Diastereoselective Michael Addition of Magnesium Amide to *O*-(2-Alkenoyl)TEMPOs and Comparison of Reactivity with Acyl Substituent-Modified Carboxylic Analogues

Li-Jian Ma,[1] Zhen-Wu Mei,[1] Keisuke Toyohara,[1] Hiroyuki Kawafuchi,[2] Junzo Nokami,[3] and Tsutomu Inokuchi*[1]

[1]Department of Medicinal and Bioengineering Science, Graduate School of Natural Science and Technology, Okayama University, Tsushima-naka, Kita-ku, Okayama 700-8530

[2]Department of Chemical and Biochemical Engineerings, Toyama National College of Technology, Hongo-machi, Toyama 939-8630

[3]Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, Ridai-cho, Kita-ku, Okayama 700-0005

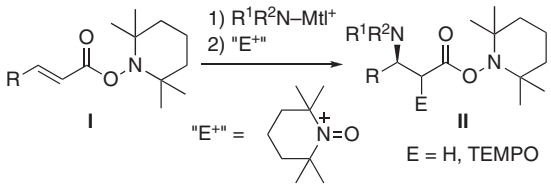
Received June 28, 2010
E-mail: inokuchi@cc.okayama-u.ac.jp

O-(2-Alkenoyl)TEMPOs bearing an O–N bond in the acyl substituent are highly reactive in Michael addition of magnesium amide compared with their acyl substituent-modified analogs. Highly diastereoselective addition is achieved to the $AlMe_3$-treated *O*-(2-alkenoyl)TEMPO as an acceptor with the Mg amide generated from optically active secondary amine.

β-Amino acids show interesting pharmacological properties and are found in free form or as components of naturally occurring biologically active peptides, and α-hydroxy-β-amino acids are also found in various peptidic enzyme inhibitors and constitute the side chain of the anticancer drug taxol®.[1,2] Although many approaches to this class of amino acid are developed by homologation of α-amino acids, hydrogenation of 3-aminoacrylates, derivatization of aspartic derivatives, and others,[1a,1c,1d] the most direct access to this structural unit must be Michael addition of amines or amide anions to acrylates and derivatives.[3]

With respect to 1,4-addition of amide anion, Yamamoto and coworkers devised a silylated amide anion to improve the yield and selectivity.[4] Davies et al. reported later that addition of a lithium amide from optically active secondary amines to 2-alkenoates proceeded with high diastereoselectivity.[3] Furthermore, Tomioka et al. developed the ligand-controlled asymmetric conjugate addition of lithium amides to enoates by employing C_2-symmetry diether,[5] and Sodeoka et al. reported Pd-catalyzed asymmetric conjugate addition of various amines toward 3-(2-alkenoyl)-2,3-dihydroisoxazole-2-one.[6] However, efficient procedures for the preparation of β-amino acids are of continuous interest,[7] because of increasing importance of β-amino acid moieties in bioactive molecules.[8,9]

As far as the 1,4-addition of amide anion is concerned, we have shown in a previous paper that the conjugate addition of the lithium amide from secondary amine to *O*-(2-alkenoyl)TEMPO (TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl) followed by aldol reaction of the resulting enolate with aldehyde proceeded to give the three-component combined products in good yields.[10] We therefore examined the diastereoselective addition of optically active amides to *O*-(2-alkenoyl)TEMPOs **I** to produce the optically pure β-amino acid derivatives **II** (E = H). Meanwhile, we also studied the effect of TEMPO as the acyl substituent[11] in comparison with other acyl substituent-modified analogs such as Weinreb amides. Furthermore, we attempted to introduce a hydroxy group or its equivalent at the C2 position by trapping the resulting enolate, after the amide anion addition, with the N–O double bond of the *N*-oxoammonium salt, forming **II** (E = TEMPO) (Scheme 1).



Scheme 1. Addition of amide anion to *O*-(2-alkenoyl)-TEMPOs and reaction with electrophiles.

Results and Discussion

Prior to executing the 1,4-addition of amide anions, we reinvestigated the electronic structure of the carbonyl function of *O*-(2-butenoyl)TEMPO (**1c**) in comparison with analogs bearing different hetero–hetero atom bonds such as Weinreb amide **1d**,[12] peroxy ester **1e**, and carbazide **1f**.[13]

As shown in Table 1, **1c** shows IR absorption at 1752 cm^{-1}, which is much higher than Weinreb amide **1d** (1668 cm^{-1}) and carbazides **1f** (1662 cm^{-1}). Accordingly, **1c** has a stronger carbonyl vibration than Weinreb amide **1d**. This implies that contribution of the charged resonance structure of **1c** is less important for *O*-(2-alkenoyl)TEMPOs, in contrast to Weinreb amide **1d**, in which the amide-resonance structure is most important. Therefore, it is expected that *O*-(2-alkenoyl)TEMPOs would be more reactive as a Michael acceptor of various amide nucleophiles than other acyl substituent-modified derivatives, **1d** and **1f**.

