

Silyl-modified Belluř–Claisen Rearrangement

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Experimental procedures and spectroscopic data/physical characteristics of all compounds prepared in this work

General Experimental

Anhydrous dichloromethane was obtained by heating under reflux over calcium hydride followed by distillation. Anhydrous tetrahydrofuran and diethyl ether were obtained by heating under reflux over sodium–benzophenone ketyl followed by distillation. Anhydrous toluene was obtained by heating under reflux over sodium followed by distillation. Other solvents and reagents were purified according to standard procedures. All purification procedures and reactions were carried out under dry, oxygen-free nitrogen, and all reagents were used as received unless otherwise stated.

General Procedure 1: Preparation of allylic amines.

To a solution of the allylic alcohol (19.96 mmol, 1.0 equiv.) and triphenylphosphine (21.57 mmol, 1.1 equiv.) in tetrahydrofuran (40 mL) was added *N*-bromosuccinimide (21.57 mmol, 1.1 equiv.). After 15 min, morpholine (47.52 mmol, 2.4 equiv.) was added dropwise and the resulting brown solution heated to 70 °C for 2.5 h. Upon cooling to rt, the reaction mixture was diluted with diethyl ether (50 mL) and filtered through a pad of Celite[®]. The filtrate was then extracted with aqueous HCl (1M; 300 mL). The product-containing aqueous layer was then washed with diethyl ether (3 × 200 mL) and made alkaline by the addition of NaOH (16.0 g). The aqueous solution was extracted with diethyl ether (3 × 200 mL) and the combined organic layers dried (Na₂SO₄). Concentration under reduced pressure and chromatography yielded the desired allylic amine.

General Procedure 2: Lewis acid-assisted Belluř–Claisen rearrangement.

Procedure 2A: TiCl₄ Lewis acid

To a solution of titanium tetrachloride (0.118 mmol, 0.1 equiv.) in dichloromethane (10 mL) at rt, was added a solution of the allylic amine (1.18 mmol, 1.0 equiv.) in dichloromethane (1 mL), followed by *N,N*-diisopropylethylamine (1.77 mmol, 1.5 equiv.). The solution was stirred for 5 min before a solution of phenylacetyl chloride (1.42 mmol, 1.2 equiv.) in dichloromethane (1 mL) was added dropwise during 1 min. The dark red mixture was then stirred for 1 h. The reaction was then diluted with diethyl ether (12 mL), washed with aqueous NaOH (1 M; 5 mL). The aqueous layer

was extracted with diethyl ether (3×20 mL), the combined organic layers washed with brine (3×10 mL), and dried (Na_2SO_4). Concentration under reduced pressure and chromatography yielded the desired amide.

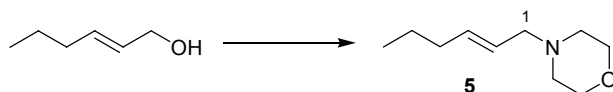
Procedure 2B: “ $\text{TiCl}(\text{OTf})_3$ ” Lewis acid.

To a suspension of silver triflate (0.27 mmol, 0.3 equiv.) in dichloromethane (10 mL) at rt, was added titanium tetrachloride (0.09 mmol, 0.1 equiv.) and the reaction mixture stirred for 5 min. To this mixture was added a solution of the allylic amine (0.87 mmol, 1.0 equiv.) in dichloromethane (1 mL), followed by *N,N*-diisopropylethylamine (1.33 mmol, 1.5 equiv.). The solution was stirred for 5 min before a solution of phenylacetyl chloride (1.06 mmol, 1.2 equiv.) in dichloromethane (5 mL) was added dropwise over 5 h. The dark red reaction mixture was then stirred for a further 2 h. The reaction was then diluted with diethyl ether (12 mL), washed with aqueous NaOH (1 M; 5 mL). The aqueous layer was extracted with diethyl ether (3×20 mL), the combined organic layers washed with brine (3×10 mL), and dried (Na_2SO_4). Concentration under reduced pressure and chromatography yielded the desired amide.

Procedure 2C: TMSOTf.

To a solution of the allylic amine (1.18 mmol, 1.0 equiv.) in dichloromethane (10 mL) at rt, was added TMSOTf (1.18 mmol, 1.0 equiv.) followed by *N,N*-diisopropylethylamine (1.77 mmol, 1.5 equiv.). The solution was stirred for 5 min before a solution of phenylacetyl chloride (1.42 mmol, 1.2 equiv.) in dichloromethane (5 mL) was added dropwise over 4 h. The resulting mixture was then stirred for 30 min. The reaction was then diluted with diethyl ether (10 mL), and treated with aqueous NaOH (1 M; 5 mL) and stirred for a further 10 min. The aqueous layer was extracted with diethyl ether (3×20 mL), the combined organic layers washed with brine (3×10 mL), and dried (Na_2SO_4). Concentration under reduced pressure and chromatography yielded the desired amide.

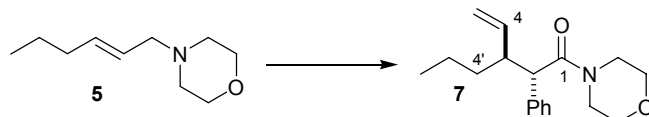
(*E*)-4-(Hex-2-enyl)morpholine (5)



General Procedure 1 was implemented using (*E*)-hex-2-en-1-ol (2.00 g, 19.96 mmol, 1.0 equiv.), triphenylphosphine (5.66 g, 21.57 mmol, 1.1 equiv.), *N*-bromosuccinimide (3.84 g, 21.57 mmol, 1.1 equiv.) and morpholine (4.14 mL, 47.52 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (10% ethyl acetate–petrol) gave *trans*-4-hex-2-enyl-morpholine **8** (2.71 g, 80%) as a pale yellow oil; R_f 0.10 (10% ethyl acetate–petrol); ν_{max} (film) 2958, 2928, 2855, 2805, 2763, 1453, 1366, 1349, 1304, 1119, 1004, 973, 901, 866 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.58–5.28

(2H, m, H-2, H-3), 3.62 (4H, t, J 4.0 Hz, 2 × O-CH₂), 2.84 (2H, d, J 6.5 Hz, CH₂-1), 2.42 (4H, t, J 4.0 Hz, 2 × N-CH₂), 1.98-1.86 (2H, m, CH₂-4), 1.40-1.17 (2H, m, CH₂-5), 0.89-0.69 (3H, m, CH₃-6); δ_C (67.5 MHz, CDCl₃) 134.9 (C-3), 125.9 (C-2), 67.0 (2 × O-CH₂), 61.4 (C-1), 53.5 (2 × N-CH₂), 34.6 (C-4), 22.3 (C-5), 13.7 (C-6); *m/z* (CI) 170 [M+H]⁺, 116, 52 (Found: [M+H]⁺, 170.1549. C₁₀H₁₉NO requires [M+H]⁺, 170.1545).

(2*R,3*R**)-1-Morpholino-2-phenyl-3-vinylhexan-1-one (7)**



General Procedure 2A was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), titanium tetrachloride (12.9 μL, 0.118 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (307 μL, 1.77 mmol, 1.5 equiv.) and phenylacetyl chloride (187 μL, 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave (2*R**,3*R**)-1-morpholino-2-phenyl-3-vinylhexan-1-one **7** (284 mg, 79%) as a pale yellow solid.

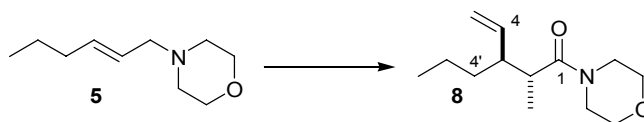
General Procedure 2B was implemented using amine **5** (150 mg, 0.87 mmol, 1.0 equiv.), silver triflate (68.3 mg, 0.27 mmol, 0.3 equiv.), titanium tetrachloride (9.7 μL, 0.09 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (229 μL, 1.33 mmol, 1.5 equiv.) and phenylacetyl chloride (141 μL, 1.06 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave **7** (212 mg, 84%) as a pale yellow solid.

General Procedure 2C was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), TMSOTf (214 μL, 1.18 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (307 μL, 1.77 mmol, 1.5 equiv.) and phenylacetyl chloride (187 μL, 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave **7** (256 mg, 74%) as a pale yellow solid.

