Reversal of Diastereoselectivity of the Reaction of Chiral Boron and Titanium Enolates with Nitrones *via* *N*-Acyloxyiminium Intermediates. Asymmetric Synthesis of Diastereomeric α-Substituted β-Amino Acids

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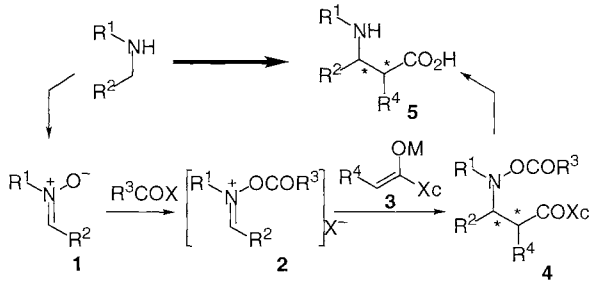
Reaction of nitrones and acyl halides gives *N*-acyloxyiminium species, which are more reactive toward soft carbon nucleophiles than nitrones. Addition of chiral enolates to the *N*-acyloxyiminium species gave *N*-hydroxy-β-amino acid derivatives highly diastereoselectively. Reversal of diastereoselectivity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

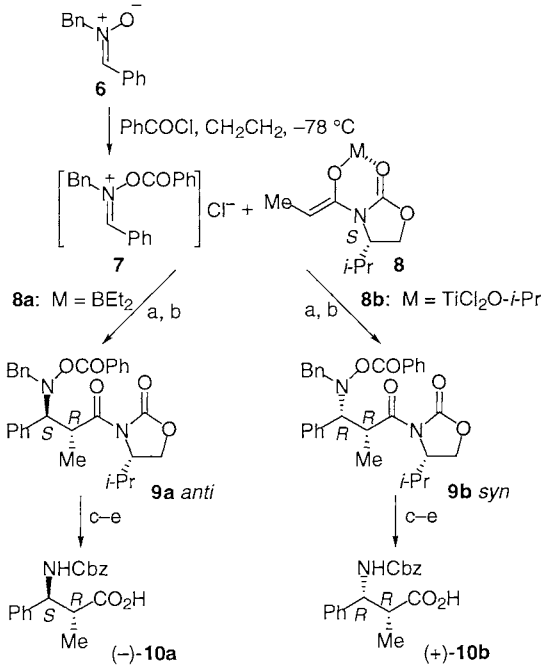
β-Amino acids[1] are of interest in view of pharmacological activity,[2] structural properties,[3] and also useful precursors for synthesis of nitrogen containing biologically active compounds such as β-lactam antibiotics.[4]

Nitrones are highly valuable synthetic intermediates for synthesis of nitrogen containing biologically active compounds.[5] Introduction of various hard nucleophiles such as Grignard reagents at the carbon α to the nitrogen gives α-substituted hydroxylamines.[6,7] If nitrones react with enolates, a convenient method for synthesis of β-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.[8] It was found that the highly reactive *N*-acyloxyiminium species **2** undergoes reaction with enolates **3** at low temperature before the rearrangement, giving α-substituted hydroxylamine derivatives **4** as shown in Scheme 1. *N*-Hydroxy-β-amino acids are of importance and also useful as the precursor of the corresponding β-amino acids **5**. The present reaction provides a useful method for the synthesis of the β-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.[9] Facile asymmetric synthesis of β-amino acids from secondary amines can be demonstrated by synthesis of all of the four isomers of α-methyl-β-phenylalanines as enantiomerically pure forms highly efficiently.



Scheme 1.

N-Benzylidenebenzylamine *N*-oxide (**6**) was treated with benzoyl chloride in dichloromethane at –78 °C to give *N*-benzoyloxyiminium intermediate **7**. Addition of the chiral enolates **8**,[9] which were prepared from (*S*)-3-propionyl-4-isopropyloxazolidin-2-one, to the intermediate at –78 °C gave the corresponding β-amino acid derivatives **9** diastereoselectively (Scheme 2).[10] 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 ^{1}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 stereomers were obtained among the possible four stereoisomers. The diastereomers **9a** (mp 153.5–154 °C, $[\alpha]^{29}_D$ +103.9° (*c* 1.02, $CHCl_3$)) and **9b** (mp 158–159 °C, $[\alpha]^{20}_D$ –41.4° (*c* 0.99, $CHCl_3$)) 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 β-amino acids readily. Thus, *N*-Cbz-β-amino acids (–)-**10a** (mp 133–134 °C, $[\alpha]^{25}_D$ –22.3° (*c* 1.01, $CHCl_3$) and (+)-**10b** (mp 167–169 °C, $[\alpha]^{31}_D$ +36.1° (*c* 0.97, MeOH) were obtained upon



a) CH_2Cl_2, –78 °C; b) SiO_2 column; c) H_2, Pd/C, AcOH; d) CbzCl, K_2CO_3; e) LiOH, H_2O_2

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-isopropyloxazolidin-2-one (Scheme 2).[11,12]

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.

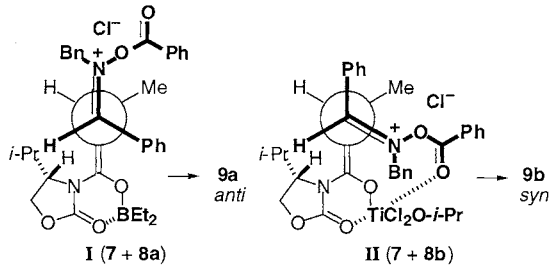
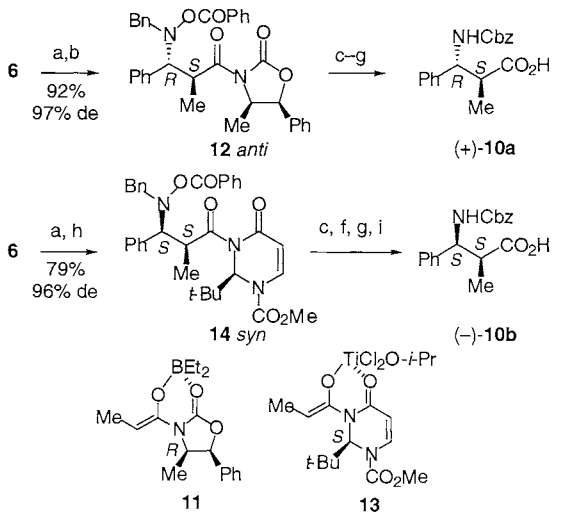


Figure 1. Proposed open (**I**) and closed (**II**) transition state models for addition of enolates **8** to *N*-benzoyloxyiminium ion **7**.

Next, we examined various oxazolidinone and pyrimidinone[13] 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** 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[13] was used in dichloromethane (79%, 96% de). These isomers **12** (mp 140.5–142 °C, $[\alpha]^{24}_D$ +20.2° (*c* 1.02, $CHCl_3$)) and **14** ($[\alpha]^{27}_D$ +98.2° (*c* 0.97, $CHCl_3$)) 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, $[\alpha]^{23}_D$ +22.2° (*c* 1.03, $CHCl_3$)) and (–)-**10b** (mp 169–171 °C, $[\alpha]^{31}_D$ –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.



a) PhCOCl; b) **11**, toluene; c) SiO_2 column; d) Zn, AcOH; e) LiOH, H_2O; f) H_2, Pd/C; g) CbzCl, K_2CO_3, h) **13**, CH_2Cl_2; i) LiOH, H_2O_2.

Scheme 3.

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References and notes

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