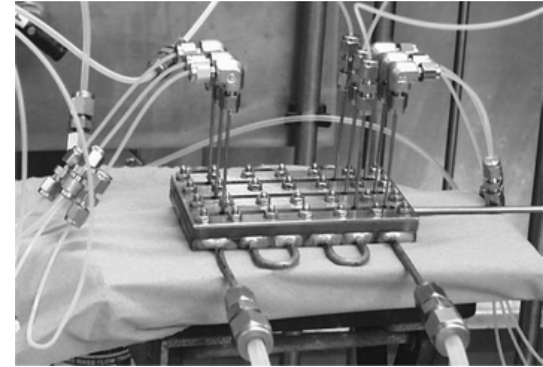


Gas-Liquid Microreactors for Selective Fluorination and Inhibitors of Cdc-25- Application of New E-alkene Dipeptide Isostere β -turn mimics

Juraj Reháč, PhD.
Research Topic Seminar
12-feb-2011



Gas-Liquid Microreactors for Selective Fluorination

Fluorine in Organic Molecules

Benefits:

High Biologic Activity

Mimicking of Enzyme Substrates

Blocking Effect in Metabolic Transformations

Increased Lipophilicity to Enhance Bioavailability

Better Thermal Stability

Drawback:

Toxicity

Dangerous Preparation Methods

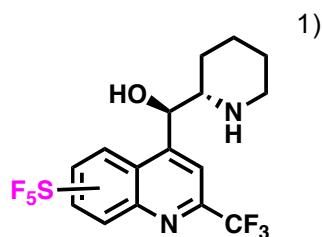
Synthesis of Fluorinated Organic Molecules

- *Introduction of F-building (CnFm, XnFm)*
- *Nucleophilic Fluorination*
- *Electrophilic Fluorination*
- *Electrochemical Fluorination*

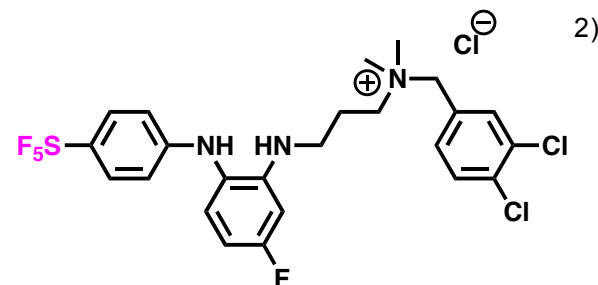
Reagents:

- *Inorganic Salts: (KF·Cl₂, AgF₂, PbF₂(OAc)₂...)*
- *Ammonium Fluorides: (Et₃N·₃HF, (HF)_x·Pyridine)*
- *N-Fluoro Reagents: (NSFI)*
- *Fluoroaminosulfuranes: (DAST)*
- *Other Reagents: XeF₂, F₂*

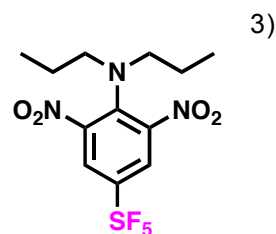
Biological Activity Sulfur pentafluoride Aryls



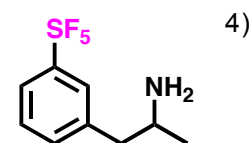
Analoge of **Mefloquine**
Antimalarial activity



Antiprotozoal Activities



Analog of **Trifluralin**
Herbicidal activity

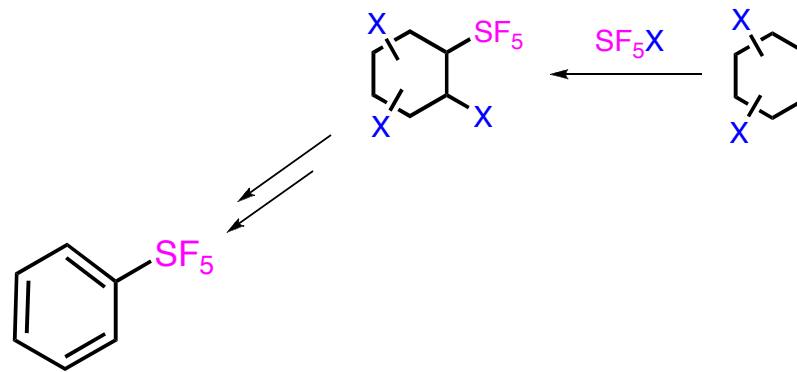


Analog of **Norfenfluramine**
Inhibitors of serotonin 5-HT_{2b}, 5-HT_{2c}, and 5-HT₆ receptors