For (2*R**,3*R**)-1-morpholino-2-phenyl-3-vinylhexan-1-one **12**; *R*_f 0.42 (50% ethyl acetate–petrol); mp 77-79 °C; ν_{max} (film) 2959, 2931, 2861, 1728, 1640 (C=O), 1455, 1434, 1299, 1266, 1116, 1033, 701 cm⁻¹; δ_H (270 MHz, CDCl₃) 7.31-7.01 (5H, m, Ph), 5.65 (1H, ddd, J 17.0, 10.0, 8.5 Hz, H-4), 5.13-4.99 (2H, m, CH₂-5), 3.67-3.58 (4H, m, 2 × O-CH₂), 3.56-3.33 (4H, m, 2 × N-CH₂), 3.26-3.12 (1H, m, H-2), 2.98-2.82 (1H, m, H-3), 1.42-0.94 (4H, m, CH₂-4', CH₂-5'), 0.78-0.66 (3H, m, CH₃-6'); δ_C (67.5 MHz, CDCl₃) 171.4 (C-1), 140.6 (C-4), 137.9 (*ipso* Ph), 129.4 (*ortho* and *meta* Ph), 127.3 (*para* Ph), 116.4 (C-5), 66.9 (O-CH₂), 66.5 (O-CH₂), 53.1 (2 × N-CH₂), 46.4 (C-2), 42.5

(C-3), 33.8 (C-4'), 20.1 (C-5'), 14.0 (C-6'); m/z (CI) 288 $[M+H]^+$, 244, 220, 206, 176, 154 (Found: $[M+H]^+$, 288.1959. $C_{18}H_{25}NO_2$ requires $[M+H]^+$, 288.1964) (Found: C, 75.27; H, 8.88; N, 4.77. $C_{18}H_{25}NO_2$ requires C, 75.22; H, 8.77; N, 4.87).

(2*R,3*S**)-2-Methyl-1-morpholino-3-vinylhexan-1-one (8)**



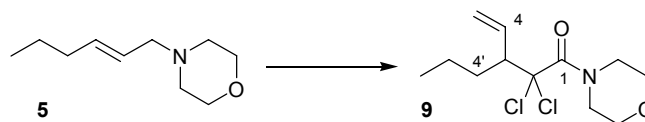
General Procedure 2A was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), titanium tetrachloride (12.9 μL , 0.118 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and propionyl chloride (123 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (2*R**,3*S**)-2-methyl-1-morpholino-3-vinylhexan-1-one **8** (153 mg, 58%) as a colourless oil.

General Procedure 2B was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), silver triflate (91.0 mg, 0.35 mmol, 0.3 equiv.), titanium tetrachloride (12.9 μL , 0.12 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and propionyl chloride (123 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave **8** (265 mg, 96%) as a colourless oil.

General Procedure 2C was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), TMSOTf (214 μL , 1.18 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and propionyl chloride (124 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and subsequent chromatography (20% ethyl acetate–petrol) gave **8** (229 mg, 83%) as a colourless oil.

For (2*R**,3*S**)-2-methyl-1-morpholino-3-vinylhexan-1-one **8**; R_f 0.10 (20% ethyl acetate–petrol); ν_{max} (film) 2959, 2930, 2859, 1640 (C=O), 1461, 1432, 1299, 1266, 1116, 1026, 913 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.67-5.45 (1H, m, H-4), 5.04-4.88 (2H, m, CH_2 -5), 3.61 (4H, t, J 4.0 Hz, $2 \times \text{O-CH}_2$), 3.48 (4H, m, $2 \times \text{N-CH}_2$), 2.72-2.53 (1H, m, H-2), 2.31-2.12 (1H, m, H-3), 1.51-0.98 (7H, m, CH_3 -3', CH_2 -4', CH_2 -5'), 0.91-0.73 (3H, m, CH_3 -6'); δ_{C} (67.5 MHz, CDCl_3) 174.6 (C-1), 140.5 (C-4), 115.9 (C-5), 67.2 (O- CH_2), 66.9 (O- CH_2), 46.8 (N- CH_2), 46.4 (N- CH_2), 42.1 (C-2), 39.2 (C-3), 32.7 (C-4'), 20.3 (C-5'), 14.8 (C-6'), 14.1 (C-3'); m/z (CI) 226 $[\text{M}+\text{H}]^+$, 210, 182, 168 (Found: $[\text{M}+\text{H}]^+$, 226.1801. $\text{C}_{13}\text{H}_{23}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 226.1807) (Found: C, 69.25; H, 10.18; N, 6.35. $\text{C}_{13}\text{H}_{23}\text{NO}_2$ requires C, 69.29; H, 10.29; N, 6.22).

(±)-2,2-Dichloro-1-morpholino-3-vinylhexan-1-one (**9**)



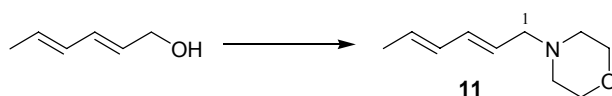
General Procedure 2A was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), titanium tetrachloride (12.9 μL , 0.118 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and dichloroacetyl chloride (136 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave (±)-2,2-dichloro-1-morpholino-3-vinylhexan-1-one **9** (146 mg, 44%) as a pale yellow oil.

General Procedure 2B was implemented using amine **5** (200 mg, 1.18 mmol, 1.0 equiv.), silver triflate (91.0 mg, 0.35 mmol, 0.3 equiv.), titanium tetrachloride (12.9 μL , 0.12 mmol, 0.1 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and dichloroacetyl chloride (136 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave **9** (209 mg, 64%) as a pale yellow oil.

General Procedure 2C was implemented using amine **8** (200 mg, 1.18 mmol, 1.0 equiv.), TMSOTf (214 μL , 1.18 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (307 μL , 1.77 mmol, 1.5 equiv.) and dichloroacetyl chloride (136 μL , 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and subsequent chromatography (30% ethyl acetate–petrol) gave **9** (179 mg, 57%) as a pale yellow oil.

For (±)-2,2-dichloro-1-morpholino-3-vinylhexan-1-one **9**; R_f 0.47 (30% ethyl acetate–petrol); ν_{max} (film) 2961, 2927, 2861, 1659 (C=O), 1454, 1426, 1271, 1239, 1118, 1021, 923, 812, 711, 668 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.86-5.66 (1H, m, H-4), 5.28-5.03 (2H, m, CH_2 -5), 4.05-3.46 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 3.07-2.91 (1H, m, H-3), 1.74-1.08 (4H, m, CH_2 -4', CH_2 -5'), 0.86 (3H, t, J 7.0 Hz, CH_3 -6'); δ_{C} (67.5 MHz, CDCl_3) 163.7 (C-1), 135.9 (C-4), 119.8 (C-5), 87.5 (C-2), 66.6 ($2 \times \text{O-CH}_2$), 57.1 (C-3), 48.4 ($2 \times \text{N-CH}_2$), 34.0 (C-4'), 20.7 (C-5'), 14.0 (C-6'); m/z (CI) 297 [$\text{M}+\text{NH}_4$]⁺, 280 [$\text{M}+\text{H}$]⁺, 227, 210, 202, 86 (Found: [$\text{M}+\text{H}$]⁺, 280.0884. $\text{C}_{12}\text{H}_{19}\text{Cl}_2\text{NO}_2$ requires [$\text{M}+\text{H}$]⁺, 280.0871).

