Supporting Information

An Addition Reaction of Ethers to Imines Initiated by Dimethylzinc

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Experimental Section

General. Purification was carried out using silica gel column chromatography. NMR (500 MHz for ^1H and 125 MHz for ^{13}C) was measured in CDCl_3 and chemical shift was presented in ppm δ . The wave-numbers of maximum absorption peaks of IR spectroscopy were presented in cm^{-1} .

The General Procedure for Addition of Ethers to Imines (Method A). *N*-[4-methoxy- α -(tetrahydrofuran-2-yl)benzyl]-4-toluenesulfonamide (**2k**) (Table 1, entry 6): a 1.0 M solution of dimethylzinc in hexane (2.4 mL, 2.4 mmol, 3.0 equiv) was added to a solution of imine **1c** (232 mg, 0.80 mmol) in THF (17.5 mL, 0.22 mol, 270 equiv) at room temperature. The mixture was vigorously stirred for 16 h. The reaction was quenched by the addition of 10% hydrochloric acid, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, and then concentrated. The purification of the

resulting crude material by column chromatography (hexane/ethyl acetate 7/3) gave THF adduct **2k** (233 mg, 80%) as a 3:2 mixture of the diastereomers. The diastereomers were separated by column chromatography (chloroform/diethyl ether 19/1).

The major and less polar isomer was recrystallized from ethyl acetate–hexane to give colorless prisms of mp 143.0–143.5 °C. ¹H NMR: 7.45 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 5.48 (br d, *J* = 5.7 Hz, 1H, NH), 4.09 (dd, *J* = 5.7, 5.7 Hz, 1H, ArCH), 3.92 (m, 1H, OCH), 3.75 (m, 2H, OCH₂), 3.72 (s, 3H, OCH₃), 2.33 (s, 3H, ArCH₃), 1.82 (m, 2H, CH₂), 1.73 (m, 1H, CH₂), 1.66 (m, 1H, CH₂). ¹³C NMR: 158.9 (MeOC), 142.6 (C), 137.5 (C), 130.4 (C), 129.0 (CH), 128.6 (CH), 127.1 (CH), 113.5 (CH), 81.7 (OCH), 68.5 (OCH₂), 60.7 (ArCH), 55.1 (OCH₃), 28.3 (CH₂), 25.5 (CH₂), 21.3 (CH₃). IR (KBr): 3167, 2924, 1609, 1508, 1454, 1323, 1238, 1083, 1057. EIMS (*m/z*): 290 (*M*⁺ – C₄H₈O), 206 (*M*⁺ – Ts), 155 (Ts), 134, 91 (tolyl), 71 (C₄H₈O). Anal. Calcd. for C₁₉H₂₃NO₄S: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.16; H, 6.49; N, 3.90.

The minor and more polar isomer was recrystallized from ethyl acetate–hexane to give a white powder of mp 128.0–128.5 °C. ¹H NMR: 7.46 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 5.33 (br d, *J* = 7.7 Hz, 1H, NH), 4.27 (dd, *J* = 4.3, 7.7 Hz, 1H, ArCH), 3.12 (dt, *J* = 4.3, 7.1 Hz, 1H, OCH), 3.74 (s, 3H, OCH₃), 3.65 (m, 2H, OCH₂), 2.34 (s, 3H, ArCH₃), 1.82 (m, 1H, CH₂), 1.70 (m, 1H, CH₂), 1.53 (m, 1H, CH₂), 1.47 (m, 1H, CH₂). ¹³C NMR: 159.0 (MeOC), 142.7 (C), 137.6 (C), 129.2 (C), 129.2 (CH), 129.1 (CH), 127.1 (CH), 113.4 (CH), 81.5 (OCH), 68.7 (OCH₂), 60.2 (ArCH), 55.2 (OCH₃), 27.6 (CH₂), 25.5 (CH₂), 21.4 (CH₃). IR (KBr): 3275, 2955, 2874, 1612, 1516, 1458, 1319, 1161, 1029. EIMS (*m/z*): 290 (*M*⁺ – C₄H₈O), 206 (*M*⁺ – Ts), 155 (Ts), 134, 91 (tolyl), 71 (C₄H₈O). Anal. Calcd. for C₁₉H₂₃NO₄S: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.34; H, 6.55; N, 3.89.

***N*-[α -(Tetrahydrofuran-2-yl)benzyl]-4-toluenesulfonamide (2a):** purified by column chromatography (hexane/acetone 4/1) to give a 3:2 mixture of the diastereomers, which were separated by column chromatography (hexane/ethyl acetate 5/1 to 3/1).

The major and less polar isomer was recrystallized from ethyl acetate–hexane to give colorless needles of mp 147.5–148.5 °C. ¹H NMR: 7.48 (d, *J* = 8.3 Hz, 2H), 7.12 (m, 3H), 7.07 (m, 4H), 5.45 (br d, *J* =

5.8 Hz, 1H, NH), 4.17 (dd, $J = 5.8, 5.8$ Hz, 1H, ArCH), 3.95 (m, 1H, OCH), 3.80 (m, 1H, OCH₂), 3.77 (m, 1H, OCH₂), 2.33 (s, 3H, CH₃), 1.85 (m, 2H, CH₂), 1.77 (m, 1H, CH₂), 1.72 (m, 1H, CH₂). ¹³C NMR: 142.8 (C), 138.4 (C), 137.4 (C), 129.0 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.1 (CH), 81.7 (OCH), 68.6 (OCH₂), 61.2 (ArCH), 28.4 (CH₂), 25.5 (CH₂), 21.4 (CH₃). IR (nujol): 3300, 1600, 1320, 1160, 1070. EIMS (m/z): 260 ($M^+ - C_4H_7O$), 176 ($M^+ - Ts$), 155 (Ts), 71 (C_4H_7O). Anal. Calcd. for C₁₈H₂₁NO₃S: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.19; H, 6.46; N, 4.21.

