Terpene Cyclization inside supramolecular capsule catalyst

2017 8/26

M2 Kei Ito

1. Introduction

2. Today`s contents
~tail-to-head terpene (THT)
cyclization in capsule catalyst~

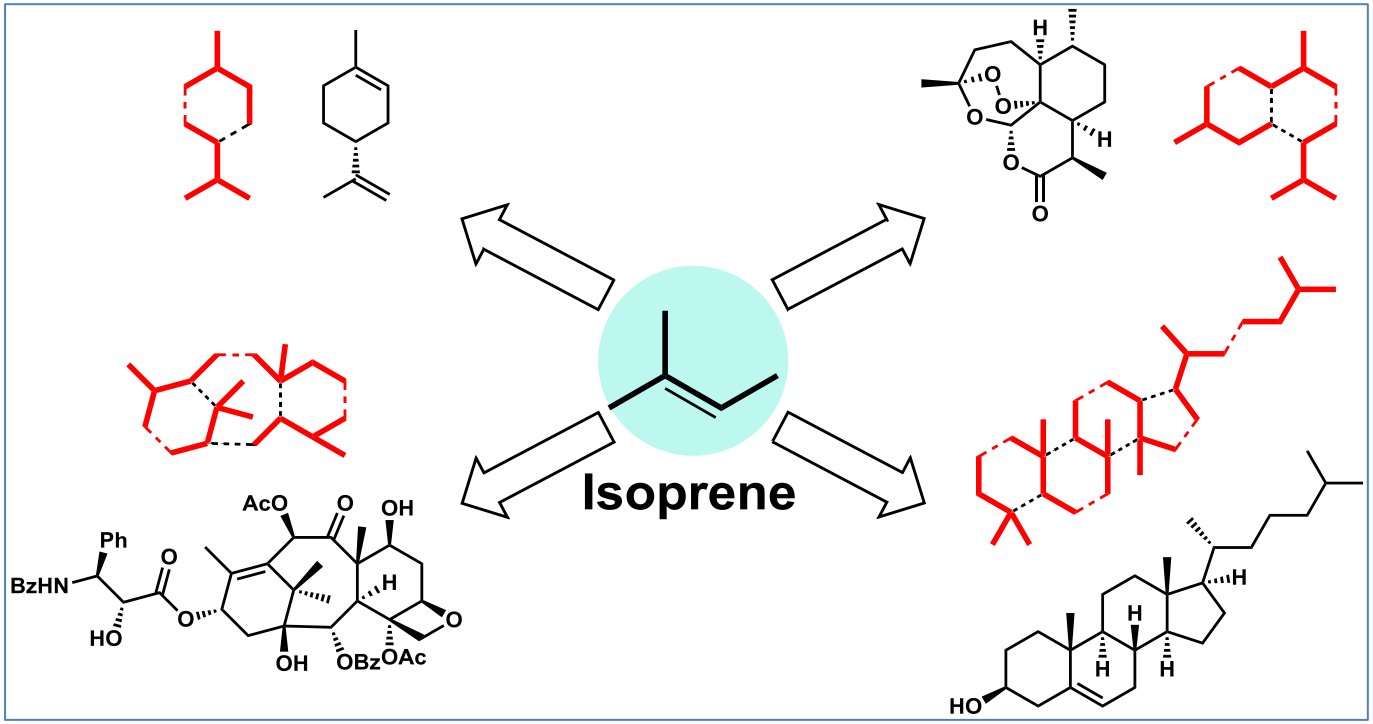
3. Summary

Terpenes, Terpenoids

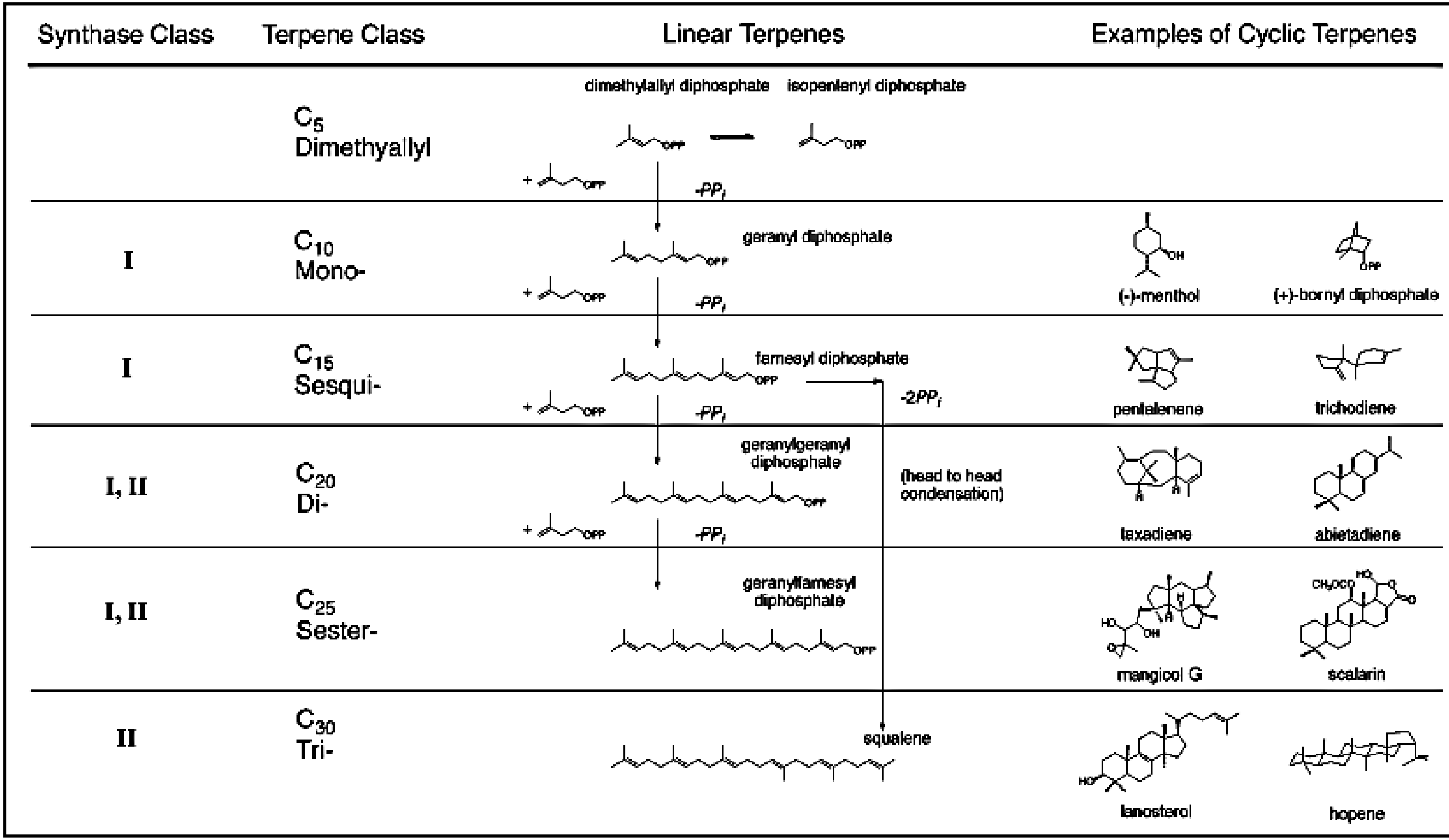
Isoprenoids ••• Compounds formally derived from isoprene

- **Terpenes ••• Hydrocarbons of biological origin having carbon skeltons derived from isoprene**
- **Terpenoids ••• Natural products and related compounds formally derived from isoprene units (Contain oxygen in vrious functional groups)**

IUPAC GOLD BOOK

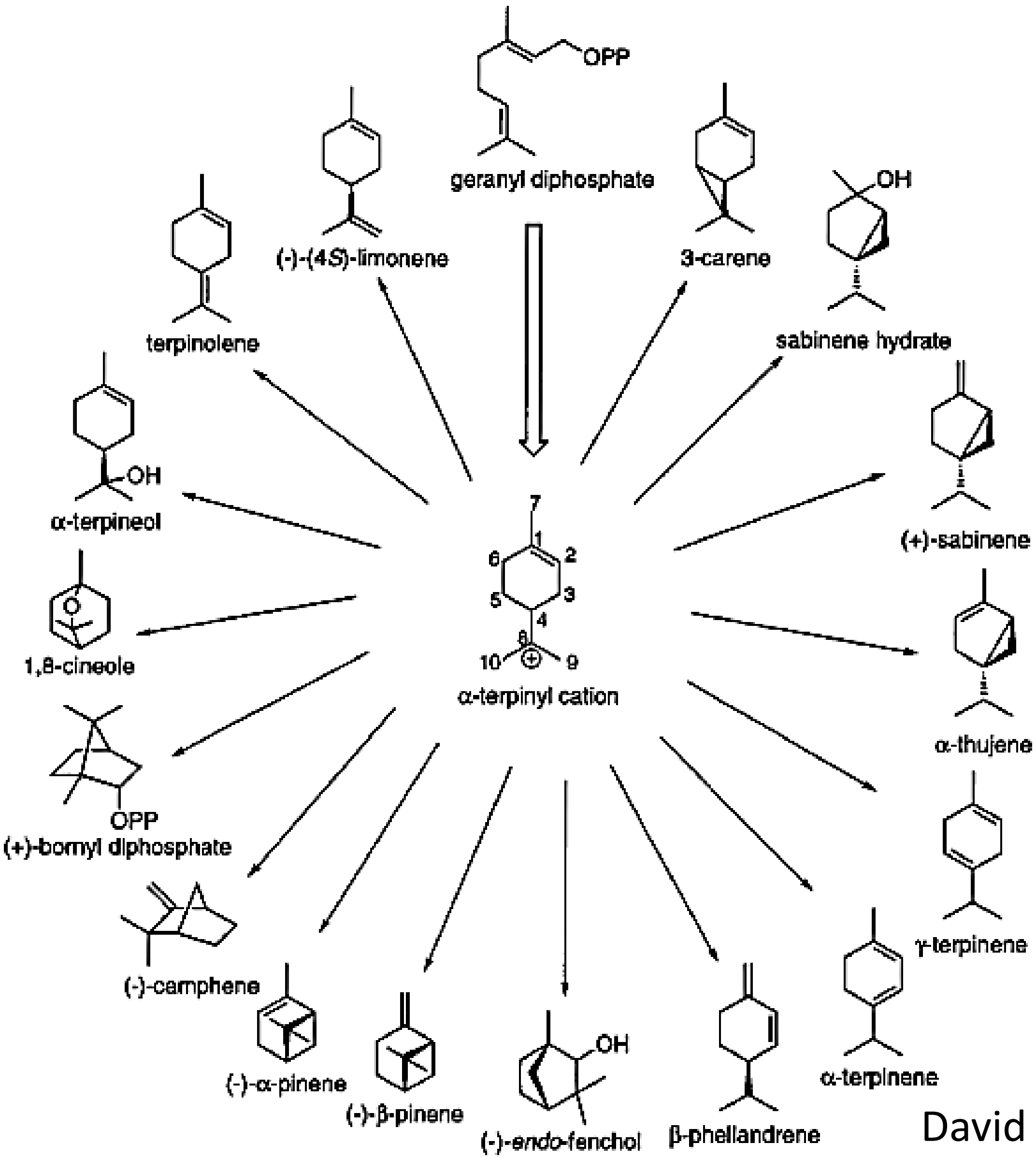


Category of terpene, terpenoid



David W. *Chem. Rev*, **2006**, 106, 3412-3442

Diversity of terpene, terpenoid



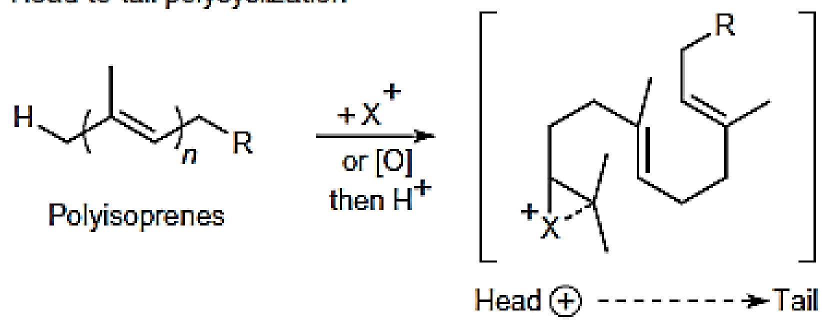
Simple Mono-Terpene has structurally diversity

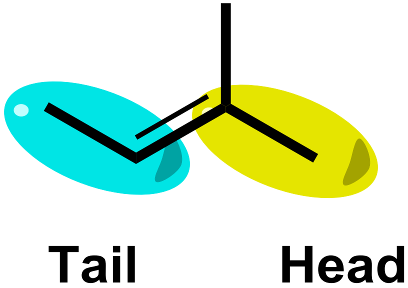
David W. *Chem. Rev*, **2006**, 106, 3412-3442

HTT and THT cyclization

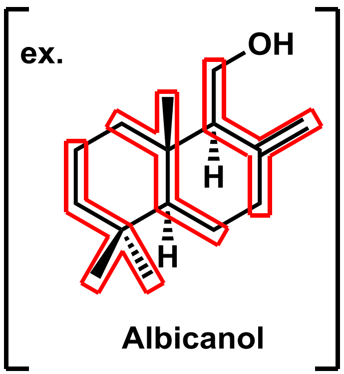
HTT (Head-to-Tail Terpene)

a Head-to-tail polycyclization



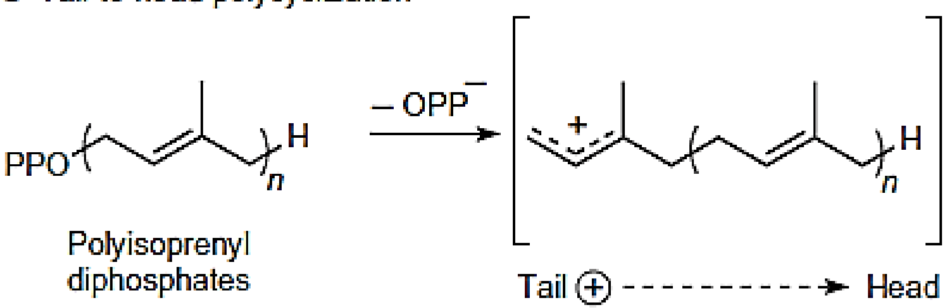


- **Reproducible in bulk solvent**
- **Mainly yielding decaline framework**



THT (Tail-to-Head Terpene)

b Tail-to-head polycyclization

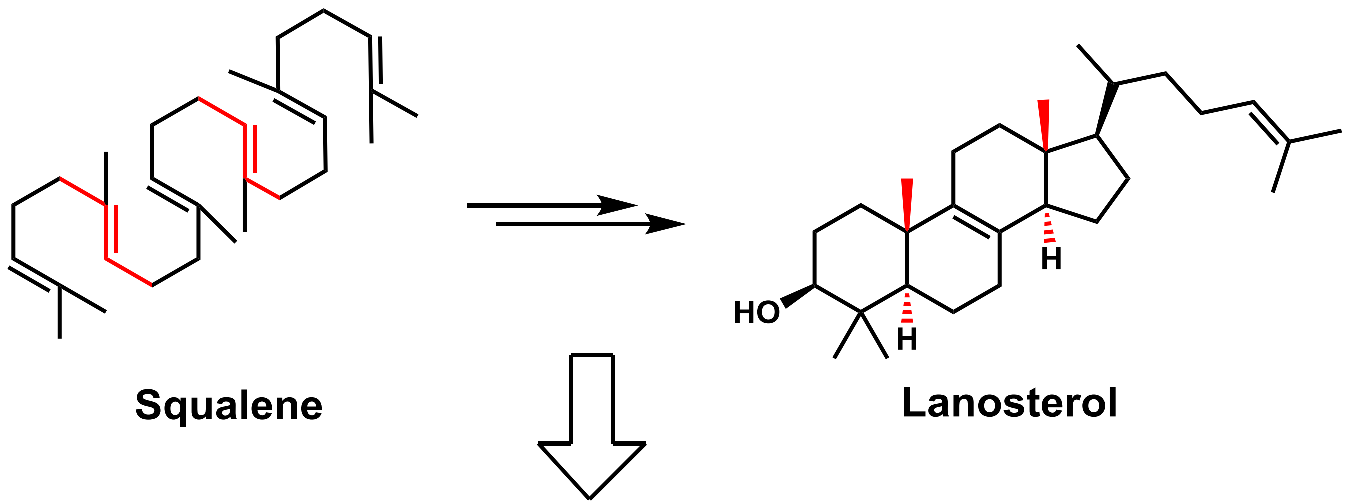


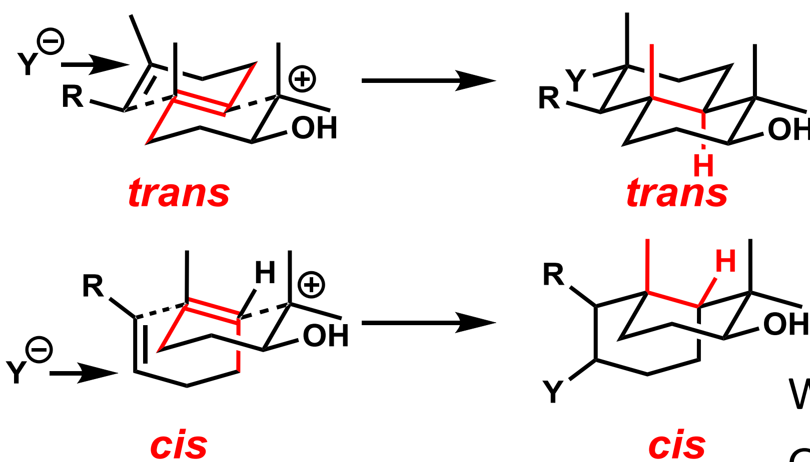
- **Lacking example in bulk solvent (Man-made catalyst)**
- **Produce a diverse variety of frameworks**

