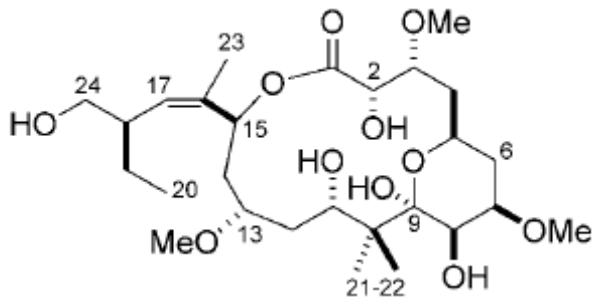
Feb. 9th 2011
Y-F, Wang

Total Synthesis of (+)-Peloruside A



1a: (+)- peloruside A

Total synthesis:
E.N. Jacobsen *et al.ACIE,* **2010,** *49,* 6147-50

Other total synthesis route:
J.K. De Brabander *et al. ACIE,* **2003,** *42*, 1648-52 ((-)-peloruside)
D.A. Evans *et al. JACS,* **2009**, *131*, 3840-41
T.R. Hoye *et al. ACIE,* **2010**, *49*, 6151-55

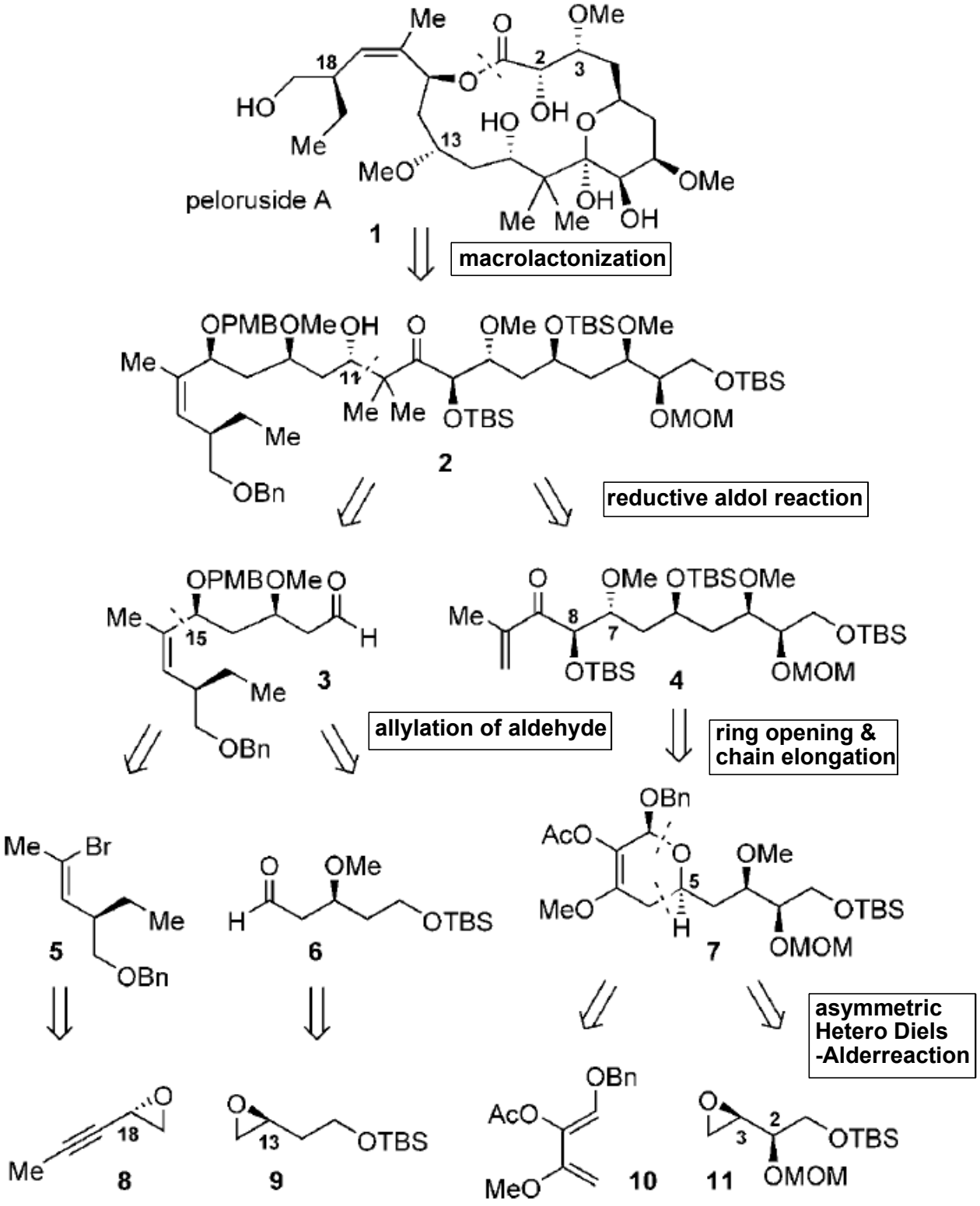
Isolation: from *Mycale hentscheli* (a marine sponge of the Pelorus Sound in New Zealand), and it also produces two other useful secondary metabolites mycalamide A (antiviral&antitumor), pateamine (imminosuppression).
(L.M. West, P.T. Northcote, *J. Org. Chem*. **2000**, *65*, 445-449)

Stuctural feature:
Relative stereochemistry determined by Northcote et al.(*JOC,* **2000**, *65*, 445-449); absolute one was determined by J.K De Brabander et al.(*ACIE*, **2003**, *42*, 1648-52).
Polyoxygenated 16-membered macrolide containing 10 stereogenic centres. Becides above, highly substituded pyranose ring, Z-configured trisubstituded olefin and sterically crowded C8-C11 unit would also become challenges in synthesis.
Peloruside A and B is differentiated in the methylation at C15.

Biological activity:
A potent antitumor agent with microtubule-stabilizing activity, induces cell-cycle arrest in the G2-M phase acting in the similar manner as paclitaxel(Taxol), but in different binding site. The C24 primary alchohol and pyranose ring are reported to be essential in peloruside's bioactivity.
(J.H. Miller *et al. Cancer Res.* **2002**, *62*, 3356-60; J.F. Diaz *et al. ChemBioChem*. **2010**, *11*, 1669-78)

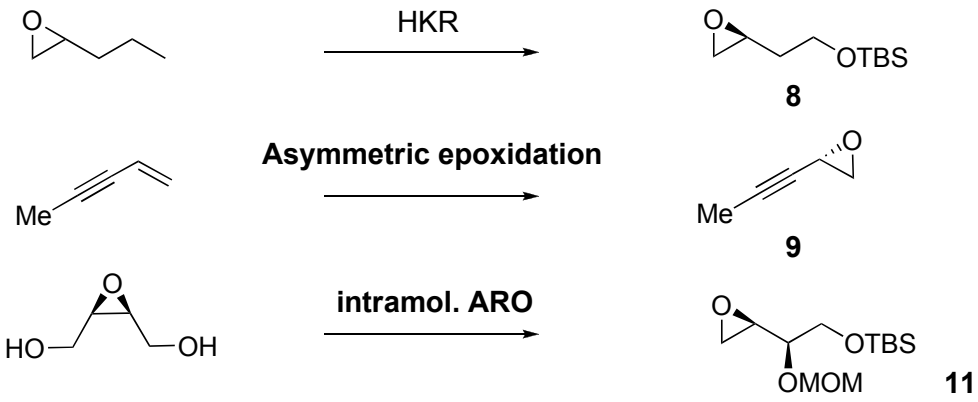
Contents:

1.Retrosynthetic analysis



Key strategy:

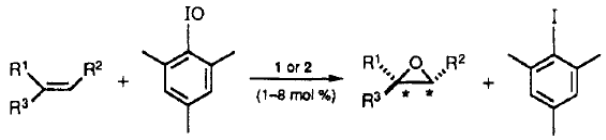
1. Construction of three different enantioenriched epoxides (**8**,**9** and **11**) by using catalytic asymmetric epoxidation and series of asymmetric ring opening (ARO) reaction of nonoptical epoxide (e.g. Asymmetric Payne rearrangement, Hydrolytic kinetic resolution)

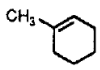
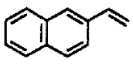


2. Asymmetric hetero DIels-Alder reaction in synthesizing multisubstituded pyranose ring.
(In this route, by using tridentate chromium(III)-salen catalyst)

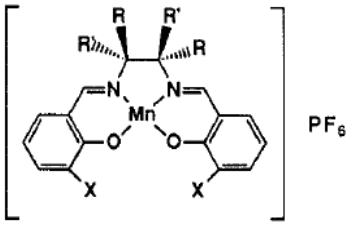
2. Jacobsen-Katsuki Epoxidation ~Focus on Metal-Salen Complexes (I)~

Initial report (1) E.N. Jacobsen et al. J. Am. Chem. Soc. 1990, 112, 2801-03;

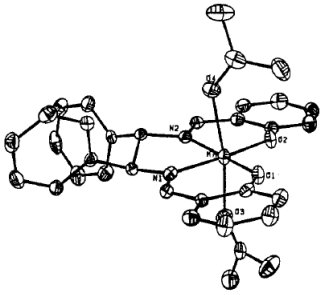


entry	olefin[a]	catalyst[b]	yield,[c] %	ee, %	config[d]
1		(*R*,*R*)-**2**	50	59	1*R*,2*S*-(−)
2		(*S*,*S*)-**1**[g]	63	33	*S*,*S*-(−)
3		(*S*,*S*)-**1**	93[h]	20	1*S*,2*S*-(−)
4		(*R*,*R*)-**2**[g]	75	57	*R*-(+)
5		(*R*,*R*)-**2**[g]	72	67	(+)[j]
6		(*R*,*R*)-**2**	52	93	(−)[j]
7		(*R*,*R*)-**2**	73	84	1*R*,2*S*-(−)
8		(*R*,*R*)-**2**	72	78	1*R*,2*S*-(+)
9		(*R*,*R*)-**2**	36	30	*R*-(+)

[a] Reactions were run at 25 °C unless otherwise noted. [b] Reactions with **1** were run in CH_3CN, while those with **2** were run in CH_2Cl_2. [c] Isolated yields based on olefin. [d] The sign corresponds to that of $[\alpha]_D$. Absolute configurations and ee's were established as described in the supplementary material. [e] These values correspond to the highest ee's previously reported for nonenzymatic catalysts. [f] From ref 1c. [g] Reaction run at 5 °C. [h] Based on 76% conversion of *trans*-β-methylstyrene. [i] From ref 1a. [j] Absolute configuration not ascertained. [k] From ref 1f.



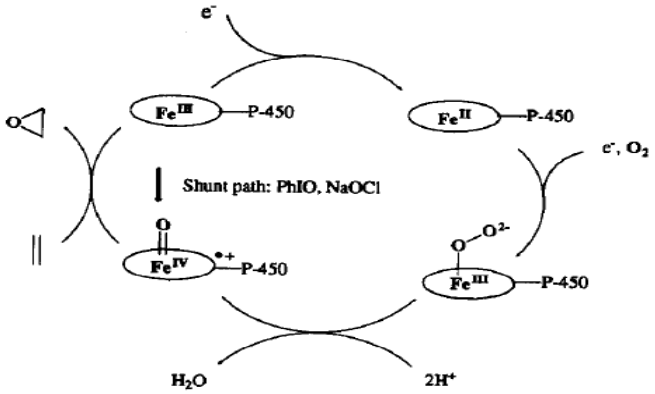
(*S*,*S*)-**1**: R = Ph, R' = H, X = H
(*R*,*R*)-**1**: R = H, R' = Ph, X = H
(*R*,*R*)-**2**: R = H, R' = Ph, X = ^{t}Bu



ORTEP view of the cation of (S,S)-**1**-[acetone]$_2$

Catalytically Active Spiecies in Jacobsen-Katsuki Epoxidation

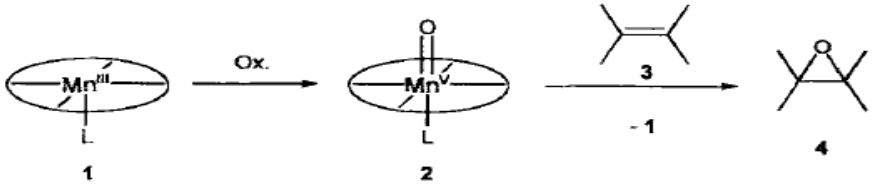
Remembering a well-known and ubiquitous oxo-transfer model in living body--- **cytochrome P-450**, which possesses an iron-porphyrin active site wherein the molecular oxygen is activated as a form of iron-oxo species and then transfered to substrate.



Catalytic cycle of cytochrome P-450

Groves J.T. et al. Adv. Inorg. Biochem. 1979, 119-45

Proposal: Formation of Mn-oxo complexes 2 in the Jacobsen-Katsuki epoxidation



Though no direct observation of Mn^{V}-oxo complex was achieved, the similar Cr^{V}-oxo model was unambiguously clarified by Kochi et al. (*JACS*, **1985**,*107*, 7606-17) and the direct indentification of Mn^{V}-oxo complex with electrospray tandem mass spectrometry was achieved by Plattner et al. (*ACIE,* **1997**, *36*, 1718-19)

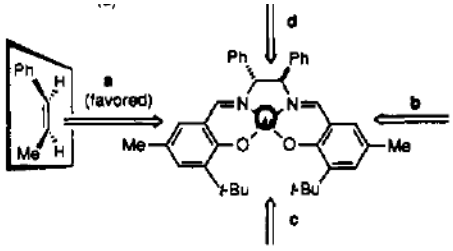
Studies on enantioselectivity

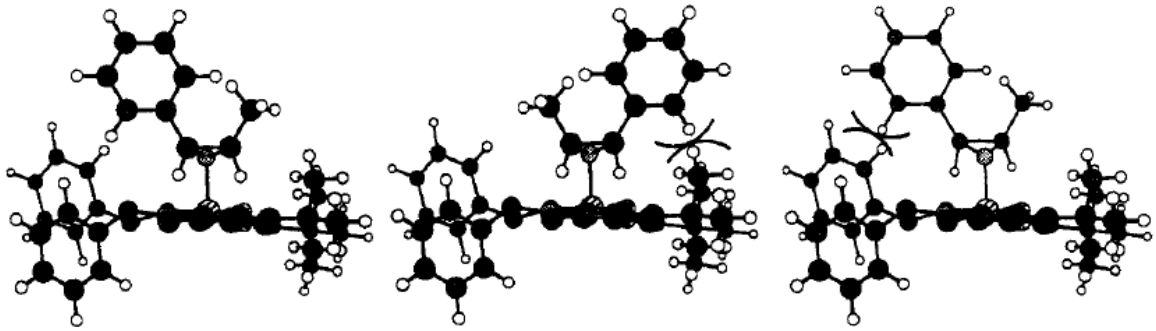
From the result on fomer page, three structural features of the catalyst 2:

(1) the presence of bulky ^{t}Bu-groups to prevent substrate away from the diimine bridge (approach c)

(2) the dissymmetry of the diimine bridge, which defavors attack from the side syn to the phenyl group

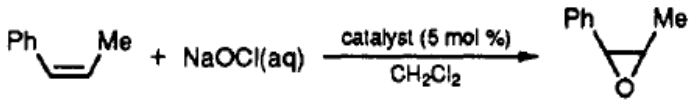
(3) the steric bulk of diimine's two phenyl groups disfavors attack from the other side of diimine bridge





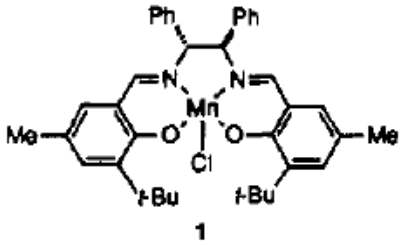
approach a (favored) approach c (disfavored) approach b (disfavored)

(2) E.N. Jacobsen et al. J.Am. Chem. Soc. 1991, 113, 7063-64

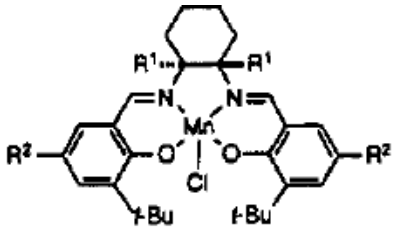


entry	catalyst	yield,[a] %	ee, %	epoxide confign
1	(*R*,*R*)-**1**	88	84	1*R*,2*S*-(+)
2	(*S*,*S*)-**2**	54	49	1*S*,2*R*-(−)
3	(*S*,*S*)-**3**	87	80	1*S*,2*R*-(−)
4	(*S*,*S*)-**4**	56	55	1*S*,2*R*-(−)
5	(*S*,*S*)-**5**	81	92	1*S*,2*R*-(−)

[a] Determined by GC by integration against an internal quantitative standard.