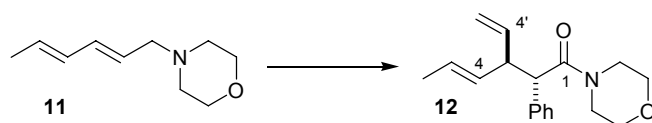
4-((2E,4E)-Hexa-2,4-dienyl)morpholine (**11**)



General Procedure 1 was implemented using sorbyl alcohol (500 mg, 5.09 mmol, 1.0 equiv.), triphenylphosphine (1.44 g, 5.50 mmol, 1.1 equiv.), *N*-bromosuccinimide (979 mg, 5.50 mmol, 1.1 equiv.) and morpholine (1.04 mL, 11.97 mmol, 2.4 equiv.). Concentration under reduced pressure

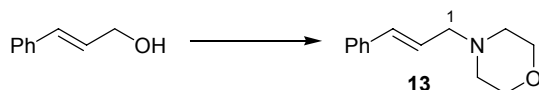
and chromatography (20% ethyl acetate–petrol) gave 4-((2*E*,4*E*)-hexa-2,4-dienyl)morpholine **11** (597 mg, 69%) as a pale yellow oil; R_f 0.13 (20% ethyl acetate–petrol); ν_{\max} (film) 2958, 2855, 2805, 2763, 1453, 1350, 1288, 1118, 1071, 990, 902, 867 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 6.11–5.88 (2H, m, H-3, H-4), 5.66–5.40 (2H, m, H-2, H-5), 3.61 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 2.90 (2H, d, J 7.0 Hz, CH_2 -1), 2.34 (4H, t, J 4.5 Hz, $2 \times \text{N-CH}_2$), 1.66 (3H, d, J 7.0 Hz, CH_3 -6); δ_{C} (67.5 MHz, CDCl_3) 133.9 (C-4), 131.0 (C-3), 129.0 (C-2), 126.7 (C-5), 66.9 ($2 \times \text{O-CH}_2$), 61.1 (C-1), 53.6 ($2 \times \text{N-CH}_2$), 18.0 (C-6); m/z (CI) 168 $[\text{M}+\text{H}]^+$, 88 (Found: $[\text{M}+\text{H}]^+$, 168.1385. $\text{C}_{10}\text{H}_{17}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 168.1388). *In agreement with published data.*¹

(2*R**,3*S**,*E*)-1-Morpholino-2-phenyl-3-vinylhex-4-en-1-one **12**



General Procedure 2C was implemented using amine **15** (200 mg, 1.20 mmol, 1.0 equiv.), TMSOTf (217 μL , 1.20 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (310 μL , 1.79 mmol, 1.5 equiv.) and phenylacetyl chloride (190 μL , 1.44 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (2*R**,3*S**,*E*)-1-morpholino-2-phenyl-3-vinylhex-4-en-1-one **12** (269 mg, 79%) as a pale yellow oil; R_f 0.19 (20% ethyl acetate–petrol); ν_{\max} (film) 2963, 2918, 2855, 1642 (C=O), 1454, 1431, 1270, 1226, 1116, 1032, 969, 917, 701 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.29–7.10 (5H, m, Ph), 5.93–5.77 (1H, m, H-4'), 5.17–4.97 (4H, m, H-4, H-5, CH_2 -5'), 3.71–3.29 (9H, m, H-2, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 3.18–3.04 (1H, m, H-3), 1.39 (3H, d, J 5.5 Hz, CH_3 -6); δ_{C} (67.5 MHz, CDCl_3) 170.7 (C-1), 139.9 (C-4'), 137.9 (*ipso* Ph), 130.5 (C-4), 128.7 (*ortho* Ph), 128.5 (*meta* Ph), 127.2 (*para* Ph), 127.0 (C-5), 115.2 (C-5'), 66.8 (O-CH_2), 66.4 (O-CH_2), 52.8 ($2 \times \text{N-CH}_2$), 46.2 (C-2), 42.4 (C-3), 17.9 (C-6); m/z (CI) 286 $[\text{M}+\text{H}]^+$, 205, 176, 81 (Found: $[\text{M}+\text{H}]^+$, 286.1805. $\text{C}_{18}\text{H}_{23}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 286.1807).

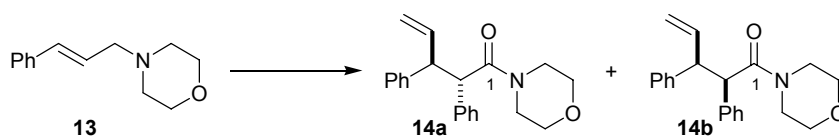
4-Cinnamylmorpholine (**13**)



General Procedure 1 was implemented using cinnamyl alcohol (500 mg, 3.73 mmol, 1.0 equiv.), triphenylphosphine (1.06 g, 4.02 mmol, 1.1 equiv.), *N*-bromosuccinimide (714 mg, 4.02 mmol, 1.1 equiv.) and morpholine (764 μL , 8.76 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave 4-cinnamylmorpholine **13** (518 mg, 67%) as a pale yellow oil; R_f 0.08 (20% ethyl acetate–petrol); ν_{\max} (film) 2957, 2855, 2806, 1495, 1452, 1352, 1277, 1118, 1006, 968, 869, 742, 693 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.39–7.11 (5H, m, Ph), 6.48 (1H, d, J 16.0 Hz, H-3), 6.21 (1H, dt, J 16.0, 6.5 Hz, H-2), 3.68 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 3.08 (2H,

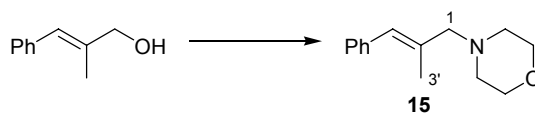
dd, J 6.5, 1.0 Hz, CH_2 -1), 2.44 (4H, t, J 4.5 Hz, $2 \times \text{N-CH}_2$); δ_{C} (67.5 MHz, CDCl_3) 136.9 (*ipso* Ph), 133.3 (C-3), 128.6 (*meta* Ph), 127.6 (*para* Ph), 126.4 (*ortho* Ph), 126.2 (C-2), 67.0 ($2 \times \text{O-CH}_2$), 61.5 (C-1), 53.8 ($2 \times \text{N-CH}_2$); m/z (CI) 204 $[\text{M}+\text{H}]^+$, 112 (Found: $[\text{M}+\text{H}]^+$, 204.1385. $\text{C}_{13}\text{H}_{17}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 204.1388). *In agreement with published data.*²

(2*R,3*R**)-1-Morpholino-2,3-diphenylpent-4-en-1-one (14a) and (2*R**,3*S**)-1-morpholino-2,3-diphenylpent-4-en-1-one (14b)**



General Procedure 2C was implemented using amine **13** (200 mg, 0.98 mmol, 1.0 equiv.), TMSOTf (179 μL , 0.98 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (255 μL , 1.48 mmol, 1.5 equiv.) and phenylacetyl chloride (156 μL , 1.18 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave an inseparable mixture (88:12) of (2*R**,3*R**)-1-morpholino-2,3-diphenylpent-4-en-1-one **14a** and (2*R**,3*S**)-1-morpholino-2,3-diphenylpent-4-en-1-one **14b** (275 mg, 90%) as a colourless solid; R_{f} 0.12 (20% ethyl acetate–petrol); ν_{max} (film) 3029, 2964, 2899, 2855, 1640 (C=O), 1493, 1451, 1302, 1220, 1112, 1032, 918, 876, 743, 701 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.42–7.14 (10H, m, $2 \times \text{Ph}$ -minor), 7.12–6.87 (10H, m, $2 \times \text{Ph}$ -major), 6.23–6.06 (1H, m, H-4-major isomer), 5.81–5.66 (1H, m, H-4-minor isomer), 5.18–5.02 (2H, m, CH_2 -5-major isomer), 4.85–4.67 (2H, m, CH_2 -5-minor isomer), 4.28–4.01 (2H, m, H-2, H-3), 3.80–3.05 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$); δ_{C} (67.5 MHz, CDCl_3) 170.7 (C-1), 140.9 (C-4-minor isomer), 140.2 (C-4-major isomer), 139.0 ($2 \times \text{ipso}$ Ph-minor isomer), 137.3 ($2 \times \text{ipso}$ Ph-major isomer), 128.8 (*meta* Ph), 128.6 (*meta* Ph), 128.4 (*ortho* Ph), 128.1 (*ortho* Ph), 126.9 (*para* Ph), 126.3 (*para* Ph), 116.7 (C-5-minor isomer), 115.4 (C-5-major isomer), 66.9 (O- CH_2), 66.5 (O- CH_2), 53.3 (N- CH_2), 53.0 (N- CH_2), 46.3 (C-2), 42.6 (C-3); m/z (CI) 322 $[\text{M}+\text{H}]^+$, 206, 176 (Found: $[\text{M}+\text{H}]^+$, 322.1796. $\text{C}_{21}\text{H}_{23}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 322.1807).

