Electronic Supplementary Material (ESI) for Chemical Science

Supporting Information

Platinum-Catalyzed Cyclizations via Carbene Intermediates: Syntheses of Complementary Positional Isomers of Isoxazoles

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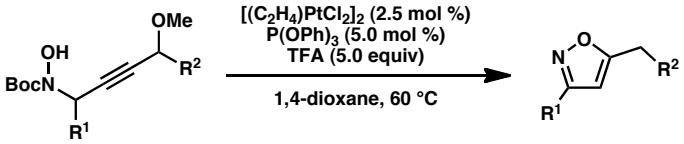
Materials and Methods: Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns. 1,4-dioxane was distilled over sodium/benzophenone. Triphenyl phosphite was purified by passing through an alumina column under an argon atmosphere. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or $KMnO_4$ solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on a Varian 400 MR (at 400 MHz), and are reported relative to $SiMe_4$ (δ 0.00). ^{2}H NMR spectra were acquired on a Varian 400 MR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27. All gas chromatography was performed on a Varian CP-3800 gas chromatograph. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.

Platinum Catalyzed Isoxazole Synthesis, *N*-Hydroxycarbamates:

Table 2.



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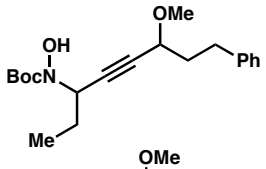
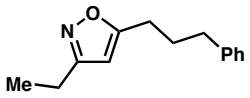
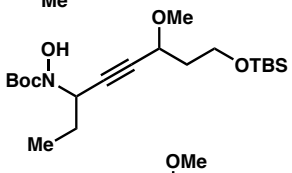
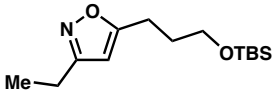
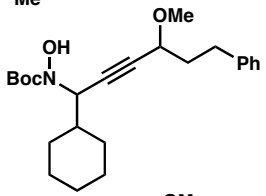
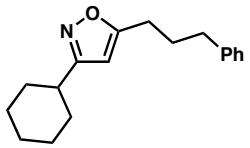
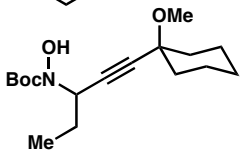
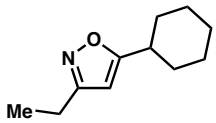
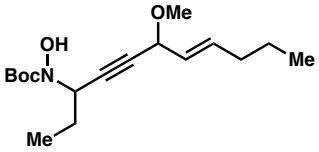
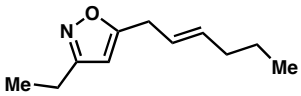
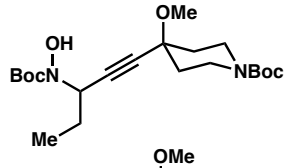
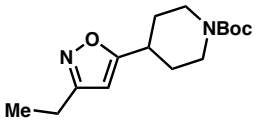
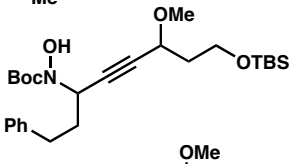
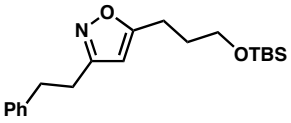
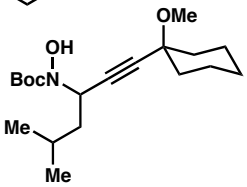
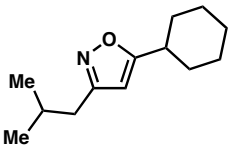
1			12	84
2			1	79
3			4	68
4			12	70
5			7	61
6			40	71
7			16	63
8			16	63

[a] Isolated yields

General procedure for the platinum catalyzed isoxazole synthesis from propargylic *N*-hydroxycarbamates. To a solution of triphenylphosphite (5.0 mol %) in 1,4-dioxane (1/3 of reaction volume) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min, trifluoroacetic acid (5.00 equiv) was added and the mixture was stirred for 1 min. The

resulting solution was then added to a solution of the *N*-hydroxycarbamates in 1,4-dioxane (2/3 of reaction volume, 0.10 M in substrate–final concentration), and the mixture was heated at 60 °C in a sealed vial. Upon completion, as determined by TLC, the reaction was quenched with of Et_3N (0.500 mL), and filtered through a plug of silica gel. The plug was washed with additional solvent (2x reaction volume). The solvent was then removed via rotary evaporation, and the crude isoxazole was purified by silica gel flash chromatography.

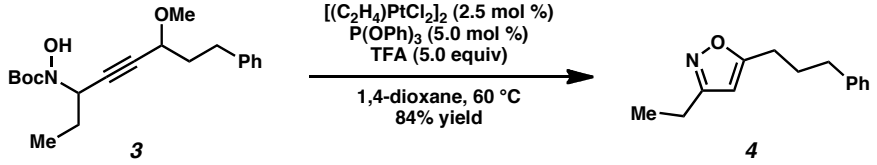


Table 2, Entry 1. According to the general procedure, to a solution of triphenylphosphite (39.3 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **3** (0.104 g, 0.300 mmol) in 1,4-dioxane (1.87 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 12 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **4** (54.1 mg, 84% yield, R_F = 0.54 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 5.83 (s, 1H), 2.69 (comp m, 6H), 2.02 (quintet, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 165.3, 141.4, 128.59, 128.57, 126.2, 100.3, 35.2, 29.2, 26.3, 19.7, 12.8; IR (film) 2936, 2360, 1602, 1455, 1368, 1159, 746 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{17}NO + H]^+$: 216.1383, found 216.1372.

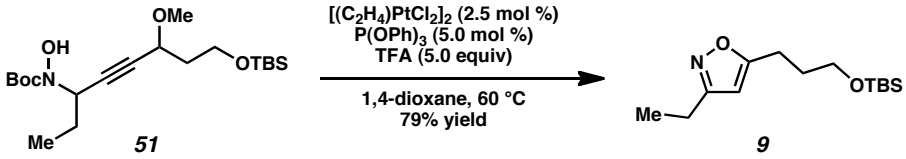


Table 2, Entry 2. According to the general procedure, to a solution of triphenylphosphite (39.3 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere, was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **51** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1

hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **9** (63.7 mg, 79% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.92-1.85 (m, 3H), 1.25 (t, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 165.3, 100.3, 61.9, 30.7, 26.1, 23.4, 19.7, 18.4, 12.8, -5.22; IR (film) 2956, 1604, 1255, 1104, 836 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{27}NO_2Si + H]^+$: 270.1884, found 270.1892.

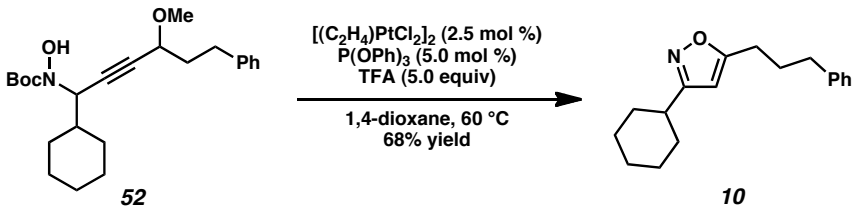


Table 2, Entry 3. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **52** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 4 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **10** (55.0 mg, 68% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (comp m, 2H), 7.22-7.18 (comp m, 3H), 5.82 (s, 1H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.02 (sextet, *J* = 7.6 Hz, 2H), 1.97-1.95 (comp m, 2H), 1.83-1.79 (comp m, 2H), 1.75-1.71 (m, 1H), 1.48-1.33 (comp m, 5H), 1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.5, 141.4, 128.57, 128.54, 126.1, 99.19, 99.17, 36.0, 35.3, 32.2, 29.2, 26.29, 26.13, 26.04; IR (film) 2929, 1602, 1450, 902, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{23}NO + H]^+$: 270.1852, found 270.1850.

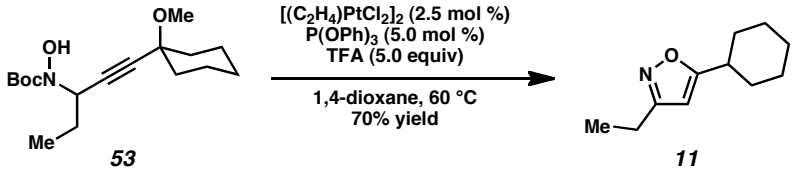


Table 2, Entry 4. According to the general procedure, to a solution of triphenylphosphite (65.6 μL, 10% (v/v) solution in 1,4-dioxane, 0.0250 mmol) in 1,4-dioxane (1.50 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (7.3 mg, 0.0125 mmol). After 15 min, trifluoroacetic acid (0.186 mL, 2.00 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **53** (0.156 g, 0.500 mmol) in 1,4-dioxane (3.50 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred

for 12 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (8.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **11** (62.8 mg, 70% yield, R_F = 0.64 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 2.71 (ddd, *J* = 14.6, 7.2, 3.7 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.04-2.00 (comp m, 2H), 1.79 (comp m, 2H), 1.70 (m, 1H), 1.46-1.31 (comp m, 5H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 165.0, 98.3, 36.5, 31.3, 25.97, 25.84, 19.8, 12.8; IR (film) 2933, 1680, 1597, 1450, 981, 801 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{17}NO + H]^+$: 180.1383, found 180.1377.

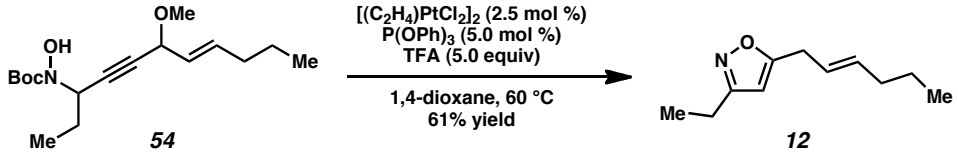


Table 2, Entry 5. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **54** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 7 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **12** (32.7 mg, 61% yield, R_F = 0.60 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.68-5.61 (m, 1H), 5.57-5.50 (m, 1H), 3.42 (dt, *J* = 6.5, 1.0 Hz, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.07-2.01 (m, 2H), 1.43 (sextet, *J* = 7.4 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.4, 134.6, 123.5, 100.5, 34.7, 30.4, 22.5, 19.8, 13.8, 12.9; IR (film) 2965, 1700, 1460, 1251, 966 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{17}NO + H]^+$: 180.1383, found 180.1374.

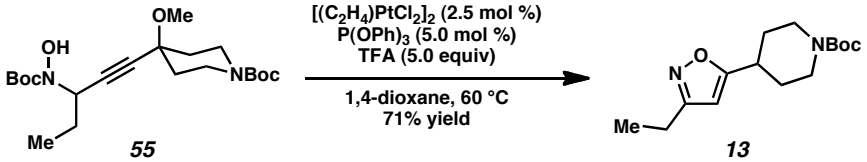


Table 2, Entry 6. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **55** (0.124 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial

was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 40 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **13** (68.4 mg, 71% yield, R_F = 0.40 in 2:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 13: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (app d, *J* = 0.7 Hz, 1H), 4.12 (comp m, 2H), 2.92-2.82 (comp m, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.00-1.95 (m, 2H), 1.65-1.53 (m, 2H), 1.44 (s, 9H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 165.2, 154.8, 98.9, 79.8, 43.44, 43.40, 34.7, 30.2, 28.5, 19.7, 12.7; IR (film) 2976, 1695, 1599, 1423, 1169, 770 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{24}N_2O_3 + Na]^+$: 303.1679, found 303.1685.

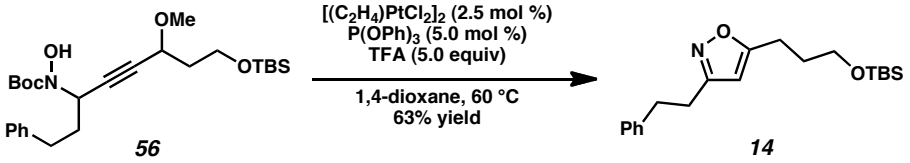


Table 2, Entry 7. According to the general procedure, to a solution of triphenylphosphite (39.3 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **56** (0.142 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 16 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **14** (64.7 mg, 63% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 14: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 5.76 (s, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.00-2.92 (m, 4H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.91-1.84 (m, 2H), 0.91-0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.3, 140.9, 128.61, 128.49, 126.4, 100.7, 61.9, 34.6, 30.6, 28.1, 26.1, 23.3, 18.4, -5.2; IR (film) 2930, 1710, 1603, 1256, 1104, 837 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{31}NO_2Si + H]^+$: 346.2197, found 346.2200.

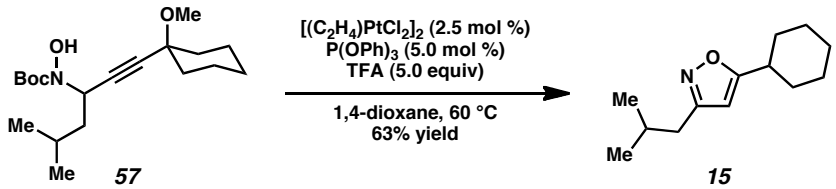


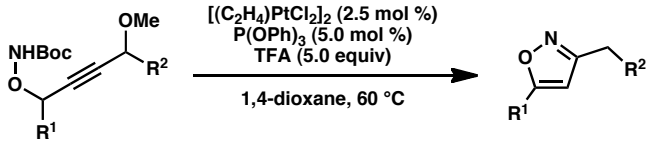
Table 2, Entry 8. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic

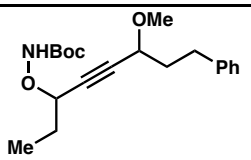
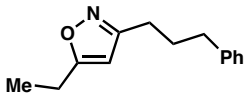
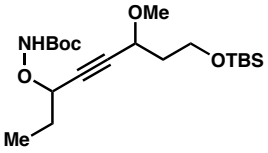
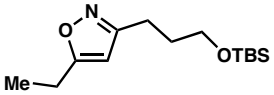
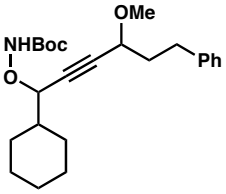
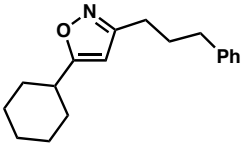
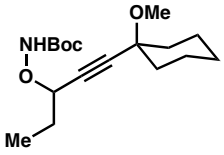
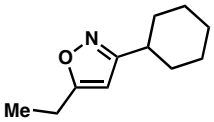
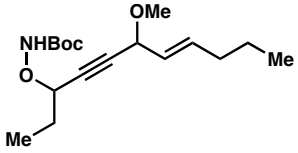
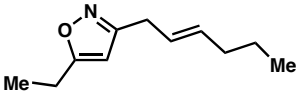
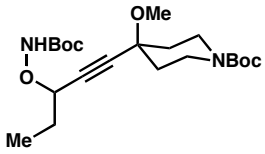
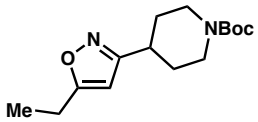
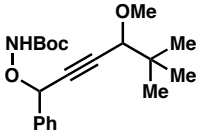
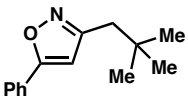
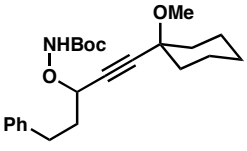
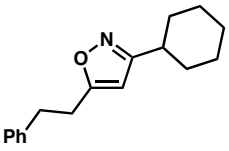
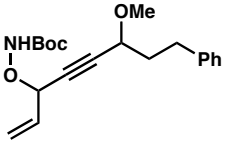
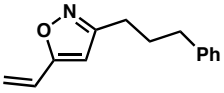
acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **57** (0.102 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 16 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **15** (39.1 mg, 63% yield, R_F = 0.61 in 4:1 hexanes/EtOAc) as a colorless oil.

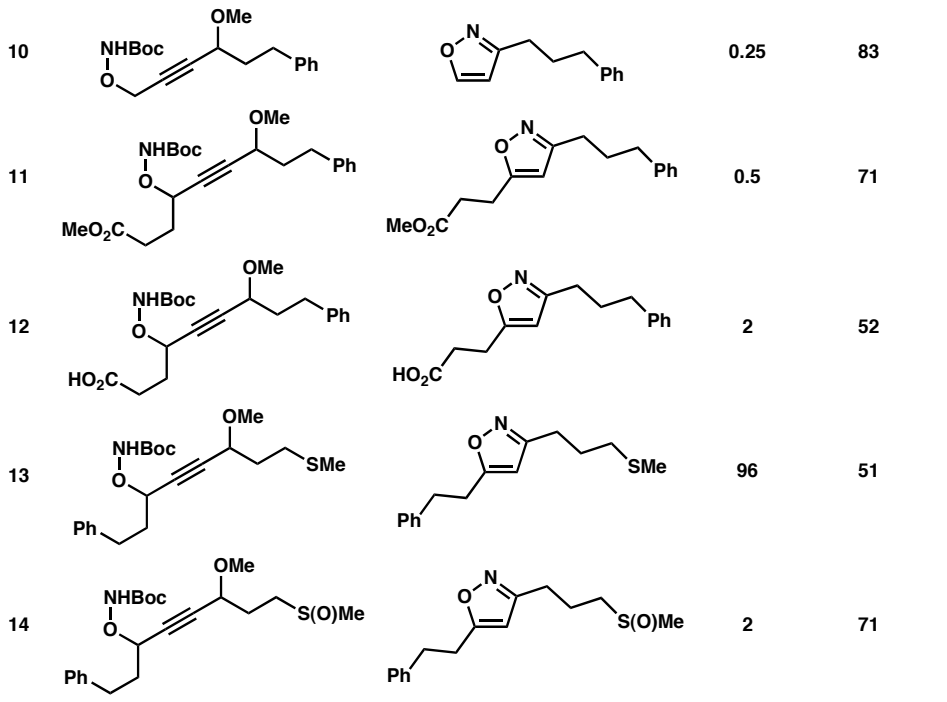
Isoxazole 15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 2.72 (ddd, *J* = 8.2, 6.5, 6.3 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 2.04-2.02 (m, 2H), 1.94 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.79 (dt, *J* = 8.3, 3.8 Hz, 2H), 1.73-1.69 (m, 1H), 1.49-1.23 (m, 5H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 163.0, 99.0, 36.4, 35.2, 31.3, 28.1, 25.98, 25.84, 22.6; IR (film) 2932, 1597, 1450, 1170, 1022, 792 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{21}NO + H]^+$: 208.1696, found 208.1696.

Platinum Catalyzed Isoxazole Synthesis, Carbamoyl Ethers:

Table 3.



Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			4	93
2			1.5	96
3			0.25	96
4			1.5	86
5			0.25	88
6			1.5	93
7			0.5	75
8			0.5	75
9			0.25	89



[a] Isolated yields

General procedure for the platinum catalyzed isoxazole synthesis from propargylic carbamoyl ethers. To a solution of triphenylphosphite (5.0 mol %) in 1,4-dioxane (1/3 of reaction volume) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min, trifluoroacetic acid (5.00 equiv) was added and the mixture was stirred for 1 min. The resulting solution was then added to a solution of the carbamoyl ethers in 1,4-dioxane (2/3 of reaction volume, 0.10 M final concentration), and the mixture was heated at 60 °C in a sealed vial. Upon completion, as determined by TLC, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel, washing with additional solvent (2x reaction volume). The solvent was then removed via rotary evaporation, and the crude isoxazole was purified by silica gel flash chromatography.

