

Stereocontrolled lithiation/trapping of chiral 2-alkylideneaziridines: investigation into the role of the aziridine nitrogen stereodynamics

Rosmara Mansueto,^{a,c} Leonardo Degennaro,^a Jean-François Brière,^b Karen Griffin,^c Michael Shipman,^c Saverio Florio^a and Renzo Luisi^{*,a}

^aDepartment of Pharmacy & Drug Sciences University of Bari ðA. Moroð, Via E. Orabona 4, I-70125,

E-mail: renzo.luisi@uniba.it

^b Normandie University, COBRA, UMR 6014 et FR 3038; University of Rouen; INSA Rouen; CNRS, IRCOF, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France

^c Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK

Supporting information

General

THF was freshly distilled under nitrogen atmosphere over Na/benzophenone. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and toluene were distilled over finely powdered CaH₂, *s*-BuLi was purchased as hexane solution and the 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, or Bruker 400, 500 and 600 MHz spectrometers. For the ¹H, ¹³C spectra (¹H NMR 400, 500, 600 MHz, ¹³C NMR 100, 125, 150 MHz), CDCl₃, methanol-*d*₄, THF-*d*₈ 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. IR spectra of the compounds were recorded neat, as film, as KBr disc as indicated, by a Perkin-Elmer 283 spectrometer. For flash chromatography 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 (CH₃OH or CH₃OH + 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 (N₂), and the drying gas (N₂) 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),

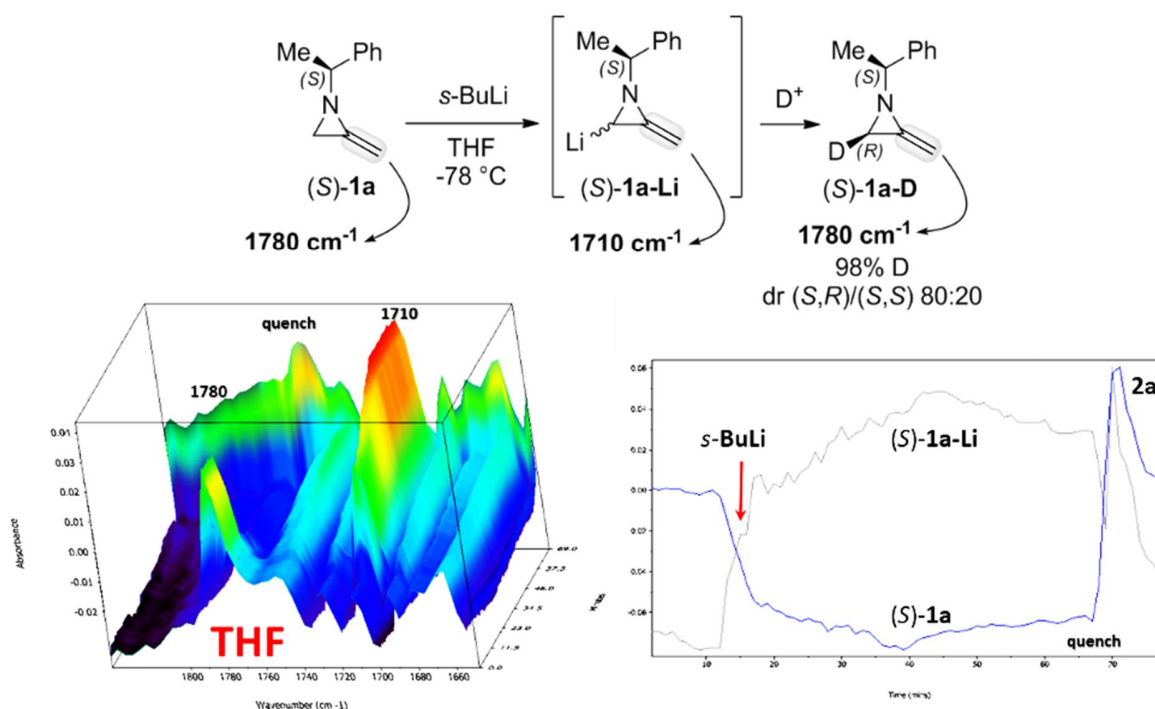
¹ L. Degennaro, A. Giovine, L. Carroccia, R. Luisi in *Lithium Compounds in Organic Synthesis: From Fundamental to Applications* Ch. 18, (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**.

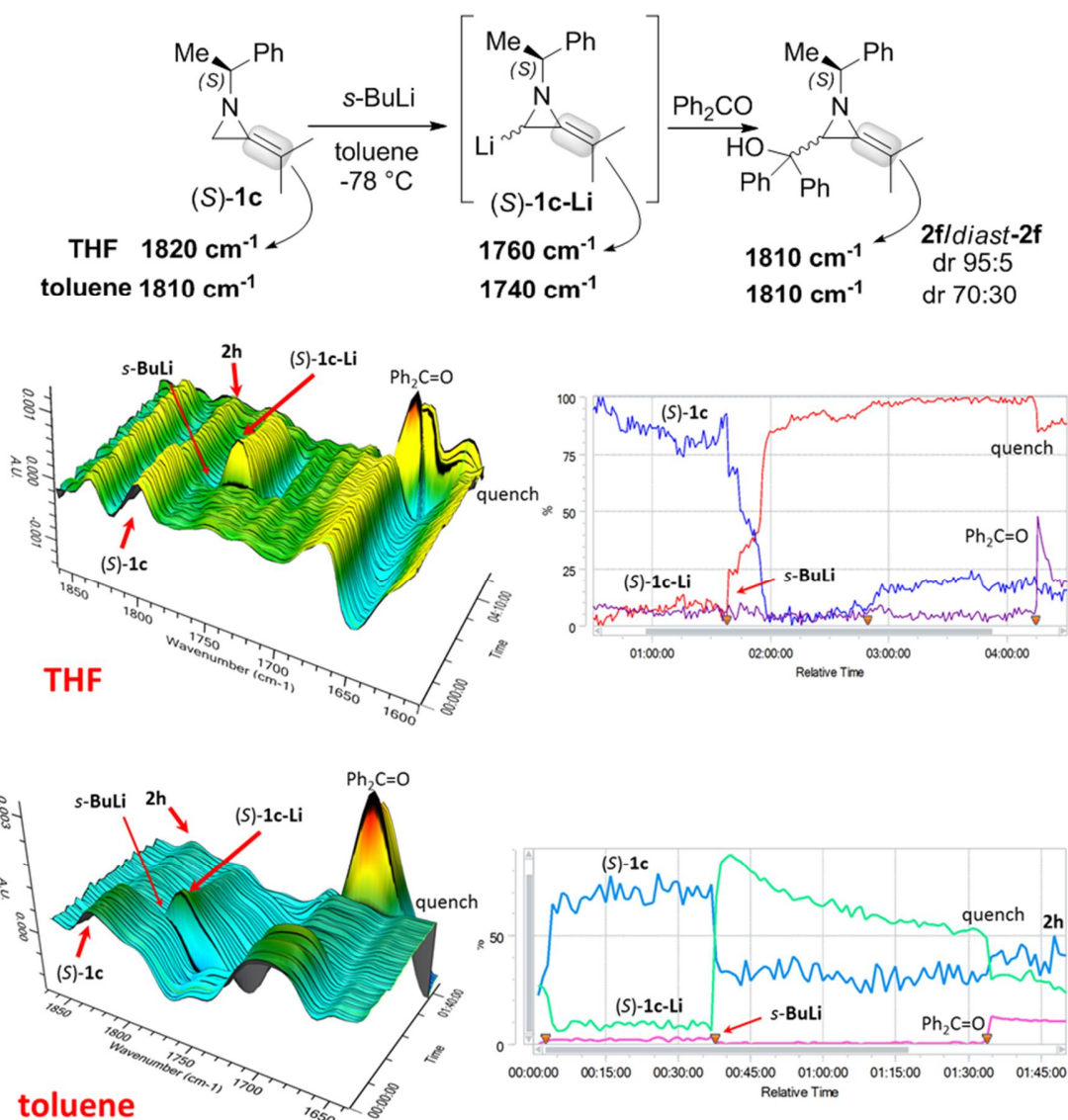
490 μl of *i*-propanol and 490 μl of deionized water. The software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique.

In Situ IR Spectra

In situ infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR 4000 and Ic15 instruments equipped with a diamond-tipped (DiComp®) probe.

