Synthesis E. Capel et al. Feature

Preparation of Morpholines and Benzoxazines Starting from Nitroepoxides

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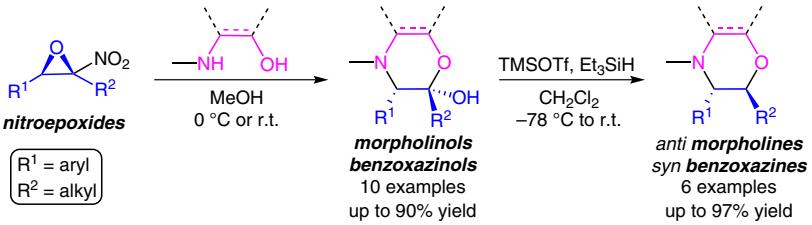

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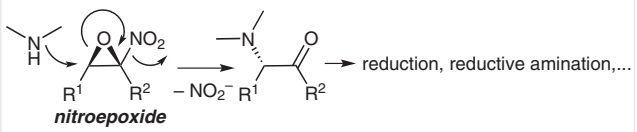
Abstract Nitroepoxides are easily transformed into 2,3-disubstituted morpholines and 2,3-disubstituted benzoxazines in a two-step sequence by treatment with *N*-methylethanolamine and *N*-methyl-2-hydroxyaniline, respectively, in a highly stereoselective fashion.

Key words nitroepoxides, morpholinols, morpholines, benzoxazines

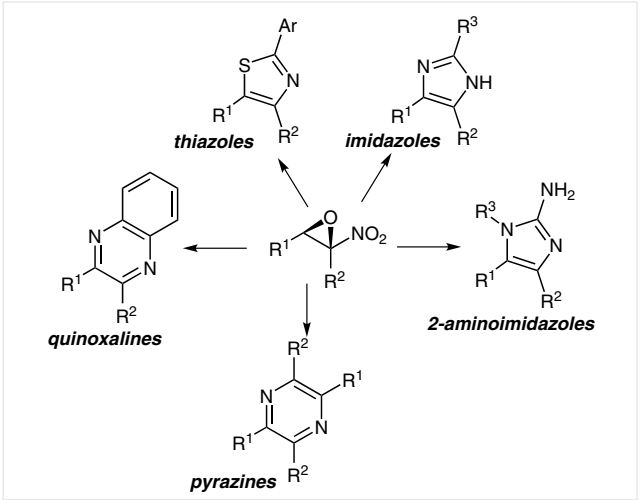
Nitroepoxides are an underdeveloped class of compounds with wide potential for use in chemical synthesis.[1] Nitroepoxides represent strained systems displaying two highly oxidized vicinal positions by nature of their chemical connectivity and hence are potentially exploitable as synthons with vicinal electrophilic centers.

In 1991, Vankar reported the transformation of nitroepoxides into amino ketones.[1d] Nucleophilic attack of the amine to the β-position of the nitroepoxide followed by nitrite extrusion affords the amino ketone (Scheme 1).



Scheme 1 Reactivity of nitroepoxides with amines

Resulting amino ketones can be further transformed into interesting moieties in one-pot processes starting from nitroepoxides. During the last few years a number of studies have appeared reporting the transformation of nitroepoxides into aromatic heterocycles. Hence nitroepoxides have been transformed into thiazoles when reacted with benzothioamides,[1b] imidazoles if guanidines are used as nitrogenated nucleophiles,[1f] and aminoimidazoles in a one-pot-process by using isonitriles and amines[1a] (Scheme 2). We have recently reported the preparation of quinoxalines by reaction between nitroepoxides and 1,2-benzenediamines, and also the synthesis of pyrazines when ammonia is used as a nucleophile (Scheme 2).[2]



Scheme 2 Nitroepoxides into aromatic heterocycles

Nitroepoxides can be also transformed into 1,2-diamines[3] if a reductive amination is performed on the resulting amino ketone, or 1,2-amino alcohols if the resulting amino ketone is subjected to a reduction step[4] (Scheme 3).

We recently reported the preparation of saturated 1,4-diamino-heterocycles, such as piperazines and tetrahydroquinoxalines (Scheme 3),[2] when nitroepoxides are treated with 1,2-diamines and then a reductive agent. The diamino ketone intermediate resulting from the opening of the nitroepoxide by 1,2-diamine cyclizes to afford an aminoimine that upon reduction affords the corresponding satu-

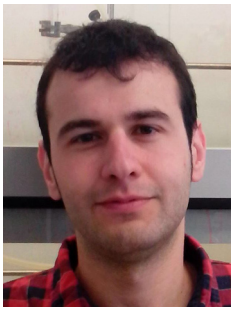
rated 1,4-diamino-heterocycle (Scheme 4). Reductive amination of the amino-imine intermediate affords the *syn* isomer as the major isomer in both cases (*syn*/*anti* ca. 3:1).

We envisioned nitroepoxides to be transformed into morpholines if treated with 1,2-amino alcohols. It is expected that the amino group would open the nitroepoxide and the resulting hydroxy ketone would to cyclize into a stable morpholinol. Morpholinols could be then transformed into the desired morpholines by reduction (Scheme 4). We report herein the synthetic transformation of nitroepoxides into morpholines and benzoxazines by reaction with 1,2-amino alcohols and a reductive agent.