The minor and more polar isomer was recrystallized from ethyl acetate–hexane to give colorless prisms of mp 139–140.5 °C. ¹H NMR: 7.46 (d, $J = 8.3$ Hz, 2H), 7.12 (m, 3H), 7.05 (m, 4H), 5.37 (br d, $J = 7.5$ Hz, 1H, NH), 4.32 (dd, $J = 4.6, 7.5$ Hz, 1H, ArCH), 4.14 (dt, $J = 4.6, 6.9$ Hz, 1H, OCH), 3.65 (dt, $J = 1.9, 6.7$ Hz, 2H, OCH₂), 2.33 (s, 3H, CH₃), 1.81 (m, 1H, CH₂), 1.69 (m, 1H, CH₂), 1.52 (m, 1H, CH₂), 1.44 (m, 1H, CH₂). ¹³C NMR: 142.8 (C), 137.4 (C), 137.1 (C), 129.2 (CH), 128.0 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 81.4 (OCH), 68.7 (OCH₂), 60.6 (ArCH), 27.6 (CH₂), 25.4 (CH₂), 21.4 (CH₃). IR (nujol): 3250, 1600, 1320, 1160, 1060. EIMS (m/z): 260 ($M^+ - C_4H_7O$), 176 ($M^+ - Ts$), 155 (Ts), 71 (C_4H_7O). Anal. Calcd. for C₁₈H₂₁NO₃S: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.04; H, 6.41; N, 4.26.

***N*-[4-Chloro- α -(tetrahydrofuran-2-yl)benzyl]-4-toluenesulfonamide (2b):** purified by column chromatography (hexane/acetone 4/1) to give a 11:9 mixture of the diastereomers, which were separated by column chromatography (chloroform/diethyl ether 19/1).

The major and less polar (*RS,RS*)-isomer was recrystallized from ethyl acetate–hexane to give colorless prisms of mp 126.5–127.5 °C. ¹H NMR: 7.44 (d, $J = 8.0$ Hz, 2H), 7.09 (m, 4H), 7.01 (d, $J = 8.2$ Hz, 2H), 5.37 (br d, $J = 5.5$ Hz, 1H, NH), 4.15 (dd, $J = 5.5, 5.5$ Hz, 1H, ArCH), 3.90 (m, 1H, OCH), 3.81 (m, 1H, OCH₂), 3.74 (m, 1H, OCH₂), 2.36 (s, 3H, CH₃), 1.85 (m, 2H, CH₂), 1.79 (m, 1H, CH₂), 1.70 (m, 1H, CH₂). ¹³C NMR: 143.2 (C), 137.3 (C), 137.0 (C), 133.3 (C), 129.2 (CH), 128.9 (CH), 128.3 (CH), 127.1 (CH), 81.5 (OCH), 68.7 (OCH₂), 60.6 (ArCH), 28.5 (CH₂), 25.5 (CH₂), 21.4 (CH₃). IR (KBr): 3263, 2947, 2885, 1597, 1497, 1420, 1327, 1165, 1088, 1065, 1026. EIMS (m/z): 296 ($M^+ + 2 - C_4H_7O$), 294 ($M^+ - C_4H_7O$), 212 ($M^+ + 2 - Ts$), 210 ($M^+ - Ts$), 155 (Ts), 71 (C_4H_7O). Anal. Calcd. for C₁₈H₂₀ClNO₃S: C, 59.09; H, 5.51; N, 3.83. Found: C, 59.06; H, 5.48; N, 3.76.

The minor and more polar (*RS,SR*)-isomer was recrystallized from ethyl acetate–hexane to give a white powder of mp 119.5–120.5 °C. ¹H NMR: 7.45 (d, *J* = 8.2 Hz, 2H), 7.08 (m, 4H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.63 (br d, *J* = 7.8 Hz, 1H, NH), 4.29 (dd, *J* = 4.4, 7.8 Hz, 1H, ArCH), 4.12 (m, 1H, OCH), 3.64 (m, 2H, OCH₂), 2.35 (s, 3H, CH₃), 1.82 (m, 1H, CH₂), 1.71 (m, 1H, CH₂), 1.46 (m, 2H, CH₂). ¹³C NMR: 143.2 (C), 137.3 (C), 135.6 (C), 133.4 (C), 129.5 (CH), 129.2 (CH), 128.1 (CH), 127.0 (CH), 81.1 (OCH), 68.7 (OCH₂), 60.1 (ArCH), 27.6 (CH₂), 25.4 (CH₂), 21.4 (CH₃). IR (KBr): 3449, 3283, 2974, 2848, 1493, 1447, 1435, 1327, 1165, 1092. EIMS (*m/z*): 296 (*M*⁺ + 2 – C₄H₇O), 294 (*M*⁺ – C₄H₇O), 212 (*M*⁺ + 2 – Ts), 210 (*M*⁺ – Ts), 155 (Ts), 71 (C₄H₇O). Anal. Calcd. for C₁₈H₂₀ClNO₃S: C, 59.09; H, 5.51; N, 3.83. Found: C, 58.80; H, 5.51; N, 3.83.

