One Point Optimization in Medicinal Chemistry

Renaissance of "Deuterium" and "Fluorine"

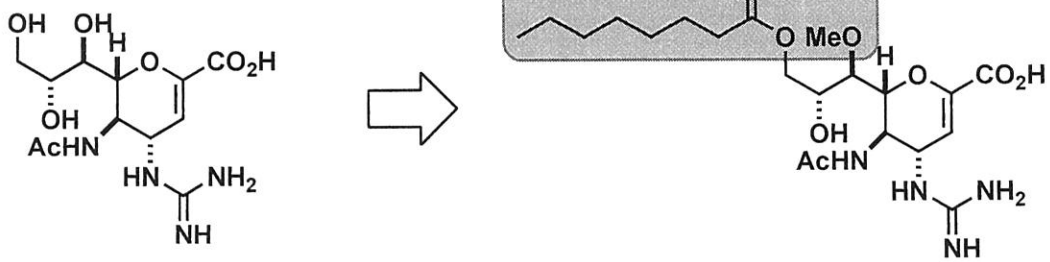
29 / July / 2009 M1 Part

Takafumi Yukawa

0. Introduction

Recentry, new domestic drug has attracted much attention under the global epidemic of flu.

Anti-Influenza Drug



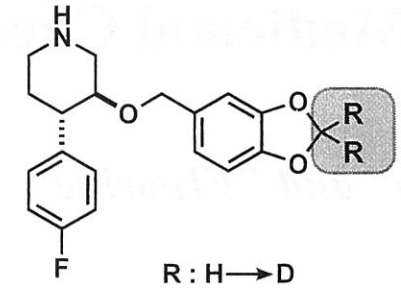
Zanamivir (*GSK* "Relenza")

CS-8959 (*Daiichi-Sankyo*)
Long Acting Neuraminidase Inhibitor

Dose: twice daily for 5 days —*pharmacokinetic change*→ **"only one time"**
(*Daiichi-Sankyo* Press)

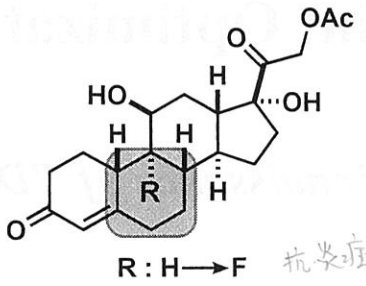
It is possible to create new medicines **only by changing some structures** of existing drugs.

Metabolism can be also improved only by changing "H" to "D" and "F" in a proper position.



R : H→D

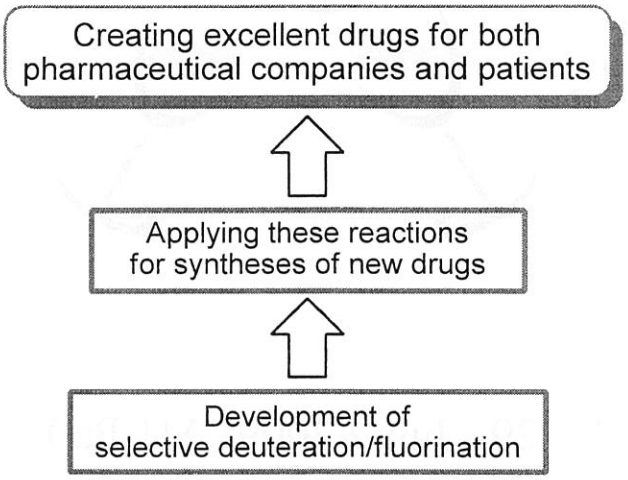
Less inactivation of CYP2D6



R : H→F

10 times activity

Optimization of adequate protons can enhance the value of medicine.



Selective H/D or H/F exchange reactions should be necessary.

⇒ Let me focus on the reaction development and drug creation.

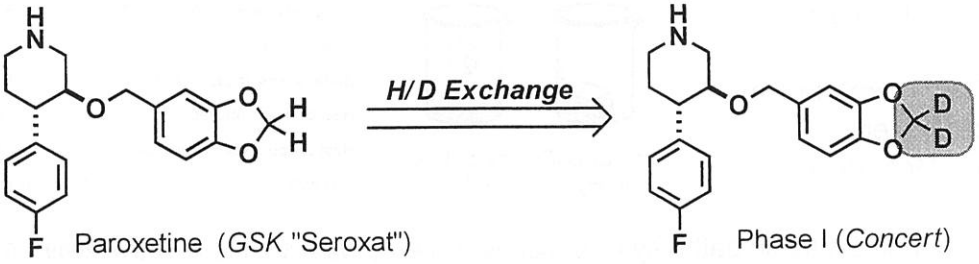
Today's Outline

0. Introduction
1. "D" in Medicinal Chemistry
   - 1-1. Deuterated Drug
   - 1-2. Deuterium's Feature
   - 1-3. Application for Blocking Group
   - 1-4. H/D Exchange reactions
2. "F" in Medicinal Chemistry
   - 2-1. Fluorinated Drug
   - 2-2. Fluorine's Feature
   - 2-3. Catalytic Asymmetric Fluorination
   - 2-4. Catalytic Asymmetric Trifluoromethylation
3. Conclusion

1. "D" in Medicinal Chemistry

1-1. Deuterated Drugs

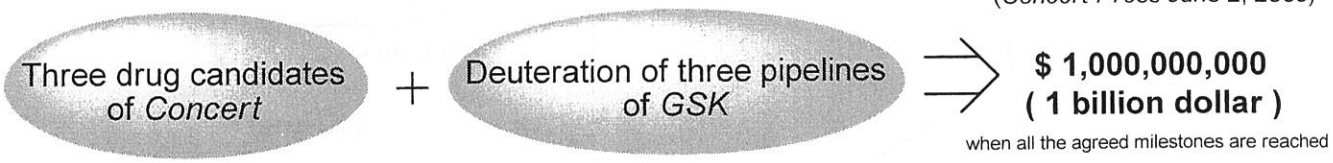
In May, one news was reported in the journal *Nature*. (*Nature* **2009**, *458*, 269)



New drug candidate developing by pharma venture has already had its own "patent".

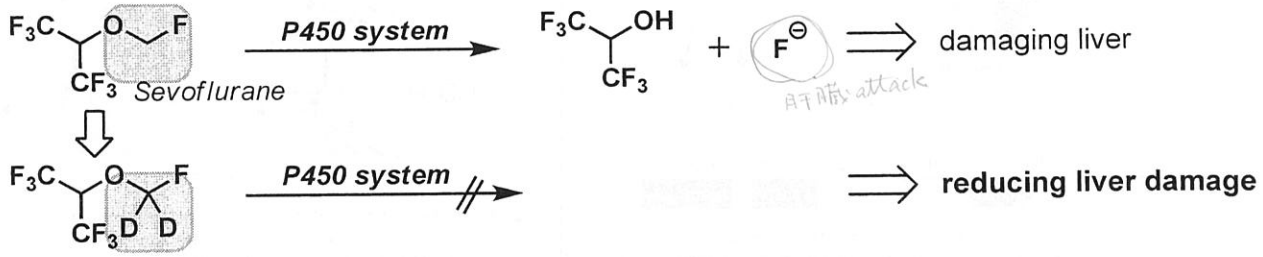
Later, *GSK* and *Concert* announced that they collaborate to commercialize deuterated drugs.

(*Concert Press* June 2, 2009)



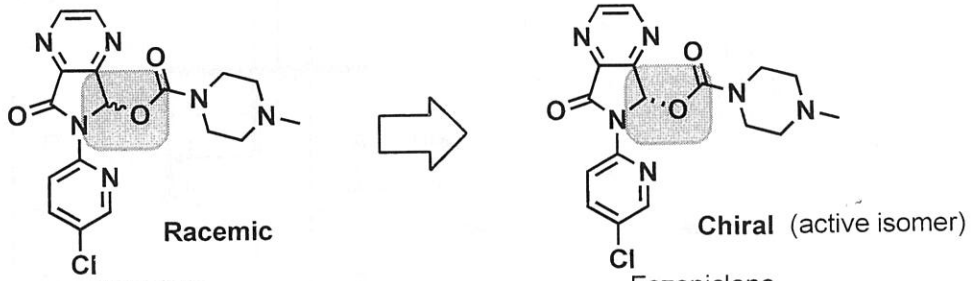
Deuteration of drug is now hot topic !

The effect of deuteration of drugs was known before. (Kushner et al *Can. J. Physiol. Pharmacol.* **1999**, 77, 79)



Many scientists have already known that deuteration is good tool.

There was a very similar case in 1990s.



Sepracor has succeeded by filing patents on active enantio-isomers of known drugs.

There is a possibility that all patents of deuterated drugs are licenced as the *Sepracor*'s case.

1-2. Deuterium's Feature

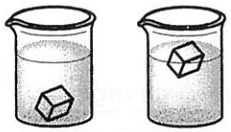
0.015% (1/6500) in nature (largely as HDO in water)
Stable (not radioisotope)
Double heavier than hydrogen
→ Deuterium Isotope Effect (DIE)

水素の同位体 計7種	存在比 (半減期)	陽子数=1 中性子数
^{1}H	99.985%	0
$^{2}H(=D)$	0.015%	1
$^{3}H(=T)$	(12.33 y)	2
^{4}H	(1.39×10^{-22} s)	3
^{5}H	(>9.1×10^{-22} s)	4
^{6}H	(2.90×10^{-22} s)	5
^{7}H	(2.3×10^{-23} s)	6

D_2O

Sparated from H_2O by chemical exchange processes
Weight more than H_2O (ice of D_2O sinks in H_2O)
Various usage

- NMR Spectroscopy
- Nuclear Fusion
  ($^2D+^3T \longrightarrow ^4He + n$)
- Isotope Tracer
- Neutron Moderator



ice of D_2O in H_2O | ice of H_2O in H_2O

Property	D_2O (Heavy water)	H_2O (Light water)
Freezing point (°C)	3.82	0.0
Boiling point (°C)	101.4	100.0
Density (at 20°C, g/mL)	1.1056	0.9982
Temp. of maximum density (°C)	11.6	4.0
Viscosity (at 20°C, mPa·s)	1.25	1.005
Surface tension (at 25°C, μJ)	7.193	7.197
Heat of fusion (cal/mol)	1,515	1,436
Heat of vaporisation (cal/mol)	10,864	10,515
pH (at 25°C)	7.41 (sometimes "pD")	7.00

ex) Analysis of biosynthetic pathways (Muranaka et al *Proc. Natl. Acad. Soc. U.S.A.* **2009**, *106*, 725)

two sterol biosynthetic pathways

{ Lanosterol pathway (only mammals/yeast)
{ Cycloartenol pathway (only higher plants)

⟹ Is that right that lanosterol pathway doesn't exist in higher plants?

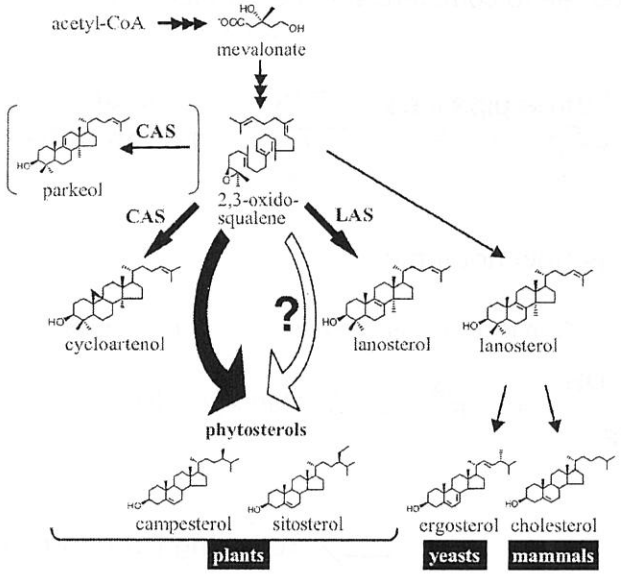


Fig. 1. Cyclization step of oxidosqualene in yeasts, mammals, and plants. Recently, lanosterol synthase genes were identified from several plants, *Arabidopsis thaliana*, *Panax ginseng*, and *Lotus japonica* (6–8). However, no clear data confirm the existence of that biosynthetic pathway of phytosterol via lanosterol in the plant kingdom. CAS, cycloartenol synthase; LAS, lanosterol synthase.

