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Suzuki–Miyaura Coupling Reaction of Boronic Acids and Ethyl Glyoxylate: Synthetic Access to Mandelate Derivatives

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The palladium-catalyzed coupling reaction of arylboronic acids with ethyl glyoxylate provides a straightforward method for the synthesis of mandelic esters. $Pd_2(dba)_3 \cdot CHCl_3$ in combination with 2-di-*tert*-butylphosphanylbiphenyl as the catalytic system and Cs_2CO_3 as the base were used. The reaction tolerates a wide range of functionalized boronic acids. Mandelic esters were isolated in good-to-excellent yields with a variety of neutral, slightly electron-rich, and slightly electron-poor substituents.

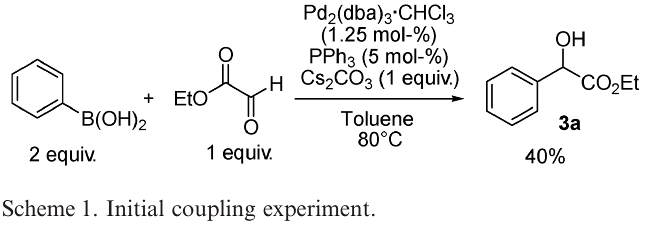
Introduction

As a result of their high stability, easy handling, and nontoxicity, organoboronic acids are useful reagents for carbon–carbon bond formation reactions with various electrophiles in the presence of transition metals.[1] Recently, more attention has been directed to the addition of a metal–carbon bond to electrophiles bearing a carbon–heteroatom double bond. Particularly, the addition of organometallic reagents to aldehydes remains an attractive topic, especially for the asymmetric issue of the products, and it is relatively undiscovered if we consider the limited examples in which transition metals are used. In 1998, Miyaura and coworkers reported that 1,2-addition of phenylboronic acid to aldehydes was catalyzed by a rhodium(I) complex.[2] In the following years, different procedures using Rh catalysts were developed.[3] In comparison to Rh catalysts, Pd catalysts for the 1,2-addition of arylboronic acids to aldehydes are relatively rare. Ohta described addition reactions of arylboronic acids to aromatic aldehydes catalyzed by Pd/PPh_3 complexes in the presence of chloroform.[4] Kondo and Aoyama reported the $Pd(OAc)_2$/tol-binap complex as a chloroform-free catalyst.[5] Hu proposed anionic palladacycles for the 1,2-addition of arylboronic acids to aromatic and aliphatic aldehydes at room temperature.[6] More recently, Shirai and Kuriyama described efficient 1,2-addition reactions of aryl-, heteroaryl-, and alkenylboronic acids to aromatic, heteroaromatic, and aliphatic aldehydes catalyzed by a palladium/thioether–imidazolinium chloride system.[7] In connection with a project devoted to extend new developments around the Suzuki coupling reaction,[8] we recently described the first stereoselective application of Pd-catalyzed addition of boronic acids to aldehydes for the synthesis of pure chiral carbinols.[9]

Herein we report a new catalytic system for the Pd-catalyzed coupling reaction of arylboronic acids and ethyl glyoxylate to give an original method for the preparation of α-hydroxy esters. Indeed, mandelate derivatives are important synthetic building blocks in preparative organic chemistry owing to their versatile functional groups, which may be easily transformed into other functionalities, for example, diols, halo or amino derivatives, and epoxides. This methodology provides an efficient strategy for the addition of organometallic compounds to highly functionalized glyoxylates under mild conditions.

Results and Discussion

Our first experiment was performed by the addition of phenylboronic acid (2 equiv.) to ethyl glyoxylate (1 equiv.) by using the conditions already described,[4,9] that is, $Pd_2(dba)_3 \cdot CHCl_3$ (1.25 mol-%), triphenylphosphane (5 mol-%), and Cs_2CO_3 (1 equiv.) in toluene at 80 °C, and we obtained ethyl mandelate **3a** as the cross-coupling product in only 40% yield (Scheme 1).



Scheme 1. Initial coupling experiment.

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Because ligands always play important roles in metal-catalyzed chemistry, we then turned our attention to the effect of ligands. We screened a wide range of mono- and bidentate ligands (Figure 1).

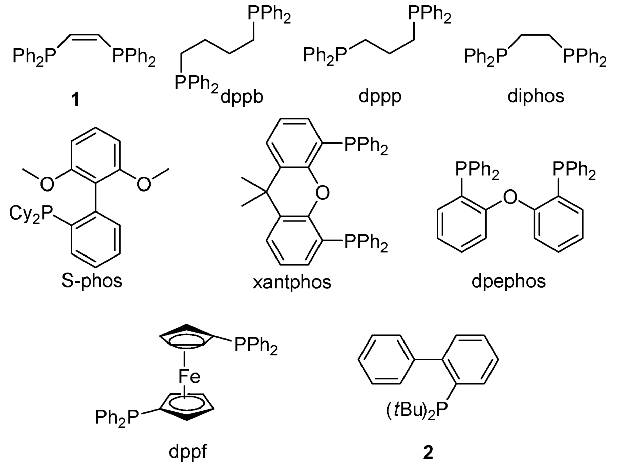
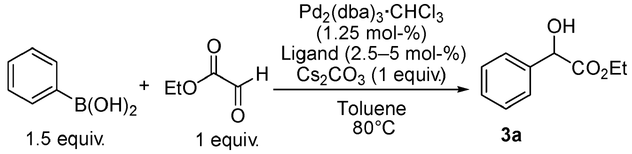


Figure 1. Tested phosphane ligands in Pd-catalyzed addition of phenylboronic acid to ethyl glyoxylate.

