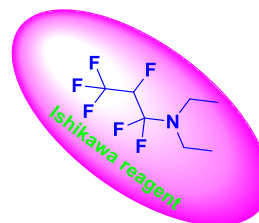
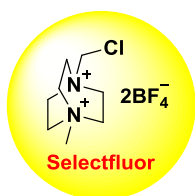
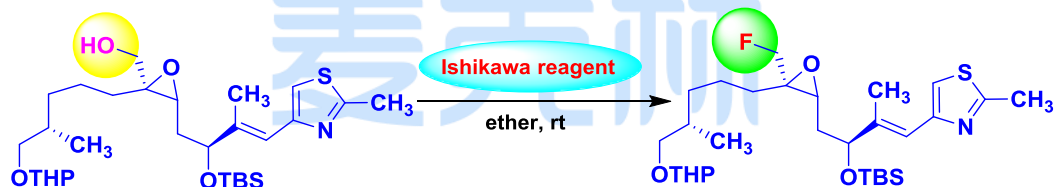
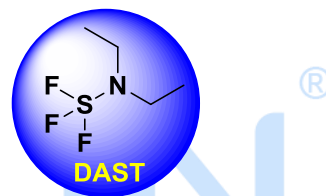
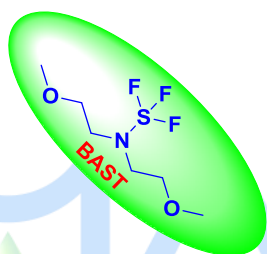




MACKLIN[®]
麦克林[®]

有机氟化合物的合成

Synthesis of Organic Fluorine Compound



上海麦格林生化科技有限公司项目部

上海麦恪林生化科技有限公司简介

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麦克林成立于 2013 年，公司总部设在上海浦东新区张江高科技园区，在美国加州、北京、广州、成都、济南、武汉、郑州等主要城市设立有分公司和办事处，可为全球客户提供便捷全方位的服务。

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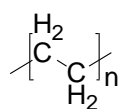
1. 前言

1771 年 Scheele 第一次报导了氟化氢，1836 年 Dumas 和 Peligot 报导了第一个有机氟化合物：一氟甲烷的合成，而元素氟的制备则在 50 年后，1886 年 Henri Moissan 分离到了氟气。

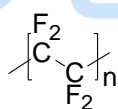
Table 1 H, F, Cl 的比较

	H	F	Cl
电子排布	1s ¹	2s ² 2p ⁵	3s ² 3p ⁵ 3d ⁰
电负性	2.1	4.0	3.0
电离能(kcal/mol)	315	403	300
键能 C-X (kcal/mol)	99	111	78
键长 C-X (Å)	1.09	1.32	1.77

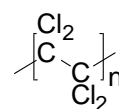
氟原子半径小，是电负性最强的元素，这种极强烈的电负性增加了氟与碳的亲合力。因此它们所形成的 C-F 键要比 C-H 键能大得多，明显地增强了含氟有机化合物的稳定性。如下面三个聚合物，聚乙烯和聚四氟乙烯都很稳定，而聚四氯乙烯则不稳定。



stable



stable



unstable

氟原子的引入导致有机及无机化合物具有独特的物理、化学性能及生理活性。从二十世纪三十年代初期氟里昂问世以来，氟化学一直表现出蓬勃发展的趋势。许多尖端技术（原子能工业、火箭、宇航等），和一些重大的工业项目及药物都采用了含氟的化合物。如 ²³⁵U 的浓缩，将铀转化为 UF₆，通过气体扩散从 ²³⁸U 中分离出同位素 ²³⁵U，这是原子弹制造的核心技术；在液晶材料中，用于 TFT-LCD 的高档液晶必须是对热化学、光、电稳定性好，电荷保持中间、粘度低、电阻率大（ρ≥1.0×10³Ωm）的高性能 TN 材料，以往，含氟基和酯类化合物无法满足这些要求，只有含氟液晶材料才能适用于 TFT-LCD，近十年来，几乎所有向列相材料的开发都是含氟液晶化合物；而号称塑料王的聚四氟乙

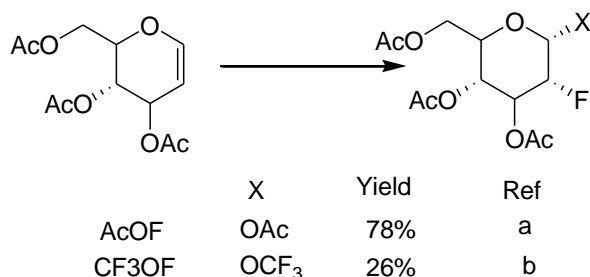
烯现在正应用在各个工业领域中。

在医药方面，含氟芳香族化合物为活性基团的一类药物有着举足轻重的作用。当氟原子或含氟基团（尤其是 CF_3 基团）引入化合物中，其电效应和模拟效应改变了分子内部电子密度的分布，影响了化合物内部结构的酸碱性，进而改变了其活性，而且还能提高化合物的脂溶性。氟原子取代了化合物中的氢原子，其类酯化合物在生物膜上的溶解性得到了增强，促进其在生物体内吸收的传递速度，使生理作用发生变化。所以不少含氟化合物比不含氟化合物在医药、农药等药物性能上具有用量少、毒性低、药效高、代谢能力强的优点。

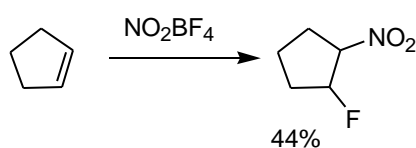
比如氟喹诺酮类抗菌素，是 20 世纪 70 年代初发展起来的一类新型抗感染药。用量最大、使用面最广的传统抗生素青霉素由于使用多年，已产生某些抗药性，导致部分人群对它过敏而不能使用。而氟喹诺酮类抗菌素则杀菌谱较广、毒副作用较小，且价格适中，是近年来发展较快的一类抗菌素。Lily 开发的氟西汀 (Fluoxetine)，是全球第一个上市的 SSRI 抗抑郁症药物，由于三氟甲基的引入，使其具有独特的药理性质和临床[®]疗效，倍受医生患者的青睐。

因此，有机氟化合物的合成是有机合成领域的一个重要的分枝。

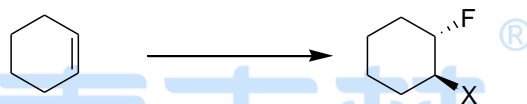
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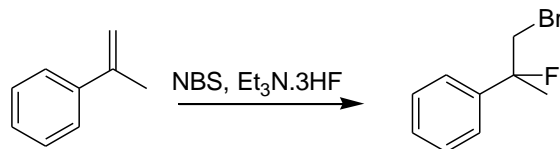
NO_2BF_4 对烯烃加成得到邻硝基氟化物，引入一个含氮官能团⁴。



邻卤氟化物可以通过不同试剂对烯烃的加成制得，如环己烯，在不同的条件下生成邻氯，邻溴和邻碘的氟代环己烷。



Reagent	Condition	X	Yield(%)	Ref
$\text{CH}_3\text{OCl}, \text{BF}_3$	CCl_4, rt	Cl	77	7
$\text{NCS}, \text{Et}_3\text{N} \cdot 3\text{HF}$	ether, rt	Cl	82	8
$\text{NCS}, \text{HF}/\text{Pyridine}$	TMS, rt	Cl	85	5
Br_2, F_2	$\text{CCl}_3\text{F}, -78^\circ\text{C}$	Br	61	6
$\text{CH}_3\text{OBr}, \text{BF}_3$	CCl_4, rt	Br	63	7
$\text{NBS}, \text{Et}_3\text{N} \cdot 3\text{HF}$	ether, rt	Br	88	8
$\text{NBS}, \text{HF}/\text{Pyridine}$	TMS, rt	Br	90	5
I_2, F_2	$\text{CCl}_3\text{F}, -78^\circ\text{C}$	I	64	6
$\text{NIS}, \text{Et}_3\text{N} \cdot 3\text{HF}$	ether, rt	I	75	8
$\text{NIS}, \text{HF}/\text{Pyridine}$	TMS, rt	I	75	5
AgF, I_2	CH_3CN	I	60	9

反应示例¹⁰:

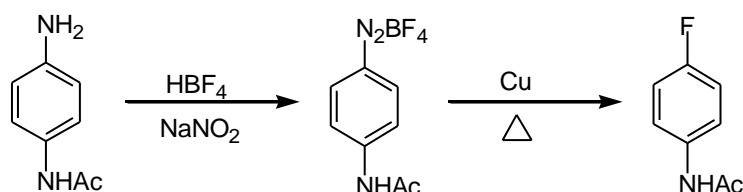
1-Bromo-2-fluoro-2-phenylpropane. A magnetically stirred mixture of α -methylstyrene (7.1 g, 60 mmol), triethylamine trihydrofluoride and (14.7 mL, 90 mmol) and dichloro- methane (60 mL) contained in a 250 mL, single-necked, round-bottomed flask is treated with N-bromosuccinimide (11.8 g, 66 mmol) at 0 °C. After 15 min, the bath is removed, and stirring is continued at room temperature for 5 hr. The reaction mixture is poured into ice water (1000 mL), made slightly basic with aqueous 28% ammonia, and extracted with dichloromethane (4 \times 150 mL). The combined extracts are washed with 0.1 N hydrochloric acid (2 \times 150 mL) and 5% sodium hydrogen carbonate solution (2 \times 150 mL) and then dried over magnesium sulfate . After removal of the solvent by rotary evaporation, the crude product is distilled to give the product: 11.6 g (89%); bp 50-52 °C (0.15 mm), n_D^{20} 1.5370.