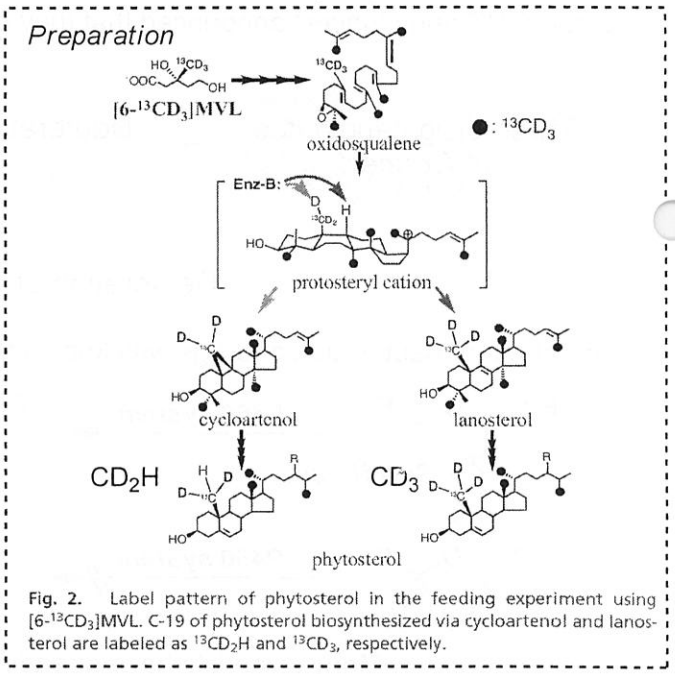


Fig. 2. Label pattern of phytosterol in the feeding experiment using [6-$^{13}CD_3$]MVL. C-19 of phytosterol biosynthesized via cycloartenol and lanosterol are labeled as $^{13}CD_2H$ and $^{13}CD_3$, respectively.

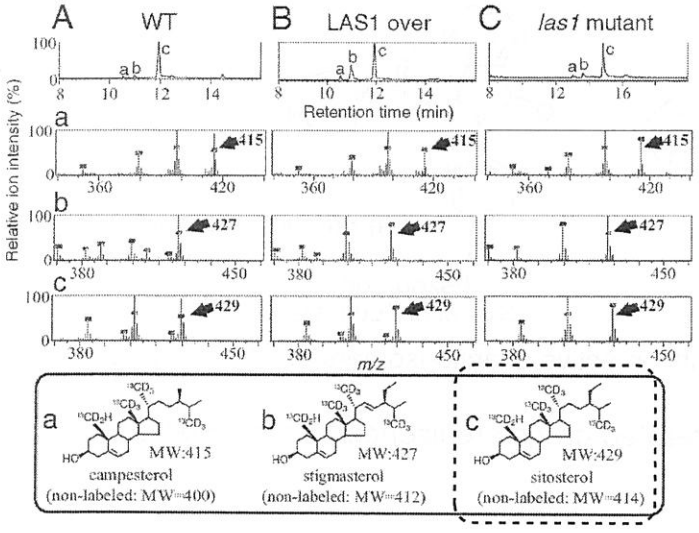
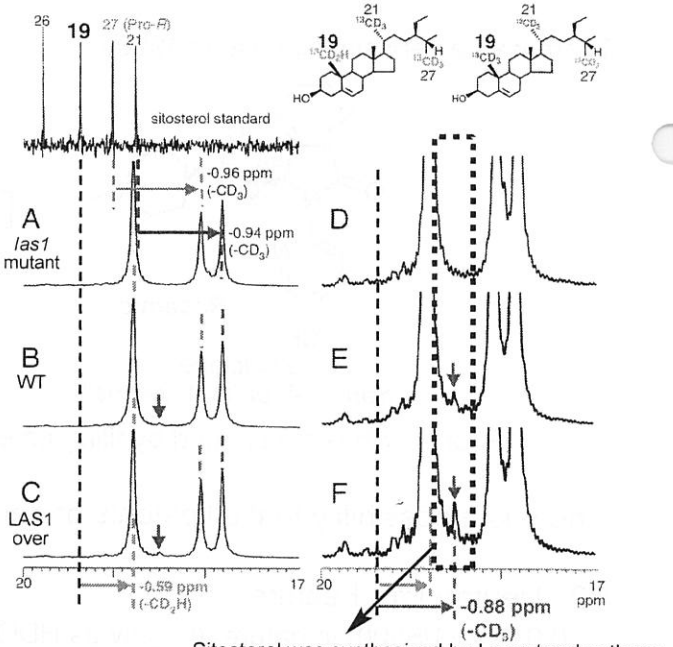


Fig. 4. GC chromatographs of sterol fractions and MS data for labeled phytosterols in (*A*) WT, (*B*) LAS1 overexpressing plant, and (*C*) *las1* mutant. Nonlabeled campesterol, stigmasterol, and sitosterol have molecular ions at *m/z* = 400, 412, and 414, respectively. Extracted phytosterols (*a*) campesterol, (*b*) stigmasterol, and (*c*) sitosterol have major molecular ions at *m/z* = 415, 427, and 429, respectively. Structures estimated by molecular ions are shown. GC analyses were performed with an HP-5 column and DB-1 column for WT and LAS1 overexpression, and *las1* mutant, respectively. MW, molecular weight. LAS1 over, LAS1 overexpressing plant.



Sitosterol was synthesized by Lanosterol pathway.

Fig. 5. Expanded C-19 region (17–20 ppm) of the ^{13}C-{^1H}{^2H}NMR spectra of labeled sitosterols in (*A*) *las1* mutant, (*B*) WT, and (*C*) LAS1-overexpressing plant. Enlargements of the *y*-scale from spectra *A*–*C* are shown in *D*–*F*, respectively.

Lanosterol pathway exists
(only 1.5% compared to cycloartenol pathway)

Deuterium Isotope Effect (DIE)

Kinetic Isotope Effect (KIE) between H and D.
Effect is the largest when the relative mass change is the greatest

ex) relative mass change

^{1}H to ^{2}D : 100% **cf. ^{12}C to ^{13}C : 8%**

Actually,

- ^{12}C-^{1}H reacts **6~10 times faster** than ^{12}C-^{2}D.
  (cf. ^{12}C-^{1}H reacts only **1.04 times faster** than ^{13}C-^{1}H)
- Frequency for ^{12}C-^{1}H bond is 1.4 time that of ^{12}C-^{2}D.

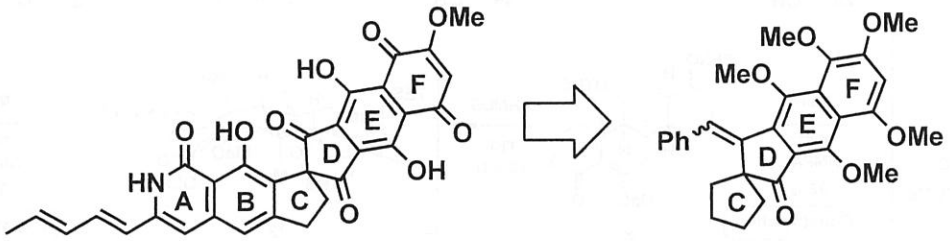
$\Leftrightarrow$ C-D reacts much slower than C-H

$\Rightarrow$ Application for "protecting in organic synthesis" and "drugs".

1-3. Application for Blocking Group

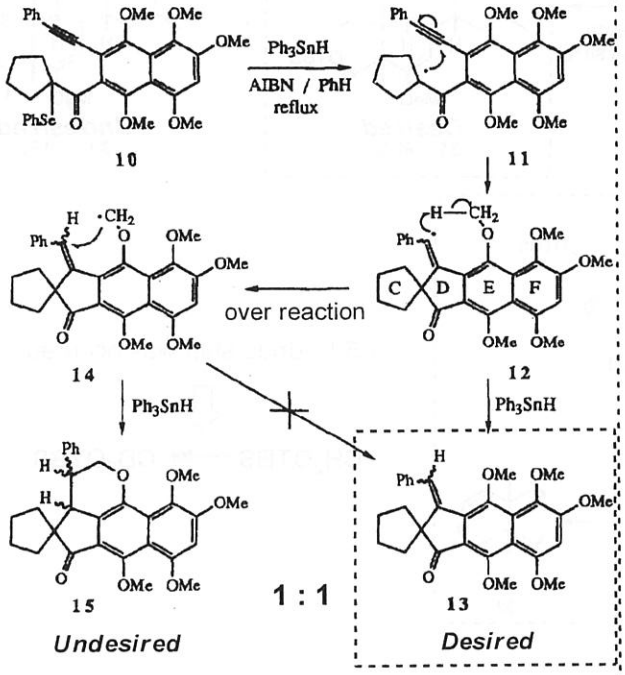
DIE can be used in total synthesis to avoid undesired reactions.

Model Study of Fredericamycin A (Clive et al *J. Am. Chem. Soc.* **1994**, *116*, 11275)



Fredericamycin A *for model study*

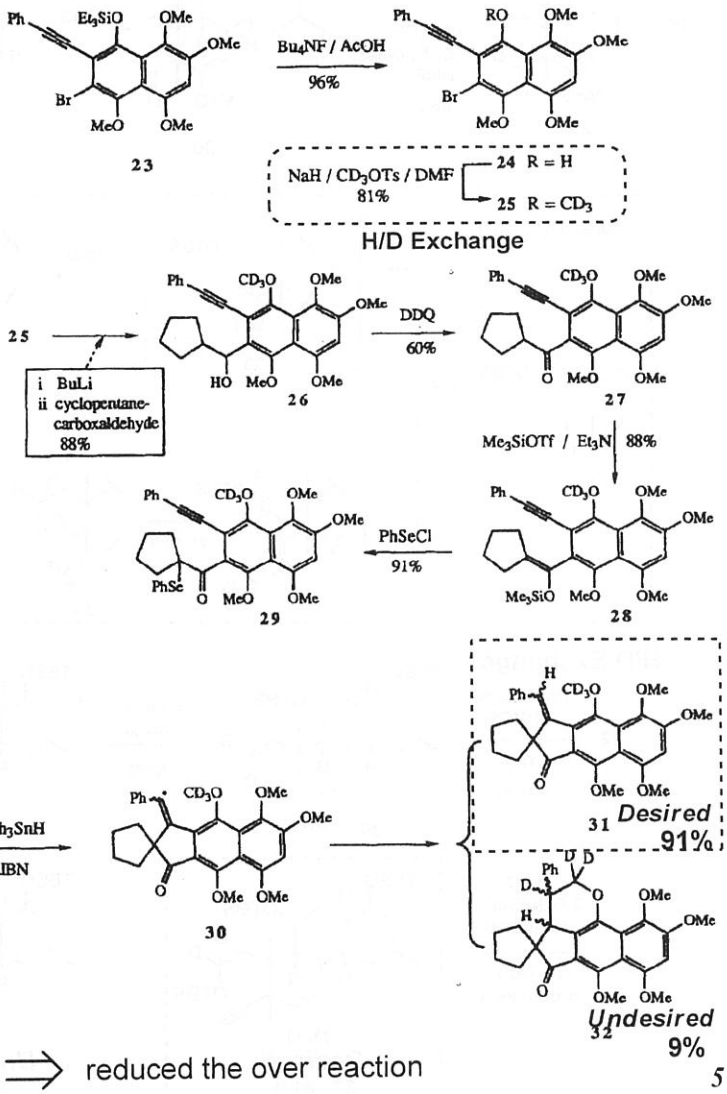
Initial trial



Further radical cyclization was occurred with neighbor MeO group.