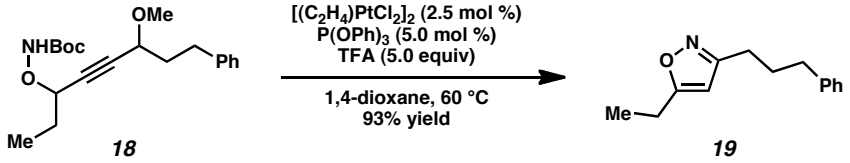


Table 3, Entry 1. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **18** (0.104 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 4 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation,

and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **19** (59.8 mg, 93% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 19: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.81 (s, 1H), 2.76-2.64 (m, 6H), 1.99 (quintet, *J* = 7.7 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 163.8, 141.8, 128.60, 128.50, 126.0, 99.8, 35.4, 30.1, 25.8, 20.3, 11.9; IR (film) 2977, 1603, 1454, 1345, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{17}NO + H]^+$: 216.1383, found 216.1377.

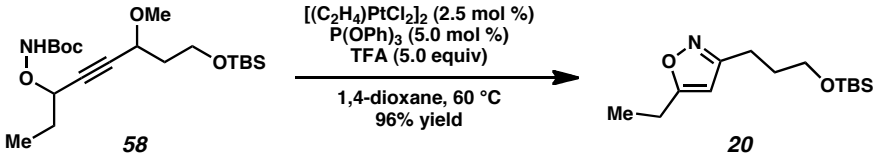


Table 3, Entry 2. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **58** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **20** (77.8 mg, 96% yield, R_F = 0.63 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.75-2.67 (comp m, 4H), 1.90-1.83 (m, 2H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 163.9, 100.0, 62.4, 31.5, 26.1, 22.8, 20.3, 18.5, 11.9, -5.2; IR (film) 2955, 1604, 1255, 1104, 837 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{27}NO_2Si + H]^+$: 270.1184, found 270.1189.

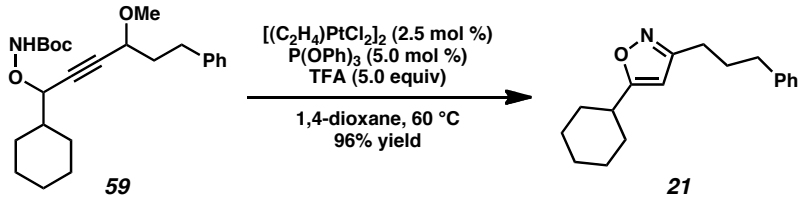


Table 3, Entry 3. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **59** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica

gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **21** (77.7 mg, 96% yield, R_F = 0.61 in 4:1 hexanes/EtOAc) as a colorless oil.
Isoxazole 21: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.77 (s, 1H), 2.70 (comp m, 5H), 2.05-1.95 (comp m, 4H), 1.82-1.78 (comp m, 2H), 1.74-1.70 (m, 1H), 1.49-1.32 (comp m, 4H), 1.26 (dtd, *J* = 14.7, 7.2, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 163.5, 141.8, 128.60, 128.49, 126.0, 98.6, 36.4, 35.5, 31.3, 30.1, 25.96, 25.82, 25.80; IR (film) 2932, 1597, 1451, 1351, 1029, 747 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{23}NO + H]^+$: 270.1852, found 270.1844.

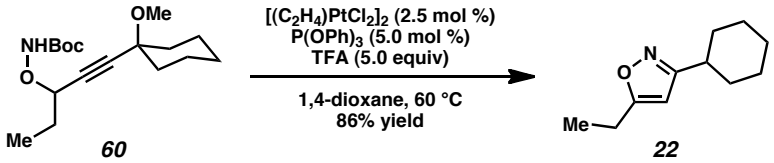


Table 3, Entry 4. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **60** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **22** (46.5 mg, 86% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a colorless oil.
Isoxazole 22: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 2.76-2.68 (m, 1H), 2.73 (q, *J* = 7.6 Hz, 2H) 1.98-1.95 (comp m, 2H), 1.82-1.78 (comp m, 2H), 1.76-1.71 (m, 1H), 1.50-1.36 (comp m, 5H), 1.29 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 168.5, 98.4, 36.1, 32.2, 26.15, 26.06, 20.4, 11.9; IR (film) 2977, 1602, 1449, 1139, 813 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{16}O + H]^+$: 180.1383, found 180.1385.

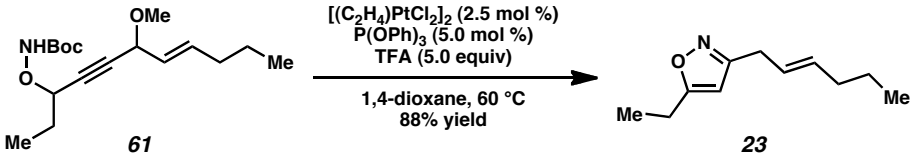


Table 3, Entry 5. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **61** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica

gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **23** (47.2 mg, 88% yield, R_F = 0.58 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 23: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.63-5.48 (comp m, 2H), 3.34-3.32 (comp m, 2H), 2.76-2.70 (qd, *J* = 7.3, 0.8 Hz, 2H), 2.03-1.98 (comp m, 2H), 1.39 (hextet, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 163.1, 133.7, 125.2, 100.0, 34.7, 29.7, 22.5, 20.4, 13.8, 11.9; IR (film) 2961, 1603, 1422, 1222, 968 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{17}NO + H]^+$: 180.1383, found 180.1380.

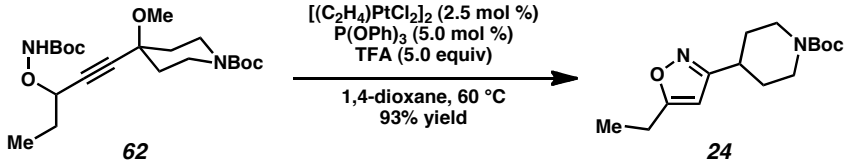


Table 3, Entry 6. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **62** (0.124 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **24** (78.0 mg, 93% yield, R_F = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 24: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 4.16 (d, *J* = 13.3 Hz, 2H), 2.88 (tt, *J* = 13.0, 3.2 Hz, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.95-1.91 (comp m, 2H), 1.64 (qd, *J* = 12.4, 4.0 Hz, 2H), 1.48 (s, 9H), 1.29 (td, *J* = 7.6, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 166.9, 154.9, 98.3, 79.7, 43.7, 34.3, 31.0, 28.6, 20.4, 11.8; IR (film) 2977, 1694, 1422, 1170, 770 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{28}N_2O_3 + H]^+$: 303.1679, found 303.1678.

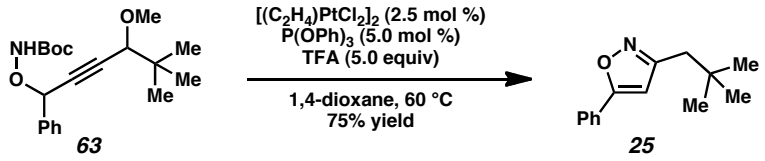


Table 3, Entry 7. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **63** (0.104 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred

for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **25** (48.1 mg, 75% yield, R_F = 0.67 in 2:1 hexanes/EtOAc) as a colorless oil.
Isoxazole 25: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.76 (comp m, 2H), 7.47-7.36 (comp m, 3H), 6.36 (s, 1H), 2.60 (s, 2H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.4, 130.0, 129.0, 127.8, 125.8, 100.9, 40.2, 31.2, 29.7; IR (film) 2959, 1955, 1615, 1575, 1451, 1101, 948 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{17}NO + H]^+$: 216.1383, found 216.1381.

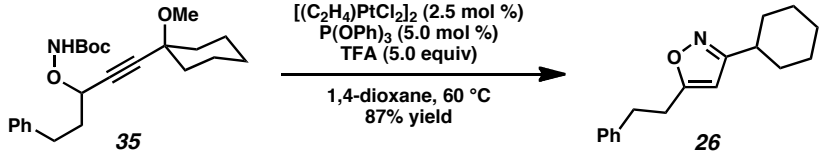


Table 3, Entry 8. According to the general procedure, to a solution of triphenylphosphite (4.5 mg, 0.0150 mmol) in 1,4-dioxane (0.870 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.2 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.107 mL, 1.43 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **35** (0.111 g, 0.287 mmol) in 1,4-dioxane (2.00 mL, 0.10 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **26** (66.6 mg, 87% yield, R_F = 0.59 in 4:1 hexanes/EtOAc) as an off white solid.
Isoxazole 26: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.23-7.17 (comp m, 3H), 5.78 (s, 1H), 3.00 (app s, 4H), 2.70 (tt, *J* = 11.3, 3.6 Hz, 1H), 1.95-1.93 (comp m, 2H), 1.85-1.78 (comp m, 2H), 1.75-1.68 (m, 1H), 1.47-1.32 (comp m, 4H), 1.30-1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.5, 140.4, 128.6, 128.4, 126.5, 99.54, 99.52, 36.0, 33.8, 32.2, 28.8, 26.12, 26.05; IR (film) 3113, 2927, 1601, 1450, 1002, 894 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{21}NO + H]^+$: 256.1696, found 256.1698.

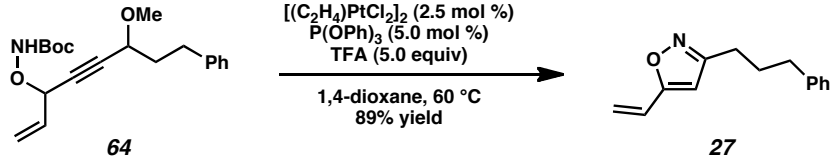


Table 3, Entry 9. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **64** (0.103 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica

gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **27** (57.0 mg, 89% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a colorless oil.
Isoxazole 27: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 6.58 (dd, *J* = 17.7, 11.3 Hz, 1H), 6.05 (s, 1H), 5.98 (dd, *J* = 17.7, 0.8 Hz, 1H), 5.53 (dd, *J* = 11.3, 0.9 Hz, 1H), 2.70 (t, *J* = 5.1 Hz, 2H), 2.69 (t, *J* = 7.6 Hz), 2.04-1.97 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.0, 141.6, 128.61, 128.53, 126.1, 122.6, 120.3, 101.3, 35.4, 30.0, 25.7; IR (film) 2938, 1566, 1424, 1278, 983 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{15}NO + H]^+$: 214.1226, found 214.1235.

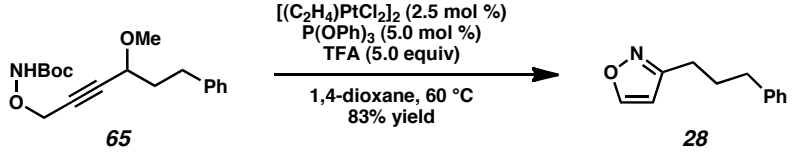


Table 3, Entry 10. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **65** (95.8 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **28** (46.4 mg, 83% yield, R_F = 0.59 in 4:1 hexanes/EtOAc) as a colorless oil.
Isoxazole 28: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32-8.31 (m, 1H), 7.31-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 6.19 (d, *J* = 1.7 Hz, 1H), 2.74 (t, *J* = 7.7 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.02 (quintet, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 158.3, 141.6, 128.61, 128.55, 126.1, 104.1, 35.4, 30.0, 25.5; IR (film) 2938, 1950, 1566, 1418, 1118, 875 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{13}NO + H]^+$: 188.1070, found 188.1069.

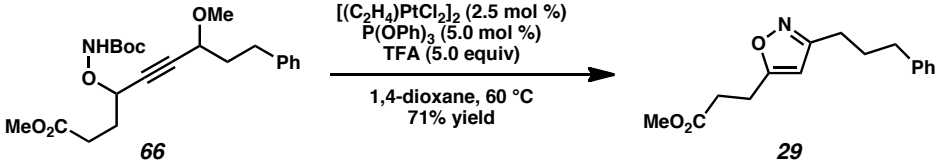


Table 3, Entry 11. According to the general procedure, to a solution of triphenylphosphite (36.5 μL, 10% (v/v) solution in 1,4-dioxane, 0.0139 mmol) in 1,4-dioxane (0.780 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.1 mg, 0.00695 mmol). After 15 min, trifluoroacetic acid (0.103 mL, 1.39 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **66** (0.112 g, 0.278 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a

plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford isoxazole **29** (53.7 mg, 71% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 29: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.86 (s, 1H), 3.70 (s, 3H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.68-2.63 (comp m, 4H), 1.98 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.1, 163.9, 141.6, 128.57, 128.47, 126.0, 101.0, 52.0, 35.4, 31.7, 29.9, 25.7, 22.2; IR (film) 2950, 1738, 1603, 1496, 1198 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{19}NO_3 + H]^+$: 274.1438, found 274.1439.

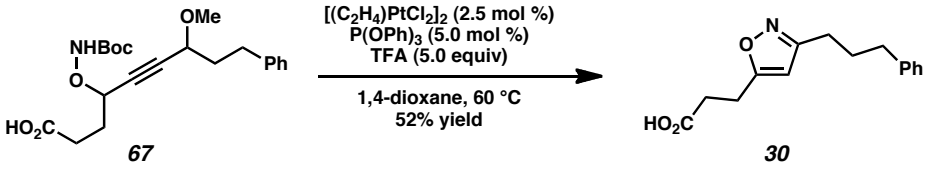


Table 3, Entry 12. According to the general procedure, to a solution of triphenylphosphite (31.7 μL, 10% (v/v) solution in 1,4-dioxane, 0.0121 mmol) in 1,4-dioxane (0.800 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (3.6 mg, 0.00605 mmol). After 15 min, trifluoroacetic acid (0.103 mL, 1.39 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **67** (94.8 mg, 0.242 mmol) in 1,4-dioxane (1.60 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 2 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm, SiO_2 acidified w/ 0.5% AcOH:Et_2O), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (1:1 hexanes/Et_2O w/ 0.5% AcOH as eluent) to afford isoxazole **30** (32.7 mg, 52% yield, R_F = 0.29 in 1:2 hexanes/Et_2O w/ 1% AcOH) as a white solid.

Isoxazole 30: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.88 (s, 1H), 3.05 (t, *J* = 7.4 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.67 (app q, *J* = 7.5 Hz, 4H), 1.98 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 170.9, 164.0, 141.6, 128.61, 128.52, 126.1, 101.2, 35.4, 31.6, 29.9, 25.7, 22.0; IR (film) cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{17}NO_3 + H]^+$: 260.1281, found 260.1292.

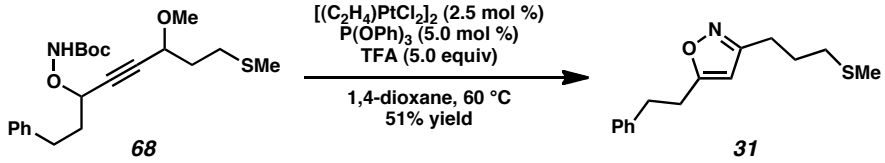


Table 3, Entry 13. According to the general procedure, to a solution of triphenylphosphite (39.4 μL, 10% (v/v) solution in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **68** (0.118 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was

sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 96 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **31** (39.7 mg, 51% yield, R_F = 0.51 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 31: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.24-7.16 (comp m, 3H), 5.77 (s, 1H), 3.05-2.97 (comp m, 4H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.98-1.90 (quintet, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.3, 140.3, 128.7, 128.4, 126.6, 101.1, 33.74, 33.58, 28.7, 27.7, 25.2, 15.6; IR (film) 3280, 2931, 1748, 1604, 1455, 1017 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{19}NOS + H]^+$: 262.1260, found 262.1254.

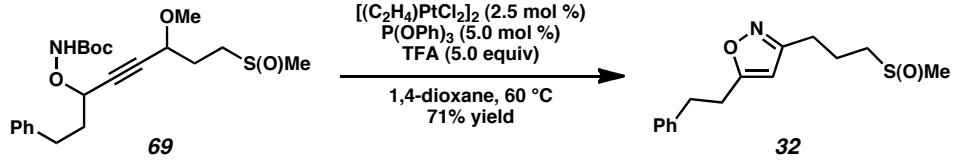
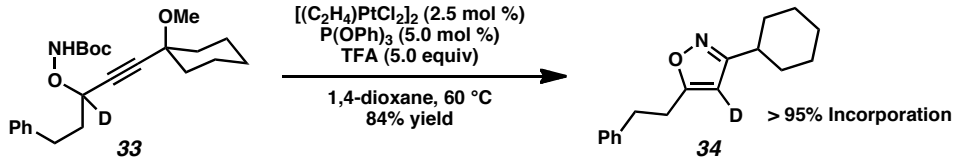


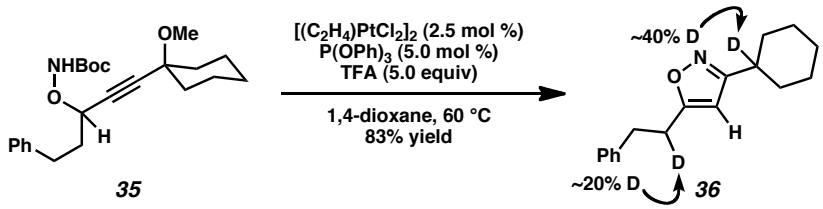
Table 3, Entry 14. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **69** (0.123 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 2 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (0→10% MeOH/EtOAc eluent) to afford isoxazole **32** (59.1 mg, 71% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as an off white solid.

Isoxazole 32: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 8.1 Hz, 3H), 5.84 (s, 1H), 3.04-2.97 (comp m, 4H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 2.50 (s, 3H), 2.08 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 162.8, 140.7, 128.78, 128.62, 126.7, 101.1, 39.1, 33.8, 28.8, 25.4, 21.6; IR (film) 3178, 2933, 2349, 1739, 1368, 1106, 753 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{19}NO_2S + H]^+$: 278.1209, found 278.1212.

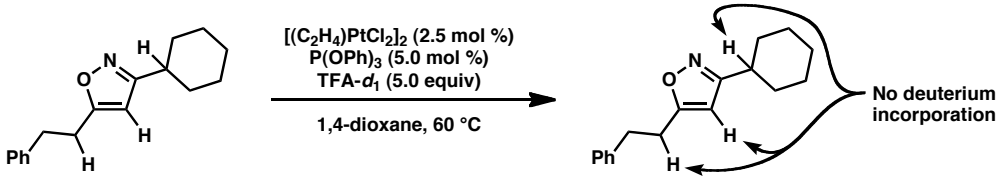
Deuterium Labeling Studies:



Scheme 4, Entry 1. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **33** (0.116 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **34** (64.3 mg, 84% yield, R_F = 0.59 in 4:1 hexanes/EtOAc) as a pale yellow solid.
Isoxazole 34: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (comp m, 2H), 7.23-7.17 (comp m, 3H), 3.01 (comp m, 4H), 2.73-2.66 (m, 1H), 1.95-1.93 (comp m, 2H), 1.82-1.78 (comp m, 2H), 1.75-1.69 (m, 1H), 1.47-1.32 (comp m, 5H), 1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.5, 140.4, 128.6, 128.4, 126.5, 36.0, 33.8, 32.2, 28.8, 26.12, 26.04; IR (film) 2927, 1582, 1496, 1070, 699 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{20}DNO + H]^+$: 257.1759, found 257.1765.

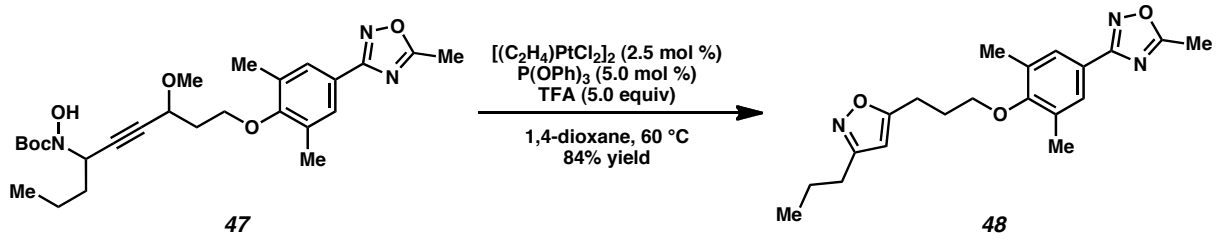


Scheme 4, Entry 2. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid-d_1 (112 μL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **35** (0.116 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole 36 (63.8 mg, 83% yield, R_F = 0.59 in 4:1 hexanes/EtOAc) as a pale yellow solid.
Isoxazole 36: See spectral information for ^{1}H and ^{2}H NMR's.



