

# Reversal of Diastereoselectivity of the Reaction of Chiral Boron and Titanium Enolates with Nitrones *via* *N*-Acyloxyiminium Intermediates. Asymmetric Synthesis of Diastereomeric $\alpha$ -Substituted $\beta$ -Amino Acids

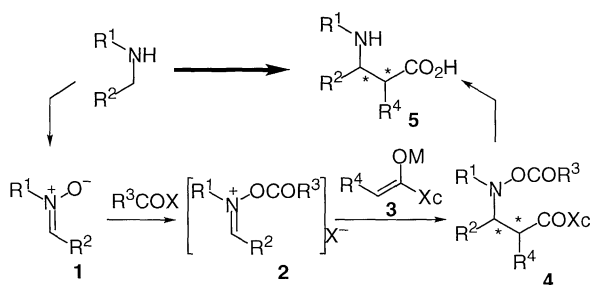
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(Received May 21, 1999; CL-990414)

Reaction of nitrones and acyl halides gives *N*-acyloxyiminium species, which are more reactive toward soft carbon nucleophiles than nitrones. Addition of chiral enolates to the *N*-acyloxyiminium species gave *N*-hydroxy- $\beta$ -amino acid derivatives highly diastereoselectively. Reversal of diastereoselectivity was observed between the boron enolates and titanium enolates. Using this method all of the four stereoisomers of  $\alpha$ -methyl- $\beta$ -phenylalanines can be prepared as enantiomerically pure forms.

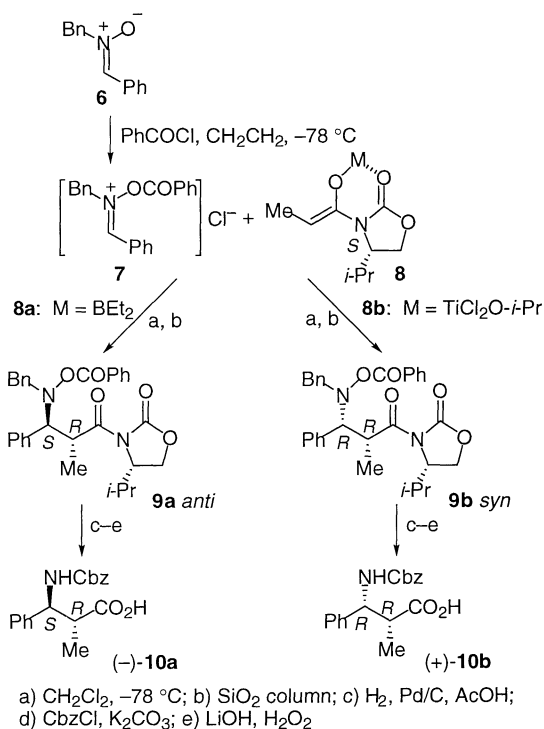
$\beta$ -Amino acids<sup>1</sup> are of interest in view of pharmacological activity,<sup>2</sup> structural properties,<sup>3</sup> and also useful precursors for synthesis of nitrogen containing biologically active compounds such as  $\beta$ -lactam antibiotics.<sup>4</sup>

Nitrones are highly valuable synthetic intermediates for synthesis of nitrogen containing biologically active compounds.<sup>5</sup> Introduction of various hard nucleophiles such as Grignard reagents at the carbon  $\alpha$  to the nitrogen gives  $\alpha$ -substituted hydroxylamines.<sup>6,7</sup> If nitrones react with enolates, a convenient method for synthesis of  $\beta$ -amino acid derivatives can be explored; however, nitrones can not react with enolates directly because of their low reactivity. We tried to activate the nitrones towards soft nucleophiles. It is known that the reaction of nitrones **1** with acyl halides gives *N*-acyloxyiminium species **2**, which undergo rearrangement to give the corresponding rearranged products such as amides.<sup>8</sup> It was found that the highly reactive *N*-acyloxyiminium species **2** undergoes reaction with enolates **3** at low temperature before the rearrangement, giving  $\alpha$ -substituted hydroxylamine derivatives **4** as shown in Scheme 1. *N*-Hydroxy- $\beta$ -amino acids are of importance and also useful as the precursor of the corresponding  $\beta$ -amino acids **5**. The present reaction provides a useful method for the synthesis of the  $\beta$ -amino acid derivatives from secondary amines, because nitrones **1** can be prepared conveniently by the catalytic oxidation of secondary amines upon treatment with hydrogen peroxide.<sup>9</sup> Facile asymmetric synthesis of  $\beta$ -amino acids from secondary amines can be demonstrated by synthesis of all of the four isomers of  $\alpha$ -methyl- $\beta$ -phenylalanines as enantiomerically pure forms highly efficiently.