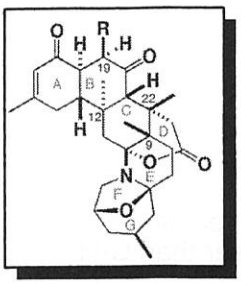
$CH_3O \longrightarrow CD_3O$

H/D Exchange



$\Rightarrow$ reduced the over reaction

Norzoanthamine (Miyashita et al *Science* **2004**, *305*, 495 / Miyashita *Pure Appl. Chem.*, **2007**, *79*, 651)



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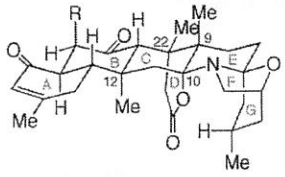
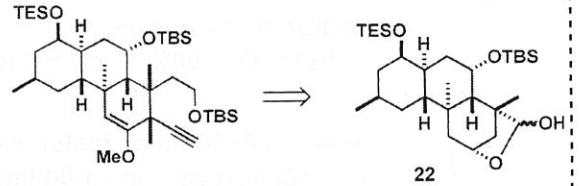


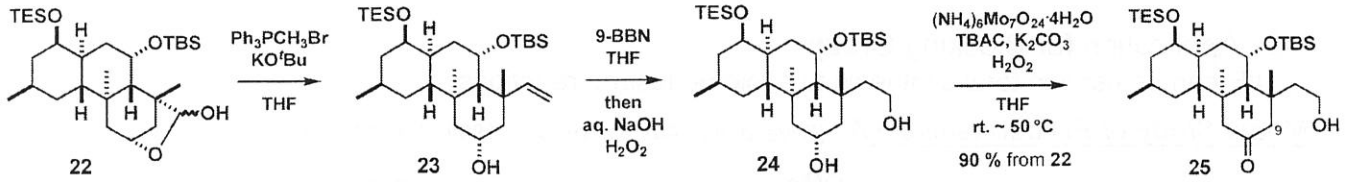
Norzoanthamine (1) R = H

<Retrosynthesis>

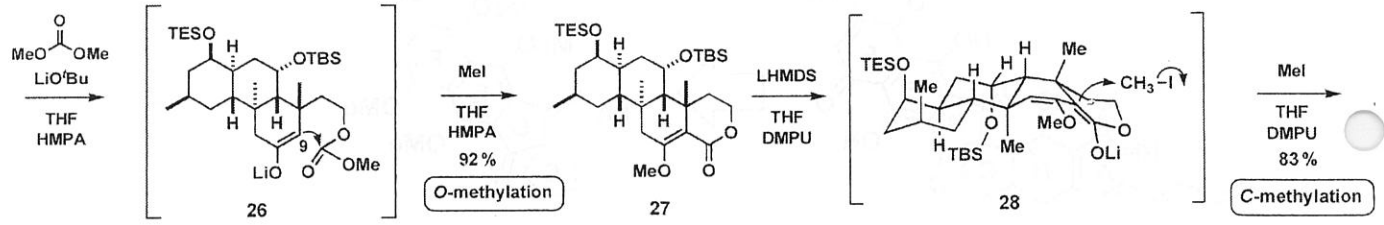


31 22

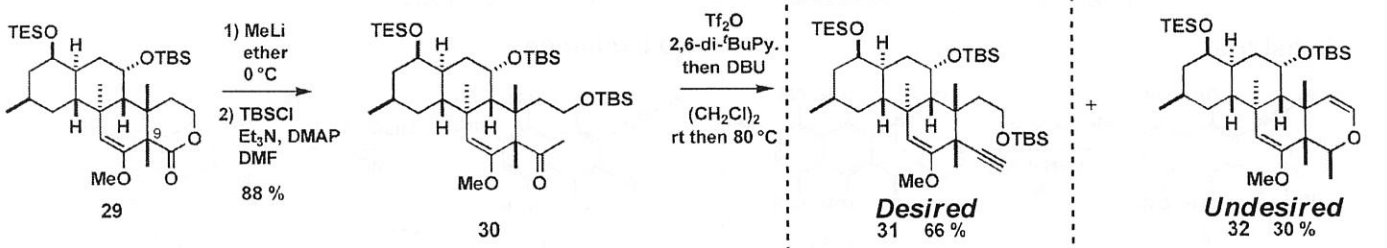
Initial Trial



22 23 24 25

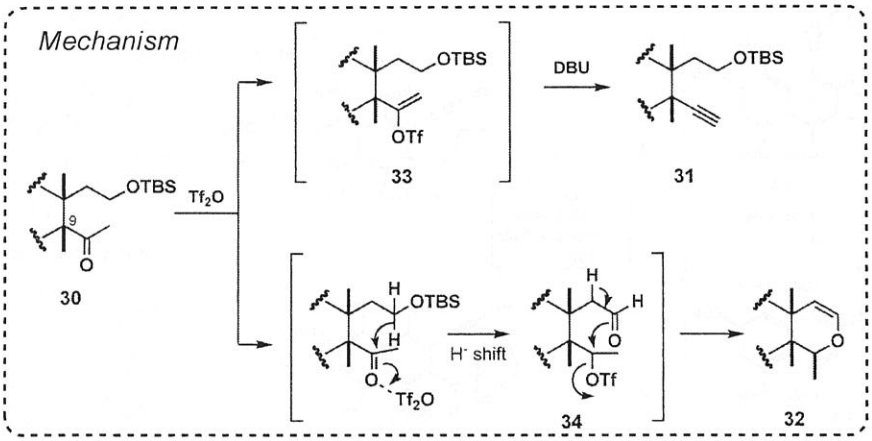


26 27 28



29 30 31 32

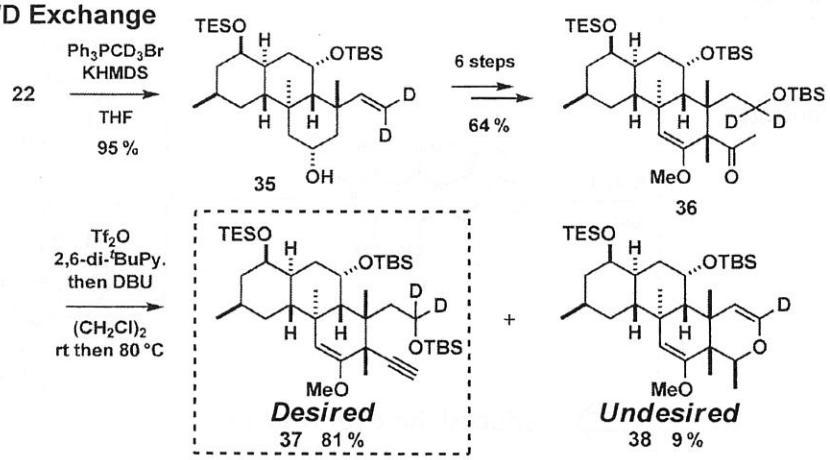
Mechanism



1,5-Hydride shift was occured.

$CH_2OTBS \longrightarrow CD_2OTBS$

H/D Exchange



35 36 37 38

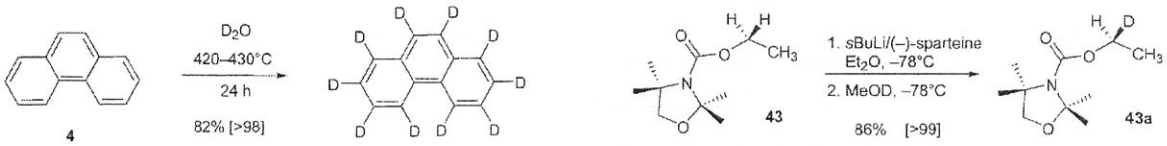
⟹ reduced 1,5-hydride shift

1-4. H/D Exchange Reactions

Hydrogens in acidic positions can be exchanged to deuterium easily.
In many cases,

{ Reactions proceed under high temperature and/or pressure.
{ More than equiva lent amount of storong base is used.

ex)



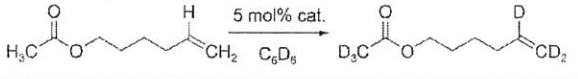
High Temperature

Strong Base

⇒ Focusing on catalytic H/D exchange reactions under mild condition.

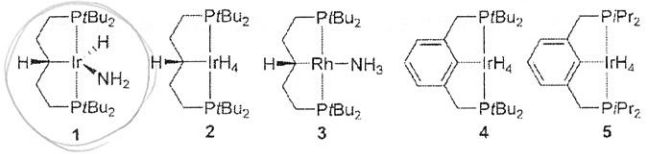
Selective H/D Exchange at Vinyl Groups (Zhou and Hartwig *Angew. Chem., Int. Ed.* **2008**, *47*, 5783)

Table 1: Selectivity pattern of H/D exchange catalysts (percentage of deuterium incorporation).



Entry	Catalyst	Conditions	α-CD_3	CD=C	$C=CD_2$
1	**1**	RT, 10 h	23	87	94
2	**2**	RT, 10 h	37	96	98[a]
3	**3**	RT, 3 h	32	0	52
4	**3**	RT, 10 h	74	2	61
5	**4**	RT, 10 h	0	0	0[b]
6	**4**	50°C, 8 h	0	0	0[b]
7	**5**	RT, 10 h	0	30	6[c]
8	**5**	50°C, 8 h	0	45	21[d]

[a] 11% hydrogenation byproduct. [b] 8% hydrogenation byproduct. [c] 4% hydrogenation byproduct. [d] 5% hydrogenation byproduct and 8% olefin isomers.



Substrate Scope

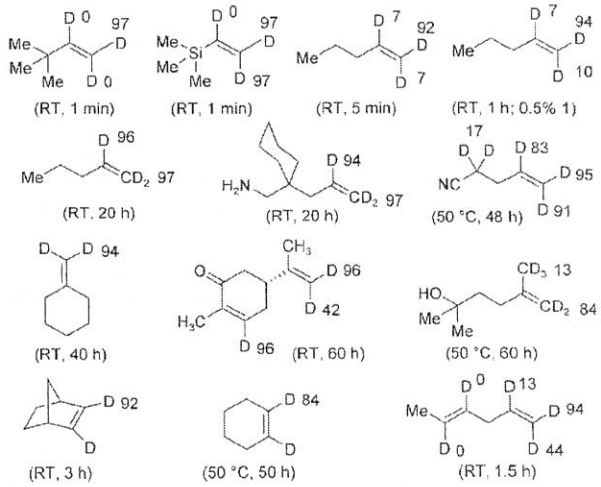


Figure 1. Percentage of deuterium incorporation into olefinic substrates catalyzed by 5 mol% 1 in C_6D_6.

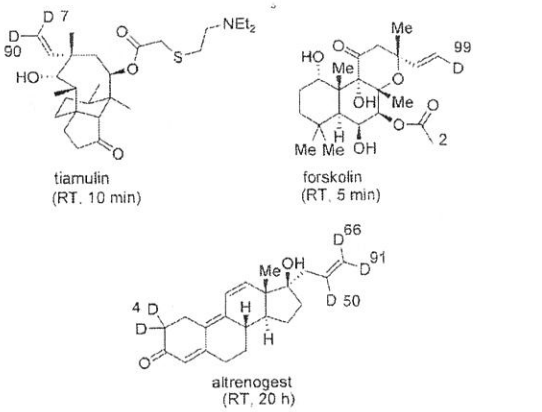
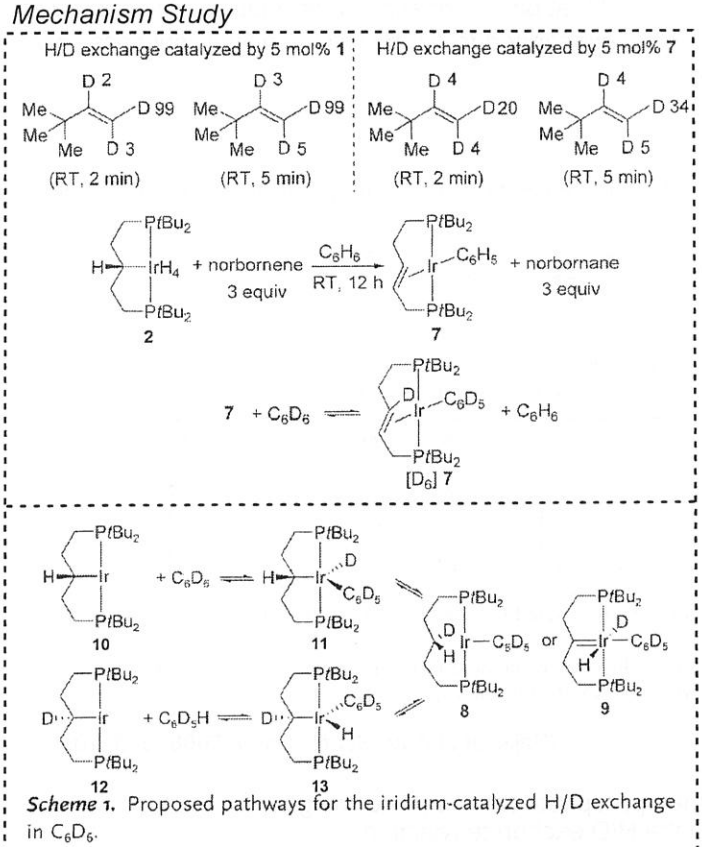


Figure 3. H/D Exchange of vinylic hydrogen atoms in complex molecules (percentage of deuterium incorporation).

Mechanism Study

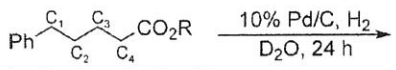


Scheme 1. Proposed pathways for the iridium-catalyzed H/D exchange in C_6D_6.

Catalyst 1 and 2 showed almost the same reactivity.
However, slower reactivity was observed
as catalyst 7 was used.

⇒ Catalyst 8 should be the active spieces.

