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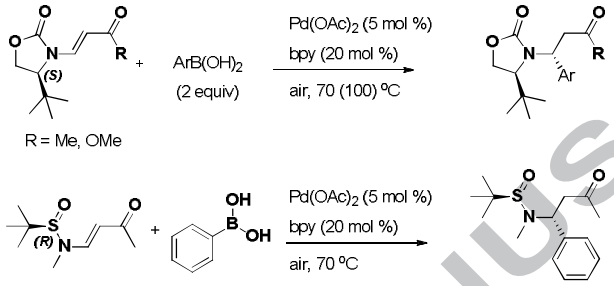

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Diastereoselective Synthesis of β-Amino Ketone and Acid Derivatives by Palladium-Catalyzed Conjugate Addition

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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, 4d] 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]

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

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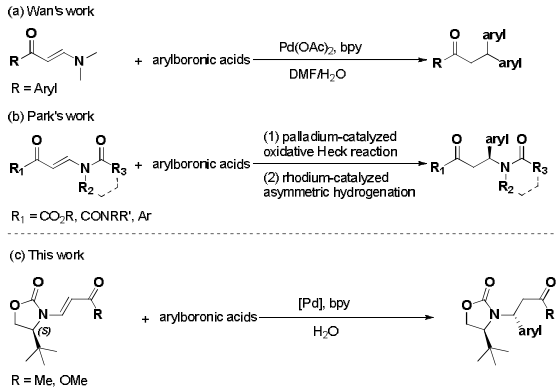
efficient diastereoselective conjugate addition of arylboronic acids to chiral β-enamino carbonyl compounds to give β-amino carbonyl derivatives in high yields with excellent diastereoselectivity by using $Pd(OAc)_2$/bpy complex as the catalyst. Notably, in this approach, water is used as the reaction solvent, which is green and economic (scheme 1).



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

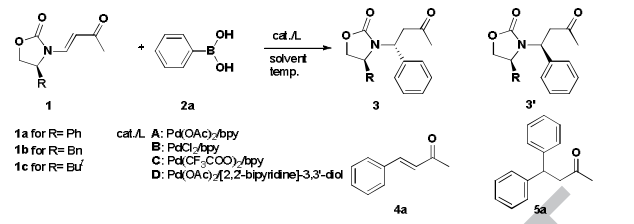
Results and Discussion

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]

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.

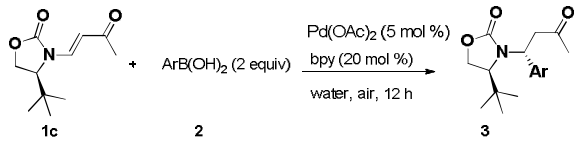
Finally, the reaction temperature was tested. Increasing the reaction temperature to 100 °C, the side product **4a** and **5a** were formed (entries 11-12, Table 1). Decreasing the reaction temperature from 80 °C to 70 °C, full conversion and high diastereoselective ratio **3c/3'c** (99:1) were detected without the formation of the side product (entry 13, Table 1).

With the optimal conditions in hand, we began to survey the scope of the reaction of different arylboronic acids with diverse substituents on the benzene rings, and the results were summarized in Table 2.

The reactions of arylboronic acids with electron-donating substituents such as methyl and methoxyl on the benzene rings (entries 2-7, Table 2) proceeded smoothly under the optimal conditions to give the desired products in high yields with excellent diastereoselectivity (99:1). Arylboronic acids substituted with hydroxyl gave lower yield together with the formation of side products **4h** and **5h** of the domino reactions[3a, 8] (entry 8, Table 2). When (3-aminophenyl)boronic acid was reacted with **1c**, only side products of **4i** and **5i** were found (entry 9, Table 2). Arylboronic acids with electron-withdrawing substituents on the benzene rings (entries 6-11, Table 2) could not reacted with **1c** at 70 °C. When the reaction temperature was increased to 100 °C, all the reaction could gave high conversion together with excellent diastereoselectivity except for (2-(trifluoromethyl)phenyl)boronic acid (entry 10, Table 2) and

[1,1'-biphenyl]-2-ylboronic acid (entry 16, Table 2). The reason for the failure of these two substrates was possibly due to steric hindrance in the *ortho*-position. Arylboronic acids possessing trifluoromethyl gave the desired products in lower yield together with the formation of the side products **4** and **5** (entries 11-12, Table 2). When the reaction time was prolonged to 24 h, (2-chlorophenyl)boronic acid gave the target product in 90% of conversion (entry 13, Table 2).

