Literature Report

Iridium-Catalyzed Enantioselective Fluorination of Racemic Allylic Trichloroacetimidates

Reporter: Mu-Wang Chen
Checker: Xiao-Yong Zhai
Date: 2018-03-19

Jason C. Mixdorf, Alexandre M. Sorlin, Qi Zhang and Hien M. Nguyen
ACS Catal. **2018**, *8,* 790-801.

CV of Hien M. Nguyen

Education:

- 1996 B.S., Tufts University
- 2003 Ph.D., University of Illinois at Urbana-Champaign
- 2004–2006 Postdoc., Stanford University
- 2006–Now Associate professor, Iowa University

Research:

Research in our group focuses on developing new methods and reagents that can potentially solve long standing synthetic problems. In particular, we are interested in exploring transition metals-catalyzed stereoselective formation of C-C, C-O, and C-N bonds. The methods that we have developed will be applied as the key steps toward the synthesis of complex oligosaccharides, amphidinoline N, communesin B, and phorbaside.

Contents

Introduction

元素信息

气体元素 F 原子序数 9 相对原子质量 (^{12}C = 12.0000) 18.9984 质子数：9 中子数：10 周期：2 族数：VIIA 氧化态：Main F^{-1} 晶体结构：简单立方晶胞

原子结构

原子半径/Å: 0.57 原子体积/cm^3/mol: 17.1 共价半径/Å: 0.72 电子构型: $1s^2 2s^2p^5$ 离子半径/Å: 1.33

来 源

以萤石（fluorite，CaF_2）和冰晶石（cryolite，Na_3AlF_6)存在于自然界

用 途

用于生产制冷剂，以及其它氯氟烃类化合物，也用于制造树脂特氟纶(Teflon)

物理性质

状态：黄绿色气体 熔 点(℃): -219.52 沸 点(℃): -188.05 密度(g/L, 273K, 1atm): 1.696 比热/J/gK : 0.82 蒸发热/KJ/mol : 3.2698 熔化热/KJ/mol: 0.2552 导热系数 / W/cmK: 0.000279

地质数据

滞留时间/年: 400 000 太阳(相对于 H=1×10^{12}): 3.63 × 10^{-4}
海水/ p.p.m.: 1.3 地壳/p.p.m.: 950 大西洋表面: 1.0 × 10^{-4}
太平洋表面:1.0 × 10^{-4} 大西洋深处: 0.96 × 10^{-4} 太平洋深处: 0.4 × 10^{-4}

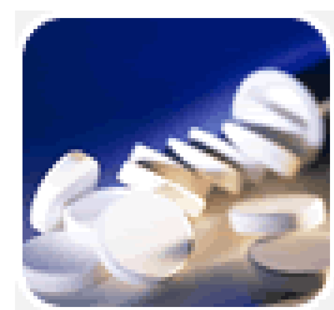
生物数据

人体中含量 肝/p.p.m.: 0.22-7 肌肉/p.p.m.: 0.05 血/mg /dm^3 : 0.5
骨/p.p.m.: 2000-12000 日摄入量/mg: 0.3-0.5 人(70Kg)均体内总量/g: 2.6

Introduction

原子	电负性 (Pauling)	Pauling原子半径(Å)	Bondi原子半径(Å)	键能(CH_3-X) (kcal/mol)	键长 CH_3-X(Å)
H	2.1	1.20	1.20	99	1.09
F	4.0	1.35	1.47	116	1.39
Cl	3.0	1.80	1.75	81	1.77
Br	2.8	1.95	1.85	68	1.93
O(OH)	3.5	1.40	1.52	86	1.43
S(SH)	2.5	1.85	1.80	65	1.82

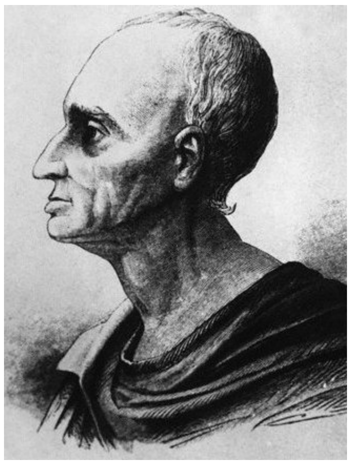
尖端材料：在军用尖端材料中，含氟材料占近一半（由于其独特优异的稳定性和其它物理特性）



医药农药：最近报道，全球新注册的医药中10%含有氟元素；新注册的农药中，40%含有氟元素

Introduction

在化学元素发现史上，氟单质的制取是持续时间最长、参加人数最多、危险最大、工作最难的研究课题！



萤石 (Fluorite)
主要成分是氟化钙 (CaF_2)

$$CaF_2 + H_2SO_4 \longrightarrow CaSO_4 + 2HF\uparrow$$

1768年 Andreas Sigismund Marggraf（1709-1782）将萤石与硫酸混合从萤石制取氢氟酸； 1771年 Carl Wilhelm Scheele（1742-1786）利用这一方法得到纯的氢氟酸

Introduction

1886年 Henri Moissan (1852-1907)
 分离得到单质氟（铂制U型管中用铂铱合金作电极电解干燥的氟氢化钾可制得单质氟）

1906 年度诺贝尔化学奖得主

1892年 Frederic Swarts（1866-1940）发现了三氟化锑作用下的氯/氟卤素交换反应；1896年首次合成一氟乙酸乙酯

揭开了研究有机氟化学的序幕，标志着有机氟化学的开端！

Introduction

破坏臭氧的机理主要是氟利昂进入平流层后，在紫外照射下分解出Cl自由基，再与O_3发生链反应。反应机理：
臭氧在紫外线作用下

$$O_3 \longrightarrow O_2 + O$$

氯氟烃分解（以CF_2Cl_2为例）

$$CF_2Cl_2 \longrightarrow CF_2Cl\cdot + Cl\cdot$$

自由基链反应

$$Cl\cdot + O_3 \longrightarrow ClO\cdot + O_2$$

$$ClO\cdot + O \longrightarrow Cl\cdot + O_2$$

总反应： $O_3 + O \longrightarrow 2O_2$

一个氟利昂分子就能破坏多达10万个臭氧分子，增加温室效应的效果相当于1万个二氧化碳分子。

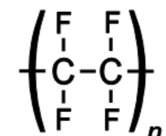
1928年 Thomas Midgley, Jr.(1889-1944) 发明了“氟利昂”，并因此被授予珀金奖章，但在1974年时发现了氟利昂对臭氧层的破坏作用

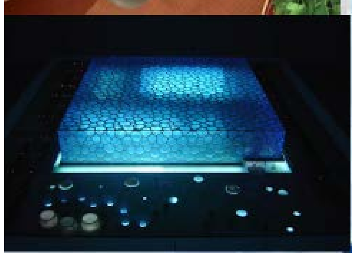
氟利昂，几种氟氯代甲烷和氟氯代乙烷的总称 。氟里昂在常温下都是无色气体或易挥发液体，略有香味，低毒，化学性质稳定。其中最重要的是二氯二氟甲烷CCl_2F_2(F-12)。

Introduction

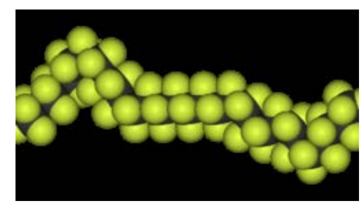
1938年 Roy J. Plunkett （1910-1994）发现了聚四氟乙烯，标志着含氟聚合物的诞生

聚四氟乙烯是以氟取代聚乙烯中所有氢原子的人工合成高分子材料。这种材料具有抗酸抗碱、抗各种有机溶剂的特点，几乎不溶于所有的溶剂。同时，聚四氟乙烯具有耐高温、摩擦系数极低的特点。





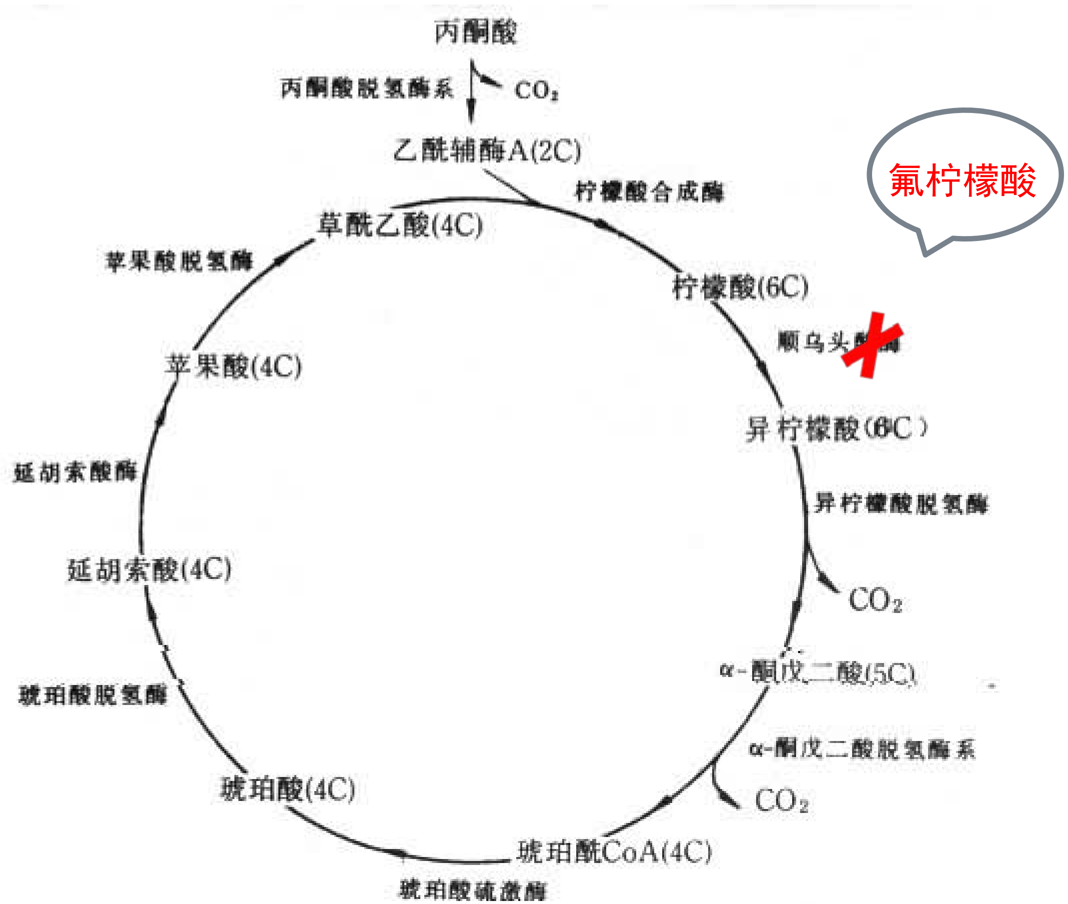
聚四氟乙烯广泛应用于各种需要抗酸碱和有机溶剂的场合，并被用来制作不粘锅以及干式变压器。聚四氟乙烯很软，因此经常用于涂层。 聚四氟乙烯最出名的应用是北京水立方的外墙材料，是世界上面积最大的集中使用，在它研究出来的时候使用领域主要是高温的发射火箭的内壁涂层。



聚四氟乙烯, 商标名 Teflon. (Polytetrafluoroethene, PTFE)

Introduction

1943年 单氟乙酸的剧毒作用逐渐被人们发现，推动了有机氟化学毒理学和药理学的研究



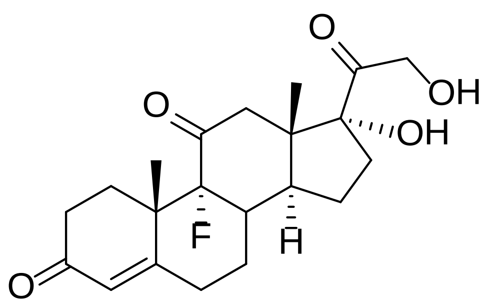
三 羧 酸 循 环

Gifblaar
生长在南美洲的一种含单氟乙酸的有毒植物

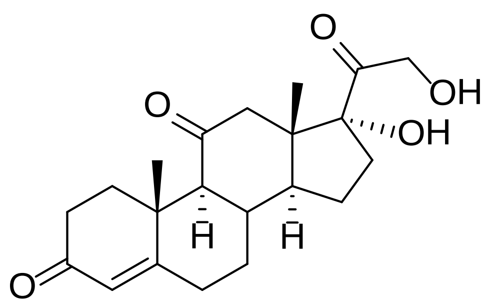
K. Gregg, *Appl. Environ. Microbiol*. **1998**, *64*, 3496.