1



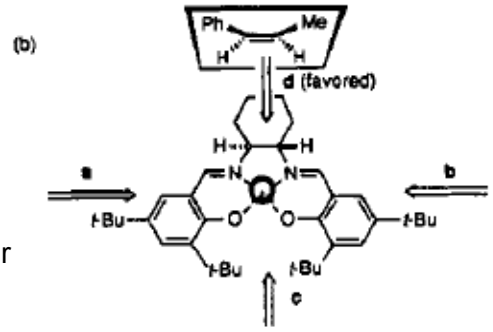
2: R^1 = Me, R^2 = Me
3: R^1 = H, R^2 = Me
4: R^1 = Me, R^2 = t-Bu
5: R^1 = H, R^2 = t-Bu

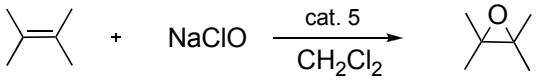
The possible reason for steric inversion:

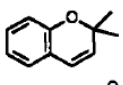
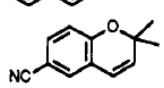
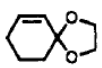
In case of cat. 2~5, it is less hindered than 1 in the vincinity of the diimine bridge, and this arise competitive attack from approach d.

Further more, when changing Me on the Salen's benzen ring into much bulkier t-Bu(cat 5), attack from approach a was blocked thus approach d become dominant pathway.

Face selectivity may be attributed to the axial hydrogen's hinder to the larger substituent.





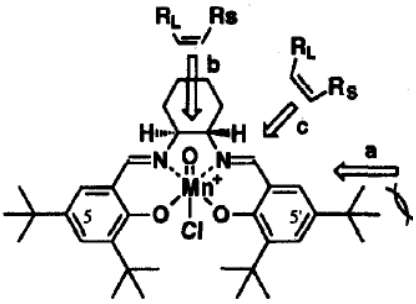
entry	olefin	epoxide yield,[b] %	ee,[c] %	equiv of **5** required for complete reactn
1	Ph, Me	84	92	0.04
2	*p*-ClC_6H_4, Me	67	92	0.04
3		72	98	0.02
4		96	97	0.03
5		63	94	0.15
6[d]	Ph, CO_2Me	65[e]	89	0.10

[a] Reactions were run at 4 °C according to the general procedure outlined in ref 4. [b] Isolated yields based on olefin unless otherwise indicated. [c] Determined by analysis of the isolated epoxides by ^1H NMR in the presence of $Eu(hfc)_3$ and by capillary GC using a commercial chiral column (J & W Scientific Cyclodex-B column, 30 m × 0.25 mm i.d., 0.25-μm film). All reactions were run in duplicate with both enantiomers of **5**, and ee values were reproducible to ±2%. [d] Reaction carried out in the presence of 0.4 equiv of 4-phenylpyridine *N*-oxide. [e] Yield determined by GC.

* Two proposal for approach of olefins to the Mn-oxo salen complex **5**

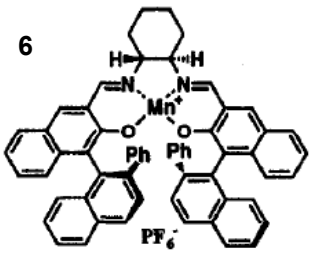
Jacobsen's proposal:

The bulky t-Bu groups blocks all the possible access direction except the diimine bridge side (b). At the same time, the axial hydrogen atom on diimine bridge directed away the larger sub -stituent on the olefin.

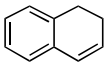
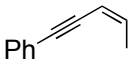


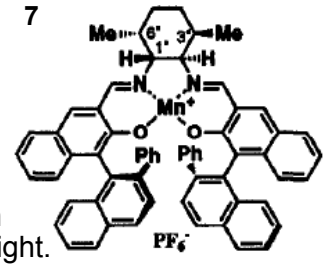
Katsuki's proposal:

The direction of olefins approach was determined not only by steric pulsions but the repulsive π-π interactions between the benzene ring of salen ligand and the unsaturated olefinic substituent.



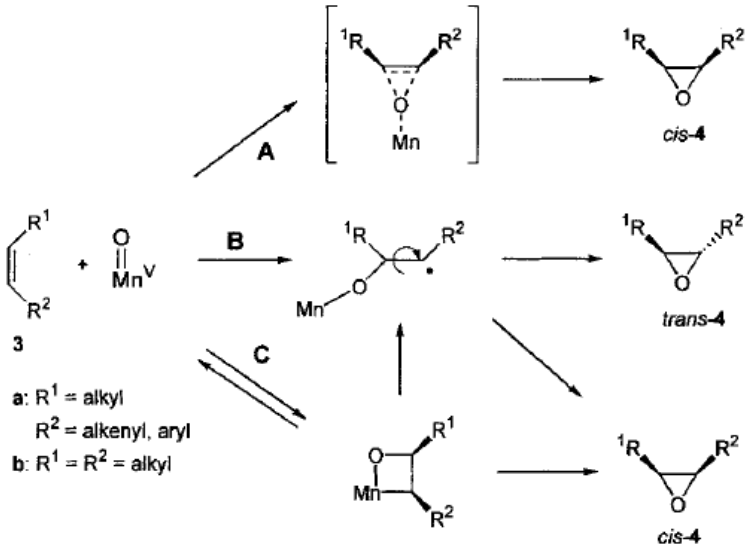
Katsuki *et al. Chem. Lett.* **1995**, 339

entry	substrate	catalyst	solvent	oxidant	temp.	yield(%)	% ee	Confign.
1		6	CH_2Cl_2	NaOCl	0°C	78	91	1R,2S
2	"	7	↓	↓	↓	78	97	1R,2S
3		6	↓	↓	↓	75	91	3R,4S
4	"	7	↓	↓	↓	70	97	3R,4S



Above was proofs that contradict Jacobsen's axial steric repulsion propasal by Katsuki et al.. Since complex 7 bears axial methyl groups at C3" and C6" which should lead to opposite streostructure of products if Jacobsen's proposal was right.

Mechanistic Study of One Oxygen Atom Transfer from Mn-oxo Salen Complex to Olefins



Concerted path

Radical path

Manganaoxetane path

Although the factors controlling the enantiselectivity of Mn-salen comolexes are well understood, the mechanism of oxygen transfer stage remains controversial.

From first experimental results, it was summarized that
(a)alkyl-substituted alkenes proceeds though concerted path (A), as they only gave cis-product
(b)conjugated alkenes proceeds in radical path (B),

However, compare experiments with same substrate cis-β-methylstyrene under different conditions, it becomes clear that this conclusion is incorrect.

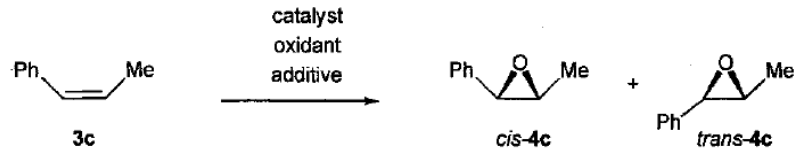
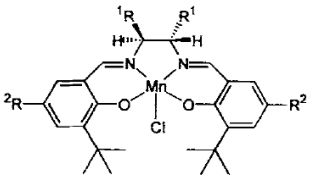


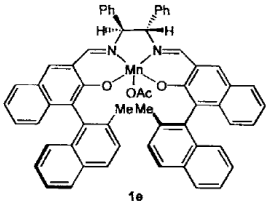
Table 1. Epoxidation of *cis*-β-methylstyrene (**3c**) with 0.04 equiv catalyst.

Cat.	Oxidant[a]	Additive	Yield [%]	*cis*:*trans*	ee_{fac} [%][e]
1d	NaOCl	4-PPNO [b]	98	95:5	81
1d	MCPBA	NMO[c]	91	94:6	82
1a	NaOCl	–	86	92:8	81
1e	PhIO	4-PPNO[b]	48	77:23	88
1d	PhIO	4-PPNO[b]	76	75:25	72
1c	NaOCl	–	86	71:29	81
1c	NaOCl	QAS[d]	86	5:95	81

[a] NaOCl: in phosphate buffer/chlorobenzene; *m*-chloroperbenzoic acid (MCPBA): in dichloromethane; iodosobenzene (PhIO): in acetonitrile. [b] 0.2–0.4 equiv 4-phenylpyridine *N*-oxide (4-PPNO). [c] 10.0 equiv *N*-methylmorpholine *N*-oxide (NMO). [d] 0.2 equiv of a quaternary quinine ammonium salt (QAS). [e] $ee_{fac} = \%\,cis \times ee_{cis} + \%\,trans \times ee_{trans}$.

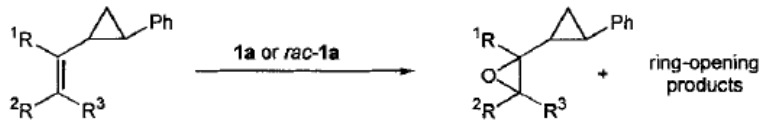


1a: $R^1, R^1 = -(CH_2)_4-$, $R^2 = t$Bu
1b: $R^1, R^1 = -(CH_2)_4-$, R^2 = OMe
1c: $R^1, R^1 = -(CH_2)_4-$, $R^2 = OSi^iPr_3$
1d: R^1 = Ph, R^2 = Br



Extract from:
E.N. Jacobsen *et al. JACS*,1997, 109, 1798-1801;
E.N. Jacobsen *et al. JACS*,1994, 116, 6937-38;
T. Katsuki *et al. J. Mol. Catal*. 1996, 87-107

The epoxidation of vinylcyclopropanes provide a good indication for radical intermediates, as these "radical clocks" undergo ring-opening at a rate of approximately10^{11} s^{-1}.



3	oxidant	*cis*-**4** : ring-opening
d: $R^1 = R^2 = R^3$ = H	NaOCl	100 : 0
e: R^1 = Ph, $R^2 = R^3$ = H	NaOCl	100 : 0
e: R^1 = Ph, $R^2 = R^3$ = H	PhIO	57 : 43
f: R^1 = Ph, R^2 = H, R^3 = Me	NaOCl	100 : 0
f: R^1 = Ph, R^2 = H, R^3 = Me	PhIO	83 : 17
g: R^1 = Ph, R^2 = Me, R^3 = H	NaOCl	56 : 44
g: R^1 = Ph, R^2 = Me, R^3 = H	PhIO	54 : 46

Extract from:
E.N. Jacobsen et al. JOC, 1991, 56, 6497-6500
B. Akermark et al. ACIE, 1997, 36, 1723-25

To sum up above experimental results, it becomes clear that the diastereoselectivity are strongly dependent on the oxidant, the catalyst and the additives.

Summary:

1. J-K epoxidation is one of the most efficient methods for asymmetric epoxidation of unfunctionalized olefins (complementary to Prilezhaev reaction (racemic), and Sharpless AE(allyl alchohol)).

2. High enantioselectivity can be achieved in cis-olefins, cyclic olefins, and conjugated olefins. However, terminal olefins and trans-olefins are usually poor substrate (in contrast of Shi-epoxidation, which is efficient in trans-olefins and tri-substitude olefins).

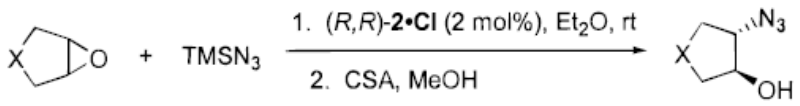
3. Asymmetric Ring-Opening (ARO) Reactions of Epoxides

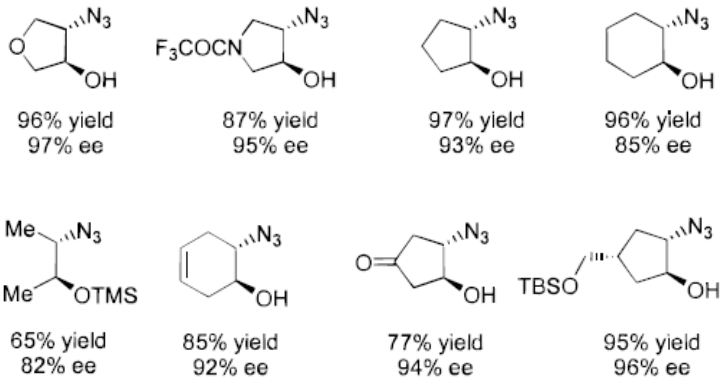
~Focus on Metal-Salen Complexes (II)~

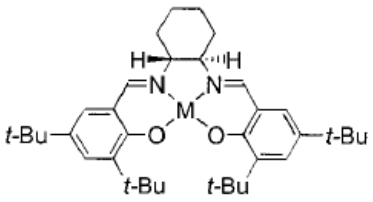
3-1 Asymmetric Ring-Opening (ARO) Reaction of Epoxide by Metal-Salen Catalyst

Initial Report

E.N. Jacobsen et al. J. Am. Chem. Soc. 1995, 117, 5897-98
E.N. Jacobsen et al. J. Org. Chem. 1996, 61, 7963-7966



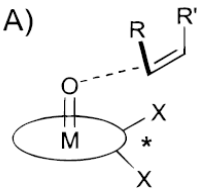




(*R*,*R*)-**1**: M = H
(*R*,*R*)-**2•Cl**: M = CrCl
(*R*,*R*)-**3•I**: M = CoI

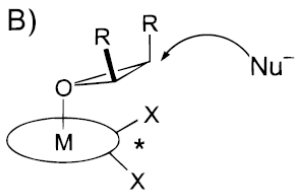
Initial conception of ARO strategy

The groud state structure of epoxides coordinate to metal complex may share similar pattern as the transition state of olefin's epoxidation by metal complex oxo transfer.



