Selective Lithiation of 2-Methyloxazoles: Applications to Pivotal Bond Constructions in the Phorboxazole Nucleus

David A. Evans, Victor J. Cee, Thomas E. Smith, and Keith J. Santiago

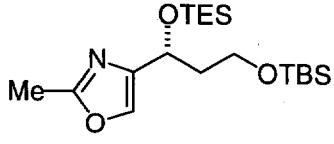
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

General Information. Unless noted, all reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane was distilled from calcium hydride under nitrogen. Tetrahydrofuran was distilled from benzophenone ketyl under nitrogen. Diethylamine, diisopropylamine, tetramethylpiperidine, and 2,4-lutidine were distilled from calcium hydride under nitrogen. *n*-Butyllithium was purchased from Aldrich Chemical Co. and was periodically titrated. Methyl triflate, hydrocinnamaldehyde, and benzaldehyde were obtained from Aldrich Chemical Co. and were distilled prior to use. Purification of reaction products was carried out by flash chromatography using EM Reagents silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating.

Infrared spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Brucker AM-500 (500 MHz) and AM-400 (400 MHz) spectrometers at ambient temperature unless otherwise noted. Data are reported as follows: chemical shift in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 7.26 ppm, or THF-d8 at 3.58 ppm) multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR spectra were recorded on Brucker AM-500 (125 MHz) and AM-400 (100 MHz) spectrometers at ambient temperature with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 77.07 ppm). Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Gas chromatography was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using a DB 1701 capillary column (30 m x 0.25 mm). Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using a Zorbax Sil column.

I. Synthesis of 2-Methyl- and 2-*tert*-Butyl-Oxazoles and Thiazoles

2-methyl-4-phenyloxazole[1] **(1a)** and **2-methyl-4-(hydroxymethyl)oxazole**[2] **(1b)** were synthesized according to known procedures.

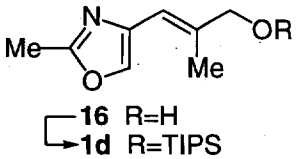


(3*R*)-1-*tert*-butyldimethylsilyloxy-3-(2-methyl(1,3-oxazol-4-yl))-3-triethylsilyloxypropane (1c). Analytical data: $[\alpha]_D^{25}$ +47.4° (*c* 1.75, CH_2Cl_2); IR (film) 2954, 2877, 1582, 1472, 1255, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H, oxazole-**H**), 4.82 (t, 1H, *J* = 6.0 Hz, C_3-**H**), 3.73 (dt, 1H, *J* = 10.1, 6.7 Hz, one of C_1-$\mathbf{H}_2$), 3.60 (dt, 1H, *J* = 10.2, 6.0 Hz, one of C_1-$\mathbf{H}_2$), 2.41 (s, 3H, oxazole-$\mathbf{CH}_3$) 2.00-1.90 (m, 2H, C_2-$\mathbf{H}_2$), 0.91 (t, 9H, *J* = 8.1 Hz, O-Si-(CH_2-$\mathbf{CH}_3$)$_3$), 0.87 (s, 9H, $OSi(CH_3)_2C(\mathbf{CH}_3)_3$), 0.58 (q, 6H, *J* = 8.0, O-Si-($\mathbf{CH}_2$-CH_3)$_3$), 0.020 (s, 3H, one of $OSi(\mathbf{CH}_3)_2C(CH_3)_3$), 0.014 (s, 3H, one of $OSi(\mathbf{CH}_3)_2C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 144.6, 134.2, 64.9, 59.3, 40.6, 26.0, 18.3, 14.0, 6.84, 4.82, -5.30; TLC (15%

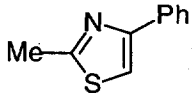
1) Rickborn, B.; Whitney, S. E. *J. Org. Chem.* **1991**, *56*, 3058-3063.

2) Garey, D.; Ramirez, M.; Gonzales, S.; Wertsching, A.; Tith, S.; Keefe, K.; Pena, M. R. *J. Org. Chem.* **1996**, *61*, 4853-4856.

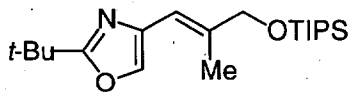
EtOAc/hexanes) R_f 0.48; HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI): Exact mass calcd for $C_{19}H_{40}NO_3Si_2$ $[M+H]^+$, 386.2547. Found 386.2555.



(2*E*)-2-methyl-3-(2-methyl(1,3-oxazol-4-yl))-1-triisopropylsilyloxyprop-2-ene (1d). The known alcohol[3] **16** (569 mg, 3.71 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (17 mL) and cooled with stirring to 0 °C under a nitrogen atmosphere. To this solution was added 2,6-lutidine (0.52 mL, 4.45 mmol, 1.2 equiv), followed by TIPSOTf (0.95 mL, 3.52 mmol, 0.95 equiv). The clear solution was allowed to stir 15 minutes and was then quenched with methanol (1 mL) and allowed to warm to room temperature. The mixture was partitioned between 30 mL dichloromethane and 50 mL saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with 30 mL dichloromethane. The combined organic extracts were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (hexanes to 10% EtOAc/hexanes) gave 933 mg (91%) as a clear and colorless oil: IR (film) 3154, 2943, 2866, 1587, 1464, 1382, 1308, 1161, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H, oxazole-**H**), 6.34 (s, 1H, C_3-**H**), 4.23 (s, 2H, C_1-$\mathbf{H}_2$), 2.44 (s, 3H, oxazole-$\mathbf{CH}_3$), 1.88 (s, 3H, C_2-$\mathbf{CH}_3$), 1.16-1.06 (m, 21H, $OSi(\mathbf{CH}(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 139.2, 138.5, 135.0, 112.8, 67.9, 18.1, 15.8, 13.9, 12.1; TLC (5% EtOAc/hexanes) R_f 0.1; HRMS (EI): Exact mass calcd for $C_{17}H_{31}NO_2Si$ $[M]^+$, 309.2124. Found 309.2121.



