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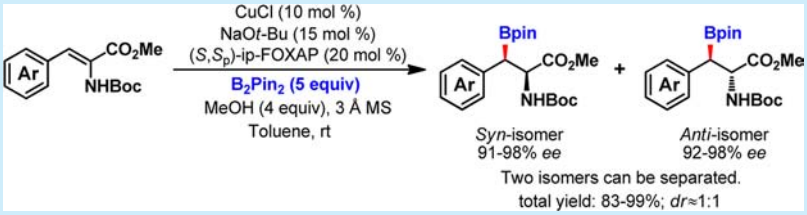
Copper-Catalyzed Asymmetric Hydroboration of α-Dehydroamino Acid Derivatives: Facile Synthesis of Chiral β-Hydroxy-α-amino Acids

Zhi-Tao He, Yi-Shuang Zhao, Ping Tian,* Chuan-Chuan Wang, Han-Qing Dong,† and Guo-Qiang Lin*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

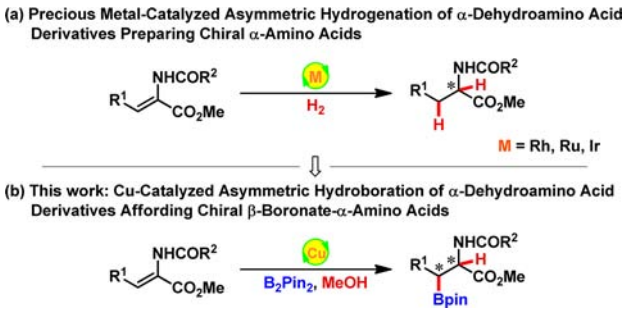
Supporting Information



ABSTRACT: The Cu-catalyzed asymmetric conjugate hydroboration reaction of β-substituted α-dehydroamino acid derivatives has been established, affording enantioenriched *syn*- and *anti*-β-boronate-α-amino acid derivatives with excellent combined yields (83−99%, dr ≈ 1:1) and excellent enantioselectivities (92−98% ee). The hydroboration products were expediently converted into valuable β-hydroxy-α-amino acid derivatives, which were widely used in the preparation of chiral drugs and bioactive molecules.

Precious-metal-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives has been recognized as one of the most important methods for the synthesis of various chiral α-amino acids, which are of great synthetic importance in the preparation of chiral drugs and natural products.[1] However, transition-metal-catalyzed asymmetric hydroboration of α-dehydroamino acid derivatives has never been explored. As shown in Scheme 1, this new approach can deliver a chiral β-functionality, i.e., adding β-boronate into α-amino acids, which should be quite attractive to chemists. These chiral β-boronate-α-amino acids can be easily transformed by oxidation to β-hydroxy-α-amino acids, which represent a unique amino acid motif existing in numerous chiral drugs and bioactive molecules, for instance, L-DOPS (Droxidopa),[2] mugineic acid,[3] mcivicin,[4] (3*S*,4*S*)-DHGA,[5] L-(+)-furanomycin,[6] and hydroxyectoine[7] (Figure 1). Herein, we present our findings in Cu-catalyzed asymmetric hydroboration of α-dehydroamino acid derivatives leading to chiral β-boronate-α-amino acids.

Scheme 1. Cu-Catalyzed Asymmetric Hydroboration of α-Dehydroamino Acid Derivatives



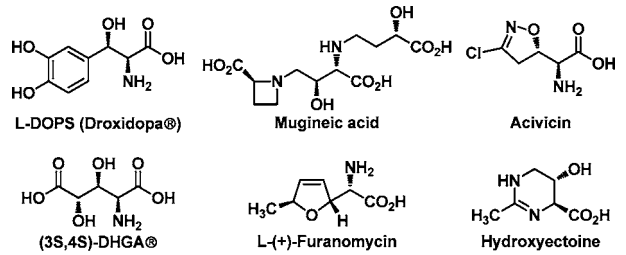


Figure 1. Chiral drugs and bioactive molecules containing chiral β-hydroxy-α-amino acid framework.