Table 1. Temperature Dependence of 10% Pd/C−H_2-Catalyzed H−D Exchange in D_2O[a]



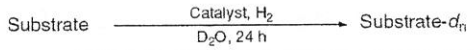
1a; R = Na, **1b**; R = H

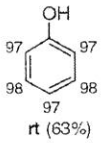
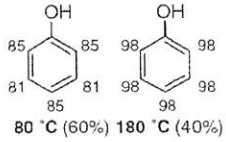
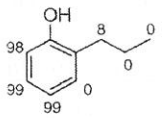
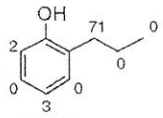
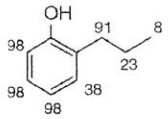
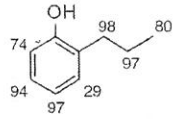
			D content[b] (%)			
entry	compd	T (°C)	Ph	C_1	$C_2 + C_3$	C_4
1[c]	**1a**	rt	0	89	0	0
2	**1a**	110	34	98	89	12
3[d]	**1b**	110	0	0	0	0
4[e]	**1b**	110	0	0	0	0
5	**1b**	110	26	97	80	0
6[f]	**1b**	140	63	96	84	29
7[f]	**1b**	160	67	95	94	94
8[f,g]	**1b**	180	0	48	13	5

[a] Unless otherwise noted, 0.25 mmol of the substrate was used and reactions were carried out under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate, Aldrich) in D_2O (99.8% D content, 1 mL). [b] D content was determined by ^1H NMR. [c] 0.5 mmol of the substrate was used in 2 mL of D_2O. [d] Without hydrogen. [e] Without 10% Pd/C. [f] The reaction was performed in a sealed tube. [g] The reaction was performed under D_2 atmosphere in dry EtOAc instead of H_2 and D_2O.

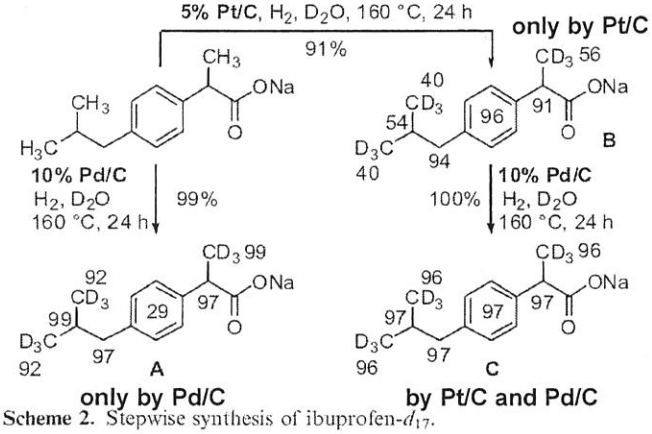
(Sajiki and Hirota et al *Org. Lett.* **2004**, *6*, 1485)

Table 1. Comparison of deuterium efficiency of aromatic compounds using 5% Pt/C and 10% Pd/C as a catalyst[a,b,c]



Entry	5% Pt/C	10% Pd/C
1	 rt (63%)	 **80 °C** (60%) **180 °C** (40%)
2	 rt (92%)	 rt (92%)
	 **80 °C** (76%)	 **80 °C** (61%)

(Sajiki et al *Tetrahedron Lett.* **2005**, *46*, 6995)



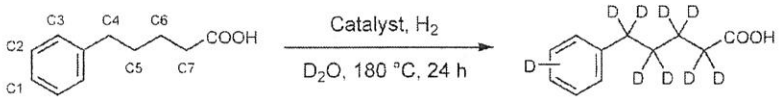
Scheme 2. Stepwise synthesis of ibuprofen-d_{17}.

using Pd/C :
Aliphatic protons are selectively exchanged.
using Pt/C :
Aromatic protons are selectively exchanged.

⇓

"H" at both aliphatic and aromatic position can be exchanged to "D" by Pt/C and Pd/C successively.

Table 1. Comparison of deuterium efficiencies of 5-phenylvaleric acid using Pd/C or Pt/C independently and by mixing them as a catalyst.[a]



Entry	Catalyst (wt %)	D content [%][b] C1	C2	C3	C4	C5, C6	C7	Yield [%]
1	10% Pd/C (10%)	96	96	14	98	96	96	88
2	10% Pd/C (20%)	>93	93	<36	98	97	97	82
3	5% Pt/C (20%)	97	97	19	28	8	10	92
4	5% Pt/C (40%)	95	95	13	6	2	7	92
5[c]	10% Pd/C (10%)	97	97	30	97	97	97	84
6	10% Pd/C (10%) + 5% Pt/C (20%)	97	97	97	97	97	94	84

[a] 500 mg (2.81 mmol) of the substrate were used and reactions were carried out under ordinary H_2 pressure using the catalyst in D_2O (99.9% D content, 17 mL) in a sealed tube.
[b] D contents were determined by ^1H NMR after conversion of the carboxylic acid to the methyl ester on the basis of the integration of the methyl protons and confirmed by ^2H NMR, ^{13}C NMR and mass spectrometry.
[c] The product of entry 3 was used as starting material.

(Sajiki et al *Adv. Synth. Catal.* **2006**, *348*, 1025)

Mixing Pd/C and Pt/C at the appropriate ratio is performing a synergistic effect in the H/D exchange reaction.

2. "F" in Medicinal Chemistry

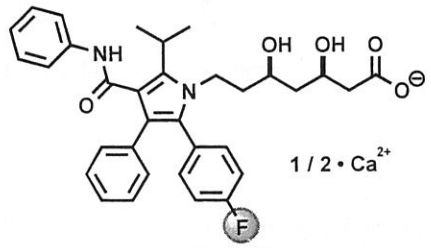
2-1. Fluorinated Drugs

Fluorinated drugs are widely used all over the world.

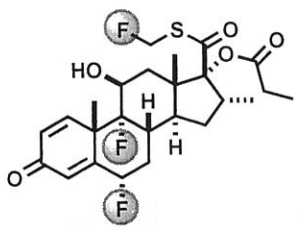
世界の大型医薬品売上ランキング2007

順	製品名	一般名	薬効等	メーカー	百万ドル 2007年	前期比	百万ドル 2006年
1	リピトール	アトルバスタチン	高脂血症/スタチン	ファイザー/ｱｽﾃﾗｽ/ｱﾙﾐﾗﾙ	13,682	-1%	13,793
2	プラビックス	クロピドグレル	抗血小板薬	サノフィ・A/BMS	8,325	34%	6,200
3	セレタイド/アドベア	ｻﾙﾒﾃﾛｰﾙ+ﾌﾙﾁｶｿﾞﾝ	抗喘息薬	グラクソSK/ｱﾙﾐﾗﾙ/UCB	7,154	8%	6,627
4	リツキサン/マブセラ	リツキシマブ	非ホジキンリンパ腫	ﾊﾞｲｵｼﾞｪﾝ･ｱｲﾃﾞｯｸ/ロシュ	5,826	22%	4,781
5	ｴﾎﾟｼﾞｪﾝ/ﾌﾟﾛｸﾘｯﾄ/ｴｽﾎﾟｰ	エポエチンα	腎性貧血	アムジェン/J&J/キリン	5,746	-5%	6,029
6	エンブレル	エタネルセプト	関節リウマチ/乾癬他	アムジェン/ワイス/武田	5,442	22%	4,475
7	レミケード	インフリキシマブ	関節リウマチ/ｸﾛｰﾝ病他	J&J(ｾﾝﾄｺｱ)/SP/田辺三菱	5,230	18%	4,425
8	ネクシアム	エソメプラゾール	抗潰瘍剤/PPI	アストラゼネカ	5,216	-2%	5,182
9	ディオバン/ニシス	バルサルタン	降圧剤/ARB	ノバルティス/ｲﾌﾞｾﾝ	5,091	17%	4,350
10	ジプレキサ	オランザピン	統合失調症薬	イーライリリー	4,761	9%	4,364
11	リスパダール	リスペリドン	統合失調症薬	J&J	4,697	9%	4,183
12	シングレア/キプレス	モンテルカスト	抗喘息/気管支喘息	メルク/キョーリン	4,436	20%	3,705
13	ﾊﾟﾝﾄｿﾞｰﾙ/ﾌﾟﾛﾄﾆｯｸｽ	パントプラゾール	抗潰瘍剤/PPI	ﾆｺﾒｯﾄﾞ(ｱﾙﾀﾅ)/ﾜｲｽ/ﾚｺﾙﾀﾞﾁ	4,420	8%	4,079
14	ハーセプチン	トラスツズマブ	抗がん剤/HER2乳がん	ｼﾞｪﾈﾝﾃｯｸ/ロシュ/中外	4,311	23%	3,222
15	セロクエル	フマル酸クエチアピン	統合失調症薬	アストラゼネカ/ｱｽﾃﾗｽ	4,198	18%	3,557
16	アクトス	塩酸ピオグリタゾン	2型糖尿病	武田薬品/リリー	3,901	19%	3,275
17	エフェクサー	ベンラファキシン	抗うつ剤/SNRI	ワイス/アルミラル	3,868	2%	3,793
18	ロペノックス	エノキサパリン注	抗血栓薬	サノフィ・アベンティス	3,847	13%	3,215
19	タケプロン/ﾌﾟﾚﾊﾞｼｯﾄﾞ	ランソプラゾール	抗潰瘍剤/PPI	武田/TAP/アボット他	3,796	-10%	4,218
20	レクサプロ/ｼﾌﾟﾗﾚｯｸｽ	エスシタロプラム	抗うつ剤/SSRI	ﾙﾝﾄﾞﾍﾞｯｸ/ﾌｫﾚｽﾄ/ﾚｺﾙﾀﾞﾁ	3,698	19%	3,107

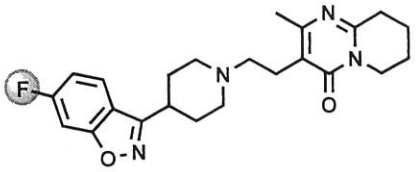
ユート・ブレインの調査より



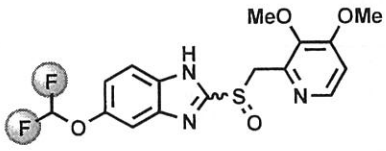
Lipitor (1)



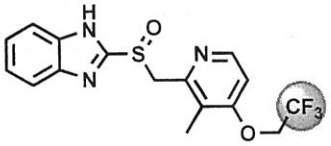
Adoair (3)



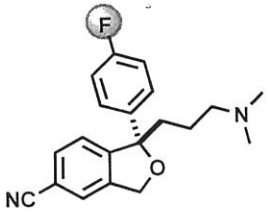
Risperdal (11)



Pantozol (13)



Takepron / Prevacid (19)



Lexapro / Cipralex (20)

In the top 20, 40% of drugs are including fluorine in their structure (besides biological drugs).
There are about 20% of all pharmaceuticals and 30-40% of agrochemicals on the market.
(*Tetrahedron Asymmetry* **2008**, *19*, 2633 and reference therein)

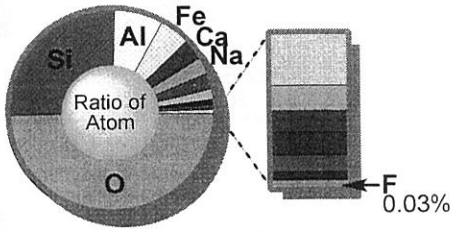
⇨ Fluorine is absolutely important for creating drugs.

