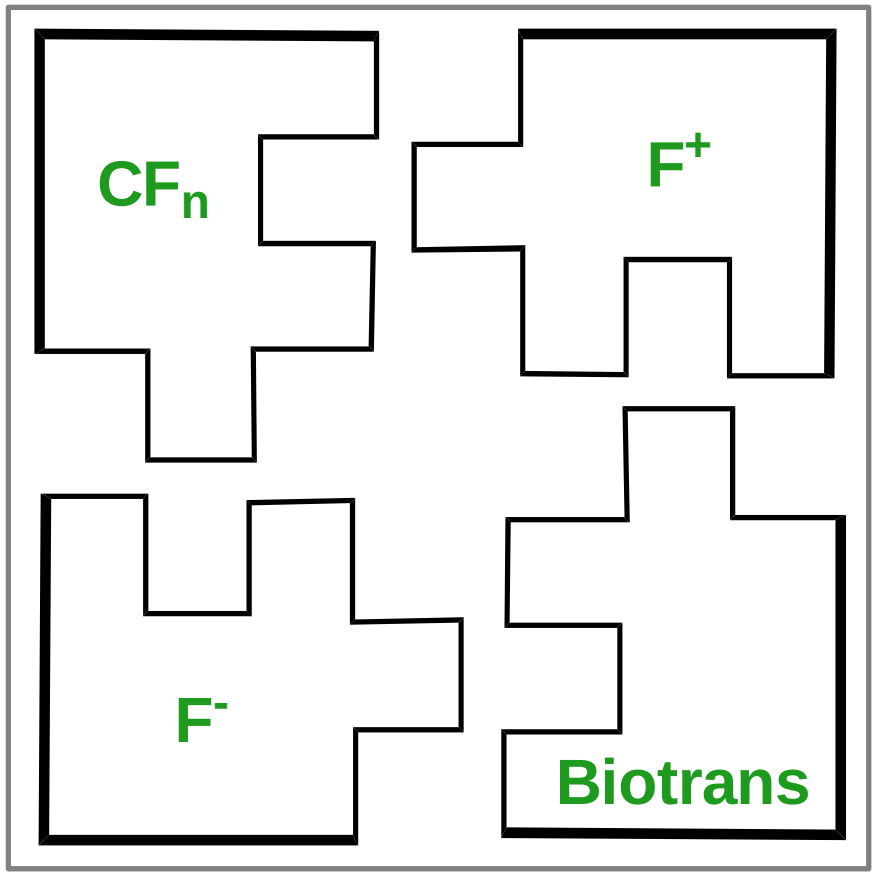
Fluorine in the Future...



Novel effective chemical entities

Fluorination technologies
- Nucleophilic
- Electrophilic

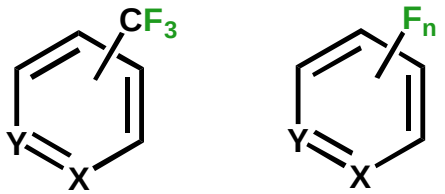
Building Blocks
Biotransformations
Fluorous tools

Understanding F effects

University of Leicester

Fluorine in the Future...

Arenes and heteroarenes



Fluorinated and perfluoroalkylated

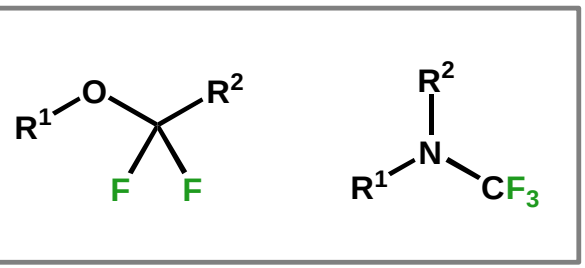
Traditional
Ubiquitous

Agrochem
Pharma
Materials

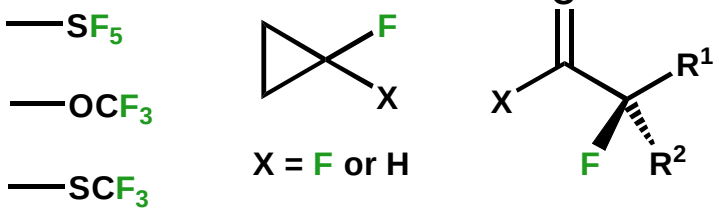
Established sourcing and scale-up

Major technology gaps between conception and delivery

Novel



Emerging



An Agrochem Perspective...

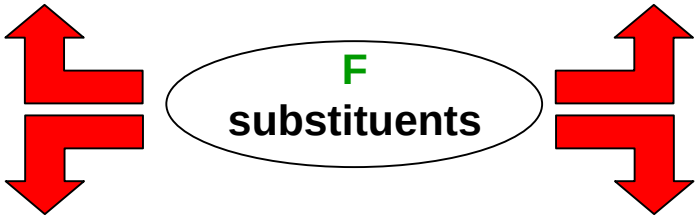
P. Jeschke, *ChemBioChem*, 2004, *5*, 570.

Efficacy

- high and reliable biological activity
- high selectivity
- rapid onset of action
- subsequent distribution in the plant
- optimal duration of action
- good crop tolerance
- low risk resistance

Environmental safety

- low toxicity to beneficial organisms
- good environmental degradability
- low soil mobility
- no significant residue in foodstuffs and animal feeds



User friendliness

- low rate of application low acute toxicity
- low toxicity on long-term exposure
- safe packing
- good formulation properties
- problem-free application
- long storage stability

Economic viability

- favourable cost/benefit relation for the user to be investigated
- suitability for use in integrated crop management
- broad range of application
- innovative product characteristics
- competitiveness
- patentability

How Does Nature Do It?

REVIEW

NPR

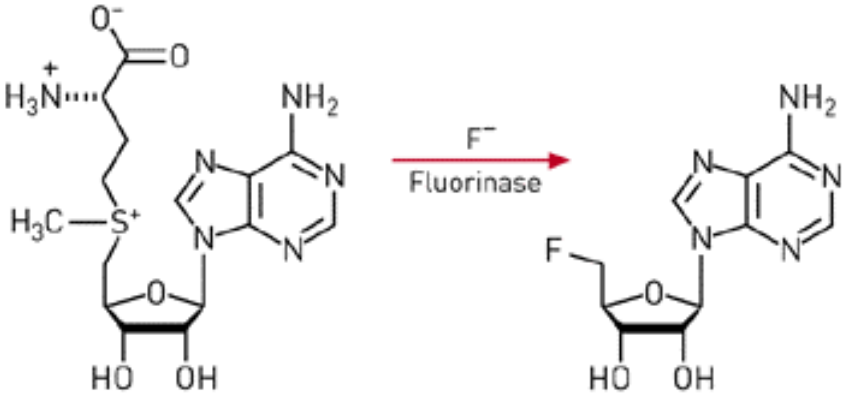
www.rsc.org/npr

Fluorometabolite biosynthesis and the fluorinase from *Streptomyces cattleya*

Hai Deng,[a] David O'Hagan*[b] and Christoph Schaffrath[a]

[a] *School of Chemistry and Centre for Biomolecular Science, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK*

[b] *School of Chemistry and Centre for Biomolecular Science, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK. E-mail: do1@st-andrews.ac.uk*



S-Adenosylmethionine **5′-Fluoro-5′-deoxyadenosine**

Raw Material to Final Product...

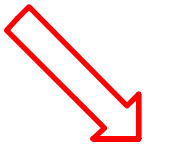
Photograph of a fluorite specimen from Hunan Province, China taken by Dlloyd. Sharp, violet coloured cubic fluorite crystals, measuring up to 1.6 cm (0.6") across, on dolomite (www.wikipedia.com)

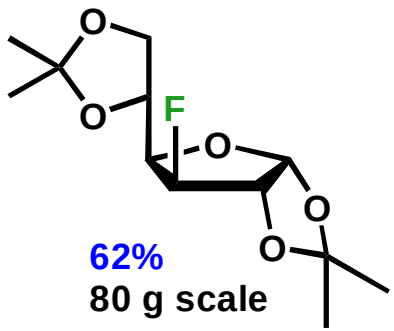
via

HF

F_2

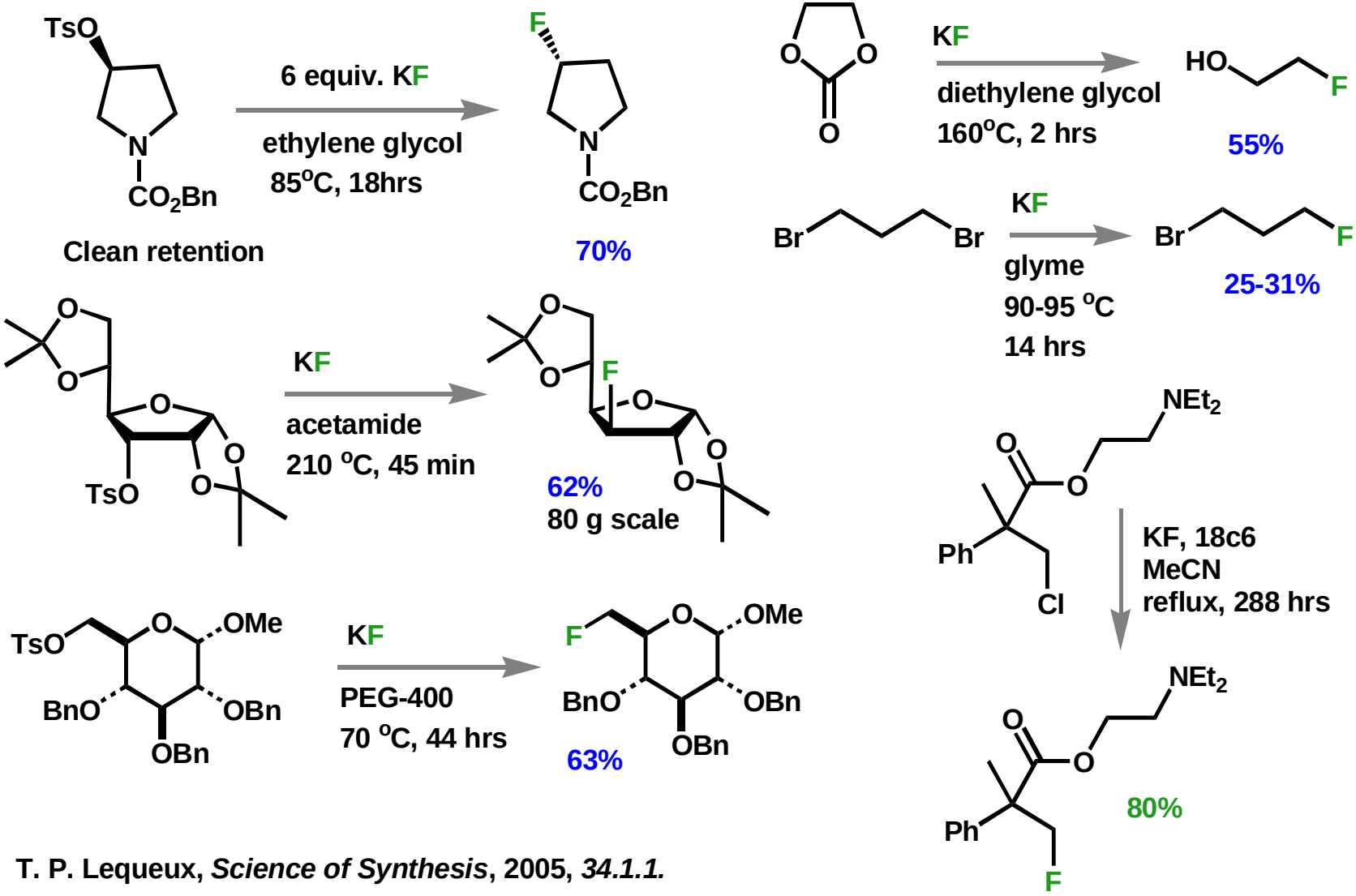
KF
CsF
Bu_4NF
$Et_3N.HF$
Pyridine.HF





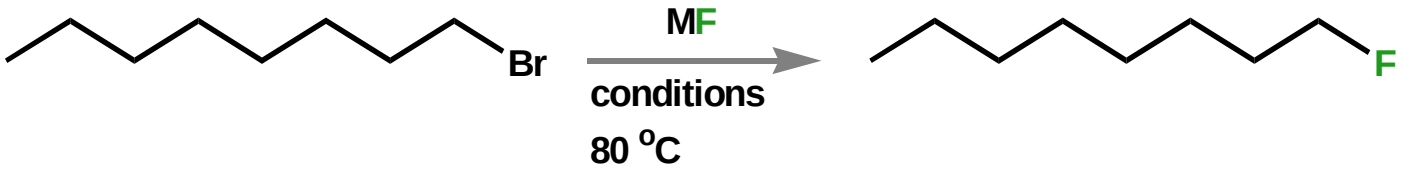
62%
80 g scale

Nucleophilic Substitution with KF...



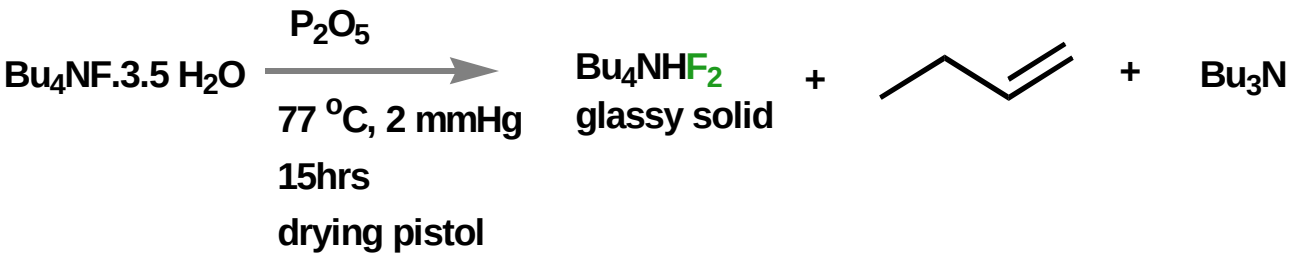
T. P. Lequeux, *Science of Synthesis*, 2005, *34.1.1.*

TBAF Behaviour and Water Content...



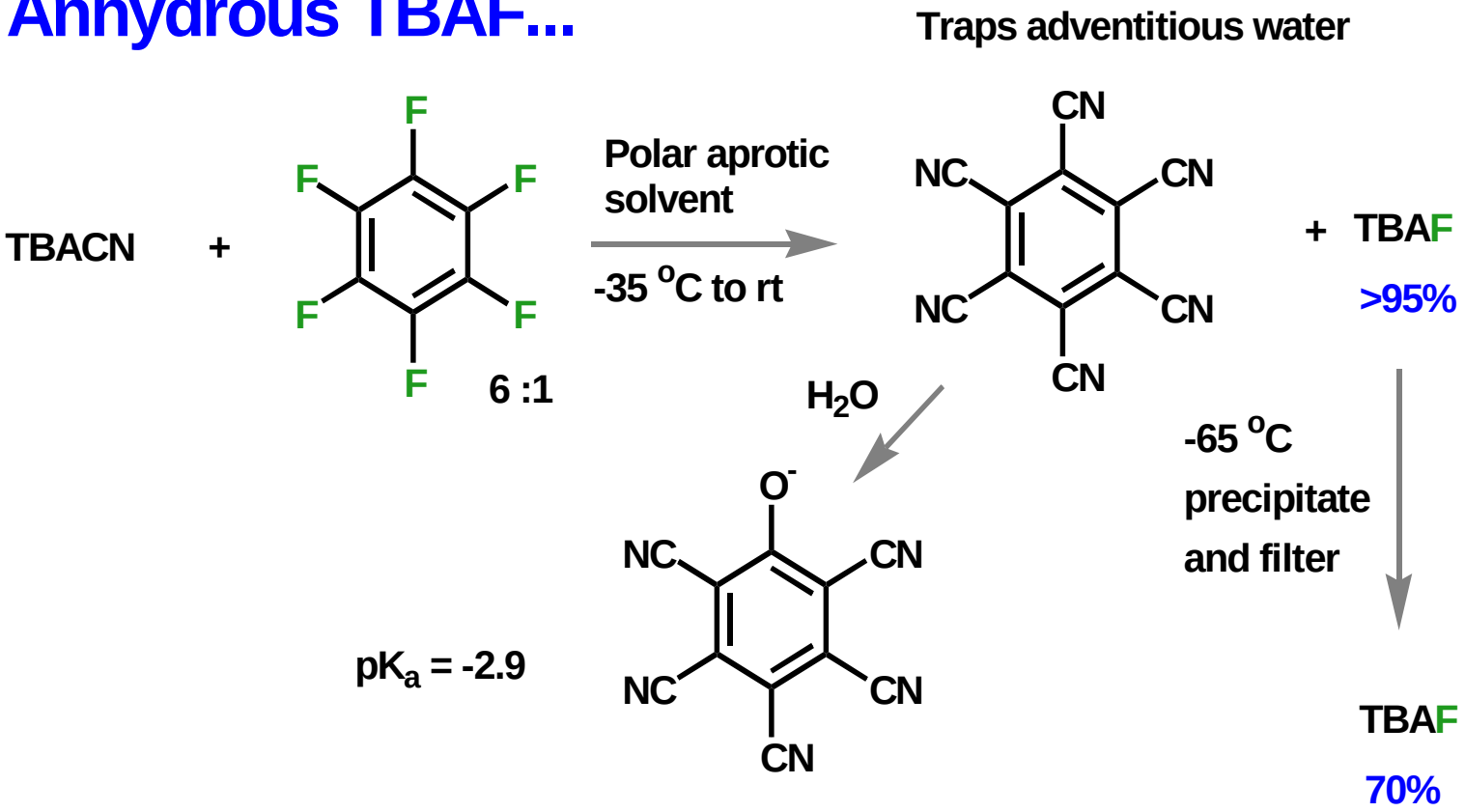
	Solvent	Time (hrs)	%Substitution	%Elimination
$Bu_4NF.0.5\ H_2O$	MeCN	0.25	56	44
$Bu_4NF.0.5\ H_2O$	none	0.25	53	37
$Bu_4NF.3.5\ H_2O$	MeCN	0.5	87	13
$Bu_4NF.3.5\ H_2O$	none	0.25	92	9
$Bu_4NF.5.0\ H_2O$	MeCN	2	91	9
$Bu_4NF.5.0\ H_2O$	none	0.5	81	6

If you dry it...