Table 1, entry 1: *N*-[α -(1,3-dioxolan-2-yl)benzyl]-4-toluenesulfonamide (2c) and *N*-[α -(1,3-dioxolan-4-yl)benzyl]-4-toluenesulfonamide (2d): purified by column chromatography (hexane/acetone 3/1) to give a 39:11 mixture of the regioisomers **2c** and **2d**. The diastereomer ratio of **2d** was 9:2. A colorless solid of mp 115–117 °C. ¹H NMR: 7.57 (d, *J* = 8.3 Hz, 1.56H, 2-adduct), 7.52 (d, *J* = 8.6 Hz, 0.08H, minor 4-adduct), 7.47 (d, *J* = 8.3 Hz, 0.36H, major 4-adduct), 7.17 (m, 4H), 7.08 (m, 3H), 5.48 (br d, *J* = 5.5 Hz, 0.18H, major 4-adduct NH), 5.43 (br d, *J* = 7.9 Hz, 0.82H, 2-adduct and minor 4-adduct NH), 5.02 (d, *J* = 2.5 Hz, 0.78H, 2-adduct OCHO), 4.94 (s, 0.18H, major 4-adduct OCH₂O), 4.87 (s, 0.04H, minor 4-adduct OCH₂O), 4.78 (s, 0.18H, major 4-adduct OCH₂O), 4.72 (s, 0.04H, minor 4-adduct OCH₂O), 4.57 (dd, *J* = 2.5, 7.9 Hz, 0.78H, 2-adduct ArCH), 4.40 (dd, *J* = 5.8, 7.7 Hz, 0.04H, minor 4-adduct ArCH), 4.27 (dd, *J* = 5.5, 5.8 Hz, 0.22H, minor 4-adduct OCH and major 4-adduct ArCH), 4.15 (m, 0.18H, major 4-adduct OCH), 3.75 (m, 3.56H, OCH₂), 2.35 (s, 3H, CH₃). ¹³C NMR: 142.9 (minor 4-adduct C), 142.8 (major 4-adduct C), 142.7 (2-adduct C), 137.7 (2-adduct C), 137.3 (major 4-adduct C), 137.2 (minor 4-adduct C), 137.2 (major 4-adduct C), 136.9 (minor 4-adduct C), 136.2 (2-adduct C), 129.0 (minor 4-adduct CH), 129.0 (major 4-adduct CH), 129.0 (2-adduct CH), 128.2 (major 4-adduct CH), 128.1 (minor 4-adduct CH), 127.9 (2-adduct CH), 127.6 (major 4-adduct CH), 127.6 (2-adduct CH), 127.5 (minor 4-adduct CH), 127.5 (major 4-adduct CH), 127.3 (major 4-adduct CH), 127.2 (minor 4-adduct CH), 126.9 (2-adduct and 4-adduct CH), 104.2 (2-adduct OCHO), 95.4 (minor 4-adduct OCH₂O), 95.4 (major 4-adduct OCH₂O), 78.0 (major 4-adduct OCH), 77.5 (minor 4-adduct OCH), 66.9 (minor 4-adduct OCH₂), 66.8 (major 4-adduct OCH₂), 65.3 (2-adduct

OCH₂), 65.1 (2-adduct OCH₂), 59.5 (minor 4-adduct ArCH), 59.3 (2-adduct ArCH), 59.1 (major 4-adduct ArCH), 21.2 (CH₃). IR (nujol): 3250, 1600, 1320, 1160. EIMS (*m/z*): 260 ($M^+ - C_3H_5O_2$), 178 ($M^+ - Ts$), 155 (Ts), 73 ($C_3H_5O_2$). HRMS–FAB: [$M + H$]⁺ calcd for C₁₇H₂₀NO₄S, 334.1113; found, 334.1111.

Table 1, entry 2: purified by column chromatography (hexane/ethyl acetate 9/1 to 13/7) to give **2e** and **2f**. ***N*-[α -(tetrahydropyran-2-yl)benzyl]-4-toluenesulfonamide (2e):** a 13:7 mixture of the diastereomers of mp 128–130 °C. ¹H NMR: 7.44 (m, 2H), 7.09 (m, 7H), 5.60 (br d, *J* = 3.5 Hz, 0.6H, major NH), 5.57 (br d, *J* = 7.6 Hz, 0.4H, minor NH), 4.30 (dd, *J* = 4.0, 7.6 Hz, 0.35H, minor ArCH), 4.09 (dd, *J* = 3.5, 6.3 Hz, 0.65H, major ArCH), 3.94 (m, 1H, OCH), 3.52 (m, 0.35H, minor OCH₂), 3.33 (m, 1.65H, OCH₂), 2.33 (s, 1.95H, major CH₃), 2.31 (s, 1.05H, minor CH₃), 1.72 (m, 1H, CH₂), 1.37 (m, 4.65H, CH₂), 0.89 (m, 0.35H, minor CH₂). ¹³C NMR: 142.7 (major C), 142.6 (minor C), 137.8 (major C), 137.6 (minor C), 137.3 (major C), 137.0 (minor C), 129.1 (minor CH), 129.0 (major CH), 128.3 (minor CH), 128.0 (major CH), 127.9 (major CH), 127.8 (minor CH), 127.5 (major CH), 127.2 (minor CH), 127.2 (major CH₂), 126.9 (minor CH₂), 79.8 (major OCH), 79.6 (minor OCH), 68.8 (minor OCH₂), 68.5 (major OCH₂), 62.5 (major ArCH), 61.2 (minor ArCH), 28.1 (major CH₂), 27.6 (minor CH₂), 25.7 (minor CH₂), 25.6 (major CH₂), 22.9 (minor CH₂), 22.8 (major CH₂), 21.4 (major CH₃), 21.4 (minor CH₃). IR (KBr): 3283, 2939, 2839, 1323, 1165, 1091. EIMS (*m/z*): 260 ($M^+ - C_5H_9O$), 190 ($M^+ - Ts$), 155 (Ts), 106 (PhCHNH₂), 91 (tol), 85 (C_5H_9O). Anal. Calcd. for C₁₉H₂₃NO₃S: C, 66.06; H, 6.71; N, 4.05. Found: C, 66.08; H, 6.72; N, 4.11.

