COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Novel intermolecular carbon radical addition to a nitrone: asymmetric synthesis of α-amino acids†

Masafumi Ueda, Hideto Miyabe, Masako Teramachi, Okiko Miyata and Takeaki Naito*
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan.
E-mail: taknaito@kobepharma-u.ac.jp

Received (in Cambridge, UK) 21st November 2002, Accepted 23rd December 2002
First published as an Advance Article on the web 14th January 2003

A nitrone was used as a synthetically useful radical acceptor in carbon–carbon bond-forming radical reactions; the intermolecular addition of alkyl radicals to chiral glyoxylic nitrone was studied; a high degree of stereocontrol in radical addition to glyoxylic nitrone was achieved to provide a new method for asymmetric synthesis of α-amino acids.

The carbon–nitrogen double bond of imine derivatives has emerged as a radical acceptor and thus numerous useful intramolecular carbon–carbon bond-forming reactions are available.[1] However, intermolecular radical additions to imine derivatives have not been widely studied, and therefore the development of intermolecular radical reactions of imines has been a subject of current interest.[2] Hart's group reported the first studies on intermolecular radical addition to formaldoxime ether.[3] Recently, intermolecular radical reactions of α-sulfonyl oxime ethers, aldoxime ethers, hydrazones, glyoxylic imine derivatives, acylhydrazones and *N*-sulfonylimines have been investigated mainly by the groups of Kim,[4] Bertrand,[5] Friestad,[6] as well as ourselves.[7]

Nitrones are well-known to be reactive substrates for 1,3-dipolar cycloaddition reactions, for nucleophilic additions of organometallic reagents, and so on.[8] Although nitrones have also evolved as useful traps for short-lived reactive free radicals,[9] no synthetically useful radical reactions are available to our knowledge.[10] We have developed a novel carbon–carbon forming reaction for the first time establishing the synthetic utility of a nitrone as a radical acceptor in intermolecular reactions with nucleophilic carbon radicals. Additionally, the radical reaction was successfully applied to the asymmetric synthesis of α-amino acids.

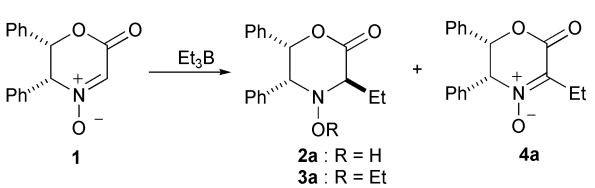
We first investigated ethyl radical addition to chiral glyoxylic nitrone **1**.[11] A high degree of stereocontrol was observed in ethyl radical addition to **1** by using Et_3B as an ethyl radical source (Scheme 1). To a solution of **1** in undegassed CH_2Cl_2 was added a 1.0 M solution of Et_3B in hexane (5 equiv.), and then the reaction mixture was stirred at 20 °C for 2 h. As expected, nitrone **1** exhibits a good reactivity towards the nucleophilic ethyl radical to give the desired ethylated product **2a** in 50% yield as a single diastereomer, along with a 32% yield of the *C*,*O*-diethylated product **3a** and a trace of the ethylated nitrone **4a** (Table 1, entry 1).[12]

As shown in Scheme 2, the ethylated nitrone **4a** would be obtained as a result of a disproportionation reaction of the intermediate radical **B**. After further investigations, the disproportionation reaction was found to be dependent on the amount of Et_3B; thus the reaction using 1 equiv. of Et_3B afforded a significant amount of **4a**. These results indicate that Et_3B worked as not only a radical initiator but also a radical chain terminator to trap the intermediate radical **B** to give an adduct **C** and a chain-propagating ethyl radical; therefore, a large amount of Et_3B is required for suppressing the formation of the ethylated nitrone **4a** (Scheme 2).[13] Changing the temperature from 20 to −78 °C led to an increase in the formation of undesired products to give a 22% yield of **3a** and 14% yield of **4a** (entry 2). The reaction in boiling benzene afforded a good yield of **2a**, accompanied with a 15% yield of the diethylated product **3a** (entry 3). To suppress the formation of the undesired products **3a** and **4a**, Bu_3SnH was employed as a hydride atom donor (entries 4 and 5). In the case of the reaction using Bu_3SnH (1.2 equiv.), the formation of **3a**