In a Schlenk tube equipped with a stirrer bar and the React-IR probe, under inert atmosphere, a 0.2 M THF (or toluene) solution of aziridine **1** is introduced via syringe and cooled to $-78\text{ }^\circ\text{C}$. Reference spectra for the pure solvent and aziridine were collected separately before starting the experiment. The solution was stirred for 10 min (to verify the stability of the readout) and a collected spectra reference for the neutral aziridine. Then, *s*-BuLi (1.2 mmol, 1.4 M solution in hexane) was added dropwise and spectra collected every 30 sec. The solution was stirred for 2 h and monitored by IR spectroscopy. Signals in the range 1820-1780 cm^{-1} were observed for the neutral aziridines **1** which was assigned to $\text{C}=\text{C}$. After addition of *s*-BuLi, new signals in the range 1760-1710 cm^{-1} were observed and assigned to $\text{C}=\text{C}$ of the lithiated intermediates.

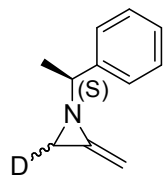




General procedure for the lithiation/electrophile trapping of alkydeneaziridines **1**.

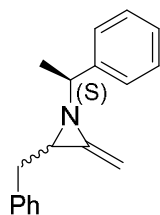
To a stirred solution of alkydene aziridine (1.0 mmol) in 8 mL of THF (or toluene) at $-78\text{ }^{\circ}\text{C}$, *s*-BuLi (1.3 equiv) was added dropwise. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 0.5 h , then quenched with the electrophile ($0.9\text{--}1.5\text{ equiv}$) and stirred for 1 h at this temperature before warming to room temperature. Water was added, the layers separated, and the aqueous phase extracted with diethyl ether. The combined organic extracts were dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Purification by column chromatography or bulb-to-bulb distillation provided the adducts **2**. For some reactions using benzophenone, an additional reductive step was included in the work-up to facilitate removal of excess electrophile.

The spectroscopic data of functionalized alkylideneaziridines **2a**, **2d**, *diast-2d*, **2e**, *diast-2e*, **2f**, *diast-2f*, **2h**, *diast-2h*, have been already reported.² Spectroscopic data of new compounds are reported here.



(S)-**1a-D**

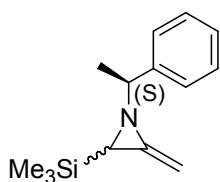
Mixture of rapidly equilibrating invertomers (T = 298 K) (80%), white oil. ¹H NMR (CDCl₃, 300 MHz) : 1.44 (d, *J* = 6.6 Hz, 3 H), 1.92 (s, 0.3 H), 2.10 (s, 0.8 H), 2.85 (q, *J* = 6.6 Hz, 1 H), 4.56-4.58 (m, 2 H), 7.17-7.32 (m, 5 H). ¹³C NMR (CDCl₃, 100 MHz) : 23.4, 29.4 (t), 68.3, 83.0, 126.7, 127.1, 128.3, 136.9, 143.8. HRMS (ES⁺) calcd for C₁₁H₁₅DNO [M + H + H₂O]⁺: 179.1110, found 179.1289. ν_{max} (film) 3076, 1751, 1502, 1450, 699 cm⁻¹.



mixture of diastereoisomers **2a/diast-2a** (dr 70/30) Colorless oil. ¹H NMR (400 MHz,

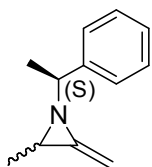
CDCl₃) 7.3767.20 (m, 7H major + minor), 7.1967.11 (m, 2H major + minor), 7.0667.01 (m, 1H major + minor), 4.80 (s, H minor), 4.70 (s, H minor), 4.50 (s, H major), 4.20 (s, H major), 2.95 (q, *J* = 6.7 Hz, H minor), 2.90 (q, *J* = 6.7 Hz, H major), 2.7562.86 (m, 2 H major + 1 H minor), 2.64 (dd, *J* = 14.3, 6.4 Hz, 1 H minor), 2.12 (t, *J* = 6.4 Hz, 1H major), 2.03 (t, *J* = 6.4 Hz, 1H minor), 1.51 (d, *J* = 6.7 Hz, 3H minor), 1.26 (d, *J* = 6.7 Hz, 3H major); ¹³C NMR (100 MHz, CDCl₃) 143.94, 143.90, 142.3, 141.6, 139.2, 138.7, 129.0, 128.6, 128.49, 128.47, 128.4, 128.3, 127.2, 127.1, 126.8, 126.4, 126.2, 125.9, 83.5, 83.4, 68.2, 67.6, 43.3, 42.6, 39.1, 38.9, 23.9, 23.1. IR (film) 3062, 3032, 2965, 2919, 2832, 1767, 1495, 1449, 1152, 830, 748, 702 cm⁻¹. MS (EI) m/z 249 (M⁺); HRMS (CI) calcd for C₁₈H₂₀N 250.1595, found 250.1593.

² a) J. F. Hayes, N. Prévost, I. Prokes, M. Shipman, A. M. Z. Slawin, H. Twin, *Chem. Commun.* **2003**, 1344. b) C. Montagne, N. Prévost, J. J. Shiers, G. Prie, S. Rahman, J. Ince, J. F. Hayes, M. Shipman, *Tetrahedron* **2006**, 62, 8447.



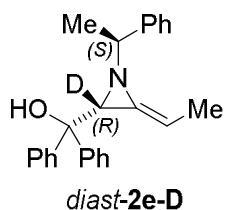
mixture of diastereoisomers **2b**/*diast-2b* (dr 80/20)

(70%), white oil. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : -0.2 (m, 1.8 H minor), 0.01 (s, 9 H major) 1.06 (s, 0.2 H minor), 1.19 (s, 1 H major), 1.31 (d, $J = 6.7$ Hz, 2.1 H major), 1.46 (d, $J = 6.7$ Hz, 0.9 H minor), 2.70-2.80 (2 x q, 1.2 H major + minor), 4.13 (s, 1 H major), 4.24 (s, 1 H major), 4.44 (s, 0.2 H minor), 4.72 (s, 0.2 minor), 7.35-7.54 (m, 6 H major + minor). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) : -2.9, -3.0 (major + minor), 23.5 (major), 24.1 (minor), 33.5 (major), 34.0 (minor), 69.6 (major), 71.0 (minor), 80.6 (major + minor), 126.5 (minor), 126.7 (minor), 126.9 (major), 126.9 (major), 126.9 (major), 127.0 (minor), 128.1 (major), 128.4 (minor), 141.5 (major), 142.6 (minor), 144.4 (minor), 144.6 (major). HRMS (ES^+) calcd for $\text{C}_{14}\text{H}_{22}\text{NSi}$ $[\text{MH}]^+$ 232.1521, found 232.1517. ν_{max} (film) 2960, 1752, 1450, 1250, 1137, 938, 702 cm^{-1} .

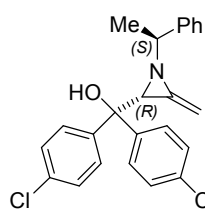


mixture of diastereoisomers **2c**/*diast-2c* (dr 70/30)

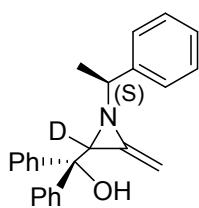
(87%), white oil. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : 1.17 (d, $J = 5.6$ Hz, 0.9 H), 1.30 (d, $J = 5.6$ Hz, 2.1 H), 1.39-1.44 (m, 3 H), 1.82-2.02 (m, 2 H), 2.82-3.00 (m, 2 H), 4.18 (s, 0.7 H), 4.44 (s, 0.7 H), 4.63 (s, 0.3 H), 4.73 (s, 0.3 H), 7.14-7.31 (m, 5 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) : 17.4, 17.5, 23.1, 24.4, 37.4, 37.4, 67.3, 68.4, 81.3, 126.4, 126.7, 126.9, 127.0, 127.0, 127.2, 128.2, 128.3, 142.6, 144.0. HRMS (ES^+) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}$ $[\text{M} + \text{H} + \text{H}_2\text{O}]^+$: 192.1200, found 179.1383. ν_{max} (film) 2966, 1763, 1449, 1174, 822 cm^{-1} .



