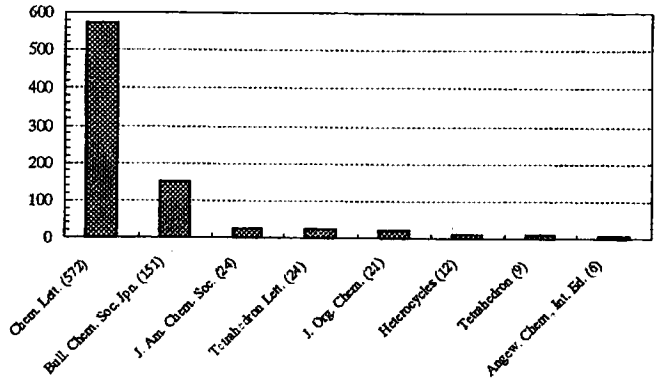
05/02/09 Tsuyoshi MITA (D1)

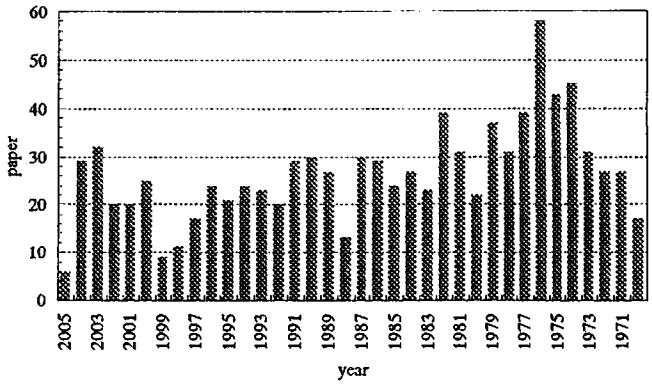
Teruaki Mukaiya's Recent Studies

Teruaki Mukaiyama was born in 1927. He received his B.Sc. from the Tokyo Institute of Technology (T.I.T.) in 1948, and Ph.D. from the University of Tokyo in 1957. He first became Assistant Professor at Gakusyuin University in 1953 and then at T.I.T. in 1958. He was appointed Full Professor at TIT in 1963 and moved to the University of Tokyo in 1974. In 1987 he became Professor of Chemistry at the Science University of Tokyo. Since 2002 he has been Professor at the Kitasato Institute; as well as Emeritus Professor at the University of Tokyo, the T.I.T., and the Science University of Tokyo. He is a recipient of many major awards and is currently a member of the Japan Academy as well as a foreign member of the Academy of Sciences in France and Poland.

1953-1958(学習院), 1958-1974(東工大), 1974-1987(60) (東大), 1987-2002(東京理科大), 2002-(北里)

Up to now, over 1000 papers were published. (examined by SciFinder)





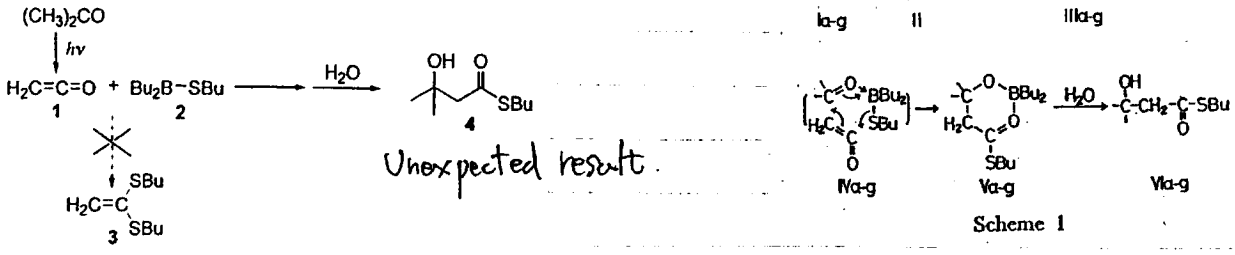
2005(6), 2004(29), 2003(32)

Today's Contents

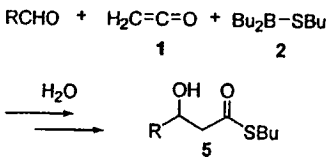
Year	Aldol Reaction	Oxd-Red Condensation	Oxidation	Condensation Reagent	Glycosylation	Total Synthesis
1963 1964 1967		$HgAr_2$, Bu_3P 1,2-Dibenzoylethylene, Bu_3P etc. Mitsunobu-Reaction				
1971	Boron Enolate					
1973 1976	**Silicon Enolate (Mukaiyama-Aldol-Reaction)**			Mukaiyama-Reagent		
1981 1985	$TrClO_4$				Glycosyl Fluoride ($SnCl_2$, $AgClO_4$)	
1989	**Asym. Reaction**					
1994				4-Trifluoromethyl benzoic Anhydride	Activated Reagent	
1997 1998				Di-2-pyridyl Thiocarbonate	One-pot Synthesis	**Taxol**
2000 2002 2004	**Lewis-Base Catalyzed Reaction**	**Quinone-Mediated Oxidation**	**Sulfinimidoyl Chloride**	**Di-2-thienyl Carbonate**	Acid Catalyzed Glycosylation	

• Aldol Reaction

Boron Enolate BCSJ, 1971



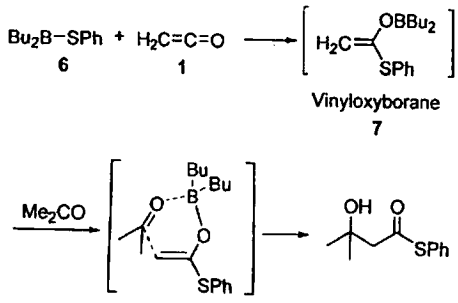
Scheme 1



good yield

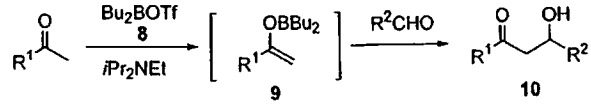
We recently reported a convenient method for preparation of β-hydroxyalkanethioates by the reaction of thioboronite and carbonyl compounds with ketene, and it was suggested that the reaction proceeded by initial formation of a coordination complex of a carbonyl compound with thioboronite, followed by a nucleophilic attack of the thiolate anion on ketene. However, the present investigation shows that the key intermediate of this reaction is vinyloxyborane formed from thioboronite and ketene.

JACS, 1973



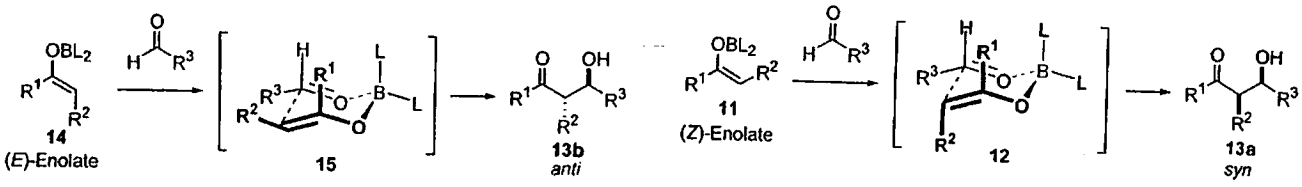
¹HNMR analysis.

Practical synthesis of boron enolate Chem. Lett., 1976

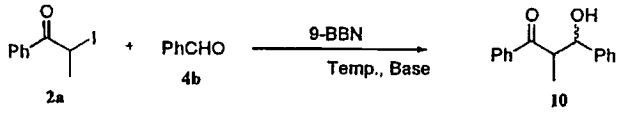


good-high yield

The length of the B-O bond (1.36-1.47Å) was shorter than other metal-O bonds such as Ti-O (1.62-1.73 Å), Al-O (1.92 Å), Mg-O (2.01-2.13 Å) and Sn-O (2.70A). Thus, the aldol reaction of boron enolates with aldehydes proceeded via rigid chair-like six-membered transition state to afford the corresponding aldols stereoselectively.

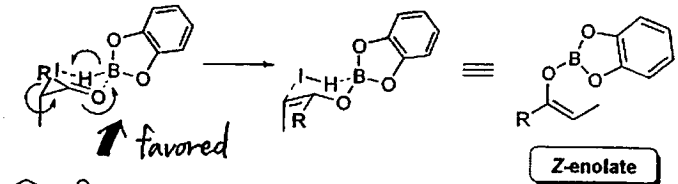


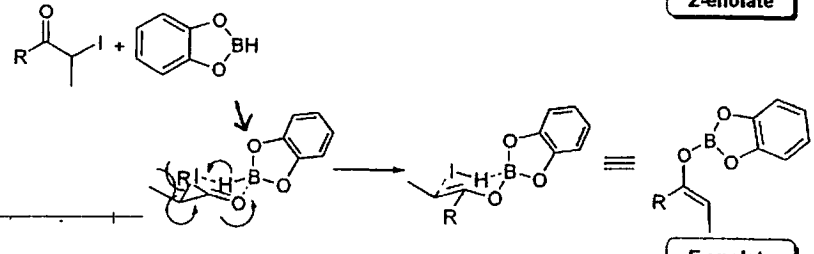
BCSJ, 2003.