Introduction

1954年 Josef Fried (1914-2001) 对有机含氟物质在医学上的应用进行研究；9位氟取代的可的松衍生物作为糖皮质激素其活性比未取代的高10-20倍，第一次向人们展示了将氟原子引入有机分子中对改善其生理活性的重要作用



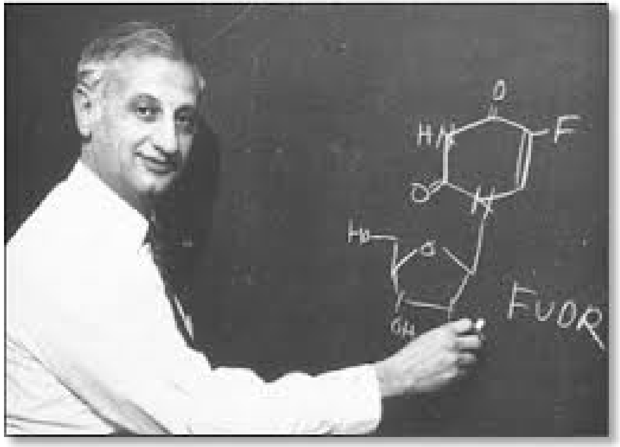
9-F-Cortisone



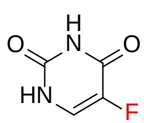
Cortisone

J. Fried, *J. Am. Chem. Soc.* **1954**, *76*, 1455.

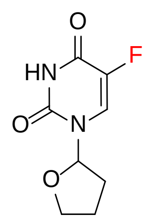
Introduction



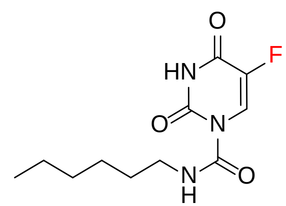
1957年 Charles Heidelberger (1920-1983)合成5-氟尿嘧啶，实现了癌症治疗的历史性突破



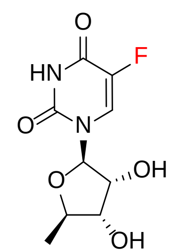
Fluorouracil (5-FU)



Tegafur
(Taiho) 1984

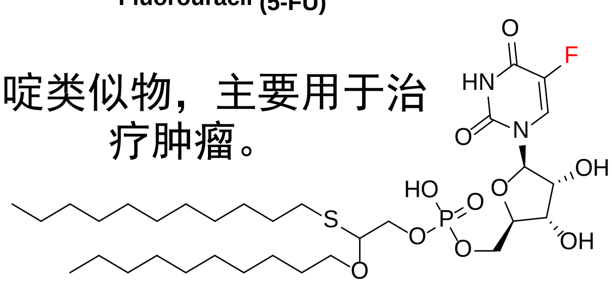


Carmofur
(Schering) 1981

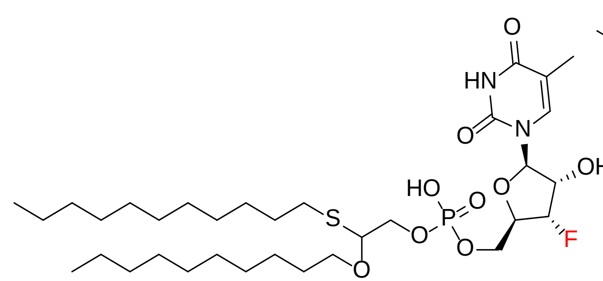


Doxifluridine
(Hoffman-Laroche) 1987

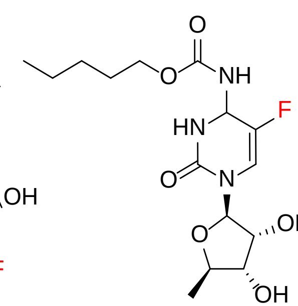
嘧啶类似物，主要用于治疗肿瘤。



Fosfluridine tidoxil
(Heidelberg Pharma) Phase II

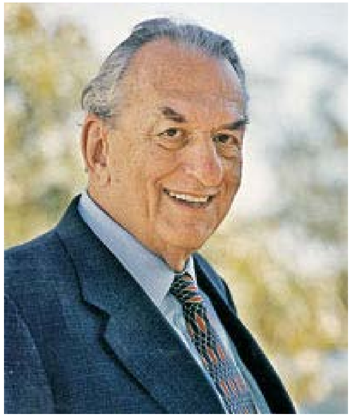


Fosalvudine tidoxil
(Heidelberg Pharma) Phase II



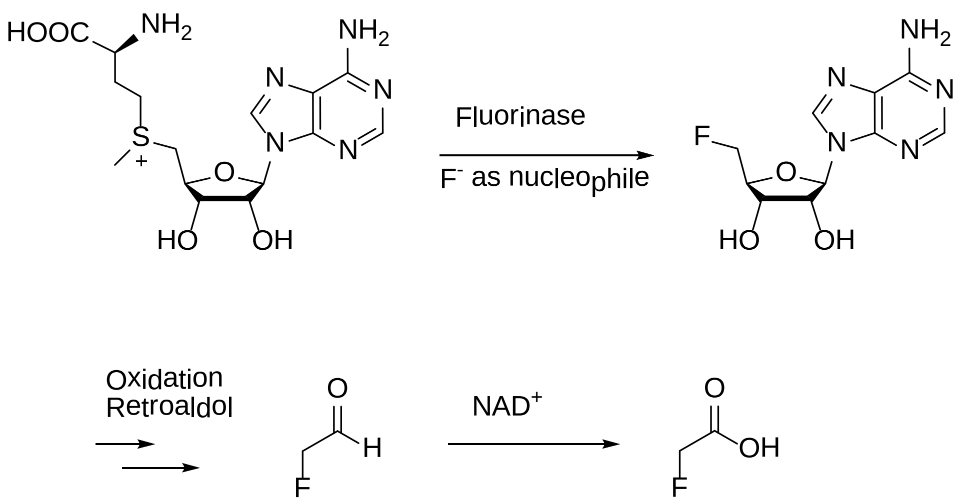
Capecitabine
(Holfman-Laroche) 1987

Introduction



1962年 George Andrew Olah(1927---)利用含氟物质首次发现稳定的碳正离子存在

发现了质子化的甲烷可被超强酸（如FSO_3H-SbF_5）所稳定

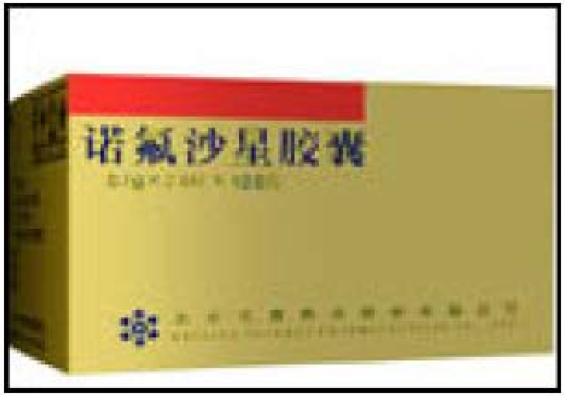


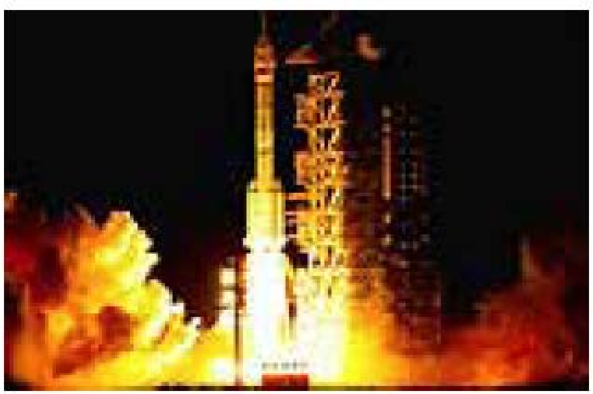
Fluorinase(ca. 32000 Dalton) from bacterium *Streptomyces cattleya*

2002年 David O'Hagan分离出了第一个氟化酶

Introduction

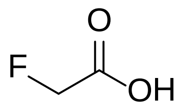
与生命、材料、人类健康、国家安全、国民经济密切相关



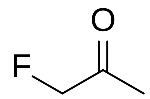


Introduction: Natural Organofluorine Compounds

1. Only 13 naturally occurring fluorinated compounds are known



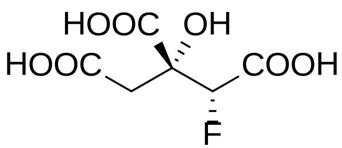
Fluoroacetic acid



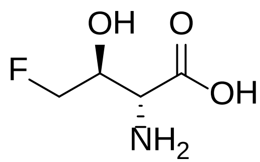
Fluoroacetone

$F(CH_2)_8CH{=}CH(CH_2)_7COOH$

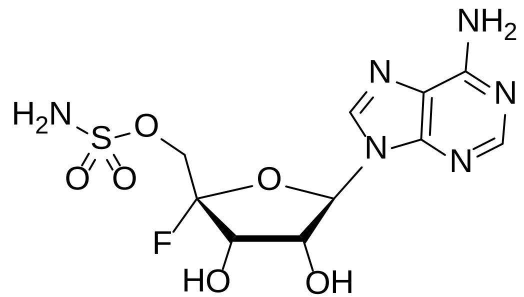
ω-Fluorooleic acid (and some other fatty acids)



2-Fluorocitric acid



4-Fluorothreonine



4'-Fluoro-5'-*O*-sulfamoyladenosine

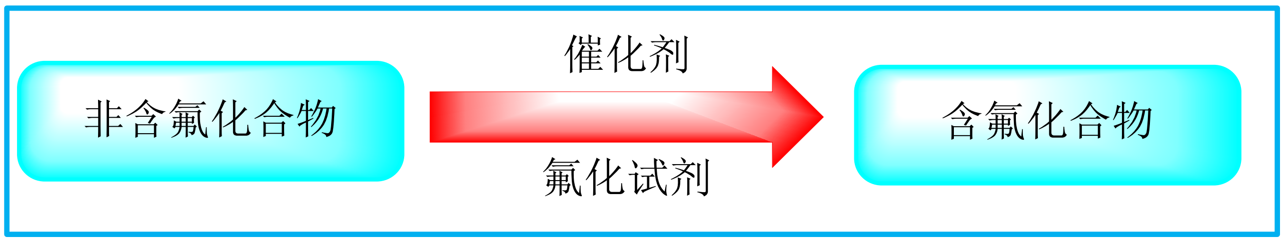
D. B. Harper, D. O'Hagan, *Nat. Prod. Rep.* **1994**,123.