D. Landini, *J. Org. Chem.*, 1998, *63*, 9587; J. L. Fry, *J. Org. Chem.*, 1983, *48*, 2112.

Anhydrous TBAF...

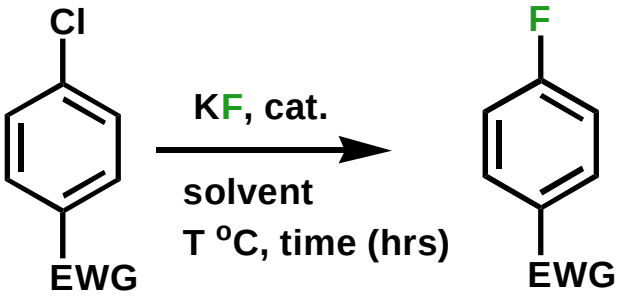


HCB/TBAF mixture in excess converts R-OH to R-F directly
Extremely high yields with bromides, tosylates, denitration, acid chlorides
Secondary bromides, tosylates not reported
Fluoride appears less basic than anticipated
Hydroxide implicated as base in TBAF decomposition

S. G. DiMagno, *J. Am. Chem. Soc.*, 2005, *127*, 2050.

Aromatic Halex...

A. Plescke *et al*., *J. Fluorine Chem*., 2004, *125*, 1031-1038.



Solubility!!

Maximum fluoride solubility in sulfolane at 180 °C 5.2×10^{-4} M

Catalysts operate by solid-liquid anion extraction followed by rate determining addition

G. Scorrano *et al*., *Gazz. Chim. Italia*, 1996, *126*, 457.

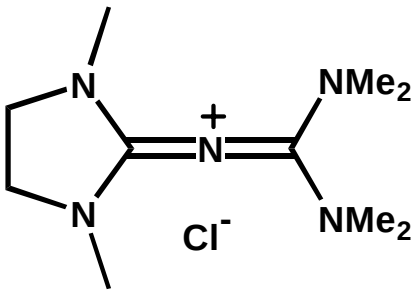
Established

Ph_4PBr

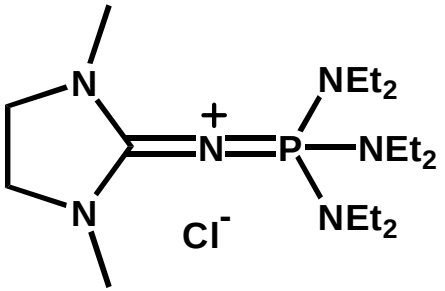
$(Et_2N)_4PBr$

Target properties

High thermal stability
Solvent free use?
Low stoichiometry
Low dermal toxicity
Patent free



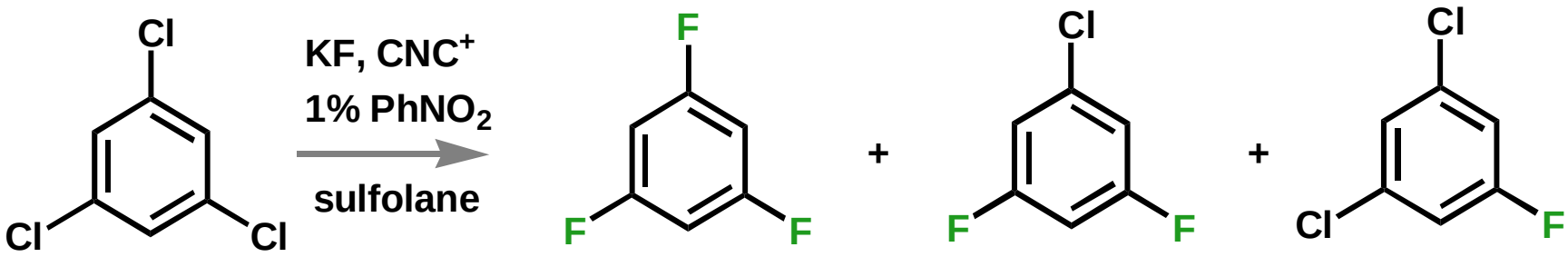
CNC^+



PNC^+

Higher Temperature Application...

Ph_4PBr decomposes above 180 ^oC



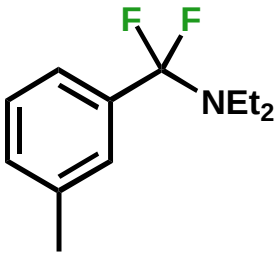
Step 1

230 ^oC, 12 hrs 18 : 61 : 20%

Step 2

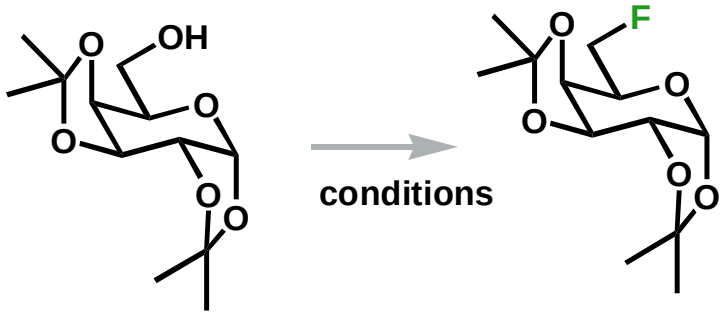
230 ^oC, 4hrs 87 : 8 : 1%

A New Thermally-stable Reagent for Deoxyfluorination...

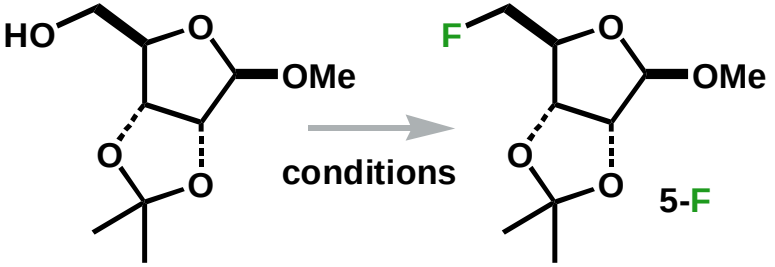


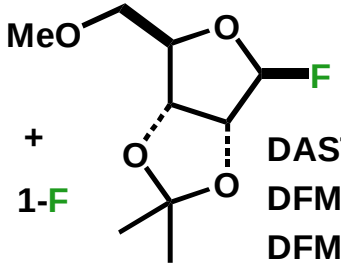
DFMBA
(Mitsubishi Gas Chemical Co. Inc.)
Exothermic starting point 180°C

W. Dmowski and M. Kaminski, *J. Fluorine Chem.*, 1983, *23*, 219.
S. Hara *et al.*, *Tetrahedron Lett.*, 2004, *45*, 1287.
Microwave compatible



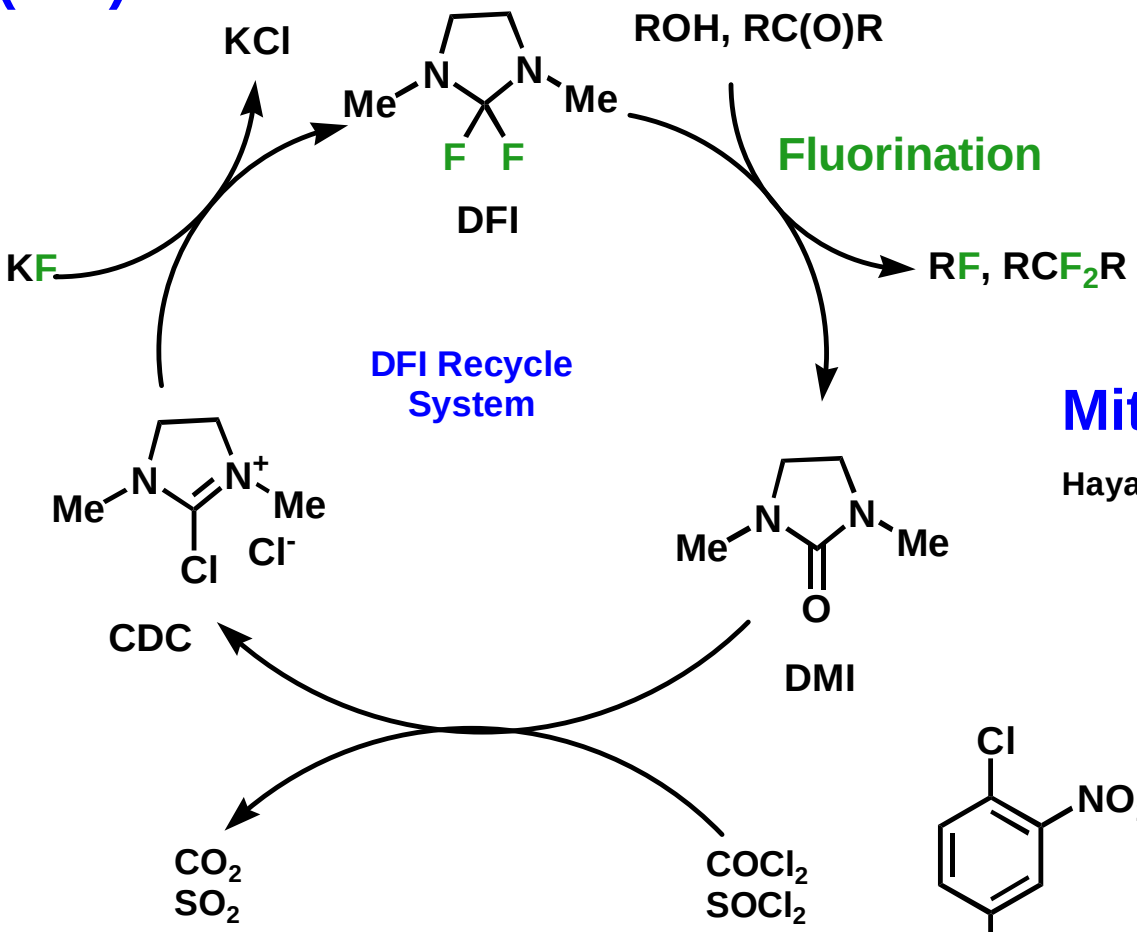
DFMBA, 150°C, 72 hours, 20% conversion
DFMBA, heptane, reflux, μW, 20 mins, 72%





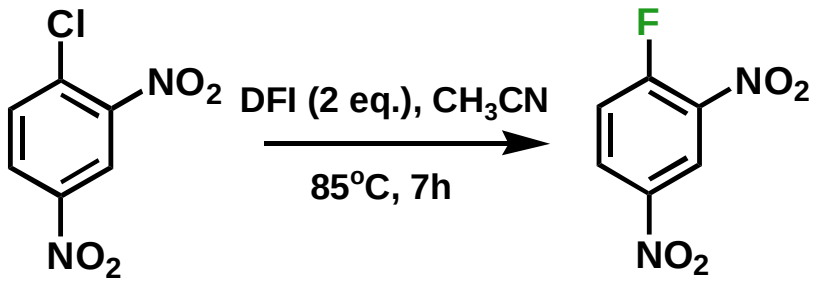
DAST delivers 1-F only!
DFMBA, heptane, reflux, μW, 5-F 51%, 1-F 20%
DFMBA/KF, dioxane, 100°C, 5-F 67%

A New Fluorinating Agent: 2,2-difluoro-1,3-dimethylimidazolidine (DFI)



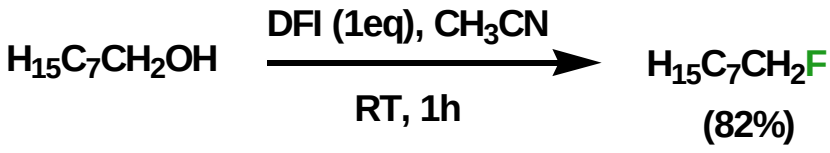
Mitsui Chemicals, Inc

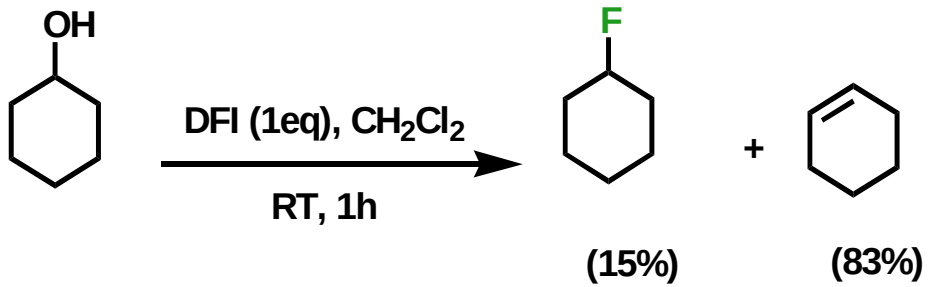
Hayashi, *Chem. Commun*., 2002, 1619.

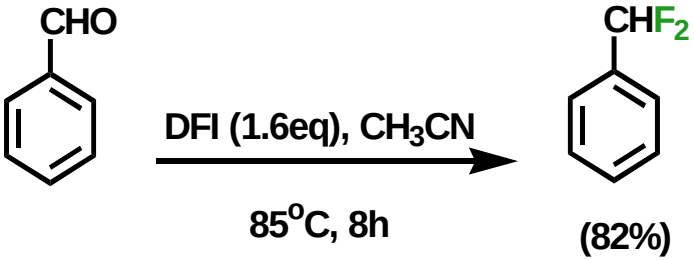


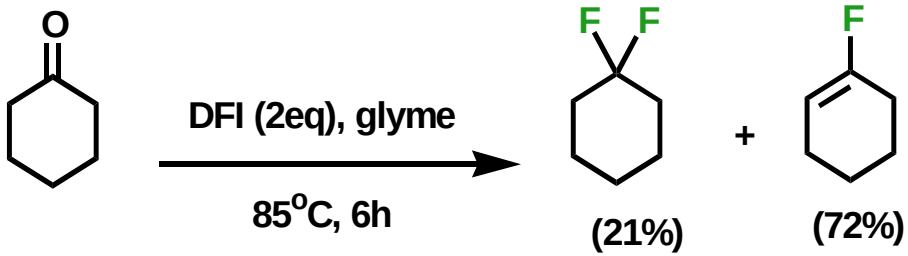
(96%)

Transformations with DFI...









Alkene + HF increases difluoride yield

Hayashi, *Chem. Commun.*, 2002, 1619.

Electrophilic Fluorinating Agents...

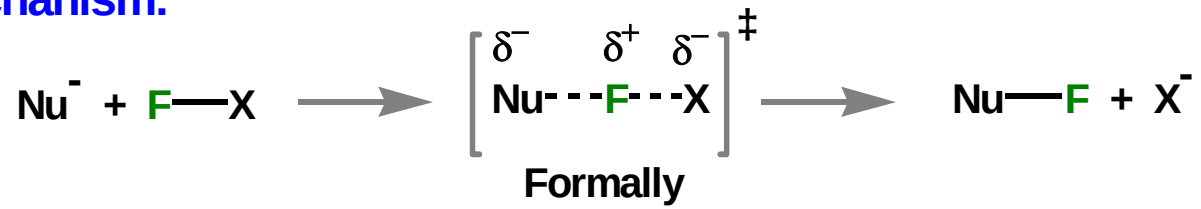
Based on X - F moiety

X is a highly electronegative atom or group

Synthesised using F_2

F_2 is the simplest most cost effective reagent.