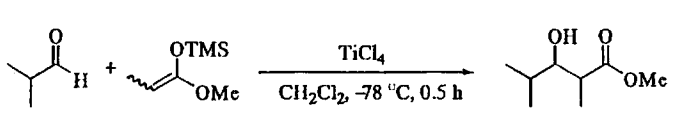
Temp = -98°c
Base ; 2,6-lutidine

95% yield
syn/anti = 99/1

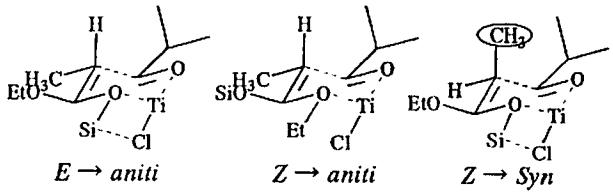




3/12



E enolate → *anti/syn* = 100/1
Z enolate → *anti/syn* = 52/48
(Z enolate→ *anti/syn* = 61/39, TBSO)



Silicon Enolate

Activated by $TiCl_4$, { Chem. Lett., 1973. JACS, 1974

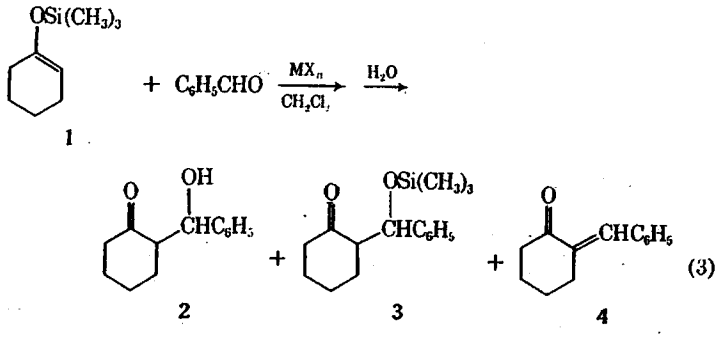
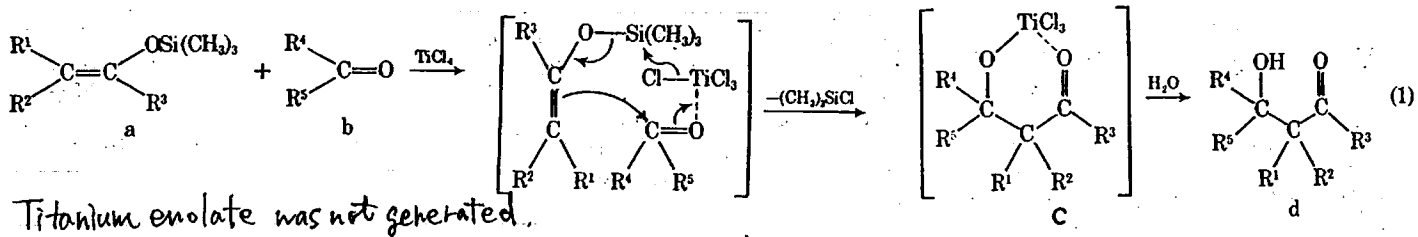


Table I. Reaction of the Silyl Enol Ether **2** with Benzaldehyde in the Presence of Various Metal Salts

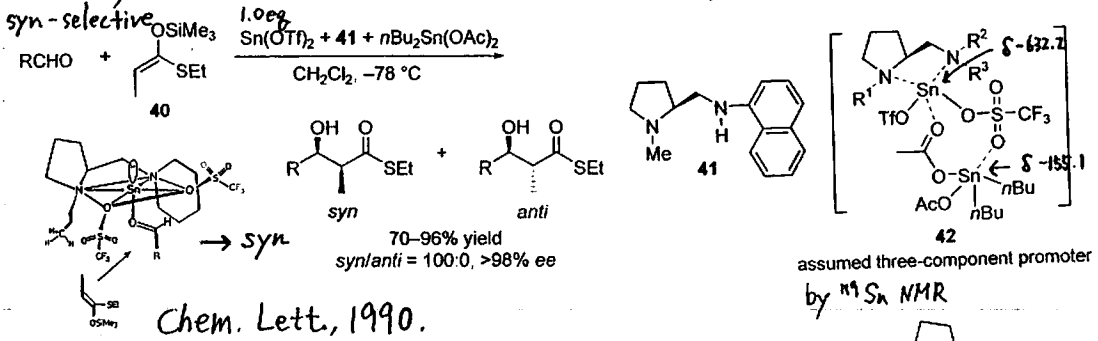
(1.0eq) Metal salts	Conditions— Temp, °C	Time, hr	Yield of products, % — anti 2 syn (threo:erythro)	3[a]	4
$TiCl_4$	RT[b]	2	82 (63:19)	Trace[c]	2
$TiCl_4$	−78	1	92 (69:23)	0	0
$SnCl_4$	RT	1	33 (25:8)	Trace	28
$SnCl_4$	−78	1	83 (63:20)	Trace	Trace
$FeCl_3$	RT	1	0	0	12
$AlCl_3$	RT	1	55 (41:14)	Trace	Trace
BCl_3	RT	1	26 (18:8)	0	24
$Et_2O \cdot BF_3$	−78	1	80 (59:21)	12	0
$ZnCl_2$	RT	10	69 (51:18)	8	3
$ZnCl_2$	−78	12	Trace	0	0
$(n\text{-}C_4H_9)_3SnCl$	RT	24	0	0	0
$MgCl_2$	RT	24	0	0	0
$CdCl_2$	RT	24	0	0	0
LiCl	RT	24	0	0	0

[a] Threo and erythro mixture. [b] Room temperature. [c] By tlc analysis.



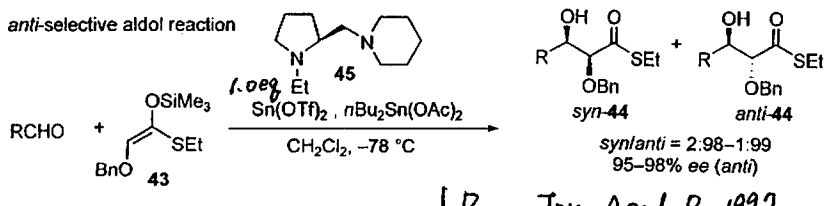
Titanium enolate was not generated.
The syn/anti ratio is influenced both by steric factors of the aldehyde and silyl enolate.

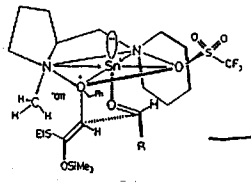
Asymmetric Aldol Reaction, { Chem. Lett., 1989. JACS, 1991. (stoichiometric)



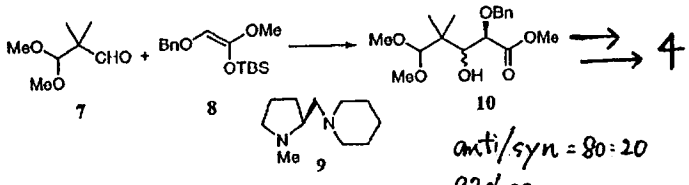
¹H NMR analysis indicated that no metal exchange took place from silicon to tin(II) or tin(IV). Aldehyde was directly attacked by silyl enolate.

Chem. Lett., 1990.

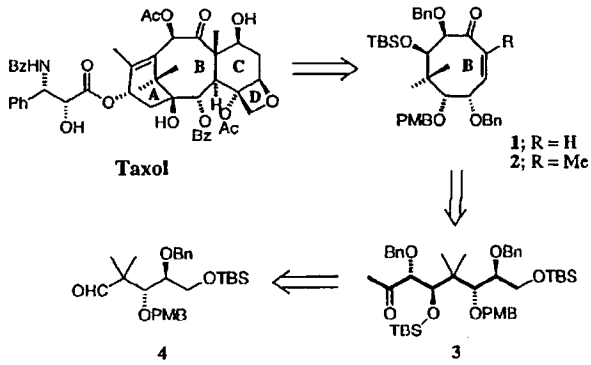




Total synthesis of Taxol, { Proc. Jpn. Acad. B, 1997. Chem. Eur. J. 1999.



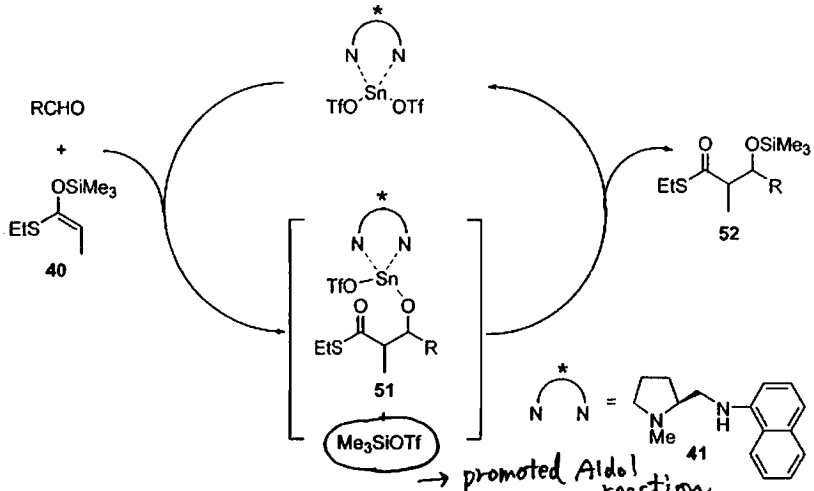
anti/syn = 80:20
93% ee
above condition



Scheme 1. Retrosynthesis of Taxol from optically active linear compounds **3** and **4**.

Catalytic Asymmetric Aldol Reaction

In order to keep TMSOTf in low concentration during the reaction, slow addition of substrates was performed.



