Complex Induced Proximity Effects. Temperature Dependent Regiochemical Diversity in Lithiation-Electrophilic Substitution Reactions of *N*-BOC-2-Azabicyclo[2.1.1]hexane. 2,4- and 3,5-Methanoprolines

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Supplemental

Experimental Section

General Section. Reagent chemicals were obtained from commercial suppliers. TMEDA and methyl chloroformate were used from Aldrich Sure-Seal bottles. Ether and DMF were dried using commercially available Glass Contour alumina columns; carbon dioxide was dried by gently heating dry ice and allowing the gas to bubble through anhydrous calcium chloride and then concentrated sulfuric acid.[17] ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$, unless otherwise noted. Low temperature NMR spectra of **4** were recorded in CD_3OD. Chemical shifts are expressed in parts per million related to internal TMS. High resolution mass spectra were performed at the University of Pennsylvania, Drexel University or Merck Research Laboratories, West Point, PA.

Flash column chromatography was performed using Fisher Davisil Grade 633 silica gel Type 60A (200-425 mesh) or Biotage ® Flash 40 KP-Sil cartridges. TLC was performed on silica gel GF 500 or 1000μm (Analtech, Inc.). TLC plates were developed using para-anisaldehyde/EtOH/H_2SO_4.

Preparation of *N*-(*t*-Butoxycarbonyl)-2-azabicyclo[2.1.1]hexane (4). *N*-(Benzyloxycarbonyl)-2-azabicyclo[2.1.1]hexane (100 mg, 0.455 mmol), prepared following the procedure for the *N*-(methoxycarbonyl) analog,[12] was dissolved in MeOH (6.0 mL) in a 25 mL round bottom flask. The vessel was purged with hydrogen and BOC_2O (130 mg, 0.59 mmol, 1.3eq.) was added as well as Pd/C (11 mg, 10 mol%).[16] The solution was stirred under 1 atm of hydrogen for 2 h at room temperature. Afterward, the solution was diluted with 10 mL of MeOH and filtered through Celite. Evaporation of the solvent followed by preparative TLC (2:1 hexanes: diethyl ether) yielded **4** (34 mg, 40%), R_f = 0.52 (1:1 hexanes/ether); ^{1}H NMR: δ1.30 (2H, d, J = 4.8 Hz), 1.42, 1.41 (9H, s), 1.83 (2H, br), 2.75 (1H, br), 3.23 (2H, s), 4.27 (1H, dd, J = 7.8, 1.8 Hz); ^{13}C NMR: δ 28.4, 38.3, 40.4, 49.0, 60.5, 78.8, 155.9; HRMS *m/z* 184.1342, calcd for $C_{10}H_{18}NO_2$ (M + H) 184.1332.

General Procedure for the β-Lithiation of *N*-(*t*-Butoxycarbonyl)-2-azabicyclo[2.1.1]hexane (4). The lithiation procedure follows that developed by Beak.[13a] Lithiations were carried out in small vials (4 mL) under an inert argon atmosphere. Glassware was dried overnight in an oven, syringes were placed under high vacuum for at least 24 h and were not removed until immediately before use. Septa were stored in a dessicator. All joints were sealed with parafilm and/or Teflon tape. Concentrations of *s*-BuLi were determined by titration with diphenylacetic acid. The reaction vessel was prepared as described above. To this carbamate **4** was added, the vessel was sealed with a septum and placed under high vaccum (via a syringe needle) for 30 m at rt. The vessel was then purged with argon and an appropriate amount of freshly distilled diethyl ether was added via a canula. The vessel was sealed with parafilm and fitted with a positive

pressure of argon. The vessel then was cooled to the desired temperature. TMEDA was added slowly, equilibration was allowed to occur over 15 min., the appropriate amount of *s*-BuLi was added dropwise via syringe, and stirring was continued for 2-2.5 h. The electrophile was then added, stirring was continued for an additional 30 min, followed by the appropriate workup to afford products.

