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Chemistry of α-CF_3 Carbonyl Compounds:

Development of Selective Reactions and their Theoretical Studies

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Yoshimitsu Itoh

Abbreviations

Å	angstrom
Ac	acetyl
aq.	aqueous
Ar	aryl
AT	atom transfer
B	base
BE	bond energy
Bn	benzyl
Bp	boiling point
bs	broad singlet
BTF	benzotrifluoride
Bu	butyl
°C	degrees Celsius
C	carbon
cat.	catalyst(s)
CNDO	complete neglect of differential overlap
COSMO	conductor-like screening model
CP	complex
d	doublet (spectral), day(s)
de	diastereomeric excess
DFT	density functional theory
DIBAL	diisobutylalminum hydride
δ	chemical shift in parts per million down field
EA	electron affinity
ee	enantiomeric excess
EN	electronegativity
eq.	equivalent
Et	ethyl
ET	electron transfer
ether	diethylether
ΔE	electronic energy change
ΔG	Gibbs free energy change
h	hour(s)
HF	Hartree-Fock
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
Hz	hertz
i	iso
IP	ionization potential
IPA	isopropyl alcohol
J	coupling constant (in NMR)
k, K	kilo
L.A.	Lewis acid
LDA	lithium diisopropyl amide
LUMO	lowest unoccupied molecular orbital
m	multiplet (spectral)
M	moles per liter, metal
MC	Monte Carlo
*m*CPBA	meta-chloroperbenzoic acid
MD	molecular dynamics
Me	methyl
min.	minute(s)
ml	milliliter
MM	molecular mechanics
MO	molecular orbital
mol	mole(s)
n	normal
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile

PCM	polarized continuum model
PD	product
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet (spectral)
R	alkyl
R_f	fluoroalkyl
R_H	alkyl
RT	reactant
r.t.	room temperature
s	singlet (spectral), second(s)
sat.	saturated
t	triplet (spectral)
t	tertiary
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butylhydroperoxide
tert	tertiary
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFPA	trifluoroperacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
TS	transition state
vdW	van der Walls

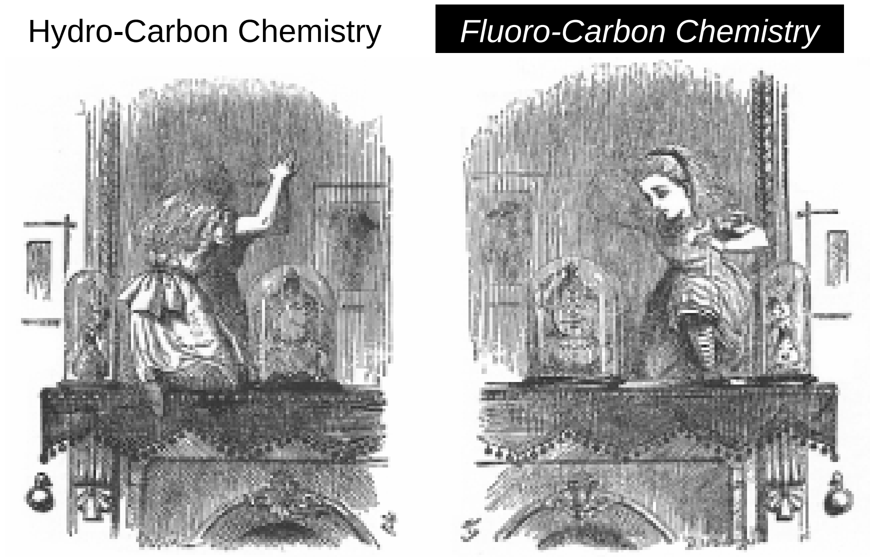
Table of Contents

Chapter 1

General Introduction

1-1. Introduction.

The synthesis of organofluorine compounds has attracted explosive interest in recent years owing to the anomalous physical properties and less availability of these compounds (Art 1-1).[1] In the synthesis that fluorine atoms are introduced in the number of 1 or 3 and in specific absolute configuration, these organofluorine compounds exhibit particularly high physiological activity and remarkable physical properties, when used in medicines, liquid crystals, and other materials.[2]


Hydro-Carbon Chemistry

Fluoro-Carbon Chemistry

Art 1-1. Oh, Kitty, how nice it would be if we could only get through into Fluoro-Carbon Chemistry! I'm sure it's got, oh! such beautiful things in it!

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(1) (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds, 2nd edn*; Ellis Horwood: Chichester, 1976. (b) Ishikawa, N.; Kobayashi, Y. *Fluorine Compounds*; Koudansha: Tokyo, 1979. (c) Ishikawa, N. Ed. *Synthesis and Reactivity of Fluorocompounds*; CMC: Tokyo, Vol. 3, 1987. (d) Kitazume, T.; Ishihara, T.; Taguchi, T. *Chemistry of Fluorine*; Koudansha: Tokyo, 1993. (e) Banks, R. E.; Smart, B. E.; Tatlow, J. C. Eds. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York. 1994. (f) Smart, B. E., Ed. *Chem Rev.* **1996**, *96,* No. 5 (Thematic issue of fluorine chemistry). (g) Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington DC, 1996. (h) Iseki, K. *Tetrahedron* **1998**, *54*, 13887-13914. (i) Chambers, R. D. Ed. *Organofluorine Chemistry*, Springer, Berlin 1997. (j) Soloshonok, V. A. Ed. *Enantiocontrolled Synthesis of Fluoro-OrganicCompounds*; Wiley: Chichester, 1999. (k) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Springer-Verlag: Berlin Heidelberg, 2000. (l) Mikami, K.; Itoh, Y.; Yamanaka, M. *Fine Chemical* **2003**, *32(1),* 35-50. (m) Mikami, K.; Itoh, Y.; Yamanaka, M. *Fine Chemical* **2003**, *32(2),* 11-20. (n) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104,* 1-16. (o) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104,* 6119-6146.

(2) (a) Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1496-1513. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3-11.

A liquid crystal such as TFMHPOBC [4-{1-(trifluoromethyl)hexyloxycarbonyl} phenyl-4’-octyloxybiphenyl-4-carboxylate] is an interesting example (Figure 1-1). TFMHPOBC shows an anti-ferroelectric SmC$_A$* liquid crystalline phase, while mono- or difluoro analogues, in sharp contrast, exhibit a ferroelectric SmC* phases.[3] Additional methyl group in TFMHPOBC shows a significant effect to stabilize a bent conformation for SmC$_A$* phase (*anti*-β-Me-TFMHPOBC), while the diastereomer (*syn*-β-Me-TFMHPOBC) shows SmC* phase.[4]

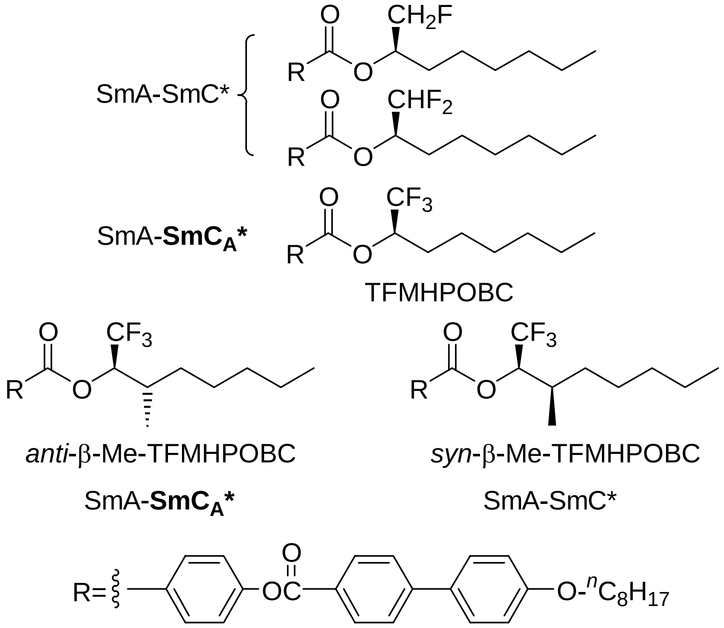

Figure 1-1. Remarkable effect of CF$_3$ group in the fluorine-containing liquid crystals.

9-Fluorohydrocortisone acetate is the first successful example of fluorinated drug in the modern and hence designed medicinal chemistry (Figure 1-2).[5] Fried clearly showed the effectiveness of fluorination to enhance biological activity and to improve the versatility. The recent anti-allergy agent Fuluticason propionate for fey fever (kafun-sho, in Japanese) is a further fluorinated analogue.[6]

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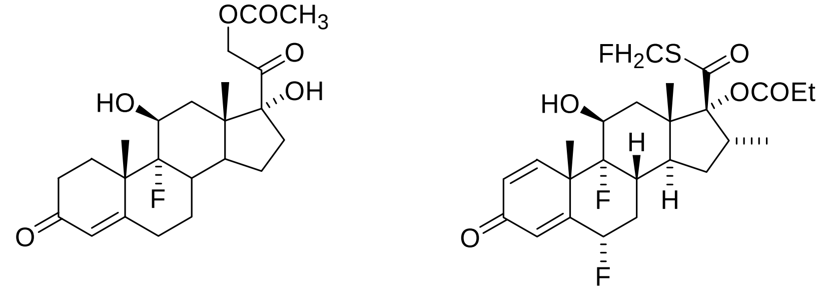
(3) Suzuki, Y.; Nonaka, O.; Koide, Y.; Okabe, N.; Hagiwara, T.; Kawamura, I.; Yamamoto, N.; Yamada, Y.; Kitazume, T. *Ferroelectrics* **1993**, *147*, 109-119.

(4) (a) Mikami, K.; Yajima, T.; Siree, N.; Terada, M.; Suzuki, Y.; Kobayashi, I. *Synlett* **1996**, 837-838. (b) Mikami, K.; Yajima, T.; Terada, M.; Kawauchi, S.; Suzuki, Y.; Kobayashi, I. *Chem. Lett.* **1996**, 861-862. (c) Mikami, K.; Yajima, T.; Terada, M.; Suzuki, Y.; Kobayashi, I. *Chem. Commun.* **1997**, 57-58. (d) Takanishi, Y.; Takezoe, H.; Suzuki, Y.; Kobayashi, I.; Yajima, T.; Terada, M.; Mikami, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 2353-2356.

(5) (a) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1953**, *75*, 2273-2274. (b) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456

(6) Dewick, P. M. *Medicinal Natural Products*, 2nd Edition; Wiley: Chichester, 2002; p 268.



9-Fluorohydrocortisone acetate Fuluticason propionate

Figure 1-2. The first and recent examples of fluorinated cortisone.

1-2. General characteristics of organofluorine compounds

Important properties of fluorine atom and effects of the fluorine-containing compounds are as follows.

(1) Steric effect: F is not sterically demanding and has the smallest van der Waals (vdW) radius apart of H.
(2) Electronic effect: F has the largest electronegativity.
(3) Bond energy: C-F bond is much stable toward metabolic transformations.
(4) Lipophilicity: Large lipophilicity assists to distribute the fluorine-containing compounds in living organisms.
(5) Hydrogen bonding: Lone electron pair of F readily participates in hydrogen bonding as an acceptor.
(6) PET (positron emission tomography): A short lived isotope ^{18}F ($t_{1/2}$ = 110 min) is useful for PET analyses.

1-2-1. Properties of the fluorine atom.

The vdW radius of fluorine is the smallest after hydrogen, and the closest to that of oxygen. On the other hand, the size of CF_3 is relatively large, in the order of Me < ^{i}Pr < CF_3 < ^{t}Bu.[7,8] In estimating the size of the substituent group based on single bond rotational barriers of biphenyl derivatives, CF_3 is approximately equivalent to ^{i}Pr, and hence, in sharp contrast to the small vdW radius of fluorine, a rather bulky substituent (Figure 1-3).[9]

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(7) Taft's Es values: H=1.24, Me=0, ^{i}Pr=-0.47, CF_3 =-1.16, ^{t}Bu=-1.54. Taft, R. W. *Jr.* In *Steric Effects in Organic Chemistry*; Newman, M. S. Eds.; John Wiley & Sons: New York, 1956; p 598.

(8) A-values: Me=~1.70 ^{i}Pr=~2.15, CF_3=2.4~2.5, ^{t}Bu=>4 (kcal/mol). Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139-195.

(9) (a) de Riggi, I.; Virgili, A.; de Moragas, M.; Jaime, C. *J. Org. Chem.* **1995**, *60*, 27-31. (b) Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1995**, 781-786.

R=^{i}Pr, $\Delta G^{\ddagger}$=14.0 kcal/mol
R=CF_3 , $\Delta G^{\ddagger}$=14.5 kcal/mol

R=^{i}Pr , $\Delta G^{\ddagger}$=109.8 kcal/mol
R=CF_3, $\Delta G^{\ddagger}$=109.2 kcal/mol

Figure 1-3. Energy barriers of the single bond rotation.

As shown in Table 1-1,[10] fluorine atom has the highest electronegativity (EN) among all elements. The ionization potential (IP) is the highest except for those of helium and neon. Therefore, electrons are drawn strongly towards the fluorine nucleus. For this reason, the electron dipole of fluorine atoms is small, and as a result, intermolecular vdW attractive force between fluorine-containing compounds is small. The C-F bond has much greater bond energy than the C-H or C-X (X=Br, Cl) bonds. The Si-F bonding energy is even higher (141 kcal/mol) and hence sometimes employed as a driving force for the generation of a nucleophile (Nu^-) from Si-Nu.

Table 1-1. Several properties of H, F, Cl, and O (OH).

	IP (kcal/mol)	EA (kcal/mol)	vdW radius (Bondi) (Å)	EN (Pauling)	BE CH_3-X (kcal/mol)	CH_3-X (Å)
H	313.6	17.7	1.20	2.1	99	1.09
F	401.8	79.5	1.47	4.0	116	1.39
Cl	299.0	83.3	1.75	3.0	81	1.77
O (OH)	310.4	33.7	1.52	3.5	86	1.43

IP=Ionization potential, EA=Electron affinity, EN=Electronegativity, BE=Bond energy

Lone electron pair of a fluorine atom can also play a significant role in hydrogen bonding. Although 2-fluorophenol is considered to have two conformations, *syn* and *anti*, only the *syn* conformation has been observed (by microwave spectrometry) (Figure 1-4).[11] The fact that the H-F distance in the *syn* conformation is 2.235 Å, which is smaller than the sum of the vdW radii of hydrogen and fluorine atoms (2.67 Å), is considered to be a proof for hydrogen bonding between O*<u>H</u>* and *<u>F</u>* (Figure 1-4, a). Among the enol forms of 2-fluoroacetaldehyde, a *Z,syn* conformer is calculated at MP2

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(10) David R. Lide, ed., *CRC Handbook of Chemistry and Physics, Internet Version 2005,* <http://www.hbcpnetbase.com>, CRC Press, Boca Raton, FL, 2005.

(11) Dutta, A.; Jaman, A. I.; Nandi, R. N. *J. Mol. Spectrosc.* **1985**, *114*, 274-297.

level to be 3.2 kcal/mol more stable by hydrogen bonding between C=C-O<u>H</u> and <u>F</u> than a *Z,anti* isomer (Figure 1-4, b).[12]

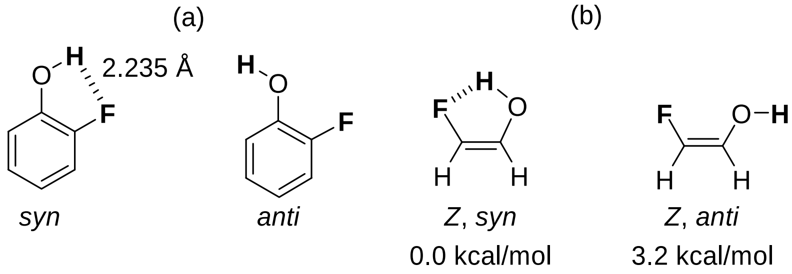

Figure 1-4. Hydrogen bonding effect of fluorine-containing compounds.

In a similar way to hydrogen bonding, the fluorine atom can coordinate to metals. The interaction between the metal and fluorine atom can be confirmed by the difference (Δ) between the metal fluorine distance determined by X-ray crystal analyses[13] and the sum of the vdW radius of fluorine and atomic radii of the metal (rF+rM) (Table 1-2). The large negative values of '$\Delta/(r\text{F}+r\text{M})$' for main group element, Al (-35.6%) and early transition metal, Ti (-27%) indicate the strong interactions and hence short bond lengths between the metals and fluorine atom.

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(12) Dixon, D. A.; Smart, B. E. *J. Phys. Chem.* **1991**, *95*, 1609-1612.

(13) (a) Murray-Rust, P.; Stallings, W. C.; Monti, C. T.; Preston, R. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3206-3214. (b) Shibakami, M.; Sekiya, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 315-316. (c) Shimoni, L.; Glusker, J. P.; Bock, C. W. *J. Phys. Chem.* **1995**, *99*, 1194-1198. (d) Fernandez-G., J. M.; Rodriguez-Romero, A.; Panneerselvam, K.; Soriano-Garcia, M. *Acta. Crystallogr. Sect. C* **1995**, *51*, 1643-1646. (e) Murphy, E. F.; Lubben, T.; Herzog, A.; Roesky, H. W.; Demsar, A.; Noltemeyer, M.; Schmidt, H. -G. *Inorg. Chem.* **1996**, *35*, 23-29. (f) Murphy, E. F.; Yu, P.–H.; Dietrich, S.; Roesky, H. W.; Parisini, E.; Noltemeyer, M. *J. Chem. Soc., Dalton Trans.* **1996**, 1983-1987. (g) Herzog, A.; Roesky, H. W.; Jäger, F.; Steiner, A. *Chem. Commun.* **1996**, 29-30. (h) Shah, S. A. A.; Dorn, H.; Voigt, A.; Roesky, H. W.; Parisini, E.; Schmidt, H.–G.; Noltemeyer, M. *Organometallics* **1996**, *15*, 3176-3181. (i) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363-3384. (j) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425-3468.

Table 1-2. Comparison of the M-F length with the sum of the vdW radii of fluorine and atomic radii of the metal.

	Li	Na	K	Cs	Al	Ti	Zr	Hf	Sn	Zn	Pd	Ag
M-F (=A) (Å)[a]	2.23-2.29	2.15-2.91	2.67-3.39	2.87-3.61	1.77-1.81	2.03-2.10	1.94-2.18	2.31-2.38	2.05-2.46	2.80	3.13-3.16	2.64-2.72
*r*F+*r*M (=B) (Å)[b]	2.92	3.26	3.70	4.07	2.78	2.82	2.95	2.94	2.93	2.72	2.72	2.79
Δ: A-B (Å)	-0.66	-0.73	-0.67	-0.83	-0.99	-0.76	-0.89	-0.60	-0.68	+0.08	+0.43	-0.11
Δ/B (%)	-22.6	-22.4	-18.1	-20.4	-35.6	-27.0	-30.2	-20.4	-23.2	+2.90	+15.8	-3.90

[a] Determined by X-ray crystal structure.
[b] Sum of vdW radius of F and atomic radius of M.

The chelate stabilization of alkaline metal enolates of 2-fluoroacetaldehyde has been computationally analyzed. The *Z*(O), *syn*-enolate conformer is calculated to be 11-14 kcal/mol more stable due to a strong chelate structure between H and Li, Na, or K than a *Z*(O), *anti*-isomer. The chelate structure is also suggested by the shorter M-F bond lengths for Li: 1.86 Å; Na: 2.21 Å; K: 2.62 Å (Table 1-3).[14]

Table 1-3. Chelate stabilization of alkaline metal enolates of 2-fluoroacetaldehyde.

M	ΔE(*anti*-*syn*) (kcal/mol)	M-F (*syn*) (Å)
	1.8	
Li	13.2	1.86
Na	13.6	2.21
K	10.8	2.62

The M-F chelate structures may control the stereoselectivity of reactions with fluorine-containing compounds, but examples are still limited.

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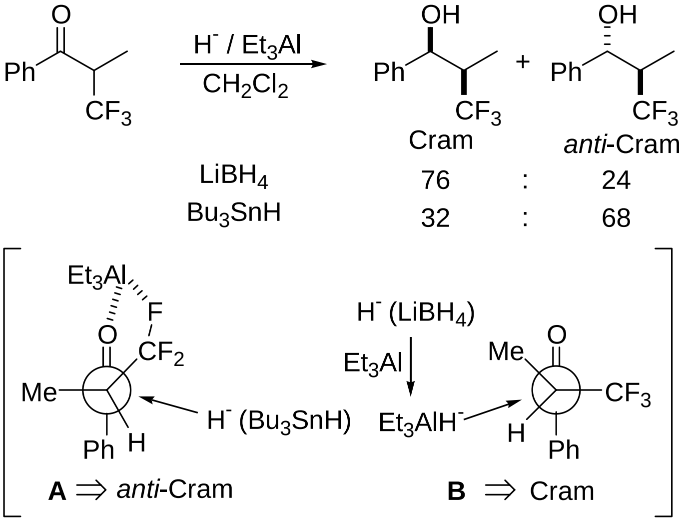
(14) Dixson, D. A.; Smart, B. E. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington D.C., 1991; p 18-35.

One typical example is the reduction of 3,3,3-trifluoro-2-methyl-1-phenyl-propan-1-one.[15] Reversal of the stereoselectivity was observed by the use of $LiBH_4$ vs. Bu_3SnH in the presence of $AlEt_3$ (Scheme 1-1). The cyclic intermediate **A** may be formed in the presence of $AlEt_3$, prior to the addition of a reducing reagent. With Bu_3SnH, the reduction proceeds through the cyclic intermediate **A** to give the *anti*-Cram selectively. On the other hand, with $LiBH_4$, hydride can attack the aluminum reagent to destroy the cyclic intermediate to form **B**. As a result, bulky hydride complex may be generated *in situ*, and the reduction takes place through the Felkin-Anh model, giving the Cram isomer selectively.

Scheme 1-1.



Another example of Al-F interaction-controlled selectivity has been reported for epoxide ring opening reaction.[16] Excellent regioselectivity is observed in the ring opening reaction by organoaluminum compounds when fluorine atom is incorporated in the substrate (Scheme 1-2). When a non-fluorinated substrate is subjected to the ring opening alkylation by organoaluminum alkynides, only low regioselectivity is observed. On the other hand, when fluorine atom is introduced to nearby the epoxide ring to form a cyclic intermediate **A**, perfect regioselectivity is observed. Existence of the cyclic intermediate **A** was supported by ^{13}C and ^{27}Al NMR spectroscopy.

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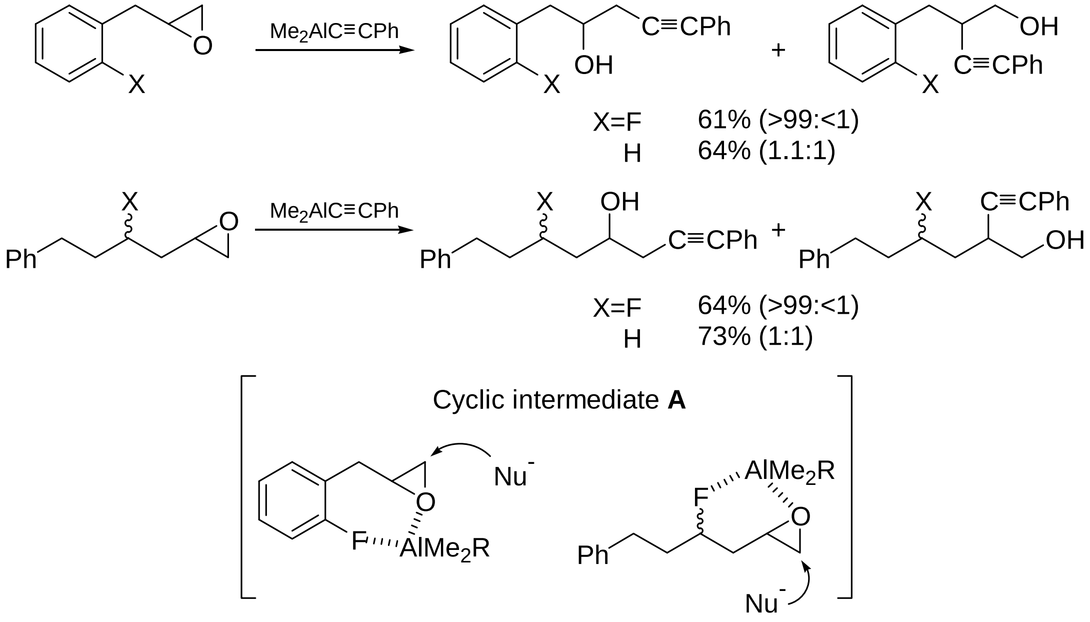
(15) Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969-4971.

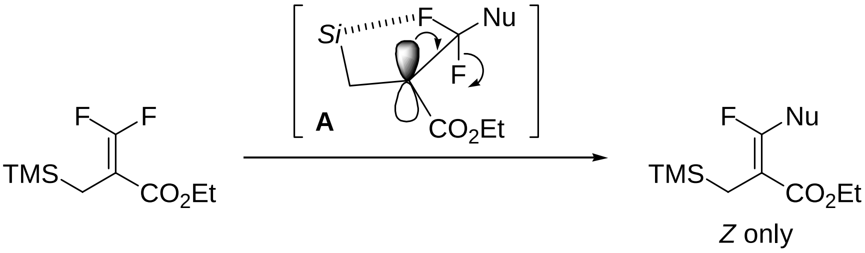
(16) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754-5755.

Scheme 1-2.



Selectivity control by Si-F interaction has also been reported.[17] Excellent stereoselectivity is observed in addition-elimination reaction of β,β-difluoro-α,β-unsaturated ester substituted with a Si group. Si-F interaction is suggested to play an important role on the reaction intermediate, as in **A**, to stabilize one conformer and thus give only one stereoisomer (Scheme 1-3). This is in sharp contrast with the result from the LAH reduction of a simple 2-alkyl- rather than 2-[(trimethylsilyl)methyl]-substituted 3,3-defluoropropentanoate, which led to monofluoroallic alcohols with low stereoselectivity.[18] Involvement of Si-F interaction in the reaction intermediate was supported by ^{29}Si NMR spectroscopic analysis.

Scheme 1-3



Nu	*E*:*Z*
(EtO$_2$C)$_2$CHCH$_3$ / NaH	0:100
cyclohexanone / LDA	0:100

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(17) Huang, X.-H.; He, P.-Y.; Shi, G.-Q. *J. Org. Chem.* **2000**, *65*, 627-629.

(18) Watanabe, S.; Sugahara, K.; Fujita, T.; Sakamoto, M.; Kitazume, T. *J. Fluorine Chem.* **1993**, *62*, 201-206.

These characteristics of fluorine atom serve as a basis for the following unique effects of these types of organofluorine compounds.

1-2-2. Fluorine effects.

A fluorine atom has a vdW radius similar to those of hydrogen or oxygen, and constitutes the structure that is isoelectronic ($2s^22p^6$ configuration) to oxygen (or alcohol). Therefore, fluoroalkanes, -alkenes, and difluoromethylene groups are referred to as isosters; substitutes isosterically as hydrogen bond acceptors to the alkanols, amides, and ethers, respectively (bioisosterism) (Figure 1-5).[1g, 19] As a result, fluorine-containing compounds obtained by substitution of hydrogen atoms or hydroxyl groups of physiologically active compounds with fluorine atoms can be dealt with similarly by biological systems. This is referred to as the mimic effect and makes it possible to greatly change the electronic environment of a physiologically active substance, without changing its steric environment.

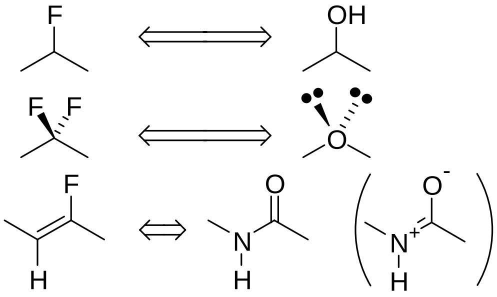

Figure 1-5. Mimic effect of the fluorine atom.

Physiologically active fluorinated compounds can be similarly recognized (mimic effect) but resistant in metabolic degradation by virtue of the strong C-F bond energy. This is referred to as the block effect which greatly increases the metabolic resistance of a physiologically active substance. Fluorinated compound is rendered resistant to oxidation by the much greater bond energy than C-H or C-X (X = Br, Cl) bonds, thus allowing it to escape or survive metabolic processes.

The fluorine atom has reduced lipophilic effects relative to Cl or CH_3, but SCF_3 group has greater lipophilic effects than CF_3 or OCF_3. Such XCF_3 groups are named pseudohalogens,[1b] and have significant electron withdrawing effects, while being more

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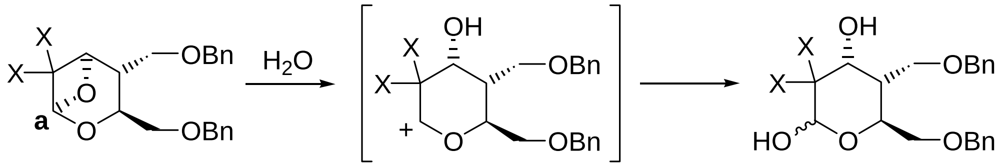
(19) (a) Allmendinger, T.; Furet, P; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297-7300. (b) O'Hagan, D.; Rzepa, H. S. *Chem. Comm.* **1997**, 645-652.

stabilized than halogen atoms.[20] Thus, such XCF_3 molecules readily pass through cell membranes and reach active sites without being broken down. As a result, drug potency is increased, and side effects are suppressed.

The reactivity of some fluorinated compounds can be, some times, lowered and hence controlled by the effect of fluorine. For example, oxetane acetals are compounds that are hydrolyzed extremely easily (X=H), but hydrolysis is retarded when the group (X) is changed to F (Scheme 1-4).[21] The decreased electron density of the proximal oxygen atom, due to the electron-withdrawing properties of fluorine atom, disfavor the cation generation at carbon **a**.

Scheme 1-4.



$k_H/k_F=2X10^8$

By virtue of the strongest electronegativity of a fluorine atom, the LUMO level of fluorinated carbonyl compounds, e.g. trifluoroacetaldehyde (fluoral) is greatly reduced relative to non-fluorinated acetaldehyde (fluoral: -5.40 eV, acetaldehyde: -4.09 eV at the HF/6-31G** level).[22] For this reason, the electrophilicity is dramatically increased, and fluoral readily undergoes addition reactions. The hydrate of the fluorinated carbonyl compound (e.g. $CF_3CH(OH)_2$) and hemiacetal (e.g. $CF_3CH(OH)(OR)$) are more stable than the carbonyl form.[23] Difluoromethylene-ketones are also highly electrophilic to provide their hydrate forms. Their tetrahedral structures mimic the transition state of hydrolysis by protease enzyme and the tetrahedral intermediates act as reversible protease inhibitors.[24] Orally active protease inhibitors are important for AIDS,

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(20) (a) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979. (b) Yoshioka, H.; Takayama, C.; Matsuo, N. *J. Synth. Org. Chem. Jpn*. **1984**, *42*, 809-821.

(21) Premchandran, R. H.; Ogletree, M. L.; Fried, J. *J. Org. Chem.* **1993**, *58*, 5724-5731.

(22) (a) Linderman, R. J.; Jamois, E. A. *J. Fluorine Chem.* **1991**, *53*, 79-91. (b) Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1992**, *57*, 1904-1916. (c) Milkami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591-7594.

(23) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898-905.

(24) For crystallographic evidence see: (a) Takahashi, L. H.; Rosenfield, R. E.; Meyer, Jr., E. F.; Trainor, D. A.; Stein, M. *J. Mol. Biol.* **1988**, *201*, 423-428. (b) Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E.; Meyer, Jr., E. F.; Trainor, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 3368-3374. (c) Brady, K.; Wei, A. –Z.; Ringe, D.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7600-7607. (d) Veale, C. A.; Bernstein, P. R.; Bryant, C. B.; Ceccarelli, C.; Damewood, Jr., J. R.; Earley, R. A.; Feeney,

metastatic cancer, arthritis, and sleeping sickness, etc.

Fluorine has the highest EN, and IP (except for He and Ne) (cf. Table 1-1) and, therefore, fluorine compounds exhibit characteristic reactivity and physical properties due to the stereoelectronic effect of the F and CF_3 groups (Figure 1-6). Fluorine could stabilize α-cation by lone electron pair donation rather than the inductive effect working the opposite way. On the other hand, CF_3 group destabilize α-cation due to the strong electron-withdrawing nature (Figure 1-7). Bis(trifluoromethyl) groups may possess *anti*-periplanar (di-axial) conformations in the ground states and, on the basis of theoretical calculations, in the transition states, because of dipole or steric repulsion resulting from the high electro-negativity of the trifluoromethyl group.[25]

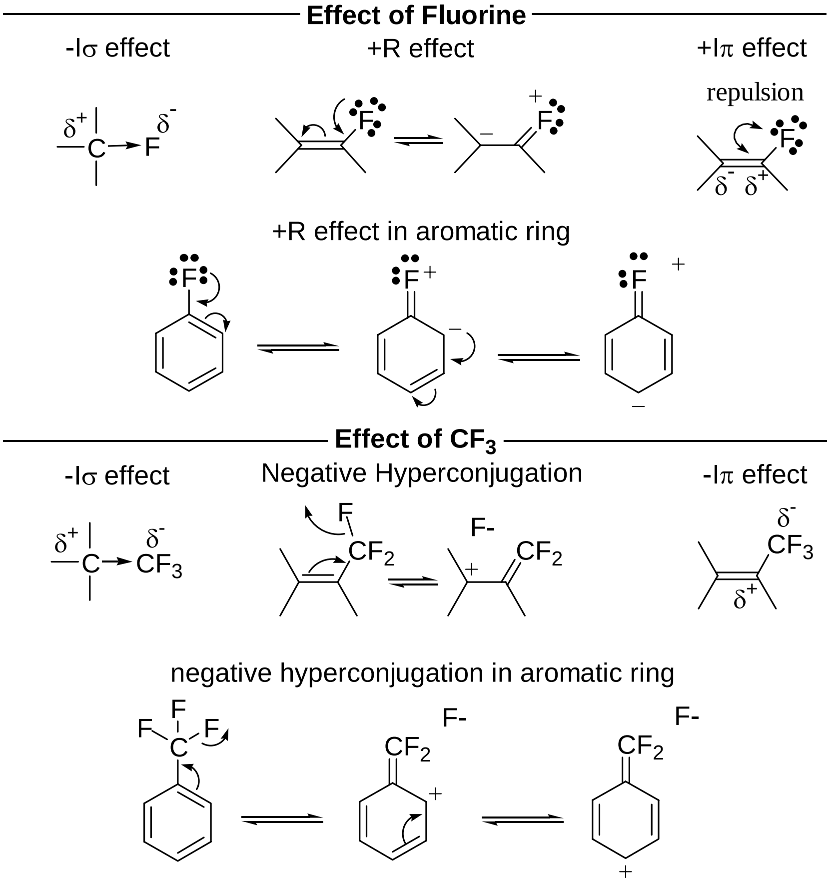

Figure 1-6. Various effects of the fluorine atom and the trifluoromethyl group.

S. W.; Gomes, B.; Kosmider, B. J.; Steelman, G. B.; Thomas, R. M.; Vacek, E. P.; Williams, J. C.; Wolanin, D. J.; Woolson, S. A. *J. Med. Chem.* **1995**, *38*, 98-108. (e) Harel, M.; Quinn, D. M.; Nair, H. K.; Silman, I.; Sussman, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 2340-2346. (f) Silva, A. M.; Cachau, R. E.; Sham, H. L.; Erickson, J. W. *J. Mol. Biol.* **1996**, *255*, 321-346.

(25) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807-4809.

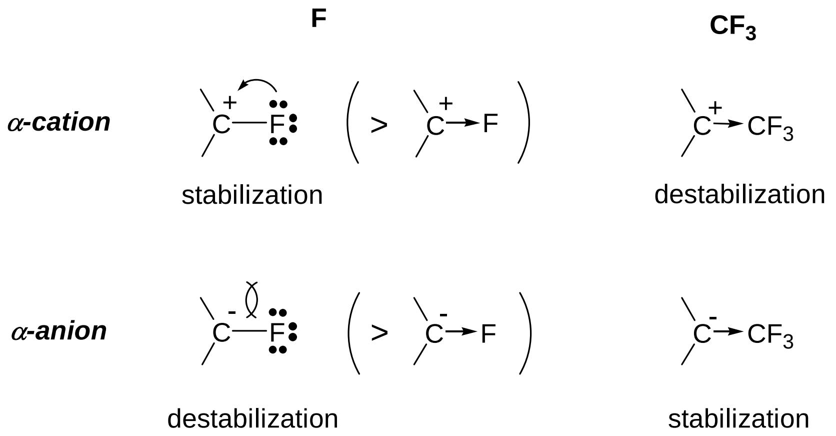

Figure 1-7. Stabilization and destabilization of fluororine groups.

1,2-Difluoroethane exhibits clear *syn*-clinal conformations on the basis of infrared (IR), Raman,[26] nuclear magnetic resonance (NMR),[27] atomic diffraction[28] and theoretical calculations,[29] in spite of dipole or steric repulsion resulting from the high electronegativity of the fluorine atoms. This *syn*-clinal effect is due to the fact that the electron flow towards the $\sigma^*_{C\text{-}F}$ bond from the $\sigma_{C\text{-}H}$ bond is very large relative to the flow towards the $\sigma^*_{C\text{-}F}$ bond from the $\sigma_{C\text{-}F}$ bond in the *anti*-periplanar conformation. As a result, the *syn*-clinal conformation is stabilized (Figure 1-8). In a similar manner, fluorocarbonyl compounds exhibit clear *anti*-periplanar conformations to the incoming “naked” nucleophile in the carbonyl addition reactions on the basis of theoretical calculations. This is due to the effective orbital interaction between the $\sigma^*_{C\text{-}F}$ bond and the $\pi^*_{C\text{-}O}$ double bond, and further with the incoming nucleophile σ in the *anti*-periplanar conformation as compared to the outside or -inside orientation of the C-F bond.[30]

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(26) Klaboe, P.; Nielsen, J. R. *J. Chem. Phys.* **1960**, *33*, 1764-74.

(27) Hirano, T.; Nonoyama, S.; Miyajima, T.; Kurita, Y.; Kawamura, T.; Sato, H. *J. Chem. Soc., Chem. Commun.* **1986**, 606-607.

(28) (a) Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* **1980**, *102*, 3987-3994. (b) Fernholt, L.; Kveseth, K. *Acta Chem. Scand. A* **1980**, *34*, 163-70.

(29) (a) Dixon, D. A.; Smart, B. E. *J. Phys. Chem.* **1988**, *92*, 2729-2733. (b) Dixon, D. A.; Matsuzawa, N.; Walker, S. C. *J. Phys. Chem.* **1992**, *96*, 10740-10746. (c) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229-234. (d) Berry, R. J.; Ehlers, C. J.; Burgess, Jr., D. R.; Zachariah, M. R.; Nyden, M. R.; Schwartz, M. *J. Mol. Struct.* **1998**, *422*, 89-98.

(30) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Comm.* **1990**, 456-458.

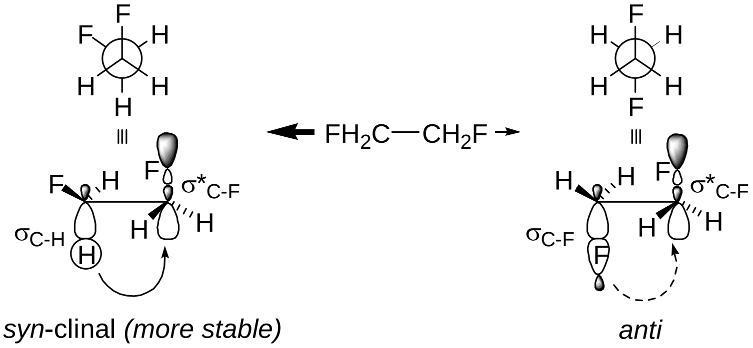

Figure 1-8. *syn*-Clinal effect of difluoroethane.

1-2-3. Disadvantage of fluorine effect in synthetic organic chemistry.

Although these fluorine effects give rise to the interesting characteristics of organofluorine compounds, it often causes a difficulty in synthetic organic chemistry.

Standard synthetic methods involving ionic (anionic or cationic) carbon-carbon bond forming reactions, which have already been established for non-fluorinated substrates, are often not applicable to fluorinated substrates. For example, carbon-carbon bond forming reactions employing stock solutions of perfluoroalkyllithium reagents are not general. Perfluoroalkyllithiums are thermally unstable because of their rapid α- and β-Li-F elimination. A co-existing electrophile can only be used for *in situ* generated perfluoroalkyllithium reagents at low temperature. Particularly, trifluoromethyllithium has not yet been reported in synthetic applications.[31] Therefore, trifluoromethyltrimethylsilane (TMSCF$_3$) is useful as a source of "CF_3^-".[32]

Another example is perfluoroalkyl halides. In sharp contrast to normal alkyl halides, perfluoroalkyl halides cannot undergo nucleophilic alkylation, because the electronegativities of perfluoroalkyl groups are higher than those of halogens.[33] Thus the polarization of perfluoroalkyl halides is as $R_f^{\delta-}$-$I^{\delta+}$ and treatment with nucleophile (Nu) could not produce R_f-Nu.

Fluorine-containing carbonyl compounds can also be employed as fluorine-substituted building blocks. However, metal enolates of carbonyl compounds as nucleophiles, which are of central importance in the synthesis of non-fluorinated compounds, have been severely limited on α-F metal enolates to be stabilized by M-F

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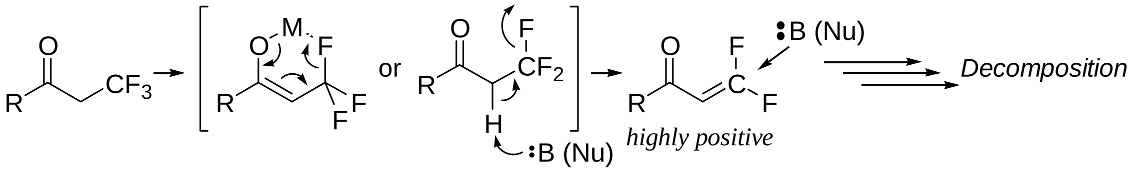
(31) Review: (a) Burton, D. J.; Yang, Z. -Y. *Tetrahedron* **1992**, *48*, 189-275. (b) Burton, D. J.; Yang, Z.-Y.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993-3063.

(32) Review: (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757-786. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613-7632.

(33) (a) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284-3291. (b) Yoshida, M.; Kamigata, N *J. Fluorine Chem.* **1990**, *49*, 1-20.

chelate structures.[34] On the other hand, α-CF_3 metal enolates have been generally recognized to be very unstable and hence difficult to prepare because of the rapid β-M-F elimination (Scheme 1-5).[35]

Scheme 1-5.



1-3. Synthesis of organofluorine compounds.

Despite the natural abundance of fluorine,[36] only 12 kinds of natural organofluorine compounds are reported to date (Figure 1-9).[37] 8 of them are terminally-fluorinated higher fatty acids which are found from the same plant. Recently, O'Hagan and co-workers have discovered natural C-F bond forming enzyme "fluorinase enzyme". The new enzyme, "fluorinase" have attracted much attention.[38] However, most of the origins of the natural organofluorine compounds have not been clarified yet. Thus we could not expect natural source of organofluorine compounds as in hydrocarbon chemistry, in which various kinds of compounds could be obtained from nature.

---

(34) (a) Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247-5250. (b) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720-4721. (c) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5403-5405. (d) Welch, J. T.; Herbert, R. W. *J. Org. Chem.* **1990**, *55*, 4782-4784. (e) Ishihara, T.; Matsuda, T.; Imura, K.; Matsui, H.; Yamanaka, H. *Chem. Lett.* **1994**, 2167-2170. (f) Ishihara, T.; Ichihara, K.; Yamanaka, H. *Tetrahedron Lett.* **1995**, *36*, 8267-8270. (g) Ishihara, T.; Ichihara, K.; Yamanaka, H. *Tetrahedron* **1996**, *52*, 255-262.

(35) Only limited example of covalently bonded α-CF_3 metal enolate are reported. B enolate: (a) Ishihara, T.; Kuroboshi, M.; Yamaguchi, K. *Chem. Lett.* **1990**, 211-214. (b) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1191-1195. Al enolate: Ishihara, T.; Kuroboshi, M.; Yamaguchi, K.; Okada, Y. *J. Org. Chem.* **1990**, *55*, 3107-3114.

(36) Clarke number of F is 0.03 and it is higher than Cl.

(37) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127-133.

(38) (a) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002**, *416*, 279-279. (b) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561-565.

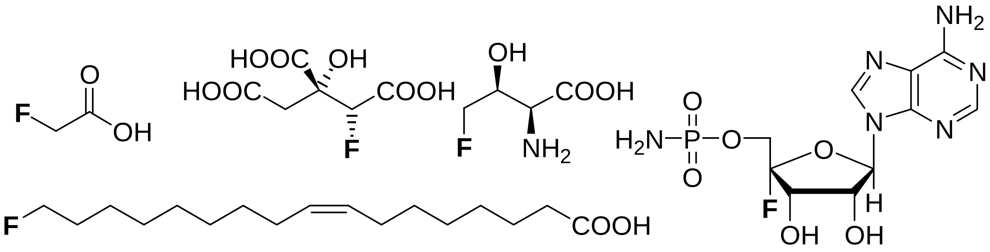


Figure 1-9. Natural organofluorine compounds.

The most abundant natural source of fluorine is ore: fluorite (CaF_2), fluoroapatite ($CaF_2{\cdot}3Ca_3(PO_4)_2$), sodium cryolite ($Na_3AlF_6$). When CaF_2 reacts with sulfuric acid, $CaSO_4$ and HF are generated. Electrolysis of anhydrous HF with small amount of KF gives F_2 gas. F_2 gas is extremely reactive and can fluorinate organic compounds. However, it is extremely dangerous due to high reactivity. This limits the use of F_2 gas in synthetic organic chemistry. F_2 gas can be transformed to fluorinating reagents which are easier to handle (Figure 1-10). F_2 gas and/or fluorinating reagent could also introduce fluorine to relatively simple organic molecules which could be used as a building block of organofluorine compounds (Figure 1-11).

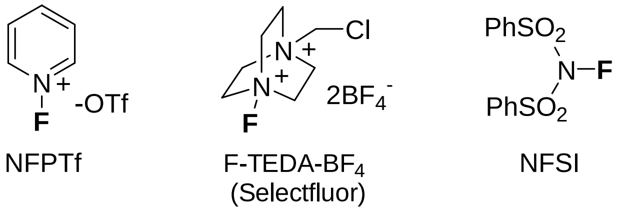


Figure 1-10. Examples of fluorinating reagent.

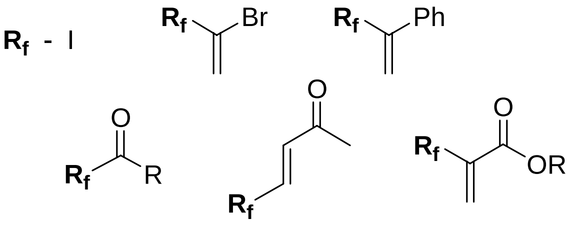


Figure 1-11. Examples of building blocks for organofluorine compounds.

Therefore, synthetic methods for fluorine-containing compounds can be broadly classified into two types: carbon-fluorine bond forming reactions (fluorination with fluorinating reagents); and carbon-carbon bond forming reactions (employing fluorine-substituted building blocks such as perfluoro-alkanes and -alkenes, or fluorine-containing carbonyl compounds). The former can be further classified into formal electrophilic (F^+) and nucleophilic (F^-) fluorination. A variety of fluorinating reagents have been developed for these types of specific reaction. The carbon-carbon bond forming reactions involve ionic (electrophilic or nucleophilic) and radical reactions.

1-4. Theoretical investigation of organic reaction mechanisms.

Recent development in computers and their network environment encourage chemists to use computers as one of the tools for chemical research. Computers could be used to predict the properties of unknown compounds and unstable species (such as transition states) which are impossible to deal experimentally. The word "computational chemistry"[39] could be classified into two categories.

(1) Molecular orbital (MO) calculation: This calculation evaluates the electronic state of a molecule according to the variation principle. This type of the calculation is used for the analysis of electronic properties or reaction pathway of an isolated molecule.
(2) Computer simulation: This calculation is aimed to reveal the molecular properties as a group, which means intermolecular interaction, liquid, solid, and super critical liquid phase properties and so on. Furthermore, this type of calculation could be classified into three kinds. Which are, molecular dynamics (MD) simulation, Monte Carlo (MC) simulation, and molecular mechanics (MM).

The author focuses on the (1) MO calculations, which are suitable for investigating specific properties of organofluorine compounds at molecular level.

1-4-1. MO method.

Electronic energy E and wavefunction Ψ of many-electron system could be obtained by solving the Schrödinger equation based on quantum mechanics.[40] Under the Born-Oppenheimer approximation, time-independent Schrödinger equation and

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(39) (a) Cramer, C. J. *Essentials of Computational Chemistry 2nd Ed.*; John Wiley & Sons: Chichester, 2004. (b) *The Fifth Series of Experimental Chemistry, Chemical Calculation*; Chemical Society of Japan Eds.; Maruzen: Japan, 2004; Vol 12.

(40) (a) Szabo, A.; Ostlund, N. S. *Modern Quantum Chemistry 1st Ed., rev.*; McGraw-Hill: New York, 1989. (b) Nagase, S.; Hirao, K. *Development of Molecular Theory*; Iwanami Shyoten: Japan, 2002.

Hamiltonian is expressed as eq. 1.1.

$$\hat{H}\Psi = E\Psi \qquad \text{(eq. 1.1)}$$

$$\hat{H} = -\frac{1}{2}\sum_{i}^{N}\nabla_i^2 + \hat{V} + \sum_{i<j}^{N}\frac{1}{|\mathbf{r}_i - \mathbf{r}_j|} = \hat{T} + \hat{V} + \hat{G} \qquad \text{(eq. 1.2)}$$

Here,

$\hat{T}$ refers to the kinetic energy of an electron,

$\hat{V}$ refers to the interaction of an electron and external potential (coulomb potential by nuclei),

$\hat{G}$ refers to the coulomb interaction between electrons.

Given a normalized trial wave function Ψ_T that satisfies the appropriate boundary conditions (usually the requirement that the wave function vanishes at infinity), then the expectation value of the Hamiltonian is an upper bound to the exact ground state energy E_0 (eq. 1.3).

$$E = \langle \Psi_T | \hat{H} | \Psi_T \rangle \geq \langle \Psi_0 | \hat{H} | \Psi_0 \rangle = E_0 \qquad \text{(eq. 1.3)}$$

The equality holds only when Ψ_T is identical to Ψ_0. This is called the *variation principle*. The variation principle for the ground state tells us that the energy of an approximate wave function is always too high. Thus one measure of the quality of a wave function is its energy; the lower the energy is, the better the wave function is. This is the basis of the variation method in which we take a normalized trial function Ψ_T, which depends on certain parameters, and vary these parameters until the expectation value E reaches a minimum. This minimum value of E is then our variational estimate of the exact ground state energy. However, except for the simplest cases, Schrödinger equation could not be solved exactly. In order to solve the Schrödinger equation for general molecule, many approximation methods have been developed and it could be classified into 4 categories.

(A) Empirical molecular orbital theory (HMO,[41] EHMO[42] etc.)
(B) Semiempirical molecular orbital theory (MNDO,[43] PM3,[44] AM1[45] etc.)

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[41] (a) Hückel, E *Z. Phys.* **1931**, *70*, 204-286. (b) Frenking, G. *Theor. Chem. Acc.* **2000**, *103*, 187-189.

[42] (a) Wolfsberg, M.; Helmholz, L. *J. Chem. Phys.* **1952**, *20*, 837-843. (b) Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397-1412.

[43] (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907-4917. (b) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899-4907.

[44] Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209-220.

[45] Dewar, M. J. S. Zoebish, E. G. Healy, E. F. Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*,

(C) *ab initio* molecular orbital theory (HF,[46] MP2[47] etc.)
(D) Density functional theory (DFT)[48]

(A) Empirical method and (B) semiempirical methods neglect several integral calculations and use empirical parameters (ionization potential, electron affinity, dipole moment etc.) to reduce the total amount of calculation. The results of calculations give qualitative description of a molecule. These methods are effective for large molecular systems, and were important during the early days of computational chemistry, when computational power was minimal. However, recent improvement of the computational power encourage us to use more precise (C) *ab initio* or (D) DFT method particularly for the investigation of the small size molecular properties which are investigated in this thesis.

1-4-1-1. Hartree-Fock (HF) method.[46]

In contrast to empirical and semiempirical methods, (C) *ab initio* method calculates every integral without using empirical parameters. The most popular *ab initio* method is the Hartree-Fock (HF) method. HF method employ independent particle model which gives the all-electron wave function as an antisymmeterized product of orthonormalized one-electron wave functions (Slater determinant, Φ_{SD}). That is,

$$\Psi(\mathbf{x}_1,\mathbf{x}_2,\cdots,\mathbf{x}_N) = \hat{A}[\phi_1(\mathbf{x}_1)\phi_2(\mathbf{x}_2)\cdots\phi_N(\mathbf{x}_N)] \qquad \text{(eq. 1.4)}$$

Here,

$$\hat{A}[\phi_1(\mathbf{x}_1)\phi_2(\mathbf{x}_2)\cdots\phi_N(\mathbf{x}_N)] = \Phi_{\mathrm{SD}} = \frac{1}{\sqrt{N!}}\begin{vmatrix} \phi_1(\mathbf{x}_1) & \phi_2(\mathbf{x}_1) & \cdots & \phi_N(\mathbf{x}_1) \\ \phi_1(\mathbf{x}_2) & \phi_2(\mathbf{x}_2) & \cdots & \phi_N(\mathbf{x}_2) \\ \vdots & \vdots & \ddots & \vdots \\ \phi_1(\mathbf{x}_N) & \phi_2(\mathbf{x}_N) & \cdots & \phi_N(\mathbf{x}_N) \end{vmatrix} \qquad \text{(eq. 1.5)}$$

The solution (wave function) of this equation satisfies the Pauli principle. Two kinds of methods are representative for HF method. That is, restricted HF (RHF), in which the spatial orbitals are restricted to be the same for α and β spins, and unrestricted HF (UHF), which allows electrons of α and β spin to be described by different special

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3902-3909.

(46) (a) Roothan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69-89. (b) Pople, J. A.; Nebset, R. K. *J. Chem. Phys.* **1954**, *22*, 571-572. (c) McWeeny, R. Dierksen, G. *J. Chem. Phys.* **1968**, *49*, 4852-4856.

(47) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618-622.

(48) (a) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974-12980. (b) Head-Gordon, M. *J. Phys. Chem.* **1996**, *100*, 13213-13225.

functions (Figure 1-12, a). Fundamental assumption of HF theory is that each electron sees all the others as an average field (Figure 1-12, b), which means neglect of electron correlation.

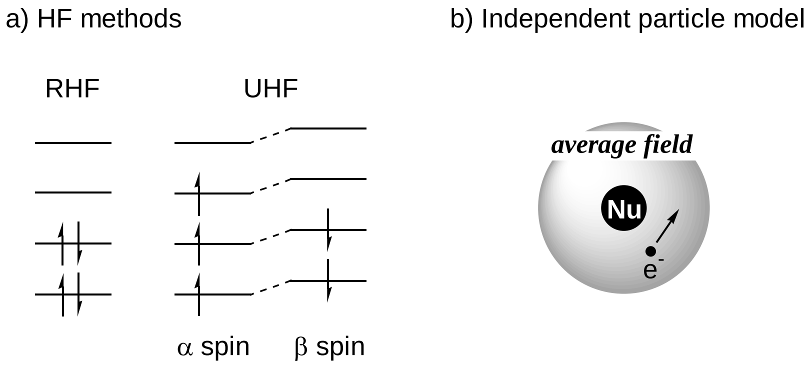

Figure 1-12. Hartree-Fock method.

With respect to RHF, HF energy (E^{HF}) could be expressed as.

$$E^{\mathrm{HF}} = \sum_{i=1}^{N/2} 2H_i + \sum_{i>j}^{N/2}(2J_{ij} - K_{ij}) + \sum_{i}^{N/2} J_{ii} \tag{eq. 1.6}$$

Here,

$$H_i = \int \varphi_i^*(\mathbf{r})\left(-\frac{1}{2}\nabla^2 - \sum_{k}^{M}\frac{Z_k}{|\mathbf{R}_k - \mathbf{r}|}\right)\varphi_i(\mathbf{r})\mathrm{d}\mathbf{r} \tag{eq. 1.7}$$

$$J_{ij} = \iint \varphi_i^*(\mathbf{r})\varphi_i(\mathbf{r})\frac{1}{|\mathbf{r}' - \mathbf{r}|}\varphi_j^*(\mathbf{r}')\varphi_j(\mathbf{r}')\mathrm{d}\mathbf{r}\mathrm{d}\mathbf{r}' \tag{eq. 1.8}$$

$$K_{ij} = \iint \varphi_i^*(\mathbf{r})\varphi_j(\mathbf{r})\frac{1}{|\mathbf{r}' - \mathbf{r}|}\varphi_j^*(\mathbf{r}')\varphi_i(\mathbf{r}')\mathrm{d}\mathbf{r}\mathrm{d}\mathbf{r}' \tag{eq. 1.9}$$

By minimizing the energy expression for a single Slater determinant, Hartree-Fock equation could be obtained (eq. 1.10).

$$\hat{f}\varphi_i = \varepsilon_i \varphi_i \tag{eq. 1.10}$$

$$\hat{f} = -\frac{1}{2}\nabla^2 - \sum_{k}^{M}\frac{Z_k}{|\mathbf{R}_k - \mathbf{r}|} + \sum_{j}(2\hat{J}_j - \hat{K}_j) \tag{eq. 1.11}$$

Here,

$\hat{J}$ refers to the coulomb operator,

$$\hat{J}_j\varphi(\mathbf{r}) = \left[\int \frac{\varphi_j^*(\mathbf{r}')\varphi_j(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|}\mathrm{d}\mathbf{r}'\right]\varphi(\mathbf{r}) \tag{eq. 1.12}$$

$\hat{K}$ refers to the exchange operator,

$$\hat{K}_j \varphi(\mathbf{r}) = \left[\int \frac{\varphi_j^*(\mathbf{r}')\varphi(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} dr' \right] \varphi_j(\mathbf{r}) \qquad \text{(eq. 1.13)}$$

Neglect of electron correlation allows for tremendous progress in carrying out practical MO calculation. However, this can also have profound chemical consequences when it comes to determining accurate wave functions and properties derived from them. If one wants to investigate the system which involves a bond formation/dissociation phenomenon, transition metal system, or a quantitative argument of chemical reaction, electron correlation must be considered. There are multiconfiguration self-consistent field theory (MCSCF),[49] perturbation theory,[47] configuration interaction (CI),[50] coupled-cluster theory (CC)[51] which could deal with electron correlation (post-HF). Among them, Møller-Plesset method,[47] particularly MP2 method, is the one of the most convenient methods to include electron correlation in MO theory.

1-4-1-2. DFT method.[48]

In contrast to the MO method, which utilizes wave function Ψ_T with 3×N (N: total electron number) dimension as a trial function, DFT utilizes electron density ρ as a trial function to obtain ground state energy based on variation principle. DFT is based on the Hohenberg-Kohn theorem[52] which proved that the energy and all properties of a molecular system is determined by a functional of electron density for a given nuclear coordinates, and only one exact electron density function, which minimizes the total energy, exists.

$$E = E[\rho(\mathbf{r})] \qquad \text{(eq. 1.14)}$$

The energy E could be expressed without approximation as eq. 1.15.

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(49) (a) Hegarty, D.; Robb, M. A. *Mol. Phys.* **1979**, *38*, 1795-1812. (b) Eade, R. H. A.; Robb, M. A. *Chem. Phys. Lett.* **1981**, *83*, 362-368. (c) Bernardi, F.; Bottoni, A.; McDouall, J. J. W.; Robb, M. A.; Schlegel, H. B. *Far. Symp. Chem. Soc.* **1984**, *19*, 137-147. (d) Frisch, M.; Ragazos, I. N.; Robb, M. A.; Schlegel, H. B. *Chem. Phys. Lett.* **1992**, *189*, 524-528. (e) Yamamoto, N.; Vreven, T.; Robb, M. A.; Frisch, M. J.; Schlegel, H. B. *Chem. Phys. Lett.* **1996**, *250*, 373-378.

(50) (a) Pople, J. A.; Seeger, R.; Krishnan, R. *Int. J. Quant. Chem. Symp.* **1977**, *11*, 149-163. (b) Krishnan, R.; Schlegel, H. B.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4654-4655. (c) Raghavachari, K.; Pople, J. A. *Int. J. Quant. Chem.* **1981**, *20*, 1067-1071.

(51) (a) Cizek, J. *J. Chem. Phys.* **1966**, *45*, 4256-4266. (b) Pople, J. A.; Krishnan, R.; Schlegel, H. B.; Binkley, J. S. *Int. J. Quant. Chem.* **1978**, *14*, 545-560. (c) Bartlett, R. J.; Purvis, G. D. *Int. J. Quant. Chem.* **1978**, *14*, 561-581.

(52) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864-871.

$$E[\rho(\mathbf{r})] = T_{\mathrm{ni}}[\rho(\mathbf{r})] + V_{\mathrm{ne}}[\rho(\mathbf{r})] + V_{\mathrm{ee}}[\rho(\mathbf{r})] + E_{\mathrm{xc}}[\rho(\mathbf{r})] \qquad \text{(eq. 1.15)}$$

Here,

T_{ni} refers to the kinetic energy of the non-interacting electrons,

$$T_{\mathrm{ni}} = -\frac{1}{2}\sum_{i}^{N}\langle\varphi_i|\nabla_i^2|\varphi_i\rangle \qquad \text{(eq. 1.16)}$$

V_{ne} refers to the nuclear-electron interaction,

$$V_{\mathrm{ne}} = \sum_{k}^{\mathrm{M}}\int\frac{Z_k}{|\mathbf{R}_k - \mathbf{r}_i|}\rho(\mathbf{r})d\mathbf{r} = \sum_{i}^{N}\langle\varphi_i|\sum_{k}^{\mathrm{M}}\frac{\mathrm{Z}_k}{|\mathbf{R}_k - \mathbf{r}_i|}|\varphi_i\rangle \qquad \text{(eq. 1.17)}$$

V_{ee} refers to the classical electron-electron repulsion.

$$V_{\mathrm{ee}} = \frac{1}{2}\iint\frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|}d\mathbf{r}_1 d\mathbf{r}_2 = \frac{1}{2}\sum_{i}^{N}\langle\varphi_i|\int\frac{\rho(r')}{|\mathbf{r}_i - \mathbf{r}'|}d\mathbf{r}'|\varphi_i\rangle \qquad \text{(eq. 1.18)}$$

Orbital φ, which minimize E in eq. 1.15, will satisfy Kohn-Sham (KS)[53] equation (eq. 1.19).

$$\hat{h}^{\mathrm{KS}}\varphi_i = \varepsilon_i\varphi_i \qquad \text{(eq. 1.19)}$$

$$\hat{h}^{\mathrm{KS}} = -\frac{1}{2}\nabla^2 - \sum_{k}^{\mathrm{M}}\frac{\mathrm{Z}_k}{|\mathbf{R}_k - \mathbf{r}|} + \int\frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}\mathrm{d}\mathbf{r}' + V_{\mathrm{XC}}(\mathbf{r}) \qquad \text{(eq. 1.20)}$$

V_{XC} is a so-called functional derivative.

$$V_{XC}(\mathbf{r}) = \frac{\delta E_{\mathrm{XC}}[\rho(\mathbf{r})]}{\delta\rho(\mathbf{r})} \qquad \text{(eq. 1.21)}$$

There has been a problem what form could be given for $E_{\mathrm{xc}}[\rho(\mathbf{r})]$ (exchange-correlation energy). E_{xc} consist of self-interaction correlation, exchange correlation, and the part of the true kinetic energy which is not covered by T_{ni}. Normally, E_{xc} is not known and should be given as an approximation. Many approximations have been developed and most of them contain empirical parameters. The development of hybrid functional made a significant contribution to DFT method which leads to great acceptance of DFT method among chemists as a practical tool. The most popular hybrid functional known as B3LYP yields good agreement with the experimental results. B3LYP (Becke's three-parameter hybrid functional[54] combined with the Lee, Yang,

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(53) Kohn, W.; Sham, L. *J. Phys. Rev.* **1965**, *140*, A1133-1138.
(54) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

Parr (LYP) correlation functional[55]) could be expressed as

$$E_{\mathrm{xc}}^{\mathrm{B3LYP}} = (1-\mathrm{a})\,E_{\mathrm{x}}^{\mathrm{LSDA}} + \mathrm{a}\,E_{\mathrm{x}}^{\mathrm{HF}} + \mathrm{b}\Delta E_{\mathrm{x}}^{\mathrm{B88}} + \mathrm{c}\,E_{\mathrm{c}}^{\mathrm{LYP}} + (1-\mathrm{c})\,E_{\mathrm{c}}^{\mathrm{VWN}} \qquad \text{(eq. 1.22)}$$

Here,

$E_{\mathrm{x}}^{\mathrm{HF}}$ refers to the HF exact exchange,

$E_{\mathrm{x}}^{\mathrm{LSDA}}$ refers to the local exchange energy from local spin density approximation (LSDA),

$\Delta E_{\mathrm{x}}^{\mathrm{B88}}$ refers to the Becke's gradient correction for the exchange functional,[56]

$E_{\mathrm{c}}^{\mathrm{LYP}}$ refers to the correlation functional developed by Lee, Yang, and Parr,[55]

$E_{\mathrm{c}}^{\mathrm{VWN}}$ refers to the local correction functional of Vosko, Wilk, and Nissair.[57]

Three parameters (a, b, and c) are determined by fitting the atomization energies, ionization potentials, proton affinities, total atomic energies of Gaussian-1 (G1) data base of Pople. The values of these parameters for B3LYP are a=0.20, b=0.72, c=0.81.

DFT method can be performed with lower computational cost than *ab initio* post-HF methods with inclusion of electron correlation effect.

1-4-1-3. Basis set.[58]

When solving the HF or KS equation, orbital function φ is expanded by atomic wave function, where the set of functions $\{\chi_p\}$ is called the 'basis set'.

$$\varphi_i = \sum_p C_{pi}\chi_p \qquad \text{(eq. 1.23)}$$

This construction is known as the linear combination of atomic orbitals (LCAO) approach. Several basis sets are commonly used.

(1) Minimal basis set (STO-3G, STO-6G etc.): There is only one basis function defined for each type of orbital core through valence.

$$\text{s-type function: } \chi_i = \sum_{r=1}^{n} d_{r,i}\exp(-\alpha_r r^2)$$

$$\text{p-type function: } \chi_i = \sum_{r=1}^{n} d_{r,i}x\exp(-\alpha_r r^2)$$

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(55) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789. (b) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200-206.

(56) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098-3100.

(57) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200-1211.

(58) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*, Wiley: New York, 1986, and references cited therein.

(2) Multiple-ζ basis set (D95, cc-pCVDZ, cc-pCVTZ etc.): To increase the flexibility of a basis set, two basis functions are used for the construction of each atomic orbital (AO). This basis set is called "double-ζ" (Figure 1-13). If three basis functions are used for each AO, it would be "triple-ζ".

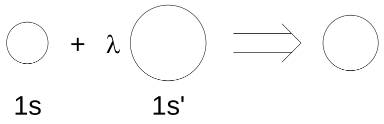

Figure 1-13. Double-ζ basis set.

(3) Split-valence basis set (3-21G, 6-31G, 6-311G etc.): The core orbitals are only weakly affected by chemical bonding. On the other hand, valence orbitals could vary widely as a function of chemical bonding. Therefore, there is more to be gained by having flexibility in the valence basis functions than in the core. In "split-valence" or "valence multiple-ζ" basis set, core orbitals continue to be represented by a single basis function, while valence orbitals are split into many functions. The nomenclature tells us the contraction scheme. The first number indicates the number of primitives used in the contracted core functions. The numbers after the hyphen indicate the numbers of primitives used in the valence functions; if there are two such numbers, it is a valence-doubleζ.

(4) Polarization functions (3-21G*, 6-31G*, 6-31G** etc.): AO is not in its shape when incorporated into a molecule. Therefore, "polarization functions", which corresponds to one quantum number of higher angular momentum than the valence orbitals, is almost always added in the form of basis functions. For s-orbital, p orbital is added, and for p orbital, d orbital is added (Figure 1-14). In the Pople family of basis set, they add '*' after the basis set name (eg. 6-31G*).

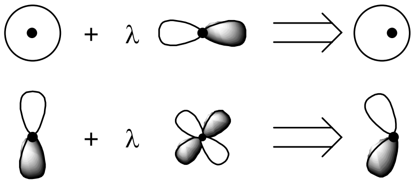

Figure 1-14. Polarization function.

(5) Diffuse functions (6-31+G, 6-311++G** etc.): The highest energy MOs of anions, highly excited electronic states, and loose supermolecular complexes tend to be much more spatially diffuse. In order to add flexibility, which could allow a weakly

bound electron to localize far from the remaining density, “diffuse functions” are often augmented. In the Pople family of basis sets, the presence of diffuse functions is indicated by a ‘+’ in the basis set name (eg. 6-31+G).

(6) Effective core potentials (LANL2DZ,[59] CEP-31G[60] etc.): When dealing with heavy atoms, the number of the electron would become a problem. Technically, calculation of a molecule with a large number of electrons becomes heavy. Also, more electrons mean more energy associated with electron correlation. In order to solve this problem, effective core potential (ECP) was developed. ECP replace the electrons with analytical functions that would reasonably, accurately, and efficiently represent the combined nuclear-electronic core to the remaining electrons. ECP could reduce the amount of the electrons to calculate, and relativistic effect could be taken into account.

1-4-2. Choice of the method and basis set.

The choice of the calculation method and basis set is not an easy issue. However, the author has set a kind of standard for investigation of the reaction mechanisms which are discussed in this thesis.

(1) Use HF for the system which is constituted of only 1st, 2nd, and 3rd row elements. If the system contains the elements of 4th row and after, use B3LYP.
(2) When calculating a radical species, use UHF (or UB3LYP).
(3) For computational power and efficiency, use 6-31G* basis set for 1st, 2nd, and 3rd row elements and ECP for the elements in 4th row and after.
(4) When calculating an anion species, add diffuse function to the basis set.

After computation by this arbitrary standard, further conformation for the level of the theory is required, and some times higher level calculation is necessary.

1-5. Objective of this thesis.

As mentioned before, CF_3 group is one of the most important fluorine functionalities because of its specific material and medicinal properties. In order to construct CF_3 containing organofluorine compounds, the author focuses on α-CF_3

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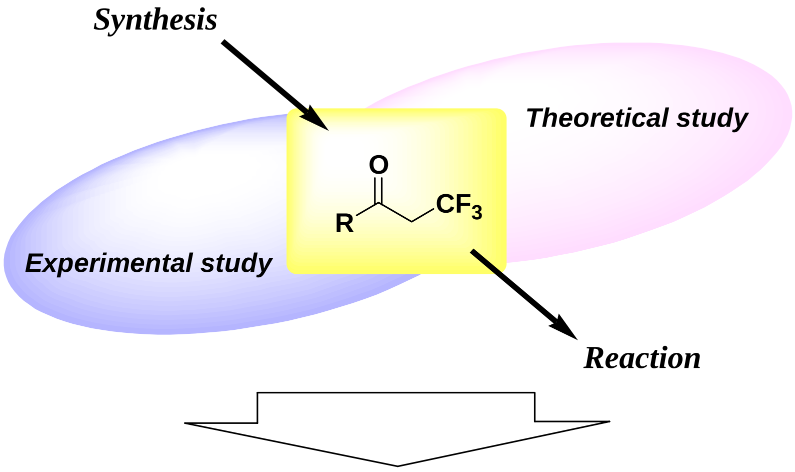
(59) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310.

(60) (a) Stevens, W. J.; Basch, H.; Krauss, M. *J. Chem. Phys.* **1984**, *81*, 6026-6033. (b) Stevens, W. J.; Krauss, M.; Basch, H.; Jasien, P. G. *Can. J. Chem.* **1992**, *70*, 612-630. (c) Cundari, T. R.; Stevens, W. J. *J. Chem. Phys.* **1993**, *98*, 5555-5565.

carbonyl compounds as a building block. Central importance of carbonyl compounds in modern synthetic organic chemistry might lead us to think about utilizing α-CF_3 carbonyl compounds as the first choice. However, α-CF_3 carbonyl compounds are sensitive to base and easily decompose to limit their usage (Scheme 1-5). The synthesis, reaction, and origin of the reactivity of α-CF_3 carbonyl compounds are not enough explored to date.

The theme of this thesis is the development of the synthetic methodologies and the selective reactions of α-CF_3 carbonyl compounds, and, understanding specific chemical properties of α-CF_3 carbonyl compounds in these reactions by computational approaches (Figure 1-15).



Development of new building block for CF_3 compounds

Figure 1-15. Basic concept of the thesis.

1-6. Back ground of the research.

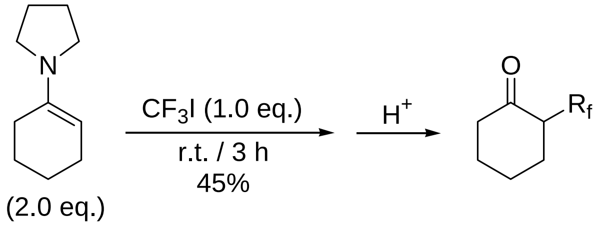
For the synthesis of α-CF_3 carbonyl compounds, the author focused on direct introduction of CF_3 to the α position of carbonyl group. It would be useful if CF_3 group could be introduced to various carbonyl compounds. As for the reactions of α-CF_3 carbonyl compounds, the author focused on aldol and Baeyer-Villiger reactions. These reactions are typical synthetic transformations.

1-6-1. Synthesis of α-CF_3 carbonyl compounds.

Radical trifluoromethylation of metal enolates is, in principle, one of the simplest and efficient ways to introduce a CF_3 unit at the α position of a carbonyl group. However defluorination (Scheme 1-5) is problematic and hence thought to be difficult to carry out. In turn, several alternative methods, which avoid using metal enolates, have been developed as follow:

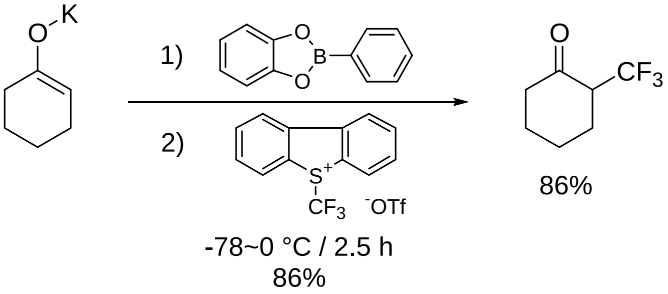
Introduction of CF_3 group to the α position of carbonyl compounds was first reported by Cantacuzène and co-workers in 1975.[61] They used the reaction of emanine with R_f-I to give α-R_f ketone in fair yields (Scheme 1-6). Later, Ishikawa and Kitazume succeeded in asymmetric perfluoroalkylation by using chiral enamine.[62] This reaction is speculated to be a radical reaction.

Scheme 1-6.



Umemoto and co-workers reported the "cationic" trifluoromethylation (Scheme 1-7).[63] This method gave α-CF_3 ketone in good yield. However, CF_3^+ reagent is too expensive for practical use[64] and is hardly soluble in organic solvents. Recently, Cahard and co-workers reported the trifluoromethylation of β-ketoesters.[65]

Scheme 1-7.



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(61) (a) Cantacuzène, D.; Dorme, R. *Tetrahedron Lett.* **1975**, *16*, 2031-2034. (b) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365-1371. (c) Rico, I.; Cantacuzène, D.; Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 3405-3408.

(62) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.

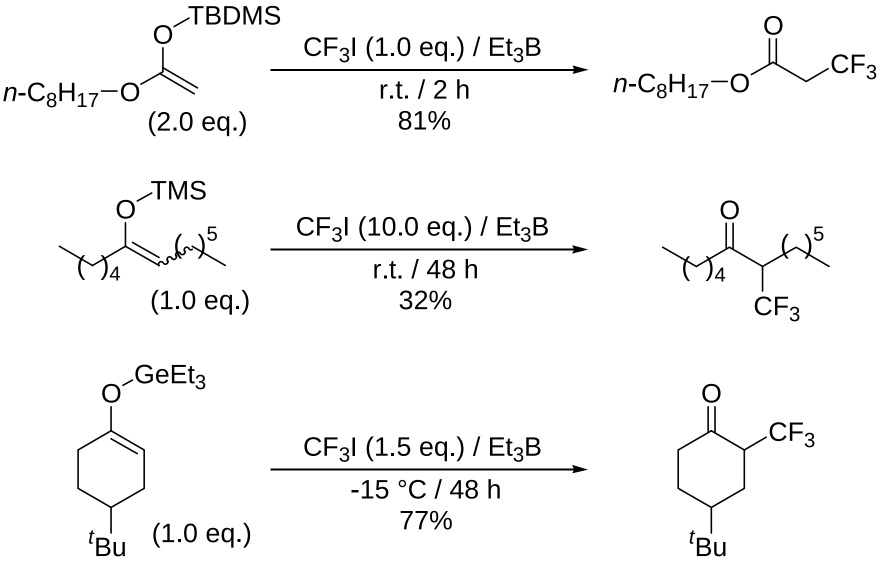
(63) (a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579-3582. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164. (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692-5699.

(64) ¥5713.-/1 mmol. (cf. CF_3I: ¥286.-/1 mmol). Aldrich catalog 2005-2006 Japan.

(65) Ma, J.-A.: Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726-8729.

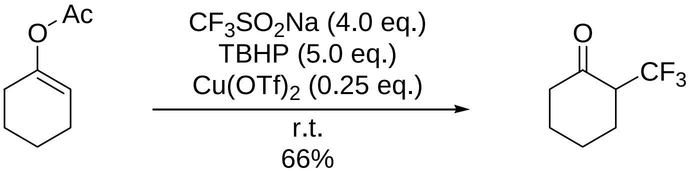
Oshima, Utimoto and co-workers reported the radical trifluoromethylation of silyl and germyl enol ethers (Scheme 1-8).[66] They used Et_3B as a radical initiator. The radical trifluoromethylation of silyl enol ethers works only for ester enol ethers, and gave poor results for ketone enol ethers. On the other hand, germyl enol ethers of ketone worked well for trifluoromethylation.

Scheme 1-8.



Langlois and co-workers reported the use of sodium trifluoromethanesulfinate as a CF_3 source (Scheme 1-9).[67] They proposed a radical mechanism for this reaction.

Scheme 1-9.



Iseki, Kobayashi and co-workers reported the radical trifluoromethylation of imide enolates (Scheme 1-10).[68] They used Li enolates of imides. It is recognized that highly

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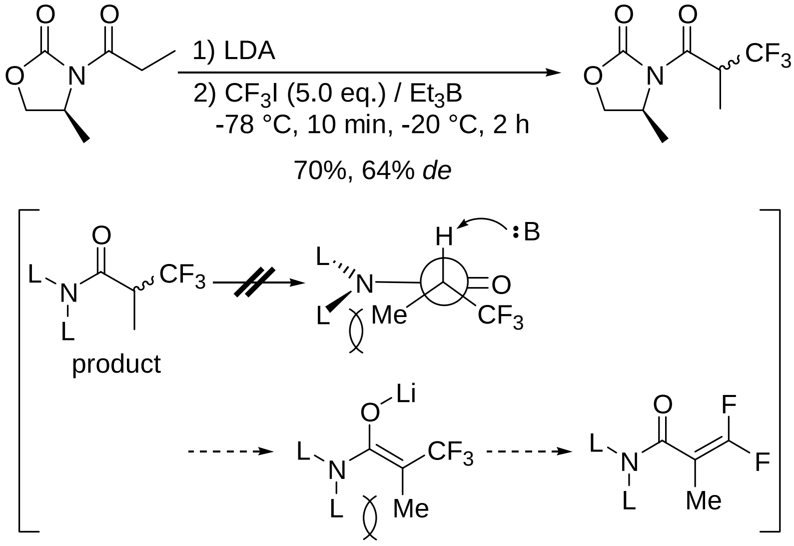
(66) (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391-6394. (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553.

(67) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291-1294.

(68) (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169-2170. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961-974. (c) Iseki, K.; Takahashi, M.; Asada, D.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem.* **1995**, *74*, 269-271.

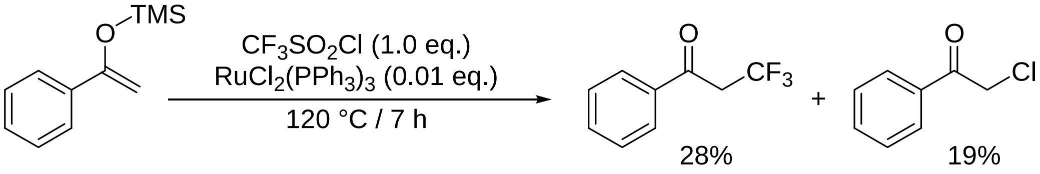
basic Li enolates could decompose the α-CF_3 product and thus could not be employed to trifluoromethylation. However, they introduced bulky substituents on α position to carbonyl group and oxazolidinone moiety to suppress defluorination by the parent Li enolate.

Scheme 1-10.



The first report of trifluoromethylation of silyl enol ether catalyzed by transition metal was reported by Kamigata and co-workers using Ru(II) complex (Scheme 1-11).[69] However, the yields were poor to fair. Trifluoromethylation and chlorination occurred depending on the substituent of the silyl enol ether.

Scheme 1-11.



Ando, Kumadaki and co-workers reported the rhodium catalyzed α trifluoromethylation of α,β-unsaturated ketones (Scheme 1-12).[70] This methodology is different from the previous trifluoromethylation of enolates or enolate equivalents. It gives fair to good yields of α-CF_3 ketones.

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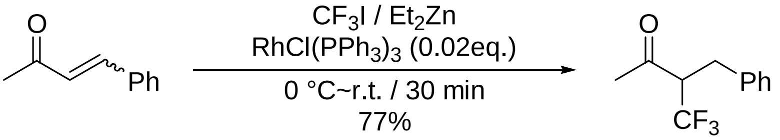
(69) Kamigata, N.; Udodaira, K.; Shimizu, T. *Phosphorus, Sulfur, and Silicon* **1997**, *129*, 155-168.
(70) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Lett.* **2004**, *6*, 4359-4361.

Scheme 1-12.

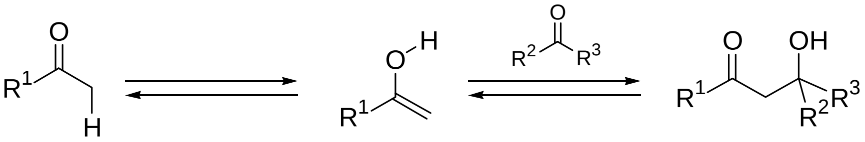


As can be seen, the practical way of introducing CF_3 group into α position of carbonyl compounds is quite limited. Among them, radical trifluoromethylation of metal enolate should be, in principle, the most direct and efficient way to synthesize α-CF_3 carbonyl compounds. However, the example is only limited for Li enolates of sterically demanding imides; the substrate was designed not to decompose. There is no example of radical trifluoromethylation of ketone enolates. Therefore, the author focused on experimental and theoretical investigation of the radical trifluoromethylation of ketone enolates.

1-6-2. Aldol reaction of α-CF_3 carbonyl compounds.