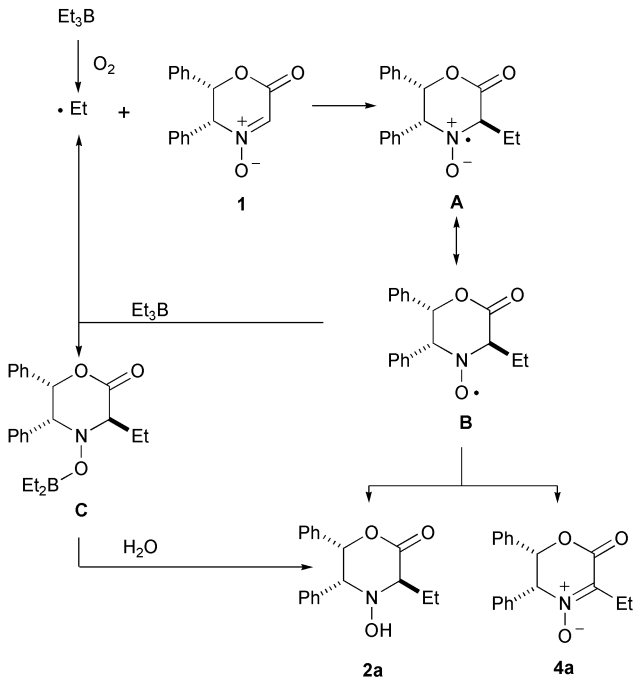
Table 1 Ethyl radical addition to nitrone **1**

Entry	Solvent	*T*/°C	Yield[a] (%) **2a**	**3a**	**4a**	Selectivity of **2a**
1[b]	CH_2Cl_2	+20	50	32	Trace	> 98% de
2[b]	CH_2Cl_2	−78	36	22	14	> 98% de
3[b]	Benzene	Reflux	55	15	Trace	> 98% de
4[c]	Benzene	+20	50	Trace	Trace	> 98% de
5[c]	CH_2Cl_2	−78	64	Trace	16	> 98% de

[a] Isolated yields. [b] Reactions were carried out with Et_3B (5 equiv.). [c] Reactions were carried out with Bu_3SnH (1.2 equiv.) and Et_3B (5 equiv.).



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/cc/b2/b211570k/

DOI: 10.1039/b211570k

diminished remarkably leading to a 64% yield of the desired product **2a** as a single diastereomer after being stirred in CH_2Cl_2 at −78 °C for 2 h, though the ethylated nitrone product **4a** was still obtained in 16% yield (entry 5).

The absolute configuration of **2a** was assigned to be *R* by converting the product **2a** into authentic *N*-Cbz-amino acid **5**.[14] The reductive cleavage of the N–O bond of **2a** with $Mo(CO)_6$, subsequent hydrogenolysis in the presence of $Pd(OH)_2$, and treatment with CbzCl afforded the enantiomerically pure (*R*)-*N*-Cbz-amino acid **5** without any loss of stereochemical purity (Scheme 3).