With this knowledge in hand, we examined the Michael addition of lithium benzylamide from the amine **6a** to **1c**, and results were compared with those of alkyl butenoates **1a** and **1b**, butenoic Weinreb amide **1d**, and the peroxy ester **1e** (Table 2). Thus, the reaction of lithium benzylamide and **1c** proceeds at −78–−70 °C to give the corresponding adduct **2c** in 94% yield (Entry 3). Neither of the nucleophilic acyl substitutions were found except for a small amount of the deconjugated **5** due to γ-deprotonation. In contrast, the reaction of crotonates **1a** and **1b** with lithium benzylamide suffers from low yield (Entry 2) and considerable amount of acyl substitution, forming **3** (Entry 1).[4] Furthermore, the reaction of Weinreb amide **1d** with lithium benzylamide produces the acyl substitution **4** as a major product, without forming 1,4-addition products (Entry 4). In addition, the reaction of the peroxy ester **1e** produces no desired amination, but the acyl group substitution product **4** as a major product. Thus,

Published on the web December 2, 2010; doi:10.1246/bcsj.20100172

Table 1. Acyl Substituent-Modified Derivatives and Their Resonance Structure, and IR Absorptions of ν_{CO}/cm^{-1}

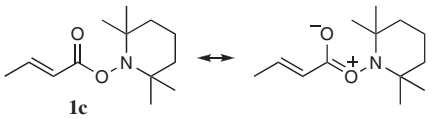
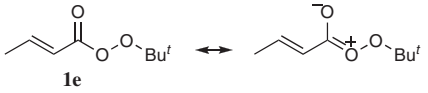
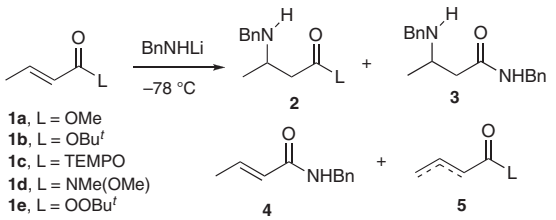
 **1c**	1752
 **1d**	1668
 **1e**	1761
 **1f**	1662

Table 2. Effect of Acyl Substituents on Michael Addition of Amide Anions[a)]



Entry	1	Product, Yield/%[b)]			
		1,4-add **2**	1,4-add/subst. **3**	acyl subst. **4**	SM/ isomer **5**
1[c)]	**a**	20	60	—	2
2	**b**	72	1–2	—	2–3
3	**c**	94	—	—	2–3
4	**d**	—	—	76	15
5	**e**	—	—	61	28

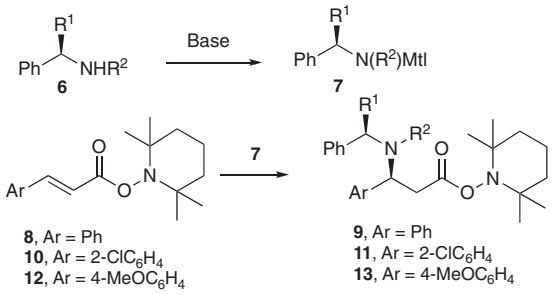
a) Carried out with **1** (0.5 mmol) and BnNHLi (**7a**, 1.0 mmol) in THF (3 mL) at −78 °C for 100 min. b) Based on isolated products after column chromatography. c) Data taken from Ref. 4.

among the 2-butenoyl derivatives examined, the *O*-(2-alkenoyl)-TEMPO, i.e., **1c**, is most promising as a Michael acceptor for the reaction of the amide anions from amines.