^1H NMR (CDCl_3 , 400 MHz) : 1.40 (d, $J = 6.5$, 3 H), 1.88 (d, $J = 6.5$, 3 H), 3.62 (q, $J = 6.5$, 1 H), 3.67 (bs, 1 H), 5.10 (q, $J = 6.5$, 1 H), 6.98-7.31 (m, 15 H). ^{13}C NMR (CDCl_3 , 100 MHz) : 13.9, 22.5, 46.0, 64.6, 74.5, 96.5, 126.0, 126.5, 126.7, 127.1, 127.2, 127.5, 127.3, 128.0, 128.1, 129.1, 141.3, 144.9, 146.3. ν_{max} (film) 2249, 1449, 1032, 903, 1006, 726, 701 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ ($c = 1$, CHCl_3) = -11.5. ESI-MS m/z (rel. int): 357 $[\text{M}+\text{H}]^+$

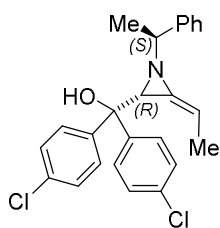


(70%) white oil. ^1H NMR (CDCl_3 , 600 MHz) : 1.53 (d, $J = 6.7$ Hz, 3 H), 2.83 (s, 1 H), 3.22 (q, $J = 6.7$ Hz, 1 H), 3.51 (bs, exchange with D_2O , 1 H), 4.76 (s, 1 H), 4.99 (s, 1 H), 6.93 (bs, 4 H), 7.04 (d, $J = 7.7$ Hz, 2 H), 7.11 (t, $J = 7.7$ Hz, 2 H), 7.19-7.30 (m, 5 H). ^{13}C NMR (CDCl_3 , 125 MHz) : 23.1, 48.9, 67.7, 74.1, 85.1, 126.9, 127.4, 127.9, 128.1, 128.3, 128.4, 132.6, 133.4, 136.9, 142.2, 142.7, 143.6. HRMS (ES^+) calcd for $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{NO}$ $[\text{MH}]^+$ 410.1078, found 410.1077. ν_{max} (film) 3467, 3030, 2975, 2871, 1779, 1661, 1592, 1490, 1167, 1092, 1014, 827, 699 cm^{-1} . $[\alpha]_{\text{D}} = +7.2$ ($c = 1$, CHCl_3).



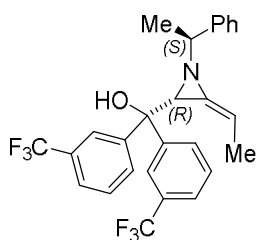
mixture **2d-D**/*diast-2d-D*

(70%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : 0.93 (d, $J = 6.7$ Hz, 0.2 H minor), 1.48 (s, $J = 6.7$ Hz, 0.8 H major), 3.21 (q, $J = 6.7$ Hz, 0.2 H minor), 3.31 (q, $J = 6.7$ Hz, 0.8 H major), 3.51 (s, exchange with D_2O , 0.8 H major), 3.77 (s, exchange with D_2O , 0.2 H minor), 4.41 (s, 0.2 H minor), 4.68 (s, 0.2 H minor), 4.74 (s, 0.8 H major), 4.94 (s, 0.8 H major), 7.00-7.54 (m, 15 H major + minor). ESI-MS m/z (rel. int): 343 $[\text{M}+\text{H}]^+$ (100). ν_{max} (film) 3026, 1768, 1447, 1153, 1030, 824, 696 cm^{-1} .



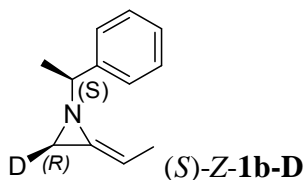
diast-2i (major diastereoisomer isolated from lithiation/trapping in toluene).

(81%) white solid. $^1\text{H NMR}$ (CDCl_3 , 600 MHz) : 1.40 (d, $J = 6.6$ Hz, 3 H), 1.49 (d, $J = 6.7$ Hz, 3 H), 2.95 (s, 1 H), 3.14 (q, $J = 6.7$ Hz, 1 H), 3.69 (bs, exchange with D_2O , 1 H), 5.41 (q, $J = 6.6$ Hz, 1 H), 6.88 (bs, 4 H), 7.10 (d, $J = 7.7$ Hz, 2 H), 7.14 (t, $J = 7.7$ Hz, 2 H), 7.20-7.32 (m, 5 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) : 14.1, 23.5, 49.2, 68.1, 73.7, 97.2, 126.9, 127.5, 127.6, 127.8, 128.1, 128.3, 128.4, 128.7, 132.5, 133.0, 142.9, 143.6, 143.9. HRMS (ES^+) calcd for $\text{C}_{25}\text{H}_{23}\text{Cl}_2\text{NO}$ $[\text{MH}]^+$ 424.1235, found 424.1237. ν_{max} (film) 3030, 2925, 2855, 1779, 1663, 1591, 1490, 1092, 1014, 833, 699 cm^{-1} . $[\alpha]_{\text{D}} = +7.2$ (c 0.25, CHCl_3).



diast-2j (major diastereoisomer isolated from lithiation/trapping in toluene).

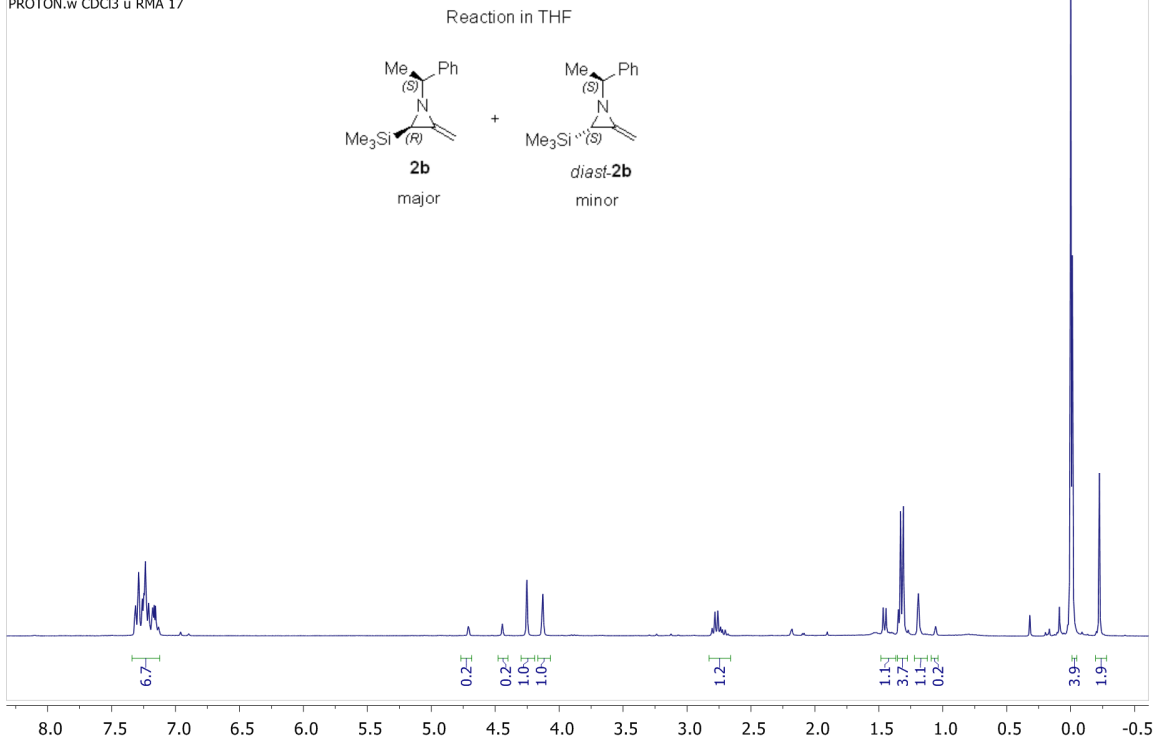
(78%), white oil, 70/30 diastereomeric mixture. $^1\text{H NMR}$ (CDCl_3 , 600 MHz) : 1.04 (d, $J = 6.6$ Hz, 0.9 H), 1.33 (d, $J = 6.6$ Hz, 0.9 H), 1.39 (d, $J = 6.7$ Hz, 2.7 H), 1.49 (d, $J = 6.7$ Hz, 2.7 H), 3.06 (s, 0.7 H), 3.09 (s, 0.3 H), 3.18 (q, $J = 6.7$ Hz, 0.7 H), 3.28 (q, $J = 6.7$ Hz, 0.3 H), 3.95 (s, 0.7 H), 4.19 (s, 0.3 H), 4.85 (q, $J = 6.7$ Hz, 0.3 H), 5.44 (q, $J = 6.7$ Hz, 0.7 H), 7.02-8.04 (m, 13 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) : 13.7 (major), 13.9 (minor), 22.8 (minor), 23.5 (major), 49.0 (major), 49.8 (minor), 66.4 (minor), 67.9 (major), 97.3 (major), 97.7 (minor), 122.7- 131.7 (ArC major/minor + CF_3), 126.5 (minor), 133.0 (major), 137.4 (minor), 142.5 (major), 142.8 (minor), 145.2 (minor), 145.8 (major), 146.1 (major), 147.0 (minor). HRMS (ES^+) calcd for $\text{C}_{27}\text{H}_{23}\text{F}_6\text{NO}$ $[\text{MH}]^+$ 492.1757, found 492.1757. ν_{max} (film) 3338, 3033, 2930, 1781, 1673, 1612, 1446, 1329, 1167, 1127, 700 cm^{-1} .