Surgey V. *et. al, Nat. Chem,* **2012**, 4, 915

HTT cyclization(1)

Stork-Eschenmoser`s hypothesis (1950`s)





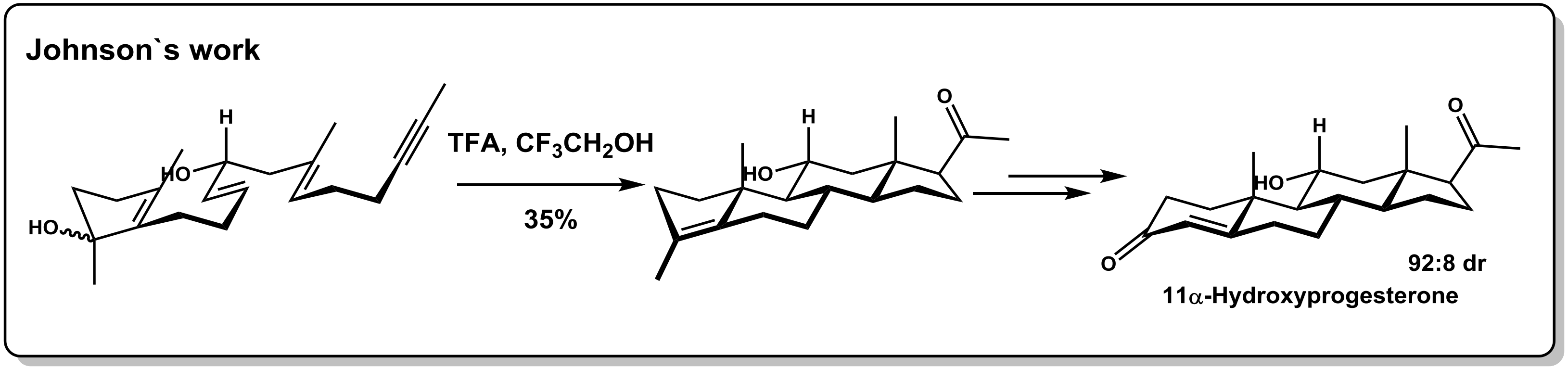
W. S. Johnson, *Acc. Chem. Res*, **1968**, 1, 1

G. Stork. *et. al*, *J. Am. Chem. Soc*, **1955**, 77, 5068

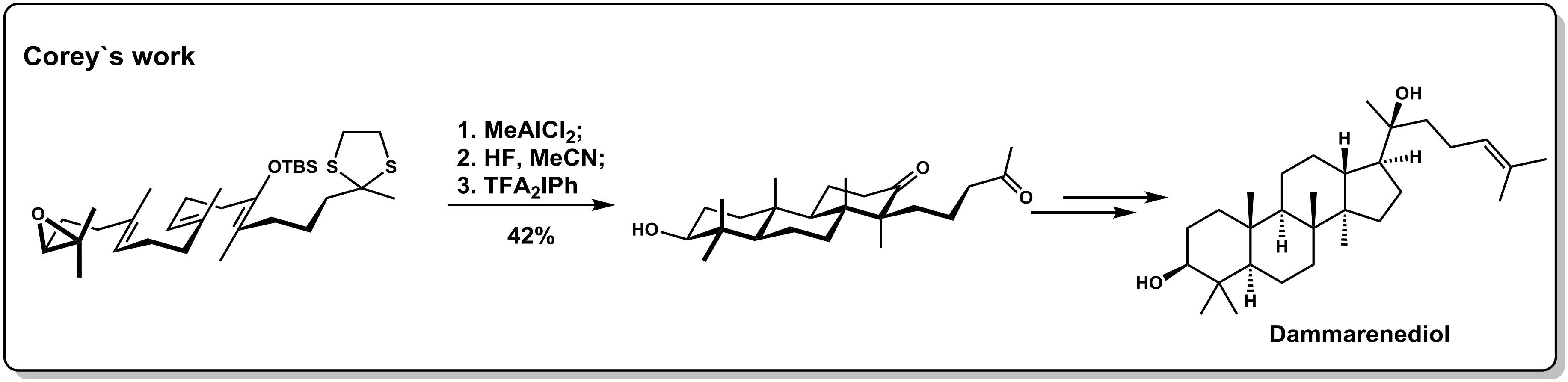
A. Eschenmoser. *et. al*, *ibid*, **1955**, 38, 1890

HTT cyclization(2)

Biomimetic synthesis of steroids



William. S. Johnson. *et. al*, *J. Am. Chem. Soc*, **1977**, 99, 8341



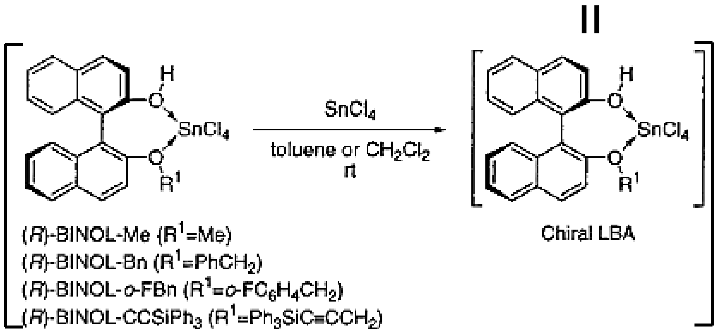
Corey. E. J. *et. al, J. Am. Chem. Soc*, **1996**, 118, 8765

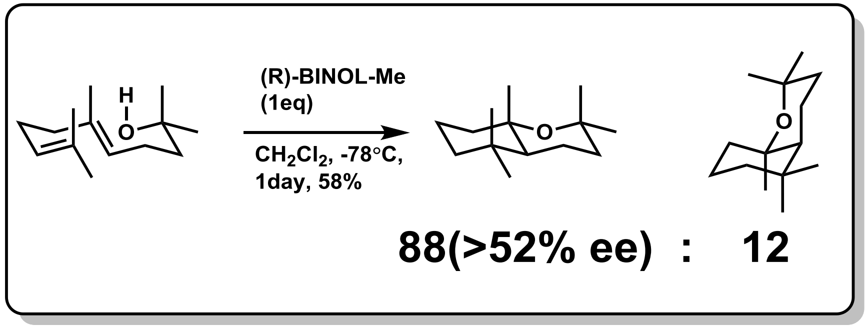
HTT cyclization(3)

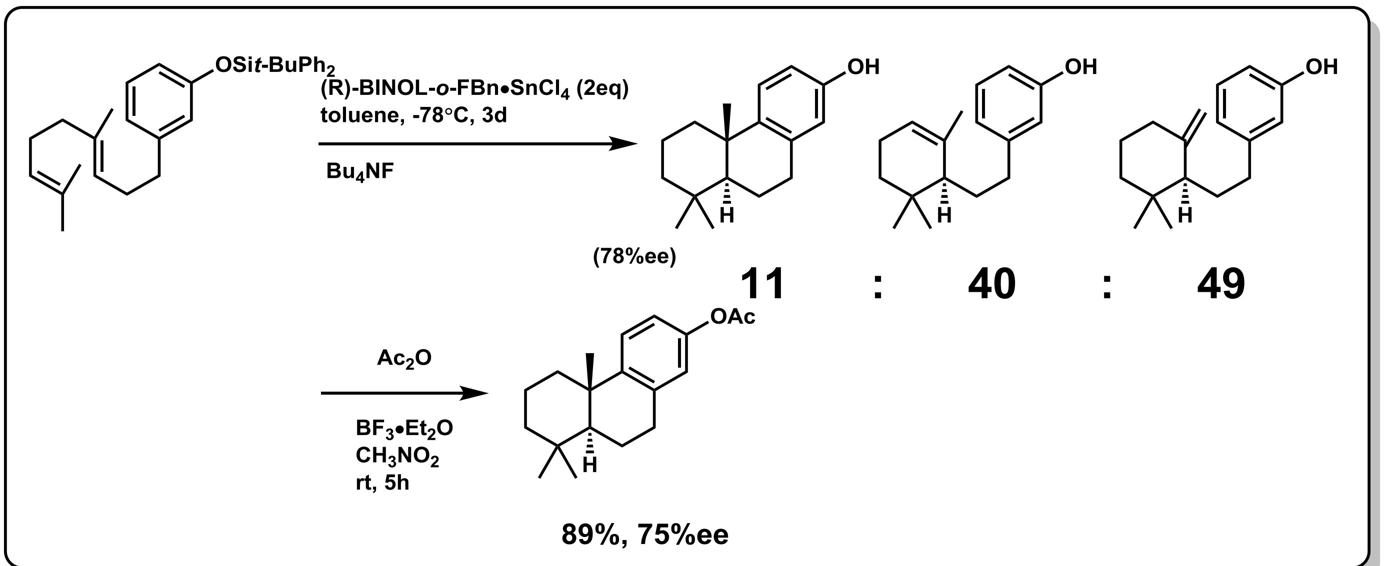
Enantioselective biomimetic cyclization

Chiral LBA(Lewis-Base assisted chiral Brφnsted Acids)

First example of enantioselective cyclization





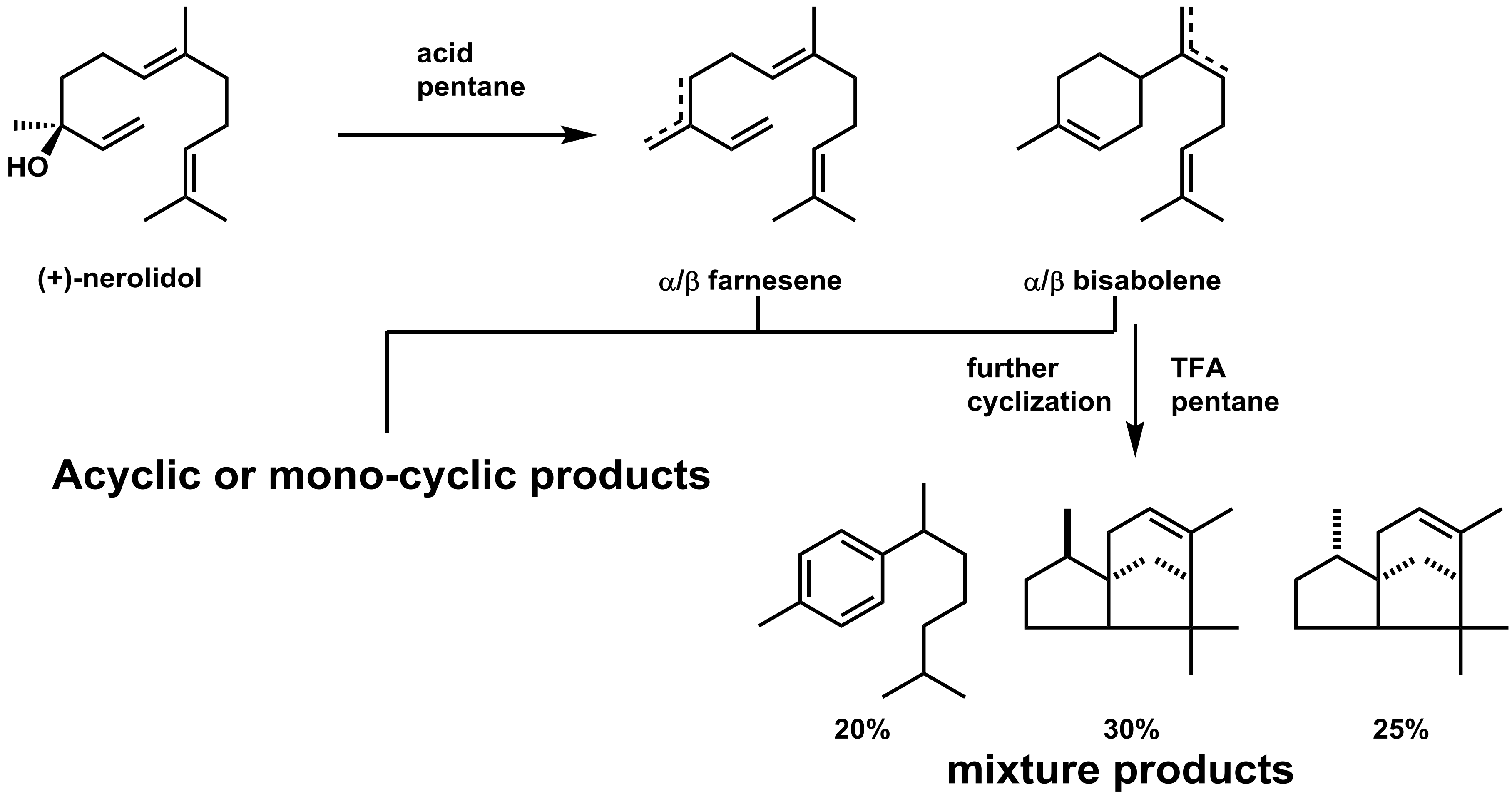


Yamamoto. H. *et. al*, *J. Am. Chem. Soc*, **1999**, 121, 4906

Yamamoto. H. *et. al*, *J. Am. Chem. Soc*, **2002**, 124, 3647

Difficulty of THT cyclization(1)

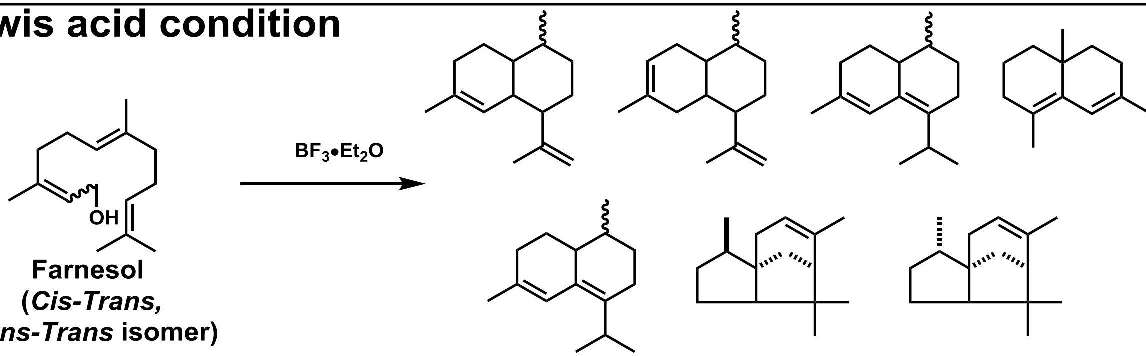
THT cyclization in acidic condition



D. D. Syrdal. *et.al*, *Tetrahedron. Lett*, **1972**, 24, 2455

Difficulty of THT cyclization(2)

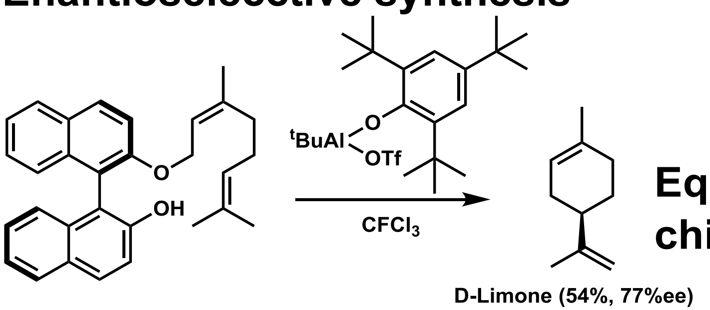
Lewis acid condition



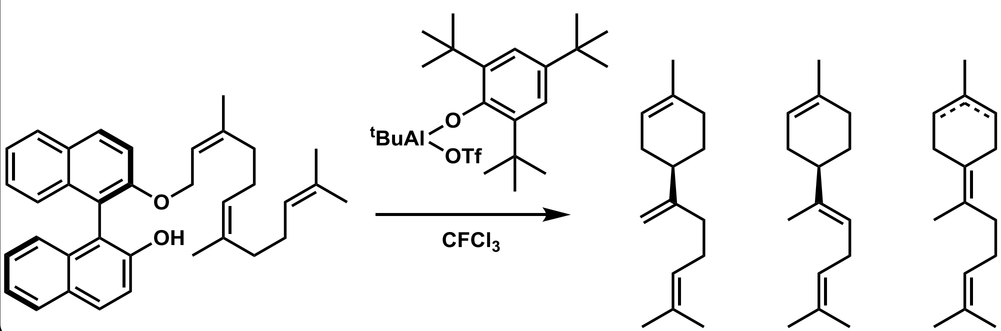
Mixture products

Hirose. Y. *et.al*, *Chem. Lett*, **1972**, 263

Enantioselecctive synthesis



Equivalent amount of chiral binol is need•••

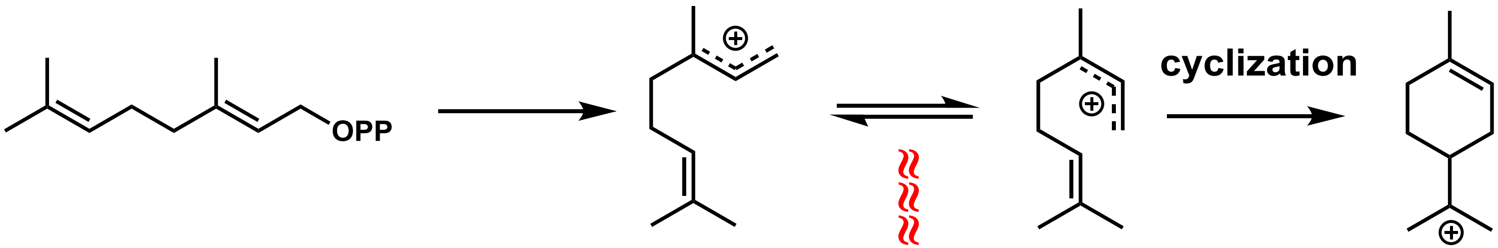


Mono-cyclized product only•••

Yamamoto. H. *et.al*, *J. Am. Chem. Soc*, **1983**, 105, 6154

What makes THT cyclization difficult?(1)