2. Only 21 biosynthesized natural molecules containing fluorine are known

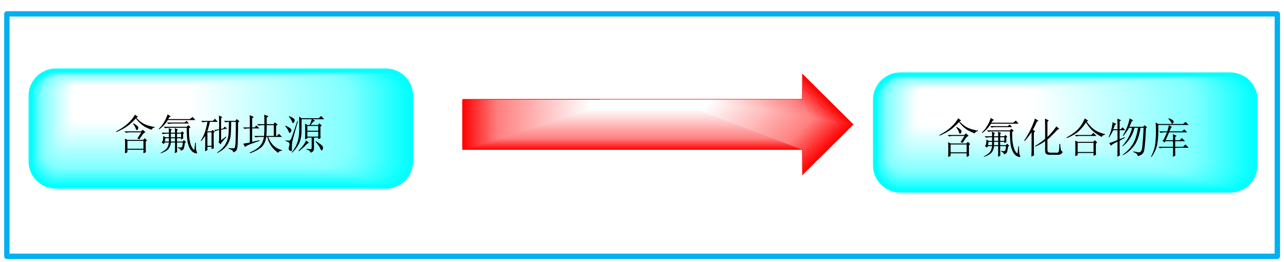
G. W. Gribble, in Progress in the Chemistry of Organic Natural Products Vol. 91 (eds A. D. Kinghord, H. Falk & J. Kobayashi) 1–613 (Springer, 2009).

