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Total Synthesis of Limaol

J. Am. Chem. Soc. **2021** , 143, 6, 2464–2469

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Journal Club – 21.04.2021 – Gaetano Geraci

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Alois Fürstner

July 1962

Born on 23° July, 1962 in Bruck/Mur (Austria)

1987

PhD at the Technical University Graz, Austria (H. Weidmann)

1990–1991

Postodoctoral fellow at the University of Geneva (CH) (W. Oppolzer)

1993–1998

Group leader at the Max-Planck-Institut für Kohlenforschung and Lecturer at the University of Dortmund

Since 1998

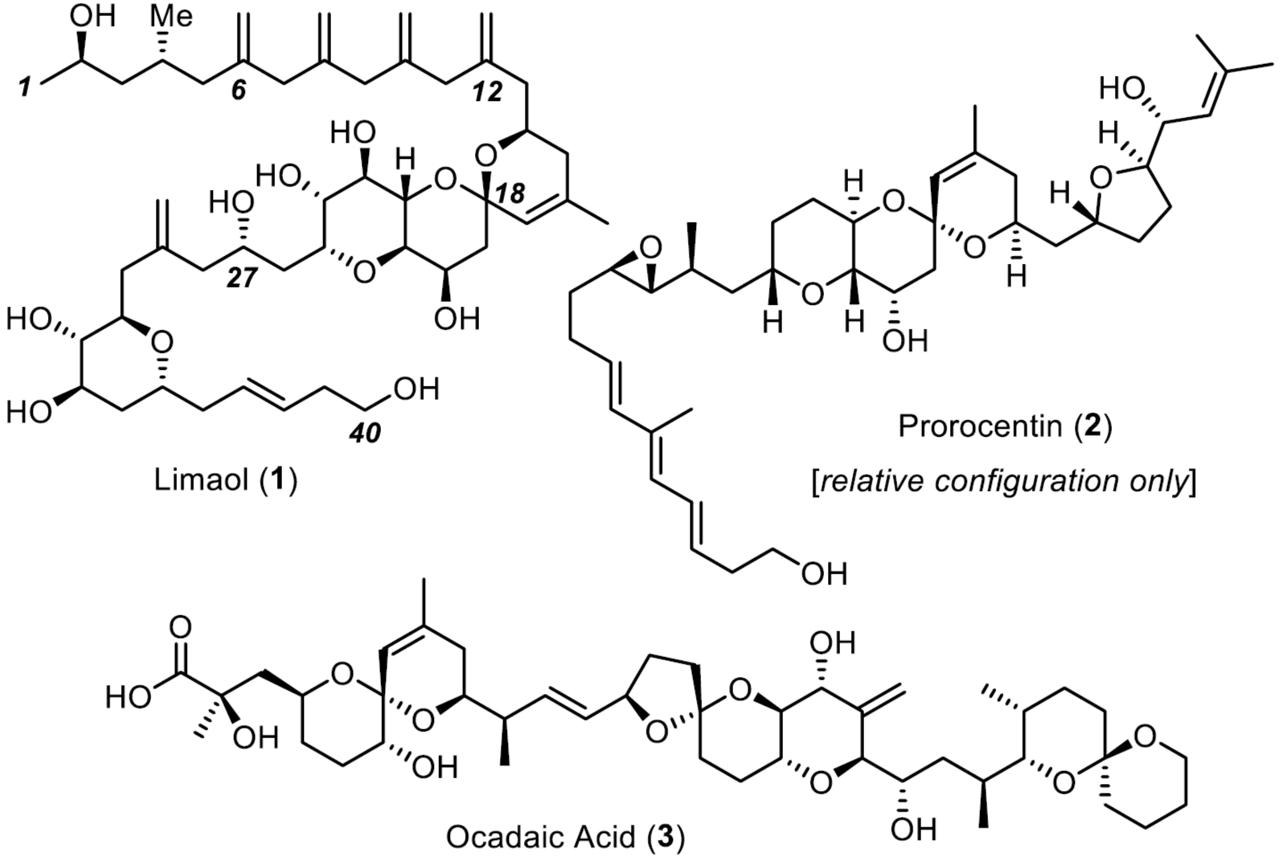
Director at the Max-Planck-Institut für Kohlenforschung and Professor at the Technical University of Dortmund

Research Topics

- **Alkyne metathesis:** Catalysts development (latest: molybdenum-nitrides and molybdenum-alkylidynes endowed with silanolate ligands) and application in total synthesis.
- **Alkene metathesis:** synthetic methods
- **n-acid catalysis:** Catalysis based on the activation of p-systems with the aid of carbophilic Lewis acids such as Pt(2+) and Au(1+).
- **Iron catalysis:** Iron catalysts for cross coupling, cycloisomerization reactions, cycloadditions of unactivated substrates, and carbometalations of π-bonds
- **New concepts for catalysis**
- **Total synthesis**

Natural Products derived from *P.lima*

- Dinoflagellates: single-celled eucaryotes, usually called algae
- Very large genome -> additional secondary metabolites could be available
- Ocadaic Acid: highly potent and specific inhibitor of the Ser/Thr-protein phosphatases PP1 and PP2A
- Limaol: moderate cytotoxicity, quite stable structure



Limaol (**1**)

Prorocentin (**2**)

[*relative configuration only*]

Ocadaic Acid (**3**)

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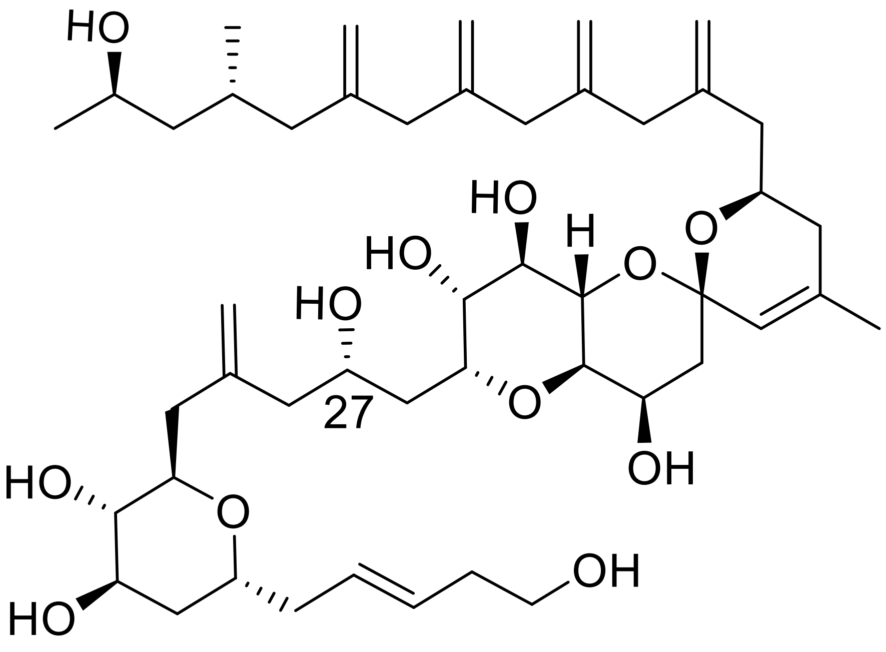
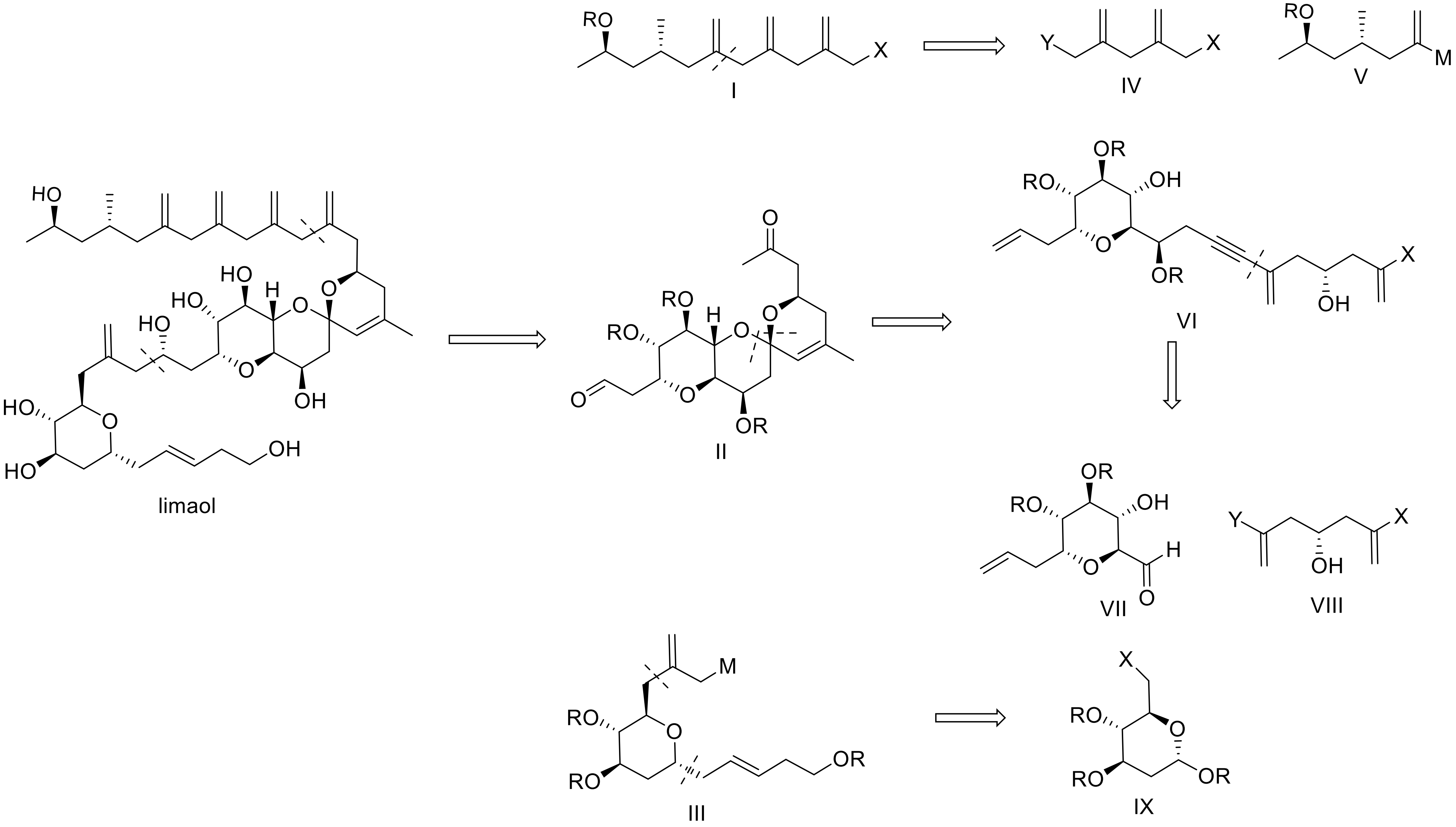
Structure of Limaol



limaol

- 40-carbon backbone
- Five exo-methylene groups, 4 clustered in a skipped array
- Spirotricyclic core
- Homoallylic alcohol at C27

Retrosynthetic Approach



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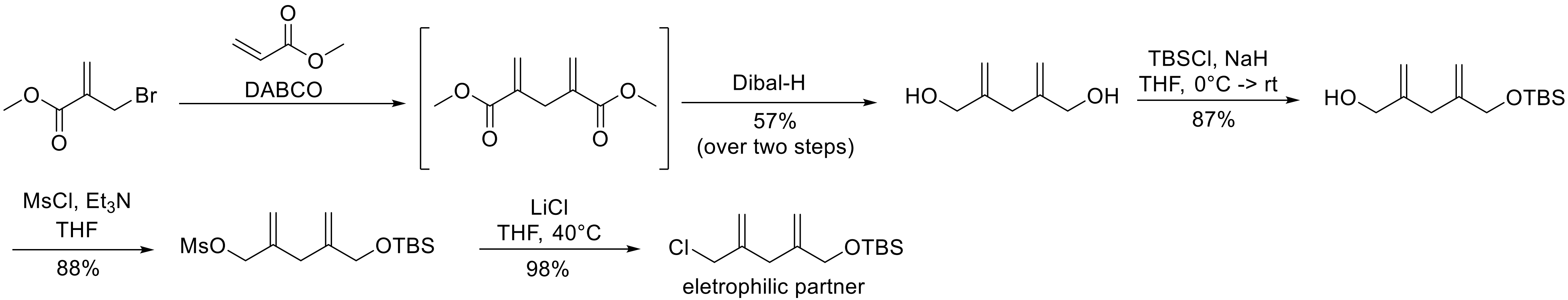
Synthesis of Fragment I (A)



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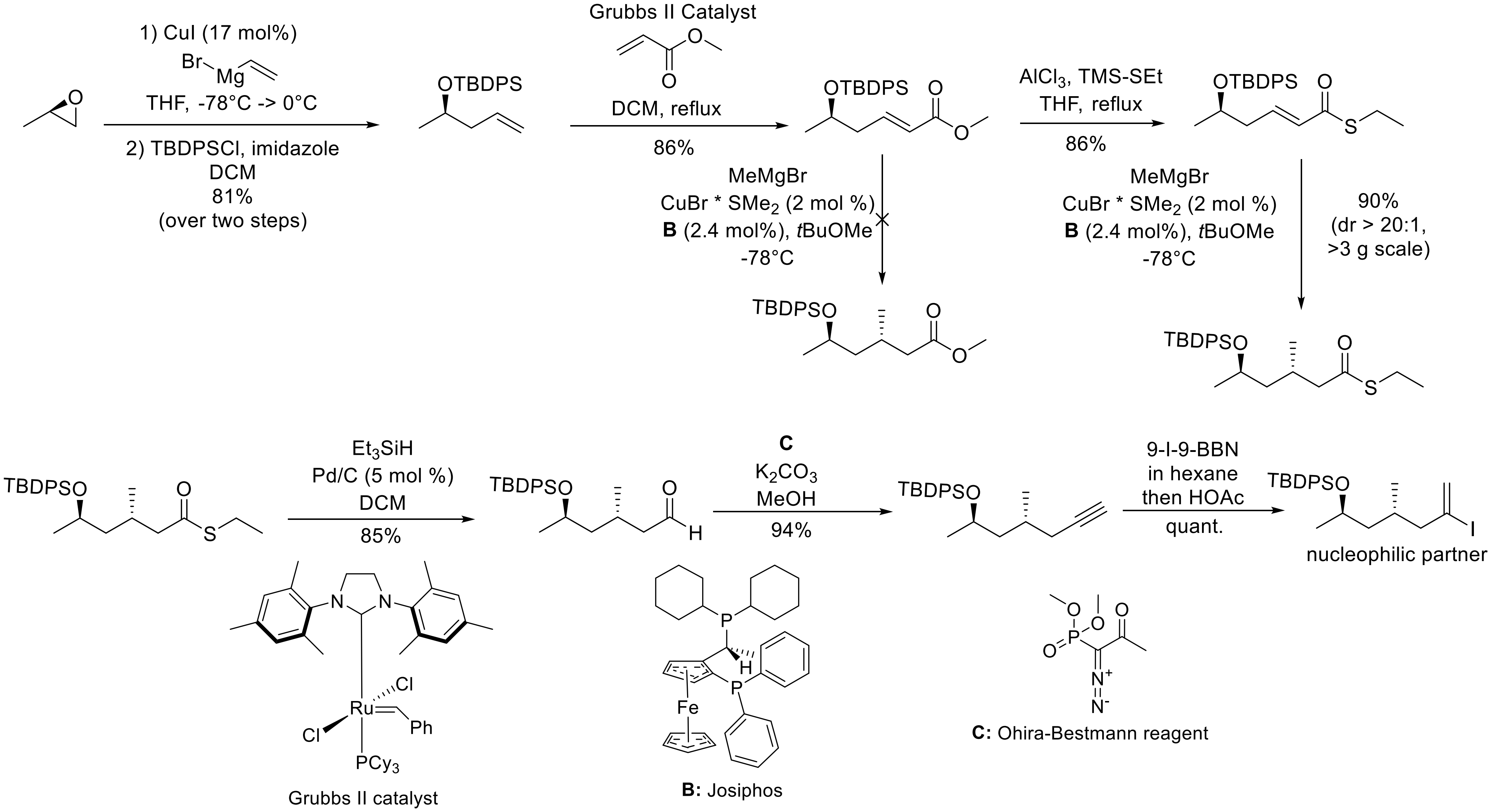
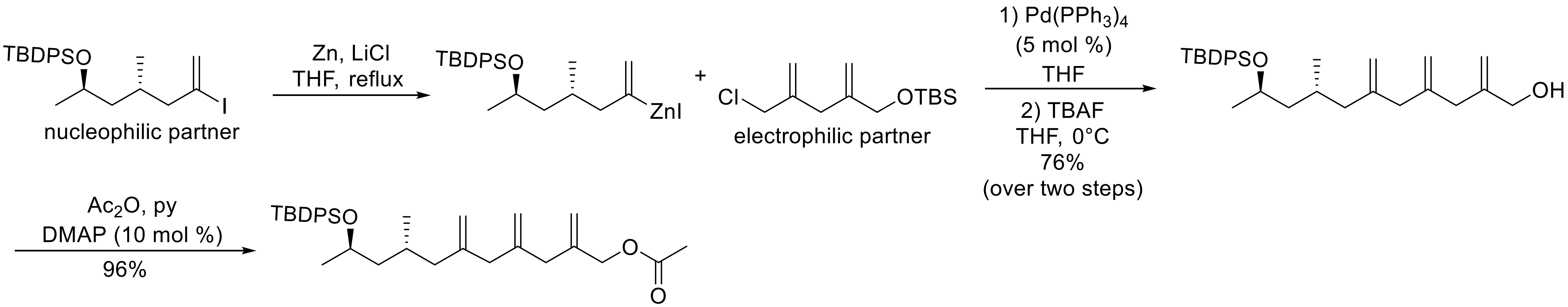
Synthesis of Fragment I (B)



