Supporting Information for the Paper

A One-Pot Three-Component Reaction for the Synthesis of α -(Aminoethyl)- α,β -Enones

Fabio Bertozzi, Magnus Gustafsson and Roger Olsson*

Discovery Chemistry, ACADIA Pharmaceuticals A/S, Fabriksparken 58, DK-2600 Glostrup, Denmark

General.

All reactions were carried out in 7 ml vials purchased from Supelco. All the commercial available compounds were used without further purification. Magnesium iodide (MgI_2 >99%) (Riedel-de Haën) and potassium *tert*-butoxide (KO^tBu >95%) (Aldrich) were stored over an argon atmosphere and quickly weighted before use. $\text{Et}_2\text{Al-I}$ (25wt % solution in toluene) was purchased from Acros. Tetrahydrofuran (THF) and Acetonitrile (CH_3CN) (Fluka) were used without further purification and stored over MS ($4\text{\AA}$). PS-Isocyanate scavenger resin (Argonaut Tech.) and ionic exchange columns (IEC) (Isolute SCX from IST) were used in the purification of all the reactions carried out in a 0.1 mmol scale.

Purification of compounds was achieved by flash chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as the eluting mixture. Diastereoisomeric ratios were determined by ^1H -NMR analysis. All ^1H and ^{13}C -NMR spectra were recorded using a Varian XL 400MHz. NMR spectra were recorded in CDCl_3 solutions; chemical shifts are given in ppm relative to TMS (^1H , 0.0 ppm) or CDCl_3 (^{13}C , 77.2 ± 0.06 ppm). UV-purity was determined using a Waters HPLC-system (600E pump, 2700 autosampler, 996 PDA-detector) (UV scan: 190-450 nm).

General Procedure for the MgI_2 -Promoted One-Pot Three-Component Synthesis of α -(Aminoethyl)- α,β -Enones.

(*E/Z*)-2-(4-Fluorobenzylidene)-1-phenyl-4-(4-methylpiperazin-1-yl)-butan-1-one (4a and 5a).

In a 7ml vial, 4-fluoro-benzaldehyde (**2a**) (124 mg; 108 μ L; 1.0 mmol; 1.0 eq.), MgI_2 (278 mg; 1.0 mmol; 1.0 eq) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μ L; 1.0 mmol; 1.0 eq.) were added sequentially to a solution of 1-methyl-piperazine (**3b**) (100 mg; 111 μ L; 1.0 mmol; 1.0 eq.) in THF (4.0 mL) at room temperature and the resulting mixture was shaken at 80 $^{\circ}\text{C}$. After 7h, the reaction was cooled to ambient temperature and then KO^tBu (168 mg, 1.5 mmol, 1.5 eq.) was added. After 2h the reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (2.0 mL) and the mixture was extracted with EtOAc (5.0 mL). The organic phase was washed with saturated aqueous NaHCO_3 solution (2.0 mL) and brine (2.0 mL), dried over Na_2SO_4 , filtered and concentrated. The corresponding crude reaction mixture was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4% to 8%) to afford a 4:1 mixture of *E/Z* stereoisomers **4a/5a** (255 mg; 72% yield) as a solid.

Data for the *E/Z* stereoisomeric mixture: M.p.: 77.0-78.0 $^{\circ}\text{C}$; R_f : 0.39 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.81-7.76 (m, 4H); 7.51-7.46 (m, 1H, *E*); 7.42-7.37 (m, 2H, *E*); 7.33-7.27 (m, 3H); 7.22-7.18 (m, 2H, *Z*); 7.05-6.96 (m, 4H); 6.91 (s, 1H, *E*); 6.71 (s, 1H, *Z*); 6.69-6.65 (m, 2H, *Z*); 2.87 (dd, 2H, $J=7.2$ Hz and 7.2 Hz, *E*); 2.68 (dd, 2H, $J=7.1$ Hz and 6.9 Hz, *Z*); 2.53-2.45 (m, 6H); 2.43-2.33 (m, 8H); 2.27-2.16 (m, 6H); 2.13 (s, 3H, *E*); 2.09 (s, 3H, *Z*). ^{13}C NMR (100 MHz, CDCl_3) δ 199.5 (*Z*); 198.5 (*E*); 162.7 ($J_{\text{C-F}}=249.4$ Hz, *E*); 162.1 ($J_{\text{C-F}}=247.5$ Hz, *Z*); 140.9 ($J_{\text{C-F}}=1.2$ Hz, *E*); 140.5 ($J_{\text{C-F}}=1.2$ Hz, *Z*); 138.5; 138.4; 136.5; 132.9; 132.1; 131.9; 131.8; 131.0 (2C, $J_{\text{C-F}}=8.1$ Hz, *E*); 130.4 (2C, $J_{\text{C-F}}=8.1$ Hz, *Z*); 130.1 (2C, *E*); 129.9 (*Z*); 129.5 (2C); 128.3(2C); 128.2 (2C); 115.7 (2C, $J_{\text{C-F}}=21.5$ Hz, *E*); 115.1 (2C, $J_{\text{C-F}}=21.5$ Hz, *Z*); 57.2 (*Z*); 56.9 (*E*); 55.1 (2C, *E*); 54.8 (2C, *Z*); 53.0 (2C, *E*); 52.7 (2C, *Z*); 46.1 (*E*); 46.0 (*Z*); 34.9 (*Z*); 25.8 (*E*). HRMS Calcd for $\text{C}_{22}\text{H}_{25}\text{FN}_2\text{O}$ (M^+): 352.1951 Found: 352.1951.