Introduction

一、直接氟化：

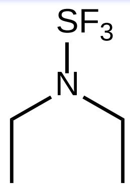


二、含氟砌块的转化：

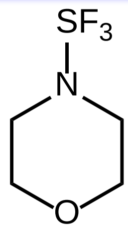


Introduction

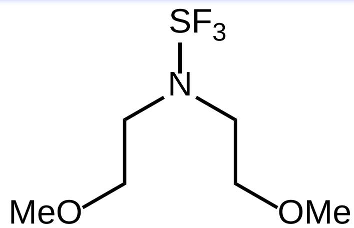
亲核氟化试剂



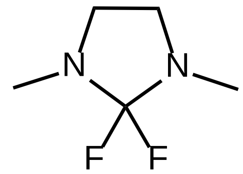
DAST



Morpho-DAST



Deoxofluor

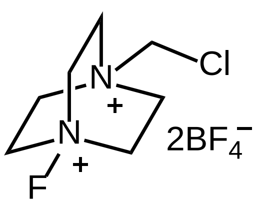


DFI

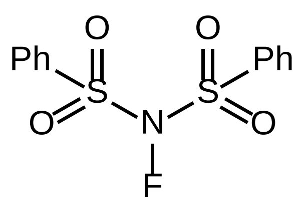
$Et_3N\cdot 3HF$

AgF

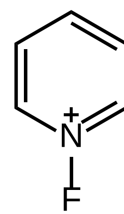
亲电氟化试剂



Selectfluor



NFSI



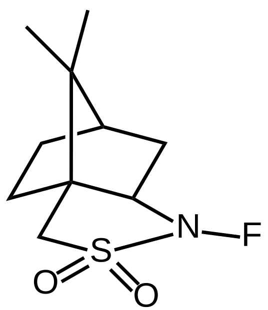
X^-

$X = BF_4^-$, TfO^-

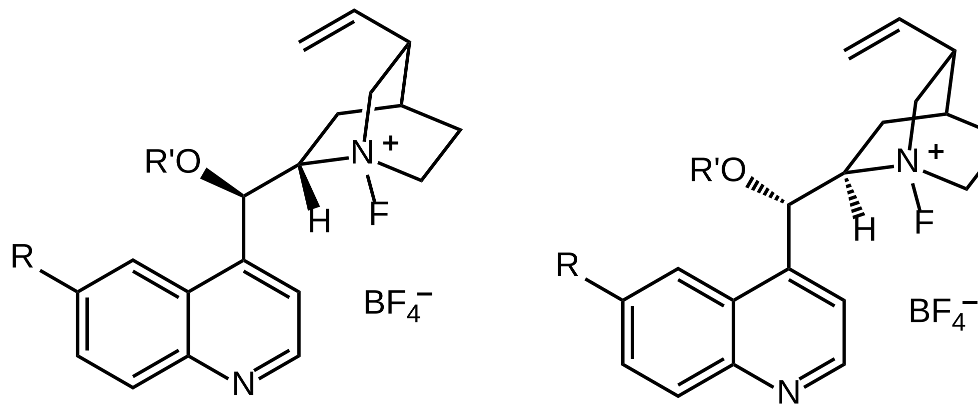
NFPY-X

Introduction

手性亲电氟化试剂



Differding & Lang



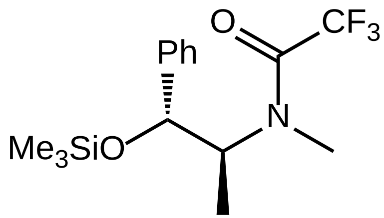
Cahard & Shibata

Introduction

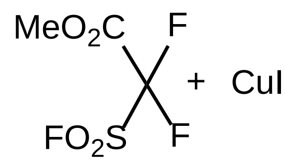
亲核三氟甲基化试剂

$TMSCF_3$

Ruppert-Prakash

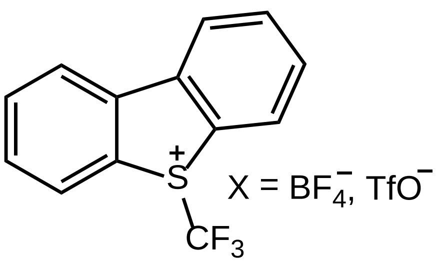


Langlois

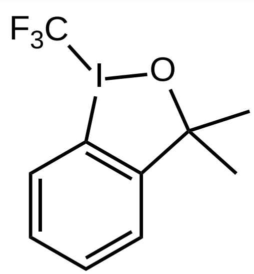


Chen

亲电三氟甲基化试剂



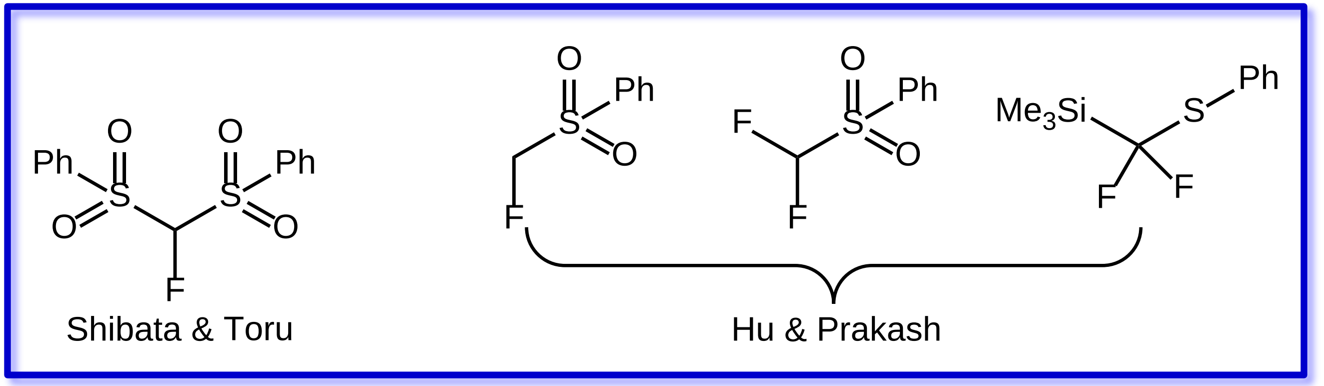
Umemoto



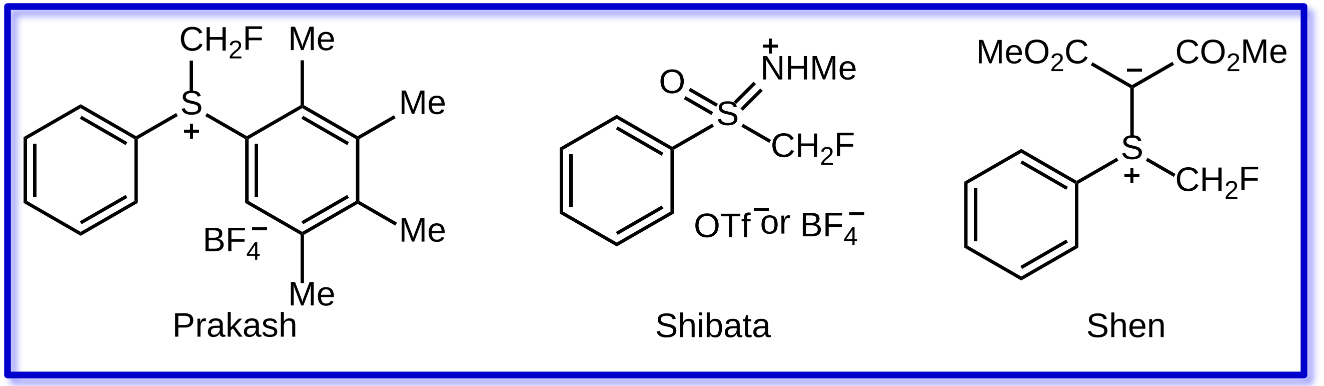
Togni

Introduction

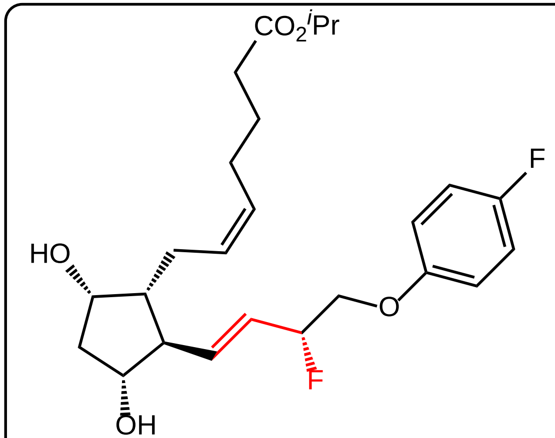
亲核单、二氟甲基化试剂



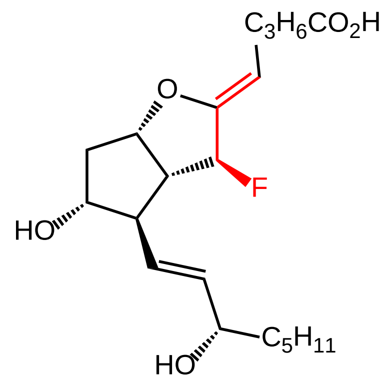
亲电二氟甲基化试剂



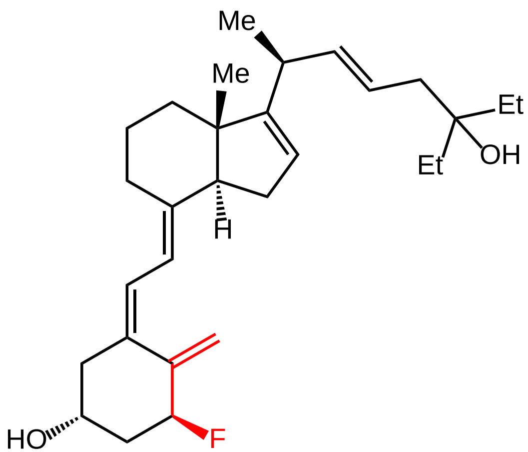
Introduction



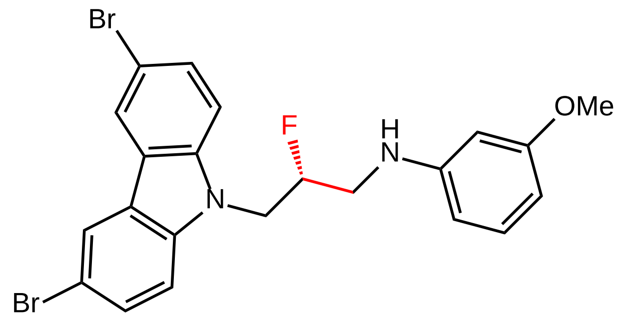
1 15-Fluoro-Proataglandin



2 7-Fluoro-Prostacyclin

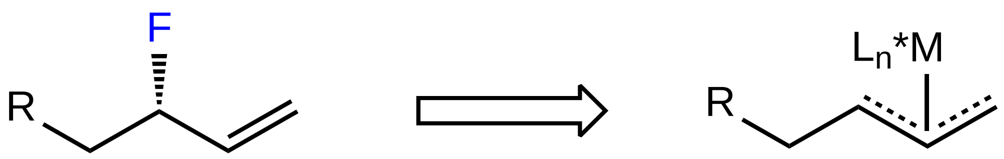


3 Elocalcitol



4 P7C3-A20

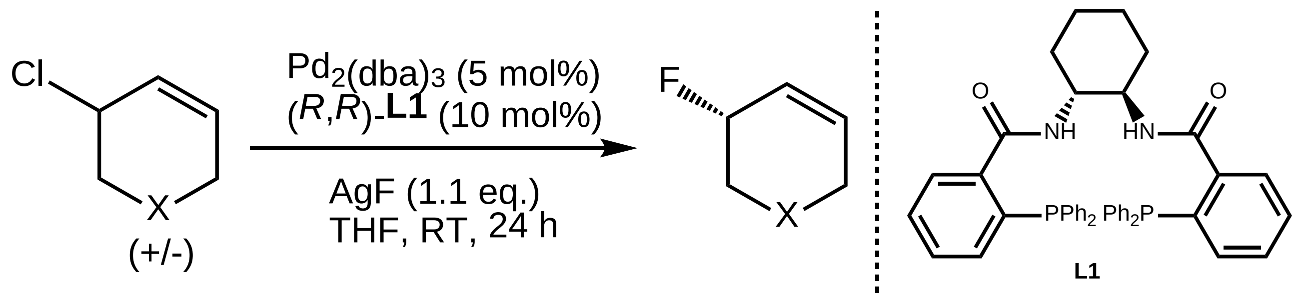
Introduction

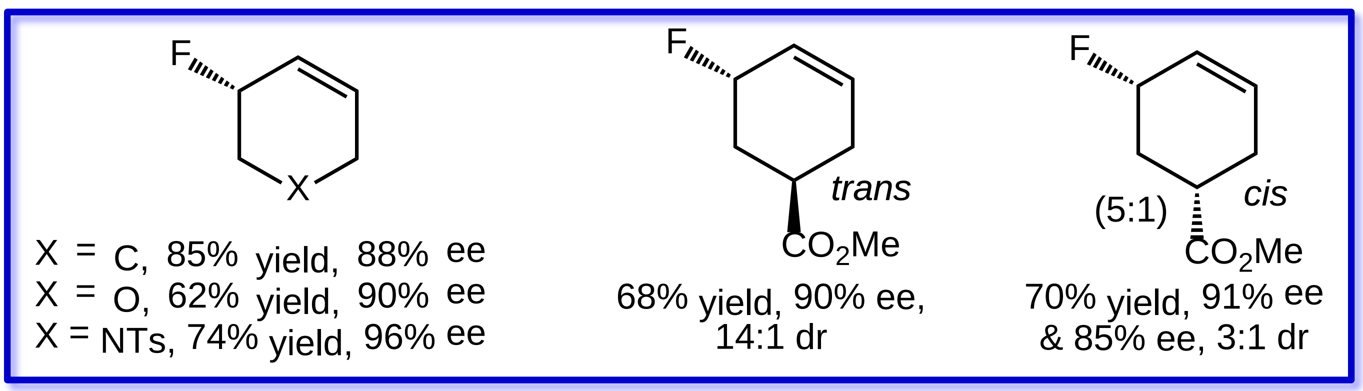


Challenges:

- **Strong metal-fluoride bonding**
- **High basicity of desolvated fluoride**
- **Allylic fluorides to act as a leaving group**

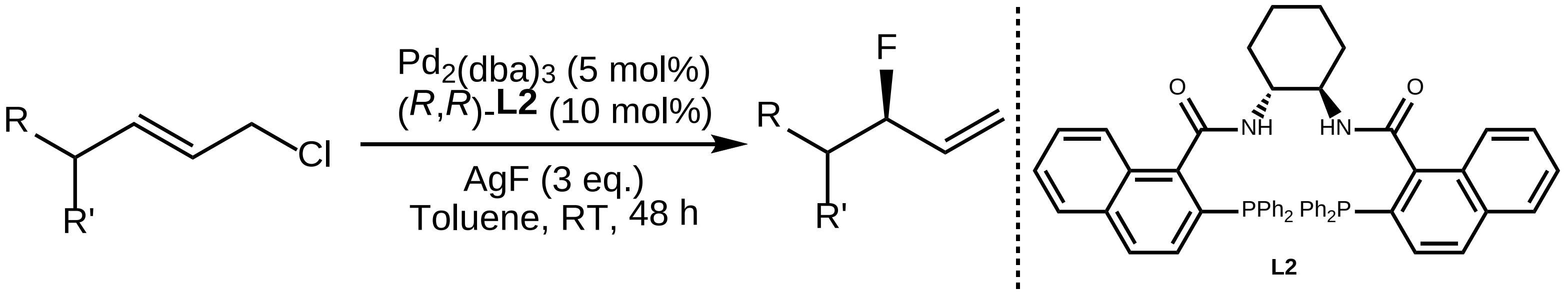
Pd-Catalyzed Asymmetric Synthesis of Allylic Fluorides

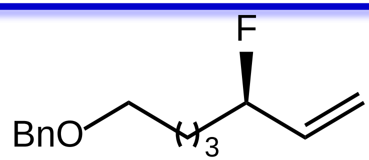




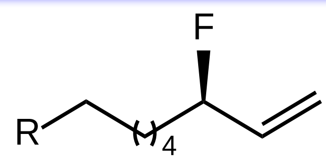
M. H. Katcher and A. G. Doyle, *J. Am. Chem. Soc*. **2010**, *132,* 17402.

Pd-Catalyzed Asymmetric Synthesis of Allylic Fluorides

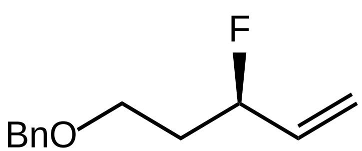




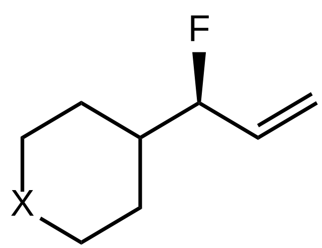
78% yield, 58% ee



R = OTBS, 84% yield, 58% ee
R = CHO, 67% yield, 71% ee
R = Br, 66% yield, ee: ND



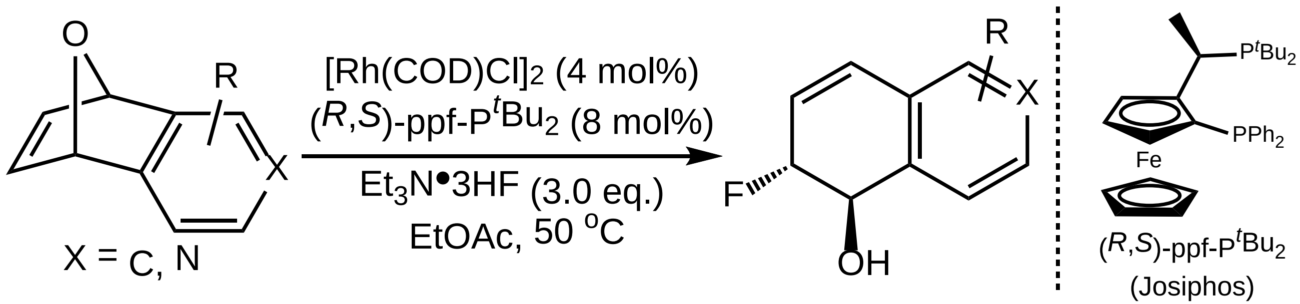
83% yield, 21% ee

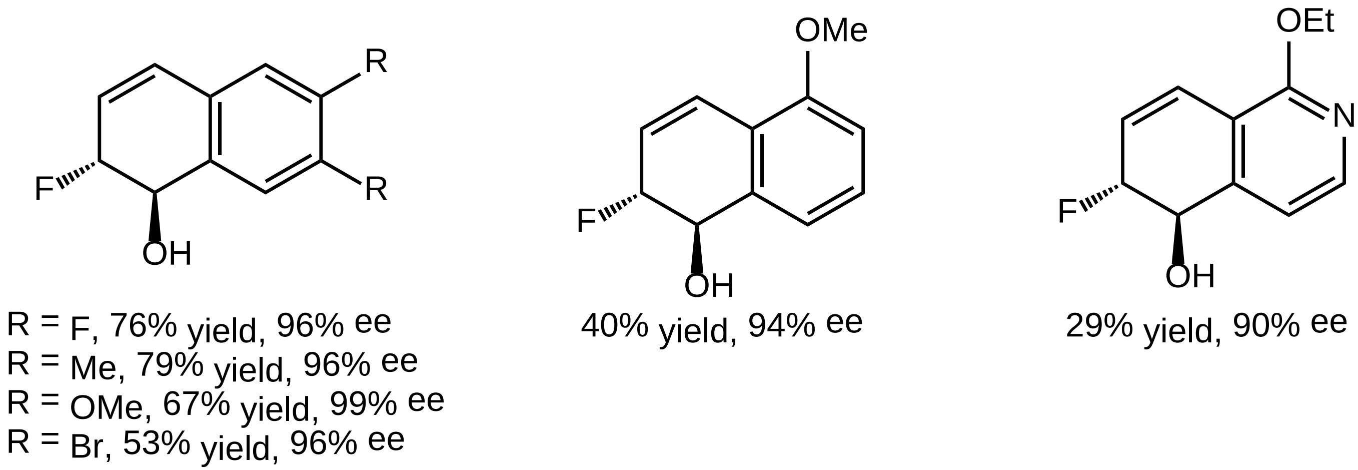


X = C, 84% yield, 90% ee
X = O, 62% yield, 97% ee
X = NBoc, 85% yield, 93% ee
X = NCbz, 88% yield, 93% ee

M. H. Katcher, A. Sha and A. G. Doyle, *J. Am. Chem. Soc*. **2011**, *133,* 15902.

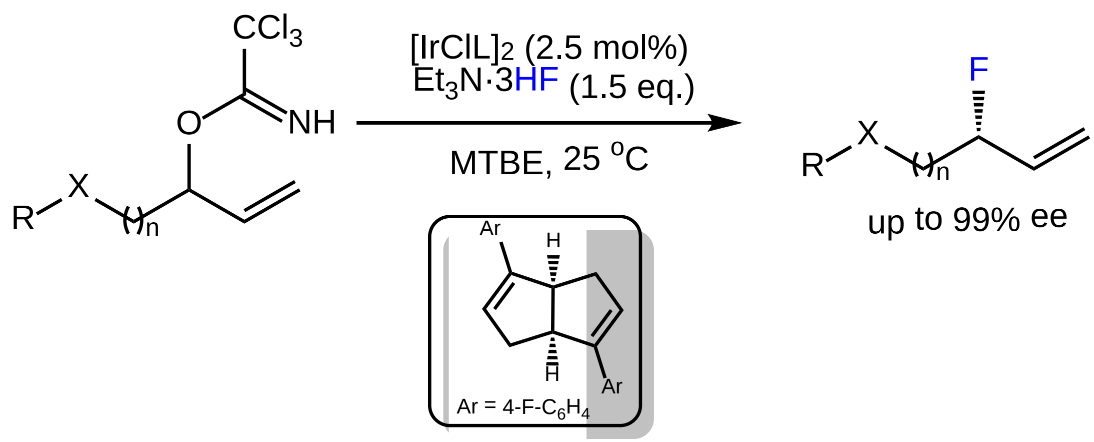
Rh-Catalyzed Asymmetric Synthesis of Allylic Fluorides





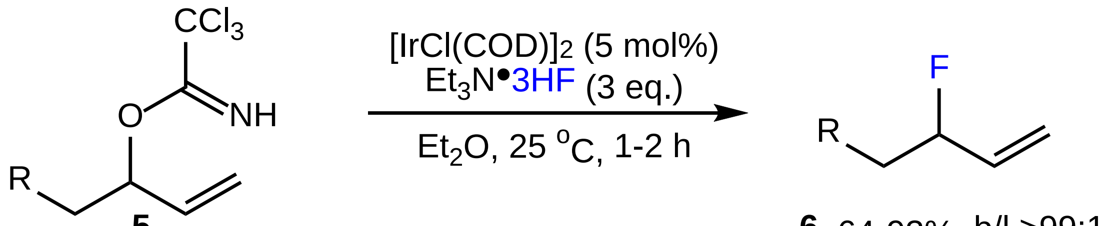
J. Zhu, G. C. Tsui and M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 12353.

