Intermolecular addition of alkyl radicals to imines in the absence and in the presence of a Lewis acid

Nis Halland and Karl Anker Jørgensen *

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000, Aarhus C, Denmark. E-mail: kaj@kemi.aau.dk; Fax: 45-86-19-61-99

Received (in Cambridge, UK) 23rd February 2001, Accepted 6th April 2001
First published as an Advance Article on the web 2nd May 2001

The metal-catalyzed, and metal-catalyzed enantioselective, intermolecular additions of alkyl radicals to imines have been investigated. The reaction proceeds well for imines having both activating and deactivating nitrogen substituents, and can be controlled and accelerated to a high extent by the use of Lewis acids. For imines having different carbon substituents, it has been observed that those derived from glyoxylate react much faster than those derived from 3-oxopropionate or benzaldehyde. The intermolecular radical addition can be carried out for different types of imines with alkyl and alkoxyalkyl radicals and it is demonstrated that it is possible to perform the radical addition in a catalytic enantioselective fashion with moderate yield and enantioselectivity. On the basis of the experimental results and theoretical calculations the mechanism for the radical addition to imines is discussed.

Introduction

The catalysis and control of intermolecular radical addition to alkenes, carbonyl compounds and imines are a challenge and only recently have the first examples of diastereo- and enantioselective control in these transformations appeared.[1]

Intermolecular radical addition to C=N bonds catalyzed by Lewis-acid complexes is a rarely studied reaction, although it is a powerful method for the formation of C–C bonds. Naito *et al.* have shown, in a series of papers, that BF_3 in particular can be used to promote radical addition to oxime ethers and they used this approach *e.g.* in diastereoselective reactions, employing mainly Oppolzer's camphorsultam as the chiral auxiliary, and in solid-phase reactions.[2] Addition of alkyl radicals to chiral glyoxylate imines has been studied in the presence of $ZnEt_2$ and depending on the reaction conditions addition to both the carbon atom and the nitrogen atom of the C=N bond was observed.[3] However, it should be noted that the addition to the nitrogen atom is not a radical process. More recently it has been shown that Lewis acids can catalyze the diastereoselective radical addition to chiral hydrazones giving *N*-acylhydrazines in moderate yield and with high stereocontrol.[4]

This paper presents an investigation of the metal-catalyzed, and the metal-catalyzed, enantioselective intermolecular radical addition to C=N bonds of various alkyl halides. The influence of different Lewis acids on the reaction course is investigated and it is shown that it is possible to perform catalytic enantioselective radical addition to C=N bonds using chiral Lewis acids as the catalyst.

Results and discussion

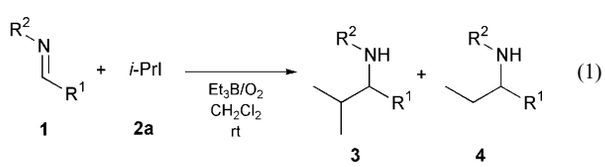
A challenge for the Et_3B-mediated intermolecular tin-free radical addition to C=N bonds is to control the reactivity and selectivity of the radical attack as addition of both isopropyl and ethyl (from Et_3B) radicals can take place [eqn. (1)]. In Table 1 are shown the results for the reaction of different imines in eqn. (1) with *i*-PrI in the presence of Et_3B–O_2 as a radical initiator under various reaction conditions.

It appears from the results in Table 1 that the range of imines (**1a**–**i**) that can be used in the radical addition is large and that the imine substituents have an influence on which radical attacks the imine carbon atom, leading to products **3** or **4**. The nitrogen substituent (R^2) can be varied from the deactivating benzyloxy group (*e.g.* **1a**) to the strongly activating tosyl group

Table 1 The reaction of different imines **1a**–**i** with *i*-PrI in the presence of Et_3B–O_2 as radical initiator, in the absence or presence of $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst

Entry	Substrate	Reaction time/h	Yield (%)	Yield (%)
1	**1a**	2	**3a** 69	**4a** 17
2[a]	**1a**	0.5	**3a** 91	**4a** 0
3	**1b**	20	**3b** 50	**4b** 0
4[a]	**1b**	0.5	**3b** 87	**4b** 0
5	**1c**	0.5	**3c** 45	**4c** 25
6	**1d**	1	**3d** 59	**4d** 40
7	**1e**	20	**3e** 8	**4e** 0
8[a]	**1e**	2	**3e** 78	**4e** 0
9	**1f**	20	**3f** 0	**4f** 0
10	**1g**	20	**3g** 72	**4g** 0
11	**1h**	0.5	**5a** 32[c]	**5b** 64[c]
12	**1i**	20	**3i** 0	**4i** 0

[a] One equiv. $BF_3{\cdot}OEt_2$ added. [b] 1.5 : 1 mixture of *E*- and *Z*-isomers. [c] Cyclised products **5a** and **5b** are obtained (see text).