2-methyl-4-phenylthiazole (1e). The following procedure was adapted from that of Holzapfel, *et al.*[4] To a stirring solution of potassium bicarbonate (7.23 g, 72.3 mmol, 8 equiv) and thioacetamide (0.679 g, 9.03 mmol, 1 equiv) in dimethoxyethane (30 mL) was added bromoacetophenone (4.85g, 24.4 mmol, 2.7 equiv) The heterogeneous mixture was allowed to stir for 4.5 hours, and was then cooled to 0 °C. Pyridine (6.2 mL, 76.7 mmol, 8.5 equiv) was added, resulting in a bright yellow solution, followed by trifluoroacetic anhydride (5.2 mL, 37.0 mmol, 4.1 equiv) which resulted in the evolution of a large amount of gas. The mixture was allowed to warm to room temperature overnight, and was then filtered through a pad of celite (1 cm), rinsed with THF, and concentrated *in vacuo*. The resulting slurry was taken up in dichloromethane and was washed with water twice and saturated aqueous $CuSO_4$ once. The organic layer was dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to give a dark red oil. Purification by flash chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) provided 692 mg (44%) of an oil which crystallized at 0°C to an off-white powder. This material was identical in all respects (^1H NMR, ^{13}C NMR, MS, mp) to that reported by De Kimpe et al.[5]



(2*E*)-3-[2-(*tert*-butyl)(1,3-oxazol-4-yl)]-2-methyl-1-triisopropylsilyloxyprop-2-ene (13). Synthesized in a manner analogous to **1d**. Analytical Data: IR (film) 2944, 2867, 1570, 1464, 1366, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H, oxazole-**H**), 6.35 (s, 1H, C_3-**H**), 4.23 (s, 2H, C_1-$\mathbf{H}_2$), 1.92 (s, 3H, C_2-$\mathbf{CH}_3$), 1.38 (s, 9H, $C(\mathbf{CH}_3)_3$), 1.16-1.05 (m, 21H, $OSi(\mathbf{CH}(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 139.2, 137.9, 134.7, 113.5, 68.3, 33.6, 28.6, 18.1, 15.8, 12.1; TLC (5% EtOAc/hexanes) R_f 0.21; HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI): Exact mass calcd for $C_{20}H_{38}NO_2Si$ $[M+H]^+$, 352.2672. Found 352.2677.

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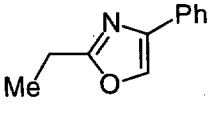
3) Nakada, M.; Susumu, K.; Shibasaki, M.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1039-1042.

4) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Comm.* **1990**, *20*, 2235-2249.

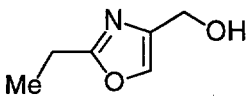
5) De Kimpe, N.; De Cock, W.; Keppens, M.; De Smaele, D.; Meszaros, A. *J. Heterocyclic Chem.* **1996**, *33*, 1179-1183.

II. Oxazole and Thiazole Methylation: Product Identification

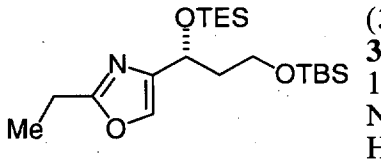
The following compounds were identified by comparison to reported spectral data: **2, 5-dimethyl-4-phenyloxazole (7a)**,[6] **2,5-dimethyl-4-(hydroxymethyl)oxazole (7b)**,[7] **2-ethyl-4-phenylthiazole (6e)**,[8] **2,5-dimethyl-4-phenylthiazole (7e)**.[9]



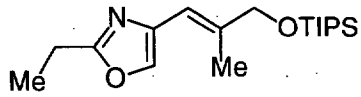
2-ethyl-4-phenyloxazole (6a). Analytical Data: IR (film) 3130, 3061, 2982, 2940, 1570, 1449, 1114, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H, oxazole-**H**), 7.73-7.70 (m, 2H, Ph**H**), 7.42-7.37 (m, 2H, Ph**H**), 7.30 (tt, 1H, J = 7.4, 1.5 Hz, Ph$\mathbf{H}_p$), 2.85 (q, 2H, J = 7.6, $\mathbf{CH_2}CH_3$), 1.38 (t, 3H, J = 7.6, $CH_2\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 140.6, 133.0, 131.4, 128.7, 128.0, 125.5, 21.9, 11.4; TLC (15% EtOAc/hexanes) R_f 0.41; HRMS (EI): Exact mass calcd for $C_{11}H_{11}NO$ $[M]^+$, 173.0841. Found 173.0849.



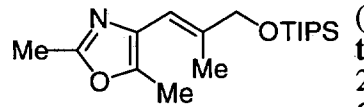
2-ethyl-4-(hydroxymethyl)oxazole (6b). Analytical Data: IR (film) 3327, 1573, 1461, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H, oxazole-**H**), 4.53 (d, 2H, J = 5.9 Hz, $\mathbf{CH_2}OH$), 4.48 (br s, 1H, O**H**), 2.75 (q, 2H, J = 7.6, $\mathbf{CH_2}CH_3$), 1.29 (t, 3H, J = 7.6, $CH_2\mathbf{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.1, 134.7, 56.0, 21.6, 11.1; TLC (30% acetone/CH_2Cl_2) R_f 0.24; HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$, 127.0633. Found 127.0634.