Ir-Catalyzed Asymmetric Synthesis of Allylic Fluorides



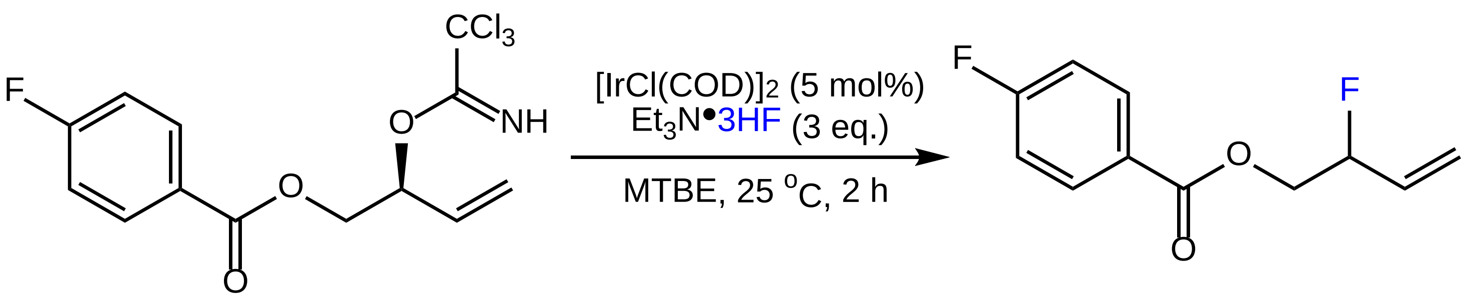
H. M. Nguyen *et al. J. Am. Chem. Soc.* **2015**, *137,* 11912*;*
ACS Catal. **2018**, *8,* 790*.*

Discovery of Ir-Catalyzed Allylic Fluorination



5

6, 64-93%, b/l >99:1

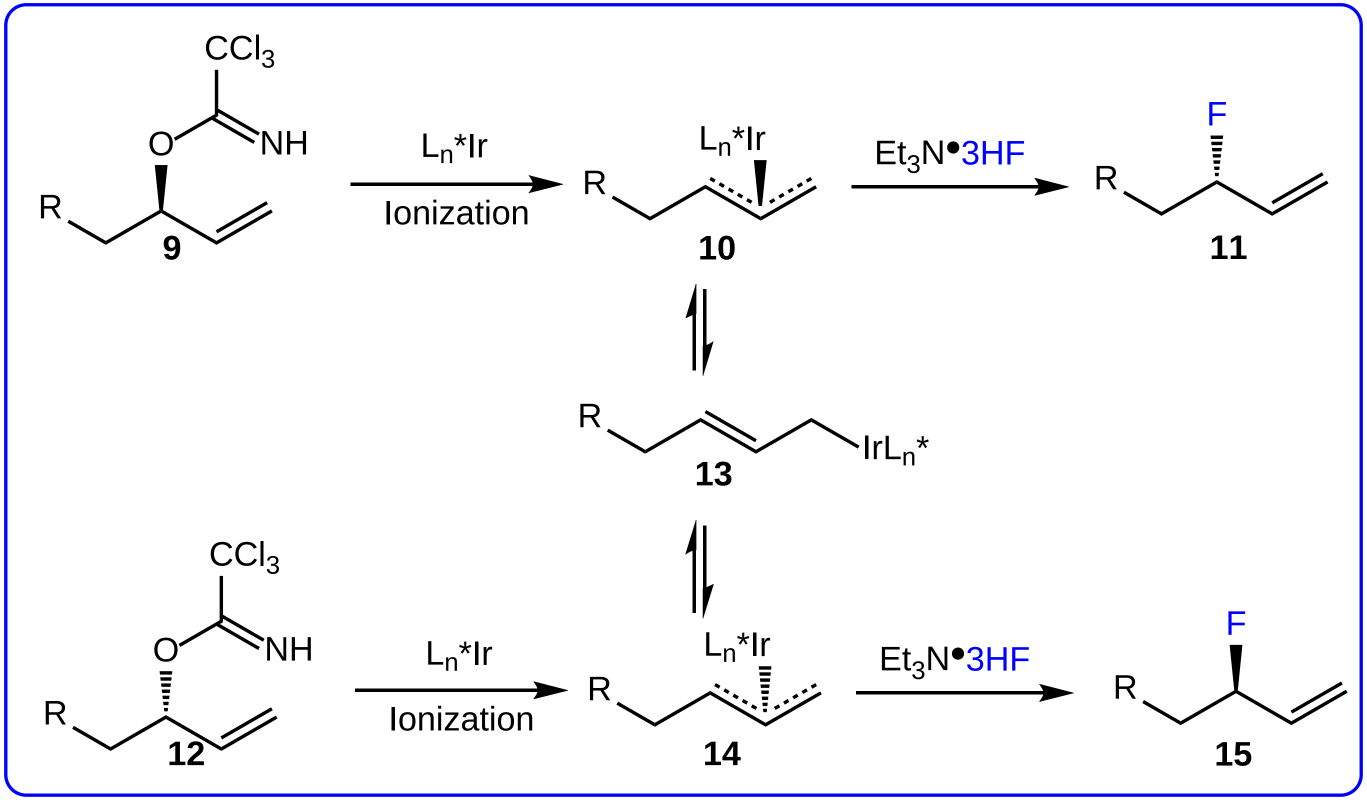


7, 94% ee

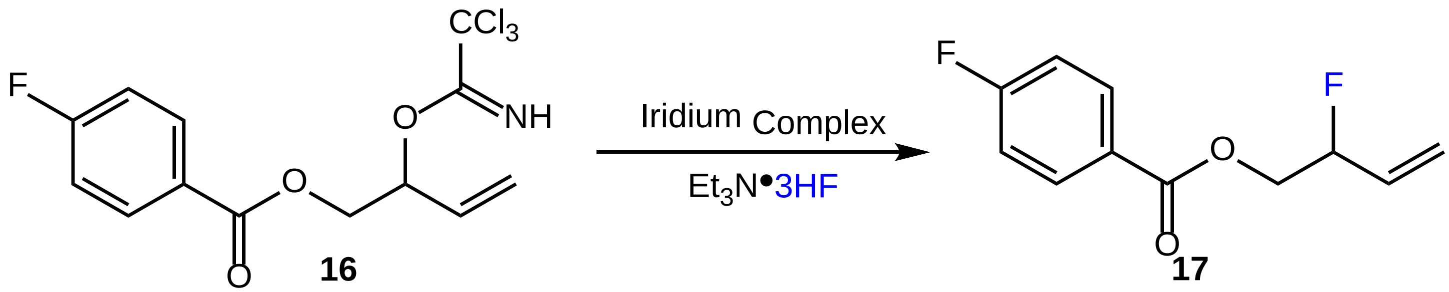
8, >99% *Conv.* 0% ee

J. C. Mixdorf, A. M. Sorlin, Q. Zhang and H. M. Nguyen, *ACS Catal*. **2018**, *8,* 790.

Proposed DYKAT-Based Synthesis of Allylic Fluorides

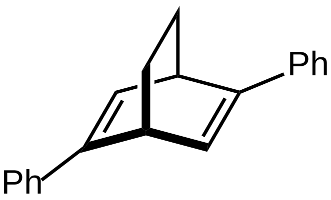


Reaction Optimization

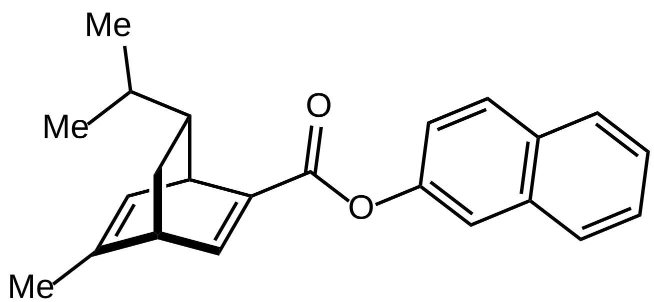


entry	Ir complex	solvent	temp (° C)	$Et_3N{\cdot}HF$ (eq.)	time (h)	yield (%)[c]	ee (%)[d]
1[a]	$[IrCl(COE)_2]_2$/**L2**	Et_2O	25	3	12	51	13
2[a]	$[IrCl(COE)_2]_2$/**L3**	Et_2O	25	3	12	36	13
3[a]	$[IrCl(COE)_2]_2$/**L4**	Et_2O	25	3	12	52	3
4[a]	$[IrCl(COE)_2]_2$/**L5**	Et_2O	25	3	6	95	66
5[a]	$[IrCl(COE)_2]_2$/**L6**	Et_2O	25	3	6	95	62
6[a]	$[IrCl(COE)_2]_2$/**L1**	Et_2O	25	3	6	95	81
7[b]	$[IrCl($**L5**$)]_2$	Et_2O	25	3	6	91	79
8[b]	$[IrCl($**L5**$)]_2$	Et_2O	25	1.5	6	95	84

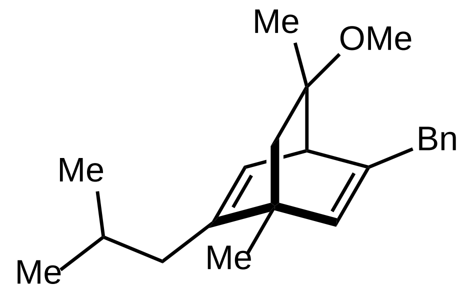
Chiral Diene Ligands



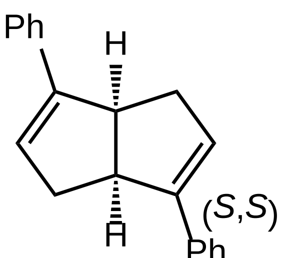
L2



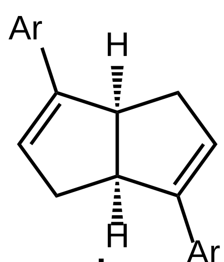
L3



L4



L5



L

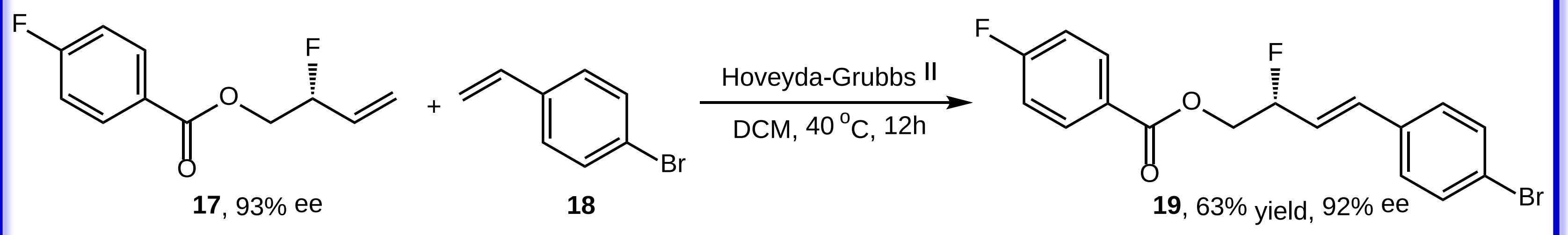
L6: Ar = 4-MeO-C_6H_4
L1: Ar = 4-F-C_6H_4

