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# Highly Diastereoselective Radical Addition to Oxime Ethers: Asymmetric Synthesis of β-Amino Acids

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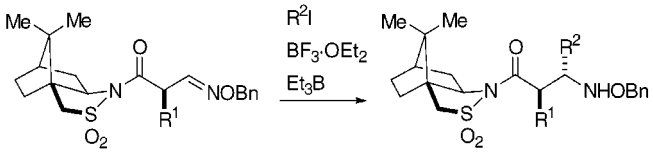
## ABSTRACT




**Highly diastereoselective alkyl radical addition to Oppolzer's camphorsultam derivatives of oxime ethers provided a convenient method for preparing the enantiomerically pure α,β-dialkyl-β-amino acids. The phase-transfer-catalyzed alkylation was an excellent method for the selective monoalkylation of the *N*-(β-oximino)acyl derivative of Oppolzer's sultam, with no detection of dialkylated products. In the presence of $BF_3$·$OEt_2$, the carbon radical addition to the oxime ethers proceeded smoothly to give the α,β-dialkyl-β-amino acid derivatives with excellent diastereoselectivity.**

Stereocontrol in free radical-mediated carbon−carbon bond-forming reactions has been of great importance in organic synthesis.[1] The carbon−nitrogen double bond of imine derivatives has attracted significant attention as an excellent radical acceptor in the radical cyclizations, and thus numerous, powerful synthetic methods for the intramolecular carbon−carbon bond construction have been reported.[2] In contrast, however, only two studies have been directed toward stereocontrol in the intermolecular carbon radical addition to imine derivatives.[3,4] Bertrand's and our group recently reported studies on stereocontrol in the radical addition to activated imine derivatives such as glyoxylic oxime ethers and imines,[5] which were successfully used for the novel asymmetric synthesis of α-amino acids.[3,4] However, a general solution to the problem of stereoselection in the intermolecular radical addition to unactivated imine derivatives has remained elusive. Following our studies on the synthesis of α-amino acids,[6] we now describe a novel asymmetric synthesis of α,β-dialkyl-β-amino acids based on the highly diastereoselective carbon radical addition to the unactivated oxime ethers bearing Oppolzer's camphorsultam. As shown below, the radical reaction is rapid and can be easily carried out very conveniently at room temperature without any special precautions such as drying, degassing, and purification of solvents and reagents.[7]

In a preliminary study, the auxiliary of choice was Oppolzer's camphorsultam since it had shown good characteristics in our previous work on the radical addition to glyoxylic oxime ethers.[3] The camphorsultam derivative of oxime ether **1** would be flexible to allow access to a wide range of α,β-dialkyl-β-amino acids.[8,9] Oxime ether **1** was

(1) For reviews, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (d) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996.

(2) For reviews, see: (a) Naito, T. *Heterocycles* **1999**, *50*, 505. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

(3) Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789.

(4) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780.

(5) Glyoxylic oxime ethers and imines are activated by the adjacent electron-withdrawing substituent.

(6) (a) Miyabe, H.; Fujishima, U.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174. (b) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465. (c) Miyabe, H.; Yoshioka, N.; Ueda, M.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3659.

(7) All radical reactions were run in commercially available solvents and with reagents not requiring any special precautions.

(8) For a review on asymmetric synthesis of β-amino acids, see: Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117.

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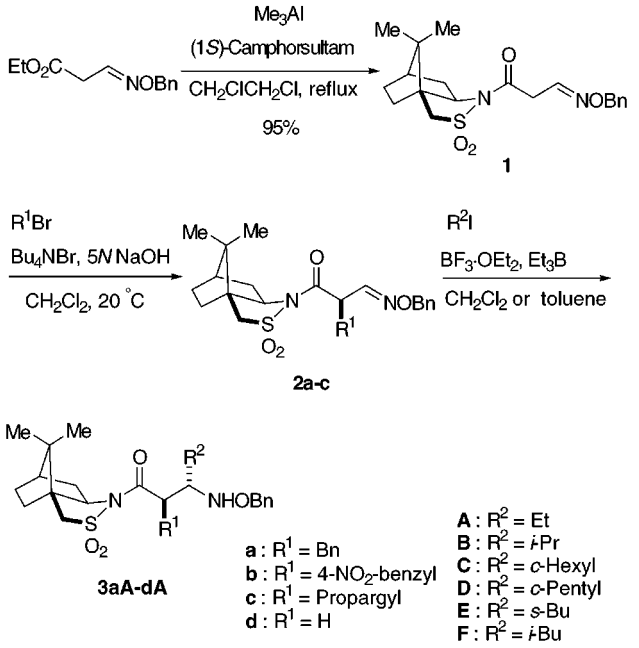
readily prepared by treatment of ethyl 1-[*N*-(phenylmethoxy)-imino]propionate[10] with (1*S*)-(−)-2,10-camphorsultam in the presence of trimethylaluminum in boiling 1,2-dichloroethane (Scheme 1). The screening of several methods for the anionic