Synthesis of Fragment I (C)



Fragment I

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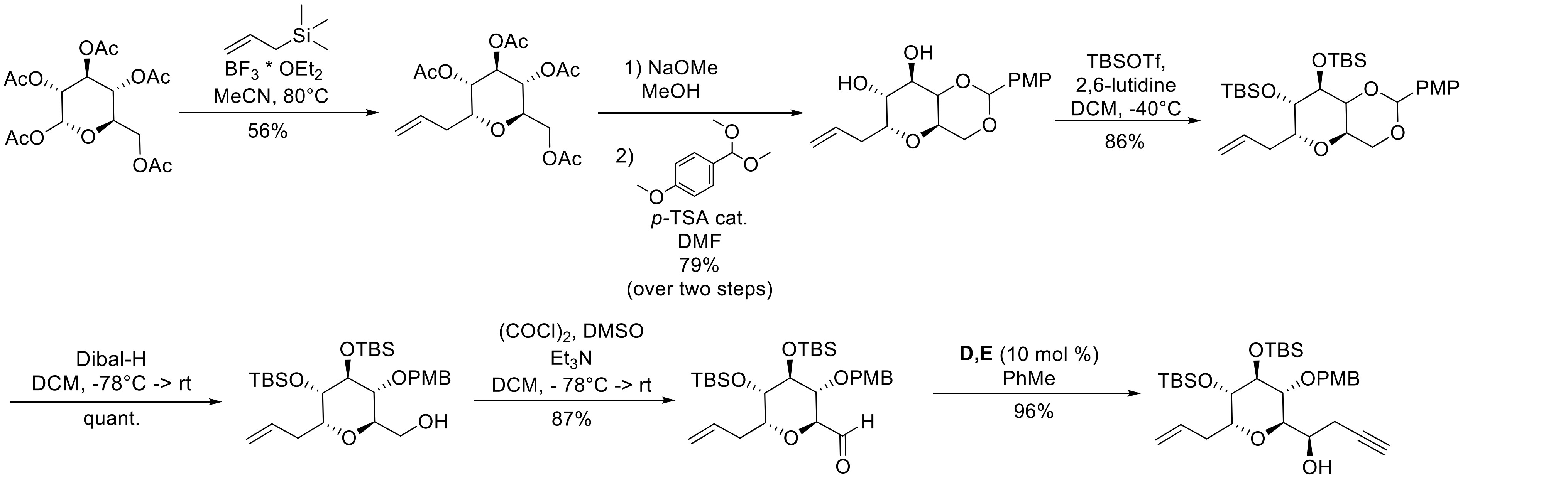
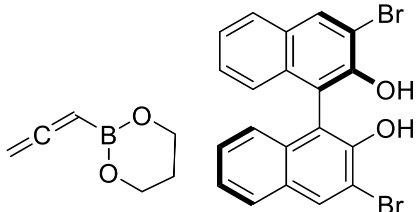
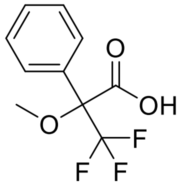
Synthesis of Fragment II (A)



The configuration was ascertained by Mosher ester analysis.

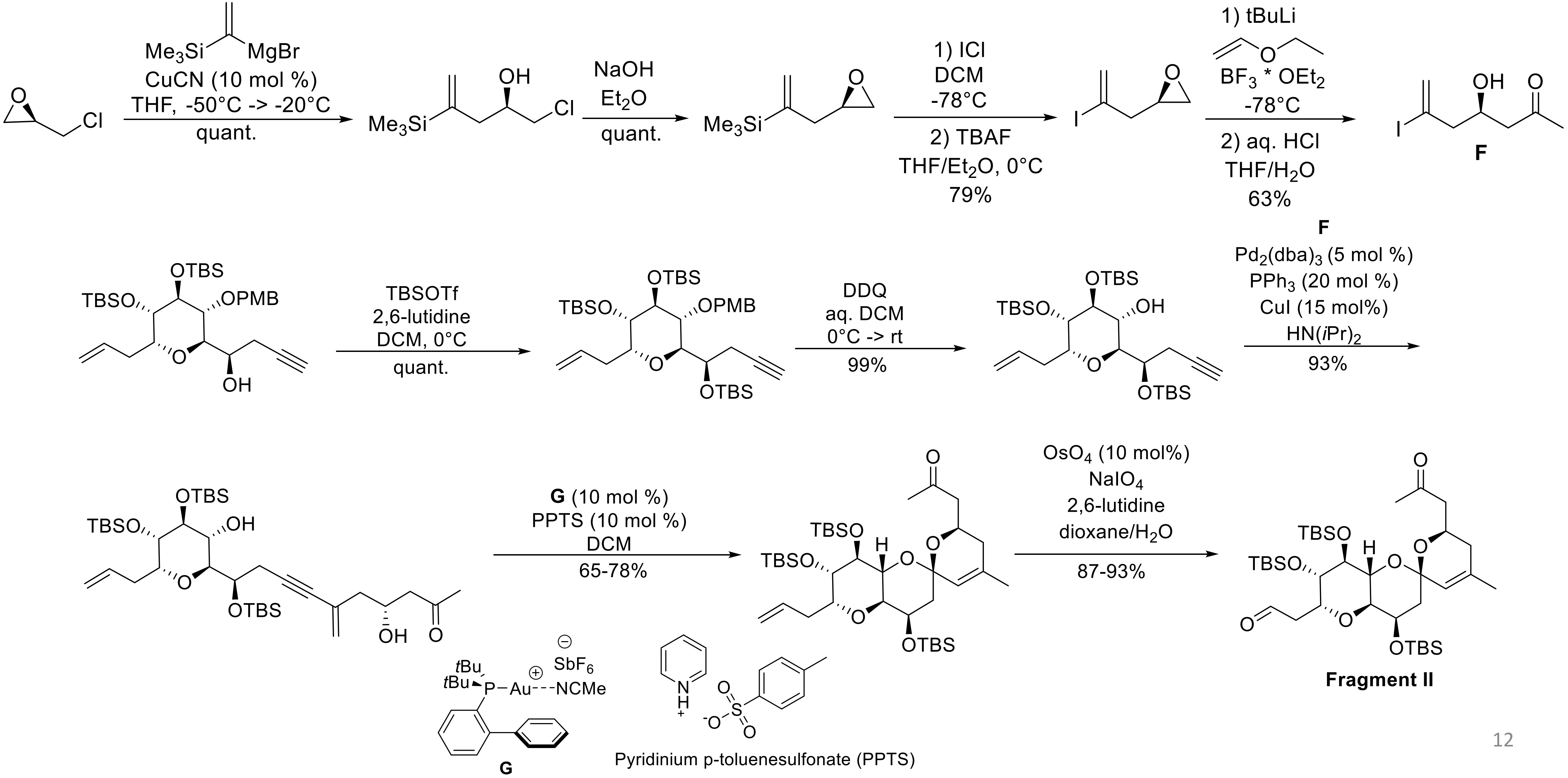


D E

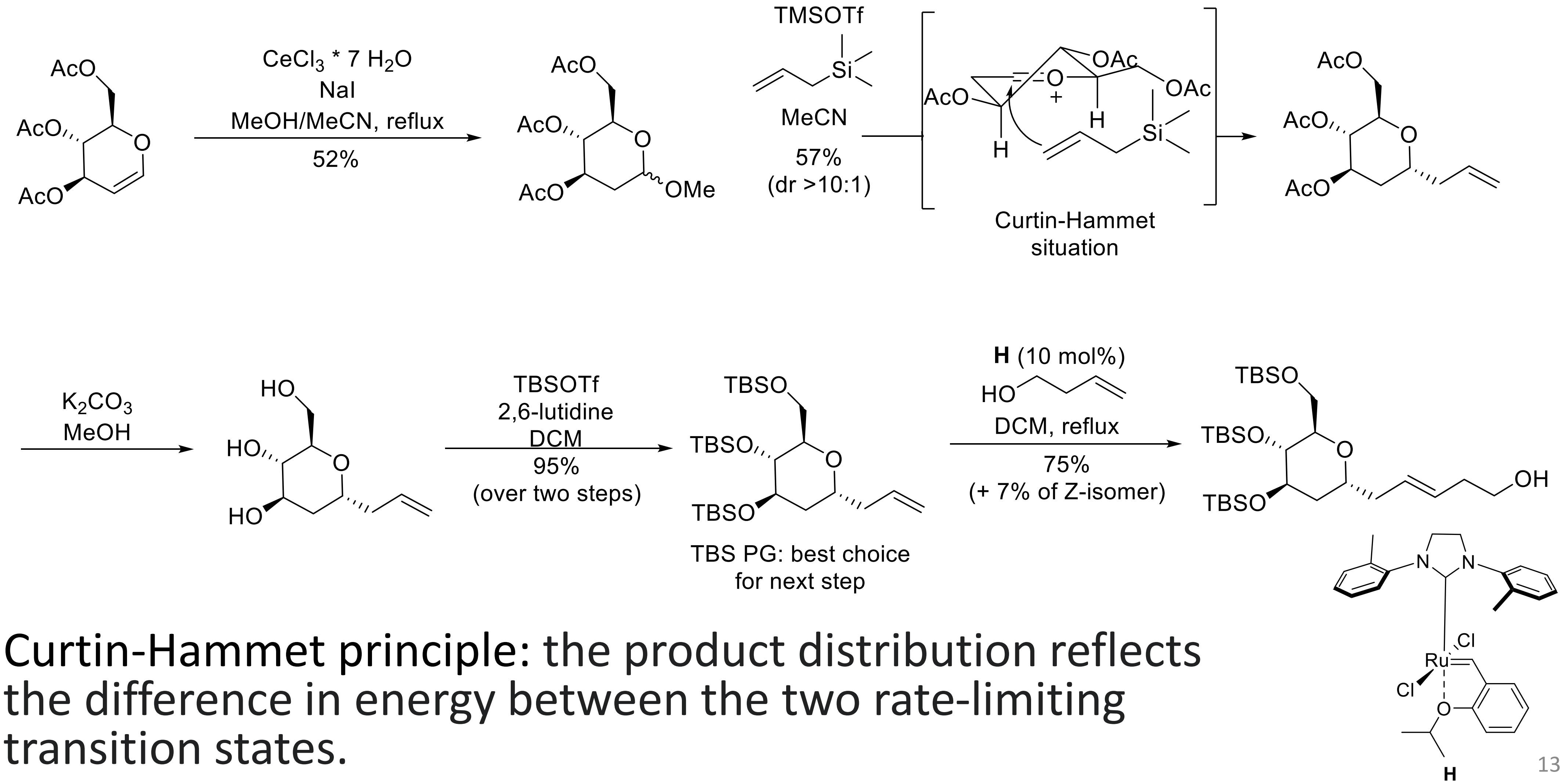


Mosher Ester

Synthesis of Fragment II (B)



Synthesis of Fragment III (A)



- **Curtin-Hammet principle:** the product distribution reflects the difference in energy between the two rate-limiting transition states.

