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Diastereoselective synthesis of β-amino ketone and acid derivatives by palladium-catalyzed conjugate addition

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ABSTRACT

The first diastereoselective synthesis of β-amino ketone and β-amino acid derivatives by palladium-catalyzed conjugate addition of arylboronic acids to chiral β-enamino ketones and β-enamino esters is reported. The catalytic system employing (S)-4-(*tert*-butyl)oxazolidin-2-one as the chiral auxiliary in water under an air atmosphere provides β-amino ketone and β-amino acid derivatives in high yields with excellent diastereoselectivity.

Introduction

Chiral β-amino ketones, β-amino acids and their derivatives are important structural motifs in a number of natural products and biologically active compounds, and various synthetic methods for their preparation have been developed in recent years [1]. Most of these approaches are based on the enzyme-catalyzed enantioselective hydrolysis of β-amino acid derivatives [2], enantioselective conjugate addition of carbon nucleophiles to β-enamino ketone and β-enamino acid derivatives [3,4], organocatalytic asymmetric Mannich reaction of imines with aldehydes or ketones [5], and diastereoselective reduction of β-enamino carbonyl compounds [6]. Among these methods, conjugate addition of carbon nucleophiles to β-enamino carbonyl compounds is most reported.

For enantioselective conjugate addition toward the synthesis of β-amino carbonyl compounds, most of the works are focused on conjugate addition of arylboronic nucleophiles to N, *N*-disubstituted α, β-unsaturated cyclic enaminones [3b,4], only a few are focused on acyclic enaminones. For example, Sibi reported addition of chiral organomagnesium amides to enamidomalonates [3c]. Hayashi [3a] and Wu [7] reported rhodium-catalyzed 1, 4-addition of arylboronic acids to β-enamino carbonyl compounds.

For most of conjugate addition of arylboronic acids to N, *N*-disubstituted acyclic enaminones, often accompanied by elimination reactions [3a,8], for example, Wan reported the reaction of N, *N*-disubstituted enaminones and boronic acids via palladium-catalyzed domino reaction to provide β, β-diaryl propiophenones [8].

For palladium-catalyzed reaction of arylboronic acids with β-enamino carbonyl compounds, conjugate addition and oxidative Heck reaction are competitive [4e–g]. Although several works about synthesis of β-aryl-substitued 4-piperidinone were reported [4a,b and d], none works about conjugate addition of arylboronic acids to acyclic enaminones were found, which could be easily converted to chiral primary amines or secondary amines. Palladium-catalyzed oxidative Heck reaction was reported by Park and coworkers, highly substituted enamides were synthesized via palladium-catalyzed oxidative Heck reaction of arylboronic acids with β-enamino ester, then via rhodium-catalyzed asymmetric hydrogenation to transform the enamides into β-amino acid derivatives [9].

On the other hand, rhodium [10] and palladium [11] catalyzed diastereoselective addition of arylboronic acids to chiral imines was successfully applied to the synthesis of α-amino carbonyl compounds. However, metal-catalyzed diastereoselective synthesis of β-amino carbonyl compounds was rarely reported [9].

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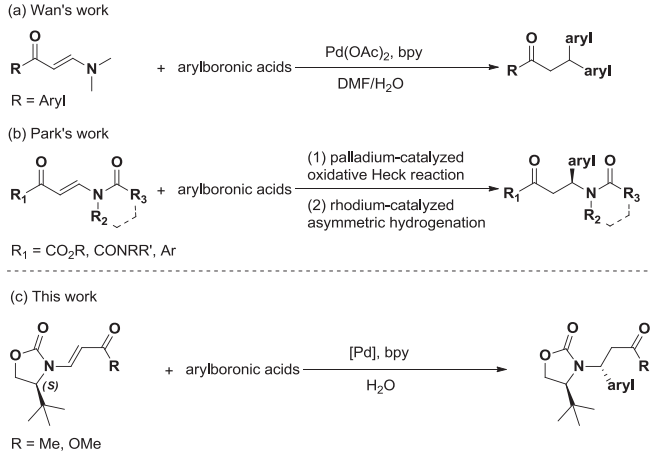
Recently, we have explored the palladium-catalyzed diastereoselective conjugate addition of arylboronic acids to chiral imides as a convenient method to obtain optically active 3-arylsubstitued acids [12]. Here we report a new and efficient diastereoselective conjugate addition of arylboronic acids to chiral β-enamino carbonyl compounds to give β-amino carbonyl derivatives in high yields with excellent diastereoselectivity by using $Pd(OAc)_2$/bpy complex as the catalyst. Notably, in this approach, water is used as the reaction solvent, which is green and economic (Scheme 1).