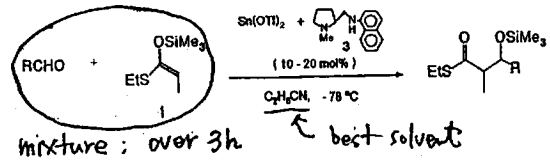
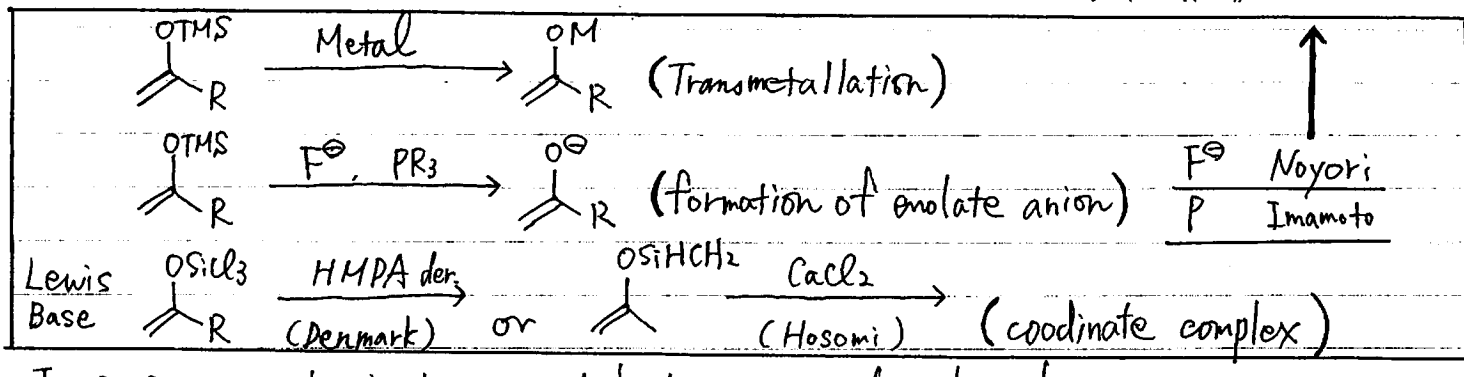


Table 2. Synthesis of syn-α-Methyl-β-hydroxythioesters

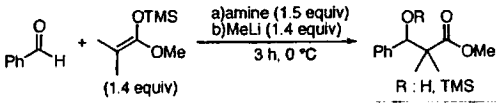
R	Cat./mol%	Yield / %	syn / anti	ee / %
Ph	20	77	93 / 7	90
p-Me Ph	20	75	89 / 11	91
(E)-CH_3CH=CH	20	76	96 / 4	93
(E)-$CH_3(CH_2)_2CH$=CH (4)	20	73	97 / 3	93
4	15	67	96 / 4	92
4	10	65	95 / 5	89
$CH_3(CH_2)_6CHO$	20	80	100 / 0	>98
c-$C_6H_{11}CHO$	20	71	100 / 0	>98

Scheme 28. A proposed catalytic cycle for the enantioselective aldol reaction.

Lewis Base Catalyst



In 2002, new Lewis base catalysts were developed.
Chem. Lett., 2002.



amine; Ph_2NH was best.

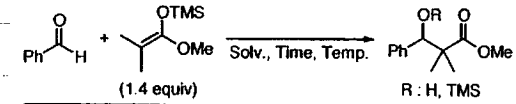
Various solvents were examined

THF; 81% yield	H:TMS = 2:1
DMF; quant	H:TMS = 1:35
Pyridine; quant	H:TMS = 1:6

The major product was TMS ether with indicated the possibility to perform a catalytic cycle.

Without cat.

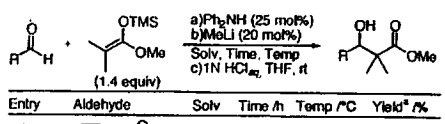
Table 2.

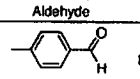
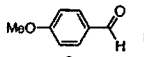
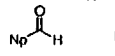


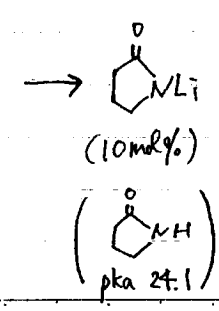
Entry	Solvent	Time /h	Temp. /°C	Yield[a] /%
1	DMF	1	0	84
2	DMF	1	-19	43
3	DMF	1	-45	trace
4	DMF	1	-78	trace
5	Pyridine	4	0	n.d.

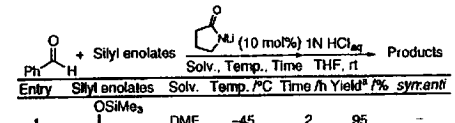
[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Table 3.



Entry	Aldehyde	Solv	Time /h	Temp /°C	Yield[a] /%
1		DMF	1	-45	96
2		Pyridine	7	0	98
3		DMF	1	-45	98
4		Pyridine	1	0	97
5[b]		DMF	1	-45	97
6[b]		Pyridine	6	0	95





Entry	Silyl enolates	Solv.	Temp. /°C	Time /h	Yield[a] /%	syn:anti
1		DMF	-45	2	95	-
2		DMF	-45	3	77	-
3		DMF	-45	3	trace	-
4		DMF	-45	3	42	1.7 : 1
5		DMF	0	3	50	1.6 : 1
6	E:Z = 5:1	Pyridine	-19→0	18	4	1.6 : 1
7		DMF	-45	3	88	2.7 : 1
8		DMF	0	3	95	2.4 : 1
9	E:Z = 1:9	Pyridine	-19→0	18	70	2.4 : 1

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

syn selective

↓

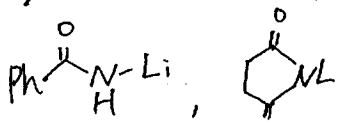
acyclic transition state

(Ph_2N-H pka 25.0)

5/12

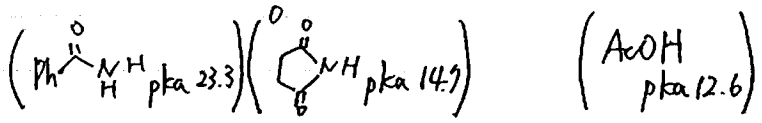
Michael addition

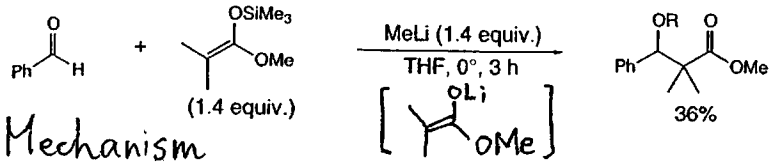
Chem. Lett., 2003.



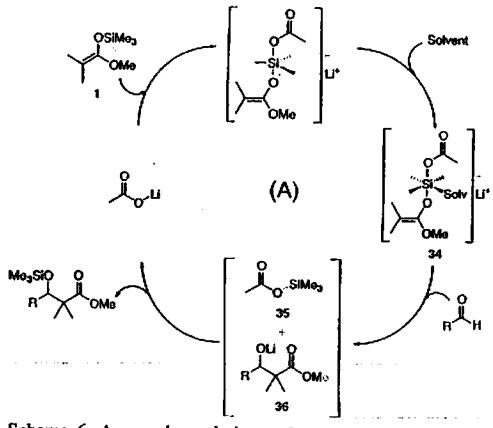
same pka → AcOLi

AcONa, AcOK were also effective.

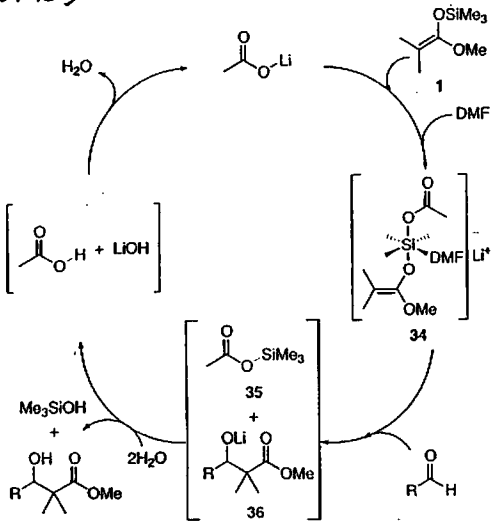




Mechanism

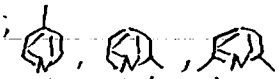


Scheme 6. Assumed catalytic cycle of AcOLi-catalyzed aldol reaction in anhydrous DMF or pyridine.



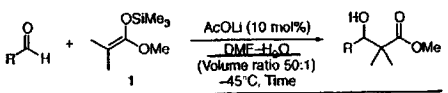
Scheme 8. Assumed catalytic cycle of AcOLi-catalyzed aldol reaction in water-containing DMF.

Solvent;



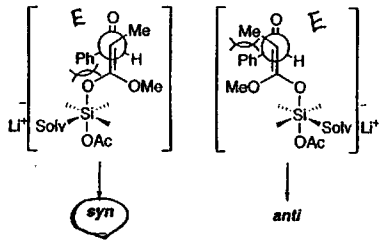
54% 18% trace

Table 1.



Entry	Aldehyde	Time /h	Yield[a] /%
1	O_2N–CHO	3	97[b] (69)
2	Cl–CHO	3	94 (63)
3	–O–CHO	3	99
4	–CHO	3	93[b]
5	–CHO	16	78 (84)
6	MeO–CHO	17	62 (94[b])
7	Ph–CHO	18	84[b] (65[b])
8	–CHO	2.5	97 (84)
9	OH, –CHO	14	84
10	–NH, –CHO	3	92[b]
11[c]	HO, –CHO	24	52

[a] Yield was determined by ^{1}H-NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses were yields under non-aqueous condition (ref 2b). [b] Isolated yield. [c] Reaction temperature was gradually warmed up to rt.



Comparison with Donmark's case, JACS, 1998, 120, 12990.

Acyclic transition state same as F⊖ and P casies.

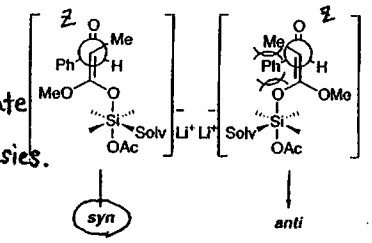
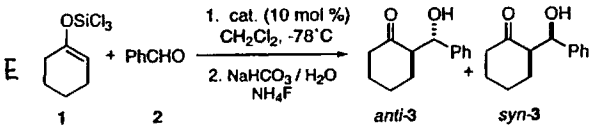


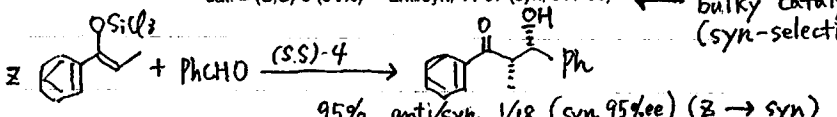
Fig. 1. Difference of reactivity between *E*- and Z-enolate.

