Master Course
in Organic Chemistry

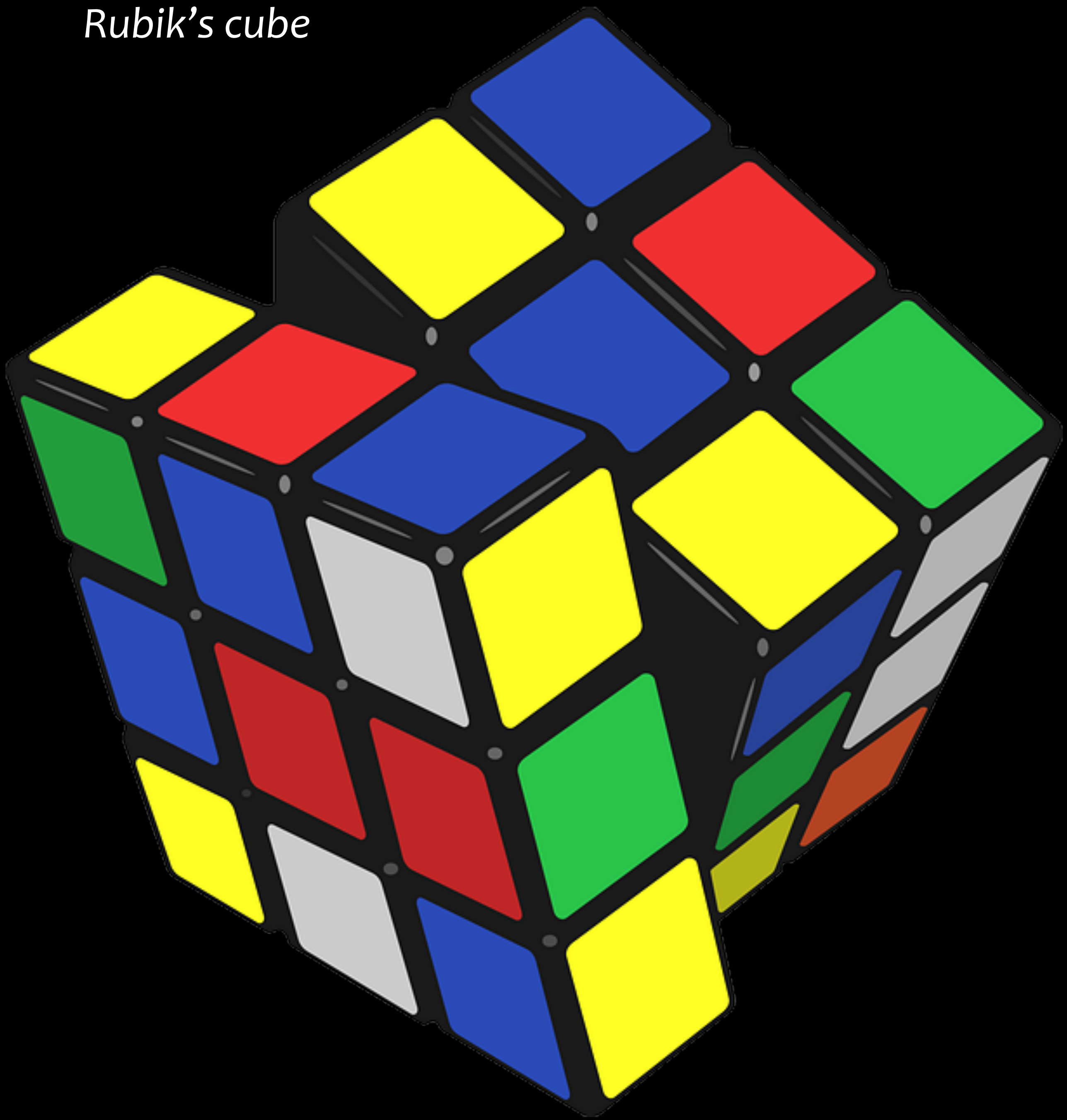
2018-19

methods **and design in organic synthesis**

UNIVERSITAT DE BARCELONA

Pere Romea

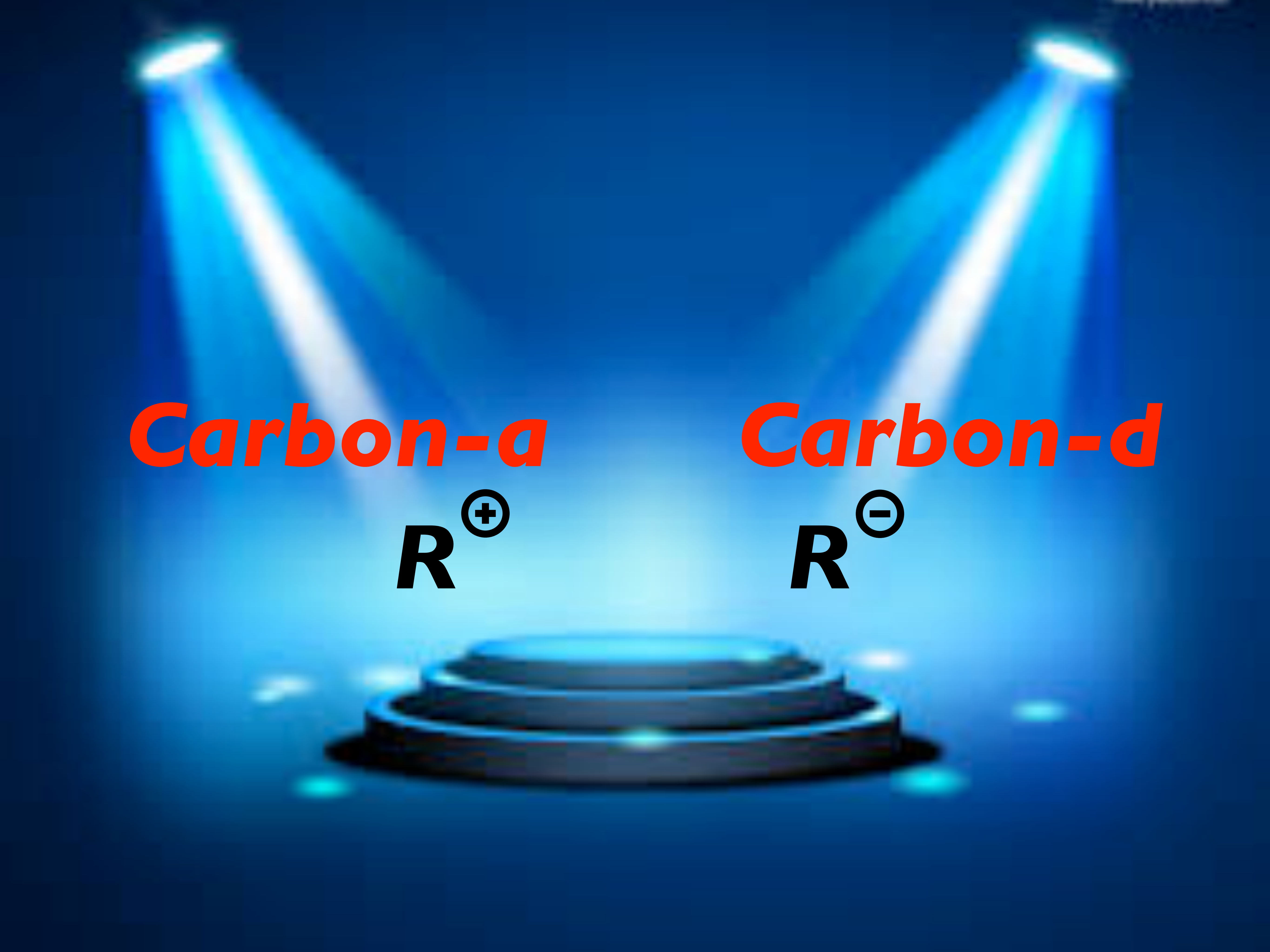
Rubik's cube

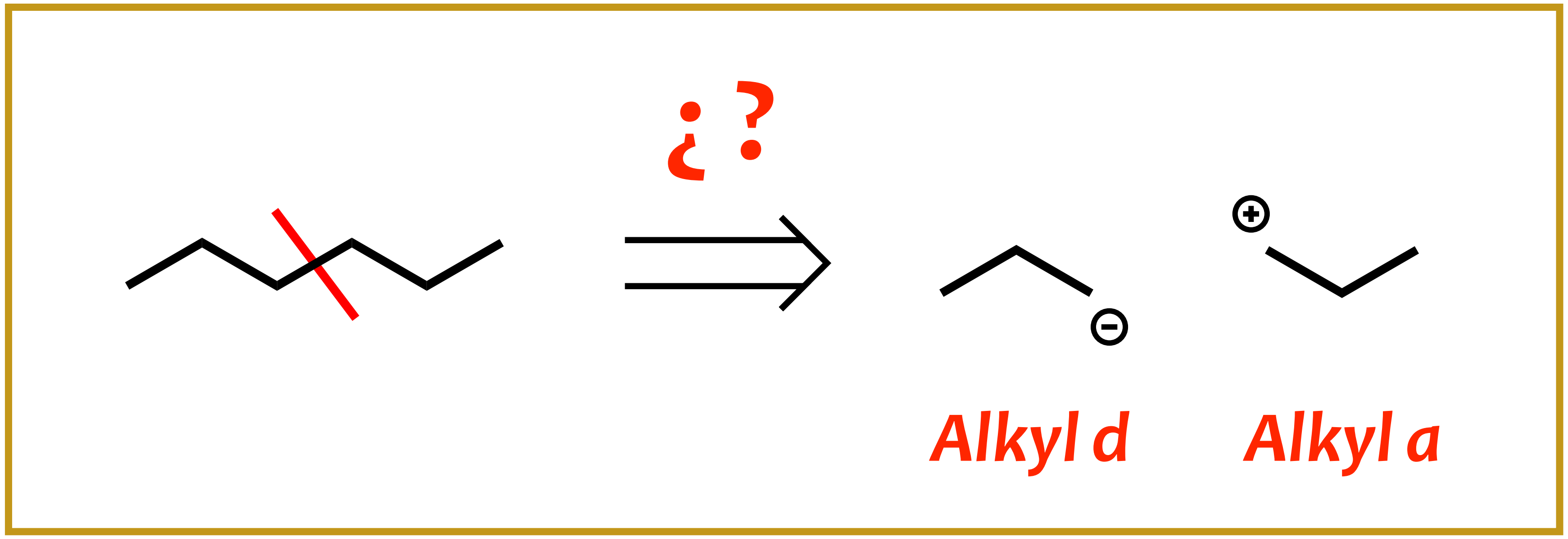


4.2. Single & Double Bonds

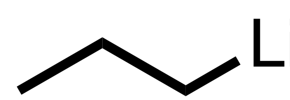
Non functional group

R-*R* disconnection

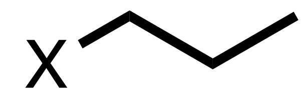

Carbon-a
Carbon-d
$R^{\oplus}$
$R^{\ominus}$



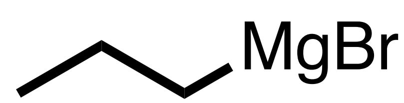
Potential precursors



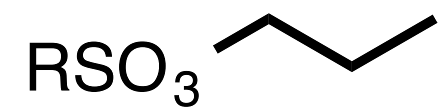
Alkyl lithium



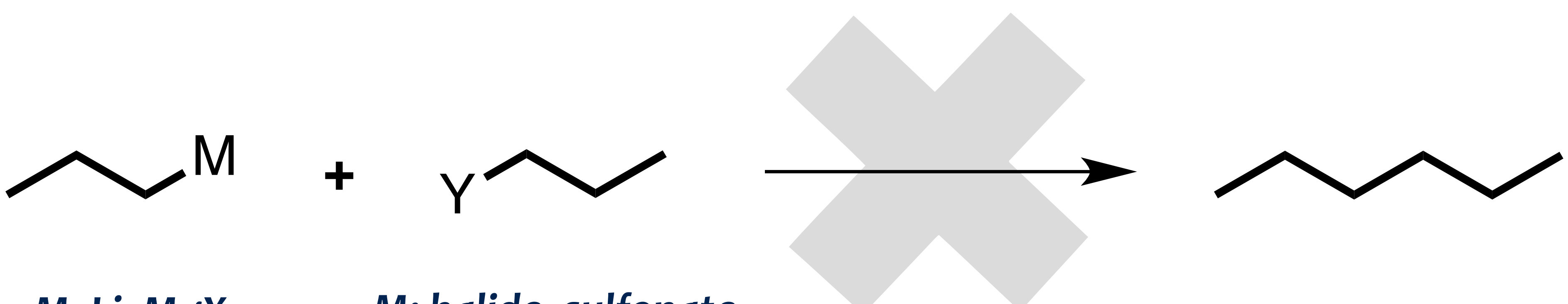
Alkyl halide, X: Cl, Br, I



Alkyl magnesium halide



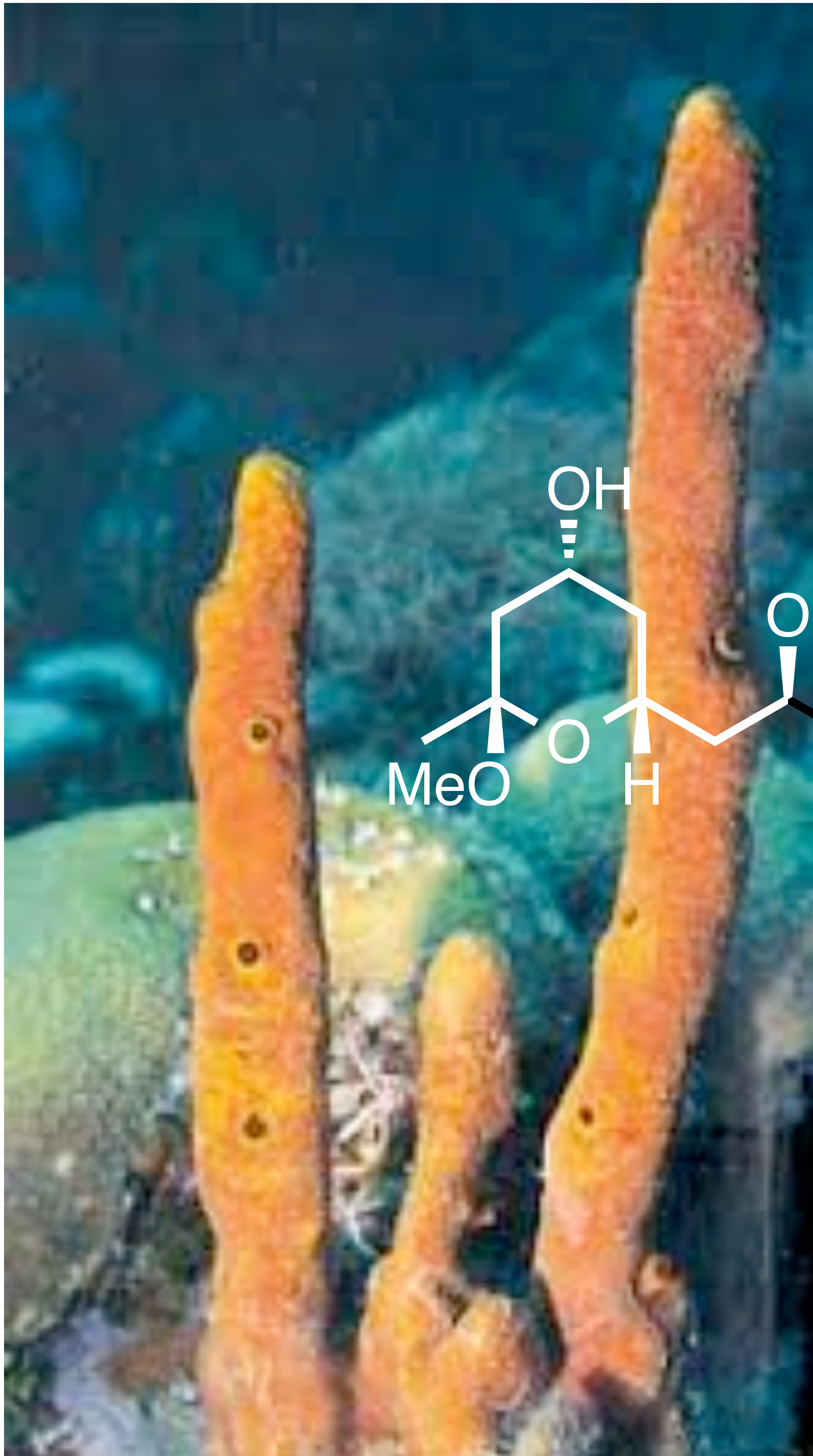
Alkyl sulfonates

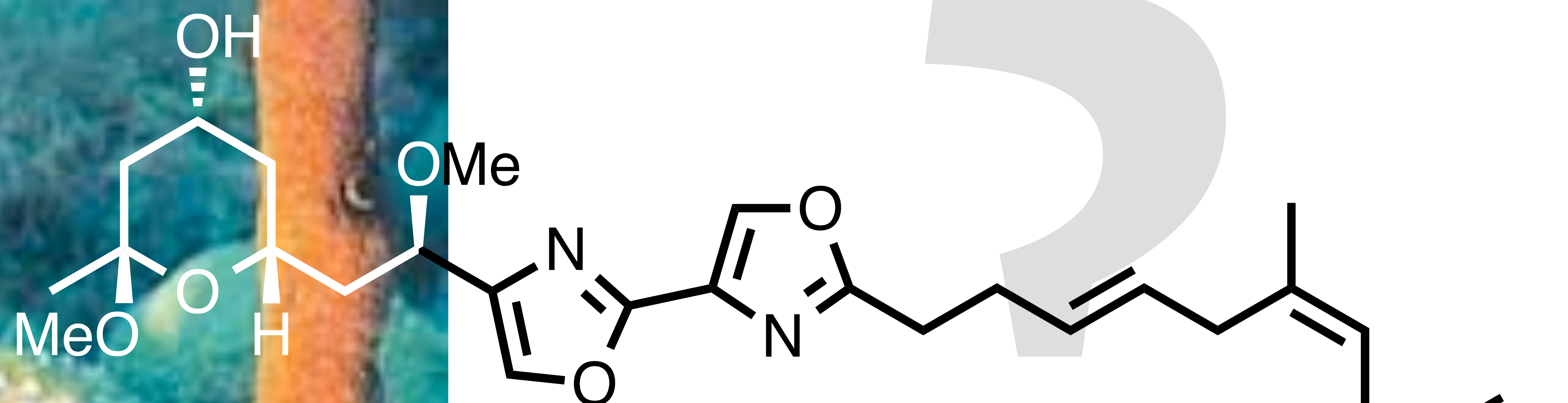


M: Li, MgX

M: halide, sulfonate

The reaction is plagued by many side reactions due to high pK_a of Alkyl-d (pK_a 45–50)



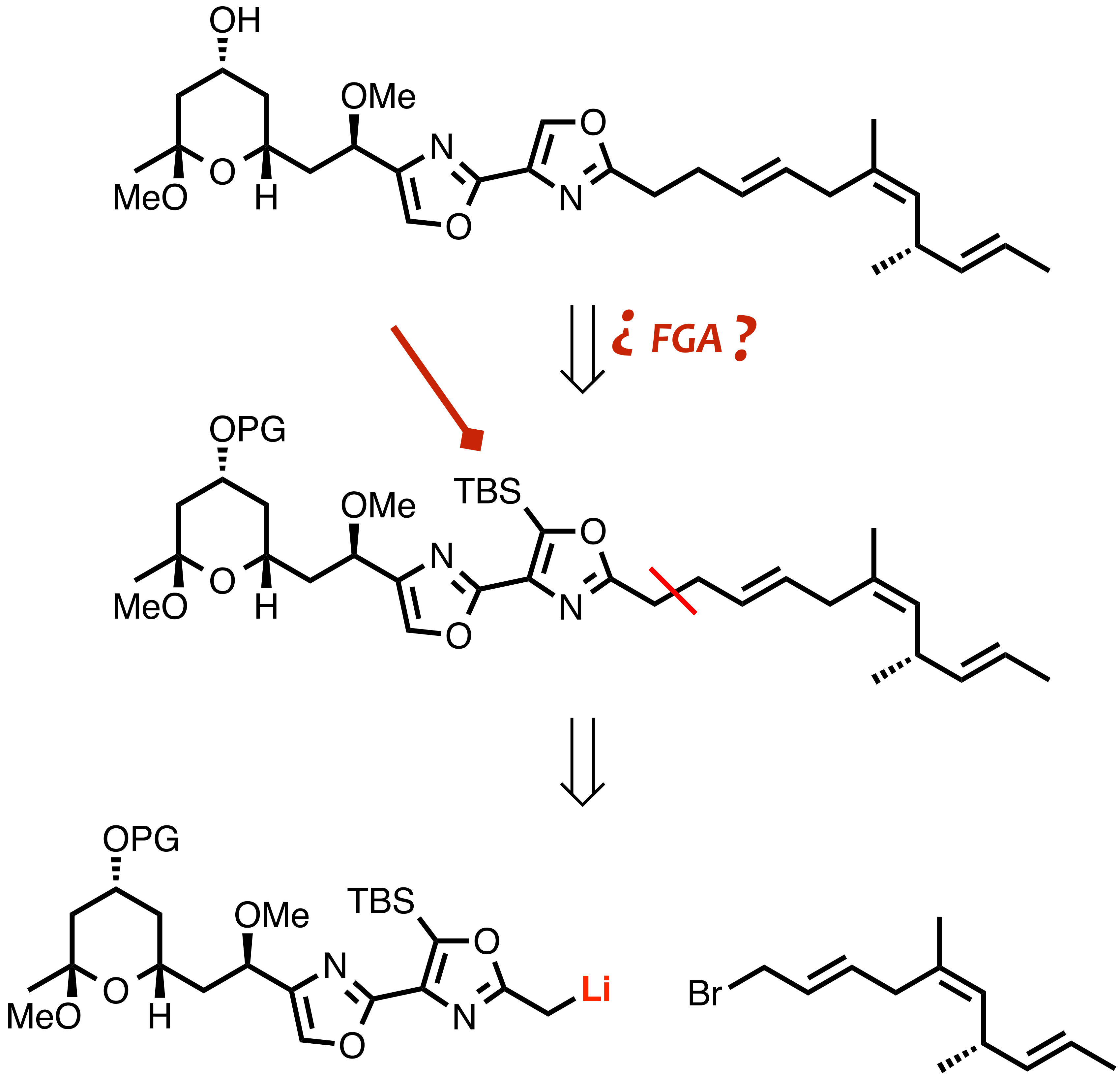


Polyfibrospongia

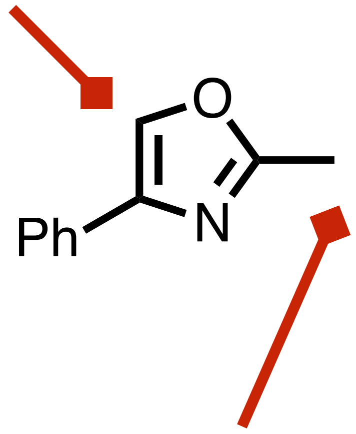
(–) Hennoxazole A

antiviral

Smith, T. E. *JOC* **2008**, *73*, 142

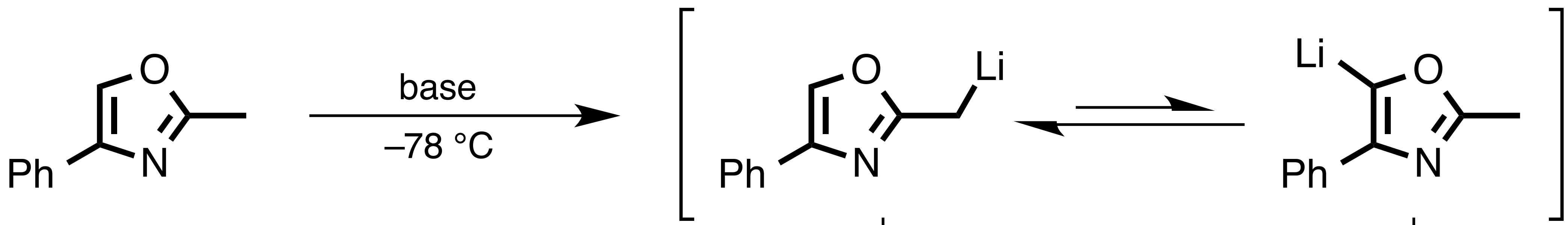

¿ FGA ?

Oxazole alkylation studies



two potential
reacting sites

Oxazole alkylation studies



1 2

ratio 1:2		
BuLi	LDA	LiNEt2
(14:86)	(37:63)	(99:1)

This reversal of **regioselectivity** is thought to arise from the ability of Et2NH to mediate the low-temperature equilibration of a kinetic mixture of otherwise noninterconverting lithiated intermediates

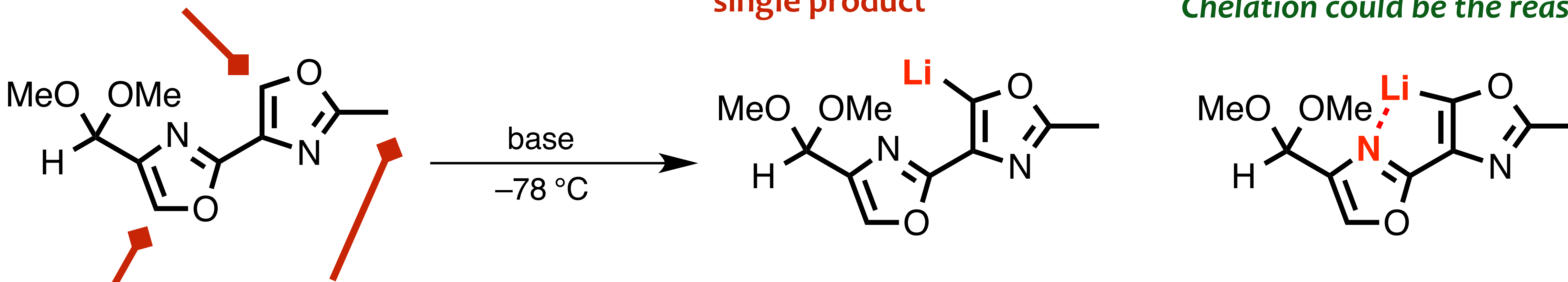
However, such a situation was dramatically modified in a model close to the TGT structure

TAKE-HOME MESSAGE: the model should be as similar as possible to the real system

Oxazole alkylation studies

single product

Chelation could be the reason

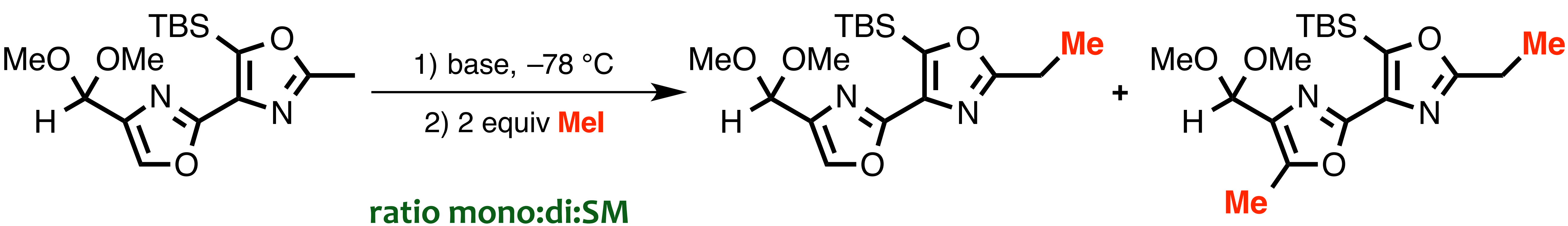


three potential reacting sites

base: BuLi, LDA, $LiNEt_2$

These results suggest that deprotonation at the heterocycle is **thermodynamically as well as kinetically favored**

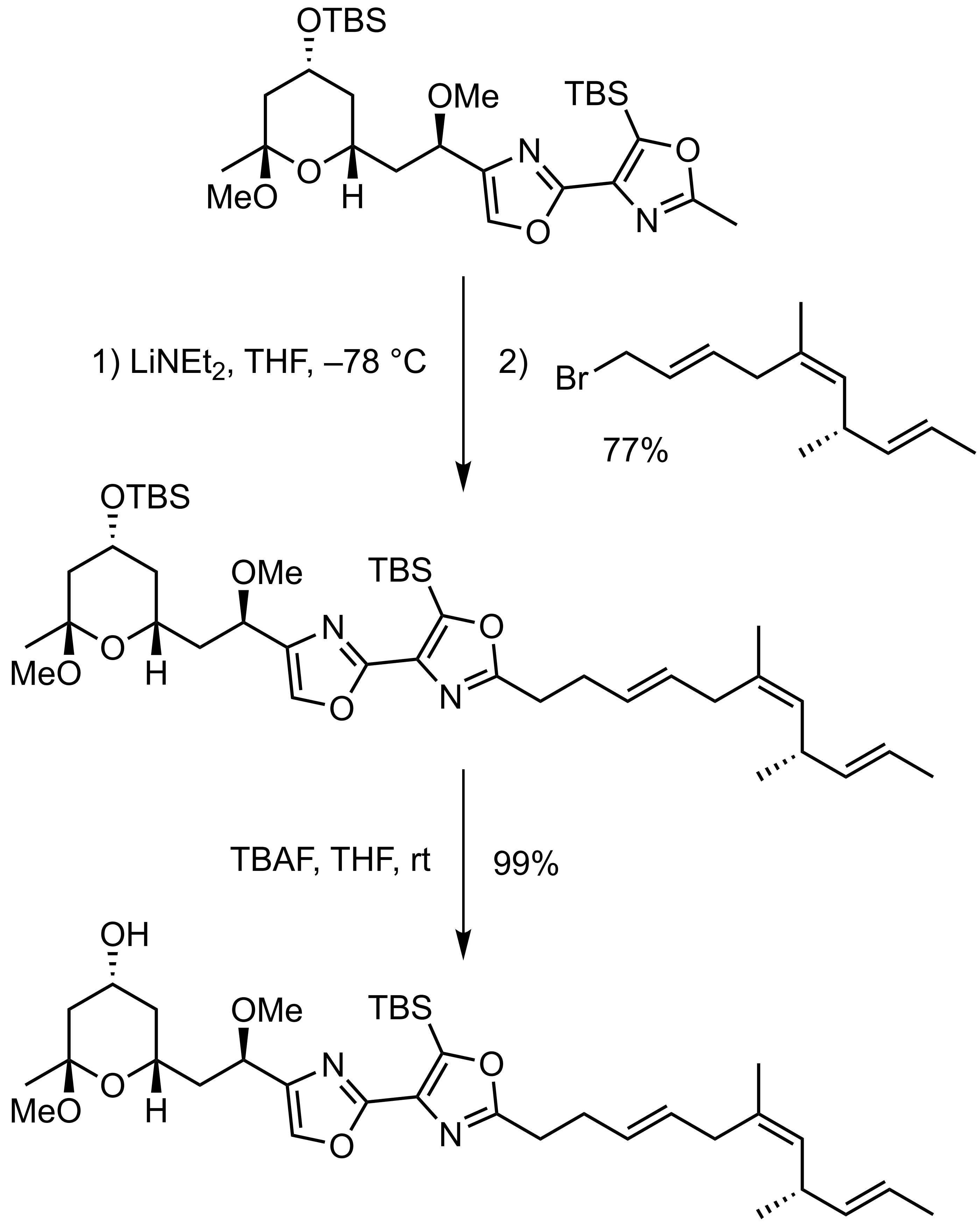
SOLUTION: BLOCKING THAT POSITION?



ratio mono:di:SM

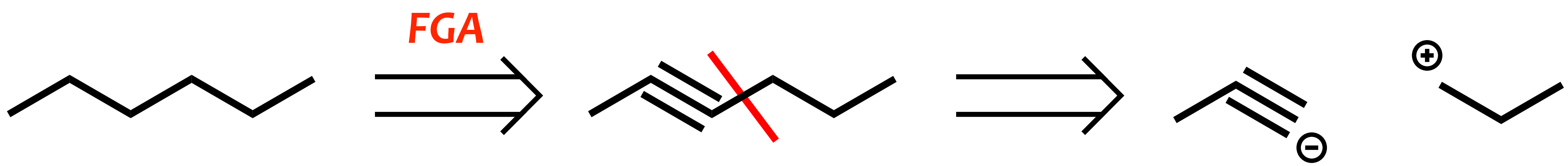
BuLi	LDA	$LiNEt_2$
(60:12:28)	(43:8:48)	(88:5:7)

