Supporting Information for
"Dynamic Biphasic Counterion Exchange in a Configurationally Stable Aziridinium Ion: Efficient Synthesis and Isolation of a Koga C_2-Symmetric Tetraamine Base"

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In-Process Control Method for Koga Amine Synthesis Steps 1 and 2 and Final Purity (HPLC)

I. Analytical Method Information

HPLC: Agilent 1100 Series
Column: Waters X-Bridge, 3.5 µm, 150 x 4.6 mm, (Waters, part #186003034)
Mobile Phase A: (90% 25 mM Ammonium Acetate in water, 10% Acetonitrile; pH 6.5)
Mobile Phase B: (90% Acetonitrile, 10% 25 mM Ammonium Acetate in water)
Flow: 1.0 mL/min
Detector: UV at 215 nm
Injection Volume: 5 µL
Gradient:

Time (min)	% Mobile Phase A	% Mobile Phase B
0.00	100	0
2.00	100	0
10.50	76	24
20.00	0	100
21.00	0	100
21.50	100	0

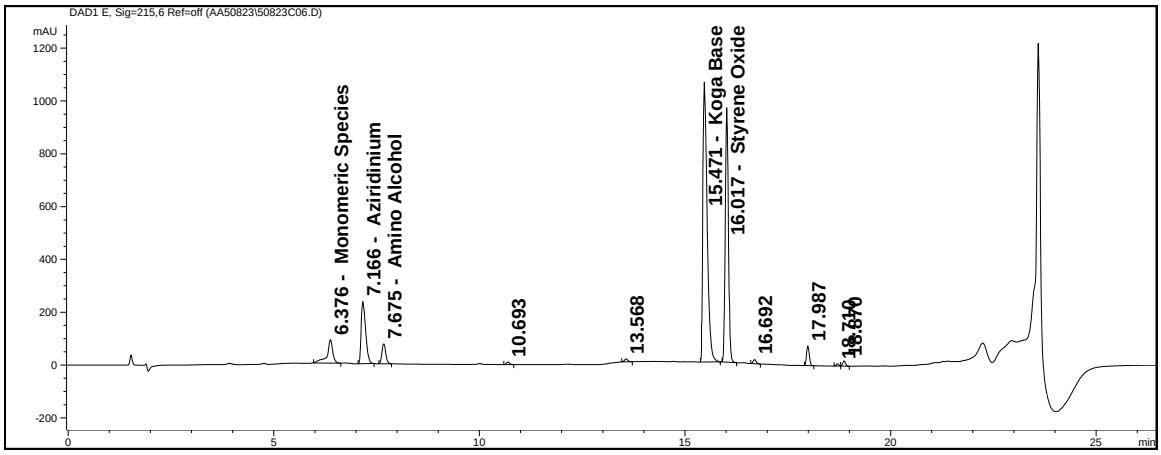
II. Sample Preparation for Step 1 (Synthesis of aminoalcohols **8a** and **8b**)

Weigh 14.0 to 16.0 mg.
Transfer to a 5 mL volumetric flask.
Add approximately 2 mL of the Mobile Phase B. Mix, and sonicate as needed for approximately 3 minutes or until completely dissolved. Cool to room temperature. Dilute to volume with the Mobile Phase B. Mix well.

III. Sample Preparation for Step 2 (Formation of Aziridinium ion **10b**)

Same as for Step 1

IV. Representative Chromatogram



Concentration In-Process Control Method for Koga Amine Formation (HPLC)

I. Analytical Method Information

Same as above with reaction MTBE layer ONLY. Compare to standard of (*R*,*R*)-**5**.

II. Sample Preparation

Same as above only using a measured volume of MTBE layer.