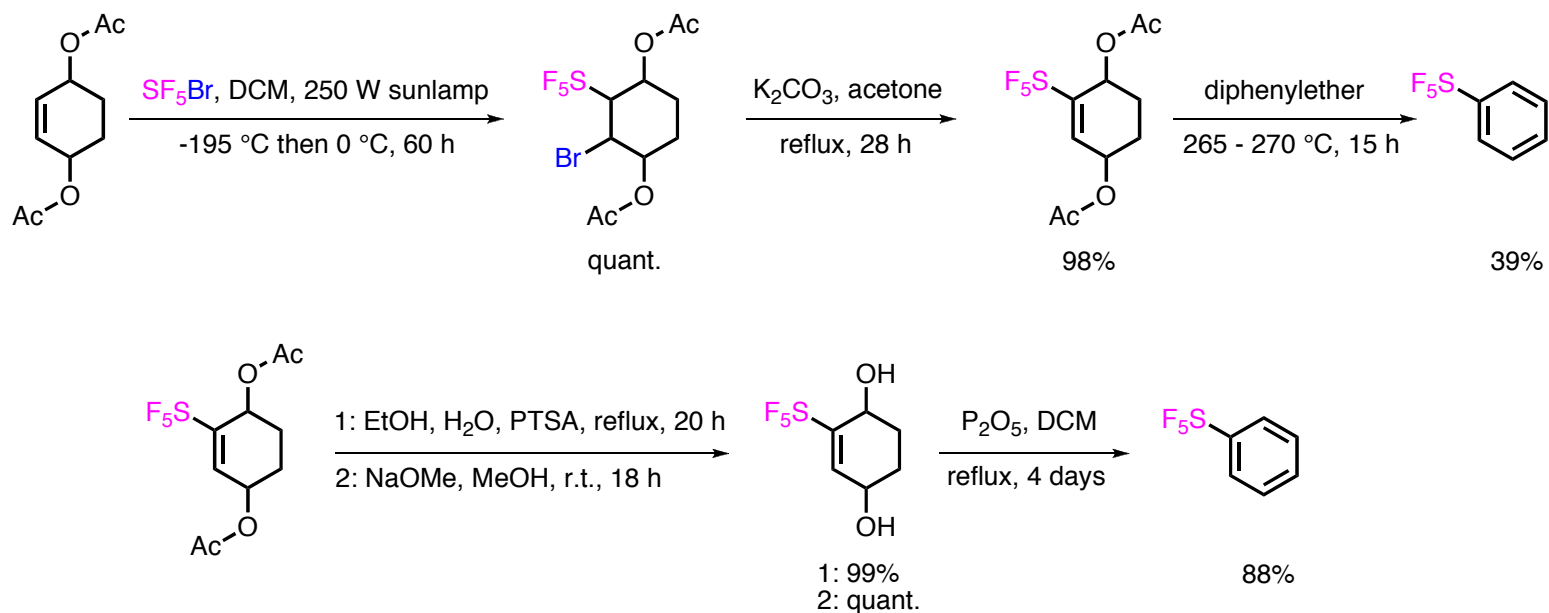
- 1) P. Wipf; T. Mo; S. J. Geib; D. Caridha; G. S. Dow; L. Gerena; N. Roncal; E. E. Milnerc: *Org. Biomol. Chem.* **7**, **2009**, 416
2) B. Stump; C. Eberle; W. B. Schweizer; M. Kaiser; R. Brun; R. L. K. Siegel; D. Lentz; F. Diederich: *ChemBioChem* **10**, **2009**, 79
3) D. S. Lim; J. S. Choi; C. S. Pak; J. T. Welch: *J. Pestic. Sci.* **32**, **2007**, 255
4) J. T. Welch; D. S. Lim: *Bioorg. & Med. Chem.* **15**, **2007**, 6659