The diastereoselectivity was determined by integration of the peaks at δ 6.91 (**4a**) and δ 6.71 (**5a**).

(*E/Z*)-5,5-Dimethyl-1-phenyl-2-[2-(4-phenylpiperazin-1-yl)-ethyl]-hex-2-en-1-one (4b and 5b).

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing 1-phenyl-piperazine (**3a**) (162 mg; 152 μL ; 1.0 mmol; 1.0 eq.), 3,3-dimethyl-butyraldehyde (**2b**) (100 mg; 125 μL ; 1.0 mmol; 1.0 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μL ; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4%) to afford a 1:1 mixture of *E/Z* stereoisomers **4b/5b** (253 mg; 65% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.59 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.98-7.93 (m, 2H); 7.75-7.70 (m, 2H); 7.56-7.47 (m, 2H); 7.46-7.38 (m, 4H); 7.27-7.20 (m, 4H); 6.92-6.80 (m, 6H); 6.23 (dd, 1H, $J=7.6$ Hz and 7.6 Hz); 5.84 (dd, 1H, $J=7.8$ Hz and 7.8 Hz); 3.09 (dd, 4H, $J=5.1$ Hz and 4.9 Hz); 2.96 (dd, 4H, $J=5.1$ Hz and 4.9 Hz); 2.75 (dd, 2H, $J=7.6$ Hz and 7.1 Hz); 2.66-2.60 (m, 6H); 2.54-2.48 (m, 8H); 2.22 (d, 2H, $J=7.8$ Hz); 1.76 (d, 2H, $J=7.6$ Hz); 0.95 (s, 9H); 0.84 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 199.5; 198.6; 151.3; 141.8; 140.7; 139.9; 138.8; 137.6; 136.9; 133.0; 132.8; 131.6; 129.8; 129.5 (2C); 129.3 (2C); 129.0 (2C); 128.9 (2C); 128.5; 128.4 (2C); 128.1; 127.9 (2C); 119.5; 115.9; 115.8; 57.3; 57.1; 53.0 (2C); 52.7 (2C); 48.9 (2C); 48.7 (2C); 43.4; 42.6; 33.8; 31.5; 31.2; 29.5 (3C); 29.3 (3C); 24.5. HRMS Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}$ (M) $^+$: 390.2671 Found: 390.2663.

(*E/Z*)-5,5-Dimethyl-1-phenyl-2-[2-(4-methylpiperazin-1-yl)-ethyl]-hex-2-en-1-one (4c and 5c).

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing 1-methyl-piperazine (**3b**) (100 mg; 112 μL ; 1.0 mmol; 1.0 eq.), 3,3-dimethylbutyraldehyde (**2b**) (100 mg; 125 μL ; 1.0 mmol; 1.0 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μL ; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4% to 8%) to afford a 1:1 mixture of *E/Z* stereoisomers **4c/5c** (218 mg; 66% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.30 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.88-7.85 (m, 2H); 7.65-7.61 (m, 2H); 7.48-7.41 (m, 2H); 7.39-7.31 (m, 4H); 6.13 (dd, 1H, $J=7.6$ Hz and 7.6 Hz); 5.74 (dd, 1H, $J=7.8$ Hz and 7.8 Hz); 2.65-2.61 (m, 2H); 2.52-2.47 (m, 2H); 2.45-2.34 (m, 12H); 2.33-2.22 (m, 8H); 2.14 (s, 3H); 2.13 (d, 2H, $J=7.6$ Hz); 2.10 (s, 3H); 1.68 (d, 2H, $J=7.8$ Hz); 0.86 (s, 9H); 0.75 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 199.5; 198.6; 141.9; 140.8; 140.2; 138.9; 137.7; 132.9; 131.7; 129.9; 129.7 (2C); 129.5 (2C); 128.5 (2C); 128.1 (2C); 57.4; 57.2; 55.1 (2C); 54.9 (2C); 53.1 (2C); 52.8 (2C); 46.1; 46.0; 43.6; 42.7; 33.9; 31.6; 31.4; 29.7 (3C); 29.5 (3C); 24.7. HRMS Calcd for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}$ (M) $^+$: 328.2514 Found: 328.2518.

