Enantioselective radical addition reactions to the C=N bond utilizing chiral quaternary ammonium salts of hypophosphorous acid in aqueous media

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An enantioselective addition of alkyl radicals to glyoxylate oxime ether mediated by *Cinchona* alkaloid derived chiral ammonium salts of hypophosphorous acid, QP and QDP, has been developed.

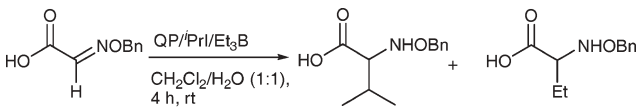
The formation of a carbon–carbon bond is extremely important in organic synthesis, especially the asymmetric formation of a carbon–carbon bond. Radical addition reactions have become a powerful and versatile tool for forming new carbon–carbon bonds because the reactions can be accomplished under mild and neutral reaction conditions in which a broad range of functional groups of polyfunctionalized molecules is compatible.[1] Considerable effort has been devoted to the development of asymmetric radical reactions, and the majority of the asymmetric radical reactions have been accomplished using chiral auxiliaries.[2] However, recent progress has shown that the stereochemistry of radical reactions could be controlled without using chiral auxiliaries. Although this development was achieved mainly during radical conjugate addition promoted by chiral Lewis acids, which formed the chiral environment by coordinating the substrates,[3] there have been no reports on asymmetry induction in radical reactions through a π-stacking and/or hydrogen bonding chiral environment.[4]

Here we report on the development of an enantioselective radical addition reaction to glyoxylate oxime ether for the preparation of α-amino acids[5] under mild reaction conditions with chiral quaternary ammonium salts of hypophosphorous acid in aqueous media.

Hypophosphorous acid has been used as a radical chain carrier and a radical hydrogen source in radical reactions.[6] We assumed that quaternary ammonium hypophosphites prepared from H_3PO_2 and chiral amines such as *Cinchona* alkaloids[7] can readily generate radicals from alkyl halides and form the chiral environment. We also assumed that they play a role as surfactants that would result in an increase in the solubility of the organic substrates in aqueous media.[8]

The quaternary ammonium hypophosphites QP and QDP were readily prepared as white solid by mixing quinine or quinidine with an equimolar amount of H_3PO_2 at room temperature. First, the reaction of glyoxylate oxime ether (**1**), which was generated *in situ* with ^{i}PrI, was carried out in a biphasic dichloromethane–water system in the presence of QP using Et_3B/O_2 as an initiator at room temperature (Table 1). The reaction proceeded smoothly to afford the addition adduct **2a** in 87% yield (entry 1). As the amount of ^{i}PrI decreased, the addition adduct **2b** produced by the addition reaction of ethyl radical to **1** increased. We performed the same reaction by varying the ratios of QP, ^{i}PrI and Et_3B to establish the optimal reaction conditions for radical addition reactions. Optimal reaction conditions were established with 2 equiv. of QP, 5 equiv. of ^{i}PrI, and 0.5 equiv. of Et_3B in aqueous CH_2Cl_2 (entry 6).† The reaction was also carried out in pure water or CH_2Cl_2 affording 50% and 23% yields of the addition product **2a**, respectively (entries 7 and 8). It is inferred that low yields of the addition product **2a** are attributed to the low solubility of the substrate in water or QP in CH_2Cl_2. The addition product **2a** was converted into its ester derivative **3a** in 80% yield when treated[9] with Ph_3P–CCl_3CN and MeOH–Et_3N to determine the enantiomeric ratio (er), which was found to be 21 : 79 by HPLC analysis (Table 2, entry 1).

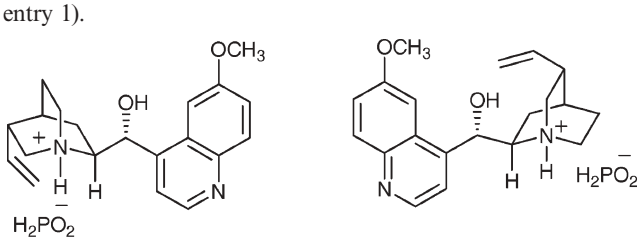
Table 1 Radical addition reactions to glyoxylic oxime ether under various reaction conditions



1 **2a** **2b**

Entry	QP (equiv.)	^{i}PrI (equiv.)	Et_3B (equiv.)	Isolated yield (%) of **2a** (**2b**)
1	5	30	1	87 (0)
2	5	5	1	85 (10)
3	2	5	1	86 (7)
4	2	0	1	0 (54)
5	2	0	0.5	0 (12)
6	2	5	0.5	83 (7)
7	2	5	0.5	50[a]
8	2	5	0.5	23[b]

[a] The reaction was carried out in water. [b] The reaction was carried out in CH_2Cl_2.