General Mechanism:

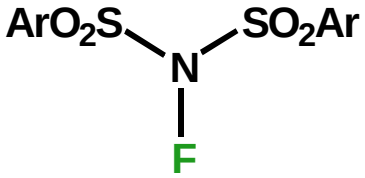


Hypofluorites

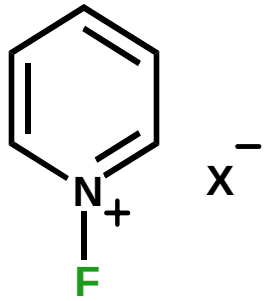
$FClO_3$
$AcOF$
CF_3CO_2F
CF_3OF
$CsSO_4F$

$MeOF$ Not fluorine electrophiles
HOF

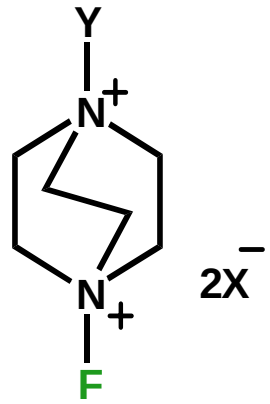
Fluoraza reagents



Neutral



Monocationic



Dicationic

Elemental Fluorine...

Pale, greenish-yellow gas (bp -188 ^{o}C)

Generated by electrolysis of KF.2HF

Very reactive, strong oxidising agent

Low solubility - reactions proceed at liquid- gas interface;

Low bond dissociation energy of fluorine (BDE, F-F 157.7 kJ mol^{-1}) *cf* strong C-F bond (BDE, 452-531 kJ mol^{-1})

Highly exothermic reactions between organic componds and fluorine

High reactivity controlled by:

Dilution with inert gases, i.e. 5-10% F_2/N_2

Low reaction temperatures

Many users insist diluted F_2/N_2 or F_2/He *is no more hazardous than Cl_2*

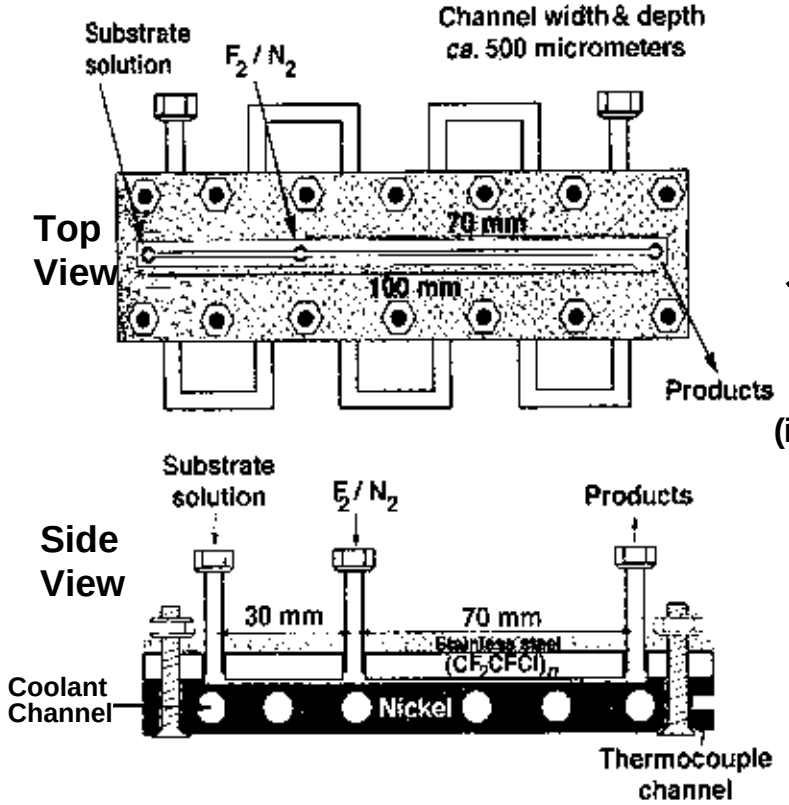
Microreactors for elemental fluorinations

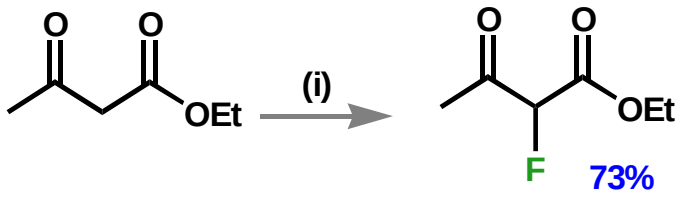
Advantages: i) small amount of fluorine

ii) excellent gas/liquid mixing via cylindrical flow

iii) excellent heat exchange and temperature control

iv) straightforward scale-up

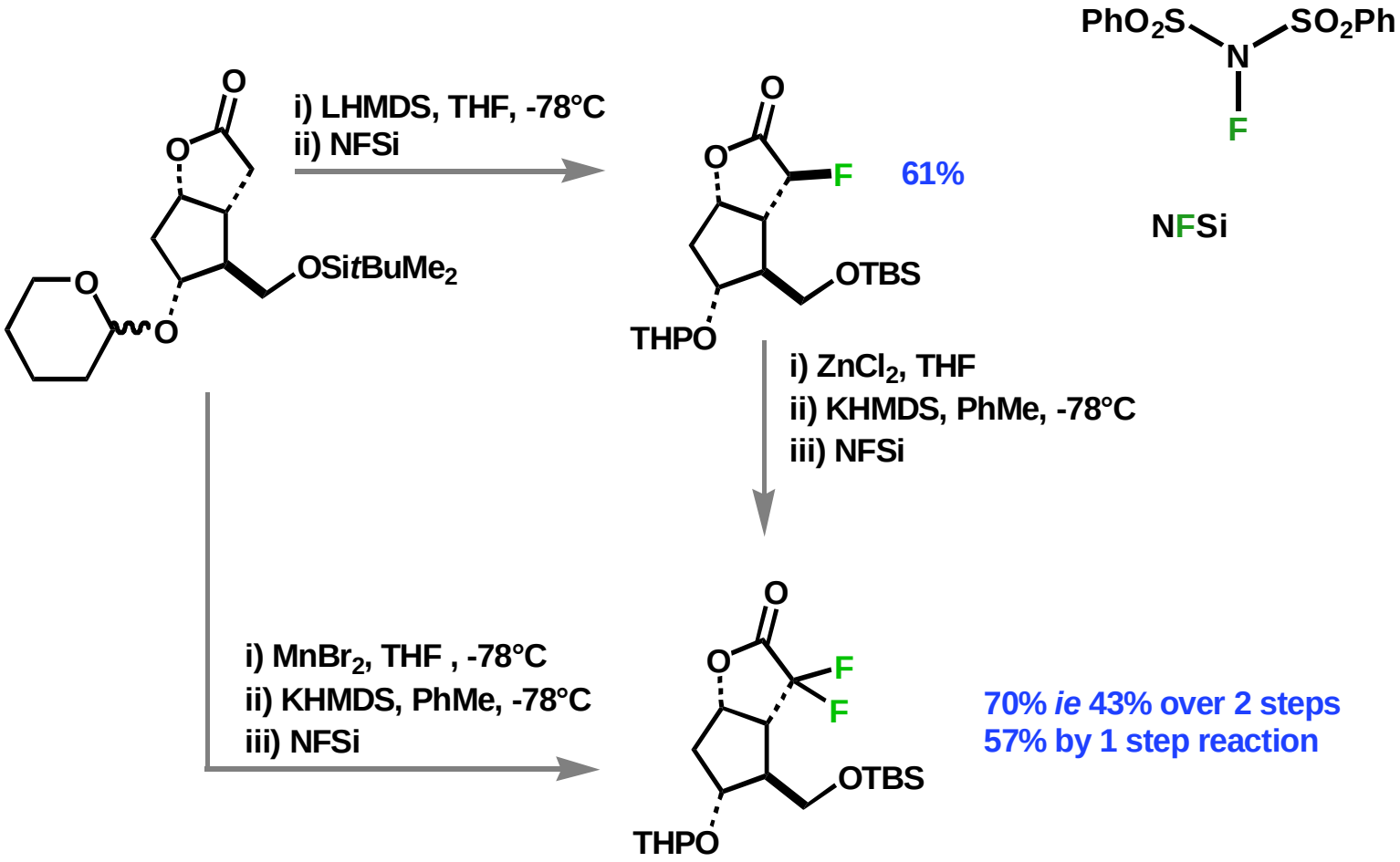




(i) 10% F_2/N_2 (10 ml min^{-1}), 5°C, HCO_2H(0.5 ml h^{-1})

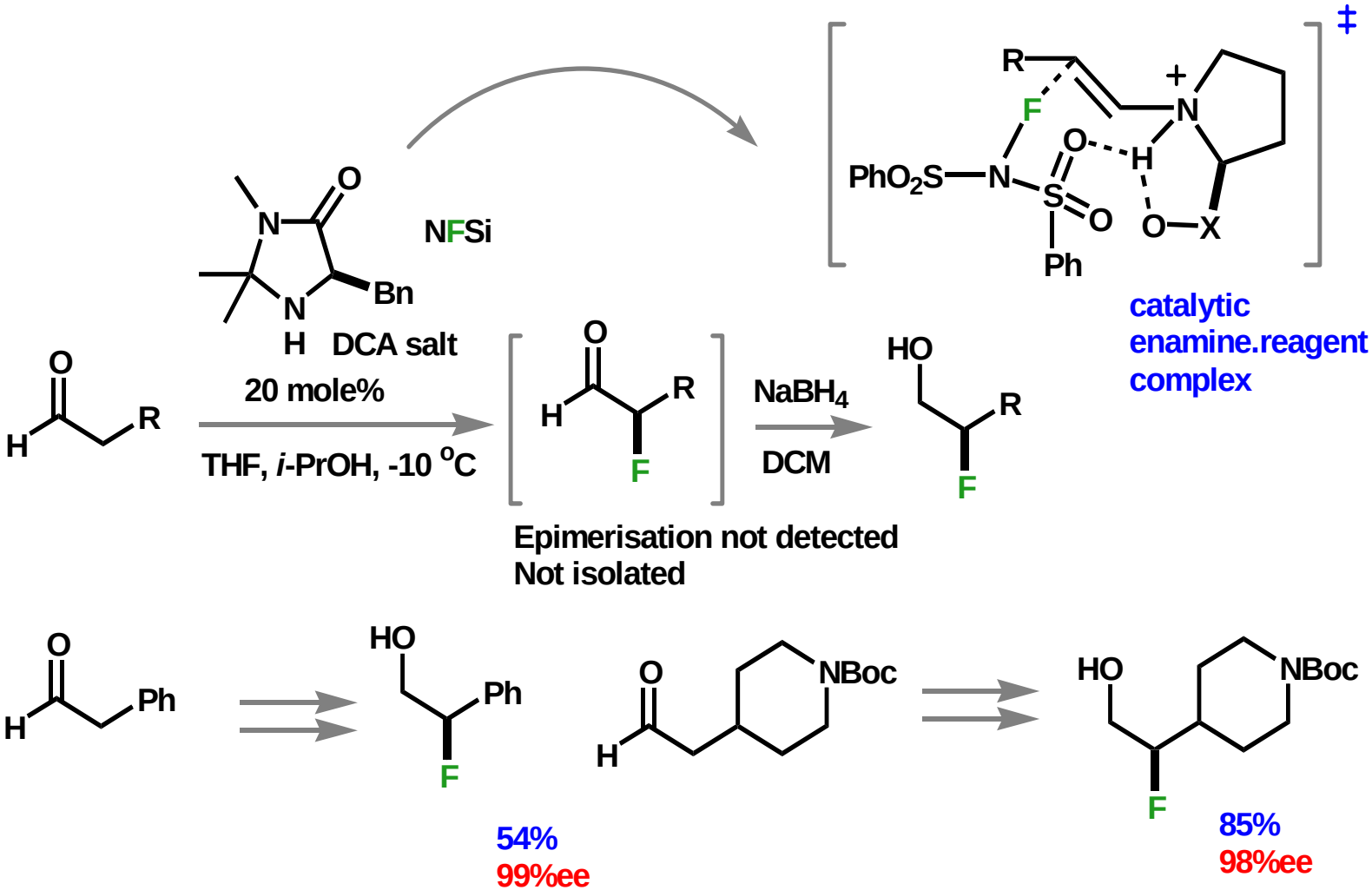
Chambers, *J. Chem. Soc., Chem. Commum.*, 1999, 883.

Lactone Fluorination: Role of the Metal...



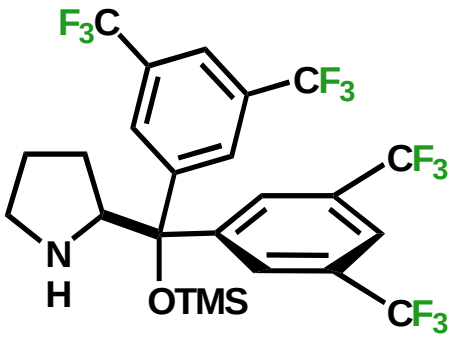
Matsumura, *Angew. Chem., Int. Ed. Engl*., 1996, *35*, 1019-1021.

Organocatalytic Enantioselective Fluorination...



D. W. C. MacMillan, J. Am. Chem. Soc., 2005, *127*, 8826.

Other Organocatalytic Aldehyde Fluorinations...



Jørgensen

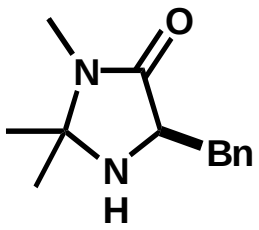
1 mol% cat.

MTBE, rt

8 linear aldehydes

55-95%

91-97%ee (*S*)



Barbas

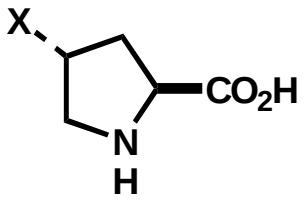
30-100 mol% cat.

DMF, 4 ^{o}C

6 linear aldehydes

40-90%

86-96%ee (*S*)



Enders

30 mol% cat.

MeCN, 0 ^{o}C *eg*. X = OH

4 linear aldehydes

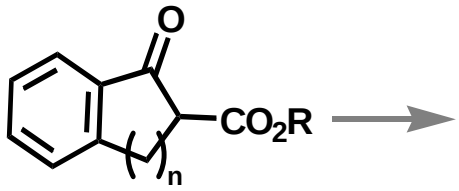
60-75%

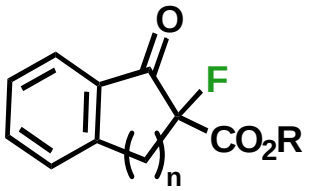
low ee

(1.5 eq. F-TEDA used)

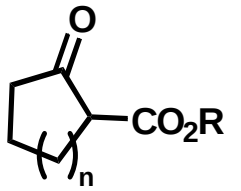
D. Enders, *Synlett*, 2005, 991; K. A. Jørgensen, *Angew. Chem. Int. Ed*., 2005, *44*, 3703; C. F. Barbas III, *ibid*, 3706.; see also P. M. Pihko, *ibid*, 2006, *45*, 544.

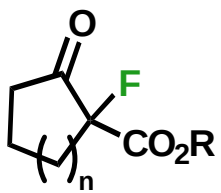
Shibata/Toru Ni(II)-Catalysed Fluorination...