In the past 5 years, Cu-catalyzed asymmetric conjugate hydroboration of α,β-unsaturated carboxylic derivatives with bis(pinacolato)diboron (B_2Pin_2) as "boron" source and MeOH as "hydrogen" source has been established, but the research was mainly focused on the field of β-substituted[8] and β,β-disubstituted[9] α,β-unsaturated compounds. With regard to α,β-disubstituted α,β-unsaturated compounds, only α-methyl α,β-unsaturated esters have been executed in the Cu-catalyzed asymmetric hydroboration reaction with the enantiomeric excess (ee) of the product generally below 70%.[10]

The existence of the electron-donating amino group at the double bond of α,β-unsaturated esters will have great influence

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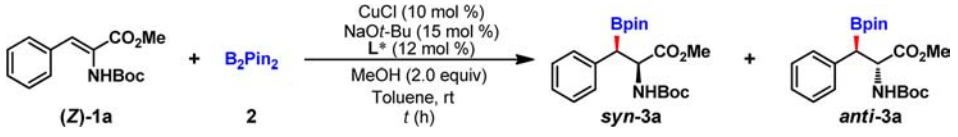
Table 1. Evaluation of Chiral Ligands for Cu-Catalyzed Asymmetric Hydroboration of α-Dehydroamino Acid Derivative (*Z*)-1a[a]



entry	L*	**2** (*x* equiv)	time (h)	yield[b] (%)	*syn*-**3a**[c] (%)	*anti*-**3a**[d] (%)	ee (*syn*-**3a**, %)[e]	ee (*anti*-**3a**, %)[e]
1	**L1**	1.1	17	NR				
2[f]	**L2**	1.1	12	51	20	31	60	62
3	**L3**	1.1	17	74	67	7	9	−10
4	**L4**	1.1	18	30	20	10	−22	−33
5	**L5**	1.1	17	64	20	44	−50	−40
6	**L6**	1.1	15	38	16	22	96	95
7[g]	**L6**	2.0	15	49	22	27	95	93
8[g,h]	**L6**	2.0	12	57	24	33	90	91
9[g,h,i]	**L6**	4.0	13	91	50	41	95	95
10[g,h,i]	**L6**	5.0	12	>99	54	46	97	96

[a]Reactions were performed under argon atmosphere. [b]Combined yield of *syn*-**3a** and *anti*-**3a**. [c]Yield of the isolated product *syn*-**3a**. [d]Yield of the isolated product *anti*-**3a**. [e]Determined by HPLC analysis using a chiral stationary phase. [f]NaO-*t*-Bu (25 mol %) was used. [g]MeOH (4.0 equiv) was used. [h]Molecular sieves (3 Å) were added. [i]**L6** (20 mol %) was used. B_2Pin_2 = bis(pinacolato)diboron, Boc = *tert*-butoxycarbonyl.

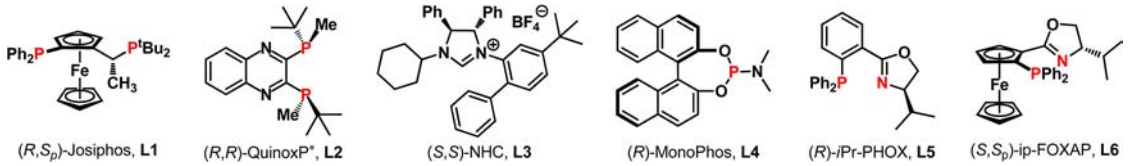
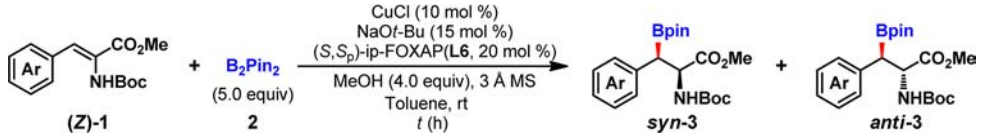


Table 2. Substrate Scope of β-Aryl-Substituted α-Dehydroamino Acid Derivatives (*Z*)-1[a]



entry	**1**		(Ar =)	time (h)	yield[b] (%)	*syn*-**3**[c] (%)	*anti*-**3**[d] (%)	ee (*syn*-**3**, %)[e]	ee (*anti*-**3**, %)[e]
1	**1**	**a**	(C_6H_5−)	12	>99	54	46	97	96
2	**1**	**b**	(4-Br-C_6H_4−)	1	93	42	51	98	96
3	**1**	**c**	(4-Cl-C_6H_4−)	1	92	45	47	98	96
4	**1**	**d**	(4-Me-C_6H_4−)	5	96	44	52	92	94
5	**1**	**e**	(4-Ph-C_6H_4−)	4	92	37	55	96	94
6	**1**	**f**	(3-Cl-C_6H_4−)	11	91	41	50	96	97
7	**1**	**g**	(3-F-C_6H_4−)	2	83	33	50	96	96
8	**1**	**h**	(3-MeO-C_6H_4−)	2	94	45	49	95	94
9	**1**	**i**	(3-Me-C_6H_4−)	12	>99	50	50	95	92
10	**1**	**j**	(2-Me-C_6H_4−)	4	>99	35	65	97	98
11	**1**	**k**	(2-naphthyl−)	24	99	49	50	98	95
12	**1**	**m**	(3-Br-5-Me-C_6H_3−)	16	94	43	51	98	97
13	**1**	**n**	(2,3-Me_2-C_6H_3−)	4	>99	50	50	95	94
14	**1**	**o**	(3,5-(*t*-Bu)$_2$-C_6H_3−)	2	95	50	45	98	97
15	**1**	**p**	(3,4-(−OCH_2O−)-C_6H_3−)	4	96	47	49	91	92