Scheme 1



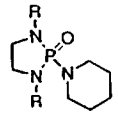
cat. = (*S*,*S*)-**4** (95%) anti/syn, 60 / 1 (anti, 92%ee) (E → anti)

cat. = (*S*,*S*)-**6** (94%) anti/syn, 1 / 97 (syn, 51%ee) ← bulky catalyst (syn-selective)



95% anti/syn 1/18 (syn 95%ee) (Z → syn)

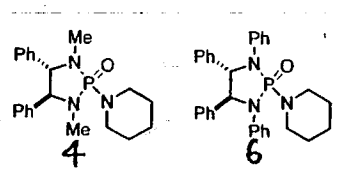
Mechanism

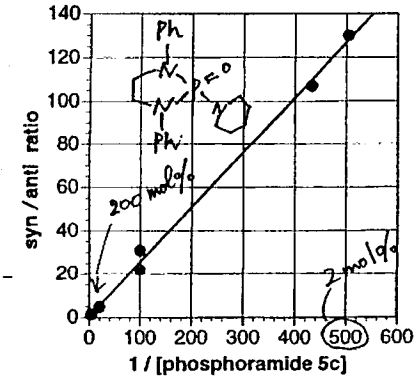


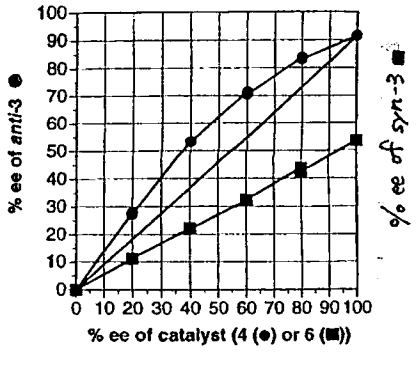
5a R = Me
5b R = iPr
5c R = Ph
5d R = 1-Np

phosphoramide	time, h	syn/anti[b]	yield,[c] %
5a	1.5	1/2.8	99
5b	6.0	27/1	93
5c	1.5	31/1	96
5d	1.5	40/1	95

[a] Reaction with 10 mol % **5** at −75 °C. [b] Determined by ^{1}H NMR analysis. [c] Isolated, purified product.







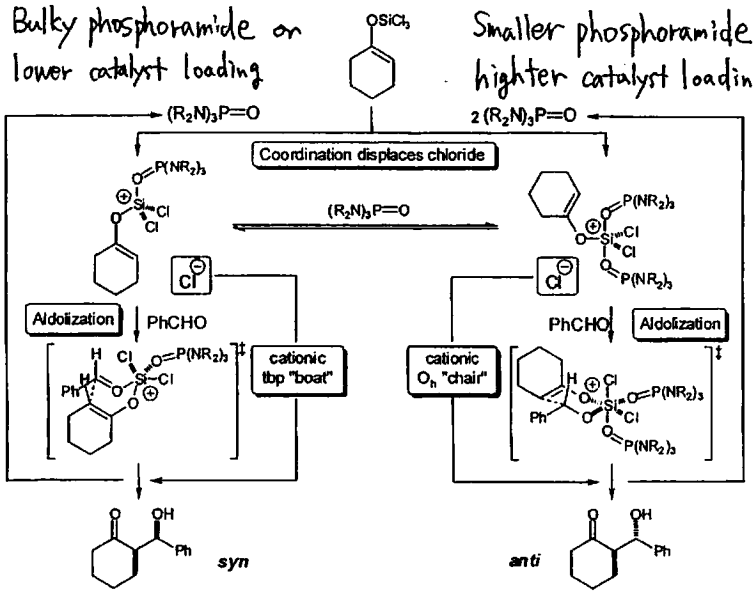
6/12

Transition state

Scheme 2. *Divergent Mechanistic and Stereochemical Pathways*

Bulky phosphoramide or lower catalyst loading

Smaller phosphoramide or higher catalyst loading



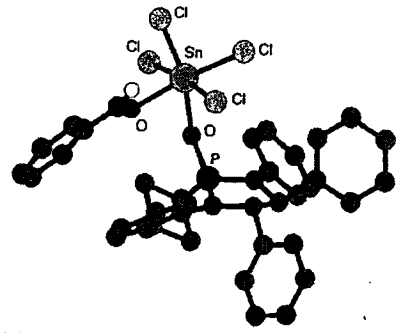
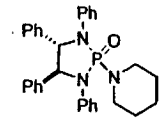
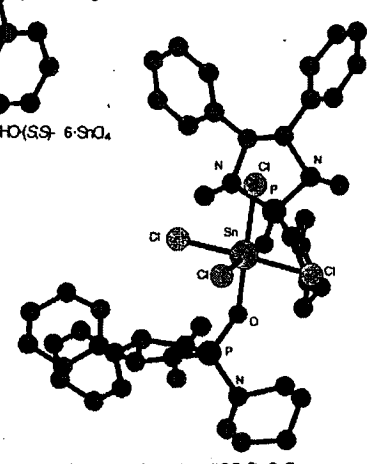
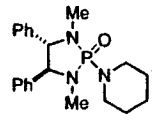


FIGURE 5. X-ray crystal structure of PhCHO·(*S,S*)-6·$SnCl_4$



(*S,S*)-6



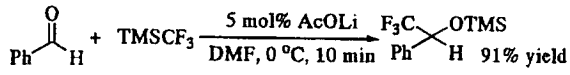


(*S,S*)-4

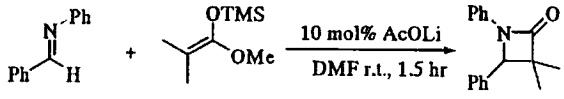
FIGURE 4. X-ray crystal structure $((S,S)\text{-}4)_2\cdot SnCl_4$

OTher examples

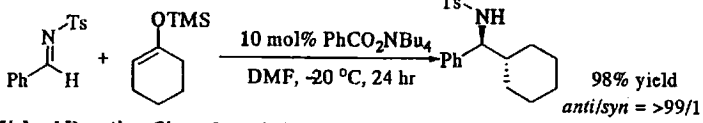
Trifluoromethylation, *Chem. Lett.*, 2005.



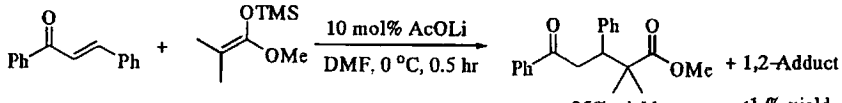
β-Lactam Synthesis *Chem. Lett.*, 2005.



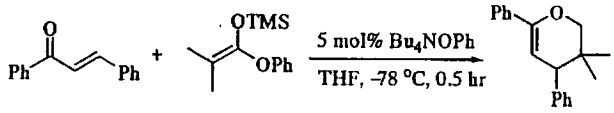
Mannich Reaction *Chem. Lett.*, 2005.



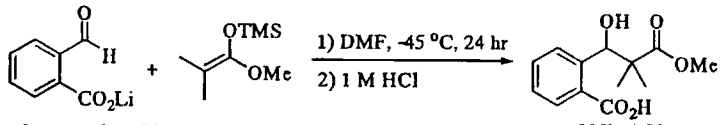
Michael Reaction *Chem. Lett.*, 2004.



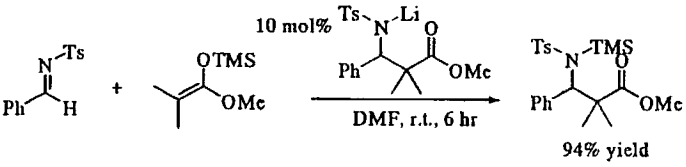
Pyranone Synthesis *Chem. Lett.*, 2004.

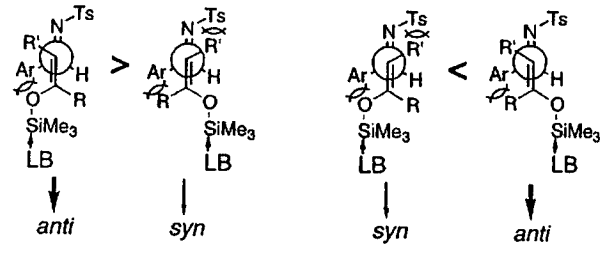


Self-promoted Aldol Reaction *Chem. Lett.*, 2004.



Product-catalyzed Mannich Reaction *Chem. Lett.*, 2004.

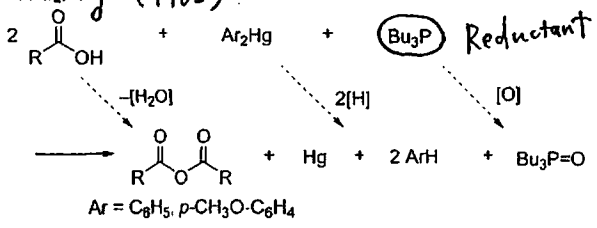




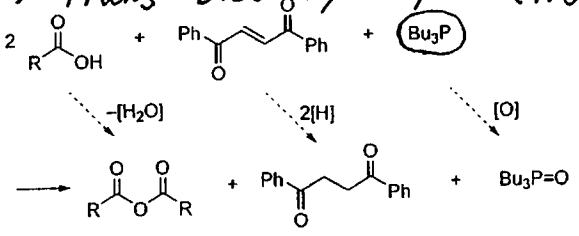
Scheme 1.