(*E/Z*)-5,5-Dimethyl-1-phenyl-2-[2-(benzyl-methylamino)-ethyl]-hex-2-en-1-one (4d** and **5d**).**

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing *N*-methylbenzylamine (**3c**) (121 mg; 129 μL ; 1.0 mmol; 1.0 eq.), 3,3-dimethyl-

butyraldehyde (**2b**) (100 mg; 125 μ L; 1.0 mmol; 1.0 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μ L; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4%) to afford a 2:1 mixture of *E/Z* stereoisomers **4d/5d** (182 mg; 52% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.49 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.94-7.89 (m, 2H); 7.68-7.65 (m, 2H); 7.56-7.48 (m, 4H); 7.46-7.39 (m, 4H); 7.28-7.18 (m, 8H); 6.26 (dd, 1H, $J=7.6$ Hz and 7.6 Hz, major); 5.83 (dd, 1H, $J=7.8$ Hz and 7.6 Hz, minor); 3.54 (s, 2H, major); 3.43 (s, 2H, minor); 2.75-2.70 (m, 2H); 2.60-2.57 (m, 2H); 2.55-2.50 (m, 4H); 2.25 (s, 3H, major); 2.13 (d, 2H, $J=7.6$ Hz, major); 2.08 (s, 3H, minor); 1.77 (d, 2H, $J=7.8$ Hz, minor); 0.89 (s, 9H, major); 0.83 (s, 9H, minor). ^{13}C NMR (100 MHz, CDCl_3) δ 200.1; 198.8; 143.4; 140.7; 140.1; 139.2; 139.1; 139.0; 137.6; 133.2; 131.7; 130.4; 129.7 (2C); 129.5 (2C); 129.3 (2C); 129.2 (2C); 128.7; 128.3 (2C); 128.2; 128.1 (2C); 127.1; 127.0; 62.3; 62.2; 56.8; 56.2; 43.7; 42.9; 42.1; 41.7; 34.0; 31.7; 31.4; 29.7 (3C); 29.5 (3C); 25.1. HRMS Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}$ (M) $^+$: 349.2406 Found: 349.2403.

The diastereoselectivity was determined by integration of the peaks at δ 6.26 (**4d**) and δ 5.83 (**5d**).

(*E/Z*)-4-Diethylamino-2-(4-fluorobenzylidene)-1-phenyl-butan-1-one (4e** and **5e**).**

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing diethylamine (**3d**) (73 mg; 103 μ L; 1.0 mmol; 1.0 eq.), 4-fluoro-benzaldehyde (**2a**) (124 mg; 108 μ L; 1.0 mmol; 1.0 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μ L; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4% to 8%) to afford a 6:1 mixture of *E/Z* stereoisomers **4e/5e** (185 mg; 56% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.27 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.82-7.79 (m, 2H); 7.77-7.73 (m, 2H); 7.52-7.46 (m, 1H);