Alkylation of the real system

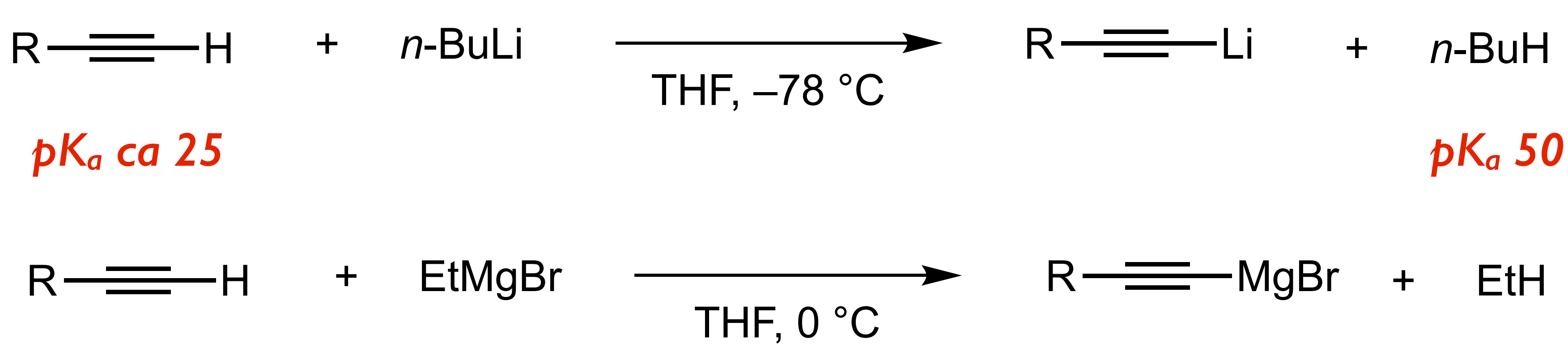


(–) Hennoxazole A

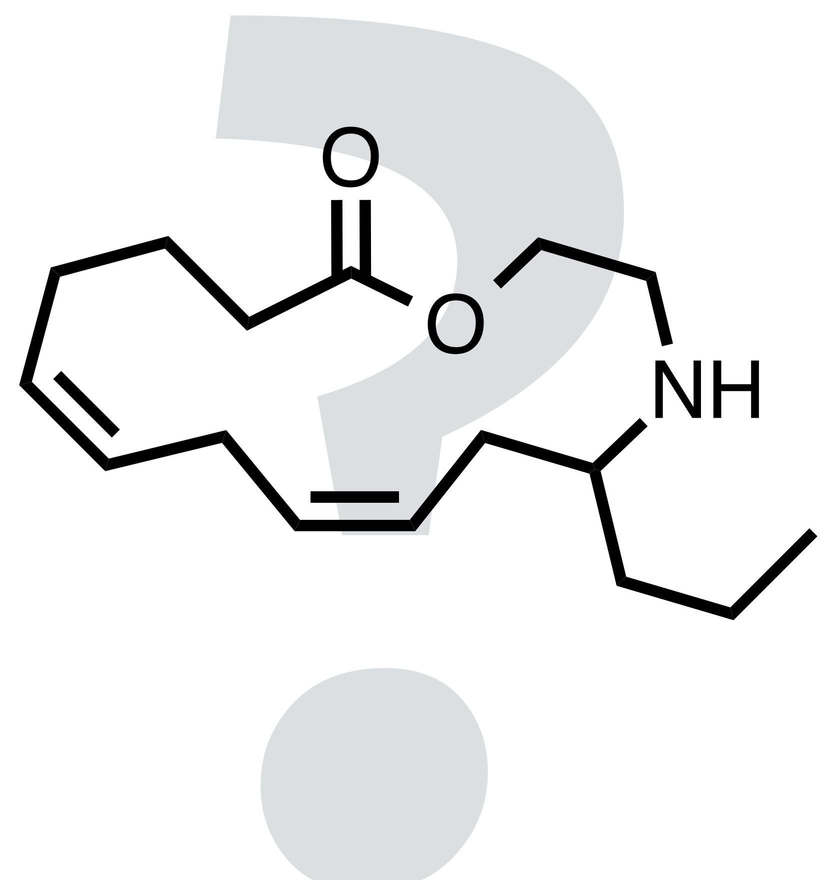
Alternative (I): Terminal Alkynes



Alkynyl d ***Alkyl a***



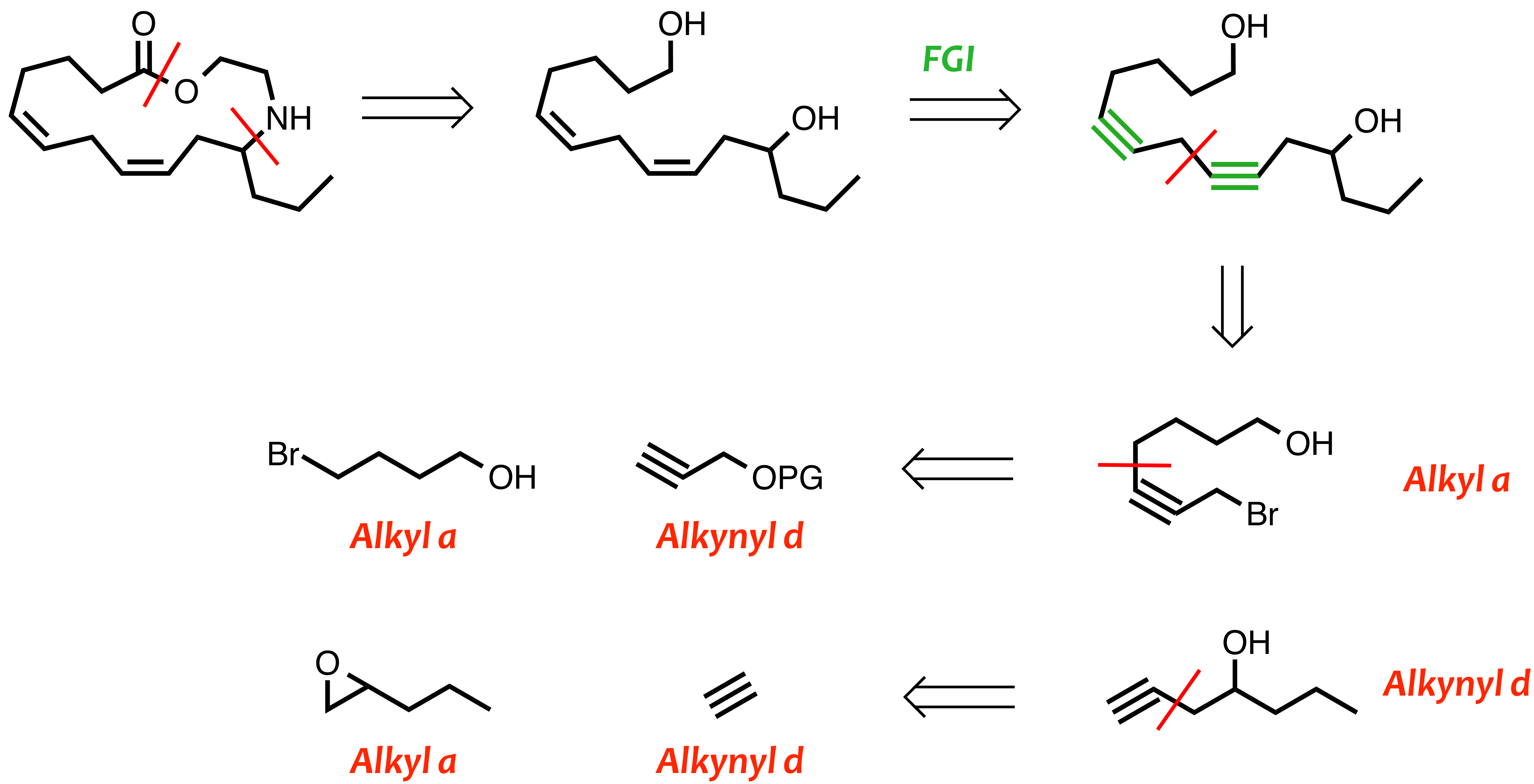
Larva of Mexican bean beetle



Epilachnadiene

defense agains ants

Rao, B. V. *TL* **1995**, *36*, 147



Rao, B. V. *TL* **1995**, *36*, 147

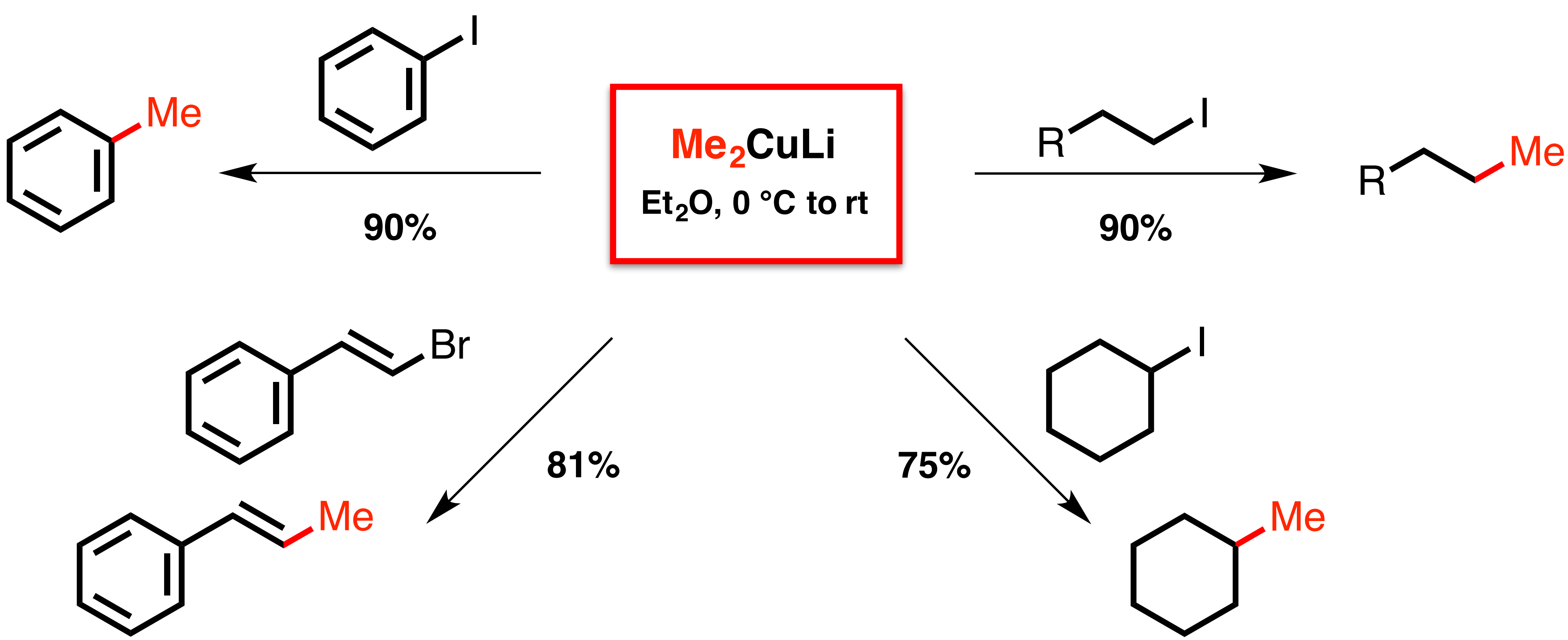
Alternative (II): Organocuprates

ORGANOCOPPER REAGENTS, *easily prepared by transmetallation, are very selective*

$RLi + CuX \longrightarrow RCu + LiX$ — *Monoorganocopper*

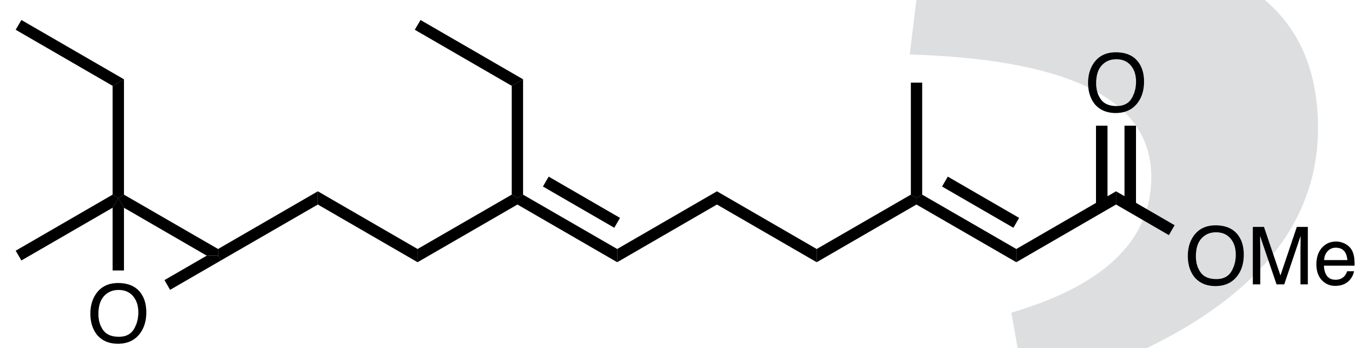
$2\,RLi + CuX \longrightarrow R_2CuLi + LiX$ — *Homocuprates or Gilman's reagents*

$RLi + CuCN \longrightarrow RCu(CN)Li$ — *Heterocuprates*



Cecropia moth

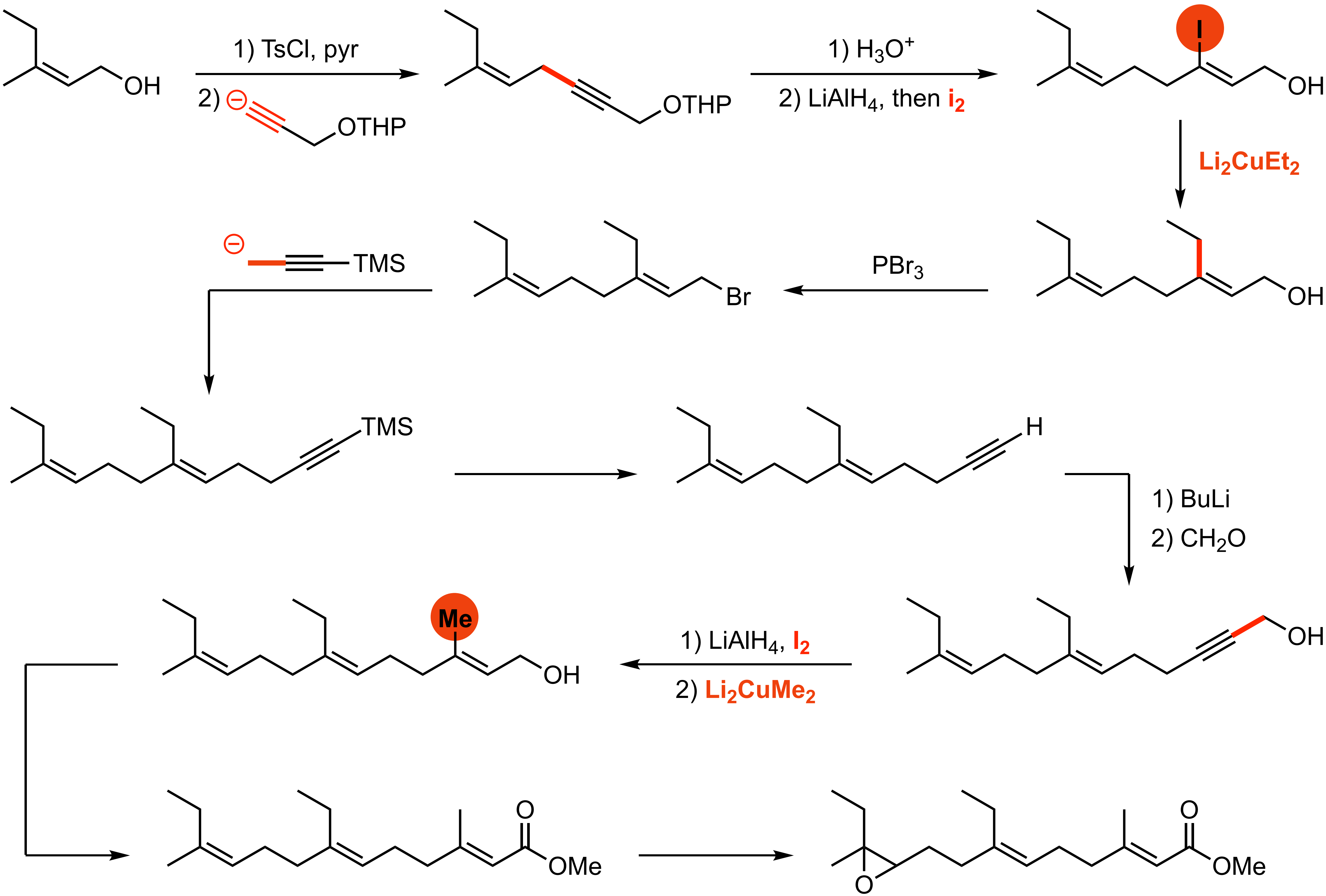
A classical synthesis

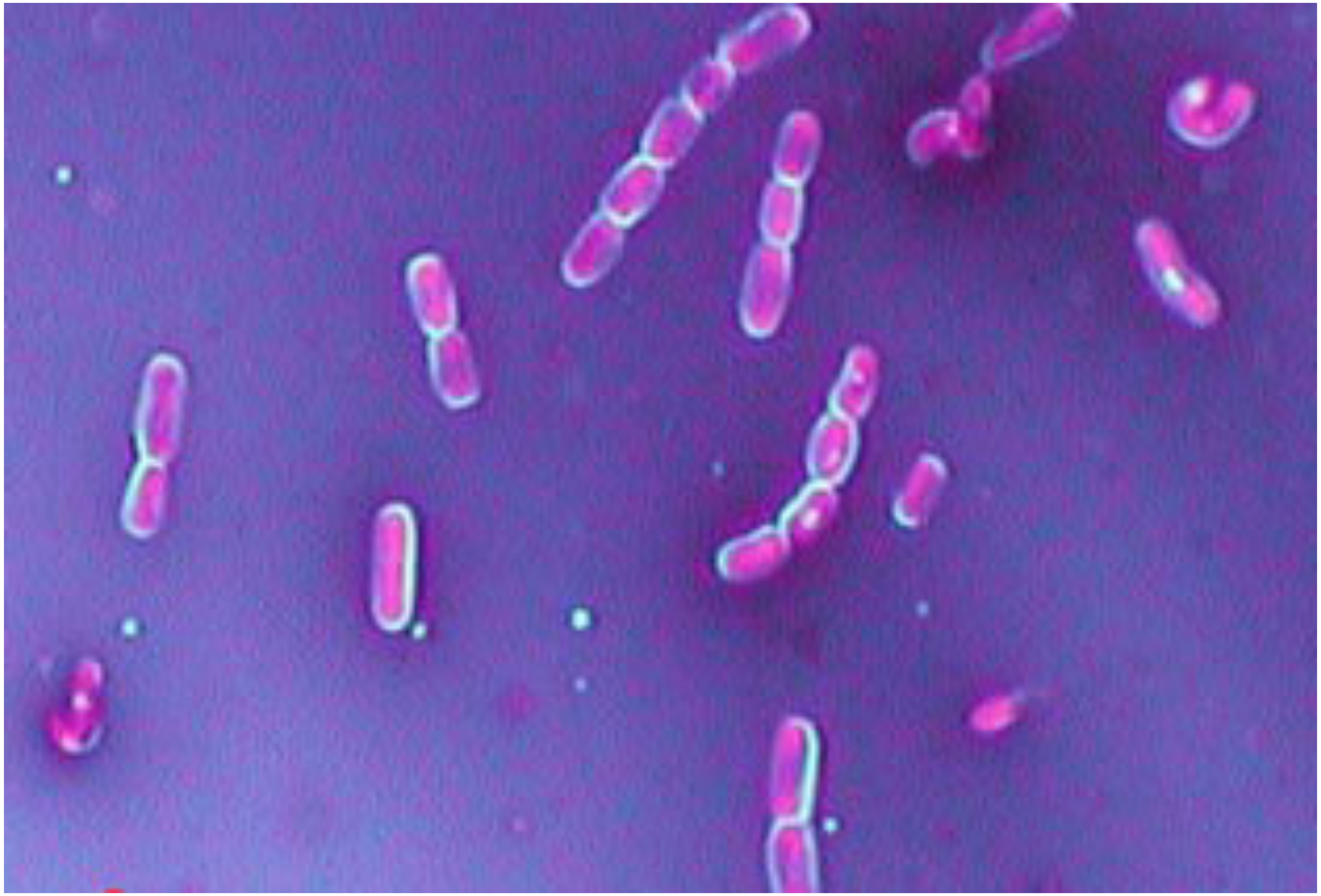


(±) Cecropia Juvenile Hormone

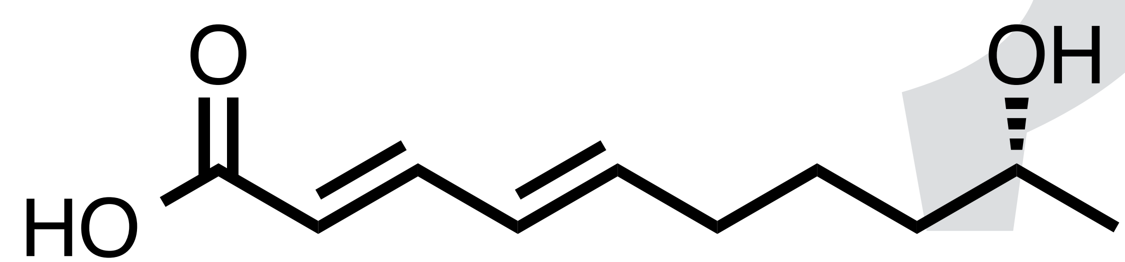
Hormone involved in the development of larvae

Corey, E. J. *JACS* **1968**, *90*, 5618


OH
1) TsCl, pyr
2) OTHP
OTHP
1) H_3O^+
2) $LiAlH_4$, then i_2
I
OH
Li_2CuEt_2
OH
PBr_3
Br
TMS
TMS
H
1) BuLi
2) CH_2O
OH
1) $LiAlH_4$, I_2
2) Li_2CuMe_2
Me
OH
O
OMe
O
O
OMe

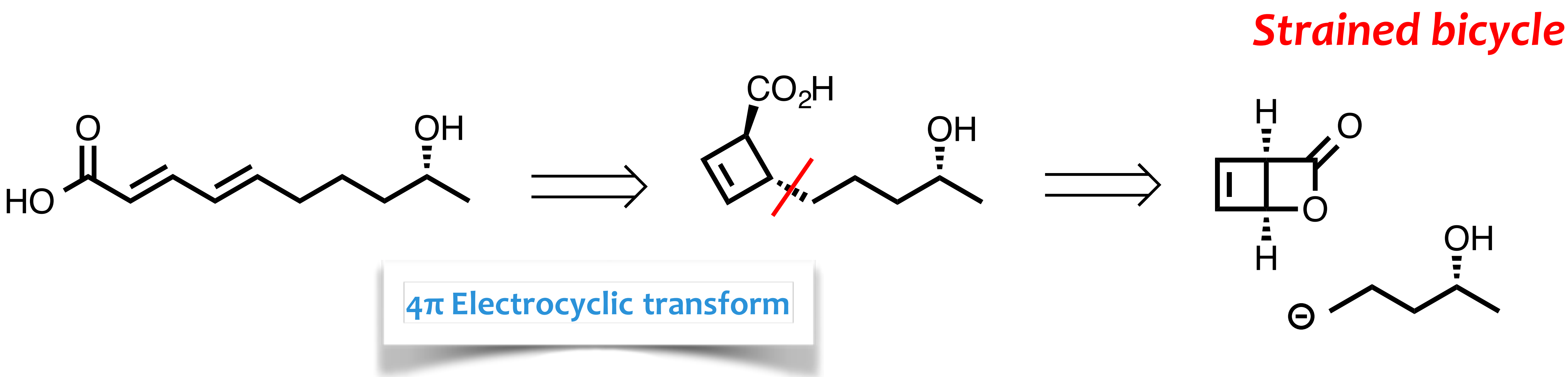


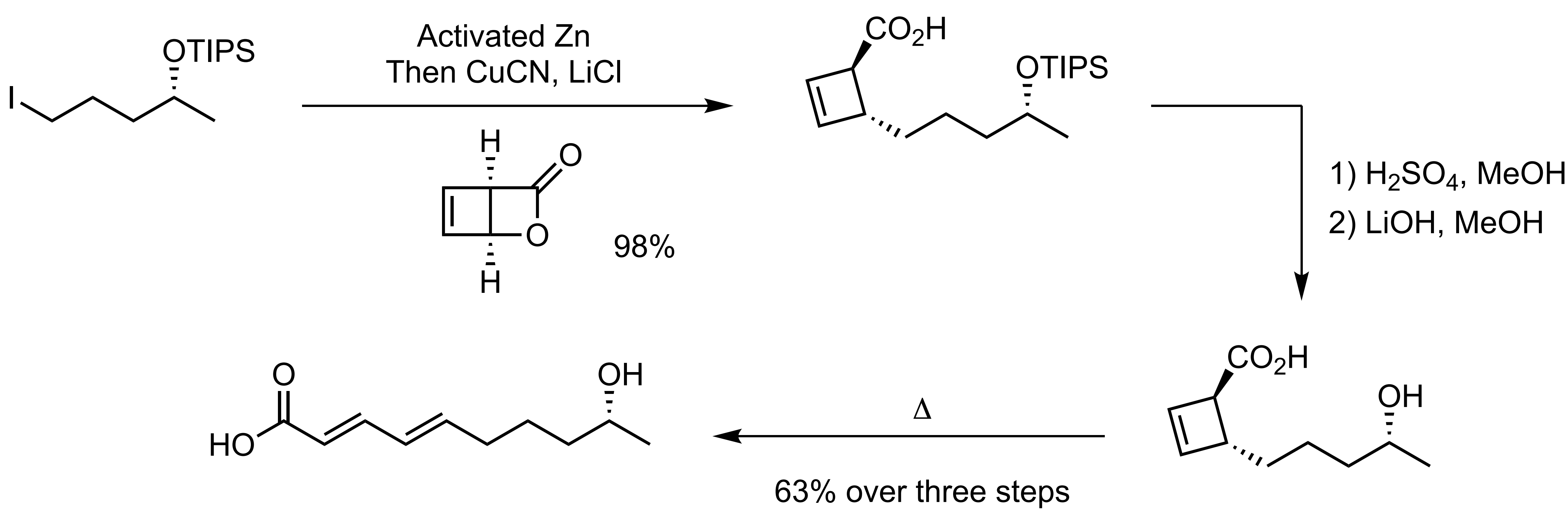
Bacillus species



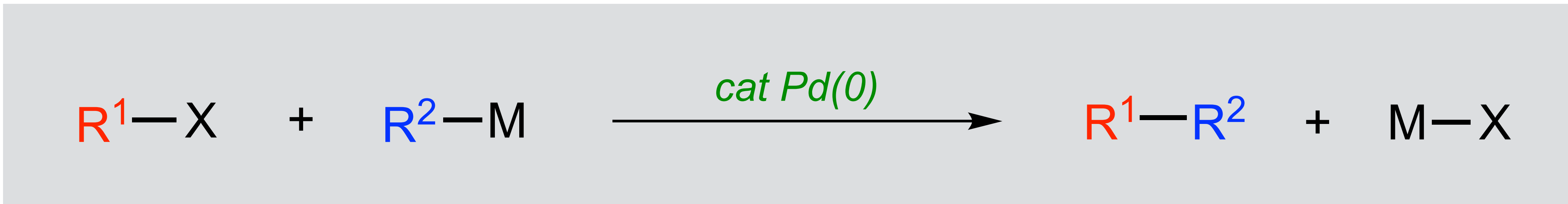
Iedomycin D

Maulide, N. *OL* **2015**, *17*, 4486

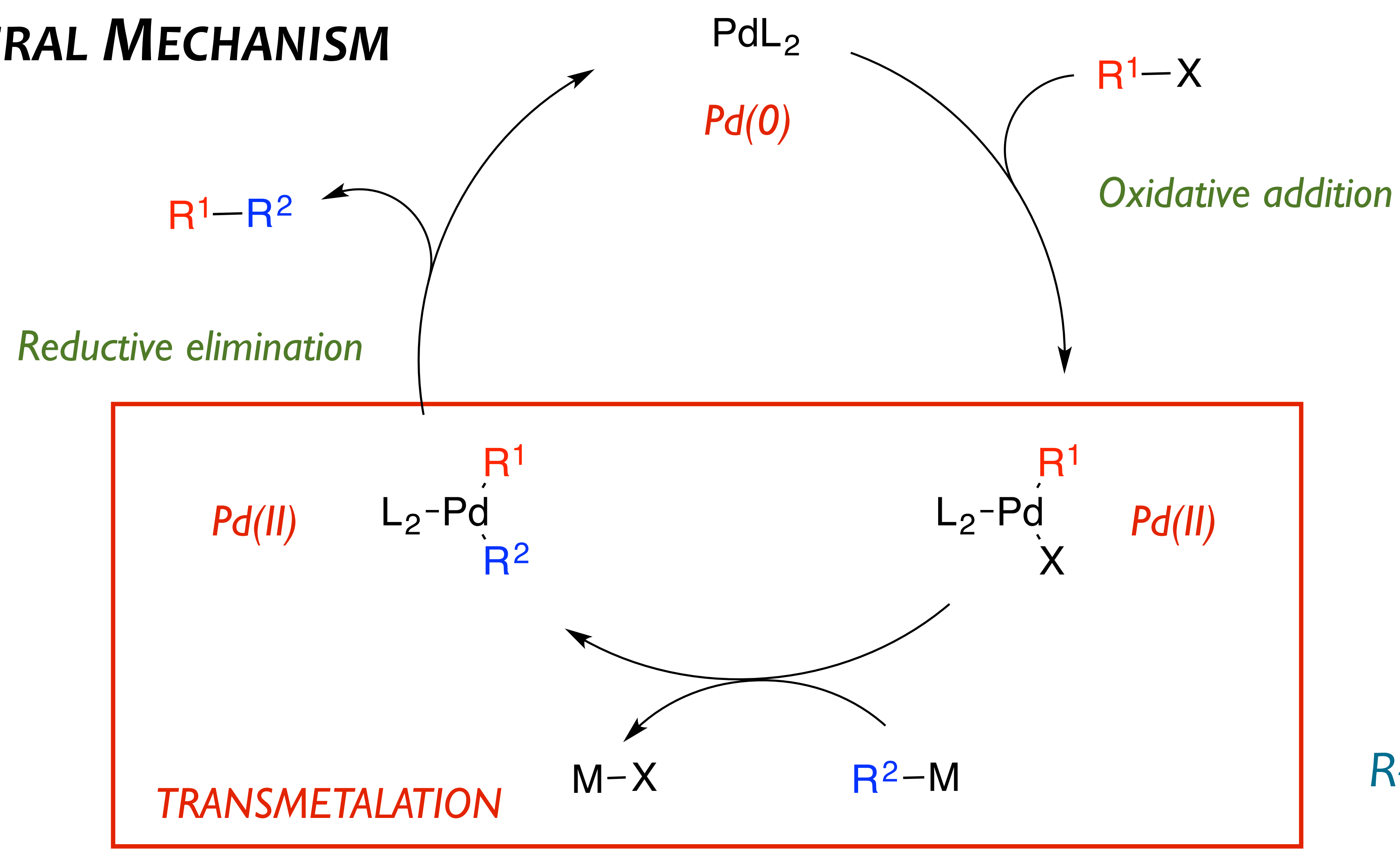

Strained bicycle
O
HO
OH
CO2H
OH
H
O
O
H
OH
4π Electrocyclic transform


OTIPS
I
Activated Zn
Then CuCN, LiCl
H
O
O
H
98%
CO2H
OTIPS
1) H2SO4, MeOH
2) LiOH, MeOH
CO2H
OH
O
OH
HO
Δ
63% over three steps

Alternative (III): Pd-Mediated Cross-Coupling Reactions



GENERAL MECHANISM



R^1: better no ß-H

X: I, Br, (Cl), OTf

R^2: alkyl, alkenyl, alkynyl, aryl

Fürstner, A. *ACIE* **2005**, 44, 674

TRANSMETALATION

Transfer of an organic group from one metal center to another.