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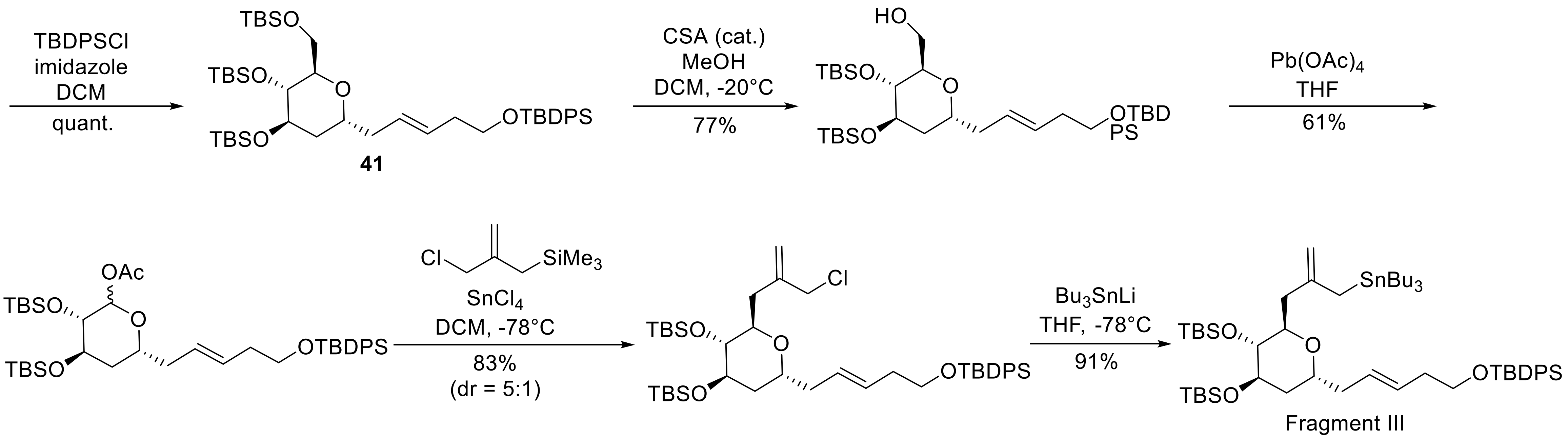
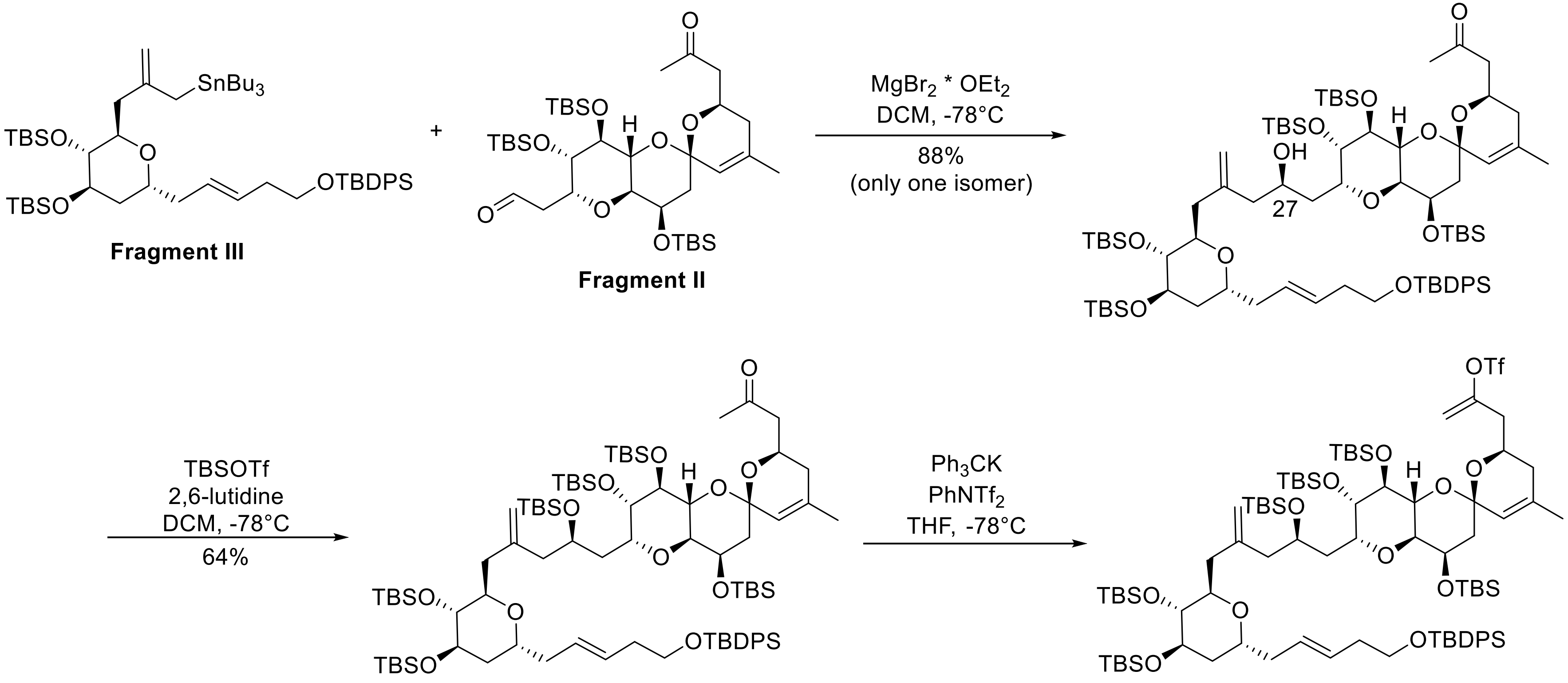
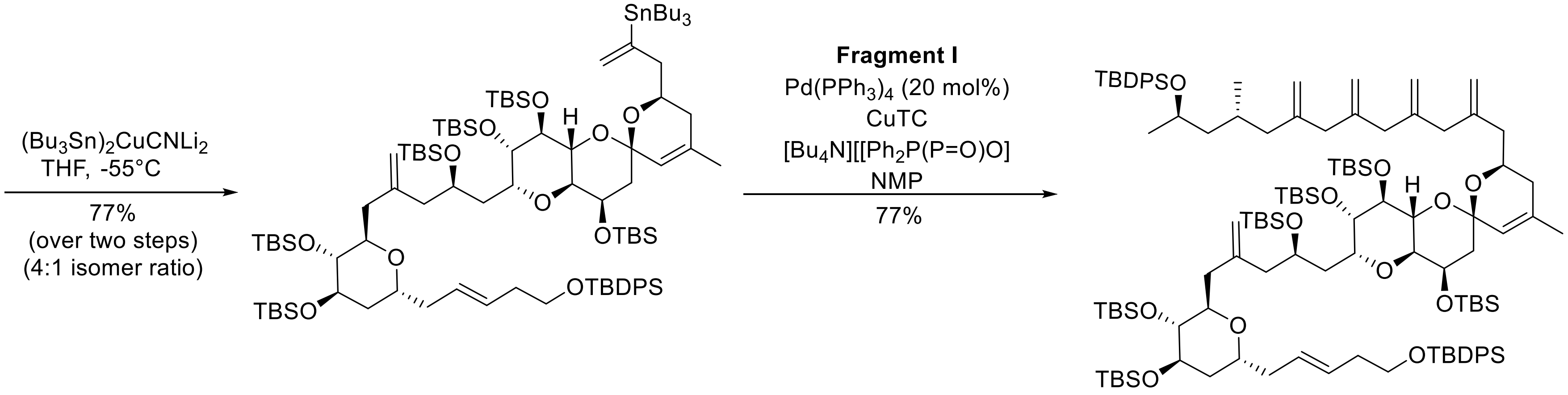
Synthesis of Fragment III (B)

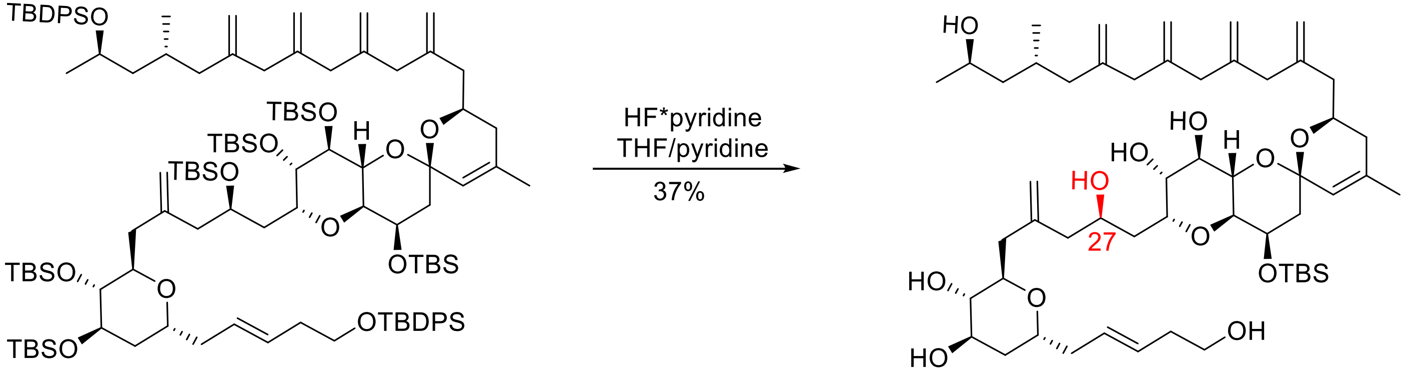


Assembly of the three fragments (A)



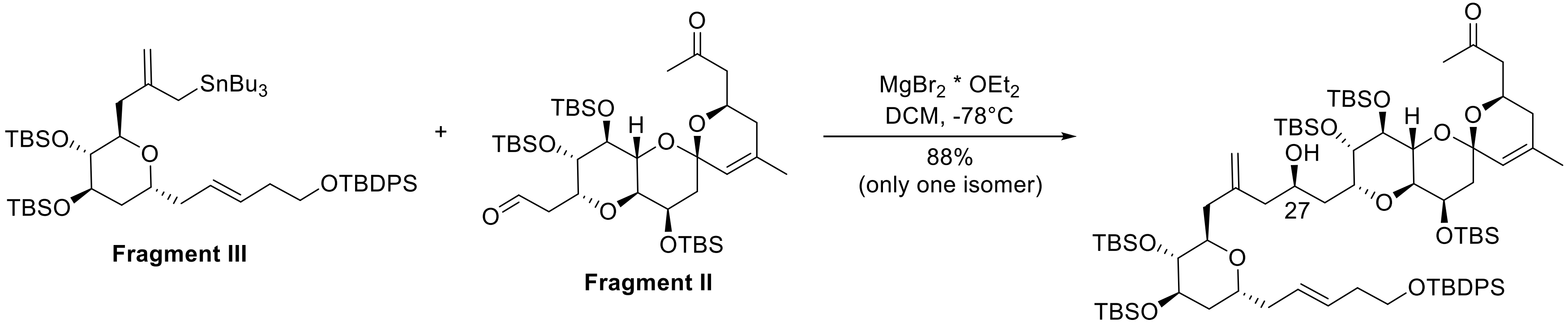
Assembly of the three fragments (B)





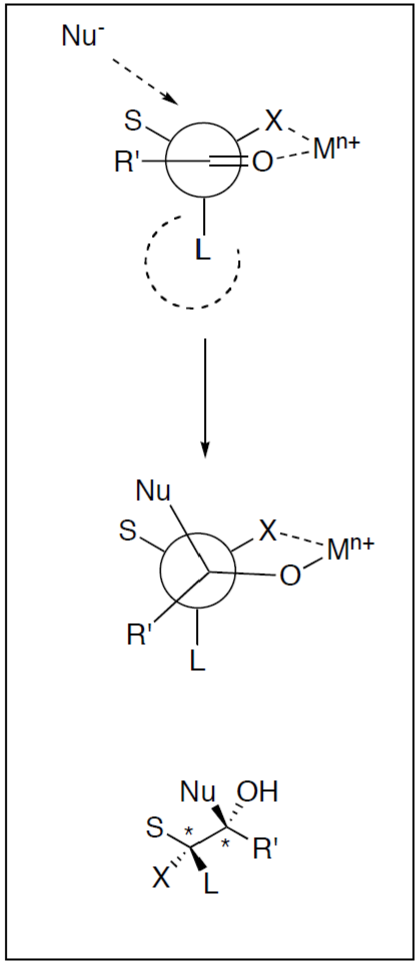
Epi-limaol!!

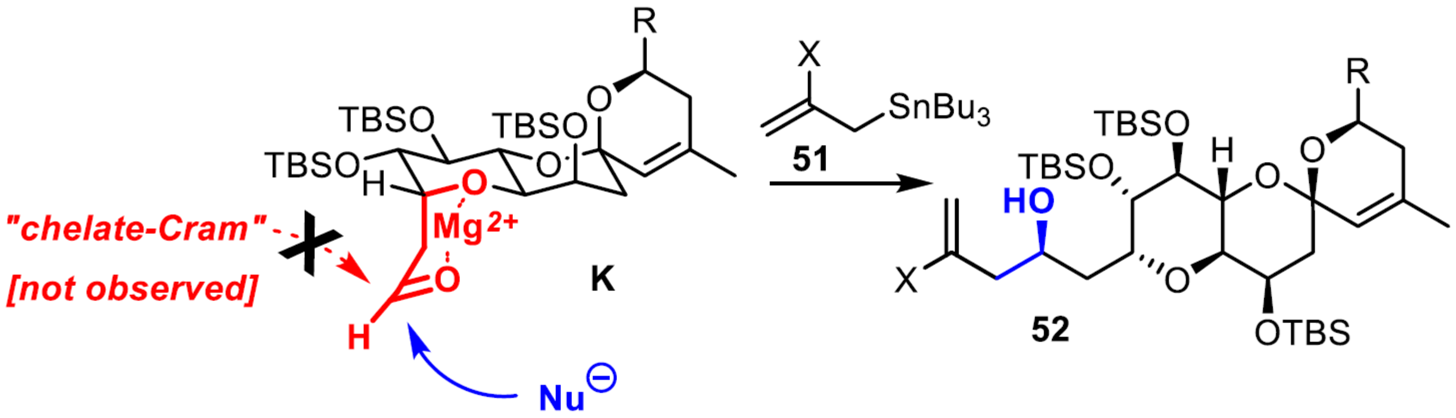
Chemistry is pain



- This reaction does not follow the Cram-Chelate model
- The result is confirmed by reaction with less complicated substrate of the same type
- Varying the Lewis acid led to product mixtures in low yields

Cram-chelate model

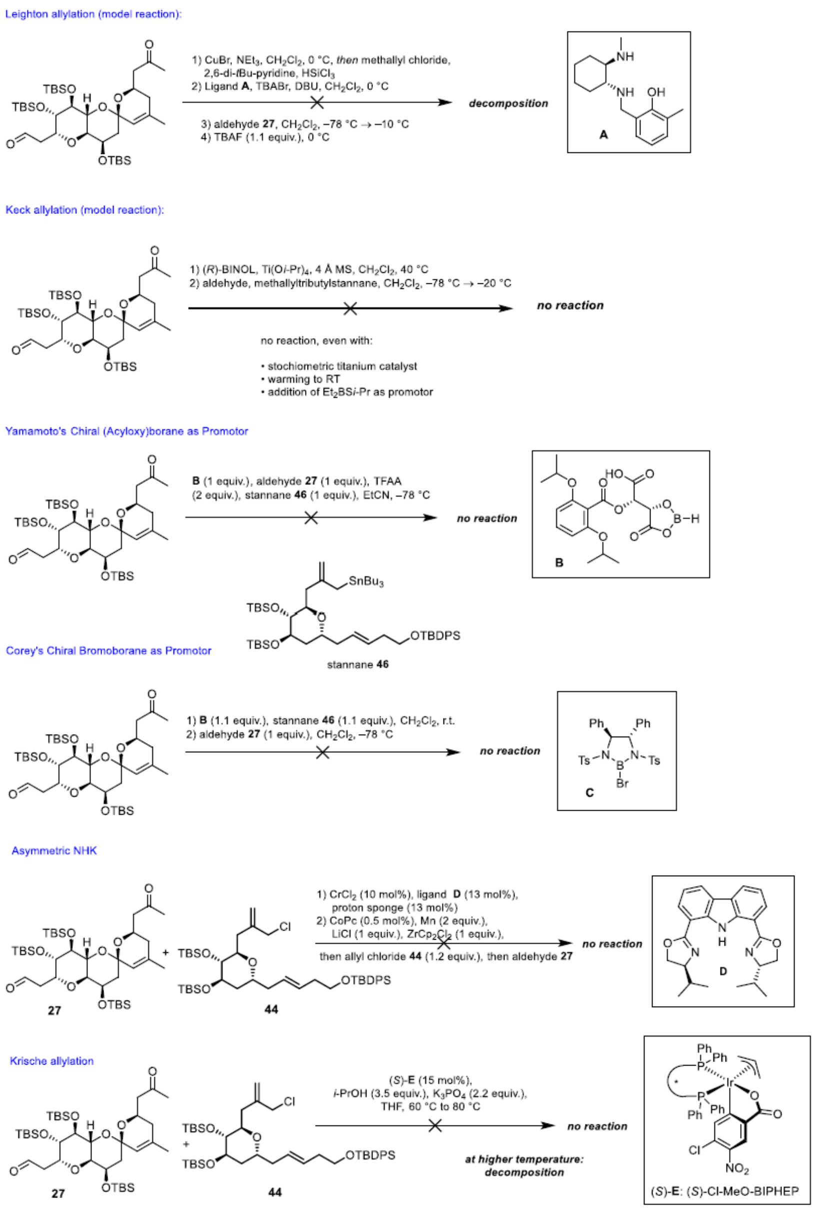




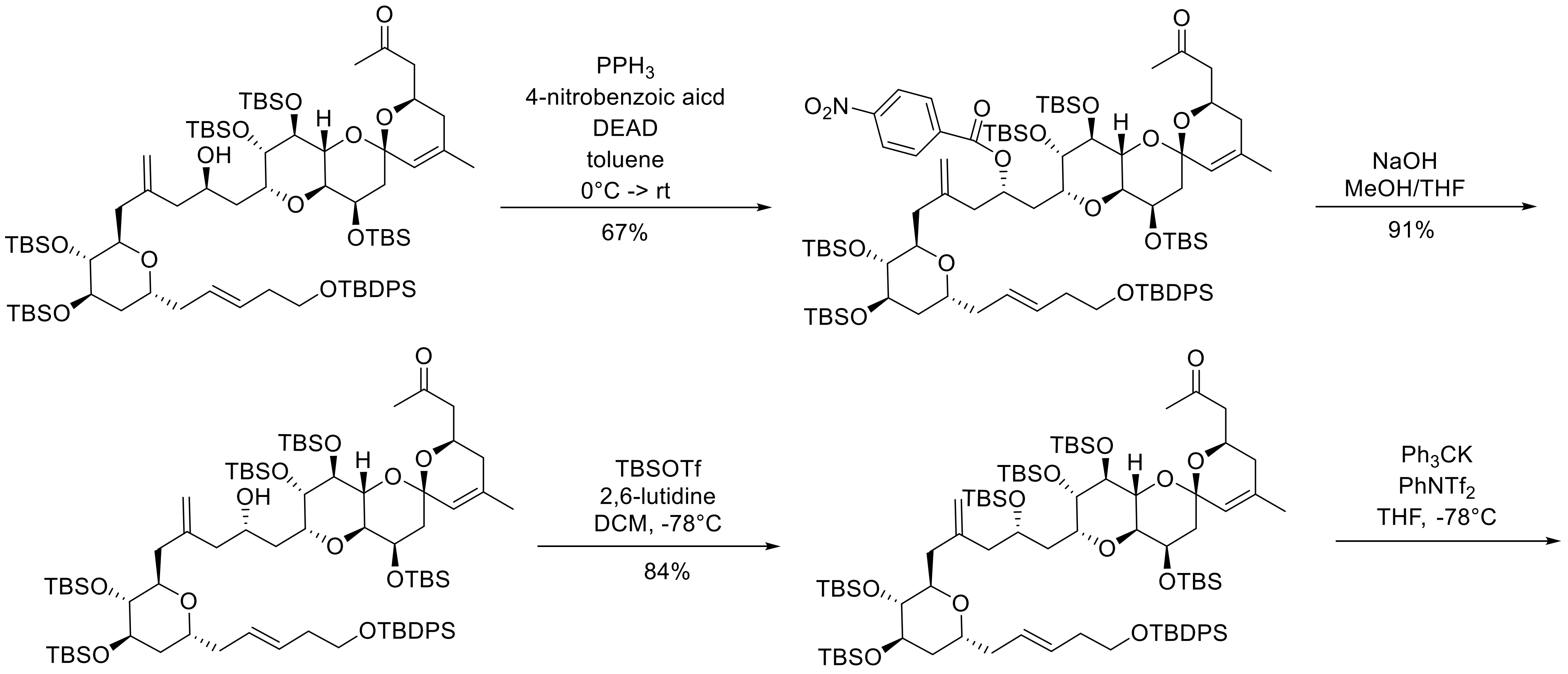
For further informations about Cram-Chelate model, see:
J.Org.Chem **1986**, 51, 5478-5480
JACS **1986**, 108, 3847-3849