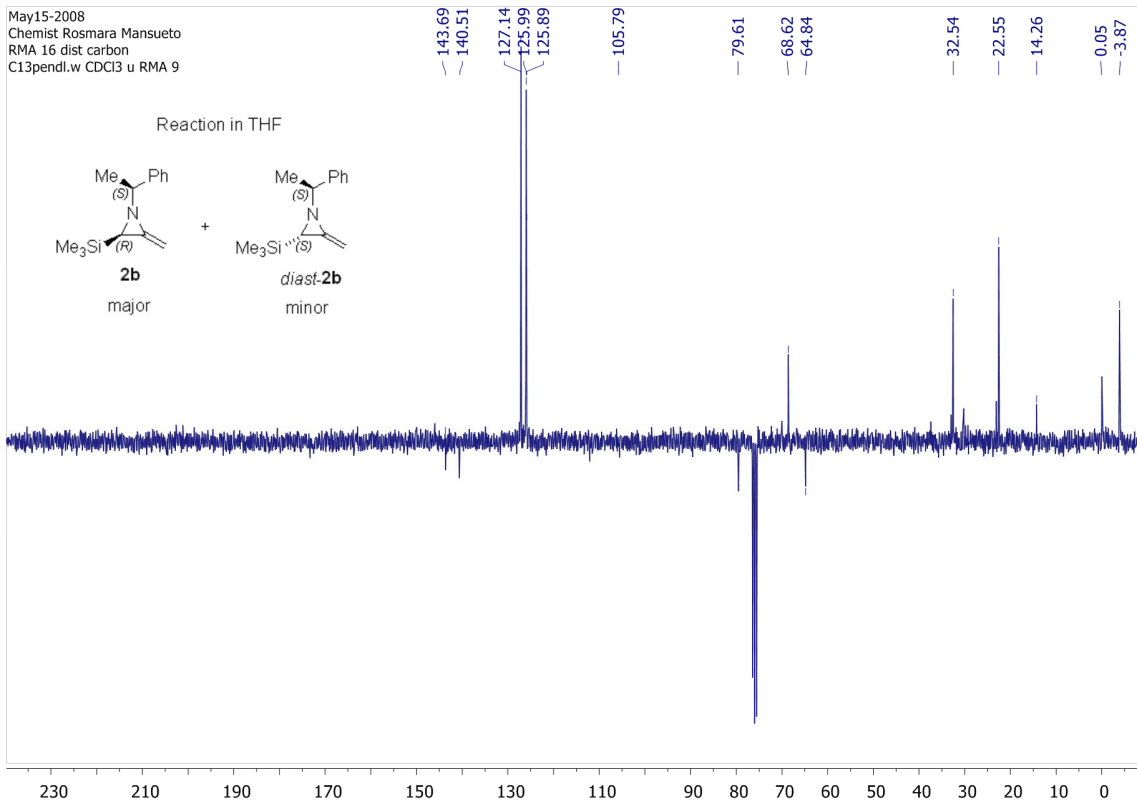
(*S*)-**Z-1b-D**

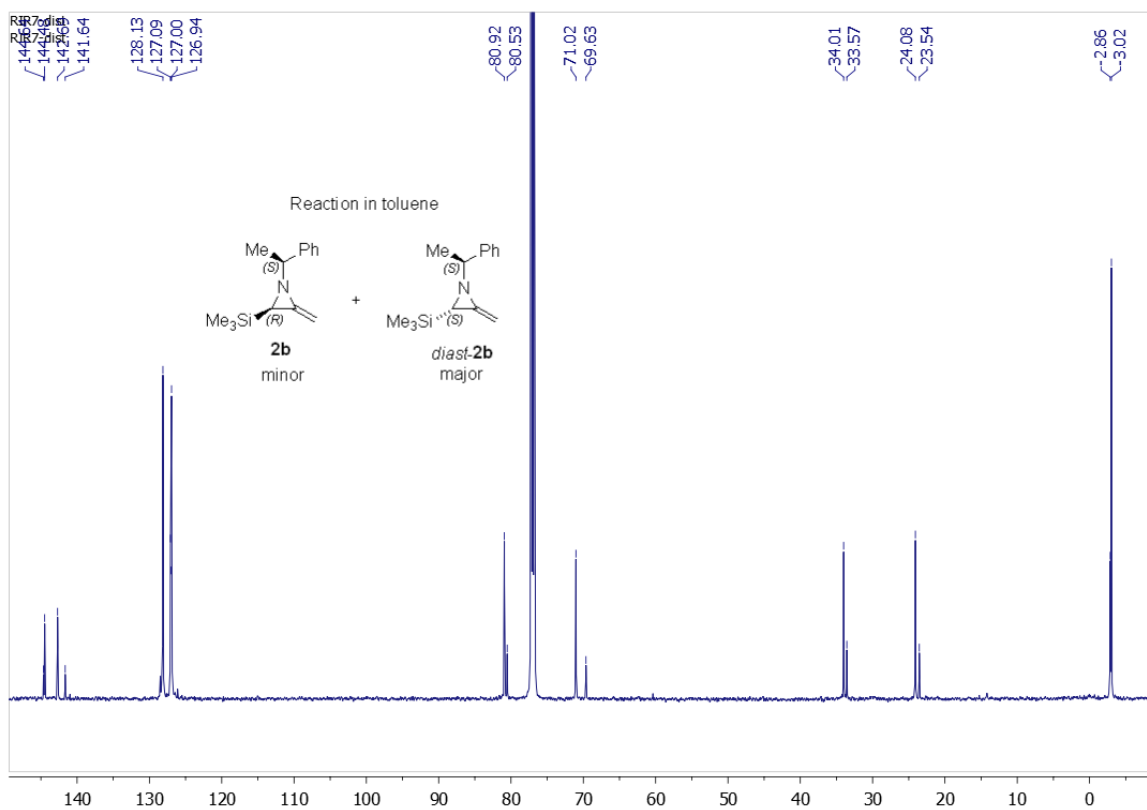
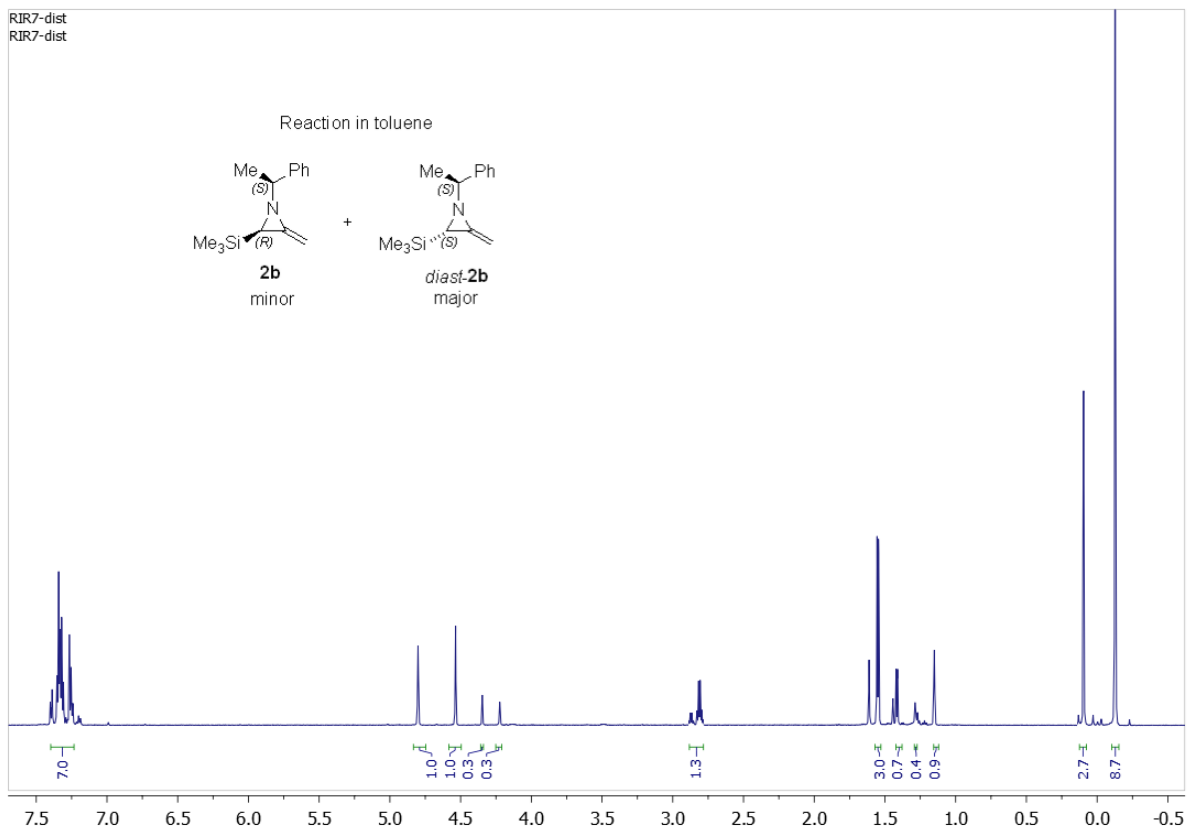
(70%, white oil), $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : 1.40 (bs, 3 H), 1.54 (d, $J = 6.7$ Hz, 3 H), 1.95 (s, 1 H), 2.98 (q, $J = 6.7$ Hz, 1H), 5.05 (q, $J = 6.4$ Hz, 1 H), 7.24-7.40 (m, 5 H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) : 13.6, 23.7, 29.6 (t), 68.2, 95.2, 126.4, 126.6, 127.7, 143.8. ESI-MS m/z (rel. int): 175 $[\text{M}+\text{H}]^+$ (100). $[\alpha]_{\text{D}}^{20}$ ($c = 1$, CHCl_3) = -128.2. HRMS (ES^+) calcd for $\text{C}_{12}\text{H}_{17}\text{DNO}$ $[\text{M} + \text{H} + \text{H}_2\text{O}]^+$: 193.1270, found 193.1446. ν_{max} (film) 2970, 1777, 1450, 1137, 1001, 698 cm^{-1} .