*The process involves **no formal change in oxidation state** for either metal.*

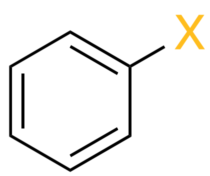
For palladium-mediated cross-coupling reactions

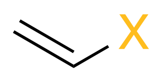
$$R^1{-}X \quad + \quad Pd \longrightarrow R^1{-}Pd{-}X$$

*R^1**Li**, R^1**Mg**Y*	*Kumada*
*R^1**B**$(OR)_2$*	***SUZUKI***
*R^1**Cu**L_n*	***SONOGASHIRA***
*R^1**Zn**Y*	*Negishi*
*R^1**Sn**R_3*	***STILLE***

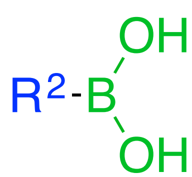
Mignani, G. *CR* **2006**, *106*, 2651

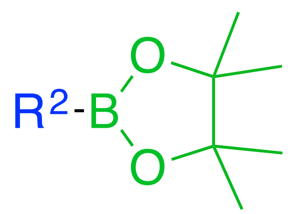
Magano, J.; Dunetz, J. R. *CR* **2011**, *111*, 2177

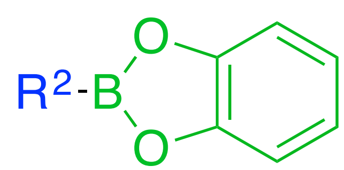
C_{sp2} 



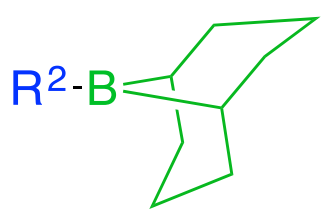
X: I > Br > OTf >> Cl

C_{sp2} 



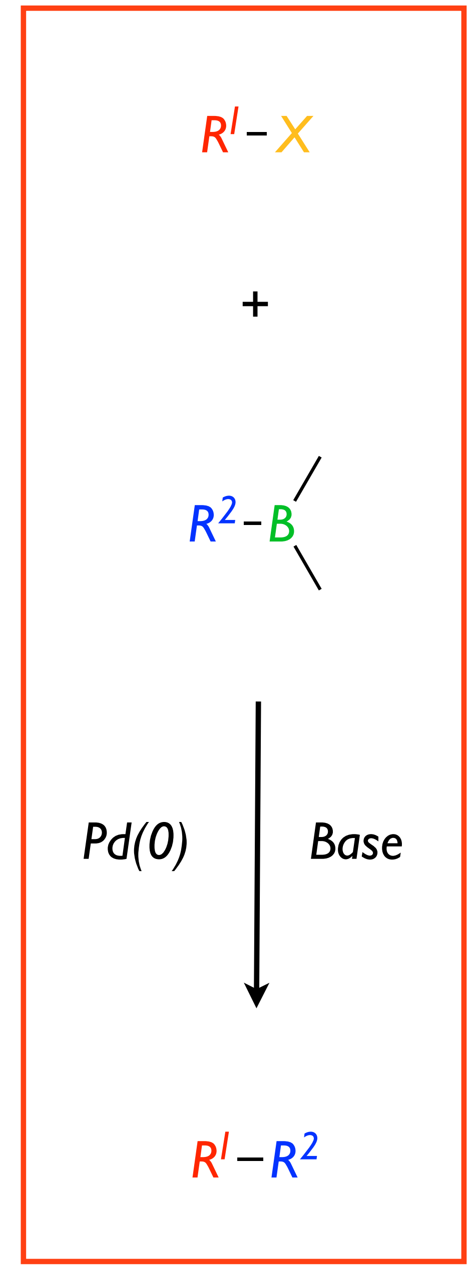


R^2: alkenyl, aryl

C_{sp3} 

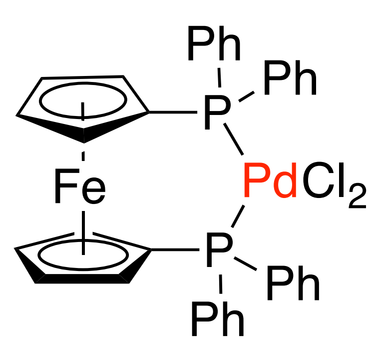
[R^2-9-BBN]

R^2: alkyl



Pd(0): *$Pd(PPh_3)_4$*

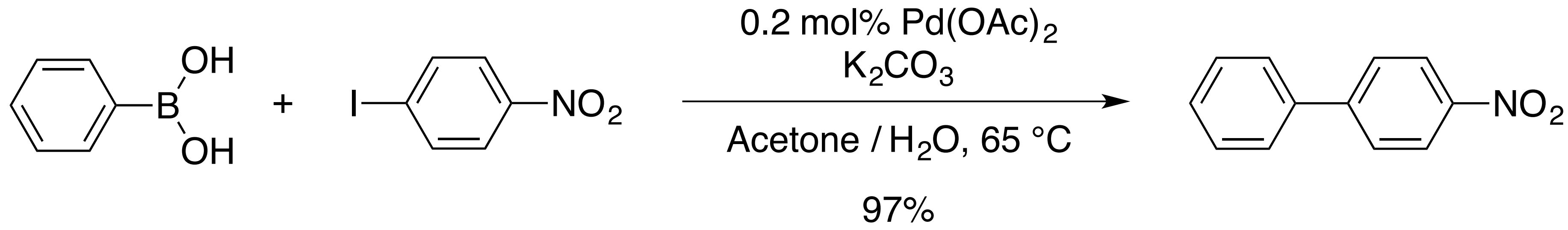
Pd(II): *$Pd(OAc)_2$ / PR_3 or AsR_3*

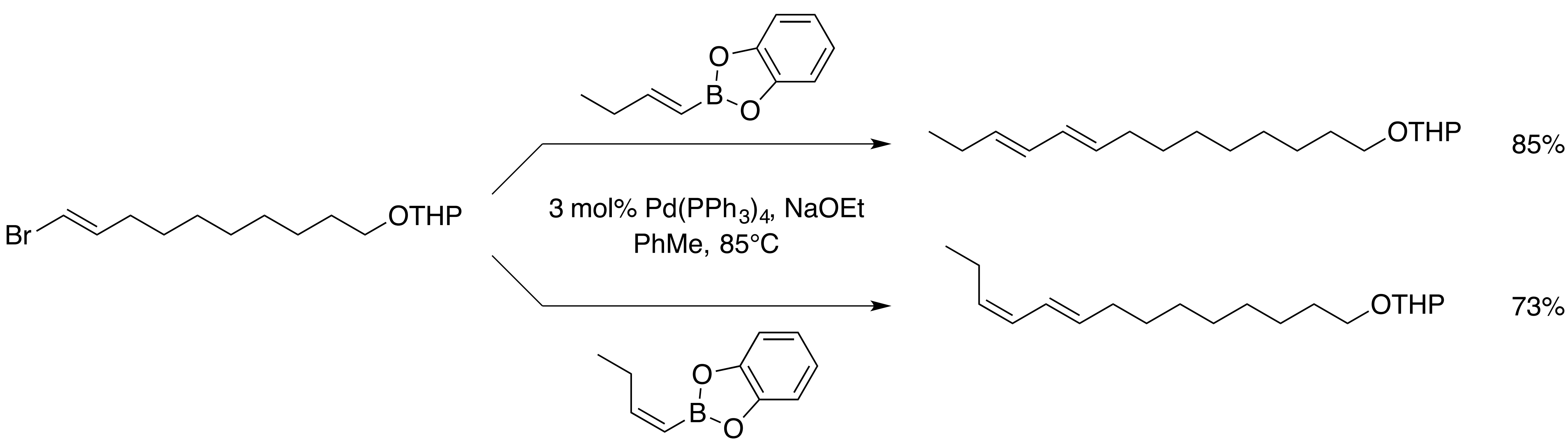


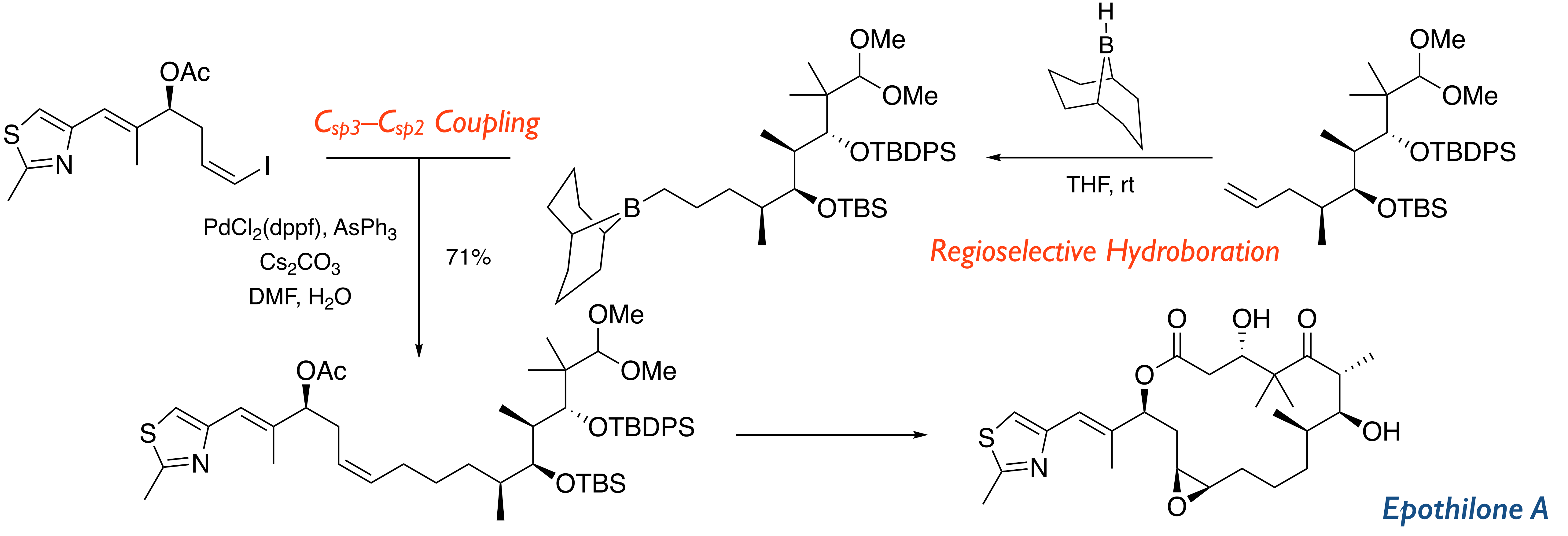
dppf

for C_{sp3}–C_{sp2}

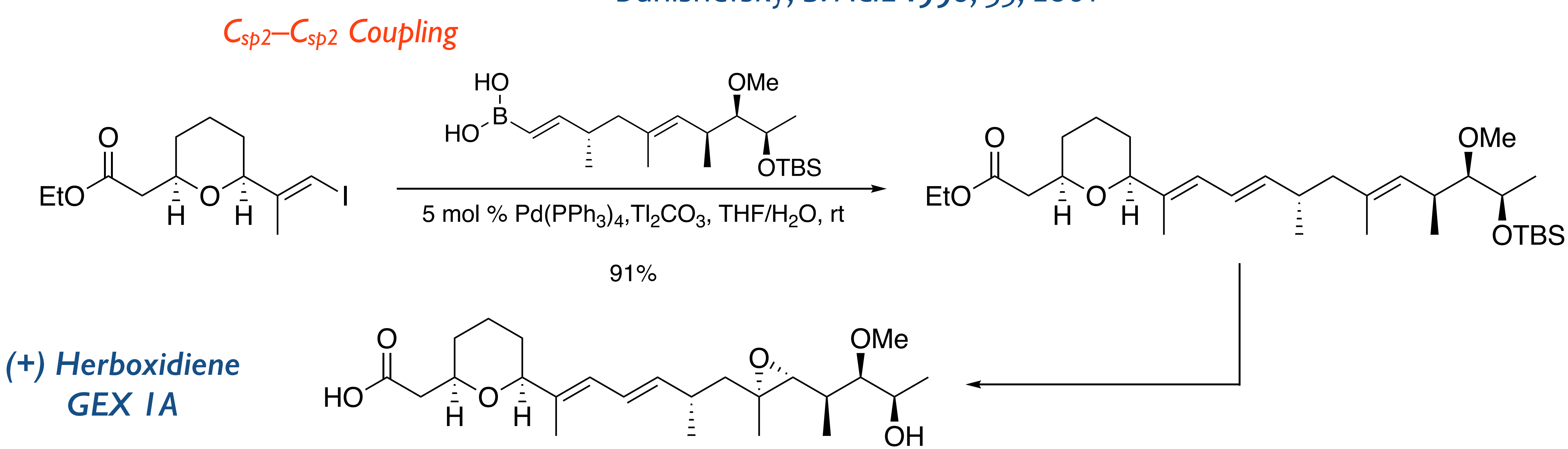
Suzuki Cross-Coupling Reactions





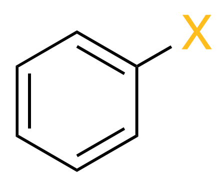


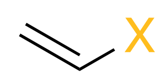
Danishefsky, S. *ACIE* **1996**, *35*, 2801



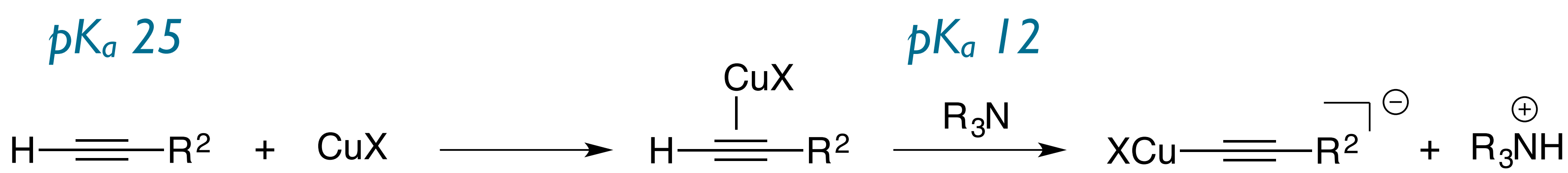
Romea P.; Urpí, F. *OL* **2011**, *13*, 5350; *OBC* **2017**, *15*, 1842

C_{sp2}





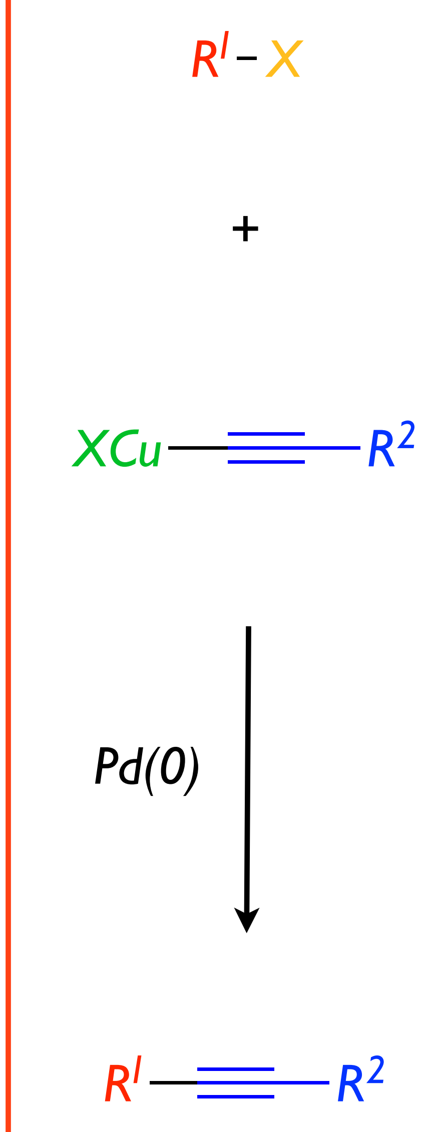
X: I > Br ≈ OTf >> Cl



The acidity of C_{sp}–H is enhanced via π-complexation

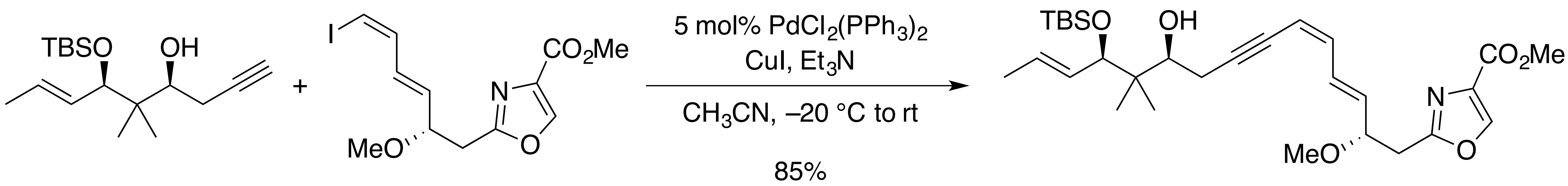
Pd(0): $Pd(PPh_3)_4$

Pd(II): $PdCl_2(PPh_3)_2$

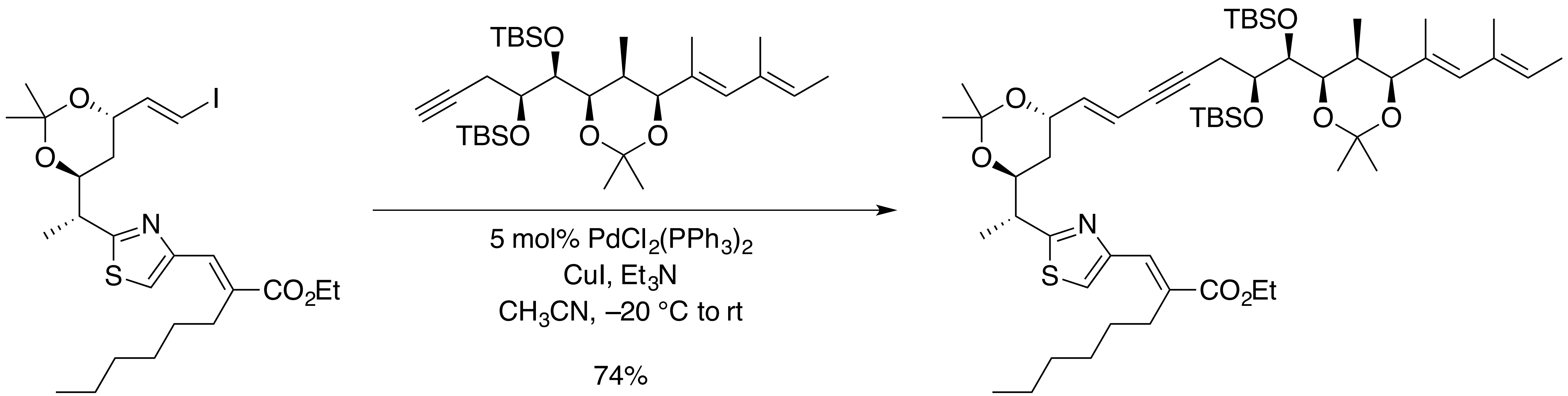


Doucet, H.; Hierso, J.-C. *ACIE* **2007**, 46, 834

Sonogashira Cross-Coupling Reactions



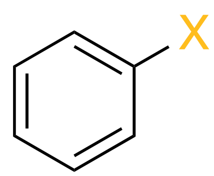
Meyers, A. I. *JOC* **2001**, 66, 6037

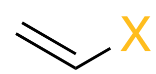


Kirschning, A. *ACIE* **2008**, *47*, 9134

Stille Cross-Coupling Reaction

C_{sp2}





X: I > Br > OTf >> Cl

R^2: *alkynyl > alkenyl > aryl > benzyl ≈ allyl > alkyl*

Pd(0): $Pd(PPh_3)_4$, $Pd_2(dba)_3$ / PR_3 or AsR_3

Pd(II): $Pd(OAc)_2$ / PR_3 or AsR_3

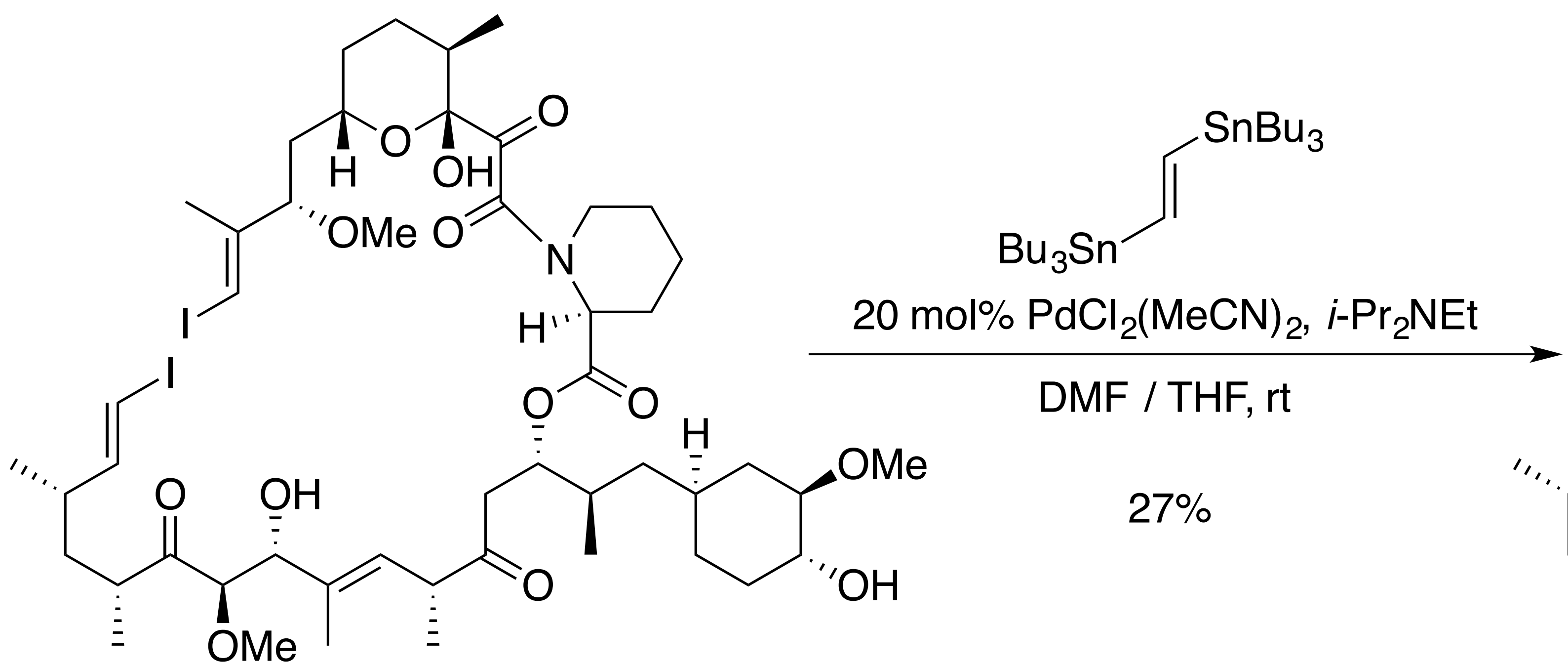
$R^1 - X$

\+

$R^2 - SnR_3$

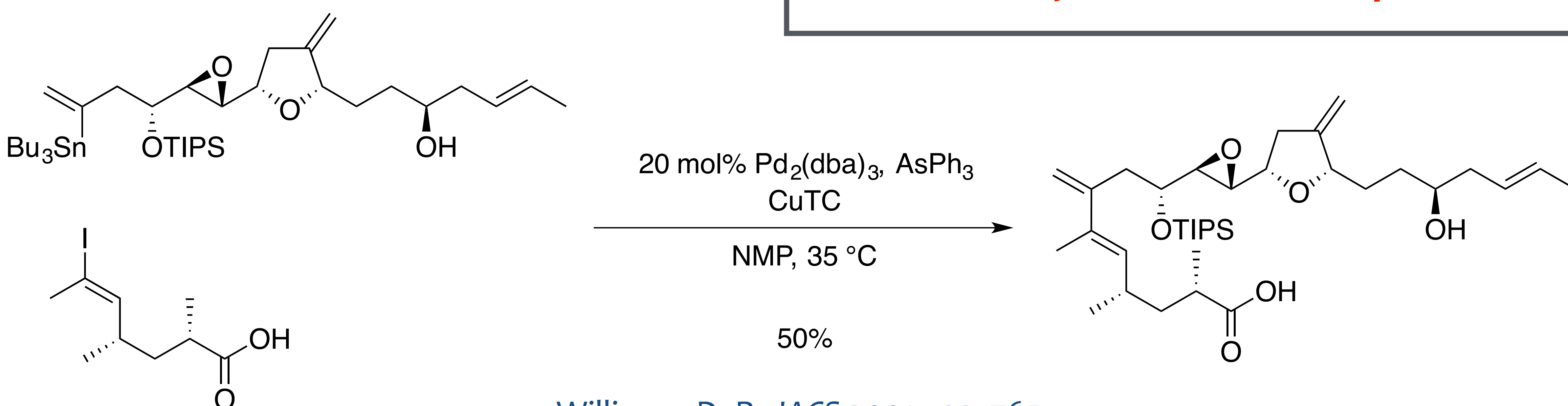
↓ Pd(0)

$R^1 - R^2$



Nicolaou, K. C. *JACS* **1993**, *115*, 4419

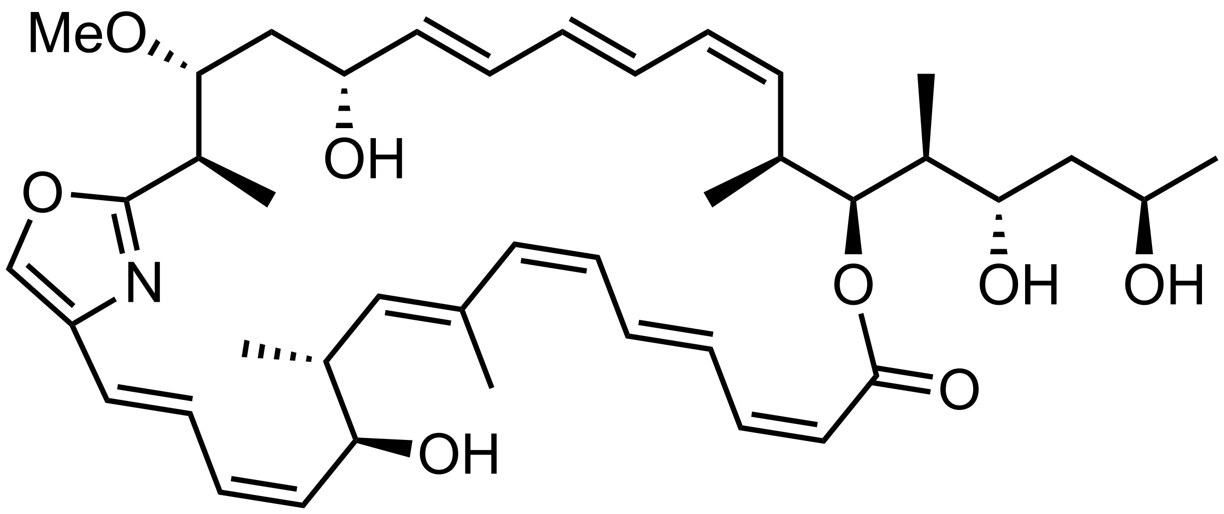
Extraordinary Functional Group Tolerance



Williams, D. R. *JACS* **2001**, *123*, 765

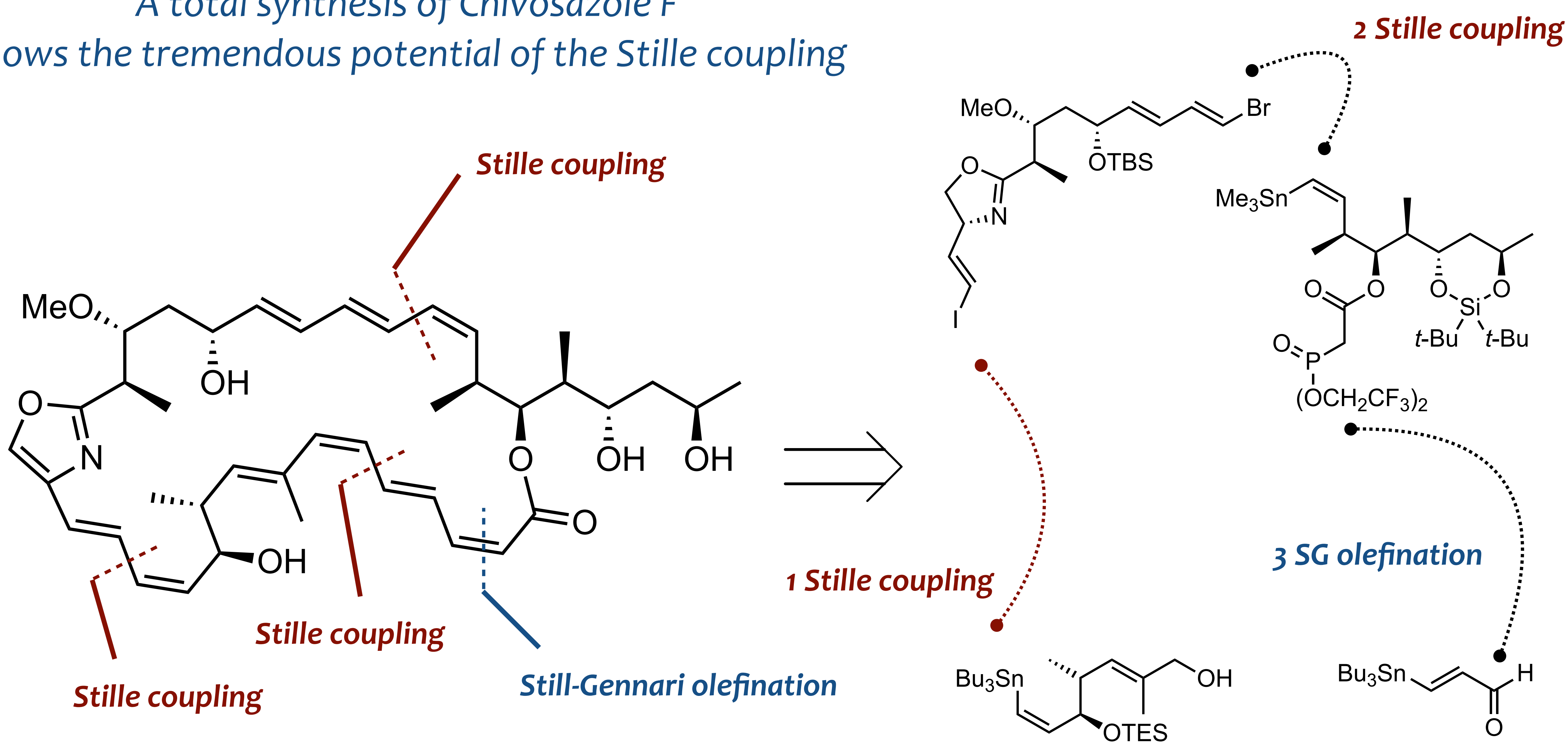
A total synthesis of Chivosazole F
shows the tremendous potential of the Stille coupling

Chivosazole F



Paterson, I. *ACIE* **2017**, 56, 645

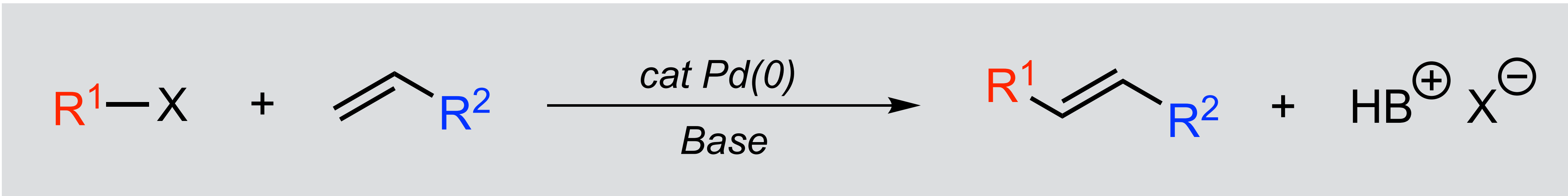
A total synthesis of Chivosazole F
shows the tremendous potential of the Stille coupling