Left: Image taken from Lecture Notes of 'Stéréochimie Organique' by Prof. C.Bochet – Unifr – AS2018

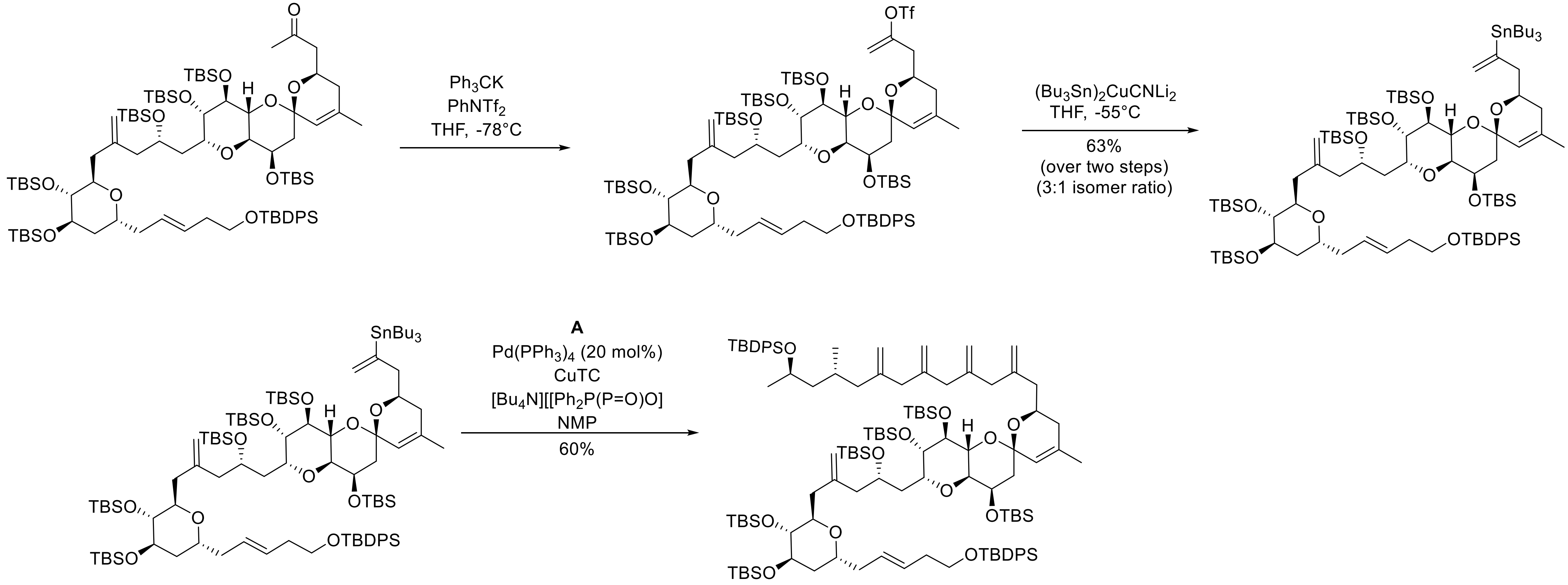
Attempted Reagent- or Catalyst-Controlled Allylation Reactions of the Central Fragment



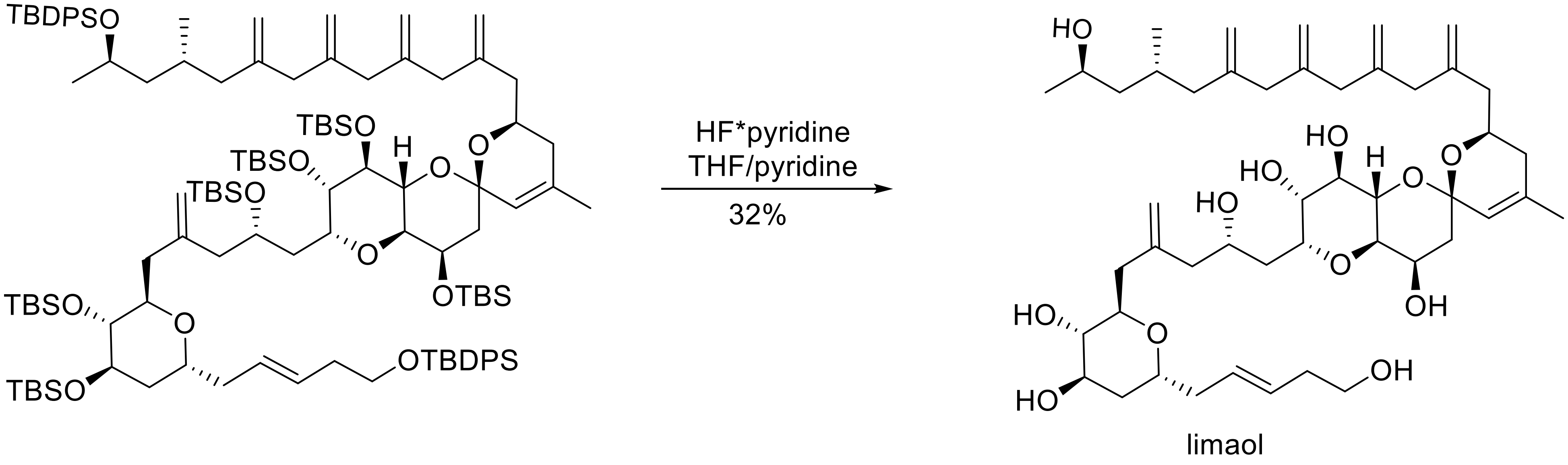
But… less is more: Mitsunobu reaction – Synthesis of limaol (A)



Synthesis of Limaol (B)



Synthesis of Limaol (C)



- Nearly 50 total synthetic steps
- Access to limaol and *epi*-limaol

Conclusion

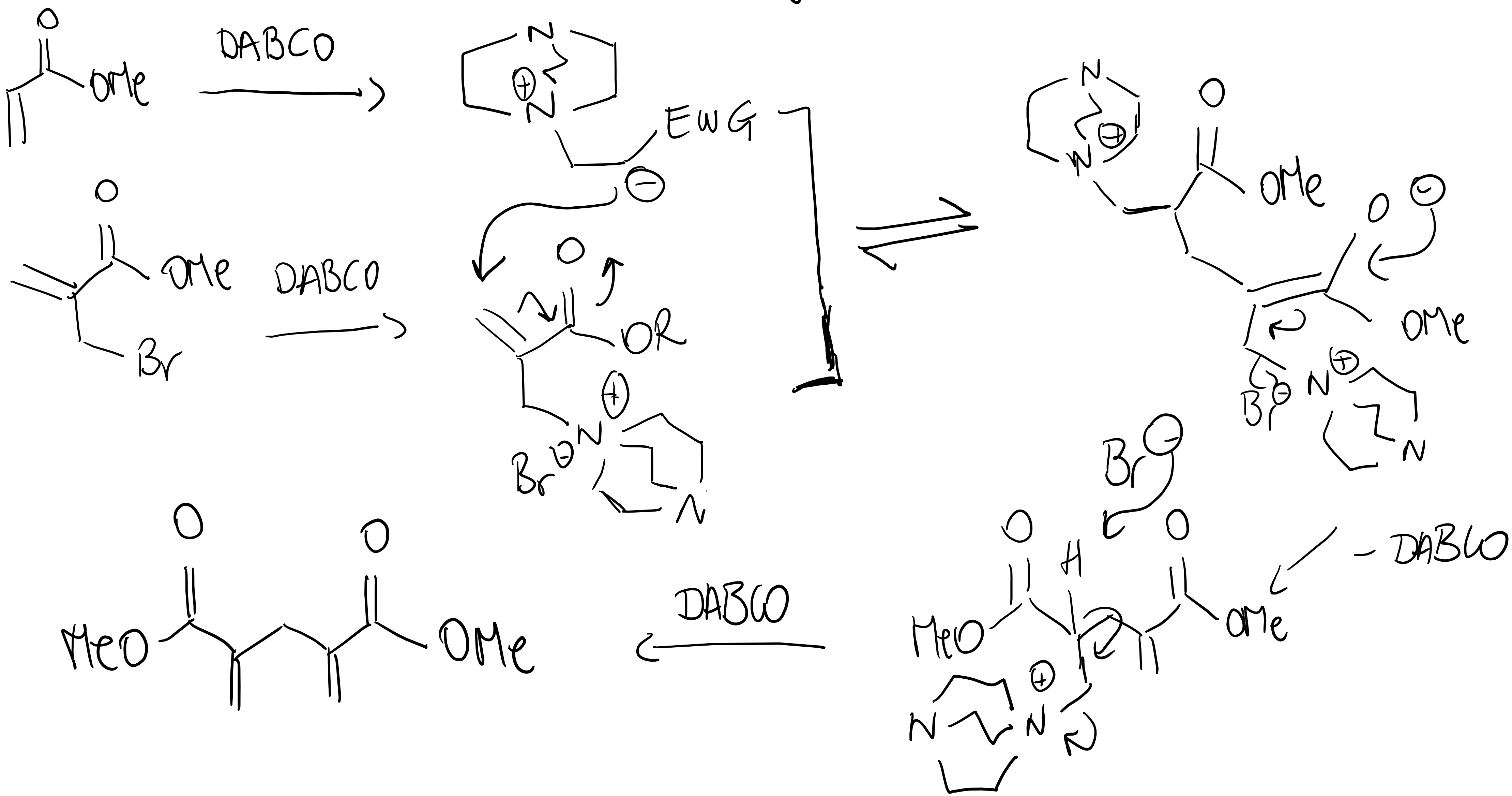
- Successful synthesis of target molecule
- Successful application of the Au(+) complex for the construction of the spirotricyclic core
- Problem of the epimerization of C27 solved

Thanks for your attention. I am now glad to answer your questions.

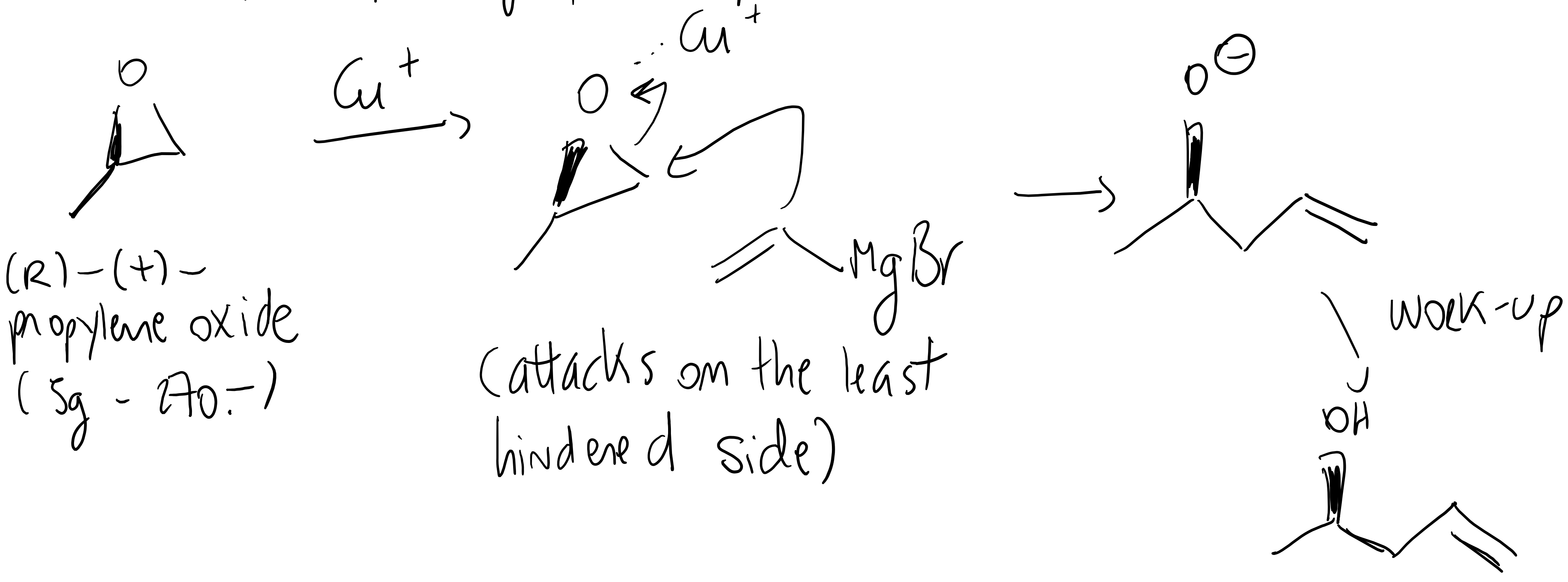
Reaction mechanisms

Synthesis of fragment I

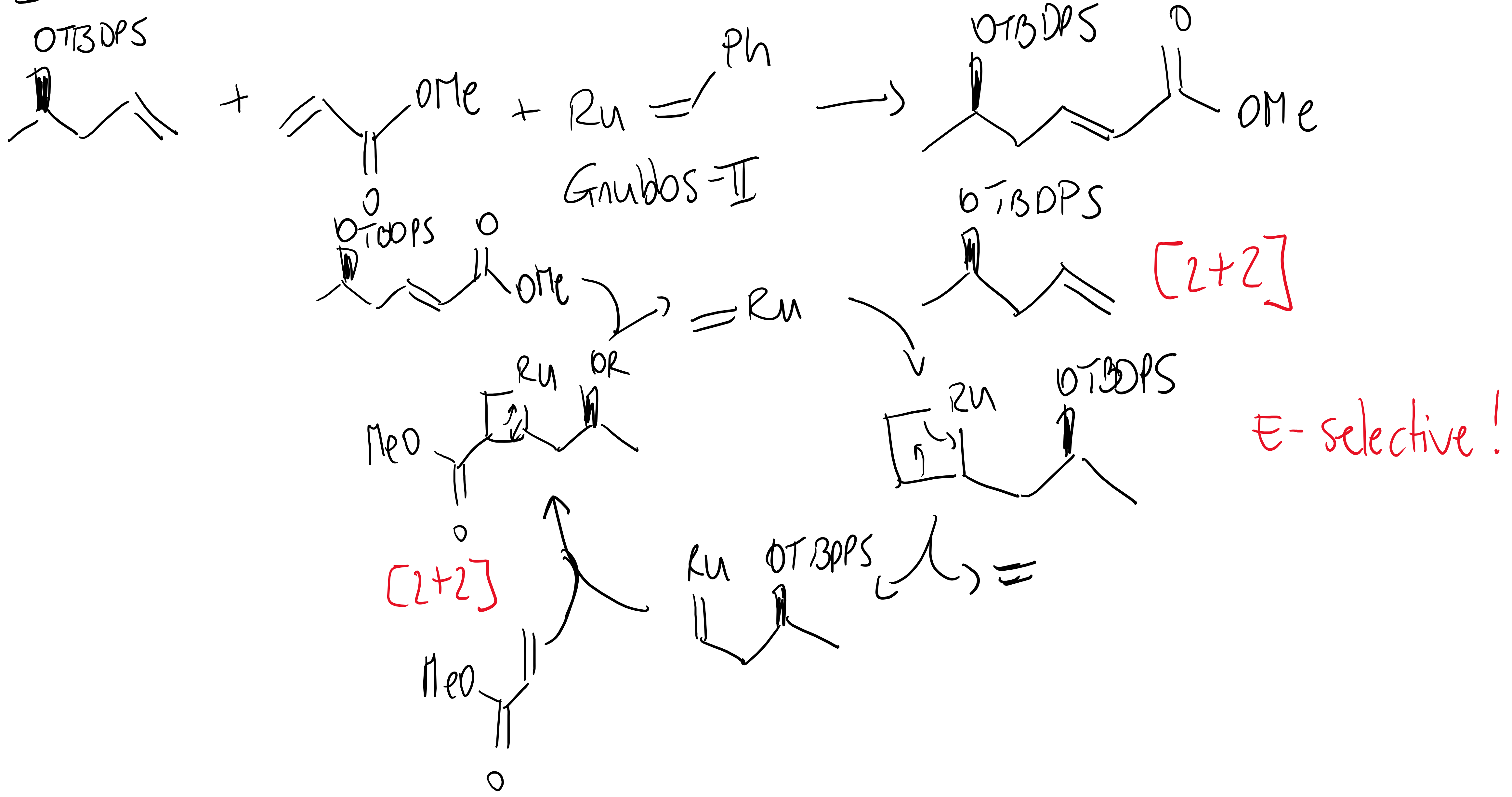
A Baylis-Hillman reaction - J. Org. Chem 2002, 67, 7135-7137



