

Stereoselective Formation of *N*-Acyliminium Ion via Chiral *N,O*-Acetal TMS Ether and Its Application to the Synthesis of β -Amino Acids

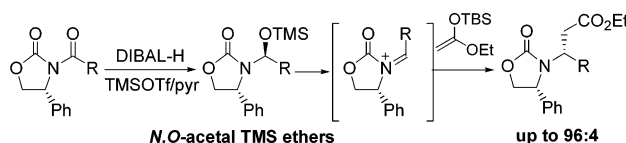
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ABSTRACT



The highly stereoselective synthesis of β -amino acids via the chiral 4-phenyloxazolidinone-controlled linear *N*-acyliminium ion reaction has been achieved by employing chiral *N,O*-acetal TMS ethers. In addition, the mechanism of the excellent stereochemical outcome has been elucidated. The oxazolidinone auxiliary plays a dual role in stereocontrol: the *E/Z* geometry control of the *N*-acyliminium ion induced by an initial stereoselective amide reduction, leading to the chiral *N,O*-acetal TMS ether, and face control of the nucleophile attack in the *N*-acyliminium ion reaction.

The development of new synthetic methods for the asymmetric synthesis of β -amino acids¹ is of considerable current interest, because β -amino acids possess unique biological activities as well as a wide range of synthetic utilities, as key components of antibiotics, peptides, and other bioactive materials.² For this purpose, a number of reactions of imine species with ester enolates or ketenes have been developed.^{3,4}

Recently, we have reported a novel *N*-acyliminium ion precursor of *N,O*-acetal TMS ethers, as well as their efficient preparation.⁵ In particular, *N,O*-acetal TMS ethers turned out to be one of the most general and practical precursors, since

they are superior to other *N*-acyliminium ion precursors in terms of their convenient preparation, functional group compatibility, substituent diversity, and facile conversion to the corresponding *N*-acyliminium ion. Moreover, their suc-

(3) For recent reports about the asymmetric synthesis of β -amino acids utilizing imine species, see: (a) Murahashi, S.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888. (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Alvarez-Larena, A.; Moltrasio, G. Y.; Branchadell, V.; Ortuno, R. M. *J. Org. Chem.* **2002**, *67*, 2402. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (d) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (e) Kise, N.; Uena, N. *Org. Lett.* **1999**, *1*, 1803. (f) Muller, R.; Goessmann, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *37*, 184 and related references are therein.

(4) For excellent reviews on the chemistry of *N*-acyliminium ions and related intermediates, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (b) Hiernstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047–1082.

(5) (a) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165. (b) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commun.* **2002**, 1064.

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(1) For a review, see: Juaristi, E., Ed., *Enantioselective Synthesis of β -Amino Acids*. Wiley-VCH: New York, 1997.

(2) 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) Bewley, C. A.; Faulkner, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2162.

successful synthetic application to the amidoalkylation of acyclic systems enabled us to introduce a variety of chiral auxiliaries at the nitrogen atom for the asymmetric version.

As part of our ongoing studies, we herewith report a novel asymmetric synthetic route to β -amino acids via the stereoselective formation of *N*-acyliminium ions, using 4-phenyl-oxazolidinone as both a chiral auxiliary and as an amine source. In addition, the important dual role of the chiral oxazolidinone in the outstanding stereochemical outcome of this method is described.

For the asymmetric induction (**2** \rightarrow **3**) at the newly formed stereogenic center in the *N*-acyliminium ion species, two important stereocontrolling factors were considered, as shown in Figure 1. The first factor is the *E/Z* geometry control of

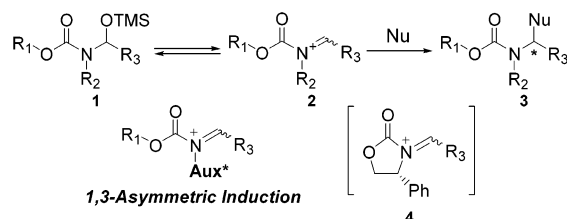


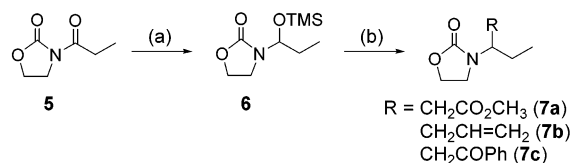
Figure 1.

$C=N^+$ (e.g., **2**), and the second factor is the face control of nucleophile attack in the iminium ion. The *E/Z* geometry control is expected to be dependent on the energy difference of the two geometric isomers, although they are highly influenced by substituents.^{4,6} The face selectivity of the nucleophilic attack is expected to be directed by the chiral auxiliary. Considering these points, we chose the easily cleavable 4-phenyl-oxazolidinone as a chiral auxiliary, in which both the alkoxycarbonyl protecting group of the amine and the nucleophilic face-controlling phenyl group are fixed by the ring system.

