A New Alternative to the Mannich Reaction: Tandem Radical Addition–Cyclization Reaction for Asymmetric Synthesis of γ-Butyrolactones and β-Amino Acids

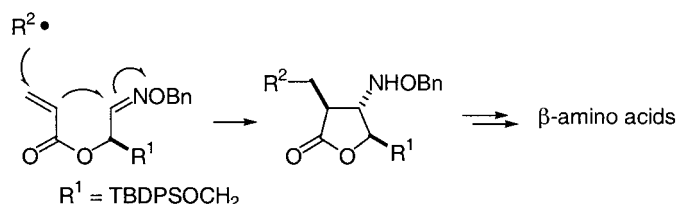Hideto Miyabe, Kayoko Fujii, Takuya Goto, and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

taknaito@kobepharma-u.ac.jp

ABSTRACT

The radical addition–cyclization reaction of substrates having two different radical acceptors such as acrylate and aldoxime ether moieties was studied. This new free radical-mediated Mannich-type reaction proceeded smoothly via a tandem C–C bond-forming process. Furthermore, the diastereoselective tandem reaction provides the novel method for asymmetric synthesis of γ-butyrolactones and β-amino acid derivatives.

The Mannich reaction is an important method for the preparation of β-amino carbonyl compounds. The classical reaction is, however, plagued by a number of serious disadvantages, and the range of applications is limited.[1] Therefore, numerous modern versions of the Mannich reaction have been developed for overcoming the drawbacks of the classical method.[1] In general, the improved methodologies rely on ionic chemistry using preformed electrophiles such as imines and/or stable nucleophiles such as enolates, enol ethers, and enamines. We now report a new Mannich-type reaction based on free radical chemistry,[2] which has

been successfully applied to the asymmetric synthesis of γ-butyrolactones and β-amino acids (Figure 1).[3,4]
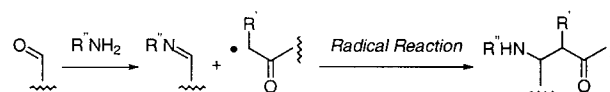

Figure 1. Mannich-type radical reaction.

In studies on the reactivity of various radical acceptors, we have found that the intermolecular reactivity of acrylate derivatives as acceptors toward nucleophilic alkyl radical addition is higher than those of aldoxime ethers but lower

(1) For a review on the Mannich reaction, see: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Overmann, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007. (c) Tramontiti, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

(2) For reviews on radical reactions, see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (b) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (d) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996.

(3) For reviews on asymmetric synthesis of γ-butyrolactones and β-amino acids, see: (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; John Wiley & Sons: New York, 1993.

(4) For our studies on asymmetric synthesis of β-amino acids, see: Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569.

than those of glyoxylic oxime ethers and BF_3-activated aldoxime ethers.[5] As a preliminary study based on these reactivities, we examined the radical addition—cyclization reaction of substrates **1A** and **1B** having two different radical acceptors such as acrylate and aldoxime ether moieties (eqs 1 and 2).[6] Although a wide range of radical reactions of
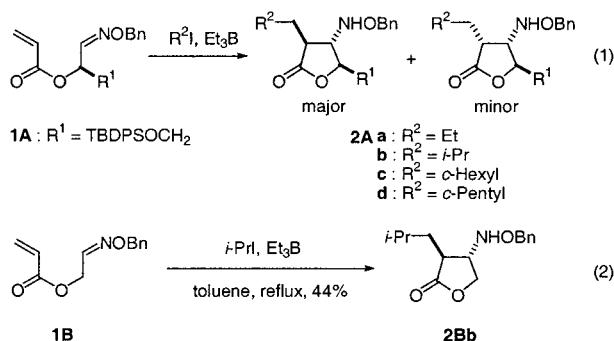
oxime ethers and hydrazones and several synthetic studies of oxacycles have been reported,[7] the present reaction is the first example of the reaction between oxime ethers and alkoxycarbonyl-stabilized radicals.[8]

The success of this free radical-mediated Mannich-type reaction reflects the following points: (i) the overall difference in the intermolecular reactivity of a nucleophilic carbon radical between two electrophilic radical acceptors in the first step and (ii) the high reactivity of triethylborane as a trapping reagent toward a key intermediate aminyl radical, **B** (Figure 2). A remarkable feature of this reaction is the construction of two C—C bonds and two chiral centers via a tandem process. A favorable experimental feature of this method is that the reaction proceeds smoothly even in the absence of toxic tin hydride or heavy metals via a route involving an iodine atom-transfer process.[9] However, it is also important to note the limitation that a primary radical and unstabilized alkyl radical other than the ethyl radical will not work as R^2 radical under the iodine atom-transfer reaction conditions.

(5) Unpublished results.

(6) The intermolecular tandem radical addition—addition approach using three components such as acrylate, aldoxime ether, and alkyl radical was difficult to achieve, due to the low intermolecular reactivity of a resonance-stabilized radical, generated by the initial addition of alkyl radical to acrylate, toward aldoxime ether.