Morpholines are considered to be privileged scaffolds in medicinal chemistry.[5] Some commercial drugs display morpholine moiety (Figure 1). For example, reboxetine (Edro-

Biographical Sketches

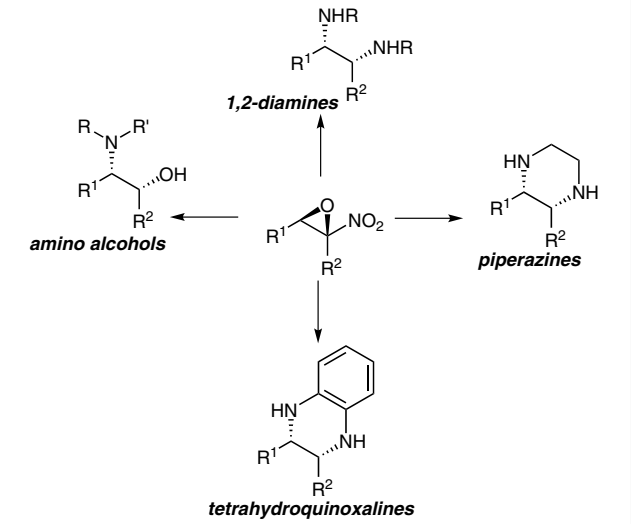
Estefanía Capel received her B.Sc. in chemistry from Universitat Jaume I (Spain) in 2015. She is currently an M.Sc. student in medicinal chemistry under the guidance of Prof. Florenci V. González at Universitat Jaume I. Her research focuses on the synthetic transformations of nitroepoxides.



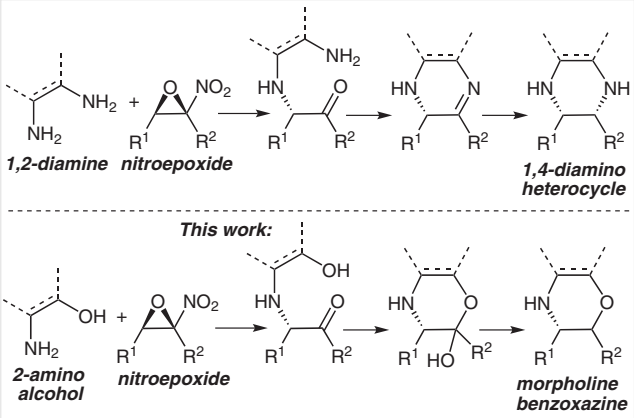
Andreu Vidal Albalat was born in Albocàsser (Spain). He received his M.Sc. in medicinal chemistry from Universitat Jaume I (Spain), in 2012 with a thesis on the synthesis of vicinal diamines from nitroepoxides. He is currently a Ph.D. student under the supervision of Prof. Florenci V. González at Universitat Jaume I. His research focuses on the development of new organocatalytic epoxidation methodologies and synthetic applications of chiral building blocks.

Santiago Rodríguez graduated from the School of Chemistry at the University of Valencia. His Ph.D. thesis was directed by Prof. Ana M. Costero. He had a postdoctoral stay with Prof. J. Fraser Stoddart at Birmingham University. He also did a postdoctoral stay at the University of Basque Country in the group of Prof. Claudio Palomo.

Florenci V. González carried out his undergraduate studies at Universitat de València. He obtained his Ph.D. under the guidance of Prof. J. Alberto Marco and Prof. Miguel Carda at Universitat Jaume I. He had a postdoctoral stay at Indiana University and University of Michigan in the group of Prof. William R. Roush, he also had a postdoctoral stay at Colorado State University in the group of Prof. Robert M. Williams. Since 2001 he has been associate professor at Universitat Jaume I. His current research interests are synthetic methodology including organocatalytic processes and the design and synthesis of protease inhibitors.



Scheme 3 Nitroepoxides into saturated compounds



Scheme 4 Mechanism for the transformation of nitroepoxides into saturated 1,4-diamino-heterocycles and for the reaction to prepare morpholines and benzoxazines

nax, Prolift) a selective norepinephrine reuptake inhibitor (NRI), is an antidepressant currently approved and marketed in over 60 countries;[6] phenmetrazine is a potent releaser of [^{3}H]norepinephrine and [^{3}H]dopamine,[7] phendimetrazine (Bontril) is an anorexigenic drug;[8] aprepitant (Emend) is a potent and orally active NK1 receptor antagonist for chemotherapy induced emesis, depression and other potential indications[9] (Figure 1). Although there have been reported routes for the preparation of morpholines,[10] their use is currently limited by the scarcity of methods for their preparation, particularly for 2,3-disubstituted morpholines.

Benzoxazine moiety is displayed by compounds with a wide range of biological activities like neuroprotective agents,[11] PPARγ agonists,[12] intracellular calcium antagonist,[13] antiangiogenic therapeutic agents,[14] estrogen receptor β-agonists,[15] and antitumour.[16]

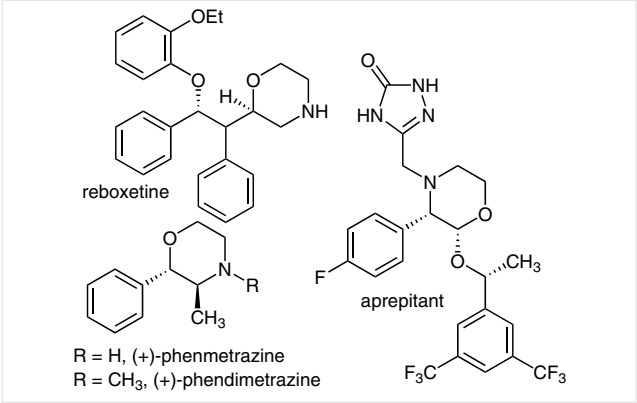
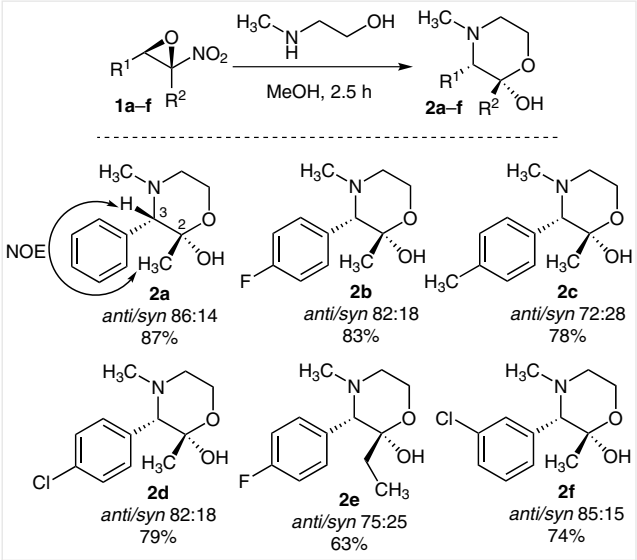


