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Enantioselective Addition of Ketene Silyl Acetals to Nitrones Catalyzed by Chiral Titanium Complexes. Synthesis of Optically Active β-Amino Acids

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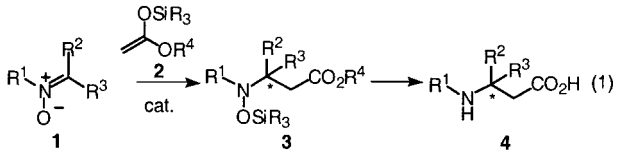
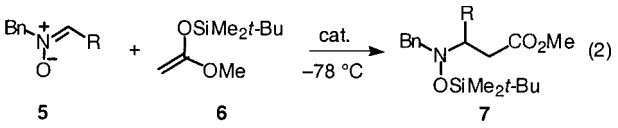
The synthesis of enantiomerically pure β-amino acids and their derivatives has attracted increasing attention in view of their pharmacological activities,[1] structural properties,[2] and usefulness as precursors of biologically active compounds such as β-lactam antibiotics.[3] Various methods for diastereoselective synthesis of β-amino acids have been reported;[4] however, the number of catalytic and enantioselective methods is small and limited to hydrogenation of aminoacrylates,[5] aminohydroxylation of olefins,[6] addition of aminonucleophiles to acrylates,[7] and Mannich-type reaction of aldimines with silyl enolates.[8] We report the first catalytic, enantioselective synthesis of optically active *N*-hydroxyl-β-amino acid derivatives **3**, which are related to natural products of biological significance,[9] and β-amino acids **4**, from nitrones **1** (eq 1). This is a rare case of a catalytic, enantioselective carbon−carbon bond formation reaction.[10]



Nitrones **1** have become highly valuable intermediates for the synthesis of nitrogen-containing biologically active compounds, because they are prepared readily by catalytic oxidation of secondary amines with H_2O_2[11a−g] as well as condensation of carbonyl compounds with *N*-hydroxylamines,[11h] which can be obtained by hydrolysis of the corresponding nitrones.[12] Diastereoselective additions of chiral enolates to nitrones have been performed with excellent selectivity, giving optically active β-amino acids and their derivatives.[12,13] This method is very useful for the synthesis of biologically active compounds, such as β-lactams and indolizidine alkaloids.[12,13b] Catalytic, enantioselective addition of ketene silyl acetals **2** to nitrones **1** is a very attractive proposition for the synthesis of β-amino acid derivatives **3**, and is comparable, or in some cases superior, to the asymmetric Mannich-type addition to imines[8] because of the configurational stability of nitrones, ease of handling, and readiness of preparation.

Various catalysts were evaluated for the reaction of *N*-benzylidenebenzylamine *N*-oxide (**5a**, R = Ph), which was prepared by the Na_2WO_4-catalyzed oxidation of dibenzylamine with H_2O_2,[11a] with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (**6**) (1.2 equiv) in CH_2Cl_2 at −78 °C (eq 2). In the absence of a catalyst the reaction did not occur, and only a small amount of methyl 3-(*N*-*tert*-butyldimethylsilyloxy-*N*-benzylamino)-3-phenylpropanoate (**7a**, R = Ph) was obtained with Ti(O*i*-Pr)$_4$ catalyst. However, the adduct **7a** was obtained in 85% isolated yield, when the reaction was carried out in the presence of Ti(OPh)$_4$ catalyst. Apparently, the phenoxy ligand is suitable for the carbon−carbon bond formation with an increase in the Lewis acidity of titanium. Next, we examined the enantioselectivity of the reaction of **5a** with **6** in the presence of various titanium(IV)-BINOL catalysts **8** (20 mol %) in toluene at −78 °C. The representative results are summarized in Table 1.



In the presence of chiral titanium catalyst **8a** prepared from Ti(O*i*-Pr)$_4$ and (*S*)-BINOL (1:1),[14] the adduct (*R*)-**7a** was obtained in 99% yield with 18% ee (entry 1). Additional ligands affect the enantioselectivity of the reaction dramatically.[15] The catalysts Ti-(*S*)-BINOL-2ArOH **8b**,**c** and Ti-(*S*)-BINOL-Ar(OH)$_2$ **8d**,**e** were prepared in situ by the reaction of Ti(O*i*-Pr)$_4$ with 2 equiv of phenols or 1 equiv of catechols, respectively, in toluene at room temperature in the presence of MS 4A, followed by treatment with 1 equiv of (*S*)-BINOL. In the presence of the titanium catalyst **8b**, the adduct (*R*)-**7a** was obtained in 99% yield with 34% ee (entry 2). With use of sterically bulky phenols, such as 1-naphthol (55% ee) (entry 3), 2,6-dimethylphenol (50% ee), and 2-phenylphenol (49% ee), (*R*)-**7a** was obtained with higher enantioselectivities. Interestingly, the adduct (*S*)-**7a** with inverse absolute configuration was obtained when catechols were used as additional ligands. Thus, the reaction in the presence of the titanium catalyst **8d** gave the (*S*)-β-amino acid derivative **7a** in 73% ee (entry 4). Furthermore, when 4-*tert*-butylcatechol was used, the adduct (*S*)-**7a** was obtained in 99% yield with 92% ee (entry 5). The cleavage of the nitrogen−oxygen bond of the (*S*)-**7a** with Zn/H_2SO_4 and recrystallization of the oxalic acid salt of the product gave optically pure *N*-benzyl-β-phenylalanine methyl ester. With use of the (*R*)-BINOL catalyst, the (*R*)-enantiomer was obtained in pure form.

