Easy access to constrained peptidomimetics and 2,2-disubstituted azetidines by unexpected reactivity profile of α-lithiated N-Boc-azetidines

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Content

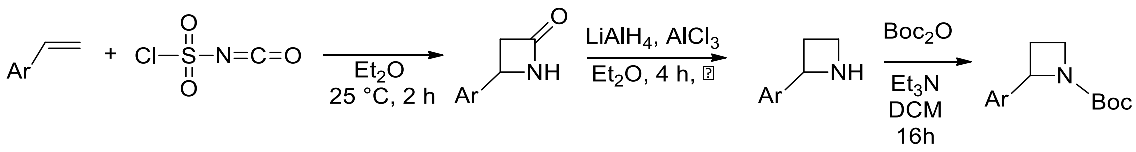
General

THF and Et_2O was freshly distilled under a nitrogen atmosphere over Na/benzophenone. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2, hexyllithium was purchased as hexane solution and was filtered on celite before using and title established by titration method.[1] All the other chemicals were commercially available and used without further purification. Magnetic Resonance spectra were recorded using Varian 400 and 500 MHz, and Bruker 600 MHz spectrometers. For the ^{1}H, ^{13}C NMR spectra (^{1}H NMR 400, 500, 600 MHz, ^{13}C NMR 100, 125, 150 MHz), $CDCl_3$, methanol-d_4 and toluene-d_8 were used as the solvents.
MS-ESI analyses were performed on LC/MSD trap system VL. Melting points were uncorrected. GC-MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 200 °C for some time until blue spots appear. Infra-red spectra of the compounds were recorded neat, as film, as KBr disc as indicated, by a Perkin-Elmer 283 spectrometer. For flash chromathography silica Gel 60, 0.04-0.063 mm particle size was used. CHN analyses were performed on a EuroEA 3000 analyzer. The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. The sample solutions (CH_3OH or CH_3OH + 0.1%v/v HCOOH) were introduced by continuous infusion at a flow rate of 180 mL min^{-1} with the aid of a syringe pump. The instrument was operated with end-plate offset and capillary voltages set to −500 V and −4500 V respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min^{-1}. The capillary exit and skimmer 1 voltages were 90 V and 30 V, respectively. The drying gas temperature was set at 180 °C. The calibration was carried out with sodium formate: a solution made up of 10 μl of 98% formic acid, 10 μl of sodium hydroxide (1.0 M), 490 μl of *i*-propanol and 490 μl of deionized water. The software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique. Optical rotation $[\alpha]_D^{20}$ values were measured by using a polarimeter with 1 dm cell path length; the concentration (c) is expressed in g/100mL. Enantiomeric ratios were determined by chiral HPLC, by chiral Gas Chromatography (GC), following the condition reported.

[1] Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.

Synthesis of N-Boc-2-arylazetidines

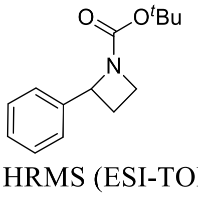
N-Boc-2-arylazetidines were prepared as shown in Scheme 1, following a reported procedure.[2] As example, the synthesis of azetidine **1a** is reported.



Scheme 1

N-Chlorosulfonyl isocyanate (36 mmol, 1.2 equiv.) was added dropwise to styrene (30 mmol, 1 equiv.) in dry diethyl ether (15 mL), at room temperature under an inhert atmosphere over 10 minutes. The mixture was stirred at room temperature for 2 h under a dry nitrogen atmosphere, and the solvent was removed under reduced pressure. The residue obtained was taken up in diethyl ether (20 mL) and added dropwise over 10 minutes to a vigorously stirred solution of water (20 mL), sodium carbonate (99 mmol, 3.3 equiv), sodium sulphite (45 mmol, 1.5 equiv), and ice (20 g). The solution was stirred for 1 h and filtered under vacuum. The organic layer was separated, and the acqueous layer was extracted with diethyl ether (5 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent evaporated under *vacuum* to yield the pure product (90 %). To 0.5 g (3.4 mmol) of 4-phenyl-2-azetidinone in 5 mL anhydrous Et_2O under nitrogen at 0 °C lithium aluminum hydride was added portion-wise (259 mg, 6.8 mmol), and the mixture was refluxed for 4 hours. The reaction mixture was cooled to room temperature, 20% aqueous sodium hydroxide (10 mL) was added and the mixture was filtered. The filtrate was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent the product was used in the next step without further purification. Di-*tert*-butyl dicarbonate (763 mg, 3.5 mmol) was added to a mixture of the azetidine (452 mg, 3.4 mmol) and Et_3N (1.34 mL, 10.2 mmol) in CH_2Cl_2 (40 ml) and the mixture was stirred for 16 h. The water was added to the mixture and after extraction with Et_2O, anhydrification over Na_2SO_4, evaporation of the solvent and purification by column chromatography on silica gel (hexane/EtOAc 9:1) 657 mg (83% yield) of *N*-*tert*-butoxycarbonyl-2-phenylazetidine **1a** were isolated as colorless oil.

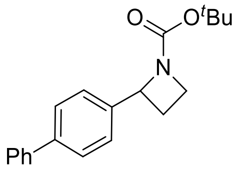
[2] a) Hemming, K.; Khan, M. N.; Kondakal, V. V. R.; Pitard, A.; Qamar, M. I.; Rice C. R. *Org. Lett.* **2012**, *14*, 126-129; b) Bergmann, H.-J.; Mayrhofer, R.; Otto, H.-H. *Arch. Parm.* **1986**, *319*, 203-216; c) Van Driessche, B.; Van Brabandt, W.; D' hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron*, **2006**, *62*, 6882-6892.



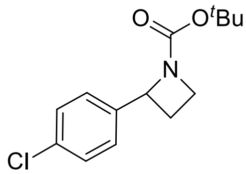
1-*tert*-Butoxycarbonyl-2-phenylazetidine 1a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22-1.44 (m, 9H), 2.13 (m, 1H), 2.62 (m, 1H), 3.99 (t like, J = 7.6 Hz, 2H), 5.18 (m, 1H), 7.24-7.27 (m, 1H), 7.33-7.35 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.6, 28.2, 46.4, 65.6, 79.4, 125.8, 127.2, 128.3, 142.5, 156.5. FT-IR (film, cm^{-1}) 2974, 1701, 1389, 1364, 1132, 698. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{14}H_{19}NO_2Na$ 256.1308; found 256.1318.

Enantioenriched azetidine (*R*)-**1a** was prepared using a commercially available β-amino acid following a reported procedure[3]

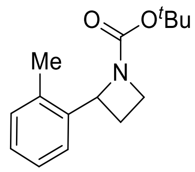
(2*R*)-1-*tert*-Butoxycarbonyl-2-phenylazetidine (*R*)-1a: $[\alpha]_D^{20}$ = + 127 (c = 1 $CHCl_3$). The enantiomeric ratio (*er* = 99.4:0.6) was determined by HPLC on a chiral stationary phase-(AD-H 0.46 x 25 cm, Daicel) using hexane:isopropanol (90:10), 1 mL/min 230 nm. For enantioenriched resulted t_1 = 4.612 min (Area% 0.659), t_2 = 4.909 min (Area% 99.341). See page S15



1-*tert*-Butoxycarbonyl-2-diphenylazetidine 1b: Sticky oil 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (br. s., 9H), 2.18 (m, 1H), 2.64 (m, 1H), 4.00 (t like, J = 7.6 Hz, 2H), 5.23 (m, 1H), 7.32-7.34 (m, 1 H), 7.37-7.48 (m, 4H), 7.54-7.64 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.4, 28.3, 46.7, 64.0, 79.5, 126.3_5, 126.6, 127.5, 127.2, 128.7,140.2, 140.9, 141.6, 156.6; FT-IR (film, cm^{-1}) 2976, 1487, 1390, 1255, 1133, 763, 730, 698. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{23}NO_2Na$ 332.1621; found 332.1621.



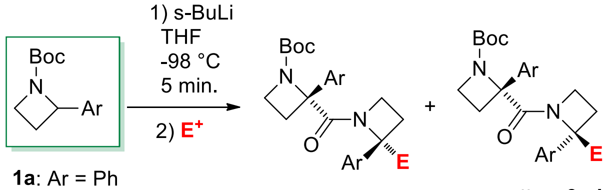
1-*tert*-Butoxycarbonyl-2-(4'chloro)phenylazetidine 1c: colorless oil, 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.44 (br. s., 9H), 2.13 (m, 1H), 2.62 (m, 1H), 3.99 (m, 2H), 5.15 (m, 1H), 7.28 (m, 2 H), 7.32 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.3, 28.3, 46.5, 63.7, 79.6, 127.3, 128.5, 132.9, 141.1, 156.4. FT-IR (film, cm^{-1}) 2976, 1701, 1389, 1364, 1135, 861, 828, 777. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{14}H_{18}ClNO_2Na$ 290.0918; found 290.0923.



1-*tert*-Butoxycarbonyl-2-diphenylazetidine 1d: colorless oil, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (br. s., 9H), 1.98 (m, 1H), 2.23 (s, 3H), 2.67 (m, 1H), 3.86-4.05 (m, 2H), 5.38 (m, 1H), 7.12 (d, J= 7.1 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.44 (d, J = 7.1 Hz, 1H). ^{13}C NMR: (150 MHz, $CDCl_3$) δ 18.8, 24.8, 28.3, 46.4, 61.9, 79.5, 124.6, 126.0, 129.9, 133.7, 140.3, 156.8. FT-IR (film, cm^{-1}): 2974, 1694, 1455, 1372, 1255, 1138, 752. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{15}H_{21}NO_2Na$ 270.1465; found 270.1468.

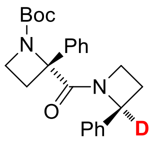
[3] M. F. Loewe, R. J. Cvetovich, G. G. Hazen, *Thetraedron Lett.*, **1991**, 32, 2299-2302

General procedure for the preparation of dimers 3a-h and *diast*-3a-h



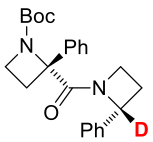
1a: Ar = Ph
1b: Ar = 4-PhC6H4
1c: Ar = 4-ClC6H4
3a-h Major
diast-**3a-h** Minor

To a stirred solution of azetidine (0.5 mmol) in dry THF (10 mL) cooled at -98 °C, a solution of *s*-BuLi (1.5 M in hexane, 1.5 mmol) was added dropwise. After stirring for 5 min. at -98 °C, the electrophile (0.65 mmol) neat if liquid and in 1.0 ml of solvent if solid was added to the resulting deep red solution and stirred for 30 min at this temperature. After the reaction was complete, as determined by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) poured in a separatory funnel and extracted with AcOEt (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. Chromatography on silica gel (Hexane/AcOEt 8/2 or CH_2Cl_2/MeOH) afforded the dimeric azetidines **3** and *diast*-**3**.



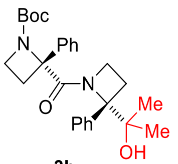
3a-D

3a-D: Colourless oil, (56%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major). δ 1.63-1.57 (bs, 10H, 3 × CH_3 *t*-Bu overlapping 1 × C*H*H), 1.96-1.85 (m, 1H), 2.18-2.09 (m, 1H), 2.61-2.70 (m, 1H), 3.25-3.14 (m, 1H), 3.75 (m, 1H), 4.35-4.22 (m, 2H, 2 × C*H*H), 7.22-7.11 (m, 2H), 7.33-7.22 (m, 4H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 25.3 (CH_2), 28.9 (*t*Bu), 31.7 (CH_2), 48.2 (CH_2N), 51.4 (CH_2N), 63.9 (t, *J* = 22 Hz, *C*-D), 74.1 (Ar*C*CO), 80.1 (*C*-OtBu), 126.6, 126.8, 127.5, 127.6, 128.9, 143.6, 143.8, 157.8, 173.5. FT IR (film, cm^{-1}) 2917, 1698, 1640, 1365, 1245, 1192, 798, 697. HRMS (ESI-TOF) *m*/*z* [M+Na]$^+$ calcd for $C_{24}H_{27}DN_2O_3Na$ 416.2055; found 416.2059.



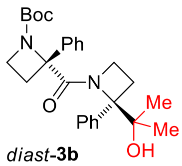
diast-**3a-D**

diast-**3a-D**: Colourless oil (24%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major). δ 1.65-1.50 (bs, 10H, 3 × CH_3 *t*-Bu overlapping 1 × C*H*H), 2.06-1.90 (m, 2H), 2.88-2.72 (bs, 1H), 3.38-3.21 (bs, 1H), 3.77-3.62 (m, 1H), 4.21-4.05 (m, 2H), 7.72-7.08 (m, 10H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 26.4 (CH_2CH_2N), 28.9 (*t*Bu), 29.7 (CH_2), 47.5 (CH_2N), 51.5 (CH_2N), 65.5 (bs, *C*-D), 74.7 (Ph*C*CO), 79.8 (*C*-OtBu), 126.9, 127.5, 127.8, 128.9, 143.3, 156.3, 167.9. FT IR (film, cm^{-1}) 2917, 1698, 1640, 1365, 1245, 1192, 798, 697. HRMS (ESI-TOF) *m*/*z* [M+Na]$^+$ calcd for $C_{24}H_{27}DN_2O_3Na$ 416.2055; found 416.2078.



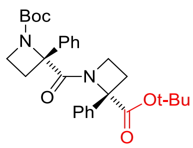
3b

3b: White solid, 180 °C dec., (53%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.13 (s, 3H), 1.58 (s, 9H, 3 × CH_3 *t*-Bu), 1.78 (s, $CH_3C(OH)$, 3H), 1.87 (m, 1H), 1.95 (like q, *J* = 8.5 Hz, 1H), 2.12 (like q, *J* = 8.5 Hz, 1H), 2.60 (like q, *J* = 8.5 Hz, 1H), 3.42 (td, *J* = 9.6, 4.3 Hz, 1H), 3.75 (td, *J* = 8.7, 4.6 Hz, 1H), 4.17 (td, *J* = 9.7, 4.4 Hz, 1H), 4.34 (like q, *J* = 7.6 Hz, 1H), 6.46 (s, O*H*, 1H), 6.98-7.08 (m, 3H), 7.19 (m, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 23.9 (CH_3), 26.7 (CH_3), 27.8 (CH_2), 28.0 (*t*Bu), 31.3 (CH_2), 47.1 (CH_2N), 49.1 (CH_2N), 72.5, 74.4 (Ar*C*CO), 79.5 (*C*-OtBu), 86.1, 125.5, 126.6, 126.9, 127.0, 127.8, 128.4, 142.1, 143.7, 155.8, 171.3. FT IR (film, cm^{-1}) 2917, 1705, 1621, 1245, 1196, 699. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{34}N_2O_4Na$ 473.2411; found 473.2414.



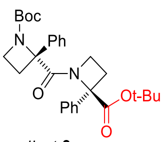
diast-**3b**

diast-**3b:** White solid, 205 °C dec. (22%). ^{1}H NMR (600 MHz, CD3OD, mixture of rotamers, selected data for the major) δ 1.10 (s, 3H), 1.37 (s, 9H, 3 × CH_3 *t*-Bu), 1.59 (s, $CH_3C(OH)$, 3H), 2.39 (m, 1H), 2.69-2.55 (m, 2H), 3.03 (like q, *J* = 8.5 Hz, 1H), 3.24 (like q, *J* = 8.5 Hz, 1H), 3.51 (m, 1H), 3.90 (m, 1H), 3.98 (like q, *J* = 7.6 Hz, 1H), 7.42-7.27 (m, 6H), 7.64-7.54 (m, 4H). ^{13}C NMR (150 MHz, CD3OD, mixture of rotamers, selected data for the major) δ 22.4 (CH_3), 25.2 (CH_3), 25.8 (CH_2), 27.2 (*t*Bu), 27.8 (CH_2), 43.7 (CH_2N), 47.4 (CH_2N), 73.3, 74.0 (Ar*C*HCO), 80.3 (*C*-OtBu), 84.8, 125.9, 127.0, 127.8, 127.9, 128.0, 136.7, 142.3, 156.7, 172.6. FT IR (film, cm^{-1}) 2917, 1705, 1621, 1245, 1196, 699. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{34}N_2O_4Na$ 473.2411; found 473.2423.



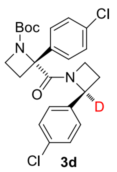
3c

3c: Colourless oil, (33%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.63-1.34 (bs, 19H, 6 × CH_3 *t*-Bu overlapping 1 × C*H*H), 1.96-1.80 (m, 1H), 2.15 (m, 1H), 2.75 (ddd, *J* = 11.2, 9.4, 4.5 Hz, 1H), 3.10-2.99 (m, 1H), 3.55 (m, 1H, C*H*H), 4.06-3.88 (m, 1H, C*H*H), 4.12 (like q, *J* = 7.8 Hz, 1H), 7.33-6.90 (m, 10H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 26.0 (CH_2), 28.1 (2 × *t*Bu), 29.9 (CH_2), 46.1 (CH_2N), 49.6 (CH_2N), 73.7 (Ar*C*CO), 77.6, 80.1 (*C*-OtBu), 82.0, 126.3, 126.7, 126.8, 127.0, 127.3, 127.9, 128.1, 128.6, 130.2, 131.1, 138.4, 140.1, 142.0, 147.8, 155.4, 156.1, 169.8. FT IR (film, cm^{-1}) 2917, 1693,1365, 1247, 1153, 699. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{29}H_{36}N_2O_5Na$ 515.2516; found 515.2522.

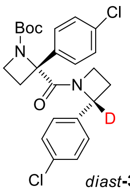


diast-**3c**

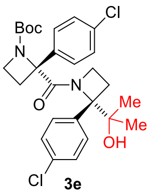
diast-**3c**: Colourless oil, (22%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.63-1.40 (bs, 18H, 6 × CH_3 *t*-Bu), 2.11-1.84 (m, 1H), 2.50-2.27 (m, 1H), 2.81-2.52 (m, 1H), 3.23-2.89 (m, 1H), 3.65-3.41 (m, 1H), 3.93-3.70 (m, 1H), 4.30-3.97 (m, 2H), 7.80-7.15 (m, 10H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 28.3 (*t*Bu), 28.9 (*t*Bu), 30.3 (CH_2), 31.2 (CH_2), 47.5 (CH_2N), 50.3 (CH_2N), 74.6 (Ar*C*CO), 75.2, 79.8.1 (*C*-OtBu), 81.6, 127.5, 127.9, 128.3, 128.6, 128.9, 141.4, 141.9, 156.4, 170.6. FT IR (film, cm^{-1}) 2917, 1693,1365, 1247, 1155, 700. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{29}H_{36}N_2O_5Na$ 515.2516; found 515.2525.



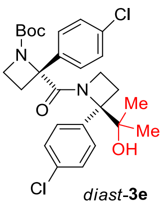
3d: Colourless oil, (52%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.61-1.42 (bs, 10H, 3 × CH_3 *t*-Bu overlapping 1 × C*H*H), 1.79 (m, 1H), 2.06 (m, 1H), 2.55 (m, 1H), 3.10 (m, 1H), 3.70 (dd, *J* = 13.0, 8.3 Hz, 1H), 4.14 (dd, *J* = 14.9, 8.5 Hz, 1H), 4.27 (dd, *J* = 15.6, 7.6 Hz, 1H), 7.14-7.06 (m, 2H), 7.26-7.17 (m, 6H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 25.0 (CH_2), 28.8 (*t*Bu), 31.5 (CH_2), 48.1 (CH_2N), 51.5 (CH_2N), 63.2 (t, *J* = 23 Hz, *C*-D), 73.6 (Ar*C*CO), 80.5 (*C*-OtBu), 128.3, 129.2, 133.6, 141.9, 157.7, 173.4. FT IR (film, cm^{-1}) 2973, 1698, 1644, 1366, 1257, 1154, 826, 730. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{24}H_{24}D_2Cl_2N_2O_3Na$ 485.1338; found 485.1352.



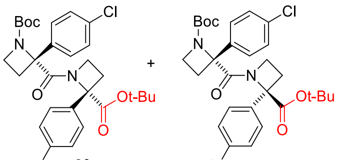
diast-**3d**: Colourless oil, (28%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.60-1.35 (bs, 10H, 3 × CH_3 *t*-Bu overlapping 1 × C*H*H), 1.93-1.78 (bs, 2H), 2.76-2.62 (bs, 1H), 3.25-3.11 (bs, 1H), 3.65 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.02-3.91 (bs, 1H), 4.17-4.04 (bs, 1H), 7.45-7.08 (m, 8H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 26.1 (CH_2CH_2N), 28.7 (*t*Bu), 30.2 (CH_2), 47.6 (CH_2N), 51.7 (CH_2N), 64.6 (bs, *C*-D), 74.0 (Ar*C*CO), 80.2 (*C*-OtBu), 125.8, 128.3, 128.6, 129.5, 133.3, 133.8, 141.6, 156.5, 167.6. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{24}H_{24}D_2Cl_2N_2O_3Na$ 485.1338; found 485.1354.



3e: Colourless oil, (56%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 1.04 (s, 3H), 1.56 (s, 9H, 3 × CH_3 *t*-Bu), 1.74-1.69 (singlet $CH_3C(OH)$ overlapping multiplet C*H*HCH$_2$, 4H), 1.82 (ddd, *J* = 9.11, 7.2, 2.4 Hz, 1H), 2.04 (*m*, 1H), 2.52 (like q, *J* = 8.5 Hz, 1H), 3.29 (td, *J* = 9.7, 4.4 Hz, 1H), 3.70 (ddd, *J* = 9.0, 7.6, 4.5 Hz, 1H), 4.07 (td, *J* = 9.7, 4.4 Hz, 1H), 4.28 (like q, *J* = 7.6 Hz, 1H), 6.25 (s, O*H*, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 24.5 (CH_3), 27.3 (CH_3), 28.4 (CH_2), 28.7 (*t*Bu), 31.9 (CH_2), 47.8 (CH_2N), 50.0 (CH_2N), 73.1, 74.5 (Ar*C*CO), 80.6 (*C*-OtBu), 86.4, 125.8, 127.7, 128.6, 129.6, 130.0, 133.6, 133.9, 141.1, 142.9, 156.4, 171.9. FT IR (film, cm^{-1}) 2973, 1687, 1614, 1378, 1245, 1154, 822, 771. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{32}Cl_2N_2O_4Na$ 541.1631; found 541.1645.

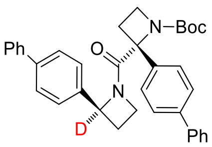


diast-**3e**: Colourless oil, (24%). ^{1}H NMR (600 MHz, CD3OD, mixture of rotamers, selected data for the major) δ 1.08 (s, 3H), 1.38 (s, 9H, 3 × CH_3 *t*-Bu), 1.56 (s, $CH_3C(OH)$, 3H), 2.39 (m, 1H), 2.70-2.55 (m, 2H), 3.06 (like q, *J* = 8.5 Hz, 1H), 3.21 (m, 1H), 3.53 (m, 1H), 3.87 (m, 1H), 3.96 (like q, *J* = 7.6 Hz, 1H), 7.39-7.27 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, CD3OD, mixture of rotamers, selected data for the major) δ 23.8 (CH_3), 26.5 (CH_3), 27.2 (CH_2), 28.7 (*t*Bu), 29.1 (CH_2), 45.1 (CH_2N), 47.4 (CH_2N, overlapping CD_3OD signal), 70.8, 74.7 (Ar*C*CO), 81.9 (*C*-OtBu), 85.8, 128.5, 129.6, 130.8, 134.4, 135.7, 136.8, 142.7, 157.9, 173.7. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{32}Cl_2N_2O_4Na$ 541.1631; found 541.1640.



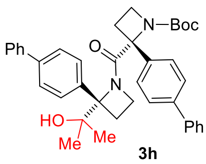
3f *diast*-3f

Complex mixture of rotamers (63%). See 1H, and HSQC-DEPT spectra (pag. S55) HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{29}H_{34}Cl_2N_2O_5Na$ 583.1737; found 583.1749.



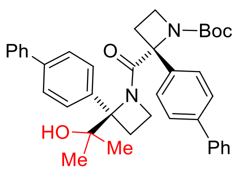
3g

3g-D: Colourless oil, (77%). ^{1}H NMR (600 MHz, toluene-d_8, mixture of rotamers, 2:1 ratio, selected data for the major) δ 1.71-1.57 (bs, 10H, 3 × CH_3 *t*-Bu overlapping 1 × C*H*H), 2.01 (like q, *J* = 15.9, 8.1 Hz, 1H), 2.24 (m, 1H), 2.87 (m, 1H), 3.31 (m, 1H), 3.83 (dd, *J* = 13.0, 8.4 Hz, 1H), 4.44-4.33 (m, 2H), 7.38-7.21 (m, 7H), 7.66-7.47 (m, 11H). ^{13}C NMR (150 MHz, toluene-d_8, mixture of rotamers, selected data for the major) δ 25.3 (*C*H_2), 28.9 (*t*Bu), 31.7 (*C*H_2), 48.2 (*C*H_2N), 51.7 (*C*H_2N), 63.8 (bs, *C*-D), 74.0 (Ar*C*CO), 80.2 (*C*-OtBu), 127.2, 127.3, 127.7, 127.8, 129.3, 129.4, 140.6, 140.7, 140.9, 141.3, 141.9, 142.5, 142.7, 157.8, 173.5. FT IR (film, cm^{-1}) 2972, 1698, 1644, 1366, 1258, 1154, 765, 697. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{35}DN_2O_3Na$ 568.2681; found 568.2675.



3h

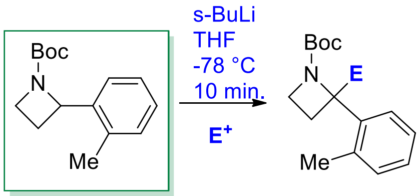
3h: Colourless oil, (59%). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers, selected data for the major) δ 1.09 (s, 3H), 1.54 (s, 9H, 3 × CH_3 *t*-Bu), 1.61 (s, 3H), 2.32-2.17 (m, 2H), 2.41 (like q, *J* = 8.4 Hz, 1H), 2.77 (like q, *J* = 8.4 Hz, 1H), 3.38 (td, *J* = 9.5, 4.4 Hz, 1H), 4.03-3.83 (m, 2H), 4.28 (like q, *J* = 7.6 Hz, 1H), 6.26 (s, O*H*, 1H), 7.68-7.28 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers, selected data for the major) δ 23.9 (*C*H_3), 26.3 (*C*H_3), 28.3 (*C*H_2), 28.4 (*t*Bu), 31.4 (*C*H_2), 47.2 (*C*H_2N), 49.5 (*C*H_2N), 72.8, 74.2 (Ar*C*CO), 80.2 (*C*-OtBu), 85.8, 126.1, 126.2, 126.9, 127.1, 127.3, 128.0, 128.7, 128.8, 139.9, 140.2, 140.4, 140.8, 142.6, 155.9, 171.6. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{42}N_2O_4Na$ 625.3037; found 625.3026.



diast-3h

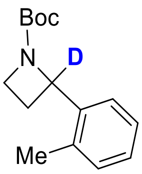
diast-**3h**: Colourless oil, (20%). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers, selected data for the major) δ 1.12 (s, 3H), 1.40 (s, 9H, 3 × CH_3 *t*-Bu), 1.61 (s, *C*H_3C(OH), 3H), 2.62-2.35 (m, 3H), 2.95 (m, 1H), 3.10 (m, 1H), 3.50 (m, 1H), 3.95 (m, 1H), 4.11 (m, 1H), 5.9 (bs, O*H*, 1H), 7.74-7.27 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers, selected data for the major) δ 23.5 (*C*H_3), 26.0 (*C*H_3), 26.5 (*C*H_2), 28.3 (*t*Bu), 28.5 (*C*H_2), 44.1 (*C*H_2N), 47.7 (*C*H_2N), 73.2, 73.8 (Ar*C*CO), 80.5 (*C*-OtBu), 85.1, 126.1, 127.0, 127.1, 128.1, 128.3, 128.8, 136.2, 140.1, 141.0, 141.6, 156.3, 172.1. FT IR (film, cm^{-1}) 2917, 1720, 1614, 1389, 1262, 1099, 727, 695. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{42}N_2O_4Na$ 625.3037; found 625.3036.

General procedure for the lithiation/trapping sequence on N-Boc azetidine 1d.



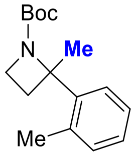
1d **4a-d**

To a stirred solution of *N*-Boc-azetidine **1d** (0.5 mmol) in THF (4 mL) at -78 °C, a solution of *s*-BuLi (1.7 M in hexane, 0.65 mmol) was added dropwise. After 10 minutes at this temperature, a solution of the electrophile (0.55 mmol) was added dropwise and stirred continued for 30 minutes at -78 °C. After the reaction was complete, as determined by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. Chromatography on silica gel afforded the α-substituted azetidines **4**.



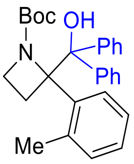
4a

***tert*-Butyl-2-(deuterio)-2-(o-tolyl)azetidine-1-carboxylate 4a**: Colourless oil (94%). ^{1}H NMR (500 MHz, CD_3OD): δ: 1.37 (br. s., 9 H), 1.92 (br. s., 1 H), 2.25 (s, 3 H), 2.73 (m, 1 H), 3.92-4.05 (m, 2H), 7.10-7.18 (m, 2 H), 7.19-7.25 (m, 1H), 7.39 (d, *J*= 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 18.8, 25.8, 28.6, 47.0, 63.0, 80.9, 127.0, 128.0, 129.8, 131.0, 141.4, 158.4. FT IR: cm^{-1} 747, 858, 851, 1005, 1158, 1256, 1366, 1455, 1479, 1698, 2891, 2974, 3370. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{20}DNO_2Na$ 271.1527; found 271.1537;



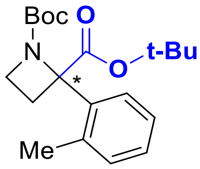
4b

***tert*-Butyl-2-(methyl)-2-(o-tolyl)azetidine-1-carboxylate 4b**: Colourless oil, (96%). Mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (br. s., 9H), 1.76-1.84 (m, 3H), 2.27 (s, 3 H), 2.41 (m, 2 H), 3.75 (br. s., 1H), 3.97 (m, 1H), 7.00-7.23 (m, 3H), 7.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, selected data): δ 25.6, 28.5, 28.7, 32.1, 43.6, 45.3, 60.5, 79.3, 80.1, 125.5, 125.9, 126.8, 131.5, 144.7, 156.7. FT IR: cm^{-1} 725, 759, 859, 874, 1057, 1157, 1365, 1455, 1488, 1698, 2975, 3372. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{23}NO_2Na$ 284.1621; found 284.1621;



4c

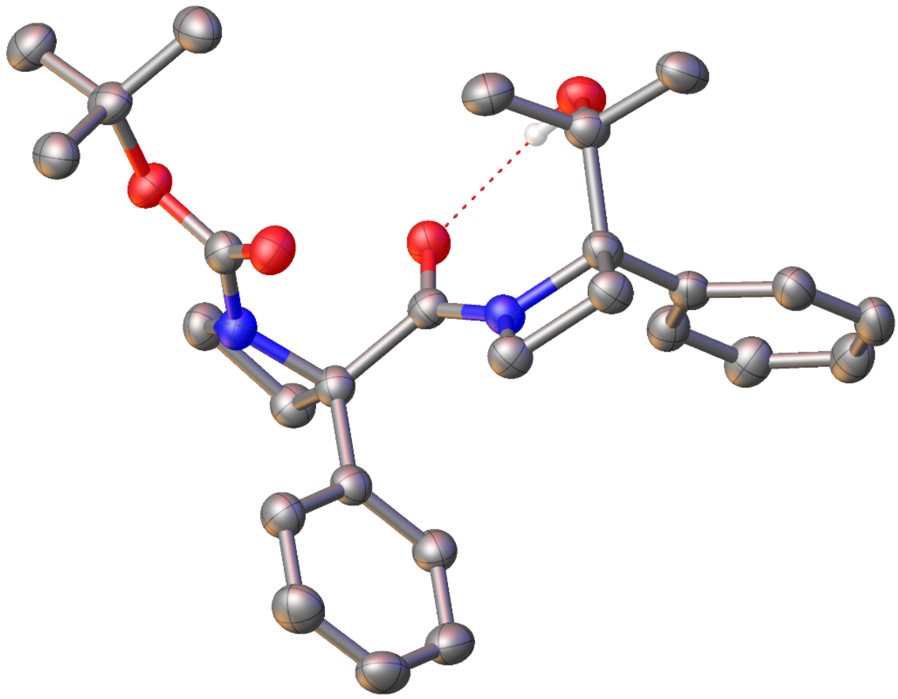
***tert*-Butyl-2-(hydroxydiphenylmethyl)-2-(o-tolyl)azetidine-1-carboxylate 4c**: Colourless oil, (75%). ^{1}H NMR (500 MHz, $CDCl_3$): *δ:* 1.20 (s, 9 H), 1.37 (s, 3 H), 2.61-2.68 (m, 1 H), 3.24-3.34 (m, 1 H), 3.56-3.7 (m, 1 H), 3.79-3.85 (m, 1 H), 6.76 (s, 1H, O*H*), 6.90-7.40 (m, 10 H), 7.39-7.66 (m, 2 H), 7.70-7.78 (m, 2 H); ^{13}C (125 MHz, $CDCl_3$, selected data) δ: 19.86, 28.5, 46.1, 80.3, 81.8, 126.7, 126.9, 126.9, 127.5, 127.7, 128.2, 131.3, 135.6, 142.9, 147.3, 156.7; FT IR: cm^{-1} 701, 752, 853, 1162, 1252, 1395, 1447, 1493, 1661, 1709, 2975, 3057, 3338. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{31}NO_3Na$ 452.2196; found 452.2212;



4d

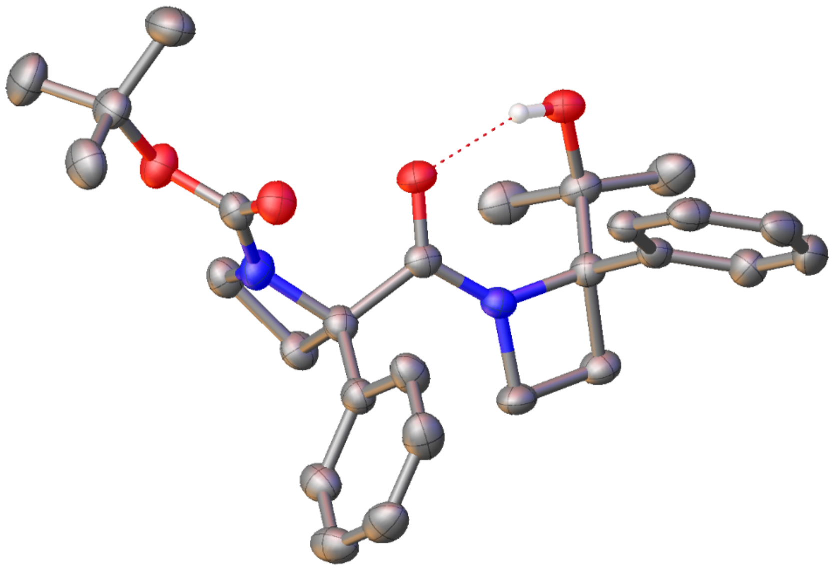
di-*tert*-Butyl-2-(o-tolyl)azetidine-1,2-dicarboxylate 4d: Colourless oil, (87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40-1.53 (br. s., 18H), 2.12 (s, 3 H), 2.27-2.36 (m, 1 H), 2.88 (br. s., 1 H), 3.80-3.85 (m, 1 H), 4.14-4.21 (m, 1 H), 7.01-7.26 (m, 3 H), 7.37-7.47 (m, 1 H); ^{13}C (125 MHz, $CDCl_3$ selected data): δ 21.0, 27.4, 28.3, 47.4, 47.5, 74.6, 80.1, 81.8, 85.1, 124.9, 125.9, 127.2, 131.0, 134.6, 146.7, 155.9; 156.7. FT IR: cm^{-1} 604, 755, 846, 970, 1116, 1372, 1256, 1372, 1456, 1477, 1717, 1809, 2932, 3413. HRMS (ESI-TOF) *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{29}NO_4Na$ 370.1989; found 370.1993.

X-ray analysis for **3b** and *diast*-**3b**



3b most hydrogens removed for clarity and trying to show the stereocenter of the first azetidine in the same orientation as in *diast*-**3b** to highlight they are diastereomers

Crystal Data for $C_{27}H_{34}N_2O_4$ (M =450.56 g/mol): colourless block 0.25 × 0.12 × 0.09, monoclinic, space group $P2_1/n$ (no. 14), a = 10.0556(2) Å, b = 23.0371(5) Å, c = 10.8204(3) Å, β = 106.221(3)°, V = 2406.78(10) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.667 mm^{-1}, $Dcalc$ = 1.243 g/cm^3, 19755 reflections measured (7.676° ≤ 2Θ ≤ 159.864°), 5102 unique (R_{int} = 0.0376, R_{sigma} = 0.0296) which were used in all calculations. The final R_1 was 0.0406 (I > 2σ(I)) and wR_2 was 0.1136 (all data).



diast-3b most hydrogens removed for clarity and trying to show the stereocenter of the first azetidine

Crystal Data for $C_{27}H_{34}N_2O_4$ (M =450.56 g/mol): colourless block 0.14 × 0.04 × 0.04, monoclinic, space group $P2_1/n$ (no. 14), a = 15.0493(5) Å, b = 6.6839(2) Å, c = 24.3241(10) Å, β = 100.495(4)°, V = 2405.77(15) Å^3, Z = 4, T = 180(2) K, μ(CuKα) = 0.667 mm^{-1}, $Dcalc$ = 1.244 g/cm^3, 8764 reflections measured (7.58° ≤ 2Θ ≤ 156.16°), 4971 unique (R_{int} = 0.0515, R_{sigma} = 0.0780) which were used in all calculations. The final R_1 was 0.0503 (>2sigma(I)) and wR_2 was 0.1218 (all data).

Stereochemical assignment for dimers 3 and *diast*-3

The relative stereochemistry of dimers **3** and *diast*-**3** was assigned by analogy to **3b** and *diast*-**3b** used as reference compounds (X-ray available).

X-Ray analysis of **3b** displays, in the solid state, a torsional angle of -80.40° between the C=O groups. In contrast *diast*-**3b** discloses a torsional angle between the C=O groups of 129.52°. We believe that such preferential conformation, related to their stereochemistry, could be kept in solution and in all cases were such relative configuration is observed. In fact, as consequence of this stereochemical preference, it results a marked difference in the chemical shifts of the methylene protons α to the nitrogen atoms for **3** and *diast*-**3** (Figure 1). By ^{1}H NMR it was found that stereoisomer **3b** showed sharper and more deshielded signals. Stereoisomers *diast*-**3b** gave broadest and more shielded signals with respect to **3b** (Figure 1-3). In addition, in all the cases where stereoisomers **3** and *diast*-**3** were separable by chromatography, it resulted that the first eluted was **3** and second eluted *diast*-**3**. A difference in retention factors of 0.3 was always observed.