To a solution of triphenylphosphite (1.6 mg, 0.00500 mmol) in 1,4-dioxane (0.330 mL) was added $[(C_2H_4)PtCl_2]_2$ (1.5 mg, 0.00250 mmol). After 15 min, trifluoroacetic acid-d_1 (38.3 μL, 0.500 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of isoxazole **26** (25.5 mg, 0.100 mmol) in 1,4-dioxane (0.660 mL, 0.1 M final concentration) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 24 h. The reaction was diluted with Et_2O (2.0 mL) and washed with saturated $NaHCO_3$ solution (5.0 mL). The aqueous layer was extracted with Et_2O (2.0 mL), and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation. Deuterium incorporation in the product was not observed.

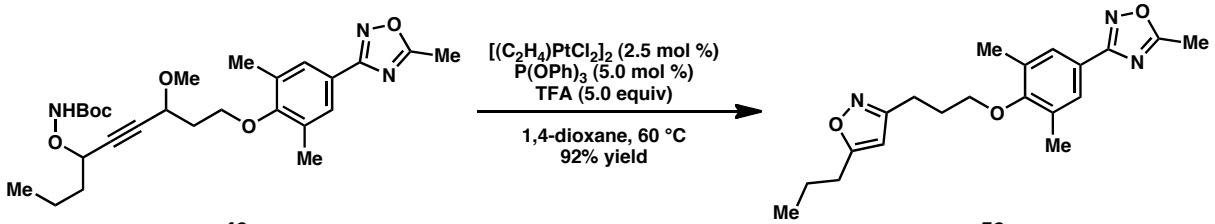
Rhinovirus Analogues:



47 *48*

According to the general procedure, to a solution of triphenylphosphite (2.0 mg, 0.00654 mmol) in 1,4-dioxane (0.300 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (1.9 mg, 0.00327 mmol). After 15 min, trifluoroacetic acid (48.7 μL, 0.654 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **47** (63.7 mg, 0.131 mmol) in 1,4-dioxane (1.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 7 h. The reaction was quenched with Et_3N (0.250 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (4.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to afford isoxazole **48** (39.0 mg, 84% yield, R_F = 0.47 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 48: Spectroscopic data matched that previously reported.[1] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (s, 2H), 5.89 (s, 1H), 3.85 (t, *J* = 6.1 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.30 (s, 6H), 2.21 (comp m, 2H), 1.68 (sextet, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 172.3, 168.2, 164.1, 158.4, 131.7, 128.1, 122.2, 100.8, 70.8, 28.4, 28.1, 23.6, 21.8, 16.4, 13.9, 12.5.



49 *50*

According to the general procedure, to a solution of triphenylphosphite (2.2 mg, 0.00720 mmol) in 1,4-dioxane (0.440 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (2.1 mg, 0.00360 mmol). After 15 min, trifluoroacetic acid (53.6 μL, 0.720 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of carbamoyl ether **49** (70.2 mg, 0.144 mmol) in 1,4-dioxane (1.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N

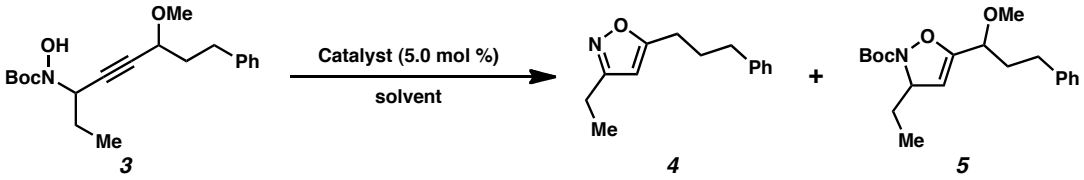
[1] (a) Diana, G. D., *et al. J. Med. Chem.* **1994**, *37*, 2421-2436. (b) The data in this manuscript does have one discrepancy: the singlet we observe at 7.72 ppm is reported at 7.44 ppm. We believe this may be a reporting error; similar compounds in this manuscript had data with a consistently reported singlet at approx. 7.73 ppm.

(0.250 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (4.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to afford isoxazole **50** (47.0 mg, 92% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 50: ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (s, 2H), 5.88 (s, 1H), 3.86 (t, *J* = 6.3 Hz, 2H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.72-2.68 (t, *J* = 8.0 Hz, 2H), 2.63 (s, 3H), 2.31 (s, 6H), 2.23-2.16 (comp m, 2H), 1.72 (q, *J* = 7.5 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 173.6, 168.3, 163.3, 158.5, 131.8, 128.1, 122.1, 100.6, 71.3, 29.0, 28.8, 23.1, 21.1, 16.5, 13.8, 12.5; IR (film) 2963, 1755, 1603, 1362, 1207, 1116. HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{25}N_3O_3 + H]^+$: 356.1969, found 356.1976.

Optimization of Pt-Catalyst Conditions:

Table 4.



3 *4* *5*

Entry	Catalyst	Solvent	Temp (° C)	Time (h)	Yield *4* (%)[a]	Yield *5* (%)[a]
1	$[(C_2H_4)PtCl_2]_2$[b]	THF	70	18	15	7
2	$[(C_2H_4)PtCl_2]_2$[b]	1,4 dioxane	70	18	22	12
3	$[(C_2H_4)PtCl_2]_2$[b]	DCM	70	66	9[c]	0[c]
4	$[(C_2H_4)PtCl_2]_2$[b]	DCE	70	66	23[c]	14[c]
5	$[(C_2H_4)PtCl_2]_2$[b]	PhMe	70	18	18	12
6	$[(C_2H_4)PtCl_2]_2$[b]	PhH	70	66	21[c]	18[c]
7	$[(C_2H_4)PtCl_2]_2$[b]	MeCN	70	66	44[c]	17[c]
8	$[(C_2H_4)PtCl_2]_2$[b]	PhMe	60	16	22	9
9	$PtCl_2$/1-octene[d]	PhMe	60	16	35	9
10	K_2PtCl_4	PhMe	60	48	0	0
11	$(PPh_3)_2PtCl_2$	PhMe	60	48	0	0
12	$(PhCN)_2PtCl_2$	PhMe	60	48	0	0
13	$(PPh_3)_2PtHCl$	PhMe	60	48	0	0
14	$Pd(OAc)_2$	PhMe	60	16	0	18
15	$Pd(TFA)_2$	PhMe	60	16	0	36
16	$PPh_3AuCl/AgSbF_6$[e]	DCM	-10	0.5	0	44
17	$IprAuCl/AgSbF_6$[e]	DCM	-10→23	3.0	3	50
18	$Bp(t\text{-}Bu)_2PAuCl/AgSbF_6$[e]	DCM	-10	0.5	2	73

[a] Yield determined by GC with 4,4'-*tert*-butylbiphenyl as the internal standard. [b] Used 2.5 mol % catalyst. [c] Reaction did not go to completion. [d] Used 1.0 equiv. 1-octene as an additive. [e] Used 5 mol % $AgSbF_6$.

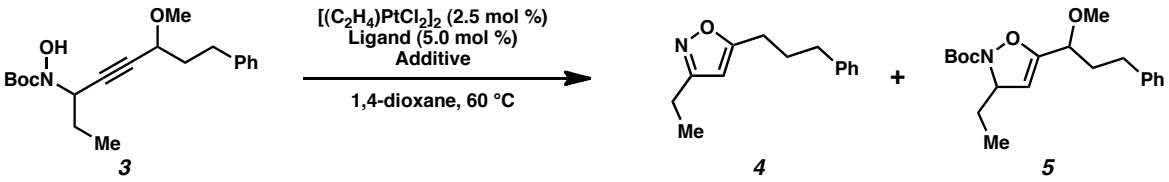
General Procedures:

Table 4, entries 1-7: A solution of *N*-hydroxycarbamate **3** (0.121 g, 0.350 mmol) and 4,4'-di-*t*-butylbiphenyl (23.1 mg, 0.0875 mmol) in CH_2Cl_2 (7.00 mL, 0.1 M) was prepared under ambient atmosphere. The solution was transferred to separate vials and the solvent was then removed by rotary evaporation. The resulting residue was dissolved in the desired solvent (0.500 mL, 0.10 M). The resulting solutions were added to vials containing $[(C_2H_4)PtCl_2]_2$ (0.7 mg, 0.00125 mmol), and the reactions were placed in an aluminum block preheated to 70 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 4, entries 8-15: A solution of *N*-hydroxycarbamate **3** (83.2 mg, 0.240 mmol) and 4,4'-di-*t*-butylbiphenyl (16.0 mg, 0.0600 mmol) in PhMe (2.40 mL, 0.1 M) was prepared under ambient atmosphere. The solution (0.300 mL, 0.300 mmol) was transferred to separate vials, the desired catalyst (5.0 mol %) was added, and the reactions were placed in an aluminum block preheated to 60 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 4, entries 16-18: To a solution of the gold catalyst (5.0 mol %) and $AgSbF_6$ (5.0 mol %) in CH_2Cl_2 (0.100 mL) cooled to -10 °C under argon was added a solution of *N*-hydroxycarbamate **3** (10.4 mg, 0.0300 mmol) and 4,4'-di-*t*-butylbiphenyl (2.0 mg, 0.00750 mmol) in CH_2Cl_2 (0.200 mL, 0.10 M final concentration). The reactions were stirred at -10 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield. Entry 17 was warmed to 23 °C after 30 min.

Table 1 (duplicate from main text).



3 ***4*** ***5***

Entry	Ligand	Additive (equiv)	Time (h)	Yield *4* (%)[a]	Yield *5* (%)[a]
1	PPh_3	AcOH (10)	17	48	14
2	PPh_3	$(NH_4)HCO_2$ (10)	70	0	0
3	PPh_3	H_3PO_4 (10)	70	76	11
4	PPh_3	TFA (10)	16	81	1
5	PPh_3	TsOH (2)	17	0	0
6	PPh_3	Na_2CO_3 (1)	60	6	< 1
7	PPh_3	TFA (5)	16	96	1
8	PCy_3[b]	TFA (5)	70	57	3
9	P(*n*-Bu)$_3$[b]	TFA (5)	70	49	4
10	P(*t*-Bu)$_2$(*o*-biphenyl)[b]	TFA (5)	70	47	2
11	$P(OPh)_3$	TFA (5)	16	96	1

[a] Yield determined by GC with 4,4'-*tert*-butylbiphenyl as the internal standard. [b] Run under an argon.

General Procedures:

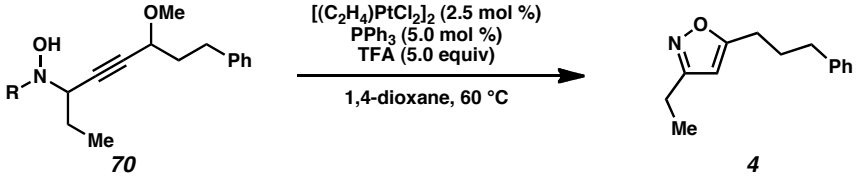
Table 1, entries 1-6: A solution of *N*-hydroxycarbamate **3** (62.4 mg, 0.180 mmol) and 4,4'-di-*t*-butylbiphenyl (12.0 mg, 0.0450 mmol) in 1,4-dioxane (1.20 mL, 0.1 M) was prepared under ambient atmosphere. The solution (0.200 mL, 0.0300 mmol) was transferred to separate vials, and the desired additive was added. To this was added 0.100 mL of a solution of $[(C_2H_4)PtCl_2]_2$ (2.4 mg, mmol, 0.00450 mmol) and PPh_3 (2.4 mg, 0.00900 mmol) in 1,4-dioxane (0.600 ml). The reactions were sealed and placed in an aluminum block that was preheated to 60 °C. Upon

completion, as determined by TLC, the acidic reactions were quenched with Et_3N (0.250 mL), filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). Basic reactions were plugged directly through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 1, entries 7-11: A solution of *N*-hydroxycarbamate **3** (52.0 mg, 0.150 mmol) and 4,4'-di-*t*-butylbiphenyl (10.0 mg, 0.0375 mmol) in 1,4-dioxane (1.00 mL, 0.66 M) was prepared under ambient atmosphere. The solution (0.200 mL, 0.0300 mmol) was transferred to separate vials containing a solution of $[(C_2H_4)PtCl_2]_2$ (0.4 mg, 0.000750 mmol), and the desired ligand (0.00150 mol) in 1,4-dioxane (0.100 ml). TFA (11.2 μL, 0.150 mmol) was immediately added, and the reactions were placed in an aluminum block that was preheated to 60 °C. Upon completion, as determined by TLC, the reactions were quenched with Et_3N (0.250 mL), and filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield. Entries **8**, **9** and **10** were run under an argon atmosphere.

Nitrogen Protecting Group Screen:

Table 5.



70 ***4***

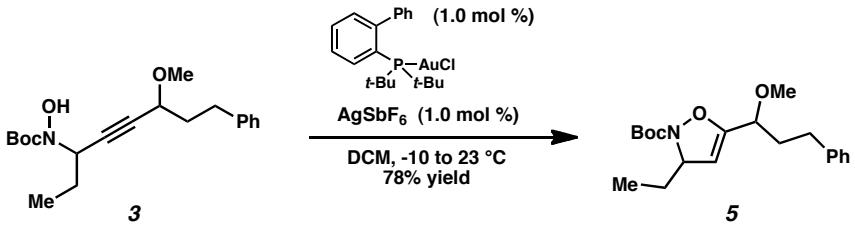
Entry	R	Time (h)	Yield *4* (%)[a]
1	CO_2Me	96	71
2	CO_2Et	96	59
3	CO_2allyl	72	72
4	CO_2*i*-Bu	42	48
5	CO_2Bn	96	53
6	CO_2*t*-Bu	17	96
7	Ac	20	64
8	H	6	7

[a] Yield determined by GC with 4,4'-*tert*-butylbiphenyl as the internal standard.

General Procedure:

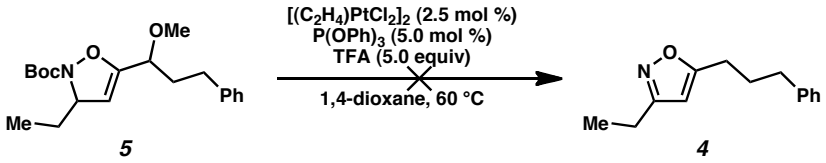
To 1,4-dioxane (1/3 of reaction volume) was added triphenylphosphine (5.0 mol %) followed by the addition of $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min, trifluoroacetic acid (5.00 equiv) was added and the mixture was stirred for 1 min. The resulting solution was then added to a solution of the *N*-hydroxycarbamates/amide/amine (0.0300 mmol) and 4,4'-*tert*-butylbiphenyl (0.00750 mmol) in 1,4-dioxane (2/3 of reaction volume, 0.10 M final concentration), and the mixture was heated at 60 °C in a sealed vial. Upon completion, as determined by TLC, the reaction was quenched with Et_3N (0.100 mL), and filtered through a plug of silica gel. The plug was washed with Et_2O (2x reaction volume), and the resulting solution was injected directly onto a GC to determine yields.

Hydroalkoxylation Experiments:



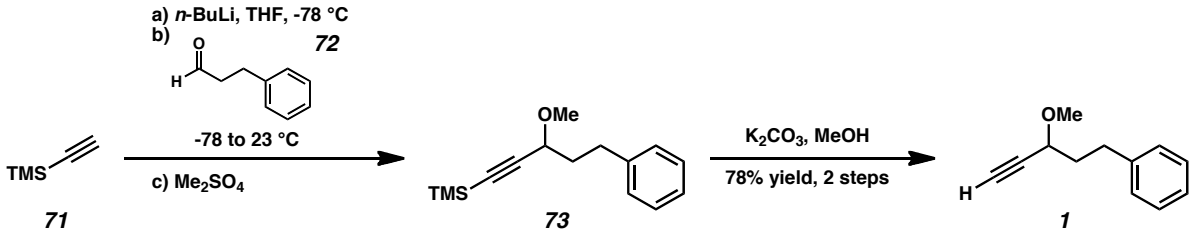
To a solution of (*t*-Bu)$_2$*o*-biphenylPAuCl (4.2 mg, 0.00800 mmol) and $AgSbF_6$ (2.7 mg, 0.00800 mmol) in CH_2Cl_2 (0.400 mL) at -10 °C under argon was added a solution of *N*-hydroxycarbamate **3** (0.278 g, 0.800 mmol) in CH_2Cl_2 (0.400 mL, 0.10 M final concentration). The reaction was stirred at -10 °C for 2 h, then warmed to 23 °C and stirred for an additional 2 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (4.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazoline **5** (0.218 g, 78% yield, R_F = 0.60 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazoline 5: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.20-7.16 (comp m, 3H), 4.91 (ddd, *J* = 3.4, 2.5, 0.7 Hz, 1H), 4.85 (td, *J* = 5.7, 2.3 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 1H), 3.38 (d, 3H), 2.79-2.65 (comp m, 2H), 2.08-1.97 (comp m, 2H), 1.66-1.56 (comp m, 2H), 1.50 (d, *J* = 0.8 Hz, 9H), 0.95 (td, *J* = 7.4, 4.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.6, 154.9, 154.2, 141.5, 128.64, 128.62, 128.5, 126.0, 98.5, 98.2, 82.40, 82.34, 74.75, 74.58, 66.96, 66.89, 57.4, 57.1, 35.5, 35.1, 31.52, 31.47, 29.19, 29.17, 28.3, 9.37, 9.27; IR (film) 2972, 1741, 1496, 1456, 1369, 1165, 749 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{29}NO_4 + H]^+$: 348.2169, found 348.2140.



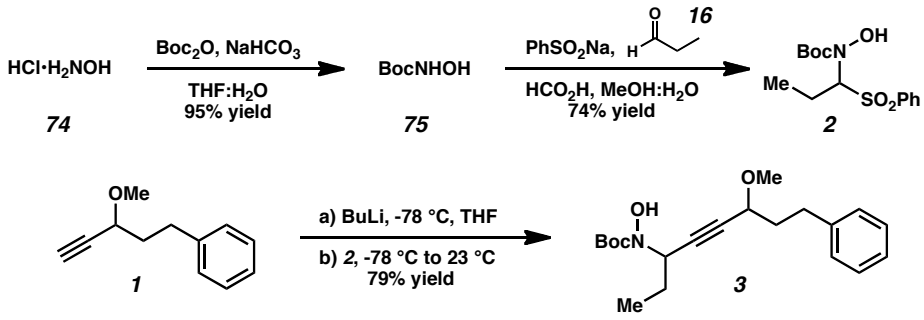
According to the general procedure, to a solution of triphenylphosphite (19.7 μL, 10% solution in 1,4-dioxane, 0.00750 mmol) in 1,4-dioxane (0.500 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (2.2 mg, 0.00375 mmol). After 15 min, trifluoroacetic acid (56.0 μL, 0.750 mmol) was added and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of isoxazoline **5** (52.1 mg, 0.150 mmol) in 1,4-dioxane (1.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap and placed in an aluminum block that was preheated to 60 °C. After 24 h the reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). ^{1}H NMR and GC analysis indicated isoxazole **4** did not form.

Substrate Synthesis, *N*-Hydroxycarbamates:



To a solution of TMS-acetylene (**71**, 5.65 mL, 40.0 mmol) in THF (120 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (16.0 mL, 2.5 M in hexanes, 40.0 mmol), and the resulting solution was stirred for 30 min. Hydrocinnamaldehyde (**72**, 5.26 mL, 40.0 mmol) was added and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me_2SO_4 (4.20 mL, 44.0 mmol) was added and the reaction was stirred for 14 h. The reaction was quenched with 10% aq. NH_4OH (40 mL), stirring for 15 min. The mixture was diluted with Et_2O (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **73** (10.1 g crude, R_F = 0.57 in 9:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **73** (10.1 g crude, assumed 40.0 mmol) in MeOH (200 mL, 0.20 M) at 23 °C was added K_2CO_3 (6.07 g, 44.0 mmol) and the reaction was stirred for 5 h. The reaction was diluted with brine (200 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **1** (5.43 g, 78% yield over 2 steps, R_F = 0.54 in 9:1 hexanes/EtOAc) as a colorless oil.