Epoxidation Catalysis

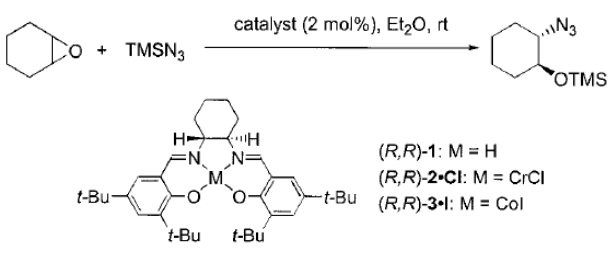
(A) Schematic representation of the side-on approach model for olefin epoxidation by chiral salen complexes

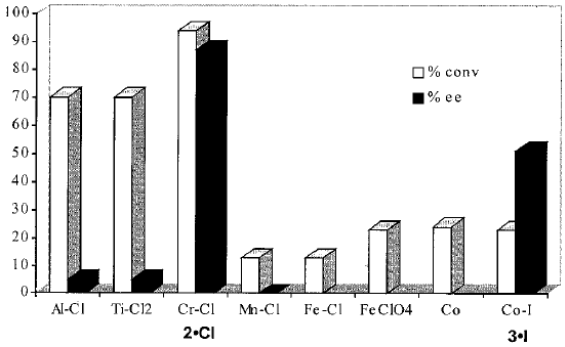


Lewis Acid Activation of Epoxides

(B) Possible model of epoxide activation to asymmetric ring-opening by similar catalyst

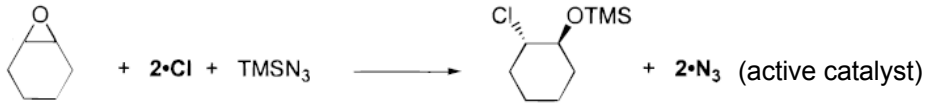
Preliminary screen of metal salen complexes for ARO of epoxide



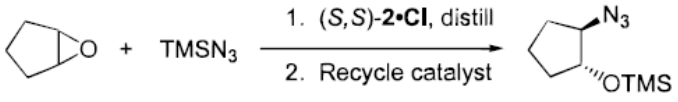


Mechanism of ARO

Active catalyst in ARO of epoxide by $TMSN_3$



5



cycle	yield (%)	ee (%)	cycle	yield (%)	ee (%)
1	84	93	7	95	94
2[a]	92	94	8	94	94
3	93	94	9	95	94
4	95	94	10	95	95
5	91	94	11	92	95
6	95	94			

E.N. Jacobsen *et al. Acc. Chem. Res.* **2000**, *33*, 421-31

Evidence:

1. Byproduct 5 is generated only in the initial stages and in yields propational to the amount of catalyst employed.
2. The catalyst separated after 1st cycle reveals N-Cr in molar ratio of 5:1 and the absence of Cl atom, also shows strong IR absorbence at 2058 cm^{-1} which is consistent with Cr-N_3 N=N stretch.
3. No measurable loss of activity and enantioselectivity occurs when recycled up to another 10 times.

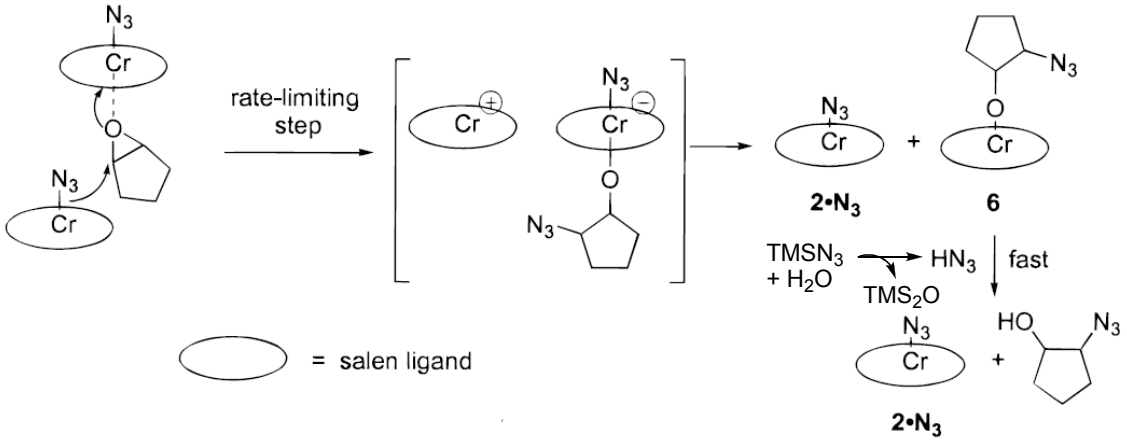
In fact, 2-N_3 serves as both a Lewis acid for epoxide activation and an N_3-dilivery agent. And the actual active catalyst is in form of (salen)Cr(N_3)(epoxide).

Unusual rate expression

The reaction of HN_3 with cyclopentene oxide in presence of catalystic 2-N_3 obeys the following rate law:

$$\text{rate} = k[\text{2-}N_3]^2[\text{epoxide}]^{-1}[HN_3]^0$$

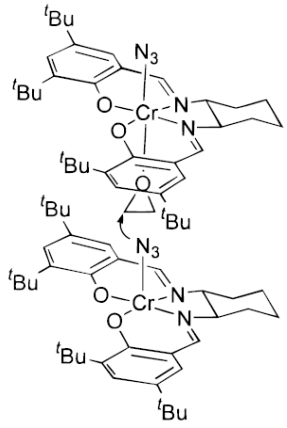
A second order dependence on 2-N_3 is observed. Based on this rate expression, the mechanism of metal -salen catalyzed ARO of epoxidation is proposed as follow:



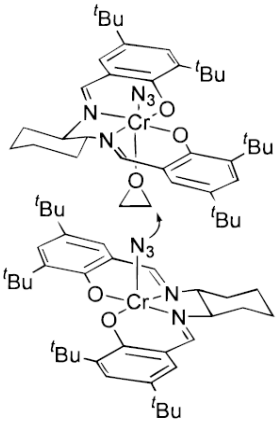
Studies on cooperative reactivity of metal-salen complexes in ARO

This second-order dependence on the catalyst strongly implicating the possibility of its showing extra coorpertive effect when designed as dimeric or polymeric form.

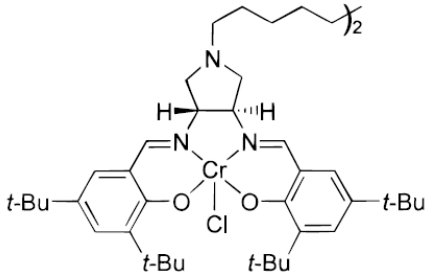
Two limiting geometries of metal-salen complex dimer can be envisioned, respectively as "head to head" and "head to tail".



"head to head"

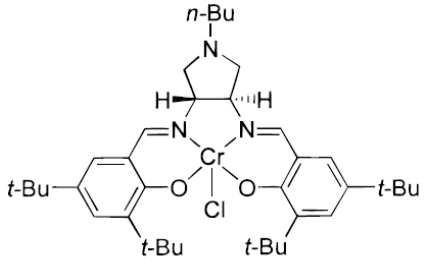


"head to tail"



7

8**%** ee in ARO
of cyclopentene oxide
@ [catalyst] = 1 x 10^{-3}M



8

90% ee in ARO
of cyclopentene oxide
(independent of [catalyst])

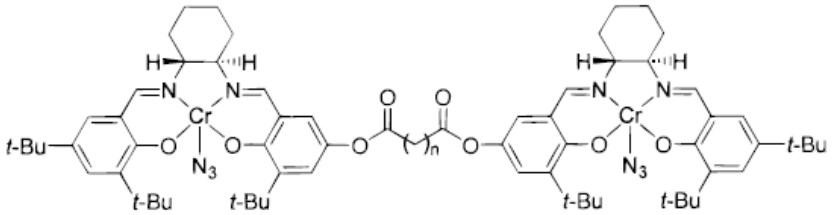
E.N. Jacobsen *et al. JACS*, **1998**, *120*,10780-81

Designed as the "head to head" transition stategeometry. Accelerated rate of ARO was observed. Kinetic experiments by plots of k_{obs}/[cat] vs [cat] (fighur in next page) shows complex **7** catalyzed the ARO primaryly through a first-order pathway.

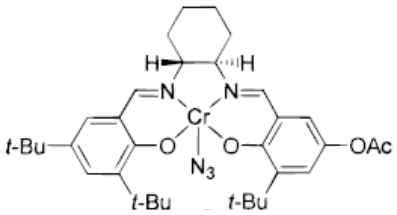
Results earned from complex **7** and **8** suggest:

1. Cooperative reactivity was in fact occuring within the dimeric complex
2. The placement of tether (the link part) was critical to enantioselectivity
3. The "head to head" arrangement was not optimal geometry

Redesign dimeric complexes (**4a~4g**)in order to allow intramolecular reaction with a greater range of transtion state.



4a: n=2, **4b**: n=4, **4c**: n=5, **4d:** n=6, **4e**: n=7, **4f**: n=8, **4g**: n=10



5

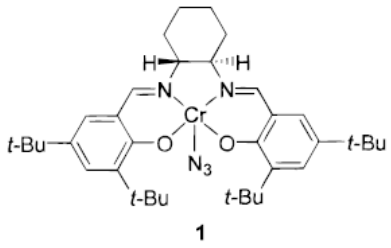
Considering a two-term rate equation involving both intra- and intermolecular components:

$$\text{rate} = k_{intra}[cat] + k_{inter}[cat]^2$$

Table 1. Rate Constants and Enantioselectivity Data for the Ring Opening of Cyclopentene Oxide Catalyzed by (salen)Cr−N_3 Complexes

catalyst	n	% ee of product[a]	k_{intra} ($min^{-1} \times 10^{-2}$)[b]	k_{inter} ($M^{-1}\ min^{-1}$)[b]	M_{eff} ($M \times 10^{-3}$)[b]
1		93		0.6	
5		94		1.2	
4a	2	90	4.4	15.7	2.8
4b	4	90	5.4	15.1	3.6
4c	5	93	42.9	27.4	15.7
4d	6	93	31.7	15.8	20.1
4e	7	93	20.9	7.9	26.3
4f	8	94	14.7	10.5	14.0
4g	10	92	3.8	4.4	8.6

[a] From the reaction of cyclopentene oxide with $TMSN_3$. [b] Kinetic studies were carried out with HN_3 as the azide source (ref 4; see Supporting Information).



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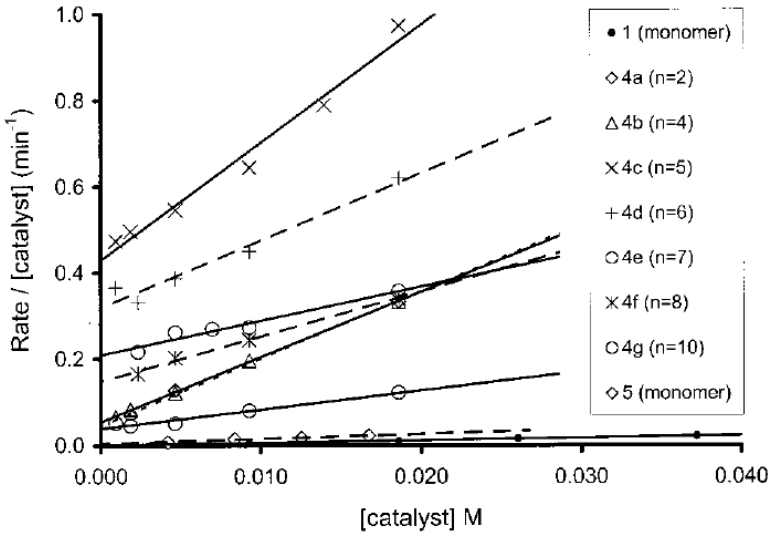
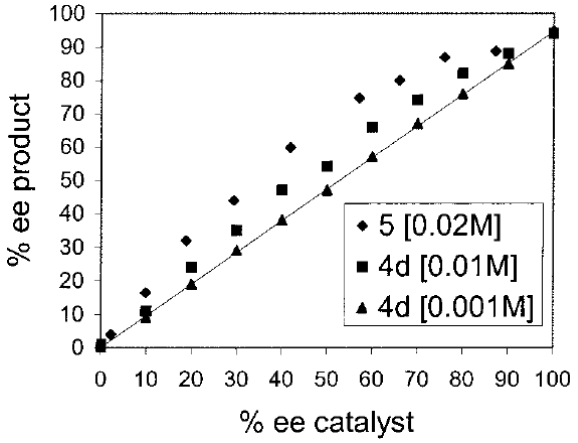


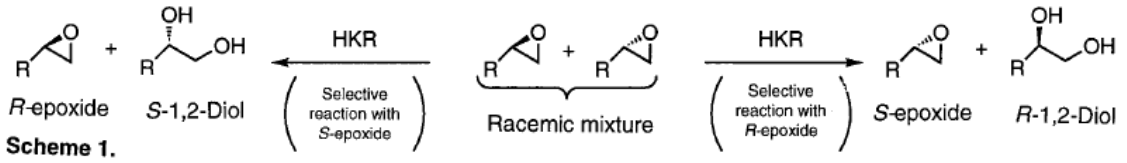


nonlinear effects in ARO of cyclopentene oxide with $TMSN_3$ catalyzed by **5** and **4d**

4. Hydrolytic Kinetic Resolution (HKR) of Terminal Epoxide
--- Practical Application of the ARO

General and practical method for enantioselective synthesis of terminal epoxide is still unavailable (refer to Summary of J-K asymmetric epoxidation), thus kinetic resolution of terminal epoxide from its inexpensively available racemic mixtures becomes a very attractive strategy.

The strategy of epoxide HKR:

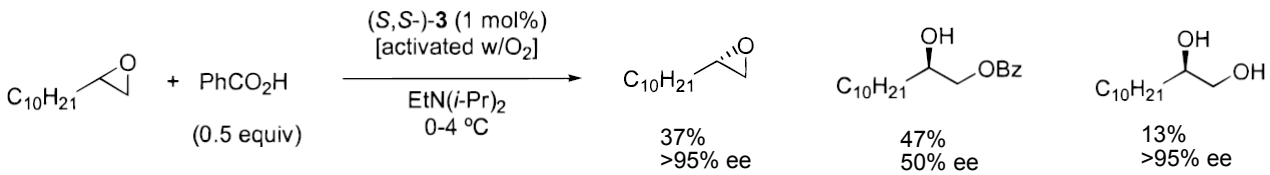


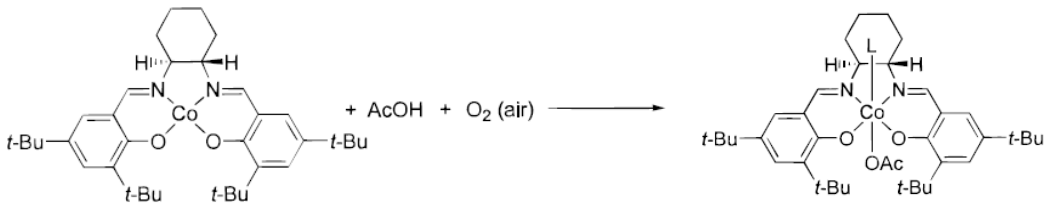
Scheme 1.