[a]Reactions were performed under argon atmosphere. [b]Combined yield of *syn*-**3a** and *anti*-**3a**. [c]Yield of the isolated product *syn*-**3a**. [d]Yield of the isolated product *anti*-**3a**. [e]Determined by HPLC analysis using a chiral stationary phase.

on the substrate reactivity. Meanwhile, the stereoselective control remains quite challenging.

With this mindset, a set of representative chiral ligands were investigated for the Cu-catalyzed asymmetric hydroboration of β-phenyl-α-dehydroamino acid methyl ester (*Z*)-**1a**, and the screening results are summarized in Table 1. Chiral bisphosphine ligands, (R,S_p)-Josiphos (**L1**) and (*R*,*R*)-QuinoxP* (**L2**) have been successfully employed in the Cu-catalyzed asymmetric conjugate hydroboration reaction.[8,9] However, no borylated product was observed for **L1** ligand, and only 51% combined yield of *syn*-**3a** and *anti*-**3a** in about 60% ee value each was observed for **L2** ligand in our case (Table 1, entries 1 and 2). Next, chiral N-heterocyclic carbene (NHC, **L3**),[11] phosphoramidite ((*R*)-MonoPhos, **L4**),[8i] and phosphinooxazoline ((*R*)-*i*-Pr-PHOX, **L5**) ligands were subjected to this reaction, although no promising outcomes were obtained (Table 1, entries 3−5). To our delight, the ee values of *syn*-**3a** and *anti*-**3a** dramatically raised to 96% and 95%, albeit in a low

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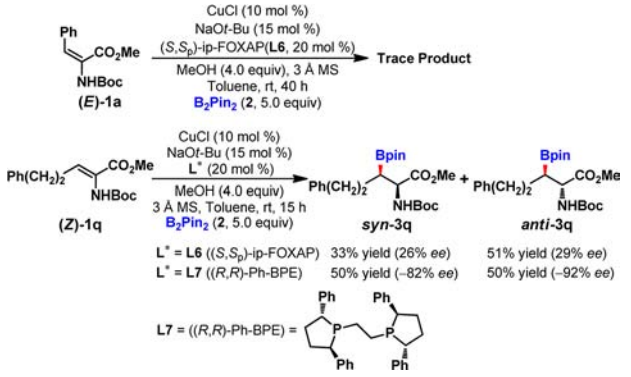
yield, when (S,S_p)-ip-FOXAP (**L6**) served as ligand (Table 1, entry 6).[12] Increasing the B_2Pin_2 (**2**) loading led to great improvement of yields (Table 1, entries 7−10). In particular, quantitative yields of *syn*-**3a** and *anti*-**3a** (dr ≈ 1:1) were accomplished, and their individual ee values reached 97% and 96% when 5 equiv of B_2Pin_2 and molecular sieve (3 Å) were used.

With the optimal reaction conditions identified, various *β*-aryl-substituted substrates were investigated, and the results are summarized in Table 2. All 4-substituted and 3-substituted phenyl substrates, regardless of the electron-donating or electron-withdrawing property of the substitutent at the phenyl ring, afforded the conjugate hydroboration products, *syn*-**3** and *anti*-**3**, in about 1:1 dr ratio with excellent yields and enantioselectivities (Table 2, entries 2−9). Interestingly, 2-methyl-substituted phenyl substrate (**1j**) gave the products *syn*-**3j** and *anti*-**3j** in about 1:2 dr ratio, probably due to the steric hindrance of the neighboring substituent in the stereocontrol (Table 2, entry 10). As for 2-naphthyl and some disubstituted phenyl substrates, the conjugate hydroboration reaction also proceeded smoothly with about 1:1 dr ratio, excellent yields, and enantioselectivities (Table 2, entries 11−15).

Given the highly enantioselective nature of this conjugate hydroboration reaction, the *E*-isomer of *β*-phenyl-substituted substrate, (*E*)-**1a**, was applied under the standard conditions. Unfortunately, trace product was observed, which indicated that the geometry of the double bond played an important role in the substrate reactivity (Scheme 2).