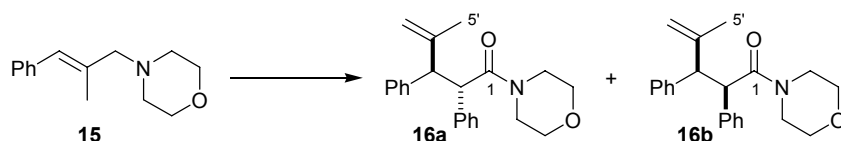
(*E*)-4-(2-Methyl-3-phenylallyl)morpholine (15)



General Procedure 1 was implemented using (*E*)-2-methyl-3-phenyl-2-propen-1-ol (500 mg, 3.37 mmol, 1.0 equiv.), triphenylphosphine (956 mg, 3.64 mmol, 1.1 equiv.), *N*-bromosuccinimide (649 mg, 3.64 mmol, 1.1 equiv.) and morpholine (691 μL , 7.93 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (*E*)-4-(2-methyl-3-phenylallyl)morpholine **15** (655 mg, 88%) as a pale yellow oil; R_{f} 0.17 (20% ethyl acetate–petrol);

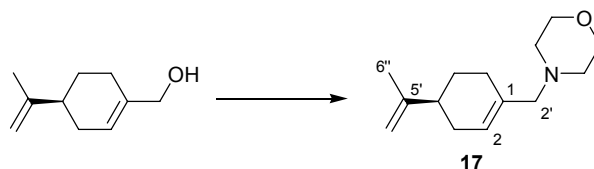
ν_{\max} (film) 2957, 2853, 2806, 1492, 1452, 1345, 1268, 1118, 1071, 1008, 872, 746, 699 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.37-7.13 (5H, m, Ph), 6.42 (1H, s, H-3), 3.71 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 2.99 (2H, d, J 1.0 Hz, CH_2 -1), 2.43 (4H, t, J 4.5 Hz, $2 \times \text{N-CH}_2$), 1.90 (3H, d, J 1.5 Hz, CH_3 -3'); δ_{C} (67.5 MHz, CDCl_3) 137.9 (*ipso* Ph), 135.5 (C-2), 128.9 (*ortho* Ph), 128.1 (*meta* Ph), 127.8 (*para* Ph), 126.4 (C-3), 68.4 (C-1), 67.2 ($2 \times \text{O-CH}_2$), 53.7 ($2 \times \text{N-CH}_2$), 16.8 (C-3'); m/z (CI) 218 $[\text{M}+\text{H}]^+$, 131, 100 (Found: $[\text{M}+\text{H}]^+$, 218.1541. $\text{C}_{14}\text{H}_{19}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 218.1544).

(2*R,3*S**)-4-Methyl-1-morpholino-2,3-diphenylpent-4-en-1-one (16a) and (2*R**,3*R**)-4-methyl-1-morpholino-2,3-diphenylpent-4-en-1-one (16b)**



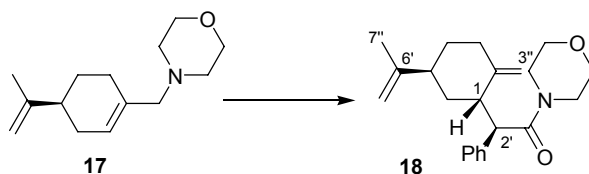
General Procedure 2C was implemented using amine **15** (200 mg, 0.92 mmol, 1.0 equiv.) TMSOTf (167 μL , 0.92 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (239 μL , 1.38 mmol, 1.5 equiv.) and phenylacetyl chloride (146 μL , 1.10 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave an inseparable mixture (84:16) of (2*R**,3*S**)-4-methyl-1-morpholino-2,3-diphenylpent-4-en-1-one **16a** and (2*R**,3*R**)-4-methyl-1-morpholino-2,3-diphenylpent-4-en-1-one **16b** (168 mg, 56%) as a white solid; R_f 0.09 (20% ethyl acetate–petrol); mp 151–153 $^{\circ}\text{C}$ (major isomer); ν_{\max} (film) 3027, 2966, 2918, 2855, 1642 (C=O), 1452, 1431, 1266, 1115, 1031, 910, 740, 699 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.44-7.15 (10H, m, $2 \times \text{Ph}$ -minor), 7.14-6.80 (10H, m, $2 \times \text{Ph}$ -major), 4.93 (2H, d, J 9.5 Hz, CH_2 -5-major isomer), 4.68 (2H, d, J 12.5 Hz, CH_2 -5-minor isomer), 4.43 (1H, d, J 11.5 Hz, H-3-minor isomer), 4.31 (1H, d, J 11.5 Hz, H-2-minor isomer), 4.14 (1H, d, J 11.0 Hz, H-3-major isomer), 4.00 (1H, d, J 11.0 Hz, H-2-major isomer), 3.79-2.99 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 1.71 (3H, s, CH_3 -5'-major isomer), 1.49 (3H, s, CH_3 -5'-minor isomer); δ_{C} (67.5 MHz, CDCl_3) 171.4 (C-1), 137.9 (C-4), 135.4 ($2 \times ipso$ Ph), 128.9 ($2 \times meta$ Ph), 128.1 ($2 \times ortho$ Ph), 127.8 ($2 \times para$ Ph), 126.4 (C-5), 67.2 ($2 \times \text{O-CH}_2$), 68.3 (C-3), 53.7 ($2 \times \text{N-CH}_2$), 53.5 (C-2), 16.8 (C-5'); m/z (CI) 336 $[\text{M}+\text{H}]^+$, 218, 206, 131 (Found: $[\text{M}+\text{H}]^+$, 336.1955. $\text{C}_{22}\text{H}_{25}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 336.1964) (Found: C, 78.66; H, 7.48; N, 4.26. $\text{C}_{22}\text{H}_{25}\text{NO}_2$ requires C, 78.77; H, 7.51; N, 4.18).

(S)-4-((4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl)morpholine (17)



General Procedure 1 was implemented using (*S*)-(-)-perillyl alcohol (500 mg, 3.28 mmol, 1.0 equiv.), triphenylphosphine (930 mg, 3.55 mmol, 1.1 equiv.), *N*-bromosuccinimide (631 mg, 3.55 mmol, 1.1 equiv.) and morpholine (673 μ L, 7.72 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (*S*)-4-((4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl)morpholine **17** (558 mg, 76%) as a colourless oil; R_f 0.13 (20% ethyl acetate–petrol); $[\alpha]_D^{25}$ -59.8 (c 0.97, CHCl_3); ν_{max} (film) 2917, 2854, 2803, 1453, 1347, 1287, 1119, 1004, 887, 866 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.58-5.49 (1H, m, H-2), 4.64 (2H, q, J 1.5 Hz, CH_2 -6'), 3.62 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 2.75 (2H, s, CH_2 -2'), 2.27 (4H, t, J 4.5 Hz, $2 \times \text{N-CH}_2$), 2.15-1.21 (7H, m, H-4, CH_2 -3, CH_2 -5, CH_2 -6), 1.67 (3H, s, CH_3 -6''); δ_{C} (67.5 MHz, CDCl_3) 149.8 (C-5'), 134.3 (C-1), 124.5 (C-2), 108.6 (C-6'), 67.1 ($2 \times \text{O-CH}_2$), 66.0 (C-2'), 53.7 ($2 \times \text{N-CH}_2$), 41.3 (C-4), 30.7 (C-5), 27.8 (C-3), 27.6 (C-6), 20.8 (C-6''); m/z (CI) 222 $[\text{M}+\text{H}]^+$, 152, 100, 86 (Found: $[\text{M}+\text{H}]^+$, 222.1855). $\text{C}_{14}\text{H}_{23}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 222.1858).