First finding connected to the establishment of HKR

E.N. Jacobsen *et al. Tetrahedron Lett.* **1997**, *38*, 773-76

(1)





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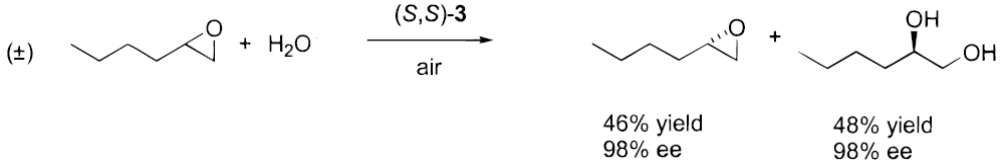
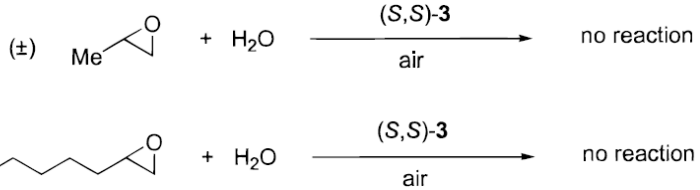
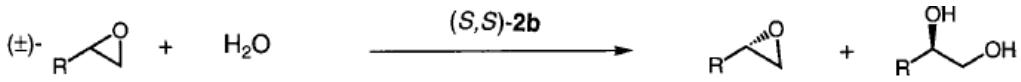


BUT:



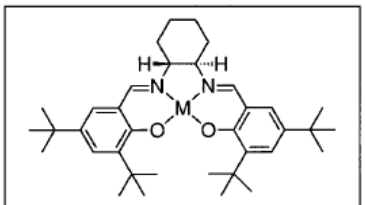
Initial report of metal-salen catalyzed epoxide HKR

E.N. Jacobsen et al. Science, 1997, 277, 936-38

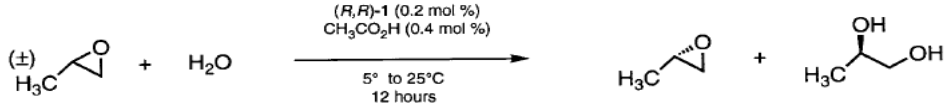


Entry	R	Concentration		Time (hours)	Epoxide		Diol		k_{rel}
		2b (mol %)	Water (equiv)		ee (%)	Isolated yield (%)	ee (%)	Isolated yield (%)	
1	CH_3	0.2	0.55	12	>98	44	98	50	>400
2	CH_2Cl	0.3	0.55	8	98	44	86	38	50
3	$(CH_2)_3CH_3$	0.42	0.55	5	98	46	98	48	290
4	$(CH_2)_5CH_3$	0.42	0.55	6	99	45	97	47	260
5	Ph	0.8	0.70	44	98	38	98*	39*	20
6	$CH{=}CH_2$	0.64	0.50	20	84	44	94	49	30
7	$CH{=}CH_2$	0.85	0.70	68	99	29	88	64	30

*After recrystallization.

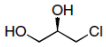


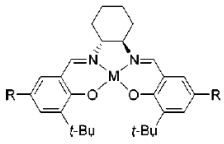
k_{rel} = ln[(1- c)(1- ee)]/[(1- c)(1+ ee)], where ee is the enantiomeric excess of the epoxide and c is the fraction of epoxide remaining in the final reaction mixture.

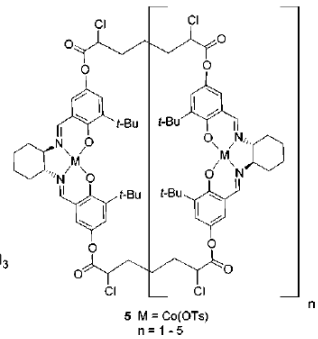


Cycle 1	44% yield 98.6% ee	50% yield 98% ee
Cycle 2	46% yield 98.5% ee	50% yield 98% ee
Cycle 3	48% yield **98.5% ee**	50% yield **98% ee**

In cases of HKR, polymeric matal-salen complexes also represent coorperative effect just as ARO

Entry	Isolated Product	Catalyst	Co (Mol%)[a]	Time	(h) % yield[c] (ee)
Epoxides[a]					
1		Monomer (**1b**)	0.5[e]	18	42 (99)
		Oligomer (**5**)	0.01	11	45 (99)
2		**1b**	0.85[f]	68	26 (99)
		5	0.05	24	36 (99)
3		**1b**	0.8[e]	72	44 (99)
		5	0.08	24	37 (99)
4		**1b**	2.0[e]	48	41 (99)
		5	0.1	24	41 (99)
Diols[a]					
5		**1b**	2.0[e]	24	50 (96)
		5	0.01	1.5	40 (97)
6		**1b**	0.64[f]	20	49 (94)
		5	0.03	4	46 (97)
7		**1b**	0.8[e]	12	41 (98)
		5	0.08	4	43 (96)
8		**1b**	2.0[e]	20	40 (95)
		5	0.05	18	49 (95)



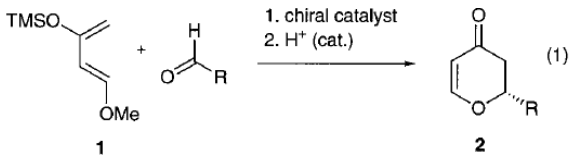


E.N. Jacobsen *et al. JACS*, **2001**, *123*, 2687-88

5. Asymmetric Hetero Diels-Alder Reactions of Carbonyl Compounds
~Focus on Metal-Salen Complexes (III)~

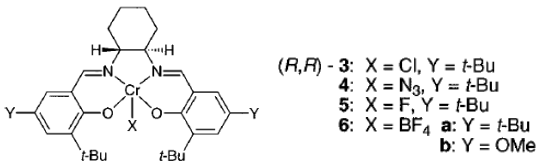
a. Danishefski's diene as enophile

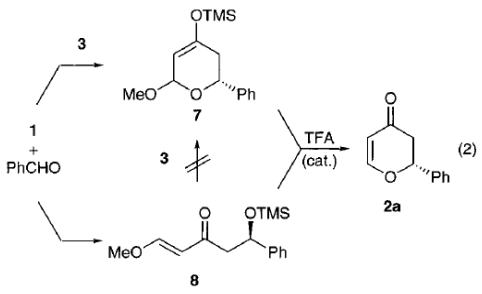
(1)



			cat. **6a**		cat. **6b**	
entry	R	temp (°C)	ee (%)[b]	yield (%)[c]	ee (%)[b]	yield (%)[c]
a	Ph	−30	87	85	65	98
b	C_6H_{11}	−20	93	71	85	76
c	n-C_5H_{11}	−40	83	86	62	85
d	2-furyl	−10	76 (99)	89 (63)	68	80
e	(*E*)-PhCH=CH	0	70	65	73 (99)	96 (64)
f	p-$BrC_6H_4CH_2OCH_2$	−30	79	67	84 (99)[d]	94 (70)[d]
g	o-$ClC_6H_4CO_2CH_2$	−20	83 (99)[d]	92 (67)[d]	72	86

[a] Unless noted otherwise, all reactions were run at 5.0 M in TBME using 2 mol % catalyst, 1.0 mmol of aldehyde, 1.0 mmol of diene **1**, and 300 mg of oven-dried 4 Å molecular sieves for 24 h. [b] Enantiomeric excesses in parentheses were obtained after recrystallization (see Experimental). [c] Yields in parentheses refer to recrystallized yields. [d] Reactions were run on 10.0 mmol scale.





E.N. Jacobsen *et al. JOC*, **1998**, *63*, 403-05

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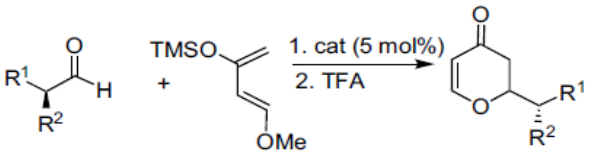
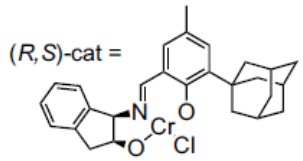
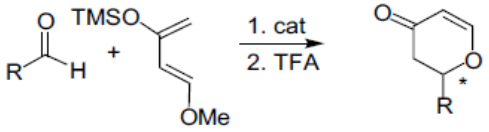


with (*S*,*R*)-cat:
R^1 = Me, R^2 = OTBS: 97% de = 88% ee > 99%
with (*R*,*S*)-cat:
R^1 = CH_2OPMB, R^2 = Me: 90% de = 84% ee > 99%
R^1 = Ph, R^2 = OTBS: 58% de = 56% ee = 99%

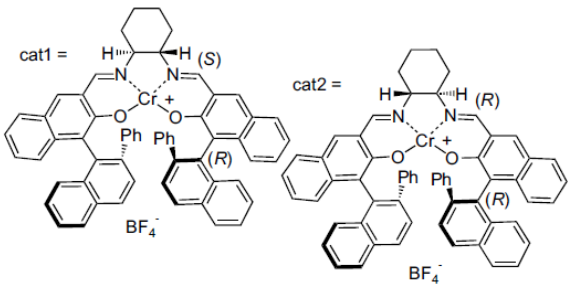


E.N. Jacobsen *et al. OL*, **2002**, *4*, 1795-98

(3)

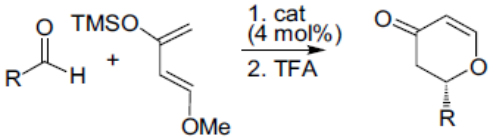


with cat1:
R = Ph: 96% ee = 78% (-)
R = p-$MeOC_6H_4$: 88% ee = 96% (-)
with cat2:
R = Ph: 93% ee = 93% (+)
R = p-$MeOC_6H_4$: 90% ee = 63% (+)
R = Cy: 92% ee = 96%
R = n-Hex: 98% ee = 97%
R = (*E*)-PhCH=CH: 100% ee = 91%

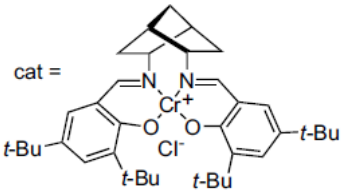


T. Katsuki et al. Tetrahedron, 57, 845-51

(4)



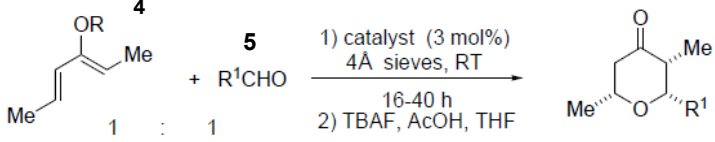
R = Ph: 84% ee = 95%
R = n-Hex: 85% ee = 90%
R = Cy: 32% ee = 96%
R = 2-Fu: 93% ee = 90%
R = (*E*)-PhCH=CH: 54% ee = 79%



A. Berkessel *et al. JOC*, **2006**, 5029-35

(b) other type diene

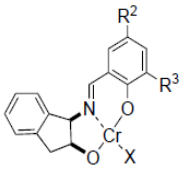
(1)



4a: R = $SiMe_3$ (TMS)
b: R = $SiEt_3$ (TES)
c: R = Si(*t*Bu)Me_2 (TBS)
d: R = Si(*i*Pr)$_3$ (TIPS)

5a: R^1 = Ph
b: R^1 = CH_2OTBS
c: R^1 = CH_2OBn
d: R^1 = n-C_5H_{11}
e: R^1 = $(CH_2)_4CH{=}CH_2$
f: R^1 = CH_2CH_2Ph
g: R^1 = CH_2CH_2NHBoc
h: R^1 = 2-furyl

Entry	Diene	Aldehyde	Conditions[b]	Catalyst	Yield [%][c]	ee [%][d]
1	**4b**	**5a**	A	**1b**	50	80
2	**4b**	**5b**	A	**1b**	n. d.	57
3	**4b**	**5b**	A	**2b**	n. d.	85
4	**4b**	**5b**	A	**3a**	88	98
5	**4b**	**5b**	A	**3b**	93	98
6	**4b**	**5a**	A	**3a**	n. d.	65
7	**4b**	**5a**	A	**3b**	n. d.	81
8	**4b**	**5a**	B	**3b**	72 (80)[e]	90
9	**4b**	**5b**	B	**3a**	90	99
10	**4b**	**5b**	B	**3b**	97	> 99
11	**4b**	**5c**	B	**3b**	89	94
12	**4b**	**5d**	A	**3b**	85	98
13	**4b**	**5e**	A	**3b**	78	98
14	**4b**	**5f**[f]	B	**3b**	78 (84)[e]	98
15	**4b**	**5g**	B	**3b**	28 (31)[e]	96
16	**4b**	**5h**	B	**3b**	77 (86)[e]	95
17	**4a**	**5d**	A	**3b**	81	98
18	**4c**	**5d**	A	**3b**	93	96
19	**4b**	**5d**	A	**3b**	77	94



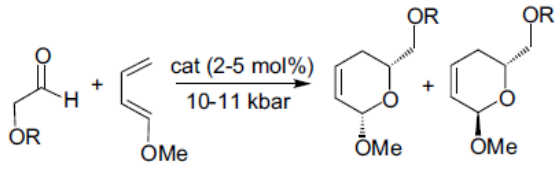
(1*R*,2*S*)-**1a,b** R^2 = *t*Bu R^3 = *t*Bu
(1*R*,2*S*)-**2a,b** R^2 = H R^3 =
(1*R*,2*S*)-**3a,b** R^2 = Me R^3 =

a : X = Cl **b** : X = SbF_6

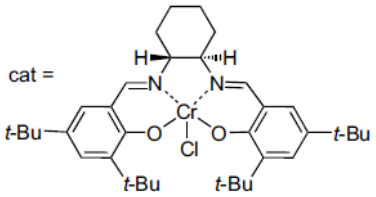
[a] Unless noted otherwise, reactions were carried out with 1:1 diene and aldehyde on a 1.0 mmol scale with 3 mol % catalyst and powdered 4 Å molecular sieves for 16–40 h as outlined in Scheme 1. [b] A: No solvent added. B: 200 µL acetone added. [c] Yields of isolated product after flash column chromatography on silica gel. In cases where nonoptimal catalyst combinations are described, yields of isolated product were not determined accurately and are therefore not reported (n.d.). [d] Enantiomeric excesses (*ee*) were determined by GC using a commercial (Cylcodex-β) column. [e] Reaction did not reach complete substrate conversion after 40 h. Numbers in parentheses correspond to substrate conversion upon work-up. [f] Two equivalents of aldehyde used.

