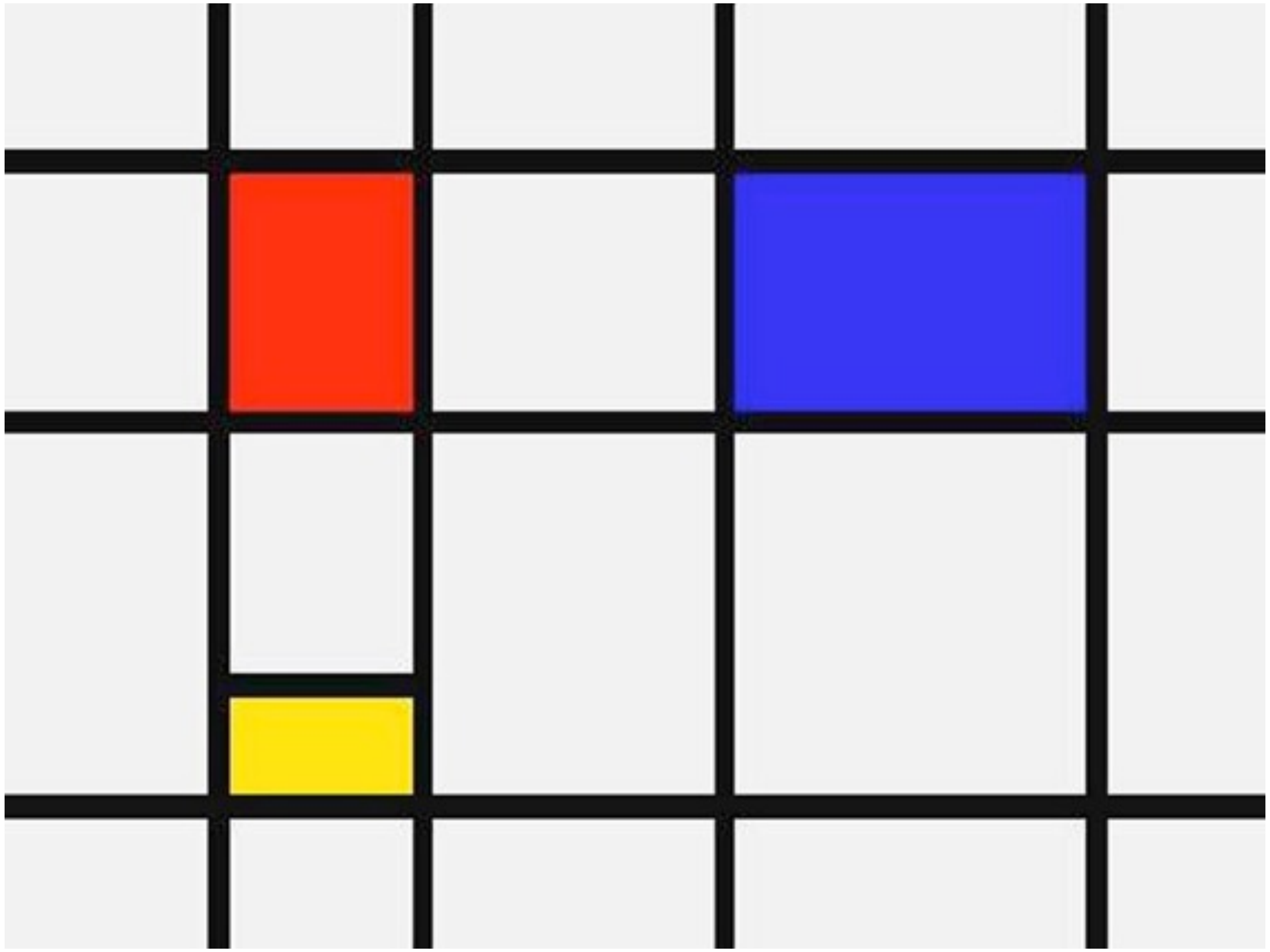


Piet Mondrian

Universitat de Barcelona

Dr. Pere Romea
Department of Organic Chemistry

3. Synthesis of C=C Bonds

Organic Synthesis 2014-2015 Autumn Term

Introduction: Strategies for the Synthesis of C=C

There are three main avenues for the synthesis of C=C bonds

1. Elimination of HX from halocompounds

2. Reactions of carbanions with aldehydes and ketones

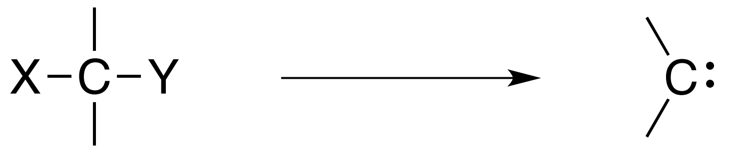
(Wittig & Julia-Kocienski Reactions)

3. Rearrangement of C=C bonds

(Metathesis)

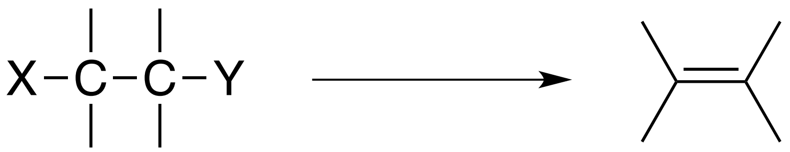
Concept of elimination ....

α–Elimination

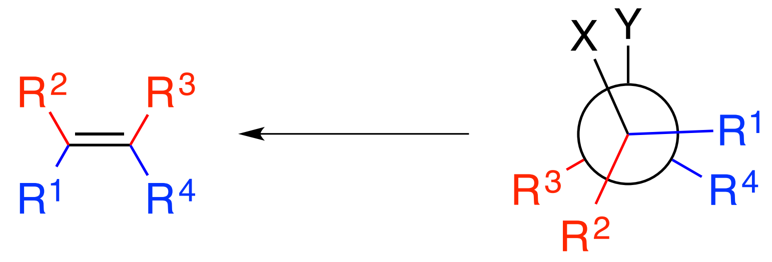


carbene

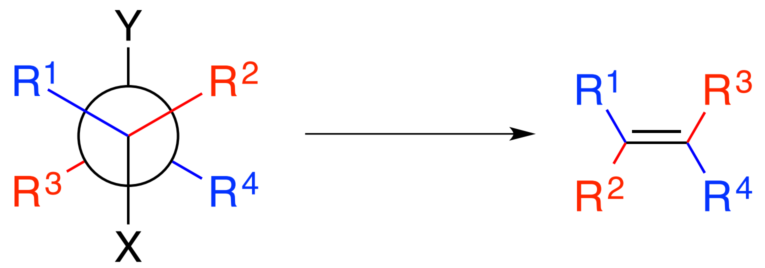
β–Elimination



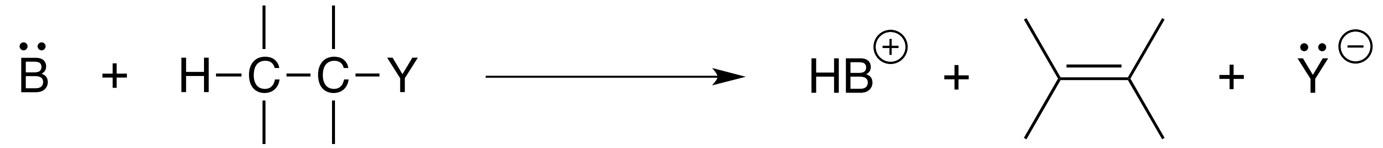
olefin



syn *elimination*



anti *elimination*



Base

RY

Leaving group

ß-Eliminations: Mechanisms

- *E1, unimolecular elimination*

  $v = k\,[RY]$

  The base has no influence

  Carbocations as intermediates

- *E2, bimolecular elimination*

  $v = k\,[RY]\,[B]$

  The base is crucial.

