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The synthesis of oximes and nitroalkanes bearing a chiral auxiliary unit: convenient substrates for the preparation of enantiomerically pure nitrile oxides

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Abstract—We report the synthesis of four new oximes and three nitroalkanes bearing a chiral unit. All these compounds were converted into nitrile oxides and subjected to 1,3-dipolar cycloaddition with 3-*E*-hexene, giving the corresponding 2-isoxazolines in fair yields but only with moderate stereoselectivities.

1. Introduction

For many years, we have been interested in the applications of various chiral glyoxylates and glyoximides bearing different types of auxiliaries to diverse diastereoselective processes, such as pericyclic reactions,[1] organometallic additions,[2] nitroaldol condensations,[3] etc. Recently, we extended the scope of our synthetic interest to the 1,3-dipolar cycloaddition of nitrile oxides containing a chiral auxiliary in their structure.

Nitrile oxides are usually generated in situ to avoid the dimerization process.[4] Two convenient substrates for their synthesis are primary nitroalkanes, easily transformed to nitrile oxides by the Mukayiama and Hoshino procedure[5] or by a broad spectrum of dehydration agents,[6] and aldoximes, treated with halogenating reagent/weak base systems[7] or with oxidants.[8] To our surprise, a literature search revealed only one example for both classes of these compounds containing the menthyl residue as an auxiliary.[9]

2. Results and discussion

We started our investigations from the synthesis of four novel aldoximes, **2a**–**d**, derived from the Oppolzer's (2*R*)-bornane-10,2-sultam **A**, 7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone **B**, *N*,*N*-dicyclohexyl-10-sulfamoyl-(2*R*)-isobornane **C**, and (1*R*)-8-phenylmenthol **D**. The fifth aldoxime, **2e**, was the known derivative of (1*R*)-menthol **E**. Compounds **2a**–**e** are readily available in high chemical yields (89–93%) by oximation of the corresponding glyoximides **1a** and **b** or glyoxylates **1c**–**e** with hydroxylamine hydrochloride (Scheme 1). The *anti* configuration of the aldoximes was revealed by their NMR spectra and proven by X-ray crystallographic measurements. The results of X-ray studies are presented in Figures 1–4.

Recently, manganese(IV) oxide was found to oxidize aldoximes to nitrile oxides, which were trapped in situ with dipolarophiles to afford 2-isoxazolines.[10] We have chosen 3-*E*-hexene as a model dipolarophile. In our hands, chiral aldoximes reacted slowly and required the use of a 15-fold excess of MnO_2. However, this afforded the corresponding 2-isoxazolines in fair yields. We did not observe the aldehydes which usually form as by products of oxidation (Scheme 2, Table 1).[10]

The synthesized aldoximes were in turn very convenient substrates for the synthesis of other classes of compounds, namely nitroalkanes. Attempts to oxidize the oximes **2a**,**b**, and **e** with Oxone® or the hydrogen peroxide–urea complex gave only poor yields of the desired products, while application of trifluoroperoxyacetic acid

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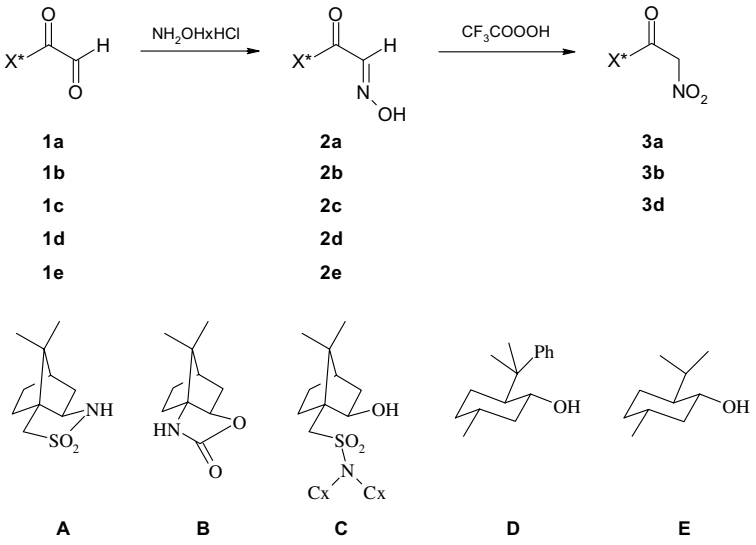


Scheme 1.