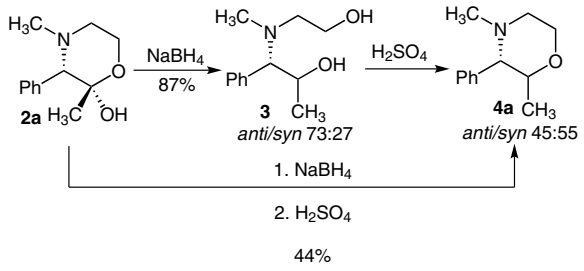
Figure 1 Commercial drugs displaying a morpholine moiety

We began our studies of the preparation of morpholinols by combining nitroepoxide **1a** with *N*-methylethanolamine (1.5 equiv) in methanol. We were pleased to see that the reaction afforded morpholinol **2a** in high chemical yield (Scheme 5). A series of morpholinols were prepared starting from the corresponding nitroepoxide following the same experimental procedure (Scheme 5). Stereochemistry was assigned by NMR measurements: NOE effect was observed between methyl group and benzylic hydrogen (Scheme 5).



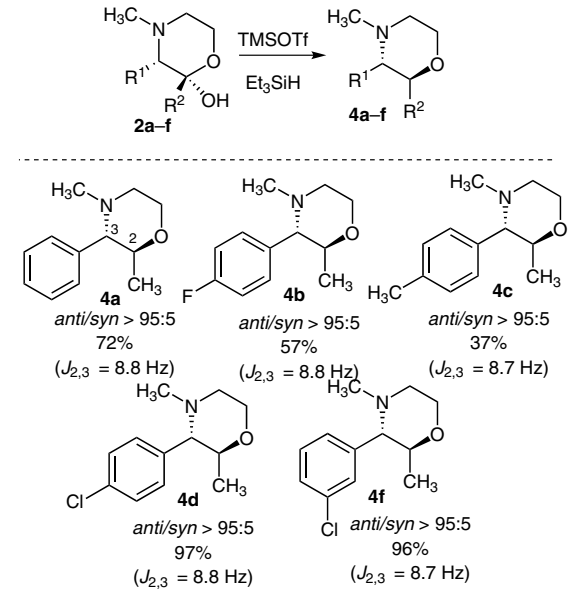
Scheme 5 Conversion of nitroepoxides into morpholinols

The conversion of morpholinols into morpholines was carried out by a sequence of two steps.[17] Reduction of morpholinol **2a** with sodium borohydride afforded diol **3** as a mixture of stereoisomers. Then sulfuric acid treatment of compound **3** gave morpholine **4a** as a 45:55 mixture of stereoisomers (Scheme 6). This transformation has also been performed in one-pot (Scheme 6).



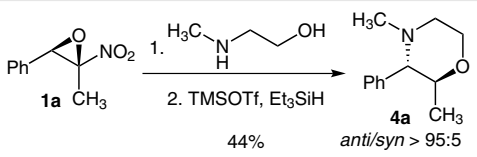
Scheme 6 Conversion of morpholinol into an equimolecular mixture of morpholines

In order to improve the chemical yield and diastereoselectivity of the reaction, other conditions were evaluated. Treatment of nitroepoxide **1a** with trimethylsilyl triflate (2 equivalents) and triethylsilane (8 equivalents)[18] in dichloromethane afforded *anti* morpholine **4a** as a single isomer (Scheme 7). Morpholinols **2b**–**f** were transformed into the corresponding *anti* morpholines **4b**–**f** (Scheme 7).



Scheme 7 Conversion of morpholinols into morpholines

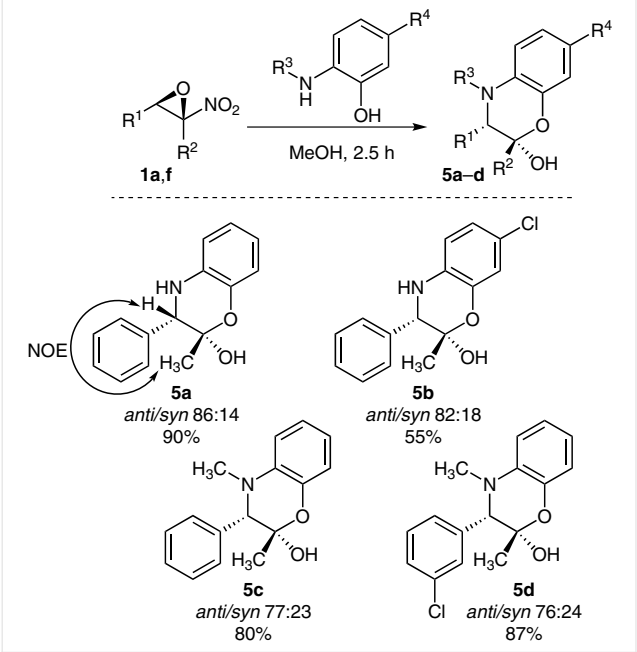
Stereochemical assignments were made by NMR coupling constants and by NOE experiments (Scheme 8). Similar coupling constants were observed for *anti* morpholines **4a**–**f** (Scheme 7) denoting relative *anti* stereochemistry. According to the literature *anti* morpholines show higher coupling constants ($J_{2,3}$ = 9.0 Hz for phendimetrazine[10s]) than *syn* morpholines ($J_{2,3}$ = 4.4 Hz[10r]). *syn*-**4a** Compound (Scheme 7) showed coupling constant $J_{2,3}$ = 3.4 Hz.