Procedure for titrating s-BuLi-TMEDA system with diphenylacetic acid (DPA). A known amount of oven dried DPA was placed in a stringently dried vial that has been purged vigorously with argon (via a vacuum-purge process) while being heated with a hand dryer and equipped with a stir bar. After sealing the vial with a septum, 1 molar equivalent (based on the amount of 4 to be used in the forthcoming experiment) of distilled TMEDA was injected followed by 1-2 mL of freshly dried diethyl ether. Dropwise addition of *s*-BuLi via a syringe was carried out with vigorous stirring until a pale yellow color persisted. The volume of *s*-BuLi added was determined and from this (using the known amount of DPA) the concentration of *s*-BuLi was determined. This procedure corrects for any water that may be present in the TMEDA as well as any LiOH that may be present in the base solution.

***N*-(*t*-Butoxycarbonyl)-1-carboxy-2-azabicyclo[2.1.1]hexane (8a). CO_2 Quench at 0 °C.** According to the general procedure *s*-BuLi (125 μL, 0.16 mmol, 1.25 M solution in cyclohexane, 1.2 eq) was added to **4** (23.8 mg, 0.13 mmol) and TMEDA (18 mg, 0.16 mmol, 24 μL, 1.2 eq) in ether (0.5 mL) cooled to 0 °C. After stirring for 2 h, excess CO_2 was bubbled through the reaction vial for 7 min, the reaction was stirred an additional 30 min at 0 °C, warmed to room temperature, and the solution was washed with 3 x 0.5 mL of distilled water. The layers were separated and the aqueous layer was acidified with

dilute HCl solution until the pH was approximately 3. The aqueous layer was then extracted with ethyl acetate (5 x 1 mL). The combined extracts were washed with brine (1 mL), dried over magnesium sulfate, filtered and concentrated in *vacuo* to yield 29.2 mg (98 %) of acid **8a**; ^{1}H NMR: δ 1.47 (9H, s), 1.77 (2H, m), 2.33 (2H, s, br), 2.76 (1H, br), 3.50 (2H, s), 9.89 (1H, br). ^{13}C NMR: δ 28.6, 30.1, 34.5, 44.3, 53.8, 82.7, 158.2, 154.3; HRMS 172.0634, calcd for $C_7H_{10}NO_4$ (M – C_4H_8) 172.0604.

***N*-(*t*-Butoxycarbonyl)-1-carbomethoxy-2-azabicyclo[2.1.1]hexane 8b via Acid 8a.** Following the reported procedure acid **8a** (21.4 mg, 0.094 mmol) was dissolved in 2.0 mL of 1:1 hexanes: isopropanol under argon and trimethylsilyldiazomethane[18] (47 µl, 0.094 mmol, 2.0 M solution in hexanes) was added. The yellow solution was stirred 30 min at rt and the clear solution was evaporated to afford 22.5 mg (100%) of ester **8b**; R_f = 0.36 (1:1 hexanes/ether); ^{1}H NMR: δ 1.35 (9H, s), 1.61 (2H, dd, J = 4.74, 1.97 Hz), 2.02 (2H, m), 2.66 (1H, m), 3.38 (2H, s), 3.7 (3H, s); ^{13}C NMR δ 28.7, 28.8, 35.1, 43.1, 52.3, 52.8, 70.4, 81.0, 157.8, 169.6; HRMS *m/z* 242.1395, calcd for $C_{12}H_{20}NO_4$ (M + H) 242.1387.

***N*-(*t*-Butoxycarbonyl)-3-carbomethoxy-2-azabicyclo[2.1.1]hexane (6b) and *N*-(*t*-Butoxycarbonyl)-1-carbomethoxy-2-azabicyclo[2.1.1]hexane (8b) from Carbamate 4. CO_2 Quench at -78 °C.** According to the general procedure *s*-BuLi in cyclohexane (176 µL, 0.234 mmol, 1.2 eq., 1.33 M) was added to carbamate **4** (35.7 mg, 0.195 mmol) and TMEDA (27.2 mg, 35.3 µL, 0.234 mmol, 1.2 eq) dissolved in 1.0 mL diethyl ether in a lithation vial and cooled to –78 °C. The solution was stirred 2 h at -78 °C. Excess CO_2 gas was blown through the reaction vial for approximately 5 min. The solution was stirred at -78 °C 30 min and warmed to rt. The ether was extracted with 3 x 0.5 mL of