① *Transoid-Cisoid* isomerization (1`st cyclization)

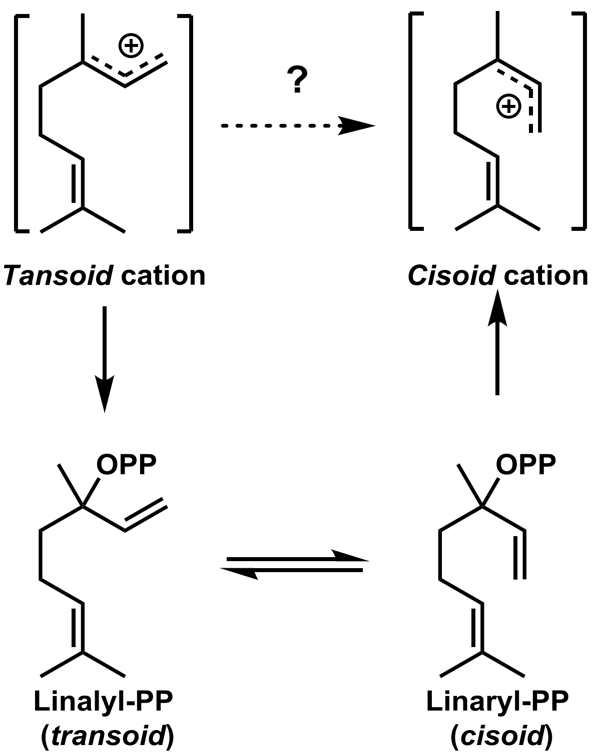


Tansoid cation *Cisoid* cation

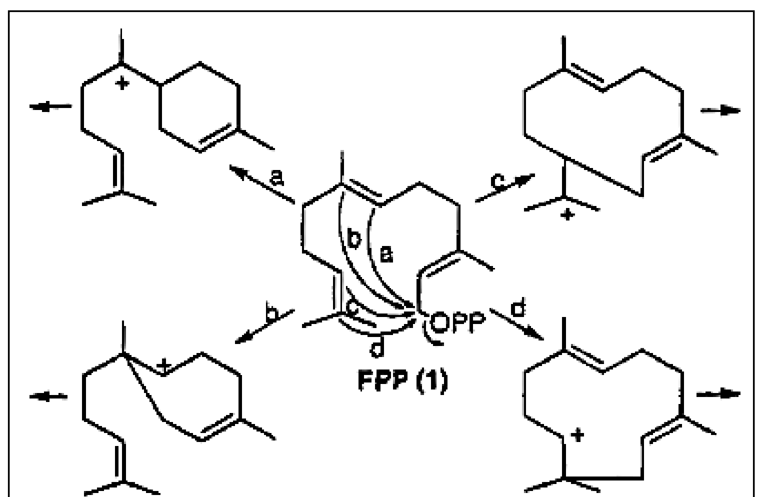
high energy barrier
(12 kcal/mol)

Norman. L. Allinger. *et. al*, *J. Am. Chem. Soc*, **1975**, 97, 752

In biosynthesis



In case of FPP

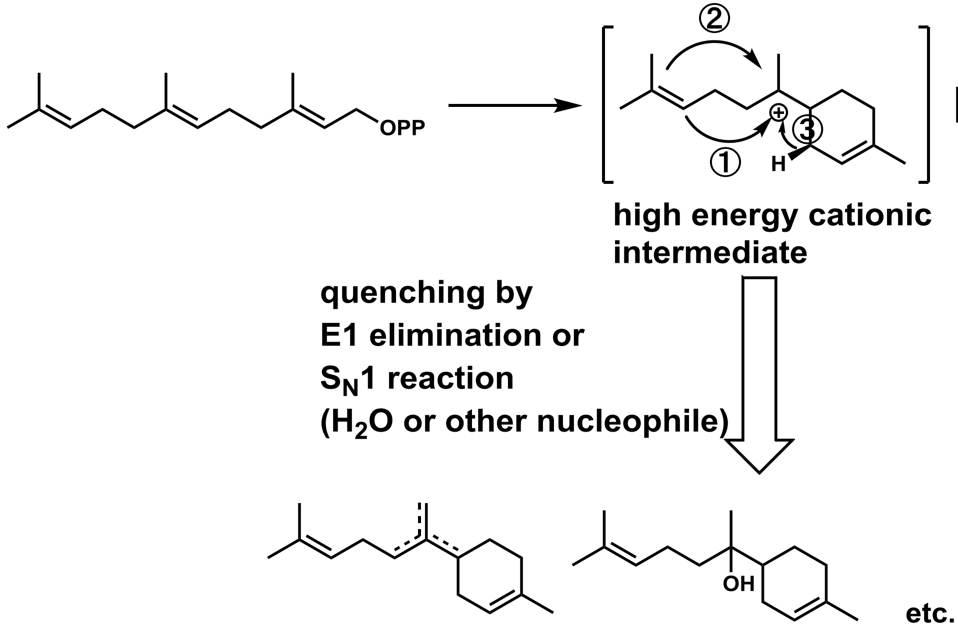


4 possible first cyclizations

David W. *Chem. Rev*, **2006**, 106, 3412-3442

What makes THT cyclization difficult?(2)

② Stabilization of cationic intermediate

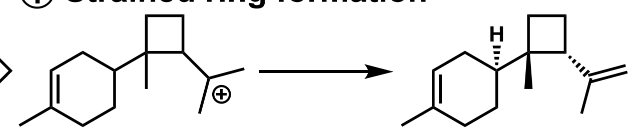


In bulk solvent

Stabilization of cationic intermediate is absent

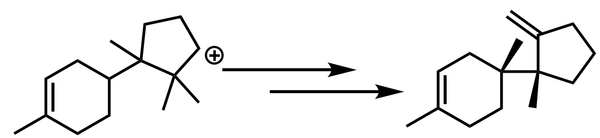
For further cyclization…

① Strained ring formation



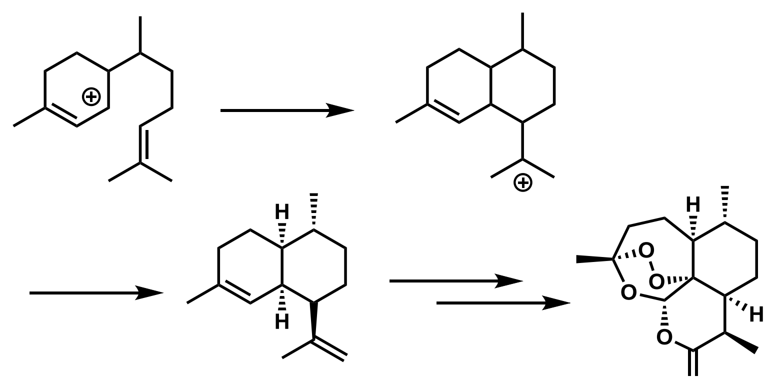
Cumacrene

② Anti-Markovnikov alkene addition



Trichodiene

③ Wagner-Meerwein rearrangement ([1,3]-hydride shift)



Amorpha-4,11-diene

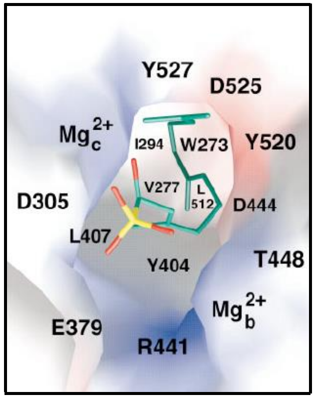
Artemisinin

Surgey V. *et. al, Nat. Chem,* **2012**, 4, 915

Rudolf. K. Allemann, *et. al, Bioorganic & Medicinal Chemistry,* **2017**, ASAP

What makes THT cyclization difficult?(3)

③ **Random conformations of substrates**



In biosynthesis

Conformation of substrate is restricted in enzyme pocket

Joseph. P. Noel. *et. al*, *Science*, **1997**, 277, 1815

In bulk solvent

Substrates adopt random conformations

⇩

Giving complex product mixtures(Previous slide)

1. Introduction

2. Today`s contents
~tail-to-head terpene (THT)
cyclization in capsule catalyst~

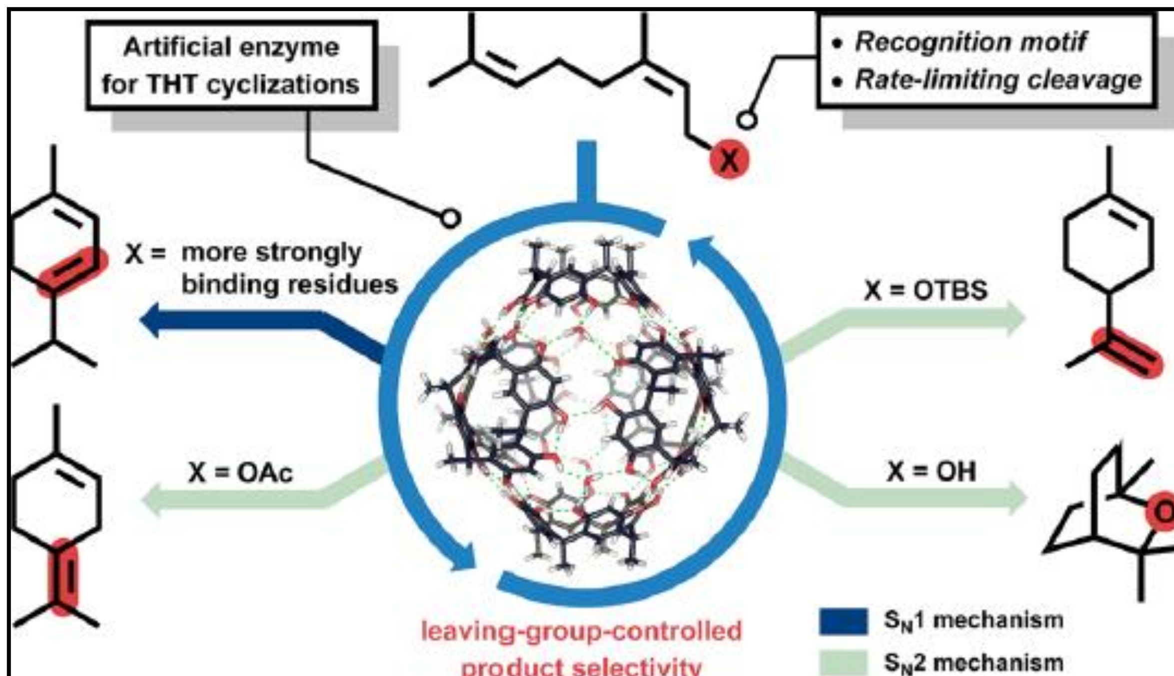
3. Summary

Today`s topic

Konard Tiefenbacher

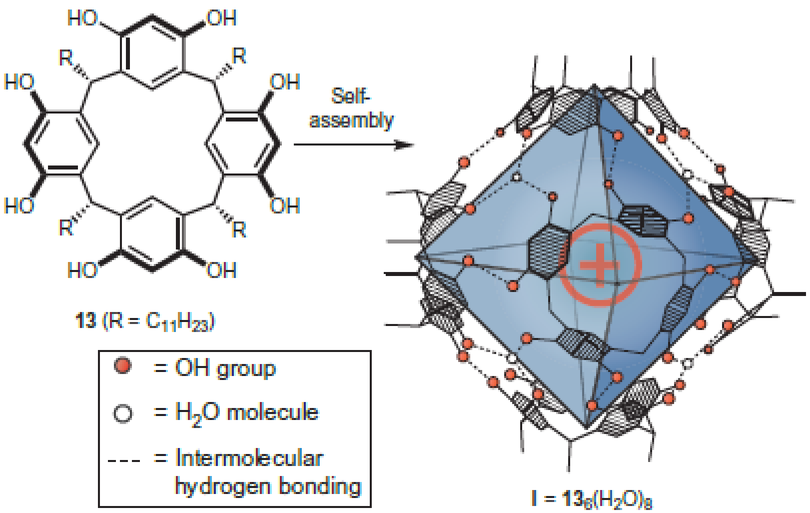
University of Basel Department of chemistry
ETH Zürich Department of Biosystems Science and Engineering

https://nanocat.chemie.unibas.ch/en/welcome/konrad/



Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

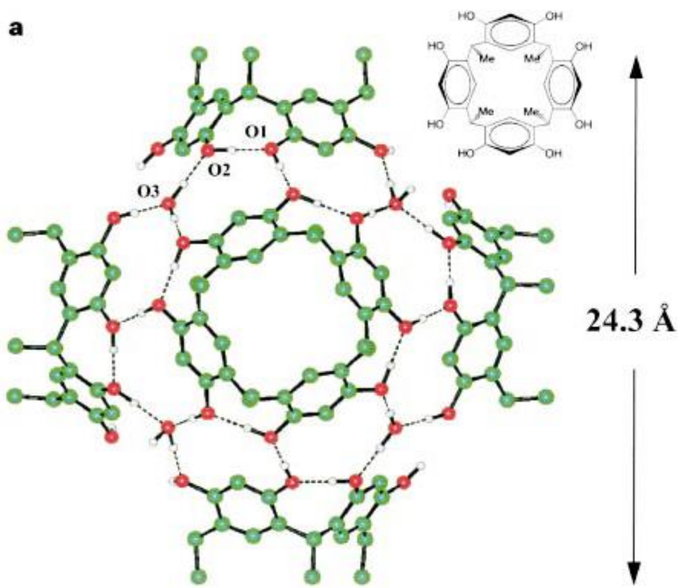
Supramolecular capsule

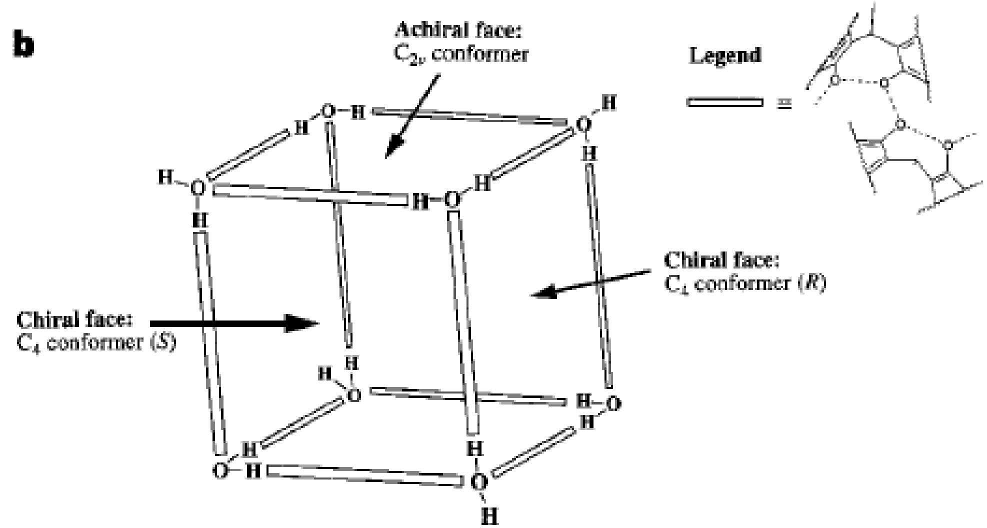


- Octahedral capsule (6* Resorcinarene +8*H_2O)
- Self-assembly by 60 H-bonds

{ intermolecular O-H···O
intramolecular O-H···O
intramolecular (with H_2O) O-H···O