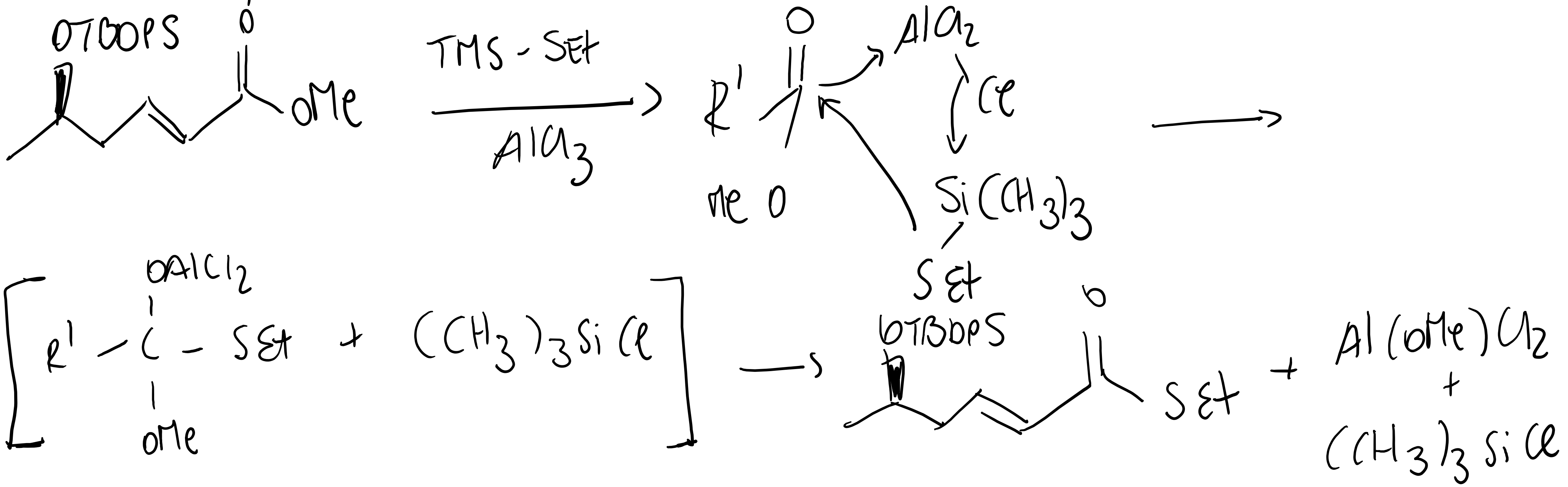
E Cu catalyzed opening of an epoxide



G Cross-metathesis – JACS 2003, 125, 11360–11370

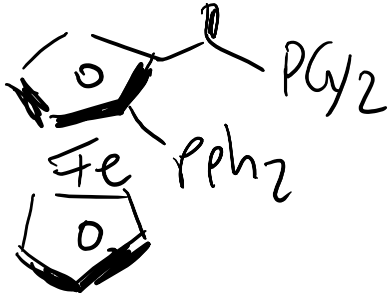


H Thioester synthesis - Chem. Lett, 1974, 3, 187-188



I Asymmetric 1,4-addition to thioester - Feringa et al., JACS, 2005, 127, 9966-9967

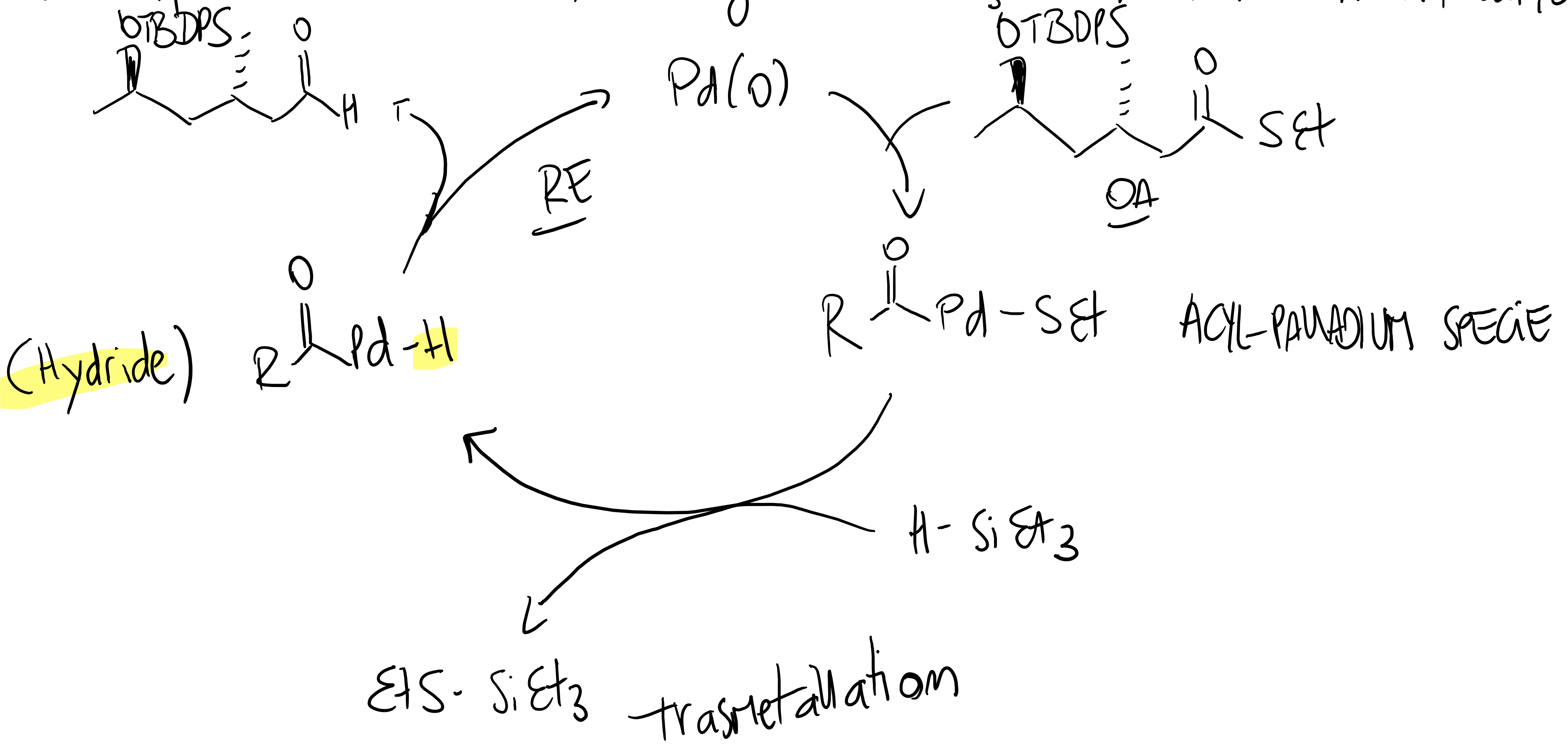
A) In situ complex between $CuBr \cdot SMe_2$ and Joliphos



B) Coordination of the catalyst with S atom of thioester

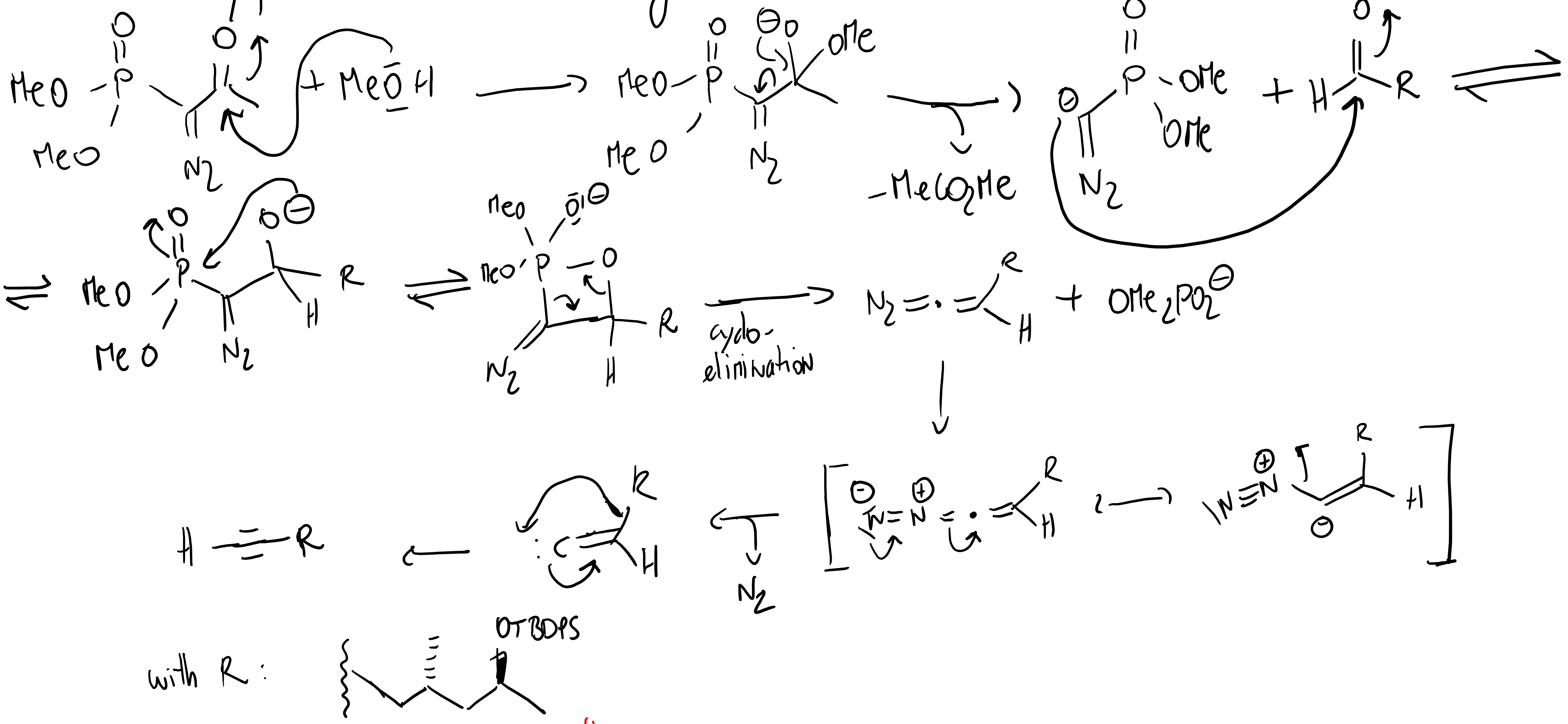
⇝ enhanced tendency to 1,4-addition

J Reduction of thioesters to aldehydes using Pd/C & Et_3SiH - Aldrichimica Acta, 2004, 37, 87-96

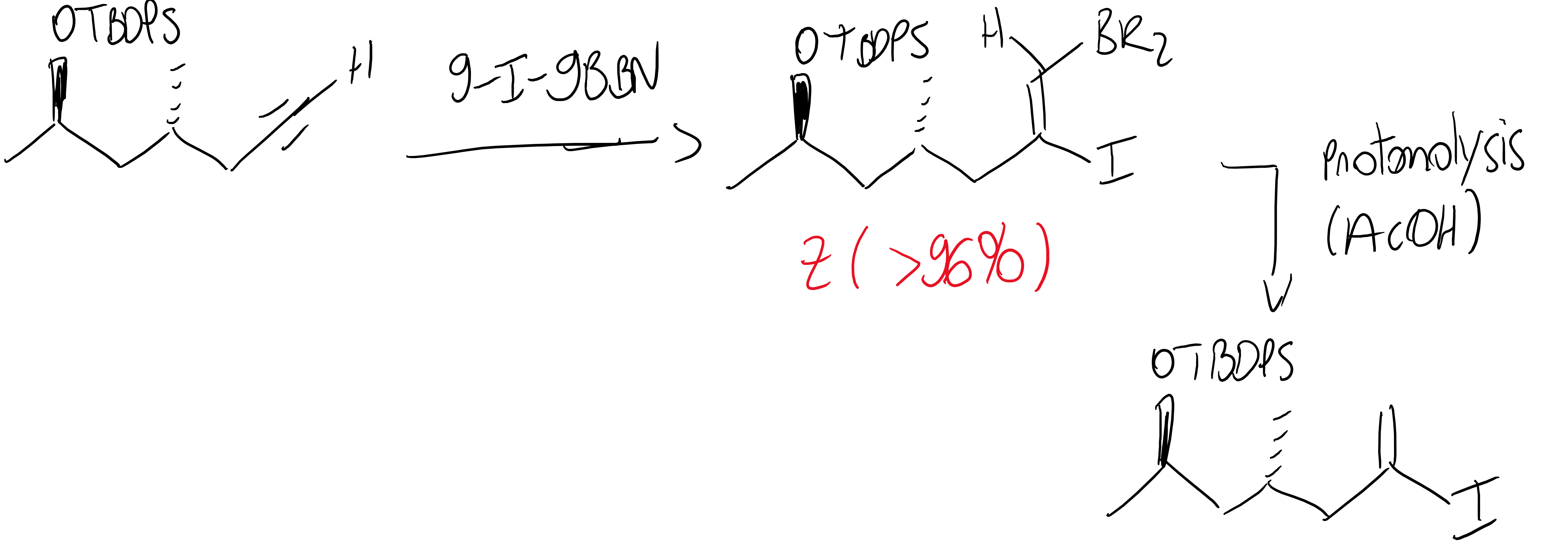


IX Aldehyde to alkyne via Ohira-Bestmann reagent

→ Seyferth-Gilbert homologation

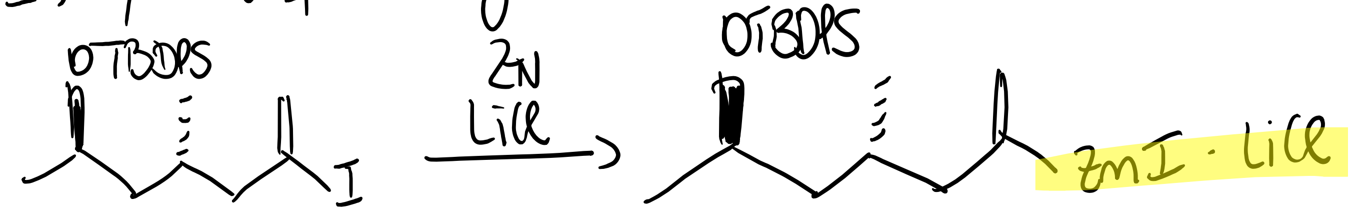


ANALOGUE REACTION: Corey-Fuchs alkyne synthesis alkenyl iodide synthesis using B-iodo-9-boracyclo[3.3.1] nonane