**Scheme 1**




alkylation of sultam compounds showed that the phase-transfer-catalyzed reaction was an excellent method for the selective monoalkylation of the active methylene in sultam derivative **1** with no detection of dialkylated products.[11,12] All alkylations of sultam derivative **1** were run by using alkyl bromides (1.1 equiv) and tetrabutylammonium bromide (0.1 equiv) as a phase-transfer catalyst in 5 N NaOH/$CH_2Cl_2$ at 20 °C for 1 h (Table 1). In the case of benzylation using

**Table 1.** PTC-Catalyzed Alkylation of **1**[a]

| entry | $R^1$ | product (% yield)[b] | ratio[c] *R,Z*:*R,E*:*S,Z* | selectivity[d] |
|---|---|---|---|---|
| 1 | Bn | **2a** (99) | 15.7:1.0:1.3 | >95% de |
| 2 | 4-$NO_2$-benzyl | **2b** (98) | 7.6:1.0:1.0 | >95% de |
| 3 | propargyl | **2c** (90) | 9.7:1.2:1.0 | >95% de |

[a] Alkylation reaction of **1** was carried out with $R^1Br$ (1.1 equiv) and $Bu_4NBr$ (0.1 equiv) in 5 N NaOH/$CH_2Cl_2$ at 20 °C. [b] Combined yields. The diastereomerically pure materials (*R,Z*)-**2a**−**c** were obtained in ca. 60−80% yields after recrystallization. [c] Ratios were determined by $^1H$ NMR analysis. [d] Diastereoselectivities of **2a**−**c** are for the selectivities after recrystallization.

benzyl bromide, the desired monobenzylated oxime ether **2a** was obtained in 99% combined yield in favor of the (*R,Z*)-isomer (entry 1).[13] The diastereomerically pure oxime ether (*R,Z*)-**2a** was easily obtained by recrystallization from hexane/AcOEt.[14] The *E*/*Z*-isomers with respect to the geometry of the oxime ether group were easily determined by $^1H$ NMR spectroscopy.[15] The absolute configuration of the major product was determined to be *R* by X-ray analysis of (*R,Z*)-**2a**. The other diastereomerically pure monoalkylated products (*R,Z*)-**2b** and (*R,Z*)-**2c** could be also obtained under similar reaction conditions after the recrystallization (entries 2 and 3).[16]

We first investigated the ethyl radical addition to the oxime ethers (*R,Z*)-**2a**−**c** by using triethylborane as an ethyl radical source under several reaction conditions (Table 2). We

**Table 2.** Ethyl Radical Addition to **1** and **2**

| entry | oxime ether | solvent | *T* (°C) | product (% yield)[c] | selectivity[d] |
|---|---|---|---|---|---|
| 1 | (*R,Z*)-**2a** | $CH_2Cl_2$ | −78[a] | **3aA** (95) | >95% de |
| 2 | (*R,Z*)-**2a** | $CH_2Cl_2$ | 20[b] | **3aA** (99) | >95% de |
| 3 | (*R,Z*)-**2a** | toluene | 20[b] | **3aA** (99) | >95% de |
| 4 | (*R,Z*)-**2b** | $CH_2Cl_2$ | −78[a] | **3bA** (66) | >95% de |
| 5 | (*R,Z*)-**2b** | toluene | −78[a] | **3bA** (72) | >95% de |
| 6 | (*R,Z*)-**2c** | $CH_2Cl_2$ | −78[a] | **3cA** (43) | >95% de |
| 7 | **1** | $CH_2Cl_2$ | −78[a] | **3dA** (84) | 5% de |

[a] Radical addition at −78 °C was carried out with $BF_3$·$OEt_2$ (9 equiv) and $Et_3B$ in hexane (9 equiv). [b] Radical addition at 20 °C was carried out with $BF_3$·$OEt_2$ (5 equiv) and $Et_3B$ in hexane (5 equiv). [c] Isolated yields. [d] Diastereoselectivities were determined by $^1H$ NMR analysis.

recently reported the potentiality of $BF_3$·$OEt_2$ as a Lewis acid in achieving the intermolecular radical addition to

(9) Among the different types of radical acceptors containing a carbon−nitrogen double bond, oxime ethers are well-known to be excellent radical acceptors because of the extra stabilization of the intermediate aminyl radical provided by the adjacent oxygen atom. See: (a) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (b) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711. (c) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877. (d) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (e) Clive, D. L. J.; Zhang, J. *Chem. Commun.* **1997**, 549. (f) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366. (g) Bhat, B.; Swayze, E. E.; Wheeler, P.; Dimock, S.; Perbost, M.; Sanghvi, Y. S. *J. Org. Chem.* **1996**, *61*, 8186. (h) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138. (i) Hollingworth, G. J.; Pattenden, G.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 381. (j) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010. (k) Santagostino, M.; Kilburn, J. D. *Tetrahedron Lett.* **1995**, *36*, 1365. (l) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253.