***N*-[α -(Tetrahydropyran-4-yl)benzyl]-4-toluenesulfonamide (2f):** a white solid of mp 152.5–153.5 °C. ¹H NMR: 7.47 (d, *J* = 8.3 Hz, 2H), 7.12 (m, 3H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.88 (m, 2H), 5.33 (br d, *J* = 8.9 Hz, 1H, NH), 4.00 (m, 2H, ArCH and OCH₂), 3.84 (m, 1H, OCH₂), 3.30 (m, 1H, OCH₂), 3.20 (m, 1H, OCH₂), 2.32 (s, 3H, CH₃), 1.88 (m, 1H, CH₂), 1.78 (m, 1H, CH), 1.33 (m, 1H, CH₂), 1.20 (m, 1H, CH₂), 1.13 (m, 1H, CH₂). ¹³C NMR: 142.9 (C), 139.1 (C), 137.4 (C), 129.2 (CH), 128.3 (CH), 127.3 (CH), 127.0 (CH), 126.8 (CH), 67.7 (OCH₂), 67.4 (OCH₂), 63.2 (ArCH), 41.2 (CH), 29.9 (CH₂), 29.8 (CH₂), 21.4 (CH₃). IR (KBr): 3287, 2924, 2851, 1385, 1157, 1092. EIMS (*m/z*): 345 (M^+), 344 ($M^+ - 1$), 260 ($M^+ - C_5H_9O$), 190 ($M^+ - Ts$), 155 (Ts), 91 (tol), 85 (C_5H_9O). Anal. Calcd. for C₁₉H₂₃O₃NS: C, 65.99; H, 6.71; N, 4.05. Found: C, 65.99; H, 6.68; N, 3.79.

Table 1, entry 3: *N*-[α -(1,4-dioxan-2-yl)benzyl]-4-toluenesulfonamide (**2g**): purified by column chromatography (hexane/acetone 3/1) to give a 10:3 mixture of the diastereomers as a white solid of mp 136–137 °C. ¹H NMR: 7.48 (d, *J* = 8.2 Hz, 0.46H), 7.47 (d, *J* = 7.9 Hz, 1.54H), 7.1 (m, 7H), 5.60 (br m, 1H, NH), 4.33 (dd, *J* = 4.9, 7.8 Hz, 0.23H, minor ArCH), 4.24 (dd, *J* = 4.8, 6.8 Hz, 0.77H, major ArCH), 3.66 (m, 5H, CH and CH₂ x 2), 3.38 (m, 1.77H, CH₂), 3.03 (m, 0.23H, CH₂), 2.33 (s, 3H, CH₃). ¹³C NMR: 143.0 (minor C), 142.9 (major C), 137.4 (minor C), 137.2 (major C), 136.8 (major C), 136.6 (minor C), 129.2 (minor CH), 129.1 (major CH), 128.3 (major CH), 128.1 (minor CH), 127.9 (CH), 127.7 (minor CH), 127.1 (major CH), 126.9 (minor CH), 76.9 (major OCH), 76.7 (minor OCH), 68.2 (minor OCH₂), 68.0 (major OCH₂), 67.0 (minor OCH₂), 66.3 (major OCH₂), 66.1 (OCH₂), 58.5 (minor ArCH), 58.5 (ArCH), 21.4 (CH₃). IR (KBr): 3294, 2963, 2916, 2858, 1597, 1454, 1315, 1164, 1123, 1096, 1069. EIMS (*m/z*): 347 (M⁺), 260 (M⁺ – C₄H₇O₂), 192 (M⁺ – Ts), 155 (Ts). Anal. Calcd. for C₁₉H₂₁NO₄S: C, 62.23; H, 6.09; N, 4.03. Found: C, 61.95; H, 5.99; N, 4.05.

Table 1, entry 4: *N*-(2-ethoxy-1-phenylpropyl)-4-toluenesulfonamide (**2h**): imine **1a** (127 mg, 0.50 mmol), diethyl ether (22 mL, 0.21 mol, 420 equiv) and a 1.0 M solution of dimethylzinc in hexane (3.0 mL, 3.0 mmol, 6.0 equiv) were used. The reaction mixture was stirred and quenched at 0 °C. Purification by column chromatography (hexane/acetone 9/1) gave a 11:9 mixture of the diastereomers as colorless prisms of mp 92–94 °C. ¹H NMR: 7.40 (d, *J* = 8.3 Hz, 0.88H, minor), 7.36 (d, *J* = 8.3 Hz, 1.12H, major), 7.0 (m, 7H), 5.59 (br d, *J* = 5.2 Hz, 0.56H, major NH), 5.49 (br d, *J* = 7.0 Hz, 0.44H, minor NH), 4.31 (dd, *J* = 4.0, 7.0 Hz, 0.44H, minor ArCH), 4.09 (dd, *J* = 5.2 Hz, 0.56H, major ArCH), 3.57 (m, 0.44H, minor OCH), 3.4 (m, 1.56H, major OCH and OCH₂), 3.1 (m, 1H, OCH₂), 2.33 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 1.32H, CH₃ of minor), 1.11 (t, *J* = 7.0 Hz, 1.68H, CH₃ of major), 1.01 (d, *J* = 6.5 Hz, 1.68H, CH₃ of major), 0.88 (d, *J* = 6.4 Hz, 1.32H, CH₃ of minor). ¹³C NMR: 142.8 (C), 142.7 (C), 138.7 (C), 137.4 (C), 137.4 (C), 137.0 (C), 129.2 (CH), 129.1 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 127.1 (CH), 78.0 (OCH), 77.3 (OCH), 64.3 (OCH₂), 64.3 (OCH₂), 62.7 (ArCH), 60.9 (ArCH), 21.4 (CH₃ of Ts), 16.5 (CH₃), 15.7 (CH₃), 15.3 (CH₃), 15.3 (CH₃). IR (nujol): 3250, 1600, 1320, 1160, 1090. FABMS (*m/z*):