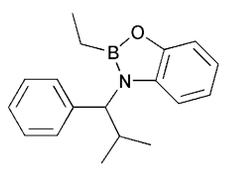


(1)

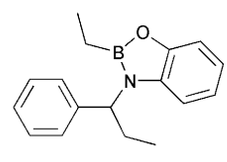
a: R^1 = COOEt, R^2 = BnO
b: R^1 = CH_2COOEt, R^2 = BnO
c: R^1 = COOEt, R^2 = Tos
d: R^1 = COOEt, R^2 = *p*-MeOPh
e: R^1 = *o*-MeOPh, R^2 = BnO
f: R^1 = *o*-NO_2Ph, R^2 = BnO
g: R^1 = Ph, R^2 = *o*-MeOPh
h: R^1 = Ph, R^2 = *o*-HOPh
i: R^1 = $(CH_3)_2CHCH_2$, R^2 = NHTos

 DOI: 10.1039/b101762o

(*e.g.* **1c**) to give **3a** and **3c** as the major products, respectively, and the ethylated compounds **4a** and **4c** as the minor products (entries 1 and 5). The carbon substituent (R^1) has, on the other hand, a strong influence on the reactivity of the imine. In general, imines derived from glyoxylate (R^1 = COOEt), **1a**,**c**,**d**, react much faster than the substrates derived from 3-oxopropionate ($R^1 = CH_2COOEt$), **1b**, or benzaldehyde, **1g**,**h**. The latter substrates often require activation by Lewis acids to give reasonable yields as seen in entry 3 *vs*. 4 and entry 7 *vs*. 8. The activation and selectivity by the Lewis acid are also pronounced for the activated imine **1a** (entry 1 *vs*. 2). It is notable that **1f** and **1i** do not react under these conditions. The results in Table 1 show that the addition of the isopropyl radical to the various types of imine proceeds well in several cases, as up to 91% yield of the radical addition product is isolated. For the reaction using **1h** as the imine, the cyclised products **5a** and **5b** are formed in 32 and 64% yield, respectively.

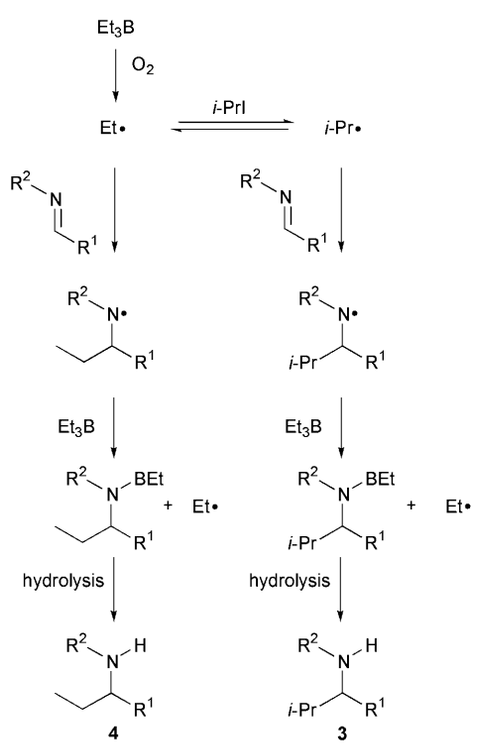


5a



5b

The mechanism for the formation of **3** and **4** in eqn. (1) is outlined in Scheme 1.[5] The first step is generation of the ethyl



Scheme 1

radical by reaction of O_2 with Et_3B. The amount of ethylated product (**4**) is dependent on the efficiency of the iodine atom-transfer step. At low temperature the iodine atom-transfer step is slow and the concentration of the isopropyl radical is low leading to formation of **4** as the major product, although the isopropyl radical is more reactive due to its higher nucleophilicity. At the temperature of the present reactions, the concentration of the isopropyl radical is increased and, due to its higher reactivity, the formation of **3** is now favoured. It appears also from the results in Table 1 that the distribution between **3** and **4** is dependent on the reactivity of the imine; imines activated by electron-withdrawing groups give a higher amount of

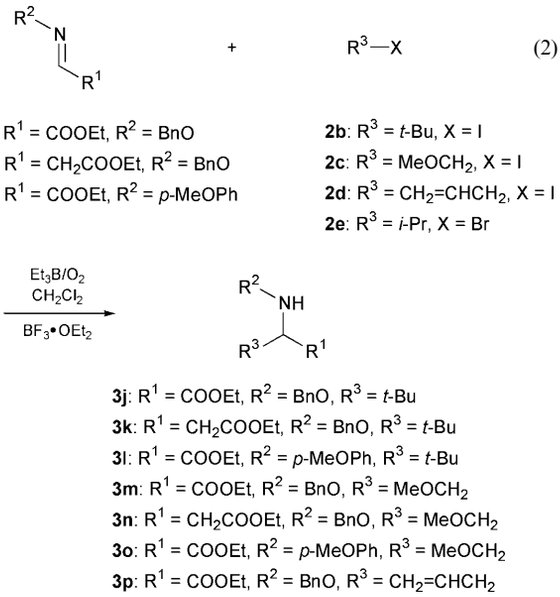


Table 2 Metal-catalyzed radical addition to imines **1a**,**b**,**d**,**e** by reaction of alkyl and alkoxyalkyl halides in the presence of Et_3B–O_2 as radical initiator

Entry	Imine	Alkyl halide	Yield (%)
1	**1a**	**2b**	**3j** 85
2[a]	**1b**	**2b**	**3k** 60
3[a]	**1d**	**2b**	**3l** 80
4[c]	**1a**	**2c**	**3m** 84
5[ac]	**1b**	**2c**	**3n** 62
6[ac]	**1e**	**2c**	**3o** <5
7	**1a**	**2d**	**3p** <5
8[b]	**1a**	**2e**	**3a** 25

[a] One equiv. BF_3·OEt_2 added. [b] One equiv. of Bu_3SnH added. [c] The reactions of methoxymethyl iodide were performed at −78 °C.

the ethylated by-product **4**, while unactivated imines, or imines substituted with an electron-donating substituent produce none, or only a small amount, of **4** (entries 1–4, 7, 8, 10).