QP **QDP**

With these optimal reaction conditions established, addition reactions of various alkyl halides to **1** were carried out. The results

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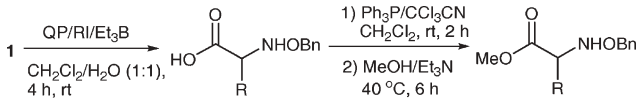
Table 2 Enantioselective alkyl radical addition to glyoxylic oxime ether in the presence of QP



Entry	RI	Product	Isolated yield[a] (%)	**3** (Yield (%))	er[b] of **3** *R* : *S*
1	^{i}Pr-I	**2a**	83 (7)	**3a** (80)	21 : 79
2	^{c}Hex-I	**2c**	80 (10)	**3c** (81)	21 : 79
3	^{t}Bu-I	**2d**	60 (30)	**3d** (83)	1 : >99
4	1-Ad-I	**2e**	45 (35)	**3e** (82)	1 : >99
5	^{n}Oct-I	**2f**	50 (25)	**3f** (85)	40 : 60

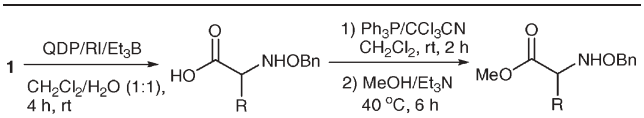
[a] The yield in parenthesis is for **2b**. [b] Enantiomeric ratio was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H) with hexane–isopropanol as the solvent.

are presented in Table 2. The reaction of secondary alkyl halides afforded the addition products in high yields with high er values (entries 1 and 2). In the case of tertiary alkyl halides, moderate chemical yields with extremely high er values were obtained without a trace of other enantiomers (entries 3 and 4). However, the reaction with primary alkyl halides such as 1-octyl iodide gave a low chemical yield with low enantioselectivity (entry 5).

Next, we investigated the radical addition reaction to **1** in aqueous solvent with quaternary ammonium hypophosphite, QDP, prepared from quinidine and H_3PO_2 (Table 3). The reaction proceeded smoothly to furnish the addition adducts, although compared to QP, QDP gave relatively lower enantioselectivity, when secondary and primary alkyl halides were used as substrates (entries 1, 2 and 5). However, with the tertiary halides, only one enantiomer was observed under these conditions (entries 3 and 4).

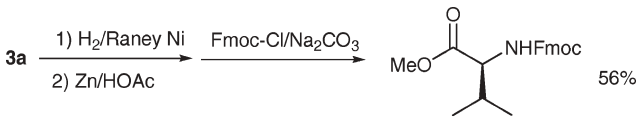
The absolute configuration of the addition adduct **3a** was established by conversion to **4** and by synthesis from known compounds, D-Val–OH and L-Val–OH independently. **3a** was converted into an amino ester by subsequent treatment with Raney Ni/H_2 and Zn/HOAc. After it was treated with Fmoc-Cl, **4** was obtained in 56% overall yield from **3a**. The major enantiomer in **4**, which was prepared in the presence of QP, was found to have an *S*-configuration (Scheme 1).

Table 3 Enantioselective alkyl radical addition to glyoxylic oxime ether in the presence of QDP



Entry	RI	Product	Isolated yield[a] (%)	**3** (Yield (%))	er[b] of **3** *R* : *S*
1	^{i}Pr-I	**2a**	82 (10)	**3a** (81)	62 : 38
2	^{c}Hex-I	**2c**	82 (9)	**3c** (80)	72 : 28
3	^{t}Bu-I	**2d**	62 (27)	**3d** (82)	>99 : 1
4	1-Ad-I	**2e**	47 (37)	**3e** (79)	>99 : 1
5	^{n}Oct-I	**2f**	48 (30)	**3f** (79)	58 : 42

[a] The yield in parenthesis is for **2b**. [b] Enantiomeric ratio was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H) with hexane–isopropanol as the solvent.



Scheme 1

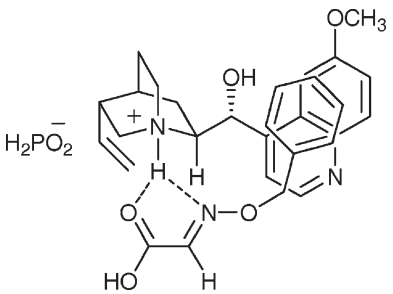


Fig. 1 Model to explain enantioselectivity.

The absolute configuration of the addition adduct allows a plausible rationalization for the observed *si*-face attack of the alkyl radical on the substrate **1** involving π-stacking and hydrogen bonding as shown in Fig. 1. The substrate **1** is bound to QP by hydrogen bonds between N–H and C=O/C=N in **1** with a CO/CN s-*cis* planar conformation and also through π-stacking. In this arrangement, the *re*-face of C=N bond is blocked by the quinoline ring of QP. An alkyl radical then attacks the C=N bond from the *si*-face to afford the addition product.