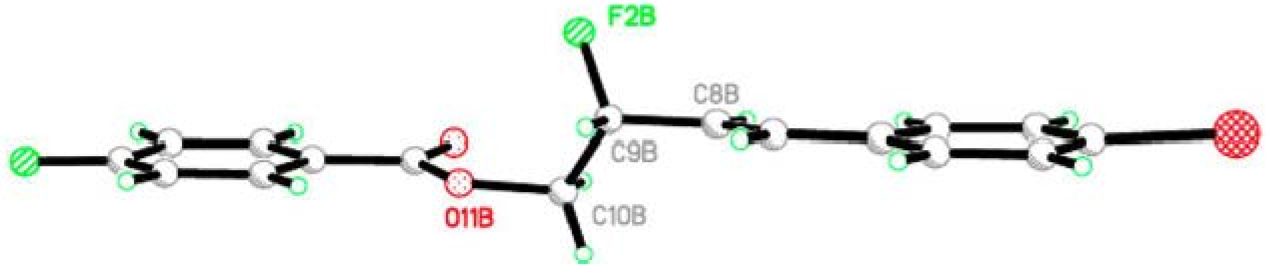
Reaction Optimization

entry	Ir complex	solvent	temp (° C)	$Et_3N·HF$ (eq.)	time (h)	yield (%)[c]	ee (%)[d]
9[b]	$[IrCl(\mathbf{L5})]_2$	Toluene	25	1.5	6	95	83
10[b]	$[IrCl(\mathbf{L5})]_2$	DCM	25	1.5	6	95	77
11[b]	$[IrCl(\mathbf{L5})]_2$	THF	25	1.5	6	95	87
12[b]	$[IrCl(\mathbf{L5})]_2$	MTBE	25	1.5	6	95	88
13[b]	$[IrCl(\mathbf{L5})]_2$	MTBE	40	1.5	4	95	86
14[b,e]	**$[IrCl(L1)]_2$**	**MTBE**	**25**	**1.5**	**1**	**99 (82)**	**93 (93)**

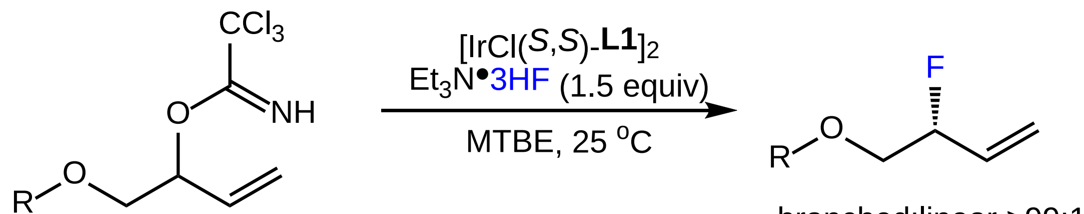
[a] The diene-ligated iridium complex was generated *in situ* from 2.5 mol % $[IrCl(COE)_2]_2$ with 5 mol % ligand, **L1−L6**. [b] 2.5 mol % $[IrCl(L_n)]_2$ complex (**L5** or **L1**) was utilized in the reaction. [c] Determined by ^{19}NMR analysis using $PhCF_3$ as an internal standard. [d] Determined by chiral HPLC. [e] Isolated yield.

Derivatization of Allylic Fluoride 17 for X-ray Analysis

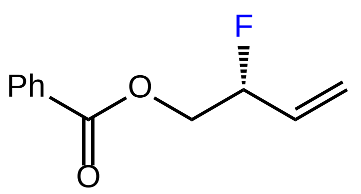




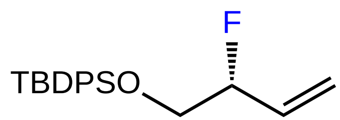
Scope of β-Oxygen-Substituted Imidate Substrates



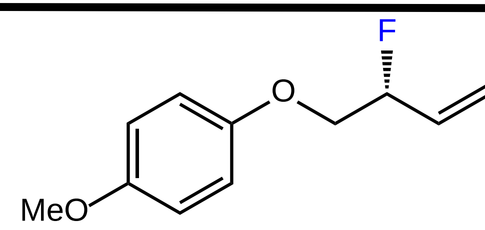
branched:linear >99:1



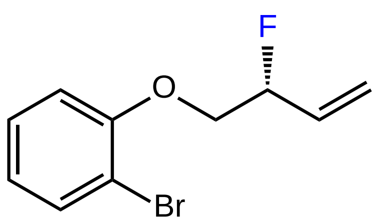
20, 75% yield, 93% ee



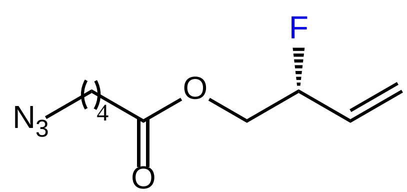
21, 70% yield, 95% ee



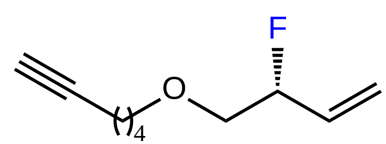
22, 77% yield, 95% ee



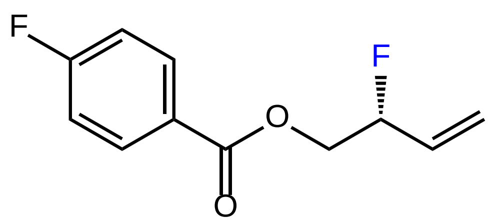
23, 70% yield, 92% ee



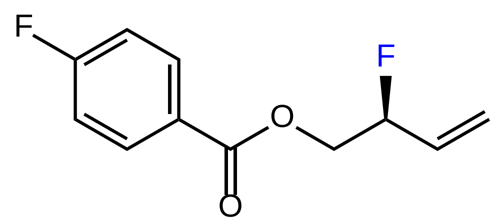
24, 61% yield, 95% ee



25, 74% yield, 99% ee

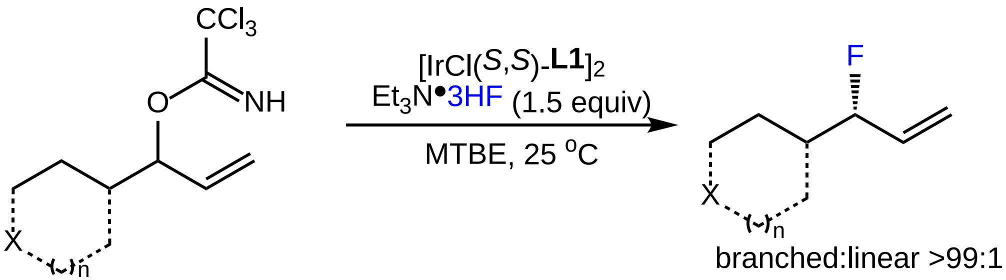


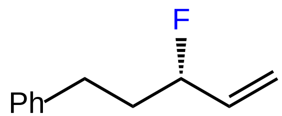
17, 83% yield, 93% ee



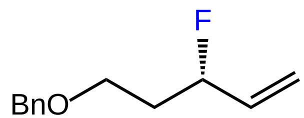
***ent*-17**, 63% yield, 91% ee

Scope of *α*-Linear and *α*-Branching Substituted Imidates

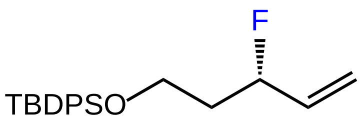




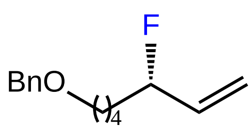
26, 82% yield, 90% ee



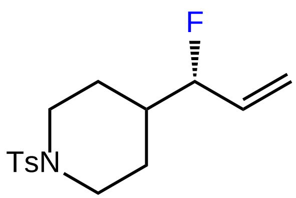
27, 90% yield, 92% ee



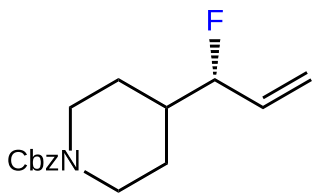
28, 69% yield, 95% ee



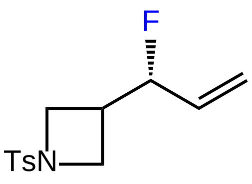
29, 75% yield, 94% ee



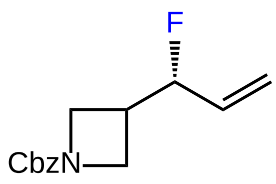
30, 69% yield, 93% ee



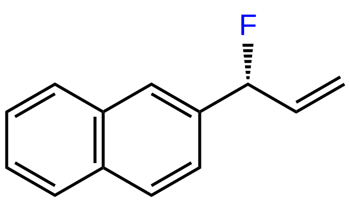
31, 90% yield, 94% ee



32, 78% yield, 86% ee

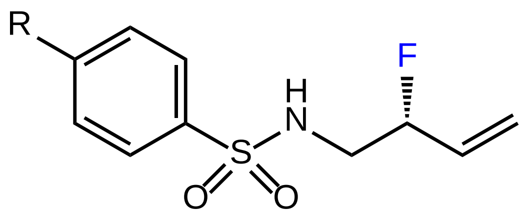


33, 77% yield, 88% ee

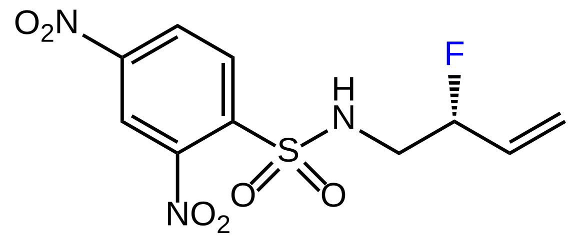


34, 65% yield, 0% ee

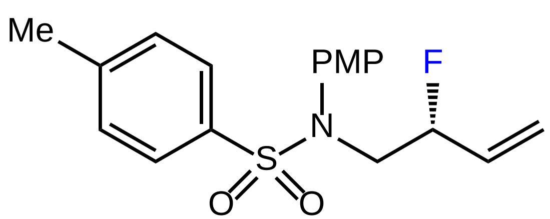
Scope of Nitrogen-Containing Imidate Substrates



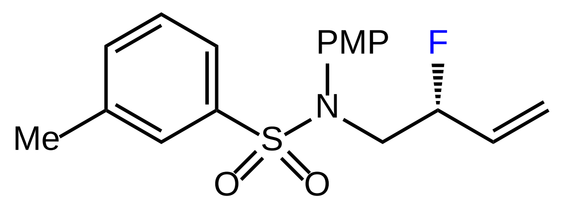
35, R = Me, 88% yield, 49% ee
36, R = NO_2, 95%yield, 82% ee



37, 90% yield, 91% ee

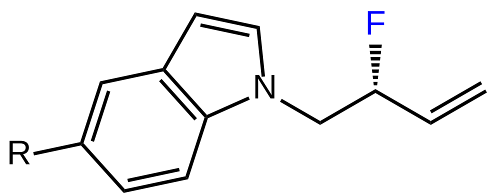


38, 79%yield, 90% ee

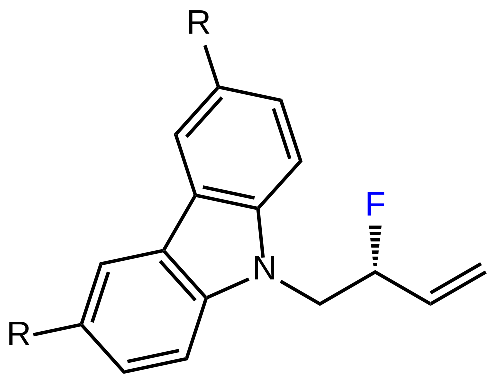


39, 93% yield, 91% ee

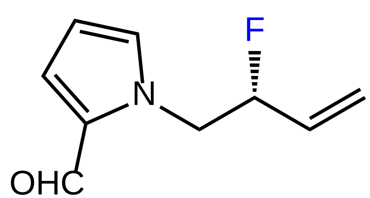
Scope of Nitrogen-Heterocycle-Substituted Substrates