Table 2. Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to Chiral β-Enamino Ketone[a]



entry	Ar	temp (°C)	conv.(%)[b]	dr[b]	yield(%)[c]
1	Ph	70	100	99:1	**3ca** 96
2	*o*-MeC_6H_4	70	91	99:1	**3cb** 85
3	*m*-MeC_6H_4	70	100	99:1	**3cc** 95
4	*p*-MeC_6H_4	70	98	99:1	**3cd** 93
5	*o*-$OMeC_6H_4$	70	91	95:5	**3ce** 89
6	*m*-$OMeC_6H_4$	70	100	96:4	**3cf** 90
7	*p*-$OMeC_6H_4$	70	98	97:3	**3cg** 92
8[d]	*p*-HOC_6H_4	70	100	99:1	**3ch** 49
9[d]	*m*-$NH_2C_6H_4$	70	100	-	-
10	*o*-$CF_3C_6H_4$	100	0	-	-
11[d]	*m*-$CF_3C_6H_4$	100	100	99:1	**3ck** 47
12[d]	*p*-$CF_3C_6H_4$	100	100	98:2	**3cl** 45
13[d, e]	*o*-ClC_6H_4	100	90	99:1	**3cm** 71
14[d]	*m*-ClC_6H_4	100	>99	98:2	**3cn** 82
15[d]	*p*-ClC_6H_4	100	>99	98:2	**3co** 85
16	2-phenyl	100	0	-	-

[a]Reaction conditions: under an air atmosphere, chiral β-enamino ketone (**1c**) (0.5 mmol), arylboronic acids (**2**) (1 mmol), $Pd(OAc)_2$ (0.025 mmol), 2,2'-bipyridine (0.1 mmol), H_2O (2 mL), time (12 h), in a sealed Schlenk tube.

[b]Determined by ^1H NMR analysis of the crude reaction mixture.

[c]Isolated yield.

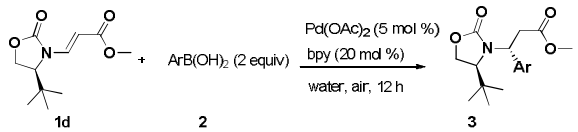
[d]Side product **4** and **5** are detected.

[e]The reaction time is 24 h.

Having these good results in hand, we began to apply this reaction to synthesize β-amino acid derivatives. Then chiral β-enamino ester (**1d**) was synthesized[15] to react with various arylboronic acids (entries 1-8, Table 3) under the optimal conditions. Gladly, all the reactions proceeded smoothly and gave the desired products in high yield with excellent diastereoselectivity. In addition, thiophen-3-ylboronic acid also worked well in the reaction (entry 9, Table 3). All of the major diastereomers **3** could be easily isolated by column chromatography.

Gram-scale experiment was also performed and optically pure **3ca** was obtained with high yield (95%), together with excellent diastereoselectivity (dr up to 99:1). The results indicated that the present method was practical and effective for gram-scale experiment.

Table 3. Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to β-Enamino Ester[a]



entry	Ar	temp (°C)	conv.(%)[b]	dr[b]	yield(%)[c]
1	Ph	70	100	99:1	**3da** 97
2	*o*-MeC_6H_4	70	90	99:1	**3db** 82
3	*m*-MeC_6H_4	70	100	98:2	**3dc** 93
4	*p*-MeC_6H_4	70	100	98:2	**3dd** 95
5[d]	*p*-HOC_6H_4	70	100	94:6	**3dh** 65
6[d, e]	*o*-ClC_6H_4	100	92	93:7	**3dm** 82
7	*m*-ClC_6H_4	100	100	99:1	**3dn** 95
8	*p*-ClC_6H_4	100	100	98:2	**3do** 91
9	3-thienyl	70	96	96:4	**3dr** 86

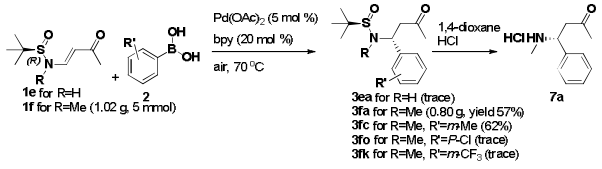
[a]Reaction conditions: under an air atmosphere, chiral β-enamino ester (**1d**) (0.5 mmol), arylboronic acids (**2**) (1 mmol), $Pd(OAc)_2$ (0.025 mmol), 2,2'-bipyridine (0.1 mmol), H_2O (2 mL), time (12 h), in a sealed Schlenk tube.

