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Construction of highly enantiopure β,β-diaryl substituted glycine containing two contiguous stereocenters *via* asymmetric 1,6-conjugate addition

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ABSTRACT

Asymmetric construction of β,β-diaryl substituted glycine bearing two contiguous chiral centers remains a significant challenge. Herein, the application of the *para*-quinone methides (*p*-QMs) and Ni(II)- complex of glycine *via* 1,6-conjugate addition to achieve asymmetric synthesis of β,β-diaryl substituted glycine has been explored successfully. This protocol features operational simplicity, high diastereoselectivity, and recyclable chiral ligand, which provides a versatile approach to the synthesis of highly enantiopure β,β-diaryl substituted glycine.

1. Introduction

Non-natural α-amino acids widely exist in peptides, proteins, natural products and they play an important role in modern synthetic chemistry especially in medicinal chemistry due to their promising biological and pharmaceutical activities. Particularly, the enantiopure non-natural α-amino acids have attracted more attention among scientists.[1] Chiral β,β-diaryl substituted non-natural α-amino acids are an intriguing series which can be founded in a number of natural products and biologically active compounds, such as Hyalachelin A-C,[2] dipeptidyl peptidase IV (DPP-IV) inhibitor Denagliptin,[3] HIV inhibitor,[4] and thrombin inhibitor (Fig. 1),[5] and they normally performed as a key composition of the privileged structures in these biologically active molecules. Consequently, various powerful synthetic methods have been reported for the construction of chiral β,β-diaryl substituted α-amino acids, such as the simple nucleophilic addition to imino-esters, Michael addition, asymmetric hydrogenation, ring-opening strategies from aziridines and azetidines.[6] However, at present, most reported methods approaching to the construction of β,β-diaryl substituted glycine focused on molecules bearing identical β-aryl substituents.[7] Yu et al. used pyridine-type ligand to promote selective di-β-arylation of a broad range of carboxylic acids to synthesis chiral β,β-diaryl substituted α-amino acids.[8] Asymmetric synthesis of β,β-diaryl substituted glycine containing two contiguous chiral centers remains a significant challenge.

In recent years, *para*-quinone methides (*p*-QMs) has attracted much attention in the asymmetric synthesis[9] and the application of *p*-QMs to construct diaryl functionalized molecules *via* 1,6-conjugate addition is a prevailing strategy which is efficient and convenient. Recently, Molinaro et al. applied Suzuki-Miyaura coupling reaction to the synthesis of β,β-diaryl substituted α-amino acids (Scheme 1a), but multi-steps are proceeded.[10] Deng et al. reported copper-catalyzed addition of *p*-QMs with glycine Schiff bases for the synthesis of β,β-diaryl substituted α-amino acid

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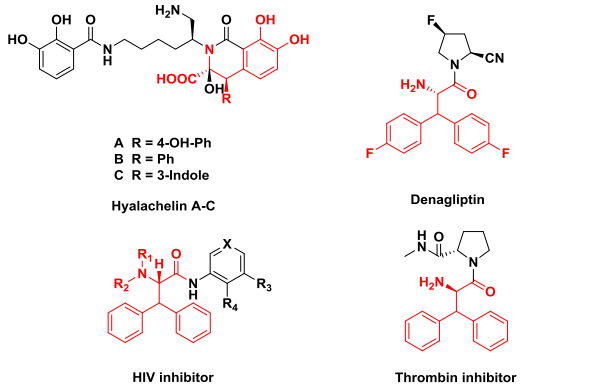
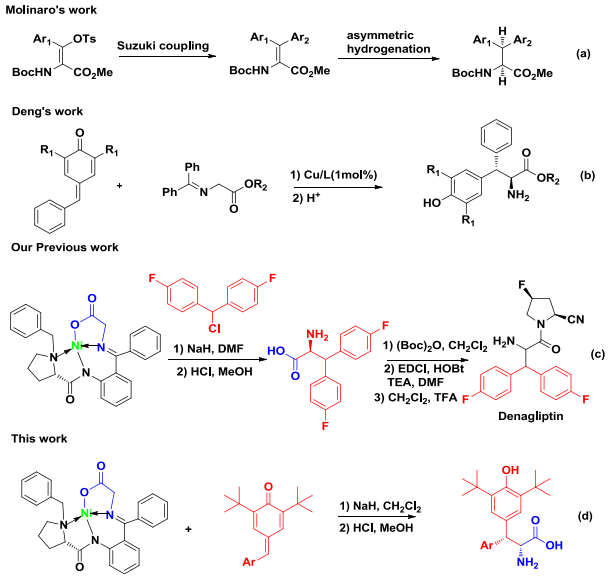


Fig. 1. Representative natural products and biologically active molecules containing β,β-diaryl substituted α-amino acids.