40, R = H, 73% yield, 88% ee
41, R = F, 55% yield, 90% ee
42, R = OMe, 67% yield, 91% ee

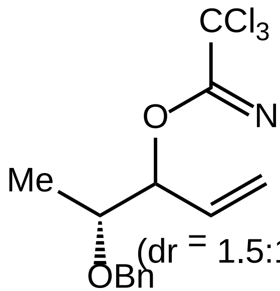
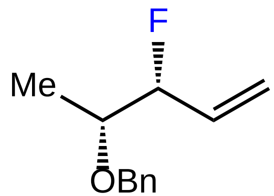
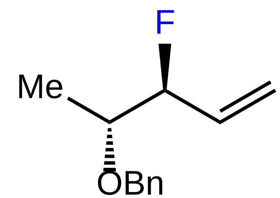
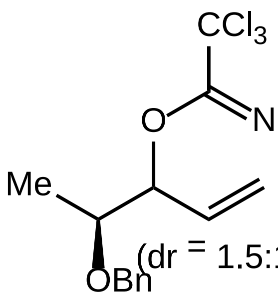
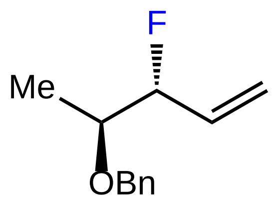
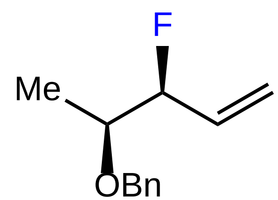
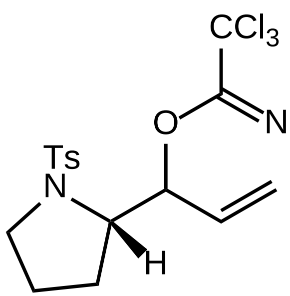
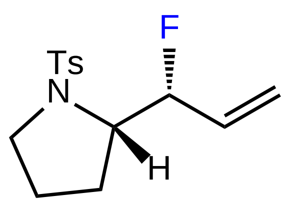
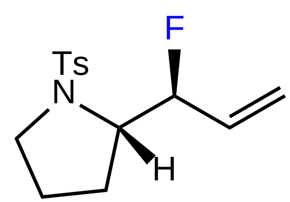


43, R = H, 65% yield, 94% ee
44, R = OMe, 62% yield, 84% ee

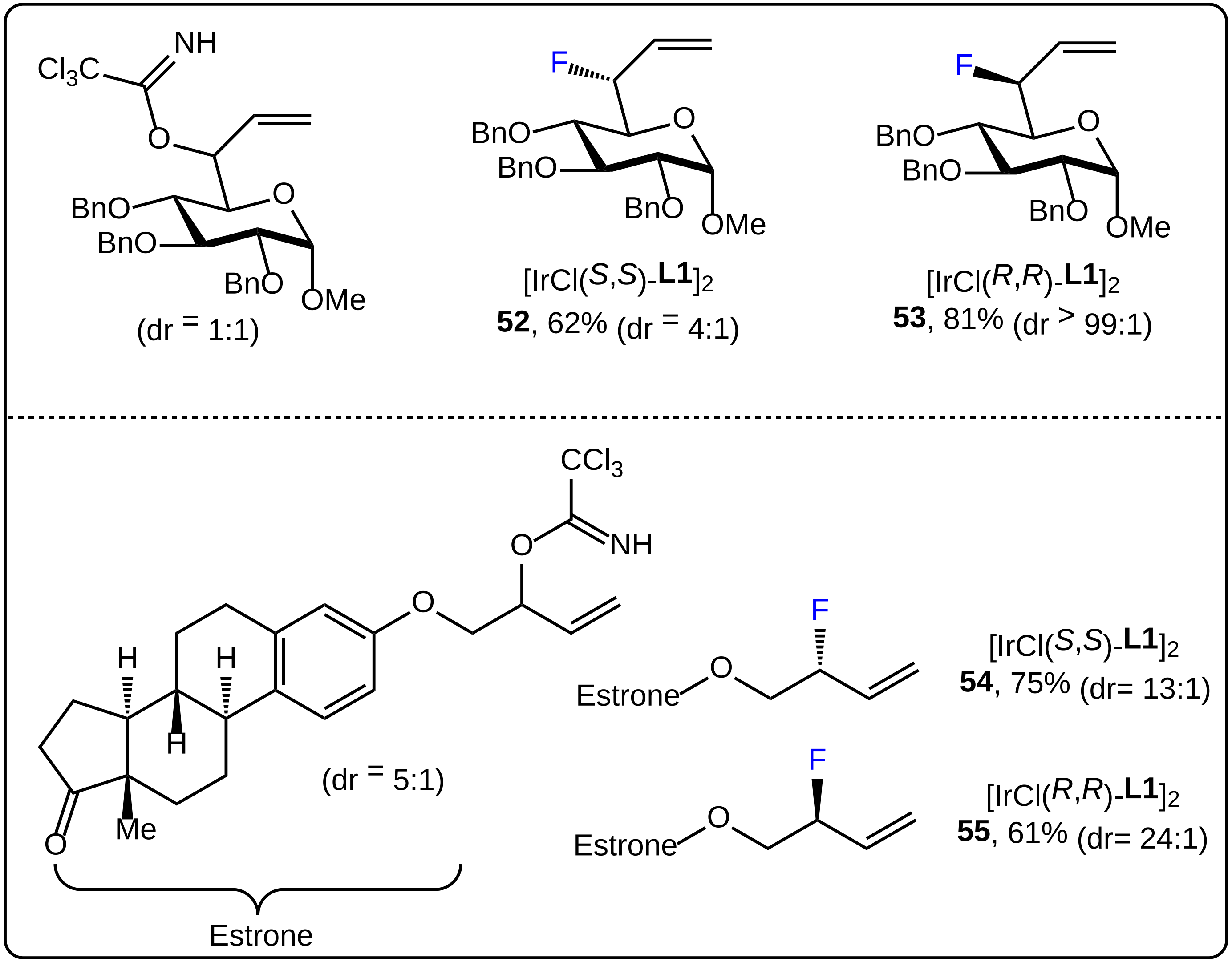


45, 57% yield, 96% ee

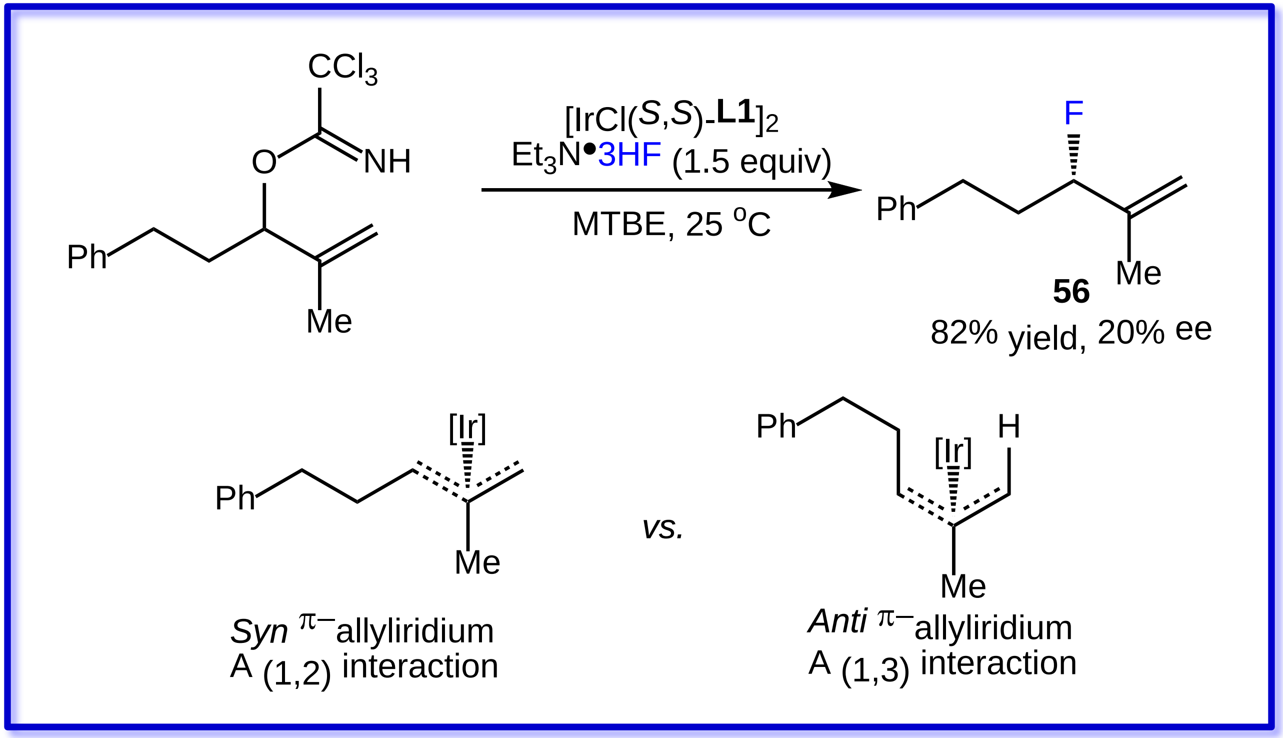
Scope of Allylic Imidate Substrates Bearing *α*-Stereocenter

imidates	$[IrCl((S,S)\text{-}\mathbf{L1})]_2$	$[IrCl((R,R)\text{-}\mathbf{L1})]_2$
 (dr = 1.5:1)	 **46**, 52% (dr = 14:1)	 **47**, 98% (dr = 43:1)
 (dr = 1.5:1)	 **48**, 55% (dr = 17:1)	 **49**, 63% (dr = 13:1)
 (dr > 25:1)	 **50**, 62% (dr = 17:1)	 **51**, 71% (dr > 99:1)