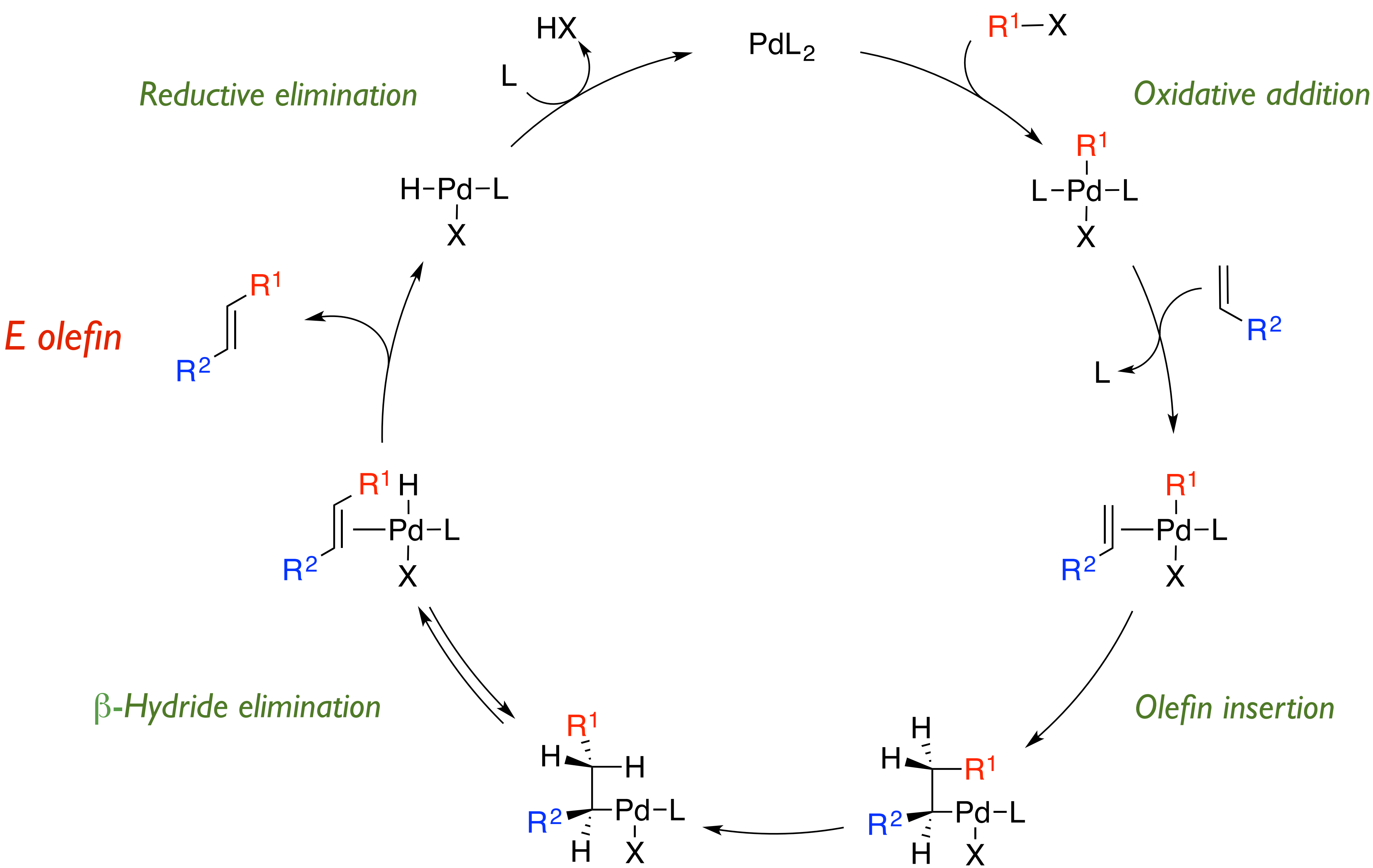


The Stille coupling were carried out using Pd(PPh3)4 and CuTC [copper thiophene-2-carboxylate]
See Fürstner, A. Chem Commun. ***2008***, *2873*

Paterson, I. *ACIE* **2017**, 56, 645

Heck Reaction





R^1: no ß-H

X: I, Br, (Cl), OTf

Pd(o): $Pd(PPh_3)_4$, $Pd(dba)_2$+PR_3

Pd(II): $Pd(OAc)_2$, $PdCl_2(PR_3)_2$, $PdCl_2(CH_3CN)_2$

Base: R_3N, R_2NH

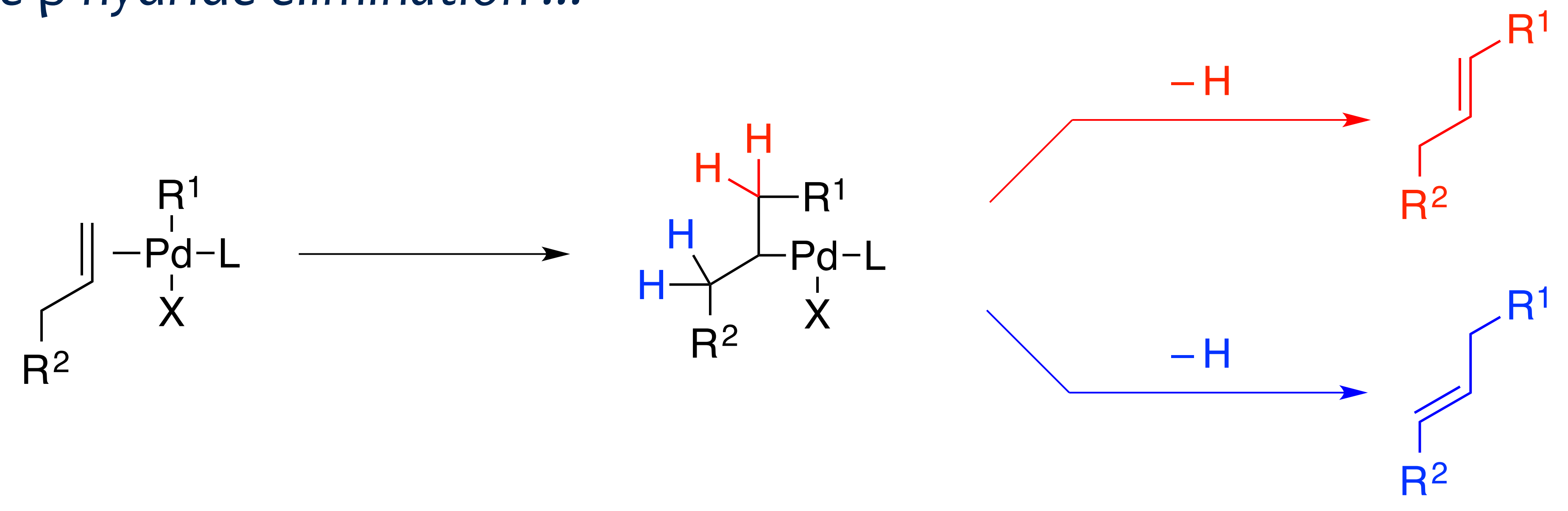
AcO^-, CO_3^{2-}

*The **regioselectivity** of the Heck reaction is not completely defined.*

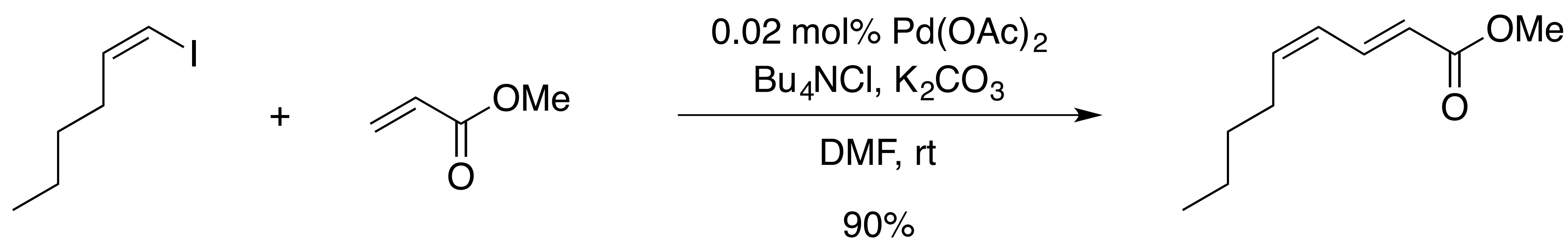
Two pathways are available for the olefin insertion ...

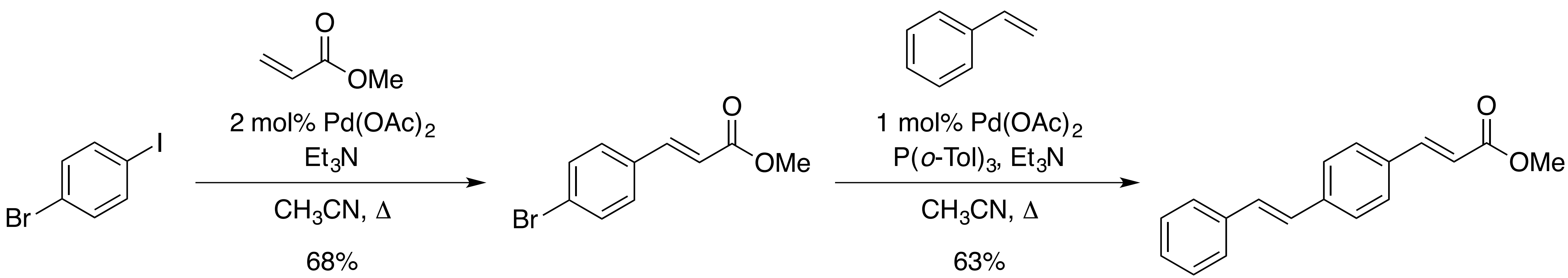
Particularly important when R²: EDG

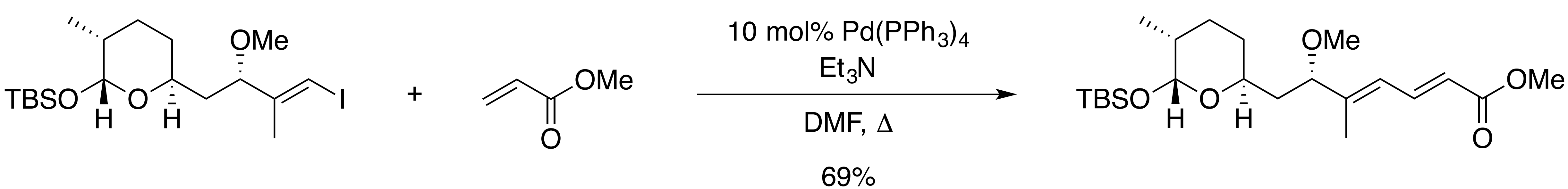
or the β-hydride elimination ...



Heck Reactions

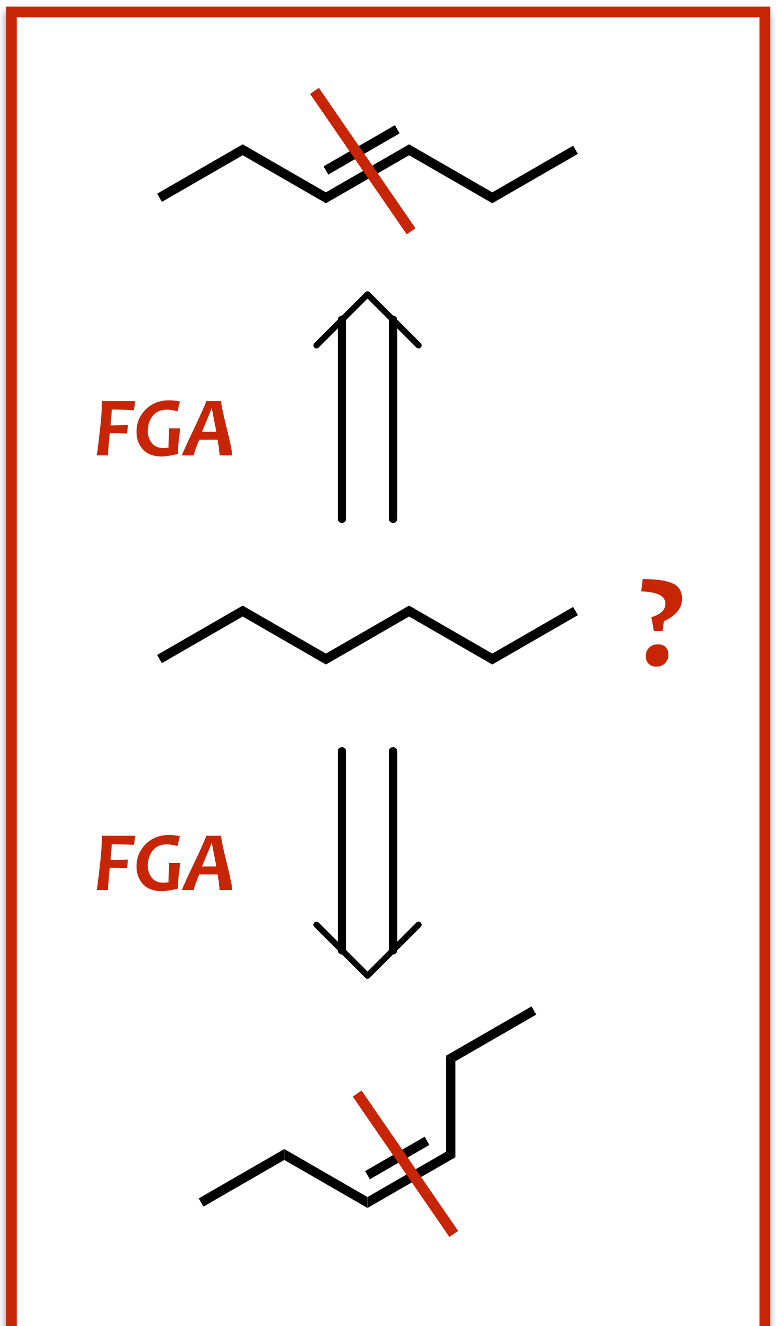






Alternative (IV): C=C Bond Forming Reactions

E- Alkene

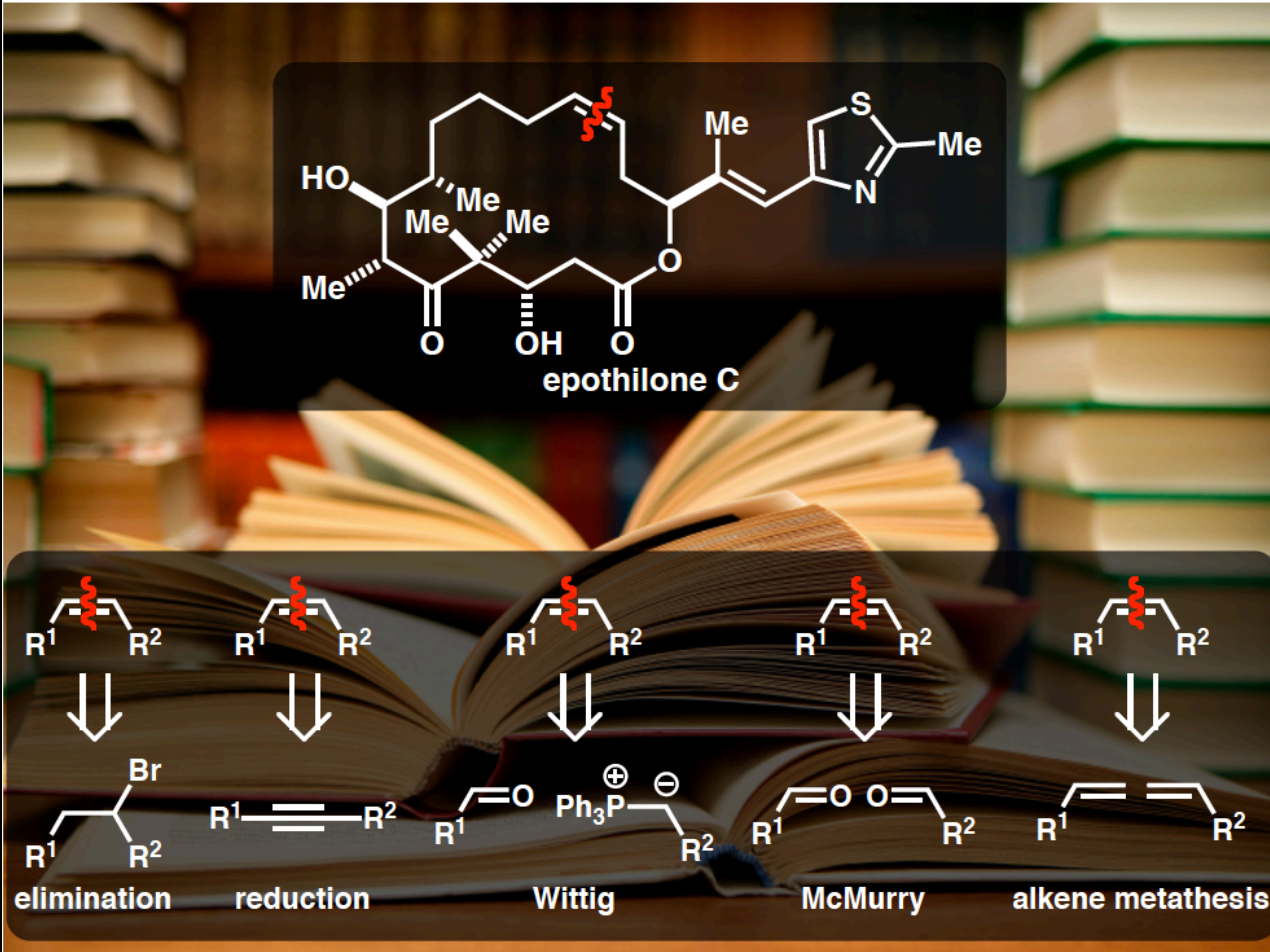


Z- Alkene

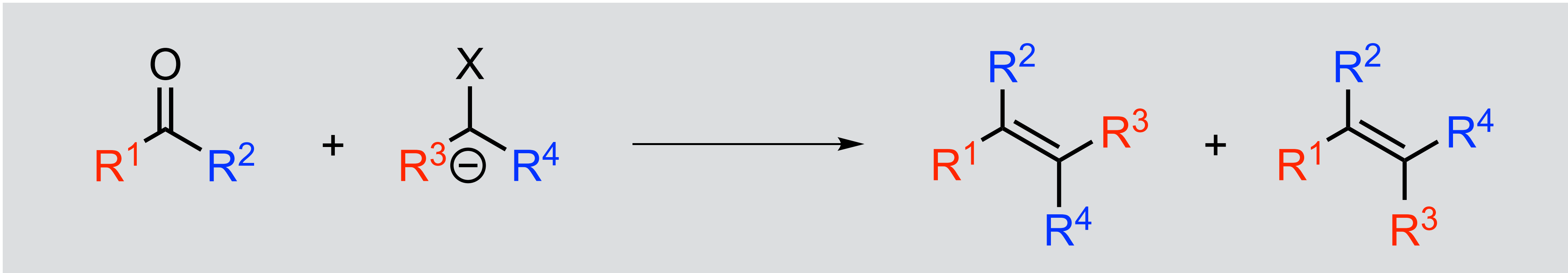
Wittig (stabilized ylides)
HWE
Julia- Kocienski
Metathesis

Peterson olefination
Tebbe olefination
Takai olefination

Wittig (non-stabilized ylides)
Still-Gennari, Ando


HO
Me
Me
Me
Me
O
OH
O
O
Me
S
N
Me
epothilone C
R1 R2
Br
R1 R2
R1 R2
R1 R2
O
Ph3P
R2
R1 O O R2
R1 R2
elimination
reduction
Wittig
McMurry
alkene metathesis

C=C Forming Reactions: Carbanions and Carbonyls



Regioselectivity is not a problem ... The only concern is stereoselectivity!

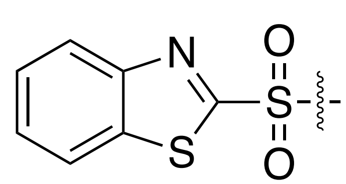
C	*N*	*O*
Si	***P***	***S***

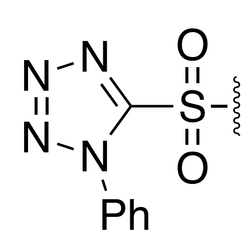
- *X: Si, Peterson Reaction*
- *X: P, Wittig Reaction and variants*

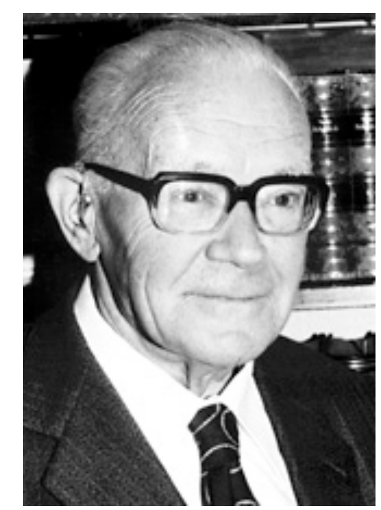
  R_3P^+, Wittig Reaction

  $R_2P{=}O$, Horner-Wittig

  $(RO)_2P{=}O$, Horner-Wadsworth-Emmons (HWE)
- *X: S, Julia-Kocienski Reaction*



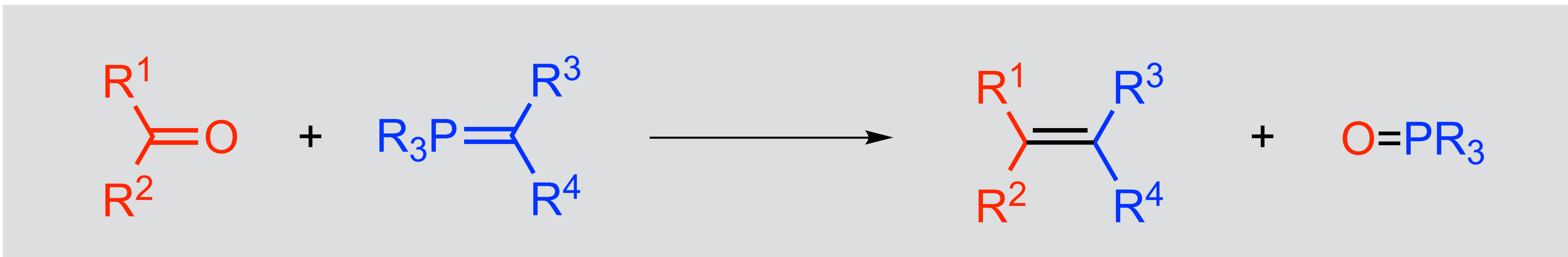




Georg Wittig
Nobel Prize in Chemistry 1979

... for the development of the use of phosphorus-containing compounds into important reagents in organic synthesis

Wittig reaction: addition of a phosphorus ylide to a carbonyl



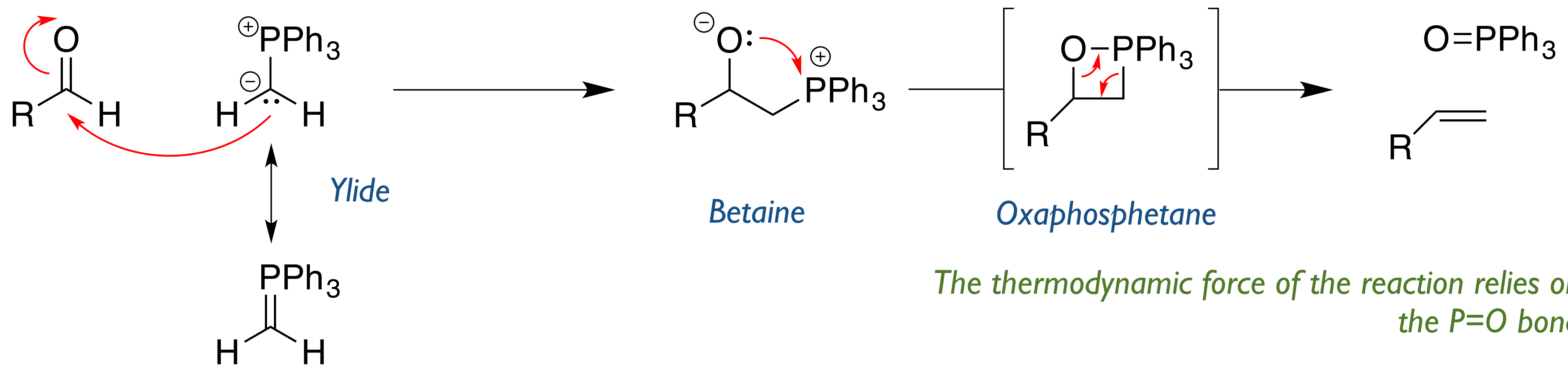
Phosphorus Ylide *Phosphine Oxide*

Thermodynamically favored

Non-stabilized ylides	*R^2: alkyl*	*minor*	*MAJOR*
Semi-stabilized ylides	*R^2: aryl*	*mixtures (E > Z)*	
Stabilized ylides	*R^2: CO_2R, CN*	*MAJOR*	*minor*

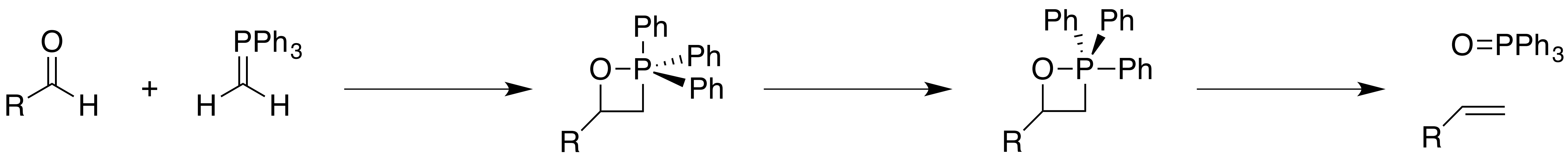
Maryanoff, B. E. CR **1989**, *89*, 863
Nicolaou, K. C. *Liebigs Ann.* **1997**, *7*, 1283

The mechanism of the Wittig reaction has been the subject of much debate.
Initially, Wittig described this reaction as an addition to a carbonyl…



The thermodynamic force of the reaction relies on the P=O bond

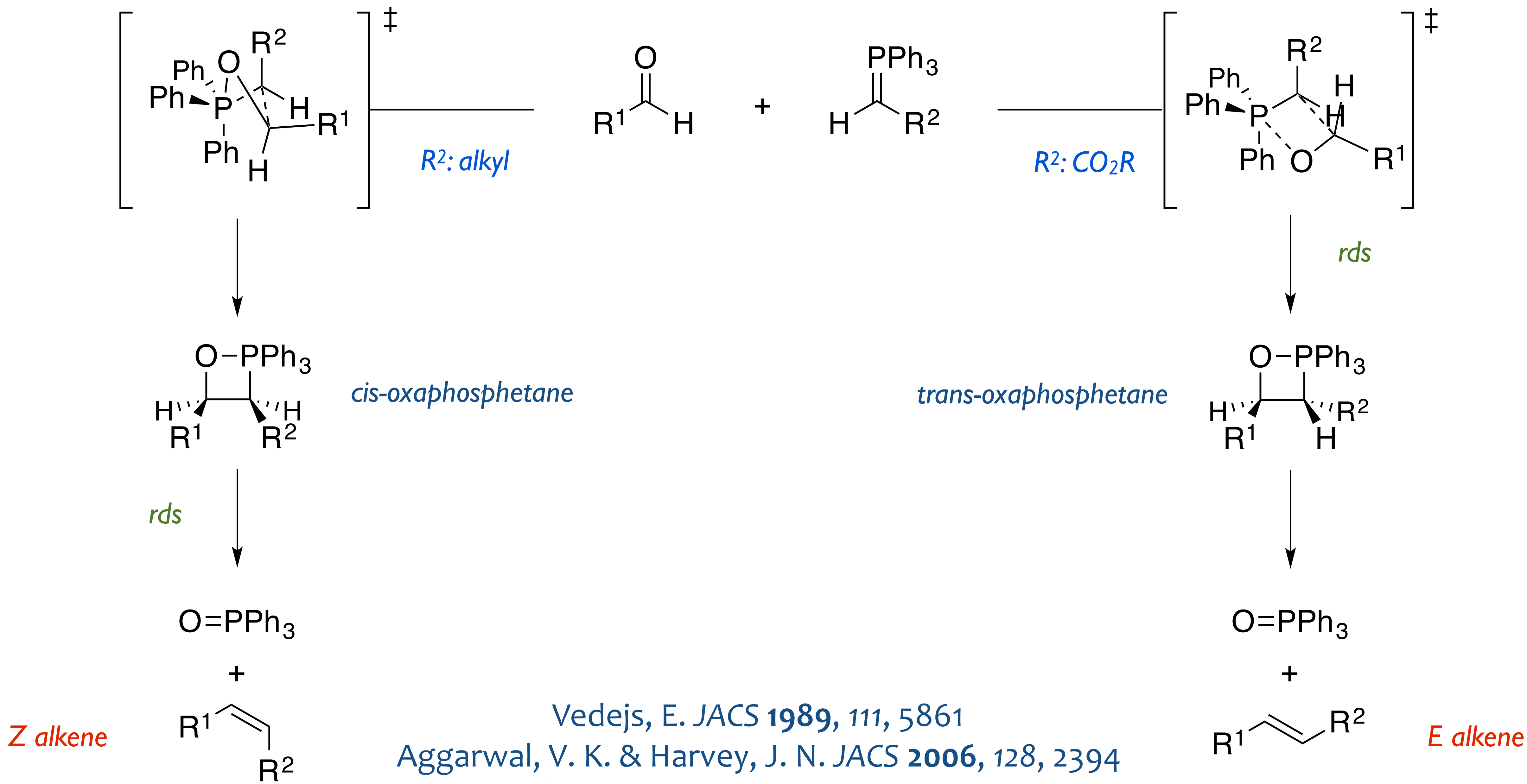
… but the accepted picture ***in the absence of lithium salts*** *is rather different nowadays*



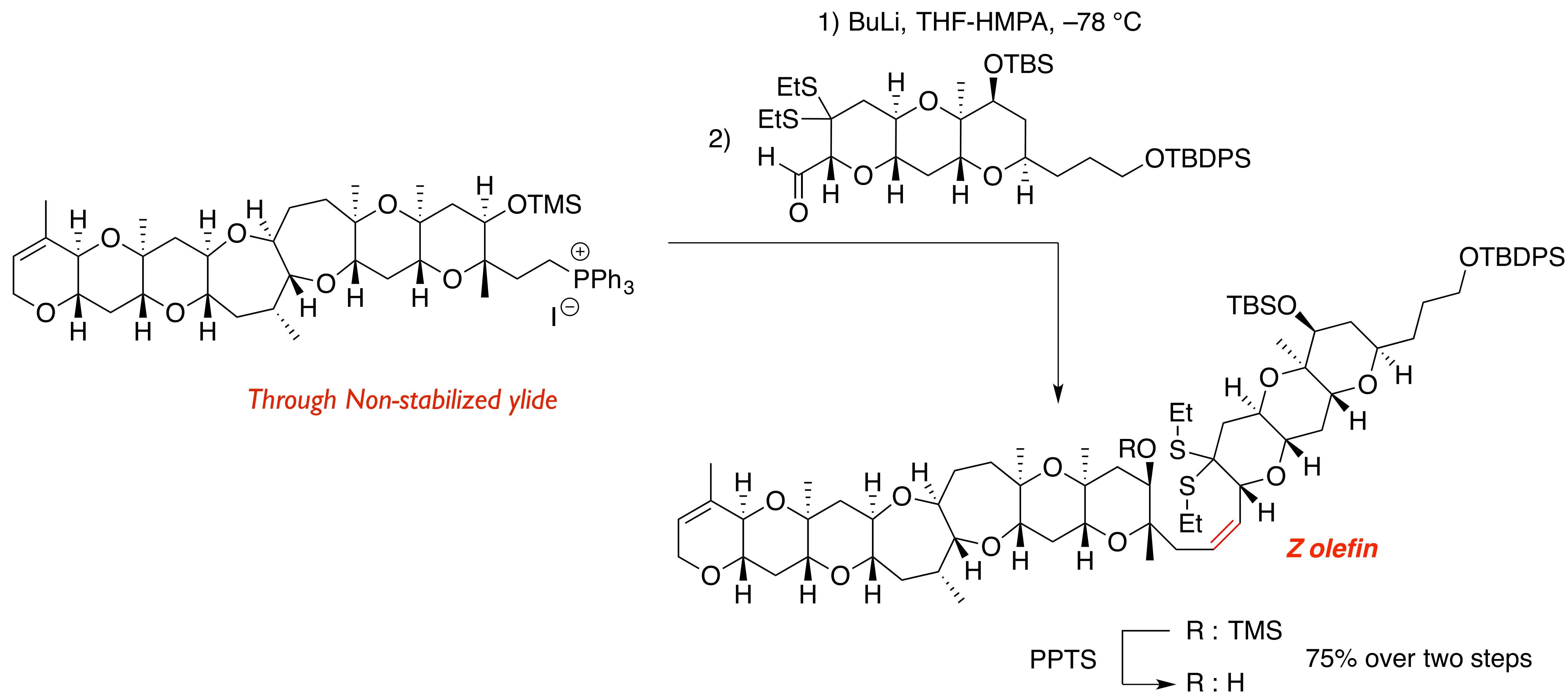
Formal [2,2] Cycloaddition

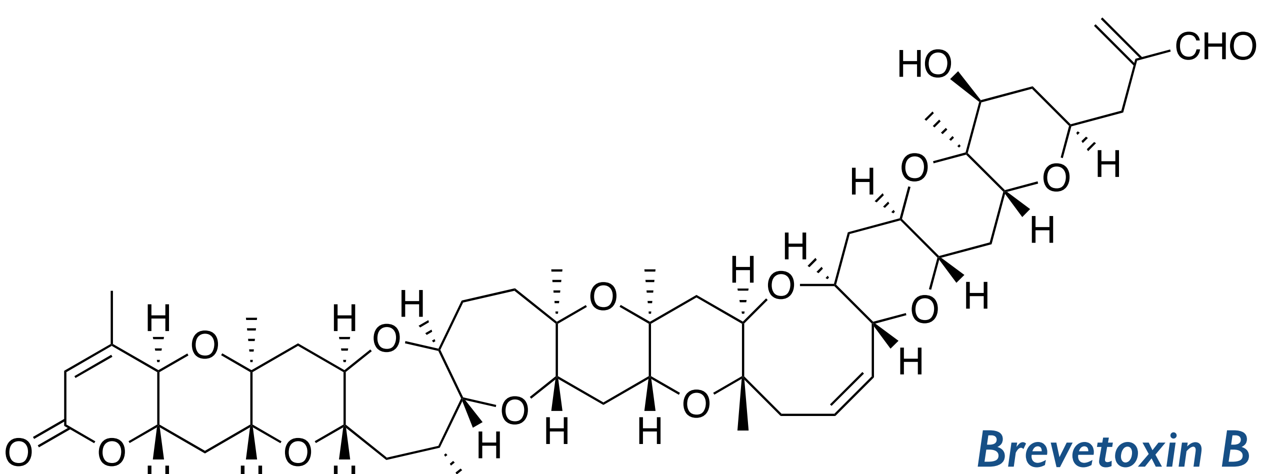
Pseudorotation

*Wittig reactions carried out in the absence of lithium salts (**salt-free Wittig reactions**) are described as kinetically–controlled transformations…*