[b]Determined by ^1H NMR analysis of the crude reaction mixture.

[c]Isolated yield.

[d]Side product **4** and **5** are detected. [e]The reaction time is 24 h.

2-Methylpropane-2-sulfinamide used as chiral auxiliary had been applied in lots of diastereoselective synthesis of chiral amino compounds.[10, 18] However, its application in the synthesis of β-amino carbonyl compounds used as chiral auxiliary for conjugate addition was rarely reported. Firstly, when chiral β-enamino ketone **1e** containing amino hydrogen reacted with phenylboronic acid **2a** under the optimal conditions, only trace product was detected. Then methyl iodide reacted with **1e** to obtain β-enamino ketone **1f**. When **1f** reacted with phenylboronic acid **2a** or *m*-tolylboronic acid **2c** under the optimal conditions, **3fa** (dr: 90:10) or **3fc** (dr > 99:1) was obtained in moderate yield with good diastereoselectivity, together with the formation of side product **5a** or **5c**[3a, 8]. When (4-chlorophenyl)boronic acid **2o** or (3-(trifluoromethyl)phenyl)boronic acid **2k** reacted with **1f**, the major product was **5o or 5k**, only trace amount of **3fo** or **3fk** could be found. When β-enamino ketone **1f** was scaled up to 5 mmol, **3fa** was obtained with 57% isolated yield. **3fa** could be easily hydrolyzed to give (S)-4-(methylamino)-4-phenylbutan-2-one hydrochloride **7a** with 100% yield, as shown in Scheme 2.



Scheme 2. Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to Chiral β-Enamino Ketone **1f**, and Deprotection of **3fa** Leading to **7a**.

Then, single crystals of **3dn** were prepared to further confirm the absolute configuration, and the structure was unambiguously confirmed by X-ray diffraction analysis (Figure 1). The X-ray diffraction analysis indicated that the conjugate addition intends to form the product **3dn** with the R-configuration.[19]

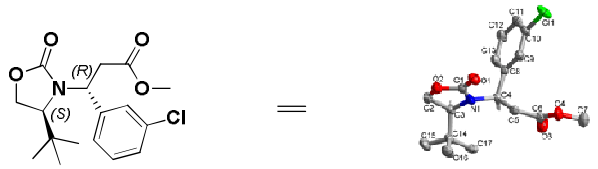
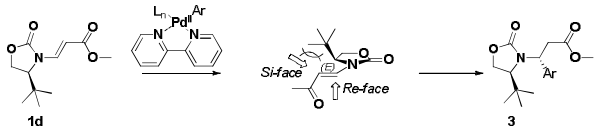


Figure 1. X-ray structure of 3dn

On the basis of the observed stereochemical outcome, the chiral induction can be explained using the model shown in Scheme 3. With the conformational preference, the chiral oxazolidinone auxiliary plays a distinct role in providing a key facial bias for the nucleophilic aryl group to approach from the less hindered *Re*-face, provides the preferred diastereomer **3** as illustrated.



Scheme 3. A Proposed Stereochemical Model

Conclusion

In summary, a high efficient palladium-catalyzed diastereoselective conjugate addition for the synthesis of optically active β-amino carbonyl compounds was developed by using (S)-4-(tert-butyl)oxazolidin-2-one and (R)-2-methylpropane-2-sulfinamide as chiral auxiliary, respectively. In this protocol, water is used as the reaction solvent, which is economical and green. Therefore, the present method provides a novel and valuable strategy for the synthesis of diverse optically active β-amino carbonyl compounds. In particular, (R)-2-methylpropane-2-sulfinamide works well in this protocol as a chiral auxiliary and the further study to improve the performance with various substrates is underway in our lab.

Acknowledgments

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19. Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1584454). See the Supporting Information for details. The absolute configuration of other products was tentatively assigned by analogy.

Highlights

- Palladium-catalyzed diastereoselective synthesis of optically active chiral β-amino ketone and β-amino acid derivatives.
- Employing (S)-4-(tert-butyl)oxazolidin-2-one and (R)-2-methylpropane-2-sulfinamide as the chiral auxiliary.
- Water was used as the reaction solvent.
- With high yields and excellent diastereoselectivity.