III. Representative Chromatogram

Same as above

Chiral Method for Koga Amine (HPLC)

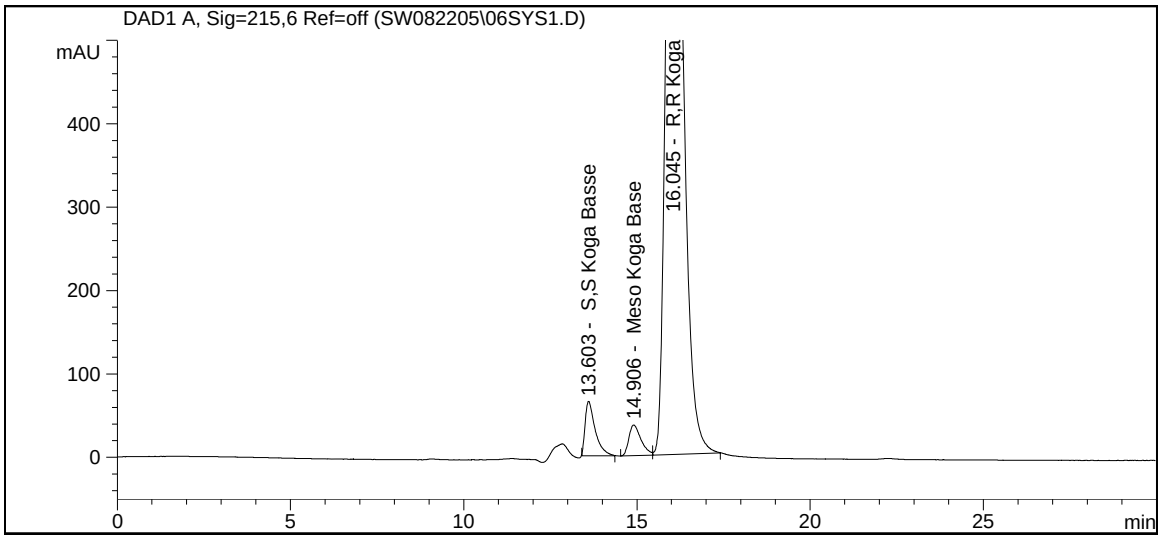
I. Analytical Method Information

HPLC: Agilent 1100
Column: Chiralpak® AD-H 4.6x250mm (Chiral Technologies, Inc., cat.# 19325)
Mobile phase: 35/10/55/0.03 Hexane:EtOH:MeOH:TEA, v/v
Flow: 0.25 ml/min
Column Temperature: 20°C
Detector: UV at 215nm
Run Time: 30 min
Injection volume: 10µl

II. Sample Preparation

Weigh about 27-33 mg of Koga base
Transfer into a 50 mL volumetric flask
Dissolve with the Mobile phase
Dilute to volume with Mobile phase and mix well

III. Representative Chromatogram



Method for Determination of Residual Solvents (GC)

I. Analytical Method Information

GC: Agilent 6890
Column: RTX-624, 30m x 0.25mm, 1.4µm (Restek, part # 10968)
Temperatures: 35°C, hold for 0.5 min, 15°C/min → 170°C
Run Time: 9.5 min
Pressure/Flow: constant pressure at 20psi
Split Ratio: 20:1
Injection Volume: 1µl

Method for Determining Partitions of (*R,R*)-5, Monomer (*R*)-13, and Diamine 11 (GC)

I. Analytical Method Information

GC: Agilent 6890
Column: HP-5, 30m x 0.32mm, 0.25um (Agilent, part # 19091J-413)
Temperatures: 35°C, 15°C/min →325°C, hold for 5 min

Run Time: 24.33 min
Pressure/Flow: Constant flow at 2.0 ml/min
Split Ratio: 20:1
Injection Volume: 1μl injection volume

II. Sample Preparation

Inject partition layer

Method for Determining Impurities in Mother Liquor (GC/MS)

