Electronic Supplementary Material (ESI) for Chemical Communications

Chiral Brønsted Acid-Catalyzed Diastereo- and Enantioselective Synthesis of CF_3-Substituted Aziridines

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Supporting Information

Contents

General Information:

^{1}H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F (282 MHz) NMR spectra were recorded on a Bruker AVANCE 300. Chemical shifts in NMR spectra are reported in parts per million with reference to solvent residues in $CDCl_3$ (7.26 for proton and 77.0 for carbon, internal standard) or $CFCl_3$ (external standard for fluorine). IR spectra were recorded on a Perkin-Elmer IRFT 1650 spectrometer. The enantiomeric excesses (ee's) were determined by HPLC analysis. HPLC analysis were performed on Agilent HPLC 1100 Series system, column DAICEL CHIRALCEL OD-H or OJ-H, mobile phase, *n*-heptane / 2-propanol, UV detector at 254 or 210 nm. Toluene was distilled from sodium benzophenone ketyl under a positive pressure of nitrogen. The substituted aryl glyoxal monohydrates were prepared using literature methods.[1]

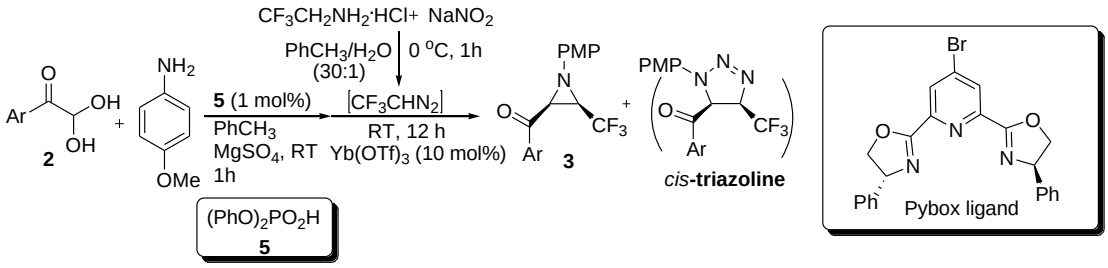
Typical procedure for the asymmetric aza-Darzens reaction of imines derived from aryl glyoxal hydrates:

CAUTION: Trifluoromethyl diazomethane (CF_3CHN_2) is potentially explosive, although no accident occurred during the course of this study, in which this reagent was in situ generated and used in solution.

To a 5-mL flask charged with $CF_3CH_2NH_2{\cdot}HCl$ (30 mg, 0.22 mmol) and $NaNO_2$ (18 mg, 0.26 mmol) was added 0.6 mL of toluene and 20 μL of distilled H_2O, and the resultant mixture was stirred vigorously at 0 ^{o}C for 1 h. Meanwhile, to another 5-mL flask charged with phenylglyoxal hydrate **1a** (16.7 mg, 0.11 mmol), (*S*)-TRIP (2.1 mg, 2.5 mol%), anhydrous $MgSO_4$ (~250 mg) and *p*-anisidine (13.5 mg, 0.11 mmol) was added 0.5 mL of toluene and the mixture was stirred at r.t. for 1 h. Then, anhydrous $MgSO_4$ (~250 mg) was added to the *in situ* prepared CF_3CHN_2 solution and stirred at 0 ^{o}C for 2 min and the supernatant clear yellow solution was transferred via pipette to the second flask containing the *in situ* generated imine and the resulting mixture was stirred at r.t. for 12 h. At this time, a second batch of (*S*)-TRIP (1.7 mg, 2.0 mol%) was added to the reaction mixture and stirring was continued for another 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and sat. $NaHCO_3$ (15 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (15 mL×2) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography on silica gel eluting with 5%→10% (volume%) ethyl acetate in petroleum ether (bp 40-60 ^{o}C) to furnish the desired aziridine **3a**.

Preparation of racemic products by $Yb(OTf)_3$-catalyzed reactions

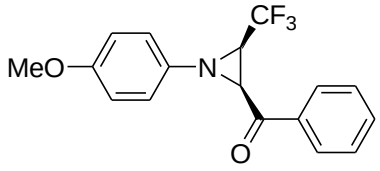
A similar procedure as above was adopted with the following exceptions: all the amount of solvent were doubled (0.05 M for imine); for the in of the imine, $(PhO)_2PO_2H$ (1 mol%) was used; after the mixing of the imine and CF_3CHN_2 solution, $Yb(OTf)_3$ (10 mol%) was added and the reaction was stirred at r.t. for 12 h. After the work-up, the residue was purified by column chromatography on silica gel eluting with 10% (volume%) ethyl acetate in petroleum ether (bp 40-60 ^{o}C) to furnish the desired aziridine product.



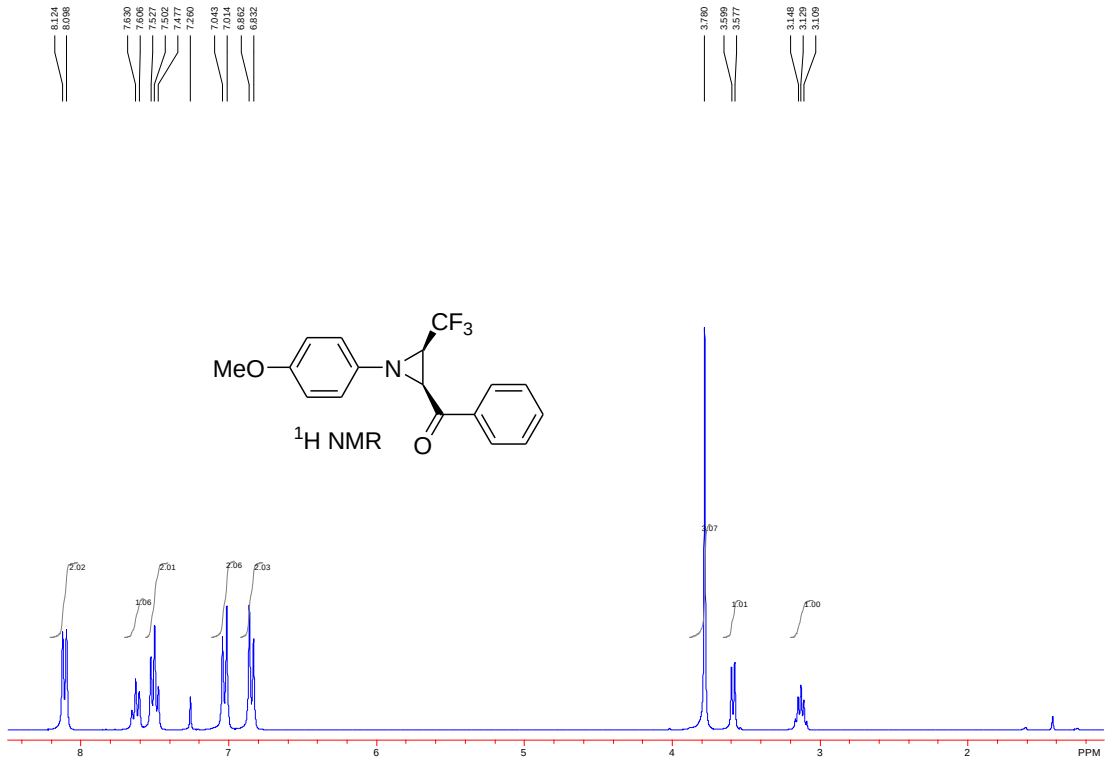
Entry	**2** (Ar)	**3**	Yield (%)[a]	Product ratio (*cis*-**3**:*trans*-**3**:*cis*-triazoline)[b]
1	**2a** (Ph)	**3a**	81	17.4:2.5:1
2	**2b** (4-BrC_6H_4)	**3b**	85	7.9:1.6:1
3	**2c** (3-BrC_6H_4)	**3c**	68	8.3:1.3:1
4	**2d** (4-ClC_6H_4)	**3d**	84	9.1:1.5:1
5	**2e** (3,4-$Cl_2C_6H_3$)	**3e**	65	4.5:1:1
6	**2f** (4-MeC_6H_4)	**3f**	75	16:1.5:1
7	**2g** (4-MeOC_6H_4)	**3g**	86	6.9:1:1
8	**2h** (2-benzofuryl)	**3h**	70	6.6:1:1.8
9[c]	**2a** (Ph)	**3a**	14	11:1.5:1

[a]Combined isolated yield of *cis*-**3** and the corresponding *cis*-triazolines; [b] Estimated by ^{19}F NMR analysis of the crude reaction mixture; [c]12 mol% of pybox ligand was used and the *cis*-**3a** was obtained in 14% ee using CH_2Cl_2 as solvent.

Characterizing data and copies of NMR spectroscopy and HPLC trace for chiral aziridines and related compounds:



Aziridine *cis*-**3a**[2a,c] was obtained as a pale yellow solid in 65% yield using 2.5+2 mol% of **1a** at a time interval of 12 h; $[\alpha]^{22}_{D}$ = -297.9 (*c* 0.76, CH_2Cl_2); ee = 99.4%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ=254 nm, t_R(major) = 13.6 min, t_R(minor) = 17.6 min; **IR** (neat): 1684, 1508, 1240, 1138, 1037, 732, 688 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.6 Hz, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 6.94 (AB, *J* = 8.9 Hz, 4H), 3.78 (s, 3H), 3.59 (d, *J* = 6.6 Hz, 1H), 3.13 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 190.5, 156.6, 143.5, 135.2, 134.1, 128.8, 128.7, 123.2 (q, *J* = 274.6 Hz), 120.7, 114.6, 55.5, 45.6, 44.4 (q, *J* = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.8 (d, *J* = 5.1 Hz).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3.599
3.577
3.148
3.129
3.109
CF3
MeO
N
O
1H NMR
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2.01
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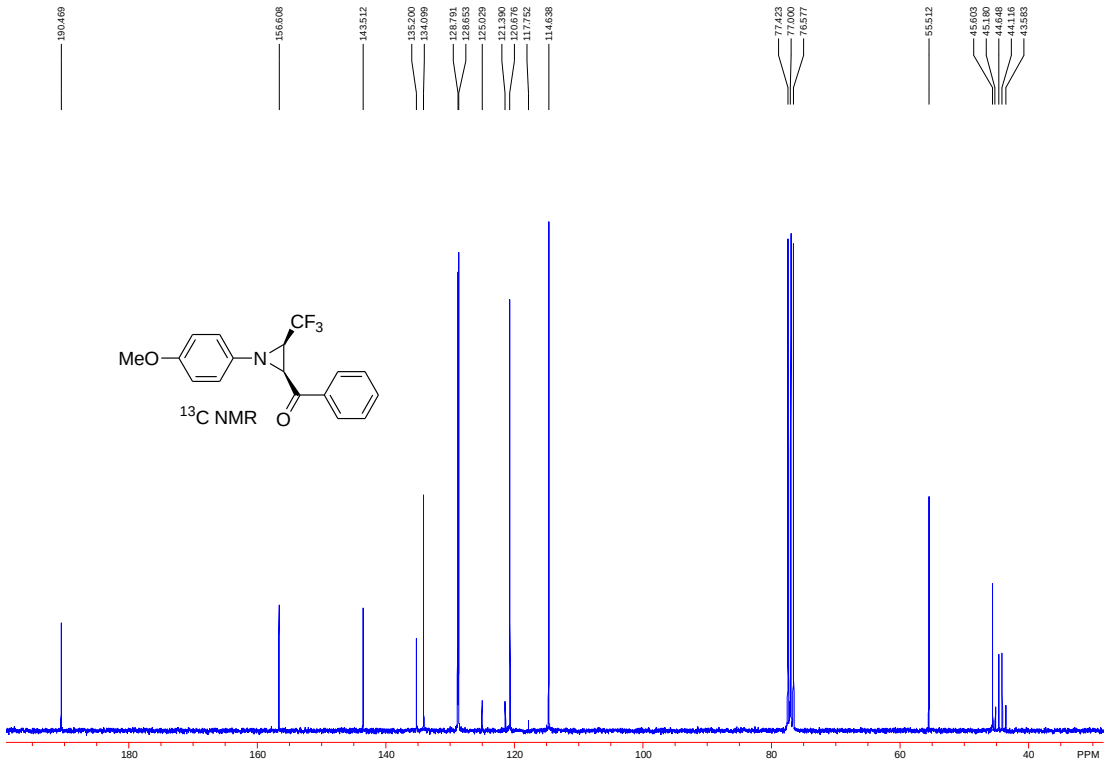
2.03
1.06
3.07
1.01
1.00
8
7
6
5
4
3
2
PPM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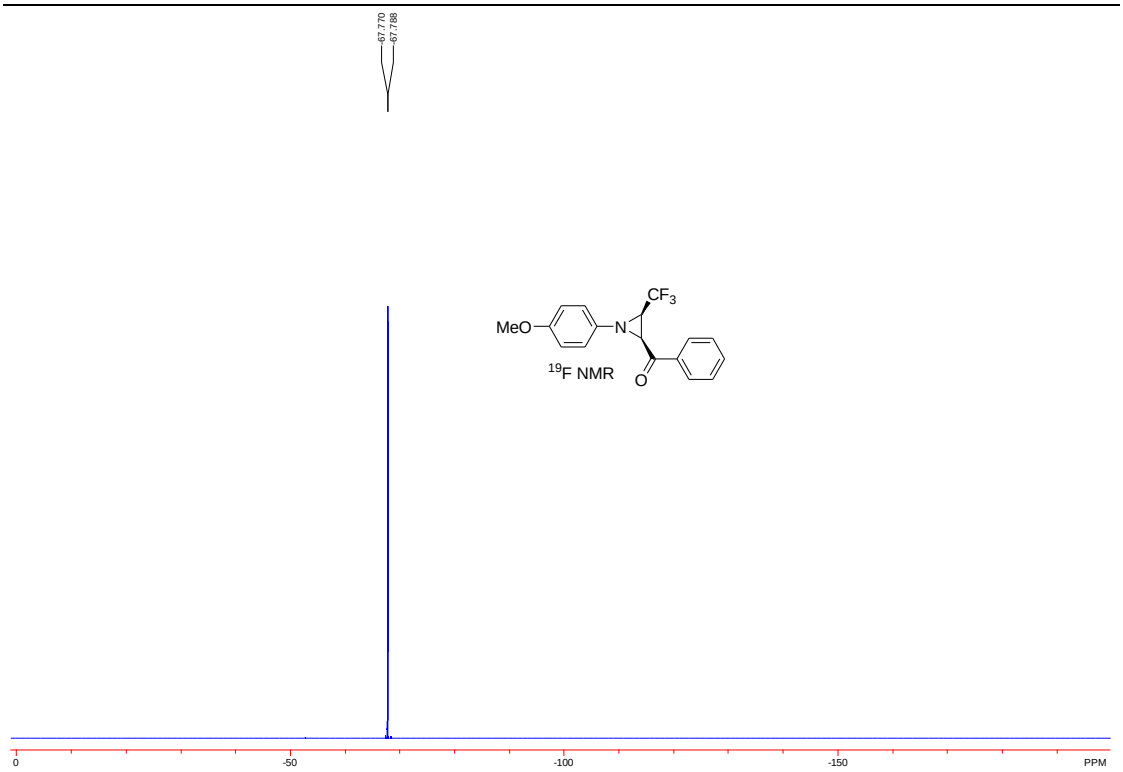
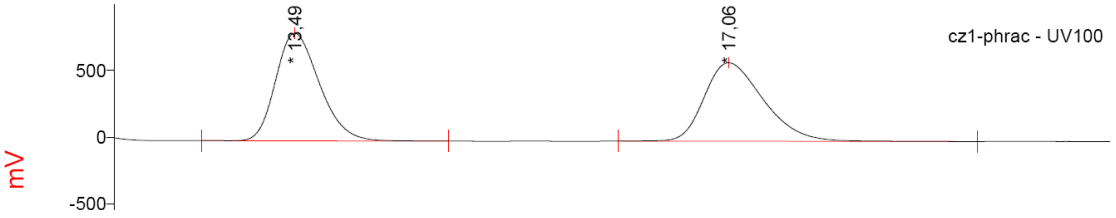
PPM



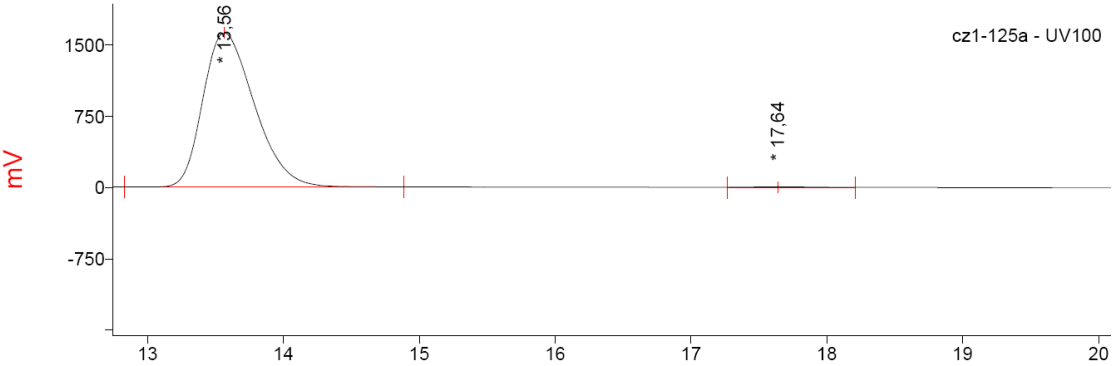
Résultats d'intégration

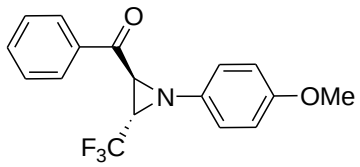
#	Nom du pic	Tr.	Aire	% Aire
1		13,49	20182,05	**50,34**
2		17,06	19908,23	**49,66**
SOMME			**40090,28**	**100,00**



Résultats d'intégration

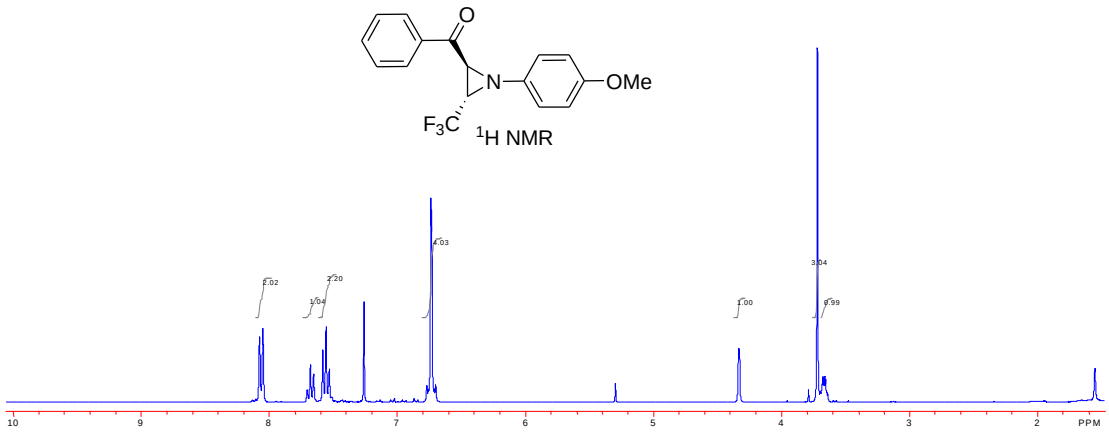
#	Nom du pic	Tr.	Aire	% Aire
1		13,56	42678,76	**99,72**
2		17,64	121,69	**0,28**
SOMME			**42800,45**	**100,00**

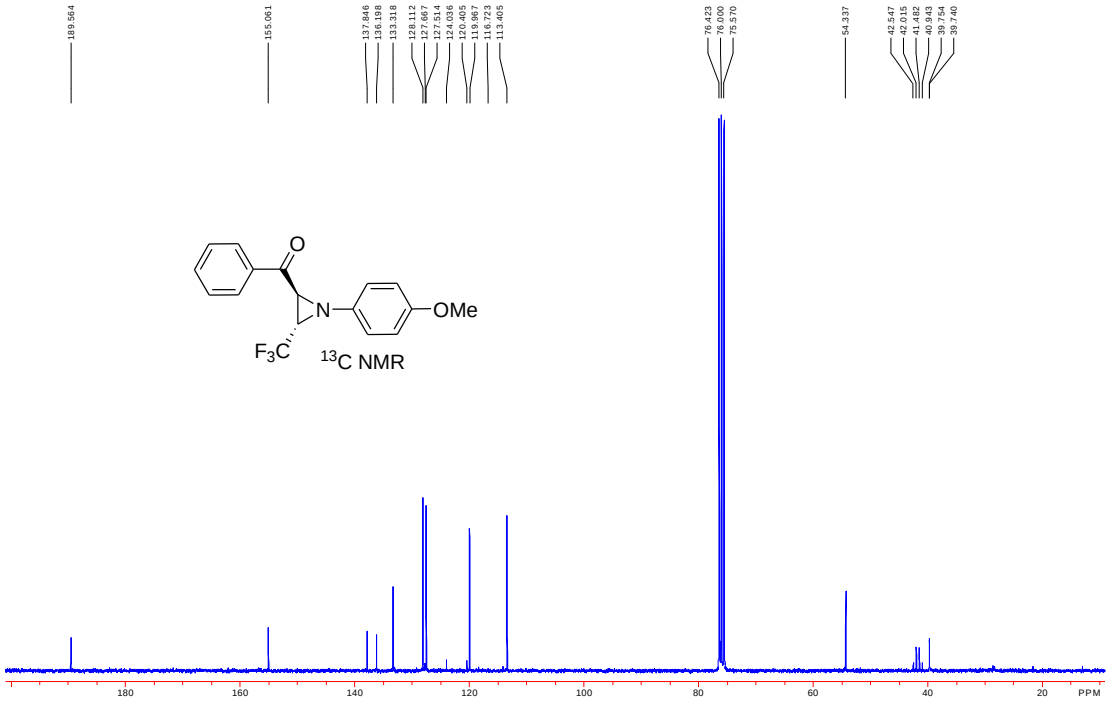


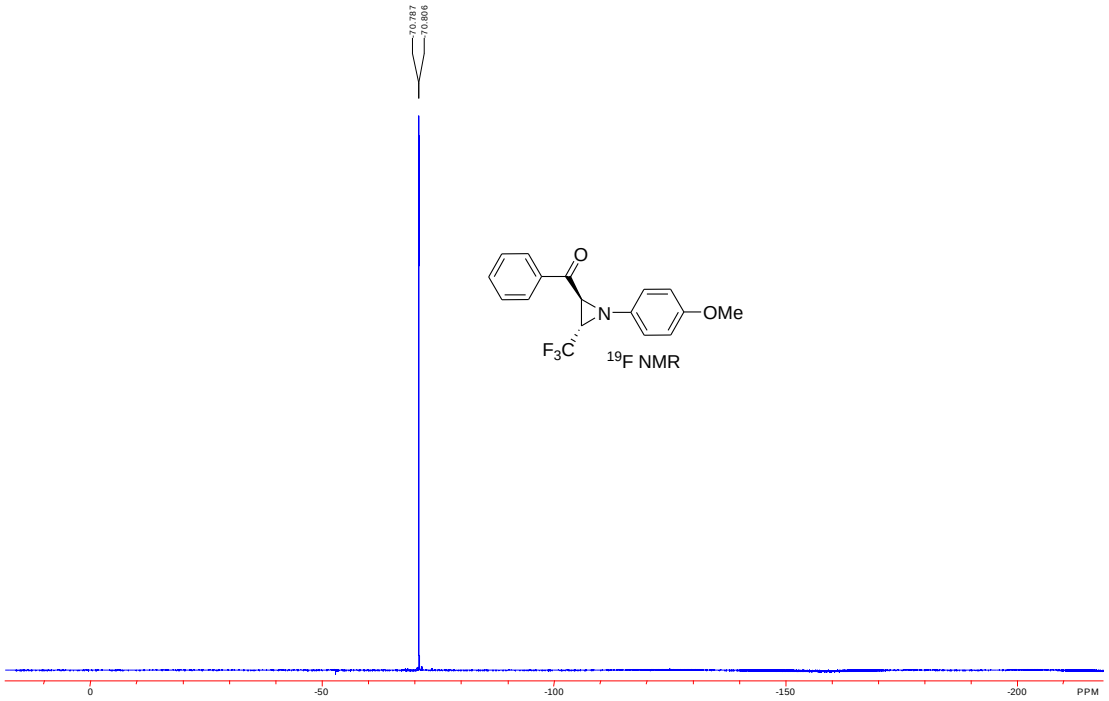


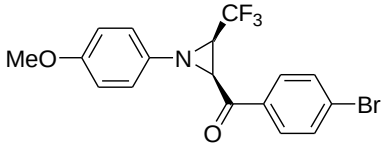
Characterizing data for *trans*-**3a** (obtained by repetitive purification of the corresponding collected fractions from the column chromatography purification of several different runs during the screen of the reaction conditions (see Table 1 in the main text).

Pale yellow solid; **IR** (neat): 2921, 1683, 1667, 1506, 1244, 1151, 802, 694 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.06 (d, J = 7.4 Hz, 2H), 7.68 (m, 1H), 7.56 (m, 2H), 6.73 (AB, J = 9.3 Hz, 4H), 4.33 (d, J = 2.2 Hz, 1H), 3.72 (s, 3H), 3.67 (dq, J = 2.2, 5.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 189.6, 155.1, 137.8, 136.2, 133.3, 128.1, 127.5, 122.2 (q, J = 274.0 Hz), 120.0, 113.4, 54.3, 41.7 (q, J = 40.1 Hz), 39.7 (q, J = 1.1 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -70.8 (d, J = 5.1 Hz). **HRMS (ESI)** Calculated for $C_{17}H_{15}NO_2F_3$ ($[M+H]^+$): 322.1055, found: 322.1039.