Scheme 1.

*N*-Benzylidenebenzylamine *N*-oxide (**6**) was treated with benzoyl chloride in dichloromethane at  $-78^{\circ}\text{C}$  to give *N*-benzoyloxyiminium intermediate **7**. Addition of the chiral enolates **8**,<sup>9</sup> which were prepared from (*S*)-3-propionyl-4-isopropylloxazolidin-2-one, to the intermediate at  $-78^{\circ}\text{C}$  gave the corresponding  $\beta$ -amino acid derivatives **9** diastereoselectively (Scheme 2).<sup>10</sup> Reversal of diastereoselectivity was observed by means of changing the metal of enolates **8**. Addition of chiral boron enolate **8a** to the intermediate **7** gave the *anti* adduct **9a** as a major isomer (82%, **9a:9b** = 80:20 by <sup>1</sup>H NMR). In contrast, when the titanium enolate **8b** was used, the *syn* adduct **9b** was obtained predominantly (69%, **9a:9b** = 16:84). In each case, only two stereoisomers were obtained among the possible four stereoisomers. The diastereomers **9a** (mp 153.5–154  $^{\circ}\text{C}$ , [ $\alpha$ ]<sub>D</sub><sup>29</sup> +103.9 $^{\circ}$  (c 1.02, CHCl<sub>3</sub>)) and **9b** (mp 158–159  $^{\circ}\text{C}$ , [ $\alpha$ ]<sub>D</sub><sup>20</sup> -41.4 $^{\circ}$  (c 0.99, CHCl<sub>3</sub>)) can be separated simply as enantiomerically pure forms by column chromatography on silica gel. The diastereomers **9a** and **9b** could be transformed to the corresponding *N*-protected  $\beta$ -amino acids readily. Thus, *N*-Cbz- $\beta$ -amino acids (-)-**10a** (mp 133–134  $^{\circ}\text{C}$ , [ $\alpha$ ]<sub>D</sub><sup>25</sup> -22.3 $^{\circ}$  (c 1.01, CHCl<sub>3</sub>) and (+)-**10b** (mp 167–169  $^{\circ}\text{C}$ , [ $\alpha$ ]<sub>D</sub><sup>31</sup> +36.1 $^{\circ}$  (c 0.97, MeOH)) were obtained upon

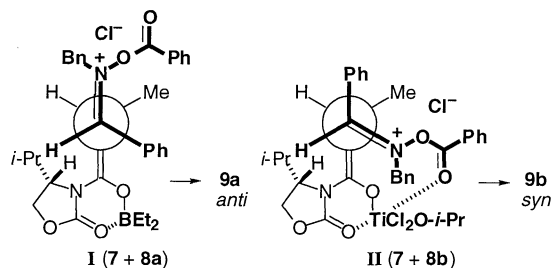


Scheme 2.



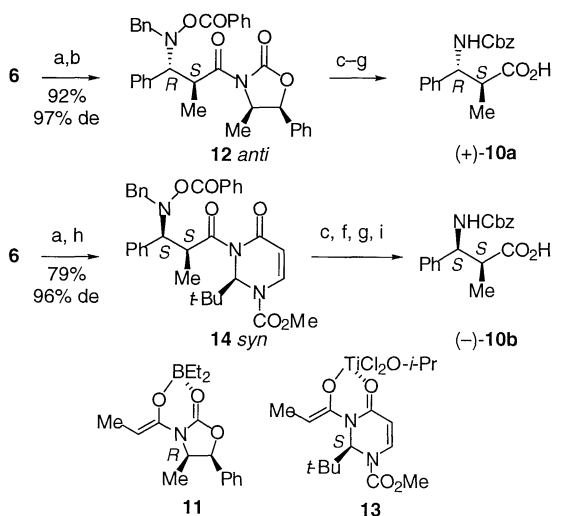
hydrogenation over Pd/C catalyst in acetic acid and subsequent treatment with benzyloxycarbonyl chloride (CbzCl) and then with hydrogen peroxide in the presence of lithium hydroxide in 75% and 76% yields, respectively, along with recovering chiral auxiliary, (*S*)-4-isopropylloxazolidin-2-one (Scheme 2).<sup>11,12</sup>