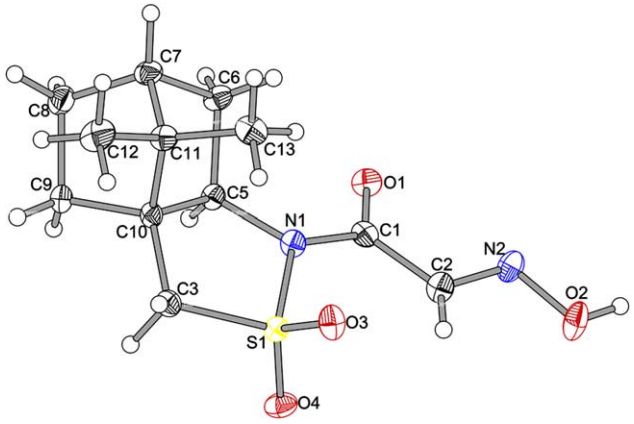


Figure 1. X-ray structure of 2-*N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam oxime **2a**.

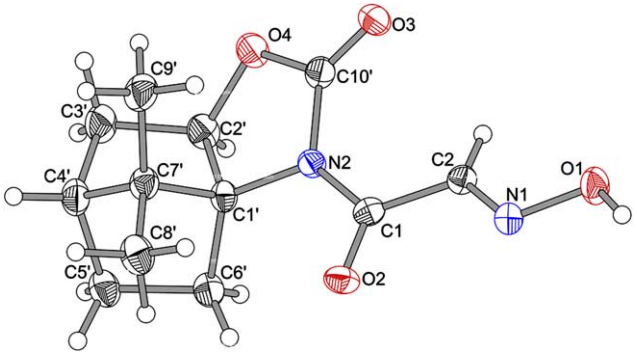


Figure 2. X-ray structure of 2-*N*-glyoxyloyl-7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone oxime **2b**.

(prepared using 90% H_2O_2) afforded the nitroalkanes in good chemical yields (70–85%).[11]

The obtained nitroalkanes were converted into the nitrile oxides using di-*tert*-butyl dicarbonate and DMAP, while the nitriles were reacted in situ with the 3-*E*-hex-

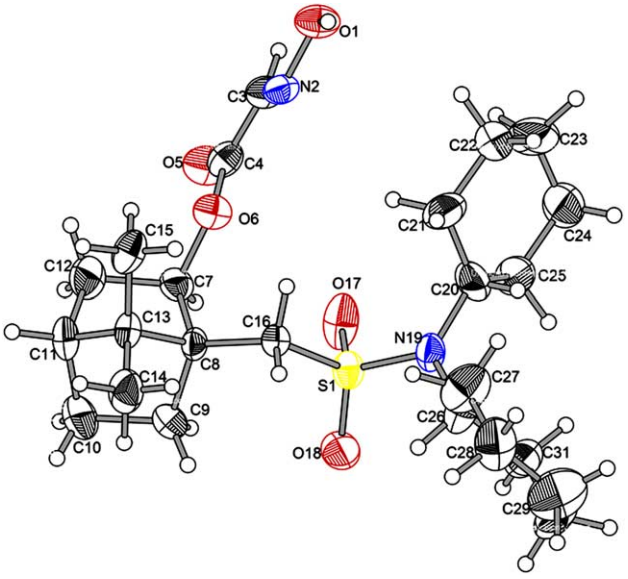


Figure 3. X-ray structure of 2-*O*-glyoxyloyl-*N*,*N*-dicyclohexyl-10-sulfamoyl-(2*R*)-isobornane oxime **2c**.

