

Miteni

Hexafluoroxylene: Fluorine Chemistry and Beyond

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Chemsource Symposium 2006
Geneva, June 14 & 15, 2006

1960

RIMAR

The production of fluorinated intermediates starts in Trissino.

1988

MITENI

MITENI (“MIT”-”ENI”) joint venture
EniChem Synthesis – Italy - & Mitsubishi Corporation – Japan.
Headquarters in Milan – Production plant in Trissino.

1996

MITENI

MITENI becomes an affiliated Company of Mitsubishi Corporation
(91% Mitsubishi Corporation – 9% Jemco)





Early 60's

First ECF cell

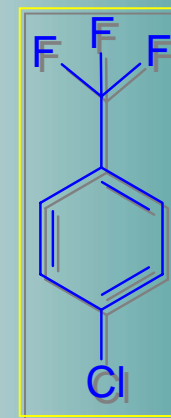
1st Technology

The electrochemical fluorination plant that comes on stream in the early 60's is the first of its kind in Europe for the production of n-perfluorooctanoic acid

2nd Technology

During the 70's benzotrifluorides are produced by the halogen exchange technology.

The aim is to produce PCBTF (*p*-chlorobenzotrifluoride) which is the basic intermediate for the synthesis of the herbicide "Trifluralin"



3rd Technology

Fluoroaromatics production also begins in the 70's and the first advanced intermediates (fluorobenzene derivatives) are produced through a diazotization process.

A BROAD RANGE OF TECHNOLOGIES, NOT JUST FLUORINATION

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RIMAR (1960 -1987)

HALOGEN EXCHANGE – DIAZOTIZATION - ELECTROFLUORINATION

MITENI (Joint venture; 1988 - 1995)

**Nitration
Ring chlorination
Bromination**

**Photo-chlorination
Amidation**

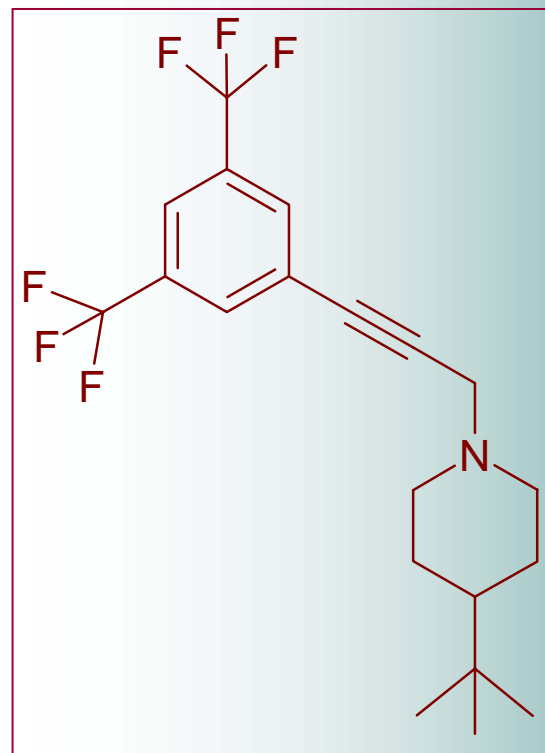
MITENI (100% Mitsubishi; 1996 -)

**Sandmeyer
Amination
Friedel-Crafts**

**Grignard reactions
Hydrogenation
Oxidation**

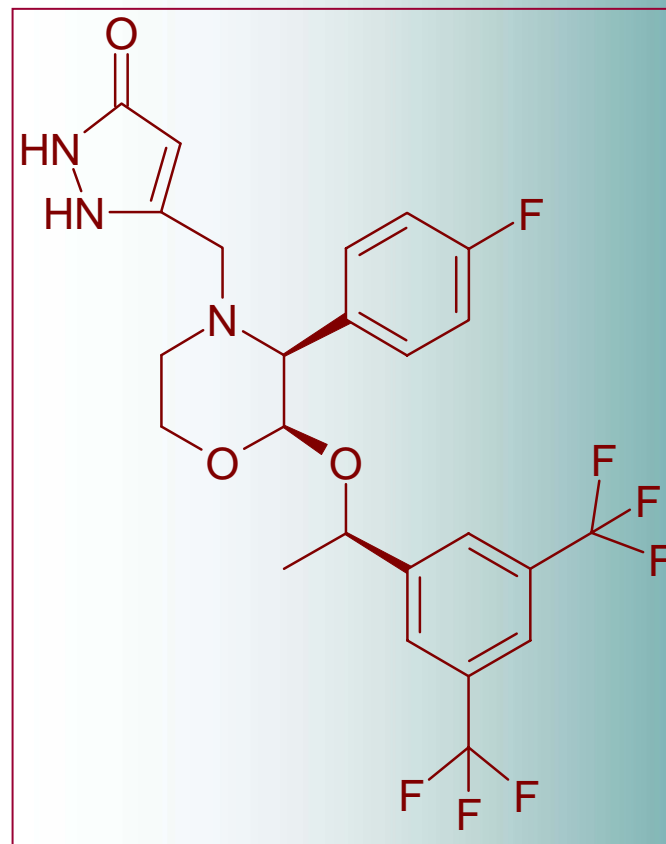
Representative structures of compounds containing the HFX core

Flupropadine
(May & Baker)
Rodenticide
withdrawn



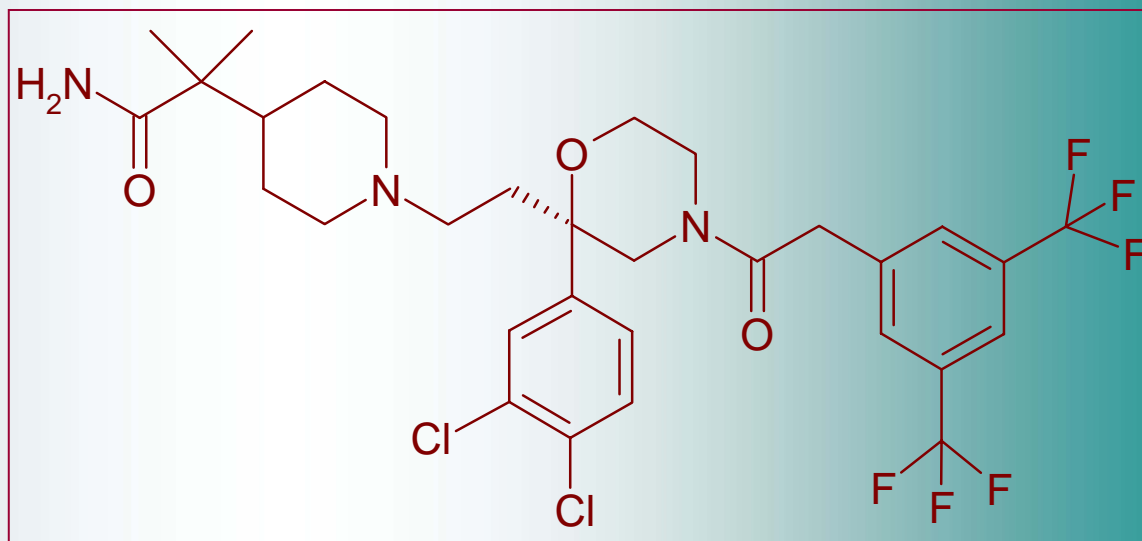
Representative structures of compounds containing the HFX core

