

Supporting Information for

**Tandem Aza [4+2] / Allylboration:
A Novel Multicomponent Reaction for the
Stereocontrolled synthesis of α -Hydroxyalkyl
Piperidine Derivatives**

Jyoti Tailor and Dennis Hall*

Department of Chemistry
University of Alberta
Edmonton, Alberta
T6G 2G2
Canada

EXPERIMENTAL

General

Unless otherwise noted, all operations were carried out in oven- or flame-dried glassware under a dry, oxygen-free nitrogen atmosphere. Acetone, CH_2Cl_2 , cyclohexene, DME, EtOH, Et_2O , MeOH and toluene were freshly distilled from calcium hydride prior to use. Anhydrous THF was distilled from sodium in a recycling still. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Pinacol was recrystallized from benzene and dried under vacuum. All organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated with a rotary evaporator under reduced pressure. Chromatography refers to flash chromatography on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on 0.25 mm Merk precoated silica plates (60F-254). Visualization was obtained by exposure to 5% phosphomolybdic acid in ethanol. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz in CDCl_3 as solvent unless otherwise mentioned. Protons chemical shifts are expressed in parts per million (ppm) and recorded relative to tetramethylsilane as an internal standard. Coupling constants are expressed as J values in hertz units. The following abbreviation are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer in CDCl_3 as solvent, and chemical shifts are expressed in ppm. Infrared spectra were obtained on a Nicolet Magna-IRTM 750. Frequencies are expressed in cm^{-1} . Melting points were determined in a capillary tube on a Gallemankamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed by the microanalytical laboratory of our department. High resolution electrospray mass spectra (HRMS) were obtained on a Micromass ZabSpec oa TOF instrument. Significant protonated molecular ions ($\text{M}+\text{H}$)⁺ as well as peaks corresponding to sodiated molecular ions ($\text{M}+\text{Na}$)⁺ were present in most of the spectra because of trace amounts of sodium salts in the samples. X-ray analysis was performed by Dr. R. MacDonald at University of Alberta.

Procedure for the preparation of dienes 1a-c.

To a solution of Hydrazine (1 equiv) and sodium hydrogen phosphate (1 equiv) in water (2 mL), a solution of α,β -unsaturated carbonyl compound **2** (1 equiv) in anhydrous Et₂O (10 mL) was added. After vigorous stirring of the mixture for 30 minutes at 50 °C, the mixture was extracted three times with ether (25 mL each). These extracts were dried over anhydrous magnesium sulfate and evaporated to give dienes **1a-c** as pale yellow oil. These compounds were used for the next reaction without further purification.

Procedure for the preparation of diene **1d.**

To a solution of α,β -unsaturated carbonyl compound **2** (1.01 g, 5.55 mmol, 1 equiv) in anhydrous EtOH (20 mL), acetic hydrazide (0.41 g, 5.55 mmol, 1 equiv) was added. After vigorous stirring of the mixture for 1 h at 85 °C, the mixture was evaporated and dried over vacuum to give **1d** as pale yellow solid. The crude product was subjected to flash chromatography on silica gel, eluting with 10% MeOH in dichloromethane, to give **1d** in 62% yield.

General procedure for the preparation of bicyclic alcohols **3a-3h, 7.**

To a solution of diene **1** (1 equiv) in toluene (5 mL) was added aldehyde (1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. Dienophile (2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (15 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **3** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **3** as pale yellow solid in 42-52% yield.