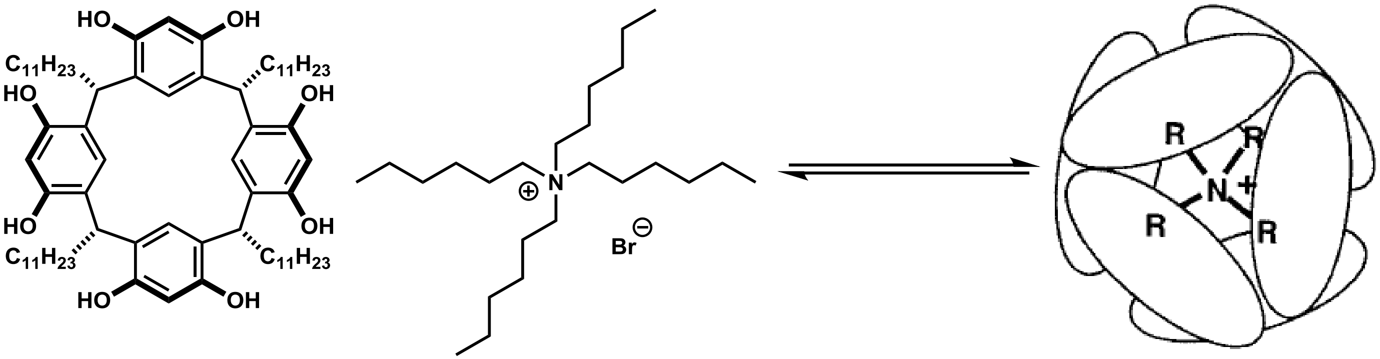
K. Tiefenbacher *et. al, Nat. chem*, **2015,** 7, 197



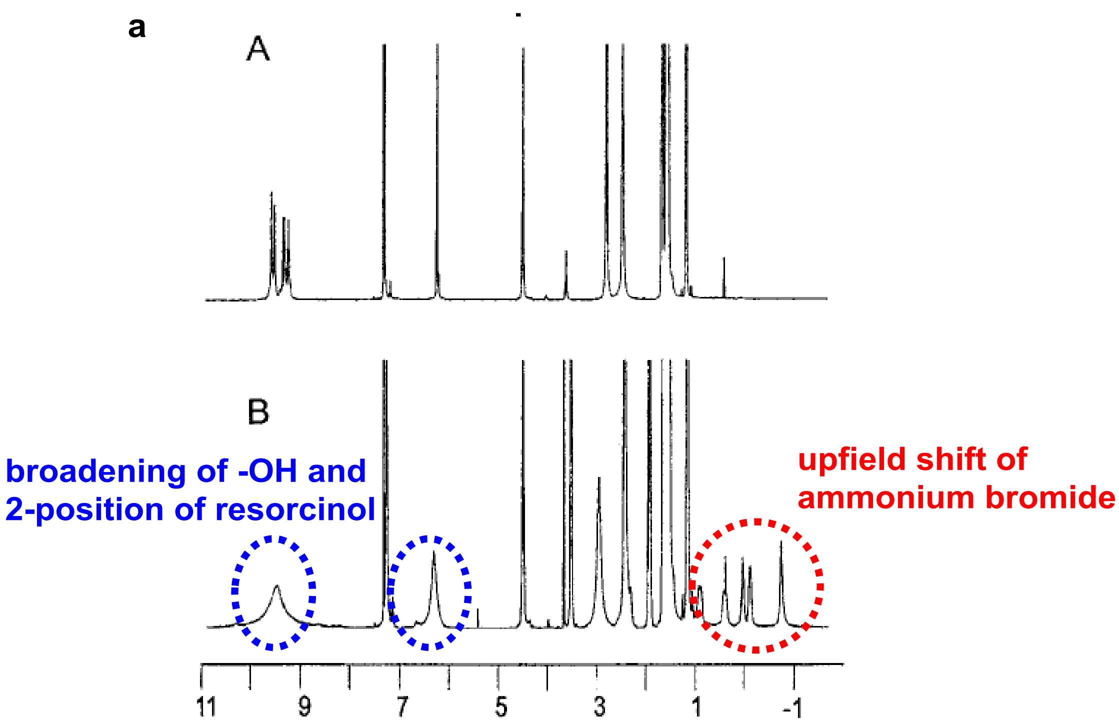


Leonard. R. MacGillvray. *et.al*, Nature, **1997**, 389, 469

Capsule stabilizing cationic guest



Cation-π interaction
stabilize cationic guest in cavity



NMR spectra in $CDCl_3$ saturated with H_2O
A. only a, B. a + b

Shivanyuk. A *.et.al, Proc. Natl. Acad. Sci,* **2001**, 98, 7662

Merits of using capsule catalyst

① Limited space in the capsule

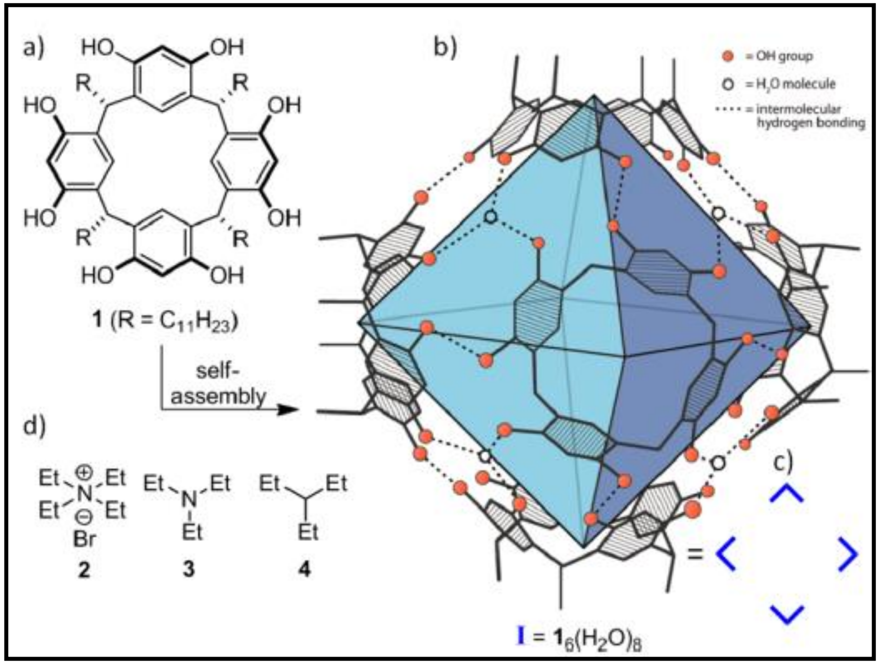
➡ •Regulate the substrate conformations
(= improve reaction specificity)

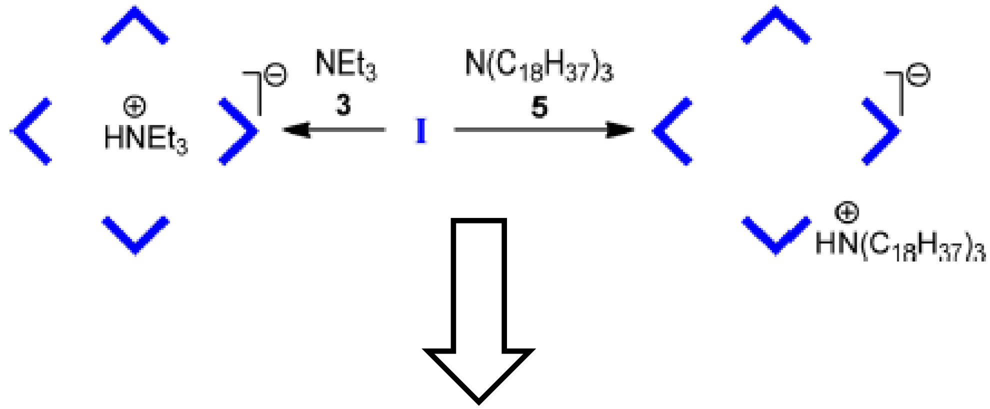
•Block the access of undesired nucleophile
to prevent the quenching of reaction
(S_N1 reaction)

② Cation-π interactions

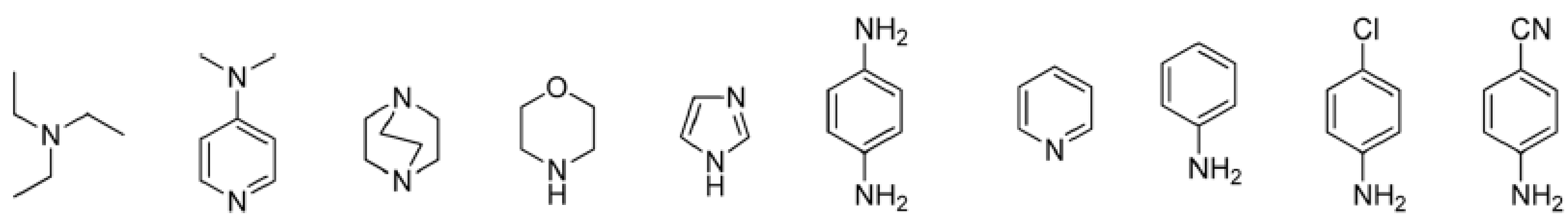
➡ •Stabilize high energy cationic intermediates

Potential of capsule catalyst for THT(1)





Capsule works as a brønsted acid

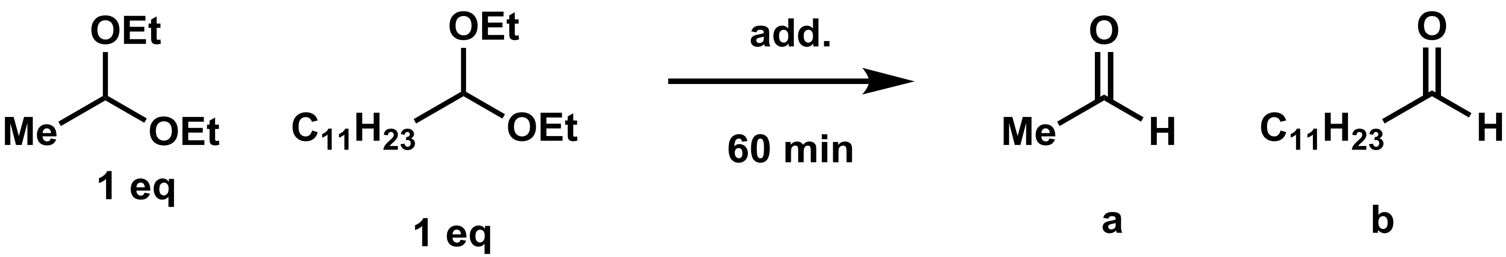


pK_a	11	9.2	8.8	8.4	7.0	6.1	5.2	4.6	3.8	1.7
degree of protonation (%)	80 ± 2	80 ± 2	77 ± 2	86 ± 3	83 ± 3	80 ± 2	53 ± 1	23 ± 2	np[a]	np[a]

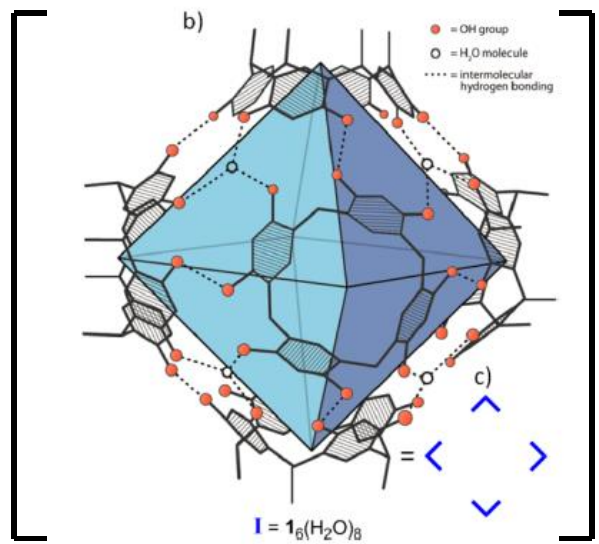
Estimated p*K*a: 5.5~6.0

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2013**, 135, 16213

Potential of capsule catalyst for THT(2)



capsule I



add.	conversion (%)	a:b
capsule I (10 mol%)	85	98:2
TFA (400 mol%)	65	37:73
CH_3CO_2H * (pK_a: 4.8) (10 mol%)	0	-

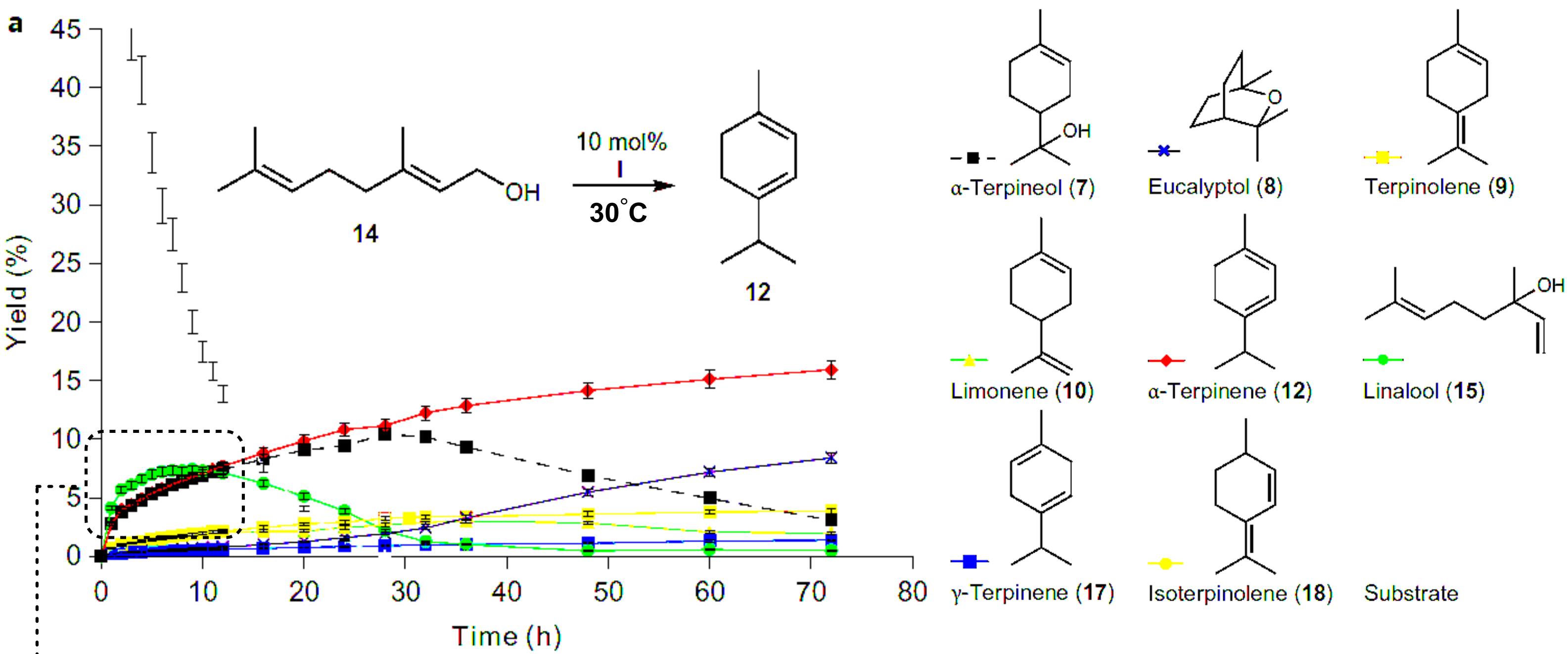
* reaction time: 15h

⇒ **Potential for activation of acyclic terpene by protonation**

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2013**, 135, 16213

Results of THT cyclization(1)