Aprepitant
(Merck)
NK-1 antagonist
launched



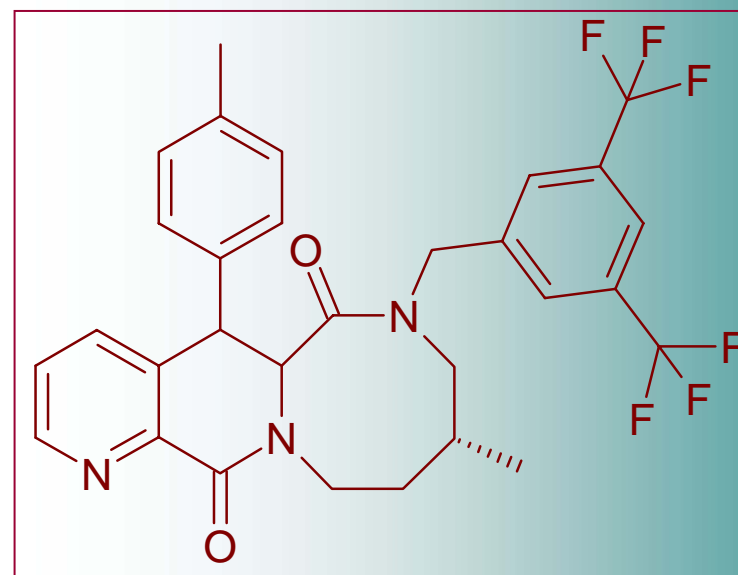
Representative structures of compounds containing the HFX core

SSR-240600
(SanofiAventis)
NK-1 antagonist
Phase I



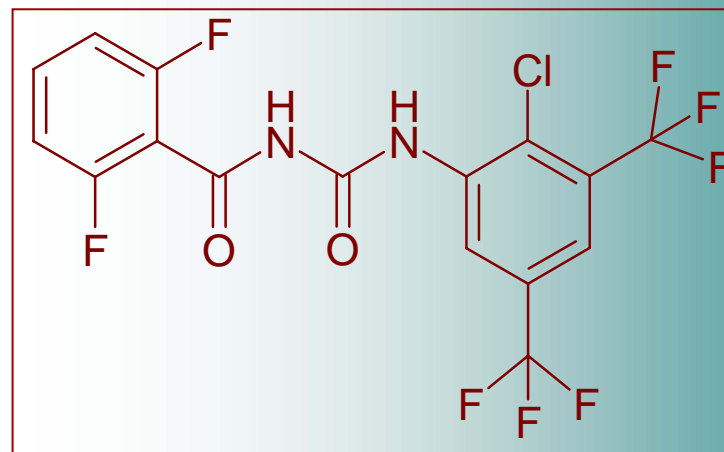
Representative structures of compounds containing the HFX core

TAK-637
(Takeda)
Urinary incontinence
discontinued



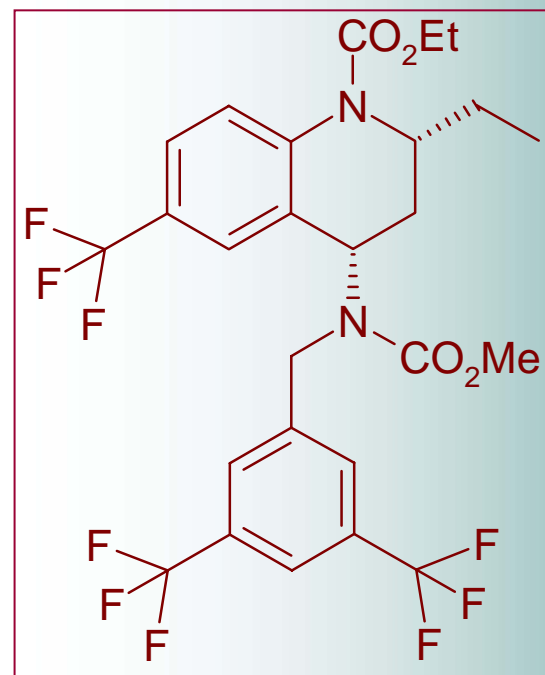
Representative structures of compounds containing the HFX core

Bistrifluron
(DongbuHannong)
Insecticide
Development

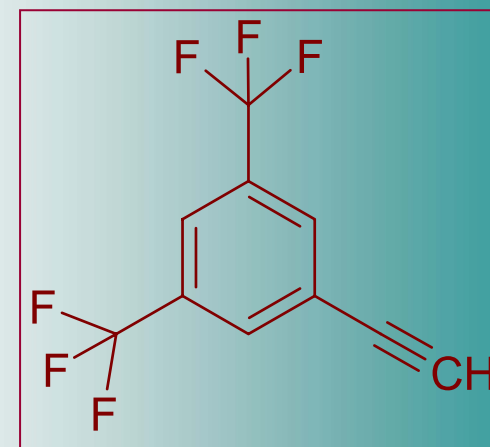
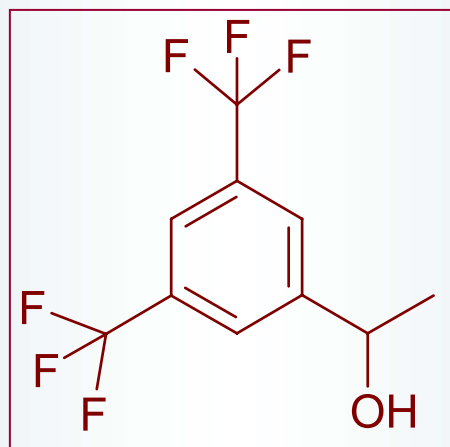
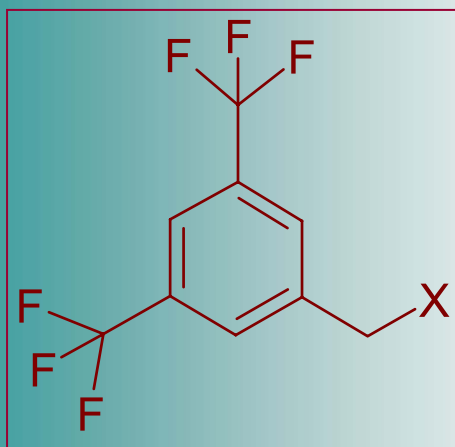