7.43-7.40 (m, 2H); 7.39-7.34 (m, 4H); 7.26-7.21 (m, 2H); 7.07-7.01 (m, 4H); 6.74 (s, 1H, *Z*); 6.72-6.68 (m, 2H); 2.88-2.84 (m, 4H); 2.66-2.62 (m, 4H); 2.54-2.44 (m, 8H); 0.94 (t, 6H, *J*=7.1 Hz, *E*); 0.91 (t, 6H, *J*=7.2 Hz, *Z*). ¹³C NMR (100 MHz, CDCl₃) δ 200.2 (*Z*); 198.9 (*E*); 162.8 (*J*_{C-F}=249.4 Hz, *E*); 162.1 (*J*_{C-F}=247.9 Hz, *Z*); 140.5 (*J*_{C-F}=1.2 Hz, *E*); 140.2 (*J*_{C-F}=1.2 Hz, *Z*); 138.6 (*E*); 136.2 (*Z*); 133.3; 132.2; 132.2; 131.9; 131.8; 131.2 (2C, *J*_{C-F}=8.5 Hz, *E*); 130.4 (2C, *J*_{C-F}= 8.1 Hz, *Z*); 130.2; 129.9 (2C, *E*); 129.6 (2C, *Z*); 128.5 (2C, *Z*); 128.4 (2C, *E*); 115.8 (2C, *J*_{C-F}=21.5 Hz, *E*); 115.2 (2C, *J*_{C-F}=21.5 Hz, *Z*); 51.9 (*Z*); 51.2 (*E*); 46.8 (*E*); 46.5 (*Z*); 34.5 (2C, *Z*); 25.6 (2C, *E*); 11.7 (2C, *E*); 11.5 (2C, *Z*). HRMS Calcd for C₂₁H₂₄FNO (M)⁺: 325.1842 Found: 325.1858.

The diastereoselectivity was determined by integration of the peaks at δ 0.94 (**4e**) and δ 0.91 (**5e**).

(*E/Z*)-2-(4-Fluorobenzylidene)-4-(4-phenylpiperazin-1-yl)-1-thiophen-2-yl-butan-1-one (4f** and **5f**).**

The reaction was carried out following the general procedure for the MgI₂-promoted one-pot three-component synthesis of α-(aminoethyl)-α,β-enones employing 1-phenyl-piperazine (**3a**) (162 mg; 152 μL; 1.0 mmol; 1.0 eq.), 4-fluoro-benzaldehyde (**2a**) (124 mg; 108 μL; 1.0 mmol; 1.0 eq.) and cyclopropyl-2-thienyl-ketone (**1b**) (152 mg; 130 μL; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH₂Cl₂+MeOH 4%) to afford a 3:1 mixture of *E/Z* stereoisomers **4f/5f** (332 mg; 79% yield) as a solid.

Data for the *E/Z* stereoisomeric mixture: M.p.: dec. 95 °C; R_f: 0.58 (silica gel, CH₂Cl₂+MeOH 4%); ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.69 (m, 2H); 7.64-7.61 (m, 2H); 7.47-7.43 (m, 1H); 7.42-7.37 (m, 3H); 7.28-7.19 (m, 6H); 7.16-7.08 (m, 5H); 6.88-6.79 (m, 6H); 6.76 (s, 1H, minor); 3.01-2.95 (m, 8H); 2.93-2.90 (m, 2H, major); 2.79-2.75 (m, 2H, minor); 2.62-2.51 (m, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 192.1 (minor); 190.7 (major); 162.7 (*J*_{C-F}=249.1 Hz, major); 162.2 (*J*_{C-F}=247.5 Hz, minor);

151.5; 144.3; 141.4; 140.7; 135.9; 134.2; 133.8; 133.7; 132.3; 131.9; 131.8; 131.0 (2C, $J_{\text{C-F}}=8.1$ Hz, major); 130.4 (2C, $J_{\text{C-F}}=8.1$ Hz, minor); 130.1; 129.5; 129.3 (2C); 128.1 (2C); 127.9; 119.8; 119.7; 116.5; 116.2; 116.1; 115.9 (2C, $J_{\text{C-F}}=21.5$ Hz, major); 115.3 (2C, $J_{\text{C-F}}=21.5$ Hz, minor); 113.9; 57.3 (minor); 57.1 (major); 53.1 (2C, major); 52.9 (2C, minor); 49.1 (2C, major); 49.0 (2C, minor); 34.8 (minor); 26.5 (major). HRMS Calcd for $\text{C}_{25}\text{H}_{25}\text{FN}_2\text{OS}$ (M)⁺: 420.1672 Found: 420.1670.

The diastereoselectivity was determined by integration of the peaks at δ 2.93 (**4f**) and δ 2.79 (**5f**).