(3*R*)-1-*tert*-butyldimethylsilyloxy-3-(2-ethyl(1,3-oxazol-4-yl))-3-triethylsilyloxypropane (6c). Analytical Data: $[\alpha]_D^{25}$ +34.8° (*c* 1.46, CH_2Cl_2); IR (film) 2956, 2878, 1576, 1462, 1255, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H, oxazole-**H**), 4.83 (t, 1H, J = 6.2 Hz, C_3-**H**), 3.74 (dt, 1H, J = 10.2, 6.8 Hz, one of C_1-$\mathbf{H_2}$), 3.61 (dt, 1H, J = 10.1, 6.2 Hz, one of C_1-$\mathbf{H_2}$), 2.74 (q, 2H, J = 7.6 Hz, $\mathbf{CH_2}$-CH_3) 1.99-1.94 (m, 2H, C_2-$\mathbf{H_2}$), 1.30 (t, 3H, J = 7.6 Hz, CH_2-$\mathbf{CH_3}$), 0.91 (t, 9H, J = 8.0 Hz, O-Si-$(CH_2$-$\mathbf{CH_3})_3$), 0.88 (s, 9H, $OSi(CH_3)_2C(\mathbf{CH_3})_3$), 0.58 (q, 6H, J = 8.0 Hz, O-Si-$(\mathbf{CH_2}$-$CH_3)_3$), 0.021 (s, 3H, one of $OSi(\mathbf{CH_3})_2C(CH_3)_3$), 0.017 (s, 3H, one of $OSi(\mathbf{CH_3})_2C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 144.3, 133.9, 65.1, 59.4, 40.6, 26.0, 21.8, 18.3, 11.3, 6.86, 4.85, -5.35; TLC (10% EtOAc/hexanes) R_f 0.33; HRMS (CI, NH_3): Exact mass calcd for $C_{20}H_{42}NO_3Si_2$ $[M+H]^+$, 400.2704. Found 400.2697.



(2*E*)-3-(2-ethyl(1,3-oxazol-4-yl))-2-methyl-1-triisopropylsilyloxyprop-2-ene (6d). Analytical Data: IR (film) 3152, 2942, 2866, 1680, 1581, 1463, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H, oxazole-**H**), 6.36 (br s, 1H, C_3-**H**), 4.23 (d, 2H, J = 0.7 Hz, C_1-$\mathbf{H_2}$), 2.77 (q, 2H, J = 7.6 Hz, $\mathbf{CH_2}$-CH_3), 1.89 (d, 3H, J = 0.7, C_2-$\mathbf{CH_3}$), 1.33 (t, 3H, J = 7.6 Hz, CH_2-$\mathbf{CH_3}$), 1.16-1.05 (m, 21H, $OSi(\mathbf{CH}(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 139.2, 138.2, 134.8, 113.1, 68.1, 21.7, 18.1, 15.8, 12.1, 11.3; TLC (10% Et_2O/hexanes) R_f 0.28; HRMS (CI, NH_3): Exact mass calcd for $C_{18}H_{34}NO_2Si$ $[M+H]^+$, 324.2350. Found 324.2359.



(2*E*)-3-(2,5-dimethyl(1,3-oxazol-4-yl))-2-methyl-1-triisopropylsilyloxyprop-2-ene (7d). Analytical Data: IR (film) 2943, 2866, 1593, 1464, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (br s, 1H, C_3-**H**), 4.20 (s, 2H, C_1-$\mathbf{H_2}$), 2.39 (s, 3H, 2-$\mathbf{CH_3}$-oxazole), 2.23 (s, 3H, 5-

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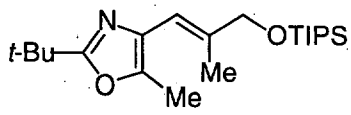
6) Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1992**, *57*, 3331-3336.

7) Kukla, M. J.; Fortunato, J. M. *J. Org. Chem.* **1984**, *49*, 5003-5006.

8) Aune, J. P.; Phan Tan Luu, R.; Vincent, E. J.; Metzger, J. *Bull. Chem. Soc. Fr.* **1972**, *7*, 2679-2684.

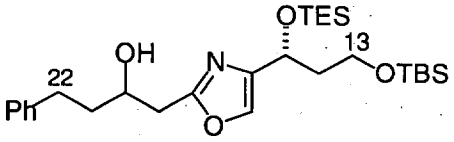
9) Vernin, G.; Aune, J. P.; Dou, H. J. M.; Metzger, J. *Bull. Chem. Soc. Fr.* **1967**, *12*, 4523-4533.

CH_3-oxazole), 1.99 (s, 3H, C_2-CH_3), 1.17-1.06 (m, 21H, $OSi(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 144.6, 137.7, 133.1, 110.8, 68.0, 18.1, 14.9, 14.0, 12.1, 10.4; TLC (10% EtOAc/hexanes) R_f 0.3; HRMS (EI): Exact mass calcd for $C_{18}H_{33}NO_2Si$ $[M]^+$, 323.2281. Found 323.2272.

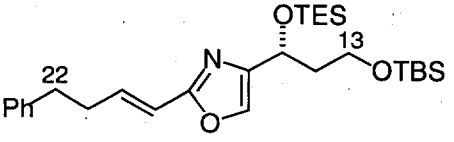


(2*E*)-3-[2-(*tert*-butyl)-5-methyl(1,3-oxazol-4-yl)]-2-methyl-1-triisopropylsilyloxyprop-2-ene (15). Analytical Data: IR (cell, CH_2Cl_2) 2964, 2945, 2867, 1572, 1463, 1388, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H, C_3-**H**), 4.21 (s, 2H, C_1-H_2), 2.24 (s, 3H, oxazole-CH_3), 2.02 (s, 3H, C_2-CH_3), 1.35 (s, 9H, $C(CH_3)_3$), 1.15-1.06 (m, 21H, $OSi(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 144.1, 137.9, 132.6, 111.2, 68.2, 33.5, 28.7, 18.1, 14.9, 12.2, 10.5; TLC (10% EtOAc/hexanes) R_f 0.47; HRMS (EI): Exact mass calcd for $C_{21}H_{39}NO_2Si$ $[M]^+$, 366.2828. Found 366.2829.