Representative structures of compounds containing the HFX core

Torcetrapib
(Pfizer)
CETP inhibitor
Phase III

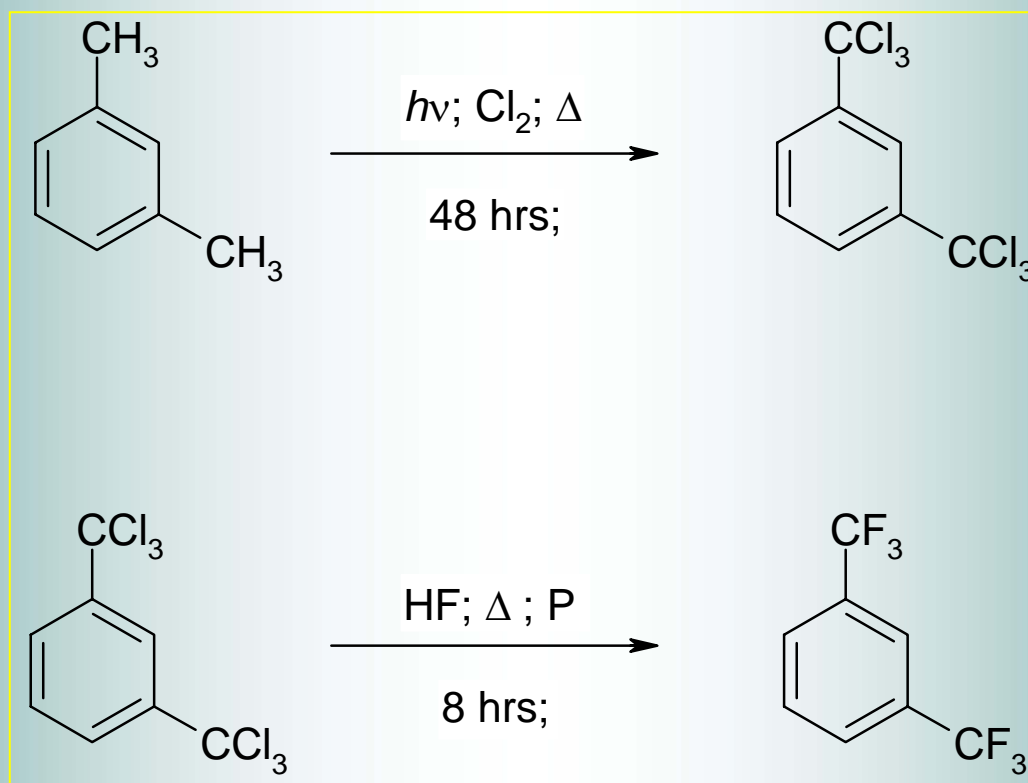


Interesting Cores

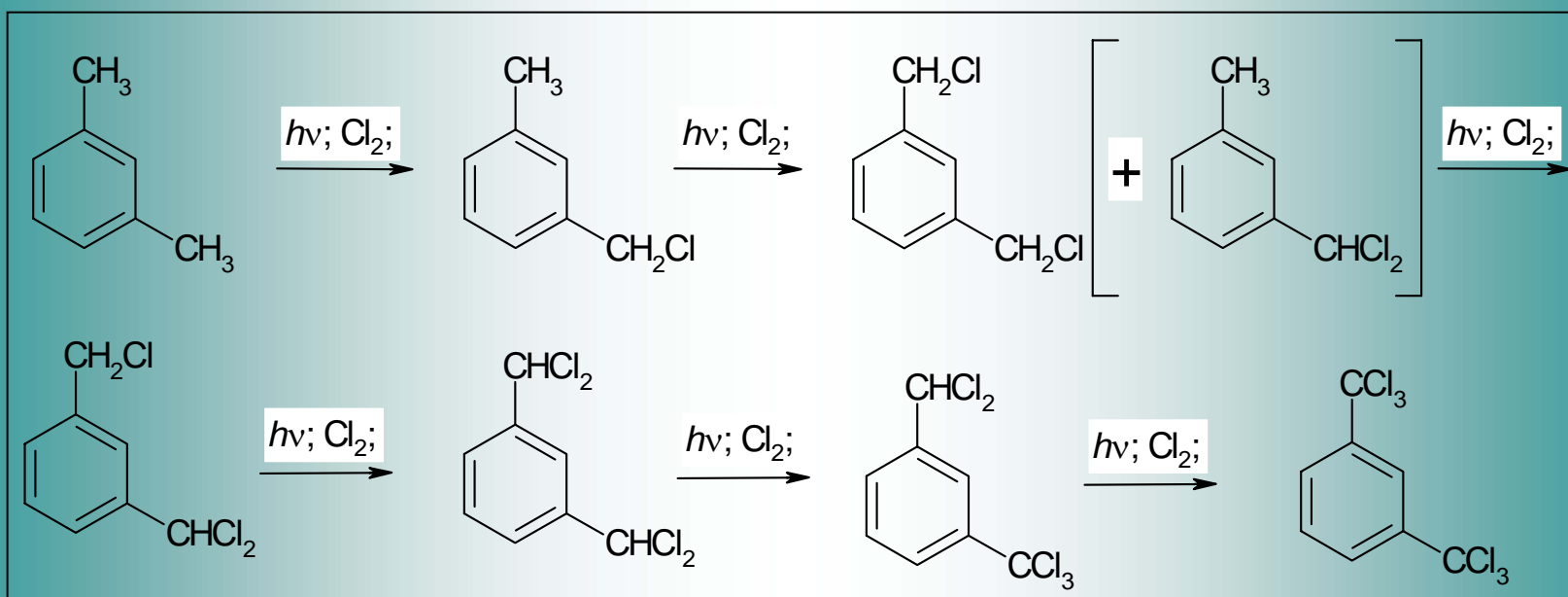


Preparation of *m*-HF_X

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Mechanism of Photochlorination



What you get in is what you get out at least for impurities

Specs for purchased material:

m-xylene	98.5% min
p-xylene	0.6% max
o-xylene	0.6% max

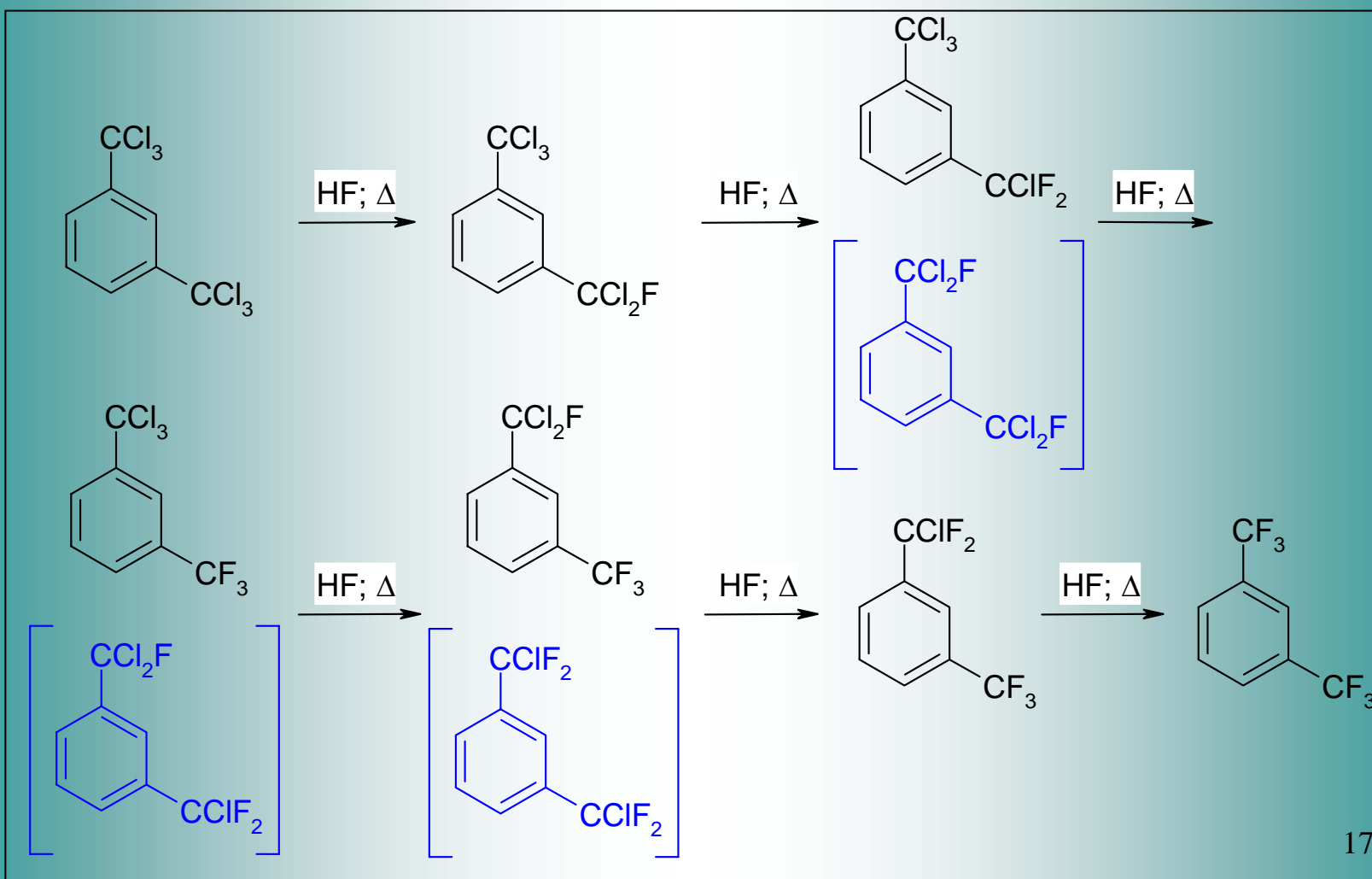
Specs (Miteni) for *m*-HFX:

<i>m</i> -HFX	99% min
<i>p</i> -HFX	0.6% max

Halogen Exchange – (1)

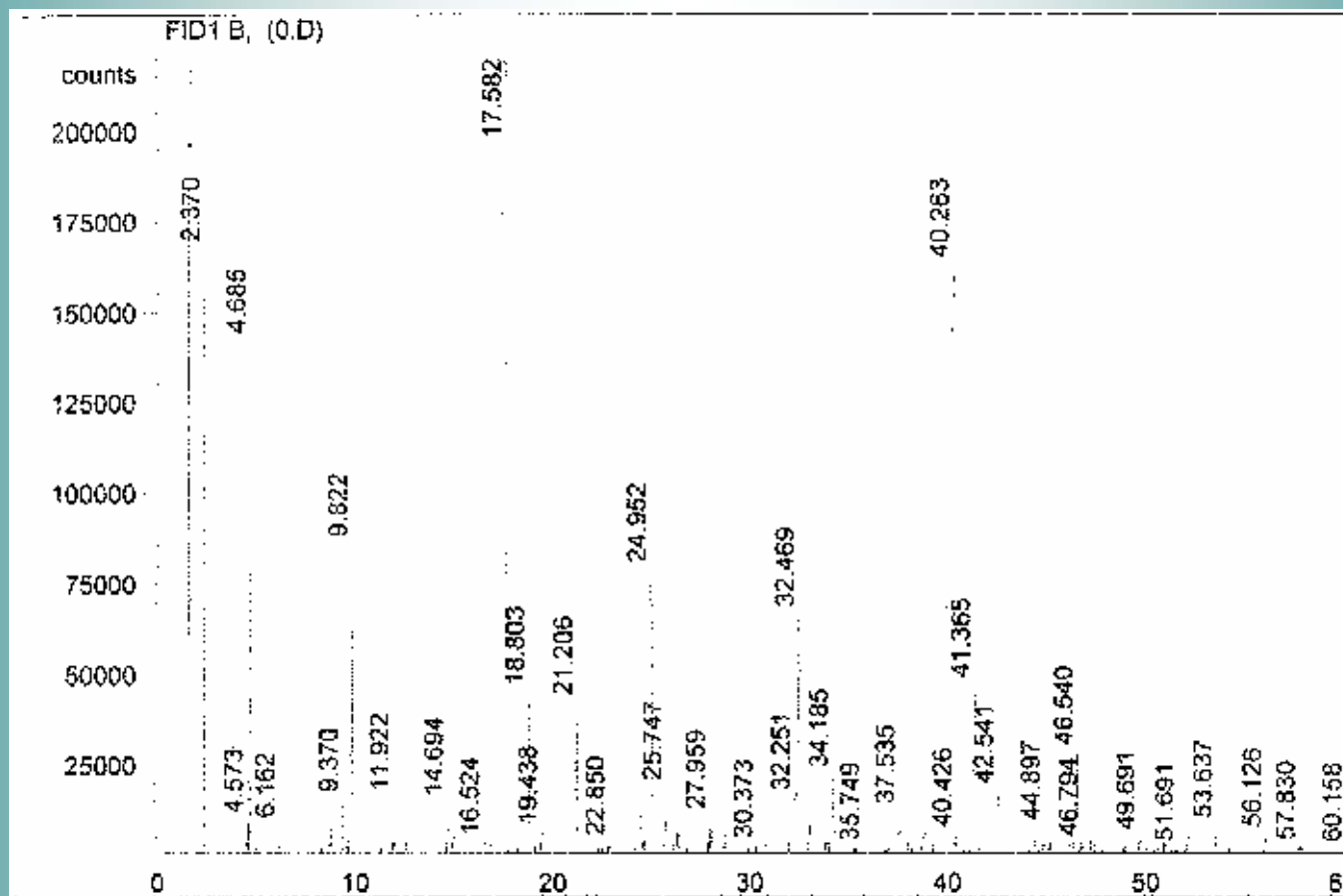
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Mechanism of Halogen Exchange



Halogen Exchange – (2)