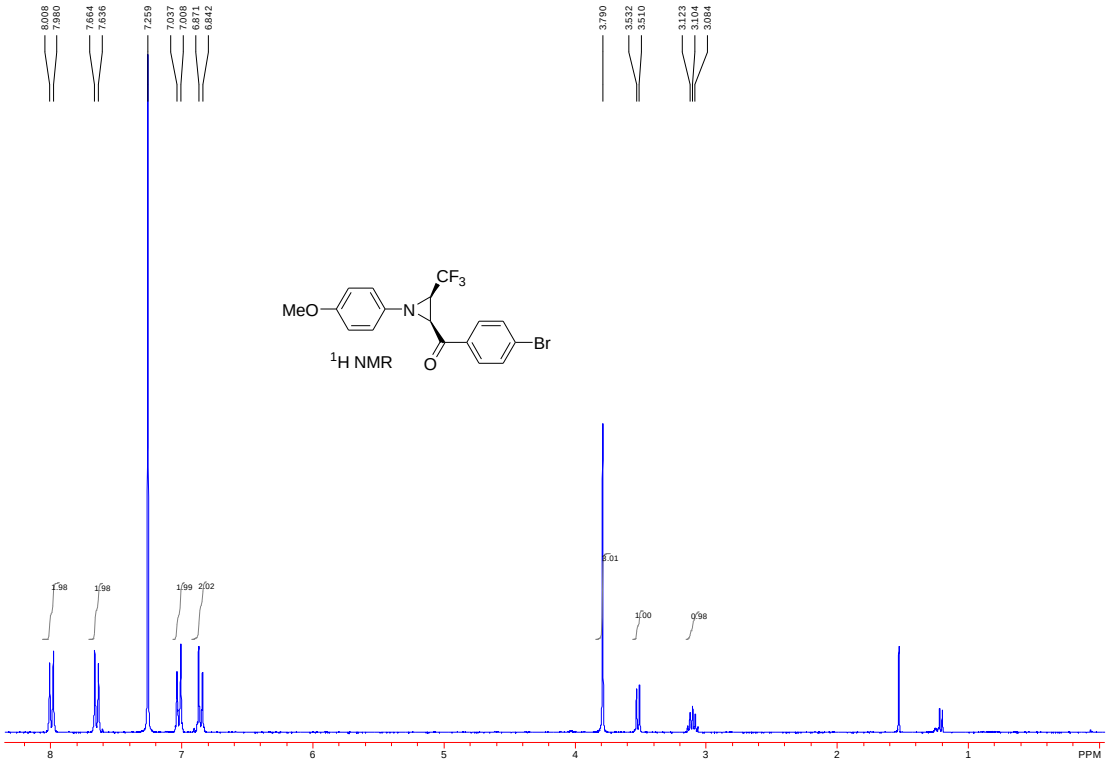


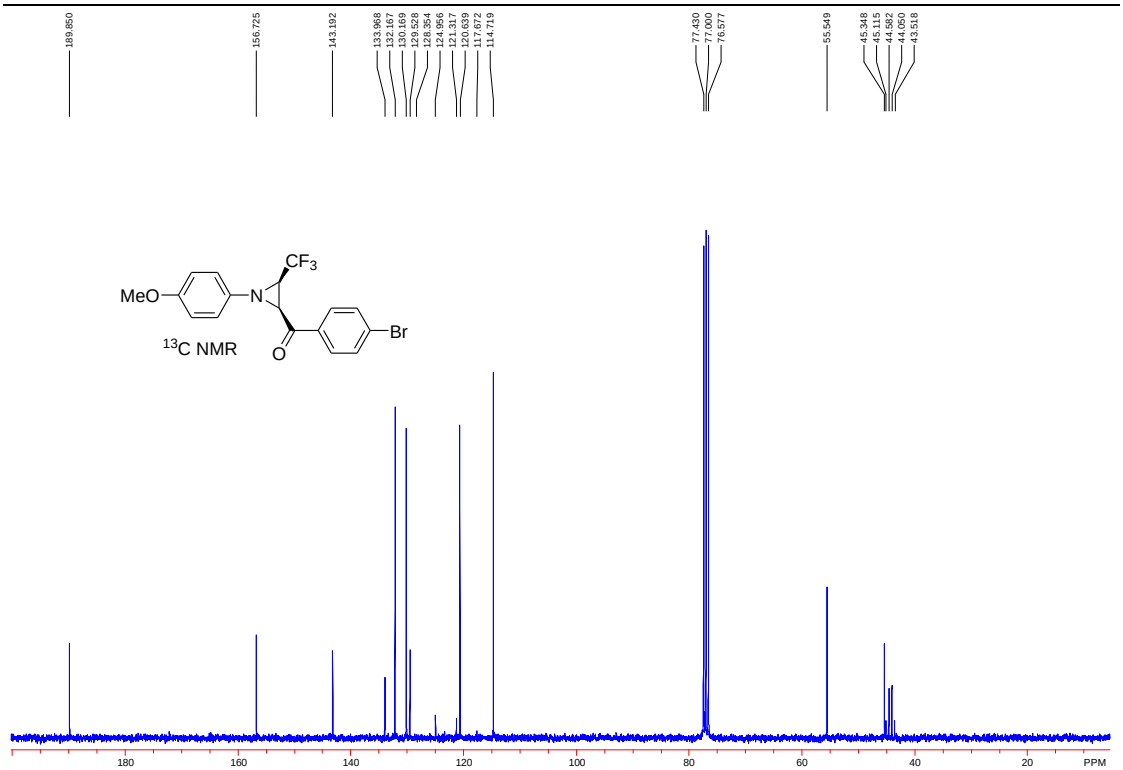


cis-Aziridine **3b**[2a] was obtained as a pale yellow solid in 82% yield using 2.5+2 mol% of **1a** at a time interval of 12 h; $[\alpha]^{21}_{,D}$ = -170.3 (*c* 1.51, CH_2Cl_2); ee = 99.6%; **IR** (neat): 2923, 1746, 1513, 1244, 1177, 1128, 1036, 825 cm^{-1}; **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ＝254 nm, t_R(major) = 18.3 min, t_R(minor) = 26.4 min; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.01 (AB, *J* = 8.9 Hz, 4H), 3.79 (s, 3H), 3.52 (d, *J* =

6.5 Hz, 1H), 3.10 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 189.9, 156.7, 143.2, 134.0, 132.2, 130.2, 129.5, 123.1 (q, *J* = 274.6 Hz), 120.6, 114.7, 55.5, 45.3, 44.3 (q, *J* = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.8 (d, *J* = 5.1 Hz); **HRMS (ESI)** Calculated for $C_{17}H_{14}NO_2F_3{}^{79}Br$ ($[M^{79}Br+H]^+$): 400.0160, found: 400.0164.

Crystallographic data for **3b**: $C_{17}H_{13}BrF_3NO_2$: FW = 400.19; T = 293 K; Monoclinic, P 1 21 1; wavelength 0.71 Å; a = 7.6615(9), b = 5.6473(6), c = 19.224(2), α = 90°, β = 93.0°, γ = 90°; V = 830.59(16) Å^3; Z = 2; absorption coefficient: 2.515; F (000) = 400; size: 0.5*0.1*0.1 mm; 1.06<θ<27.4; reflections collected 3297; goodness of fit on F2 1.073; final R indices: R1 = 0.0321, wR2 = 0.08. Full crystallographic data for this compound can also be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_ request /cif (CCDC 872137).

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55.549
45.348
45.115
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80
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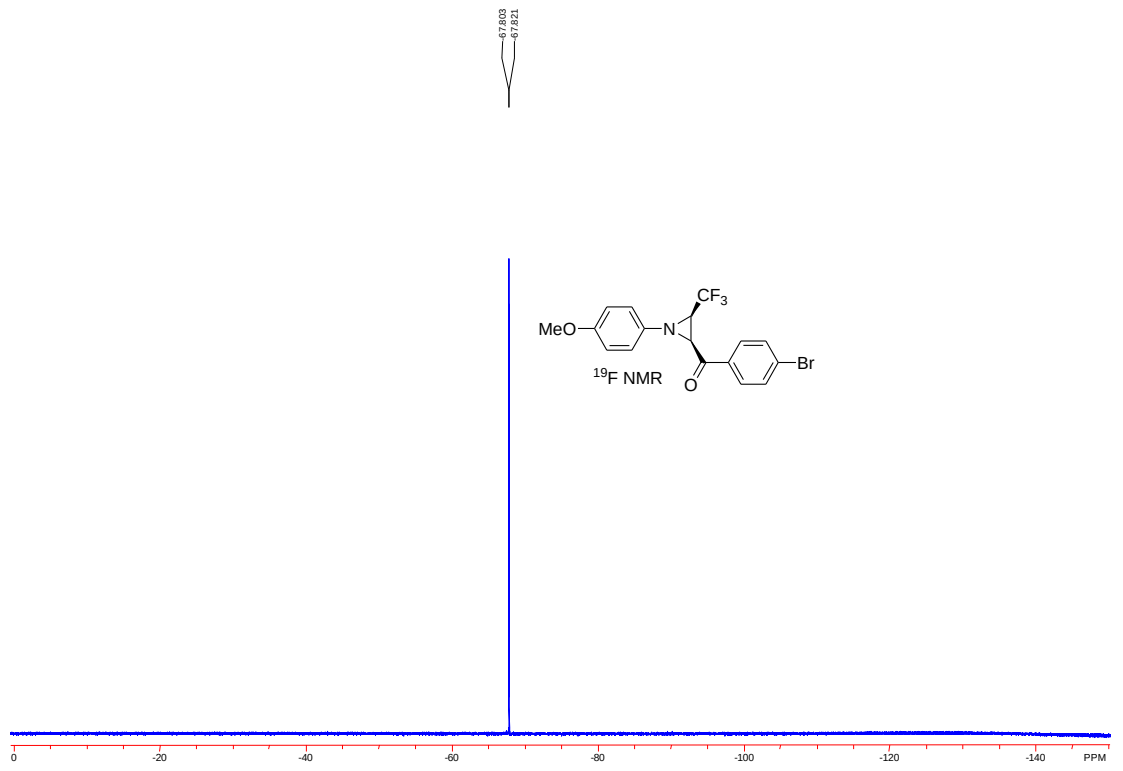
40
20
PPM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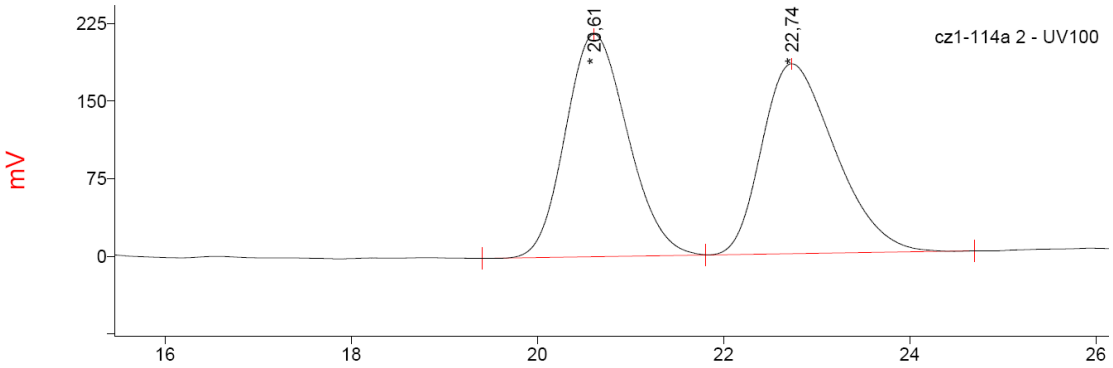
-140
PPM

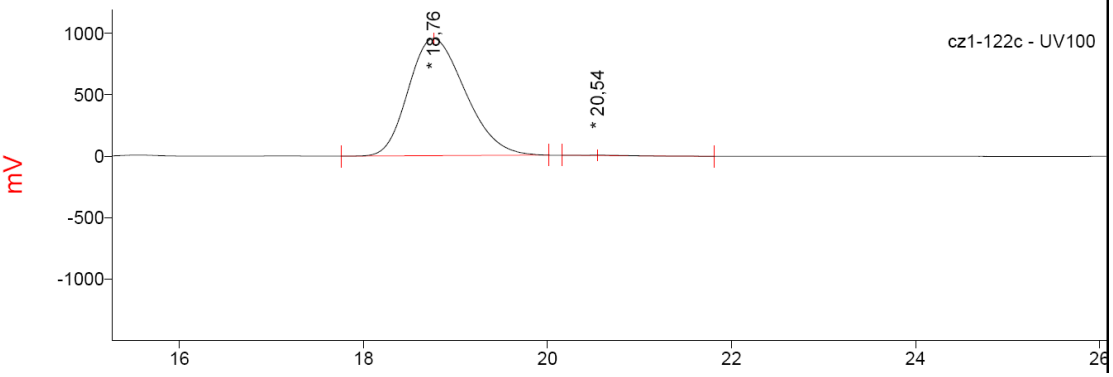
Résultats d'intégration

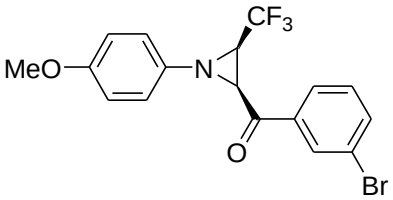
#	Nom du pic	Tr.	Aire	% Aire
1		20,61	9995,35	**49,94**
2		22,74	10019,25	**50,06**
SOMME			**20014,60**	**100,00**



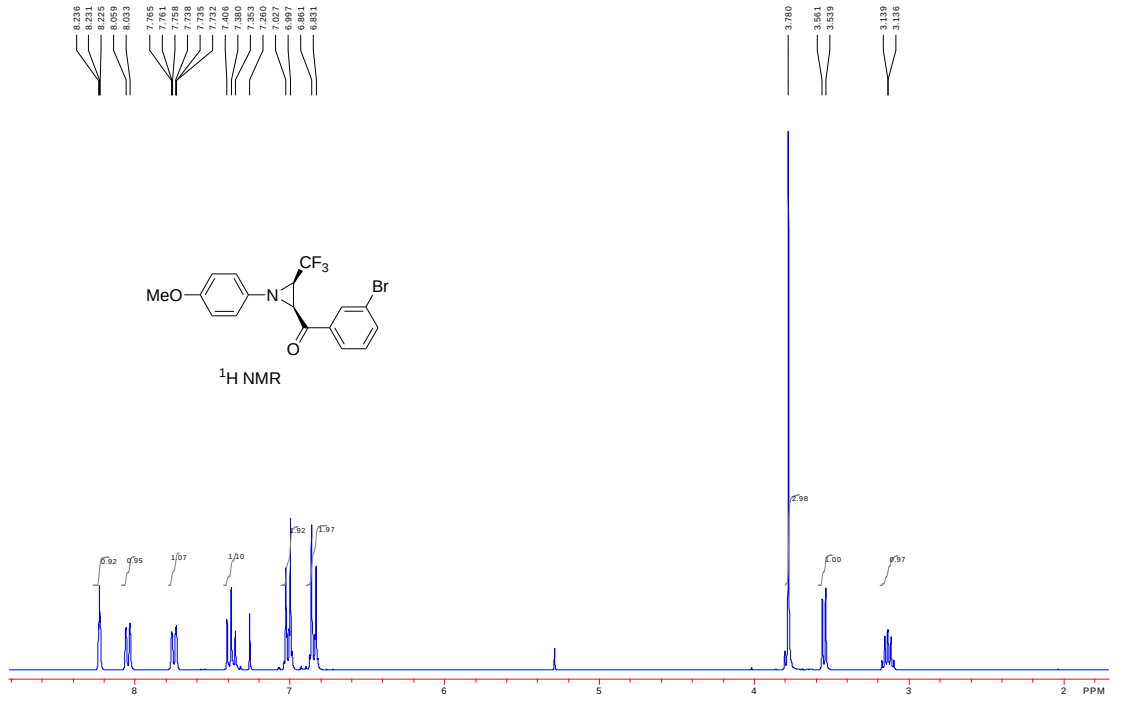
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire
1		18,76	40912,63	**99,83**
2		20,54	67,99	**0,17**
SOMME			**40980,63**	**100,00**





cis-Aziridine **3c** was obtained as a pale yellow oil in 78% yield using 2.5+2 mol% of **1a** at a time interval of 12 h; $[\alpha]^{22}_{,D}$ = -152.2 (*c* 1.2, CH_2Cl_2); ee = 97.6%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ = 254 nm, t_R(major) = 16.1 min, t_R(minor) = 19.6 min; **IR** (neat): 2921, 1698, 1509, 1241, 1145, 830, 750, 728 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.23 (t, *J* = 1.7 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.76-7.73 (m, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.92 (AB, *J* = 8.9 Hz, 4H), 3.78 (s, 3H), 3.52 (d, *J* = 6.5 Hz, 1H), 3.14 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 189.5, 156.7, 143.1, 137.0, 136.9, 131.6, 130.4, 127.2, 123.15, 123.1 (q, *J* = 274.5 Hz), 120.6, 114.7, 55.5, 45.4, 44.4 (q, *J* = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.7 (d, *J* = 5.1 Hz); **HRMS (ESI)** Calculated for $C_{17}H_{14}NO_2F_3{}^{79}Br$ ($[M^{79}Br+H]^+$): 400.0160, found: 400.0146.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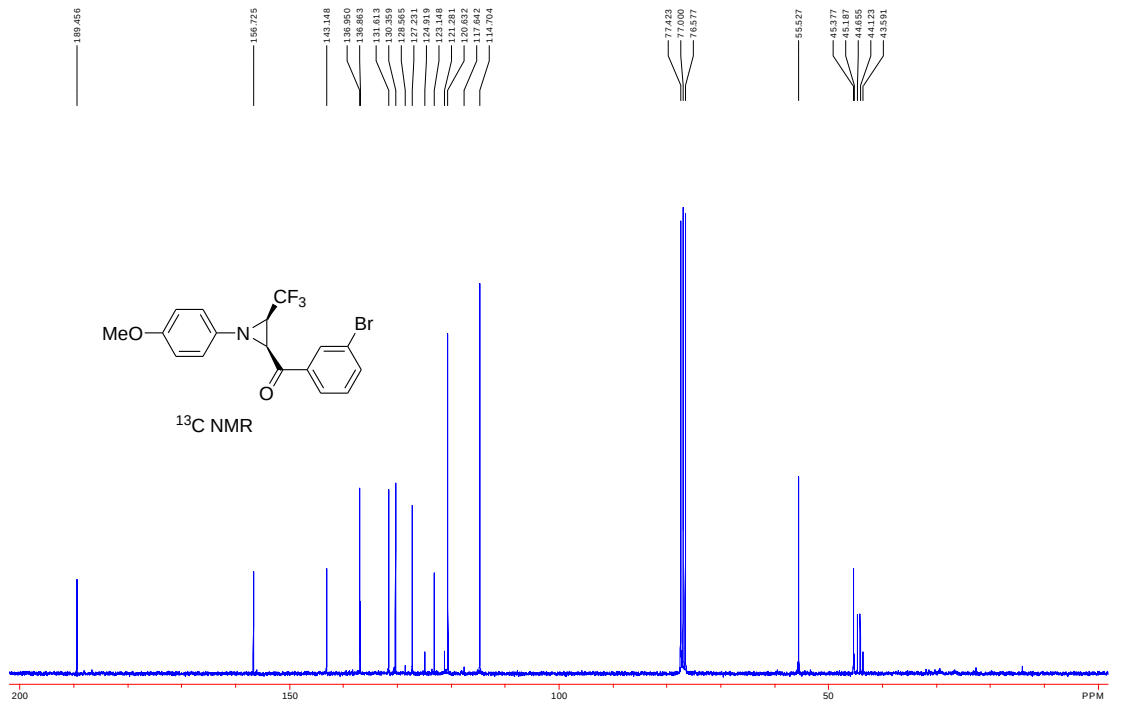
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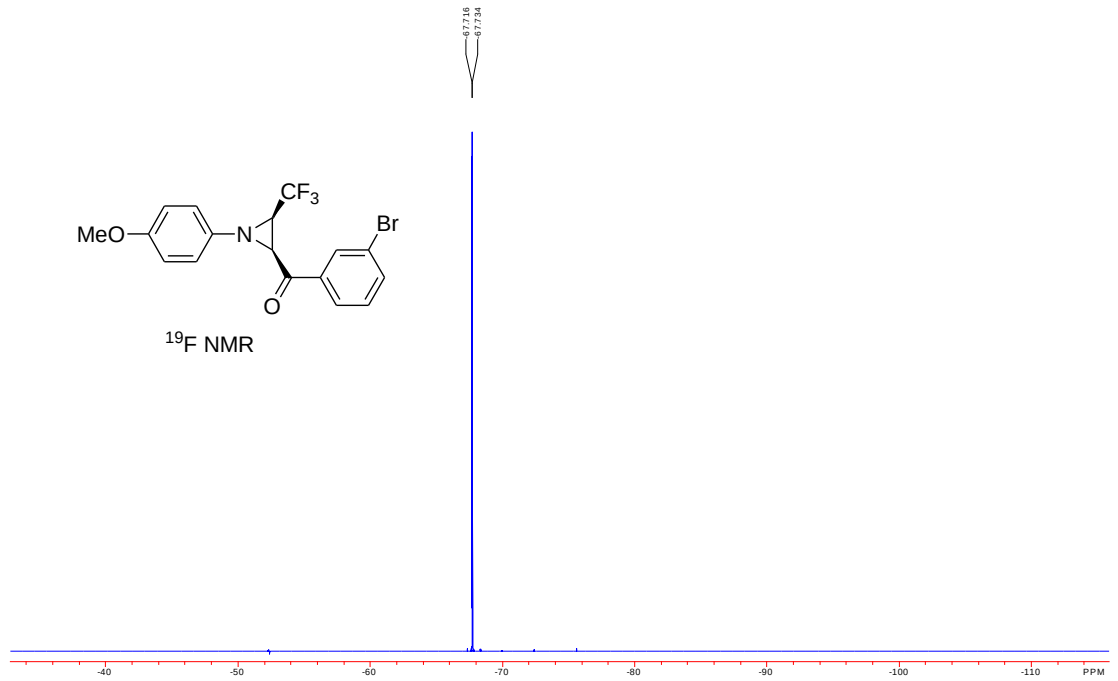
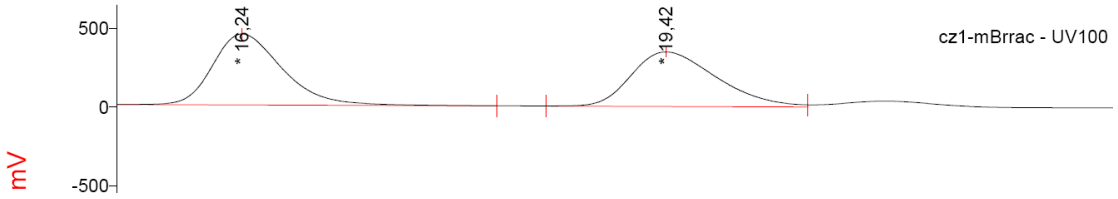


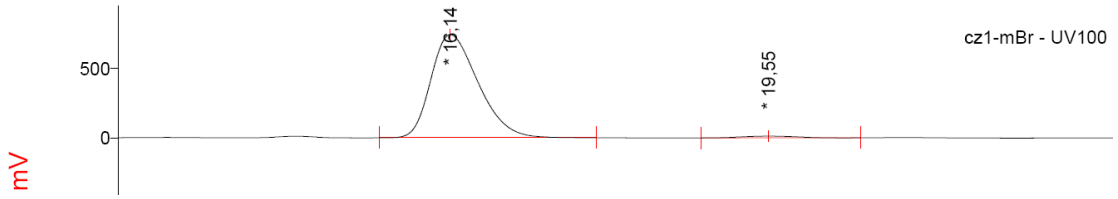
Résultats d'intégration

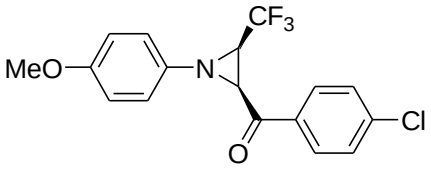
#	Nom du pic	Tr.	Aire	% Aire
1		16,24	16381,82	**51,63**
2		19,42	15344,83	**48,37**
SOMME			**31726,64**	**100,00**



Résultats d'intégration

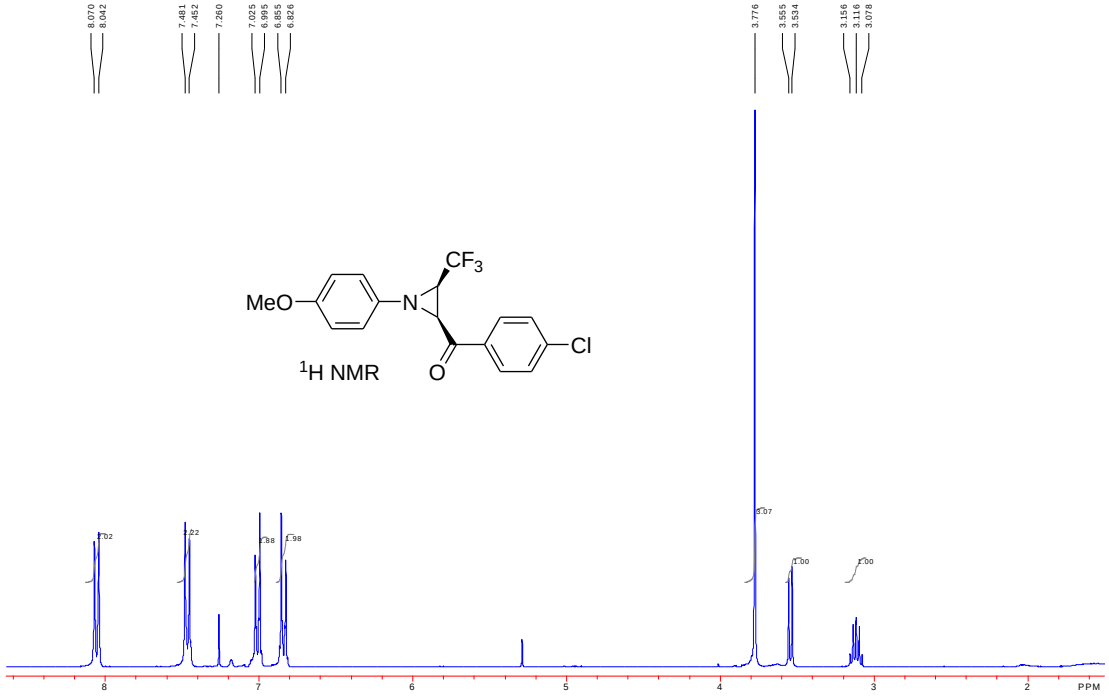
#	Nom du pic	Tr.	Aire	% Aire
1		16,14	26102,76	**98,28**
2		19,55	456,17	**1,72**
SOMME			**26558,93**	**100,00**