distilled water, and the combined aqueous layers were then acidified with dilute HCl to pH = 3. The aqueous layer was then extracted with 5 x 1 mL of ethyl acetate, which was then concentrated. The crude oil was then taken up in 2 mL of hexanes and 2 mL of isopropyl alcohol. Trimethylsilyldiazomethane (97 μL, 0.195 mmol, 2.0 M solution in hexanes) was added and the reaction was stirred 12 h. The solvent was removed in *vacuo* to furnish 35.6 mg (76 %) of a mixture of 3-methyl ester **6b** and 1-methyl ester **8b**, which we were unable to separate. The isomer ratio was determined to be 43:57 of **6b**:**8b** by ^{1}H NMR integration of the resonances for H_1 of ester **6b** and H_3 of ester **8b**. The R_f value and ^{1}H NMR spectra agree with those of **8b** and of **6b** synthesized independently (See below).

Preparation of *N*-(*t*-Butoxycarbonyl)-1-carbomethoxy-2-azabicyclo[2.1.1]hexane (8b) from Carbamate 4. ClCOOMe Quench at 0 ^{0}C. According to the general procedure, carbamate **4** (23.9 mg, 0.195 mmol) and TMEDA (18.2 mg, 24 μL, 0.157 mmol, 1.2 eq) in diethyl ether (0.5 mL) in a lithation vial was cooled to 0 ^{o}C and *s*-BuLi (115 μL, 0.157 mmol, 1.2 eq, 1.36 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h at 0 ^{o}C and then methyl chloroformate (74 mg, 60.6 μL, 0.79 mmol, 5.0 eq) was injected quickly into the reaction vial. The solution was stirred at 0 ^{o}C 30 min and allowed to warmed to rt. The solution was washed with 3 x 0.5 mL saturated ammonium chloride, 0.5 mL brine, and then dried over magnesium sulfate. After filtration and concentration a mixture of 21 mg of ester **8b** (70 %) and 6.3 mg (26%) of starting material **4** was obtained.

Preparation of *N*-(*t*-Butoxycarbonyl)-3-carbomethoxy-2-azabicyclo[2.1.1]hexane (6b) and *N*-(*t*-Butoxycarbonyl)-1-carbomethoxy-2-azabicyclo[2.1.1]hexane (8b) from

Carbamate 4. **ClCOOMe Quench at -78 °C.** According to the general procedure, carbamate **4** (40.5 mg, 0.22 mmol) and TMEDA (30.9 mg, 40.2 μL, 0.266 mmol, 1.2 eq) in diethyl ether (0.5 mL) in a lithiation vial was cooled to –78 °C and *s*-BuLi (15 mg, 198 μL, 0.266 mmol, 1.2 eq, 1.345 M solution in cyclohexane) was added dropwise. The reaction was stirred at –78 °C for 2 h, methyl chloroformate (104 mg, 1.105 mmol, 5.0 eq., 85.4 μL) was then injected into the reaction vial, the solution was stirred at –78 °C for 30 m and warmed gradually to rt. The solution was washed with 3 x 0.5 mL saturated ammonium chloride, 0.5 mL water, and 0.5 mL brine. After drying over magnesium sulfate, the solution was filtered and evaporated to furnish 46.9 mg of a crude oil. TLC (1:1 hexanes:diethyl ether) furnished carbamate 4, R_f = 0.48, and a mixture of esters **6b** and **8b**, R_f = 0.36. ^{1}H NMR of the crude mixture revealed a ratio of 3.5:3.5:1 ratio of esters **6b**:**8b**:**4**. The methyl esters did not resolve using several solvent systems (1:1 hexanes:ether, methylene chloride, 2 % Acetone in methylene chloride, 5 % acetone in methylene chloride, 6:3:1 hexanes:ethyl acetate:methanol, 4:6 hexanes:ethyl acetate, 4:4:2 hexanes:ethylacetate:methanol, 5 % methanol in methylene chloride). Based on ^{1}H integration and the mass of the mixture, the yield of methyl esters 6b and 8b was 81 % (95 % after correcting for unreacted carbamate 4 in the mixture).