1. Geraniol (14)



•α-Terpineol, α-Terpinene, Linalool ••• Initial main product

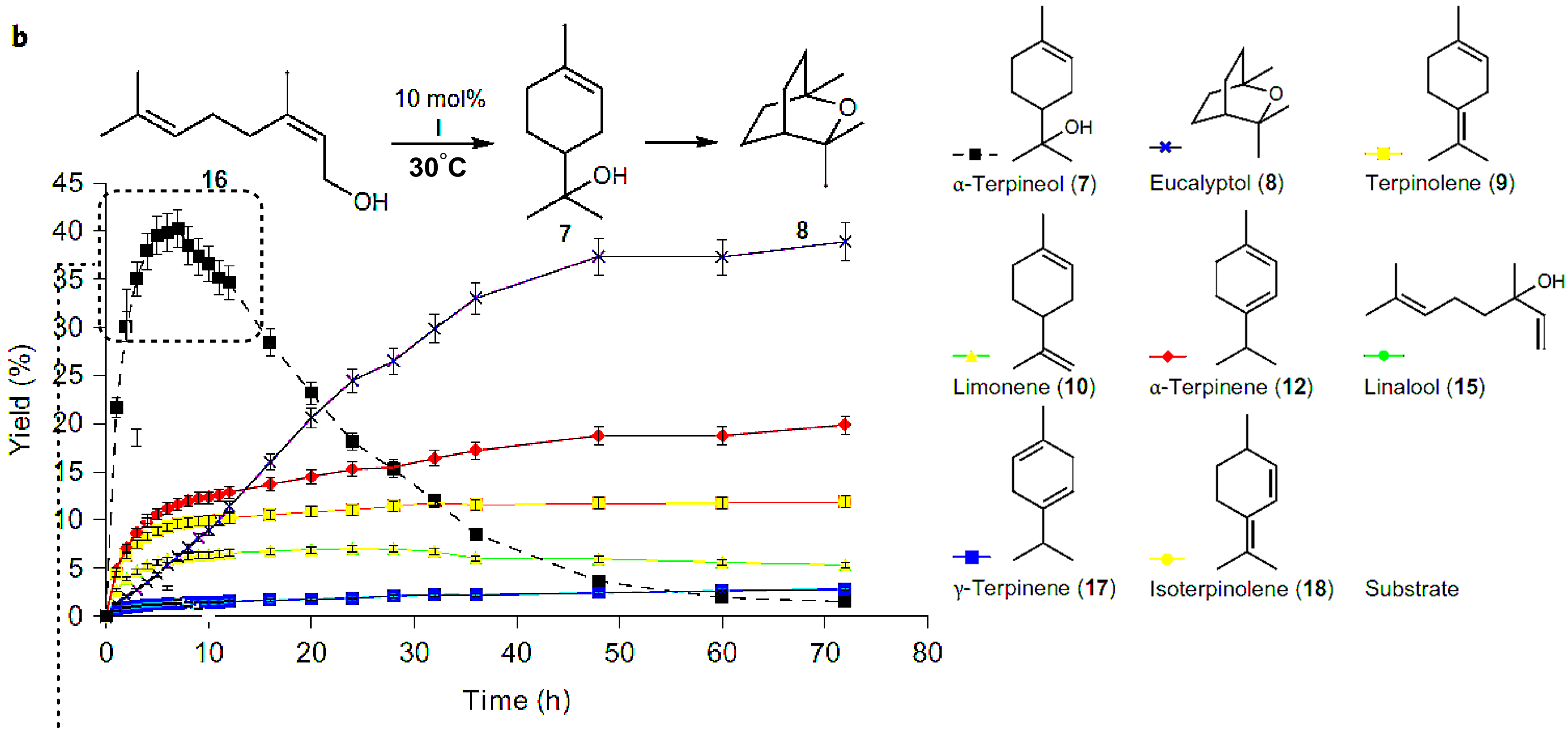
(Analogy of biosynthesis)

•α-Terpineol, Linalool decrease, Eucalyptol start to form

K. Tiefenbacher *et. al, Nat. chem*, **2015,** 7, 197

Results of THT cyclization(2)

2. Nerol (16)



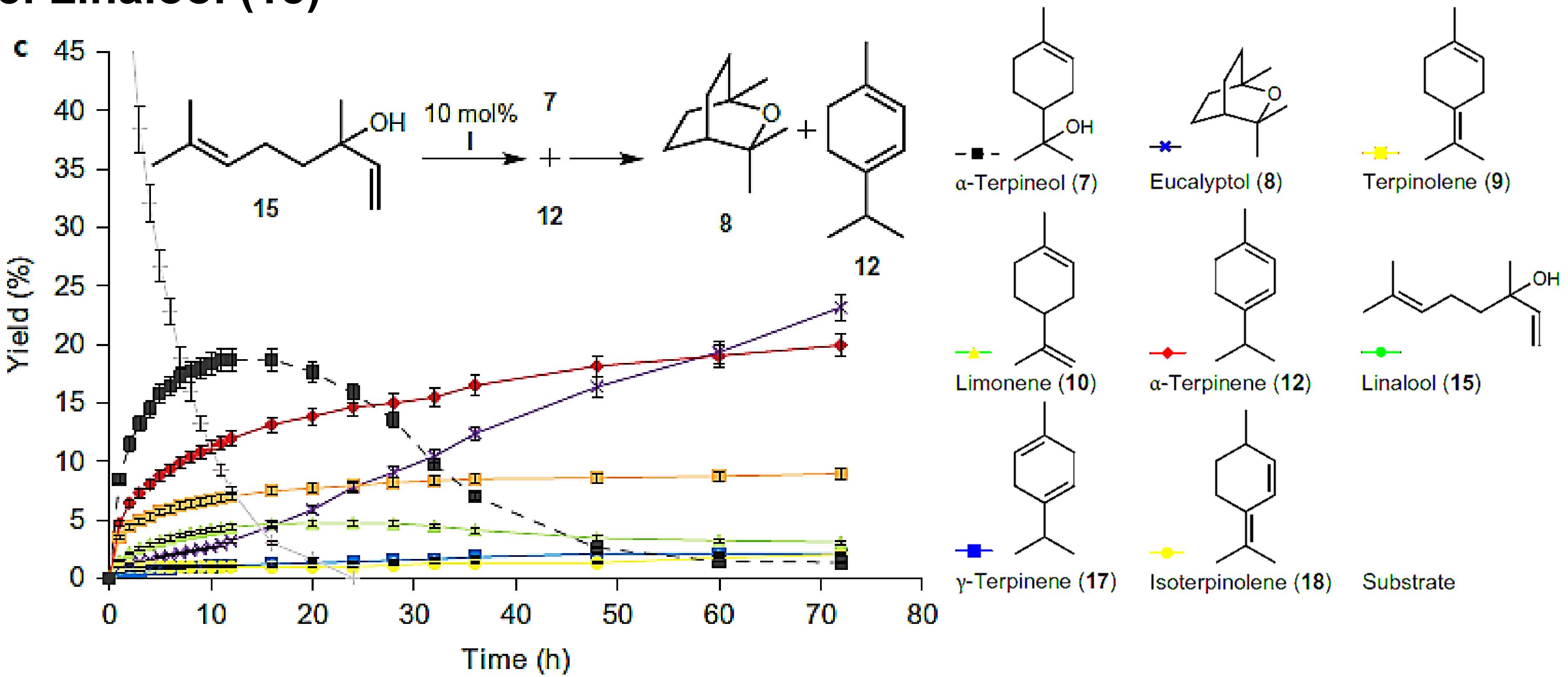
•α-Terpineol ••• Initial main product

•α-Terpineol decrease, Eucalyptol is final main product

K. Tiefenbacher *et. al, Nat. chem*, **2015,** 7, 197

Results of THT cyclization(3)

3. Linalool (15)

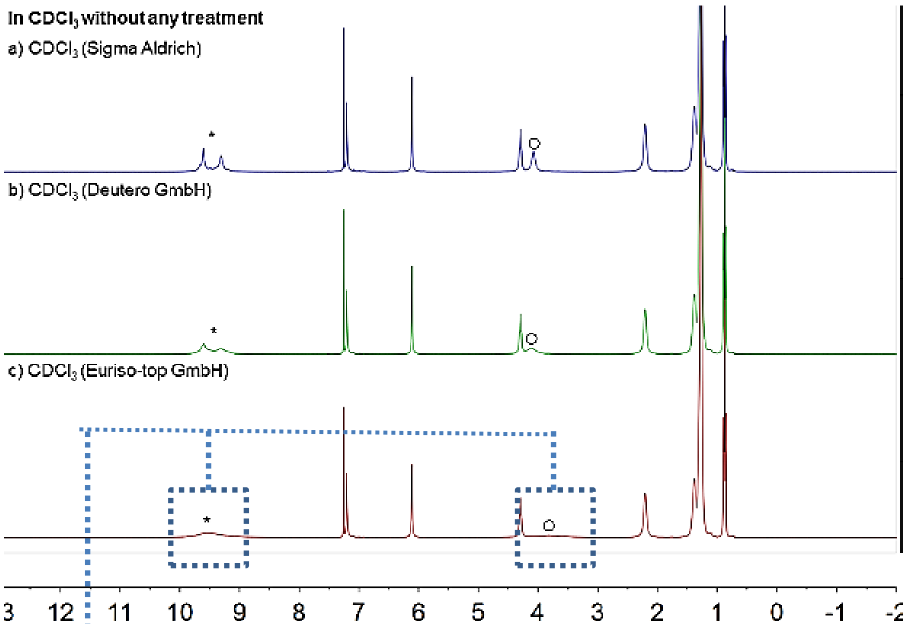


- **Composite result of Geraniol(14) and Nerol(16)**

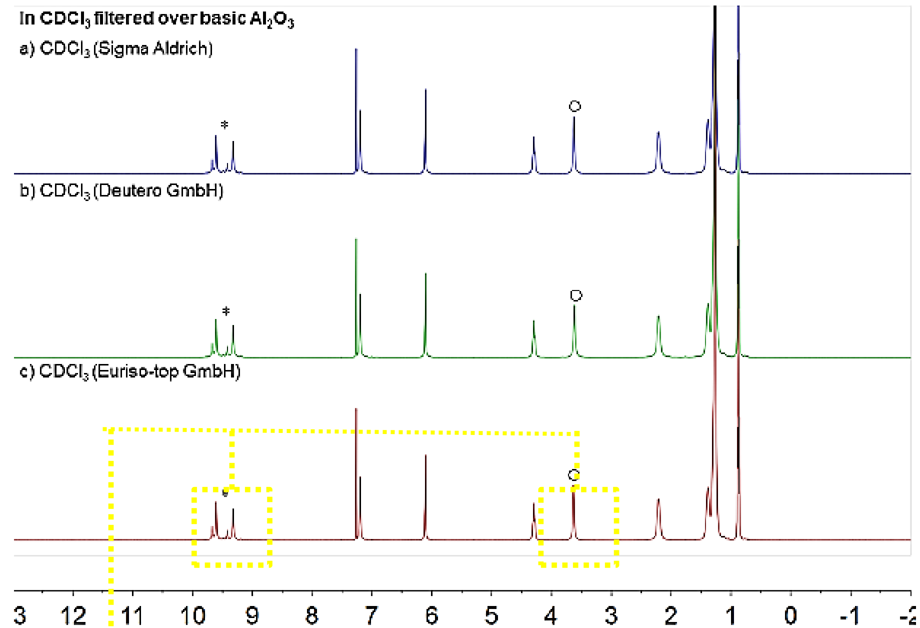
K. Tiefenbacher *et. al, Nat. chem*, **2015,** 7, 197

Reaction condition (Effect of acid)(1)

Different cyclization yield depending on supplier of $CDCl_3$



NMR spectrum of catalyst in $CDCl_3$



NMR spectrum of catalyst in $CDCl_3$(treat with Al_2O_3)

Broadening of OH and H_2O is observed with $CDCl_3$ without stabilizer (Fast proton exchange)

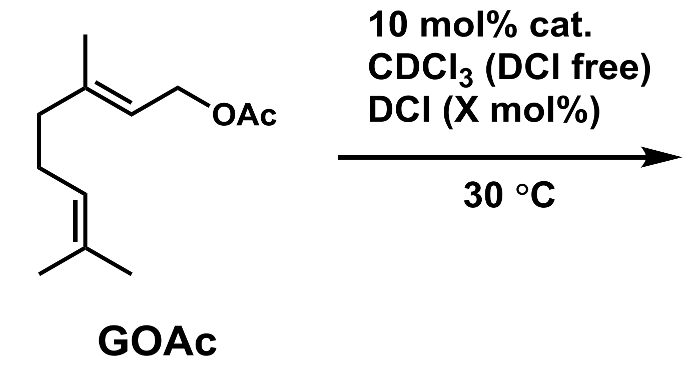
Removal of DCl gives sharp peaks of OH and H_2O

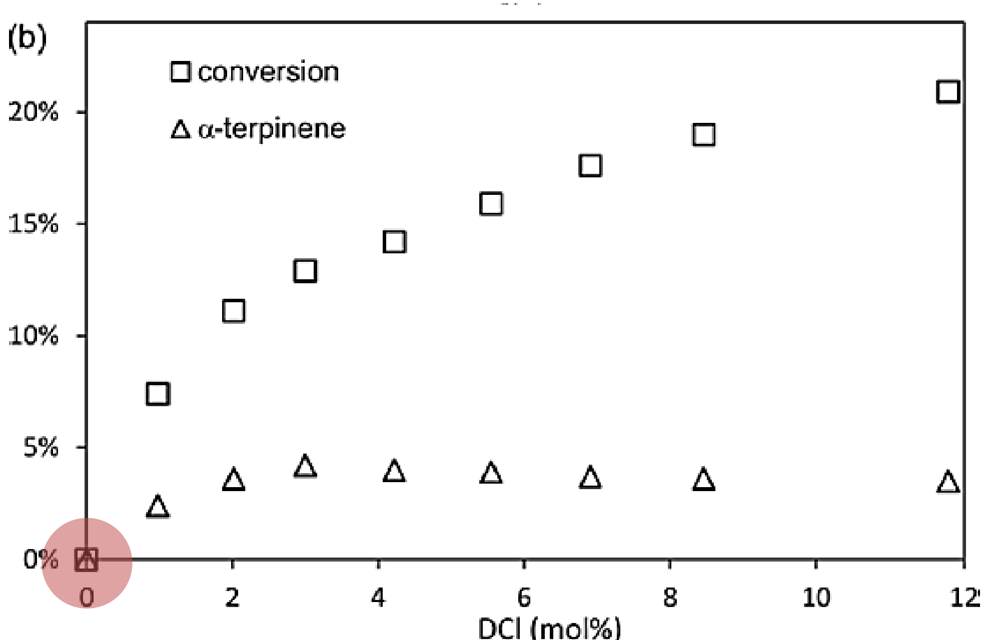
Trace DCl causes protonation of capsule

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

Reaction condition (Effect of acid)(2)

Cyclization with different amount of DCl





0 mol% DCl → No conversion

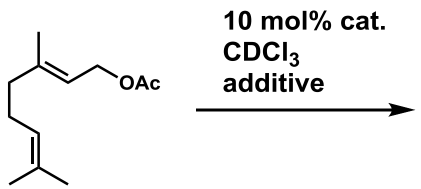
- Removal of capsule (3 mol% DCl) → No conversion

Combination of capsule and acid is necessary for cyclization

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

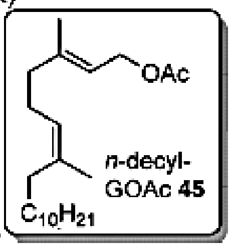
Reaction inside the capsule

Reaction inside the capsule

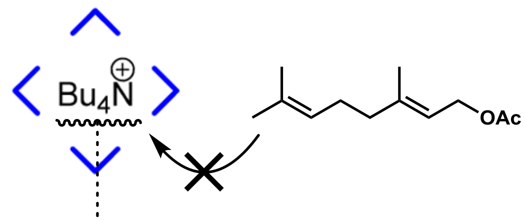


GOAc

entry	I	additive	conversion
1	10 mol%	none	94% (1 d)
2	10 mol%	15 mol% Bu_4NBr	4% (3 d, no THT product)
3[a]	10 mol%	0.5 eq **45**	1 d: 81% for GOAc (**20**) 2% for **45**
4	10 mol%	10 eq DMSO	0% (7 d)
5	none	none	0% (20 d)



2.



Strongly binding guest

II

"Inhibitor"

3.

n-decyl-GOAc(45)

II

"Large substrate" (Weak binding guest)

4.

