On the Lewis acid-induced [1,3]-dipolar cycloaddition of allylic and homoallylic alcohols to *N*-methyl-*C*-phenyl nitrone

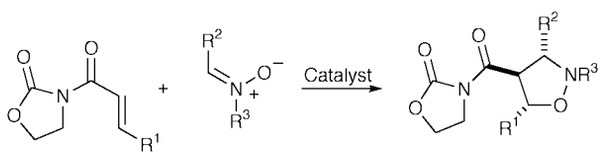
Andrew D. Jones, David W. Knight *† and Steven R. Thornton

Chemistry Department, University Park, Nottingham, UK NG7 2RD

Received (in Cambridge, UK) 12th August 1999, Accepted 13th September 1999

Both the rate and stereoselectivity of [1,3]-dipolar cycloadditions between monosubstituted allylic and homoallylic alcohols **7**, **17**, **25**, **28** and **34** and the benzaldehyde-derived nitrone **8** are increased enormously when the reactions are carried out in the presence of one equivalent of magnesium bromide–diethyl ether. Stereoselectivities in the range of 5 : 1 up to >95 : 5 are achieved in 2–5 hours at 80 °C, in contrast to purely thermal reactions which are almost stereorandom and which require over 48 hours at this temperature. The major products **9**, **18**, **26**, **29** and **35** are *endo* adducts with the opposite *trans*-stereochemistry across the isoxazolidine ring relative to the *exo* adducts **42** obtained from similar catalysed reactions using *C*-acyl nitrones **4**. Models which account for this difference are proposed.

Despite the importance in general synthetic methodology, protocols for accelerating and for inducing chirality into [1,3]-dipolar cycloadditions[1] using Lewis acid catalysts are far less developed relative to similar technology in that other classic pericyclic reaction, the Diels–Alder cycloaddition.[2] However, during the past six years, some significant advances have been made in this area, albeit with a somewhat limited range of reactants.[3] Much attention has been focussed on the catalysed additions of cinnamate derivatives **1**, or the related succinimides, to simple nitrones (**2**; typically R^2 = Ph; R^3 = Ph, Pr, Bn) which usually lead selectively to the *endo*-adducts **3** (Scheme 1),

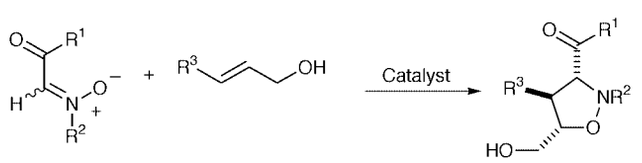


1 **2** **3**

Scheme 1

with significant rate enhancements with respect to the purely thermal reaction and also often with good to excellent optical yields. Lanthanide triflates have proven especially useful in this respect, giving excellent diastereoselections and some reasonable levels of asymmetric induction in the presence of a bis-oxazoline ligand and molecular sieves; magnesium complexes of this ligand system can also be used.[4] By contrast, catalysis by titanium complexes of TADDOL give very largely the corresponding *exo*-diastereoisomers.[5] Similar high levels of acceleration and diastereoselection in favour of the *endo*-isomers **3** have been observed by *in situ* generation of the nitrones **2** in the presence of a lanthanide triflate; further, in the presence of (*R*)-(+)-1,1′-BINOL, >90% enantiomeric enrichment has been achieved in the products **3**.[6] Such catalysis is evidently quite subtle: with ytterbium(III) triflate, *endo*-**3** is formed in toluene but *exo*-**3** is the main product in acetonitrile.[7] Variable returns in terms of stereoselection have also been observed with various binaphthyl–palladium(II) complexes, but only with crotyl derivatives (**1**; R^1 = Me), although *endo*-isomers (**3**; R^1 = Me) can be secured with 90% ee;[8] chiral palladium(II)–phosphine complexes have also been exploited in this context.[9] Titanium complexation provides good rate enhancement with enones which also contain a suitably positioned alkoxy group[10] and zinc iodide has been shown to be effective in accelerating cycloadditions between crotonic acid derivatives (*e.g.* **1**) and cyclic nitrones.[11] High *endo*-selectivity has also been observed in cycloadditions of a series of nitrones with homochiral diiron acyl complexes derived from crotonic acids.[12] [1,3]-Dipolar cycloadditions of electron-rich alkenes have also been successfully catalysed in an asymmetric fashion using homochiral oxazaborolidines; rate accelerations are considerable (the reactions can occur at −78 °C) in additions of vinyl ethers and simple ketene acetals to nitrones (**2**; R^2 = Ph; R^3 = Ph, Me, Bn) but optical yields are, as yet, only moderate in most cases.[13] Cycloadditions of such alkenes can also be catalysed using binaphthyl–Lewis acid complexes, either in solution or bound to a polymer,[14] by palladium(II) species,[15] or by copper(II)–bis-oxazoline complexes, but only in the case of electron-deficient nitrones **4**.[16] Again, the range of substrates is rather limited but some encouraging enantioselections have been achieved. Europium shift reagents can also be used to catalyze cycloadditions involving electron-deficient nitrones **4**.[17] The stereochemistry of [1,3]-dipolar additions between a variety of alkenes and nitrone **4**, when R^1 = OH (*i.e.* the free acid), is dramatically altered by the addition of triethylamine.[18] This salt effect accelerates such cycloadditions, which are otherwise quite insensitive to solvent effects; naturally, such selective rate enhancements result in better stereo- and regio-control.[19]

As might be expected, allylic alcohols **5** are suited to this type of Lewis acid activation, as the hydroxy group can participate in complexation with the catalyst. In general, these reactions have been carried out using only electron deficient nitrones **4** and tend to lead largely or exclusively to the *exo*-regioisomers **6** (Scheme 2). In an early report, a variety of Lewis acids



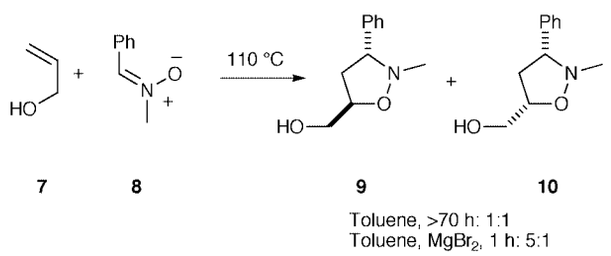
4 **5** **6**

Scheme 2

† Present address: Chemistry Department, Cardiff University, PO Box 912, Cardiff, UK CF10 1TB.

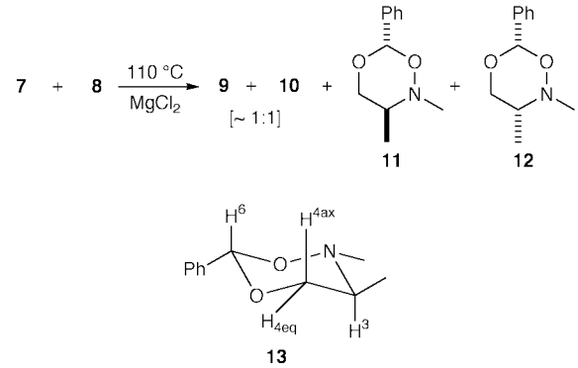
(*e.g.* diethylzinc, ethylmagnesium bromide, magnesium bromide) were used with a *C*-benzoyl nitrone (**4**; R^1 = Ph) to obtain isomers **6**.[20] Later work revealed that the Lewis acid promotes nitrone isomerization from an original (*E*)/(*Z*) mixture to a proposed (*Z*)-nitrone–$MgBr_2$ complex; despite the enhanced stereoselection in favour of *exo*-isomers **6**, surprisingly, little rate enhancement was observed.[21] Further, the term 'catalytic' does not apply in the formal sense, as one equivalent of the Lewis acid is required for an effective transformation. Asymmetric variants of this method have been effected using complexes formed between diethylzinc and tartrate esters and some good enantiomeric enrichments being achieved.[22] A neat extension of this type of cycloaddition involves sequential transesterification of nitrone (**4**; R^1 = OMe) with an allylic alcohol **5** and subsequent intramolecular [1,3]-dipolar cycloaddition, all under the influence of a titanium(IV) Lewis acid.[23] Magnesium bromide is also effective in accelerating [1,3]-cycloaddition of allylic alcohols **5** to cyclic versions of the electron-deficient nitrones **4**.[24]