Preparation of *N*-(*t*-Butoxycarbonyl)-1-formyl-2-azabicyclo[2.1.1]hexane (8c). DMF Quench at 0 °C. According to the general procedure carbamate **4** (26.6 mg, 0.145 mmol) and TMEDA (20.2 mg, 26 μL, 0.174 mmol, 1.2 eq) in ether (0.5 mL) was cooled to 0 °C and *s*-BuLi (129 μL, 0.174 mmol, 1.2 eq, 1.35 M solution in cyclohexane) was added dropwise. The reaction was stirred 2.0 h at 0 °C and then transferred via a canula to a precooled solution of freshly columned DMF (68.7 mg, 56 μL, 0.73 mmol, 5.0 eq) in

ether (0.5 mL). The solution was stirred at 0 °C for 1 h, warmed slowly to room temperature, 0.5 mL of ammonium chloride and 0.5 mL of diethyl ether were added. The organic layer was washed with 2 x 0.5 mL of saturated ammonium chloride followed by 0.5 mL distilled water and 0.5 mL brine. The organic layer was dried over magnesium sulfate and then filtered and concentrated. Purification via flash chromatography (3:1 hexanes: ether) furnished 20.9 mg of a mixture of carbamate **4** and aldehyde **8c** in the ratio 49:51 (by ^{1}H NMR integration). Correcting for recovered carbamate **4**, the yield of **8c** is 57% (38 % uncorrected); R_f = 0.45 (1:1 hexanes/ether), ^{1}H NMR (500 MHz) δ 1.43 and 1.56 (9H, s), 1.63 (2H, d, J = 6.5 Hz), 2.09 (2H, br), 2.80 (1H, br), 3.47 (2H, s,), 9.79 (1H, br); ^{13}C NMR (100 MHz) δ 28.8, 35.4, 41.8, 52.8 (2C), 152.4, 194.6, (tBu_{quat} not observed); HRMS (CI) *m/z* 212.1285, calcd for $C_{11}H_{18}NO_3$ (M + H) 212.1286.

Preparation of *N*-(*t*-Butoxycarbonyl)-3-formyl-2-azabicyclo[2.1.1]hexane (6c) and *N*-(*t*-Butoxycarbonyl)-1-formyl-2-azabicyclo[2.1.1]hexane (8c). DMF Quench at -78 °C. According to the general procedure, carbamate **4** (27 mg, 0.15 mmol) and TMEDA (19 mg, 24.5 μL, 0.17 mmol, 1.1 eq) in ether (0.5 mL) was cooled to -78 °C and *s*-buLi (115 μL, 0.16 mmol, 1.2 eq, 1.4 M solution in cyclohexane) was added dropwise. The solution was stirred 2.0 h and then transferred via a canula to a precooled solution of DMF (54 mg, 58 μL, 0.74 mmol) in diethyl ether (0.5 mL). The solution was warmed slowly to room temperature and washed with 2 x 0.25 mL of saturated ammonium chloride. The ether layer was washed with 0.25 mL distilled water and 0.25 mL brine. After drying over magnesium sulfate, the solution was filtered and concentrated to give 26 mg of crude oil. ^{1}H NMR analysis of the crude mixture revealed a mixture of 3-CHO **6c**, 1-CHO **8c** and starting material **4** in the proportion 1:1:1.2. TLC (1:1 hexanes:diethyl

ether) furnished carbamate **4**, R_f= 0.53, aldehyde **8c**, R_f = 0.45, and aldehyde **6c**, R_f = 0.33. Purification via a small silica gel column (2:1 hexanes: diethyl ether) gave 4.8 mg of **4**, 3.7 mg (12%) of **8c**, and 6.3 mg (20 %) of **6c**. After correcting for recovered **4**, the isolated yields of **8c** and **6c** were 15% and 25%, respectively. Spectral data for aldehyde **6c** are ^{1}H NMR (400 MHz) δ 1.44 (9H, s, tBu), 1.65 (2H, m), 1.94 (1H, d, J = 8 Hz), 2.14 (1H, d, J = 6.5 Hz), 3.16 (1H, br), 4.1 (1H, br), 4.53 (1H, br), 9.79 (1H, br); ^{13}C NMR (100 MHz) δ 28.8, 37.8, 43.1, 60.7, 66.5, 80.8, 202.1, BOC carbonyl was not observed; HRMS (CI) *m/z* 212.1282, calcd for $C_{11}H_{18}NO_3$ (M + H) 212.1286.