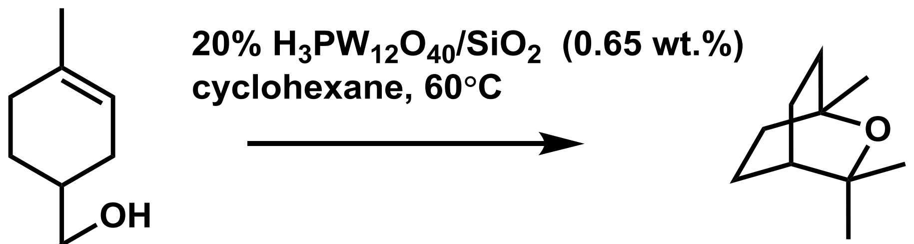
In DMSO ➡ Capsule collapse to monomer

Reaction inside the capsule is necessary for cyclization

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

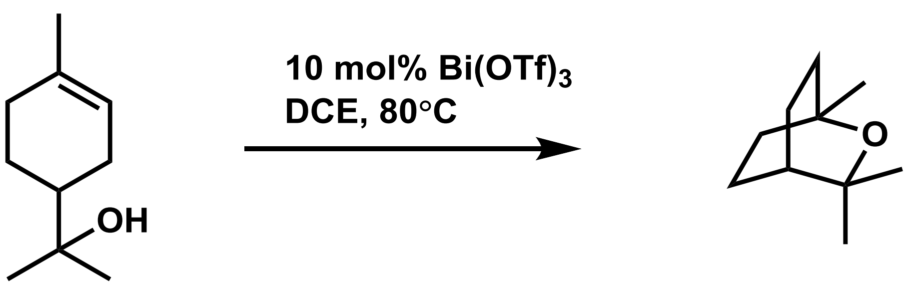
Remarkable point of capsule catalyst

Previous report of synthesis of Eucalyptol using "strong" Brϕnsted or Lewis Acid ⇒ **First example from "acyclic" terpenes**



33%
(100% conversion, 33% selectivity)

E.J. Leɑ̀o Lana. *et. al*, *J. Mol. Catal,* **2006**, 259, 99



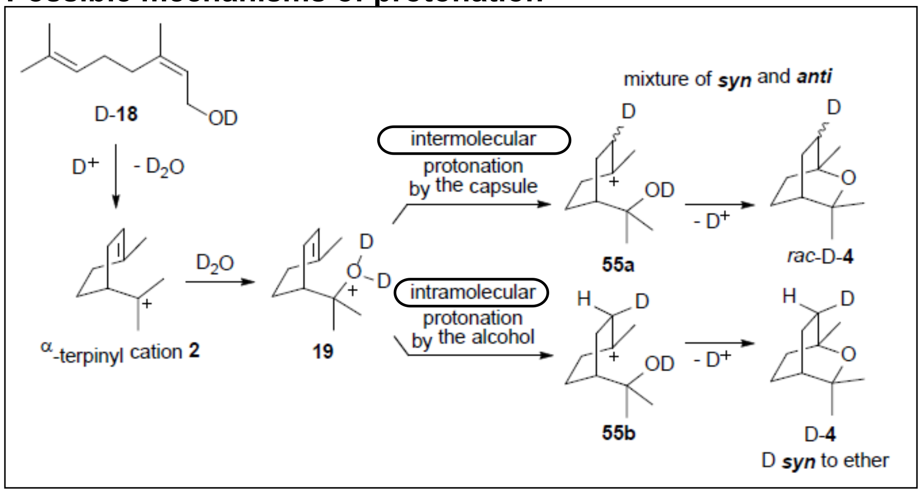
67%

Tristan. H. Lambert, *et. al*, *Org. Lett*, **2009**, 11, 1381

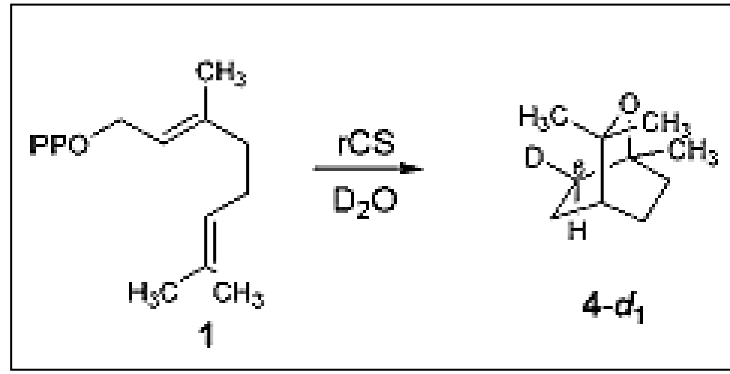
Mechanism analysis (Eucalyptol)

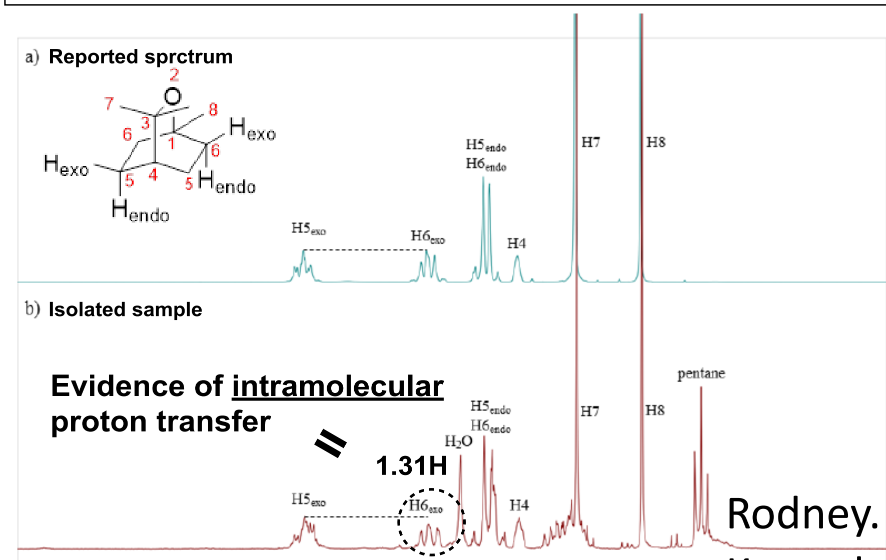
1. Protonation step

Possible mechanisms of protonation



rCS= recombinant 1,8-cineol synthase





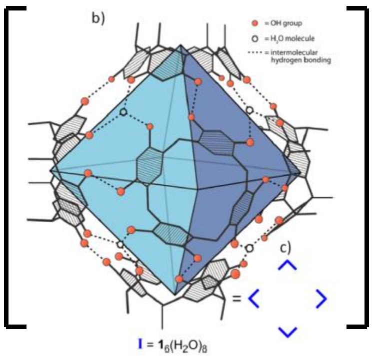
Similar protonation to cyclase enzyme

Rodney. Croteau, *et. al, J. Am. Chem. Soc*, **2002**, 124, 8546

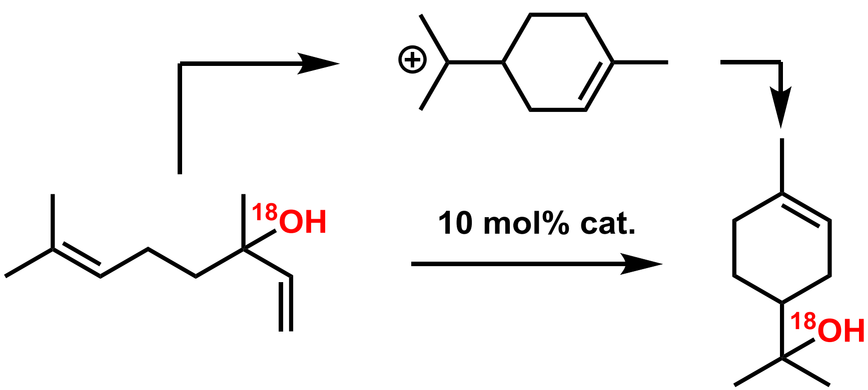
Konard. Tiefenbacher. *et. al, J. Am. Chem. Soc*, **2017**, ASAP

Mechanism analysis (Isotope-labeling)

Nucleophilic attack of water



excess(8) amount of $H_2{}^{16}O$
present close to intermediate



^{18}OH-linalool (88.1% ^{18}OH)

^{18}OH-α-terpineol

Time [h]	^{18}O content [%]
3	65.2
6	65.1
9	65.0
12	64.6
23	63.1

≈75% of OH is from leaving OH

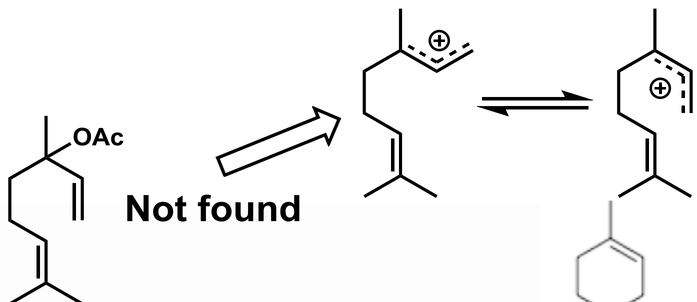
Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

Results of THT cyclization (other LGs)(1)

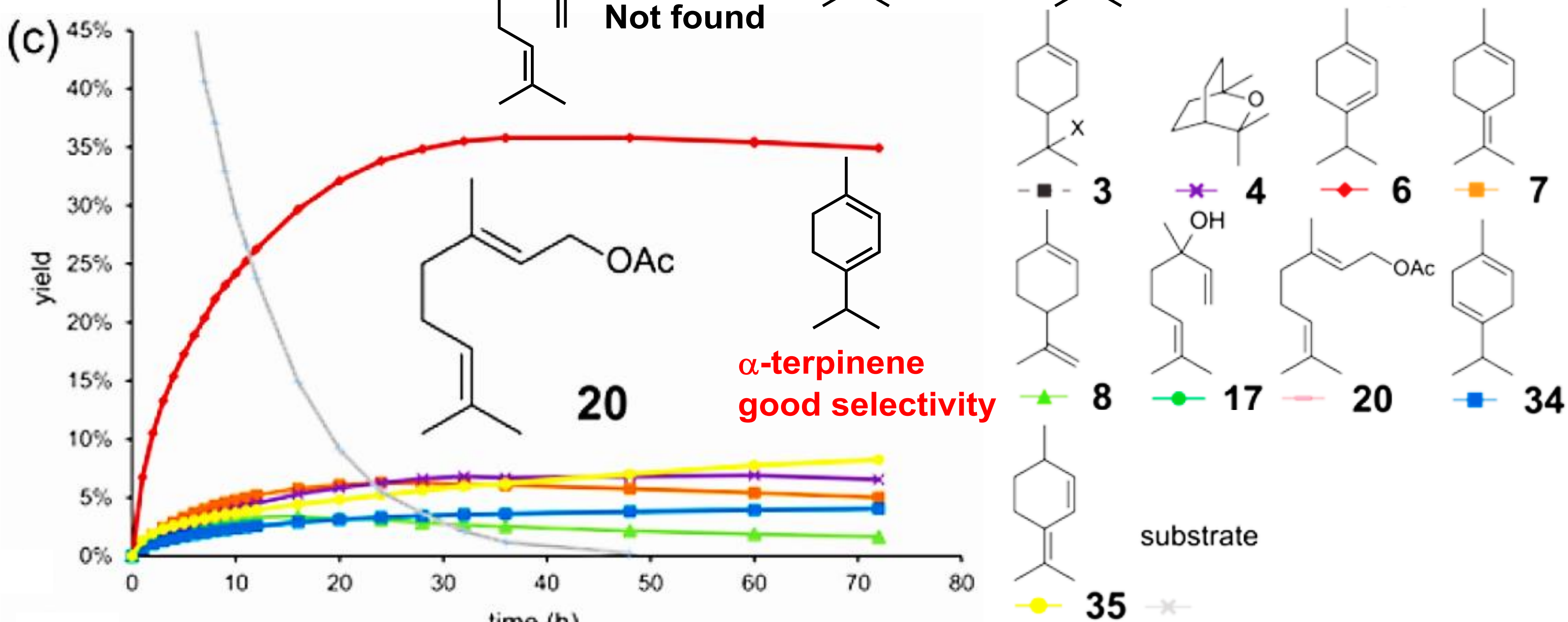
- H_2O (leaving group) causes quenching of cationic intermediate

Other leaving group (weak nucleophilicity) shows other selectivity?

3. Geranyl acetate (20)



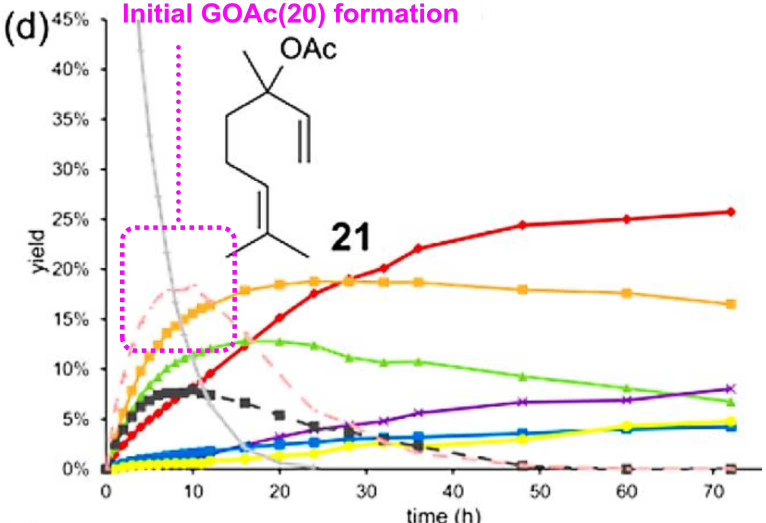
Direct isomelization

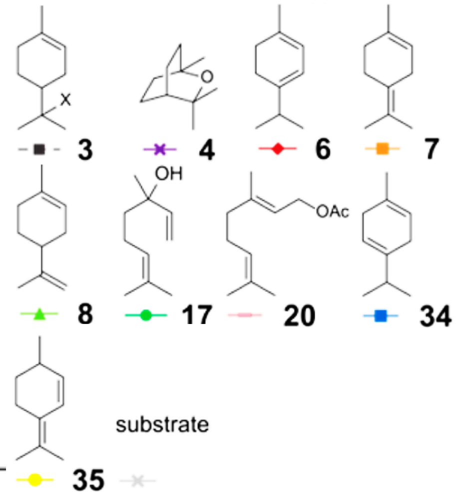


Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

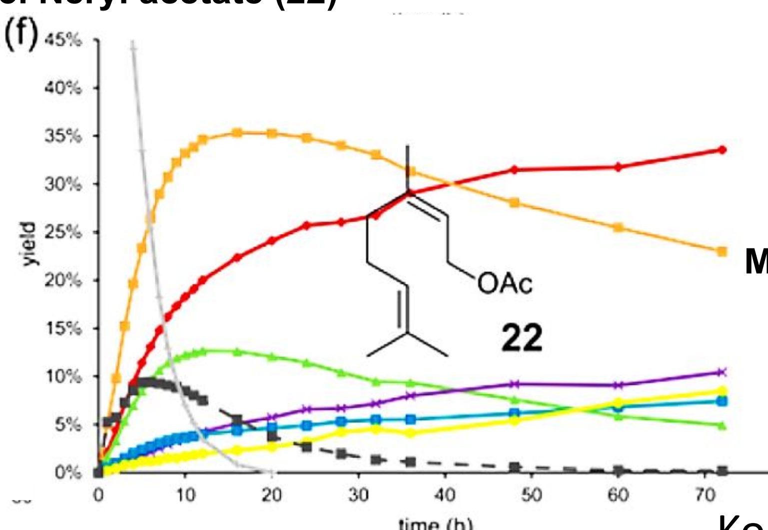
Results of THT cyclization (other LGs)(2)

4. Linalyl acetate (21)

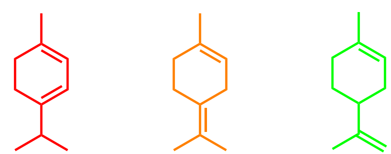




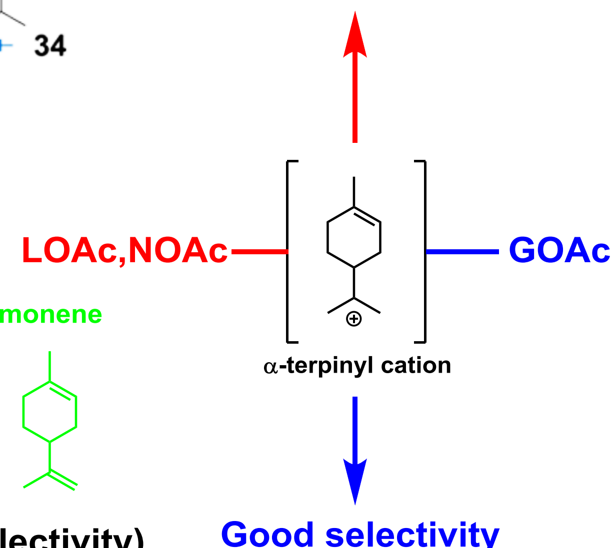
5. Neryl acetate (22)



α-teripnene, terpinolene, limonene



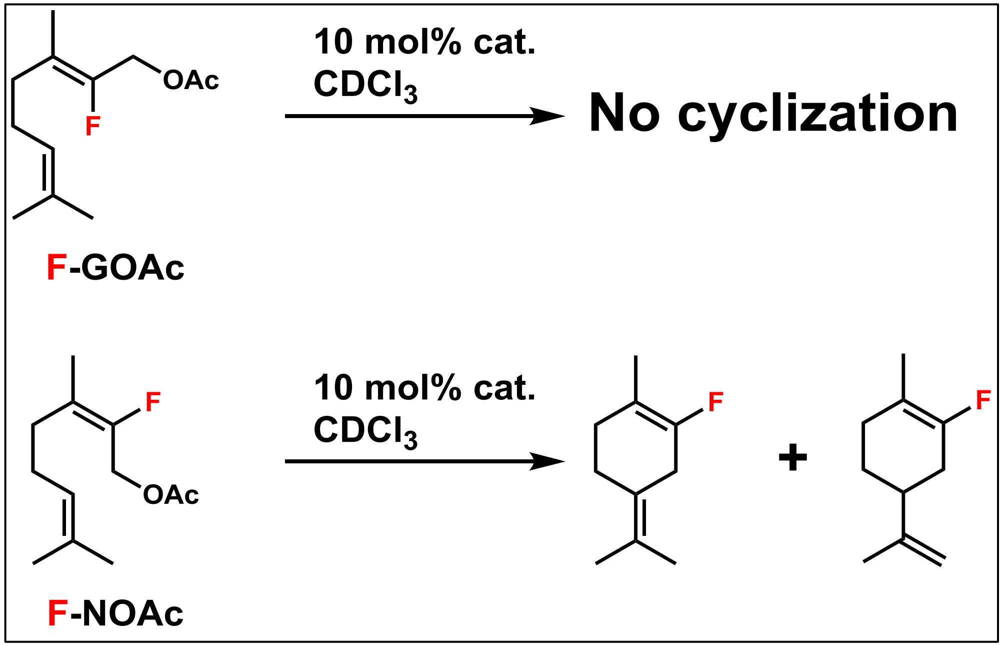
Main product (Less selectivity)

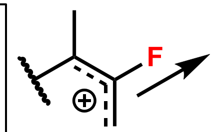


What makes the difference from the same intermediate?