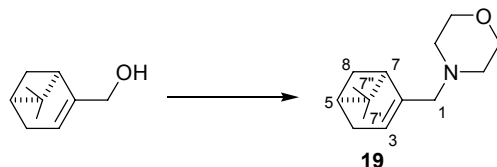
(R)-2-((1*S*,5*S*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl)-1-morpholino-2-phenylethanone (18)



General Procedure 2C was implemented using amine **17** (200 mg, 0.90 mmol, 1.0 equiv.), TMSOTf (164 μ L, 0.90 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (235 μ L, 1.36 mmol, 1.5 equiv.) and phenylacetyl chloride (144 μ L, 1.08 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (*R*)-2-((1*S*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)-1-morpholino-2-phenylethanone **18** (238 mg, 76%) as a colourless solid; R_f 0.11 (20% ethyl acetate–petrol); mp 122–124 $^{\circ}\text{C}$; $[\alpha]_D^{21}$ $+9.7$ (c 0.98, CHCl_3); ν_{max} (film) 2954, 2928, 2853, 1622 (C=O), 1454, 1435, 1258, 1211, 1109, 1067, 1033, 888, 701 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.42-7.14 (5H, m, Ph), 4.86 (1H, d, J 2.0 Hz, H-3''), 4.75 (1H, s, H-3''), 4.54 (2H, d, J 7.0 Hz, CH_2 -7'), 4.09 (1H, d, J 11.0 Hz, H-2'), 3.71-3.39 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 3.38-3.21 (1H, m, H-1), 2.34-1.13 (7H, m, H-5, CH_2 -3, CH_2 -4, CH_2 -6), 1.45 (3H, s, CH_3 -7''); δ_{C} (67.5 MHz, CDCl_3) 171.2 (C-3'), 149.2 (C-2), 148.1 (C-6'), 137.7 (*ipso* Ph), 128.8 (*ortho* Ph), 128.7 (*meta* Ph), 127.3 (*para* Ph), 111.2 (C-7'), 108.8 (C-3''), 67.0 (O- CH_2), 66.7 (O- CH_2), 53.7 ($2 \times \text{N-CH}_2$), 48.2

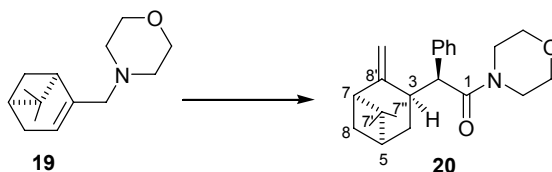
(C-2'), 45.6 (C-5), 39.5 (C-1), 34.1 (C-3), 32.8 (C-2), 31.8 (C-4), 20.8 (C-7''); m/z (CI) 340 $[M+H]^+$, 222, 205, 135, 88 (Found: $[M+H]^+$, 340.2269. $C_{22}H_{29}NO_2$ requires $[M+H]^+$, 340.2277) (Found: C, 77.79; H, 8.75; N, 4.26. $C_{22}H_{29}NO_2$ requires C, 77.84; H, 8.61; N, 4.13).

4-(((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)morpholine (**19**)



General Procedure 1 was implemented using (–)-myrtenol (500 mg, 3.28 mmol, 1.0 equiv.), triphenylphosphine (930 mg, 3.55 mmol, 1.1 equiv.), *N*-bromosuccinimide (631 mg, 3.55 mmol, 1.1 equiv.) and morpholine (673 μ L, 7.72 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave 4-(((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)morpholine **19** (570 mg, 77%) as a colourless oil; R_f 0.12 (20% ethyl acetate–petrol); $[\alpha]_D^{25}$ -4.4 (c 1.14, $CHCl_3$); ν_{max} (film) 2936, 2913, 2854, 2803, 1452, 1346, 1288, 1267, 1119, 1007, 866, 782 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 5.33-5.27 (1H, m, H-3), 3.59 (4H, t, J 4.5 Hz, $2 \times O-CH_2$), 2.79 (1H, dq, J 13.0, 2.0 Hz, H-1), 2.68 (1H, dd, J 13.0, 1.0 Hz, H-1), 2.36-1.97 (9H, m, $2 \times N-CH_2$, CH_2 -4, CH_2 -8, H-7), 1.20 (3H, s, CH_3 -7'), 1.03 (1H, d, J 8.5 Hz, H-5), 0.75 (3H, s, CH_3 -7''); δ_C (67.5 MHz, $CDCl_3$) 145.1 (C-2), 120.1 (C-3), 67.0 ($2 \times O-CH_2$), 64.9 (C-1), 53.9 ($2 \times N-CH_2$), 44.4 (C-5), 40.9 (C-7), 37.9 (C-6), 31.7 (C-4), 31.4 (C-8), 26.3 (C-7''), 21.1 (C-7''); m/z (CI) 222 $[M+H]^+$, 134, 100, 88, 86 (Found: $[M+H]^+$, 222.1857. $C_{14}H_{23}NO$ requires $[M+H]^+$, 222.1858).

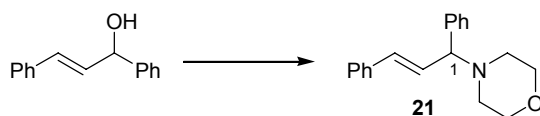
(*S*)-2-(((1*S*,3*R*,5*R*)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)-1-morpholino-2-phenylethanone (**20**)



General Procedure 2C was implemented using amine **19** (200 mg, 0.90 mmol, 1.0 equiv.), TMSOTf (164 μ L, 0.90 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (235 μ L, 1.36 mmol, 1.5 equiv.) and phenylacetyl chloride (144 μ L, 1.08 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (*S*)-2-(((1*S*,3*R*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)-1-morpholino-2-phenylethanone **20** (228 mg, 73%) as a colourless solid; R_f 0.18 (20% ethyl acetate–petrol); mp 116-118 $^{\circ}C$; $[\alpha]_D^{21}$ $+15.5$ (c 1.03, $CHCl_3$); ν_{max} (film) 2976, 2918, 2863, 1639, 1454, 1429, 1270, 1223, 1116, 1033, 740, 700 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 7.36-7.14 (5H, m, Ph), 4.89 (1H, t, J 1.5 Hz, H-9'), 4.70 (1H, t, J 1.5 Hz, H-9'), 3.97

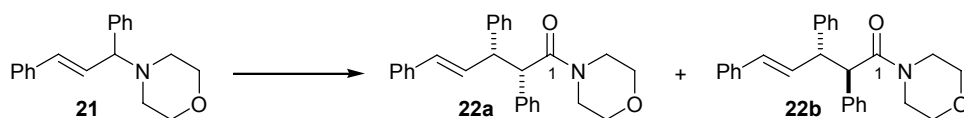
(1H, d, J 10.0 Hz, H-2), 3.70-2.26 (9H, m, 2 × N-CH₂, 2 × O-CH₂, H-3), 2.41 (1H, t, J 5.5 Hz, H-7), 2.28-2.13 (1H, m, H-8_{ax}), 1.90-1.73 (2H, m, H-8_{eq}, H-4_{eq}), 1.42 (1H, dt, J 14.0, 3.0 Hz, H-4_{ax}), 1.17 (3H, s, CH₃-7'), 0.94 (1H, d, J 10.0 Hz, H-5), 0.71 (3H, s, CH₃-7''); δ_C (67.5 MHz, CDCl₃) 172.9 (C-1), 153.0 (C-8'), 138.7 (*ipso* Ph), 129.6 (*meta* Ph), 128.6 (*ortho* Ph), 127.2 (*para* Ph), 110.1 (C-9'), 66.9 (O-CH₂), 66.6 (O-CH₂), 56.3 (C-7), 52.9 (2 × N-CH₂), 46.7 (C-5), 42.6 (C-2), 41.1 (C-3), 36.6 (C-6), 28.1 (C-4), 27.9 (C-8), 25.8 (C-7'), 21.7 (C-7''); *m/z* (CI) 340 [M+H]⁺, 222, 52 (Found: [M+H]⁺, 340.2274. C₂₂H₂₉NO₂ requires [M+H]⁺, 340.2277) (Found: C, 75.37; H, 8.84; N, 3.98. C₂₂H₂₉NO₂ requires C, 77.84; H, 8.61; N, 4.13).