Spectroscopic data for **3a**: mp 80-82 °C; IR (CHCl₃ cast) 3475, 2944, 1783, 1597, 1454, 1199, 1059, 864, 667, 646, 621 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.55 (m, 10H), 6.01 (ddd, *J* = 1.5, 3.7, 10.5 Hz, 1H), 5.75 (ddd, *J* = 1.5, 4.3, 10.6 Hz, 1H), 4.62 (d, *J* = 8.4 Hz, 1H), 4.24 (br s, 1H, OH), 3.89 (d, *J* = 9.5 Hz, 1H), 3.52-3.63 (m, 2H), 2.50 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ: 176.1, 174.0(CO), 140.1, 131.6 (C), 130.6, 129.2, 128.7, 128.5, 128.2, 127.2, 126.3, 121.1, 76.6, 61.4, 57.2, 38.9 (CH), 43.7 (N-CH₃); MS (ES) *m/z* 400 (M+Na)⁺, 378 (M+H)⁺, 360 (M-H₂O)⁺; HRMS (ES) *m/z* calcd. for C₂₂H₂₃N₃O₃Na (M+Na)⁺ 400.1637, found 400.1639.

Spectroscopic data for **3b**: mp 110-112 °C; IR (CHCl₃ cast) 3463, 2945, 1779, 1704, 1454, 1434, 1279, 1199, 1124, 990, 809, 775, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.24-7.32 (m, 5H), 5.92 (ddd, *J* = 1.6, 3.6, 10.5 Hz, 1H), 5.66 (ddd, *J* = 2.1, 4.4, 10.6 Hz, 1H), 4.42 (d, *J* = 8.5 Hz, 1H), 4.26 (br s, 1H, OH), 3.73 (d, *J* = 9.6 Hz, 1H), 3.46-3.40 (m, 2H), 3.05 (s, 3H) 2.46 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ 177.0, 175.1 (CO), 140.2 (C), 130.2, 128.4, 128.1, 127.1, 121.2, 75.6, 61.2, 57.3, 38.7 (CH), 43.7 [N-N(CH₃)₂], 25.3 (N-CH₃); MS (ES) *m/z* 338 (M+Na)⁺, 316 (M+H)⁺; HRMS (ES) *m/z* calcd for C₁₇H₂₁N₃O₃Na (M+Na)⁺ 338.1481, found 338.1481. Anal. Calcd: C, 64.8; H, 6.7; N, 13.3. Found: C, 64.1; H, 6.6; N, 12.6.

Spectroscopic data for **3c**: mp 90-92 °C; IR (CHCl₃ cast) 3439, 2922, 2852, 1778, 1597, 1499, 1376, 1197, 1108, 1072, 752, 691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, 2H), 7.24-7.54 (m, 7H), 6.10 (ddd, *J* = 1.4, 3.8, 10.6 Hz, 1H), 5.75 (ddd, *J* = 2.2, 5.3, 10.2 Hz, 1H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.31 (br s, 1H, OH), 4.02 (d, *J* = 9.6 Hz, 1H), 3.59 (m, 1H), 3.39 (m, 1H), 2.49 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ 176.1, 176.0 (CO), 147.8, 147.7, 131.4 (C), 131.4, 129.4, 129.2, 126.5, 126.2, 123.6, 122.1, 76.1, 62.1, 56.2, 38.9 (CH), 43.5 [N-N(CH₃)₂]; MS (ES) *m/z* 445 (M+Na)⁺, 423 (M+H)⁺; HRMS (ES) *m/z* Calcd for C₂₂H₂₂N₄O₅Na (M+Na)⁺ 445.1488, found 445.1482.

Spectroscopic data for **3d**: mp 107-110 °C; IR (CHCl₃, cast) 3476, 2919, 2850, 1651, 1597, 1513, 1302, 1137, 832, 806, 692, 405 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.21-7.49 (m, 7H), 6.87 (d, 2H), 5.98 (ddd, *J* = 1.5, 3.7, 10.5 Hz, 1H), 5.73 (ddd, *J* = 2.2, 4.5, 10.5 Hz, 1H), 4.60 (d, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.76 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.45 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ 176.0, 174.0 (CO), 159.6, 132.1, 131.6 (C), 130.7, 129.3, 128.9, 128.3, 126.2, 121.1, 113.9, 75.6, 61.5, 57.2, 55.3 (CH), 38.8 (OCH₃), 43.7 [N-N(CH₃)₂]; MS (ES) *m/z* 430 (M+Na)⁺, 408 (M+H)⁺, 390 (M-H₂O)⁺; HRMS (ES) *m/z* calcd for C₂₃H₂₅N₃O₄Na (M+Na)⁺ 430.1743, found 430.1742.