Our interest in the reactions between nitrones and allylamines and allylthiols[25] led us to speculate that it might be possible to influence the reactivity of allylic alcohols with other types of nitrones using a Lewis acid, although we were well aware that all of the foregoing examples[20–24] involve highly distorted, electron-deficient nitrones **4**. Herein, we report that such activation of [1,3]-dipolar cycloadditions between nitrones (**2**; R^2 = Ph) derived from benzaldehyde and allylic alcohols is indeed possible and that spectacular increases in both rate of reaction and stereoselection can be achieved in suitable cases. We firstly confirmed the complete lack of stereoselection in the known[26] thermal [1,3]-dipolar cycloaddition between allyl alcohol **7** and the benzaldehyde-derived nitrone **8** (Scheme 3).[27]



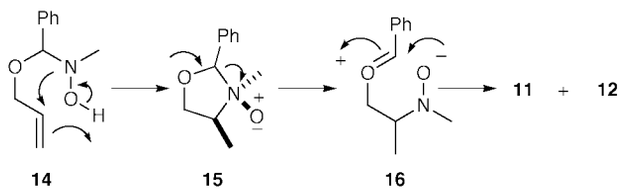
Scheme 3

The two expected diastereomeric isoxazolidines **9** and **10** were isolated in >90% combined yield only after prolonged reaction in refluxing toluene, but in essentially equivalent quantities. The stereochemistry of the separated isomers was inferred from comparisons with later spectroscopic data as NOE measurements proved uninformative. Of a number of Lewis acids subsequently tested, one equivalent of magnesium bromide–diethyl ether provided the best results, giving a useful and unoptimized 5:1 ratio of the two products **9** and **10** in only one hour in toluene at reflux in a slightly reduced isolated yield of 83%. Magnesium bromide is evidently very special in this respect;[20,21,24] under similar conditions, magnesium chloride failed to significantly increase either the rate of reaction or to induce any level of stereoselection, as the two isoxazolidines **9** and **10** were formed in almost equivalent amounts (Scheme 4). Interestingly, minor by-products (*ca.* 3%) were the unusual dioxazinanes **11** and **12**. The structures were assigned from spectroscopic and analytical data; ^{1}H NMR data was especially useful in defining the likely shape of the major *trans*-isomer **11**, which displayed coupling constants consistent with a regular chair conformation **13**, supported by NOE difference spectra which showed strong enhancements between H_{4ax} and H_6 (10%), H_{4ax} and 3-CH_3 (7%) and between H_3 and H_{4eq} (6%). The corresponding *cis*-isomer **12** showed data consistent with this conformation, but having an axial 3-methyl group [NOE



Scheme 4

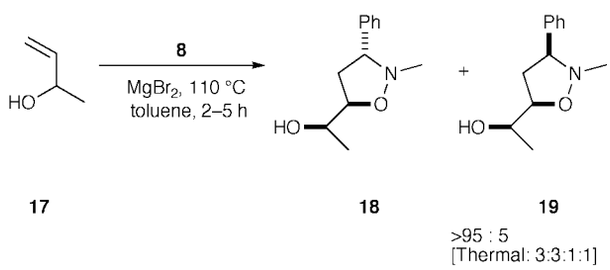
data: H_{4ax}–H_6 (10%), H_{4ax}–H_{3eq} (6%), 3-CH_3–H_{4eq} (2%)]. These products were presumably formed from an alternative pathway in which nucleophilic addition of the alcohol oxygen to the nitrone **8** generates the hydroxylamine **14**, which then undergoes a thermally-induced reverse-Cope elimination leading to the *N*-oxide **15** and thence to the observed products **11** and **12**, following Meisenheimer rearrangement *via* the ring-opened oxonium species **16** (Scheme 5). This sequence has precedent in



Scheme 5

examples featuring additions of allylic amines and thiols to nitrones[25] and the Meisenheimer rearrangement was used in the first approach to such dioxazinanes by *N*-oxidation of the corresponding isoxazolidines to give the transient intermediates **15**.[28]

Thus encouraged, we next studied similar reactions between nitrone **8** and but-3-en-2-ol **17**, in order to assess the ability of a stereogenic centre in the allylic alcohol to control such cycloadditions. Firstly, the purely thermal [1,3]-cycloaddition was carried out in toluene (Scheme 6). This gave an excellent yield



Scheme 6

of all four possible products in a ratio of 3:3:1:1; subsequently, it was clear that the two major products in this gross mixture corresponded to the two products (**18** and **19**) formed in the catalysed reaction using magnesium bromide–diethyl ether. We then conducted an optimization study of the latter and found that pre-complexation between the nitrone **8** and one equivalent of magnesium bromide was essential. The best conditions found consisted of heating the nitrone and the magnesium bromide in toluene at 80 °C until the initial precipitate adhered to the sides of the flask. Without cooling, five equivalents of the allylic alcohol were then added, which

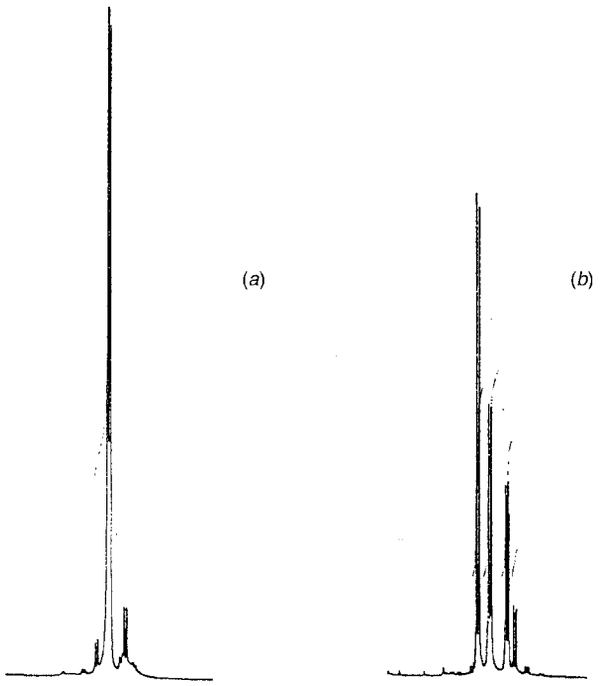
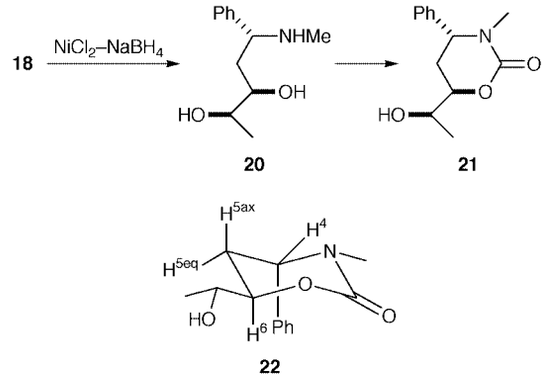


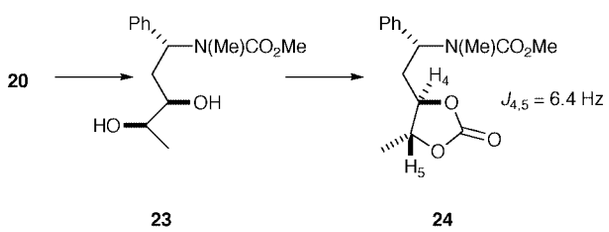
Fig. 1 ^{1}H NMR spectra at δ_H 1.0 for the crude products from (*a*) the catalysed and (*b*) the thermal reaction of **8** with but-3-en-2-ol **17**.