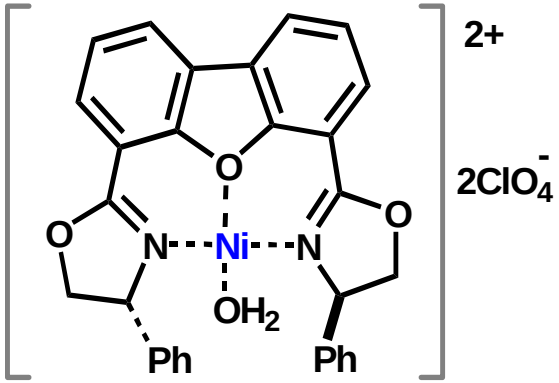
4 examples
n = 1 or 2
66-93%
95-99% ee



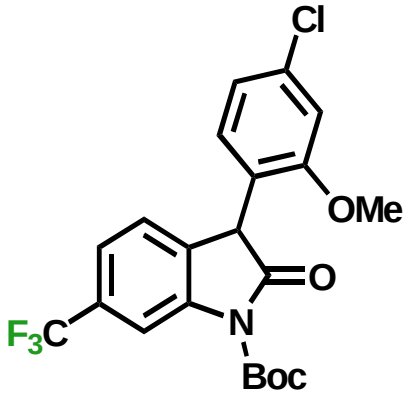


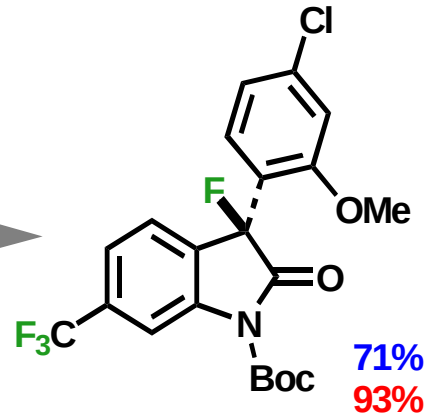
2 examples
n = 1 or 2
84, 64%
93, 99% ee

dbfox-Ph
ligand

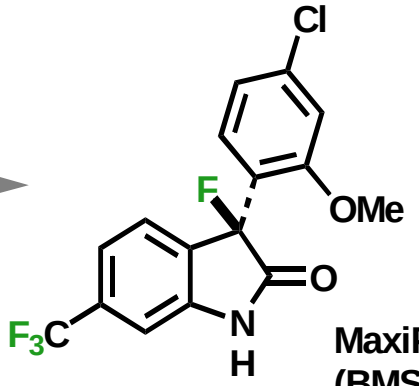


Conditions: 2-10 mol% cat.
NFSi (1.2 eq.), DCM, rt
4Å sieves





71%
93% ee

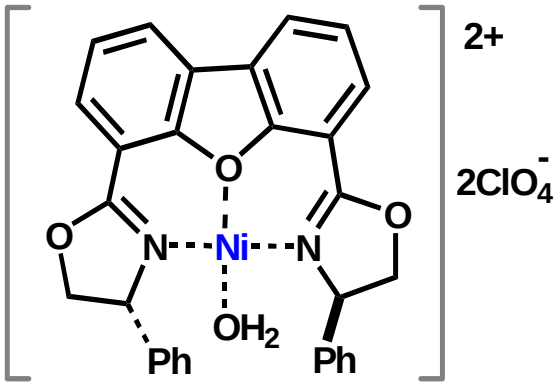


MaxiPost
(BMS-204352)

N. Shibata, *Angew. Chem. Int. Ed.*, 2005, *44*, 4204.

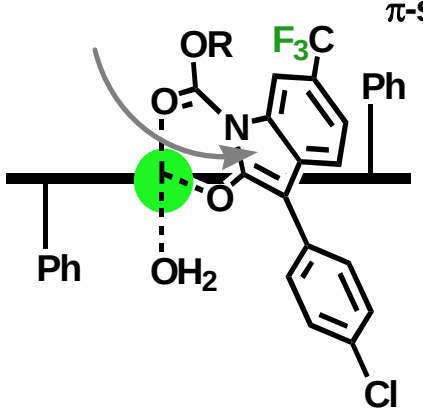
Shibata/Toru Ni(II)-Catalysed Fluorination...

dbfox-Ph ligand



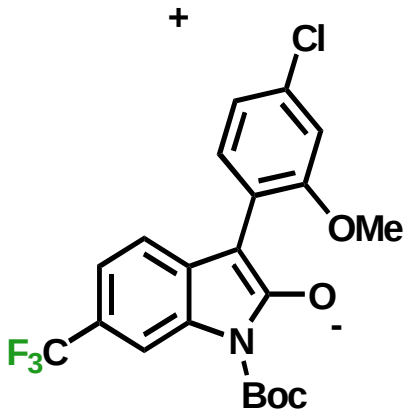
this face open for NFSi to approach

π-systems aligned



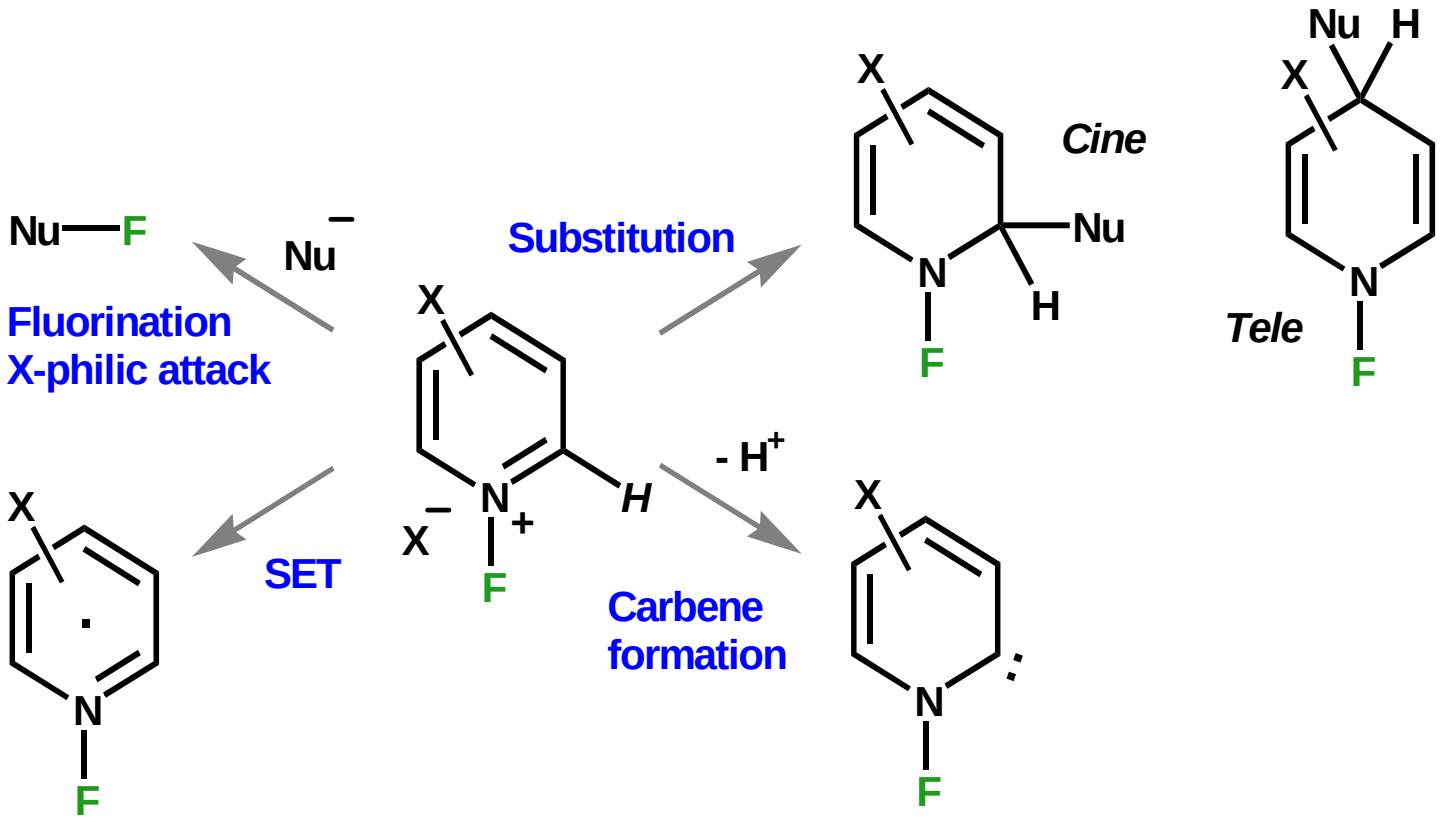
Octahedral Ni(II)

Cu(II) square pyramidal geometry changes the sense of enantioselection



Two-point binding ligand

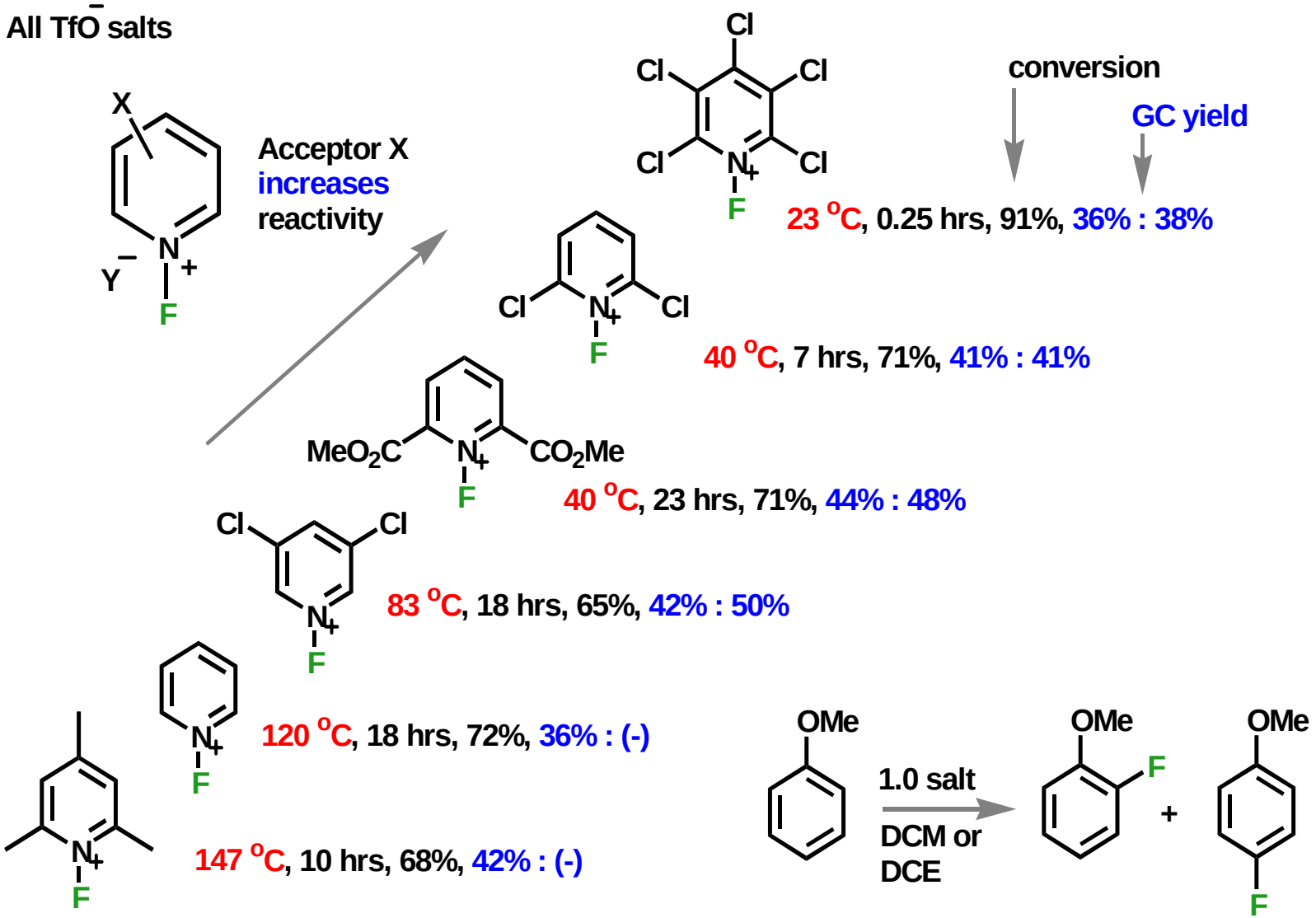
General Properties of *N*-Fluoropyridinium Salts...



X modulates this manifold of reactions

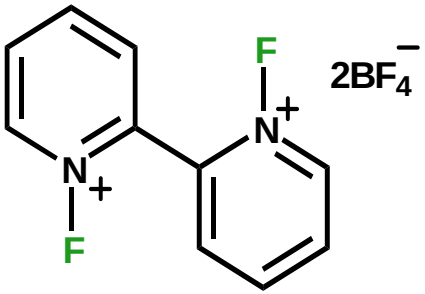
A. S. Kiselyov, *Chem. Soc., Rev.*, 2005, *34*, 1031.

N-Fluoropyridinium Salts for Fluorination...



T. Umemoto *et al*., *J. Am. Chem. Soc*., 1990, *112*, 8563.

N,N'-DiFluorobipyridinium Salts for Fluorination...

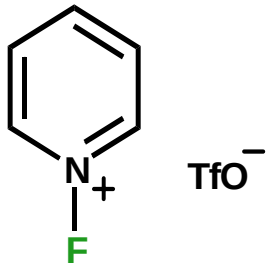


MEC-31

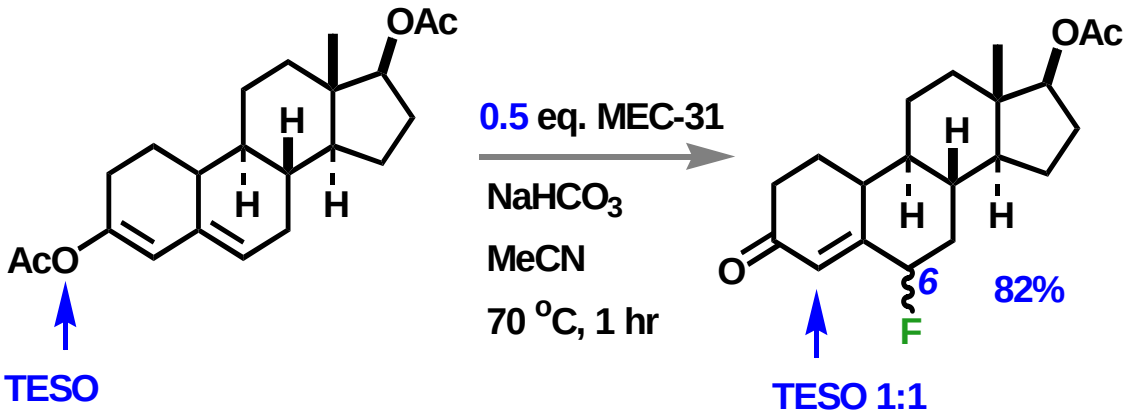
High F content

103 g Kg^{-1}

Bipy salt reacts with:
active methylenes
phenols
resorcinol
anisole
phenylurethane
tetralone
vinyl acetates
silyl enol ethers