  Strong bases are usually required

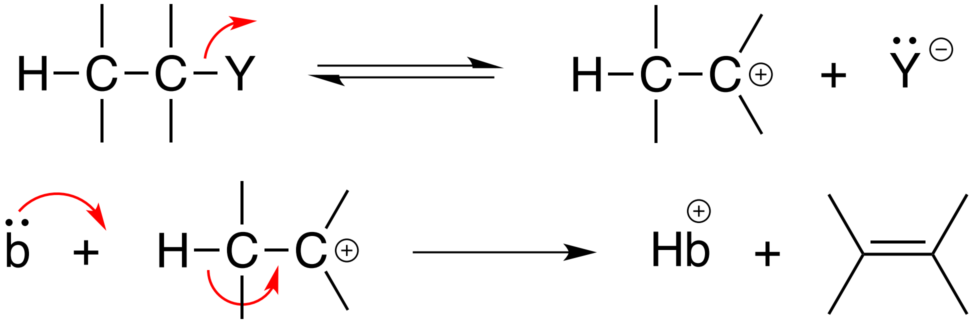
  No intermediates

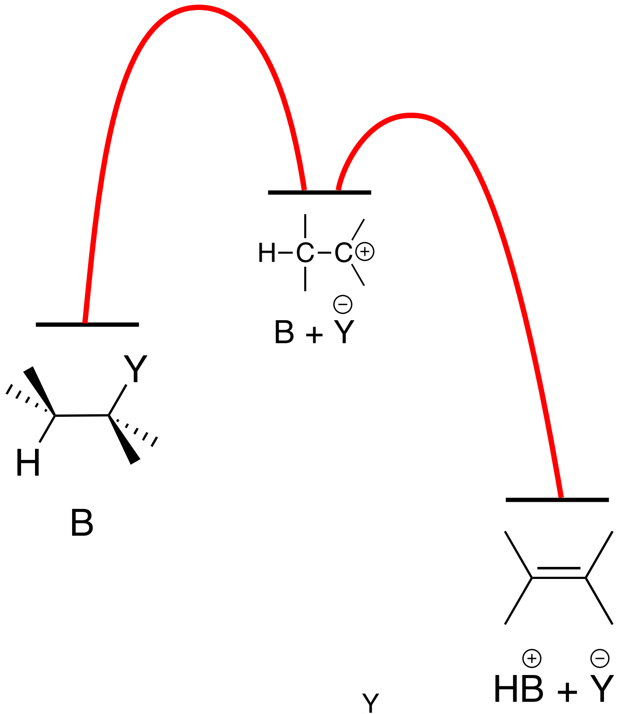
  Antiperiplanar stereochemistry

- *E1cB, from E1 conjugate Base*

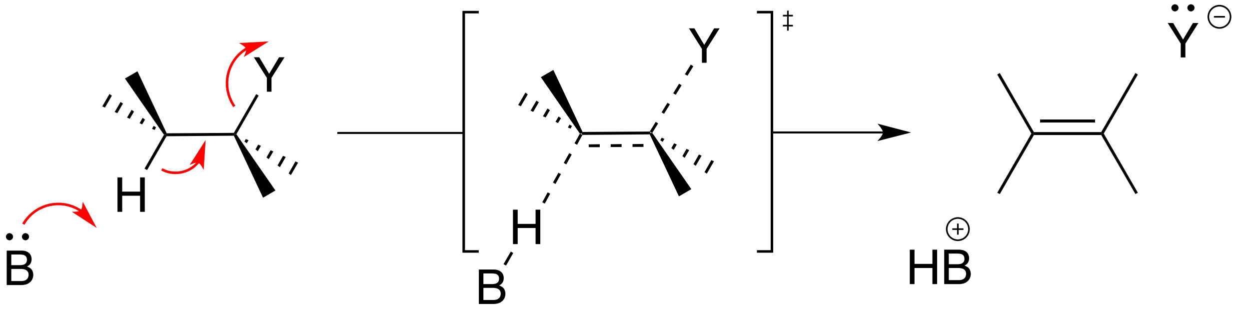
ß-Eliminations: Mechanisms

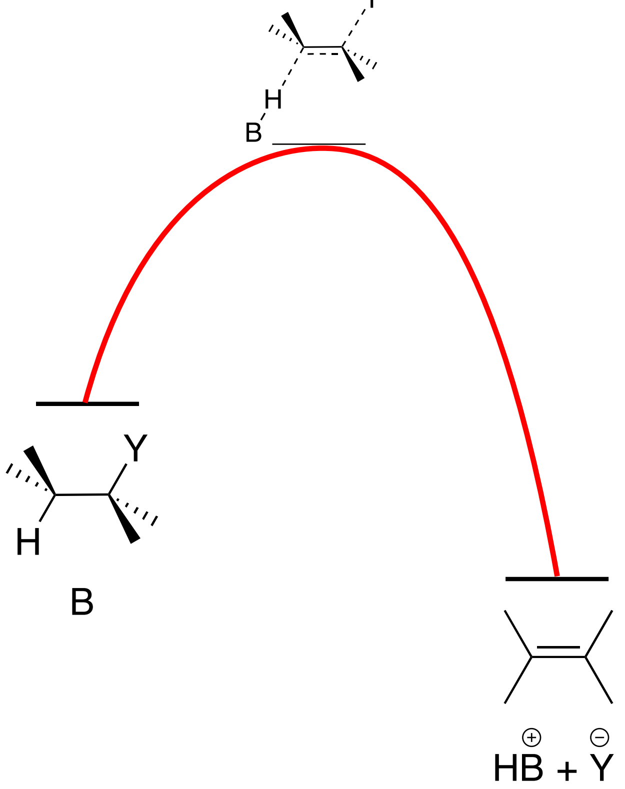
E1, unimolecular elimination: *step process*