Scheme 8 One-pot process for the conversion of nitroepoxide **1a** into morpholine **4a**

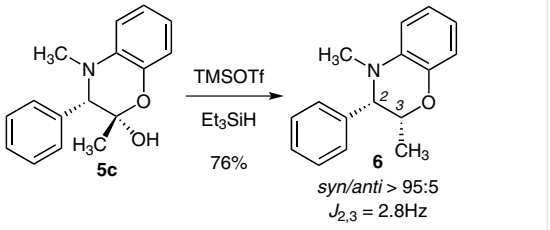
We then evaluated a one-pot procedure for the preparation of 2,3-disubstituted morpholines starting from nitroepoxides. Some experimental work was performed to optimize the transformation. Morpholine **4a** was prepared starting from nitroepoxide **1a** by treatment with *N*-methylethanolamine (2 equiv) followed by addition of trimethylsilyl triflate (6 equiv) and triethylsilane (24 equiv) in dichloromethane (Scheme 8).

In order to prepare benzoxazines, nitroepoxides were treated with 2-hydroxyanilines. The resulting benzoxazinol would be further transformed into benzoxazines in a similar sequence as applied for the synthesis of morpholines. Firstly nitroepoxide **2a** was treated with 2-hydroxyaniline at room temperature, compound **5a** was obtained, but the yield was not satisfactory. Then the reaction was carried out at low temperature (0 °C) and an improvement in the chemical yield was observed (Scheme 9). Stereochemistry was assigned by NMR measurements: an NOE effect was observed between the methyl group and the benzylic hydrogen.



Scheme 9 Conversion of nitroepoxides into benzoxazinols

2-Hydroxybenzoxazine **5c** was submitted to same reaction as morpholinols with trimethylsilyl triflate and triethylsilane to furnish *syn* benzoxazine **6** in good chemical yield (Scheme 10). Compound **6** was formed as a single isomer. The relative stereochemistry of **6** was assigned as *syn* based upon coupling constants and NOE experiments (Scheme 10). For **6**, a coupling constant $J_{2,3}$ = 2.8 Hz is in accordance with *syn* benzoxazines in the literature (for *anti*: $J_{2,3}$ = 4.5 Hz; for *syn*: $J_{2,3}$ = 2.0 Hz).[19]



Scheme 10 Conversion of nitroepoxides into benzoxazines

Curiously same reaction by using trimethylsilyl triflate and triethylsilane afforded the *anti* isomer in the case of morpholines and the *syn* isomer for benzoxazines. Anomeric effect is ascribed to n → s* hyperconjugation between the nonbonding orbital on the oxygen and the antibonding orbital of the anomeric position.[20] In the silane reaction starting from morpholinols, hydride attack on the oxocarbenium intermediate would occur predominantly from the axial direction due to the kinetic anomeric effect (Figure 2).[21] In case of benzoxazinols, restricted conformation of the oxocarbenium intermediate directs hydride attack to the less hindered face (Figure 2).

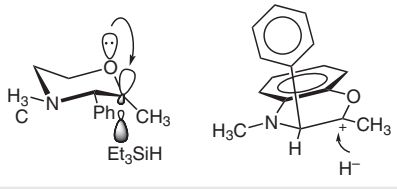
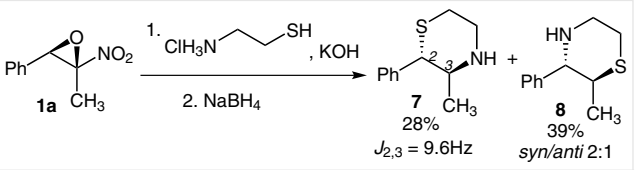


Figure 2 Stereoelectronic effects to explain observed diastereoselectivity

Nitroepoxides have also been converted into thiomorpholines. When nitroepoxide **1a** was treated with thioethanolamine and then with sodium borohydride in a one-pot process a mixture of regiomeric thiomorpholines **7** and **8** was obtained. Compound **7** is a sulfur analogue of the drug phenmetrazine (Scheme 11).

In summary, we report herein that morpholines and benzoxazines can be easily prepared by treating nitroepoxides with *N*-methylethanolamine and *N*-methyl-2-hydroxyaniline, respectively. The transformations comprise two steps: firstly is the formation of 2-hydroxymorpholines



Scheme 11 Conversion of nitroepoxides into thiomorpholines

and 2-hydroxybenzoxazine, followed by their transformation into morpholines and benzoxazines by reduction. The whole process can also be performed in one-pot starting from the nitroepoxide. Further investigations of the utility of nitroepoxides in synthesis are ongoing and will be reported in the future.

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ (^{1}H, δ = 7.24; ^{13}C, δ = 77.0) solution at 30 °C on a 300 MHz, 400 MHz, or 500 MHz NMR spectrometer. HRMS were measured on a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface. Mass spectra were measured on a GCMS (single quadrupole). IR spectra were recorded as oily films on KBr plates using a FT-IR spectrophotometer. EM Science Silica Gel 60 was used for column chromatography while TLC was performed with precoated plates (0.25 mm). Unless otherwise specified, all reactions were carried out under an N_2 atmosphere with magnetic stirring.

Nitroepoxides 1a–f; General Procedure

To a stirred ice-bath cold suspension of the corresponding nitroalkene (3.07 mmol) in MeOH (9.5 mL) containing 50% aq H_2O_2 solution (690 µL, 12.28 mmol) was added 2 M aq NaOH (770 µL, 1.54 mmol) and the mixture was stirred at 0 °C for 10 min. Then, iced water (ca. 20 mg) was added, the mixture was extracted with Et_2O (3 × 30 mL), and the combined organic phases were washed with brine (45 mL), dried (Na_2SO_4), and concentrated under vacuum to obtain the product as yellow oil without further purification.

2-Methyl-2-nitro-3-phenyloxirane (1a)

Yellow oil; yield: 451 mg (82%).

IR (KBr): 3062, 3028, 2948, 1555, 1495, 1448, 1354, 1158, 1105, 982, 899 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 3 H), 7.34–7.28 (m, 2 H), 4.54 (s, 1 H), 1.80 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 131.0, 129.3, 128.7, 126.3, 88.8, 62.6, 12.2.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_9NO_3$: 179.0582; found: 179.0587.