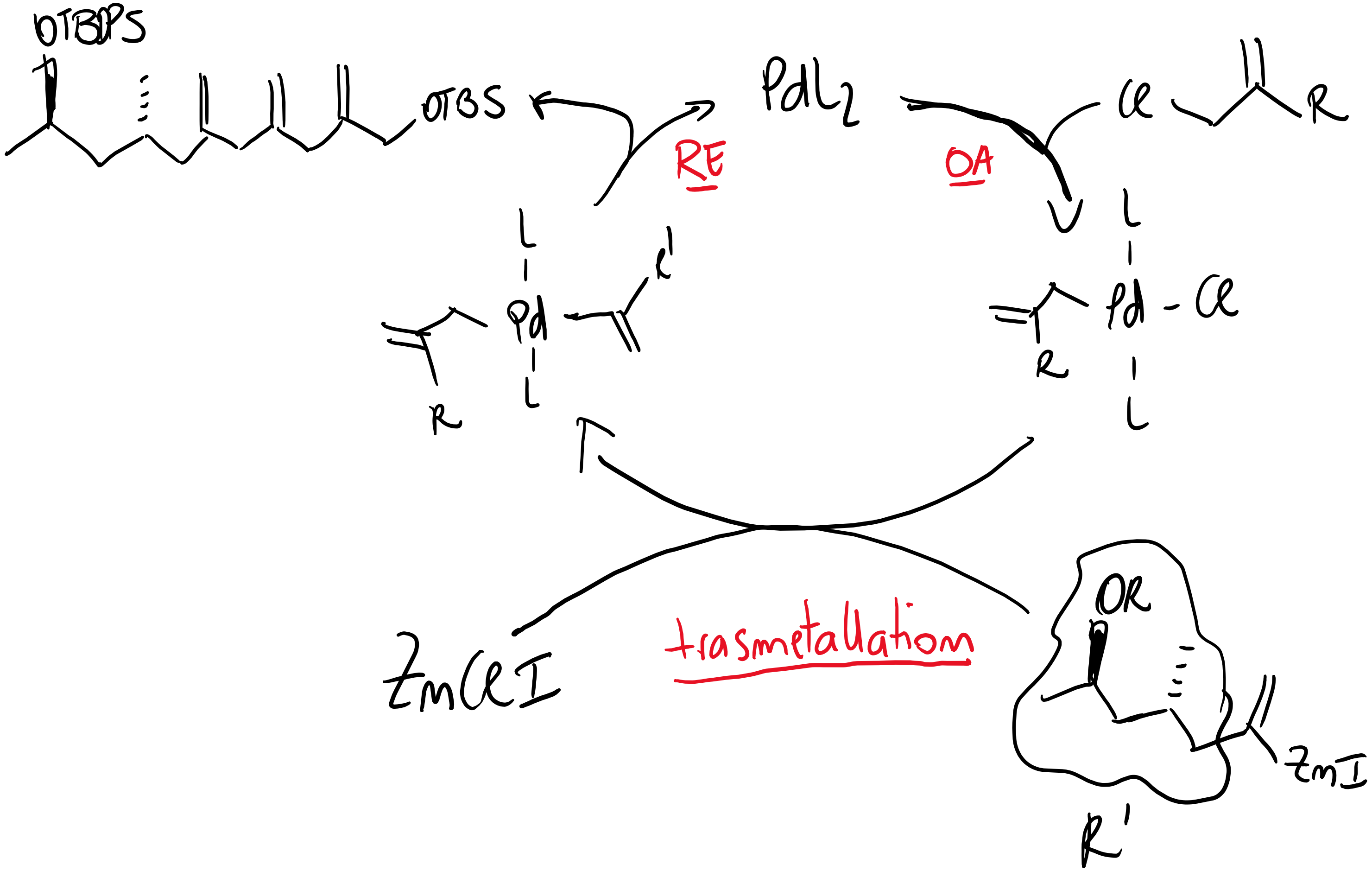


M Negishi Coupling

I) Synthesis of the organozinc

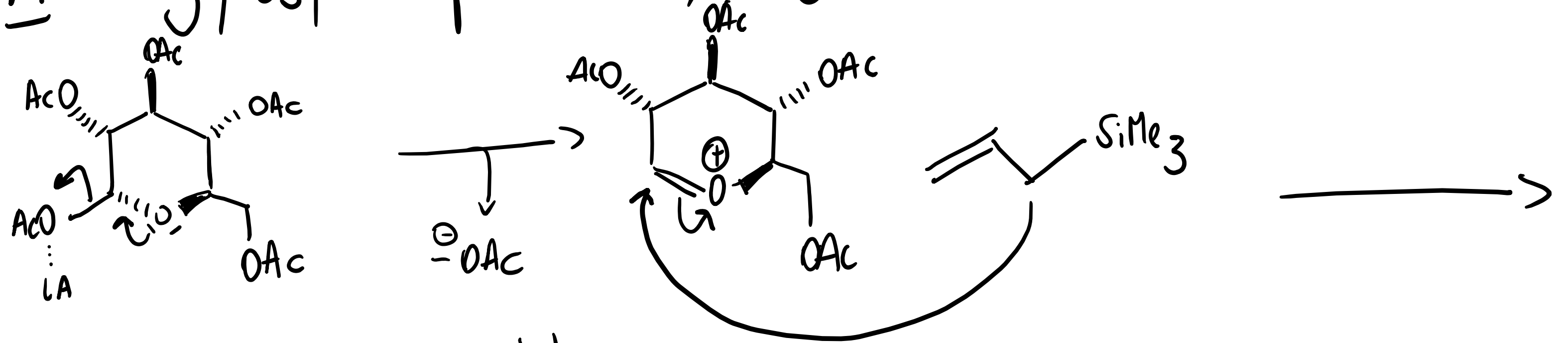


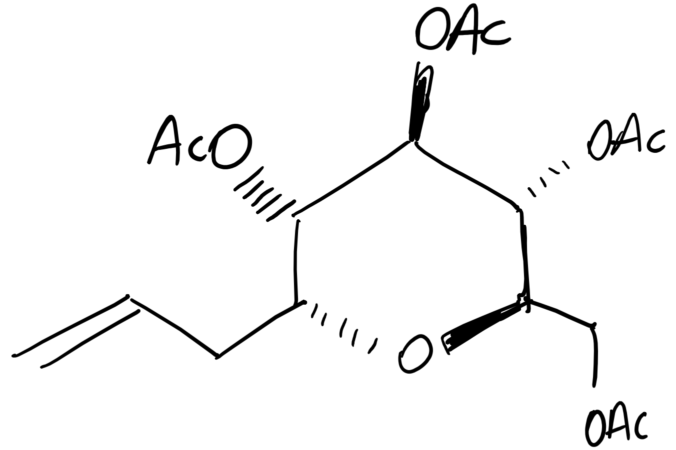
· LiCl forms a soluble act with the organozinc compound, thus removing it from the metal surface.



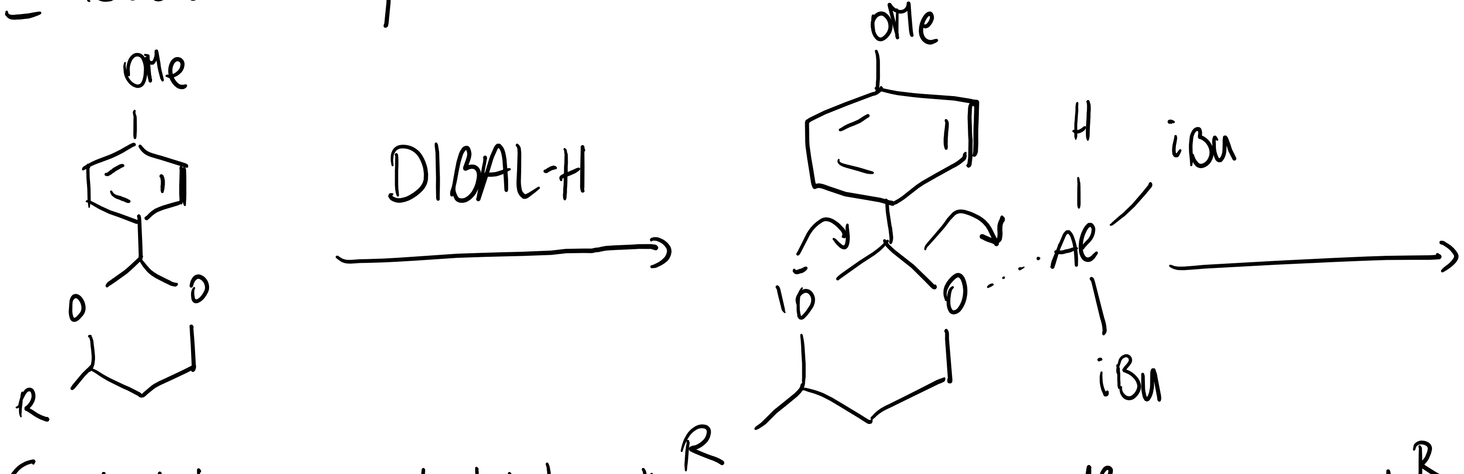
Synthesis of Fragment II

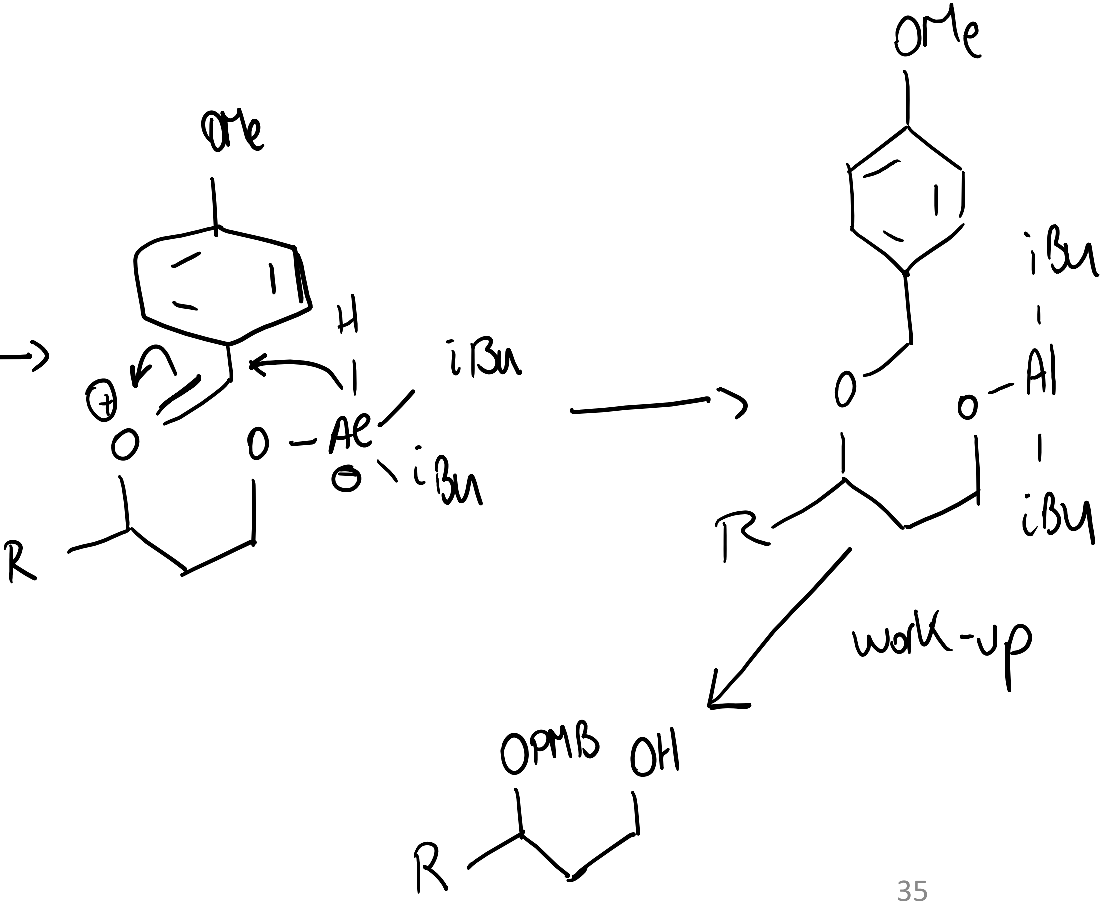
A C-glycosylation promoted by $BF_3 \cdot OEt_2$ (neutral conditions)



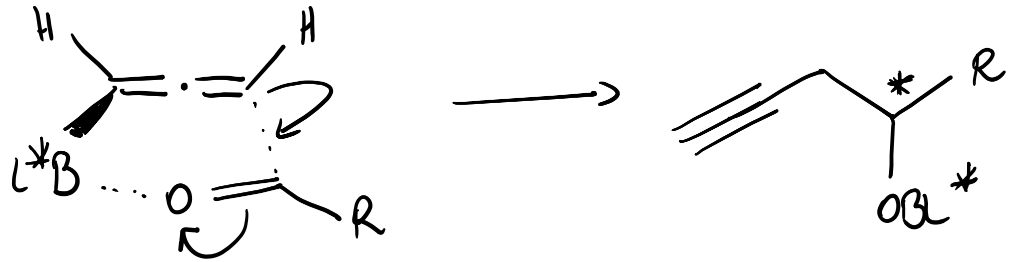


B Reduction of acetals with DIBAL-H

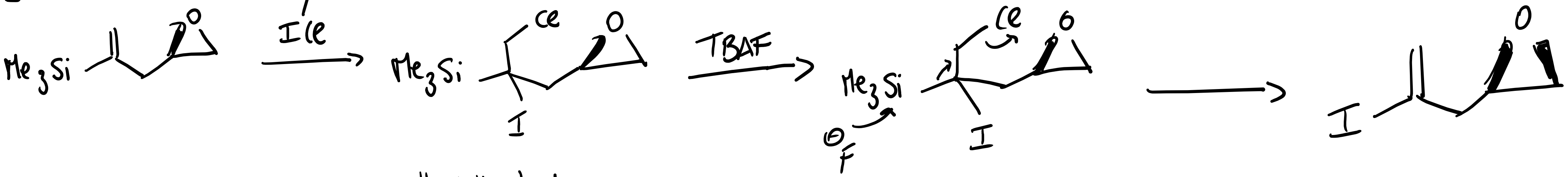




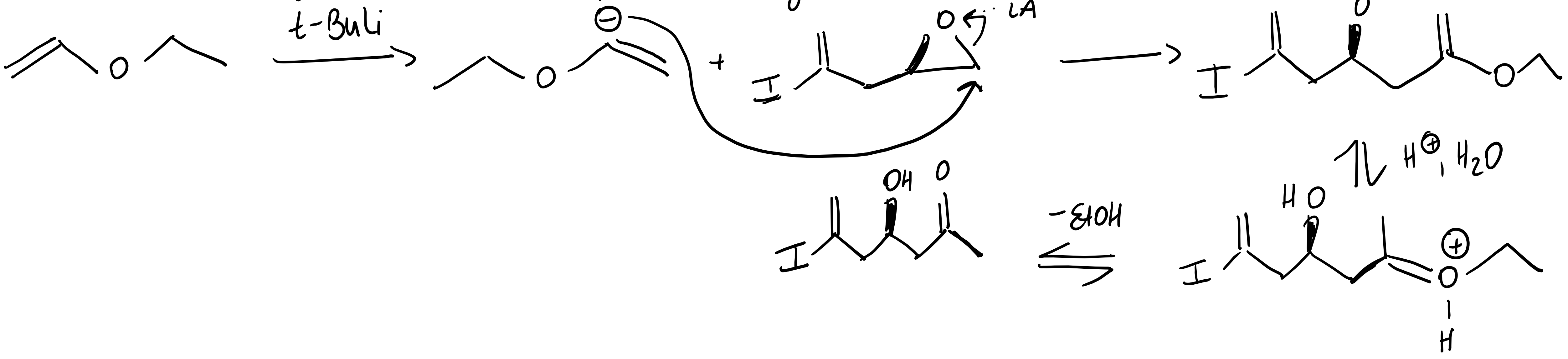
C chiral homopropargyl alcohol synthesis - Org. lett. 2011, 13, 4020-4023