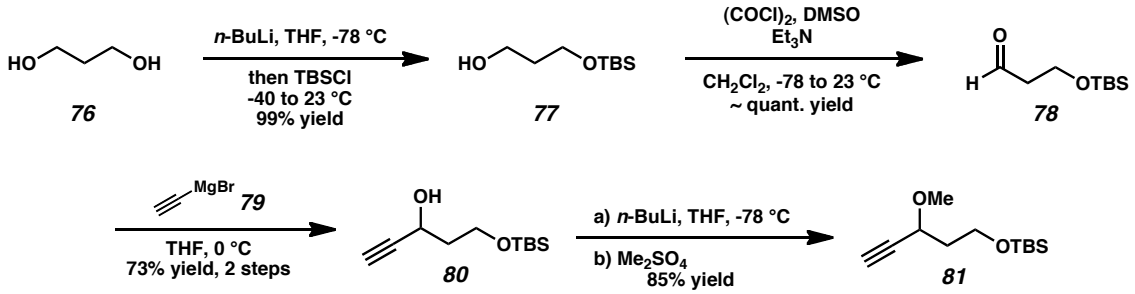


To a solution of NH_2OH•HCl (**74**, 5.21 g, 75.0 mmol) in THF:H_2O (1:1, 166 mL, 0.45 M) at 0 °C was added $NaHCO_3$ (12.6 g, 150 mmol), and the solution was stirred for 5 min. Boc_2O (16.4 g, 75.0 mmol) was added and the reaction was stirred at 0 °C for 2 h. The reaction was diluted with EtOAc (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL), and the combined organic phases were washed sequentially with sat. aq. $NaHCO_3$ (150 mL), H_2O (150 mL), brine (150 mL), dried over $MgSO_4$. The solvent was removed by rotary evaporation affording carbamate **75** (9.46 g, 95% yield) as a white solid.

Following the procedure of Denis,[2] to a solution of sodium benzenesulfinate (1.54 g, 9.40 mmol) in MeOH:H_2O (1:2, 11.1 mL, 0.85 M) was added carbamate **75** (0.500 g, 3.76 mmol), propionaldehyde (**16**, 0.539 mL, 7.52 mmol), and formic acid (0.327 mL, 7.52 mmol). The reaction was stirred at room temperature for 16 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The solid was dried under reduced pressure affording *N*-hydroxycarbamate **2** (0.879 g, 74% yield) as a white solid.

To a solution of alkyne **1** (3.96 g, 22.8 mmol) in THF (25.4 mL, 0.90 M) at -78 °C under argon was added *n*-BuLi (9.12 mL, 2.5 M in hexanes, 22.8 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **2** (3.61 g, 11.4 mmol) in THF (25.4 mL, 0.45 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **3** (3.13 g, 79% yield, R_F = 0.43 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 3**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.30-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 4.64 (td, *J* = 8.0, 0.8 Hz, 1H), 3.94 (td, *J* = 6.8, 1.6 Hz, 1H), 3.38 (app d, 3H), 2.77 (t, *J* = 7.9 Hz, 2H), 2.07-1.95 (comp m, 2H), 1.94-1.80 (comp m, 2H), 1.51 (s, 9H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 141.5, 128.66, 128.54, 126.1, 83.23, 82.90, 70.46, 70.44, 56.5, 54.2, 37.41, 37.35, 31.58, 31.56, 28.4, 28.2, 26.42, 26.40, 10.9; IR (film) 3281, 2976, 1699, 1369, 1106, 701 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{29}NO_4 + Na]^+$: 370.1997, found 370.2002.



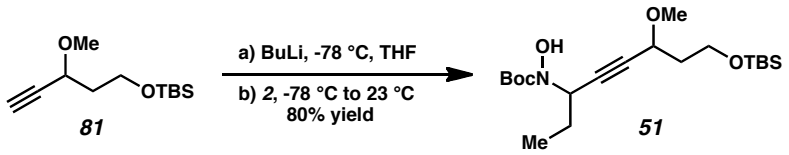
To a solution of 1,3-propanediol (**76**, 7.22 mL, 100 mmol) in THF (300 mL, 0.33 M) at -40 °C under argon was added *n*-BuLi (40 mL, 2.5 M in hexanes, 100 mmol). The resulting solution was stirred for 30 min at -40 °C, then warmed to 0 °C. The slurry was then added to a solution of TBSCl (15.1 g, 100 mmol) in THF (100 mL) and the resulting mixture was stirred at 0 °C for 10 min, then warmed to room temperature and stirred for 3 h. The solvent was removed in vacuo, and to the resulting slurry was added Et_2O (200 mL) and water (200 mL). The layers were separated and the aqueous phase was extracted with Et_2O (100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed via rotary evaporation affording silyl ether **77** (18.9 g, 99% yield, R_F = 0.40 in 4:1 hexanes/EtOAc) as a clear oil.

[2] X. Guinchard, Y. Vallée, J. -N. Denis, *Org. Lett.* **2005**, *7*, 5147-5150.

To a solution of oxalyl chloride (4.91 mL, 58.0 mmol) in CH_2Cl_2 (120 mL, 0.48 M) at -78 °C under argon was added DMSO (8.52 mL, 120 mmol) dropwise. The solution was stirred at -78 °C for 10 min. A solution of alcohol **77** (9.51 g, 50.0 mmol) in CH_2Cl_2 (10 mL) was then added slowly, and the reaction was stirred at -78 °C for 1 h. Et_3N (35.5 mL, 253 mmol) was then added, and the reaction mixture was maintained at -78 °C for 10 min before being warmed to room temperature and stirred for 30 min. The reaction was then quenched with water (200 mL), and the phases were separated. The organic layer was washed sequentially with 1 N HCl (100 mL), sat. aq. $NaHCO_3$ (100 mL), and brine (100 mL), and was dried over $MgSO_4$. The solvent was removed via rotary evaporation affording aldehyde **78** (9.60 g crude) as an amber oil.

To a solution of ethynyl Grignard (**79**, 100 mL, 0.50 M in THF, 50.0 mmol) at 0 °C was added a solution of the crude aldehyde **78** (9.60 g crude, assumed 50.0 mmol) in Et_2O (10 mL) and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL), and diluted with hexanes (100 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (50 mL). The organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude material was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording alcohol **80** (7.84 g, 73% yield over 2 steps, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

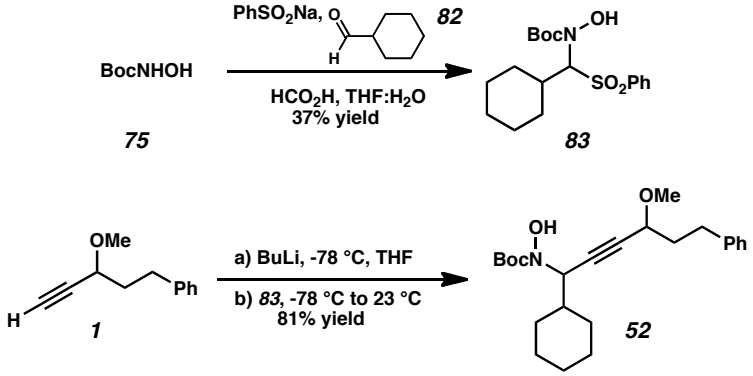
To a solution of alcohol **80** (7.25 g, 33.9 mmol) in THF (100 mL, 0.34 M) at -78 °C under argon was added *n*-BuLi (14.4 mL, 2.35 M in hexanes, 33.9 mmol) and the reaction was stirred for 30 min. Me_2SO_4 (3.22 mL, 33.9 mmol) was then added and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with water (100 mL), and diluted with hexanes (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude material was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording ether **81** (6.61 g, 85% yield, R_F = 0.73 in 4:1 hexanes/EtOAc) as a colorless oil.



To a solution of alkyne **81** (0.912 g, 4.00 mmol) in THF (6.0 mL, 0.67 M) at -78 °C under argon was added *n*-BuLi (1.70 mL, 2.35 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **2** (0.630 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) was added dropwise and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 4 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **51** (0.645 g, 80% yield, R_F = 0.36 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 51**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (br s, 1H), 4.62 (td, *J* = 7.7, 1.5 Hz, 1H), 4.17-4.13 (m, 1H), 3.78-3.68 (comp m,

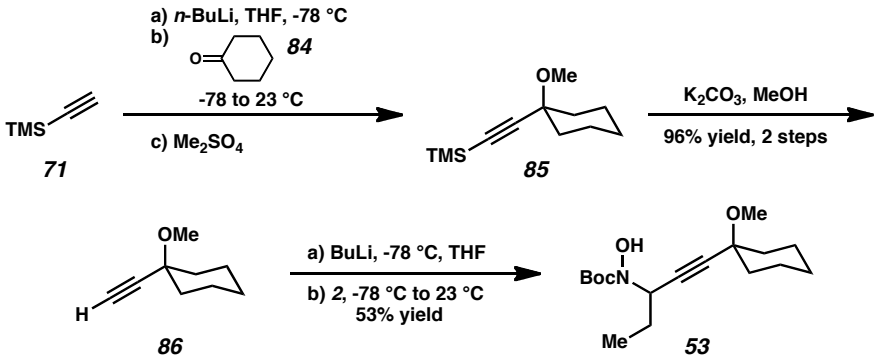
2H), 3.37 (d, *J* = 3.0 Hz, 3H), 2.75 (q, *J* = 7.4 Hz,), 1.97-1.79 (comp m, 4H), 1.50 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 82.93, 82.75, 68.1, 59.2, 56.5, 54.1, 39.00, 38.96, 28.4, 28.2, 26.36, 26.35, 26.1, 18.5, 10.9, -5.2; IR (film) 3264, 2932, 1700, 1463, 1109, 835 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{39}NO_5Si + Na]^+$: 424.2490, found 424.2497.



To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in THF:H_2O (1:1, 22.0 mL, 0.85 M) was added carbamate **75** (1.00 g, 7.52 mmol), cyclohexanecarboxaldehyde (**82**, 1.82 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for 16 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The solid was dried under reduced pressure affording hydroxycarbamate **83** (1.02 g, 37% yield) as a white solid.

To a solution of alkyne **1** (0.523 g, 3.00 mmol) in THF (3.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **83** (0.553 g, 1.50 mmol) in THF (3.00 mL, 0.50 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 15 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **52** (0.618 g, 81% yield, R_F = 0.40 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 52**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.19 (comp m, 3H), 6.13 (br s, 1H), 4.43 (d, *J* = 9.9 Hz, 1H), 3.95 (t, *J* = 6.2 Hz, 1H), 3.39 (d, *J* = 3.2 Hz, 3H), 2.77 (t, *J* = 7.8 Hz, 2H), 2.09-1.94 (comp m, 2H), 1.92-1.65 (comp m, 5H), 1.50 (s, 9H), 1.34-1.12 (comp m, 4H), 1.09-0.91 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.50, 157.47, 141.5, 128.66, 128.53, 126.1, 83.44, 83.38, 82.69, 82.63, 70.51, 70.47, 57.8, 56.6, 40.09, 40.02, 37.48, 37.39, 31.62, 31.58, 30.5, 29.7, 28.4, 26.4, 26.0, 25.8; IR (film) cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{24}H_{35}NO_4 + Na]^+$: 424.2464, found 424.2453.

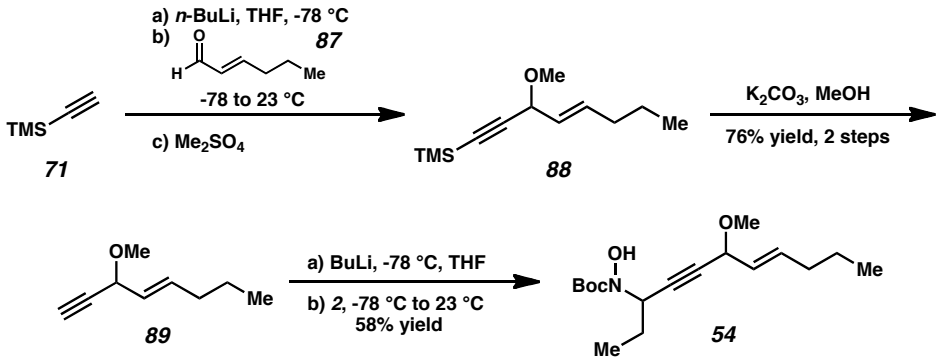


To a solution of TMS-acetylene (**71**, 7.07 mL, 50.0 mmol) in THF (150 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (20.0 mL, 2.5 M in hexanes, 50.0 mmol), and the resulting solution was stirred for 30 min. Cyclohexanone (**84**, 5.18 mL, 50.0 mmol) was added and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 2 h. Me_2SO_4 (5.71 mL, 60.0 mmol) was added and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH_4OH (75 mL), stirring for 15 min. The mixture was diluted with Et_2O (100 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **85** (10.5 g crude, R_F = 0.73 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **85** (10.5 g crude, assumed 50.0 mmol) in MeOH (300 mL, 0.15 M) at 23 °C was added K_2CO_3 (8.28 g, 60.0 mmol), and the reaction was stirred for 15 h. The reaction was diluted with brine (300 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **86** (6.60 g, 96% yield over 2 steps, R_F = 0.68 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alkyne **86** (0.552 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **2** (0.630 g, 2.00 mmol) in THF (4.00 mL, 0.50 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic phases were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **53** (0.329 g, 53% yield, R_F = 0.37 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 53**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (br s, 1H), 4.61 (t, *J* = 7.7 Hz, 1H), 3.34 (s, 3H), 1.90-1.80 (comp m, 4H), 1.63 (comp m, 2H), 1.55-1.51 (comp m, 2H), 1.50 (s, 9H), 1.49-1.45 (comp m, 3H), 1.30-1.24 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 85.2, 83.1, 82.7, 74.2, 54.3, 50.8, 37.00, 36.91, 28.4, 26.5, 25.6, 23.05, 23.02, 11.0; IR (film) 3281, 2937, 1700, 1368, 1170, 926 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{17}H_{29}NO_4 + Na]^+$: 334.1989, found 334.1972.

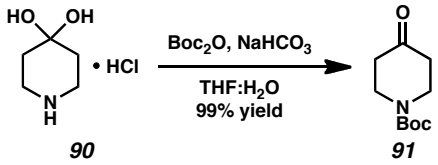


To a solution of TMS-acetylene (**71**, 1.41 mL, 10.0 mmol) in THF (30.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min. *Trans*-2-hexenal (**87**, 1.16 mL, 10.0 mmol) was added and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me_2SO_4 (1.04 mL, 11.0 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH_4OH (20 mL), stirring for 15 min. The mixture was diluted with Et_2O (30 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **88** (2.21 g crude, R_F = 0.74 in 4:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **88** (2.21 g crude, assumed 10.0 mmol) in MeOH (40.0 mL, 0.25 M) at 23 °C was added K_2CO_3 (1.65 g, 12.0 mmol), and the reaction was stirred for 16 h. The reaction was diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording alkyne **89** (1.04 g, 76% yield over 2 steps, R_F = 0.69 in 4:1 hexanes/EtOAc) as a colorless oil.

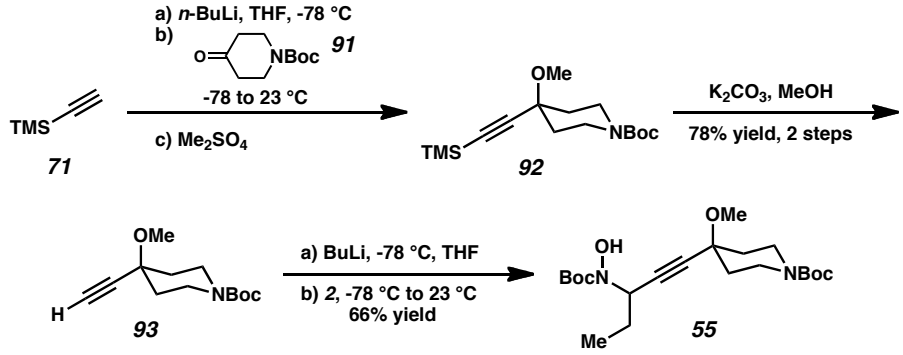
To a solution of alkyne **89** (0.544 g, 3.97 mmol) in THF (12.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (1.59 mL, 2.50 M in hexanes, 3.97 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **2** (0.624 g, 1.98 mmol) in THF (12.0 mL, 0.17 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 15 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **54** (0.357 g, 58% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 54**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (br s, 1H), 5.87 (dtd, *J* = 15.2, 6.9, 1.2 Hz, 1H), 5.52-5.46 (m, 1H), 4.65 (td, *J* = 7.7, 1.4 Hz, 1H), 4.49 (dd, *J* = 6.3, 1.0 Hz, 1H), 3.34 (d, *J* = 1.4 Hz, 3H), 2.07-2.01 (comp m, 2H), 1.93-1.80 (comp m, 2H), 1.48-1.47 (comp m, 9H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 135.4, 126.9, 84.16, 84.13, 82.8, 81.46, 81.40, 71.4, 55.44, 55.42, 54.1, 34.2, 28.4, 26.3, 22.2, 13.8, 10.9; IR (film) 2962, 1996, 1703, 1603, 1165, 968 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M - H)$^-$ [$C_{17}H_{29}NO_4$ - H]$^-$: 310.2024, found 310.2019.



90 *91*

To a solution of 4-piperidone monohydrate hydrochloride (**90**, 7.68 g, 50.0 mmol) in THF:H_2O (1:1, 100 mL, 0.50 M) at 23 °C was added $NaHCO_3$ (8.40 g, 100 mmol), and the solution was stirred for 15 min. Boc_2O (13.1 g, 60.0 mmol) was added, and the reaction was stirred for 12 h. The reaction was diluted with Et_2O (50 mL), and washed with 5% aq. $KHSO_4$ (100 mL). The aqueous layer was extracted with Et_2O (50 mL), and the combined organic layers were washed sequentially with 5% $KHSO_4$ (50 mL), H_2O (50 mL), and brine (50 mL). The organic material was dried over $MgSO_4$, and the solvent was removed by rotary evaporation affording ketone **91** (10.0 g, 99% yield, R_F = 0.51 in 1:1 hexanes/EtOAc) as a white solid.



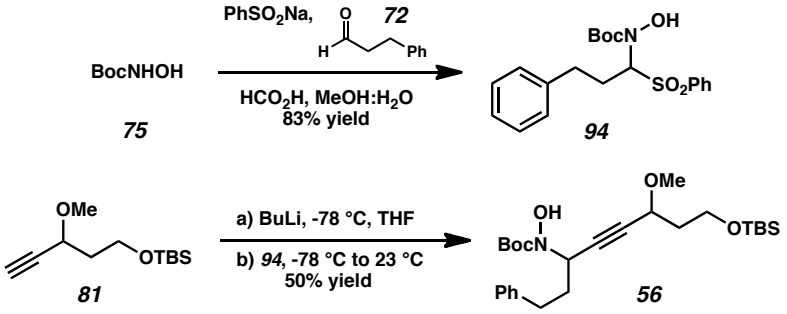
To a solution of TMS-acetylene (**71**, 1.44 mL, 10.2 mmol) in THF (30 mL, 0.34 M) at -78 °C under argon was added *n*-BuLi (4.08 mL, 2.5 M in hexanes, 10.2 mmol), and the resulting solution was stirred for 30 min. A solution of ketone **91** (2.04 g, 10.2 mmol) in THF (10 mL, 1.0 M) was added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 4 h. Me_2SO_4 (1.07 mL, 11.3 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH_4OH (20 mL), stirring for 15 min. The mixture was diluted with Et_2O (30 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **92** (3.15 g crude, R_F = 0.59 in 4:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **92** (3.15 g crude, assumed 10.2 mmol) in MeOH (68 mL, 0.15 M) at 23 °C was added K_2CO_3 (1.68 g, 12.2 mmol), and the reaction was stirred for 5 h. The reaction was diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→6:1 hexanes/EtOAc eluent) affording alkyne **93** (1.90 g, 78% yield over 2 steps, R_F = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alkyne **93** (0.956 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **2** (0.630 g, 2.00 mmol) in THF (4.00 mL, 0.50 M) was added dropwise and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C

and stirred for 12 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic phases were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording hydroxycarbamate **55** (0.540 g, 66% yield, R_F = 0.41 in 2:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (t, *J* = 7.7 Hz, 1H), 3.73 (dt, *J* = 13.7, 4.7 Hz, 2H), 3.34 (s, 3H), 3.25-3.18 (comp m, 2H), 1.88-1.82 (comp m, 4H), 1.64 (ddd, *J* = 13.2, 9.5, 3.8 Hz, 2H), 1.49 (s, 9H), 1.44 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 154.8, 84.6, 83.3, 82.9, 79.8, 72.6, 54.0, 51.0, 38.9, 36.3, 28.6, 28.4, 26.4, 10.9; IR (film) 3286, 2976, 1714, 1456, 768 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{21}H_{36}N_2O_6 + Na]^+$: 435.2466, found 435.2443.