Oxidation-Reduction Condensation

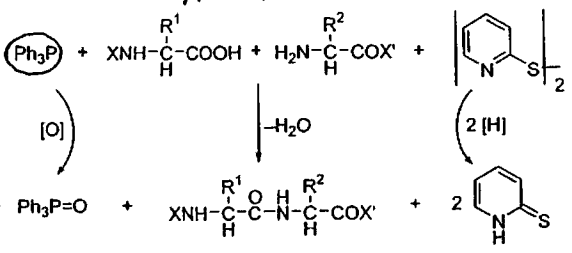
1) Ar_2Hg (1963)



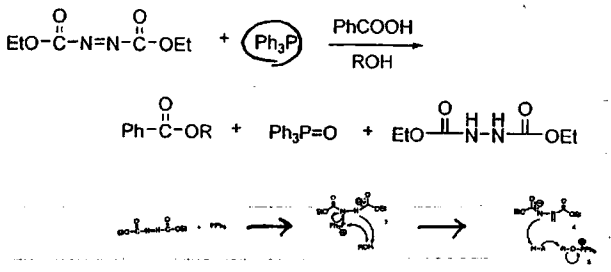
2) Trans-Dibenzoylethylene (1964)



3) 2,2'-Dipyridyl disulfide (1970)



4) DEAD (Mitsunobu-Reaction) (1967)



In 2002, Mukaiya developed new ox.-red. condensation using quinones. Chem. Lett., 2002.

(primary and secondary alcohols)

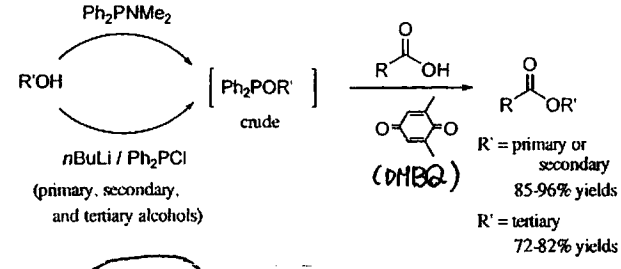
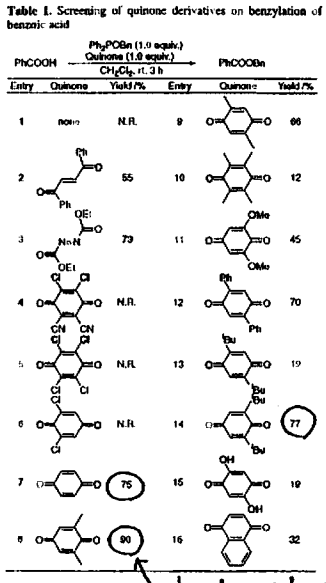
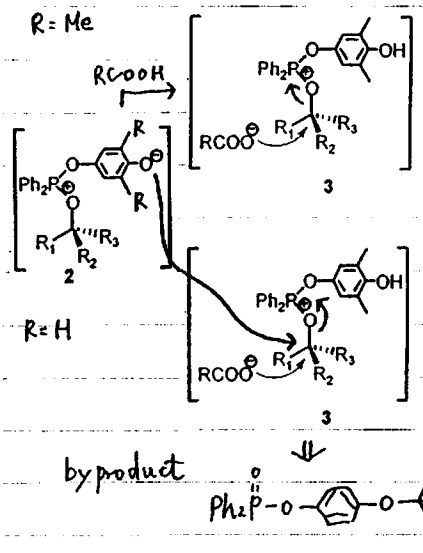


Table 1. Screening of quinone derivatives on benzylation of benzoic acid

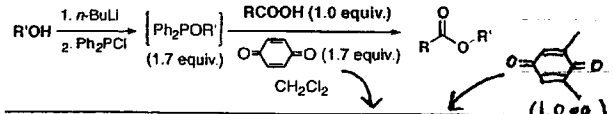


best oxidant



byproduct

Table 2. Esterifications of various carboxylic acids using sveral alcohols



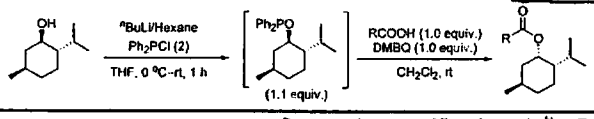
Entry	R'OH	RCOOH	Time /h	Yield /%	Yield /% [a]
1	BnOH	PhCOOH	1.0	98	98
2		p-MeO-C_6H_4COOH	1.0	95	95
3		p-NO_2-C_6H_4COOH	1.0	96	95
4		$PhCH_2CH_2$COOH	1.0	92	93
5		PhCH=CHCOOH	1.0	98	92
6		$CH_3(CH_2)_3$COOH	1.0	90	93
7	p-MeO-$C_6H_4CH_2$OH	PhCOOH	1.0	93	91
8	$CH_3(CH_2)_3$OH	PhCOOH	1.0	90	88
9		PhCOOH	3.0	90	94
10[b]		PhCOOH	3.0	91 (>99.9%)	86 (>99.9%)
11[b]		p-NO_2-C_6H_4COOH	3.0	96 (>99.9%)	95 (>99.9%)
12		PhCOOH	15.0	75	69
13			15.0	95	96
14			15.0	95	96
15[b]		PhCOOH	15.0	95 (>99%)	96 (>99%)

[a] Esterifications of various carboxylic acids with various alcohols using 2,6-dimethyl-1,4-benzoquinone. [Alcohols (1.1–1.2 equiv.), carboxylic acids (1.0 equiv.), 2,6-dimethyl-1,4-benzoquinone (1.0 equiv.)]

[b] Yields in the parenthesis are inversion.

JACS, 2003.

Table 20. Comparison of Esterification of Several Carboxylic Acids and (L)-(−)-Menthol by Means of Several Methods

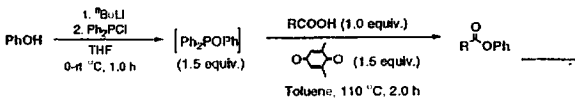


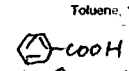
Entry	RCOOH		pK_a	Product	Present reaction Time/h	Present reaction Yield/%(a/%)	Mitsunobu reaction[b] Yield/%(a/%)	Tsunoda method[c] Yield/%(a/%)
1	o-NO_2-PhCOOH	6o	2.16	18a	3	54(>99.9)	33(>99.9)	—
2	p-NO_2-PhCOOH	6d	3.41	18b	1	87(>99.9)	84(>99.9)	26(0.082)
3	m-NO_2-PhCOOH	6p	3.47	18c	3	53(>99.9)	55(>99.9)	—
4[d]	m-NO_2-PhCOOH	6p	3.47	18c	2	86(>99.9)[d]		
5	o-MeO-PhCOOH	6q	4.09	18d	3	53(>99.9)	0	—
6	PhCOOH	6a	4.19	15g	3	86(>99.9)	27(>99.9)	91(10.6)
7	p-MeO-PhCOOH	6d	4.47	18e	1	88(>99.9)	17(>99.9)	98(>99)

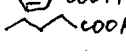
a) Inversion ratio. Diastereoselectivities determined by ^1H NMR spectroscopy. Corresponding isomer (15g', 18a', 18b', 18c', 18d', 18e') was prepared by using RCOCl (1.0 eq.), (L)-(−)-menthol (1.0 eq.), and Et_3N (1.0 eq.). b) (L)-(−)-menthol (1.0 eq.), RCOOH (4.0 eq.), PPh_3 (4.0 eq.), EtO_2CN=NCO_2Et (4.0 eq.), THF, rt, 24 h. c) (L)-(−)-menthol (1.0 eq.), RCOOH (1.5 eq.), $^tBu_3P$ (1.5 eq.), Me_2NOCN=$NCONMe_2$ (1.5 eq.), benzene, 60 °C, 24 h. d) (L)-(−)-menthoxydiphenylphosphine (1.5 eq.).

Synthesis of phenyl ester

Table 6. Esterifications of Various Carboxylic Acids with Phenol

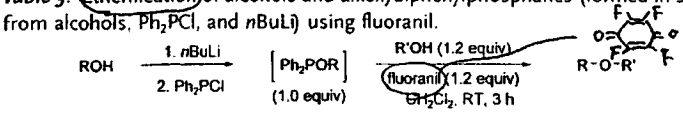


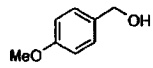
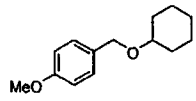
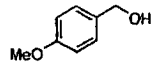
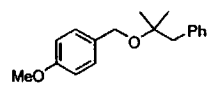
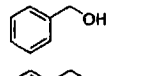
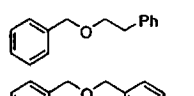
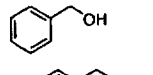
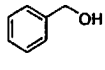
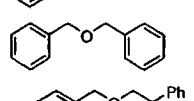
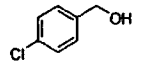
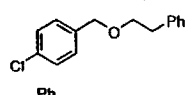
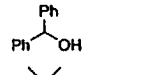
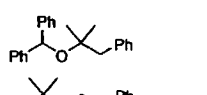
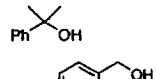
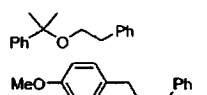
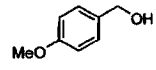
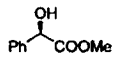
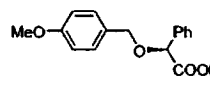
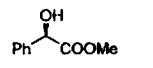
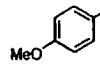
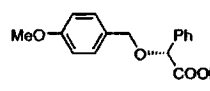
RCOOH;  88% yield

 90% yield

Chem. Lett., 2003. JACS, 2004.

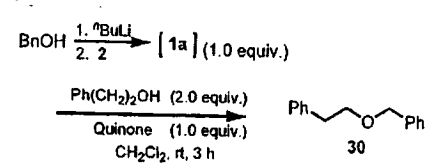
Table 3: Etherification of alcohols and alkoxydiphenylphosphanes (formed in situ from alcohols, Ph_2PCl, and *n*BuLi) using fluoranil.