resulted in rapid dissolution of the presumed nitrone–$MgBr_2$ complex. Continued heating at 80 °C led to slow formation of a second precipitate while TLC analysis indicated that the reactions were complete within 2–5 h under these conditions, once again, a very significant rate enhancement relative to the uncatalyzed thermal reaction. Treatment of the crude reaction product with excess 2,6-dinitrobenzoyl chloride resulted in the isolation of *ca.* 3.5 equivalents of the expected allylic benzoate, indicating that the excess allylic alcohol was not consumed in any way. If this excess was necessary simply to form an intermediate magnesium complex, we reasoned that addition of four equivalents of methanol along with the one equivalent of allylic alcohol necessary for the cycloaddition would be a considerable benefit, especially in examples with precious reactants. Unfortunately, this was unsuccessful; however, in many of the runs, use of less allylic alcohol (2–3 equivalents) resulted in only small (*ca.* 10%) reductions in overall yields. We were delighted to find that the catalysed reaction was also highly stereoselective, as illustrated by the ^{1}H NMR data in Fig. 1, which shows the methyl resonances [CH_3CH(OH)] in the crude products from the catalysed [Fig. 1(*a*)] and the thermal reactions [Fig. 1(*b*)]. Integration indicated that the latter provided a 95 : 5 ratio of only two isomers (in both spectra, the far right doublet is due to residual but-3-en-2-ol). Once again, NOE measurements were not informative and so the structures of the two separated products were established by chemical transformations to more easily measured derivatives. The major product was determined to be diastereoisomer **18** by reductive ring opening using nickel boride at −40 °C in methanol.[29] This method proved superior to reductions using lithium aluminium hydride, zinc or hydrogenation and delivered an excellent yield of the amino-diol **20** which was subsequently converted into the cyclic carbamate **21** using 1,1′-carbonyldiimidazole (Scheme 7). ^{1}H NMR analysis clearly indicated that this had the chair conformation **22**; in particular, a large *trans*-diaxial coupling between H_{5ax} and H_6 of 12.1 Hz and two much smaller couplings (6.2 and 2.0 Hz) associated with H_4 showed that the hydroxyethyl side chain was equatorial but the phenyl positioned axially. Hence, the major isoxazolidine is *trans*-substituted. The relative configuration of the secondary alcohol centre was determined by conversion of the amino diol **20**



Scheme 7

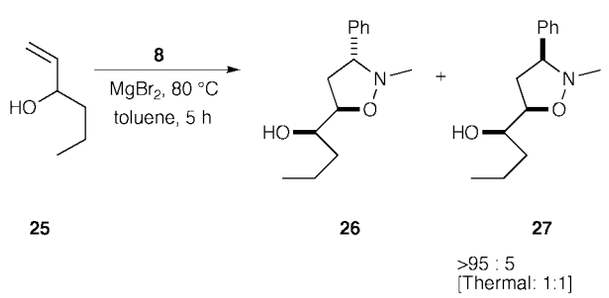
into the dioxolan-2-one **24** by sequential reaction with methyl chloroformate to give the carbamate **23** and, again, reaction with 1,1′-carbonyldiimidazole (Scheme 8). A value of 6.4 Hz



Scheme 8

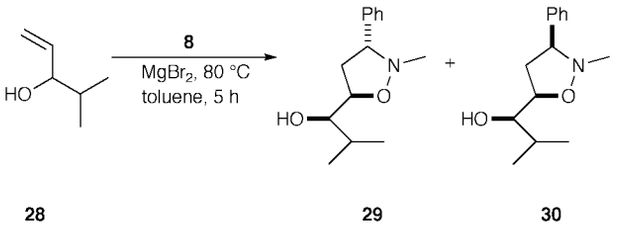
for $J_{4,5}$ revealed that the dioxolanone was *trans*-substituted, as the alternative *cis*-isomer would have $J_{4,5}$ 9–10 Hz,[30] and hence the complete structure of the major product from the catalysed cycloaddition as diastereoisomer **18**. The minor isomer was assigned structure **19**, mainly due to its very closely similar ^{1}H NMR data which differed only in the appearance of the benzylic methine; hence, the assignment as the *cis*-isomer having the same relative configuration at the two centres carrying oxygen. This also fits well with the transition state speculations set out below.

Cycloaddition of a higher homologue, hex-1-en-3-ol **25**, was even more stereoselective in the presence of magnesium bromide, although somewhat slower and less efficient, and only the isomer **26** was isolated, while the uncatalyzed thermal reaction was again non-stereoselective, giving a 1 : 1 mixture of the expected products **26** and **27**, along with traces of the two other possible isomers (Scheme 9). Branching α to the alcohol

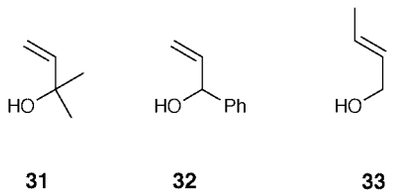


Scheme 9

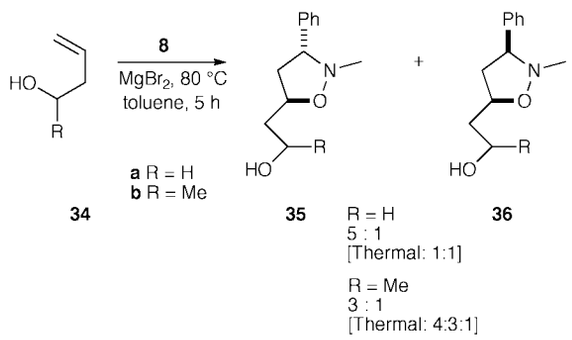
was also accommodated: a similar result was obtained using 4-methylpent-1-en-3-ol **28** which led only to the isoxazolidine **29** using magnesium bromide but to a 3 : 2 mixture of the products **29** and **30** under thermal conditions (Scheme 10). However, additional branching, as in the tertiary alcohol **31**, prevented any cyclisation from occurring. No isoxazolidine products were isolated from catalysed reactions of the secondary benzylic alcohol **32**, presumably due to decomposition



Scheme 10



of this highly reactive substrate and, disappointingly, crotyl alcohol also failed to react with nitrone **8**, hence removing the opportunity to create a third stereocentre. Gratifyingly, homoallylic alcohols also exhibited a high level of stereocontrol. But-3-en-1-ol **34a** again gave a stereorandom mixture of the two possible products **35a** and **36a** under thermal conditions but an encouraging 5 : 1 ratio in favour of isomer **35a** in the presence of magnesium bromide (Scheme 11). The influence



Scheme 11

of a distal methyl group was still significant in cyclisations of the homologous pent-4-en-2-ol **34b** which gave a 3 : 1 ratio of products **35b** and **36b** in the catalysed reaction but three products (4 : 3 : 1) in the thermal reaction. In all the foregoing examples, the relative stereochemistries of the products were determined by comparison with the established structure **18**, with the exception of the final compounds **35b** and **36b**, where the relative configuration at the secondary alcohol centre was not established.

It seems likely that the major isomers (*e.g.* **18**) are formed *via* the *endo* transition state **37** (Fig. 2); such *endo* selectivity is commonly observed in such cycloadditions, assuming that the nitrone **8** retains its (*Z*)-geometry.[4–10] The minor isomers (*e.g.* **19**) then arise by the alternative and evidently less favoured *exo* conformation **38**. The two other possible formulations of a magnesium chelate involve significant unfavourable steric interactions: in the alternative *endo* conformation **39**, the two methyl groups are in close proximity and, in the corresponding *exo* conformation **40**, the allylic methyl is rather close to the phenyl substituent of the nitrone. These conclusions are in complete contrast to those deduced previously in the case of electron-deficient nitrones (**4**; R^1 = Ph), in which *exo* products **42** are formed with excellent selectivities.[20,21] In these examples,

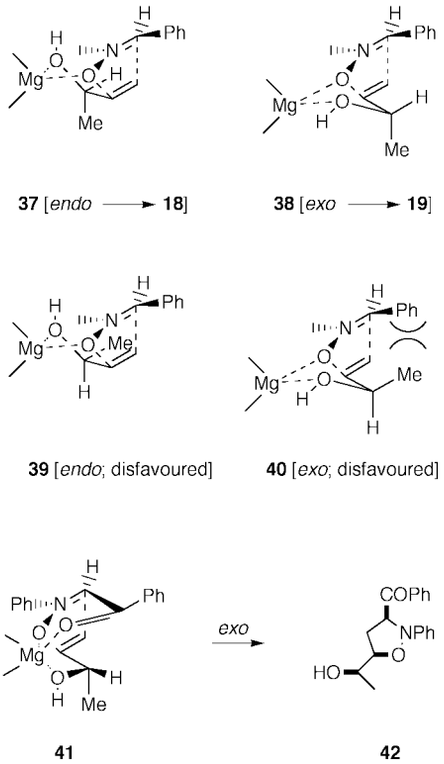


Fig. 2

presumably participation by the additional carbonyl function favours the *exo* conformation **41**, due to additional bonding with the magnesium.

The enormous rate enhancements and the attendant increases in stereoselectivity suggest that this will be a useful method, especially when single enantiomers of the allylic alcohols are used, which will result in the creation of two new asymmetric centres, with retention of the initial centre, with good to virtually complete control. Further, the complete contrast in selectivity between nitrone **8** and the previously reported electron-deficient relatives **4** provides complementarity to this methodology. The limitation at present is that only allylic and homoallylic alcohols which have monosubstituted alkene functions can be used. However, the method will still afford a range of useful products and further developments in terms of the use of other catalysts and nitrones could obviate this drawback in the future.