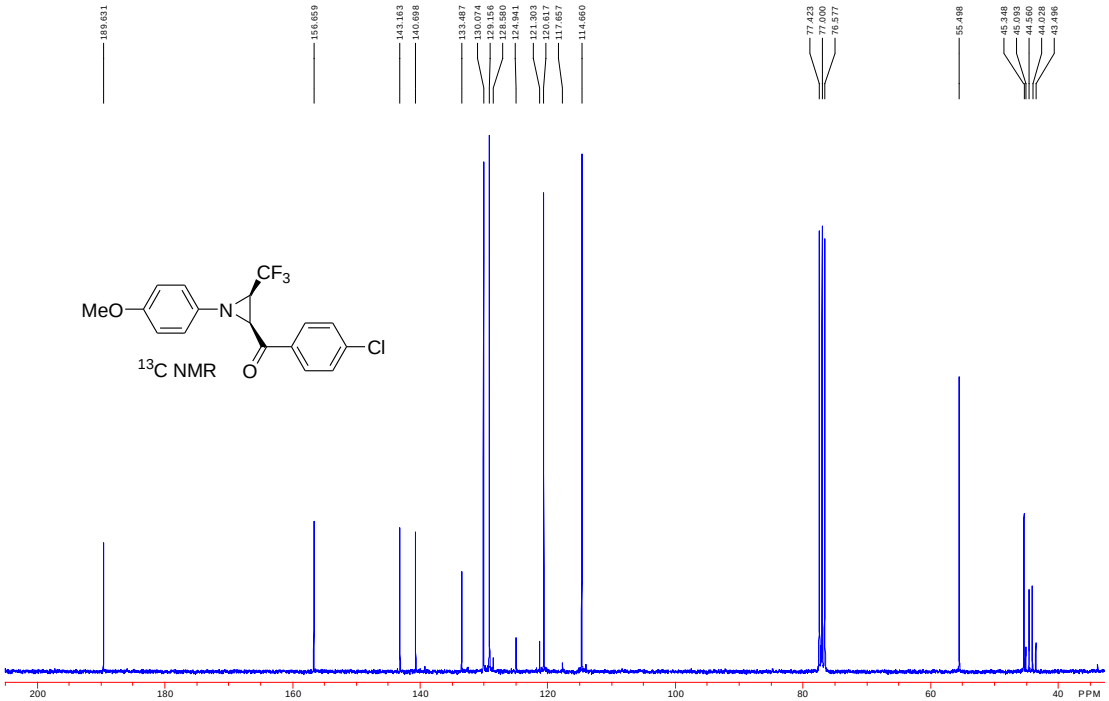


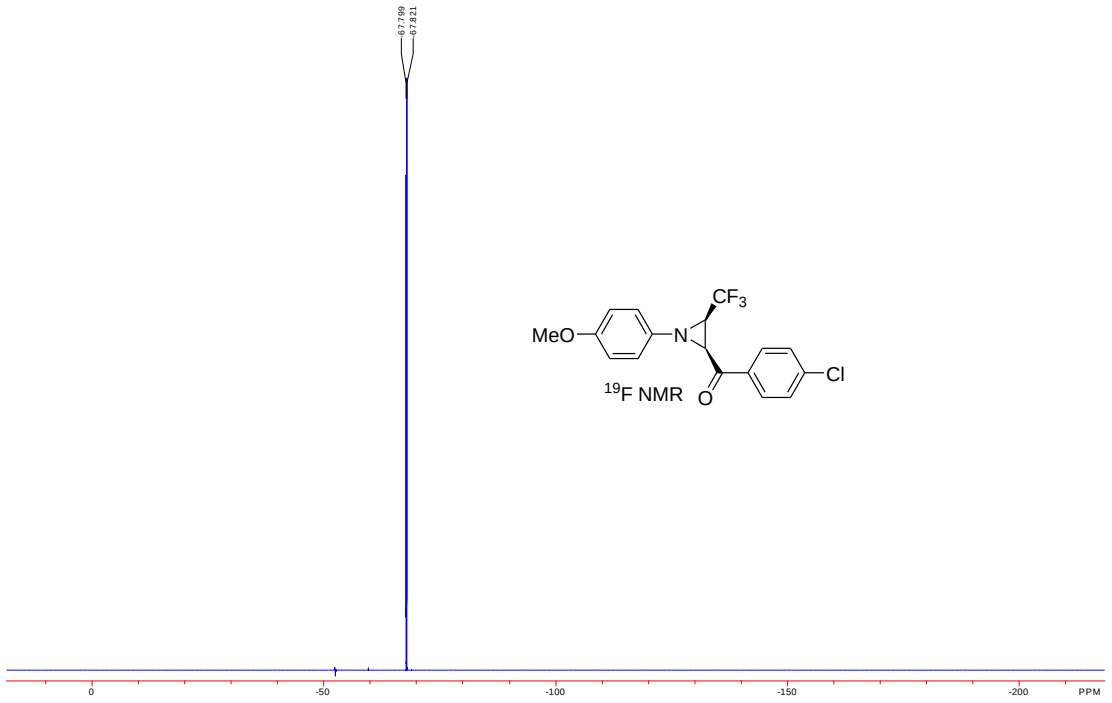


cis-Aziridine **3d** was obtained as a pale yellow solid in 75% yield using 2.5+2 mol% of **1a** at a time interval of 12 h; $[\alpha]^{21}_{,D}$ = -149.4 (*c* 1.43, CH_2Cl_2); ee >99%, **HPLC**: Daicel CHIRALCEL OD-H column, 2% IPA in *n*-heptane, 0.75

mL/min, λ＝254 nm, t_R(major) = 57.0 min, t_R(minor) = 62.5 min; **IR** (neat): 2954, 1687, 1592, 1513, 1229, 1142, 833, 743 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 6.98 (AB, J = 8.9 Hz, 4H), 3.78 (s, 3H), 3.54 (d, J = 6.5 Hz, 1H), 3.12 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 189.6, 156.7, 143.2, 140.7, 133.5, 130.1, 129.2, 123.1 (q, J = 274.6 Hz), 120.6, 114.7, 55.5, 45.3, 44.3 (q, J = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.8 (d, J = 6.1 Hz); **HRMS (ESI)** Calculated for $C_{17}H_{14}NO_2F_3{}^{35}Cl$ ($[M+H]^+$): 356.0665, found: 356.0671.

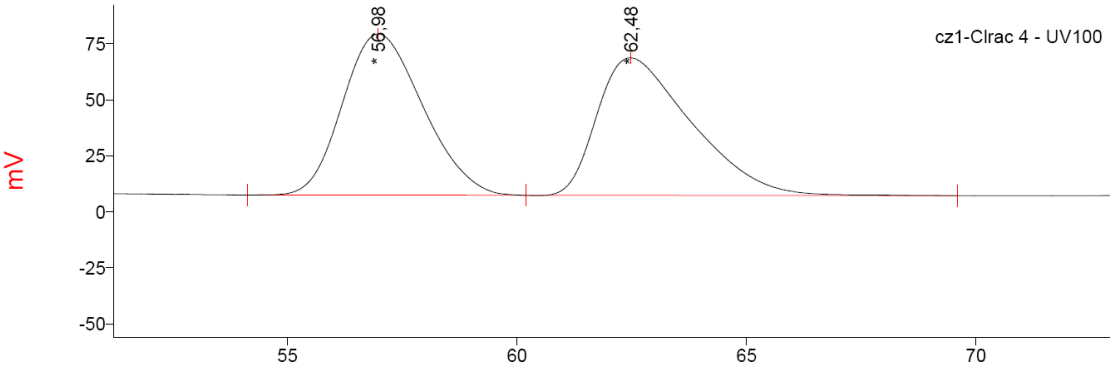






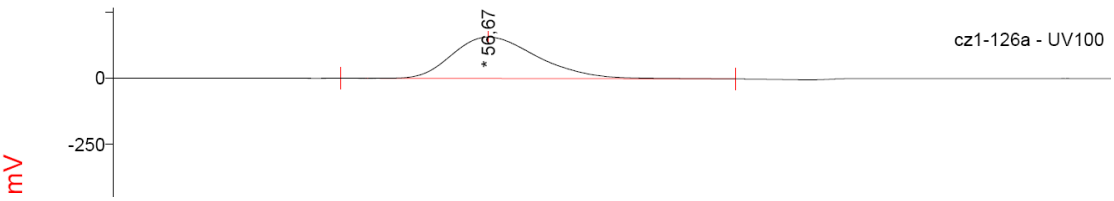
Résultats d'intégration

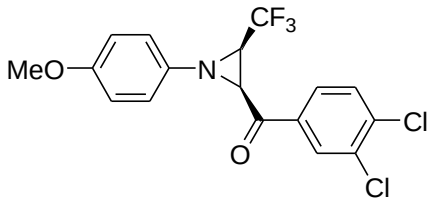
#	Nom du pic	Tr.	Aire	% Aire
1		56,98	8739,28	**49,91**
2		62,48	8771,96	**50,09**
SOMME			**17511,24**	**100,00**



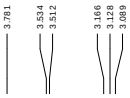
Résultats d'intégration

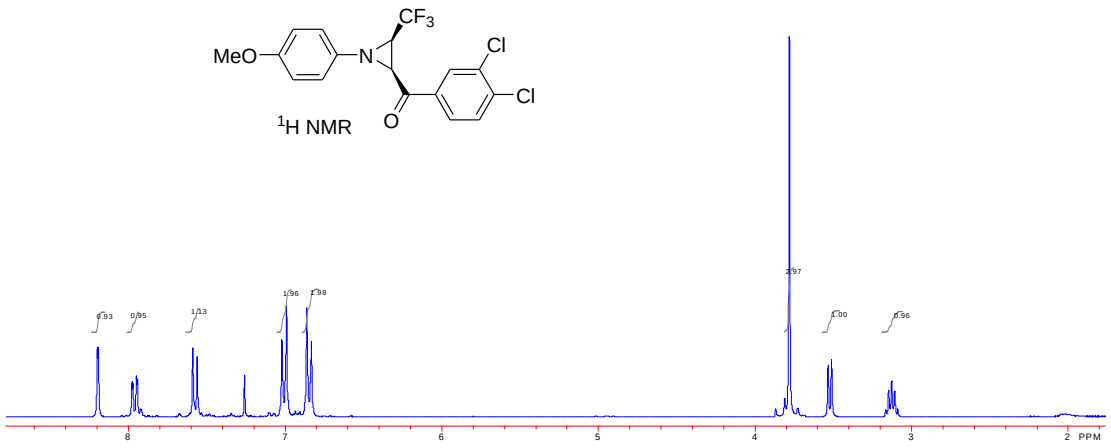
#	Nom du pic	Tr.	Aire	% Aire
1		56,67	21872,92	**100,00**
SOMME			**21872,92**	**100,00**

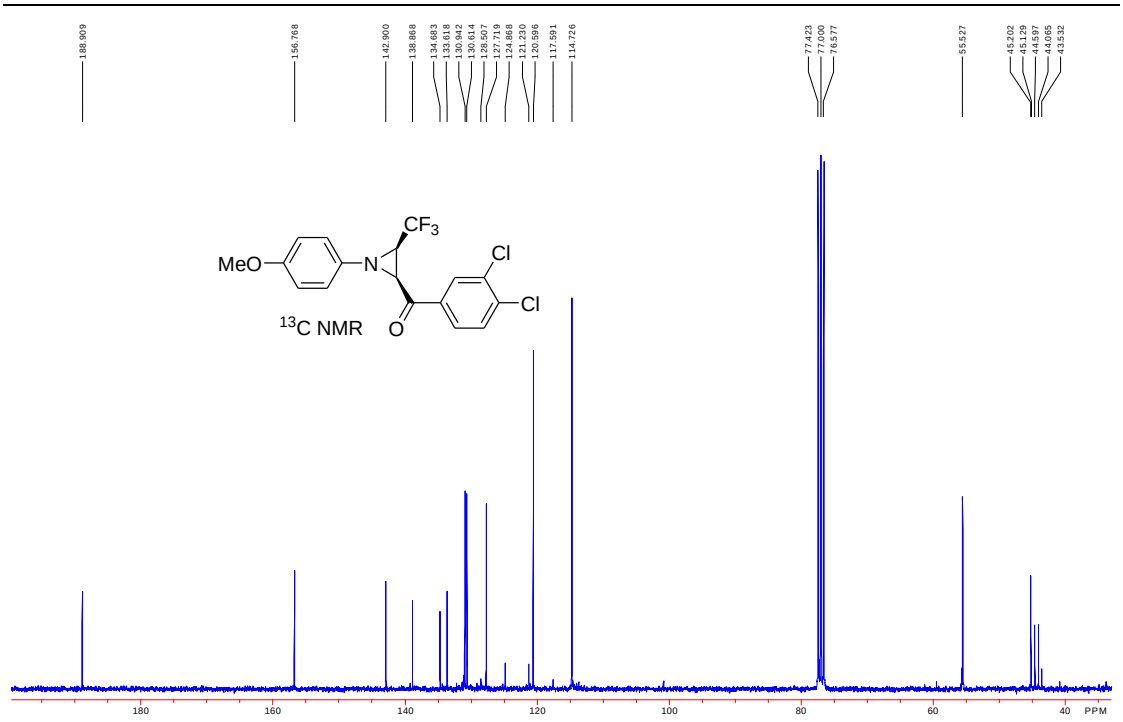


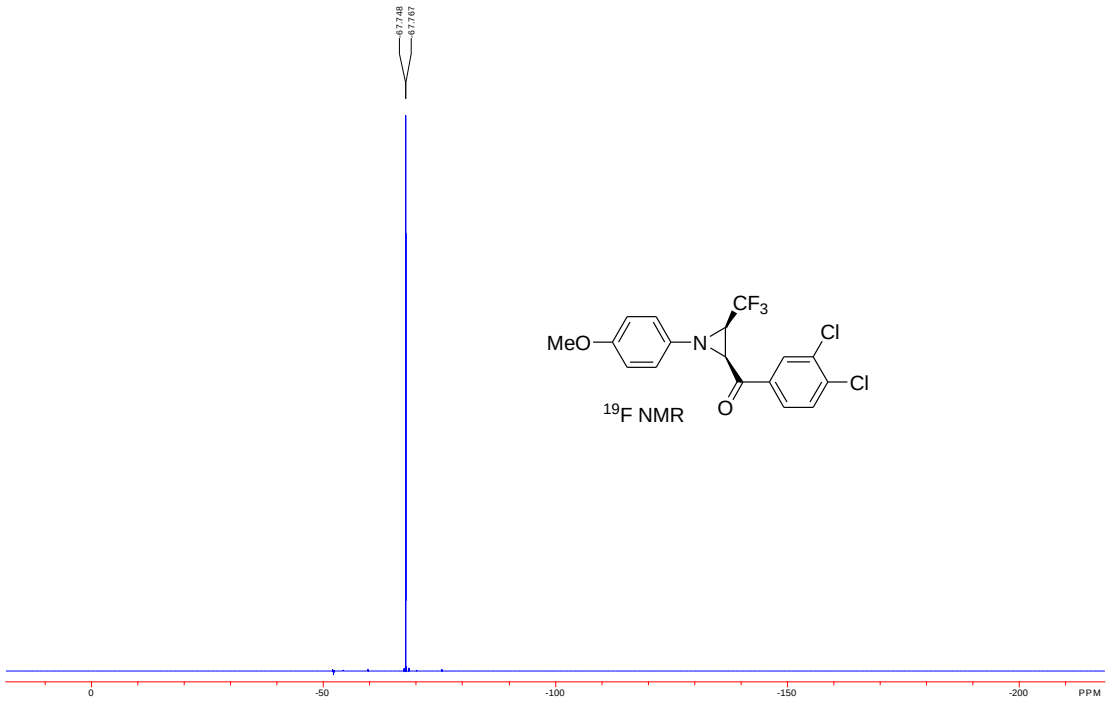


cis-Aziridine **3e** was obtained as a pale yellow oil in 71% yield using 2.5+2 mol% of **1a** at a time interval of 12 h; $[\alpha]^{23}_{,D}$ = -116.8 (*c* 1.44, CH_2Cl_2); ee = 95.8%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ＝254 nm, t_R(minor) = 19.3 min, t_R(major) = 20.8 min; **IR** (neat): 2928, 1698, 1509, 1238, 1145, 1033, 830, 768, 746 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.19 (d, *J* = 1.8 Hz, 1H), 7.96 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 6.93 (AB, *J* = 8.9 Hz, 4H), 3.78 (s, 3H), 3.52 (d, *J* = 6.6 Hz, 1H), 3.13 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 188.9, 156.8, 142.9, 138.9, 134.7, 133.6, 130.9, 130.6, 127.7, 123.0 (q, *J* = 274.6 Hz), 120.6, 114.7, 55.5, 45.2, 44.3 (q, *J* = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.7 (d, *J* = 5.1 Hz); **HRMS (ESI)** Calculated for $C_{17}H_{13}NO_2F_3{}^{35}Cl_2$ ($[M+H]^+$): 390.0275, found: 390.0277.



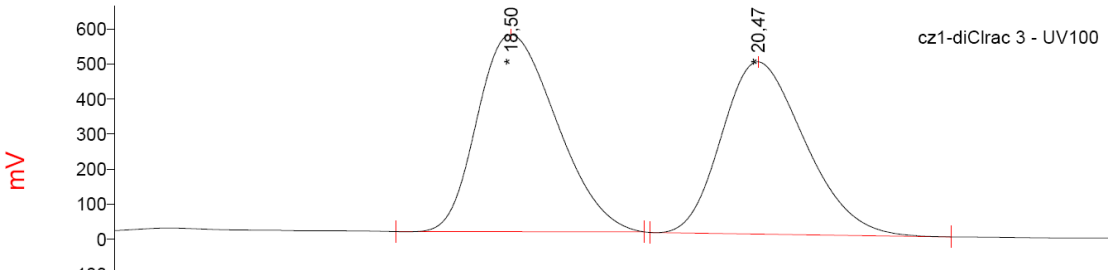



188.909
156.768
142.900
138.868
134.683
133.618
130.942
130.614
128.507
127.719
124.868
121.220
120.596
117.591
114.726
77.423
77.000
76.577
55.527
45.202
45.129
44.597
44.065
43.532
MeO
N
CF3
Cl
Cl
O
13C NMR
180
160
140
120
100
80
60
40
PPM


-67.748
-67.767
MeO
N
CF3
Cl
Cl
O
19F NMR
0
-50
-100
-150
-200
PPM

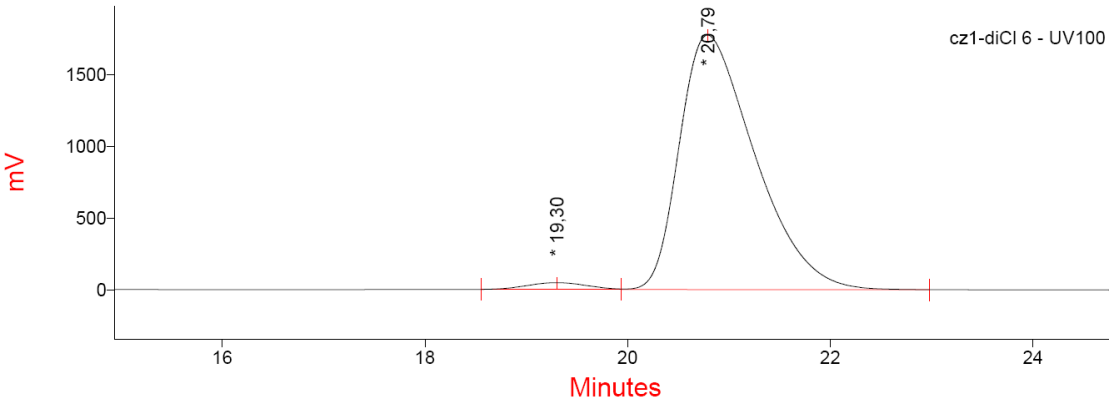
Résultats d'intégration

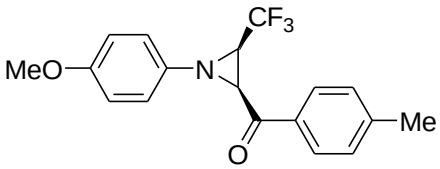
#	Nom du pic	Tr.	Aire	% Aire
1		18,50	24620,34	**52,09**
2		20,47	22642,42	**47,91**
SOMME			**47262,76**	**100,00**



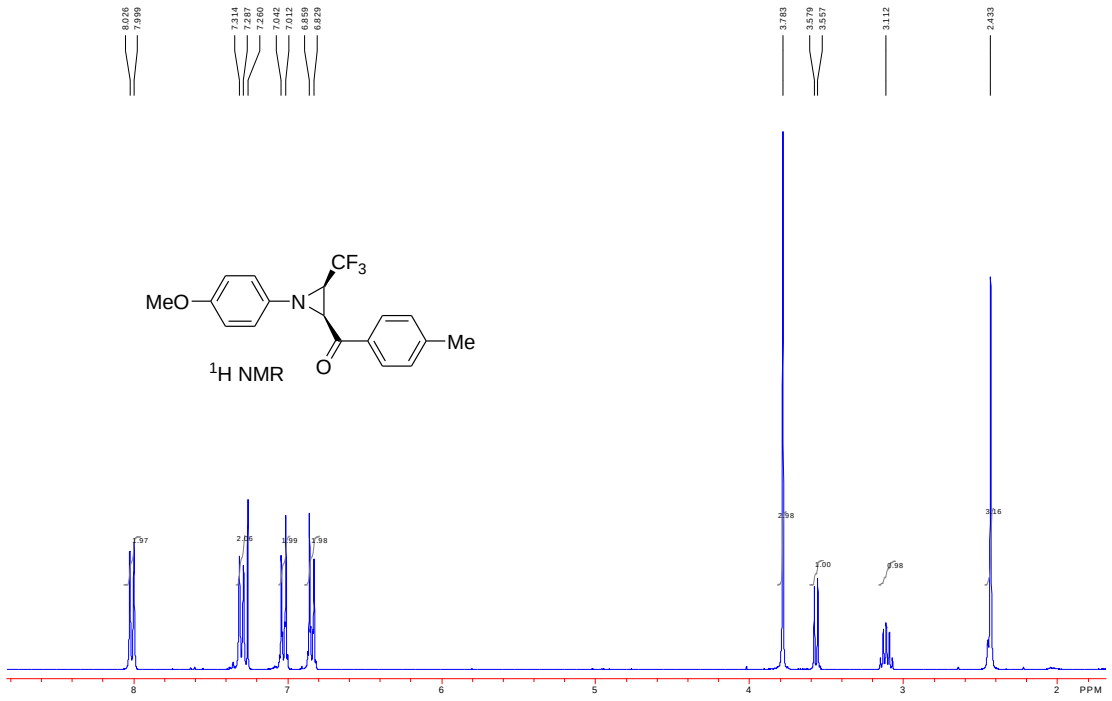
Résultats d'intégration

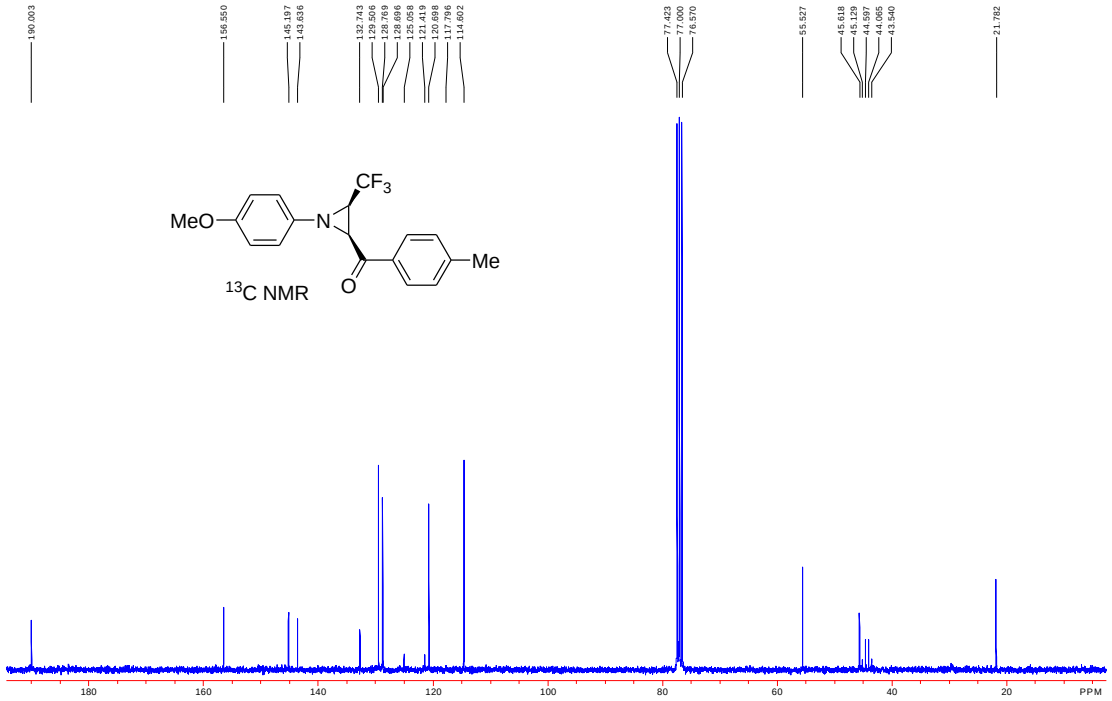
#	Nom du pic	Tr.	Aire	% Aire
1		19,30	1938,65	**2,08**
2		20,79	91490,00	**97,92**
SOMME			**93428,65**	**100,00**

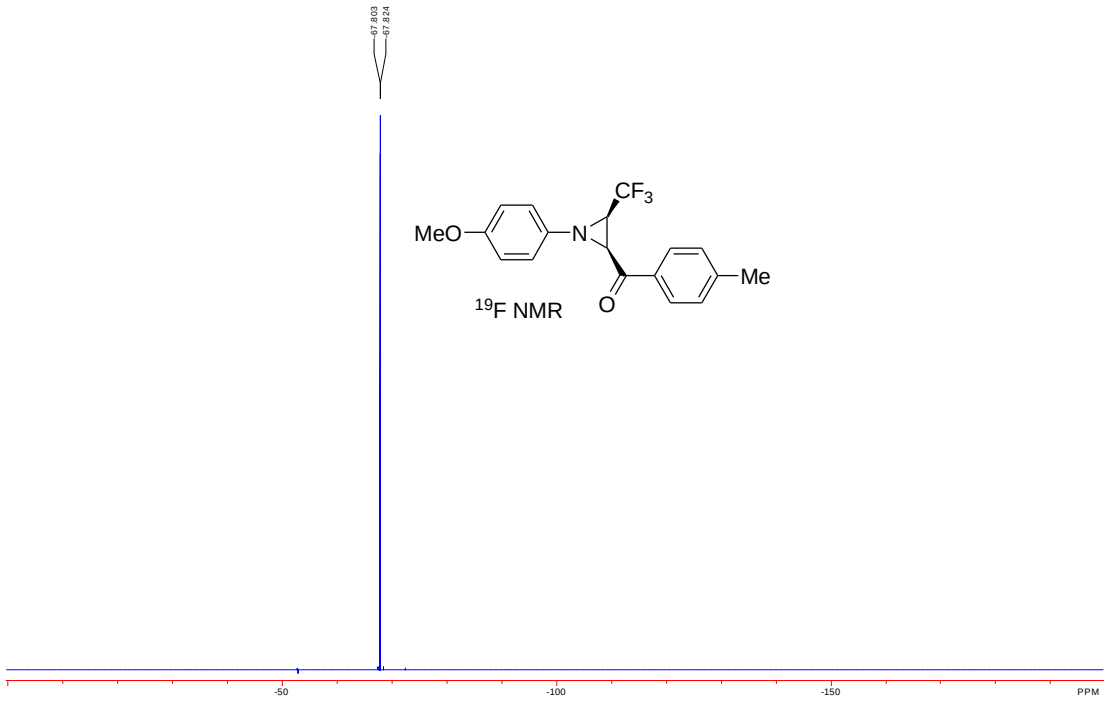




cis-Aziridine **3f**[2a] was obtained as a pale yellow solid in 80% yield using 3+2 mol% of **1a** at a time interval of 16 h; $[\alpha]^{23}_{,D}$ = -167.3 (*c* 1.0, CH_2Cl_2); ee = 99.6%, **HPLC**: Daicel CHIRALCEL OD-H column, 5% IPA in *n*-heptane, 0.75 mL/min, λ=254 nm, t_R(major) = 28.0 min, t_R(minor) = 30.7 min; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.93 (AB, *J* = 8.9 Hz, 4H), 3.78 (s, 3H), 3.57 (d, *J* = 6.6 Hz, 1H), 3.11 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 190.0, 156.6, 145.2, 143.6, 132.7, 129.5, 128.8, 123.2 (q, *J* = 274.6 Hz), 120.7, 114.6, 55.5, 45.6, 44.3 (q, *J* = 40.2 Hz), 21.8; **^{19}F NMR** (282 MHz, $CDCl_3$): -67.8 (d, *J* = 6.1 Hz).