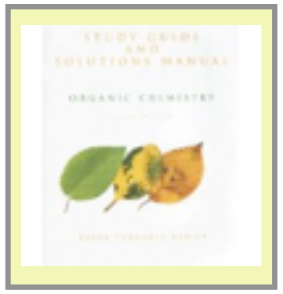


E2, bimolecular elimination: *concerted process*

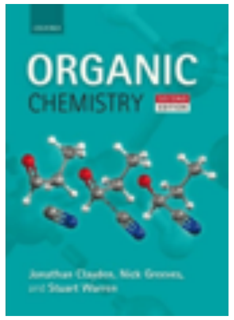




Química Orgànica I



Chap. 9



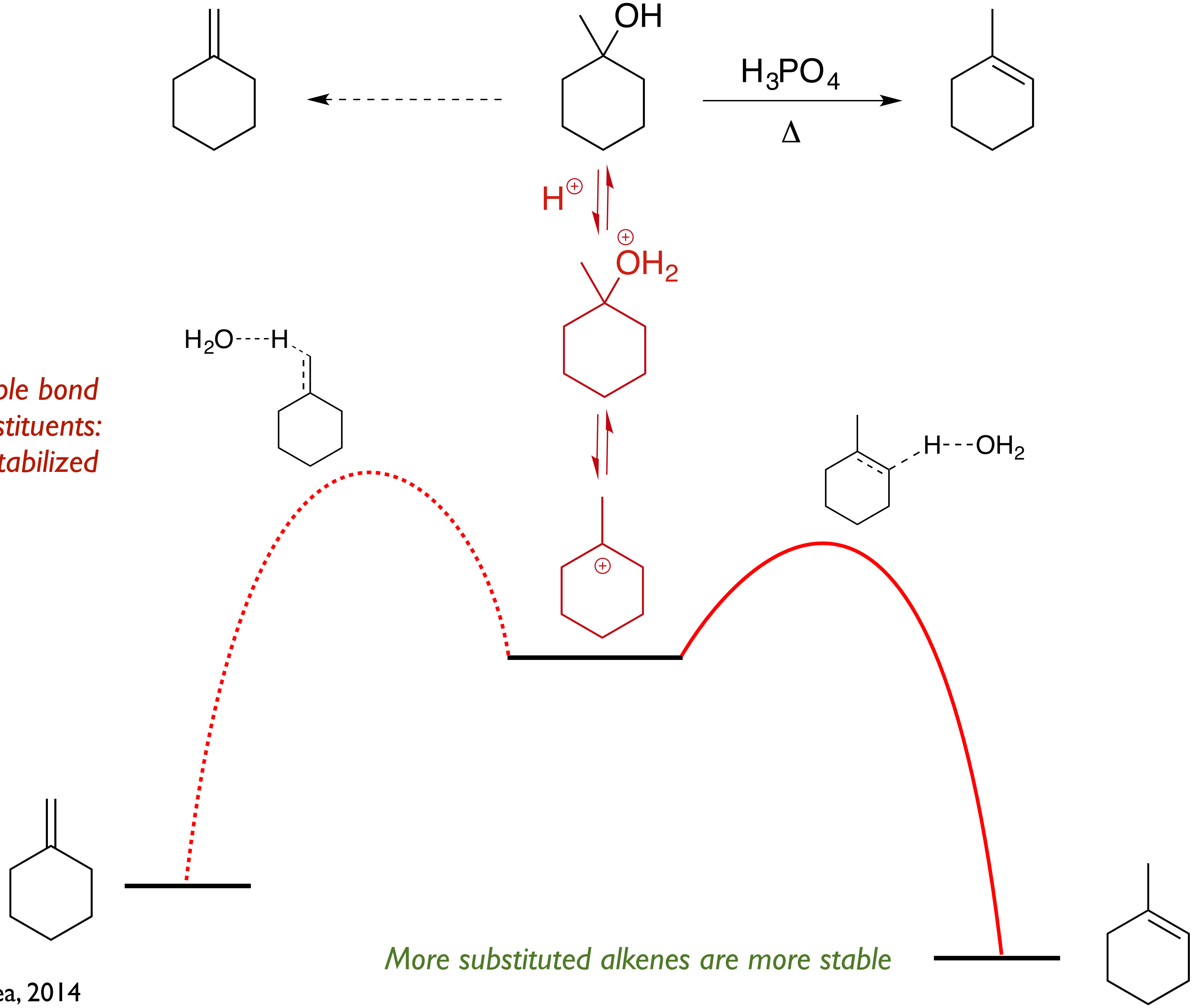
Chap. 17

For recent analyses on E2 eliminations

Gronett, S. *JOC* **2013**, *78*, 8606; Rablen, P. R. *JOC* **2014**, *79*, 867

ß-Eliminations: Regioselectivity

E1 Elimination reactions can be regioselective …

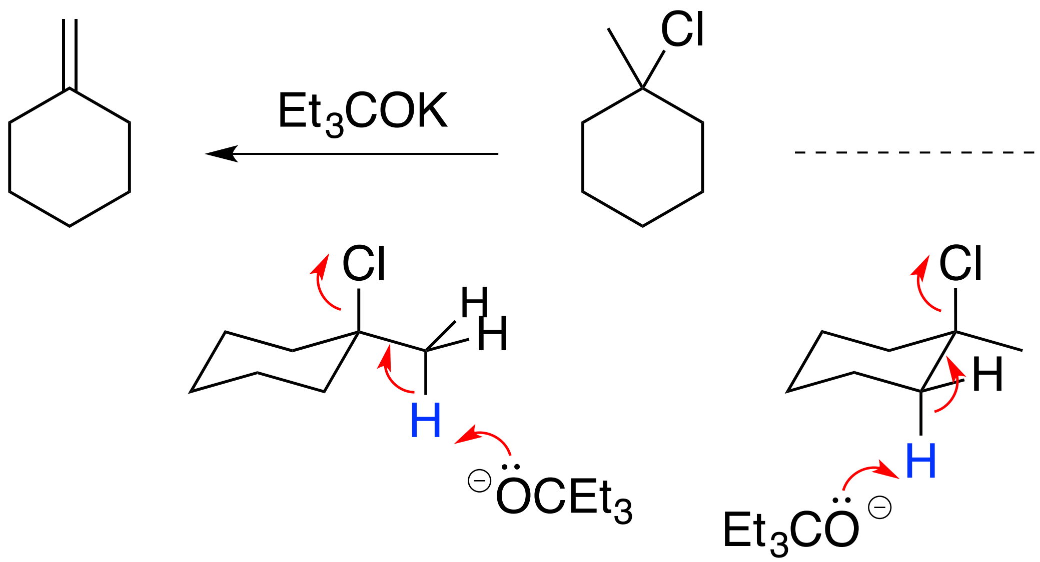


Partial double bond has two substituents: less stabilized

More substituted alkenes are more stable

ß-Eliminations: Regioselectivity

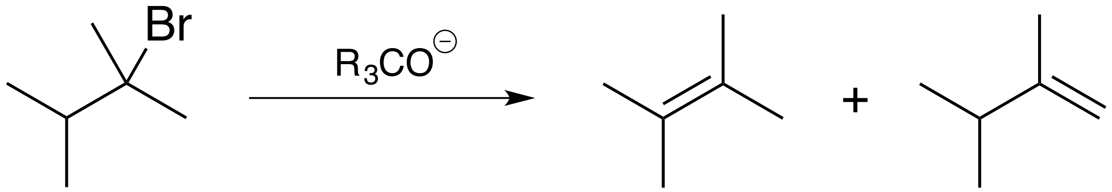
E2 Elimination reactions can be regioselective ...