A series of other alkyl halides **2b**–**e** also reacts with the different imines **1a**,**b**,**d**,**e** [eqn. (2)] with various degrees of success under the present reaction conditions and the results are presented in Table 2.

The results in Table 2 show that metal-catalyzed radical addition to the various types of imine proceeds well for nucleophilic alkyl and alkoxyalkyl radicals (entries 1–5). Furthermore, alkyl bromides can also be used instead of alkyl iodides, however, in this case the addition of Bu_3SnH is necessary for the generation of the alkyl radical (entry 8), since the atom-transfer process to the ethyl radical (Scheme 1) is only effective for iodine. It has been observed that the methoxymethyl radical gives the fastest and cleanest reaction due to the higher nucleophilicity of this radical compared to the alkyl radicals.

The difference in reactivity of the imines can be accounted for by an FMO approach as outlined in Fig. 1. The reaction takes place by an interaction of the SOMO of the radical with the LUMO of the imine and this explains why the ethyl glyoxylate derived imine **1a** (R^1 = COOEt, Table 1, entry 1) is more reactive than the 3-oxopropionate derived imine **1b** (R^1 = CH_2COOEt, Table 1, entry 3). The LUMO of **1a** is located lower in energy than that of **1b** and therefore the interaction with the SOMO of the radical is more favourable for compound **1a** than for **1b**. However, both imines have the ability to coordinate in a mono- or bidentate fashion to a Lewis acid, depending on the type of Lewis acid. The coordination of the imine to the Lewis acid causes a further lowering of the LUMO energy, which will enhance the imine's reactivity towards the

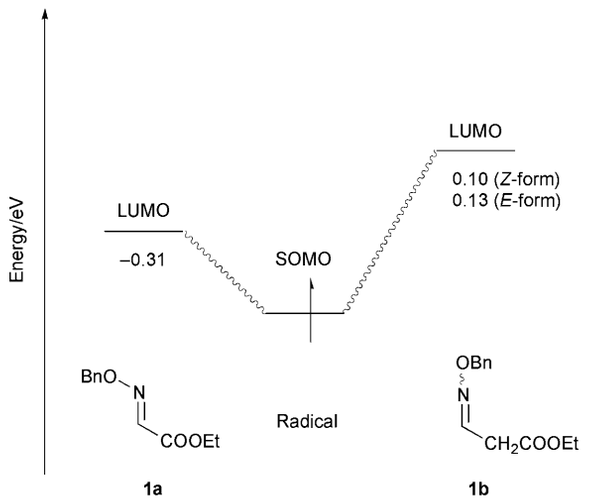


Fig. 1 Calculated LUMO energies of **1a** and **1b**. The lines show the interaction with the SOMO of the alkyl radical.

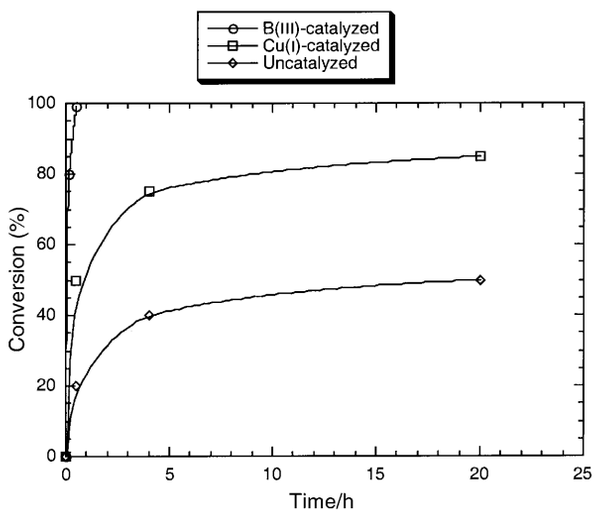
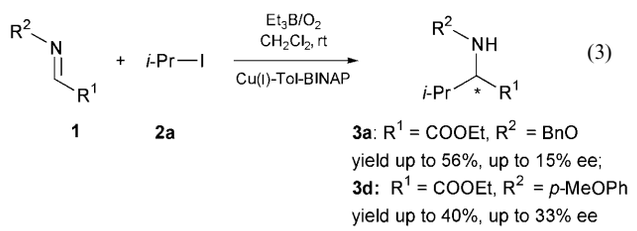


Fig. 2 Conversion as a function of time for the reaction of imine **1b** with *i*-PrI in the presence of Et_3B–O_2 as a radical initiator in the absence and presence of Lewis acid activation $BF_3{\cdot}OEt_2$ and $CuPF_6{\cdot}4MeCN$.

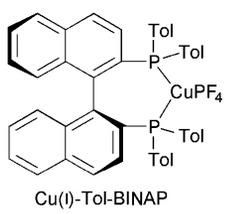
radical, leading to a smaller LUMO–SOMO energy gap compared to the reaction in the absence of a Lewis acid.