The reaction was repeated using 1.6 eq of *s*-BuLi. According to the above procedure carbamate **4** (20.4 mg, 0.11 mmol) and TMEDA (20.7 mg, 27 μL, 0.178 mmol, 1.6 eq), *s*-BuLi (124 μL, 0.178 mmol, 1.6 eq, 1.44 M solution in cyclohexane), and DMF (52.6 mg, 43 μL, 0.56 mmol, 5.0 eq.) afforded 19.6 mg of a 5:1 mixture of aldehydes **6c/8c** and unreacted **4**. The ratio of **6c**:**8c** was determined to be 49:51, by ^{1}H NMR integration. Thus, the corrected yield of aldehydes is 83 % (71 % uncorrected).

Preparation of *N*-(*t*-Butoxycarbonyl)-3-hydroxymethyl-2-azabicyclo[2.1.1]hexane (6d) and *N*-(*t*-Butoxycarbonyl)-1-hydroxymethyl-2-azabicyclo[2.1.1]hexane (8d) from aldehydes 6c/8c. According to the general procedure, carbamate **4** (167 mg, 0.91 mmol) and TMEDA (126 mg, 164 μL, 1.01 mmol, 1.2 eq) in ether (3 mL) was cooled to -78 °C and *s*-BuLi (885 μL, 1.01 mmol, 1.2 eq, 1.13 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h and then transferred via a canula to a precooled solution of DMF (333 mg, 353 μL, 4.55 mmol, 5 eq) in diethyl ether (3 mL). The solution was warmed slowly to room temperature and quenched with 1 mL saturated

aqueous ammonium chloride. The ether layer was then washed with 2 x 2 mL distilled water and dried over magnesium sulfate. After filtration and concentration, the oil was sampled by NMR analysis to show a 1:1 mixture of aldehydes **6c/8c**. The oil was then taken up in 1.0 mL of dry MeOH and cooled to 0 °C. $NaBH_4$ (173 mg, 4.55 mmol, 5.0 eq.) was added slowly; the reaction was stirred 15 min, then warmed to rt and 1.0 mL of saturated ammonium chloride was added slowly, followed by 3.0 mL of CH_2Cl_2. The aqueous layer was extracted with 3 x 3 mL of CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to furnish 169 mg (87 %) of a mixture of 1-CH_2OH **8d**, R_f = 0.36, and 3-CH_2OH **6d**, R_f = 0.21. Silica gel chromatography using a small Biotage ® column (1:1 hexanes:diethyl ether) furnished 45.5 mg (24 %) of alcohol **6d**; ^{1}H NMR (400 MHz) δ 1.36 and 1.41 (9H, s), 1.5 (2H, d, J = 1.5 Hz), 1.69 (2H, br), 2.68 (1H, br), 3.0 (2H, s), 3.3 (2H, s), 4.82 (1H, br); ^{13}C NMR (100 MHz) δ 28.9, 34.6 , 42.1, 52.8, 62.1, 74.5, 80.3, 125.9, 156.0; HRMS (CI) *m/z* 214.1451, calcd for $C_{11}H_{20}NO_3$ (M + H) 214.1443. Also obtained was 50.5 mg (27%) of alcohol **8d**; ^{1}H NMR (300 MHz) δ 1.48 and 1.53 (10H, m), 1.61 (t, 1H, J = 7.8 Hz), 1.86 (1H, d, J = 9 Hz), 1.99 (1H, d, J = 9 Hz), 2.71 (1H, br), 3.82 (m, 3H), 4.33 (1H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz: δ 28.1, 29.3, 37.1, 40.1, 42.2, 61.1, 62.1, 65.5, 80.1, 125.1, 157.4; HRMS (CI) *m/z* 214.1444, calcd for $C_{11}H_{20}NO_3$ (M + H) 214.1443.