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3. 通过重氮盐合成氟化合物

3.1 Balz-Schiemann 反应

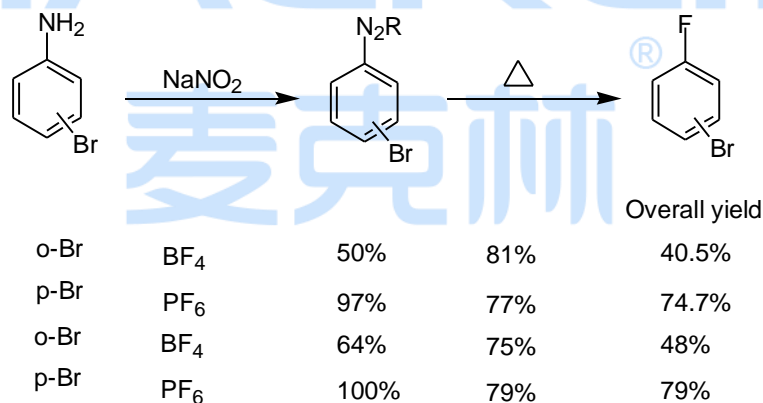
芳香胺类化合物通过重氮盐热解而得到相应的氟化物，是合成氟化合物的一个重要方法，我们称为 Balz-Schiemann 反应。一般情况下将重氮盐转变为不溶于水的硼氟酸盐 ArN_2BF_4 ，或直接在硼氟酸存在下重氮化，再加热分解重氮盐，便得到氟化物¹¹。



对一些热稳定性差的化合物，也可以通过光解或超声波¹²分解得到相应的氟化物。

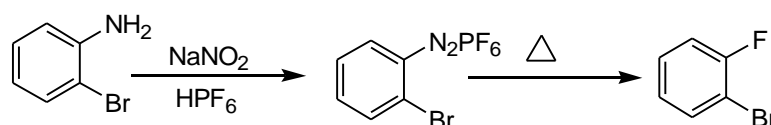
用六氟磷酸代替氟硼酸，得到的重氮盐 ArN_2PF_6 溶解性更小，因此提高了反应产率

13。



另外，其他重氮盐如 ArN_2SbF_6 ， ArN_2AsF_6 ， ArN_2SiF_6 也有报道。

这个方法的缺点是有时候硼氟酸盐 ArN_2BF_4 不太稳定，容易分解，其制备和分离比较困难，反应的重复性较差。

反应示例^{13c}:

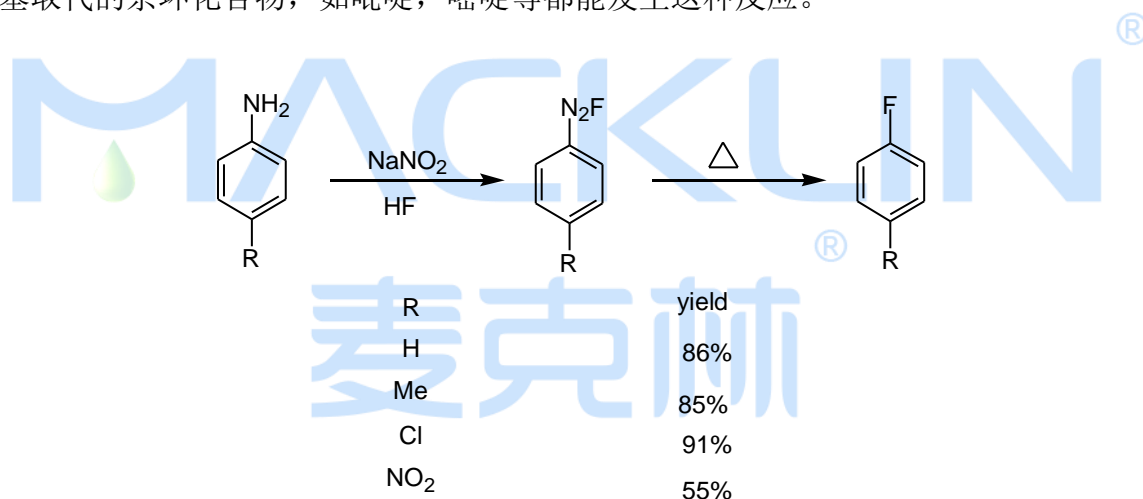
A. *o*-Bromobenzenediazonium hexafluorophosphate. A solution of 95 mL of 12*N* hydrochloric acid in 650 ml. of water is added with stirring to 60 g. of *o*-bromoaniline (0.35 mole; in a 2-L. three-necked flask equipped with stirrer and thermometer. Solution is effected by heating the mixture on a steam bath. A solution of 29 g. (0.42 mole) of sodium nitrite in 75 ml. of water is added with stirring while the mixture is maintained at -5° to -10° by means of a bath of ice and salt or of dry ice and acetone. At the end of the addition there is an excess of nitrous acid, which can be detected with starch iodide paper. Seventy-four milliliters (134 g., 0.60 mole) of 65% hexafluorophosphoric acid is added in one portion, with vigorous stirring, to the cold solution of the diazonium salt. Cooling and slow stirring are continued for an additional 30 minutes, and the precipitated diazonium hexafluorophosphate is then collected on a Büchner funnel. The diazonium salt is washed on the funnel with 300 ml. of cold water and with a solution of 80 ml. of methanol in 320 ml. of ether. The salt is partly dried by drawing air through the funnel for 2 hours. It is then transferred to a pile of several filter papers, powdered with a spatula, and dried at about 25 %1 mm. for at least 12 hours. The dried *o*-bromobenzenediazonium hexafluorophosphate is cream-colored; weight 108–111 g. (94–97%); m.p. $151\text{--}156^{\circ}$ (dec.).

B. *1*-Bromo-2-fluorobenzene. **Caution! This step should be carried out in a hood because the PF_5 evolved on thermal decomposition of the diazonium salt is poisonous.** The apparatus consists of a 1-L, three-necked, round-bottomed flask equipped with a thermometer, a condenser, a magnetic stirrer (optional), and a 250-mL Erlenmeyer flask that is attached by means of a short rubber Gooch connecting tube. The dry powdered hexafluorophosphate salt is placed in the Erlenmeyer flask, and 300 mL of heavy mineral oil is placed in the round-bottomed flask. The mineral oil is heated to $165\text{--}170^{\circ}$ by means of an oil bath or electric heating mantle and maintained at this temperature while the salt is added rapidly in portions over a

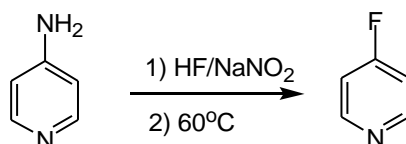
period of 30 minutes. The flask is cooled rapidly to room temperature, the side flask is removed, and 400 mL of 10% aqueous sodium carbonate is added slowly through the condenser. The mixture is steam-distilled until no more oil is visible in the distillate.

The oil, which is heavier than water, is separated, and the aqueous layer is extracted with three 50-mL portions of methylene chloride. The oil and extracts are combined, dried over anhydrous sodium sulfate, and distilled from a Claisen flask with an indented neck. Colorless 1-bromo-2-fluorobenzene is collected at 58–59 °/17 mm. or 156–157 °/760 mm.; weight 45–47 g. (73–75% based on *o*-bromoaniline); n_D^{25} 1.5320–1.5325.

这个反应的另一个改进方法就是直接用 HF/NaNO₂ 进行重氮化, 或在一些碱如吡啶, 2-羟基吡啶, 哌啶等存在下重氮化, 然后热解生成相应的氟化合物¹⁴, 苯胺类化合物和氨基取代的杂环化合物, 如吡啶, 嘧啶等都能发生这种反应。



反应示例¹⁴:



In a 100-mL PFA made reactor equipped with a reflux condenser, 4-aminopyridine (470 mg, 5mmol) was added to HF/Pyridine (70% HF, 10 mL) at 0°C. The mixture was allowed to stand at room temperature until 4-aminopyridine was completely dissolved. After cooling down to -78°C, NaNO₂ (380 mg, 5.5 mmol) was added to a solution of 4-aminopyridine in HF,

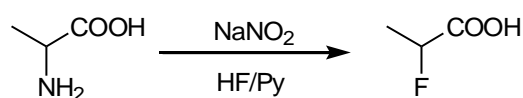
the stirred solution was allowed to stand at 0°C for 30 min and then stand at 60°C for 15-30 min. By quenching the resultant solution with ice water, followed by the neutralization with cold saturated NaHCO₃, the resulting mixture was extracted with CH₂Cl₂, the combined organic phase was dried over MgSO₄, and evaporated under reduced pressure to give the crude product, which was distilled to give the desired product (460 mg, 95%).

3.2 从 α-氨基酸合成 α-氟代羧酸

在 Olah 试剂 (HF/pyridine) 存在下, α-氨基酸的氨基在重氮化后被氟取代, 生成 α-氟代羧酸。高 HF/pyridine 比例(70/30)可能导致重排生成 β-氟代羧酸, 通常情况下使用的 HF/pyridine 比例为 48/52。α-氨基酸酯也能发生同样的反应。

RCH(NH ₂)COOH	R	HF : Pyridine (w/w)		RCH(F)COOH Yield(%)	Ref
Glycine	H	48	52	41	15
Alanine	CH ₃	48	52	76	15
2-amino-butanoic acid	C ₂ H ₅	48	52	82	15
Valine	i-C ₃ H ₇	48	52	75	15
Leucine	i-C ₄ H ₉	70	30	88	16,17
Isoleucine	s-C ₄ H ₉	48	52	71	15
Phenylalanine	PhCH ₂	48	52	86	16,17
Tyrosine	p-OHPhCH ₂	48	52	58(α : β 80/20)	15
Serine	HOCH ₂	70	30	80	16
Threonine	CH ₃ CH(OH)	48	52	43(α : β 80/15)	15
Aspartic acid	HOOCCH ₂	70	30	52	16,17

Glutamic acid	HOOC(CH ₂) ₂	70	30	28	16,17
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反应示例¹⁵:

To the alanine (1.74 g, 20 mmol) in pyridinium polyhydrogen fluoride (50 mL) in polyolefin bottle with good stirring at 0°C was added NaNO₂ (2.1 g, 30 mmol) in three portions over a period of 30 min. Stirring was continued at room temperature for 5 h, then quenched with 100 mL of ice water and extracted with ether. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, the residue was recrystallized to give the desired product (1.39 g, 76%)

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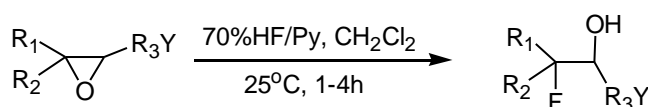
4. 亲核氟代

亲核性的氟代试剂如 HF，包括 HF 的盐(HF/Pyridine, Bu₄NH₂F₃, Et₃N·3HF, Me₃N·2HF), SbF₃, SbF₅, FBr₃, MF(M 为碱金属), MoF₆, SiF₄, SF₄, Ishikawa reagent 和 DAST 及其衍生物 Deoxo-Fluor 等，能对含氧和含硫底物（如环氧，醇，醛，酮，酸，酯，硫醇，硫羰基化合物，磺酸酯）发生亲核取代，生成相应的氟化合物。

4.1. 环氧开环合成氟化合物

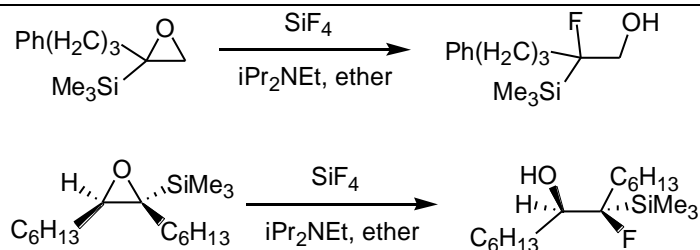
环氧化合物在 HF/Pyridine, Bu₄NH₂F₃, Et₃N·3HF, Me₃N·2HF, SiF₄, DAST 等亲核试剂作用下开环，生成邻位氟代的醇。

HF/Pyridine 在温和的条件下高产率的使环氧开环，有些底物的区域选择性和立体选择性也不错¹⁸。

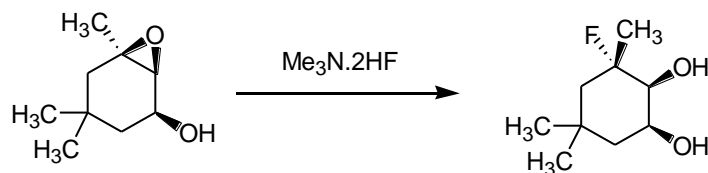


R ₁	R ₂	R ₃	Y	cis/trans %	Yield %	threo/erythro %
Ph	H	H	COOEt	22/78	95	20/80
Ph	H	CH ₃	COOMe	41/59	95	46/54
Ph	H	H	COOMe	0/100	95	5/95
-(CH ₂) ₅ -	H	H	COOEt		90	
Ph	H	H	CONH ₂	0/100	94	8/92
Ph	H	H	CN	59/41	91	57/43
Ph	CH ₃	H	CN	56/44	96	55/45
Ph	H	CH ₃	CN	49/51	90	50/50
-(CH ₂) ₄ -		H	CN		88	

SiF₄ 是更温和的一个试剂，很多官能团如双键，醚键，C-Si 键在这个条件下也不会断裂^{19,20}。



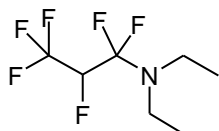
反应示例²¹:



The mixture of epoxide (1.56 g, 10 mmol) and $\text{Me}_3\text{N}\cdot 2\text{HF}$ (1.48 g, 15 mmol) in CH_2Cl_2 (50 mL) was heated to reflux for 2 hours. The resulting mixture was extracted with CH_2Cl_2 and washed with aq. K_2CO_3 solution and brine, the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired product (1.1 g, 63%).