The catalytic effect of coordination of the imine to the Lewis acid is also apparent from Table 1. A graphical representation, as a function of time, of the addition of two different Lewis acids to the reaction of the 3-oxopropionate derived imine **1b** with *i*-PrI in the presence of Et_3B–O_2 as a radical initiator is shown in Fig. 2. It is obvious that the presence of a Lewis acid in the radical-addition reaction has a rate-accelerating effect. For the reaction activated by $BF_3{\cdot}OEt_2$, to which the imine can coordinate in a monodentate fashion, full conversion is accomplished within 30 min, while in the presence of $CuPF_6{\cdot}4MeCN$ a slower reaction seems to take place. The imine **1b** exists in an approximately 2 : 3 ratio of the *E*- and *Z*-isomers at room temperature and only the *E*-isomer can coordinate in a bidentate fashion to the Cu(I)-Lewis acid. ^1H NMR spectroscopy shows that the *E*-isomer of **1b** has been consumed after a reaction time of 30 min in the presence of Cu(I) as the catalyst. The *Z*-isomer of **1b** cannot coordinate in a bidentate fashion to Cu(I) and no activation of **1b** is therefore observed. The remaining part of the reaction takes place by the uncatalyzed addition of the isopropyl radical to the *Z*-isomer of **1b** and it appears from Fig. 2 that the conversion of **1b**, after all the *E*-isomer has been consumed, follows the conversion of the uncatalyzed reaction.

The activation of the imines by Lewis acids leads us to investigate the possibility of performing enantioselective addition reactions of radicals to the various types of imines **1a–i** with *i*-PrI (**2a**) using Et_3B–O_2 as a radical initiator and in the presence of chiral Lewis acids. A variety of different combinations of Lewis acids and chiral ligands have been screened for their ability to induce enantioselectivity in these reactions. Among the different combinations, it was found that Cu(I)–Tol-BINAP† catalyzed a reaction with enantioselectivity and the most promising results are outlined in eqn. (3).



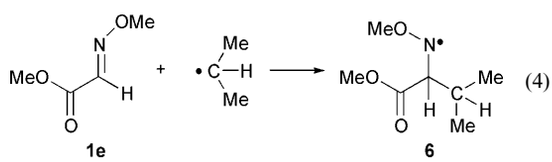
(3)



Cu(I)-Tol-BINAP

The chiral copper Lewis acids tested for the radical addition to imines have very recently been found to be very enantioselective catalysts for other addition reactions to similar, related imines.[6] In the present catalytic, enantioselective reactions the radical-addition proceeds in moderate yield for imines **1a**,**c** with *i*-PrI (**2a**) and an enantioselectivity of up to 33% ee is obtained for imine **1d**. It should also be mentioned that *t*-BuI also can be used and similar enantioselectivities are obtained to those for *i*-PrI.

In an attempt to account for the moderate enantioselectivity obtained for the present Cu(I)–Tol-BINAP-catalyzed enantioselective addition of *e.g.* the isopropyl radical to the imines a series of theoretical investigations have been performed [eqn. (4)].



1e 6 (4)

Calculations have been performed using DFT[7] with an unrestricted B3LYP/6-31G** basis set to obtain information about the transition-state structure for the reaction and the influence of the Lewis acid on the transition-state structure. According to our knowledge, no theoretical calculations have been reported for radical addition to imines, while several investigations have been performed for radical-addition reactions to alkenes.[8] The calculated transition state for the reaction of the glyoxylate oxime ether **1e** with the isopropyl radical [eqn. (4)] is shown in Fig. 3. The calculated transition-state structure is very similar to the calculated transition-state structures for radical addition to alkenes.[8] The C–C bond being formed is 2.39 Å in the transition state and the approaching carbon atom is in the C–N plane (Fig. 3, top). The ∠C–C–N angle for the incoming radical is 104.4°. The calculated transition-state energy is very low, as the energy barrier for the reaction is only 1.6 kcal mol^{-1} relative to the total energy for the imine **1e** and isopropyl radical (−555.4905 E_h). This transition-state energy is slightly lower than those calculated for radical addition to

† Tol-BINAP = 2,2′-bis(ditolylphosphino)-1,1′-binaphthyl.

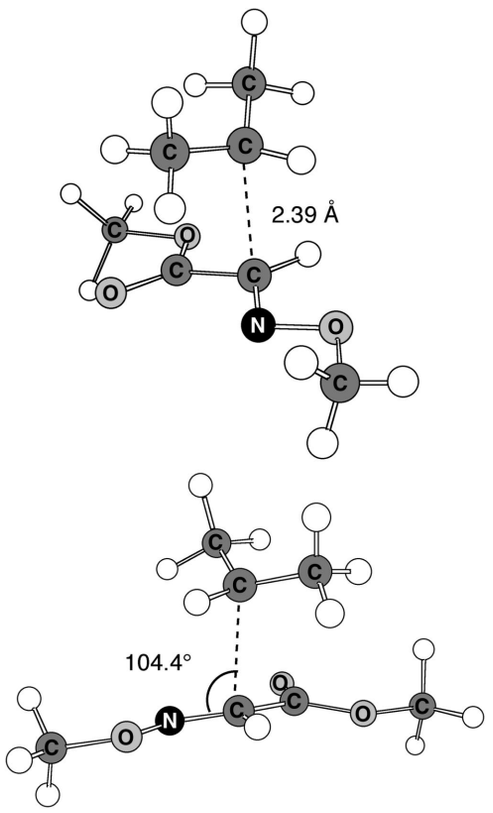


Fig. 3 Calculated transition state for the reaction of the glyoxylate oxime ether **1a** with isopropyl radical from DFT calculations with the B3LYP/6-31G** basis set.

alkenes using a smaller basis set.[8] The total energy of the radical product (**6**) is calculated to be −555.5300 E_h. We have also tried to locate a transition state for the Lewis-acid catalyzed [*e.g.* B(III) and Cu(I)] addition of the isopropyl radical to imine **1e**. However, in all the cases investigated, no transition state could be located, and the calculations show that the radical product was formed without any transition state. These results for the transition state (in the absence of a Lewis-acid catalyst) show that the reaction proceeds through an early transition state. We have used this transition-state structure to model the catalytic enantioselective reaction in the presence of a chiral Lewis acid and found that the face-shielding of the imine is very small in agreement with the moderate enantioselectivity obtained for these reactions.