Our studies began with an examination of oxazolidinone in the acyclic *N*-acyliminium ion, because the exocyclic *N*-acyliminium ions of oxazolidinone from other precursors are known to have serious limitations such as poor reactivity and/or poor stereoselectivity in adopting various nucleophiles.⁷

As shown in Scheme 1, *N*-propionyl-oxazolidinone **5** was reduced to the aminal aluminum alkoxide, which was trapped in situ with TMSOTf/pyridine to afford the *N,O*-acetal TMS ether **6**.⁵ Subsequent amidoalkylation of the TMS ether was performed by reaction with ketene acetal, allylsilane, and silyl enol ether as nucleophiles under the established conditions to afford the corresponding alkylation products (**7a–c**) in high yields. Thus, *N,O*-acetal TMS ether was

Scheme 1^a



^a Reagents and conditions: (a) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; then, pyridine, TMSOTf, 93%. (b) $BF_3 \cdot OEt_2$, $CH_2=C(OTBS)OEt$ or $CH_2=CHCH_2TMS$ or $CH=C(OTMS)Ph$, CH_2Cl_2 , -78 to $-30\text{ }^\circ\text{C}$; 94, 85, and 89%, respectively.

considered to be one of the most suitable precursors for an *N*-acyliminium ion bearing a chiral auxiliary from the viewpoints of high reactivity and generality.

Preparation of the chiral *N,O*-acetal TMS ethers **9** from the chiral acyloxazolidinones was carried out by analogy with the procedure of Scheme 1, as shown in Table 1. The amide

Table 1.

entry	8	R	<i>N,O</i> -TMS ether (9) ^a	yield (%) ^b	dr ^c
1	8a	CH_3	9a	92	>98:2
2	8b	CH_2CH_3	9b	93	>98:2
3	8c	$CH_2(CH_2)_2CH_3$	9c	87	>98:2
4	8d	CH_2Ph	9d	89	>98:2
5	8e	$CH_2CH_2CH=CH_2$	9e	90	>98:2
6	8f	$CH_2(CH_2)_7CH_3$	9f	81	89:11
7	8g	CH_2CH_2Ph	9g	83	93:7

^a All of the *N,O*-acetal TMS ethers **9** were sufficiently stable for storage at room temperature. ^b Isolated yields. ^c Determined by 1H NMR spectra of the diastereomeric mixture **9** or the isolation yield of each isomer by flash column chromatography.

precursors possessing various alkyl substituents were prepared by *n*-BuLi treatment of (*R*)-(-)-4-phenyl-oxazolidinone, followed by the addition of the corresponding acyl chlorides in THF at $-78\text{ }^\circ\text{C}$.⁸ Reduction of the acylamides **8** with DIBAL-H, followed by in situ trapping of the resulting aluminum alkoxide with TMSOTf, gave the corresponding *N,O*-acetal TMS ethers **9** in high yields as well as in high diastereoselectivities. The absolute configurations of the newly generated stereogenic centers in the major stereoisomers of **9a–g** were confirmed by the X-ray crystallographic analysis of **14a**, the major product of **13** (Figure 2, vide infra).⁹ The two diastereomers of **9f** and **9g**, shown in entries **6** and **7**, respectively, were readily separable by a simple column chromatography step.

(8) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.

(9) For details, see Supporting Information.

(6) (a) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121. (b) Al-Talib, M.; Zaki, M.; Hehl, S.; Stumpf, R.; Fischer, H.; Jochims, J. C. *Synthesis* **1996**, 1115.

(7) Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2002**, *67*, 2989. We are very thankful to Professor M. Petrini for his kind and helpful discussion on this topic.

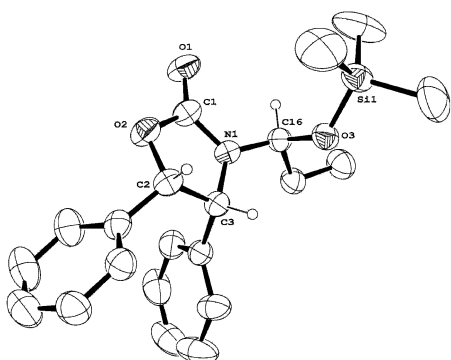


Figure 2. ORTEP drawing of the X-ray structure of *N,O*-acetal TMS ether **14a**. Other hydrogens have been omitted for clarity.

