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Asymmetric Synthesis of β-Amino Acids by Addition of Chiral Enolates to *N*-Acyloxyiminium Ions and Application for Synthesis of Optically Active 5-Substituted 8-Methylindolizidines

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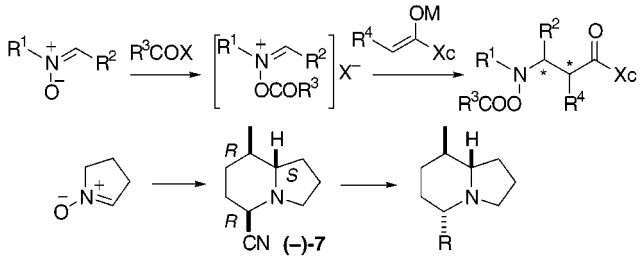
ABSTRACT



***N*-Acyloxyiminium species generated from nitrones with acyl halides are highly reactive and can undergo reaction with soft nucleophiles such as enolates. Optically active β-amino acid derivatives can be prepared using chiral enolates bearing chiral auxiliary. The usefulness of the present method is demonstrated by the enantioselective synthesis of (5*R*,8*R*,8a*S*)-5-cyano-8-methylindolizidine ((−)-7), which is a common key intermediate for 5-substituted 8-methylindolizidines.**

Nitrones are highly valuable intermediates for synthesis of various nitrogen-containing biologically active compounds.[1] Various hard carbon nucleophiles can be introduced at the position α to the nitrogen of nitrones to give α-substituted hydroxylamines;[2,3] however, soft nucleophiles such as enolates cannot be introduced because of low reactivity of nitrones toward soft nucleophiles. To raise the reactivity, we examined the generation of *N*-acyloxyiminium species **2** which are known to be formed by the reaction of nitrones **1** with acylating reagents and undergo rearrangement to give

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(1) Recent reports for asymmetric synthesis of nitrogen-containing biologically active compounds utilizing diastereoselective addition of nucleophiles to chiral nitrones are given in the following. (a) (+)-Zileuton: Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103−6106. (b) Amino sugars: Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505−520. (c) (+)-Lentiginosine: Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706−5707. (d) (+)-Polyoxin J: Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497−5507.

(2) (a) Breuer, E. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, Part 1; Patai, S., Ed.; Wiley: New York, 1982; pp 459−564. (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988.

(3) (a) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744. (b) Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265−271. (c) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383−2386. (d) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170−6172.

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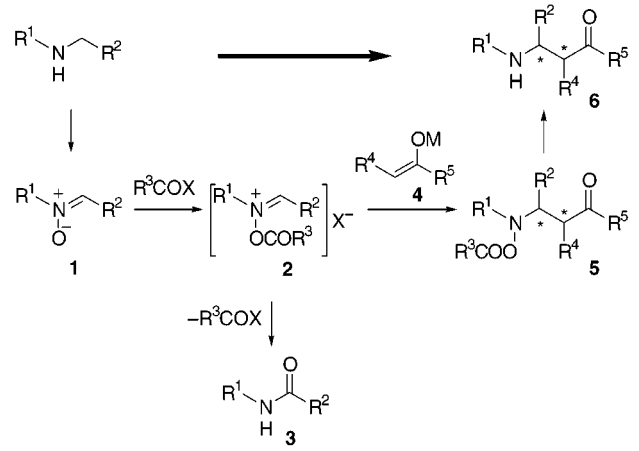
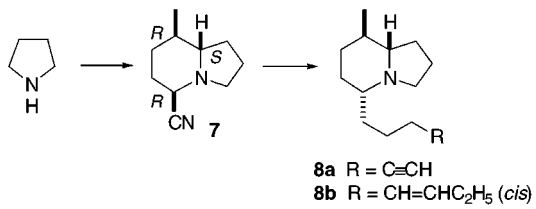
amides **3**[4] or α-acyloxyimines.[5] The active intermediates **2** thus formed have never been used as the precursors for synthesis of α-substituted nitrogen compounds. Therefore, we examine the possibility of trapping the highly reactive *N*-acyloxyiminium species **2** with soft nucleophiles before the rearrangement. Actually we succeeded in trapping **2** with enolates **4** to give α-substituted hydroxylamine derivatives **5**. Since nitrones **1** can be prepared conveniently by catalytic oxidation of secondary amines with H_2O_2,[3] the present reaction provides a highly useful method for the synthesis of α-substituted amine derivatives **6** from secondary amines (Scheme 1).