Aldol reaction is one of the most basic reactions in organic chemistry. "Aldol" was named after the self condensation product of acetaldehyde in 1872 by Wurtz.[71] A classical aldol reaction utilizes Brønsted acid or base to carbonyl compounds bearing α proton to generate enol. The reaction of enol with carbonyl compounds gives β-hydroxy ketone (Scheme 1-13).

Scheme 1-13.



This type of the reaction is in equilibrium with the substrate. Therefore, reactivity depends on the stability of the product. Moreover, by using Brønsted acid or base, it is

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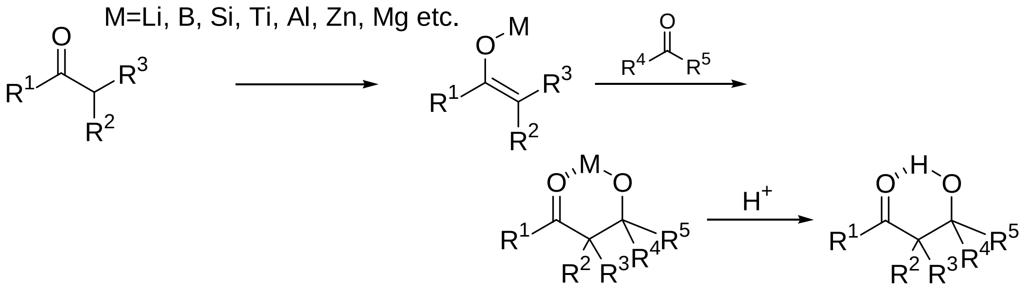
[71] Review: (a) Mukaiyama, T.; *Org. React.* **1982**, *28*, 203-331. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In Topics in Stereochemistry; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1982; Vol. 13, p 1-115. (c) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; B. M. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol 2, p 99-132. (d) Heathcock, C. H. In *Comprehensive Organic Synthesis*; B. M. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol 2, p 133-180 & 181-238. (e) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; B. M. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol 2, p 239-276. (f) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; B. M. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol 2, p 277-300. (g) Paterson, I. In *Comprehensive Organic Synthesis*; B. M. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol 2, p 301-320.

difficult to suppress the self condensation or polymerization especially for cross aldol reaction. To conquer the difficulty, it is more common to use metal enolate or enol ether instead of enol for the efficient aldol reaction (Scheme 1-14).

Scheme 1-14.



When employing a metal enolate as an intermediate, the choice of the metal and the method of the enolate generation would be an important factor. The regioselectivity of the enolate, *E-Z* stereoselectivity, and the metal employed could change the reactivity of the enolate dramatically.

In the case of α-CF_3 carbonyl compounds, the preparation of the enolate is a serious problem. The generation of enolates normally requires a base for abstracting α proton. However, as mentioned before (Scheme 1-5), α-CF_3 carbonyl compounds are sensitive to base and readily decompose. There are several reports which dealt with the aldol reaction of α-CF_3 carbonyl compounds and all of them invented the way of the generation of the enolate to make the aldol reaction to work.

The first report of the aldol reaction of α-CF_3 carbonyl compounds was done by Yokozawa, Nakai, and Ishikawa (Scheme 1-15).[72] They prepared ketene silyl acetal of α-CF_3 ester but not metal enolate. However, its isolation was difficult and they directly used for the aldol reaction. The aldol reaction with dimethyl acetal of ketones and aldehydes catalyzed by TMSOTf proceeded well to give the aldol product in high yields, but in low selectivity.[73] The ketene silyl acetal did not react with aldehydes (except for benzaldehyde). When $TiCl_4$ was used as a catalyst, defluorination took place.

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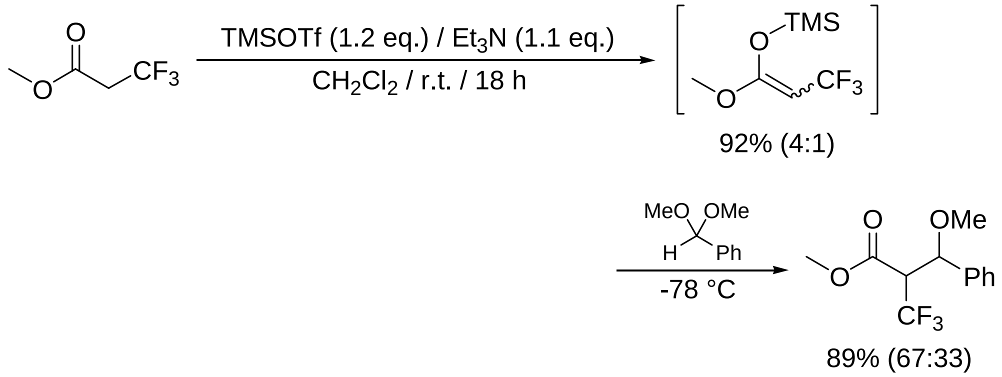
(72) (a) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987-3990. (b) Yokozawa, T.; Yamaguchi, M.; Nakai, T.; Ishikawa, N. *J. Chem. Soc. Jpn. (Nippon kagakukai shi)* **1985**, 2202-2204.

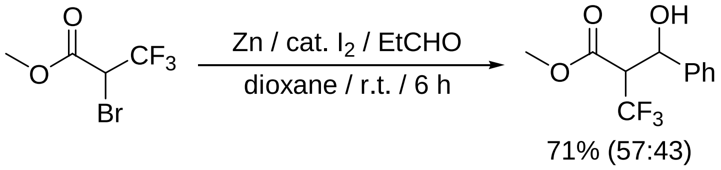
(73) Later, Kitazume and co-workers reported the aldol reaction of α-CF_3 ketone using the same method. Tominaga, T.; Nishi, K.; Kitazume, T. *J. Fluorine Chem.* **2004**, *125*, 67-71.

Scheme 1-15.



Reformatsky reaction of α-CF_3 ester was reported by the same workers (Scheme 1-16).[74] A Zn enolate intermediate could react with aldehydes, which ketene silyl acetal could not undergo a reaction. However, ketene silyl acetals could not react with ketones and defluorination occured. By this method, they could avoid using base.

Scheme 1-16.



Ishihara and co-workers reported the generation of B and Al enolates of α-CF_3 carbonyl compound and successive aldol reaction.[35] In fact this is the only report of metal enolates of an α-CF_3 carbonyl compound. The concept is to avoid generation of anion at α position adjacent to CF_3 group in order to suppress defluorination. For B enolates, they add Bu_2BOTf to α-CF_3 amide to form a complex and then add $EtN^{i}Pr_2$ (Scheme 1-17). By this method, they reported that the generation of anion at α position could be avoided. Successive aldol reaction gave good yield and diastereoselectivity.

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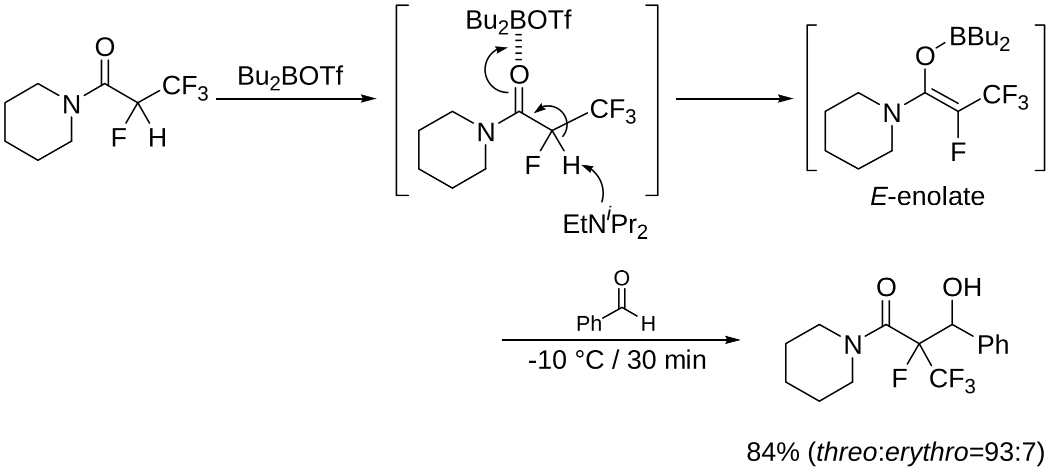
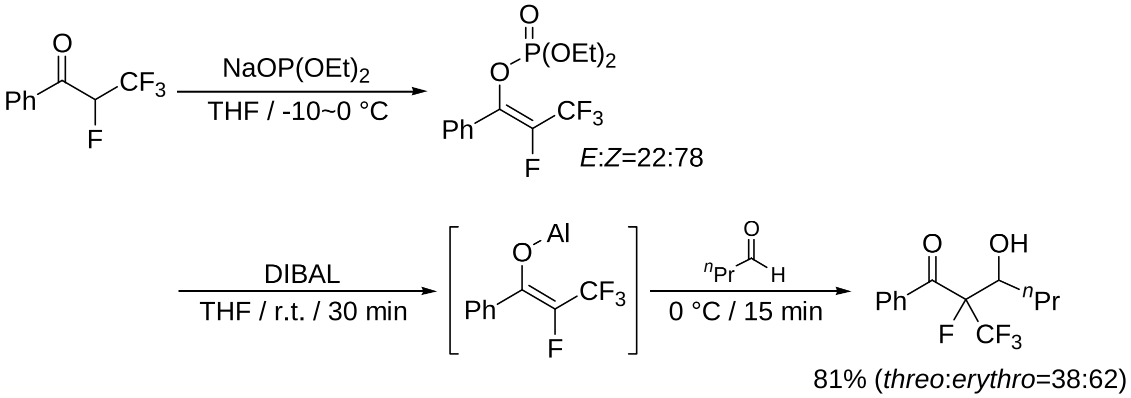
(74) Yokozawa, T.; Ishikawa, N.; Nakai, T. *Chem. Lett.* **1987**, 1971-1974.

Scheme 1-17.



They also reported Al enolate of α-CF_3 ketone and its aldol reaction (Scheme 1-18). Generation of the Al enolate was achieved by DIBAL reduction of alkenyl phosphate.

Scheme 1-18.



Nakai and co-workers reported an “electrophile-coexisting” procedure for the aldol reaction of Li enolate of α-CF_3 ester (Scheme 1-19).[75] When the enolate was separately prepared by LDA before the addition of aldehyde, the aldol product was obtained only in 36% with a complex mixture of other by-products. However, when LDA was added to the α-CF_3 ester in the presence of aldehyde, the aldol product was obtained in 80% yield.

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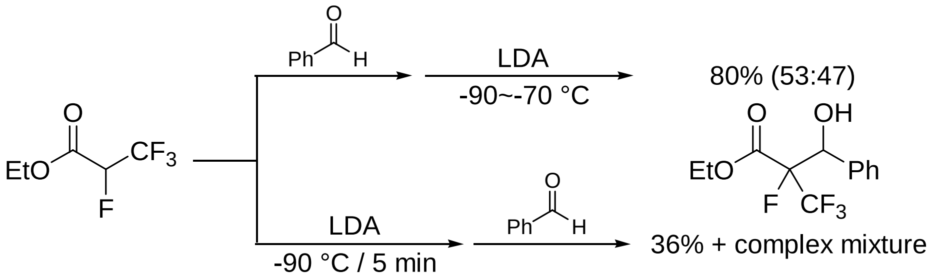
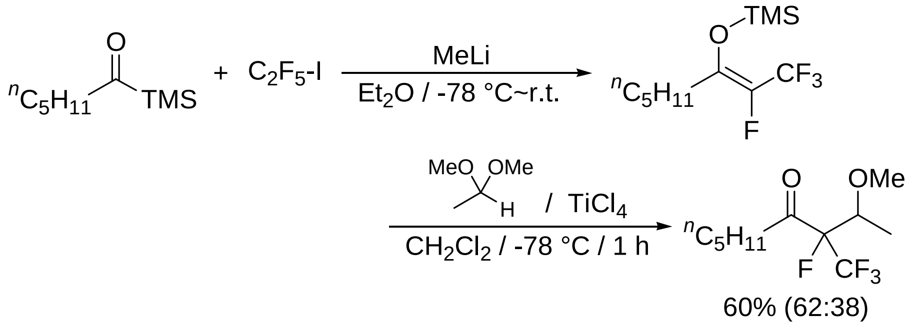
(75) (a) Qian, C.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4602-4604. (b) Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 7043-7046.

Scheme 1-19.



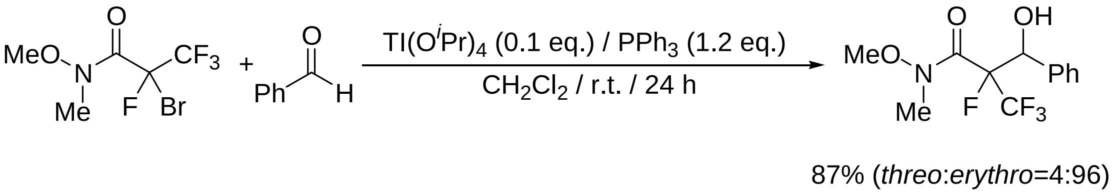
Portella and co-workers reported the synthesis of silyl enol ether of α-CF_3 ketone by the reaction of perfluoroalkyl iodide and acylsilane (Scheme 1-20).[76] This silyl enol ether reacted only with ketal and not with aldehyde. They used $TiCl_4$ as a Lewis acid for the aldol reaction. This is in contrast with the aldol reaction of the ketene silyl acetal (Scheme 1-15),[72] in which defluorination occurred upon addition of $TiCl_4$.

Scheme 1-20.



Quite recently, Ishihara, Yamanaka and co-workers reported the aldol-type reaction of α-CF_3 amide (Scheme 1-21).[77] Combination of PPh_3-$Ti(O^iPr)_4$ system on α-Br amide generate Ti enolate of α-CF_3 amide.

Scheme 1-21.



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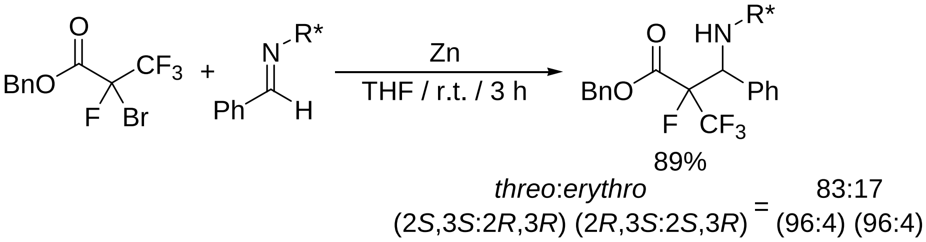
[76] Doussot, P.; Portella, C. *J. Org. Chem.* **1993**, *58*, 6675-6680.

[77] (a) Sato, K.; Sekiguchi, T.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2004**, *33*, 154-155. (b) Sato, K.; Sekiguchi, T.; Ishihara, T.; Konno, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 5041-5047.

They also reported the Reformatsky-type reaction of α-CF_3 ester with imine (Scheme 1-22).[78]

Scheme 1-22.



Enolate generation is the key for success in aldol reaction of α-CF_3 ketone. Most of the examples listed above overcame this difficulty by modifying the enolate generation procedure. Moreover, all of the previous report of the generation and aldol reaction of α-CF_3 carbonyl compounds utilize α,α-CF_3,F substrate and there is no report which makes use of ketone. Enolate generation of an α-CF_3 carbonyl compound, especially ketone, is therefore a challenging problem. Moreover, none of the previous works gave satisfactory result for both yield and diastereoselecivity. Therefore, the author investigated the enolate generation and aldol reaction of α-CF_3 ketone as one of the functionalization reaction of α-CF_3 ketone which the author would also investigate its synthetic methods.

1-6-3. Baeyer-Villiger reaction.

Baeyer-Villiger (B-V) reaction (Scheme 1-23) is a reaction which could transform ketone into ester or lactone by peroxide.[79] Since its discovery in 1899 by Adolf von Baeyer and Victor Villiger,[80] The B-V reaction has become one of the most important synthetic methodologies. A two-step mechanism has been well accepted; (1) carbonyl addition of a peroxy acid to form a peroxy acid/carbonyl adduct, the Criegee intermediate,[81] and then (2) skeletal rearrangement of the Criegee intermediate. Many

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(78) Sekiguchi, T.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2004**, *33*, 666-667.

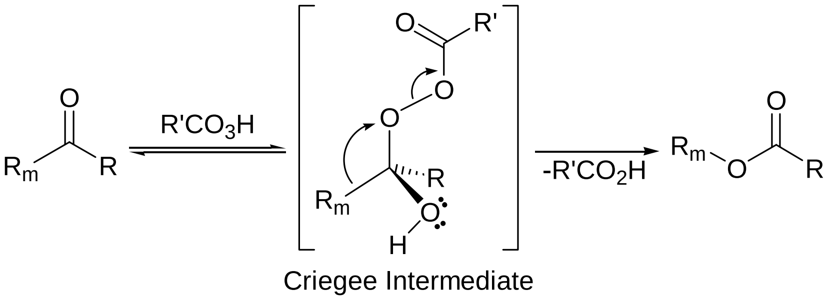
(79) Reviews: (a) Krow. G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, 671. (b) Krow, G. R. *Org. React.* **1993**, *43*, 251-798. (c) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1198-1209. (d) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737-750. (e) Brink, G.-J. ten; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105-4123.

(80) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625-3633.

(81) Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127-135.

kinetic studies[82] had been carried out to reveal that rearrangement of the Criegee intermediate is a concerted process and, with some exceptions,[82f,i] it is a rate-determining step

Scheme 1-23.



Many outstanding aspects support its success in synthetic applications.

1. A variety of carbonyl compounds can be oxidized; ketones to esters, cyclic ketones to lactones, benzaldehydes to phenols, or carboxylic acids, and α-diketones into anhydrides.
2. Migrating group retains its configuration.
3. A variety of oxidants could be used by its reactivity. The order of the reactivity of the oxidant: trifluoroperacetic acid (TFPA) > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitro perbenzoic acid > *m*-chloroperbenzoic acid (*m*CPBA) ~ performic acid > perbenzoic acid > peracetic acid >> hydrogen peroxide > *tert*-butyl hydroperoxide (TBHP).
4. The regioselectivity is highly predictable for hydrocarbon functionalities. The order of the migratory aptitude: *tert*-alkyl > cyclohexyl > *sec*-alkyl > benzyl > phenyl > *n*-alkyl > Me.

Concerning the regioselectivity of the B-V reaction, the ketonic substituent, that can best stabilize a partial positive charge, usually migrates referentially.[83] Stereoelectronic

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(82) (a) Hawthorne, M. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 6398-6404. (b) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1969**, *34*, 3985-3991. (c) Palmer, B. W.; Fry, A. *J. Am. Chem. Soc.* **1970**, *92*, 2580-2581. (d) Mitsuhashi, T.; Miyadera, H.; Simamura, O. *J. Chem. Soc., Chem. Commun.* **1970**, 1301-1302. (e) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1972**, *94*, 4189-4196. (f) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, *37*, 2953-2957. (g) Winnik, M. A.; Stoute, V. *Can. J. Chem.* **1973**, *51*, 2788-2793. (h) Winnik, M. A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* **1974**, *96*, 1977-1979. (i) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455-9456.

(83) Doering, W. von E.; Speers, L. *J. Am. Chem. Soc.* **1950**, *72*, 5515-5518.

components of this reaction have been discussed for two factors (Figure 1-16).

a) Primary stereoelectronic effect: Correct *anti*-periplaner alignment of the migrating substituent (R_m) and O-O bond of the leaving group.
b) Secondary stereoelectronic effect: Correct *anti*-periplanar alignment of the migrating substituent (R_m) and one of the lone electron pair of acetal oxygen.

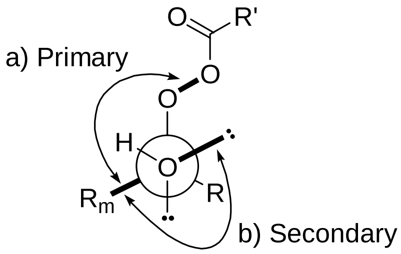
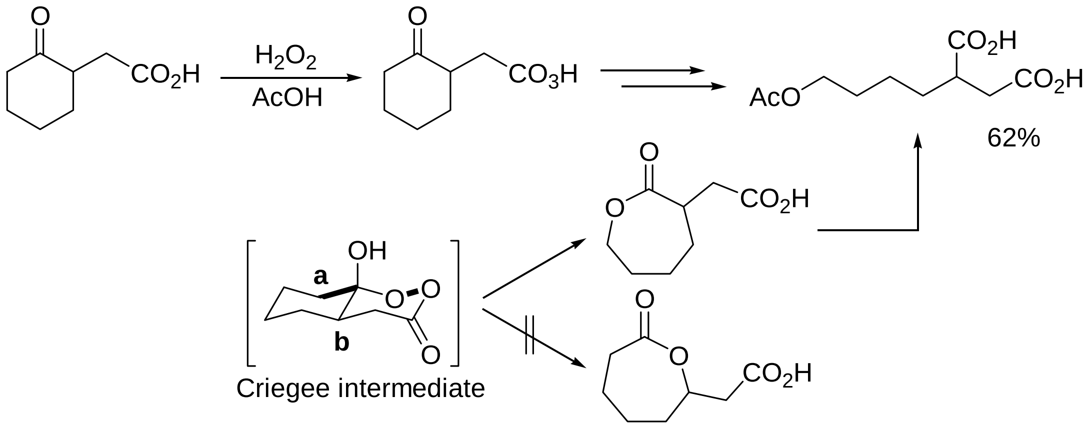


Figure 1-16. Stereoelectronic effect of B-V reaction.

Primary stereoelectronic effect is based on the interaction between migrating C-C σ orbital and leaving O-O σ* orbital. There are two experimental evidences for primary stereoelectronic effect.

Chandraskhar used a substrate which bears carboxylic acid moiety (Scheme 1-24).[84] Hydrogen peroxide could form intramolecular peracid to fix the Criegee intermediate. Between two carbons **a** and **b**, only the migration of the carbon **a** is observed which is in correct *anti*-periplanar alignment.

Scheme 1-24.



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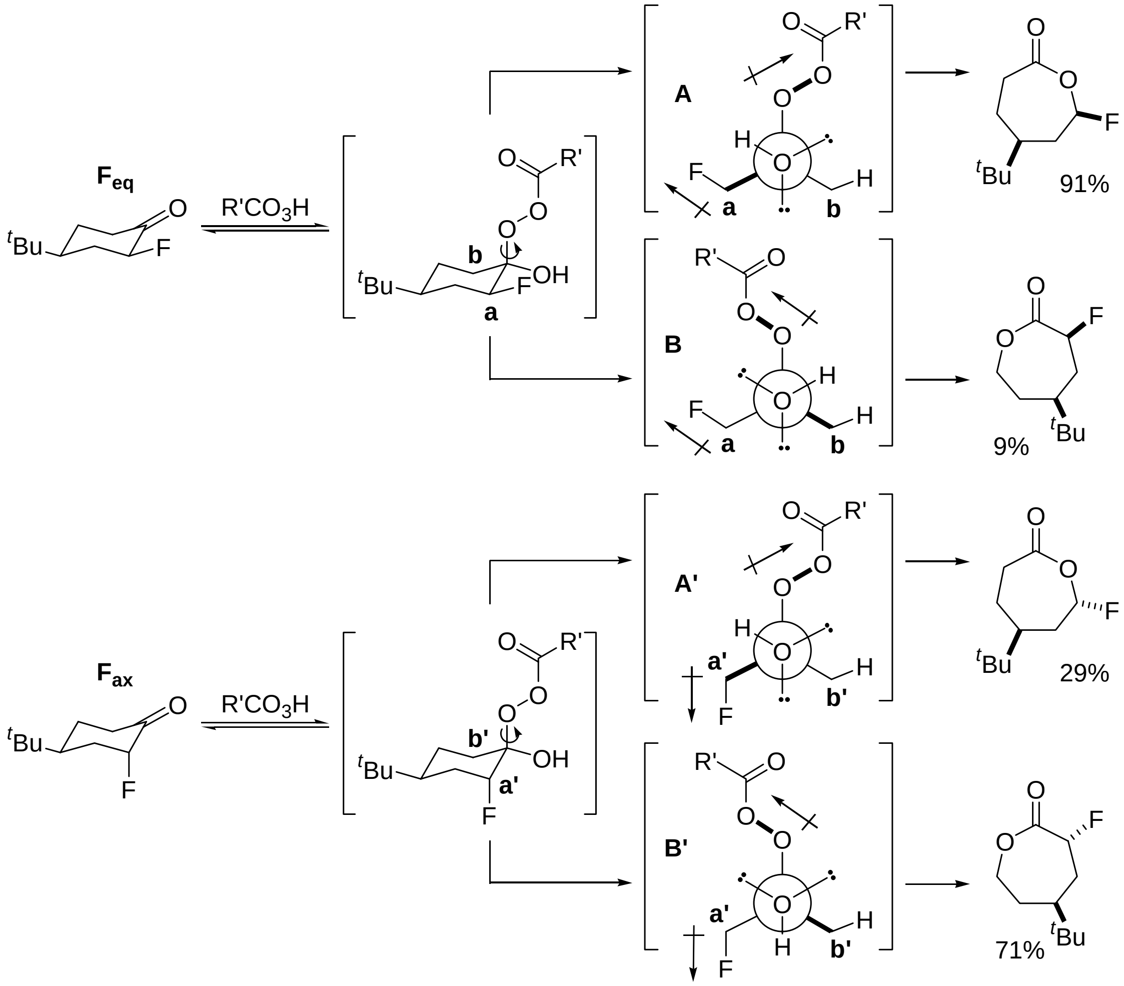
(84) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371-6372.

Crudden used α-F cyclohexanone derivatives to prove the primary stereoelectronic effect (Scheme 1-25).[85] ^{t}Bu substituent could fix the conformation of F group to equatorial position. The B-V reaction was carried out using α-F$_{eq}$ cyclohexanone by *m*CPBA. The carbon with fluorine substituent migrated preferentially which one might think strange because of its electron withdrawing nature to destabilize partial positive charge. This could be ascribed to the primary stereoelectronic effect. Between two intermediates **A** and **B**, **B** is destabilized relative to **A** in terms of dipole repulsion to bring about the migration of carbon **a** bearing fluorine substituent. In fact, the reaction of α-F$_{ax}$ cyclohexanone, which the difference of the dipole interaction between two isomeric Criegee intermediates is not apparent, showed the preferential migration of the non-substituted carbon.

Scheme 1-25.



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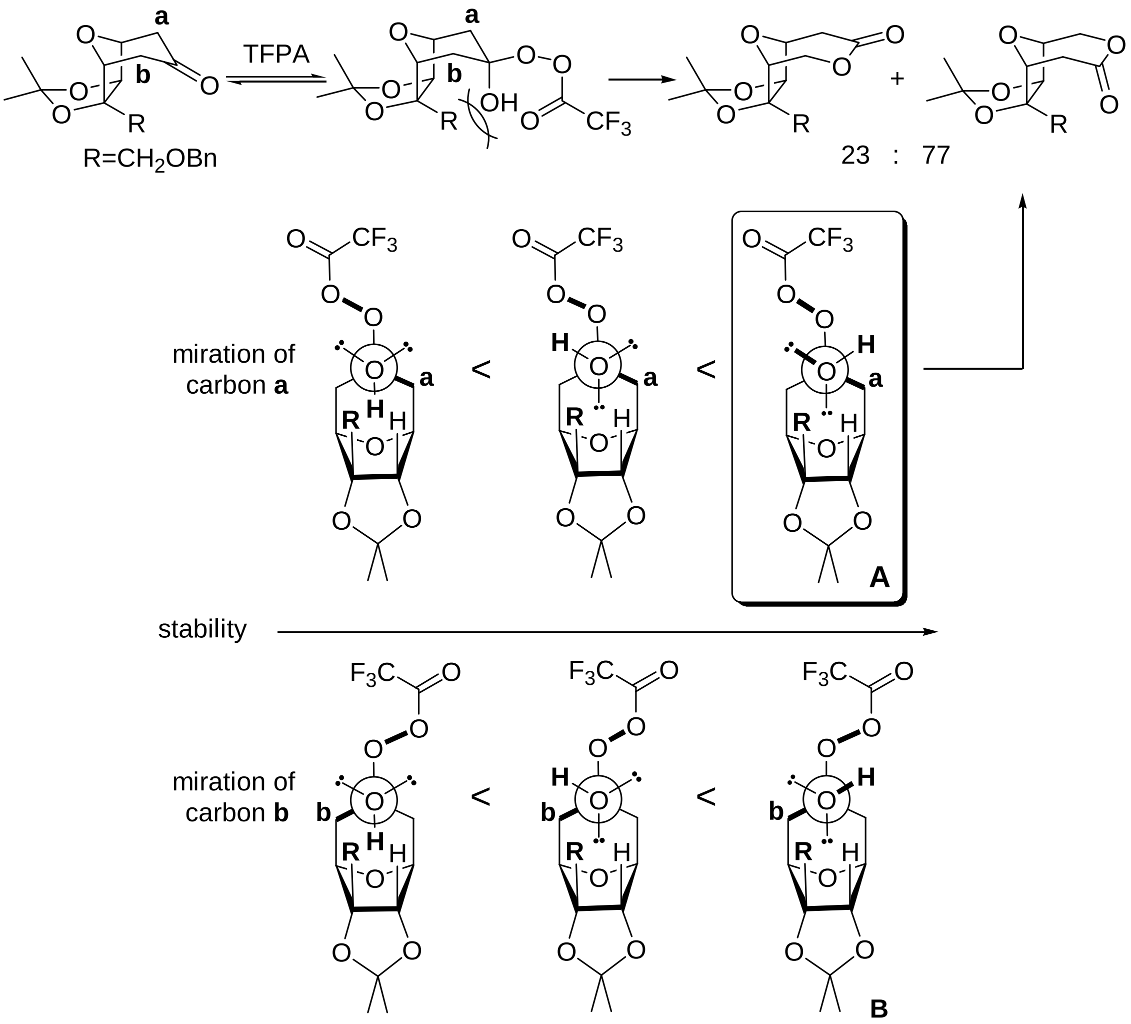
(85) Crudden C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2852-2855.

Secondary stereoelectronic effect is based on a donation of lone electron pair on acetal oxygen to the migrating C-C bond. There is only one experimental support for secondary stereoelectronic effect.

Noyori and co-workers reported the B-V reaction of a rigid bicyclic substrate (Scheme 1-26).[86] In this system, there are 6 possible conformations for the Criegee intermediate based on the migrating carbon (2 kinds) and the orientation of the acetal hydroxyl group (3 kinds). Steric repulsion makes the conformation **A** and **B** more stable for the migration of carbon **a** and **b** respectively. Experimantal results show the preferential migration of carbon **a** to support the correct *anti*-periplanar alignment of the lone electron pair of the acetal oxygen and the migrating C-C bond.

Scheme 1-26.



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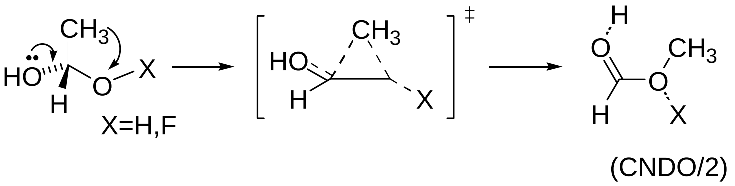
(86) (a) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569-2572. (b) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573-2576.

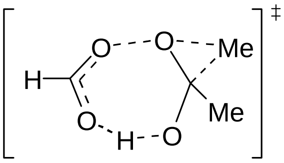
Mechanistic studied has been carried out not only experimentally, but also computationally. The first computational study of B-V reaction was reported by Winnik and co-workers (Scheme 1-27).[87] They used semiempirical method to conclude that the rearrangement occurs concertedly not ionically.

Scheme 1-27.



Cárdenas, Reyes and co-workers reported *ab initio* and semiempirical calculation of B-V reaction of acetone by performic acid using several methods and basis sets (Scheme 1-28).[88] They observed that irrespective of the methods of calculations, the topology of the TSs and the general orientation of the transition vectors are invariant. Later, they reported a semiempirical study on the transition structure of the reaction of acetone with alkyl and aryl peracids.[89]

Scheme 1-28.



Okuno reported the *ab initio* calculations on the effect of carboxylic acid (Scheme 1-29).[90] He found that acid catalysis changes the rate-determining step to the rearrangement step from the carbonyl addition step.

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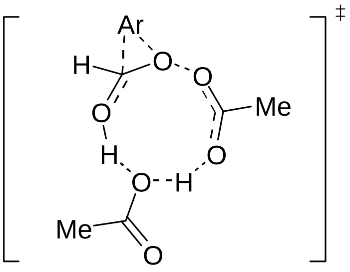
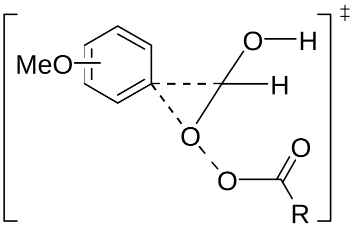
[87] Stoute, V. A.; Winnik, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1974**, *96*, 6388-6393.
[88] Cárdenas, R.; Cetina, R.; Lagúnez-Otero, J.; Reyes, L. *J. Phys. Chem.* **1997**, *101*, 192-200.
[89] Cádenas, R.; Reyes, L.; Lagúnez-Otero, J.; Cetina, R. *J. Mol. Struct.* **2000**, *497*, 211-225.
[90] Okuno, Y. *Chem. Eur. J.* **1997**, *3*, 212-218.

Scheme 1-29.



Chermette and co-workers reported the semiempirical study of the B-V reaction of polymethoxybenzaldehydes with peroxysuccinic acid (Scheme 1-30).[91] They investigated the stereoelectronic effect of methoxy group on the benzene ring.

Scheme 1-30.



Brinck and co-workers reported the *ab initio* and DFT study of BF_3 assisted B-V reaction (Scheme 1-31).[92] They found that the main function of BF_3 in both the addition and the rearrangement steps is to facilitate proton transfer (Scheme 1-31). Later, they reported *ab initio* and DFT studies of the B-V reaction of aetone with hydrogen peroxide catalyzed by Ser105-A1a.[93]

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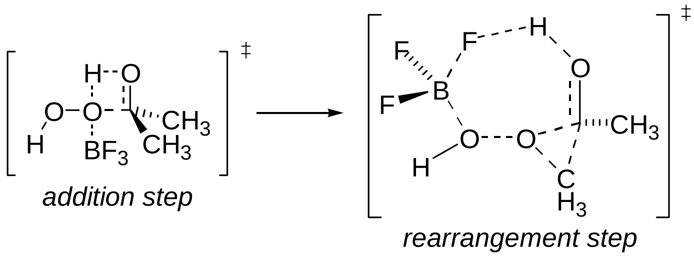
(91) Hannachi, H.; Anoune, N.; Arnaud, C.; Lantéri, P.; Longeray, R.; Chermette, H. *J. Mol. Struct.* **1998**, *434*, 183-191.

(92) Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* **2001**, *66*, 1193-1199.

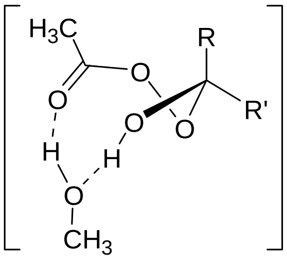
(93) Carlqvist, P.; Eklund, R.; Hult, K.; Brinck, T. *J. Mol. Model* **2003**, *9*, 164-171.

Scheme 1-31.



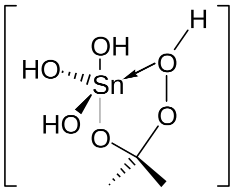
Lehtinen and co-workers reported the DFT study of the effect of alcohol at the rearrangement step of the B-V reaction of aldehydes with dioxygen and *m*CPBA (Scheme 1-32).[94] They investigated the stabilization effect of TS by methanol.

Scheme 1-32.



Root and co-workers reported the DFT study of tin-catalyzed B-V reaction by hydrogen peroxide (Scheme 1-33).[95] They investigated for several mechanisms for the reaction and found that the reaction is most likely to proceeds through a Criegee intermediate that contains a five-membered chelate ring structure with the tin center.

Scheme 1-33.



Reyes and co-workers reported the computational study of the B-V reaction of substituted acetophenones with *m*CPBA (Scheme 1-34).[96] They investigated the

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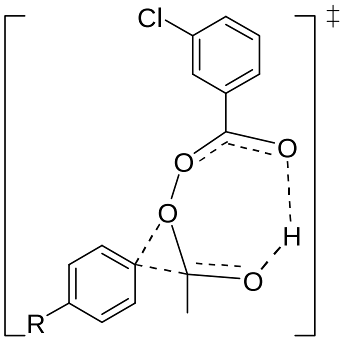
(94) Lehtinen, C.; Nevalainen, V.; Brunow, G. *Tetrahedron* **2001**, *57*, 4741-4751.
(95) Sever, R. R.; Root, T. W. *J. Phys. Chem. B* **2003**, *107*, 10848-10862.
(96) Reyes, L.; Castro, M.; Cruz, J.; Rubio, M. *J. Phys. Chem. A* **2005**, *109*, 3383-3390.

substituent effect on the benzene ring and found that the rate-determining step can change with variations in the substituent group.

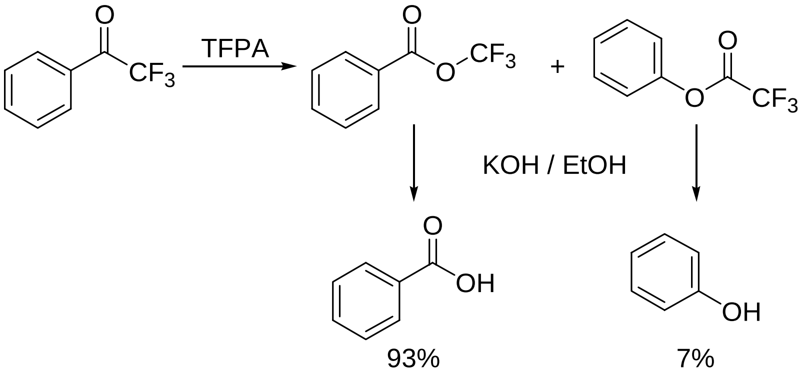
Scheme 1-34.



In view of the author’s research interest on organofluorine compounds, intriguing stereoelectronic effects were reported for ketone which is functionalized with fluorine substituents.

Smissman, Li, and Israili reported the B-V reaction of 1,1,1-trifluoroacetophenone (Scheme 1-35).[97] After base catalyzed hydrolysis, benzoic acid and phenol was detected in 72% combined yield and in 93:3 ratio. This indicates the preferential migration of CF_3 group; however, they mentioned about the possibility that the formation of the benzoic acid might be the result of haloform type reaction of unchanged starting material could not be ignored.

Scheme 1-35.



In sharp contrast to the above result, Kitazume and co-worker reported the preferential migration of Ph group at the B-V reaction of 1,1,1-trifluoroacetophenone

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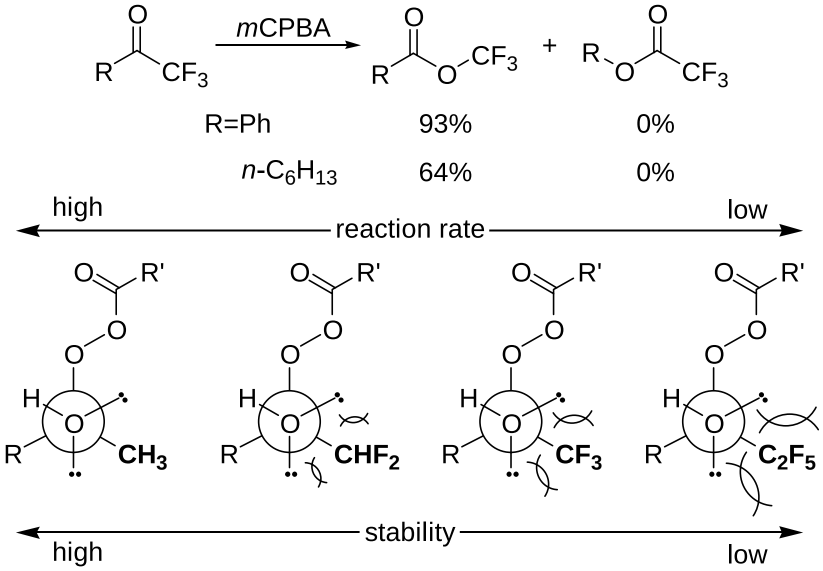
(97) Smissman, E. E.; Li, J. P.; Israili, Z. H. *J. Org. Chem.* **1968**, *33*, 4231-4236.

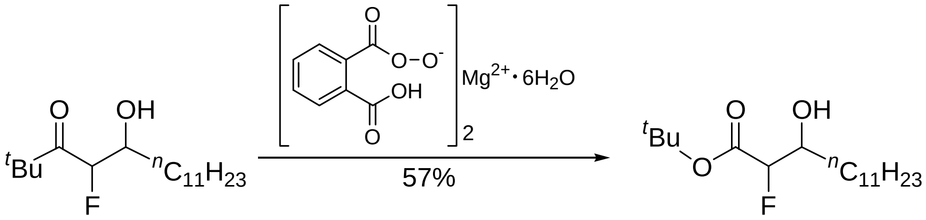
with *m*CPBA (Scheme 1-36).[98] They investigated several α fluorinated ketones and found that the migratory aptitude of the group is phenyl>alkyl>methyl>CHF_2 >CF_3>>C_2F_5. This order was attributed to the stability of the Criegee intermediate based on the electronic repulsion between the lone electron pair of the oxygen and the fluoroalkyl group.

Scheme 1-36.



Shiozaki and co-worker reported the B-V reaction of fluorinated ketone to obtain α-monofluoroester (Scheme 1-37).[99] *m*CPBA or TFPA gave the product in poor yield. The use of 5 eq. of magnesium monoperphthalate provide the product in increased yield, though in 57% yield.

Scheme 1-37.



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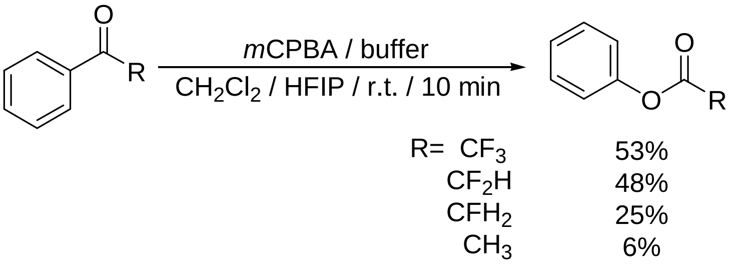
(98) Kitazume, T.; Kataoka, J. *J. Fluorine Chem.* **1996**, *80*, 157-158.
(99) Shiozaki, M.; Arai, M. *J. Org. Chem.* **1989**, *54*, 3754-3755.

Uneyama and co-workers reported the B-V reaction of several α-fluorinated ketones (Scheme 1-38).[100] They found the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and the aqueous buffer were effective for the B-V reaction. IR absorption of the carbonyl group in the substrate revealed that the fluoromethyl groups activate carbonyl group electronically, and make the nucleophilic addition of peracid to the carbonyl carbon easier.

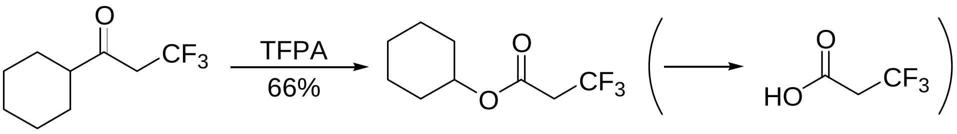
Scheme 1-38.



As cited before,[85] Crudden and co-workers reported the interesting stereoelectronics of the B-V reaction of the α-F cyclohexanone (Scheme 1-25).

On account of the author's research project on α-CF_3 carbonyl compounds, stereoelectronic effects of the B-V reaction of α-CF_3 ketone are quite interesting. However, there is only one example of the B-V reaction of α-CF_3 ketone which is in one step of the synthesis of 3,3,3-trifluoropropionic acid (Scheme 1-39).[101] They observed the exclusive migration of the carbon without CF_3 substituent. No experimental or theoretical investigation of the mechanism of this reaction was conducted.

Scheme 1-39.



Therefore, the author investigated the B-V reaction of the α-CF_3 ketones. Although several computational studies were reported, to the best of the author's knowledge, no one has done computationally on the origin of the regioselectivity of the B-V

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(100) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547-1552.
(101) Wakselman, C.; Tordeux, M. *J. Fluorine Chem.* **1982**, *21*, 99-106.

reaction.[102] Therefore, computational study of the specific stereoelectronic effect for the regioselectivity of the B-V reaction was carried out not only for the α-CF_3 ketone but also for α-Me and F substrates in order to clarify the regioselectivity of the B-V reaction in general.

1-7. Constitution of the thesis.

The goal of this research is the development of synthetic methods for the construction of CF_3-containing compounds using α-CF_3 carbonyl compounds and the theoretical investigation of specific properties (Figure 1-17).

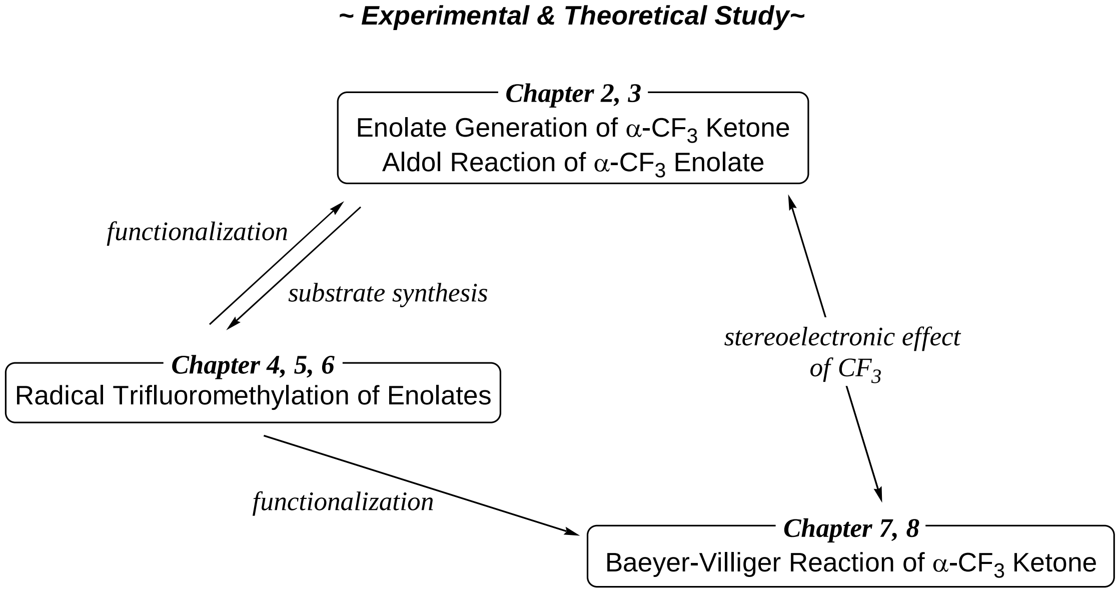
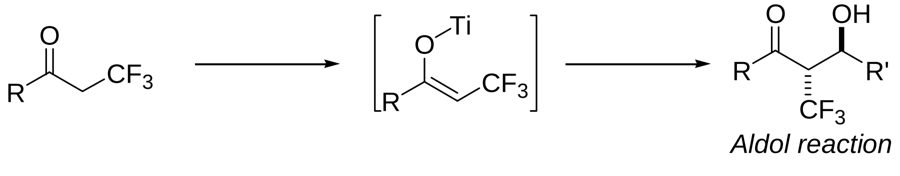


Figure 1-17. Key map of the thesis.

In chapter 2, direct generation of enolates of α-CF_3 ketones and its application to aldol reaction are investigated experimentally (Scheme 1-40).

Scheme 1-40.



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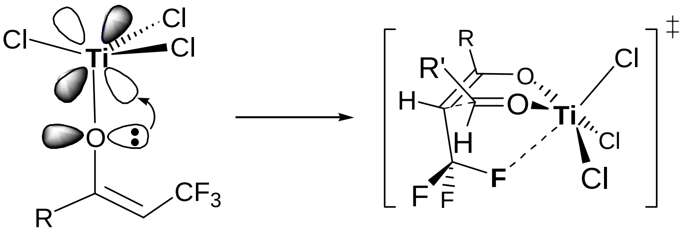
(102) During the preparation of this thesis, Crudden and co-workers have reported a computational study of the B-V reaction of α-F, Cl ketones. Grein, F.; Chen, A. C.; Edwards, D.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 861-872.

Chapter 3 will deals with anomalous properties of the enolate and its aldol reaction theoretically (Scheme 1-41).

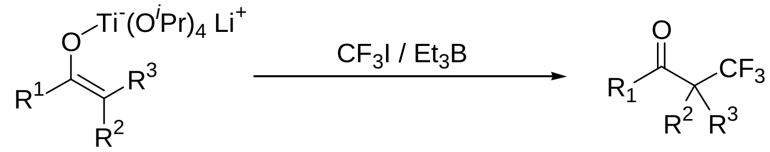
Scheme 1-41.



Linearity of Ti-O-C bond and Ti-F interaction

Radical trifluoromethylation of Ti ate enolates is described experimentally in Chapter 4 (Scheme 1-42).

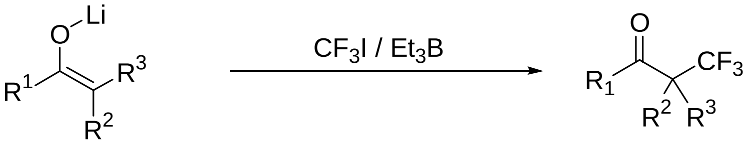
Scheme 1-42.



Titanium ate enolate

Highly basic Li enolates are reported for radical trifluoromethylation experimentally in Chapter 5 (Scheme 1-43).

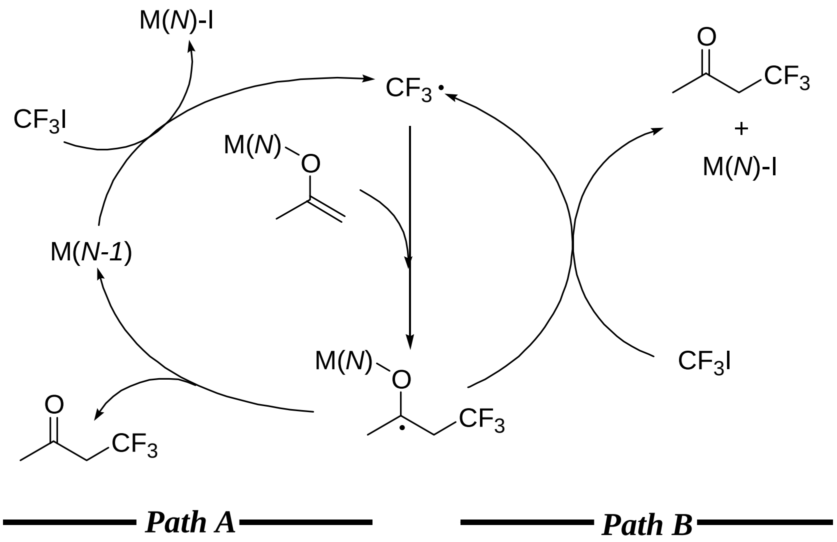
Scheme 1-43.



Highly basic Li enolate

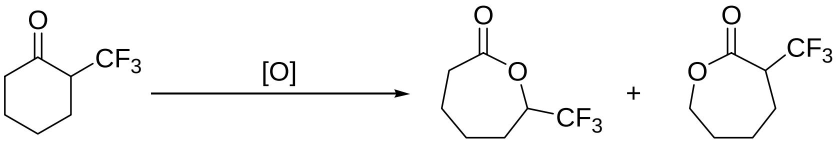
In chapter 6, radical trifluoromethylation mechanisms are clarified theoretically for Ti ate and Li enolates (Scheme 1-44).

Scheme 1-44.



The B-V reaction of α-CF_3 ketone is investigated experimentally in Chapter 7 (Scheme 1-45).

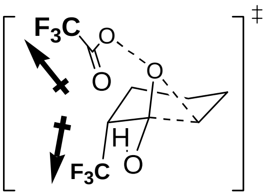
Scheme 1-45.



Regioselectivity?

Finally, the B-V reaction of α-Me, F, CF_3 cyclohexanone was investigated theoretically in Chapter 8 (Scheme 1-46).

Scheme 1-46.



Stereoelectronic effect of fluorine

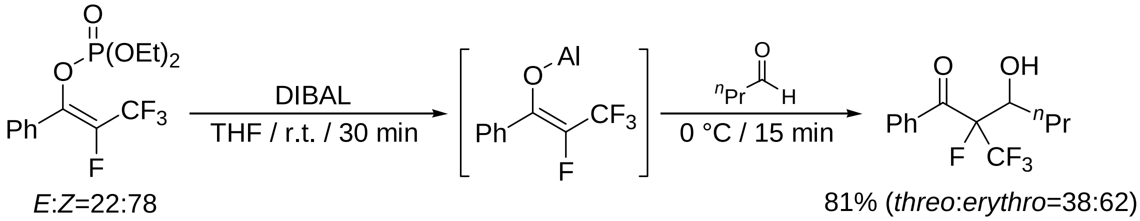
Chapter 2

Direct Generation and Aldol Reaction of Ti Enolate of α-CF_3 Ketone

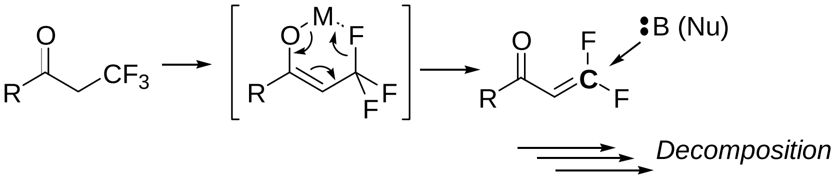
2-1. Introduction.

The author has been interested in developing synthetic methods for the construction of CF_3 containing compounds because of their specific physical properties and less availabilities. α-CF_3 Enolate methodology is, in principal, one of the most effective ways for constructing CF_3 containing compounds. However, there is only one example of generation of the α-CF_3 ketone Al enolate *via* DIBAL reduction of alkenyl phosphate (Scheme 2-1).[1] Facile defluorination is always an obstacle in the generation of an α-CF_3 metal enolate (Scheme 2-2). We herein report our discovery of efficient generation of Ti enolates directly from α-CF_3 ketones and their highly diastereoselective aldol reactions.[2]

Scheme 2-1



Scheme 2-2



2-2. Direct generation of Ti enolate of α-CF₃ ketone.

Upon generation of a variety of metal enolates of α-CF_3 ketones, we discovered that the enolate could be formed quantitatively by using $TiCl_4$ and Et_3N (Table 2-1) according to the enolate generation of non-fluorinated ketones.[3] The α-deuteriated

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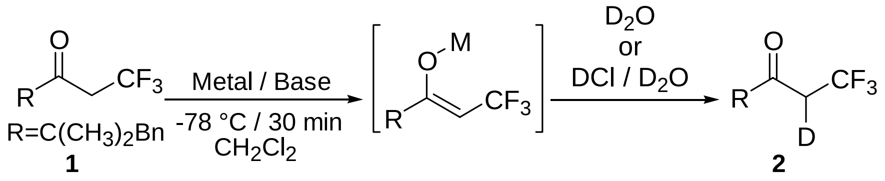
[1] Ishihara, T.; Kuroboshi, M.; Yamaguchi, K.; Okada, Y. *J. Org. Chem.* **1990**, *55*, 3107-3114. For B-enolate from amid, see: Ishihara, T.; Kuroboshi, M.; Yamaguchi, K. *Chem. Lett.* **1990**, 211-214; Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1191-1195.

[2] (a) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807-4809. (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174-13175.

[3] (a) Harrison. C. R. *Tetrahedron Lett.* **1987**, *28*, 4135-4138. (b) Evans, D. A.; Clark, J. S.; Metternich, Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868. (c) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215-8216. (d) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049. (e) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**,

ketone (**2**) was obtained in quantitative yield using 35wt% DCl/D_2O for quenching the enolate (entry 2).[4] This result clearly shows that $TiCl_3$ enolates can be directly generated quantitatively from α-CF_3 ketones. In sharp contrast, common methods for generating boron[5] or tin[6] enolate could not be applied to generate the corresponding enolate of the α-CF_3 ketone at all (entries 3, and 4) and the starting material was recovered. On the other hand, the Li enolate was formed only in low yield using LDA and the total recovery of **1** and **2** was only 35% (entry 5). This result indicates that defluorination took place in the case of Li enolate.[7]

Table 2-1. Formation of the $TiCl_3$ enolate of α-CF_3 ketone.



entry	Metal/Base (eq.)	Reagent for quench	yield (%)[a] 1	yield (%)[a] 2
1	$TiCl_4$ (1.2) / Et_3N (1.4)	D_2O	16	81
2		DCl/D_2O	trace	>99
3	$Sn(OTf)_2$ (1.2) / 1-Et-piperidine (1.4)	D_2O	>99	0
4	$^{n}Bu_2BOTf$ (1.2) / Et_3N (1.4)	D_2O	>99	0
5[b]	LDA (1.0)	D_2O	31	4

[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] THF was used as a solvent.

The Ti/amine system is known to give (*Z*)-enolates.[3] Indeed, when the α-CF_3 ketone (**1**) was transformed to the silyl enol ether, only the (*Z*)-enolate was obtained on the basis of NMR experiment (Scheme 2-3).[8]

40, 5079-5082. (f) Tanabe, Y.; Matsumoto, N.; Higashi, T.; Misaki, T.; Itoh, T.; Yamamoto, M.; Mitarai, K.; Nishii, Y. *Tetrahedron* **2002**, *58*, 8269-8280. (g) Solsona, J. G.; Romea P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519-522.

(4) When the enolate was quenched with D_2O, the yield of **2** was only 81% (entry 1). This is presumably due to the protonation by HCl salt of Et_3N (formed as a byproduct of enolate formation).

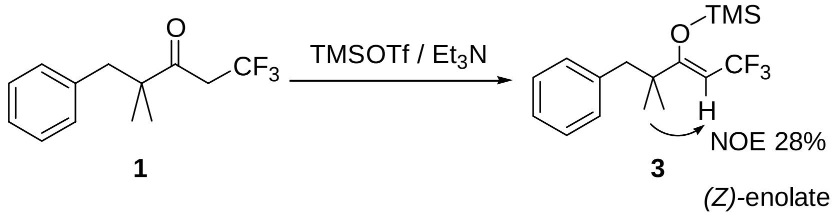
(5) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559-562. (b) Mukaiyama, T.; *Org. React.* **1982**, *28*, 203-331.

(6) (a) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381-1390. (b) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1-103.

(7) Defluorination also took place when the $TiCl_3$-enolate of α-CF_3 ketone was warmed above -78 ˚C. Therefore, low temperature reaction is essential.

(8) Trapping experiment of the$TiCl_3$ enolate of α-CF_3 ketone by TMSCl or TMSOTf was carried out.

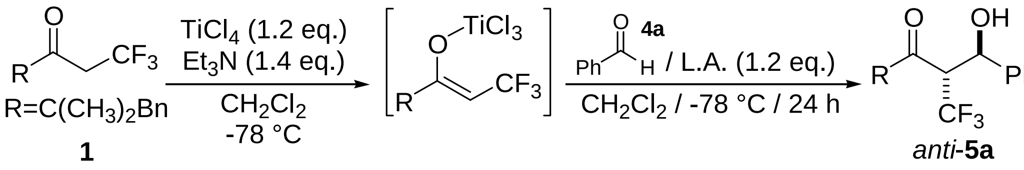
Scheme 2-3.



2-3. Aldol reaction of the Ti enolate of α-CF_3 ketone.

The aldol reaction of the $TiCl_3$ enolate of the α-CF_3 ketone was then examined (Table 2-2). Upon addition of benzaldehyde to the *in situ* generated $TiCl_3$ enolate of the α-CF_3 ketone, the aldol product was obtained in high diastereoselectivity (*anti*:*syn*=>99:<1), though in moderate yield (46%) (entry 1). Several Lewis acids were examined as an additive in order to increase the yield. The most typical Lewis acid $BF_3{\cdot}OEt_2$ did not affect the reaction (entry 2). $SnCl_4$ (entry 3) and $TiCl_4$ (entry 4) decreased the yield. A defluorination product was observed on TLC when using $TiCl_4$ and $SnCl_4$ which accounts for the low yield. $Ti(O^iPr)_4$ was extremely effective to produce the product in almost perfect yield and diastereoselectivity (97% yield, *anti*:*syn*=99:1) (entry 5).

Table 2-2. Aldol reaction of Ti enolate of α-CF_3 ketone with various Lewis acids.



entry	L.A.	yield (%)	*anti*:*syn*[a]
1	-	46[b]	>99:<1
2	$BF_3{\cdot}OEt_2$	45[b]	99:1
3	$SnCl_4$	27[a]	99:1
4	$TiCl_4$	11[a]	>99:<1
5	$Ti(O^iPr)_4$	97[b]	99:1

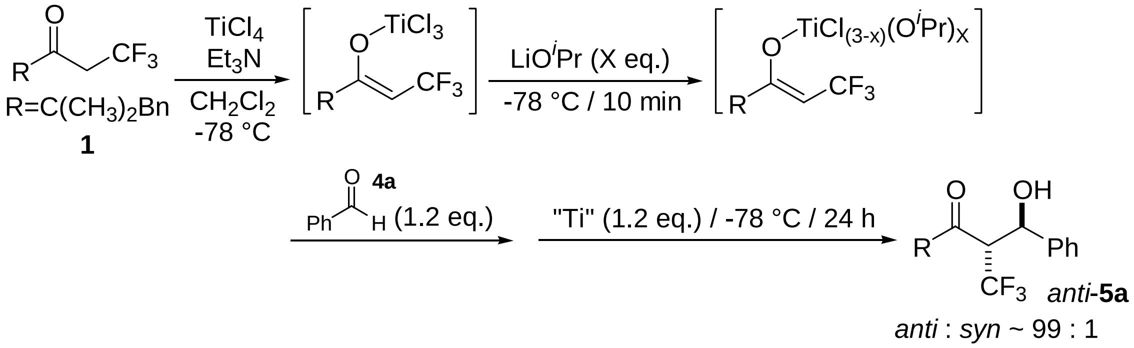
[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] Yield of the isolated products.

However, they did not react with the enolate.

2-4. Effect of $Ti(O^iPr)_4$.

It is quite strange that strong Lewis acid ($BF_3{\cdot}OEt_2$) did not affect the reaction and weaker Lewis acid like $Ti(O^iPr)_4$ significantly increased the product yield. One possibility is ligand exchange between $TiCl_3$ enolate and $Ti(O^iPr)_4$. If one of the ligands of the $TiCl_3$ enolate exchange, $TiCl_3$ enolate would transform to the $TiCl_2(O^iPr)$ enolate to enhance its nucleophilicity. At the same time, $Ti(O^iPr)_4$ would become $TiCl(O^iPr)_3$ to amplify its Lewis acidity to activate the aldehyde. Both nucleophilic and Lewis acidic effects would work for increasing the reaction rate. If two or more of the ligand exchange, these effects would incerase. To confirm this postulate, ligand exchange was separately examined; LiO^iPr was added to the $TiCl_3$ enolate to exchange the Cl ligand with O^iPr and then the aldol reaction was carried out in the presence of “Ti” Lewis acid ($TiCl_x(O^iPr)_{4\text{-}x}$). These results are listed in Table 2-3.

Table 2-3. The effects of $Ti(O^iPr)_4$.



entry	LiO^iPr (X eq.)	“Ti”	yield (%)[a]
1	0	-	46
2		$TiCl_4$	11[b]
3		$TiCl_2(O^iPr)_2$	25
4		$Ti(O^iPr)_4$	97
5	1.0	-	65
6		$TiCl_2(O^iPr)_2$	74
7		$TiCl(O^iPr)_3$	88
8	2.0	-	80
9		$TiCl_2(O^iPr)_2$	84
10		$TiCl(O^iPr)_3$	80

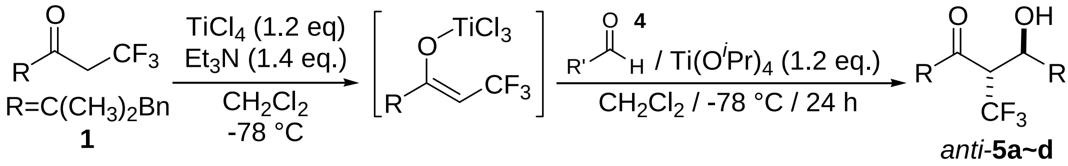
[a] Yields of the isolated products.
[b] Determined by ^{19}F NMR using BTF as an internal standard.

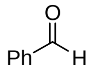
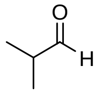
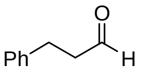
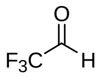
When the reaction was carried out without the additional “Ti”, the product yield increased in accordance with the increased amount of the LiO^{i}Pr added (entries 1, 5, and 8), indicating that the ligand exchange of Cl with O^{i}Pr surely enhanced the nucleophilicity of the enolate. The additional “Ti” increased the reactivity even more. $TiCl_2(O^iPr)_2$ and $TiCl(O^iPr)_3$ were added to the aldol reaction system of the one-ligand exchanged enolate (entries 6, and 7). Although the Lewis acidity is lower than $TiCl_2(O^iPr)_2$, $TiCl(O^iPr)_3$ gave higher yield, which corresponds to the correct ratio of one-ligand exchange in the original system of $TiCl_3$ enolate and $Ti(O^iPr)_4$. When $TiCl_2(O^iPr)_2$ and $TiCl(O^iPr)_3$ were added to the aldol reaction system of the two-ligand exchanged enolate (entries 9, and 10), the difference was not significant. All the trial could not reproduce the highest yield in entry 4, however, these results support the proposed ligand exchange mechanism.

2-5. Aldol reaction of $TiCl_3$ enolate of α-CF_3 ketone with various aldehydes.

Several aldehydes were reacted with the $TiCl_3$ enolate of the α-CF_3 ketone (**1**) (Table 2-4). In the case of aliphatic aldehydes (entries 2, and 3), the products (**5b, c**) were obtained in good yields and excellent diastereoselectivities. The reaction with fluoral deserves special comments because of its high reactivity and polymerizable nature. The use of $^nBu_3N$ instead of Et_3N in the preparation of the enolate was essential for giving sufficient yield. In the case of $^nBu_3N$, fluoral could be introduced smoothly to the reaction mixture with moderate polymerization to give the aldol product in 83% yield. However, in the case of EtN^iPr_2, significant polymerization occurred and the reaction mixture was capped with gummy “poly-fluoral” to prevent further introduction of fluoral into the reaction mixture and gave only 41% yield. In the case of Et_3N, polymerization also took place but not so significantly as compared with EtN^iPr_2 (61% yield). Polarity of the whole system could be responsible for the polymerization since $^nBu_3N$ with the longer alkyl chain could reduce its polarity. For the same reason of “poly-fluoral” formation, the use of $Ti(O^iPr)_4$ was not effective (entry 4).

Table 2-4. Aldol reaction of $TiCl_3$ enolate of α-CF_3 ketone with various aldehydes.



			yield[a] and diastereoselectivity[b]	
entry			without $Ti(O^iPr)_4$	with $Ti(O^iPr)_4$
1		**4a**	46% (>99:<1)	97% (99:1)
2		**4b**	45% (98:2)	80% (99:1)
3		**4c**	42% (98:2)	74% (97:3)
4[c]		**4d**	83% (90:10)	75% (91:9)

[a] Yields of the isolated products.
[b] Determined by ^{19}F NMR using BTF as an internal standard.
[c] $^nBu_3N$ was used instead of Et_3N in the preparation of the enolate. Aldol reaction time was 3-4 h.

2-6. Determination of the relative stereochemistry of the aldol reaction.

Diastereoselectivity of the major product of the aldol reaction with benzaldehyde (**5a**) was determined to be *anti* by X-ray crystal structure analysis (Figure 2-1).

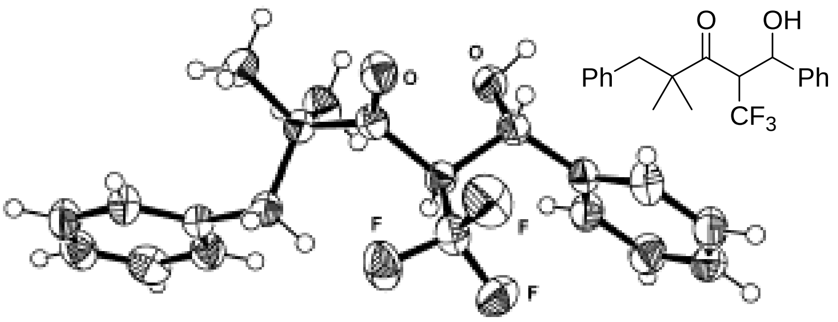
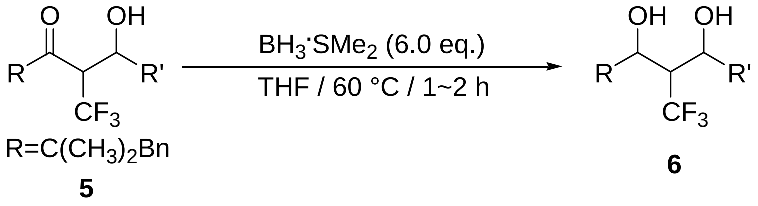


Figure 2-1. X-ray structure of *anti*-**5a**.

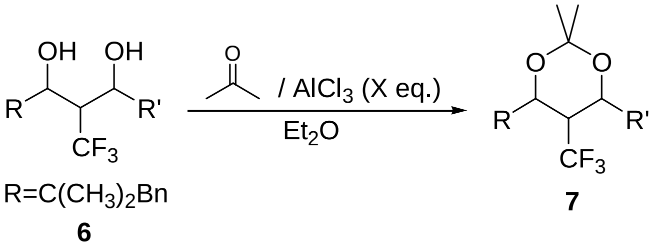
To determine the relative stereochemistry of **5b** and **d**, the aldol products were converted to acetonides by reduction ($BH_3{\cdot}SMe_2$) and successive protection of the 1,3-diols (acetone/$AlCl_3$). The results of the transformation are summarized in Scheme 2-4 and Scheme 2-5.

Scheme 2-4. Transformation of the aldol products to the 1,3-diols.



R'	**5**	**6**	
^{i}Pr (**5b**)	91% *de*	59% yield	84% *de*
CF_3 (**5d**)	84% *de*	38% yield	>99% *de*

Scheme 2-5. Transformation of the 1,3-diols to the acetonides.



R'	**6**	condition	**7**
^{i}Pr (**6b**)	84% *de*	X=1.1 eq. / r.t. / 7 h	67% yield, >92% de
CF_3 (**6d**)	>99% *de*	X=1.3 eq. / 40 ºC / 21 h	58% yield, >99% de

First, relative stereochemistry of the 1,3-diol (**6**) could be determined by the difference of the ^{13}C NMR chemical shift of the two acetonide carbons according to Rychnovsky's method;[9] if the difference is more than 9 ppm, the diol has *syn*-stereochemistry, and if the difference is less than 5 ppm, the diol has *anti*-stereochemistry. In this case, the difference for **7b** and **7d** were 2.8 and 2.7 ppm respectively. Thus both of the 1,3-diols (**6**) have *anti*-stereochemistry. By considering the bulkiness of the substituent R (~^{t}Bu), R' could be deduced to be in axial orientation. Next, the orientation of CF_3 group could be assigned by analyzing the coupling constants of the acetonide. For **7b** (R'=^{i}Pr), $^3J_{HaHb}$ (~0 Hz) and $^3J_{HbHc}$ (6.6 Hz) could be

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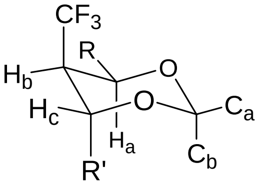
(9) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.

the strong evidence for axial position of the CF_3 group. For **7d** (R'=CF_3), $^3J_{HaHb}$ (~0 Hz) and $^3J_{HbHc}$ (5.7 Hz) could also be the strong evidence for axial orientation of the CF_3 group. Thus, both aldol products **5b** and **d** have *anti*-stereochemistry (Table 2-5).

Table 2-5. Summary of the NMR analysis.

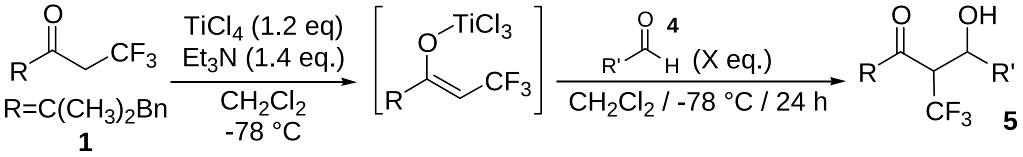


R=C(CH_3)$_2$Bn

R'	|δC_a-δC_b| (ppm)	($^3J_{HaHb}$, $^3J_{HbHc}$) (Hz)		
^{i}Pr	2.8 (*anti*-diol (**6b**))	(~0, 6.6)	→	*anti*-aldol (**5b**)
CF_3	2.7 (*anti*-diol (**6d**))	(~0, 5.7)	→	*anti*-aldol (**5d**)

For the minor isomers of the aldol products, only *syn*-**5a** could be isolated by silica gel column chromatography. The ratio of the minor isomer (*syn*-**5a**) increased when the aldol reaction was carried out with an excess amount of benzaldehyde (**4a**) (Table 2-6). The small peaks in ^{19}F NMR of the aldol products **5b** and **c**, which are speculated to be minor isomer, showed the same tendency. Therefore, those peaks were determined to be the minor isomer. In the case of **5a** and **5b**, the minor isomers were assigned to be *syn*.

Table 2-6. Diastereoselectivity in different amount of the aldehydes.



R’	X (eq.)	yield (%)[a]	major:minor[b]
Ph (**4a**)	1.2	46	>99:<1
	2.0	47	94:6
	5.0	23[c]	88:12
^{i}Pr (**4b**)	1.2	45	98:2
	2.0	20	97:3
	5.0	29	90:10
CH_2CH_2Ph (**4c**)	1.2	42	98:2
	2.0	46	89:11
	5.0	36	67:33

[a] Yield of the isolated product.
[b] In the case of **5a** and **5b**, major isomer corresponds to *anti*-isomer and minor to *syn*-isomer.
[c] Determined by ^{19}F NMR using BTF as an internal standard.

For the relative stereochemistry of **5c**, it was determined by ^{19}F NMR chemical shift of the CF_3 group. The ^{19}F NMR chemical shifts of CF_3 groups of *syn*-**5a**, **b**, and **d** appeared in lower magnetic field relative to the *anti*-**5a**, **b**, and **d** respectively. By analogy, two sets of ^{19}F NMR peaks in **5c** could be assigned; peak in low magnetic field for *syn*-isomer, and those in high magnetic field for *anti*-isomer (Table 2-7).

Table 2-7. ^{19}F NMR chemical shift of the aldol product.

	^{19}F NMR (ppm)	
R’	*syn*-isomer	*anti*-isomer
Ph (**5a**)	-61.4	-62.6
^{i}Pr (**5b**)	-59.6	-62.5
CH_2CH_2Ph (**5c**)	-60.3	-62.3
CF_3 (**5d**)[a]	-60.6	-63.0

[a] ^{19}F NMR of the α-CF_3.

All the aldol products thus show *anti*-selectivity. With the Ti/amine system, there are many examples that support for the formation of (*Z*)-enolates to give *syn*-aldol products *via* the six-membered transition state.[3] Therefore, this result implies the involvement of some unique effects of CF_3 substituents.

2-7. Conclusion.

In conclusion, the author has discovered that the Ti enolate of an α-CF_3 ketone could be easily generated and that the subsequent aldol reaction proceeds in up to quantitative yield and virtually perfect diastereoselectivity. Thus one of the difficult and important issues in organofluorine chemistry, direct generation of metal enolate of α-CF_3 ketone, was achieved successfully.

Interesting questions arose. Why does the Ti enolate of an α-CF_3 ketone is stable and why the Li enolate is not? Why does the aldol reaction of the Ti (*Z*)-enolate of an α-CF_3 ketone gave *anti*-product? Those questions are discussed in Chapter 3.

Experimental Section for Chapter 2

General

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ^{1}H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ=77.0) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard (δ=-63.24) in $CDCl_3$.Important NMR data were tabulated in following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sext: sextet, sept: septet, bs: broad singlet, bd: broad doublet, m: multiplet) and coupling constant (*J* (Hz)).

IR spectrum was measured on JASCO FT/IR-5000 spectrometer.

EI Mass spectra were measured on Shimazu QP-5000 spectrometer and JEOL JMS-700 spectrometer.

X-ray analysis was made on Rigaku Saturn 70 CCD area detector.

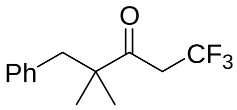
Analytical thin layer chromatographies (TLC) were performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid.

Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane and ethyl acetate as an eluent.

THF and Et_2O were distilled over benzophenone-ketyl under Ar prior to use. CH_2Cl_2 (dehydrate) was purchased from Kanto Chemical Co., Inc.

All experiments were carried out under argon atmosphere unless otherwise noted.

1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (1)



See Chapter 4, **3e** for the synthesis.

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.16 (s, 6H), 2.81 (s, 2H), 3.17 (q, *J*=9.9 Hz, 2H), 7.07 (ddd, *J*=1.7, 2.1, 6.3 Hz, 2H), 7.19~7.32 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.8, 41.4 (q, *J*=28.1 Hz), 45.3, 48.9, 123.9 (q, *J*=277.1 Hz), 126.8, 128.2, 130.2, 136.8, 205.2 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -63.0 (t, *J*=9.8 Hz) (ppm).

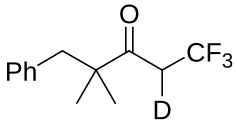
IR (neat)

3034, 2976, 1721, 1369, 1282, 1133, 1100 (cm^{-1}).

EI-MS

m/z=244 [$M^{+\bullet}$].

deuterio-1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (2)



General procedure for Ti enolate formation and the reaction with D_2O or DCl.

To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**) (17.1 mg, 0.07 mmol) in CH_2Cl_2 (0.7 ml) was added titanium tetrachloride (9.2 μl, 0.084 mmol) at 0 ºC and stirred for 10 min under argon atmosphere. Then the reaction mixture was cooled to -78 ºC and was added triethylamine (13.7 μl, 0.098 mmol) at the temperature. The reaction mixture was stirred for 15 min and then was quenched with D_2O or 35wt% DCl/D_2O (0.1 ml) and warmed to room temperature. The crude mixture was directly analyzed by ^{19}F NMR using BTF as an internal standard.

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.16 (s, 6H), 2.81 (s, 2H), 3.15 (tq, *J*=2.6, 9.9 Hz, 1H), 7.07 (ddd, *J*=1.7, 2.1, 5.7 Hz, 2H), 7.19~7.32 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.8, 41.0 (m), 45.2, 48.9, 123.9 (q, *J*=277.2 Hz), 126.7, 128.2, 130.2, 136.7, 205.2 (ppm).

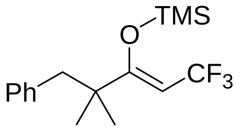
^{19}F NMR ($CDCl_3$, 376 MHz)

δ -63.1 (bd, *J*=10.5 Hz) (ppm).

EI-MS

m/z=245 [$M^{+\bullet}$].

3,3-Dimethyl-4-phenyl-1-trifluoromethyl-2-(trimethylsilyloxy)-1-butene (3)



To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**) (488 mg, 2.0 mmol) in CH_2Cl_2 was added triethylamine (0.92 ml, 6.6 mmol) and trimethylsilyl trifluoromethanesulfonate (1.09 ml, 6.0 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 d. To the reaction mixture was added ice water and extracted 3 times with hexane. Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude mixture was purified by neutral silica gel column chromatography (hexane only). 489 mg of 3,3-dimethyl-4-phenyl-1-trifluoromethyl-2-(trimethylsilyloxy)-1-butene was obtained (77%).

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.32 (s, 9H), 1.02 (s, 6H), 2.69 (s, 2H), 4.75 (q, *J*=8.4 Hz, 1H), 7.08~7.13 (ddd, *J*=1.8, 2.1, 6.0 Hz, 2H), 7.17~7.30 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 0.7, 25.3, 41.4, 45.7, 97.2 (q, *J*=33.0 Hz), 124.1 (q, *J*=269.8 Hz), 126.5, 128.0, 130.6, 138.0, 167.4 (q, *J*=6.1 Hz) (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -56.5 (d, *J*=7.9 Hz) (ppm).

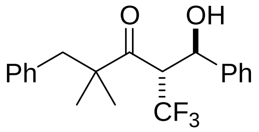
IR (neat)

2972, 1659, 1379, 1359, 1259, 1189, 1154, 1114, 847, 702, 679 (cm^{-1}).

EI-MS

m/z=316 [M$^{+\bullet}$].

5-Hydroxy-2,2-dimethyl-1,5-diphenyl-4-trifluoromethyl-3-pentanone (5a)



General Experimental procedure for Ti enolate formation and aldol reaction.

To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**) (17.1 mg, 0.07 mmol) in CH_2Cl_2 (0.7 ml) was added titanium tetrachloride (9.2 μl, 0.084 mmol) at 0 °C and stirred for 10 min under argon atmosphere. Then the reaction mixture was cooled to -78 °C and was added triethylamine (13.7 μl, 0.098 mmol) at the temperature. The reaction mixture was stirred for 15 min and then was added benzaldehyde (8.5 μl, 0.084 mmol) and titanium (IV) isopropoxide (24.8 μl, 0.084 mmol). After stirring for 24 h at -78 °C, the reaction was quenched by adding phosphorous buffer (pH=7) at the temperature. The mixture was extracted 3 times with ether. Combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane:acetone=10:1 to 6:1). 23.8 mg of 5-hydroxy-2,2-dimethyl-1,5-diphenyl-4-trifluoromethyl-3-pentanone (**5a**) was obtained (97%).

anti-**5a**

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.89 (s, 3H), 1.01 (s, 3H), 2.63 (d, *J*=13.5 Hz, 1H), 2.73 (d, *J*=13.5, 1H), 3.15 (d, *J*=5.7 Hz, 1H), 4.18 (dq, *J*=6.6, 8.1 Hz, 1H), 5.27 (dd, J=6.0, 6.3 Hz, 1H), 7.07~7.10 (m, 2H), 7.16~7.42 (m, 8H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 22.9, 23.2, 43.3, 49.4, 54.9 (q, *J*=24.4 Hz), 72.6 (q, *J*=2.4 Hz), 123.4 (q, *J*=282.6 Hz), 126.5, 126.6, 128.0, 128.8, 128.9, 131.1, 137.2, 140.9, 211.2 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -62.6 (d, *J*=7.9 Hz) (ppm).

IR (neat)

3484, 3034, 2978, 2932, 1715, 1495, 1470, 1458, 1338, 1241, 1160, 1129, 700 (cm^{-1}).

HRMS (EI)
calcd for $C_{20}H_{21}O_2F_3$, 350.1494 ($[M^{+\bullet}]$); found 350.1488 ($[M^{+\bullet}]$).

syn-**5a**
^{1}H NMR ($CDCl_3$, 300 MHz)
δ 0.50 (s, 3H), 0.83 (s, 3H), 2.17 (d, *J*=1.5 Hz, 1H), 2.24 (d, *J*=13.2, 1H), 2.41 (d, *J*=12.9 Hz, 1H), 4.17 (dq, *J*=7.8, 8.1 Hz, 1H), 5.26 (bd, *J*=8.7 Hz, 1H), 6.91~6.96 (m, 2H), 7.16~7.34 (m, 8H) (ppm).
^{19}F NMR ($CDCl_3$, 376 MHz)
δ -61.4 (d, *J*=7.9 Hz) (ppm).