I. Analytical Method Information

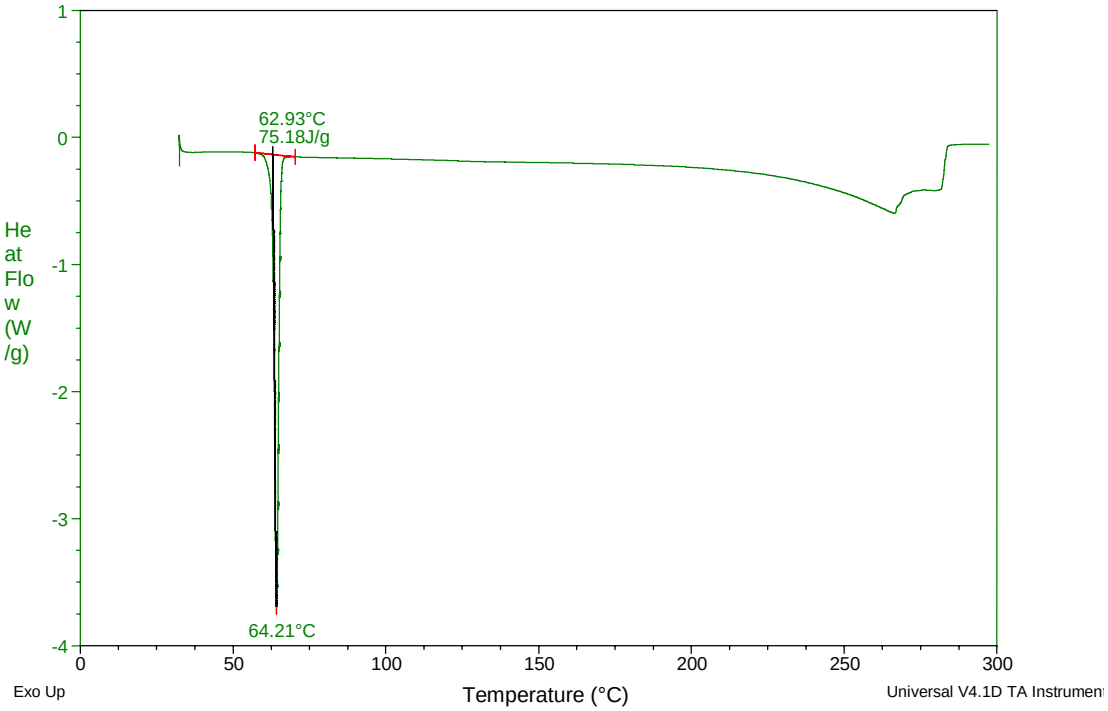
GC/MS: Agilent 6890 (GC) and 5973 (MSD)
Column: HP-5MS, 30m x 0.25mm, 0.25um (Agilent, part # 19091S-433)
Temperatures: 35°C, 5°C/min →75°C, hold for 5 min, 25°C → 325°C
Run Time: 23 min
Pressure/Flow: Constant flow at 1.3 ml/min
Split Ratio: 10:1
Injection Volume: 1μl
Source: Chemical Ionization (methane used as ionizing gas)

II. Sample Preparation

Inject reaction mixture/mother liquor

Differential Scanning Calorimetry Trace for (*R*,*R*)-5

DSC



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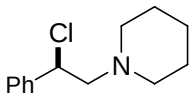
^{1}H NMR Data and Spectrum for β-Chloroamine 12 and Precipitate[1]