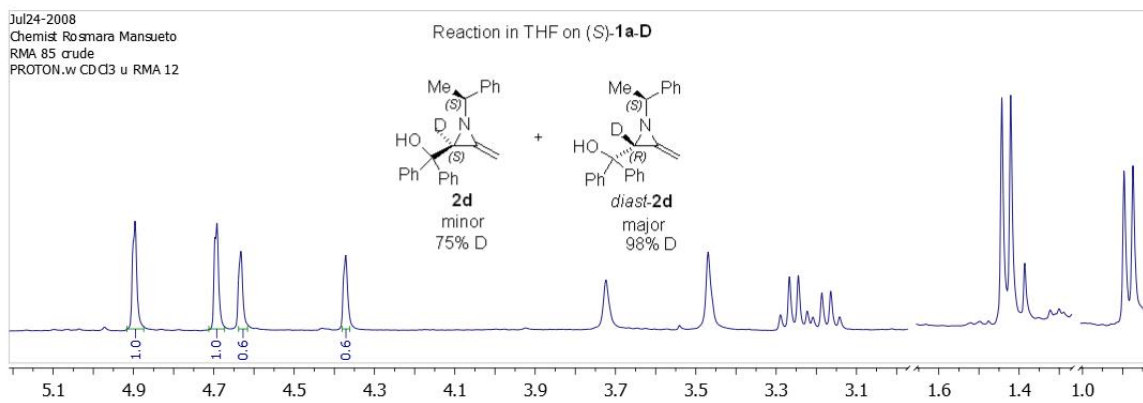
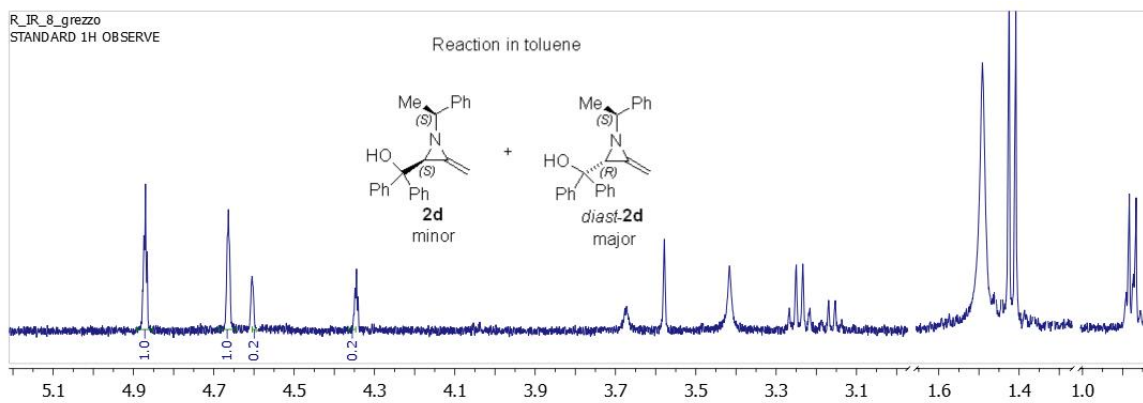
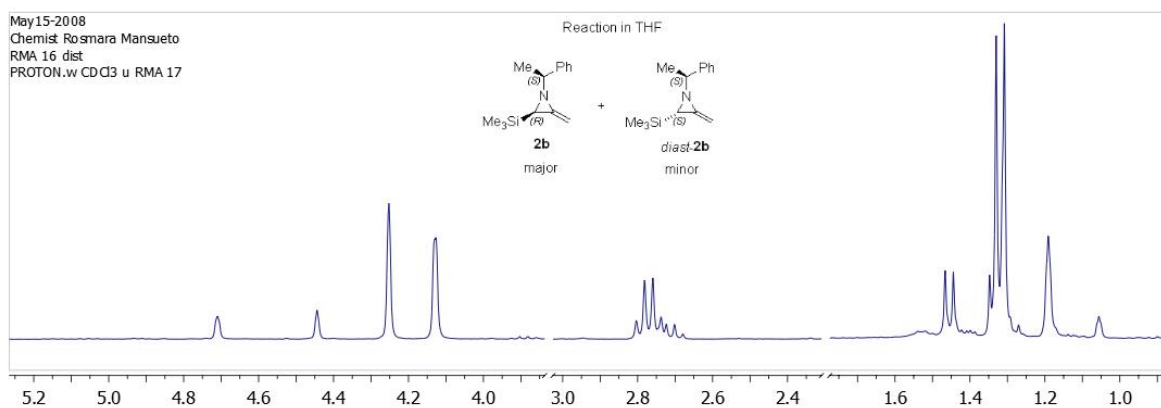
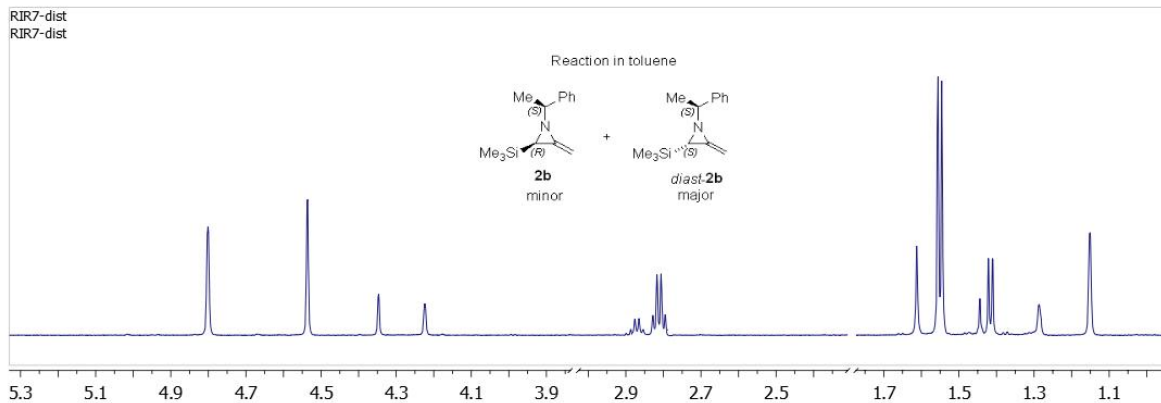
May15-2008
Chemist Rosmara Mansueto
RMA 16 dist
PROTON.w CDCI3 u RMA 17