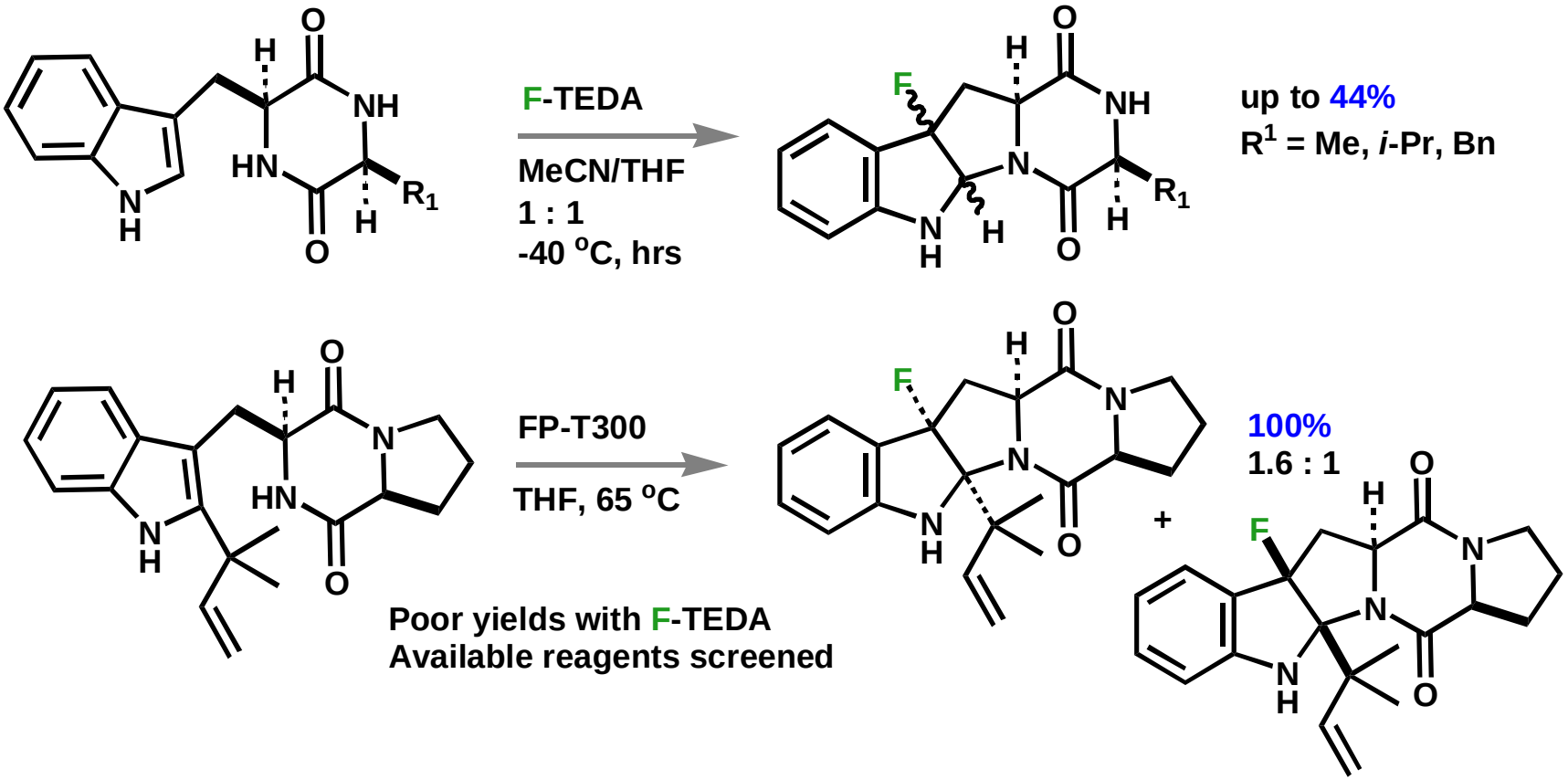


Similar content
Less reactive



T. Umemoto *et al*., *J. Am. Chem. Soc*., 1998, *63*, 3379.

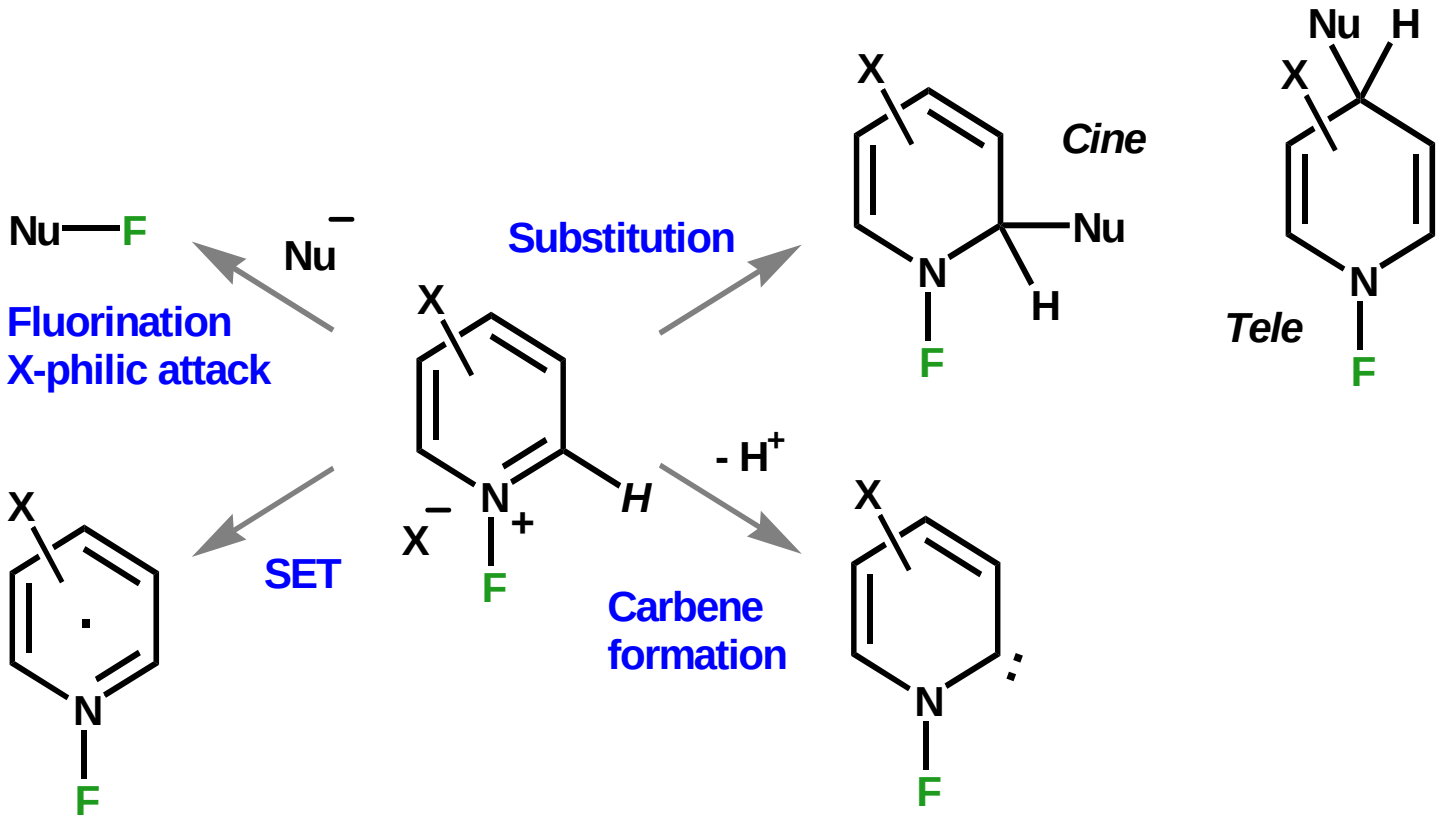
Cyclisation Triggered by Electrophilic Fluorination...



N. Shibata *et al*., *Angew. Chem. Int. Ed*., 2001, *40*, 4461.

cf brevianamide E

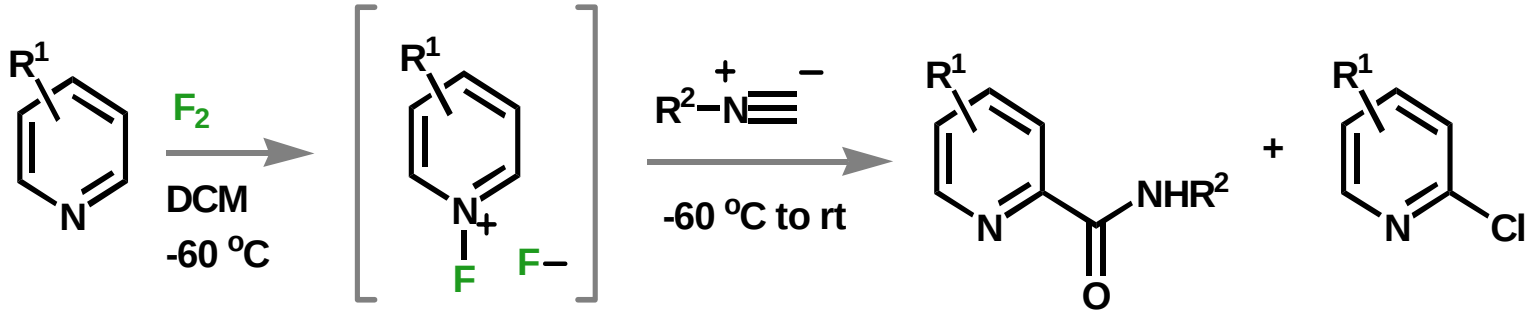
General Properties of *N*-Fluoropyridinium Salts...



X modulates this manifold of reactions

A. S. Kiselyov, *Chem. Soc., Rev.*, 2005, *34*, 1031.

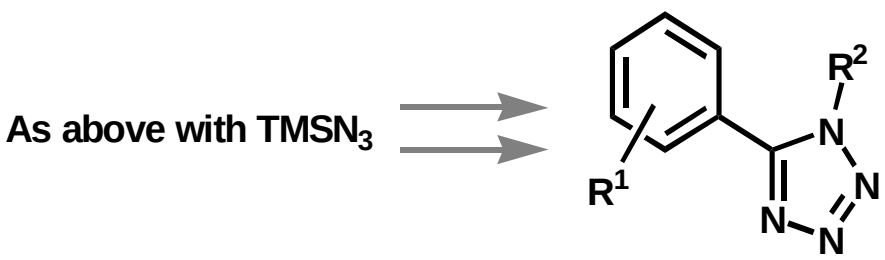
Carbenes from *N*-Fluoropyridinium Salts...

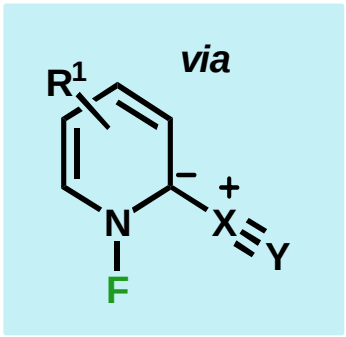


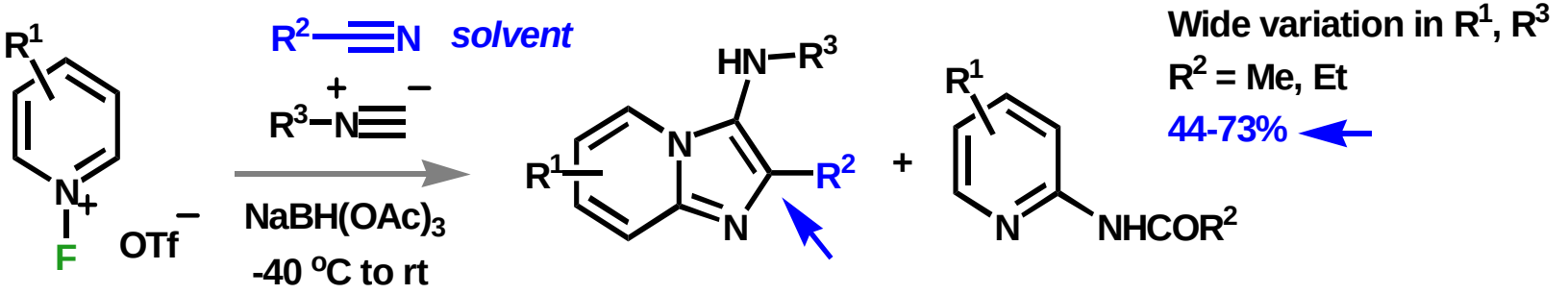
R^1 = H, 2-Me, 3-Me, 4-Me, 2-Cl, 4-Cl, 2-OMe, 2-Ph, 2-CO_2Me

R^2 = *n*-Bu, *t*-Bu, C_6H_{11}, CH_2CO_2Et, Bn, $PhNO_2$

Ester 31-71%, chloride 40-11%







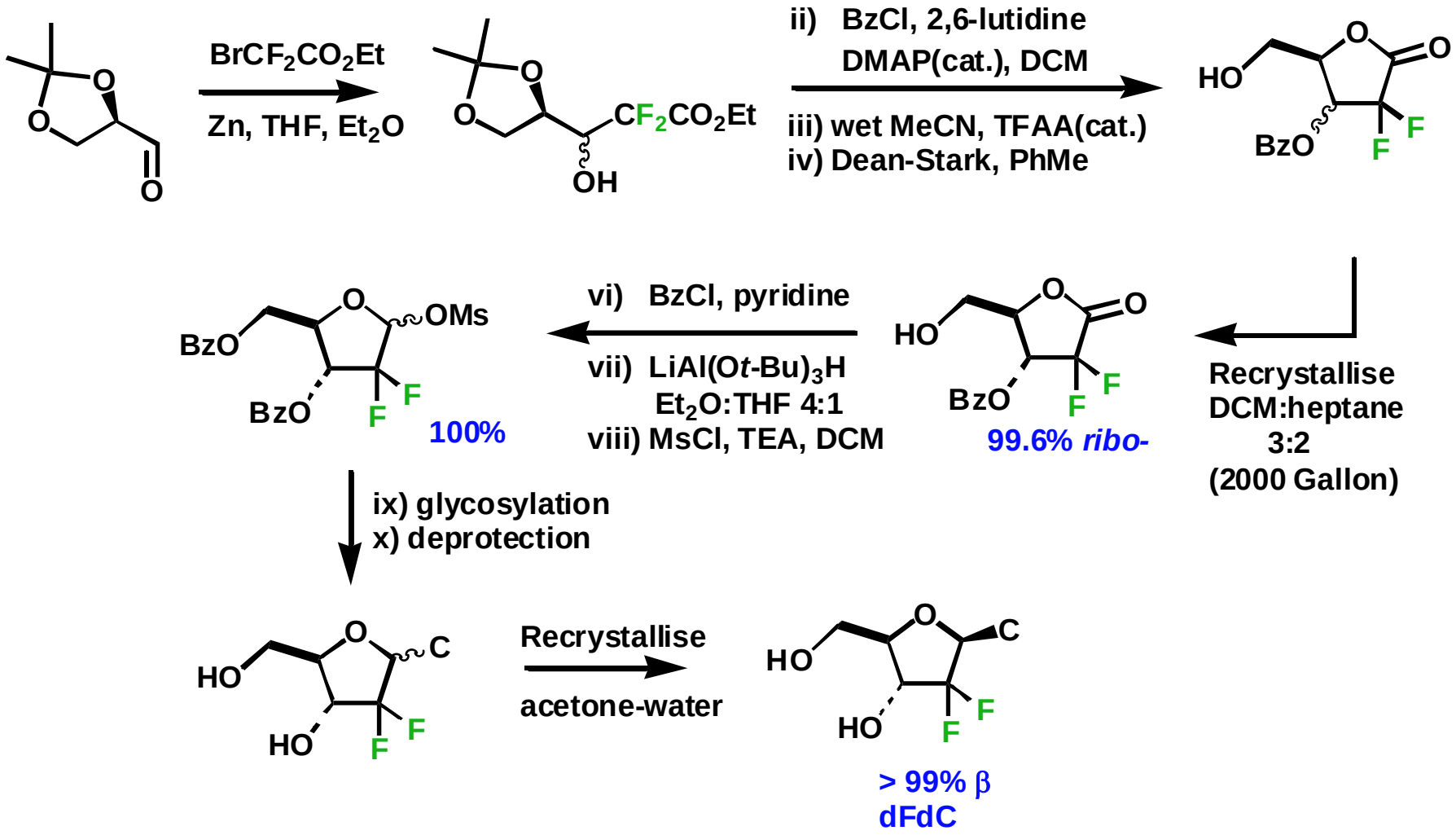
Wide variation in R^1, R^3

R^2 = Me, Et

44-73%

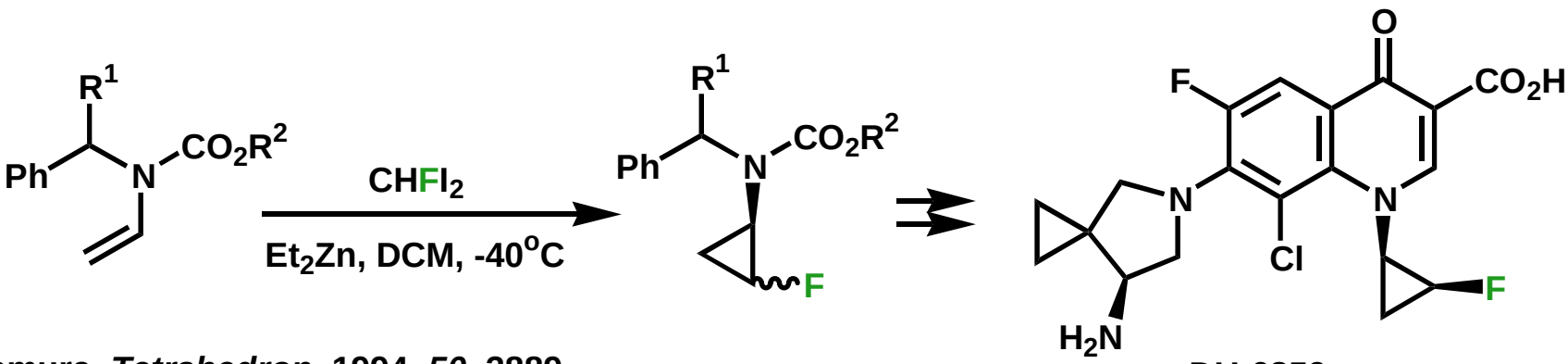
A. S. Kiselyov, *Tetrahedron Lett.*, 2005, *46*, 2279; *ibid*, 4852, 4487.

Gemcitabine (dFdC) by the Kilogramme: A Building Block Approach...



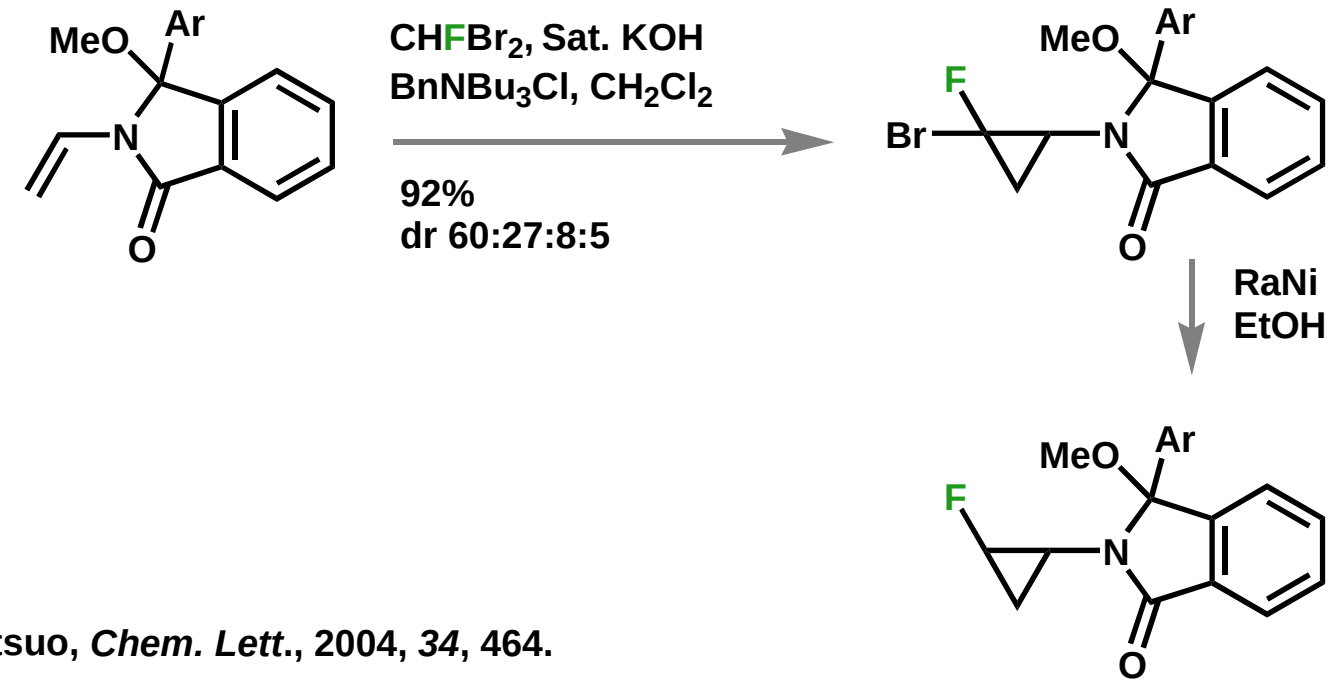
T.S. Chou *et al.*, *Synthesis*, 1992, 565-568.