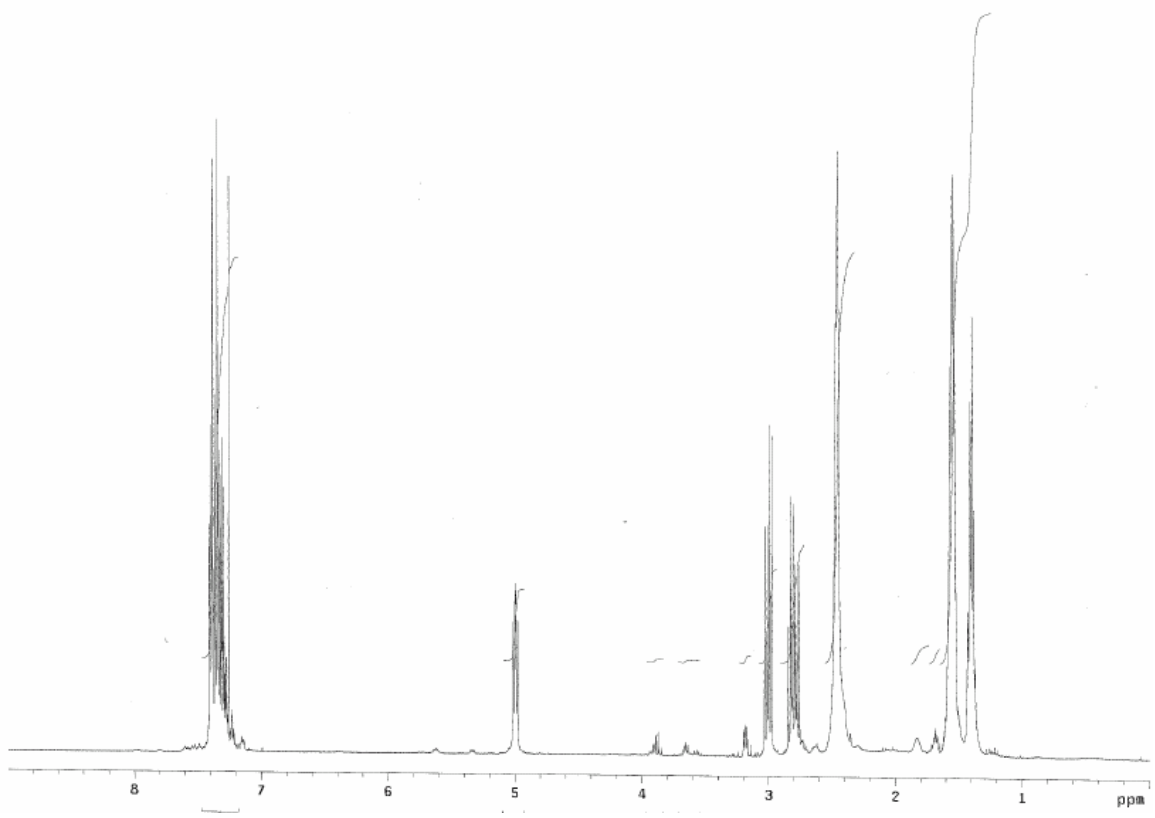


12

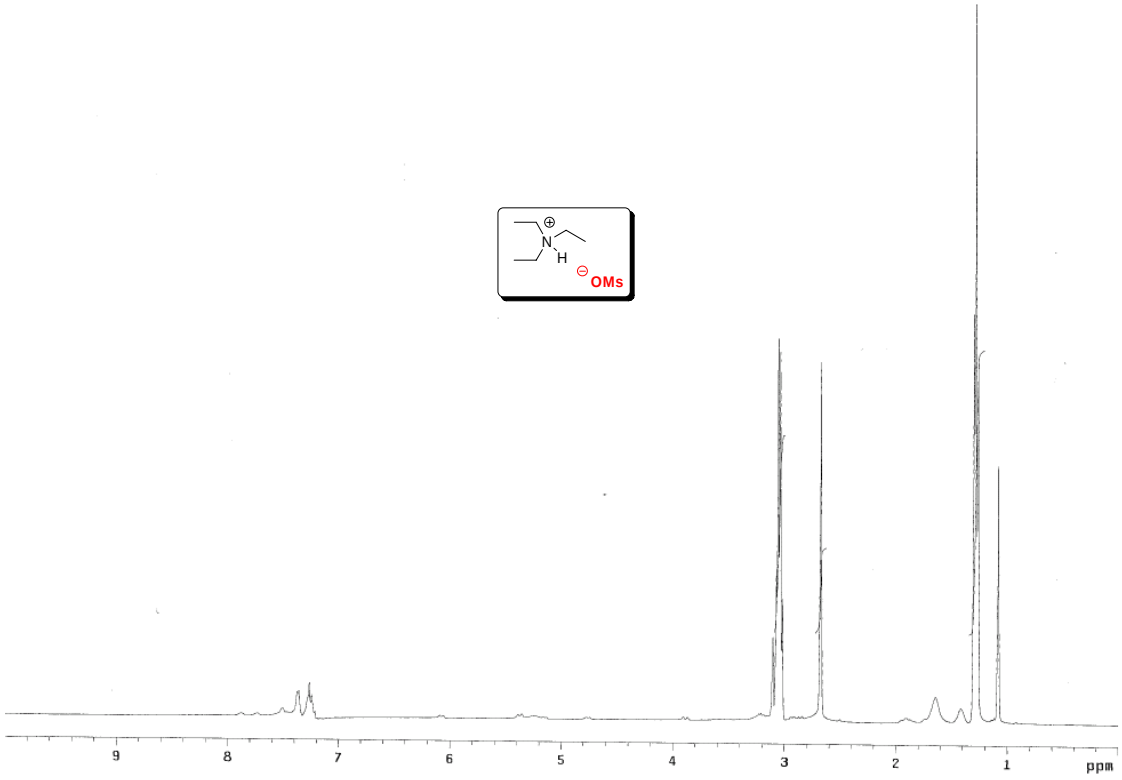
A. ^{1}H NMR Data for **12:**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.40 (comp. m, 5H); 5.00 (dd, *J* = 6.0, 8.0 Hz, 1H); 3.18 (t, *J* = 5.6 Hz, 1H); 3.01 (dd, *J* = 8.0 Hz, 13.6 Hz, 1H); 2.80 (dd, *J* = 5.6, 13.6 Hz, 1H); 2.50 (m, 4H); 1.37-1.58 (comp. m, 6H).

