Highly diastereoselective radical addition to glyoxylic oxime ether: asymmetric synthesis of α-amino acids

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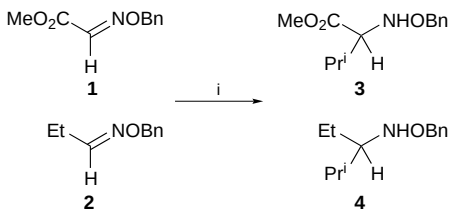
A high degree of stereocontrol in radical addition to the Oppolzer's camphor sultam derivative of glyoxylic oxime ether was achieved, providing a convenient method for preparing a variety of enantiomerically pure α-amino acids.

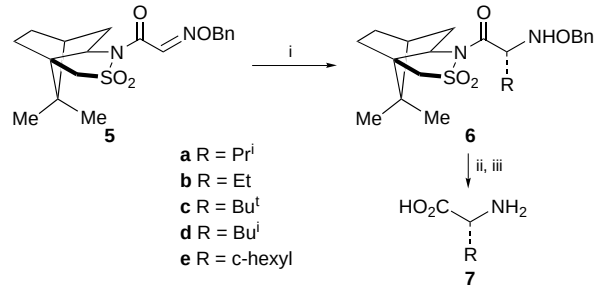
Asymmetric induction in free radical-mediated reactions of acyclic systems is a subject of current interest.[1] Oxime ethers are well known to be excellent radical acceptors because of the extra stabilisation of the intermediate aminyl radical provided by the lone pair on the adjacent oxygen atom.[2] We now describe the first example of an efficient and diastereoselective carbon radical addition to acyclic oxime ethers which was successfully applied to the novel asymmetric synthesis of α-amino acids.

Studies on the radical reaction of oxime ethers have concentrated on radical cyclisation,[3] except for a few outstanding examples of intermolecular radical reaction.[4] Therefore, stereocontrol in intermolecular radical addition to oxime ethers is a challenging problem. Prior to exploring diastereoselective radical addition to acyclic oxime ethers, we first investigated competitive reactions using two types of oxime ether in order to survey the intermolecular reactivity of oxime ethers with carbon radicals. Treatment of a 1 : 1 mixture of glyoxylic oxime ether **1** and aldoxime ether **2** with isopropyl radical, generated from Pr^iI, Bu_3SnH and Et_3B as a radical initiator, at −78 °C for 30 min gave the isopropylated product **3** in 78% yield with no detection of the other adduct **4** (Scheme 1). As expected, the addition of an isopropyl radical to **2** under the same reaction conditions did not take place and 90% of the starting compound **2** was recovered. These results suggest that the carbon radical does not add to the aldoxime ether **2**, but does add to glyoxylic oxime ether **1** even at −78 °C.

We then extended the carbon radical addition to the Oppolzer's camphor sultam derivative of glyoxylic oxime ether **5**[5] which would allow access to a wide range of enantiomerically pure natural and unnatural α-amino acids (Scheme 2). The reaction of **5** with Pr^iI, Bu_3SnH and Et_3B in CH_2Cl_2 at 20 °C proceeded smoothly to give a 86 : 14 diastereomeric mixture of the desired isopropylated product **6a** accompanying by a small amount of the ethylated product **6b**, which would be formed by a competitive reaction with ethyl radical generated from Et_3B and O_2 (Table 1, entry 1). In the absence of Pr^iI, treatment of **5** with Bu_3SnH and Et_3B afforded exclusively the corresponding ethylated product **6b** as the result of a similar stereoselective radical reaction. In order to optimise the reaction conditions, we then investigated the reaction by varying the



Scheme 1 *Reagents and conditions*: i, Pr^iI (1.1 equiv.), Bu_3SnH (1.1 equiv.), Et_3B (1.1 equiv.), CH_2Cl_2, −78 °C, 30 min