Preparation of Sulfur pentafluoride Aryls

Addition of SF₅-Halides and Aromatisation by elimination



Addition of SF₅-Halides and Aromatisation by elimination



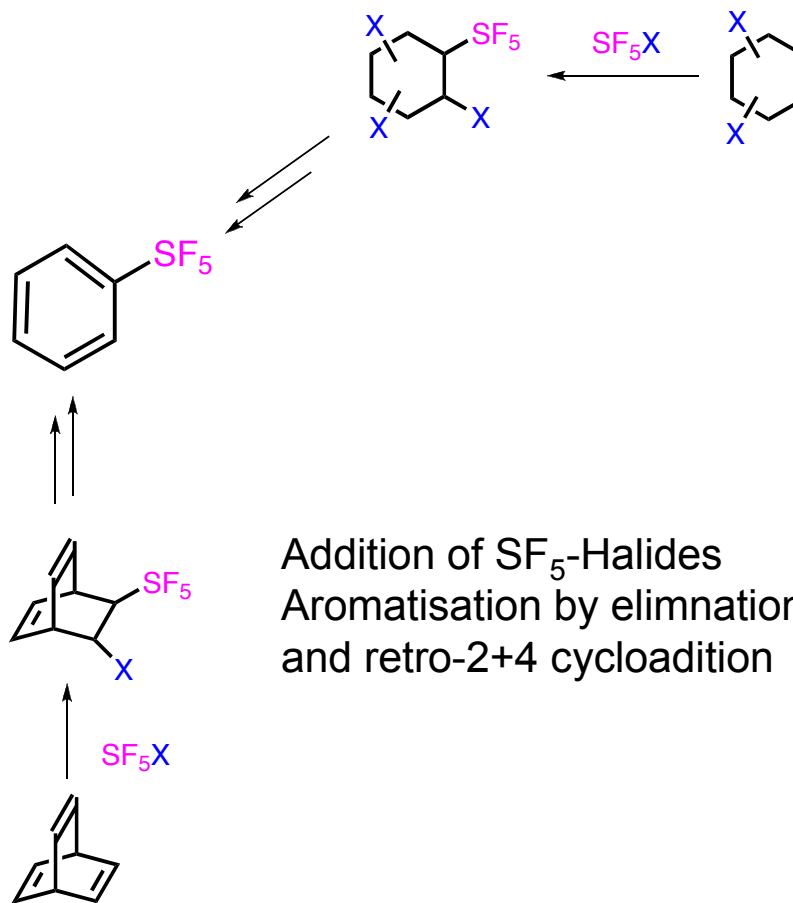
R. W. Winter; G. L. Gard: *J. Fluor. Chem.* 125, 2004, 549

Addition of SF₅-Halides and Aromatisation by elimination



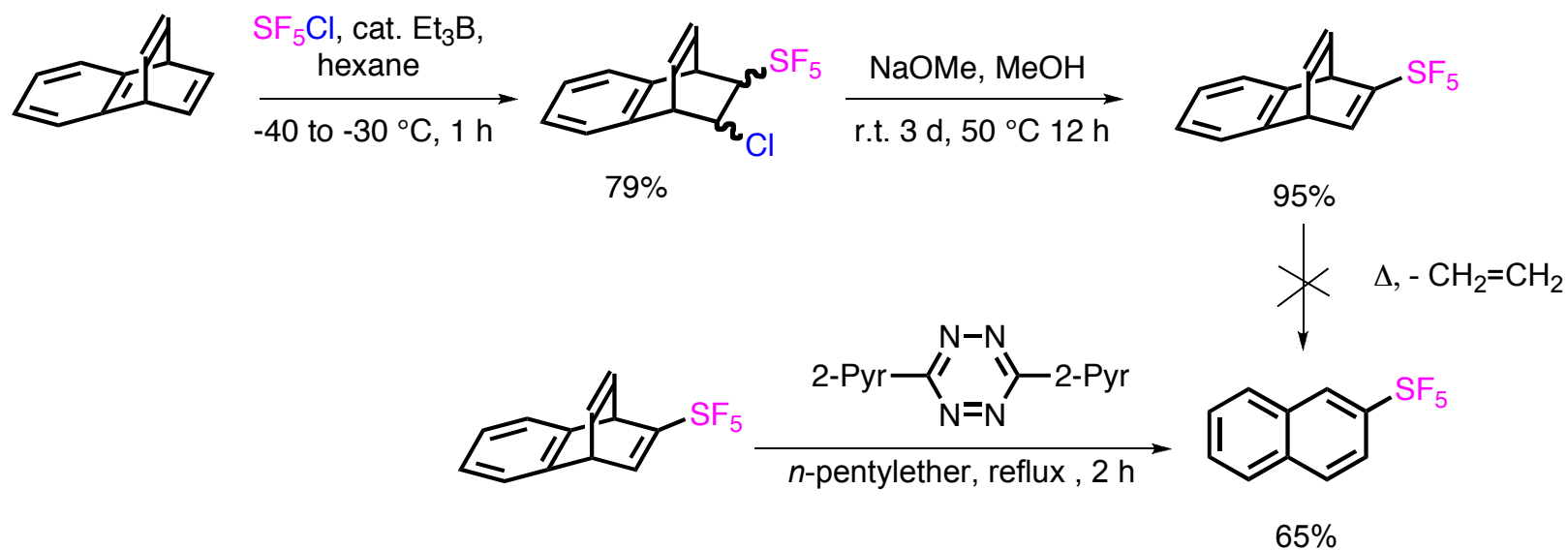
T. A. Sergeeva; W. R. Dolbier Jr.: *Org. Lett.* **6**, **2004**, 2417