E.N. Jocobsen *et al. JOC*, **1999**, *38*, 2398-99

(2)

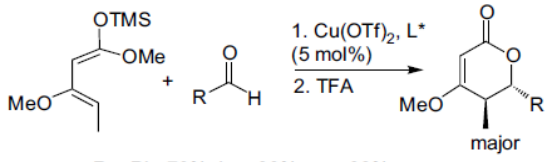


R = TBS: 84% de = 92% ee (*cis*) = 87% ee (*trans*) = 78%
R = TBDPS: 55% de = 94% ee (*cis*) = 56% ee (*trans*) = 32%
R = $SiPh_3$: 49% de = 92% ee (*cis*) = 52% ee (*trans*) = 31%

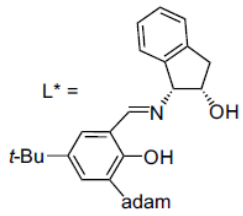


A. Umani-Ronchi *et al. Chem. Commun.* **2002**, 919-27

(3)



R = Ph: 70% de = 90% ee = 98%
R = *o*-Tol: 52% de = 98% ee = 94%
R = *p*-Tol: 40% de = 96% ee = 96%
R = *p*-FC_6H_4: 60% de = 94% ee = 97%
R = *p*-ClC_6H_4: 55% de > 90% ee > 94%
R = *p*-BrC_6H_4: 65% de > 88% ee > 91%
R = *p*-$NO_2C_6H_4$: 64% de = 78% ee = 94%
R = 1-Naph: 57% de = 96% ee = 92%
R = 2-Naph: 63% de > 94% ee > 97%
R = 2-Fu: 40% de = 96% ee = 99%



Q. Feng *et al. JOC.* **2006**, *71*, 4141-46

Summary:

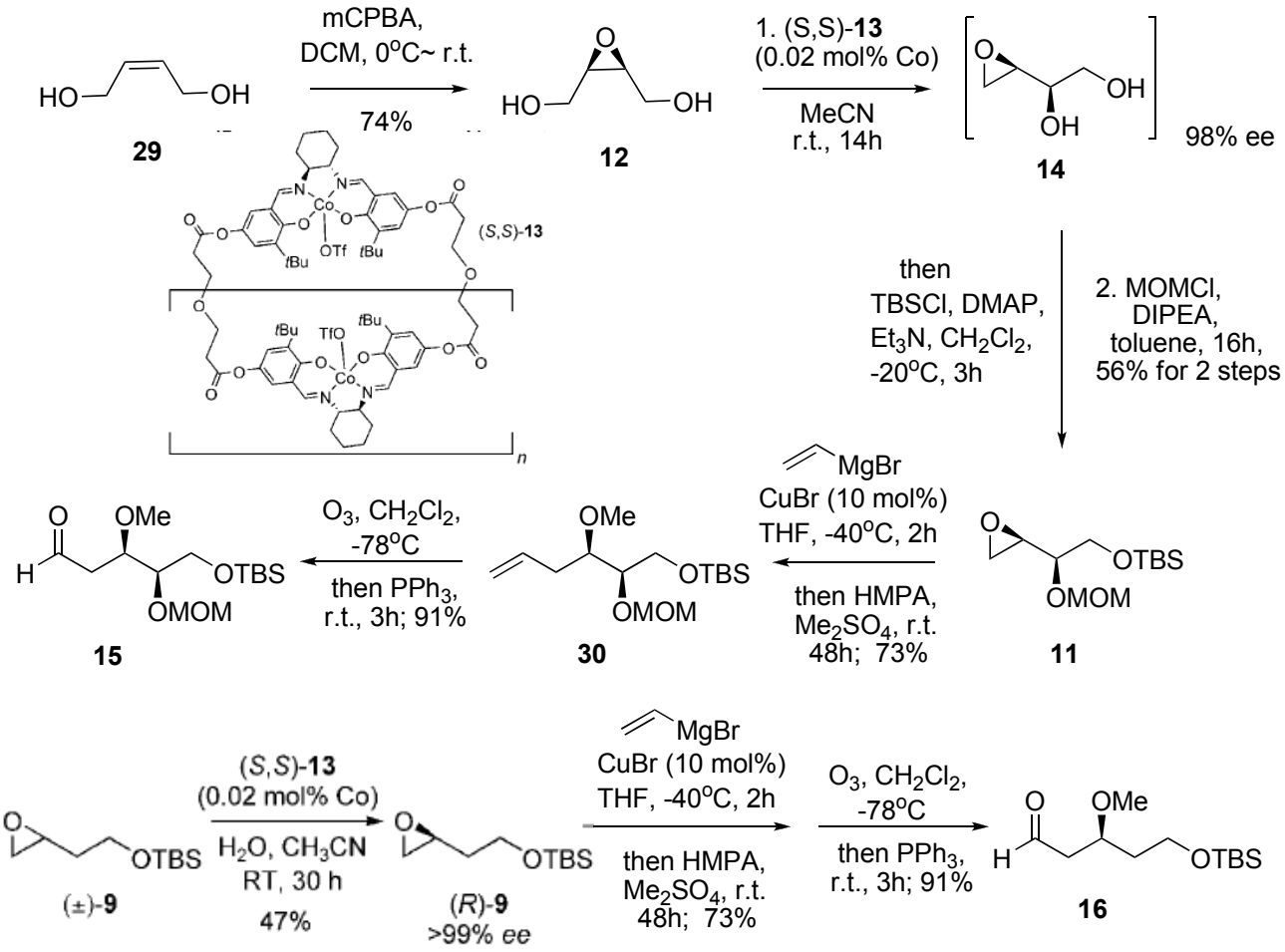
After decades of studies, it has been proved to be effective in asymmetric imine-cyanation, conjugate addition, carbenoid insertion besides mentioned reaction types above. Thus makes it one of the so-called "priviledged catalysts"*.

The first inspiration from heme-containing enzymes finally develops into salen's great hit, similarly shared many other "priviledge catalysts" such as Bi-oxazoline(BOX) ligand which was inspired by vitamin B_{12}, These all reminds us nature could always provides "nutrients" in ligand design.

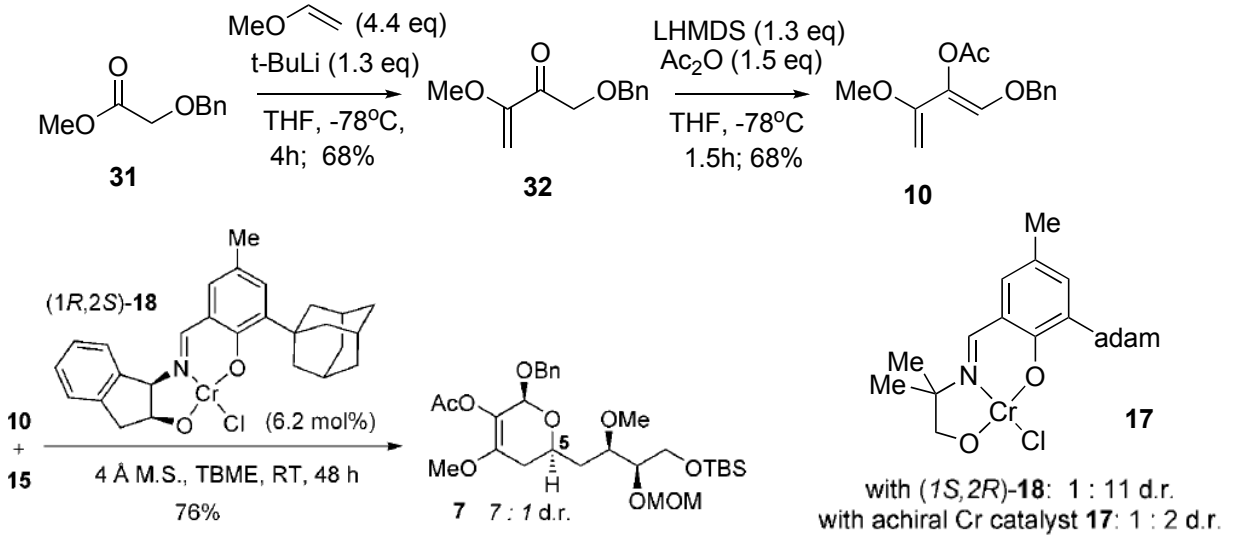
* Reviewed by:
E.N. Jacobsen *et al. Science*, **2003**, *299*, 1691-93

Total Synthesis of (+)-Peloruside A

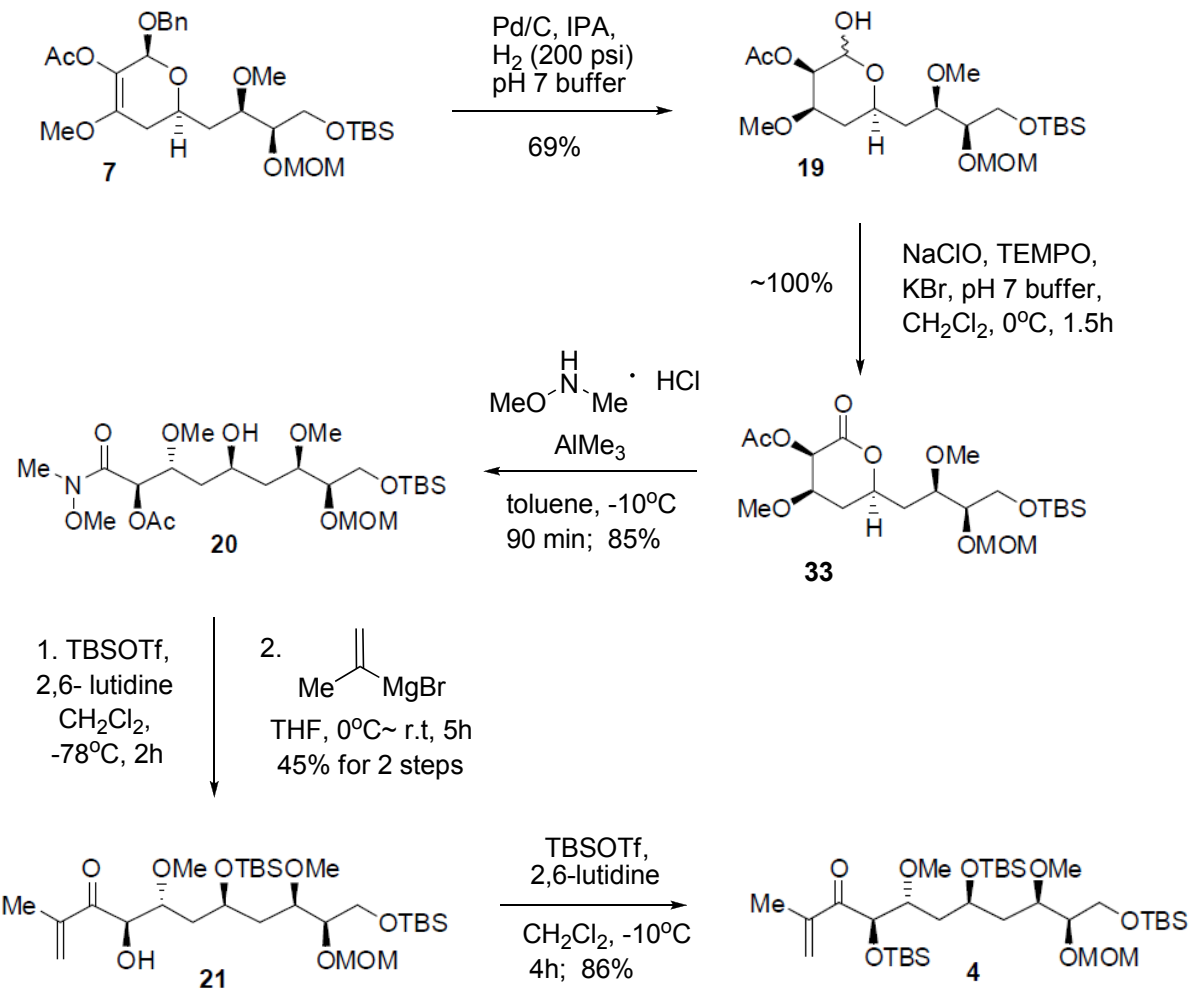
Synthesis of Intermediate **15** and **16**