Experimental

General details

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1720 series Fourier transform spectrometer using thin films between sodium chloride plates, unless otherwise stated. ^{1}H NMR spectra were determined using a Bruker WM-250 or a Bruker AM-400 spectrometer. ^{13}C NMR spectra were determined using a JEOL EX270 spectrometer operating at 67.8 MHz or the Bruker AM-400 instrument operating at 100 MHz. Unless otherwise stated, all spectra were determined using dilute solutions in deuteriochloroform and tetramethylsilane as internal standard. *J* Values are expressed in Hz. Molecular weights and mass spectra were measured using a VG 7070E instrument, operating in the electron impact mode.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry nitrogen in anhydrous solvents which were obtained by the usual methods.[31] All organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. Solvents were

removed by rotary evaporation. CC refers to column chromatography over Sorbsil C60-H (40–60 μm) silica gel using the eluants specified. Petrol refers to light petroleum with bp 40–60 °C. Ether refers to diethyl ether.

(3*RS*,5*RS*)- and (3*RS*,5*SR*)-2-Methyl-3-phenylisoxazolidine-5-methanol 9 and 10

(i) Thermal method.[26] A solution of **8**[27] (0.95 g, 7.04 mmol) and allyl alcohol **7** (0.50 g, 8.0 mmol) in toluene (30 ml) was refluxed for 80 h then cooled and evaporated to leave a yellow oil, CC [ether–petrol, 2:1] of which separated the *trans-(3RS,5RS)-isoxazolidinemethanol* **9** (0.68 g, 47%), R_f 0.33, as a colourless solid, mp 99–100 °C [Found: C, 68.5; H, 7.8; N, 7.3. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.8; N, 7.3%], ν_{max}/cm^{-1} 918; δ_H(400 MHz) 2.27 (1H, ddd, *J* 12.4, 9.6 and 5.4, 4-H_a), 2.57 (3H, s, 2-CH_3), 2.76 (1H, ddd, *J* 12.4, 8.3 and 7.8, 4-H_b), 3.44 (1H, s, OH), 3.51 (1H, app br t, *J ca.* 8.5, 3-H), 3.75 (1H, dd, *J* 11.5 and 8.3, 1′-H_a), 3.80 (1H, dd, *J* 11.5 and 2.4, 1′-H_b), 4.33 (1H, dddd, *J* 8.3, 8.3, 5.4 and 2.4, 5-H) and 7.28–7.40 (5H, m, Ph); δ_C(67.5 MHz) 41.0 (4-CH_2), 42.8 (2-CH_3), 65.8 (1′-CH_2), 73.6 (3-CH), 76.9 (5-CH), 127.6, 127.9, 128.6 (all PhCH) and 138.3 (PhC); *m*/*z* 193 (M^+, 100%), 134 (82), 116 (36), 91 (42) and 77 (21) [Found: M^+, 193.1089. $C_{11}H_{15}NO_2$ requires *M*, 193.1103] and the *cis-(3RS,5SR)-isoxazolidinemethanol* **10** (0.65 g, 45%), R_f 0.25, as a colourless solid, mp 93–94 °C [Found: C, 68.6; H, 7.9; N, 7.3], ν_{max}/cm^{-1} 922; δ_H(400 MHz) 2.38 (1H, app br q, *J ca.* 10.0, 4-H_a), 2.51 (1H, ddd, *J* 12.3, 7.9 and 5.8, 4-H_b), 2.58 (3H, s, 2-CH_3), 3.13 (1H, br s, OH), 3.45–3.55 (1H, m, 3-H), 3.65 (1H, dd, *J* 12.3 and 4.7, 1′-H_a), 3.82 (1H, dd, *J* 12.3 and 3.1, 1′-H_b), 4.39 (1H, m, 5-H) and 7.25–7.41 (5H, m, Ph); δ_C(67.5 MHz) 41.0 (4-CH_2), 43.1 (2-CH_3), 63.5 (1′-CH_2), 73.4 (3-CH), 77.3 (5-CH), 127.6, 127.8, 128.6 (all PhCH) and 138.8 (PhC); *m*/*z* 193 (M^+, 92%), 134 (100), 116 (96), 91 (71) and 77 (46) [Found: M^+, 193.1086].

(ii) Magnesium bromide-catalysed method. A solution of **8** (0.95 g, 7.04 mmol) and magnesium bromide–diethyl ether (1.80 g, 7.04 mmol) were stirred and heated together in toluene (30 ml) at 80 °C before the dropwise addition of allyl alcohol **7** (1.0 g, 17.6 mmol). The resulting mixture was refluxed for 1 h, cooled to 80 °C, treated with water (30 ml) and cooled to ambient temperature. Dichloromethane (50 ml) was added and the organic layer separated, dried and evaporated. ^{1}H NMR analysis of the residue showed an isomer ratio of 5:1; subsequent CC, as above, separated the *trans-(3RS,5RS)-isoxazolidinemethanol* **9** (0.78 g, 69%) and the *cis-(3RS,5SR)-isoxazolidinemethanol* **10** (0.16 g, 14%) which showed identical mp, spectroscopic and analytical data to the foregoing samples.

trans-(3*SR*,6*SR*)- and *cis*-(3*RS*,6*SR*)-2,3-Dimethyl-6-phenyl-1,5,2-dioxazinane 11 and 12 and (3*RS*,5*RS*)- and (3*RS*,5*SR*)-2-methyl-3-phenylisoxazolidine-5-methanol 9 and 10

Compound **8** (1.0 g, 8.0 mmol), powdered 4 Å molecular sieves (2 g), magnesium chloride (0.68 g, 7.0 mmol) and allyl alcohol **7** (0.50 g, 8.0 mmol) were stirred and refluxed together in toluene (20 ml) for 24 h. The cooled mixture was filtered and evaporated and the residual yellow oil separated by CC [ether–petrol, 1:2] into (i) a 1:1 mixture of the forgoing isoxazolidinemethanols **9** and **10** (1.34 g, 95%), (ii) the *trans-dioxazinane* **11** (31 mg, 2.3%), R_f 0.39 as an oil, ν_{max}/cm^{-1} 915; δ_H(400 MHz) 0.98 (3H, d, *J* 6.4, 3-CH_3), 2.73 (3H, s, 2-CH_3), 2.86 (1H, dqd, *J* 10.3, 6.4 and 3.2, 3-H_{ax}), 3.66 (1H, dd, *J* 11.2 and 10.3, 4-H_{ax}), 3.97 (1H, dd, *J* 11.2 and 3.2, 4-H_{eq}), 5.86 (1H, s, 6-H), 7.34–7.39 (3H, m) and 7.48–7.50 (2H, m); δ_C(100 MHz) 13.9 (3-CH_3), 43.5 (2-CH_3), 60.2 (3-CH), 71.3 (4-CH_2), 102.0 (6-CH), 126.5, 128.3, 129.1 (all PhCH) and 136.8 (PhC); *m*/*z* 193 (M^+, 2%), 105 (69), 91 (19), 77 (68) and 70 (16) [Found: M^+, 193.1072. $C_{11}H_{15}NO_2$ requires *M*, 193.1103] and (iii) the *cis-dioxazinane* **12** (8.5 mg, 0.6%), R_f 0.21 as an oil, ν_{max}/cm^{-1} 911; δ_H(400 MHz) 1.32 (3H, d, *J* 6.4, 3-CH_3), 2.65 (3H, s, 2-CH_3), 2.90 (1H, m, 3-H), 3.93 (1H, br d, *J* 10.8, 4-H_a), 4.20 (1H, br d, *J* 10.8, 4-H_b), 5.86 (1H, s, 6-H), 7.34–7.38 (3H, m) and 7.48–7.51 (2H, m); δ_C(100 MHz) 8.7 (br s, 3-CH_3), 42.6 (2-CH_3), 56.4 (br s, 3-CH), 71.4 (br s, 4-CH_2), 102.6 (br s, 6-CH), 126.6, 128.4, 129.2 (all PhCH) and 137.2 (PhC); *m*/*z* 193 (M^+, 51%), 91 (23) and 87 (100) [Found: M^+, 193.1094].

Lewis acid-catalysed procedure: general procedure A

To a stirred solution of **8** (0.135 g, 1.0 mmol) in toluene (5 ml) was added magnesium bromide–diethyl ether (0.26 g, 1.0 mmol). The resulting suspension stirred and heated at 80 °C until the initial suspension adhered to the side of the flask. At this point, the allylic or homoallylic alcohol (5.0 mmol) was added dropwise to the mixture with the result that the solid residue dissolved. The mixture was kept at 80 °C and progress monitored by TLC until adjudged complete, usually within 2–5 h. The mixture was then cooled and evaporated and the residue subjected directly to CC.