In line with the above considerations, we assumed that the first eluted (major stereoisomers **3**) have the (R*,S*) relative configuration, while the second eluted (minor stereoisomers *diast*-**3**) have the (R*,R*) relative configuration just as observed with reference compounds **3b** and *diast*-**3b**. .

Figure 1. Comparison of torsional angles and ^{1}H NMR spectra for **3b** and *diast*-**3b**.

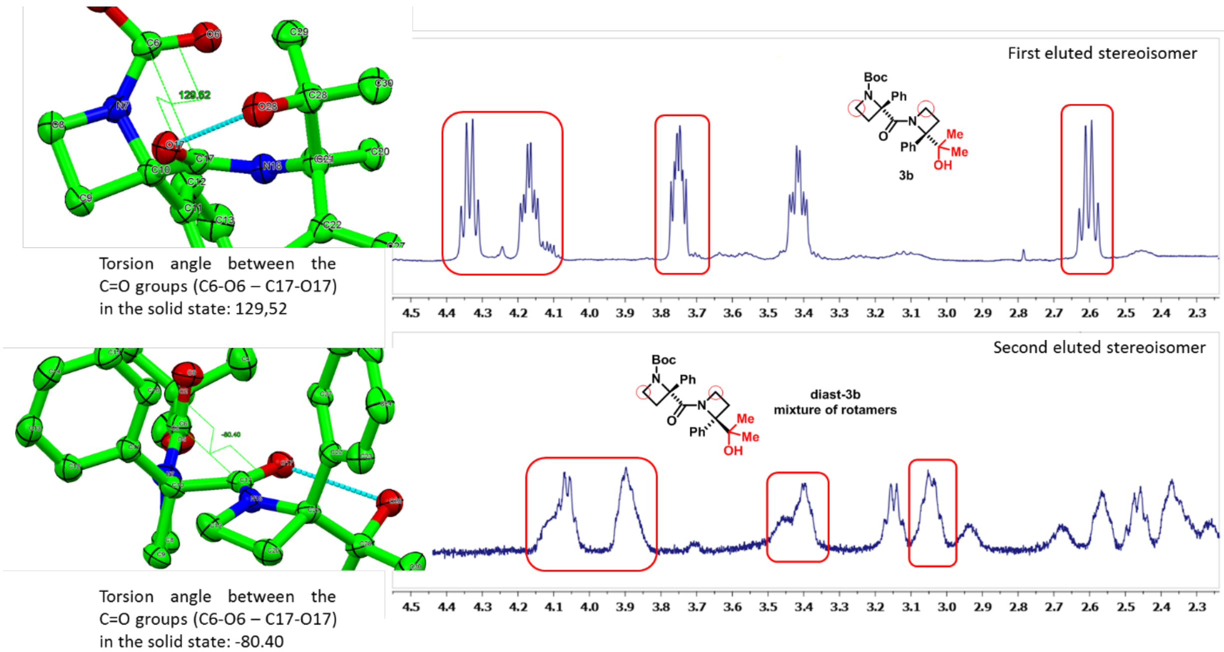


Figure 2. Comparison of ^{1}H NMR spectra for major stereoisomers **3** having (R*,S*) relative configuration

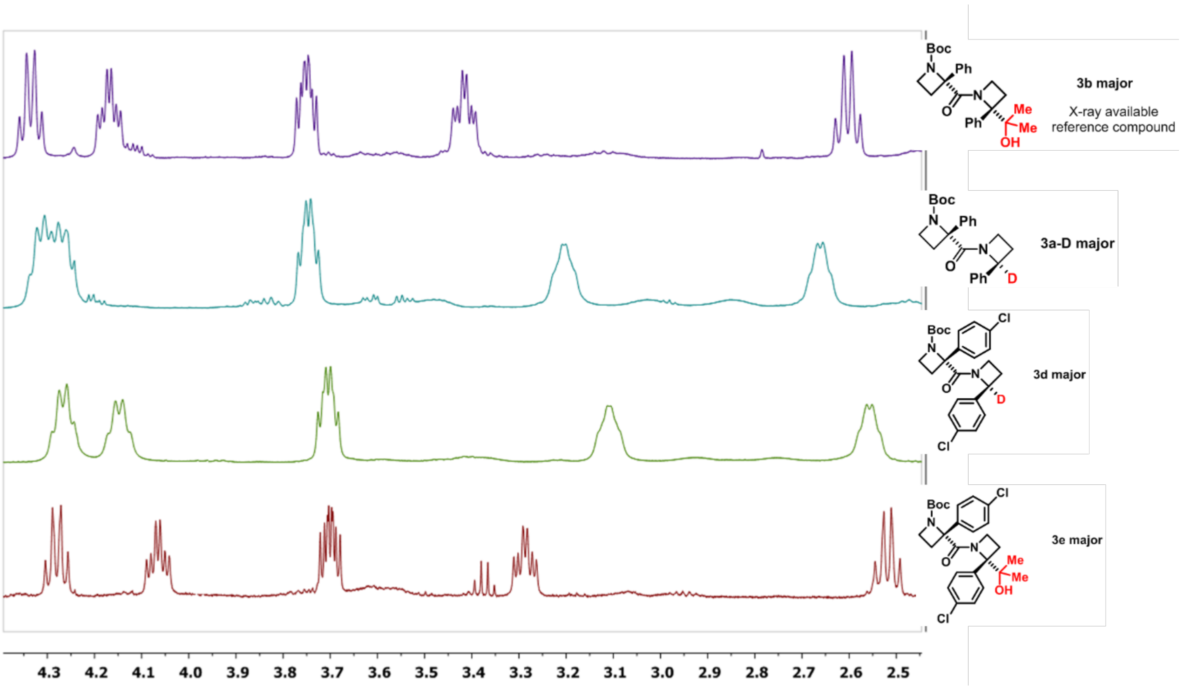
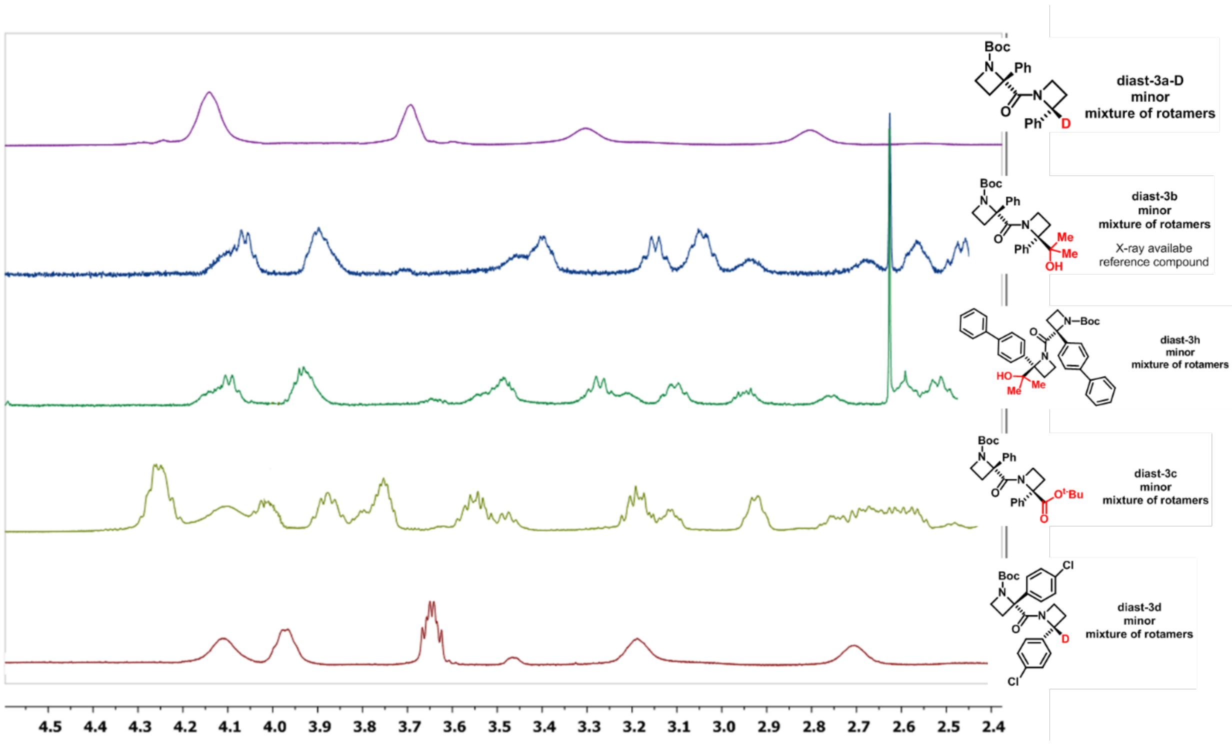
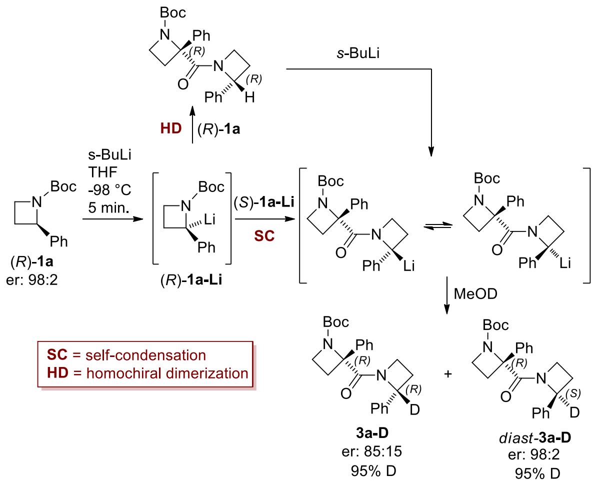


Figure 2. Comparison of 1H NMR spectra for major stereoisomers **3** having (R*,R*) relative configuration

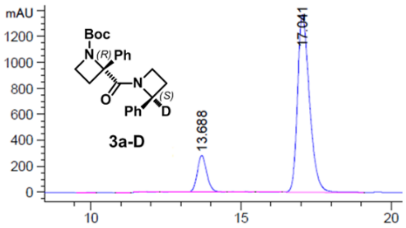


HPLC Analysis of chiral dimers

Stereochemical investigation on the dimerization process. The Scheme below reports the investigated process.



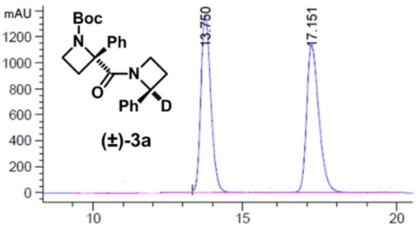
Sample Info : lux 1 Cellulose 0,5 ml/min hex:iPrOH=95:5



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
8	13.688	VB	0.3355	6183.07422	282.32080	13.4165
11	17.041	BB	0.4227	3.77885e4	1366.17981	81.9966

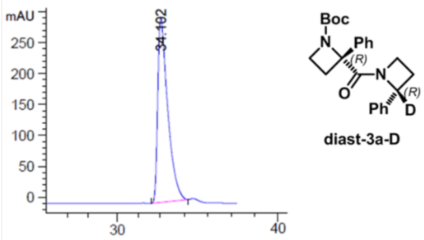
Sample Info : lux 1 Cellulose 0,5 ml/min hex:iPrOH=95:5



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
13	13.750	VB	0.3611	4.01897e4	1729.38281	46.0552
16	17.151	BB	0.4344	4.10876e4	1442.29810	47.0840

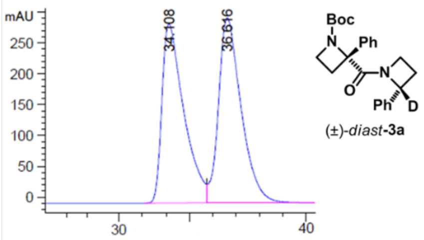
Sample Info : lux 1 Cellulose 0,4 ml/min hex:iPrOH=97:3



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
7	34.102	BB	0.9539	1.95480e4	298.54388	95.5628

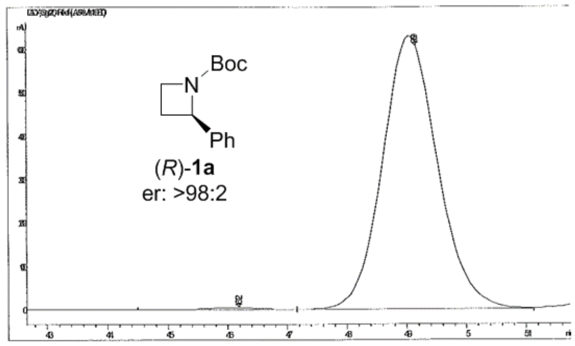
Sample Info : lux 1 Cellulose 0,4 ml/min hex:iPrOH=97:3



Signal 1: DAD1 A, Sig=220,4 Ref=off

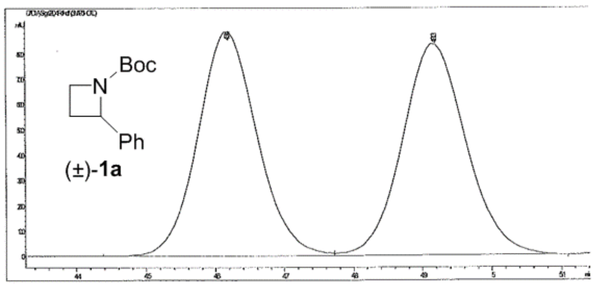
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	34.108	BV	0.9425	1.69018e4	257.93103	47.9638
5	36.616	VB	0.9934	1.80781e4	266.49329	51.3018

VAN 116 FR22-25 CHIRAL



#	Time	Area	Height	Width	Area%	Symmetry
1	4.612	26.7	4.4	0.0925	0.659	0.886
2	4.909	4022.9	631.1	0.0964	99.341	0.91

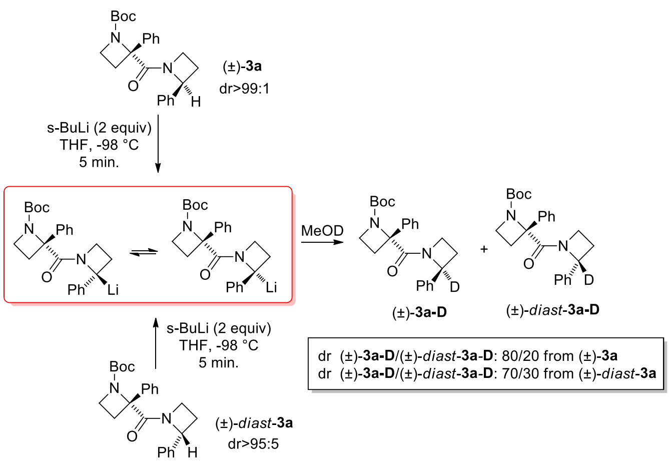
RAC NBOC



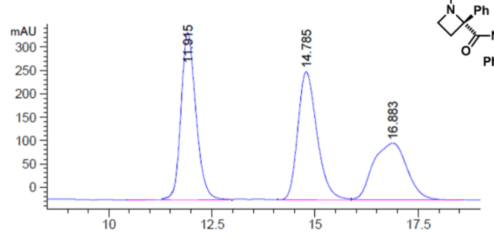
#	Time	Area	Height	Width	Area%	Symmetry
1	4.614	5282.2	886.3	0.0915	49.843	0.913
2	4.913	5315.6	833.8	0.0984	50.157	0.906

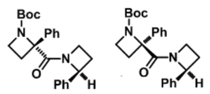
Proving the equilibrium for lithiated dimers.

In order to analyze, by HPLC, the crude reaction mixture avoiding possible artifacts due to chromatographic separation, a method for separating the mixture of **3a** and *diast*-**3a** was developed. A chiral stationary phase was used even if the experiment was run on racemic samples.



Sample Info : ODH 0.5 ml/min hex:iPrOH=95:5



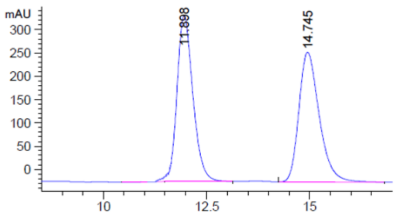


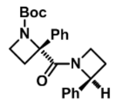
MIXTURE

Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	11.915	VB	0.3840	8945.82813	357.46689	35.2553
5	14.785	BV	0.4972	8879.16992	274.59882	34.9926
6	16.883	VB	0.8060	6921.66699	121.99220	27.2781

Sample Info : ODH 0.5 ml/min hex:iPrOH=95:5



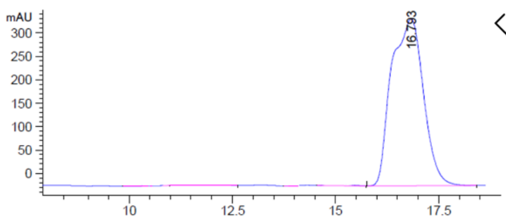


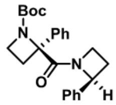
3a

Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
6	11.898	VB	0.3902	1.49650e4	589.41980	48.7495
7	14.745	BB	0.5020	1.49795e4	459.85410	48.7967

Sample Info : ODH 0.5 ml/min hex:iPrOH=95:5



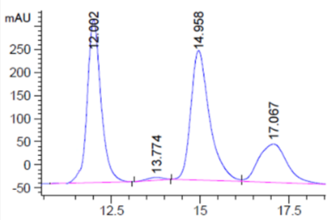


diast-3a

Signal 1: DAD1 A, Sig=220,4 Ref=off

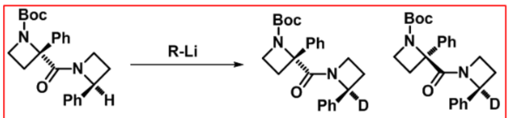
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
6	16.793	BB	0.8256	1.82402e4	305.05481	95.3961

Sample Info : ODH 0.5 ml/min hex:iPrOH=95:5



Signal 1: DAD1 A, Sig=220,4 Ref=off

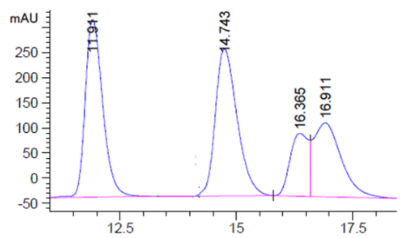
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
7	12.002	VB	0.4008	9368.68652	353.96353	35.5656
9	14.958	BV	0.5493	1.02881e4	280.87430	39.0560
10	17.067	VB	0.8973	4629.80518	83.44457	17.5758



3a 3a-D *diast*-3a-D

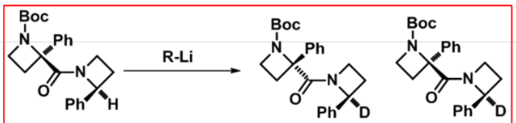
MIXTURE

Sample Info : ODH 0.5 ml/min hex:iPrOH=95:5



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	11.911	BB	0.4054	4.40897e4	1684.45300	30.6768
11	14.743	VB	0.4999	4.54349e4	1395.22974	31.6127
12	16.365	BV	0.4151	1.61380e4	597.56567	11.2285
13	16.911	VB	0.6185	2.92539e4	701.58209	20.3543



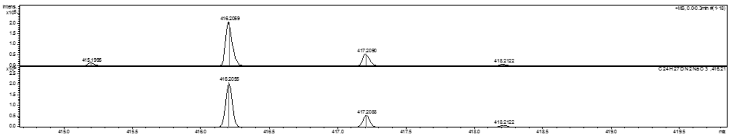
diast-3a 3a-D *diast*-3a-D

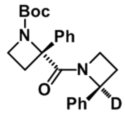
MIXTURE

Evaluation of deuterium content by HRMS in 3a-D and *diast*-3a-D.

Chemical Formula: $C_{24}H_{27}DN_2O_3$

HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd for $C_{24}H_{27}DN_2O_3Na$ 416.2055; found 416.2059.





3a-D

Intensità sperimentali di $C_{24}H_{27}DN_2O_3Na$

#	m/z	I
329	415.1995	14059
330	415.9794	770
331	**416.2059**	**208740**
332	416.7084	615
333	416.8899	603
334	**417.2090**	**57446**
335	417.6275	262
336	417.7462	267
337	417.9576	251
338	**418.2122**	**8412**

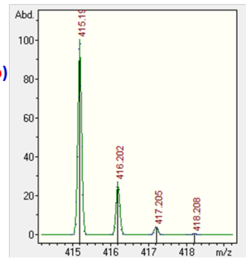
Intensità calcolate di $C_{24}H_{27}DN_2O_3Na$

#	m/z	I
1	**416.2055**	**208740**
2	**417.2088**	**56613**
3	**418.2122**	**8664**
4	**419.2156**	**962**

#	m/z	Abundance
1	416.205491	100.000
2	417.208710	27.121
3	418.211599	4.153
4	419.214345	0.462

Intensità calcolate di $C_{24}H_{28}N_2O_3Na$ (non deuterato)

#	m/z	Abundance
1	415.199214	100.000
2	416.202435	27.133
3	417.205325	4.156
4	418.208072	0.462

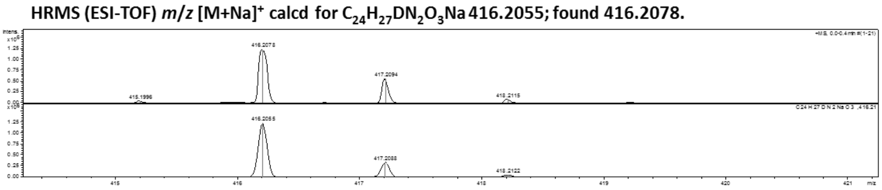


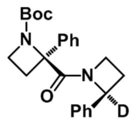
Deuterium content

$$\frac{208740 - 14059x0.27133}{208740}x100 = $$
$$\cong 98,17\,\%$$

Chemical Formula: $C_{24}H_{27}DN_2O_3$

HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd for $C_{24}H_{27}DN_2O_3Na$ 416.2055; found 416.2078.





diast-**3a-D**

Intensità sperimentali di $C_{24}H_{27}DN_2O_3Na$

#	m/z	I
46	415.1996	45932
47	415.7285	5053
48	415.9886	7250
49	**416.2078**	**1223866**
50	416.7098	5782
51	416.9126	5095
52	**417.2094**	**570306**
53	417.5864	2144
54	417.7698	1945
55	**418.2115**	**89495**

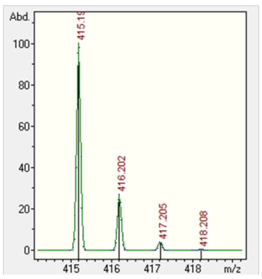
Intensità calcolate di $C_{24}H_{27}DN_2O_3Na$

#	m/z	I
1	**416.2055**	**1223866**
2	**417.2088**	**331928**
3	**418.2122**	**50799**
4	**419.2156**	**5643**

#	m/z	Abundance
1	416.205491	100.000
2	417.208710	27.121
3	418.211599	4.153
4	419.214345	0.462

Intensità calcolate di $C_{24}H_{28}N_2O_3Na$ (non deuterato)

#	m/z	Abundance
1	415.199214	100.000
2	416.202435	27.133
3	417.205325	4.156
4	418.208072	0.462

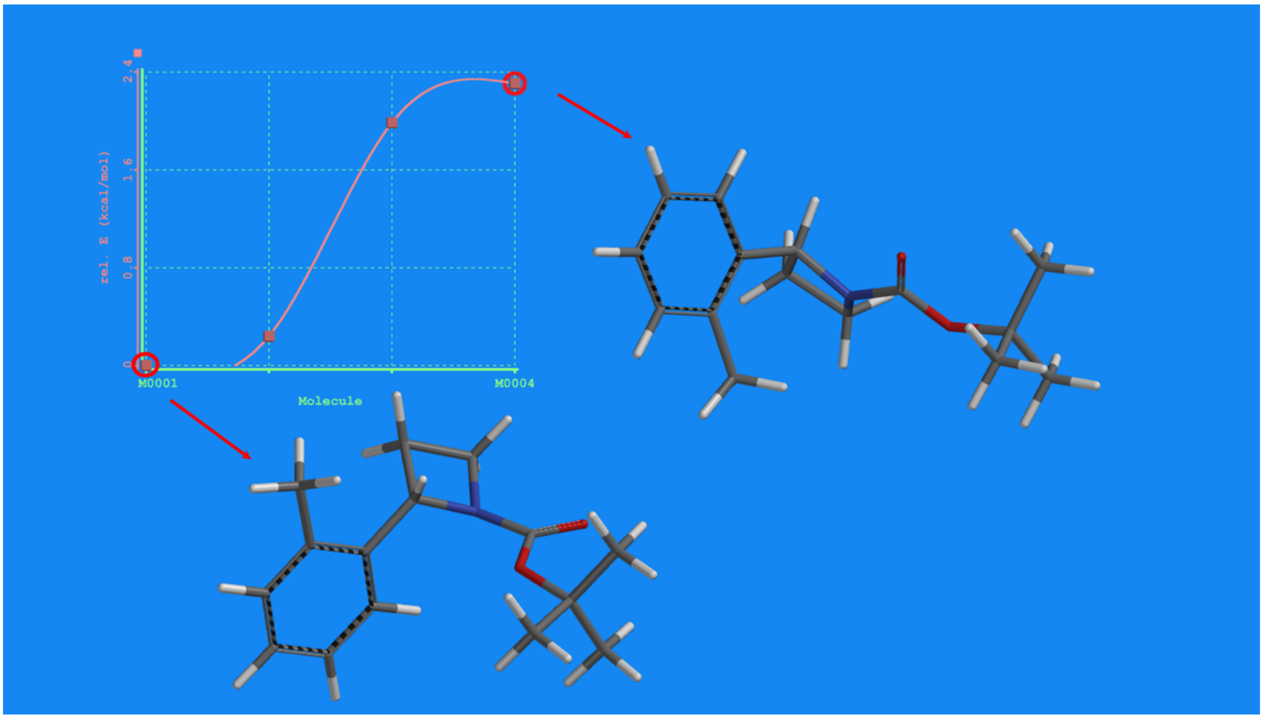


Deuterium content

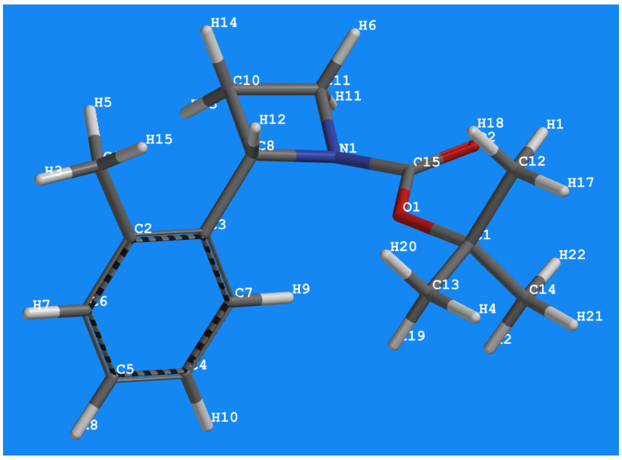
$$\frac{1223866 - 45932x0.27133}{1223866}x100 = $$
$$\cong 98,98\,\%$$

Conformational analysis on azetidine 1d

Conformational analysis on **1d** was performed at DFT level of theory using a B3LYP/6311++G* functional using Spartan 08 package.[4] The equilibrium geometry of **1d** was subjected to conformational analysis and the more stable conformers included in a range of 4 kcal/mol were kept. The plot of the conformer energies as function of the aryl orientation is reported below. The most stable conformers (A and B) were subjected to further optimization. The conformer that set the ortho-methyl substituent syn to the α-proton to be removed during the lithiation (conformer A), was found as the more stable.



[4] Wavefunction Inc. Irvine CA; Web: www.wavefun.com Wavefunction Developers: B.J. Deppmeier, A.J. Driessen, T.S. Hehre, W.J. Hehre, J.A. Johnson, P.E. Klunzinger, J.M. Leonard, I.N. Pham W.J. Pietro, Jianguo Yu Q-Chem Developers: Y. Shao, L. Fusti-Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko,S. V. Levchenko, D. P. O'Neill, R. A. DiStasio Jr., R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M., Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer III, J. Kong, A. I. Krylov, P. M. W. Gill, M. Head-Gordon,



Conformer A of azetidine 1d

E = -495525.74 kcal/mol

GEOMETRY OPTIMIZATION IN DELOCALIZED INTERNAL COORDINATES **
Searching for a Minimum
Optimization Cycle: 7
Coordinates (Angstroms)
ATOM X Y Z
1 C 2.796084 1.104778 -0.360131
2 C -2.796385 0.319392 -0.767347
3 C -2.519479 1.453359 1.789622
4 C -1.756913 -0.101269 0.087023
5 C -3.677999 1.304629 -0.314035
6 C -3.547556 1.872848 0.951543
7 C -1.632437 0.471056 1.354042
8 H -4.479212 1.634117 -0.968249
9 H -4.244678 2.637240 1.276761
10 H -0.825993 0.142052 1.998822
11 H -2.403642 1.888611 2.776030
12 C -0.815383 -1.194702 -0.363836
13 N 0.368746 -1.462504 0.482556
14 C -1.258381 -2.677392 -0.106190
15 C 0.088326 -2.899825 0.630606
16 H 0.810094 -3.526150 0.099391
17 H 0.025453 -3.233984 1.668151
18 H -0.523217 -1.027917 -1.405264
19 H -2.134963 -2.752884 0.535912
20 H -1.407844 -3.280094 -1.001187
21 C 3.798637 0.398199 -1.276262
22 H 4.161452 -0.525021 -0.826468
23 H 4.651779 1.057312 -1.460395
24 H 3.336945 0.167225 -2.240133
25 C 2.253566 2.371253 -1.022584
26 H 3.069483 3.075318 -1.203523
27 H 1.513269 2.853321 -0.380743
28 H 1.780492 2.134794 -1.978335
29 C 3.391845 1.426694 1.013094
30 H 2.633411 1.877528 1.658564
31 H 4.206988 2.145817 0.894082
32 H 3.783466 0.532591 1.496403
33 O 1.583154 0.277444 -0.206102
34 C 1.627860 -0.936228 0.387045
35 O 2.621939 -1.502862 0.799583
36 C -2.973209 -0.267269 -2.149153
37 H -3.843087 0.167823 -2.644456
38 H -3.118216 -1.351726 -2.119669
39 H -2.101508 -0.076286 -2.784349
Point Group: c1 Number of degrees of freedom: 111
Energy is -789.669862999
Hessian Updated using BFGS Update
internal optimization with constraints (0)
111 Hessian modes will be used to form the next step
Hessian Eigenvalues:
0.001326 0.001875 0.002253 0.003520 0.004205
0.004768
0.006416 0.012766 0.016438 0.019513 0.021384
0.022798
0.023687 0.025213 0.027175 0.030141 0.031977
0.032583
0.033716 0.035889 0.037227 0.038906 0.039978
0.042965
0.044710 0.046752 0.049940 0.051219 0.052445
0.053187
0.056004 0.057789 0.061432 0.061657 0.063636
0.066738
0.067477 0.074382 0.075635 0.078384 0.080186
0.100140
0.116431 0.121245 0.128172 0.129489 0.131879
0.133787
0.136564 0.139860 0.143902 0.148588 0.152632
0.155994
0.157061 0.161983 0.179376 0.188642 0.195572
0.197824
0.203008 0.213971 0.217186 0.226581 0.229869
0.236140
0.246957 0.248932 0.255682 0.271728 0.272213
0.290120
0.296354 0.297896 0.305588 0.309219 0.315753
0.319066
0.320476 0.321152 0.326264 0.327651 0.333313
0.337549
0.342134 0.347056 0.349335 0.355321 0.356676
0.364911
0.372305 0.373565 0.380927 0.386724 0.396153
0.409016
0.419729 0.427775 0.442396 0.477310 0.491688
0.507283
0.544214 0.553962 0.577702 0.644411 0.721520
0.820585
0.840074 1.350845 2.150482
Minimum Search - Taking Simple RFO Step
Searching for Lamda that Minimizes Along All modes
Value Taken Lamda = 0.00000000
Step Taken. Stepsize is 0.001782
Maximum Tolerance Cnvgd?
Gradient 0.000069 0.000300 YES
Displacement 0.000788 0.001200 YES
Energy change 0.000002 0.000001 NO

****
** OPTIMIZATION CONVERGED **
****

- Entering anlman on Thu Jul 09 18:15:51 2015 -

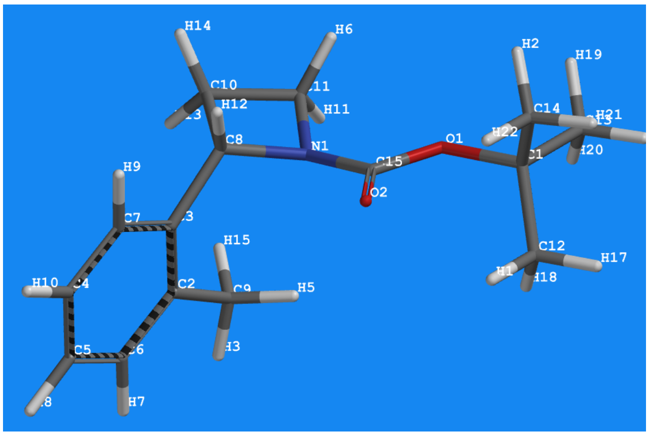
Analysis of SCF Wavefunction
Ground-State Mulliken Net Atomic Charges
Atom Charge (a.u.)
----
1 C -0.227850
2 C 0.126059
3 C -0.182062
4 C 0.077322
5 C -0.040519
6 C -0.162851
7 C -0.063921
8 H 0.111406
9 H 0.121774
10 H 0.117706
11 H 0.121698
12 C -0.089506
13 N -0.030341
14 C -0.514663
15 C -0.165589
16 H 0.153947
17 H 0.164889
18 H 0.145902
19 H 0.163820
20 H 0.157894
21 C -0.379872
22 H 0.186286
23 H 0.139045
24 H 0.142303
25 C -0.440392
26 H 0.145792
27 H 0.162046
28 H 0.151878
29 C -0.334696
30 H 0.146054
31 H 0.138351
32 H 0.184356
33 O 0.075891
34 C 0.073345
35 O -0.287030
36 C -0.536730
37 H 0.142780
38 H 0.151596
39 H 0.153882

Sum of atomic charges = 0.000000

Cartesian Multipole Moments

Charge (ESU x 10^10)
0.0000
Dipole Moment (Debye)
X -1.7384 Y 0.5494 Z -1.7676
Tot 2.5393
Quadrupole Moments (Debye-Ang)
XX -111.3166 XY 7.5320 YY -106.1411
XZ -1.5781 YZ 3.6695 ZZ -106.8835
Traceless Quadrupole Moments (Debye-Ang)
QXX -9.6087 QYY 5.9180 QZZ 3.6908
QXY 22.5959 QXZ -4.7342 QYZ 11.0085
Octapole Moments (Debye-Ang^2)
XXX 14.4926 XXY 39.3317 XYY -4.6625
YYY -21.3797 XXZ -24.1241 XYZ 0.8539
YYZ 0.5641 XZZ -0.5972 YZZ 1.2441
ZZZ 0.7621
Traceless Octapole Moments (Debye-Ang^2)
XXX 134.2926 YYY -493.4603 ZZZ 216.6132
XXY 532.3868 XXZ -293.4684 XYY -97.6361
XYZ 12.8083 XZZ -36.6565 YYZ 76.8552
YZZ -38.9265
Hexadecapole Moments (Debye-Ang^3)
XXXX -4318.6609 XXXY 8.6058 XXYY -988.8526
XYYY 9.7903 YYYY -1714.6108 XXXZ 42.7050
XXYZ 22.6483 XYYZ -21.5425 YYYZ 13.4267
XXZZ -877.8699 XYZZ -12.4851 YYZZ -430.8051
XZZZ 25.4487 YZZZ 13.7543 ZZZZ -894.9035
Traceless Hexadecapole Moments (Debye-Ang^3)
XXXX -483.9667 XXXY 637.6194 XXXZ 2386.5236
XXYY 1395.5662 XXYZ 1641.9461 XXZZ -911.5995
XYYY 761.9851 XYYZ -2961.1340 XYZZ -1399.6045
XZZZ 574.6103 YYYY -1659.0408 YYYZ -798.5718
YYZZ 263.4746 YZZZ -843.3743 ZZZZ 648.1249

Total job time: 7795.16s(wall), 7721.91s(cpu)



Conformer B of azetidine 1d

E = -495523.31 kcal/mol

Cartesian Hessian Update
Hessian Updated using BFGS Update
** GEOMETRY OPTIMIZATION IN DELOCALIZED INTERNAL COORDINATES **
Searching for a Minimum
Optimization Cycle: 9
Coordinates (Angstroms)
ATOM X Y Z
1 C -3.568295 0.542836 -0.080385
2 C 2.559564 0.107814 -0.952026
3 C 4.160755 1.088828 1.154617
4 C 2.218530 -0.177829 0.388939
5 C 3.699803 0.882023 -1.194401
6 C 4.500033 1.369009 -0.163947
7 C 3.024654 0.328261 1.414887
8 H 3.964050 1.109506 -2.222332
9 H 5.375548 1.966132 -0.393657
10 H 2.746478 0.126809 2.444587
11 H 4.763314 1.465232 1.973479
12 C 1.049266 -1.042102 0.811878
13 N -0.247354 -0.900365 0.115612
14 C 1.024231 -2.556938 0.410411
15 C -0.414147 -2.342594 -0.131267
16 H -1.205802 -2.792166 0.474549
17 H -0.582430 -2.597481 -1.180219
18 H 0.914201 -0.915712 1.890840
19 H 1.754763 -2.819016 -0.353340
20 H 1.117290 -3.248857 1.246314
21 C -3.290315 1.818750 -0.879735
22 H -2.511246 2.416394 -0.408757
23 H -4.203827 2.416726 -0.939217
24 H -2.981038 1.569918 -1.898439
25 C -4.644561 -0.302054 -0.763517
26 H -5.580000 0.259967 -0.822353
27 H -4.828585 -1.220556 -0.201413
28 H -4.337081 -0.571347 -1.776346
29 C -3.955860 0.840471 1.370483
30 H -4.101758 -0.091202 1.923563
31 H -4.897985 1.395729 1.385762
32 H -3.191213 1.433342 1.869609
33 O -2.388328 -0.344032 -0.124456
34 C -1.190692 0.050418 0.375621
35 O -0.961548 1.094543 0.954366
36 C 1.748054 -0.362324 -2.139274
37 H 2.222742 -0.041940 -3.068931
38 H 0.733878 0.040630 -2.115832
39 H 1.658999 -1.451492 -2.178343
Point Group: c1 Number of degrees of freedom: 111
Energy is -789.665994581
Hessian Updated using BFGS Update
internal optimization with constraints (0)
111 Hessian modes will be used to form the next step
Hessian Eigenvalues:
0.001992 0.002596 0.003061 0.004259 0.005639
0.007280
0.008186 0.010211 0.021113 0.022429 0.024630
0.025918
0.027786 0.029882 0.030789 0.033049 0.033811
0.035225
0.036601 0.037489 0.038748 0.040178 0.040765
0.041103
0.041971 0.042346 0.044427 0.046227 0.046481
0.048183
0.049625 0.053251 0.053768 0.055108 0.060976
0.063750
0.065495 0.070840 0.074039 0.075028 0.079483
0.099840
0.117103 0.123732 0.126656 0.128331 0.129477
0.129886
0.131671 0.134128 0.139204 0.139886 0.144127
0.146533
0.149309 0.154155 0.157312 0.161407 0.165047
0.172404
0.181435 0.187337 0.195030 0.198304 0.211462
0.212502
0.218604 0.221078 0.228497 0.229317 0.246756
0.250897
0.256380 0.267595 0.271876 0.277691 0.285521
0.286014
0.292014 0.294572 0.296388 0.299935 0.305045
0.306561
0.309463 0.313223 0.317180 0.323169 0.326624
0.339994
0.342381 0.349717 0.353413 0.361143 0.364342
0.383455
0.395169 0.397062 0.421184 0.430423 0.451084
0.465190
0.476331 0.504138 0.512599 0.529136 0.557748
0.573274
0.645873 0.956246 1.001807
Minimum Search - Taking Simple RFO Step
Searching for Lamda that Minimizes Along All modes
Value Taken Lamda = -0.00000137
Step Taken. Stepsize is 0.014683
Maximum Tolerance Cnvgd?
Gradient 0.000241 0.000300 YES