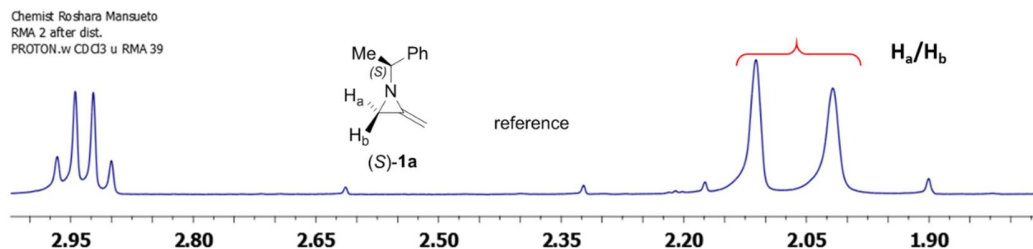
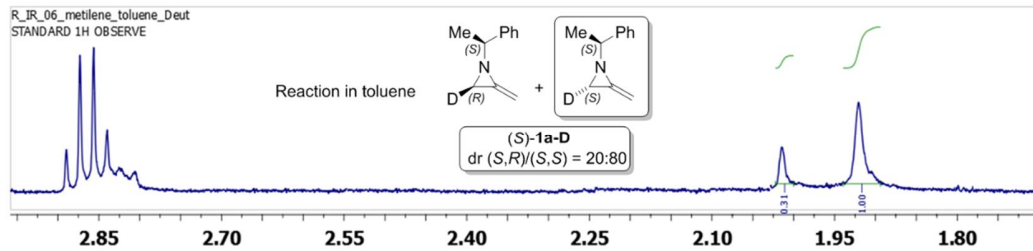
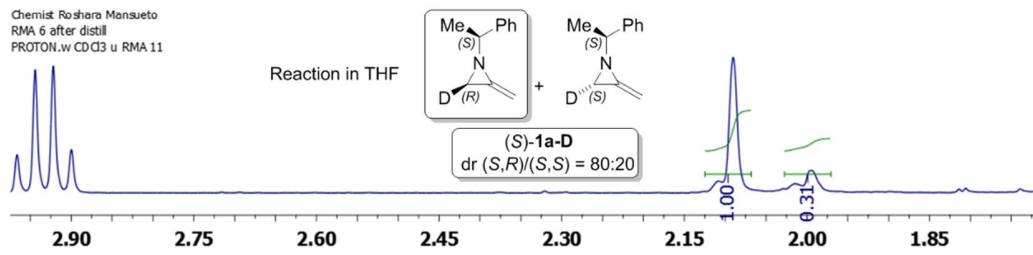
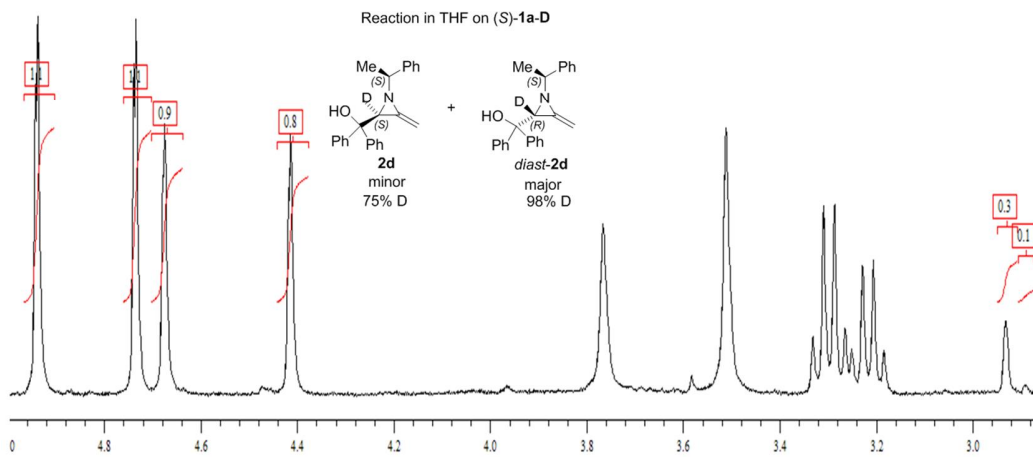
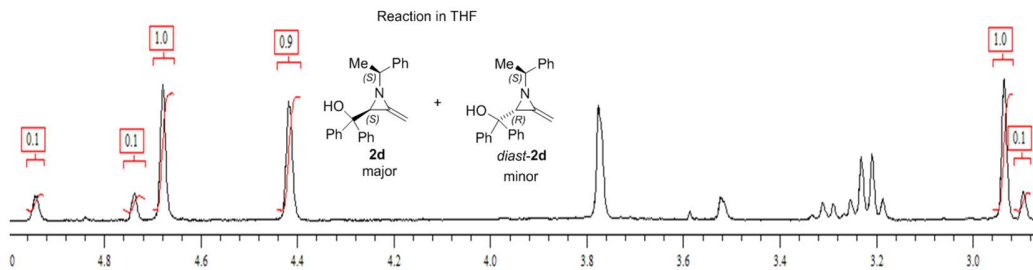


May15-2008
Chemist Rosmara Mansueto
RMA 16 dist carbon
C13pendl.w CDCI3 u RMA 9

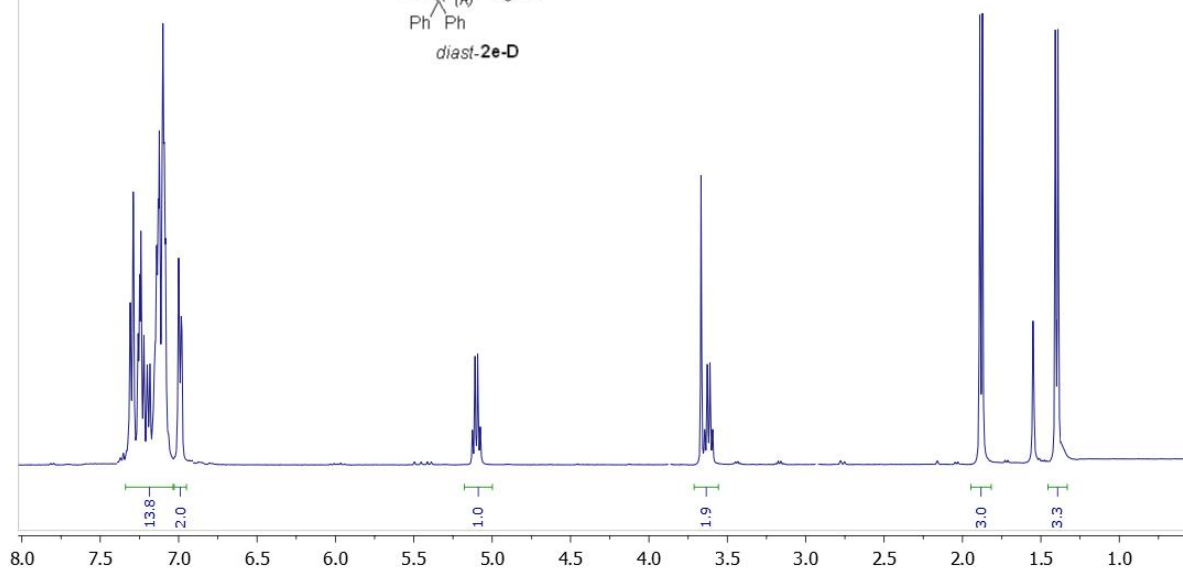
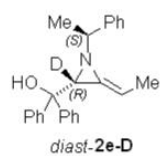




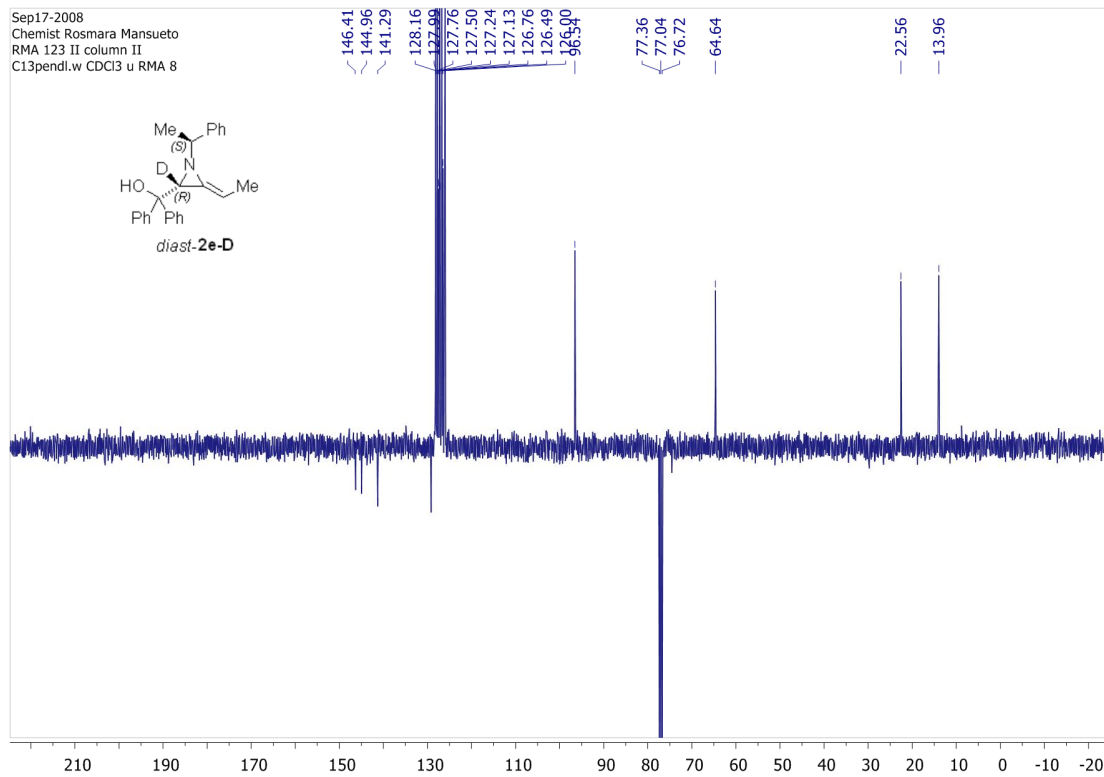
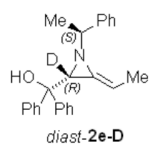