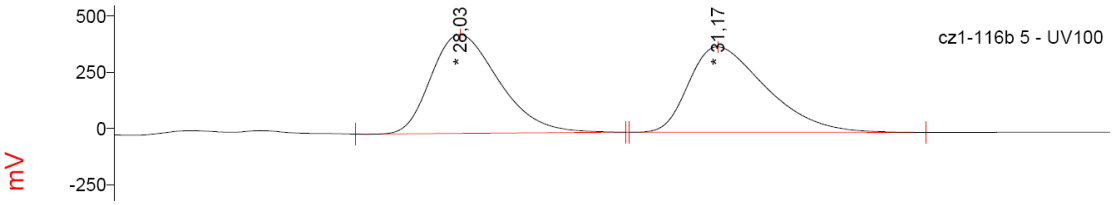

8.026
7.999
7.314
7.287
7.260
7.042
7.012
6.859
6.829
3.783
3.579
3.557
3.112
2.433
MeO
N
CF3
O
Me
1H NMR
1.97
2.05
1.99
1.98
2.98
1.00
0.98
3.16
8
7
6
5
4
3
2
PPM


190.003
156.550
145.197
143.636
132.743
129.506
128.769
128.696
125.058
121.419
120.698
117.766
114.692
77.423
77.000
76.570
55.527
45.618
45.139
44.597
44.065
43.540
21.782
MeO
N
CF3
O
Me
13C NMR
180
160
140
120
100
80
60
40
20
PPM



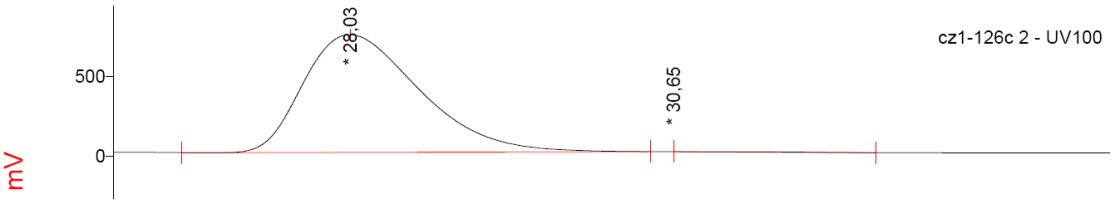
Résultats d'intégration

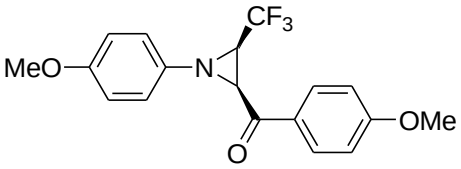
#	Nom du pic	Tr.	Aire	% Aire
1		28,03	25152,99	**50,40**
2		31,17	24753,71	**49,60**
SOMME			**49906,70**	**100,00**



Résultats d'intégration

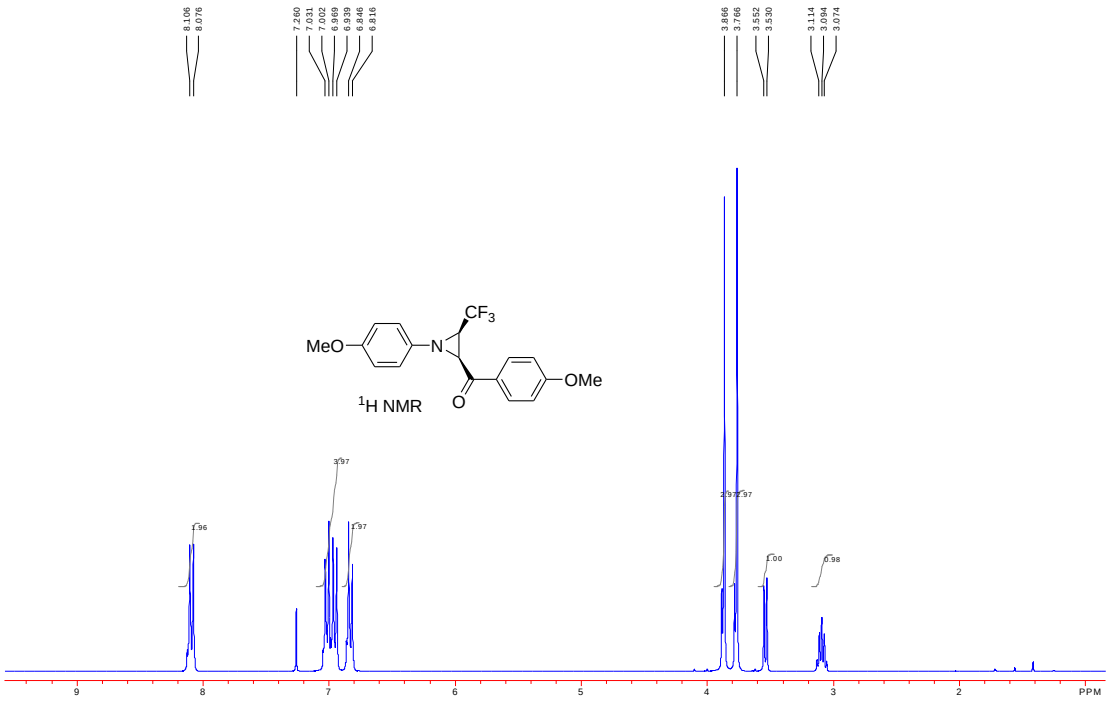
#	Nom du pic	Tr.	Aire	% Aire
1		28,03	47912,55	**99,84**
2		30,65	78,04	**0,16**
SOMME			**47990,60**	**100,00**

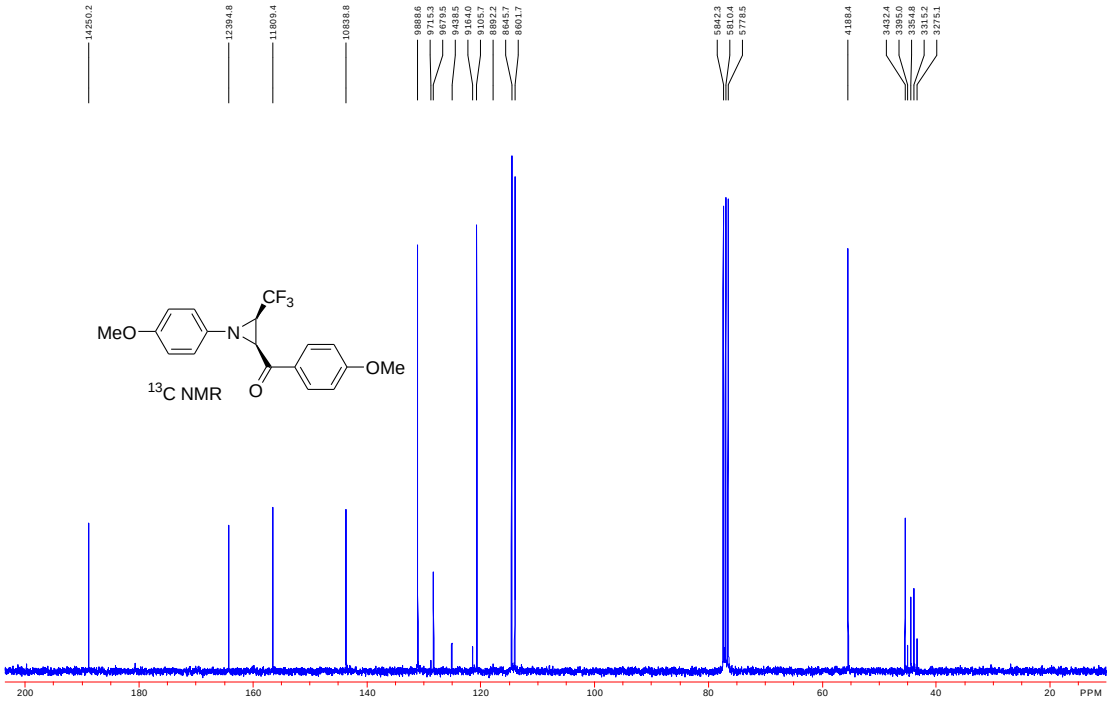


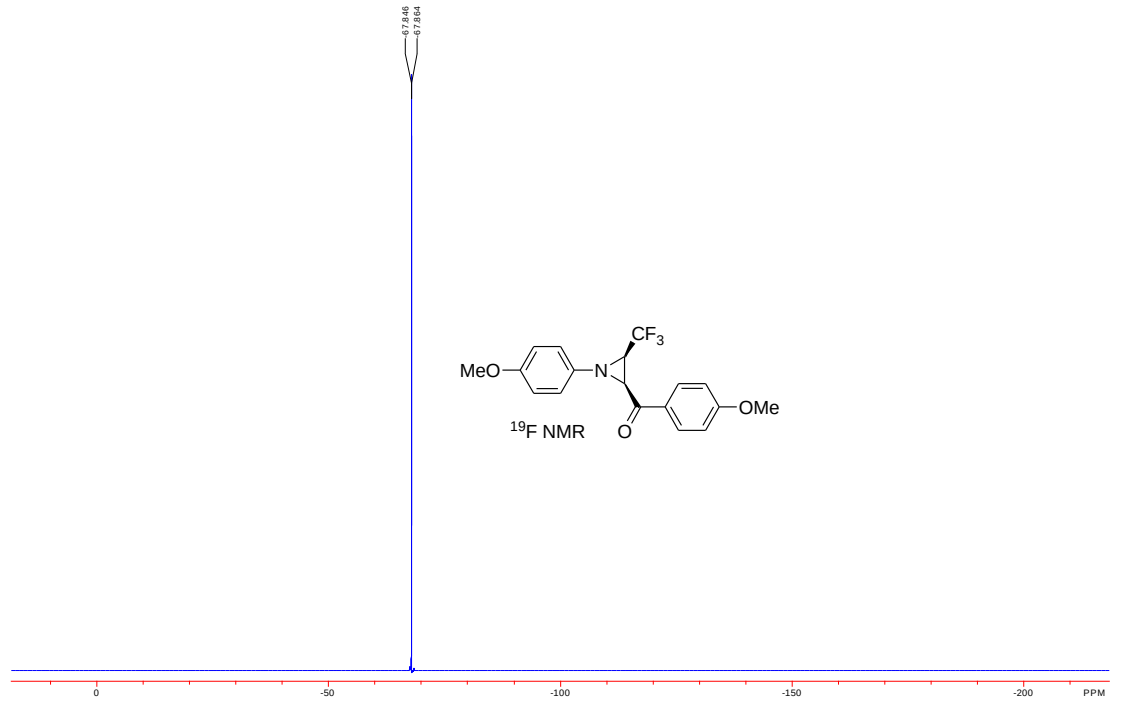


cis-Aziridine **3g**[2a] was obtained as a pale yellow solid in 85% yield using 3+2 mol% of **1a** at a time interval of 16 h; $[\alpha]^{22}_{D}$ = -200.1 (*c* 0.69, CH_2Cl_2); ee = 99.3%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-

heptane, 0.75 mL/min, λ＝254 nm, t_R(major) = 21.5 min, t_R(minor) = 26.3 min; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.01 (AB, *J* = 8.8 Hz, 4H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.54 (d, *J* = 6.6 Hz, 1H), 3.09 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 188.8, 164.3, 156.5, 143.6, 131.0, 128.3, 123.3 (q, *J* = 274.5 Hz), 120.7, 114.6, 114.0, 55.5, 45.5, 44.2 (q, *J* = 39.6 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.9 (d, *J* = 5.1 Hz).

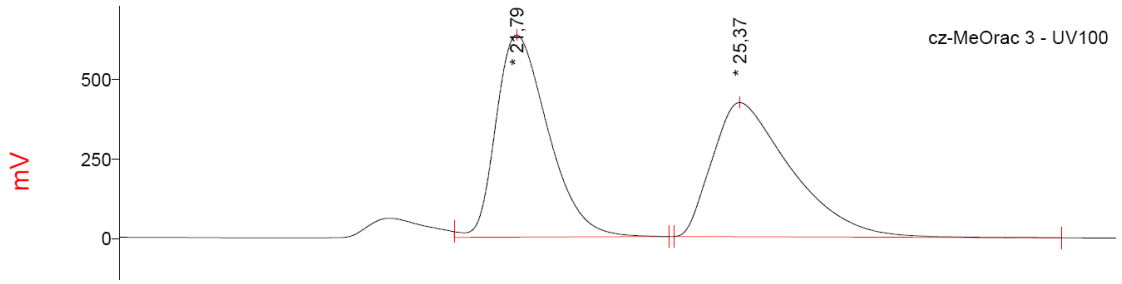






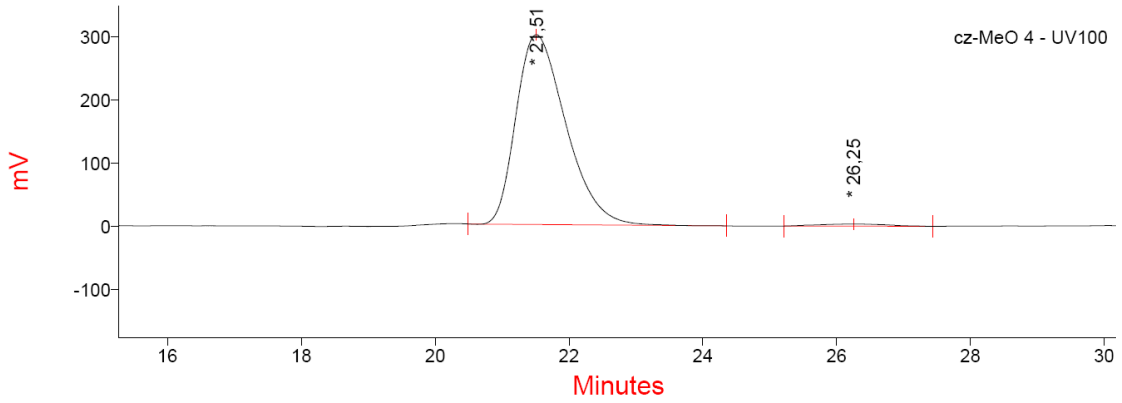
Résultats d'intégration

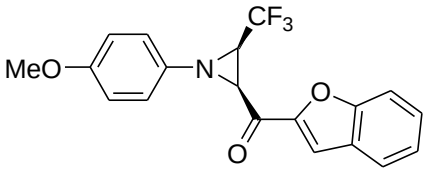
#	Nom du pic	Tr.	Aire	% Aire
1		21,79	36840,22	**50,01**
2		25,37	36825,47	**49,99**
SOMME			**73665,69**	**100,00**



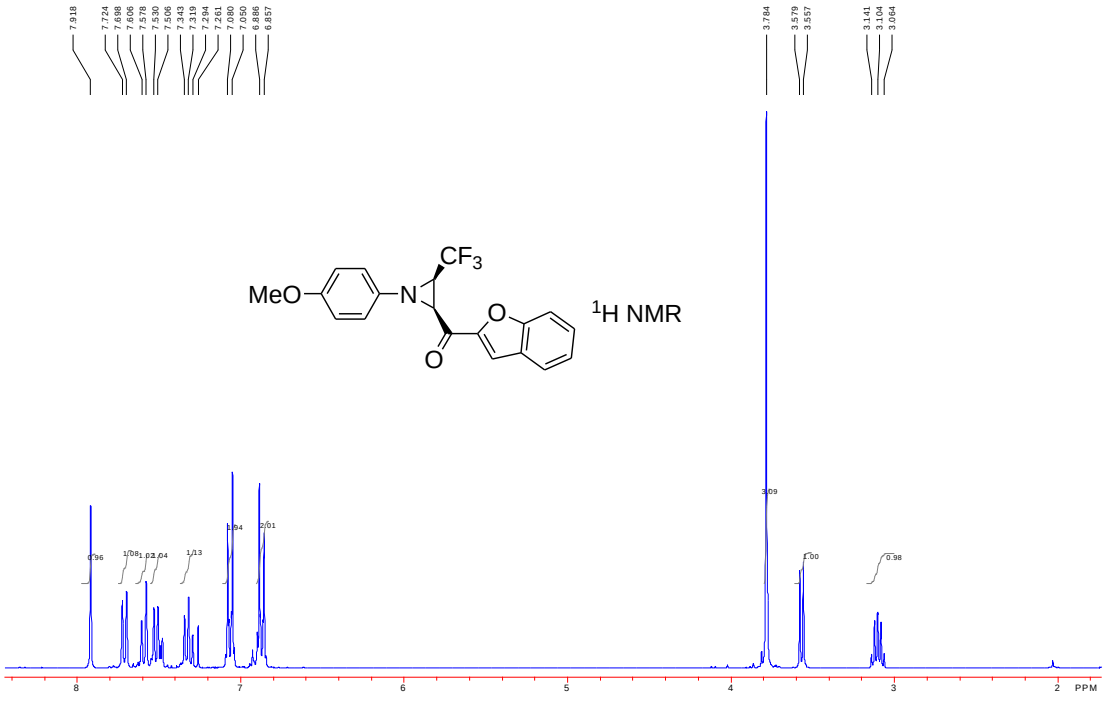
Résultats d'intégration

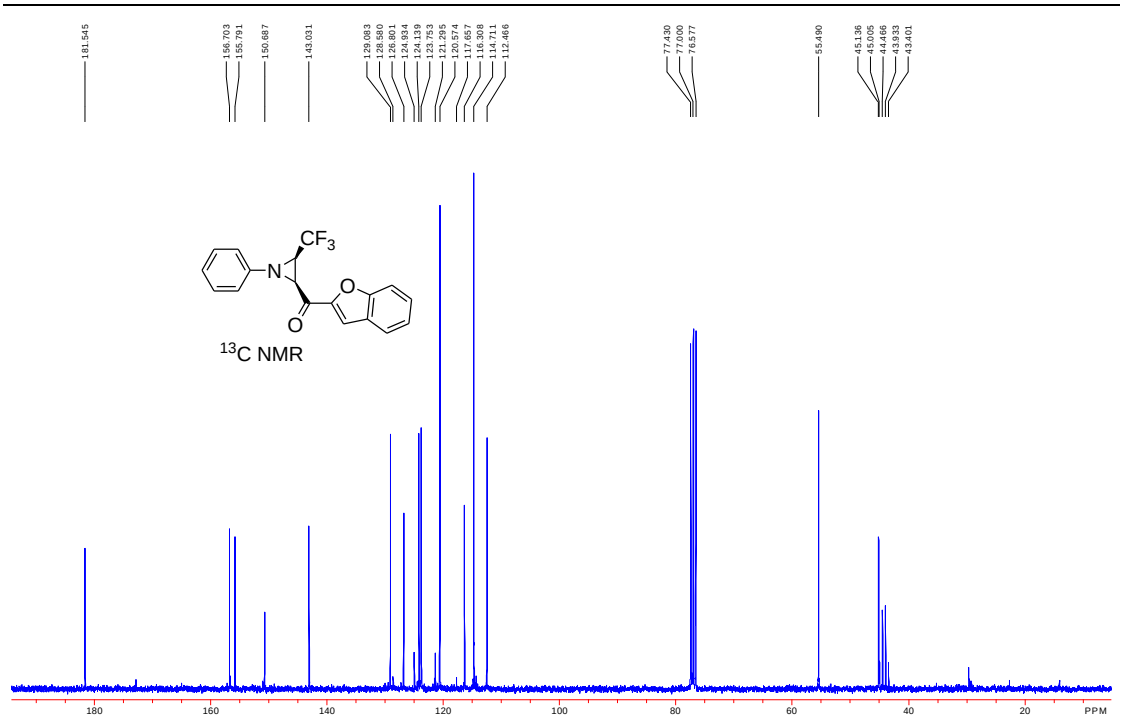
#	Nom du pic	Tr.	Aire	% Aire
1		21,51	15533,31	**98,47**
2		26,25	241,26	**1,53**
SOMME			**15774,56**	**100,00**

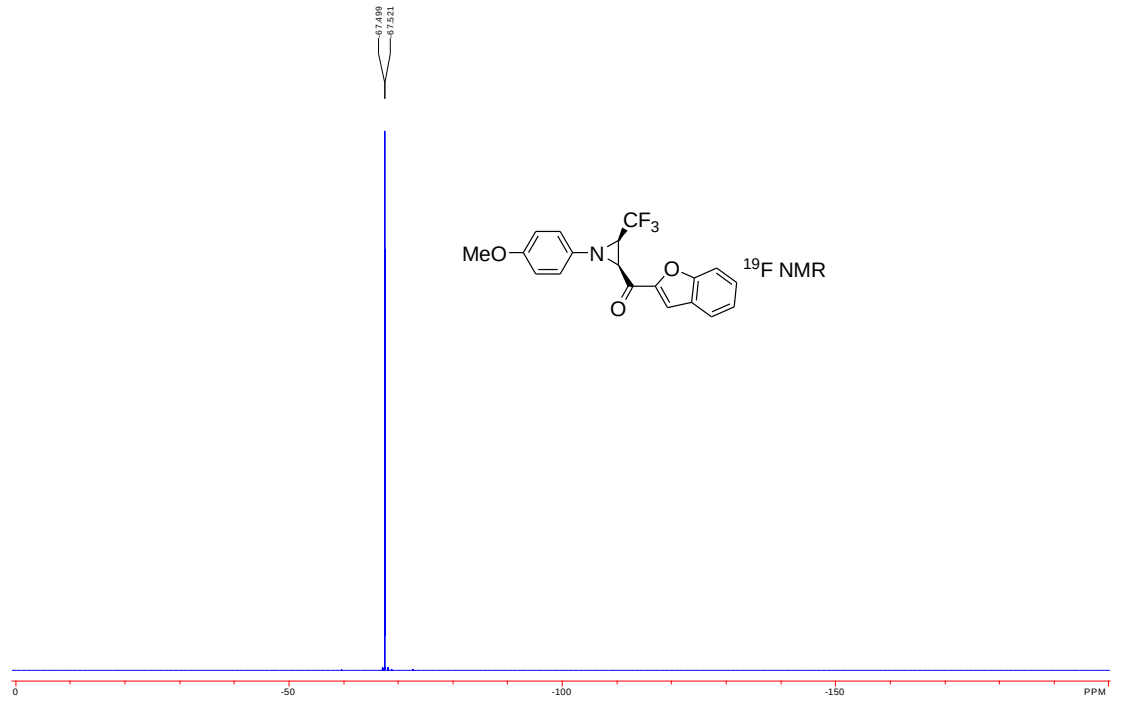




Aziridine *cis*-**3h** was obtained as a pale yellow solid in 79% yield using 3+2 mol% of **1a** at a time interval of 16 h; $[\alpha]^{21}_{D}$ = -187.1 (*c* 2.24, CH_2Cl_2); dr = 39:1, ee = 99.3%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ＝210 nm, t_R(major) = 17.7 min, t_R(minor) = 26.4 min; **IR** (neat): 2955, 1682, 1510, 1136, 1030, 833, 746 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.97 (AB, *J* = 8.9 Hz, 4H), 3.78 (s, 3H), 3.56 (d, *J* = 6.6 Hz, 1H), 3.10 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 181.5, 156.7, 155.8, 150.7, 143.0, 129.1, 126.8, 124.1, 123.8, 123.0 (q, *J* = 274.5 Hz), 120.6, 116.3, 114.7, 112.5, 55.5, 45.1, 44.2 (q, *J* = 40.2 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.5 (d, *J* = 6.1 Hz); **HRMS (ESI)** Calculated for $C_{19}H_{15}NO_3F_3$ ($[M+H]^+$): 362.1004, found: 362.1020.

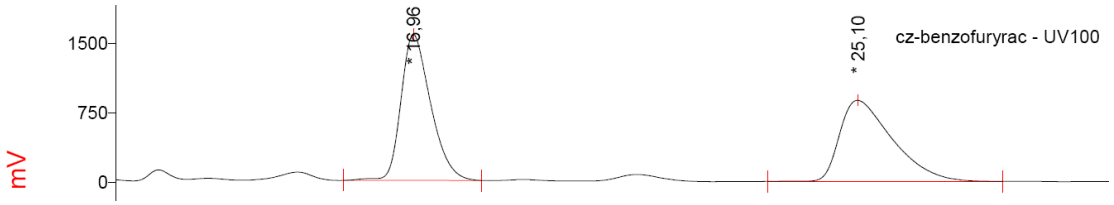



181.545
156.703
155.791
150.687
143.031
129.083
128.580
126.801
124.934
124.139
123.753
121.295
120.574
116.467
115.708
114.711
112.466
77.430
77.000
76.577
55.490
45.136
45.005
44.466
43.933
43.401
CF3
N
O
O
13C NMR
180
160
140
120
100
80
60
40
20
PPM


67.499
67.521
CF3
MeO
N
O
O
19F NMR
0
-50
-100
-150
PPM

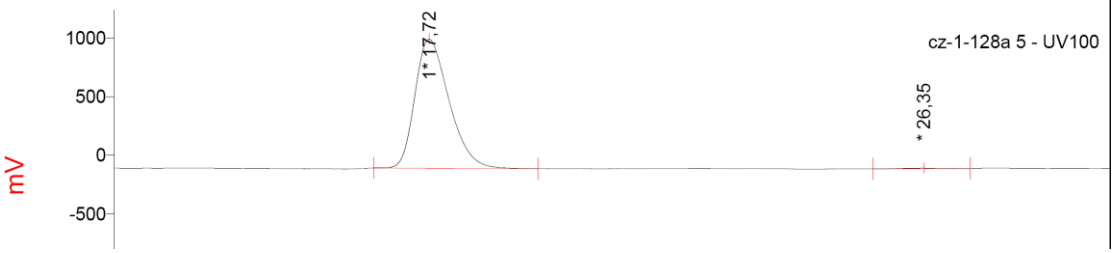
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire
1		16,96	59470,74	**50,32**
2		25,10	58708,83	**49,68**
SOMME			**118179,57**	**100,00**

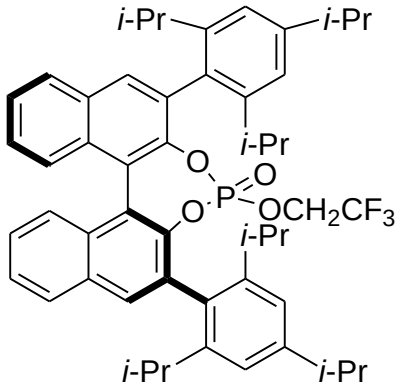


Résultats d'intégration

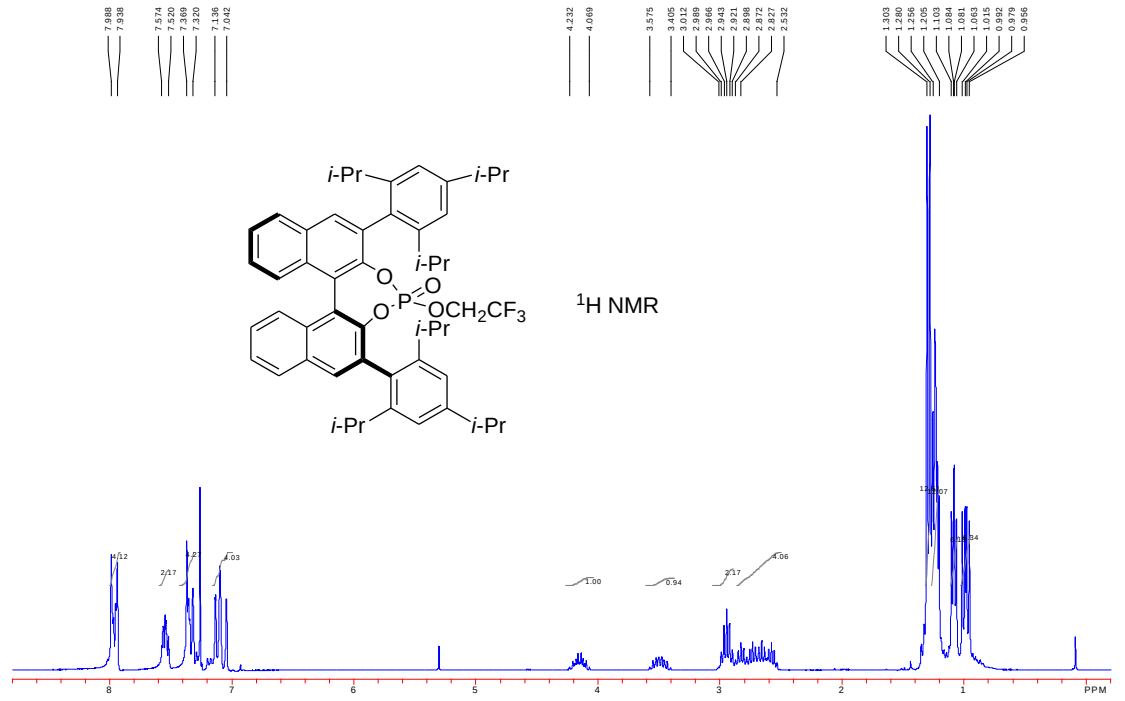
#	Nom du pic	Tr.	Aire	% Aire
1	1	17,72	45512,85	**99,65**
2		26,35	160,05	**0,35**
SOMME			**45672,90**	**100,00**