III. Experimental Procedures: Synthetic Utility[10]



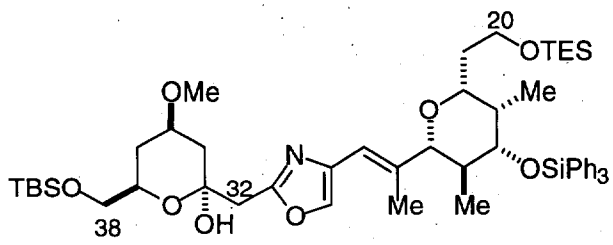
1-{4-[(1*R*)-3-*tert*-butyldimethylsilyloxy-1-triethylsilyloxy-propyl](1,3-oxazol-2-yl)}-4-phenylbutan-2-ol (8). The oxazole **1c** (53.4 mg, 0.138 mmol, 1 equiv) was dissolved in anhydrous THF (0.8 mL) and cooled with stirring to -78 °C under an argon atmosphere. A solution of lithium diethylamide was prepared by adding *n*-butyllithium (75 μL of a 2.03 M solution in hexanes, 0.152 mmol, 1.1 equiv) to a solution of diethylamine (17 μL, 0.166 mmol, 1.2 equiv) in THF (0.6 mL) at -78 °C. This solution was warmed to 0 °C for 10 min, then recooled to -78 °C and added to the oxazole solution *via* cannula. The resulting light yellow reaction mixture was allowed to stir for 10 minutes. Hydrocinnamaldehyde (22 μL, 0.166 mmol, 1.2 equiv) was then added *via* syringe, causing the color to fade. The reaction mixture was allowed to stir for 20 minutes at -78 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (5% EtOAc/hexanes to 10% EtOAc/hexanes) provided 52.6 mg (73%) of **8** (1:1 mixture of diastereomers) as a clear and colorless oil and 14.5 mg (27%) recovered **1c**. Analytical data for both diastereomers of **8**: IR (film) 3441, 2955, 2877, 1570, 1462, 1255, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 1H, J = 0.7 Hz, oxazole-**H**), 7.31-7.27 (m, 2H, Ph**H**), 7.23-7.17 (m, 3H, Ph**H**), 4.86 (t, 1H, J = 6.2 Hz, C_{15}-**H**), 4.12-4.05 (m, 1H, C_{20}-**H**) 3.87-3.84 (m, 1H, O**H**), 3.76 (dt, 1H, J = 10.2, 6.7 Hz, one of C_{13}-H_2), 3.66-3.60 (m, 1H, one of C_{13}-H_2), 2.93-2.71 (m, 4H, C_{19}-H_2 and C_{22}-H_2), 2.01-1.86 (m, 3H, C_{14}-H_2 and one of C_{21}-H_2), 1.79 (dtd, 1H, J = 17.6, 6.9, 4.2 Hz, one of C_{21}-H_2) 0.93 (t, 9H, J = 8.0 Hz, O-Si-$(CH_2$-$CH_3)_3$), 0.90 (s, 9H, $OSi(CH_3)_2C(CH_3)_3$), 0.61 (q, 6H, J = 8.0 Hz, O-Si-$(CH_2$-$CH_3)_3$), 0.044 (s, 3H, one of $OSi(CH_3)_2C(CH_3)_3$), 0.040 (s, 3H, one of $OSi(CH_3)_2C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 144.5, 141.9, 134.1, 128.5, 128.4, 125.9, 68.1, 64.8, 59.2, 40.5, 38.2, 35.4, 31.9, 30.0, 18.3, 6.84, 4.84, -5.29; TLC (15% EtOAc/hexanes) R_f 0.2; HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI): Exact mass calcd for $C_{28}H_{49}NO_4Si_2Na$ $[M+Na]^+$, 542.3071. Found 542.3098. Anal. Calcd. for $C_{28}H_{49}NO_4Si_2$: C, 64.69; H, 9.50; N, 2.69. Found: C, 64.82; H, 9.51; N, 2.78.



(3*R*)-1-*tert*-butyldimethylsilyloxy-3-[2-((1*E*)-4-phenylbut-1-enyl)(1,3-oxazol-4-yl)]-3-triethylsilyloxypropane (9). A dry tear-shaped flask with magnetic stirrer was charged with Martin sulfurane (181 mg, 0.269 mmol, 2 equiv) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box, flushed with argon, and dichloromethane (1 mL) was added *via* syringe. In a separate flask, the alcohol **8** (69.9 mg, 0.134 mmol, 1 equiv) was dissolved in dichloromethane (1.6 mL) under argon and cooled to 0 °C with stirring. The solution of the sulfurane was then added *via* cannula, and the resulting mixture was allowed to stir 5 minutes, at which point it was partitioned between

10) The phorboxazole numbering system is used for compounds in this section. See: Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126-8131.