3-(4-Fluorophenyl)-2-methyl-2-nitrooxirane (1b)

Pale yellow oil; yield: 472 mg (78%).

IR (KBr): 3059, 3024, 2944, 1546 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–6.88 (m, 4 H), 4.53 (s, 1 H), 1.79 (s, 3 H).

^{13}C NMR (75 MHz, CDCl3): δ = 163.2 (d, *J* = 247.8 Hz), 128.3 (d, *J* = 8.4 Hz), 126.8 (d, *J* = 4.0 Hz), 115.8 (d, *J* = 22.0 Hz), 88.8, 62.1, 12.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_8NFO_3$: 197.0488; found: 197.0492.

2-Methyl-2-nitro-3-(*p*-tolyl)oxirane (1c)

Yellow oil; yield: 444 mg (75%).

IR (KBr): 3062, 3025, 2948, 1552 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (q, *J* = 8.5 Hz, 4 H), 4.50 (s, 1 H), 2.38 (s, 3 H), 1.80 (s, 3 H).

^{13}C NMR (75 MHz, CDCl3): δ = 139.6, 129.5, 128.0, 126.4, 89.1, 62.8, 21.1, 12.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}NO_3$: 193.0739; found: 193.0745.

3-(4-Chlorophenyl)-2-methyl-2-nitrooxirane (1d)

Pale yellow oil; yield:616 mg (94%).

IR (KBr): 3052, 2984, 1560, 1420, 1259, 894, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 2 H), 7.29–7.22 (m, 2 H), 4.52 (s, 1 H), 1.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.47, 129.47, 129.02, 127.74, 88.60, 61.95, 12.30.

MS (EI): *m*/*z* $[M - NO_2]^+$ calcd for C_9H_8ClO: 167.0; found: 167.1; *m*/*z* $[M - C_3H_4NO_3]^+$ calcd for C_6H_4Cl: 111.0; found: 111.0.

2-Ethyl-3-(4-fluorophenyl)-2-nitrooxirane (1e)

Pale yellow oil; yield: 583 mg (90%).

IR (KBr): 3052, 2979, 1710, 1606, 1552, 1510 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 2 H), 7.21–7.05 (m, 2 H), 4.50 (s, 1 H), 2.47 (dq, *J* = 14.9, 7.4 Hz, 1 H), 1.68 (td, *J* = 14.9, 7.5 Hz, 1 H), 1.08 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (d, *J* = 247.5 Hz), 128.2 (d, *J* = 8.3 Hz), 127.0 (d, *J* = 2.3 Hz), 115.9 (d, *J* = 21.8 Hz), 92.37, 62.62, 19.44, 7.53.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}FNO_3$: 211.0645; found: 211.0651.

3-(3-Chlorophenyl)-2-methyl-2-nitrooxirane (1f)

Yellow oil; yield: 213 mg (86%).

IR (KBr): 3052, 2982, 1559, 1419, 1259, 893, 700, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 3 H), 7.24–7.18 (m, 1 H), 4.52 (s, 1 H), 1.80 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.97, 133.03, 130.12, 129.66, 126.46, 124.59, 88.54, 61.72, 12.40.

MS (EI): *m*/*z* $[M - NO_2]^+$ calcd for C_9H_8ClO: 167.0; found: 167.0; *m*/*z* $[M - C_3H_4NO_3]^+$ calcd for C_6H_4Cl; 111.0; found: 111.0.

Morpholinols 2a–f; General Procedure

To an ice-bath cold solution of the corresponding nitroepoxide **1a–f** (0.56 mmol) in MeOH (1 mL), *N*-methylethanolamine (90 µL, 1.12 mmol) was added. The resulting mixture was stirred for 3.5 h at r.t., then H_2O (5 mL) was added; the mixture was extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated under vacuum. The resulting crude oil was purified through flash liquid chromatography (silica gel, hexanes/EtOAc, 1:1, EtOAc, and EtOAc/MeOH, 9:1) to afford the desired product.

2,4-Dimethyl-3-phenylmorpholin-2-ol (2a)

White solid; yield: 101 mg (87%); mp 64–66 °C; R_f = 0.43 (EtOAc).

IR (KBr): 3500, 3049, 2985, 1601 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.27 (m, 5 H), 5.29 (s, 1 H), 4.23 (ddd, *J* = 15.4, 8.8, 2.6 Hz, 1 H), 3.68 (ddd, *J* = 12.0, 4.0, 1.1 Hz, 1 H), 3.07 (s, 1 H), 2.87 (ddd, *J* = 11.6, 2.9, 1.0 Hz, 1 H), 2.50 (ddd, *J* = 12.5, 11.7, 4.0 Hz, 1 H), 2.04 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.53, 128.04, 127.85, 95.69, 77.24, 59.44, 56.15, 44.15, 25.03.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}NO_2$: 208.1338; found: 208.1335.

3-(4-Fluorophenyl)-2,4-dimethylmorpholin-2-ol (2b)

Yellow pale solid; yield: 104 mg (83%); mp 99–101 °C; R_f = 0.66 (EtOAc/MeOH 95:5).

IR (KBr): 3490, 3050, 2987, 1608 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.28 (m, 2 H), 7.02 (t, *J* = 8.3 Hz, 2 H), 4.22 (td, *J* = 12.1, 1.7 Hz, 1 H), 3.68 (dd, *J* = 12.0, 4.0 Hz, 1 H), 3.05 (s, 1 H), 2.89–2.81 (m, 1 H), 2.49 (td, *J* = 11.6, 2.8 Hz, 1 H), 2.02 (d, *J* = 1.2 Hz, 3 H), 1.10 (d, *J* = 1.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.03, 160.77, 133.29, 133.25, 114.71, 95.57, 76.36, 59.38, 56.10, 44.04, 25.16.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}FNO_2$: 226.1243; found: 226.1246.

2,4-Dimethyl-3-(*p*-tolyl)morpholin-2-ol (2c)

Yellow solid; yield: 97 mg (78%); mp 105–107 °C; R_f = 0.56 (EtOAc/MeOH, 95:5).