Characterization data for the trifluoroethylation product 4:



Compound **4**; White waxy solid; $[\alpha]^{20}_{,D}$ = +36.4 (*c* 0.79, CH_2Cl_2); **IR** (neat): 2959, 2928, 2156, 2025, 1312, 1166, 980, 905, 745 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.96 (m, 4H), 7.54 (m, 2H), 7.34 (m, 4H), 7.07 (m, 4H), 4.23-4.07 (m, 1H), 3.58-3.41 (m, 1H), 2.94-2.87 (heptuplet, *J* = 6.9 Hz, 2H), 2.87-2.53 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 12H), 1.26-1.21 (m, 12H), 1.09 (d, *J* = 5.4 Hz, 3H), 1.07 (d, *J* = 5.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 5.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, carbon signal of the CF_3 group was not observed): 147.9, 147.7, 146.9, 146.8, 146.2, 145.9, 145.1, 145.0, 143.8, 143.7, 131.7, 131.66, 131.2, 130.5, 130.45, 130.3, 130.2, 129.9, 129.6, 129.3, 127.4, 127.3, 126.4, 125.4, 125.1, 124.9, 120.8, 120.1, 119.8, 119.7, 119.0, 62.8 (dq, $^2J_{C\text{-}P}$ = 4.4 Hz, $^2J_{C\text{-}F}$ = 40.0 Hz), 33.4, 33.37, 30.3, 30.2, 30.0, 29.5, 25.7, 25.5, 24.4, 24.1, 23.13, 23.1, 23.06, 22.9, 22.2, 21.9, 21.8; **^{19}F NMR** (282 MHz, $CDCl_3$): -75.5 (pseudo t, *J* = 8.2 Hz); **HRMS (ESI)** Calculated for $C_{52}H_{59}O_5F_3P$ ($[M+OH]^-$): 851.4052, found: 851.4066.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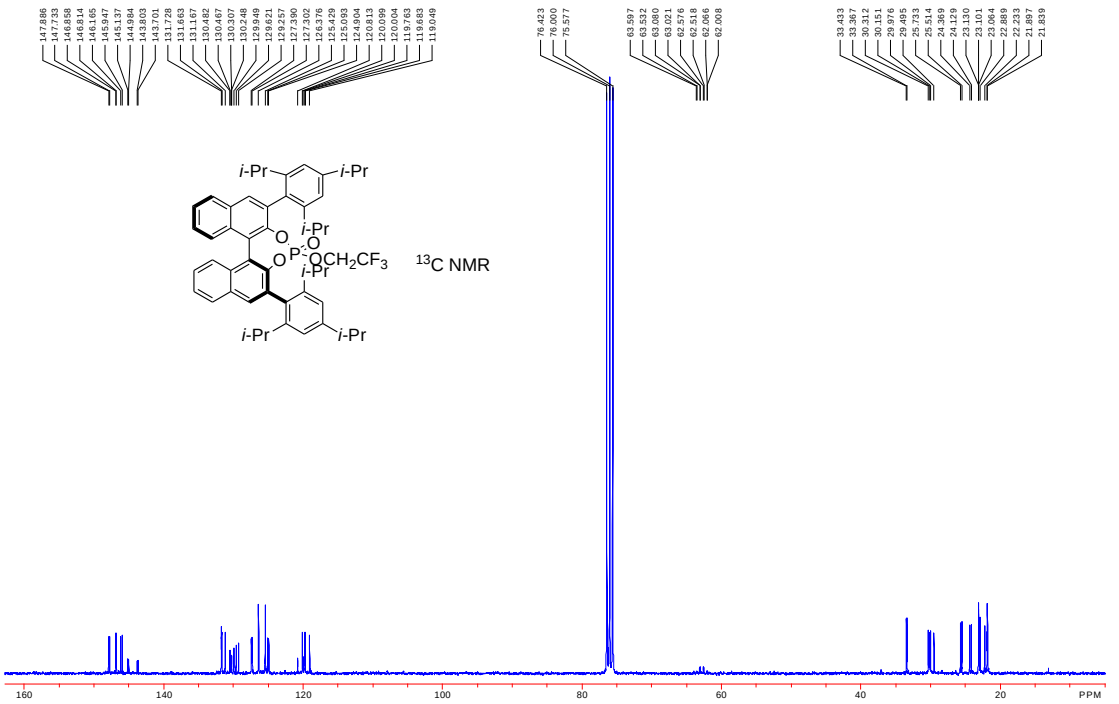
P
O
OCH2CF3
O
i-Pr
i-Pr
i-Pr
1H NMR
PPM


i-Pr
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i-Pr
O
P
O
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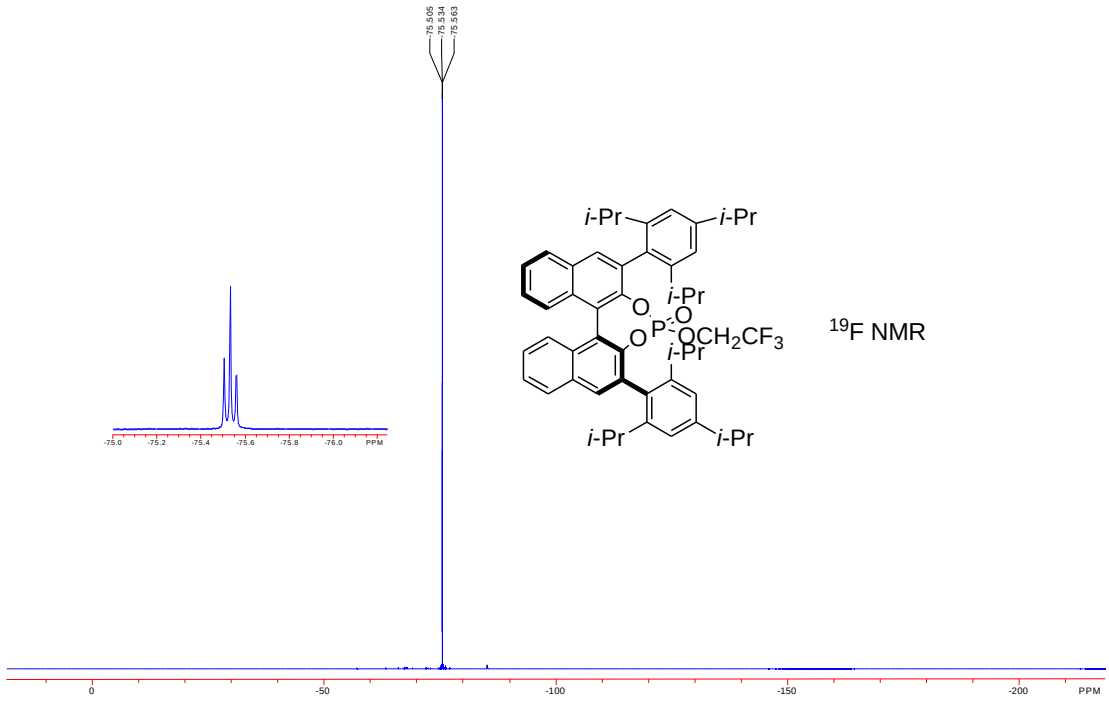
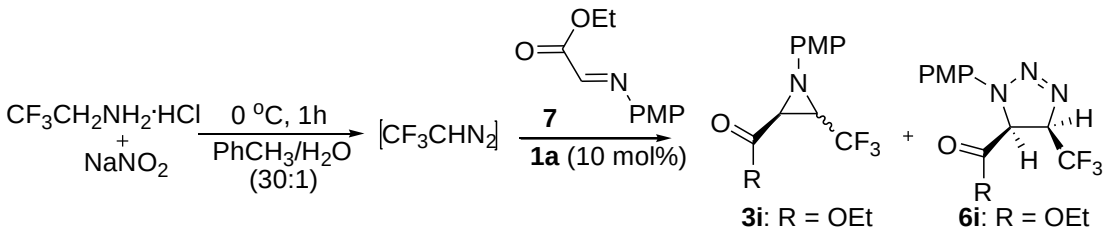
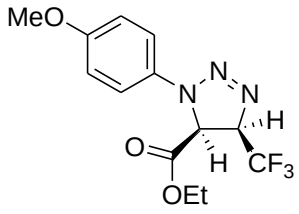
i-Pr
i-Pr
i-Pr
13C NMR
PPM



Asymmetric aza-Darzens reactions of preformed imines 7 and 8.

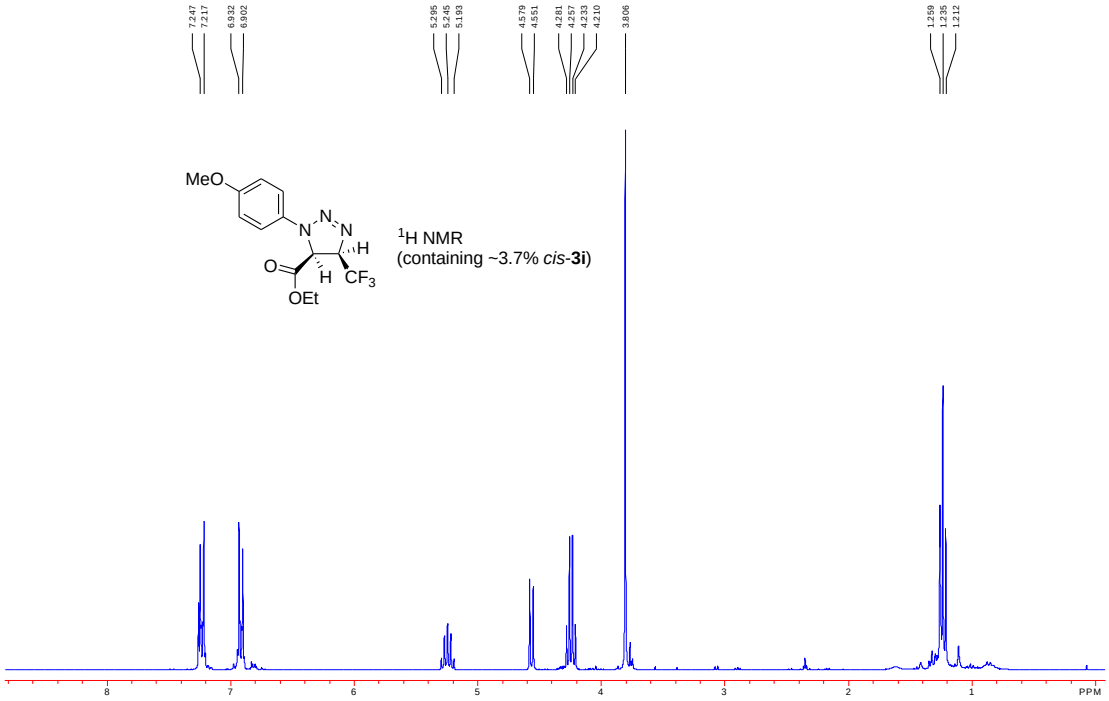


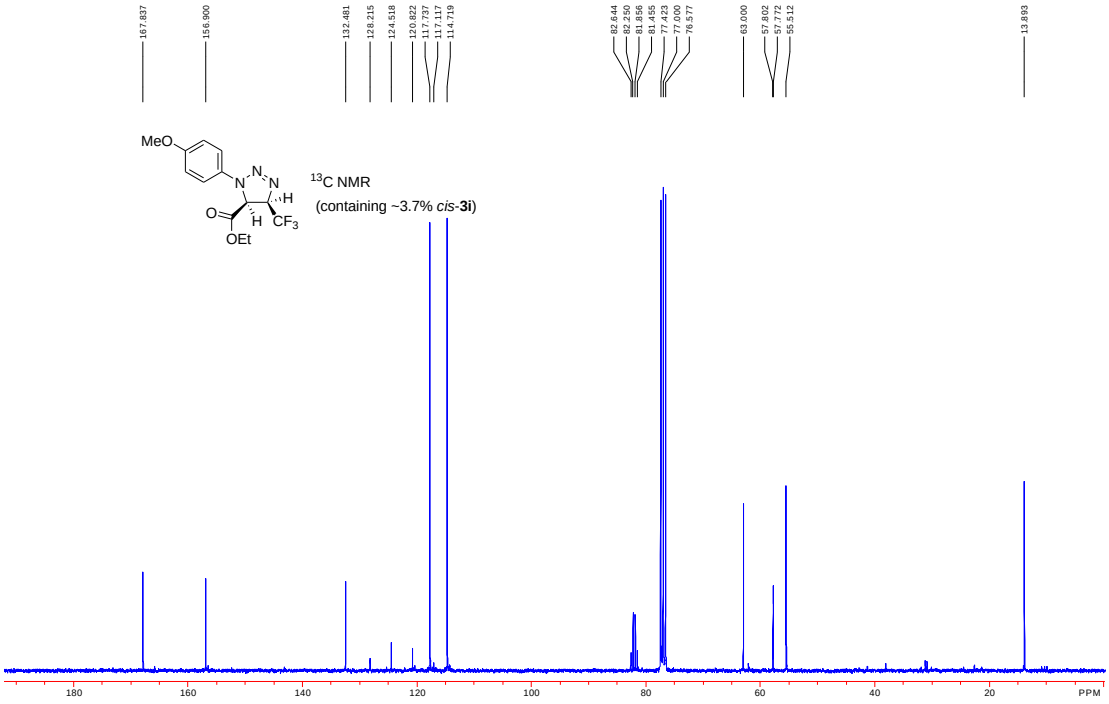
To a 5-mL flask charged with $CF_3CH_2NH_2$·HCl (30 mg, 0.22 mmol) and $NaNO_2$ (18 mg, 0.26 mmol) was added 1.0 mL of toluene and 30 μL of distilled H_2O, and the resultant mixture was stirred vigorously at 0 °C for 1 h. Then, anhydrous $MgSO_4$ (~250 mg) was added to the *in situ* prepared CF_3CHN_2 solution and stirred at 0 °C for 2 min and the supernatant clear yellow solution was transferred via pipette to another 5-mL flask containing the imine **7**, (*S*)-TRIP (8.4 mg, 10 mol%), and anhydrous $MgSO_4$ (~250 mg) in 0.5 mL of CH_3CH_2CN and the mixture was stirred at RT for 6-12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and sat. NH_4Cl (15 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (15 mL×2) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography on silica gel eluting with 5%→10% (volume%) ethyl acetate in petroleum ether (bp 40-60 °C) to furnish the desired products (*cis*-**3i**[2a] and **6i** was an inseparable mixture). Product ratio: *cis*-**3i**:*trans*-**3i**:**6i** = 1.4:1:25.7.

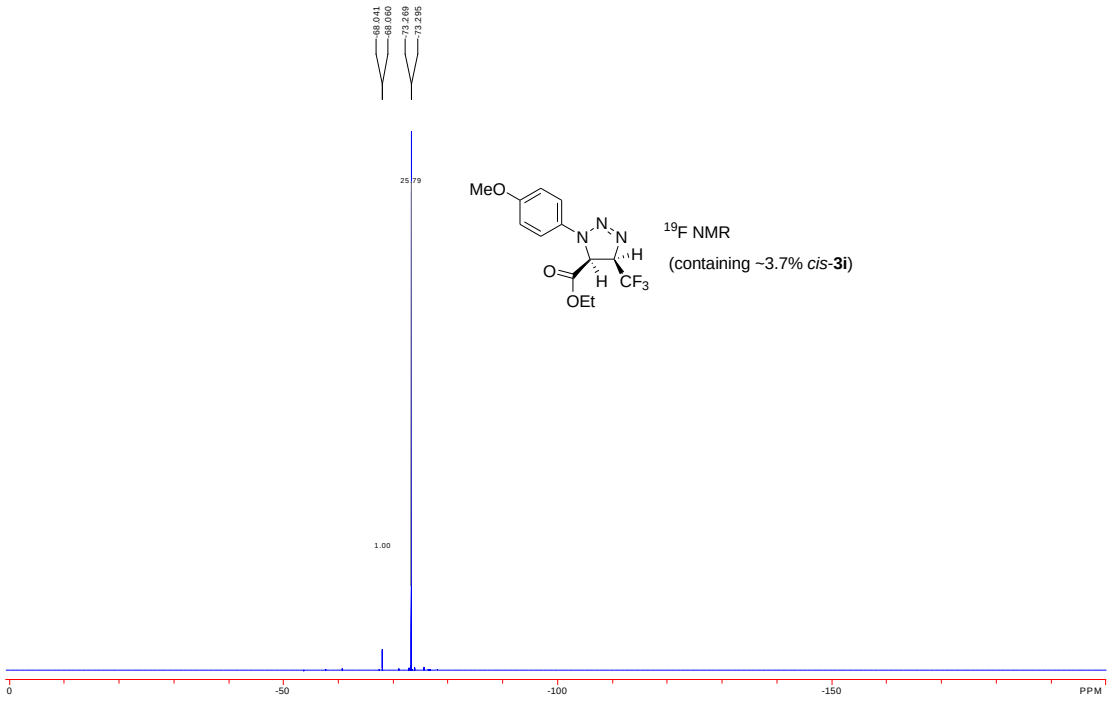


Triazoline **6i** was obtained as a pale yellow viscous oil in 82 % yield (containing ~3.7% *cis*-**3i**); $[\alpha]^{22}_{,D}$ = +4.0 (*c* 2.15, CH_2Cl_2); ee = 95%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.5 mL/min, λ=210 nm, t_R(minor) = 10.8 min, t_R(major) = 13.1 min; **IR** (neat): 2925, 2851, 1745, 1516, 1467, 1179, 1126, 826 cm^{-1}; **^{1}H NMR**

(300 MHz, $CDCl_3$): δ 7.07 (AB, J = 8.9 Hz, 4H), 5.25 (m, 1H), 4.56 (d, J = 8.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): 167.8, 156.9, 132.5, 122.7 (q, J = 279.0 Hz), 117.7, 114.7, 82.1 (q, J = 29.7 Hz), 63.0, 57.8 (q, J = 2.2 Hz), 55.5, 13.9; **^{19}F NMR** (282 MHz, $CDCl_3$): -73.3 (d, J = 7.2 Hz); **HRMS (ESI)** Calculated for $C_{13}H_{15}N_3O_3F_3$ ($[M+H]^+$): 318.1066, found: 318.1062.



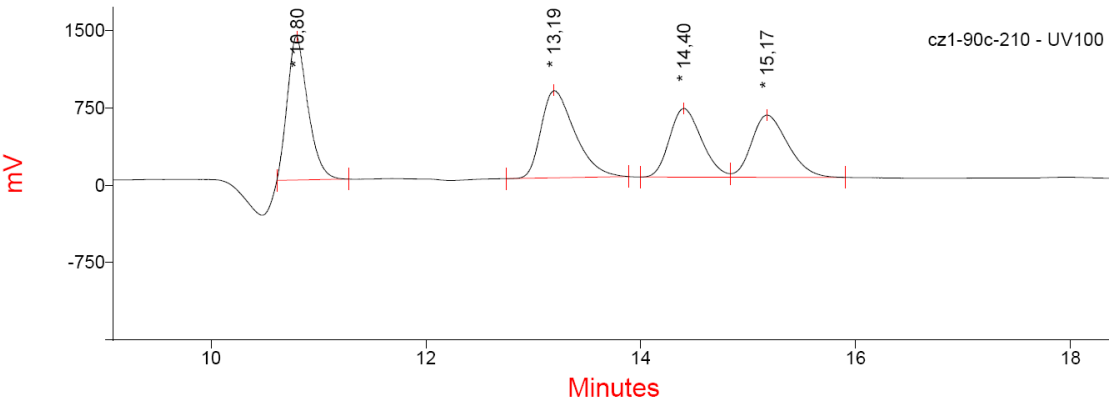




The racemic product used for HPLC assay shown below was obtained with $Yb(OTf)_3$ (10 mol%) in toluene, which gave a product ratio of *cis*-**3i**:*trans*-**3i**:**6i** = 18.7:1:16.7.

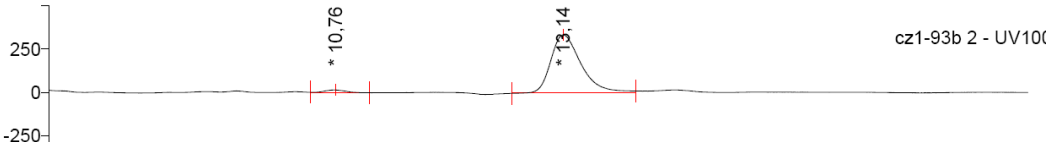
Résultats d'intégration

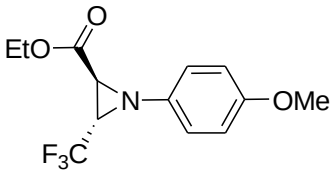
#	Nom du pic	Tr.	Aire	% Aire
1		10,80	18467,36	**28,43**
2		13,19	18452,63	**28,41**
3		14,40	13850,98	**21,33**
4		15,17	14176,82	**21,83**
SOMME			**64947,77**	**100,00**



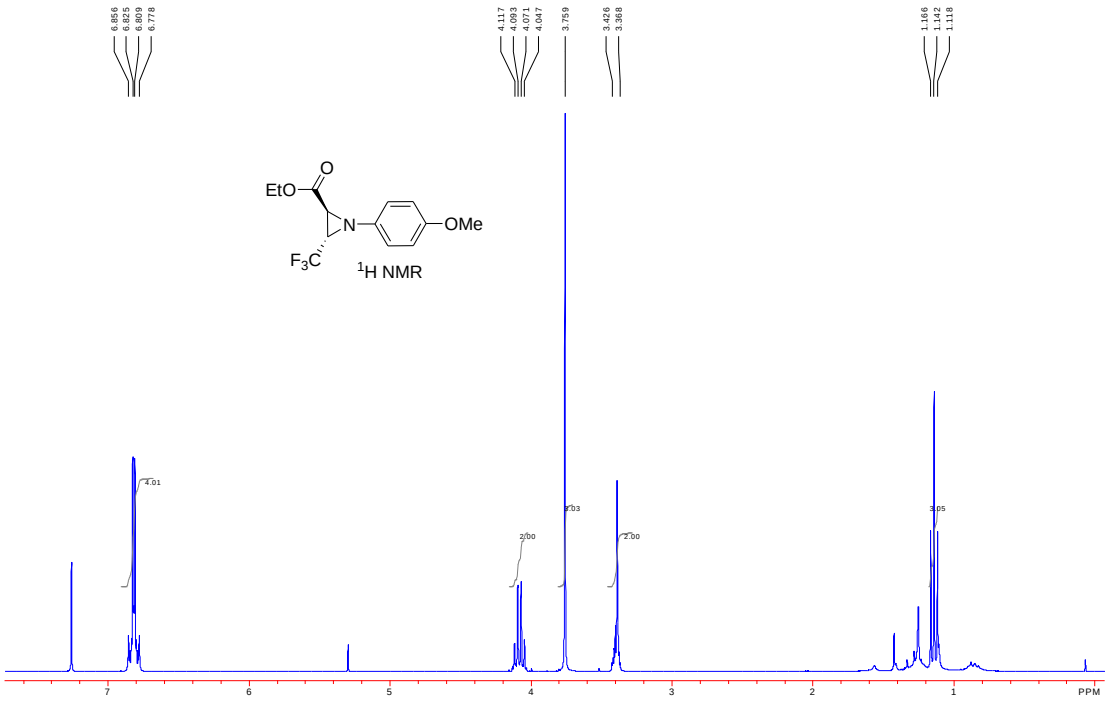
Résultats d'intégration

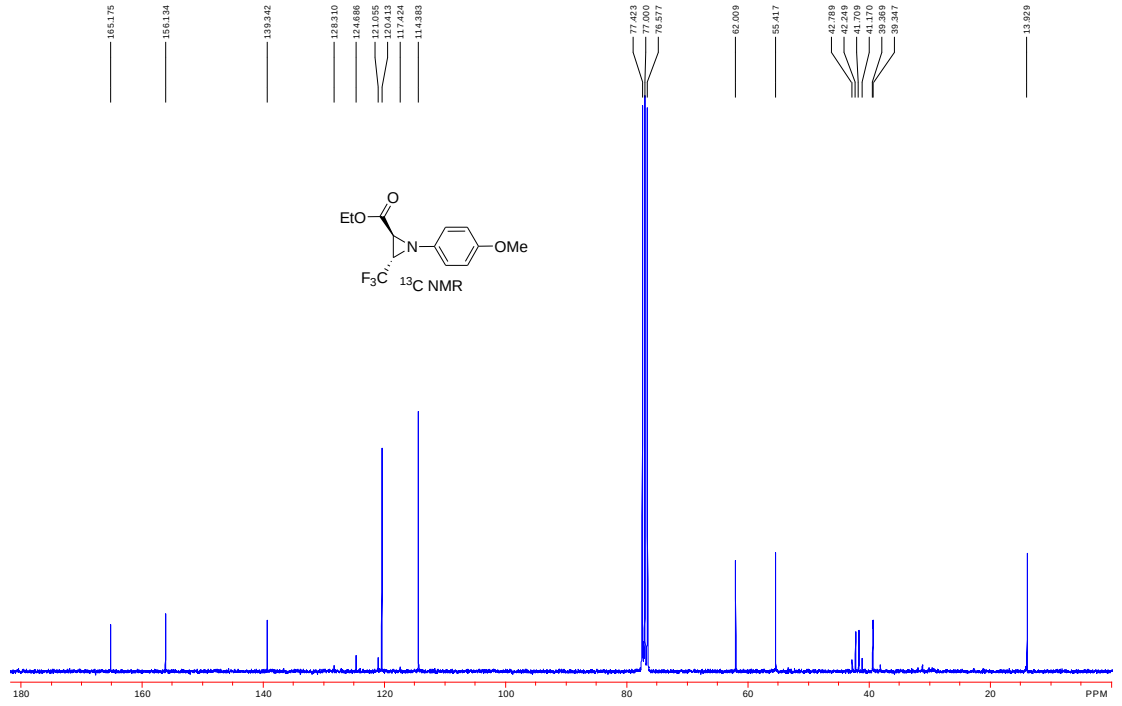
#	Nom du pic	Tr.	Aire	% Aire
1		10,76	189,16	**2,57**
2		13,14	7167,64	**97,43**
SOMME			**7356,80**	**100,00**

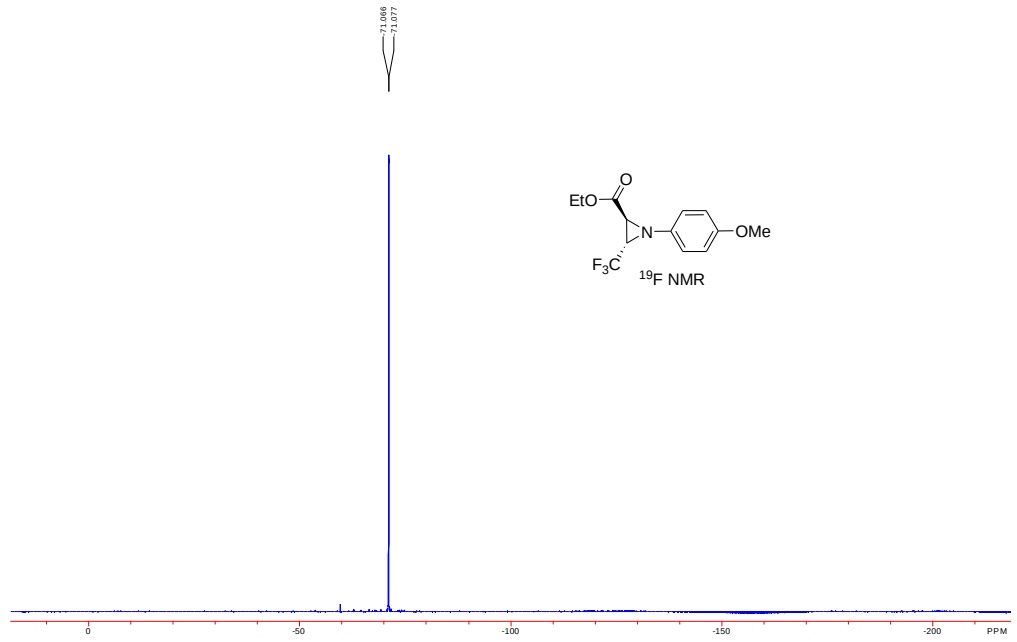




trans-aziridine **3i**[2b] was obtained a pale yellow oil; **HPLC**: Daicel CHIRALCEL OD-H column, 10% IPA in *n*-heptane, 0.5 mL/min, λ = 210 nm, t_R(minor) = 7.07 min, t_R(major) = 7.67 min; 20% ee, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.86-6.78 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.43-3.37 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): 165.2, 156.1, 139.3, 122.9 (q, J = 274.0 Hz), 120.4, 114.4, 62.0, 55.4, 42.0 (q, J = 40.7 Hz), 39.3 (q, J = 1.7 Hz), 13.9; **^{19}F NMR** (282 MHz, $CDCl_3$): -71.1 (d, J = 3.0 Hz).




