **3n**, respectively (Entries 13 and 14). Not only ferulic acid but also sinapinic acid (**1b**) and coumaric acid (**1c**), which are also present in plants, reacted with **2a** to afford the corresponding hydroxylated stilbenes **3o** and **3p** (Entries 15 and 16). Cinnamic acids possessing an electron-donating group at their 4-position are known to readily undergo decarboxylation.[1b,8] As expected, 4-(dimethylamino)cinnamic acid (**1d**) underwent the decarboxylatve coupling to give 4-dimethylaminostilbene (**3q**) in 71% yield (Entry 17). In contrast, the reaction of unsubstituted cinnamic acid was sluggish even at 120 °C to form stilbene in only 14% yield.

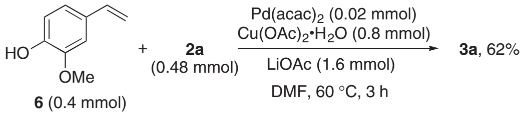
It was found that 5-phenyl-2,4-pentadienoic acid (**4**) also underwent the decarboxylative coupling at 40 °C to afford 1,4-diphenyl-1,3-butadiene (**5**) in 77% yield (eq 2).



(2)

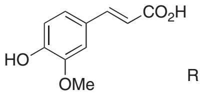
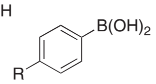
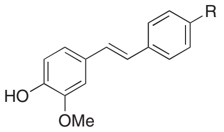
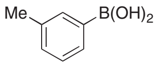
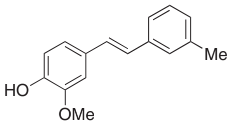
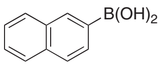
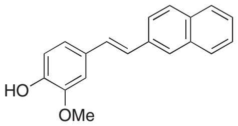
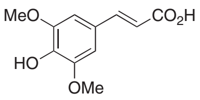
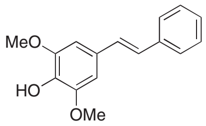
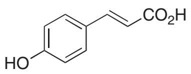
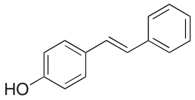
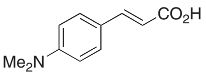
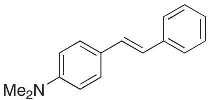
A plausible mechanism for the present coupling is illustrated in Scheme 2. Initial transmetalation of the added Pd(II) species with arylboronic acids **2** followed by ligand exchange with cinnamic acids **1** gives arylpalladium carboxylate intermediates **A**.[2] The subsequent decarboxylation and reductive elimination afford stilbenes **3**. The resulting Pd(0) species may be reoxidized with the added Cu(II) compound.

Another possible reaction sequence may involve the initial decarboxylation of **1** to form the corresponding styrenes which then undergo arylation with **2** (oxidative Mizoroki–Heck reaction).[9] It was confirmed that during the reaction of **1a** with **2a** at an elevated temperature of 120 °C, a small amount of 4-hydroxy-3-methoxystyrene (**6**) was detected by GC-MS,[8] while not at all at 60 °C. The reaction of **6** with **2a** at 60 °C proceeded to give **3a** in a meaningfully lower yield (62% GC yield) than that from **1a** and **2a** (Entry 1 in Table 1), part of **6** being consumed by unidentified side reactions (eq 3).

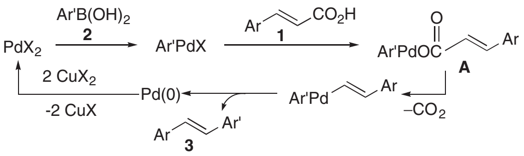


(3)

Table 1. Reaction of cinnamic acids **1** with arylboronic acids **2**[a]

Entry	1	2	Product, yield/%[b]
			
1	**1a**	**2a**: R = H	**3a**: R = H, 90 (76)
2		**2b**: R = Me	**3b**: R = Me, 92 (81)
3		**2c**: R = *t*-Bu	**3c**: R = *t*-Bu, 81 (76)
4		**2d**: R = OMe	**3d**: R = OMe, 76 (62)
5		**2e**: R = NMe$_2$	**3e**: R = NMe$_2$, 70 (51)
6		**2f**: R = F	**3f**: R = F, 72 (61)
7		**2g**: R = Cl	**3g**: R = Cl, 80 (60)
8		**2h**: R = Br	**3h**: R = Br, 41 (36)
9		**2i**: R= Ph	**3i**: R = Ph, 66 (61)
10		**2j**: R = CO$_2$Me	**3j**: R = CO$_2$Me, 68 (58)
11		**2k**: R = CF$_3$	**3k**: R = CF$_3$, 62 (62)
12		**2l**: R= CHO	**3l**: R = CHO, 60 (57)
			
13	**1a**	**2m**	**3m**, 91 (74)
			
14	**1a**	**2n**	**3n**, 80 (72)
			
15	**1b**	**2a**	**3o**, 89 (82)
			
16[c]	**1c**	**2a**	**3p**, 53 (53)
			
17	**1d**	**2a**	**3q**, 71 (70)

[a]Reaction conditions: **1** (0.4 mmol), **2** (0.48 mmol), Pd(acac)$_2$ (0.02 mmol), Cu(OAc)$_2$•H$_2$O (0.8 mmol), and LiOAc (1.6 mmol) in DMF (2.5 mL) at 60 °C for 8 h under N$_2$. [b]GC yield based on the amount of **1** used. Value in parentheses indicates yield after purification. [c]At 80 °C.



Scheme 2.

These facts suggest that the sequence involving oxidative Mizoroki–Heck reaction may partly participate to variable extent depending on the reaction conditions, while the catalytic cycle in Scheme 2 may occur as the significant route. No matter which sequences are involved, the direct use of cinnamic acids **1** rather than the corresponding styrenes appears to be advantageous due to their stabilities and availabilities.[10]

In summary, we have demonstrated that the palladium-catalyzed arylation of hydroxylated and aminated cinnamic acids with arylboronic acids proceeds efficiently accompanied by decarboxylation.[11] These reactions provide straightforward routes to the corresponding stilbene derivatives, which are of interest due to their biological and photophysical properties.

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10. For example, ferulic acid (Aldrich, U.S.$ 87 for 100 g) is significantly cheaper than the corresponding styrene **6** (Aldrich, U.S.$ 496 for 100 g).
11. Supporting Information is available electronically on the CSJ-Journal Website, http://www.csj.jp/journals/chem-lett/index.html.