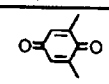
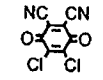
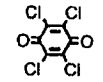
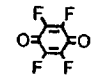


Entry	ROH	R'OH	Product	Yield [%]
1				90
2				94
3				92
4				94
5				75
6				90
7				92
8[a]			 Retention	83
9[b]			 Inversion	89

[a] 1.0 equivalent of fluoranil was used. No racemization was observed by HPLC (Daicel Chiralcel OD). [b] The ether was obtained with 95% inversion.

Table 7. Effect of Quinone Derivatives on Etherification of Phenylethyl Alcohol



entry	quinone	yield (%)
1		N.R.
2		18
3		6
4	 (fluoranil)	72

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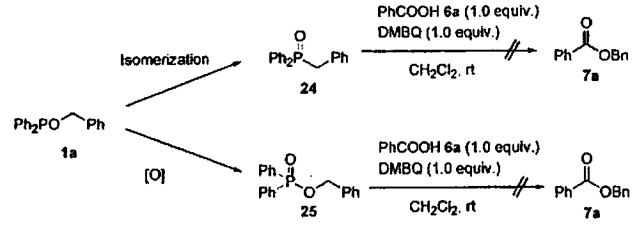
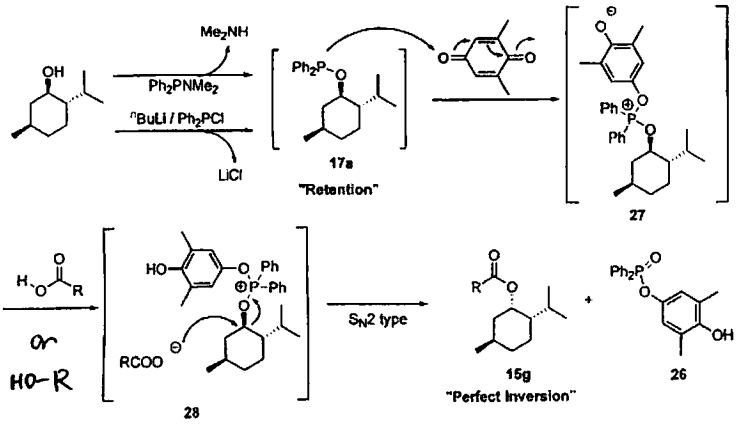
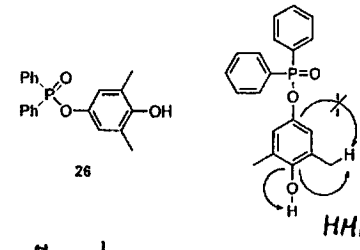
Mechanism



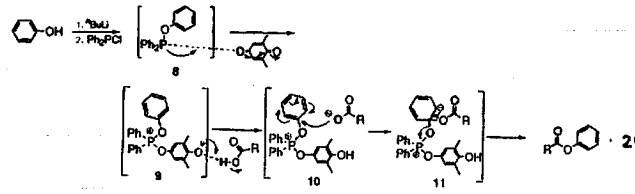
Scheme 6.



Scheme 8.

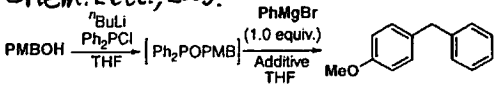


Phenyl ester



Other example

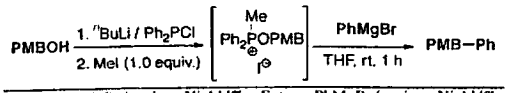
Chem. Lett., 2003.



Entry	Additive	Condition	Yield/%	Yield/%[a]
1	None	100 °C, 0.5 h	10	53
2[b]	None	100 °C, 0.5 h	10	—
3	2,6-Dimethyl-1,4-benzoquinone	−78 °C, 3 h	N.D.	
4	BnBr	50 °C, 2 h	38	Trace

[a] Yields of by-product (PPh_3). [b] 5 equivalent of PhMgBr was used.

BnBr → MeI

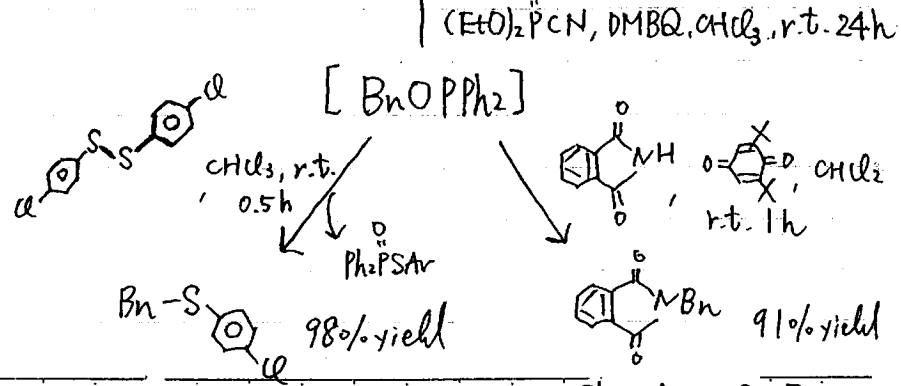


Entry	PhMgBr/equiv.	Yield/%	Entry	PhMgBr/equiv.	Yield/%
1	1.0	59	4	2.0	quant.
2	1.3	75	5	3.0	quant.
3	1.5	97			

Other Nucleophiles

Chem. Lett., 2004.

BnCN 82% yield



Chem. Lett., 2004. Chem. Lett., 2005.

Synthesis of sulfinimidoyl chloride.

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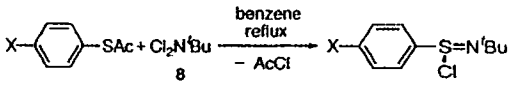
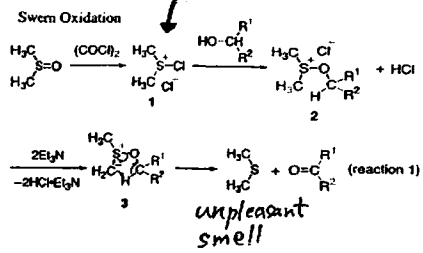


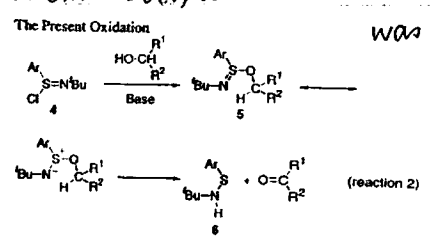
Scheme 2.

• Oxidation

unstable above -20°C

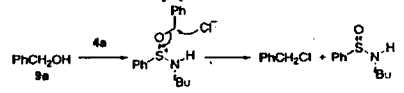


Chem. Lett., 2000.



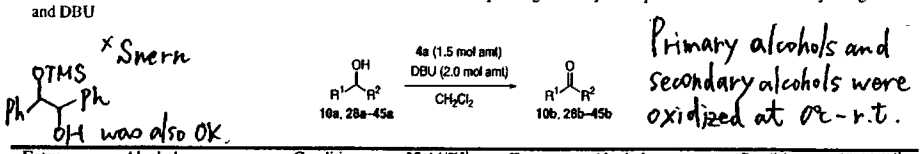
In 2000, new oxidation system was developed.

Benzylic and allylic alcohols were oxidized even at -78°C. Using these substrats, a small amount of alkyl chlorides were obtained at r.t. (ca. 5%).



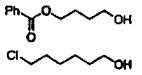
Scheme 3.

Table 3. Oxidation of Various Alcohols **10a** and **28–45a** to the Corresponding Carbonyl Compounds **10b** and **28–45b** by using **4a** and DBU



X Swern was also OK

Primary alcohols and secondary alcohols were oxidized at 0°C-r.t.

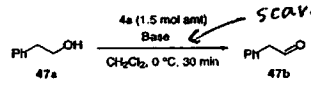
Entry	Alcohol		Conditions	Yield/%[a]	Entry	Alcohol		Conditions	Yield/%[a]
1	$Ph(CH_2)_3OH$	**28a**	0 °C, 30 min	94[b]	13		**39a**	rt, 30 min	49
2	$CH_3(CH_2)_7OH$	**29a**	0 °C, 30 min	97(98)[b,c]					
3	$BnO(CH_2)_3OH$	**30a**	0 °C, 30 min	87[c]	14		**40a**	rt, 30 min	98
4	$BnO(CH_2)_{10}OH$	**31a**	0 °C, 1 h	92[c]					
5		**32a**	0 °C–rt, 1 h	75 (77)[d]	15		**41a**	rt, 30 min	82
6		**33a**	0 °C, 30 min	76[e]	16		**42a**	rt, 30 min	78 74[f] 83[g]
7		**34a**	0 °C–rt, 1 h	99					
8		**35a**	rt, 30 min	82	17		**43a**	rt, 1 h	78
9		**10a**	rt, 30 min	> 99					
10		**36a**	rt, 30 min	91	18		**44a**	rt, 30 min	97
11		**37a**	rt, 30 min	87					
12		**38a**	rt, 30 min	82	19		**45a**	rt, 30 min	74

a) Determined by GC-analysis unless otherwise mentioned. b) Isolated yields of the corresponding 2,4-dinitrophenylhydrazones. c) Isolated yield. d) Reactions were quenched by addition of saturated aqueous sodium hydrogencarbonate. e) Reaction conditions: rt, 30 min. f) **4b** was used instead of **4a**. g) **4c** was used instead of **4a**.

Mechanism of chloride formation.