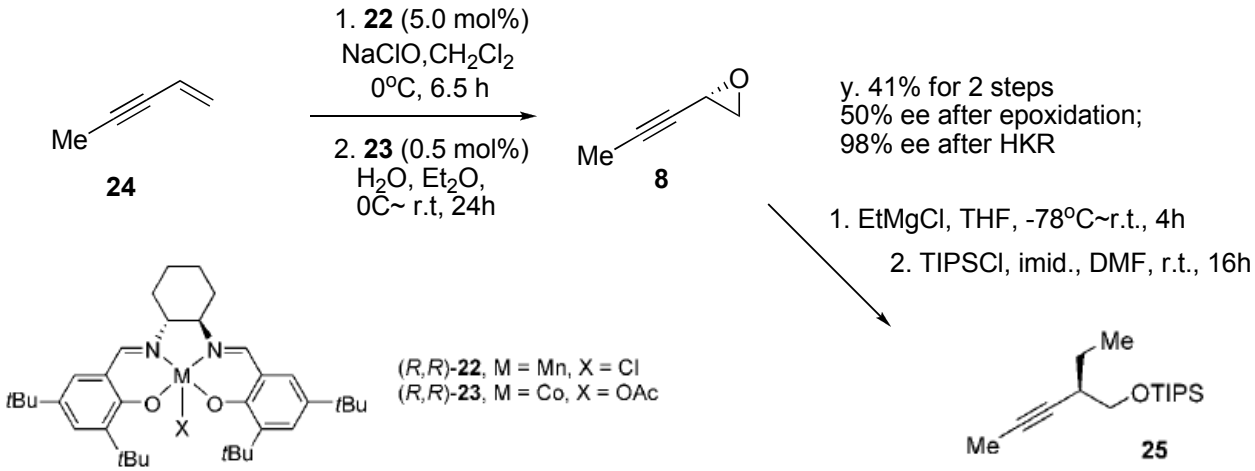
Synthesis of intermediate **7**

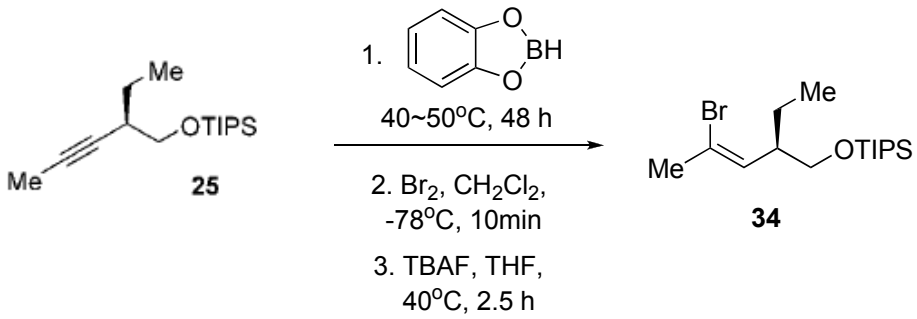


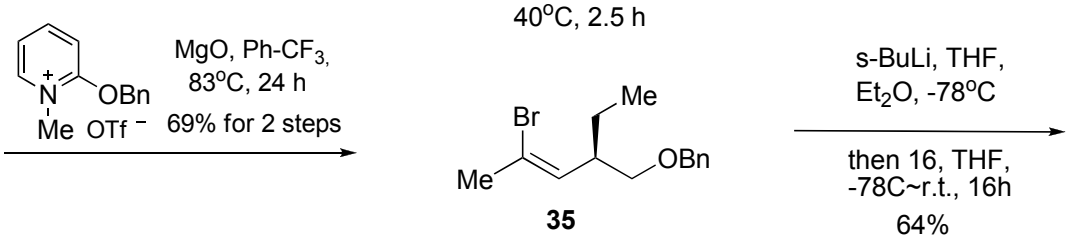
Synthesis of intermediate **4**

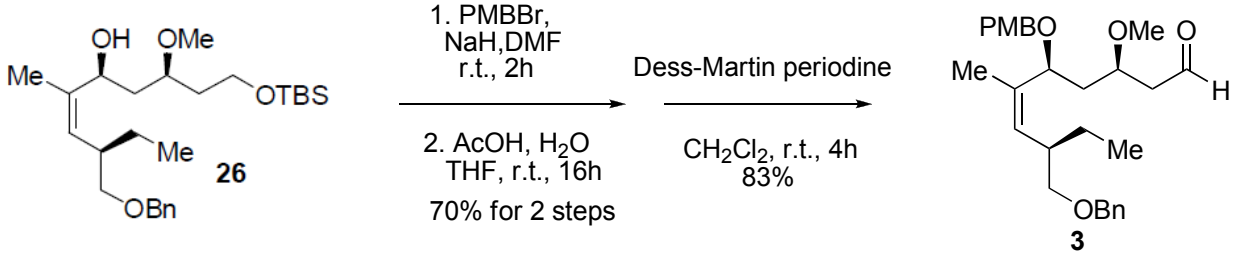


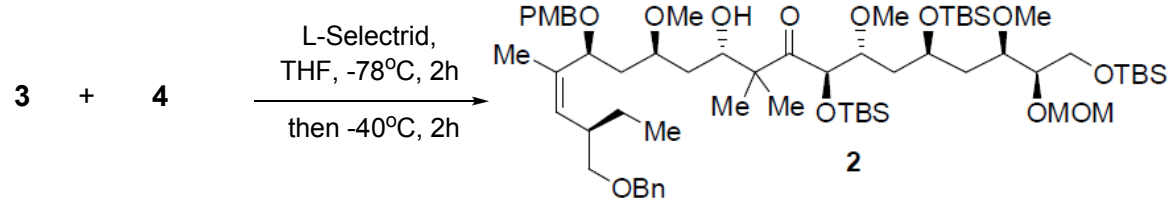
Synthesis of intermediate **3**

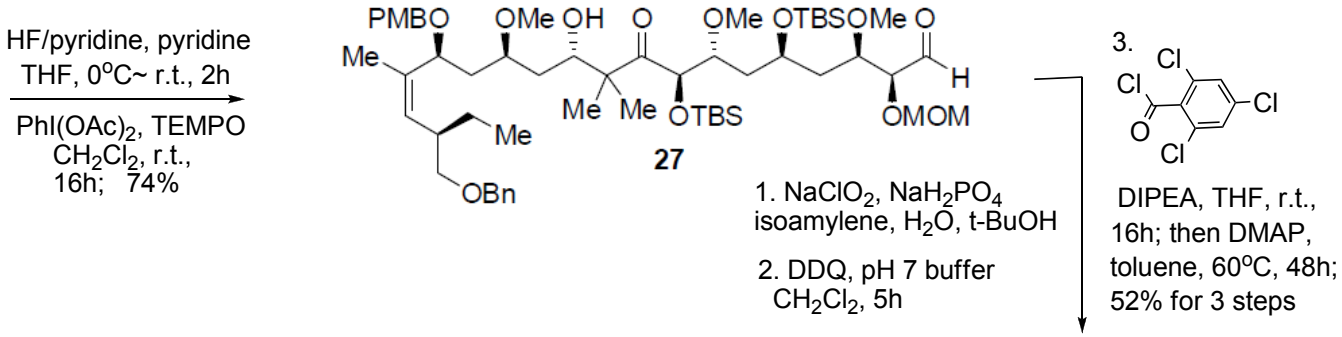


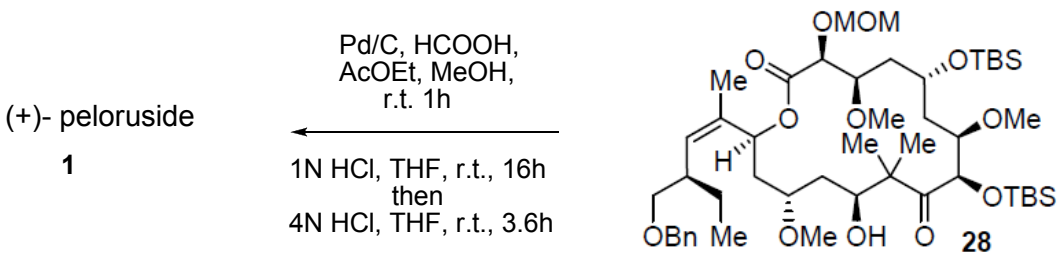

Me
OTIPS
Me
25
1.
O
BH
O
40~50°C, 48 h
2. Br2, CH2Cl2,
-78°C, 10min
3. TBAF, THF,
40°C, 2.5 h
Br
Me
Me
OTIPS
34


OBn
N
Me OTf −
MgO, Ph-CF3,
83°C, 24 h
69% for 2 steps
Br
Me
Me
OBn
35
s-BuLi, THF,
Et2O, -78°C
then 16, THF,
-78C~r.t., 16h
64%


OH
OMe
Me
OTBS
Me
26
OBn
1. PMBBr,
NaH,DMF
r.t., 2h
2. AcOH, H2O
THF, r.t., 16h
70% for 2 steps
Dess-Martin periodine
CH2Cl2, r.t., 4h
83%
PMBO
OMe
O
Me
H
Me
OBn
3

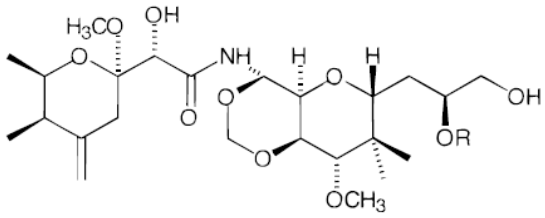

3 + 4
L-Selectrid,
THF, -78°C, 2h
then -40°C, 2h
PMBO
OMe
OH
O
OMe
OTBSOMe
Me
Me
Me
OTBS
OTBS
OMOM
Me
OBn
2


HF/pyridine, pyridine
THF, 0°C~ r.t., 2h
PhI(OAc)2, TEMPO
CH2Cl2, r.t.,
16h; 74%
PMBO
OMe
OH
O
OMe
OTBSOMe
O
Me
Me
Me
OTBS
OMOM
H
Me
OBn
27
1. NaClO2, NaH2PO4
isoamylene, H2O, t-BuOH
2. DDQ, pH 7 buffer
CH2Cl2, 5h
3.
Cl
Cl
O
Cl
Cl
DIPEA, THF, r.t.,
16h; then DMAP,
toluene, 60°C, 48h;
52% for 3 steps


(+)- peloruside
1
Pd/C, HCOOH,
AcOEt, MeOH,
r.t. 1h
1N HCl, THF, r.t., 16h
then
4N HCl, THF, r.t., 3.6h
OMOM
O
OTBS
Me
O
OMe
OMe
H
Me
Me
OTBS
OBn
Me
OMe
OH
O
28

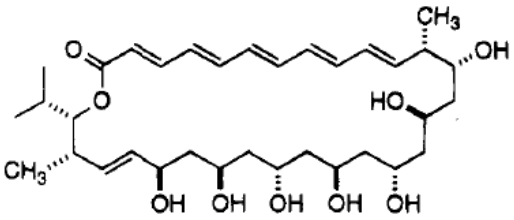
Topic: All Roads Lead to Rome-------
Approach to the Synthesis of 1,3-Diol Moiety via "inconventional" pathway

As seen in pelorudside, 1,3-diol moiety is one of the most common structural units in many natural products.

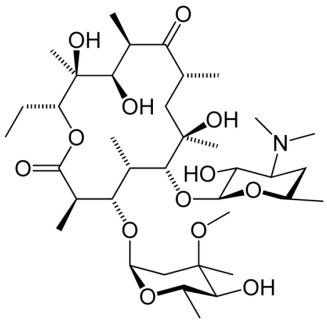


R = H mycalamide A **2**
R = CH_3 mycalamide B **4**

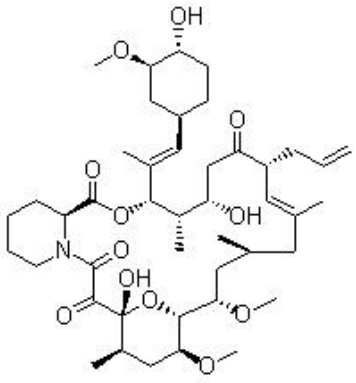
(antiviral, antitumor)



Roxaticin
(antifungal, antibiotic)



Erythromycin
(antibiotic)



Tacrolimus (FK506)
(immunosuppressant)

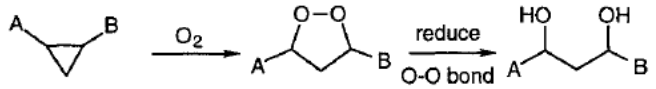
Although the defination of "conventional" would be quite controversial, here I simply categorize these methodologies (vida infra) as "traditional":

1. Selective reduction of 1,3-hydroxyketones or 1,3-diketones
2. Alkyl/allylation of 1,3-hydroxyketone moieties (Keck reaction, Prins reaction etc.)
3. Aldol(+reduction)
4. Conjugate addition by O-nucleophile/reduction
5. Manipulation of allylic or homoallylic alchohol (including addition of O-nucleophiles and iodocarbonation etc.)

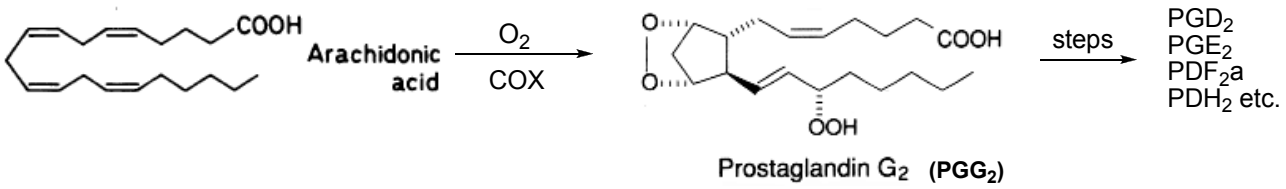
Above all are some "traditional" way for synthesizing 1,3-diol moieties. All of them are well develpoed and have been widely utilized. However, nevertheless the traditional methods have achieved great efficiency and mature system, methods for oxidative approach or direct convertion from C-H bond are still limited. Here I would like to introduce some thus "inconventional " method for constructing 1,3-diol moiety.

1. Oxygenation of Vinylcyclopropanes

Strategy:

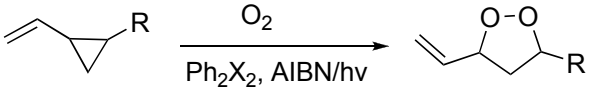


The idea was inspired by the biosynthesis route of prostaglandin family:



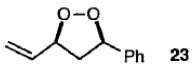
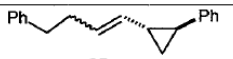
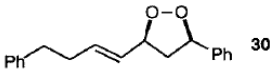
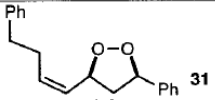
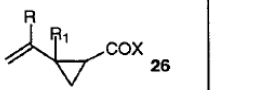
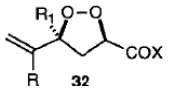
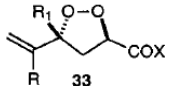
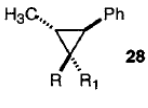
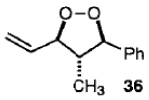
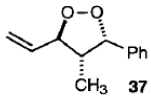
Prostaglandin G_2 **(PGG_2)**

Report: K.S. Feldman, Synlett. 1995, 217-225



(X= S or Se)

Table 1. Oxygenation of Substituted Vinylcyclopropanes to form 1,2-Dioxolanes.

entry	Vinylcyclopropane	Notable Conditions[a]	Yield (%)	Dioxolane Products
a)	 **22**		63	 **23**
	 **25**			 **30**  **31**
b)	(*E*) alkene	Ph_2Se_2	76	2 / 1.0
c)	(*E*) alkene	Ph_2S_2	69	10 / 1.0
d)	(*Z*) alkene	Ph_2Se_2	73	4 / 1.0
e)	(*Z*) alkene	Ph_2S_2	69	13 / 1.0
	 **26**			 **32**  **33**
	R / R_1 / X			
f)	H / H / Ot-Bu		66	1.0 / 1.8
g)	CH_3 / H / Ot-Bu		70	1.0 / 1.7
h)	t-Bu / H / Ot-Bu		84	1.0 / 1.0
i)	H / CH_3 / Ot-Bu		83	1.5 / 1.0
j)	H / H / NHC_8H_{17}		40	1.0 / 1.4
k)	H / H / St-Bu		52	1.0 / 2.8
l)	H / H / SC_6H_5		46	1.0 / 3.4
m)	H / H / OC_6H_5		63	1.0 / 3.0
n)	H / H / OC_6H_4OMe		43	1.0 / 2.9
o)	H / H / OC_6F_5		66	1.0 / 5.4
p)	H / H / $OCH(CF_3)_2$		70	1.0 / 6.0
q)	H / H / $OCH(CF_3)_2$	-50 °C	65	< 1.0 / >10
	 **28**			 **36**  **37**
	R / R_1			
u)	H / $CH=CH_2$	CH_3OH, -50 °C	73	2.8 / 1.0
v)	$CH=CH_2$ / H	CH_3OH, -50 °C	63	2.8 / 1.0

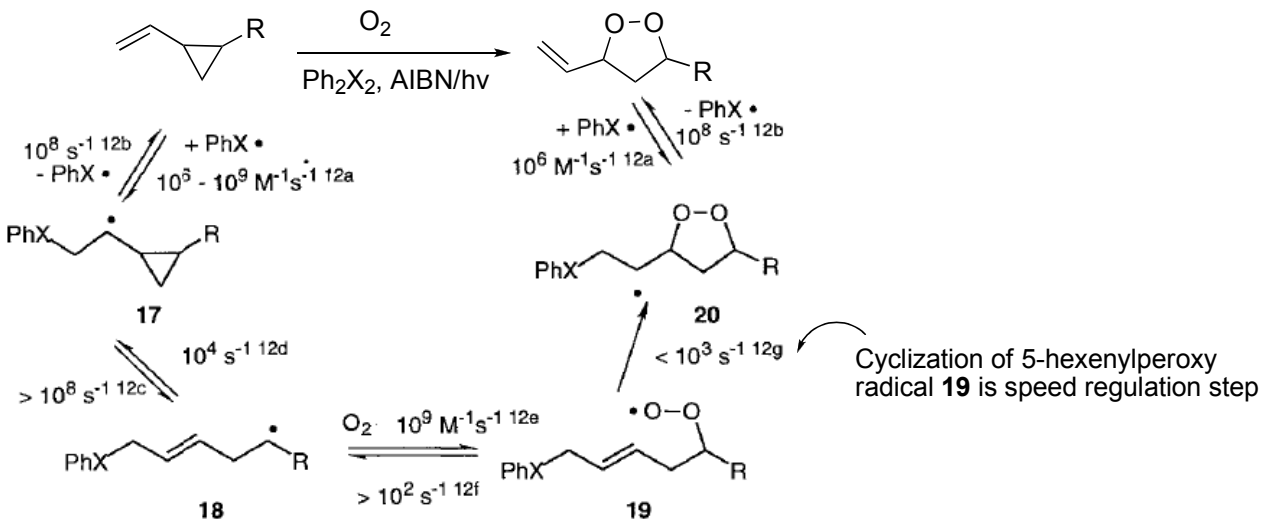
Pros:

1. Can induce two oxygen atom for diol in single step.
2. DIrectly using molecular O_2 as oxidant
3. Also promising in direct oxidizing poly-unsaturated moiety

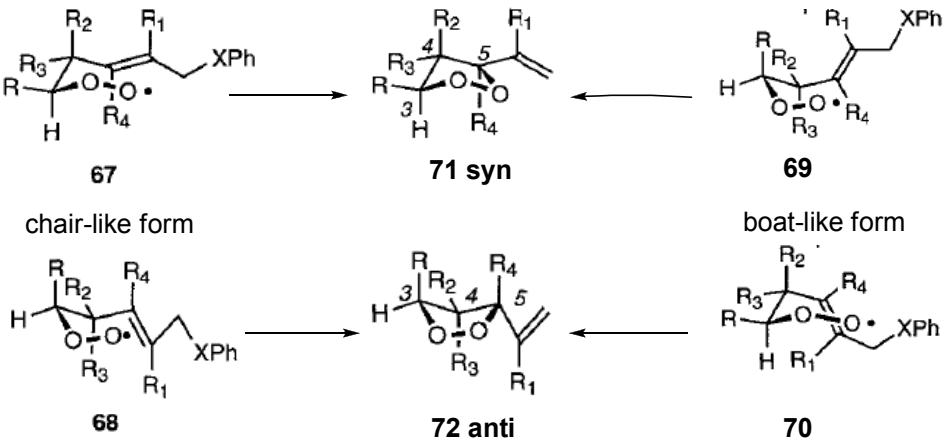
Cons:

1. Not easy to control (low dr. and ee)
2. Need reductive procesure
3. Initiator of S or Se compound is needed

Mechanistic study



Steric effect of substituents in syn/anti selectivity



1. Chair-like conformation and an equatorial substituent R at C(3) provides the lowest energy pathway in most cases, which makes syn-form **71** as major product.