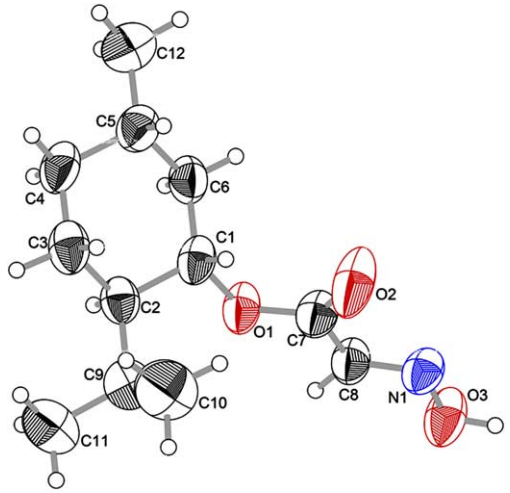
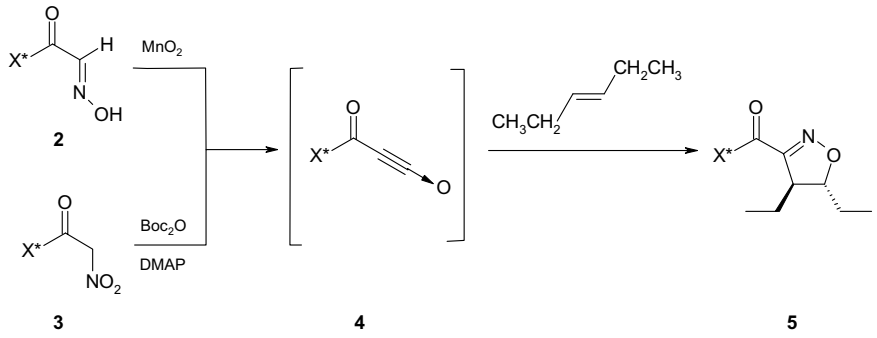


Figure 4. X-ray structure of *O*-glyoxyloyl-(1*R*)-menthyl oxime **2e**.



Scheme 2.

Table 1.

Product	Yield [%]	de[a] (*trans*)
5a	58	15
5b	55	13
5c	59	10
5d	68	—*
5e	70	—*

*Not determined, overlapping of signals.
[a] Determined by ^{1}H NMR.

ene.[12] 2-Isoxazolines were readily formed again, but without real improvement of yields and stereoselectivities. The described nitroalkanes are also very convenient substrates for the synthesis of nitro and amino alcohols; this is currently under investigation in our laboratory.

3. Conclusion

In conclusion, four new chiral oximes and three nitroalkanes bearing various types of chiral auxiliaries were synthesized and converted into nitrile oxides, and then into 2-isoxazolines. Only moderate diastereoselectivities were obtained. Further investigations including the application of the other, more sterically demanding olefins are currently in progress.

4. Experimental

All reactions were carried out under an argon atmosphere with anhydrous solvents dried according to standard laboratory methods. ^{1}H and ^{13}C NMR spectra were measured on Bruker AM and Varian Gemini spectrometers using residual $CHCl_3$ as the internal reference. Mass spectra were carried out with AMD-604 Intectra instrument. Optical rotations were measured on a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. Infrared spectra were recorded on Perkin–Elmer 1640 FTIR spectrometer. Melting points were determined with Köfler hot-stage apparatus and are uncorrected. Flash column chromatography was performed on silica gel (Kieselgel 60, Merck, 200–400 mesh). TLC was performed on Merck aluminum plates (Kieselgel 60 F_{254}) and compounds were visualized with a solution of MoO_3 and $Ce_2(SO_4)_3$ in 15% H_2SO_4.

4.1. General procedure for the preparation of oximes 2

To a solution of glyoximide or glyoxylate **1** (1.2 mmol) and K_2CO_3[†] (6 mmol) in a mixture of THF and H_2O (10 ml, 2:1), $NH_2OH \times HCl$ (2.4 mmol) was added. The progress of the reaction was monitored by TLC. When finished, THF was evaporated and the aqueous phase extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was evaporated and the residue was purified on silica gel (hexane/AcOEt 9:1–1:1).