Displacement 0.007823 0.001200 NO
Energy change 0.000000 0.000001 YES
****
** OPTIMIZATION CONVERGED **
****

- Entering anlman on Fri Jul 10 13:35:29 2015 -

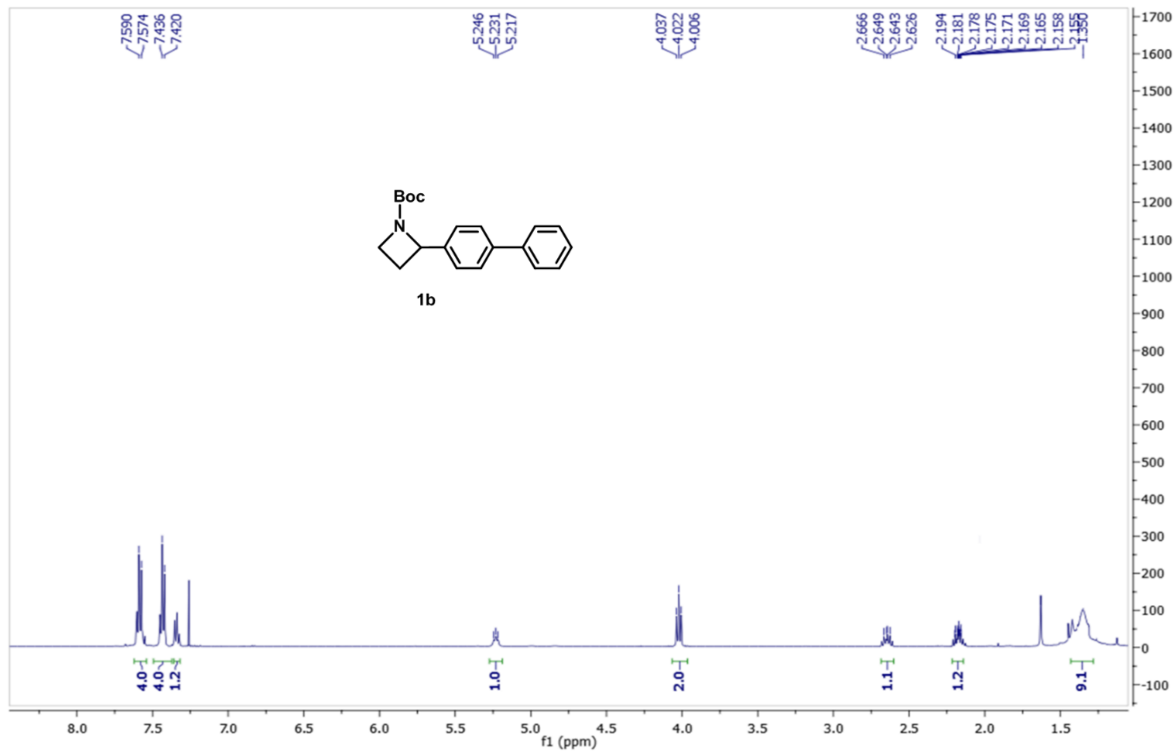
Analysis of SCF Wavefunction
Ground-State Mulliken Net Atomic Charges
Atom Charge (a.u.)
----
1 C -0.236699
2 C 0.227137
3 C -0.193005
4 C 0.370349
5 C -0.113454
6 C -0.304389
7 C -0.234705
8 H 0.110618
9 H 0.122367
10 H 0.103796
11 H 0.121495
12 C 0.000249
13 N -0.054752
14 C -0.476845
15 C -0.183270
16 H 0.150933
17 H 0.158816
18 H 0.119722
19 H 0.156542
20 H 0.155545
21 C -0.333685
22 H 0.186206
23 H 0.137949
24 H 0.144497
25 C -0.450390
26 H 0.145988
27 H 0.152547
28 H 0.154991
29 C -0.324262
30 H 0.142428
31 H 0.137128
32 H 0.184895
33 O 0.084031
34 C -0.051266
35 O -0.267436
36 C -0.493384
37 H 0.138218
38 H 0.171087
39 H 0.140007

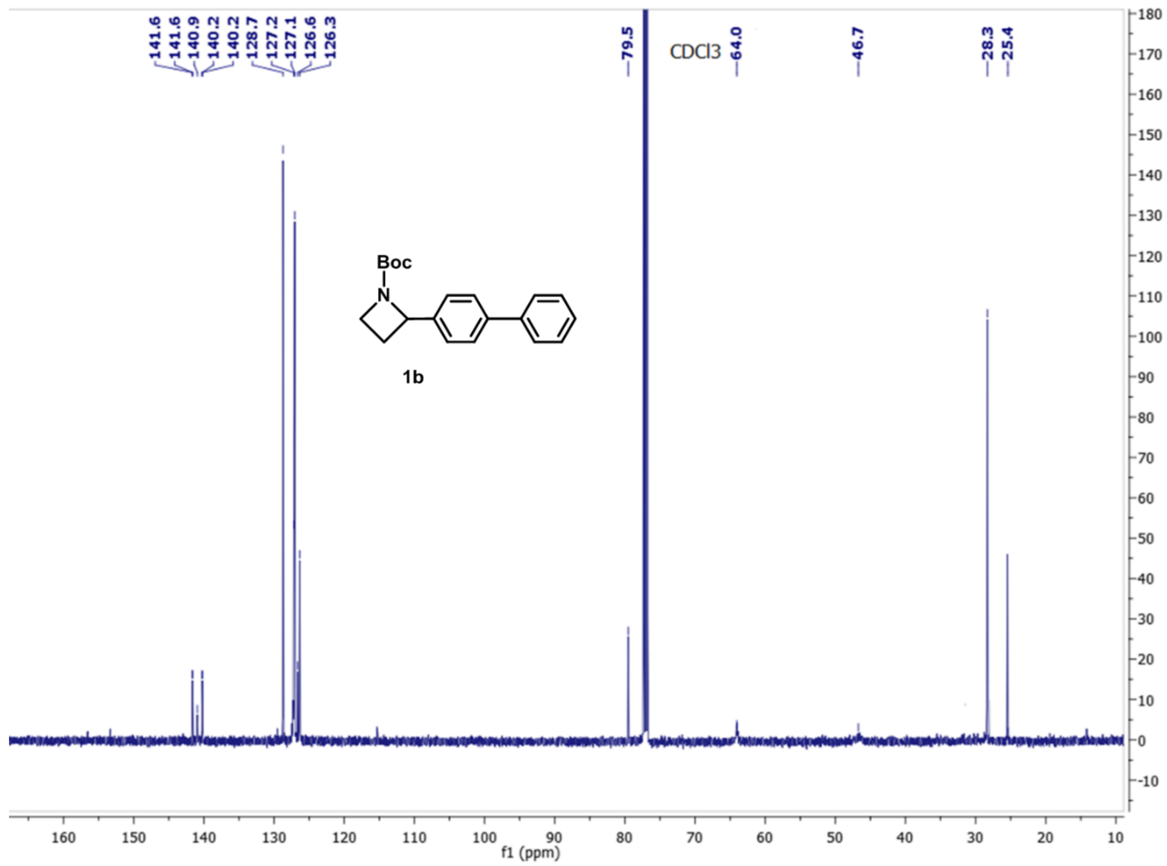
Sum of atomic charges = 0.000000

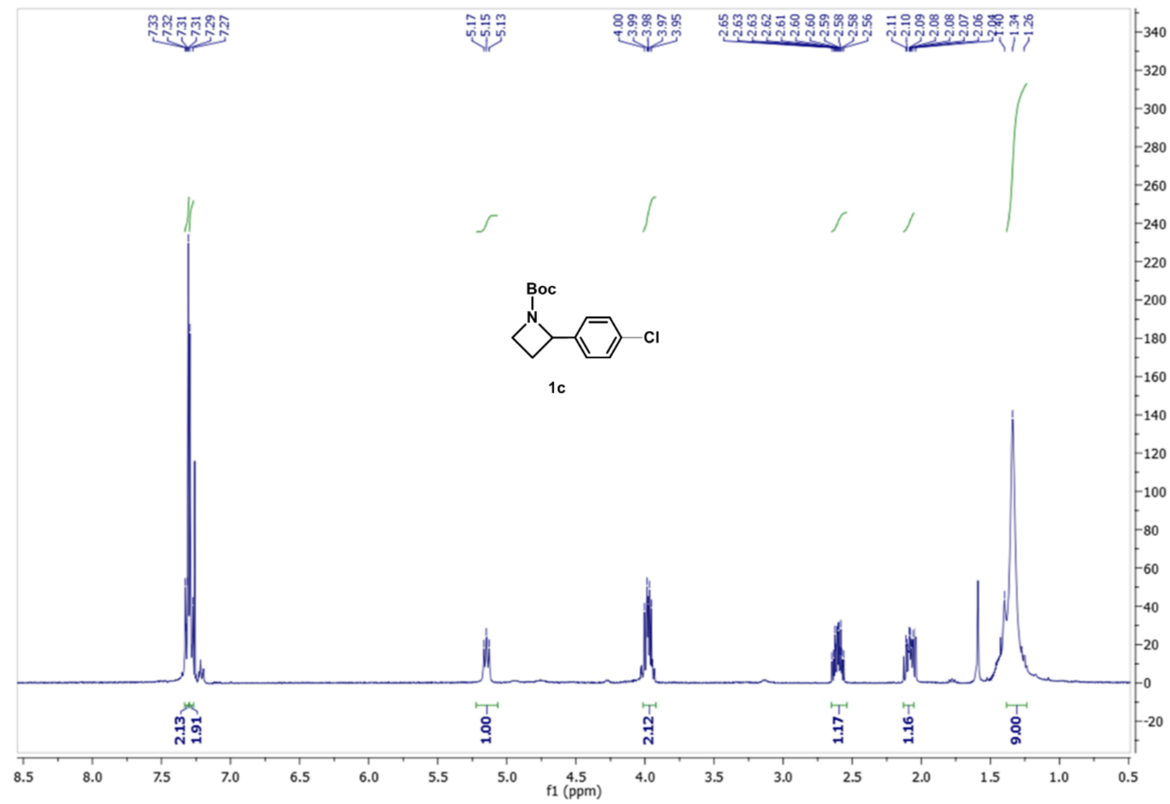
Cartesian Multipole Moments

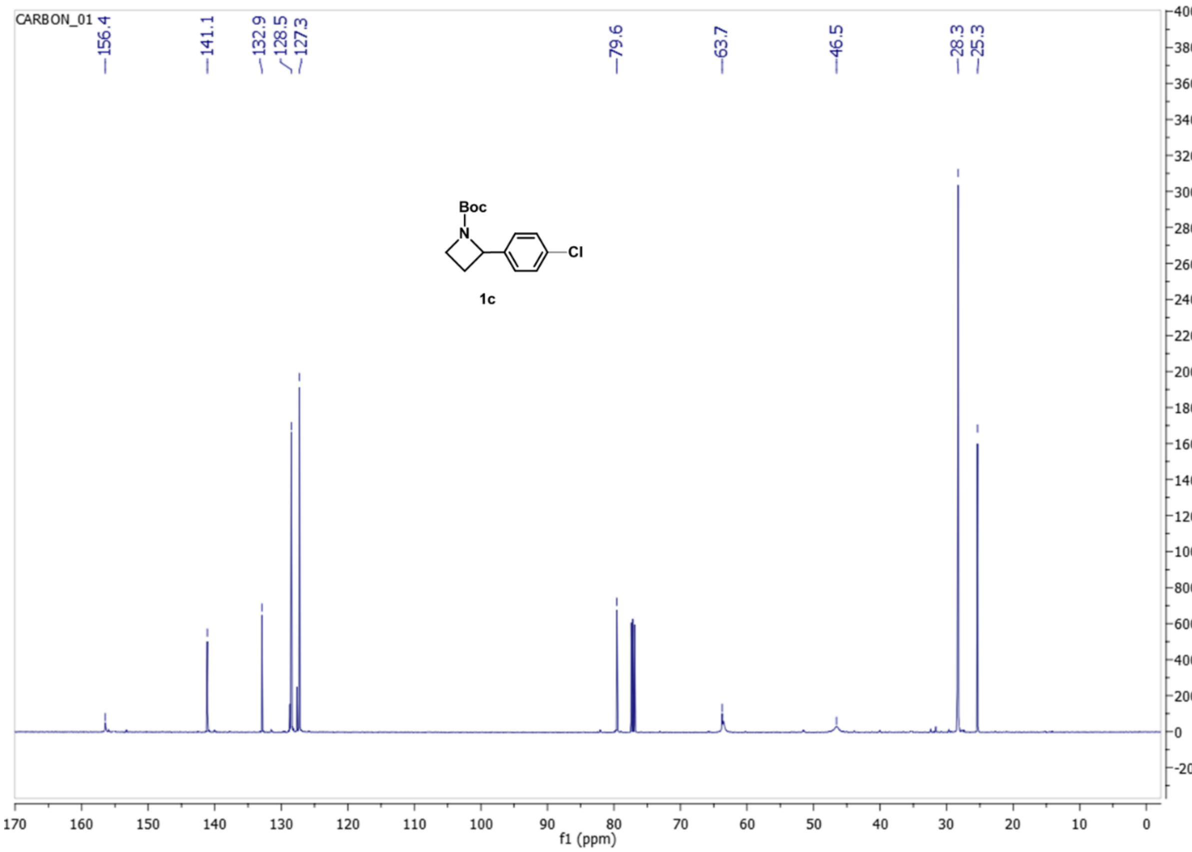
Charge (ESU x 10^10)
0.0000
Dipole Moment (Debye)
X -0.7794 Y -2.2674 Z -0.7767
Tot 2.5203
Quadrupole Moments (Debye-Ang)
XX -101.4756 XY 0.6806 YY -108.8946
XZ 0.6384 YZ -3.4132 ZZ -106.1085
Traceless Quadrupole Moments (Debye-Ang)
QXX 12.0520 QYY -10.2052 QZZ -1.8468
QXY 2.0418 QXZ 1.9152 QYZ -10.2397
Octapole Moments (Debye-Ang^2)
XXX -53.4060 XXY 35.3518 XYY -7.8279
YYY -17.0445 XXZ 0.8963 XYZ 3.0129
YYZ -1.0219 XZZ 6.8604 YZZ -2.8933
ZZZ 0.6357
Traceless Octapole Moments (Debye-Ang^2)
XXX -311.7284 YYY -394.3935 ZZZ 4.9443
XXY 484.0347 XXZ 11.9147 XYY 45.7023
XYZ 45.1928 XZZ 266.0261 YYZ -16.8590
YZZ -89.6413
Hexadecapole Moments (Debye-Ang^3)
XXXX -5606.2855 XXXY 80.1150 XXYY -1126.0099
XYYY -11.3541 YYYY -1142.6614 XXXZ 4.0130
XXYZ -5.0274 XYYZ -2.8632 YYYZ -10.4499
XXZZ -1075.1957 XYZZ 18.7832 YYZZ -334.5703
XZZZ 9.4688 YZZZ -10.0984 ZZZZ -847.7536
Traceless Hexadecapole Moments (Debye-Ang^3)
XXXX -0.0478 XXXY 4472.5923 XXXZ -56.4686
XXYY -74.8071 XXYZ -145.7215 XXZZ 74.8549
XYYY -5131.6637 XYYZ -459.9178 XYZZ 659.0714
XZZZ 516.3864 YYYY 298.0277 YYYZ 49.2422
YYZZ -223.2206 YZZZ 96.4793 ZZZZ 148.3657

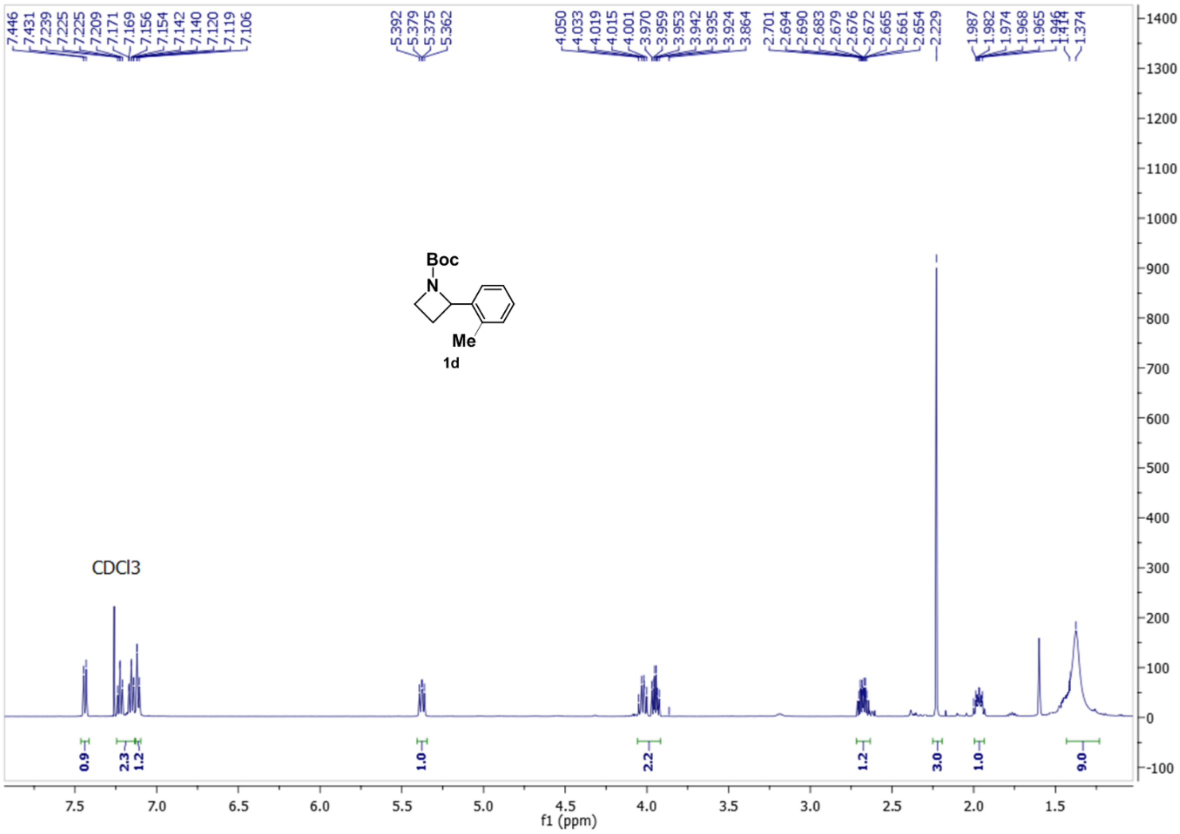
Total job time: 10655.76s(wall), 9637.27s(cpu)

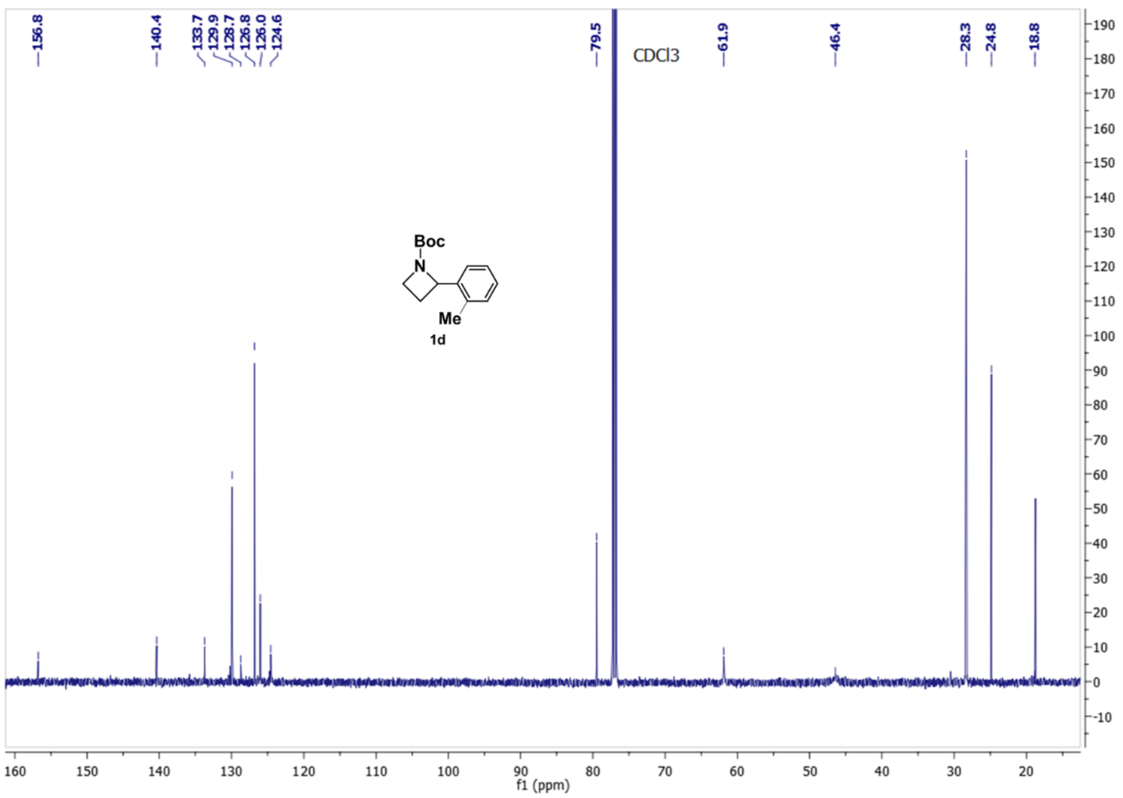

7.590
7.574
7.436
7.420
5.246
5.231
5.217
4.037
4.022
4.006
2.666
2.649
2.643
2.626
2.194
2.181
2.178
2.175
2.171
2.169
2.165
2.158
1.350
Boc
N
1b
4.0
4.0
1.2
1.0
2.0
1.1
1.2
9.1
f1 (ppm)


141.6
141.6
140.9
140.2
140.2
128.7
127.2
127.1
126.6
126.3
79.5
CDCl3
64.0
46.7
28.3
25.4
Boc
N
1b
f1 (ppm)

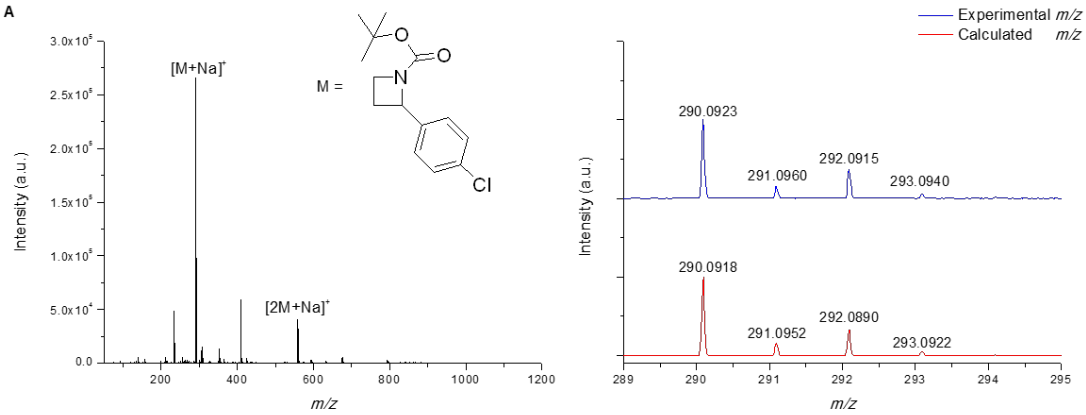

7.33
7.32
7.31
7.31
7.29
7.27
5.17
5.15
5.13
4.00
3.99
3.98
3.97
3.95
2.65
2.63
2.63
2.62
2.61
2.60
2.60
2.59
2.58
2.58
2.58
2.56
2.11
2.10
2.09
2.08
2.08
2.07
2.06
1.34
1.26
Boc
N
Cl
1c
2.13
1.91
1.00
2.12
1.17
1.16
9.00
f1 (ppm)

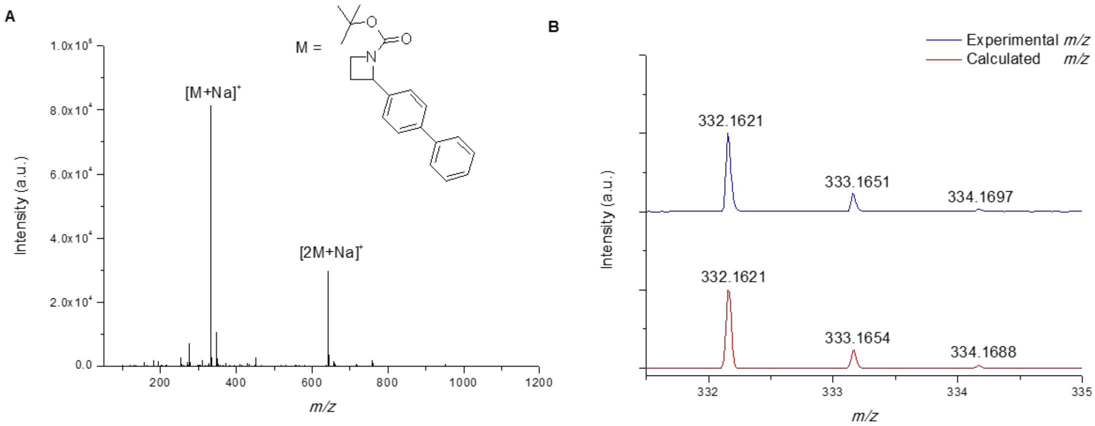

CARBON_01
156.4
141.1
132.9
128.5
127.3
79.6
63.7
46.5
28.3
25.3
Boc
N
Cl
1c
f1 (ppm)

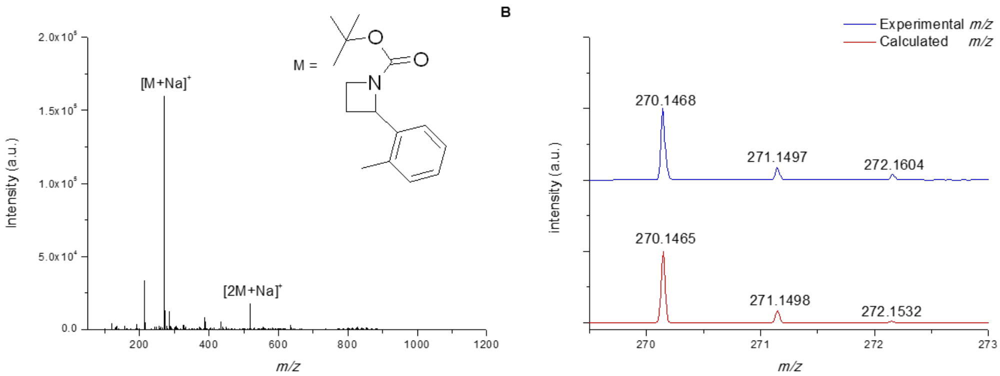


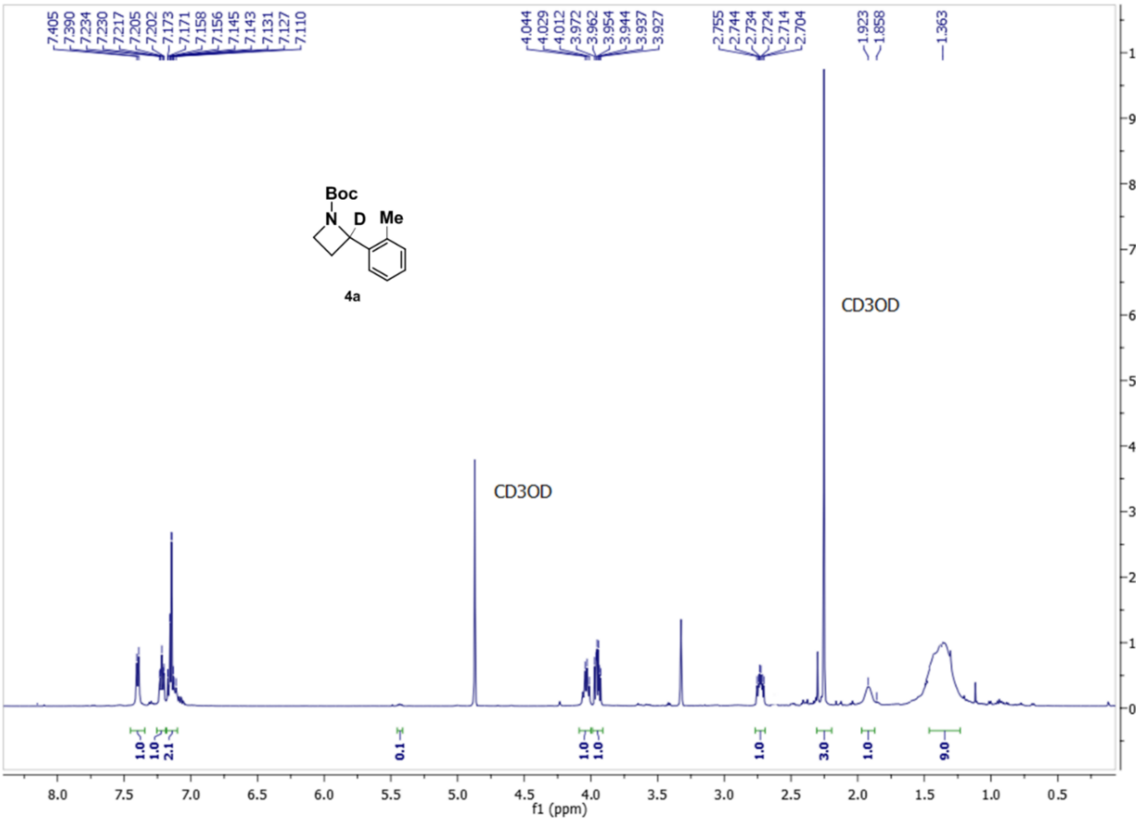


HRMS of N-Boc azetidines **1b-d**

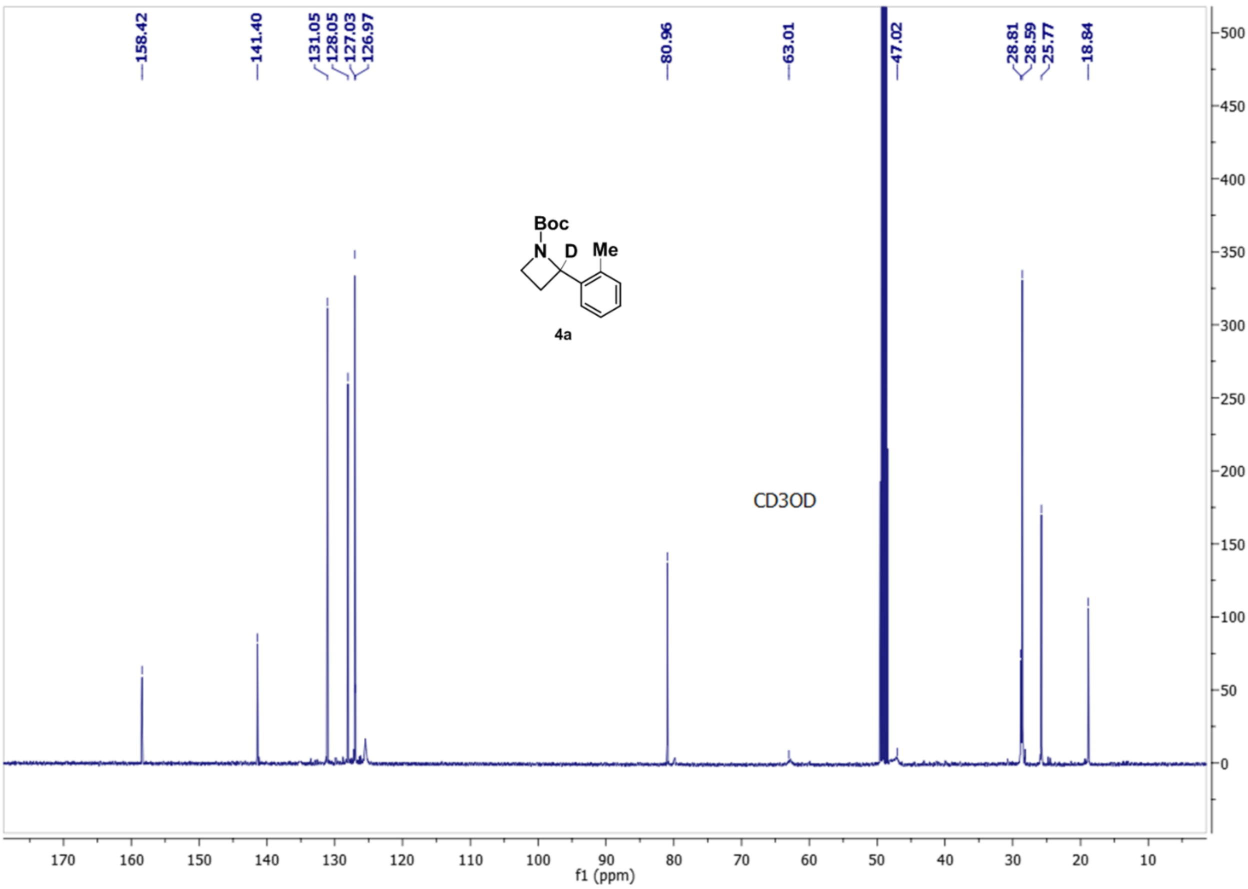

A
[M+Na]+
[2M+Na]+
M =
Cl
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
290.0923
291.0960
292.0915
293.0940
290.0918
291.0952
292.0890
293.0922


A
B
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
332.1621
333.1651
334.1697
332.1621
333.1654
334.1688

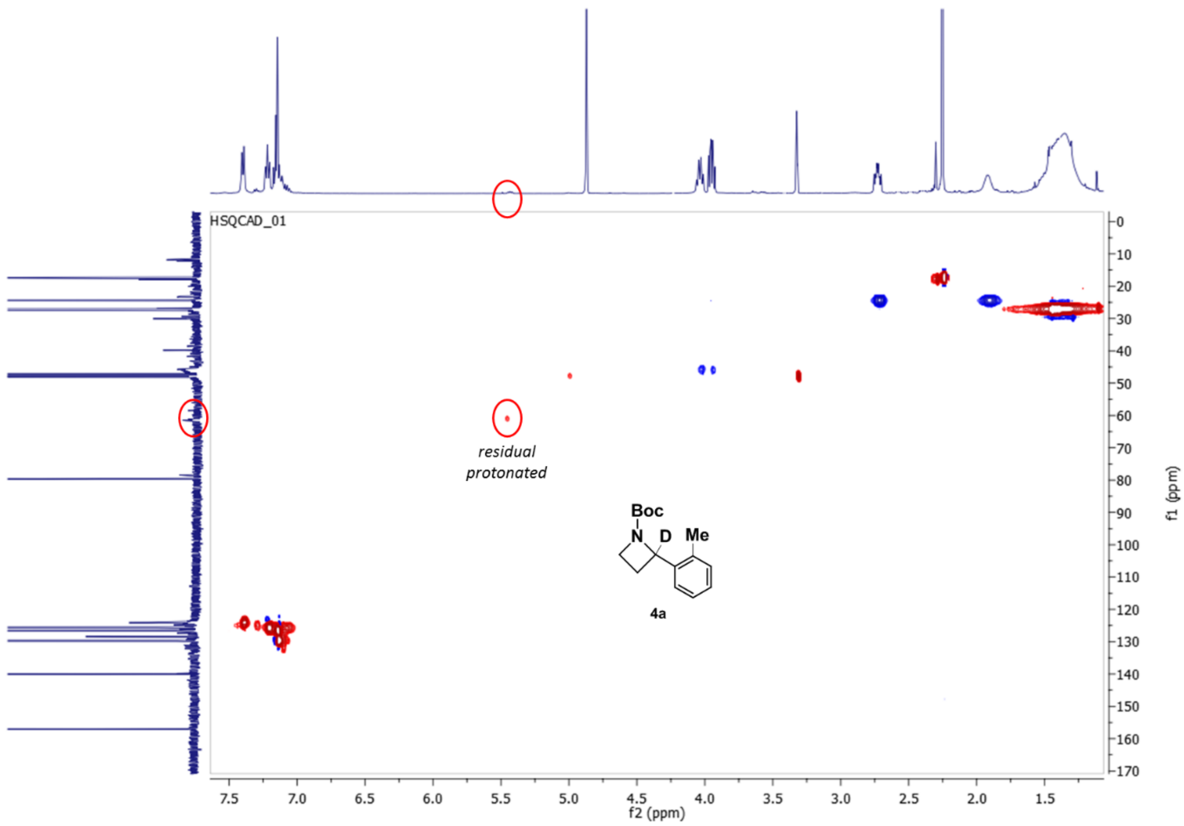

B
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
270.1468
271.1497
272.1604
270.1465
271.1498
272.1532