Thermal cycloadditions: general procedure B[26]

A stirred solution of **8** (0.135 g, 1.0 mmol) and an allylic or homoallylic alcohol (1.5 mmol) in toluene (5 ml) was refluxed until TLC analysis showed complete consumption of **8**, typically 24–48 h. The cooled solution was evaporated and the residue separated by CC. The ratio of isomers was determined by careful integration of *N*-methyl group resonances in the ^{1}H NMR spectrum of the crude product mixtures.

(1′*RS*,3*RS*,5*RS*)- and (1′*RS*,3*SR*,5*RS*)-2-Methyl-5-(1′-hydroxyethyl)-3-phenylisoxazolidine 18 and 19

(i) By general procedure A, reaction between **8** and but-3-en-2-ol **17** for 3 h gave two products which were separated by CC [hexane–EtOAc, 3:2] to give (i) the (1′*RS*,3*RS*,5*RS*)-*isoxazolidine* **18** (0.15 g, 72%), R_f 0.42, as an oil, ν_{max}/cm^{-1} 3416, 2973, 2875, 1603, 1495 and 1455; δ_H(400 MHz) 1.00 (3H, d, *J* 6.5, 1′-CH_3), 2.08–2.50 (3H, m, 4-CH_2 and OH), 2.50 (3H, s, 2-CH_3), 3.38–3.50 (1H, br m, 3-H), 3.68 (1H, qd, *J* 6.5 and 6.2, 1′-H), 4.03 (1H, ddd, *J* 8.2, 6.2 and 6.0, 5-H) and 7.06–7.28 (5H, m); δ_C(100) 19.5 (1′-CH_3), 41.9 (4-CH_2), 43.3 (2-CH_3), 69.7 (1′-CH), 73.2 (3-CH), 81.1 (5-CH), 127.7, 127.9, 128.6 (all PhCH) and 139.0 (PhC); *m*/*z* 207 (M^+, 26%), 189 (6), 161 (10), 136 (49), 118 (89), 104 (42), 91 (14), 77 (45) and 43 (100) [Found: M^+, 207.1239. $C_{12}H_{17}NO_2$ requires *M*, 207.1260] and (ii) the (1′*RS*,3*SR*,5*RS*)-*isoxazolidine* **19** (0.01 g, 4%), R_f 0.50, as an oil, ν_{max}/cm^{-1} 3420, 2973, 2867, 1598 and 1490; δ_H(400 MHz) 1.08 (3H, d, *J* 6.5, 1′-CH_3), 2.17 (1H, ddd, *J* 12.5, 9.8 and 5.8, 4-H_a), 2.48 (3H, s, 2-CH_3), 2.74 (1H, ddd, *J* 12.5, 8.2 and 8.2, 4-H_b), 3.41 (1H, dd, *J* 9.8 and 8.2, 3-H), 3.68 (1H, qd, *J* 6.5 and 6.3, 1′-H), 3.96 (1H, ddd, *J* 8.2, 6.3 and 5.8, 5-H) and 7.27–7.38 (5H, m); δ_C(100 MHz) 18.9 (1′-CH_3), 42.1 (4-CH_2), 42.8 (2-CH_3), 70.7 (1′-CH), 73.9 (3-CH), 80.9 (5-CH), 127.9, 128.0, 128.7 (all PhCH) and 138.8 (PhC); *m*/*z* 207 (M^+, 28%), 161 (20), 136 (52), 118 (86), 104 (42), 91 (33), 77 (54) and 43 (100) [Found: M^+, 207.1243].

(ii) By general procedure B, thermal reaction between **8** and but-3-en-2-ol **17** gave a mixture of all four possible products which was separated into two mixtures by CC as above. The less polar mixture (0.09 g, 44%) contained the minor product **19** from the catalysed reaction, together with a second isomer of unknown stereochemistry, in a ratio of 3:1. The second minor isomer was recognized by δ_H(400 MHz) 0.87 (3H, d, *J* 6.4, 1′-CH_3), 2.46 (3H, s, 2-CH_3), 2.34–2.55 (2H, m, 4-CH_2), 3.52 (1H, dd, *J* 9.6 and 8.1, 3-H), 3.75–3.82 (1H, m), 4.38–4.44 (1H, m) and 7.22–7.40 (5H, m); δ_C(100 MHz) 17.8 (1′-CH_3), 37.9 (4-CH_2), 42.7 (2-CH_3), 70.5 (1′-CH), 73.8 (3-CH), 79.9 (5-CH), 127.7, 128.1, 128.7 (all PhCH) and 138.2 (PhC); the mixture showed *m*/*z* 207 (M^+, 70%), 161 (22), 136 (50), 118 (84), 104

(36), 91 (30), 77 (50) and 43 (100). The more polar mixture (0.095 g, 46%) contained the major product **18** of the catalysed reaction, together with a fourth unidentified minor isomer which showed δ_H(400 MHz) 0.89 (3H, d, *J* 6.5, 1′-CH_3), 2.15–2.32 (1H, m, 4-H_a), 2.42 (3H, s, 2-CH_3), 2.51–2.72 (1H, m, 4-H_b), 3.30–3.39 (1H, m, 3-H), 4.01–4.23 (2H, m, 1′- and 5-H) and 7.03–7.30 (5H, m); the whole sample showed *m*/*z* 207 (M^+, 35%), 161 (24), 136 (57), 118 (76), 104 (44), 91 (32), 77 (50) and 43 (100).

(1*RS*,3*RS*,4*RS*)-*N*-Methyl-3,4-dihydroxy-1-phenylpentanamine 20

To a stirred solution of isoxazolidine **18** (0.50 g, 2.4 mmol) in methanol (25 ml) was added portionwise nickel(II) chloride hexahydrate (1.15 g, 4.8 mmol). The resulting mixture was cooled to −40 °C then sodium borohydride (0.46 g, 12 mmol) was added portionwise, resulting in effervescence and a colour change from green to black.[29] After 0.5 h at this temperature, the methanol was evaporated. To the resulting black residue was added aqueous ammonia (0.88 M, 100 ml) and dichloromethane (100 ml). The resulting pale brown mixture was separated and the aqueous layer extracted with dichloromethane (2 × 50 ml). The combined organic solutions were dried and evaporated to leave the *amino diol* **20** (0.37 g, 73%), R_f 0.10 [CH_2Cl_2–MeOH, 4:1], as an oil, ν_{max}/cm^{-1} 3318 (br, OH and NH), 2925, 2854, 1454 and 1375; δ_H(250 MHz) 1.04 (3H, d, *J* 6.3, 5-CH_3), 1.71 (1H, ddd, *J* 14.6, 7.6 and 3.7, 2-H_a), 1.86 (1H, ddd, *J* 14.6, 7.5 and 3.5, 2-H_b), 2.25 (3H, s, N-CH_3), 3.36–3.45 (3H, br s, 3-H and 2 × OH), 3.56 (1H, dq, *J* 6.2 and 6.2, 4-H), 3.82 (1H, dd, *J* 7.6 and 3.5, 1-H) and 7.17–7.32 (5H, m); δ_C(100 MHz) 19.0 (5-CH_3), 33.9 (N-CH_3), 37.5 (2-CH_2), 62.7 (4-CH), 70.5 (3-CH), 73.7 (1-CH), 126.6, 127.5, 128.7 (all PhCH) and 141.9 (PhC); *m*/*z* 164 (M^+ − 45, 3%), 121 (10), 120 (100), 119 (16), 118 (5), 91 (5), 77 (6) and 51 (5).