IR (KBr): 3526, 3050, 2987, 1608 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–6.98 (m, 4 H), 4.21 (td, *J* = 12.2, 3.0 Hz, 1 H), 3.65 (dd, *J* = 11.9, 4.0 Hz, 1 H), 3.01 (s, 1 H), 2.83 (dd, *J* = 11.6, 2.8 Hz, 1 H), 2.46 (td, *J* = 12.0, 3.9 Hz, 1 H), 2.32 (s, 3 H), 2.01 (s, 3 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.49, 134.45, 130.77, 128.74, 128.40, 95.76, 76.91, 59.44, 56.20, 44.10, 25.12, 21.05.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{20}NO_2$: 222.1494; found: 222.1493.

3-(4-Chlorophenyl)-2,4-dimethylmorpholin-2-ol (2d)

White solid; yield: 106 mg (79%) mp 128–130 °C; R_f = 0.65 (EtOAc/MeOH, 95:5).

IR (KBr): 3488, 3052, 2985, 1599 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.24 (m, 4 H), 4.19 (td, *J* = 12.2, 3.0 Hz, 1 H), 4.06 (bs, 1 H), 3.65 (ddd, *J* = 11.9, 3.9, 1.0 Hz, 1 H), 3.01 (s, 1 H), 2.83 (dd, *J* = 12.1, 2.4 Hz, 1 H), 2.45 (td, *J* = 12.3, 4.0 Hz, 1 H), 1.99 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.12, 133.64, 130.70, 128.23, 95.44, 76.46, 59.40, 56.01, 44.11, 25.19.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}ClNO_2$: 242.0948; found: 242.0945.

2-Ethyl-3-(4-fluorophenyl)-4-methylmorpholin-2-ol (2e)

Yellow solid; yield: 84 mg (63%); mp 61–63 °C; R_f = 0.53 (EtOAc/MeOH, 95:5).

IR (KBr): 3491, 3056, 2986, 1602 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.28 (m, 2 H), 7.02 (t, *J* = 8.3 Hz, 2 H), 4.22 (td, *J* = 12.1, 1.7 Hz, 1 H), 3.68 (dd, *J* = 12.0, 4.0 Hz, 1 H), 3.05 (s, 1 H), 2.89–2.81 (m, 1 H), 2.49 (td, *J* = 11.6, 2.8 Hz, 1 H), 2.02 (d, *J* = 1.2 Hz, 3 H), 1.23 (d, *J* = 1.3 Hz, 2 H), 1.10 (d, *J* = 1.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.37, 161.41, 133.21, 131.01, 114.55, 96.54, 96.54, 75.24, 59.31, 56.21, 44.12, 30.67, 6.42.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}FNO_2$: 240.1400; found: 240.1399.

3-(3-Chlorophenyl)-2-methylmorpholin-2-ol (2f)

Yellow solid; yield: 100 mg (74%); mp 63–65 °C; R_f = 0.52 (EtOAc/MeOH, 95:5).

IR (KBr): 3418, 3051, 2983, 1602 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 38.4, 16.9 Hz, 3 H), 7.24 (s, 1 H), 4.19 (td, *J* = 12.2, 3.0 Hz, 1 H), 3.64 (dd, *J* = 11.4, 4.5 Hz, 1 H), 2.99 (s, 1 H), 2.82 (dd, *J* = 13.1, 1.4 Hz, 1 H), 2.52–2.35 (m, 1 H), 1.99 (s, 3 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.78, 133.92, 129.22, 128.04, 95.37, 76.69, 59.37, 55.95, 44.19, 25.31.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}ClNO_2$: 242.0948; found: 242.0953.

1-[(2-Hydroxyethyl)(methyl)amino]-1-phenylpropan-2-ol (3)

To an ice-bath cooled solution of **2a** (30 mg, 0.14 mmol) in a mixture of EtOH/H_2O (360 µL each), a cold solution of $NaBH_4$ (22 mg, 0.58 mmol) in H_2O (250 µL) was added dropwise. The mixture was allowed to warm up to r.t. and stirred overnight. The mixture was cooled to 0 °C and concd HCl (200 µL) was added dropwise. Then EtOH was removed under reduced pressure and the crude mixture was diluted with water (3 mL), chilled to 0 °C, and made basic with 40% aq NaOH (tested with litmus). It was then extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (20 mL), dried (anhyd Na_2SO_4), and finally concentrated under vacuum. The crude product was purified with flash liquid chromatography [silica gel, hexane/EtOAc, 1:1 (impurities), then pure EtOAc, and EtOAc/MeOH, 7:3 (product)] to give a pale yellow oil; yield: 26 mg (87%); R_f = 0.83 (CH_2Cl_2/MeOH, 95:5).

IR (KBr): 3049, 2986, 1634, 1455, 1048 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.16 (m, 4 H), 7.07 (d, *J* = 7.9 Hz, 1 H), 4.34–4.28 (m, 1 H, major), 4.15 (dt, *J* = 15.8, 5.9 Hz, 1 H, minor), 3.71–3.42 (m, 2 H), 3.27 (d, *J* = 10.1 Hz, 1 H, minor), 3.18 (d, *J* = 5.8 Hz, 1 H, major), 2.47 (t, *J* = 5.5 Hz, 2 H, major), 2.60–2.25 (m, 2 H, minor), 2.15 (s, 3 H, major), 2.11 (s, 3 H, minor), 1.02 (d, *J* = 6.3 Hz, 3 H, major), 0.96 (d, *J* = 6.0 Hz, 1 H, minor).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.0, 129.7, 128.2, 127.8, 75.0, 66.2, 58.6, 56.1, 38.5, 20.4.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}NO_2$: 210.2; found: 210.2.