X-ray analysis of *anti*-**5a** (CCDC 240382)

Empirical Formula	$C_{20}H_{21}F_3O_2$	2θmax	62.4°
Formula Weight	350.38	No. of Reflections Measured	3713
Crystal Description	Prism	No. of Unique Reflections	3486 (R_{int} = 0.018)
Crystal Color	Colorless	Abs. Correction Type	multi-scan
Crystal Size	0.20×0.20×0.20 mm	Abs. Transmission	0.4690~1.0000
Crystallizing Method	neat (-30 °C)	Structure Solution	Direct Methods (SIR92)
Crystal System	Triclinic	Residuals	R_1 ($I>2\sigma(I)$) = 0.096
Space Group	*P-1* (#2)		wR_2 ($I>0\sigma(I)$) = 0.162
Lattice Parameters	a = 6.469(4) Å	Restrains	0
	b = 10.934(6) Å	No. of Variables	247
	c = 13.371(9) Å	Goodness of Fit Indicator	0.991
	α = 73.90(2)°	Maximum Peak in Final Diff. Map	0.28 e·Å^{-3}
	β = 88.25(3)°	Minimum Peak in Final Diff. Map	-0.27 e·Å^{-3}
	γ = 76.29(2)°		
	V = 882.2(10) Å^3		
Z value	2		
D_{calc}	1.319 g·cm^{-3}		
Temp	-80 °C		
μ(MoKα)	1.05 cm^{-1}		
Detector	Rigaku Saturn		
Goniometer	Rigaku AFC10		
Radiation	MoKα		
	(λ = 0.71070 Å)		
Monochrometer	Graphite		

Bond lengths (Å)

F(2) C(15) 1.339(4)
F(3) C(15) 1.346(4)
F(4) C(15) 1.331(5)
O(1) C(20) 1.211(4)
O(2) C(18) 1.417(3)
C(1) C(2) 1.398(4)
C(1) C(7) 1.373(5)
C(1) C(10) 1.515(4)
C(2) C(3) 1.389(5)
C(3) C(4) 1.363(6)
C(4) C(5) 1.379(5)
C(5) C(7) 1.385(5)
C(6) C(8) 1.392(4)
C(6) C(18) 1.513(3)
C(6) C(19) 1.380(5)
C(8) C(13) 1.383(4)
C(9) C(12) 1.529(4)
C(10) C(12) 1.547(4)
C(11) C(15) 1.501(4)
C(11) C(18) 1.554(4)
C(11) C(20) 1.545(3)
C(12) C(16) 1.531(4)
C(12) C(20) 1.534(4)
C(13) C(14) 1.376(6)
C(14) C(21) 1.381(5)
C(19) C(21) 1.384(4)

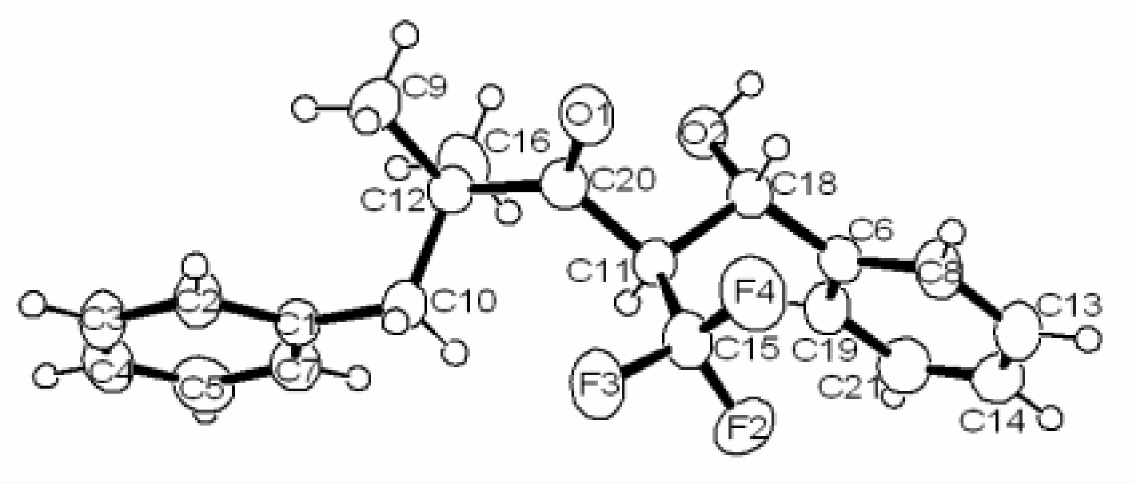
Bond angles (˚)

C(2) C(1) C(7) 118.3(3)
C(2) C(1) C(10) 120.5(3)
C(7) C(1) C(10) 121.2(2)
C(3) C(2) C(1) 120.2(3)
C(4) C(3) C(2) 120.6(3)
C(5) C(4) C(3) 119.6(3)
C(7) C(5) C(4) 120.1(4)
C(8) C(6) C(18) 120.6(3)
C(8) C(6) C(19) 119.1(2)
C(18) C(6) C(19) 120.3(3)
C(1) C(7) C(5) 121.1(3)
C(13) C(8) C(6) 120.2(3)
C(12) C(10) C(1) 115.5(2)
C(15) C(11) C(18) 112.5(2)
C(15) C(11) C(20) 109.3(2)
C(18) C(11) C(20) 107.9(2)
C(16)C(12)C(20) 108.8(2)
C(16)C(12)C(9) 110.0(2)
C(16)C(12)C(10) 110.6(3)
C(20)C(12)C(9) 108.3(3)
C(20) C(12) C(10) 108.8(2)
C(9) C(12) C(10) 110.2(2)
C(14) C(13) C(8) 120.2(3)
C(21) C(14) C(13) 120.1(3)
F(2) C(15) F(3) 105.3(3)
F(2) C(15) F(4) 106.3(2)
F(2) C(15) C(11) 112.9(3)
F(3) C(15) F(4) 105.6(3)
F(3) C(15) C(11) 112.2(2)
F(4) C(15) C(11) 113.9(3)
O(2) C(18) C(6) 112.0(2)
O(2) C(18) C(11) 104.0(2)
C(6) C(18) C(11) 113.3(2)
C(21) C(19) C(6) 120.7(3)
O(1) C(20) C(11) 118.0(2)
O(1) C(20) C(12) 121.2(2)
C(11) C(20) C(12) 120.8(3)
C(14) C(21) C(19) 119.8(4)

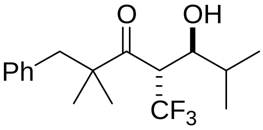
Torsion Angles(˚)

C(7) C(1) C(2) C(3) 0.7(4)
C(10) C(1) C(2) C(3) -177.0(3)
C(2) C(1) C(7) C(5) -1.4(5)
C(10) C(1) C(7) C(5) 176.3(3)
C(2) C(1) C(10) C(12) -85.1(3)
C(7) C(1) C(10) C(12) 97.2(3)
C(1) C(2) C(3) C(4) 0.1(5)
C(2) C(3) C(4) C(5) -0.3(5)
C(3) C(4) C(5) C(7) -0.4(5)
C(4) C(5) C(7) C(1) 1.2(5)
C(18) C(6) C(8) C(13) 178.5(3)
C(19) C(6) C(8) C(13) -1.6(5)
C(8) C(6) C(18) O(2) 136.8(3)
C(8) C(6) C(18) C(11) -106.0(3)
C(19) C(6) C(18) O(2) -43.2(4)
C(19) C(6) C(18) C(11) 74.1(3)
C(8) C(6) C(19) C(21) 1.5(5)
C(18) C(6) C(19) C(21) -178.6(3)
C(6) C(8) C(13) C(14) 0.8(5)
C(1) C(10) C(12) C(9) 63.1(3)
C(1) C(10) C(12) C(16) -58.8(3)
C(1) C(10) C(12) C(20)-178.3(2)
C(18) C(11) C(15) F(2) -75.8(4)
C(18) C(11) C(15) F(3) 165.4(3)
C(18) C(11) C(15) F(4) 45.6(3)
C(20) C(11) C(15) F(2) 164.4(3)
C(20) C(11) C(15) F(3) 45.6(4)
C(20) C(11) C(15) F(4) -74.3(3)
C(15) C(11) C(18) O(2) -179.3(2)
C(15) C(11) C(18) C(6) 58.9(3)
C(20) C(11) C(18) O(2) -58.6(3)
C(20) C(11) C(18) C(6) 179.6(2)
C(15) C(11) C(20) O(1) 66.6(3)

C(15) C(11) C(20) C(12) -114.2(3)
C(18) C(11) C(20) O(1) -56.0(3)
C(18) C(11) C(20) C(12) 123.2(3)
C(9) C(12) C(20) O(1) -3.9(4)
C(9) C(12) C(20) C(11) 176.9(2)
C(10) C(12) C(20) O(1) -123.7(3)
C(10) C(12) C(20) C(11) 57.1(3)
C(16) C(12) C(20) O(1) 115.7(3)
C(16) C(12) C(20) C(11) -63.5(3)
C(8) C(13) C(14) C(21) 0.2(5)
C(13) C(14) C(21) C(19) -0.3(5)
C(6) C(19)C(21)C(14)-0.5(5)



5-Hydroxy-2,2-dimethyl-6-methyl-1-phenyl-4-trifluoromethyl-3-heptanone (5b)



anti-**5b**

^{1}H NMR (CDCl$_3$, 300 MHz)

δ 0.94 (s, 3H), 0.97 (s, 3H), 1.14 (d, *J*=3.3 Hz, 6H), 1.75~1.88 (m, 1H), 2.03 (d, *J*=5.4 Hz, 1H), 2.78 (d, *J*=13.2 Hz, 1H), 2.89 (d, *J*=13.2 Hz, 1H), 3.98~4.11 (m, 2H), 7.12~7.17 (m, 2H), 7.19~7.32 (m, 3H) (ppm).

^{13}C NMR (CDCl$_3$, 75 MHz)

δ 14.8, 19.8, 23.5, 24.1, 30.6, 43.9, 49.6, 51.2 (q, *J*=24.4 Hz), 74.6 (q, *J*=2.4 Hz), 123.8 (q, *J*=280.8 Hz), 126.5, 127.9, 131.0, 137.2, 210.9 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -62.5 (d, *J*=7.2 Hz) (-59.6 (d, *J*=7.9 Hz) for *syn*-**5b**) (ppm).

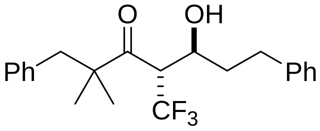
IR (KBr)

3538, 2970, 2880, 1712, 1496, 1468, 1345, 1248, 1144, 1092, 1008, 874, 760, 728, 707 (cm^{-1}).

HRMS (EI)

calcd for $C_{17}H_{23}F_3O_2$, 316.1650 ($[M^{+\bullet}]$); found 316.1656 ($[M^{+\bullet}]$).

5-Hydroxy-2,2-dimethyl-1,7-diphenyl-4-trifluoromethyl-3-heptanone (5c)



anti-**5c**

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.14 (s, 3H), 1.15 (s, 3H), 1.69~1.81 (m, 1H), 1.83~1.97 (m, 1H), 2.27 (d, *J*=6.9 Hz, 1H), 2.55~3.00 (m, 4H), 3.90 (qd, *J*=7.8, 7.8 Hz, 1H), 4.11~4.22 (m, 1H), 7.09~7.33 (m, 10H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.4, 23.9, 31.4, 36.8, 43.7, 49.6, 53.8 (q, *J*=23.2 Hz), 69.6 (q, 2.4 Hz), 123.8 (q, *J*=282.0 Hz), 126.3, 126.7, 128.1, 128.5, 128.7, 131.1, 137.2, 141.1, 211.1 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -62.28 (d, *J*=9.0 Hz) (-60.27 (d, *J*=8.3 Hz) for *syn*-**5c**) (ppm).

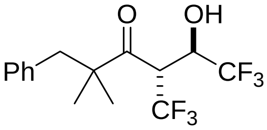
IR (neat)

3508, 3030, 2976, 2932, 1713, 1497, 1470, 1456, 1334, 1257, 1156, 1125, 702 (cm^{-1}).

HRMS (EI)

calcd for $C_{22}H_{25}F_3O_2$, 378.1807 ($[M^{+\bullet}]$); found 378.1802 ($[M^{+\bullet}]$).

5-Hydroxy-2,2-dimethyl-1,5-diphenyl-4-trifluoromethyl-3-pentanone (5d)



anti-**5d**

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.15 (s, 3H), 1.17 (s, 3H), 2.77 (d, *J*=13.2 Hz, 1H), 2.90 (d, *J*=13.5, 1H), 4.19 (dq, *J*=2.8, 7.7 Hz, 1H), 4.44~4.58 (m, 2H), 7.10~7.16 (m, 2H), 7.21~7.33 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.3, 23.7, 43.8, 45.9 (q, *J*=26.9 Hz), 50.1, 69.6 (qq, *J*=33.0, 3.7 Hz), 122.9 (q, J=283.2 Hz), 123.8 (q, *J*=284.5 Hz), 126.9, 128.2, 131.2, 136.5, 211.8 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -77.7 (dd, *J*=2.3, 3.4 Hz, 3F), -63.0 (dd, *J*=2.6, 7.9 Hz, 3F) (-77.3 (dd, *J*=2.3, 6.8 Hz, 3F), -60.6 (dd, *J*=2.3, 7.9 Hz, 3F) for *syn*-**5d**) (ppm).

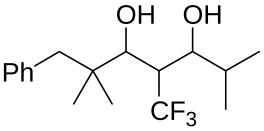
IR (neat)

3448, 3034, 2982, 2936, 1717, 1251, 1156, 741, 704 (cm^{-1}).

HRMS (EI)

calcd for $C_{15}H_{16}F_6O_2$, 342.1054 ([M$^{+\bullet}$]); found 342.1053 ([M$^{+\bullet}$]).

2,2,6-Trimethyl-1-phenyl-4-trifluoromethyl-heptane-3,5-diol (6b)



General procedure for hydroboration of the aldol product.

To a solution of 5-hydroxy-2,2-dimethyl-6-methyl-1-phenyl-4-trifluoromethyl-3-heptanone (**5b,** 91% *de*) (35.3 mg, 0.11 mmol) in THF was added borane-methyl sulfide complex (48.5 μl, 0.67 mmol) under argon atmosphere. The reaction mixture was refluxed for 1.5 h and then quenched with 1N HCl. The mixture was extracted 3 times with ether, washed with saturated aqueous solution of sodium bicarbonate, washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude mixture (mixture of two diastereomer) was purified by silica gel column chromatography (hexane:ethylacetate=3:1). 2,2,6-trimethyl-1-phenyl-4-trifluoromethyl-heptane-3,5-diol (**6b**) was obtained in 59% yield (84% *de*).

^{1}H NMR (CDCl$_3$, 300 MHz)

δ 0.77 (d, *J*=6.3 Hz, 3H), 0.86 (s, 3H), 0.98 (s, 3H), 1.02 (d, *J*=6.3 Hz, 3H), 1.52~1.69 (m, 1H), 2.42 (d, *J*=5.1 Hz, 1H), 2.47~2.63 (m, 3H), 2.81 (d, *J*=12.9 Hz, 1H), 3.68 (dd, *J*=4.5, 9.9 Hz, 1H), 3.89 (bs, 1H), 7.15~7.33 (m, 5H) (ppm).

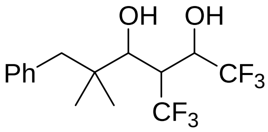
^{13}C NMR (CDCl$_3$, 75 MHz)

δ 18.7, 19.0, 22.34, 22.37, 23.6, 30.9, 38.5, 44.2 (q, *J*=23.2 Hz), 45.6, 73.6, 126.2, 127.5 (q, *J*=282.0 Hz), 127.9, 131.0, 138.6 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -61.1 (d, *J*=10.5 Hz) (ppm).

1,1,1-Trifluoro-5,5-dimethyl-6-phenyl-3-trifluoromethyl-hexane-2,4-diol (6d)



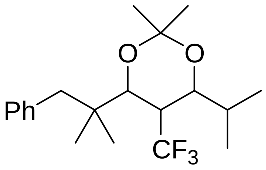
^{1}H NMR ($CDCl_3$, 400 MHz)

δ 0.85 (s, 3H), 0.95 (s, 3H), 2.15 (d, *J*=6.4 Hz, 1H), 2.56 (d, *J*=13.2, 1H), 2.74 (d, *J*=13.2 Hz, 1H), 2.82 (dq, *J*=1.2, 9.6 Hz, 1H), 3.54 (d, *J*=6.0 Hz, 1H), 4.12 (d, *J*=6.0 Hz, 1H), 4.47 (quint, *J*=7.2 Hz, 1H), 7.11~7.16 (m, 2H), 7.17~7.30 (m, 3H) (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -77.0 (d, *J*=7.9 Hz, 3F), -61.5 (d, *J*=9.4 Hz, 3F) (ppm).

4-(1,1-Dimethyl-2-phenyl-ethyl)-6-isopropyl-2,2-dimethyl-5-trifluoromethyl-[1,3]dioxane (7b)



General procedure for acetonide protection of the 1,3-diol.

To a solution of 2,2,6-trimethyl-1-phenyl-4-trifluoromethyl-heptane-3,5-diol (**6b**) (21.8 mg, 0.068 mmol) in acetone (0.5 ml) was added $AlCl_3$ (10.3 mg, 0.077 mmol) dissolved in ether (1 ml) at 0 ºC under argon atmosphere. The reaction mixture stirred for 2 h at room temperature and 7 h at 40 ºC. The reaction was quenched with saturated aqueous solution of sodium bicarbonate and extracted 3 times with CH_2Cl_2. Combined organic layer was washed with brine, filtered through filt paper and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane:ethylacetate=100:0 to 30:1) to afford 16.3 mg (67 %, >92% *de*) of 4-(1,1-dimethyl-2-phenyl-ethyl)-6-isopropyl-2,2-dimethyl-5-trifluoromethyl-[1,3]dioxane (**7b**).

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.91 (s, 6H), 0.93 (d, *J*=6.9 Hz, 3H), 1.02 (d, *J*=6.6 Hz, 3H), 1.30 (s, 3H), 1.39 (s, 3H), 1.83 (dqq, *J*=2.4, 6.3, 6.3 Hz, 1H), 2.52 (m, 1H), 2.61 (d, *J*=12.9, 3H), 2.74 (d, *J*=12.9, 3H), 3.62 (q, *J*=1.8 Hz, 1H), 3.79 (dd, *J*=2.7, 6.6 Hz, 1H), 7.12~7.32 (m, 5H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 14.5, 19.7, 22.1, 22.8, 25.6, 32.8, 37.0, 44.0, 44.9 (q, *J*=23.2 Hz), 71.2 (q, *J*=2.5 Hz), 75.2, 100.9, 126.0, 127.7, 127.8 (q, *J*=282.0 Hz), 131.2, 138.7 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -62.2 (d, *J*=10.2 Hz) (ppm).

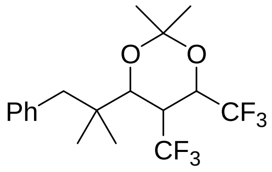
IR (KBr)

3066, 3030, 2970, 1946, 1873, 1810, 1495, 1455, 1374, 1234, 1181, 1144, 1098 (cm^{-1})

EI-MS

m/z=358 [M$^{+\bullet}$].

4-(1,1-Dimethyl-2-phenyl-ethyl)-2,2-dimethyl-5,6-bis-trifluoromethyl-[1,3]dioxane (7d)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.92 (s, 3H), 0.93 (s, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 2.61 (d, J=13.2 Hz, 1H), 2.75 (d, *J*=13.2 Hz, 1H), 2.86 (m, 1H), 3.82 (bq, J=1.8 Hz, 1H), 4.38 (quint., J=5.7 Hz, 1H), 7.12~7.17 (m, 2H), 7.19~7.32 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 21.9, 22.6, 23.0, 25.7, 37.0, 41.8 (q, *J*=25.4 Hz), 44.0, 67.3 (qq, *J*=3.6, 31.6 Hz), 74.7, 102.4, 124.0 (q, *J*=279.1 Hz), 126.2 (q, *J*=280.3 Hz), 126.3, 127.9, 131.1, 138.1 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -79.4 (quint., *J*=5.7 Hz, 3F), -62.1 (m, 3F) (ppm).

IR (KBr)

3030, 2992, 2936, 1957, 1881, 1815, 1496, 1457, 1417, 1396, 1319, 1237, 1186, 1149, 1121, 1025 (cm^{-1})

EI-MS

m/z=384 [M$^{+\bullet}$].

Chapter 3

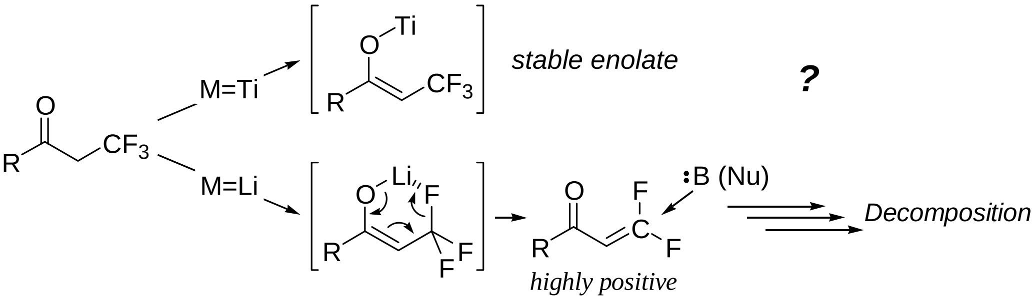
Theoretical Study on the Stability of the α-CF_3 Ti Enolate and Anomalous *Anti*-selective Aldol Reaction

3-1. Introduction.

In Chapter 2, the author describes that the Ti enolates of α-CF_3 ketones can be easily generated and the subsequent aldol reactions proceed in up to quantitative yield and with virtually perfect diastereoselectivity. Concerning these results, there are some anomalous outcomes;

(1) According to crystallographic data, Ti is of strong affinity to fluorine rather than Li.[1] Therefore, it seems strange that the Ti enolate of the α-CF_3 ketones could be formed without defluorination (Scheme 3-1).

Scheme 3-1.



(2) It is well known that the aldol reaction of a Ti (*Z*)-enolate would produce *syn*-aldol *via* cyclic transition state.[2] In the case of the aldol reaction of α-CF_3 Ti enolates, all the reactions were found to give opposite *anti*-selectivity (Scheme 3-2).

In Chapter 3, theoretical investigation is shown to shed light on these anomalies.

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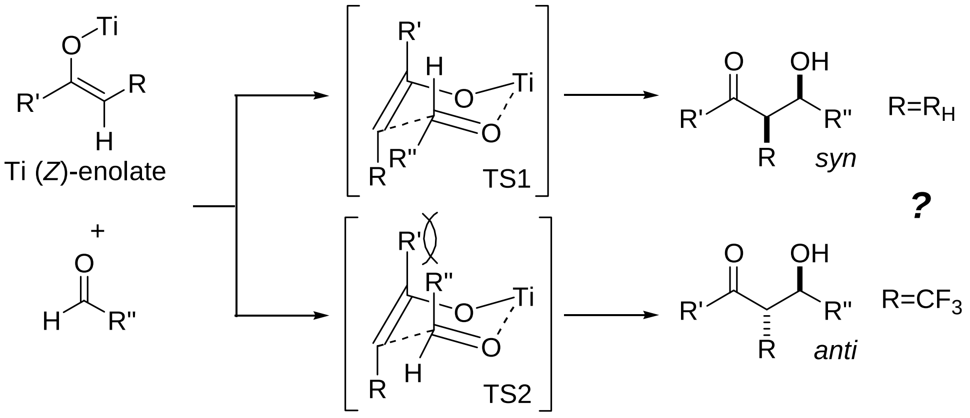
(1) Li: Künzel, A.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H.–G. *J. Chem. Soc., Chem. Commun.* **1995**, 2145-2146. Ti: Liu, F. –Q.; Stalke, D.; Roesky, H. W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1872-1873. For reviews of organometallic fluorides see: Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425-3468; Plenio, H. *Chem. Rev.* **1997**, *97*, 3363-3384. See also Chapter 1 and Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1-16.

(2) With the Ti/amine system, there are many examples that support the formation of (*Z*)-enolate to give *syn*-aldol product via a cyclic transition state. (a) Harrison. C. R. *Tetrahedron Lett.* **1987**, *28*, 4135-4138. (b) Evans, D. A.; Clark, J. S.; Metternich, Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868. (c) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215-8216. (d) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049. (e) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5079-5082. (f) Tanabe, Y.; Matsumoto, N.; Higashi, T.; Misaki, T.; Itoh, T.; Yamamoto, M.; Mitarai, K.; Nishii, Y. *Tetrahedron* **2002**, *58*, 8269-8280. (g) Solsona, J. G.; Romea P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519-522.

Scheme 3-2.



3-2. Chemical models and computational methods.

3-2-1. Chemical models.

Ti[3] and Li[4,5] complexes are known to form oligomeric structures. However, for computational efficiency, all the structures were approximated to be monomer. This approximation should give at least qualitative computation. Since the structures were simplified as a monomer, an extra coordination site would be available. Ti and Li have several coordination sites (normally 6 for Ti and 4 for Li), and this site must be filled by a solvent. However, the reaction of the Ti enolate was carried out in CH_2Cl_2, which has low coordinating ability. Therefore, no additional solvent molecule was attached for the monomeric model of $TiCl_3$ enolates of α-CF_3 ketones. For Li enolates, the solvent for the actual reaction was THF and, hence, Me_2O was employed as a computational model of the solvent. Instead of the ketone which were exactly used for the aldol reaction,

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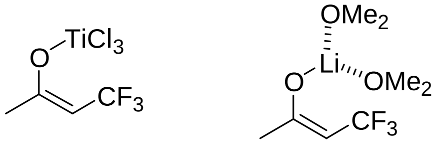
(3) Aggregation of Ti complexes: (a) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218-2229. (b) Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Chem. Ber.* **1996**, *129*, 1361-1368. (c) Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936-2941. (d) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267-272. (e) Hwang, T.-Y.; Cho, J.-Y.; Jiang, M.-K.; Gau, H.-M. *Inorg. Chim. Acta* **2000**, *303*, 190-198. (f) Pescitelli, G.; Bari, L. D.; Salvadori, P. *Organometallics* **2004**, *23*, 4223-4229. (g) Mikami, K.; Matsumoto, Y. *Tetrahedron* **2004**, *60*, 7715-7719.

(4) Experimental investigation of the aggregation of Li enolates: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654. (b) Suzuki, M.; Koyama, H.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 259-268.

(5) Theoretical investigation of the aggregation of Li enolates: (a) Weiss, H.; Yakimansky, A. V. Müller, A. H. E. *J. Am. Chem. Soc.* **1996**, *118*, 8897-8903. (b) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255-11268.

α-CF_3 acetone was employed as a simple model (Figure 3-1). Likewise, acetaldehyde was employed as an electrophile for the aldol reaction.



TiCl$_3$ enolate Li enolate

Figure 3-1. Chemical model for Ti and Li enolate.

3-2-2. Computational methods.

All the calculations were performed with GAUSSIAN 03 program package.[6] All the structures were optimized at B3LYP/631LAN (LANL2DZ for Ti, 6-31G* for others)[7,8] level in the presence of dielectric field as described by the C-PCM (COSMO (conductor-like screening model)) model[9] unless otherwise noted. The solvent definition is CH_2Cl_2 (ε=8.93) for Ti species and THF (ε=7.58) for Li species. The energies shown in this report are Gibbs free energies and thus contain zero-point, thermal and entropy effects at 195.15 K (-78 ºC: actual reaction temperature) and 1 atm pressure ($\Delta G_{sol,-78}$) unless otherwise noted.

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(6) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(7) B3LYP utilizes Becke's three-parameter exchange functional and the Lee-Yang-Parr correlation functional. (a) Becke, A.D. *Phys. Rev.* **1988**, *A38*, 3098-3100. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys Rev.* **1988**, *B37*, 785-788. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372-1377. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

(8) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310. (d) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*, Wiley: New York, 1986, and references cited therein.

(9) (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans.2* **1993**, 799-805. (b) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995-2001. (c) Cossi, M.; Rega, N.; Scalamani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669-681.

3-3. Energy profile of the aldol reaction and defluorination.

Energy diagram of defluorination and aldol reaction is shown in Figure 3-2. Energy diagram starts from the middle part of the figure. **CP1** is the enolate and **CP2** is the enolate coordinated with aldehyde. By looking the diagram to the left hand side from **CP1**, the energetics for the defluorination reaction can be seen. In the same manner, the diagram to the right hand side from **CP2** describe the energetics for the aldol reaction.

For the $TiCl_3$ enolate, equilibrium of aldehyde coordination to the enolate (**Ti-CP1** and **CP2**) does not have large energy difference (-1.2 kcal/mol). The transition state energy of the defluorination reaction is 15.1 kcal/mol (**Ti-TS1**) and the product (**Ti-PD1**) is in lower energy (-6.3 kcal/mol) than **Ti-CP1**. However, the transition state of the aldol reaction is 9.9 kcal/mol (**Ti-TS2-*anti***) and is lower in energy than **Ti-TS1**. This indicates that the aldol reaction is favorable than the defluorination reaction, which is in accordance with the experimental observation. On the other hand, the transition state energy of the defluorination reaction for the Li enolate (**Li-TS1**) is 8.0 kcal/mol which is lower than that of the aldol reaction (10.8 kcal/mol, **Li-TS2-*anti'***[10]). Activation energy of the aldol reaction itself is 7.2 kcal/mol and smaller than that of the aldol reaction of the $TiCl_3$ enolate (11.1 kcal/mol). However, coordination of the aldehyde to the Li enolate of the α-CF_3 ketone is unfavorable by 3.6 kcal/mol, which is in contrast with the case of the Ti enolate (only 1.2 kcal/mol difference), and this unfavorable coordination could account for the retardation of the aldol reaction.[11]

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(10) **Li-TS2-*anti*** could not be optimized in the presence of dielectric field probably due to the complex hypersurface. In turn, the structure was optimized in gas phase (**Li-TS2-*anti'***) and then single point calculation was carried out in the presence of dielectric field at the same level of theory.

(11) The "electrophile-coexisting" method (LDA was added to the α-CF_3 ketone in the presence of aldehyde) also could not produce the aldol product at all. This is in accordance with the calculation result. "Electrophile-coexisting" method: Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 7043-7046.

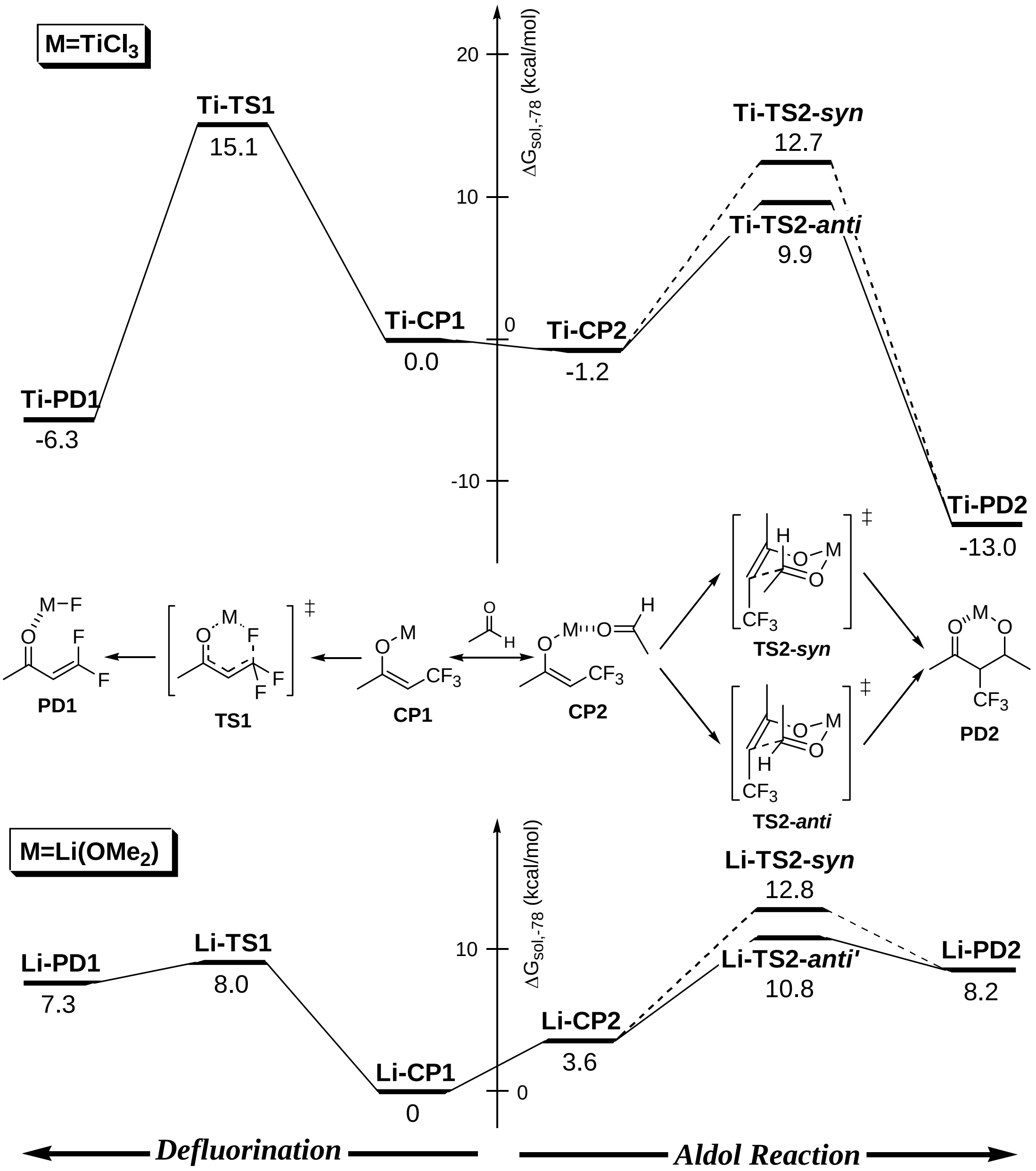

Figure 3-2. Energy diagram of defluorination and aldol reaction of the $TiCl_3$ and Li enolates of α-CF_3 ketone at B3LYP/631LAN level.

3-4. Energetics and structures of the equilibrium of the aldehyde coordination to the α-CF_3 enolates.

Three-dimensional structures of the enolates (**CP1**) and enolate coordinated with aldehyde (**CP2**) are shown in Figure 3-3. The structure of **Li-CP1** has intramolecular coordination of Li with F. The Li-F distance in **Li-CP1** is 2.00 Å and it is shorter than the sum of the vdW radius of F and ionic radius of Li (2.08 Å). Since Li has only 4 coordination sites available, Li-F interaction should be broken when aldehyde coordinates to Li. Therefore, the structure of the Li-enolate changes significantly: Li-O-C angle was changed from 123.1° to 143.1° and Li-F distance was changed from 2.00 Å to 2.72 Å. 2.72 Å is longer than the sum of the vdW radius of F and ionic radius of Li (2.08Å) indicating that there are no Li-F interaction any more at **Li-CP2**. Breaking the Li-F interaction and the structural change make the aldehyde coordination unfavorable. In sharp contrast, the distance between Ti and F in **Ti-CP1** is 3.37 Å and it is longer than the sum of the vdW radius of F and ionic radius of Ti (2.10 Å), which means that the Ti enolate does not have intramoleclar coordination of Ti and F even with an empty site available for F (normally, the maximum coordination number for Ti is 6). Therefore, coordination of the aldehyde does not make significant structural change and thus energies of **Ti-CP1** and **-CP2** are almost the same. Interestingly, Ti-O-C bond is almost linear (171.2° in **Ti-CP1** and 167.9° in **Ti-CP2**). This linearity accounts for suppressing Ti-F interaction (*vide infra*).

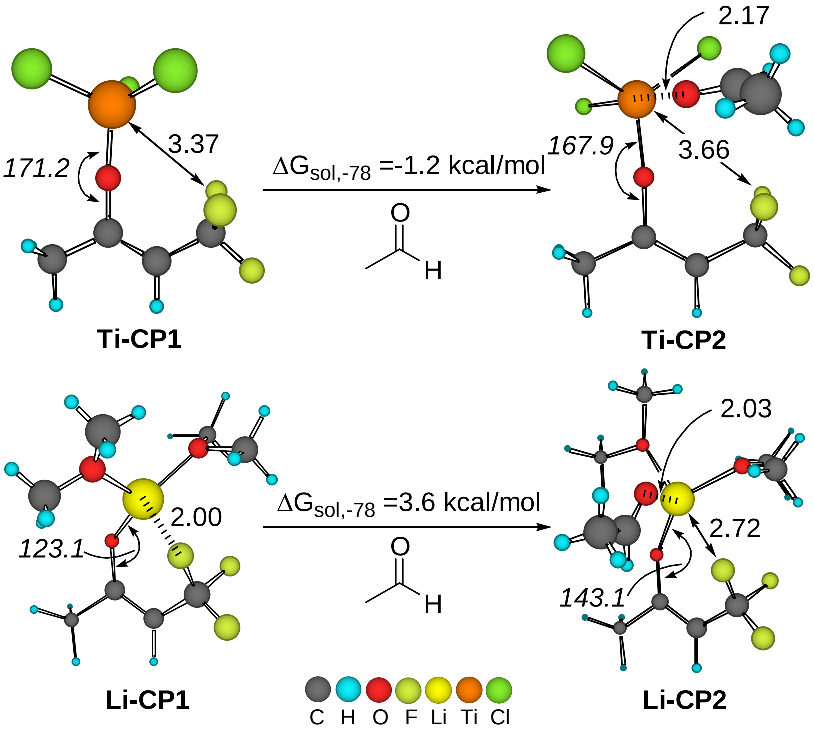

Figure 3-3. Three-dimensional structures of TiCl$_3$ and Li enolates of α-CF$_3$ ketone. The structures were optimized at B3LYP/631LAN level in the presence of corresponding dielectric field. The bond lengths are in Å and bond angles (italics) in degrees.

3-5. Energetics and structures of the defluorination reaction.

Three-dimensional structures of the substrate (**CP1**), transition state (**TS2**), and product (**PD1**) are shown in Figure 3-4. As already mentioned before, the Ti enolate (**Ti-CP1**) does not have intramolecular coordination with F but the Li enolate (**Li-CP1**) does. For the defluorination of the Li enolate of the α-CF_3 ketone, the structural change is very small throughout the reaction; Li-O-C angle changes from 123.1° to 117.1° and finally 119.4°. Other parameters also change in only requisite amounts for the defluorination (single bond to double bond, and *vice versa*). Therefore, the activation energy for defluorination of the Li enolate of the α-CF_3 ketone is very low (8.3 kcal/mol). On the other hand, in order to reach the transition state of defluorination of the Ti enolate of the α-CF_3 ketone, the Ti enolate (**Ti-CP1**) has to change its structure to interact with fluorine; Ti-O-C angle changes from 171.2° to 137.7°. This accounts for the higher activation energy for defluorination of the Ti enolate (15.8 kcal/mol) than that of the Li enolate (8.3 kcal/mol).

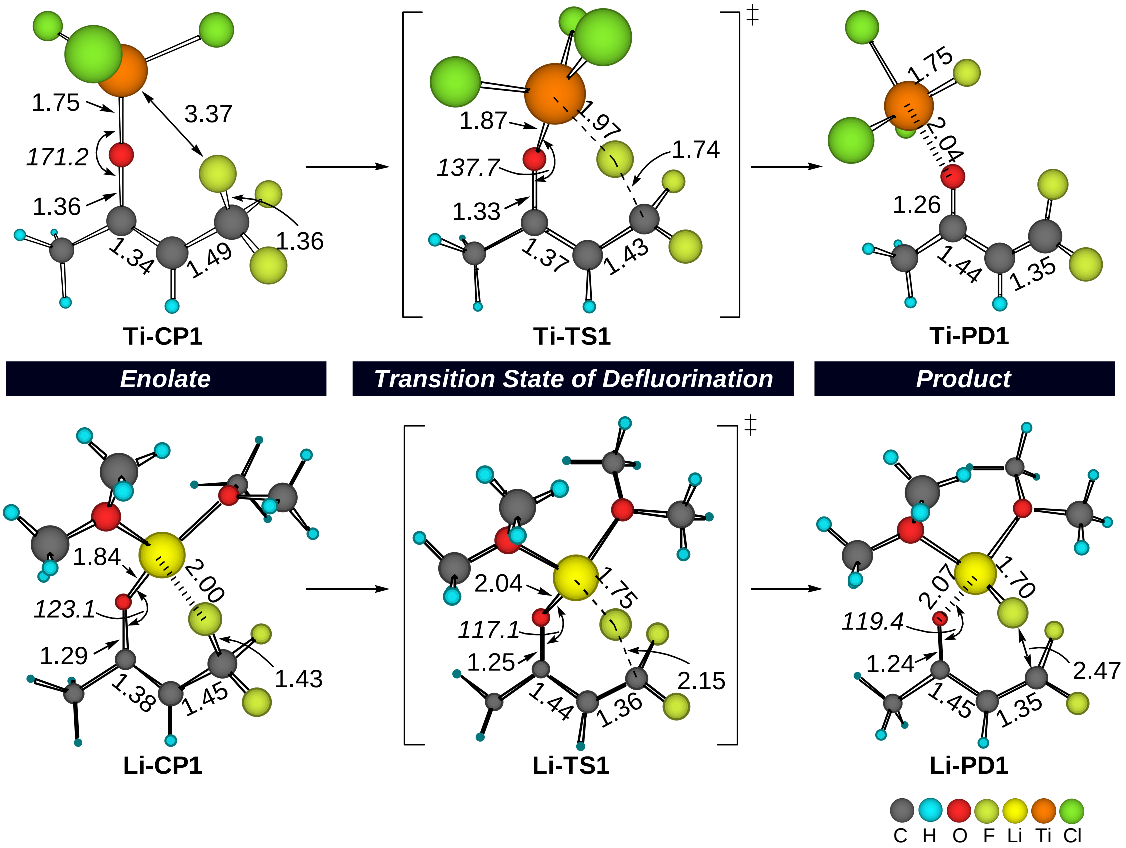

Figure 3-4. Three-dimensional structures of the defluorination reaction. The structures were optimized at B3LYP/631LAN level in the presence of corresponding dielectric field. The bond lengths are in Å and bond angles (italics) in degrees.

From the discussion above, the key for the stability of the Ti enolate of the α-CF_3 ketone is speculated to be the linearity of Ti-O-C bond. To identify the origin of the linear nature of Ti-O-C bond, Kohn-Sham orbital was analyzed. Important orbital interactions are shown in Figure 3-5 and multiple bonding nature was found. LUMO+4 and HOMO-22 show the interaction between σ-orbital of C-O bond and d_{Z^2}-orbital of Ti (σ-bond). LUMO+1 and HOMO-7 show the interaction between lone electron pair of O and d-orbital of Ti (π-bond). In LUMO+5, LUMO, HOMO, and HOMO-20, enolate double bond is also incorporated in the orbital interaction between lone electron pair of O and d-orbital of Ti (π-bond).[12]

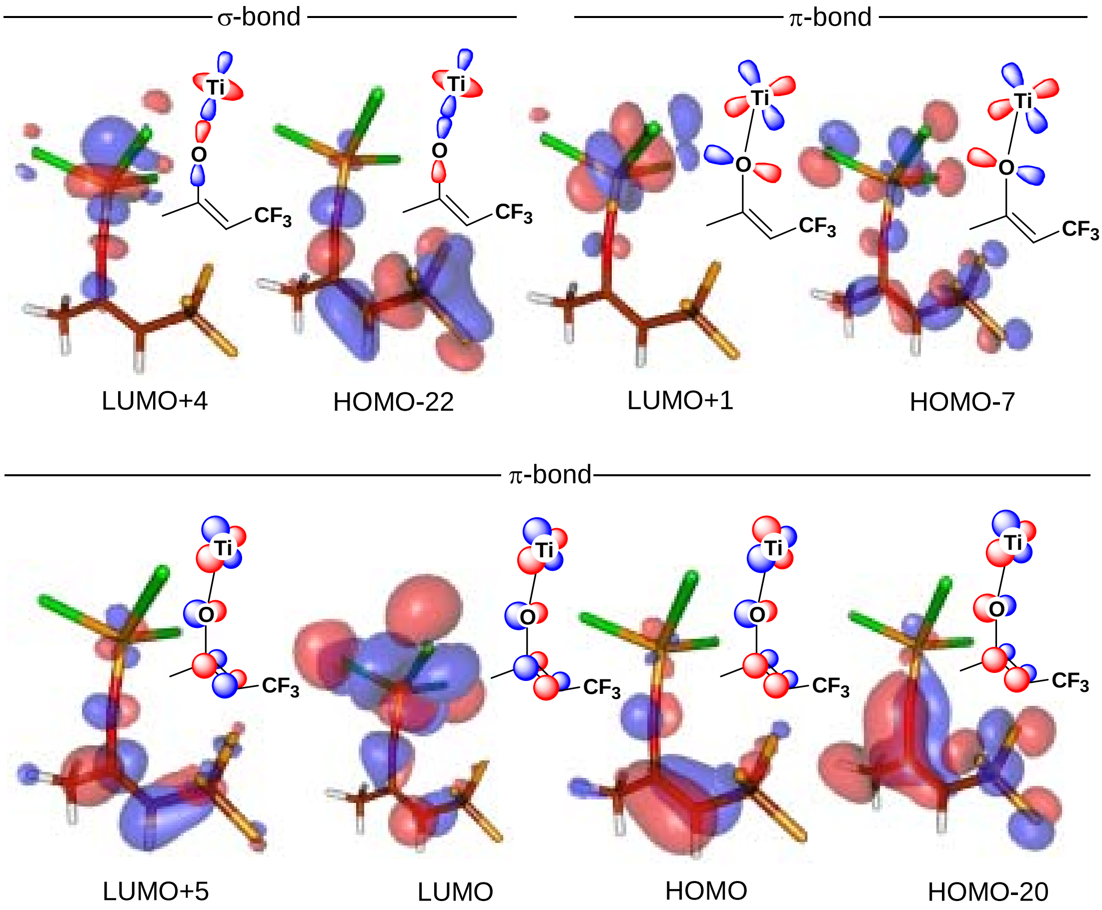

Figure 3-5. Kohn-Sham orbital interaction in $TiCl_3$ enolate of α-CF_3 ketone (**Ti-CP1**).

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[12] The multiple bonding nature of Ti-O bonds has been observed in X-ray structure of Ti complexes and in computational study. (a) Nielson, A. J.; Schwerdtfeger, P.; Waters, J. M. *J. Chem. Soc., Dalton Trans.* **2000**, 529-537. (b) Dobado, J. A.; Molina, J. M.; Uggla, R.; Sundberg, M. R. *Inorg. Chem.* **2000**, *39*, 2831-2836.

3-6. Origin of *anti*-selective aldol reaction.

3-6-1. Transition state structures of the aldol reaction.

The author focuses on the anomalous *anti*-selective aldol reaction. The energy diagram in Figure 3-2 shows that the transition state leading to *anti*-product (**Ti-TS2-*anti***, **Ti-PD2**) is in lower energy. In order to see the steric interactions clearly, more realistic model (**Ti-TS3-*anti’***, **Ti-TS3-*syn’***) (Figure 3-6) was optimized in gas phase.[13] The structure, the Gibbs free energy at 280.15 K, 1 atm pressure (ΔG), and the electronic energy (ΔE) were shown in Figure 3-7.

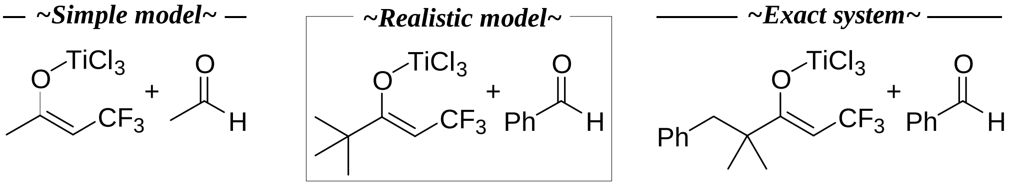
~Simple model~
~Realistic model~
~Exact system~

Figure 3-6. Realistic model.

Surprisingly, the interaction between Ti and CF_3 group was observed at both transition states, which was not observed at the starting Ti enolate, presumably because the donation of the lone electron pair of enolate oxygen to the empty d orbital of Ti was weaken at the reaction transition state. Owing to the Ti-F interaction, both transition structures (**Ti-TS3-*anti’*** and ***–syn’***) were fixed to boat forms; CF_3 group in the enolate moiety would be attracted by Ti to enhance the steric repulsion with equatorial substituent in the aldehyde moiety (benzene ring) (**B**). Along with this motion of the CF_3 group, ^{t}Bu group in the enolate moiety would move away from the 6-membered ring to reduce the steric repulsion with axial substituent in the aldehyde moiety (**A**). Therefore, the transition state leading to *anti*-aldol would be stabilized.

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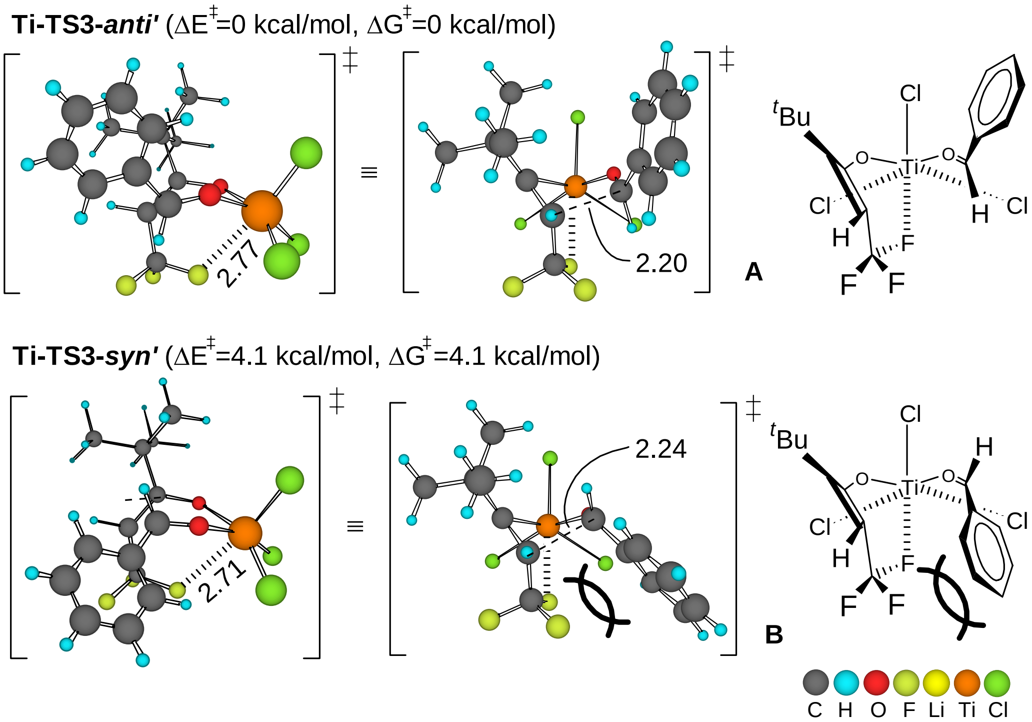
(13) The realistic model system (**Ti-TS3**) is larger than the simple model system (**Ti-TS2**). Therefore, structure optimization was carried out in the gas phase. Structural difference between the structure optimized in gas phase and in dielectric field was small. For instance, **Ti-TS2-*anti*** and ***-syn*** was optimized in gas phase (**Ti-TS2-*anti’*** and ***–syn’*** respectively). The bond lengths of the C-C bond forming part were 2.285 Å in **Ti-TS2-*anti*** and 2.251 Å in **Ti-TS2-*anti’***. The difference was only 1.5%. In the same way, the bond lengths of the C-C bond forming part were 2.336 Å in **Ti-TS2-*syn*** and 2.310 Å in **Ti-TS2-*syn’***, and the difference was only 1.1%.


Ti-TS3-*anti'* ($\Delta E^{\ddagger}$=0 kcal/mol, $\Delta G^{\ddagger}$=0 kcal/mol)

Ti-TS3-*syn'* ($\Delta E^{\ddagger}$=4.1 kcal/mol, $\Delta G^{\ddagger}$=4.1 kcal/mol)

Figure 3-7. Three-dimensional structures of the aldol reaction of $TiCl_3$ enolate for realistic model. The structures were optimized at B3LYP/631LAN level. The bond lengths are in Å and bond angles (italics) in degrees.

3-6-2. *Tracing the Ti-F interaction.*

The lengths of Ti-F interactions in **Ti-TS3-*anti'*** and ***–syn'*** are 2.77 Å and 2.71 Å respectively. Those values are longer than the sum of the vdW radius of F and ionic radius of Ti (2.10 Å). However, the octahedral structure of Ti clearly shows the Ti-F interaction. Interestingly, this Ti-F interaction could be seen only at the transition state. The octahedral structure is broken in **Ti-CP3** and **Ti-PD3** and Ti takes trigonal bipyramidal geometry (Figure 3-8).

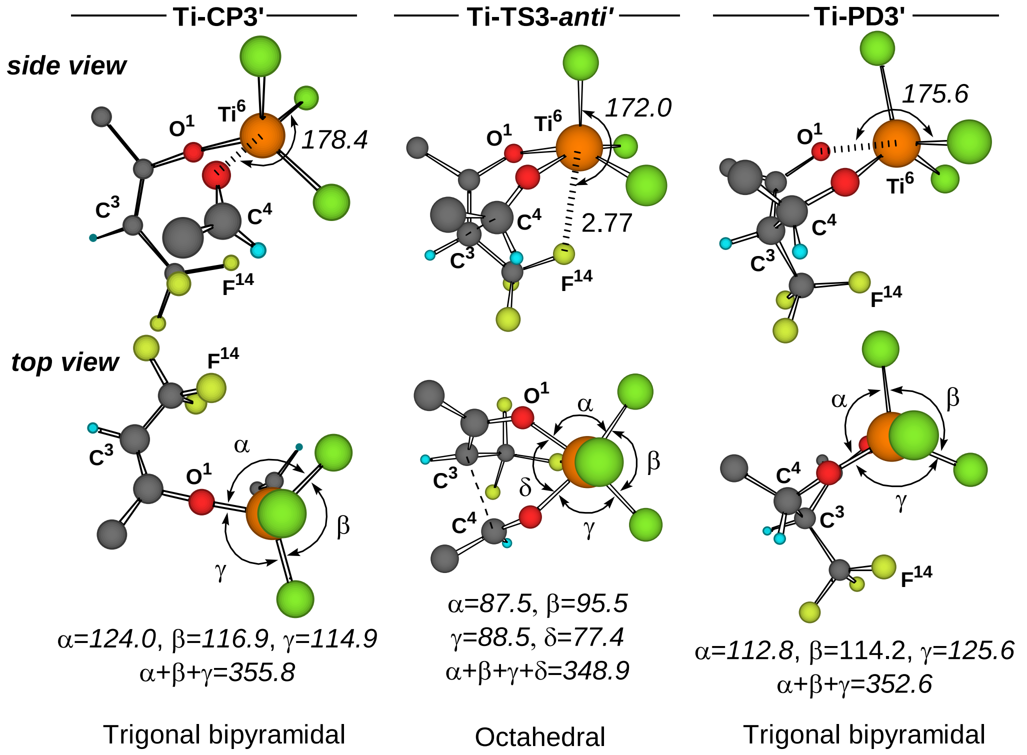


Figure 3-8. Geometries of Ti in **Ti-CP3'**, **Ti-TS3-*anti*'**, and **Ti-PD3'**. The structures were optimized at B3LYP/631LAN level. The bond lengths are in Å and bond angles (italics) in degrees. Several substituents were omitted for clarity.

It is quite interesting to investigate when Ti and F start to interact. In order to look into the Ti-F interaction, the reaction path was followed by an intrinsic reaction coordinate (IRC) analysis[14] and the results were shown in Figure 3-9. Horizontal axis is the bond length of C^3 and C^4 ($R(C^3,C^4)$). Four parameters were followed along the reaction coordinate: total electronic energy (ΔE), distance between F^{14} and Ti^6 ($R(F^{14},Ti^6)$), dihedral angle of F^{14}-C^8-C^3-C^2 ($D(F^{14},C^8,C^3,C^2)$), and angle of Ti^6-O^1-C^2 ($A(Ti^6,O^1,C^2)$). IRC analysis could follow the reaction in the range of $R(C^3,C^4)$=2.54~1.80 Å. Further points were obtained by standard optimization.

---

[14] (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154-2161. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523-5527.

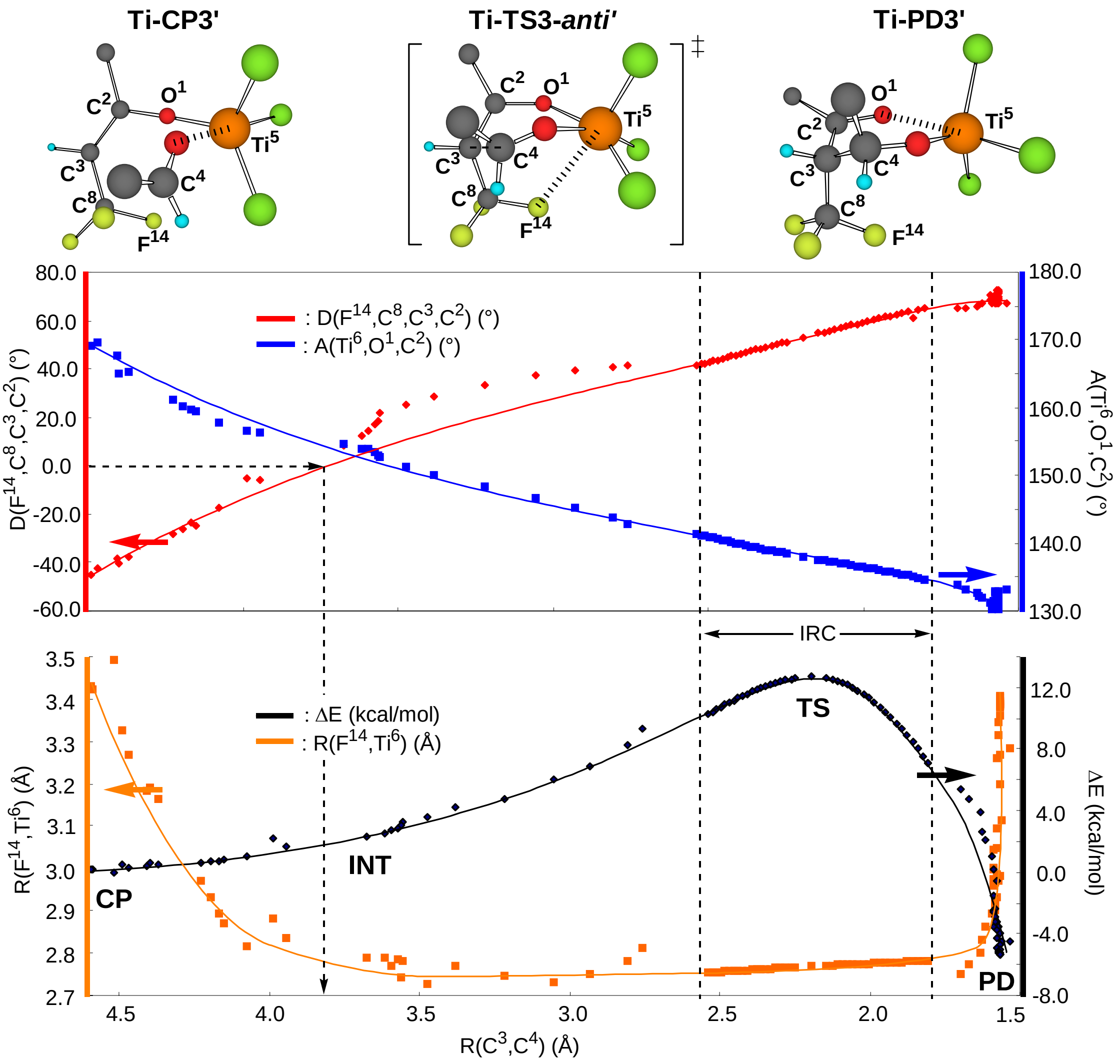


Figure 3-9. IRC analysis of the aldol reaction. Several substituents in the three-dimensional structures were omitted for clarity.

R(C^3,C^4) ranges from 4.5~1.6 Å, and at the transition state (**Ti-TS3-*anti'***), R(C^3,C^4) is 2.2 Å, which means a late transition state.[15] The curve for R(F^{14},Ti^6) (orange line) reveals that Ti-F interaction begins at the early stage of the reaction and becomes constant at about R(C^3,C^4)=3.6 Å. R(F^{14},Ti^6) keeps the distance even after the transition state and dissociate just before reaching the product (**Ti-PD3**). The curve for A(Ti^6,O^1,C^2) (blue line) shows that linearity of Ti-O-C bond found in the enolate substrate is lost gradually. The curve for D(F^{14},C^8,C^3,C^2) (red line) also shows linear

---

(15) According to Hammond postulate, transition state structure of an exothermic reaction resembles reactant. However, this is not the case.

change. At about $R(C^3,C^4)$=3.7 Å, the sign of $D(F^{14},C^8,C^3,C^2)$ changes from minus to plus. This means that at this point, CF_3 group goes beyond the rotation barrier (Figure 3-10). Immediately after the sigh changes to plus, $R(F^{14},Ti^6)$ becomes constant. It could be explained that Ti-F interaction assisted CF_3 group to go beyond the rotation barrier. Otherwise, there is no reason for the rotation of CF_3 group.

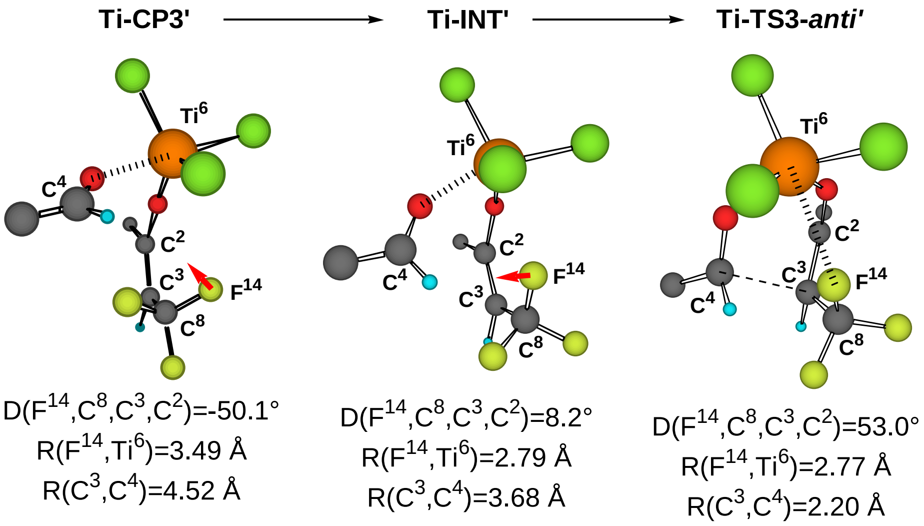


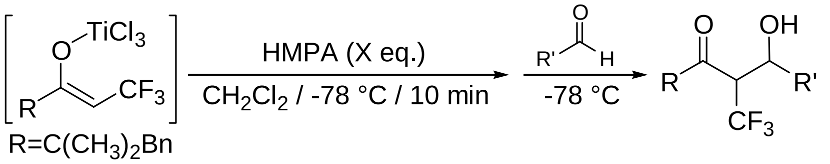
Figure 3-10. Rotation of CF_3 group.

3-6-3. Experimental evidence for Ti-F interaction.

To confirm the effect of Ti-F interaction at the transition state, the reaction was carried out in the presence of HMPA to cleave Ti-F coordination leading to usual *syn*-selectivity. In fact, when HMPA was added in the reaction mixture, *syn*-selectivity was obtained (*anti*:*syn*=20:80) (Table 3-1, R'=Ph). Therefore, it can be concluded that the *anti*-selective aldol reaction stems from Ti-F interaction at the aldol transition state, which is not observed in the Ti enolate.

Interesting result was obtained when the same reaction was carried out with fluoral instead of benzaldehyde. The sense of *anti*-diastereoselectivity did not change (*anti*:*syn*=62:38) even in the presence of HMPA, though only in 1% yield (Table 3-1, R'=CF_3). Strong dipole interaction could account for the *anti*-selectivity for fluoral. *Anti*-diastereoselectivity could be attained if the stabilization by two CF_3 groups overcomes the steric repulsion (Figure 3-11). Thus, a paradigm shift from steric to electronic control of reaction stereoselectivity has been disclosed; strong dipole interaction could overcome the steric effect to control the stereoselectivity.

Table 3-1. Aldol reaction of Ti enolate of α-CF$_3$ ketone in the presence of HMPA**.**



R’	X (eq.)	time (h)	yield (%)[a]	*anti*:*syn*
Ph	0	24	46	>99:<1
	2.0	24	17	20:80
CF$_3$[b]	0	4	83	90:10
	2.0	3	1[c]	62:38

[a] Yields for the isolated products.

[b] ^{n}Bu$_3$N was used for the preparation of the enolate.

[c] Determined by ^{19}F NMR. Significant polymerization occurred.

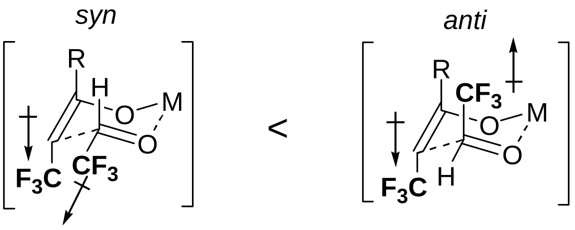


Figure 3-11. Dipole interaction controlled stereoselectivy in the case of the aldol reaction of Ti enolate of α-CF$_3$ ketone with fluoral.

3-7. Conclusion.

In this chapter, the author theoretically investigates the defluorination reaction and the aldol reaction of TiCl$_3$ and Li enolates. Ti-F interaction plays an important role in the course of these reactions. In the Ti enolate of α-CF$_3$ ketone, there is no Ti-F interaction because of the multiple bonding nature of Ti-O bond which retards F-elimination. On the other hand, at the transition state of the aldol reaction, there is a clear Ti-F interaction and, as a result, the aldol reaction shows *anti*-diastereoselectivity.

Experimental Section for Chapter 3

General

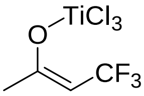
Computational calculations were executed on SGI Origin2000 (Tokyo Institute of Technology), Compaq AlphaServer GS320 (Tokyo Institute of Technology), SGI2800 (Institute of Molecular Science), SGI Origin3800 (Institute of Molecular Science), and Fujitsu VPP5000 (Institute of Molecular Science).

Computational Methods

All the calculations were performed with GAUSSIAN 03 program package. All the structures were optimized at B3LYP/631LAN (LANL2DZ for Ti, 6-31G* for others) level in the presence of dielectric field (E_{sol}) as described by the C-PCM (COSMO (conductor-like screening model)) model unless otherwise noted. The solvent definition is CH_2Cl_2 (ε=8.93) for Ti species and THF (ε=7.58) for Li species. The energies shown in this report are Gibbs free energies and thus contain zero-point, thermal and entropy effects at 195.15 K (-78 ºC) and 1 atm pressure ($G_{sol,-78}$) unless otherwise noted.

Molecular Geometries and Energies

Ti-CP1



E_{sol}(B3LYP/631LAN) = -1968.4915812 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -1968.434390 a.u.

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    3          6           0        2.427793    1.110820   -0.014437
    4         22           0       -1.289567   -0.124810   -0.012893
    5          6           0        2.642752   -0.367697   -0.005588
    6          1           0        3.323132    1.725946    0.020156
    7          6           0        0.963486    3.170348   -0.136168
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    9          9           0        3.913614   -0.661839    0.332241
   10          9           0        2.406846   -0.931826   -1.216134
   11         17           0       -3.069844    0.950323   -0.706219
   12         17           0       -1.002299   -1.948517   -1.187954
   13         17           0       -1.535354   -0.606577    2.108661
   14          1           0        0.342791    3.466214    0.718208
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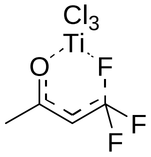
Ti-TS1



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4	22	0	-0.861987	0.054466	0.006038
5	6	0	2.210773	-1.013554	-0.060124
6	1	0	3.599777	0.489758	-0.748059
7	6	0	2.184129	2.808468	-0.013250
8	9	0	2.772863	-1.950467	-0.760439
9	9	0	0.600788	-1.032863	-0.727668
10	9	0	1.857943	-1.459834	1.123867
11	17	0	-1.694851	-0.105490	2.040147
12	17	0	-1.878313	1.679378	-1.093864
13	17	0	-2.104200	-1.634518	-0.893097
14	1	0	2.085607	3.290642	0.966686
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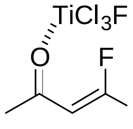
Ti-PD1



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4	22	0	1.230789	-0.285493	-0.029102
5	6	0	-3.483255	-0.577903	-0.047742
6	1	0	-3.792643	1.474079	0.116266
7	6	0	-1.265414	2.495498	0.162221
8	9	0	-4.751374	-0.875884	-0.049100
9	9	0	0.735823	-1.944845	-0.247012
10	9	0	-2.743938	-1.641022	-0.141820

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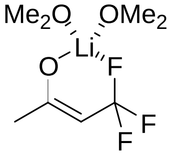
Li-CP1



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  14         8           0       -1.896684    1.650729   -0.345947
  15         6           0       -3.164990    1.461778   -0.965167
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  24         1           0       -2.893056   -2.940259    0.161893
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  26         1           0       -2.481976   -2.296606    2.487370
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  29         1           0        2.955095    1.891302    2.419956
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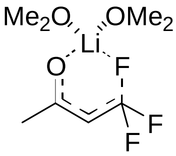
Li-TS1



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   27          1           0       -2.697283   -0.132932    2.074937
   28          1           0       -2.184009   -1.760732    2.615806
   29          1           0        3.511668    2.042758    1.851962
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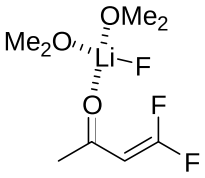
Li-PD1



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     20          1           0       -0.821216    3.027701    0.107857
     21          1           0       -2.524835    3.489588   -0.191309
     22          1           0       -1.458256    3.069625   -1.566275
     23          1           0       -0.936976   -2.506591   -0.850616
     24          1           0       -2.501075   -3.132309   -0.204674
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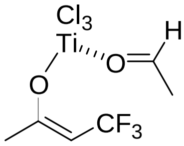
     26          1           0       -3.424584   -1.836365    1.729536
     27          1           0       -2.537275   -0.344403    2.159238
     28          1           0       -1.868983   -1.944708    2.605484
     29          1           0        3.424202    2.290921    1.746772
     30          1           0        1.927783    3.229190    1.490207
     31          1           0        3.096351    2.976078    0.154995
 ---------------------------------------------------------------------
```

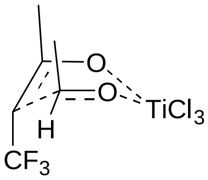
Ti-CP2



E_{sol}(B3LYP/631LAN) = -2122.34142883 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -2122.228621 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.121313	-0.873285	-0.569823
2	6	0	-1.093550	-1.740113	-0.936087
3	6	0	-2.359079	-1.549648	-0.524474
4	6	0	-0.367412	2.645876	-0.307607
5	8	0	0.325863	1.719975	-0.731393
6	22	0	1.288365	-0.035519	0.092491
7	1	0	-0.478057	2.786239	0.781285
8	6	0	-2.785110	-0.407380	0.334978
9	6	0	-1.065810	3.598010	-1.207710
10	1	0	-3.140197	-2.238135	-0.834213
11	6	0	-0.624793	-2.858836	-1.815887
12	9	0	-4.085672	-0.517928	0.668673
13	9	0	-2.639404	0.800840	-0.284994
14	9	0	-2.079728	-0.315804	1.490737
15	1	0	-0.864929	3.382239	-2.258876
16	1	0	-0.757069	4.621303	-0.953828
17	1	0	-2.143757	3.539617	-1.002461
18	17	0	2.927185	0.477664	-1.328116
19	17	0	1.147240	1.022200	2.060696
20	17	0	2.273185	-1.882172	0.951630
21	1	0	0.143646	-3.446866	-1.300731
22	1	0	-0.176097	-2.453581	-2.730784
23	1	0	-1.455587	-3.515104	-2.086073

Ti-TS2-*anti*

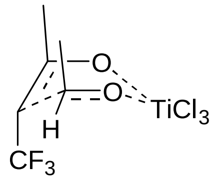


E_{sol}(B3LYP/631LAN) = -2122.32748756 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -2122.210891 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.151289	0.486965	-1.292199
2	6	0	-1.393376	0.856757	-1.252609
3	6	0	-2.291118	0.254623	-0.376317

```
    4          6           0       -1.219056    1.186457    1.413977
    5          8           0        0.012015    1.097889    1.077407
    6         22           0        1.215654    0.037918   -0.019244
    7          1           0       -1.648478    0.352804    1.978414
    8          6           0       -2.171885   -1.182079    0.028498
    9          6           0       -1.827109    2.540931    1.605801
   10          1           0       -3.321899    0.607200   -0.370447
   11          6           0       -1.756308    2.046157   -2.090148
   12          9           0       -2.498620   -2.022709   -0.970482
   13          9           0       -2.976669   -1.458851    1.071829
   14          9           0       -0.900733   -1.534529    0.419332
   15          1           0       -1.482822    3.249779    0.848224
   16          1           0       -1.498612    2.908446    2.589383
   17          1           0       -2.918627    2.485837    1.614927
   18         17           0        2.803884    1.508866   -0.413330
   19         17           0        1.933870   -0.971389    1.874498
   20         17           0        1.854495   -1.667423   -1.356830
   21          1           0       -1.610358    1.788204   -3.146648
   22          1           0       -1.085020    2.883716   -1.865942
   23          1           0       -2.795306    2.347786   -1.941265
---------------------------------------------------------------------
```

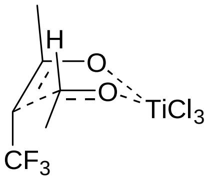
Ti-TS2-*anti’*



```
Optimized in the gas phase.
E(B3LYP/631LAN) =  -2122.31139572 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0       -0.120515    0.482466   -1.308342
    2          6           0       -1.342590    0.872066   -1.276903
    3          6           0       -2.267376    0.314686   -0.388398
    4          6           0       -1.184411    1.162315    1.393556
    5          8           0        0.038703    1.138386    1.041693
    6         22           0        1.276831    0.005468   -0.014505
    7          1           0       -1.574281    0.299122    1.939439
    8          6           0       -2.226997   -1.128937    0.009945
    9          6           0       -1.836022    2.490678    1.661536
   10          1           0       -3.281663    0.701007   -0.413851
   11          6           0       -1.679334    2.063425   -2.131751
   12          9           0       -2.628117   -1.943959   -0.983341
   13          9           0       -3.046182   -1.350611    1.064134
   14          9           0       -0.985581   -1.553124    0.385389
   15          1           0       -1.560939    3.228250    0.903229
   16          1           0       -1.467129    2.853772    2.630887
   17          1           0       -2.923075    2.397167    1.724888
   18         17           0        2.868152    1.457594   -0.385145
   19         17           0        1.861409   -0.983179    1.895108
```

```
     20         17           0        1.844456   -1.689660   -1.336285
     21          1           0       -1.502943    1.803446   -3.181939
     22          1           0       -1.006148    2.894272   -1.890593
     23          1           0       -2.718596    2.378840   -2.015807
 ---------------------------------------------------------------------
```

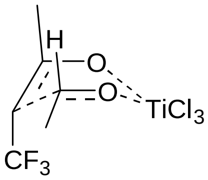
Ti-TS2-*syn*



E_{sol}(B3LYP/631LAN) = -2122.32255498 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -2122.206364 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          8           0        0.054576    1.314558    0.586048
      2          6           0        1.239447    1.703625    0.222385
      3          6           0        2.243499    0.773975   -0.015186
      4          6           0        1.128831    0.227256   -1.994251
      5          8           0       -0.075599    0.132057   -1.574488
      6          6           0        1.899475   -0.994896   -2.392926
      7          6           0        2.273196   -0.532109    0.717486
      8          1           0        1.395480    1.163599   -2.502532
      9          1           0        3.228830    1.129885   -0.311762
     10          6           0        1.406039    3.169710   -0.042902
     11          1           0        2.974024   -0.802979   -2.423666
     12          1           0        1.569673   -1.221484   -3.419054
     13          1           0        1.673302   -1.855314   -1.763402
     14          9           0        2.475102   -0.366646    2.040934
     15          9           0        3.252910   -1.329584    0.258292
     16          9           0        1.101832   -1.249478    0.609318
     17         22           0       -1.220195    0.010815   -0.013396
     18         17           0       -2.930659    1.221928   -0.686977
     19         17           0       -1.813056   -2.076591   -0.654679
     20         17           0       -1.770053   -0.347159    2.150984
     21          1           0        1.242724    3.716629    0.894107
     22          1           0        0.646579    3.512393   -0.755446
     23          1           0        2.404410    3.403382   -0.419122
 ---------------------------------------------------------------------
```

Ti-TS2-*syn'*

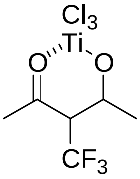


Optimized in the gas phase.