4.2. 2-*N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam oxime 2a

89% yield. $R_f = 0.5$ hexane/AcOEt 6:4; HRMS-ESI: calcd for $C_{12}H_{19}O_4N_2S$ $(M+H)^+$: 287.1060. Found: 287.1073. Anal. Calcd C, 50.33; H, 6.33; N, 9.78; S, 11.20. Found: C, 50.44; H, 6.43; N, 9.59; S, 11.15; IR (KBr): 3367, 2979, 1678, 1598, 1456, 1336, 1269, 1140, 1074, 1002, 884, 762, 543; $[\alpha]_D^{20} = -111$ (c 1.02, $CHCl_3$); mp = 163 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.84 (br s, 1H), 8.13 (s, 1H), 4.02 (dd, J = 5.4, 7.6 Hz, 1H), 3.55 (d_{AB}, J = 13.8 Hz, 1H), 3.48 (d_{AB}, J = 13.8 Hz, 1H), 2.16–1.84 (m, 6H), 1.50–1.30 (m, 2H), 1.17 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 160.0, 141.9, 65.2, 53.2, 48.8, 47.8, 44.8, 38.2, 32.9, 26.3, 20.9, 19.8.

4.3. 2-*N*-Glyoxyloyl-7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone oxime 2b

91% yield. $R_f = 0.5$ hexane/AcOEt 1:1; HRMS-ESI: calcd for $C_{12}H_{16}O_4N_2Na$ $(M+Na)^+$: 275.1002. Found: 275.10996. Anal. Calcd C, 56.30; H, 6.30; N, 10.94. Found: C, 56.46; H, 6.39; N, 10.95; IR (KBr): 3290, 2961, 1781, 1682, 1597, 1450, 1363, 1173, 1084, 1003, 776, 763; $[\alpha]_D^{20} = +102$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.91 (br s, 1H), 8.62 (s, 1H), 4.37 (dd, J = 5.1, 8.1 Hz, 1H), 2.31 (ddt, J = 3.7, 3.6, 13.7 Hz, 1H), 2.12–2.01 (m, 1H), 1.88 (dd, J = 8.1, 13.7 Hz, 1H), 1.87–1.84 (m, 1H), 1.40–1.26 (m, 2H), 1.18 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.4, 154.6, 143.1, 85.7, 72.5, 48.5, 42.4, 34.6, 25.9, 25.1, 21.4, 19.0.

[†] In the case of glyoximide **1a**, the reaction proceeded without using potassium dicarbonate.

4.4. 2-*O*-Glyoxyloyl-*N,N*-dicyclohexyl-10-sulfamoyl-(2*R*)-isobornane oxime 2c

91% yield. HRMS-ESI: calcd for $C_{24}H_{40}O_5N_2SNa$ $(M+Na)^+$: 491.2555. Found: 491.2572. Anal. Calcd C, 61.5; H, 8.5; N, 6.0; S, 6.8. Found: C, 61.5; H, 8.8; N, 5.9; S, 6.7; IR (KBr): 3242, 3200, 2934, 2852, 1685, 1454, 1327, 1141, 1094, 1025, 981, 771, 573; $[\alpha]_D^{20} = -42.3$ (*c* 1.0, CH_2Cl_2); mp = 193–195 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.95 (br s, 1H), 7.54 (s, 1H), 5.21–5.15 (m, 1H), 3.27 (d_{AB}, J = 13.0 Hz, 1H), 3.26–3.16 (m, 2H), 2.69 (d_{AB}, J = 13.0 Hz, 1H), 2.06–1.59 (m, 20H), 1.32–1.18 (m, 5H), 1.12–1.04 (m, 2H), 1.00 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 160.6, 142.5, 79.6, 57.5, 53.6, 49.6, 49.1, 44.5, 39.2, 32.8, 32.9, 29.9, 26.9, 26.4, 25.1, 20.4, 19.9.