(7) For reviews, see: (a) Naito, T. *Heterocycles* **1999**, *50*, 505. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. For some examples of the radical reaction of oxime ethers, see: (c) Friestad, G. K. *Org. Lett.* **1999**, *1*, 1499. (d) Zhang, J.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 770. (e) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164. (f) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (g) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711. (h) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877. (i) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (j) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745. (k) Booth, S. E.; Jenkins, P. R.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1248.

(8) For study on the intramolecular reactions of alkoxycarbonyl-stabilized radicals with electron rich alkene acceptor, see: Russell, G. A.; Li, C. *Tetrahedron Lett.* **1996**, *37*, 2557.

(9) We previously investigated the intermolecular reaction of oxime ethers via the iodine atom-transfer process between alkyl iodide and ethyl radical generated from triethylborane as a radical initiator. See: (a) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (b) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413. (c) Miyabe, H.; Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209. Bertrand's group reported the
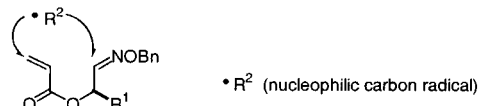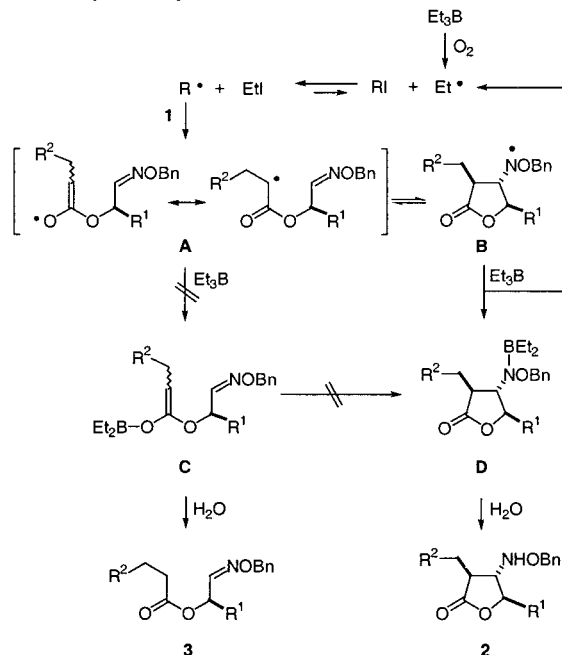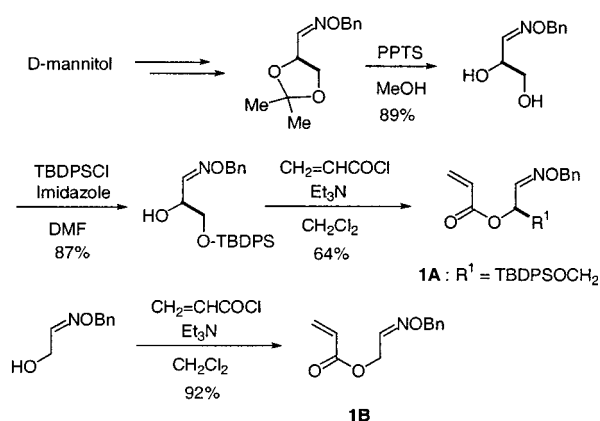
Figure 2. Mannich-type tandem radical addition—cylization.

As shown in Scheme 1, the substrates having acrylate and aldoxime ether moieties were prepared. The chiral substrate **1A** was readily prepared from D-mannitol.[10]

Scheme 1

The results of the radical reaction of **1A** are summarized in Table 1. We initially studied a simple reaction with an

similar studies. See: (d) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. (e) Bertrand, M. P.; L. Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (f) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189.

Table 1. Mannich-Type Radical Reaction of **1A**

run	R²	solvent	T (°C)	yield (%)[a]	selectivity[b]
1[c]	Et	toluene	reflux	70	8:1
2[c]	Et	toluene	20	53	18:1
3[c]	Et	benzene	reflux	64	12:1
4[c]	Et	CH₂Cl₂	20	53	10:1
5[c]	Et	H₂O:MeOH, 1:4	reflux	55	9:1
6[d]	i-Pr	benzene	reflux	68	12:1
7[e]	i-Pr	H₂O:MeOH, 1:4	reflux	80	7:1
8[f]	c-hexyl	benzene	reflux	64	12:1
9[e]	c-hexyl	H₂O:MeOH, 1:4	reflux	56	8:1
10[f]	c-pentyl	benzene	reflux	70	12:1

[a] Isolated yields of major diastereomer. [b] Diastereoselectivities were determined by ¹H NMR analysis and indicate the ratio of a major diastereomer and a second diastereomer. [c] With Et₃B (5 equiv). [d] With i-PrI (6 equiv) and Et₃B (3 equiv). [e] With RI (12 equiv) and Et₃B (3 equiv). [f] With RI (12 equiv) and Et₃B (6 equiv).