In summary, it has been shown that different radicals can be added to various types of imines in the presence of Lewis acids as the catalyst. The reaction proceeds well for imines having both activating and deactivating nitrogen substituents, and the reaction can be controlled and accelerated to a large extent by the use of Lewis acids. For imines having different carbon substituents it has been observed that those derived from glyoxylate react much faster than substrates derived from 3-oxopropionate or benzaldehyde. The intermolecular Lewis-acid catalyzed radical addition can occur for different types of imines with both alkyl and alkoxyalkyl radicals and it is demonstrated that it is possible to perform the radical addition in a catalytic, enantioselective fashion in moderate yield and with enantioselectivities of up to 33% ee. DFT calculations show that the radical attack in the uncatalyzed reaction has a very low transition-state energy and an early transition state with bond length of 2.39 Å for the carbon–carbon bond being formed.

Experimental

General

Solvents were dried using standard procedures. All glassware used in Lewis-acid catalyzed reactions were flame-dried before use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 at 400 and 100 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ and measured in ppm downfield from tetramethylsilane (TMS). Enantiomers were separated by HPLC on a Waters instrument, or by GC/GC-MS on an HP 6890 instrument, using a chiral column as indicated in the respective entries.

Materials

All substrates were prepared according to literature procedures. Et_3B (1.0 M solution in hexanes) and $CuPF_6$·4MeCN were purchased from Aldrich and used as received. (*R*)-Tol-BINAP was purchased from Strem.

General procedure for Lewis-acid catalyzed and enantioselective Lewis-acid catalyzed radical-addition reactions

$CuPF_6$·4MeCN (14.9 mg, 0.04 mmol) and (*R*)-Tol-BINAP (29.0 mg, 0.042 mmol) were added to a flame-dried Schlenk flask and dried for 1 h under vacuum. Dry CH_2Cl_2 (2 ml) was added and the solution was stirred for 1 h at room temperature, which was followed by addition of compound **1d** (47.5 mg, 0.23 mmol) and 2-iodopropane (200 μl, 2.0 mmol). Et_3B (1.0 ml, 1.0 M solution in hexanes, 1.0 mmol) was added followed by O_2 (5 ml) and the mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with brine and extracted with CH_2Cl_2 and the solvent was removed *in vacuo*. The product was isolated by flash column chromatography on silica gel using 12% Et_2O–pentane to yield **4d** (48.4 mg, 89%) as a colorless oil, and **3d** (2.9 mg, 5%) as a colorless oil in 30% ee as measured by GC/GC-MS using an Astec B-DM column.

2-Benzyloxyamino-3-methylbutyric acid ethyl ester (3a). ^{1}H NMR δ 0.82 (d, J = 6.8 Hz, 3H, CH_3), 0.83 (d, J = 6.8 Hz, 3H, CH_3), 1.21 (t, J = 7.6 Hz, 3H, CH_3), 1.70 (octet, J = 6.8 Hz, 1H, CH), 3.26 (dd, J = 6.8, 10.8 Hz, 1H, CH), 4.16 (q, J = 7.6 Hz, 2H, OCH_2), 4.60 (s, 2H, OCH_2), 5.94 (d, J = 10.8 Hz, 1H, NH), 7.19–7.32 (m, 5H, ArH); ^{13}C NMR δ 14.3, 19.3, 29.2, 60.7, 69.5, 75.9, 127.7, 128.2, 128.6, 137.9, 174.0; HRMS *m*/*z* 274.1421 $(M + Na)^+$, calc. for $C_{14}H_{21}NO_3Na$ 274.1419; *m*/*z* (EI) 178 (27%), 91 (100), 77 (23). Enantiomers were separated by HPLC using a Chiralcel OJ column with 99 : 1 v/v hexane–*i*-PrOH.

2-Benzyloxyaminobutyric acid ethyl ester (4a). ^{1}H NMR δ 0.85 (t, J = 7.2 Hz, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3), 1.52 (m, 2H, CH_2), 3.43 (dt, J = 10.0, 6.8 Hz, 1H, CH), 4.18 (q, J = 7.2 Hz, 2H, OCH_2), 4.61 (s, 2H, OCH_2), 5.89 (d, J = 10.0 Hz, 1H, NH), 7.19–7.32 (m, 5H, ArH); ^{13}C NMR δ 10.4, 14.3, 22.9, 60.8, 65.1, 76.0, 127.7, 128.2, 128.4, 137.8, 174.0; HRMS *m*/*z* 260.1260 $(M + Na)^+$, calc. for $C_{13}H_{19}NO_3Na$ 260.1263; *m*/*z* (EI) 164 (21%), 91 (100), 77 (25).