The stereochemistry of the present reaction can be rationalized by assuming the models shown in Figure 1. The *N*-benzoyloxyiminium ion intermediate **7** approaches the chelated (*Z*)-enolate **8** from the opposite side of the *i*-Pr group to give 2'-*R*-isomer exclusively. The stereochemistry at the C-3' position reflects the coordination number of the metal of the chelated enolate. The *N*-benzoyloxyiminium intermediate **7** would react with the boron enolate **8a** without coordination to the boron as shown in the open transition model **I** to give the 3'-*S*-isomer **9a**. On the other hand, in case of titanium enolate **8b**, the benzoyl group of the *N*-benzoyloxyiminium ion **7** would coordinate to the titanium of the enolate **8b** as shown in the closed transition state model **II**, and the reaction of **7** with **8b** would give the 3'-*R*-isomer **9b** predominantly.



**Figure 1.** Proposed open (**I**) and closed (**II**) transition state models for addition of enolates **8** to *N*-benzoyloxyiminium ion **7**.

Next, we examined various oxazolidinone and pyrimidinone<sup>13</sup> chiral auxiliaries to find the suitable chiral auxiliary for the present reaction. As expected, both *anti* and *syn* adducts were obtained highly diastereoselectively when boron and titanium enolates were used (Scheme 3). Thus, the reaction of *N*-benzoyloxyiminium intermediate **7** derived from the nitrone **6**



a) PhCOCl; b) **11**, toluene; c) SiO<sub>2</sub> column; d) Zn, AcOH; e) LiOH, H<sub>2</sub>O; f) H<sub>2</sub>, Pd/C; g) CbzCl, K<sub>2</sub>CO<sub>3</sub>; h) **13**, CH<sub>2</sub>Cl<sub>2</sub>; i) LiOH, H<sub>2</sub>O<sub>2</sub>.

**Scheme 3.**

with the boron enolate **11** derived from (4*S*,5*R*)-3-propionyl-4-methyl-5-phenyloxazolidin-2-one in toluene gave the corresponding *anti* adduct **12** (92%, 97% *de*). In contrast, the *syn* adduct **14** was obtained, when the titanium enolate **13** bearing (2*S*)-2-*t*-butyl-1-methoxycarbonyl-2,3-dihydro-4(1*H*)-pyrimidinone<sup>13</sup> was used in dichloromethane (79%, 96% *de*). These isomers **12** (mp 140.5–142 °C, [α]<sub>D</sub><sup>24</sup> +20.2° (*c* 1.02, CHCl<sub>3</sub>)) and **14** ([α]<sub>D</sub><sup>27</sup> +98.2° (*c* 0.97, CHCl<sub>3</sub>)) could be isolated simply as enantiomerically pure forms by short column chromatography, and hence the corresponding optically pure *N*-protected β-amino acids (+)-**10a** (mp 135–137.5 °C, [α]<sub>D</sub><sup>23</sup> +22.2° (*c* 1.03, CHCl<sub>3</sub>)) and (–)-**10b** (mp 169–171 °C, [α]<sub>D</sub><sup>31</sup> –36.7° (*c* 1.10, MeOH)) were obtained, respectively.

In conclusion, nitrones can be converted to the corresponding *N*-acyloxyiminium intermediates, which react with enolates bearing chiral auxiliary to give *N*-hydroxy-β-amino acid derivatives highly diastereoselectively. Change of the metals of the enolates from boron to titanium afforded reversal of the diastereoselectivity.

This work was supported by Research for the Future program, the Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research, the Ministry of Education, Science, Sports and Culture of Japan.

## References and notes

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