To establish the optimal reaction conditions for the asymmetric alkylation, the conversion of **9b** to **10b** was initially examined under various reaction conditions as shown in Table 2. The yield and stereoselectivity were not influ-

Table 2.

entry	Lewis acid (equiv)	solvent	temp (°C)	yield (%) ^a	dr ^b
1	BF ₃ ·OEt ₂ (0.2)	CH ₂ Cl ₂	−78 → 0	35	^c
2	BF ₃ ·OEt ₂ (0.5)	CH ₂ Cl ₂	−78 → 0	91	96:4
3	BF ₃ ·OEt ₂ (1.0)	CH ₂ Cl ₂	−78 → 0	95	95:5
4	BF ₃ ·OEt ₂ (2.0)	CH ₂ Cl ₂	−78 → 0	92	95:5
5	BF ₃ ·OEt ₂ (1.0)	CH ₂ Cl ₂	−78		
6	BF ₃ ·OEt ₂ (1.0)	CH ₂ Cl ₂	0	91	89:11
7	BF ₃ ·OEt ₂ (1.0)	CH ₂ Cl ₂	−23	95	93:7
8	BF ₃ ·OEt ₂ (1.0)	CH ₂ Cl ₂	−41	89	96:4
9	BF ₃ ·OEt ₂ (1.0)	PhCH ₃	−78 → 0	89	91:9
10	BF ₃ ·OEt ₂ (1.0)	CH ₃ CN	−10	26	67:33

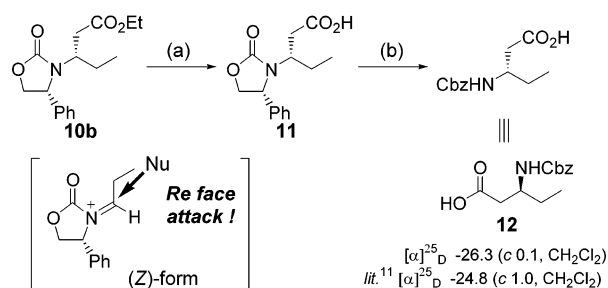
^a Isolated yields. ^b Determined by both ¹H NMR spectra and HPLC measurement of the diastereomeric mixture. ^c Not determined.

enced by the amount of Lewis acid. However, they were very sensitive to the reaction temperature and the solvent. These results imply that the temperature and polarity of the solvent significantly affect the selective formation of the (*E*)- or (*Z*)-geometry of the *N*-acyliminium ion.

To determine the stereochemistry of the newly generated stereogenic center, the ester **10b** was hydrolyzed to the acid **11**, and then the 4-phenyloxazolidinone auxiliary was cleaved under reductive conditions with Li/NH₃ (Scheme 2).¹⁰ Cbz protection of the resulting amino acid gave the known

(10) (a) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977 (b) Lucet, D.; Sabelle, S.; Kostelitz, O.; Gall, T. L.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583.

Scheme 2^a



^a Reagents and conditions: (a) LiOH–H₂O, THF/H₂O (1/1), 99%. (b) Li, liquid NH₃, THF/*t*-BuOH; then, CbzCl, Na₂CO₃, 82%.

protected β -amino acid **12**,¹¹ which was identical in all aspects. The stereochemical outcome can be understood by the preferred formation of the (*Z*)-isomer of the *N*-acyliminium ion,¹² which was contrary to our initial assumption (vide infra).

The efficient and highly diastereoselective conversion of other *N,O*-acetal TMS ethers to the corresponding esters is summarized in Table 3. All of the *N,O*-acetal TMS ethers

Table 3.

entry	9	10	yield (%) ^b	dr ^c
1	9a	10a	99	95:5
2	9b	10b	98	96:4
3	9c	10c	87	92:8
4	9d	10d	47	96:4
5	9e	10e	96	93:7
6	9f	10f	70	91:9
7	9g	10g	74	96:4

^a Only the major component of the two diastereomers was used for the alkylation reaction. ^b Isolated yields. ^c Determined by ¹H NMR spectra for all compounds and HPLC measurement for **10a** and **10b**; both experiments showed the same results

possessing various alkyl substituents gave excellent yields and diastereoselectivities. The stereochemistry of the newly formed stereogenic center was determined by analogy with **10b**. The byproduct (especially in entry 4) was mainly the enamine, which resulted from elimination rather than ketene

(11) Palomo, C.; Oiarbide M.; Condepcion Gonzalez-Rego, M.; Sharma, A. K.; Garcia, J. M.; Gonzalez, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063.

(12) Formation of *N*-acyliminium ion was partly confirmed by the observation of the change of ¹H NMR spectrum at −40 °C after an addition of BF₃·OEt₂ to the *N,O*-acetal TMS ether in CD₂Cl₂ in the absence of the nucleophiles. We thank the referees for their valuable advice on the mechanistic aspects.

addition. We have also investigated the mechanistic basis for the excellent stereochemical outcome of this transformation.