(10) Ethyl 1-[*N*-(phenylmethoxy)imino]propionate was readily prepared from commercially available ethyl 3,3-diethoxypropionate and *O*-benzyloxyamine hydrochloride. See: Macchia, M.; Menchini, E.; Nencetti, S.; Orlandini, E.; Rossello, A.; Belflore, M. S. *Il Farmaco* **1996**, *51*, 255.

(11) (a) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241. (c) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39. (d) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

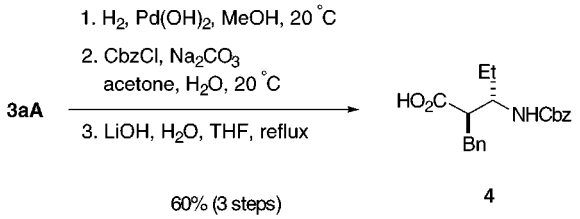
(12) For some examples of the phase-transfer-catalyzed reaction, see: (a) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (b) Oppolzer, W.; Bienaymé, H.; Genevois-Borella, A. *J. Am. Chem. Soc.* **1991**, *113*, 9660. (c) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009.

(13) The stereochemical feature of this reaction can be rationalized in terms of stereoelectronic effect in the chelated (*Z*)-enolate anion as proposed by Oppolzer et al. See reference 11.

(14) Full characterization data of all obtained compounds and general experimental procedures are given in the Supporting Information.

unactivated oxime ethers.[17] As indicated in our previous studies, the activation of the oxime ether group by $BF_3$·$OEt_2$ was essential for the successful radical addition reaction of oxime ethers (*R*,*Z*)-**2a**−**c**. In the presence of $BF_3$·$OEt_2$, the reaction of (*R*,*Z*)-**2a** with triethylborane in $CH_2Cl_2$ proceeded smoothly within 15 min even at −78 °C to give a 95% yield of the ethylated product **3aA** (Table 2, entry 1), while no reaction occurred in the absence of $BF_3$·$OEt_2$. The diastereomeric purity of (*R*,*Z*)-**2a** was found to be not less than 95% de by $^1$H NMR analysis of the crude products. The high diastereoselectivity and chemical yield were still maintained in the reaction at 20 °C (entry 2). It should be noted that the unactivated oxime ether having acidic α-hydrogen reacted smoothly with a carbon radical. In regard to the solvent effect, the replacement of $CH_2Cl_2$ with a nonpolar aromatic solvent such as toluene was also effective for the radical reaction to give the ethylated product **3aA** in 99% yield with excellent diastereoselectivity (entry 3). The absolute configuration at the newly formed stereocenter of the ethylated product **3aA** was determined to be *S* by X-ray analysis. Hydrogenolysis of the benzyloxy group of **3aA** in the presence of $Pd(OH)_2$ in MeOH, subsequent protection of the resulting amine with benzyloxycarbonyl chloride, and final removal of the sultam auxiliary by standard hydrolysis[18] afforded the enantiomerically pure α,*β*-dialkyl-*β*-amino acid **4** in 60% overall yield from **3aA** without any loss of stereochemical purity (Scheme 2). Excellent diastereoselectivities were also observed in the radical addition to different radical acceptors (*R*,*Z*)-**2b** and **2c** containing a 4-nitrobenzyl group or a carbon−carbon triple bond to afford the ethylated products **3bA** and **3cA** with slightly low efficiencies (entries 4−6). In the case of radical addition to the oxime ether **1**, the ethylated product **3dA** was obtained with low diastereoselectivity, probably because the approaching radical was too far away from the sultam (entry 7). Thus, the high stereocontrol in the radical addition to (*R*,*Z*)-**2a**−**c** was regarded as the result of high 1,2-asymmetric induction. In the case of (*R*,*Z*)-**2a**−**c**, the conformer **A** minimizing $A^{1,3}$-strain effects would be favored (Figure 1). Additionally, the stable conformation was also supported by the crystal structure resulting from X-ray analysis of (*R*,*Z*)-**2a**. Thus, an ethyl radical addition takes place predominantly from the less-hindered *π*-face of oxime ethers activated by $BF_3$, in which the bulky alkyl group ($R^1$) shields the opposite face.