saturated aqueous sodium bicarbonate and dichloromethane. The aqueous layer was extracted two times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (hexanes to 7.5% Et_2O/hexanes) and concentration *in vacuo* under 60 mm Hg overnight provided 67.7 mg (quant.) of **9** as a clear and colorless oil. HPLC analysis (Zorbax Sil, 4% EtOAc/hexanes, 0.7 mL/min, 254 nm; t_r (minor) = 9.5, t_r (major) = 14.9) gave the isomeric composition of the product as 95:5. Analytical data: IR (film) 3027, 2954, 2877, 1662, 1533, 1456, 1255, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H, oxazole-**H**), 7.30-7.28 (m, 2H, Ph**H**), 7.22-7.20 (m, 3H, Ph**H**), 6.72 (dt, 1H, *J* = 16.0, 6.9 Hz, C_{20}-**H**), 6.30 (dt, 1H, *J* = 16.0, 1.5 Hz, C_{19}-**H**), 4.87 (t, 1H, *J* = 6.3 Hz, C_{15}-**H**), 3.76 (dt, 1H, *J* = 10.2, 6.6 Hz, one of C_{13}-$\mathbf{H_2}$), 3.63 (dt, 1H, *J* = 10.2, 6.0 Hz, one of C_{13}-$\mathbf{H_2}$), 2.81 (t, 2H, *J* = 7.4 Hz, C_{22}-$\mathbf{H_2}$), 2.60-2.54 (m, 2H, C_{21}-$\mathbf{H_2}$), 2.03-1.91 (m, 2H, C_{14}-$\mathbf{H_2}$), 0.93 (t, 9H, *J* = 8.0 Hz, O-Si-(CH_2-$\mathbf{CH_3}$)$_3$), 0.89 (s, 9H, OSi(CH_3)$_2$C($\mathbf{CH_3}$)$_3$), 0.60 (q, 6H, *J* = 8.0 Hz, O-Si-($\mathbf{CH_2}$-CH_3)$_3$), 0.041 (s, 3H, one of OSi($\mathbf{CH_3}$)$_2$C(CH_3)$_3$), 0.037 (s, 3H, one of OSi($\mathbf{CH_3}$)$_2$C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 145.6, 141.1, 138.6, 133.7, 128.5, 128.4, 126.1, 117.3, 65.1, 59.3, 40.7, 34.9, 34.5, 26.0, 18.3, 6.85, 4.83, -5.28; TLC (10% EtOAc/hexanes) R_f 0.3; HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI): Exact mass calcd for $C_{28}H_{47}NO_3Si_2Na$ $[M+Na]^+$, 524.2992. Found 524.2994. Anal. Calcd. for $C_{28}H_{47}NO_3Si_2$: C, 67.01; H, 9.44; N, 2.79. Found: C, 67.17; H, 9.44; N, 2.77.



2-{[4-((*E*)-2-{(3*S*,4*S*,5*S*,2*R*,6*R*)-3,5-dimethyl-6-triethylsilyloxy-4-triphenylsilyloxy-tetrahydro-2*H*-pyran-2-yl}prop-1-enyl)(oxazol-2-yl)]methyl}(2*S*,4*R*,6*R*)-6-[(*tert*-butyldimethlsilyloxy)methyl]-4-methoxy-tetrahydro-2*H*-pyran-2-ol (12).
A 10-mL concentration flask containing a solution of oxazole **10** (99.7 mg, 0.149 mmol, 1 equiv) in THF (0.50 mL) was cooled to –78 °C. A $LiNEt_2$ solution [prepared at –78 °C from diethylamine (23 μL, 0.224 mmol, 1.5 equiv), *n*-butyllithium (88.5 μL of a 2.36 M solution in hexanes, 0.209 mmol, 1.4 equiv), and THF (1.00 mL)] was added dropwise *via* gastight syringe. The oxazole solution turned a characteristic bright yellow color. After exactly 10 min of stirring at –78 °C a solution of lactone **11** (56.0 mg, 0.208 mmol, 1.4 equiv, azeotropically dried 3 X 5 mL benzene) in THF (0.50 mL) at –78 °C was added to the lithiooxazole solution *via* canula. The color faded to a very light brownish-yellow before all of the lactone was added. After 15 min, the reaction was quenched with 20 mL water and diluted with 20 mL CH_2Cl_2. The layers were separated and the aqueous phase was extracted 3 X 10 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a glass frit, and concentrated *in vacuo*. The light yellow product was purified by flash chromatography (silica gel; 17.5% to 20% EtOAc/hexanes) to give the lactol **12** (120.0 mg, 85%) as a clear oil. Also recovered from the chromatography were unreacted oxazole **10** (4.0 mg, 4%) and excess lactone **11** (12.5 mg, 0.30 equiv). Analytical data for **12**: $[\alpha]_D^{25}$ +5.1° (*c* 1.00, CH_2Cl_2); IR (film) 3358, 3070, 2951, 2929, 2876, 1573, 1461, 1429, 1379, 1361, 1251, 1163, 1115, 1088, 1019, 970, 837, 777, 740, 711, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.62 (m, 6H, Ar$\mathbf{H}_o$), 7.48 (s, 1H, C_{30}-**H**), 7.46–7.41 (m, 3H, Ar$\mathbf{H}_p$), 7.40–7.36 (m, 6H, Ar$\mathbf{H}_m$), 6.09 (s, 1H, C_{28}-**H**), 5.36 (d, 1H, *J* = 2.2 Hz, C_{33}-O**H**), 3.91 (dddd, 1H, *J* = 11.9, 5.0, 5.0, 2.0 Hz, C_{37}-**H**), 3.78 (dddd, 1H, *J* = 11.2, 11.1, 4.5, 4.5 Hz, C_{35}-**H**), 3.70 (dd, 1H, *J* = 10.1, 4.6 Hz, C_{24}-**H**), 3.57 (dd, 1H, *J* = 10.6, 5.1 Hz, one of C_{38}-$\mathbf{H_2}$), 3.57–3.51 (m, 2H, C_{20}-**H**), 3.49 (dd, 1H, *J* = 10.6, 5.1 Hz, one of C_{38}-$\mathbf{H_2}$), 3.41 (ddd, 1H, *J* = 8.3, 4.0, 1.3 Hz, C_{22}-**H**), 3.38 (s, 3H, C_{35}OC$\mathbf{H_3}$), 3.29 (d, 1H, *J* = 10.2 Hz, C_{26}-**H**), 3.08 (d, 1H, *J* = 15.3 Hz, one of C_{32}-$\mathbf{H_2}$), 2.99 (d, 1H, *J* = 15.3 Hz, one of C_{32}-$\mathbf{H_2}$), 2.29 (ddd, 1H, *J* = 12.0, 4.5, 2.1 Hz, C_{34}-$\mathbf{H_{eq}}$), 2.10 (dddd, 1H, *J* = 12.3, 4.4, 2.2, 2.2 Hz, C_{36}-$\mathbf{H_{eq}}$), 1.94–1.85 (m, 1H, C_{25}-**H**), 1.92 (s, 3H, C_{27}-$\mathbf{CH_3}$), 1.76–1.65 (m, 2H, C_{23}-**H** and one of C_{21}-$\mathbf{H_2}$), 1.49–1.42 (m, 1H, one of C_{21}-$\mathbf{H_2}$), 1.32 (ddd, 1H, *J* = 11.4, 11.4, 2.3 Hz, C_{34}-$\mathbf{H_{ax}}$), 1.14 (ddd, 1H, *J* = 11.8, 11.8, 11.8 Hz, C_{36}-$\mathbf{H_{ax}}$), 1.03 (d, 3H, *J* = 6.8 Hz, C_{23}-$\mathbf{CH_3}$), 0.90 (t, 9H, *J* = 8.0 Hz, OSi($CH_2\mathbf{CH_3}$)$_3$), 0.83 (s, 9H, OSi(CH_3)$_2$C($\mathbf{CH_3}$)$_3$), 0.66 (d, 3H, *J* = 6.5 Hz, C_{25}-$\mathbf{CH_3}$), 0.54 (q, 6H, *J* = 7.9 Hz, OSi($\mathbf{CH_2}CH_3$)$_3$), –0.28 (s, 3H, one of OSi($\mathbf{CH_3}$)$_2$C(CH_3)$_3$), –0.59 (s, 3H, one of OSi($\mathbf{CH_3}$)$_2$C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 138.8, 137.7, 135.6, 135.4, 134.8, 130.0, 127.8, 117.8, 96.5, 88.5, 78.9, 74.5, 73.2, 69.9, 66.3, 59.4, 55.6, 40.8, 39.7, 38.9, 36.0, 35.1, 33.7, 25.9, 18.3, 14.5, 14.2, 6.82, 6.41, 4.37, –5.31, –5.37; TLC (30% EtOAc/hexanes) R_f 0.4;

HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI): Exact mass calcd for $C_{53}H_{79}NO_8Si_3Na$ $[M+Na]^+$, 964.5011. Found 964.5012.

IV. Experimental Procedure: Lithiated Oxazole Equilibration

Representative procedure: The oxazole **1d** (39.5 mg, 0.128 mmol, 1 equiv) was dissolved in anhydrous THF (1.3 mL) and was cooled with stirring to -78 °C under an argon atmosphere. A solution of *n*-butyllithium (66 μL of a 2.03 M solution in hexanes, 0.134 mmol, 1 equiv) was added dropwise *via* syringe. The resulting yellow reaction mixture was allowed to stir for 10 minutes, after which diethylamine (40 μL, 0.384 mmol, 3 equiv) was added. After ten minutes, methyl triflate (29 μL, 0.256 mmol, 2 equiv) was added, which resulted in the complete disappearance of color. The solution was allowed to stir 20 minutes at -78 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted two times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford 40.0 mg as a crude yellow oil. This material was identified by ^1H NMR (400 MHz, $CDCl_3$) to contain **6d** as the only methylated product along with ≤7% starting material **1d**.

V. Experimental Procedure: Crossover Experiments

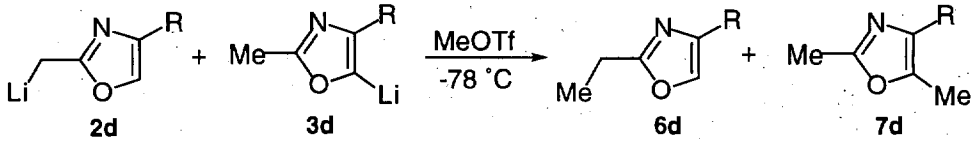
Crossover experiment (no amine): The oxazole **13** (21.06 mg, 0.06 mmol, 1 equiv) was dissolved in anhydrous THF (0.67 mL) and was cooled with stirring to -78 °C under an argon atmosphere. A solution of *n*-butyllithium (30 μL of a 2.03 M solution in hexanes, 0.06 mmol, 1 equiv) was added dropwise *via* syringe. The resulting faint-yellow reaction mixture was allowed to stir for 10 minutes, after which the oxazole **1d** (63 μL of a 0.957 M solution in anhydrous THF, 0.06 mmol, 1 equiv) was added. The reaction was allowed to stir for 10 minutes, and was then treated with methyl triflate (14 μL, 0.12 mmol, 2 equiv) which resulted in the complete disappearance of color. The solution was allowed to stir 20 minutes at -78 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted two times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford 33.7 mg as a crude yellow oil. This material was identified by ^1H NMR (400 MHz, $CDCl_3$) to contain **15** as the only methylated product along with unreacted **1d**.