Preparation of *N*-(*t*-Butoxycarbonyl)-3-carbomethoxy-2-azabicyclo[2.1.1]hexane 6b via alcohol 6d. The 3-CH_2OH **6d** (45.0 mg, 0.213 mmol) was dissolved in a solution of CH_2Cl_2 (1.0 mL) TEMPO (2 mg), saturated $NaHCO_3$ (0.8 mL), KBr (4mg), and Bu_4NCl (5 mg). The solution was cooled to 0 ^{o}C and a solution of NaOCl (1.0 mmol), saturated $NaHCO_3$ (0.4 mL) and brine (0.8 mL) was added dropwise over 30 m. The

solution was stirred an additional 15 min and warmed to rt. The layers were separated; the organic layer was washed with 3 x 5 mL of 50 % $NaHCO_3$. The combined aqueous layers were washed with 2 x 2 mL CH_2Cl_2 and then acidified with dilute HCl. Extraction with 5 x 15 mL ethyl acetate was followed by the drying over Na_2SO_4. The solvent was removed, the residue was taken up in isopropyl alcohol (1 mL) and hexanes (1 mL), and $TMSCHN_2$ (448 μL, 2.0 M solution in hexanes) was added slowly. The solution was stirred at rt for 2 h, the solvent was removed, and column chromatography (CH_2Cl_2, then ethyl acetate) furnished 33.4 mg (66 %) of the desired methyl ester **6b**, R_f = 0.38 (1:1 hexanes:diethyl ether); ^{1}H NMR (300 MHz) δ 1.49 (10H, br), 1.85 (2H, d, J = 6 Hz), 2.03 (1H, d, J = 6.5 Hz), 2.96 (1H, br), 3.76 (3H, s), 4.21 (1H, br), 4.38 (1H, br); ^{13}C NMR (100 MHZ) δ 28.8, 37.5, 43.2, 43.7, 52.5, 60.6, 80.3, 172.2, (BOC carbonyl not observed); HRMS *m/z* 242.1383, calcd for $C_{12}H_{20}NO_4$ (M + H) 242.1392.

Preparation of *N*-(*t*-Butoxycarbonyl)-3-carbomethoxy-2-azabicyclo[2.1.1]hexane (6b) and *N*-(*t*-Butoxycarbonyl)-1-carbomethoxy-2-azabicyclo[2.1.1]hexane (8b) from via aldehydes 6c/8c. According to the general procedure, carbamate **4** (36 mg, 0.74 mmol) and TMEDA (104 mg, 135 μL, 0.89 mmol, 1.2 eq) in ether (3 mL) was cooled to -78 °C and *s*-BuLi (881 μL, 0.89 mmol, 1.2 eq, 1.1 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h at –78 °C and the reaction was then transferred via a canula into a precooled solution of DMF (272 mg, 288 μL, 3.72 mmol, 5.0 eq.) in diethyl ether (1.0 mL). The solution was stirred at -78 °C 30 min and warmed to rt and 1.5 mL of saturated ammonium chloride was added followed by 2 x 1 mL of distilled water. After washing once with 1 mL brine, the organic layer was dried over magnesium sulfate, solvent was removed to afford 47:53 ratio of 3-formyl **6c** and 1-formyl **8c**

products. The crude oil was taken up in CH_2Cl_2 (2 mL) and TEMPO (7 mg), saturated $NaHCO_3$ (2.8 mL), KBr (14 mg) and Bu_4NCl (20 mg) were added. The solution was cooled to 0 °C under argon. A 5% aq. solution of NaOCl (6.0 g), saturated $NaHCO_3$ (1.4 mL) and brine (2.8 mL) was added dropwise over 1 h. The reaction was stirred an additional h at 0 °C and warmed to rt. The layers were separated and the organic layer was washed with water (4 x 3 mL). The combined aqueous layers were acidified with dilute HCl and extracted with ethyl acetate (5 x 15 mL). After drying over magnesium sulfate, the organic layers were concentrated, the residue was taken up in 1 mL hexane and 1 mL isopropanol, and $TMSCHN_2$ (1.6 mL, 2.0 M solution in hexanes) was added slowly. The reaction was stirred for 2.0 h at rt, the solvent was removed in vacuo, and the residue was purified by column chromatography (1:1 hexanes:diethyl ether) to furnish 56 mg (31 %) of the isomeric methyl esters **6d/8d**.