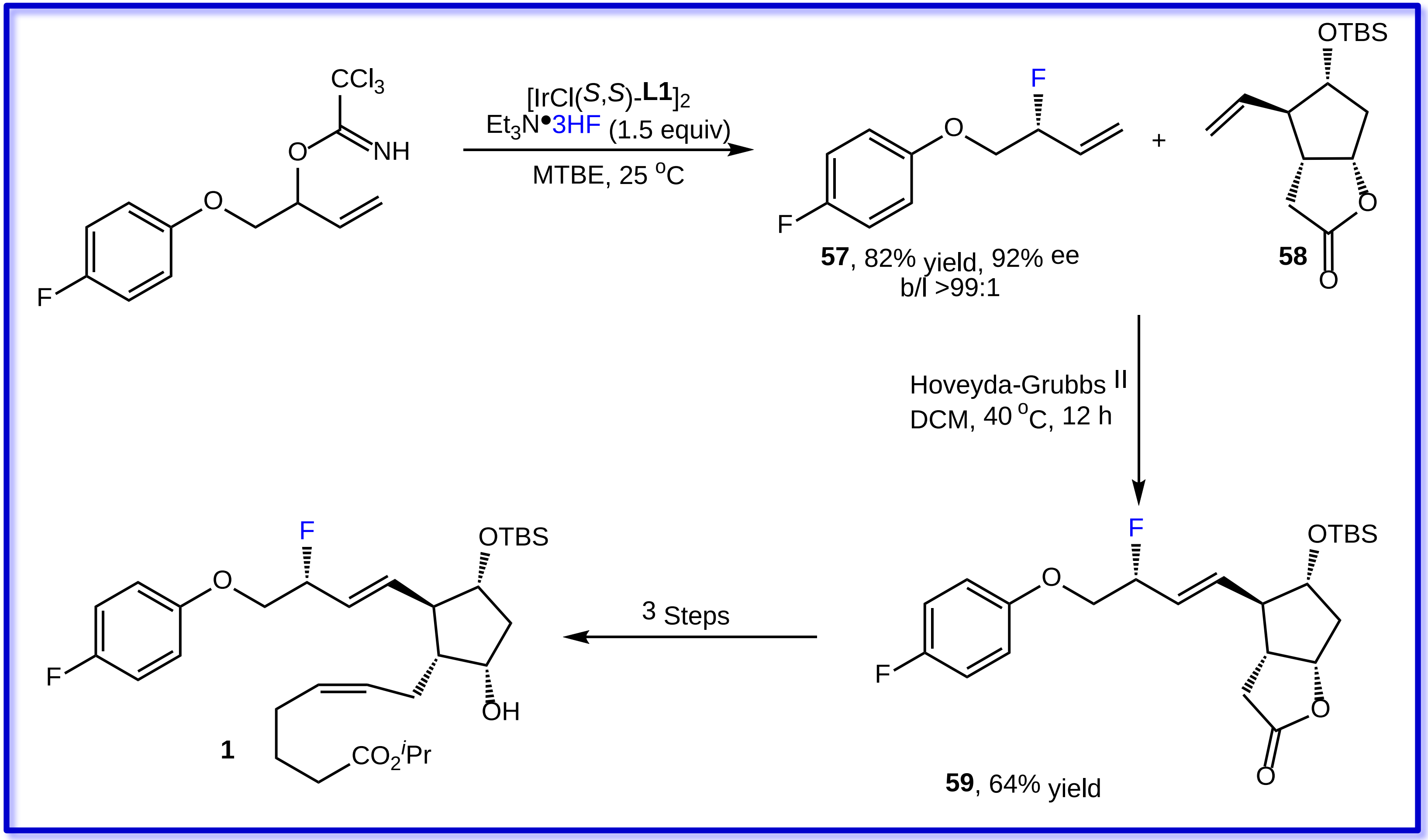
Fluorination of Carbohydrate and Estrone



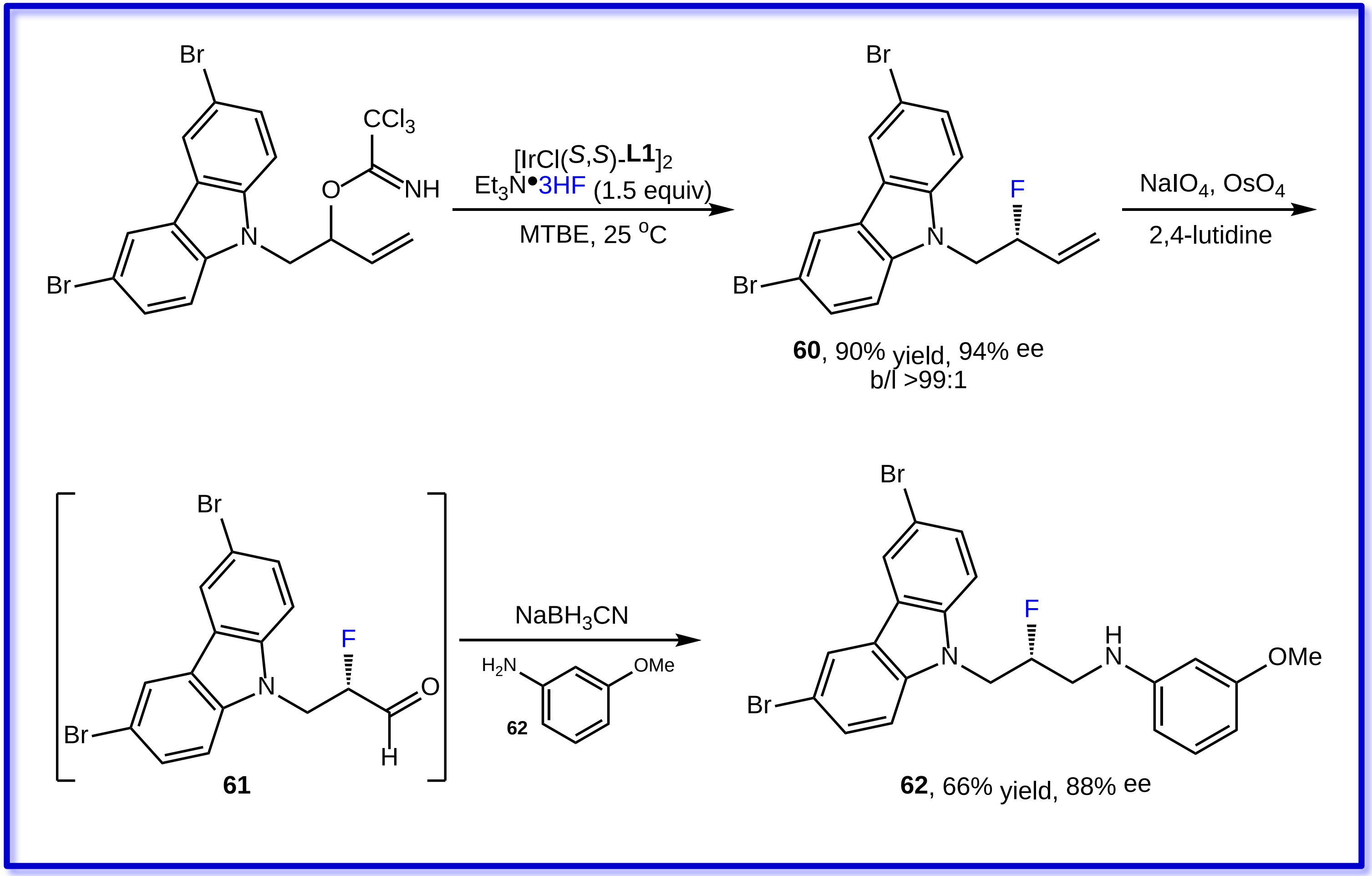
Asymmetric Synthesis of Disubstituted Allylic Fluoride



Synthesis of a 15-Fluoro-Prostaglandin Fragment

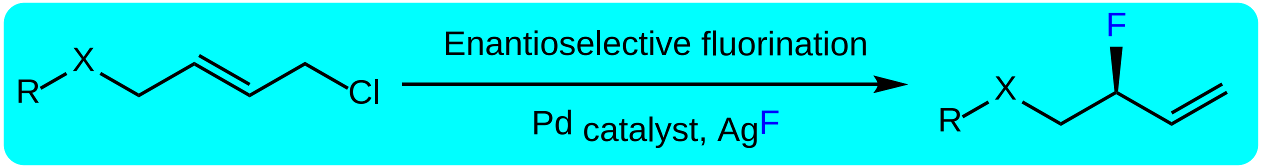


Synthesis of Bioactive P7C3-A20 Target

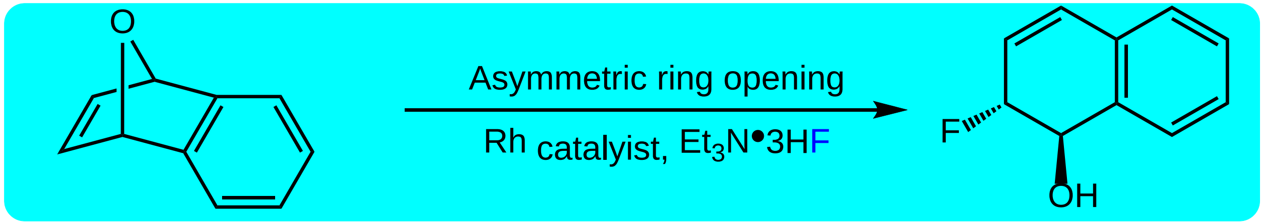


Summary

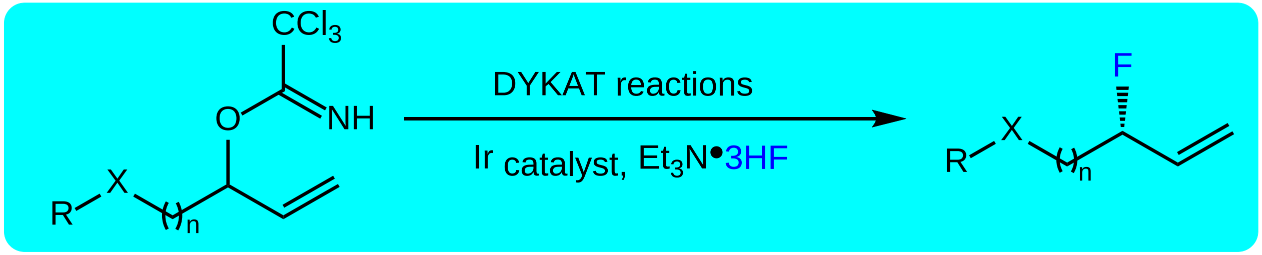
Doyle's work



Lautens' work



Nguyen's work



The First Paragraph

Over the past decade, fluorine-containing molecules have become increasingly important in several fields including medicinal chemistry, positron emission tomography (PET) imaging, agriculture, and materials science. The introduction of carbon−fluorine bonds into organic molecules can lead to improved bioavailability and, in turn, the efficacy of fluorinated drug candidates over their nonfluorinated parent compounds by affecting a wide variety of properties including pK_a, lipophilicity, metabolic stability, and binding affinity. Roughly 30% of agrochemicals and 20% of pharmaceutical targets currently on the market contain at least one fluorine atom. As a result, numerous methods have been developed to address the unmet challenges previously associated with the syntheses of aryl fluorides and enantioenriched aliphatic fluorides *via* nucleophilic fluorination.

The Last Paragraph

A useful catalytic enantioselective synthesis of branched allylic fluorides, from the reaction of racemic allylic tricloroacetimidate substrates with a mild $Et_3N \cdot 3HF$ reagent, has been developed utilizing chiral bicyclo[3.3.0]octadiene-ligated iridium complexes. We propose this catalytic process is likely to operate through dynamic kinetic asymmetric transformation (DYKAT) of racemic secondary allylic substrates. The scope is suitable for a wide variety of allylic trichloroacetimidates bearing *α*-branching, *α*-linear, *β*-oxygen, and *β*-nitrogen substituents, providing the fluorinated products in good yields with excellent branched-to-linear ratios and enantioselectivities. The current fluorination methodology is also suitable to generate allylic fluorides possessing two contiguous stereocenters with excellent catalyst-controlled diastereoselectivities using either $[IrCl(S,S)\text{-L1}]_2$ and $[IrCl(R,R)\text{-L1}]_2$ catalysts. Importantly, the

The Last Paragraph

fluorination of carbohydrate and estrone-derived substrates, bearing multiple stereocenters, proceeds with excellent diastereocontrol. The methodology is, however, limited to allylic imidate substrates having 1,1-disubstituted double bonds. The utility of the fluorination process has been demonstrated in the rapid and asymmetric synthesis of biologically relevant 15-fluoro-prostaglandin and neuroprotective P7C3-A20. We anticipate that these findings have important future implications for designing other catalytic enantioselective processes utilizing racemic allylic trichloroacetimidate substrates and transforming this methodology to radiofluorination.

Acknowledgement

本课件内容部分参考了上海有机所卿凤翎，胡金波等老师的授课课件，在此对所有有机所及国内从事氟化学研究的老师们表示敬意与感谢！