2-2. Fluorine's Feature (Ma and Cahard *Chem. Rev.* **2004**, *104*, 6119)

Origin of Fluorine

F : 0.03% on earth (13th most abundant atom)
mainly included in fluorite crystal (CaF_2) ホタル石

CaF_2 : Strong hexagonal crystal structure
Generating fluorescene under ultra violet
Flux to lower the melting point of raw materials
High performance telescopes and camera lens elements
(very low dispersion, transparence, evenly refracting light)



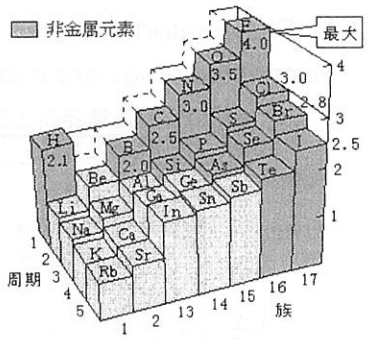
Element Ratio in the Earth

Fluorite (CaF_2)

Characteristic Feature of Fluorine and Fluorinated Compounds

1. Most Electronegative, Most Powerful Oxidant
   (High Induce Effect <Table 1.5>, OH Analog)
2. van der Waals' Radii : 2nd Smallest
   (H Analog, Mimic/Block Effect)
3. Stability of C-F Bond <Table 1>
   (Low Metabolism)
4. Low Polarizability
   (High Lipophilicity, Low Refractive Index, High Volatility)

Electronegativity

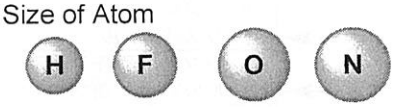


元素の電気陰性度

Table 1.1 *Representative physical data of selected elements [33–35]*

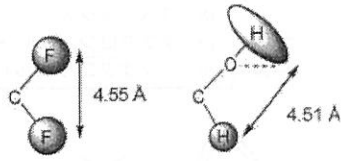
	Element (X)					
	H	C	O	F	Cl	Br
Electronegativity[a]	2.20	2.55	3.44	**3.98**	3.16	2.96
van der Waals radius[b] (Å)	1.20	1.70	1.52	**1.47**	1.75	1.85
H_3C–X bond length[a] (Å)	1.087	1.535[d]	1.425[e]	**1.382**	1.785	1.933
H_3C–X dissociation energy[c] (kcal/mol)	103.1	88.0[d]	90.2[e]	**108.1**	81.1	67.9
Ionization potential[a] (kcal/mol)	313.9	259.9	314.3	**402.2**	299.3	272.7
Electron affinity[a] (kcal/mol)	17.42	29.16	3.73	**78.52**	83.40	77.63

Size of Atom



1.20 Å 1.35 Å 1.52 Å 1.55 Å

→ "F" is similar to "H"



→ "F" is similar to "OH"

Table 1.5 *Selected pK_a values of various fluorinated compounds [35, 59]*

Compound	pK_a	Compound	pK_a	Compound	pK_a
CH_3CO_2H	4.76	$CH_3CH_2CO_2H$	4.87	$(CH_3)_2CHOH$	17.1[a]
CH_2FCO_2H	2.59	$CF_3CH_2CO_2H$	3.06	$(CF_3)_2CHOH$	9.3[a]
CH_2ClCO_2H	2.87	$C_6H_5CO_2H$	4.21[a]	$(CH_3)_3COH$	19.0[a]
CH_2BrCO_2H	2.90	$C_6F_5CO_2H$	1.7[a]	$(CF_3)_3COH$	5.4[a]
CHF_2CO_2H	1.33	CH_3CH_2OH	15.93[a]	C_6H_5OH	9.99
CF_3CO_2H	0.50	CF_3CH_2OH	12.39[a]	C_6F_5OH	5.5[a]

Table 1. *Physical properties of the C–F bond.*[77]

Compound	Dipole moments [debye]	Compound	Refractive index	b.p. [°C]
CH_3F	1.85	perfluorohexane	1.2515	57.1
CH_2F_2	1.97	hexane	1.3751	69
fluorobenzene	1.70	hexafluorobenzene	1.3777	80.5
		benzene	1.5011	80.1

Table 2. *Steric consequences of fluorine substitution. For the CHOH group, the measured distance is to the center of the cone swept out by the hydroxy-proton.*

Bond	Length [Å]	van der Waals radius [Å]	Total size [Å]
C–H	1.09	1.20	2.29
C=O	1.23	1.50	2.73
C–O–	1.43	1.52	2.95
C–F	1.35	1.47	2.82
O–H	0.96	1.20	2.16

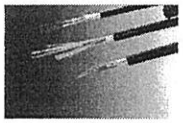
(DiMagno et al *ChemBioChem* **2004**, *5*, 622)

Fluorinated Chemicals (Cahard et al *Chem. Rev.* **2004**, *104*, 6119)

Noncombustibility

CFC for Fire Extinguishants, Refrigerants

Low Refractive Index

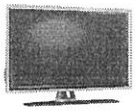


Optical Fiber

Teflon

Stability

Functionalized Polymer



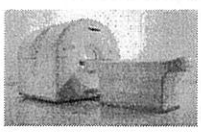
Liquid Crystal

Biological activity

Medicine

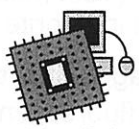
Agrichemical

Radioisotope



PET
^{18}F used for diagnosis

High Volatility

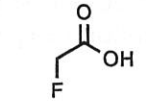


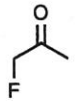
Washing Solvent used in Precision Industry

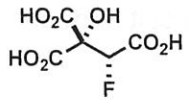
UF_6 for Uranium Enrichment

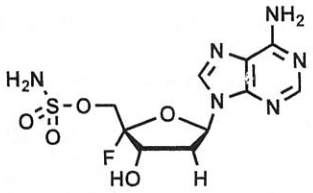
Fluorinated chemicals are now definitely vital elements in human civilization.

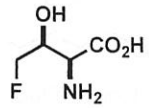
Natural Fluorinated Products

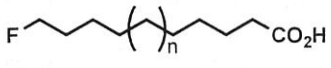

fluoroacetic acid


fluoroacetone


(*2R,3R*)-fluorocitric acid


nucreocidin


4-fluorothreonine


ω-fluoro-*aliphatic* acid

Only a few compounds were discovered so far.

⟹ To satisfy social demands for fluorinated chemicals, they must be synthesized artificially.

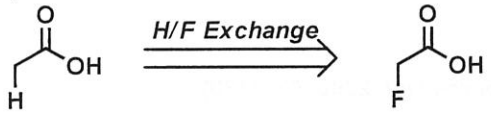
Mimic Effect / Block Effect (Kirk *Org. Process Res. Dev.* **2008**, *12*, 305)

< Mimic Effect >

There are almost no difference between C-F and C-H in atom size.

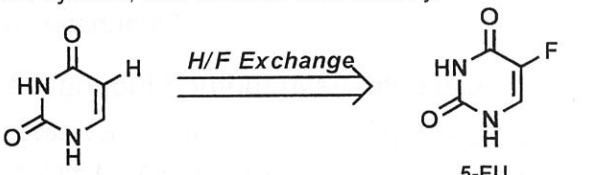
⟶ Fluorinated compounds can be taken up into the metabolic system, and achieve their activity.

ex1)

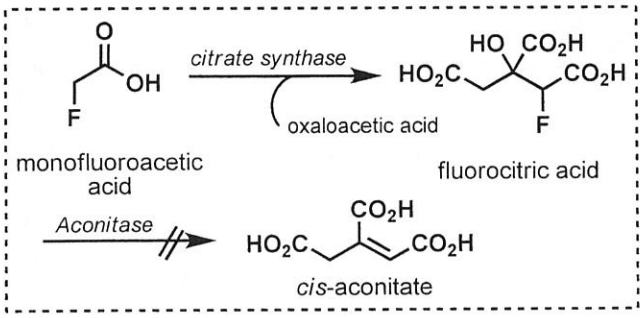


monofluoroacetic acid

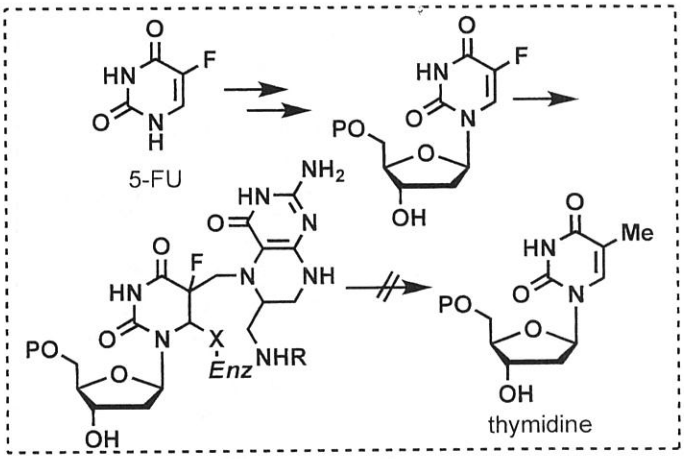
ex2)



uracil — **5-FU** — *anti*-cancer effect



Monofluoroacetic acid inhibits citric acid cycle (extremely poisonous).



Biosynthesis of thmidine is inhibited because F^+ can not be desorped.

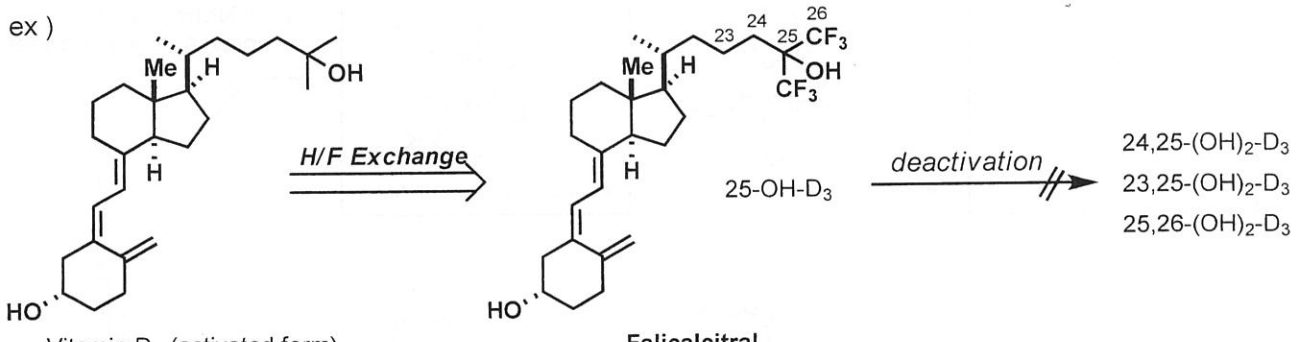
⟹ Most of the case, fluorinated compounds react with enzymes irreversibly.

< Block Effect >

C-F bond is more stable than C-H bond. / Electron density around F gets lower.

⟶ Blood concentration can maintained at high level and hold on its activity.

ex)



Vitamin D_3 (activated form) — **Falicalcitral**

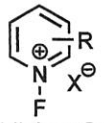
Trifluoromethyl groups are protecting from deactivation by hydroxylation.

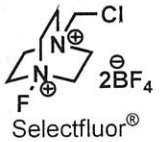
⟹ To maximize "mimic effect" and "block effect", introducing fluorine in proper position is critically important in medicinal chemistry.

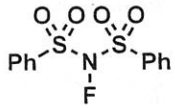
Fluorination Reagents

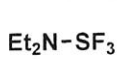
HF, F_2 : high reactivity, unstability (difficult to deal) ⟹ Needs for developing easy fluorination reagents

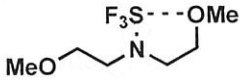
Achiral Fluorination Reagents


Pyridinium Salt

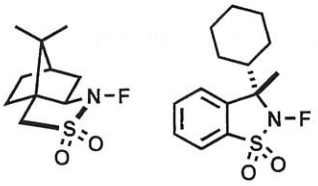

Selectfluor®

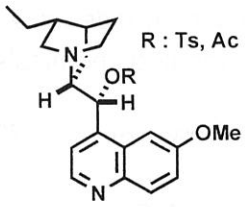

NFSI

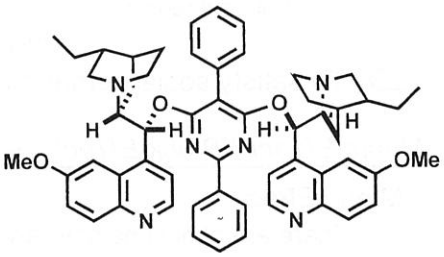

DAST


Deoxo-Fluor

Chiral Fluorination Reagents


difficult to synthesis (using F_2 gas)


DHQBH + Selectfluor®

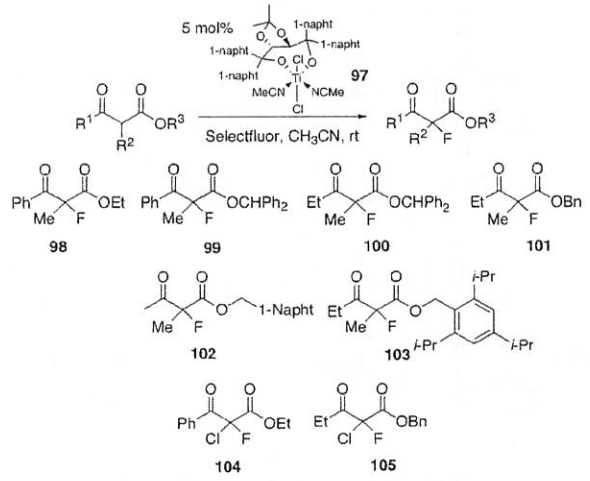

$(DHQ)_2PYR$ + Selectfluor®

Fluorination reagents were widely broadened.