Vedejs, E. *JACS* **1989**, *111*, 5861
Aggarwal, V. K. & Harvey, J. N. *JACS* **2006**, *128*, 2394
Gilheany, D. G. *JACS* **2012**, *134*, 9225
For a review, Gilheany, D. G. *CSR* **2013**, *42*, 6670

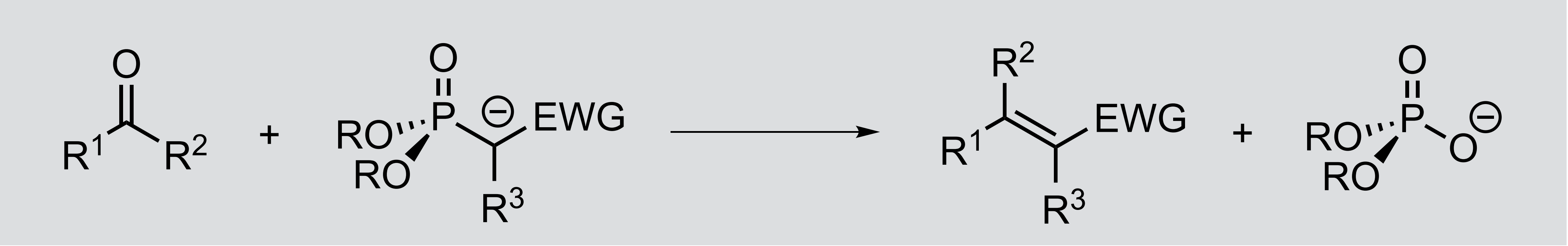




Brevetoxin B

Nicolaou, K. C. *JACS* **1995**, *117*, 10252

Wittig variants: addition of phosphonate carbanions to carbonyls

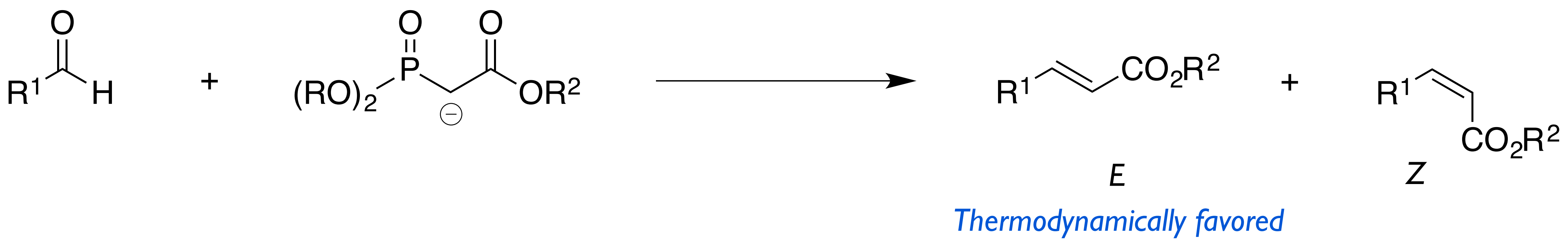


Phosphonate Carbanion

Phosphate salt

Phosphonate	
(AlkylO)$_2$POCH$_2$CO$_2$R^2	*Horner-Wadsworth-Emmons*
(CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$R^2	*Still-Gennari*
(ArylO)$_2$POCH$_2$CO$_2$R^2	*Ando*

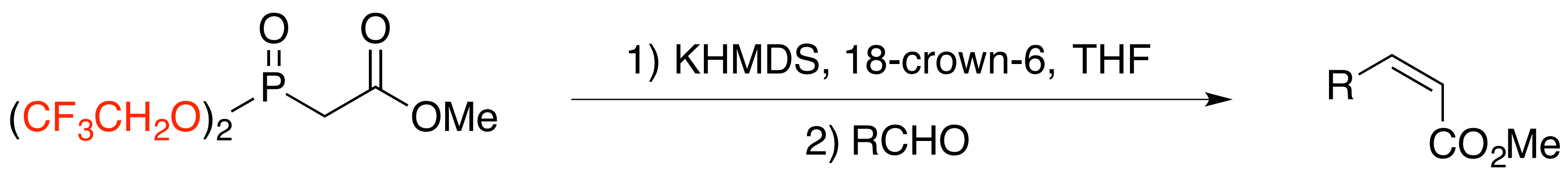
HWE, Still-Gennari & Ando Reactions: Stereoselectivity

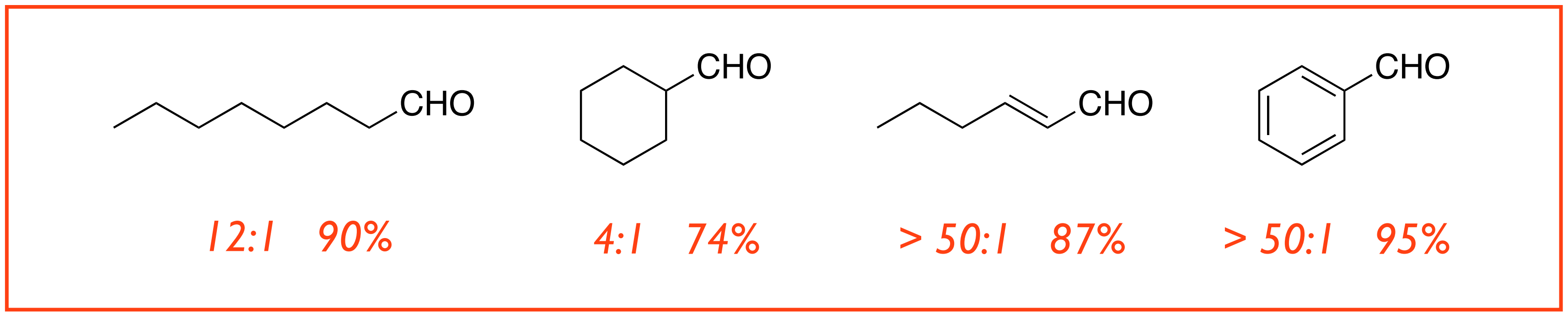


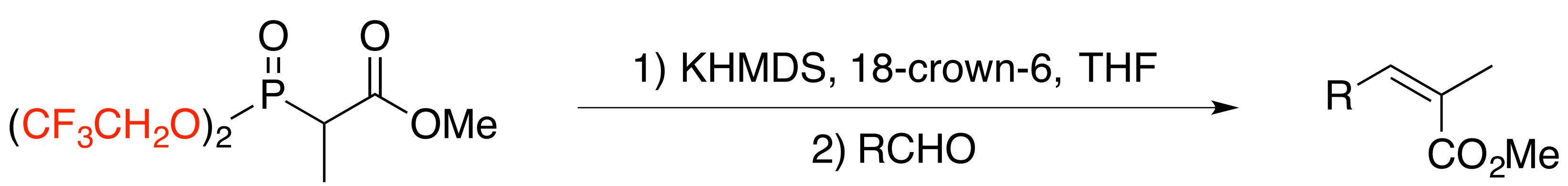
	Phosphonate	E	Z
Horner-Wadsworth-Emmons	*(AlkylO)$_2$POCH$_2$CO$_2$R^2*	*MAJOR*	*minor*
Still-Gennari	*(CF$_3$CH$_2$O)$_2$POCH$_2$CO$_2$R^2*	*minor*	*MAJOR*
Ando	*(ArylO)$_2$POCH$_2$CO$_2$R^2*	*minor*	*MAJOR*

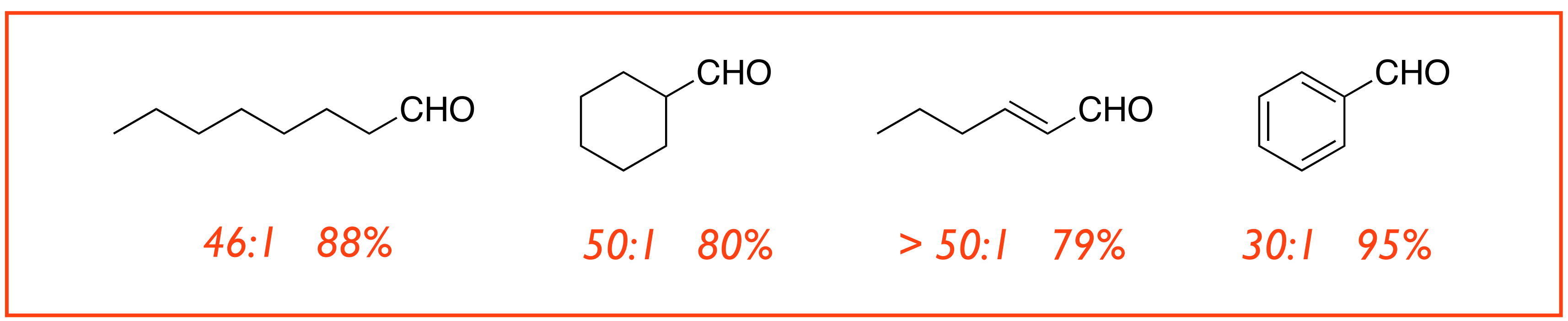
Still-Gennari Reaction: Stereoselectivity

Still-Gennari reaction provides a reliable entry to Z olefines ...



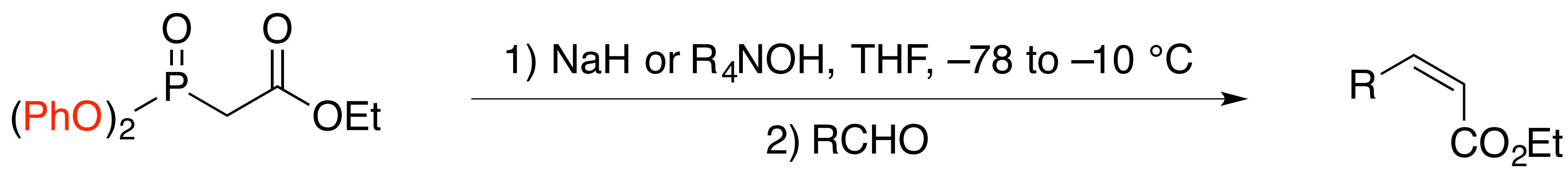


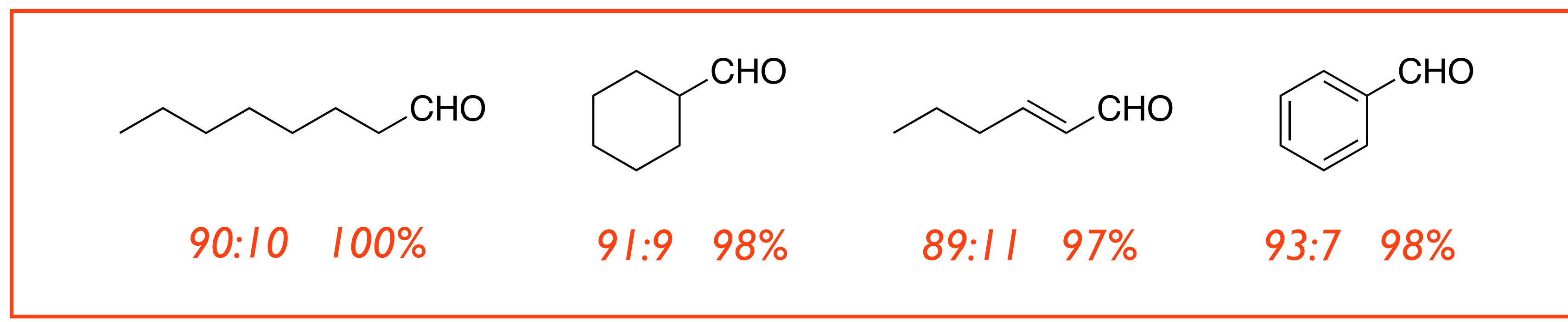


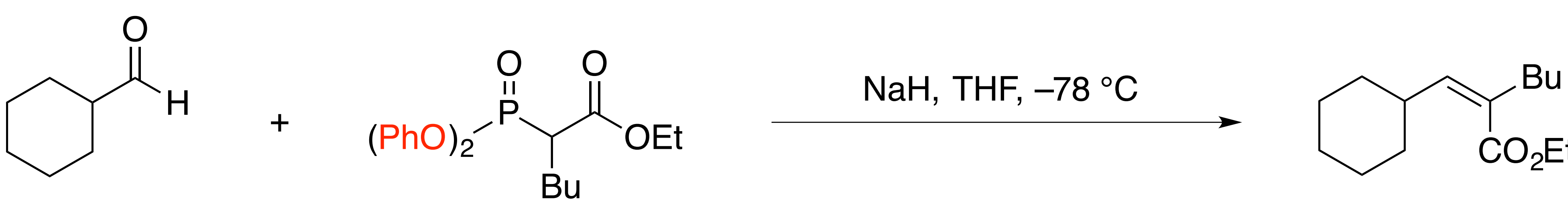


Still, W. C. & Gennari, C. *TL* **1983**, *23*, 4405

Ando reaction also gives Z olefins ...



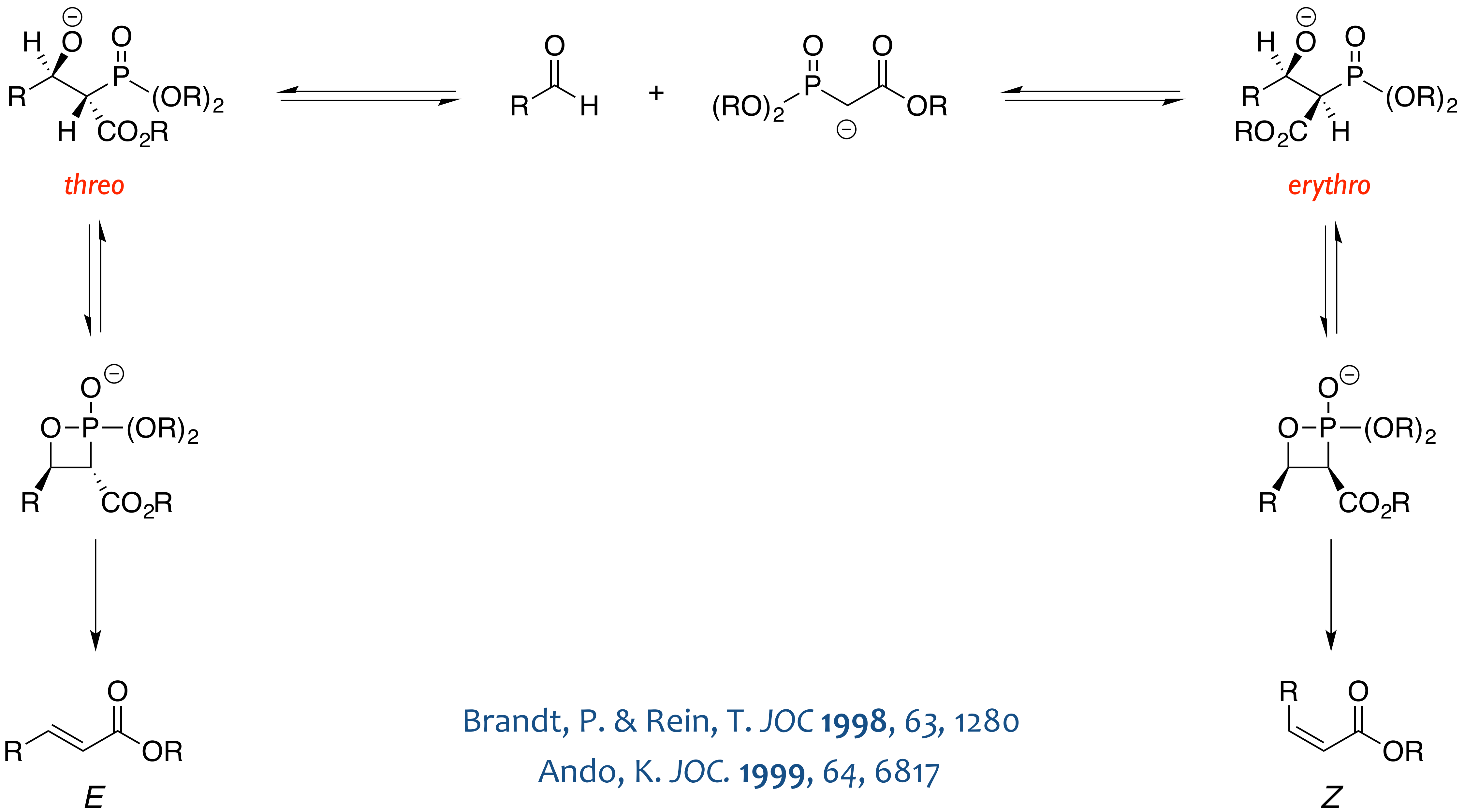




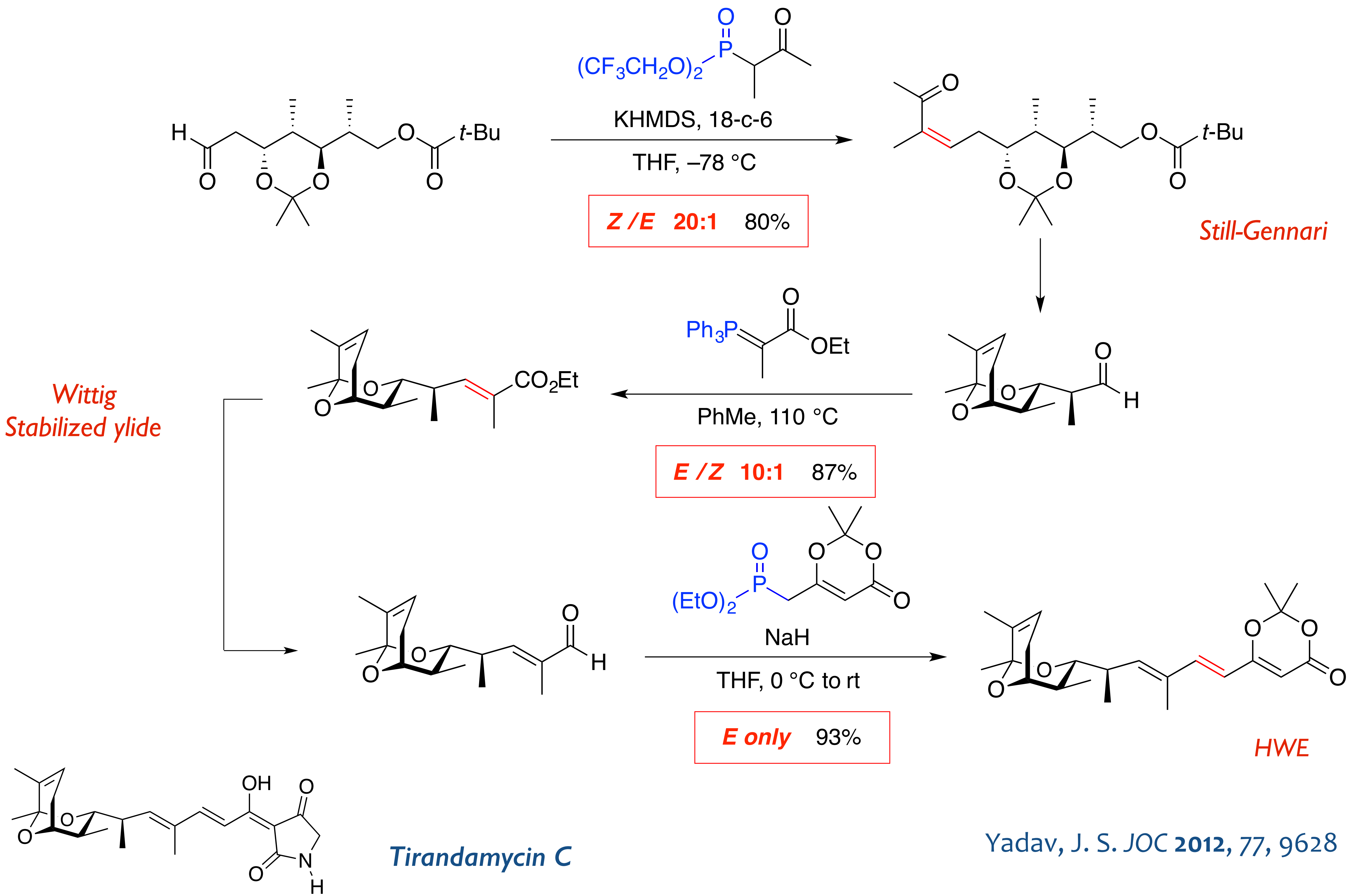
Z / *E* 95:5 85%

Ando, K. *JOC.* **1997**, 62, 1934; *JOC.* **1998**, 63, 8411

It is generally accepted that the stereoselectivity of the HWE reaction is a result of both kinetic and thermodynamic control upon the reversible formation of the erythro and threo adducts followed by the oxaphosphetane formation, pseudorotation, and decomposition to olefins.



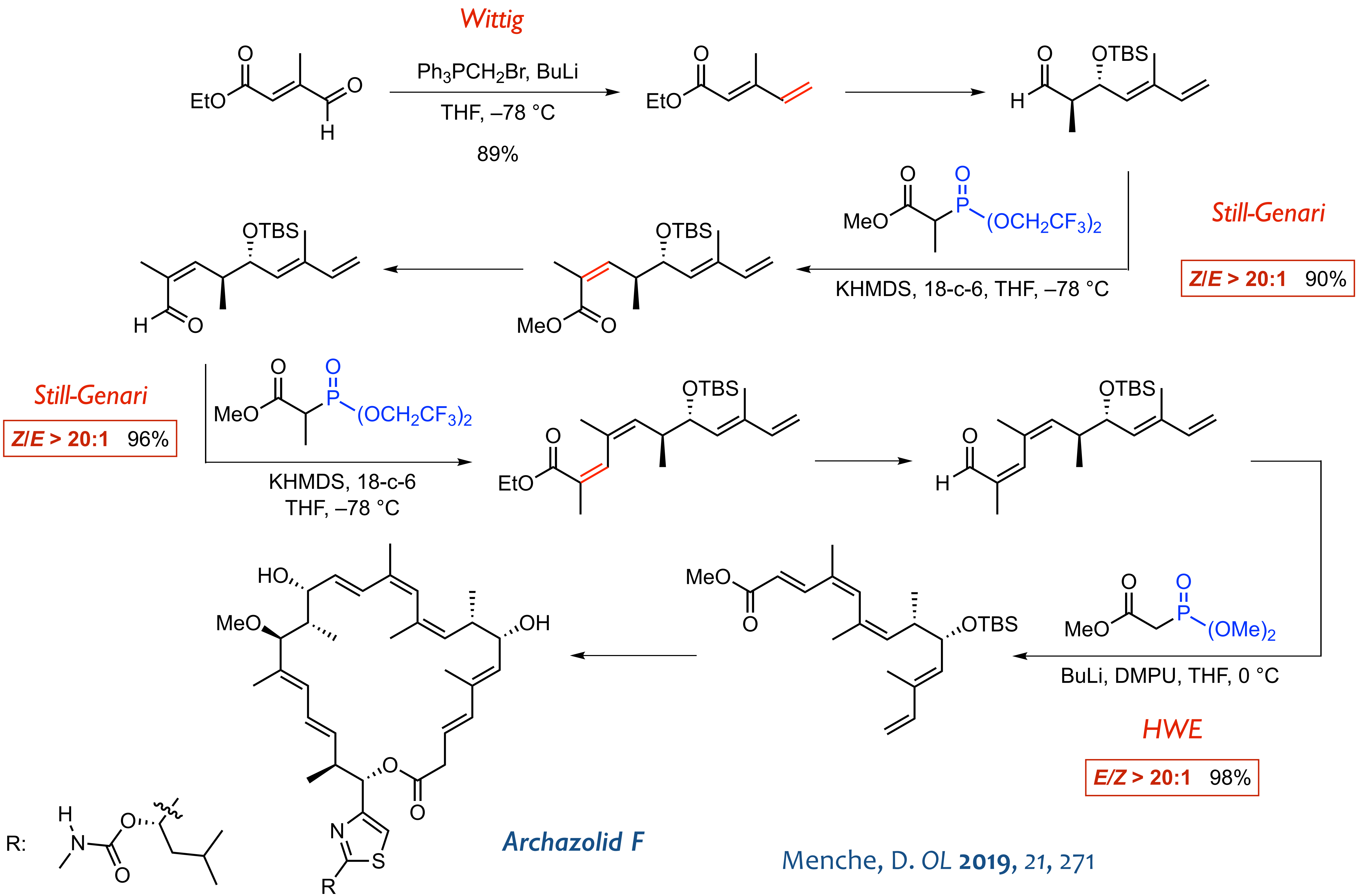
Brandt, P. & Rein, T. *JOC* **1998**, 63, 1280
Ando, K. *JOC*. **1999**, 64, 6817



Tirandamycin C

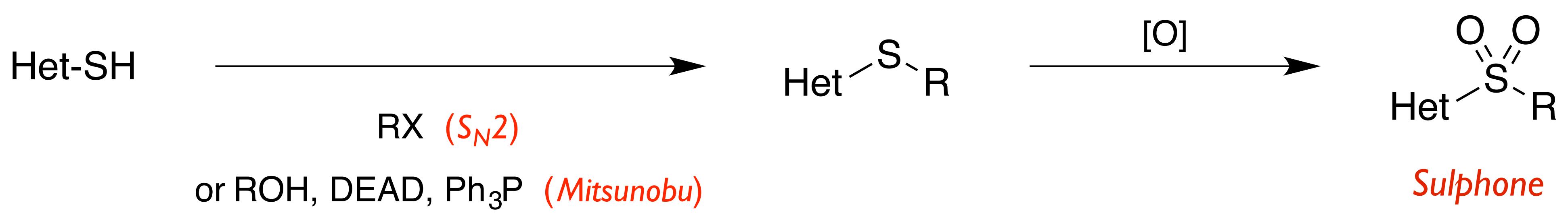
Yadav, J. S. *JOC* **2012**, *77*, 9628

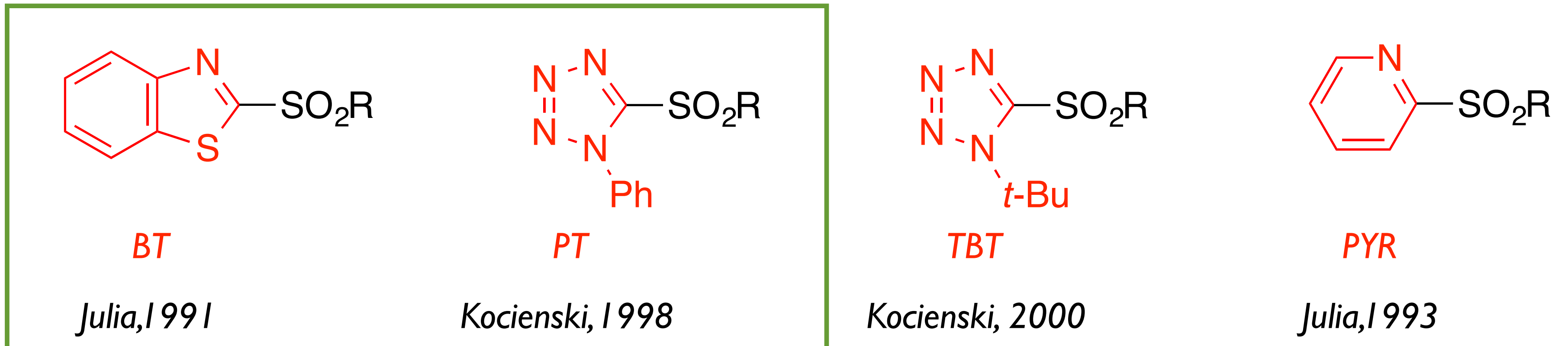
Wittig, HWE & Variants in Synthesis



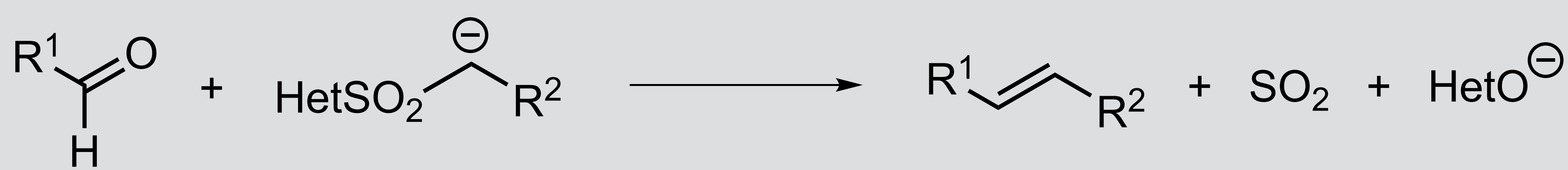
Menche, D. *OL* **2019**, *21*, 271

Julia-Kocienski Reaction: Concept



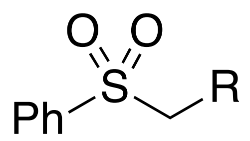


Julia-Kocienski reaction: addition of sulfone carbanions to aldehydes

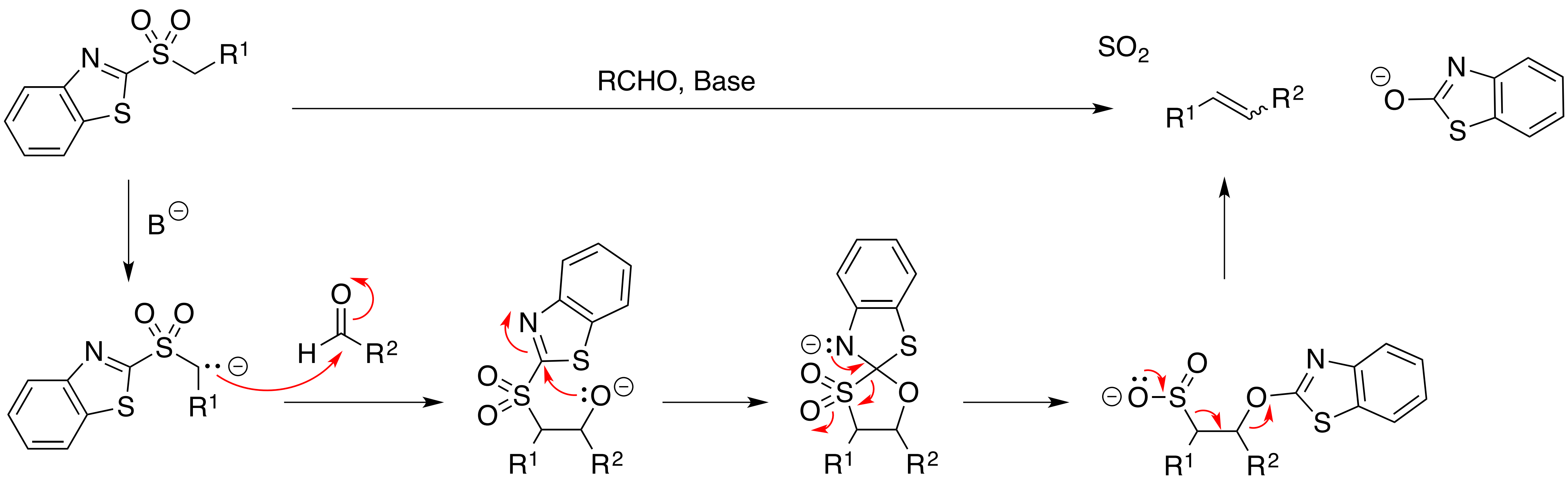


Blakemore, P. R. *JCS Perkin Trans 1* **2002**, 2563; Aïssa, C. *EJOC* **2009**, 1831