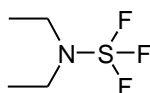
4.2. 氧被氟取代合成氟化合物

含氧官能团如羟基，醛，酮，羧酸及其衍生物在亲核氟代试剂作用下，氧原子被氟原子取代，生成相应的氟化合物，是合成氟化合物最常用的方法之一。常用试剂包括 $\text{HF}/\text{Pyridine}$ ， $\text{Bu}_4\text{NH}_2\text{F}_3$ ， $\text{Et}_3\text{N}\cdot 3\text{HF}$ ， SbF_3 ， SbF_5 ， FBr_3 ， MoF_6 ， SF_4 等，最常用的有三种： Ishikawa reagent ， SF_4 和 DAST 及其衍生物如 Deoxo-Fluor 等，其中 DAST 的应用最为广泛。



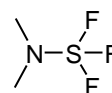
1,1,2,3,3,3-hexafluoro-propyldiethylamine

Ishikawa reagent

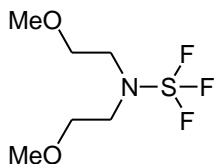


Diethylaminosulfur trifluoride

DAST

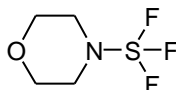


Dimethylaminosulfur trifluoride

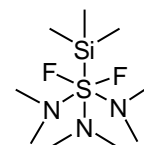


Bis(2-methoxyethyl)aminosulfur trifluoride

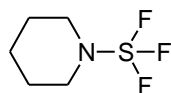
Deoxo-Fluor (BAST)



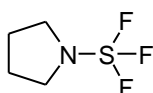
Morpholinosulfur trifluoride



Tris(dimethylamino)sulfur (trimethylsilyl)difluoride



Piperidinosulfur trifluoride



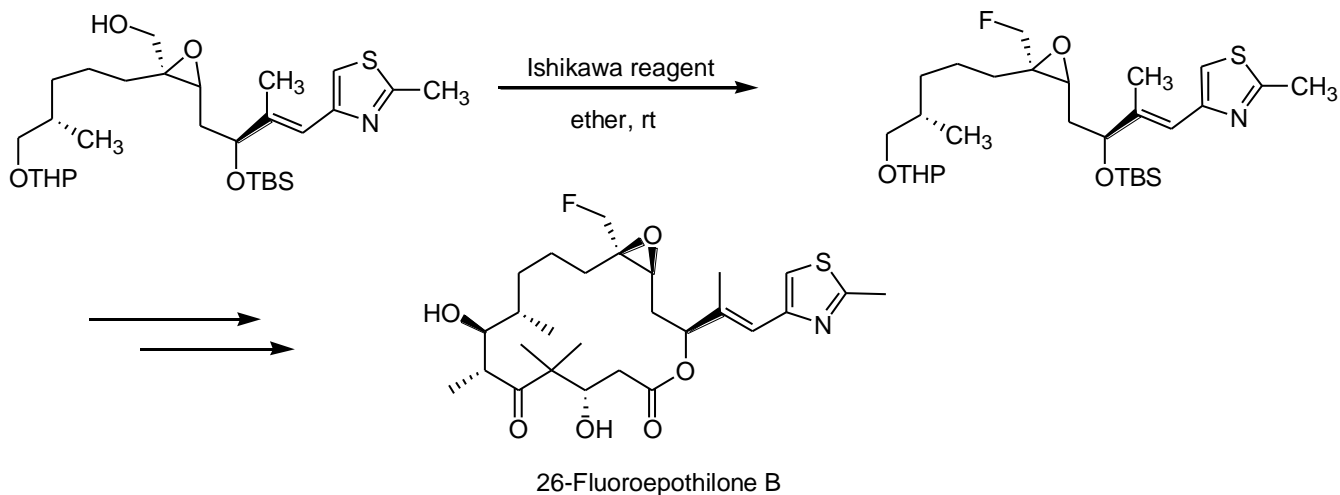
Pyrrolidinosulfur trifluoride

Ishikawa 试剂

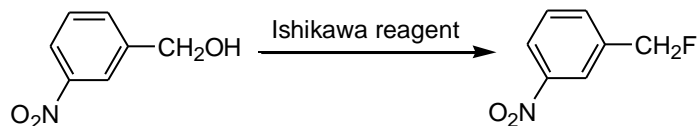
Ishikawa 试剂能将伯醇，仲醇和叔醇转化为相应的氟化合物，对羰基没有影响。其中伯醇反应性能比较好，仲醇和叔醇会有消除或偶联的副产物产生。反应通常在乙醚或二氯甲烷中进行。

ROH	Ishikawa reagent		RF
	rt		
R	solvent	Yield %	Reference
Cl(CH ₂) ₄	ether	64	22
CH ₃ CH ₂ CHBrCH ₂	ether	50	22
Br(CH ₂) ₈	ether	55	22
CH ₃ (CH ₂) ₇	ether	87	22
p-ClPhCH ₂	DCM	48	22
m-BrPhCH ₂	DCM	38	22
p-NO ₂ PhCH ₂	DCM	60	23
C ₆ H ₁₃ CH(CH ₃)	ether	62	24
(CH ₃) ₃ C	CCl ₄	78	24

用 Ishikawa 试剂氟代条件比较温和，选择性也很好，如下面这个分子的全合成中，环氧，双键和保护基都没被破坏²⁵。



反应示例²³:

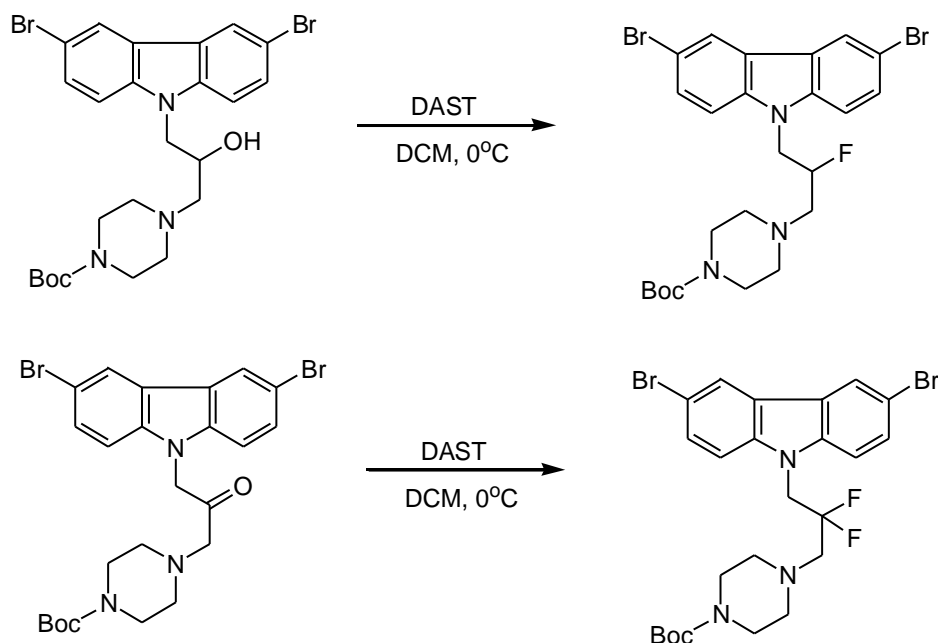


To a solution of Ishikawa reagent (3 g, 13.5 mmol) in dry dichloromethane (30 mL), a solution of 3-nitrobenzyl alcohol (1.5 g, 9.6 mmol) in dichloromethane (10 ml) was added dropwise at room temperature. After stirring for 6 h, the reaction mixture was left overnight. It was then poured into water and the oily product was extracted with diisopropyl ether. The ether extract was washed with water, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was distilled to give the desired product (1 g, 48%).

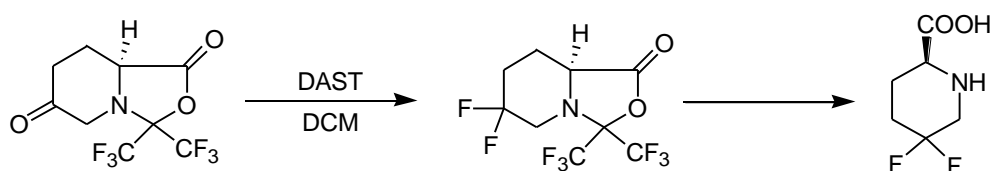
DAST

DAST 是液体，在干燥情况下室温或冰箱能长期保存，DAST 在 90°C 会分解，处理不当会有爆炸的危险。但由于操作简单和通用性强，DAST 是使用得最广泛的氟代试剂

之一。这个试剂能将羟基化合物转化为单氟代化合物，醛和酮转化为二氟代化合物²⁶，而对羧酸及其衍生物的羰基则没有影响。



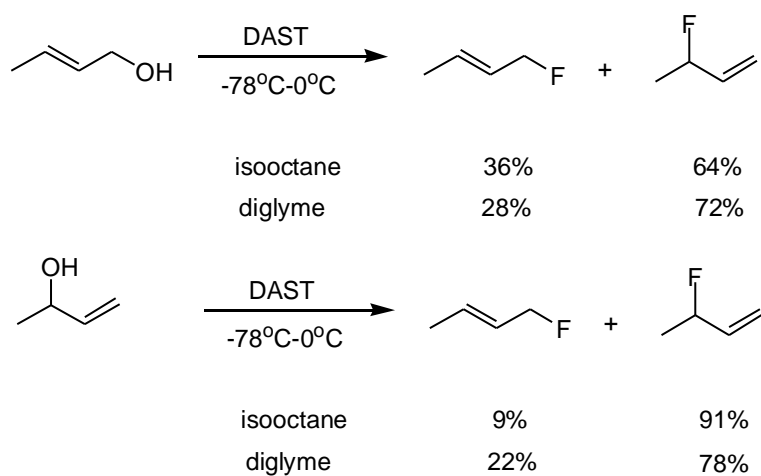
所以在羧酸及其衍生物如酯，内酯，酰胺，内酰胺等存在下，能选择性的取代羟基，醛和酮²⁷。



脂肪族和芳香族的伯，仲，叔醇都能高产率的转化为相应的氟化合物。反应通常用二氯甲烷，一氟三氯甲烷等作溶剂，取代羟基通常在较低温度下反应（-78°C），取代羰基一般在 0°C-40°C 反应。