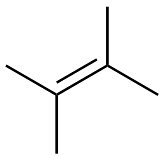
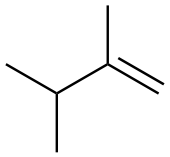


Ring hydrogens more hindered

... they can give the more substituted alkene,

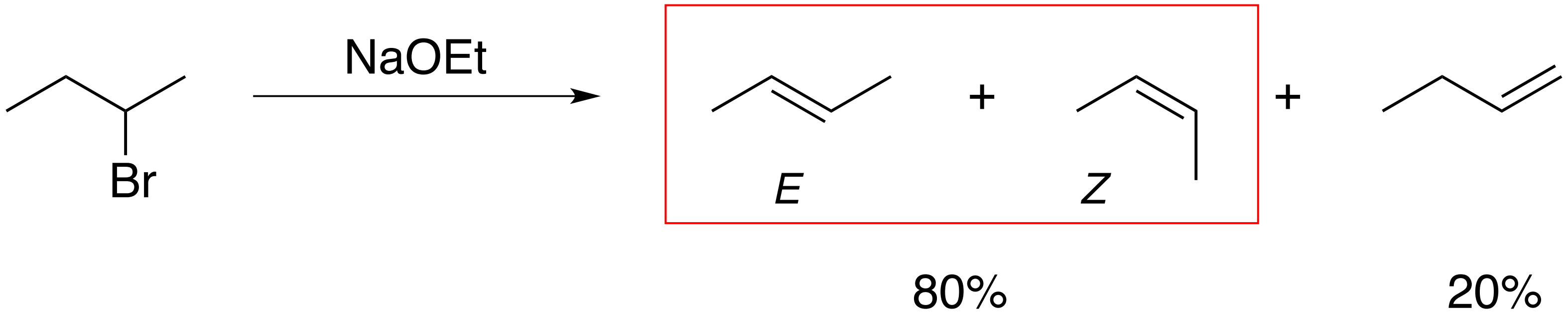
but become more regioselective for the less substituted alkene with more hindered bases



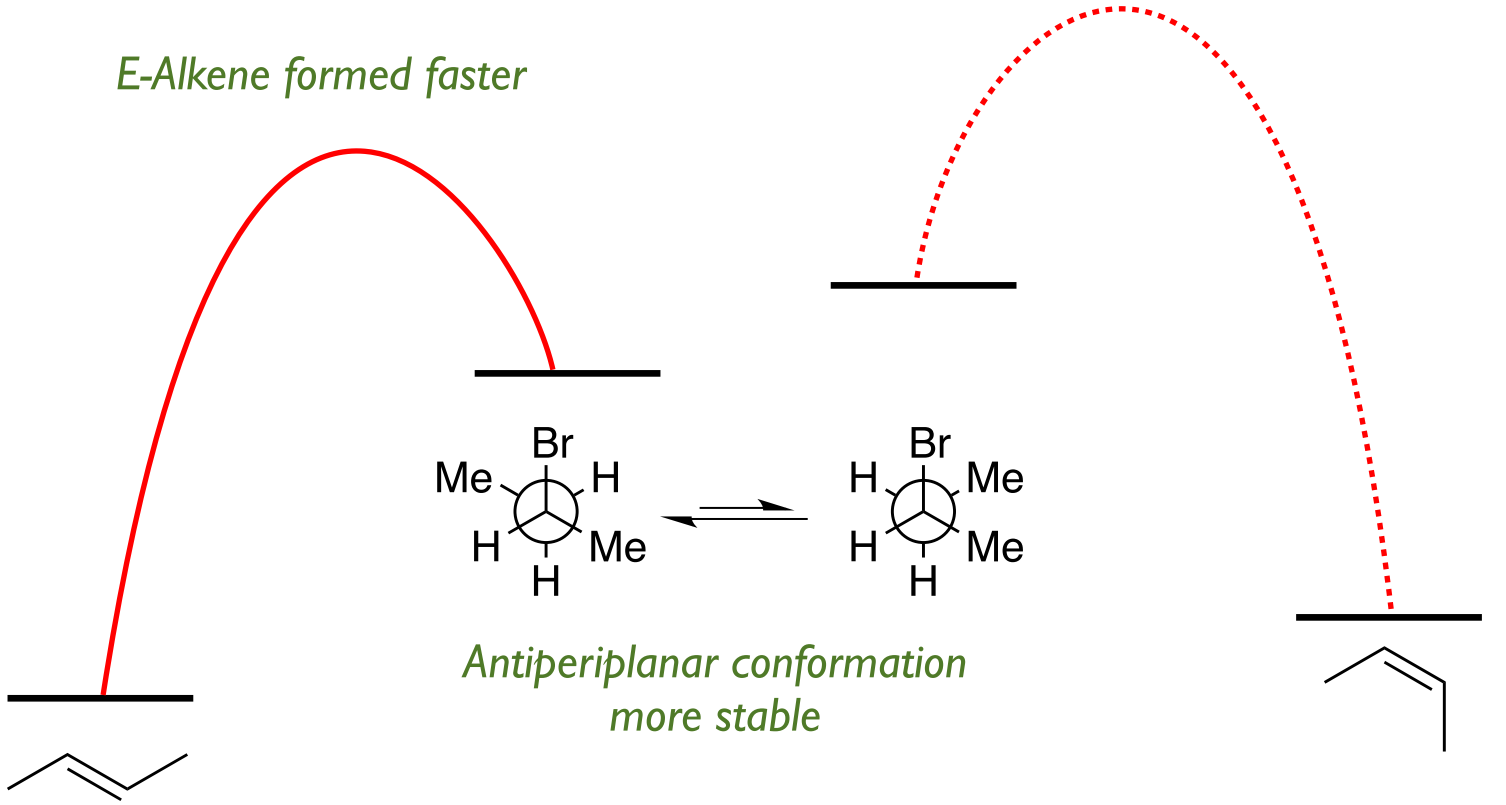
R$_3$CO$^{\ominus}$		
MeCH$_2$O$^{\ominus}$	79	21
Me$_3$CO$^{\ominus}$	27	73
Me$_2$EtCO$^{\ominus}$	19	81
Et$_3$CO$^{\ominus}$	8	92

ß-Eliminations: Stereoselectivity

The stereoselectivity (E vs Z) of elimination reactions relies on conformational grounds …



E-Alkene formed faster



E-Alkene more stable

Antiperiplanar conformation
more stable

E-2-Butene

Z-2-Butene

ß-Eliminations: Synthetic Challenges

Elimination reactions confront several challenges ...