The enantioselective addition of ketene silyl acetal **6** to nitrones **5a**−**e** catalyzed by chiral titanium complex **8e** gave β-amino acid derivatives **7a**−**e** in high yields as shown in Table 2.

α-2-Naphthyl and α-*p*-tolyl substituted nitrones **5b**,**c** underwent reaction with **6** smoothly to give the desired adducts with 88% ee each (entries 2 and 3). The β-amino-β-arylpropanoic acid derivatives **7b**,**c** thus obtained can be readily converted into the corresponding esters of β-amino acids upon treatment with Zn/H_2SO_4 and hydrogenation over palladium on charcoal catalyst. The adduct **7e** can be converted to ethyl 3-amino-3-[5-(benzo-1,3-dioxole)]propanoate, which is an important precursor of the aspartic acid

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Table 1. Asymmetric Reactions of Nitrone **5a** with Ketene Silyl Acetal **6** in the Presence of Ti-(*S*)-BINOL-2ArOH (or $Ar(OH)_2$) **8** To Give *N*-Hydroxyl-β-amino Acid Derivative **7a**

entry	ArOH or $Ar(OH)_2$ of **8**		yield of **7a**/%	ee of **7a**[a]/%	config. of **7a**
1	none	**8a**	99	18	(*R*)
2	phenol	**8b**	99	34	(*R*)
3	1-naphthol	**8c**	99	55	(*R*)
4	catechol	**8d**	95	73	(*S*)
5	4-*tert*-butylcatechol	**8e**	99	92	(*S*)

[a] Determined by HPLC analysis using CHIRALCEL OD-H after conversion to the corresponding β-amino acid ester with Zn/H_2SO_4.

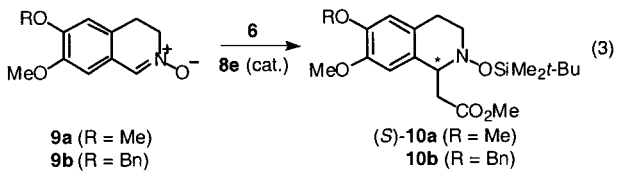
Table 2. Asymmetric Reactions of Nitrones **5a**−**e** with Ketene Silyl Acetal **6** in the Presence of Titanium Catalyst **8e** To Give **7a**−**e**[a]

entry	R of **5**		yield of **7**/%	ee of **7**/%	config. of **7**
1	phenyl	**5a**	99	92[a]	(*S*)
2	2-naphthyl	**5b**	94	88[b]	(−)
3	*p*-MeC_6H_4	**5c**	66	88[a]	(−)
4	3-pyridyl	**5d**	90	80[c]	(+)
5	3,4-$(OCH_2O)C_6H_3$	**5e**	74	80[a]	(*S*)

[a] Determined by HPLC analysis using CHIRALCEL OD-H after conversion to the corresponding β-amino acid esters with Zn/H_2SO_4. [b] Determined by HPLC analysis using CHIRALPAK AD after conversion to the corresponding β-amino acid ester with Zn/H_2SO_4. [c] Determined by HPLC analysis using CHIRALCEL OD-H.

mimetic of the RDG (Arg-Gly-Asp) peptide mimetic fibrinogen receptor antagonist, anti-platelet aggregation agent.[16]

A variety of cyclic nitrones were found to undergo the chiral titanium catalyzed reaction with **6**. The addition of **6** to 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide (**9a**), derived by the catalytic oxidation of the corresponding 1,2,3,4-tetrahydroisoquinoline, in the presence of the titanium catalyst **8e** gave 1,2,3,4-tetrahydro-1-isoquinolineacetic acid derivative **10a** in 84% yield with 83% ee (eq 3).



Recrystallization of the adduct thus obtained from 2-propanol gave optically pure **10a**. Treatment of **10a** with Zn/H_2SO_4 gave methyl 6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolineacetate, which is an important precursor of isoquinoline alkaloids. Similarly, the corresponding adduct **10b** was obtained in 88% yield with 90% ee. Optically active *N*-hydroxyl-β-amino acids or β-amino acids can be prepared in large scale from the corresponding secondary amines by two catalytic processes in combination with the catalytic synthesis of nitrones from secondary amines.

The reactions exhibit a positive nonlinear relationship between the enantiomeric purities of the chiral titanium catalyst **8e** and the products **7a** and **10a**, indicating that binaphtholato-bridged dimeric complex seems to be involved as the active species in these reactions. The origin of the reversed sense of stereoinduction using catechol ligands remains unclear. Experiments are underway to examine the mechanism.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7** and **10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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