3-Benzyloxyamino-4-methylpentanoic acid ethyl ester (3b). ^{1}H NMR δ 0.84 (d, J = 7.2 Hz, 3H, CH_3), 0.87 (d, J = 7.2 Hz, 3H, CH_3), 1.19 (t, J = 6.8 Hz, 3H, CH_3), 1.83 (octet, J = 7.2 Hz, 1H, CH), 2.35 (m, 2H, CH_2), 3.08 (m, 1H, CH), 4.02 (q, J = 6.8 Hz, 2H, OCH_2), 4.60 (s, 2H, OCH_2), 5.78 (br s, 1H, NH), 7.19–7.32 (m, 5H, ArH); ^{13}C NMR δ 14.2, 18.2, 19.2, 29.0, 34.0, 60.4, 62.7, 76.3, 127.7, 128.3, 128.4, 137.9, 173.0; HRMS *m*/*z* 288.1571 $(M + Na)^+$, calc. for $C_{15}H_{23}NO_3Na$ 288.1576; *m*/*z* (EI) 222 (37%), 91 (100). Enantiomers were separated by HPLC using a Chiralcel OJ column with 99.5 : 0.5 v/v hexane–*i*-PrOH.

3-Methyl-2-(4-tolylsulfonylamino)butyric acid ethyl ester (3c). ^{1}H NMR δ 0.79 (d, J = 7.4 Hz, 3H, CH_3), 0.92 (d, J = 7.4 Hz, 3H, CH_3), 1.02 (t, J = 7.6 Hz, 3H, CH_3), 1.95 (octet, J = 7.4 Hz, 1H, CH), 2.35 (s, 3H, $ArCH_3$), 3.63 (dd, J = 11.0, 7.4 Hz, 1H, CH), 3.81 (q, J = 7.6 Hz, 2H, OCH_2), 4.99 (d, J = 11.0 Hz, 1H, NH), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.63 (d, J = 8.0 Hz, 2H,

ArH); ^{13}C NMR δ 12.9, 16.3, 17.9, 20.5, 30.7, 60.0, 60.4, 126.4, 128.5, 135.7, 142.5, 170.3; HRMS *m/z* 322.1090 (M + Na)$^+$, calc. for $C_{14}H_{21}NO_4SNa$ 322.1090; *m/z* (EI) 226 (100%), 155 (64), 91 (64).

2-(4-Tolylsulfonylamino)butyric acid ethyl ester (4c). ^{1}H NMR δ 0.84 (t, J = 7.6 Hz, 3H, CH_3), 1.03 (t, J = 7.2 Hz, 3H, CH_3), 1.56–1.75 (m, 2H, CH_2), 2.35 (s, 3H, $ArCH_3$), 3.76 (m, 1H, CH), 3.85 (q, J = 7.2 Hz, 2H, OCH_2), 5.08 (d, J = 9.2 Hz, 1H, NH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 7.65 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR δ 9.5, 14.2, 21.8, 27.0, 57.0, 61.8, 127.5, 129.8, 136.9, 143.8, 171.9; HRMS *m/z* 308.0937 (M + Na)$^+$, calc. for $C_{13}H_{19}NO_4SNa$ 308.0933; *m/z* (EI) 212 (60%), 171 (29), 155 (53), 91 (100).

2-(4-Methoxyphenylamino)-3-methylbutyric acid ethyl ester (3d). ^{1}H NMR δ 0.95 (d, J = 7.2 Hz, 3H, CH_3), 0.97 (d, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.0 Hz, 3H, CH_3), 2.01 (octet, J = 7.2 Hz, 1H, CH), 3.65 (s, 3H, OCH_3), 3.70 (m, 1H, CH), 3.81 (br, 1H, NH), 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 6.55 (d, J = 8.4 Hz, 2H, ArH), 6.70 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR δ 14.3, 18.7, 19.1, 31.5, 55.7, 60.7, 63.8, 114.8, 115.3, 141.5, 152.7, 174.0; HRMS *m/z* 274.1419 (M + Na)$^+$, calc. for $C_{14}H_{21}NO_3Na$ 274.1419; *m/z* (EI) 251 (M$^+$, 19%), 208 (15), 178 (100), 134 (56), 122 (21). Enantiomers were separated by GC/GC-MS using a Chrompack chirasil-Dex CB column.

2-(4-Methoxyphenylamino)butyric acid ethyl ester (4d). ^{1}H NMR δ 0.92 (t, J = 7.6 Hz, 3H, CH_3), 1.18 (t, J = 6.4 Hz, 3H, CH_3), 1.65–1.85 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.80 (br, 1H, NH), 3.86 (m, 1H, CH), 4.11 (q, J = 6.4 Hz, 2H, OCH_2), 6.55 (d, J = 6.8 Hz, 2H, ArH), 6.70 (d, J = 6.8 Hz, 2H, ArH); ^{13}C NMR δ 9.0, 13.3, 25.2, 54.7, 58.0, 59.9, 113.8, 114.1, 140.0, 151.6, 173.3; HRMS *m/z* 260.1261 (M + Na)$^+$, calc. for $C_{13}H_{19}NO_3Na$ 260.1263; *m/z* (EI) 237 (M$^+$, 16%), 164 (100), 134 (17), 122 (7).

***O*-Benzyl-*N*-[1-(2-methoxyphenyl)-2-methylpropyl]hydroxylamine (3e).** ^{1}H NMR δ 0.64 (d, J = 6.8 Hz, 3H, CH_3), 0.91 (d, J = 6.8 Hz, 3H, CH_3), 1.85–2.05 (octet, J = 6.8 Hz, 1H, CH), 3.72 (s, 3H, OCH_3), 3.98 (d, J = 8.0 Hz, 1H, CH), 4.57 (s, 2H, OCH_2), 6.00 (br s, 1H, NH), 6.75–6.91 (m, 2H, ArH), 7.11–7.22 (m, 7H, ArH); ^{13}C NMR δ 20.8, 21.6, 30.5, 57.3, 61.3, 76.1, 110.5, 120.3, 127.4, 127.9, 128.0, 128.2, 128.4, 129.3, 138.0, 157.3; HRMS *m/z* 308.1629 (M + Na)$^+$, calc. for $C_{18}H_{23}NO_2Na$ 308.1626; *m/z* (EI) 242 (100%), 136 (40), 121 (48), 91 (86), 77 (23).