- *Competing reactions? Remember Elimination/Substitution issue*
- *Regioselectivity: where is the double bond?*
- *Stereoselectivity: what is the geometry of the double bond?*

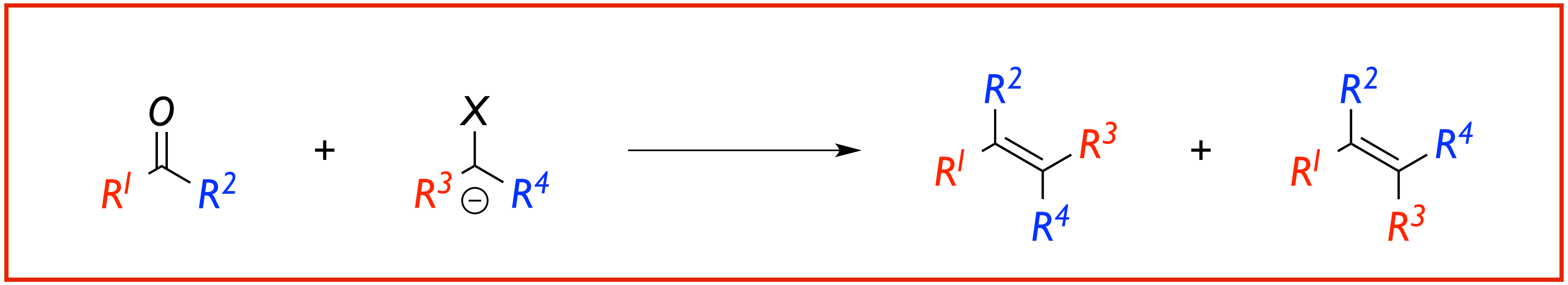
... the construction of C=C bonds requires other synthetic methodologies

Wittig and variants 🟥

Julia-Kocienski 🟥

Metathesis 🟩

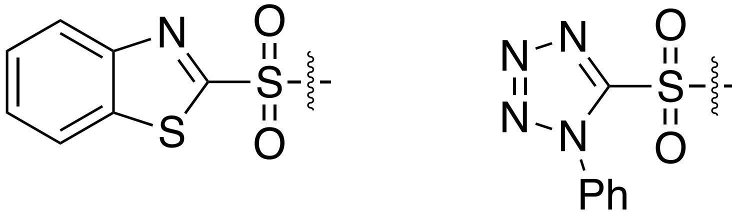
New C=C Forming Reactions: Carbanions and Carbonyls



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*



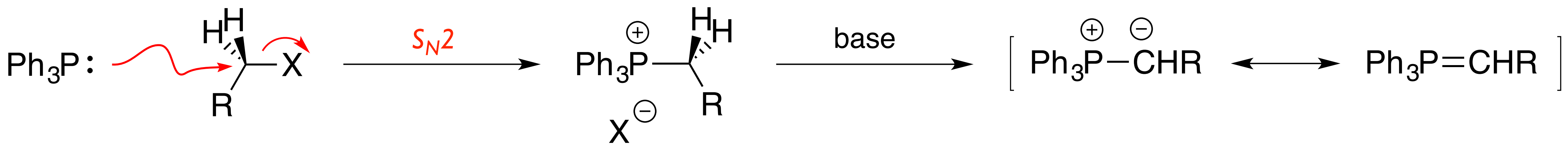
Georg Wittig
Nobel Prize in Chemistry 1979

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

Phosphorus Ylides: Carbon Nucleophiles

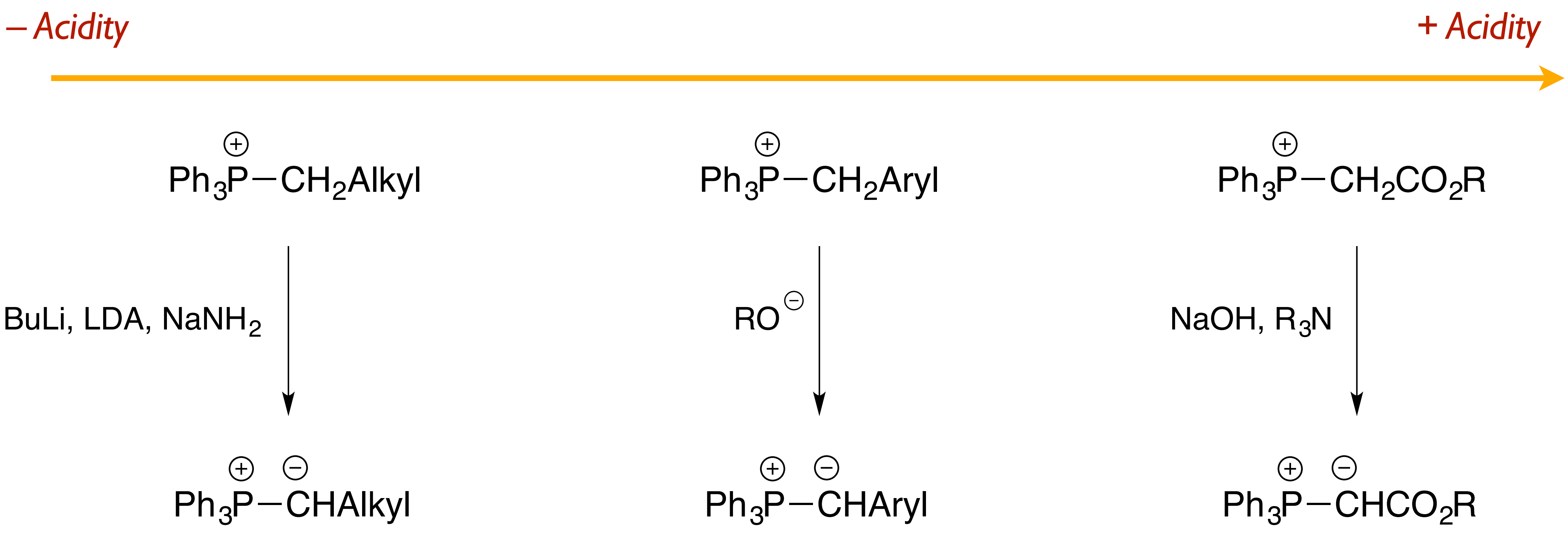
Ylide (ilur): *Compound in which an anionic site Y^- (originally on carbon, but now including other atoms) is attached directly to a heteroatom X^+ (usually nitrogen, phosphorus or sulfur) carrying a formal positive charge.*

Phosphorus ylides are prepared by deprotonation of phosphonium salts



Phosphonium salt

Ylide



– Acidity *+ Acidity*

$Ph_3\overset{\oplus}{P}-CH_2Alkyl \xrightarrow{\text{BuLi, LDA, NaNH}_2} Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}HAlkyl$

Non-stabilized ylide

$Ph_3\overset{\oplus}{P}-CH_2Aryl \xrightarrow{RO^{\ominus}} Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}HAryl$