In order to prepare optically active β-aminocarboxylic derivatives, we then examined the diastereoselective addition of the corresponding amides **7**, derived from optically active secondary amines **6b** and **6c**, to *O*-(cinnamoyl)TEMPO (**8**), by exploring the effect of the substituents on the amino group, kind of metal ion, and additives (Table 3). As shown in Entries 1 and 2, the Michael additions of the lithium amides **7** from benzylamine (**6a**) and *R*-(+)-α-methylbenzylamine (**6b**) to **8** proceed cleanly at −78 °C, giving the corresponding **9a** and **9b**, but in low diastereoselectivity (2.7:1) with respect to **9b** (Entry 2). The ratio of diastereomers is slightly improved by using the lithium amides **7** from (*R*)-(+)-*N*-benzyl(1-α-methylbenzyl)-amine (**6c**), giving the 1,4-adducts **9c** in a 4:1 ratio (Entry 3). Gratifyingly, the diastereoselectivity of **9c** is greatly improved to 22:1 by using the magnesium amide **7** from **6c**, but in low yield (62%) and with longer reaction period (12 h) (Entry 4).[3c]

In order to improve these inferiorities, we focused our attention on activating the Michael acceptor **8** with Lewis acid such as Me_3Al prior to the reaction.[14] Thus, to our delight, as shown in

Table 3. Addition of Chiral Benzylamide Anions **7** to *O*-(Cinnamoyl)TEMPOs **8**, **10**, and **12**[a)]



Entry	Sub.	Amines, **6** R^1	R^2		Base[b)]	Temp/°C (Time/h)	Product (Yield/%)[c)]	dr[d)]
1	**8**	H	H	**a**	(a)	−78 (2)	**9a** (98)	—
2	**8**	Me	H	**b**	(a)	−78 (2)	**9b** (98)	2.7:1
3	**8**	Me	Bn	**c**	(a)	−78 (2)	**9c** (94)	4:1
4	**8**	Me	Bn	**c**	(b)	−78 (12)	**9c** (62)	22:1
5[e)]	**8**	Me	Bn	**c**	(b)	−78 (1)	**9c** (85)	28:1
6[e)]	**10**	Me	Bn	**c**	(b)	−78 (1)	**11c** (92)	38:1
7[e)]	**12**	Me	Bn	**c**	(b)	−78 (1)	**13c** (77)	25:1

a) Carried out with **8**, **10**, and **12** (0.5 mmol) and **6** (0.75 mmol) in THF. b) Base: (a) BuLi, (b) BuMgCl. c) Based on isolated products after column chromatography. d) Diastereomers ratio on the basis of ^{1}H NMR analyses. e) The Me_3Al-treated **8**, **10**, and **12** were used.

Entry 5, **8** is treated with an equal amount of Me_3Al and allowed to react, after aging, with the magnesium amide **7** derived from **6c** at −78 °C, giving **9c** in 85% yield and with 28:1 of diastereoselectivity within 1 h. Furthermore, the reactions of the magnesium amide **7** derived from **6c** with 3-(2-chlorophenyl)acryloyl- and 3-(4-methoxyphenyl)acryloylTEMPOs (**10** and **12**) under the above conditions afford the corresponding β-amino acid derivatives **11** and **13** in similar yields and diastereoselectivities (25–38:1), showing generality of the present protocol (Entries 6 and 7).

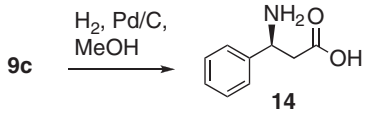
Pleasantly, removal of both the chiral auxiliary and the acyl substituent of **9c** were easily achieved by hydrogenolysis with H_2–Pd/C under balloon pressure, giving the corresponding known β-amino acid **14** in an optically pure form (Scheme 2).[15]

Subsequently, we examined introduction of a hydroxy group at the C2 position by trapping of the enolate anion, after the addition of amide anion, with hetero–hetero double bonds or their equivalent such as *N*-oxoammonium **15**.[16] Thus, the successive treatment of **8** with lithium benzylamide followed with **15**, which is available from TEMPO radical and easy to handle,[17] afforded the desired α-oxygenated product **16** in moderate yields (30–40%) as a 13:1 diastereomeric mixture (Scheme 3).[18]

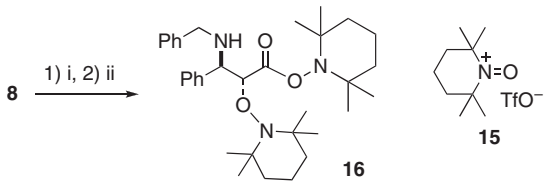
In summary, *O*-(2-alkenoyl)TEMPOs were shown to be more electron deficient than usual alkyl 2-alkenoate and other *N*-acyl substituent-modified analogs such as Weinreb amide and prone to undergo 1,4-addition of amide anions. Highly diastereoselective addition was achieved by making use of the Mg amide from optically active *N*-benzyl(1-α-methylbenzyl)amine in the presence of Lewis acid (Me_3Al).