47b was decomposed under basic condition

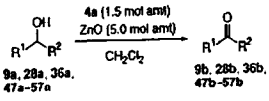
Table 4. Effect of Solid Bases on the Oxidation of 2-Phenylethanol (**47a**) to Phenylacetaldehyde (**47b**) by Using **4a**

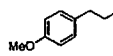


scavenger of HCl

Entry	Base	Yield/%[a]
1	DBU (2 mol amt)	24
2	MS3A (1 g/mmol)	21
3	MS4A (1 g/mmol)	73(56)[b]
4	MS5A (1 g/mmol)	35
5	CsF (5 mol amt)	6
6	MgO (10 mol amt)	58
7	CaO (5 mol amt)	56
8	BaO (5 mol amt)	70
9	TiO_2 (5 mol amt)	0
10	NiO (5 mol amt)	trace
11	CuO (5 mol amt)	37
12	ZnO (5 mol amt)	91(35)[c] (0)[d]
13	Al_2O_3 (5 mol amt)	trace

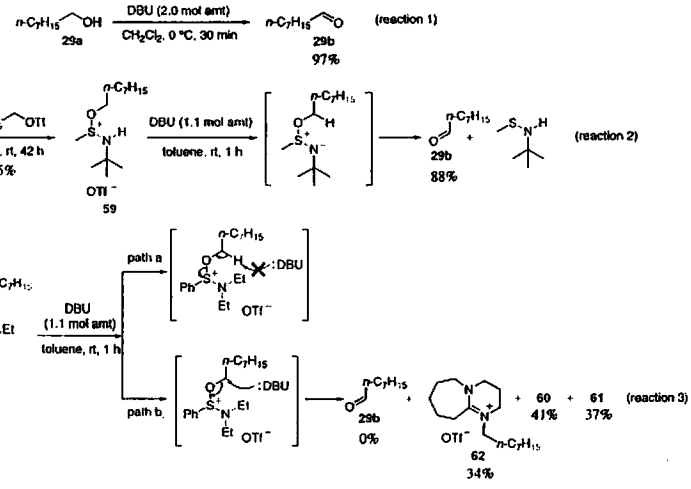
a) Determined by GC-analysis using an internal standard. b) MS4A (3 g/mmol) was used. c) Zinc oxide (2 mol amt) was used. d) **4a** was not used.



Entry	Alcohol		Conditions	Yield/%[a]
1		**47a**	0°C, 30 min	91 (24)
2			Swern Oxidation	23[b]
3			PDC	31
4	**47a**		TPAP/NMO	trace
5			Dess–Martin Oxidation	96
6		**48a**	0 °C, 30 min	94 (0)
7	**48a**		Swern Oxidation	38[b]
8		**49a**	0 °C, 30 min	91
9		**50a**	rt, 30 min	66 (62)
10		**51a**	0 °C, 30 min	84[d]

BCSJ, 2002.

Mechanism



Scheme 6.

Further, this oxidation method has some advantages over Swern oxidation. (i) The oxidizing agent **4** is quite stable and can be used directly without any treatment. (ii) The reaction conditions are not required to be strictly controlled and the oxidation reaction can be conducted even at room temperature. (iii) The oxidation reaction is applicable to the oxidation of acid-labile compounds since the present reaction can be conducted under basic conditions.

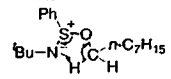
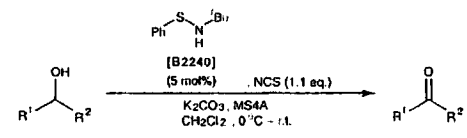


Fig. 1.

commercially available from TCI.

アルコールの新しい酸化触媒 10/12

N-tert-Butylbenzenesulfenamide 1g 7,850円 [B2240]

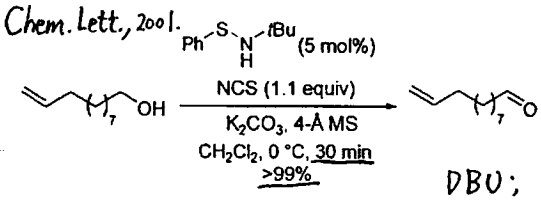


Entry	Alcohol	Conditions	Yield/%
1		r.t., 30 min	>99
2		0°C, 1 h	>99
3		r.t., 1 h	93
4		r.t., 1 h	>99

文献) T. Mukaiyama, J. Matsuo, D. Iida, H. Kitagawa, *Chem. Lett.* 2001, 846; 東京化成工業(株), 特願 2001-247454.

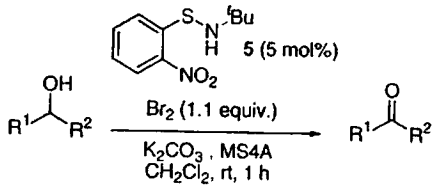
Catalytic reaction was developed.

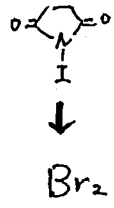
Chem. Lett., 2001.



DBU; 86%

Chem. Lett., 2003.





catalytic cycle.

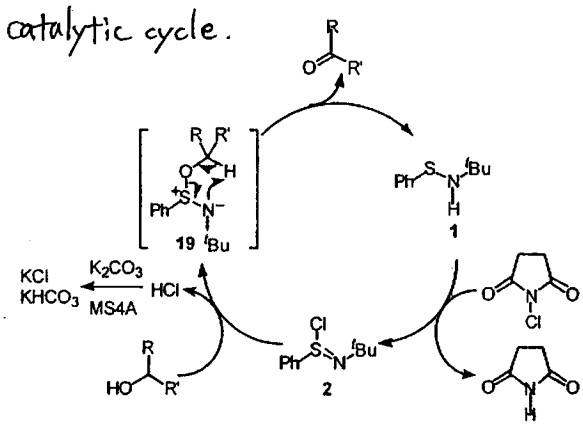
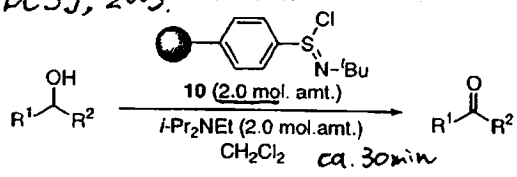


Figure 2. Assumed catalytic cycle of **1**-catalyzed oxidation of alcohols with NCS in the coexistence of K_2CO_3 and MS4A.

Polymer-supported sulfinimidoyl chloride

BCSJ, 2003.

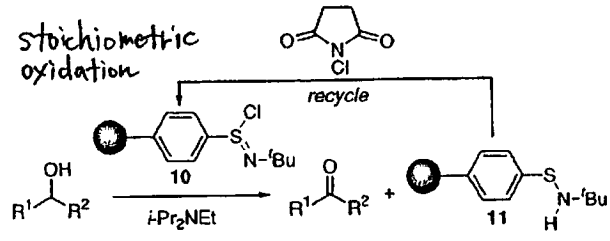


↕Stoichiometric reaction

The catalyic oxidation required a longer reaction time in comparison to the case of monomeric sulfenamide (ca. 1h – 16h)

Table 3. Oxidation of Alcohols by Recycling Polymer-Supported Sulfinimidoyl Chloride **10**

stoichiometric oxidation



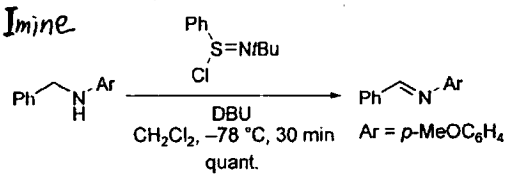
Alcohol	Yield/%[a] Recycle:	1st	2nd	3rd
Ph–CH(OH)–Me		97	quant.	98
Ph–C6H10–OH		95	98	87

a) Yield of the corresponding carbonyl compound.

Other examples

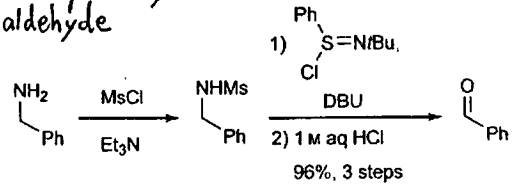
Chem. Lett., 2001.

Imine



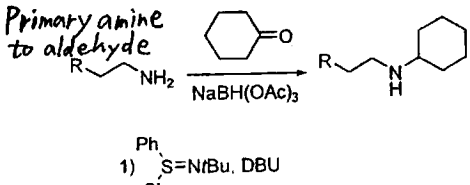
Chem. Lett., 2001.

Aromatic primary amine to aldehyde



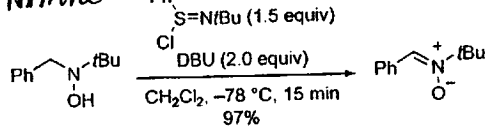
Chem. Lett, 2001.

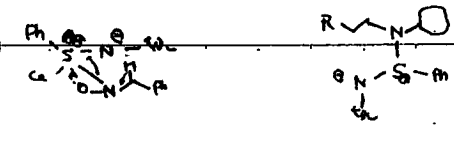
Primary amine to aldehyde



Arch. Org. Chem., 2001.

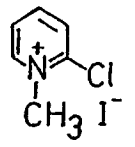
Nitrone



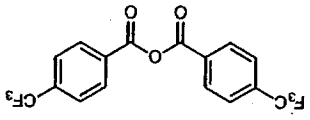


• Condensation Reagent

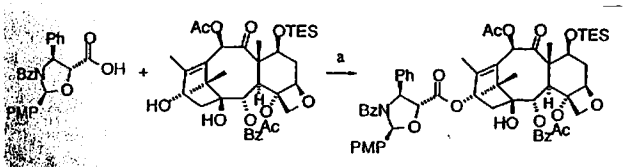
Mukaiyama developed several condensation reagent.



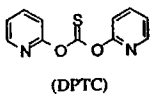
Chem. Lett., 1976.



Chem. Lett., 1994.



a) DPTC (6.0 eq.), DMAP (2.0 eq.), toluene, 73 °C, 95% based on 93% conversion.

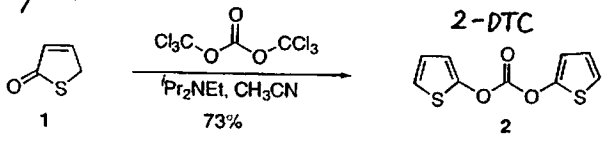


(DPTC)

Chem. Lett., 1998.

