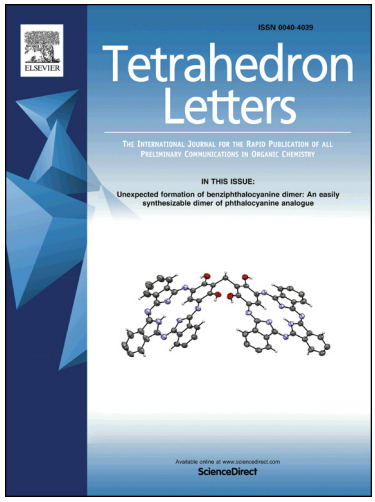

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Palladium Catalyzed Synthesis of Mandelate Derivatives from Arylboronic Acids and Glyoxylate Hemiacetals

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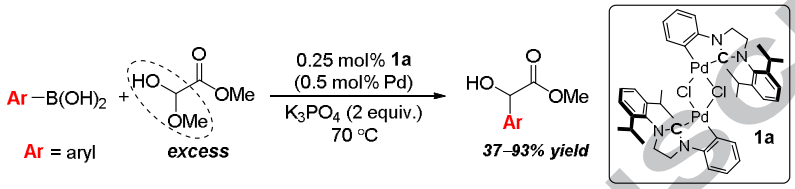
Mariko Sugaya[a], Tetsuya Yamamoto[b,] * and Hiraku Shinozaki



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Palladium Catalyzed Synthesis of Mandelate Derivatives from Arylboronic Acids and Glyoxylate Hemiacetals

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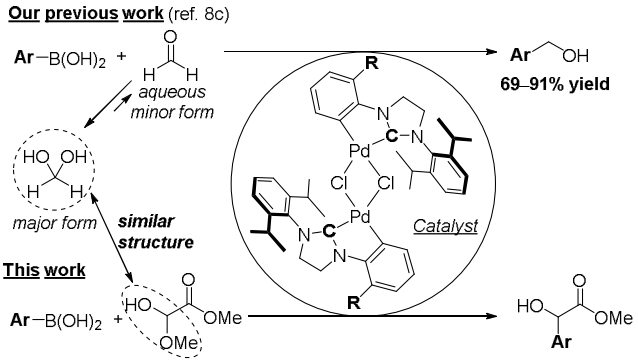
ABSTRACT

NHC-coordinated cyclometalated palladium(II) catalyzed addition of arylboronic acids to methyl 2-hydroxy-2-methoxyacetate gave corresponding various functionalized methyl mandelate derivatives in good yields.

As mandelate derivatives are scalable synthetic building blocks and will be readily transformed to other utilized functionalized molecules such as 1,2-diols β-amino alcohols and α-amino acid derivatives, they are key intermediates for various medicine such as Plavix[1] and Duloxetine.[2] The traditional syntheses of mandelate derivatives are two routes, the hydrolysis of cyanohydrins[3] and the Friedel-Crafts arylation of glyoxalate derivatives,[2,4,5] although each have their specific limitations. The former route needs the use of toxic cyano reagents such as HCN in its synthetic process. The latter route is limited to electron-rich aromatic compounds[5c,e] and five-membered heteroaromatic compounds.[2,5a,b,d–g] In the past two decades, transition-metal catalyzed 1,2-addition of arylboron reagents to carbonyl compounds has been developed as the one of the important synthesis of benzylic alcohols with wide range of functional group. [6–8] Although the catalytic additions have been applied to synthesis of mandelate derivatives from glyoxalates,[9] the use of glyoxalate hemiacetals as substrate have not been examined in these reaction.

Previously, we demonstrated that the NHC-coordinated cyclometalated palladium (II) complexes have excellent catalytic activity for the hydroxymethylation of arylboronic acids using aqueous formaldehyde.[8c] Although aqueous formaldehyde is an equilibrium mixture of formaldehyde and its hydrated form (methanediol) and the dominant form is methanediol in this equilibrium,[10] the palladium catalyzed hydoxymethylation of arylboronic acids was proceeded smoothly and effectively. From the results, we have focused our attention on structures of glyoxylate hemiacetals which have a similar structure as methanediol and envisaged that the palladium catalysts would be useful for the arylation of glyoxylate hemiacetals using arylboronic acids (Scheme 1).



Scheme 1. Strategy of Pd-catalyzed 1,2-addition to hemiacetal.