Experimental

A Typical Procedure for Michael Addition; Preparation of 9c. A solution of magnesium (*R*)-*N*-benzyl(1-α-methylbenzyl)-amide was prepared from (*R*)-PhCH(CH$_3$)NH(CH$_2$Ph) (1.5 mmol) and *n*-BuMgCl (0.9 M in THF, 1.5 mmol) at room temperature for



Scheme 2. Removal of chiral auxiliary and acyl substituent by hydrogenolysis.



Scheme 3. Addition of amide anion to **8** followed by enolate-trapping. Reagent; i) $PhCH_2NH_2$, BuLi, ii) **15**. Tf: CF_3SO_2.

1 h and cooled to −78 °C. A solution of *O*-(cinnamoyl)TEMPO (**8**, 287 mg, 1.0 mmol) in THF (3 mL) and Me_3Al (1 M in hexane, 1.0 mmol) was mixed at room temperature and stirred for 1 h prior to the reaction. To the above Mg amide was added dropwise at −78 °C a THF solution of **8**–Me_3Al and stirred for 1 h at the same temperature. The reaction was quenched with cold aqueous NH_4Cl, and extracted with AcOEt. Extracts were worked up in the usual manner and products were purified by LC (SiO_2, hexane–AcOEt, by increasing the gradient from 20:1 to 7:1 V/V) to give 424 mg (85%) of **9c** ($R^1 = Me$, $R^2 = PhCH_2$): $R_f = 0.45$ (hexane–AcOEt 5:1); $[a]_D^{25}$ −7.2 (*c* 0.57, $CHCl_3$); IR (neat): 2978, 1759, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 0.62, 0.71, 0.77, 0.92 (s, 12H), 1.27 (d, $J = 6.6$ Hz, 3H), 1.28–1.56 (m, 6H), 2.68 (dd, $J =$ 15.3, 3.5 Hz, 1H), 2.80 (dd, $J = 15.3$, 11.4 Hz, 1H), 3.63 and 3.78 (d, $J = 15.0$ Hz, 2H), 3.99 (q, $J = 6.8$ Hz, 1H), 4.56 (dd, $J = 11.4$, 3.5 Hz, 1H), 7.15–7.44 (m, 15H); ^{13}C NMR ($CDCl_3$, 150.8 MHz): δ 16.8, 18.2, 20.1, 20.3, 31.3, 31.5, 34.3, 38.9, 39.0, 50.5, 57.6, 58.1, 59.7, 59.8, 126.5, 126.9, 127.2, 127.7 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.4 (2C), 141.3, 141.5, 144.0, 171.2. Anal. Calcd for $C_{33}H_{42}N_2O_2$: C, 79.48; H, 8.49; N, 5.62%. Found: C, 79.62; H, 8.69; N, 5.57%.

(*S*)-3-Amino-3-phenylpropanoic Acid (14). A solution of **9c** (200 mg, 0.56 mmol) in MeOH (5 mL) was hydrogenated in the presence of 10% Pd/C (20 mg) with H_2 under balloon pressure overnight. The mixture was passed through a Celite® pad and the filtrate was concentrated to afford white solids, washing of which with AcOEt left 158 mg (96%) of **14**: mp 214.5–216 °C (Lit.[15] 215–217 °C); $[a]_D^{25}$ −6.9 (*c* 0.74, H_2O) (Lit.[15] −6.9); IR (KBr): 2758, 1626, 1558, 1537 cm^{-1}; ^1H NMR (D_2O, 600 MHz): δ 2.65 (dd, $J = 16.1$, 6.5 Hz, 1H), 2.74 (dd, $J = 16.1$, 7.9 Hz, 1H), 4.48 (m, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 150.8 MHz): δ 40.1, 52.3, 126.5 (2C), 128.83 (2C), 128.85, 135.6, 176.9.

Preparation of 16. A lithium benzylamide solution (1.0 mmol) was added dropwise to a solution of **8** (144 mg, 0.5 mmol) in THF (2 mL) at −78 °C. After being stirred for 100 min at −78 to −70 °C, this solution was added to a suspension of the *N*-oxoammonium triflate **15** (305 mg, 1.0 mmol) in THF (3 mL). After being stirred at −78 °C for 5 h, the mixture was worked up in the usual manner, purified by LC (SiO_2, hexane–AcOEt 20:1) to give 198 mg (36%) of a 13:1 diastereomeric mixture of the TEMPO-substituted **16** ($R_f = 0.54$, hexane–AcOEt 5:1) as an oil.