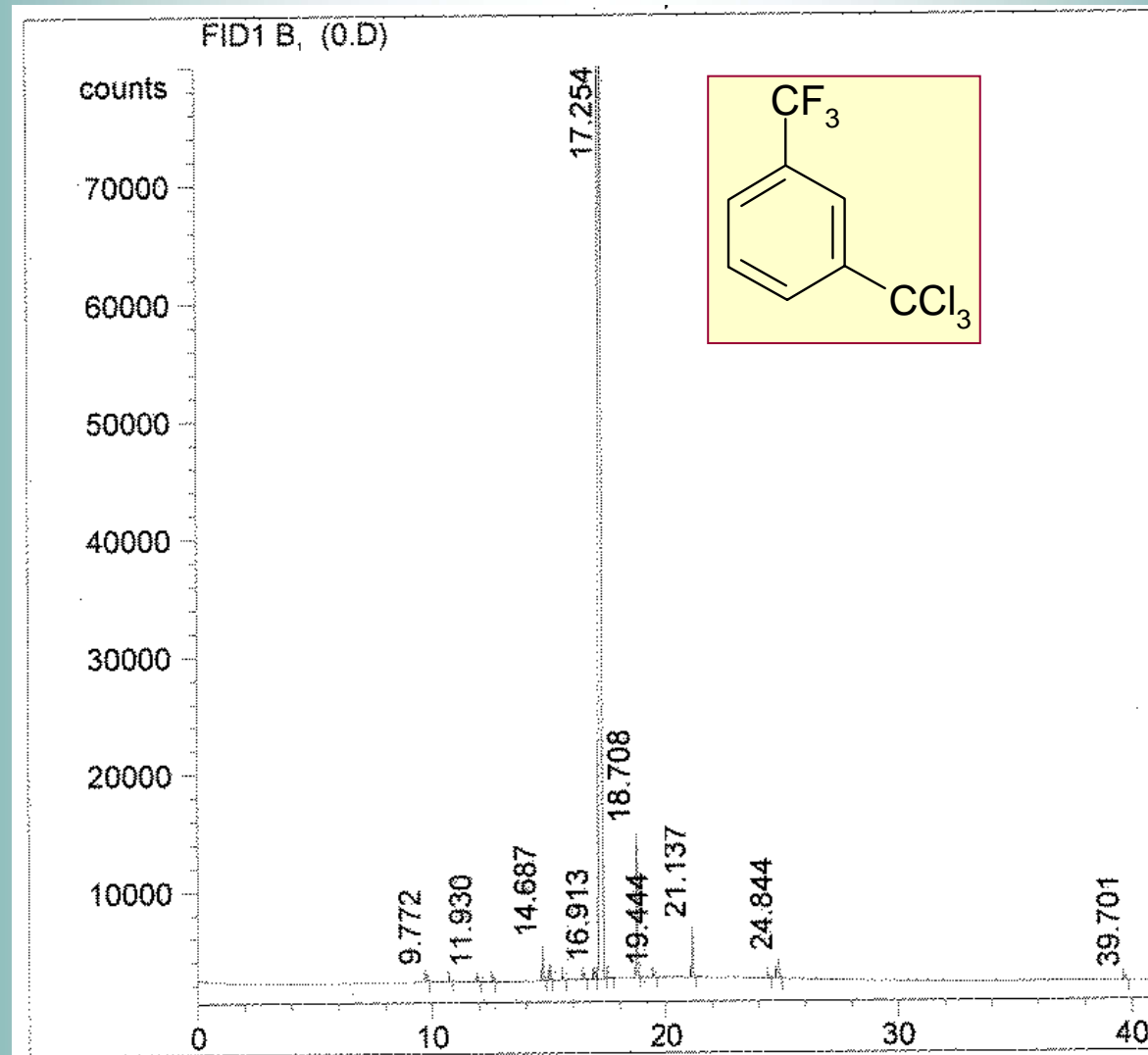
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GC @ 10 h	<i>m</i> -HFX	F ₅ Cl	F ₄ Cl ₂	F ₃ Cl ₃	F ₂ Cl ₄	FCl ₅	<i>m</i> -HCX
RT (min)	2,37	4,68	9,82	17,58	24,95	32,47	40,26

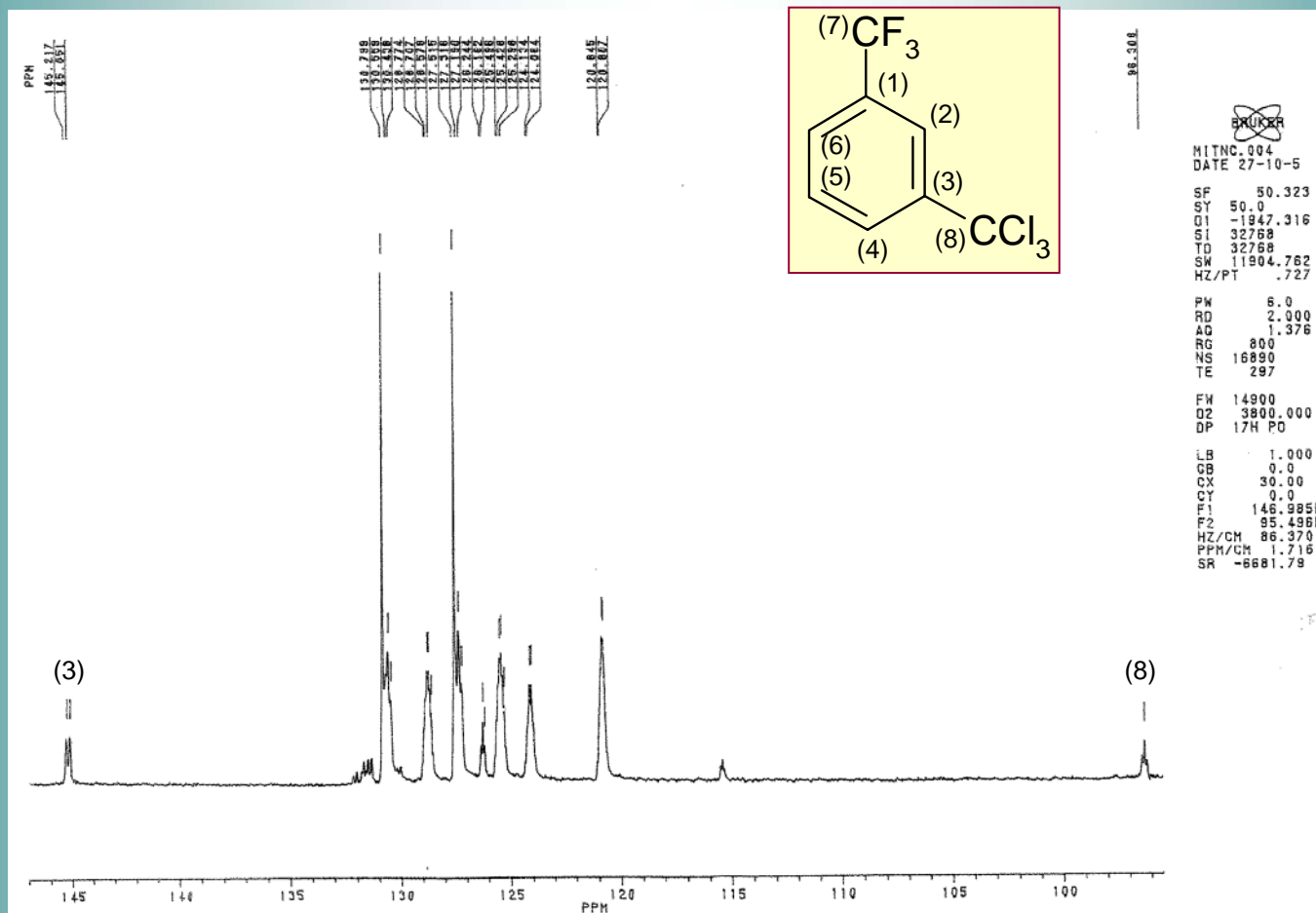
Halogen Exchange – (3)