**Scheme 2**



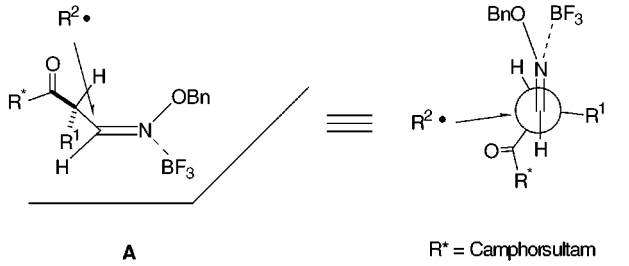




**Figure 1.** 1,2-Asymmetric induction.

To investigate the generality and practicality of this reaction, the present procedure was successfully extended to the radical addition reactions using different radical precursors (Table 3). The isopropyl radical addition to (*R*,*Z*)-**2a** was run in toluene at 20 °C for 15 min by using isopropyl iodide and $Et_3B$ in the presence of $BF_3$·$OEt_2$ (entry 1). As expected, the reaction proceeded smoothly in the absence of tin hydride to give a good yield of isopropylated products **3aB** with a high level of diastereoselectivity.[19] Other secondary alkyl radicals also worked well under similar reaction conditions, allowing facile incorporation of structural variety (entries 2−4). A low chemical yield was obtained in the reaction using an unstable primary alkyl radical such as

**Table 3.** Alkyl Radical Addition to **2**[a]

| entry | oxime | $R^2$ | product | % yield[b] | selectivity[c] |
|---|---|---|---|---|---|
| 1 | (*R*,*Z*)-**2a** | *i*-Pr | **3aB** | 70 | >95% de |
| 2 | (*R*,*Z*)-**2a** | c-hexyl | **3aC** | 57 | >95% de |
| 3 | (*R*,*Z*)-**2a** | c-pentyl | **3aD** | 59 | >95% de |
| 4 | (*R*,*Z*)-**2a** | *s*-Bu | **3aE** | 50 | >95% de |
| 5 | (*R*,*Z*)-**2a** | *i*-Bu | **3aF** | 20 (39)[d] | >95% de |
| 6 | (*R*,*Z*)-**2b** | *i*-Pr | **3bB** | 40 (16) | >95% de |

[a] Radical addition was carried out with $R^2I$ (30 equiv), $BF_3$·$OEt_2$ (9 equiv), and $Et_3B$ in hexane (9 equiv) in toluene at 20 °C. [b] Isolated yields; yields in parentheses are for the recovered starting material. [c] Diastereoselectivities were determined by $^1$H NMR analysis. [d] Ethylated product **3aA** was also obtained in 29% yield.

(15) In general, the signals due to the imino hydrogen of the *E*-oxime ether are shifted downfield by the influence of the alkoxy group of the oxime ether moiety. See: McCarty, C. G. In *The Chemistry of Functional Groups; The chemistry of the carbon−nitrogen double bond*; Patai, S., Ed.; John Wiley & Sons Inc.: New York, 1970; pp 383−392.

(16) The absolute configuration of major products **2b** and **2c** was assigned to be *R* since their $^1$H NMR data showed similarity with that of (*R*,*Z*)-**2a**.

(17) (a) Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631. (b) Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431.

(18) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.

(19) The reaction proceeded via a route involving the iodine atom-transfer process between isopropyl iodide and ethyl radical generated from $Et_3B$. In this reaction, $Et_3B$ acts as a radical initiator and a radical terminator to trap the intermediate benzyloxy radical. Thus, the radical chain reaction proceeds via the regeneration of the ethyl radical by the simple procedure, which does not require the tedious workup to remove the tin residues from the reaction mixture. See refs 4, 6b, and 6c.

an isobutyl radical because of the competitive formation of a significant amount of the ethylated products **3aA** as a byproduct, which were formed by the reaction with the ethyl radical generated from $Et_3B$ (entry 5). Similar trends were observed in our previous studies on the radical addition to activated glyoxylic oxime ethers.[6] The isopropyl radical addition to oxime ether having a 4-nitrobenzyl group (*R*,*Z*)-**2b** also proceeded in excellent diastereoselectivity under similar reaction conditions (entry 6).

In conclusion, we have succeeded in the asymmetric synthesis of α,*β*-dialkyl-*β*-amino acids based on the phase-transfer-catalyzed alkylation of Oppolzer's camphorsultam derivative followed by the highly diastereoselective carbon radical addition to the resulting oxime ethers. The stereocontrol in the carbon−carbon bond construction through the intermolecular carbon radical addition to unactivated oxime ethers presents new opportunities for stereoselective synthesis of α,*β*-dialkyl-*β*-amino acids.

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**Supporting Information Available:** General experimental procedures and characterization data for obtained compounds **1**, **2a**−**c**, **3aA**−**3bB**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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