Scheme 1



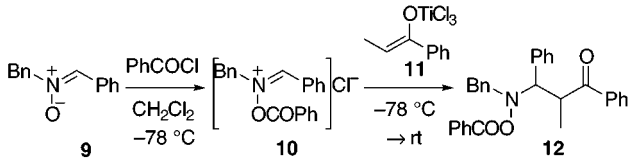
We wish to report a highly convenient method for synthesis of optically active *β*-amino acids,[6] which are of interest in view of pharmacological activity[7] and useful precursors for synthesis of nitrogen-containing biologically active compounds such as *β*-lactam antibiotics,[8] by addition of chiral enolates to *N*-acyloxyiminium ions thus formed. Further, we wish to show the usefulness of the present method by demonstrating enantioselective synthesis of (5*R*,8*R*,8a*S*)-5-cyano-8-methylindolizidine (**7**),[9] which is a common key intermediate for the synthesis of indolizidine alkaloids such as 205A (**8a**) and 235B (**8b**), from pyrrolidine (Scheme 2).

Scheme 2



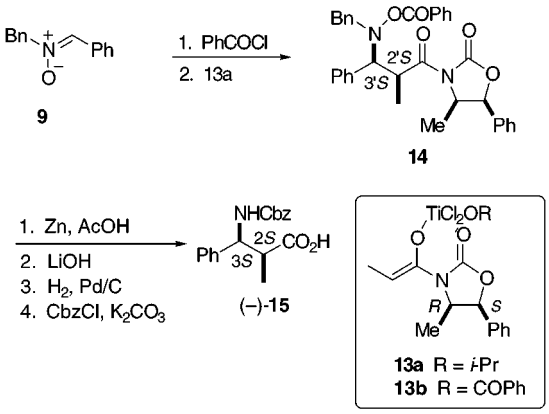
The reaction of (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (**9**)[3b] with the titanium enolate **11**, generated from propiophenone, $TiCl_4$, and *i*-Pr_2NEt in CH_2Cl_2,[10] did not occur even at room temperature. However, treatment of nitrone **9** with benzoyl chloride in CH_2Cl_2 at −78 °C to give *N*-benzoyloxyiminium ion **10** and subsequent addition of the titanium enolate **11** and warming up to room temperature gave 3-(*N*-benzoyloxybenzylamino)-2-methyl-3-phenylpropiophenone (**12**) (79%, (2*R**,3*R**)-**12**/(2*R**,3*S**)-**12** = 64:36) (Scheme 3). Apparently, the reactivity of the nitrone improved significantly by converting it to the corresponding *N*-acyloxyiminium ion.

Scheme 3



This method can be applied to the diastereoselective addition of chiral enolates to nitrones. Thus, the reaction of *N*-acyloxyiminium ion **10** with chiral titanium enolate **13a**, prepared upon treatment of (4*R*,5*S*)-4-methyl-5-phenyl-3-propanoyloxazolidinone[11] with (*i*-PrO)$TiCl_3$ and *i*-Pr_2NEt,[10] gave α-methyl-*β*-phenylalanine derivative **14** in 65% isolated yield (Scheme 4). Only two diastereomers (2′*S*,3′*S*)-**14** and