4.5. *O*-Glyoxyloyl-(1*R*)-8-phenylmenthyl oxime 2d

93% yield. R_f = 0.4 hexane/AcOEt 7:3; HRMS-LSIMS(+): calcd for $C_{18}H_{25}O_3NNa$ $(M+Na)^+$: 326.17321. Found: 326.17182. Anal. Calcd C, 71.31; H, 8.31; N, 4.62. Found: C, 71.48; H, 8.13; N, 4.54; IR (film): 3337, 2956, 2924, 1717, 1444, 1305, 1208, 1014, 759, 700; $[\alpha]_D^{20} = -87$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.31 (br s, 1H), 7.29–7.21 (m, 4H), 7.16–7.10 (m, 1H), 6.78 (s, 1H), 4.97 (dt, J = 10.7, 10.7, 4.5 Hz, 1H), 2.08 (ddd, J = 10.7, 14.2, 3.6 Hz, 1H), 1.92–1.86 (m, 1H), 1.79 (dq, J = 13.4, 3.4, 3.4 Hz, 1H), 1.71–1.65 (m, 1H), 1.55–1.44 (m, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.15 (dq, J = 13.4, 3.4, 3.4 Hz, 1H), 1.09–0.90 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50 MHz; $CDCl_3$): δ 161.9, 151.7, 142.3, 129.5, 128.5, 125.9, 76.1, 51.1, 42.0, 40.1, 34.9, 31.8, 29.0, 26.9, 24.6, 22.3.

4.6. *O*-Glyoxyloyl-(1*R*)-menthyl oxime 2e

72% yield. HRMS-EI: calcd for $C_{12}H_{21}O_3NNa$ $(M+Na)^+$: 250.1419. Found: 250.1439; IR (KBr): 3341, 2958, 2939, 2868, 1726, 1621, 1459, 1311, 1213, 1015, 1005, 759, 701; $[\alpha]_D^{20} = -87.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.63 (br s, 1H), 7.55 (s, 1H), 4.90–4.85 (m, 1H), 2.07–2.03 (m, 1H), 1.92–1.83 (m, 1H), 1.73–1.68 (m, 2H), 1.56–1.45 (m, 2H), 1.26–1.04 (m, 2H), 0.93–0.88 (m, 7H), 0.77 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 161.8, 142.2, 76.0, 46.8, 40.6, 34.1, 31.4, 26.2, 23.4, 21.9, 20.6, 16.2.

4.7. General procedure for the preparation of nitroalkanes 3

To a precooled solution (0 °C) of $(CF_3CO)_2O$ (2.5 mmol) in acetonitrile (0.5 ml), 90% H_2O_2 was added slowly (3.0 mmol), and the reaction mixture stirred for 30 min. The solution of peroxyacid was then slowly added to a mixture of oxime **2** (1 mmol), urea (0.35 mmol), and Na_2HPO_4 (5.7 mmol) in acetonitrile (2 ml). The progress of the reaction was monitored by TLC. When finished, the phases were separated and the aqueous phase extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvents were evaporated, and the residue purified on silica gel (hexane/AcOEt 9:1–1:1).

4.8. 2′-*N*-(2-Nitroethanoyl)-(2′*R*)-bornane-10′,2′-sultam 3a

70% yield. R_f = 0.6 hexane/AcOEt 7:3; HRMS-ESI: calcd for $C_{12}H_{18}O_5N_2SNa$ $(M+Na)^+$: 325.0829. Found: 325.0829. Anal. Calcd C, 47.67; H, 6.00; N, 9.26; S, 10.61. Found: C, 47.64; H, 6.19; N, 9.28; S, 10.43; IR (KBr): 3405, 2966, 1717, 1566, 1350, 1327, 1272, 1172, 1138, 868, 825, 530, 481; $[\alpha]_D^{20} = -25$ (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.58 (d_{AB}, J = 14.8 Hz, 1H), 5.50 (d_{AB}, J = 14.8 Hz, 1H), 3.92 (dd, J = 4.9, 7.9 Hz, 1H), 3.54 (d_{AB}, J = 13.9 Hz, 1H), 3.49 (d_{AB}, J = 13.9 Hz, 1H), 2.30–1.75 (m, 6H), 1.50–1.25 (m, 2H), 1.13 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 158.9, 77.0, 65.2, 52.3, 49.3, 47.9, 44.4, 37.5, 32.6, 26.2, 20.5, 19.7.