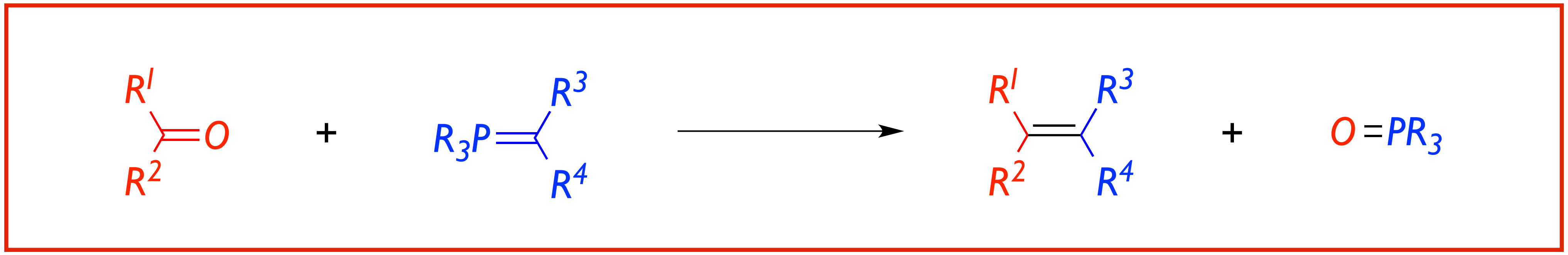
Semi-stabilized ylide

$Ph_3\overset{\oplus}{P}-CH_2CO_2R \xrightarrow{\text{NaOH, R}_3\text{N}} Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}HCO_2R$

Stabilized ylide

Wittig Reaction: Concept

- *Wittig reaction: addition of a phosphorus ylide to a carbonyl*

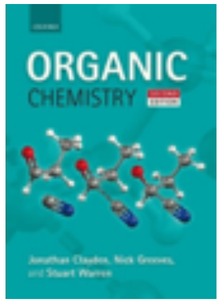


Phosphorus Ylide

Phosphine Oxide

Química Orgànica II

Chap. 17



Chap. 12, 26, and 27

Wittig Reaction: Stereoselectivity

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*

*The **E/Z selectivity** also depends on …*

*… the **R groups** (Ph_3P favor Z, $Alkyl_3P$ favor E),*

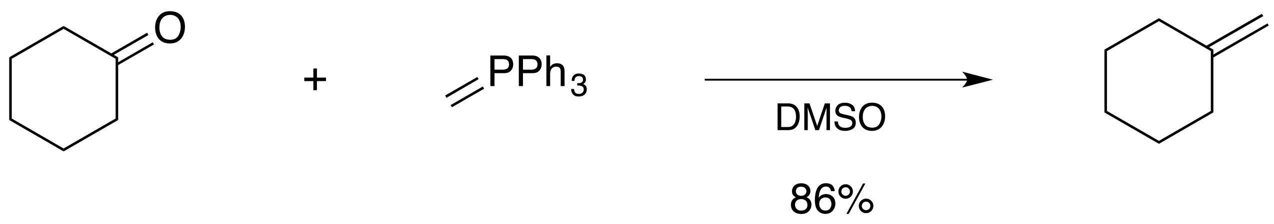
*presence of lithium salts (**salt free conditions** favor Z, LiX favor E)*

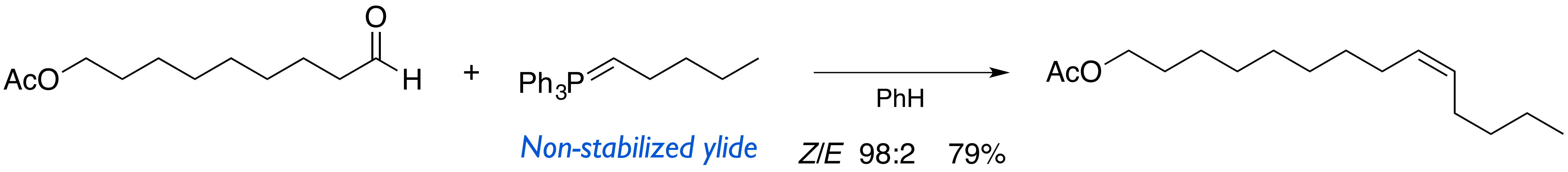
solvent

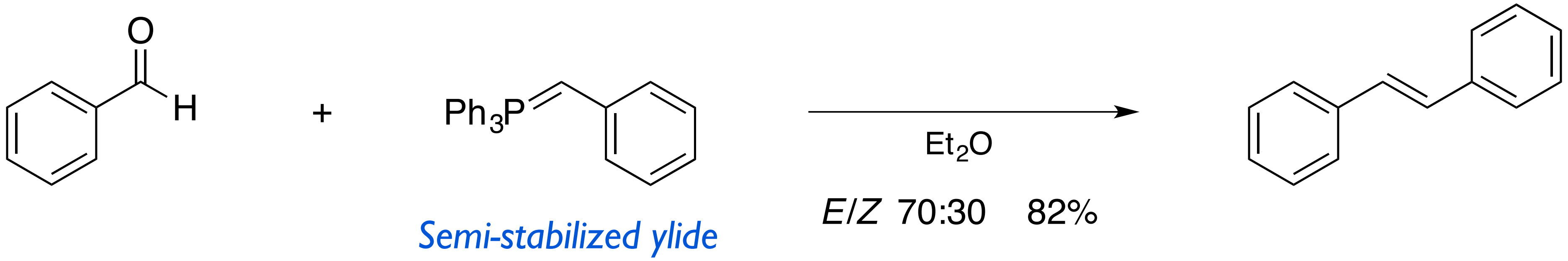
Maryanoff, B. E. *Chem. Rev.* **1989**, *89*, 863

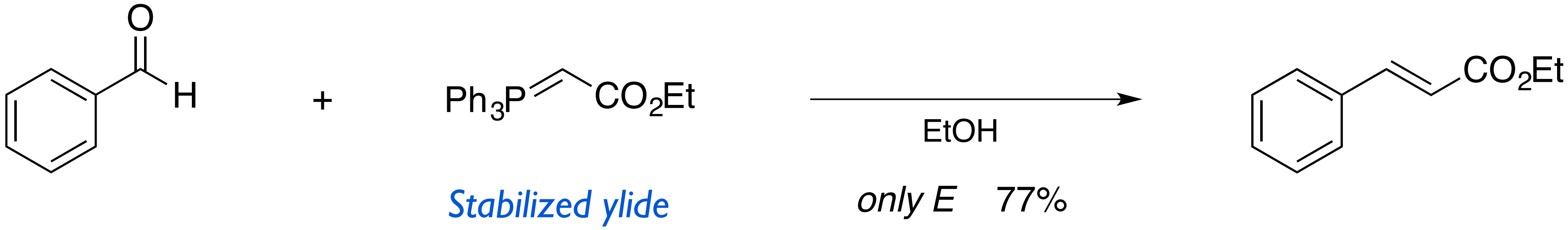
Nicolaou, K. C. *Liebigs Ann.* **1997**, *7*, 1283