2-3. Catalytic Asymmetric Fluorination

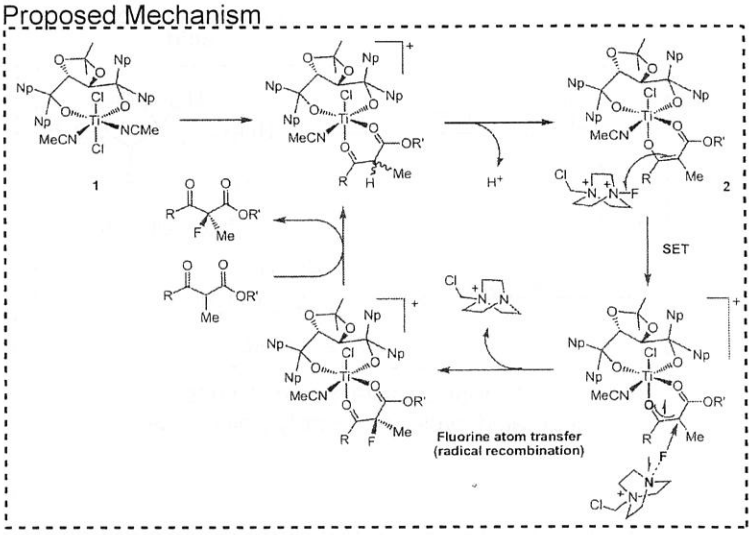
Togni's Work (*Angew. Chem., Int. Ed.* **2000**, *39*, 4359 / *Tetrahedron Lett.* **2006**. *62*. 7180)

Table 9. Enantioselective Fluorination Catalyzed by TADDOL–Titanium Complexes



product	yield, %	ee, %	product	yield, %	ee, %
98	≥80	62	**102**	≥80	68
99	≥80	82	**103**	89	90
100	≥80	81	**104**	53	33
101	82	71	**105**	57	60

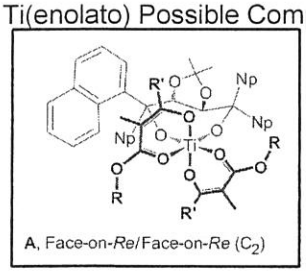
Proposed Mechanism

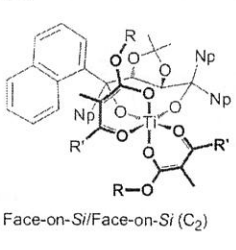


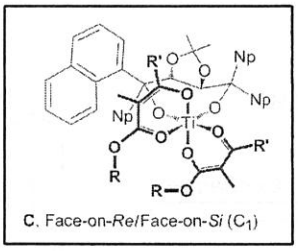
Steric bulk of ester is important for stereoselectivity.

Bulky ester can take complex A (most shielded)

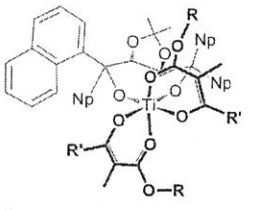
Ti(enolato) Possible Complexes

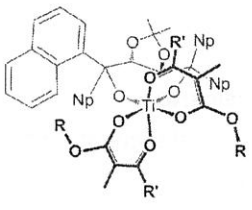

A, Face-on-*Re*/Face-on-*Re* (C_2)

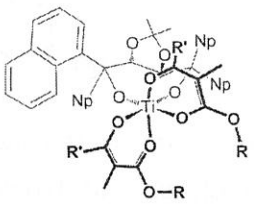

B, Face-on-*Si*/Face-on-*Si* (C_2)


C, Face-on-*Re*/Face-on-*Si* (C_1)

From NMR analysis, complex A, C were observed.


D, Edge-on-*Re*/Edge-on-*Re* (C_2)


E, Edge-on-*Si*/Edge-on-*Si* (C_2)


G, Edge-on-*Re*/Edge-on-*Si* (C_1)

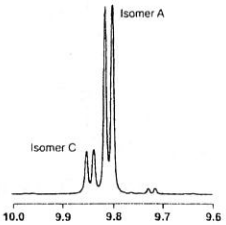
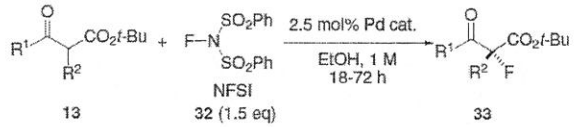
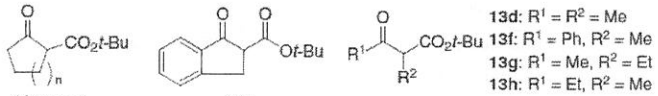


Figure 1. Section of the ^1H NMR spectrum (500 MHz, C_6D_6) of complex 3a showing the signals of the hydrogen atoms in position 2 of an *edge-on* naphthyl group.

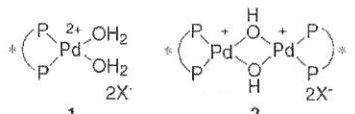
J. Am. Chem. Soc. **2002**, *124*, 14530 / *Org. Lett.* **2003**, *5*, 3225 / *Tetrahedron Lett.* **2006**, *62*, 7168 / *J. Org. Chem.* **2007**, *72*, 246

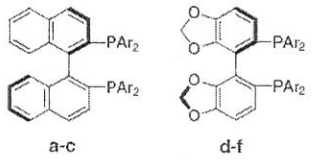




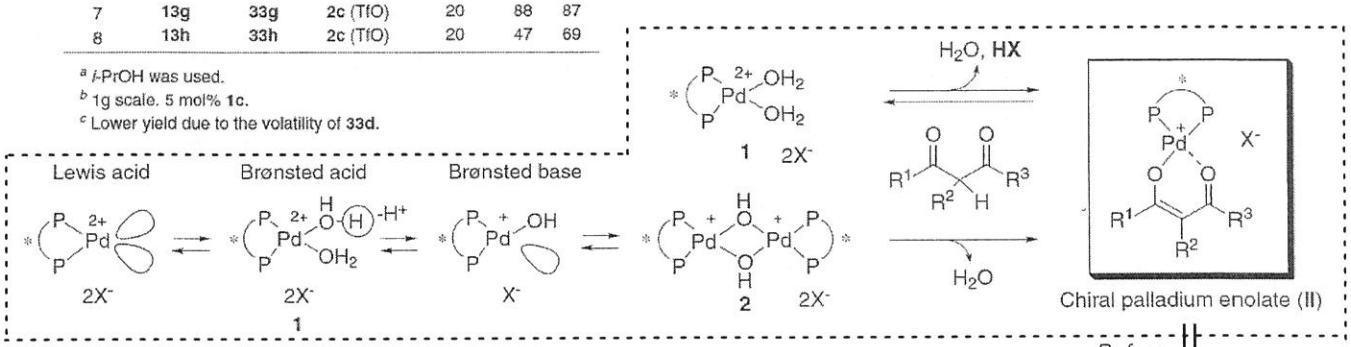
entry	ketoester	product	catalyst (X)	temp. (°C)	yield (%)	ee (%)
1[a]	**13a**	**33a**	**2f** (TfO)	20	90	92
2	**13b**	**33b**	**2c** (BF_4)	-10	91	94
3	**13c**	**33c**	**2c** (TfO)	-20	85	83
4	**13d**	**33d**	**2f** (TfO)	20	49[c]	91
5	**13f**	**33f**	**2c** (BF_4)	20	92	91
6[b]	**13f**	**33f**	**1c** (TfO)	20	96	91
7	**13g**	**33g**	**2c** (TfO)	20	88	87
8	**13h**	**33h**	**2c** (TfO)	20	47	69

[a] *i*-PrOH was used.
[b] 1g scale. 5 mol% **1c**.
[c] Lower yield due to the volatility of **33d**.



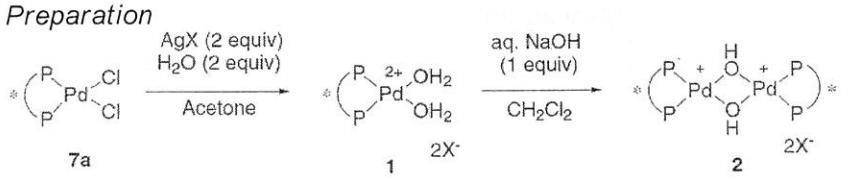


a: Ar = Ph: (*R*)-BINAP
b: Ar = 4-MeC_6H_4: (*R*)-Tol-BINAP
c: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-BINAP
d: Ar = Ph: (*R*)-SEGPHOS
e: Ar = 3.5-$Me_2C_6H_3$: (*R*)-DM-SEGPHOS
f: Ar = 3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$: (*R*)-DTBM-SEGPHOS



It has both Lewis acidic and brønsted basic features. ⟶ make enolate form easily

Preparation



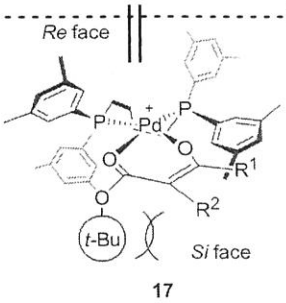
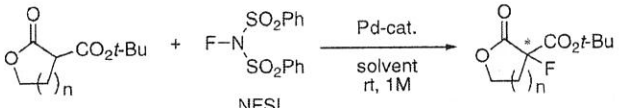


TABLE 1. Catalytic Enantioselective Fluorination of the Lactone Substrates 3



entry	3	solvent	Pd cat. (mol %)	time (h)	yield[a] (%)	ee[b] (%)
1	**3a**	CH_2Cl_2	**1b** (5)	24	trace	
2	**3a**	acetone	**1b** (5)	24	10	51
3	**3a**	THF	**1b** (5)	24	49	75
4	**3a**	EtOH	**1b** (5)	6	54	82
5	**3a**	*i*-PrOH	**1b** (5)	6	96	79
6	**3a**	*t*-BuOH	**1b** (5)	6	89	80
7	**3a**	*i*-PrOH	**1a** (5)	6	79	77
8	**3a**	*i*-PrOH	**1c** (5)	6	78	87
9	**3a**	*i*-PrOH	**1d** (5)	24	74	97
10	**3a**	*i*-PrOH	**2d** (2.5)	24	75	98
11	**3b**	*t*-BuOH	**2d** (2.5)	27	35[c]	97[d]

[a] Isolated yield of **4a** except for entry 11. [b] ee values of **4a** except for entry 11. [c] Isolated yield of **5b**. [d] ee value of **5b**.

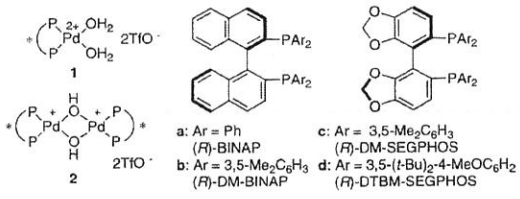
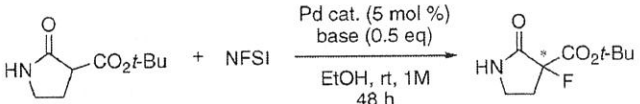


TABLE 3. Effect of Amine Bases



entry	Pd cat.	base	yield (%)	ee[a] (%)
1	**1b**	Et_3N	59	90
2	**1b**	morphorine	49	88
3	**1b**	pyridine	trace	*b*
4	**1b**	quinoline	NR[c]	*b*
5	**1b**	isoquinoline	NR[c]	*b*
6	**1b**	DMAP	trace	*b*
7	**1b**	2,6-lutidine	80	91
8	**1b**	2,6-(*t*-Bu)$_2$-pyridine	65	91
9	**1d**	2,6-lutidine	50	99
10	**2d**	2,6-lutidine	58	>99

[a] ee values of **7b**. The ee was determined after *N*-benzylation. [b] Not determined. [c] No reaction.

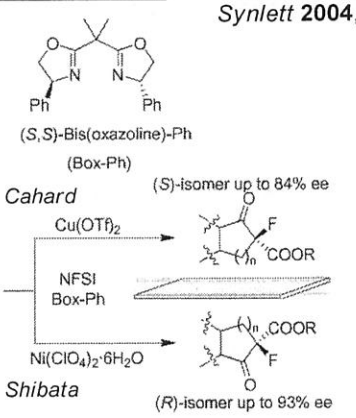
Acidity of α-proton is reduced.