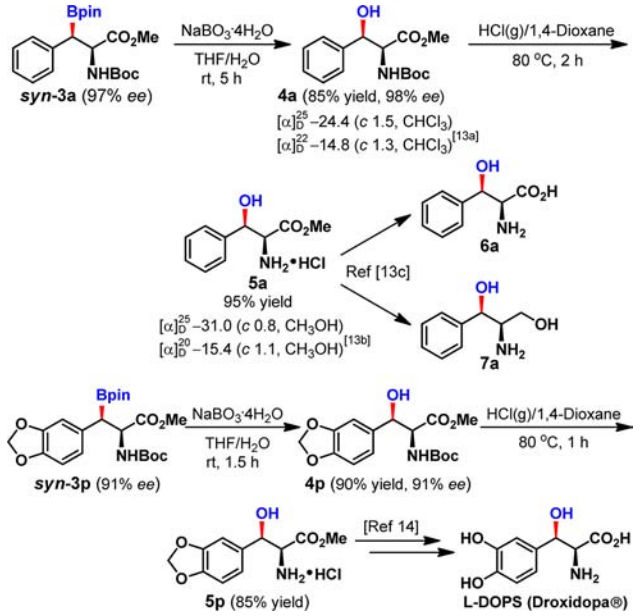
Scheme 2. Cu-Catalyzed Asymmetric Hydroboration of (*E*)-1a and (*Z*)-1q



Next, *β*-alkyl-substituted substrate (*Z*)-**1q** was investigated in this reaction. By utilizing (S,S_p)-ip-FOXAP (**L6**) as ligand, the reaction afforded the desired products in high yield, but with <30% ee for both *syn*-**3q** and *anti*-**3q**. After further screenings of different ligands, a quantitative yield of *syn*-**3q** and *anti*-**3q** (dr = 1:1) was accomplished by using (*R*,*R*)-Ph-BPE (**L7**) as ligand, and their ee values could reach −82% and −92%, respectively (Scheme 2).[12]

The chiral *β*-boronate-*α*-amino acids could be readily converted into the useful *β*-hydroxy-*α*-amino acids related to chiral drugs and bioactive molecules (Scheme 3). For example, *syn*-**3a** went through a mild oxidation with sodium perborate to give *β*-hydroxyphenylalanine derivate **4a**. The absolute configurations of **4a** were unambiguously assigned as 2*S*,3*R* by chemical correlation (NMR and optical rotation) with the known compound (2*S*,3*R*)-**4a**.[13a] Removal of the *tert*-butoxycarbonyl (Boc) group in **4a** under gaseous HCl at 80 °C generated *β*-hydroxyphenylalanine methyl ester hydrochloride salt **5a**, of which absolute configurations were further confirmed by comparing the NMR and optical rotation with the known compound (2*S*,3*R*)-**5a**.[13b] According to the literature,[13c] free (*R*)-*β*-hydroxy-L-phenylalanine **6a** and (*R*)-*β*-hydroxy-L-phenylalaninol **7a** could be respectively achieved through a simple hydrolytic and reductive procedure. In a similar way, the oxidation reaction of *syn*-**3p** and subsequent *N*-Boc deprotection reaction of **4p** also proceeded equally well to deliver the chiral intermediate **5p**, which can be used for the preparation of chiral drug L-DOPS.[14]

Scheme 3. Transformations of the Hydroboration Products



It should be noted that the absolute configuration of other conjugate hydroboration products were assigned on the basis of their chemical correlation with *syn*-**3a** and *anti*-**3a**.[15]

In summary, the Cu-catalyzed asymmetric conjugate hydroboration reaction of *β*-substituted *α*-dehydroamino acid derivatives with B_2Pin_2 and MeOH has been established.[16] This reaction was conducted under convenient conditions, simultaneously affording enantioenriched *syn*- and *anti*-*β*-boronate-*α*-amino acid derivatives in about 1:1 dr ratio with excellent yields and excellent enantioselectivities. The functional group of *β*-boronate could be expediently converted into the useful *β*-hydroxy derivatives, which could be applied in the preparation of chiral drugs and bioactive molecules, thus demonstrating their synthetic utility. The present results extend the realm of the Cu-catalyzed asymmetric conjugate hydroboration reaction. Further studies on the applications of hydroboration products are in progress in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and details of modification of reaction conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: tianping@sioc.ac.cn.
*E-mail: lingq@sioc.ac.cn.

Present Address

[†]Arvinas, Inc., 5 Science Park, New Haven, CT 06511.

Notes

The authors declare no competing financial interest.

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(12) For more chiral ligands screening, see the Supporting Information (section 2).

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(15) The *syn*-**3a** isomer appeared in an upper position on the silica gel TLC plate relative to the *anti*-**3a** isomer (eluent: ethyl acetate/petroleum ether = 1/8).

(16) For the mechanistic studies, see the Supporting Information (section 5).