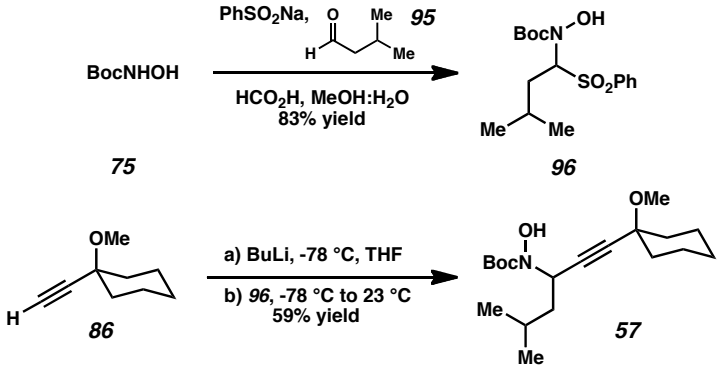


To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in MeOH:H_2O (1:2, 22.5 mL, 0.84 M) was added carbamate **75** (1.00 g, 7.52 mmol), hydrocinnamaldehyde (**72**, 1.98 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for 14 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 25 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **94** (2.45 g, 83% yield) as a white solid.

To a solution of alkyne **81** (0.912 g, 4.00 mmol) in THF (6.0 mL, 0.67 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **94** (0.780 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 14 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **56** (0.472 g, 50% yield, R_F = 0.36 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 56**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 3H), 7.25-7.20 (comp m, 2H), 4.67 (t, *J* = 7.7 Hz, 1H), 4.16 (td, *J* = 7.2, 1.9 Hz, 1H), 3.78-3.68 (comp m, 2H), 3.38 (d, *J* = 3.8 Hz, 3H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.25-2.05 (comp m, 2H), 1.98-1.80 (comp m, 2H), 1.48 (s, 1H), 1.47 (s, 8H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 141.1, 128.6, 126.2, 83.36, 83.30, 82.9, 82.69, 82.65, 68.09, 67.99, 59.1, 56.61, 56.54, 51.93, 51.82, 39.01, 38.98, 34.4, 32.2, 28.34, 28.29,

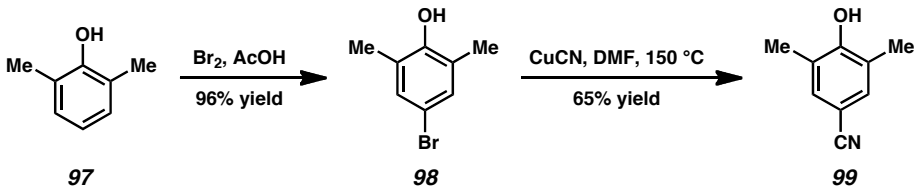
26.10, 26.04, 18.5, -5.20, -5.25; IR (film) 3264, 2931, 1699, 1456, 1106, 835 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{26}H_{43}NO_5Si + Na]^+$: 500.2803, found 500.2823.



To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in MeOH:H_2O (1:2, 22.5 mL, 0.84 M) was added carbamate **75** (1.00 g, 7.52 mmol), isovaleryldehyde (**95**, 1.63 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for 18 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **96** (2.13 g, 83% yield) as a white solid.

To a solution of alkyne **86** (0.552 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **96** (0.684 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) was added drop wise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **57** (0.397 g, 59% yield, R_F = 0.43 in 4:1 hexanes/EtOAc) as an amber oil.

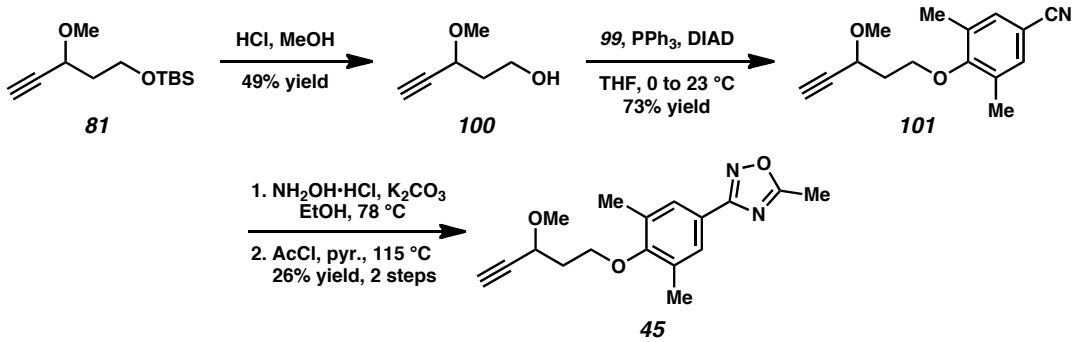
***N*-Hydroxycarbamate 57**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, *J* = 7.5 Hz, 1H), 3.34 (s, 3H), 1.89-1.86 (comp m, 2H), 1.79-1.70 (comp m, 3H), 1.68-1.59 (comp m, 3H), 1.52-1.48 (comp m, 14H), 0.94 (dd, *J* = 6.1, 3.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 85.1, 83.3, 82.8, 74.2, 51.23, 51.15, 50.84, 50.80, 41.6, 36.98, 36.90, 28.4, 25.6, 25.0, 23.05, 23.03, 22.44, 22.39; IR (film) 3280, 2937, 1699, 1454, 1170, 1094, 925 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{19}H_{33}NO_4 + Na]^+$: 362.2302, found 362.2302.



97 ***98*** ***99***

To a solution of phenol **97** (0.892 g, 7.30 mmol) in acetic acid (5.00 mL, 1.5 M) at 0 °C was added a solution of Br_2 (0.373 mL, 7.30 mmol) in acetic acid (5.00 mL, 1.5 M). The reaction was warmed to 23 °C and stirred for 20 min. The reaction was poured into $NaHCO_3$ (100 mL, 1% aq.) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with water (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation producing bromide **98** (1.40g, 96% yield, R_F = 0.26 in 9:1 hexanes/EtOAc) as an off-white solid.

A solution of bromide **98** (1.40 g, 7.00 mmol) in DMF (5.50 mL, 1.3 M) was degassed with argon via bubbling for 15 min. CuCN (0.721 g, 8.05 mmol) was added and the reaction was heated at 150 °C for 6 h. The reaction mixture was cooled to room temperature and then poured into a mixture of $FeCl_3$ (1.60 g), concentrated HCl (0.70 ml) and water (5 ml). The resulting slurry was filtered, washed with water (5 ml) and ethanol (20 ml), and the EtOH was removed by rotary evaporation. To the aqueous mixture was added NaOH (50 ml, 1.0 M), and the resulting mixture was stirred at 50 °C for 30 min. The solid was filtered and washed with water (20 ml). 1 M HCl was added to the filtrate until the pH ~ 4. The precipitate was extracted with EtOAc (2 x 20 mL), and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation producing nitrile **99** (0.665 g, 65% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as a yellow solid.



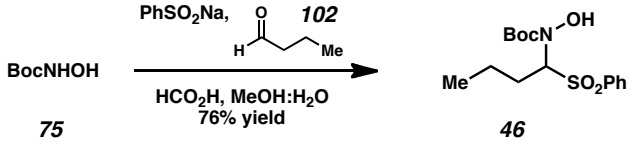
81 ***100*** ***101*** ***45***

To a solution of alkyne **81** (0.922 g, 4.05 mmol) in MeOH (20.0 mL, 0.2 M) was added HCl (0.500 mL, 10% aq.) and the reaction was stirred at 23 °C for 4 h. The reaction was poured into water (100 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) producing alcohol **100** (0.227 g, 49% yield, R_F = 0.38 in 1:1 hexanes/EtOAc) as a colorless oil.

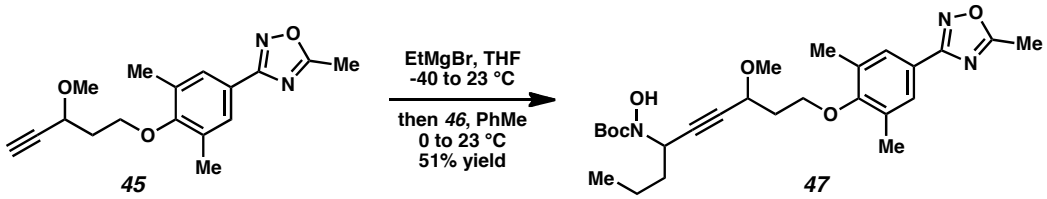
To a solution of alcohol **100** (0.492 g, 4.32 mmol), PPh_3 (1.36 g, 5.18 mmol) and nitrile **99** (0.665 g, 4.52 mmol) in THF (29.0 mL, 0.15 M) at 0 °C was added DIAD (0.919 mL, 4.75 mmol). The reaction was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 10 h. The solvent was removed via rotary evaporation, and the residue was purified by flash

chromatography (9:1 hexanes/EtOAc eluent) producing ether **101** (0.765 g, 73% yield, R_F = 0.48 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **101** (0.765 g, 3.15 mmol) in absolute EtOH (9.30 mL, 0.34 M) was added K_2CO_3 (2.17 g, 15.7 mmol) and NH_2OH•HCl (**74**, 1.09 g, 15.7 mmol). The reaction was heated at 85 °C for 17 h, then filtered. The filter cake was washed with warm absolute EtOH (10 mL), and the combined filtrates were concentrated under reduced pressure producing the crude amidoxime (0.851 g, R_F = 0.59 in 2:1 EtOAc/hexanes) as an amber oil. The crude amidoxime (0.851 g, assumed 3.15 mmol) was dissolved in pyridine (0.97 mL, 3.2 M), and acetyl chloride (0.448 mL, 6.30 mmol) was added dropwise. The reaction was heated at 115 °C for 1 h, then cooled to 23 °C and diluted with Et_2O (20 mL). The solution was washed with water (20 mL), brine (20 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the recovered residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) producing oxadiazole **45** (0.249 g, 26% yield over 2 steps, R_F = 0.37 in 4:1 hexanes/EtOAc) as a colorless oil.



To a solution of sodium benzenesulfinate (1.54 g, 9.40 mmol) in MeOH:H_2O (1:2, 11.3 mL, 0.84 M) was added carbamate **75** (0.500 g, 3.76 mmol), butyraldehyde (**102**, 0.678 mL, 7.52 mmol) and formic acid (0.327 mL, 7.52 mmol). The reaction was stirred at room temperature for 20 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **46** (0.945 g, 76% yield) as a white solid.

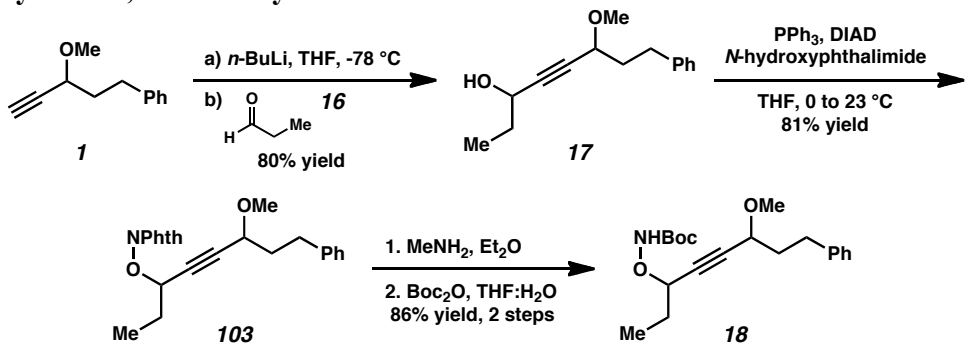


To a solution of alkyne **45** (180.0 mg, 0.600 mmol) in THF (0.600 mL, 1.0 M), cooled to -40 °C under argon was added ethylmagnesium bromide (0.200 mL, 0.600 mmol, 3.0 M solution in Et_2O) and the reaction was stirred at -40 °C for 15 min, then warmed to 23 °C. The magnesium acetylide was then added to a solution of *N*-hydroxycarbamate **46** (98.7 mg, 0.300 mmol) in toluene (3.00 mL, 0.1 M) at 0 °C. The reaction was warmed to 23 °C and stirred for 1 h. HCl (5.0 mL, 0.5 N) was added and the mixture was extracted with Et_2O (2 x 10 mL). The combine organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) producing *N*-hydroxycarbamate **47** (73.9 mg, 51% yield, R_F = 0.21 in 4:1 hexanes/EtOAc) as a colorless oil.

***N*-hydroxycarbamate 47:** Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (s, 2H), 4.74 (td, *J* = 7.7, 1.1 Hz, 1H), 4.39-4.35 (m, 1H), 3.95-3.91 (comp m, 2H), 3.45-3.41 (m, 3H), 2.63 (s, 3H), 2.33 (s, 6H), 2.23-2.15 (comp m, 2H), 1.88-1.75 (comp m,

2H), 1.47 (s, 9H), 1.46-1.39 (comp m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 168.3, 158.4, 157.4, 157.3, 131.9, 128.1, 122.2, 83.61, 83.59, 82.8, 82.40, 82.38, 68.1, 56.7, 52.1, 36.6, 34.9, 28.3, 19.4, 16.3, 13.6, 12.5; IR (film) 3283, 2963, 1700, 1353, 1207, 1114. HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{26}H_{37}N_3O_6 + Na]^+$: 510.2575, found 510.2584.

Substrate Synthesis, Carbamoyl ethers:



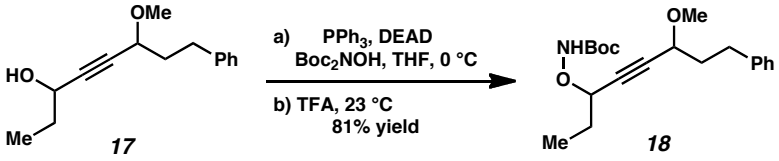
To a solution of alkyne **1** (0.870 g, 5.00 mmol) in THF (15.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (2.12 mL, 2.35 M in hexanes, 5.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**16**, 0.361 mL, 5.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (15 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording alcohol **17** (0.933 g, 80% yield, R_F = 0.20 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.485 g, 1.85 mmol) in THF (10.0 mL, 0.19 M) at 0 °C under argon was added DIAD (0.313 mL, 1.62 mmol) dropwise. After 10 min a solution of alcohol **17** (0.359 g, 1.54 mmol) in THF (3.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.264 g, 1.62 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **103** (0.468 g, 81% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

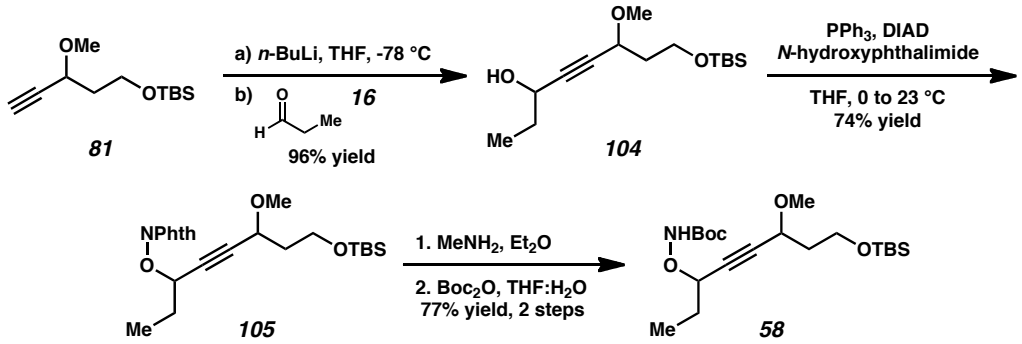
To a solution of phthalimide **103** (0.468 g, 1.24 mmol) in Et_2O (5.0 mL, 0.25 M) at 23 °C was added $MeNH_2$ (0.228 mL, 40% solution in H_2O, 2.61 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (5.0 mL). The filtrate was concentrated in vacuo and redissolved in THF:H_2O (5:1, 6.20 mL, 0.20 M). Boc_2O (0.270 g, 1.24 mmol) was added and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (5 mL) and sat. aq. $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (5 mL). The combined organic layers were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording carbamoyl ether **18** (0.350 g, 86% yield over 2 steps, R_F = 0.47 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 18: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.23-7.16 (comp m, 3H), 4.55-4.52 (m, 1H), 3.98 (t, *J* = 6.4 Hz, 1H), 3.41 (d, *J* = 0.9 Hz, 3H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.12-1.96 (comp m, 2H), 1.89-1.72 (comp m, 2H), 1.48 (s, 9H), 1.06 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.4, 128.65,

128.56, 126.1, 85.37, 85.29, 83.93, 83.90, 82.0, 70.44, 70.42, 56.62, 56.61, 37.33, 37.28, 31.58, 31.57, 28.4, 27.1, 9.7; IR (film) 3285, 2977, 1747, 1455, 1104, 700 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + NH_4)^+$ $[C_{20}H_{29}NO_4 + NH_4]^+$: 365.2435, found 365.2434.



To a solution of alcohol **17** (0.116 g, 0.500 mmol) in THF (1.00 mL, 0.50 M) under argon was added PPh_3 (0.157 g, 0.600 mmol) and Boc_2NOH (0.140 g, 0.600 mmol).[3] The resulting solution was cooled to 0 °C, and a solution of DEAD (0.094 mL, 0.600 mmol) in THF (0.200 mL) was added dropwise over 40 minutes. The reaction was stirred at 0 °C for 8 h. TFA (0.900 mL) was then added dropwise, and the reaction was warmed to 23 °C, and stirred until the reaction was complete by TLC. The reaction was poured into sat. aq. Na_2CO_3 (15.0 mL) and stirred for 10 min. The mixture was diluted with Et_2O (5.0 mL), and the phases were separated. The aq. phase was extracted with Et_2O (5.0 mL), and the combined organics were dried over $MgSO_4$. The solvent was removed by rotary evaporation and the recovered oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) producing carbamoyl ether **18** (0.140 g, 81% yield) as a colorless oil.



To a solution of alkyne **81** (0.684 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**16**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation affording alcohol **104** (0.820 g, 96% crude yield, R_F = 0.39 in 4:1 hexanes/EtOAc) as a colorless oil.