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

Cyclization in S*N*1 or S*N*2 type manner(1)

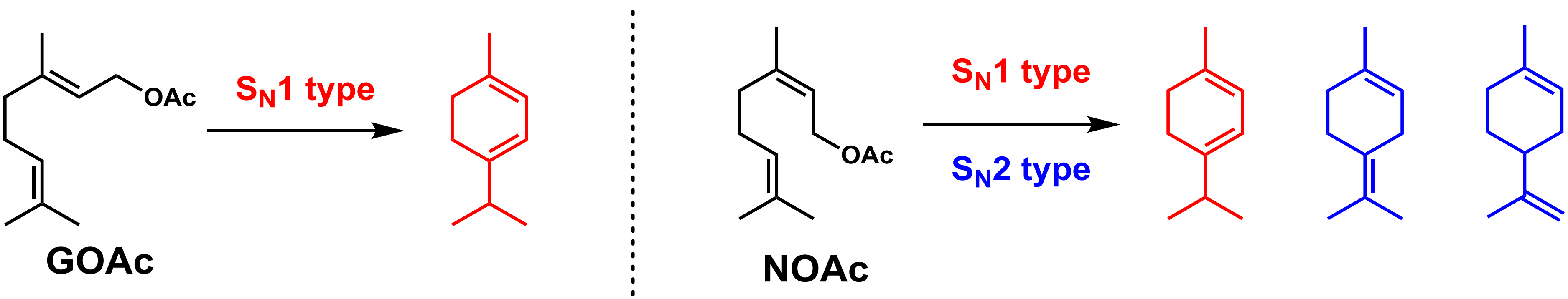




F destabilize cation intermediate

× S_N1-type cyclization

○ S_N2-type cyclization

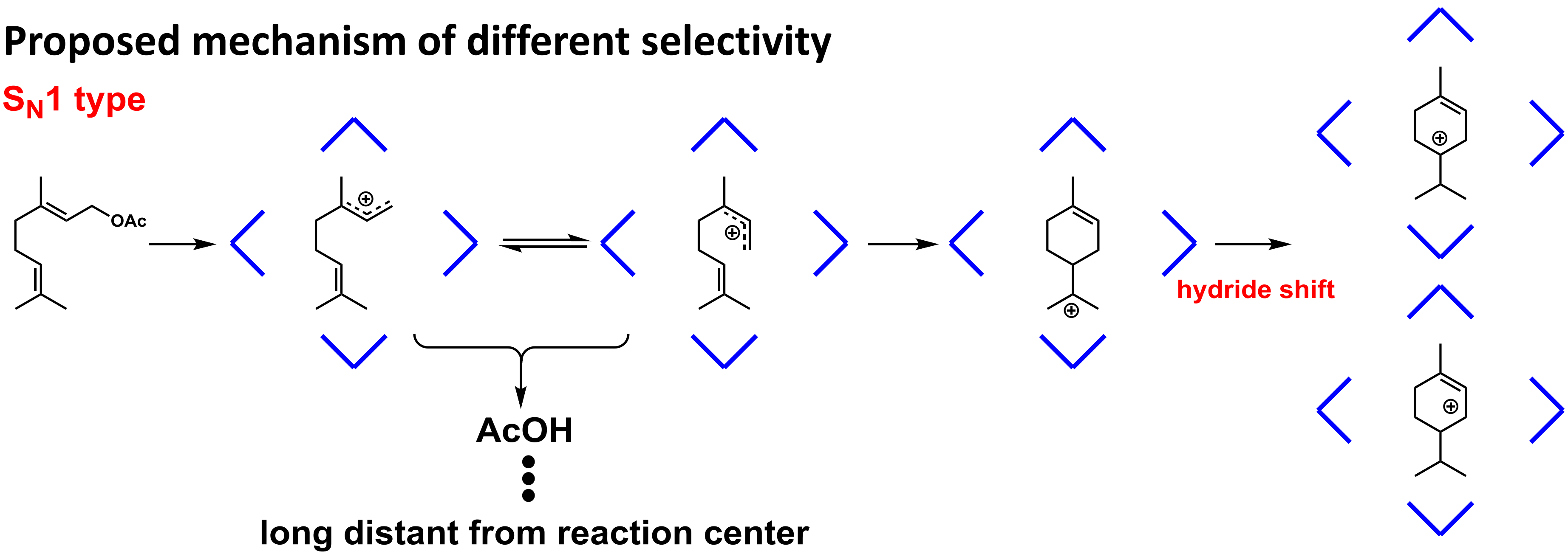


Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

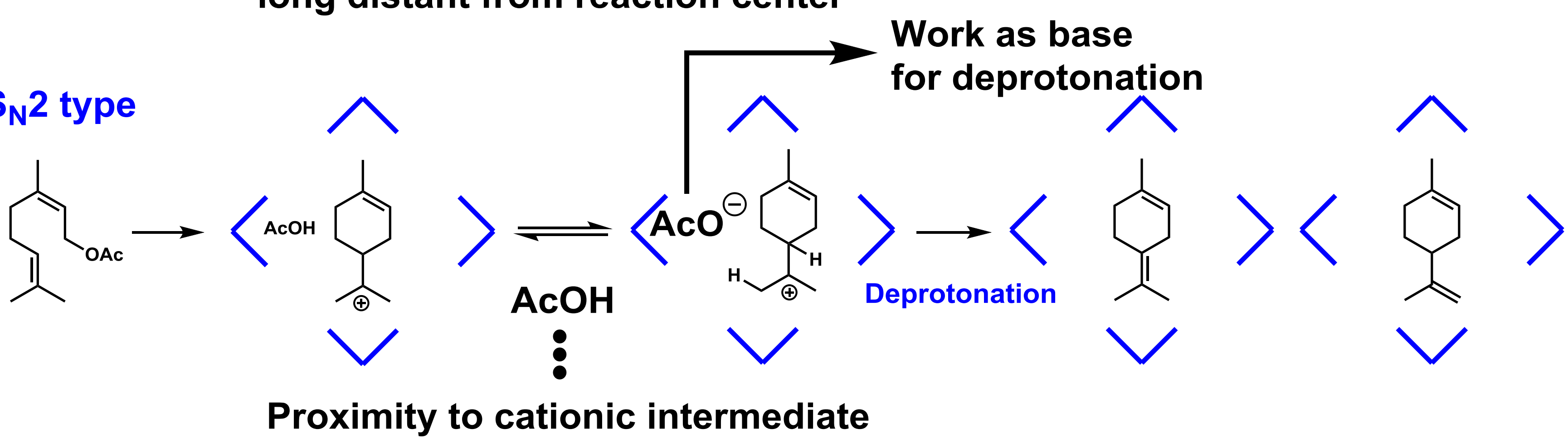
Cyclization in SN1 or SN2 type manner(2)

Proposed mechanism of different selectivity

S_N1 type

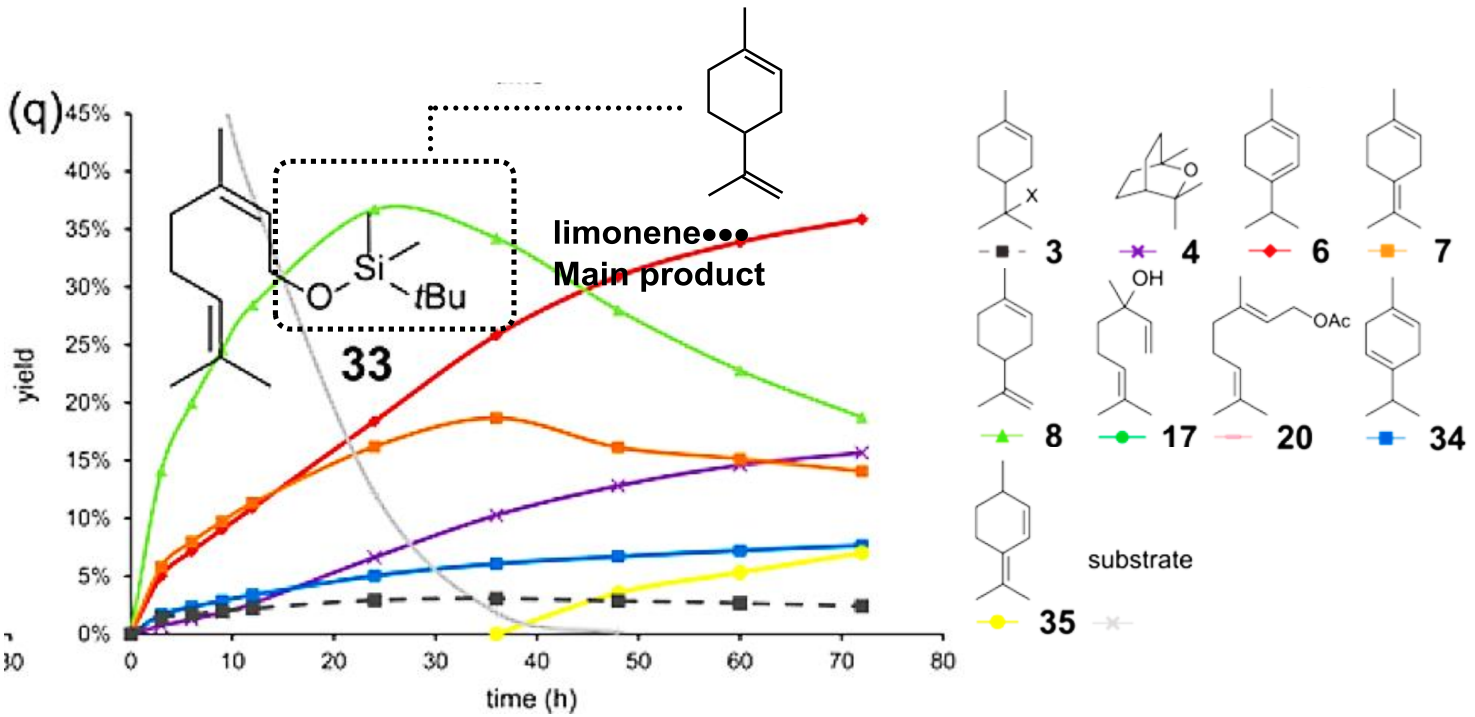


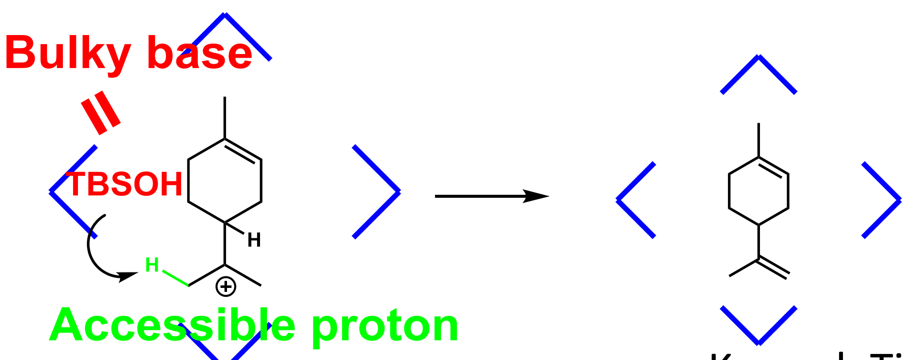
S_N2 type



Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

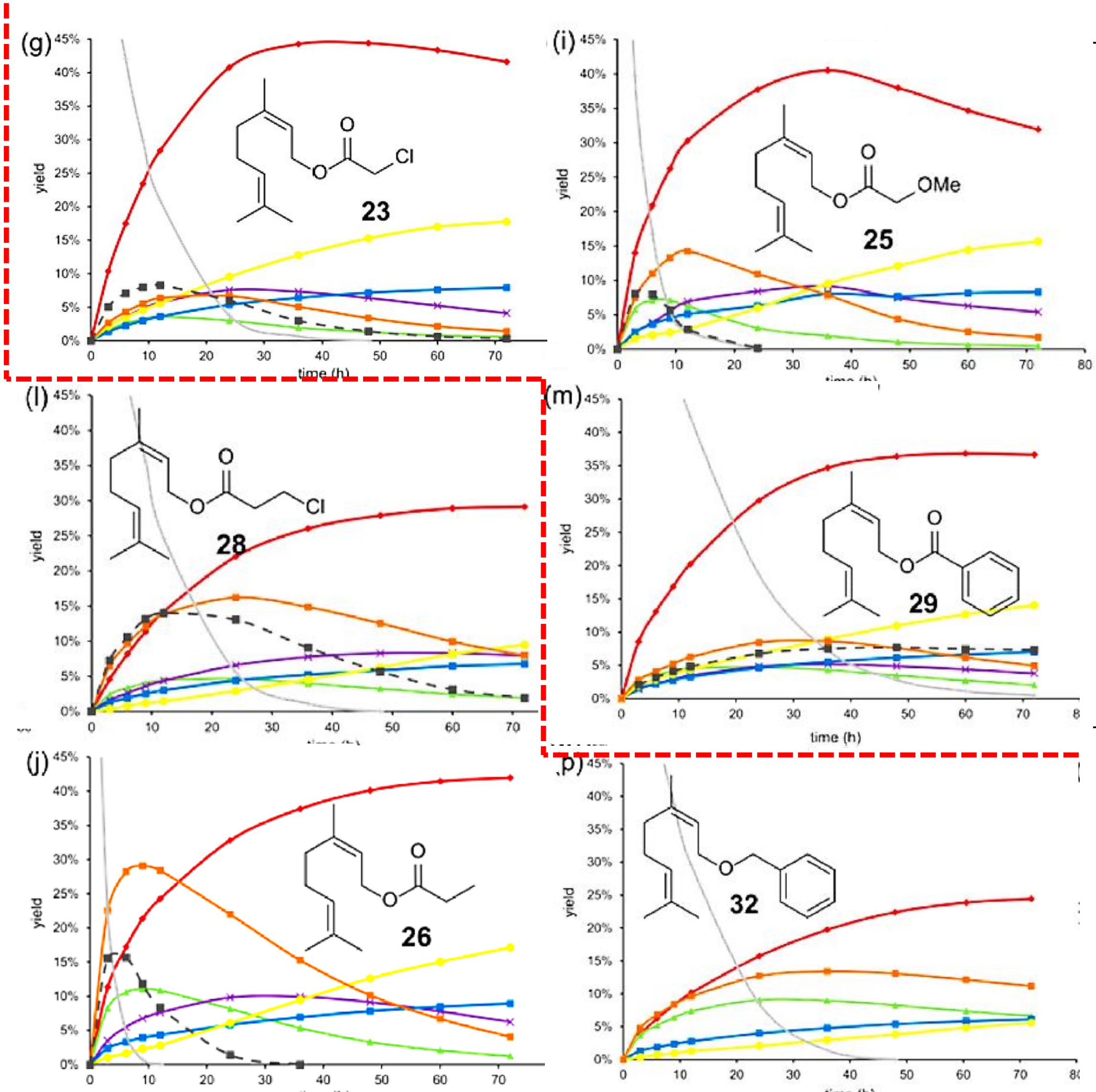
Results of THT cyclization (other LGs)(3)





Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

Results of THT cyclization (other LGs)(4)



S_N1 cyclization for neryl substrate

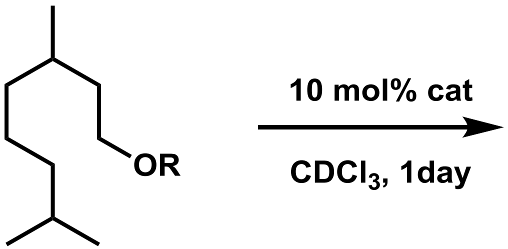
What difference?