Crossover experiment (amine): The oxazole **13** (21.06 mg, 0.06 mmol, 1 equiv) was dissolved in anhydrous THF (0.67 mL) and was cooled with stirring to -78 °C under an argon atmosphere. A solution of *n*-butyllithium (30 μL of a 2.03 M solution in hexanes, 0.06 mmol, 1 equiv) was added dropwise *via* syringe. The resulting faint yellow reaction mixture was allowed to stir for 10 minutes, after which the oxazole **1d** (63 μL of a 0.957 M solution in anhydrous THF, 0.06 mmol, 1 equiv) was added. The reaction was allowed to stir for 10 minutes. At this point, diethylamine (9 μL, 0.09 mmol, 1.5 equiv) was added. The solution immediately became bright yellow. After ten minutes, methyl triflate (14 μL, 0.12 mmol, 2 equiv) was added, which resulted in the complete disappearance of color. The solution was allowed to stir 20 minutes at -78 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted two times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford 34.8 mg as a crude yellow oil. This material was identified by ^1H NMR (400 MHz, $CDCl_3$) to contain **6d** as the only methylated product along with unreacted **13**.

VI. Low-Temperature ^1H NMR Studies of Metallated Oxazoles

The possibility raised in footnote 18 that the lithiated oxazole **2d** could give rise to **7d** by ring alkylation and aromatization was investigated by low-temperature ^1H NMR. Treatment of oxazole **1d** with lithium diethylamide (entry 1) allowed the observation of a species that is consistent with **2d**. The use of LDA (entry 2) generated a mixture of two species which were identified as **2d** and a new intermediate consistent with **3d**. This mixture could be converted almost completely to **2d** upon warming. The reactions were treated with methyl triflate at -78 °C, and the ratios of **6d** to **7d** were measured by ^1H NMR. The agreement between the ratio of isomeric lithio-oxazoles and methylated products indicates that ring alkylation of intermediate **2d** is not occurring.

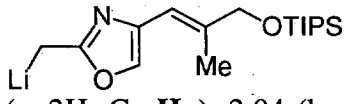
Table 3. Observation of Lithiated Intermediates by ^{1}H NMR[a]



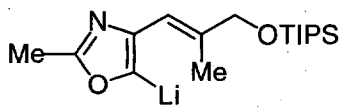
entry	base	temp.[b]	time	**2d**:**3d**	**6d**:**7d**[c]
1	Et_2NH	-	-	>95:5	>95:5
2	LDA	-	-	36:64	38:62
3	LDA	-30 °C	30 min.	95:5	95:5

[a]All reactions were carried out in THF-d8 and proceeded to ≥87% conversion. [b]After lithiation at -78 °C, the oxazole and base were warmed to this temperature for the indicated amount of time, then recooled to -78 °C prior to the addition of methyl triflate. [c]Ratio determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectra of the isolated crude product.

Representative procedure: A solution of lithium diethylamide in THF was prepared using diethylamine (103 µL, 1 mmol), *n*-butyllithium (494 µL of a 2.03 M solution in hexanes, 1 mmol) and 0.5 mL anhydrous THF at -78 °C under an argon atmosphere. The solution was concentrated (1 mm Hg) for 10 minutes at 0 °C, then warmed to room temperature over 17 minutes while under vacuum. The flask was backfilled with argon and the white solid material was taken up in THF-d8 (0.5 mL). The solution of lithium diethylamide was determined to be 0.181 M by titration (2,6-di-*tert*-butyl-4-methylphenol with fluorene as indicator). To an oven-dried 5-mm NMR tube fitted with a septa was added a solution of oxazole **1d** in THF-d8 (636 µL of a 0.110 M solution, 0.07 mmol, 1 equiv). This was cooled under an argon atmosphere to -78 °C, and then lithium diethylamide (54 µL, 0.098 mmol, 1.4 equiv) was added. The solution was mixed manually by shaking, resulting in a bright yellow color, and was immediately placed in the probe of a Brucker AM-400 (400 MHz) spectrometer that had been cooled to -78 °C. After approximately ten minutes, the reaction was quenched at -78 °C with methyl triflate (16 µL, 0.14 mmol, 2 equiv), with mixing accomplished by manual shaking. The clear reaction mixture was allowed to stand for up to two hours at -78 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted two times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford 19 mg of a crude yellow oil, which was identified to contain **6d** as the only methylated product along with ≤12% starting material **1d**.



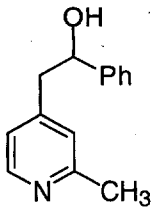
(2E)-2-methyl-3-[2-(lithiomethyl)(1,3-oxazol-4-yl)]-1-triisopropylsilyloxyprop-2-ene (2d). Spectral Data: ^{1}H NMR (400 MHz, THF-d8, -78 °C) δ 6.50 (s, 1H, oxazole-**H**), 6.02 (s, 1H, C_3-**H**), 4.17 (s, 2H, C_1-$\mathbf{H}_2$), 2.04 (br s, 1H, one of $\mathbf{CH}_2$Li), 1.98 (s, 1H, one of $\mathbf{CH}_2$Li), 1.71 (s, 3H, C_2-$\mathbf{CH}_3$), 1.08-0.90 (m, 21H, OSi(C**H**($\mathbf{CH}_3$)$_2$)$_3$).[11]



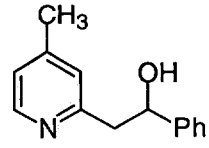
(2E)-2-methyl-3-(5-lithio-2-methyl(1,3-oxazol-4-yl))-1-triisopropylsilyloxyprop-2-ene (3d). Spectral Data: ^{1}H NMR (400 MHz, THF-d8, -78 °C) δ 6.45 (s, 1H, C_3-**H**), 4.14 (s, 2H, C_1-$\mathbf{H}_2$), 2.25 (s, 3H, oxazole-C**H**$_3$), 2.20 (s, 3H, C_2-C**H**$_3$), 1.07-0.93 (m, 21H, OSi(C**H**($\mathbf{CH}_3$)$_2$)$_3$).