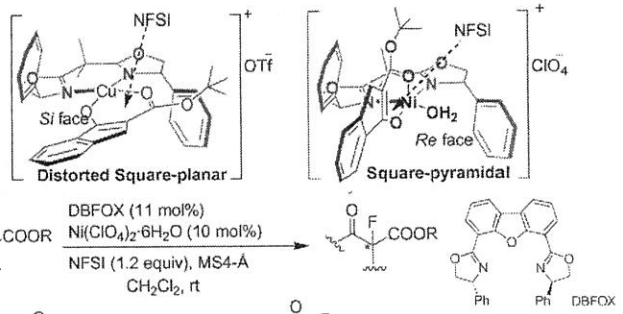
⟶ adding 0.5 eq of base

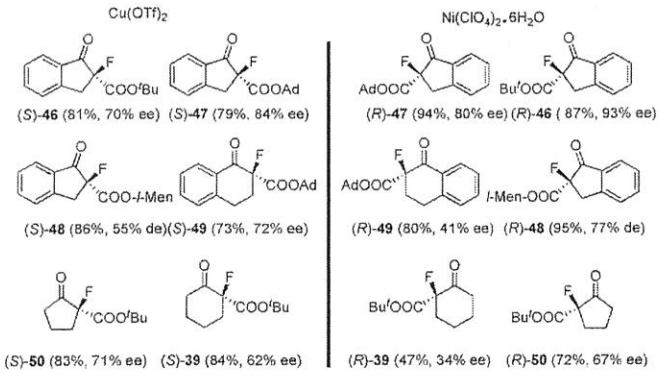
Not real catalytic

Cahard's / Shibata's Work

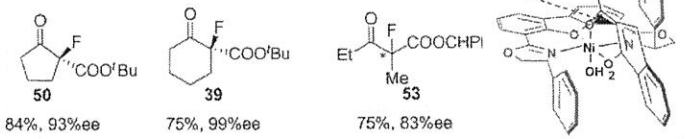
Tetrahedron Asymmetry **2004**, *15*, 1007
Synlett **2004**, *10*, 1703 / *Angew. Chem., Int. Ed.* **2005**, *44*, 4204





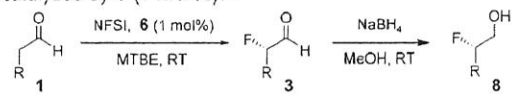


46: R=^{t}Bu, 93%, 99% ee
47: R=1-adamantyl, 71%, 99% ee
48: R=*l*-menthyl, 66%, 99% ee
51: R=cyclohexyl, 97%, 92% ee
52: R=^{t}Bu, 86%, 96% ee
49: R=1-adamantyl, 97%, 98% ee



Jørgensen's Work (*Angew. Chem., Int. Ed.* **2005**, *44*, 3703)

Table 2: Organocatalytic enantioselective α-fluorination of aldehydes by NFSI, catalyzed by **6** (1 mol%).[a]



Entry	Aldehyde	R	*t* [h]	Yield [%]	*ee* [%][b]
1[c]	**1b**	Pr	6	**3b** >95	96
2[c]	**1c**	Bu	28	**3c** >90	91
3[d,e]	**1d**	Hex	4	**8d** 55	96
4[d]	**1e**	BnO(CH$_2$)$_3$	2	**8f** 64	91
5[d]	**1a**	Bn	2	**8a** 74	93
6[d]	**1f**	Cy	5	**8g** 69	96
7[c]	**1g**	*t*Bu	2	**3e** >90	97
8[d]	**1h**	1-Ad	2	**8h** 75	96

[a] Compound **2** (0.25 mmol) was added to a mixture of **1** (0.38 mmol) and **6** (0.0025 mmol) in MTBE (0.5 mL) at room temperature for the stated period of time; Ad = adamantyl; Bn = benzyl; Cy = cyclohexyl. [b] Percent *ee* values were determined by GC or HPLC on a chiral phase; see Supporting Information for separation conditions. [c] Yields were based on GC analysis of the crude mixtures before reduction owing to the volatility of the products. [d] Isolated yields of the alcohol after reduction with $NaBH_4$. [e] 1.1 equiv NFSI; 1 equiv aldehyde.

Results of Other Organocatalysts

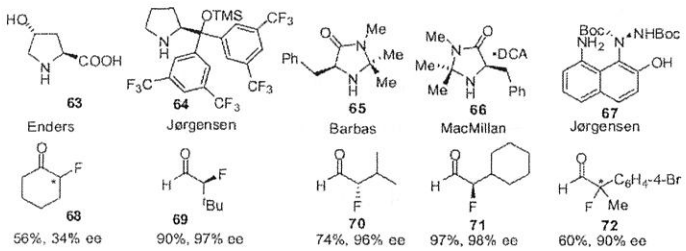
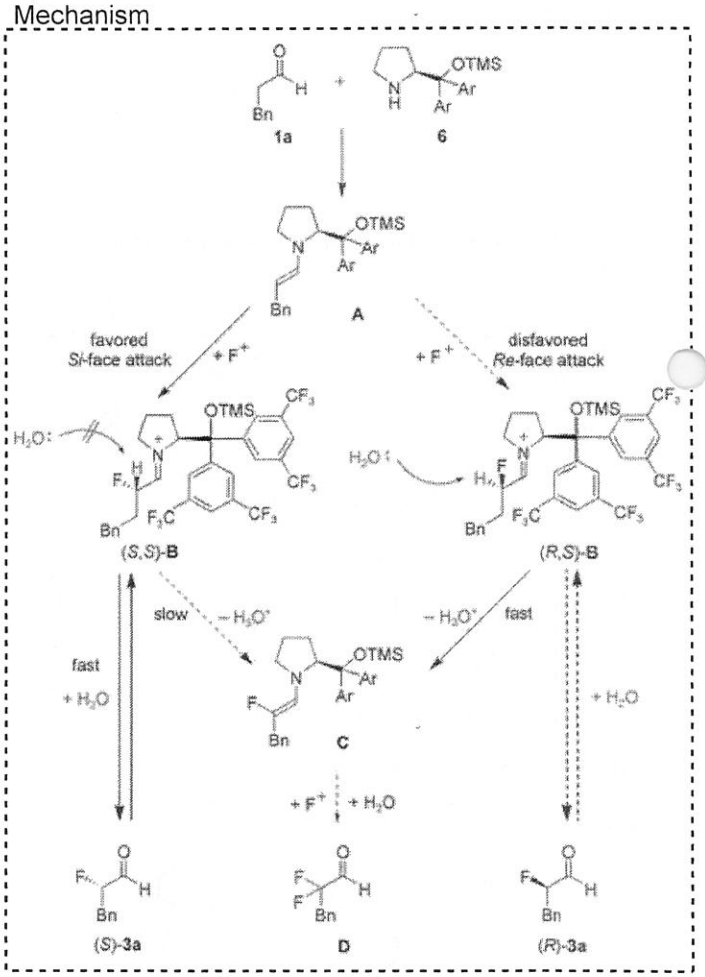


Fig. 14. Selected examples of organocatalytic fluorination from Enders, Jørgensen, Barbas and MacMillan groups.

Mechanism

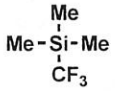


2-4. Catalytic Asymmetric Trifluoromethylation

Ma and Cahard *J. Fluor. Chem.* **2007**, *128*, 975
Shibata et al *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 215
Shibata et al *Tetrahedron Asymmetry* **2008**, *19*, 2633

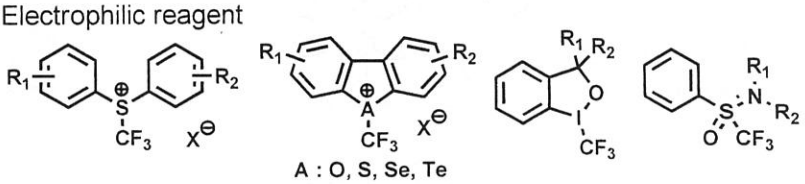
Reagents

Nucleophilic reagent



Ruppert reagent

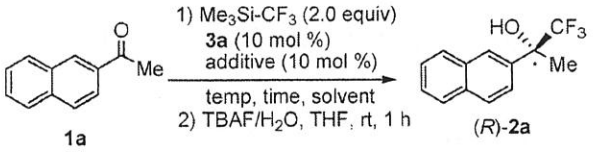
Electrophilic reagent



A : O, S, Se, Te

Shibata and Toru's Work (*Org. Lett.* **2007**, *9*, 3707)

Table 1. Optimization of Additives for Enantioselective Trifluoromethylation Catalyzed by Chiral Ammonium Bromide



run	additive[a]	solvent	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	KF/2H$_2$O	toluene	−40	24	NR[j]	–
2	KF/2H$_2$O	toluene/CH$_2$Cl$_2$[e]	−40	24	NR[j]	–
3	TBAH$_2$F$_3$	toluene/CH$_2$Cl$_2$[e]	−40	2	83	25
4	TBAT	toluene/CH$_2$Cl$_2$[e]	−40	2	89	18
5	LiOAc	toluene/CH$_2$Cl$_2$[e]	−40	2	99	19
6	TMAA	toluene/CH$_2$Cl$_2$[e]	−40	24	NR[j]	–
7	TBAF/H$_2$O	toluene/CH$_2$Cl$_2$[e]	−40	2	94	22
8	TEAF/H$_2$O	toluene/CH$_2$Cl$_2$[e]	−40	2	38	66
9	TMAF	toluene/CH$_2$Cl$_2$[e]	−40	8	65	70
10	TMAF	toluene/CH$_2$Cl$_2$[e]	−60	2	65	81
11	TMAF	toluene/CH$_2$Cl$_2$[d]	−60	8	70	82
12	TMAF	toluene/CH$_2$Cl$_2$[e]	−60	8	48	79
13	TMAF	toluene/CH$_2$Cl$_2$[c]	−80	2	53	80
14	TMAF	toluene	−80	24	30	72
15	TMAF	CH$_2$Cl$_2$	−80	3	56	71
16[f]	TMAF	toluene/CH$_2$Cl$_2$[c]	−80	12	87	87
17[g]	TMAF	toluene/CH$_2$Cl$_2$[c]	−60	6	87	85
18[h]	TMAF	toluene/CH$_2$Cl$_2$[c]	−60	3	70	77[i]

[a] TBAH$_2$F$_3$, tetrabutyl ammonium dihydrogen trifluoride; TBAT, tetrabutylammonium triphenyldifluorosilicate; TMAA, tetramethylammonium acetate; TBAF, tetrabutylammonium fluoride; TEAF, tetraethylammonium fluoride. [b] Determined by Chiralcel OD-H eluting with 5% *i*-PrOH in hexane. (*R*)-**2a** was obtained. The absolute stereochemistry of **2a** was tentatively assumed. See footnote in Table 2. [c] Toluene/CH$_2$Cl$_2$ = 2:1. [d] Toluene/CH$_2$Cl$_2$ = 1:1. [e] Toluene/CH$_2$Cl$_2$ = 1:2. [f] 20 mol % of TMAF was used. [g] Catalyst **3b** was used instead of **3a**. [h] Catalyst **3c** was used instead of **3a**. [i] (*S*)-**2a** was obtained. [j] NR: no reaction.

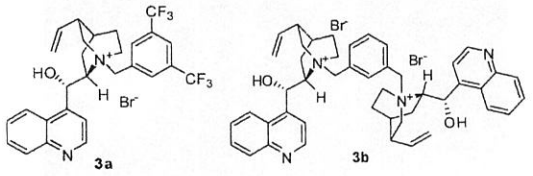
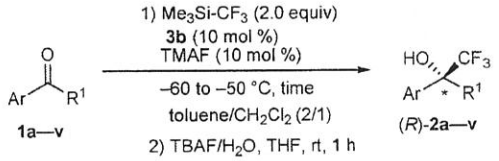


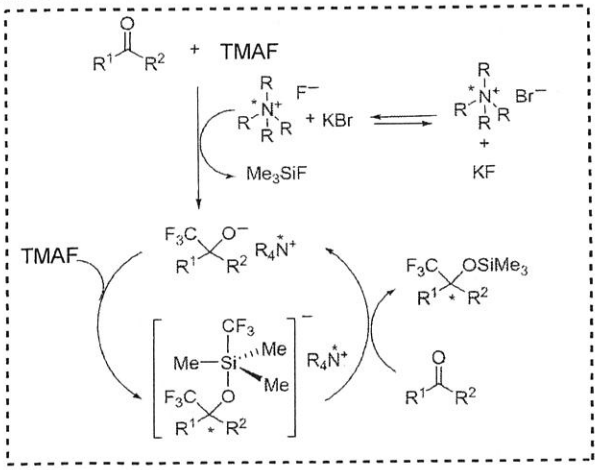
Table 2. Enantioselective Trifluoromethylation of **1** with Me$_3$SiCF$_3$ Catalyzed by a **3b**/TMAF Combination[a]



entry	1	Ar	R^1	time (h)	yield (%)	ee[b] (%)
1	**1a**	naphthyl	Me	6	87	85
2[c,d,e]	**1b**	6-Me-2-naphthyl	Me	30	72	91
3	**1b**	6-Me-2-naphthyl	Me	30	74	88
4[c]	**1c**	6-MeO-naphthyl	Me	24	59	78
5	**1c**	6-MeO-naphthyl	Me	8	74	87
6[c]	**1d**	4-BrC$_6$H$_4$	Me	3	71	70
7	**1d**	4-BrC$_6$H$_4$	Me	3	81	86
8[g]	**1e**	4-BrC$_6$H$_4$	Et	12	84	93
9	**1f**	Ph	Et	14	65	82
10	**1g**	Ph	propyl	7	83	76
11[d]	**1h**	4-MeOC$_6$H$_4$	Me	7	84	89
12	**1i**	4-ClC$_6$H$_4$	Me	14	71	87
13	**1j**	4-FC$_6$H$_4$	Me	7	96	87
14	**1k**	4-MeC$_6$H$_4$	Me	12	94	88
15	**1l**	3-BrC$_6$H$_4$	Me	8	73	71
16[d]	**1m**	3-ClC$_6$H$_4$	Me	4	80	74
17[c,f]	**1n**	3-NO$_2$C$_6$H$_4$	Me	7	96	64
18[c,d]	**1o**	4-NO$_2$C$_6$H$_4$	Me	3	97	52
19	**1p**	1-tetralone		3	75	94
20[d,g]	**1q**	6-methoxy-1-tetralone		24	82	86
21	**1r**	1-indanone		12	34	74
22	**1s**	1-benzosuberon		2	53	73
23	**1t**	PhCH=CH	Me	3	85	70
24	**1u**	2-natphtyl	H	24	93	41
25	**1v**	PhCH$_2$CH$_2$	Me	6	37	10

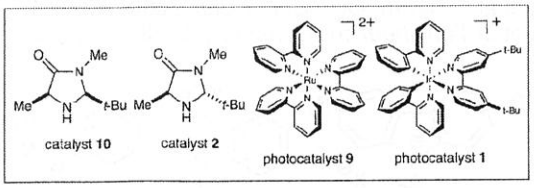
[a] The reaction started at −60 °C, and it was kept at −60 °C to −50 °C. [b] Determined by HPLC analysis (Chiralcel OD-H, AD-H, or OJ-H eluting with 5% *i*-PrOH in hexane) or GC analysis. The absolute stereochemistry of the newly generated stereocenter in **2n** was determined by comparing retention times of HPLC analysis reported by Mukaiyama et al.,[10] and the stereochemistry of other trifluoromethylated alcohols **2** was tentatively assumed by analogy. [c] Catalyst **3a** was used instead of **3b**. [d] 20 mol % of TMAF was used. [e] The reaction was carried out at −80 °C to −70 °C. [f] The reaction was carried out in the presence of MS 4A. [g] The reaction was carried at −50 °C to −40 °C.