Preparation of Sulfur pentafluoride Aryls



Addition of SF_5 -Halides
Aromatisation by elimination of HX
and retro-2+4 cycloaddition

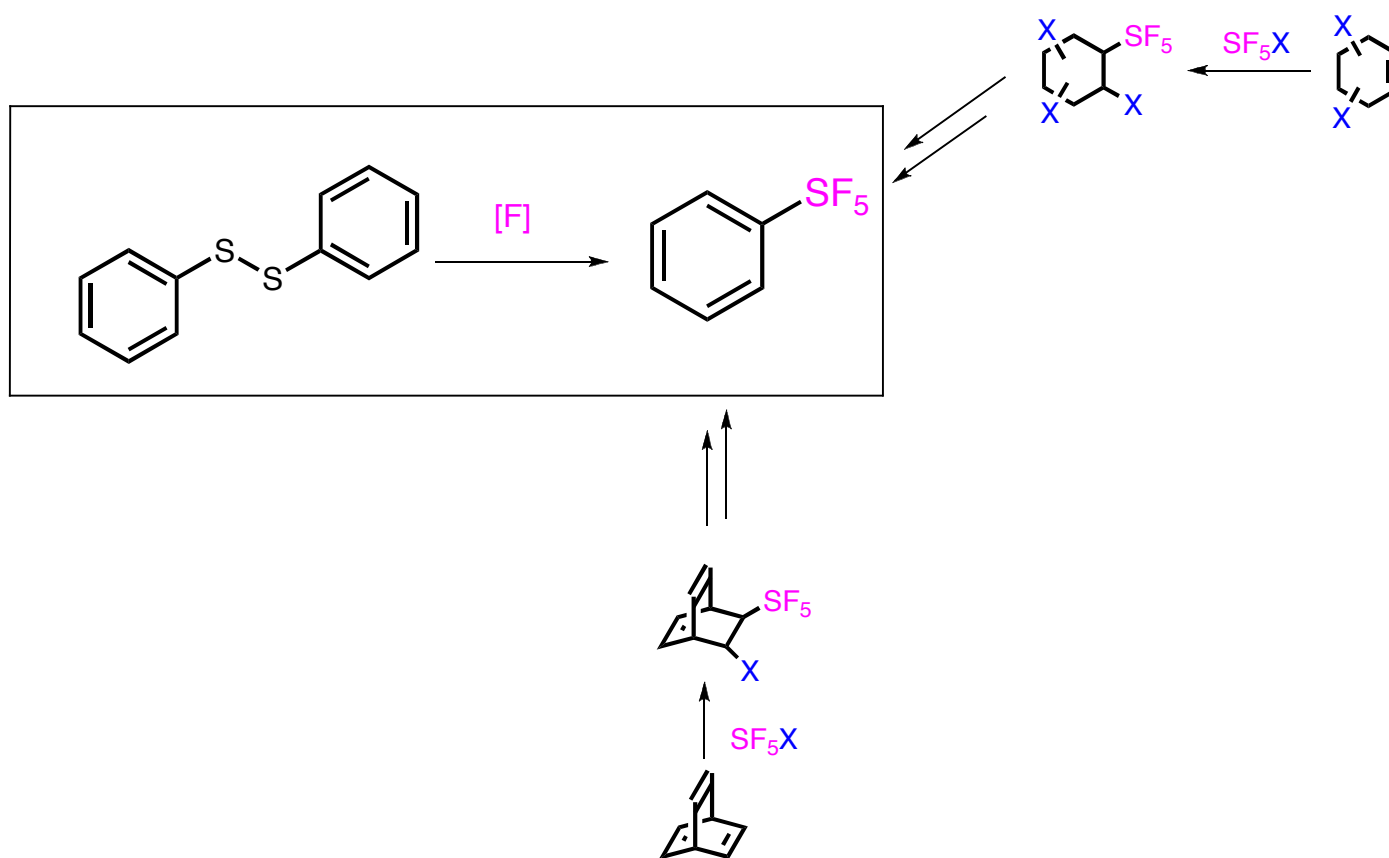
Addition of SF₅-Halides and Aromatisation by retro-2+4 cycloaddition