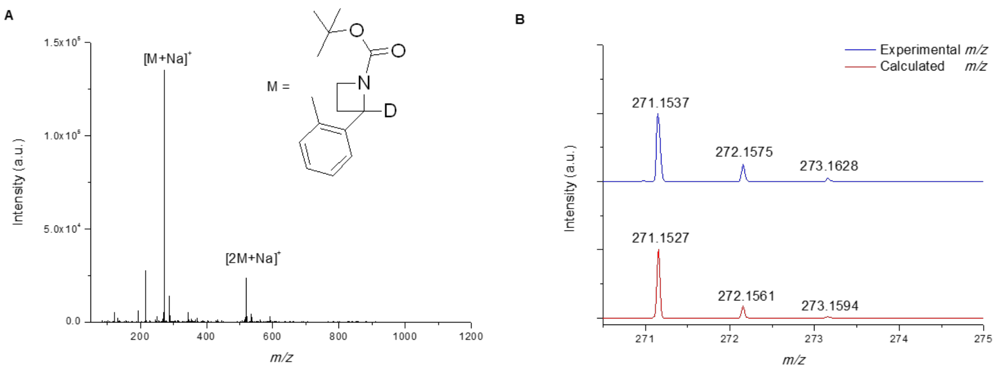


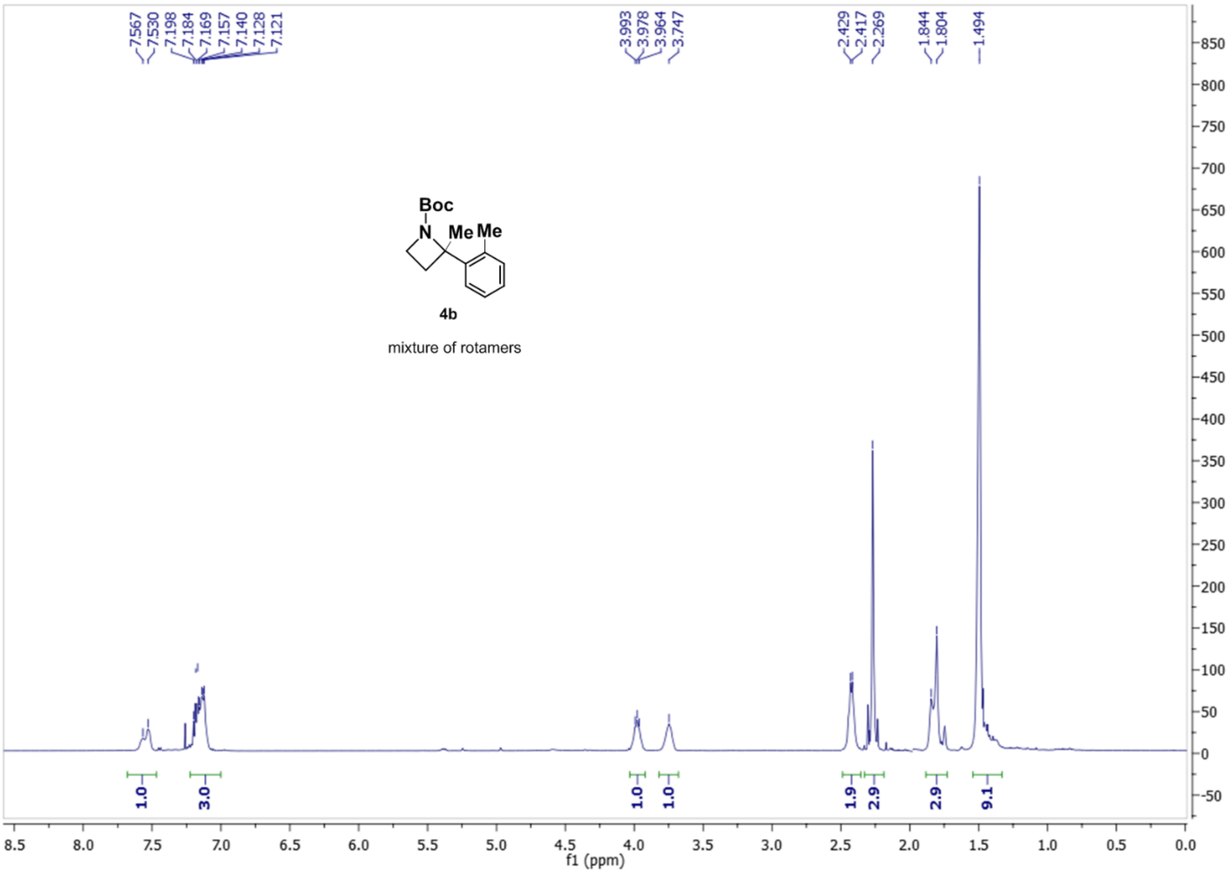
7.405
7.390
7.234
7.230
7.217
7.205
7.202
7.173
7.171
7.158
7.156
7.145
7.143
7.131
7.127
7.110
4.044
4.029
4.012
3.972
3.962
3.954
3.944
3.937
3.927
2.755
2.744
2.734
2.724
2.714
2.704
1.923
1.858
1.363
Boc
N
D
Me
4a
CD3OD
CD3OD
1.0
1.0
2.1
0.1
1.0
1.0
1.0
3.0
1.0
9.0
f1 (ppm)



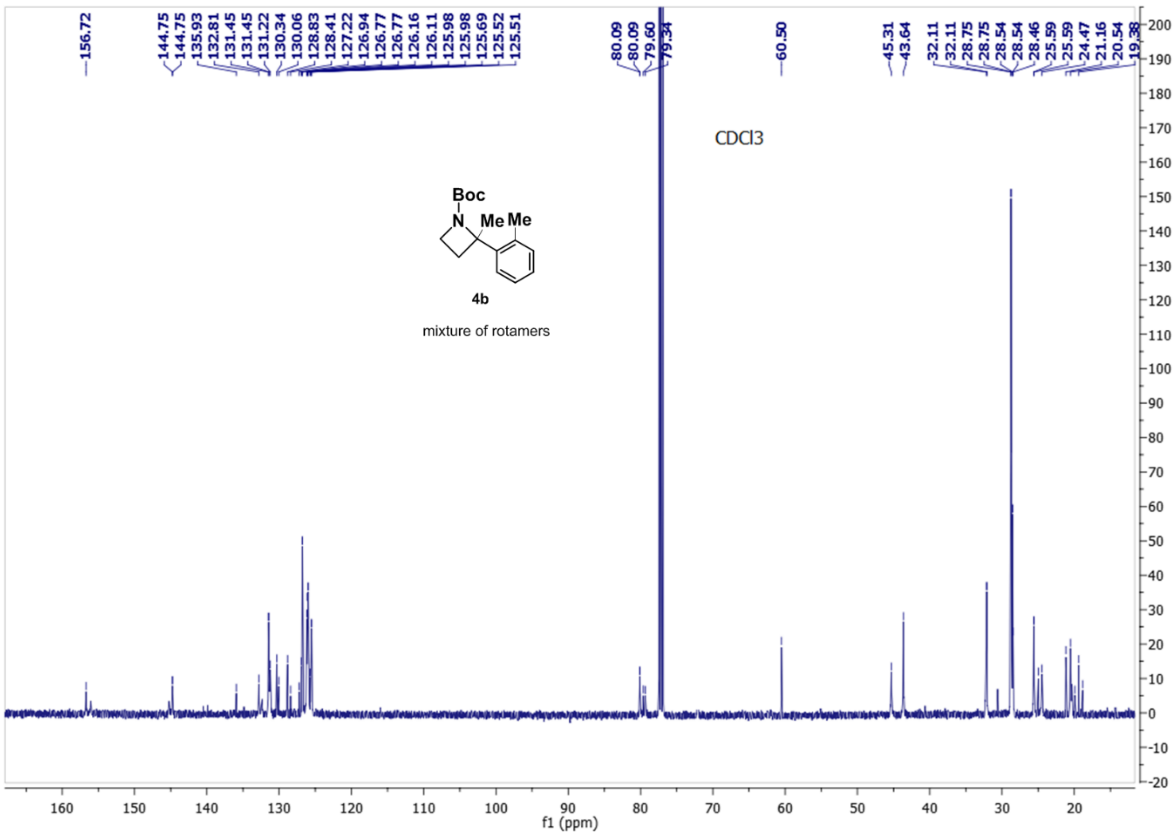
158.42
141.40
131.05
128.05
127.03
126.97
80.96
63.01
47.02
28.81
28.59
25.77
18.84
Boc
N
D
Me
4a
CD3OD
f1 (ppm)


HSQCAD_01
residual
protonated
Boc
N
D
Me
4a
f2 (ppm)
f1 (ppm)

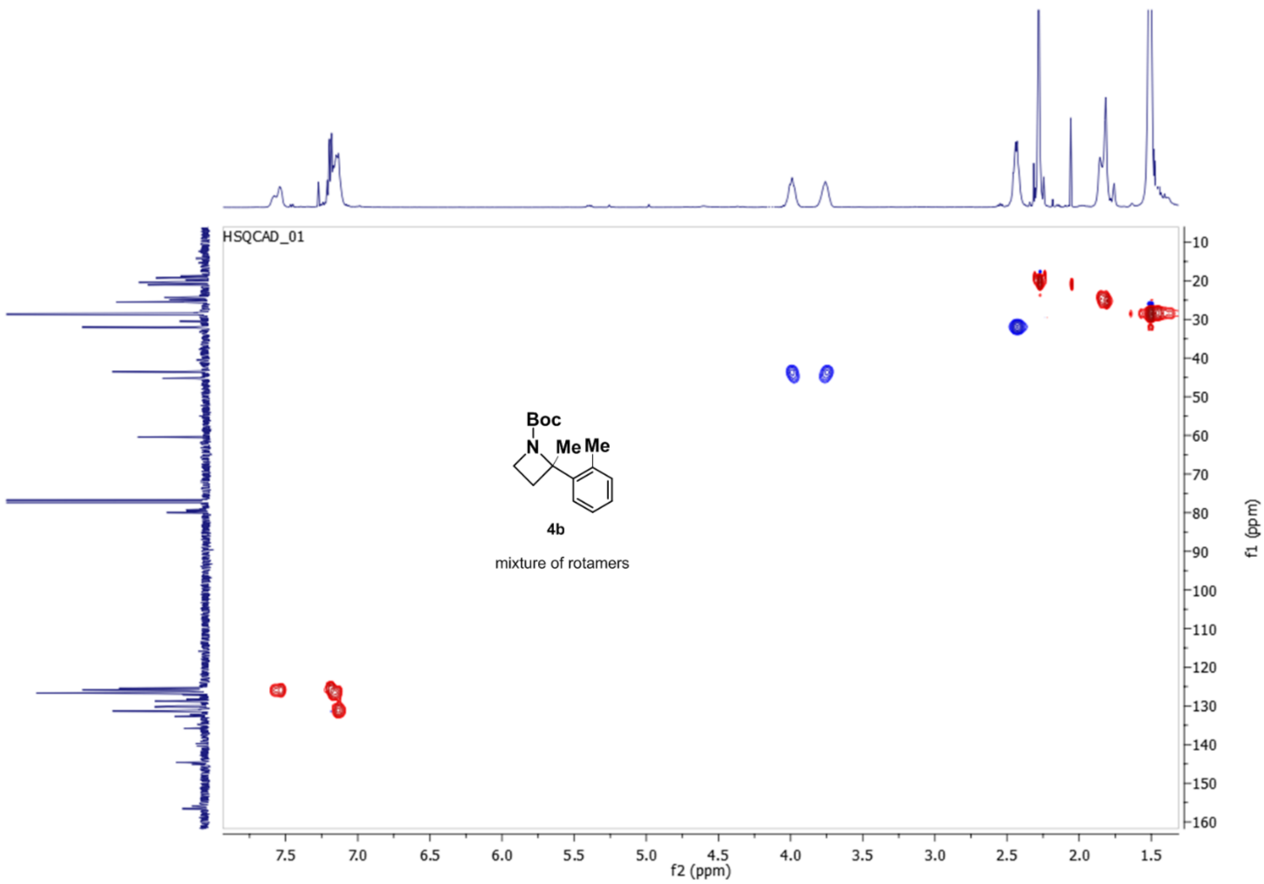

A
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
271.1537
272.1575
273.1628
271.1527
272.1561
273.1594
Intensity (a.u.)
m/z

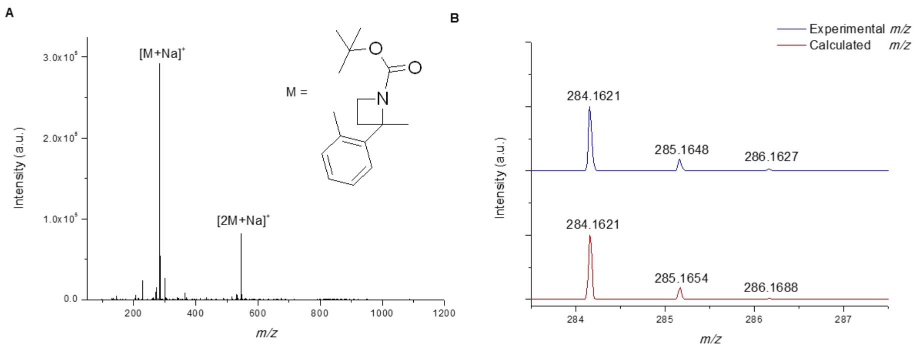


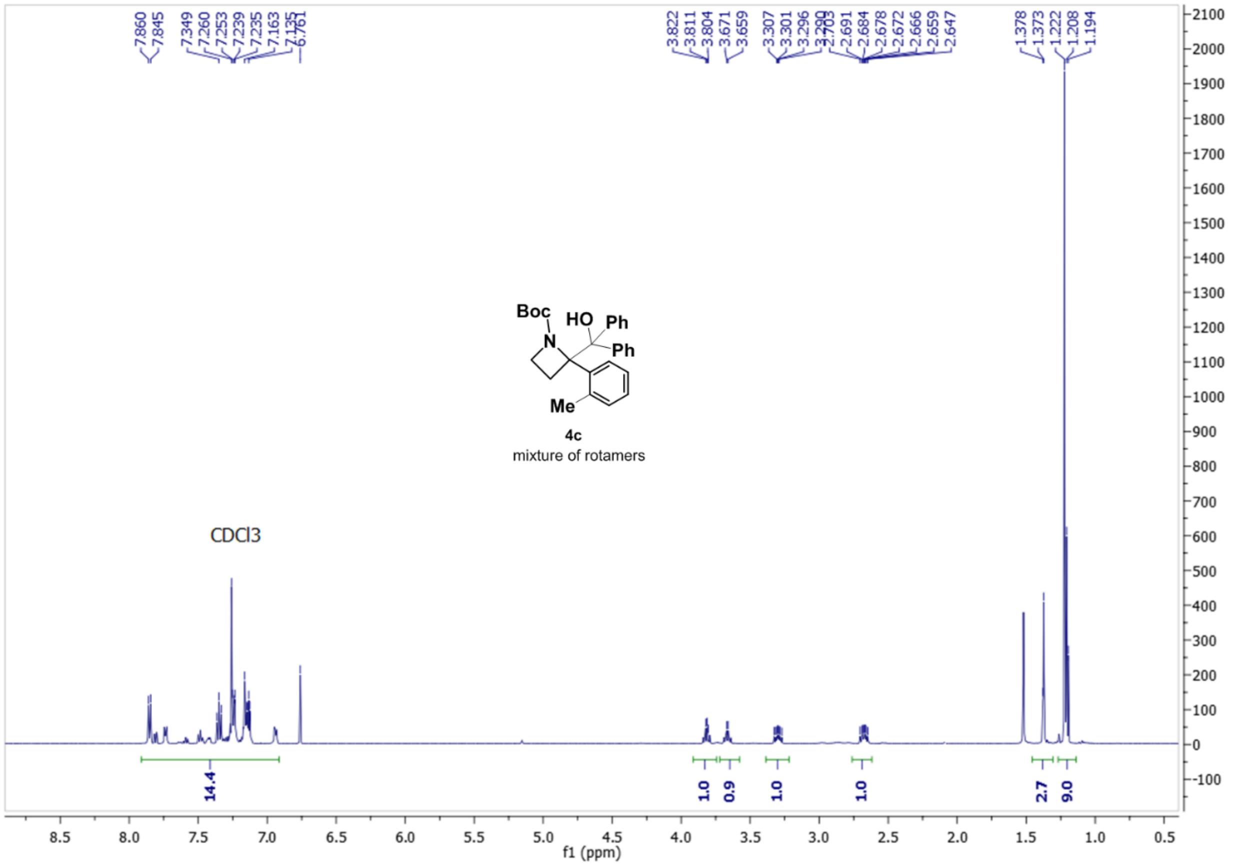
7.567
7.530
7.198
7.184
7.169
7.157
7.140
7.128
7.121
3.993
3.978
3.964
3.747
2.429
2.417
2.269
1.844
1.804
1.494
Boc
N
Me
Me
4b
mixture of rotamers
1.0
3.0
1.0
1.0
1.9
2.9
2.9
9.1
f1 (ppm)

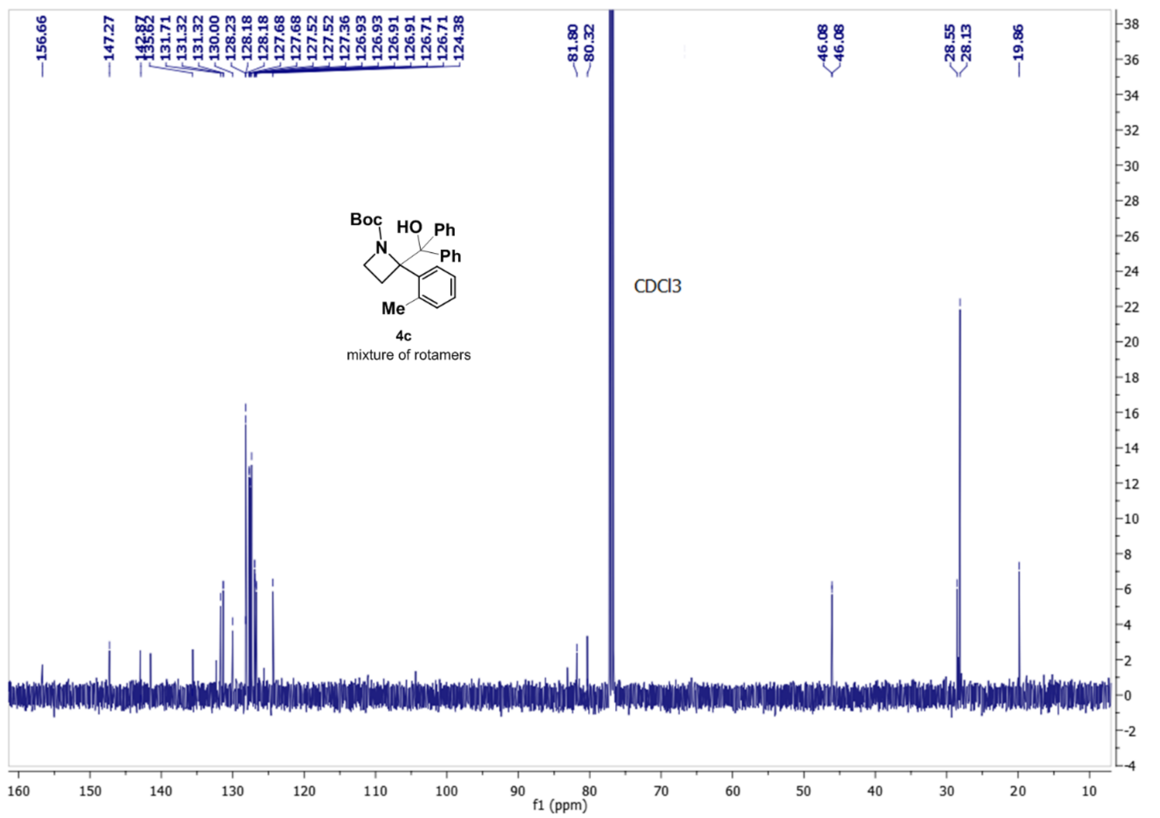


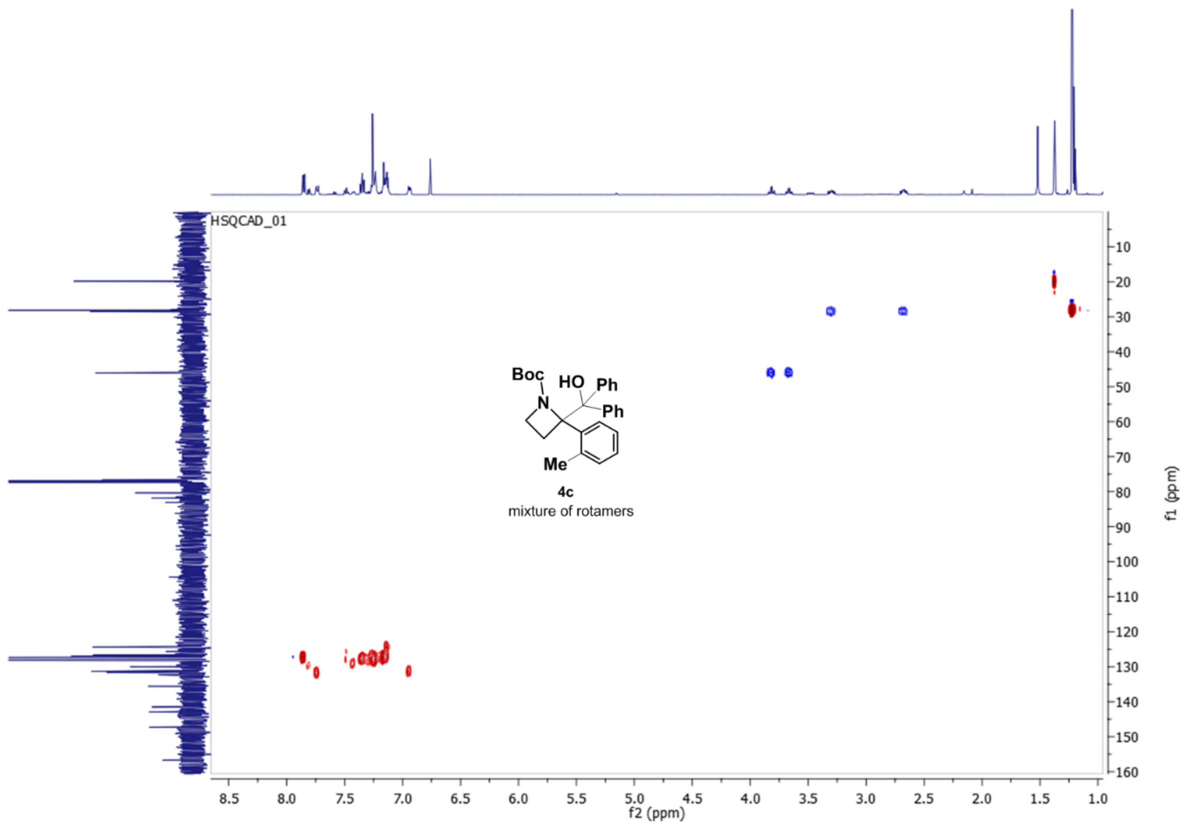
156.72
144.75
144.75
135.93
132.81
131.45
131.45
131.22
130.34
130.06
128.83
128.41
127.22
126.94
126.77
126.77
126.16
126.11
125.98
125.98
125.69
125.52
125.51
80.09
80.09
79.60
79.34
60.50
45.31
43.64
32.11
32.11
28.75
28.75
28.54
28.54
28.46
25.59
25.59
24.47
21.16
20.54
19.38
CDCl3
Boc
N
Me
Me
4b
mixture of rotamers
f1 (ppm)

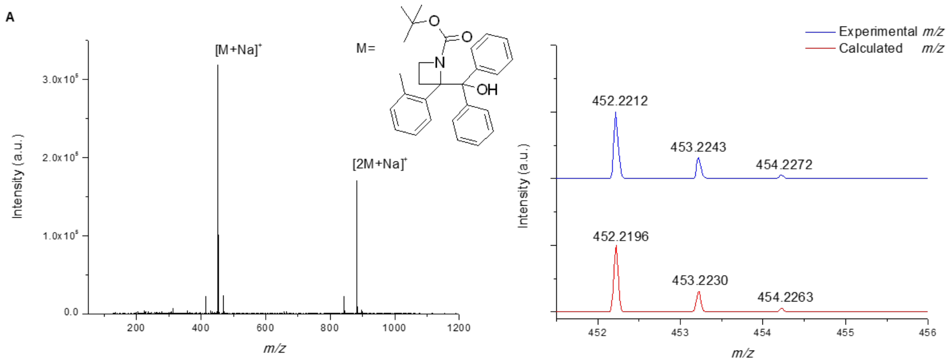

HSQCAD_01
Boc
N
Me
Me
4b
mixture of rotamers
f2 (ppm)
f1 (ppm)

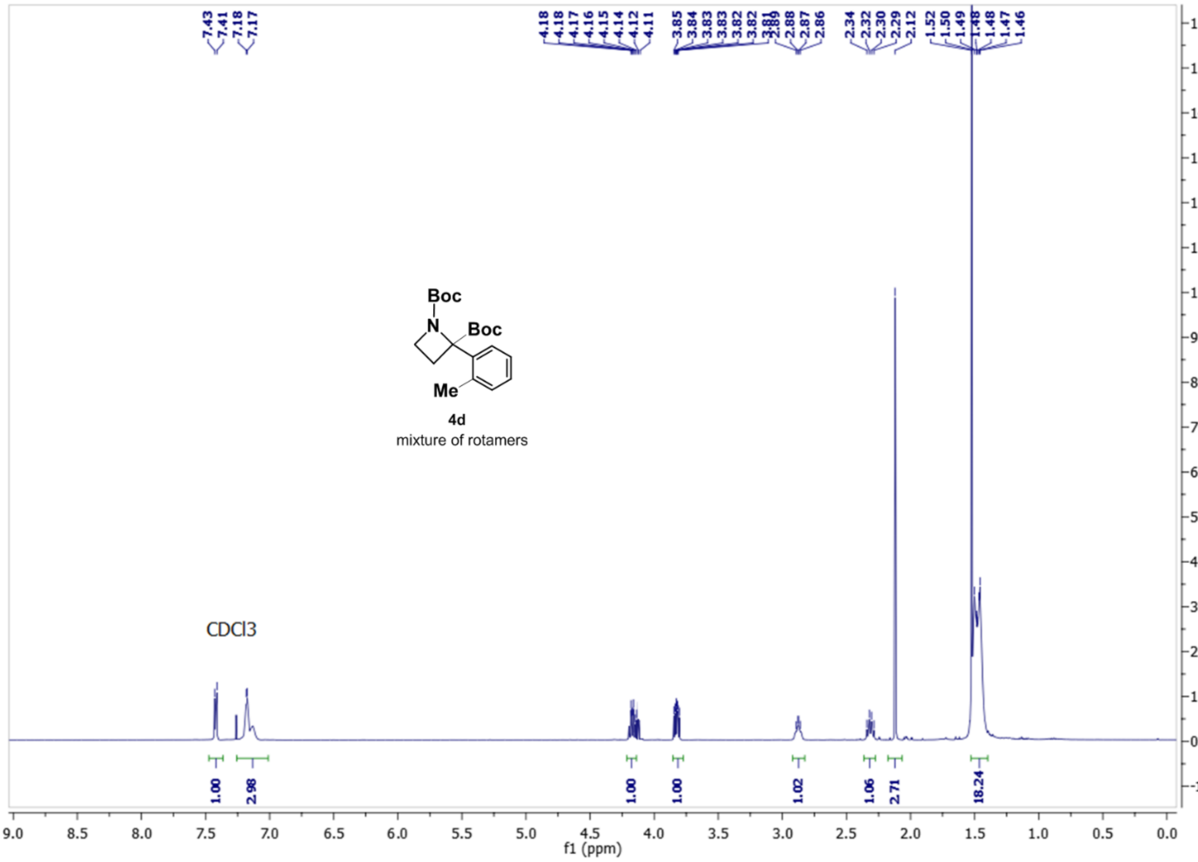

A
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
284.1621
285.1648
286.1627
284.1621
285.1654
286.1688
Intensity (a.u.)
m/z


Boc
N
HO
Ph
Ph
Me
4c
mixture of rotamers
CDCl3
f1 (ppm)

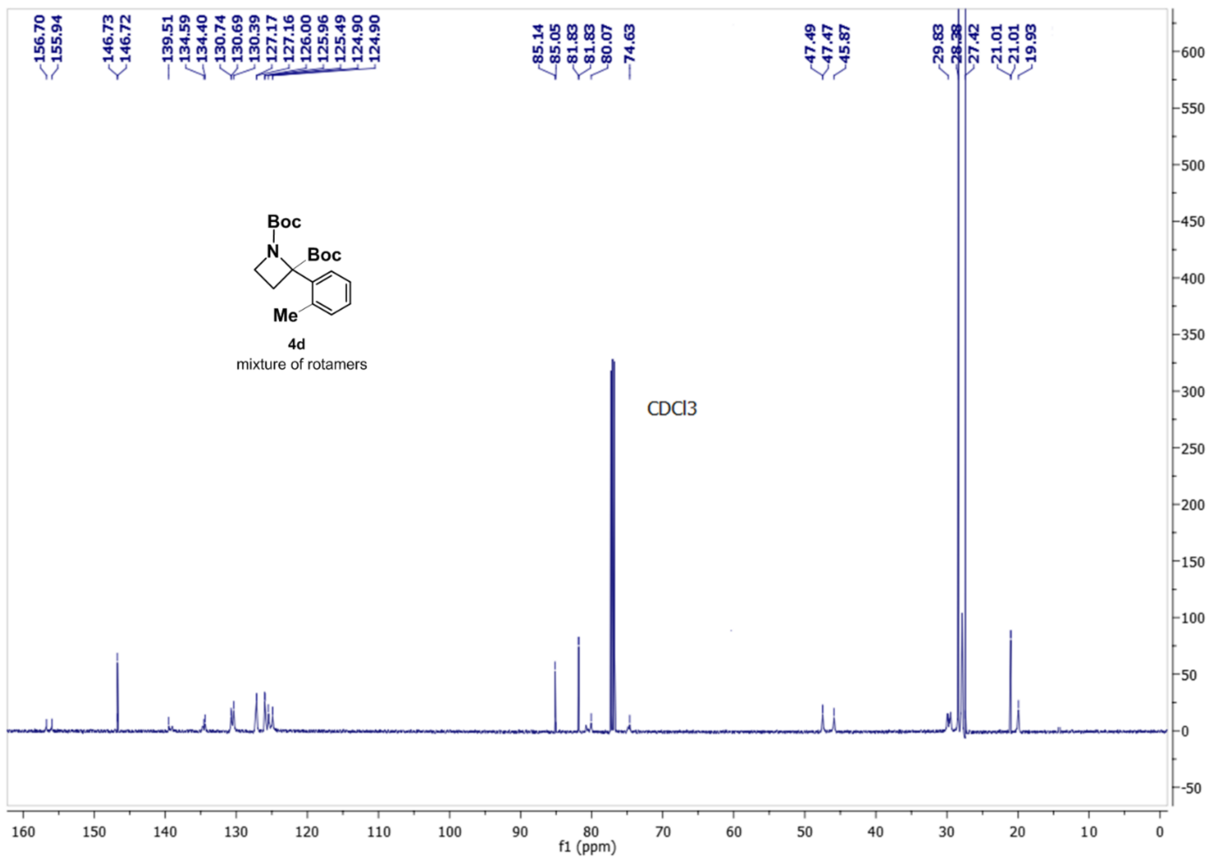

Boc
N
HO
Ph
Ph
Me
4c
mixture of rotamers
CDCl3
f1 (ppm)


HSQCAD_01
Boc
HO
Ph
N
Ph
Me
4c
mixture of rotamers
f1 (ppm)
f2 (ppm)

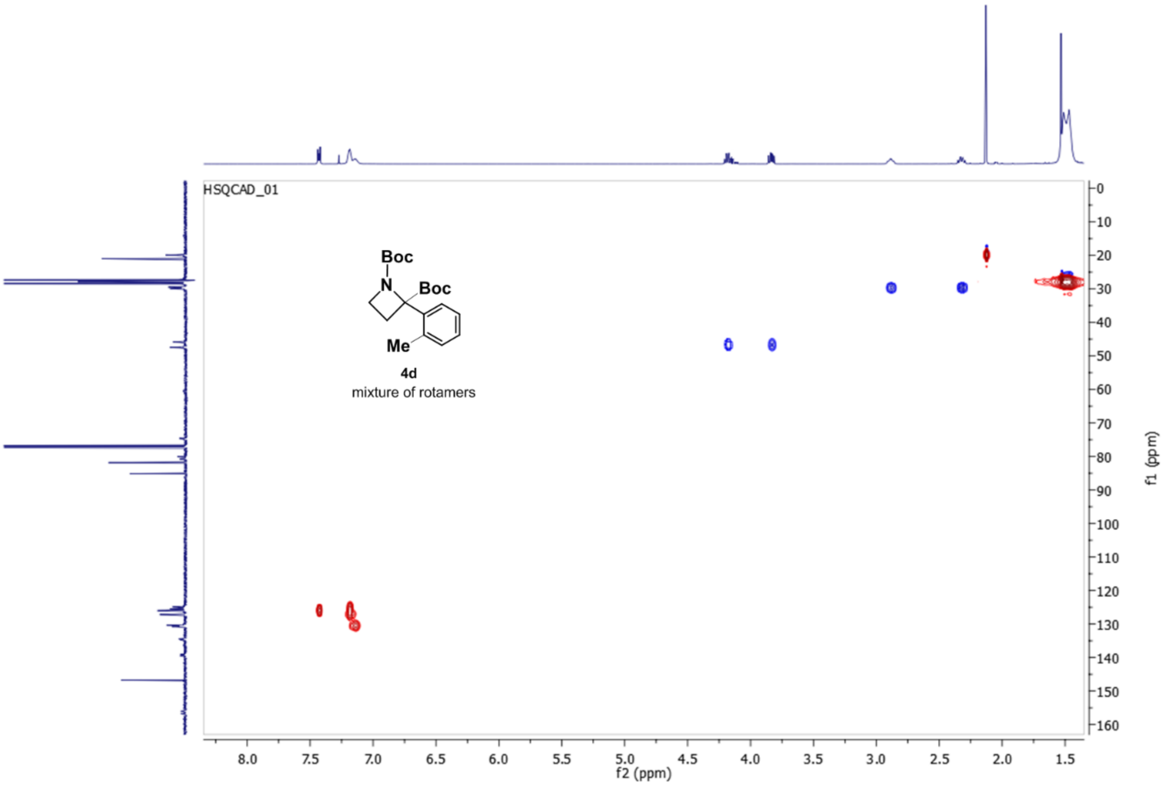

A
[M+Na]+
[2M+Na]+
M=
N
O
OH
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
452.2212
453.2243
454.2272
452.2196
453.2230
454.2263

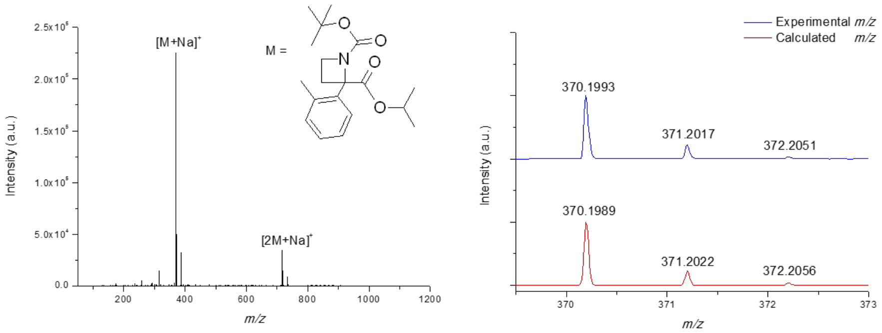


7.43
7.41
7.18
7.17
4.18
4.18
4.17
4.16
4.15
4.14
4.12
4.11
3.85
3.84
3.83
3.83
3.82
3.82
2.88
2.87
2.86
2.34
2.32
2.30
2.29
2.12
1.52
1.50
1.49
1.48
1.48
1.47
1.46
Boc
N
Boc
Me
4d
mixture of rotamers
CDCl3
1.00
2.98
1.00
1.00
1.02
1.06
2.71
18.24
f1 (ppm)

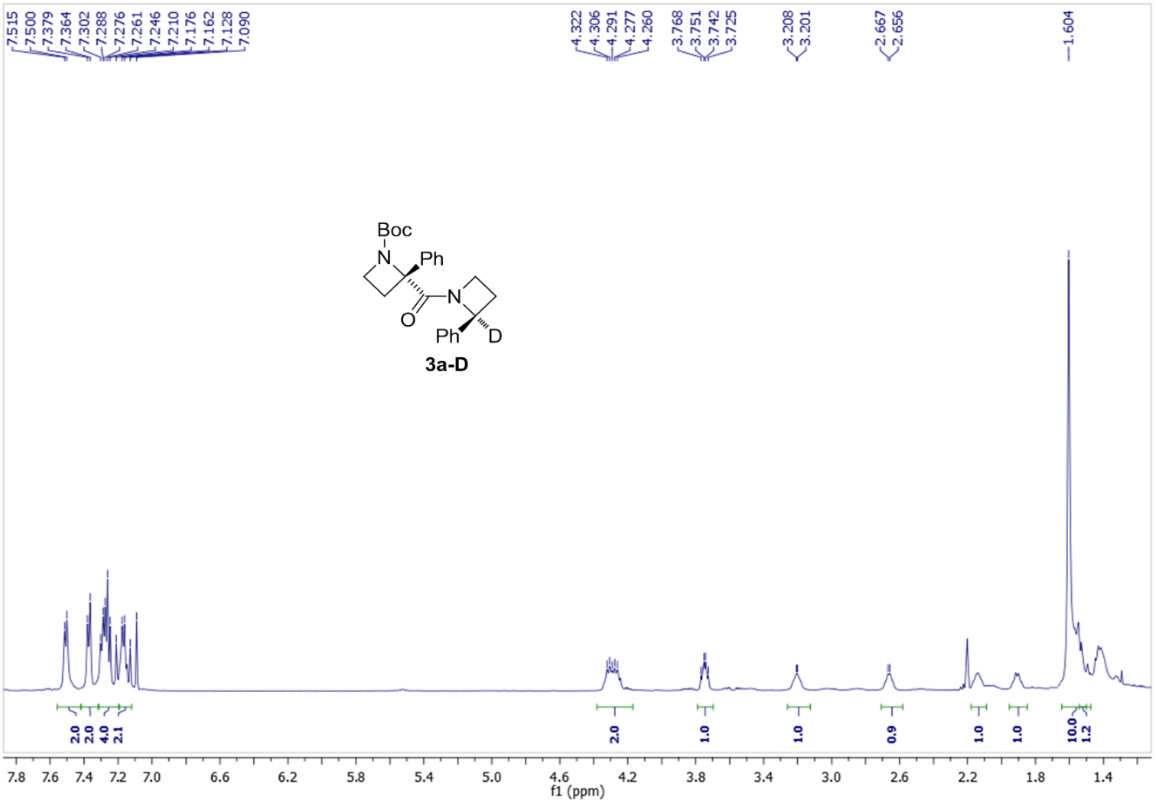


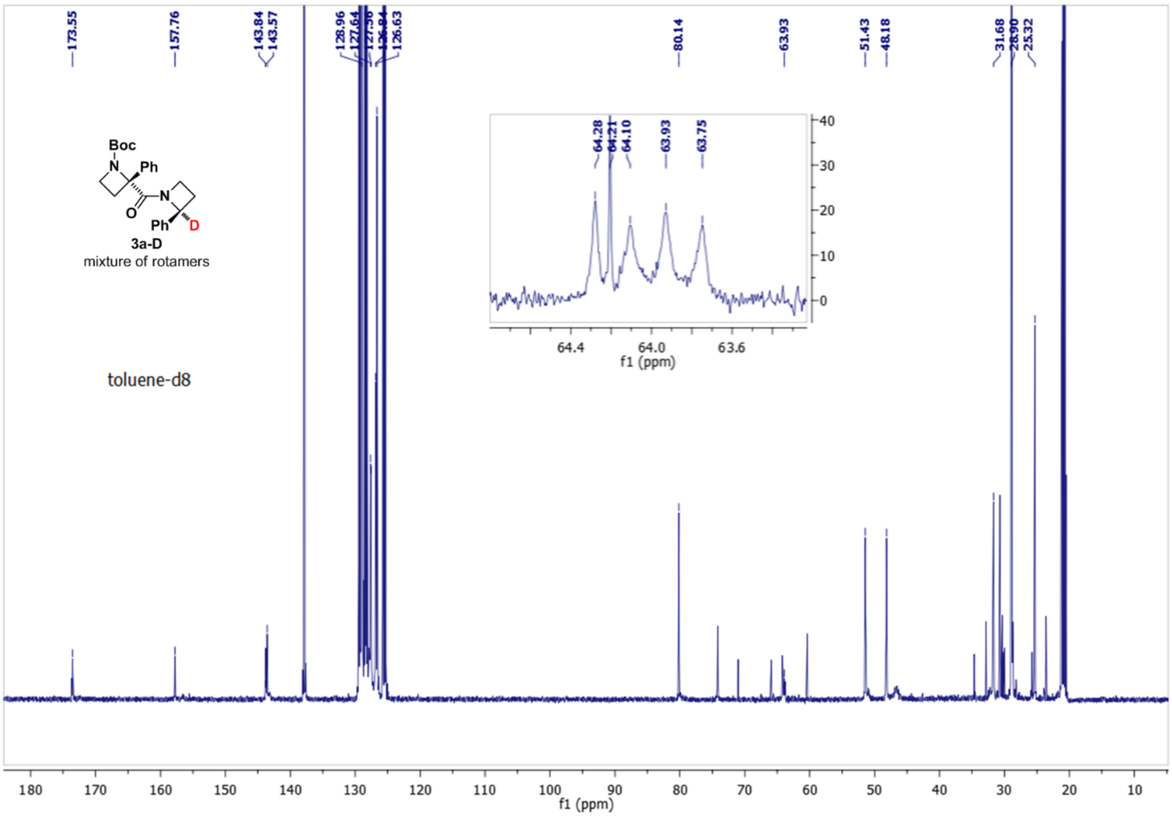
156.70
155.94
146.73
146.72
139.51
134.59
134.40
130.74
130.69
130.39
127.17
127.16
126.00
125.96
125.49
124.90
124.90
85.14
85.05
81.83
81.83
80.07
74.63
47.49
47.47
45.87
29.83
27.42
21.01
21.01
19.93
Boc
N
Boc
Me
4d
mixture of rotamers
CDCl3
f1 (ppm)

