Highly Diastereoselective Addition of a Chiral Ketene Silyl Acetal to Nitrones: Asymmetric Synthesis of β-Amino Acids and Key Intermediates of β-Lactam Antibiotics

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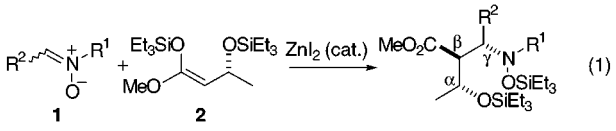
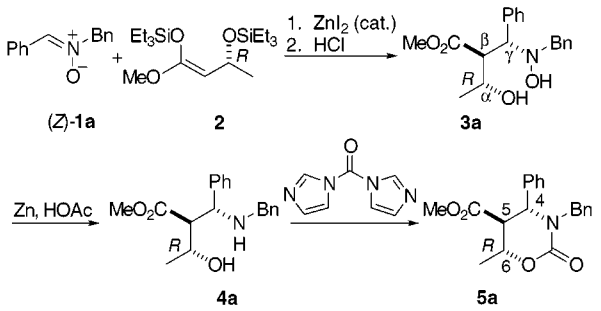
Addition of nucleophiles to nitrones is rapidly developing as one of the most effective methods for the synthesis of α-substituted amines and *N*-hydroxy derivatives,[1] because efficient catalytic methods for synthesis of nitrones from secondary amines were explored recently.[2] Syntheses of optically active nitrogen-containing natural products[3] from chiral nitrones have been reported; however, a few attempts have been made on asymmetric synthesis by addition of chiral nucleophiles to prochiral nitrones[4] with poor diastereoselectivities except one example of double stereodifferentiation with the matched set of chiral nucleophile and chiral nitrone.[4d] We wish to report here highly diastereoselective zinc iodide-catalyzed reaction of nitrones **1** with (*Z*)-(*R*)-1,3-bis(triethylsilyloxy)-1-methoxy-1-butene (**2**) derived from methyl (*R*)-3-hydroxybutanoate, which is readily available either by catalytic asymmetric hydrogenation[5] or by biological processes,[6] as depicted in eq 1. The present reaction has advantages over Mannich-like additions to imines because nitrones are more stable than imines and easily controlled.



(1)

The reaction of (*Z*)-*N*-benzylidenebenzylamine *N*-oxide (**1a**) (R^1 = Bn, R^2 = Ph) with dilithium enolate derived from methyl (*R*)-3-hydroxybutanoate gave no adduct even under a variety of reaction conditions. However, the reaction of (*Z*)-**1a** with chiral ketene silyl acetal **2** in the presence of a Lewis acid catalyst gives a desired adduct quite efficiently. Actually, the reaction of (*Z*)-**1a** with **2** in the presence of zinc iodide (20 mol %) and 4A molecular sieves at 0 °C gave 2-[(*N*-benzyl-*N*-hydroxyamino)phenylmethyl]-3-hydroxybutanoate (**3a**) in 89% yield after treatment with a 6 M HCl solution. Inspection of ^{1}H and ^{13}C NMR spectra of the crude product and those of purified **3a** showed that only one stereoisomer was formed among the possible four stereoisomers. *N*-Hydroxy-β-amino ester **3a** was easily converted to β-amino ester **4a** upon treatment with zinc powder in acetic acid in 88% yield. To determine the stereochemistry of **3a**, amino alcohol **4a** was further transformed into the corresponding cyclic urethane, (4*R*,5*S*,6*R*)-3-benzyl-6-methyl-5-methoxycarbonyl-4-phenylperhydro-1,3-oxazin-2-one (**5a**) (95%) upon treatment with carbonyl diimidazole. The stereochemical assignment of **5a** was made to be 4,5-*anti*-5,6-*anti* on the basis of ^{1}H NMR analysis ($^3J_{4,5}$ = 10.5 Hz, $^3J_{5,6}$ = 10.3 Hz). Thus, the absolute configuration of **3a** was established to be (α*R*,β*S*,γ*R*), and hence the diastereoselective addition of **2** occurred with α,β-*anti*-β,γ-*anti* stereochemistry.