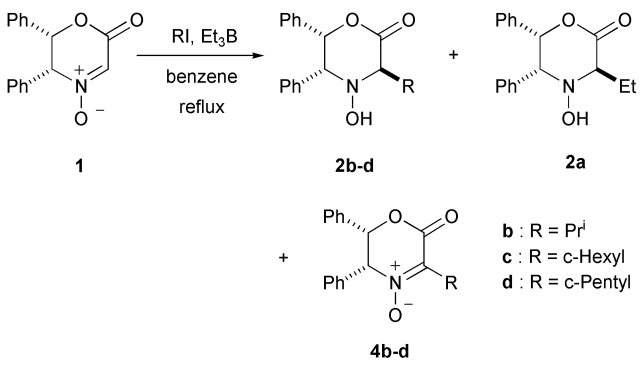
2a **5**

Scheme 3 *Reagents and conditions*: i, $Mo(CO)_6$, H_2O–MeCN, 20 °C (84%); ii, H_2, $Pd(OH)_2$/C, MeOH, 20 °C; iii, CbzCl, Na_2CO_3, acetone–H_2O, 20 °C (38%, 2 steps).

Since most radical reactions are carried out using toxic tin reagents, an area of continuing and important research is to develop new methods for radical generation that avoid the use of tin reagents. Therefore, we have explored the tin-free reactions of nitrone **1** with alkyl radicals under iodine atom-transfer reaction conditions using Et_3B as a radical initiator (Scheme 4).[15] Good chemical yields of the desired alkylated products **2b**–**d** were observed in the reaction of **1** with more nucleophilic secondary alkyl radicals. The formation of the ethylated byproduct **2a** was shown to be dependent on the reaction temperature; thus changing the temperature from 20 °C to reflux in benzene led to a decrease in the ratio of ethylated byproduct **2a** to the desired alkylated products **2b**–**d**. A similar trend has been observed in our recent studies in the radical reactions of oxime ethers.[15]

Isopropyl radical addition to nitrone **1** proceeded smoothly by using isopropyl iodide (90 equiv.) and Et_3B (5 equiv.) in boiling benzene, to give the desired isopropylated product **2b** in 60% yield, accompanied with an 18% yield of the ethylated product **2a** (Table 2, entry 1). A high degree of diastereoselectivity was observed even at the high reaction temperature. As the best result, the predominant formation of the desirably alkylated products **2b**–**d** and excellent diastereoselectivity were achieved in the reaction using Et_3B (5 equiv.) in RI–benzene (3 : 1, v/v) at reflux, although a small amount of undesirably alkylated nitrones **4b**–**d** were formed (entries 2–4). However, bulky tertiary alkyl radicals were less effective in reaction with nitrone **1**.

The stereochemical features of this reaction can be explained as follows. The alkyl radical addition takes place predominantly from the less hindered *re*-face of **1** to avoid steric interaction with the phenyl group.



1 **2b-d** **2a** **4b-d**

Scheme 4

Table 2 Alkyl radical addition of **1** *via* iodine atom-transfer process using Et_3B

Entry	Conditions	Product	Yield[a] (%) **2b–d**	Yield[a] (%) **2a**	Selectivity of **2b–d**
1[b]	Pr^iI in benzene	**2b**	60	18	> 98% de
2[c]	Pr^iI : benzene (3 : 1)	**2b**	82	Trace	> 98% de
3[c]	*c*-$C_6H_{11}I$: benzene (3 : 1)	**2c**	72	3	> 98% de
4[c]	*c*-C_5H_9I : benzene (3 : 1)	**2d**	72	12	> 98% de

[a] Isolated yields. [b] Reaction of **1** (50 mg) was carried out with Pr^iI (90 equiv.) and Et_3B (2.5 equiv.) in benzene (5 mL). [c] Reactions of **1** (50 mg) were carried out with Et_3B (2.5 equiv.) in RI–benzene (3 : 1, v/v, 5 mL).

In conclusion, we have succeeded in the alkyl radical addition to chiral glyoxylic nitrone with excellent diastereoselectivities for the first time, providing a synthetic approach to enantiomerically pure α-amino acids.

We thank a Grant-in-Aid for Scientific Research on Priority Areas (A) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation.