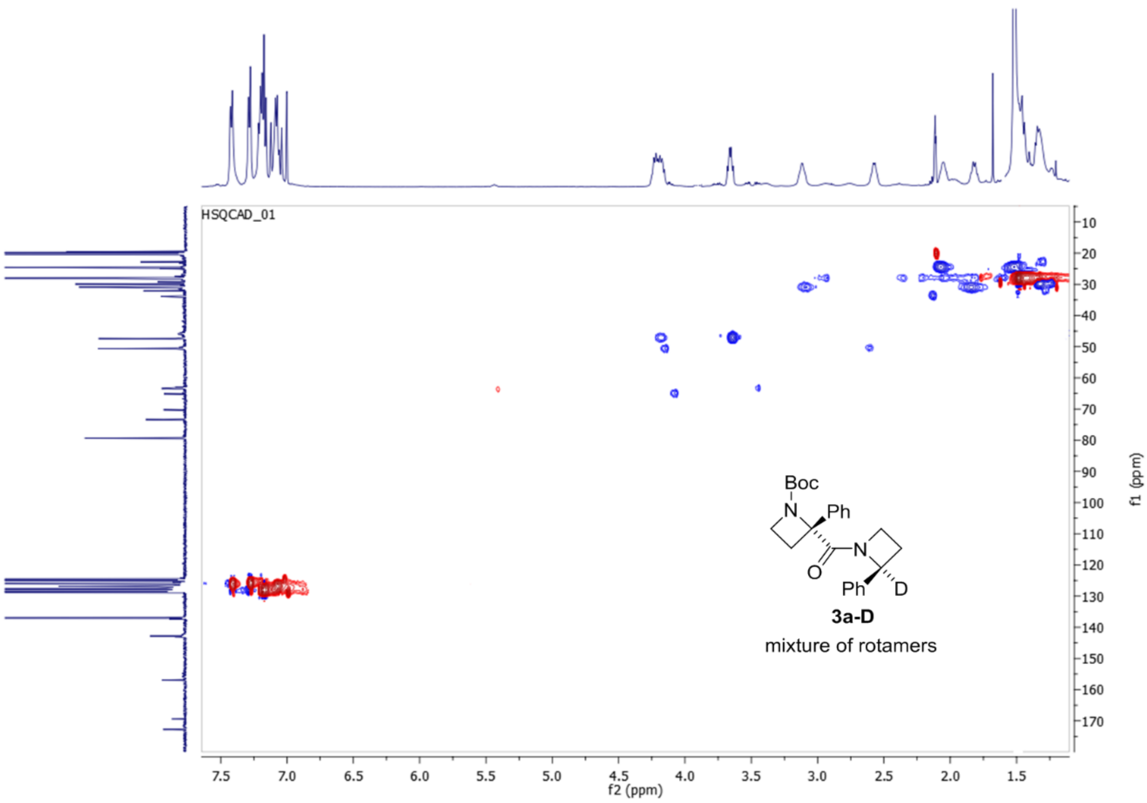

HSQCAD_01
Boc
N
Boc
Me
4d
mixture of rotamers
f2 (ppm)
f1 (ppm)

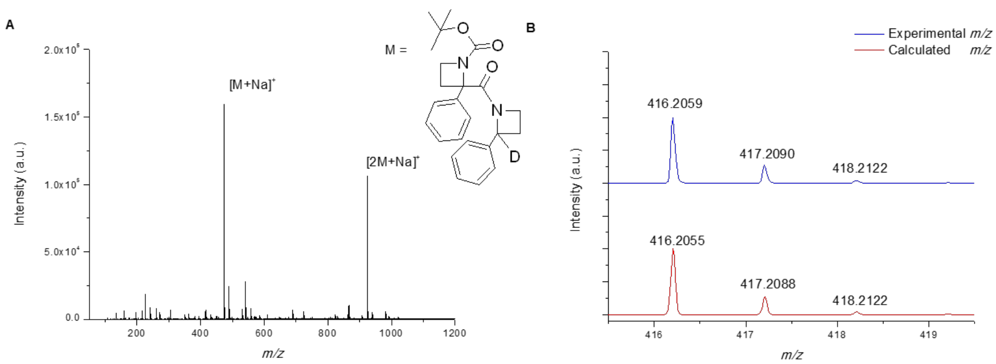

[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
370.1993
371.2017
372.2051
370.1989
371.2022
372.2056

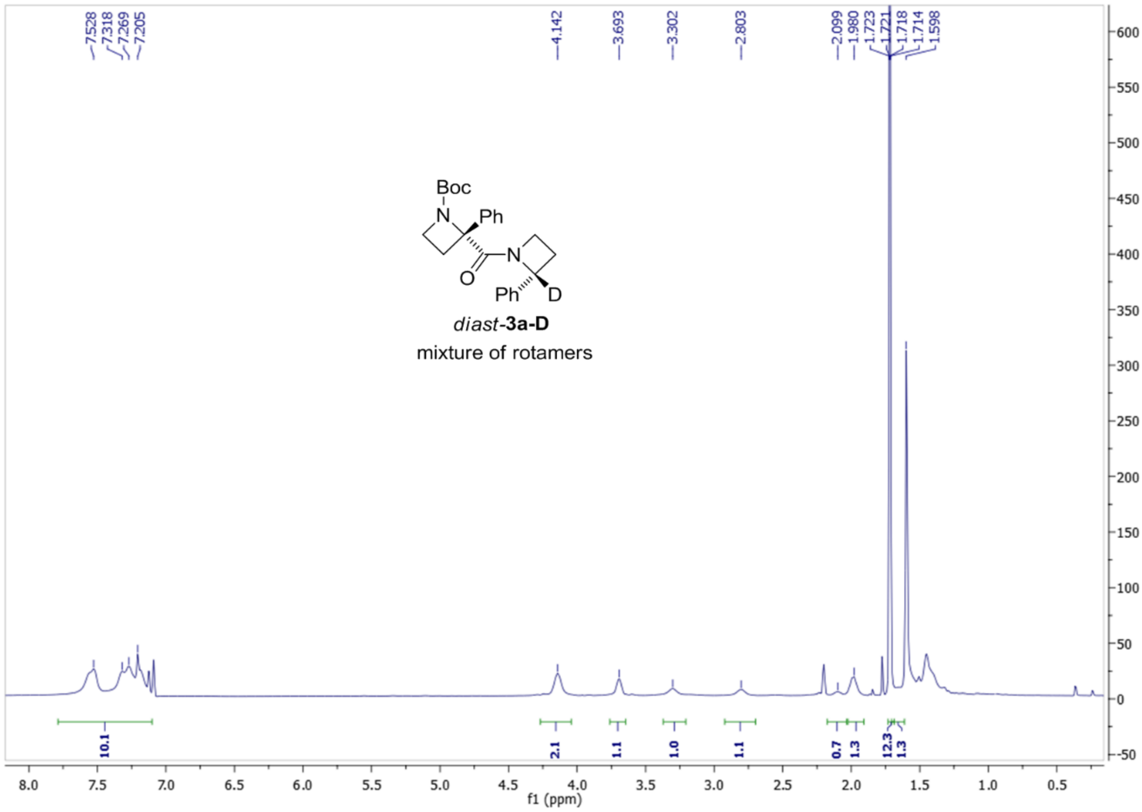
Dimeric azetidines



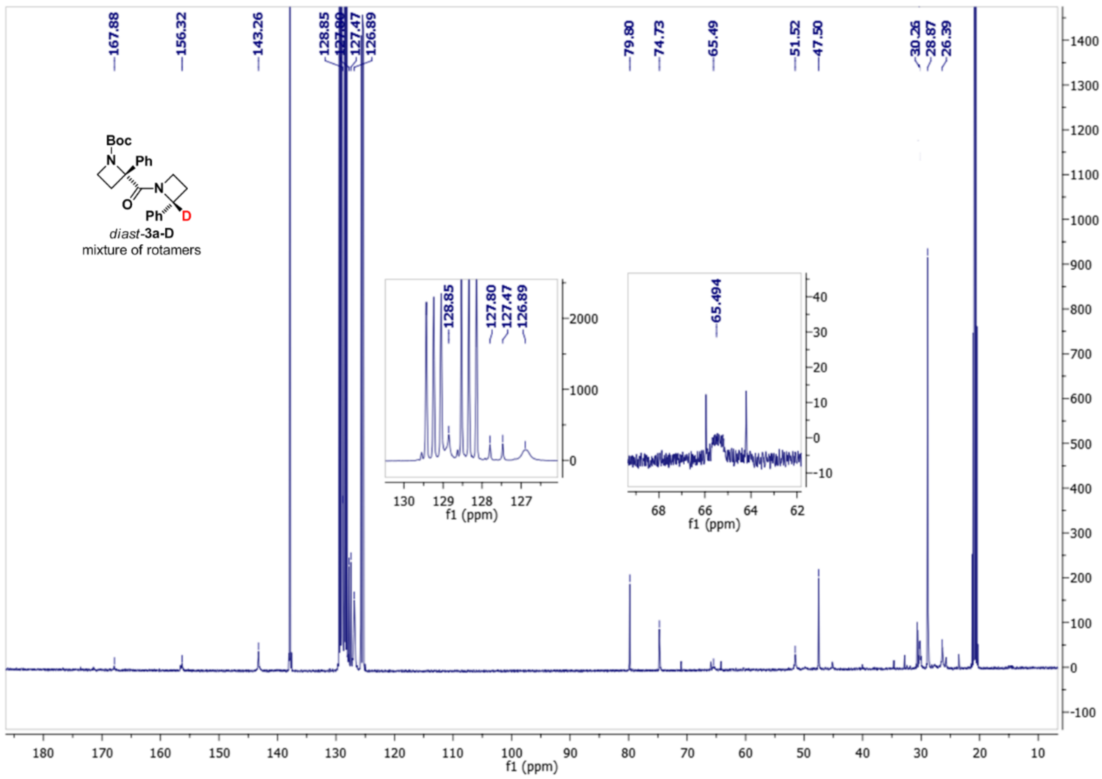



HSQCAD_01
Boc
N
Ph
O
N
Ph
D
3a-D
mixture of rotamers
f2 (ppm)
f1 (ppm)

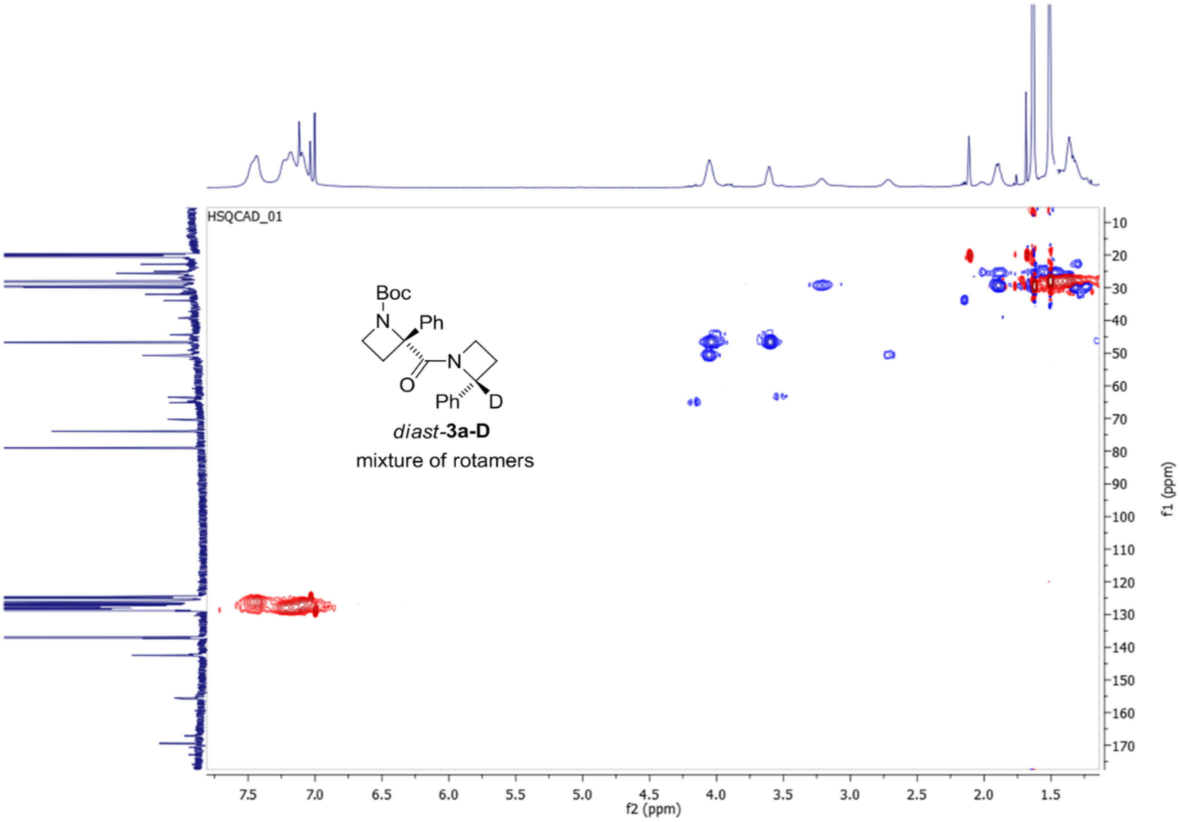

A
B
M =
[M+Na]+
[2M+Na]+
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
416.2059
417.2090
418.2122
416.2055
417.2088
418.2122

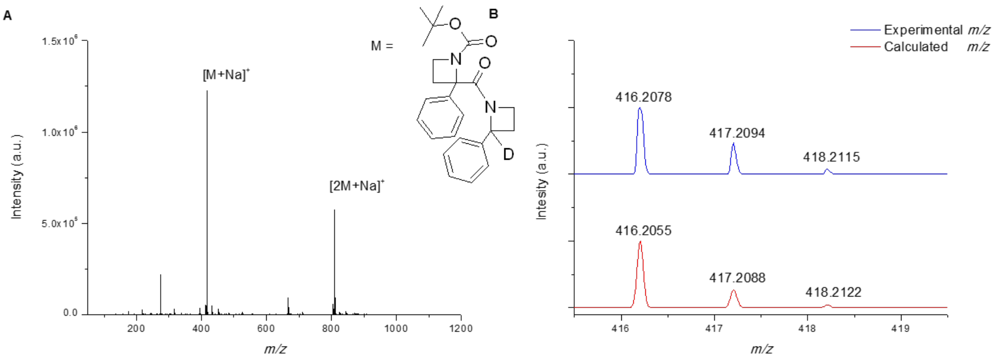


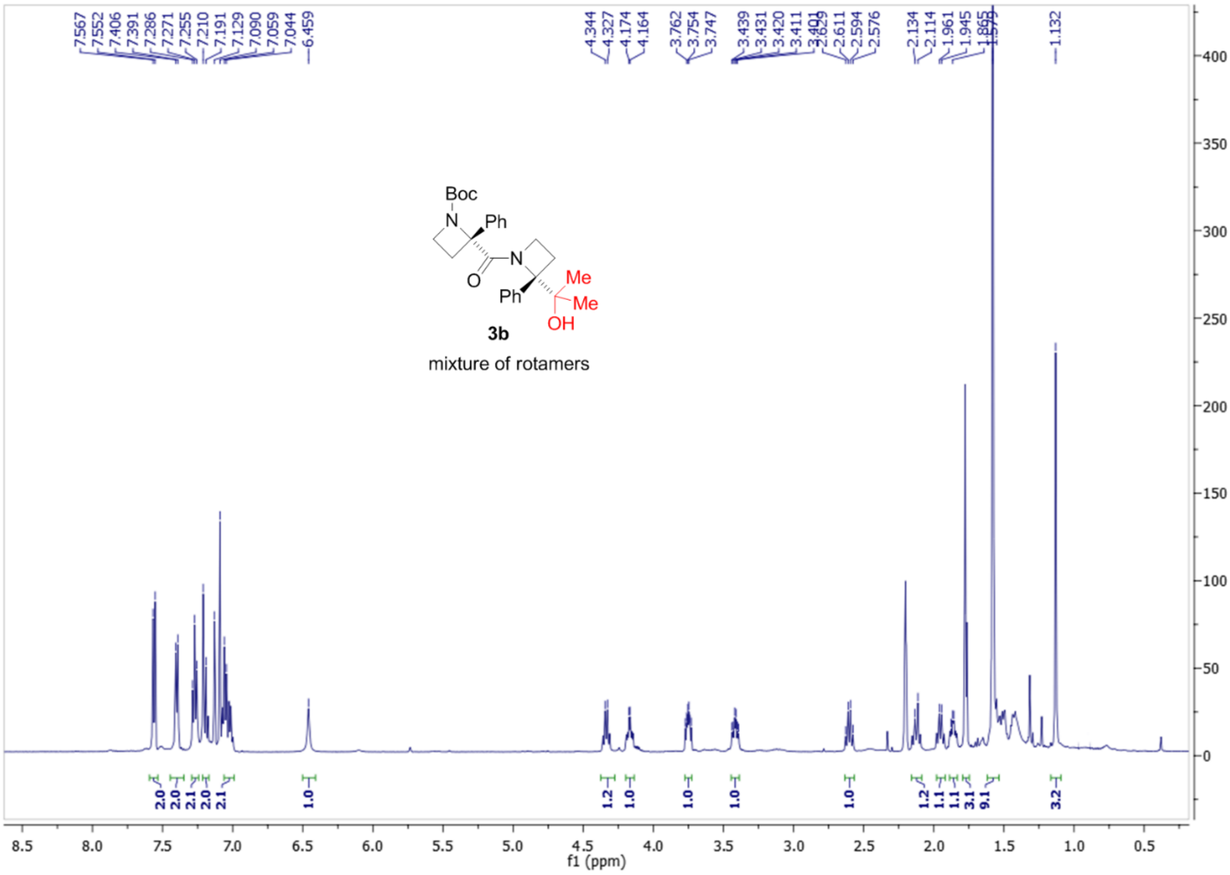
Boc
N
Ph
N
O
Ph
D
diast-3a-D
mixture of rotamers
7.528
7.318
7.269
7.205
4.142
3.693
3.302
2.803
2.099
1.980
1.723
1.721
1.718
1.714
1.598
10.1
2.1
1.1
1.0
1.1
0.7
1.3
12.3
1.3
f1 (ppm)

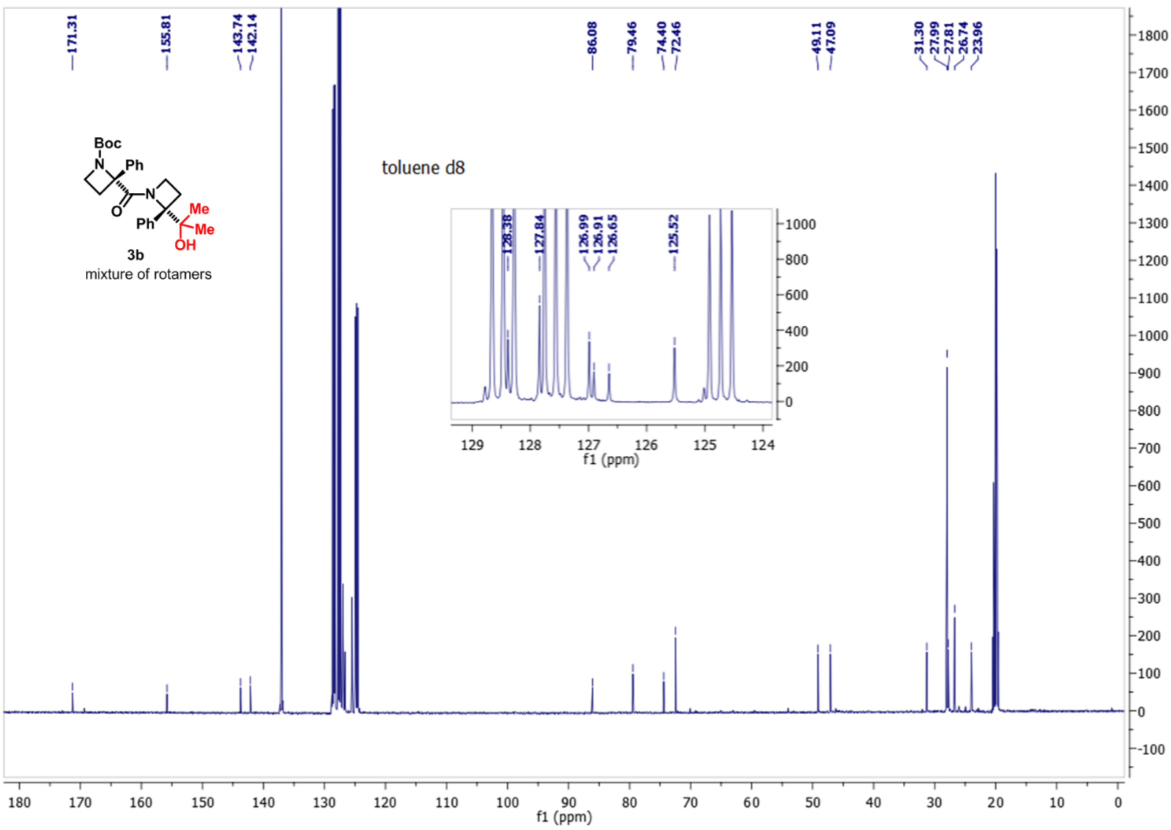


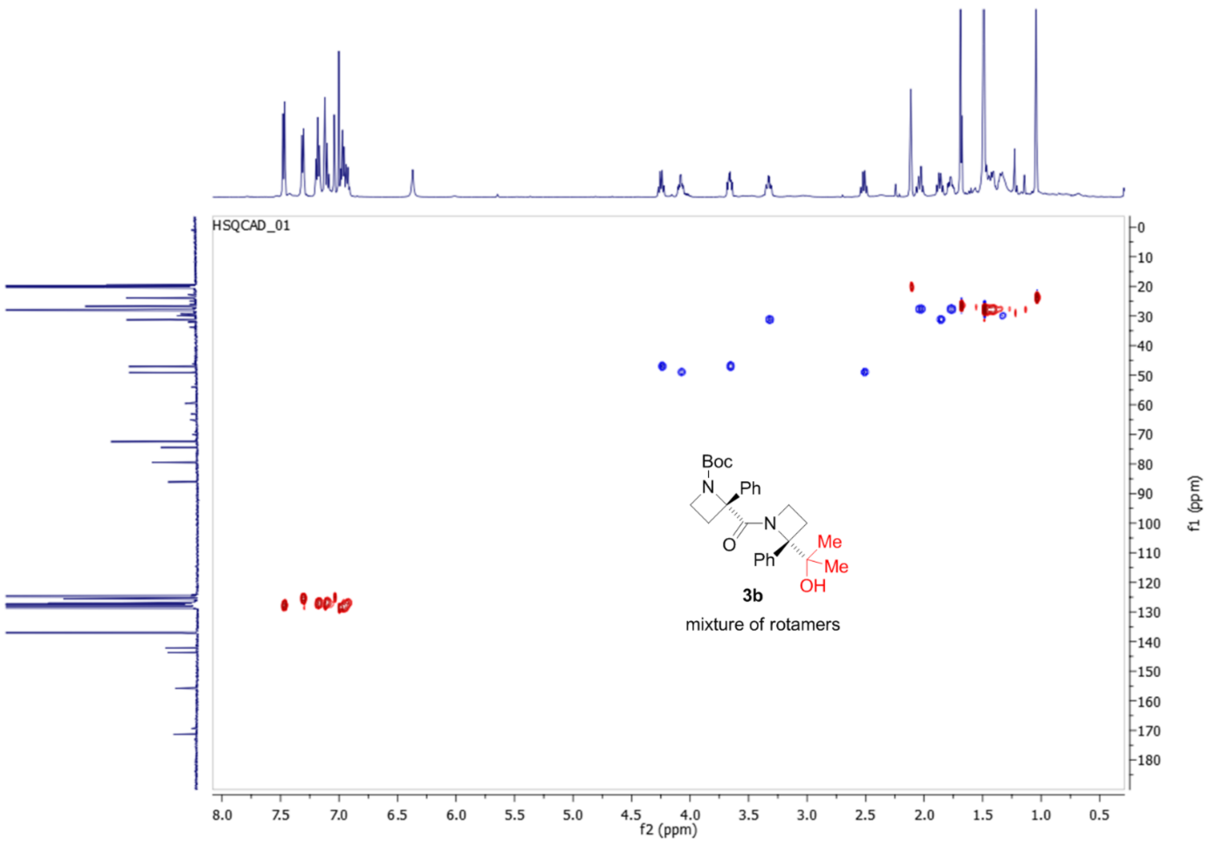
Boc
N
Ph
N
O
Ph
D
diast-3a-D
mixture of rotamers
167.88
156.32
143.26
128.85
127.47
126.89
79.80
74.73
65.49
51.52
47.50
30.26
28.87
26.39
128.85
127.80
127.47
126.89
65.494
f1 (ppm)


HSQCAD_01
Boc
N
Ph
N
O
Ph
D
diast-3a-D
mixture of rotamers
f2 (ppm)
f1 (ppm)

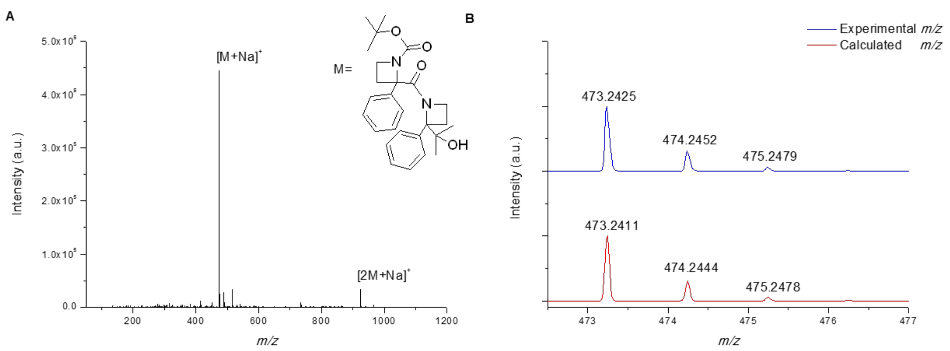

A
[M+Na]+
[2M+Na]+
Intensity (a.u.)
m/z
B
M =
Experimental m/z
Calculated m/z
416.2078
417.2094
418.2115
416.2055
417.2088
418.2122
Intesity (a.u.)
m/z



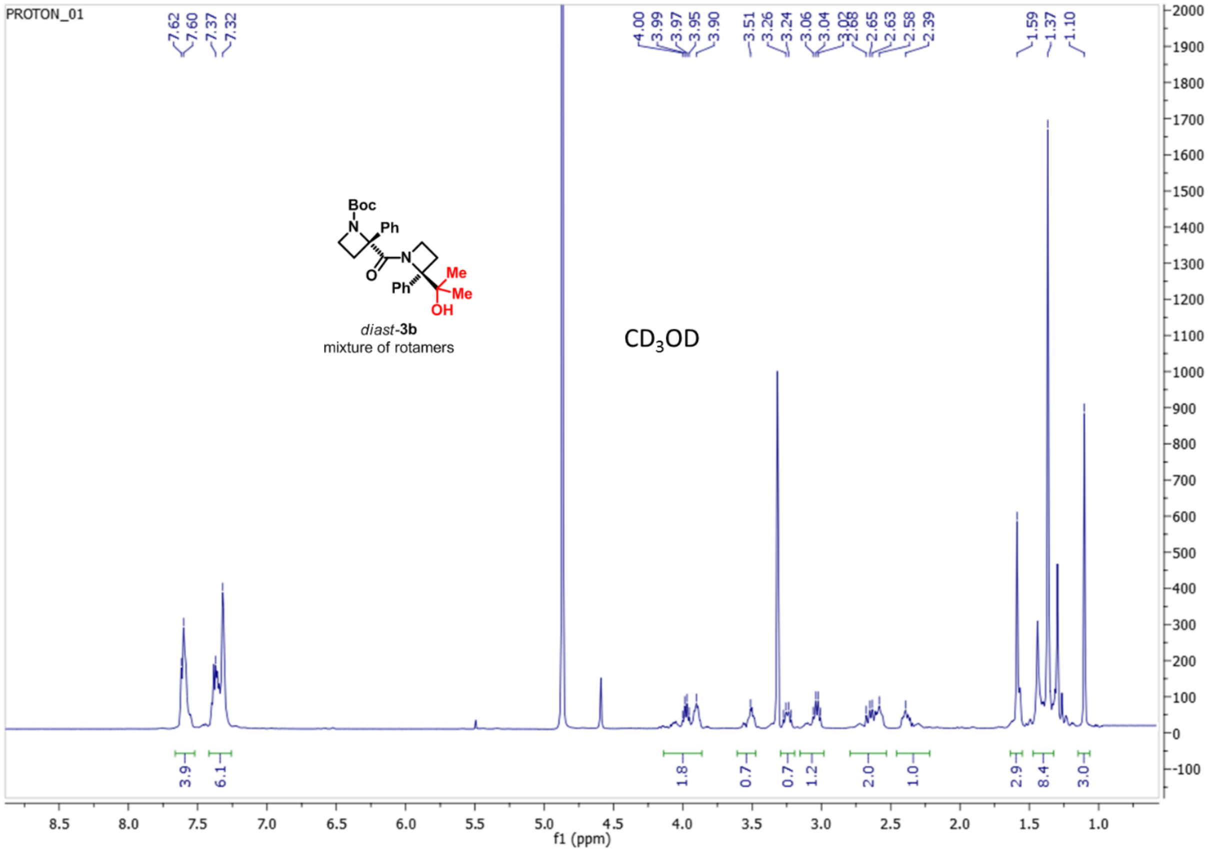


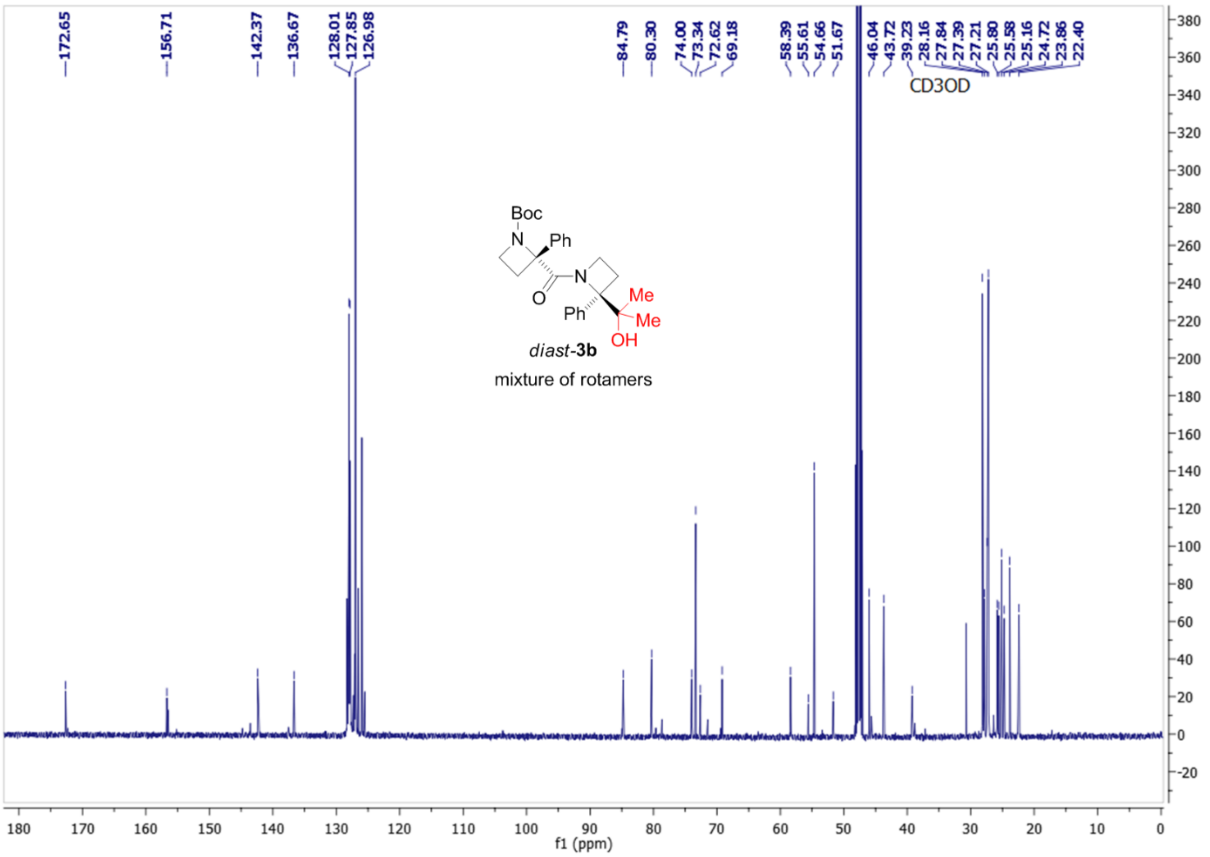


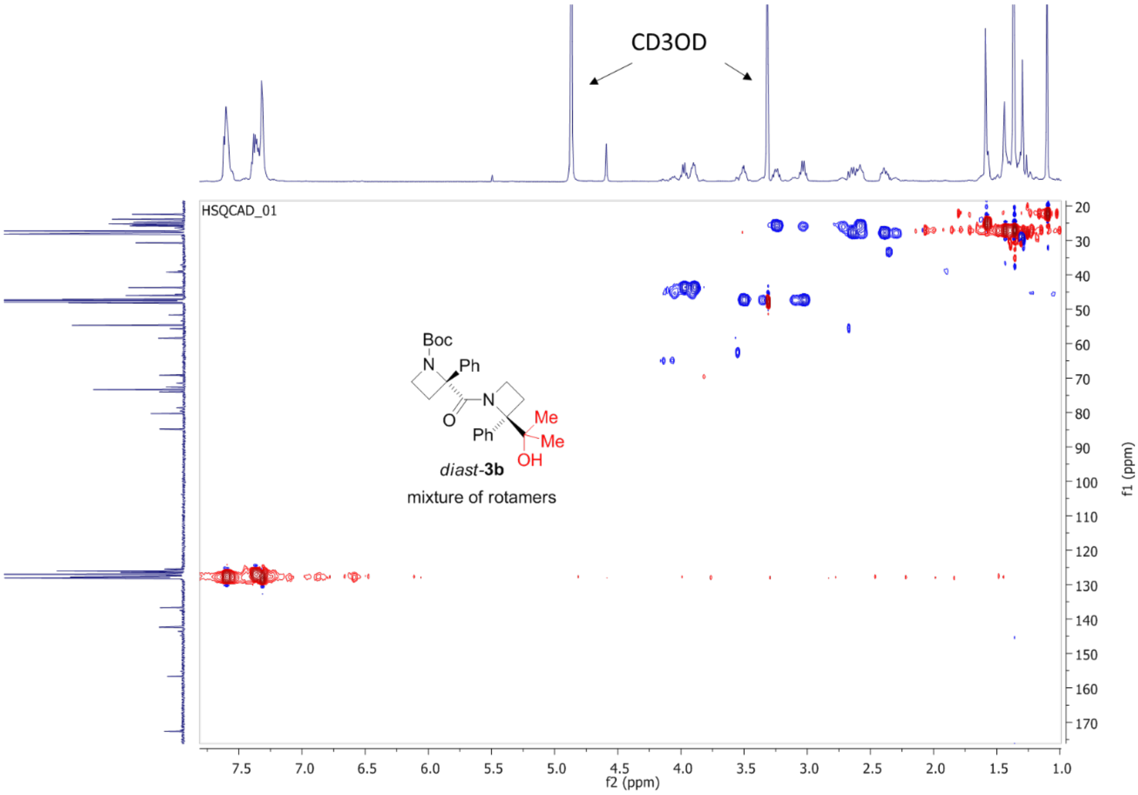
HSQCAD_01
Boc
N
Ph
O
N
Ph
Me
Me
OH
3b
mixture of rotamers
f2 (ppm)
f1 (ppm)