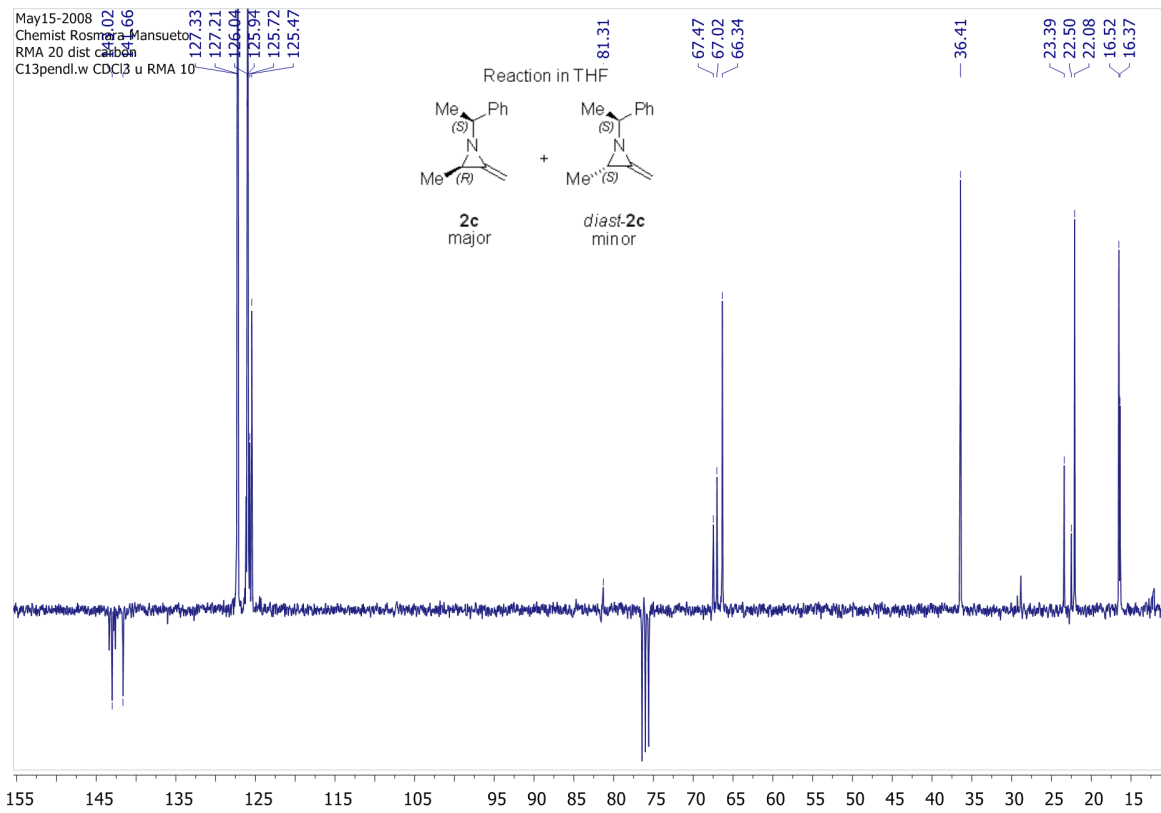
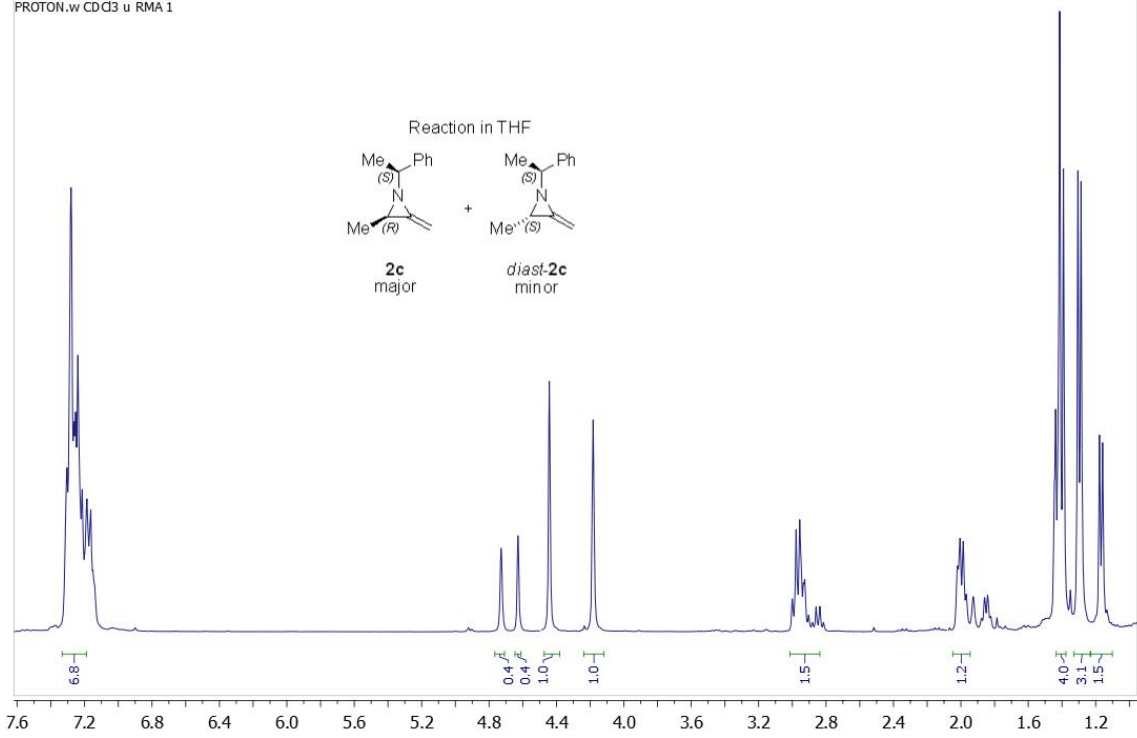
Sep17-2008
Chemist Rosmara Mansueto
RMA 123 II column II
PROTON.w CDCl3 u RMA 8



