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Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to β-Phthaliminoacrylate Esters toward the Synthesis of β-Amino Acids

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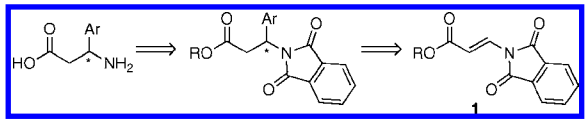
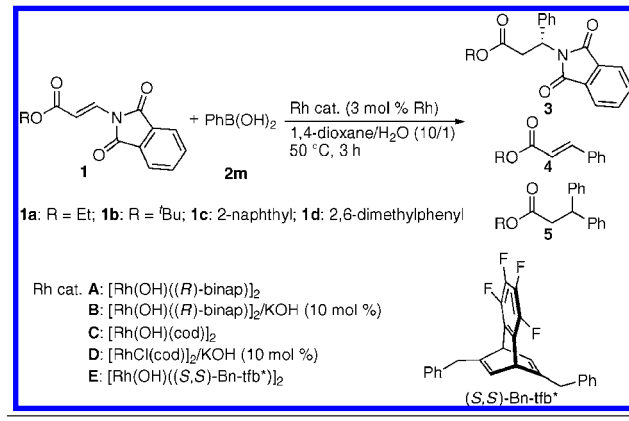
β-Amino acids and their derivatives are important structural components of a number of biologically active compounds, and many synthetic approaches to this class of compounds have been developed in recent years.[1] Of a variety of methods to create stereogenic centers of β-amino acid derivatives, enantioselective conjugate addition of carbon nucleophiles to β-dehydroamino acid derivatives has high synthetic utility in view of the versatility of the nucleophiles.[2] Sibi reported the enantioselective addition of chiral organomagnesium amides[2a] or silylketene acetals[2b] to enamidomalonates toward the synthesis of β-amino acid derivatives. On the other hand, rhodium-catalyzed 1,4-addition of arylboron reagents[3] to α-amino acrylates was successfully applied to the synthesis of α-amino acid derivatives, where the enantioselective protonation creates a stereogenic center at the α-position.[4] A similar protocol was used in the rhodium-catalyzed 1,4-addition to α-aminomethyl acrylates giving α-substituted-β-amino acid esters.[5] In this context, we focused on a new approach for the synthesis of β-substituted-β-amino acids, which involves the asymmetric addition of arylboronic acids to β-phthaliminoacrylate esters **1** (Scheme 1).[6] Here we report that the reaction is efficiently catalyzed by a hydroxorhodium/chiral diene complex, giving β-aryl-β-*N*-phthaloylamino acid esters in high yields with high enantioselectivity.