E(B3LYP/631LAN) = -2122.30579138 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0        0.048240    1.362973    0.463523
    2          6           0        1.213430    1.721712    0.055889
    3          6           0        2.230547    0.785919   -0.133884
    4          6           0        1.097888    0.026321   -1.998517
    5          8           0       -0.106255    0.027939   -1.594637
    6          6           0        1.822387   -1.263308   -2.273486
    7          6           0        2.323166   -0.433654    0.731602
    8          1           0        1.409271    0.887105   -2.604629
    9          1           0        3.200742    1.144866   -0.462145
   10          6           0        1.366088    3.166089   -0.334726
   11          1           0        2.902983   -1.121005   -2.336294
   12          1           0        1.464194   -1.600139   -3.257576
   13          1           0        1.578093   -2.034806   -1.544028
   14          9           0        2.587703   -0.123728    2.016949
   15          9           0        3.313504   -1.247699    0.308271
   16          9           0        1.176877   -1.179298    0.748790
   17         22           0       -1.272796   -0.010195    0.014199
   18         17           0       -2.975149    1.116001   -0.770865
   19         17           0       -1.757926   -2.135120   -0.452432
   20         17           0       -1.753216   -0.148634    2.178845
   21          1           0        1.202859    3.788496    0.552852
   22          1           0        0.593805    3.438235   -1.063105
   23          1           0        2.356839    3.384093   -0.740210
---------------------------------------------------------------------
```

Ti-PD2



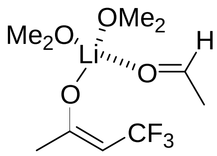
E_{sol}(B3LYP/631LAN) = -2122.36597483 a.u.

$G_{sol,-78}$(B3LYP/631LAN) = -2122.247462 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0       -0.201593    0.754337   -1.248512
    2          6           0       -1.382166    0.992084   -0.982682
    3          6           0       -1.979817    0.616040    0.377452
```

4	6	0	-0.970504	0.763880	1.540358
5	8	0	0.241673	0.071870	1.232568
6	22	0	1.441794	-0.124562	-0.041086
7	1	0	-1.387698	0.260765	2.421746
8	6	0	-2.594741	-0.790281	0.320074
9	6	0	-0.666227	2.220967	1.880967
10	1	0	-2.831735	1.282421	0.579224
11	6	0	-2.256472	1.676114	-1.983566
12	9	0	-3.530494	-0.864401	-0.651366
13	9	0	-3.191684	-1.090701	1.486437
14	9	0	-1.678312	-1.744758	0.068931
15	1	0	-0.249051	2.760503	1.023736
16	1	0	0.059990	2.258742	2.697833
17	1	0	-1.581317	2.727344	2.206473
18	17	0	2.489469	1.750382	-0.625683
19	17	0	3.088291	-1.040087	1.192022
20	17	0	1.252327	-1.787207	-1.525739
21	1	0	-3.200457	1.131203	-2.093334
22	1	0	-1.745140	1.767412	-2.943358
23	1	0	-2.512211	2.675762	-1.602709

Li-CP2

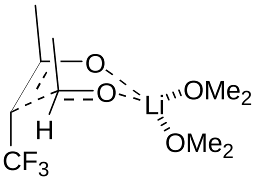


E_{sol}(B3LYP/631LAN) = -1001.12177142 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -1000.853309 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.158300	-0.817293	-1.251325
2	6	0	1.372231	-1.174093	-1.489255
3	6	0	2.502292	-0.606936	-0.936187
4	6	0	-0.223344	-1.856019	1.921921
5	8	0	-1.029967	-0.958463	1.716651
6	3	0	-0.903861	0.055447	-0.034653
7	1	0	0.557073	-2.065232	1.170527
8	6	0	2.444865	0.541899	-0.037912
9	6	0	-0.221528	-2.706488	3.153022
10	1	0	3.495720	-0.945884	-1.206644
11	6	0	1.546858	-2.331581	-2.463225
12	9	0	2.027938	1.732649	-0.608162
13	9	0	3.658233	0.822281	0.512636
14	9	0	1.577012	0.397097	1.034042
15	1	0	-1.027524	-2.421897	3.833482
16	1	0	0.750622	-2.612102	3.655953
17	1	0	-0.321489	-3.762347	2.866639
18	8	0	-1.107301	2.014482	0.347651
19	6	0	-0.502169	2.668083	1.460351

```
   20        6           0      -1.136488   2.837574  -0.816643
   21        8           0      -2.749733  -0.171910  -0.818604
   22        6           0      -3.934675   0.257994  -0.162550
   23        6           0      -2.968706  -1.251441  -1.722156
   24        1           0      -4.682545   0.598004  -0.892957
   25        1           0      -3.653344   1.088567   0.487215
   26        1           0      -4.367815  -0.553742   0.439410
   27        1           0      -1.986091  -1.522304  -2.109884
   28        1           0      -3.635800  -0.941405  -2.539104
   29        1           0      -3.418230  -2.109770  -1.201649
   30        1           0      -0.524059   1.965460   2.295321
   31        1           0      -1.068688   3.571430   1.725104
   32        1           0       0.536084   2.936233   1.234445
   33        1           0      -1.705203   3.757440  -0.622855
   34        1           0      -1.632377   2.260157  -1.599327
   35        1           0      -0.118195   3.095011  -1.132515
   36        1           0       1.113742  -2.061967  -3.434753
   37        1           0       0.990792  -3.204446  -2.099040
   38        1           0       2.593873  -2.614260  -2.611235
---------------------------------------------------------------------
```

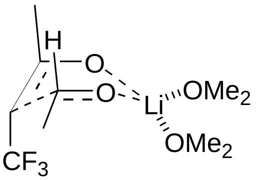
Li-TS2-*anti’*



```
Optimized in the gas phase.
E(B3LYP/631LAN) =  -1001.10531431 a.u.
Single point calculation in the presence of dielectricfield.
E(sol)(B3LYP/631LAN) =  -1001.11230417 a.u.
G(sol,-78)(B3LYP/631LAN) =  -1000.841955 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1        8           0       0.140581  -1.000143  -1.274157
    2        6           0       1.286584  -1.330464  -0.882525
    3        6           0       2.121504  -0.460637  -0.113616
    4        6           0       1.124625  -0.561817   1.731270
    5        8           0      -0.128729  -0.472545   1.536137
    6        3           0      -1.027327  -0.048316  -0.042079
    7        1           0       1.666460   0.340877   2.061991
    8        6           0       2.114883   0.996122  -0.418614
    9        6           0       1.681123  -1.844196   2.334111
   10        1           0       3.136439  -0.804203   0.071376
   11        6           0       1.739337  -2.759264  -1.129601
   12        9           0       2.586626   1.293506  -1.661222
   13        9           0       2.899098   1.684960   0.451802
   14        9           0       0.877378   1.572591  -0.356654
   15        1           0       1.295479  -2.724232   1.810243
   16        1           0       1.337180  -1.904720   3.375843
   17        1           0       2.775768  -1.864174   2.333669
```

18	8	0	-1.922748	1.771609	0.133635
19	6	0	-1.500474	2.580678	1.229368
20	6	0	-2.211200	2.524763	-1.036635
21	8	0	-2.771966	-1.038280	-0.376604
22	6	0	-3.845539	-0.859505	0.536466
23	6	0	-2.689248	-2.369476	-0.875398
24	1	0	-4.808815	-1.073891	0.051178
25	1	0	-3.818313	0.183745	0.853552
26	1	0	-3.730381	-1.516018	1.410844
27	1	0	-1.803385	-2.406597	-1.509063
28	1	0	-3.589322	-2.619573	-1.455214
29	1	0	-2.583055	-3.087389	-0.049227
30	1	0	-1.201368	1.893793	2.022159
31	1	0	-2.323964	3.225222	1.567932
32	1	0	-0.642560	3.203056	0.946390
33	1	0	-3.018289	3.246908	-0.847671
34	1	0	-2.532094	1.815416	-1.802911
35	1	0	-1.318878	3.061855	-1.385343
36	1	0	1.850117	-2.913630	-2.209834
37	1	0	0.966742	-3.454040	-0.780660
38	1	0	2.689617	-2.999327	-0.645400

Li-TS2-*syn*

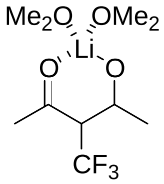


E_{sol}(B3LYP/631LAN) = -1001.11148263 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -1000.838563 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.023438	1.238498	-1.123268
2	6	0	-1.030482	1.702417	-0.616225
3	6	0	-2.037474	0.867988	-0.040940
4	6	0	-1.088062	0.618624	1.826990
5	8	0	0.130016	0.294359	1.640250
6	6	0	-2.020526	-0.372264	2.510932
7	6	0	-2.247554	-0.477585	-0.637569
8	1	0	-1.307495	1.665099	2.107938
9	1	0	-2.982972	1.344032	0.212889
10	6	0	-1.162177	3.208070	-0.481240
11	1	0	-3.067968	-0.060864	2.466120
12	1	0	-1.721194	-0.422669	3.567468
13	1	0	-1.915015	-1.371344	2.082255
14	9	0	-2.482233	-0.448740	-1.986909
15	9	0	-3.328703	-1.097589	-0.095348
16	9	0	-1.196933	-1.334561	-0.484891
17	3	0	1.064739	0.031458	0.023916
18	8	0	1.697498	-1.853379	-0.193204

```
   19          6           0        1.181255   -2.866966    0.666409
   20          6           0        2.178781   -2.363776   -1.431356
   21          8           0        2.907112    0.866376   -0.089596
   22          6           0        3.956155    0.380084    0.740048
   23          6           0        3.018211    2.262159   -0.353118
   24          1           0        0.771384   -2.353837    1.537330
   25          1           0        1.981751   -3.555591    0.969828
   26          1           0        0.385377   -3.434392    0.166655
   27          1           0        2.984142   -3.092414   -1.265107
   28          1           0        2.568702   -1.515640   -1.998558
   29          1           0        1.368794   -2.845138   -1.996517
   30          1           0        4.933041    0.533142    0.260525
   31          1           0        3.779141   -0.687138    0.880706
   32          1           0        3.952355    0.889045    1.714626
   33          1           0        2.154283    2.531349   -0.961194
   34          1           0        3.948782    2.479199   -0.895923
   35          1           0        3.007395    2.837528    0.583805
   36          1           0       -1.085591    3.666726   -1.474112
   37          1           0       -0.326920    3.591476    0.117524
   38          1           0       -2.104666    3.515728   -0.020712
---------------------------------------------------------------------
```

Li-PD2

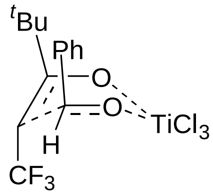


E_{sol}(B3LYP/631LAN) = -1001.12119184 a.u.
$G_{sol,-78}$(B3LYP/631LAN) = -1000.846021 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0        0.232731   -0.982792   -1.273450
    2          6           0        1.393734   -1.196384   -0.915869
    3          6           0        2.023561   -0.396471    0.197521
    4          6           0        1.230537   -0.642943    1.594133
    5          8           0       -0.039396   -0.191598    1.575066
    6          3           0       -1.015398   -0.041850    0.052059
    7          1           0        1.881482   -0.089895    2.308158
    8          6           0        2.083375    1.079155   -0.146919
    9          6           0        1.346739   -2.140725    1.958473
   10          1           0        3.068158   -0.701730    0.335146
   11          6           0        2.206857   -2.302637   -1.538894
   12          9           0        2.943525    1.295879   -1.183101
   13          9           0        2.533426    1.823983    0.886437
   14          9           0        0.899017    1.609849   -0.534382
   15          1           0        0.761158   -2.754252    1.262210
   16          1           0        0.921147   -2.288284    2.957465
   17          1           0        2.383874   -2.503424    1.972333
   18          8           0       -2.007495    1.703732   -0.079205
   19          6           0       -1.585908    2.762835    0.775855
```

```
  20         6           0       -2.789478    2.146532   -1.180193
  21         8           0       -2.683304   -1.176037   -0.261891
  22         6           0       -3.669466   -1.034946    0.756709
  23         6           0       -2.561441   -2.521618   -0.712565
  24         1           0       -4.659957   -1.325111    0.379435
  25         1           0       -3.677621    0.017714    1.043677
  26         1           0       -3.420522   -1.654260    1.629860
  27         1           0       -1.775145   -2.533764   -1.467785
  28         1           0       -3.507956   -2.868740   -1.149949
  29         1           0       -2.283891   -3.187838    0.116800
  30         1           0       -0.940298    2.306496    1.527841
  31         1           0       -2.453971    3.240519    1.251197
  32         1           0       -1.021831    3.518531    0.212657
  33         1           0       -3.696532    2.661560   -0.833668
  34         1           0       -3.071417    1.258252   -1.749326
  35         1           0       -2.214057    2.830335   -1.820340
  36         1           0        3.072558   -1.870385   -2.058311
  37         1           0        1.601423   -2.874035   -2.246036
  38         1           0        2.604530   -2.966762   -0.761804
---------------------------------------------------------------------
```

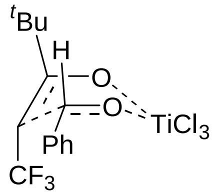
Ti-TS3-*anti'*



```
Optimized in the gas phase.
E(B3LYP/631LAN) =  -2431.98683106 a.u.
G(B3LYP/631LAN) =  -2431.760967 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1         8           0        0.897642    0.855532    0.770506
   2         6           0       -0.222301    1.419230    0.510840
   3         6           0       -0.737464    1.380401   -0.799653
   4         6           0       -0.946813   -0.802637   -0.902069
   5         8           0        0.024712   -1.234682   -0.178255
   6        22           0        1.876504   -0.772536    0.241333
   7         1           0       -0.763846   -0.700969   -1.973630
   8         6           0        0.156946    1.559116   -1.988506
   9         6           0       -2.340503   -1.111576   -0.522300
  10         1           0       -1.708883    1.828065   -0.972242
  11         6           0       -0.953782    2.045130    1.702142
  12         9           0        0.648299    2.810864   -2.075003
  13         9           0       -0.529778    1.321191   -3.132495
  14         9           0        1.231715    0.718850   -2.000228
  15         6           0       -2.633318   -1.765421    0.684173
  16         6           0       -3.954224   -2.077468    1.000907
  17         6           0       -4.986642   -1.738854    0.120925
  18        17           0        2.126654   -1.844803    2.135235
```

```
    19         17           0        2.530186   -2.233562   -1.313544
    20         17           0        3.717800    0.483603    0.139483
    21          6           0       -0.995382    1.041801    2.875579
    22          6           0       -2.382514    2.499013    1.354734
    23          6           0       -0.104254    3.279702    2.107010
    24          6           0       -4.697563   -1.094656   -1.086222
    25          6           0       -3.378700   -0.786389   -1.409865
    26          1           0       -1.820562   -2.042162    1.348037
    27          1           0       -4.178976   -2.591777    1.930854
    28          1           0       -6.014960   -1.984122    0.371232
    29          1           0       -5.498207   -0.840882   -1.774851
    30          1           0       -3.145717   -0.289775   -2.349219
    31          1           0        0.005674    0.689709    3.136222
    32          1           0       -1.615147    0.171943    2.633137
    33          1           0       -1.430515    1.529722    3.754689
    34          1           0       -2.851221    2.921168    2.249914
    35          1           0       -3.007711    1.664615    1.017837
    36          1           0       -2.392366    3.278095    0.584269
    37          1           0       -0.571608    3.773829    2.966083
    38          1           0       -0.041006    4.006598    1.289128
    39          1           0        0.911216    2.983389    2.384626
 ---------------------------------------------------------------------
```

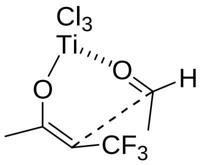
Ti-TS3-*syn'*



```
Optimized in the gas phase.
E(B3LYP/631LAN) =  -2431.98036301 a.u.
G(B3LYP/631LAN) =  -2431.754479 a.u.
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
     1          8           0       -1.545264    0.688230    0.183883
     2          6           0       -0.753648    1.698302    0.165911
     3          6           0        0.564898    1.553824    0.624072
     4          6           0        1.081218    0.284637   -1.149590
     5          8           0        0.145883   -0.596818   -1.125597
     6          6           0        2.483440   -0.070961   -0.867576
     7          6           0        0.864128    0.666705    1.796068
     8          1           0        0.949175    1.117144   -1.850088
     9          1           0        1.222625    2.413395    0.591557
    10          6           0       -1.318553    2.980152   -0.452796
    11          6           0        2.828458   -1.344640   -0.385713
    12          6           0        4.168966   -1.665058   -0.187603
    13          6           0        5.167532   -0.726042   -0.462373
    14          9           0        0.261874    1.113051    2.921015
    15          9           0        2.184953    0.622563    2.045130
    16          9           0        0.445028   -0.626590    1.635804
```

```
   17         22            0      -1.452502   -1.237218   -0.205570
   18         17            0      -2.827033   -1.434641   -1.900999
   19         17            0      -0.522460   -3.271852   -0.056859
   20         17            0      -2.813870   -1.528447    1.539461
   21          6            0      -1.903875    2.660801   -1.847238
   22          6            0      -0.270368    4.099889   -0.568766
   23          6            0      -2.459957    3.441786    0.491412
   24          6            0       4.827999    0.540251   -0.949903
   25          6            0       3.491230    0.865232   -1.155397
   26          1            0       2.049305   -2.073398   -0.190871
   27          1            0       4.436439   -2.652075    0.178063
   28          1            0       6.211411   -0.982976   -0.305291
   29          1            0       5.604327    1.266135   -1.173473
   30          1            0       3.222261    1.846174   -1.541696
   31          1            0      -2.642987    1.857623   -1.795308
   32          1            0      -1.121479    2.358593   -2.553984
   33          1            0      -2.390443    3.554652   -2.252699
   34          1            0      -0.736746    4.985524   -1.012838
   35          1            0       0.568891    3.815427   -1.215028
   36          1            0       0.128612    4.394412    0.408089
   37          1            0      -2.918983    4.350846    0.087204
   38          1            0      -2.080328    3.668289    1.494202
   39          1            0      -3.230305    2.671206    0.580553
---------------------------------------------------------------------
```

Ti-INT'



```
Structure in the gas phase.
E(B3LYP/631LAN) =  -2432.00332164000 a.u.
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
    1          8            0      -1.373033    0.468745   -0.519521
    2          6            0      -1.016155    1.732327   -0.277324
    3          6            0      -0.706748    2.179720    0.960847
    4          6            0       1.691522   -0.578051    0.566808
    5          8            0       0.805936   -0.913003   -0.228412
    6         22            0      -1.324389   -1.332441   -0.258009
    7          1            0       1.436596   -0.391197    1.618616
    8          6            0      -0.791429    1.434846    2.244043
    9          6            0       3.088420   -0.423838    0.183564
   10          1            0      -0.442317    3.218883    1.105408
   11          6            0      -1.004483    2.604652   -1.536323
   12          9            0      -1.727809    1.950574    3.065303
   13          9            0       0.391362    1.502311    2.926832
   14          9            0      -1.065302    0.107855    2.118017
   15          6            0       3.510331   -0.685658   -1.134452
   16          6            0       4.851159   -0.538587   -1.467318
```