(*E*)-4-(1,3-Diphenylallyl)morpholine (**21**)



General Procedure 1 was implemented using (*E*)-1,3-diphenylprop-2-en-1-ol³ (500 mg, 2.38 mmol, 1.0 equiv.), triphenylphosphine (674 mg, 2.57 mmol, 1.1 equiv.), *N*-bromosuccinimide (457 mg, 2.57 mmol, 1.1 equiv.) and morpholine (487 μL, 5.59 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (*E*)-4-(1,3-diphenylallyl)morpholine **21** (395 mg, 62%) as a pale yellow oil; R_f 0.25 (20% ethyl acetate–petrol); ν_{max} (film) 3082, 3058, 3027, 2959, 2855, 2807, 1599, 1493, 1451, 1267, 1117, 1005, 969, 880, 744, 701 cm⁻¹; δ_H (270 MHz, CDCl₃) 7.51-7.18 (10H, m, Ph), 6.62 (1H, d, J 16.0 Hz, H-3), 6.34 (1H, dd, J 16.0, 9.0 Hz, H-2), 3.84 (1H, d, J 9.0 Hz, H-1), 3.75 (4H, t, J 4.5 Hz, 2 × O-CH₂), 2.68-2.53 (2H, m, N-CH₂), 2.51-2.37 (2H, m, N-CH₂); δ_C (67.5 MHz, CDCl₃) 141.7 (*ipso* Ph), 136.9 (*ipso* Ph), 131.7 (C-3), 131.6 (C-2), 128.8 (*ortho* Ph), 128.7 (*meta* Ph), 128.2 (*meta* Ph), 127.7 (*para* Ph), 127.4 (*para* Ph), 126.5 (*ortho* Ph), 74.9 (C-1), 67.3 (2 × O-CH₂), 52.3 (2 × N-CH₂); *m/z* (CI) 280 [M+H]⁺, 193, 115, 88 (Found: [M+H]⁺, 279.1622. C₁₉H₂₁NO requires [M+H]⁺, 279.1623).

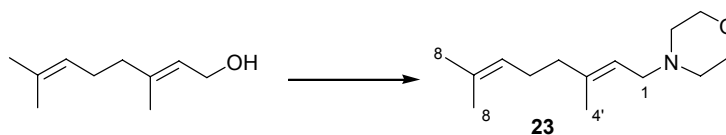
(2*R**,3*R**,*E*)-1-Morpholino-2,3,5-triphenylpent-4-en-1-one (**22a**) and (2*R**,3*S**,*E*)-1-morpholino-2,3,5-triphenylpent-4-en-1-one (**22b**)



General Procedure 2C was implemented using amine **21** (200 mg, 0.72 mmol, 1.0 equiv.), TMSOTf (130 μL, 0.72 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (186 μL, 1.07 mmol, 1.5 equiv.) and phenylacetyl chloride (114 μL, 0.86 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave an inseparable mixture (80:20) of (2*R**,3*R**,*E*)-1-

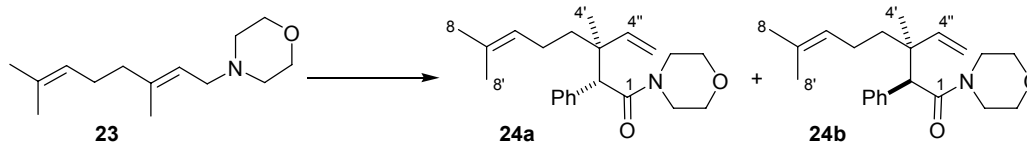
morpholino-2,3,5-triphenylpent-4-en-1-one **22a** and (2*R**,3*R**,*E*)-1-morpholino-2,3,5-triphenylpent-4-en-1-one **22b** (214 mg, 79%) as a colourless solid; R_f 0.11 (20% ethyl acetate–petrol); ν_{\max} (film) 3059, 3027, 2965, 2855, 1640 (C=O), 1453, 1432, 1269, 1223, 1115, 1032, 965, 745, 699 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.49-7.02 (15H, m, 3 \times Ph), 6.63-6.42 (2H, m, H-4-major isomer, H-5-major isomer), 6.18-6.02 (2H, m, H-4-minor isomer, H-5-minor isomer), 4.48-4.36 (1H, m, H-3), 4.27 (1H, d, J 11.0 Hz, H-2-minor isomer), 4.21 (1H, d, J 10.5 Hz, H-2-major isomer), 3.76-3.12 (8H, m, 2 \times N- CH_2 , 2 \times O- CH_2); δ_{C} (67.5 MHz, CDCl_3) 170.6 (C-1-major isomer), 170.4 (C-1-minor isomer), 143.0 (C-4-minor isomer), 141.2 (C-4-major isomer), 137.0 (3 \times *ipso* Ph-minor isomer), 137.5 (3 \times *ipso* Ph-major isomer), 128.9, 128.8, 128.6, 128.5, 128.2, 127.3, 127.0, 126.4, 126.3 (3 \times *ortho* Ph, 3 \times *meta* Ph, 3 \times *para* Ph), 126.2 (C-5), 66.9 (O- CH_2 -major), 66.7 (O- CH_2 -minor), 66.6 (O- CH_2 -major), 66.4 (O- CH_2 -minor), 53.6 (N- CH_2), 52.8 (N- CH_2), 46.4 (C-2), 42.7 (C-3-major), 42.5 (C-3-minor); m/z (CI) 398 $[\text{M}+\text{H}]^+$, 342, 206, 193 (Found: $[\text{M}+\text{H}]^+$, 398.2121. $\text{C}_{27}\text{H}_{27}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 398.2120). Small quantity of major isomer isolated pure, mp 141–143 $^\circ\text{C}$; (Found: C, 81.49; H, 6.90; N, 3.48. $\text{C}_{27}\text{H}_{27}\text{NO}_2$ requires C, 81.58; H, 6.85; N, 3.52).

(*E*)-4-(3,7-Dimethylocta-2,6-dienyl)morpholine (**23**)



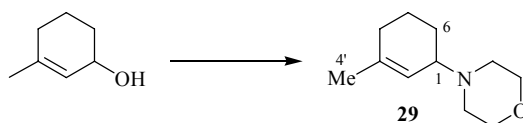
General Procedure 1 was implemented using geraniol (500 mg, 3.24 mmol, 1.0 equiv.), triphenylphosphine (918 mg, 3.50 mmol, 1.1 equiv.), *N*-bromosuccinimide (623 mg, 3.50 mmol, 1.1 equiv.) and morpholine (664 μL , 7.62 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (40% ethyl acetate–petrol) gave (*E*)-4-(3,7-dimethylocta-2,6-dienyl)morpholine **23** (582 mg, 79%) as a colourless oil; R_f 0.11 (40% ethyl acetate–petrol); ν_{\max} (film) 2961, 2916, 2854, 2809, 1452, 1377, 1286, 1269, 1119, 1005, 866 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.16 (1H, t, J 7.0 Hz, H-2), 4.98 (1H, t, J 6.0 Hz, H-6), 3.62 (4H, t, J 4.5 Hz, 2 \times O- CH_2), 2.87 (2H, d, J 7.0 Hz, CH_2 -1), 2.35 (4H, t, J 4.5 Hz, 2 \times N- CH_2), 2.08-1.88 (4H, m, CH_2 -4, CH_2 -5), 1.58 (3H, s, CH_3 -8), 1.54 (3H, s, CH_3 -8), 1.50 (3H, s, CH_3 -4'); δ_{C} (67.5 MHz, CDCl_3) 139.1 (C-3), 131.4 (C-7), 124.1 (C-6), 120.4 (C-2), 67.0 (2 \times O- CH_2), 56.4 (C-1), 53.6 (2 \times N- CH_2), 39.8 (C-4), 26.4 (C-8), 25.7 (C-5), 17.7 (C-8), 16.4 (C-4'); m/z (CI) 224 $[\text{M}+\text{H}]^+$, 154, 124, 100 (Found: $[\text{M}+\text{H}]^+$, 224.2014. $\text{C}_{14}\text{H}_{25}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 224.2014). *In agreement with published data.*⁴

(2*R,3*R**)-3,7-Dimethyl-1-morpholino-2-phenyl-3-vinyloct-6-en-1-one (24a) and (2*R**,3*S**)-3,7-dimethyl-1-morpholino-2-phenyl-3-vinyloct-6-en-1-one (24b)**