Fluorocyclopropane Synthesis...



Tamura, *Tetrahedron*, 1994, *50*, 3889.

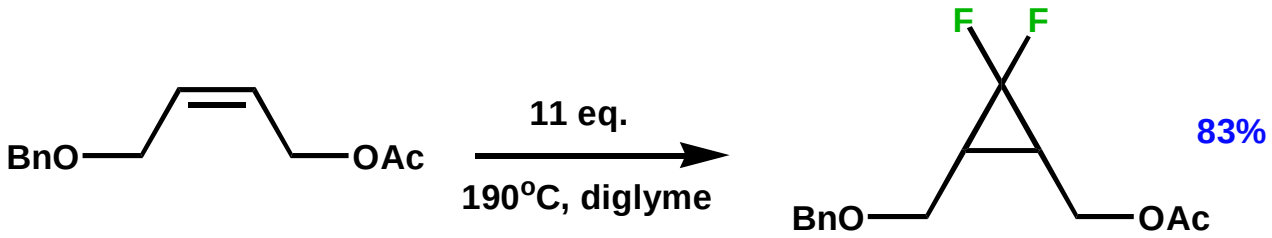
DU-6859



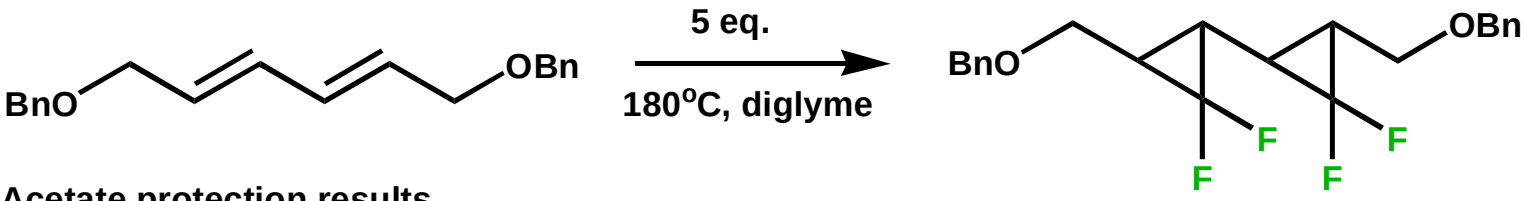
Matsuo, *Chem. Lett.*, 2004, *34*, 464.

Low-cost Difluorocyclopropanation...

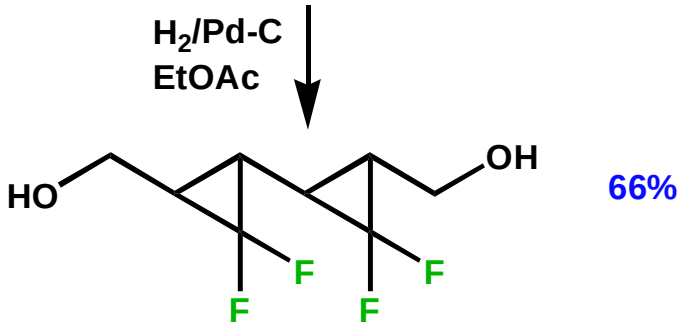
$ClCF_2CO_2Na$ is a cheap (though inefficient) source of difluorocarbene



Csuk, *Tetrahedron*, 1998, *64*, 6445.



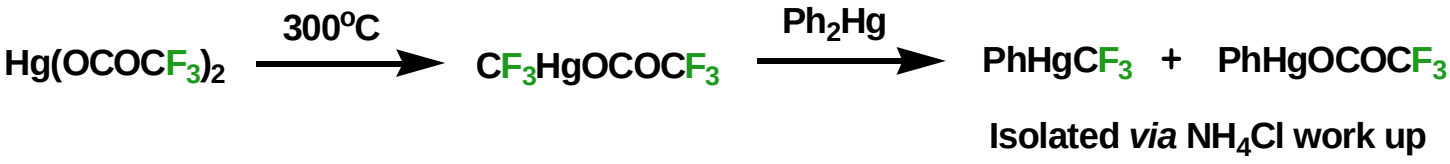
Acetate protection results in much lower yields

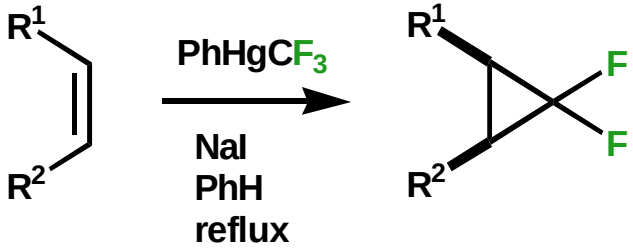


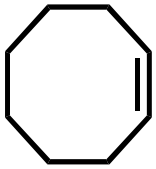
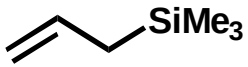
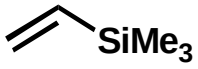
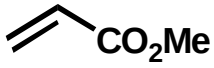
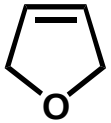
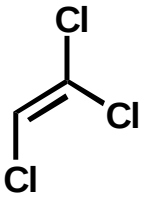
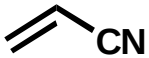
Itoh, *Tetrahedron Lett.*, 1999, *40*, 5739-5742.

***trans, trans* as *meso*,dl mixture**

The Most Reactive Reagent for Difluorocarbene Transfer...

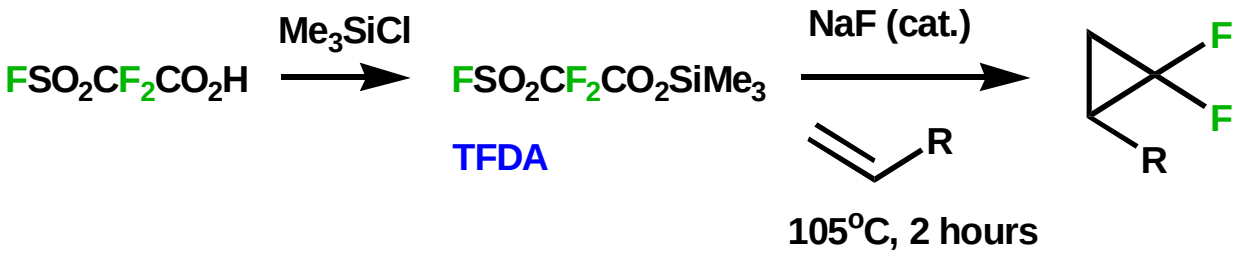


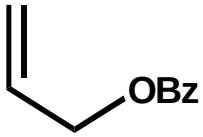


Substrate	Yield of cyclopropane							
	83%		100%		53%		84%
	70%		67%		72%		26%

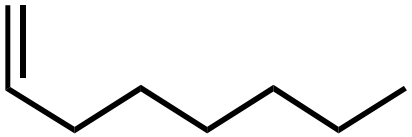
D. Seyferth and S. P. Hopper, *J. Org. Chem.*,1972,*37*, 4070.

The Most Reactive Practical Reagent for Difluorocyclopropanation...

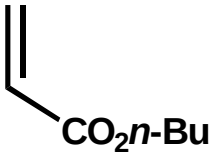




78%



74% $PhCO_2Me$ added (0.5 eq.)

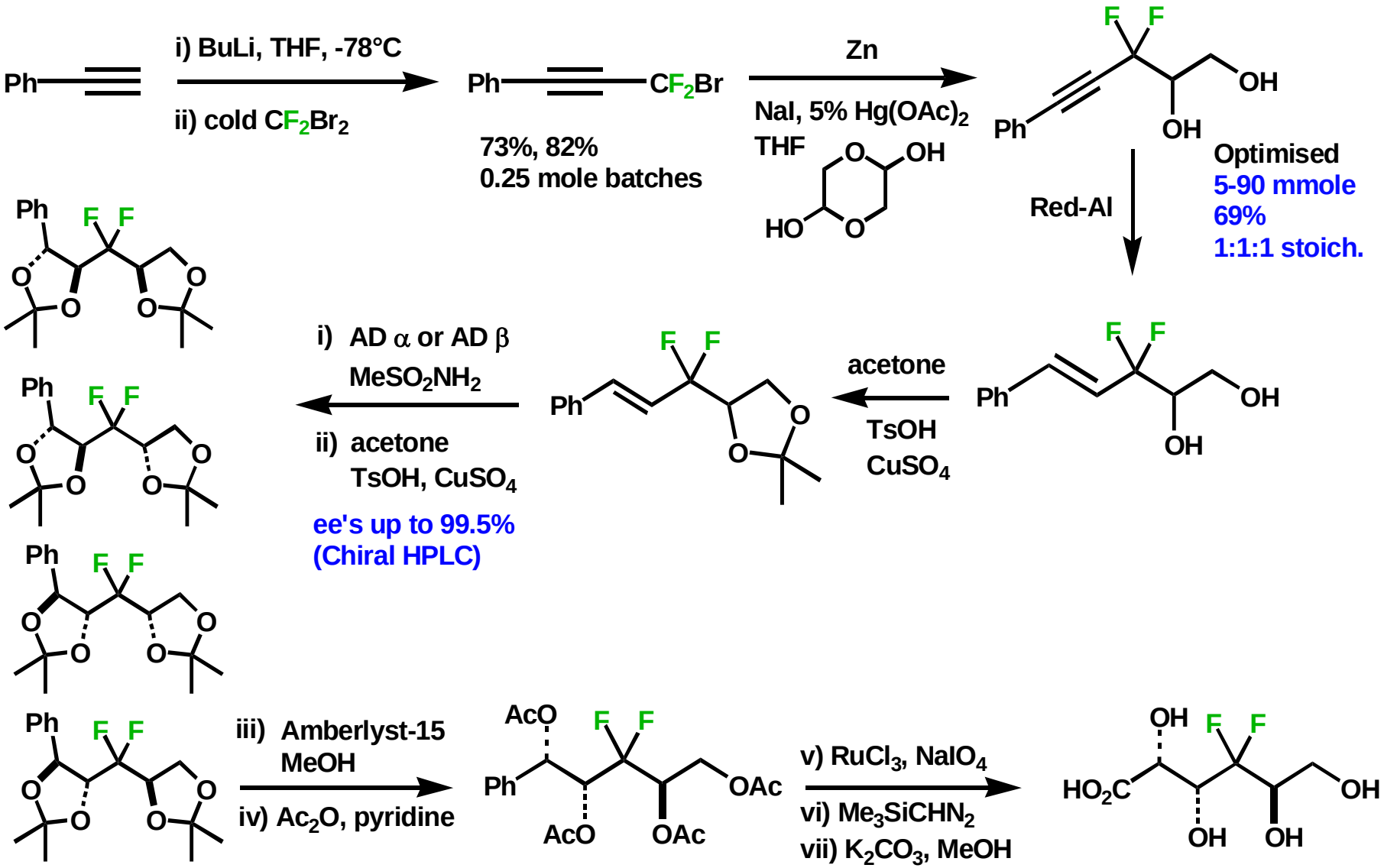


73% $PhCO_2Me$ added (2.0 eq.)

All other methods fail for such deactivated substrates

Dolbier, *Org. Lett.*, 2000, *2*, 563-564.

An Asymmetric Route to Difluorinated Aldonic Acids...



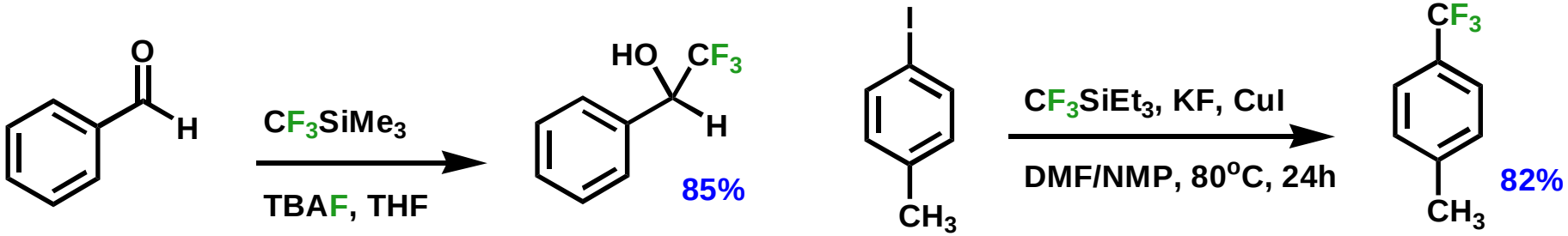
C. Audouard *et al*.,*Chem. Commun*., 2004, 1526.

Alternative Reagents for Trifluoromethylation...

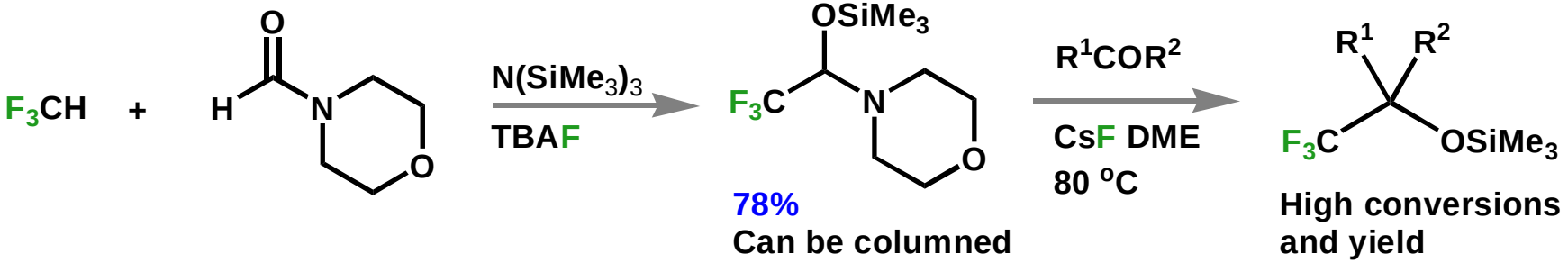
F_3CSiMe_3
Wide and useful chemistry
Transfers trifluoromethyl group
Ruppert's Reagent