(1′*RS*,4*RS*,6*RS*)-3-Methyl-6-(1′-hydroxyethyl)-4-phenyl-1,3-oxazinan-2-one 21

A solution of the amino diol **20** (0.30 g, 1.4 mmol) and 1,1′-carbonyldiimidazole (0.23 g, 1.4 mmol) in tetrahydrofuran (5 ml) and benzene (5 ml) was stirred at ambient temperature for 72 h then quenched by the dropwise addition of 2 M hydrochloric acid (10 ml). The aqueous layer was separated and extracted with dichloromethane (2 × 10 ml) and the combined organic solutions dried and evaporated to leave a dark orange oil which was purified by CC [CH_2Cl_2–MeOH, 9:1] to give the *oxazinanone* **21** (0.22 g, 68%), R_f 0.62, as a viscous oil [Found: C, 66.3; H, 7.5; N, 6.0. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%], ν_{max}/cm^{-1} 3591, 2932, and 1691; δ_H(250 MHz) 1.16 (3H, d, *J* 6.5, 1′-CH_3), 1.89 (1H, ddd, *J* 13.7, 2.4 and 2.0, 5-H_{eq}), 2.21 (1H, br s, OH), 2.39 (1H, ddd, *J* 13.7, 12.1 and 6.2, 5-H_{ax}), 2.97 (3H, s, N-CH_3), 3.67 (1H, qd, *J* 6.5 and 5.1, 1′-H), 4.00 (1H, ddd, *J* 12.1, 5.1 and 2.4, 6-H), 4.57 (1H, dd, *J* 6.2 and 2.0, 4-H) and 7.20–7.46 (5H, m); δ_C(67.8 MHz) 18.2 (1′-CH_3), 32.8 (5-CH_2), 36.6 (N-CH_3), 59.8 (4-CH), 69.1 (1′-CH), 76.7 (6-CH), 126.0, 127.1, 127.9 (all PhCH), 140.0 (PhC) and 151.2 (CO); *m*/*z* 235 (M^+, 2%), 220 (5), 191 (11), 173 (39), 133 (39), 118 (52), 105 (100), 96 (51), 91 (35) and 77 (35) [Found: M^+, 235.1206. $C_{13}H_{17}NO_3$ requires *M*, 235.1208].

(1*RS*,3*RS*,4*RS*)-*N*-Methoxycarbonyl-*N*-methyl-3,4-dihydroxy-1-phenylpentanamine 23

To a stirred solution of the amino diol **20** (0.60 g, 0.30 mmol) in dichloromethane (1 ml) was added triethylamine (0.04 g, 0.36 mmol) followed by methyl chloroformate (0.03 g, 0.36 mmol) and the resulting mixture stirred at ambient temperature for 18 h then quenched with water (1 ml) and extracted with dichloromethane (3 × 5 ml). The combined extracts were dried and evaporated and the residue separated by CC [CH_2Cl_2–MeOH, 9:1] to give the *carbamate* **23** (0.06 g, 74%), R_f 0.56, as an oil, ν_{max}/cm^{-1} 3407, 2957, 2883, 1697, 1503 and 1421; δ_H(250 MHz; 60 °C) 1.24 (3H, d, *J* 6.6, 5-CH_3), 1.90 (1H, ddd, *J* 12.5, 11.9 and 3.2, 2-H_a), 2.03 (1H, ddd, *J* 12.5, 12.1 and 2.6, 2-H_b), 2.48 (3H, s, N-CH_3), 2.63 (1H, br s, OH), 3.08 (1H, br s, OH), 3.23–3.30 (1H, m, 4-H), 3.68–3.73 (1H, m, 3-H), 3.78 (3H, s, OCH_3), 6.64 (1H, dd, *J* 12.5 and 3.2, 1-H) and 7.24–7.37 (5H, m); *m*/*z* 231 (M^+ − 36, 25%), 192 (65), 178 (42), 121 (53), 104 (20), 91 (21) and 77 (11).

(1*RS*,3*RS*,4*RS*)-4-[2′-(*N*-Methoxycarbonyl-*N*-methylamino)-2′-phenylethyl]-5-methyl-1,3-dioxolan-2-one 24

A stirred solution of the carbamate **23** (0.14 g, 0.50 mmol) and 1,1′-carbonyldiimidazole (0.32 g, 2.0 mmol) in benzene (5 ml) was refluxed for 16 h then evaporated. The residue was treated with 2 M hydrochloric acid and the resulting mixture extracted with dichloromethane (3 × 10 ml). The combined extracts were dried and evaporated and the residue purified by CC [CH_2Cl_2–MeOH, 98:2] to give the *dioxolanone* **24** (0.109 g, 74%), R_f 0.64, as an oil [Found: C, 61.3; H, 6.7; N, 5.0. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.5; N, 4.8%], ν_{max}/cm^{-1} 2957, 1777, 1716, 1543 and 1324; δ_H(400 MHz) 1.39 (3H, d, *J* 6.2, 5-CH_3), 2.31 (1H, ddd, *J* 14.2, 7.4 and 5.1, 1′-H_a), 2.43 (1H, br m, 1′-H_b), 2.60 (3H, s, N-CH_3), 3.72 (3H, s, OCH_3), 4.19 (1H, ddd, *J* 7.2, 6.4 and 5.1, 4-H), 4.45 (1H, dq, *J* 6.4 and 6.2, 5-H), 5.32–5.41 (1H, m, 2′-H) and 7.19–7.23 (5H, m); δ_C(67.8 MHz) 19.1 (5-CH_3), 30.9 (N-CH_3), 34.2 (1′-CH_2), 52.2 (OCH_3), 78.2 (4-CH), 80.6 (2′- and 5-CH), 127.3, 128.1, 128.8 (all PhCH), 138.2 (PhC), 153.5 and 156.7 (both CO); *m*/*z* 232 (M^+ − 61, 4%), 192 (7), 178 (100) and 121 (85) [Found: M^+ − 61, 232.1342. $C_{14}H_{18}NO_2$ requires *M*, 232.1338].

(1′*RS*,3*RS*,5*RS*)-2-Methyl-5-(1′-hydroxybutyl)-3-phenylisoxazolidine 26

By general procedure A, reaction between **8** and hex-1-en-3-ol **25** for 5 h followed by CC [hexane–EtOAc, 1:1] separated the (1′*RS*,3*RS*,5*RS*)-*isoxazolidine* **26** (0.15 g, 58%), R_f 0.49, as an oil, ν_{max}/cm^{-1} 3424, 1965, 1870, 1599 and 1490; δ_H(400 MHz) 0.95 (3H, t, *J* 6.9, 4′-CH_3), 1.23–1.57 (4H, m, 2′- and 3′-CH_2), 2.00 (1H, br s, OH), 2.58 (3H, s, 2-CH_3), 2.41–2.60 (2H, m, 4-CH_2), 3.40–3.63 (2H, m, 1′- and 3-H), 4.22 (1H, ddd, *J* 8.3, 6.3 and 6.1, 5-H) and 7.30–7.39 (5H, m); δ_C(100 MHz) 14.0 (4′-CH_3), 18.9 (3′-CH_2), 36.1 (2′-CH_2), 41.9 (4-CH_2), 43.2 (2-CH_3), 74.1, 74.4 (1′- and 3-CH), 79.9 (5-CH), 127.8, 128.0, 128.7 (all PhCH) and 138.8 (PhC); *m*/*z* 235 (M^+, 29%), 189 (5), 158 (7), 136 (100), 119 (37), 91 (26) and 71 (65) [Found: M^+, 235.1555. $C_{14}H_{21}NO_2$ requires *M*, 235.1572].

By general procedure B, thermolysis of **8** and hex-1-en-3-ol **25** for 48 h gave, after CC, a 1:1 mixture (0.20 g, 85%) of the (1′*RS*,3*RS*,5*RS*)-isomer **26** and the (1′*RS*,3*SR*,5*RS*)-isomer **27**, recognized by δ_H(400 MHz) 0.94 (3H, t, *J* 7.0, 4′-CH_3), 1.40–1.57 (4H, m, 2′- and 3′-CH_2), 2.28 (1H, ddd, *J* 12.5, 9.8 and 5.3, 4-H_a), 2.55 (3H, s, 2-CH_3), 2.75 (1H, ddd, *J* 12.5, 8.4 and 8.3, 4-H_b), 3.40–3.67 (2H, m, 1′- and 3-H), 4.05 (1H, ddd, *J* 8.4, 5.3 and 5.3, 5-H) and 7.14–7.41 (5H, m); δ_C(100) 14.1 (4′-CH_3), 19.1 (3′-CH_2), 36.0 (2′-CH_2), 42.3 (4-CH_2), 42.9 (2-CH_3), 74.2, 74.5 (1′- and 3-CH), 79.5 (5-CH), 127.9, 128.1, 128.8 (all PhCH) and 138.4 (PhC). The whole sample showed *m*/*z* 235 (M^+, 41%), 159 (13), 136 (100), 119 (38), 91 (23) and 71 (54).