```
  17          6           0        5.773280   -0.132460   -0.493332
  18         17           0       -1.223401   -2.212243   -2.269767
  19         17           0       -0.678844   -2.944576    1.179385
  20         17           0       -3.481090   -1.522916    0.240730
  21          6           0       -0.048785    1.968406   -2.573412
  22          6           0       -0.548472    4.043999   -1.242064
  23          6           0       -2.443070    2.629860   -2.107346
  24          6           0        5.359358    0.128033    0.816428
  25          6           0        4.017484   -0.018246    1.157157
  26          1           0        2.778501   -1.005699   -1.869265
  27          1           0        5.185041   -0.741088   -2.480538
  28          1           0        6.821322   -0.021455   -0.757624
  29          1           0        6.080878    0.441279    1.564835
  30          1           0        3.681518    0.182605    2.171455
  31          1           0       -0.361937    0.954717   -2.837709
  32          1           0        0.977428    1.924048   -2.189674
  33          1           0       -0.041721    2.572552   -3.487811
  34          1           0       -0.562546    4.625618   -2.169922
  35          1           0        0.473718    4.075101   -0.847033
  36          1           0       -1.212364    4.544788   -0.528938
  37          1           0       -2.462700    3.217419   -3.032464
  38          1           0       -3.141189    3.088140   -1.397666
  39          1           0       -2.798936    1.620885   -2.332936
---------------------------------------------------------------------
```

Tabulated data of the IRC analysis of Ti-TS3-*anti’* (Figure 3-9).

	C^3-C^4 (Å)	F^{14}-Ti^6 (Å)	Ti^6-O^1-C^2 (º)	F^{14}-C^8-C^3-C^2 (º)	E (kcal/mol)
CP	4.51537	3.49253	176.261	-50.120	0.00000000000
	4.71981	3.69473	179.929	-62.263	0.39525597487
	4.63230	3.46819	174.893	-52.267	0.19437440010
	4.59380	3.42873	173.979	-50.454	0.17848610005
	4.58870	3.42393	173.867	-50.232	0.17833549993
	4.48863	3.32693	169.077	-44.961	0.45227062487
	4.47010	3.26835	169.604	-42.578	0.28978577510
	4.40647	3.18169	167.762	-38.293	0.36350447508
	4.39687	3.19215	165.140	-40.205	0.61920444997
	4.36959	3.16473	165.356	-37.906	0.49992925009
	4.22723	2.97152	161.212	-28.510	0.64266667510
	4.19270	2.93050	160.303	-26.259	0.69351299999
	4.16689	2.89447	159.787	-23.766	0.73854240004
	4.14984	2.87034	159.586	-24.703	0.86965225004
	4.07606	2.81648	157.876	-17.240	1.07240377501
	3.98912	2.88128	156.565	-5.535	2.15022915004

	3.94326	2.83462	156.440	-6.144	1.69837267506
INT	3.67590	2.79053	154.560	8.212	2.34967374988
	3.61422	2.78826	154.027	12.332	2.56639342495
	3.59516	2.76981	153.841	14.268	2.71192322511
	3.57300	2.78583	153.439	17.085	2.85860762505
	3.56267	2.74336	153.059	18.763	3.01020534996
	3.55587	2.78193	152.635	21.663	3.24605122507
	3.47191	2.72835	151.306	25.041	3.59305245005
	3.38317	2.76838	149.946	28.713	4.20524772495
	3.21907	2.74613	148.347	33.079	4.76957730012
	3.05358	2.73071	146.751	37.430	6.01444317497
	2.93013	2.74940	145.214	39.246	6.84145680007
	2.80739	2.78046	143.689	41.038	8.30684500000
	2.75931	2.81260	142.727	41.362	9.36692467493
IRC	2.53713	2.75331	141.388	41.338	10.27037407510
↓	2.52357	2.75401	141.231	41.801	10.41924844999
	2.50982	2.75473	141.072	42.271	10.56856207509
	2.49594	2.75544	140.915	42.746	10.71710387508
	2.48182	2.75615	140.756	43.230	10.86555154991
	2.46746	2.75687	140.597	43.721	11.01324622501
	2.45291	2.75759	140.437	44.221	11.16019417502
	2.43856	2.75830	140.280	44.710	11.30337712489
	2.42344	2.75902	140.120	45.230	11.44625259987
	2.40821	2.75973	139.961	45.752	11.58634197493
	2.39278	2.76045	139.802	46.282	11.72276674993
	2.37712	2.76116	139.644	46.818	11.85469862508
	2.36125	2.76187	139.486	47.363	11.98130930000
	2.34519	2.76257	139.331	47.913	12.10143162505
	2.32892	2.76326	139.175	48.470	12.21422475000
	2.31243	2.76395	139.022	49.032	12.31850270011
	2.29584	2.76464	138.869	49.600	12.41323637514
	2.27933	2.76530	138.720	50.161	12.49508120008
	2.26263	2.76595	138.583	50.735	12.56425679988
	2.24749	2.76663	138.431	51.230	12.61887440012
TS	2.19544	2.76850	138.006	52.989	12.69751270001
	2.14340	2.77038	137.579	54.702	12.60587260008

	2.12546	2.77097	137.454	55.310	12.53292572493
	2.10797	2.77158	137.310	55.876	12.43567577497
	2.09131	2.77214	137.181	56.414	12.32160254986
	2.07373	2.77274	137.044	56.982	12.17686339990
	2.05665	2.77331	136.911	57.527	12.01285372498
	2.03913	2.77390	136.775	58.084	11.81890602493
	2.02112	2.77450	136.634	58.651	11.59330722489
	2.00275	2.77512	136.488	59.227	11.33618282494
	1.98439	2.77573	136.341	59.794	11.05225790007
	1.96602	2.77635	136.191	60.358	10.74190267506
	1.94766	2.77697	136.039	60.915	10.40657294993
	1.92932	2.77759	135.885	61.467	10.04811985007
	1.91113	2.77842	135.722	62.008	9.66887140012
	1.89295	2.77888	135.558	62.543	9.27088580001
	1.87487	2.77954	135.390	63.069	8.85710602499
	1.85690	2.78021	135.215	63.584	8.43084527513
↑	1.83901	2.78089	135.037	61.092	7.99574932512
	1.82159	2.78163	134.842	64.578	7.55545767497
IRC	1.80421	2.78236	134.646	65.056	7.11421222493
	1.80421	2.78236	134.646	65.056	7.11421850014
	1.69492	2.75001	133.837	65.042	5.41112075011
	1.67049	2.77223	133.209	65.317	4.71654727492
	1.63349	2.79877	132.569	65.814	3.95410967505
	1.62487	2.83003	132.257	66.639	2.66770330006
	1.61741	2.86097	131.964	67.399	2.05163635001
	1.59080	2.89170	131.212	68.515	0.98420237495
	1.58761	2.99589	131.187	70.463	-2.42838107490
	1.58714	3.00157	130.301	67.705	-3.53801442498
	1.58612	3.04520	131.105	69.289	-1.51794132503
	1.58505	2.96009	131.218	69.586	-2.61770410006
	1.58497	2.97264	131.249	69.757	0.16797547492
	1.58381	2.91617	131.257	68.498	-2.34208099999
	1.58295	2.90252	131.276	67.213	-3.19585750014
	1.58197	2.96789	131.520	68.312	-2.88407157513
	1.57938	2.91987	131.345	67.523	-3.25239525004
	1.57837	2.93380	131.398	67.761	-3.21780117506

	1.57647	3.09441	130.597	69.415	-4.23568147498
	1.57587	3.25928	132.639	66.907	-4.94084087508
	1.57524	2.98656	130.656	67.442	-3.73312927495
	1.57450	3.04761	130.745	70.677	-0.55292790004
	1.57210	3.31483	132.938	70.062	-5.13736132503
	1.56996	3.34716	132.737	70.924	-5.22653535007
	1.56893	2.97077	131.047	67.148	-3.54411372496
	1.56787	3.36010	132.350	71.397	-5.27590704986
	1.56685	3.40184	132.243	72.613	-5.29626942496
	1.56585	3.39293	132.137	71.726	-5.32179612495
	1.56584	3.39531	132.124	72.342	-5.30921475003
	1.56567	3.38410	132.135	71.570	-5.33604664991
	1.56564	3.38900	132.159	71.658	-5.32957712513
	1.56502	3.38430	132.154	71.527	-5.33309112506
	1.56502	3.38016	132.104	71.573	-5.33971124997
	1.56492	3.38936	132.102	71.936	-5.31705850012
	1.56464	3.38890	132.130	71.652	-5.32528502486
	1.56447	3.26628	132.792	66.906	-5.01381912490
	1.56402	3.19766	131.809	69.265	-4.74863134991
	1.56330	2.98345	130.297	68.426	-4.00935477493
	1.56106	3.11473	130.788	70.028	-4.45256430003
	1.53542	3.28382	133.180	66.903	-4.53602180004
PD	1.56390	3.40892	132.398	71.553	-5.39451709993

For the experimental procedure and the physical data of the product, see the experimental section of Chapter 2.

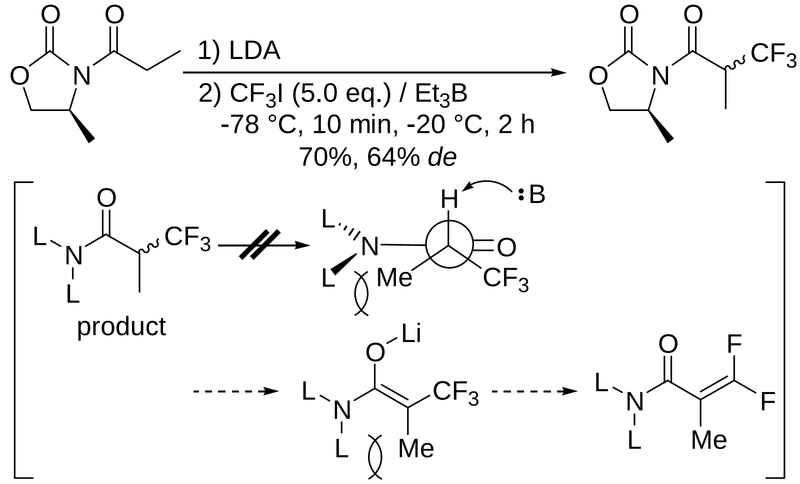
Chapter 4

Radical Trifluoromethylation of Ti Ate Enolate

4-1. Introduction.

The α-CF_3 carbonyl compounds are one of the most useful synthetic intermediates for functionalization with CF_3. Radical trifluoromethylation of enolates is, in principle, one of the simplest ways to introduce a CF_3 unit at the α position of a carbonyl group. However, there are only limited examples especially in the case of ketones.[1,2,3,4,5] It has been reported that the synthetic difficulty is due to the defluorination of the α-CF_3 ketone product by the parent enolate or a base during the reaction.[6]

Scheme 4-1.



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(1) Trifluoromethylation of lithium enolate of hindered imides (only exception for the use of Li enolate): (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169-2170. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961-974. They have succeeded in trifluoromethylation by adopting Evans oxazolidinones with bulky substituent at α position to suppress defluorination.

(2) Perfluoroalkylation of silyl and germyl enolates of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391-6394. (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553. Perfluoroalkylation of silyl enol ethers provided the products in good yields except for trifluoromethylation. Trifluoromethylation of ketone germyl enolates proceeds in good yield.

(3) Trifluoromethylation of enamines: (a) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365-1371. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.

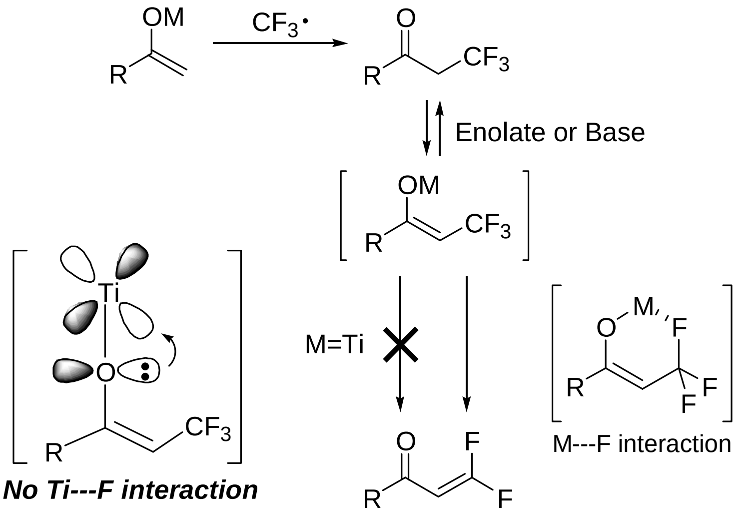
(4) Trifluoromethylation of enol acetates: Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291-1294.

(5) There are some reports of trifluoromethylation using CF_3^+: (a) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 115-118. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164. (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692-5699.

(6) M-F interaction plays an important role in defluorination of α-CF_3 carbonyl compounds. (a) Schlosser, M. In *Organometallics in Synthesis-A Manual*; Schlosser, M. Ed.; John Wiley & Sons: Chichester, 1994; p 1-166. (b) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425-3468. (c) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363-3384.

Indeed, the only example of the radical trifluoromethylation of metal enolate[1] was achieved by introducing bulky substituent on α position to carbonyl group and oxazolidinone moiety to suppress defluorination by the parent Li enolate (Scheme 4-1). To avoid the defluorination reaction of the α-CF_3 ketone products, less reactive enolate equivalents such as silyl or germyl enol ethers have been used for radical trifluoromethylation.[2] In Chapter 2 and 3, the author has reported the efficient generation of Ti enolates of α-CF_3 ketones and their aldol reactions in high chemical yields.[7] The stability of the Ti enolates of α-CF_3 ketones stems from the linearity of Ti-O-C bonds caused by the donation of the lone electron pair of the oxygen to the empty d-orbital of Ti to suppress the unfavorable Ti-F interaction and, hence, the successive defluorination. On the basis of the fact that Ti enolates of α-CF_3 ketones are stable to defluorination, the author reports here that Ti ate enolates can be applied to the radical trifluoromethylation for the synthesis of α-CF_3 ketones.[8]

Scheme 4-2.



4-2. Radical trifluoromethylation of Ti enolates.

First, several Ti enolates of cyclohexanone (**1a**) were reacted with a CF_3 radical, which was generated by CF_3I (ca. 5 eq.) and Et_3B[9] (1.0 eq.). The reaction was carried out at -78 ˚C for 2 h. The yields were determined by ^{19}F NMR analyses using BTF as an internal standard (Figure 4-1). In the case of the $TiCl_3$ enolate (formed by $TiCl_4$ and Et_3N in CH_2Cl_2 at -78 ˚C), no α-CF_3 ketone (**3a**) was obtained. In the case of the

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(7) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174-13175.
(8) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649-651. (b) Itoh, Y.; Mikami, K. *J. Fluorine Chem.* In press.
(9) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547-2549.

Ti(O^{i}Pr)$_3$ enolate (formed by the addition of Ti(O^{i}Pr)$_3$Cl to the corresponding Li enolate in THF at -78 ˚C), the α-CF$_3$ ketone (**3a**) was formed, however, in low yield (23%). In order to increase the reactivity of the enolate, Ti ate[10,11] enolate was examined. Ti ate enolates could be easily formed just by adding Ti(O^{i}Pr)$_4$ to Li enolate at low temperature.[10] Upon treatment of Ti ate enolate (**2a**) with the CF$_3$ radical, the α-CF$_3$ ketone (**3a**) was obtained in an increased yield (56%).

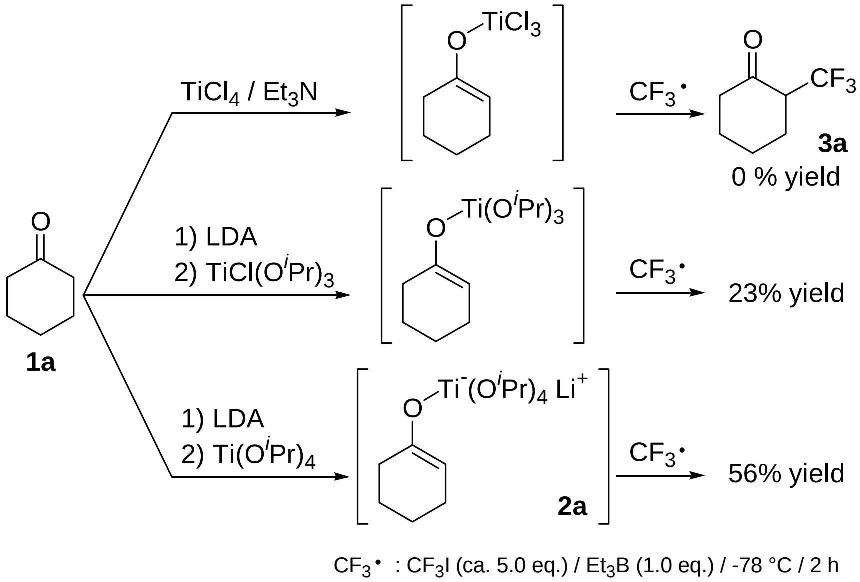

Figure 4-1. Trifluoromethyation of various Ti enolates.

Therefore, the radical trifluoromethylation of Ti ate enolates was further investigated and the use of excess amounts of LDA and Ti(O^{i}Pr)$_4$ was found to be important in increasing the yield (Table 4-1). When the enolate (**2a**) was formed by 1.0 eq. of LDA and 1.0 eq. of Ti(O^{i}Pr)$_4$, the product (**3a**) was formed in 56% yield (entry 1).

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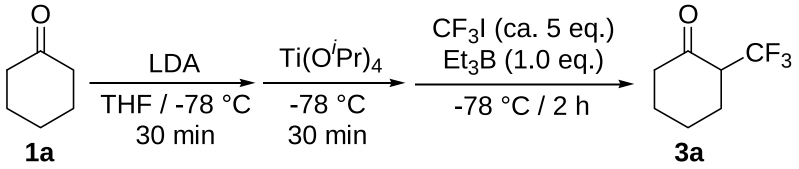
(10) Some reactions involving titanium ate enolates: (a) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722-5728. (b) Bernardi, A.; Cavicchioli, M.; Marchionni, C.; Potenza, D.; Scolastico, C. *J. Org. Chem.* **1994**, *59*, 3690-3694. (c) Yachi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **1999**, *121*, 9465-9466. (d) Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2000**, *41*, 4415-4418.

(11) Some reactions involving other titanium ate complexes: (a) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259-5262. (b) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421-1440. (c) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441-1454. (d) Takahashi, H.; Kawabata, A.; Niwa, H.; Higashiyama, K. *Chem. Pharm. Bull.* **1988**, *36*, 803-806. (e) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1988**, 238-240. (f) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 260-265. (g) Bernardi, A.; Cavicchioli, M.; Scolastico, C. *Tetrahedron* **1993**, *49*, 10913-10916. (h) Bernardi, A.; Marchionni, C.; Pilati, T.; Scolastico, C. *Tetrahedron Lett.* **1994**, *35*, 6357-6360. (i) Mahrwald, R. *Tetrahedron* **1995**, *51*, 9015-9022.

When 1.6 eq. of LDA and 1.6 eq. of Ti(O^{i}Pr)$_4$ were used, the yield increased up to 81% (entry 3). Using 1.0 eq. of LDA and 1.6 eq. of Ti(O^{i}Pr)$_4$ gave the α-CF$_3$ ketone (**3a**) in almost the same yield as in entry 1 (52%, entry 5). Therefore, both LDA and Ti(O^{i}Pr)$_4$ should be used in excess amounts.

Table 4-1. Trifluoromethylation of Ti ate enolates.



entry	LDA (eq.)	Ti(O^{i}Pr)$_4$ (eq.)	yield (%)^a
1	1.0	1.0	56
2	1.3	1.3	72
3	1.6	1.6	81
4	2.0	2.0	80
5	1.0	1.6	52

^{a} Determined by ^{19}F NMR using BTF as an internal standard.

4-3. Investigation of the effect of amine.

The Ti ate enolate is prepared from the parent Li enolate. When LDA was used for the preparation of the Li enolate, 1 eq. of ^{i}Pr$_2$NH was formed simultaneously. In order to investigate the effect of ^{i}Pr$_2$NH, ^{n}BuLi was added to the corresponding silyl enol ether.[12] By this silyl-to-lithium transmetallation method, Li enolate could be generated without formation of ^{i}Pr$_2$NH and the amount of ^{i}Pr$_2$NH could be controlled (Table 4-2). When the reaction was carried out without the addition of ^{i}Pr$_2$NH, the yields did not change significantly by increasing the amount of ^{n}BuLi and/or Ti(O^{i}Pr)$_4$ (entries 1~3). On the contrary, when three reagents (^{n}BuLi, ^{i}Pr$_2$NH, and Ti(O^{i}Pr)$_4$) were used in 1.0 eq. each, the yield was decreased (entry 4 (vs. entry 1)). In the case that the three reagents were used in 1.6 eq. each, the yield was significantly increased (entry 5). Although the yields of entries 4 and 5 in Table 4-2 were slightly decreased compared to those in entries 1 and 3 in Table 4-1, a similar tendency was observed in the relationship of the yields and the amounts of the reagents.

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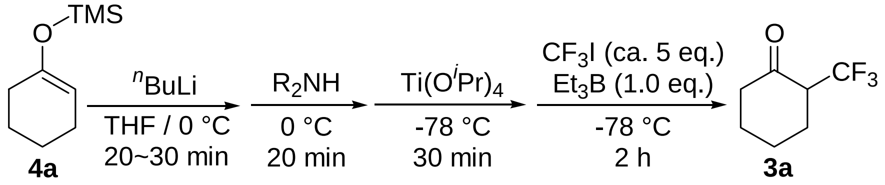
(12) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462-4464. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464-4465.

Table 4-2. Trifluoromethylation of Ti ate enolates starting from the silyl enol ether.



entry	^{n}BuLi (eq.)	R_2NH (eq.)	Ti(O^{i}Pr)$_4$	yield (%)
1	1.0	-	1.0	63
2	1.0	-	1.6	62
3	1.6	-	1.6	68
4	1.0	$^{i}\text{Pr}_2\text{NH}$ (1.0)	1.0	49
5	1.6	(1.6)	1.6	74
6	1.0	2,2,6,6-tetramethylpiperidine (1.0)	1.0	57
7	1.6	(1.6)	1.6	72
8	1.0	Et_2NH (1.0)	1.0	6
9	1.6	(1.6)	1.6	11

[a] Determined by ^{19}F NMR using BTF as an internal standard.

From these results, the effect of $^{i}\text{Pr}_2\text{NH}$ could be rationalized as follows (Scheme 4-3); $^{i}\text{Pr}_2\text{NH}$, which is formed from LDA in the preparation of the Ti ate enolate (**2a**), would exchange with $^{-}$O^{i}Pr ligand to form ^{i}PrOH. ^{i}PrOH could protonate the enolate to form the parent ketone and the Ti amide complex (LDA/Ti(O^{i}Pr)$_4$).[13] This mechanism rationalizes not only the decrease in yield upon addition of $^{i}\text{Pr}_2\text{NH}$ (Table 4-2, entry 4) (protonation of the enolate to reduce the amount of the reactive enolate species) but also the increase in yield using excess amount of LDA and Ti(O^{i}Pr)$_4$ (the equilibrium shifts to the Ti ate enolate). In order to support the proposal, 2,2,6,6-tetramethylpiperidine and Et_2NH were investigated. 2,2,6,6-Tetramethyl- piperidine is more bulky than $^{i}\text{Pr}_2\text{NH}$ and its coordinating ability is lower than $^{i}\text{Pr}_2\text{NH}$. Thus it could be expected that the equilibrium (Scheme 4-3) would shift to the Ti ate enolate (**2a**). In fact, when 2,2,6,6-tetramethylpiperidine was used in 1.0 eq. (entry 6), the decrease in the yield was not significant relative to $^{i}\text{Pr}_2\text{NH}$ (entry 4), and, when 2,2,6,6-tetramethylpiperidine was used in 1.6 eq. (entry 7), the yield was increased as the case with $^{i}\text{Pr}_2\text{NH}$ (entry 5). On the other hand, Et_2NH is less bulky than $^{i}\text{Pr}_2\text{NH}$ and its coordination ability is higher than $^{i}\text{Pr}_2\text{NH}$. Thus it could be expected that the equilibrium (Scheme 4-3) would shift to the ketone (**1a**). In fact, when Et_2NH was used in 1.0 eq. (entry 8) and 1.6 eq. (entry 9),

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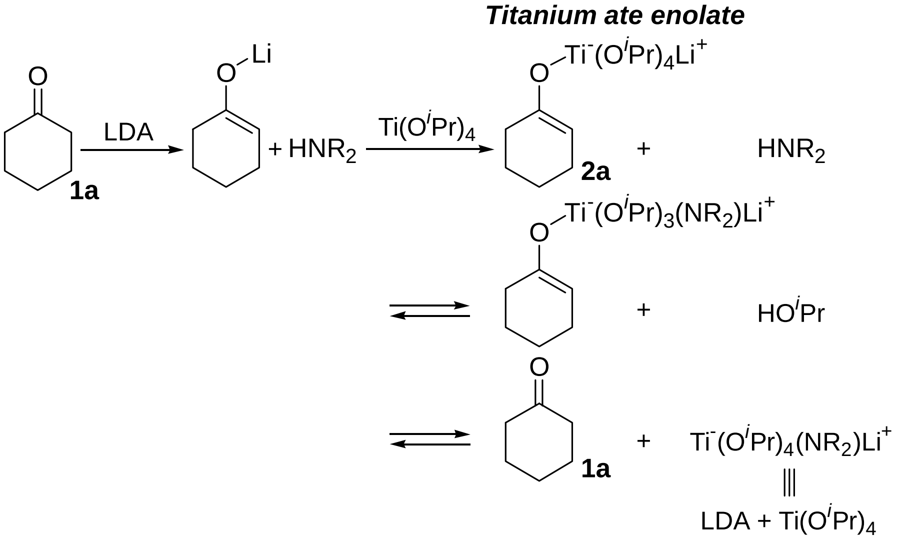
(13) NMR study of a Ti ate enolate (ref. 10-(b)) showed that the ketone was formed in the generation of the Ti ate enolate (although this is only mentioned in the foot note of Figure 2 of the literature). This fact also supports the proposed mechanism.

the yield was decreased. It should be noted that the LDA/Ti(O^{i}Pr)$_4$ complex, which might act as a base, works not for the decomposition of the α-CF_3 ketone product but for increasing the yield.

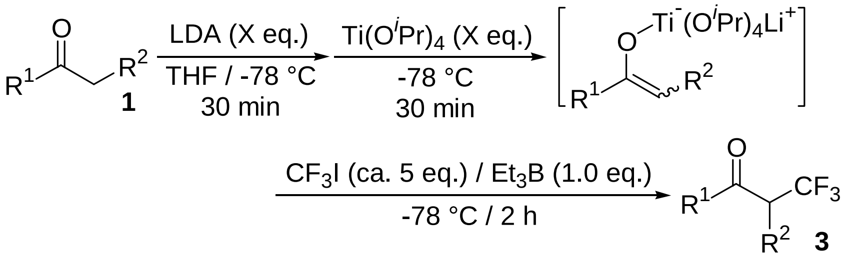
Scheme 4-3.

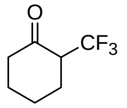
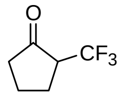
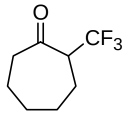
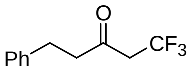
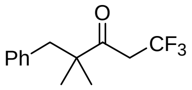
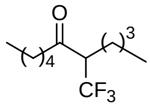
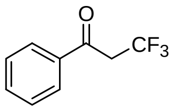
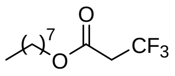
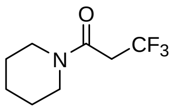


4-4. Radical trifluoromethylation of various substrates.

Several ketonic substrates were investigated (Table 4-3). Although cyclohexanone gave the α-CF_3 product (**3a**) in 81% yield under LDA=Ti(O^{i}Pr)$_4$=1.6 eq. condition (entry 2), cyclopentanone gave poor yield (**3b**) for both LDA=Ti(O^{i}Pr)$_4$=1.0 and 1.6 eq. conditions (38% in entry 3 and 33% in entry 4). In the case of cycloheptanone, the α-CF_3 product (**3c**) was obtained in good yield (61%) by LDA=Ti(O^{i}Pr)$_4$=1.6 eq. condition (entry 6). For acyclic substrates, **1e** and **1f** gave the products in good yield (65% in entry 10 and 64% in entry 12). The yield of **3d** was poor in the case that LDA=Ti(O^{i}Pr)$_4$=1.6 eq. (entry 8, 14%). Interestingly however, when the number of equivalents were decreased (LDA=Ti(O^{i}Pr)$_4$=1.0 eq.), the yield increased (38%, entry 7) than that in 1.6 eq. condition for this acyclic substrate. When acetophenone (**1g**) (entry 13), ester (**1h**) (entry 14), and amide (**1i**) (entry 15) were used as substrates, the α-CF_3 products were not obtained at all. The reaction of acetophenone (**1g**) and ester (**1h**) resulted in a complex mixture. For acetophenone (**1g**), it is probably due to the high acidity of α-proton of the α-CF_3 product, which might lead to the decomposition (Scheme 4-2). For ester **1h**, the Claisen condensation might be the reason for the complex mixture. The reaction of the amide **1i** gave the self-coupling product of the amide enolate.

Table 4-3. Trifluoromethylation of various substrates.

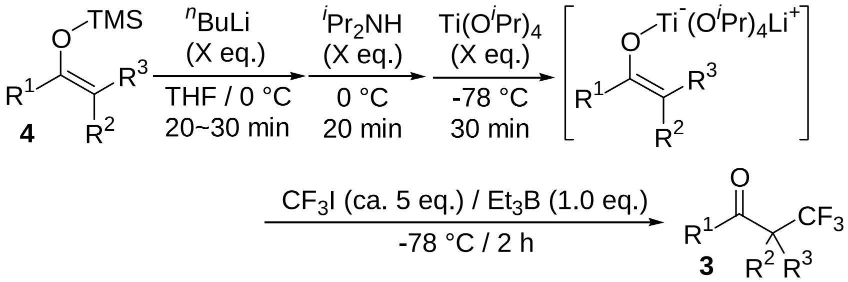


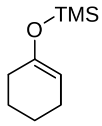
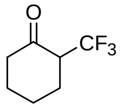
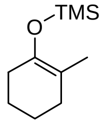
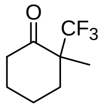
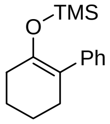
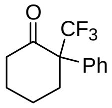
entry	product	X (eq.)	yield (%)[a]
1	 **3a**	1.0	63
2		1.6	81
3	 **3b**	1.0	38
4		1.6	33
5	 **3c**	1.0	49
6		1.6	61
7	 **3d**	1.0	38
8		1.6	14
9	 **3e**	1.0	(50)
10		1.6	69 (65)
11	 **3f**	1.0	32
12		1.6	64
13	 **3g**	1.3	-
14	 **3h**	1.0	-
15	 **3i**	1.3	-

[a] Determined by ^{19}F NMR using BTF as an internal standard. The numbers in parentheses refer to the yields of the isolated products.

Although LDA could generate only the kinetic Li enolate, the thermodynamic enolate could also be prepared from silyl enol ethers. Therefore, the thermodynamic Ti ate enolate of an α-substituted ketone could be generated by the silyl-to-lithium transmetallation method to obtain a quaternary carbon center attached to the CF_3 substituent. In the case of α-Me (**4j**) and α-Ph (**4k**) substituted cyclohexanones, the products were obtained in reasonable yields (42% and 43% yield each) (Table 4-4).

Table 4-4. Trifluoromethylation of various substrates.



entry	substrate	product	X (eq.)	yield (%)[a]
1	 **4a**	 **3a**	1.0	49
2			1.6	74
3	 **4j**	 **3j**	1.0	30
4			1.6	42
5	 **4k**	 **3k**	1.0	32 (35)
6			1.6	44 (43)

[a] Determined by ^{19}F NMR using BTF as an internal standard. The numbers in parentheses refer to the yields of the isolated products.

4-5. Radical reaction mechanism.

When the reaction was carried out by using 0.1 eq. of Et_3B, the yield was only 5 %. This result implies the existence of a radical termination step which would interrupt the radical cycle. The proposed radical reaction mechanism is shown in Figure 4-2. Iseki and coworkers proposed a mechanism in the case of Li amide enolates as path **A** in Figure 4-2.[1b] However, this mechanism does not involve any radical termination step. Based on the fact that Ti has a stable oxidation state Ti(III), we propose a radical termination step as path **B**. In fact, calculated spin density of the Ti(IV) ketyl radical intermediate has 20% of its spin on the Ti(IV) part[14,15] to facilitate the elimination of Ti(III) (Figure 4-3).

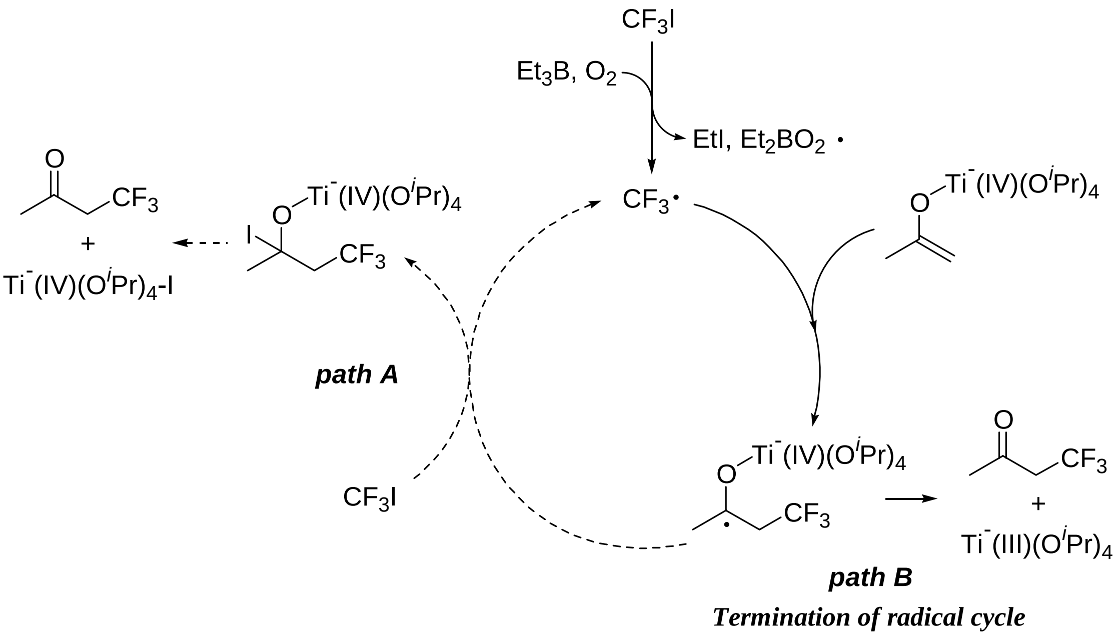


Figure 4-2. Radical reaction mechanism.

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(14) Geometry optimization was done using Gaussian 03 program package. Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(15) The structure of the Ti(IV) ketyl radical intermediate was optimized at UB3LYP/631+LAN (LANL2DZ for Ti, 6-31+G* for others) level. (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310. (d) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*, Wiley: New York, **1986**, and references cited therein. (e) Becke, A.D. *Phys. Rev.* **1988**, *A38*, 3098-3100. (f) Lee, C.; Yang, W.; Parr, R. G. *Phys Rev.* **1988**, *B37*, 785-788. (g) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372-1377. (h) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

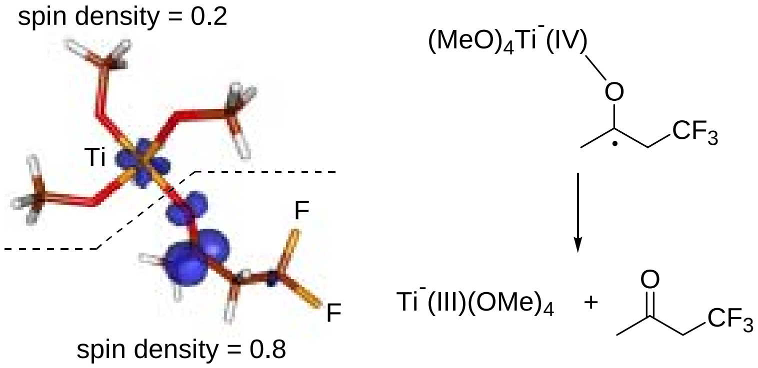


Figure 4-3. Spin density of the Ti(IV) ketyl radical intermediate.

4-6. Conclusion.

In conclusion, the author has developed a radical trifluoromethylation of Ti ate enolates. The key to the success is the use of an excess amount of ^{n}BuLi, ^{i}Pr$_2$NH and Ti(O^{i}Pr)$_4$ to generate the Ti ate enolates. A CF$_3$ substituent can be introduced to various ketones by this method even when quaternary carbon centers are formed. Elimination of Ti(III) from Ti(IV) ketyl radical intermediate is proposed as a termination step of the radical trifluoromethylation. Detailed reaction mechanisms are discussed in Chapter 6.

Experimental Section for Chapter 4

General

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ^{1}H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ=77.0) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard (δ=-63.24) in $CDCl_3$.Important NMR data were tabulated in following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sext: sextet, sept: septet, bs: broad singlet, bd: broad doublet, m: multiplet) and coupling constant (*J* (Hz)).

IR spectrum was measured on JASCO FT/IR-5000 spectrometer.

EI Mass spectra were measured on Shimazu QP-5000 spectrometer.

Analytical thin layer chromatographies (TLC) were performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid.

Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane and ethyl acetate as an eluent.

THF and was distilled over benzophenone-ketyl under Ar prior to use.

All experiments were carried out under argon atmosphere unless otherwise noted.

Typical experimental procedure for radical trifluoromethylation of titanium ate enolate.

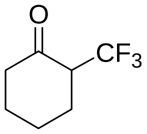
A: Reaction of ketone

To a solution of ^{i}Pr$_2$NH (44.9 μl, 0.32 mmol) in THF (2.0 ml) was added ^{n}BuLi (205.1 μl of 1.56 M solution in hexane, 0.32 mmol) at -78 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then cooled to -78 °C. To the solution was added cyclohexanone (**1a**) (20.7 μl, 0.2 mmol) and stirred for 30 minutes at the temperature. Then $Ti(O^iPr)_4$ (94.5 μl, 0.32 mmol) was added to the solution. After stirring for 30 minutes at -78 °C, gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 hours at -78 °C and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at the temperature. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (81%) (**3a**).

B: Reaction of silyl enol ether

To a solution of 1-(trimethylsilyloxy)cyclohexene (**4a**) (38.9 μl, 0.2 mmol) in THF (2.0 ml) was added ^{n}BuLi (205.1 μl of 1.56 M solution in hexane, 0.32 mmol) at 0 °C and stirred for 20 minutes at the temperature. Next, ^{i}Pr$_2$NH (44.9 μl, 0.32 mmol) was added to the solution and stirred for another 20 minutes. Then, the reaction mixture was cooled to -78 °C. To the mixture was added gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 hours at -78 °C and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at the temperature. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (74%) (**3a**).

2-Trifluoromethyl-cyclohexanone (3a)



^{1}H NMR ($CDCl_3$, 400 MHz)

δ 1.62~1.88 (m, 3H), 1.92~2.14 (m, 2H), 2.24~2.39 (m, 2H), 2.42~2.53 (m, 1H), 2.98~3.13 (m, 1H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.7, 27.1, 27.5 (q, *J*=2.4 Hz), 42.2, 53.6(q, *J*=25.7 Hz), 124.6(q, *J*=279.5 Hz), 203.0 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -69.3 (d, 7.9 Hz) (ppm).

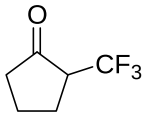
IR (neat)

2954, 2876, 2364, 1729, 1272, 1170, 1125, 1060 (cm^{-1})

EI-MS

m/z=166 [$M^{+\bullet}$].

2-Trifluoromethyl-cyclopentanone (3b)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.77~2.00 (m, 1H), 2.01~2.21 (m, 2H), 2.22~2.48 (m, 3H), 2.78~2.97 (qm, *J*=9.6 Hz, 1H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 20.0, 24.4, 38.5, 51.1 (q, *J*=26.9 Hz), 124.6 (q, *J*=278.3 Hz), 209.4 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -67.9 (d, *J*=10.5) (ppm).

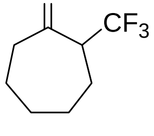
IR (neat)

2986, 2896, 2366, 2344, 1758, 1638, 1367, 1313, 1257, 1187, 1151, 1096, 1046 (cm^{-1}).

EI-MS

m/z=152 [$M^{+\bullet}$].

2-Trifluoromethyl-cycloheptanone (3c)

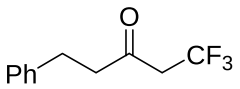


^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.22~1.48 (m, 2H), 1.48~1.75 (m, 2H), 1.86~2.05 (m, 3H), 2.09~2.20 (m, 1H),

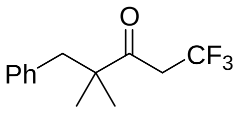
2.54~2.61 (m, 2H), 3.16~3.31 (qdd, *J*=4.1, 8.9, 11.1 Hz, 1H) (ppm).
^{13}C NMR ($CDCl_3$, 75 MHz)
δ 24.4, 24.7 (q, *J*=2.4 Hz), 27.5, 29.1, 43.1, 55.5 (q, *J*=24.5 Hz), 124.9 (q, *J*=280.8 Hz), 205.9 (ppm).
^{19}F NMR ($CDCl_3$, 376 MHz)
δ -69.0 (d, 9.0 Hz) (ppm).
IR (neat)
2940, 2866, 1721, 1178, 1151, 1096 (cm^{-1}).
EI-MS
m/z=180 [$M^{+\bullet}$].

1,1,1-Trifluoro-5-phenyl-3-pentanone (3d)



^{1}H NMR ($CDCl_3$, 300 MHz)
δ 2.80~3.00 (m, 4H), 3.19 (q, *J*=10.2 Hz, 2H), 7.14~7.35 (m, 5H) (ppm).
^{13}C NMR ($CDCl_3$, 75 MHz)
δ 29.2, 44.9, 46.5 (q, *J*=28.1 Hz), 123.5 (q, *J*=277.1 Hz), 126.4, 128.3, 128.6, 140.1, 199.1 (ppm).
^{19}F NMR ($CDCl_3$, 376 MHz)
δ -62.9 (t, *J*=10.2 Hz) (ppm).
IR (neat)
3068, 3032, 2922, 1734, 1605, 1497, 1456, 1419, 1377, 1261, 1154, 1096, 750, 700 (cm^{-1}).
EI-MS
m/z=216 [$M^{+\bullet}$].

1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (3e)



^{1}H NMR (CDCl$_3$, 300 MHz)

δ 1.16 (s, 6H), 2.81 (s, 2H), 3.17 (q, *J*=9.9 Hz, 2H), 7.07 (ddd, *J*=1.7, 2.1, 6.3 Hz, 2H), 7.19~7.32 (m, 3H) (ppm).

^{13}C NMR (CDCl$_3$, 75 MHz)

δ 23.8, 41.4 (q, *J*=28.1 Hz), 45.3, 48.9, 123.9 (q, *J*=277.1 Hz), 126.8, 128.2, 130.2, 136.8, 205.2 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -63.0 (t, *J*=9.8 Hz) (ppm).

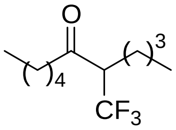
IR (neat)

3034, 2976, 1721, 1369, 1282, 1133, 1100 (cm^{-1}).

EI-MS

m/z=244 [M$^{+\bullet}$].

7-Trifluoromethyl-6-undecanone (3f)



^{1}H NMR (CDCl$_3$, 300 MHz)

δ 0.90 (t, *J*=3.9 Hz, 6H), 1.18~1.41 (m, 8H), 1.53~1.65 (m, 2H), 1.65~1.79 (m, 1H), 1.81~1.97 (m, 1H), 2.47 (dt, *J*=18.0, 7.2 Hz, 1H), 2.61 (dt, *J*=7.4, 18.0 Hz, 1H), 3.11~3.26 (m, 1H) (ppm).

^{13}C NMR (CDCl$_3$, 75 MHz)

δ 13.6, 13.8, 22.4, 22.7, 25.59, 25.62, 29.0, 31.1, 43.6, 55.6 (q, *J*=24.4 Hz), 124.9 (q, *J*=280.7 Hz), 204.5 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -67.4 (d, *J*=9.0 Hz) (ppm).

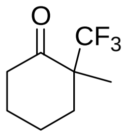
IR (neat)

2966, 2938, 2870, 1731, 1263, 1164 (cm^{-1}).

EI-MS

m/z=238 [M$^{+\bullet}$].

2-Metyl-2-trifluoromethyl-cyclohexanone (3j)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.36 (s, 3H), 1.70~2.00 (m, 5H), 2.06~2.20 (m, 1H), 2.35~2.58 (m, 2H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 17.7 (q, *J*=2.4 Hz), 20.5, 26.4, 33.5, 39.4, 53.7 (q, *J*=23.2 Hz), 126.5 (q, *J*=283.2 Hz), 206.2 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -73.6 (s) (ppm).

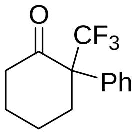
IR (neat)

2936, 2874, 1725, 1274, 1170, 1137 (cm^{-1}).

EI-MS

m/z=180 [M$^{+\bullet}$].

2-Phenyl-2-trifluoromethyl-cyclohexanone (3k)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.63~1.86 (m, 3H), 1.89~2.00 (m, 1H), 2.12~2.25 (m, 1H), 2.31~2.40 (m, 2H), 2.91 (qd, *J*=3.0, 14.4 Hz, 1H), 7.29~7.35 (m, 2H), 7.35~7.47 (m, 3H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 20.2, 27.4, 29.9 (q, *J*=2.4 Hz), 39.8, 62.2 (q, *J*=22.0 Hz), 125.1 (q, *J*=283.2 Hz), 128.7, 128.8, 129.0, 131.8, 204.7 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -72.9 (s) (ppm).

IR (neat)

3066, 2954, 2874, 1725, 1282, 1255, 1176, 1152 (cm^{-1}).

EI-MS

m/z=242 [M$^{+\bullet}$].

Chapter 5

Radical Trifluoromethylation of Li Enolates

5-1. Introduction.

The α-CF_3 carbonyl compounds are one of the most useful synthetic intermediates for functionalization with CF_3. However, defluorination of the α-CF_3 carbonyl compounds is problematic.[1] This difficulty could also be encountered in radical trifluoromethylation of metal enolates, which is, in principle, the most direct and efficient way to synthesize α-CF_3 carbonyl compounds. It has been widely recognized that highly basic conditions with Li enolates[2] could not be applied to the trifluoromethylation (Scheme 5-1);[3] there are indeed only limited examples especially for ketones.[3,4,5,6,7] To avoid defluorination of α-CF_3 ketone products, less reactive enolate equivalents such as silyl or germyl enol ethers have been used for radical trifluoromethylation.[4] Therefore, it usually requires a long reaction time (more than 40 h in the case of ketone). During the course of exploration of the radical trifluoromethylation of Ti ate enolates (Chapter 4),[8] the author discovered that Li enolate could be, in fact, employed for radical trifluoromethylation and that the reaction proceeded extremely fast. Facile radical trifluoromethylation of Li enolates is reported in this chapter.[9]

---

(1) M-F interaction plays an important role in defluorination of α-CF_3 carbonyl compounds: (a) Schlosser, M. In *Organometallics in Synthesis-A Manual*; Schlosser, M. Ed.; John Wiley & Sons: Chichester, 1994; 1-166. (b) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425-3468. (c) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363-3384. See also Chapter 1 and Itoh, Y.; Yamanaka, M.; Mikami, K. *Chem. Rev.* **2004**, *104*, 1-16.

(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654.

(3) Trifluoromethylation of Li enolate of hindered imides (only exception for the use of Li enolate): (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169-2170. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961-974. They have succeeded in trifluoromethylation by adopting Evans oxazolidinones with bulky substituent at α position to suppress defluorination.

(4) Perfluoroalkylation of silyl and germyl enol ethers of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391-6394. (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553. Perfluoroalkylation of silyl enol ethers provided the products in good yields except for trifluoromethylation. Trifluoromethylation of ketone germyl enol ethers proceeds in good yield.

(5) Trifluoromethylation of enamines: (a) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365-1371. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.

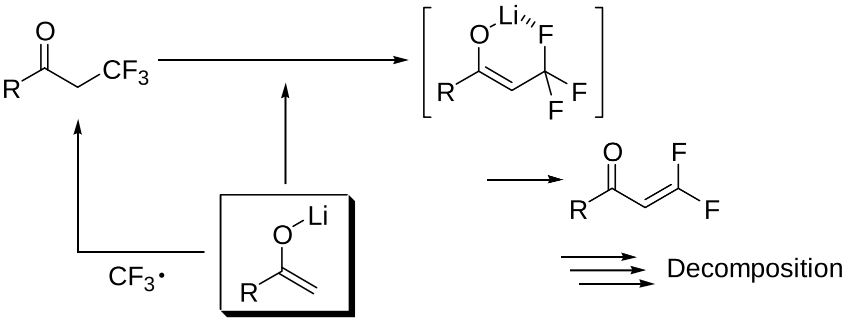
(6) Trifluoromethylation of enol acetates: Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291-1294.

(7) There are some reports of trifluoromethylation using CF_3^+: (a) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 115-118. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164. (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692-5699.

(8) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649-651. (b) Itoh, Y.; Mikami, K. *J. Fluorine Chem.* In press.

(9) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883-4885. (b) Itoh, Y.; Mikami, K. *Tetrahedron*. In press.

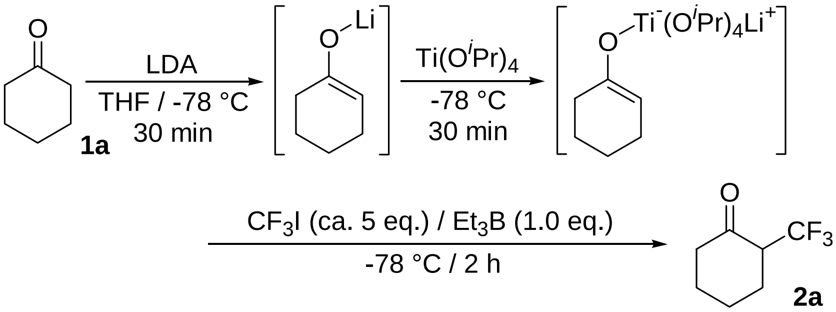
Scheme 5-1.



5-2. Discovery of radical trifluoromethylation of Li enolates.

Radical trifluoromethylation of the Ti ate enolate of cyclohexanone gave 81% yield of α-CF_3 cyclohexanone (Table 5-1, entry 1).[8] The yield significantly decreased without $Ti(O^iPr)_4$ (41%, entry 2), presumably because of the decomposition of the α-CF_3 product due to an excess amount of LDA. Surprisingly, the use of just 1.0 eq. of LDA gave 63% yield of the α-CF_3 product (entry 3). Therefore, the radical trifluoromethylation of Li enolates was further investigated.

Table 5-1. Radical trifluoromethylation of Li enolate.



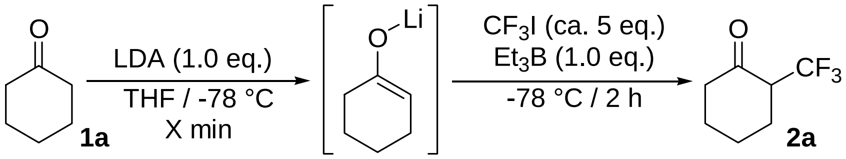
entry	LDA (eq.)	$Ti(O^iPr)_4$ (eq.)	yield (%)[a]
1	1.6	1.6	81
2	1.6	0	41
3	1.0	0	63

[a] Determined by ^{19}F NMR using BTF as an internal standard.

5-3. Optimization of the reaction conditions.

First, preparation time of the Li enolate was investigated (Table 5-2). In the case of the trifluoromethylation of Ti ate enolates, the Li enolates has to be prepared before transforming to the the Ti ate enolate and the preparation of the Li enolates took only 30 min. It is speculated that the Ti ate enolate is in equilibrium with the parent ketone and the ate complex (LDA/Ti(O^{i}Pr)$_4$).[10] Therefore, even if the enolization by LDA was not completed in 30 min, enolization by the Ti ate complex (LDA/Ti(O^{i}Pr)$_4$) would take place during the reaction. There is no such equilibrium in the case of the trifluoromethylation of the Li enolates. Therefore, 60 min of the preparation time was necessary to give sufficient yield of the α-CF_3 product (entry 3). Longer preparation time (120 min) was not necessary (entry 4). When the reaction was carried out without radical initiator Et_3B (entry 2), no product was detected and large amount of cyclohexanone was recovered. This result indicates that the reaction had proceeds by a radical mechanism.

Table 5-2. Preparation time of the Li enolate from ketone.



entry	X (min)	yield (%)[a]
1	30	63
2[b]	30	0
3	60	73
4	120	72

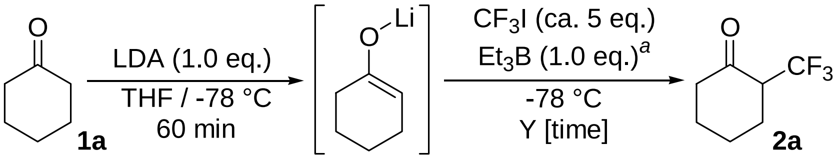
[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] The reaction was carried out without Et_3B.

---

[10] (10) See ref. 8 and Chapter 4.

The radical reaction time was investigated using Li enolate prepared over 60 min (Table 5-3). When the radical trifluoromethylation was carried out in 1 h, the yield was 80% (entry 3). Longer reaction time decreased the yield; the α-CF_3 product was obtained in 62% yield when the reaction was quenched after 13 h (entry 1). This is probably due to the decomposition of the α-CF_3 product when exposed to the basic condition for prolonged period of time. Shorter reaction time did not affect the yield; Even the ~1 s reaction gave the α-CF_3 product in 81 % yield (entry 5).[11] Compared to the radical trifluoromethylation of the Ti ate enolate, which took 2 h to give 81% yield, the reaction of Li enolate is extremely fast.

Table 5-3. Investigation of the trifluoromethylation time of the enolate prepared from ketone.



entry	reaction time Y	yield (%)[b]
1	13 h	62
2	2 h	73
3	1 h	80
4	1 min	83
5	~1 s	81

[a] Et_3B was added in flat 15 s.
[b] Determined by ^{19}F NMR using BTF as an internal standard.

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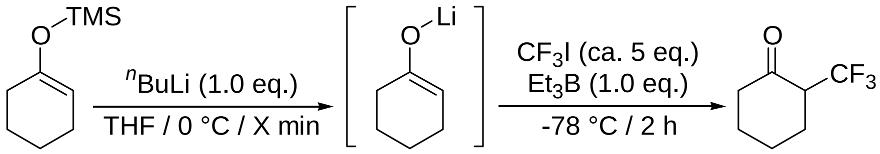
[11] For accuracy, Et_3B was added in flat 15 s and the reaction time was counted from the time when the addition of Et_3B was completed.

5-4. Radical trifluoromethylation of Li enolates prepared from silyl enol ether.

By using LDA for the formation of Li enolate, only kinetic enolate could be formed. However, thermodynamic Li enolate could also be generated by treatment of the corresponding silyl enol ether with 1.0 eq. of ^{n}BuLi[12] to give the regioisomeric α-CF_3 product. From this synthetic point of view, radical trifluoromethylation of Li enolates prepared from silyl enol ether was explored. First, preparation time of Li enolate from silyl enol ether was investigated (Table 5-4). From Table 5-4, the yields of the α-CF_3 product did not change among the preparation time investigated. This indicates that silyl-to-lithium transmetallation is completed within 15 min. However, 30 min was adopted to make sure that the transmetallation was finished.

Table 5-4. Preparation time of the Li enolate from silyl enol ether.



entry	X (min)	yield (%)[a]
1	15	77
2	30	77
3	60	74
4	120	74

[a] Determined by ^{19}F NMR using BTF as an internal standard.

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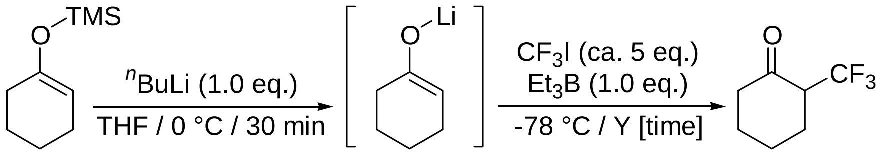
(12) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462-4464. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464-4465.

As in the case of Li enolate prepared from ketone and LDA, radical reaction time of the Li enolate prepared from the silyl enol ether and ^{n}BuLi was investigated (Table 5-5). In sharp contrast to the ketone/LDA method, the maximum yield was given at 2 h reaction time (entry 2, 77% yield). Shorter reaction time decreases the yield and ~1 s reaction time gave only 34 % of the α-CF_3 product. In order to use the same condition for the ketone/LDA method, the reaction was carried out in the presence of ${}^{i}Pr_2NH$ (entry 5). However, it did not affect the reaction. The difference between those two methods is not clear so far. However, it can be said that 2 h of reaction time is required for the silyl-to-lithium method.

Table 5-5. Investigation of the trifluoromethylation time of the enolate prepared from silyl enol ether.



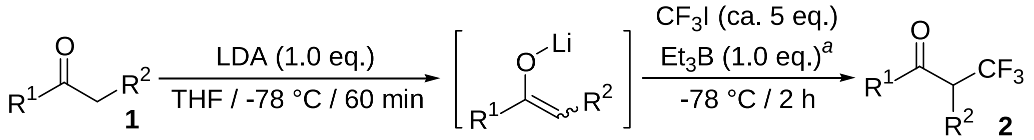
entry	reaction time Y	yield (%)[a]
1	13 h	52
2	2 h	77
3	30 min	67
4	~1 s	34
5[b]	~1 s	36

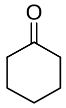
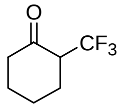
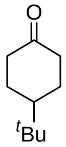
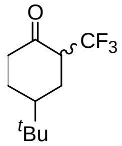
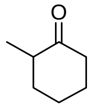
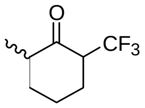
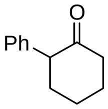
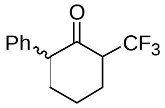
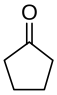
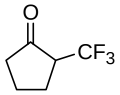
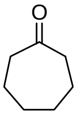
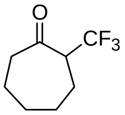
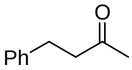
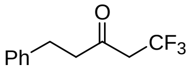
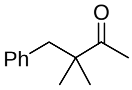
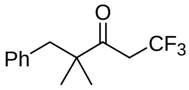
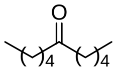
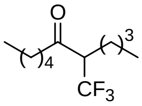
[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] ${}^{i}Pr_2NH$ was added before the addition of CF_3I and stirred for 20 min at 0 °C.

5-5. Radical trifluoromethylation of various Li enolates.

A variety of ketonic substrates were investigated using LDA to generate Li enolate (Table 5-6). In the case of cyclohexanone (entry 1), and 4-^{t}Bu (entry 2), 2-Me (entry 3), 2-Ph (entry 4) cyclohexanones, the reactions proceeded with extremely fast reaction rates and provided the α-CF_3 products in fair to good yield. The reaction rates of cyclopentanone (entry 5) and cycloheptanone (entry 6) were relatively slow (5 min). For acyclic substrates (entries 7, 8, and 9), the yields were poor. Ester and amide were also investigated but did not give the α-CF_3 products at all. From these results, cyclohexanone derivatives are most suitable substrate for this reaction system.

Table 5-6. Radical trifluoromethylation of Li enolates prepared from ketone and LDA.



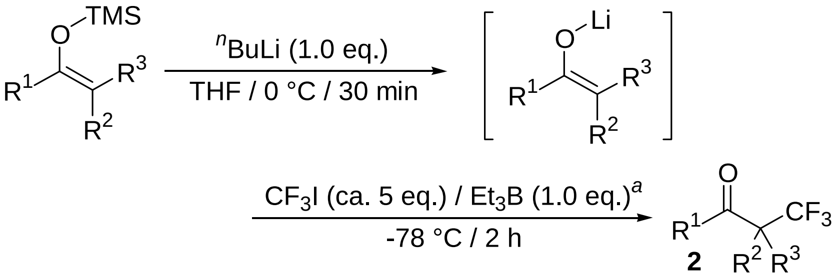
entry	substrate		product		reaction time	yield (%)[b]
1		**1a**		**2a**	~1 s	81
2		**1b**		**2b**	~1 s	71 (67) [73:27]
3		**1c**		**2c**	~1 s	74 [57:43]
4		**1d**		**2d**	~1 s	43 (40) [57:43]
5		**1e**		**2e**	5 min	40
6		**1f**		**2f**	5 min	48
7		**1g**		**2g**	5 min	25
8		**1h**		**2h**	5 min	17
9		**1i**		**2i**	1 min	35

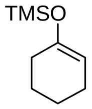
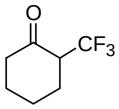
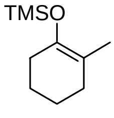
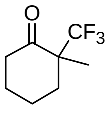
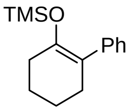
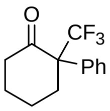
[a] Et_3B was added in flat 15 s.

[b] Determined by ^{19}F NMR using BTF as an internal standard. The values in ( ) refer to the yields of isolated products. The values in [ ] are the diastereomeric ratio.

The Li enolates prepared by the silyl-to-lithium transmetallation method were also investigated for the most suitable cyclohexanone derivatives (Table 5-7). α-Me and α-Ph substituted substrates provided the products, which bear quaternary carbon center attached with CF_3, in fair yields (entries 2, and 3).

Table 5-7. Radical trifluoromethylation of Li enolates prepared from silyl enol ether and ^{n}BuLi.



entry	substrate		product		yield (%)
1		**1a’**		**2a**	77
2		**1j**[c]		**2j**	58
3		**1k**[d]		**2k**	45 (45)

[a] Et_3B was added in flat 15 s.
[b] Determined by ^{19}F NMR using BTF as an internal standard. The values in ( ) refer to the yields of isolated products.
[c] Silyl enol ether of α-Me cyclohexanone consists of thermodynamic and kinetic enol ethers (87:13).
[d] Silyl enol ether of α-Ph cyclohexanone consists of only thermodynamic enol ether.

Considering the facts that the reaction did not proceed without Et_3B (Table 5-2, entry 2), and that CF_3I does not react in an S_N2-type trifluoromethylation,[13] a radical reaction mechanism is proposed for the trifluoromethylation of Li enolates (Scheme

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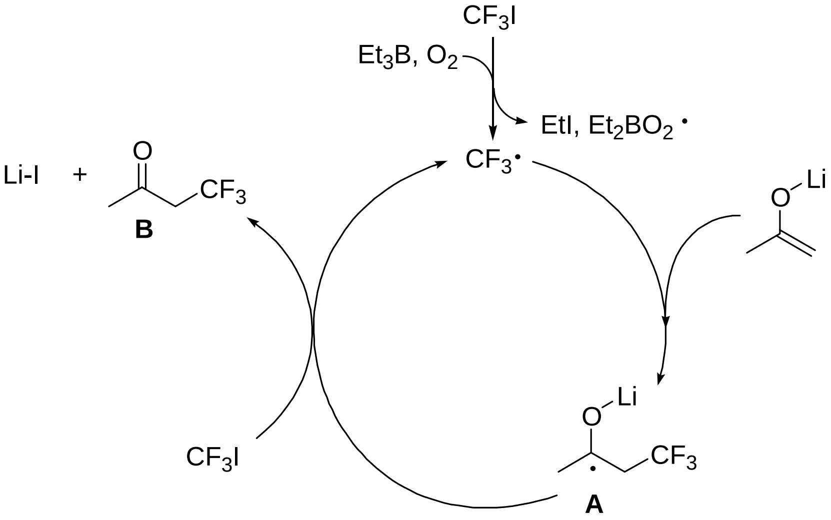
(13) In sharp contrast to normal alkyl halides, perfluoroalkyl halides cannot undergo nucleophilic alkylation, because the electronegativities of perfluoroalkyl groups are higher than those of halogens. Thus the polarization of perfluoroalkyl halides is as $R_f^{\delta-}$-$I^{\delta+}$ and treatment with nucleophile could not produce R_f-Nu. (a) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284-3291. (b) Yoshida, M.; Kamigata, N *J. Fluorine Chem.* **1990**, *49*, 1-20.

5-2).[3b] The CF_3 radical is generated by Et_3B and goes on to react with Li enolate. The radical intermediate (**A**) then reacts with another CF_3I to reproduce the CF_3 radial along with the formation of the α-CF_3 product (**B**).[14]

Scheme 5-2.



5-6. Conclusion.

In summary, the author has discovered that highly basic Li enolates can be employed for radical trifluoromethylation. The reaction rate is extremely fast compared to the previous radical trifluoromethylation. The direct use of Li enolate as a substrate is simpler and faster than that of Ti ate enolates or any other previous methods.

Detailed reaction mechanisms are described theoretically in Chapter 6.

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(14) When Et_3B was used in 20 mol%, the product was obtained in 75% yield. This indicates the involvement of chain-propagation step.

Experimental Section for Chapter 5

General

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ^{1}H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ=77.0) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard (δ=-63.24) in $CDCl_3$.Important NMR data were tabulated in following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sext: sextet, sept: septet, bs: broad singlet, bd: broad doublet, m: multiplet) and coupling constant (*J* (Hz)).

IR spectrum was measured on JASCO FT/IR-5000 spectrometer.

EI Mass spectra were measured on Shimazu QP-5000 spectrometer.

Analytical thin layer chromatographies (TLC) were performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid.

Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane and ethyl acetate as an eluent.

THF was distilled over benzophenone-ketyl under Ar prior to use.

All experiments were carried out under argon atmosphere unless otherwise noted.

Typical experimental procedure of radical trifluoromethylation for lithium enolate

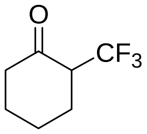
A: Reaction of ketone

To a solution of ^{i}Pr$_2$NH (28.0 μl, 0.20 mmol) in THF (2.0 ml) was added ^{n}BuLi (126.3 μl of 1.58 M solution in hexane, 0.20 mmol) at -78 ºC. The reaction mixture was stirred at 0 ºC for 30 minutes and then cooled to -78 ºC. To the solution was added cyclohexanone (**1a**) (20.7 μl, 0.2 mmol) and stirred for 60 minutes at the temperature. Then, gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula. Next, a syringe, which was filled with 0.12 ml of 5M solution of acetic acid in THF, was set to the reaction vessel and kept untouch till quenching the reaction. Then Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol) was added in flat 15 s to start the radical addition reaction. The reaction mixture was immediately quenched (in ~1 s) by acetic acid solution, which was set beforehand, at -78 ºC. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (81% (**2a**)).

B: Reaction of silyl enol ether

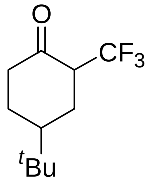
To a solution of 1-(trimethylsilyloxy)cyclohexene (**1a’**) (38.9 μl, 0.2 mmol) in THF (2.0 ml) was added ^{n}BuLi (128.2 μl of 1.56 M solution in hexane, 0.20 mmol) at 0 ºC and stirred for 30 minutes at the temperature. Then, the reaction mixture was cooled to -78 ºC. To the mixture was added gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 hours at -78 ºC and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at -78 ºC. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (77% (**2a**)).

2-Trifluoromethyl-cyclohexanone (2a)



See Chapter 4, **3a**.

4-Tertiarybutyl-2-trifluoromethyl-cyclohexanone (2b)



Major isomer

^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.94 (s, 9H), 1.42~1.68 (m, 3H), 2.18~2.20 (m, 1H), 2.26~2.42 (m, 2H), 2.44~2.56 (m, 1H), 3.00~3.16 (m, 1H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 27.5, 28.1, 28.6, 32.5, 41.7, 46.1, 53.0 (q, *J*=25.7 Hz), 124.6 (q, *J*=279.6 Hz), 203.2 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -69.7 (d, *J*=7.9 Hz) (ppm).

IR (KBr)

2970, 2878, 1734, 1392, 1369, 1274, 1170, 1120, 1067 (cm^{-1}).

EI-MS

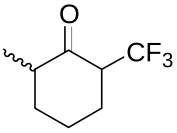
m/z=222 [$M^{+\bullet}$].

Minor isomer (Isonerization was observed during isolation. Therefore, only ^{19}F NMR data, which was taken from the ^{19}F NMR data of the crude reaction mixture, could be shown)

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -66.1 (d, *J*=10.5 Hz) (ppm).

2-Methyl-6-trifluoromethyl-cyclohexanone (2c)



Major isomer

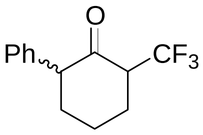
^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.03 (d, *J*=6.3 Hz, 3H), 1.34~1.49 (m, 1H), 1.63~1.87 (m, 2H), 1.88~2.03 (m, 1H),

2.08~2.19 (m, 1H), 2.30~2.49 (m, 2H), 2.98~3.16 (m, 1H) (ppm).
^{13}C NMR (CDCl$_3$, 75 MHz)
δ 13.8, 24.0, 28.3, 36.3, 45.9, 53.7 (q, *J*=25.7 Hz), 124.8 (q, *J*=279.5 Hz), 204.6 (ppm).
^{19}F NMR (CDCl$_3$, 376 MHz)
δ -69.8 (d, *J*=8.3 Hz) (ppm).
IR (neat)
2942, 2874, 2366, 1731, 1456, 1392, 1332, 1272, 1170, 1137, 1123, 1038, 832, 688 (cm^{-1}).
EI-MS
m/z=180 [M$^{+\bullet}$]

Minor isomer
^{1}H NMR (CDCl$_3$, 300 MHz)
δ 1.11 (d, *J*=6.6 Hz, 3H), 1.46~2.21 (m, 6H), 2.57~2.71 (m, 1H), 3.07~3.22 (m, 1H) (ppm).
^{13}C NMR (CDCl$_3$, 75 MHz)
δ 15.0, 20.2, 26.9, 29.6, 34.2, 44.5, 52.3 (q, *J*=25.7), 125.2 (q, *J*=280.7 Hz), 206.3 (ppm).
^{19}F NMR (CDCl$_3$, 376 MHz)
δ -66.7 (d, *J*=10.2 Hz) (ppm).
IR (neat)
2928, 2858, 2364, 2344, 1725, 1458, 1265, 1143, 801 (cm^{-1}).
EI-MS
m/z=180 [M$^{+\bullet}$]

2-Phenyl-6-trifluoromethyl-cyclohexanone (2d)



Major isomer
^{1}H NMR (CDCl$_3$, 300 MHz)
δ 1.83~2.21 (m, 4H), 2.28~2.40 (m, 1H), 2.40~2.56 (m, 1H), 3.16~3.35 (m, 1H), 3.56~3.68 (dd, *J*=5.4, 12.6 Hz, 1H), 7.11~7.17 (m, 2H), 7.25~7.40 (m, 3H) (ppm).
^{13}C NMR (CDCl$_3$, 75 MHz)

δ 24.2, 28.3, 35.6, 54.1 (q, *J*=25.6 Hz), 57.8, 124.6 (q, *J*=280.8 Hz), 127.4, 128.4, 128.8, 137.0, 201.6 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -69.6 (d, *J*=7.9 Hz) (ppm).

IR (KBr)

3036, 2946, 2872, 1722, 1605, 1452, 1385, 1270, 1168, 1133, 1045, 761, 704, 592 (cm^{-1}).

EI-MS

m/z=242 [M$^{+\bullet}$]

Minor isomer

^{1}H NMR (CDCl$_3$, 300 MHz)

δ 1.86~2.28 (m, 5H), 2.37~2.52 (m, 1H), 3.12~3.30 (dq, *J*=6.0, 9.3 Hz, 1H), 3.82~3.92 (distorted t, *J*=6.3 Hz, 1H), 7.17~7.43 (m, 5H) (ppm).

^{13}C NMR (CDCl$_3$, 75 MHz)

δ 20.4, 27.4, 31.3, 52.0 (q, *J*=26.9 Hz), 55.1, 125.1 (q, *J*=280.8 Hz), 127.4, 127.6, 129.0, 136.7, 203.5 (ppm).

^{19}F NMR (CDCl$_3$, 376 MHz)

δ -67.9 (d, *J*=9.0 Hz) (ppm)

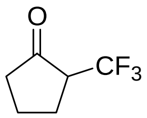
IR (neat)

3066, 3032, 2954, 2878, 2364, 1725, 1603, 1584, 1499, 1454, 1390, 1332, 1274, 1183, 1141, 698 (cm^{-1}).

EI-MS

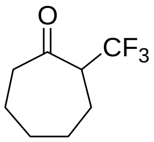
m/z=242 [M$^{+\bullet}$].

2-Trifluoromethyl-cyclopentanone (2e)



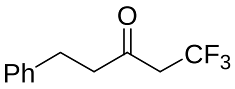
See Chapter 4, **3b**.

2-Trifluoromethyl-cycloheptanone (2f)



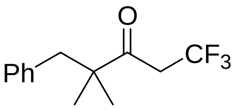
See Chapter 4, **3c**.

1,1,1-Trifluoro-5-phenyl-3-pentanone (2g)



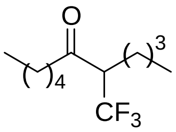
See Chapter 4, **3d**.

1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (2h)



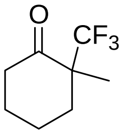
See Chapter 4, **3e**.

7-Trifluoromethyl-6-undecanone (2i)



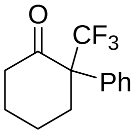
See Chapter 4, **3f**.

2-Metyl-2-trifluoromethyl-cyclohexanone (2j)



See Chapter 4, **3j**.

2-Phenyl-2-trifluoromethyl-cyclohexanone (2k)



See Chapter 4, **3k**.

Chapter 6

Experimental and Theoretical Studies on Radical Trifluoromethylation Mechanisms of Ti Ate and Li Enolates

6-1. Introduction.

Introducing CF_3 group by CF_3 radical addition to enolates is one of the most straightforward and effective ways to obtain α-CF_3 carbonyl compounds. The author investigated the radical trifluoromethylation of enolates; the use of Ti ate enolates[1] and Li enolates[2] turned out to be an efficient way to synthesize α-CF_3 ketone (Chapter 4 and 5). Except for the author's report, there is only one example of the radical trifluoromethylation of Li enolates of sterically demanding imides to retard defluorination by Iseki and co-workers.[3,4] For Li enolates, they proposed a radical mechanism (Figure 6-1). However, in our investigation of the amount of radical initiator (Et_3B), interesting results were obtained in terms of the relationship between the amount of Et_3B and the product yield critically depending on the metals on enolates. The author herein reports the experimental and theoretical studies on the mechanism to clarify the difference in the radical trifluoromethylation of Ti ate and Li enolates.

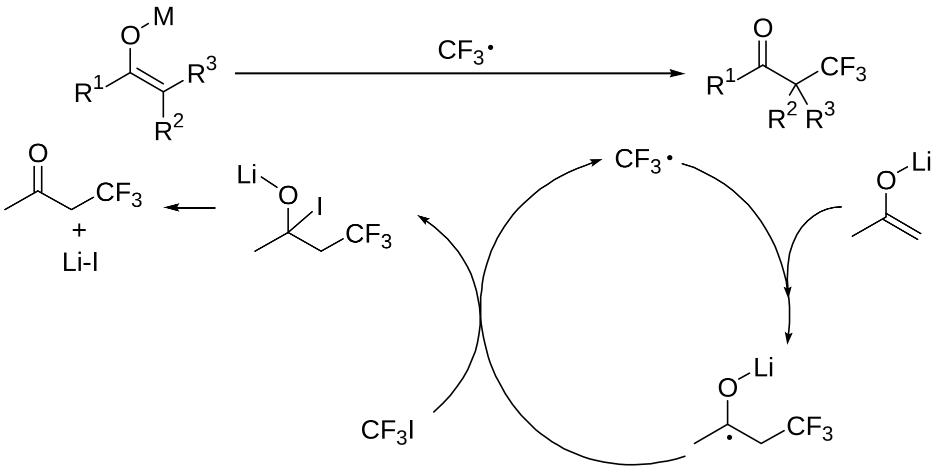


Figure 6-1. Previously proposed mechanism of the radical trifluoromethylation of Li enolates.

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(1) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649-651. (b) Itoh, Y.; Mikami, K. *J. Fluorine Chem.* In press.

(2) (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *22*, 4883-4885. (b) Itoh, Y.; Mikami, K. *Tetrahedron*. In press.

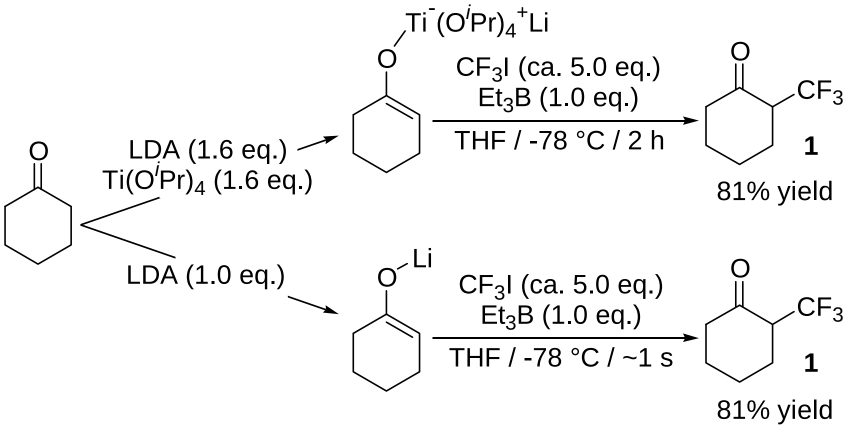
(3) Trifluoromethylation of lithium enolate of imides: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169-2170. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961-974.

(4) Other examples of radical trifluoromethylation of enolate equivalents. (a) Perfluoroalkylation of silyl and germyl enol ethers of esters and ketones. Perfluoroalkylation of silyl enol ethers provided the products in good yields except for trifluoromethylation. Trifluoromethylation of ketone germyl enol ethers proceeds in good yield: (i) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391-6394. (ii) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553. (b) Trifluoromethylation of enamines: (i) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365-1371. (ii) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.

6-2. Experimental Study.

Radical trifluoromethylation of Ti ate enolates[1] and Li enolates[2] are reported in Chapter 4 and 5 to provide the α-CF_3 product in good yield (Scheme 6-1).

Scheme 6-1



In investigating the amount of radical initiator (Et_3B), interesting results were obtained. The relationship between the amount of Et_3B and the product yield were shown in Figure 6-2. In the case of Ti ate enolates, the yields gradually decreased along with the amount of Et_3B decreased under the reaction conditions (LDA=$Ti(O^iPr)_4$=1.0 eq. and 1.6 eq.).[5] In sharp contrast, this is not the case with Li enolates; the α-CF_3 product could be obtained in good yield (71%) even when the amount of Et_3B was reduced to 5 mol%. This indicates that radical cycle does not work well for Ti ate enolate but does works well for Li enolate.

---

(5) It is speculated that the Ti ate enolate is in equilibrium with the parent ketone and ate complex (LDA/$Ti(O^iPr)_4$). Although Ti ate enolate could be generated by using LDA=$Ti(O^iPr)_4$=1.0 eq., excess amount of LDA and $Ti(O^iPr)_4$ (LDA=$Ti(O^iPr)_4$=1.6 eq.) increases the yield of the α-CF_3 product probably due to the equilibrium shift to the Ti ate enolate. See ref.1 and Chapter 4.

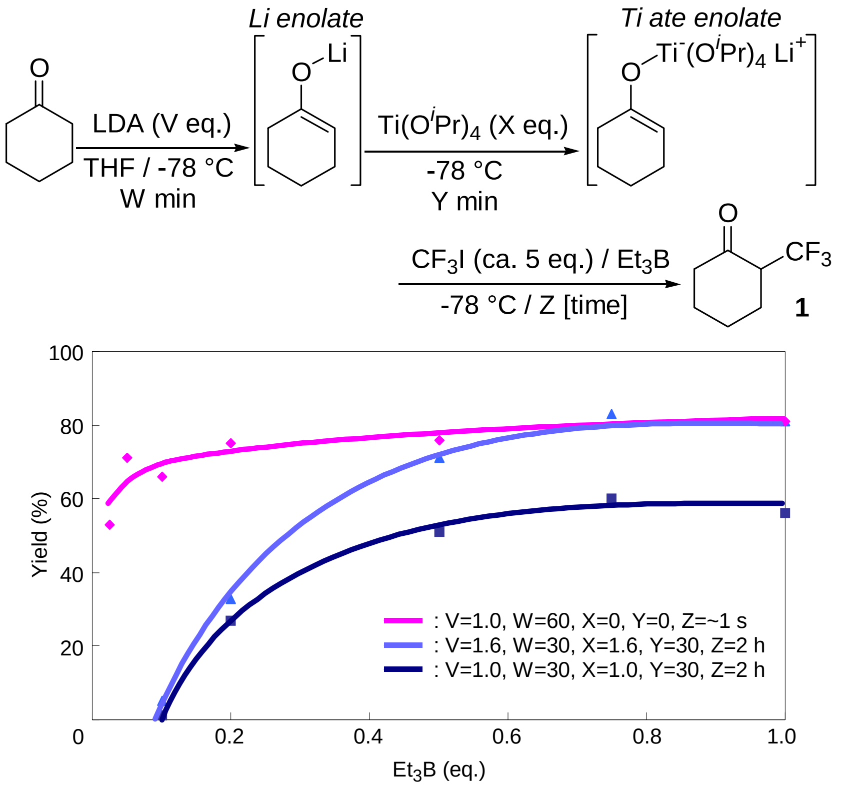


Figure 6-2. Relationship between the amount of the Et_3B and the yields.

Considering the fact that Ti has two stable oxidation states (III and IV), two reaction mechanisms could be proposed (Figure 6-3). First, the CF_3 radical goes on to react with enolate (Step (1)). From the radical adduct (**2**), one possibility is Path A; elimination of metal from ketyl radical intermediate **2** by reducing its oxidation number by one along with the formation of the α-CF_3 product (Step (2)). Regeneration of CF_3 radical can be achieved by the reaction of CF_3I with the metal (Step (3)). Another possibility is Path B, which is similar to Scheme 6-1; the ketyl radical intermediate **2** directly react with CF_3I to regenerate CF_3 radical along with α-CF_3 product (Step (4)).

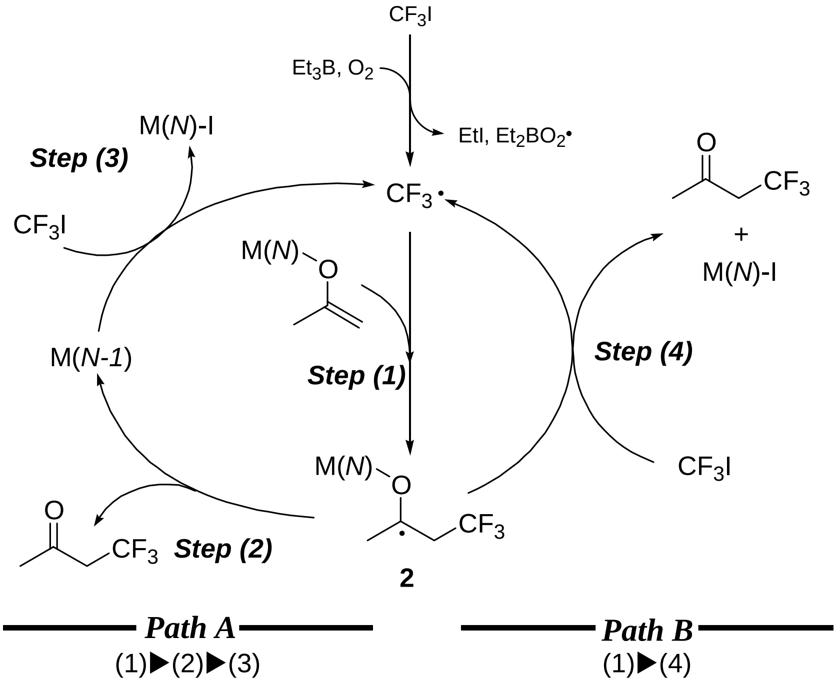


Figure 6-3. Proposed CF_3 radical addition mechanism.

Computational studies were thus carried out to evaluate the reaction mechanism and uncover the origin of the difference of the reactions between Ti ate and Li enolate.

6-3. Theoretical Study.

6-3-1. Chemical Models.

For computational efficiency, lack of precise structural information on the reactive intermediate, and our qualitative goal, several simplifications were adopted; (1) Ignore Li$^+$ in Ti ate enolate.[6] (2) Adopt Ti methoxide instead of the actually used Ti isopropoxide. (3) Ignore aggregation.[7,8] (4) Adopt acetone as a substrate.

---

(6) When the radical trifluoromethylation of Ti ate enolates were carried out in the presence of 12-crown-4, the yield did not change in any significant amount (1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanon was used as a substrate. Ti ate enolate was prepared by LDA=Ti(O^{i}Pr)$_4$=1.0 eq. condition. The reaction was carried out at -78 ºC for 2 h. The chemical yields were 52% (without 12-crown-4) and 53% (with 12-crown-4)). This could be the rationale for the computational model which ignored Li$^+$ in Ti ate enolate.

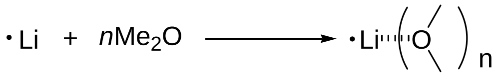
(7) Aggregation of Li enolates: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654. (b) Weiss, H.; Yakimansky, A. V. Müller, A. H. E. *J. Am. Chem. Soc.* **1996**, *118*, 8897-8903. (c) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255-11268. (d) Suzuki, M.; Koyama, H.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 259-268.

(8) Aggregation of Ti ate complexes: (a) Mehrotra, R. C.; Agrawal, M. M. *J. Chem. Soc. A* **1967**, 1026-1030. (b) Hampden-Smith, M. J.; Williams, D. S.; Rheingold, A. L. *Inorg. Chem.* **1990**, *29*, 4076-4081. (c) Kuhlman, R.; Vaartstra, B. A. Streib, W. E. Huffman, J. C.; Caulton, K. G. *Inorg. Chem.* **1993**, *32*, 1272-1278. (d) Boyle, T. J.; Alam, T. M. Tafoya, C. J.; Mechenbier, E. R.; Ziller,

It is very important to consider the solvent, since all the reactions were carried out in THF. There are empty site available on the metal for the coordination of THF to stabilize both the intermediate and the transition state. The usual maximum coordination number is four for Li and six for Ti. Therefore, in preliminary study, stabilization energies of the Li radical, Li$^+$, Ti$^-$(III)(OMe)$_4$, and Ti(IV)(OMe)$_4$ were investigated with dimethyl ether (Table 6-1~4). All the structures were optimized at UB3LYP/631+LAN (LANL2DZ for Ti, 6-31+G* for others) level (ΔE). Gibbs free energies (ΔG) contain zero-point, thermal and entropy effects at 298.15 K and 1 atm pressure. In the case of Li, both radicals and cations are stabilized by coordination of ethers (Table 6-1, and 2). One exception is ΔG of Li radical; the first and second ethers stabilized the system but third and forth ethers raised the energies though in small value (Table 6-1, entries 3 and 4). This effect is due to the entropy effect. On the other hand, in the case of Ti, there was no stabilization by the coordination of ether (Table 6-3, and 4). When the optimization was started with one ether, the ether fall apart along with the optimization in both the Ti$^-$(III) and Ti(IV) cases. When the optimization was started with two ethers, hexacoordinated Ti complex was optimized. But the energy was higher compared with the non-coordinated species.

From these results, solvated models were constructed by the following conditions; (1) Maximum allowed numbers of ether were attached to Li species. (2) Solvated models were not considered for Ti species.

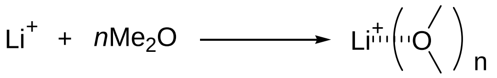
Table 6-1. Stabilization of Li radical by solvation.



n	ΔE (kcal/mol)	ΔG (kcal/mol)
0 (**3**)	0	0
1 (**4**)	-11.3	-3.9
2 (**5**)	-19.8	-2.6
3 (**6**)	-27.3	1.7
4 (**7**)	-35.3	6.4

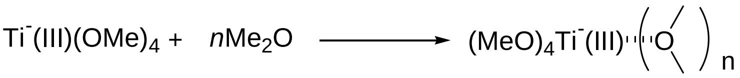
J. W. *Inorg. Chem.* **1999**, *38*, 2422-2428.

Table 6-2. Stabilization of Li^+ by solvation.



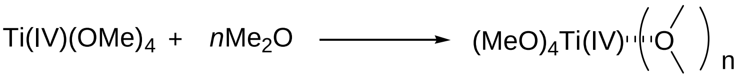
n	ΔE (kcal/mol)	ΔG (kcal/mol)
0 (**8**)	0	0
1 (**9**)	-39.6	-31.5
2 (**10**)	-73.2	-54.3
3 (**11**)	-95.8	-65.4
4 (**12**)	-109.4	-67.3

Table 6-3. Stabilization of $Ti^-(III)(OMe)_4$ by solvation.



n	ΔE (kcal/mol)	ΔG (kcal/mol)
0 (**13**)	0	0
1	-	-
2 (**14**[9])	25.9	40.4

Table 6-4. Stabilization of $Ti(IV)(OMe)_4$ by solvation.



n	ΔE (kcal/mol)	ΔG (kcal/mol)
0 (**15**)	0	0
1	-	-
2 (**16**[10])	11.8	42.3

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(9) The structure **14** has imaginary frequency (-8 cm^{-1}) corresponding to vibration of ether.

(10) The structure **16** has imaginary frequencies (-35, -28 cm^{-1}) corresponding to vibration of ether.

6-3-2. Computational Methods.

All the calculations were performed with GAUSSIAN 03 program package.[11] All the structures were optimized at UB3LYP/631+LAN (LANL2DZ for Ti, I, 6-31+G* for others)[12,13] level (ΔE). Then the energies were recalculated in the presence of dielectric field (THF, ε=7.58) as described by the C-PCM (COSMO (conductor-like screening model)) model[14] at UB3LYP/6311+LAN (LANL2DZ for Ti, I, 6-311+G* for others) level (ΔE(sol)). The energies shown in this report are Gibbs free energies and thus contain zero-point, thermal and entropy effects at 195.15 K (-78 ºC: actual reaction temperature) and 1 atm pressure (ΔG(sol,-78)) unless otherwise noted. The natural charges were calculated by the natural population analysis[15] at the same level of the theory as the one used for geometry optimization.

To evaluate the calculation method, electron affinities (EA) of CF_3I (neutral: **17**, anion radical: **18**) and benzophenone (neutral: **19**, anion radical: **20**) were calculated and compared with the experimental values (Table 6-5). The structures were optimized at UB3LYP/631+LAN level and energies were recalculated by UB3LYP/6311+LAN level using the optimized geometry. Calculated EA was comparable to the experimental value. Therefore, adopted calculation level should give reasonable energetics.

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(11) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(12) B3LYP utilizes Becke’s three-parameter exchange functional and the Lee-Yang-Parr correlation functional. (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785-788. (b) Becke, A.D. *Phys. Rev.* **1988**, *A38*, 3098-3100. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372-1377. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652.

(13) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284-298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310. (d) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*, Wiley: New York, 1986, and references cited therein.

(14) (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans.2* **1993**, 799-805. (b) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995-2001. (c) Cossi, M.; Rega, N.; Scalamani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669-681.

(15) Reed, A.E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735-746.

Table 6-5. Calculated and experimental value of electron affinity of CF_3I and benzophenone.

		EA (eV)	
	Method and basis set[a]	Calc.	Exp.
CF_3I	UB3LYP/631+LAN	1.57	1.57±0.2[16]
	UB3LYP/6311+LAN	1.58	
benzophenone	UB3LYP/631+LAN	0.69	0.62±0.1[17]
	UB3LYP/6311+LAN	0.71	

[a] All the structures were optimized at UB3LYP/631+LAN level.

6-4. Step (1)

6-4-1. Step (1)-Ti.

As shown in Figure 6-4, CF_3 radical addition to Ti ate enolate is an exothermic reaction (-28.0 kcal/mol). Transition state calculation was also tried, but could not be optimized (no saddle point could be found). This reaction might proceed without significant energy barrier.

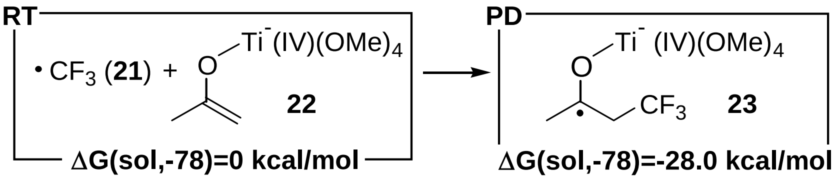

Figure 6-4. Step (1) Ti: CF_3 radical addition to Ti ate enolate.

6-4-2. Step (1)-Li.

The energietics for the reaction without solvent were shown in Figure 6-5. The reaction was exothermic (-22.3 kcal/mol). This value is slightly smaller than in the case of Ti. The structure of the product has an intramolecular coordination with fluorine. Transition state calculation was also tried, but could not be optimized (no saddle point could be found). Instead, transition state could be optimized by using UHF/6-31+G* level theory. At present level of theory, the reaction has no significant barrier.

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(16) Compton, R. N.; Reinhardt, P. W. *J. Chem. Phys.* **1978**, *68*, 4360-4367.

(17) Chowdhury, S.; Heinis, T.; Grimsrud, E. P.; Kebarle, P. *J. Phys. Chem.* **1986**, 90, 2747-2752.

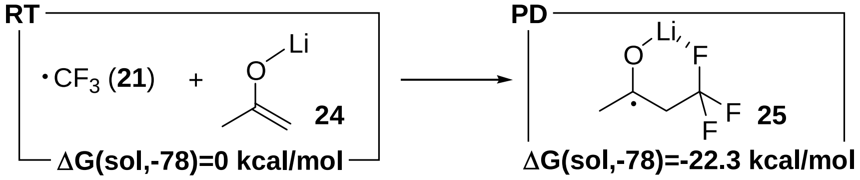


Figure 6-5. Step (1) Li: CF_3 radical addition to Li enolate (without solvent).

Without solvent, coordination number of Li changes from one to two during the reaction. The Li on the product should have maximum coordination (four) to gain the highest stabilization by coordination. There are two possible product structures for four coordinated Li. One structure has three ethers and the other has two ethers and intramolecular coordination with fluorine. Energies of these structures were compared in Figure 6-6 and it was found that **26** without Li-F coordination is less stable than **27** in terms of ΔG(sol). However, when the optimization of **26** was started with Li-F coordination, Li and F gradually fall apart and the energy of **26** is more stable than **27** in terms of ΔE(sol).[18] Since the initial product of Step (1) is **26**, it could be concluded that initial product **26** will soon form **27** to stabilize the system.

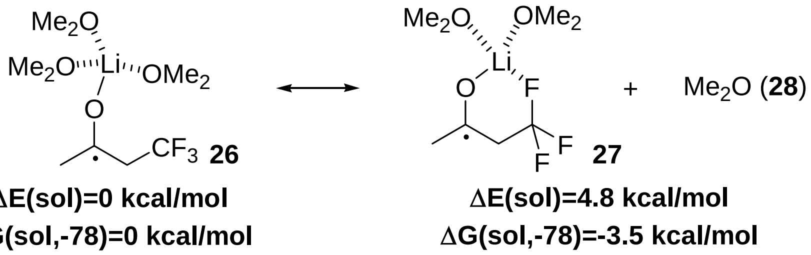


Figure 6-6. Comparison of the radical intermediate with or without Li-F coordination.

There are three vacant sites on Li in the substrate. Therefore, three ethers were attached to the substrate.[19] The energetics for solvated model of Step (1) is shown in Figure 6-7. The reaction was also exothermic (-26.5 kcal/mol) and this value is almost the same as in the case of Ti.

---

(18) This energy was obtained by UB3LYP/6-311+G*//UB3LYP/6-31+G* level theory. Single point energy calculation was carried out in the presence of dielectric field (THF, ε=7.58), as described by the C-PCM model.

(19) Although it is known that π-enolate could be optimized and some times it is more stable than O-enolate in the case without solvent, O-enolate was adopted since non-solvated model is far from realistic model compared to solvated model. Getting further into non-solvated model is worthless in this study. See ref. 8-(d).

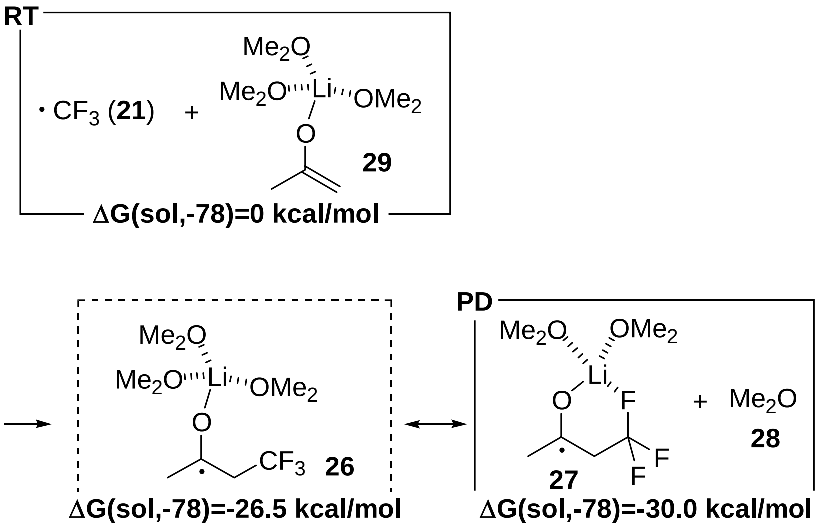


Figure 6-7. Step (1) Li: CF_3 radical addition to Li enolate (with solvent).

6-4-3. Step (1)-naked enolate.

Energetics for naked enolate were also calculated (Figure 6-8). Again, the reaction was exothermic (-24.9 kcal/mol) in about the same value to the other enolates.

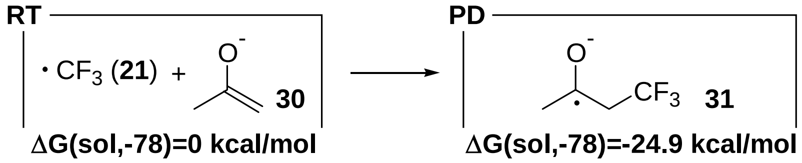
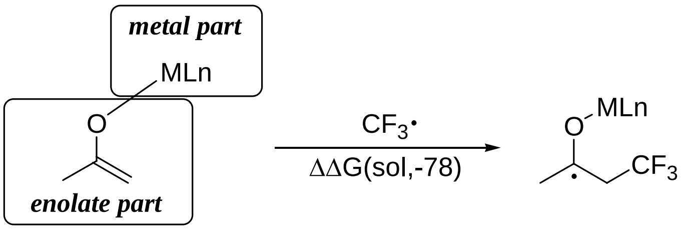


Figure 6-8. Step (1) no metal: CF_3 radical addition to naked enolate.

This phenomenon could be rationalized by charge distribution. Charge distribution of enolates was calculated by natural population analysis. They are listed in Table 6-6. All the enolate including naked enolate has its charge on enolate part for more than -0.7. This means that metal on the enolate is almost separated and leave the enolate almost naked. In the Step (1), there is apparently no difference between Li and Ti.

Table 6-6. Charge distribution of enolates.



	Natural charge		ΔΔG(sol,-78)
	Metal	Enolate	(kcal/mol)
Ti ate enolate (**22**)	-0.30	-0.70	-28.0
Li enolate without solvent (**24**)	0.96	-0.96	-22.3
Li enolate with three solvents (**29**)	0.94	-0.94	-26.5
Naked enolate (**30**)	0	-1	-24.9

6-5. Step (2).

6-5-1. Step (2)-Ti.

The energetics of Step (2) including all possible equilibrium of the product are shown in Figure 6-9. Transition state was also optimized and is shown together in Figure 6-9. The activation free energy was relatively low (3.8 kcal/mol) and the reaction was slightly exothermic. Dissociation of ketone from Ti(III) lowered the energy to -9.9 kcal/mol. Interestingly, dissociation of $^{-}$OMe from Ti(III) ate type complex raised the energy by 23.2 kcal/mol.

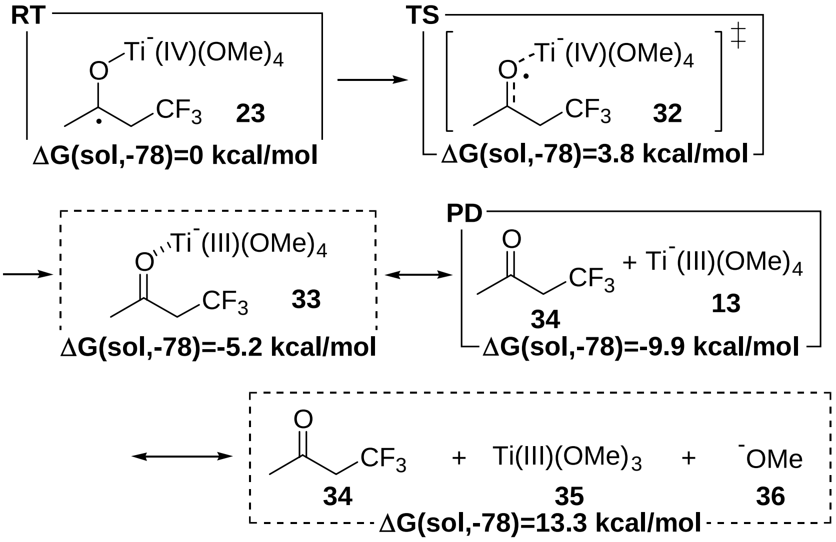


Figure 6-9. Step (2) Ti: Ti elimination from the radical intermediate.[20]

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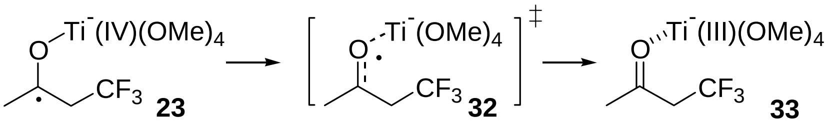
[20] The structure **33** has imaginary frequency (-29 cm^{-1}) corresponding to rotation of Me group on the ligand.

By analogy with charge distribution of enolate, charge distribution and spin density of Ti species in Step (2) should be checked to confirm that the optimized structures are really the desired structure and not just dissociation for Ti(IV) and radical anion. The results are shown in Table 6-7. Electron in Ti species gradually moves from ketone part to Ti part as the reaction proceeds. Therefore, it could be concluded that the optimized structures are the desired Ti(III) elimination path. Moreover, dissociation of Ti(IV) from the radical intermediate is less thermodynamically favorable than Ti(III) elimination (0.7 kcal/mol vs. -9.9 kcal/mol) (Figure 6-10).

Table 6-7. Charge distribution of Ti species in Step (2).



		Natural charge	Spin density
23	Ti part	-0.46	0.20
	ketone part	-0.54	0.80
32	Ti part	-0.86	0.87
	ketone part	-0.14	0.13
33[20]	Ti part	-0.98	0.998
	ketone part	-0.02	0.002

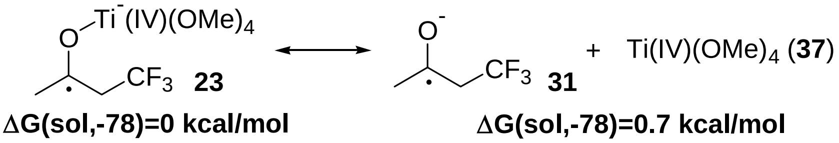


Figure 6-10. Dissociation of Ti(IV) from the radical intermediate.

6-5-2. Step (2)-Li.

Energetics of the reaction without solvent are shown in Figure 6-11. Fluorine atom has coordinative lone electron pair. Therefore, the initial product should have coordination with Li radical. The reaction was endothermic (28.3 kcal/mol). Dissociation of Li radical from α-CF_3 ketone made only slight difference in the total energy (0.6 kcal/mol difference).

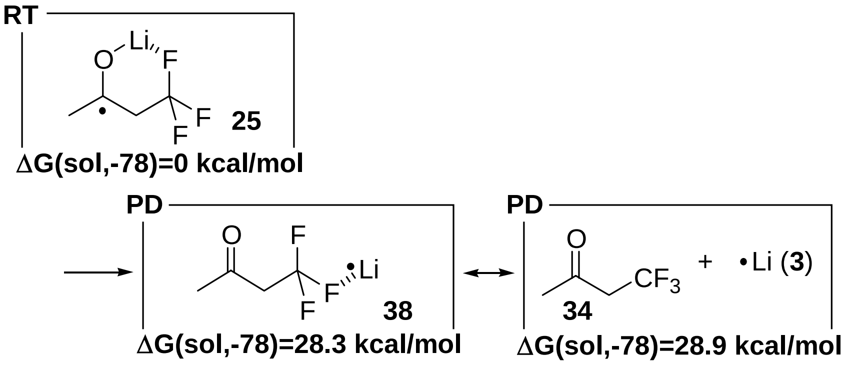
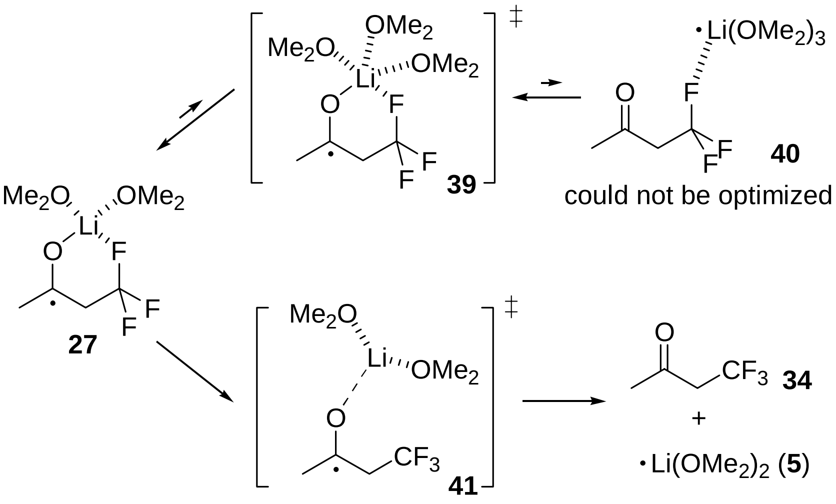


Figure 6-11. Step (2) Li: Li elimination from the radical intermediate (without solvent).

The coordination number of ether is important and confusing in the case of Li. During the optimization of the product of Step (2)-Li (**38**) (Figure 6-11), it was found that carbonyl group would be readily reduced when the Li radical was in close distance. Therefore, the Li radical in **38** is coordinated to the farthest fluorine to carbonyl group. In order to reach this structure, the Li radical should go over the rotation barrier of CF_3 group. This is against the “least motion principle” and thus Figure 6-11 does not describe this reaction correctly. For that reason, when building the solvated model, Li radical in the product should have the maximum coordination number to avoid reduction of the carbonyl group nearby (Route A). Otherwise, Li radical should be completely separated from ketone (Route B) (Figure 6-12). However, optimization of the product of route A (**40**) failed because of the spontaneous reduction of the carbonyl group even the vacant site of Li was filled with ether. Therefore, the product of the Step (2) should be ketone completely separated from Li radical (Route B).

Route A) ***Li radical attached to fluorine.***



Route B) ***Li radical fall apart.***

Figure 6-12. Two possible transition states for Li elimination.

There are also several structures to consider for the substrate. As discussed in Step (1)-Li (Figure 6-6), between two possible substrate structures for four coordinated Li, **27**, which has Li-F coordination, is in lowest energy. Therefore, **27** was adopted as a substrate. The energetics of Step (2) for Li are shown in Figure 6-13. This step is endothermic by 27.2 kcal/mol and, hence, probably hard to take place.

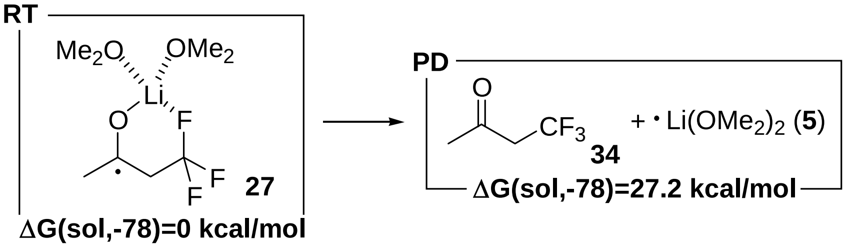


Figure 6-13. Step (2) Li: Li elimination from the radical intermediate.

6-6. Step (3).

There are two possible reaction paths for Step (3). That is a) electron transfer (denoted as ET), and b) atom transfer (denoted as AT). These two pathways should be considered in both Ti and Li cases.

6-6-1. Step (3)-Ti.

The energetics for regeneration of CF_3 radical by Ti(III) are shown in Figure 6-14. The initial product of AT is the Ti(IV) ate complex and CF_3 radical. If AT takes place, CF_3 radical would be generated in one step. As already discussed before (Step (1)-Ti, Figure 6-4), CF_3 radical addition to the Ti ate enolate is a highly exothermic reaction ($\Delta\Delta G$(sol,-78)=-28.0 kcal/mol) without significant reaction barrier. Therefore, once CF_3 radical was generated, it should immediately react with enolate. However, according to the experimental observation that radical cycle does not works well in the case of Ti (Figure 6-2), AT might not be the reaction pathway. The initial product of ET is Ti(IV) and radical anion of CF_3I. In order to regenerate CF_3 radical, I^- should be pulled out from CF_3 radical anion. However, extraction of I^- by Ti(IV) is thermodynamically unfavorable (Figure 6-14, (A)). Spontaneous dissociation of I^- from CF_3 radical anion is slightly unfavorable by 0.9 kcal/mol (Figure 6-14, (B)). Overall, regeneration of CF_3 radical is unfavorable and it matches the experimental observation.

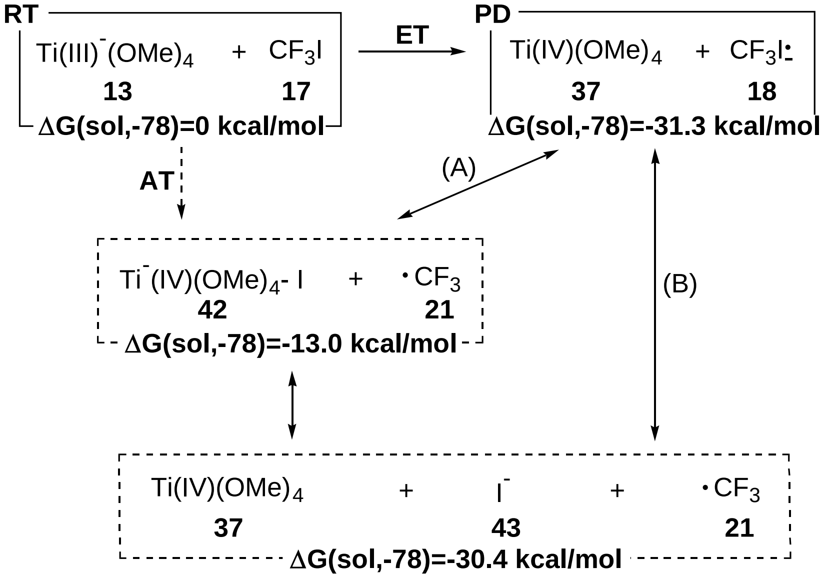


Figure 6-14. Step (3) Ti: Regeneration of CF_3 radical by Ti(III).

6-6-2. Step (3)-Li.

Energetics of the reaction without solvent is shown in Figure 6-15. The initial product of AT is Li-I and CF_3 radical, and the initial product of ET is Li^+ and radical anion of CF_3I. In sharp contrast to the reaction of Ti(III), regeneration of CF_3 radical is thermodynamically favorable by 8.6 kcal/mol.

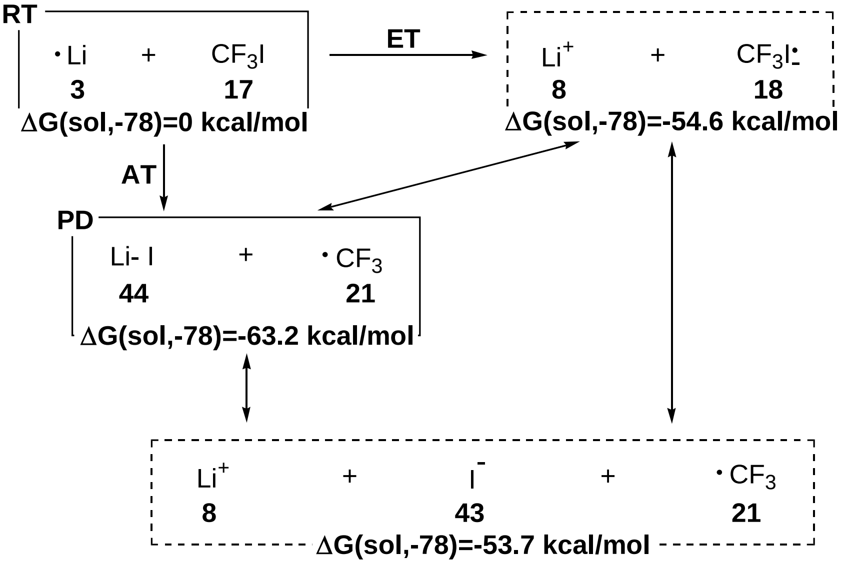


Figure 6-15. Step (3) Li: Regeneration of CF_3 radical by Li radical (without solvent).

As shown in Figure 6-15, the number of the ligand on Li changes during the reaction. According to Figure 6-13, product of solvated Li model of Step (2) has two ethers coordinated to Li radical (Route A). Other possibility is Li radical with three ethers which fills all vacant site of the product Li-I (Route B). Both routes were calculated (Figure 6-16). Both routes A and B came up with the same tendency. Regeneration of the CF_3 radical is thermodynamically favorable (up to -60.5 kcal/mol). However, because of the high reaction barrier in Step (2), Step (3) might not take place.

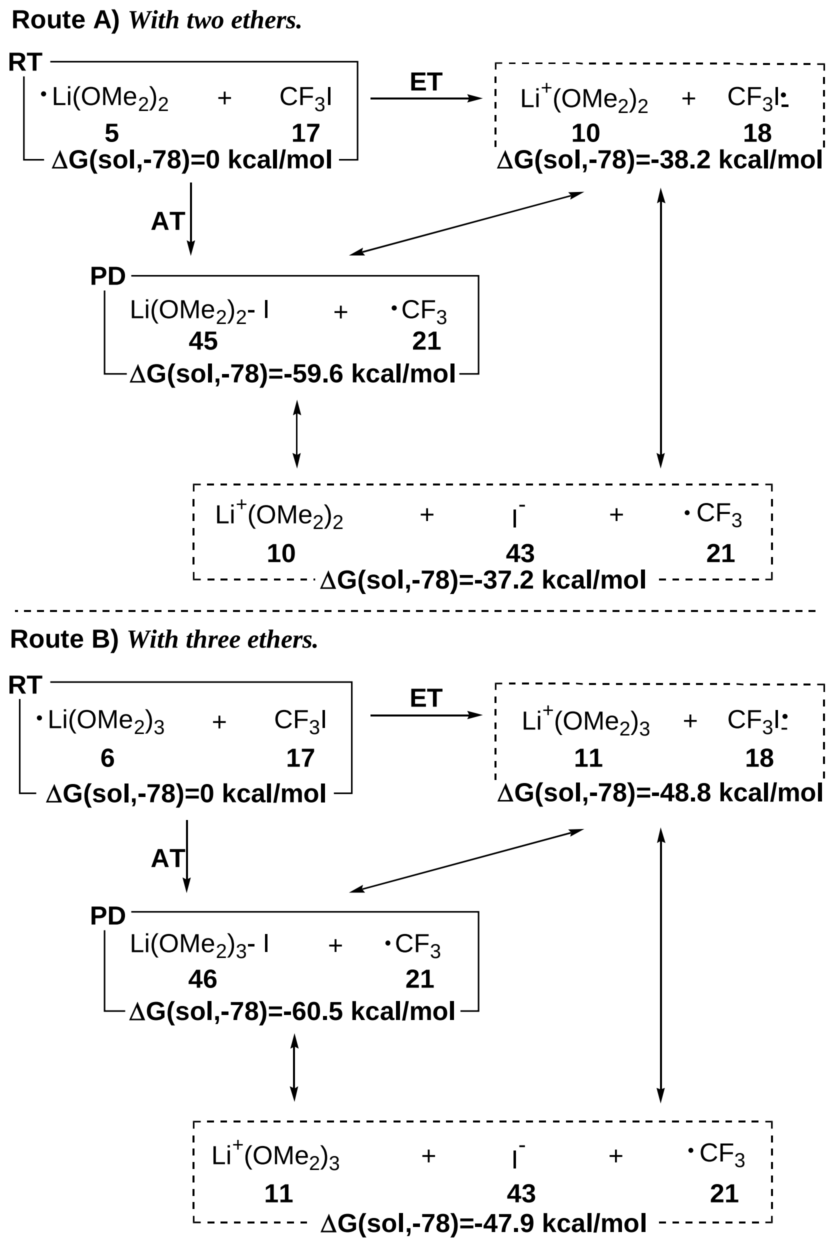


Figure 6-16. Step (3) Li: Regeneration of CF_3 radical by Li radical (with solvents).[21]

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(21) The structure **46** has imaginary frequencies (-30, -13 cm^{-1}) corresponding to vibration of ether.

6-7. Step (4).

As in the case of path (3), there are two possible pathways, that is, ET and AT pathways.[22,23] Furthermore, in AT, there are two possible routes; that is A) C-I bond forming path and B) M-I bond path (Figure 6-17). Route A involves α-iodo alkoxide intermediate **48**. Decomposition of **48** gives the α-CF_3 product. However, the structure **48** could not be optimized because I^- fall apart during the optimization and no C-I bond was formed. This phenomenon was observed in both Ti and Li cases. Therefore, route B would be the favorable pathway for AT in Step (4).

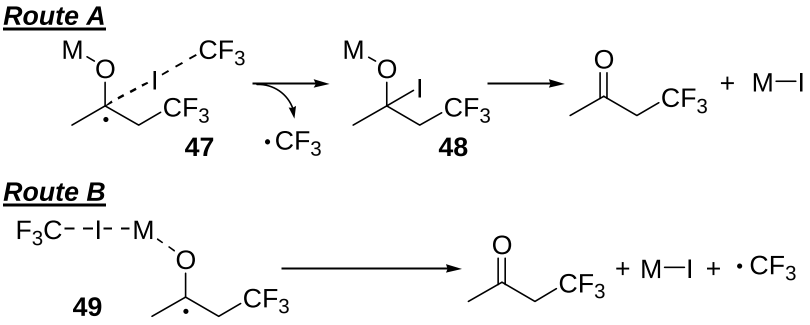

Figure 6-17. Two possible reaction pathways in AT for Step (4).

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(22) Theoretical study of the reaction of ketyl radical and alkyl halide. (a) Sastry, G. N.; Shaik, S. *J. Am. Chem. Soc.* **1995**, *117*, 3290-3291. (b) Sastry, G. N.; Shaik. S. *J. Phys. Chem.* **1996**, *100*, 12241-12252. (c) Bertran, J.; Gallardo, I.; Moreno, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1996**, *118*, 5737-5744. (d) Sastry, G. N.; Danovich, D.; Shaik, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1098-1100. (e) Shaik, S.; Danovich, D.; Sastry, G. N.; Ayala, P. Y.; Schlegel, H. B. *J. Am. Chem. Soc.* **1997**, *119*, 9237-9245. (f) Yamataka, H.; Aida, M.; Dupuis, M. *Chem. Phys. Lett.* **1999**, *300*, 583-587. (g) Bakken, V.; Danovich, D.; Shaik, S.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 130-134.

(23) Experimental study of the reaction of ketyl radical and alkyl halide. (a) Kimura, N.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2433-2437. (b) Kimura, N.; Takamuku, S.; *J. Am. Chem. Soc.* **1994**, *116*, 4087-4088.

6-7-1. Step (4)-Ti.

Energetics of Step (4) for Ti are shown in Figure 6-18. Regeneration of CF_3 radical is completed in one step in the case of AT. However, as discussed in Step (3)-Ti, AT should not take place as experimentally observed. In the case that ET takes place, it requires at least one more step to regenerate CF_3 radical. Although the reaction is exothermic, regeneration of CF_3 radical is unfavorable overall. This trend is exactly the same as in Step (3).

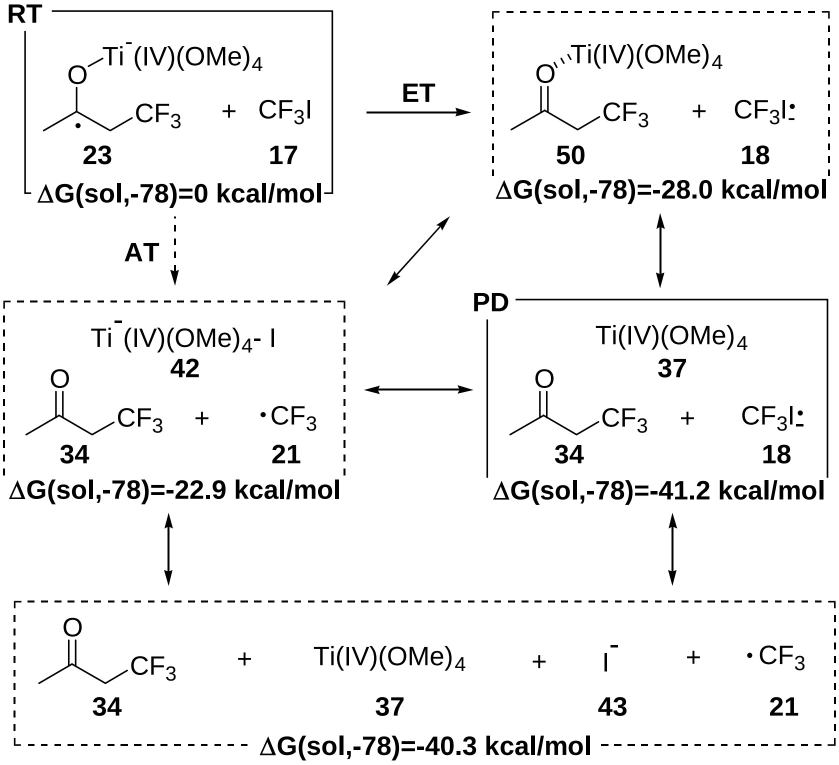

Figure 6-18. Step (4) Ti: Regeneration of CF_3 radical by radical intermediate.

6-7-2. Step (4)-Li.

Energetics of the reaction without solvent is shown in Figure 6-19. The same trend as in Step (3) was observed. Both AT and ET could be considered, and AT generates CF_3 radical in one step and ET requires at least one more step to regenerate CF_3 radical. However, in sharp contrast to Ti, regeneration of CF_3 radical from the ET product (**51**) is thermodynamically favorable because of positive bond formation of Li-I. I$^-$ could be effectively extracted from the radical anion of CF_3I to regenerate CF_3 radical.

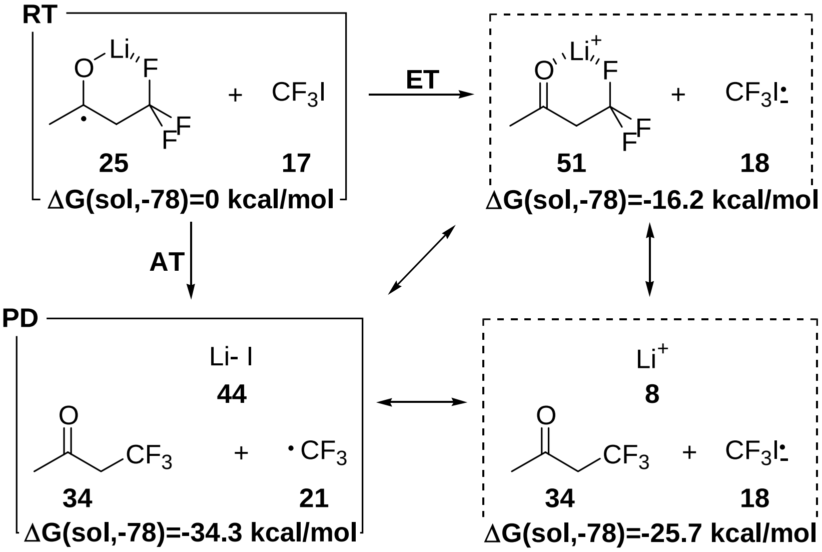

Figure 6-19. Step (4) Li: Regeneration of CF_3 radical by radical intermediate (without solvent).

In contrast to Step (3), coordination number of Li does not change during the reaction. Therefore, solvated model was constructed by attaching two ethers on Li to fill up the empty site on Li. The result of the calculations was shown in Figure 6-20. Energetics were almost the same as non-solvated model and CF_3 radical could be regenerated by extraction of I$^-$ from CF_3I radical anion (ET) or CF_3I itself (AT) by Li$^+$, although AT processes bear the lower ΔG energies; whichever routes could regenerate CF_3 radical to make the radical cycle work as experimentally observed.

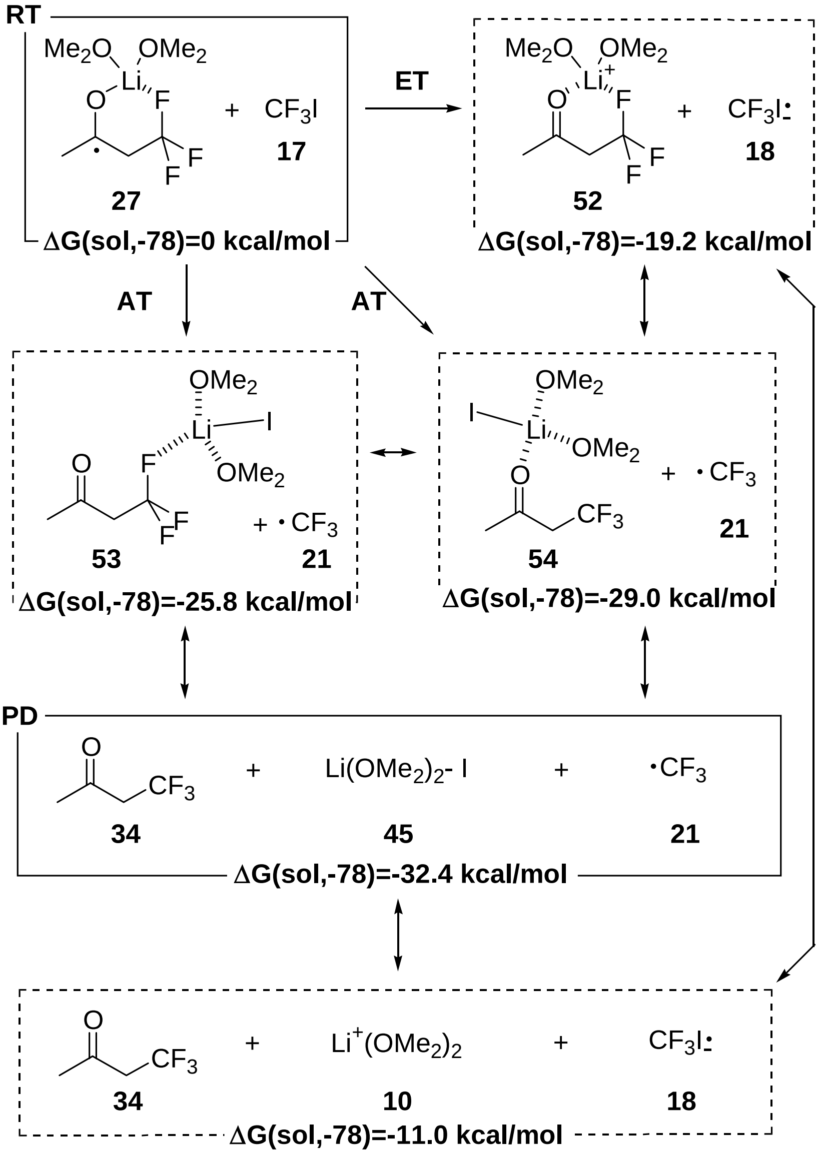

Figure 6-20. Step (4) Li: Regeneration of CF$_3$ radical by radical intermediate (with solvent).[24]

6-8. Radical anion of MeI and CF$_3$I.

It is well known that radical anion of MeI (**55**) does not have a stable form and I$^-$ will be dissociated spontaneously (Figure 6-21).[25] For the radical anion of CF$_3$I,[26]

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(24) The structure **52** has imaginary frequency (-17 cm^{-1}) corresponding to vibration of ether.

(25) (a) Rossi, R. A.; Pierini, A. B.; Palacios, S. M. In *Advances in Free Radical Chemistry*; Tanner, D. D., Eds.; Jai Press: London, 1990; Vol. 1, p 193-252. (b) Bertran, J.; Gallardo, I.; Moreno, M.; Savéant, J.-M *J. Am. Chem. Soc.* **1992**, *114*, 9576-9585. (c) Zhou, Z. Y.; Xing, Y. M. *J. Mol. Struct.* **2000**, *532*, 87-93. (d) Mariano, D.; Vera, A.; Pierini, B. *J. Phys Org. Chem.* **2002**, *15*, 894-902.

(26) Roszak, S.; Koski, W. S.; Kaufman, J. J.; Balasubramanian, K. *J. Chem.Phys.* **1997**, *106*,

strong electron withdrawing nature of F stabilizes the anion species to prevent the spontaneous dissociation of I^- and thus prevent the regeneration of CF_3 radical. This is the controlling factor of the effectiveness of the radical cycle. Although there are two routes (ET and AT) to regenerate CF_3 radical, something is required to extract I^- from CF_3I itself or the radical anion of CF_3I. In the case of Li, Li^+ has a positive bond formation with I^- but Ti(IV) does not.[27] This could be the rationale for Figure 6-2; Ti ate enolate requires equimolar amount of radical initiator and Li enolate requires only catalytic amount there of.

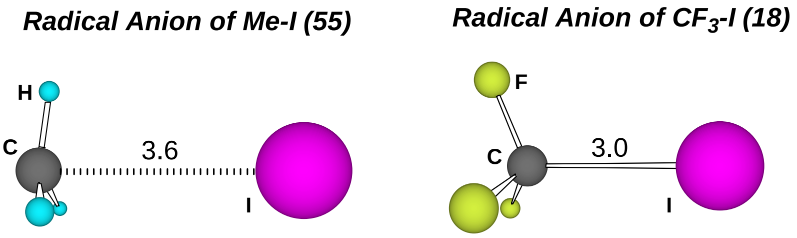

Figure 6-21. Structures of the radical anion of Me-I and CF_3-I optimized at UB3LYP/631+LAN level.

6-9. Conclusion.

The schematic reaction path is shown in Figure 6-22 and energy diagram of the reaction mechanism is shown in Figure 6-23. In the case of Ti ate enolate, the CF_3 radical addition step (Step (1)) does not have significant reaction barrier and thus readily occur. Ti(IV) ketyl radical intermediate could proceed in either Step (2) or Step (4). For Step (2), the reaction barrier is very low (3.8 kcal/mol). Ti(III) species, which was generated after Step (2), could react as a one electron reductant to CF_3I but does not have an extracting ability of I^- from radical anion of CF_3I to regenerate CF_3 radical. If Ti(IV) ketyl radical proceed to Step (4), it could produce α-CF_3 product but could not regenerate CF_3 radical as in the case in Step (3). In the case of Li enolate, the CF_3 radical addition step (Step (2)) also does not have significant reaction barrier. The difference between the reactions of Ti ate enolate and Li enolate could be first found at Step (2). Although the reaction barrier of Step (2) of Ti(IV) ketyl radical is very low (3.8 kcal/mol), Li ketyl radical has very high reaction barrier (at least 27.2 kcal/mol) and

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7709-7713.

(27) It is known that when the structure optimization was carried out in the presence of dielectric field, the $CF_3Cl + e^- \rightarrow CF_3\bullet + Cl^-$ reaction appears as a concerted electron transfer-bond breaking process as in the case of alkyl halide (see ref. 25-(b)). However, there is extra driving force for the regeneration of CF_3 radical for Li^+, which is Li-I bond formation, to facilitate the radical cycle. Therefore, even if the structure optimization was carried out in the presence of dielectric field, the major conclusion would not be changed.

thus Li ketyl radical would proceed to Step (4). Another difference between Ti and Li was observed at Step (4). Li ketyl radical could react with CF_3I to produce α-CF_3 product and Li^+ species. Li^+ could extract I^- from radical anion of CF_3I to regenerate CF_3 radical (ET). Another possibility is AT which could regenerate CF_3 radical in one step. Effective regeneration of CF_3 radical is based on positive bond formation of Li-I in either (ET or AT) case. The experimentally observed difference between Ti ate enolate and Li enolate in Figure 6-2 could be attributed to the bond forming ability of the metal species and I^- to regenerate CF_3 radical.

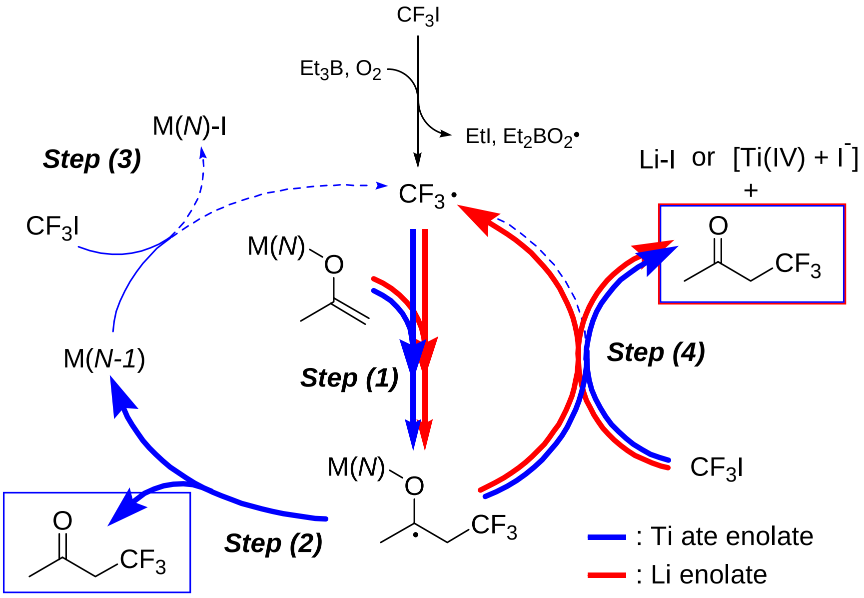


Figure 6-22. Reaction mechanism of radical trifluoromethylation of Ti ate and Li enolates.

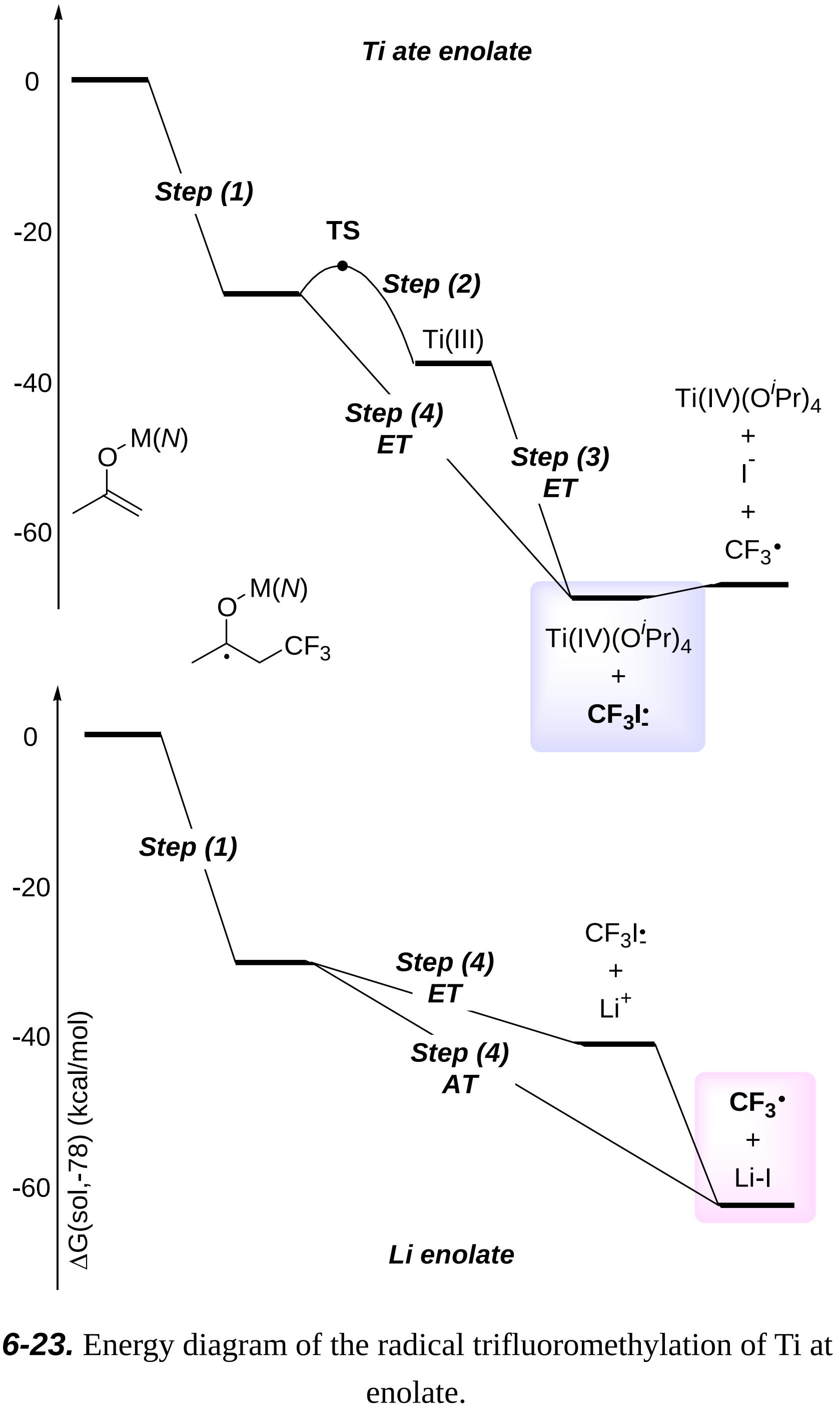


Figure 6-23. Energy diagram of the radical trifluoromethylation of Ti ate and Li enolate.

Experimental Section for Chapter 6

General

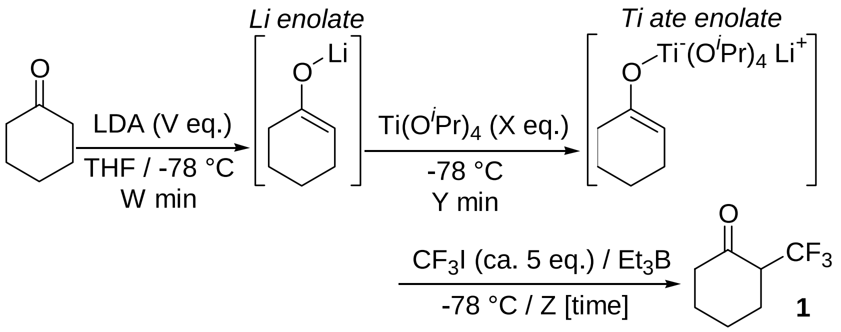
All experiments were carried out under argon atmosphere unless otherwise noted.

Analytical thin layer chromatographies (TLC) were performed on a glass plates and /or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid.

THF were distilled over benzophenone-ketyl under Ar prior to use.

Computational calculations were executed on SGI Origin2000 (Tokyo Institute of Technology), Compaq AlphaServer GS320 (Tokyo Institute of Technology), SGI2800 (Institute of Molecular Science), SGI Origin3800 (Institute of Molecular Science), and Fujitsu VPP5000 (Institute of Molecular Science).

Tabulated experimental data for the investigation of the relationship between the amount of the Et_3B and the yields (Figure 6-2).



enolate	V, W, X, Y, Z	Et_3B (eq.)	yield (%)
Li	V=1.0, W=60, X=0, Y=0, Z=~1 s	1.0	81
		0.5	76
		0.2	75
		0.1	66
		0.05	71
		0.025	53
Ti ate	V=1.6, W=30, X=1.6, Y=30, Z=2 h	1.0	81
		0.75	83
		0.5	71
		0.2	33
		0.1	5

Ti ate	V=1.0, W=30, X=1.0, Y=30, Z=2 h	1.0	56
		0.75	60
		0.5	51
		0.2	27
		0.1	1

For the experimental procedure and the physical data of the product, see the experimental section of Chapter 4 and 5.

Computational Methods

All the calculations were performed with GAUSSIAN 03 program package. All the structures were optimized at UB3LYP/631+LAN (LANL2DZ for Ti, I, 6-31+G* for others) level (E). Gibbs free energies (G) contain zero-point, thermal and entropy effects at 298.15 K and 1 atm pressure. Then the energies were recalculated in the presence of dielectric field (THF, ε=7.58) as described by the C-PCM (COSMO (conductor-like screening model)) model at UB3LYP/6311+LAN (LANL2DZ for Ti, I, 6-311+G* for others) level (E(sol)). Gibbs free energies (G(sol,-78)) contain zero-point, thermal and entropy effects at 195.15 K (-78 ºC) and 1 atm pressure.

Molecular Geometries and Energies

3: Li radical.

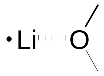
```
Charge=0, Multiplicity=2
```

•Li

```
E(UB3LYP/631+LAN)=  -7.49111328996 a.u.
G(UB3LYP/631+LAN)=  -7.504516 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -7.524294 a.u.
```

4: Li radical with one dimethyl ether.

```
Charge=0, Multiplicity=2
```

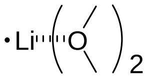


```
E(UB3LYP/631+LAN)=  -162.540264501 a.u.
G(UB3LYP/631+LAN)=  -162.487524 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
    1          3           0       -0.013338    2.239848    0.000000
```

```
     2          8              0         0.000000    0.330203    0.000000
     3          6              0         1.197847   -0.454594    0.000000
     4          1              0         1.239245   -1.082862    0.898823
     5          1              0         1.239245   -1.082862   -0.898823
     6          1              0         2.038350    0.244348    0.000000
     7          6              0        -1.193732   -0.461071    0.000000
     8          1              0        -1.231729   -1.089553    0.898824
     9          1              0        -2.038058    0.233306    0.000000
    10          1              0        -1.231729   -1.089553   -0.898824
 ---------------------------------------------------------------------
```

5: Li radical with two dimethyl ethers.

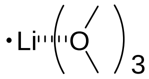
```
Charge=0, Multiplicity=2
```



```
E(UB3LYP/631+LAN)=  -317.585341556 a.u.
G(UB3LYP/631+LAN)=  -317.462352 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -317.529107 a.u.
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
     1          3              0        -0.055546   -0.054371   -1.270073
     2          8              0         1.533741   -0.007939   -0.125303
     3          6              0         2.228501    1.229180    0.066180
     4          1              0         1.486165    2.029074    0.000730
     5          1              0         2.706226    1.242325    1.055325
     6          1              0         2.984158    1.369698   -0.717614
     7          6              0         2.403299   -1.144974   -0.076542
     8          1              0         2.870817   -1.216422    0.915072
     9          1              0         1.787524   -2.028593   -0.264145
    10          1              0         3.176342   -1.070137   -0.852368
    11          8              0        -1.618526   -0.006345   -0.139263
    12          6              0        -1.624232   -0.116899    1.284776
    13          1              0        -2.118676    0.755083    1.733498
    14          1              0        -2.144227   -1.032976    1.595449
    15          1              0        -0.580910   -0.156921    1.605395
    16          6              0        -2.933565    0.059119   -0.703748
    17          1              0        -3.496519   -0.850966   -0.456457
    18          1              0        -3.462599    0.944116   -0.324927
    19          1              0        -2.807395    0.134549   -1.787204
 ---------------------------------------------------------------------
```

6: Li radical with three dimethyl ethers.

`Charge=0, Multiplicity=2`



```
E(UB3LYP/631+LAN)=  -472.628763985 a.u.

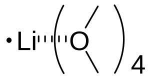
G(UB3LYP/631+LAN)=  -472.432311 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -472.534280 a.u.
```

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          3           0        0.004195   -0.002530   -0.669307
    2          8           0       -1.525450   -1.035941   -0.046170
    3          6           0       -2.010143   -2.148537   -0.807331
    4          1           0       -1.238604   -2.392512   -1.543676
    5          1           0       -2.189032   -3.007953   -0.145067
    6          1           0       -2.936529   -1.875803   -1.330776
    7          6           0       -2.467827   -0.572272    0.922010
    8          1           0       -2.696470   -1.369460    1.642170
    9          1           0       -2.009683    0.274809    1.438499
   10          1           0       -3.393766   -0.246391    0.428348
   11          8           0        1.671387   -0.796145   -0.035472
   12          6           0        1.731790   -1.908042    0.859817
   13          1           0        2.530299   -1.758288    1.598960
   14          1           0        0.764509   -1.968503    1.364479
   15          1           0        1.915336   -2.837776    0.303721
   16          6           0        2.885498   -0.610360   -0.773767
   17          1           0        3.713321   -0.386478   -0.085512
   18          1           0        3.114803   -1.509896   -1.360773
   19          1           0        2.721284    0.230247   -1.454237
   20          8           0       -0.145261    1.835423   -0.036044
   21          6           0       -0.925924    2.786466   -0.770235
   22          1           0       -1.540359    3.382315   -0.079764
   23          1           0       -0.270884    3.445016   -1.356102
   24          1           0       -1.565348    2.217577   -1.451663
   25          6           0        0.785046    2.451319    0.856845
   26          1           0        1.491978    3.080645    0.298856
   27          1           0        0.252581    3.063741    1.597149
   28          1           0        1.327928    1.648163    1.360761
---------------------------------------------------------------------
```

7: Li radical with four dimethyl ethers.

```
Charge=0, Multiplicity=2
```



```
E(UB3LYP/631+LAN)=  -627.673050021 a.u.

G(UB3LYP/631+LAN)=  -627.401664 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          3           0       -0.000330   -0.001610    0.001252
    2          8           0        1.199075    0.792698   -1.342109
    3          6           0        1.134505    2.147099   -1.797999
    4          1           0        0.280128    2.616968   -1.305316
    5          1           0        2.053703    2.684798   -1.526530
    6          1           0        0.997404    2.176920   -2.888015
    7          6           0        2.313789    0.083208   -1.889268
    8          1           0        3.256694    0.562048   -1.589504
    9          1           0        2.281051   -0.936178   -1.494660
   10          1           0        2.249289    0.056476   -2.986115
   11          8           0       -1.194826    1.345093    0.795482
   12          6           0       -1.129189    1.801661    2.149657
   13          1           0       -0.997236    2.892336    2.178751
   14          1           0       -2.045612    1.525714    2.689809
   15          1           0       -0.271064    1.313627    2.617712
   16          6           0       -2.312698    1.888574    0.088032
   17          1           0       -3.253774    1.585958    0.568652
   18          1           0       -2.251635    2.985595    0.061171
   19          1           0       -2.280577    1.493988   -0.931386
   20          8           0       -1.212244   -1.328486   -0.797258
   21          6           0       -1.135288   -1.801208   -2.145259
   22          1           0       -0.974095   -2.888268   -2.160679
   23          1           0       -2.059518   -1.557267   -2.687424
   24          1           0       -0.291404   -1.295678   -2.620514
   25          6           0       -2.318815   -1.886045   -0.083218
   26          1           0       -3.264971   -1.615721   -0.572973
   27          1           0       -2.231229   -2.980597   -0.034594
   28          1           0       -2.300435   -1.471063    0.928501
   29          8           0        1.209537   -0.802060    1.327950
   30          6           0        1.129974   -2.149030    1.803294
   31          1           0        2.053356   -2.693297    1.560826
   32          1           0        0.968001   -2.162068    2.890283
   33          1           0        0.285462   -2.623943    1.298363
   34          6           0        2.316748   -0.088761    1.885225
   35          1           0        2.300885    0.921900    1.467611
   36          1           0        2.227772   -0.037325    2.979527
   37          1           0        3.262301   -0.581047    1.617447
---------------------------------------------------------------------
```

8: Li cation.

Charge=1, Multiplicity=1

Li^+

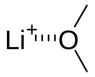
E(UB3LYP/631+LAN)= -7.28456710192 a.u.

G(UB3LYP/631+LAN)= -7.297315 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -7.479987 a.u.

9: Li cation with one dimethyl ether.

Charge=1, Multiplicity=1



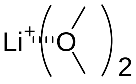
E(UB3LYP/631+LAN)= -162.378864248 a.u.

G(UB3LYP/631+LAN)= -162.324303 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          3           0        0.012597    2.163533   -0.000001
    2          8           0        0.000758    0.353290   -0.000014
    3          6           0       -1.206703   -0.450337   -0.000002
    4          1           0       -1.233093   -1.073528    0.898939
    5          1           0       -2.058880    0.233426   -0.000234
    6          1           0       -1.232849   -1.073998   -0.898646
    7          6           0        1.202216   -0.458972    0.000004
    8          1           0        1.224360   -1.082588   -0.898824
    9          1           0        2.059436    0.218554    0.000276
   10          1           0        1.224094   -1.082925    0.898599
 ---------------------------------------------------------------------
```

10: Li cation with two dimethyl ethers.

Charge=1, Multiplicity=1



E(UB3LYP/631+LAN)= -317.463877779 a.u.

G(UB3LYP/631+LAN)= -317.337579 a.u.

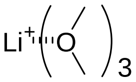
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -317.458589 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          3           0        0.000000   -0.000111   -0.000165
    2          8           0        1.838476    0.000009   -0.000022
    3          6           0        2.641814    0.849498    0.848789
    4          1           0        3.266313    1.505986    0.233989
```

```
     5          1             0        1.959200    1.451462    1.453011
     6          1             0        3.269074    0.235228    1.503147
     7          6             0        2.641962   -0.849452   -0.848726
     8          1             0        3.266401   -1.505920   -0.233846
     9          1             0        1.959451   -1.451443   -1.453042
    10          1             0        3.269283   -0.235164   -1.503007
    11          8             0       -1.838476   -0.000036   -0.000038
    12          6             0       -2.641872   -0.848814    0.849430
    13          1             0       -3.266256   -0.233992    1.506005
    14          1             0       -3.269247   -1.503045    0.235144
    15          1             0       -1.959299   -1.453171    1.451306
    16          6             0       -2.641904    0.848822   -0.849398
    17          1             0       -3.266499    0.234059   -1.505827
    18          1             0       -3.269068    1.503181   -0.235032
    19          1             0       -1.959352    1.453046   -1.451434
 ---------------------------------------------------------------------
```

11: Li cation with three dimethyl ethers.

Charge=1, Multiplicity=1



E(UB3LYP/631+LAN)= -472.531328303 a.u.

G(UB3LYP/631+LAN)= -472.332090 a.u.

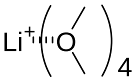
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -472.480714 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
     1          3             0        0.000111   -0.000191   -0.001175
     2          8             0        0.505031    1.824112    0.000748
     3          6             0       -0.161893    2.839516   -0.768896
     4          6             0        1.604073    2.346870    0.766933
     5          8             0        1.326587   -1.348678    0.001694
     6          6             0        2.524332   -1.298104   -0.792756
     7          6             0        1.244286   -2.543414    0.798124
     8          8             0       -1.832736   -0.471229   -0.003409
     9          6             0       -2.824535    0.171689    0.815826
    10          6             0       -2.385536   -1.519413   -0.818233
    11          1             0        0.537080    3.293281   -1.480961
    12          1             0       -0.976323    2.355251   -1.311607
    13          1             0       -0.567582    3.611846   -0.105065
    14          1             0        1.245720    3.106939    1.470752
    15          1             0        2.042669    1.513235    1.319292
    16          1             0        2.355790    2.785068    0.100051
    17          1             0        2.505870   -0.360034   -1.351395
    18          1             0        3.408854   -1.326171   -0.145863
    19          1             0        2.549512   -2.142623   -1.491067
    20          1             0        1.251603   -3.429568    0.152856
    21          1             0        2.086161   -2.588361    1.498649
    22          1             0        0.305512   -2.500703    1.354274
```

```
   23         1            0      -3.605292   0.614921   0.186817
   24         1            0      -3.271970  -0.553059   1.505837
   25         1            0      -2.319835   0.956271   1.383401
   26         1            0      -2.838249  -2.291709  -0.185546
   27         1            0      -3.140068  -1.109633  -1.499583
   28         1            0      -1.565200  -1.950886  -1.395572
---------------------------------------------------------------------
```

12: Li cation with four dimethyl ethers.

`Charge=1, Multiplicity=1`



```
E(UB3LYP/631+LAN)=  -627.584655641 a.u.

G(UB3LYP/631+LAN)=  -627.311971 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
    1         3            0       0.000752  -0.002758  -0.010741
    2         8            0      -1.144381  -0.229016   1.585785
    3         6            0      -0.802394  -1.072716   2.692554
    4         1            0       0.070030  -1.656507   2.395919
    5         1            0      -0.564448  -0.468450   3.577259
    6         1            0      -1.633386  -1.749789   2.926266
    7         6            0      -2.325657   0.542118   1.833811
    8         1            0      -2.183255   1.197132   2.703087
    9         1            0      -2.513062   1.145411   0.943618
   10         1            0      -3.181520  -0.119497   2.017339
   11         8            0      -1.288482   0.153376  -1.491497
   12         6            0      -2.396812  -0.736841  -1.670117
   13         1            0      -2.423611  -1.401026  -0.804029
   14         1            0      -3.335352  -0.171381  -1.727588
   15         1            0      -2.273267  -1.325939  -2.587906
   16         6            0      -1.175183   1.105063  -2.556931
   17         1            0      -1.002907   0.594058  -3.512577
   18         1            0      -2.088224   1.709499  -2.625636
   19         1            0      -0.327535   1.751553  -2.325436
   20         8            0       1.170526   1.578982   0.124026
   21         6            0       0.947126   2.656086   1.043076
   22         1            0       1.827359   2.801497   1.681692
   23         1            0       0.732207   3.585445   0.500729
   24         1            0       0.089841   2.382934   1.660043
   25         6            0       2.295341   1.817009  -0.730675
   26         1            0       2.137829   2.722640  -1.330348
   27         1            0       3.209836   1.932236  -0.135483
   28         1            0       2.394414   0.951854  -1.389060
   29         8            0       1.228096  -1.540176  -0.204301
   30         6            0       1.015626  -2.618449  -1.123878
   31         1            0       0.058472  -2.441557  -1.616486
   32         1            0       1.815518  -2.643515  -1.874730
   33         1            0       0.985321  -3.576610  -0.590241
```

```
   34         6           0        2.465597   -1.666591    0.505759
   35         1           0        2.481159   -2.598423    1.085160
   36         1           0        3.311683   -1.661047   -0.193131
   37         1           0        2.542705   -0.811639    1.180064
---------------------------------------------------------------------
```

13: Ti^-(III)(OMe)$_4$.