334 ($M^+ + 1$), 288 ($M^+ - \text{OEt}$), 260 ($M^+ - \text{C}_4\text{H}_9\text{O}$), 178 ($M^+ - \text{Ts}$), 155 (Ts), 73 ($\text{C}_4\text{H}_9\text{O}$). Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{S}$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.82; H, 7.25; N, 3.96.

Table 1, entry 5: *N*-(2,2-dimethoxy-1-phenylethyl)-4-toluenesulfonamide (2i) and *N*-[2-(methoxymethoxy)-1-phenylethyl]-4-toluenesulfonamide (2j): imine **1a** (127 mg, 0.50 mmol), dimethoxymethane (22 mL, 0.25 mol, 500 equiv) and a 1.0 M solution of dimethylzinc in hexane (3.0 mL, 3.0 mmol, 6.0 equiv) were used. The reaction mixture was stirred and quenched at 0 °C. Purification by column chromatography (hexane/ethyl acetate 9/1 to 17/3) gave a 4:3 mixture of the regioisomers, which were separated by column chromatography (chloroform/ethyl acetate 97/3).

Major and less polar **2i** was recrystallized from ethyl acetate–hexane to give colorless prisms of mp 87–87.5 °C. ^1H NMR: 7.50 (d, 2H, $J = 8.2$ Hz), 7.15 (m, 5H), 7.09 (d, $J = 8.0$ Hz, 2H), 5.37 (br d, $J = 5.8$ Hz, 1H, NH), 4.40 (dd, $J = 4.6, 5.8$ Hz, 1H, ArCH), 3.33 (d, $J = 4.6$ Hz, 1H, OCHO), 3.29 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 2.34 (s, 3H, ArCH_3). ^{13}C NMR: 142.9 (C), 137.3 (C), 136.5 (C), 129.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.1 (CH), 106.1 (OCHO), 59.1, (ArCH), 55.9 (OCH_3), 55.0 (OCH_3), 21.4 (ArCH_3). IR (KBr): 3283, 2924, 1327, 1161, 1096. EIMS (m/z): 260 ($M^+ - \text{C}_3\text{H}_7\text{O}_2$), 180 ($M^+ - \text{Ts}$), 155 (Ts). Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{S}$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.89; H, 6.34; N, 3.97.

Minor and more polar **2j**: colorless oil. ^1H NMR: 7.57 (d, 2H, $J = 8.3$ Hz), 7.56 (d, $J = 8.6$ Hz, 2H), 7.16 (m, 7H), 5.48 (br d, $J = 5.5$ Hz, 1H, NH), 4.51 (s, 1H, OCH_2O), 4.51 (s, 1H, OCH_2O), 4.50 (m, 1H, ArCH), 3.67 (dd, $J = 4.6, 10.4$ Hz, 1H, OCH_2), 3.63 (dd, $J = 6.4, 10.4$ Hz, 2H, OCH_2), 3.22 (s, 3H, OCH_3), 2.47 (s, 3H, ArCH_3). ^{13}C NMR: 143.1 (C), 137.8 (C), 137.4 (C), 129.3 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 127.1 (CH), 96.6 (OCH_2O), 71.0, (OCH_2), 57.3 (ArCH), 55.5 (OCH_3), 21.4 (ArCH_3). IR (neat): 3414, 2924, 1628, 1327, 1157, 1092, 1038. EIMS (m/z): 260 ($M^+ - \text{C}_3\text{H}_7\text{O}_2$), 155 (Ts), 91 (tolyl), 75 ($\text{C}_3\text{H}_7\text{O}_2$). HRMS–FAB: $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_4\text{S}$, 336.1270; Found, 336.1280.

Table 1, entry 7: *N*-[4-methyl- α -(tetrahydrofuran-2-yl)benzyl]-4-toluenesulfonamide (2l): purified by column chromatography (hexane/acetone 9/1 to 17/3) to give a 13:7 mixture of the diastereomers as colorless prisms of mp 126.5–127.5 °C. ^1H NMR: 7.46 (m, 2H), 7.07 (m, 2H), 6.94 (m,