ethyl radical by using triethylborane under several reaction conditions. The reaction in refluxing toluene proceeded smoothly to give a major diastereomer, **2Aa**, in 70% isolated yield along with a small amount of the other diastereomers (run 1).[11] The degree of stereoselectivity was shown to be dependent on the reaction temperature; thus, changing the temperature to 20 °C led to an increase in diastereoselectivity to 18:1 (run 2). The treatment in refluxing benzene and CH₂Cl₂ at 20 °C also gave the major diastereomer **2Aa** in 64% and 53% isolated yields, respectively, with moderate diastereoselectivities (runs 3 and 4). From the viewpoint of elucidating the reaction mechanism, it is important to note that the tandem reaction proceeded even in aqueous media (run 5). These observations suggest that the major reaction pathway is not a route involving the conversion of water-unstable boryl enolate **C** into cyclic product **D** but a tandem radical route involving the conversion of water-resistant radical intermediate **B** into cyclic product **D** (Figure 2).[12] In marked contrast to the difficulty in achieving the intermolecular reactions of aldoxime ethers with the resonance-stabilized carbon radicals bearing an electron-withdrawing substituent,[6] resonance-stabilized radical **A** was intramolecularly trapped by an oxime ether group with high efficiency even under mild conditions. We also investigated the substituent effect by using the conformationally flexible substrate **1B** (R¹ = H) under similar reaction conditions. The reaction of **1B** proceeded with a slightly low chemical efficiency to give **2Bb** in 44% yield (eq 2);[10] thus, the bulky substituent R¹ at the chiral center was important not only for stereoselectivity but also for efficient cyclization of intermediate **A** into **D**. Additionally, the high yields were

(10) See the Supporting Information for details on the preparation of **1A**, **1B**, and **4** and experimental procedures.
(11) Radical cascade reaction of oxime ethers was recently reported. See: Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190.
(12) The reaction between Et₃B and the radical α to an ester is less effective than the corresponding reaction of the radical deriving from ketones and aldehydes. For the discussions, see: (a) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925. (b) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1971**, *93*, 3777. (c) Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195.

obtained at higher temperatures due to higher population of the reactive conformer of ester moiety. These similar trends concerning the conformer of ester moiety have also been reported in the radical cyclization.[13]

The diastereoselectivity observed for the reaction can be explained by invoking a favorable conformer minimizing $A^{1,3}$-strain effects between the Et₃B bonding−oxime ether group and substituents at the chiral carbon (Figure 3).[25]
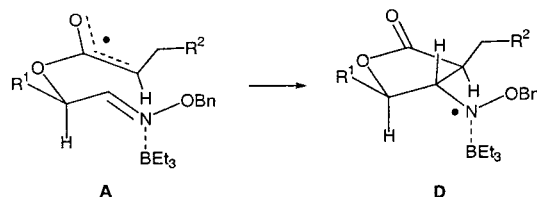
Figure 3. Stereocontrol in radical cyclization process.

As shown in Scheme 2, the γ-butyrolactone **2Aa** was easily converted to β-amino acid derivative **4** by standard methods.

Scheme 2
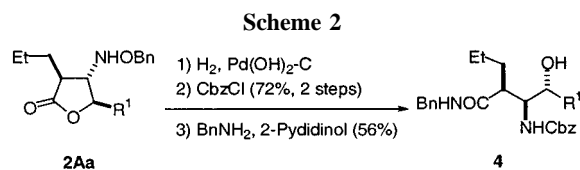
For the asymmetric synthesis of various types of γ-butyrolactones, we next investigated the reaction using different radical precursors RI and Et₃B under the iodine atom-transfer reaction conditions. The isopropyl radical addition to **1A** was run in boiling benzene for 15 min by using isopropyl iodide (6 equiv) and triethylborane (3 equiv). As expected, the reaction proceeded smoothly in the absence of tin hydride to give the isopropylated product **2Ab** in 68% yield (run 6). In our recent studies on the radical addition to highly reactive acceptors such as glyoxylic oxime ethers and BF₃-activated aldoxime ethers, the competitive addition of an ethyl radical, generated from triethylborane, was observed as a significant side reaction.[6] In the present reactions, it is noteworthy that no competitive addition of ethyl radical was observed, due to the slightly low reactivity of the acrylate moiety on **1A** as a radical acceptor. Other secondary alkyl radicals worked well under similar reaction conditions, allowing facile incorporation of structural variety (runs 8−10).

In conclusion, we have shown a new free radical-mediated Mannich-type reaction via a tandem C−C bond-forming

(13) (a) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2066. (b) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.
(14) The absolute configuration of major product **2Aa** was determined by its NOESY spectrum. Stereochemical purity of the major product was checked by converting **2Aa** into MTPA-amide derivative. See the Supporting Information.

4073

process. Furthermore, this tandem reaction provides direct access to γ-butyrolactones and β-amino acid derivatives.

Supporting Information Available: General experimental procedures and characterization data for all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006716G