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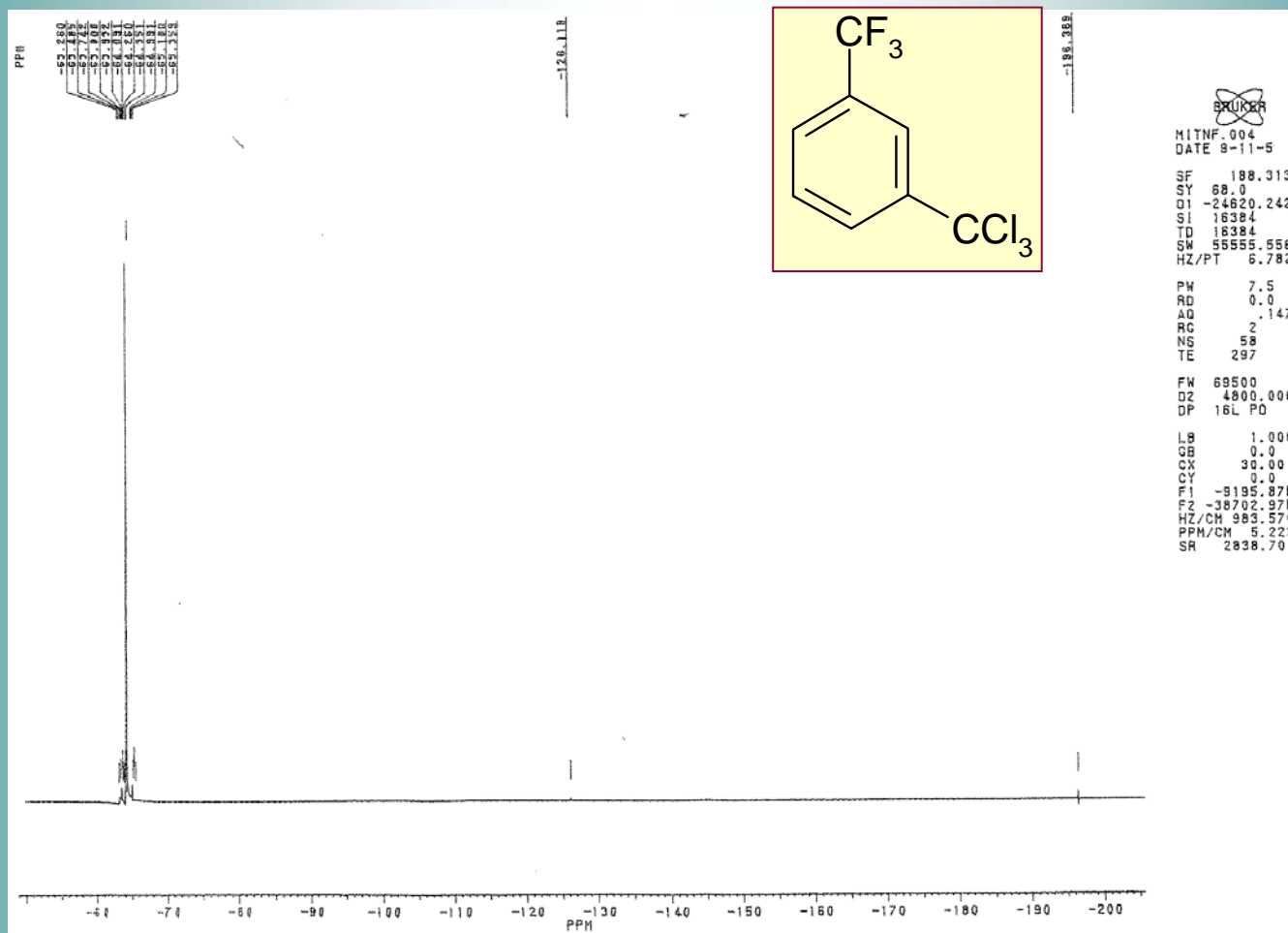
Halogen Exchange – (4)

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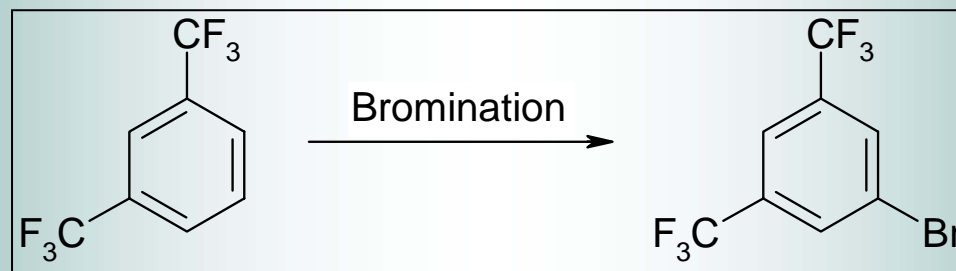
Halogen Exchange – (5)

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Bromination (1)

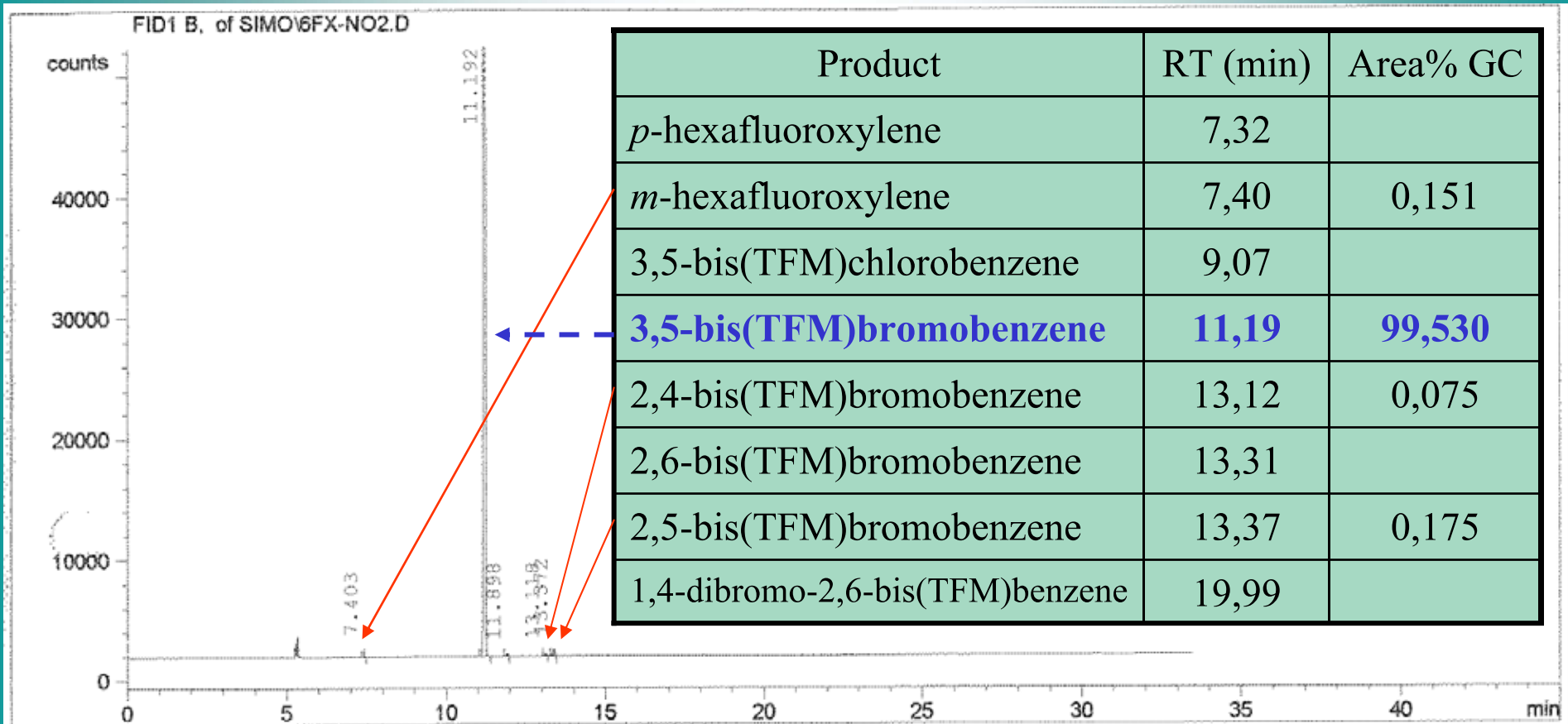
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Brominating Agent	Conditions	Comments
Br ₂	FeCl ₃ ; SbCl ₃ ; SbCl ₅ ; 70°C; 7-24 h	Yield: max 5.2%
NBS	H ₂ SO ₄ ; 4°C; 4 h; then RT; 17 h	Yield: 93.5%
DBH	H ₂ SO ₄ ; -5 → 35°C; 6 h;	Yield: 90.8% May contain 1,3-DCH
M ⁺ BrO ₃ ⁻	H ₂ SO ₄ ; RT → 50°C; 7 h	Yield: 71% K ⁺ salt is carcinogen