(1′*RS*,3*RS*,5*RS*)-2-Methyl-5-(1′-hydroxy-2′-methylpropyl)-3-phenylisoxazolidine 29

By general procedure A, reaction between **8** and 4-methylpent-1-en-3-ol **28** for 5 h followed by CC [hexane–EtOAc, 1:1] separated the (1′*RS*,3*RS*,5*RS*)-*isoxazolidine* **29** (0.13 g, 48%), R_f 0.48, as an oil, ν_{max}/cm^{-1} 3430, 1967, 1860, 1611 and 1456; δ_H(400 MHz) 1.01 (3H, d, *J* 6.8, 2′-CH_3), 1.02 (3H, d, *J* 6.8,

2′-CH_3), 1.78–1.84 (1H, m, 2′-H), 2.02 (1H, br s, OH), 2.35–2.59 (2H, m, 4-CH_2), 2.60 (3H, s, 2-CH_3), 3.25 (1H, dd, *J* 6.6 and 3.7, 1′-H), 3.50–3.56 (1H, m, 3-H), 4.44 (1H, ddd, *J* 8.6, 5.4 and 3.8, 5-H) and 7.26–7.41 (5H, m); δ_C(100 MHz) 18.3 (2′-CH_3), 19.6 (2′-CH_3), 31.9 (2′-CH), 42.1 (4-CH_2), 43.3 (2-CH_3), 73.2 (3-H), 77.4 (1′-CH), 92.7 (5-CH), 127.6, 127.7, 128.8 (all PhCH) and 139.2 (PhC); *m*/*z* 235 (M^+, 26%), 136 (100), 118 (29), 95 (27), 77 (27) and 71 (42) [Found: M^+, 235.1598. $C_{14}H_{21}NO_2$ requires *M*, 235.1572].

By general procedure B, thermolysis of **8** and 4-methylpent-1-en-3-ol **28** for 48 h gave, after CC, a 3:2 mixture (0.19 g, 82%) of the (1′*RS*,3*RS*,5*RS*)-isomer **29** and the (1′*RS*,3*SR*,5*RS*)-isomer **30**, recognized by δ_H(400 MHz) 1.04 (3H, d, *J* 6.8, 2′-CH_3), 1.06 (3H, d, *J* 6.8, 2′-CH_3), 1.69–1.84 (1H, m, 2′-H), 2.42 (1H, ddd, *J* 12.4, 9.8 and 5.3, 4-H_a), 2.57 (3H, s, 2-CH_3), 2.80 (1H, ddd, *J* 12.4, 8.5 and 8.4, 4-H_b), 3.30 (1H, dd, *J* 6.5 and 3.6, 1′-H), 3.49–3.56 (1H, m, 3-H), 4.32 (1H, ddd, *J* 8.5, 5.3 and 3.6, 5-H) and 7.14–7.36 (5H, m); δ_C(100 MHz) 18.6 (2′-CH_3), 19.0 (2′-CH_3), 32.2 (2′-CH), 42.7 (4-CH_2), 42.9 (2-CH_3), 73.8 (3-H), 77.9 (1′-CH), 98.2 (5-CH), 127.9, 128.4, 128.6 (all PhCH) and 138.7 (PhC). The whole sample showed *m*/*z* 235 (M^+, 25%), 136 (100), 118 (32), 95 (27), 77 (8) and 71 (45).

(3*RS*,5*RS*)- and (3*SR*,5*RS*)-2-Methyl-5-(2′-hydroxyethyl)-3-phenylisoxazolidine 35a and 36a

By general procedure A, reaction between **8** and but-3-en-1-ol **34a** for 5 h followed by CC [hexane–EtOAc, 3:2] separated (i) the (3*RS*,5*RS*)-*isoxazolidine* **35a** (0.11 g, 50%), R_f 0.32, as an oil, ν_{max}/cm^{-1} 3436, 1972, 1840, 1613 and 1459; δ_H(400 MHz) 1.80–1.87 (2H, m, 1′-CH_2), 2.32–2.37 (2H, m, 4-CH_2), 2.51 (3H, s, 2-CH_3), 3.40–3.51 (1H, m, 3-H), 3.72 (2H, app td, *J* 6.1 and 1.6, 2′-CH_2), 4.31–4.38 (1H, m, 5-H) and 7.18–7.30 (5H, m); δ_C(100 MHz) 37.7 (1′-CH_2), 43.3 (2-CH_3), 45.1 (4-CH_2), 60.3 (2′-CH_2), 73.0 (3-H), 75.8 (5-CH), 127.7, 127.8, 128.6 (all PhCH) and 139.3 (PhC); *m*/*z* 207 (M^+, 79%), 134 (100), 130 (21), 91 (39) and 77 (27) [Found: M^+, 207.1259. $C_{12}H_{17}NO_2$ requires *M*, 207.1260] and (ii) the (3*SR*,5*RS*)-*isoxazolidine* **36a** (0.02 g, 10%), R_f 0.24, as an oil, ν_{max}/cm^{-1} 3440, 1970, 1840, 1613 and 1471; δ_H(400 MHz) 1.87–1.93 (2H, m, 1′-CH_2), 2.13 (1H, ddd, *J* 12.5, 9.6 and 6.6, 4-H_a), 2.57 (3H, s, 2-CH_3), 2.81 (1H, ddd, *J* 12.5, 7.8 and 7.8, 4-H_b), 3.47–3.54 (1H, m, 3-H), 3.85 (2H, app td, *J* 6.1 and 1.6, 2′-CH_2), 4.45–4.48 (1H, m, 5-H) and 7.25–7.37 (5H, m); δ_C(100 MHz) 37.8 (1′-CH_2), 43.1 (2-CH_3), 44.6 (4-CH_2), 59.3 (2′-CH_2), 73.3 (3-H), 75.0 (5-CH), 127.3, 127.7, 128.7 (all PhCH) and 138.9 (PhC); *m*/*z* 207 (M^+, 72%), 143 (13), 134 (100), 131 (69), 119 (83), 117 (31), 104 (23), 91 (45) and 77 (30) [Found: M^+, 207.1268].

By general procedure B, thermolysis of **8** and but-3-en-1-ol **34a** for 48 h gave, after CC, the (3*RS*,5*RS*)-isomer **35a** (0.10 g, 44%) and the (3*SR*,5*RS*)-isomer **36a** (0.09 g, 42%), both of which exhibited spectroscopic and analytical data identical to the foregoing samples.

(2′*RS*,3*RS*,5*RS*)- and (2′*RS*,3*SR*,5*RS*)-2-Methyl-5-(2′-hydroxypropyl)-3-phenylisoxazolidine 35b and 36b

By general procedure A, reaction between **8** and pent-4-en-2-ol **34b** for 5 h followed by CC [hexane–EtOAc, 3:2] separated a mixture of the (2′*RS*,3*RS*,5*RS*)- and (2′*RS*,3*SR*,5*RS*)-isoxazolidines **35b** and **36b** (0.13 g, 60%) in a 3:1 ratio, R_f 0.31, as an oil, ν_{max}/cm^{-1} 3423, 1970, 1840, 1614 and 1519; *m*/*z* 221 (M^+, 36%), 134 (75), 131 (41), 120 (100), 118 (27), 104 (25), 91 (41) and 77 (28) [Found: M^+, 221.1425. $C_{13}H_{19}NO_2$ requires *M*, 221.1416]. Diagnostic resonances for the major isomer **35b** were δ_H(400 MHz) 1.16 (3H, d, *J* 6.2, 2′-CH_3), 1.70 (2H, app dd, *J* 6.1 and 6.1, 1′-CH_2), 2.19–2.40 (2H, m, 4-CH_2), 2.62 (3H, s, 2-CH_3), 4.35 (1H, app tt, *J* 8.0 and 7.3, 5-H); δ_C(100 MHz) 23.3 (2′-CH_3), 43.4 (2-CH_3), 44.3 (1′-CH_2), 45.8 (4-CH_2), 67.1 (2′-CH), 73.3 (3-CH), 76.8 (5-CH), 127.7, 128.1, 128.6 (all PhCH) and 139.6 (PhC) while the minor isomer **36b** showed δ_H(400) 1.18 (3H, d, *J* 6.2, 2′-CH_3), 1.70 (2H, app. dd, *J* 6.2 and 6.1, 1′-CH_2), 1.96–2.14 (1H, m, 4-H_a), 2.60 (3H, s, 2-CH_3), 2.68–2.80 (1H, m, 4-H_b), 4.39–4.44 (1H, m, 5-H); δ_C(100 MHz) 23.8 (2′-CH_3), 42.9 (2-CH_3), 44.4 (1′-CH_2), 45.5 (4-CH_2), 67.0 (2′-CH), 73.1 (3-CH), 76.4 (5-CH), 127.6, 127.8, 128.7 (all PhCH) and 141.1 (PhC).