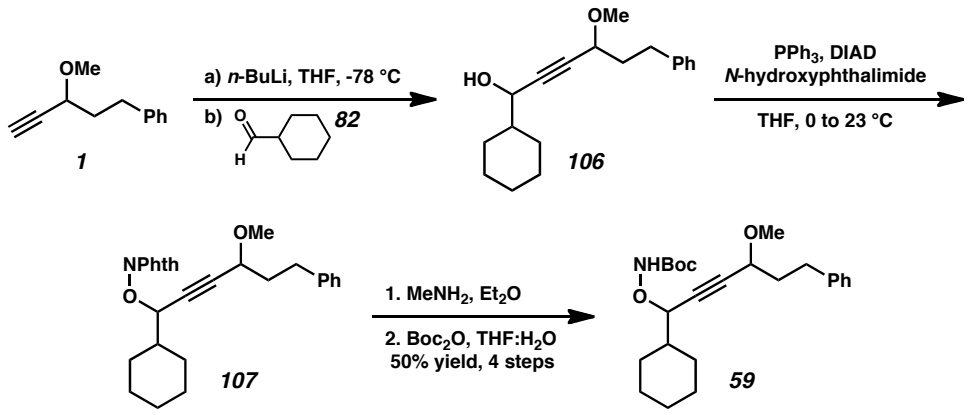
To a solution of PPh_3 (0.903 g, 3.44 mmol) in THF (17.2 mL, 0.20 M) at 0 °C under argon was added DIAD (0.583 mL, 3.01 mmol) dropwise. After 10 min a solution of alcohol

[3] A. H. Gouliaev, W. D. Brown, F. Waetjen WO Patent WO2004018466, 2004.

104 (0.820 g, 2.87 mmol) in THF (5.7 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.490 g, 3.01 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording phthalimide **105** (0.920 g, 74% yield, R_F = 0.40 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **105** (0.920 g, 2.13 mmol) in Et_2O (10.6 mL, 0.25 M) at 23 °C was added $MeNH_2$ (0.390 mL, 40% solution in H_2O, 4.48 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo and redissolved in THF:H_2O (4:1, 12.5 mL, 0.20 M). Boc_2O (0.464 g, 2.13 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), sat. aq. $NaHCO_3$ (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL), and the combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording carbamoyl ether **58** (0.659 g, 77% yield over 2 steps, R_F = 0.51 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 58: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.6 Hz, 1H), 4.53-4.49 (m, 1H), 4.19 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 1H), 3.80-3.69 (comp m, 2H), 3.40 (s, 3H), 1.99-1.72 (comp m, 4H), 1.48 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.51, 156.49, 85.56, 85.50, 83.62, 83.58, 81.9, 68.1, 59.1, 56.68, 56.66, 38.9, 28.4, 27.1, 26.1, 18.5, 9.7, -5.2; IR (film) 3282, 2932, 1750, 1472, 1251, 813 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{39}NO_5Si + Na]^+$: 424.2490, found 424.2481.



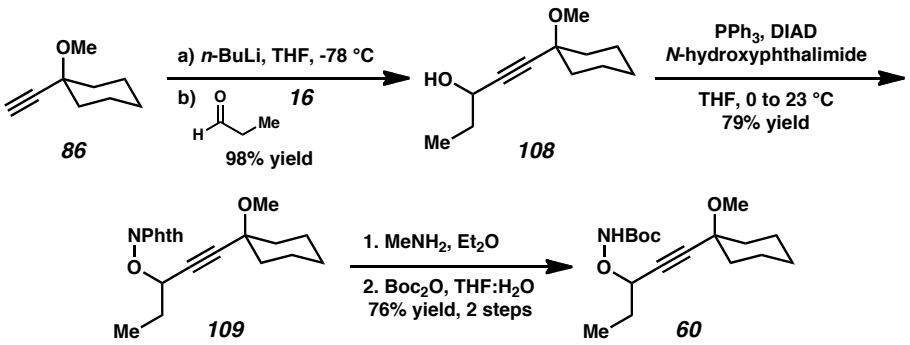
To a solution of alkyne **1** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Cyclohexanecarboxaldehyde (**82**, 0.363 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent

was removed by rotary evaporation affording alcohol **106** (0.923 g crude, R_F = 0.40 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **106** (0.585 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **107** (1.43 g, R_F = 0.34 in 4:1 hexanes/EtOAc) as a pale yellow oil that contained the hydrazine byproduct.

To a solution of phthalimide **107** (1.43 g, assumed 3.00 mmol) in Et_2O (12.0 mL, 0.25 M) at 23 °C was added $MeNH_2$ (0.550 mL, 40% solution in H_2O, 6.30 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (4:1, 15.0 mL, 0.20 M). Boc_2O (0.654 g, 3.00 mmol) was added, and the reaction was stirred for 12 h. The reaction was diluted with Et_2O (10 mL), sat. aq. $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL), and the combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **59** (0.607 g, 50% yield over 4 steps, R_F = 0.51 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 59: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (comp m, 2H), 7.20-7.16 (comp m, 4H), 4.38 (ddd, *J* = 5.9, 3.2, 1.4 Hz, 1H), 3.99-3.95 (m, 1H), 3.40 (d, *J* = 1.6 Hz, 3H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.11-1.95 (comp m, 2H), 1.90-1.87 (comp m, 2H), 1.75-1.70 (comp m, 2H), 1.67-1.62 (m, 1H), 1.46 (d, *J* = 0.6 Hz, 9H), 1.30-1.09 (comp m, 5H), 0.96-0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 141.5, 128.65, 128.56, 126.1, 86.10, 86.00, 83.1, 81.9, 80.64, 80.61, 70.49, 70.47, 56.65, 56.63, 41.18, 41.15, 37.43, 37.36, 31.63, 31.61, 29.16, 29.12, 28.37, 28.35, 26.47, 26.45, 25.97, 25.89; IR (film) 3282, 2979, 1946, 1748, 1453, 1166, 753 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{24}H_{35}NO_4 + Na]^+$: 424.2458, found 424.2462.



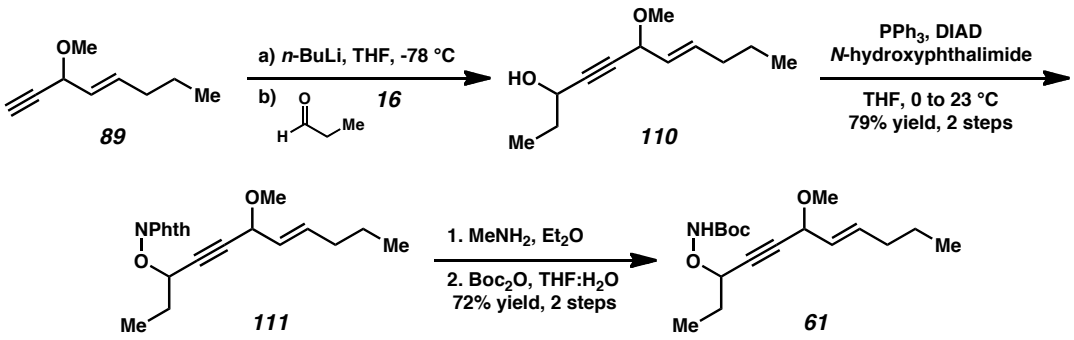
To a solution of alkyne **86** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**16**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The

reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed by rotary evaporation affording alcohol **108** (0.577 g, 98% crude yield, R_F = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.926 g, 3.53 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.597 mL, 3.08 mmol) dropwise. After 10 min a solution of alcohol **108** (0.577 g, 2.94 mmol) in THF (6.00 mL, 0.48 M) was added. After 5 min *N*-hydroxyphthalimide (0.502 g, 3.08 mmol) was added, the reaction was warmed to 23 °C, and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford phthalimide **109** (0.796 g, 79% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **109** (0.796 g, 2.33 mmol) in Et_2O (12.0 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.428 mL, 40% solution in H_2O, 4.90 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (3:1, 15.0 mL, 0.20 M). Boc_2O (0.508 g, 2.33 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **60** (0.557 g, 76% yield over 2 steps, R_F = 0.45 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 60: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 4.54 (t, *J* = 6.4 Hz, 1H), 3.36 (s, 3H), 1.92-1.87 (comp m, 2H), 1.86-1.71 (comp m, 2H), 1.68-1.62 (comp m, 2H), 1.60-1.52 (comp m, 4H), 1.48 (s, 9H), 1.33-1.24 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 87.9, 83.6, 81.9, 77.1, 74.1, 50.9, 36.85, 36.82, 28.4, 27.2, 25.6, 23.0, 9.7; IR (film) 3265, 2937, 1996, 1747, 1169, 926 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{17}H_{29}NO_4 + Na]^+$: 334.1989, found 334.1989.



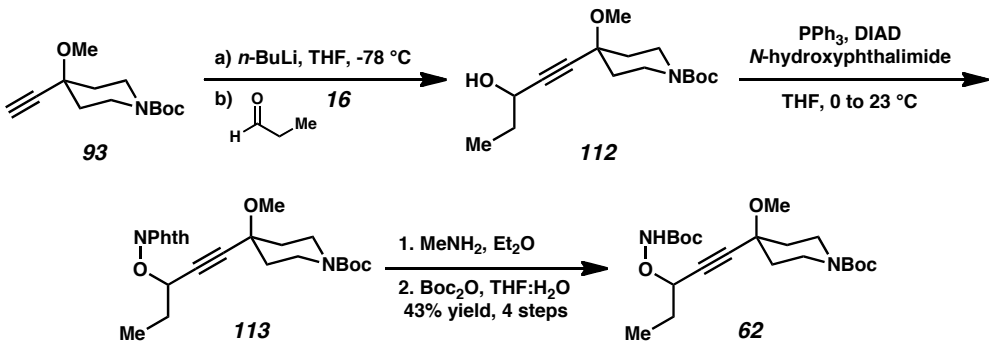
To a solution of alkyne **89** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**16**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The

reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **110** (0.585 g crude, R_F = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **110** (0.585 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **111** (0.808 g, 79% yield over 2 steps, R_F = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **111** (0.808 g, 2.37 mmol) in Et_2O (12.0 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.434 mL, 40% solution in H_2O, 4.98 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (4:1, 12.0 mL, 0.20 M). Boc_2O (0.517 g, 2.37 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **61** (0.534 g, 72% yield over 2 steps, R_F = 0.50 in 4:1 hexanes/EtOAc) as a pale yellow oil.

Carbamoyl ether 61: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (br s, 1H), 5.87 (dt, *J* = 15.2, 6.9 Hz, 1H), 5.50 (ddd, *J* = 15.3, 6.4, 1.3 Hz, 1H), 4.53-4.49 (comp m, 2H), 3.35 (d, *J* = 0.8 Hz, 3H), 2.06-2.01 (comp m, 2H), 1.86-1.72 (comp m, 2H), 1.46 (s, 9H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 135.62, 135.57, 126.84, 126.80, 84.72, 84.69, 84.04, 84.01, 81.9, 71.5, 55.57, 55.55, 34.2, 28.4, 27.0, 22.2, 13.8, 9.7; IR (film) 3282, 2970, 1722, 1461, 1392, 1164, 969 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{17}H_{29}NO_4 + Na]^+$: 334.1989, found 334.1984.



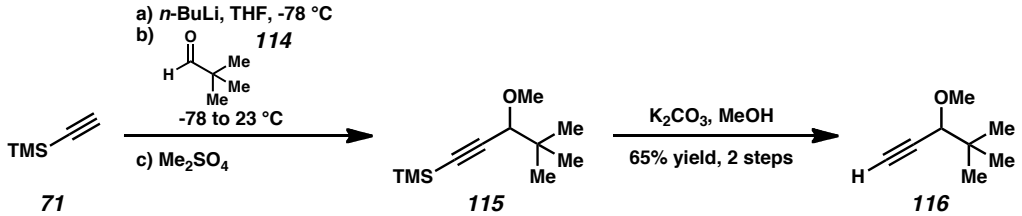
To a solution of alkyne **93** (0.717 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**16**, 0.220 mL, 3.30 mmol) was added dropwise, and the

reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **112** (0.914 g crude, R_F = 0.10 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **112** (0.914 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **113** (1.17 g, R_F = 0.42 in 2:1 hexanes/EtOAc) as a yellow oil that was carried on with a small amount of the hydrazine byproduct.

To a solution of phthalimide **113** (1.17 g, 2.64 mmol) in Et_2O (13.0 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.483 mL, 40% solution in H_2O, 5.54 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (4:1, 15.0 mL, 0.20 M). Boc_2O (0.576 g, 2.64 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording carbamoyl ether **62** (0.539 g, 43% yield over 4 steps, R_F = 0.25 in 4:1 hexanes/EtOAc) as a pale yellow oil.

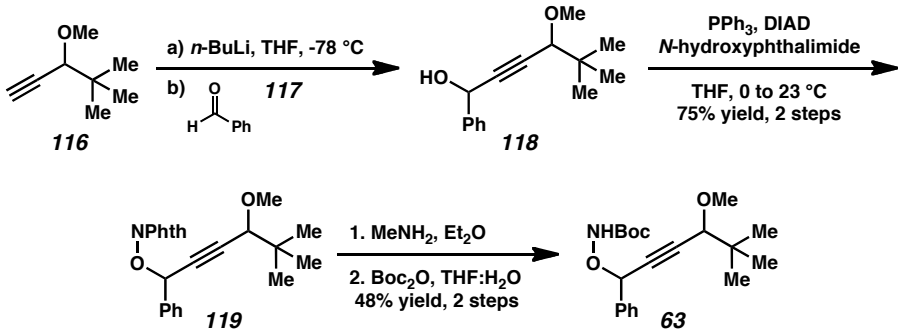
Carbamoyl ether 62: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 4.52 (t, *J* = 6.5 Hz, 1H), 3.71 (dt, *J* = 14.3, 5.0 Hz, 2H), 3.36 (s, 3H), 3.25 (ddd, *J* = 13.3, 9.5, 3.6 Hz, 2H), 1.91-1.65 (m, 6H), 1.47 (s, 9H), 1.44 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 154.8, 86.0, 84.9, 82.0, 79.8, 77.0, 72.5, 51.11, 51.09, 40.7, 36.1, 28.6, 28.4, 9.7; IR (film) 3265, 2976, 1747, 1698, 1165, 771 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{21}H_{36}N_2O_6 + Na]^+$: 435.2466, found 435.2465.



To a solution of TMS-acetylene (**71**, 1.41 mL, 10.0 mmol) in THF (30.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min. Pivalaldehyde (**114**, 1.10 mL, 10.0 mmol) was added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me_2SO_4 (1.04 mL, 11.0 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH_4OH (20 mL), stirring for 15 min. The mixture was

diluted with Et_2O (30 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (15 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **115** (1.95 g crude) as a pale yellow oil.

To a solution of ether **115** (2.21 g crude, assumed 10.0 mmol) in MeOH (40.0 mL, 0.25 M) at 23 °C was added K_2CO_3 (1.65 g, 12.0 mmol) and the reaction was stirred for 16 h. The reaction was diluted with brine (50 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1 pentane/Et_2O eluent) affording alkyne **116** (0.817 g, 65% yield over 2 steps) as a volatile, colorless oil.



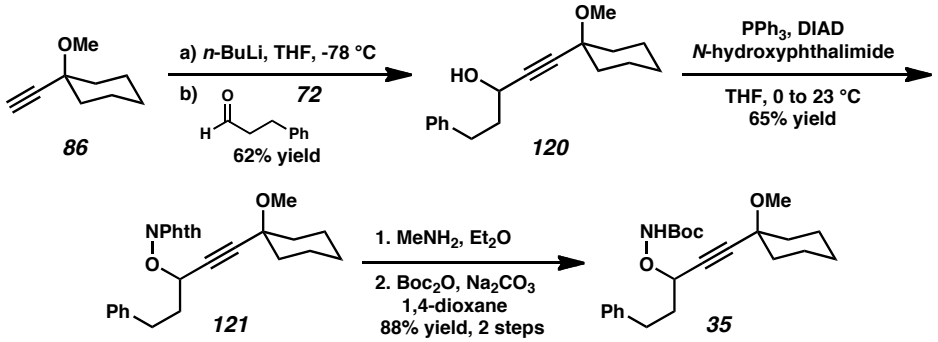
To a solution of alkyne **116** (0.378 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Benzaldehyde (**117**, 0.305 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **118** (0.695 g, 99% crude yield, R_F = 0.46 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.218 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **118** (0.695 g, 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording phthalimide **119** (0.850 g, 75% yield, R_F = 0.36 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **119** (0.850 g, 2.25 mmol) in Et_2O (11.2 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.413 mL, 40% solution in H_2O, 4.73 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (3:1, 14.0 mL, 0.16 M). Boc_2O (0.491 g, 2.25 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over

$MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **63** (0.378 g, 48% yield over 2 steps, R_F = 0.43 in 4:1 hexanes/EtOAc) as a pale yellow oil.

Carbamoyl ether 63: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.41-7.36 (m, 3H), 7.19 (s, 1H), 5.66 (t, *J* = 1.8 Hz, 1H), 3.66 (d, *J* = 1.5 Hz, 1H), 3.45 (d, *J* = 1.8 Hz, 3H), 1.48 (s, 9H), 1.02 (d, *J* = 1.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 136.06, 136.04, 129.3, 128.76, 128.73, 128.64, 86.99, 86.94, 82.80, 82.76, 82.1, 80.9, 57.8, 35.8, 28.4, 26.0; IR (film) 3285, 2977, 1723, 1367, 1098 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{29}NO_4 + Na]^+$: 370.1989, found 370.1981.



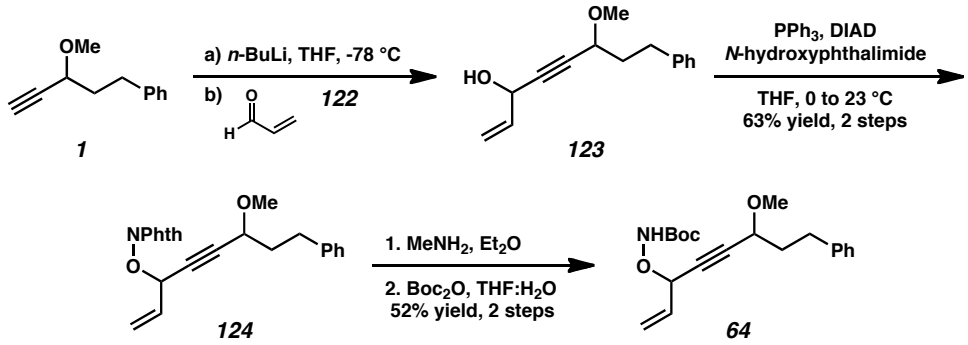
To a solution of alkyne **86** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Hydrocinnamaldehyde (**72**, 0.395 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent), affording alcohol **120** (0.503 g, 62% yield, R_F = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.582 g, 2.22 mmol) in THF (12.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.376 mL, 1.94 mmol) dropwise. After 10 min a solution of alcohol **120** (0.503 g, 1.85 mmol) in THF (3.60 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.316 g, 1.94 mmol) was added, and the reaction was slowly warmed to 23 °C, and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording phthalimide **121** (0.504 g, 65% yield, R_F = 0.51 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **121** (0.504 g, 1.21 mmol) in Et_2O (6.00 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.222 mL, 40% solution in H_2O, 2.54 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (5.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (4.80 mL, 0.25 M). Na_2CO_3 (0.128 g, 1.21 mmol) was added, followed by Boc_2O (0.264 g, 1.21 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$

(10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording carbamoyl ether **35** (0.411 g, 88% yield over 2 steps, R_F = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 35: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.22-7.17 (comp m, 4H), 4.61 (t, *J* = 6.5 Hz, 1H), 3.38 (s, 3H), 2.85 (td, *J* = 8.0, 2.0 Hz, 2H), 2.19-2.00 (comp m, 2H), 1.94-1.90 (comp m, 2H), 1.70-1.50 (comp m, 7H), 1.48 (s, 9H), 1.35-1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.3, 128.6, 126.2, 88.3, 83.5, 82.0, 75.3, 74.1, 50.96, 50.93, 36.84, 36.81, 35.8, 31.6, 28.36, 28.25, 25.6, 23.0; IR (film) 3265, 2936, 1748, 1164, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{23}H_{33}NO_4 + Na]^+$: 410.2302, found 410.2295.