General Procedure 2C was implemented using amine **23** (200 mg, 0.9 mmol, 1.0 equiv.), TMSOTf (162 μ L, 0.90 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (232 μ L, 1.34 mmol, 1.5 equiv.) and phenylacetyl chloride (142 μ L, 1.07 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (40% ethyl acetate–petrol) gave an inseparable mixture (97:3) of (2*R**,3*R**)-3,7-dimethyl-1-morpholino-2-phenyl-3-vinyloct-6-en-1-one **24a** and (2*R**,3*S**)-3,7-dimethyl-1-morpholino-2-phenyl-3-vinyloct-6-en-1-one **24b** (277 mg, 89%) as a pale yellow oil; R_f 0.44 (40% ethyl acetate–petrol); ν_{\max} (film) 2967, 2920, 2856, 1642 (C=O), 1454, 1427, 1266, 1221, 1116, 1036, 913, 733, 704 cm^{-1} ; δ_H (270 MHz, CDCl_3) 7.31–7.09 (5H, m, Ph), 6.20 (1H, dd, J 18.0, 11.0 Hz, H-4''-major isomer), 5.89 (1H, dd, J 17.5, 11.0 Hz, H-4''-minor isomer), 5.01 (1H, dd, J 11.0, 1.5 Hz, *cis*-H-5''), 5.00 (1H, t, J 1.5 Hz, H-6), 4.73 (1H, dd, J 17.5, 1.5 Hz, *trans*-H-5''), 3.73–3.20 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 3.03–2.86 (1H, m, H-2), 1.92–1.73 (2H, m, CH_2 -5), 1.60 (3H, s, CH_3 -8), 1.59–1.35 (2H, m, CH_2 -4), 1.51 (3H, s, CH_3 -8'), 1.05 (3H, s, CH_3 -4'); δ_C (67.5 MHz, CDCl_3) 170.8 (C-1), 144.5 (C-4''), 135.9 (*ipso* Ph), 131.1 (C-7), 130.5 (*meta* Ph), 127.9 (*ortho* Ph), 127.1 (*para* Ph), 124.8 (C-6), 113.5 (C-5''), 66.8 (O- CH_2), 66.4 (O- CH_2), 60.3 (C-2), 57.2 ($2 \times \text{N-CH}_2$), 43.7 (C-4), 39.3 (C-3), 25.7 (C-8), 23.0 (C-5), 20.5 (C-4'), 17.6 (C-8'); m/z (CI) 342 $[\text{M}+\text{H}]^+$, 205, 52 (Found: $[\text{M}+\text{H}]^+$, 342.2432. $\text{C}_{22}\text{H}_{31}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 342.2433).

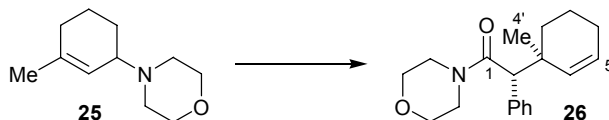
(\pm)-4-(3-Methylcyclohex-2-enyl)morpholine (25)



General Procedure 1 was implemented using (\pm) 3-methyl-2-cyclohexen-1-ol (500 mg, 4.46 mmol, 1.0 equiv.), triphenylphosphine (1.26 g, 4.81 mmol, 1.1 equiv.), *N*-bromosuccinimide (857 mg, 4.81 mmol, 1.1 equiv.) and morpholine (914 μ L, 10.48 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (20% ethyl acetate–petrol) gave (\pm)-4-(3-methylcyclohex-2-enyl)morpholine **25** (430 mg, 54%) as a colourless oil; R_f 0.11 (20% ethyl acetate–petrol); ν_{\max} (film) 2955, 2933, 2853, 1453, 1360, 1286, 1259, 1118, 996, 968, 860, 737, 695 cm^{-1} ; δ_H (270 MHz, CDCl_3) 5.68 (1H, dt, J 10.0, 3.5 Hz, H-1), 5.42 (1H, dq, J 10.0, 1.5 Hz, H-2), 3.65 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 2.64–2.46 (4H, m, $2 \times \text{N-CH}_2$), 1.94–1.84 (2H, m, H-4, H-6), 1.82–1.64 (2H, m, H-4, H-6), 1.61–1.43 (1H, m, H-5), 1.40–1.29 (1H, m, H-5), 1.10 (3H, s, CH_3 -4'); δ_C (67.5 MHz, CDCl_3)

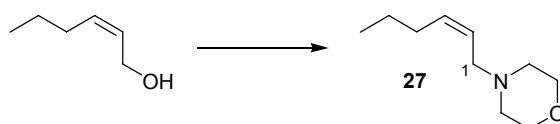
137.6 (C-3), 127.8 (C-2), 67.8 ($2 \times \text{O-CH}_2$), 49.3 (C-1), 46.4 ($2 \times \text{N-CH}_2$), 28.5 (C-6), 25.0 (C-4), 24.7 (C-5), 20.1 (C-4'); m/z (CI) 182 $[\text{M}+\text{H}]^+$, 141, 107, 88 (Found: $[\text{M}+\text{H}]^+$, 182.1547. $\text{C}_{11}\text{H}_{19}\text{NO}$ requires $[\text{M}+\text{H}]^+$, 182.1545). *In agreement with published data.*⁵

(*R)-2-((*S**)-1-Methylcyclohex-2-enyl)-1-morpholino-2-phenylethanone (26)**



General Procedure 2C was implemented using amine **25** (200 mg, 1.10 mmol, 1.0 equiv.), TMSOTf (200 μL , 1.10 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (286 μL , 1.65 mmol, 1.5 equiv.) and phenylacetyl chloride (175 μL , 1.32 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (40% ethyl acetate–petrol) gave (*R**)-2-((*S**)-1-methylcyclohex-2-enyl)-1-morpholino-2-phenylethanone **26** (158 mg, 49%) as a colourless oil; R_f 0.31 (40% ethyl acetate–petrol); ν_{max} (film) 2959, 2923, 2857, 1643 (C=O), 1453, 1427, 1270, 1214, 1116, 1036, 734, 704 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.36-7.13 (5H, m, Ph), 5.73-5.52 (2H, m, H-4, H-5), 3.76-3.23 (8H, m, $2 \times \text{N-CH}_2$, $2 \times \text{O-CH}_2$), 3.10-2.87 (1H, m, H-2), 1.92-1.43 (6H, m, CH_2 -6, CH_2 -7, CH_2 -8), 1.14 (3H, s, CH_3 -4'); δ_{C} (67.5 MHz, CDCl_3) 171.1 (C-1), 136.2 (*ipso* Ph), 134.8 (C-4), 130.4 (*meta* Ph), 128.1 (*ortho* Ph), 127.1 (*para* Ph), 126.1 (C-5), 66.9 (O- CH_2), 66.5 (O- CH_2), 56.5 ($2 \times \text{N-CH}_2$), 46.7 (C-2), 42.2 (C-8), 38.6 (C-3), 34.0 (C-6), 25.0 (C-7), 19.2 (C-4'); m/z (CI) 300 $[\text{M}+\text{H}]^+$, 220, 205, 118, 95 (Found: $[\text{M}+\text{H}]^+$, 300.1969. $\text{C}_{19}\text{H}_{25}\text{NO}_2$ requires $[\text{M}+\text{H}]^+$, 300.1964) (Found: C, 76.05; H, 8.37; N 4.52. $\text{C}_{19}\text{H}_{25}\text{NO}_2$ requires C, 76.22; H, 8.42; N, 4.68).

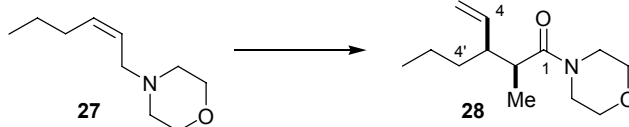
(*Z*)-4-(Hex-2-enyl)morpholine (27)



General Procedure 1 was implemented using *cis*-2-hexen-1-ol (500 mg, 4.99 mmol, 1.0 equiv.), triphenylphosphine (1.41 g, 5.39 mmol, 1.1 equiv.), *N*-bromosuccinimide (960 mg, 5.39 mmol, 1.1 equiv.) and morpholine (1.04 mL, 11.90 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (10% ethyl acetate–petrol) gave (*Z*)-4-(hex-2-enyl)morpholine **27** (599 mg, 71%) as a colourless oil; R_f 0.08 (10% ethyl acetate–petrol); ν_{max} (film) 2959, 2933, 2872, 1744, 1599, 1455, 1328, 1274, 1116, 1085, 971, 813, 730, 647 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 5.57-5.31 (2H, m, H-2, H-3), 3.65 (4H, t, J 4.5 Hz, $2 \times \text{O-CH}_2$), 2.94 (2H, d, J 7.0 Hz, CH_2 -1), 2.38 (4H, t, J 4.5 Hz, $2 \times \text{N-CH}_2$), 2.04-1.88 (2H, m, CH_2 -4), 1.41-1.23 (2H, m, CH_2 -5), 0.84 (3H, t, 7.5 Hz, CH_3 -6); δ_{C} (67.5 MHz, CDCl_3) 133.5 (C-3), 125.6 (C-2), 67.0 ($2 \times \text{O-CH}_2$), 55.5 (C-1), 53.7 ($2 \times \text{N-CH}_2$),

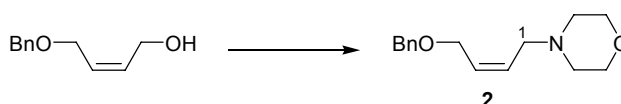
29.6 (C-4), 22.7 (C-5), 13.8 (C-6); m/z (CI) 170 $[M+H]^+$, 87 (Found: $[M+H]^+$, 170.1545. $C_{10}H_{19}NO$ requires $[M+H]^+$, 170.1545).