4.9. 2′-*N*-(2-Nitroethanoyl)-7′,7′-dimethylnorbornane-(1′*S*,2′*R*)-oxazolidinone 3b

85% yield. R_f = 0.6 hexane/AcOEt 1:1; HRMS-ESI: calcd for $C_{12}H_{16}O_6N_2Na$ $(M+Na)^+$: 291.0951. Found: 291.0945; IR (film): 2966, 1784, 1714, 1565, 1362, 1322, 1079, 765, 668; $[\alpha]_D^{20} = +79$ (*c* 0.21, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.85 (dd_{AB}, J = 15.5 Hz, 1H), 5.62 (dd_{AB}, J = 15.5 Hz, 1H), 4.40 (dd, J = 4.3, 8.2 Hz, 1H), 2.99–2.88 (m, 1H), 2.35–2.30 (m, 1H), 2.14–2.02 (m, 3H), 1.95–1.86 (m, 2H), 1.42–1.32 (m, 2H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 161.5, 154.7, 86.0, 78.3, 72.4, 48.4, 42.2, 34.5, 25.7, 25.1, 21.0, 18.9.

4.10. *O*-(Nitroethanoyl)-(1′*R*)-8′-phenylmenthol 3d

85% yield. R_f = 0.5 hexane/AcOEt 6:4; HRMS-ESI: calcd for $C_{18}H_{25}O_4NNa$ $(M+Na)^+$: 342.1676. Found: 342.1657. Anal. Calcd C, 67.69; H, 7.89; N, 4.38. Found: C, 67.57; H, 7.79; N, 4.40; IR (KBr): 3026, 2971, 2919, 1753, 1566, 1334, 1217, 769, 708; $[\alpha]_D^{20} = +80$ (*c* 1.24, $CHCl_3$); mp = 114 °C (CH_2Cl_2/hexane); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36–7.28 (m, 4H), 7.19–7.15 (m, 1H), 4.95 (dt, J = 11.0, 11.0, 4.8 Hz, 1H), 4.33 (dd_{AB}, J = 14.3 Hz, 1H), 4.02 (dd_{AB}, J = 14.3 Hz, 1H), 2.11 (ddd, J = 10.8, 12.3, 3.8 Hz, 1H), 1.96 (dq, J = 13.6, 3.5, 3.5 Hz, 1H), 1.91–1.84 (m, 1H), 1.77–1.70 (m, 1H), 1.56–1.42 (m, 1H), 1.31 (s, 3H), 1.28–1.16 (m, 1H), 1.19 (s, 3H), 1.06–0.93 (m, 2H), 0.90 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.1, 151.7, 128.1, 125.3, 125.2, 76.8, 75.5, 50.0, 41.2, 39.2, 34.2, 31.2, 30.4, 25.9, 21.7, 21.6.

4.11. General procedure for the oxidation of the oximes

To a solution of oxime **2** (1.0 mmol) in CH_2Cl_2 (5 ml), 3 mmol of MnO_2, and 3 mmol of 3-hexene were added at rt. The progress of the reaction was monitored by TLC and every 3 h, more MnO_2 (3 mmol each time) was added. When finished, the solids were filtered off, the solvent evaporated, and the residue purified on silica gel (hexane/AcOEt).

4.12. General procedure for the conversion of nitroalkanes 3 into the nitrile oxides 4

To a solution of di-*tert*-butyl dicarbonate (1.5 mmol), 3-hexene (5 mmol), and DMAP (0.15 mmol) in acetonitrile (5 ml), nitroalkane **3** (1 mmol) in acetonitrile (3 ml) was slowly added at rt. The progress of the reaction was monitored by TLC and, when finished, the reaction mixture was evaporated and purified on silica gel (hexane/AcOEt).

4.13. 4,5-Diethyl-2-isoxazoline-3-carboxylic acid (2′*R*)-*N*-bornane-10′,2′-sultam imide 5a

HRMS-EI: calcd for $C_{18}H_{28}O_4N_2S$ $(M+H)^+$: 368.1769. Found: 368.1764; IR (KBr): 2964, 2939, 1670, 1584, 1459, 1344, 1237, 1170, 1138, 1113, 1062, 932, 756, 539, 494; ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.39–4.35 (m, 1H), 4.23–4.20 (m, 0.58H), 4.14–4.11 (m, 0.42H), 3.49–3.43 (m, 2H), 3.31–3.27 (m, 0.58H), 3.09–3.06 (m, 0.42H), 2.12–1.84 (m, 5H), 1.76–1.35 (m, 6H), 1.23 (s, 3H), 0.99 (s, 3H), 0.98–0.90 (m, 6H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 161.2, 155.7, 89.5, 65.8, 53.1, 52.8, 48.9, 47.9, 4.4, 39.5, 33.3, 28.0, 26.3, 24.0, 21.5, 19.9, 11.2, 9.3.