Morpholines 4a–f; General Procedure

The corresponding morpholin-2-ol (0.22 mmol) was dissolved with freshly distilled CH_2Cl_2 (5 mL) and cooled to –78 °C under N_2 atmosphere. Et_3SiH (290 µL, 1.76 mmol) was added dropwise to the cool mixture followed by the dropwise addition of TMSOTf (80 µL, 0.44 mmol). The mixture was allowed to warm up to r.t. and stirred overnight. The mixture was then cooled to 0 °C, quenched by the addition of sat. aq $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 15 mL); the combined organic phases were washed with brine (20 mL), dried (anhyd $MgSO_4$), filtered, and concentrated under vacuum to afford a yellow oil that was purified by flash liquid chromatography (silica gel, CH_2Cl_2).

2,4-Dimethyl-3-phenylmorpholine (4a)

Yellow oil; yield: 30 mg (72%); R_f = 0.83 (CH_2Cl_2/MeOH, 95:5).

IR (KBr): 3049, 2986, 1634, 1455, 1048 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 7.32–7.23 (m, 5 H), 3.95–3.84 (m, 2 H), 3.59–3.51 (m, 1 H), 2.82 (d, *J* = 11.8 Hz, 1 H), 2.64 (d, *J* = 8.8 Hz, 1 H), 2.41 (tt, *J* = 11.3, 5.6 Hz, 1 H), 1.98 (s, 3 H), 0.87 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.01, 128.4, 127.7, 126.9, 76.99, 75.9, 66.8, 55.5, 44.0, 18.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO$: 192.1388; found: 192.1384.

3-(4-Fluorophenyl)-2,4-dimethylmorpholine (4b)

Yellow oil; yield: 26 mg (57%); R_f = 0.47 (EtOAc).

IR (KBr): 3048, 2933, 1637, 1508, 1453, 1226, 1068 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.15 (m, 1 H), 7.07–6.87 (m, 2 H), 3.89–3.73 (m, 1 H), 3.51–3.34 (m, 1 H), 2.79–2.71 (m, 1 H), 2.57 (d, *J* = 8.8 Hz, 1 H), 2.39–2.29 (m, 1 H), 2.28 (s, 3 H), 0.79 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 262.6 Hz), 135.7 (d, *J* = 3.0 Hz), 129.2 (d, *J* = 8.4 Hz), 115.32 (d, *J* = 20.3 Hz), 77.0, 75.0, 66.7, 55.4, 43.8, 18.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}FNO$: 210.1294; found: 210.1291.

2,4-Dimethyl-3-(*p*-tolyl)morpholine (4c)

Yellow oil; yield: 17 mg (37%); R_f = 0.49 (EtOAc).

IR (KBr): 3049, 2985, 1631, 1455, 1283, 1283, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–6.98 (m, 4 H), 3.86 (d, *J* = 7.1 Hz, 1 H), 3.56–3.45 (m, 1 H), 2.79 (d, *J* = 11.6 Hz, 1 H), 2.58 (d, *J* = 8.7 Hz, 1 H), 2.37 (dt, *J* = 11.6, 7.6 Hz, 1 H), 2.27 (s, 3 H), 1.95 (s, 3 H), 0.82 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.43, 129.21, 76.91, 75.61, 66.65, 55.57, 43.83, 21.13, 18.58.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}NO$: 206.1545; found: 206.1541.

3-(4-Chlorophenyl)-2,4-dimethylmorpholine (4d)

Yellow oil; yield: 48 mg (97%); R_f = 0.47 (EtOAc).

IR (KBr): 3052, 2988, 1635, 1491, 1234, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.13 (m, 4 H), 3.92–3.75 (m, 2 H), 3.50–3.34 (m, 1 H), 2.75 (d, *J* = 11.7 Hz, 1 H), 2.57 (d, *J* = 8.8 Hz, 1 H), 2.35 (td, *J* = 11.6, 3.9 Hz, 1 H), 1.91 (s, 3 H), 0.81 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6, 133.3, 128.7, 128.7, 128.5, 128.4, 76.9, 75.1, 66.9, 55.3, 43.9, 18.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}ClNO$: 226.0999; found: 226.0994.

3-(3-Chlorophenyl)-2,4-dimethylmorpholine (4f)

Yellow oil; yield: 47 mg (96%); R_f = 0.59 (EtOAc).

IR (KBr): 3063, 2978, 1636, 1453, 1233, 1123 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.07 (m, 4 H), 3.93–3.77 (m, 2 H), 3.53–3.39 (m, 1 H), 2.77 (d, *J* = 11.7 Hz, 1 H), 2.59 (d, *J* = 8.7 Hz, 1 H), 2.37 (td, *J* = 11.4, 4.5 Hz, 1 H), 1.94 (s, 3 H), 0.83 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.9, 134.5, 129.8, 128.0, 125.0, 76.8, 75.3, 66.7, 55.3, 43.9, 18.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}ClNO$: 226.0999; found: 226.0997.

Benzoxazinols 5a,b; General Procedure

To a cooled solution (0 °C) of 2-aminophenol (67 mg, 0.60 mmol) in MeOH (1 mL), a solution of nitroepoxide (0.40 mmol) in MeOH (3 mL) was added and the mixture was stirred at 0 °C for 2 d. Then, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic phases were washed with brine (20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, hexanes/EtOAc, 7:3).

2-Methyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-ol (5a)

Brown oil; yield: 87 mg (90%); R_f = 0.38 (hexane/EtOAc, 7:3).

IR (KBr): 3562, 3387, 3021, 2981, 1441, 1172, 1085 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 4 H), 7.17 (d, *J* = 10.7 Hz, 1 H), 6.85–6.70 (m, 3 H), 6.64–6.59 (m, 1 H), 4.02 (s, 1 H), 1.31 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.9, 137.4, 132.5, 128.8, 128.6, 128.4, 127.7, 121.5, 120.9, 117.6, 115.4, 96.3, 62.3, 23.6.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_2$: 242.1181; found: 242.1174.

7-Chloro-2-methyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-ol (5b)

Brown oil; yield: 53 mg (55%); R_f = 0.72 (hexane/EtOAc, 7:3).