Bad selectivity

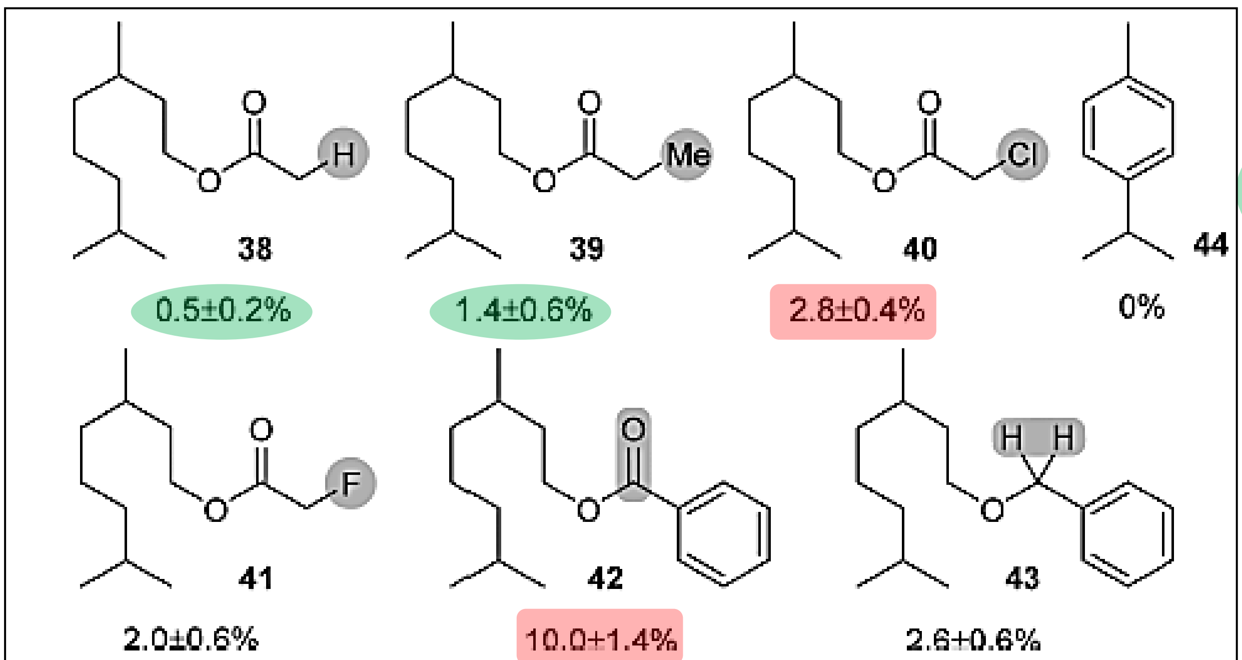
Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

Affinity and reaction selectivity(1)

Encapsulation ratio of substrates with different LGs (Affinity)



Encapsulation ratio analysis (NMR)



Lower affinity
⇒ **Lower selectivity (S_N2 (+ S_N1))**

Higher affinity
⇒ **Higher selectivity (S_N1)**

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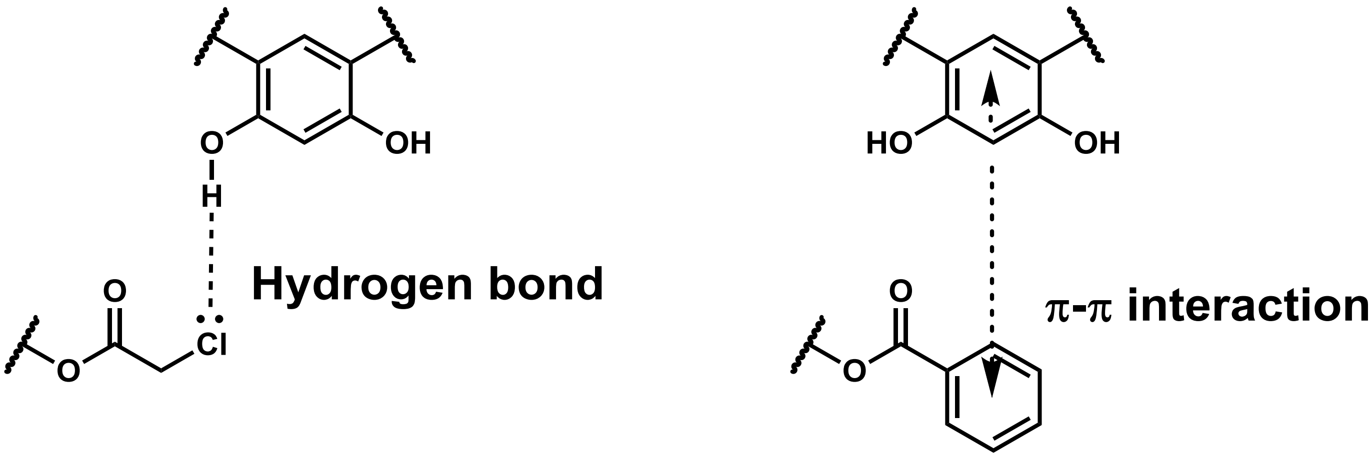
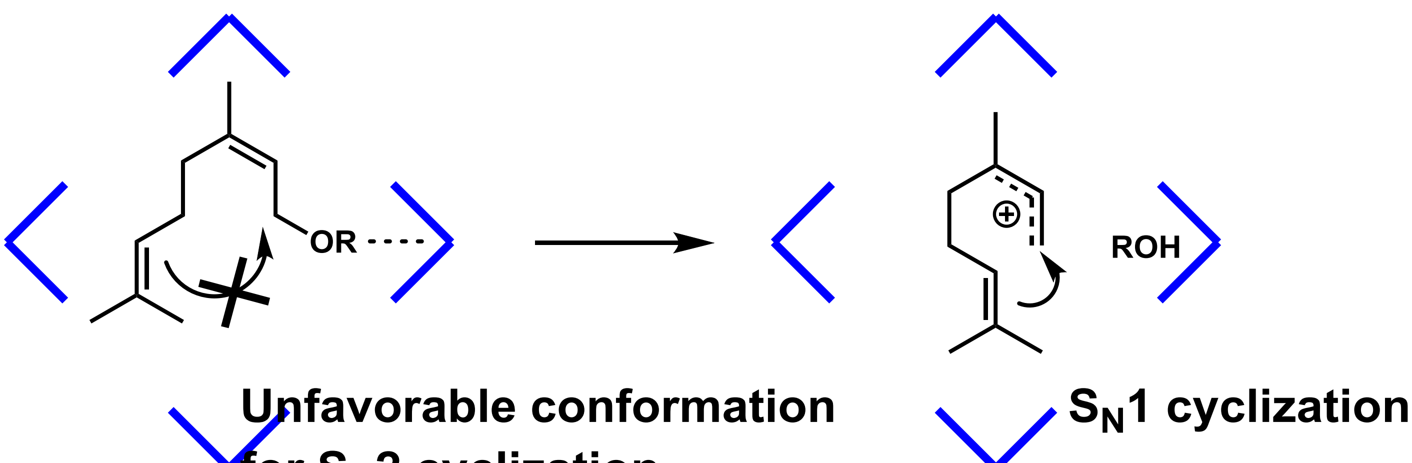
Affinity and reaction selectivity(2)

Additional interaction with substrate and capsule wall

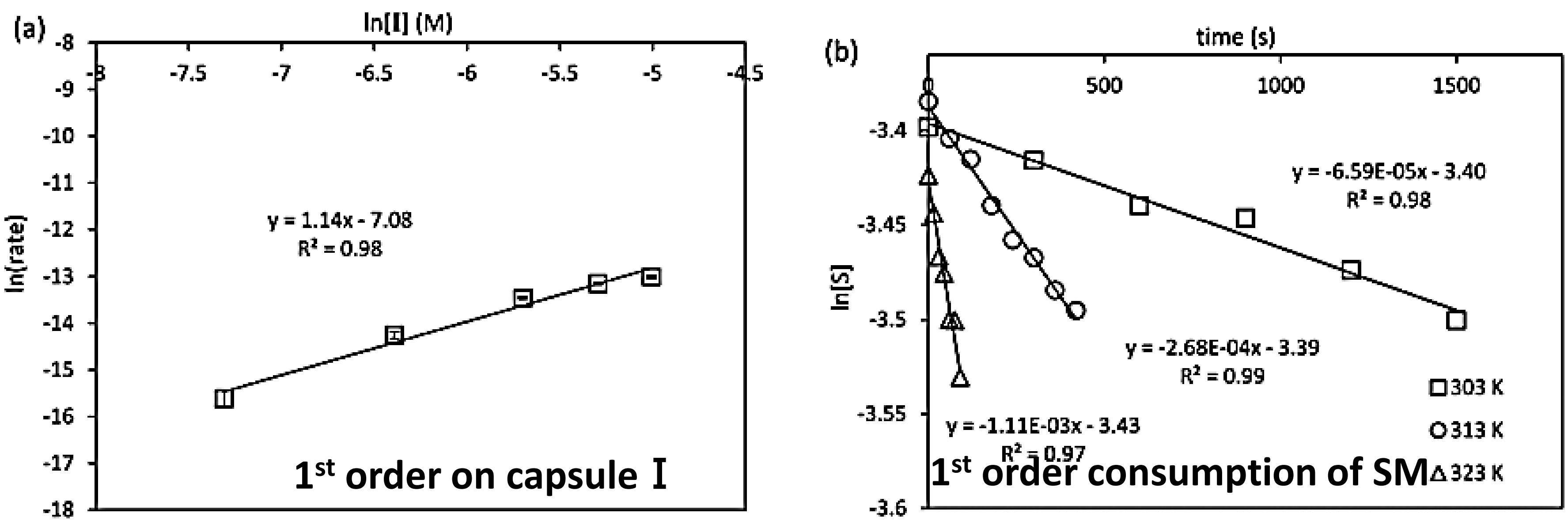


Proposed mechanism of tendency for S_N1 cyclization



Kinetic investigations(1)

GOAc $\xrightarrow[\text{CDCl}_3\text{, 30°C}]{\text{10 mol\% cat.}}$



$v = k_{obs}$[GOAc][I]

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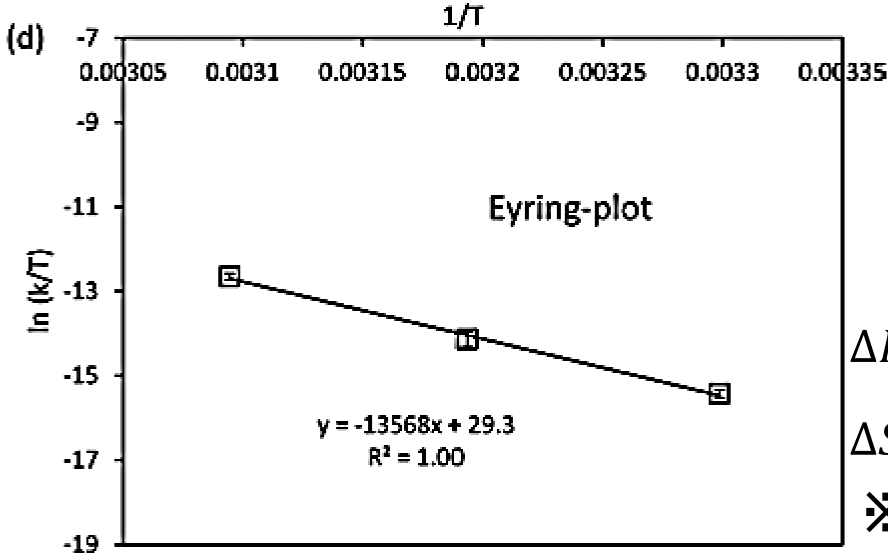
Kinetic investigations(2)



Eyring equation

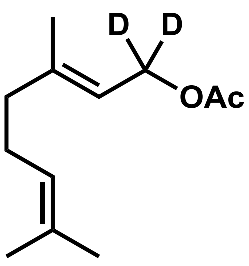
$$\ln\frac{k}{T} = -\frac{\Delta H^{\neq}}{R}\frac{1}{T} + \frac{\Delta S^{\neq}}{R} + \ln\frac{k_B}{h}$$

$$\Delta H^{\neq} = -(-13568) \times 8.31/4.2 \approx 27.0\ (\text{kcal}\cdot\text{mol}^{-1})$$

$$\Delta S^{\neq} = (29.3 - 23.76) \times 8.31/4.2 \approx 11.0 (\text{cal}\cdot\text{mol}^{-1})$$

※$\ln\frac{k_B}{h}$=23.76

$\Delta S^{\neq} > 0 \Rightarrow$ Disordered state = Rate determining step



1,1-D_2-GOAc

k_H/k_D = 1.22

Secondary isotope effect

Cleavage of LG

II

Rate determining step

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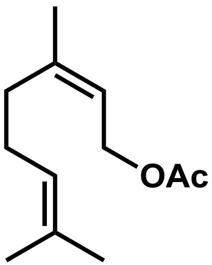
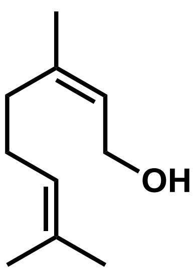
Kinetic investigations(3)



NOAc

$\Delta S^{\neq}$= 2.24 (J/mol•K)



NOH

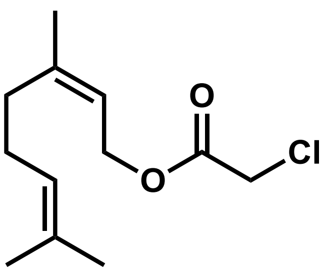
$\Delta S^{\neq}$= 3.62 (J/mol•K)

Lower $\Delta S^{\neq}$

⇓

S_N2-type cyclization

(Restricted conformation at cleavage of LG)



Neryl chloroacetate

$\Delta S^{\neq}$= 9.02 (J/mol•K)

Higher $\Delta S^{\neq}$

⇓

S_N1-type cyclization

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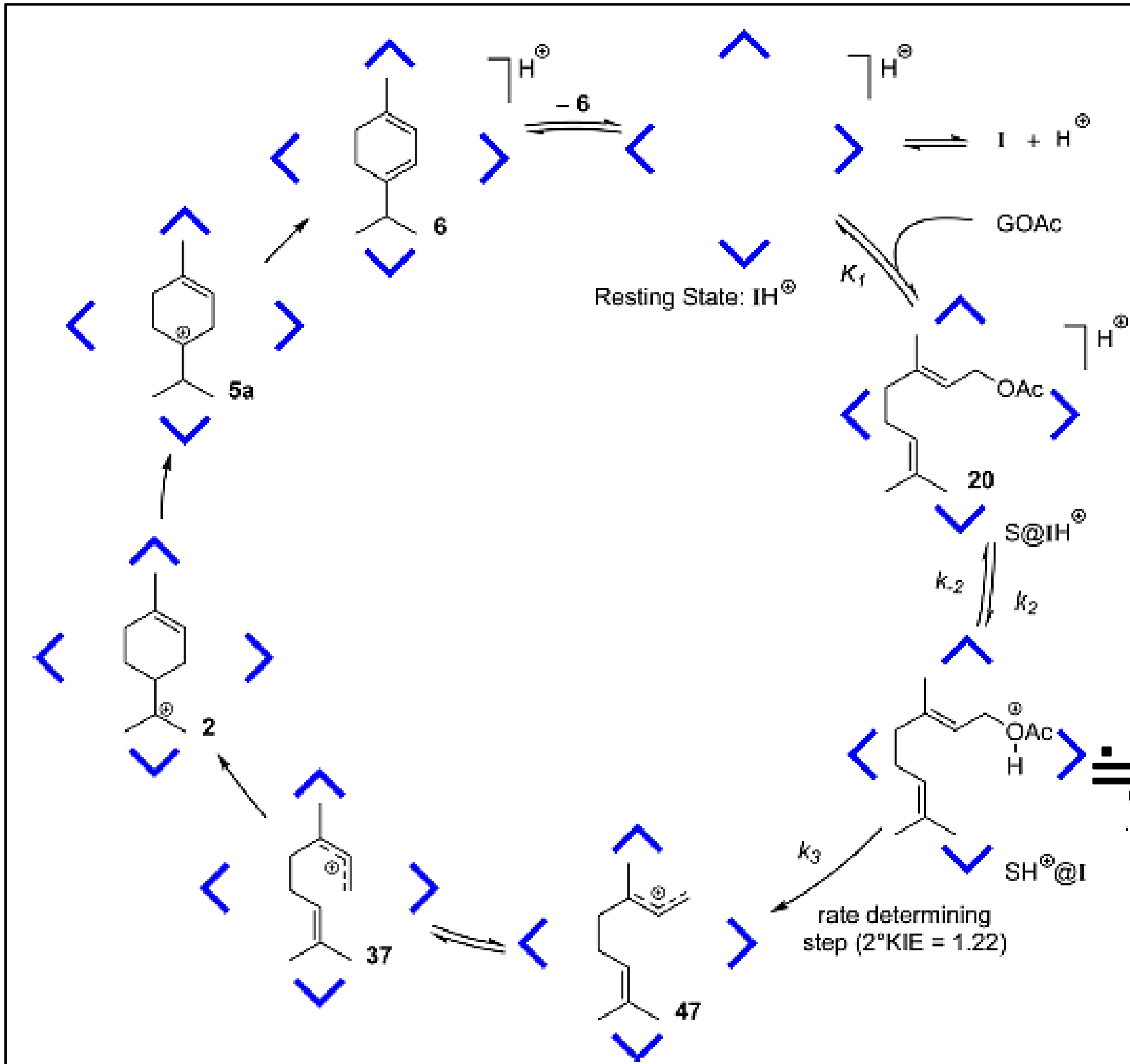
Kinetic investigations(4)

Proposed mechanism for cyclization of GOAc



$$k_2[\mathbf{S@IH^+}] = (k_{-2}+k_3)[\mathbf{SH^+@I}]$$

$$K_1 = \frac{[\mathbf{S@IH^+}]}{[\mathbf{IH^+}][\mathbf{S}]} \approx \frac{[\mathbf{S@IH^+}]}{[\mathbf{I}][\mathbf{S}]}$$

$$v = k_3[\mathbf{SH^+@I}] = \frac{K_1 k_2 k_3}{k_{-2}+k_3}[[\mathbf{I}][\mathbf{S}]$$

≒ **Steady-state**

Konard. Tiefenbacher. *et. al*, *J. Am. Chem. Soc*, **2017**, ASAP

1. Introduction

2. Today`s contents
~tail-to-head terpene (THT) cyclization in capsule catalyst~

3. Summary

Summary

- Self assembly capsule can catalyze THT cyclization

- Selectivity of the reaction is changed by

①Substrate
(Geranyl ••• S_N1 Neryl ••• S_N2 + S_N1)

②Leaving group
(Nucleophillicity, Affinity, Size)