The zinc iodide-catalyzed condensations have been carried out for cyclic nitrones **1b**−**d**, which have *E*-geometry with carbon−nitrogen double bonds. 1-Pyrroline *N*-oxide (**1b**), prepared by a single pot oxidation of pyrrolidine,[2] smoothly reacted with **2** to give *N*-hydroxy-β-amino ester **3b** as a single isomer with α,β-*anti*-β,γ-*anti* stereochemistry in 78% yield. 2,3,4,5-Tetrahydropyridine *N*-oxide (**1c**) and 3,4-dihydroisoquinoline *N*-oxide (**1d**), prepared from piperidine and 1,2,3,4-tetrahydroisoqunoline,[2] underwent addition with **2** to give adducts **3c** (72%) and **3d** (71%), respectively. The stereochemistries of **3b**−**d** were also confirmed on the basis of ^{1}H NMR analysis of the corresponding cyclic urethanes **5b**−**d**. The hydroxylamines **3b**−**d** thus obtained can be easily converted into the corresponding amines **4b** (81%), **4c** (95%), and **4d** (80%) by catalytic hydrogenation in acetic acid. These β-amino acid derivatives **4b**−**d** are enantiomerically pure and highly useful for the synthesis of a wide range of pyrrolidine, piperidine, and isoquinoline alkaloids, respectively.

These results reveal that the condensation of nitrones **1** with **2** exhibits extremely high α,β-*anti*-β,γ-*anti* diastereofacial selection, regardless of the geometry of nitrones **1**. The α,β-*anti* selectivity, which reflects the π-facial selectivity of ketene silyl acetal **2**, is best accounted for in terms of the attack of nitrone from the less hindered top side (*si*-face) in the preferred conformation (a)[7] as shown in Figure 1. The β,γ-*anti* stereoselectivity reflects the π-facial selectivity of

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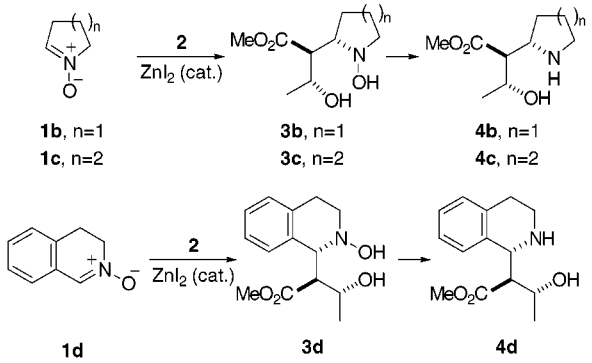


nitrones **1** activated by the coordination of a weak Lewis acid of zinc iodide to the oxygen atom. This is understandable as a result of the favorable antiperiplanar open transition state (b)[8] in Figure 1, where the R^2 group in the nitrone−Lewis acid complex occupies a less hindered position between H and the methoxy group in **2** to avoid unfavorable steric interactions.

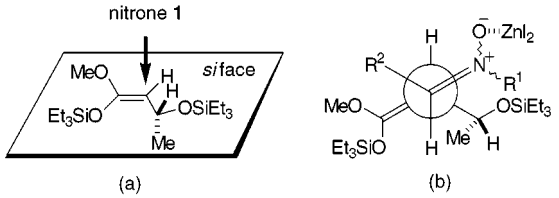
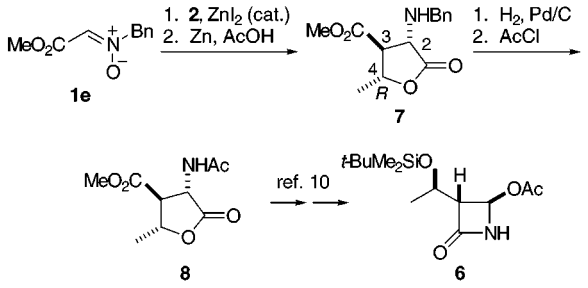