⇨

F_3CBr
Ecotoxic

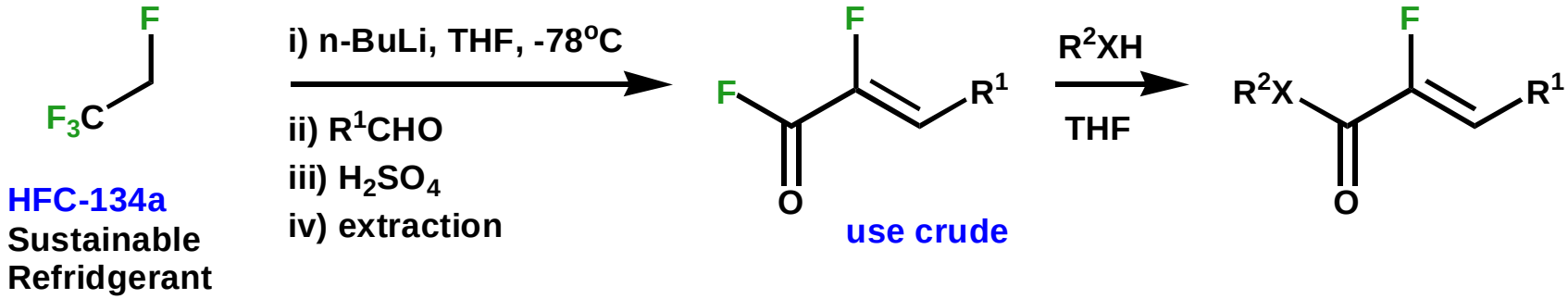


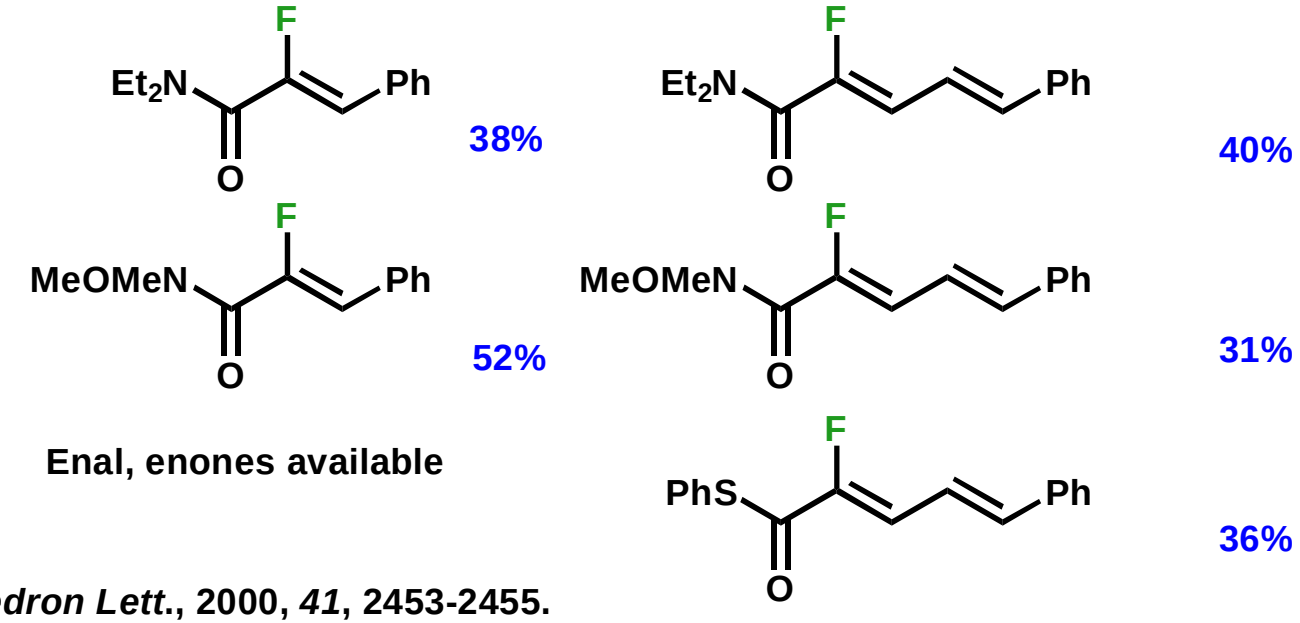
F_3CH
Sustainable



B. Langlois, *J. Org. Chem*., 2000, *65*, 8848.

α-Fluoro-α,β-Unsaturated Carbonyl Derivatives...

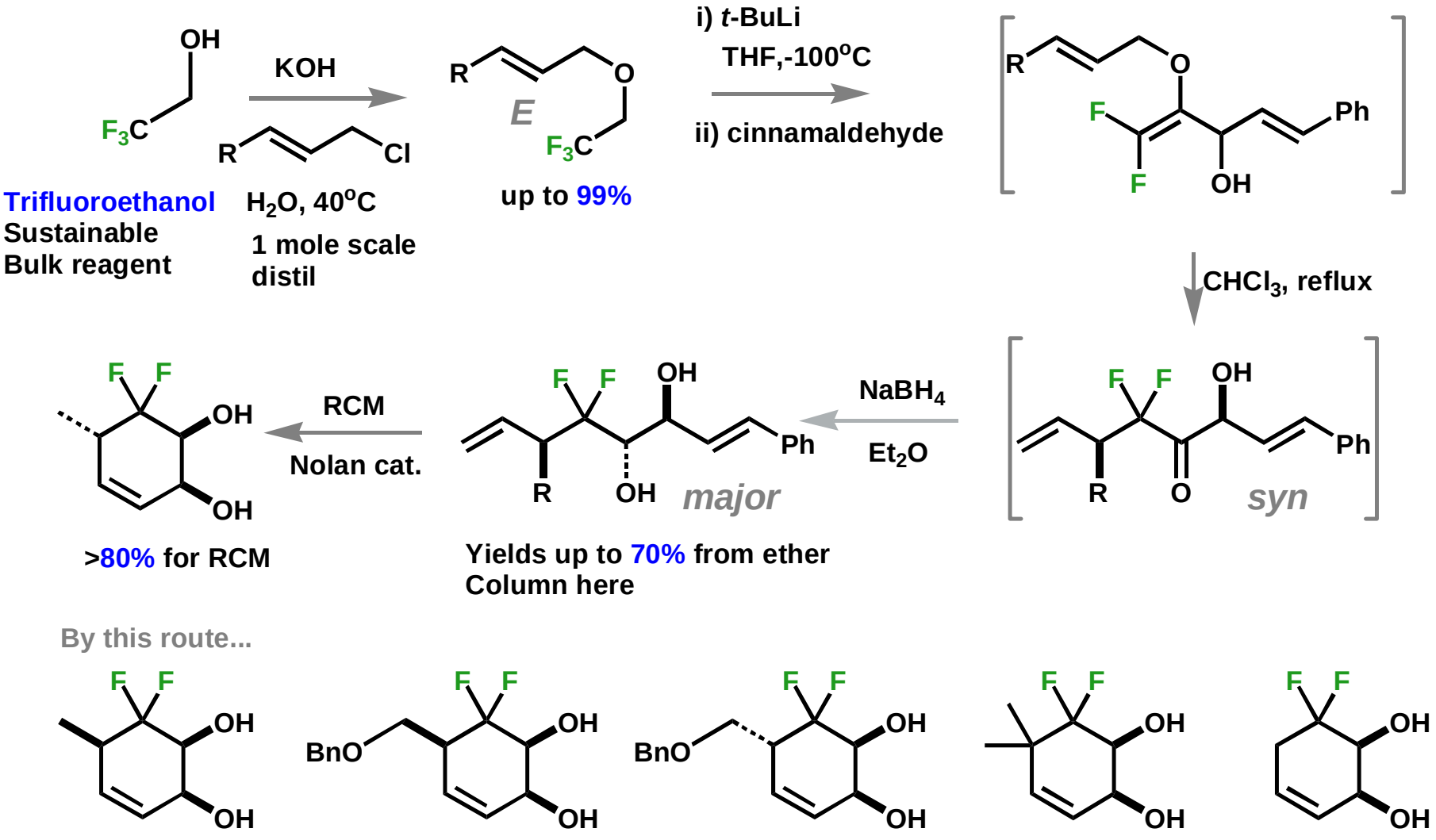




Enal, enones available

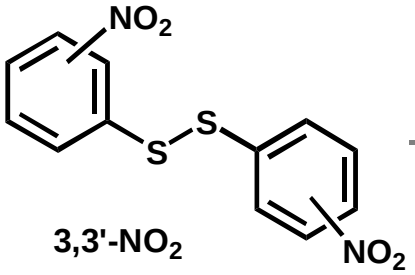
Kanai, *Tetrahedron Lett.*, 2000, *41*, 2453-2455.

Rapid Synthesis of Complex Molecules from Trifluoroethanol...



C. A. Audouard *et al.*, *Org. Lett.*, 2004, *6*, 4269.

Introducing the -SF_5 Group...



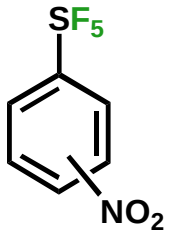
3,3'-NO_2

or 4,4'-NO_2

10% F_2/N_2

MeCN

-5°C, 6-24hrs.

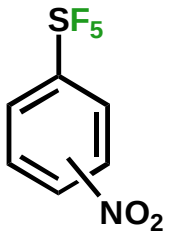


3-NO_2 39%

4-NO_2 41%

Fluorination of 2-NO_2 stops at -SF_3 stage (hindrance)

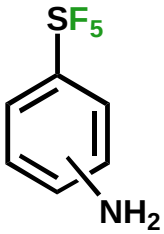
Subsequent reactions...



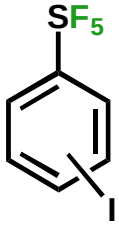
H_2/Pd-C

EtOH, rt

3-72hrs



i, ii



i. $NaNO_2$, HCl, H_2O, 0°C.

ii KI, H_2O, 0°C.

3-NH_2 70%

4-NH_2 48%

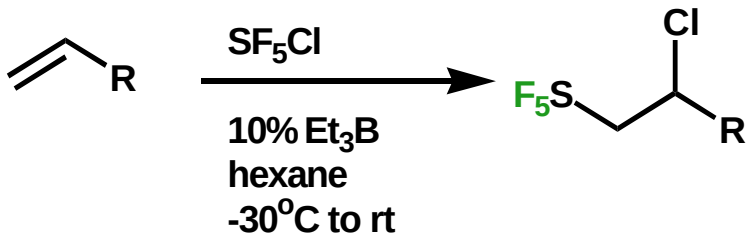
3-I 63%

4-I 50%

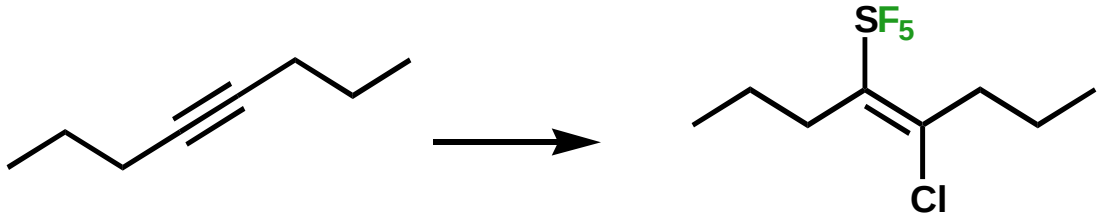
Iodide used in Heck, Suzuki, Stille, Sonogashira couplings

Originally, Sheppard, *J. Am. Chem. Soc.*, 1962, *84*, 3064.
More recently, Bowden, *Tetrahedron*, 2000, *56*, 3399-3408. See also G. L. Gard *et al*, *J. Fluorine Chem.*, 2004, *125*, 549; W. R. Dolbier *et al*., *Org. Lett*., 2004, 6, 2417; P. J. Crowley *et al*, *Chimia*, 2004, *58*, 138.

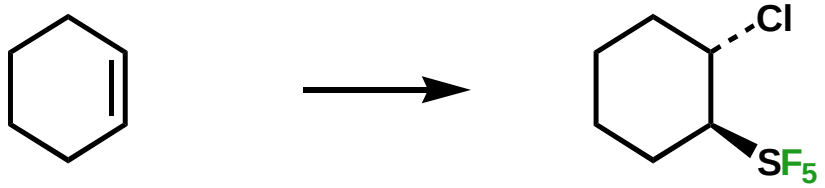
Alkyl -SF_5 Derivatives *via* Free Radical Chemistry...



R	% yield (adduct)
n-hex	95
t-Bu	96
Et	89
p-tol	79



93%

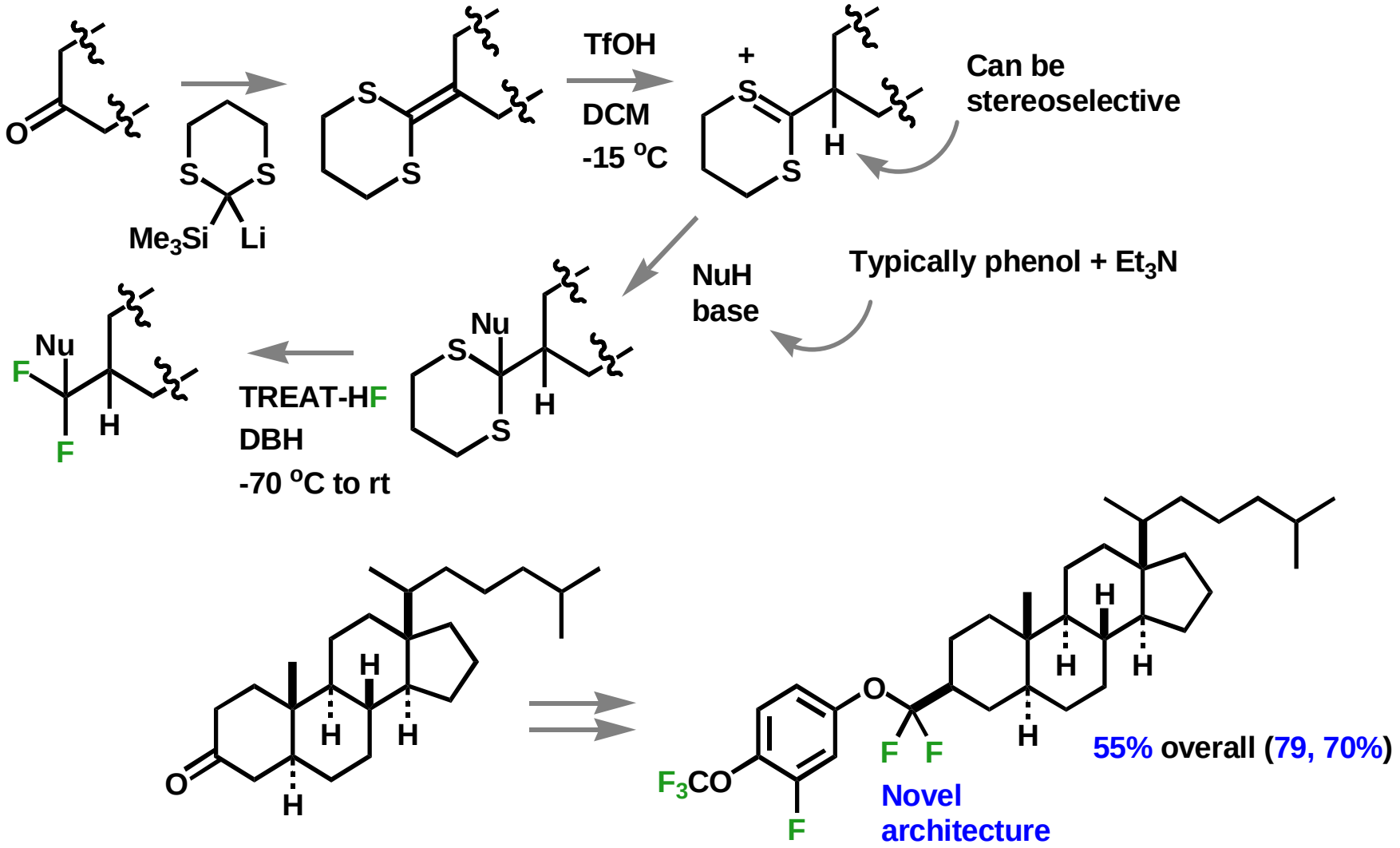


98%

Facile procedure

Dolbier, *Org. Lett.*, 2002, *4*, 3013-3015

Merck Route to the Difluorooxymethylene Bridge...

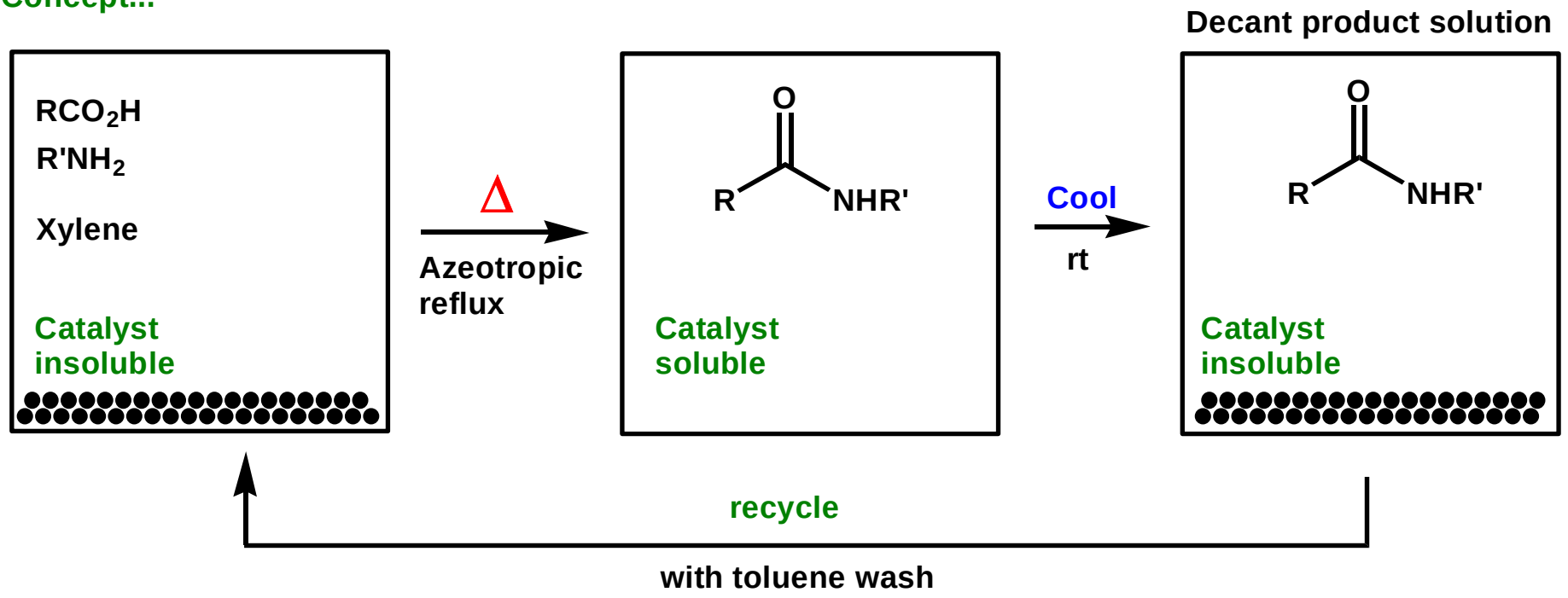


P. Kirsch, *J. Fluorine Chem*., 2006, *127*, 146.

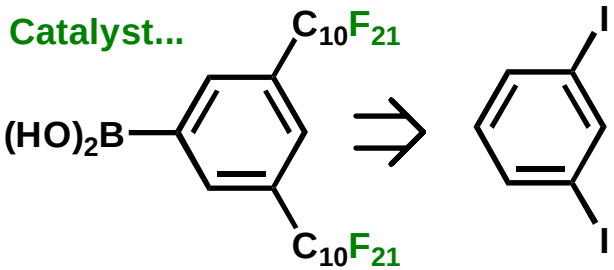
Fluorous Biphasic *Amide Condensation*...