IR (KBr): 3565, 3390, 3054, 2987, 1448, 1186, 1092 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.37 (m, 5 H), 6.80 (d, *J* = 8.6 Hz, 1 H), 6.76 (d, *J* = 2.3 Hz, 1 H), 6.70 (d, *J* = 2.3 Hz, 1 H), 4.13 (s, 1 H), 1.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 136.9, 133.4, 130.3, 129.4, 128.9, 128.7, 128.3, 127.6, 120.5, 118.5, 115.0, 96.2, 62.0, 23.6.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}ClNO_2$: 276.1; found: 276.2.

Benzoxazinols 5c,d; General Procedure

To a solution 2-(methylamino)phenol[22] (0.80 mmol) in MeOH (1 mL), a solution of nitroepoxide (0.40 mmol) in MeOH (3 mL) was added and the mixture was stirred at r.t. until consumption of the starting nitroepoxide. Then, water (3 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic phases were washed with brine (20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2).

2,4-Dimethyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-ol (5c)

Brown oil; yield: 58 mg (80%); R_f = 0.52 (CH_2Cl_2).

IR (KBr): 3500, 3053, 2986, 1608, 1422, 1220, 1002 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 3 H), 7.02 (dt, *J* = 4.8, 1.9 Hz, 2 H), 6.92–6.79 (m, 2 H), 6.75–6.68 (m, 1 H), 6.62 (dd, *J* = 7.9, 1.4 Hz, 1 H), 4.04 (s, 1 H), 2.74 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 137.0, 133.7, 129.2, 128.7, 128.6, 128.2, 128.0, 122.5, 119.1, 117.1, 111.8, 95.0, 69.3, 36.7, 24.4.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_2$: 256.1; found: 256.2.

3-(3-Chlorophenyl)-2,4-dimethyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-ol (5d)

Brown oil; yield: 53 mg (87%); R_f = 0.54 (CH_2Cl_2).

IR (KBr): 3501, 3008, 2942, 1502, 1217, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.03 (m, 4 H), 6.93–6.79 (m, 2 H), 6.76–6.70 (m, 1 H), 6.62 (dd, *J* = 8.0, 1.3 Hz, 1 H), 4.01 (s, 1 H), 2.75 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.13, 139.17, 134.38, 133.18, 130.00, 129.92, 129.38, 128.78, 128.45, 128.43, 125.92, 122.68, 122.27, 119.51, 119.34, 117.21, 117.13, 111.90, 94.62, 68.92, 36.71, 24.44.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}ClNO_2$: 290.1; found: 290.2.

2,4-Dimethyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (6)

Prepared using the procedure for morpholines **4a**–**f**.

Yellow oil; yield: 40 mg (76%); R_f = 0.74 (CH_2Cl_2).

IR (KBr): 3029, 2984, 1505, 1225, 1044 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.15 (m, 3 H), 7.05–7.01 (m, 2 H), 6.87–6.81 (m, 1 H), 6.80–6.77 (m, 1 H), 6.60–6.55 (m, 2 H), 4.39 (qd, *J* = 6.5, 2.8 Hz, 1 H), 4.08 (d, *J* = 2.8 Hz, 1 H), 2.73 (s, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.9, 138.1, 135.7, 128.4, 128.3, 127.7, 122.3, 116.7, 115.9, 110.6, 71.9, 66.3, 36.7, 17.9.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO$: 240.1; found: 240.2.

Thiomorpholines 7 and 8; General Procedure

2-Aminoethanethiol hydrochloride (55 mg, 0.47 mmol) was dissolved with a solution of KOH (53 mg, 0.95 mmol) in EtOH (1.2 ml) at 0 °C and under inert conditions. To this mixture, a previously purged solution of nitroepoxide **1a** (85 mg, 0.47 mmol) in dry EtOH (0.4 ml) was added and the mixture was stirred below 5 °C until consumption of the nitroepoxide (ca. 3 h). Then, solid $NaBH_4$ (37 mg, 0.95 mmol) was added to the cold mixture and stirring maintained for 1.5 h. Then, the mixture was quenched with 5% aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL); the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and finally concentrated under vacuum to afford a yellow oil. The crude product was purified by flash column chromatography (silica gel, EtOAc/MeOH, 9:1 to 7:3) to afford **7** and **8**.

3-Methyl-2-phenylthiomorpholine (7)

Pale yellow solid; yield: 26 mg (28%); R_f = 0.48 (EtOAc/MeOH, 7:3).

IR (KBr): 3360, 3032, 2940, 1574, 1404, 1268, 1070, 707 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H), 3.60 (d, *J* = 9.6 Hz, 1 H), 3.44 (dt, *J* = 12.0, 2.7 Hz, 1 H), 3.25–3.12 (m, 2 H), 3.10–2.98 (m, 1 H), 2.63 (bs, 1 H), 2.59–2.50 (m, 1 H), 0.91 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.77, 128.61, 128.22, 127.66, 58.14, 52.00, 48.09, 30.18, 20.57.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{15}NS$: 193.1; found: 193.1.

2-Methyl-3-phenylthiomorpholine (8)

Yellow oil; yield: 35 mg (39%); R_f = 0.36 (EtOAc/MeOH, 7:3).

IR (KBr): 3307, 3022, 2918, 1595, 1448, 1268, 1024, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.14 (m, 10 H), 4.16 (dd, *J* = 8.3, 1.7 Hz, 1 H, minor), 4.06 (d, *J* = 3.2 Hz, 1 H, major), 3.49 (qd, *J* = 6.6, 3.3 Hz, 1 H, major), 3.32–3.24 (m, 1 H), 3.14–3.05 (m, 1 H), 2.90 (m, 3 H), 2.84–2.68 (m, 4 H), 1.07 (d, *J* = 6.7 Hz, 1 H, major), 0.91 (d, *J* = 6.4 Hz, 1 H, minor).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 128.3, 127.8, 127.2, 127.0, 77.7, 77.2, 60.1, 54.3, 48.2, 45.2, 42.5, 39.1, 27.2, 16.6, 15.4.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{15}NS$: 193.1; found: 193.1.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561466.

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