B. ^{1}H NMR Spectrum for **12:**



C. ^{1}H NMR Spectrum for Precipitate from MsCl Reaction:

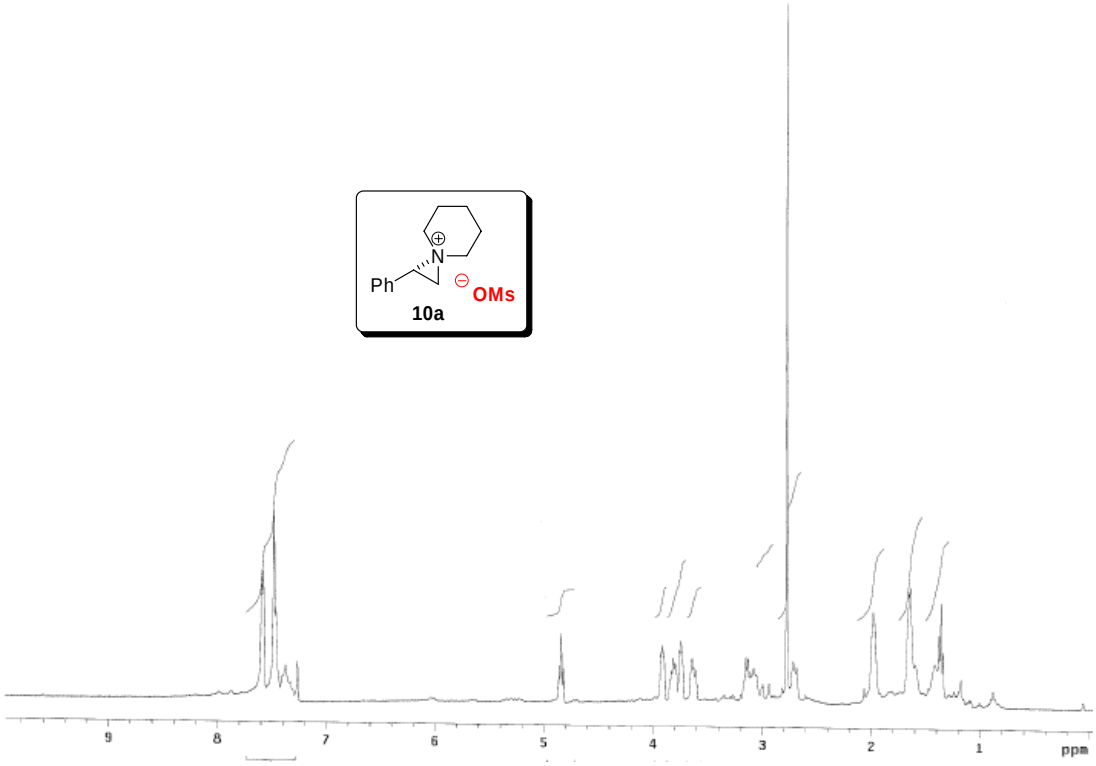


Synthesis of Aziridinium Mesylate (10a):