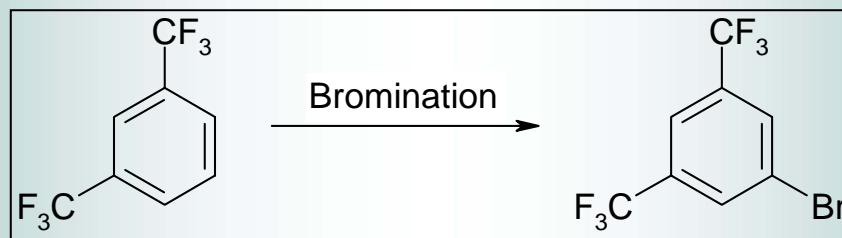
Bromination (2)

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Bromination (3)

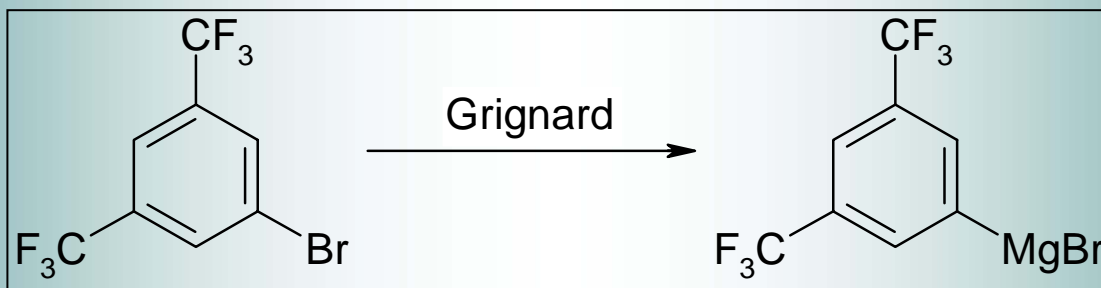
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	NBS	DBH
PM	177,98	285,92
Bromine content %	44,9	55,9
Price	\$\$	\$
Selectivity %	> 98	90
Specificity %	99,4	99,5

Grignard Reagent

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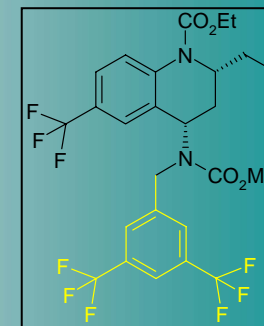
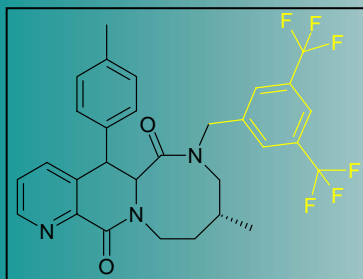
T: 45 °C; no initiator necessary; t: 6-8 hrs

**Safety is Mandatory:
Solvent Choice is Critical
(Flash Point; Peroxides)**

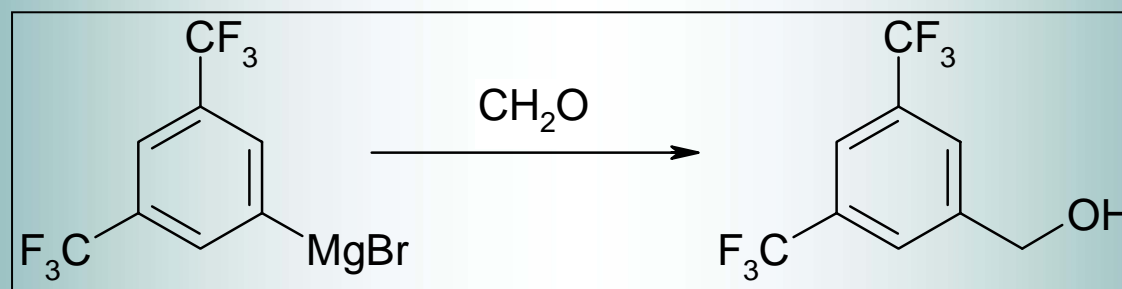
	Et ₂ O	THF	<i>n</i> -Hexane	Toluene	<i>m</i> -Xylene
Flash-Point (°C)	- 45	- 14	- 22	4	27
Boiling Point (°C)	34	66	68	110	138

Benzyl Alcohol

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Yield: 70%



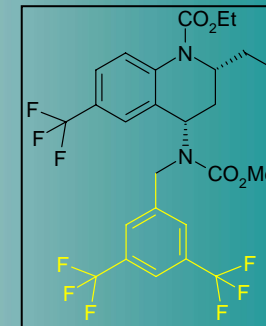
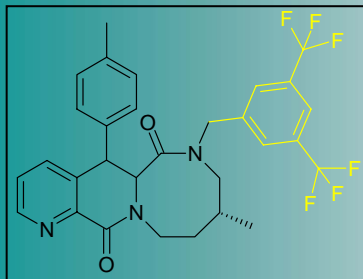
Safety is Mandatory:
Source of CH₂O is Critical