(*E/Z*)-5,5-Dimethyl-2-[2-(4-methylpiperazin-1-yl)-ethyl]-1-thiophen-2-yl-hex-2-en-1-one (4g** and **5g**).**

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing 1-methyl-piperazine (**3b**) (100 mg; 112 μL ; 1.0 mmol; 1.0 eq.), 3,3-dimethylbutyraldehyde (**2b**) (100 mg; 125 μL ; 1.0 mmol; 1.0 eq.) and cyclopropyl-2-thienylketone (**1b**) (152 mg; 130 μL ; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4% to 8%) to afford a 1:1 mixture of *E/Z* stereoisomers **4g/5g** (232 mg; 69% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.24 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.52 (m, 2H); 7.51-7.48 (m, 2H); 7.03-6.98 (m, 2H); 6.29 (dd, 1H, $J=7.6$ Hz and 7.4 Hz); 5.64 (dd, 1H, $J=7.8$ Hz and 7.8 Hz); 2.58-2.52 (m, 2H); 2.47-2.42 (m, 2H); 2.38-2.28 (m, 12H); 2.23-2.12 (m, 10H); 2.10 (s, 3H); 2.08 (s, 3H); 1.75 (d, 2H, $J=7.8$ Hz); 0.87 (s, 9H); 0.73 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 191.9; 189.8; 145.1; 144.3; 141.1; 140.3; 138.0; 134.0; 133.9; 133.1; 132.9; 129.6; 128.1; 127.7; 57.4; 57.0; 55.0 (2C); 54.9 (2C); 52.7 (2C); 52.6 (2C); 46.0; 43.7; 42.6; 33.7; 31.5; 31.3; 29.7 (3C); 29.4 (3C); 25.4. HRMS Calcd for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{OS}$ (M)⁺: 334.2079 Found: 334.2081.

(*E/Z*)-2-{2-[(2-hydroxyethyl)-methylamino]-ethyl}-5,5-dimethyl-1-thiophen-2-yl-hex-2-en-1-one (4h** and **5h**).**

The reaction was carried out following the general procedure for the MgI_2 -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing 2-(methylamino)-ethanol (**3e**) (75 mg; 80 μL ; 1.0 mmol; 1.0 eq.), 3,3-dimethylbutyraldehyde (**2b**) (100 mg; 125 μL ; 1.0 mmol; 1.0 eq.) and cyclopropyl-2-thienylketone (**1b**) (152 mg; 130 μL ; 1.0 mmol; 1.0 eq.) in THF (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4% to 8%) to afford a 4:1 mixture of *E/Z* stereoisomers **4h/5h** (115 mg; 37% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.12 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.65-7.64 (m, 1H, *Z*); 7.62-7.60 (m, 2H); 7.58-7.55 (m, 1H, *E*); 7.11-7.08 (m, 2H); 6.52 (dd, 1H, $J=7.6$ Hz and 7.6 Hz, *E*); 5.75 (dd, 1H, $J=7.8$ Hz and 7.6 Hz, *Z*); 3.58-3.51 (m, 4H); 3.18 (*OH*); 2.70-2.65 (m, 2H); 2.61-2.54 (m, 8H); 2.52-2.47 (m, 2H); 2.29 (s, 3H, *E*); 2.20 (d, 2H, $J=7.6$ Hz, *E*); 2.17 (s, 3H, *Z*); 1.84 (d, 2H, $J=7.6$ Hz, *Z*); 0.97 (s, 9H, *E*); 0.82 (s, 9H, *Z*). ^{13}C NMR (100 MHz, CDCl_3) δ 192.4 (*Z*); 190.1 (*E*); 144.6; 143.9; 140.7; 140.3; 139.8; 134.8; 134.2; 133.5; 133.3; 130.5; 128.4; 127.9; 59.2 (*Z*); 59.0 (*E*); 58.6 (*Z*); 58.4 (*E*); 57.0 (*Z*); 56.6 (*E*); 43.8; 42.9 (*E*); 41.5 (*E*); 41.4 (*Z*); 33.9; 31.7; 31.4; 29.7 (3C, *E*); 29.5 (3C, *Z*); 25.4 (*E*). HRMS Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_2\text{S}$ (M^+): 309.1762 Found: 309.1745.

The diastereoselectivity was determined by integration of the peaks at δ 6.52 (**4h**) and δ 5.75 (**5h**).

General Procedure for the Et_2AlI -Promoted One-Pot Three-Component Synthesis of α -(Aminoethyl)- α,β -enones.