4H) 5.36 (br d, $J = 4.9$ Hz, 0.6H, major NH), 5.24 (br d, $J = 7.5$ Hz, 0.3H, minor NH), 4.27 (dd, $J = 4.4, 7.5$ Hz, 0.35H, minor ArCH), 4.12 (m, 1H, major ArCH and minor OCH), 3.94 (dt, $J = 6.4, 6.6$ Hz, 0.65H, major OCH), 3.75 (m, 1.3H, major OCH₂), 3.64 (t, $J = 6.7$ Hz, 0.7H, minor OCH₂), 2.34 (s, 1.95H, major CH₃), 2.33 (s, 1.05H, minor CH₃), 2.25 (s, 3H, CH₃), 1.78 (m, 3.3H, CH₂), 1.51 (m, 0.7H, minor CH₂). ¹³C NMR: 142.7 (C), 137.5 (minor C), 137.4 (major C), 137.1 (major C), 137.1 (minor C), 135.3 (major C), 134.2 (minor C), 129.1 (minor CH), 129.0 (major CH), 128.8 (major CH), 128.6 (minor CH), 127.8 (minor CH), 127.4 (major CH), 127.1 (major CH), 127.0 (minor CH), 81.7 (major OCH), 81.4 (minor OCH), 68.6 (major OCH₂), 68.5 (minor OCH₂), 61.0 (major ArCH), 60.5 (minor ArCH), 28.4 (major CH₂), 27.6 (minor CH₂), 25.5 (major CH₂), 25.4 (minor CH₂), 21.4 (CH₃), 21.0 (CH₃). IR (KBr): 3271, 2978, 2878, 1327, 1157, 1096, 1065. EIMS (m/z): 274 ($M^+ - C_4H_7O$), 190 ($M^+ - Ts$), 155 (Ts), 120 (tolCHNH₂), 91 (tol), 71 (C₄H₇O). Anal. Calcd. for C₁₉H₂₃NO₃S: C, 66.06; H, 6.71; N, 4.05. Found: C, 66.17; H, 6.71; N, 4.01.

Table 1, entry 8: *N*-[2-methyl- α -(tetrahydrofuran-2-yl)benzyl]-4-toluenesulfonamide

(2m): purified by column chromatography (hexane/acetone 9/1 to 17/3) to give a 7:3 mixture of the diastereomers as colorless prisms of mp 105–128 °C. ¹H NMR: 7.46 (d, $J = 8.3$ Hz, 0.6H, minor), 7.41 (d, $J = 8.3$ Hz, 1.4H, major), 7.13 (d, $J = 7.7$ Hz, 0.3H, minor), 7.0 (m, 5.7H), 5.69 (br d, $J = 5.5$ Hz, 0.3H, minor NH), 5.60 (br d, $J = 7.3$ Hz, 0.7H, major NH), 4.67 (dd, $J = 4.6, 7.3$ Hz, 0.3H, minor ArCH), 4.56 (dd, $J = 5.5, 5.5$ Hz, 0.7H, major ArCH), 4.09 (m, 0.3H, minor OCH), 3.95 (m, 0.7H, major OCH), 3.82 (m, 0.7H, major OCH₂), 3.7 (m, 1.3H, OCH₂), 2.30 (s, 0.9H, minor CH₃), 2.29 (s, 2.1H, major CH₃), 2.29 (s, 2.1H, major CH₃), 2.20 (s, 0.9H, minor CH₃), 1.8 (m, 3.4H, CH₂ x 2), 1.60 (m, 0.3H, minor CH₂), 1.48 (m, 0.3H, minor CH₂). ¹³C NMR: 142.6 (minor C), 142.6 (major C), 137.4 (major C), 137.4 (minor C), 136.3 (major C), 135.8 (minor C), 135.5 (minor C), 135.0 (major C), 130.1 (major CH), 129.7 (minor CH), 129.0 (minor CH), 128.8 (major CH), 127.3 (major CH), 127.3 (minor CH), 127.0 (CH), 126.8 (major CH), 126.8 (minor CH), 125.9 (minor CH), 125.8 (major CH), 81.3 (major OCH), 81.2 (minor OCH), 68.5 (minor OCH₂), 68.5 (major OCH₂), 56.3 (major ArCH), 55.6 (minor ArCH), 28.2 (major CH₂), 27.5 (minor CH₂), 25.6 (minor CH₂), 25.5 (major CH₂), 21.3 (CH₃), 19.4 (CH₃). IR (KBr): 3290, 2970, 2878, 1327, 1161, 1092, 1057. EIMS (m/z): 274 ($M^+ - C_4H_7O$), 190 ($M^+ - Ts$), 155 (Ts), 120, 91 (tol), 71 (C₄H₇O). Anal. Calcd. for C₁₉H₂₃NO₃S: C, 66.06;

H, 6.71; N, 4.05. Found: C, 66.00; H, 6.72; N, 3.89.

Table 1, entry 9: methyl *N*-[α -tetrahydrofuran-2-yl]benzyl]carbamate (2n**):** purified by column chromatography (hexane/ethyl acetate 3/1 to 7/3) to give a 7:3 mixture of the diastereomers as a white solid of mp 74–76 °C. ^1H NMR: 7.3 (m, 5H), 5.48 (br m, 1H, NH), 4.69 (br m, 1H, ArCH), 4.23 (br m, 0.3H, minor OCH), 4.09 (br m, 0.7H, major OCH), 3.92 (m, 0.7H, major OCH₂), 3.75 (m, 0.7H, major OCH₂), 3.66 (m, 0.6H, minor OCH₂), 3.64 (s, 2.1H, major CH₃), 3.62 (s, 0.9H, major CH₃), 1.5 (m, 4H, CH₂ x 2). ^{13}C NMR: 156.9 (major NCO₂), 156.4 (minor NCO₂), 141.1 (C), 128.4 (CH), 128.2 (CH), 127.4 (CH), 127.3 (CH), 81.4 (major OCH), 80.9 (minor OCH), 68.7 (major OCH₂), 68.6 (minor OCH₂), 57.7 (ArCH), 52.1 (CH₃), 28.9 (CH₂), 25.6 (major CH₂), 25.5 (minor CH₂). IR (KBr): 3317, 2951, 2874, 1713, 1535, 1504, 1242, 1069. EIMS (m/z): 236 ($\text{M}^+ + 1$), 177 ($\text{M}^+ + 1 - \text{CO}_2\text{Me}$), 165 ($\text{M}^+ + 1 - \text{C}_4\text{H}_7\text{O}$), 160 ($\text{M}^+ - \text{NHCO}_2\text{Me}$), 91 (PhCH₂), 71 (C₄H₇O), 59 (CO₂Me). Anal. Calcd. for C₁₉H₂₃NO₄S: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.29; N, 5.96.