165.175
156.134
139.342
128.310
124.686
121.055
120.413
117.424
114.383
77.423
77.000
76.577
62.009
55.417
42.789
42.248
41.709
41.170
39.369
39.347
13.929
EtO
O
N
OMe
F3C
13C NMR
180
160
140
120
100
80
60
40
20
PPM


71.066
71.077
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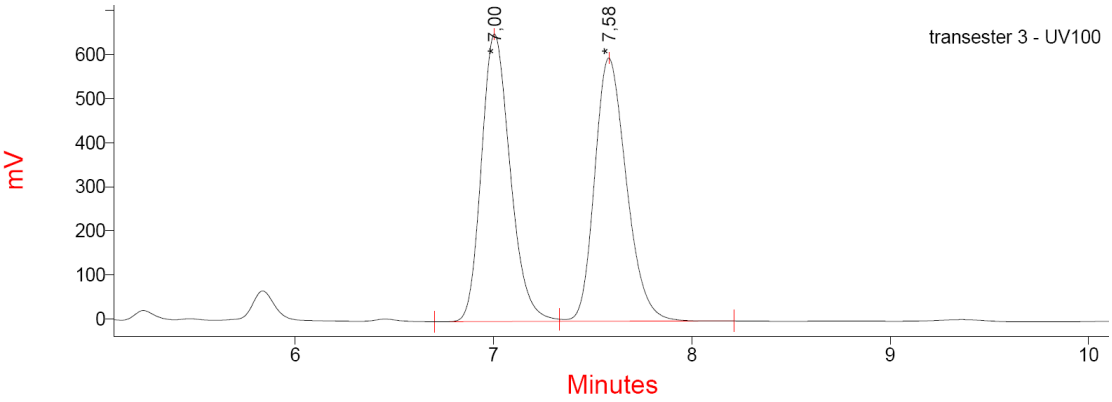
O
N
OMe
F3C
19F NMR
0
-50
-100
-150
-200
PPM

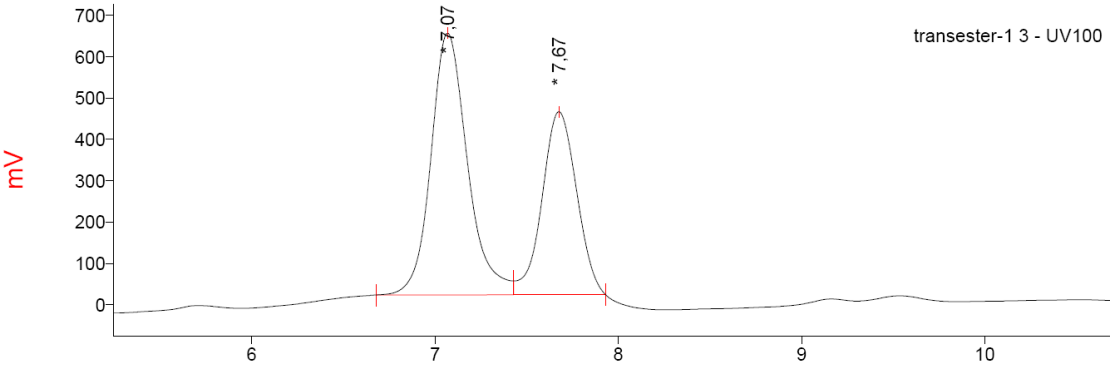
Résultats d'intégration

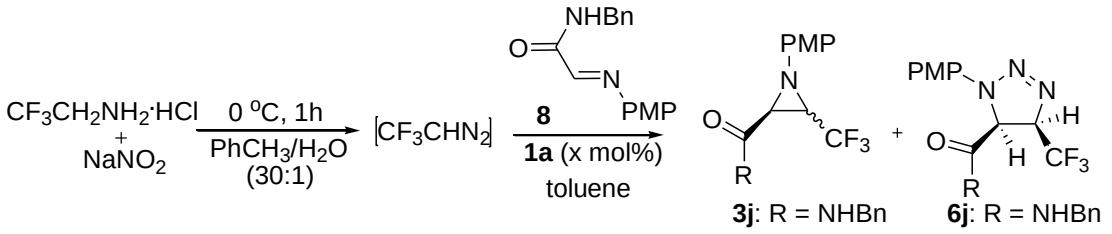
#	Nom du pic	Tr.	Aire	% Aire
1		7,00	6591,92	**49,77**
2		7,58	6651,70	**50,23**
SOMME			**13243,62**	**100,00**



Résultats d'intégration

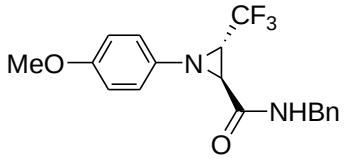
#	Nom du pic	Tr.	Aire	% Aire
1		7,07	8813,70	**60,21**
2		7,67	5825,18	**39,79**
SOMME			**14638,89**	**100,00**





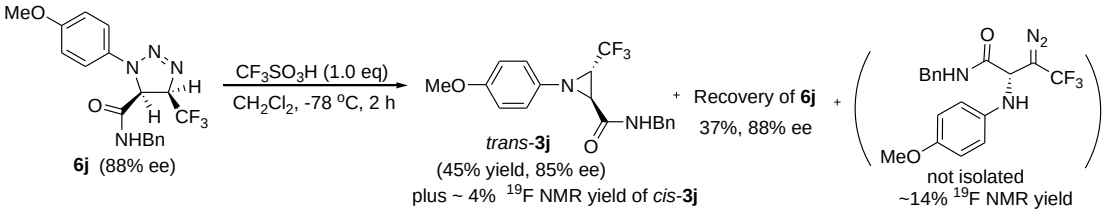
To a 5-mL flask charged with $CF_3CH_2NH_2$·HCl (30 mg, 0.22 mmol) and $NaNO_2$ (18 mg, 0.26 mmol) was added 1.2 mL of toluene and 30 μL of distilled H_2O, and the resultant mixture was stirred vigorously at 0 °C for 1 h. Then, anhydrous $MgSO_4$ (~250 mg) was added to the *in situ* prepared CF_3CHN_2 solution and stirred at 0 °C for 2 min and the supernatant clear yellow solution was transferred via pipette to another 5-mL flask containing the imine **8**, (*S*)-TRIP (2.5 mg, 3 mol%), and anhydrous $MgSO_4$ (~250 mg) in 1.0 mL of toluene and the mixture was stirred at RT for 1 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and sat. NH_4Cl (15 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (15 mL×2) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography on

silica gel eluting with 15%→50% (volume%) ethyl acetate in petroleum ether (bp 40-60 °C) to furnish the desired products *trans*-**3j**, **6j** and *cis*-**3j** (product ratio: 1:6:6), sequentially.

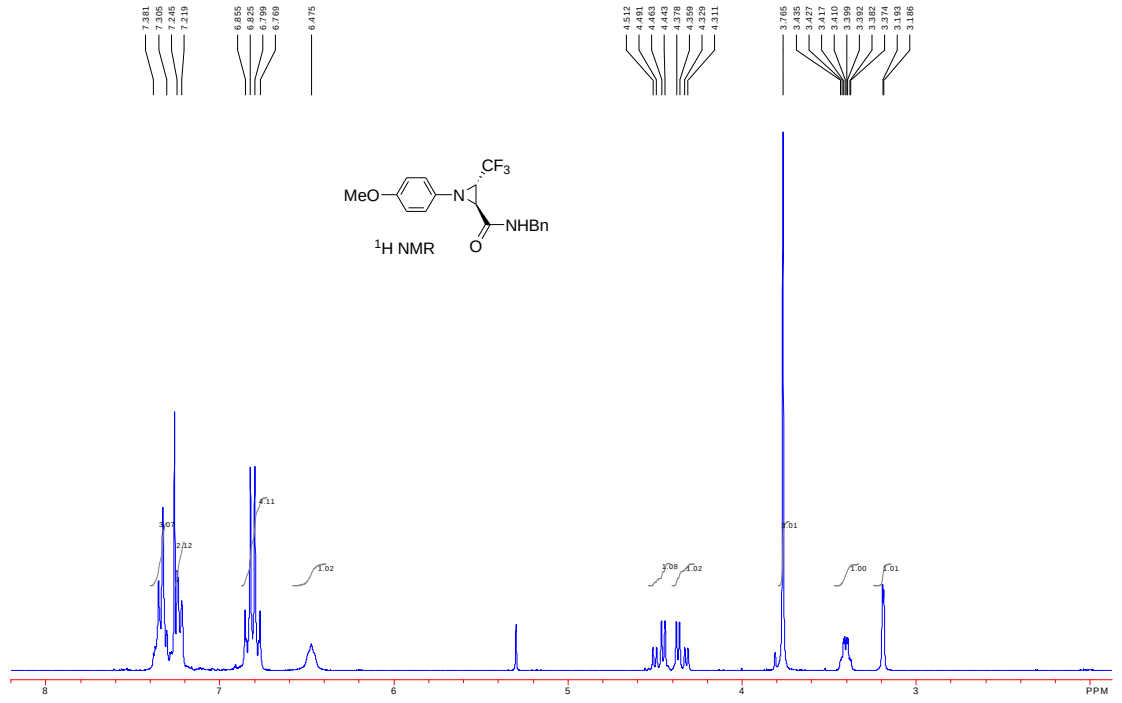


Aziridine *trans*-**3j** was obtained as a white solid in 8% yield; ee = 57%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.5 mL/min, λ = 210 nm, t_R(minor) = 10.4 min, t_R(major) = 11.5 min; **IR** (neat): 3282, 2921, 1655, 1506, 1241, 1144, 864, 697 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38-7.22 (m, 5H), 6.81 (AB, J = 9.1 Hz, 4H), 6.48 (brs, 1H), 4.51-4.31 (ABX, $^3J_{H\text{-}H}$ = 5.5 Hz, $^3J_{H\text{-}H}$ = 6.1 Hz, $^2J_{H\text{-}H}$ = 14.5 Hz, 2H), 3.77 (s, 3H), 3.41 (d, $^3J_{H\text{-}H}$ = 2.1 Hz, $^3J_{H\text{-}F}$ = 5.2 Hz, 1H), 3.19 (d, J = 2.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 163.9, 156.1, 138.7, 137.2, 128.8, 128.0, 127.9, 123.0 (q, J = 275.1 Hz), 120.5, 114.4, 55.4, 43.9, 41.9 (q, J = 39.1 Hz), 40.2; **^{19}F NMR** (282 MHz, $CDCl_3$): -69.0 (m); **HRMS (ESI)** Calculated for $C_{18}H_{18}N_2O_2F_3$ ($[M+H]^+$): 351.1320, found: 351.1311.

Conversion of **6j** to *trans*-**3j**:[4]



To a stirred solution of **6j** (19 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) placed in a dry ice-acetone bath (-78 °C) was added CF_3SO_3H (4.5 μL, 0.05 mmol) in 10 μL of CH_2Cl_2 dropwise. The resulting solution was stirred at this temperature for 2 h before 5 mL of sat. $NaHCO_3$ solution was added to quench the reaction. The reaction mixture was diluted with 5 mL of CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2 (5 mL×2). The combined organic phases were washed with brine, dried over $MgSO_4$, concentrated and purified by column chromatography eluting with 15%→30% (volume%) ethyl acetate in petroleum ether (bp 40-60 °C) to furnish *trans*-**3j**, **6j**. Diagnostic ^{19}F NMR signals for the presumed α-diazo byproduct: δ_F = -57.4 (s). This byproduct was not isolated during the column chromatography, which might be due to its decomposition or isomerisation during this process. However, for the time being, we are unable to provide a rationale for the formation of small amount of the *cis*-**3j** in this process. See page S46 for a brief discussion on the mechanistic implication of this result.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6.799
6.769
6.475
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4.491
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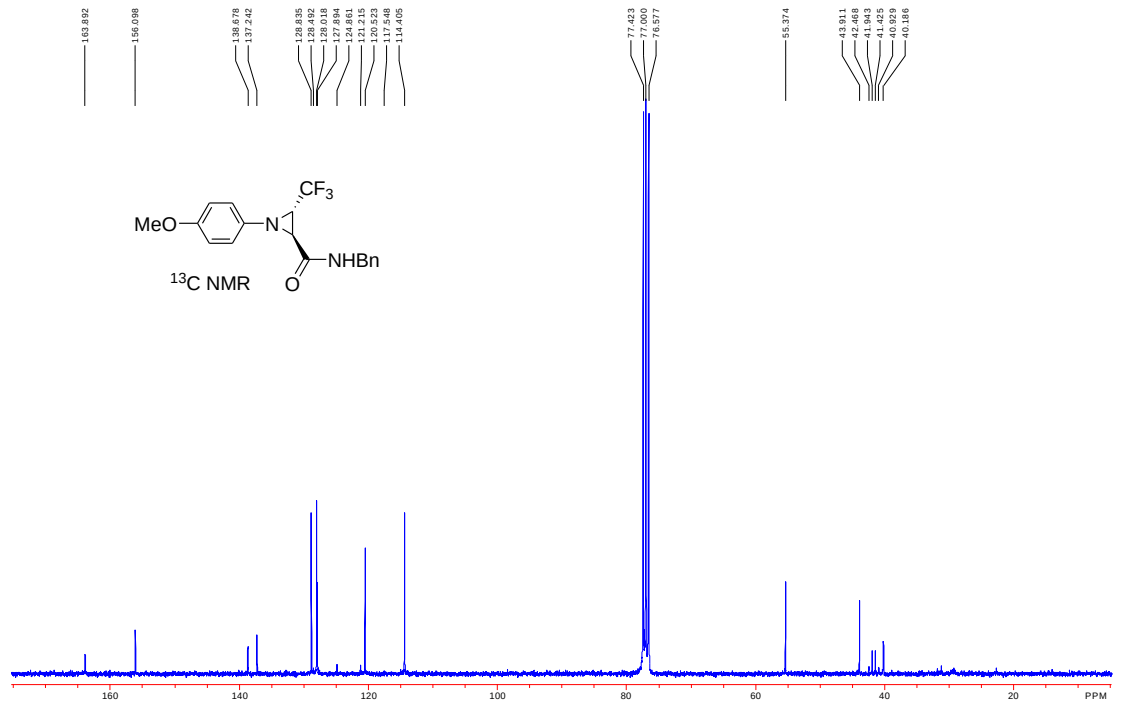
4.378
4.359
4.329
4.311
3.765
3.435
3.427
3.417
3.410
3.399
3.392
3.382
3.374
3.193
3.186
CF3
MeO
N
NHBn
O
1H NMR
3.07
2.12
4.11
1.02
1.08
1.02
7.01
1.00
1.01
8
7
6
5
4
3
PPM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128.018
127.894
124.861
121.215
120.523
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77.423
77.000
76.577
55.374
43.911
42.468
41.943
41.425
40.929
40.186
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NHBn
O
13C NMR
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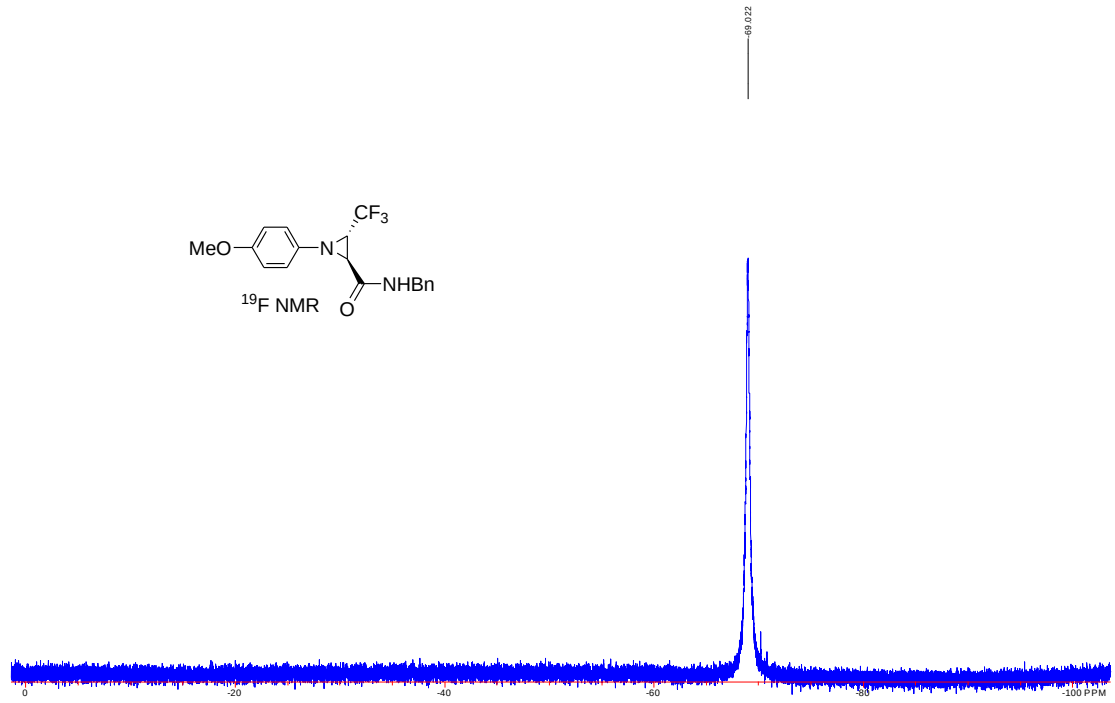
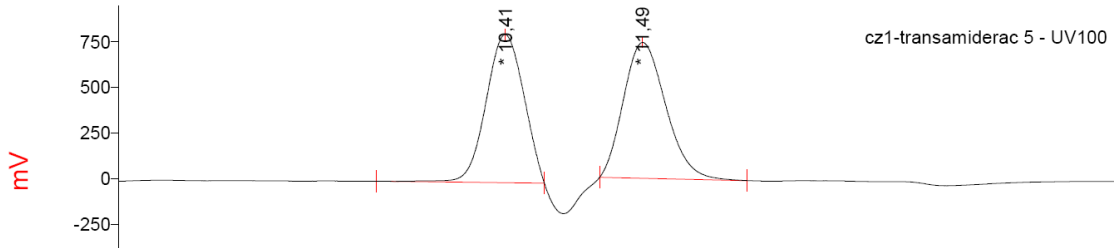
140
120
100
80
60
40
20
PPM



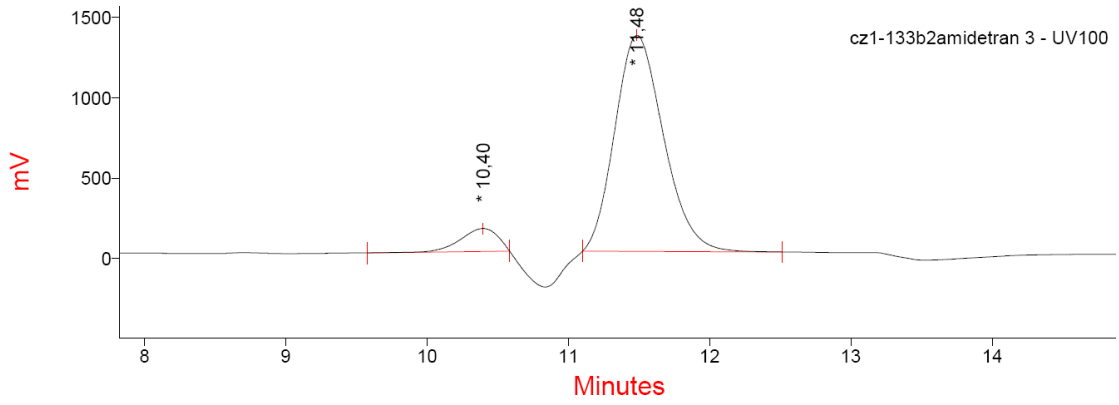
Résultats d'intégration

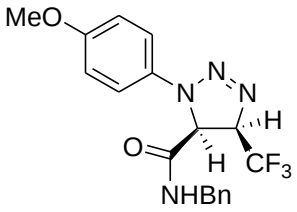
#	Nom du pic	Tr.	Aire	% Aire
1		10,41	16647,54	**49,16**
2		11,49	17217,94	**50,84**
SOMME			**33865,48**	**100,00**



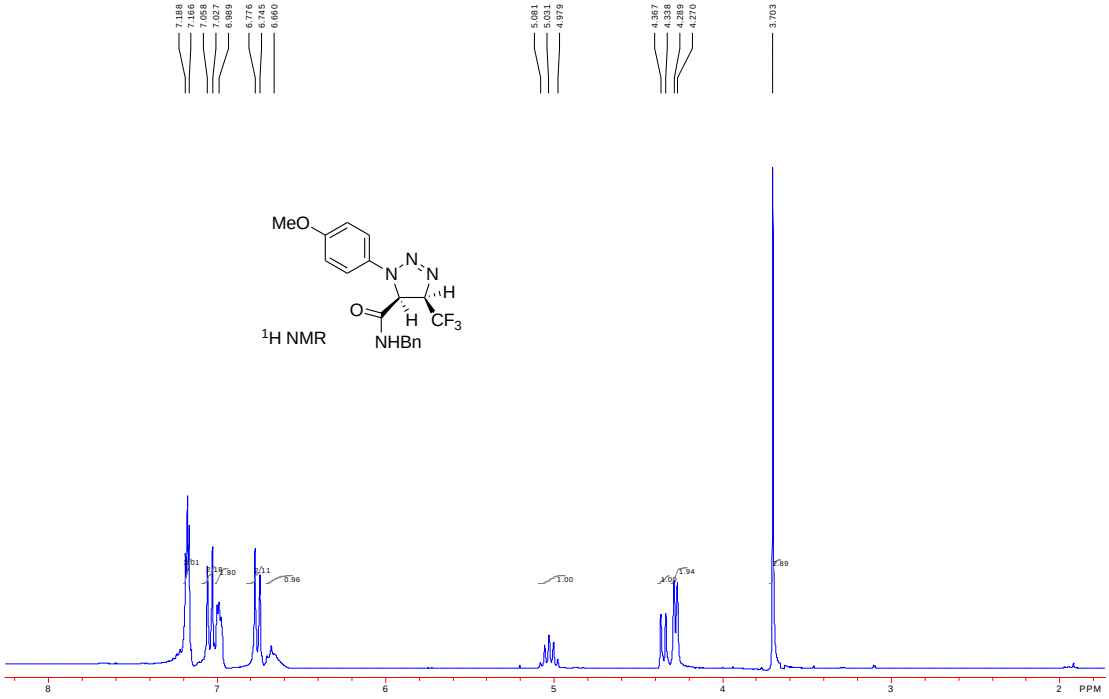
Résultats d'intégration

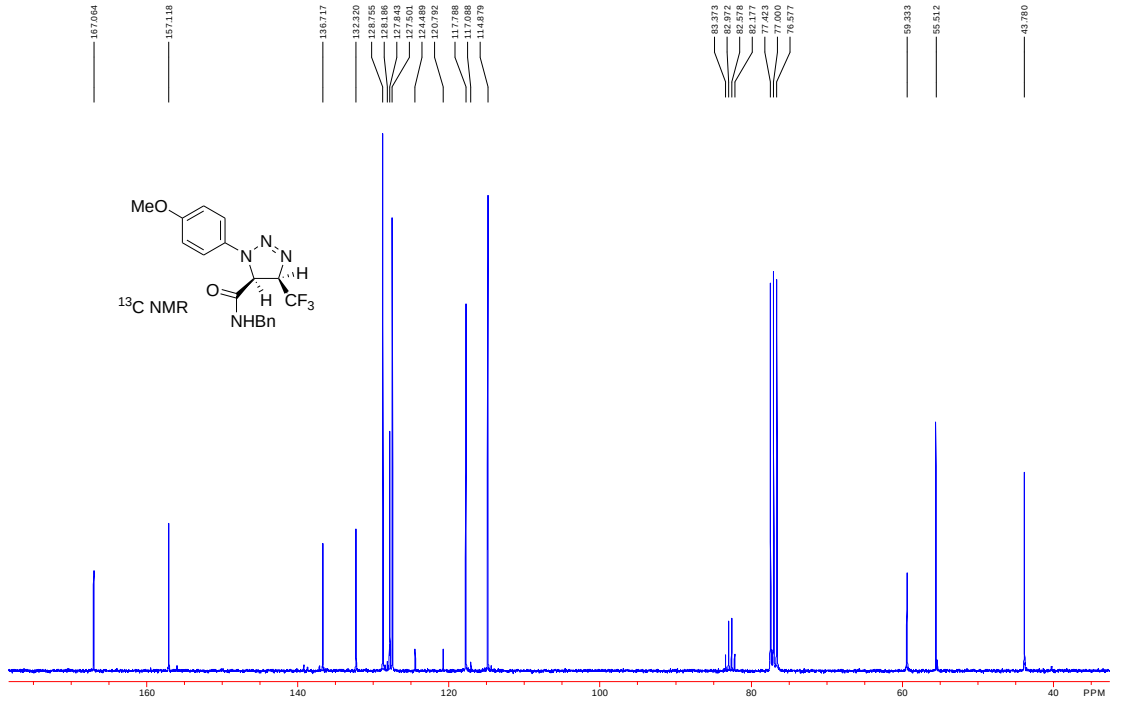
#	Nom du pic	Tr.	Aire	% Aire
1		10,40	2628,16	**7,54**
2		11,48	32224,15	**92,46**
SOMME			**34852,30**	**100,00**





Triazoline **6j** was obtained as a white solid in 45% yield; $[\alpha]^{21}_{D}$ = -19.4 (*c* 0.88, CH_2Cl_2); ee = 89%, **HPLC**: Daicel CHIRALCEL OD-H column, 20% IPA in *n*-heptane, 0.5 mL/min, λ=210 nm, t_R(minor) = 17.7 min, t_R(major) = 19.2 min; **IR** (neat): 3287, 2925, 1656, 1513, 1127, 825, 696 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.17 (m, 3H), 6.99 (m, 2H), 6.95 (AB, *J* = 9.1 Hz, 4H), 6.66 (brs, 1H), 5.03 (m, 1H), 4.35 (d, *J* = 8.7 Hz, 1H), 4.28 (d, *J* = 5.7 Hz, 2H), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): 167.1, 157.1, 136.7, 132.3, 128.8, 127.8, 127.5, 122.6 (q, *J* = 279.0 Hz), 117.8, 114.9, 82.8 (q, *J* = 30.2 Hz), 59.3, 55.5, 43.8; **^{19}F NMR** (282 MHz, $CDCl_3$): -73.2 (d, *J* = 7.1 Hz); **HRMS (ESI)** Calculated for $C_{18}H_{18}N_4O_2F_3$ ($[M+H]^+$): 379.1382, found: 379.1386.