Sulfone acidity

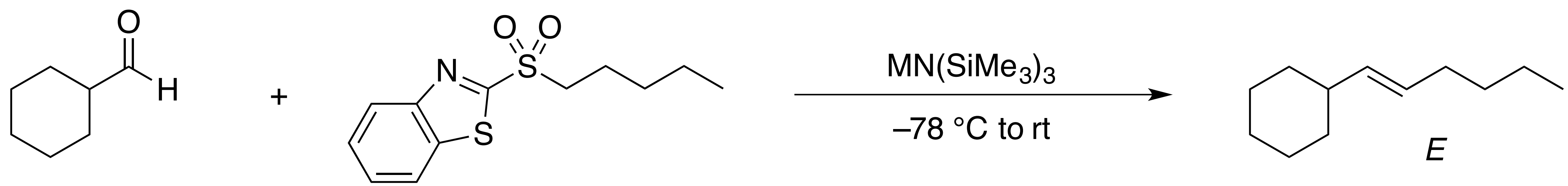


R	*H*	*Me*	*t-Bu*	*Ph*
pK_a	*29.0*	*31.0*	*31.2*	*23.4*



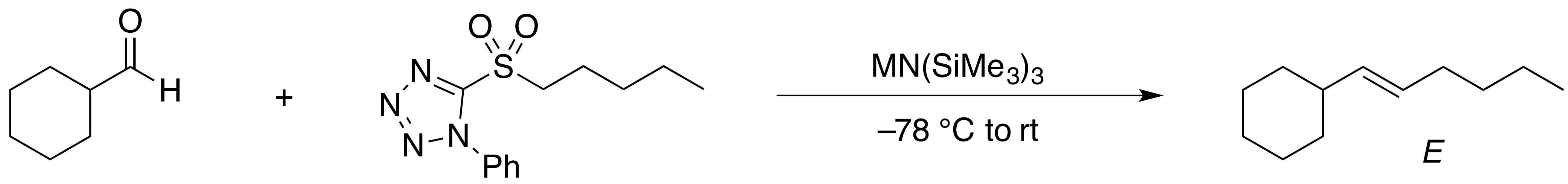
For a computational analysis of the Julia Kocienski reaction, see
Legnani, L.; Vidari, G. *JOC* **2015**, *80*, 3092

Julia-Kocienski Reaction: Stereoselectivity



More *E* →

M	*PhMe*	*Et₂O*	*THF*	*DME*
Li	*50 : 50*	*50 : 50*	*66 : 34*	*70 : 30*
Na	*54 : 46*	*50 : 50*	*62 : 38*	*75 : 25*
K	*54 : 46*	*50 : 50*	*54 : 46*	*76 : 24*



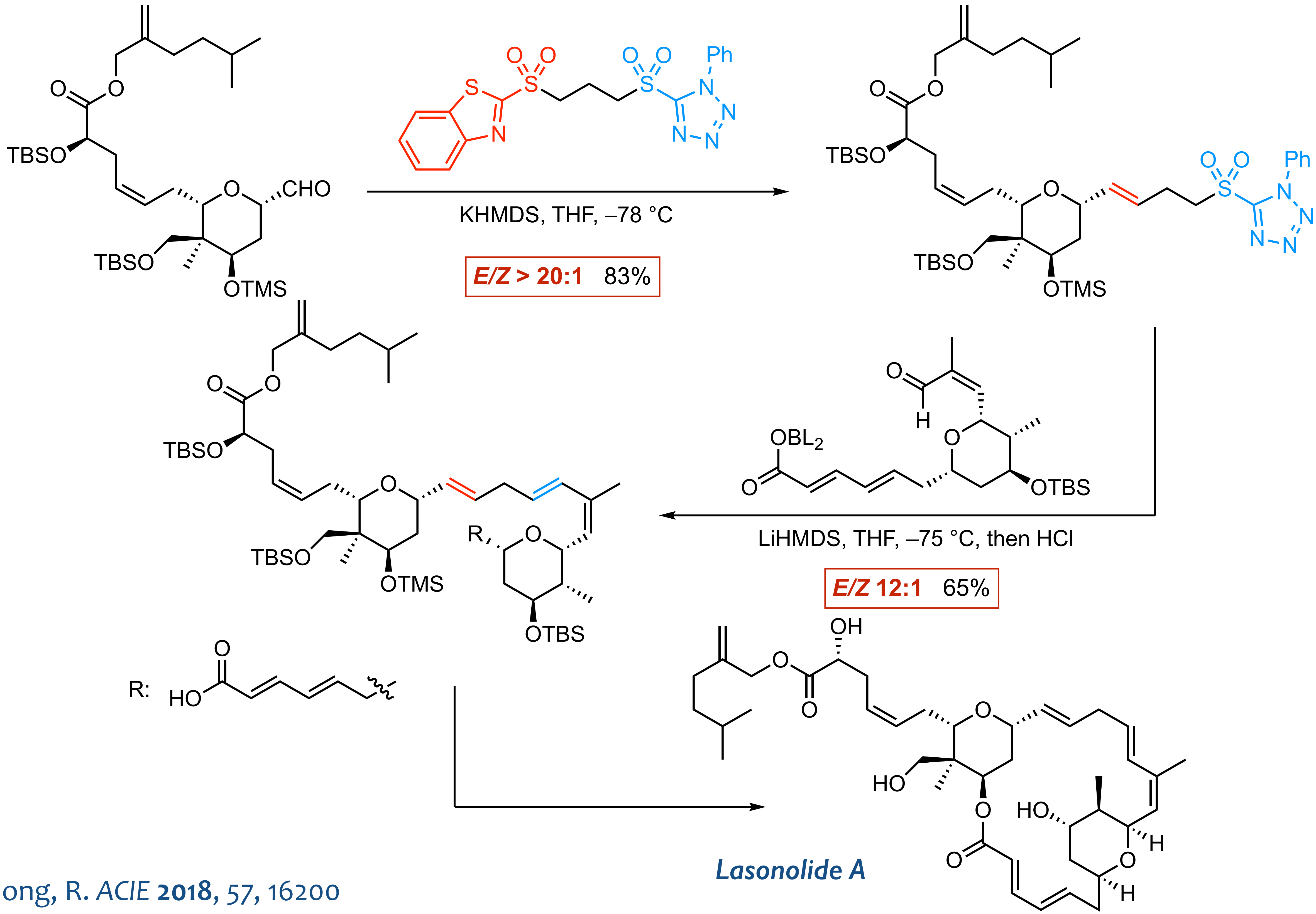
More *E* →

M	*PhMe*	*Et₂O*	*THF*	*DME*
Li	*51 : 49*	*61 : 39*	*69 : 31*	*72 : 28*
Na	*65 : 35*	*65 : 35*	*73 : 27*	*89 : 11*
K	*77 : 23*	*89 : 11*	*97 : 3*	*99 : 1*

↓ More *E*

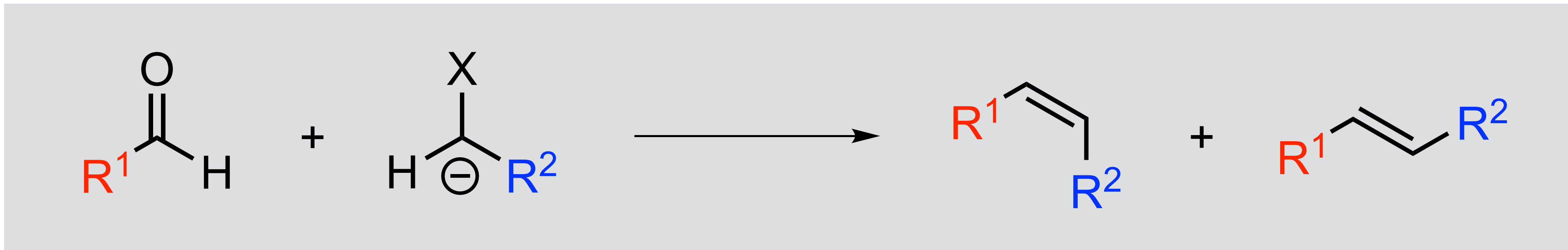
Kocienski, P. J. *Synthesis* **1998**, 26

Julia-Kocienski Reaction: Stereoselectivity



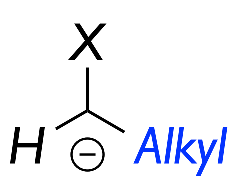
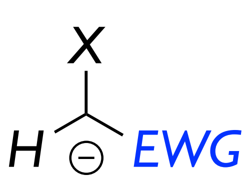
Hong, R. *ACIE* **2018**, 57, 16200

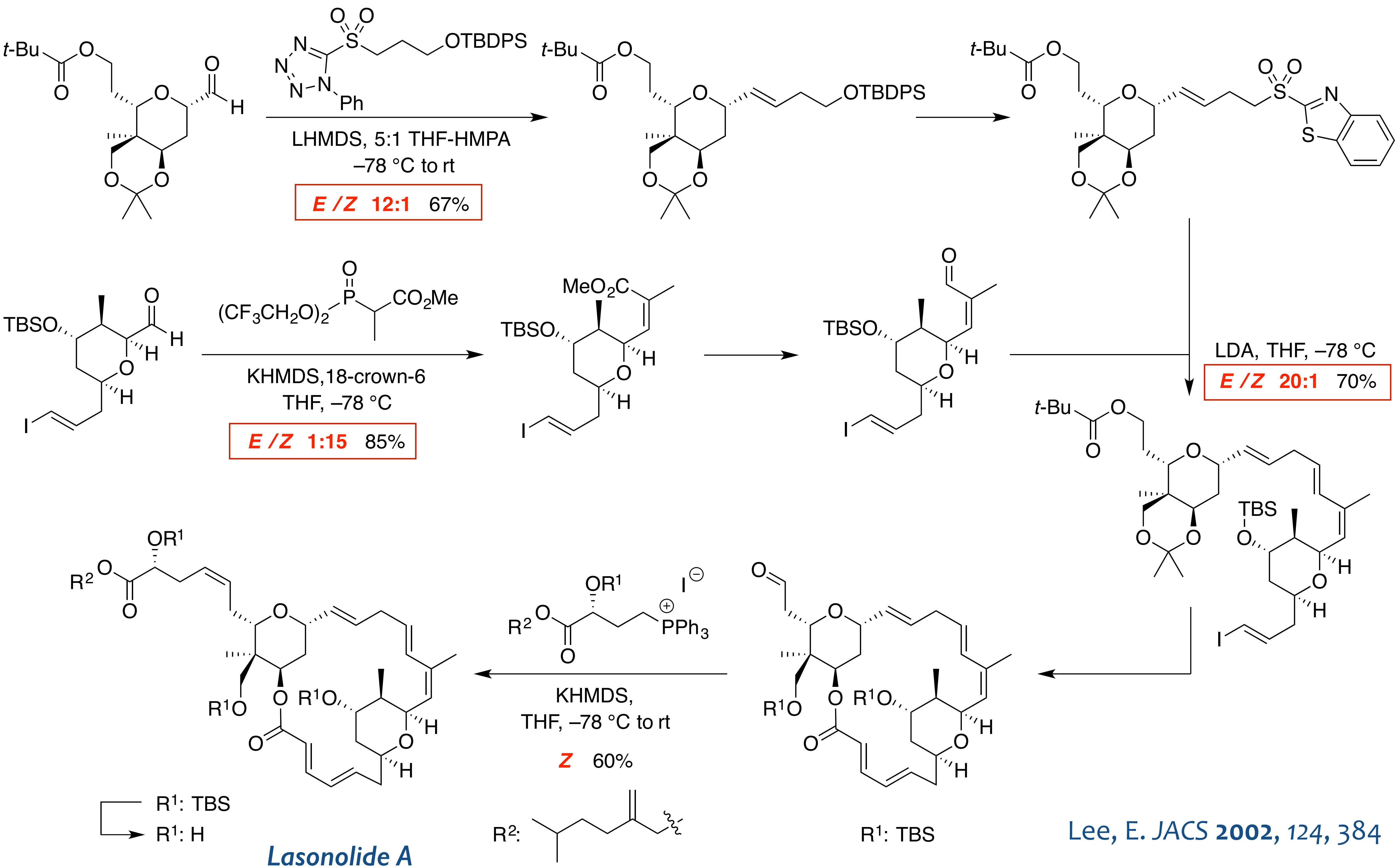
Stereoselectivity of Wittig, HWE & Variants



Z olefin *E olefin*

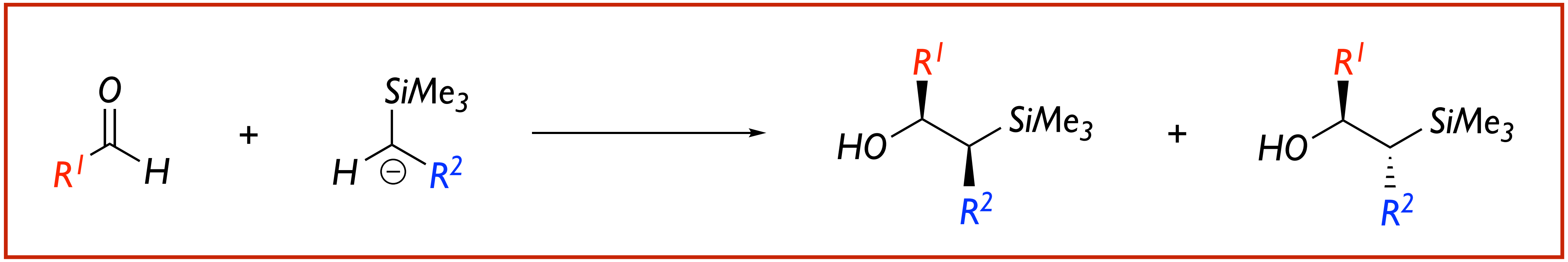
Regioselectivity ✓ Stereoselectivity (Z versus E) ?

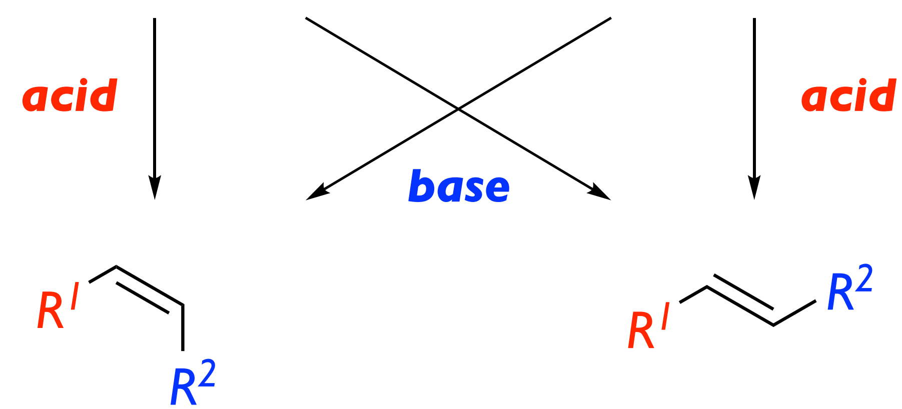
	Z olefin	***E olefin***
	*Wittig*	*Julia-Kocienski*
	*Still-Gennari & Ando*	*Wittig & HWE*



Lee, E. *JACS* **2002**, *124*, 384

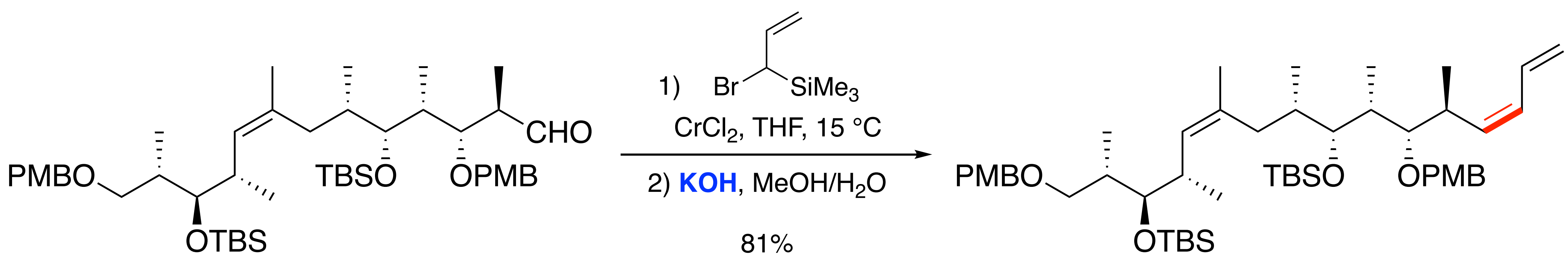
Other C=C Bond Forming Reactions: Peterson Olefination



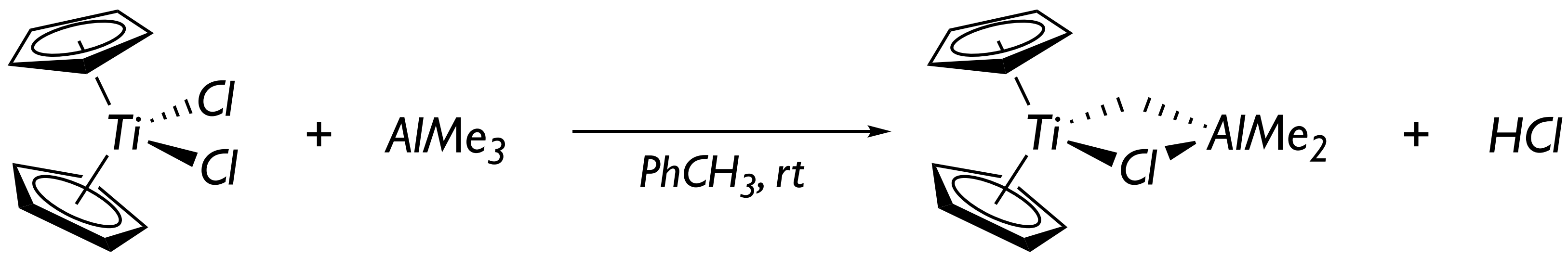


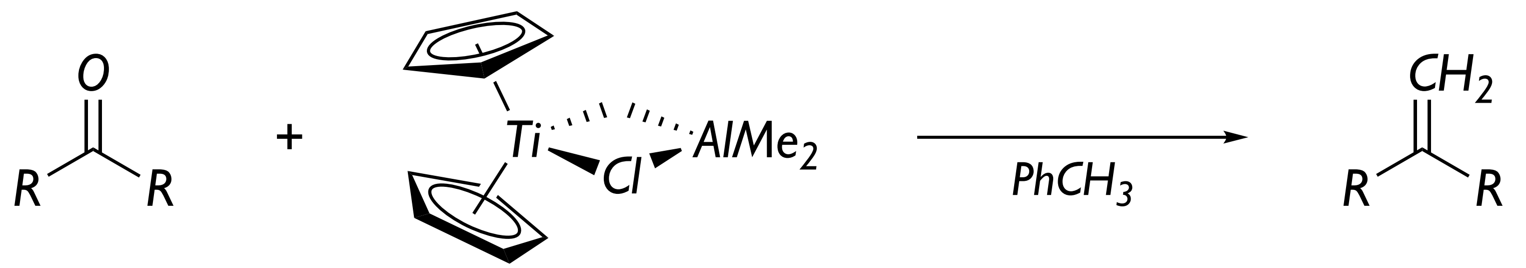
Remember elimination reactions
to understand the mechanism

Nozaki-Hiyama-Kishi-type coupling

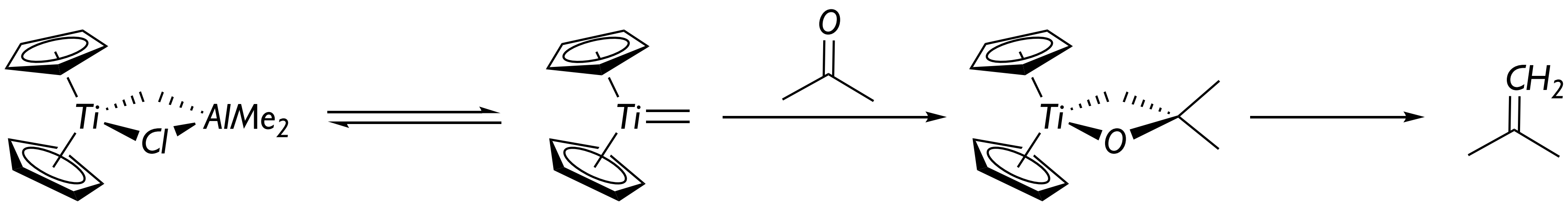


Novartis approach to Discodermolide. *OPRD* **2004**, *8*, 92, 101, 107, 113 & 122

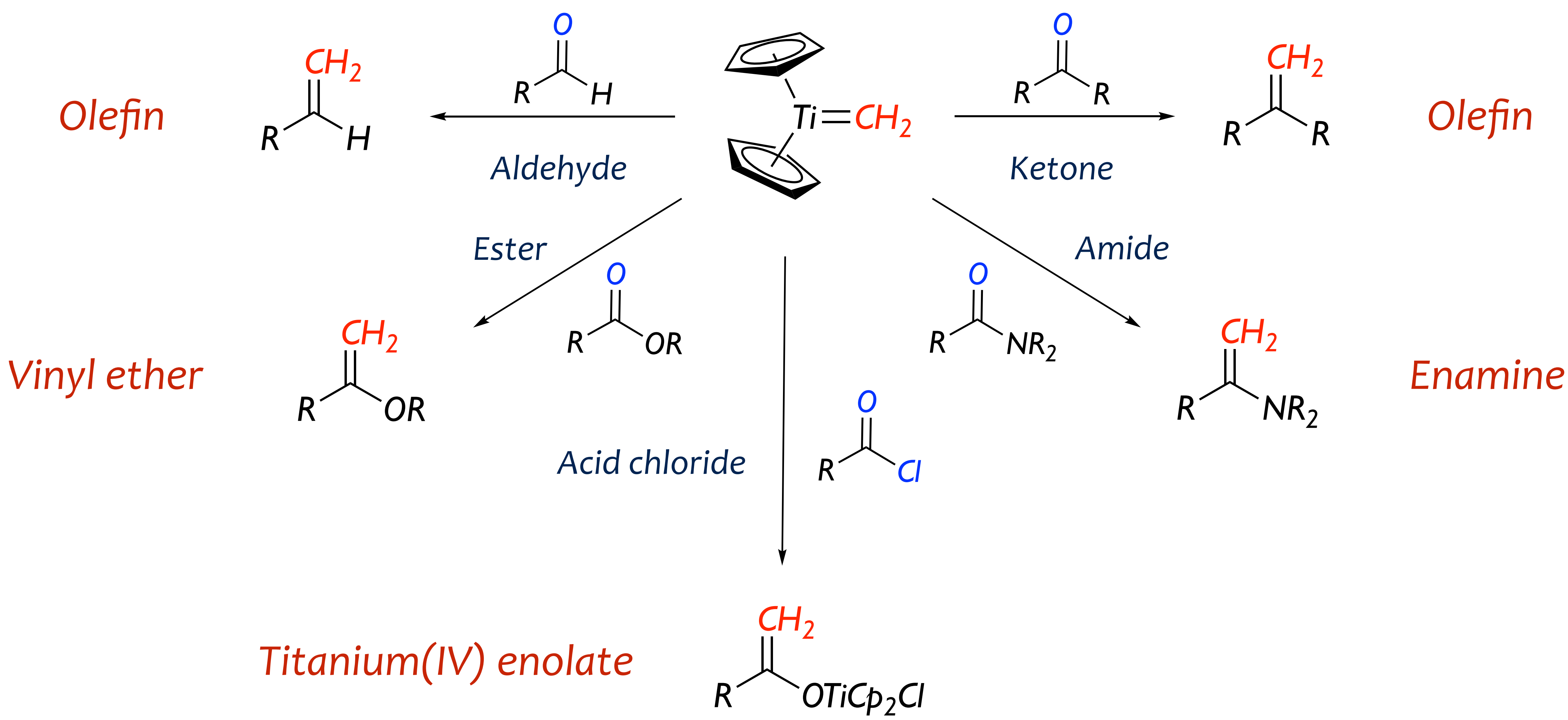




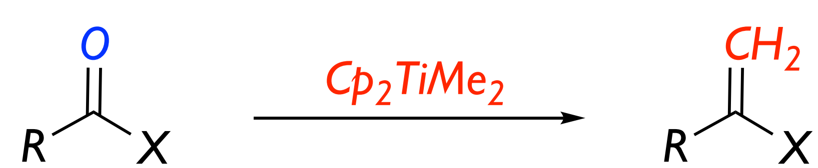
From a mechanistic point of view, it looks like a metathesis



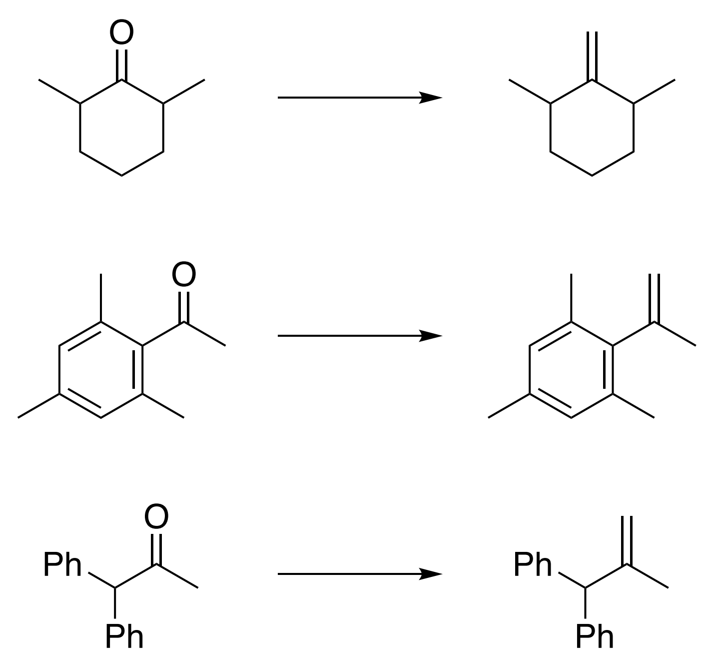
Other C=C Bond Forming Reactions: Tebbe Olefination



The Tebbe-Petasis variant utilizes Cp_2TiMe_2



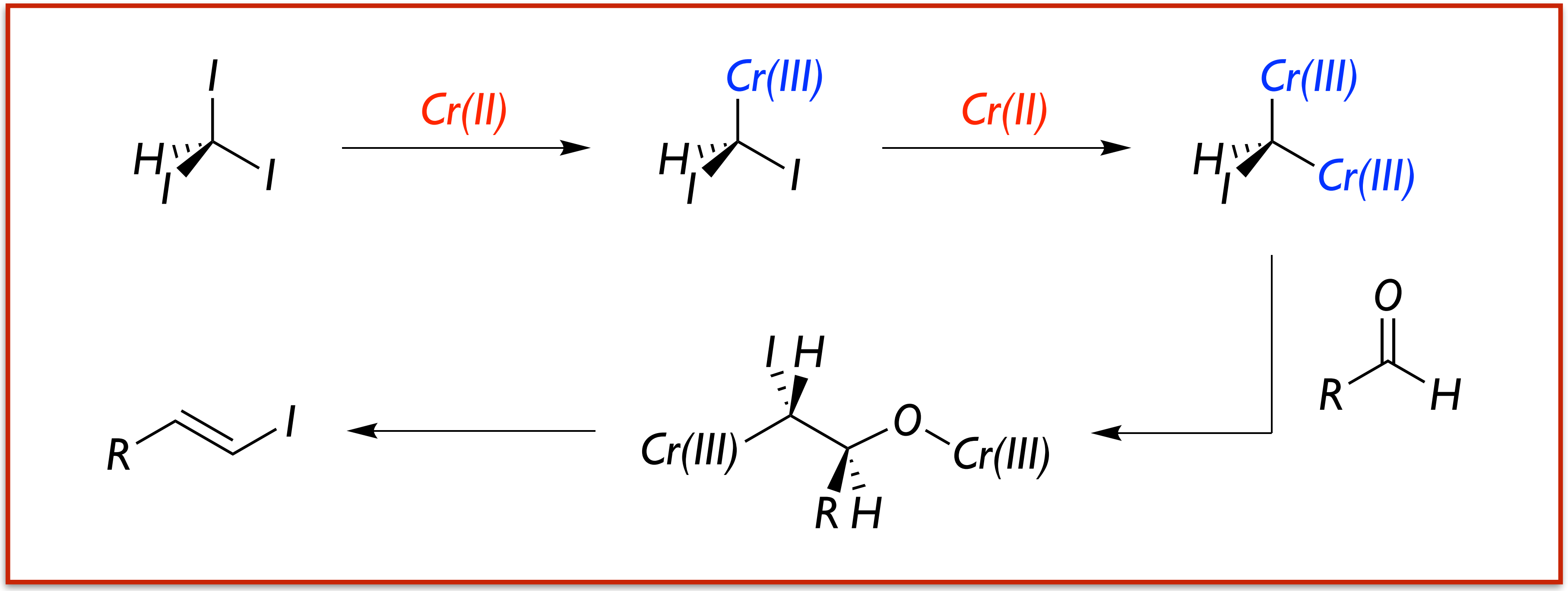
- *The Tebbe reagent is a non-basic reagent*
- *Highly reactive in front of sterically hindered carbonyl groups*



	Wittig	*Tebbe*
	89%	97%
	4%	77%
Pine, S. H. *Synthesis* **1991**, 165	38%	63%

- *The Tebbe reagent is generated and reacts at low temperature*
- *The Tebbe reagent is a Lewis acid sensitive to moist and oxygen*
- *The Tebbe reagent is limited to methylenation*

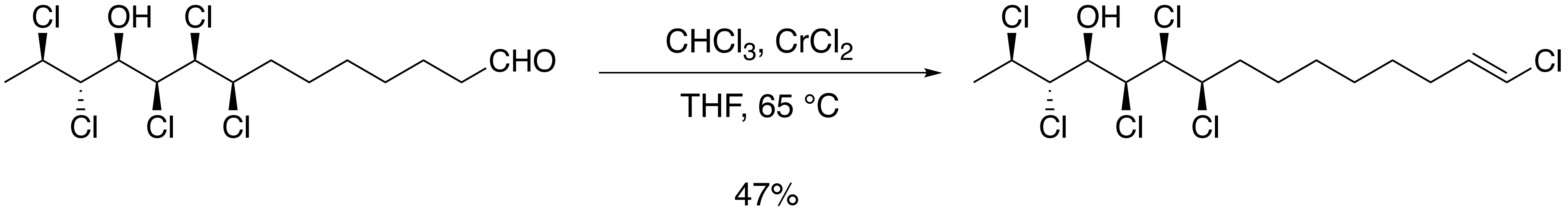
Other C=C Bond Forming Reactions: Takai Olefination



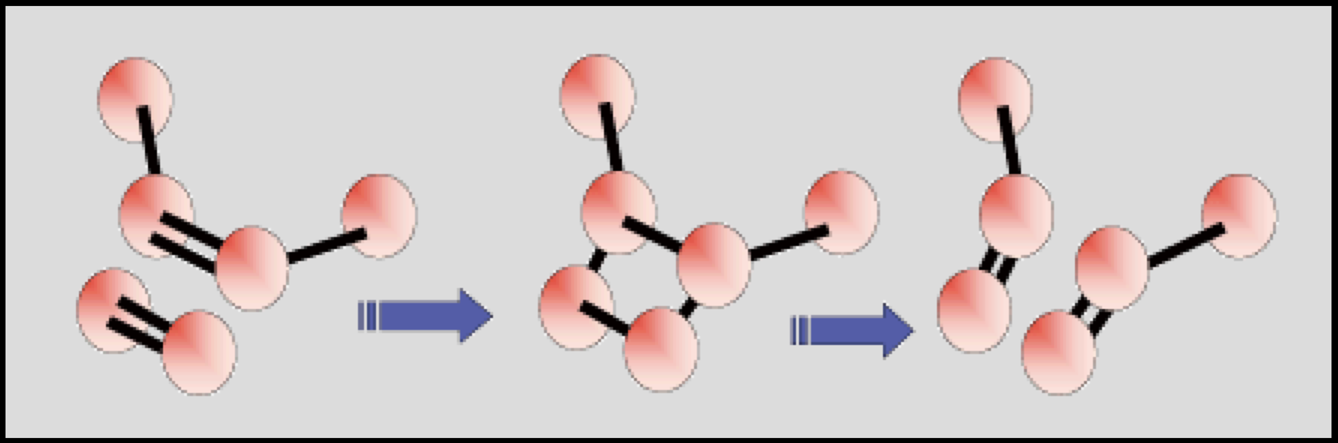
Iodoolefins are very useful intermediates for Pd-mediated couplings

For an insightful analysis of the mechanism, see Anwander, R. *JACS* **2018**, *140*, 14334

Occasionally, it can be applied to bromo and chloroderivatives

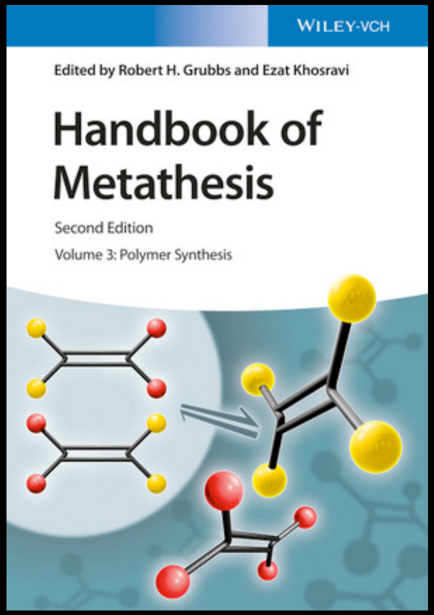


Carreira, E. M. *Nature* **2009**, *457*, 573



Metathesis

a key reaction beyond ionic analysis

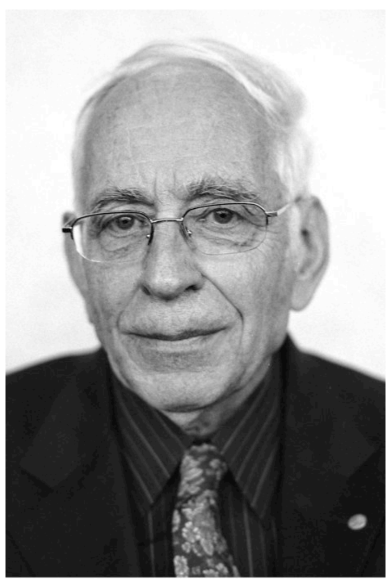


Olefin Metathesis: A New Reaction?