Table 1 lists the survey of a NHC-coordinated cyclometalated palladium (II) complex in the arylation of methyl 2-hydroxy-2-methoxyacetate **2** using 4-biphenylboronic acid **3a**. Predictably, complex **1a** acted as a suitable catalyst for this reaction with 0.5 mol% catalyst loading and provided the corresponding alcohol **4a** in 88% yield (entry 1). Methyl or phenylthio-substituted NHC coordinated complexes **1b** and **1c** that exhibited remarkable catalytic activity compared to **1a** in the catalytic

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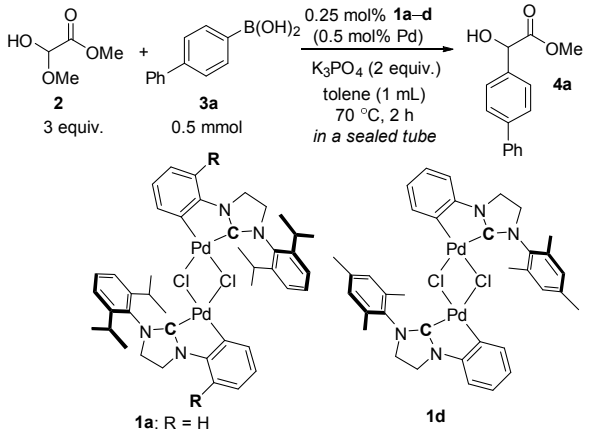
hydroxymethylation of arylboronic acids[8c] although showed slightly poor catalytic activity in this reaction (entries 2 and 3). The catalytic activity significantly decreased by replacing the 2,6-diisopropylphenyl group of **1a** with mesityl groups (entry 4).

Table 1. Survey of NHC-coordinated cyclometalated palladium (II) complexes



Entry	Catalyst	Yield (%)[a]
1	**1a**	88
2	**1b**	83
3	**1c**	85
4	**1d**	67

[a] Isolated Yields.

Then, we examined the correlation of the yield of **4a** on the amount of hemiacetal **2** in **1a** catalyzed addition of **3a** (Figure 1). The yields tended to rise as the increase of the amount of **1a.** In the region of 1–2 equivalent of hemiacetal **2**, the yields and the amount of hemiacetal **2** showed good linear correlation. The yield improved dramatically by using more than 2 equivalent of hemiacetal **2** but scarcely raised even if the amount of hemiacetal **2** increased to 4 from 3 equivalent.

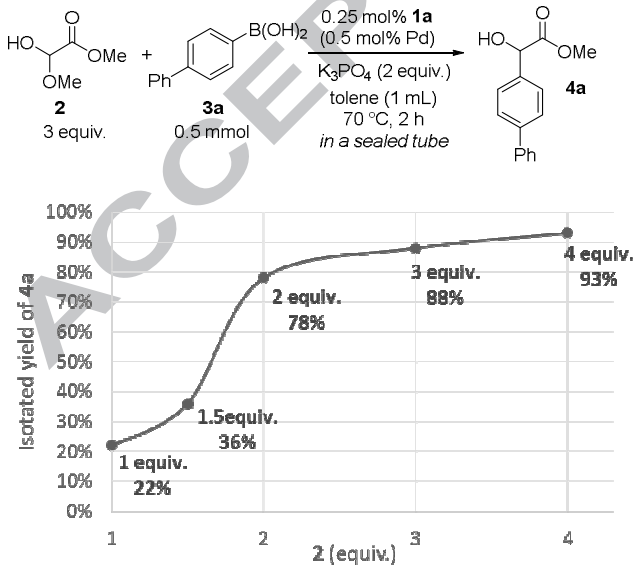
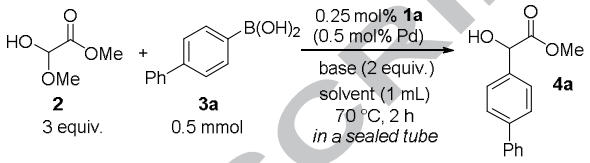


Figure 1. The dependence of the yield of **4a** on the amount of **2**

Further optimization of reaction conditions of the **1a**-catalyzed addition of 4-biphenylboronic acid **3a** and hemiacetal **2** is summarized in Table 2. Although high polar solvent such as DMF was no effective for the reaction, the yield by the use of low polor solvents such as 1,4-dioxane, THF and 1,2-dichloroethane instead of toluene provided almost the same yields (entries 1–4). Carbonate salts such as Cs_2CO_3 and K_2CO_3 were slightly less effective than K_3PO_4 for this addition (entries 5 and 6). The yield was declined to 39% by the use of CsF. (entry 7). Ethyl 2-hydroxy-2-ethoxyacetate instead of hemiacetal **2** was usable for this reaction and afforded the corresponding ethyl 2-([1,1'-biphenyl]-4-yl)-2-hydroxyacetate in 81% yield (entry 8).