Spectroscopic data for **3e**: mp 75-78 °C; IR (CHCl₃, cast) 2953, 1777, 1713, 1597, 1499, 1455, 1383, 1180, 751, 691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.58 (m, 5H), 6.17 (dd, *J* = 0.9, 2.2, 4.6, 8.4 Hz, 1H), 6.04 (ddd, *J* = 2.1, 4.0, 10.5 Hz, 1H), 4.52 (d, *J* = 8.6 Hz, 1H), 3.54 (m, 1H), 3.24 (m, 2H), 2.49-2.52 (m, 8H), 1.91 (m, 1H), 1.22 (m, 2H), 0.92 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ 176.4, 174.1 (CO), 131.6 9 (C), 130.9, 129.2, 129.2, 126.2, 121.2, 70.7, 60.0, 57.4, 57.2, 43.7 (CH), 42.4 (CH₂), 38.6 [N-N(CH₃)₂], 24.6, 23.9 (CH₃); MS (ES) *m/z* 380 (M+Na)⁺, 358 (M+H)⁺; HRMS (ES) *m/z* calcd for C₂₀H₂₈N₃O₃ (M+H)⁺ 358.2131, found 358.2136.

Spectroscopic data for **3f**: mp 180-182 °C; IR (CHCl₃, cast) 3515, 3028, 2920, 1715, 1600, 1495, 1454, 1384, 1371, 1247, 1195, 1058, 971, 828, 751, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+D₂O) δ 7.49-6.92 (m, 15H), 6.19 (m, 1H), 5.59 (ddd, *J* = 2.2, 4.4, 10.4 Hz, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.91 (br s, 1H, OH), 3.73 (m, 2H); ¹³C (300 MHz, CDCl₃) δ 173.6, 173.5 (CO), 147.1 139.4, 131.3 (C), 129.6, 129.4, 129.3, 129.1, 128.6, 128.4, 127.1, 126.2, 126.1, 121.1, 114.13, 76.3, 68.1, 68.1, 38.3 (CH); MS (ES) *m/z* 448 (M+Na)⁺; HRMS (ES) *m/z* calcd for C₂₆H₂₃N₃O₃Na (M+Na)⁺ 448.1637, found 448.1636. Anal. Calcd: C, 73.5; H, 5.4; N, 9.9. Found: C, 73.2; H, 5.2; N, 9.6.

Spectroscopic data for **3g**: mp 190-192 °C; IR (CHCl₃ cast) 3497, 2921, 1716, 1597, 1496, 1454, 1384, 1371, 1244, 1141, 971, 829, 792, 692, 622 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.20 (m, 15H), 6.10 (ddd, *J* = 1.5, 3.5, 9.0 Hz, 1H), 5.81 (ddd, *J* = 2.4, 4.1, 10.6 Hz, 1H), 4.41 (d, *J* = 8.3 Hz, 1H), 4.20 (d, *J* = 8.9 Hz, 1H), 3.96 (br s, 1H, OH), 3.71-3.62 (m, 2H), 3.01 (s, 3H); ¹³C (300 MHz, CD₂Cl₂) δ 175.7, 173.6 (CO), 149.3, 139.8, 131.4 (C), 131.4, 131.0, 129.5, 129.3, 128.9, 128.5, 128.2, 127.2, 126.1, 120.1, 114.4, 76.6, 66.3, 58.6, 39.5 (CH), 35.6 (CH₃); MS (ES) *m/z* 462 (M+Na)⁺; HRMS (ES) *m/z* calcd for C₂₇H₂₅N₃O₃Na (M+Na)⁺ 462.1794, found 462.1792.