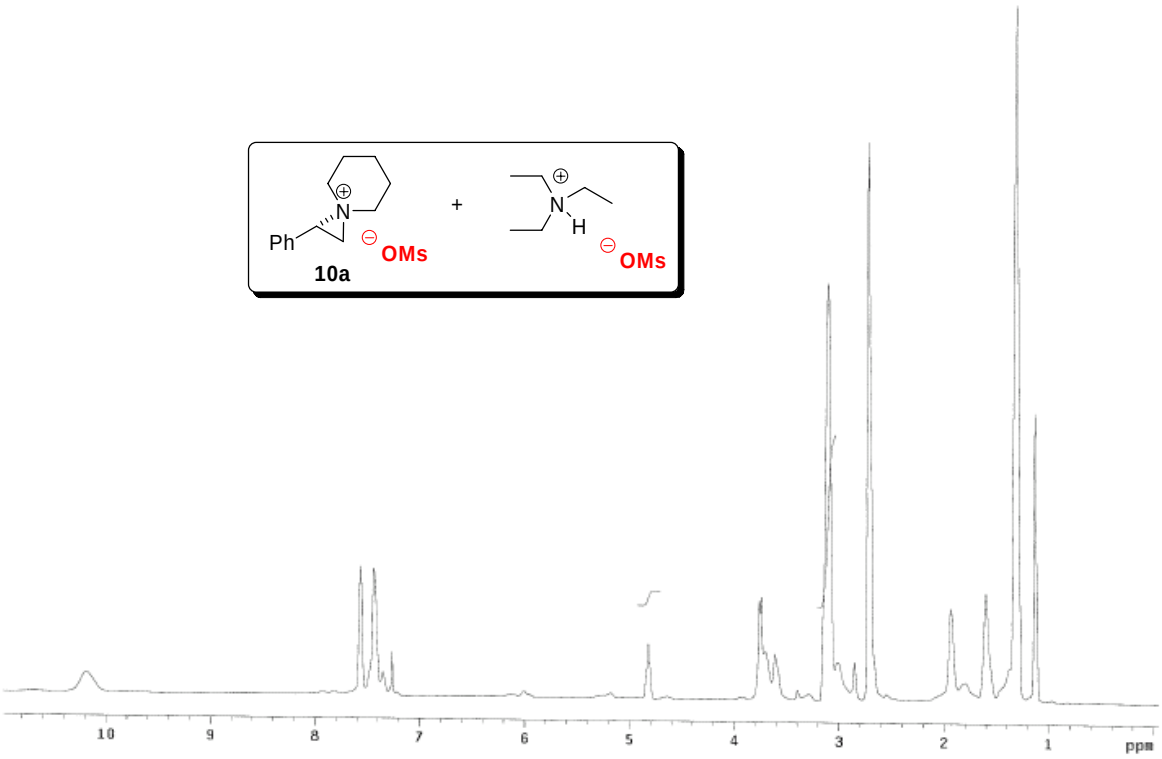
To a 100 mL round-bottom flask was added a mixture of aminoalcohols **8a** and **8b** (5.26g, 25.6 mmol, 1.0 equiv). The flask was sealed and purged with N_2(g) and MTBE (30 mL) was added followed by Et_3N (4.3 mL, 30.6 mmol, 1.2 equiv). The mixture was cooled to 10 °C and Methanesulfonic anhydride (5.34g, 30.6 mmol, 1.2 equiv) was added portionwise with stirring at such a rate as to maintain the internal temperature below 20 °C. Once addition was complete the mixture was allowed to warm to 22 °C with concomitant formation of a gummy orange precipitate. The mixture was stirred for 1.5 h at 22 °C and then the gummy precipitate was allowed to settle. The clear MTBE solution was sampled (5 mL), concentrated, and the resulting residue (25 mg) analyzed by 1H NMR to reveal aziridinium mesylate **10a**. The lower gum was sampled and also subjected to 1H NMR analysis to reveal a mixture of **10a** and triethylammonium mesylate.