Scheme 4



(2′*S*,3′*R*)-**14** were obtained in a ratio of 85:15 among the possible four stereoisomers. A major diastereomer (2′*S*,3′*S*)-

(4) Heine, H. W.; Zibuck. R.; VandenHeuvel, W. J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3691−3694 and references therein.
(5) Coates, R. M.; Cummins, C. H. *J. Org. Chem.* **1986**, *51*, 1383−1389.
(6) For a review, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1996.
(7) For reviews, see: (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; pp 25−54. (b) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855−878.
(8) For a review, see: Berks, A. H. *Tetrahedron* **1996**, *52*, 331−375.
(9) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868−4874.
(10) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

14 ([α]$^{24.5}_{D}$ +73.4° (*c* 1.02, $CHCl_3$)) was isolated in 50% yield by column chromatography on silica gel. The compound (2′*S*,3′*S*)-**14** was converted to (2*S*,3*S*)-3-(*N*-benzyloxycarbonylamino)-2-methyl-3-phenylpropanonic acid ((−)-**15**) (mp 169.0−171.0 °C, [α]$^{31}_{D}$ −36.7° (*c* 1.10, MeOH)) along with the recovered chiral auxiliary upon hydrolysis, catalytic hydrogenation, and N-protection.

The stereochemistry obtained can be rationalized by assuming the chelation model shown schematically in Figure 1. The stereochemistry at the C-2′ position of **14** arises from a diastereofacial selection of chelated (*Z*)-enolate **13a** induced by its bulky substituents. Thus, the *N*-benzoyloxyiminium ion **10** approaches from the opposite side of the methyl and phenyl groups (*re* face) of **13a** to give **14** with 2′*S*-configuration. The stereochemistry at the C-3′ position of **14** reflects the enantiofacial selection of (*Z*)-*N*-benzoyloxyiminium ion **10**. Coordination of the carbonyl group of **10** to the titanium of **13a** as the sixth coordinating ligand would give the most favorable transition state with *si* face selection as shown in Figure 1, which has the lowest steric repulsion, affording the major isomer (2′*S*,3′*S*)-**14**.

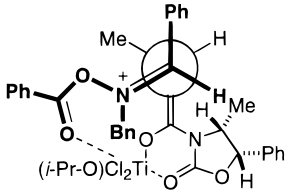
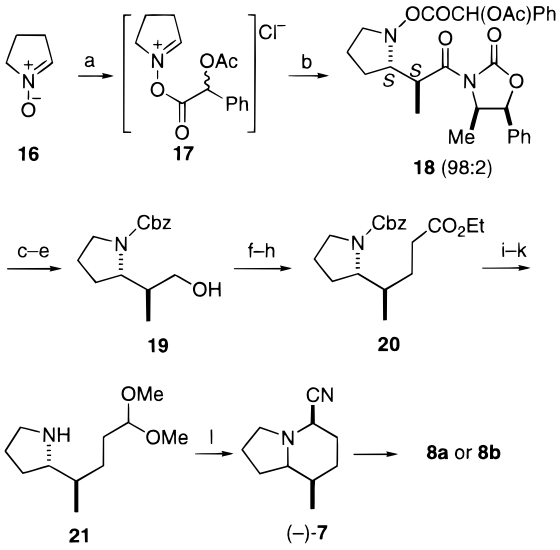


Figure 1. A proposed chelation model for the reaction of *N*-benzyloxyiminium ion **10** with titanium enolate **13a**.