2. As increasing size of vinyl substituent R only had onlymodest stereoselectivity(**26f-h**) but reversion of sterwochemical preference occured(**26f,i**), these result indicates **68** is main route attribute to anti-form **72.**

Electronic effect

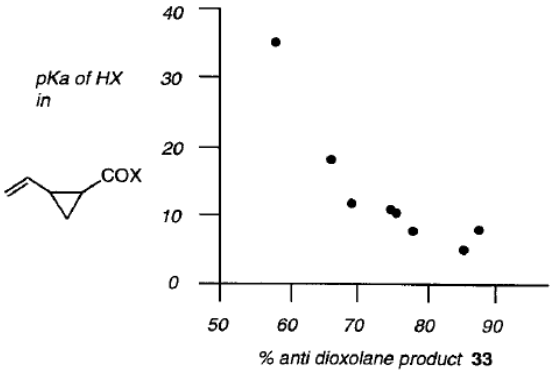
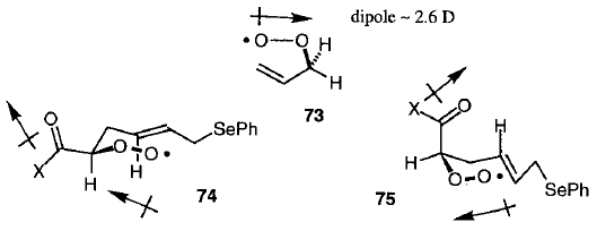
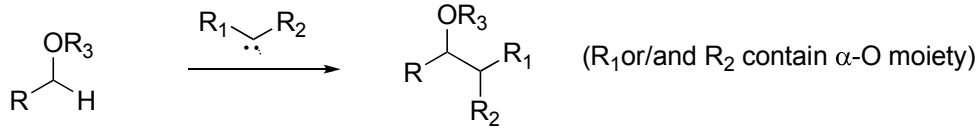


Figure 1. % Anti dioxolane vs. pKa of the parent alcohol, thiol or amine of the carbonyl substituent X in **26.**



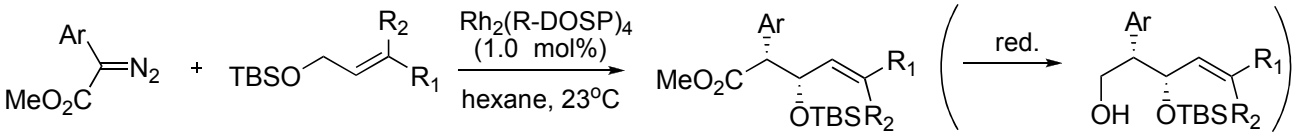
2. Carbene insertion to alchohol moiety α-C-H bond

Strategy

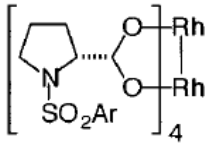


(R_1or/and R_2 contain α-O moiety)

Report H.L. Davies et al. OL, 1999, 1, 383-85



entry	Ar	R1	R2	yield, %	de, %	ee, %
1*	p-ClPh	H	Et	48	76	-
2*		Me	Me	44	70	-
3*		Me	H	72	96	-
4		Me	H	72	96	80
5		Ph	H	70	97	85
6		$CH=CH_2$	H	71	98	74
7		H	H	35	98	90
8	Ph	H	H	52	>94	92



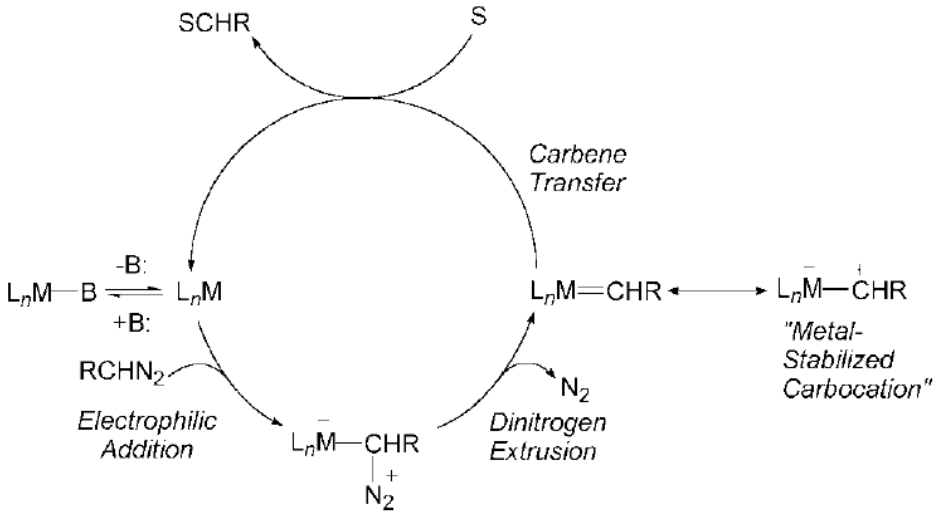
Ar = p-$C_{12}H_{25}C_6H_4$

Rh_2(*R*-DOSP)$_4$

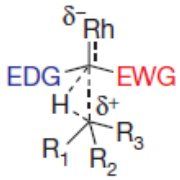
* Using racemic catalyst

Mechanistic Study

Catalytic cycle of metallo-carbenoid insertion to C-H bond



Doyle et al. Chem. Rev. 2010, 704-24



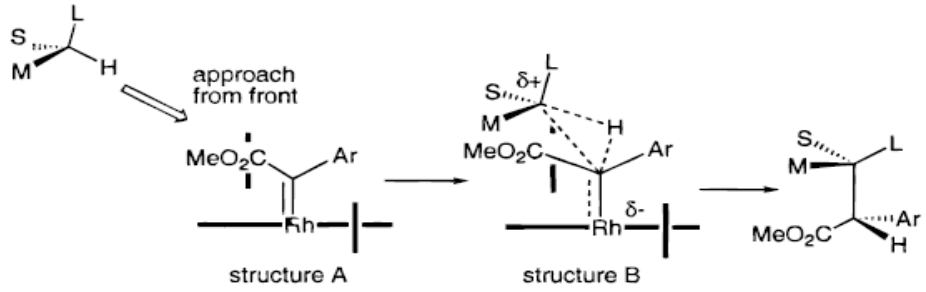
Facile C–H insertion at activated sites
positive charge buildup at insertion site
stabilized when R = N, O, aryl, vinyl

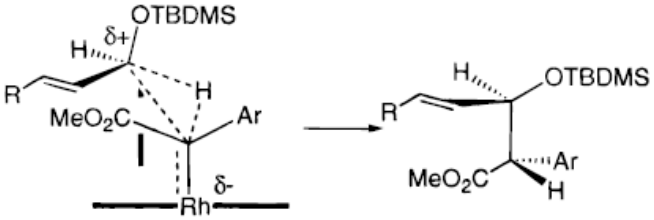
EDG/EWG co-substituted carbenoid gains unique properties:

1. Undesired carben dimerization pathway is significantly reduced.

2. Selectivity of intermolecular C-H insertions is increased.

Reviewed by:
H.M. Davies *et al. Nature*, **2006**, *451*, 417-424

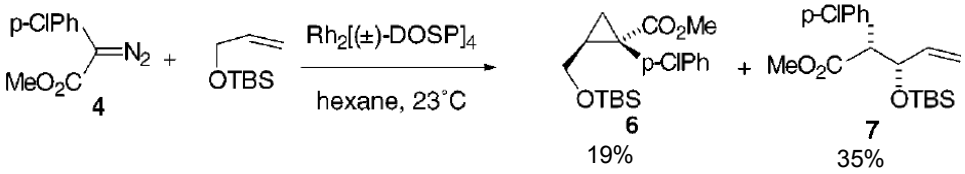




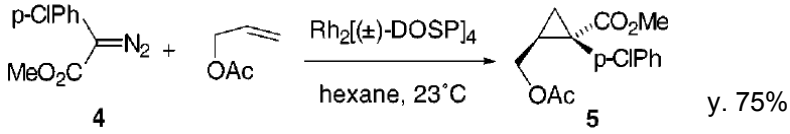
The large group(L) projects upward from cat.

The small group(S) points toward cabenoid and the middle group(M) projects away from carbenoid.

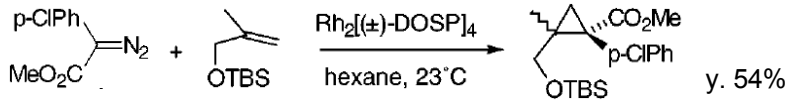
However, the substition type of the allyl substrate influence the result of this reaction significantly.
The major side reaction is cyclopropanation.



When allyl acetate was used instead of silyl-ether, cyclopropanation became exclusive reaction.

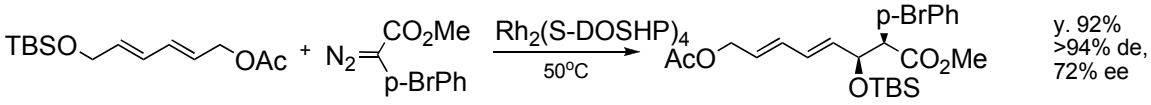


Also, when 2-methylpropenyl silyl ether was used, cyclopropantion proceeded without C-H insertion product.



These results indicate :

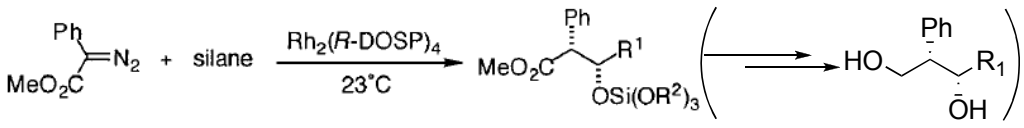
(1) Electron rich site proceeds insertion easily.Carbenoid prone to proceed insertion to C-H bond adjacent to EDG rather than EWG.



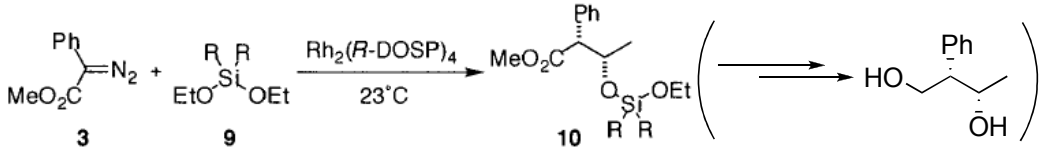
H.M. Davies et al. JOC, 2003, 68, 6126-32

(2) The steric factor influence carbenoid C-H insertion significantly.

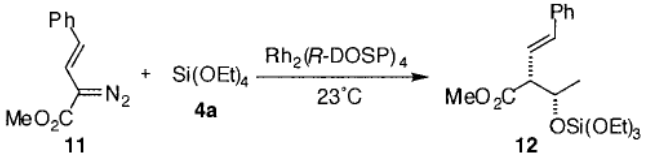
Report 2 H.M. Davies et al. OL, 2, 4153-56



	silane	R^1	R^2	yield, %	de, %	ee, %
a	$Si(OEt)_4$	CH_3	Et	70	>90	95
b	$Si(OPr\text{-}n)_4$	CH_2CH_3	Pr	52	>90	92
c	$Si(OBu\text{-}n)_4$	$CH_2CH_2CH_3$	Bu	58	>90	93
d	$Si(O\text{-}iPr)_4$	CH_3,CH_3	i-Pr	10	-	68

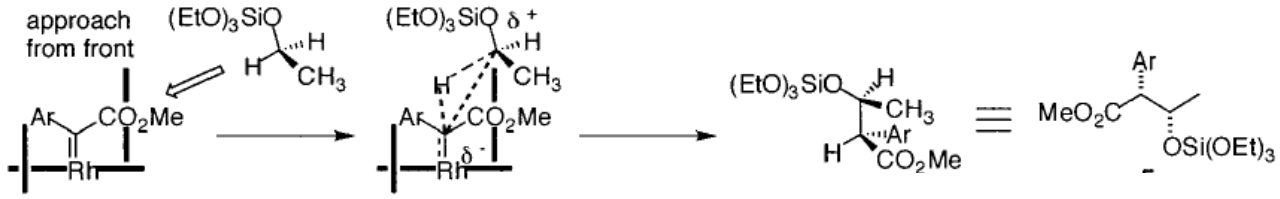


	R	yield, %	de, %	ee, %
a	Me	51	>90	93
b	Ph	52	>90	94



y. 32%
80% de
97% ee

The mechanism of this reaction is supposed to be similar to the former one.



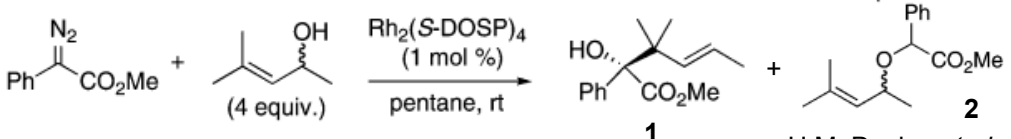
Summary:

Pros:

1. Carbenoud insertion one of the limited methods that can achieve high regioselectivity and enantioselectivity in C-H activation by now.
2. This method provides an alternative to tradittional pathways.

Cons:

1. The yield is moderate in most case and always have side reaction.
2. Substrate scope is still quite limited. And direct insertion between two alchohol would be hard to be achieved, as insertion direct O-H is highly competitive.



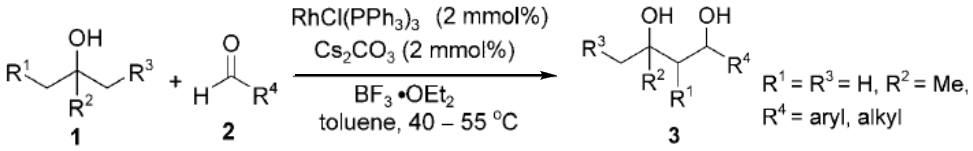
y. 86% **1**:**2**= 6:1
86% ee

H.M. Davies *et al. JACS*, **2010**, *132*, 396-401

3. Direct C-C Cross-Coupling

Coupling of Alchohols at β–position with Aldehyde

Report: Y-Q. Tu *et al. Adv. Synth. Catal.* **2008**, *350*,2189-93

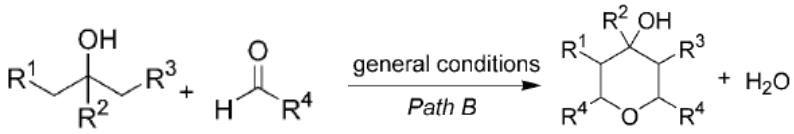


1 2 3

Entry	Substrate	Product	Yield [%][b]
1	2a	3a	65
2	2b	3b	76
3	2c	3c	47
4	2d	3d	74
5	2e	3e	55 (91[c])
6	2f	3f	42
7	2g	3g	63

[a] *General conditions:* **2** (1.0 mmol), **1** (2.5 mmol.), $RhCl(PPh_3)_3$ (2 mmol%), $CsCO_3$ (2 mmol%), and $BF_3{\cdot}OEt_2$ (1.5 mmol) in toluene for 3-12 h.
[b] Isolated yield based on the aldehyde **2** used.
[c] Yield based on recovered starting material.