Deuterium quenching of the anion derived from 4 at 0 °C to give 8e. According to the general procedure, carbamate **4** (26 mg, 0.14 mmol) and TMEDA (20 mg, 26 µL, 0.17 mmol, 1.2 eq) in ether (1 mL) in a lithation vial cooled to 0 °C were equilibrated 15 min and then *s*-BuLi (125 µL, 0.17 mmol, 1.2 eq., 1.36 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h at 0 °C, 500 µL of $DOCD_3$ was injected quickly into the reaction vial, the solution was stirred at 0 °C for 30 m, and then warmed to rt. The solution was washed with 3 x 0.5 mL saturated ammonium chloride, 0.5 mL brine, and then dried over magnesium sulfate. After filtration and concentration, 16.5 mg (63 %) of clear oil D_4-**8e** was obtained. ^{1}H NMR revealed 74 % substitution of H_1 for D; no substitution of H_3 was observed.

Deuterium quenching of the anion derived from 4 at -78 °C to give 6e/8e. According to the general procedure, carbamate **4** (49.3 mg, 0.27 mmol) and TMEDA (38 mg, 49 µL, 0.32 mmol, 1.2 eq) in ether (1 mL) in a lithation vial cooled to -78 °C were equilibrated 15 min and then *s*-BuLi (125 µL, 0.17 mmol, 1.2 eq., 1.36 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h at -78 °C, 500 µL of $DOCD_3$ was injected quickly into the reaction vial, the solution was stirred at -78 °C for 30 m, and then warmed to rt. Ether (5 mL) was added, the solution was washed with 4 x 5 mL dilute formic acid, and the aqueous layers were then washed with diethyl ether (2 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to furnish 42.7 mg (87 %) of D-4 as an oil. ^{1}H NMR revealed 47 % substitution of H_1 with D to give **8e** and 43 % substitution of an H_3 with D to give **6e**.

Deuterium quenching of the anion formed from 4 at -78 °C and raised to 0 °C to give 6e/8e. According to the general procedure, carbamate **4** (61.5 mg, 0.336 mmol) and TMEDA (47 mg, 61 µL, 0.40 mmol, 1.2 eq) in ether (1 mL) in a lithation vial cooled to -78 °C were equilibrated 15 min and then *s*-BuLi (360 µL, 0.40 mmol, 1.2 eq., 1.11 M solution in cyclohexane) was added dropwise. The solution was stirred 2 h at -78 •C and then placed in an ice water bath. The solution was stirred another 40 m and then $DOCD_3$ (250 •L) was injected quickly into the reaction vial. The solution was stirred at 0 •C for 30 min and warmed to r/t. Ether (5 mL) was added. The solution was washed with saturated ammonium chloride (4 x 0.5 mL) and then dried over magnesium sulfate. After filtration and concentration, 60.9 mg (98 %) of a clear oil was obtained. ^{1}H NMR integration revealed 54 % substitution of H_1 by D to give **8e** and 43 % substitution of an H_3 with D to give **6e**.

Low temperature ^{1}H-NMR spectra of *N*-(*t*-Butoxycarbonyl)-2-azabicyclo[2.1.1]hexane (4). A stacking of the resonances for the H_1 proton is shown below for a number of key temperatures. Peaks are not to scale. 296K dt (25 ^{o}C), 273K dt (0 ^{o}C), 242K broadened peak (-31^{o}C), 197K (two dt) broadened (-73 ^{o}C).

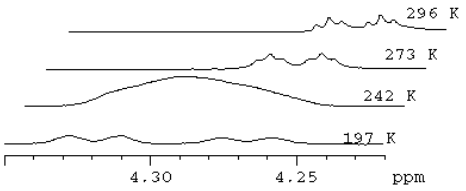

Figure 1. ^{1}H NMR peaks for H_1 of carbamate **4** at key temperatures.