Scheme 1



In the first set of experiments, addition of phenylboronic acid (**2m**) to ethyl ester **1a** was examined under several reaction conditions (Table 1). Treatment of **1a** with **2m** (3.0 equiv) in 1,4-dioxane/H_2O (10/1) at 50 °C for 3 h in the presence of [Rh(OH)((*R*)-binap)]$_2$[7] (3 mol % of Rh) (Rh cat. **A**), which is one of the best catalysts for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds,[7] gave a mixture of 1,4-addition product **3am** (54%), ethyl cinnamate (**4a**, 8%), and ethyl 3,3-diphenylpropanoate (**5a**, 12%), which is the phenylation product of **4a**. The reaction in the presence of KOH (10 mol %) (Rh cat. **B**) resulted in the lower conversion (31%) of **1a** to give **3am** in 19% yield as well as side products **4a** and **5a** (entry 2). Thus, for the present reaction, the Rh/binap system suffers from its low catalytic activity and low selectivity caused by deamination.[8] In contrast, the use of [Rh(OH)(cod)]$_2$ (Rh cat. **C**) gave high yield (83%) of the 1,4-addition product **3am** as a sole addition product (entry 3). The formation of a small amount of **5a** was observed in the use of [RhCl(cod)]$_2$ combined with KOH (10 mol %) (Rh cat. **D**), where the conversion of **1a** was low (36%) (entry 4). Although KOH is often used for the in situ generation of hydroxorhodium catalysts from chlororhodium complexes,[7,9] this method cannot be applied to the present reaction because it decreases the catalytic activity of the rhodium/diene catalyst. These results prompted us to examine hydroxorhodium complexes coordinated with chiral diene ligands[9−11] for the asymmetric addition to **1a**. Of a variety of chiral diene ligands available,[11] we focused on chiral tetrafluorobenzobarrelene (tfb) ligands[12,13] because of the high stability of their hydroxorhodium complexes. Thus, the reaction of **1a** with phenylboronic acid (**2m**, 1.5 equiv) in the presence of [Rh(OH)((*S*,*S*)-Bn-tfb*)]$_2$(Rh cat. **E**)[14] gave 93% yield of **3am** with 85% ee (entry 5). The ester group of **1** had a significant influence on the enantioselectivity. The reactions of *tert*-butyl ester (**1b**) and 2-naphthyl ester (**1c**) gave the corresponding addition products **3bm** and **3cm** with 87 and 93% ee, respectively (entries 6 and 7). The highest enantioselectivity was obtained with 2,6-dimethylphenyl ester **1d**, which gave **3dm** in 98% ee and 97% yield (entry 8). The

Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to Enoate **1**[a]



entry	1	Rh cat.	conv. (%)[b]	3 (%)[c]	4 (%)[c]	5 (%)[c]
1	**1a**	**A**	78	**3am**:54	8	12
2	**1a**	**B**	31	**3am**:19	6	2
3	**1a**	**C**	90	**3am**:83	0	0
4	**1a**	**D**	36	**3am**:32	0	5
5[d]	**1a**	**E**	96	**3am**:93 (85% ee)[e]	0	0
6[d]	**1b**	**E**	78	**3bm**:76 (87% ee)[e]	0	0
7[d]	**1c**	**E**	100	**3cm**:96 (93% ee)[e]	0	0
8[d]	**1d**	**E**	100	**3dm**:97 (98% ee)[e]	0	0

[a] Reaction conditions: **1** (0.125 mmol), **2m** (0.375 mmol), Rh catalyst (3 mol % of Rh), 1,4-dioxane (0.50 mL), H_2O (0.05 mL) at 50 °C for 3 h. [b] Conversion of **1** determined by ^{1}H NMR. [c] Determined by ^{1}H NMR. [d] Performed with **2m** (0.188 mmol) for 12 h. [e] Ee of **3** determined by HPLC analysis with a chiral stationary phase columns: Chiralpak AD-H for **3am**, Chiralcel OD-H for **3bm**−**3dm**.

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Scheme 2

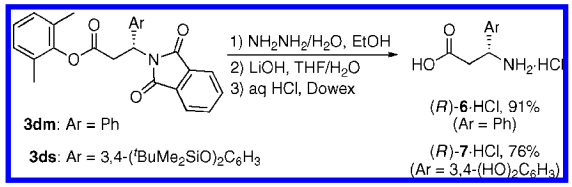
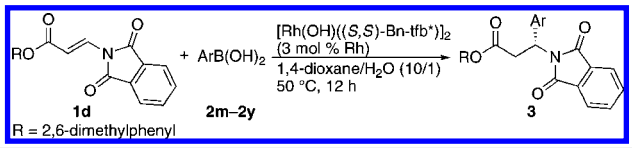