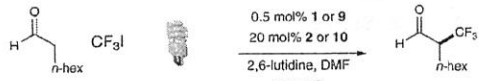
Mechanism



{ Selectivity is largely improved.
{ Excellent substrate generality

MacMillan's Work (*J. Am. Chem. Soc.* **2009**, ASAP)

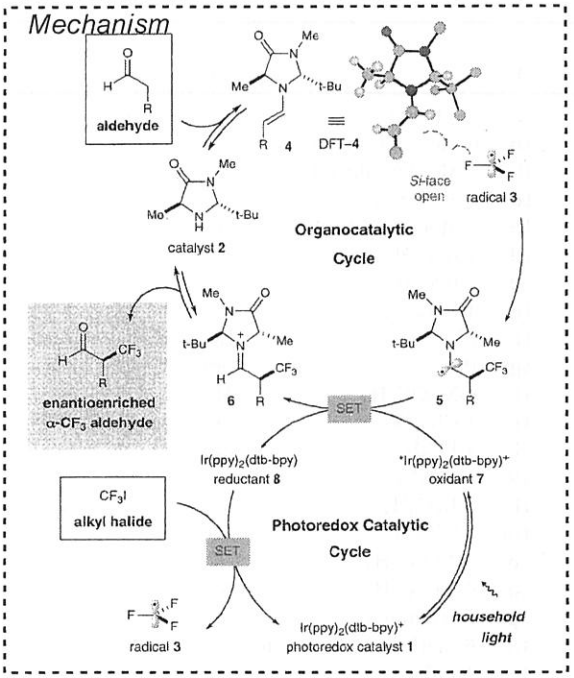




entry	organocat.	photocat.	light	temp (°C)	% yield	% ee[a]
1	**10**	**9**	yes	23	51	0
2	**10**	**9**	no	23	<5	0
3	**10**	**1**	yes	23	85	0
4	**10**	**1**	yes	–20	92	52
5	**2**	**9**	yes	–20	67	87
6	**2**	**1**	yes	–20	79	99

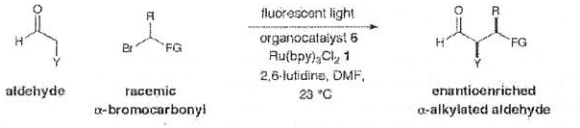
racemization

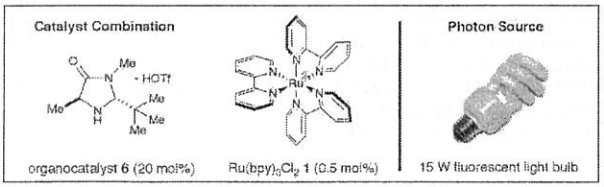
Mechanism



This synstem is developed originally for α-alkylation

(*Science*, **2008**, *322*, 77)





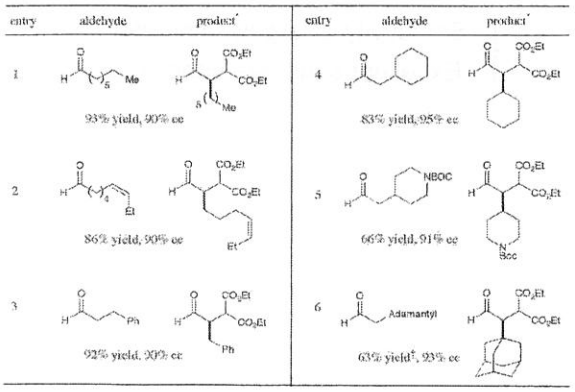
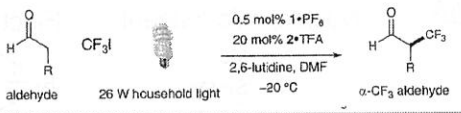
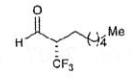
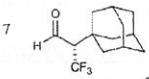
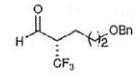
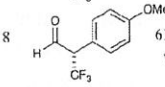
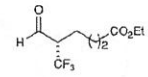
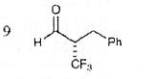
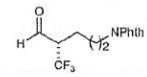
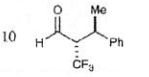
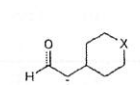
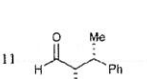
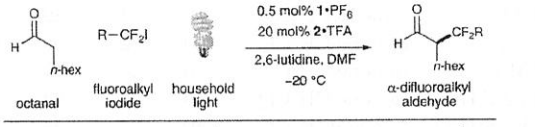
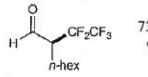
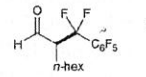
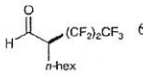
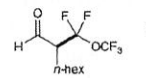
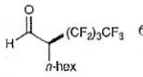
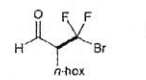
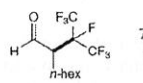
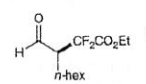


Table 2. Enantioselective α-Trifluoromethylation: Aldehyde Scope



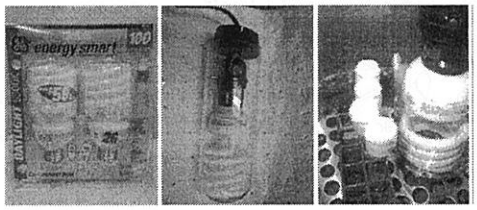
entry	product[a]	yield,[b] ee[c]	entry	product[a]	yield,[b] ee[c]
1		79% yield 99% ee	7		73% yield[d] 90% ee
2		72% yield 95% ee	8		61% yield 93% ee
3		86% yield 97% ee	9		75% yield 97% ee
4		78% yield 98% ee	10		68% yield >20:1 dr 99% ee
5 6		X = CH_2 70% yield 99% ee X = NBoc 70% yield 98% ee	11		62% yield >20:1 dr 99% ee



entry	product[a]	yield,[b] ee[c]	entry	product[a]	yield,[b] ee[c]
1		73% yield 96% ee	5		85% yield 98% ee
2		69% yield 99% ee	6		71% yield 99% ee
3		67% yield 96% ee	7		68% yield[d] 99% ee
4		72% yield 98% ee	8		89% yield[d] 99% ee

Possible to apply for perfluoroalkylation

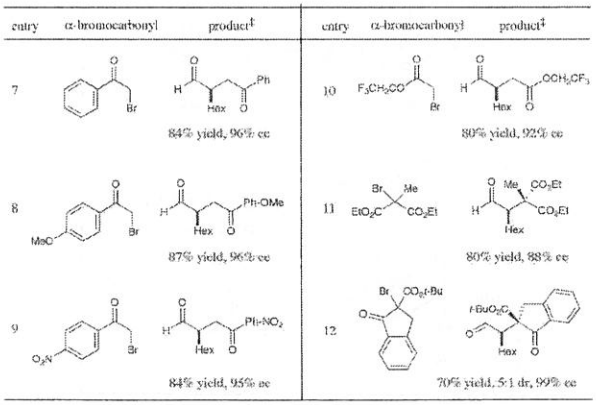
Equipment



26 W fluorescent light bulbs

Pyrex glass tube encasement with rubber stopper

Reaction set-up (side view)



3. Conclusion

As for Reaction Development

Now, using "building blocks" is the main method to introduce D or F into target compounds.

Advantage : easy to introduce, commercially available
Disadvantage : only using commercially available compounds (not full of variety)
not having stereoselectivity in general
high cost

Selective D or F reaction can solve these disadvantages.
However, there are a lot of problems.

H/D Exchange : Not acidic proton is difficult to exchange (C-H activation is a powerful tool so far).
It is almost impossible to exchange all proton (some protons are remained),
and difficult to separate from not changed.
Enantioselective reaction is only a few example (using chiral substrates)

H/F Exchange : Substrate is limiting to β-ketoester etc. in catalytic enatioselective fluorination.
Catalytic enatioselective trifluoromathylation is developed recently,
but it has much room for improving yield, ee, range of substrate.

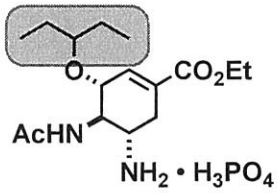
As for Drug Creation

In my opinion, D or F seem not to be tried vigorously recentry.

{ New launched medicine becomes reduced and most of the pharma companies are pressed for time.
It is necessary to pass clinical development rapidly, especially in the case of buying targets from the venture.

⇒ D or F in proper position can improve metabolism or activity much easier than we think.

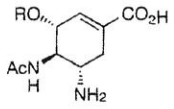
ex) Tamiful (also see Ms. Yao's lit seminar and special thanks for Mr. Yamatsugu and Mr. Kimura)



US Patent : Dec., 27, 1996 (*FILED*)
FDA Approval : Oct., 27, 1999

licensed to *Roche* for late-phase development

Table 1. Influenza Neuraminidase Inhibition and Plaque Reduction by Carbocylic Analogues



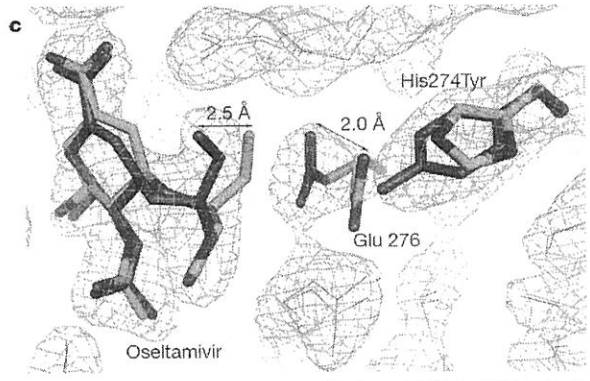
6

R	compd	enzyme[a] IC_{50} (nM)	plaque[b] EC_{50} (nM)
H	**8**	6300	ND[c]
CH_3	**6a**	3700	ND
CH_3CH_2	**6b**	2000	
$CH_3CH_2CH_2$	**6c**	180	ND
$CH_3CH_2CH_2CH_2$	**6d**	300	ND
$(CH_3)_2CHCH_2$	**6e**	200	ND
$CH_3CH_2(CH_3)CH$*	**6f**	10	80
	(*R*)-isomer		
	6g	9	135
	(*S*)-isomer		
$(CH_3CH_2)_2CH$	**6h**	1	16
$(CH_3CH_2CH_2)_2CH$	**6i**	16	ND
	2	150	2500
	3	1	15

[a] NA. [b] H1N1, A/ws. [c] ND = not determined.

Gilead Sciences' Grup *J. Am. Chem. Soc.* **1997**, *119*, 681

From this thesis, only hydrocarbons were checked.



Nature **2008**, *453*, 1258

Hydrophobic pocket becomes smaller by influence of Glu276 pushed by bulkier Tyr.

⇓

It should be an important factor that substituents can interact with Glu276 with remaining hydrophobicity.

⇓

"F" may be useful.

{ high lipophilicity
mimic for OH group