Through the screening process (Table 1), it was observed that electronic effects and steric hindrance played important roles in this system. Among various bidentate phosphanes with large bite angles and rigid or nonrigid skeletons (Table 1, entries 2–7), only diphos exhibited average catalytic activity (Table 1, entry 2). The dppp and dppb ligands (Table 1, entries 4 and 5), in which the phosphorus atoms are 1,3- and 1,4-positioned, respectively, have no catalytic activity. Furthermore, more-rigid biphosphanes **1** or dpephos as well as xantphos (Figure 1; Table 1, entries 3, 6, 7) were ineffective. To our delight, biarylphosphane ligands gave the desired product with isolated yields of 55% for S-phos[10] and 78% for 2-di-*tert*-butylphosphanylbiphenyl (**2**) (Table 1, entries 8 and 9) in reaction times of 7 and 8 h,

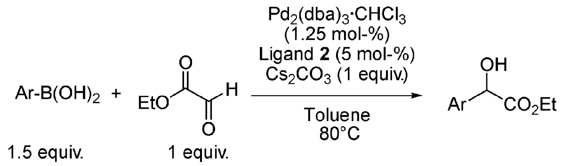
Table 1. Ligand effects in Pd-catalyzed addition of phenylboronic acid to ethyl glyoxylate.

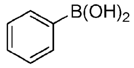
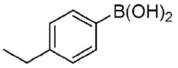
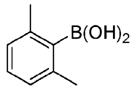
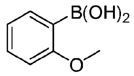
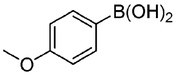
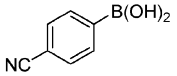
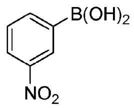
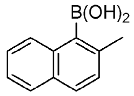
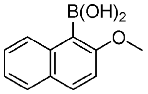
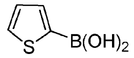
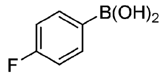
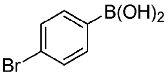
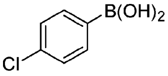
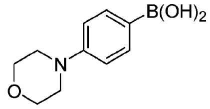
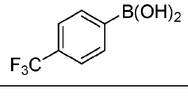


Entry	Ligand	Time [h]	Yield [%][c]
1	PPh_3[a]	24	40
2	diphos[b]	18	51
3	ligand **1**[b]	24	Trace
4	dppb[b]	27	0
5	dppp[b]	27	0
6	dpephos[b]	24	0
7	xantphos[b]	24	0
8	S-phos[a]	7	55
9	ligand **2**[a]	8	78
10	dppf[b]	30	0

[a] Reactions were carried out by using 5 mol-% ligand. [b] Reactions were carried out by using 2.5 mol-% ligand. [c] Isolated yields.

Table 2. Palladium-catalyzed addition of boronic acids to ethyl glyoxylate.[a]



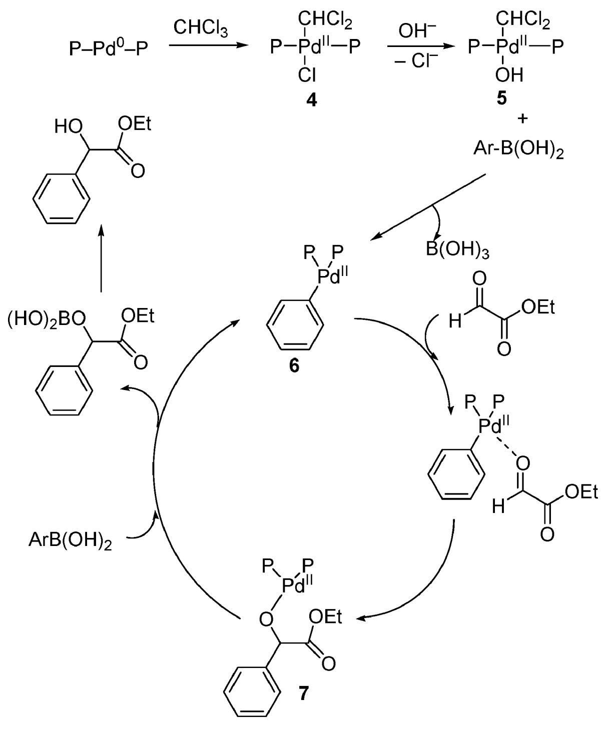
Entry	Ar-B(OH)2	Product	Time [h]	Yield [%][b]
1		**3a**	8	78
2		**3b**	9	83
3		**3c**	13	89
4		**3d**	8	87
5		**3e**	8	85
6		**3f**	23	37
7		**3g**	16	48
8		**4h**	18	41
9		**3i**	16	73
10		**3j**	16	98
11		**3k**	7	74
12		**3l**	7	79
13		**3m**	7	68
14		**3n**	7	87
15		**3o**	8	69