```
Charge=-1, Multiplicity=2
```

Ti^-(III)(OMe)$_4$

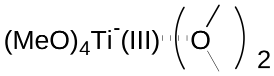
```
E(UB3LYP/631+LAN)=  -518.840710058 a.u.

G(UB3LYP/631+LAN)=  -518.727741 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -518.890711 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
    1        22           0       -0.046055    0.000358   -0.002429
    2         8           0       -1.184757    1.530963   -0.203629
    3         8           0       -1.201377   -1.518372    0.194965
    4         8           0        1.137962    0.146528    1.501546
    5         8           0        1.150675   -0.151941   -1.495409
    6         6           0        2.043813    0.797401   -1.989294
    7         6           0       -1.935508    2.220123    0.744958
    8         6           0       -1.947810   -2.209582   -0.755384
    9         6           0        2.012801   -0.813878    2.006860
   10         1           0        2.762209    1.137249   -1.218156
   11         1           0        1.528787    1.698297   -2.375482
   12         1           0        2.636252    0.376468   -2.824614
   13         1           0        2.768258   -1.126046    1.259689
   14         1           0        1.486621   -1.729033    2.341051
   15         1           0        2.563613   -0.416451    2.881311
   16         1           0       -2.124463   -3.253703   -0.431255
   17         1           0       -1.446296   -2.255546   -1.741415
   18         1           0       -2.942135   -1.747822   -0.914942
   19         1           0       -1.439584    2.261428    1.733994
   20         1           0       -2.931606    1.759722    0.897119
   21         1           0       -2.108241    3.265738    0.423518
---------------------------------------------------------------------
```

14: Ti$^-$(III)(OMe)$_4$ with two dimethyl ethers.

Charge=-1, Multiplicity=2



E(UB3LYP/631+LAN)= -828.886666499 a.u.

G(UB3LYP/631+LAN)= -828.617087 a.u.

This structure has imaginary frequency (-8 cm^{-1}) corresponding to the vibration of ether.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1         22           0       -0.098666    0.085784   -0.026261
    2          8           0       -2.330123    0.008063   -0.047378
    3          8           0        0.076852   -0.420018   -1.895918
    4          8           0       -0.058894   -1.932009    0.464649
    5          8           0        2.280034    0.121923    0.009891
    6          8           0        0.107023    0.492948    1.871688
    7          8           0       -0.337571    2.034615   -0.484693
    8          6           0       -3.154216    1.131495   -0.332539
    9          1           0       -3.669682    0.985353   -1.294745
   10          1           0       -3.902750    1.258961    0.465776
   11          1           0       -2.477637    1.987411   -0.391598
   12          6           0       -3.016620   -1.236779   -0.024254
   13          1           0       -3.749547   -1.248945    0.797673
   14          1           0       -3.539022   -1.395929   -0.980544
   15          1           0       -2.246742   -1.997488    0.121092
   16          6           0        2.976344   -0.102244   -1.206705
   17          1           0        2.420244    0.410607   -1.991327
   18          1           0        4.002825    0.293275   -1.129494
   19          1           0        3.012988   -1.176445   -1.437818
   20          6           0        2.858857   -0.568334    1.112593
   21          1           0        2.875789   -1.649860    0.919139
   22          1           0        3.884043   -0.201119    1.285634
   23          1           0        2.214641   -0.361590    1.968038
   24          6           0        0.137521    1.698409    2.556411
   25          1           0       -0.571548    1.692495    3.410225
   26          1           0        1.142322    1.899638    2.988586
   27          1           0       -0.120001    2.550563    1.903473
   28          6           0        0.574249    2.854017   -1.123080
   29          1           0        0.184146    3.889463   -1.234124
   30          1           0        1.538915    2.940548   -0.576361
   31          1           0        0.818456    2.497239   -2.146850
   32          6           0       -0.128169   -2.556705    1.690209
   33          1           0        0.149408   -1.888912    2.529616
   34          1           0       -1.152657   -2.940017    1.931036
   35          1           0        0.537546   -3.449754    1.740392
   36          6           0        0.151318   -1.632723   -2.562112
   37          1           0        1.095376   -1.722655   -3.143532
   38          1           0        0.101522   -2.488354   -1.866339
```

```
  39          1            0      -0.672264   -1.738708   -3.299258
---------------------------------------------------------------------
```

15: Ti(IV)(OMe)$_4$.

```
Charge=0, Multiplicity=1
```

Ti(IV)(OMe)$_4$

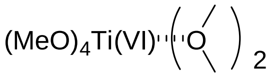
```
E(UB3LYP/631+LAN)=  -518.825262428 a.u.

G(UB3LYP/631+LAN)=  -518.708669 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -518.809260 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
   1         22            0      -0.013181    0.018412   -0.019730
   2          8            0      -1.141358    1.221388    0.696364
   3          8            0       1.139643    0.860095   -1.117957
   4          8            0       0.939777   -0.812207    1.261696
   5          8            0      -0.970880   -1.215939   -0.913231
   6          6            0      -1.422865    2.466058    1.277614
   7          1            0      -0.951441    3.277501    0.705666
   8          1            0      -2.508853    2.627185    1.288379
   9          1            0      -1.052821    2.498404    2.311795
  10          6            0       1.201836   -2.007787    1.951914
  11          1            0       0.731737   -2.863371    1.447565
  12          1            0       2.285893   -2.175667    1.999355
  13          1            0       0.812462   -1.940655    2.976679
  14          6            0      -2.176576   -1.564980   -1.543287
  15          1            0      -2.093992   -1.409852   -2.627620
  16          1            0      -2.393967   -2.624793   -1.356179
  17          1            0      -3.008940   -0.959106   -1.159039
  18          6            0       2.451101    1.025831   -1.588083
  19          1            0       2.648931    2.092375   -1.759144
  20          1            0       3.179866    0.642804   -0.859793
  21          1            0       2.582660    0.488691   -2.537518
---------------------------------------------------------------------
```

16: Ti(IV)(OMe)$_4$ with two dimethyl ethers.

```
Charge=0, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -828.874080343 a.u.
G(UB3LYP/631+LAN)=  -828.594978 a.u.
```

This structure has imaginary frequencies (-35, -28 cm^{-1}) corresponding to the vibration of ether.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         22          0       -0.003097    0.000000    0.000000
    2          8          0        2.233934   -0.000001    0.000001
    3          8          0       -0.188098    1.856755   -0.202041
    4          8          0        0.188150    0.201537    1.855891
    5          8          0       -2.236776    0.000001    0.000000
    6          8          0       -0.188099   -1.856756    0.202038
    7          8          0        0.188151   -0.201537   -1.855890
    8          6          0        3.013899   -0.861669   -0.829864
    9          1          0        3.691361   -0.266545   -1.456663
   10          1          0        3.597179   -1.550944   -0.205112
   11          1          0        2.314827   -1.414372   -1.455859
   12          6          0        3.013899    0.861667    0.829865
   13          1          0        3.691364    0.266545    1.456663
   14          1          0        3.597177    1.550944    0.205112
   15          1          0        2.314827    1.414369    1.455861
   16          6          0       -3.015817    0.830319   -0.862075
   17          1          0       -2.316300    1.458688   -1.411677
   18          1          0       -3.596112    0.205970   -1.554185
   19          1          0       -3.695784    1.454742   -0.267377
   20          6          0       -3.015818   -0.830317    0.862076
   21          1          0       -3.596113   -0.205968    1.554185
   22          1          0       -3.695785   -1.454740    0.267377
   23          1          0       -2.316302   -1.458686    1.411677
   24          6          0       -0.521338   -2.905179   -0.662999
   25          1          0        0.052261   -3.807287   -0.398968
   26          1          0       -1.592255   -3.157486   -0.581307
   27          1          0       -0.310928   -2.636063   -1.709354
   28          6          0        0.527618    0.663095   -2.902673
   29          1          0        1.598845    0.577384   -3.152221
   30          1          0       -0.044628    0.401880   -3.806448
   31          1          0        0.320377    1.709979   -2.633306
   32          6          0        0.527616   -0.663095    2.902673
   33          1          0        0.320373   -1.709979    2.633307
   34          1          0        1.598843   -0.577385    3.152221
   35          1          0       -0.044629   -0.401879    3.806449
   36          6          0       -0.521335    2.905179    0.662997
   37          1          0       -1.592252    3.157487    0.581305
   38          1          0       -0.310926    2.636063    1.709352
```

```
   39          1             0        0.052265    3.807287    0.398965
 ---------------------------------------------------------------------
```

17: CF_3I.

Charge=0, Multiplicity=1

CF_3I

E(UB3LYP/631+LAN)= -349.018444593 a.u.

E(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -349.114136646 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -349.121674 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6             0       -1.195600    0.000040   -0.000022
    2         53             0        0.984300    0.000015    0.000024
    3          9             0       -1.666640   -0.080729    1.250908
    4          9             0       -1.666242   -1.043150   -0.695391
    5          9             0       -1.666483    1.123767   -0.555643
 ---------------------------------------------------------------------
```

18: anion radical of CF_3I.

Charge=-1, Multiplicity=2

$CF_3I^{\bullet}_{-}$

E(UB3LYP/631+LAN)= -349.076225064 a.u.

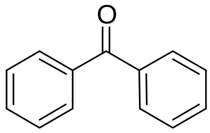
E(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -349.172090437 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -349.253018 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6             0        0.000000    0.000000   -1.654211
    2          9             0        0.000000    1.262126   -2.192298
    3          9             0        1.093033   -0.631063   -2.192298
    4          9             0       -1.093033   -0.631063   -2.192298
    5         53             0        0.000000    0.000000    1.304100
 ---------------------------------------------------------------------
```

19: benzophenone.

```
Charge=0, Multiplicity=1
```

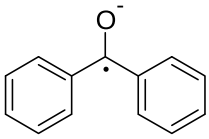


```
E(UB3LYP/631+LAN)=  -576.643660499 a.u.

E(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -576.764580737 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        0.000015    1.094974   -0.000245
    2          8           0        0.000015    2.323310   -0.000055
    3          6           0       -1.301785    0.348291   -0.026655
    4          6           0       -1.445814   -0.897559   -0.659778
    5          6           0       -2.431306    0.963085    0.540710
    6          6           0       -2.696553   -1.517594   -0.720527
    7          1           0       -0.588081   -1.370857   -1.128198
    8          6           0       -3.673780    0.332631    0.499550
    9          1           0       -2.315373    1.936250    1.008107
   10          6           0       -3.809365   -0.909163   -0.133034
   11          1           0       -2.801120   -2.473641   -1.226948
   12          1           0       -4.538448    0.809631    0.953729
   13          1           0       -4.780071   -1.397012   -0.172218
   14          6           0        1.301802    0.348279    0.026439
   15          6           0        1.445700   -0.897540    0.659655
   16          6           0        2.431433    0.963025   -0.540758
   17          6           0        2.696416   -1.517597    0.720649
   18          1           0        0.587874   -1.370799    1.127946
   19          6           0        3.673888    0.332548   -0.499352
   20          1           0        2.315598    1.936167   -1.008228
   21          6           0        3.809341   -0.909216    0.133318
   22          1           0        2.800878   -2.473622    1.227135
   23          1           0        4.538643    0.809508   -0.953408
   24          1           0        4.780030   -1.397082    0.172695
---------------------------------------------------------------------
```

20: anion radical of benzophenone.

```
Charge=-1, Multiplicity=2
```



```
E(UB3LYP/631+LAN)=  -576.669092230 a.u.
E(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -576.790650971 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -0.000009    1.017926    0.000191
    2          8           0       -0.000005    2.298555   -0.000036
    3          6           0        1.292564    0.310920    0.011236
    4          6           0        1.507300   -1.024924    0.452659
    5          6           0        2.456276    1.046178   -0.357531
    6          6           0        2.780694   -1.591265    0.479555
    7          1           0        0.671582   -1.608894    0.824746
    8          6           0        3.723368    0.473350   -0.338419
    9          1           0        2.315220    2.080876   -0.654708
   10          6           0        3.908674   -0.858987    0.071874
   11          1           0        2.899420   -2.613899    0.838201
   12          1           0        4.583905    1.069222   -0.643891
   13          1           0        4.900682   -1.306462    0.089723
   14          6           0       -1.292575    0.310911   -0.011044
   15          6           0       -1.507232   -1.024931   -0.452514
   16          6           0       -2.456350    1.046156    0.357551
   17          6           0       -2.780614   -1.591287   -0.479602
   18          1           0       -0.671451   -1.608888   -0.824481
   19          6           0       -3.723433    0.473313    0.338244
   20          1           0       -2.315348    2.080851    0.654762
   21          6           0       -3.908664   -0.859023   -0.072086
   22          1           0       -2.899276   -2.613922   -0.838269
   23          1           0       -4.584022    1.069173    0.643593
   24          1           0       -4.900664   -1.306508   -0.090085
---------------------------------------------------------------------
```

21: CF$_3$ radical.

```
Charge=0, Multiplicity=2
```

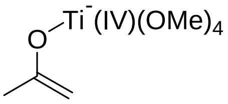
$\cdot CF_3$

```
E(UB3LYP/631+LAN)=  -337.575706492 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -337.676881 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        0.000000    0.000213    0.330477
    2          9           0       -1.096968   -0.633102   -0.073424
```

```
   3         9            0        1.096928   -0.633171   -0.073424
   4         9            0        0.000040    1.266130   -0.073469
---------------------------------------------------------------------
```

22: Ti ate enolate.

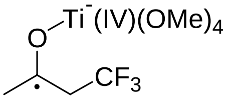
```
Charge=-1, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -711.435921430 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -711.450729 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1         8            0        1.101738   -0.753450   -0.556630
   2         6            0        2.424185   -0.678294   -0.425117
   3         6            0        2.949362   -0.973443    0.965385
   4         6            0        3.252016   -0.407531   -1.464800
   5        22            0       -0.436419    0.150776    0.239732
   6         8            0       -1.461617   -1.124914   -0.749385
   7         6            0       -1.261352   -1.896130   -1.886656
   8         1            0       -1.810159   -2.853516   -1.807798
   9         1            0       -0.191949   -2.118490   -2.032188
  10         1            0       -1.628751   -1.384658   -2.798399
  11         8            0       -1.333702    1.566691   -0.622761
  12         6            0       -2.440277    1.586523   -1.470585
  13         1            0       -2.173058    2.029411   -2.447721
  14         1            0       -3.246442    2.207248   -1.037786
  15         1            0       -2.838677    0.574692   -1.643528
  16         8            0        0.709384    1.431475    1.001165
  17         6            0        1.237455    2.641390    0.565399
  18         1            0        1.565922    3.247646    1.429248
  19         1            0        0.480839    3.216268    0.003545
  20         1            0        2.112674    2.489923   -0.090690
  21         8            0       -1.126825   -0.454094    1.850528
  22         6            0       -2.040739   -1.457754    2.176266
  23         1            0       -2.410220   -1.966162    1.272318
  24         1            0       -2.902055   -1.030942    2.720107
  25         1            0       -1.568650   -2.207195    2.835902
  26         1            0        2.609259   -1.966509    1.290202
  27         1            0        2.539427   -0.240212    1.669658
  28         1            0        4.045053   -0.944126    1.004831
  29         1            0        2.851957   -0.190877   -2.451830
  30         1            0        4.330312   -0.393801   -1.332675
---------------------------------------------------------------------
```

23: Ti ate ketyl radical.

```
Charge=-1, Multiplicity=2
```

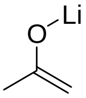


```
E(UB3LYP/631+LAN)=  -1049.078676760 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -1049.172280 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0       -0.479992    0.030411   -0.475963
    2          6           0       -1.460690   -0.827764   -0.440569
    3          6           0       -1.302583   -2.173519    0.209354
    4          6           0       -2.795869   -0.373302   -0.971713
    5         22           0        1.484252    0.098495   -0.130361
    6          8           0        1.409293    1.938090   -0.487046
    7          6           0        0.392013    2.892421   -0.512613
    8          1           0        0.362848    3.465590    0.431485
    9          1           0       -0.594336    2.427285   -0.659125
   10          1           0        0.567296    3.610920   -1.333225
   11          8           0        3.375821    0.226826    0.084059
   12          6           0        4.135521    1.270719    0.603026
   13          1           0        5.195761    1.159910    0.309328
   14          1           0        4.102107    1.296896    1.709806
   15          1           0        3.770135    2.245203    0.236427
   16          8           0        1.729670   -1.242422   -1.424641
   17          6           0        2.871588   -1.823221   -1.979032
   18          1           0        2.851600   -2.919931   -1.840983
   19          1           0        3.788800   -1.428083   -1.515361
   20          1           0        2.916533   -1.629306   -3.066307
   21          8           0        1.202354   -0.502736    1.623073
   22          6           0        2.067870   -1.104373    2.537825
   23          1           0        1.978215   -0.618621    3.526048
   24          1           0        3.118381   -1.041535    2.211280
   25          1           0        1.814605   -2.172129    2.671877
   26          1           0       -1.339969   -2.117331    1.310579
   27          1           0       -0.326184   -2.599294   -0.053081
   28          1           0       -2.093263   -2.866404   -0.112440
   29          1           0       -2.639017    0.425903   -1.706903
   30          6           0       -3.773627    0.181974    0.054565
   31          1           0       -3.336241   -1.195582   -1.465597
   32          9           0       -4.114890   -0.732718    1.006439
   33          9           0       -4.959785    0.563733   -0.532657
   34          9           0       -3.313470    1.272389    0.709908
---------------------------------------------------------------------
```

24: Li enolate without solvent.

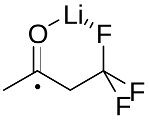
```
Charge=0, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -200.106838202 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -200.155226 a.u.
-------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type            X           Y           Z
-------------------------------------------------------------------
    1          8           0      -1.133263   -0.048423    0.013214
    2          6           0       0.182432    0.123535    0.002514
    3          6           0       0.787623    1.335337   -0.003290
    4          3           0      -2.748241   -0.178463   -0.021793
    5          1           0       0.202685    2.251609    0.002020
    6          1           0       1.869119    1.424389   -0.011698
    7          6           0       0.982806   -1.164804   -0.002529
    8          1           0       0.722698   -1.768765   -0.882797
    9          1           0       0.736727   -1.766259    0.883386
   10          1           0       2.062434   -0.982616   -0.011413
-------------------------------------------------------------------
```

25: Li ketyl radical without solvent.

```
Charge=0, Multiplicity=2
```

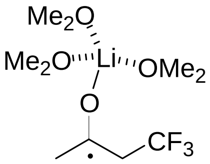


```
E(UB3LYP/631+LAN)=  -537.752166162 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -537.867652 a.u.
-------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type            X           Y           Z
-------------------------------------------------------------------
    1          8           0       1.537134    1.258773   -0.008221
    2          6           0       1.447203   -0.060938    0.070010
    3          6           0       2.720848   -0.860929    0.064988
    4          6           0       0.224922   -0.697904   -0.565396
    5          3           0       0.218800    2.326840   -0.102047
    6          1           0       3.436657   -0.428428    0.773925
    7          1           0       3.213165   -0.848355   -0.929197
    8          1           0       2.555759   -1.910943    0.338087
    9          1           0       0.163551   -0.493813   -1.656655
   10          6           0      -1.098474   -0.233224    0.003697
   11          1           0       0.229250   -1.787183   -0.443217
   12          9           0      -1.237431   -0.419693    1.324643
   13          9           0      -2.164291   -0.795988   -0.601446
```

```
  14          9           0       -1.300372    1.164124   -0.184401
---------------------------------------------------------------------
```

26: Li ketyl radical with three dimethyl ether.

`Charge=0, Multiplicity=2`

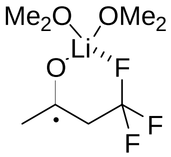


```
E(UB3LYP/631+LAN)=  -1002.90755121 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -1002.872851 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0        0.218648    1.231941   -0.268084
    2          6           0        1.450117    1.689553   -0.170878
    3          6           0        1.640211    3.184523   -0.067899
    4          6           0        2.540882    0.904335   -0.877043
    5          3           0       -1.083264    0.065486   -0.030916
    6          1           0        0.969844    3.603746    0.693624
    7          1           0        1.397103    3.702722   -1.021388
    8          1           0        2.668836    3.458680    0.198866
    9          1           0        2.204955    0.577735   -1.879736
   10          6           0        2.995845   -0.352358   -0.162941
   11          1           0        3.446817    1.506893   -1.014058
   12          9           0        3.578501   -0.101049    1.038886
   13          9           0        3.923892   -1.041878   -0.896538
   14          9           0        1.985621   -1.235968    0.079331
   15          8           0       -1.390420   -1.622580   -1.127031
   16          6           0       -0.709358   -2.833050   -0.801227
   17          6           0       -1.497014   -1.418018   -2.533995
   18          1           0        0.299236   -2.840012   -1.232726
   19          1           0       -0.631725   -2.874100    0.286334
   20          1           0       -1.276104   -3.700407   -1.169598
   21          1           0       -2.082055   -2.226640   -2.996040
   22          1           0       -2.004100   -0.462742   -2.680919
   23          1           0       -0.501635   -1.377274   -2.996697
   24          8           0       -2.831225    1.017242   -0.492121
   25          6           0       -4.167738    0.544844   -0.457654
   26          6           0       -2.733941    2.441290   -0.568873
   27          1           0       -4.719434    0.866499   -1.353682
   28          1           0       -4.126259   -0.546875   -0.432591
   29          1           0       -4.694238    0.914934    0.435007
   30          1           0       -3.216459    2.905089    0.303799
   31          1           0       -1.666576    2.669125   -0.579303
   32          1           0       -3.217622    2.805966   -1.486611
   33          8           0       -1.159188   -0.599549    1.878492
   34          6           0       -2.152974   -1.347961    2.559114
   35          6           0       -0.155475   -0.070749    2.751366
```

```
   36          1           0       -2.688247   -0.719737    3.286703
   37          1           0       -2.858540   -1.714813    1.809345
   38          1           0       -1.707117   -2.203483    3.088237
   39          1           0        0.386508   -0.888828    3.245602
   40          1           0        0.526378    0.512002    2.131174
   41          1           0       -0.617746    0.574231    3.512424
---------------------------------------------------------------------
```

27: Li ketyl radical with two dimethyl ethers and internal corrdination.

`Charge=0, Multiplicity=2`



```
E(UB3LYP/631+LAN)=  -847.865727235 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -847.869804 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8           0       -0.320944   -0.820916    1.268313
    2          6           0       -1.638628   -0.762525    1.178350
    3          6           0       -2.449404   -1.368605    2.296660
    4          6           0       -2.240650   -0.874101   -0.213096
    5          1           0       -2.049601   -1.050027    3.266922
    6          1           0       -2.404561   -2.479133    2.287217
    7          1           0       -3.508764   -1.084240    2.249511
    8          1           0       -1.983731   -1.839332   -0.699600
    9          6           0       -1.797744    0.194461   -1.188278
   10          1           0       -3.334466   -0.813043   -0.180090
   11          9           0       -2.088942    1.454970   -0.792067
   12          9           0       -2.357790    0.034267   -2.416847
   13          9           0       -0.429144    0.183953   -1.417549
   14          3           0        0.912951   -0.072748    0.235292
   15          8           0        2.346615   -1.294246   -0.292561
   16          6           0        3.485579   -1.160319   -1.130251
   17          6           0        2.189342   -2.612115    0.247370
   18          8           0        1.380925    1.776426    0.699932
   19          6           0        2.067928    2.795104   -0.012912
   20          6           0        0.615548    2.279047    1.803219
   21          1           0        3.418966   -1.842828   -1.989247
   22          1           0        3.509540   -0.128968   -1.490893
   23          1           0        4.407765   -1.371510   -0.570377
   24          1           0        3.061264   -2.873814    0.862659
   25          1           0        1.283562   -2.587337    0.857267
   26          1           0        2.081086   -3.342934   -0.565995
   27          1           0        2.775920    3.318610    0.645329
   28          1           0        2.618723    2.314879   -0.825719
   29          1           0        1.359610    3.521673   -0.435148
   30          1           0       -0.119219    3.014680    1.450277
```

```
  31          1             0        0.100210    1.421123    2.237772
  32          1             0        1.283133    2.745940    2.540566
---------------------------------------------------------------------
```

28: dimethyl ether.

`Charge=0, Multiplicity=1`

OMe_2

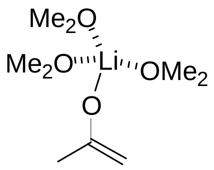
`E(UB3LYP/631+LAN)=  -155.031474215 a.u.`

`G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -155.008580 a.u.`

```
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          8             0        0.000000    0.587414    0.000000
    2          6             0        1.177447   -0.195599    0.000000
    3          1             0        1.234172   -0.836088   -0.895386
    4          1             0        2.023739    0.496096   -0.000011
    5          1             0        1.234182   -0.836072    0.895397
    6          6             0       -1.177447   -0.195599    0.000000
    7          1             0       -1.234176   -0.836081    0.895390
    8          1             0       -2.023739    0.496096    0.000002
    9          1             0       -1.234178   -0.836078   -0.895393
---------------------------------------------------------------------
```

29: Li enolate with three dimethyl ethers.

`Charge=0, Multiplicity=1`



`E(UB3LYP/631+LAN)=  -665.272285045 a.u.`

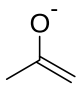
`G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -665.153754 a.u.`

```
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -2.623695   -0.013774   -0.128250
    2          6             0       -2.984413    0.108764   -1.442028
    3          8             0       -1.390430   -0.060862    0.313965
    4          3             0        0.349422    0.000979    0.061788
    5          6             0       -3.694307   -0.108957    0.950828
    6          1             0       -4.027009    0.139288   -1.743493
    7          1             0       -2.233261    0.175651   -2.227179
    8          8             0        0.978950    1.750579   -0.695672
    9          8             0        1.279184   -0.145578    1.872715
   10          8             0        1.028758   -1.591155   -0.965668
   11          6             0       -0.063710    2.585544   -1.210821
```

```
  12        6           0       2.280357   2.204837  -1.029773
  13        1           0       0.015086   3.595136  -0.782775
  14        1           0       0.006131   2.648658  -2.305885
  15        1           0      -1.010099   2.123183  -0.926925
  16        1           0       2.450480   3.221531  -0.645471
  17        1           0       2.995106   1.520570  -0.565350
  18        1           0       2.428822   2.206387  -2.119866
  19        6           0       0.891883  -1.374589   2.489183
  20        6           0       0.945806   0.983437   2.680124
  21        6           0       2.345749  -1.987954  -1.311173
  22        6           0       0.013525  -2.353231  -1.626934
  23        1           0       1.399457  -1.490810   3.457609
  24        1           0      -0.196542  -1.406813   2.625450
  25        1           0       1.196483  -2.178530   1.816229
  26        1           0       2.534288  -1.835396  -2.384382
  27        1           0       3.036189  -1.373137  -0.728068
  28        1           0       2.511570  -3.047953  -1.067722
  29        1           0       1.464029   0.925796   3.648246
  30        1           0       1.276937   1.872272   2.139308
  31        1           0      -0.139288   1.035431   2.837858
  32        1           0       0.113559  -2.254552  -2.717129
  33        1           0       0.096365  -3.413863  -1.349355
  34        1           0      -0.946422  -1.949076  -1.302790
  35        1           0      -3.580010  -1.049290   1.507663
  36        1           0      -4.710592  -0.063481   0.543899
  37        1           0      -3.568410   0.707728   1.675107
---------------------------------------------------------------------
```

30: naked enolate.

Charge=-1, Multiplicity=1



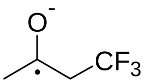
E(UB3LYP/631+LAN)= -192.564643602 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -192.645291 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1         8           0      -0.194521   1.387578  -0.000050
   2         6           0      -0.133951   0.110626   0.000187
   3         6           0      -1.192702  -0.790016  -0.000012
   4         1           0      -2.221202  -0.430819  -0.000163
   5         1           0      -1.028681  -1.866350  -0.000065
   6         6           0       1.295130  -0.483702  -0.000032
   7         1           0       1.841205  -0.121043   0.883155
   8         1           0       1.841157  -0.120499  -0.883023
   9         1           0       1.312823  -1.583356  -0.000368
---------------------------------------------------------------------
```

31: naked ketyl radical.

Charge=-1, Multiplicity=2



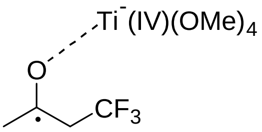
E(UB3LYP/631+LAN)= -530.207588448 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -530.361880 a.u.

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
    1          8           0       -2.354705   -1.189699    0.098145
    2          6           0       -1.513439   -0.210218    0.072558
    3          6           0       -2.045998    1.209800   -0.008869
    4          6           0       -0.204228   -0.451378   -0.682975
    5          1           0       -2.908821    1.324660    0.657393
    6          1           0       -2.405745    1.439192   -1.047134
    7          1           0       -1.300157    1.974067    0.244005
    8          1           0       -0.119105   -1.529098   -0.858546
    9          6           0        1.076731   -0.028193   -0.010126
   10          1           0       -0.192619    0.046912   -1.685007
   11          9           0        1.160452    1.313307    0.237061
   12          9           0        2.185881   -0.316179   -0.784801
   13          9           0        1.307632   -0.648039    1.178919
---------------------------------------------------------------------
```

32: TS of Ti(III) elimination from Ti ate ketyl radical (**23**).

Charge=-1, Multiplicity=2



E(UB3LYP/631+LAN)= -1049.065633820 a.u.

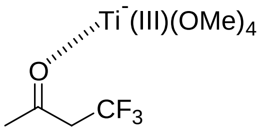
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -1049.166297 a.u.

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
    1          8           0        0.670896    0.614106   -0.965456
    2          6           0        1.399868   -0.255104   -0.487095
    3          6           0        1.357529   -1.686399   -0.968879
    4          6           0        2.411735    0.133465    0.599539
    5         22           0       -1.733732    0.187793   -0.103562
    6          8           0       -1.950233    1.954916   -0.709443
    7          6           0       -1.433269    3.228141   -0.521346
    8          1           0       -1.951181    3.956929   -1.172369
    9          1           0       -0.356954    3.269263   -0.764883
   10          1           0       -1.555424    3.578058    0.522063
   11          8           0       -3.190046    0.059620    1.156796
```

```
    12          6           0        -4.523066    0.320465    0.846727
    13          1           0        -5.184701   -0.012906    1.669482
    14          1           0        -4.863655   -0.198634   -0.072428
    15          1           0        -4.706443    1.400701    0.691397
    16          8           0        -0.453629   -0.489030    1.204034
    17          6           0        -0.717791   -1.241979    2.350912
    18          1           0        -0.576926   -2.326351    2.168658
    19          1           0        -1.748954   -1.091991    2.707533
    20          1           0        -0.026432   -0.960060    3.169762
    21          8           0        -1.999953   -1.189141   -1.395116
    22          6           0        -2.811458   -2.321169   -1.396729
    23          1           0        -3.377800   -2.398047   -2.344060
    24          1           0        -3.543713   -2.320311   -0.569553
    25          1           0        -2.210971   -3.247137   -1.302772
    26          1           0         2.074742   -1.820936   -1.793045
    27          1           0         0.349129   -1.893990   -1.341084
    28          1           0         1.623855   -2.393285   -0.175244
    29          1           0         2.157767    1.136222    0.950751
    30          6           0         3.858056    0.148807    0.161591
    31          1           0         2.333501   -0.560597    1.442810
    32          9           0         4.322512   -1.082768   -0.196941
    33          9           0         4.680934    0.580404    1.166298
    34          9           0         4.089928    0.967977   -0.896413
 ---------------------------------------------------------------------
```

33: Ti$^-$(III)(OMe)$_4$ coordinated with α-CF$_3$ ketone.

Charge=-1, Multiplicity=2



E(UB3LYP/631+LAN)= -1049.07971125 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -1049.180602 a.u.

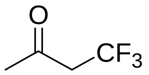
This structure has imaginary frequency (-29 cm^{-1}) corresponding to the rotation of Me group on the ligand.

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
     1          8           0         2.846884   -2.527250   -0.703254
     2          6           0         2.377956   -1.591007   -0.074169
     3          6           0         1.762876   -1.762733    1.292086
     4          6           0         2.350953   -0.190776   -0.705231
     5         22           0        -1.961143   -0.132467   -0.035390
     6          8           0        -2.286743   -1.303431   -1.490118
     7          6           0        -2.599010   -1.084140   -2.831852
     8          1           0        -3.122352   -1.961049   -3.254468
     9          1           0        -1.690816   -0.919127   -3.440164
    10          1           0        -3.256828   -0.206970   -2.975536
    11          8           0        -3.454898    1.070052    0.148984
```

```
  12         6            0      -4.763032   0.738742   0.504789
  13         1            0      -5.101333   1.332941   1.375240
  14         1            0      -4.884328  -0.329171   0.774957
  15         1            0      -5.468970   0.945708  -0.322173
  16         8            0      -0.496040   1.077117  -0.425227
  17         6            0      -0.539959   2.478836  -0.469410
  18         1            0       0.097167   2.923362   0.317791
  19         1            0      -1.564570   2.860419  -0.330610
  20         1            0      -0.165678   2.854563  -1.439894
  21         8            0      -1.557221  -0.975153   1.633482
  22         6            0      -1.508666  -0.442315   2.924066
  23         1            0      -1.763908  -1.215066   3.671858
  24         1            0      -2.214564   0.396648   3.061740
  25         1            0      -0.498865  -0.065158   3.173043
  26         1            0       1.943626  -2.779190   1.651320
  27         1            0       0.677636  -1.576445   1.244612
  28         1            0       2.170273  -1.031406   1.999792
  29         1            0       2.578027  -0.301280  -1.769308
  30         6            0       3.377296   0.760321  -0.137401
  31         1            0       1.353289   0.278635  -0.590125
  32         9            0       3.154706   1.092610   1.162938
  33         9            0       3.407103   1.929089  -0.833949
  34         9            0       4.648301   0.259923  -0.184287
---------------------------------------------------------------------
```

34: α-CF_3 ketone.

`Charge=0, Multiplicity=1`



```
E(UB3LYP/631+LAN)=  -530.215605952 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -530.297350 a.u.
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
   1         8            0      -1.405038   1.316070  -0.012039
   2         6            0      -1.480468   0.105218  -0.032304
   3         6            0      -2.805060  -0.631361   0.025441
   4         6            0      -0.241329  -0.795666  -0.114842
   5         6            0       1.094891  -0.086418   0.001002
   6         9            0       2.105865  -1.000771  -0.052875
   7         9            0       1.227464   0.573511   1.171927
   8         9            0       1.308092   0.791229  -1.000563
   9         1            0      -2.863738  -1.409806  -0.745233
  10         1            0      -3.626252   0.077928  -0.097795
  11         1            0      -2.907360  -1.131634   0.997971
  12         1            0      -0.287778  -1.559035   0.670956
  13         1            0      -0.255572  -1.332369  -1.071750
---------------------------------------------------------------------
```

35: $Ti(III)(OMe)_3$.

```
Charge=0, Multiplicity=2
```

$Ti(III)(OMe)_3$

```
E(UB3LYP/631+LAN)=  -403.632481061 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -403.632335 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1        22           0      -0.001843   -0.003350    0.003542
    2         8           0      -0.823010    1.600055    0.006221
    3         8           0       1.797063   -0.093163   -0.003746
    4         8           0      -0.978698   -1.516959    0.004608
    5         6           0      -1.514598    2.815303    0.002614
    6         1           0      -1.132418    3.467675   -0.794652
    7         1           0      -2.587787    2.647382   -0.163780
    8         1           0      -1.384409    3.327686    0.965791
    9         6           0      -1.681052   -2.725998    0.000760
   10         1           0      -0.994211   -3.570402   -0.150399
   11         1           0      -2.202158   -2.864021    0.958154
   12         1           0      -2.426543   -2.729615   -0.806400
   13         6           0       3.195309   -0.088346   -0.009221
   14         1           0       3.572547   -0.595450   -0.907968
   15         1           0       3.577219    0.942041   -0.000046
   16         1           0       3.579682   -0.614034    0.875714
---------------------------------------------------------------------
```

36: methoxide anion.

```
Charge=-1, Multiplicity=1
```

^-OMe

```
E(UB3LYP/631+LAN)=  -115.109825010 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -115.221350 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6           0       0.000013    0.543555    0.000000
    2         1           0       1.030803    1.036913    0.000000
    3         1           0      -0.515494    1.036729    0.892694
    4         1           0      -0.515494    1.036729   -0.892694
    5         8           0       0.000013   -0.796463    0.000000
---------------------------------------------------------------------
```

37: Ti(IV)(OMe)$_4$.

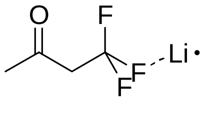
```
Charge=0, Multiplicity=1
```

Ti(IV)(OMe)$_4$

```
E(UB3LYP/631+LAN)=  -518.825262428 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -518.809260 a.u.
---------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------
    1         22           0       -0.013181    0.018412   -0.019730
    2          8           0       -1.141358    1.221388    0.696364
    3          8           0        1.139643    0.860095   -1.117957
    4          8           0        0.939777   -0.812207    1.261696
    5          8           0       -0.970880   -1.215939   -0.913231
    6          6           0       -1.422865    2.466058    1.277614
    7          1           0       -0.951441    3.277501    0.705666
    8          1           0       -2.508853    2.627185    1.288379
    9          1           0       -1.052821    2.498404    2.311795
   10          6           0        1.201836   -2.007787    1.951914
   11          1           0        0.731737   -2.863371    1.447565
   12          1           0        2.285893   -2.175667    1.999355
   13          1           0        0.812462   -1.940655    2.976679
   14          6           0       -2.176576   -1.564980   -1.543287
   15          1           0       -2.093992   -1.409852   -2.627620
   16          1           0       -2.393967   -2.624793   -1.356179
   17          1           0       -3.008940   -0.959106   -1.159039
   18          6           0        2.451101    1.025831   -1.588083
   19          1           0        2.648931    2.092375   -1.759144
   20          1           0        3.179866    0.642804   -0.859793
   21          1           0        2.582660    0.488691   -2.537518
---------------------------------------------------------------
```

38: Li radical coordinated to fluorine of α-CF$_3$ ketone.

```
Charge=0, Multiplicity=2
```



```
E(UB3LYP/631+LAN)=  -537.707925331 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -537.822498 a.u.
---------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------
    1          8           0       -1.722161   -1.158558    0.262627
    2          6           0       -1.634076    0.029640    0.033059
    3          6           0       -2.837880    0.943198   -0.063787
    4          6           0       -0.276267    0.721458   -0.172293
    5          3           0        3.208297    2.099953    0.484469
```

```
     6         6           0        0.921300   -0.197522   -0.063543
     7         9           0        0.948992   -1.155108   -0.996983
     8         9           0        1.058446   -0.762396    1.142077
     9         9           0        2.095106    0.553936   -0.267198
    10         1           0       -3.751143    0.361988    0.079080
    11         1           0       -2.868018    1.442338   -1.040779
    12         1           0       -2.782143    1.731606    0.698148
    13         1           0       -0.251265    1.198949   -1.158693
    14         1           0       -0.156395    1.525189    0.566147
---------------------------------------------------------------------
```

42: Ti(IV)(OMe)$_4$ with I$^-$.

```
Charge=-1, Multiplicity=1
```

Ti^-(IV)(OMe)$_4$-I

```
E(UB3LYP/631+LAN)=  -530.309596934 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -530.356199 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
     1        53           0        2.139617   -0.090753   -0.047275
     2        22           0       -0.960405    0.022731   -0.077527
     3         8           0       -0.763480   -1.767782    0.317522
     4         6           0       -0.141993   -2.738556    1.093136
     5         1           0       -0.509353   -3.739839    0.808742
     6         1           0       -0.363112   -2.583808    2.163447
     7         1           0        0.949229   -2.708483    0.957830
     8         8           0       -2.159049   -0.275487   -1.451545
     9         6           0       -2.940035   -1.404777   -1.726812
    10         1           0       -3.030387   -1.531595   -2.818412
    11         1           0       -3.956414   -1.283388   -1.314548
    12         1           0       -2.496384   -2.314176   -1.295444
    13         8           0       -0.631872    1.774887   -0.522543
    14         6           0        0.148816    2.903733   -0.728861
    15         1           0        0.034537    3.617866    0.105872
    16         1           0       -0.163575    3.413348   -1.656614
    17         1           0        1.211663    2.634437   -0.808701
    18         8           0       -1.896256    0.391180    1.476367
    19         6           0       -2.471683    1.587085    1.921035
    20         1           0       -2.083062    2.457520    1.372391
    21         1           0       -2.261970    1.722191    2.995203
    22         1           0       -3.567335    1.558488    1.791995
---------------------------------------------------------------------
```

43: iodide ion.

Charge=-1, Multiplicity=1

I^-

E(UB3LYP/631+LAN)= -11.4721100599 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -11.574630 a.u.

44: lithium iodide.

Charge=0, Multiplicity=1

Li-I

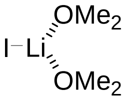
E(UB3LYP/631+LAN)= -18.9856260611 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -19.069770 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          3           0        0.000000    0.000000   -2.304908
    2         53           0        0.000000    0.000000    0.130466
---------------------------------------------------------------------
```

45: lithium iodide with two ethers.

Charge=0, Multiplicity=1



E(UB3LYP/631+LAN)= -329.111276397 a.u.

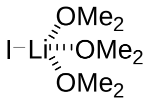
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -329.068807 a.u.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          3           0        0.705191    0.017632   -0.041124
    2          8           0        1.508216    1.786119   -0.032824
    3          6           0        1.379520    2.472743    1.218100
    4          1           0        1.698078    1.780303    2.000951
    5          1           0        2.027623    3.358813    1.228428
    6          1           0        0.336710    2.765835    1.390696
    7          6           0        1.126716    2.606072   -1.145548
    8          1           0        1.765975    3.497517   -1.188966
    9          1           0        1.270045    2.009888   -2.049477
   10          1           0        0.072502    2.896269   -1.063996
   11          8           0        1.962111   -1.416199   -0.012816
   12          6           0        3.381695   -1.323806   -0.103257
   13          1           0        3.853164   -1.782680    0.776390
   14          1           0        3.742201   -1.825205   -1.011673
   15          1           0        3.635178   -0.262170   -0.144223
```

```
   16         6            0       1.479777   -2.765986   0.046181
   17         1            0       1.779391   -3.311932  -0.857831
   18         1            0       1.881985   -3.269704   0.934755
   19         1            0       0.391174   -2.708779   0.105378
   20        53            0      -1.821480   -0.228199   0.005193
---------------------------------------------------------------------
```

46: lithium iodide with three ethers.

Charge=0, Multiplicity=1



E(UB3LYP/631+LAN)= -484.157595545 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -484.075546 a.u.

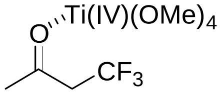
This structure has imaginary frequencies (-30, -13 cm^{-1}) cooresponding to vibration of ether.

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number     Type              X           Y           Z
---------------------------------------------------------------------
    1         3            0       0.554592    0.003410   -0.000159
    2         8            0       1.349977   -1.601561   -0.889571
    3         6            0       0.591525   -2.253378   -1.913921
    4         1            0      -0.186647   -1.556792   -2.228388
    5         1            0       1.245705   -2.516132   -2.757297
    6         1            0       0.114715   -3.158465   -1.516580
    7         6            0       2.336305   -2.446463   -0.308424
    8         1            0       3.075449   -2.754370   -1.062135
    9         1            0       2.829093   -1.874663    0.480352
   10         1            0       1.871385   -3.342598    0.126196
   11         8            0       1.328991    1.593900   -0.933611
   12         6            0       2.258125    1.516861   -2.008591
   13         1            0       3.001967    2.323382   -1.935971
   14         1            0       2.755402    0.547596   -1.937855
   15         1            0       1.739318    1.591261   -2.974686
   16         6            0       0.570813    2.808282   -0.940736
   17         1            0       1.236311    3.668480   -0.780923
   18         1            0       0.040066    2.919790   -1.894644
   19         1            0      -0.163845    2.732402   -0.138151
   20         8            0       1.319927    0.025251    1.846623
   21         6            0       0.580605   -0.624854    2.885313
   22         1            0       1.265932   -1.164180    3.554556
   23         1            0       0.001458    0.110670    3.457466
   24         1            0      -0.112280   -1.315773    2.403462
   25         6            0       2.186956    1.041125    2.338006
   26         1            0       1.617173    1.804294    2.886523
   27         1            0       2.948210    0.610800    3.004609
   28         1            0       2.669587    1.499794    1.472827
   29        53            0      -2.089621   -0.009922   -0.012383
```

```
--------------------------------------------------------------------
```

50: Ti(IV)(OMe)$_4$ coordinated to α-CF$_3$ ketone.

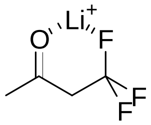
```
Charge=0, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -1049.04423485 a.u.
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -1049.085490 a.u.
--------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
--------------------------------------------------------------------
    1          8           0       -0.598111    0.442411   -0.620787
    2          6           0       -1.573640   -0.290997   -0.571671
    3          6           0       -1.487279   -1.738896   -0.170753
    4          6           0       -2.932486    0.299605   -0.972384
    5         22           0        1.819124    0.031830    0.006851
    6          8           0        1.898262    1.749724   -0.543667
    7          6           0        1.324912    2.988238   -0.861020
    8          8           0        3.540258   -0.235124    0.476668
    9          6           0        4.736669    0.506481    0.533388
   10          8           0        1.594354   -1.262406   -1.278870
   11          6           0        2.460944   -2.078037   -2.031161
   12          8           0        0.950852   -0.343465    1.573539
   13          6           0        1.336232   -0.699813    2.880003
   14          6           0       -4.028350    0.176637    0.071607
   15          9           0       -4.401140   -1.109505    0.293952
   16          9           0       -5.139830    0.845824   -0.321272
   17          9           0       -3.649523    0.691857    1.265351
   18          1           0       -1.671636   -1.812408    0.909217
   19          1           0       -0.479934   -2.106126   -0.374782
   20          1           0       -2.241559   -2.346960   -0.678717
   21          1           0       -2.794422    1.361066   -1.190718
   22          1           0       -3.290544   -0.202326   -1.879837
   23          1           0        1.259365    3.622002    0.034628
   24          1           0        0.315557    2.849195   -1.269752
   25          1           0        1.944553    3.500742   -1.609647
   26          1           0        5.096277    0.551867    1.570131
   27          1           0        4.574845    1.527964    0.162903
   28          1           0        5.504776    0.017547   -0.080553
   29          1           0        2.006963   -3.070219   -2.167303
   30          1           0        3.429727   -2.202127   -1.526144
   31          1           0        2.634523   -1.639276   -3.024590
   32          1           0        1.083715    0.109040    3.580188
   33          1           0        2.416439   -0.895422    2.937656
   34          1           0        0.798150   -1.606829    3.191206
--------------------------------------------------------------------
```

51: Li$^+$ coordinated to α-CF$_3$ ketone.

Charge=1, Multiplicity=1



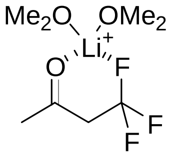
E(UB3LYP/631+LAN)= -537.578593175 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -537.762120 a.u.

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          8           0        1.354071    1.199231    0.046080
    2          6           0        1.464499   -0.024579   -0.066764
    3          6           0        2.788408   -0.708284    0.035955
    4          6           0        0.240491   -0.899114   -0.330145
    5          3           0       -0.051013    2.386487   -0.138242
    6          6           0       -1.088406   -0.255366    0.018738
    7          9           0       -1.167336    0.088325    1.317074
    8          9           0       -2.124496   -1.016402   -0.298172
    9          9           0       -1.263672    0.957433   -0.684509
   10          1           0        3.602563    0.011717   -0.065155
   11          1           0        2.884094   -1.510573   -0.704809
   12          1           0        2.858121   -1.184071    1.026119
   13          1           0        0.231186   -1.171128   -1.394833
   14          1           0        0.314095   -1.839397    0.228519
 ---------------------------------------------------------------------
```

52: Li$^+$ coordinated to α-CF$_3$ ketone with two dimethyl ethers.

Charge=1, Multiplicity=1



E(UB3LYP/631+LAN)= -847.721222700 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)= -847.769066 a.u.

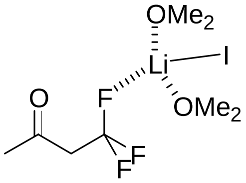
This structure has imaginary frequency (-17 cm^{-1}) cooresponding to vibration of ether

```
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          8           0        0.583984    0.948132    1.090125
    2          6           0        1.798148    1.095690    0.985318
    3          6           0        2.596069    1.864852    1.995687
    4          6           0        2.567515    0.519881   -0.203151
```

```
     5          1             0        1.936169    2.422341    2.662830
     6          1             0        3.307508    2.540882    1.506185
     7          1             0        3.192476    1.158039    2.590454
     8          1             0        2.705660    1.321427   -0.941648
     9          6             0        1.894510   -0.653514   -0.889483
    10          1             0        3.569703    0.201922    0.103604
    11          9             0        1.727111   -1.698898   -0.052193
    12          9             0        2.594930   -1.071600   -1.949567
    13          9             0        0.634486   -0.325479   -1.351965
    14          3             0       -0.902762    0.154120    0.133826
    15          8             0       -2.127578    1.402720   -0.610922
    16          6             0       -3.276682    0.988696   -1.366372
    17          6             0       -1.988822    2.829595   -0.557819
    18          8             0       -1.691188   -1.469268    0.760065
    19          6             0       -1.542602   -2.781877    0.197123
    20          6             0       -2.385094   -1.484439    2.016972
    21          1             0       -3.185272    1.318942   -2.408028
    22          1             0       -3.316072   -0.101380   -1.325618
    23          1             0       -4.189406    1.405860   -0.924539
    24          1             0       -2.878567    3.279086   -0.100967
    25          1             0       -1.114203    3.048815    0.057573
    26          1             0       -1.846988    3.236180   -1.566613
    27          1             0       -2.527656   -3.233973    0.030794
    28          1             0       -1.023066   -2.673250   -0.756366
    29          1             0       -0.951666   -3.417548    0.867074
    30          1             0       -1.831771   -2.084701    2.749164
    31          1             0       -2.453819   -0.451755    2.366325
    32          1             0       -3.393476   -1.895439    1.888017
 ---------------------------------------------------------------------
```

53: Li-I coordinated to fluorine of α-CF_3 ketone with two dimethyl ethers.

```
Charge=0, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -847.721222700 a.u.

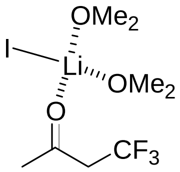
G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -847.769066 a.u.

 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
     1          8             0        2.730238    0.255257    1.649798
     2          6             0        2.907694   -0.302975    0.582525
     3          6             0        3.506797   -1.684309    0.466831
     4          6             0        2.497935    0.333597   -0.748780
     5          6             0        1.812446    1.675281   -0.639586
     6          9             0        1.436075    2.126866   -1.863757
     7          9             0        2.579176    2.632847   -0.085636
     8          9             0        0.658398    1.616533    0.108491
```

```
   9         1             0        2.711149   -2.382225    0.170874
  10         1             0        3.921278   -1.991902    1.429318
  11         1             0        4.281590   -1.722842   -0.308540
  12         1             0        3.381727    0.460969   -1.385828
  13         1             0        1.814525   -0.355593   -1.263996
  14         3             0       -1.144588    0.321320    0.270190
  15         8             0       -2.342281    1.498406   -0.688962
  16         6             0       -2.583317    2.851330   -0.308262
  17         6             0       -2.744340    1.206674   -2.032159
  18         8             0       -1.504062    0.511700    2.175533
  19         6             0       -2.755840   -0.043534    2.587323
  20         6             0       -0.449922    0.232550    3.108042
  21        53             0       -0.617631   -2.056927   -0.687309
  22         1             0       -2.253973    2.959291    0.727391
  23         1             0       -2.016825    3.540071   -0.949481
  24         1             0       -3.654710    3.083373   -0.381221
  25         1             0       -2.199349    1.846815   -2.738588
  26         1             0       -2.498546    0.159014   -2.214359
  27         1             0       -3.824785    1.368327   -2.144402
  28         1             0       -2.689833   -1.137095    2.651988
  29         1             0       -3.049917    0.371169    3.560917
  30         1             0       -3.496670    0.232121    1.833399
  31         1             0       -0.693272    0.671363    4.084719
  32         1             0       -0.311085   -0.851031    3.209266
  33         1             0        0.464164    0.680516    2.716920
---------------------------------------------------------------------
```

54: Li-I coordinated to oxygen of α-CF_3 ketone with two dimethyl ethers.

```
Charge=0, Multiplicity=1
```



```
E(UB3LYP/631+LAN)=  -859.345202220 a.u.

G(sol,-78)(UB3LYP/6311+LAN//UB3LYP/631+LAN)=  -859.360817 a.u.
```

```
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1         8             0        0.981457    0.140277    0.765316
   2         6             0        1.738172   -0.822288    0.761189
   3         6             0        1.317477   -2.206443    0.362736
   4         6             0        3.191217   -0.607847    1.210396
   5         3             0       -0.866018    0.622059    0.117678
   6         1             0        0.280356   -2.214623    0.015859
   7         1             0        1.415285   -2.873166    1.231486
   8         1             0        1.992447   -2.597329   -0.409295
   9         1             0        3.219258    0.201735    1.944554
  10         6             0        4.110343   -0.213219    0.063873
  11         1             0        3.604937   -1.517909    1.655104
```

```
    12         9           0        4.161896   -1.169416   -0.897944
    13         9           0        5.375193   -0.024318    0.507863
    14         9           0        3.718490    0.933133   -0.536945
    15         8           0       -0.476453    1.761129   -1.439844
    16         6           0       -0.868529    1.411154   -2.769546
    17         6           0        0.448284    2.842693   -1.389414
    18         1           0        0.007986    1.104558   -3.357275
    19         1           0       -1.570307    0.579582   -2.682274
    20         1           0       -1.354166    2.267252   -3.258267
    21         1           0        0.012511    3.742243   -1.846889
    22         1           0        0.663955    3.035416   -0.336533
    23         1           0        1.378766    2.583296   -1.913162
    24         8           0       -1.563177    1.890786    1.490877
    25         6           0       -2.820010    2.469433    1.125896
    26         6           0       -1.562386    1.403624    2.832812
    27         1           0       -3.053074    3.311278    1.792657
    28         1           0       -2.718640    2.828844    0.100136
    29         1           0       -3.615989    1.716229    1.169888
    30         1           0       -2.306449    0.605892    2.955468
    31         1           0       -0.563560    1.007499    3.028851
    32         1           0       -1.773788    2.223540    3.533432
    33        53           0       -2.588372   -1.349534   -0.289660
---------------------------------------------------------------------
```

55: anion radical of Me-I.