Table 2. Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to **1d**[a]



entry	Ar	isolated yield (%)	ee (%)[b]
1	Ph (**2m**)	94 (**3dm**)	98 (*R*)
2[c]	Ph (**2m**)	97 (**3dm**)	98 (*R*)
3	4-MeC_6H_4 (**2n**)	99 (**3dn**)	97 (*R*)
4[d,e]	2-MeC_6H_4 (**2o**)	90 (**3do**)	99 (*R*)
5	3,5-$Me_2C_6H_3$ (**2p**)	99 (**3dp**)	99 (*R*)
6	4-$MeOC_6H_4$ (**2q**)	98 (**3dq**)	98 (*R*)
7[e,f]	3,4-$(OCH_2O)C_6H_3$ (**2r**)	95 (**3dr**)	98 (*R*)
8[d]	3,4-$(^tBuMe_2SiO)_2C_6H_3$ (**2s**)	96 (**3ds**)	98 (*R*)
9	4-$(HO)C_6H_4$ (**2t**)	92 (**3dt**)	97 (*R*)
10[e,g]	4-FC_6H_4 (**2u**)	93 (**3du**)	97 (*R*)
11[e,f]	4-BrC_6H_4 (**2v**)	90 (**3dv**)	97 (*R*)
12[e,g]	4-$CF_3C_6H_4$ (**2w**)	81 (**3dw**)	96 (*R*)
13[f]	2-naphthyl (**2x**)	97 (**3dx**)	97 (*R*)
14[f]	1-cyclohexenyl (**2y**)	87 (**3dy**)	93 (*R*)

[a] Reaction conditions: **1d** (0.250 mmol), $ArB(OH)_2$ (**2**) (0.375 mmol), $[Rh(OH)((S,S)\text{-Bn-tfb*})]_2$ (3 mol % of Rh), 1,4-dioxane (1.0 mL), H_2O (0.1 mL) at 50 °C for 12 h. [b] The absolute configurations of **3** except for **3dm** and **3ds** were assigned by analogy with entry 1. [c] The reaction of **1d** (1.0 mmol) with **2m** (1.5 mmol) in the presence of $[Rh(OH)((S,S)\text{-Bn-tfb*}]_2$ (1 mol % of Rh). [d] Performed with $(ArBO)_3$ (0.125 mmol). [e] For 24 h. [f] Performed with $(ArBO)_3$ (0.250 mmol). [g] Performed with $ArB(OH)_2$ (0.750 mmol).

absolute configuration of **3dm** was determined to be *R*-(+) by conversion into β-phenylalanine hydrochloride (**6**·HCl) ($[\alpha]^{20}_D$ −5 (*c* 0.32, H_2O) for 98% ee (*R*); lit.[15] $[\alpha]^{25}_D$ −3 (*c* 0.30, H_2O) for (*R*)-**6**·HCl) (vide infra, Scheme 2).

The results obtained for the rhodium-catalyzed 1,4-addition of several arylboronic acids or arylboroxines to **1d** are summarized in Table 2. Aryl groups (**2m**−**2x**) having a variety of substituents were successfully introduced in the reaction of **1d** giving the corresponding addition products (**3dm**−**3dx**) in high yields, the enantioselectivities ranging from 96 to 99% ee (entries 1−13). Asymmetric addition of 1-cyclohexenylboronic acid (**2y**) to **1d** gave **3dy** in 87% yield with 93% ee (entry 14).

The β-aryl-β-*N*-phthaloylamino acid esters obtained here with high enantioselectivity are readily converted into the β-amino acid derivatives without loss of enantiomeric purity (Scheme 2). Removal of the phthaloyl group on **3dm** by treatment with hydrazine[16] followed by basic hydrolysis gave (*R*)-β-phenylalanine hydrochloride (**6**·HCl) in 91% yield with 98% ee.[17] The same hydrolysis method was successfully applied to the removal of protecting groups on **3ds** to give (*R*)-β-dopa **7** (76% yield as **7**·HCl), which is a natural product in the mushroom *Cortinarius violaceus*.[18]

In summary, we developed a rhodium-catalyzed asymmetric addition of arylboronic acids to β-phthaliminoacrylate esters, which was realized by use of a hydroxorhodium/chiral diene complex, giving β-aryl-β-*N*-phthaloylamino acid esters in high yields and high enantioselectivity.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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