Notes and references

1 For reviews, see: (*a*) T. Naito, *Heterocycles*, 1999, **50**, 505; (*b*) A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543; For some examples of the radical reaction of oxime ethers, see (*c*) H. Miyabe, K. Fujii, T. Goto and T. Naito, *Org. Lett.*, 2000, **2**, 4071; (*d*) G. K. Friestad, *Org. Lett.*, 1999, **1**, 1499; (*e*) J. Zhang and D. L. J. Clive, *J. Org. Chem.*, 1999, **64**, 770.

2 For reviews, see: (*a*) G. K. Friestad, *Tetrahedron*, 2001, **57**, 5461; (*b*) H. Miyabe and T. Naito, *J. Synth. Org. Chem., Jpn.*, 2001, **59**, 35; (*c*) *Radicals in Organic Synthesis, Vol. 1 and 2*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001.

3 D. J. Hart and F. L. Seely, *J. Am. Chem. Soc.*, 1988, **110**, 1633.

4 (*a*) S. Kim and J.-Y. Yoon, *J. Am. Chem. Soc.*, 1997, **119**, 5982; (*b*) I. Ryu, H. Kuriyama, S. Minakata, M. Komatsu, J.-Y. Yoon and S. Kim, *J. Am. Chem. Soc.*, 1999, **121**, 12190.

5 (*a*) M. P. Bertrand, L. Feray, R. Nouguier and P. Perfetti, *Synlett*, 1999, 1148; (*b*) M. P. Bertrand, L. Feray, R. Nouguier and P. Perfetti, *J. Org. Chem.*, 1999, **64**, 9189.

6 (*a*) G. K. Friestad and J. Qin, *J. Am. Chem. Soc.*, 2000, **122**, 8329; (*b*) G. K. Friestad and J. Qin, *J. Am. Chem. Soc.*, 2001, **123**, 9922.

7 (*a*) H. Miyabe, C. Konishi and T. Naito, *Org. Lett.*, 2000, **2**, 1443; (*b*) H. Miyabe, M. Ueda and T. Naito, *Chem. Commun.*, 2000, 2059; (*c*) H. Miyabe, M. Ueda, A. Nishimura and T. Naito, *Org. Lett.*, 2002, **4**, 131.

8 For reviews, see: (*a*) M. Lombardo and C. Trombini, *Synthesis*, 2000, 759; (*b*) P. Merino, S. Franco, F. L. Merchan and T. Tejero, *Synthesis*, 2000, 442.

9 (*a*) D. A. Becker, *J. Am. Chem. Soc.*, 1996, **118**, 905; (*b*) Y.-T. Park and K.-W. Kim, *J. Org. Chem.*, 1998, **63**, 4494.

10 Silylnitronates and nitroalkyl anions have been used as radical acceptors: (*a*) B. P. Branchaud and G.-X. Yu, *Tetrahedron Lett.*, 1991, **32**, 3639; (*b*) S. Kim, J.-Y. Yoon and C. J. Lim, *Synlett*, 2000, 1151.

11 Nirone **1** was easily prepared by oxidation of 5,6-diphenylmorpholin-2-one with methyltrioxorhenium: (*a*) R. M. Williams, W. Zhai, D. J. Aldous and S. C. Aldous, *J. Org. Chem.*, 1992, **57**, 6527; (*b*) A. Goti and L. Nannelli, *Tetrahedron Lett.*, 1996, **37**, 6025.

12 For an example of the reaction of nitrones with Et_3B, see: W. G. Hollis, P. L. Smith, D. K. Hood and S. M. Cook, *J. Org. Chem.*, 1994, **59**, 3485.

13 Renaud *et al.* reported that TEMPO reacts with *B*-alkylcatecholboranes to generate alkyl radicals: C. Ollivier, R. Chuard and P. Renaud, *Synlett*, 1999, 807.

14 A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, A. K. Ganguly and A. T. McPhail, *J. Org. Chem.*, 1986, **51**, 5024.

15 H. Miyabe, M. Ueda, N. Yoshioka, K. Yamakawa and T. Naito, *Tetrahedron*, 2000, **56**, 2413.