4.14. 4,5-Diethyl-2-isoxazoline-3-carboxylic acid (2′*R*)-*N*-7′,7′-dimethylnorbornane-(1′*S*,2′*R*)-oxazolidinone imide 5b

HRMS-EI: calcd for $C_{18}H_{28}O_4N_2S$ $(M+Na)^+$: 357.1797. Found: 357.1790; IR (KBr): 3431, 2966, 2939, 2879, 1791, 1696, 1555, 1458, 1367, 1322, 1303, 1292, 1252, 1229, 1174, 1074, 1051, 1007, 916, 883, 808, 780, 762; ^{1}H NMR (500 MHz; $CDCl_3$): δ 4.39–4.35 (m, 1H), 3.27–3.23 (m, 1H), 2.83–2.73 (m, 1H), 2.36–2.26 (m, 1H), 2.12–2.02 (m, 1H), 1.92–1.58 (m, 6H), 1.40–1.25 (m, 3H), 1.22 (s, 1.7H), 1.20 (s, 1.3H), 1.07 (s, 3H), 1.02–0.95 (m, 6H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 162.7, 155.1, 154.1, 89.2, 85.5, 72.6, 54.8, 53.7, 48.2, 42.5, 34.6, 27.8, 25.8, 24.5, 21.5, 19.1, 11.3, 9.1.

4.15. 4,5-Diethyl-2-isoxazoline-3-carboxylic acid *N*,*N*-dicyclohexyl-10′-sulfamoyl-(2*R*′)-*O*-isobornane ester 5c

HRMS-EI: calcd for $C_{30}H_{50}O_5N_2SNa$ $(M+Na)^+$: 573.3338. Found: 573.3334; IR (KBr): 3418, 2933, 2854, 1718, 1455, 1394, 1323, 1227, 1165, 1142, 1106, 1048, 981, 941, 853, 823, 773, 642, 576, 524; ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.12–5.05 (m, 1H), 4.39–4.31 (m, 1H), 3.43 (d, J = 13.0 Hz, 0.45H), 3.41 (d, J = 13.0 Hz, 0.55H), 3.30–3.17 (m, 2H), 3.17–3.10 (m, 0.45H), 3.10–3.07 (m, 0.55H), 2.63 (d, J = 13.0 Hz, 0.55H), 2.61 (d, J = 13.0 Hz, 0.45H), 2.08–1.48 (m, 15H), 1.44–1.05 (m, 7H), 1.04 (s, 3H), 0.99–0.91 (m, 5H), 0.88 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 159.9, 153.9, 89.6, 79.7, 57.3, 53.4, 52.6, 49.6, 49.1, 44.5, 39.5, 32.4, 30.2, 28.2, 26.3, 26.1, 25.2, 24.2, 20.4, 20.0, 10.7, 9.1.

4.16. 4,5-Diethyl-2-isoxazoline-3-carboxylic acid (1′*R*)-8′-phenylmenthyl ester 5d

HRMS-EI: calcd for $C_{24}H_{36}O_3N$ $(M+H)^+$: 386.2695. Found: 386.2687. Anal. Calcd C, 74.8; H, 9.1; N, 3.6. Found: C, 74.8; H, 9.0; N, 3.6; IR (film): 2964, 2876, 1729, 1710, 1580, 1496, 1459, 1309, 1293, 1229, 1157, 1125, 938, 765, 701, 563; $[\alpha]_D^{20} = -82.5$ (c 0.68, CH_2Cl_2); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31–7.10 (m, 5H), 5.02–4.96 (m, 1H), 4.33–4.26 (m, 1H), 2.54–2.47 (m, 1H), 2.16–1.40 (m, 10H), 1.34 (s, 3H), 1.24 (s, 3H), 1.16–1.05 (m, 2H), 0.95 (t, J = 7.0, 3H), 0.88 (s, 3H), 0.84 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 159.8, 153.7, 151.1, 128.0, 125.4, 125.2, 89.9, 76.0, 51.4, 50.2, 41.4, 39.8, 34.4, 31.3, 28.0, 27.5, 26.7, 25.9, 24.0, 21.7, 10.6, 9.2.