A. ^{1}H NMR Data for **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.58 (comp. m, 5H); 4.84 (t, *J* = 7.7 Hz, 1H); 3.91 (m, 1H); 3.81 (m, 1H); 3.74 (m, 1H); 3.63 (m, 1H); 3.07 (m, 1H); 2.77 (s, 3H); 2.69, (m, 1H); 1.98 (m, 2H); 1.64 (m, 2H); 1.40 (m, 2H).

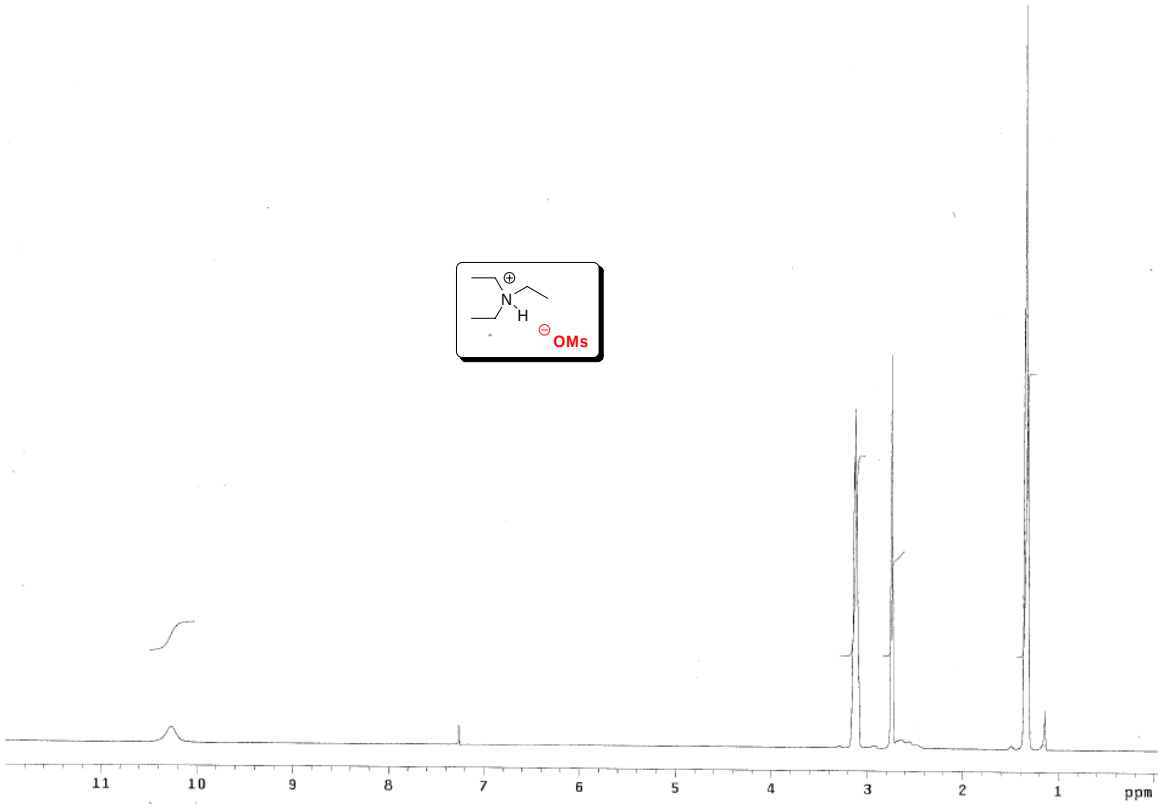
B. ^{1}H NMR Spectrum of **10a**:



C. ^{1}H NMR Spectrum of Precipitate from Ms_2O Reaction:



D. ^{1}H NMR Spectrum of Triethylammonium Mesylate Reference Standard:



References:

(1) For ^{1}H NMR Spectral data for aminoalcohols (*R*)-**8a** and (*S*)-**8b**, see: de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1483.