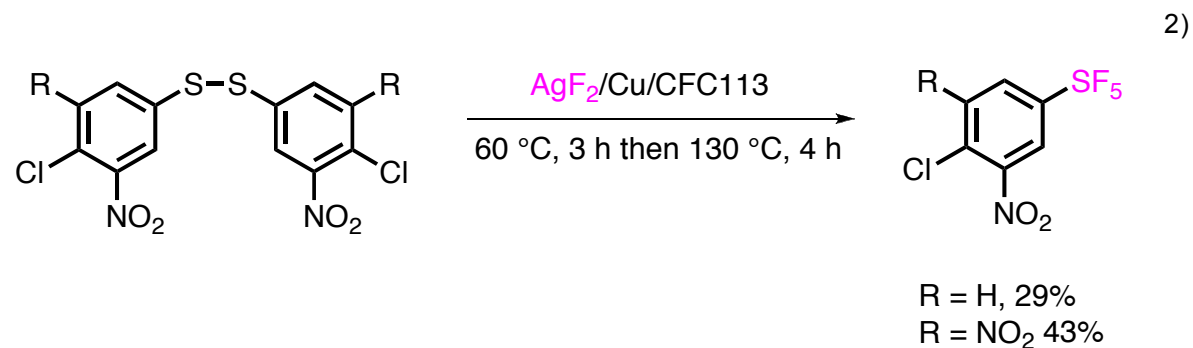
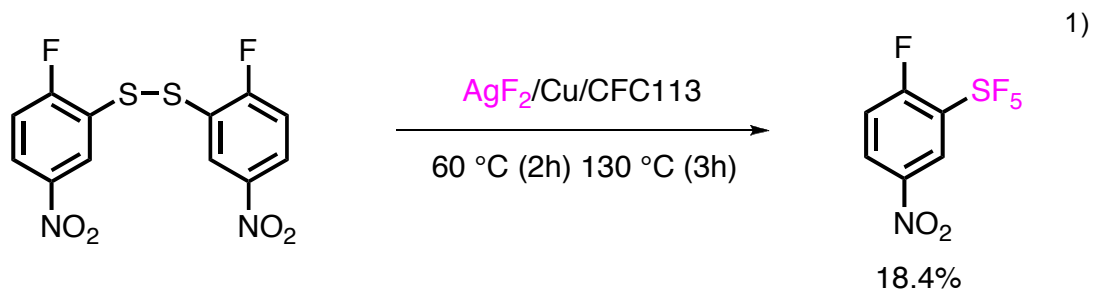
W. R. Dolbier Jr.; A. Mitani; R. D. Warren: *Tet. Lett.* 48, 2007, 1325

Preparation of Sulfur pentafluoride Aryls

Fluorination of disulphites



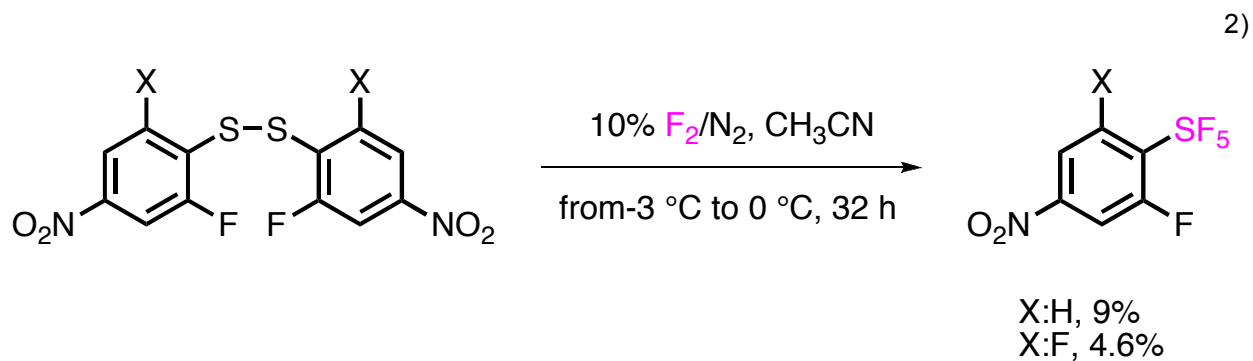
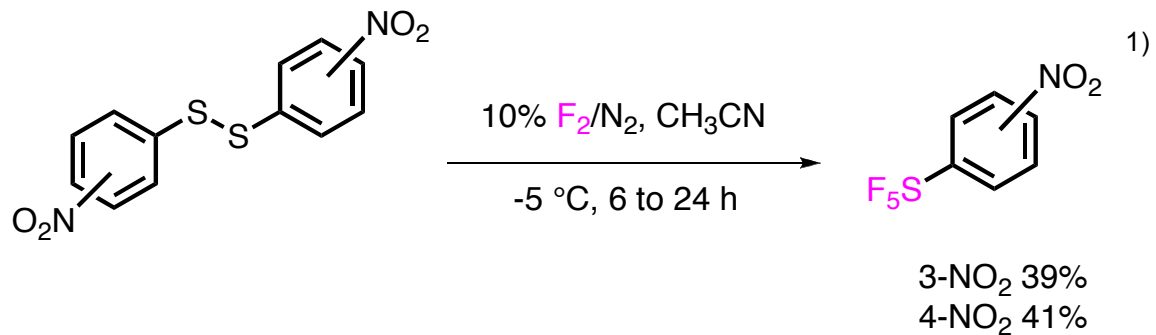
Fluorination of disulphites