11) At -30 °C, the signals for -$\mathbf{CH}_2$Li become a singlet at ca. 2.02 ppm.

VII. Lithiation of 2,4-Lutidine



2-(2-methyl(4-pyridyl))-1-phenylethan-1-ol (16). 2,6-lutidine (23 μL, 0.2 mmol, 1 equiv) was dissolved in anhydrous THF (1.2 mL) and cooled with stirring to -50 °C under an argon atmosphere. A solution of lithium diethylamide was prepared by adding *n*-butyllithium (138 μL of a 2.03 M solution in hexanes, 0.28 mmol, 1.4 equiv) to a solution of diethylamine (31 μL, 0.3 mmol, 1.5 equiv) in THF (0.8 mL) at -50 °C. This solution was warmed to 0 °C for 10 min, then recooled to -50 °C and added to the lutidine solution *via* cannula. The resulting orange reaction mixture was allowed to stir for 10 minutes, during which time the color turned to yellow. Benzaldehyde (41 μL, 0.4 mmol, 2 equiv) was then added *via* syringe, causing the color to disappear. The reaction mixture was allowed to stir for 20 minutes at -50 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford a crude oil, which contained none of the isomeric **17** by ^{1}H NMR. Purification by flash chromatography (50% EtOAc/hexanes to 80% EtOAc/hexanes) provided 40.4 mg (95%) of **16** as a clear and colorless oil. Analytical data: IR (film) 3178, 1609, 1560, 1493, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, J = 5.1 Hz, C_6py-**H**), 7.27-7.37 (m, 5H, Ph**H**), 6.96 (s, 1H, C_3py-**H**), 6.89 (d, 1H, J = 5.2 Hz, C_5py-**H**), 4.91 (dd, 1H, J = 5.5, 7.7 Hz, C_1-**H**), 3.16 (br s, 1H, C_1-O**H**), 2.92-3.00 (m, 2H, C_2-**H**$_2$), 2.45 (s, 3H, py-C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 148.8, 147.8, 143.7, 128.5, 127.8, 125.9, 124.5, 122.0, 74.5, 45.2, 24.2; TLC (30% Acetone/CH_2Cl_2) R_f 0.24; HRMS (CI, NH_3): Exact mass calcd for $C_{14}H_{16}NO$ $[M+H]^+$, 214.1232. Found 214.1235.



2-(4-methyl(2-pyridyl))-1-phenylethan-1-ol (17). 2,6-lutidine (23 μL, 0.2 mmol, 1 equiv) was dissolved in anhydrous THF (2 mL) and cooled with stirring to -50 °C under an argon atmosphere. A solution of *n*-butyllithium (99 μL of a 2.03 M solution in hexanes, 0.2 mmol, 1.0 equiv) was added dropwise *via* syringe. The resulting orange reaction mixture was allowed to stir for 10 minutes. Benzaldehyde (41 μL, 0.4 mmol, 2 equiv) was then added *via* syringe, causing the orange color to disappear. The reaction mixture was allowed to stir for 20 minutes at -50 °C, and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo* to afford a crude oil, which contained none of the isomeric **16** by ^{1}H NMR. Purification by flash chromatography (35% EtOAc/hexanes to 45% EtOAc/hexanes) provided 36.6 mg (86%) of **17** as a white solid. While the melting point matches that reported by Proctor,[12] the ^{1}H NMR does not. We believe our assignment to be correct, however, given the similarity of our NMR data to that reported by Trigo[13] for 2-(2-pyridyl)-1-phenylethan-1-ol (the desmethyl analog of **17**). Analytical data: mp 91.5-92.5 °C; IR (KBr) 3158, 1611, 1564, 1487, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1H, J = 5.1 Hz, C_6py-**H**), 7.42-7.44 (m, 2H, Ph**H**), 7.32-7.36 (m, 2H, Ph**H**), 7.23-7.28 (m, 1H, Ph**H**), 7.00 (d, 1H, J = 4.9 Hz, C_5py-**H**), 6.93 (s, 1H, C_3py-**H**) 5.89 (br s, 1H, C_1-O**H**),5.13 (dd, 1H, J = 3.7, 8.6 Hz, C_1-**H**), 3.01-3.12 (m, 2H, C_2-**H**$_2$), 2.31 (s, 3H, py-C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 148.3, 148.1, 144.3, 128.3, 127.3, 125.9, 124.7, 122.8, 73.4, 45.6, 21.0; TLC (30% Acetone/CH_2Cl_2) R_f 0.49; HRMS (CI, NH_3): Exact mass calcd for $C_{14}H_{16}NO$ $[M+H]^+$, 214.1232. Found 214.1233.

Equilibration with Et_2NH: The reaction was run exactly as indicated for the preparation of **17**, except prior to the introduction of benzaldehyde, diethylamine (31 μL, 0.3 mmol, 1.5 equiv) was added and the mixture allowed to stir for 10 minutes, over which time the color changed from orange to yellow. A crude oil was obtained which contained none of isomer **17** by ^{1}H NMR. Purification by flash chromatography (50% EtOAc/hexanes to 80% EtOAc/hexanes) provided 37 mg (87%) of **16** as a clear and colorless oil.

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12) Smith, F. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. I* **1980**, 2141-2145.
13) Trigo, G. G.; Galvez, E.; Sollhuber, M. M. *J. Heterocyclic Chem.* **1979**, *16*, 1625.