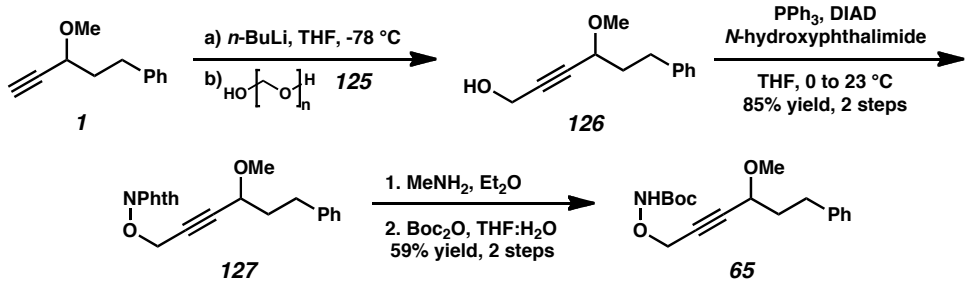
To a solution of alkyne **1** (0.696 g, 4.00 mmol) in THF (12.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. Acrolein (**122**, 0.267 mL, 4.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (12 mL), and diluted with Et_2O (12 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (12 mL). The combined organic layers were washed with brine (12 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **123** (0.842 g crude, R_F = 0.22 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (1.26 g, 4.80 mmol) in THF (26.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.813 mL, 4.20 mmol) dropwise. After 10 min a solution of crude alcohol **123** (0.842 g, assumed 4.00 mmol) in THF (8.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.685 g, 4.20 mmol) was added, and the reaction was warmed to 23 °C, and stirred for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (40 mL), and diluted with Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **124** (0.942 g, 63% yield over 2 steps, R_F = 0.54 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **124** (0.942 g, 2.51 mmol) in Et_2O (12.5 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.410 mL, 40% solution in H_2O, 5.27 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (4:1, 15.0 mL, 0.20 M). Boc_2O (0.547 g, 2.51 mmol) was added and the reaction was stirred for 16 h. The reaction was

diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **64** (0.452 g, 52% yield over 2 steps, R_F = 0.44 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 64: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.21-7.18 (comp m, 4H), 5.99 (ddd, *J* = 16.8, 10.4, 6.2 Hz, 1H), 5.58 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.38 (dd, *J* = 10.2, 0.5 Hz, 1H), 5.08 (ddd, *J* = 5.9, 2.7, 1.4 Hz, 1H), 4.02-3.98 (m, 1H), 3.42 (d, *J* = 1.3 Hz, 3H), 2.81-2.77 (comp m, 2H), 2.14-1.97 (comp m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.4, 132.8, 128.66, 128.56, 126.1, 120.72, 120.67, 87.22, 87.18, 82.1, 81.67, 81.65, 76.2, 70.4, 56.7, 37.24, 37.20, 31.5, 28.3; IR (film) 3283, 2933, 1746, 1603, 1455, 1103, 701 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{27}NO_4 + Na]^+$: 368.1832, found 368.1821.



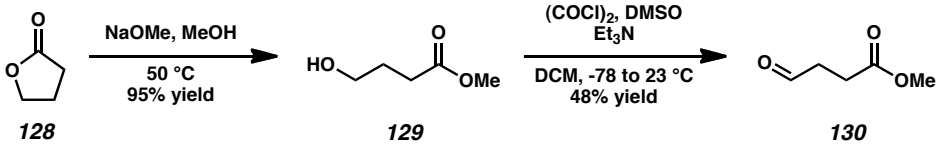
To a solution of alkyne **1** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Paraformaldehyde (**125**, 94.5 mg, 3.15 mmol) was added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 12 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **126** (0.647 g crude, R_F = 0.42 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **126** (0.647 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 20 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) affording phthalimide **127** (0.886 g, 85% yield over 2 steps, R_F = 0.42 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **127** (0.886 g, 2.53 mmol) in Et_2O (12.0 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.465 mL, 40% solution in H_2O, 5.33 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (10.0 mL, 0.25 M).

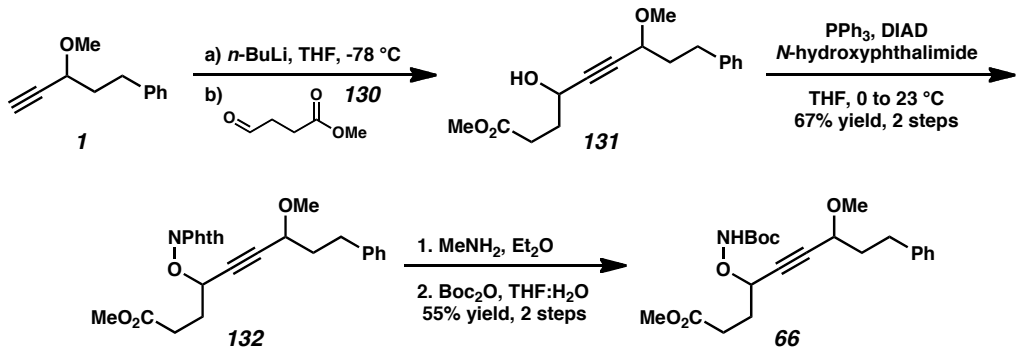
Na_2CO_3 (0.268 g, 2.53 mmol) was added, followed by Boc_2O (0.551 g, 2.53 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (20 mL), and sat. aq. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **65** (0.478 g, 59% yield over 2 steps, R_F = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 65: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (comp m, 2H), 7.16-7.12 (comp m, 3H), 4.50 (d, *J* = 1.6 Hz, 2H), 3.94-3.89 (m, 1H), 3.36 (s, 3H), 2.74 (td, *J* = 7.8, 1.8 Hz, 2H), 2.07-1.91 (comp m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.4, 128.65, 128.55, 126.1, 86.4, 82.3, 80.7, 70.4, 64.2, 56.7, 37.1, 31.5, 28.3; IR (film) 3279, 2933, 1950, 1745, 1368, 1103, 701 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + NH_4)^+$ $[C_{18}H_{25}NO_4 + NH_4]^+$: 337.2122, found 337.2125.



To MeOH (50.0 mL) cooled to 0 °C under argon was added sodium metal (0.115 g, 5.00 mmol), and the solution was stirred until the sodium fully dissolved. δ-butyrolactone (**128**, 3.81 mL, 50.0 mmol) was added, and the reaction was heated to 50 °C for 5 h. The reaction was cooled, filtered through a SiO_2 plug and concentrated. The recovered residue was redissolved in Et_2O and filtered affording ester **129** (5.61 g crude, 95% yield, R_F = 0.52 in 2:1 EtOAc/hexanes).

To a solution of oxalyl chloride (2.62 mL, 30.0 mmol) in CH_2Cl_2 (45.0 mL, 0.66 M) at -78° C under argon was added DMSO (4.26 mL, 60.0 mmol) dropwise. The solution was stirred at -78 °C for 5 min, and then a solution of alcohol **129** (3.48 g, 30.0 mmol) in CH_2Cl_2 (10.0 mL, 3.0 M) was added slowly, and then stirred for 15 min. Et_3N (21.0 mL, 150 mmol) was added, and the reaction was maintained at -78 °C for 15 min before being warmed to room temperature and stirred for 10 min. The reaction was quenched with water (100 mL), stirred for 20 min, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layers were washed sequentially with 1 N HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$, and the solvent was removed via rotary evaporation. The recovered material was purified by distillation (75 °C at 40 mm Hg) affording methyl 4-oxobutanoate (**130**, 1.67 g, 48% yield) as a colorless liquid.

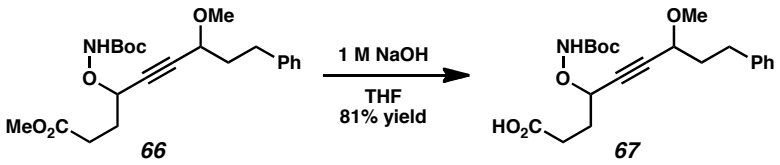


To a solution of alkyne **1** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Methyl 4-oxobutanoate (**130**, 0.314 mL, 3.00 mmol) was added and the reaction was stirred at -78 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and warmed to 23 °C. The reaction was diluted with Et_2O (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL), and the combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **131** (0.960 g crude, R_F = 0.35 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **131** (0.960 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording phthalimide **132** (1.07 g, 67% yield over 2 steps, R_F = 0.34 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **132** (1.07 g, 2.01 mmol) in Et_2O (10.0 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.368 mL, 40% solution in H_2O, 4.22 mmol) and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H_2O (4:1, 10.0 mL, 0.20 M). Boc_2O (0.438 g, 2.01 mmol) was added and the reaction was stirred for 12 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording carbamoyl ether **66** (0.448 g, 55% yield over 2 steps, R_F = 0.50 in 2:1 hexanes/EtOAc) as a colorless oil.

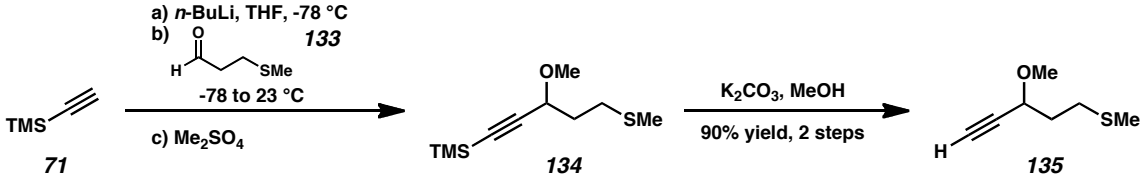
Carbamoyl ether 66: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.21-7.16 (comp m, 3H), 4.66-4.63 (m, 1H), 3.97-3.94 (m, 1H), 3.68 (s, 3H), 3.40 (s, 3H), 2.79-2.75 (m, 2H), 2.58 (td, *J* = 7.5, 3.0 Hz, 2H), 2.14-2.09 (m, 2H), 2.08-1.96 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 156.5, 141.3, 128.65, 128.56, 126.1, 85.9, 83.0, 82.1, 74.72, 74.70, 70.3, 56.7, 51.9, 37.23, 37.19, 31.5, 29.6, 28.8, 28.3; IR (film) 3300, 2980, 1740, 1440, 1168, 1104, 701 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{22}H_{31}NO_6 + Na]^+$: 428.2044, found 428.2048.



To a solution of carbamoyl ether **66** (0.206 g, 0.509 mmol) in THF (2.50 mL, 0.2 M) at 23 °C was added NaOH (2.50 mL, 1.0 M in H_2O, 2.50 mmol), and the reaction was stirred for 16

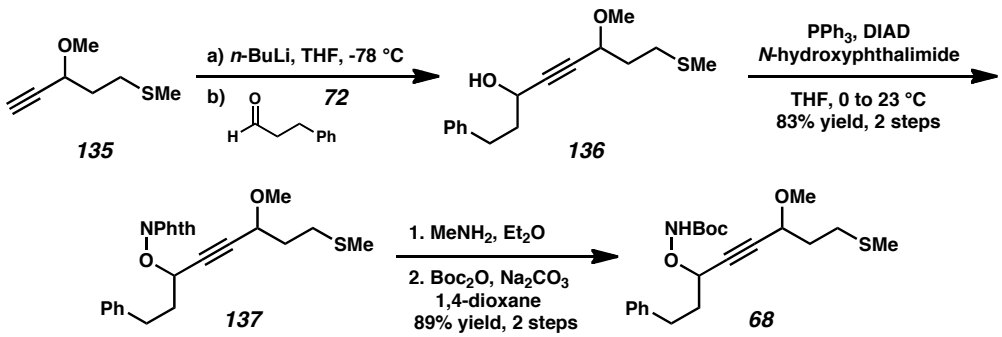
h. The THF was removed by rotary evaporation and the resulting aqueous solution was acidified to pH ~ 2.0 with 10% aq. HCl. The solution was then saturated with NaCl, and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude material was purified by flash chromatography (1:1 hexanes/Et_2O with 1% AcOH) affording carbamoyl ether **67** (0.156 g, 81% yield, R_F = 0.43 in 2:1 Et_2O/hexanes with 1% AcOH) as a colorless oil.

Carbamoyl ether 67: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 4.65 (ddd, *J* = 7.3, 5.1, 1.8 Hz, 1H), 3.98-3.94 (m, 1H), 3.40 (s, 3H), 2.79-2.75 (comp m, 2H), 2.65-2.61 (comp m, 2H), 2.14-2.08 (comp m, 2H), 2.06-1.94 (comp m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 156.8, 141.3, 128.65, 128.63, 128.57, 128.53, 126.1, 86.03, 86.02, 82.94, 82.92, 82.4, 74.62, 74.60, 70.4, 56.7, 37.18, 37.14, 31.5, 29.6, 28.7, 28.3; IR (film) 3258, 2980, 1714, 1250, 1164, 1105 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{21}H_{29}NO_6 + Na]^+$: 414.1887, found 414.1889.



To a solution of TMS-acetylene (**71**, 2.82 mL, 20.0 mmol) in THF (50.0 mL, 0.40 M) at -78 °C under argon was added *n*-BuLi (8.00 mL, 2.5 M in hexanes, 20.0 mmol), and the resulting solution was stirred for 30 min. 3-(Methylthio)propionaldehyde (**133**, 2.00 mL, 20.0 mmol) was added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me_2SO_4 (2.09 mL, 22.0 mmol) was added, and the reaction was stirred for 14 h. The reaction was quenched with 10% aq. NH_4OH (20 mL), stirring for 15 min. The mixture was diluted with Et_2O (50 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (25 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was removed by rotary evaporation affording ether **134** (4.27 g crude, R_F = 0.58 in 9:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **134** (4.27 g crude, assumed 20.0 mmol) in MeOH (100 mL, 0.20 M) at 23 °C was added K_2CO_3 (2.76 g, 22.0 mmol), and the reaction was stirred for 5 h. The reaction was diluted with brine (100 mL), and extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **135** (2.55 g, 90% yield over 2 steps, R_F = 0.50 in 9:1 hexanes/EtOAc) as a colorless oil.



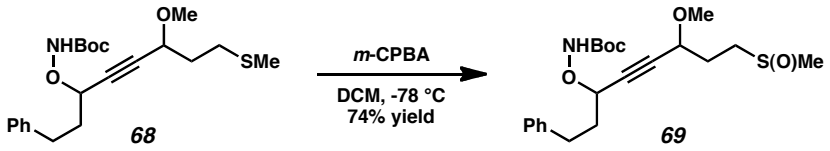
To a solution of alkyne **135** (0.427 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.29 mL, 2.32 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Hydrocinnamaldehyde (**72**, 0.395 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation affording alcohol **136** (0.836 g crude, R_F = 0.50 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **136** (0.836 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 20 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and diluted with Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **137** (1.05 g, 83% yield over 2 steps, R_F = 0.56 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **137** (1.05 g, 2.49 mmol) in Et_2O (12.5 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.456 mL, 40% solution in H_2O, 5.23 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (10.0 mL, 0.25 M). Na_2CO_3 (0.264 g, 2.49 mmol) was added, followed by Boc_2O (0.543 g, 2.49 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (20 mL), and sat. aq. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording carbamoyl ether **68** (0.877 g, 89% yield over 2 steps, R_F = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

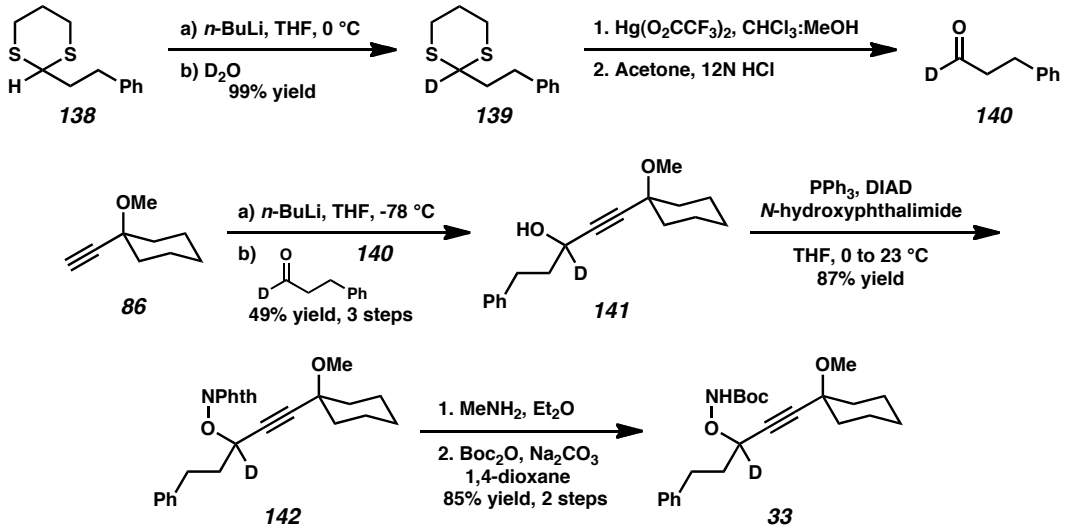
Carbamoyl ether 68: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 4.58 (tt, *J* = 6.5, 1.8 Hz, 1H), 4.18 (ddd, *J* = 7.0, 5.9, 1.2 Hz, 1H), 3.42 (d, *J* = 0.5 Hz, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.19-2.12 (m, 1H), 2.11 (s, 3H), 2.08-1.93 (comp m, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.1, 128.5, 126.1, 85.15, 85.10, 83.99, 83.95, 81.9, 75.1, 69.8, 56.70, 56.65, 35.5, 35.1, 31.5, 29.9, 28.3, 15.6; IR (film)

3280, 2931, 1748, 1604, 1368, 1247, 1103 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{31}NO_4S + H]^+$: 394.2047, found 394.2043.



To a solution of carbamoyl ether **68** (0.393 g, 1.00 mmol) in DCM (5.00 mL, 0.2 M), cooled at -78 °C under an argon atmosphere, was added *m*-CPBA (0.224 g, 77% max wt, 1.00 mmol). The reaction was stirred for 1 h, quenched with sat. aq. $Na_2S_2O_3$ (5.0 mL), and was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with DCM (5.0 mL). The organics were combined and washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, and the solvent removed by rotary evaporation. The crude oil was purified by flash chromatography (0→5% MeOH/EtOAc) affording carbamoyl ether **69** (0.301 g, 74% yield, R_F = 0.48 in 1:19 MeOH/EtOAc) as a colorless oil.

Carbamoyl ether 69: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (comp m, 2H), 7.21-7.16 (comp m, 3H), 4.57-4.54 (m, 1H), 4.23-4.18 (m, 1H), 3.41 (dd, *J* = 1.3, 0.9 Hz, 3H), 2.98-2.87 (comp m, 2H), 2.86-2.80 (comp m, 2H), 2.61-2.58 (comp m, 3H), 2.26-2.17 (comp m, 2H), 2.17-2.09 (m, 1H), 2.07-1.98 (m, 1H), 1.47 (d, *J* = 1.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 141.12, 141.09, 128.6, 126.2, 85.12, 85.10, 85.03, 84.94, 84.13, 84.08, 83.97, 81.84, 75.1, 69.7, 56.84, 50.0, 38.8, 35.4 31.5, 28.4; IR (film) 3178, 2933, 2349, 1739, 1368, 1106, 753 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{21}H_{31}NO_5S + Na]$ 432.1815, found 432.1811.



To a solution of dithiane **138**[4] (3.36 g, 15.0 mmol) in THF (30.0 mL, 0.5 M) at -30 °C under argon was added *n*-BuLi (7.20 mL, 2.50 M in hexanes, 18.0 mmol), and the reaction was stirred at -30 °C for 2 h. D_2O (0.540 mL, >99.9% D, 30.0 mmol) was added, and the reaction

[4] D. A. Rooke, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 11926-11928.

was warmed to 23 °C, and stirred for an additional 15 min. The reaction was diluted with hexanes (30 mL), and washed with H_2O (30 mL). The aqueous phase was extracted with Et_2O (30 mL), and the combined organic layers were dried over $MgSO_4$, and the solvent removed by rotary evaporation affording deuterated dithiane **139** (3.35 g, 99% yield, >98% D incorporation, R_F = 0.64 in 1:1 hexanes/CH_2Cl_2) as a colorless oil.