(*E/Z*)-2-(4-Fluorobenzylidene)-1-phenyl-4-(4-phenylpiperazin-1-yl)-butan-1-one (4i** and **5i**).**

In a 7ml vial, 4-fluoro-benzaldehyde (**2a**) (124 mg; 108 μ L; 1.0 mmol; 1.0 eq.), $\text{Et}_2\text{Al-I}$ (1.47 mL; 1.5 mmol; 1.5 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μ L; 1.0 mmol; 1.0 eq.) were added sequentially to a solution of 1-phenyl-piperazine (**3a**) (162 mg; 152 μ L; 1.0 mmol; 1.0 eq.) in CH_3CN (4.0 mL) at room temperature. The resulting mixture was vigorously shaken at room temperature overnight and then KO^tBu (168 mg, 1.5 mmol, 1.5 eq.) was added. After 2h the reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (2.0 mL) and the mixture was extracted with EtOAc (5.0 mL). The organic phase was washed with saturated aqueous NaHCO_3 solution (2.0 mL) and brine (2.0 mL), dried over Na_2SO_4 , filtered and concentrated. The corresponding crude reaction mixture was purified by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2+\text{MeOH}$ 4%) to afford a 6:1 mixture of *E/Z* stereoisomers **4i/5i** (238 mg; 58% yield) as a solid.

Data for the *E/Z* stereoisomeric mixture: M.p.: 140.0-141.5 $^\circ\text{C}$; R_f : 0.41 (silica gel, $\text{CH}_2\text{Cl}_2+\text{MeOH}$ 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.89-7.84 (m, 4H); 7.57-7.52 (m, 2H); 7.48-7.43 (m, 4H); 7.42-7.36 (m, 4H); 7.28-7.21 (m, 4H); 7.14-7.08 (m, 2H); 7.01 (s, 1H, *E*); 6.90-6.82 (m, 6H); 6.81 (s, 1H, *Z*); 6.78-6.73 (m, 2H); 3.05 (dd, 4H, $J=4.9$ Hz and 4.9 Hz, *E*); 2.98 (dd, 2H, $J=6.9$ Hz and 6.9 Hz, *E*); 2.94-2.91 (m, 4H, *Z*); 2.80 (dd, 2H, $J=6.9$ Hz and 6.9 Hz, *Z*); 2.63 (dd, 2H, $J=6.9$ Hz and 6.9 Hz, *E*); 2.61-2.56 (m, 6H); 2.54-2.50 (m, 4H, *Z*). ^{13}C NMR (100 MHz, CDCl_3) δ 199.7 (*Z*); 198.7 (*E*); 162.8 ($J_{\text{C-F}}=249.4$ Hz, *E*); 162.2 ($J_{\text{C-F}}=247.8$ Hz, *Z*); 151.5 (*E*); 141.0 ($J_{\text{C-F}}=1.1$ Hz, *E*); 140.5 ($J_{\text{C-F}}=1.1$ Hz, *Z*); 138.8; 138.5; 136.5; 133.1; 132.3; 131.9; 131.8; 131.1 (2C, $J_{\text{C-F}}=8.1$ Hz, *E*); 130.5 (2C, $J_{\text{C-F}}=8.1$ Hz, *Z*); 130.1 (2C); 129.6; 129.3 (2C); 128.8; 128.5; 128.4 (2C); 128.3; 119.8; 116.2; 116.1; 115.9 (2C, $J_{\text{C-F}}=21.5$ Hz, *E*); 115.2 (2C, $J_{\text{C-F}}=21.5$ Hz, *Z*); 57.3 (*Z*); 57.1 (*E*); 53.2 (2C, *E*); 52.9 (2C, *Z*); 49.1 (2C, *E*); 48.9 (2C, *Z*); 35.0 (*Z*); 25.8 (*E*). HRMS Calcd for $\text{C}_{27}\text{H}_{27}\text{FN}_2\text{O}$ (M^+): 414.2107 Found: 414.2094.

The diastereoselectivity was determined by integration of the peaks at δ 7.01 (**4i**) and δ 6.81 (**5i**).

(*E/Z*)-2-[2-(4-Phenylpiperazin-1-yl)-ethyl]-1-phenyl-oct-2-en-1-one (4j** and **5j**).**