Support by Okayama University (Promotion of Graduate Course Students) and the Electric Technology Research Foundation of Chugoku are sincerely acknowledged. We are thankful to Advanced Science Research Center for NMR experiments and EA. We are grateful to Japan Student Services Organization (JASSO) for a scholarship to L.J.M and to Koei Chemical Co., Ltd. for a generous gift of TEMPO•.

Supporting Information

Experimental procedure and spectral data including IR, ^1H NMR, and ^{13}C NMR spectra of **2c**, **9a**, **9b** (mixture), **9c**, **11c**, **13c**, **14**, and **16** are provided. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

References

1 Bioactive β-amino acids and syntheses, reviews: a) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517. b) E. Juaristi, D. Quintana, J. Escalante, *Aldrichimica Acta* **1994**, *27*, 3. c) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, *25*, 117. d) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991.

2 S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1.

3 The conjugate addition: a) S. G. Davies, A. D. Smith, P. D. Price, *Tetrahedron: Asymmetry* **2005**, *16*, 2833. b) S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, *2*, 183. c) M. E. Bunnage, S. G. Davies, C. J. Goodwin, I. A. S. Walters, *Tetrahedron: Asymmetry* **1994**, *5*, 35. d) J. F. Costello, S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

4 N. Asao, T. Uyehara, Y. Yamamoto, *Tetrahedron* **1988**, *44*, 4173.

5 a) H. Doi, T. Sakai, M. Iguchi, K. Yamada, K. Tomioka, *J. Am. Chem. Soc.* **2003**, *125*, 2886. b) T. Sakai, Y. Kawamoto, K. Tomioka, *J. Org. Chem.* **2006**, *71*, 4706.

6 Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.* **2004**, *6*, 1861.

7 N. Sewald, *Angew. Chem., Int. Ed.* **2003**, *42*, 5794.

8 F. von Nussbaum, P. Spiteller, in *Highlights in Bioorganic Chemistry: Methods and Applications*, ed. by C. Schmuck, H. Wennemers, Wiley-VCH, Weinheim, **2004**, Chap. 1.5.

9 Recent reviews on β-amino acids applications: a) D. L. Steer, R. A. Lew, P. Perlmutter, A. I. Smith, M.-I. Aguilar, *Curr. Med. Chem.* **2002**, *9*, 811. b) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893. c) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173.

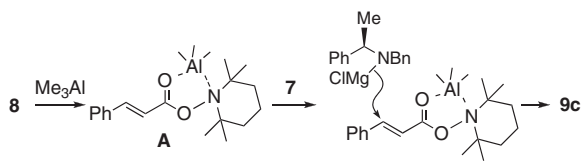
10 T. Inokuchi, H. Kawafuchi, *J. Org. Chem.* **2007**, *72*, 1472.

11 a) T. Inokuchi, H. Kawafuchi, *J. Org. Chem.* **2006**, *71*, 947. b) T. Inokuchi, H. Kawafuchi, J. Nokami, *Chem. Commun.* **2005**, 537. c) T. Inokuchi, H. Kawafuchi, *Tetrahedron* **2004**, *60*, 11969. d) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem., Int. Ed.* **2008**, *47*, 8727.

12 A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171.

13 S. Knapp, J. Calienni, *Synth. Commun.* **1980**, *10*, 837.

14 Coordination of Me_3Al to **8** to form **A** and increased reactivity of **A** toward the amide anion nucleophile, resulting in improvement of diastereoselectivity of **9c**, were assumed.



15 A. V. Sivakumar, G. S. Babu, S. V. Bhat, *Tetrahedron: Asymmetry* **2001**, *12*, 1095.

16 a) U. Jahn, F. Kafka, R. Pohl, P. G. Jones, *Tetrahedron* **2009**, *65*, 10917. b) M. Schämann, H. J. Schäfer, *Synlett* **2004**, 1601. c) T. Inokuchi, K. Nakagawa, S. Torii, *Tetrahedron Lett.* **1995**, *36*, 3223.

17 M. Shibuya, M. Tomizawa, Y. Iwabuchi, *J. Org. Chem.* **2008**, *73*, 4750.

18 The stereochemistry of the substituents at the C2 and C3 of **16** was assigned on the basis of ^1H NMR spectral data; the *anti*-**16** (major): δ 4.11 and 4.88 (d, $J = 8.5$ Hz), the *syn*-**16** (minor): δ 4.15 and 4.65 (d, $J = 7.6$ Hz). Example of similar system, see: K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 1151.