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136.717
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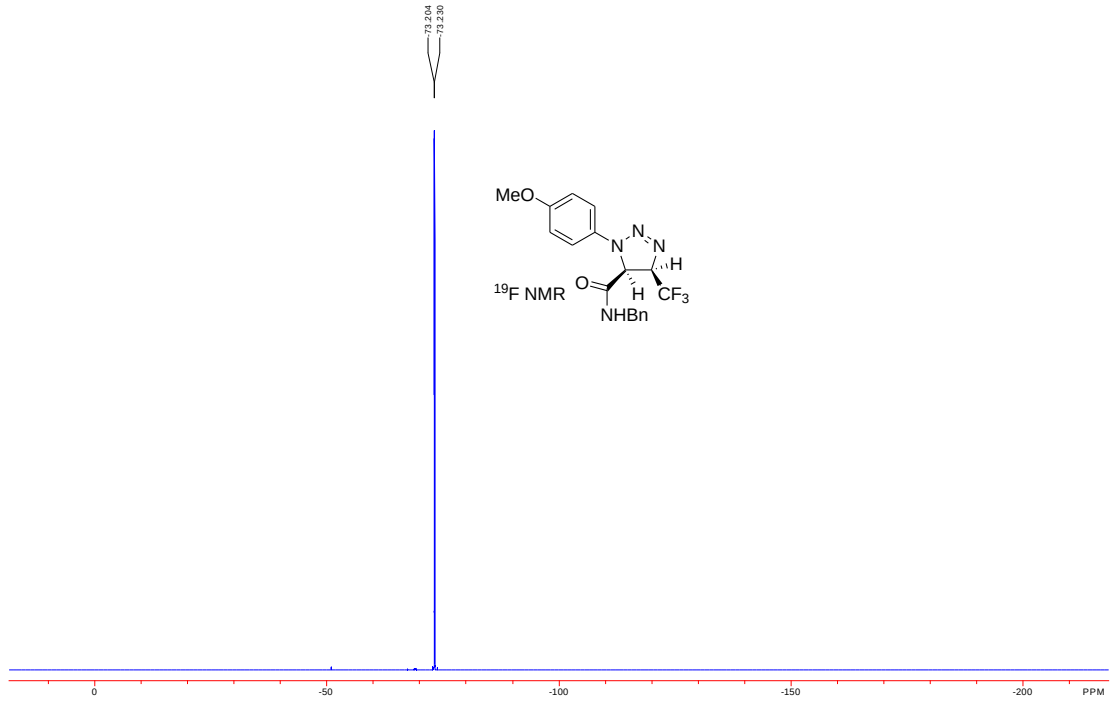
128.186
127.843
127.491
124.468
120.792
117.788
117.088
114.879
83.373
82.972
82.578
82.177
77.423
77.000
76.577
59.333
55.512
43.780
MeO
N
N
N
H
O
H
CF3
NHBn
13C NMR
160
140
120
100
80
60
40
PPM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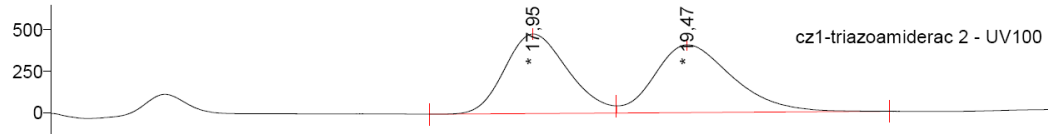
-73.230
MeO
N
N
N
H
O
H
CF3
NHBn
19F NMR
0
-50
-100
-150
-200
PPM

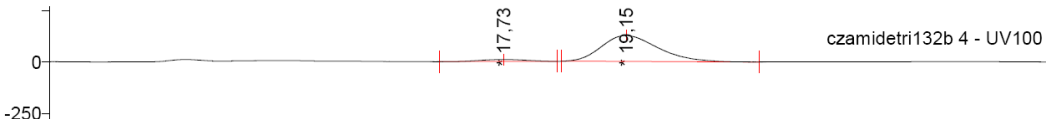
Résultats d'intégration

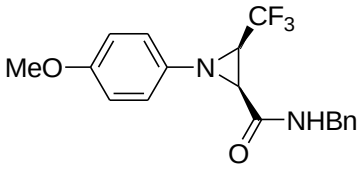
#	Nom du pic	Tr.	Aire	% Aire
1		17,95	20603,47	**48,72**
2		19,47	21689,97	**51,28**
SOMME			**42293,44**	**100,00**



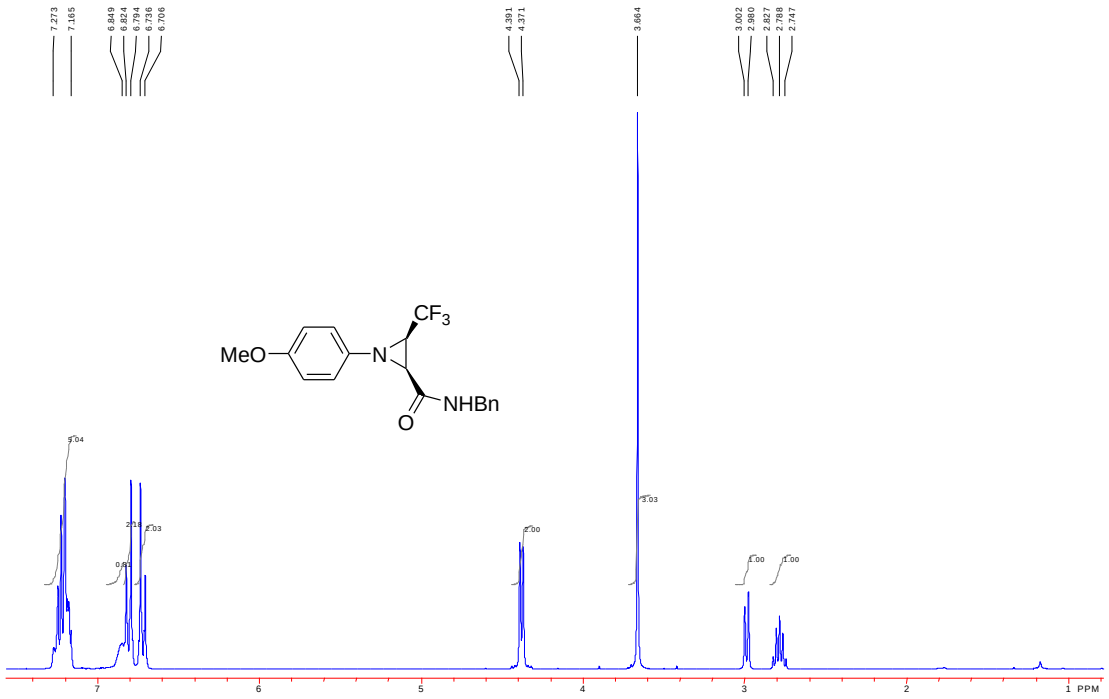
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire
1		17,73	337,34	**5,62**
2		19,15	5666,66	**94,38**
SOMME			**6003,99**	**100,00**





Aziridine *cis*-**3j** was obtained as a white solid in 46% yield; $[\alpha]^{21}_{D}$ = -118.4 (*c* 0.52, CH_2Cl_2); ee = 98.8%, **HPLC**: Daicel CHIRALCEL OJ-H column, 20% IPA in *n*-heptane, 0.75 mL/min, λ=210 nm, t_R(major) = 23.2 min, t_R(minor) = 35.6 min; **IR** (neat): 3302, 1659, 1508, 1243, 1140, 832, 697 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27-7.17 (m, 5H), 6.85 (brs, 1H), 6.77 (AB, *J* = 8.9 Hz, 4H), 4.38 (d, *J* = 5.8 Hz, 2H) 3.66 (s, 3H), 3.00 (d, *J* = 6.8 Hz, 1H), 2.79 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 164.8, 156.7, 142.5, 137.2, 128.7, 127.9, 127.6, 123.2 (q, *J* = 275.1 Hz), 120.5, 114.7, 55.5, 44.2 (q, *J* = 40.2 Hz), 43.5, 42.8 (q, *J* = 1.1 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): -67.3 (d, *J* = 6.1 Hz); **HRMS (ESI)** Calculated for $C_{18}H_{18}N_2O_2F_3$ ($[M+H]^+$): 351.1320, found: 351.1335.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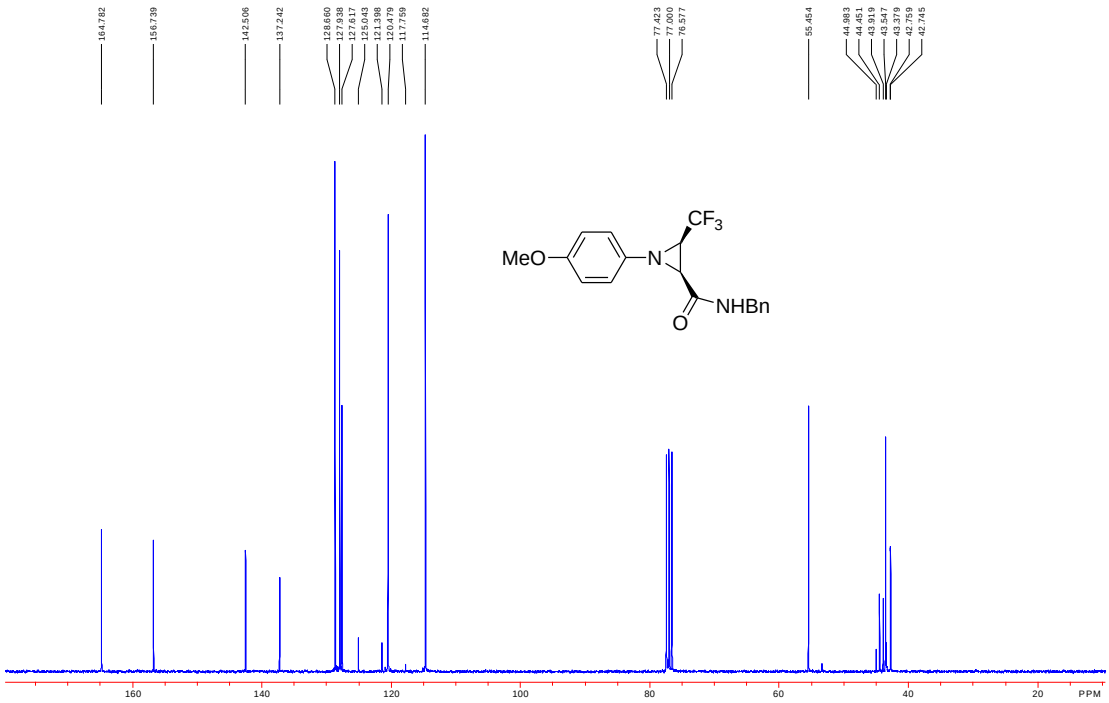
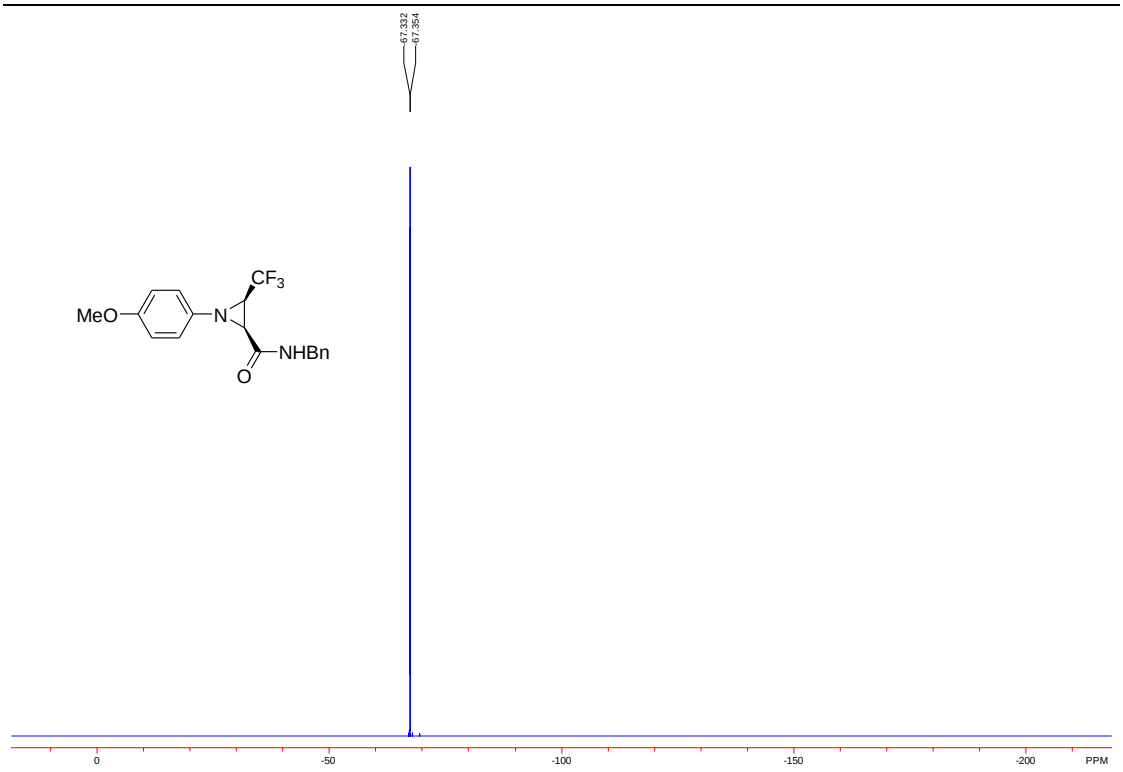
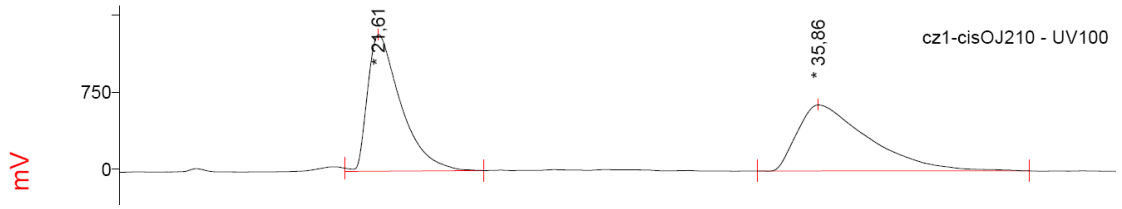
6.849
6.824
6.794
6.736
6.706
4.391
4.371
3.664
3.002
2.980
2.827
2.788
2.747
MeO
N
CF3
NHBn
O
9.04
2.16
2.03
0.81
2.00
3.03
1.00
1.00
7
6
5
4
3
2
1 PPM


164.782
156.739
142.506
137.242
128.660
127.938
127.617
125.043
121.398
120.479
117.759
114.682
77.423
77.000
76.577
55.464
44.983
44.461
43.919
43.547
43.379
43.208
42.745
MeO
N
CF3
NHBn
O
160
140
120
100
80
60
40
20
PPM



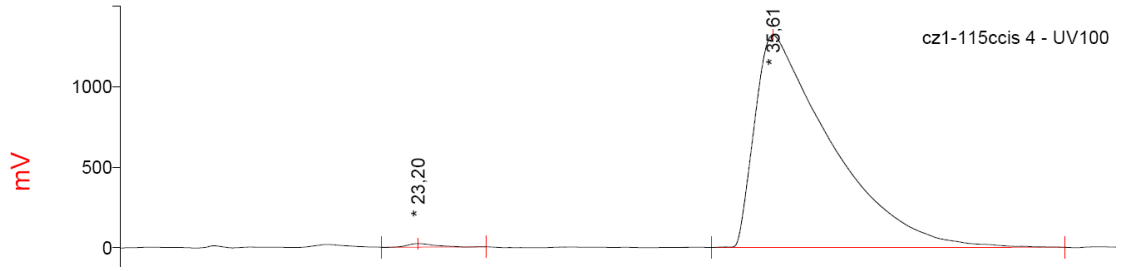
Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire
1		21,61	99664,45	**49,15**
2		35,86	103100,82	**50,85**
SOMME			**202765,27**	**100,00**

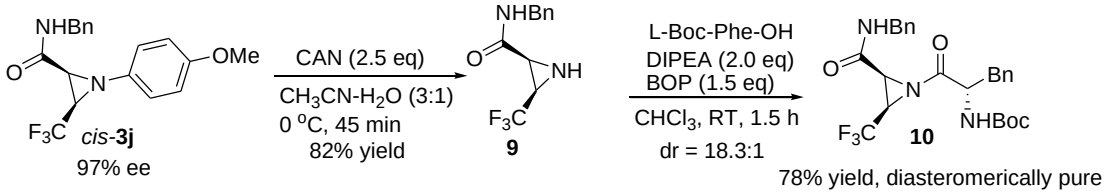


Résultats d'intégration

#	Nom du pic	Tr.	Aire	% Aire
1		23,20	1444,35	**0,59**
2		35,61	244811,05	**99,41**
SOMME			**246255,40**	**100,00**



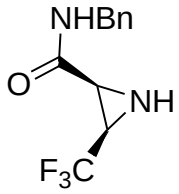
Conversion of *cis*-aziridine 3j into dipeptide 10



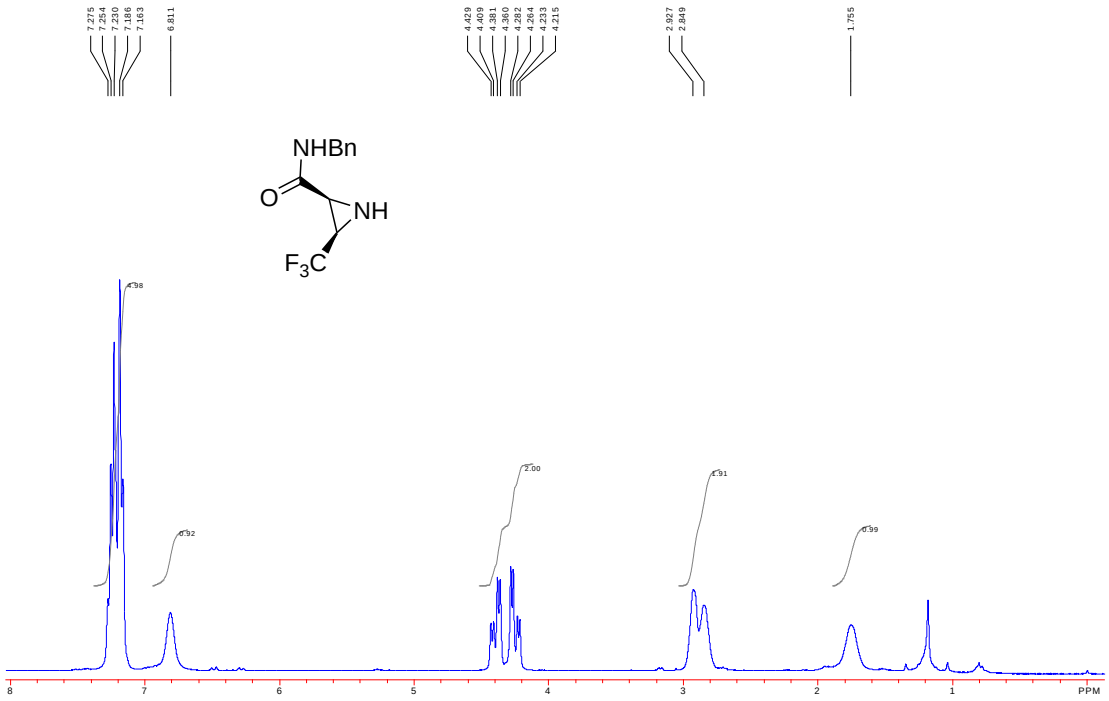
78% yield, diasteromerically pure

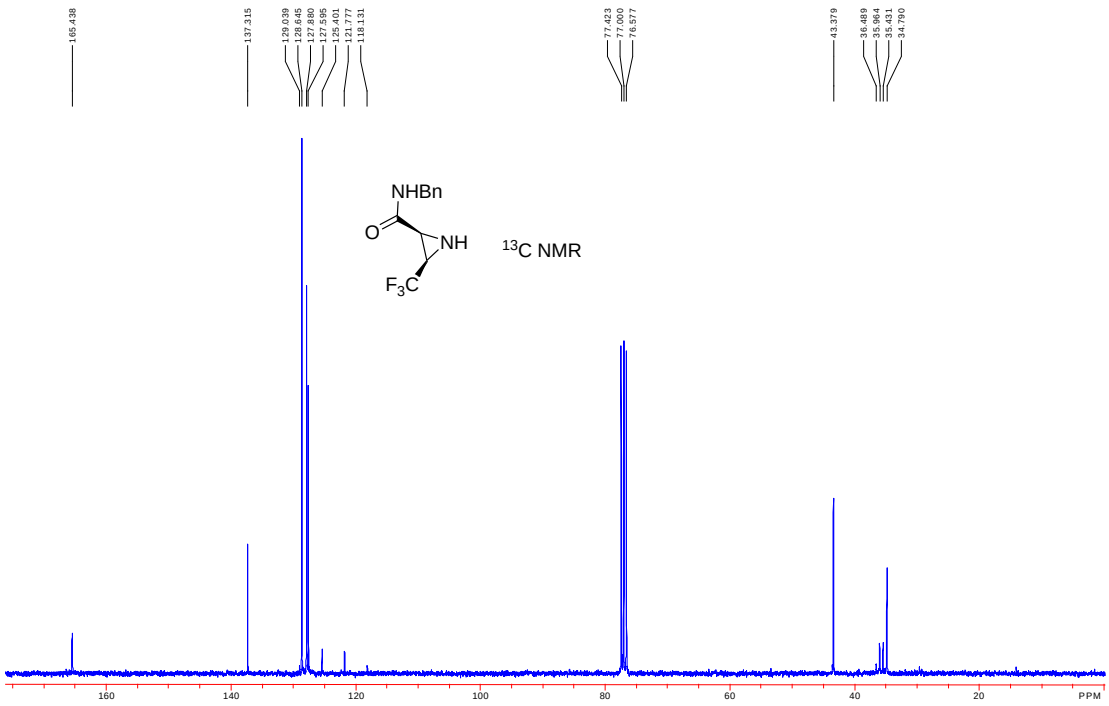
To a stirred solution of *cis*-**3j** (44.0 mg, 0.126 mmol) in 3.0 mL of CH_3CN was added $(NH_4)_2Ce(NO_3)_6$ (CAN) (173 mg, 0.315 mmol) in 0.9 mL of H_2O at 0 °C. After 45 min, the reaction mixture was diluted with 10 mL of CH_2Cl_2, 6 mL of sat. $NaHCO_3$ solution and 3 mL of sat. $NaHSO_3$ solution. After separation of the phases, the aqueous phase were extracted with CH_2Cl_2 (6 mL×4), and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel eluting with 10% MeOH in CH_2Cl_2 containing 2% of Et_3N) to give the product **9** as a colorless solid in 82% yield. This procedure follows a literature method.[2a]

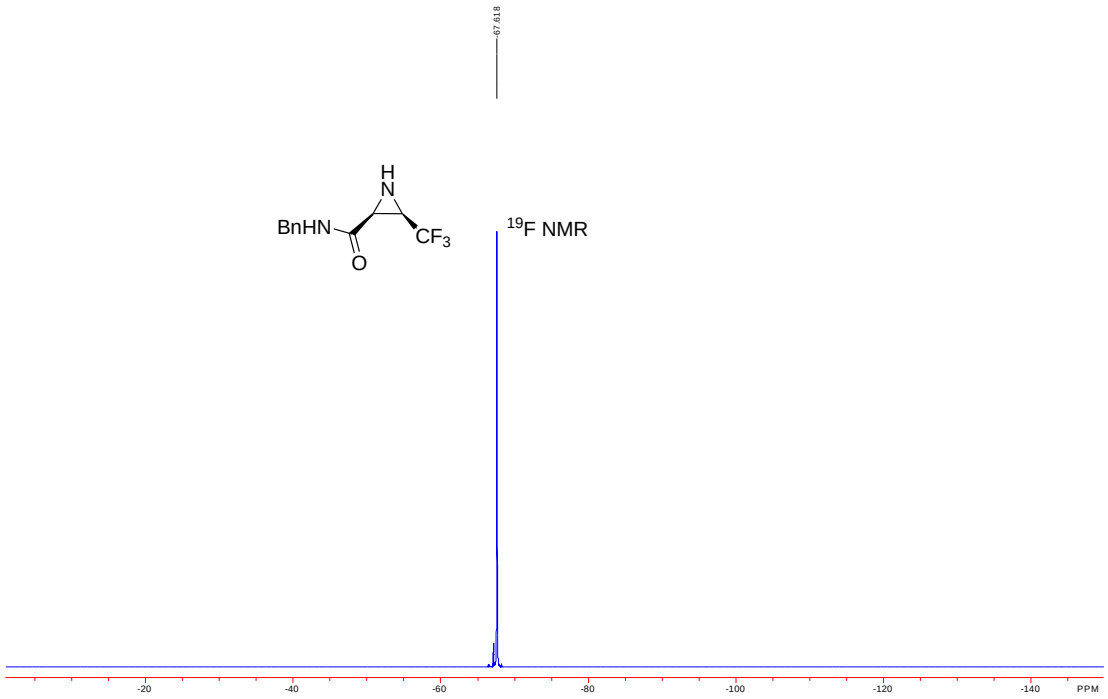
To a stirred solution of **9** (23.8 mg, 0.097 mmol) in dry $CHCl_3$ (1.1 mL) was added L-Boc-Phe-OH (38.8 mg, 0.146 mmol), DIPEA (25 mg, 0.194 mmol) and BOP (64.5 mg, 0.146 mmol) at r.t., sequentially. After stirring for 1.5 h, the reaction mixture was diluted with 20 mL of CH_2Cl_2, washed with 20 mL of aqueous 10% citric acid solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed by rotary evaporation to give the residue (crude ^{19}F NMR analysis revealed a dr of 18.3:1) was purified by column chromatography on silica gel eluting with 10% (vol%) ethyl acetate in CH_2Cl_2) to give the diastereomerically pure dipeptide **10** as a white solid in 78% yield. This procedure follows a literature method.[3]

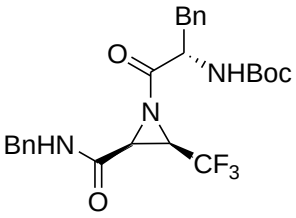


Free *cis*-aziridine **9**; $[\alpha]^{22}_{,D}$ = -11.4 (*c* 1.20, CH_2Cl_2); **IR** (neat): 3288, 1649, 1537, 1126, 911, 718, 694 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28-7.16 (m, 5H), 6.81 (brs, 1H), 4.39 (dd, *J* = 14.6, 6.0 Hz, 1H), 4.24 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.88 (m, 2H), 1.76 (brs, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 165.4, 137.3, 128.6, 127.9, 127.6, 123.6 (q, *J* = 273.5 Hz), 43.4, 35.7 (q, *J* = 40.1 Hz), 34.8; **^{19}F NMR** (282 MHz, $CDCl_3$): -67.6 (d, *J* = 6.1 Hz); **HRMS (ESI)** Calculated for $C_{11}H_{12}N_2OF_3$ ($[M+H]^+$): 245.0902, found: 245.0899.