ROH		DAST		RF
		-78°C to RT		
R	solvent	Yield %	Reference	
Cl(CH ₂) ₂	diglyme	69	28	
Br(CH ₂) ₆	DCM	53	29	
Br(CH ₂) ₈	DCM	61	29	
p-NO ₂ PhCH ₂	DCM	95	30	
i-C ₄ H ₉	DCM	49	28	
Ph ₂ CH	DCM	40	31	
Ph ₃ C	DCM	85	31	
C ₂ H ₅ C(CH ₃) ₂	DCM	88	28	

仲醇在取代时可能会发生碳正离子重排，所以异丁醇氟代后得到氟代异丁烷和氟代叔丁烷的混合物。烯丙醇类化合物同样会发生重排³²：



仲醇在取代的过程中会发生构型翻转，为手性合成提供了一个方法，如 (S)-2-辛醇在反应中构型完全翻转，得到 (R)-2-氟辛烷，ee%为 97.6%³³。这个方法在糖类和甾体的合成中应用较多³⁴。



DAST 对羰基的亲核氟代反应，醛作为底物活性比酮的活性高，所以在酮存在下可以选择性的取代醛基³⁵。

除了 DAST 以外，其他一些类似物如 Diethylaminosulfur trifluoride，Diisopropylaminosulfur trifluoride，Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor)，Morpholinosulfur trifluoride，Tris(dimethylamino)sulfur(trimethylsilyl) difluoride，Piperidinosulfur trifluoride，Pyrrolidinosulfur trifluoride 也能进行亲核氟代。特别是 Morpholinosulfur trifluoride 和 Deoxo-Fluor，其稳定性更好，所以反应能在较高的温度进行。

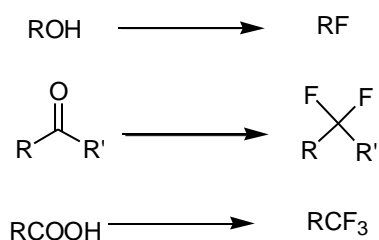
反应示例³⁶：



A dry, 1-L, three-necked, round-bottomed flask is fitted with a 500-mL dropping funnel, thermometer, a magnetic stirrer, and a reflux condenser protected from the atmosphere with a drying tube. The apparatus is flushed with dry nitrogen, and 150 mL of dry dichloromethane and 21 mL (0.16 mole) of diethylaminosulfur trifluoride [*Org. Synth.*, **Coll. Vol. 6**, 440 (1988)] are added to the flask. The contents of the flask are cooled to 10°, and a solution of 23 g (0.150 mole) of 4-nitrobenzyl alcohol in 450 mL of dichloromethane is added dropwise at a fast rate (45 minutes). The reaction mixture is allowed to come to room temperature and poured into a beaker containing 300 g of ice, decomposing any unreacted diethylaminosulfur trifluoride. The organic layer is separated, and the water layer is extracted twice with 45-mL portions of dichloromethane. The organic layer and extracts are combined, washed with 150 mL of water, and dried over anhydrous magnesium sulfate. Evaporation to dryness under reduced pressure gives 20.9–22.1 g (90–95%) of crude product. Recrystallization from 500 mL of pentane yields 15.5 g. (67%) of 4-nitrobenzyl fluoride as colorless needle-shaped crystals, m.p. 36–37°

SF₄

SF₄ 是氟代能力很强的一种试剂，通常和 HF 一起使用。除了能把羟基化合物转化为单氟代化合物，醛和酮转化为二氟代化合物之外，还能把羧基转化为三氟甲基，是合成三氟甲基化合物的一个重要方法，特别是芳香类三氟甲基化合物。



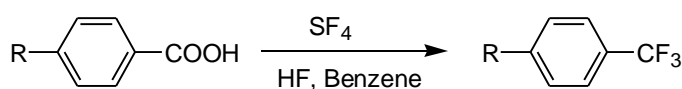
SF₄ 在氟化学的发展史上是很重要的一种氟代试剂，随着 DAST 等新型氟代试剂的发展，SF₄ 在氟化学中的应用逐渐减少，对羟基化合物和醛酮的氟代反应基本已被 DAST 等试剂取代。

SF₄ 最重要的应用就是从羧酸合成三氟甲基化合物。脂肪族羧酸为底物反应收率不高，生成的副产物是醚³⁷。

R	h	Yield%	Yield%
CH ₃	48	78	0
CH ₂ F	3	71	11
CH ₂ Cl	3	51	24
CH ₂ Br	3	67	24
CH ₃ CH ₂	20	96	0
CH ₂ ClCH ₂	3	45	21
CH ₃ CHCl	6	48	20
CH ₃ (CH ₂) ₄	20	56	0
c-C ₆ H ₁₁	3	74	0

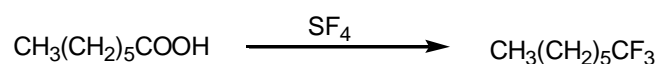
芳香族羧酸底物的产率还可以，不过反应需要加入 20—30 当量的 HF³⁸，反应操作

不方便。



R	OMe	Me	H	Cl	F	CF ₃	NO ₂	OH
Yield %	55	60	93	70	25	61	92	80

反应示例³⁹:



Twenty-six grams (0.20 mole) of heptanoic acid is placed in a 145-mL pressure vessel lined with Hastelloy-C. The air in the vessel is displaced with nitrogen, and the head of the vessel is secured in place. The vessel is cooled in a bath of acetone and solid carbon dioxide, and the nitrogen in the vessel is evacuated with a vacuum pump to a pressure of 0.5–1.0 mm. Sixty-five grams (95% pure, 0.57 mole) of sulfur tetrafluoride is transferred to the cold vessel. This is conveniently done by connecting a cylinder containing 65 g of sulfur tetrafluoride to the pressure vessel by a length of copper tubing having a 1/16-in. bore and 1/8-in. outside diameter.

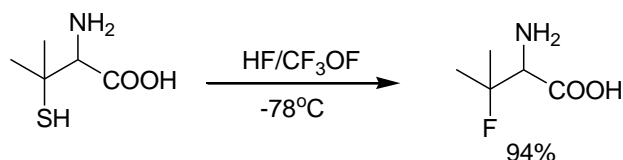
The pressure vessel is heated with agitation at 100 ° for 4 hours and at 130 ° for 6 hours. The vessel is allowed to cool to room temperature and the volatile by-products [*Caution! Toxic!*] are vented. The crude, fuming, liquid product is poured into a stirred suspension of 10 g. of finely divided sodium fluoride in 60 mL of pentane, the mixture is filtered, and the filtrate is fractionated through a 6-in. Vigreux column. 1,1,1-Trifluoroheptane is collected at 100–101 °/760 mm., n_D^{25} 1.3449. The yield is 21.7–24.6 g. (70–80%).

4.3. 硫被氟取代合成氟化合物

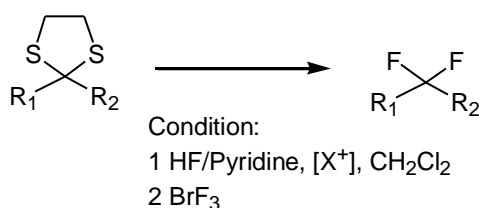
和氧一样，含硫化合物如硫醇，硫缩酮，硫缩醛以及硫羰基化合物在氟代试剂的作

用下，碳硫键断裂，硫原子被氟取代，生成相应的氟化物。这个方法于 1976 年由 Kollonitsch 和 Marburg 首次报导。和氧相比，硫更容易被取代。常用的试剂包括 HF/CF₃OF, HF/F₂, HF/Pyridine, Bu₄NH₂F₃, Tol-IF₂, SF₄, FBr₃, MoF₆ 和 DAST 等。

硫醇被氟取代生成相应的一氟代化合物⁴⁰。



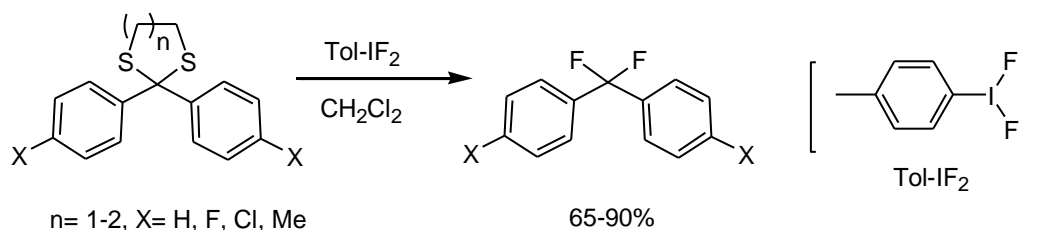
而硫缩酮和硫缩醛则生成二氟代化合物，如果底物含有对酸敏感的基团，Bu₄NH₂F₃ 是很好的替代方法。



R ₁	R ₂	Condition	Yield%	Ref
C ₅ H ₁₁	C ₅ H ₁₁	1	20	41
Ph	Ph	1	52	41
H	C ₁₁ H ₂₃	1	96	41
H	Ph	2	55-75	42

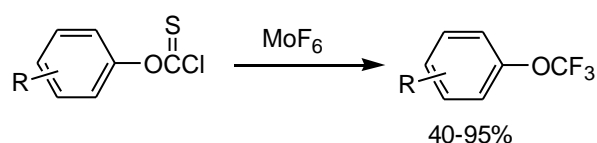
DBH= 1,3-dibromo-5, 5-dimethylhydantoin

Tol-IF₂ 也能在温和的条件下高产率的取代硫缩酮⁴³。

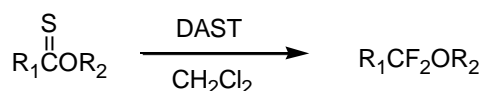


硫羰基化合物，如硫酰氯，硫酯等经 HF/Pyridine, Bu₄NH₂F₃, MoF₆ 或 DAST 处理，

也生成氟代化合物⁴⁴。



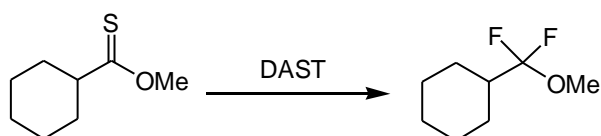
R= H, 2-Me, 3-Me, 4-Me, 4-Br,
4-Cl, 3-F, 4-F, 3-CF₃



R₁= C₇H₁₅, c-C₆H₁₁, adamantyl, Ph, PhCH=CH

R₂= Me, Et, Me₃SiCH₂

反应示例⁴⁴:



To a solution of thioester (1.58 g, 10 mmol) in dry CH₂Cl₂ (20 mL) was dropped DAST in CH₂Cl₂ (1M, 20 mL, 20 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 6 h, and then quenched by addition of saturated NaHCO₃ (30 mL). The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired product (1.32 g, 81%).