```
Charge=-1, Multiplicity=2
```

$\mathrm{MeI}^{\bullet}_{-}$

```
E(UB3LYP/631+LAN)=  -51.3194021287 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
     1         6           0        3.100062   -0.000178    0.000000
     2        53           0       -0.518041    0.000022    0.000000
     3         1           0        2.950556   -0.557268   -0.917711
     4         1           0        2.950638   -0.516529    0.941224
     5         1           0        2.954594    1.073673   -0.023509
---------------------------------------------------------------------
```

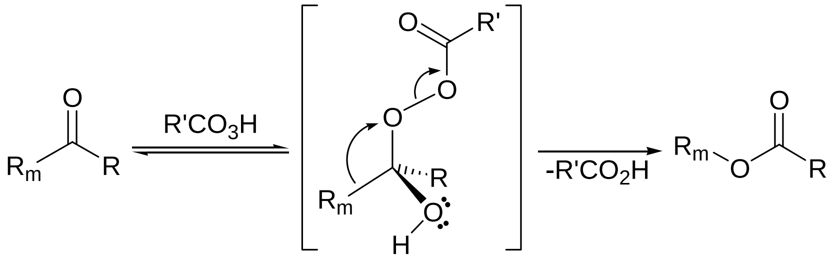
Chapter 7

Baeyer-Villiger Reaction of α-CF_3 Ketone

7-1. Introduction.

The Baeyer-Villiger (B-V) reaction[1] has been widely employed in organic synthesis by virtue of the unique transformation; an oxygen atom can be inserted regioselectively and stereospecifically into the carbon-carbon single bond (Scheme 7-1).[2]

Scheme 7-1.



Criegee Intermediate

However, the regiochemistry of the B-V reaction of ketone bearing non-hydrocarbon functionality is quite unexplored. Interesting stereoelectronic effects were reported for ketones which are functionalized with fluorine substituents,[3] but only for α-F ketones. Special effects of fluorine atom on the B-V reaction are worth investigating further. In view of the author's research interest for the synthesis and the reaction of α-CF_3 carbonyl compounds, the B-V reaction of α-CF_3 ketones[4] should be investigated[5] because not only of the interesting stereoelectronic effect but also of exploring the further functionalization of α-CF_3 ketone which the author have succeed in developing the synthetic methodology (Chapter 4 and 5).

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(1) (a) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625-3633. (b) Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127-135.

(2) Reviews: (a) Krow. G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, 671. (b) Krow, G. R. *Org. React.* **1993**, *43*, 251-798. (c) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1198-1209. (d) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737-750. (e) Brink, G.-J. ten; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105-4123.

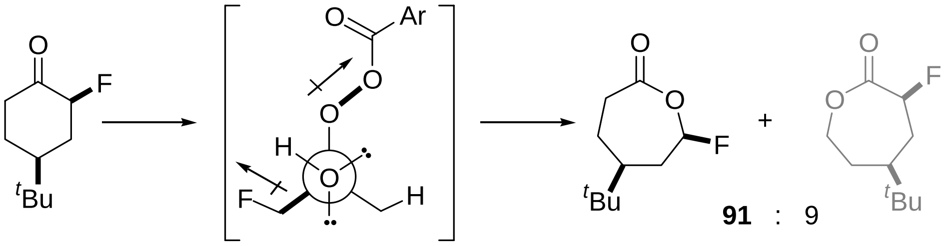
(3) (a) Smissman, E. E.; Li, J. P.; Israili, Z. H. *J. Org. Chem.* **1968**, *33*, 4231-4236. (b) Shiozaki, M.; Arai, M. *J. Org. Chem.* **1989**, *54*, 3754-3755. (c) Kitazume, T.; Kataoka, J. *J. Fluorine Chem.* **1996**, *80*, 157-158. (d) Crudden C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2852-2855. (e) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547-1552.

(4) There is only one report for the B-V reaction of α-CF_3 ketone which is in one step of the synthesis of 3,3,3-trifluoropropionic acid. They observed the exclusive migration of the carbon without CF_3 substituent. Wakselman, C.; Tordeux, M. *J. Fluorine Chem.* **1982**, *21*, 99-106.

(5) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803-4806.

Crudden has reported the B-V reaction of α-F_{eq} cyclohexanone and the migration takes place preferentially at the carbon bearing F substituent based on dipole interaction at the Criegee intermediate (Scheme 7-2).

Scheme 7-2.



On the basis of the result of Crudden's α-F_{eq} ketone, one might predict that α-CF_3 ketones should provide a similar trend for migration of the CF_3-bearing carbon because of the equatorial orientation of the sterically demanding CF_3 group.[6]

The B-V reaction of α-CF_3 ketone is reported in this chapter.

7-2. B-V reaction of α-CF_3 cyclohexanone by trifluoroperacetic acid.

First of all, the B-V reaction of α-CF_3 cyclohexanone was investigated by using trifluoroperacetic acid (TFPA) as an oxidant which has high reactivity in the B-V reaction. TFPA could be prepared by two methods.[7]

(A) Reaction of trifluoroacetic acid (TFA) with aqueous hydrogen peroxide.[8]
(B) Reaction of trifluoroacetic anhydride (TFAA) with aqueous hydrogen peroxide.[9]

The results of the B-V reaction of α-CF_3 cyclohexanone by two kinds of TFPA are listed in Table 7-1. When the TFPA prepared by the method (A) was used, the reaction did not give the product at all (entries 1, and 2). However, the B-V reaction proceeded

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(6) A-value:Me=~1.70 ^{i}Pr=~2.15, CF_3=2.4~2.5, ^{t}Bu=>4 (kcal/mol). Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139-195.

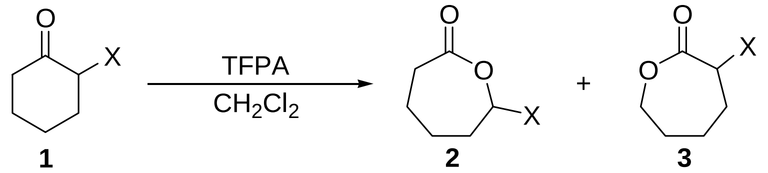
(7) Caster, K. C.; Rao, A. S.; Mohan, H. R. In *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; John Wiley & Sons: Chichester, 1999; p 483-487.

(8) Venier, C. G.; Squires, T. G.; Chen, Y.-Y.; Hussmann G. P.; Shei, J. C.; Smith, B. F. *J. Org. Chem.* **1982**, *47*, 3773-3774.

(9) (a) Ishii, A.; Kanai, M.; Higashiyama, K.; Mikami. K. *Chirality* **2002**, *14*, 709-712. (b) Ishii, A, Tokyo Institute of Technology, 2001 (Doctoral thesis).

quantitatively by using TFPA prepared by the method (B) (entry 3). Moreover, the regioselectivity of the reaction was perfect; only the product of the migration of non-substituted carbon was obtained. This regioselectivity is in sharp contrast to α-Me cyclohexanone (entry 4); Me substituted carbon migrated preferentially.

Table 7-1. B-V reaction of α-CF_3 cyclohexanone by TFPA prepared by two different methods.



entry	X	TFPA (eq.)	time (h)	temp. (ºC)	yield (%)[a]	**2:3**
1	CF_3	A (3.0)	65	r.t.	-	-
2		A (3.0)	65	40	-	-
3		B (2.0)	16	r.t.	quant., (89)	<1:>99[b]
4	Me	B (2.0)	15	r.t.	(94)	97:3[c]

[a] Determined by ^{19}F NMR using BTF as an internal standard. The values in parentheses refer to the yields of the isolated products.
[b] Determined by ^{19}F NMR.
[c] Determined by GC analysis.

Why is the reactivity so different even with the same active species? The reactions in both preparation methods are shown in eq. 7.1 and eq. 7.2.

Method (A): $CF_3CO_2H + H_2O_2 \longleftrightarrow CF_3CO_3H + H_2O$ (eq. 7.1)
Method (B): $(CF_3CO)_2O + H_2O_2 \longrightarrow CF_3CO_3H + CF_3CO_2H$ (eq. 7.2)

In the case of the method (A), TFPA and TFA are always in equilibrium and excess amount of H_2O (in *aqueous* hydrogen peroxide) shifts the equilibrium to the left to reduce the amount of the active TFPA. On the other hand, the method (B) utilizes an irreversible reaction between TFAA and H_2O_2 to form the active TFPA. The byproduct of this reaction is TFA which could enhance the B-V reaction.[10] Excess amount of H_2O could be transformed to TFA by using excess amount of TFAA (one H_2O and one TFAA provides two TFA). Therefore, concentration of the active TFPA is higher in the method (B) than in the method (A). Thus higher reactivity toward B-V reaction of α-CF_3 cyclohexanone is shown in the method (B). It could be said that α-CF_3 cyclohexanone

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(10) B-V reaction is known to be catalyzed by acid. See ref. 2-(b)

is a poor reactive substrate for B-V reaction, since TFPA is classically the strongest oxidizing agent for the B-V reaction. Further investigation is required for the effective reaction condition.

7-3. Effect of the additive and the solvent for the B-V reaction by TFPA.

The B-V reaction is known to be catalyzed by acid or base.[2b] Since TFPA contains TFA, the effect of inorganic base was investigated by using TFPA (B) (Table 7-2).[11,12] For all the additives investigated, only the product **3** was obtained. When Na_2CO_3, $NaHCO_3$, and AcONa were used, decomposition of TFPA was detected and gave a poor result (entries 1~5). For entries 2 and 4, Na_2SO_4 was added to trap water. However, it did not affect the reaction (Na_2SO_4 itself also does not affect the reaction (entry 10 vs. 11)). KH_2PO_4 and Na_2HPO_4 could inhibit the decomposition of TFPA as a base (entries 6~8). By using these bases, the reaction was completed in 5 h. Without the base, the product was obtained in 85% for 5 h reaction time. Again, Na_2SO_4 did not affect the reaction (entry 8). TFPA prepared by the method (A), which could not make the B-V reaction of α-CF_3 cyclohexanone to progress, was investigated in the presence of Na_2HPO_4 (entry 9). However, the reaction did not proceed at all. In conclusion, it is required to use the base which would not decompose TFPA (KH_2PO_4, Na_2HPO_4).

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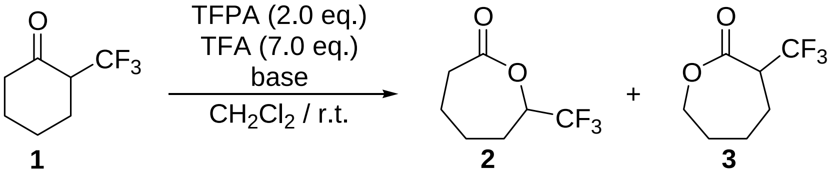
(11) Theoretically, TFPA of method (B) contains 3.5 eq. of TFA (vs. TFPA). The description “TFPA (2.0 eq.) / TFA (7.0 eq.)” means the simultaneous formation of TFA and does *not* mean “7.0 eq. of extra TFA was added”.

(12) All the TFPA from here refer to the TFPA by method (B) unless otherwise noted.

Table 7-2. B-V reaction of α-CF_3 cyclohexanone by TFPA (B) in the presence of base.

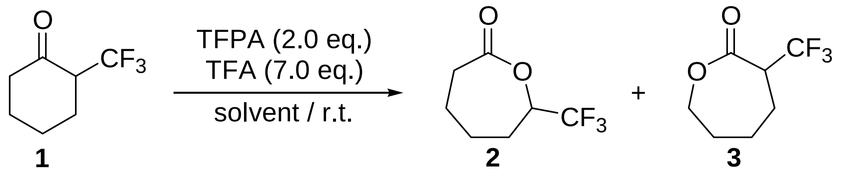


entry	base (eq.)	time (h)	yield (%)[a] 2	3
1	Na_2CO_3 (10)	5	-	-
2	Na_2CO_3 (10) / Na_2SO_4 (5)	5	-	-
3	$NaHCO_3$ (11)	46	-	-
4	$NaHCO_3$ (10) / Na_2SO_4 (5)	18	-	trace
5	AcONa (10)	43	-	15[b]
6	KH_2PO_4 (10)	5	-	95
7	Na_2HPO_4 (10)	5	-	97
8	Na_2HPO_4 (10) / Na_2SO_4 (5)	5	-	98
9[c]	Na_2HPO_4 (4.6)	20	-	-
10	Na_2SO_4 (5)	5	-	85
11	-	5	-	85

[a] Conversion yield determined by ^{19}F NMR.
[b] Yields of the isolated products.
[c] TFPA prepared by method (A) was used.

Next, the effect of the solvent was investigated. TFPA prepared by the method (A) was investigated in CH_3CN and THF but the reaction did not proceed. The solvent effects of TFPA prepared by the method (B) are listed in Table 7-3. When TFPA was prepared in CH_3CN instead of CH_2Cl_2, the product could be obtained in only 10% (entry 1). ^{19}F NMR spectrum of TFPA prepared in CH_2Cl_2 and CH_3CN are shown in Figure 7-1. TFPA prepared in CH_2Cl_2 is in the ratio of TFPA:TFA=1:4.4 which is close to the theoretical value (TFPA:TFA=1:3.5). However, the TFPA prepared in CH_3CN is in the ratio of TFPA:TFA=1:9.0. This indicates the decomposition of TFPA in CH_3CN. Therefore, preparation of TFPA was carried out in CH_2Cl_2 and then CH_3CN was added (solvent composition: CH_2Cl_2:CH_3CN=1:1). In that case, the yield was slightly increased (17%) (entry 2). Likewise, THF (entry 3) and Et_2O (entry 4) was added. However, the reaction did not proceed at all due to the decomposition of TFPA. In all cases investigated, the regioselectivity of the B-V reaction did not changed.

Table 7-3. B-V reaction of α-CF_3 cyclohexanone by TFPA (B) in various solvents.



	preparation of			yield (%)[a]	
entry	TFPA	solvent	time (h)	**2**	**3**
1	in CH_3CN	CH_3CN	6	-	10
2	in CH_2Cl_2	CH_3CN:CH_2Cl_2=1:1	6	-	17
3	in CH_2Cl_2	THF:CH_2Cl_2=1:1	2	-	-
4	in CH_2Cl_2	Et_2O:CH_2Cl_2=1:1	2	-	-

[a] Conversion yield determined by ^{19}F NMR.

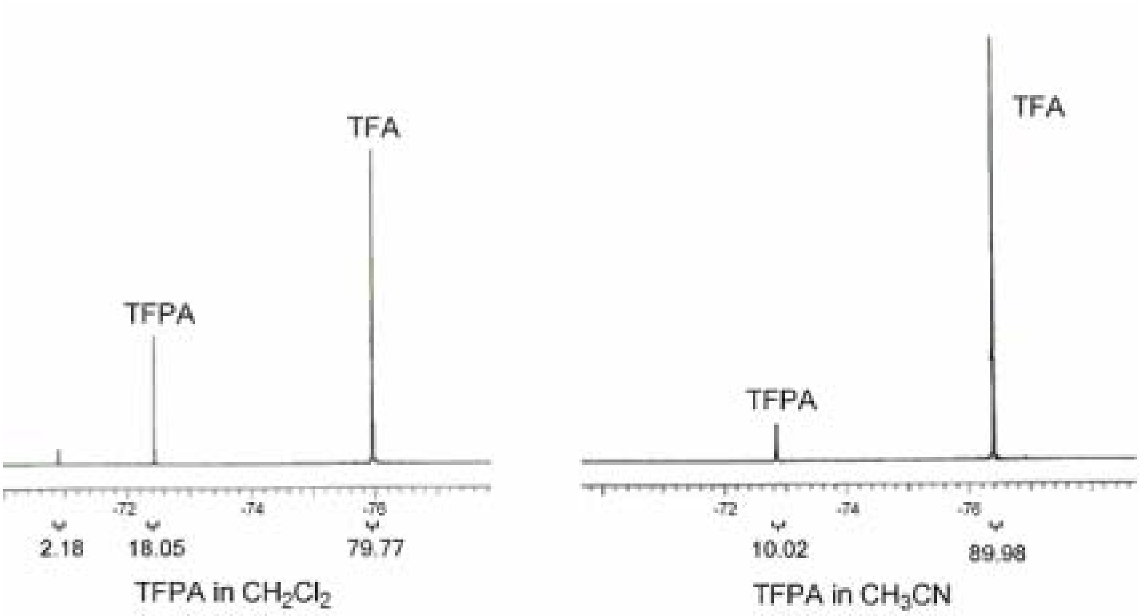


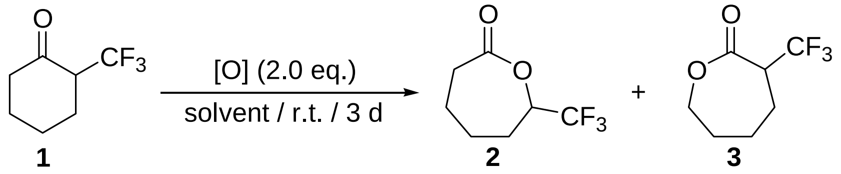
Figure 7-1. ^{19}F NMR of TFPA (B) prepared in CH_2Cl_2 and CH_3CN.

7-4. Effect of the oxidizing agent and the additive.

Although TFPA was effective reagent for B-V reaction of α-CF_3 cyclohexanone to give the α-CF_3 lactone in quantitative yield with perfect regioselectivity, it was very sensitive to other solvents and additives. To explore more effective reaction conditions, other oxidizing agents and additives were investigated.

First, various oxidizing agents were examined (Table 7-4). When *tert*-butyl hydroperoxide (TBHP) (entry 1) and H_2O_2 (entries 2, and 3) were used, no product was obtained. However, *m*CPBA provide the product in 8% (entry 4). The use of H_3PO_5[9,13] was the most effective oxidant among the oxidants investigated. 2 eq. of H_3PO_5 gave the product in 40% (entry 5) and 6 eq. of H_3PO_5 gave quantitative yield (entry 6).

Table 7-4. B-V reaction by various oxidizing agent.



			yield (%)[a]	
entry	oxidizing agent	solvent	**2**	**3**
1	TBHP	CH_2Cl_2	-	-
2[b]	31% H_2O_2	CH_2Cl_2	-	-
3		IPA	-	-
4	*m*CPBA	CH_2Cl_2	-	8
5	H_3PO_5	CH_3CN	-	40
6[c]			-	quant. (91)

[a] Determined by ^{19}F NMR using BTF as an internal standard. The number in parentheses refers to the isolated yield.

[b] Reaction time was 2 d.

[c] 6 eq. of H_3PO_5 was used.

The difference in the reactivity could be explained by the ability of leaving groups at the Criegee intermediate. The leaving group ability of the each oxidizing agent is in the order listed in Figure 7-2. Therefore, the B-V reaction of α-CF_3 cyclohexanone requires at least *m*CPBA or higher reactive oxidizing agents.

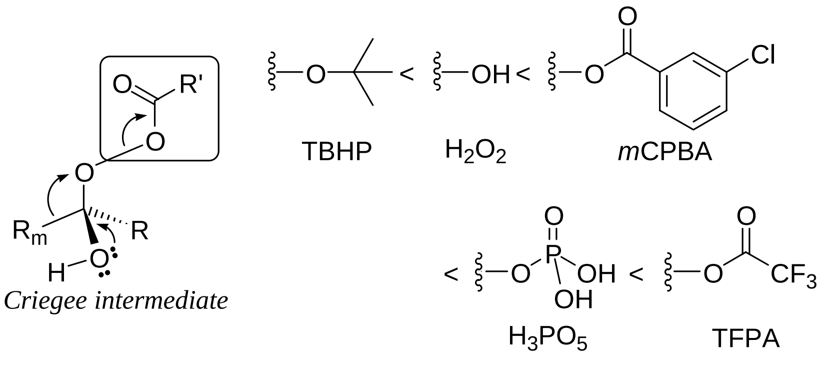


Figure 7-2. Leaveing group ability and reactivity of the oxidizing agent.

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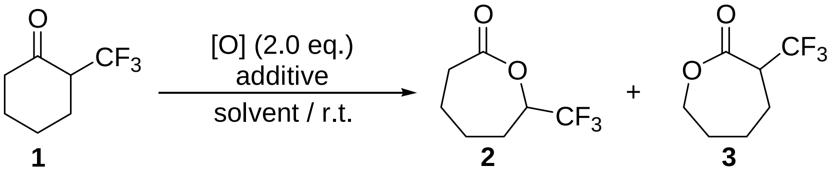
(13) Ogata, Y.; Tomizawa, K.; Ikeda, T. *J. Org. Chem.* **1978**, *43*, 2417-2419.

The effect of additives were investigated for 2.0 eq. *m*CPBA and 2.0 eq. H_3PO_5 system, since they provide the product in 8% and 40% respectively. As the B-V reaction is known to be accelerated by acids, several Lewis acids and Brønsted acids were investigated (Table 7-5).

Table 7-5. B-V reaction by various acids.



entry	oxidizing agent / solvent	additive	(eq.)	time	yield (%)[a] 2	3
1	H_3PO_5 / CH_3CN	$Cu(OTf)_2$	(1.2)	3 d	-	30
2		$Hf(OTf)_4$			-	24
3		$Yb(OTf)_3$			-	41
4		$Y(OTf)_3$			-	37
5		$Sc(OTf)_3$			-	39
6	*m*CPBA / CH_2Cl_2	$Cu(OTf)_2$	(1.2)	3 d	-	8
7		$Hf(OTf)_4$			-	7
8		$Yb(OTf)_3$			-	10
9		$Y(OTf)_3$			-	-
10		$Sc(OTf)_3$		4.5 h	-	91
11			(0.2)	2 d	-	65
12	*m*CPBA / CH_2Cl_2	TFA	(1.0)	2 d	-	11
13[b]		TsOH	(1.5)	4 d	-	25[c]
14		TfOH	(1.2)	1 h	-	91
15			(0.2)	2 d	-	36

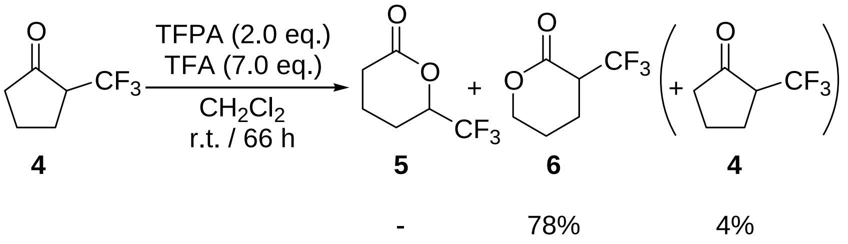
[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] 2.7 eq. of *m*CPBA was added.
[c] Yields of the isolated products.

In all entries, perfect regioselectivity is attained by any acids; product **1** was not observed at all. When H_3PO_5 was used as an oxidizing agent, no significant accelerating effects by the Lewis acids were observed (entries 1~5). However, when *m*CPBA was used as an oxidizing agent, $Sc(OTf)_3$ made a significant acceleration to complete the reaction in 4.5 h (entry 10). For Brønsted acids, TFA (entry 12) and TsOH (entry 13) made virtually no effect on the reaction. The reaction with TfOH, however, completed within 1 h (entry 14). This acceleration is even more than that by $Sc(OTf)_3$. Unfortunately, both $Sc(OTf)_3$ and TfOH could not be reduced to catalytic amount (entries 11, and 15). Since the highest acceleration effect is observed with TfOH, active species of $Sc(OTf)_3$ might be TfOH generated by the reaction with H_2O. However, other metal triflates had no acceleration effect. Mechanism for the acceleration is not clear.[14]

7-5. Other substrates.

The B-V reaction of other substrates was investigated. First, the reaction of a five-membered ring substrate was carried out (Scheme 7-3). The regioselectivity was same as six-membered ring substrate; migration of non-substituted carbon was preferential. The reaction took 66 h to give 78% of the product **6** and the substrate was still remaining (4 %). Measurement of the ^{19}F NMR of the reaction mixture revealed the existence of one unidentified product in small amount. Six-membered ring lactone **6** was slightly unstable relative to seven-membered ring lactone. Therefore, the unidentified product might be the ring-opening product of **6** or regioisomeric product **5**. However, at least the ratio of **6**/**5** is greater than 4.3 (=78/(100-78-4)). This ratio means the preferential migration of non-substituted carbon.

Scheme 7-3.



Next, the reaction of acyclic 7-trifluoromethyl-6-undecanone (**7**) was investigated (Table 7-6). The B-V reaction by 2.0 eq. of TFPA gave only 5% of the product and even the use of 4.2 eq. of TFPA gave 8% of the product. *m*CPBA/$Sc(OTf)_3$ system, which was effective for α-CF_3 cyclohexanone, did not give the product at all. Finally, the use of 4.3 eq. of *m*CPBA and 5.0 eq. of TfOH for 6 d at room temperature provide the product in 57% yield along with the 34% of the remaining substrate. Regioselectivity was identical to that of six- and five-membered ring substrates; non-substituted carbon

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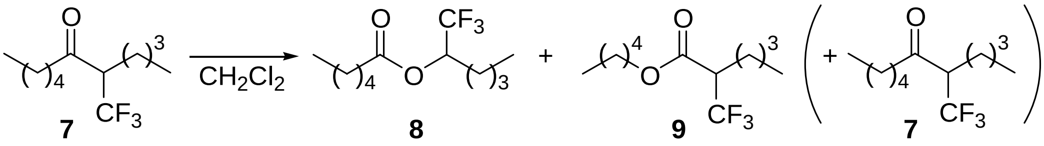
(14) Catalysis of B-V reaction by $Sc(OTf)_3$ and TfOH: Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462-464.

migrated preferentially. ^{19}F NMR of the reaction mixture showed the existence of several unidentified product in small amount. The unidentified product might be the product of the hydrolysis of **9** or regioisomeric product **8**. However, at least the ratio of **9**/**8** is greater than 6.3 (=57/(100-57-34)). This ratio implies the preferential migration of non-substituted carbon.

Table 7-6. B-V reaction of acyclic substrate.



conditions	**8**	**9**	remaining **7**
TFPA (4.2 eq.) / TFA (14.7 eq.) 5 d / r.t.	-	8%	85%
*m*CPBA (2.1 eq.) / Sc(OTf)$_3$ (1.3 eq.) 4 d / 60 ºC	-	-	87%
*m*CPBA (4.3 eq.) / TfOH (5.0 eq.) 6 d / r.t.	-	57%	34%

7-6. Conclusion.

In this chapter, the B-V reaction of α-CF_3 ketone is described. TFPA is effective for the reaction of α-CF_3 cyclohexanone to give the single regioisomer in quantitative yield. Further investigation reveals that the combination of *m*CPBA with Sc(OTf)$_3$ or TfOH are more effective than TFPA. By using *m*CPBA/TfOH system, even linear substrates, for which TFPA is not effective, can be oxidized to give α-CF_3 ester.

The origin of the regioselectivity of the B-V reaction of α-CF_3 ketone will be discussed in Chapter 8.

Experimental Section for Chapter 7

General

^1H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometers and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometers. Chemical shift of ^1H NMR was expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta=0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta=77.0$) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard ($\delta=-63.24$) in $CDCl_3$.Important NMR data were tabulated in following order: multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sext: sextet, sept: septet, bs: broad singlet, bd: broad doublet, m: multiplet) and coupling constant (*J* (Hz)).

IR spectrum was measured on JASCO FT/IR-5000 spectrometer.

EI Mass spectra were measured on Shimazu QP-5000 spectrometer.

Analytical thin layer chromatographies (TLC) were performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid.

Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane and ethyl acetate as an eluent.

THF and Et_2O were distilled over benzophenone-ketyl under Ar prior to use. CH_2Cl_2 (dehydrate), CH_3CN (dehydrate) were purchased from Kanto Chemical Co., Inc.

Preparation of trifluoroperacetic acid (TFPA)

Procedure A:

30% hydrogen peroxide (10.1 ml, 0.10 mol) was added to trifluoroacetic acid (TFA) (14.6 ml, 0.19 mol) and stirred for 40 min at room temperature. The resultant solution was used as 4 mol/l TFA solution of TFPA.

Procedure B:

To a solution of trifluoroacetic anhydride (TFAA) (0.48 ml, 3.4 mmol) in CH_2Cl_2 (4 ml) was added 60% hydrogen peroxide (85 mg, 1.4 mmol) at 0 ºC and stirred for 1 h at room temperature. The resultant solution was directly used as 0.33 mol/l TFPA solution of Dichloromethane containing TFA (TFPA:TFA=2:7).

Preparation of H_3PO_5

To a suspension of phosphorus (V) oxide (0.25 g, 1.7 mmol) in CH_3CN (4 ml) was added 60% hydrogen peroxide (0.11 g, 1.8 mmol) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC and then 2 h at room temperature. The resultant solution was directly used as 0.46 mol/l H_3PO_5 solution of CH_3CN.

General procedure for Baeyer-Villiger reaction

a) TFPA (B)

To TFPA (B) (0.6 ml) was added dichloromethane (0.4 ml) (and an additive, if needed) at room temperature. And then 2-trifluoromethyl-cyclohexanone (**1**) (16.6 mg, 0.1 mmol) was added to the mixture at the temperature. After stirring for 16 h at the temperature, the reaction mixture was directly transferred to silica gel column chromatography (dichloromethane only). Purification by column chromatography gave 2-trifluoromethyl-6-hexanolide (**3**) in 89% yield.

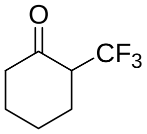
b) *m*CPBA

To a solution of *m*CPBA (80% purity) (43.1 mg, 0.2 mmol) (and an additive, if needed) in dichloromethane was added 2-trifluoromethyl cyclohexanone (**1**) (16.6 mg, 0.1 mmol) at room temperature under argon atmosphere. The reaction was monitored by ^{19}F NMR using BTF as an internal standard.

c) H_3PO_5

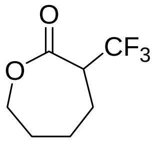
To H_3PO_5 solution in acetonitrile (1.3 ml, 0.6 mmol) was added 2-trifluoromethyl-cyclohexanone (**1**) (16.6 mg, 0.1 mmol) at room temperature. After stirring for 3 d at the temperature, the reaction mixture was directly transferred to silica gel column chromatography (dichloromethane only). Purification by column chromatography gave 2-trifluoromethyl-6-hexanolide (**3**) in 91% yield.

2-Trifluoromethyl-cyclohexanone (1)



See Chpater 4, **3a**.

2-Trifluoromethyl-6-hexanolide (3)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.55~1.90 (m, 3H), 1.95~2.28 (m, 3H), 3.24~3.40 (m, 1H), 4.19 (dd, *J*=10.7, 13.1 Hz, 1H), 4.39 (dm, *J*=13.2 Hz, 1H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 23.8, 27.2, 28.3, 47.7(q, *J*=27.3 Hz), 69.0, 124.5(q, *J*=278.3 Hz), 168.5 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -70.5 (d, *J*=6.8 Hz) (ppm).

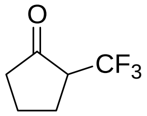
IR (neat)

1736, 1417, 1255, 1203, 1178, 1162, 1112, 1050 (cm^{-1}).

EI-MS

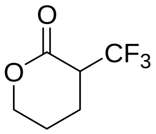
m/z=182 $[M^{+\bullet}]$

2-Trifluoromethyl-cyclopentanone (4)



See Chapter 4, **3b**.

2-Trifluoromethyl-5-hexanolide (6)



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.90~2.14 (m, 3H), 2.25~2.41 (m, 1H), 3.20~3.36 (m, 1H), 4.39 (t, *J*=5.6 Hz, 2H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 19.8 (q, *J*=2.4 Hz), 20.9, 44.3 (q, *J*=27.9 Hz), 69.0, 124.3 (q, *J*=277.8 Hz), 164.7 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -69.2 (d, *J*=7.9 Hz) (ppm).

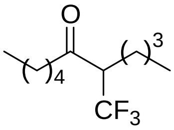
IR (neat)

2928, 2362, 1748, 1404, 1330, 1259, 1181, 1122, 1067, 961 (cm^{-1})

EI-MS

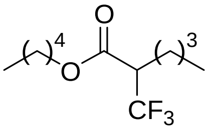
m/z=168 [$M^{+\bullet}$]

7-Trifluoromethyl-6-undecanone (7)



See Chapter 4, **3f**.

Pentyl-2-trifluoromethyl-hexanoate



^{1}H NMR ($CDCl_3$, 300 MHz)

δ 0.80~1.00 (m, 6H), 1.15~1.45 (m, 8H), 1.55~1.98 (m, 4H), 3.00~3.15 (m, 1H), 4.17 (t, *J*=6.8 Hz, 2H) (ppm).

^{13}C NMR ($CDCl_3$, 75 MHz)

δ 13.7, 13.9, 22.2, 22.4, 25.8, 27.9, 28.1, 28.8, 50.5 (q, *J*=26.7 Hz), 65.7, 124.8 (q, *J*=279.1 Hz), 167.7 (ppm).

^{19}F NMR ($CDCl_3$, 376 MHz)

δ -68.9 (d, *J*=7.9 Hz) (ppm).

IR (neat)

2966, 2938, 2878, 1750, 1218, 1125, 1102 (cm^{-1}).

EI-MS

m/z=254 [$M^{+\bullet}$].

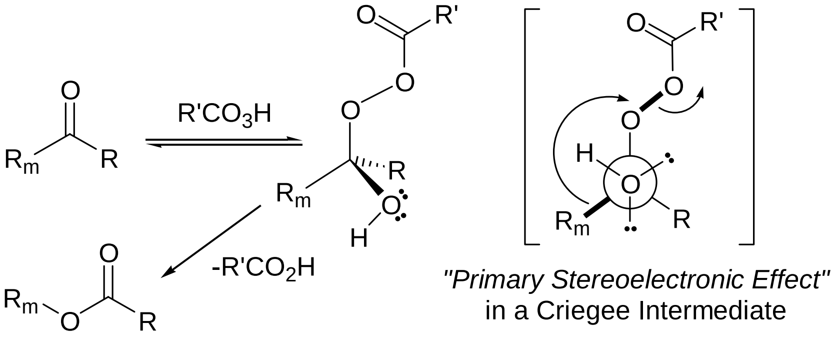
Chapter 8

Theoretical Study on the Baeyer-Villiger Reaction of α-Me, F, CF_3 Cyclohexanone

8-1. Introduction.

The Baeyer-Villiger (B-V) reaction[1] has been widely employed in organic synthesis by virtue of the unique transformation: an oxygen atom can be inserted regioselectively and stereospecifically into a carbon-carbon single bond.[2] A two-step mechanism has been well accepted; (1) carbonyl addition of a peroxy acid to form a peroxy acid/carbonyl adduct, the Criegee intermediate,[3] and then (2) skeletal rearrangement of the Criegee intermediate. Many kinetic studies[4] had been carried out to reveal that rearrangement of the Criegee intermediate is a concerted process and, with some exceptions,[4f,i] a rate-determining step (Scheme 8-1).

Scheme 8-1.



The regioselectivity has long been the most important issue in the B-V reaction. The ketonic substituent that can best stabilize a partially positive charge usually migrates preferentially. It has also been well accepted that the stereoelectronic requirement for correct antiperiplanar alignment of the migrating substituent and the O-O bond of the leaving peroxy acid (e.g., $\mathrm{R'COO^-}$), referred to as the primary

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(1) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625-3633.

(2) Reviews: (a) Krow. G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, 671. (b) Krow, G. R. *Org. React.* **1993**, *43*, 251-798. (c) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1198-1209. (d) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737-750. (e) Brink, G.-J. ten; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105-4123.

(3) Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127-135.

(4) (a) Hawthorne, M. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 6398-6404. (b) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1969**, *34*, 3985-3991. (c) Palmer, B. W.; Fry, A. *J. Am. Chem. Soc.* **1970**, *92*, 2580-2581. (d) Mitsuhashi, T.; Miyadera, H.; Simamura, O. *J. Chem. Soc., Chem. Commun.* **1970**, 1301-1302. (e) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1972**, *94*, 4189-4196. (f) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, *37*, 2953-2957. (g) Winnik, M. A.; Stoute, V. *Can. J. Chem.* **1973**, *51*, 2788-2793. (h) Winnik, M. A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* **1974**, *96*, 1977-1979. (i) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455-9456.

stereoelectronic effect, is required at the migrating step (parentheses in Scheme 8-1).[5] Such a primary stereoelectronic effect has been rationalized in a few reports, where the migration of the carbon **a** located in correct antiperiplanar alignment by (i) a conformational factor or (ii) a stereoelectronic factor by the dipole interaction (Figure 8-1).[6,7]

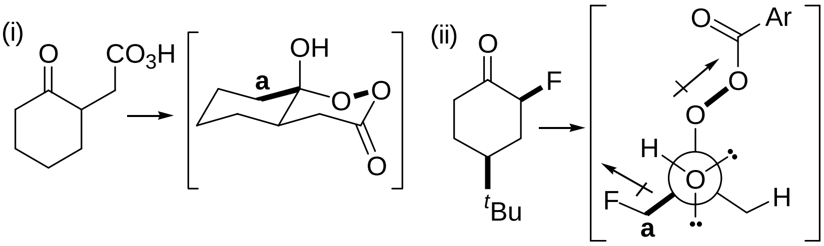

Figure 8-1. The primary stereoelectronic effect in the Ciregee intermediate of (i) Chandrasekhar's and (ii) Crudden's model.

On the basis of the result of Crudden's α-F_{eq} cyclohexanone, one might predict that α-CF_3 ketones should exhibit a similar trend for migration of the CF_3-bearing carbon because of the equatorial orientation of the sterically demanding CF_3 group.[8] Significantly however, as reported in Chapter 7,[9] the B-V reaction of α-CF_3 ketone showed the opposite regioselectivity to that of α-F_{eq} cyclohexanone. The regioselectivity of the B-V reaction of α-Me,[10] F,[7] CF_3[9] cyclohexanone are shown in Figure 8-2.

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(5) Correct anti-periplanar alignment of the lone electron pair of the hemiacetal oxygen and the migrating substituentes is also proposed for the migration step. (a) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569-2572. (b) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573-2576.

(6) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371-6372.

(7) Crudden C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2852-2855.

(8) A-value:Me=~1.70 ^{i}Pr=~2.15, CF_3=2.4~2.5, ^{t}Bu=>4 (kcal/mol). Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139-195.

(9) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803-4806.

(10) See Chapter 7.

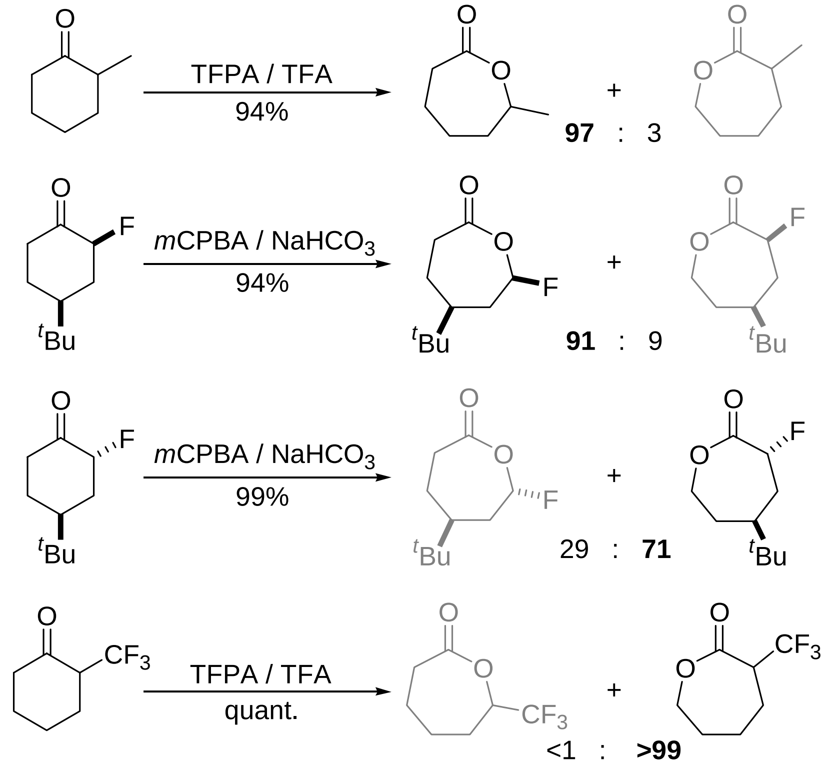

Figure 8-2. B-V reaction of α-Me, F, CF_3 cyclohexanone.

The difference in regioselectivity by α-substituent is quite interesting. In the case of α-F cyclohexanone, they suggest that the thermodynamic stability of the Criegee intermediate (thermodynamic factor) in terms of dipole interaction defines the regioselectivity (Figure 8-1, (ii)). On the other hand, in the case of α-Me cyclohexanone, it is well accepted that nucleophilicity of the migrating carbon defines the regioselectivity (kinetic factor). The regioselectivity of α-Me cyclohexanone could also be explained by thermodynamic factor by means of steric repulsion (Figure 8-3).

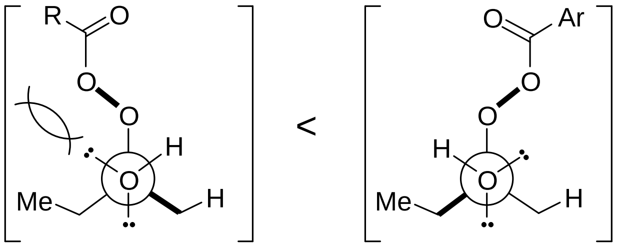

Figure 8-3. Regioselectivity of α-Me cyclohexanone by means of thermodynamic factor.

However, in the case of α-CF_3 cyclohexanone, the CF_3 group has strong electron withdrawing nature and thus it could induce strong dipole interaction and steric repulsion to stabilize the intermediate which should induce migration of CF_3 substituted carbon (thermodynamic factor). But strong electron withdrawing nature of CF_3 group could decrease the nucleophilicity of the adjacent carbon to induce the migration of non-substituted carbon (kinetic factor). The prediction of the regioselectivity of the B-V reaction of α-CF_3 cyclohexanone by thermodynamic factor and kinetic factor could lead to the opposite regioselectivity.

Although there are many theoretical investigation of the B-V reaction,[11] to the best of the author's knowledge, there is no report which investigates about the origin of the regioselectivity of the B-V reaction computationally. Therefore, we explored the regioselectivity of the B-V reaction of α-Me, F, CF_3 cyclohexanones to clarify the origin of the regioselectivity of the B-V reaction.[12] The author herein reports the theoretical investigation of total regioselectivity of B-V reaction of α-Me, F, CF_3 cyclohexanones.

8-2. Chemical models and computational methods.

8-2-1. Chemical models.

The regioselectivity of the B-V reaction is determined at the stage of the migration step from the Criegee intermediate. Therefore, the Criegee intermediate and the transition state of the migration step of the B-V reaction of cyclohexanone derivative with trifluoroperacetic acid (TFPA) were calculated. As shown in Figure 8-4, there were totally eight possible conformations in the chemical model of the rearrangement step with respect to the position (axial or equatorial) of the oxidant and R group and the regioselectivity of the migrating carbon (path ***a*** or ***b***). All the structures were calculated for each R=Me, F, CF_3 substituent. However, the author mainly focused on type I (axial attack of TFPA) to make the discussion clear.

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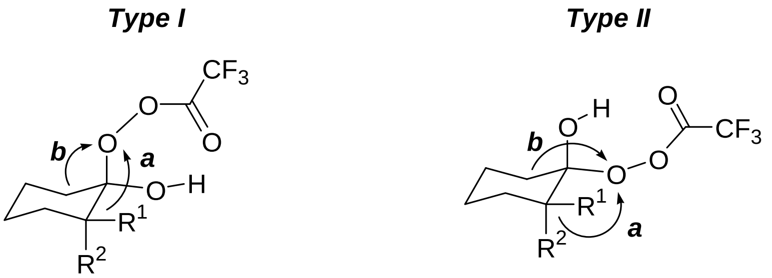
(11) (a) Stoute, V. A.; Winnik, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1974**, *96*, 6388-6393. (b) Cárdenas, R.; Cetina, R.; Lagúnez-Otero, J.; Reyes, L. *J. Phys. Chem.* **1997**, *101*, 192-200. (c) Okuno, Y. *Chem. Eur. J.* **1997**, *3*, 212-218. (d) Hannachi, H.; Anoune, N.; Arnaud, C.; Lantéri, P.; Longeray, R.; Chermette, H. *J. Mol. Struct.* **1998**, *434*, 183-191. (e) Cádenas, R.; Reyes, L.; Lagúnez-Otero, J.; Cetina, R. *J. Mol. Struct.* **2000**, *497*, 211-225. (f) Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* **2001**, *66*, 1193-1199. (g) Lehtinen, C.; Nevalainen, V.; Brunow, G. *Tetrahedron* **2001**, *57*, 4741-4751. (h) Carlqvist, P.; Eklund, R.; Hult, K.; Brinck, T. *J. Mol. Model* **2003**, *9*, 164-171. (i) Sever, R. R.; Root, T. W. *J. Phys. Chem. B* **2003**, *107*, 10848-10862. (j) Reyes, L.; Castro, M.; Cruz, J.; Rubio, M. *J. Phys. Chem. A* **2005**, *109*, 3383-3390.

(12) During the preparation of this manuscript, Crudden and co-workers have reported a computational study of the B-V reaction of α-F, Cl ketones. Grein, F.; Chen, A. C.; Edwards, D.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 861-872.



CP1, **TS1**: R^1 = R, R^2 = H, ***a***
CP2, **TS2**: R^1 = R, R^2 = H, ***b***
CP3, **TS3**: R^1 = H, R^2 = R, ***a***
CP4, **TS4**: R^1 = H, R^2 = R, ***b***

CP5, **TS5**: R^1 = R, R^2 = H, ***a***
CP6, **TS6**: R^1 = R, R^2 = H, ***b***
CP7, **TS7**: R^1 = H, R^2 = R, ***a***
CP8, **TS8**: R^1 = H, R^2 = R, ***b***

R = Me, F, CF_3

Figure 8-4. Chemical model of the B-V reaction.

8-2-2. Computational methods.

All the calculations were performed with GAUSSIAN 98[13] and 03[14] program package. All the structures were optimized at HF/6-31G*[15] and the energies were calculated at B3LYP/6-31+G**[16] using the optimized structure.[17] The energetics of

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(13) Gaussian 98, Revision A.9, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; and Pople, J. A.; Gaussian, Inc., Pittsburgh PA, 1998.

(14) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(15) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986, and references cited therein.

(16) B3LYP utilizes Becke's three-parameter exchange functional and the Lee-Yang-Parr correlation functional. (a) Becke, A.D. *Phys. Rev.* **1988**, *A38*, 3098-3100. (b) Becke, A. D. *J. Chem. Phys.*

this level of calculation has consistency with the experimental result. All stationary points were analyzed through computation of their vibrational frequencies.

8-3. α-Me cyclohexanone.

Calculated relative energies for all possible eight conformations of **CP**s and **TS**s for α-Me cyclohexanones are listed in Table 8-1. Energy diagram and the structure of the rearrangement step of B-V reaction of α-Me cyclohexanone (Type I) are shown in Figure 8-5 and Figure 8-6.

As shown in Figure 8-5, **Me-CP3** and **4** are in almost the same energy. The structural difference between **Me-CP3** and **4** is that they have the different alignment of peracid moiety. Since Me group is in axial position, alignment of the peracid moiety makes no steric or electronic energy difference. **Me-CP1** is 1 kcal/mol lower in energy than **Me-CP3** and **4**. This is because Me group which are in axial position at **Me-CP3** flip to equatorial position at **Me-CP1** to reduce 1,3-diaxial repulsion. However, **Me-CP2** also has Me group in equatorial position with higher energy. The difference between **Me-CP1** and **Me-CP2** is again the alignment of the peracid moiety, but this time the Me group is in equatorial position to cause steric repulsion between peracid moiety. In **Me-CP2**, peracid moiety is in the same direction to Me group which makes **Me-CP2** sterically unfavorable than **Me-CP1**.

Activation energies do not differ from each other; they are within 2.3 kcal/mol range. It is surprising that there are no significant difference in activation energies between ***a*** series (migration of Me substituted carbon) and ***b*** series (migration of non-substituted carbon), since the regioselectivity of the B-V reaction of α-Me ketone was believed to be determined by the nucleophilycity of the migrating carbon (kinetic factor). The most stable **TS** is **Me-TS1** which corresponds to the most stable **CP** (**Me-CP1**). Therefore, in the case of α-Me cyclohexanone, it could be concluded that thermodynamic stability of the Criegee intermediate (thermodynamic factor) determines the regioselectivity of the B-V reaction.

1993, *98*, 1372-1377. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. (d) Lee, C.; Yang, W.; Parr, R. G. *Phys Rev.* **1988**, *B37*, 785-788.

(17) HF geometry optimization gives acceptable structure for heteropolar dissociation of the O-O bond. See ref. 11-(c). However, HF energetics gave very high reaction barrier and does not have consistency with the regioselectivity of α-F cyclohexanone. Single point calculation with B3LYP/6-31+G** gave reasonable energetics and had qualitative consistency with the experimental result.

Table 8-1. Relative energies of **Me-CP**s and **Me-TS**s at B3LYP/6-31+G**// HF/6-31G* level.

Type I	ΔE (kcal/mol)		ΔE (kcal/mol)
Me-CP1	0.3	**Me-TS1**	11.1
Me-CP2	1.8	**Me-TS2**	13.6
Me-CP3	1.3	**Me-TS3**	13.0
Me-CP4	1.3	**Me-TS4**	14.4
Type II	ΔE (kcal/mol)		ΔE (kcal/mol)
Me-CP5	0.0	**Me-TS5**	11.8
Me-CP6	1.7	**Me-TS6**	13.6
Me-CP7	1.7	**Me-TS7**	13.1
Me-CP8	1.1	**Me-TS8**	14.8

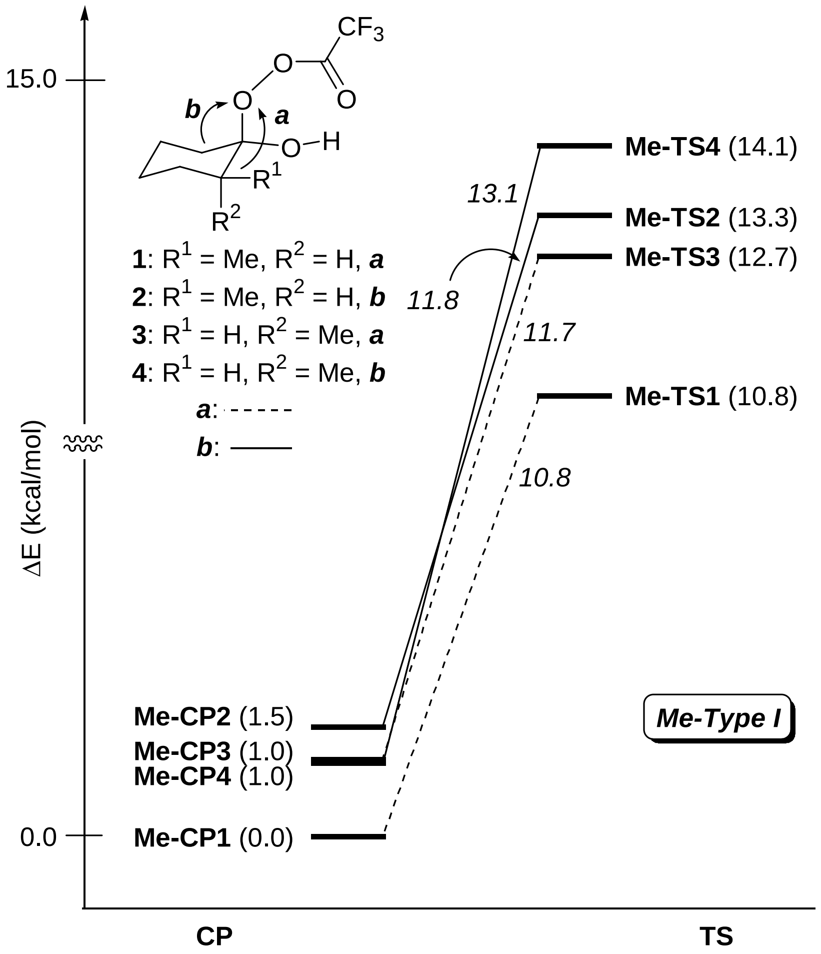


Figure 8-5. Energy diagram of the rearrangement step of α-Me cyclohexanone (Type I). The energies were corrected from Table 8-1 as to be **Me-CP1**=0 kcal/mol. The numbers in italic refer to the activation energies.

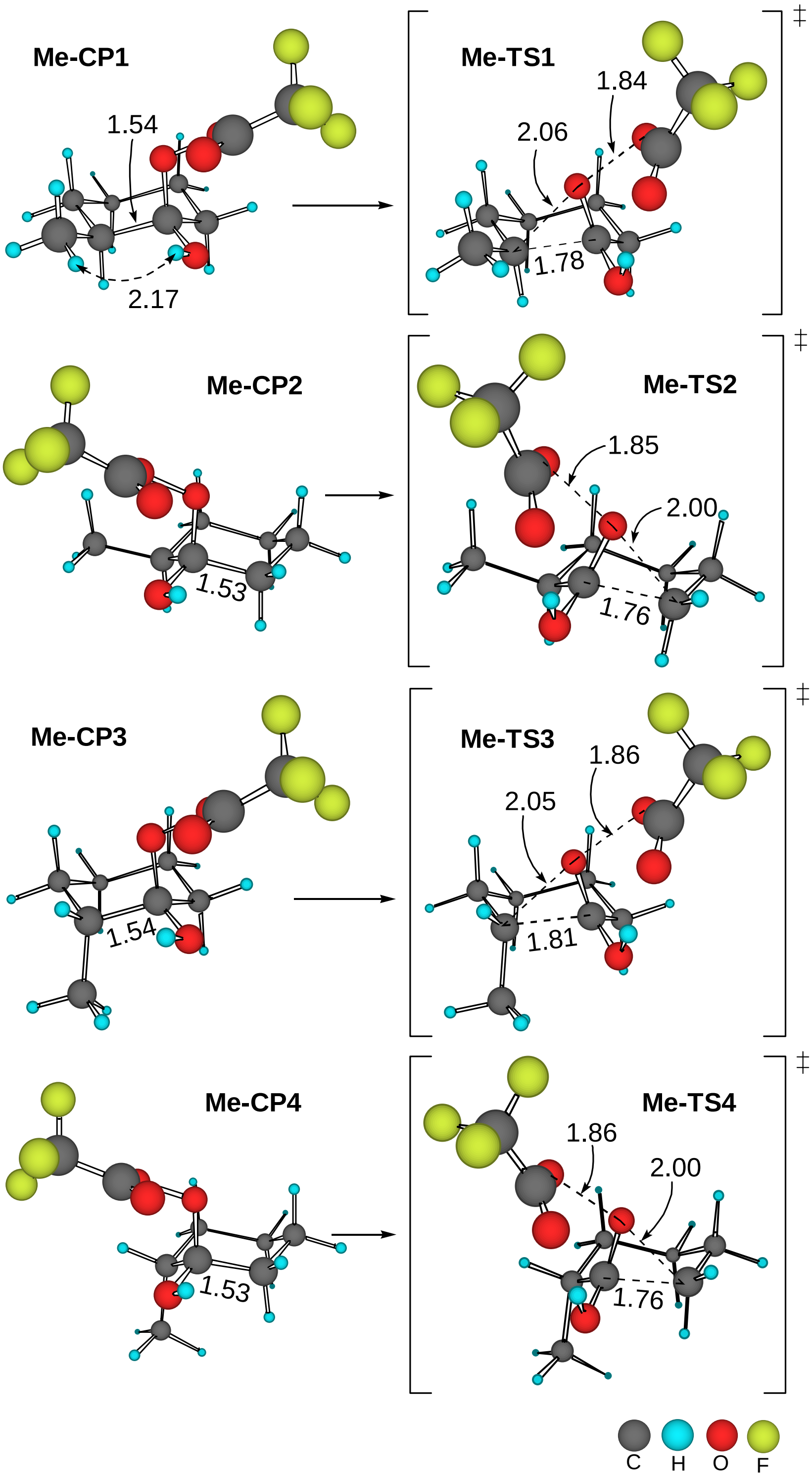


Figure 8-6. Three-dimensional structure of **Me-CP**s, **Me-TS**s. The numbers refer to the distances in Å.

8-4. α-F cyclohexanone.

Calculated relative energies for all possible eight conformations of **CP**s and **TS**s for α-F cyclohexanones are listed in Table 8-2. Energy diagram and the structure of the rearrangement step of the B-V reaction of α-F cyclohexanone (Type I) are shown in Figure 8-8 and Figure 8-9.

The order of the stability of **F-CP**s has the same tendency with **Me-CP**s; **CP3** and **4** are in almost the same energies and **F-CP1** and **F-CP2** are lower and higher than them respectively. However, the reason for this energy profile is different from **Me-CP**s. **F-CP1** has lower energy than **F-CP3** (or **4**). In the case of **Me-CP1**, it was stable for steric factor. However, this is not the case with **F-CP1** since the steric bulkiness is almost negligible (A-value: F=0.27 kcal/mol, Me=~1.7 kcal/mol).[8] Contribution of the hydrogen bonding makes **F-CP1** stable. As shown in Figure 8-9, the distance between hydroxyl H and F in **F-CP1** is 2.39 Å. This value is shorter than sum of the van der Waals radii of H (1.20 Å) and F (1.47 Å).[18] It is clearer when compared with non-substituted **H-CP** (Figure 8-7). The distance between hydroxyl H and α-H is 2.46 Å which is longer than the corresponding distance in **F-CP1**.

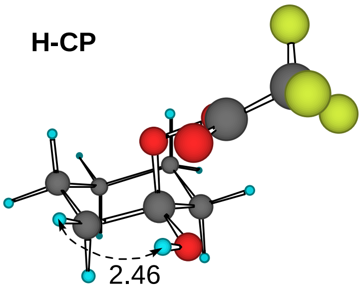


Figure 8-7. Distance between hydroxyl H and α-H in non-substituted **H-CP**.

F-CP2 has high energy than **F-CP3** (or **4**). Since F has insignificant steric effect, the reason for instability is not the same as in **Me-CP2**. In **F-CP2**, the α-F and peracid moiety are in the same direction to induce dipole repulsion. Consequently, the energy of **F-CP2** rises.

---

(18) Bondi. A. *J. Phys. Chem.* **1964**, *68*, 441-451.

Table 8-2. Relative energies of **F-CP**s and **F-TS**s at B3LYP/6-31+G**//HF/6-31G* level.

Type I	ΔE (kcal/mol)		ΔE (kcal/mol)
F-CP1	0.9	**F-TS1**	17.5
F-CP2	3.3	**F-TS2**	19.4
F-CP3	1.8	**F-TS3**	16.7
F-CP4	1.6	**F-TS4**	16.4
Type II	ΔE (kcal/mol)		ΔE (kcal/mol)
F-CP5	0.0	**F-TS5**	17.5
F-CP6	2.9	**F-TS6**	19.7
F-CP7	1.8	**F-TS7**	16.2
F-CP8	0.5	**F-TS8**	15.9

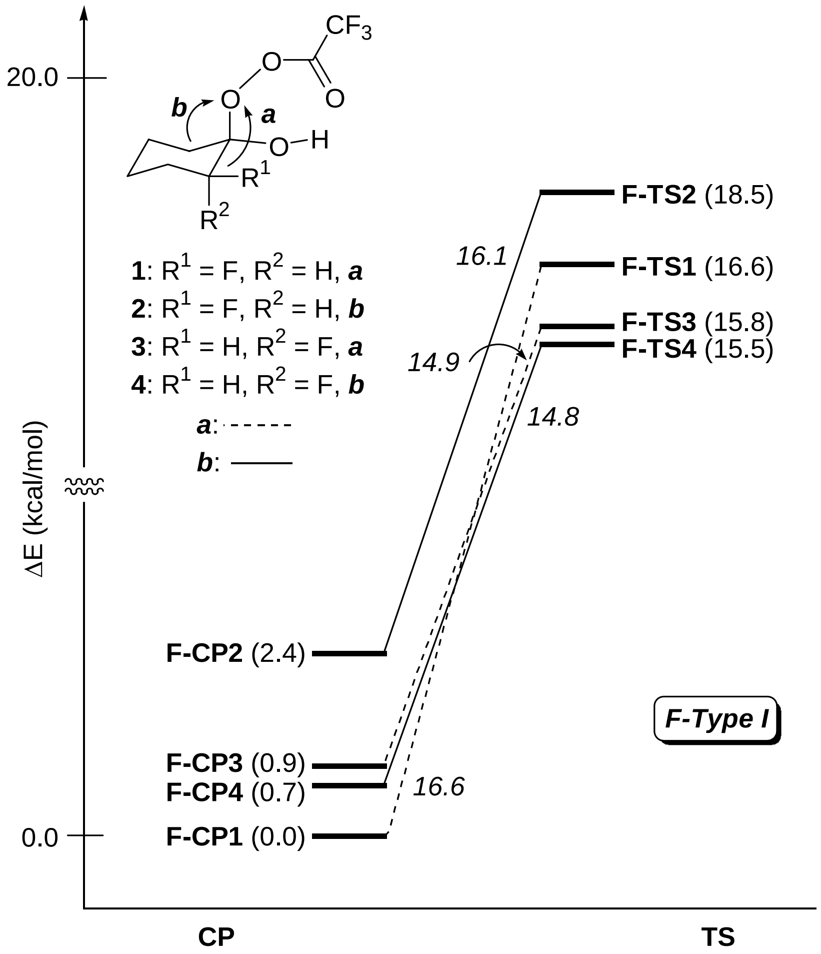


Figure 8-8. Energy diagram of the rearrangement step of α-F cyclohexanone (Type I). The energies were corrected from Table 8-2 as to be **F-CP1**=0 kcal/mol. The numbers in italic refer to the activation energies

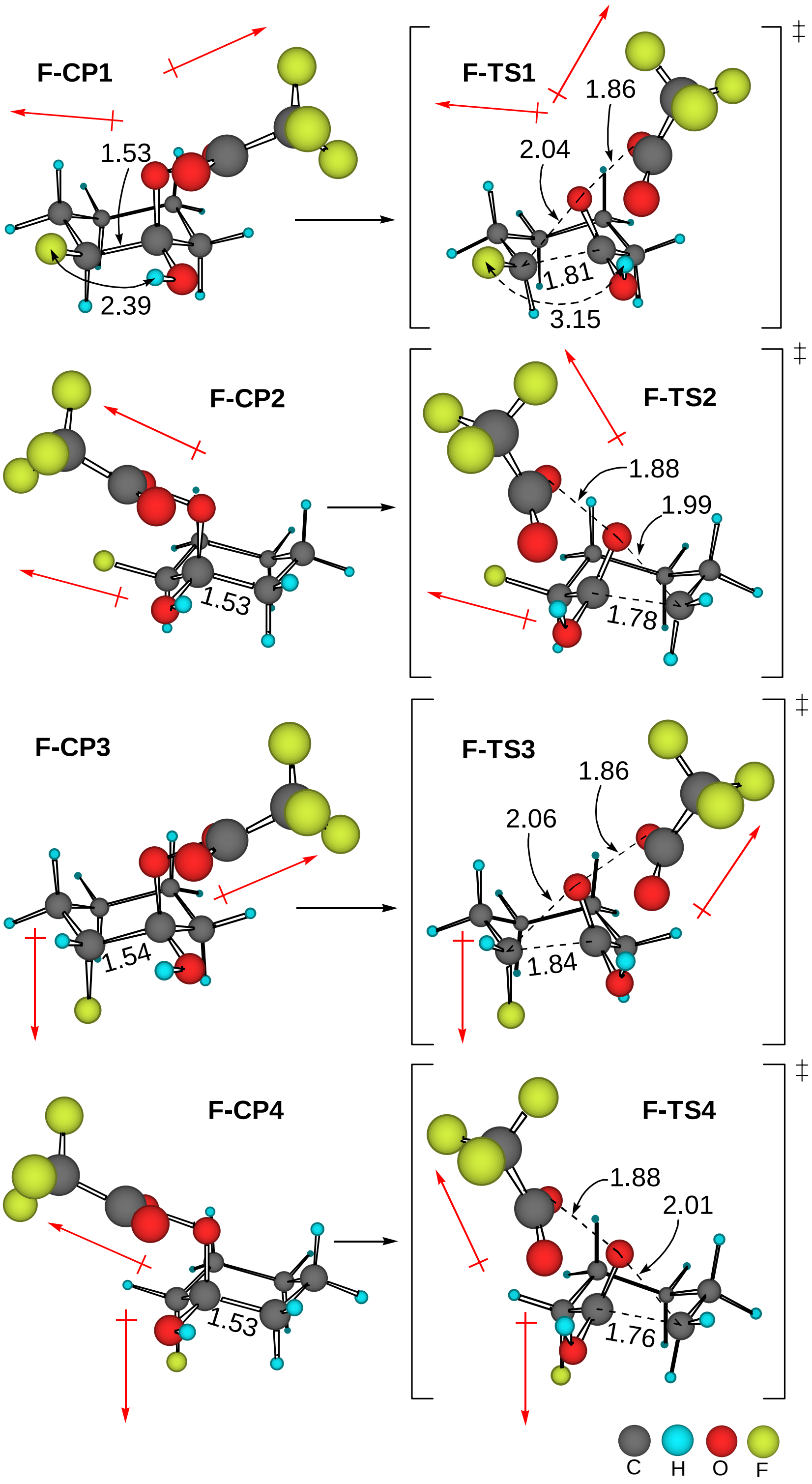


Figure 8-9. Three-dimensional structure of **F-CP**s, **F-TS**s. The numbers refer to the distances in Å.

In contrast to α-Me series, activation energies could be classified into two types in terms of energy value. One is **F-1** and **2** which have α-F in equatorial position (**F_{eq}** series) (activation energy: **F-1**=16.6 kcal/mol, **F-2**=16.1 kcal/mol). The other is **F-3** and **4** which have α-F in axial position (**F_{ax}** series) (activation energy: **F-3**=14.9 kcal/mol, **F-4**=14.8 kcal/mol). The lower activation energy in **F_{ax}** series could be explained by dipole interaction between α-F and peracid moiety (Table 8-3). When **F_{ax}** series comes to TS, stabilization effect by dipole interaction would become more effective since α-F and peracid moiety becomes more linear in **TS**s than in **CP**s. It is clear from Table 8-3 that **F_{eq}** series (**F-1**, **2**) has strong dipole moment than **F_{ax}** series (**F-3**, **4**). **F-1** has especially high activation energy because the hydrogen bonding has to be broken during the reaction.

Table 8-3. Dipole moment of **F-CP**s and **F-TS**s at B3LYP/6-31+G**//HF/6-31G* level.

F		Dipole moment (D)		Dipole moment (D)
eq.	**F-CP1**	4.1	**F-TS1**	7.7
eq.	**F-CP2**	4.5	**F-TS2**	8.4
ax.	**F-CP3**	2.6	**F-TS3**	6.6
ax.	**F-CP4**	2.8	**F-TS4**	6.4

There are no significant difference between ***a*** series (migration of F substituted carbon) and ***b*** series (migration of non-substituted carbon). This means that F substitution does not make significant change in the nucleophilicity of the migrating carbon. F has both σ-acceptor and π-donor nature and thus would cancel each other for the nucleophilicity of the attached carbon. Thermodynamic stability of Criegee intermediate (thermodynamic effect) and activation energy (kinetic effect) both contribute in determining the regioselectivity of the B-V reaction of α-F cyclohexanone. However, the effect of F substitution is only for its strong dipole moment not for lowering the nucleophilicity of the attached carbon.

8-5. α-CF_3 cyclohexanone.

Relative energies calculated for all possible eight conformations of **CP**s and **TS**s for α-CF_3 cyclohexanones are listed in Table 8-4. Energy diagram and the structure of the rearrangement step of the B-V reaction of α-CF_3 cyclohexanone (Type I) are shown in Figure 8-10 and Figure 8-11.

Table 8-4. Relative energies of CF$_3$-CPs and CF$_3$-TSs at B3LYP/6-31+G**// HF/6-31G* level.

Type I	ΔE (kcal/mol)		ΔE (kcal/mol)
CF$_3$-CP1	0.0	**CF$_3$-TS1**	18.1
CF$_3$-CP2	3.6	**CF$_3$-TS2**	18.2
CF$_3$-CP3	1.4	**CF$_3$-TS3**	21.1
CF$_3$-CP4	1.4	**CF$_3$-TS4**	16.2
Type II	ΔE (kcal/mol)		ΔE (kcal/mol)
CF$_3$-CP5	0.5	**CF$_3$-TS5**	19.8
CF$_3$-CP6	4.0	**CF$_3$-TS6**	18.3
CF$_3$-CP7	2.6	**CF$_3$-TS7**	19.7
CF$_3$-CP8	1.5	**CF$_3$-TS8**	17.3

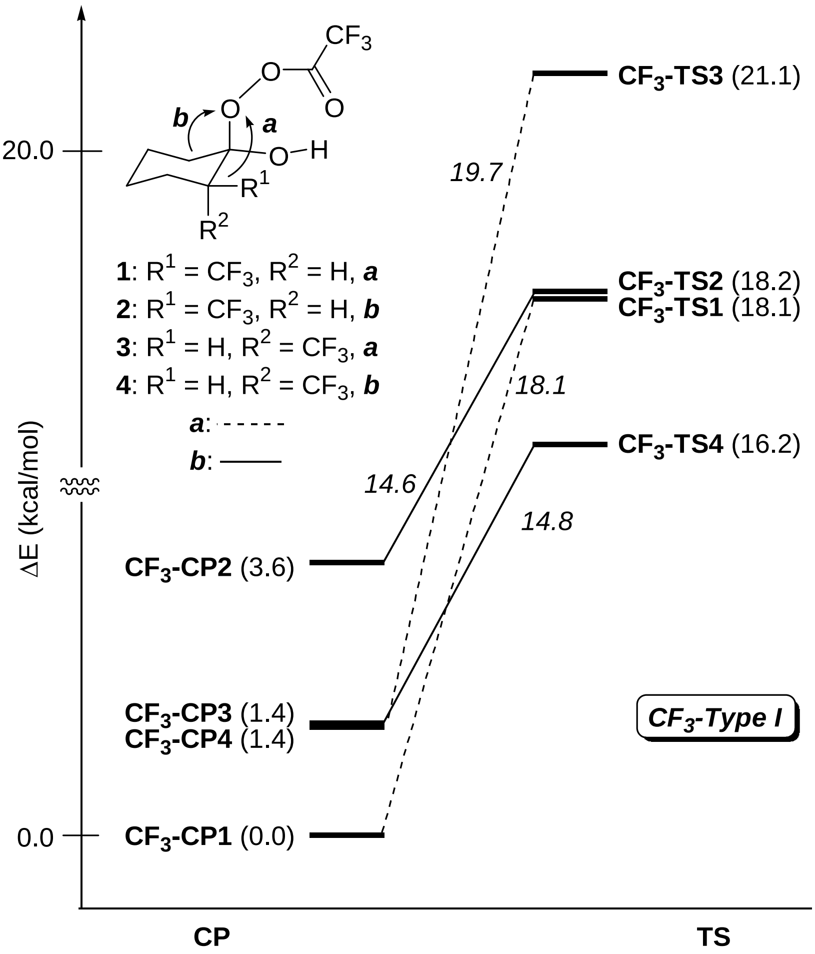


Figure 8-10. Energy diagram of the rearrangement step of α-CF$_3$ cyclohexanone (Type I). The numbers in italic refer to the activation energies.

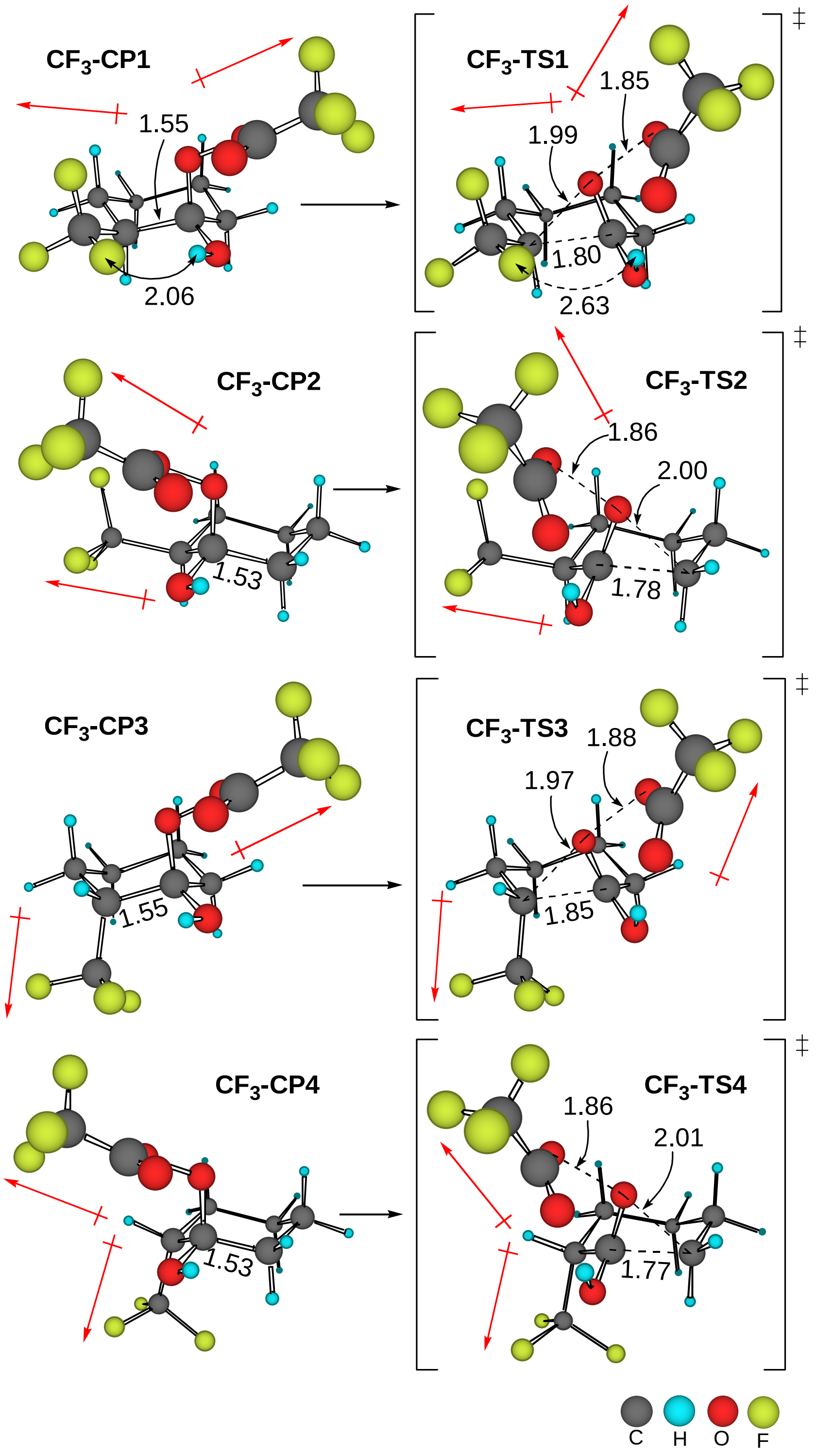


Figure 8-11. Three-dimensional structure of **CF_3-CPs**, **CF_3-TSs**. The numbers are the distances in Å.

The order of the stability of the Criegee intermediates is exactly the same as in **Me-** and **F-CP**s. **CF_3-CP3** and **4** are in almost the same energy as in **Me-** and **F-CP**s. The reason for the stability of **CP1** (compared to **CP3** and **4**) in **Me-CP** was steric and the reason for **F-CP** was hydrogen bonding. In the case of **CF_3-CP1**, both factors exist. The A-value of CF_3 group is larger than Me.[8] Therefore, when the CF_3 group comes to the equatorial position (**CP3** to **CP1**), energy stabilization is greater in **CF_3-CP** (1.4 kcal/mol) than **Me-CP** (1.0 kcal/mol). Hydrogen bonding in **CF_3-CP1** is illustrated in Figure 8-11, **CF_3-CP1**. The distance between hydroxyl H and trifluoromethyl F in **CF_3-CP1** is 2.06 Å and this value is shorter than the sum of the van der Walls radii of H (1.20 Å) and F (1.47 Å). It is clearer when compared with **Me-CP1** (Figure 8-6). The distance between hydroxyl H and methyl H is 2.17 Å which is longer than the corresponding distance in **CF_3-CP1**. On the other hand, the reason for instability of **CP2** (compared to **CP3** and **4**) in **Me-CP** was steric repulsion between peracid moiety and the reason for **F-CP** was dipole repulsion between α-F and the peracid moiety. In the case of **CF_3-CP2**, again, both factors exist. Although 1,3-diaxial repulsion is reduced when the CF_3 group comes to equatorial position, the steric repulsion with peracid moiety emerges in greater value than **Me-CP2**. In addition, since CF_3 group is a strong electron withdrawing group, there are strong dipole repulsion between peracid moiety as observed in **F-CP2**. These two effects resulted in high destabilization of **CF_3-CP2** (compared to **CF_3-CP3**: 2.2 kcal/mol), which is larger than **Me-CP2** (0.5 kcal/mol) or **F-CP2** (1.5 kcal/mol).

Activation energies could be classified into two categories; path ***a*** (migration of CF_3 substituted carbon, 18.1 kcal/mol (**CF_3-1**), 19.7 kcal/mol (**CF_3-3**)) and path ***b*** (migration of non substituted carbon, 14.6 kcal/mol (**CF_3-2**), 14.8 kcal/mol (**CF_3-4**)). In the case of α-F cyclohexanone, classification was different (**F_{eq}** and **F_{ax}**). The dipole moment of **CF_3-CP**s and **CF_3-TS**s is listed in Table 8-5.

Table 8-5. Dipole moment of **CF_3-CP**s and **CF_3-TS**s at B3LYP/6-31+G**//HF/6-31G* level.

CF_3		Dipole moment (D)		Dipole moment (D)
eq.	**CF_3-CP1**	4.0	**CF_3-TS1**	7.4
eq.	**CF_3-CP2**	4.6	**CF_3-TS2**	8.2
ax.	**CF_3-CP3**	2.7	**CF_3-TS3**	6.2
ax.	**CF_3-CP4**	3.1	**CF_3-TS4**	6.2

Although there are similar tendency of dipole moment with α-F cyclohexanone, this is not the determining factor of the classification of the activation energies. In sharp contrast to F, CF_3 group has only σ-accepting nature. Therefore, the strong electron-withdrawing CF_3 group much decreases the nucleophilicity of the migrating carbon bearing CF_3 group to increase the activation energy of path ***a*** (kinetic factor). According to such energy profiles, Curtin-Hammet kinetics should operate in the B-V reaction of the α-CF_3 cyclohexanone and hence the reaction should occur via **CF_3-TS4**. It is noted that the most stable **TS4** has the axial position of the sterically demanding CF_3 group, which is usually located in the equatorial position due to the 1,3-diaxial repulsion. The energy level of **CF_3-TS2**, which has the CF_3 group in equatorial position and has the same migration tendency with **CF_3-TS4**, is higher than that of **CF_3-TS4**.

8-6. Equatorial attack of TFPA (Type II).

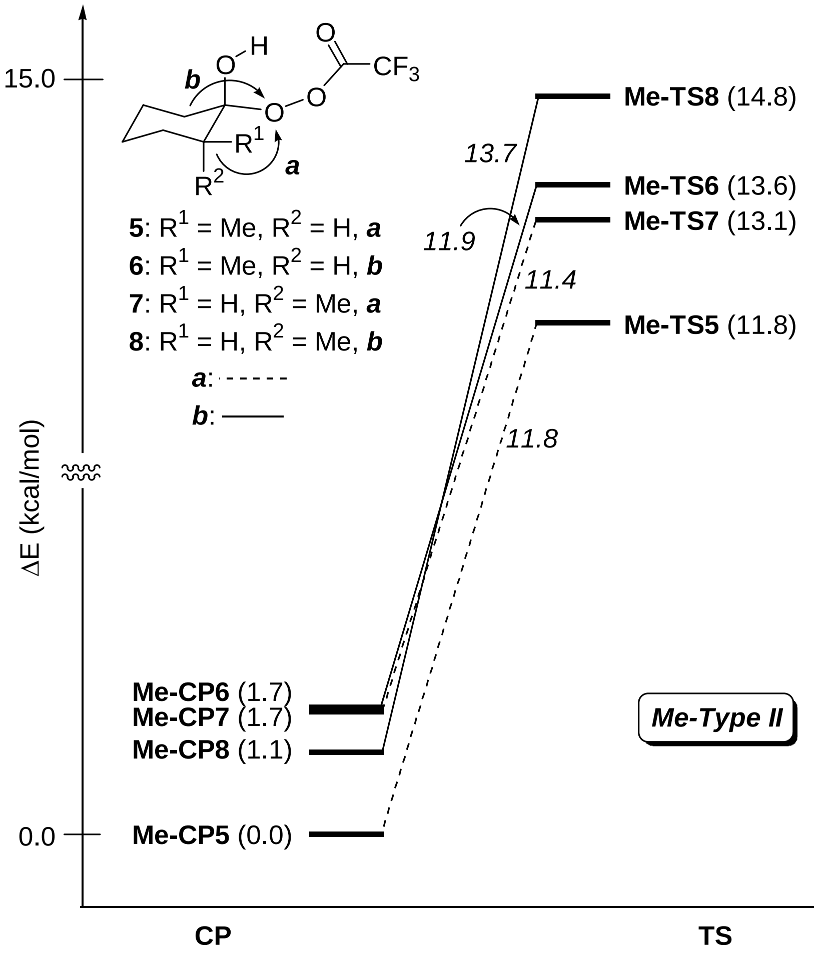


Figure 8-12. Energy diagram of the rearrangement step of α-Me cyclohexanone (Type II). The numbers in italic are the activation energies.

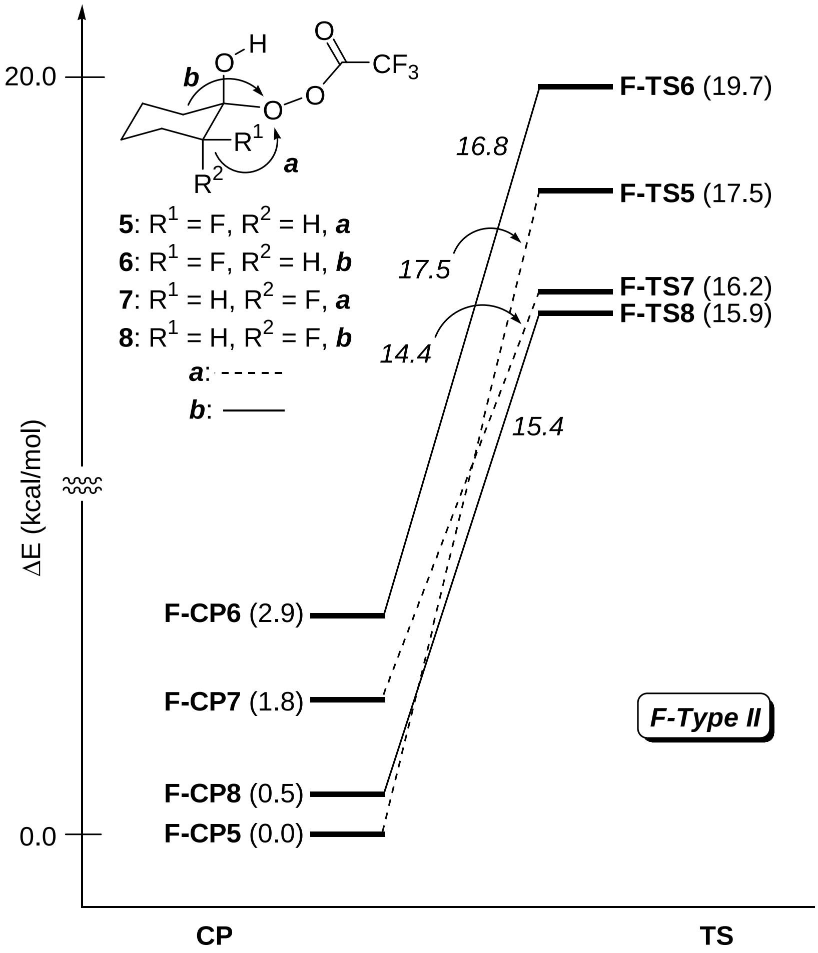


Figure 8-13. Energy diagram of the rearrangement step of α-F cyclohexanone (Type II). The numbers in italic are the activation energies.

Energy diagram of the Criegee intermediate and **TS** of Type II are shown in Figure 8-12, Figure 8-13, and Figure 8-14. Although it is less clear than Type I, energetics of Type II showed a similar tendency as in Type I. The order of the stability of the **CP**s is the same in all α-Me, F, CF_3 cases. In the case of Type I, **CP3** and **CP4** have similar energetics in all substrates. However, the energy difference between **CP7** and **8,** which correspond to **CP3** and **4** in Type I, is quite large. The axial α-substitutents in **CP3** and **4** are far from the axial peracid moiety and in opposite direction to minimize steric or dipole repulsion. In **CP7** and **8**, the peracid moiety is in equatorial position and it could induce steric or dipole repulsion between α-substituent to enlarge the energy difference. The activation energy of α-Me substrates could not be categorized in any kind (as in Type I) and its energies are within 1.8 kcal/mol. In the case of α-F substrates, it is less clear as Type I, but the activation energies could be categorized in the same way as Type I ($\mathbf{F_{ax}}$ and $\mathbf{F_{eq}}$) and it is again clear that F substitution does not have significant effect on the activation energies. α-CF_3 substituents, which CF_3 group had a large influence on the activation energies in Type I, once more affect the activation energies in Type II. In all α-Me, F, CF_3 cases, the most stable **TS**s in Type I and Type II both give the same regioisomer.

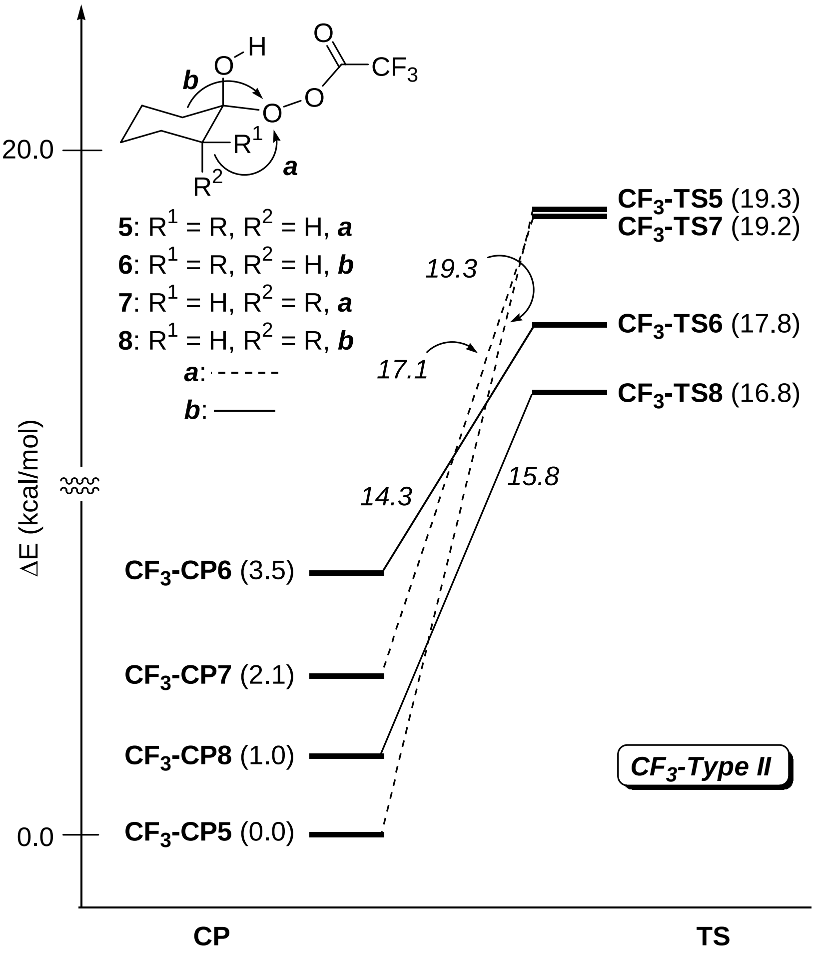


Figure 8-14. Energy diagram of the rearrangement step of α-CF_3 cyclohexanone (Type II). The energies were corrected from Table 8-4 as to be **CF_3-CP5**=0 kcal/mol. The numbers in italic are the activation energies.

8-7. Conclusion.

The regioselectivity of the B-V reaction of α-Me, F, CF_3 cyclohexanone was investigated. Investigation of the energy profiles of the rearrangement step reveal that there are two factors in determining the regioselectivity.

(1) Thermodynamic stability of the Criegee intermediate (thermodynamic effect).
(2) Activation energy (kinetic effect).

And the origins of these two factors are,

(a) Steric repulsion
(b) Dipole interaction
(c) Nucleophilicity of the migrating carbon.

In the case of α-Me cyclohexanone, (1) thermodynamic effect based on (a) steric factor predominates in determining the regioselectivity and the most stable intermediate **Me-CP1** becomes the most stable transition state **Me-TS1**. It is noted that the nucleophilicity of the migrating carbon ((2) kinetic effect), which was believed to be the regioselectivity determining factor of α-Me ketone, does not have significant influence on the regioselectivity. For α-F cyclohexanone, strong electron-withdrawing nature of F induces the (b) dipole interaction between peracid moiety to affect both (1) thermodynamic effect and (2) kinetic effect. As a result, **F-TS4** becomes the most stable transition state. Interestingly, F does not have significant influence on (c) the nucleophilicity of the migrating carbon. In α-CF_3 cyclohexanone, all the factors are combined together. (1) Thermodynamic effect is affected by (a) steric repulsion and (b) dipole interaction. And (2) activation energy is affected by (c) nucleophilicity of the migrating carbon. In sharp contrast to α-F cyclohexanone, CF_3 substituent makes a significant influence on the (c) nucleophilicity of the migrating carbon. This combined effect results in the most stale transition state **CF_3-TS4**. In particular, **CF_3-TS4** has bulky CF_3 group in axial position. Compared to **CF_3-TS2**, it could be said that dipole interaction could overcome steric repulsion.

In this chapter, the author has uncovered the origin of the regioselectivity of α-Me, F, CF_3 cyclohexanones. Steric repulsion, dipole interaction, and nucleophilicity of the migrating carbon are the key factors in determining the regioselectivity of the B-V reaction. All of these factors must be considered in order to predict the regioselectivity.

Experimental Section for Chapter 8

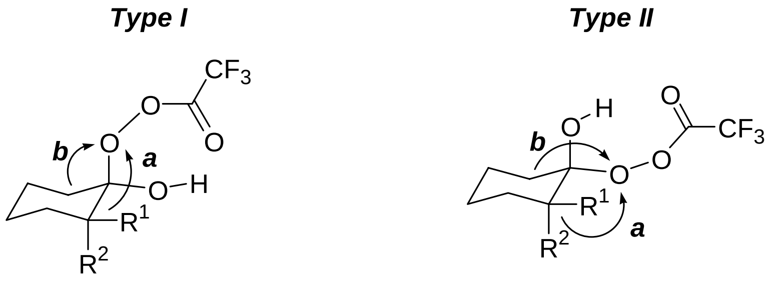
General

Computational calculations were executed on SGI Origin2000 (Tokyo Institute of Technology), Compaq AlphaServer GS320 (Tokyo Institute of Technology), SGI2800 (Institute of Molecular Science), SGI Origin3800 (Institute of Molecular Science), and Fujitsu VPP5000 (Institute of Molecular Science).

Computational Methods

All the calculations were performed with GAUSSIAN 98 and 03 program package. All the structures were optimized at HF/6-31G* and the energies were calculated at B3LYP/6-31+G** using the optimized structure.

Chemical models



CP1, **TS1**: R^1 = R, R^2 = H, ***a***
CP2, **TS2**: R^1 = R, R^2 = H, ***b***
CP3, **TS3**: R^1 = H, R^2 = R, ***a***
CP4, **TS4**: R^1 = H, R^2 = R, ***b***

CP5, **TS5**: R^1 = R, R^2 = H, ***a***
CP6, **TS6**: R^1 = R, R^2 = H, ***b***
CP7, **TS7**: R^1 = H, R^2 = R, ***a***
CP8, **TS8**: R^1 = H, R^2 = R, ***b***

R = Me, F, CF_3

Molecular Geometries and Energies

Me-CP1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.171721437 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.251372    0.193970    0.573387
    2          1           0       -2.064160   -1.187229    1.944681
    3          6           0       -2.257670   -2.055490   -0.024077
    4          6           0       -3.569455   -1.369793   -0.409648
    5          6           0       -3.330939    0.067468   -0.877858
    6          6           0       -2.556480    0.898457    0.157216
    7          8           0       -0.452215    0.237715   -0.616425
    8          6           0       -2.350564    2.340357   -0.319667
```

```
      9          1           0       -2.785252    0.060874   -1.817221
     10          1           0       -3.141906    0.928715    1.073091
     11          1           0       -4.281736    0.555240   -1.072871
     12          1           0       -4.071835   -1.933223   -1.190445
     13          1           0       -1.638549   -2.183778   -0.907235
     14          1           0       -4.238343   -1.362806    0.449426
     15          1           0       -2.452827   -3.048765    0.368507
     16          8           0        0.767899   -0.375516   -0.395903
     17          6           0       -1.495863   -1.240937    1.021420
     18          6           0        1.743604    0.500740   -0.220057
     19          1           0       -0.545078   -1.698233    1.263387
     20          8           0       -0.586719    0.834742    1.594431
     21          1           0       -0.349225    1.715138    1.327793
     22          8           0        1.667557    1.670946   -0.165268
     23          6           0        3.067558   -0.264671   -0.110117
     24          9           0        3.328057   -0.875397   -1.246781
     25          9           0        4.043763    0.561111    0.159149
     26          9           0        2.999510   -1.168477    0.843467
     27          1           0       -1.882688    2.960873    0.438300
     28          1           0       -3.312431    2.789774   -0.542756
     29          1           0       -1.743026    2.384584   -1.215436
---------------------------------------------------------------------
```

Me-CP2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.169326130 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
      1          6           0       -1.316648   -0.377284    0.574822
      2          1           0       -3.021429   -1.379497    1.316902
      3          6           0       -3.322427   -1.149940   -0.810477
      4          6           0       -3.875053    0.276087   -0.787492
      5          6           0       -2.752725    1.305534   -0.637846
      6          6           0       -1.881916    1.049488    0.600474
      7          8           0       -0.491592   -0.648272   -0.571743
      8          6           0       -0.853156    2.165651    0.809564
      9          1           0       -2.125226    1.296411   -1.525335
     10          1           0       -2.531349    1.049178    1.473233
     11          1           0       -3.174945    2.303588   -0.565606
     12          1           0       -4.440146    0.470612   -1.694230
     13          1           0       -2.750878   -1.306795   -1.719811
     14          1           0       -4.571700    0.380410    0.042722
     15          1           0       -4.134247   -1.870902   -0.820853
     16          8           0        0.689967    0.067816   -0.525586
     17          6           0       -2.431776   -1.412846    0.406065
     18          6           0        1.705783   -0.670764   -0.113014
     19          1           0       -1.979701   -2.398839    0.347265
     20          8           0       -0.590646   -0.582176    1.723836
     21          1           0       -0.275383   -1.479266    1.748654
     22          8           0        1.688501   -1.779217    0.274788
     23          6           0        2.988777    0.160483   -0.230543
     24          9           0        2.867681    1.291011    0.431286
     25          9           0        4.002865   -0.506190    0.254317
```

```
   26          9             0        3.228343    0.439710   -1.494435
   27          1             0       -0.261167    2.342644   -0.079170
   28          1             0       -0.182136    1.941434    1.628586
   29          1             0       -1.376682    3.086570    1.047445
---------------------------------------------------------------------
```

Me-CP3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.170093573 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0        1.205941   -0.393498    0.290057
    2          1             0        2.100727    0.489089    1.990603
    3          6             0        2.176952    1.943127    0.390906
    4          6             0        3.449696    1.444795   -0.298192
    5          6             0        3.159851    0.236453   -1.194976
    6          6             0        2.456033   -0.912017   -0.446746
    7          8             0        0.339076   -0.057158   -0.804588
    8          1             0        2.101766   -1.628753   -1.184737
    9          1             0        2.536003    0.554771   -2.023840
   10          6             0        3.404093   -1.657999    0.500571
   11          1             0        4.082674   -0.140005   -1.626638
   12          1             0        3.883970    2.241030   -0.895489
   13          1             0        1.495010    2.345967   -0.352172
   14          1             0        4.192062    1.185792    0.452743
   15          1             0        2.411582    2.754945    1.072598
   16          8             0       -0.860860    0.440569   -0.328560
   17          6             0        1.481188    0.821326    1.164773
   18          6             0       -1.834041   -0.453412   -0.395910
   19          1             0        0.546852    1.160205    1.593407
   20          8             0        0.589692   -1.344919    1.070314
   21          1             0        0.354223   -2.095935    0.535768
   22          8             0       -1.767919   -1.575405   -0.734615
   23          6             0       -3.141347    0.221402    0.035614
   24          9             0       -3.458936    1.171775   -0.818087
   25          9             0       -4.110006   -0.654944    0.071616
   26          9             0       -3.010041    0.759363    1.229154
   27          1             0        3.816272   -1.014434    1.268802
   28          1             0        4.234597   -2.063107   -0.068230
   29          1             0        2.905010   -2.481075    0.996046
---------------------------------------------------------------------
```

Me-CP4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.170127067 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.231931   -0.323367    0.532711
    2          1             0       -3.012367   -1.139954    1.330407
    3          6             0       -3.174069   -1.274866   -0.823207
    4          6             0       -3.646749    0.151549   -1.114719
    5          6             0       -2.474899    1.138597   -1.095658
```

```
      6          6           0       -1.680862    1.109943    0.222716
      7          8           0       -0.346297   -0.811400   -0.488973
      8          1           0       -0.778909    1.696004    0.090971
      9          1           0       -1.805377    0.905619   -1.918217
     10          6           0       -2.454442    1.735319    1.390707
     11          1           0       -2.834755    2.149036   -1.265694
     12          1           0       -4.135413    0.185845   -2.083941
     13          1           0       -2.559362   -1.629040   -1.644635
     14          1           0       -4.395784    0.444532   -0.383360
     15          1           0       -4.023197   -1.947943   -0.753196
     16          8           0        0.791838   -0.028176   -0.558041
     17          6           0       -2.370887   -1.341679    0.479514
     18          6           0        1.831025   -0.606209    0.022160
     19          1           0       -1.952341   -2.334083    0.622557
     20          8           0       -0.570235   -0.330714    1.738523
     21          1           0       -0.257619   -1.208984    1.926972
     22          8           0        1.862399   -1.619642    0.613843
     23          6           0        3.066574    0.270228   -0.214383
     24          9           0        2.848742    1.497767    0.206132
     25          9           0        4.095163   -0.219233    0.426016
     26          9           0        3.346754    0.312794   -1.499944
     27          1           0       -3.373085    1.206415    1.618907
     28          1           0       -2.721049    2.756969    1.139296
     29          1           0       -1.850882    1.755986    2.288225
---------------------------------------------------------------------
```

Me-CP5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.172234550 a.u.
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
      1          6           0        1.209351    0.020259    0.091918
      2          1           0        2.570391    0.807756    1.510015
      3          6           0        3.670484    0.376715   -0.279144
      4          6           0        3.938685   -1.100237    0.013112
      5          6           0        2.722490   -1.956402   -0.340436
      6          6           0        1.469680   -1.453274    0.378682
      7          8           0        0.805379    0.129910   -1.221091
      8          1           0        0.600436   -2.024068    0.078400
      9          1           0        2.556067   -1.932022   -1.412971
     10          1           0        1.584569   -1.566678    1.452375
     11          1           0        2.897139   -2.993448   -0.070299
     12          1           0        4.808824   -1.434195   -0.544331
     13          1           0        3.549164    0.516204   -1.350254
     14          1           0        4.176743   -1.224712    1.068249
     15          1           0        4.523022    0.979188    0.020871
     16          1           0        0.584130    1.032343   -1.420533
     17          6           0        2.419487    0.907161    0.438197
     18          6           0        2.191363    2.389974    0.124118
     19          8           0        0.183368    0.526178    0.954152
     20          8           0       -0.996122   -0.167388    0.747887
     21          6           0       -1.859310    0.521108    0.019805
     22          8           0       -1.704950    1.564584   -0.496087
```

```
   23          6             0       -3.172891   -0.266693   -0.048521
   24          9             0       -4.020570    0.339105   -0.837373
   25          9             0       -3.702662   -0.361360    1.152696
   26          9             0       -2.958522   -1.481038   -0.507356
   27          1             0        2.125036    2.566059   -0.946201
   28          1             0        3.030961    2.972811    0.487602
   29          1             0        1.291880    2.772457    0.590098
---------------------------------------------------------------------
```

Me-CP6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.169521478 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.278685   -0.312822    0.146163
    2          1             0       -2.063247    1.158542    1.433413
    3          6             0       -3.185379    1.228996   -0.392880
    4          6             0       -4.193724    0.135308   -0.039841
    5          6             0       -3.594298   -1.252371   -0.260102
    6          6             0       -2.285902   -1.405166    0.515525
    7          8             0       -0.841460   -0.418051   -1.153183
    8          1             0       -1.826384   -2.370661    0.324294
    9          1             0       -3.409438   -1.405963   -1.319422
   10          1             0       -2.477049   -1.352915    1.582585
   11          1             0       -4.288771   -2.025043    0.054966
   12          1             0       -5.093444    0.254429   -0.636277
   13          1             0       -2.984085    1.208735   -1.460424
   14          1             0       -4.493193    0.238441    1.001849
   15          1             0       -3.608657    2.204286   -0.172343
   16          1             0       -0.532881   -1.302312   -1.319035
   17          6             0       -1.853530    1.094463    0.368263
   18          6             0       -0.913528    2.243896   -0.011764
   19          8             0       -0.203520   -0.622941    1.051634
   20          8             0        0.949754    0.075697    0.745316
   21          6             0        1.811738   -0.654811    0.061091
   22          8             0        1.663148   -1.734841   -0.377262
   23          6             0        3.116777    0.137656   -0.079790
   24          9             0        3.952119   -0.504804   -0.852810
   25          9             0        2.883988    1.323836   -0.598695
   26          9             0        3.670717    0.300198    1.103129
   27          1             0       -0.591293    2.160618   -1.042883
   28          1             0       -1.441543    3.185913    0.099461
   29          1             0       -0.035598    2.283068    0.617176
---------------------------------------------------------------------
```

Me-CP7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.169536466 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.169928   -0.105780    0.094089
    2          1             0       -1.673629    0.872435   -1.731294
```

```
    3         6           0       -2.679522   1.900386  -0.112656
    4         6           0       -3.900243   0.987074   0.024066
    5         6           0       -3.557339  -0.277462   0.818305
    6         6           0       -2.373202  -1.059280   0.218317
    7         8           0       -0.706160   0.292592   1.331537
    8         1           0       -2.078932  -1.828845   0.929498
    9         1           0       -3.314985   0.004480   1.838069
   10         6           0       -2.746466  -1.771495  -1.088730
   11         1           0       -4.419726  -0.935359   0.871309
   12         1           0       -4.706244   1.518561   0.521415
   13         1           0       -2.408857   2.293399   0.861995
   14         1           0       -4.271604   0.721076  -0.962373
   15         1           0       -2.915216   2.752349  -0.743085
   16         1           0       -0.485354  -0.470976   1.853642
   17         6           0       -1.477904   1.155039  -0.702640
   18         1           0       -0.600845   1.789251  -0.700475
   19         8           0       -0.169879  -0.902068  -0.545890
   20         8           0        1.000864  -0.176214  -0.676091
   21         6           0        1.908209  -0.526697   0.220903
   22         8           0        1.800824  -1.295699   1.101274
   23         6           0        3.202648   0.239493  -0.075985
   24         9           0        4.094859  -0.009960   0.845763
   25         9           0        2.974753   1.534942  -0.107425
   26         9           0        3.684053  -0.128300  -1.244628
   27         1           0       -3.013765  -1.079500  -1.878612
   28         1           0       -3.602533  -2.415287  -0.914347
   29         1           0       -1.933983  -2.388268  -1.449790
---------------------------------------------------------------------
```

Me-CP8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.170417431 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6           0        1.214179  -0.367109  -0.135495
    2         6           0        1.768686   1.990924  -0.962302
    3         6           0        2.899899   1.003142   1.106325
    4         6           0        4.038084   0.223920   0.439245
    5         6           0        3.588467  -1.187692   0.054941
    6         6           0        2.330967  -1.155185  -0.818901
    7         8           0        0.772685  -0.983438   1.017646
    8         1           0        1.971457  -2.160649  -1.019586
    9         1           0        3.385280  -1.759741   0.955230
   10         1           0        2.550292  -0.703521  -1.779681
   11         1           0        4.379302  -1.706983  -0.477510
   12         1           0        4.886116   0.168747   1.115430
   13         1           0        2.661507   0.535268   2.055864
   14         1           0        4.386001   0.749103  -0.446764
   15         1           0        3.220044   2.017092   1.327563
   16         1           0        0.499636  -1.873243   0.822155
   17         6           0        1.621565   1.061693   0.247705
   18         1           0        0.822244   1.450181   0.868370
   19         8           0        0.170481  -0.395718  -1.112009
```

```
   20          8           0       -0.949111    0.256351   -0.623732
   21          6           0       -1.886035   -0.589038   -0.225386
   22          8           0       -1.838684   -1.761250   -0.187856
   23          6           0       -3.122239    0.218535    0.187305
   24          9           0       -4.040820   -0.577720    0.666749
   25          9           0       -2.806894    1.105788    1.106341
   26          9           0       -3.612644    0.854218   -0.855902
   27          1           0        0.841957    2.067740   -1.516464
   28          1           0        2.034688    2.986172   -0.620966
   29          1           0        2.540293    1.666570   -1.651346
---------------------------------------------------------------------
```

Me-TS1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.154565222 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.306129    0.132688    0.745169
    2          1           0       -2.533565   -1.028058    2.011714
    3          6           0       -2.544641   -1.981650    0.059655
    4          6           0       -3.726564   -1.213671   -0.533654
    5          6           0       -3.307408    0.131428   -1.131609
    6          6           0       -2.565570    1.021371   -0.151704
    7          8           0       -0.687141    0.214261   -0.377706
    8          6           0       -2.127941    2.375212   -0.675153
    9          1           0       -2.695919   -0.020934   -2.013799
   10          1           0       -3.121318    1.146101    0.771579
   11          1           0       -4.190838    0.680363   -1.451556
   12          1           0       -4.204666   -1.809322   -1.304421
   13          1           0       -1.820600   -2.208878   -0.716036
   14          1           0       -4.474672   -1.047649    0.239493
   15          1           0       -2.887504   -2.931314    0.457237
   16          8           0        0.941825   -0.627292   -0.247454
   17          6           0       -1.859029   -1.205345    1.181097
   18          6           0        1.808342    0.197340    0.149059
   19          1           0       -1.007549   -1.752878    1.572146
   20          8           0       -0.854995    0.879087    1.755320
   21          1           0        0.010501    1.245909    1.518379
   22          8           0        1.651681    1.219454    0.773977
   23          6           0        3.235572   -0.213627   -0.250009
   24          9           0        3.349559   -0.226146   -1.565939
   25          9           0        4.138231    0.609759    0.229635
   26          9           0        3.510343   -1.425839    0.195436
   27          1           0       -1.612590    2.292103   -1.622445
   28          1           0       -1.482470    2.879046    0.031951
   29          1           0       -3.012765    2.988995   -0.816629
---------------------------------------------------------------------
```

Me-TS2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.15054908 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.375254   -0.194744    0.718507
    2          1           0        2.872156    1.148058    1.281438
    3          6           0        2.844708    1.132894   -0.867354
    4          6           0        3.884482    0.021346   -1.018050
    5          6           0        3.261362   -1.371524   -0.915565
    6          6           0        2.441923   -1.542652    0.344652
    7          8           0        0.703329   -0.745842   -0.236370
    8          1           0        1.901486   -2.471182    0.418296
    9          1           0        2.639685   -1.571669   -1.780025
   10          1           0        3.004310   -1.389429    1.257990
   11          1           0        4.040844   -2.129985   -0.901961
   12          1           0        4.389617    0.115926   -1.973584
   13          1           0        2.108735    1.067083   -1.663312
   14          1           0        4.647423    0.134413   -0.250072
   15          1           0        3.332526    2.096626   -0.972368
   16          8           0       -0.867670    0.178444   -0.556614
   17          6           0        2.130461    1.109609    0.487915
   18          6           0       -1.771865   -0.271767    0.194290
   19          6           0        1.191325    2.311423    0.664853
   20          8           0        0.892712   -0.326943    1.952887
   21          1           0       -0.005018   -0.693666    1.908531
   22          8           0       -1.662561   -0.868556    1.240214
   23          6           0       -3.182572    0.010788   -0.349073
   24          9           0       -3.352713   -0.603362   -1.506094
   25          9           0       -4.120388   -0.400280    0.472253
   26          9           0       -3.351062    1.305902   -0.545771
   27          1           0        0.439993    2.340399   -0.112637
   28          1           0        1.775197    3.224623    0.616908
   29          1           0        0.693562    2.279395    1.625308
---------------------------------------------------------------------
```

Me-TS3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.151453730 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.252604    0.433411   -0.430232
    2          1           0        2.491634   -0.109922   -2.057306
    3          6           0        2.405151   -1.825215   -0.726255
    4          6           0        3.577068   -1.457235    0.183254
    5          6           0        3.149488   -0.516707    1.312874
    6          6           0        2.487437    0.773758    0.849143
    7          8           0        0.590008    0.043264    0.597529
    8          1           0        1.994231    1.279358    1.662613
    9          1           0        2.474082   -1.038083    1.980195
   10          6           0        3.395739    1.766063    0.123608
   11          1           0        4.016982   -0.230417    1.903670
```

```
   12          1            0        3.997546   -2.355473    0.623580
   13          1            0        1.642554   -2.345898   -0.156269
   14          1            0        4.370781   -1.004016   -0.405325
   15          1            0        2.740031   -2.508210   -1.500229
   16          8            0       -1.047345   -0.633596    0.039165
   17          6            0        1.787639   -0.601518   -1.396436
   18          6            0       -1.891134    0.299561    0.006599
   19          1            0        0.930036   -0.880994   -1.999751
   20          8            0        0.839759    1.550378   -1.030267
   21          1            0       -0.030584    1.796498   -0.677546
   22          8            0       -1.703762    1.489236   -0.101016
   23          6            0       -3.337462   -0.210530    0.123314
   24          9            0       -3.515157   -0.801940    1.291171
   25          9            0       -4.214533    0.760981    0.021431
   26          9            0       -3.594919   -1.093550   -0.824502
   27          1            0        3.877378    1.341144   -0.746095
   28          1            0        2.859164    2.653698   -0.172170
   29          1            0        4.169182    2.049106    0.833233
---------------------------------------------------------------------
```