Results and discussion

Oxazolidinones are one of the most popular chiral auxiliaries used in many stereoselective transformations [13]. Based on the reference, chiral *N*-alkyl-substituted oxazolidinones could be successfully converted to chiral primary amines [14]. Firstly, (*S*)-4-phenyloxazolidin-2-one was chosen as the chiral auxiliary for optimization of the reaction, which was reacted with 3-butyn-2-one to give the corresponding (*S*,*E*)-3-(3-oxobut-1-en-1-yl)-4-phenyloxazolidin-2-one (**1a**) [15].

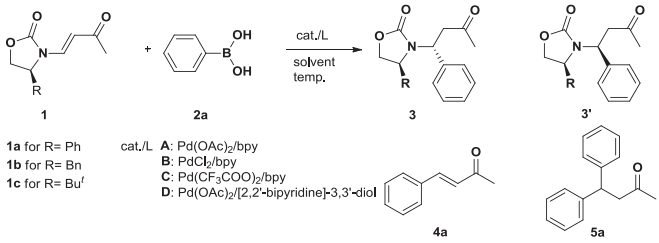


Scheme 1. Palladium-Catalyzed Reactions of Arylboronic Acids with β-Enamino Carbonyl Compounds.

Then, several reaction conditions of conjugate addition of phenylboronic acid (**2a**) to β-enamino ketone (**1a**) were examined (Table 1). A mixture of the β-enamino ketone **1a** (1 equiv), phenylboronic acid **2a** (2 equiv), $Pd(OAc)_2$ (0.05 equiv) and 2,2′-bipyridine (bpy) (0.2 equiv) in different solvents was surveyed. 1,4-Dioxane/H_2O, THF/H_2O, and MeOH which were often used for the palladium-catalyzed conjugate addition were tested for the reaction [16] (entries 1–3, Table 1). MeOH was found to perform the reaction smoothly to obtain the desired products in nearly full conversion (>99%) with a diastereoselective ratio (dr) of **3a/3′a** (71:29). And the conjugate addition products **3a** and **3′a** could be easily isolated by column chromatography. Then, different ratios of mixed solvent of water and MeOH were investigated (entries 4–5, Table 1), the results indicated that the dr value of **3a/3′a** (74:26) could be improved slightly by increasing the amout of H_2O (entry 5, Table 1). When the reaction was performed in pure water, the dr value of **3a/3′a** raised to 79:21 (entry 6, Table 1). Different catalysts were investigated when using water as reaction solvent (entries 6–9, Table 1), compared to other catalysts, $Pd(OAc)_2$/bpy showed better activity and diastereoselectivity.

Oxazolidinones with different substituents at chiral-carbon showed different diastereoselectivity [17]. When (*S*,*E*)-4-benzyl-3-(3-oxobut-1-en-1-yl)oxazolidin-2-one (**1b**) was used, 88:12 of dr value was detected (entry 10, Table 1). When (*S*,*E*)-4-(*tert*-butyl)-3-(3-oxobut-1-en-1-yl)oxazolidin-2-one (**1c**) was used, the reaction proceeded smoothly to give the desired products in excellent diastereoselectivity (98:2), and only trace of side product **4a** and **5a** were found (entry 11, Table 1) [3a,8].

Table 1
Screening of Reaction Conditions.[a]



Entry	1	cat./L	Solvent	Temp (°C)	conv. (%)[b]	dr[c] (**3**/**3′**)
1	**1a**	**A**	Dioxane/H_2O (10:1)	80	20	57:43
2	**1a**	**A**	THF/H_2O (10:1)	80	16	69:31
3	**1a**	**A**	MeOH	80	99	71:29
4	**1a**	**A**	MeOH/H_2O (1:1)	80	97	71:29
5	**1a**	**A**	MeOH/H_2O (1:3)	80	100	74:26
6	**1a**	**A**	H_2O	80	100	79:21
7	**1a**	**B**	H_2O	80	100	74:26
8	**1a**	**C**	H_2O	80	96	77:23
9	**1a**	**D**	H_2O	80	29	60:40
10	**1b**	**A**	H_2O	80	100	88:12
11[d]	**1c**	**A**	H_2O	80	100	98:2
12[e]	**1c**	**A**	H_2O	100	100	98:2
13	**1c**	**A**	H_2O	70	100	99:1
14	**1c**	**A**	H_2O	60	92	99:1

[a] Reaction conditions: under an air atmosphere, chiral β-enamino ketone **1** (0.5 mmol), phenylboronic acid (**2a**) (1 mmol), catalyst (0.025 mmol), ligand (0.1 mmol), solvent (2 mL), time (12 h), in a sealed Schlenk tube.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] The diastereoselective ratio (dr value) was determined according to the ^{1}H NMR peak areas of α-H in **3** and **3′** from the reaction mixture of **1** with **2**.
[d] 2% of **4a** was found by ^{1}H NMR analysis of the crude reaction mixture.
[e] 6% of **4a** was found by ^{1}H NMR analysis of the crude reaction mixture.