Table 2. The optimization of reaction conditions



Entry	Base	Solvent	Yield (%)[a]
1	K_3PO_4	1,4-Dioxane	81
2	K_3PO_4	THF	82
3	K_3PO_4	DCE[b]	75
4	K_3PO_4	DMF	trace
5	Cs_2CO_3	Touene	67
6	K_2CO_3	Touene	71
7	CsF	Touene	39
8[c]	K_3PO_4	Touene	81

[a] Isolated yields

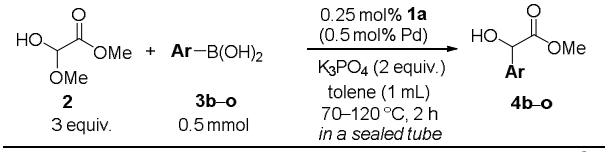
[b] 1,2-Dichloroethane

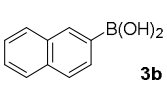
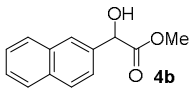
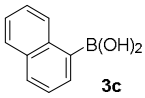
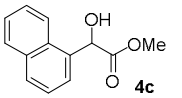
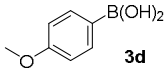
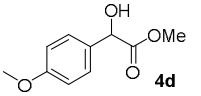
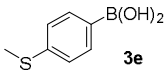
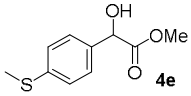
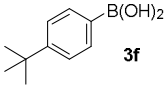
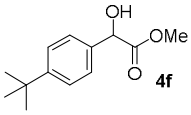
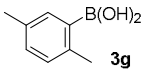
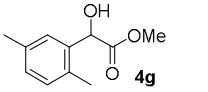
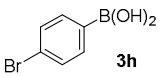
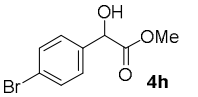
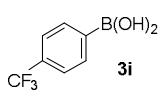
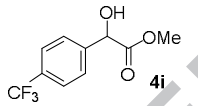
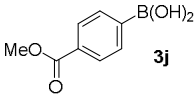
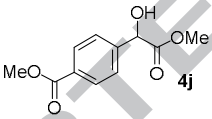
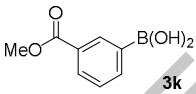
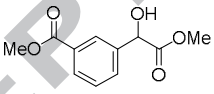
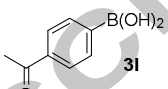
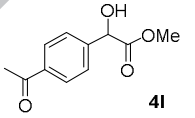
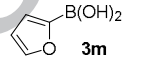
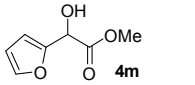
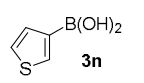
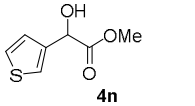
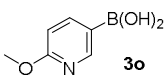
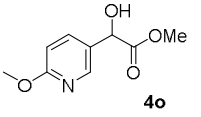
[c] Ethyl 2-hydroxy-2-ethoxyacetate was used instead of **2**.

The scope and limitation of the **1a**-catalyzed addition of arylboronic acids with various functional groups to hemiacetal **2** is summarized in Table 3. Naphthalen-2-ylboronic acid and weak electron donating or withdrawing groups such as methylthio, trifluoromethyl, *tert*-butyl and methoxycarbonyl groups substituted arylboronic acids were converted to the desired products in good to excellent yields, but 4-methoxyphenylboronic acid and 4-acetylphenylboronic acid gave the corresponding alcohols in moderate yields (entries 1, 3–5 and 9–12). Moreover, the reaction proceeded smoothly even though sterically bulky arylboronic acids such as Naphthalen-1-ylboronic acid and 2,5-dimethylphenylboronic acid was used (entries 2 and 6). Bromo substituted arylboronic acids reacted in moderate yields, although the bromine atom on the aromatic ring remained intact in this reaction condition (entry 7). Heteroarylboronic acids such as furan-, thiophen- and pyridineboronic acids were useful for this reaction but were low reactivity (entries 13–15).

In conclusion, we developed the palladium catalyzed arylation of methyl 2-hydroxy-2-methoxyacetate using aryl- and heteroarylboronic acids to give corresponding various functionalized methyl mandelate derivatives.

Table 3. Substrate scope of arylboronic acids



Entry	Arylboronic acid **3**	Product **4**	Yield (%)[a]
1	 **3b**	 **4b**	82
2	 **3c**	 **4c**	74
3	 **3d**	 **4d**	63
4	 **3e**	 **4e**	82
5	 **3f**	 **4f**	90
6	 **3g**	 **4g**	70
7	 **3h**	 **4h**	53
8	 **3i**	 **4i**	79
9	 **3j**	 **4j**	75
10	 **3k**	 **4k**	88
11	 **3l**	 **4l**	45[b]
12	 **3m**	 **4m**	56[c]
13	 **3n**	 **4n**	71
14	 **3o**	 **4o**	37[b,d]

[a] Isolated yield.
[b] The reactions using 1.0 mmol arylboronic acid were carried out at 120 °C.
[c] The reactions using 1.0 mmol arylboronic acid were carried out at 100 °C
[d] 1.0mmol of **3o** was used.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

· Synthesis of mandelate derivatives from hemiacetals such as methyl 2-hydroxy-2-methoxyacetate.
· Cyclometalated NHC-Pd(II) complex was used as highly reactive catalyst.
· The reactions showed functional groups tolerance.