Table 1, entry 10: *N*-(4-methoxyphenyl)- α -phenyltetrahydrofuran-2-methylamine (2o**):** imine **1g** (84.5 mg, 0.40 mmol), THF (17.5 mL, 0.22 mol, 540 equiv) and a 1.0 M solution of dimethylzinc in hexane (2.4 mL, 2.4 mmol, 6 equiv) were used. The reaction was quenched by the addition of 10% hydrochloric acid. The resulting mixture was basified by the addition of sodium hydroxide before extracted with ethyl acetate. Purification by column chromatography (hexane/acetone 19/1) gave a 7:3 mixture of the diastereomers, which were separated by column chromatography (hexane/diethyl ether 9/1).

The major and less polar isomer as a pale yellow oil. ^1H NMR: 7.42 (m, 2H), 7.33 (m, 2H), 7.25 (m, 1H), 6.67 (d, $J = 8.9$ Hz, 2H), 6.50 (d, $J = 8.9$ Hz, 2H), 4.5 (br s, 1H, NH), 4.14 (d, $J = 6.7$ Hz, 1H, ArCH), 4.03 (m, 1H, OCH), 3.93 (m, 1H, OCH₂), 3.82 (m, 1H, OCH₂), 3.68 (s, 3H, CH₃), 1.85 (m, 4H, CH₂ x 2). ^{13}C NMR: 152.0 (C), 142.1 (C), 141.8 (C), 128.5 (CH), 127.3 (CH), 115.0 (CH), 114.6 (CH), 83.0 (OCH), 68.5 (OCH₂), 63.1 (ArCH), 55.7 (OCH₃), 28.7 (CH₂), 25.7 (CH₂). IR (neat): 3383, 2947, 2870, 1512, 1454, 1300, 1242, 1180, 1065, 1038. FABMS (m/z): 284 ($\text{M}^+ + 1$), 283 (M^+), 212 ($\text{M}^+ - \text{C}_4\text{H}_7\text{O}$), 161 ($\text{M}^+ - \text{MeOC}_6\text{H}_4\text{NH}$). HRMS–FAB: Calcd for C₁₈H₂₁O₂N, 283.1572. Found, 283.1579.

The minor and more polar isomer as a brownish oil. ^1H NMR: 7.37 (d, $J = 7.3$ Hz, 2H), 7.30 (m, 2H), 7.26–7.20 (m, 1H), 6.66 (d, $J = 8.9$ Hz, 2H), 6.49 (d, $J = 8.9$ Hz, 2H), 4.39 (d, $J = 4.0$ Hz, 1H, ArCH), 4.23 (m, 1H, OCH), 3.78 (m, 2H, OCH_2), 3.68 (s, 3H, CH_3), 1.77 (m, 3H, $\text{CH}_2 \times 2$), 1.61 (m, 1H, CH_2). ^{13}C NMR: 152.0 (C), 141.6 (C), 140.3 (C), 128.3 (CH), 127.7 (CH), 127.2 (CH), 115.2 (CH), 114.6 (CH), 82.2 (OCH), 68.8 (OCH_2), 61.5 (ArCH), 55.6 (OCH_3), 27.0 (CH_2), 25.5 (CH_2). IR (neat): 3375, 2932, 2870, 1512, 1454, 1238, 1061, 1038. FABMS (m/z): 284 ($\text{M}^+ + 1$), 283 (M^+), 212 ($\text{M}^+ - \text{C}_4\text{H}_7\text{O}$), 161 ($\text{M}^+ - \text{MeOC}_6\text{H}_4\text{NH}$). HRMS–FAB: Calcd for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{N}$, 283.1572. Found, 283.1568.

Table 1, entry 11: *N*-(4-methoxyphenyl)- α -(2-phenylethyl)tetrahydrofuran-2-methylamine (**2p**): imine **1h** (120 mg, 0.50 mmol), THF (37 mL, 0.46 mol, 910 equiv) and a 1.0 M solution of dimethylzinc in hexane (5.0 mL, 5.0 mmol, 10 equiv) were used. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate. Purification by column chromatography (hexane/acetone 9/1) gave a 3:2 mixture of the diastereomers, which were separated by column chromatography (hexane/acetone 19/1).

The less polar isomer as a pale yellow oil. ^1H NMR: 7.24 (m, 2H), 7.16 (m, 3H), 6.73 (d, $J = 8.9$ Hz, 2H), 6.49 (d, $J = 8.9$ Hz, 2H), 4.02 (m, 1H, OCH), 3.88 (m, 1H, OCH_2), 3.74 (m, 1H, OCH_2), 3.73 (s, 3H, OCH_3), 3.33 (m, 1H, NCH), 2.71 (m, 2H, ArCH_2), 1.85 (m, 6H, $\text{CH}_2 \times 3$). ^{13}C NMR: 151.5 (C), 142.6 (C), 142.0 (C), 128.4 (CH), 128.3 (CH), 125.7 (CH), 114.9 (CH), 114.1 (CH), 80.7 (OCH), 68.7 (OCH_2), 55.8 (NCH), 55.6 (OCH_3), 34.7 (CH_2), 32.5 (CH_2), 28.1 (CH_2), 26.1 (CH_2). IR (neat): 3387, 2943, 2862, 1512, 1238, 1038. EIMS (m/z): 311 (M^+), 240 ($\text{M}^+ - \text{C}_4\text{H}_7\text{O}$), 149, 91. HRMS–EI: Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_2\text{NS}$, 311.1885. Found, 311.1877.