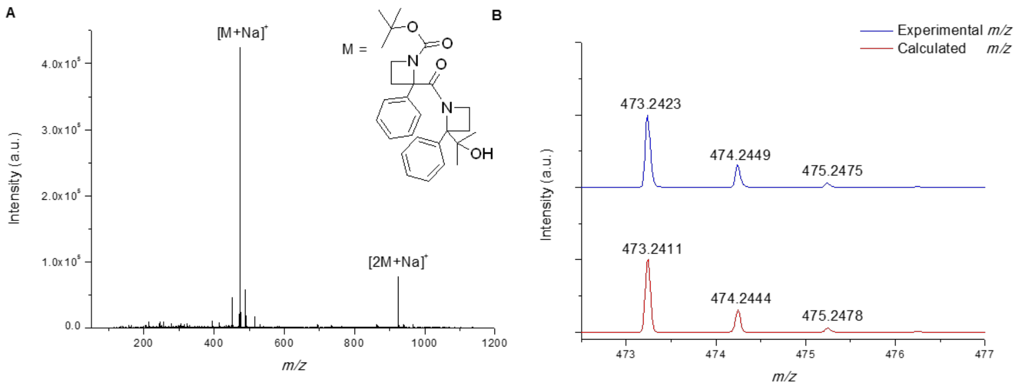


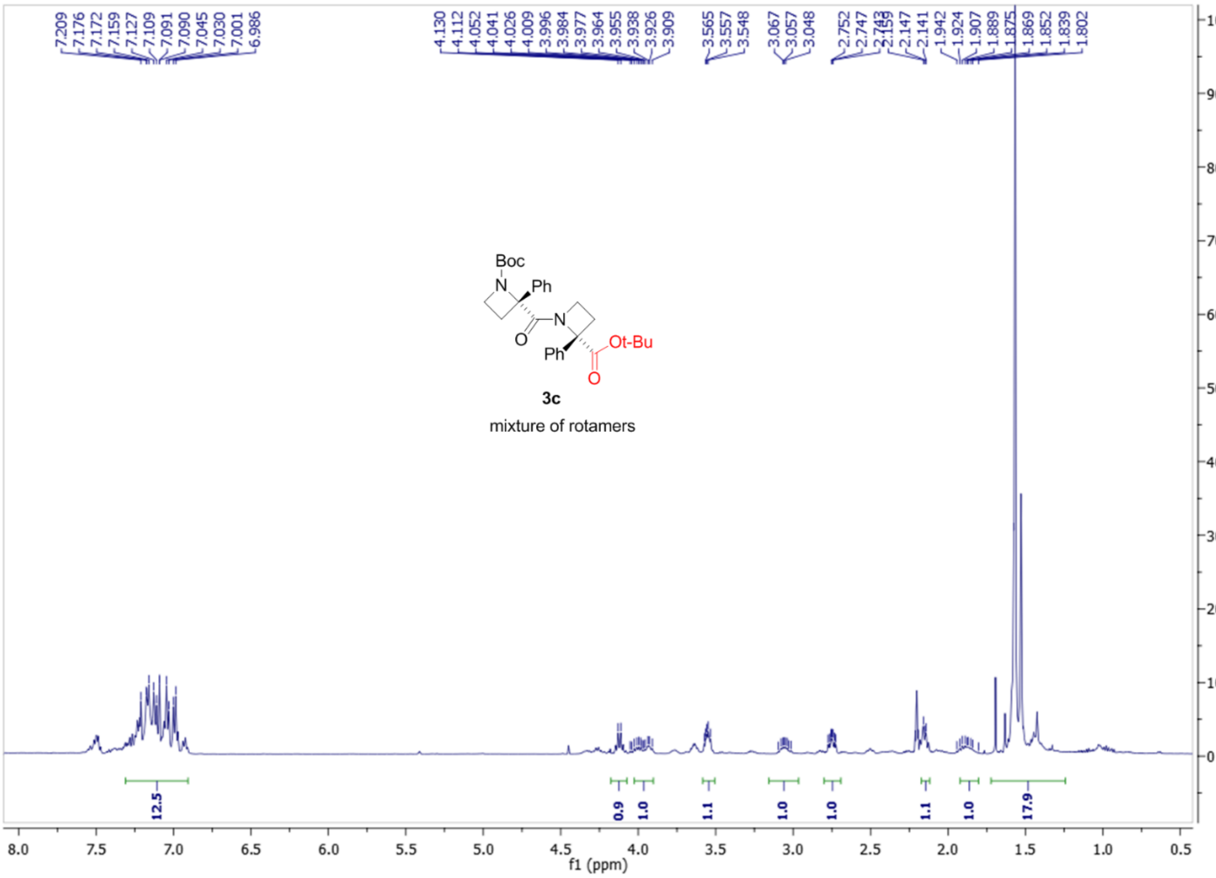
A
B
[M+Na]+
[2M+Na]+
M=
OH
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
473.2425
474.2452
475.2479
473.2411
474.2444
475.2478

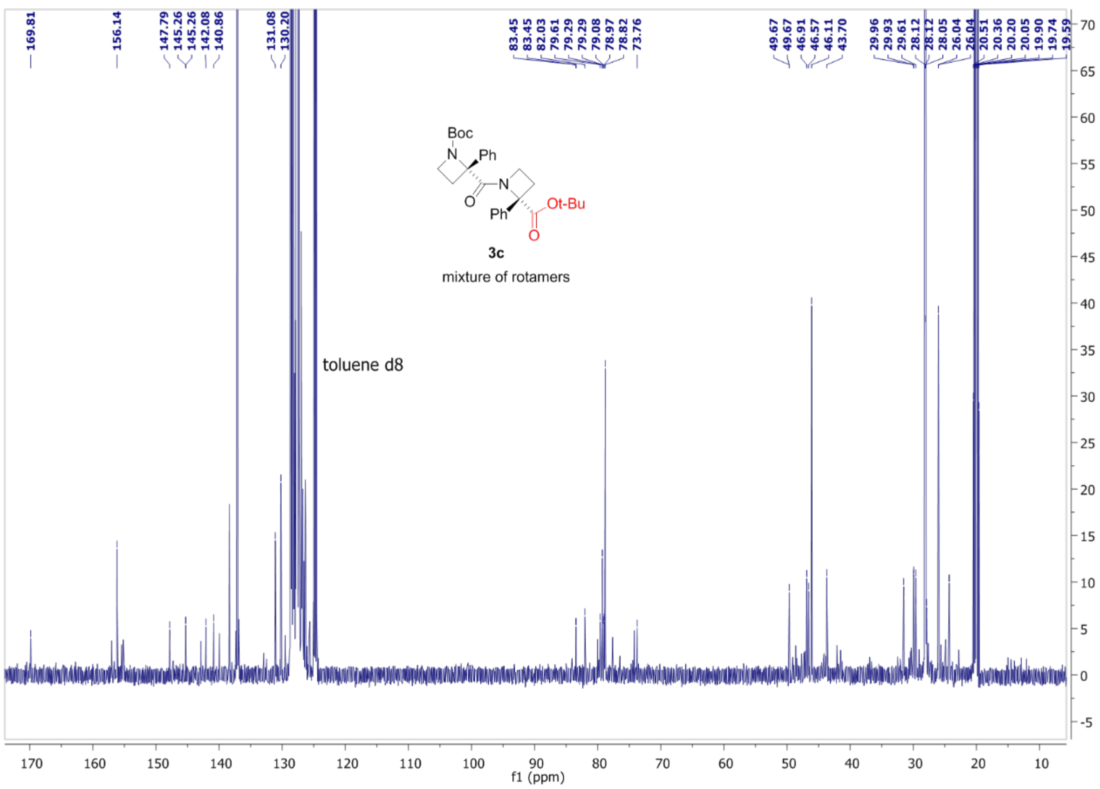

PROTON_01
7.62
7.60
7.37
7.32
4.00
3.99
3.97
3.95
3.90
3.51
3.26
3.24
3.06
3.04
3.02
2.68
2.65
2.63
2.58
2.39
1.59
1.37
1.10
Boc
N
Ph
O
N
Ph
Me
Me
OH
diast-**3b**
mixture of rotamers
CD_3OD
3.9
6.1
1.8
0.7
0.7
1.2
2.0
1.0
2.9
8.4
3.0
f1 (ppm)

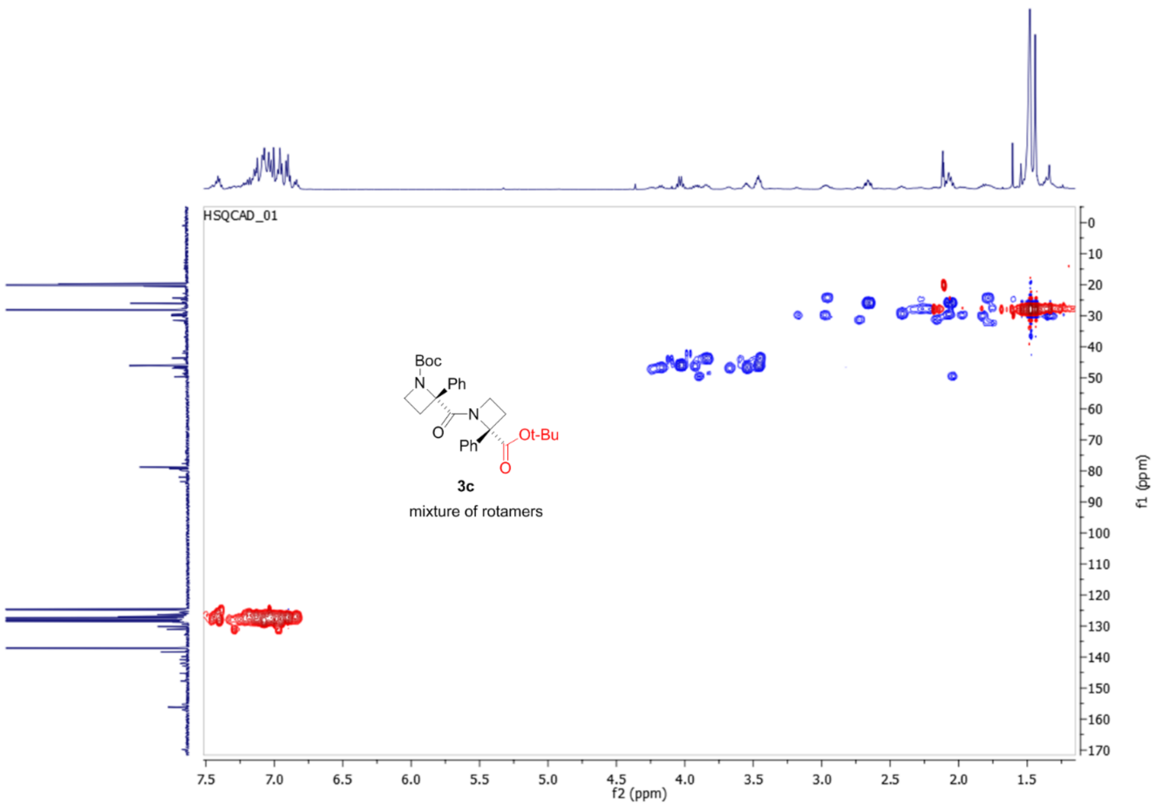

172.65
156.71
142.37
136.67
128.01
127.85
126.98
84.79
80.30
74.00
73.34
72.62
69.18
58.39
55.61
54.66
51.67
46.04
43.72
39.23
28.16
27.84
27.39
27.21
25.80
25.58
25.16
24.72
23.86
22.40
CD3OD
Boc
N
Ph
O
N
Ph
Me
Me
OH
diast-**3b**
mixture of rotamers
f1 (ppm)

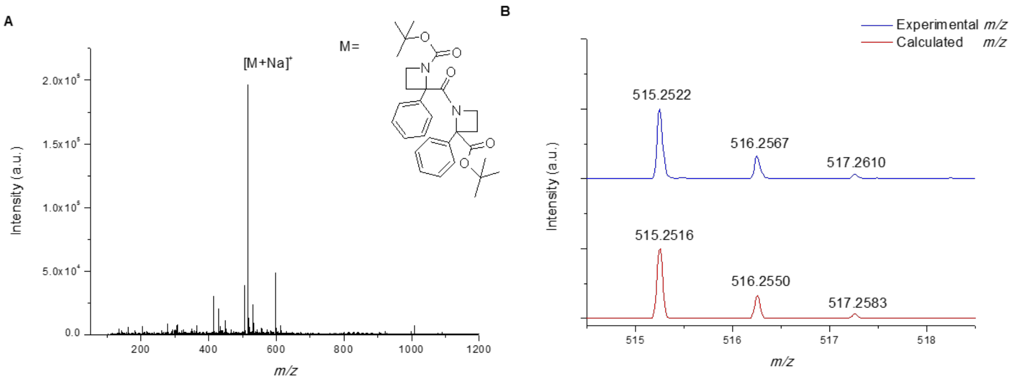

CD3OD
HSQCAD_01
Boc
N
Ph
N
O
Ph
Me
Me
OH
diast-3b
mixture of rotamers
f2 (ppm)
f1 (ppm)

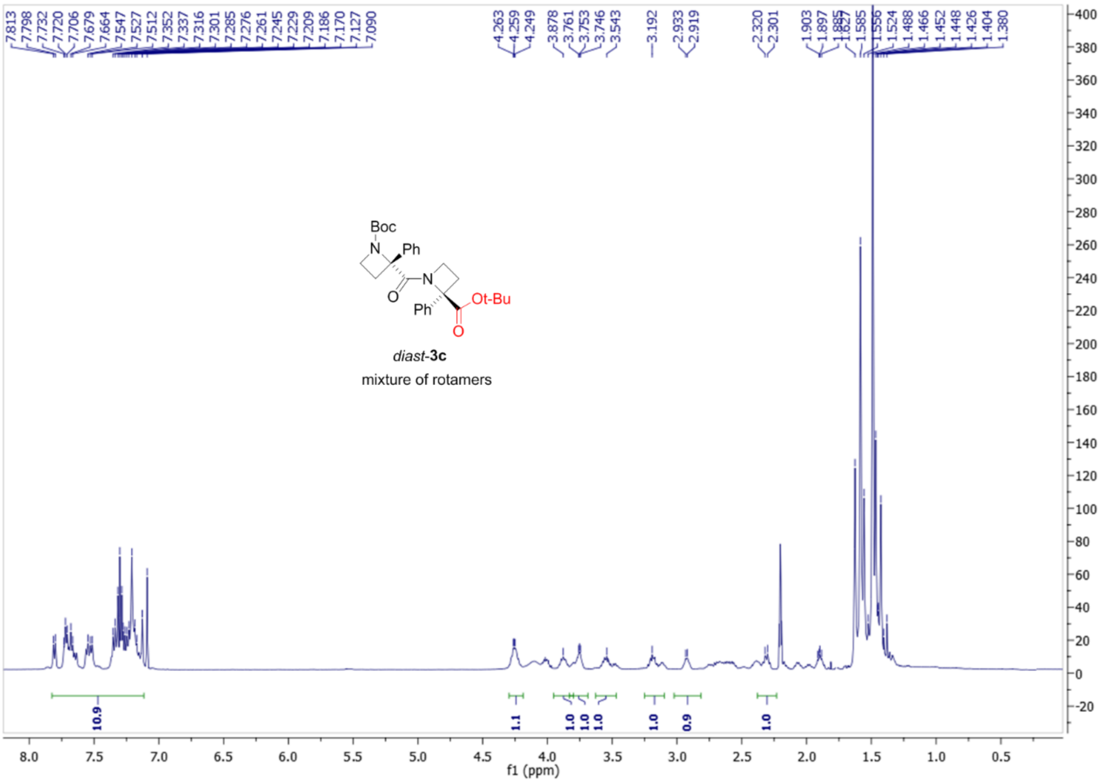

A
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
473.2423
474.2449
475.2475
473.2411
474.2444
475.2478
Intensity (a.u.)
m/z

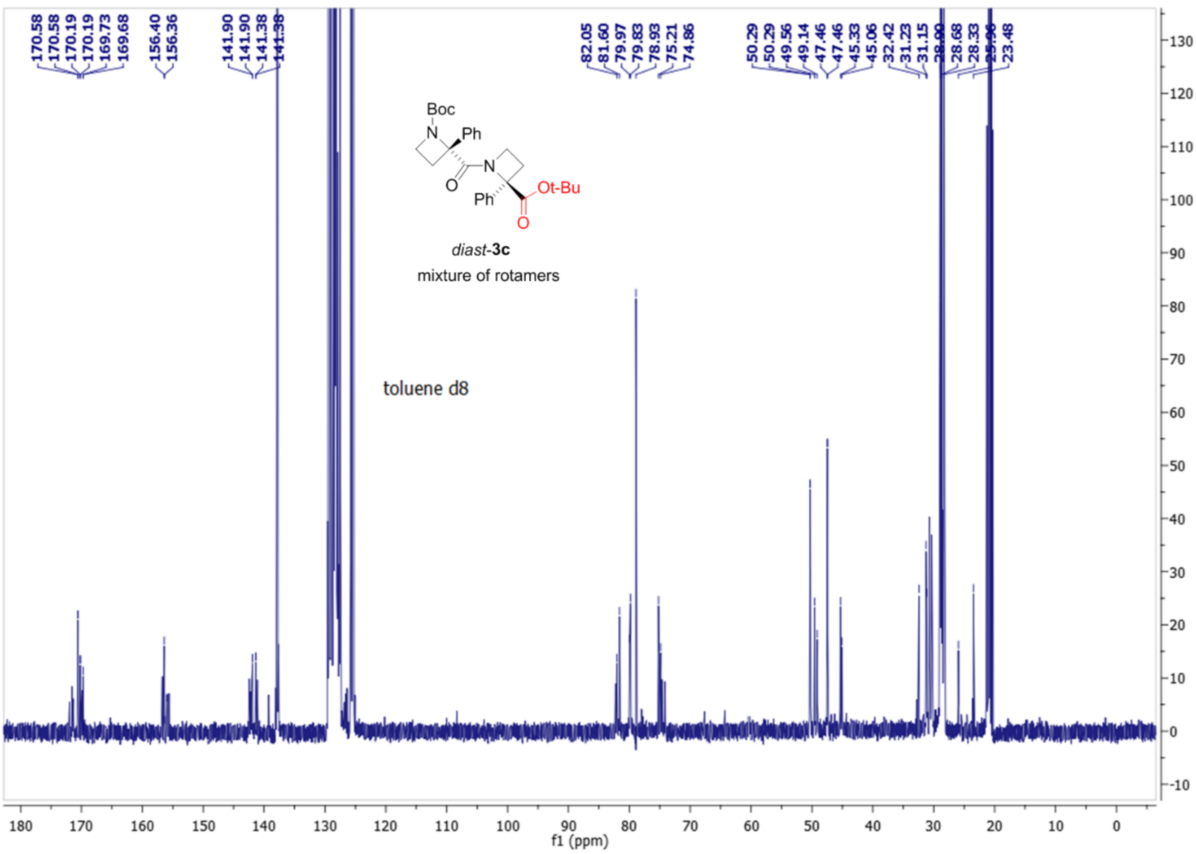

Boc
N
Ph
N
O
Ph
Ot-Bu
O
3c
mixture of rotamers
f1 (ppm)

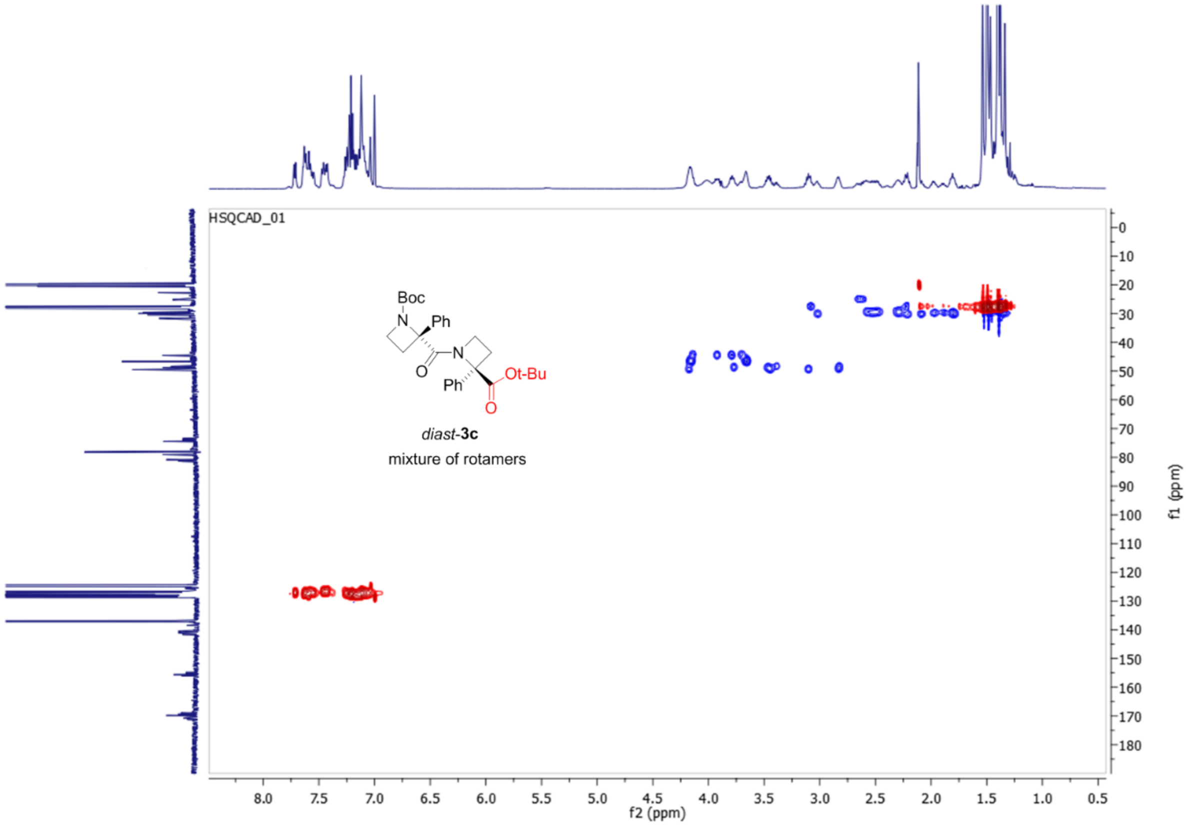

Boc
N
Ph
N
O
Ph
Ot-Bu
O
3c
mixture of rotamers
toluene d8
f1 (ppm)

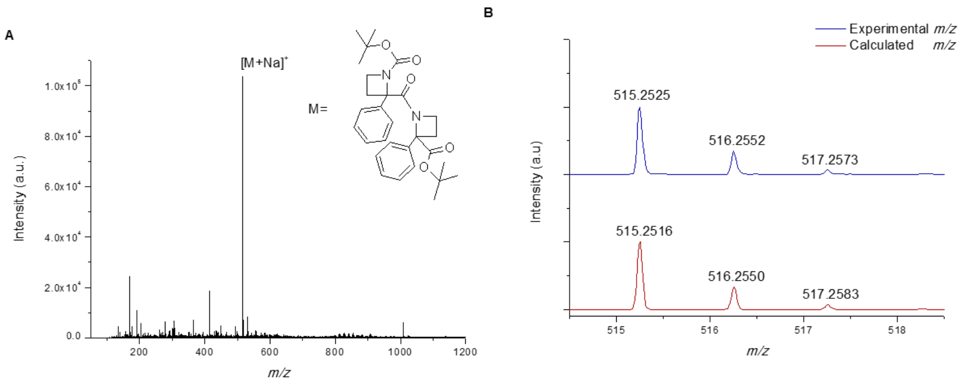

HSQCAD_01
Boc
N
Ph
O
N
Ph
Ot-Bu
O
3c
mixture of rotamers
f2 (ppm)
f1 (ppm)

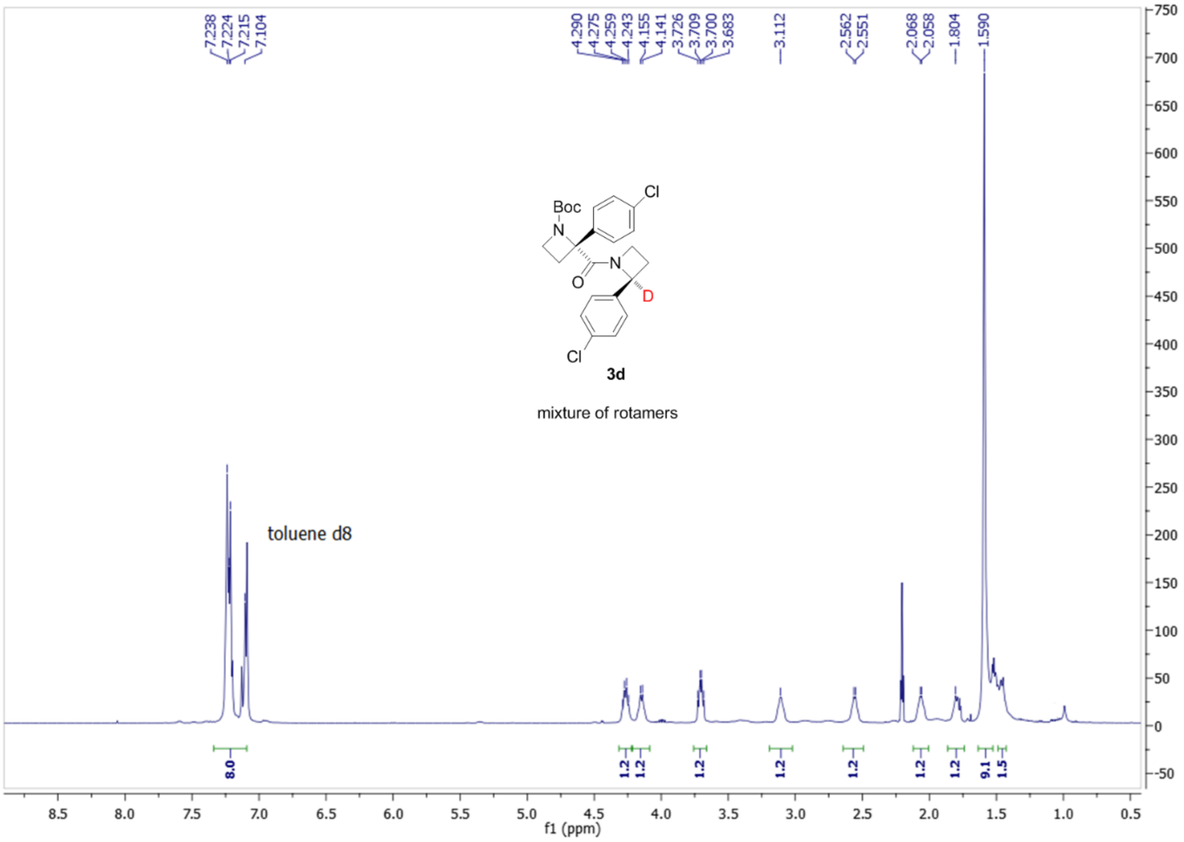

A
[M+Na]+
M=
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
515.2522
516.2567
517.2610
515.2516
516.2550
517.2583
Intensity (a.u.)
m/z

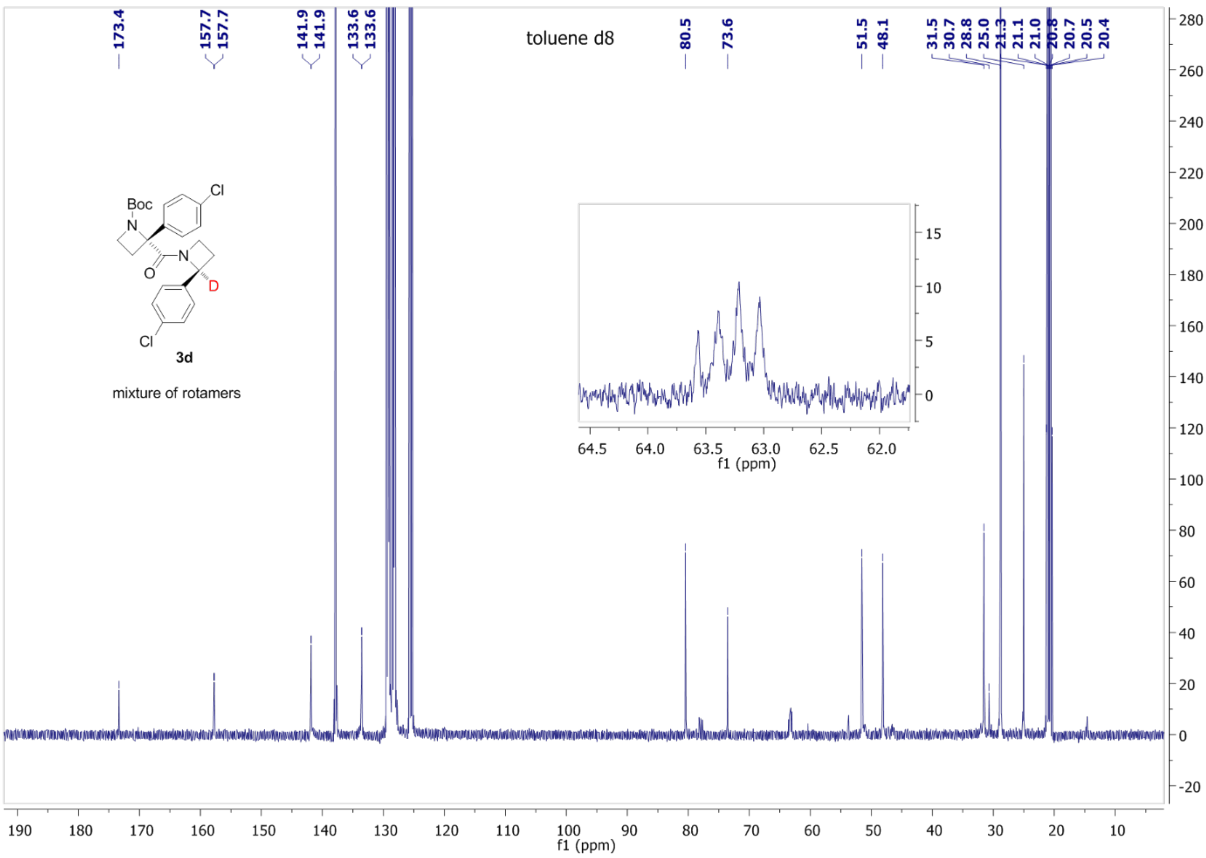

Boc
N
Ph
N
O
Ph
Ot-Bu
O
diast-3c
mixture of rotamers
f1 (ppm)

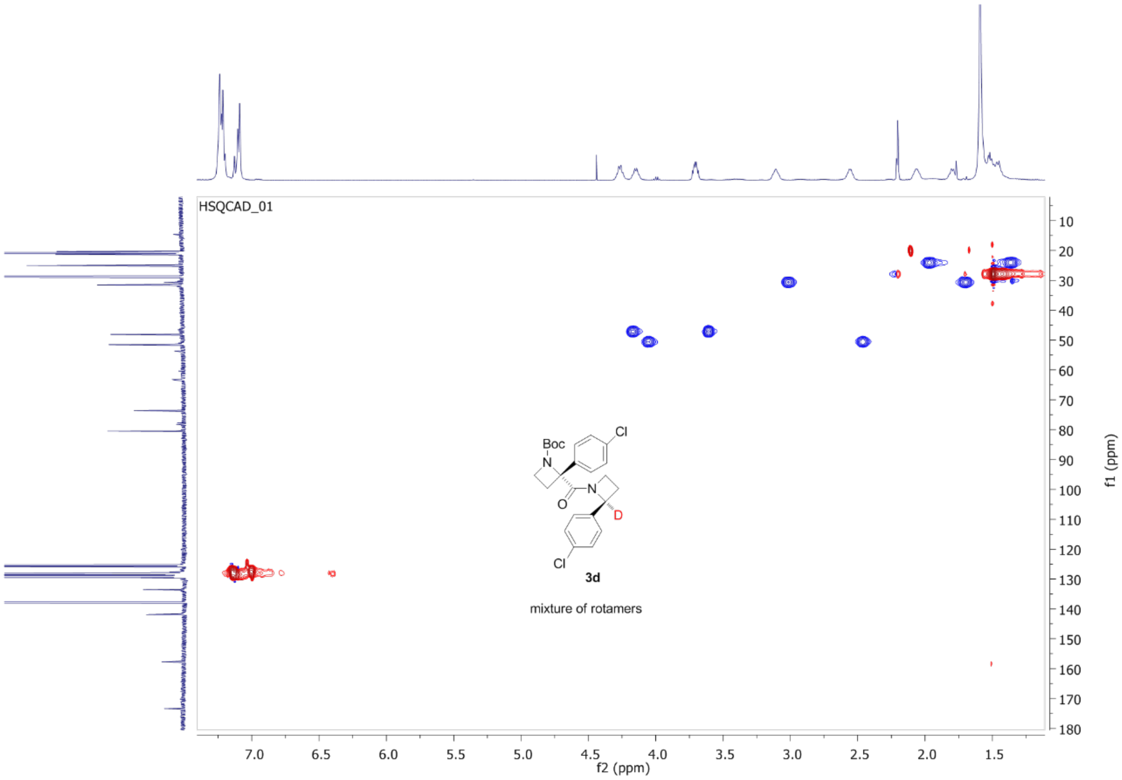

Boc
N
Ph
N
O
Ph
Ot-Bu
O
diast-3c
mixture of rotamers
toluene d8
f1 (ppm)

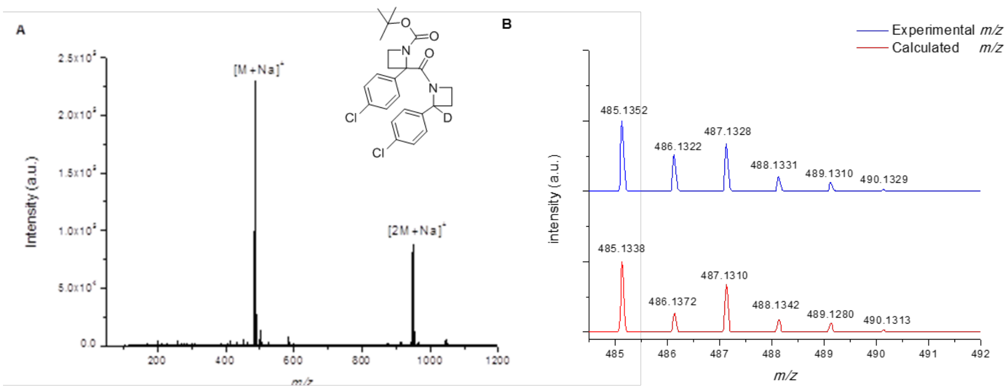

HSQCAD_01
Boc
N
Ph
N
O
Ph
Ot-Bu
O
diast-3c
mixture of rotamers
f2 (ppm)
f1 (ppm)

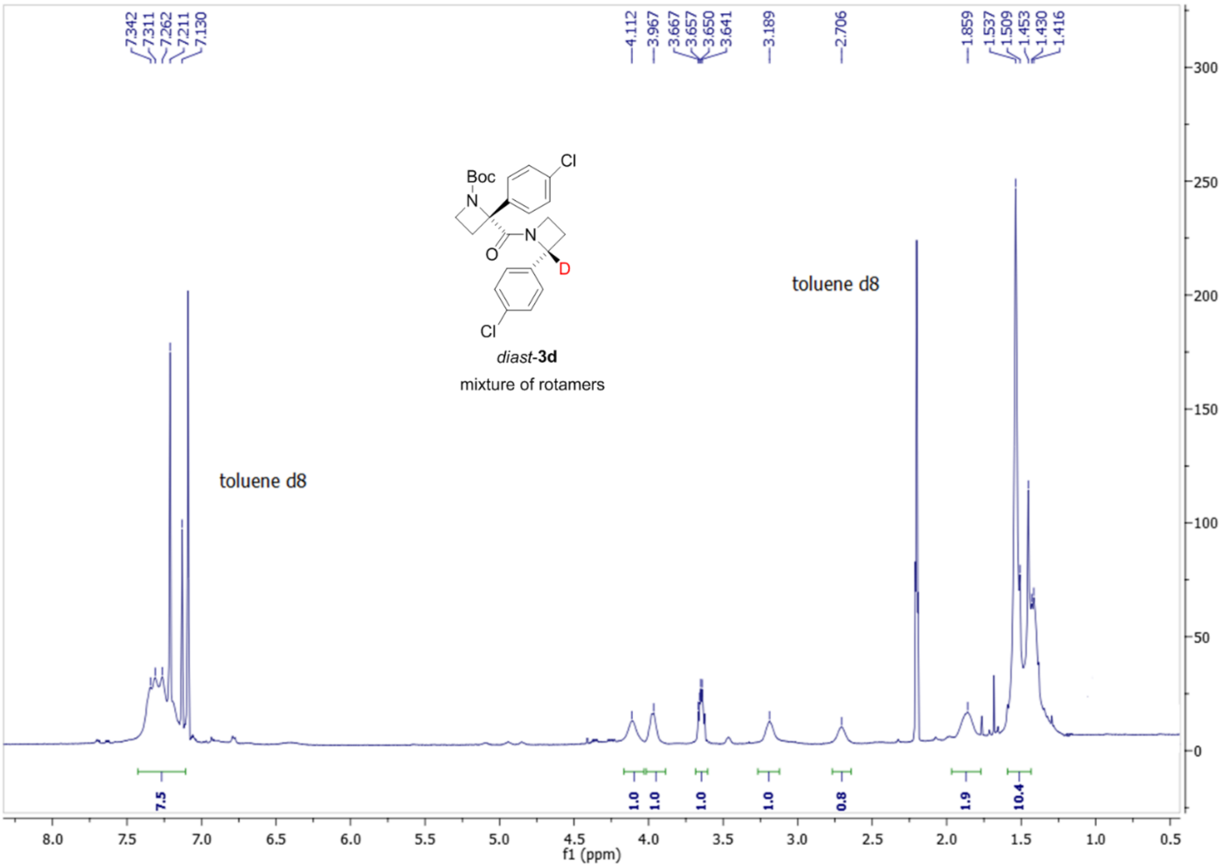

A
[M+Na]+
M=
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
515.2525
516.2552
517.2573
515.2516
516.2550
517.2583
Intensity (a.u.)
m/z


toluene d8
3d
mixture of rotamers
f1 (ppm)