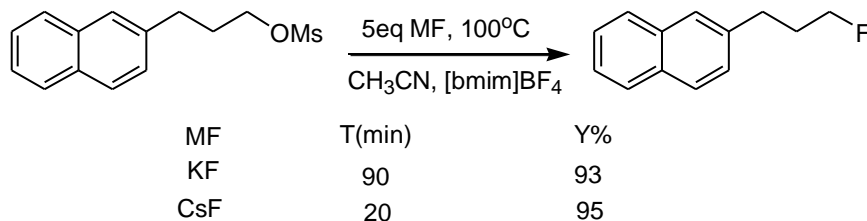
4.4. 磺酸酯被氟取代合成氟化合物

磺酸酯，如甲磺酸酯，对甲苯磺酸酯在极性非质子溶剂（DMF, CH₃CN, DMSO 等）中与碱金属氟化物发生亲核取代反应，得到氟化合物。

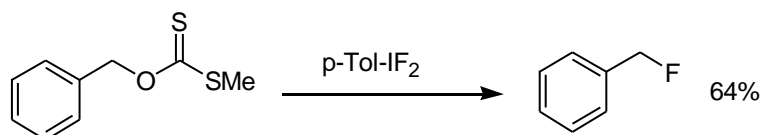
碱金属氟化物在非质子溶剂中活性如下：CsF>KF>NaF>LiF。CsF 的活性最高，但由于 KF 价格相对便宜，所以最常用。

反应体系中加入冠醚等相转移催化剂会加快反应进行，提高产率。

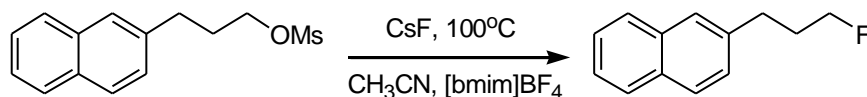
有的底物在离子液体中进行反应，能得到很好得结果。如下这个反应在离子液体 [bmim]BF₄ 中进行，产率相当高⁴⁵。



黄原酸酯也能被取代生成氟化物⁴⁶。



反应示例⁴⁵:



CsF (760 mg, 5 mmol) was added to the mixture of 2-(3-methanesulfonyloxypropyl)naphthalene (264 mg, 1.0 mmol), [bmim]-[BF₄] (3.0 mL), and H₂O (90 μL, 5 mmol) in acetonitrile (3.0 mL). The mixture was stirred at 100 °C for 20 min. The reaction was monitored by TLC. The reaction mixture was extracted from the ionic liquid phase with ethyl ether (7mL×3). The ether layer was dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/hexane) to give 2-(3-fluoropropyl)naphthalene (179 mg, 95%) as a colorless oil.

5. 亲电氟代

亲电性的氟代试剂对芳环，羰基化合物，烯醇醚，烯醇酯，烯胺，一些金属有机化合物等底物发生亲电取代，生成氟化合物，是非常重要的合成氟化合物的方法。

这些亲电氟代试剂主要包括如下几类：

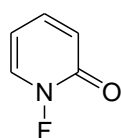
(1). F_2 , XeF_2 ,

(2). 含 O-F 键类试剂

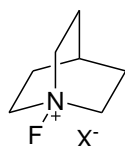
包括 CF_3OF , CH_3COOF , $CsSO_4F$

(3). 含 N-F 键类试剂

这是最为庞大的一类亲电氟代试剂，大部分已经商业化。由于使用方便，对这一类试剂的研究也很多，其在合成中的应用较为广泛。其中包括著名的 Selectfluor (F-TEDA- BF_4)。

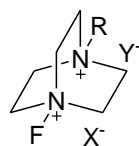


1



$X = F, OTf$

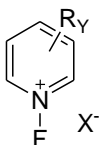
2, 3



$R = Me, CH_2Cl, CH_2CF_3$
 $X, Y = F, BF_4, OTf, OTs$

4-16

Selectfluor:
 $R = CH_2Cl$
 $X, Y = BF_4$

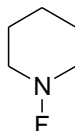


$R = Me, OMe, tBu, CH_2OCH_3,$
 $CN, CH_3CO_2, NO_2, Cl, CF_3,$
 $COCH_3$ (R often in position 2)

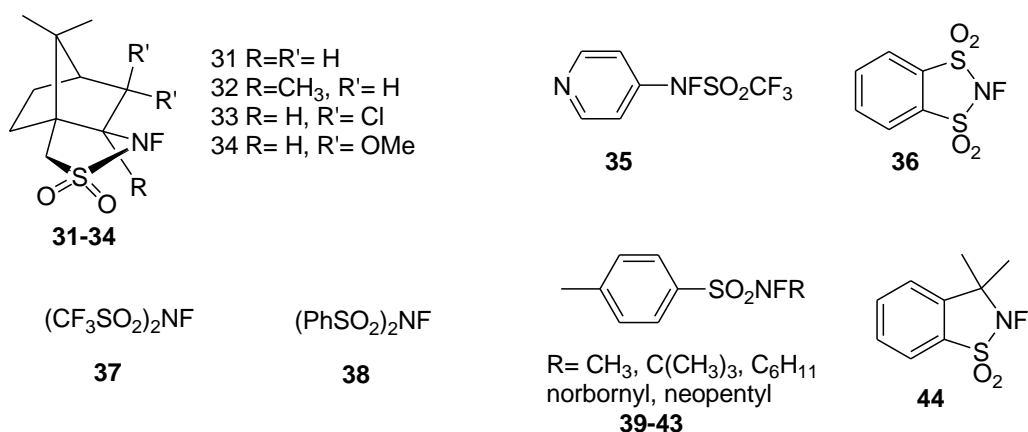
$X = BF_4, OTf, OSO_2F, SbF_6,$
 $ClO_4, PhNB_2F_7$

$Y = 1-5$

17-29



30

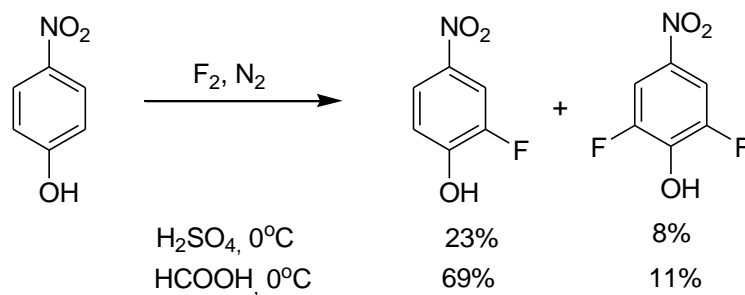


(4). 含 X-F 键类试剂:

包括 FCIO₃, Tos-IF₂

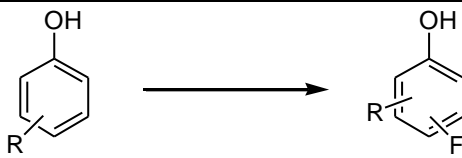
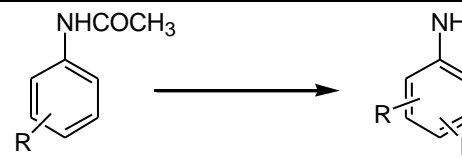
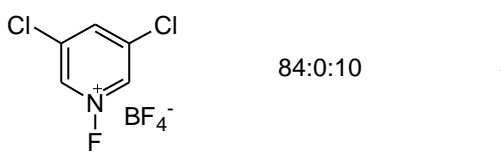
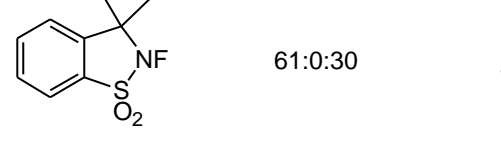
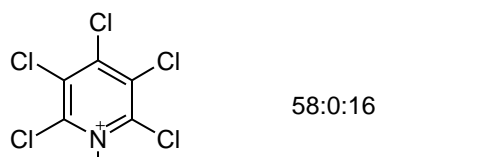
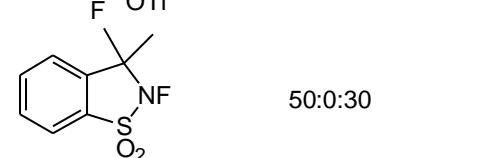
5.1 芳环的亲电氟代

用硫酸或甲酸作溶剂, 用氮气稀释的 F₂ 能直接对苯环发生亲电取代, 生成氟代苯, 不过由于用到 F₂, 其操作不方便。

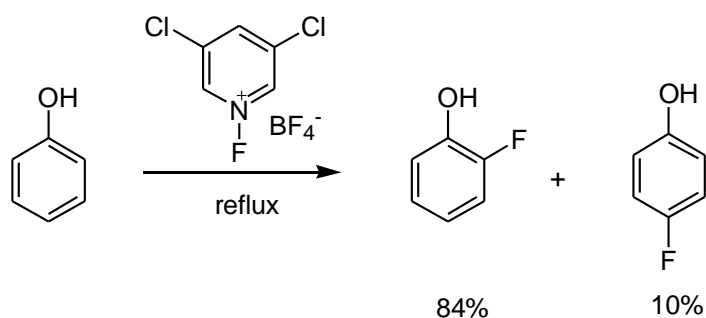


前面列出的大多数试剂, 都能对活化的芳环发生亲电取代, 得到相应的氟化合物。如下所示, 但反应的选择性不是很好, 产物主要是邻对位取代的混合物:

有机氟化合物的合成

Reagent	Yield% (o:m:p)	Reference	Reagent	Yield% (o:m:p)	Reference
					
CsSO ₄ F	56:0:11	49	CF ₃ OF	37:17:10	47
CH ₃ COOF	45:0:30	50	CsSO ₄ F	74:0:11	49
XeF ₂	19:19:9	55	CH ₃ COOF	48:0:7	48
(CF ₃ SO ₂) ₂ NF	60:0:40	51	XeF ₂	37:3:16	56
	84:0:10	53	(PhSO ₂) ₂ NF	24:0:16	54
	61:0:30	52		58:0:16	53
				50:0:30	53
			Selectfluor	49:0:31	52

反应示例⁵³:

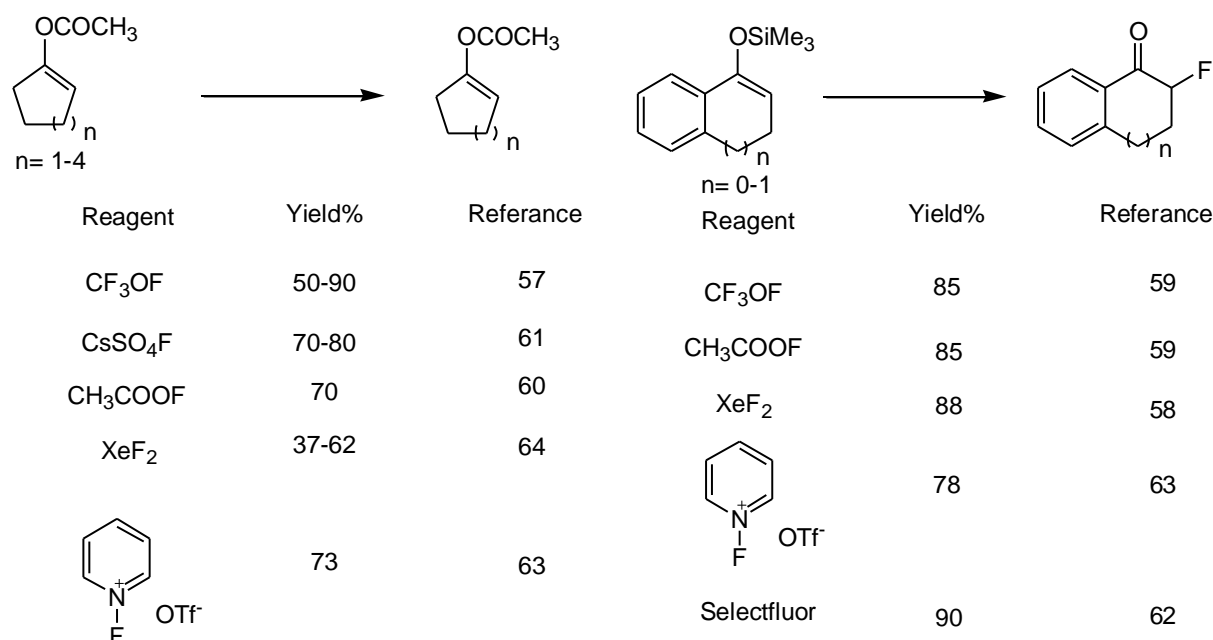


To the solution of phenol (0.94 g, 10 mmol) in dry CH₂Cl₂ (20 mL) was added N-fluoropyridinium salt (2.54 g, 10 mmol), the mixture was stirred under reflux for 24 h. The reaction was monitored by TLC. Then 20 mL of water was added to the reaction mixture, the resulting mixture was extracted with CH₂Cl₂, the organic phase was dried over Na₂SO₄, the solvent was evaporated under reduced pressure, the residue was purified by flash column