1) A. M. Sipyagina; C. P. Batemana; Y.-T. Tana; J. S. Thrashera: *J. Fluor. Chem.* 112, **2001**, 287

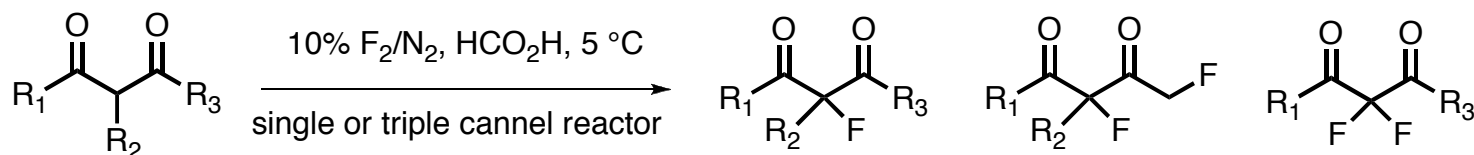
2) A. M. Sipyagina; V. S. Enshovb; S. A. Kashtanovb; C. P. Batemana; B. D. Mullena; Y.-T. Tana; J. S. Thrashera: *J. Fluor. Chem.* 125, **2004**, 1305

Fluorination of disulphites



- 1) R. D. Bowden; P. J. Comina; M. P. Greenhall; B. M. Kariuki; A. Loveday; D. Philp: *Tetrahedron* 56, **2000**, 3399
2) P. Kirsch; A. Hahn: *Eur. J. Org. Chem* **2005**, 3095

Direct Fluorination with Gas-Liquid Thin Film Microreactors



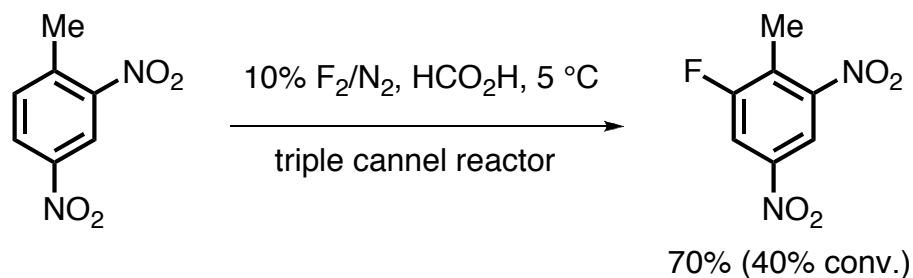
R₁: -OEt; R₂: -H, -Me, -Cl; R₃: -Me, -OEt