The more polar isomer as a pale yellow oil ^1H NMR: 7.24 (m, 2H), 7.16 (m, 3H), 6.73 (m, 2H), 6.56 (m, 2H), 3.90 (m, 1H, OCH), 3.80 (m, 1H, OCH_2), 3.73 (m, 1H, OCH_2), 3.73 (s, 3H, OCH_3), 3.3 (br s, 1H, NH), 3.32 (m, 1H, NCH), 2.83 (m, 1H, ArCH_2), 2.66 (m, 1H, ArCH_2), 1.8 (m, 6H, $\text{CH}_2 \times 3$). ^{13}C NMR: 151.8 (C), 142.4 (C), 142.2 (C), 128.5 (CH), 128.3 (CH), 125.7 (CH), 114.9 (CH), 114.8 (CH), 81.4 (OCH), 68.2 (OCH_2), 57.2 (NCH), 55.7 (OCH_3), 33.2 (CH_2), 32.3 (CH_2), 28.0 (CH_2), 25.9 (CH_2). IR (neat): 3379, 2947, 2862, 1512, 1234, 1064, 1038. EIMS (m/z): 311 (M^+), 240 ($\text{M}^+ -$

C₄H₇O), 149, 91. HRMS–EI: Calcd for C₂₀H₂₅O₂NS, 311.1885. Found, 311.1891.

The Reaction in Apparatuses whose connections were silicone greased (Method B):

imine **1a** (259 mg, 1.0 mmol) was placed in a 50 mL round-bottom flask fitted with a three-way tap, whose connections silicon grease was applied to. The flask was filled with argon by the three times evacuate-and-refill process. To the flask was added argon-bubbled THF (22 mL) to dissolve the imine, and then a 1.0 M solution of dimethylzinc (3.0 mL, 3.0 mmol) at room temperature. The mixture was vigorously stirred under argon atmosphere at the same temperature. After 48 h, the reaction was quenched by the addition of 10% hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. The concentration of the mixture afforded a crude mixture as a white solid (260 mg), which contained 4-toluenesulfonamide, benzaldehyde, imine **1a**, and THF adduct **2a** in the ratio of 16:7:7:1 according to ¹H NMR.

The Reaction with Air-bubbling (Method C): in a 50 mL three-necked flask fitted with a three-way tap, was placed imine **1a** (1.0 mmol). The flask was filled with argon by the evacuate-and-refill procedure, and an argon balloon was attached to the three-way tap. The imine was dissolved in THF (22 mL), and a 1.0 M solution of dimethylzinc in hexane (3.0 mL, 3.0 mmol) was added to the solution at room temperature. The argon balloon was replaced by a vacant balloon, and the three-way tap was opened to the balloon. The mixture was stirred for 1 h at the same temperature while air was introduced into the mixture through a sodium hydroxide tube and a syringe needle at the rate of 10 mL/h using a syringe-pump. The reaction was then quenched by addition of 10% hydrochloric acid. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, and then concentrated. The resulting residue was purified by silica gel column chromatography (hexane/acetone 3/1) to afford THF adduct **2a** as a 3:2 mixture of the diastereomers (315 mg, 95%).

The X-ray data of major 2b:

$C_{18}H_{20}ClNO_3S$

space group : $P -1$

$a = 10.218(2)$ $b = 11.247(3)$ $c = 8.086(2)$

$\alpha = 98.16(2)$ $\beta = 101.84(2)$ $\gamma = 84.16(2)$

$V = 897.7$

$Z = 2$

$D_x = 1.3532$

$R = 0.051$

Figure I. X-ray Structure of Major **2b**.

Figure II. Observed and Calculated Coupling Constants between the Adjacent Methyne Protons of **2b**.

The MM3 calculations for 2a: MM3 calculations were performed using CAChe 4.1.1 with the CONFLEX option. The coupling constants were calculated by a modified Karplus equation, $J = 3.25 -$

$1.0\cos\phi + 3.25\cos2\phi$. The calculated coupling constants in Figure II are the weight-average of the calculated coupling constants of the adjacent methyne protons of the conformers based on the population.

Table I. Energy, Population, Dihedral Angles of the Adjacent Methynes H–C–C–H, and a Calculated Coupling Constant between the Methyne Protons for the MM3 Structures of Major **2a**.

conformer	A	B	C	D	E
<i>E</i> (kcal/mol)	34.26	35.21	35.56	36.31	37.10
population at 27 °C (%)	74	15	8	2	1
H–C–C–H (deg)	–176	69	–177	–57	–58
<i>J</i> (Hz)	7.5	0.5	7.5	1.4	1.3

Table II. Energy, Population, Dihedral Angles of the Adjacent Methynes H–C–C–H, and Calculated Coupling Constants between the Methyne Protons for the MM3 Structures of Minor **2a**.

conformer	A'	B'	C'	D'	E'
<i>E</i> (kcal/mol)	34.89	35.12	35.43	35.97	36.01
population at 27 °C (%)	42	28	17	7	6
H–C–C–H (deg)	179	–57	61	179	–58
<i>J</i> (Hz)	7.5	1.4	1.0	7.5	1.3