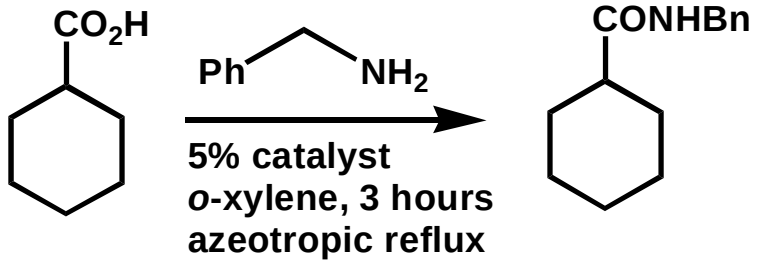
Yamamoto *et al*., *Synlett*, 2001, 1371.

Concept...



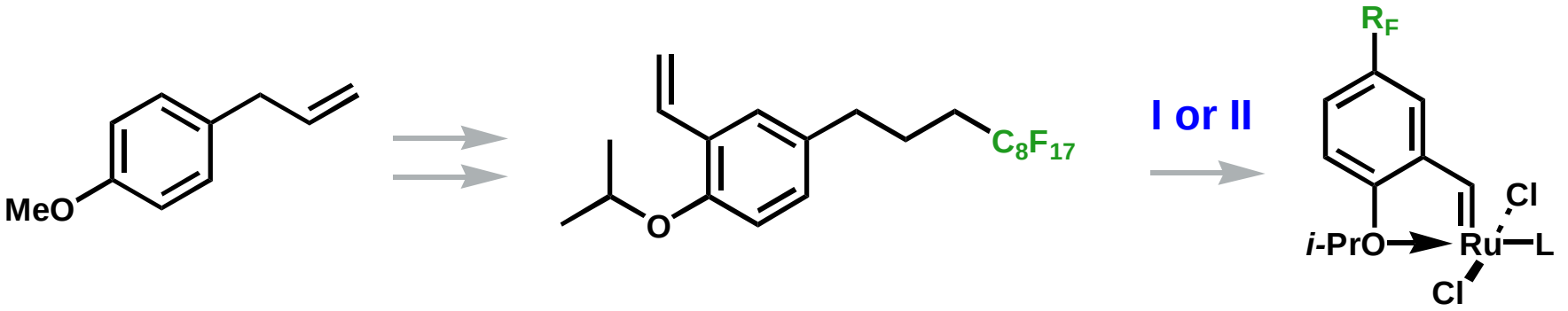
Catalyst...





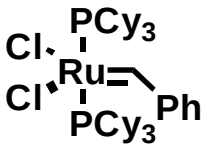
10 times, 96% total isolated yield

Light Fluorous Catalysts for RCM...

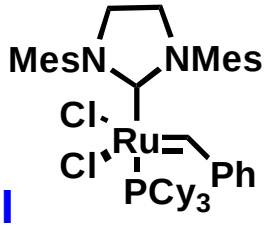


Run in DCM
Highly recycleable at 5% loading
Simple extraction/recovery procedure
Use for RCM or cross metathesis
Can use in solution or supported on fluorous silica

6 reuses possible



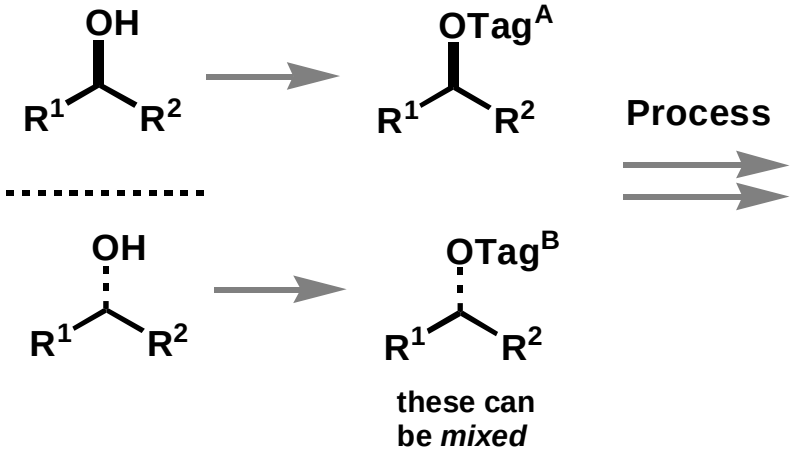
I



II

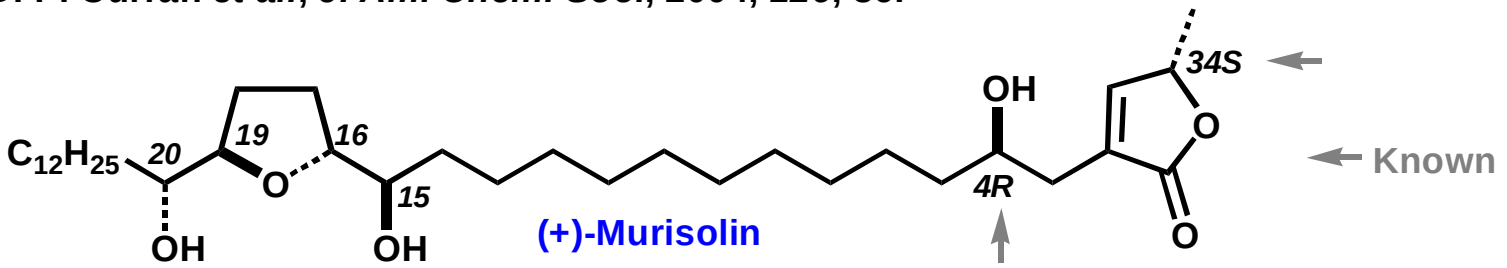
M. Matsugi and D. P. Curran, *J. Org. Chem.*., 2005, *70*, 1636-1642.

Quasiracemic Synthesis...



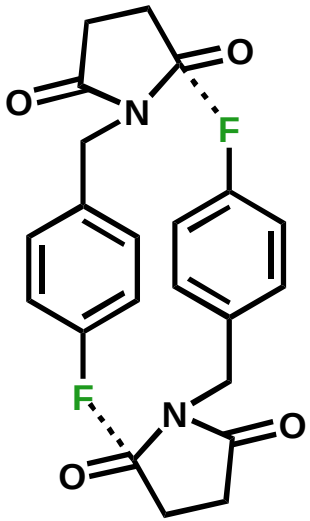
D. P. Curran *et al.*, *J. Am. Chem. Soc.*, 2002, *124*, 5774.

Application in a total synthesis of (+)-Murisolin and 15 stereoisomers
D. P. Curran *et al.*, *J. Am. Chem. Soc.*, 2004, *126*, 36.

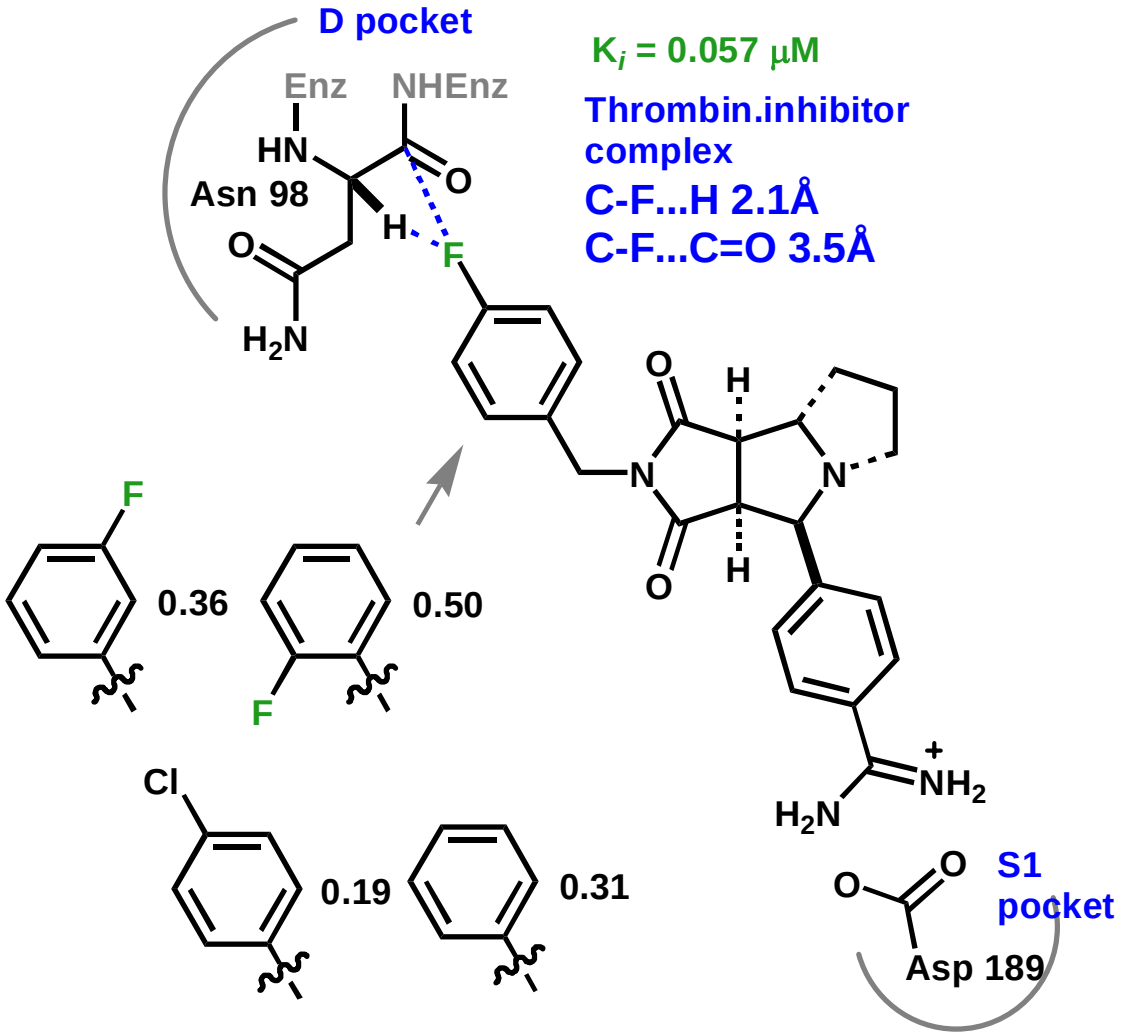


Acetogenin natural product; murisolin cytotoxicities (IC50) as low as 1 fM
Very wide spread depending on stereochemistry, assignment difficult

New C-F...C=O Interactions within Complexes...



From X-ray
F...C 2.94 Å
Closer that sum of
Van der Waals radii

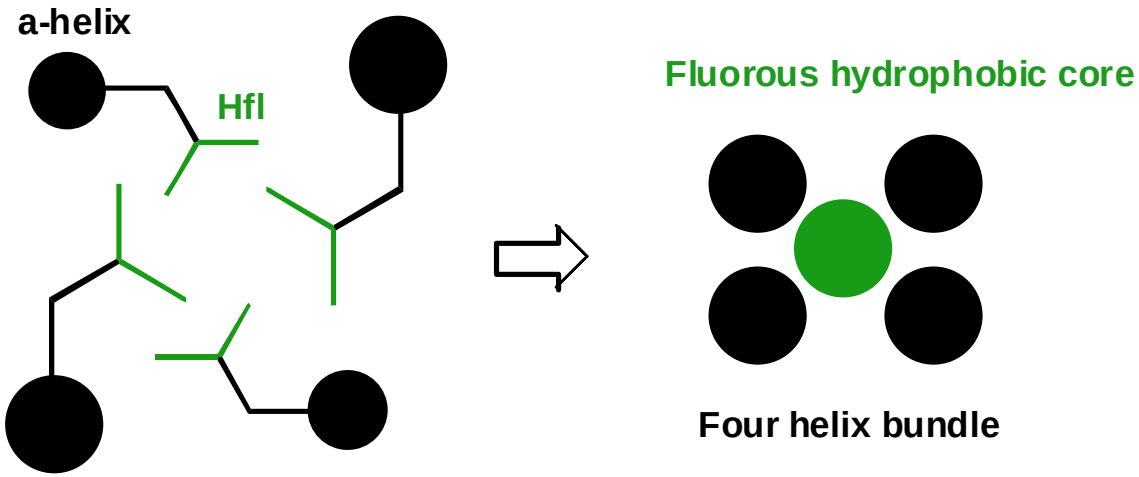


Weak but significant
attractive interactions

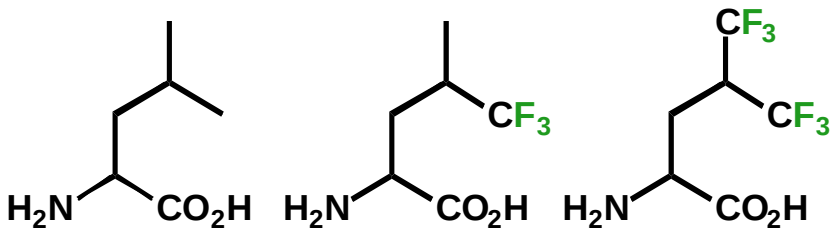
F. Diederich, *ChemBioChem*, 2004, *5*, 666.

Fluorous Proteins...

E. N. G. Marsh, *Chem. Biol*., 2000, *7*, R153-R157.



D. A. Tirrell *et al*., *Biochem*., 2001, *40*, 2790-2796.



R MKQ*L*EDK VEE*L*LSK NYH*L*ENE VAR*L*KKL VGER

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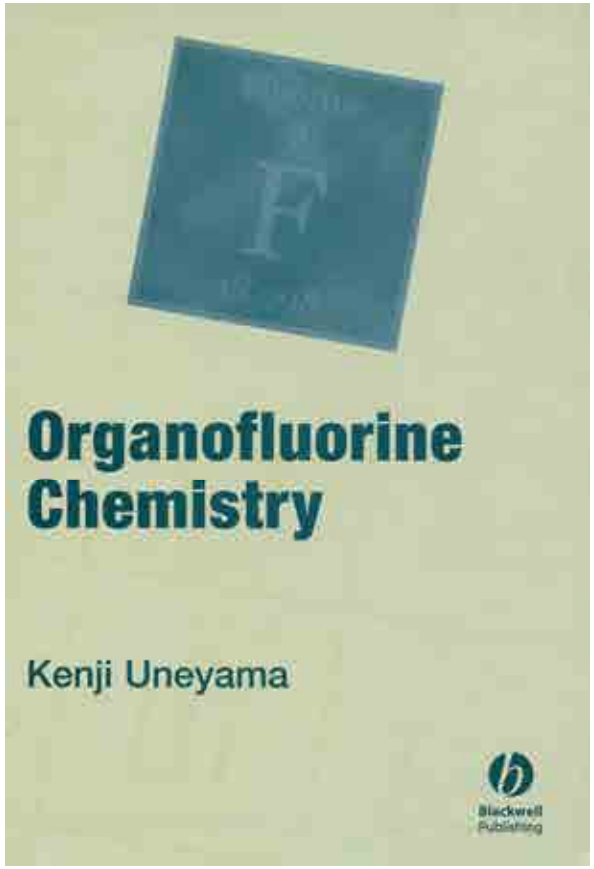

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