38-95%

0-12%

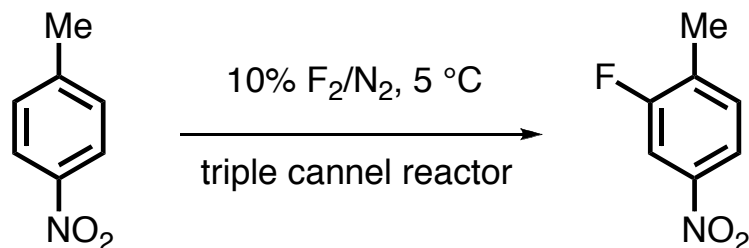
0-3%

R₁-R₂: -OCH₂CH₂-, -(CH₂)₄-



R. D. Chambers; D.Holling; R. C. H. Spink; G. Sandford: *Lab on a Chip*, 1, 2001, 132

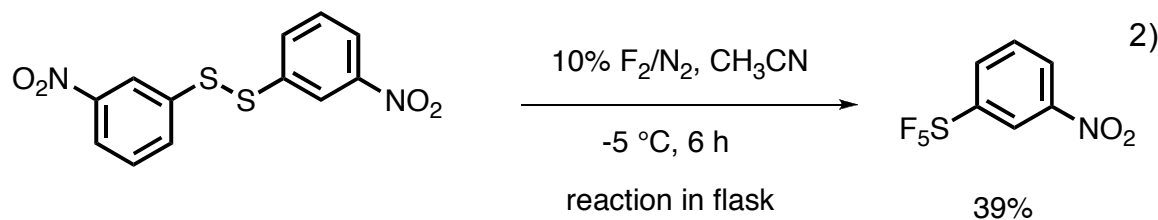
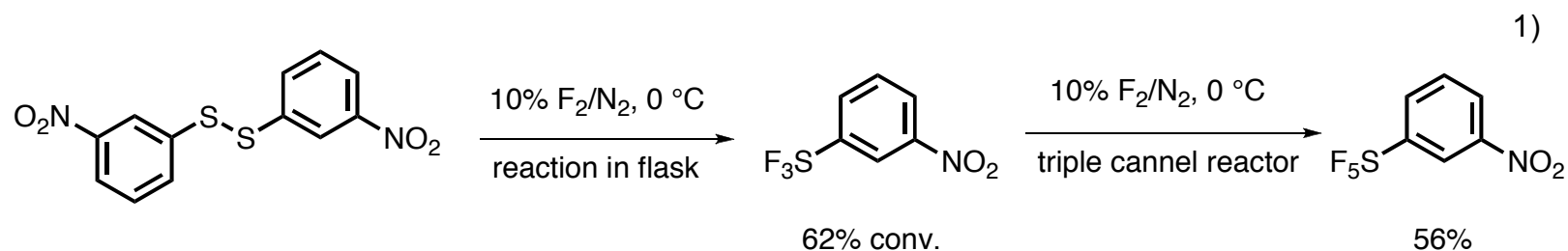
Direct Fluorination with Gas-Liquid Thin Film Microreactors



Entry	Solvent system	F ₂ :substrate	Sub. Sol. rate: ml h ⁻¹	Rate of substrate mmol h ⁻¹	T/°C	Conversion %	Yield %
1	MeCN	1.7:1	3	4.5	r.t.	15	71
2	MeCN:HCO ₂ H 3:2	3:1	3	2.7	5	44	78
3	MeCN:HCO ₂ H 3:2	3:1	3	2.7	0	66	71
4	MeCN:HCO ₂ H 3:2	3:1	6	2.7	5	53	60
5	MeCN:HCO ₂ H 3:2	3:1	6	2.7	0	77	66

R. D. Chambers; D.Holling; R. C. H. Spink; G. Sandford: *Lab on a Chip*, 1, 2001, 132

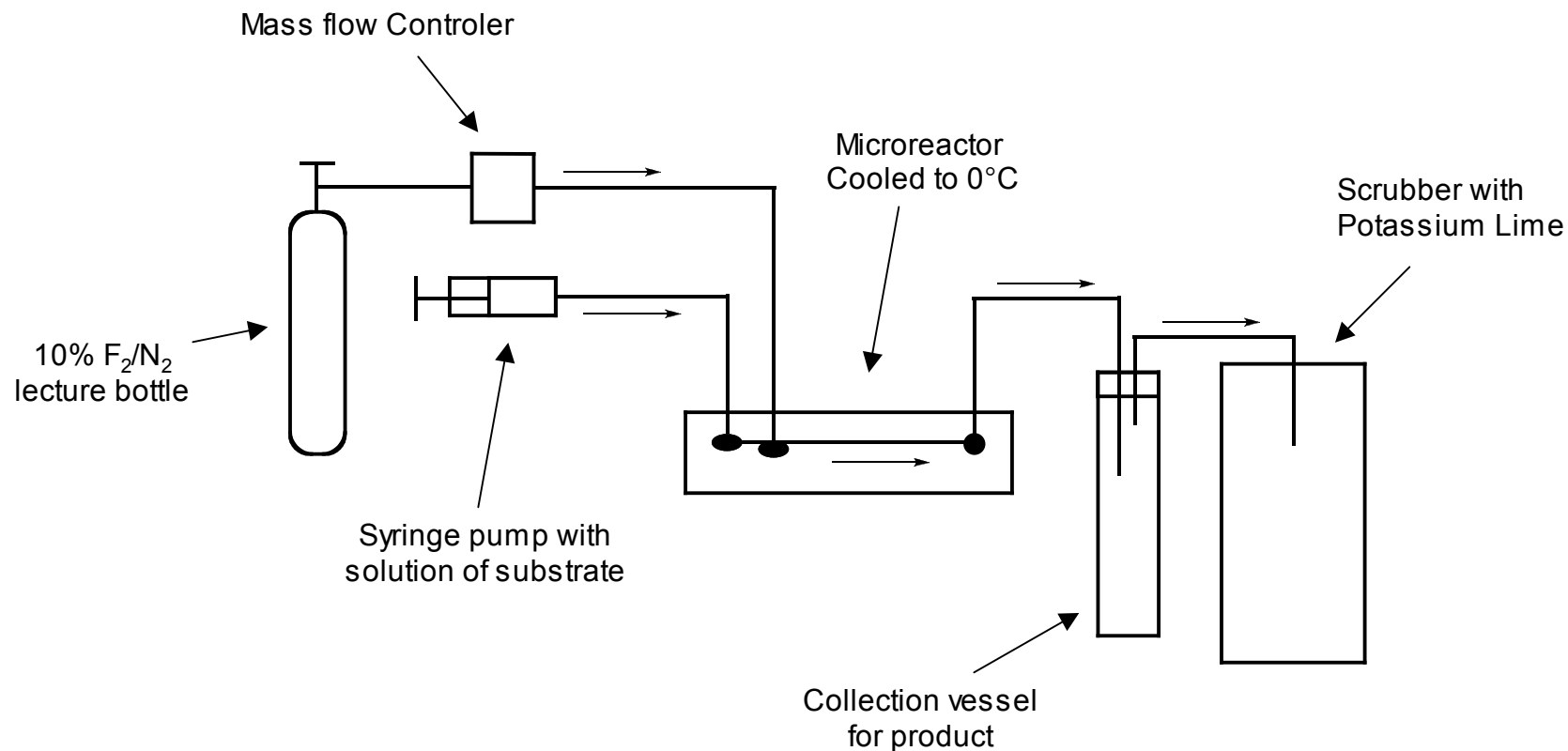
Direct Fluorination with Gas-Liquid Thin Film Microreactors



