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## Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to $\beta$ -Phthaliminoacrylate Esters toward the Synthesis of $\beta$ -Amino Acids

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 $\beta$ -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.<sup>1</sup> Of a variety of methods to create stereogenic centers of  $\beta$ -amino acid derivatives, enantioselective conjugate addition of carbon nucleophiles to  $\beta$ -dehydroamino acid derivatives has high synthetic utility in view of the versatility of the nucleophiles.<sup>2</sup> Sibi reported the enantioselective addition of chiral organomagnesium amides<sup>2a</sup> or silylketene acetals<sup>2b</sup> to enamidomalonates toward the synthesis of  $\beta$ -amino acid derivatives. On the other hand, rhodium-catalyzed 1,4-addition of arylboron reagents<sup>3</sup> to  $\alpha$ -amino acrylates was successfully applied to the synthesis of  $\alpha$ -amino acid derivatives, where the enantioselective protonation creates a stereogenic center at the  $\alpha$ -position.<sup>4</sup> A similar protocol was used in the rhodium-catalyzed 1,4-addition to  $\alpha$ -aminomethyl acrylates giving  $\alpha$ -substituted- $\beta$ -amino acid esters.<sup>5</sup> In this context, we focused on a new approach for the synthesis of  $\beta$ -substituted- $\beta$ -amino acids, which involves the asymmetric addition of arylboronic acids to  $\beta$ -phthaliminoacrylate esters 1 (Scheme 1).<sup>6</sup> Here we report that the reaction is efficiently catalyzed by a hydroxorhodium/chiral diene complex, giving  $\beta$ -aryl- $\beta$ -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 1,4dioxane/H<sub>2</sub>O (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  $\alpha,\beta$ -unsaturated carbonyl compounds,<sup>7</sup> 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.<sup>8</sup> 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 **Table 1.** Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to Enoate  $1^a$ 



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

was observed in the use of [RhCl(cod)]<sub>2</sub> 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,<sup>7,9</sup> 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,<sup>11</sup> we focused on chiral tetrafluorobenzobarrelene (tfb) ligands<sup>12,13</sup> 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  $[Rh(OH)((S,S)-Bn-tfb^*)]_2(Rh \text{ cat. } E)^{14}$  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

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*Table 2.* Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to **1d**<sup>*a*</sup>



entry	Ar	isolated yield (%)	ee (%) <sup>b</sup>
1	Ph ( <b>2m</b> )	94 ( <b>3dm</b> )	98 (R)
$2^c$	Ph ( <b>2m</b> )	97 ( <b>3dm</b> )	98 (R)
3	$4-MeC_{6}H_{4}(2n)$	99 ( <b>3dn</b> )	97 (R)
$4^{d,e}$	$2-MeC_{6}H_{4}(20)$	90 ( <b>3do</b> )	99 (R)
5	$3,5-Me_2C_6H_3(2p)$	99 ( <b>3dp</b> )	99 (R)
6	$4-\text{MeOC}_6\text{H}_4(2\mathbf{q})$	98 ( <b>3dq</b> )	98 (R)
$7^{e,f}$	$3,4-(OCH_2O)C_6H_3(2r)$	95 ( <b>3dr</b> )	98 (R)
$8^d$	$3,4-(^{t}BuMe_{2}SiO)_{2}C_{6}H_{3}(2s)$	96 ( <b>3ds</b> )	98 (R)
9	$4-(HO)C_{6}H_{4}(2t)$	92 ( <b>3dt</b> )	97 (R)
$10^{e,g}$	$4-FC_{6}H_{4}(2\mathbf{u})$	93 ( <b>3du</b> )	97 (R)
$11^{e,f}$	$4-BrC_{6}H_{4}(2v)$	90 ( <b>3dv</b> )	97 (R)
$12^{e,g}$	$4-CF_{3}C_{6}H_{4}(2w)$	81 ( <b>3dw</b> )	96 (R)
13 <sup>f</sup>	2-naphthyl (2x)	97 ( <b>3dx</b> )	97 (R)
$14^{f}$	1-cyclohexenyl (2y)	87 ( <b>3dy</b> )	93 ( <i>R</i> )

<sup>*a*</sup> Reaction conditions: **1d** (0.250 mmol),  $ArB(OH)_2$  (**2**) (0.375 mmol), [Rh(OH)((*S*,*S*)-Bn-tfb\*)]<sub>2</sub> (3 mol % of Rh), 1,4-dioxane (1.0 mL), H<sub>2</sub>O (0.1 mL) at 50 °C for 12 h. <sup>*b*</sup> The absolute configurations of **3** except for **3dm** and **3ds** were assigned by analogy with entry 1. <sup>*c*</sup> The reaction of **1d** (1.0 mmol) with **2m** (1.5 mmol) in the presence of [Rh(OH)((*S*,*S*)-Bn-tfb\*]<sub>2</sub> (1 mol % of Rh). <sup>*d*</sup> Performed with (ArBO)<sub>3</sub> (0.250 mmol). <sup>*s*</sup> Performed with ArB(OH)<sub>2</sub> (0.750 mmol).

absolute configuration of **3dm** was determined to be *R*-(+) by conversion into  $\beta$ -phenylalanine hydrochloride (**6** · HCl) ([ $\alpha$ ]<sup>20</sup><sub>D</sub> -5 (*c* 0.32, H<sub>2</sub>O) for 98% ee (*R*); lit.<sup>15</sup> [ $\alpha$ ]<sup>25</sup><sub>D</sub> -3 (*c* 0.30, H<sub>2</sub>O) 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  $\beta$ -aryl- $\beta$ -*N*-phthaloylamino acid esters obtained here with high enantioselectivity are readily converted into the  $\beta$ -amino acid derivatives without loss of enantiomeric purity (Scheme 2). Removal of the phthaloyl group on **3dm** by treatment with hydrazine<sup>16</sup> followed by basic hydrolysis gave (*R*)- $\beta$ -phenylalanine hydrochloride (**6**·HCl) in 91% yield with 98% ee.<sup>17</sup> The same hydrolysis method was successfully applied to the removal of protecting groups on **3ds** to give (*R*)- $\beta$ -dopa **7** (76% yield as **7**·HCl), which is a natural product in the mushroom *Cortinarius violaceus*.<sup>18</sup>

In summary, we developed a rhodium-catalyzed asymmetric addition of arylboronic acids to  $\beta$ -phthaliminoacrylate esters, which was realized by use of a hydroxorhodium/chiral diene complex, giving  $\beta$ -aryl- $\beta$ -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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