Spectroscopic data for **3h**: mp 110-112 °C; IR (CHCl₃ cast) 3021, 2960, 2924, 2852, 1593, 1567, 1496, 1455, 1371, 1259, 1229, 1186, 1153, 1100, 1026, 920, 867, 793, 730, 667, 620, 510 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.20 (m, 10H), 6.10 (ddd, *J* = 2.2, 3.0, 10.4 Hz, 1H), 5.98 (ddd, *J* = 2.4, 3.5, 10.4 Hz, 1H), 5.82 (d, *J* = 5.5 Hz, 1H), 5.22 (d, *J* = 9.3 Hz, 1H), 4.72 (m, 1H), 3.81 (m, 1H), 1.92 (s, 3H); ¹³C (300 MHz, CDCl₃, APT) δ 174.0, 173.4, 169.6 (CO), 136.9, 136.0 (C), 131.4, 129.1, 128.7, 128.5, 128.4, 127.6, 127.4, 121.0, 77.5, 61.8, 58.7, 39.8 (CH), 21.1 (COCH₃); MS (ES) *m/z* 414 (M+Na)⁺.

Preparation of 4. To a suspension of Raney nickel in MeOH (5 mL), under an H₂ atmosphere, was added **3b** previously prepared (0.10 g). After 24 h of stirring at 40 °C, the catalyst was filtered out. The solution was concentrated. ¹H NMR shows the expected product **4** along with cyclic ester. This outcome can be explained by the opening of the imide ring, by methanol to give cyclic ester as a byproduct.

Preparation of 5. To a suspension of 10% Pd on carbon (0.16 g) in EtOH (3 mL), under an H₂ atmosphere, was added **3b** previously prepared (0.16 g, 0.51 mmol) in EtOH (2 mL). After 18 h of stirring at rt, the catalyst was filtered out. The solution was concentrated and chromatographed on silica gel (5% MeOH in dichloromethane) affording 0.12 g (75% yield) of **5** as

pale yellow solid, which was crystallized from dichloromethane at rt. Spectroscopic data for **5**: mp 138-140 °C; IR (CHCl₃ cast) 3018, 2916, 2848, 1704, 1434, 1383, 1282, 1215, 1130, 1062, 967, 754, 702, 667 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.34 (m, 5H), 4.36 (d, *J* = 8.8 Hz, 1H), 3.98 (d, *J* = 7.2 Hz, 1H), 2.95-3.08 (m, 5H), 2.45 (s, 6H), 1.95 (m, 1H), 1.67 (m, 1H), 1.20 (m, 1H), 0.87 (m, 1H); ¹³C (300 MHz, CDCl₃, APT) δ 178.6, 178.3 (CO), 142.1 (C), 128.2, 127.5, 126.9, 78.7, 65.2, 51.8, 40.4 (CH), 22.8, 21.7 (CH₂), 42.1 [N-N(CH₃)₂], 25.17 (NCH₃); MS (ES) *m/z* 340 (M+Na)⁺, 318 (M+H)⁺; HRMS (ES) *m/e* calcd for C₁₇H₂₃N₃O₃Na (M+Na)⁺ 340.1637, found 340.1635.

Spectroscopic data for **7**: mp 80-82 °C; IR (CHCl₃ cast) 3853, 2932, 1715, 1651, 1597, 1499, 1455, 1382, 1179, 1142, 753, 692, 667, 621 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 6.01 (ddd, *J* = 1.6, 3.7, 10.6 Hz, 1H), 5.70 (ddd, *J* = 2.3, 4.5, 10.5 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 9.6 Hz, 1H), 3.62 (m, 2H), 3.21-3.42 (m, 4H), 2.94 (m, 1H), 2.61-2.78 (m, 2H), 1.51-1.90 (m, 4H), 1.12 (s, 6H); ¹³C (300 MHz, CDCl₃, APT) δ 175.2, 174.1 (CO), 140.7, 140.6, 78.5 (C), 130.8, 129.3, 129.1, 128.4, 128.0, 127.1, 126.3, 122.1, 76.1, 67.9, 63.2, 60.1, 49.1 (CH), 50.7, 25.8, 22.7 (CH₂), 38.4, 21.9, 20.6 (CH₃); MS (ES) *m/z* 475 (M+H)⁺.