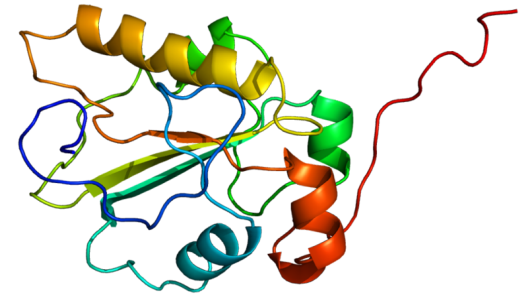
1) R. D. Chambers; D. Holling; R. C. H. Spink; G. Sandford: *Lab on a Chip*, **1**, **2001**, 132

2) R. D. Bowden; P. J. Comina; M. P. Greenhall; B. M. Kariuki; A. Loveday; D. Philp: *Tetrahedron* **56**, **2000**, 3399

Direct Fluorination with Gas-Liquid Thin Film Microreactors



R. D. Chambers; D.Holling; R. C. H. Spink; G. Sandford: *Lab on a Chip*, 1, 2001, 132



Inhibitors of Cdc-25-Application of New E-alkene Dipeptide Isostere β -turn mimics

http://en.wikipedia.org/wiki/File:Protein_CDC25A_PDB_1c25.png

Properties and functions of Cdc25

Cdc25 (Cell division cycle): group of dual-specificity phosphatases

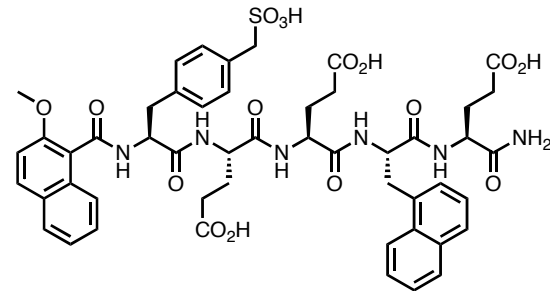
Regulation of cell-cycle progression through various phases of the cell cycle

Three homologues in humans (Cdc25A, Cdc25B, Cdc25C)

Cdc25A and Cdc25B are overexpressed in various type of cancers (lung, gastric, head, thyroid, and neck cancer, neuroblastoma,)

Inhibition of Cdc25 is a possible therapy for inhibition of growth or apoptosis of cancer cells

BASF Ligand



Patent describing discovery of Cdc25 inhibitors

Almost 380 penta and tetra peptides was described

Lead compound co-crystallized with Cdc25B (unknow biological data)

Contains a β -turn.

J. Blanchard; N. Bockovich; D. Borhani; D. Choquette; J Come; R.W. Dixon; J. Eckstein; D. Epstien; T. Fujimori; A. Haupt. M. Hediger; A. Kluge; K. Pal; K. Ritter; S. Robinson; J. Rudolph; N.R. Taylor; N. Walker: **Method of identifying inhibitors of Cdc25**. WO 0116300, Aug. 25, 2000

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Pete Chambers
Dr. Gary C. Davis
Chris Rosenker
All Wipf group members
Filip Petronijevic