(2*R,3*R*)-2-Methyl-1-morpholino-3-vinylhexan-1-one (28)**



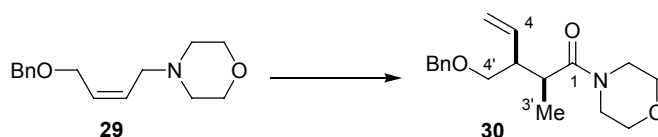
General Procedure 2C was implemented using amine **27** (200 mg, 1.18 mmol, 1.0 equiv.), TMSOTf (214 μ L, 1.18 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (307 μ L, 1.77 mmol, 1.5 equiv.) and propionyl chloride (123 μ L, 1.42 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (30% ethyl acetate–petrol) gave (2*R**,3*R*)-2-methyl-1-morpholino-3-vinylhexan-1-one **28** (228 mg, 79%) as a pale yellow oil; R_f 0.14 (30% ethyl acetate–petrol); ν_{max} (film) 2962, 2930, 2861, 1641 (C=O), 1461, 1432, 1266, 1218, 1117, 1031, 902, 847, 732, 645 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 5.41-5.18 (1H, m, H-4), 4.99-4.84 (2H, m, \underline{CH}_2 -5), 3.62-3.35 (8H, m, $2 \times N-\underline{CH}_2$, $2 \times O-\underline{CH}_2$), 2.51-2.37 (1H, m, H-2), 2.26-2.12 (1H, m, H-3), 1.28-0.94 (4H, m, \underline{CH}_2 -4', \underline{CH}_2 -5'), 0.93 (3H, d, J 7.0 Hz, \underline{CH}_3 -3'), 0.74 (3H, t, J 7.0 Hz, \underline{CH}_3 -6'); δ_C (67.5 MHz, $CDCl_3$) 174.7 (C-1), 139.8 (C-4), 116.8 (C-5), 67.1 (O- \underline{CH}_2), 66.9 (O- \underline{CH}_2), 47.4 (N- \underline{CH}_2), 46.2 (N- \underline{CH}_2), 42.1 (C-2), 39.0 (C-3), 35.1 (C-4'), 20.5 (C-5'), 15.9 (C-6'), 14.0 (C-3'); m/z (CI) 451 $[2M+H]^+$, 226 $[M+H]^+$, 210, 182, 168, 86 (Found: $[M+H]^+$, 226.1801. $C_{13}H_{23}NO_2$ requires $[M+H]^+$, 226.1807).

(*Z*)-4-(4-(Benzyloxy)but-2-enyl)morpholine (29)



General Procedure 1 was implemented using (*Z*)-4-benzyloxy-2-buten-1-ol (500 mg, 2.81 mmol, 1.0 equiv.), triphenylphosphine (795 mg, 3.03 mmol, 1.1 equiv.), *N*-bromosuccinimide (539 mg, 3.03 mmol, 1.1 equiv.) and morpholine (575 μ L, 6.59 mmol, 2.4 equiv.). Concentration under reduced pressure and chromatography (80% ethyl acetate–petrol) gave (*Z*)-4-(4-(benzyloxy)but-2-enyl)morpholine **29** (488 mg, 69%) as a colourless oil; R_f 0.10 (80% ethyl acetate–petrol); ν_{max} (film) 3062, 3029, 2955, 2853, 2811, 1496, 1453, 1324, 1295, 1116, 1073, 1012, 865, 731, 703 cm^{-1} ; δ_H (270 MHz, $CDCl_3$) 7.31-7.14 (5H, m, Ph), 5.78-5.51 (2H, m, H-2, H-3), 4.43 (2H, s, Ph- \underline{CH}_2 -O), 4.01 (2H, d, J 6.5 Hz, \underline{CH}_2 -4), 3.60 (4H, t, J 4.5 Hz, $2 \times O-\underline{CH}_2$), 2.90 (2H, d, J 6.5 Hz, \underline{CH}_2 -1), 2.32 (4H, t, J 4.5 Hz, $2 \times N-\underline{CH}_2$); δ_C (67.5 MHz, $CDCl_3$) 138.3 (*ipso* Ph), 129.8 (C-3), 129.2 (C-2), 128.4 (*ortho* Ph), 127.7 (*meta* Ph), 127.6 (*para* Ph), 72.3 (Ph- \underline{CH}_2 -O), 66.9 ($2 \times O-\underline{CH}_2$), 65.7 (C-4), 55.6 (C-1), 53.6 ($2 \times N-\underline{CH}_2$); m/z (CI) 248 $[M+H]^+$, 108 (Found: $[M+H]^+$, 248.1643. $C_{15}H_{21}NO_2$ requires $[M+H]^+$, 248.1651).

(2*R,3*R**)-3-(Benzyloxymethyl)-2-methyl-1-morpholinopent-4-en-1-one (30)**



General Procedure 2C was implemented using amine **29** (200 mg, 0.81 mmol, 1.0 equiv.), TMSOTf (147 μ L, 0.81 mmol, 1.0 equiv.), *N,N*-diisopropylethylamine (210 μ L, 1.21 mmol, 1.5 equiv.) and propionyl chloride (84.2 μ L, 0.97 mmol, 1.2 equiv.). Concentration under reduced pressure and chromatography (80% ethyl acetate–petrol) gave (2*R**,3*R**)-3-(benzyloxymethyl)-2-methyl-1-morpholinopent-4-en-1-one **30** (93.7 mg, 39%) as a white waxy solid; R_f 0.40 (100% ethyl acetate); ν_{\max} (film) 2967, 2896, 2856, 1641 (C=O), 1454, 1432, 1359, 1266, 1235, 1222, 1116, 1069, 1030, 918, 848, 731, 714 cm^{-1} ; δ_{H} (270 MHz, CDCl_3) 7.37-7.18 (5H, m, Ph), 5.84-5.67 (1H, m, H-4), 5.17-5.02 (2H, m, CH_2 -5), 4.44 (2H, s, Ph- CH_2 -O), 3.69-3.34 (10H, m, CH_2 -4', 2 \times N- CH_2 , 2 \times O- CH_2), 2.99-2.85 (1H, m, H-3), 2.67-2.52 (1H, m, H-2), 1.02 (3H, d, J 7.0 Hz, CH_3 -3'); δ_{C} (67.5 MHz, CDCl_3) 174.6 (C-1), 138.4 (C-4), 137.3 (*ipso* Ph), 128.4 (*meta* Ph), 127.6 (*para* Ph), 127.5 (*ortho* Ph), 117.5 (C-5), 73.3 (Ph- CH_2 -O), 72.2 (C-4'), 67.1 (O- CH_2), 66.9 (O- CH_2), 47.2 (N- CH_2), 46.2 (N- CH_2), 42.2 (C-3), 35.0 (C-2), 15.4 (C-3'); m/z (CI) 304 $[\text{M}+\text{H}]^+$, 196, 143, 91 (Found: $[\text{M}+\text{H}]^+$, 304.1916. $\text{C}_{18}\text{H}_{25}\text{NO}_3$ requires $[\text{M}+\text{H}]^+$, 304.1913).

References

- (1) U. M. Dzhemilev, A. Z. Yakupova, S. K. Minsker and G. A. Tolstikov, *Zh. Org. Khim.*, 1979, **15**, 1164.
- (2) L. M. Lutete, I. Kadota, A. Shibuya and Y. Yamamoto, *Heterocycles*, 2002, **58**, 347.
- (3) T. Kawakami, M. Miyatake, I. Shibata and A. Baba, *J. Org. Chem.*, 1996, **61**, 376.
- (4) K. Takabe, T. Katagiri and J. Tanaka, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 222.
- (5) T. P. Yoon, V. M. Dong and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1999, **121**, 9726.