(2-Methoxyphenyl)(2-methyl-1-phenylpropyl)amine (3g). ^{1}H NMR δ 0.84 (d, J = 6.4 Hz, 3H, CH_3), 0.95 (d, J = 6.4 Hz, 3H, CH_3), 2.00 (octet, J = 6.4 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 4.04 (d, J = 5.6 Hz, 1H, CH), 4.71 (br s, 1H, NH), 6.23 (dd, J = 7.6, 1.6 Hz, 1H, ArH), 6.49 (dt, J = 1.6, 7.6 Hz, 1H, ArH), 6.59 (dt, J =1.6, 7.6 Hz, 1H, ArH), 6.68 (dd, J = 7.6, 1.6 Hz, 1H, ArH), 7.10–7.26 (m, 5H, ArH); ^{13}C NMR δ 18.9, 20.1, 35.2, 55.8, 63.9, 109.4, 110.9, 116.1, 121.4, 126.9, 127.4, 128.4, 137.9, 143.1, 146.9; HRMS *m/z* 278.1520 (M + Na)$^+$, calc. for $C_{17}H_{21}NONa$ 278.1521; *m/z* (EI) 255 (M$^+$, 6%), 212 (100), 196 (12), 120 (15), 91 (11).

2-Ethyl-3-(2-methyl-1-phenylpropyl)-2,3-dihydro-1,3,2-benzoxazaborole (5a). ^{1}H NMR δ 0.91 (d, J = 6.8 Hz, 6H, CH_3), 1.06–1.27 (m, 5H, CH_2CH_3), 2.69 (dseptet, J = 11.2, 6.8 Hz, 1H, CH), 4.30 (d, J = 11.2 Hz, 1H, CH), 6.30–7.35 (m, 9H, ArH); ^{13}C NMR δ 8.9, 9.0, 20.9, 21.6, 30.3, 65.6, 110.6, 112.0, 119.6, 121.4, 127.0, 127.5, 128.7, 138.1, 141.5, 149.5; *m/z* (EI) 279 (M$^+$, 9%), 236 (100), 91 (11).

2-Ethyl-3-(1-phenylpropyl)-2,3-dihydro-1,3,2-benzoxazaborole (5b). ^{1}H NMR δ 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.06–1.27 (m, 5H, CH_2CH_3), 2.19 (quintet, J = 7.2 Hz, 2H, CH_2), 4.76 (t, J = 7.6 Hz, 1H, CH), 6.30–7.35 (m, 9H, ArH); ^{13}C NMR δ 8.9, 9.0, 11.9, 26.3, 58.9, 111.2, 112.0, 119.6, 121.4, 127.4, 128.1, 128.6, 137.4, 141.9, 149.8; *m/z* 265 (EI) (M$^+$, 31%), 236 (100), 91 (34).

2-Benzyloxyamino-3,3-dimethylbutyric acid ethyl ester (3j). ^{1}H NMR δ 0.96 (s, 9H, 3 CH_3), 1.23 (t, J = 8.4 Hz, 3H, CH_3), 3.28 (d, J = 10.3 Hz, 1H, CH), 4.21 (q, J = 8.4 Hz, 2H, OCH_2), 4.63 (s, 2H, OCH_2), 6.11 (d, J = 10.3 Hz, 1H, NH), 7.25–7.37 (m, 5H, ArH); ^{13}C NMR δ 13.3, 26.0, 32.0, 59.5, 71.0, 74.7, 126.6, 127.1, 127.6, 137.0, 172.9; HRMS *m/z* 288.1577 (M + Na)$^+$, calc. for $C_{15}H_{23}NO_3Na$ 288.1576; *m/z* (EI) 208 (21%), 192 (36), 91 (100).

3-Benzyloxyamino-4,4-dimethylpentanoic acid ethyl ester (3k). ^{1}H NMR δ 0.96 (s, 9H, 3 CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.49 (d, J = 6.0 Hz, 2H, CH_2), 3.18 (t, J = 6.0 Hz, 1H, CH), 4.12 (m, 2H, OCH_2), 4.65 (s, 2H, OCH_2), 5.80 (br, 1H, NH), 7.25–7.36 (m, 5H, ArH); ^{13}C NMR δ 14.4, 27.3, 33.8, 34.7, 60.6, 65.9, 76.1, 127.9, 128.5, 128.6, 138.1, 173.7; HRMS *m/z* 302.1734 (M + Na)$^+$, calc. for $C_{16}H_{25}NO_3Na$ 302.1732; *m/z* (EI) 222 (85%), 148 (14), 91 (100).