[a] The reactions were carried out with ethyl glyoxylate (solution in toluene, 50%) (1 mmol), boronic acid (1.5 mmol), Cs_2CO_3 (1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), and 2-di-*tert*-butylphosphanylbiphenyl (0.05 mmol) in dry toluene (3 mL) at 80 °C. [b] After column chromatography with unmetalated silica (see Supporting Information).

and we succeeded to decrease the amount of boronic acid involved in this reaction from 2 to 1.5 equiv. Bidentate phosphanes with large bite angles such as dppf (Table 1, entry 10), which was an excellent ligand in Rh-catalyzed additions of boronic acids to aldehydes,[2b] was completely ineffective under our reaction conditions.

To investigate the scope and limitations of this coupling reaction, we subjected various arylboronic acids bearing different electron-donating and electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions of the phenyl ring to the optimized catalytic system [i.e., $Pd_2(dba)_3 \cdot CHCl_3$ (1.25 mol-%), 2-di-*tert*-butylphosphanylbiphenyl (5 mol-%); Table 2].

We observed a high difference in the yields among phenyl boronic acids having electron-donating or electron-withdrawing groups. Nonactivated boronic acids with electron-withdrawing substituents in the *para* and *meta* positions (Table 2, entries 6 and 7) showed lower reactivities. However, in the case of the *p*-fluoro-, *p*-bromo-, *p*-chloro-, and *p*-trifluoromethylphenylboronic acids (Table 2, entries 11–13, 15), the corresponding ethyl mandelates were obtained in good yields, and these new compounds with strong withdrawing character should be very active for further reactions. However, we observed high yields for the reaction with aryl boronic acids having electron-donor substituents (Table 2, entries 2–5, 9, 14). Additionally electron-donor substituents in the *ortho* position (Table 2, entries 3, 4, 9) had no influence on the yield, which indicates that the reaction does not suffer from steric hindrance around the reacting center. Surprisingly, the mandelate derivative obtained from 2-methylnaphthylboronic acid was formed in a poor yield of 41 % (Table 2, entry 8). The palladium-catalyzed coupling reaction of ethyl glyoxylate with electron-rich thiophene boronic acid gave the corresponding coupling product in quantitative yield (Table 2, entry 10).



Scheme 2. Proposed mechanism for the addition of arylboronic acids to ethyl glyoxylate.

We propose a possible catalytic cycle of this reaction that shows that cationic Pd^{II} complexes are excellent catalysts for the addition of arylboronic acids to carbon–heteroatom multiple bonds owing to their high Lewis acidity and the existence of a vacant coordination site.[4,11] At first, oxidative addition of chloroform to phosphane-coordinated with Pd^0 would give chloromethyl-coordinated Pd^{II} intermediate **4**, which produces hydroxyl Pd^{II} species **5** by counteranion exchange. Therefore, transmetalation between the arylboronic acid and hydroxyl Pd^{II} species **5** occurs to generate aryl Pd^{II} intermediate **6** and after coordination of **6** to an aldehyde functionality, the insertion of the aldehyde into the carbon–palladium bond occurs to give palladium alkoxide **7**. Palladium alkoxide **7** is then hydrolyzed to give the corresponding alcohol and aryl Pd^{II} intermediate **6** is recovered (Scheme 2).

Conclusions

Efficient palladium-catalyzed addition of arylboronic acids to ethyl glyoxylate was realized by using the catalytic system of $Pd_2(dba)_3 \cdot CHCl_3$/2-di-*tert*-butylphosphanylbiphenyl to afford differently substituted mandelic ester derivatives in excellent yields. Further investigations on an asymmetric version of this reaction are underway.

Experimental Section

General Procedure for Coupling of Boronic Acids and Ethyl Glyoxylate: To a suspension of boronic acid (1.5 mmol) and Cs_2CO_3 (1 mmol, 326 mg) in dry toluene (3 mL) was added $Pd_2(dba)_3 \cdot CHCl_3$ (0.0125 mmol, 13 mg), 2-di-*tert*-butylphosphanylbiphenyl (0.05 mmol, 15 mg) and ethyl glyoxylate (1 mmol) under an atmosphere of argon at room temperature. The temperature was increased to 80 °C, and the mixture was stirred for 7–24 h. The reaction was quenched with water (10 mL), and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried with sodium sulfate, filtered, and concentrated under vacuum. The resulting crude mixture was purified by flash chromatography with unmetalated silica (cyclohexane/EtOAc).

Supporting Information (see footnote on the first page of this article): Experimental procedures and details of compound characterization.

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