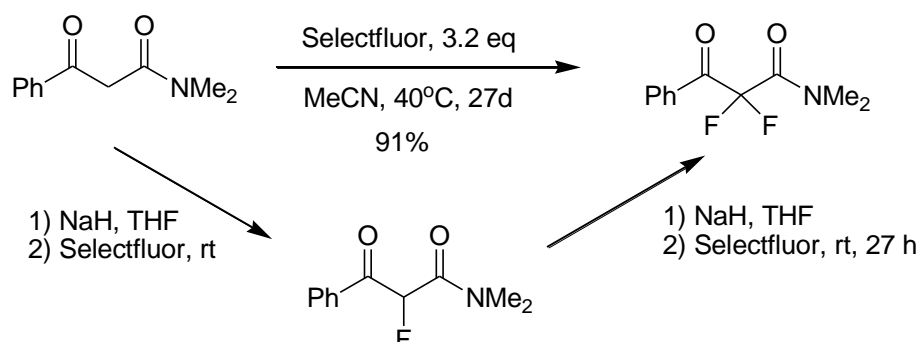
chromatography on silica gel to give the mixture of two isomers (1.05 g, 94%, o:p = 84: 10) as a colorless oil.

5.2 通过烯醇，烯醇醚，烯醇酯及烯胺合成 α -氟代羰基化合物

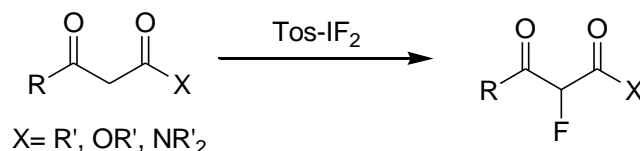
羰基化合物在碱性条件下烯醇化，或转化为烯醇醚，酯，烯胺，然后在亲电氟代试剂的作用下，能制备相应的 α -氟代羰基化合物，这是比较方便，也用的比较多的一种方法，特别在甾体化合物的合成中用的比较多。所用的氟代试剂包括 CF_3OF ， CH_3COOF ， CsSO_4F ， XeF_2 ， Tos-IF_2 以及以 Selectfluor 为主的大部分含 N-F 键的化合物等。



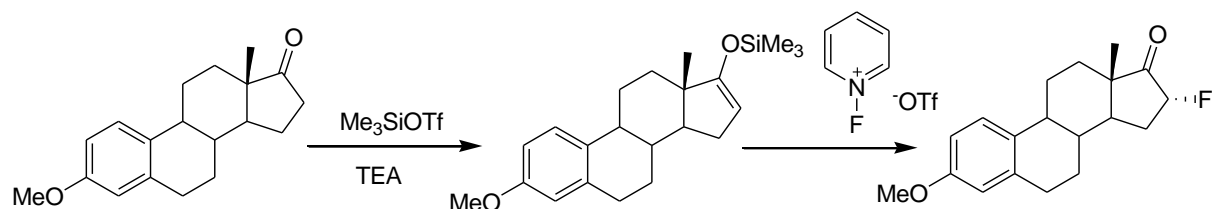
β -二羰基化合物直接氟代，往往得到一氟代和二氟代的混合物，如果延长反应时间，生成的主产物是更稳定的二氟代产物，如果分步氟代，则能缩短时间，提高效率。



如果想要得到单氟代的产物，Tos-IF₂ 是一个很好的选择。反应选择性很高，没有二氟代的产物生成⁶⁵。



反应示例⁶⁶:



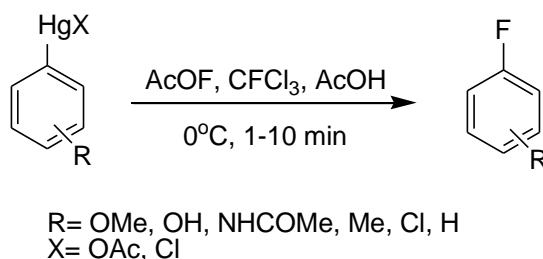
3-Methoxy-17-trimethylsiloxy-1,3,5(10)-16-estratetraene. A 125-mL, two-necked round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is purged with argon and charged with 6.8 g (0.024 mol) of estrone 3-methyl ether, 50 mL of dry benzene, and 4.0 mL (2.9 g, 0.029 mol) of triethylamine. The solution is stirred, 4.9 mL (5.6 g, 0.025 mol) of trimethylsilyl triflate is added through a syringe, and the mixture is refluxed for 1.5 hr. The reaction mixture is allowed to cool to room temperature, whereupon it separates into two layers. Dry hexane (40 mL) is added, and the upper hexane–benzene layer is separated, washed successively with saturated sodium bicarbonate and water, and then dried over magnesium sulfate. The drying agent is removed by filtration, and the filtrate is transferred to a 125-mL, round-bottomed, tared flask. The solution is evaporated to a constant weight with a rotary evaporator, initially at water-aspirator pressure and then at 0.5–1 mm, to leave 8.6 g (100%) of pale-yellow enol trimethylsilyl ether. This material is used immediately in Part C without purification.

16α-Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one (16α-fluoroestrone 3-methyl ether).

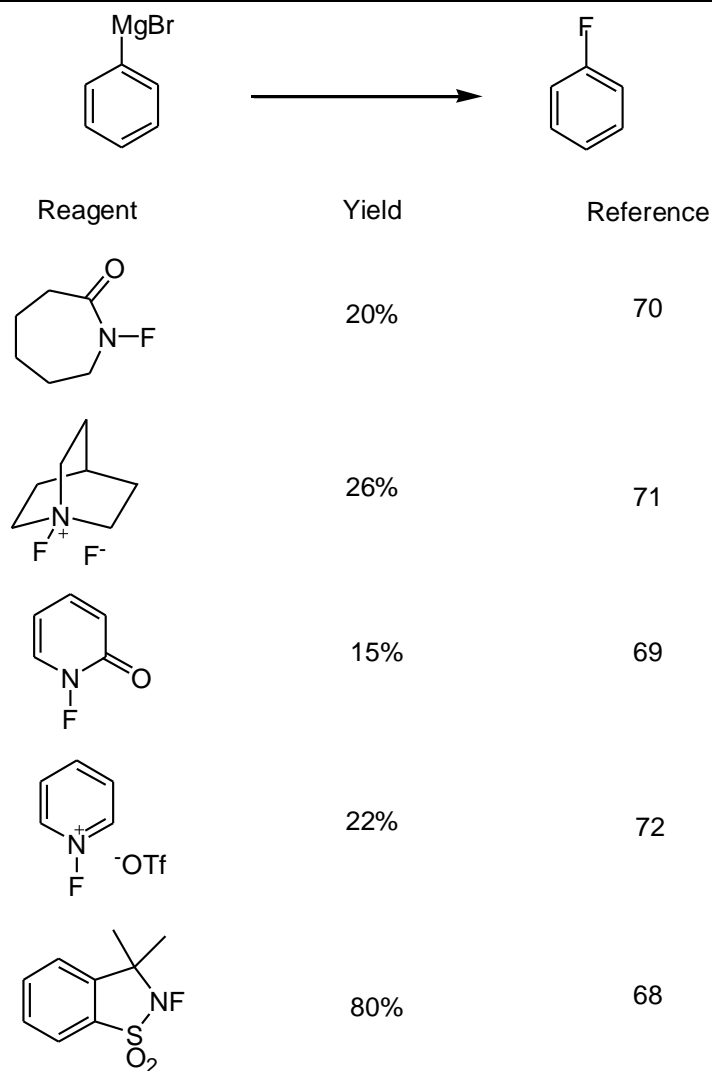
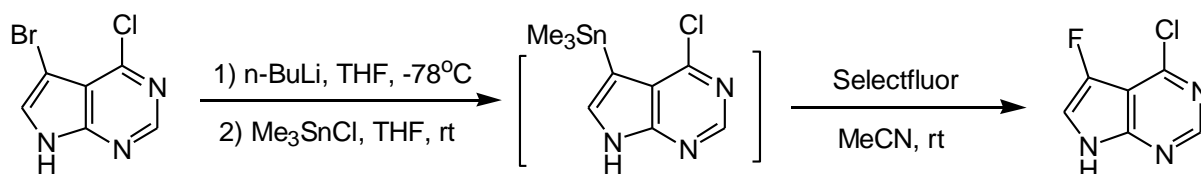
The 125-mL, round-bottomed flask containing the enol silyl ether from Part B is purged with argon, and 50 mL of dry dichloromethane is added. *N*-Fluoropyridinium triflate (6.5 g, 0.026 mol) is added in one portion, and the mixture is stirred at 20–25 °C for 8 hr. The reaction mixture is poured into water and extracted with three 60-mL portions of dichloromethane. The combined organic extracts are washed with saturated sodium bicarbonate and then with water, and dried over magnesium sulfate. The drying agent is removed by filtration and the solution is evaporated to dryness with a rotary evaporator. The resulting pale-yellow solid is column-chromatographed on silica gel (250 g, 60 × 4.5-cm column) using dichloromethane eluant to give 950 mg (14%) of estrone 3-methyl ether starting material and 4.8 g (66%) of 16 α -fluoroestrone 3-methyl ether as a colorless solid, mp 157 °C.