2-(4-Methoxyphenylamino)-3,3-dimethylbutyric acid ethyl ester (3l). ^{1}H NMR δ 1.05 (s, 9H, 3 CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.89 (br, 1H, NH), 3.92 (br, 1H, CH), 4.15 (q, J = 7.2 Hz, 2H, OCH_2), 6.63 (d, J = 9.2 Hz, 2H, ArH), 6.76 (d, J = 9.2 Hz, 2H, ArH); ^{13}C NMR δ 14.3, 26.8, 34.3, 55.7, 60.5, 67.0, 114.8, 115.6, 141.8, 152.7, 173.6; HRMS *m/z* 288.1573 (M + Na)$^+$, calc. for $C_{15}H_{23}NO_3Na$ 288.1576; *m/z* (EI) 265 (M$^+$, 21%), 208 (48), 192 (50), 134 (100).

2-Benzyloxyamino-3-methoxypropionic acid ethyl ester (3m). ^{1}H NMR δ 1.22 (t, J = 7.6 Hz, 3H, CH_3), 3.33 (s, 3H, OCH_3), 3.59 (d, J = 5.6 Hz, 2H, OCH_2), 3.78 (m, 1H, CH), 4.22 (q, J = 7.6 Hz, 2H, OCH_2), 4.73 (s, 2H, OCH_2), 6.04 (d, J = 8.4 Hz, 1H, NH), 7.25–7.37 (m, 5H, ArH); ^{13}C NMR δ 14.4, 59.5, 61.5, 64.0, 70.5, 76.6, 128.1, 128.5, 128.6, 137.9, 171.4; HRMS *m/z* 276.1210 (M + Na)$^+$, calc. for $C_{13}H_{19}NO_4Na$ 276.1212; *m/z* (EI) 208 (10%), 180 (16), 108 (12), 91 (100), 77 (17).

3-Benzyloxyamino-4-methoxybutyric acid ethyl ester (3n). ^{1}H NMR δ 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.43 (dd, J = 15.6, 5.6 Hz, 1H, CH), 2.58 (dd, J = 15.6, 5.6 Hz, 1H, CH), 3.35 (s, 3H, OCH_3), 3.42 (d, J = 5.6 Hz, 2H, OCH_2), 3.55 (sextet, J = 5.6 Hz, 1H, CH), 4.12 (q, J = 7.2 Hz, 2H, OCH_2), 4.70 (s, 2H, OCH_2), 6.06 (d, J = 5.6 Hz, 1H, NH), 7.25–7.37 (m, 5H, ArH); ^{13}C NMR δ 14.4, 34.6, 57.4, 59.3, 60.7, 72.0, 76.8, 128.0, 128.5, 128.6, 138.0, 172.2; HRMS *m/z* 290.1369 (M + Na)$^+$, calc. for $C_{14}H_{21}NO_4Na$ 290.1368; *m/z* 222 (42%), 91 (100).

Acknowledgements

We are indebted to The Danish National Research Foundation for financial support. Thanks are expressed to Dr Mark Roberson for performing the theoretical calculations.

References

1 See *e.g.* (*a*) D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1995; (*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.

2 (*a*) H. Miyabe, C. Ushiro and T. Naito, *Chem. Commun.*, 1997, 1789; (*b*) H. Miyabe, R. Shibata, M. Sangawa, C. Ushiro and T. Naito, *Tetrahedron*, 1998, **54**, 11431; (*c*) H. Miyabe, H. Tanaka and T. Naito, *Tetrahedron Lett.*, 1999, **40**, 8387; (*d*) H. Miyabe, K. Fujii and T. Naito, *Org. Lett.*, 1999, **1**, 569; (*e*) H. Miyabe, C. Konishi and T. Naito, *Org. Lett.*, 2000, **2**, 1443; (*f*) H. Miyabe, C. Ushiro, M. Ueda, K. Yamakawa and T. Naito, *J. Org. Chem.*, 2000, **65**, 176; (*g*) H. Miyabe, M. Ueda and T. Naito, *J. Org. Chem.*, 2000, **65**, 5043; (*h*) H. Miyabe, M. Ueda and T. Naito, *Chem. Commun.*, 2000, 2059.

3 M. P. Bertrand, L. Feray, R. Nouguier and P. Perfetti, *Synlett*, 1999, 1148.
4 G. F. Friestad and J. Qin, *J. Am. Chem. Soc.*, 2000, **34**, 8329.
5 For a related mechanistic approach see: H. Miyabe, N. Yoshioka, M. Ueda and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3659.
6 See *e.g.* (*a*) S. Yao, M. Johannsen, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 1999, **37**, 3121; (*b*) S. Yao, S. Saaby, R. G. Hazell and K. A. Jørgensen, *Chem. Eur. J.*, 2000, **6**, 2435; (*c*) S. Yao, X. Fang and K. A. Jørgensen, *Chem. Commun.*, 1998, 2547; (*d*) W. J. Drury, III, D. Ferraris, C. Cox, B. Young and T. Lectka, *J. Am. Chem. Soc.*, 1998, **120**, 11006; M. Johannsen, *Chem. Commun.*, 1999, 2233; (*e*) S. Saaby, X. Fang, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4114; (*f*) D. Ferraris, B. Young, C. Cox, W. J. Drury, III, T. Dudding and T. Letcka, *J. Org. Chem.*, 1998, **63**, 6090; (*g*) P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867; (*h*) H. Ishitani, S. Komiyama, Y. Hasagawa and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 762; (*i*) K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2293.
7 Gaussian 94, Revision E.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Pend, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
8 See *e.g.* (*a*) M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, 1978, **100**, 5290; (*b*) K. N. Houk, M. N. Paddon-Row, D. C. Spellmeyer, N. G. Rondan and S. Nagase, *J. Org. Chem.*, 1986, **51**, 2874.