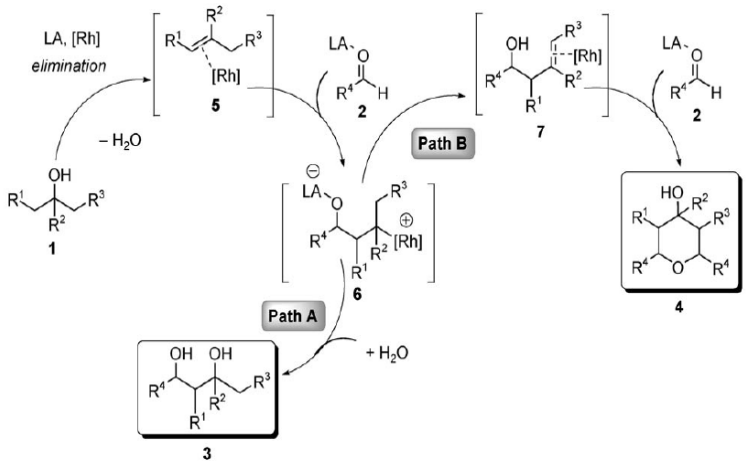
So far, this is the only report which achieved this type of reaction. However, substrate of this reaction was limited to t-BuOH only. When switch to other kinds of alchohol, a competing path which generate THP skeleton.



alchohol	aldehyde	product	yield(%)
1a			72
1a			54
			65
	2a		63
	2a		37

a. General conditions: **2** (1.0 mmol), **1** (2.5 mmol), $RhCl(PPh_3)_3$ (2 mmol%), $CsCO_3$ (2 mmol%), BF_3-Et_2O (1.5 mmol) in toluene for 3-12h.
b. The dr of **4a** is 3:2, and for **4b-4e** only one diastereomeric form was isolated.
c. Isolated yield based on the aldehyde 2 used.

Mechanism proposed by author:



Author proposed a pathway that includes dehydration and LA-activated/Rh catalyzed Prins-type reaction.

Though the detailed reaction mechanism is still unclear, the fact that either $RhCl(PPh_3)_3$ or BF_3-Et_2O alone could
not effectively promote this coupling reaction in parallel experiments suggests co-work of LA and Rh-catalyst is essential.

Summary:

Pros:

1. The only report that achieved direct coupling from alchohol and aldehyde to form 1,3-diol up to now.
2. Protection free, easily achievable reaction condition.

Cons:

1. Very limited substrate scope
2. Yields are no more than moderate
3. Competitive pathway

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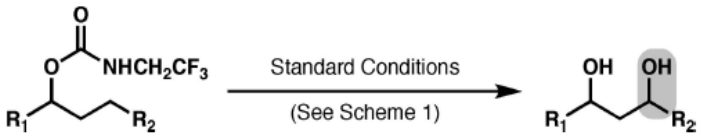
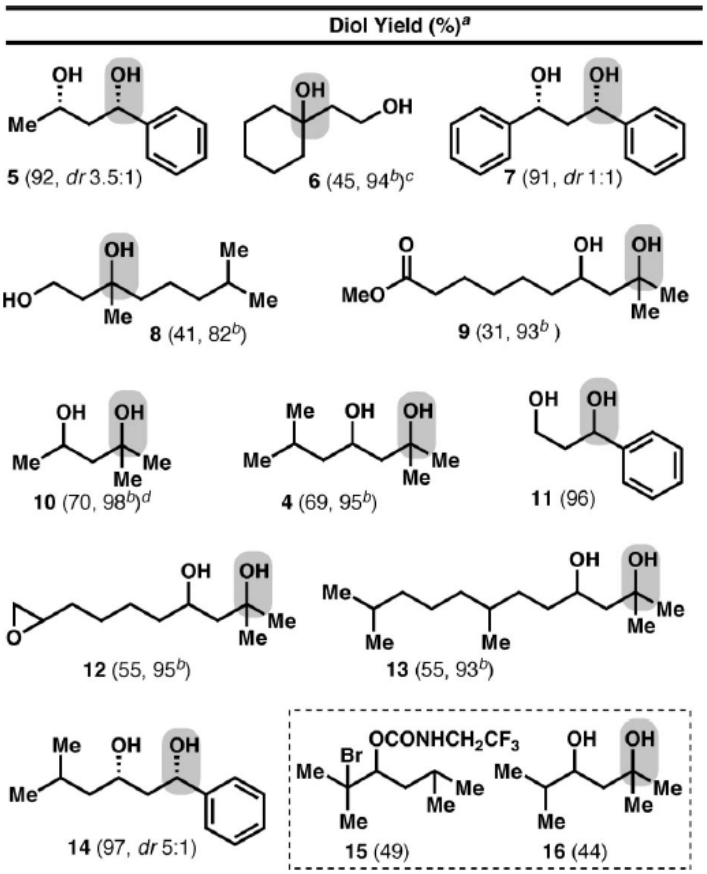
4. Selective C-H Oxidation

Selective oxidation oriented by directing group

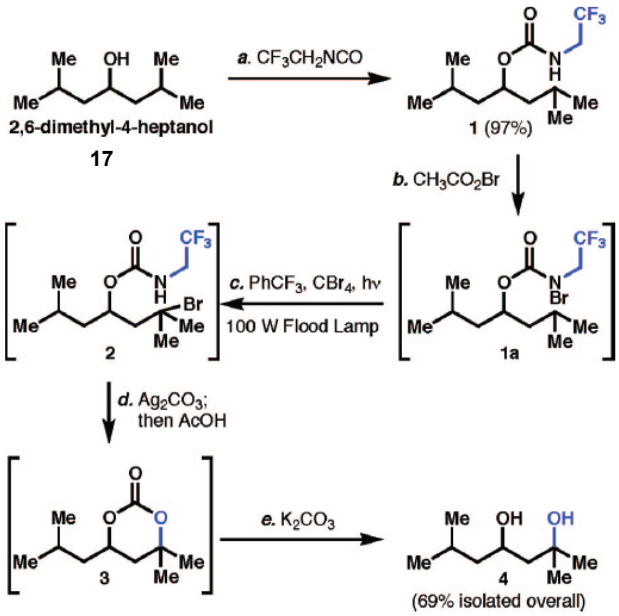
Report: P.S. Baran *et al*. *JACS*, **2008**, *130*, 7247-49





Scheme 1

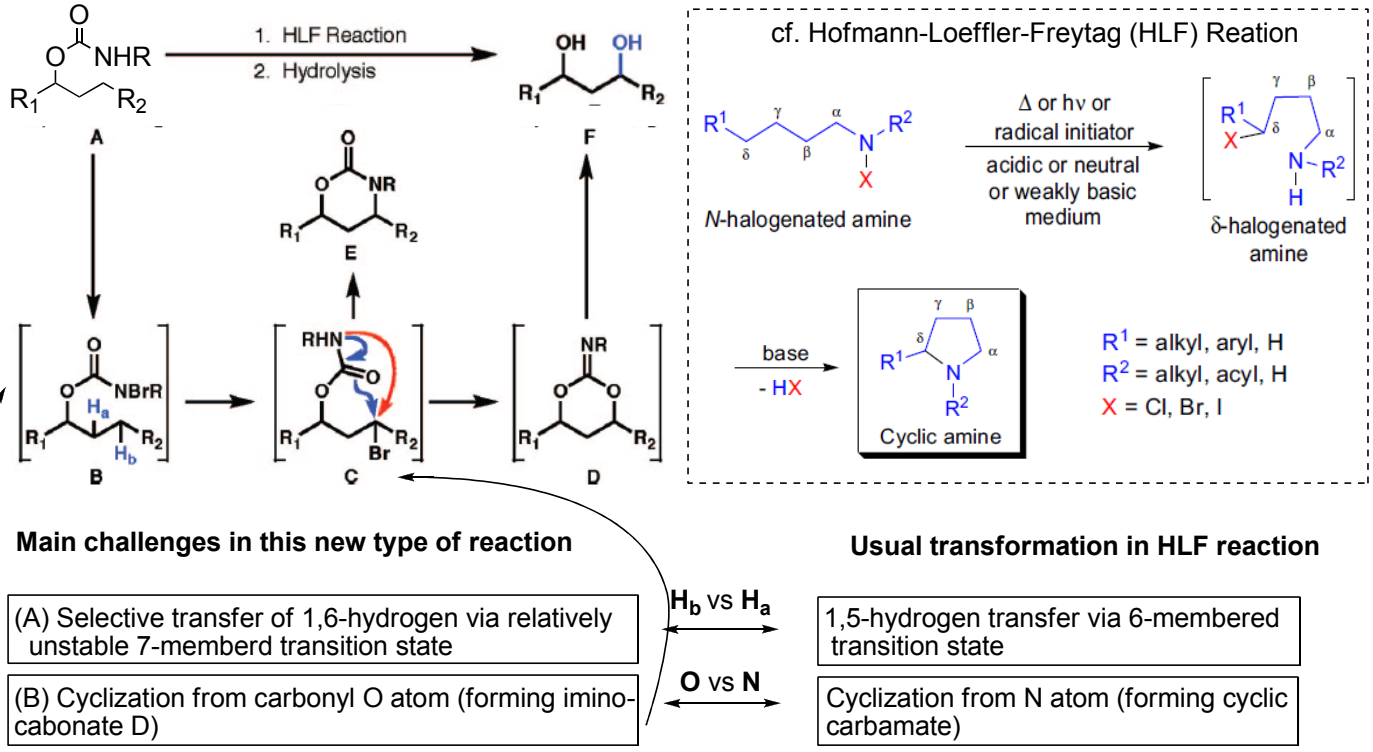
General procesure (Take **17** as example)



[a] Reagents and conditions: (a) CF_3CH_2NCO (1.0 equiv), DCM, Pyr (1.0 equiv), 23 °C, 2 h, 97%; (b) CH_3CO_2Br (1.0 equiv), DCM, 0 °C, 5 min; (c) $PhCF_3$ (0.05 M), CBr_4 (1.0 equiv), 23 °C, hν, 7 min; (d) Ag_2CO_3 (1.25 equiv), DCM, 23 °C, 1 h; then AcOH, 15 min; (e) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 2 h, 69% overall. DCM = dichloromethane, Pyr = pyridine.

[a] Isolated yield. [b] Yield brsm. [c] CBr_4 is not necessary. [d] A 56% isolated yield on gram scale; 88% yield brsm.

Strategy



Main challenges in this new type of reaction

Usual transformation in HLF reaction

(A) Selective transfer of 1,6-hydrogen via relatively unstable 7-memberd transition state	**H_b vs H_a**	1,5-hydrogen transfer via 6-membered transition state
(B) Cyclization from carbonyl O atom (forming imino-cabonate D)	**O vs N**	Cyclization from N atom (forming cyclic carbamate)

Solution to challenge A --- Tuning the side chain on N atom

The side chain on carbamate N bears great influence on the reactivity of N-bromocarbamates

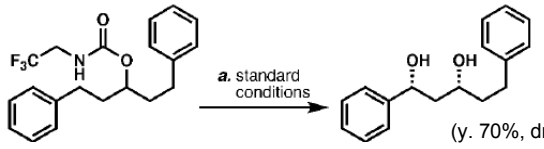
The more electron-withdrawing group it is, the higher the reactivity was obtained.

Solution to challenge B --- Employing Ag_2CO_3 to promote cyclization to iminocarbonate

Summary:

Pros:

1. Provide an unprecedent way directly convert alchohols to 1,3-diols, also with relative high efficiency.

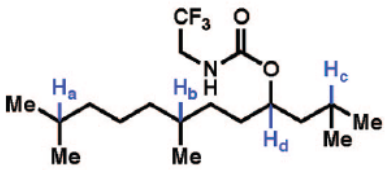


Previous synthesis: 4 steps, 12%

J.G. Rico et al. TL, 1984, 25, 5977-80

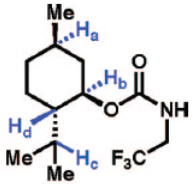
(More aplications of this method in total synthesis please refer to Dr. Yin's Lit-seminar handout)

2. Shows excellent regioselectivity among dierect C-H oxidation methods.



Oxidation prodduct

- This method: single regioisomer at H_c, 55%
- White catalyst(Fe-based): H_a : H_b in 3:1, 42%, no H_d
- Curci method(dioxirane): complex mixture, 91%



Oxidation prodduct

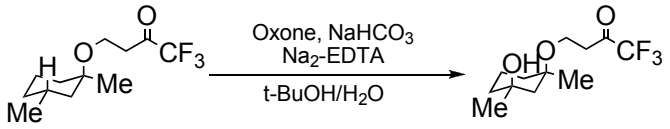
- This method: single regioisomer at H_c, 42%
- White catalyst(Fe-based): single regioisomer at Ha, 51%
- Curci method(dioxirane): complex mixture, 86%

Cons:

1. Only benzylic and tertiary C-H are oxidized in synthetically useful yields.
2. Olefins, free carboxylic acids, amines, amides, unprotected alchohols, and azides are not tolerated.

Other methods of 1,3-diol moiety construction via selective C-H oxidation via directing group

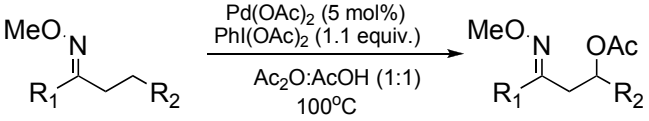
a.



y. 51% other 5 samples

M. Inoue *et al. OL*, **2009**, *11*, 3630

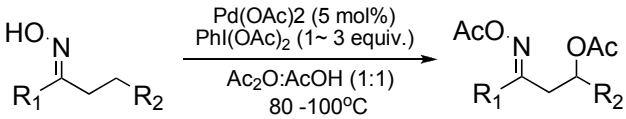
b.



y. 39%~86% 8 samples

Sanford *et al. JACS*, **2004**, *126*, 9542

c.



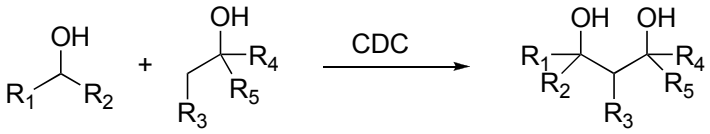
y. 33%~66% 6 samples

Sanford *et al. OL*, **2010**, *12*, 532

(More detail please refer to Dr. Yin's Lit-seminar handout)

Perspective of 1,3-Diol Moiety Induction via Selective C-H Activation

(1) Direct Cross Dehydrogenative Coupling between Two Alchohols



So far this type of reaction has not been achieved yet.

Main probable challenges in this reaction:

1.Selective activation of α-C-H bond in one alchohol and β–C-H bond in another.

2. Reactivity control to prevent over oxidation and polymerization

Perspective:

1. This type of reaction is highly atom-economic
2. Would be very friendly to environment, when O_2 is directly used as oxidant.

(2) Ultimate Oxidation ----- Selective Oxidation of C-H in "desired" site

The most ideal way to get 1,3-diol moiety would be selective oxidation to two-1,3-positioned sp^3 C-H bonds, without directing groups, only using O_2 as oxidant, hopefully also with diastereao- and enantio-selectivities. This idea sounds nearly "Mission Impossible", because even enzymes could not accomplish such task.

However, recent years some achievement in selective oxidation of unacticvted sp^3 C-H brought light on this "impossible" task.

(A)Predictable selective oxidation solely on the base of the electronic and stetic properties of C-H bond was achieved.

----"A predictablely Selective Aliphatic C-H Oxidation Reaction for Complex Molecule Synthesis"

M.C. White *et al. Science*, **2007**, *318*, 783-87

(Detail please refer to Dr. Yin's Lit-seminar handout)

(B) Predicable and high chemo-,site-, and even diastereao-selective oxidation of **methelene** C-H bonds was achieved.

----"Combined Effects on Selectivity in Fe-catalyzed Methylene Oxidation"

M.C. White e*t al. Science,* 2**010,** 327*,* 783-87