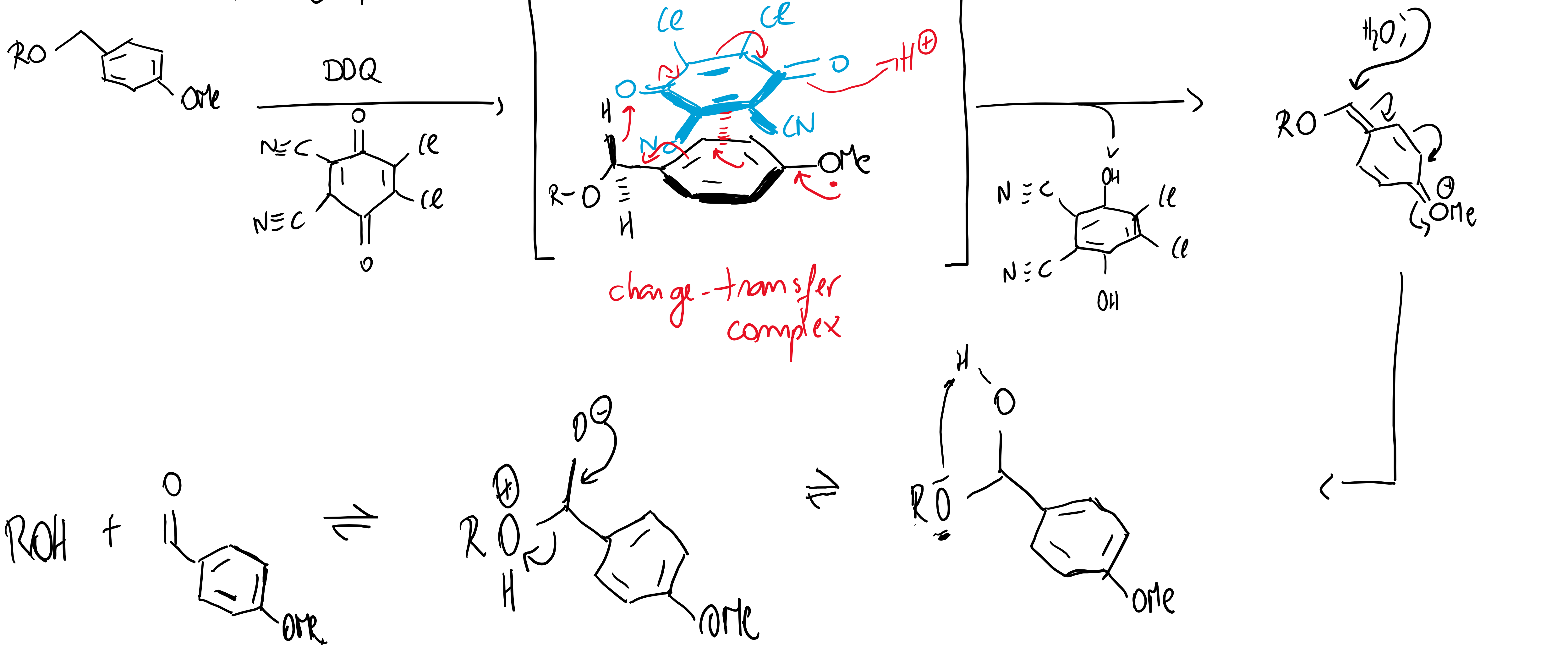
O IODODESILYLATION - Synth. Commun. 1978, 8, 291-299



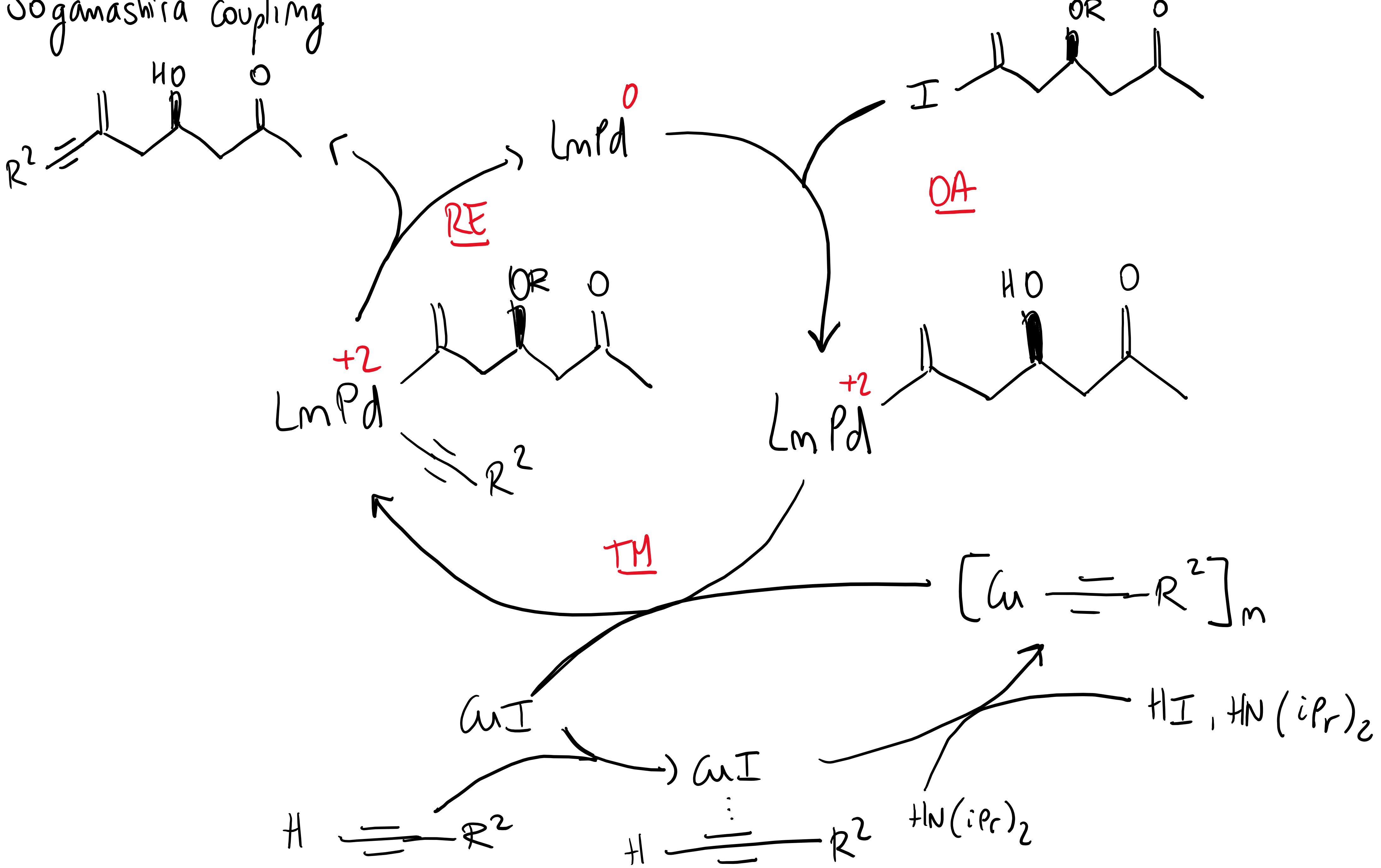
P OXIRANE RING opening with lithiated ethyl vinyl ether - J. Org. Chem - 1979, 44, 4781-4788



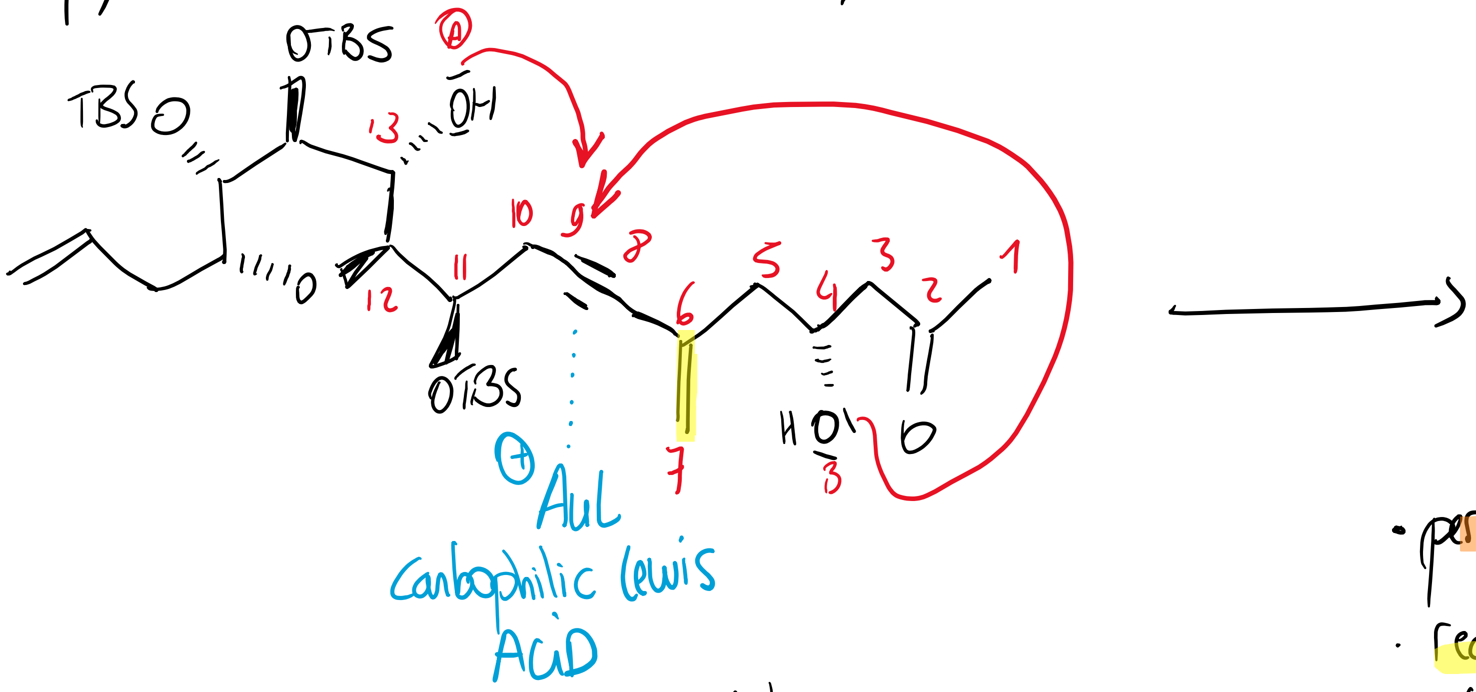
I) Deprotection of PMB group with DDQ

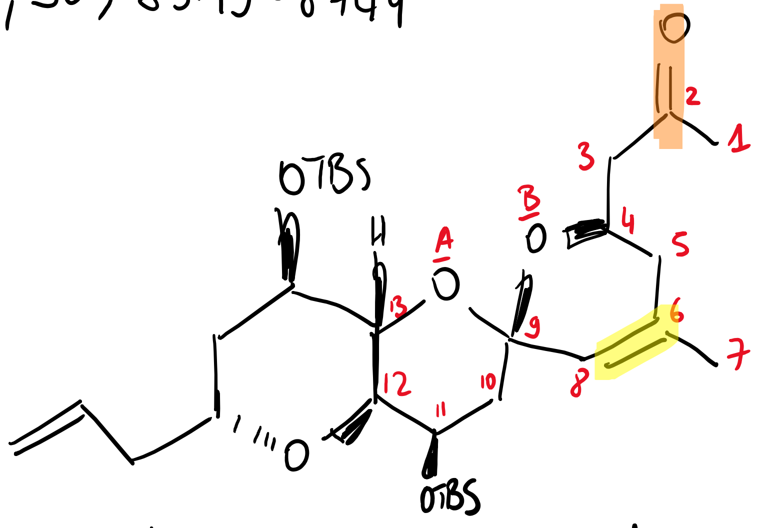


J) Sogonashira coupling



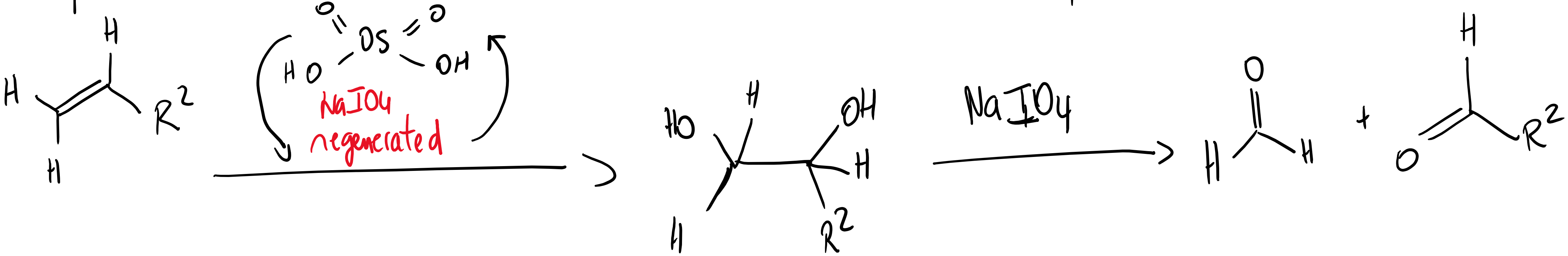
k Spyroketalization – the alkyne route – ACIE, 2011, 50, 8379-8744





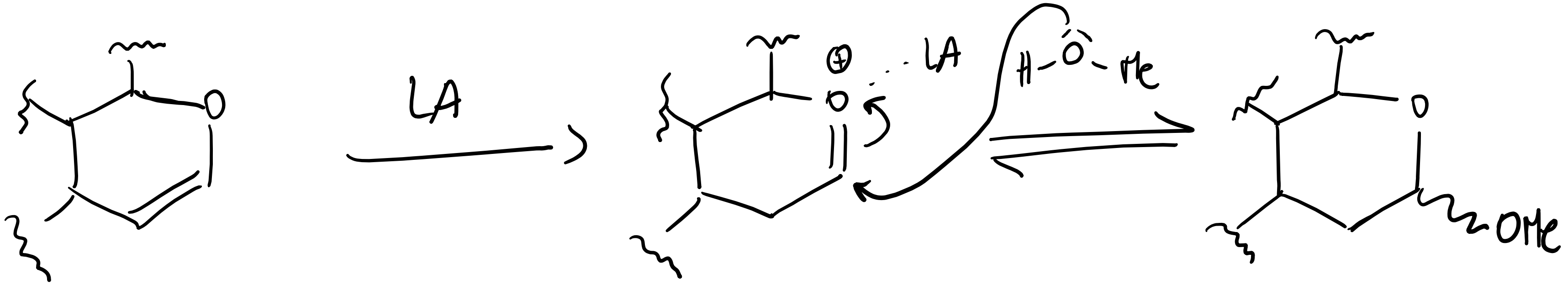
- peripherical ketone is untouched
- rearrangement of the exo-methylene group (expected)