Me-TS4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.14926791 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6            0       -1.277355    0.503512   -0.400500
    2          6            0       -2.904021    1.889092    0.959663
    3          6            0       -2.608529   -0.618556    1.440255
    4          6            0       -3.669503   -1.177823    0.488611
    5          6            0       -3.087491   -1.518468   -0.885616
    6          6            0       -2.335334   -0.359979   -1.505987
    7          8            0       -0.569067   -0.555046   -0.596367
    8          1            0       -1.808730   -0.591121   -2.416554
    9          1            0       -2.427491   -2.374384   -0.811414
   10          1            0       -2.940504    0.523753   -1.668525
   11          1            0       -3.885897   -1.791478   -1.571808
   12          1            0       -4.103131   -2.074616    0.918668
   13          1            0       -1.834590   -1.362939    1.595200
   14          1            0       -4.484427   -0.468406    0.374699
   15          1            0       -3.054244   -0.427220    2.411031
   16          8            0        0.982679   -0.438234    0.422415
   17          6            0       -1.958528    0.683873    0.950167
   18          6            0        1.874329    0.138725   -0.251920
   19          1            0       -1.123529    0.911609    1.607778
   20          8            0       -0.842016    1.630843   -0.959605
   21          1            0        0.065852    1.497287   -1.279153
   22          8            0        1.748036    0.895995   -1.186698
   23          6            0        3.293752   -0.206730    0.228629
   24          9            0        3.520048   -1.499394    0.077183
   25          9            0        4.215376    0.448789   -0.437939
   26          9            0        3.431899    0.084348    1.509474
   27          1            0       -3.742927    1.769486    0.282015
   28          1            0       -3.307506    2.020258    1.957681
```

```
  29         1           0      -2.379759    2.793739    0.684150
---------------------------------------------------------------------
```

Me-TS5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.153495886 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.264327   -0.191296    0.024738
    2          1           0        1.860231   -1.599852   -1.442503
    3          6           0        3.152799   -1.835334    0.279550
    4          6           0        4.168827   -0.769447   -0.128935
    5          6           0        3.668933    0.641348    0.179871
    6          6           0        2.400108    1.070933   -0.572061
    7          8           0        1.060571   -0.032516    1.334087
    8          6           0        1.954573    2.476259   -0.215239
    9          1           0        3.510025    0.765548    1.244386
   10          1           0        2.506110    0.918469   -1.633595
   11          1           0        4.422044    1.368101   -0.118603
   12          1           0        5.107725   -0.928993    0.391340
   13          1           0        3.046485   -1.853373    1.359084
   14          1           0        4.382331   -0.853983   -1.192611
   15          1           0        3.495905   -2.818153   -0.025105
   16          1           0        0.186039    0.369058    1.472535
   17          6           0        1.797820   -1.552784   -0.361513
   18          1           0        1.046648   -2.266409   -0.041059
   19          8           0        0.461862    0.401200   -0.779545
   20          8           0       -1.190521   -0.452501   -0.717086
   21          6           0       -1.893434    0.064741    0.187847
   22          8           0       -1.537125    0.662587    1.178134
   23          6           0       -3.400725   -0.122021   -0.054642
   24          9           0       -4.123584    0.356292    0.931600
   25          9           0       -3.693206   -1.402419   -0.190860
   26          9           0       -3.759393    0.499248   -1.163919
   27          1           0        1.140775    2.816738   -0.838653
   28          1           0        2.795952    3.149402   -0.350634
   29          1           0        1.647719    2.530796    0.821610
---------------------------------------------------------------------
```

Me-TS6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.150538938 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.329032   -0.185209   -0.008633
    2          1           0       -2.146036    1.144604   -1.420425
    3          6           0       -3.434934    1.134754    0.301442
    4          6           0       -4.291849   -0.050354   -0.142696
    5          6           0       -3.582791   -1.379750    0.102140
    6          6           0       -2.271036   -1.523894   -0.675284
    7          8           0       -1.106224   -0.383680    1.288482
    8          1           0       -1.760191   -2.442399   -0.443989
```

```
    9          1             0        -3.395233   -1.528461    1.157670
   10          1             0        -2.404203   -1.399161   -1.736131
   11          1             0        -4.201786   -2.207949   -0.237294
   12          1             0        -5.235436   -0.046330    0.393088
   13          1             0        -3.328361    1.128864    1.381850
   14          1             0        -4.531359    0.043161   -1.200026
   15          1             0        -3.926268    2.065108    0.036555
   16          1             0        -0.210885   -0.746094    1.408260
   17          6             0        -2.042326    1.119984   -0.339852
   18          6             0        -1.201639    2.323262    0.105148
   19          8             0        -0.470269   -0.675573   -0.835681
   20          8             0         1.144794    0.256789   -0.732432
   21          6             0         1.861311   -0.261791    0.159854
   22          8             0         1.523601   -0.918922    1.119225
   23          6             0         3.359915    0.012882   -0.050070
   24          9             0         4.094053   -0.472851    0.924050
   25          9             0         3.585808    1.312322   -0.121865
   26          9             0         3.765914   -0.535071   -1.181308
   27          1             0        -1.062735    2.318544    1.179576
   28          1             0        -1.719957    3.236943   -0.166959
   29          1             0        -0.230451    2.325340   -0.369105
---------------------------------------------------------------------
```

Me-TS7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.151324859 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0         1.213010   -0.186544    0.096744
    2          1             0         1.889432   -0.420652   -1.903759
    3          6             0         3.104770   -1.679268   -0.618398
    4          6             0         4.129574   -0.620987   -0.205303
    5          6             0         3.578755    0.301647    0.884152
    6          6             0         2.356006    1.147095    0.484307
    7          8             0         0.956598   -0.867746    1.216727
    8          1             0         1.917183    1.593732    1.360884
    9          1             0         3.333747   -0.274768    1.766156
   10          6             0         2.617167    2.169575   -0.607418
   11          1             0         4.334817    1.027920    1.176198
   12          1             0         5.025159   -1.103305    0.172609
   13          1             0         2.934703   -2.366864    0.203071
   14          1             0         4.434857   -0.040474   -1.071671
   15          1             0         3.483646   -2.262771   -1.450522
   16          1             0         0.079825   -0.611618    1.547868
   17          6             0         1.778469   -1.035305   -1.019560
   18          1             0         1.023622   -1.784304   -1.232270
   19          8             0         0.437135    0.792186   -0.185876
   20          8             0        -1.202980    0.117802   -0.743122
   21          6             0        -1.951263   -0.031445    0.256850
   22          8             0        -1.646932   -0.177441    1.418563
   23          6             0        -3.443389   -0.018329   -0.116180
   24          9             0        -4.215045   -0.242503    0.922198
   25          9             0        -3.702244   -0.942402   -1.023484
```

```
   26         9           0      -3.771692   1.156014  -0.624308
   27         1           0       2.835141   1.709452  -1.561953
   28         1           0       3.482625   2.760631  -0.321322
   29         1           0       1.776910   2.835998  -0.736447
---------------------------------------------------------------------
```

Me-TS8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -951.148573187 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6           0       1.262673  -0.237396  -0.029879
    2         6           0       1.947059   2.163382   0.492920
    3         6           0       3.284023   0.710589  -1.154598
    4         6           0       4.210662  -0.005566  -0.168994
    5         6           0       3.556246  -1.260815   0.406014
    6         6           0       2.277927  -0.989199   1.207324
    7         8           0       1.007324  -1.130388  -0.986336
    8         1           0       1.792466  -1.897895   1.517603
    9         1           0       3.341018  -1.973847  -0.378990
   10         1           0       2.437820  -0.322340   2.035380
   11         1           0       4.227144  -1.747041   1.111662
   12         1           0       5.127456  -0.289434  -0.675344
   13         1           0       3.139593   0.083054  -2.027522
   14         1           0       4.498366   0.660879   0.639362
   15         1           0       3.744541   1.630706  -1.498388
   16         1           0       0.103268  -1.472063  -0.868528
   17         6           0       1.912532   1.041043  -0.545913
   18         1           0       1.248775   1.348773  -1.347979
   19         8           0       0.452448  -0.192211   0.964073
   20         8           0      -1.152473   0.591041   0.374127
   21         6           0      -1.912522  -0.304777  -0.069516
   22         8           0      -1.625133  -1.397169  -0.506738
   23         6           0      -3.395668   0.099995  -0.026831
   24         9           0      -4.175740  -0.816480  -0.551866
   25         9           0      -3.586927   1.226292  -0.689897
   26         9           0      -3.775740   0.293329   1.223586
   27         1           0       0.952633   2.378008   0.860768
   28         1           0       2.336793   3.062807   0.028522
   29         1           0       2.580886   1.936399   1.342879
---------------------------------------------------------------------
```

F-CP1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09293891 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6           0      -1.242324   0.229617   0.565460
    2         1           0      -2.098420  -1.098332   1.970316
    3         6           0      -2.291561  -1.998996   0.010096
    4         6           0      -3.579659  -1.290092  -0.424297
    5         6           0      -3.304725   0.136628  -0.915383
```

```
    6          6           0       -2.541096    0.910920    0.141240
    7          8           0       -0.458293    0.227591   -0.627120
    8          9           0       -2.240618    2.174268   -0.302512
    9          1           0       -2.723679    0.120585   -1.830516
   10          1           0       -3.135873    1.025132    1.038932
   11          1           0       -4.231703    0.658485   -1.128017
   12          1           0       -4.071908   -1.855960   -1.208042
   13          1           0       -1.658248   -2.167173   -0.855297
   14          1           0       -4.272423   -1.255609    0.414737
   15          1           0       -2.526757   -2.975135    0.421753
   16          8           0        0.756415   -0.382049   -0.378506
   17          6           0       -1.521832   -1.184137    1.054430
   18          6           0        1.743850    0.496292   -0.253387
   19          1           0       -0.584307   -1.656981    1.315470
   20          8           0       -0.594564    0.932423    1.547976
   21          1           0       -0.454135    1.825922    1.248271
   22          8           0        1.680432    1.666183   -0.269518
   23          6           0        3.056350   -0.279991   -0.094152
   24          9           0        3.306496   -0.968848   -1.187650
   25          9           0        4.044633    0.546749    0.120343
   26          9           0        2.975212   -1.118342    0.917118
---------------------------------------------------------------------
```

F-CP2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.08903807 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.319140   -0.472742    0.537999
    2          1           0       -3.085926   -1.475273    1.126597
    3          6           0       -3.338671   -0.942036   -0.955395
    4          6           0       -3.814659    0.498965   -0.750932
    5          6           0       -2.640437    1.437832   -0.458471
    6          6           0       -1.837524    0.949275    0.733534
    7          8           0       -0.493928   -0.605821   -0.618627
    8          9           0       -0.805865    1.809254    0.975066
    9          1           0       -1.982274    1.503113   -1.318589
   10          1           0       -2.450087    0.931664    1.626761
   11          1           0       -2.991350    2.441583   -0.244495
   12          1           0       -4.350412    0.844024   -1.628907
   13          1           0       -2.761601   -1.010463   -1.871608
   14          1           0       -4.520713    0.533117    0.076943
   15          1           0       -4.189636   -1.606232   -1.067467
   16          8           0        0.673301    0.124719   -0.499442
   17          6           0       -2.484128   -1.415271    0.224908
   18          6           0        1.700342   -0.634460   -0.155131
   19          1           0       -2.079856   -2.405698    0.040810
   20          8           0       -0.625864   -0.830220    1.665017
   21          1           0       -0.269355   -1.705988    1.559872
   22          8           0        1.693177   -1.772563    0.136244
   23          6           0        2.976356    0.214353   -0.211502
   24          9           0        2.861274    1.277197    0.550492
   25          9           0        3.999095   -0.491054    0.195460
```

```
    26          9           0        3.196039    0.605240   -1.449409
 ---------------------------------------------------------------------
```

F-CP3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09148634 a.u.
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        1.190151   -0.392442    0.318877
    2          1           0        2.149318    0.492815    1.966935
    3          6           0        2.292489    1.885100    0.318686
    4          6           0        3.538830    1.287693   -0.340796
    5          6           0        3.186537    0.067347   -1.196949
    6          6           0        2.419520   -0.970874   -0.396330
    7          8           0        0.342433   -0.078674   -0.789724
    8          1           0        2.114649   -1.805719   -1.016280
    9          1           0        2.581608    0.365390   -2.047076
   10          9           0        3.236520   -1.468208    0.587092
   11          1           0        4.084021   -0.402167   -1.585719
   12          1           0        4.030113    2.033023   -0.958108
   13          1           0        1.635069    2.294970   -0.442787
   14          1           0        4.250192    0.992938    0.424960
   15          1           0        2.573249    2.709435    0.966371
   16          8           0       -0.852126    0.443416   -0.336119
   17          6           0        1.537785    0.837706    1.141312
   18          6           0       -1.834193   -0.446891   -0.386206
   19          1           0        0.627413    1.243803    1.563296
   20          8           0        0.574545   -1.299387    1.138892
   21          1           0        0.370405   -2.096568    0.661931
   22          8           0       -1.770850   -1.575519   -0.698779
   23          6           0       -3.137933    0.248647    0.022549
   24          9           0       -3.443048    1.178650   -0.857434
   25          9           0       -4.111935   -0.620004    0.075722
   26          9           0       -3.006777    0.815749    1.201894
 ---------------------------------------------------------------------
```

F-CP4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09176757 a.u.
 ---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
 ---------------------------------------------------------------------
    1          6           0        1.219766    0.471396    0.433220
    2          1           0        3.019931    1.401973    0.998174
    3          6           0        3.204314    0.906955   -1.100564
    4          6           0        3.632251   -0.555407   -0.944609
    5          6           0        2.433585   -1.464552   -0.654531
    6          6           0        1.657824   -0.987640    0.561148
    7          8           0        0.359664    0.622922   -0.697718
    8          1           0        0.800660   -1.609978    0.768546
    9          1           0        1.764141   -1.493214   -1.508153
   10          9           0        2.482643   -1.050647    1.658529
   11          1           0        2.763241   -2.481140   -0.468092
```

```
   12          1             0        4.135596   -0.892070   -1.845298
   13          1             0        2.610338    1.021939   -2.001792
   14          1             0        4.347184   -0.641311   -0.132182
   15          1             0        4.077626    1.540801   -1.216595
   16          8             0       -0.780381   -0.143752   -0.530784
   17          6             0        2.397190    1.386642    0.111400
   18          6             0       -1.825902    0.589976   -0.171146
   19          1             0        2.020977    2.393381   -0.046643
   20          8             0        0.553203    0.814353    1.579454
   21          1             0        0.309029    1.732936    1.550909
   22          8             0       -1.856827    1.738905    0.060535
   23          6             0       -3.059040   -0.319552   -0.121007
   24          9             0       -2.839419   -1.349986    0.666514
   25          9             0       -4.089489    0.345489    0.328253
   26          9             0       -3.333060   -0.767040   -1.328210
---------------------------------------------------------------------
```

F-CP5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09436879 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.198414   -0.038713    0.099005
    2          1             0       -2.522933   -0.934805    1.533091
    3          6             0       -3.662754   -0.460558   -0.245033
    4          6             0       -3.954080    1.017500    0.024150
    5          6             0       -2.762091    1.887982   -0.379605
    6          6             0       -1.485346    1.438120    0.334726
    7          8             0       -0.818979   -0.221964   -1.205929
    8          1             0       -0.630969    2.010790   -0.001195
    9          1             0       -2.614101    1.831633   -1.453289
   10          1             0       -1.582638    1.591821    1.405427
   11          1             0       -2.956633    2.928216   -0.139156
   12          1             0       -4.843580    1.316548   -0.520139
   13          1             0       -3.532019   -0.625111   -1.309471
   14          1             0       -4.171989    1.163900    1.080710
   15          1             0       -4.483476   -1.090488    0.080961
   16          1             0       -0.703092   -1.154219   -1.365352
   17          6             0       -2.397083   -0.916431    0.459002
   18          9             0       -2.103718   -2.198444    0.056755
   19          8             0       -0.181388   -0.514497    0.978320
   20          8             0        0.990934    0.179400    0.744307
   21          6             0        1.868062   -0.534529    0.050193
   22          8             0        1.732850   -1.604678   -0.407773
   23          6             0        3.164245    0.276866   -0.060089
   24          9             0        4.028151   -0.354975   -0.809272
   25          9             0        3.686842    0.455492    1.134733
   26          9             0        2.924154    1.457282   -0.590780
---------------------------------------------------------------------
```

F-CP6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.08971204 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.277192   -0.380134    0.122751
    2          1             0       -1.851665    1.197646    1.424180
    3          6             0       -3.044888    1.346462   -0.372261
    4          6             0       -4.142150    0.350320    0.008281
    5          6             0       -3.678975   -1.088566   -0.228031
    6          6             0       -2.373967   -1.371642    0.519580
    7          8             0       -0.890659   -0.496740   -1.188416
    8          1             0       -2.012383   -2.374759    0.316474
    9          1             0       -3.531362   -1.254453   -1.290614
   10          1             0       -2.534976   -1.304939    1.591057
   11          1             0       -4.437735   -1.790866    0.101618
   12          1             0       -5.038818    0.556554   -0.566563
   13          1             0       -2.848310    1.303249   -1.438012
   14          1             0       -4.408140    0.478045    1.056194
   15          1             0       -3.343025    2.363022   -0.139095
   16          1             0       -0.547171   -1.369837   -1.345905
   17          6             0       -1.742275    1.055629    0.355886
   18          9             0       -0.795664    1.937272   -0.080477
   19          8             0       -0.211932   -0.748545    0.994749
   20          8             0        0.922134    0.005405    0.754148
   21          6             0        1.808088   -0.647807    0.021173
   22          8             0        1.687219   -1.696224   -0.495425
   23          6             0        3.093980    0.184728   -0.050376
   24          9             0        3.960783   -0.400407   -0.835051
   25          9             0        2.843769    1.387383   -0.513485
   26          9             0        3.618196    0.296998    1.152146
---------------------------------------------------------------------
```

F-CP7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09151586 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.166750   -0.137167    0.080527
    2          9             0       -2.659716   -1.356097   -1.272275
    3          6             0       -3.580766   -0.477610    0.706170
    4          6             0       -3.931642    0.874945    0.078440
    5          6             0       -2.734330    1.829250    0.106907
    6          6             0       -1.498613    1.204925   -0.551744
    7          8             0       -0.758042    0.072774    1.380196
    8          1             0       -0.641465    1.858473   -0.455397
    9          1             0       -2.498841    2.093094    1.133178
   10          1             0       -1.676897    1.036796   -1.607472
   11          1             0       -2.981233    2.751839   -0.408464
   12          1             0       -4.771775    1.313204    0.607732
   13          1             0       -3.377168   -0.359848    1.765171
   14          1             0       -4.250994    0.718896   -0.947473
```

```
     15          1           0       -4.406862   -1.173866    0.607318
     16          1           0       -0.423478   -0.737134    1.751585
     17          6           0       -2.361529   -1.094453    0.041078
     18          1           0       -2.083391   -2.035320    0.500798
     19          8           0       -0.160570   -0.842518   -0.634258
     20          8           0        0.999510   -0.089866   -0.679337
     21          6           0        1.909468   -0.526124    0.177996
     22          8           0        1.793272   -1.366169    0.990122
     23          6           0        3.210082    0.251523   -0.055080
     24          9           0        4.100066   -0.084601    0.840240
     25          9           0        3.685041   -0.017743   -1.251666
     26          9           0        2.990523    1.546038    0.027420
---------------------------------------------------------------------
```

F-CP8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.09363940 a.u.
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
      1          6           0       -1.204523    0.380308   -0.110433
      2          9           0       -1.868062   -1.642035   -1.072208
      3          6           0       -2.870369   -1.147315    1.000403
      4          6           0       -4.016492   -0.337630    0.386464
      5          6           0       -3.598836    1.113328    0.131017
      6          6           0       -2.337303    1.188057   -0.735891
      7          8           0       -0.775540    0.879079    1.099130
      8          1           0       -2.005797    2.215045   -0.858521
      9          1           0       -3.417856    1.613264    1.078052
     10          1           0       -2.534549    0.790668   -1.724150
     11          1           0       -4.400091    1.653170   -0.363123
     12          1           0       -4.877520   -0.365865    1.046636
     13          1           0       -2.636177   -0.779296    1.993497
     14          1           0       -4.319610   -0.799216   -0.548380
     15          1           0       -3.148251   -2.191639    1.095952
     16          1           0       -0.480345    1.777066    0.992394
     17          6           0       -1.614033   -1.067427    0.149149
     18          1           0       -0.792279   -1.603457    0.598972
     19          8           0       -0.166735    0.467156   -1.075153
     20          8           0        0.949208   -0.223714   -0.636279
     21          6           0        1.888041    0.588139   -0.174064
     22          8           0        1.831606    1.751536   -0.029141
     23          6           0        3.132380   -0.245682    0.153095
     24          9           0        4.046313    0.508791    0.703293
     25          9           0        2.826047   -1.218068    0.985295
     26          9           0        3.621366   -0.774562   -0.947293
---------------------------------------------------------------------
```

F-TS1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06655465 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.285053   -0.189094    0.752145
    2          1           0        2.601023    0.839475    2.053311
    3          6           0        2.577722    1.918172    0.161220
    4          6           0        3.724871    1.168398   -0.522169
    5          6           0        3.271622   -0.135400   -1.189121
    6          6           0        2.558082   -1.031278   -0.217676
    7          8           0        0.701993   -0.191678   -0.383991
    8          9           0        2.122513   -2.167563   -0.745817
    9          1           0        2.624199    0.056748   -2.034819
   10          1           0        3.111555   -1.253822    0.683944
   11          1           0        4.130950   -0.692227   -1.554766
   12          1           0        4.182576    1.800763   -1.274313
   13          1           0        1.833812    2.210355   -0.571879
   14          1           0        4.499889    0.947757    0.209267
   15          1           0        2.959518    2.831738    0.604019
   16          8           0       -0.950601    0.650002   -0.205658
   17          6           0        1.906913    1.092716    1.258822
   18          6           0       -1.812535   -0.202434    0.135368
   19          1           0        1.088742    1.641117    1.714357
   20          8           0        0.830443   -0.991870    1.701644
   21          1           0       -0.018449   -1.372958    1.418092
   22          8           0       -1.652749   -1.259334    0.700021
   23          6           0       -3.241670    0.222287   -0.242529
   24          9           0       -3.347880    0.337447   -1.553888
   25          9           0       -4.139268   -0.644242    0.164898
   26          9           0       -3.531681    1.393679    0.294841
---------------------------------------------------------------------
```

F-TS2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06346378 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.352864   -0.357194    0.678120
    2          1           0        2.806695    0.921829    1.529744
    3          6           0        2.756216    1.348858   -0.587496
    4          6           0        3.845817    0.343535   -0.968669
    5          6           0        3.292460   -1.069679   -1.170798
    6          6           0        2.486962   -1.556907    0.014063
    7          8           0        0.734764   -0.711477   -0.386439
    8          1           0        1.982107   -2.497989   -0.119904
    9          1           0        2.679329   -1.111730   -2.062344
   10          1           0        3.035137   -1.579509    0.949117
   11          1           0        4.111246   -1.771088   -1.312472
   12          1           0        4.335972    0.667173   -1.879590
   13          1           0        1.998247    1.415248   -1.360044
   14          1           0        4.611196    0.326497   -0.195117
```

```
    15          1           0        3.183155    2.338144   -0.467276
    16          8           0       -0.860942    0.267526   -0.543197
    17          6           0        2.089437    0.977979    0.720906
    18          6           0       -1.760928   -0.276842    0.138278
    19          9           0        1.167363    1.918853    1.057468
    20          8           0        0.874384   -0.740619    1.847595
    21          1           0       -0.055118   -1.024463    1.735452
    22          8           0       -1.650522   -1.037427    1.077125
    23          6           0       -3.176129    0.097891   -0.333139
    24          9           0       -3.379192   -0.372182   -1.552017
    25          9           0       -4.106555   -0.394111    0.451933
    26          9           0       -3.324908    1.408109   -0.371365
---------------------------------------------------------------------
```

F-TS3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06781846 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
     1          6           0        1.230712    0.456459   -0.456070
     2          1           0        2.590745    0.047037   -2.011185
     3          6           0        2.513827   -1.722134   -0.746856
     4          6           0        3.637853   -1.334318    0.215939
     5          6           0        3.150773   -0.430501    1.353972
     6          6           0        2.469036    0.813666    0.859104
     7          8           0        0.591701    0.020385    0.561130
     8          1           0        1.999650    1.445873    1.588510
     9          1           0        2.465307   -0.960135    2.003145
    10          9           0        3.282691    1.549075    0.091664
    11          1           0        3.992917   -0.101328    1.957979
    12          1           0        4.075201   -2.226137    0.651052
    13          1           0        1.750950   -2.288364   -0.222629
    14          1           0        4.430016   -0.829635   -0.328706
    15          1           0        2.911279   -2.371399   -1.519692
    16          8           0       -1.050161   -0.658610   -0.000049
    17          6           0        1.873763   -0.510312   -1.421053
    18          6           0       -1.893230    0.276366    0.008270
    19          1           0        1.072594   -0.814026   -2.087810
    20          8           0        0.825096    1.587158   -1.006695
    21          1           0       -0.037188    1.832700   -0.632680
    22          8           0       -1.704153    1.469021   -0.055562
    23          6           0       -3.339560   -0.235624    0.118051
    24          9           0       -3.508451   -0.864126    1.267717
    25          9           0       -4.215242    0.739924    0.054401
    26          9           0       -3.604595   -1.087077   -0.855641
---------------------------------------------------------------------
```

F-TS4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06819444 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.261769    0.659003   -0.117049
    2          9           0       -2.888483    1.123778    1.469527
    3          6           0       -2.570870   -1.179358    1.070567
    4          6           0       -3.668416   -1.231331    0.004857
    5          6           0       -3.139913   -0.901943   -1.394026
    6          6           0       -2.393682    0.413902   -1.443319
    7          8           0       -0.591188   -0.198897   -0.787926
    8          1           0       -1.907201    0.640530   -2.376520
    9          1           0       -2.496989   -1.695557   -1.754906
   10          1           0       -2.977120    1.267929   -1.119813
   11          1           0       -3.970119   -0.822537   -2.091925
   12          1           0       -4.113222   -2.220136   -0.007994
   13          1           0       -1.794553   -1.908340    0.865862
   14          1           0       -4.456444   -0.534689    0.271342
   15          1           0       -2.987942   -1.416069    2.043135
   16          8           0        0.973466   -0.577768    0.176175
   17          6           0       -1.932436    0.192231    1.167745
   18          6           0        1.869482    0.241440   -0.154999
   19          1           0       -1.171717    0.230600    1.935450
   20          8           0       -0.833244    1.912072   -0.081642
   21          1           0        0.081327    1.943374   -0.413047
   22          8           0        1.744788    1.350358   -0.622362
   23          6           0        3.287626   -0.298769    0.092515
   24          9           0        3.498531   -1.368321   -0.653303
   25          9           0        4.211874    0.587544   -0.194323
   26          9           0        3.433997   -0.647699    1.357734
---------------------------------------------------------------------
```

F-TS5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06645860 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.248932   -0.202623    0.045460
    2          1           0        1.885404   -1.645026   -1.367629
    3          6           0        3.223019   -1.748252    0.331834
    4          6           0        4.185173   -0.663571   -0.153973
    5          6           0        3.642935    0.735710    0.131940
    6          6           0        2.354196    1.085076   -0.594160
    7          8           0        1.037856    0.015165    1.333527
    8          9           0        1.912769    2.267572   -0.182390
    9          1           0        3.474245    0.881384    1.191289
   10          1           0        2.409062    1.041784   -1.665869
   11          1           0        4.347689    1.497811   -0.193727
   12          1           0        5.146661   -0.765836    0.336541
   13          1           0        3.145332   -1.718838    1.413461
   14          1           0        4.365721   -0.779892   -1.220592
```

```
   15          1            0        3.598880   -2.729127    0.063471
   16          1            0        0.181725    0.469883    1.444546
   17          6            0        1.842459   -1.552814   -0.288300
   18          1            0        1.129650   -2.283848    0.076892
   19          8            0        0.475384    0.355799   -0.805094
   20          8            0       -1.199204   -0.495395   -0.704383
   21          6            0       -1.895477    0.071465    0.174677
   22          8            0       -1.532503    0.711698    1.136394
   23          6            0       -3.405076   -0.113484   -0.054402
   24          9            0       -4.122405    0.434829    0.898795
   25          9            0       -3.709755   -1.397967   -0.105821
   26          9            0       -3.759899    0.436069   -1.201737
---------------------------------------------------------------------
```

F-TS6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06301286 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6            0       -1.302959   -0.203725    0.010165
    2          1            0       -2.016739    1.193334   -1.425582
    3          6            0       -3.368009    1.215125    0.271274
    4          6            0       -4.264268    0.055351   -0.163443
    5          6            0       -3.615399   -1.296456    0.130962
    6          6            0       -2.315013   -1.535599   -0.640498
    7          8            0       -1.084084   -0.376317    1.299722
    8          1            0       -1.832869   -2.457431   -0.368286
    9          1            0       -3.435534   -1.416842    1.191221
   10          1            0       -2.436455   -1.442328   -1.705608
   11          1            0       -4.271853   -2.106017   -0.181805
   12          1            0       -5.214080    0.115499    0.355246
   13          1            0       -3.252031    1.223893    1.349323
   14          1            0       -4.483966    0.130239   -1.226309
   15          1            0       -3.798669    2.166754   -0.017987
   16          1            0       -0.154818   -0.666272    1.430612
   17          6            0       -1.988404    1.110243   -0.347524
   18          9            0       -1.202853    2.110135    0.132449
   19          8            0       -0.499875   -0.734117   -0.831469
   20          8            0        1.147650    0.206965   -0.779897
   21          6            0        1.855465   -0.226213    0.155810
   22          8            0        1.512115   -0.812313    1.163764
   23          6            0        3.356607    0.034672   -0.054361
   24          9            0        4.074084   -0.327672    0.984343
   25          9            0        3.581999    1.315015   -0.278802
   26          9            0        3.784821   -0.645806   -1.103777
---------------------------------------------------------------------
```

F-TS7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06854581 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.201780   -0.161011    0.070078
    2          1           0        1.961111   -0.418472   -1.891249
    3          6           0        3.138678   -1.630326   -0.521497
    4          6           0        4.136719   -0.543910   -0.111605
    5          6           0        3.544178    0.440362    0.901294
    6          6           0        2.338058    1.202320    0.372698
    7          8           0        0.964331   -0.781938    1.221686
    8          1           0        1.885930    1.873860    1.078524
    9          1           0        3.271804   -0.051740    1.824043
   10          9           0        2.640540    1.827247   -0.764167
   11          1           0        4.269535    1.215492    1.139742
   12          1           0        5.018308   -0.997351    0.327991
   13          1           0        2.943078   -2.291317    0.315574
   14          1           0        4.467896    0.003777   -0.987835
   15          1           0        3.561346   -2.235497   -1.315571
   16          1           0        0.068422   -0.543146    1.529169
   17          6           0        1.820644   -1.022372   -1.004467
   18          1           0        1.088380   -1.789846   -1.230132
   19          8           0        0.440393    0.816222   -0.236607
   20          8           0       -1.221453    0.107244   -0.773498
   21          6           0       -1.950652   -0.026830    0.238771
   22          8           0       -1.623332   -0.154126    1.399575
   23          6           0       -3.450622   -0.023937   -0.101408
   24          9           0       -4.199105   -0.230812    0.957406
   25          9           0       -3.725208   -0.965996   -0.985098
   26          9           0       -3.792674    1.139479   -0.623995
---------------------------------------------------------------------
```

F-TS8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1011.06900689 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type             X           Y           Z
---------------------------------------------------------------------
    1          6           0        1.240903   -0.210968   -0.013607
    2          9           0        2.143698    1.844179    0.624643
    3          6           0        3.239482    0.777011   -1.163045
    4          6           0        4.186456    0.025388   -0.223176
    5          6           0        3.538035   -1.230587    0.361388
    6          6           0        2.286603   -0.959724    1.205934
    7          8           0        0.980965   -1.047825   -1.008818
    8          1           0        1.811508   -1.865260    1.539711
    9          1           0        3.299227   -1.942198   -0.418002
   10          1           0        2.458001   -0.266054    2.008250
   11          1           0        4.227447   -1.719516    1.046886
   12          1           0        5.082644   -0.260194   -0.762845
   13          1           0        3.044338    0.196036   -2.056938
   14          1           0        4.497120    0.683856    0.581197
```

```
    15          1           0        3.679558    1.718580   -1.470434
    16          1           0        0.062007   -1.374643   -0.919963
    17          6           0        1.919578    1.067110   -0.475462
    18          1           0        1.215371    1.580261   -1.115732
    19          8           0        0.445080   -0.169811    0.980976
    20          8           0       -1.169148    0.622022    0.375963
    21          6           0       -1.919999   -0.266354   -0.091175
    22          8           0       -1.618196   -1.338381   -0.574210
    23          6           0       -3.409868    0.107690   -0.019578
    24          9           0       -4.177419   -0.804825   -0.569597
    25          9           0       -3.628111    1.252269   -0.640881
    26          9           0       -3.779720    0.248788    1.240159
---------------------------------------------------------------------
```

CF$_3$-CP1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.90397066 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
     1          6           0        0.755938    0.469663    0.638322
     2          1           0        1.205113    2.096894    1.903690
     3          6           0        1.284969    2.843100   -0.120253
     4          6           0        2.732901    2.443872   -0.402231
     5          6           0        2.834083    0.965759   -0.778539
     6          6           0        2.207811    0.060749    0.298342
     7          8           0        0.031703    0.150929   -0.549673
     8          6           0        2.399826   -1.399917   -0.080633
     9          1           0        2.332271    0.794586   -1.723718
    10          1           0        2.753320    0.181199    1.228432
    11          1           0        3.872173    0.683832   -0.911359
    12          1           0        3.142226    3.047242   -1.206108
    13          1           0        0.698067    2.763094   -1.030541
    14          1           0        3.342672    2.639452    0.477878
    15          1           0        1.234471    3.879959    0.196276
    16          8           0       -1.293747    0.510981   -0.404736
    17          6           0        0.677723    1.957340    0.965388
    18          6           0       -2.074159   -0.535574   -0.162362
    19          1           0       -0.358711    2.207239    1.148726
    20          8           0        0.224810   -0.198252    1.711625
    21          1           0        0.239261   -1.137199    1.565606
    22          8           0       -1.756141   -1.651081    0.004402
    23          6           0       -3.529751   -0.054733   -0.145675
    24          9           0       -3.868449    0.392639   -1.336062
    25          9           0       -4.324238   -1.039126    0.179009
    26          9           0       -3.680728    0.920193    0.725221
    27          9           0        1.785555   -2.229566    0.760275
    28          9           0        3.688802   -1.705945   -0.037884
    29          9           0        1.971291   -1.689136   -1.292334
---------------------------------------------------------------------
```

CF$_3$-CP2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.89822750 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -1.129544   -0.810446    0.573689
    2          1           0       -2.751800   -1.781040    1.515091
    3          6           0       -3.079048   -1.996657   -0.606996
    4          6           0       -3.760734   -0.647828   -0.830208
    5          6           0       -2.730805    0.476873   -0.927869
    6          6           0       -1.826783    0.538828    0.316886
    7          8           0       -0.269854   -1.220852   -0.488941
    8          6           0       -0.966112    1.797314    0.251995
    9          1           0       -2.113028    0.331627   -1.806679
   10          1           0       -2.444074    0.690551    1.195790
   11          1           0       -3.231322    1.430783   -1.044974
   12          1           0       -4.355597   -0.673015   -1.737542
   13          1           0       -2.501437   -2.266878   -1.485282
   14          1           0       -4.447483   -0.444742   -0.010609
   15          1           0       -3.818635   -2.777671   -0.462356
   16          8           0        0.839626   -0.403197   -0.572513
   17          6           0       -2.164533   -1.940468    0.616231
   18          6           0        1.906539   -0.947569   -0.005221
   19          1           0       -1.626760   -2.875198    0.742418
   20          8           0       -0.429033   -0.731987    1.750097
   21          1           0       -0.030443   -1.574422    1.941624
   22          8           0        1.967961   -1.953190    0.597529
   23          6           0        3.117513   -0.048103   -0.281165
   24          9           0        2.879822    1.182504    0.107952
   25          9           0        4.163449   -0.502399    0.357846
   26          9           0        3.377523   -0.040415   -1.571477
   27          9           0       -0.012690    1.849914    1.158153
   28          9           0       -1.753390    2.850865    0.459102
   29          9           0       -0.404490    1.979772   -0.931676
---------------------------------------------------------------------
```

CF$_3$-CP3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.90166566 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        0.620728    0.046132    0.181128
    2          1           0        1.407620    0.918419    1.936544
    3          6           0        1.246190    2.494195    0.468994
    4          6           0        2.567346    2.245854   -0.259692
    5          6           0        2.425638    1.111086   -1.277321
    6          6           0        1.891095   -0.202931   -0.669632
    7          8           0       -0.325050    0.319204   -0.862833
    8          1           0        1.604894   -0.861396   -1.483966
    9          1           0        1.725937    1.414382   -2.047771
   10          6           0        2.959944   -0.987719    0.076510
   11          1           0        3.368338    0.916893   -1.772176
```

```
    12          1             0        2.881962    3.145599   -0.779166
    13          1             0        0.503935    2.857877   -0.235755
    14          1             0        3.346537    2.012036    0.459355
    15          1             0        1.370298    3.267355    1.220365
    16          8             0       -1.569075    0.570169   -0.319865
    17          6             0        0.735916    1.221208    1.144188
    18          6             0       -2.383684   -0.469854   -0.444167
    19          1             0       -0.234626    1.378552    1.595948
    20          8             0        0.203743   -1.037646    0.907517
    21          1             0        0.131659   -1.809839    0.357048
    22          8             0       -2.140231   -1.529217   -0.884121
    23          6             0       -3.767313   -0.063819    0.076517
    24          9             0       -4.269436    0.886753   -0.682688
    25          9             0       -4.573144   -1.091534    0.057360
    26          9             0       -3.680072    0.387581    1.308899
    27          9             0        3.305673   -0.453261    1.236884
    28          9             0        4.062835   -1.073420   -0.653139
    29          9             0        2.572276   -2.232215    0.315445
 ---------------------------------------------------------------------
```

CF_3-CP4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.90167634 a.u.
 ---------------------------------------------------------------------
 Center     Atomic      Atomic              Coordinates (Angstroms)
 Number     Number       Type              X           Y           Z
 ---------------------------------------------------------------------
     1          6             0        0.733120   -0.577410   -0.544691
     2          1             0        2.422141   -1.207680   -1.649924
     3          6             0        2.365984   -2.427474    0.133648
     4          6             0        3.030697   -1.458977    1.113483
     5          6             0        2.029218   -0.417703    1.621304
     6          6             0        1.344000    0.381924    0.495180
     7          8             0       -0.313649   -1.328057    0.083182
     8          1             0        0.530594    0.954784    0.921066
     9          1             0        1.247102   -0.922171    2.178052
    10          6             0        2.255408    1.441627   -0.112551
    11          1             0        2.505628    0.268781    2.308245
    12          1             0        3.429780   -2.008464    1.960258
    13          1             0        1.633596   -3.031414    0.660048
    14          1             0        3.872739   -0.968473    0.635479
    15          1             0        3.100730   -3.111833   -0.278180
    16          8             0       -1.325587   -0.487466    0.508211
    17          6             0        1.683961   -1.679336   -1.015232
    18          6             0       -2.370522   -0.512429   -0.309441
    19          1             0        1.112781   -2.366444   -1.632943
    20          8             0        0.215308    0.154225   -1.580359
    21          1             0       -0.161406   -0.428782   -2.230963
    22          8             0       -2.476532   -1.084597   -1.327615
    23          6             0       -3.487586    0.337216    0.307506
    24          9             0       -3.048244    1.545483    0.583992
    25          9             0       -4.491297    0.429981   -0.522841
    26          9             0       -3.906409   -0.221222    1.423400
    27          9             0        3.189366    0.943522   -0.914946
    28          9             0        2.893294    2.100251    0.847683
```

```
  29        9          0       1.585993   2.342455  -0.803257
---------------------------------------------------------------------
```

CF_3-CP5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.90318397 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6          0       0.743737   0.573729  -0.096460
    2         1          0       2.299638   0.050111  -1.467675
    3         6          0       3.218047   0.751877   0.352843
    4         6          0       3.184271   2.236042  -0.015553
    5         6          0       1.804634   2.843982   0.231486
    6         6          0       0.716243   2.047464  -0.488692
    7         8          0       0.374439   0.489790   1.223507
    8         1          0      -0.263313   2.440997  -0.253165
    9         1          0       1.593665   2.858102   1.295608
   10         1          0       0.847872   2.111363  -1.564504
   11         1          0       1.779938   3.873323  -0.111749
   12         1          0       3.937993   2.765084   0.558782
   13         1          0       3.068202   0.633561   1.420711
   14         1          0       3.452110   2.352105  -1.064216
   15         1          0       4.187797   0.334881   0.114959
   16         1          0       0.378185  -0.413512   1.520057
   17         6          0       2.132007  -0.039962  -0.399801
   18         6          0       2.249831  -1.528784  -0.105644
   19         8          0      -0.150326  -0.181718  -0.908989
   20         8          0      -1.438683   0.292693  -0.752307
   21         6          0      -2.168326  -0.490208   0.032713
   22         8          0      -1.823717  -1.436533   0.632455
   23         6          0      -3.607093   0.039153   0.034800
   24         9          0      -4.338711  -0.651840   0.867488
   25         9          0      -4.124230  -0.059358  -1.171099
   26         9          0      -3.629484   1.304344   0.396828
   27         9          0       1.912944  -1.821039   1.150124
   28         9          0       3.499338  -1.936316  -0.269976
   29         9          0       1.500599  -2.271306  -0.893398
---------------------------------------------------------------------
```

CF_3-CP6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.89754109 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic             Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1         6          0      -1.059140  -0.807705   0.206739
    2         1          0      -2.183269   0.573025   1.360742
    3         6          0      -3.122574   0.398743  -0.567166
    4         6          0      -3.986634  -0.801732  -0.175790
    5         6          0      -3.190459  -2.105315  -0.198605
    6         6          0      -1.923624  -1.991502   0.650786
    7         8          0      -0.611465  -0.947614  -1.081531
    8         1          0      -1.319295  -2.889945   0.574956
```

```
      9          1           0       -2.919018   -2.348555   -1.221162
     10          1           0       -2.177391   -1.868706    1.698752
     11          1           0       -3.795797   -2.926436    0.171528
     12          1           0       -4.835845   -0.870573   -0.848016
     13          1           0       -2.815604    0.319288   -1.603986
     14          1           0       -4.390865   -0.641390    0.822054
     15          1           0       -3.700922    1.307199   -0.469239
     16          1           0       -0.188370   -1.793832   -1.183312
     17          6           0       -1.869149    0.499409    0.324769
     18          6           0       -1.118402    1.798933    0.067088
     19          8           0        0.033051   -0.885327    1.128964
     20          8           0        1.118850   -0.139565    0.714231
     21          6           0        2.027644   -0.878910    0.100969
     22          8           0        1.944356   -2.006371   -0.221196
     23          6           0        3.279287   -0.023937   -0.132118
     24          9           0        4.148337   -0.692487   -0.844199
     25          9           0        2.972363    1.084866   -0.764449
     26          9           0        3.825055    0.286020    1.024224
     27          9           0       -0.466894    1.817912   -1.078747
     28          9           0       -1.974656    2.815938    0.043678
     29          9           0       -0.256834    2.070310    1.032149
 ---------------------------------------------------------------------
```

CF$_3$-CP7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.89974953 a.u.
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        0.634882    0.436086    0.251551
      2          6           0        2.543545   -1.285764   -0.179885
      3          6           0        2.974329    0.915203    1.035203
      4          6           0        3.173717    1.889909   -0.129126
      5          6           0        1.840992    2.498417   -0.568846
      6          6           0        0.804653    1.420111   -0.900057
      7          8           0        0.051765    1.122409    1.296098
      8          1           0       -0.157913    1.873395   -1.095851
      9          1           0        1.454057    3.134340    0.220863
     10          1           0        1.097346    0.868967   -1.783475
     11          1           0        1.984983    3.128346   -1.440750
     12          1           0        3.853991    2.675916    0.183795
     13          1           0        2.595481    1.461619    1.891083
     14          1           0        3.645639    1.384762   -0.965673
     15          1           0        3.915577    0.473958    1.334661
     16          1           0       -0.182709    0.518475    1.993161
     17          6           0        1.960743   -0.207798    0.728378
     18          1           0        1.742241   -0.738247    1.650075
     19          8           0       -0.186593   -0.667365   -0.106635
     20          8           0       -1.427377   -0.218624   -0.519727
     21          6           0       -2.354198   -0.392540    0.411734
     22          8           0       -2.208544   -0.768575    1.513890
     23          6           0       -3.717241   -0.023271   -0.185349
     24          9           0       -4.642098   -0.089940    0.734596
     25          9           0       -4.020758   -0.854543   -1.158152
```

```
    26          9             0       -3.686997    1.198772   -0.671867
    27          9             0        1.818854   -2.388506   -0.172567
    28          9             0        3.754338   -1.628619    0.240946
    29          9             0        2.670968   -0.906765   -1.443902
---------------------------------------------------------------------
```

CF$_3$-CP8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.90153660 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0        0.800288   -0.825770   -0.137275
    2          6             0        1.768493    1.568120   -0.165388
    3          6             0        2.626651   -0.185724    1.468586
    4          6             0        3.646535   -0.955454    0.622754
    5          6             0        2.980080   -2.095064   -0.150802
    6          6             0        1.804536   -1.594654   -0.995811
    7          8             0        0.207158   -1.631907    0.810915
    8          1             0        1.278865   -2.426124   -1.456250
    9          1             0        2.626619   -2.847365    0.547788
   10          1             0        2.154463   -0.957766   -1.796560
   11          1             0        3.700201   -2.581577   -0.800575
   12          1             0        4.414256   -1.356773    1.277050
   13          1             0        2.232423   -0.842544    2.234790
   14          1             0        4.146160   -0.284638   -0.067848
   15          1             0        3.101600    0.642365    1.978360
   16          1             0       -0.186369   -2.387566    0.387223
   17          6             0        1.419901    0.338154    0.660253
   18          1             0        0.664783    0.683704    1.355240
   19          8             0       -0.173362   -0.403886   -1.083562
   20          8             0       -1.233493    0.208526   -0.440419
   21          6             0       -2.283615   -0.592812   -0.340949
   22          8             0       -2.361180   -1.724556   -0.642757
   23          6             0       -3.452240    0.209141    0.244088
   24          9             0       -4.475718   -0.576786    0.449561
   25          9             0       -3.103001    0.760385    1.386500
   26          9             0       -3.805948    1.161417   -0.590768
   27          9             0        0.700154    2.157108   -0.667645
   28          9             0        2.374637    2.468187    0.597858
   29          9             0        2.586568    1.316048   -1.180547
---------------------------------------------------------------------
```

CF$_3$-TS1

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87510023 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0        0.839977    0.702517    0.842693
    2          1             0        1.800249    2.305022    1.817373
    3          6             0        1.810243    2.768566   -0.305848
    4          6             0        3.132380    2.087219   -0.656029
    5          6             0        2.950228    0.602749   -0.975363
```

```
      6          6           0        2.262009   -0.157441    0.144314
      7          8           0        0.350899    0.228593   -0.251403
      8          6           0        2.099331   -1.643246   -0.129405
      9          1           0        2.381840    0.481004   -1.888092
     10          1           0        2.778683   -0.070874    1.092922
     11          1           0        3.918608    0.136414   -1.133367
     12          1           0        3.583014    2.571906   -1.515184
     13          1           0        1.118513    2.692623   -1.138349
     14          1           0        3.832476    2.201219    0.169181
     15          1           0        1.977371    3.825913   -0.130844
     16          8           0       -1.413830    0.777325   -0.367968
     17          6           0        1.170823    2.172552    0.944407
     18          6           0       -2.147636   -0.073994    0.203379
     19          1           0        0.219950    2.648063    1.162477
     20          8           0        0.448949    0.171496    1.983909
     21          1           0       -0.277644   -0.454839    1.821017
     22          8           0       -1.852432   -0.870574    1.062651
     23          6           0       -3.598935   -0.034872   -0.302995
     24          9           0       -3.637477   -0.326708   -1.589903
     25          9           0       -4.366382   -0.888110    0.333168
     26          9           0       -4.108947    1.172934   -0.142099
     27          9           0        1.611947   -1.892431   -1.323994
     28          9           0        1.340706   -2.238742    0.762742
     29          9           0        3.303235   -2.197551   -0.069422
 ---------------------------------------------------------------------
```

CF_3-TS2

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87492914 a.u.
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        1.095984   -0.642408    0.704364
      2          1           0        2.752056    0.585501    1.060448
      3          6           0        2.787661    0.133534   -1.054997
      4          6           0        3.660878   -1.113999   -0.934044
      5          6           0        2.833585   -2.362038   -0.630075
      6          6           0        1.980819   -2.188258    0.603527
      7          8           0        0.366245   -1.270990   -0.143853
      8          1           0        1.303214   -2.995277    0.822025
      9          1           0        2.205607   -2.617358   -1.475121
     10          1           0        2.540978   -1.941850    1.496954
     11          1           0        3.488077   -3.211850   -0.450156
     12          1           0        4.205418   -1.261426   -1.860071
     13          1           0        2.065405    0.006906   -1.852669
     14          1           0        4.405179   -0.968075   -0.153902
     15          1           0        3.405138    0.984135   -1.316780
     16          8           0       -1.108432   -0.230899   -0.607525
     17          6           0        2.044603    0.465364    0.247713
     18          6           0       -2.029333   -0.421223    0.225850
     19          6           0        1.369907    1.833225    0.120312
     20          8           0        0.637593   -0.493859    1.937218
     21          1           0       -0.316709   -0.702455    1.954036
     22          8           0       -1.947120   -0.811364    1.369933
```

```
   23          6            0       -3.422795  -0.110093  -0.344958
   24          9            0       -3.701074  -0.953425  -1.323695
   25          9            0       -4.363358  -0.217189   0.564438
   26          9            0       -3.464133   1.113462  -0.834951
   27          9            0        0.719896   1.971039  -1.015399
   28          9            0        2.318450   2.764281   0.141020
   29          9            0        0.538163   2.101169   1.102242
---------------------------------------------------------------------
```

CF_3-TS3

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87030980 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic            Coordinates (Angstroms)
 Number     Number      Type              X          Y          Z
---------------------------------------------------------------------
    1          6            0       -0.658549   0.129464  -0.517122
    2          1            0       -1.766664   1.008810  -2.079898
    3          6            0       -1.556429   2.532160  -0.547633
    4          6            0       -2.788528   2.189132   0.285968
    5          6            0       -2.472571   1.135098   1.348179
    6          6            0       -1.895709  -0.175755   0.825302
    7          8            0        0.006065   0.282369   0.575652
    8          1            0       -1.477496  -0.764893   1.623936
    9          1            0       -1.754552   1.538934   2.051030
   10          6            0       -2.886272  -1.111497   0.124849
   11          1            0       -3.363811   0.890273   1.915394
   12          1            0       -3.149969   3.077514   0.792664
   13          1            0       -0.765835   2.906978   0.094700
   14          1            0       -3.592564   1.849120  -0.359517
   15          1            0       -1.793508   3.325111  -1.248770
   16          8            0        1.754994   0.753191   0.089992
   17          6            0       -1.047225   1.335206  -1.342189
   18          6            0        2.429429  -0.303028  -0.020139
   19          1            0       -0.132881   1.583673  -1.871982
   20          8            0       -0.399332  -0.936751  -1.243472
   21          1            0        0.377410  -1.399558  -0.881083
   22          8            0        2.042646  -1.428174  -0.242565
   23          6            0        3.937487  -0.065777   0.164598
   24          9            0        4.177338   0.371226   1.387990
   25          9            0        4.637086  -1.160315  -0.022005
   26          9            0        4.369580   0.846136  -0.686885
   27          9            0       -3.308118  -0.670368  -1.042667
   28          9            0       -2.392815  -2.315426  -0.035386
   29          9            0       -3.948061  -1.223594   0.909597
---------------------------------------------------------------------
```

CF$_3$-TS4

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87819915 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0        0.739554    0.245993   -0.595410
    2          6           0        2.579873   -1.332255    0.152201
    3          6           0        2.029149    0.752725    1.539315
    4          6           0        2.936802    1.789594    0.872977
    5          6           0        2.210412    2.561400   -0.230944
    6          6           0        1.577949    1.655328   -1.263964
    7          8           0       -0.120833    1.158074   -0.322822
    8          1           0        0.936385    2.145374   -1.976046
    9          1           0        1.450736    3.203676    0.198200
   10          1           0        2.277873    1.021121   -1.790167
   11          1           0        2.911127    3.205093   -0.757442
   12          1           0        3.278834    2.491990    1.625238
   13          1           0        1.163129    1.246724    1.964222
   14          1           0        3.823104    1.311439    0.469389
   15          1           0        2.547823    0.274167    2.358707
   16          8           0       -1.552565    0.366982    0.569997
   17          6           0        1.509728   -0.337568    0.587138
   18          6           0       -2.395391   -0.030779   -0.276874
   19          1           0        0.764967   -0.928068    1.111408
   20          8           0        0.447403   -0.613616   -1.561547
   21          1           0       -0.498928   -0.539892   -1.781318
   22          8           0       -2.220308   -0.317738   -1.438788
   23          6           0       -3.813111   -0.144599    0.306696
   24          9           0       -4.239274    1.046289    0.686697
   25          9           0       -4.668160   -0.626047   -0.564134
   26          9           0       -3.814489   -0.936054    1.363314
   27          9           0        3.366884   -0.846574   -0.804059
   28          9           0        3.363675   -1.641172    1.173256
   29          9           0        2.065317   -2.456471   -0.293267
---------------------------------------------------------------------
```

CF$_3$-TS5

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87247147 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6           0       -0.844259    0.856942    0.010690
    2          1           0       -1.338952    2.117789   -1.622724
    3          6           0       -2.519667    2.716979    0.099112
    4          6           0       -3.667084    1.733470   -0.130060
    5          6           0       -3.318879    0.308870    0.305860
    6          6           0       -2.149433   -0.312142   -0.480852
    7          8           0       -0.626835    0.847875    1.309519
    8          6           0       -1.909133   -1.770506   -0.110901
    9          1           0       -3.103045    0.266969    1.365653
   10          1           0       -2.293895   -0.235508   -1.544736
   11          1           0       -4.166498   -0.341379    0.119107
```

```
   12          1             0       -4.545938    2.052952    0.419481
   13          1             0       -2.356191    2.859274    1.161531
   14          1             0       -3.942136    1.728428   -1.182625
   15          1             0       -2.769019    3.685146   -0.319979
   16          1             0        0.137158    0.272793    1.508327
   17          6             0       -1.235581    2.203701   -0.547699
   18          1             0       -0.394362    2.857052   -0.344792
   19          8             0       -0.190671    0.030098   -0.722607
   20          8             0        1.586898    0.626123   -0.763842
   21          6             0        2.211669    0.109740    0.197522
   22          8             0        1.775855   -0.302630    1.249418
   23          6             0        3.726295    0.025590   -0.054350
   24          9             0        4.372245   -0.469690    0.975321
   25          9             0        4.217171    1.226133   -0.305131
   26          9             0        3.969800   -0.742085   -1.100238
   27          9             0       -1.103691   -2.377988   -0.950618
   28          9             0       -3.068234   -2.414199   -0.155110
   29          9             0       -1.426476   -1.901181    1.105210
---------------------------------------------------------------------
```

CF_3-TS6

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87481964 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
    1          6             0       -1.025072   -0.695367   -0.040792
    2          1             0       -2.140537    0.433100   -1.451871
    3          6             0       -3.358032    0.168621    0.319774
    4          6             0       -3.971323   -1.160096   -0.115994
    5          6             0       -3.009719   -2.325328    0.090330
    6          6             0       -1.722186   -2.201272   -0.724199
    7          8             0       -0.780079   -0.843542    1.249139
    8          1             0       -1.032192   -3.001096   -0.522284
    9          1             0       -2.766426   -2.446955    1.137656
   10          1             0       -1.900160   -2.082444   -1.779104
   11          1             0       -3.463338   -3.254962   -0.247517
   12          1             0       -4.878858   -1.340092    0.449630
   13          1             0       -3.206743    0.177353    1.392709
   14          1             0       -4.259923   -1.106661   -1.163511
   15          1             0       -4.033155    0.978748    0.079866
   16          1             0        0.161507   -1.083297    1.374913
   17          6             0       -2.010228    0.425733   -0.375958
   18          6             0       -1.494047    1.817357   -0.024265
   19          8             0       -0.109105   -1.042720   -0.874335
   20          8             0        1.407846    0.037399   -0.737503
   21          6             0        2.150486   -0.423751    0.161051
   22          8             0        1.850836   -1.107868    1.117773
   23          6             0        3.629017   -0.047332   -0.032627
   24          9             0        4.375354   -0.445806    0.971418
   25          9             0        3.767037    1.258566   -0.151978
   26          9             0        4.090790   -0.611086   -1.135079
   27          9             0       -1.258150    1.963590    1.263647
   28          9             0       -2.415600    2.712942   -0.361151
```

```
    29          9           0       -0.400491    2.124990   -0.681855
 ---------------------------------------------------------------------
```

CF_3-TS7

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87257400 a.u.
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -0.669160   -0.806146   -0.098863
      2          1           0       -1.402482   -0.810215    1.889561
      3          6           0       -2.423790   -2.374391    0.784788
      4          6           0       -3.535837   -1.512348    0.185805
      5          6           0       -3.045719   -0.728552   -1.033938
      6          6           0       -1.928469    0.305332   -0.778315
      7          8           0       -0.253714   -1.592373   -1.077129
      8          1           0       -1.512921    0.647336   -1.710448
      9          1           0       -2.681812   -1.411587   -1.789391
     10          6           0       -2.362754    1.520187    0.031969
     11          1           0       -3.860030   -0.165576   -1.477052
     12          1           0       -4.358789   -2.143519   -0.131934
     13          1           0       -2.149587   -3.159020    0.087515
     14          1           0       -3.932606   -0.835871    0.935271
     15          1           0       -2.772686   -2.858541    1.689785
     16          1           0        0.584235   -1.240356   -1.437806
     17          6           0       -1.191025   -1.533744    1.116462
     18          1           0       -0.368449   -2.155563    1.451712
     19          8           0       -0.095039    0.335936    0.031710
     20          8           0        1.619438    0.013031    0.714500
     21          6           0        2.410307   -0.150850   -0.247660
     22          8           0        2.163263   -0.520640   -1.375519
     23          6           0        3.869057    0.171715    0.116042
     24          9           0        4.689997   -0.063588   -0.880810
     25          9           0        4.257773   -0.556605    1.146321
     26          9           0        3.980301    1.444328    0.448342
     27          9           0       -2.511902    1.258755    1.316827
     28          9           0       -3.534374    1.941447   -0.422537
     29          9           0       -1.520919    2.519893   -0.087416
 ---------------------------------------------------------------------
```

CF_3-TS8

```
E(B3LYP/6-31+G**//HF/6-31G*) =  -1248.87641035 a.u.
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        0.823407   -0.731244   -0.060902
      2          6           0        1.951850    1.577026    0.031835
      3          6           0        2.960578   -0.346994   -1.316573
      4          6           0        3.762530   -1.093622   -0.246812
      5          6           0        2.902604   -2.105738    0.508551
      6          6           0        1.724825   -1.497545    1.276550
      7          8           0        0.412296   -1.677034   -0.898083
      8          1           0        1.076725   -2.249621    1.689941
```

```
   9          1            0        2.533943   -2.870837   -0.161553
  10          1            0        2.020035   -0.768076    2.005818
  11          1            0        3.496248   -2.602531    1.273544
  12          1            0        4.577649   -1.623105   -0.728333
  13          1            0        2.656647   -1.043232   -2.088763
  14          1            0        4.211820   -0.396120    0.450511
  15          1            0        3.573361    0.406934   -1.792228
  16          1            0       -0.530625   -1.871966   -0.721603
  17          6            0        1.680845    0.313264   -0.771354
  18          1            0        1.069970    0.640403   -1.605260
  19          8            0        0.059499   -0.417180    0.913418
  20          8            0       -1.457082    0.452746    0.204075
  21          6            0       -2.329452   -0.406607   -0.067862
  22          8            0       -2.178952   -1.579361   -0.340686
  23          6            0       -3.758882    0.159527   -0.038466
  24          9            0       -4.652378   -0.734660   -0.393568
  25          9            0       -3.864356    1.189405   -0.857489
  26          9            0       -4.054300    0.572807    1.180203
  27          9            0        0.850411    2.221941    0.333784
  28          9            0        2.709628    2.396649   -0.681277
  29          9            0        2.601919    1.346788    1.169273
---------------------------------------------------------------------
```

H-CP

```
E(HF/6-31G*) =  -907.037076863 a.u.
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1          6            0       -1.375209    0.526513    0.465226
   2          1            0       -2.302519   -0.583271    1.997484
   3          6            0       -2.595505   -1.670842    0.153307
   4          6            0       -3.837283   -0.917561   -0.331465
   5          6            0       -3.458520    0.405938   -1.001699
   6          6            0       -2.593364    1.270576   -0.079157
   7          8            0       -0.564368    0.353551   -0.704506
   8          1            0       -2.258352    2.168446   -0.591059
   9          1            0       -2.919824    0.206763   -1.922884
  10          1            0       -3.167769    1.586071    0.786388
  11          1            0       -4.351793    0.960025   -1.273411
  12          1            0       -4.401350   -1.534748   -1.024302
  13          1            0       -1.997006   -1.974443   -0.700871
  14          1            0       -4.492363   -0.719532    0.515521
  15          1            0       -2.886463   -2.579960    0.670436
  16          8            0        0.602853   -0.314482   -0.379776
  17          6            0       -1.748013   -0.808962    1.091927
  18          6            0        1.640875    0.503358   -0.304255
  19          1            0       -0.844956   -1.323518    1.394395
  20          8            0       -0.678224    1.255084    1.401366
  21          1            0       -0.411023    2.087913    1.027568
  22          8            0        1.654574    1.671769   -0.414543
  23          6            0        2.900397   -0.335609   -0.058651
  24          9            0        3.127215   -1.117671   -1.093059
  25          9            0        3.934096    0.444536    0.115673
```

```
   26          9             0        2.751407   -1.089264    1.009500
---------------------------------------------------------------------
```

Chapter 9

Summary

Organofluorine compounds continue to attract much attention, because of their important applications as biological active agents, liquid crystalline materials, and so on. One of the most important fluorine-containing compounds is a CF_3 one, which exhibits specific physical and biological properties. The development of the synthetic methodologies and the selective reactions of α-CF_3 carbonyl compounds are the theme of this thesis. Furthermore, understanding specific chemical properties of α-CF_3 carbonyl compounds in these reactions by computational approaches is the primary concern (Figure 9-1).

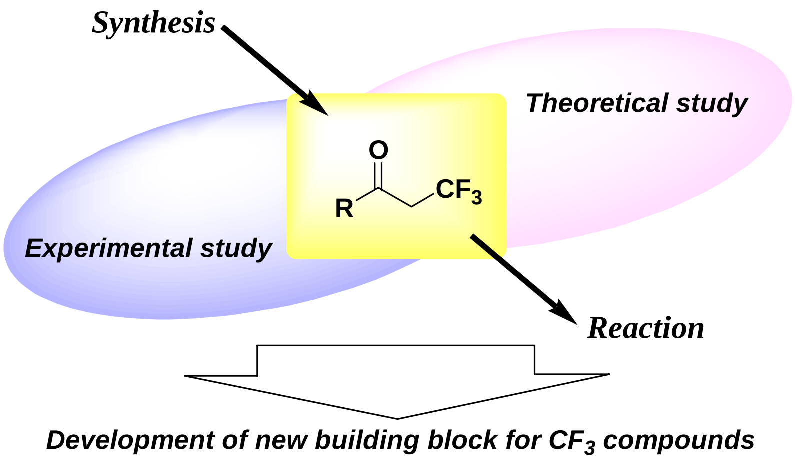
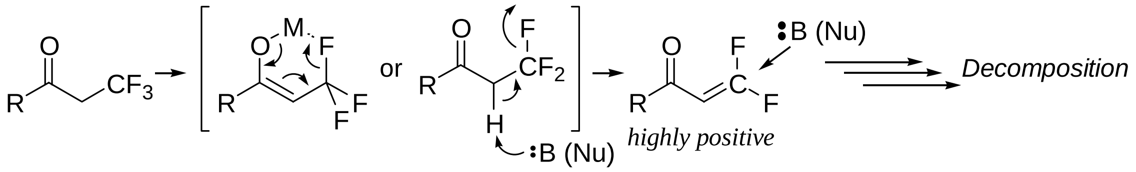


Figure 9-1. Basic concept of the thesis.

In order to make successful research, one thing has to be considered; α-CF_3 carbonyl compounds are sensitive to base and readily decompose (Scheme 9-1). This is the reason why the synthesis, reaction, and origin of the reactivity of α-CF_3 carbonyl compounds are not enough explored to date.

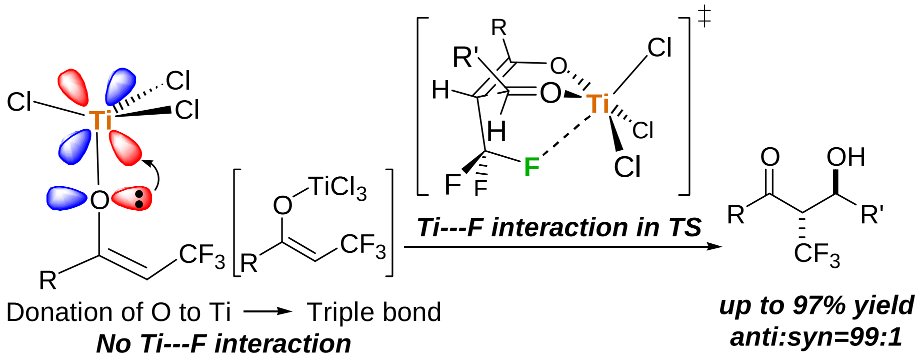
Scheme 9-1.



The author investigated three kinds of reactions concerning α-CF_3 carbonyl compounds: enolate generation and aldol reaction of α-CF_3 ketone, radical trifluoromethylation of metal enolates, and Baeyer-Villiger (B-V) reaction of α-CF_3 ketone.

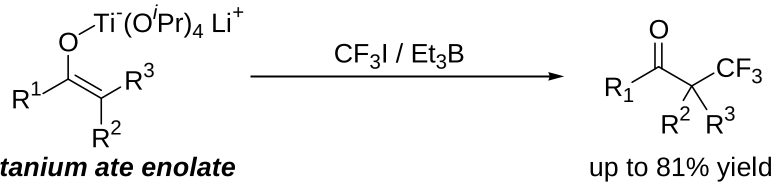
In Chapter 2 and 3, enolate generation and aldol reactions of α-CF_3 ketones are described from experimental and theoretical view points. Enolate generation of α-CF_3 carbonyl compounds is recognized to be difficult due to the rapid decomposition (Scheme 9-1). However, the author discovered that Ti enolates of α-CF_3 ketones could be generated and used for further functionalization; the aldol reactions of Ti enolates of α-CF_3 ketones proceeded in up to quantitative yield and virtually perfect diastereoselectivity. The aldol reaction of Ti enolates of α-CF_3 ketones showed *anti*-diastereoselectivity, which is quite anomalous for the aldol reaction of Ti enolates. The origin of the stability of the Ti enolates of α-CF_3 ketones was investigated theoretically; Ti-F interaction plays an important role in the course of these reactions. In the Ti enolate of α-CF_3 ketone, there is no Ti-F interaction because of the multiple bonding nature of Ti-O bond which retards F-elimination. On the other hand, at the transition state of the aldol reaction, there is a clear Ti-F interaction and, as a result, the aldol reaction shows *anti*-diastereoselectivity (Scheme 9-2).

Scheme 9-2.



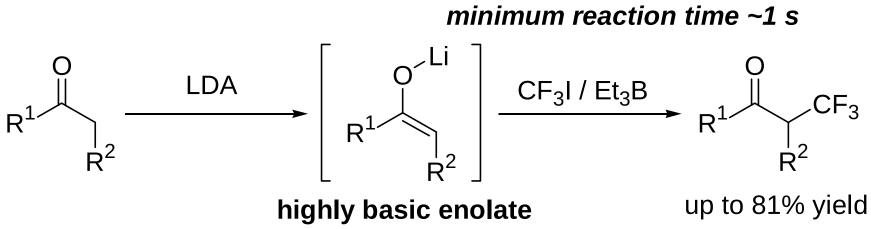
Radical trifluoromethylation of metal enolates is reported experimentally and theoretically in Chapter 4, 5, and 6. Radical trifluoromethylation of metal enolates is, in principle, one of the simplest and efficient ways to introduce a CF_3 unit at the α position of a carbonyl group. However defluorination (Scheme 9-1) is problematic and, hence, radical trifluoromethylation of metal enolates is thought to be impossible to carry out. In fact, the previous example is only limited to the Li enolate of a sterically demanding imide; the imide substrate was designed not to decompose. On the basis of the fact that Ti enolates of α-CF_3 ketones are stable to defluorination, the author investigated the radical trifluoromethylation of Ti enolate and discovered that Ti ate enolate gave the α-CF_3 ketone in up to 81% yield (Scheme 9-3).

Scheme 9-3.



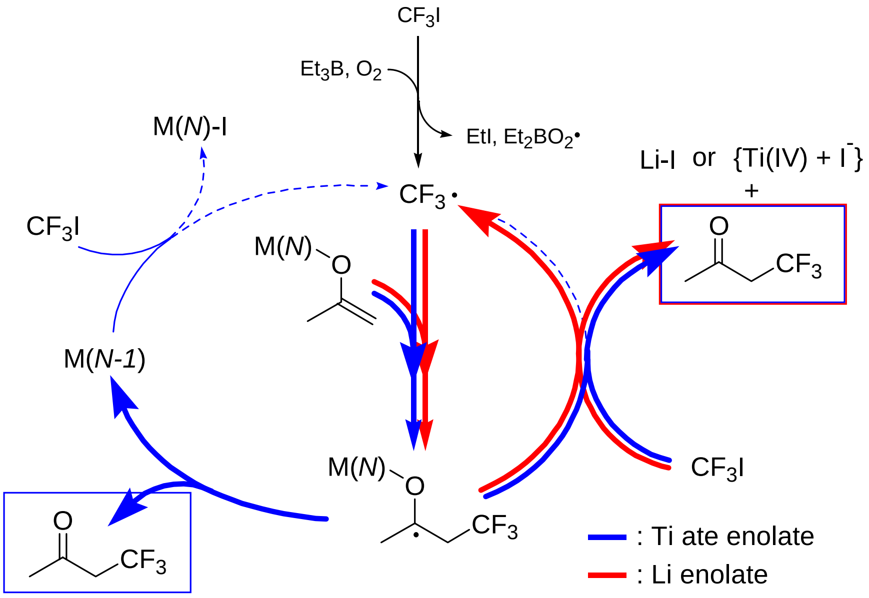
During the course of exploration of the radical trifluoromethylation of Ti ate enolates, the author discovered that Li enolates could be, in fact, employed for radical trifluoromethylation and that the reaction proceeded extremely fast; minimum reaction time is ~1 s (Scheme 9-4).

Scheme 9-4.



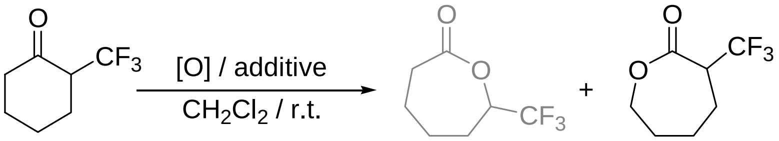
In investigating the amount of radical initiator (Et_3B), an interesting result was obtained. In the case of Ti ate enolates, the yields gradually decreased along with the amount of Et_3B decreased under the reaction conditions. In sharp contrast, this is not the case with Li enolates; α-CF_3 product could be obtained in good yield even when the amount of Et_3B was reduced to 5 mol%. This indicates that radical cycle does not work for Ti ate enolates but does works for Li enolates. Theoretical investigation of the mechanism of the radical trifluoromethylation of Ti ate and Li enolates uncovered that the key difference was in radical chain propagation step. The experimentally observed difference between Ti ate enolate and Li enolate could be attributed to the bond forming ability of the metal species with I^- to regenerate CF_3 radical; Li species could form Li-I to regenerate CF_3 radical and, however, Ti species does not have the driving force for the formation of Ti-I bond (Scheme 9-5).

Scheme 9-5.



In view of the specific stereoelectronic effects of CF_3 group, the B-V reaction of the α-CF_3 ketone is investigated experimentally and theoretically in Chapter 7 and 8. According to the B-V reaction of α-F_{ax} cyclohexanone, migration of the carbon attached with CF_3 could be expected. However, B-V reaction of α-CF_3 cyclohexanone by trifluoroperacetic acid (TFPA) gave complete migration of the non-substituted carbon. Further investigation revealed that the use of *m*CPBA in combination with Sc(OTf)$_3$ or TfOH increase the reaction rate (Scheme 9-6).

Scheme 9-6.



TFA / TFPA / 16 h	-	quant.
*m*CPBA / Sc(OTf)$_3$ / 4.5 h	-	91
*m*CPBA / TfOH / 1 h	-	91

The origin of the regioselectivity of the B-V reaction was investigated theoretically not only for α-CF_3 cyclohexanone, but also for α-Me and F cyclohexanones. Investigation of the energy profiles of the rearrangement step reveals that there are two factors in determining the regioselectivity.

(1) Thermodynamic stability of the Criegee intermediate (thermodynamic effect).
(2) Activation energy (kinetic effect).

And the origins of these two factors are,

(a) Steric repulsion
(b) Dipole interaction
(c) Nucleophilicity of the migrating carbon.

In the case of α-Me cyclohexanone, (1) thermodynamic effect based on (a) steric factor predominates in determining the regioselectivity. Strong electron-withdrawing nature of F induces the (b) dipole interaction between peracid moiety to affect both (1) thermodynamic effect and (2) kinetic effect for α-F cyclohexanone. In α-CF_3 cyclohexanone, all the factors are combined together. (1) Thermodynamic effect is affected by (a) steric repulsion and (b) dipole interaction. And (2) activation energy is affected by (c) nucleophilicity of the migrating carbon. It is noted that the most stable transition state has bulky CF_3 group in axial position (Figure 9-2).

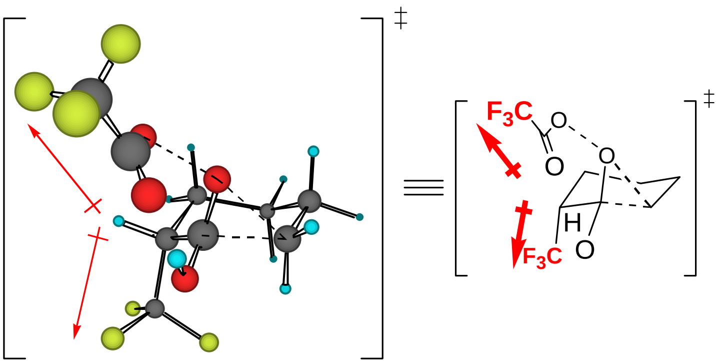


Figure 9-2. The most stable transition state of the B-V reaction of α-CF_3 cyclohexanone.

In this research project titled “Chemistry of α-CF_3 Carbonyl Compounds: Development of Selective Reactions and their Theoretical Studies”, the author discovered the synthesis and the reactions of α-CF_3 carbonyl compounds.

Generation of stable Ti enolates of α-CF_3 ketones was achieved and its aldol reaction proceeded in up to quantitative yield and virtually perfect *anti*-selectivity. Theoretical investigation reveals that the stability of the Ti enolate stems from the multiple bonding nature of the Ti-O bond, and the anomalous *anti*-stereoselecivity could be attributed to the Ti-F interaction only at the transition state.

Radical trifluoromethylation of Ti ate enolates and Li enolates were found to be one of the most efficient ways to synthesize α-CF_3 ketone. Computational tracing of the reaction of both Ti ate and Li enolates disclosed that the difference between these enolates exists in radical chain propagation step.

The Baeyer-Villiger reaction of the α-CF_3 ketone gave the product in quantitative yield and complete regioselectivity. Theoretical investigation unveiled that the regioselectivity is determined by combined effects of steric repulsion, dipole interaction, and nucleophilicity of the migrating carbon.

The author has thus made a significant breakthrough in direct generation of metal enolate of α-CF_3 ketone, synthetic methodology of the α-CF_3 ketone *via* radical trifluoromethylation of a ketone metal enolate which have been believed to be difficult. The discovery of the synthetic methods, archetype transformation, and specific characteristics of α-CF_3 carbonyl compounds in experimental and theoretical point of view should provide a basis for the further development of the chemistry of CF_3 containing compounds.

List of Research Achievements

Publication

Original publication

1) Complete Reversal in Regioselectivity in the Baeyer-Villiger Reaction of an α-CF_3-Ketone and Theoretical Rationale for Axial Orientation of Sterically Demanding CF_3 group at the Transition State.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   Org. Lett. **2003**, *5*, 4803-4806.
2) Dipole Interaction-Controlled Stereoselectivity in Aldol Reaction of α-CF_3 Enolate with Fluoral.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   Org. Lett. **2003**, *5*, 4807-4809.
3) Nanoflow system for perfect regiocontrol in the Baeyer-Villiger oxidation by aqueous hydrogen peroxide using lowest concentration of a fluorous lanthanide catalyst.
   Koichi Mikami, Md. Nazrul Islam, Masahiro Yamanaka, Yoshimitsu Itoh, Masaki Shinoda, Kenichi Kudo
   Tetrahedron Lett. **2004**, *45*, 3681-3683.
4) Hybrid Reagent of Ammonium Hydrogen Fluoride and Scandium Triflate: Highly Efficient Catalyst for Ring-Opening Fluorination of 2,3-Epoxyalcohols.
   Yoshimitsu Itoh, Sejin Jang, Shiho Ohba, Koichi Mikami
   Chem. Lett. **2004**, *33*, 776-777.
5) Direct Generation of Ti-enolate of α-CF_3 Ketone: Theoretical Study and High-Yielding and Diastereoselective Aldol Reaction.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   J. Am. Chem. Soc. **2004**, *126*, 13174-13175.
6) Radical Trifluoromethylation of Titanium Ate Enolate.
   Yoshimitsu Itoh, Koichi Mikami
   Org. Lett. **2005**, *7*, 649-651.
7) Facile Radical Trifluoromethylation of Lithium Enolates.
   Yoshimitsu Itoh, Koichi Mikami
   Org. Lett. **2005**, *7*, 4883-4885.

8) Radical Trifluoromethylation of Ti Ate Enolate: Possible Intervention of Transformation of Ti(IV) to Ti(III) for Radical Termination.
   Yoshimitsu Itoh, Koichi Mikami
   J. Fluorine Chem. In press.
9) Nanoflow Microreactor for Dramatic Increase not only in Reactivity but also in Selectivity: Baeyer-Villiger Oxidation by Aqueous Hydrogen Peroxide Using Lowest Concentration of a Fluorous Lanthanide Catalyst.
   Koichi Mikami, Masahiro Yamanaka, Md. Nazrul Islam, Takayuki Tonoi, Yoshimitsu Itoh, Masaki Shinoda, Kenichi Kudo
   J. Fluorine Chem. In press.
10) Radical Trifluoromethylation of Ketone Li Enolates.
   Yoshimitsu Itoh, Koichi Mikami
   Tetrahedron. In press.
11) Experimental and Theoretical Study of Radical Trifluoromethylation of Ti Ate and Li Enolates.
   Yoshimitsu Itoh, Kendall N. Houk, Koichi Mikami
   In preparation.
12) Theoretical Studies of the Baeyer-Villiger Reaction of α-Me, F, CF_3 Cyclohexanones.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   In preparation.
13) Theoretical Study on the Stability of the α-CF_3 Ti Enolate and Anomalous *Anti*-selective Aldol Reaction
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   In preparation.

Review, Account

14) Organic fluorine compounds with full of character: their (catalytic) asymmetric synthesis (1).
   Koichi Mikami, Yoshimitsu Itoh, Masahiro Yamanaka
   Fine Chemical **2003**, *32 (1)*, 35-50 (Japanese article).
15) Organic fluorine compounds with full of character: their (catalytic) asymmetric synthesis (2).
   Koichi Mikami, Yoshimitsu Itoh, Masahiro Yamanaka
   Fine Chemical **2003**, *32 (2)*, 11-20 (Japanese article).

16) Fluorinated Carbonyl and Olefinic Compounds: Basic Character and Asymmetric Catalytic Reactions.
Koichi Mikami, Yoshimitsu Itoh, Masahiro Yamanaka
Chem. Rev. **2004**, *104*, 1-16.

17) Fluorinated Synthon: Asymmetric Catalitic Reactions.
Koichi Mikami, Yoshimitsu Itoh, Masahiro Yamanaka
In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005; p 356-367.

18) Metal Enolates of α-CF_3 Ketones: Theoretical Guideline, Direct generation, and Synthetic Use.
Koichi Mikami, Yoshimitsu Itoh
Chem. Rec. **2006**, *6*, 1-11.

19) Trifluoromethylation of Metal Enolates and Theoretical Guideline.
Koichi Mikami, Yoshimitsu Itoh
In *Current Fluoroorganic Chemistry. New Synthetic Directions, Technologies, Materials and Biological Applications*; Soloshonok, V. A., Mikami, K., Yamazaki, T., Welch, J. T., Honec, J., Eds.; American Chemical Society: Washington, DC. In press.

Presentation

Oral presentation

1) Regioselectivity of Baeyer-Villiger Reaction of α-Trifluoromethylketone.
Koichi Mikami, Yoshimitsu Itoh, Masahiro Yamanaka
81th Annual Meeting of CSJ, 3G8-05, Waseda University, March 2002.

2) Generation of Metal Enolate of α-Trifluoromethyl Ketone and Development of its Stereoselective Aldol Reaction.
Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
83th Annual Meeting of CSJ, 4H4-12, Waseda University, March 2003.

3) Efficient Generation of Ti-enolate of α-Trifluoromethyl Ketone and its Theoretical Study.
Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
84th Annual Meeting of CSJ, 1K1-18, Kuwansei Gakuin University, March 2004.

4) Radical Trifluoromethylation of Titanium and Lithium Enolates.
Yoshimitsu Itoh, Koichi Mikami
85th Annual Meeting of CSJ, 1C2-16, Kanagawa University, March 2005.

Poster presentation

5) Regio-control of Baeyer-Villiger Reaction by Trifluoromethyl Group.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   27th Fluorine Conference of Japan, 1P-26, Nagano, November 2003.
6) Efficient Generation of Ti-enolate of α-CF_3 Ketone: Theoretical Study and Highly Stereoselective Aldol Reaction.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   The International Conference on Fluorine Chemistry '04 Kyoto, P-39, Kyoto, May 2004.
7) Direct Generation of Ti-Enolate of α-CF_3 Ketone: Theoretical Study and High-Yielding and Diastereoselective Aldol Reaction.
   Yoshimitsu Itoh, Masahiro Yamanaka, Koichi Mikami
   51th Symposium on Organometallic Chemistry, Japan, PB109, Gakushunin University
8) Radical Trifluoromethylation of Ti-enolate.
   Yoshimitsu Itoh, Koichi Mikami
   28th Fluorine Conference of Japan, 1P-41, Tokyo Institute of Technology (Yokohama), November 2004.

Patent

1) Method for Producing α-Trifluoromethyl-β-hydroxycarbonyl Compound.
   Koichi Mikami, Masahiro Yamanaka, Yoshimitsu Itoh
   JP2005008533, 13 January 2005
2) Method for Producing α-Trifluoromethyl Ketone.
   Koichi Mikami, Yoshimitsu Itoh
   On application procedure.
3) Method for Producing Optically Active α-Trifluoromethyl Ketone.
   Koichi Mikami, Yoshimitsu Itoh
   On application procedure.