The reaction was carried out following the general procedure for the Et_2AlI -promoted one-pot three-component synthesis of α -(aminoethyl)- α,β -enones employing 1-phenyl-piperazine (**3a**) (162 mg; 152 μL ; 1.0 mmol; 1.0 eq.), 1-hexanal (**2c**) (100 mg; 120 μL ; 1.0 mmol; 1.0 eq.) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μL ; 1.0 mmol; 1.0 eq.) in CH_3CN (4.0 mL). The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 4%) to afford a 1:1 mixture of *E/Z* stereoisomers **4j/5j** (258 mg; 66% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.56 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 7.88-7.85 (m, 2H); 7.64-7.60 (m, 2H); 7.45-7.30 (m, 8H); 7.19-7.12 (m, 4H); 6.84-6.73 (m, 4H); 6.09 (dd, 1H, $J=7.4$ Hz and 7.4 Hz); 5.67 (dd, 1H, $J=7.6$ Hz and 7.6 Hz); 3.03 (dd, 4H, $J=5.1$ Hz and 4.9 Hz); 2.86 (dd, 4H, $J=5.1$ Hz and 4.9 Hz); 2.67 (dd, 4H, $J=5.1$ Hz and 4.9 Hz); 2.59-2.51 (m, 6H); 2.46-2.38 (m, 6H); 2.23 (dd, 2H, $J=14.6$ Hz and 7.2 Hz); 1.79 (dd, 2H, $J=14.8$ Hz and 7.2 Hz); 1.42-1.34 (m, 2H); 1.31-1.17 (m, 8H); 1.14-1.04 (m, 2H); 0.83 (t, 3H, $J=7.2$ Hz); 0.76 (t, 3H, $J=7.1$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 199.6; 198.7; 151.4; 151.2; 146.7; 138.9; 138.8; 138.4; 138.0; 133.8; 133.2; 133.1; 131.8; 129.7 (2C); 129.4; 129.3 (2C); 129.2; 128.7; 128.6 (2C); 128.3; 128.2 (2C); 120.1; 119.8; 117.0; 116.3; 116.2; 57.5; 57.2; 53.0 (2C); 52.8 (2C); 48.7 (2C); 48.6 (2C); 33.4; 31.8; 31.4; 30.0; 29.2; 29.1; 28.9; 24.3; 22.7; 22.5; 14.2; 14.1. HRMS Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}$ (M) $^+$: 390.2671 Found: 390.2665.

(*E/Z*)-2-Benzylidene-1-phenyl-4-(piperidin-1-yl)-butan-1-one.

In a 4 ml vial, benzaldehyde (10.6 mg; 10 μ l; 0.1 mmol; 1.0 eq.), MgI_2 (27.8 mg; 0.1 mmol; 1.0 eq.) and cyclopropyl phenyl ketone (**1a**) (14.5 mg; 14 μ l; 0.1 mmol; 1.0 eq.) were added sequentially to a solution of piperidine (**3f**) (8.5 mg; 10 μ L; 1.0 mmol; 1.0 eq.) in THF (0.4 mL) at r.t., and the resulting mixture was shaken at 80 $^\circ\text{C}$. After 7h, the reaction was cooled to ambient temperature and then KO^tBu (16.8 mg, 1.5 mmol, 1.5 eq.) was added. After 2h the reaction was quenched with a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (0.5 mL) and extracted with CH_2Cl_2 (3.0 mL). The phases were separated and PS-Isocyanate scavenger resin (200 mg, 0.3 mmol; 3.0 eq.) was then added to the organic solution. The corresponding mixture was shaken at r.t. for 15 h (to scavenge the excess of the amine). Filtration (to get rid of polymeric resin) and evaporation of the solvent afforded the crude product, which was subjected to purification by IEC (Isolute SCX) affording a 4:1 mixture of *E/Z* stereoisomers **4I/5I** (18 mg; 57% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture: R_f : 0.29 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 8.05-8.02 (m, 2H, minor); 7.78-7.74 (m, 2H); 7.49-7.44 (m, 1H, major); 7.42-7.36 (m, 4H); 7.34-7.29 (m, 6H); 7.28-7.23 (m, 2H); 7.20-7.18 (m, 1H); 7.02-6.97 (m, 3H); 6.73 (s, 1H, minor); 2.90 (dd, 2H, $J=7.6$ Hz and 7.6 Hz, major); 2.68 (dd, 2H, $J=7.2$ Hz and 7.1 Hz, minor); 2.54-2.44 (m, 6H); 2.40-2.33 (m, 8H); 2.32-2.26 (m, 4H); 1.46-1.38 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.1 (minor); 199.0 (major); 140.9; 140.2; 138.7; 135.7; 133.0; 132.6; 132.1; 130.1 (2C); 129.6; 129.3 (2C); 128.8; 128.7 (2C); 128.6; 128.4; 128.3 (2C); 128.2; 128.1; 128.0; 127.6; 57.9; 57.5; 56.9; 54.3; 54.1; 51.1; 25.7; 25.5; 24.4; 24.3.