L Malapnade - Lemieux - Johnson oxidation

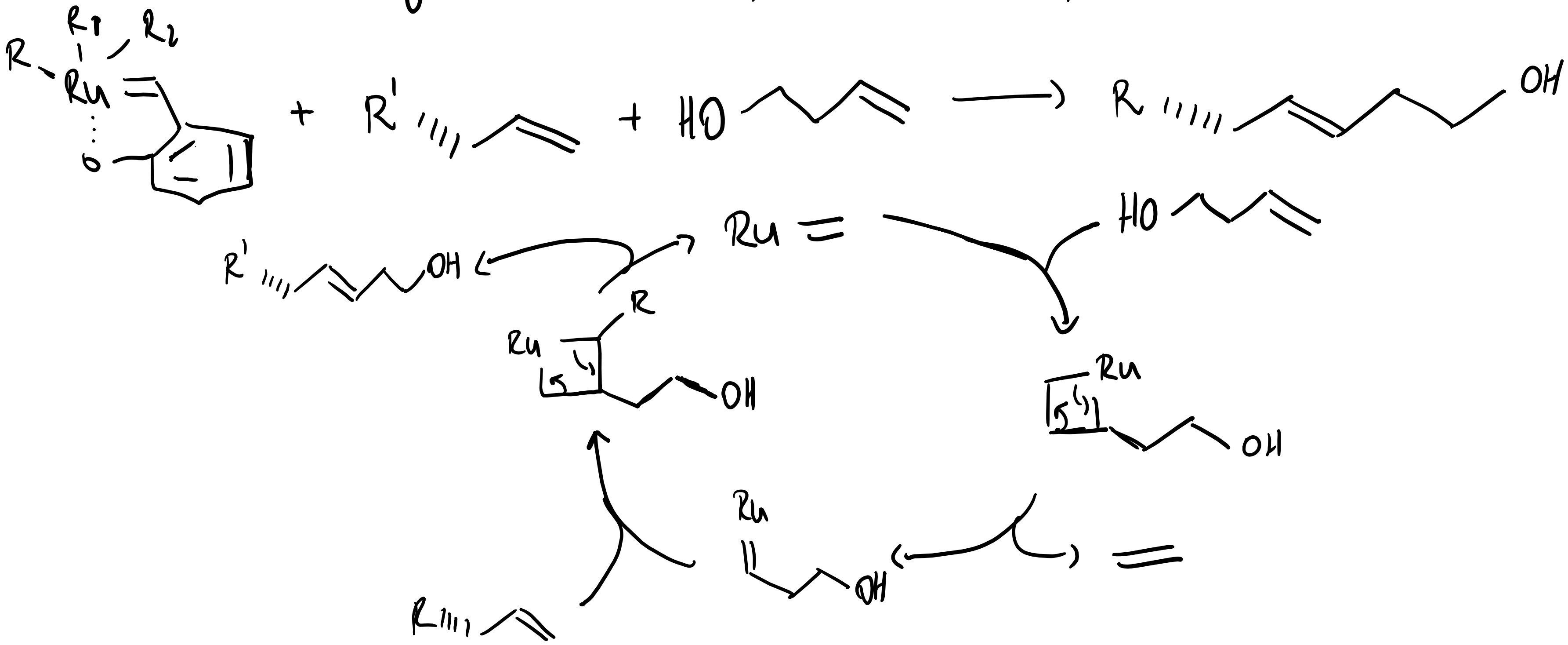


Synthesis of Fragment III

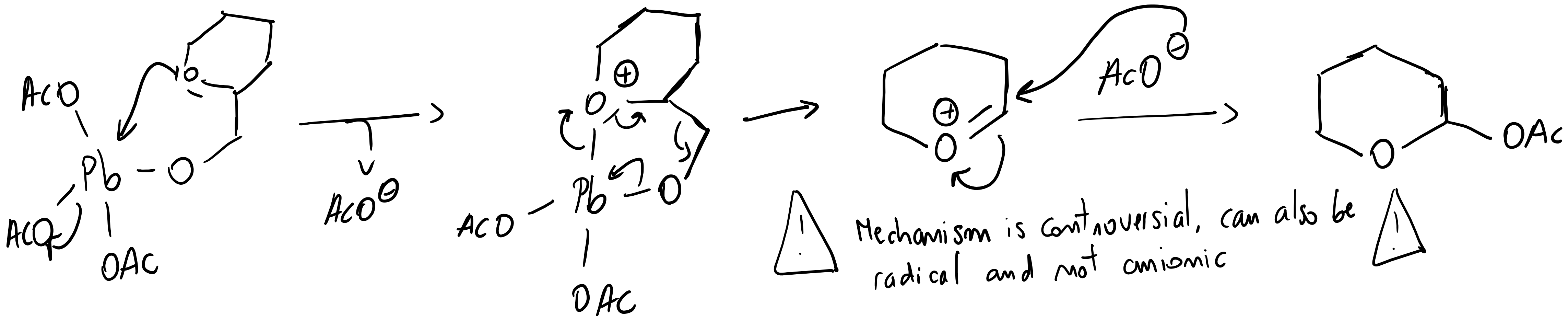
A) Substitution α to O atom



E) Cross-metathesis using a modified Hoveyda - Grubbs catalyst

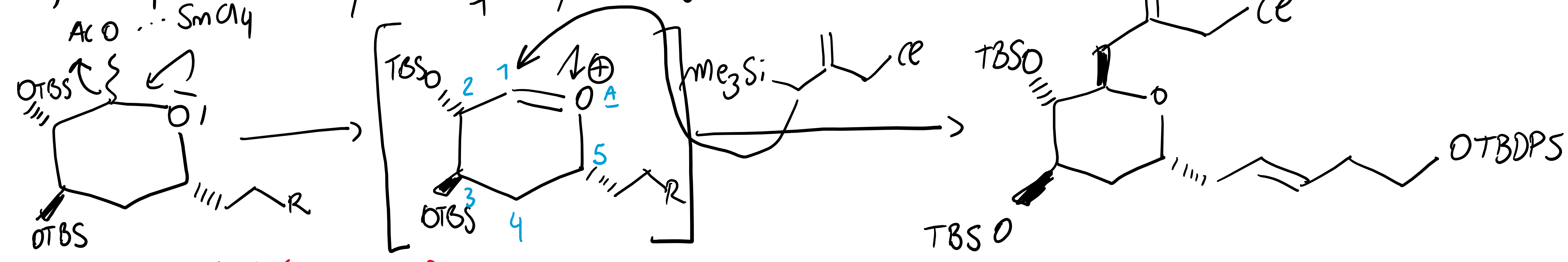


H) Anomeric acetate synthesis with $Pb(OAc)_4$ - Tetrahedron 2011, 67, 8910-8917

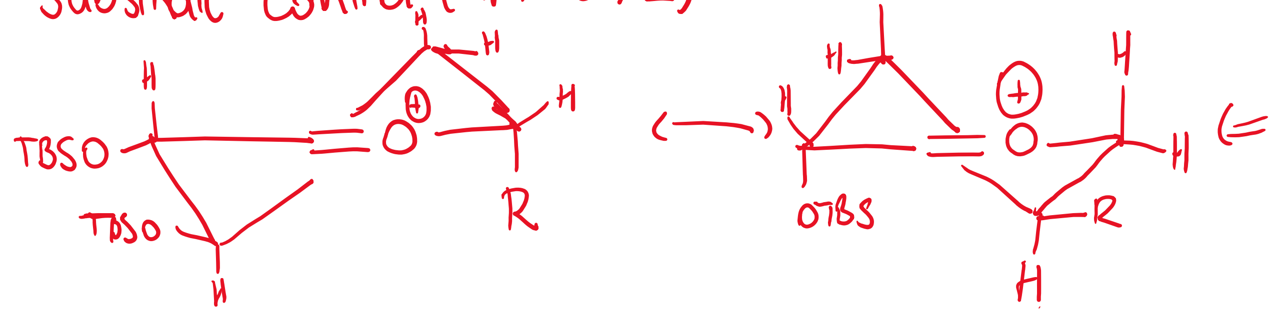


⚠ Mechanism is controversial, can also be radical and not anionic ⚠

I) $SmCl_4$ mediated synthesis of alkyl chloride



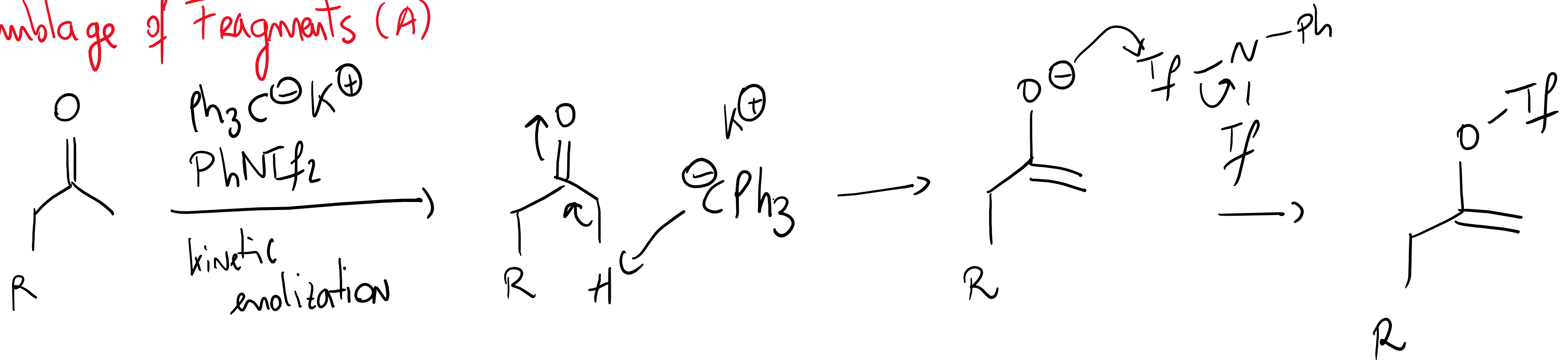
Substrate Control (dr: 10>1)



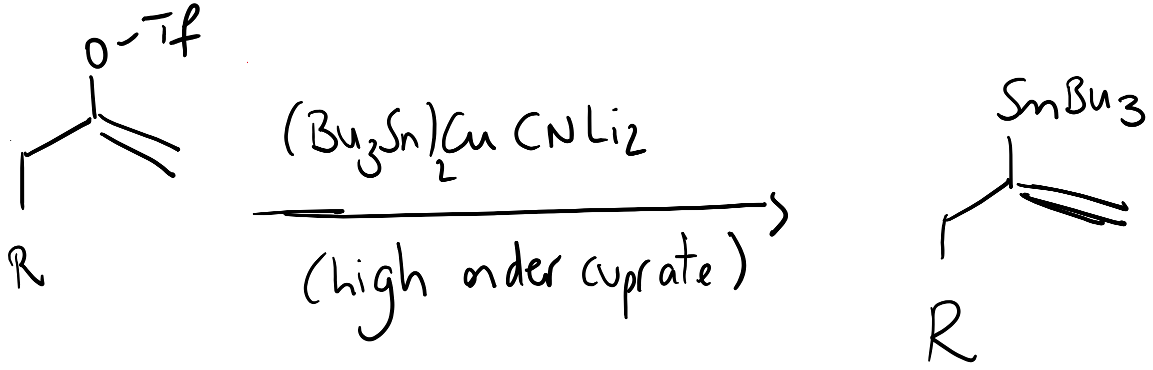
⇐ more instable (1,3-allylic strain) → reacts faster

Assemblage of Fragments (A)

c)



D)



(Tetrahedron Lett. 1988, 29, 6795-6798)

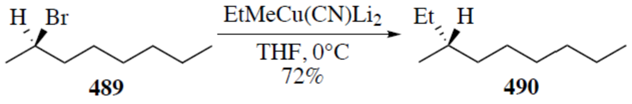
Table 8.20. Reaction of Higher Order Cyanocuprates with Alkyl Halides

R–X + 2 *n*-$Bu_2Cu(CN)Li_2$ ⟶ R–*n*-Bu

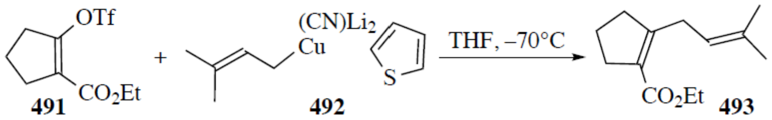
Halide	Temp. (°C)	Time (h)	% R–*n*-Bu
Iodocyclopentane	–78	2	82
Bromocyclopentane	0	6	86
Iodocyclohexane	–78	1	100
Bromocyclohexane	25	6	41
2-Iodopentane	–50	2	99
2-Bromopentane	0→25	2	94
2-Chloropentane	25	11	28
2-Tosyloctane (10 equivalents cuprate)	25	8	>80

[Reprinted with permission from Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A.; Parker, D. *J. Org. Chem.* *1984*, *49*, 3928. Copyright © *1984* American Chemical Society.]

Higher order organocuprates react with chiral halides to give chiral coupling products. When (*R*)-2-bromooctane (**489**) reacted with the mixed-cuprate [$EtMeCu(CN)Li_2$], a 72% yield of (*R*)-3-methylnonane (**490**) was obtained,[479b,c] which is the result expected of a nucleophilic S_N2 like displacement of the bromide. As mentioned in Section 8.7.A, the reaction probably proceeds via single electron-transfer process, but the stereochemistry of this reaction mimics nucleophilic substitution. The extent of inversion is very dependent on the nature of the reacted organocuprate, however. 2-Iododecane derivatives showed virtually no inversion of configuration when with Gilman-type reagent or with higher order cuprates.[479a] Bromides, on the other hand, gave virtually complete inversion with both reagents.[479a] The smallest amount of inversion was obtained with symmetrical cuprates, and the largest amount with mixed cuprates.



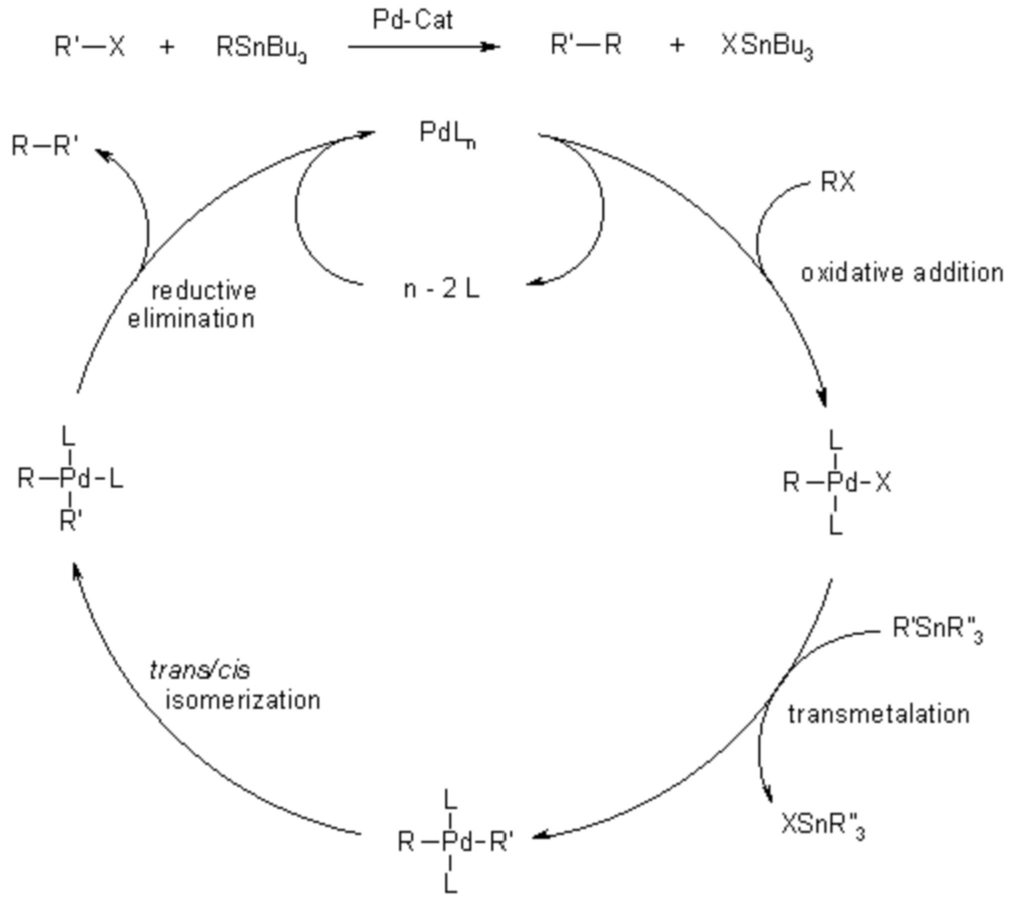
This displacement reaction is not limited to allyl derivatives or to substrates a bearing halide leaving group. Both vinyl and aryl derivatives react with higher order cuprates, similar to the Gilman reagents. Lipshutz and Elworthy found that vinyl triflates are particularly useful in cuprate coupling reactions. The reaction of vinyl triflate **491** reacted with the mixed cuprate **492**, gave **493** in 87% yield.[485] An interesting feature of cuprate **492** is the presence of 2-thienyl as an unreactive ligand (see **428**). Lipshutz et al. found this to be most effective for the selective transfer of the group other than thienyl.[486] This is analogous to the use of alkynyl groups as unreactive substituents in Gilman reagents. The mixed-alkyl cuprates are easily prepared by sequential addition of two different organolithium reagents to cuprous cyanide. In general, for reagents such as $R(Me)Cu(CN)Li_2$ (R > Me), the R group is transferred selectively for both the halide displacement and the conjugate addition.



(From Organic Synthesis, 3rd edition, Micheal B. Smith, Chapter 8)

E) Stille coupling (modified) – Chem. Commun. 2008, 2873-2875

NORMAL STILLE Coupling



https://www.organic-chemistry.org/namedreactions/stille-coupling.shtm

Modified Version (Fürstner et all.)

Scheme 1 Pre-equilibrium as one of the reasons for the co-catalytic effect of copper additives on Stille–Migita cross coupling reactions performed in polar media.

- Baldwin (2005): cat CuI, 2 eq TBAF or CsF (to displace the equilibrium)
- Fürstner (2008): 1.2 eq $[Ph_2PO_2][NBu_4]$, 1.5 eq CuTC in DMF at rt.

Assemblage of Fragments (B)

A Mitsunobu reaction