In conclusion, we have synthesized chiral quaternary ammonium hypophosphites that can be used for enantioselective radical addition reactions for preparing α-amino acids in aqueous media. The reactions afforded high yields of the addition products with a high enantioselectivity that can be attained without using metals. The reagents used in the research are inexpensive and less toxic than metal containing compounds, and the reaction affords an easy work-up process and mild reaction conditions. Especially, the chiral amines were recycled after treating with a base such as KOH.

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Notes and references

† General procedure: A mixture of $BnONH_2$·HCl (1 equiv.), glyoxylic acid (1 equiv.), and QP or QDP in CH_2Cl_2–H_2O (1 : 1) was stirred at room temperature for 1 h under argon. The alkyl halide (5 equiv.) was added, followed by Et_3B (0.5 equiv., 1 M in hexane). Air (40 mL) was added through a syringe needle (using a syringe pump) to the reaction mixture at room temperature over 4 h. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel affording the radical addition product.

1 (*a*) B. Giese, B. Kopping, T. Göbel, J. Dickhaut, G. Thoma, K. J. Kulicke and F. Trach, *Org. React.*, 1996, **48**, 301; (*b*) W. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992; (*c*) D. P. Curran, in *Comprehensive Organic Synthesis* ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 4, p. 715; (*d*) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986.

2 For reviews on stereoselective radical reactions, see: (*a*) G. Bar and A. Parsons, *Chem. Soc. Rev.*, 2003, **32**, 251; (*b*) B. Guérin, W. W. Ogilvie and Y. Guindon, in *Radicals in Organic Synthesis* ed. P. Renaud and

M. P. Sibi, Wiley-VCH, Weinheim, 2001, vol. 1; (*c*) D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996.
3 For reviews on enantioselective radical reactions and Lewis acid catalyzed radical reactions, see: (*a*) M. P. Sibi, S. Manyem and J. Zimmerman, *Chem. Rev.*, 2003, **103**, 3263; (*b*) M. P. Sibi and N. A. Porter, *Acc. Chem. Res.*, 1999, **32**, 163; (*c*) P. Renaud and M. Gerster, *Angew. Chem., Int. Ed.*, 1998, **37**, 2562.
4 For an example using hydrogen bond interactions, see: T. Aechtner, M. Dressel and T. Bach, *Angew. Chem., Int. Ed.*, 2004, **43**, 5849.
5 For examples of stereoselective radical additions to C=N bonds, see: (*a*) N. Singh, R. D. Anand and S. T. Trehan, *Tetrahedron Lett.*, 2004, **45**, 2911; (*b*) G. K. Friestad, Y. Shen and E. L. Ruggles, *Angew. Chem., Int. Ed.*, 2003, **42**, 5061; (*c*) H. Miyabe, C. Ushiro, M. Ueda, K. Yamakawa and T. Naito, *J. Org. Chem.*, 2000, **65**, 176; (*d*) N. Holland and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1290; (*e*) Y. Yamamoto and W. Ito, *Tetrahedron*, 1988, **44**, 5415.
6 (*a*) D. O. Jang, D. Y. Cho and C.-M. Chung, *Synlett*, 2001, 1923; (*b*) S. Takamatsu, S. Katayama, N. Hirose, M. Naito and K. Izawa, *Tetrahedron Lett.*, 2001, **42**, 7605; (*c*) D. O. Jang and S. H. Song, *Tetrahedron Lett.*, 2000, **41**, 247; (*d*) G. M. Concepcion, J. A. Murphy and R. S. Christopher, *Tetrahedron Lett.*, 2000, **41**, 1833; (*e*) H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi and T. Fukuyama, *J. Am. Chem. Soc.*, 1999, **121**, 3791; (*f*) S. R. Graham, J. A. Murphy and D. Coates, *Tetrahedron Lett.*, 1999, **40**, 2415; (*g*) S. R. Graham, J. A. Murphy and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3071; (*h*) R. McCague, R. G. Pritchard, R. J. Stoodley and D. S. Williamson, *Chem. Commun.*, 1998, 2691; (*i*) D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *J. Org. Chem.*, 1993, **58**, 6838; (*j*) D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1992, **33**, 5709.
7 For reviews on asymmetry synthesis using *Cinchona* alkaloids, see: (*a*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (*b*) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; (*c*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*d*) M. J. O'Donnell, *Aldrichimica Acta*, 2001, **34**, 3.
8 For examples for radical reactions in water with surfactants, see: (*a*) D. O. Jang and D. Y. Cho, *Synlett*, 2002, 631; (*b*) D. O. Jang and D. Y. Cho, *Tetrahedron Lett.*, 2002, **43**, 5921; (*c*) D. O. Jang and D. Y. Cho, *Synlett*, 2002, 1523; (*d*) H. Nambu, K. Hata, M. Matsugi and Y. Kita, *Chem. Commun.*, 2002, 1082; (*e*) Y. Kita, H. Nambu, N. G. Ramesh, G. Anikumar and M. Matsugi, *Org. Lett.*, 2001, **3**, 1157.
9 D. O. Jang, D. J. Park and J. Kim, *Tetrahedron Lett.*, 1999, **40**, 5323.