By general procedure B, thermolysis of **8** and pent-4-en-2-ol **34b** for 48 h gave, after CC, a mixture containing the (2′*RS*,3*RS*,5*RS*)- and (2′*RS*,3*SR*,5*RS*)-isomers **35b** and **36b** together with a third isomer (0.19 g, 84%) in a ratio of 4:3:1, *m*/*z* 221 (M^+, 41%), 134 (65), 131 (32), 120 (100), 91 (52) and 77 (32). The third isomer showed δ_H(400 MHz) 1.14 (3H, d, *J* 6.2, 2′-CH_3), 1.65–1.78 (2H, m), 2.19–2.40 (2H, m), 2.59 (3H, s, 2-CH_3), 3.46–3.52 (1H, m), 4.10–4.12 (1H, m) and 4.42–4.44 (1H, m).

Acknowledgements

We are grateful to Dr Kathryn E. Bell for conducting some preliminary experiments and to Zeneca Pharmaceuticals and the EPSRC for financial support.

References

1 J. J. Tufariello, *[1,3]-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley Interscience, New York, 1984, ch. 9; P. N. Confalone and E. M. Huie, *Org. React.*, 1988, **36**, 1; P. A. Wade, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 4, p. 1113; K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, Weinheim, 1988, ch. 5; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1990; E. Breuer, H. G. Aurich and A. Nielsen, *Nitrones, Nitronates and Nitroxides*, ed. S. Patai and Z. Rappoport, John Wiley and Sons, Chichester, 1989.

2 H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007; T. Oh and M. Reilley, *Org. Prep. Proced. Int.*, 1994, **26**, 129; U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, 1993, **93**, 741; J. Vaugeois, M. Simard and J. D. Wuest, *Coord. Chem. Rev.*, 1995, **145**, 55; H. Waldmann, *Synthesis*, 1994, 535.

3 M. Frederickson, *Tetrahedron*, 1997, **53**, 403; K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.

4 A. I. Sanchez-Blanco, K. V. Gothelf and K. A. Jørgensen, *Tetrahedron Lett.*, 1997, **38**, 7923; K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1998, **63**, 5483; K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1996, **61**, 346.

5 K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.*, 1994, **59**, 5687; K. B. Jensen, K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1997, **62**, 2471; K. V. Gothelf, I. Thomsen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1996, **118**, 59; D. Seebach, R. E. Marti and T. Hintermann, *Helv. Chim. Acta*, 1996, **79**, 1710; K. B. Jensen, K. V. Gothelf and K. A. Jørgensen, *Helv. Chim. Acta*, 1997, **80**, 2039; K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1995, **117**, 4435.

6 S. Kobayashi, R. Akiyama, M. Kawamura and H. Ishitani, *Chem. Lett.*, 1997, 1039; S. Kobayashi and M. Kawamura, *J. Am. Chem. Soc.*, 1998, **120**, 5840.

7 S. Minakata, T. Ezoe, K. Nakamura, I. Ryu and M. Komatsu, *Tetrahedron Lett.*, 1998, **39**, 5205.

8 K. Hori, H. Kodama, T. Ohta and I. Furukawa, *J. Org. Chem.*, 1999, **64**, 5017.

9 K. Hori, H. Kodama, T. Ohta and I. Furukawa, *Tetrahedron Lett.*, 1996, **37**, 5947.

10 S. Kanematsu, T. Uemura and E. Wada, *Tetrahedron Lett.*, 1992, **33**, 7889.

11 S.-I. Murahashi, Y. Imada, M. Kohno and T. Kawakami, *Synlett*, 1993, 395.

12 S. R. Gilbertson, D. P. Dawson, O. D. Lopez and K. L. Marshall, *J. Am. Chem. Soc.*, 1995, **117**, 4431; S. R. Gilbertson and O. D. Lopez, *J. Am. Chem. Soc.*, 1997, **119**, 3399.

13 J.-P. G. Seerden, M. M. M. Boeren and H. W. Scheeren, *Tetrahedron*, 1997, **53**, 11843; J.-P. G. Seerden, A. W. A. Scholte op Reimer and H. W. Scheeren, *Tetrahedron Lett.*, 1994, **35**, 4419; J.-P. G. Seerden, M. M. M. Kuypers and H. W. Scheeren, *Tetrahedron: Asymmetry*, 1995, **6**, 1441.

14 K. B. Simonsen, P. Bayon, R. G. Hazell, K. V. Gothelf and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1999, **121**, 3845; K. B. Simonsen, K. A. Jørgensen, Q. S. Hu and L. Pu, *Chem. Commun.*, 1999, 811.

15 K. Hori, J. Ito, T. Ohta and I. Furukawa, *Tetrahedron*, 1998, **54**, 12737.
16 K. B. Jensen, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1999, **64**, 2353.
17 O. Tamura, N. Mita, K. Gotanda, K. Yamada and M. Sakamoto, *Heterocycles*, 1998, **46**, 95. See also O. Tamura, K. Gotanda, R. Terashima, M. Kikuchi, T. Miyawaki and M. Sakamoto, *Chem. Commun.*, 1996, 1861; N. Katagiri, M. Okada, Y. Morishita and C. Kaneko, *Chem. Commun.*, 1996, 2137.
18 Y. Tokunaga, M. Ihara and K. Fukumoto, *Tetrahedron Lett.*, 1996, **37**, 6157.
19 P. J. Smith, D. J. Soose and C. J. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 7412.
20 S. Kanemasa, T. Tsuruoka and E. Wada, *Tetrahedron Lett.*, 1993, **34**, 87.
21 S. Kanemasa and T. Tsuruoka, *Chem. Lett.*, 1995, 49; S. Kanemasa, T. Tsuruoka and H. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5019.
22 Y. Ukaji, K. Taniguchi, K. Sada and K. Inomata, *Chem. Lett.*, 1997, 547. See also Y. Ukaji, K. Sada and K. Inomata, *Chem. Lett.*, 1993, 1847; M. Shimizu, Y. Ukaji and K. Inomata, *Chem. Lett.*, 1996, 455; S. Kanemasa, M. Nishiuchi, A. Kamimura and K. Hori, *J. Am. Chem. Soc.*, 1994, **116**, 2324.
23 O. Tamura, T. Yamaguchi, K. Noe and M. Sakamoto, *Tetrahedron Lett.*, 1993, **34**, 4009; O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe and M. Sakamoto, *Tetrahedron*, 1995, **51**, 107; O. Tamura, T. Okabe, T. Yamaguchi, J. Kotani, K. Gotanda and M. Sakamoto, *Tetrahedron*, 1995, **51**, 119; O. Tamura, T. Yamaguchi, T. Okabe and M. Sakamoto, *Synlett*, 1994, 620.
24 O. Tamura, T. Kuroki, Y. Sakai, J.-i. Takizawa, J. Yoshino, Y. Morita, N. Mita, K. Gotanda and M. Sakamoto, *Tetrahedron Lett.*, 1999, **40**, 895.
25 M. B. Gravestock, D. W. Knight and S. R. Thornton, *J. Chem. Soc., Chem. Commun.*, 1993, 169; K. E. Bell, M. P. Coogan, D. W. Knight and M. B. Gravestock, *Tetrahedron Lett.*, 1997, **38**, 8545; M. P. Coogan, M. B. Gravestock, D. W. Knight and S. R. Thornton, *Tetrahedron Lett.*, 1997, **38**, 8549; M. B. Gravestock, D. W. Knight, J. S. Lovell and S. R. Thornton, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3143.
26 R. Huisgen, R. Grashey, H. Hauck and H. Seidl, *Chem. Ber.*, 1968, **101**, 2043. For early reviews and a general discussion of dipolar cycloadditions, see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565 and 633; *J. Org. Chem.*, 1976, **41**, 403.
27 B. H. Todder, G. B. Mullen and V. St. Georgiev, *Helv. Chim. Acta*, 1990, **73**, 169. For general reviews, see J. Hamer and A. Macaluso, *J. Org. Chem.*, 1964, **29**, 473; G. R. Delpierre and M. Macaluso, *Quart. Rev.*, 1965, 329.
28 S. Saba, P. W. Domkowski and F. Firooznia, *Synthesis*, 1990, 921.
29 S. K. Armstrong, E. W. Collington, J. G. Knight, A. Taylor and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1433.
30 W. R. Roush, R. J. Brown and M. DiMare, *J. Org. Chem.*, 1983, **48**, 5083.
31 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth Heinemann, Oxford, 1996.

Paper 9/06573C