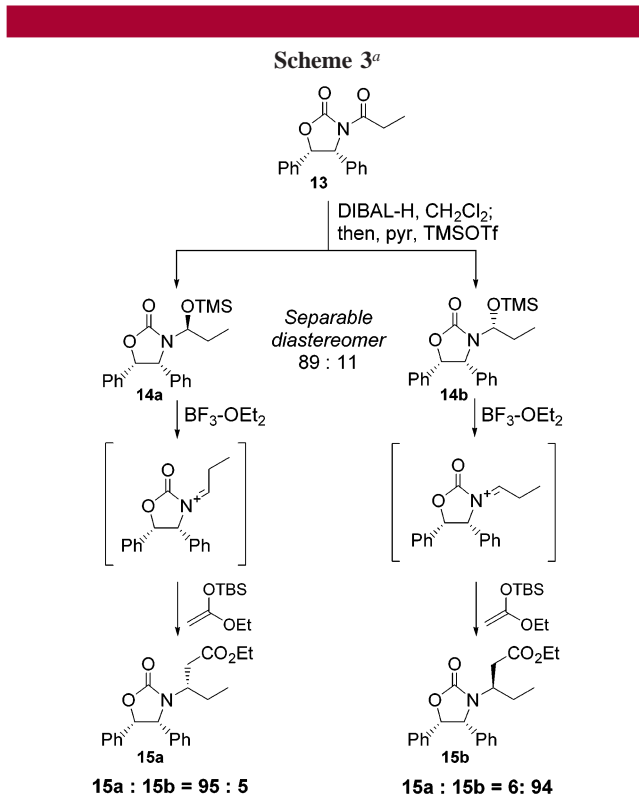
At the outset, we assumed that the selectivity for the (*E*)- or (*Z*)- geometry of the *N*-acyliminium ion would be determined by the energy difference of the two isomeric forms. Thus, we carried out a semiempirical calculation on the (*E*)- and (*Z*)-isomers generated from **9b**. However, the energy difference of the two isomers was unexpectedly only 0.005 kcal/mol,¹³ which was not at all sufficient to support our assumption. After intensively investigating the stereocontrolling factors, we realized that *the stereochemistry of the OTMS-attached carbon could crucially influence the stereoselective formation of the corresponding N-acyliminium ion*.

To certify our rationale, we performed amidoalkylations of the diastereomers **14a** and **14b**, which were prepared from the amide **13** by the same procedure employed for **9**. We chose 4,5-diphenyloxazolidinone as the most suitable chiral auxiliary for our purpose, because the two diastereomers of the TMS ethers **14** had a relatively low diastereomeric ratio (dr = 89:11) and were easily separable for the next step (Scheme 3). To our surprise, the newly formed stereogenic center of each major product possessed the exactly opposite stereochemistry. This result implies that the stereochemistry of the OTMS-bearing carbon controls the *E/Z* geometry of the *N*-acyliminium ion. Furthermore, the selective formation of (*E*)- or (*Z*)- geometry of *N*-acyliminium ion is essential for the desired asymmetric induction by the chiral auxiliary-controlled selective amidoalkylation.

To the best of our knowledge, no mechanistic studies on the diastereoselective alkylation using a chiral precursor of the *N*-acyliminium ion species have been carried out, due to the difficulty of preparing suitable chiral acyclic precursors. Obviously, this unique *N,O*-acetal TMS ether enabled us to develop this conceptually new mechanistic rationale for the outstanding stereoselectivity of our transformation as well as the new stereoselective synthesis of β -amino acids.

In conclusion, we have developed a highly stereoselective synthetic route to β -amino acids via diastereoselective amidoalkylation, which was induced by stereoselective formation of the *N*-acyliminium ion from the chiral *N,O*-acetal TMS ether. The chirality of the oxazolidinone auxiliary turned out to play a dual role for both the stereoselective reduction of the amide by DIBAL-H, leading to the chiral

(13) Calculation was carried out with SYBYL 6.6 (Tripos) on a Silicon Graphics O₂ workstation.



^a Yields of **14a** and **14b** were 89 and 56%, respectively. In the case of **14b**, a substantial amount of the enamine was formed.

N,O-acetal TMS ether and the stereoselective alkylation of the *N*-acyliminium ion. Currently, intensive studies on the detailed mechanism and generality of this new transformation, based on our observations, and its wide range of synthetic applications are in progress. Updated results will be reported in due course.

Acknowledgment. This work was supported by the Korea Research Foundation Grant (KRF-2002-070-C-00058).

Supporting Information Available: Representative experimental procedures for the synthesis of compounds **9a**, **10a**, **11**, and **12**, spectral data for all new compounds in Schemes 1–3 and Tables 1–3, and the X-ray crystallographic file (in CIF format) for **14a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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