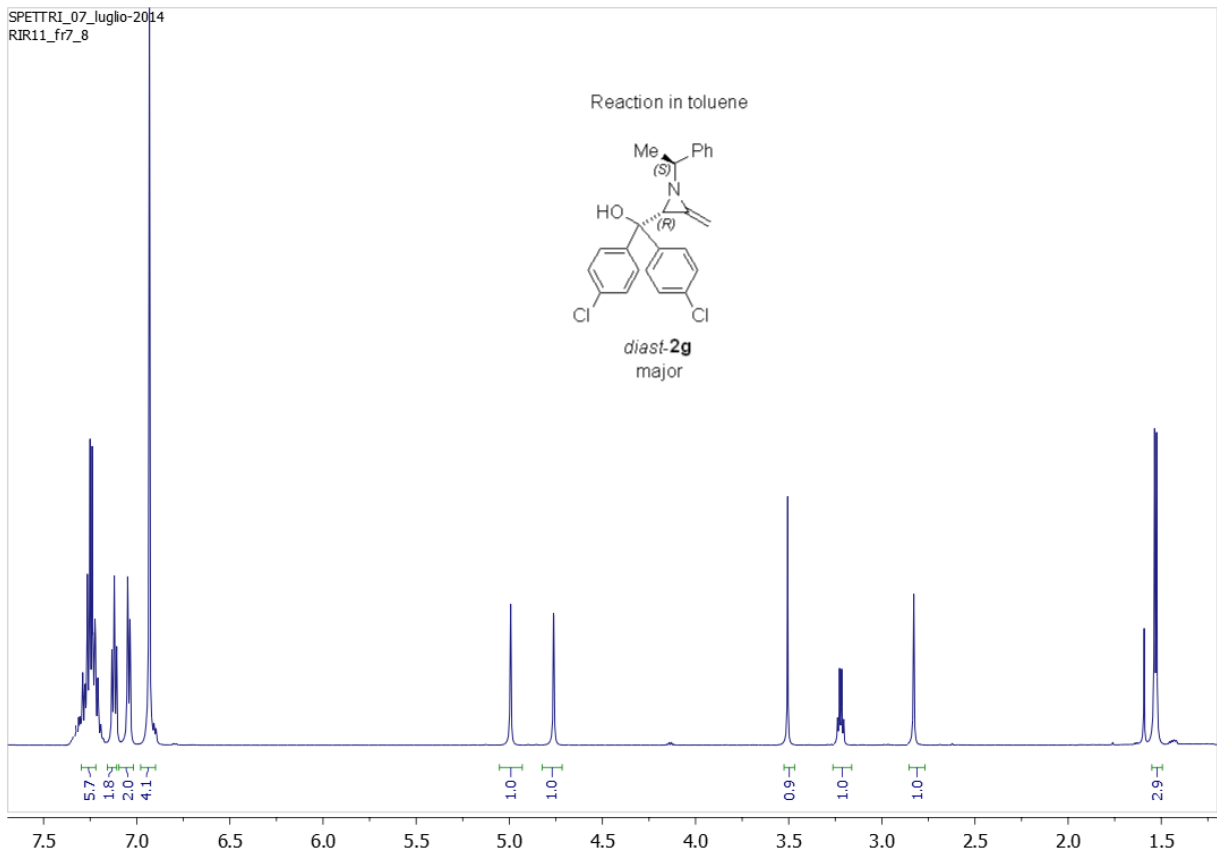
Sep17-2008
Chemist Rosmara Mansueto
RMA 123 II column II
C13pendl.w CDCl3 u RMA 8



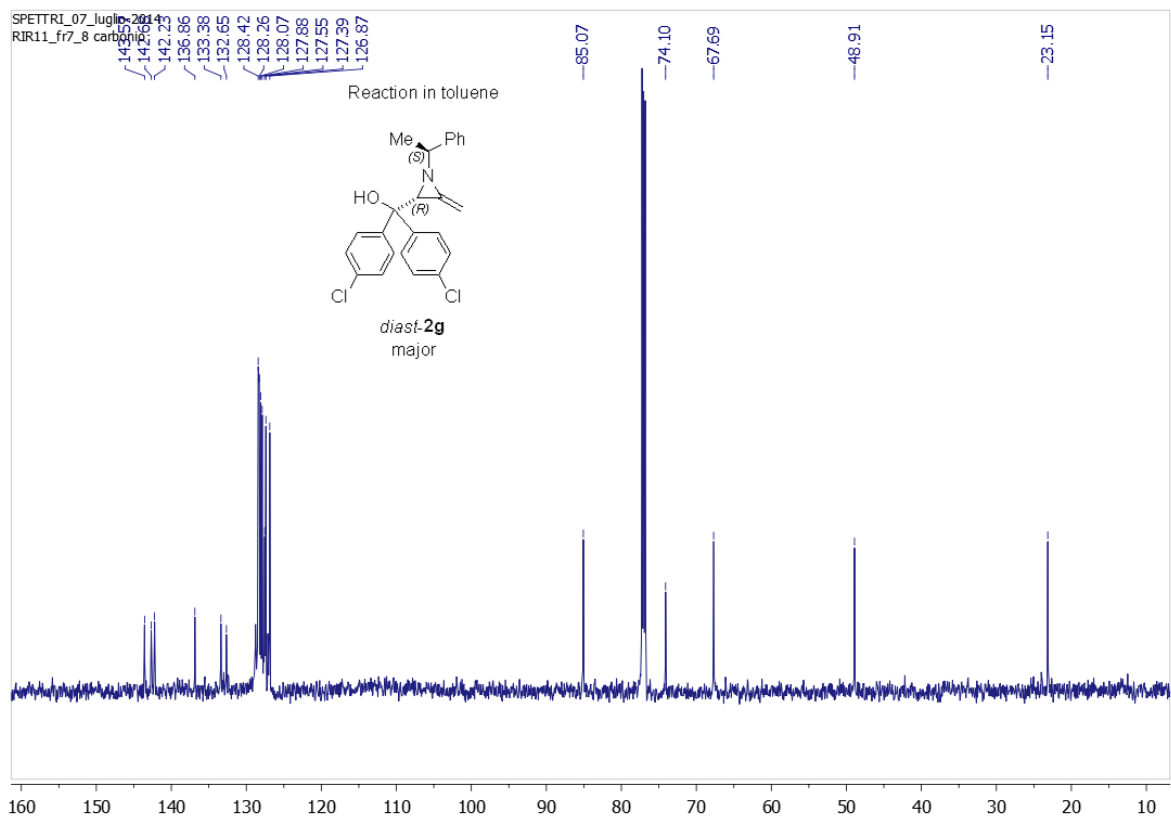
May15-2008
Chemist Rosmaria Mansueto
RMA 20 dist
PROTON.w CDCl3 u RMA 1



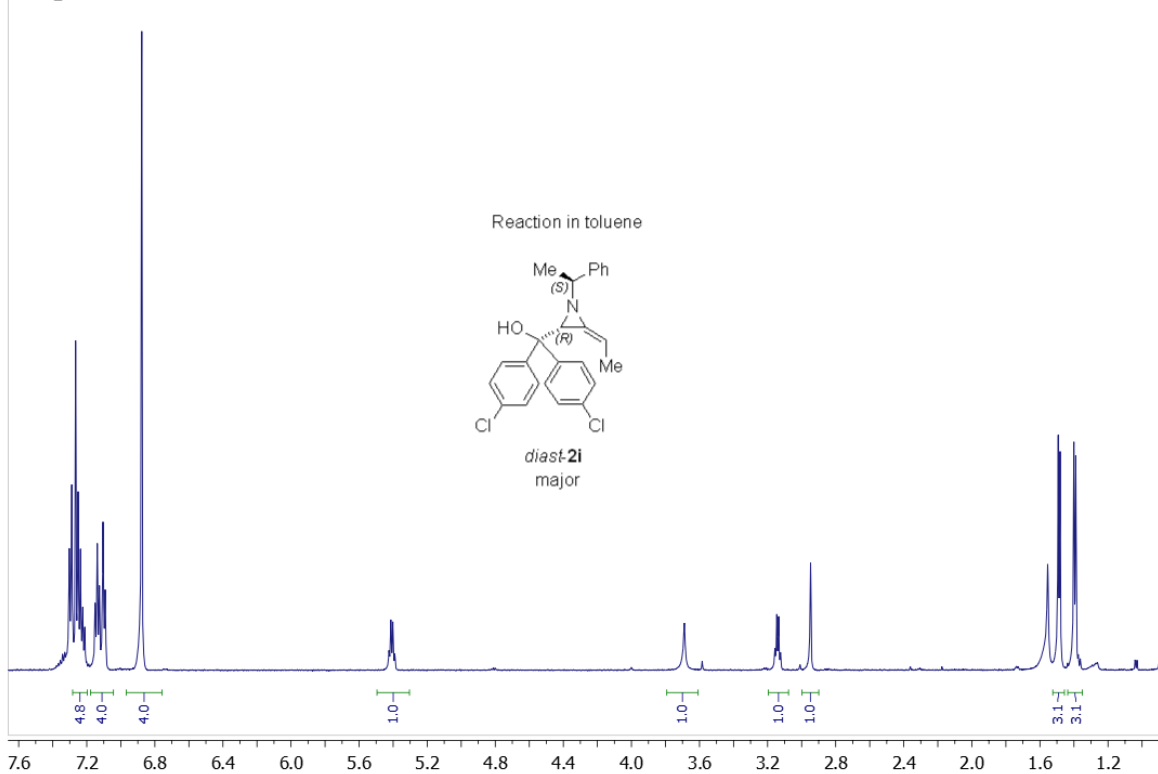
SPETTRI_07_luglio-2014
RIR11_fr7_8



SPETTRI_07_luglio-2014
RIR11_fr7_8 carboni



SPETTRI_24_giugno-2014
R-IR-10_solido



SPETTRI_25_giugno-2014
R-IR-10_solido