5.3 有机金属化合物的氟代

格式试剂，有机汞化合物，有机锡化合物等底物在一些亲电氟代试剂作用下，能转化为氟化合物⁶⁷。



其中格式试剂的应用最多，也容易操作，缺点就是产率比较低。

反应示例 ⁷³:

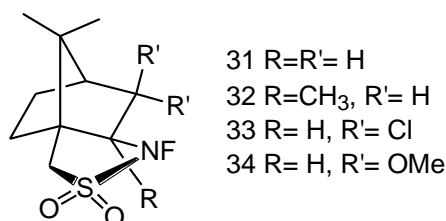
To a solution of 4-chloro-5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.92 g, 4.0 mmol) in tetrahydrofuran (25 mL) was added *n*-BuLi (2.5 M solution in hexane, 3.48 mL) dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for an additional 30 min. To this solution was added trimethylstannyl chloride (0.88 g, 4.4 mmol) in tetrahydrofuran (8 mL) dropwise over a period of 10 min. The reaction mixture was allowed to warm to room

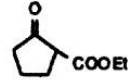
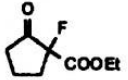
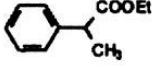
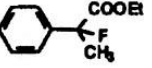
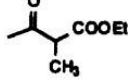
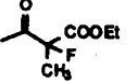
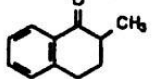
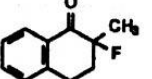
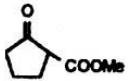



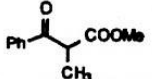
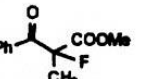
temperature and was stirred overnight. Saturated aqueous ammonium chloride (60 mL) was added and extracted with ethyl acetate (3 ×70 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, and evaporated to dryness. The residue was purified over silica gel to give the desired stannane (0.80 g, 63%) as a colorless solid.

To a solution of this compound (1.97 g, 6.20 mmol) in acetonitrile (60 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, 2.40 g, 6.5 mmol) in one portion, and the reaction mixture was stirred at room temperature for 7 h. The precipitate was filtered off, and the filtrate was evaporated in vacuo. The residue was purified on silica gel using ethyl acetate/hexane (3:7) as the eluent to give the desired compound (0.22 g, 21%) as a colorless solid.

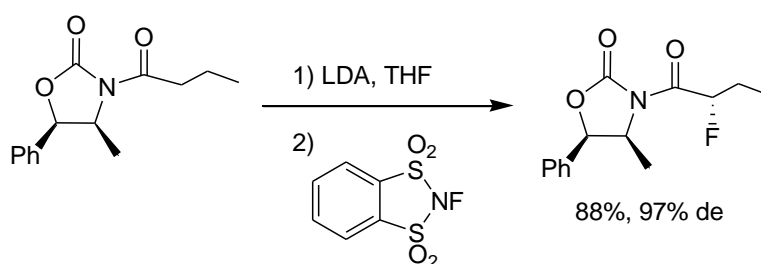
5.4 不对称亲电氟代

化合物 31–34 作为氟代试剂，在碱性条件下作用于羰基化合物，由于立体位阻的影响，往往能得到立体选择性的 α-氟代羰基化合物，但其 ee% 不是太高⁷⁴。

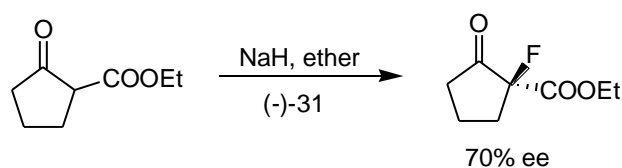


Entry	Ketone	Base	NF reagent	Product	% ee (%yield)
1		NaH	(-)-31		70 (63)
2	"	KH	(+)-32	"	<10 (<5)
3		LDA	(-)-31		35 (27)
4	"	LDA	(+)-32	"	<10 (34)
5		LiH	(-)-31		10 (31)
6		LDA	(-)-31		35 (<5)
7	"	NaHMDS	(+)-33	"	76 (S) (53)
8	"	LDA	(+)-33	"	10 (10)
9	"	NaHMDS	(+)-34	"	5 (41)
10		NaH	(+)-31		70 (63)
11		NaHMDS	(+)-33		0 (41)
12		NaHMDS	(+)-33		33 (54)

如果底物是手性的，也能得到高选择性的对映异构体⁷⁵。



反应示例⁷⁴:



Under an argon atmosphere, to a solution of 2-Oxo-cyclopentanecarboxylic acid ethyl ester (1.56 g, 10 mmol) in dry ether (20 mL) was added 60% NaH (0.48 g, 12 mmol) at 0°C, the mixture was stirred for 30 min, N-fluoro sultam (-)-**31** (3.5 g, 15 mmol) was added in several portions. The reaction mixture was stirred for another 1 h at room temperature, then quenched by saturated NH₄Cl solution, and extracted with EA. The combined organic layer was dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired product (1.09 g, 63%, 70% ee).

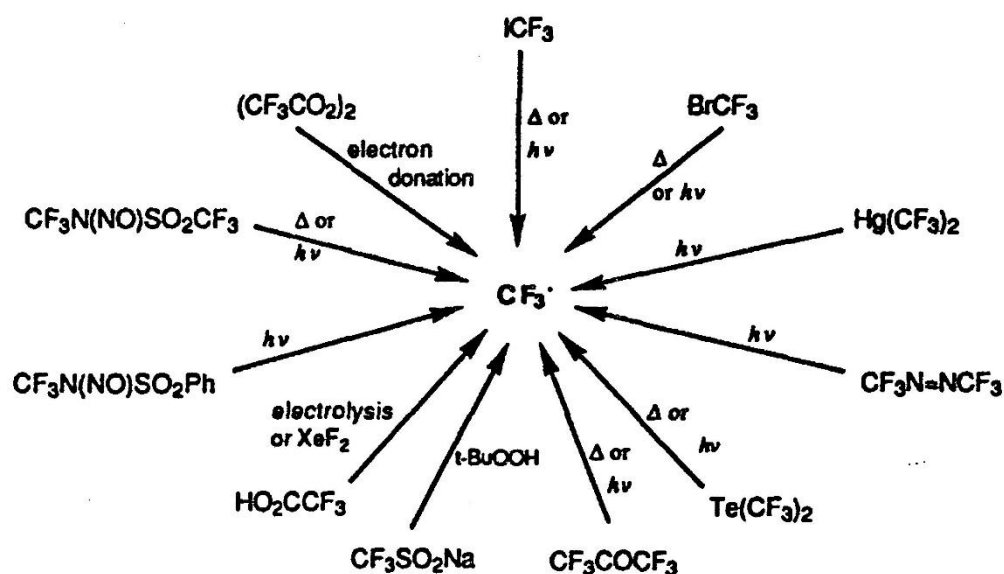


6. 三氟甲基的引入 (Trifluoromethylation)

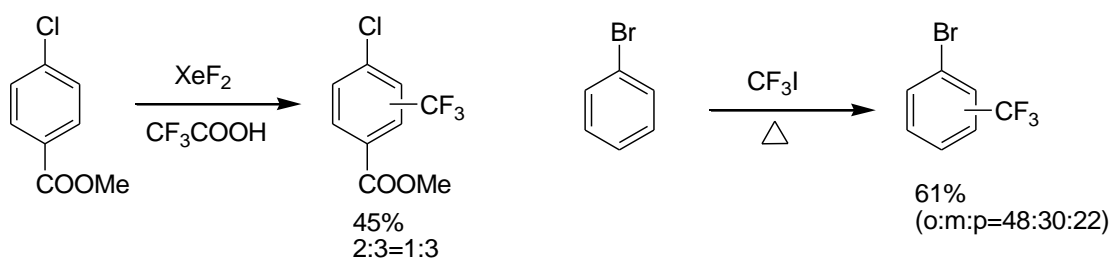
由于三氟甲基的强电负性，高稳定性和良好的脂溶性，三氟甲基的引入，往往使化合物的性质，特别是其生理活性发生显著的改变，其在新药开发中越来越被关注。所以如何将三氟甲基引入目标分子，成为氟化学中的一个重要的课题。经过多年的研究，已经发展了许多引入三氟甲基的方法，如我们前面提到的用 SF_4 将羧基转化为三氟甲基，按照反应机理，三氟甲基的引入主要分为三大类：自由基三氟甲基化，亲核三氟甲基化和亲电三氟甲基化⁷⁶。

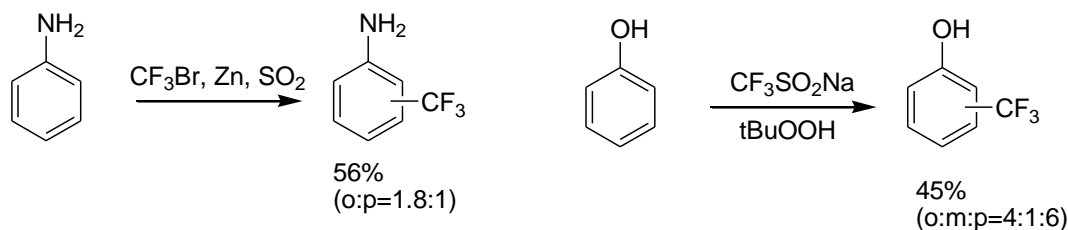
6.1 自由基三氟甲基化

三氟甲基自由基能通过多种途径得到，由于其亲电性强，所以能与富电子的苯环发生亲电加成反应。



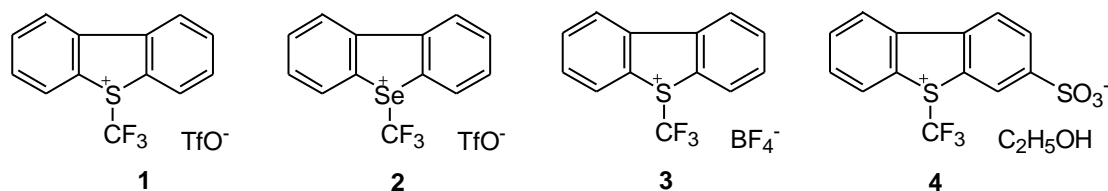
但这种方法产率低，选择性差，而且反应难于控制，所以在有机合成中的应用受到限制。





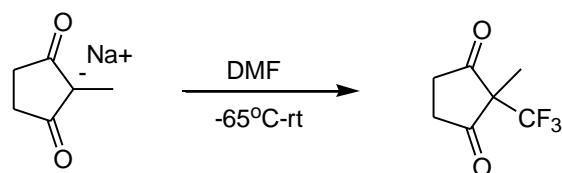
6.2 亲电三氟甲基化

1990年 Umemoto 报道了化合物 **1** 和 **2** 的合成及应用，这是第一种亲电性的三氟甲基化试剂⁷⁷。随后 Umemoto 报道了化合物 **3** 和 **4** 的合成及应用⁷⁸。

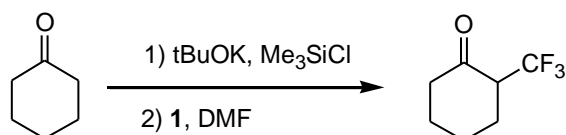


这几个化合物是稳定的晶体，具有良好的稳定性。苯并环是很好的离去基团，在取代过程中容易离去，有利反应进行。反应易于处理，特别是化合物 **4**，反应生成后的磺酸是水溶性的，极易除去。这种三氟甲基化并不是通过 CF_3^+ 进行，也不是 $\text{S}_\text{N}2$ 取代，可能是通过 SET 机理产生三氟甲基自由基，然后对碳负离子的亲电加成。

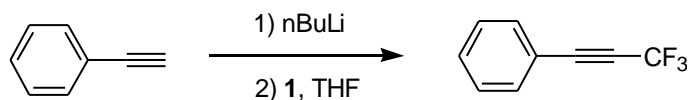
这种方法通用性强，通过这种方法，可以在多种亲核性化合物 (anions of β -diketones, β -keto esters and malonates, acetylide ions, silyl enol ethers, enamines, activated aromatics, heteroaromatics, alkane- and arenethiolate anions, halide anions, and various enolate anions) 上引入三氟甲基。但这几个试剂制备困难，价格较高，限制了其应用。



reagent	Yield%	ref
1	83	77
2	74	77
3	80	78a
4	81	78b



反应示例 ^{78a}:

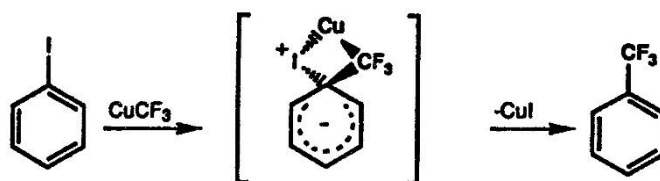


Under an argon atmosphere, to a solution of Ethynyl-benzene (1.02 g, 10 mmol) was dropped n-BuLi (2.5M, 6 mL, 15 mmol) at -78°C , the mixture was stirred for 1 h, trifluoromethyl onium salt **3** (11 mmol) was added in several portions. The reaction mixture was stirred for another 1 h at room temperature, then quenched by saturated NH_4Cl solution, and extracted with EA. The combined organic layer was dried over Na_2SO_4 , concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired product (0.58 g, 58%).