Scheme 2 *Reagents and conditions*: i, RI, Bu_3SnH, Et_3B, 30 min; ii, $Mo(CO)_6$; iii, LiOH

reaction temperature, solvent and Lewis acid. The stereoselectivity for **6a** was shown to be dependent on the reaction temperature, thus changing the temperature from 20 to −78 °C led to an effective increase in the diastereoselectivity to 94 : 6 (entry 2). The replacement of CH_2Cl_2 with Et_2O as solvent led to higher selectivity, comparable to or better than that obtained by the known addition of organometallic reagents to the oxime ethers (entry 4).[5,6] Although the addition of Lewis acids as an additive did not dramatically influence the degree of stereoselectivity, the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 was found to be useful for asymmetric induction (entry 5). The absolute configuration at the newly formed stereocentre of the major product was determined to be *R* by converting the adduct **6a** into authentic D-valine **7a**. The reductive cleavage of the nitrogen–oxygen bond of **6a** by treatment with $Mo(CO)_6$[7] and subsequent removal of the sultam auxiliary by standard hydrolysis[8] afforded the enantiomerically pure D-valine **7a** without any loss

Table 1 Radical addition to the oxime ether **5**[a]

Entry	RI[b]	Lewis acid[c]	Solvent	Yield[d] (%)	Selectivity[e]
1	Pr^iI	none	CH_2Cl_2	76[f]	86 : 14
2	Pr^iI	none	CH_2Cl_2	73[f]	94 : 6
3	Pr^iI	none	toluene	74[f]	93 : 7
4	Pr^iI	none	Et_2O	71[f]	96 : 4
5	Pr^iI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	80[f]	96 : 4
6	Pr^iI	Et_2AlCl	CH_2Cl_2	57[f]	90 : 10
7	Pr^iI	$Zn(OTf)_2$	CH_2Cl_2	81[f]	94 : 6
8	Pr^iI	$Yb(OTf)_3$	CH_2Cl_2	74[f]	92 : 8
9	EtI	none	Et_2O	54	96 : 4
10	EtI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	80	95 : 5
11	Bu^tI	none	Et_2O	25[f]	> 98 : 2
12	Bu^tI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	83[f]	> 98 : 2
13	Bu^iI	none	Et_2O	39[f]	97 : 3
14	Bu^iI	BF_3OEt_2	CH_2Cl_2	83[f]	97 : 3
15	c-HexylI	none	Et_2O	74[f]	96 : 4
16	c-HexylI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	86[f]	96 : 4

[a] Reaction was carried out with Bu_3SnH (2.5 equiv.) and Et_3B in hexane (5 equiv.) under N_2 at 20 °C (entry 1). Other reactions were carried out at −78 °C (entries 2–16). [b] 5 equiv. of RI was used. [c] 2 equiv. of Lewis acid was used. [d] Isolated yields of major diastereomer **6a**–**f**. [e] Diastereoselectivities were determined by ^1H NMR analysis. [f] The ethylated product **6b** was obtained in 3–22% yield.

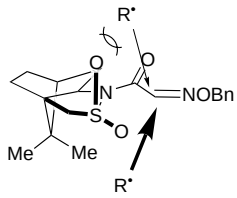


Figure 1

of stereochemical purity. High chemical yield and diastereoselectivity were also observed in radical additions using different radical precursors such as ethyl, *tert*-butyl, isobutyl and cyclohexyl iodides (entries 9–16).

The stereochemical features of this reaction can be rationalised in terms of steric control in the conformationally restricted sultam derivative **5**. The s-*cis* conformation of **5** would be preferred due to repulsion between the oxime ether and sulfonyl groups, thus alkyl radical addition takes place predominantly from the less hindered π-face of the oxime derivative **5**, as indicated (Fig. 1).

The traditional addition of anionic carbon nucleophiles to oxime ethers has been widely investigated as a carbon–carbon bond forming reaction with excellent stereoselectivity, although the addition is frequently plagued by the abstraction of α-protons adjacent to the carbon–nitrogen double bond, the lability of the nitrogen–oxygen bond, and the poor electrophilicity of the oxime ether group.[9] We suggest that many of these fundamental problems would be solved by the newly found mild addition of strictly neutral species such as uncharged free radicals.

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Footnote and References

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