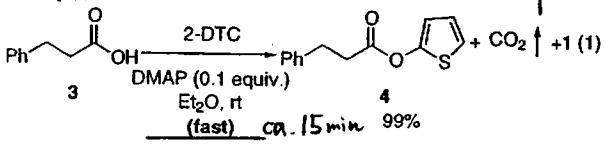
In 2004, new reagent was developed.

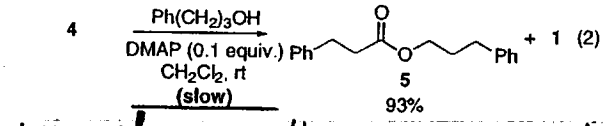
Synthesis of 2-DTC



Scheme 1. Synthesis of di-2- thienyl carbonate.

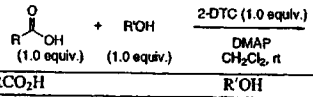
DMAP was needed in both two steps





Chem. Lett., 2004.

Table 2. Esterification using various carboxylic acids.



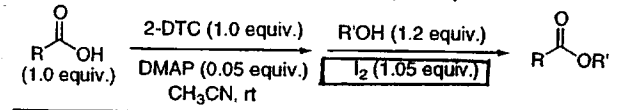
Entry	RCO_2H	R'OH	Time /h	Yield /%
1	$PhCH_2CH_2COOH$	$Ph(CH_2)_3OH$	6	94
2	$CH_3(CH_2)_3COOH$	$Ph(CH_2)_3OH$	8	91[a]
3	*m*-$PyCH_2CH_2COOH$[b]	$Ph(CH_2)_3OH$	6	84
4	$PhMeCHCOOH$	$Ph(CH_2)_3OH$	6	79
5	$PhMeCHCOOH$	*c*-$C_6H_{11}OH$	11	83
6	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_3OH$	11	87
7	*c*-$C_6H_{11}COOH$	Ph_2CHOH	22	90[a]
8	$Ph_2CHCOOH$	$Ph(CH_2)_3OH$	11	95[a]
9	$Ph_2CHCOOH$	$Ph(CH_2)_2CH(OH)CH_3$	22	86[a]

[a] 1.2 equivalent of alcohol was used. [b] 3-pyridinepropionic acid.

Chem. Lett., 2004. Various additives were examined.

Table 3. Esterification using various carboxylic acids and alcohols

I2 was best additive.



Entry	RCO_2H	R'OH	Time ( )[a] /h	Yield( )[a] /%
1	$CH_3(CH_2)_3COOH$	$Ph(CH_2)_3OH$	0.5	86
2	$PhMeCHCOOH$	$Ph(CH_2)_3OH$	2 (6)	93[b] (79)
3	$PhMeCHCOOH$	*c*-$C_6H_{11}OH$	2 (11)	81 (83)
4	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_3OH$	0.5 (11)	91 (87)
5	*c*-$C_6H_{11}COOH$	$Ph(CH_2)_2CH(OH)CH_3$	0.5 (48)	93[b] (69)
6	Me_3CCOOH	$Ph(CH_2)_3OH$	0.5 (22)	91 (N.D.)
7	Me_3CCOOH	$Ph(CH_2)_2CH(OH)CH_3$	0.5	81
8	(*E*)-$PhCH{=}CHCOOH$	$Ph(CH_2)_3OH$	0.5 (22)	88 (37)
9	(*E*)-$PhCH{=}CHCOOH$	$Ph(CH_2)_2CH(OH)CH_3$	0.5	83
10	$PhCOOH$	$Ph(CH_2)_3OH$	6 (22)	89 (33)
11	*p*-$MeOPhCOOH$	$Ph(CH_2)_3OH$	0.5 (22)	87 (3)

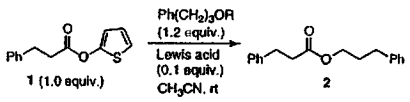
[a] Values in parentheses are those obtained previously in CH_2Cl_2 in the presence of 0.1 equiv. of DMAP.[9]

[b] Reactions were performed by using 0.1 equiv. of DMAP and 1.1 equiv. of iodine and CH_2Cl_2 as a solvent.

Catalytic amount of $Hf(OTf)_4$ was also effective.

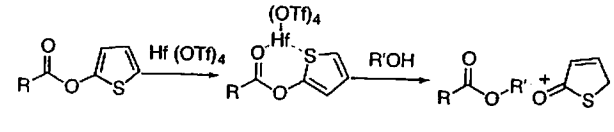
Chem. Lett, 2005.

Table 1. Esterification of 2-thienyl 3-phenylpropionate by using silyl ether or alcohol using various Lewis acids

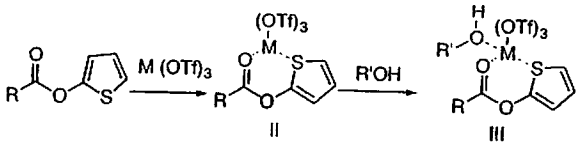


Entry	Lewis acid	R=H Time/h	R=H Yield/%
1	BF_3-OEt_2	4	7
2	$TiCl_4$	4	17
3	$SnCl_4$	4	16
4	$HfCl_4$	4	66
5	$Mg(OTf)_2$	4	2
6	$Cu(OTf)_2$	4	6
7	$Sc(OTf)_3$	4	29
8	$Hf(OTf)_4$	0.5	92
9	$La(OTf)_3$	4	N.R.
10	$Gd(OTf)_3$	4	4
11	$Yb(OTf)_3$	4	7

The mechanism of the activation of thienyl ester with iodine is not clear.



II



III

Appendix

Mukaiyama's philosophy

In basic science it is critical to find the first approach ("seeds-oriented" work), but it is equally important to optimize the approach and to develop new systems ("needs oriented"). In either case, ample time and energy need be invested before a chemist can garner anything useful. Once the fundamental target is reached, however, the whole process appears so easy that anyone else could have done it, like the episode of "Columbus' egg". However, to win through to the result, a researcher must go through unrewarding months and years of making hypotheses and repeating experiments, and this is exactly what makes a chemist. The most important thing here is "not to imitate others". If someone has already been involved with the topic, dare not to stick to the same topic, but find something of your own. This is our code, which should never be forgotten.

Experience and the accumulation of experiences play a very important role in pursuing research work. If a mature hypothesis does not lead you to a satisfactory result, just try once more from the beginning and continue to do the experiments. You will then eventually find an interesting clue, unless you give up half way. Chemistry is still more or less unpredictable. Wisdom learned not from books or what others said but from one's own experience—which I call "chemical wisdom"—will become a motivating force for associating problems with questions that give you a different idea. Those who have accumulated a lot of such "chemical wisdom" should be able to formulate a seminal hypothesis by the association of small clues. By overcoming difficulties without compromise, hard and steady work done (especially at the time of one's youth) will give you love for your work and will furnish you with "chemical wisdom", and consequently will lead you to successful later development.

The fun of chemistry is in its unexpectedness. There are times when you come to face-to-face with an unexpected phenomenon while carrying out experiments. You simply have to be sufficiently aware and open to accept the seemingly unbelievable. There are still many more valuable ideas remaining to be discovered. The question is how to find them and how to develop them into new possibilities.

基礎科学を専攻する者は、0 から 1 を拾い出すシーズ指向の仕事が第一の課題であるが、同時に、2 から 5 、5 から 8 へ発展させる、ニーズ指向の仕事をいかにして自分のユニークな考えによって展開できるかを心がけることも、また極めて重要なことである。これらの仕事をやり遂げるためには、非常に多くの時間と労力が必要であり、化学者は絶えず仕事上の仮説の立案と実践の繰り返しによって、より良い道を見つけていくのである。答えが出ると、これはコロンブスの卵であり誰にでも理解できることになるが、結論に辿り着く課程を振り返ってみると、そこには研究の歴史が残され、化学者の仕事の醍醐味が感じられる。ここでは、"物まねはしない"ことが鉄則である。人がやっていたら、それを捨ててでも自分にしかできない新しいことを求めていくことこそ最も大切な"こころ"であろう。

過去の経験の蓄積は、個々の研究を進める上で重要なものである。仕事上の仮説に基づいて具体的なアプローチが始まるが、化学は未だに unpredictable な要素が多いので、必ずしも常に予期した通りには進まない。もし予想に反した結果が出たら、また次の仮説を考え、それに基づいて実践する、この繰り返しのうちに最終の目的に到達する。

この"仕事上の仮説"を考え出すには、"活きた知恵"すなわち、本当に仕事に打ち込んで身に付けた知恵、すなわち、本で読んだことや人から聞いたことでなく、自分自身の経験によって体得した知恵、が必要になる。これが"連想"によってその時の仕事上の問題点と結びあって、新しいアイデアが生まれる。この"活きた知恵"が十分蓄積されている研究者は、小さいヒントから連想力によって、大きな実りに結びつく仮説を考え出すことができる。従って、若い人は特に、"徹底して仕事をする"、難しい問題をへこたれずに追求するうちやがて仕事が好きになり、知恵も育ち、仕事に熱中できるのでその結果として大きな展開に結びつけることができることを肝に銘じて欲しい。

化学の面白さは、その"意外性"という一面にもある。実験・実行を続けるうちに、思いもよらない現象(unexpected phenomenon)に遭遇することがあり、その驚きは感性によって拾い上げられ、活きた知恵によって展開される。また、考えても見なかったことに出会った時、それを素直に受け入れる姿勢も不可欠である。先入観や固定観念にとらわれず、今見たもの、観察したものの不思議さに素直に取り組んでみると、思わぬシーズが隠された宝の山であったりする。まだまだ誰も気が付かない大切なシーズは"無尽蔵"に残されている。それをいかに見つけだし、新しい可能性に結び付けるかが、化学のこれからの発展の鍵を握るポイントであり、これから先の化学を背負う若いみなさんの夢につながるものと確信している。

Angew. Chem. Int. Ed. 2004, 43, 5590.
"Review"