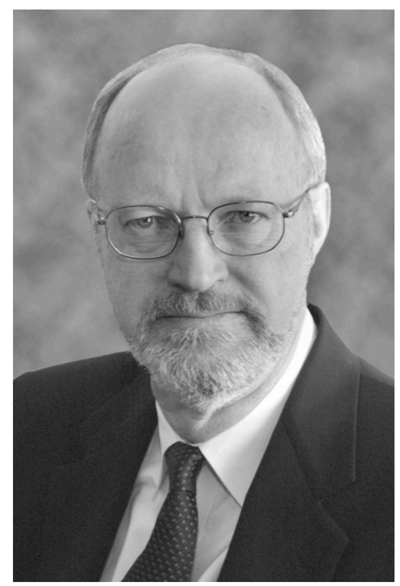
Olefin Metathesis: the reaction of the 90s?

The Nobel Prize in Chemistry 2005 …

for the development of the metathesis method in organic synthesis



Yves CHAUVIN



Robert H. GRUBBS

Richard R. GRUBBS

Alkene metathesis in all its various guises has arguably influenced and shaped the landscape of synthetic organic chemistry more than any other single process over the last 15 years

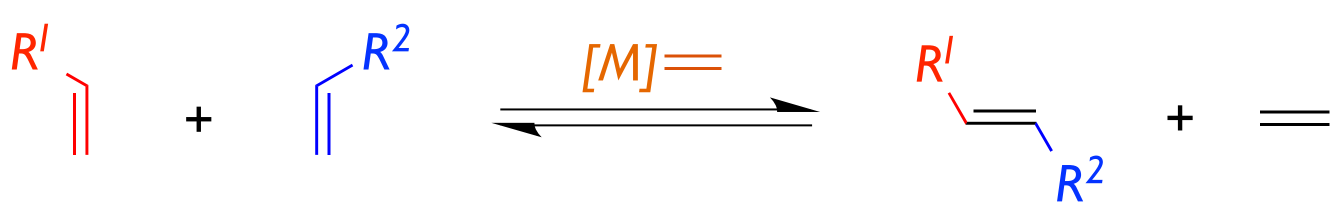
Nicolaou, K. C. *ACIE* **2005**, 44, 4490

Robert H. Grubbs. *The Development of Olefin Metathesis Catalysts: An Organometallic Success Story, in ACR* **2001**, *34*, 18–29

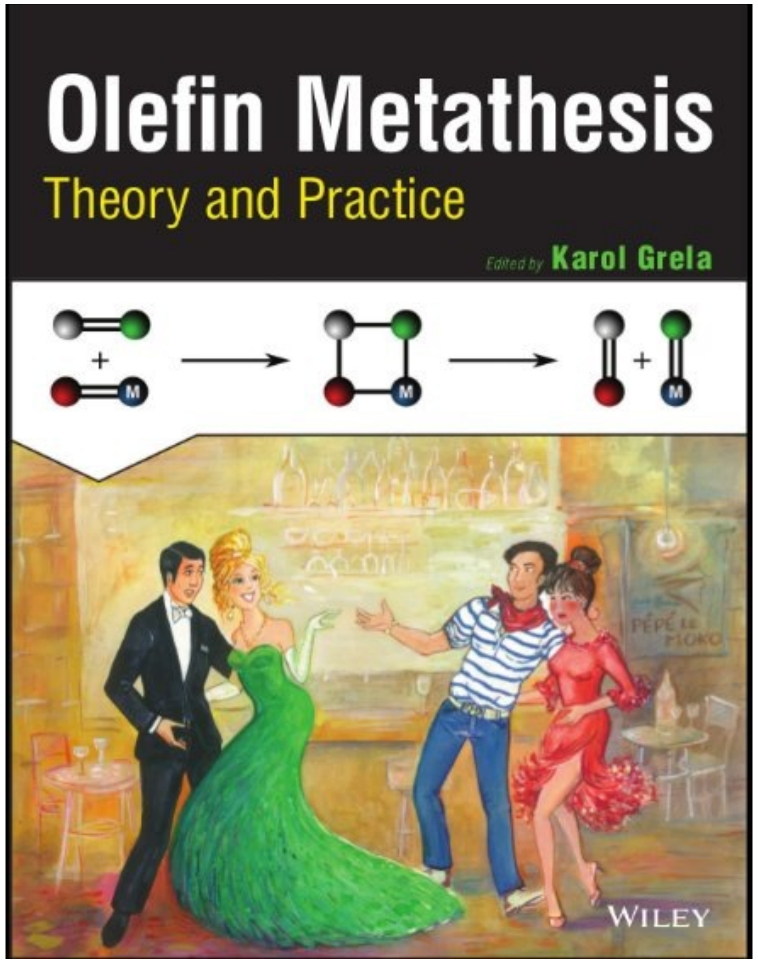
Metathesis = ***Meta*** *(change)* & ***thesis*** *(position)*

AB + **CD** ⟶ **AC** + **BD**

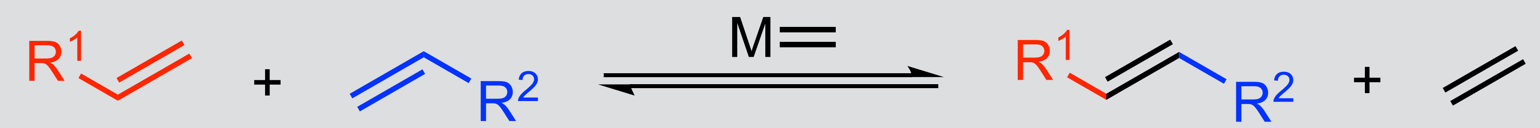
Olefin metathesis *can be formally described as the intermolecular mutual exchange of alkylidene fragments between two olefins promoted by metal-carbene complexes*



Nicolaou, K. C. *Classics in Total Synthesis II*. p. 162



Grela K. *Olefin Metathesis. Theory and Practice.* Wiley
For an analysis, see *ACIE* **2015**, 54, 3856



Olefin metathesis *is a*

reversible,

catalytic process (1–5 mol%),

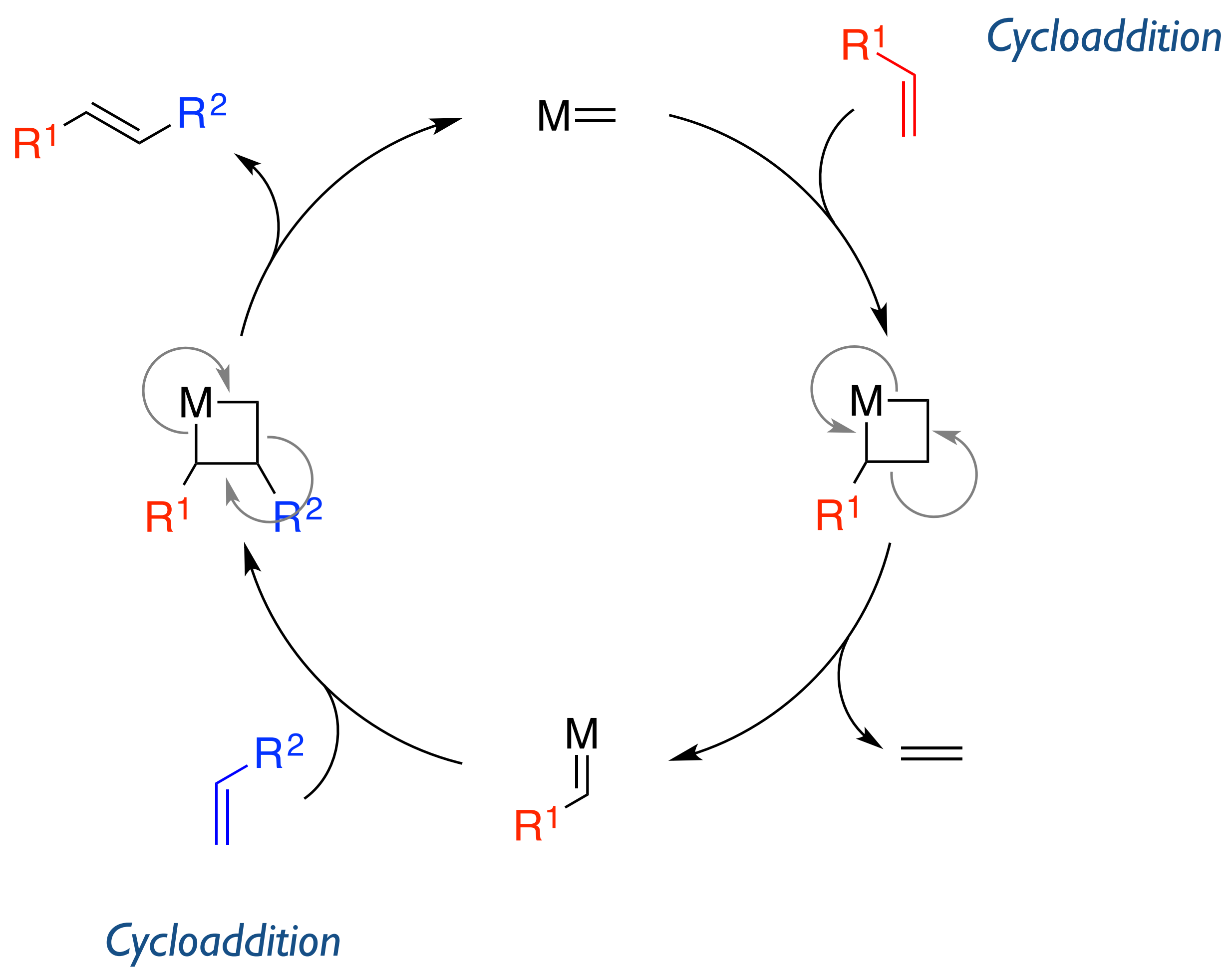
with high levels of chemo-, regio-, and stereoselectivity

Except for the synthesis of small cycles,

the reversible character of olefin metathesis usually

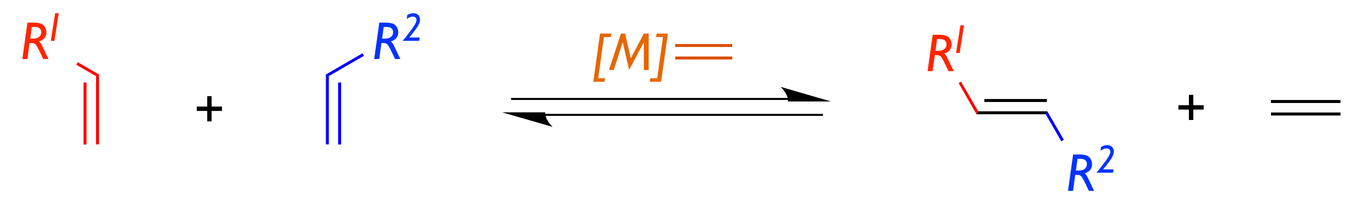
results in the formation

of the thermodynamically most favorable E product.

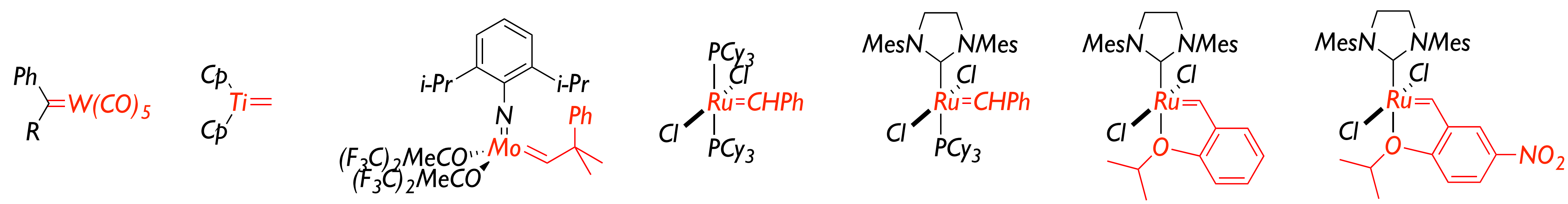


CURRENT CHALLENGE: KINETIC STEREOCONTROL

Fürstner, A, *Science* **2013**, *341*, 1357
Fischmeister, C. *ChemCatChem* **2013**, *5*, 3436
Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501



Ruthenium carbenes, [M]=, *the most common catalysts used in olefin methathesis so far*

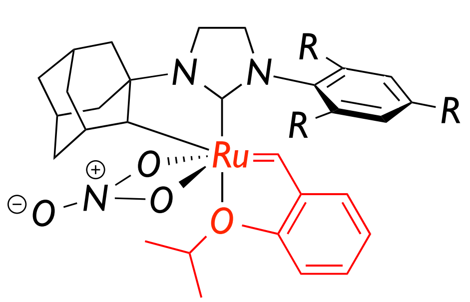


Katz 1976 Tebbe 1978 Schrock 1990 Grubbs I 1995 Grubbs II 1999 Hoveyda 2000 Grela 2002

Nicolaou, K. C. *Classics in Total Synthesis II*. p. 162

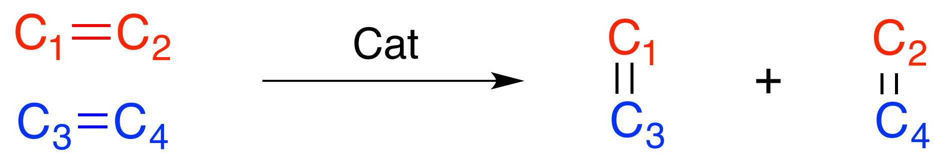
For an account of different ruthenium catalysts, Grela, K. *ASC* **2013**, *355*, 1997

For a perspective on Olefin Metathesis, Hoveyda, A. H. *JOC* **2014**, *79*, 4763

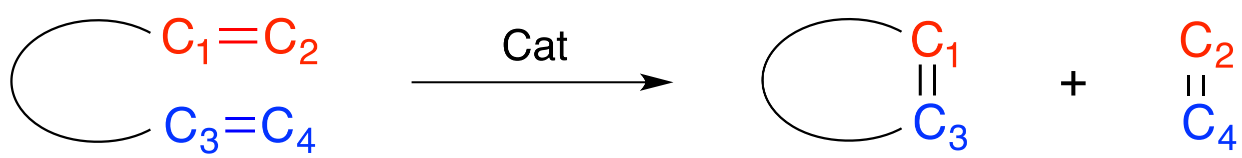


More complex ruthenium based complexes are being developed to achieve high Z stereoselectivity

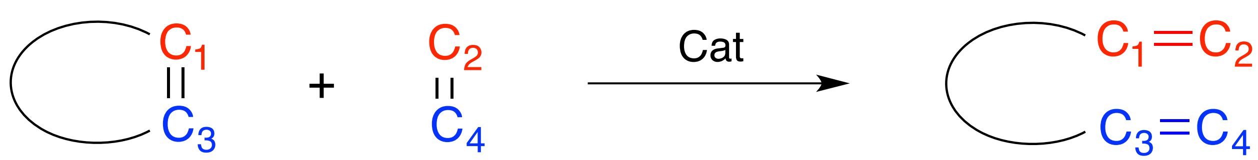
***Metathesis** is widely considered as one of the most powerful synthetic tools in organic synthesis*



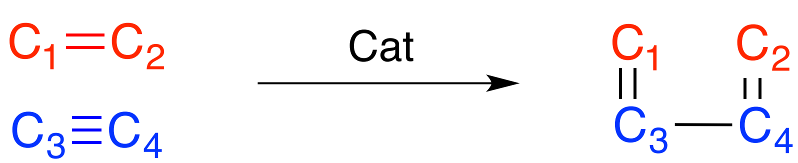
Cross Metathesis



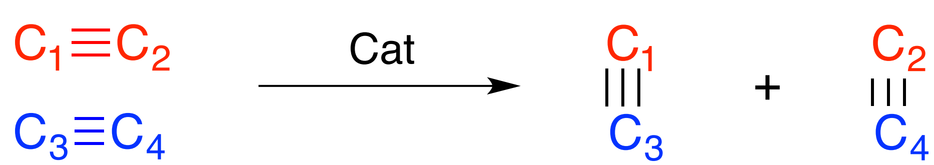
Ring-Closing Metathesis (RCM)



Ring-Opening Metathesis



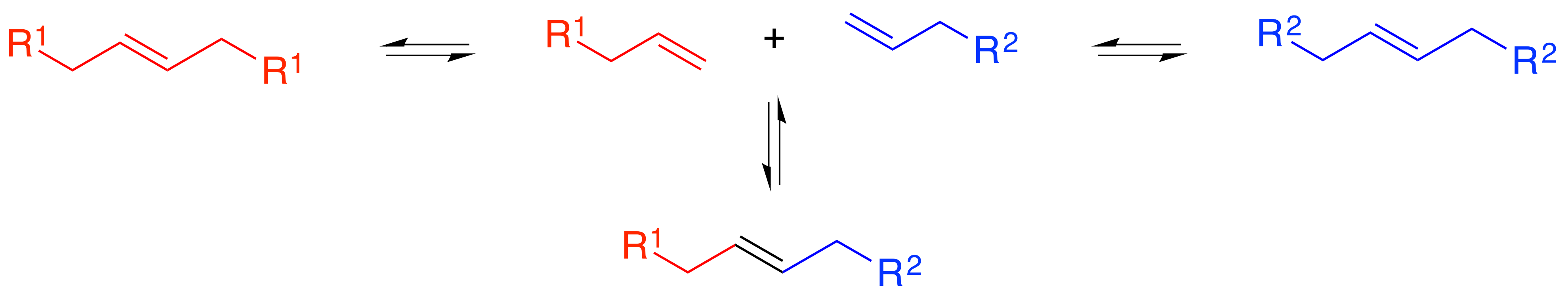
Enyne Metathesis

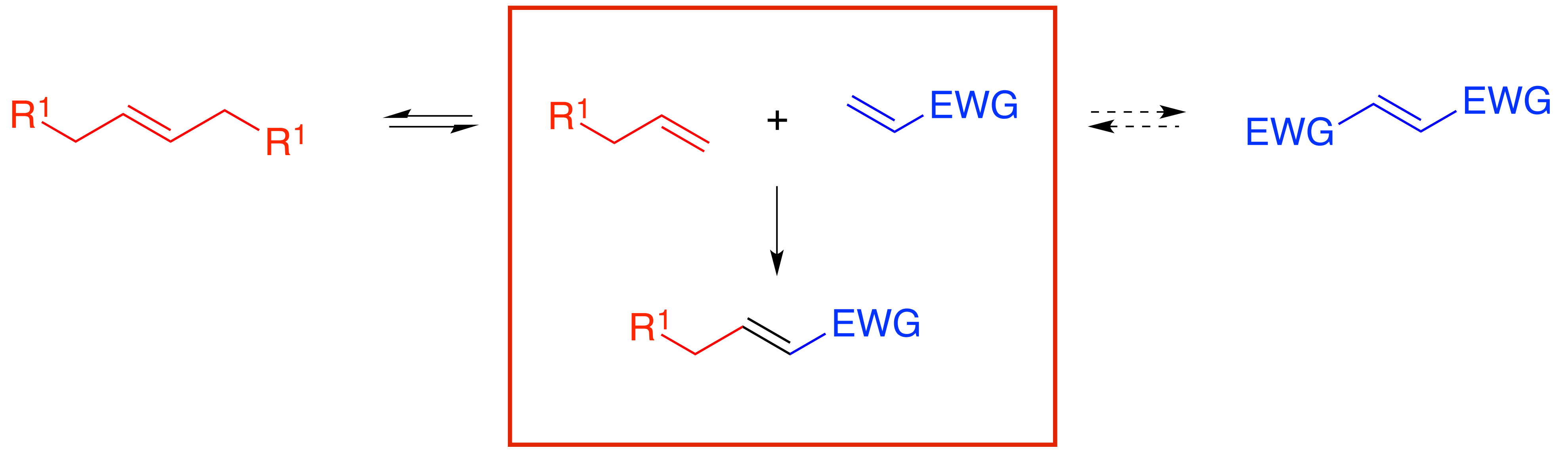


Alkyne Metathesis

Nicolaou, K. C. *Classics in Total Synthesis II*. p. 162
Blechert, S. *ACIE* **2003**, *42*, 1900; Nicolaou, K. C. **2005**, *44*, 4490
Schrodi, Y. & Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45
Hoveyda, A. H. *Nature* **2007**, *450*, 243; Mori, M. *ASC* **2007**, *349*, 121
Grela, K. *CR* **2009**, *109*, 3708; Fürstner, A. *CC* **2011**, *47*, 6505; Fürstner, A. *ACIE* **2013**, *52*, 2
Sarabia, F. *Synthesis* **2018**, *50*, 3749

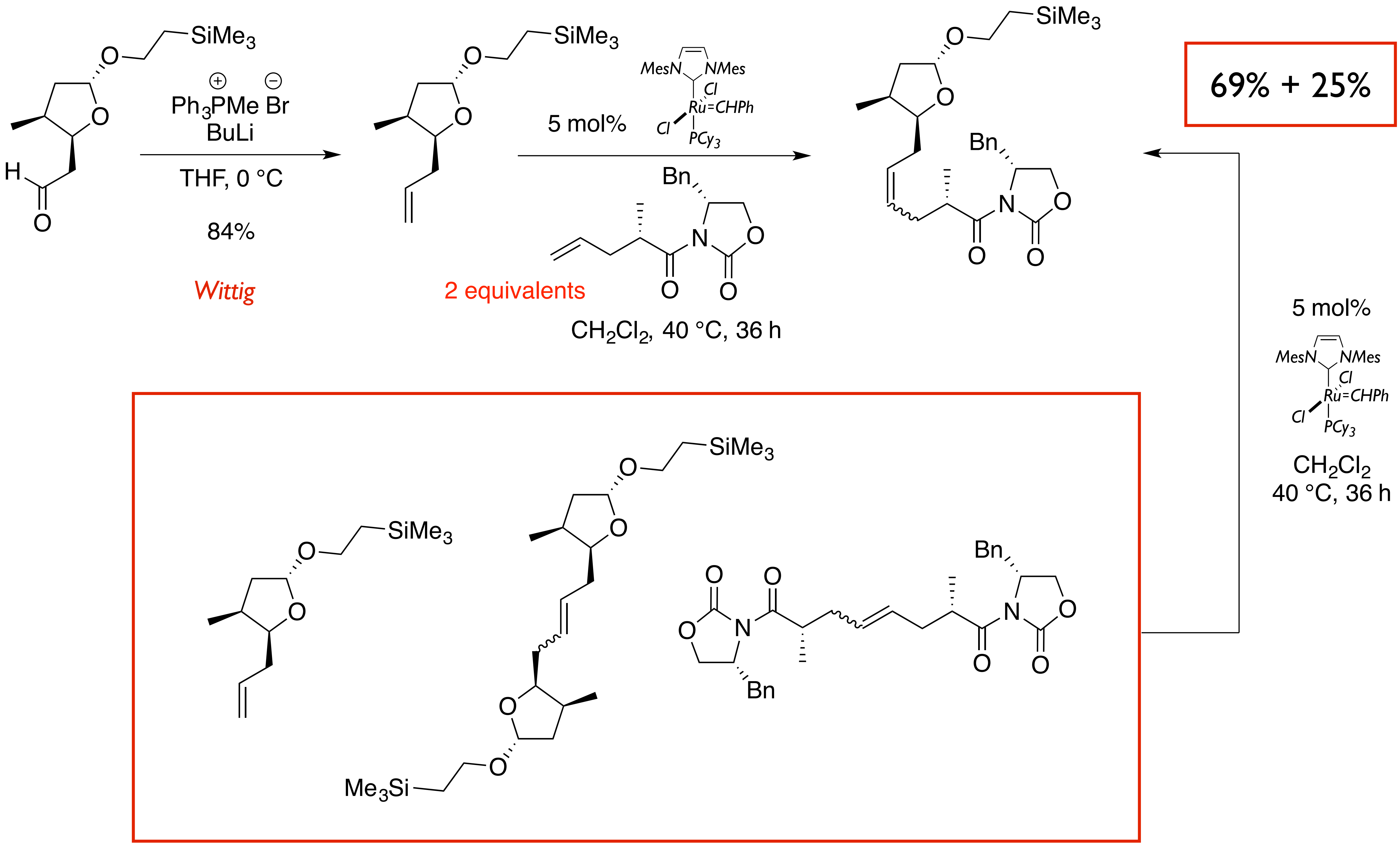
Cross Metathesis has to face non-selective couplings ...



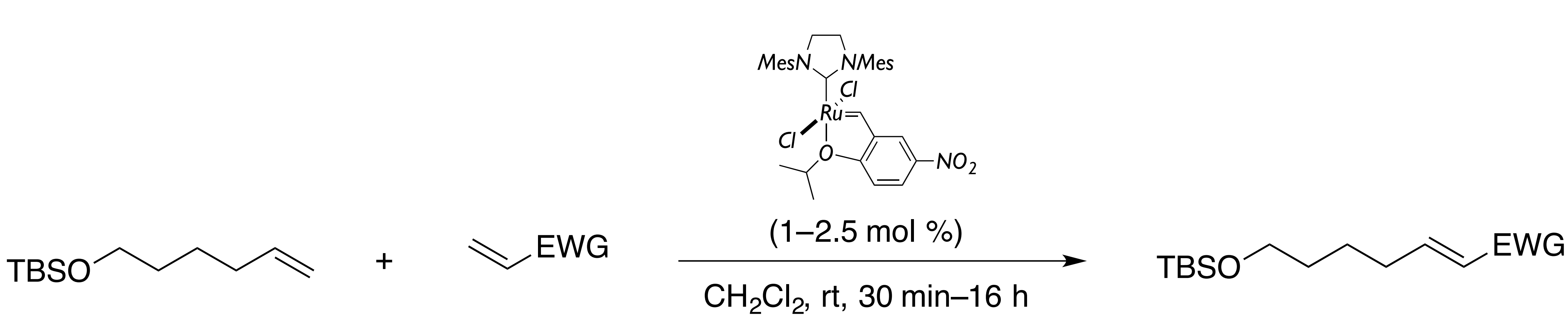


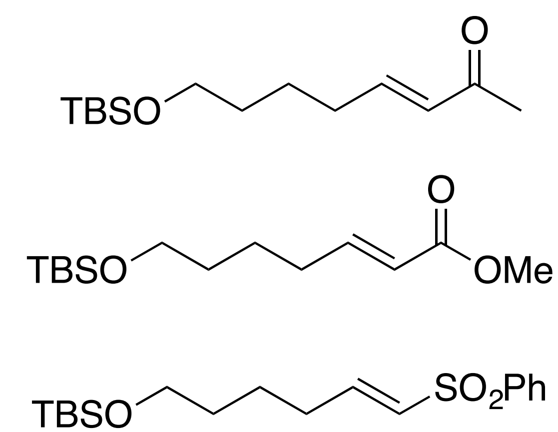
The geometry of the resultant olefin turns to be *E*,
the thermodynamically most stable isomer

Cross Metathesis



Ghosh, A. K. *JACS* **2003**, *125*, 2374



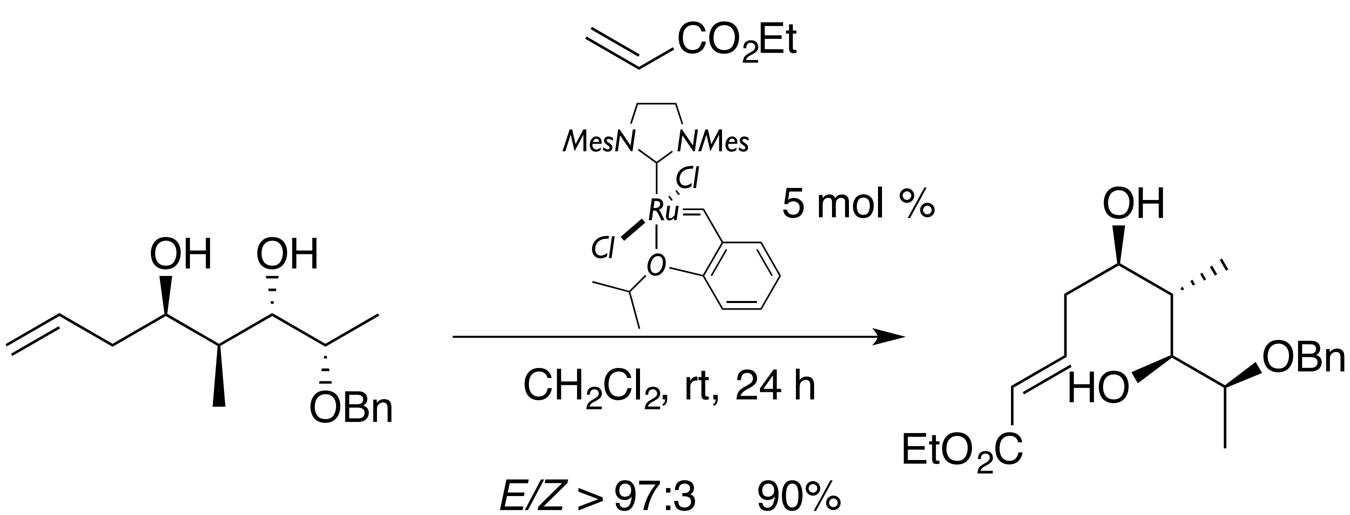


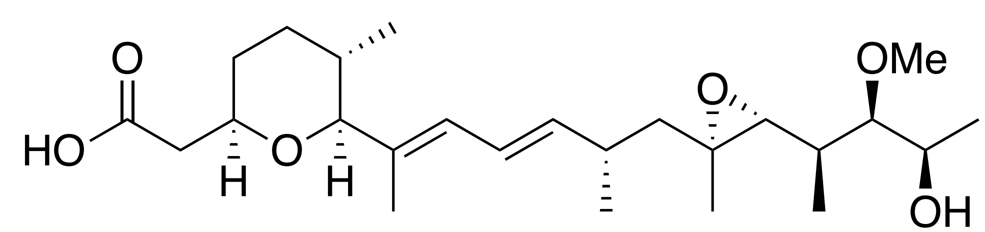
E/Z 99:1 82%

E/Z 95:5 95%

E only 90%

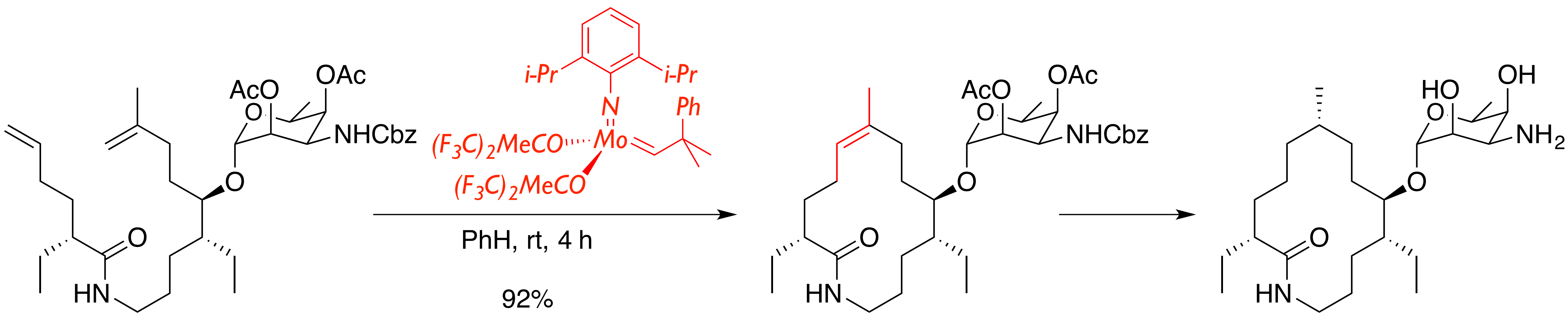
Grela, K. *ACIE* **2002**, *41*, 4038





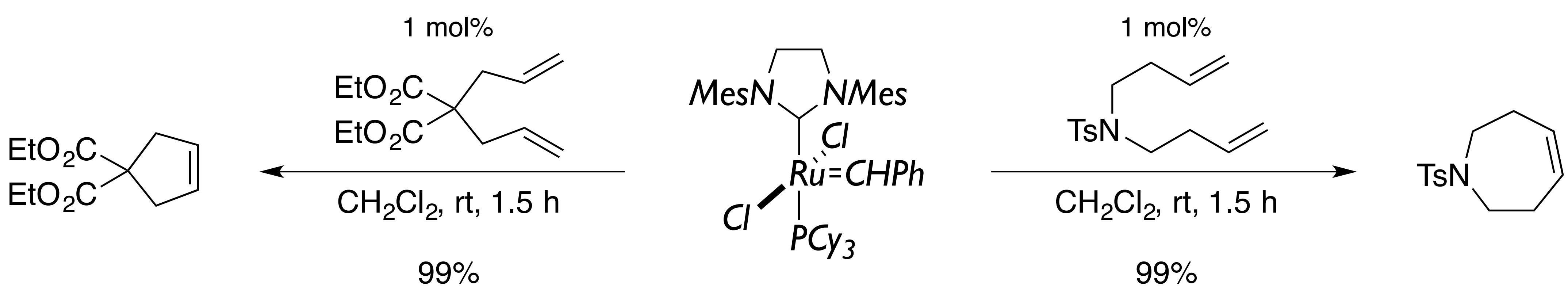
(+) Herboxidiene /GEX 1 A

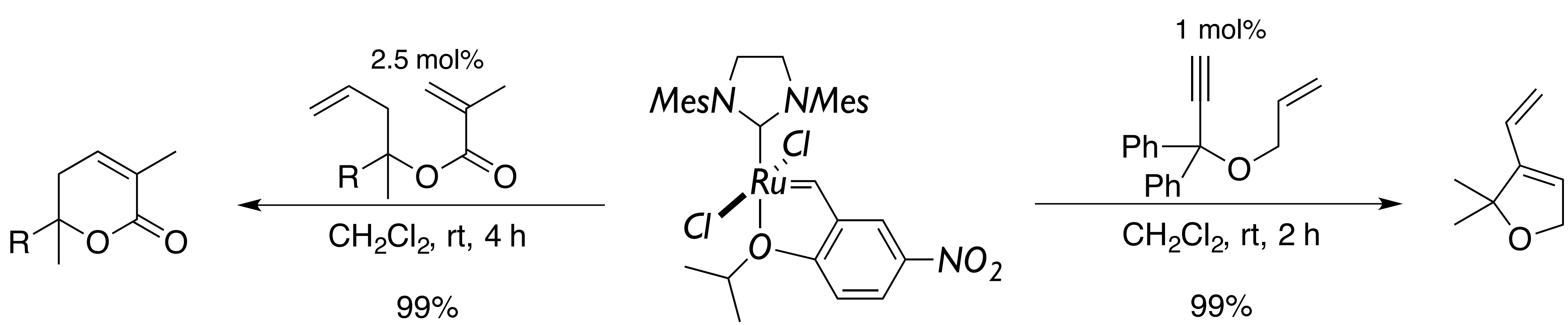
Romea, P. & Urpí, F. *OL* **2011**, *13*, 5350; *OBC* **2017**, *15*, 1842