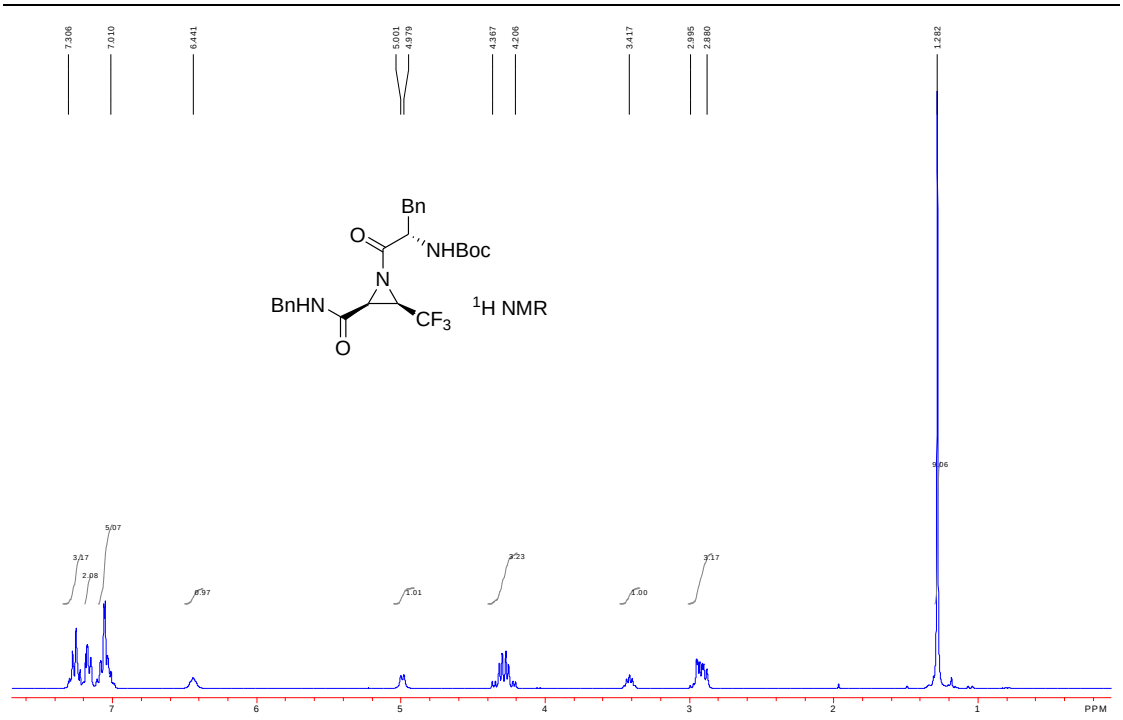

7.275
7.254
7.230
7.186
7.163
6.811
4.429
4.409
4.381
4.360
4.282
4.264
4.233
4.215
2.927
2.849
1.755
NHBn
O
NH
F3C
4.98
0.92
2.00
1.91
0.99
8
7
6
5
4
3
2
1
PPM

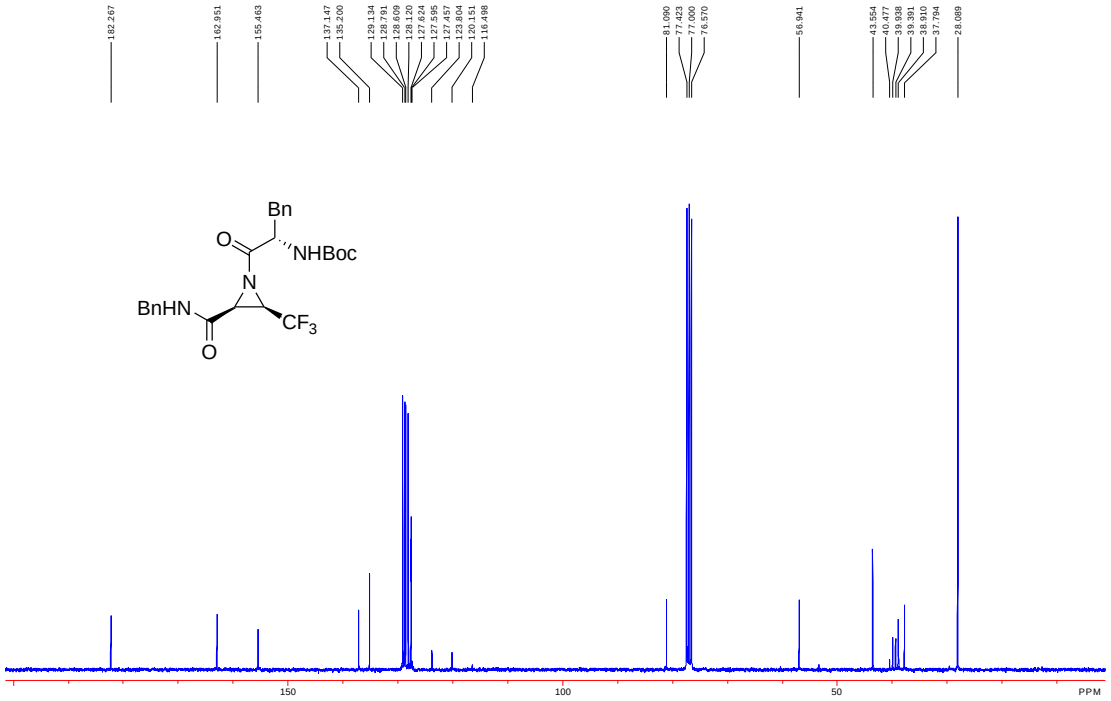

165.438
137.315
129.039
128.645
127.880
127.595
125.401
121.177
118.131
77.423
77.000
76.577
43.379
36.489
35.964
35.431
34.790
NHBn
O
NH
F3C
13C NMR
160
140
120
100
80
60
40
20
PPM





Dipeptide **10** was obtained as a white solid (78% yield); $[\alpha]^{21}_{D}$ = -10 (*c* 0.91, CH_2Cl_2); **IR** (neat): 3337, 3033, 2939, 1721, 1684, 1665, 1527, 1148, 698 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31-7.01 (m, 10H), 6.44 (brs, 1H), 5.00 (d, *J* = 6.7 Hz, 1H), 4.37-4.21 (m, 3H), 3.42 (m, 1H), 3.00-2.88 (m, 3H), 1.28(s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): 182.3, 163.0, 155.5, 137.1, 135.2, 129.1, 128.8, 128.6, 128.1, 127.62, 127.60, 123.0 (q, *J* = 275.7 Hz), 81.1, 56.9, 43.6, 39.7 (q, *J* = 41.3 Hz), 38.9, 37.8, 28.1; **^{19}F NMR** (282 MHz, $CDCl_3$): -68.2 (d, *J* = 5.1 Hz); **HRMS (ESI)** Calculated for $C_{25}H_{28}N_3O_4F_3Na$ ($[M+Na]^+$): 514.1930, found: 514.1949.


7.306
7.010
6.441
5.001
4.979
4.367
4.206
3.417
2.995
2.880
1.282
Bn
O
NHBoc
N
BnHN
CF3
O
1H NMR
9.06
5.07
3.17
2.08
0.97
1.01
3.23
1.00
3.17
7
6
5
4
3
2
1
PPM


182.267
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127.624
127.595
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123.804
120.151
116.498
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77.423
77.000
76.570
56.941
43.554
40.477
39.938
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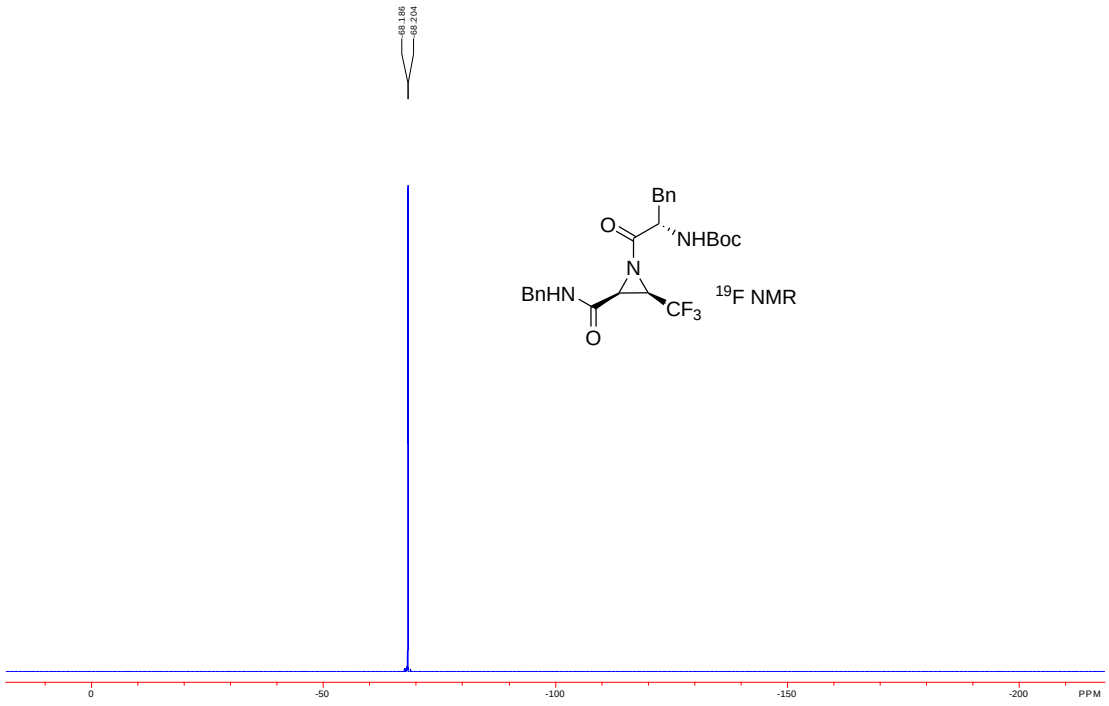
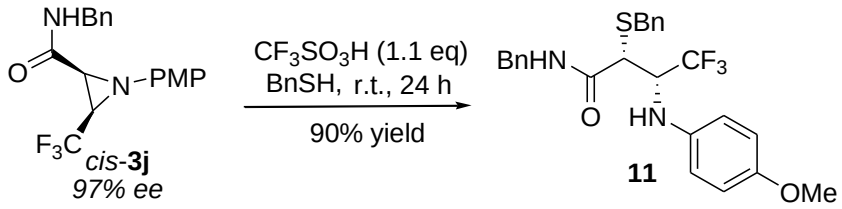
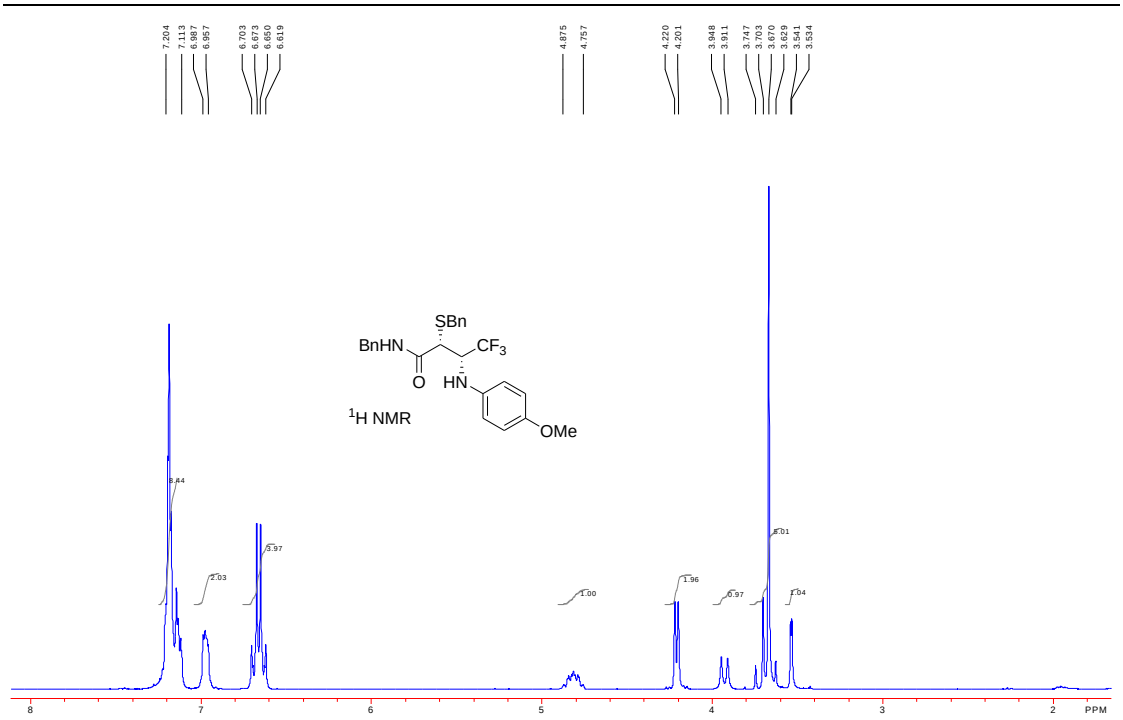
N
BnHN
CF3
O
150
100
50
PPM



Ring-opening of *cis*-aziridine 3j into isocysteine derivative 11



Under N_2, to a solution of *cis*-**3j** (11.7 mg, 36 μmol) in BnSH (85 μl, 0.72 mmol) was added fresh CF_3SO_3H (3.5μl, 40 μmol) at 0 °C. Then the reaction solution was stirred at r.t. for 24 h. After being diluted with 20 mL of CH_2Cl_2, the mixture was washed with 5% aqueous $NaHCO_3$ solution, distilled water and brine. The organic phase was dried over $MgSO_4$, concentrated and purified by column chromatography eluting with 8-25% (v%) EtOAc in petroleum ether (b.p. 40-60 °C) to give the isocysteine derivative **11** as a gel-like colorless semi-solid (15.3 mg, 90% yield); $[\alpha]^{16}_{D}$ = -44.2 (*c* 0.90, CH_2Cl_2); **IR** (neat): 3335, 2927, 1653, 1508, 1234, 1117, 732, 698 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20-7.11 (m, 8H), 6.97 (m, 2H), 6.66 (AB, *J* = 9.2 Hz, 4H), 4.88-4.78 (m, 1H), 4.21 (d, *J* = 5.8 Hz, 2H), 3.93 (d, *J* = 11.2 Hz, 1H, disappeared after shaking with D_2O), 3.69 (AB, *J* = 13.3 Hz, 2H), 3.53 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): 167.9, 153.5, 139.2, 137.3, 136.3, 128.9, 128.7, 127.8, 127.5, 127.49, 125.5 (q, *J* = 285 Hz), 116.4, 114.8, 57.7 (q, *J* = 8.6 Hz), 55.6, 49.5, 44.1, 37.2; **^{19}F NMR** (282 MHz, $CDCl_3$): -72.4 (d, *J* = 8.2 Hz); **HRMS (ESI)** Calculated for $C_{25}H_{26}N_2O_2F_3S$ ($[M+H]^+$): 475.1667, found: 475.1682.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4.757
4.220
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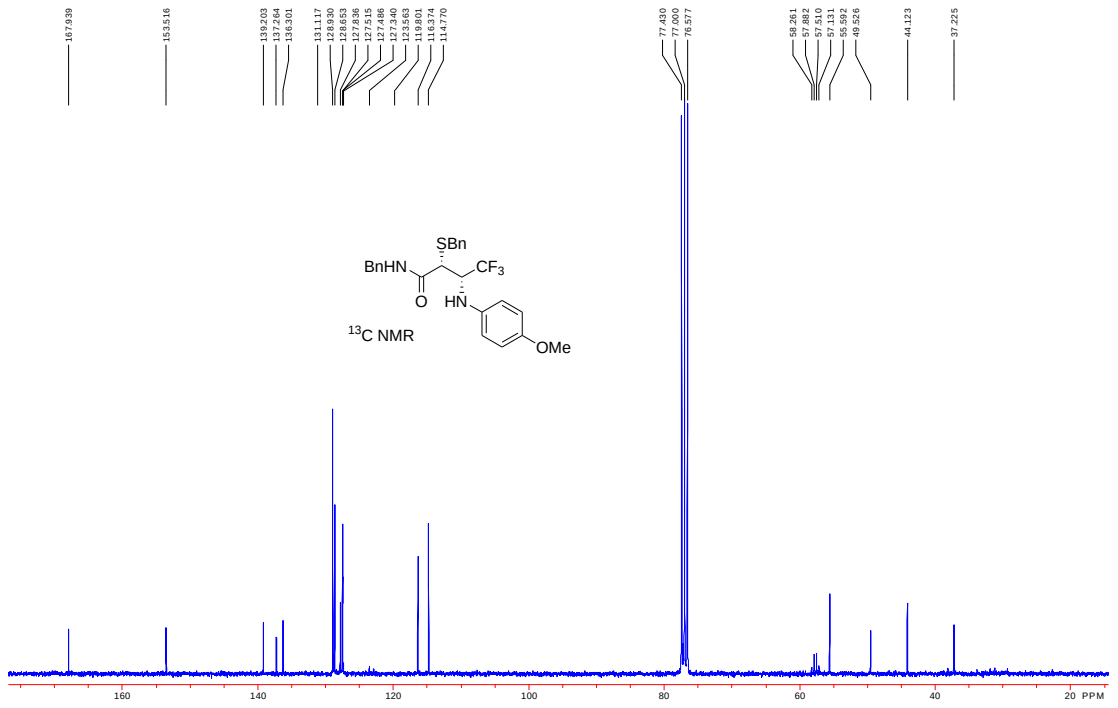
3.948
3.911
3.747
3.703
3.670
3.629
3.541
3.534
SBn
BnHN
CF3
O
HN
OMe
1H NMR
8.44
2.03
5.97
1.00
1.96
6.97
6.01
1.04
8
7
6
5
4
3
2
PPM


167.939
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136.301
131.117
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128.653
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127.486
127.340
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119.801
116.374
114.770
77.430
77.000
76.577
58.261
57.882
57.510
57.131
55.592
49.526
44.123
37.225
SBn
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CF3
O
HN
OMe
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60
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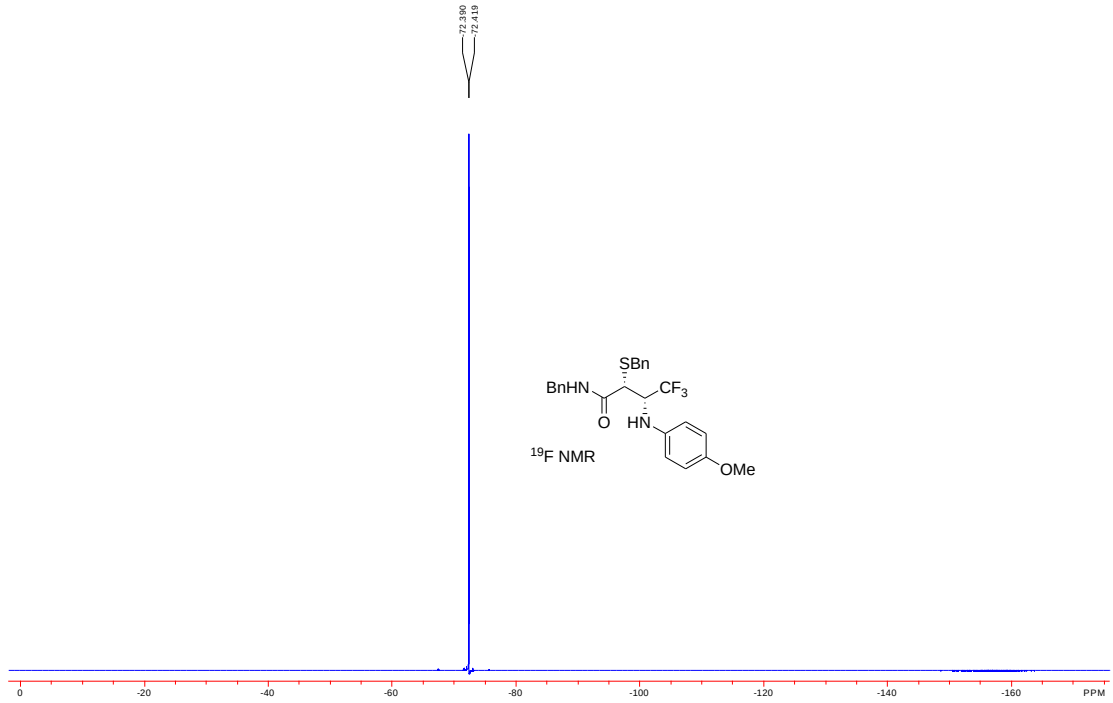
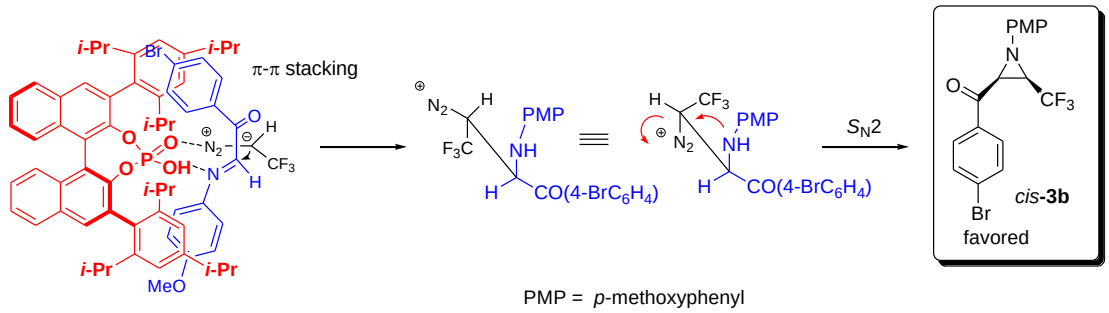
20
PPM



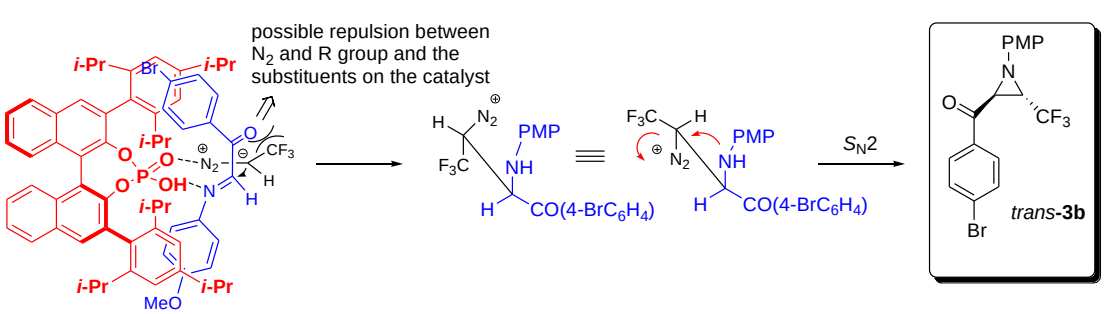
Tentative transition states for the stereoselective formation of the *cis*-aziridines

We presumed that the phosphoric acid catalyst **1a** may activate the imine through H-bond interaction.[6] Then, the bulky substituents on the catalyst would drive the nucleophilic diazo species to attack the imine from the *Si* face. Probable steric repulsion between the diazo group and the R group of the imine as well as the bulky substituents on the catalyst may render the TS-II leading to *trans*-**3b** less favored.



Si-face attack of the imine

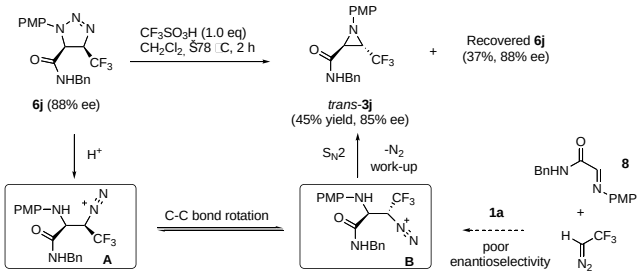
PMP = *p*-methoxyphenyl



Si-face attack of the imine

Conversion of *cis*-triazoline 6j to aziridine *trans*-3j and a mechanistic proposal

Non-fluorinated triazoline compounds have been prepared using a distinct method by Johnston and co-workers to investigate the mechanism of Brønsted acid-promoted aza-Darzens reaction.[4] In our case, the isolation of both the triazoline **6j** and the *cis*/*trans*-aziridine **3j** from the aza-Darzens reaction system allowed us to get some preliminary insights into the stereoselective formation process leading to **6j** in the reaction. Following Johnston's procedure, treatment of **6j** with triflic acid gave the *trans*-aziridine **3j** as the major product (see page S31 for experimental details). Interestingly, the optical purity of the starting material were well maintained in both *trans*-**3j** and the recovered **6j** during this process. In addition, this result is also supportive of the assignment of the *cis*-configuration of the triazoline **6j**. Thus, we presumed that the transformation from **6j** to *trans*-**3j** might proceed through intermediate **A** followed by C-C bond rotation to conformer **B** and a highly stereospecific S_N2 process. However, in light of the big difference of enantioselectivity between these two compounds (see Table 3 in the main text), the formation of *trans*-**3j** and triazoline **6j** under the aza-Darzens reaction conditions might be *via* different independent stereochemical routes. Namely, the probable route from imine **8** and CF_3CHN_2 providing *trans*-**3j** through **B** is much less stereoselective compared to that leading to **6i**. Considering the current lack of the mechanistic information of the aza-Darzens reaction with diazo compounds,[4] the peculiar reactivity of the imine **8** identified in this work may make it a worthwhile substrate to study with other common diazo compounds to get more insights into the mechanism of this type of reactions.



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