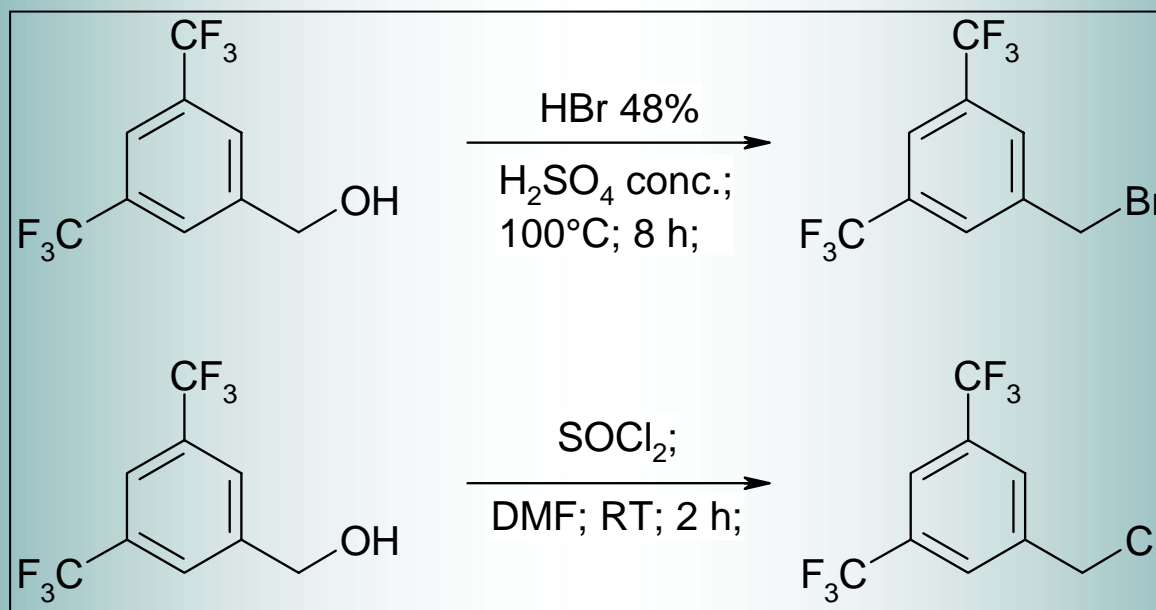
Paraformaldehyde: crystalline powder

Benzyl Halides

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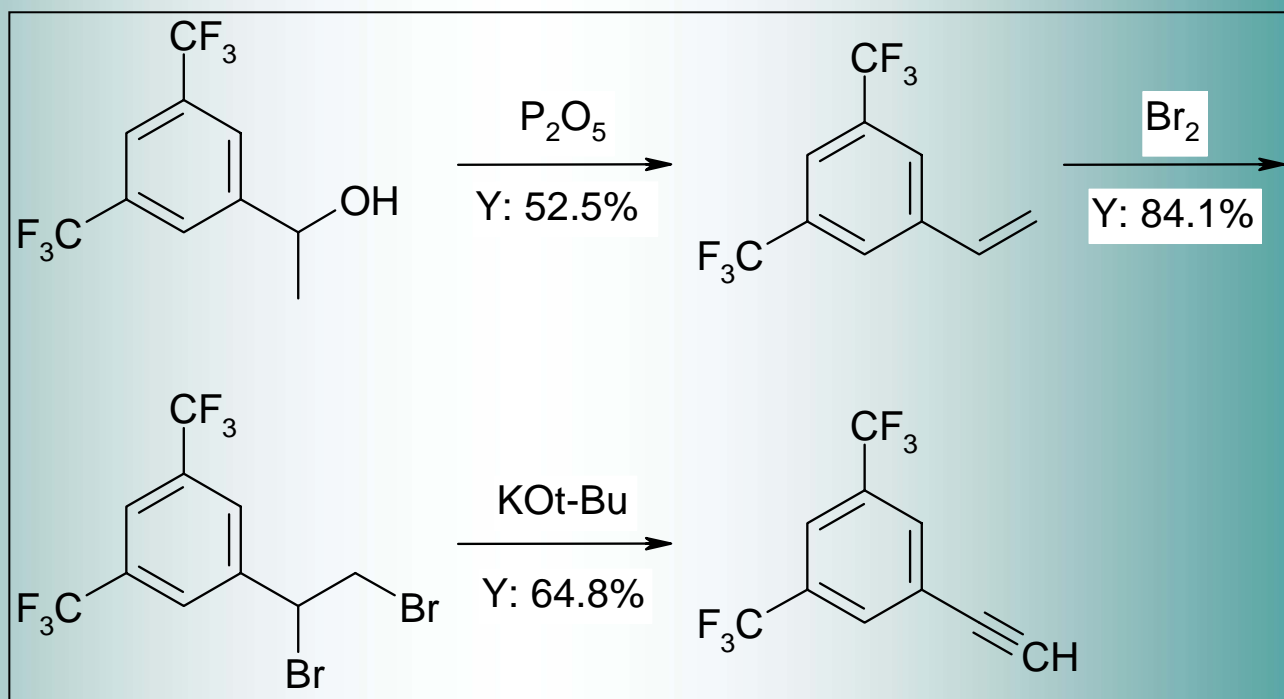
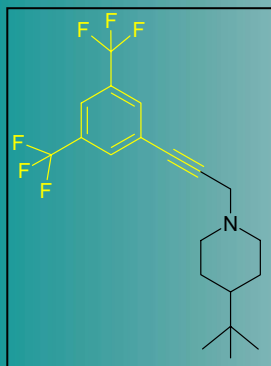
Yield: 80%



Yield: 86%

Phenylacetylene

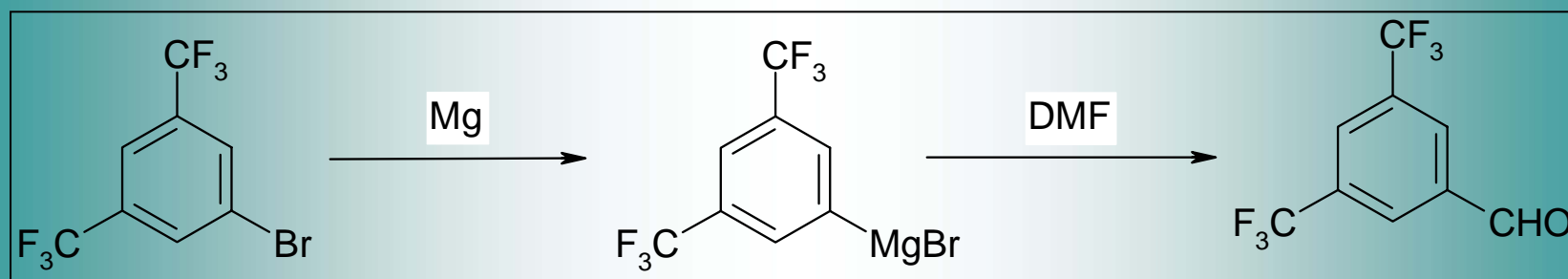
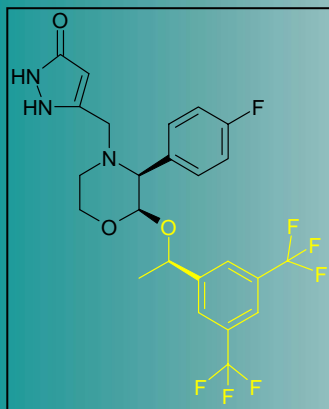
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Overall yield: 29%

Benzaldehyde

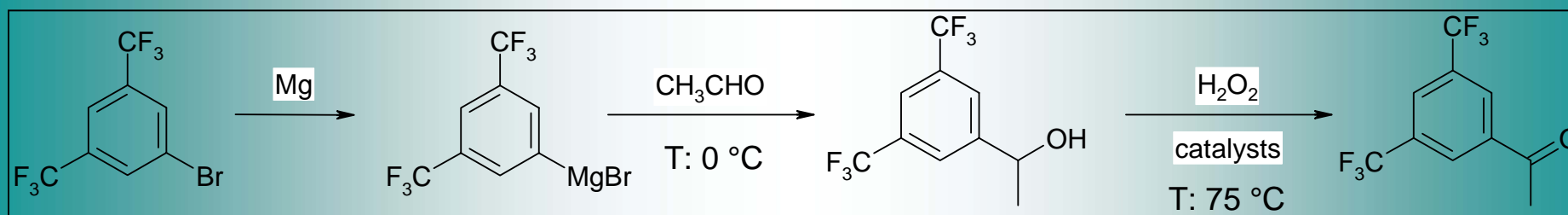
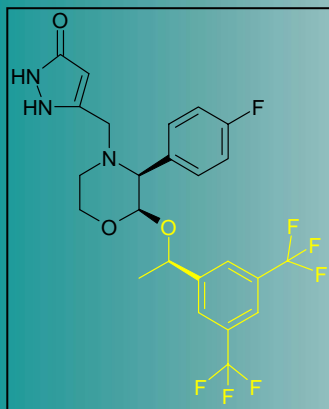
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Solvent: Et₂O; yield: 53%
THF; yield: 72%
THF/xylene; yield: 55%

Acetophenone

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Yield: 95%

Yield: 91%

Overall yield: 86.5%

ACKNOWLEDGEMENTS Miteni

Alessandro Nardello

Marisa Pretto

Andrea Faccin

Simonetta Mondini

Mirco Dall'Ava



THANK YOU

Miteni

READY FOR NEXT CHALLENGES