The stereoselective synthesis of *N*-hydroxy-*β*-amino acids can be applied to the synthesis of optically active α-substituted pyrrolidines, which are hardly accessible. Thus, this method was used for the enantioselective synthesis of (5*R*,8*R*,8a*S*)-5-cyano-8-methylindolizidine ((−)-**7**),[9] which is a common key intermediate of a series of 5-substituted 8-methylindolizidines such as (−)-205A (**8a**) and (−)-235B (**8b**). These are the skin alkaloids of neotropical arrow-poison frogs and are noncompetitive inhibitors of the acetylcholine receptor complexes.[12]

Our strategy for the synthesis of (−)-**7** is illustrated in Scheme 5. The stereocontrol at the α-position of pyrrolidines is extremely difficult because of its five-membered planar structure. We used the bulky *N*-(acetylmandelyloxy)iminium ion **17** derived from 1-pyrroline *N*-oxide (**16**)[3c] and (±)-

Scheme 5[a]



[a] Reagents: (a) PhCH(OAc)COCl; (b) **13b**; (c) Zn, HCl; (d) CbzCl, K_2CO_3; (e) $NaBH_4$; (f) PPh_3, CBr_4; (g) $NaCH(CO_2Et)_2$; (h) NaCl, DMSO; (i) DIBALH; (j) MeOH, TsOH; (k) H_2, Pd/C; (l) KCN, HCl.

acetylmandelyl chloride. Further, to avoid the decomposition of the less stable *N*-acyloxyiminium ion **17**, we used weaker Lewis acidic titanium enolate **13b**, prepared by the reaction of (4*R*,5*S*)-4-methyl-5-phenyl-3-propanoyloxazolidinone with $TiCl_4$ and *i*-Pr_2NEt,[10] and subsequent treatment with $PhCO_2H$ and *i*-Pr_2NEt. Addition of the titanium enolate **13b** to the *N*-acyloxyiminium ion **17** at −78 °C gave the adduct **18** in 84% yield in extremely high diastereoselectivity ((2′*S*,2″*S*)-**18**/(2′*S*,2″*R*)-**18** = 98:2). Reductive cleavage of the N—O bond of **18** upon treatment with Zn/HCl followed by N-protection with benzyloxycarbonyl chloride (CbzCl) gave N-protected *β*-amino acid derivative. Further, reduction with $NaBH_4$ and column chromatography on silica gel gave (2*S*,2′*S*)-*γ*-amino alcohol **19** ([α]$^{23}_{D}$ −37.3° (*c* 1.43, MeOH)) in 77% yield as a single diastereomer along with the recovered chiral auxiliary. The carbon chain elongation was accomplished by bromination of **19**, treatment with sodiomalonate, and dealkoxycarbonylation, giving amino ester (4*R*,2′*S*)-**20** ([α]$^{25}_{D}$ −26.9° (*c* 1.05, $CHCl_3$)) in 65% isolated yield. Reduction of **20** with diisobutylaluminum hydride (DIBALH), *p*-toluenesulfonic acid-catalyzed acetalization, and subsequent removal of N-protection afforded the amino acetal (4*R*,2′*S*)-**21** ([α]$^{23}_{D}$ +7.8° (*c* 1.12, CH_2Cl_2), lit.[9] [α]$^{23}_{D}$ +7.4° (*c* 1.1, CH_2Cl_2)) (55%). Treatment of amino acetal **21** with a solution of KCN and then a solution of HCl gave (−)-**7** (98%).[9,13] The transformation of (−)-**7** into (5*R*,8*R*,8a*S*)-5-substituted 8-methylindolizidines **8a** and **8b** has been performed readily by the literature procedures.[9]

(11) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(12) Examples for the asymmetric synthesis of 5-substituted 8-methylindolizidines: (a) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithendank, C. *J. Org. Chem.* **1991**, *56*, 1393−1405. (b) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625−626. (c) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883. (d) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943−945. (e) Comins, D. L.; LaMunyon, D. H.; Chen X. *J. Org. Chem.* **1997**, *62*, 8182−8187. (f) Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189−5192.

(13) The cyclization was carried out according to the reported procedure[9] to give α-amino nitrile **7**, which contains the epimer at C−5 (7% by ^{1}H NMR).

Further investigations to apply to the present method for synthesis of biologically active nitrogen-containing compounds are now in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**, **12**, **14**, **15**, and **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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