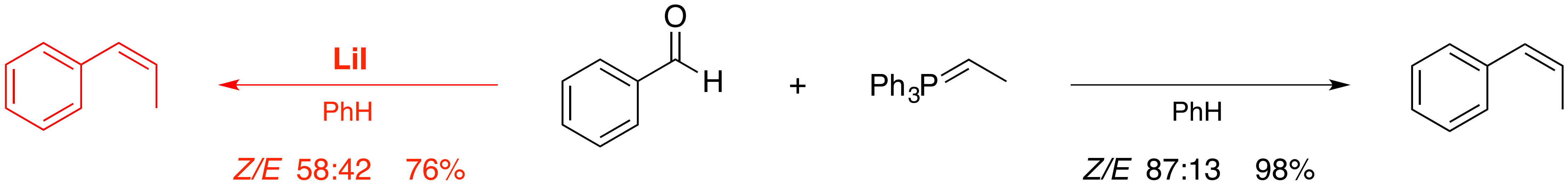
Wittig Reaction: Stereoselectivity







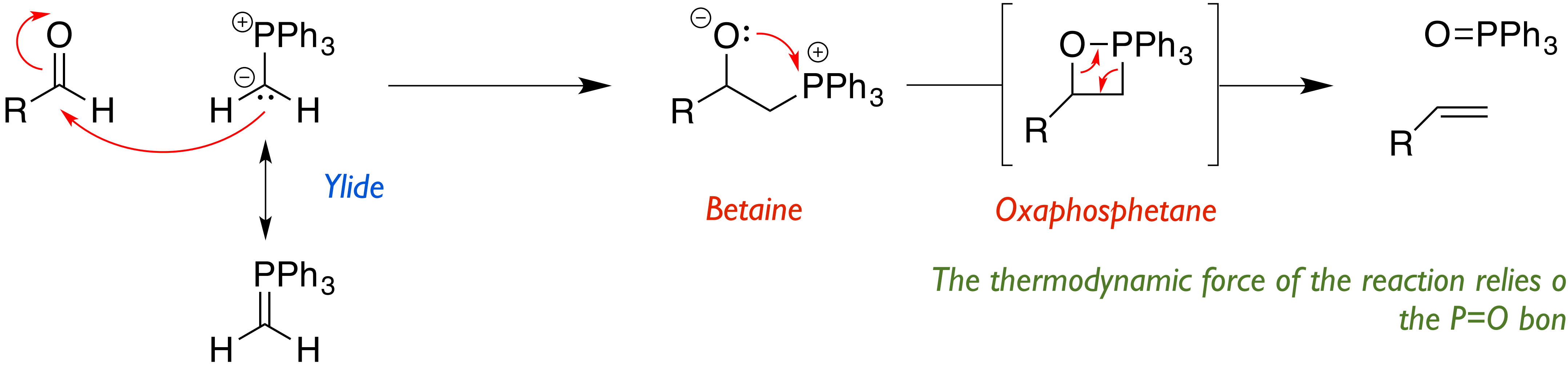




Wittig Reaction: Mechanism

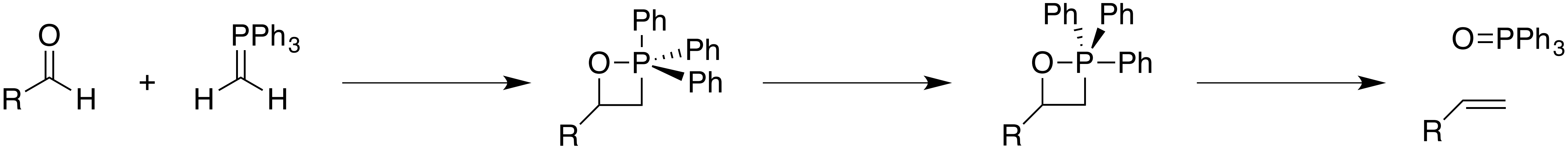
The mechanism of the Wittig reaction has been the subject of much debate.

Initially, Wittig described this reaction as an addition to a carbonyl...



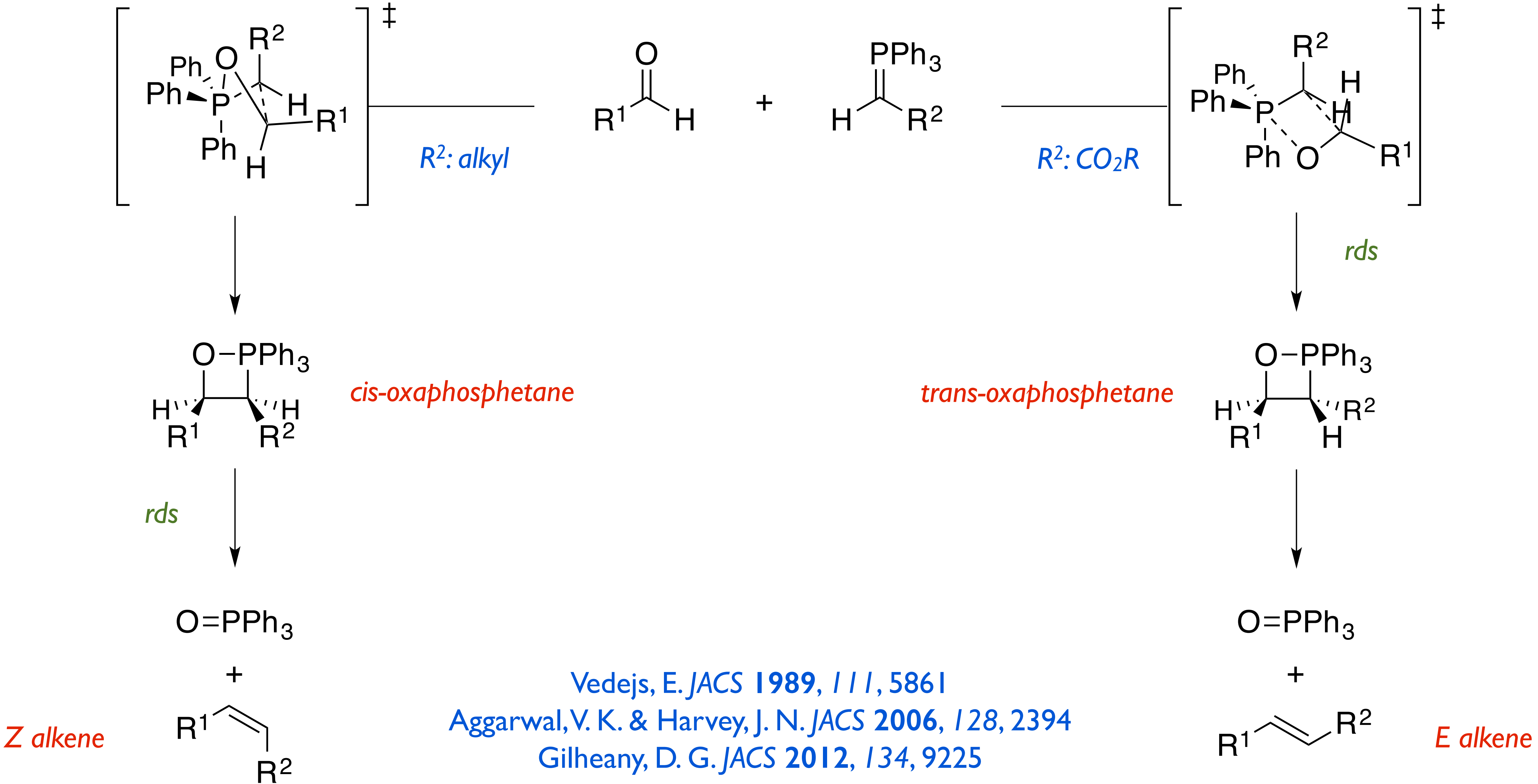
The thermodynamic force of the reaction relies on the P=O bond