4.17. 4,5-Diethyl-2-isoxazoline-3-carboxylic acid (1′*R*)-menthyl ester 5e

HRMS-EI: calcd for $C_{24}H_{36}O_3N$ $(M+Na)^+$: 332.2202. Found: 332.2202; IR (KBr): 3408, 2959, 2934, 2873, 1735, 1711, 1581, 1458, 1388, 1372, 1341, 1315, 1229, 1158, 1122, 1096, 955, 936, 914, 823; ^{1}H NMR (500 MHz; $CDCl_3$): 4.91–4.85 (m, 1H), 4.43–4.39 (m, 1H), 3.12–3.08 (m, 1H), 2.08–2.02 (m, 1H), 1.98–1.85 (m, 1H), 1.81–1.48 (m, 8H), 1.17–1.04 (m, 2H), 0.97 (t, J = 7.5, 3H), 0.93–0.86 (m, 10H), 0.79–0.77 (m, 3H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 160.5, 153.8, 89.7, 76.0, 52.2, 46.7, 40.6, 34.1, 31.4, 28.0, 26.3, 24.0, 23.5, 23.2, 20.7, 16.3, 10.6, 9.1.

4.18. X-ray data

X-ray single-crystal diffraction experiments were carried out on a Kuma KM4CCD κ-axis diffractometer using Mo K_α radiation (0.7107 Å). The program used to solve and refine was SHELX-97.

$C_{12}H_{20}N_2O_5S_1$ **2a**, M = 304.36, orthorhombic, a = 8.0503(13), b = 11.5239(16), c = 15.2014(18), α = 90, β = 90, γ = 90°, space group $P2_12_12_1$, Z = 1, D_{calcd} = 0.358 Mg/m^3, μ(Mo K_α) = 0.063 mm^{-1}, 7260 reflections measured, 3340 [R_{int} = 0.0966] unique reflections, which were used in all calculations. Data/restraints/parameters 3340/0/193. The final R_1 = 0.0612 (all data), 0.04(11). Residual electron density 0. 556 and −0.949 e Å^{-3}.

$C_{12}H_{16}N_2O_4$ **2b**, M = 252.27, orthorhombic, a = 6.9310(4), b = 8.8942(5), c = 20.0216(11), α = 90, β = 90, γ = 90°, space group $P2_12_12_1$, Z = 4, D_{calcd} = 1.358 Mg/m^3, μ(Mo K_α) = 0.103 mm^{-1}, 17511 reflections measured, 1925 [R_{int} = 0.0329] unique reflections, which were used in all calculations. Data/restraints/parameters 1925/0/228. The final R_1 = 0.0276 (all data), 0.1(9). Residual electron density 0.212 and −0.240 e Å^{-3}.

$C_{24}H_{40}N_2O_5S_1$ **2c**, M = 468.64, monoclinic, a = 11.216(2), b = 9.2187(18), c = 12.435(3), α = 90, β = 96.81(3), γ = 90°, space group $P2_1$, Z = 2, D_{calcd} = 1.219 Mg/m^3, μ(Mo K_α) = 0.162 mm^{-1}. The final R_1 = 0.0510 (all data), −0.01(15). Residual electron density 0.133 and −0.128 e Å^{-3}.

$C_{12}H_{21}NO_3$ **2e**, M = 286.35, monoclinic, a = 7.2380(14), b = 11.293(2), c = 8.7830(18), α = 90, β = 107.23(3), γ = 90°, space group $P2_1$, Z = 2, D_{calcd} = 1.101 Mg/m^3, μ(Mo K_α) = 0.078 mm^{-1}. The final R_1 = 0.0390 (all

data), 0.2(18). Residual electron density 0.106 and -0.108 e $\AA^{-3}$.

The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 269445–269448 for compounds **2b**,**a**,**c**, and **e**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk].

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