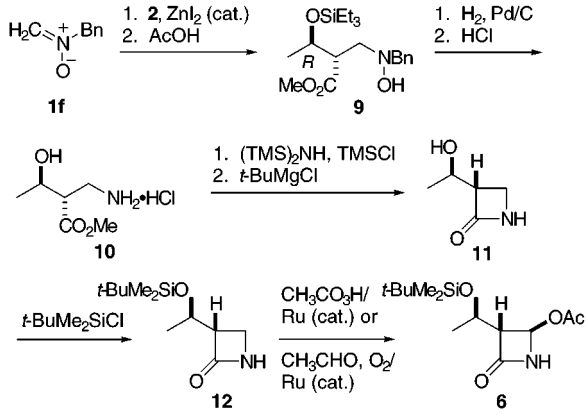
Figure 1. Proposed diastereoselection model for the addition of **2** to nitrones **1** (a) and its Newman projection (b).

This diastereoselective condensation is highly useful for synthesis of (2*R*,3*S*)-2-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**6**),[9] which is a key intermediate of β-lactam antibiotics.[10] Thus, the zinc iodide-catalyzed reaction of *N*-methoxycarbonylmethylidenebenzylamine *N*-oxide (**1e**) with **2** and subsequent treatment with zinc powder in acetic acid gave pentanolide **7** (mp 90.5−91.5 °C; $[\alpha]^{27}_D$ −28.1 (*c* 1.23, $CHCl_3$)) as a single isomer in 60% yield via cyclization of γ-hydroxypentanoate followed by concomitant epimerization at the C-2 position. The stereochemistry of **7** was assigned on the basis of the nuclear Overhauser effects between H(2) and H(4) and between H(3) and Me(4). The pentanolide **7** was easily transformed to the known **8**[11] (mp 107.5−108.7 °C; $[\alpha]^{24}_D$ −41.7 (2.9% MeOH)) by hydrogenation and subsequent acylation (95%). Further conversion of **8** to β-lactam **6** was achieved by the known method.[11]

An alternative approach to β-lactam **6** was performed starting from *N*-methylidenebenzylamine *N*-oxide (**1f**). Thus, the reaction of **2** with nitrone **1f**, prepared in situ by the reaction of *N*-benzylhydroxylamine with formaldehyde, and



subsequent treatment with acetic acid gave *N*-hydroxy-β-amino ester **9** ($[\alpha]^{25}_D$ −23.5 (*c* 1.43, $CHCl_3$)) in 75% yield as a single stereoisomer. Hydrogenation of **9** over Pd/C catalyst followed by treatment with a dilute HCl solution gave β-amino ester hydrochloride **10** ($[\alpha]^{27}_D$ −7.2 (*c* 0.85, MeOH)) in 98% yield. The β-lactam **12** (mp 60.2−61.7 °C; $[\alpha]^{21}_D$ −74.0 (*c* 1.10, $CHCl_3$); ≥99% *ee* (lit. $[\alpha]^{22}_D$ −74.4 (*c* 1.05, $CHCl_3$))[12] was obtained from **10** by ring closure and subsequent silylation of **11** (73%). Since oxidative transformation of **12** to **6** can be carried out readily by ruthenium-catalyzed reaction with peracetic acid (99%)[13] or a combination of acetaldehyde and O_2 (91%),[14] we can obtain the useful key intermediate **6** highly diastereoselectively.



Further work is currently in progress on the extension of the highly diastereoselective reaction to other systems and application to the synthesis of nitrogen-containing biologically active compounds.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **3a**−**d**, **4a**−**d**, **5a**−**d**, and **7**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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