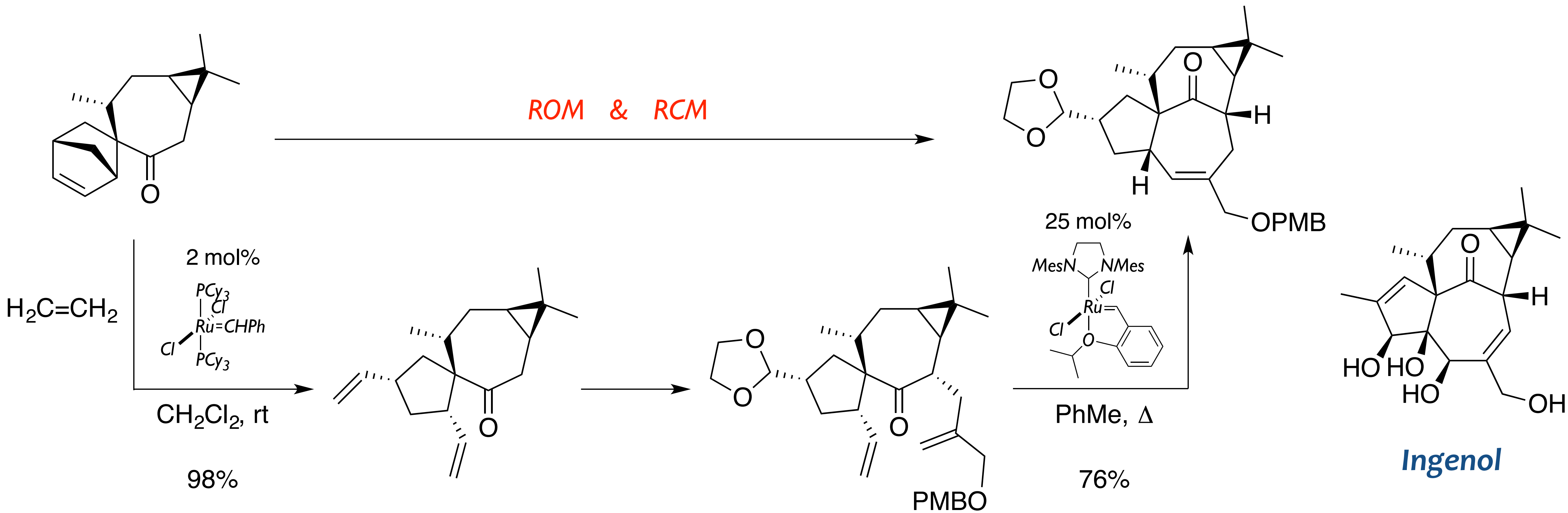
Hoveyda, A. H. *JACS* **1997**, *119*, 10302

Sch38516

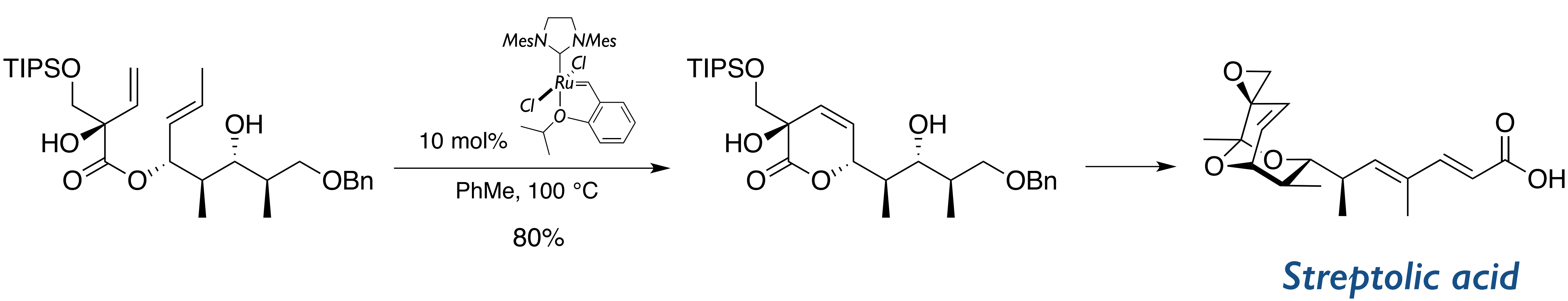




Ring-Closing Metathesis



Wood, J. L. *JACS* **2004**, *126*, 16300



Kozmin, S. *JACS* **2011**, *133*, 12172

For an insightful overview of the impact of RCM in the synthesis of pharmaceutical compounds see Yu M.; Lou, S.; Gonzalez-Bobes, F. *OPRD* **2018**, *22*, 918

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Review
Cite This: *Org. Process Res. Dev.* 2018, 22, 918–946
pubs.acs.org/OPRD

Ring-Closing Metathesis in Pharmaceutical Development: Fundamentals, Applications, and Future Directions

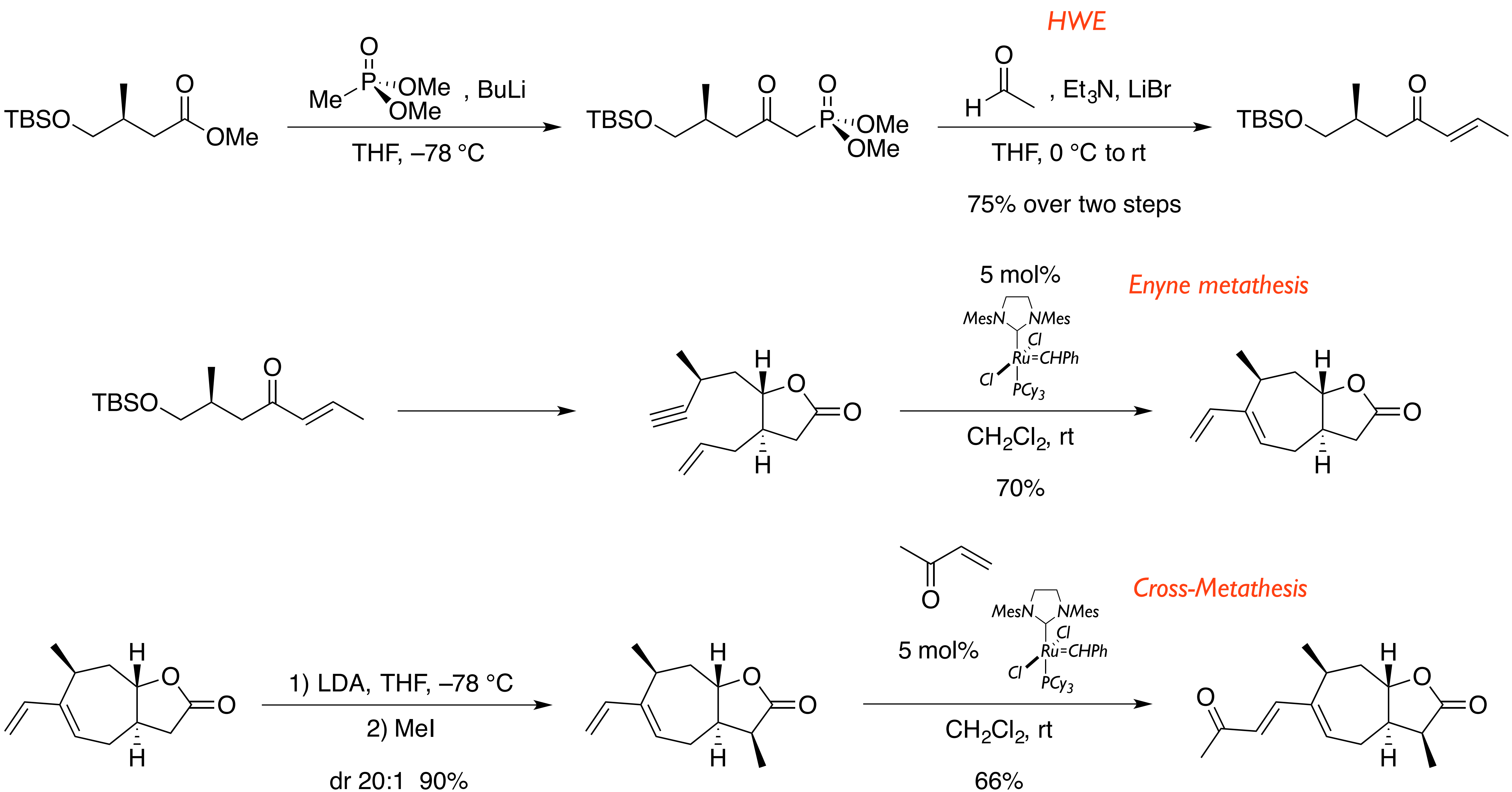
Miao Yu,* Sha Lou,* and Francisco Gonzalez-Bobes*

Chemical & Synthetic Development, Bristol-Myers Squibb Company, One Squibb Drive, New Brunswick, New Jersey 08903-0191, United States

ABSTRACT: Ring-closing metathesis (RCM) has become indispensable in organic synthesis for both academic investigations and industrial applications. This review provides an overview of RCM reactions, focusing on the practical aspects that researchers in an industrial environment may find of interest. Key elements of reaction design and lessons learned from these applications are discussed to help those considering implementing RCM reactions on scale, particularly in manufacturing active pharmaceutical ingredients (APIs). Advances in the development of more effective catalysts and new methodologies, such as enantioselective RCM and stereoselective macrocyclic RCM, are also briefly discussed.

KEYWORDS: *ring-closing metathesis, industrial application, process development, reaction scale-up, pharmaceutical manufacturing*

Total Synthesis of Dihydroxanthain: synthesis of C=C in action



Morken, J. P. *OL* **2005**, *7*, 3371

Cross Metathesis: E/Z Diastereoselectivity

Grubbs, R. H. *ACIE* **2015**, 54, 5018

Angewandte Minireviews R. H. Grubbs and M. B. Herbert

Olefin Cross Metathesis

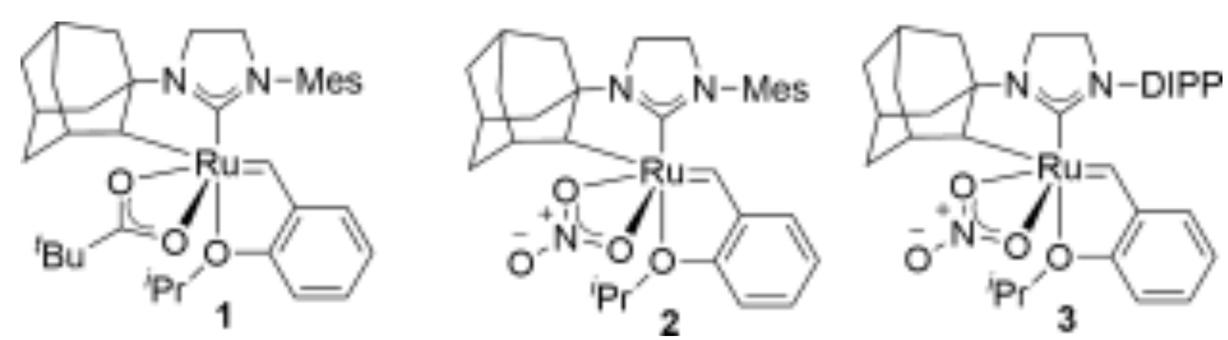
International Edition: DOI: 10.1002/anie.201411588
German Edition: DOI: 10.1002/ange.201411588

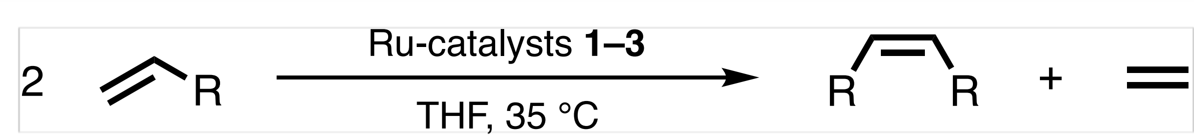
Z-Selective Cross Metathesis with Ruthenium Catalysts: Synthetic Applications and Mechanistic Implications

*Myles B. Herbert and Robert H. Grubbs**

cross metathesis · natural products · olefin metathesis · Z-alkenes

Z-Selective olefin cross metathesis can be achieved by using a new generation of ruthenium catalysts





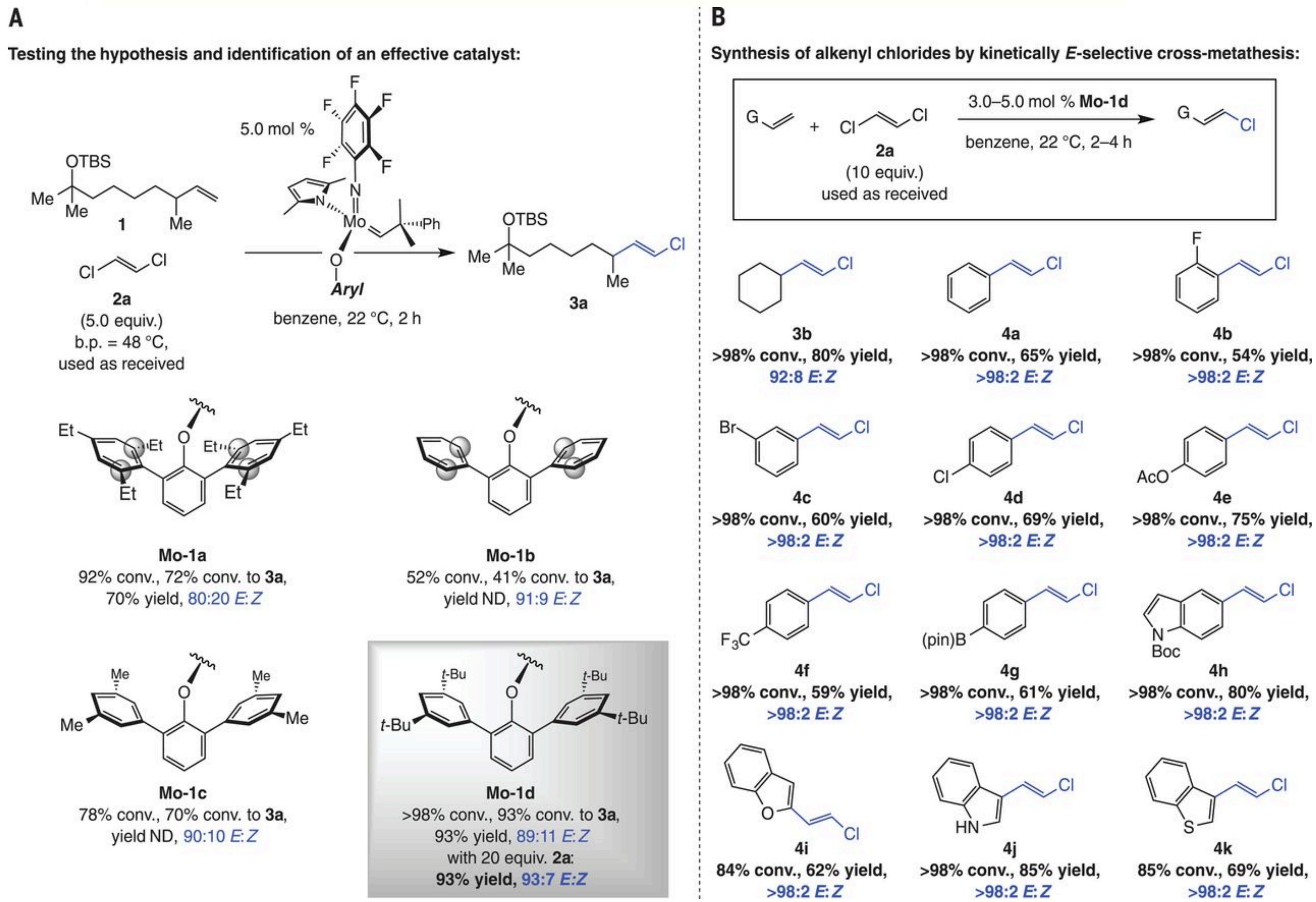
Cross Metathesis: E/Z Diastereoselectivity

Hoveyda, A. H. *Science* **2016**, *352*, 569

ORGANIC CHEMISTRY

Kinetically controlled *E*-selective catalytic olefin metathesis

Thach T. Nguyen,[1] Ming Joo Koh,[1] Xiao Shen,[1] Filippo Romiti,[1] Richard R. Schrock,[2] Amir H. Hoveyda[1]*



Thermodynamically disfavoured alkyl chlorides can also be prepared through cross metathesis

Cross Metathesis: E/Z Diastereoselectivity

Grubbs, R. H. *ACIE* **2017**, 56, 11024

GDCh **Minireviews** Angewandte Chemie International Edition

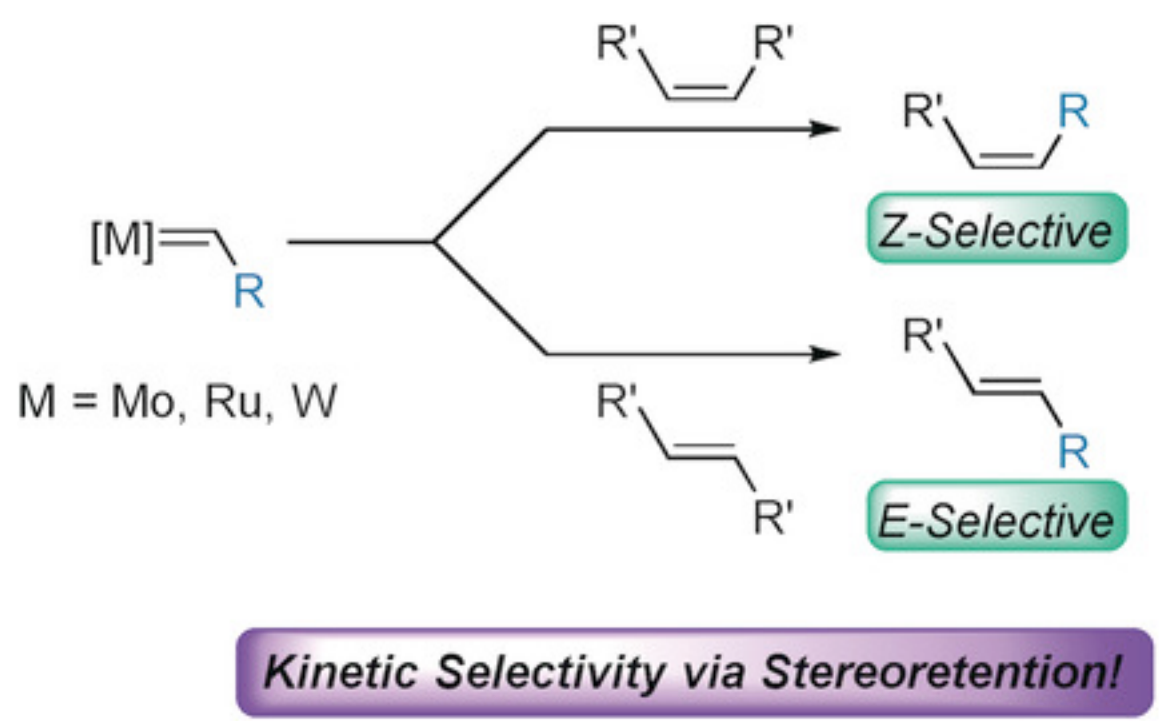
Olefin Metathesis

International Edition: DOI: 10.1002/anie.201704686
German Edition: DOI: 10.1002/ange.201704686

Stereoretentive Olefin Metathesis: An Avenue to Kinetic Selectivity

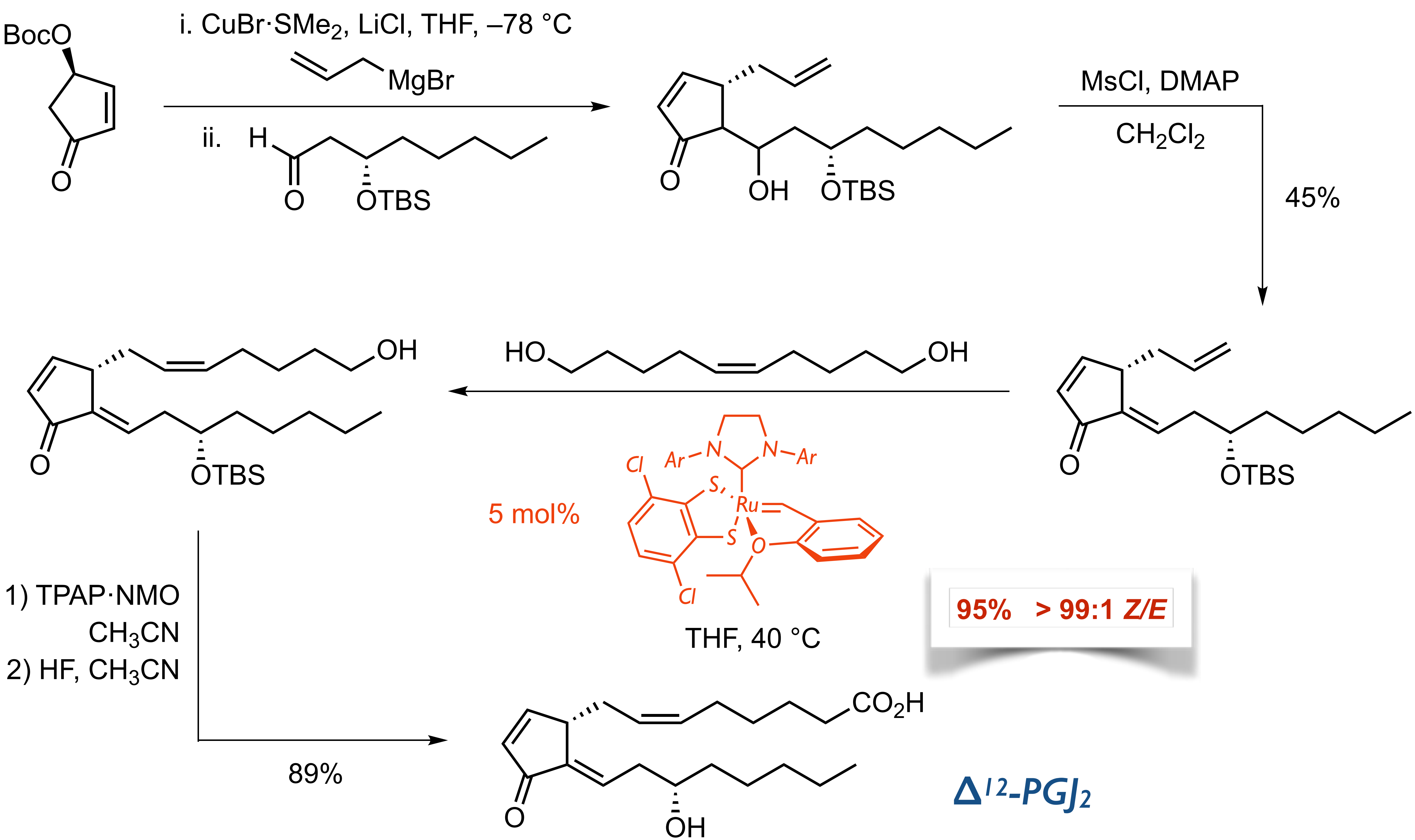
*T. Patrick Montgomery, Tonia S. Ahmed, and Robert H. Grubbs**

molybdenum · olefin metathesis · ruthenium · stereoretention · tungsten



Catalysts can nowadays provide
kinetically controlled *E* and *Z* olefin metathesis

Cross Metathesis: E/Z Diastereoselectivity

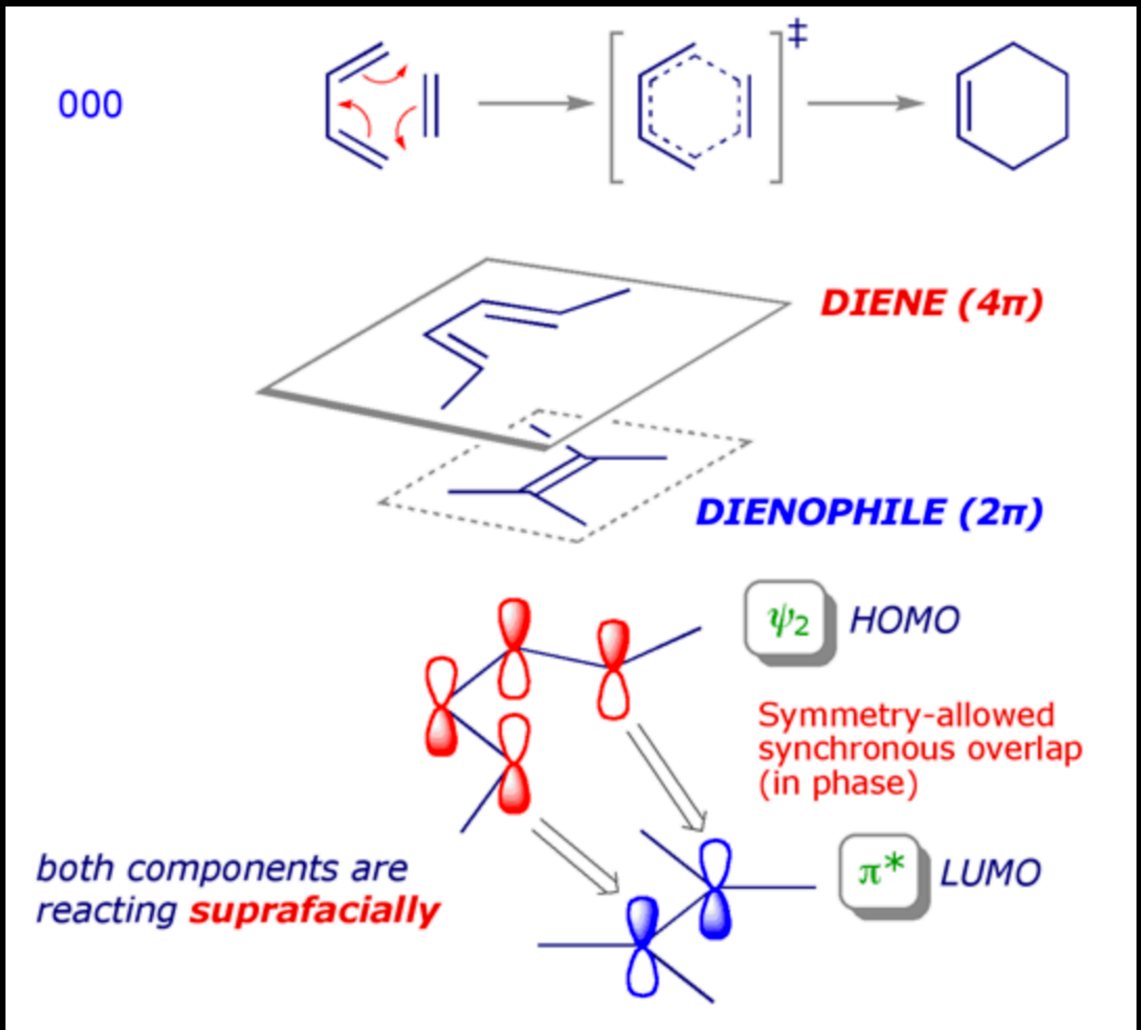


Δ[12]-PGJ$_2$

Xu, C., Stoltz, B. & Grubbs, R. H. *JACS* **2018**, *XXX*, *XXX*

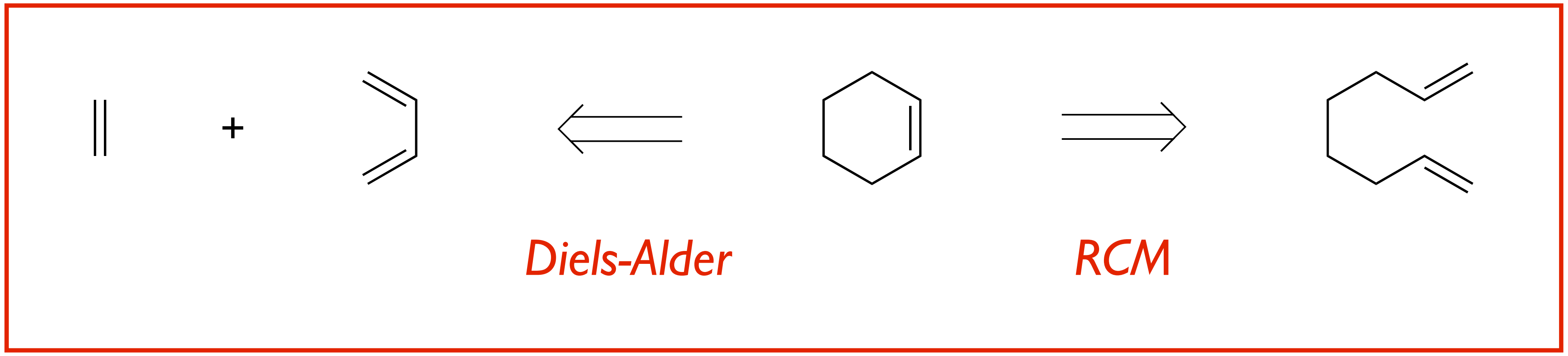
Diels-Alder

a key reaction beyond ionic analysis



See Chapter 6 & 7

Diels-Alder and **Ring-Closing Metathesis:** two approaches to cyclohexenes



+ 2 C–C & – 1 C=C	*0 C–C & 0 C=C*
(Catalytic) process	*Catalytic process*
Inter or intramolecular process	*Intramolecular process*
Reversible	*Reversible*
Up to four new stereocenters	*No new stereocenters*