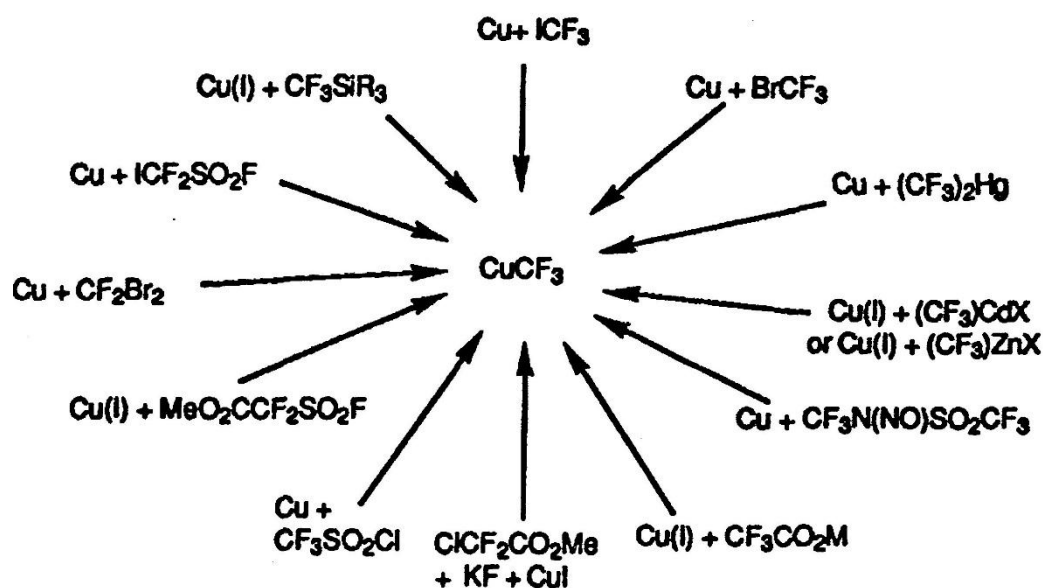
6.3 亲核三氟甲基化

在化合物中引入三氟甲基的另一类方法就是通过 CF_3^- 的亲核反应实现，主要包括两大类：基于 CuCF_3 对卤代苯的亲核取代和 TMSCF_3 对羰基化合物的亲核取代。

最早发现的方法是基于 CuCF_3 作为 CF_3^- 源对卤代苯（通常为溴代苯或碘代苯，后者活性更高）的亲核取代，从而合成三氟甲基取代的芳基化合物。这个方法是由 McLoughlin 于 1969 年首先报导，经过多年的发展，成为三氟甲基化最主要的方法之一⁷⁹。



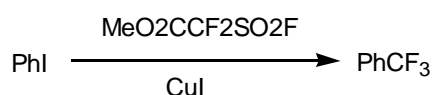
CuCF_3 可以通过多种方法，在 Cu 的存在下现制现用。



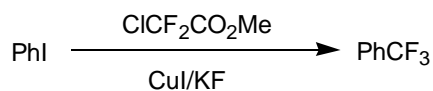
其中最常用的是 $\text{CuI}/\text{MeO}_2\text{CCF}_2\text{SO}_2\text{F}$ 和 $\text{CuI}/\text{KF}/\text{CClF}_2\text{CO}_2\text{Me}$ 这两个体系。反应操作很简单，收率较高。需要注意的是产物和原料在 TLC 上有时不会有明显的差异，需要做核磁来辨别 (^{13}C -NMR 和 ^{19}F -NMR)。

反应示例:

$\text{CuI}/\text{MeO}_2\text{CCF}_2\text{SO}_2\text{F}$ 体系⁸⁰

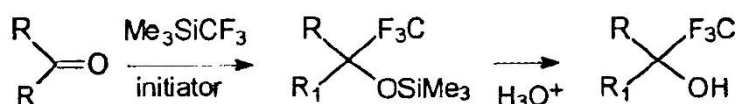


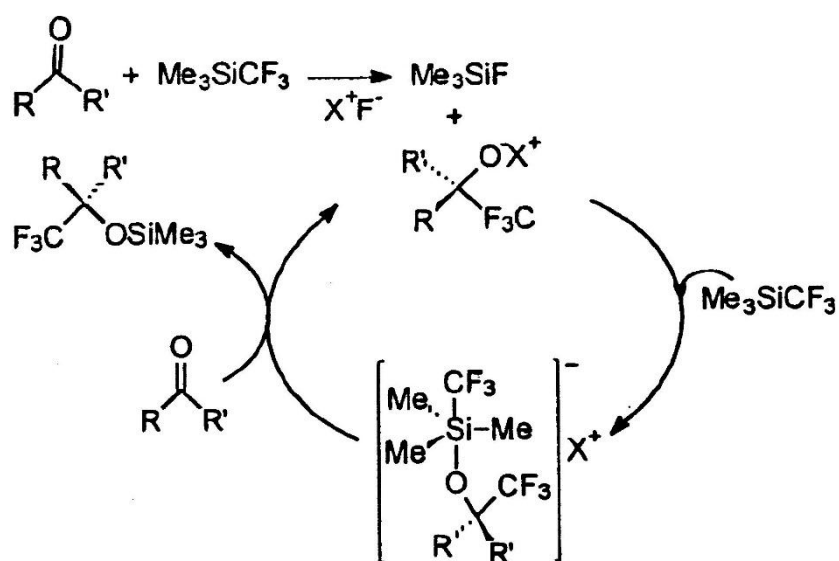
The mixture of PhI (2.04 g, 10 mmol), CuI (3.83 g, 20 mmol) and $\text{MeO}_2\text{CCF}_2\text{SO}_2\text{F}$ (4.75 g, 25 mmol) in dry DMF(50 mL) was stirred at 70°C overnight. Then 50 mL water was added to the reaction mixture, the resulting mixture was extracted with EA, washed with water and brine, the organic phase was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the desired product (1.22 g, 84%).

CuI/KF/CICF₂CO₂Me 体系⁸¹


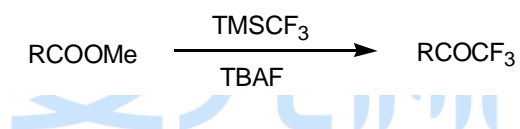
A mixture of dry KF (0.58 g, 10 mmol), CuI (2.0 g, 10 mmol), PhI (2.04 g, 10 mmol) and DMF (30 mL) was placed in a 50 mL three-necked round-bottomed flask fitted with stirrer bar, dry ice condenser and thermometer. The solution was heated to 120 °C under an Nz atmosphere for 0.5 h. Then CICF₂CO₂Me (2.89 g, 10 mmol) was added over 3 h and the contents stirred for a further 4 h. After reaction was completed, the reactants were poured into ice water (200 mL). The solution was filtered and the residue washed with ethyl ether (3×20 mL) and the aqueous layer was extracted with ethyl ether (3×20 mL). The combined extract was washed with water (30 mL) and dried over Na₂SO₄. After evaporation of the ether, distillation gave the desired product (1.3 g, 88%).

另一个方法就是 TMSCF₃ (Prakash 试剂) 对羰基化合物的亲核取代。此方法是在 1984 年由 Ruppert 首先报道, 随后 Prakash 对其应用做了大量的工作⁸², 这是从羰基化合物合成三氟甲基化合物最便捷的方法, 反应条件温和, 操作方便, 产率较高, 在有机合成中的应用也很广泛。





反应加入少量氟化物（如 TBAF, CsF 等）催化， $TMSCF_3$ 对羰基的缺电子碳进行亲核取代，最后生成三氟甲基取代的化合物，如果是酯作为底物，水解后则生成三氟甲基酮⁸³。



	Reagent 1	Solvent	<i>t</i> [h]	Product 6	Yield [%]
a	PhCO ₂ Me	toluene	18		95
b		CH ₂ Cl ₂	18		81
c		pentane	24		85
d	Ph-C≡C-CO ₂ Me	pentane	24		0 ^[a]
e	CH ₃ (CH ₂) ₁₂ CO ₂ Me	pentane	24		75
f		pentane	48		72
g	<i>t</i> Bu-CO ₂ Me	pentane	72		68
h		pentane	72		70

[a] Extensive polymerization.

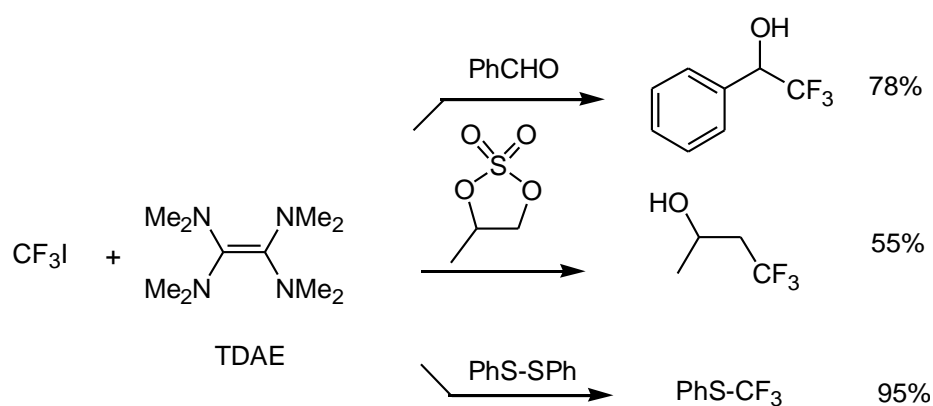
反应示例⁸³:



To the solution of methyl benzoate (1.36 g, 10 mmol) and TMSCF₃ (1.78g, 12.5 mmol) in dry toluene (20 mL) was added the initiator anhydrous tetrabutylammonium fluoride (TBAF; 2.5 mol% in THF) -78°C, and the reaction mixture was then allowed to warm slowly to room temperature, stirred for 18 h. The resulting mixture was treated with 2M hydrochloric acid (5 mL), extracted with EA, washed with water and brine, the organic phase was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to

give 1,1,1-trifluoroacetophenone (1.65 g, 95%).

另外，近来 Dolbier 等使用 $\text{CF}_3\text{I}/\text{TDAE}$ 体系，在温和的条件下也成功地实现了对亲电物种的三氟甲基化⁸⁴。



The End

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