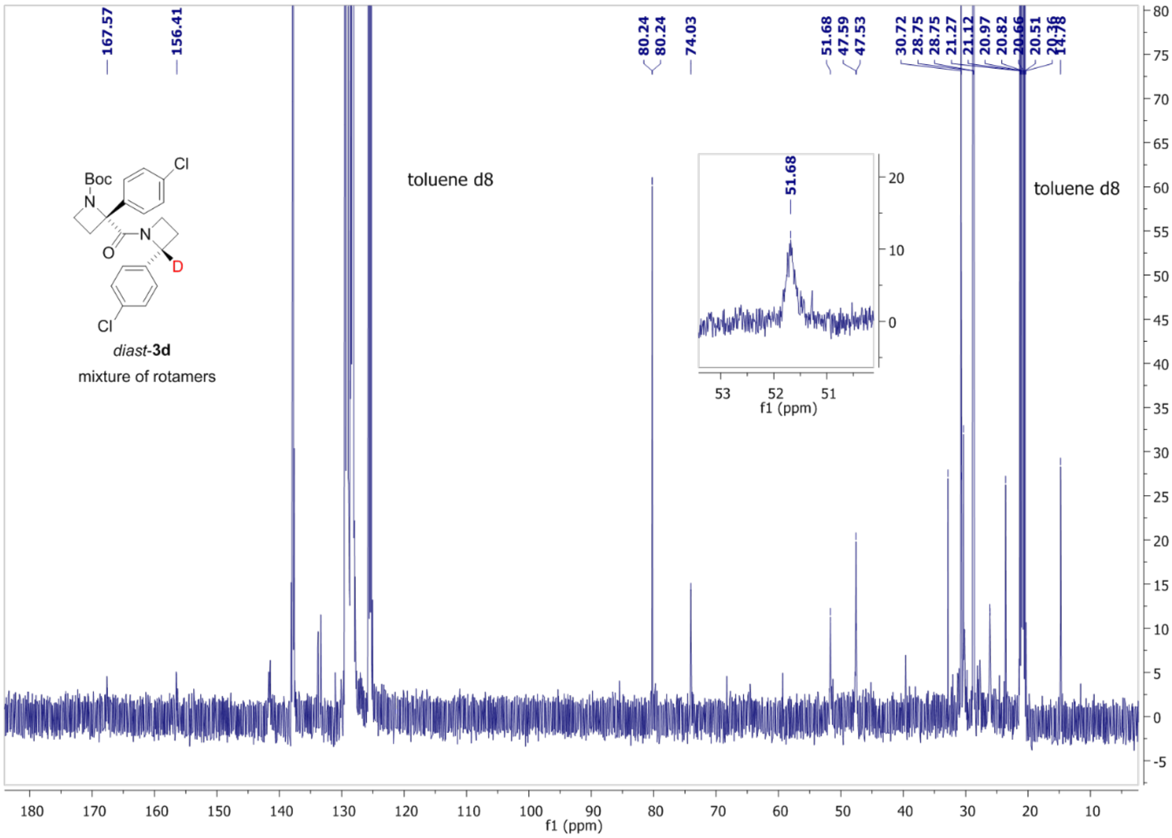

toluene d8
3d
mixture of rotamers
f1 (ppm)


HSQCAD_01
Boc
N
Cl
O
N
D
Cl
3d
mixture of rotamers
f2 (ppm)
f1 (ppm)

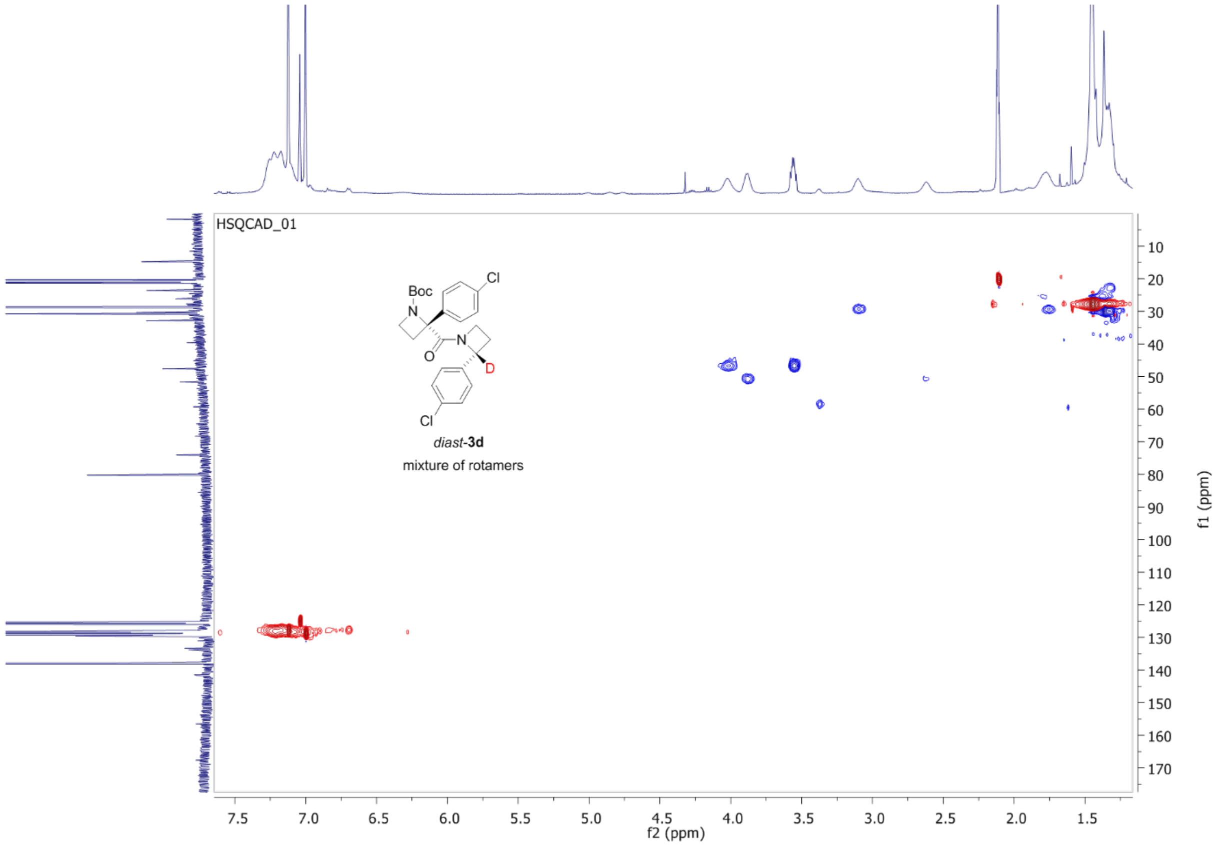

A
B
[M+Na]+
[2M+Na]+
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
485.1352
486.1322
487.1328
488.1331
489.1310
490.1329
485.1338
486.1372
487.1310
488.1342
489.1280
490.1313
intensity (a.u.)
m/z

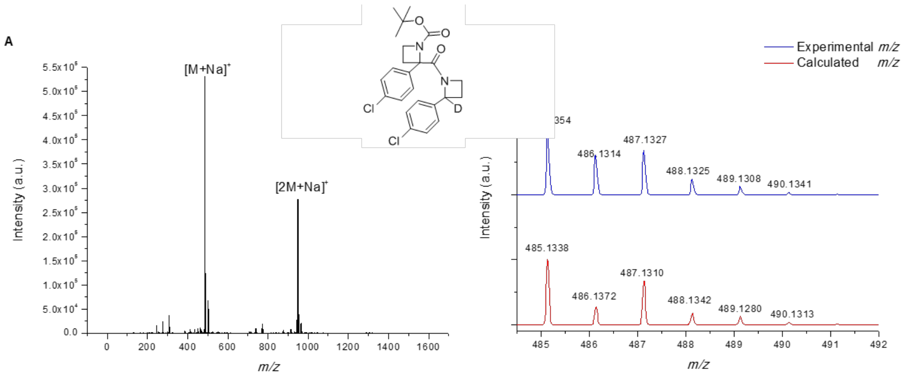


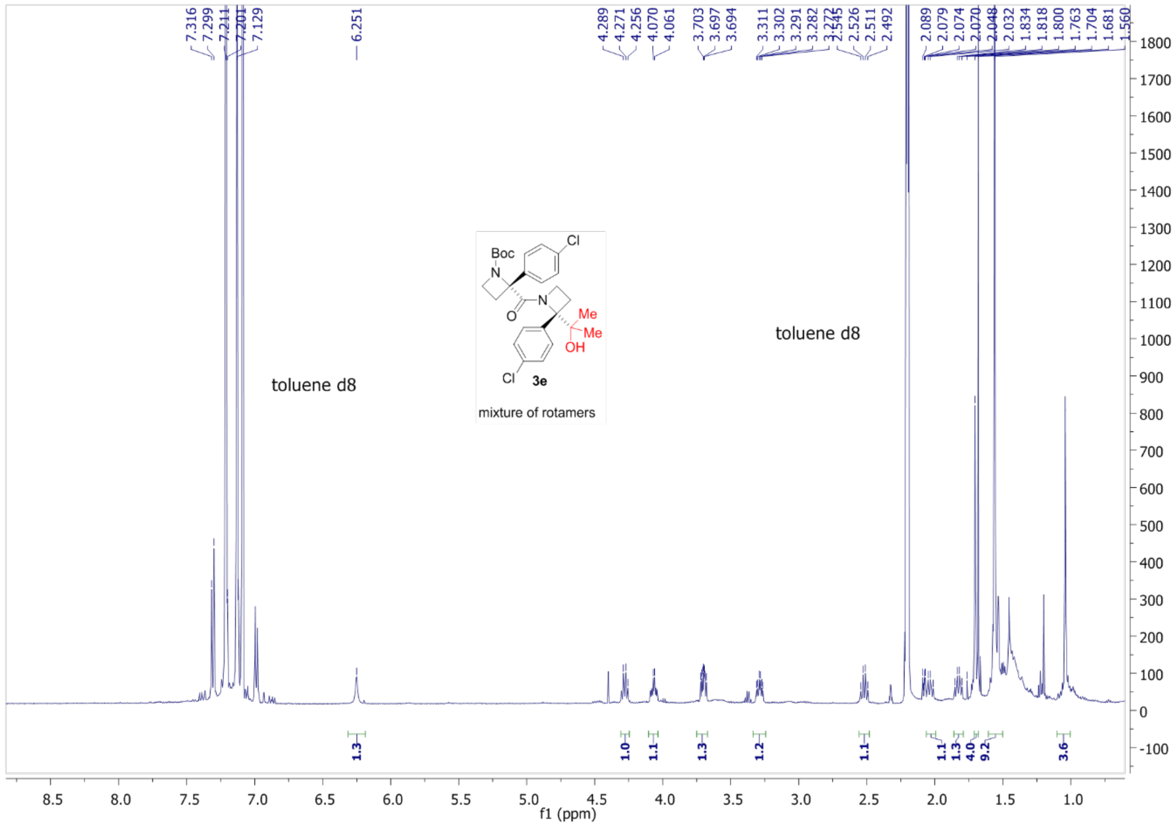
7.342
7.311
7.262
7.211
7.130
4.112
3.967
3.667
3.657
3.650
3.641
3.189
2.706
1.859
1.537
1.509
1.453
1.430
1.416
Boc
N
Cl
N
O
D
Cl
diast-**3d**
mixture of rotamers
toluene d8
toluene d8
7.5
1.0
1.0
1.0
1.0
0.8
1.9
10.4
f1 (ppm)

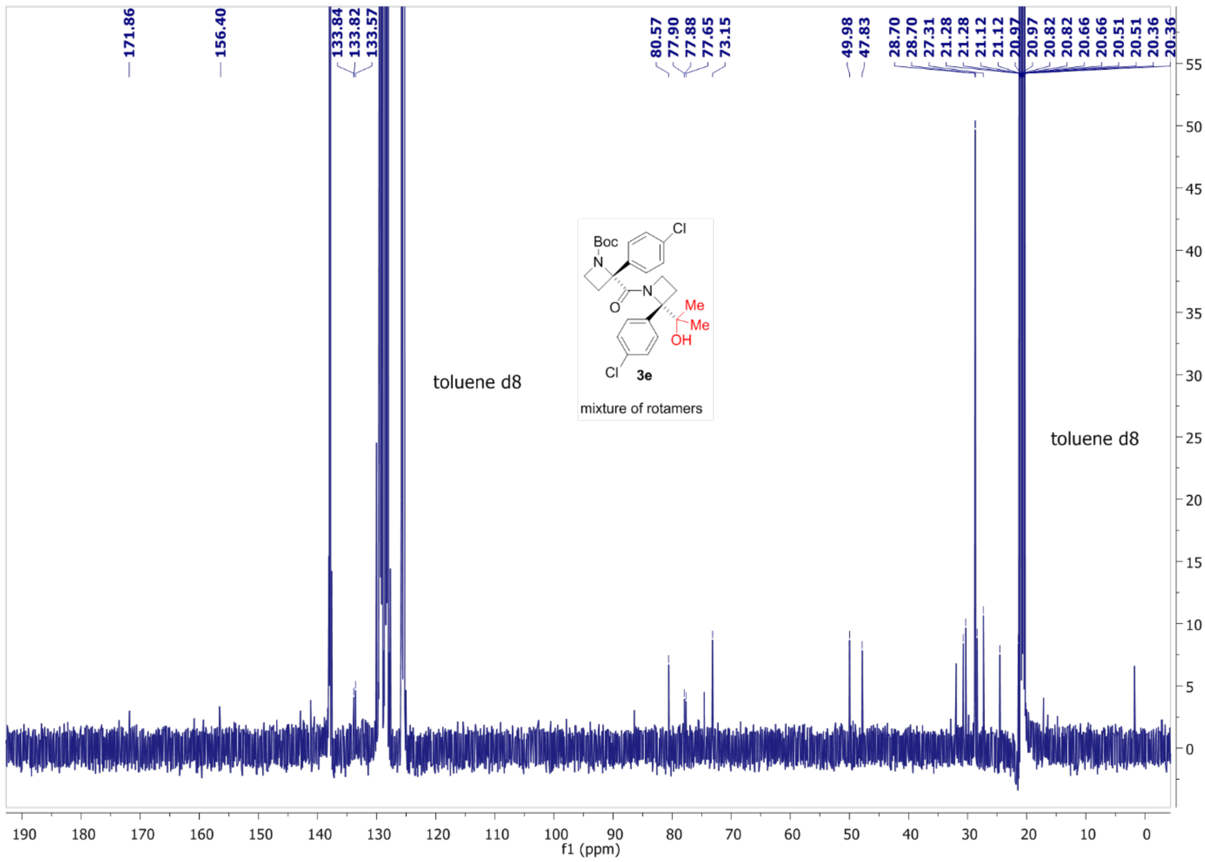


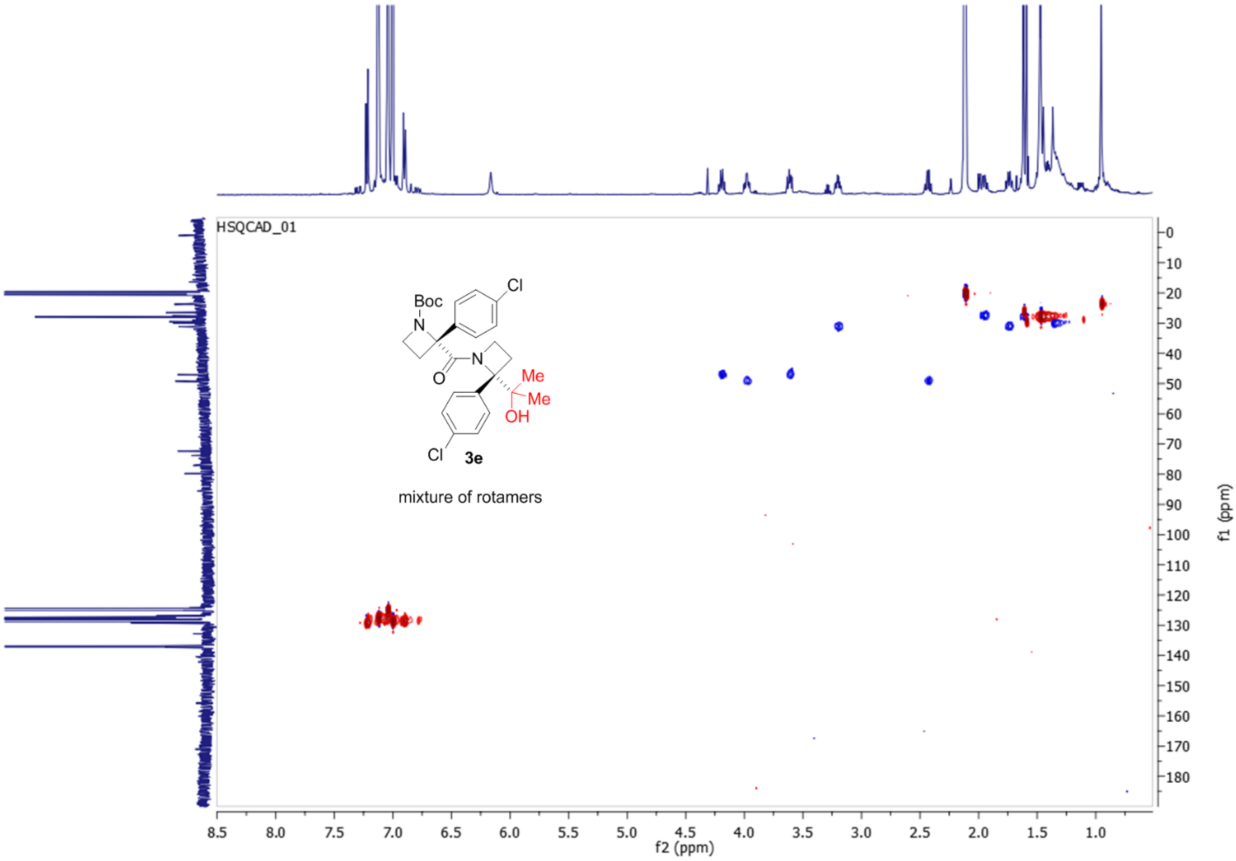
167.57
156.41
80.24
80.24
74.03
51.68
47.59
47.53
30.72
28.75
28.75
21.27
21.12
20.97
20.82
20.66
20.51
20.36
14.78
Boc
N
Cl
N
O
D
Cl
diast-**3d**
mixture of rotamers
toluene d8
toluene d8
51.68
f1 (ppm)
f1 (ppm)

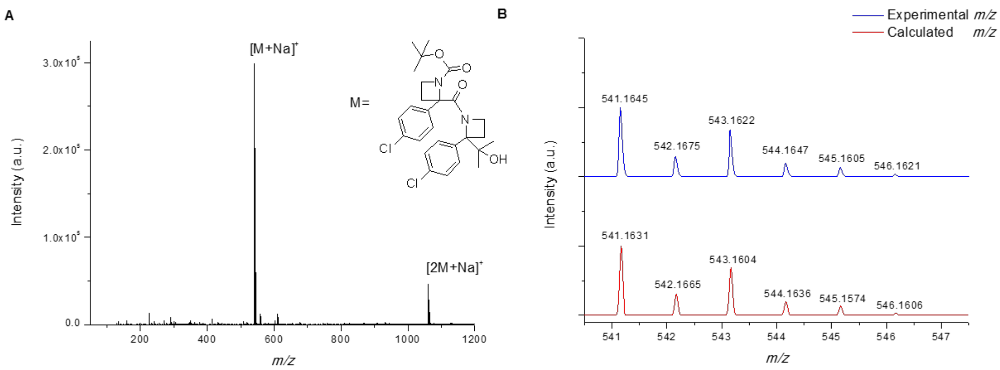

HSQCAD_01
Boc
N
Cl
O
N
D
Cl
diast-3d
mixture of rotamers
f1 (ppm)
f2 (ppm)

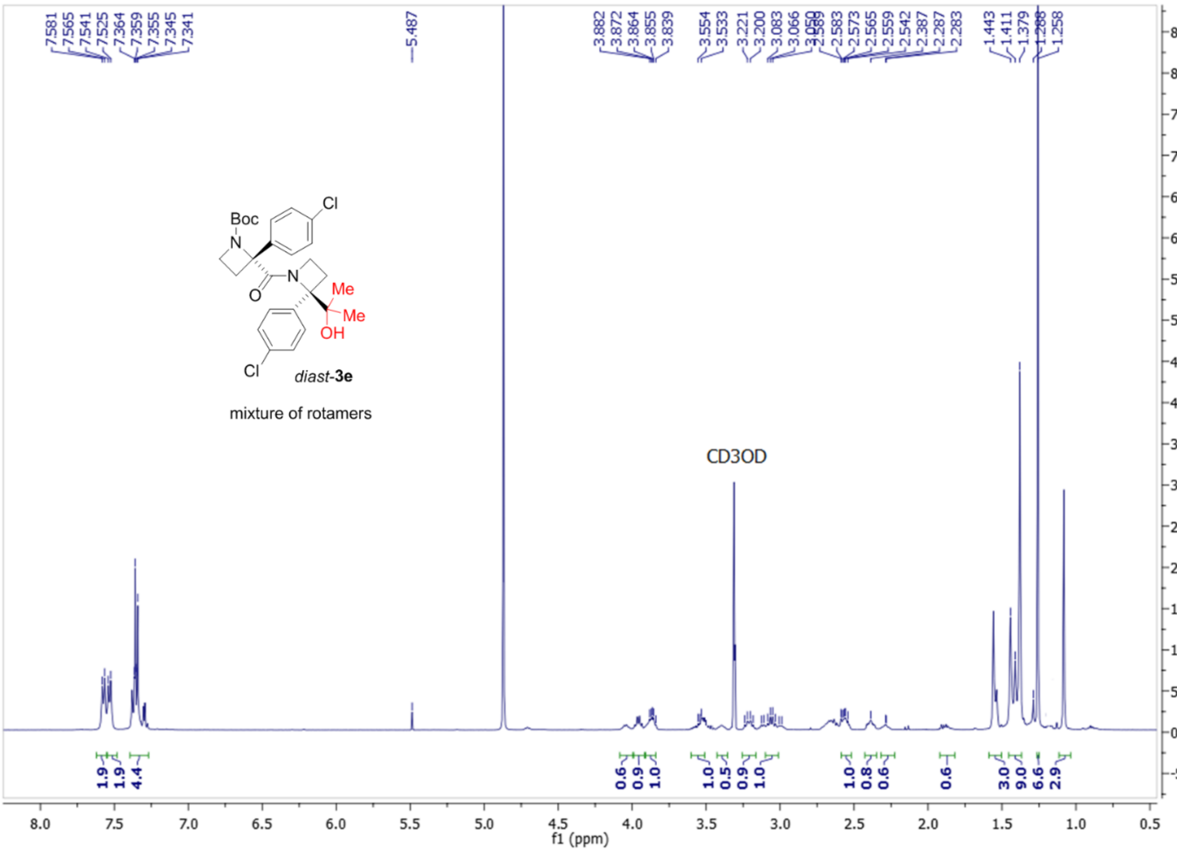

A
[M+Na]+
[2M+Na]+
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
486.1314
487.1327
488.1325
489.1308
490.1341
485.1338
486.1372
487.1310
488.1342
489.1280
490.1313



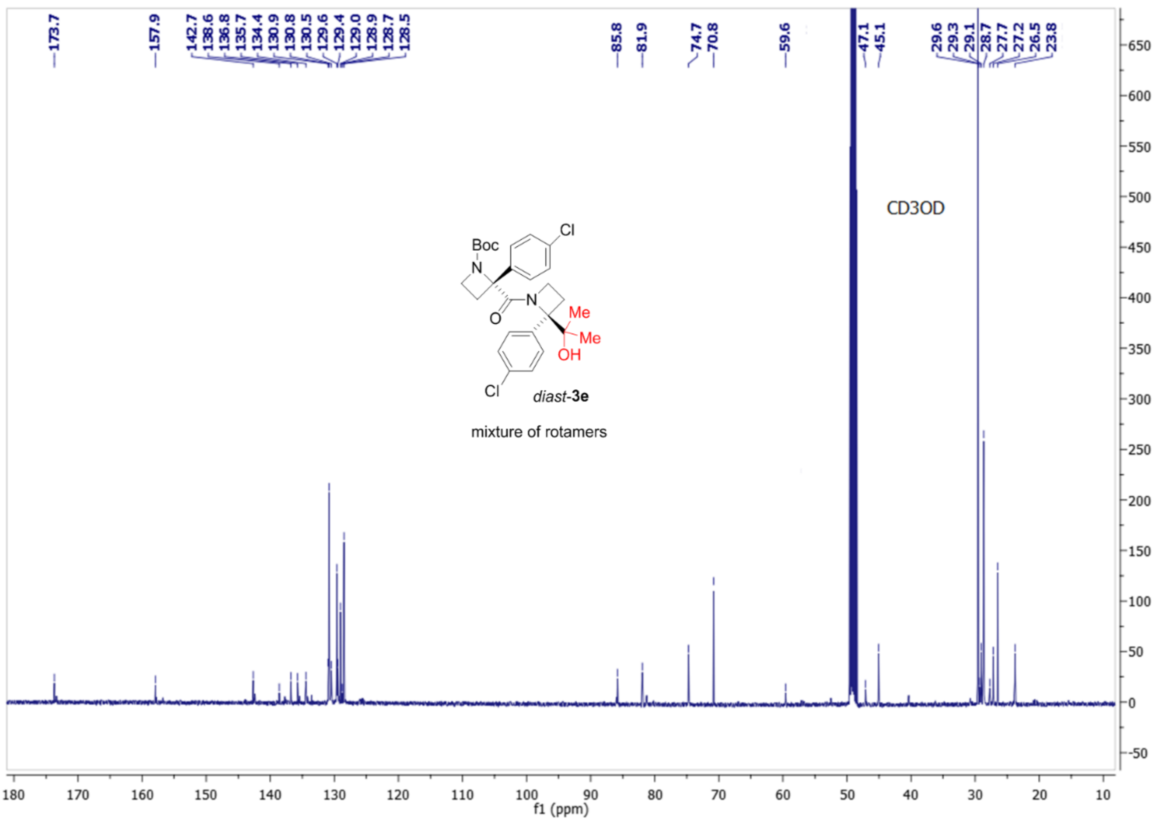



HSQCAD_01
Boc
N
Cl
N
O
Me
Me
OH
Cl
3e
mixture of rotamers
f2 (ppm)
f1 (ppm)

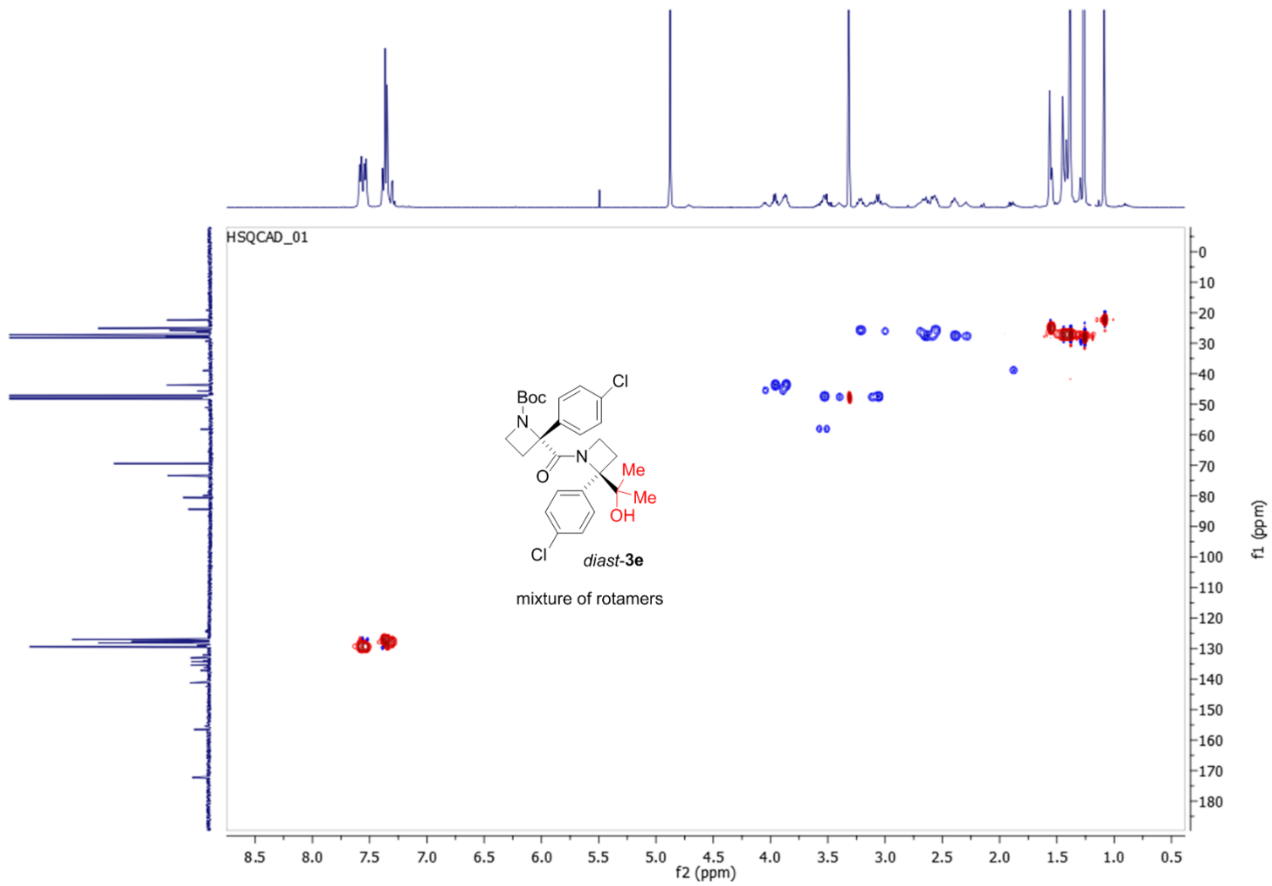

A
[M+Na]+
[2M+Na]+
M=
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
541.1645
542.1675
543.1622
544.1647
545.1605
546.1621
541.1631
542.1665
543.1604
544.1636
545.1574
546.1606
Intensity (a.u.)
m/z

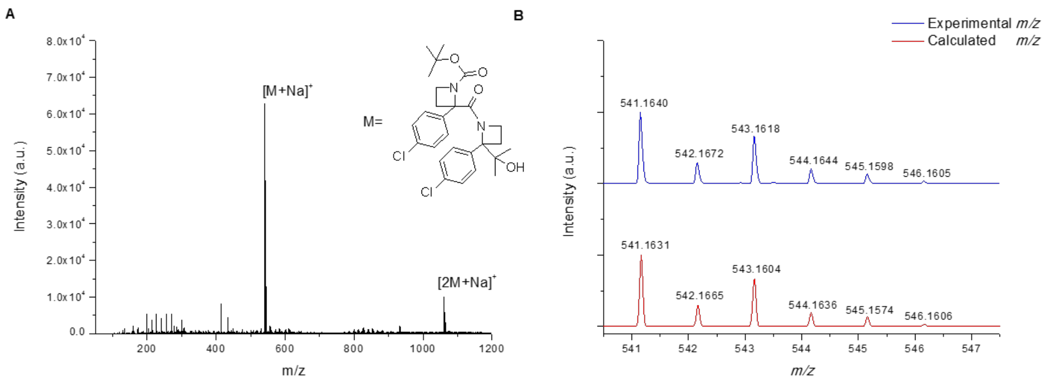


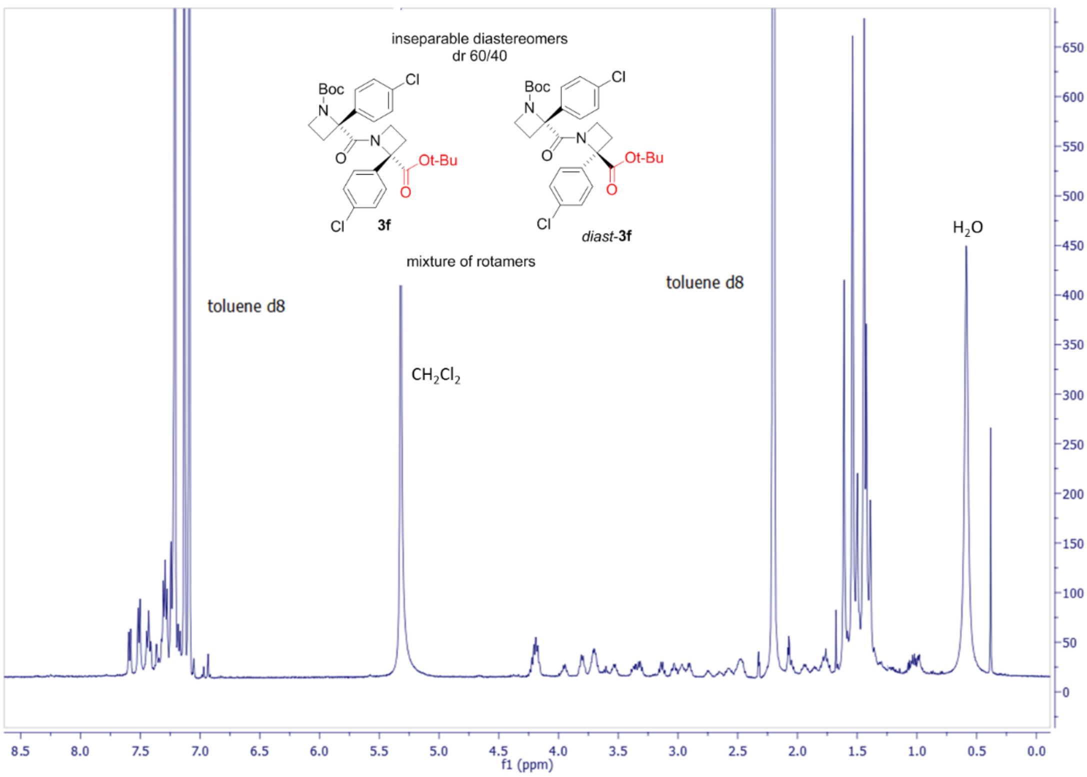
7.581
7.565
7.541
7.525
7.364
7.359
7.355
7.345
7.341
5.487
3.882
3.872
3.864
3.855
3.839
3.554
3.533
3.221
3.200
3.083
3.066
2.583
2.573
2.565
2.559
2.542
2.387
2.287
2.283
1.443
1.411
1.379
1.258
Boc
N
Cl
O
Me
Me
OH
Cl
diast-3e
mixture of rotamers
CD3OD
1.9
1.9
4.4
0.6
0.9
1.0
1.0
0.5
0.9
1.0
1.0
0.8
0.6
0.6
3.0
9.0
6.6
2.9
f1 (ppm)

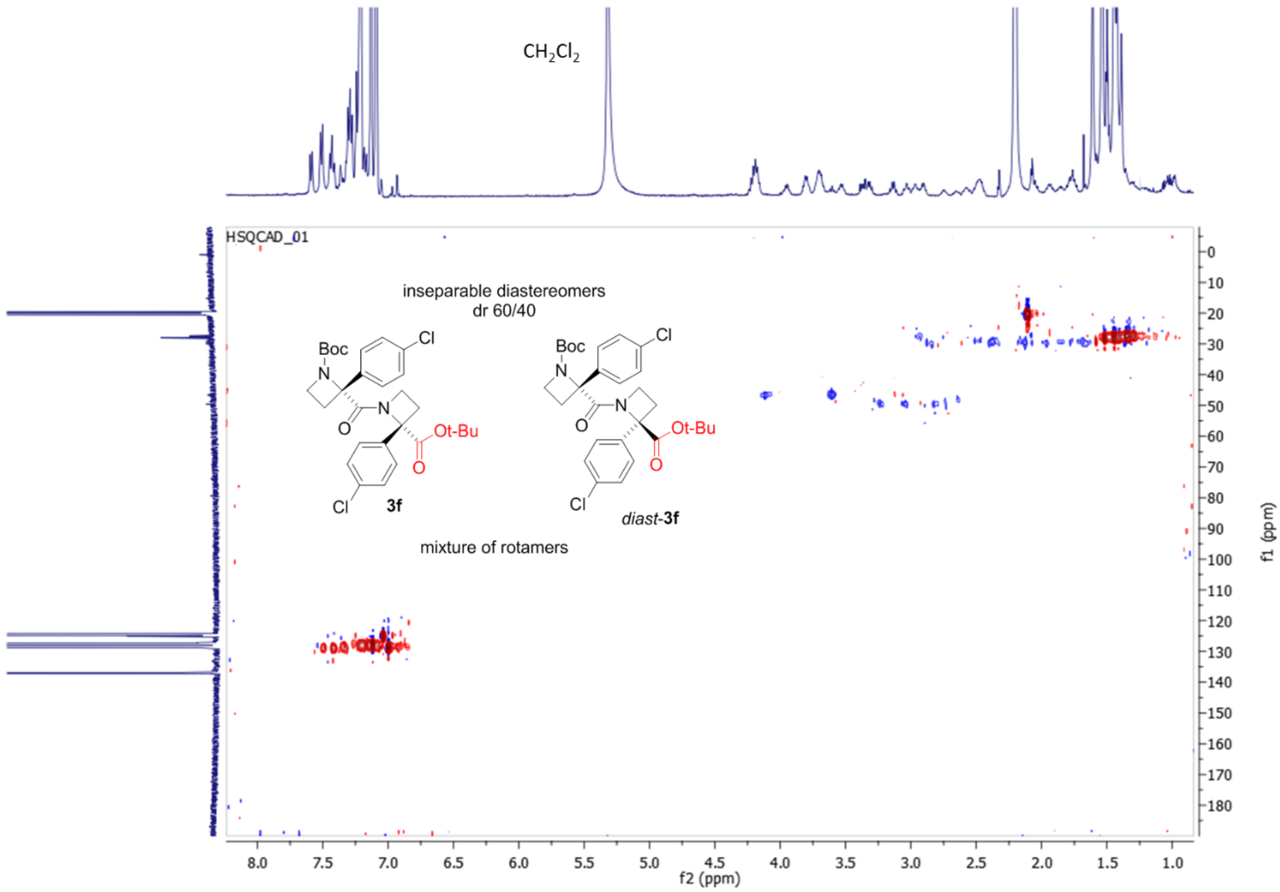


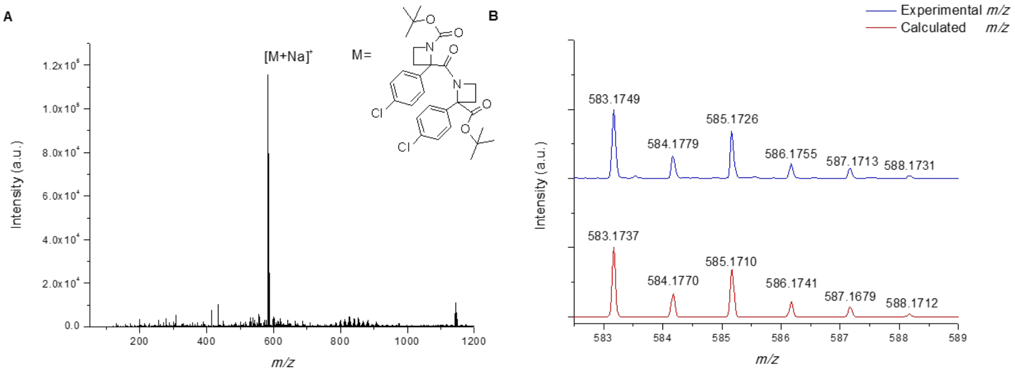
173.7
157.9
142.7
138.6
136.8
135.7
134.4
130.9
130.8
130.5
129.6
129.4
129.0
128.9
128.7
128.5
85.8
81.9
74.7
70.8
59.6
47.1
45.1
29.6
29.3
29.1
28.7
27.7
27.2
26.5
23.8
Boc
N
Cl
O
Me
Me
OH
Cl
diast-3e
mixture of rotamers
CD3OD
f1 (ppm)


HSQCAD_01
diast-3e
mixture of rotamers
f2 (ppm)
f1 (ppm)


A
B
[M+Na]+
[2M+Na]+
M=
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
541.1640
542.1672
543.1618
544.1644
545.1598
546.1605
541.1631
542.1665
543.1604
544.1636
545.1574
546.1606

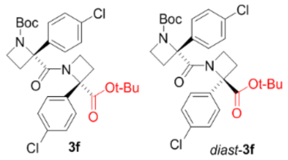

inseparable diastereomers
dr 60/40
Boc
N
Cl
O
N
Ot-Bu
O
Cl
3f
Boc
N
Cl
O
N
Ot-Bu
O
Cl
diast-3f
mixture of rotamers
toluene d8
toluene d8
CH_2Cl_2
H_2O
f1 (ppm)

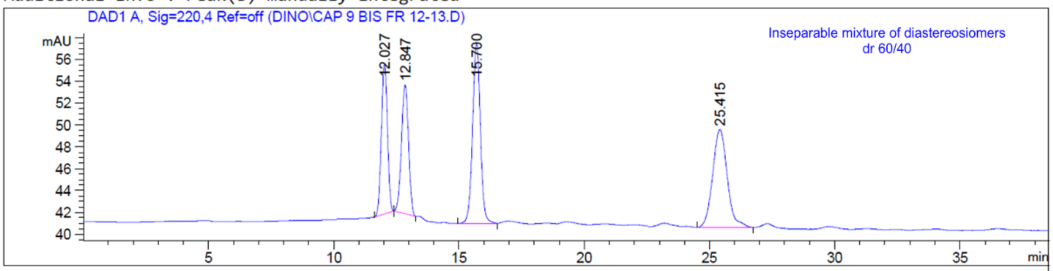

CH_2Cl_2
HSQCAD_01
inseparable diastereomers
dr 60/40
Boc
N
Cl
O
N
Ot-Bu
O
Cl
3f
Boc
N
Cl
O
N
Ot-Bu
O
Cl
diast-3f
mixture of rotamers
f2 (ppm)
f1 (ppm)



Analysis of the diasteromeric mixture of **3f** and *diast*-**3f** by HPLC using a chiral stationary phase (AD-H 0.46 x 25 cm, Daicel). The four enantiomers were detected.