HRMS Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}$ (M) $^+$: 319.1936 Found: 319.1931.

The diastereoselectivity was determined by integration of the peaks at δ 2.90 (**4I**) and δ 2.68 (**5I**).

Alternative Approach for the Synthesis of α -(Aminoethyl)- α,β -Enones.

anti-3-Benzoyl-2-(2,2-dimethylpropyl)-1-benzyl-pyrrolidine (**6**).

In a 7ml vial, 3,3-dimethyl-butyraldehyde (**2b**) (100 mg; 125 μ L; 1.0 mmol; 1.0 eq.), MgI_2 (278 mg; 1.0 mmol; 1.0 eq) and cyclopropyl-phenyl-ketone (**1a**) (146 mg; 138 μ L; 1.0 mmol; 1.0 eq.) were added sequentially to a solution of benzylamine (107 mg; 109 μ L; 1.0 mmol; 1.0 eq.) in THF (4.0 mL) at room temperature and the resulting mixture was shaken at 80 °C. After 6h, the reaction was cooled to ambient temperature and then quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (2.0 mL). The mixture was extracted with EtOAc (5.0 mL) and the organic phase washed with saturated aqueous NaHCO_3 solution (2.0 mL) and brine (2.0 mL), dried over Na_2SO_4 , filtered and concentrated. The corresponding crude reaction mixture, consisting of a >99:1 mixture of diastereoisomers, was purified by flash chromatography on silica gel (CH_2Cl_2 +MeOH 1%) to afford the major diastereoisomer **6** (225 mg; 66% yield) as a solid.

Anti diastereoisomer (**6**): M.p.: dec. 57 °C; R_f : 0.53 (silica gel, CH_2Cl_2 +MeOH 4%); ^1H NMR (400 MHz, CDCl_3) δ 8.01-7.96 (m, 2H); 7.58-7.53 (m, 1H); 7.50-7.44 (m, 2H); 7.42-7.38 (m, 2H); 7.34-7.29 (m, 2H); 7.27-7.21 (m, 1H); 4.12 (d, 1H, J =12.9 Hz); 3.79 (ddd, 1H, J =10.2 Hz and 4.5 Hz and 2.3 Hz); 3.45 (d, 1H, J =12.9 Hz); 3.40 (ddd, 1H, J =9.2 Hz and 4.5 Hz and 1.4 Hz); 2.89-2.82 (m, 1H); 2.38-2.22 (m, 2H); 1.78 (dd, 1H, J =14.4 Hz and 1.6 Hz); 1.75-1.71 (m, 1H); 1.58 (dd, 1H, J =14.4 Hz and 9.5 Hz); 0.87 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 201.5; 139.6; 136.5; 133.3; 129.3 (2C); 128.9 (2C); 128.7 (3C); 128.5; 127.2; 62.4; 58.8; 53.8; 51.9; 50.2; 30.5; 30.4; 30.2 (3C). HRMS Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}$ (M) $^+$: 335.2249 Found: 335.2250.

(*E/Z*)-5,5-Dimethyl-1-phenyl-2-[2-(benzyl-methylamino)-ethyl]-hex-2-en-1-one (4d and 5d).

In a 4 mL vial, MeI (63.5 mg; 28.0 μ L; 0.45 mmol; 3.0 eq.) was added to a solution of **6** (50 mg; 0.15 mmol; 1.0 eq.) in CH_3CN (2.0 mL) at room temperature, and the resulting mixture was vigorously shaken. After 16h, the solvent and the excess of MeI were removed under reduced pressure; the corresponding ammonium salt was then dissolved in MeOH (2.0 mL) and KOH (17.0 mg; 0.30 mmol; 2.0 eq.) was added. After 1h, the reaction was quenched with brine (0.5 mL), the organic phase was dried over Na_2SO_4 , filtered and concentrated to afford a crude reaction, consisting of a 1:2 mixture of **4d/5d**.

Stereochemical assignment *via* NOESY spectroscopy of compounds 4a/5a.

The E/Z stereochemistry was determined by NOESY experiments on a 4:1 mixture of both stereoisomers **4a** (major) and **5a** (minor) (see figure below). NOESY correlations were observed between $H_a \rightarrow H_{b'}$; $H_a \rightarrow H_{c'}$ and $H_{b''} \rightarrow H_3$ in the major isomer (*E*). Furthermore, no correlation was observed between $H_a \rightarrow H_{c'}$ in the minor isomer (*Z*).

E-stereoisomer

Z-stereoisomer