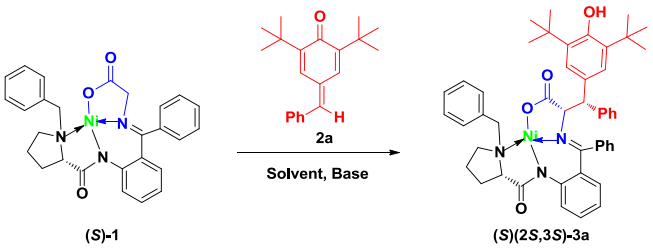
Scheme 1. Recent work and our strategies to construct chiral β,β-diaryl substituted α-amino acids.

derivatives bearing two contiguous chiral centers, but unfortunately, the reaction scope was limited due to the addition of Ph-Foxap catalyst which is noble (Scheme 1b).[11] In 2008, our group reported a method to construct a β,β-diaryl substituted amino acid with a chiral center by using Ni(II)-complex of glycine as a substrate *via* asymmetric alkylation reaction, and this methodology was successfully applied in the synthesis of a commercial DPP-IV inhibitor, Denagliptin (Scheme 1c).[12] Motivated by our strong interest in synthesizing chiral amino acids and characterizing the reactivity of *p*-QMs, we envisaged that β,β-diaryl substituted glycine containing two contiguous stereocenters could be achieved through asymmetric 1,6-conjugate addition of Ni(II)-complex of glycine to *p*-QMs (Scheme 1d).

2. Results and discussion

Initially, we used the chiral Ni(II)-complex of glycine (*S*)-**1** and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dienol **2a** as model substrates to optimize the asymmetric 1,6-conjugate reaction conditions. The results were summarized in Table 1. The model reaction was carried out in dichloromethane (CH_2Cl_2) using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the base. To our delight,

Table 1
Optimization of asymmetric 1,6-conjugate reaction conditions[a].



Entry	Base	Solvent	Temp. (°C)	Yield (%)[b]	*syn: anti*	*de* (%)[c]
1	DBU	CH_2Cl_2	r.t.	67	73:27	92
2	**NaH**	**CH_2Cl_2**	**r.t.**	**80**	**81:19**	**98**
3	*t*-BuOK	CH_2Cl_2	r.t.	56	86:14	95
4	*t*-BuONa	CH_2Cl_2	r.t.	73	83:17	93
5	CH_3ONa	CH_2Cl_2	r.t.	63	85:15	95
6	NaH	CH_3CN	r.t.	52	75:25	97
7	NaH	Acetone	r.t.	63	67:33	91
8	NaH	$CHCl_3$	r.t.	31	66:34	70
9	NaH	THF	r.t.	40	70:30	91
10	NaH	DMF	r.t.	38	70:30	94
11	NaH	MeOH	r.t.	44	67:33	82
12	NaH	CH_2Cl_2	−20	72	90:10	91
13	NaH	CH_2Cl_2	0	83	91:9	91
14	NaH	CH_2Cl_2	40	68	84:16	93

[a] Reactions were run with 0.20 mmol of (*S*)-**1**, 0.24 mmol of **2a** in 4 mL of solvent with 0.30 mmol of base for overnight at ambient temperature.
[b] Isolated yield of (*S*)(2*S*,3*S*)-**3a**.
[c] Determined by HPLC analysis.

the desired product **3a** was obtained after the mixture was stirring at ambient temperature for 10 h (Table 1, entry 1). The major diastereomer could be isolated easily by column chromatography and the isolated yield is 67%. A single crystal X-ray structural analysis was subsequently proceeded, and the result indicated that the configuration of the major diastereomer was (*S*)(2*S*,3*S*) (Fig. S1 in the Supporting Information). Inspired by this result, a series of bases, such as sodium hydride (NaH), potassium *tert*-butoxide (*t*-BuOK), sodium *tert*-butoxide (*t*-BuONa), and sodium methoxide (CH_3ONa) was investigated respectively (Table 1, entries 2–5). Interestingly, when sodium hydride (NaH) was served as the base, the reaction proceeded smoothly to accomplish the desired diastereomer (*S*)(2*S*,3*S*)**-3a** in 80% yield with good diastereoselectivity (*de* = 98%). Additionally, solvents screening further demonstrated that the reaction proceeded smoothly in CH_2Cl_2 to attain the desired product in the highest yield with good stereoselectivity (Table 1, entries 6–11). Further optimization studies established that when the reaction was treated with NaH in CH_2Cl_2, temperature variation had no effect on the reaction even a gradient of temperatures was set from −20 to 40 °C (Table 1, entries 12–14), and good yields and stereoselectivities were achieved. The protocol for this reaction process was proposed as follows: (*S*)**-1** was first treated with 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dienol **2a** in the presence of NaH (1.5 equiv.) in CH_2Cl_2 and the resulting mixture was stirred at ambient temperature overnight to obtain the (*S*)(2*S*,3*S*)**-3a** in good to high yields with good diastereoselectivity.

With the optimal reaction conditions in hand, the generality and substrate scope of this asymmetric 1,6-conjugate reaction were independently investigated and the results were summarized in Table 2. Gratifyingly, both electron-donating and electron-withdrawing substituents were tolerated in this asymmetric 1,6-conjugate addition reaction (Table 2, entries 1–10). It should be noted that a series of functional groups such as methyl, methoxy, halogen and nitro groups was compatible with this reaction and the