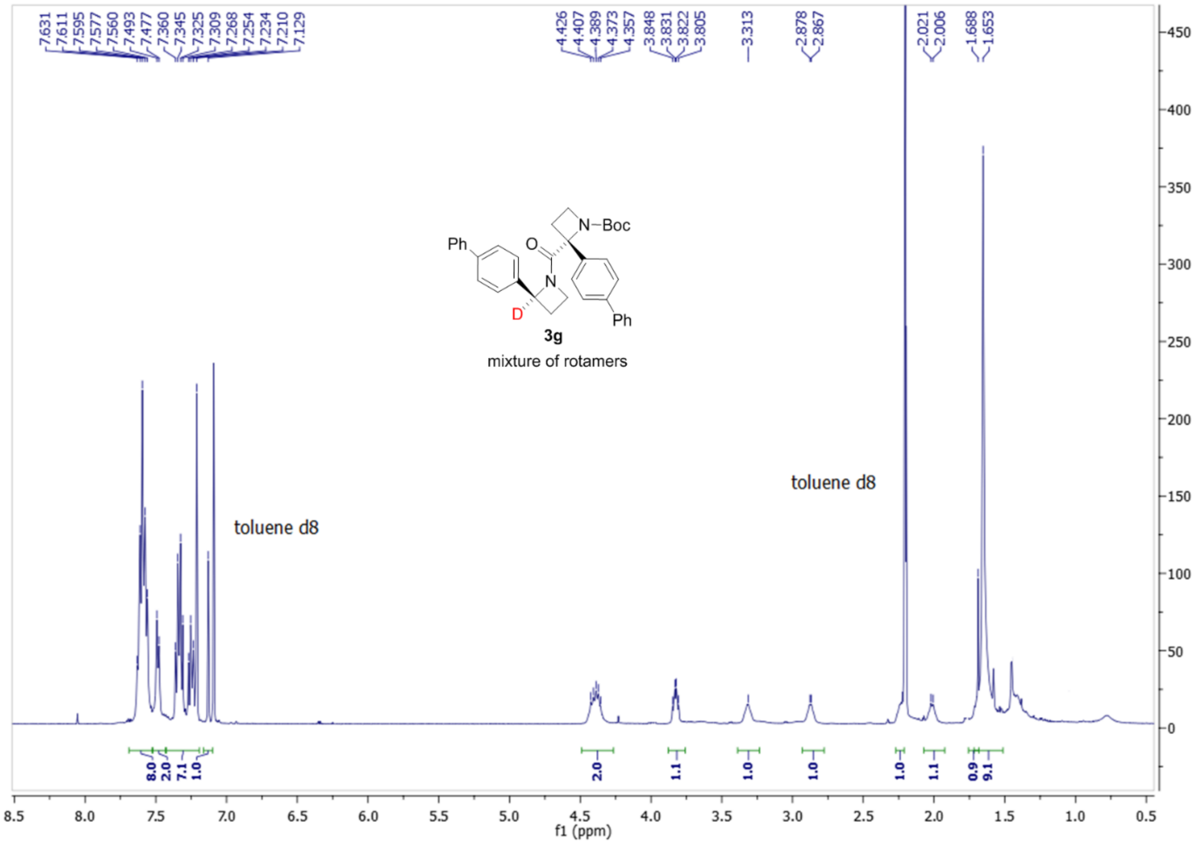
```
Acq. Method      : C:\CHEM32\1\DATA\DINO\1D CON D RAC.D\CHIRAL1.M
Last changed     : 4/2/2015 10:25:39 AM by SYSTEM
                   (modified after loading)
Analysis Method  : C:\CHEM32\1\DATA\DINO\CAP 9 BIS CORRETTO.M
Last changed     : 7/23/2015 6:41:11 PM by SYSTEM
Sample Info      : ADH 0.5ml/min 95:5=Hex:IPrO

Additional Info  : Peak(s) manually integrated
```



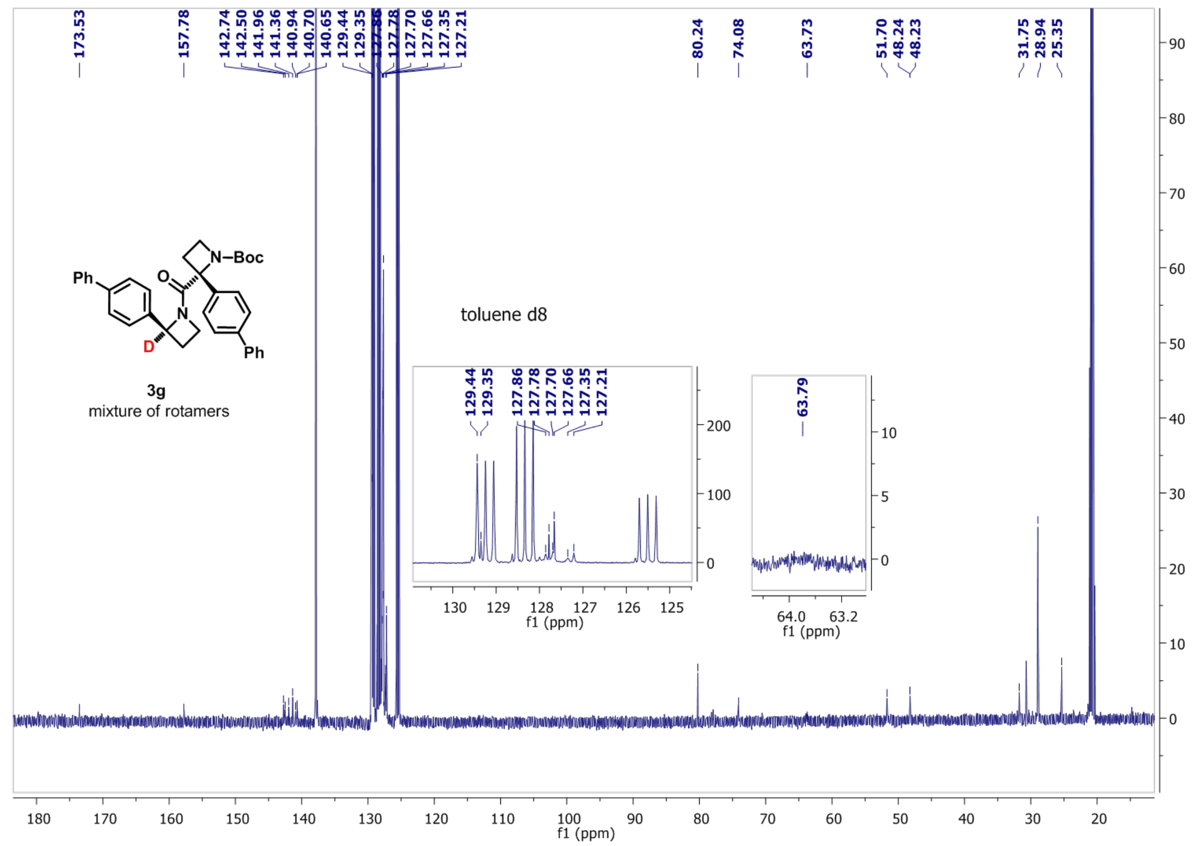


Signal 1: DAD1 A, Sig=220,4 Ref=off

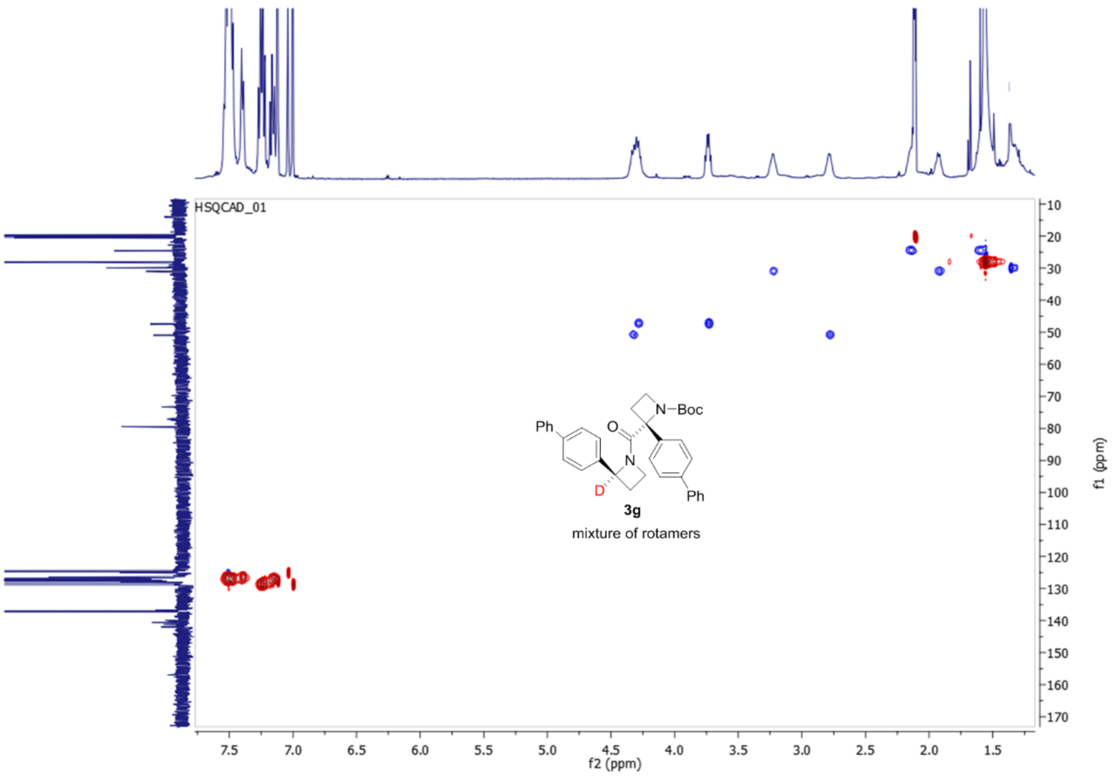
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.027	BB	0.2631	231.83919	13.72394	19.6340
2	12.847	BB	0.3037	230.51080	11.80989	19.5215
3	15.700	BB	0.3317	356.90207	16.54382	30.2254
4	25.415	BB	0.6144	361.55023	8.96755	30.6190

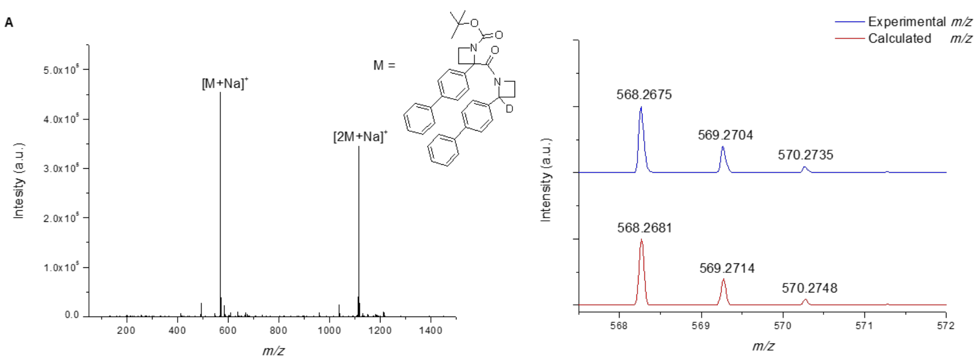


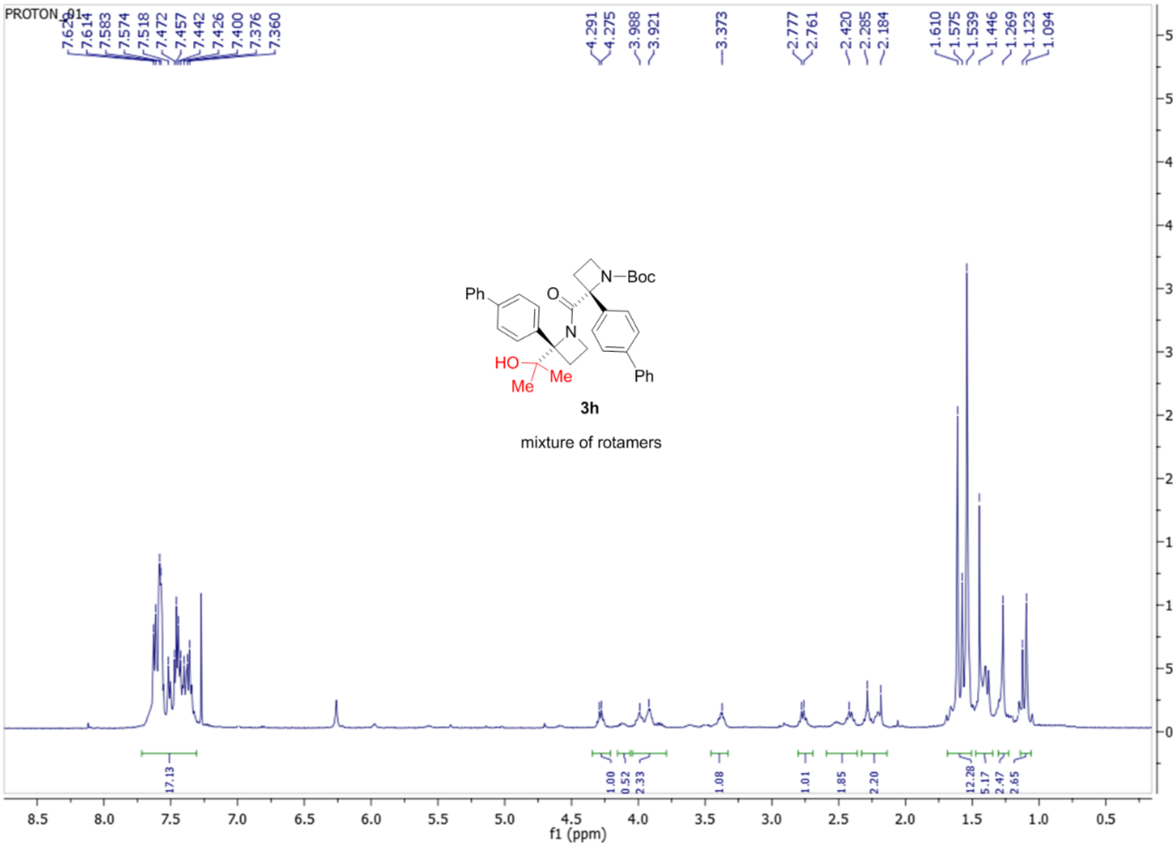
7.631
7.611
7.595
7.577
7.560
7.493
7.477
7.360
7.345
7.325
7.309
7.268
7.254
7.234
7.210
7.129
4.426
4.407
4.389
4.373
4.357
3.848
3.831
3.822
3.805
3.313
2.878
2.867
2.021
2.006
1.688
1.653
N–Boc
Ph
O
N
D
Ph
3g
mixture of rotamers
toluene d8
toluene d8
8.0
2.0
7.1
1.0
2.0
1.1
1.0
1.0
1.0
1.1
0.9
9.1
f1 (ppm)

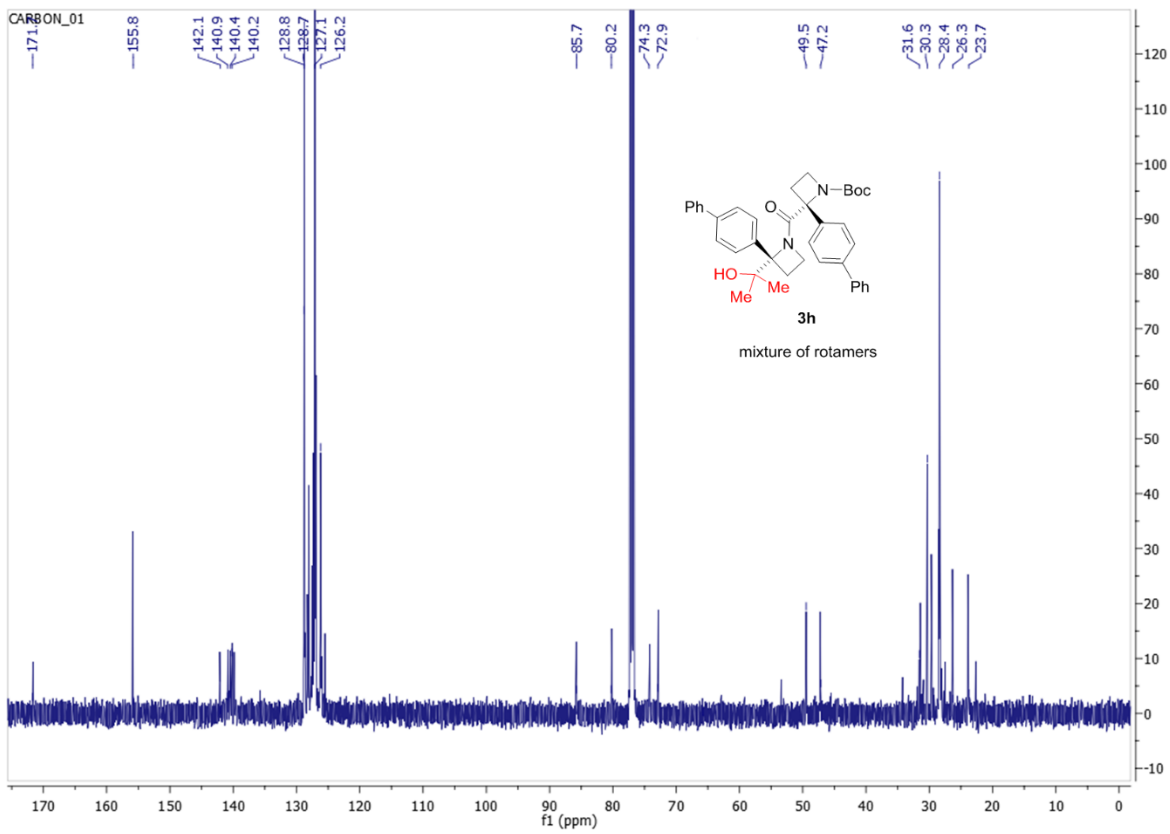


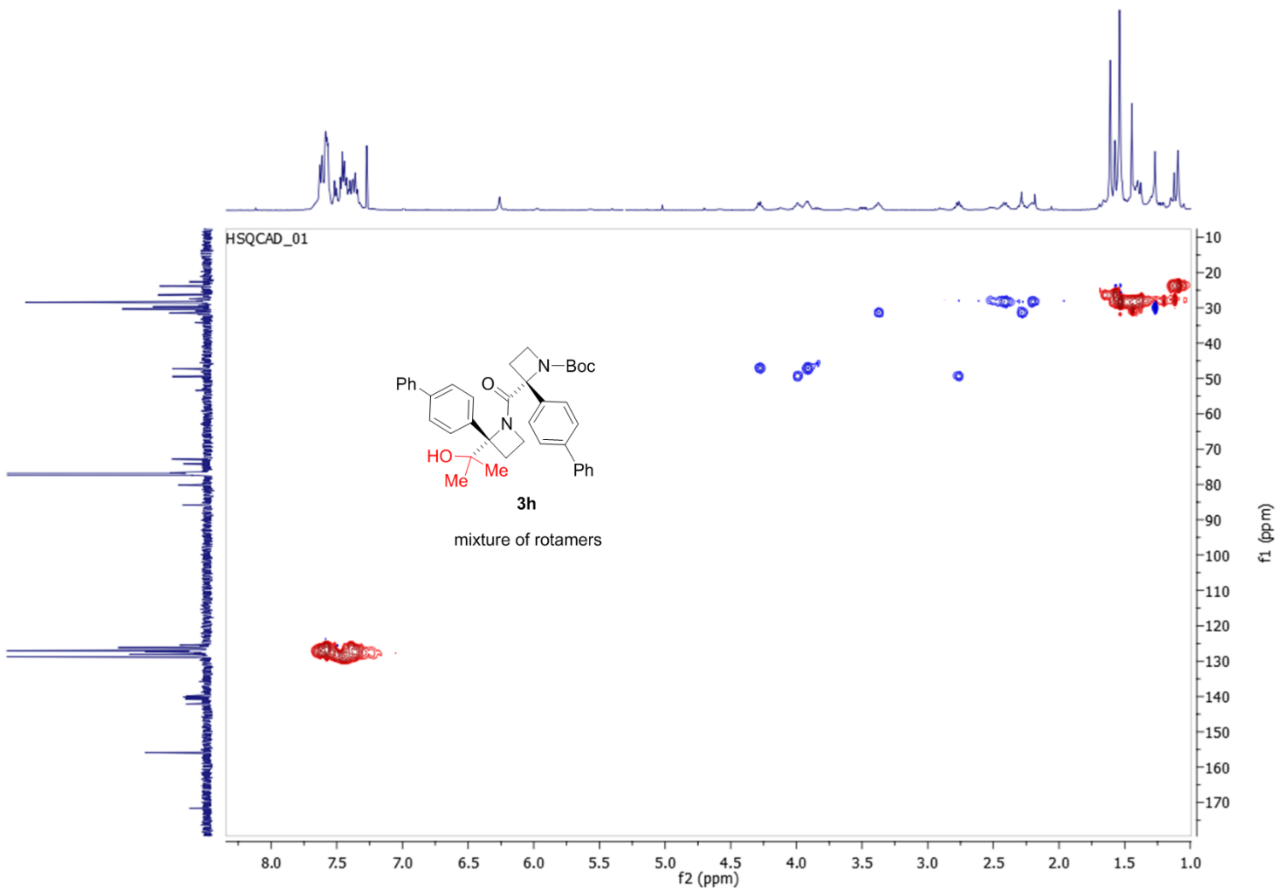
173.53
157.78
142.74
142.50
141.96
141.36
140.94
140.70
140.65
129.44
129.35
127.70
127.66
127.35
127.21
80.24
74.08
63.73
51.70
48.24
48.23
31.75
28.94
25.35
Ph
N–Boc
O
N
D
Ph
3g
mixture of rotamers
toluene d8
129.44
129.35
127.86
127.78
127.70
127.66
127.35
127.21
f1 (ppm)
63.79
f1 (ppm)
f1 (ppm)

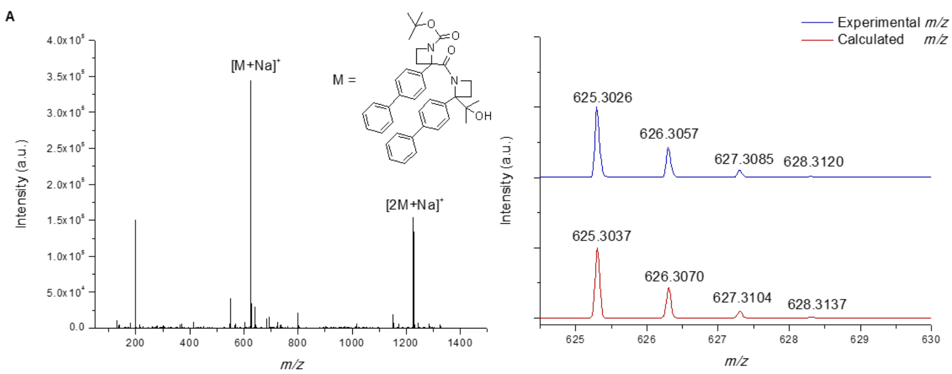

HSQCAD_01
N–Boc
Ph
O
N
D
Ph
3g
mixture of rotamers
f2 (ppm)
f1 (ppm)

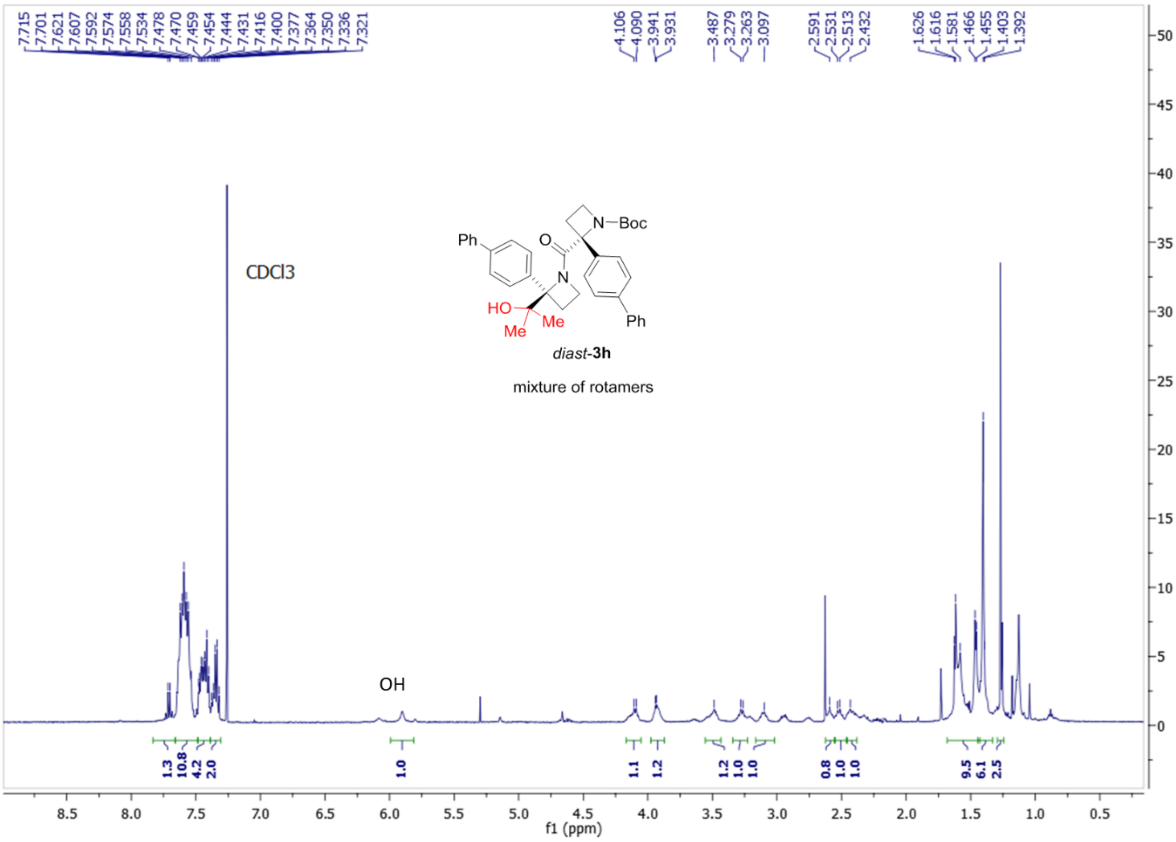

A
[M+Na]+
[2M+Na]+
M =
Intesity (a.u.)
m/z
Experimental m/z
Calculated m/z
568.2675
569.2704
570.2735
568.2681
569.2714
570.2748
Intensity (a.u.)
m/z

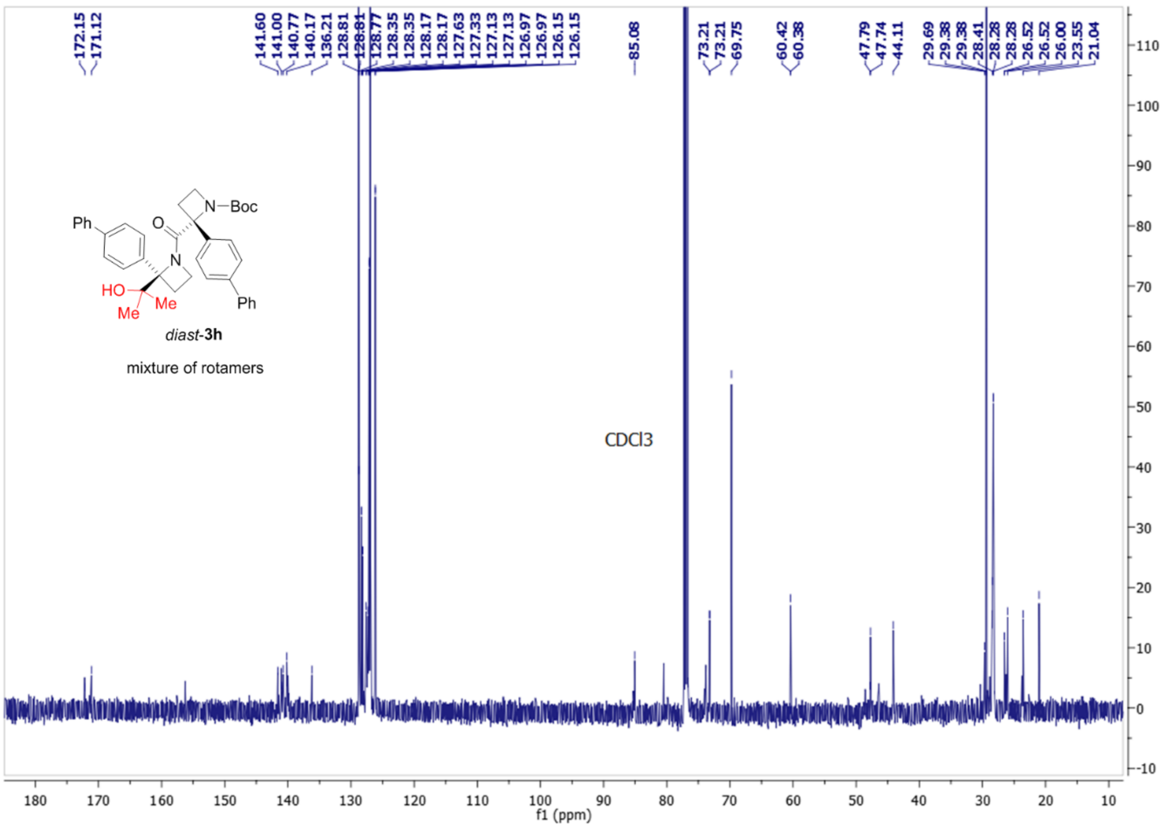

PROTON_01
7.621
7.614
7.583
7.574
7.518
7.472
7.457
7.442
7.426
7.400
7.376
7.360
4.291
4.275
3.988
3.921
3.373
2.777
2.761
2.420
2.285
2.184
1.610
1.575
1.539
1.446
1.269
1.123
1.094
Ph
N—Boc
O
N
HO
Me
Me
Ph
3h
mixture of rotamers
17.13
1.00
0.52
2.33
1.08
1.01
1.85
2.20
12.28
5.17
2.47
2.65
f1 (ppm)

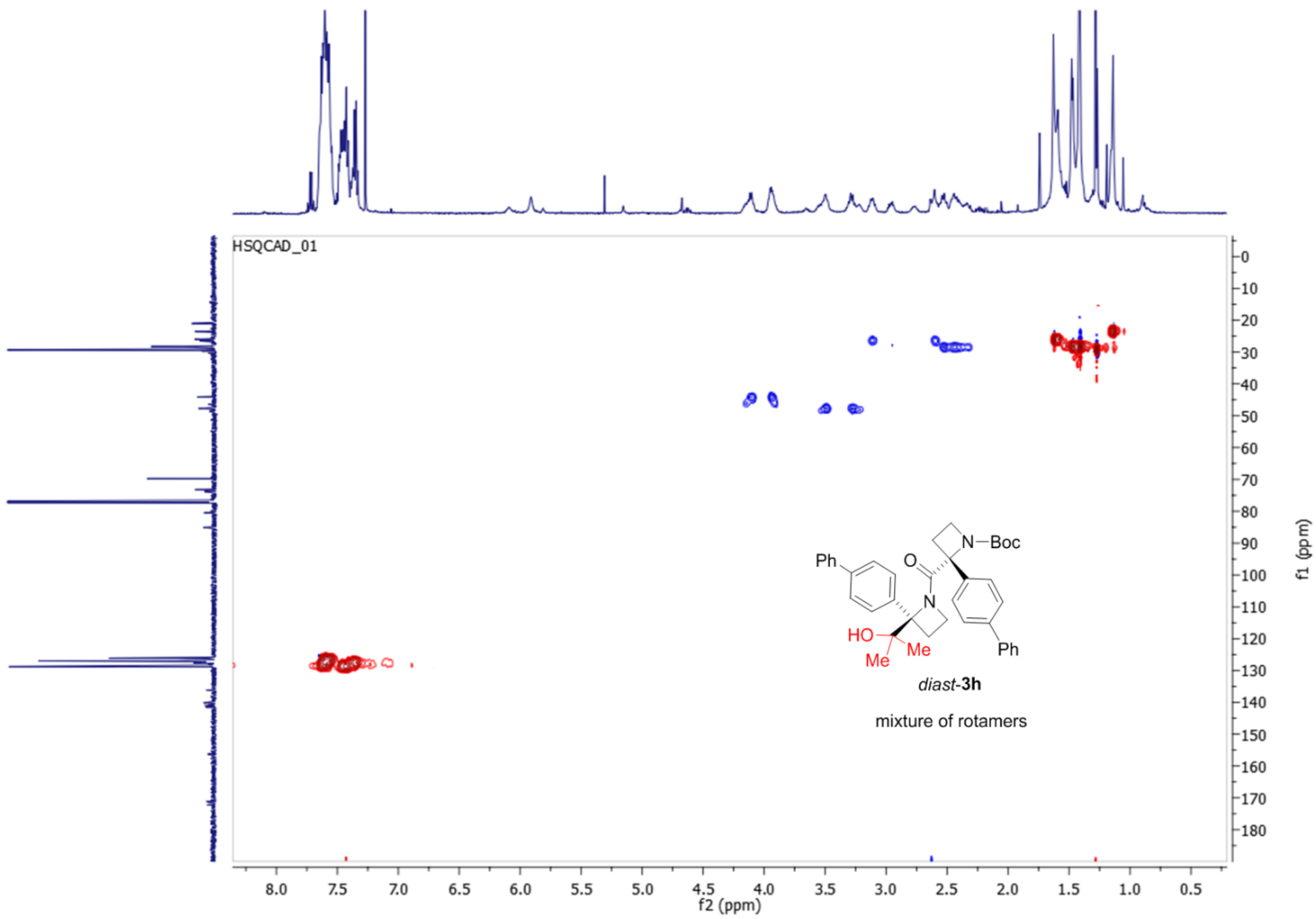

CARBON_01
171.3
155.8
142.1
140.9
140.4
140.2
128.8
128.7
127.1
126.2
85.7
80.2
74.3
72.9
49.5
47.2
31.6
30.3
28.4
26.3
23.7
Ph
N—Boc
O
N
HO
Me
Me
Ph
3h
mixture of rotamers
f1 (ppm)

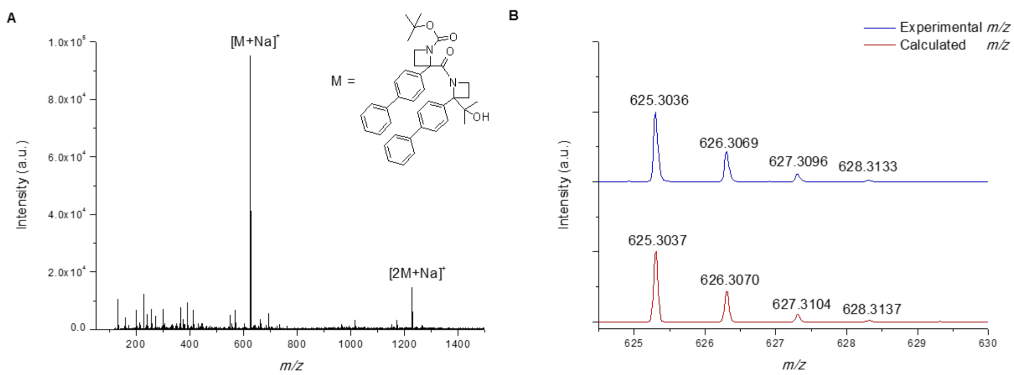

HSQCAD_01
Ph
O
N—Boc
N
HO
Me
Me
Ph
3h
mixture of rotamers
f1 (ppm)
f2 (ppm)


A
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
Experimental m/z
Calculated m/z
625.3026
626.3057
627.3085
628.3120
625.3037
626.3070
627.3104
628.3137






HSQCAD_01
f2 (ppm)
f1 (ppm)
Ph
O
N–Boc
N
HO
Me
Me
Ph
diast-3h
mixture of rotamers


A
[M+Na]+
[2M+Na]+
M =
Intensity (a.u.)
m/z
B
Experimental m/z
Calculated m/z
625.3036
626.3069
627.3096
628.3133
625.3037
626.3070
627.3104
628.3137