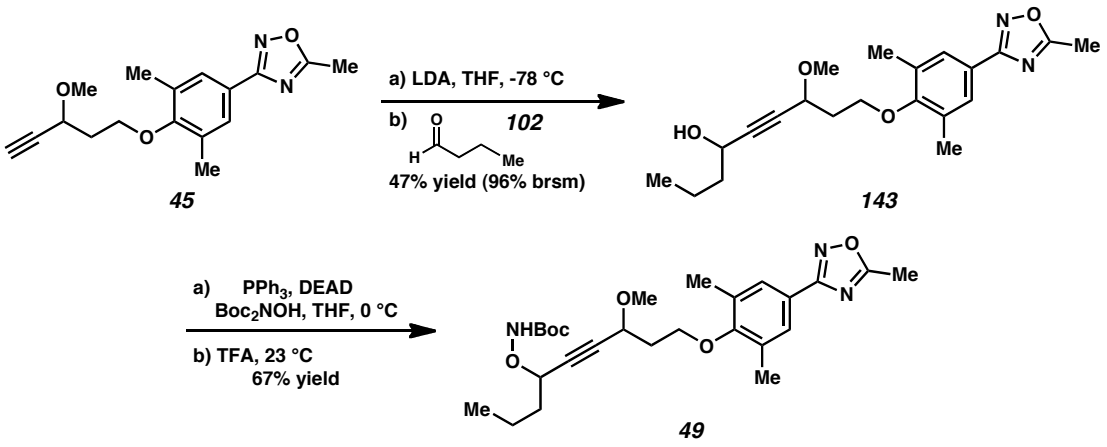
To a solution of dithiane **139** (0.450 g, 2.00 mmol) in $CHCl_3$:MeOH (100:1, 40.4 mL, 0.05 M) was added $Hg(O_2CCF_3)_2$ (1.28 g, 3.00 mmol), and the reaction was stirred for 12 h. Celite (2.0 g) was added, and the reaction was filtered, washing with $CHCl_3$ (10 mL). The solvent was removed in vacuo, and the recovered residue was dissolved into acetone (15.0 mL, 0.13 M). To this was added HCl (10.0 mL, 12.0 N) and the reaction was stirred for 40 min. The acetone was removed in vacuo, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were dried over $MgSO_4$, and the solvent removed by rotary evaporation, affording aldehyde **140** (0.378 g crude, R_F = 0.58 in 1:1 hexanes/CH_2Cl_2 eluent) as a colorless oil.

To a solution of alkyne **86** (0.276 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the reaction was stirred for 30 min. Aldehyde **140** (0.378 g, assumed 2.00 mmol) in THF (2.00 mL, 1.0 M) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent), affording alcohol **141** (0.270 g, 49% yield over 3 steps, R_F = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.309 g, 1.18 mmol) in THF (8.00 mL, 0.15 M) at 0 °C under argon was added DIAD (0.201 mL, 1.04 mmol) dropwise. After 10 min a solution of alcohol **141** (0.270 g, 0.987 mmol) in THF (2.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.169 g, 1.04 mmol) was added and the reaction was warmed to 23 °C, and stirred for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **142** (0.360 g, 87% yield, R_F = 0.51 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **142** (0.360 g, 0.860 mmol) in Et_2O (4.30 mL, 0.20 M) at 23 °C was added $MeNH_2$ (0.158 mL, 40% solution in H_2O, 1.81 mmol) and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (5.0 mL). The filtrate was concentrated in vacuo, and dissolved in 1,4-dioxane (3.50 mL, 0.25 M). Na_2CO_3 (91.2 mg, 0.860 mmol) was added, followed by Boc_2O (0.182 g, 0.860 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (5.0 mL), and sat. aq. $NaHCO_3$ (5.0 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (5.0 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording carbamoyl ether **33** (0.285 g, 85% yield over 2 steps, R_F = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil.

Carbamoyl ether 33: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.22-7.19 (comp m, 4H), 3.38 (s, 3H), 2.85 (ddd, *J* = 9.0, 7.0, 1.9 Hz, 2H), 2.18-2.00 (comp m, 2H), 1.94-1.90 (comp m, 2H), 1.70-1.50 (m, 7H), 1.48 (s, 9H), 1.35-1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.4, 128.6, 126.2, 88.2, 83.5, 82.0, 74.1, 50.97, 50.93, 36.84, 36.82, 35.6, 31.6, 28.36, 28.30, 28.26, 25.6, 23.0; IR (film) 3262, 2936, 1747, 1454, 1247, 1093 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{23}H_{32}DNO_4 + Na]^+$: 411.2365, found 411.2353.

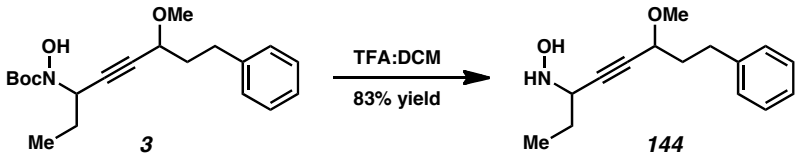


To a solution of alkyne **45** (150 mg, 0.500 mmol) in THF (2.50 mL, 0.2 M) at -78 °C under argon was added LDA (0.500 mL, 0.500 mmol, 1.0 M solution in THF freshly prepared from *i*-Pr_2NH and *n*-BuLi), and the reaction was stirred at -78 °C for 10 min., then warmed to 23 °C for 15 min. The reaction was then cooled to -78 °C, and butyraldehyde (**102**, 49.6 μL, 0.550 mmol) was added. The reaction was warmed to 23 °C and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (5.0 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) producing alkyne **45** (74.0 mg, 49% recovery), and alcohol **143** (87.0 mg, 47% yield, R_F = 0.34 in 2:1 hexanes/EtOAc) as colorless oils.

To a solution of alcohol **143** (87.0 mg, 0.234 mmol) in THF (0.468 mL, 0.50 M) under argon was added PPh_3 (73.6 mg, 0.281 mmol) and Boc_2NOH (65.5 mg, 0.281 mmol). The resulting solution was cooled to 0 °C, and a solution of DEAD (44.0 μL, 0.281 mmol) in THF (0.100 mL) was added dropwise over 30 min. The reaction was stirred at 0 °C for 14 h. TFA (0.700 mL) was then added dropwise, and the reaction was warmed to 23 °C, and stirred until the reaction was complete by TLC. The reaction was poured into sat. aq. Na_2CO_3 (5.0 mL) and stirred for 10 min. The mixture was diluted with Et_2O (5.0 mL), and the phases were separated. The aq. phase was extracted with Et_2O (5.0 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was removed by rotary evaporation and the recovered oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) producing carbamoyl ether **49** (76.1 mg, 67% yield) as a colorless oil.

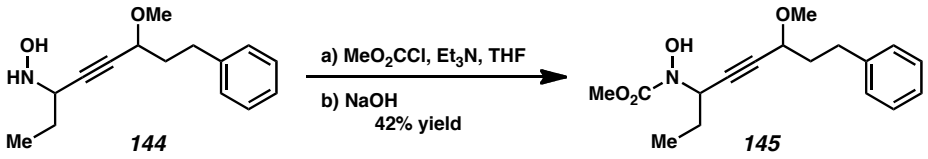
Carbamoyl ether 49: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.27 (s, 1H), 4.57 (t, *J* = 6.5 Hz, 1H), 4.41 (t, *J* = 6.7 Hz, 1H), 3.97-3.91 (comp m, 2H), 3.45 (s, 3H), 2.63 (d, *J* = 0.8 Hz, 3H), 2.32 (s, 6H), 2.23-2.19 (comp m, 2H), 1.83-1.66 (comp m, 2H), 1.57-1.50 (comp m, 2H), 1.46 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 188.5, 176.4, 168.3, 158.3, 156.5, 131.9, 128.1, 122.2, 84.9, 84.4, 82.0, 75.8, 75.7, 68.12, 68.10, 68.0, 56.8, 36.6, 35.8, 28.3, 18.7, 16.3, 13.9, 12.5; IR (film) 3282, 2964, 2251, 1748, 1584, 1353, 1107. HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{26}H_{37}N_3O_6 + Na]^+$: 510.2575, found 510.2590.



To carbamate **3** (1.39 g, 4.00 mmol) was added a CH_2Cl_2:TFA (3:1, 40.0 mL, 0.10 M) mixture, and the reaction was stirred at 23 °C for 2 h. The solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with sat. aq. $NaHCO_3$ (40 mL), and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic phases were dried over $MgSO_4$, and the solvent removed by rotary evaporation. The crude residue was purified by flash chromatography (2:1→1:1 hexanes/EtOAc eluent) affording *N*-hydroxylamine **144** (0.821 g, 83% yield, R_F = 0.35 in 1:1 hexanes/EtOAc) as a colorless oil.

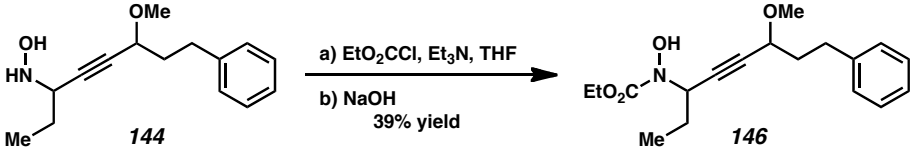
***N*-Hydroxylamine 144**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.50 (br s, 1H), 3.96 (td, *J* = 6.5, 1.5 Hz, 1H), 3.77-3.73 (m, 1H), 3.41 (s, 3H), 2.78 (td, *J* = 7.8, 2.6 Hz, 2H), 2.11-1.95 (comp m, 2H), 1.84-1.73 (m, 1H), 1.70-1.59 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.65, 128.53, 126.1, 98.8, 84.9, 83.49, 83.45, 70.51, 70.49, 56.55, 56.54, 56.34, 37.43, 37.40, 31.58, 31.57, 25.6, 10.4; IR (film) 3258, 2935, 1947, 1603, 1105, 749 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{21}NO_2 + Na]^+$: 248.1645, found 248.1646.



To a solution of *N*-hydroxylamine **144** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL, 0.600 mmol) in THF (0.800 mL, 0.5 M) cooled at -10 °C, was added methyl chloroformate (33.9 μL, 0.440 mmol), and the reaction was warmed to 23 °C and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 20 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **145** (51.7 mg, 42% yield, R_F = 0.29 in 2:1 hexanes/EtOAc) as a colorless oil.

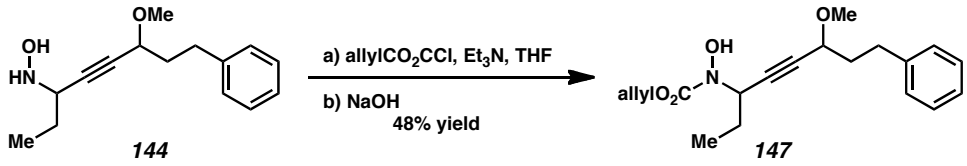
***N*-Hydroxycarbamate 145**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.93 (br s, 1H), 4.75 (t, *J* = 7.7 Hz, 1H), 3.94 (td, *J* = 6.6, 1.6 Hz, 1H), 3.80 (s, 3H), 3.38 (d, *J* = 2.3 Hz, 3H), 2.78-2.74 (comp m, 2H), 2.09-1.95 (comp m, 2H), 1.92-1.84 (comp m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 158.11, 158.09, 141.5, 128.65, 128.55, 126.1, 83.19, 83.17, 82.93, 82.90,

70.45, 70.43, 56.5, 53.8, 37.31, 37.28, 31.56, 31.54, 26.32, 26.28, 10.8; IR (film) 3300, 2936, 1951, 1745, 1603, 1455, 752 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{17}H_{23}NO_4 + Na]^+$: 328.1519, found 328.1514.



To a solution of *N*-hydroxylamine **144** (0.135 g, 0.540 mmol) and Et_3N (113 μL, 0.810 mmol) in THF (1.00 mL, 0.54 M) cooled at 0 °C, was added ethyl chloroformate (57.0 μL, 0.601 mmol), and the reaction was warmed to 23 °C and stirred for 1 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **146** (67.4 mg, 37% yield, R_F = 0.15 in 4:1 hexanes/EtOAc) as a colorless oil.

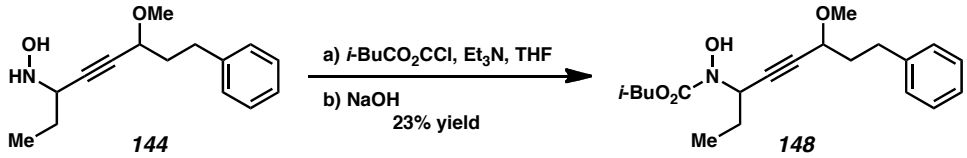
***N*-Hydroxycarbamate 146**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.99 (br s, 1H), 4.75 (td, *J* = 7.7, 1.0 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.94 (td, *J* = 6.6, 1.6 Hz, 1H), 3.39 (d, *J* = 2.5 Hz, 3H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.09-1.94 (comp m, 2H), 1.92-1.84 (comp m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.71, 189.69, 157.88, 157.85, 141.5, 128.65, 128.54, 126.1, 83.05, 83.02, 70.45, 70.43, 63.0, 56.5, 53.8, 37.33, 37.29, 31.56, 31.54, 26.33, 26.29, 14.7, 10.8; IR (film) 3304, 2936, 1949, 1699, 1455, 752 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{18}H_{25}NO_4 + Na]^+$: 342.1676, found 342.1674.



To a solution of *N*-hydroxylamine **144** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL, 0.600 mmol) in THF (0.800 mL, 0.50 M) cooled at -10 °C, was added allyl chloroformate (47.0 μL, 0.440 mmol), and the reaction was warmed to 23 °C and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **147** (63.2 mg, 48% yield, R_F = 0.22 in 4:1 hexanes/EtOAc) as a colorless oil.

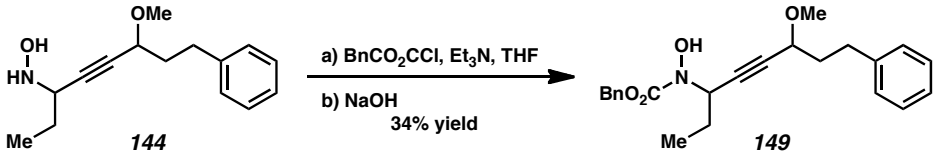
***N*-hydroxycarbamate 147**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.94 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.79-4.75 (m, 1H), 4.68 (dq, *J* = 5.7, 1.4 Hz, 2H), 3.94 (td, *J* = 6.5, 1.5 Hz, 1H), 3.38 (d, *J* = 2.4 Hz, 3H), 2.76 (t, *J* = 7.7

Hz, 2H), 2.09-1.94 (comp m, 2H), 1.93-1.84 (comp m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 141.5, 132.1, 128.66, 128.56, 126.1, 118.7, 83.3, 82.88, 82.86, 70.45, 70.43, 67.4, 56.6, 53.85, 53.83, 37.32, 37.29, 31.56, 31.54, 26.34, 26.31, 10.8; IR (film) 3306, 2936, 1950, 1706, 1100, 752 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{19}H_{25}NO_4 + Na]^+$: 354.1676, found 354.1678.



To a solution of *N*-hydroxylamine **144** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL, 0.600 mmol) in THF (0.800 mL, 0.50 M) cooled at -10 °C, was added isobutyl chloroformate (57.0 μL, 0.440 mmol), and the reaction was warmed to 23 °C and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL) and H_2O (5.0 mL) and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **148** (32.2 mg, 23% yield, R_F = 0.27 in 4:1 hexanes/EtOAc) as a colorless oil.

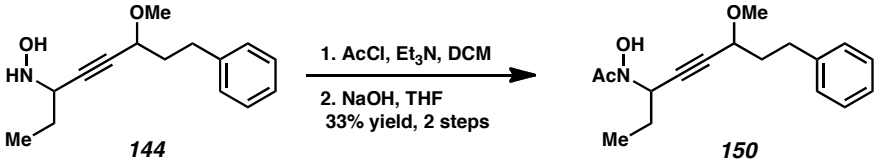
***N*-hydroxycarbamate 148**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.20-7.16 (m, 3H), 5.77 (br s, 1H), 4.73 (t, J = 7.6 Hz, 1H), 4.02-3.92 (comp m, 3H), 3.38 (d, J = 2.6 Hz, 3H), 2.76 (t, J = 7.8 Hz, 2H), 2.07-1.93 (comp m, 3H), 1.93-1.83 (comp m, 2H), 1.02 (t, J = 7.4 Hz, 3H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 158.1, 141.5, 128.65, 128.55, 126.1, 83.00, 82.98, 73.0, 70.44, 70.43, 56.5, 53.9, 37.35, 37.30, 31.56, 31.54, 28.1, 26.36, 26.34, 19.10, 19.08, 10.9; IR (film) 3300, 2964, 1947, 1703, 1456, 1104, 751 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{29}NO_4 + Na]^+$: 370.1989, found 370.1996.



To a solution of *N*-hydroxylamine **144** (46.4 mg, 0.188 mmol) and Et_3N (66.9 μL, 0.470 mmol) in THF (0.400 mL, 0.47 M) cooled at -10 °C, was added benzyl chloroformate (40.2 μL, 0.282 mmol), and the reaction was warmed to 23 °C and stirred for 3 h. NaOH (0.50 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **149** (24.2 mg, 34% yield, R_F = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

***N*-hydroxycarbamate 149**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (comp m, 7H), 7.21-7.17 (comp m, 3H), 6.16 (br s, 1H), 5.21 (s, 2H), 4.80-

4.76 (m, 1H), 4.70 (s, 1H), 3.92 (td, J = 6.5, 1.4 Hz, 1H), 3.35 (d, J = 2.6 Hz, 2H), 2.77-2.73 (comp m, 2H), 2.06-1.94 (comp m, 2H), 1.92-1.82 (comp m, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 141.4, 135.8, 128.71, 128.65, 128.54, 128.49, 128.3, 127.8, 127.1, 126.1, 83.10, 83.07, 83.00, 82.97, 70.43, 70.41, 68.5, 65.5, 56.5, 53.8, 37.27, 37.24, 31.5, 26.29, 26.27, 10.8; IR (film) 3288, 2936, 1952, 1704, 1455, 1103, 750 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + NH_4)^+$ $[C_{23}H_{27}NO_4 + NH_4]^+$: 399.2278, found 399.2280.



To a solution of *N*-hydroxylamine **144** (90.7 mg, 0.367 mmol) and Et_3N (0.141 mL, 1.10 mmol) cooled at 0 °C was added AcCl (65.5 μL, 0.918 mmol), and the reaction was warmed to 23 °C and stirred for 2 h. The reaction was diluted with CH_2Cl_2 (2.0 mL), and H_2O (2.0 mL), and the layers were separated. The aqueous was extracted with CH_2Cl_2 (2.0 mL), and the combined organics were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was dissolved in THF (1.50 mL, 0.25 M). To this was added NaOH (0.75 mL, 1.0 M aq.) and the reaction was stirred at 23 °C for 5 h. The reaction was quenched with HCl (0.50 mL, 1.0 N aq.), and diluted with Et_2O (2.0 mL). The layers were separated and the aqueous layer was extracted with additional Et_2O (2.0 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) affording *N*-hydroxyamide **150** (34.8 mg, 33% yield 2 steps, R_F = 0.30 in 1:1 hexanes/EtOAc) as a colorless oil.

***N*-hydroxyamide 150**: Characterized as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 5.30 (s, 1H), 4.54 (br s, 1H), 3.96-3.92 (m, 1H), 3.39 (d, J = 1.6 Hz, 3H), 2.78-2.74 (comp m, 2H), 2.18 (s, 3H), 2.10-1.93 (comp m, 2H), 1.85 (br s, 2H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.64, 128.57, 126.1, 70.4, 56.60, 56.58, 37.2, 31.5, 10.8; IR (film) 3164, 2934, 1619, 1496, 1174, 1104, 749 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{23}NO_3 + H]^+$: 290.1751, found 290.1747.