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



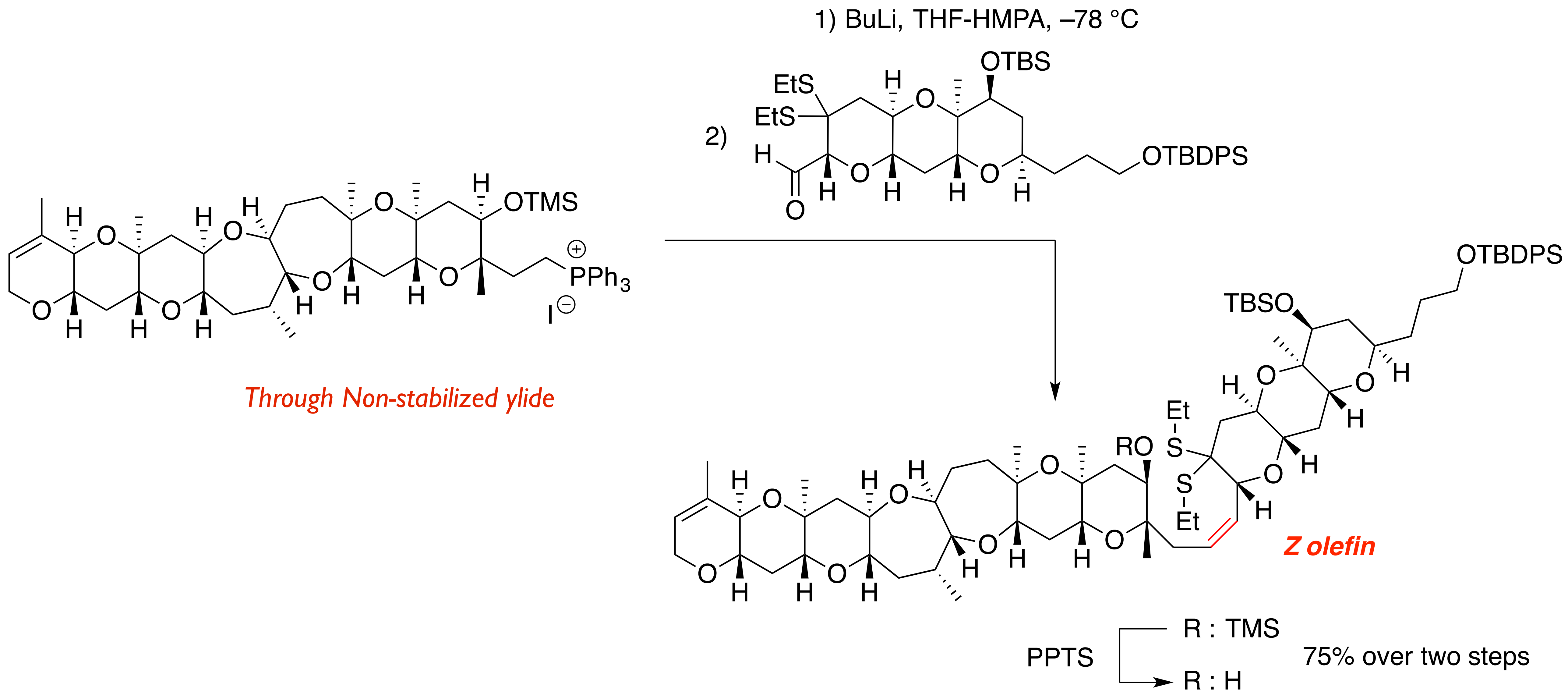
Wittig Reaction: Mechanism

Particularly,
*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. *Chem. Soc. Rev.* **2013**, *42*, 6670–6696

Wittig Reaction in Synthesis



1) BuLi, THF-HMPA, –78 °C

2)

Through Non-stabilized ylide

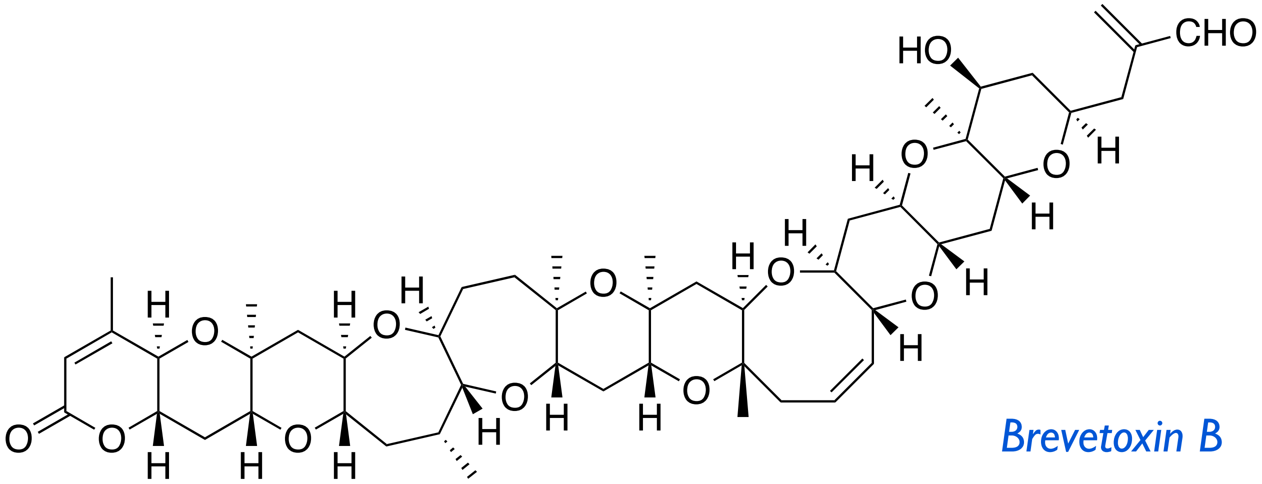
Z olefin

PPTS

R : TMS

R : H

75% over two steps



Brevetoxin B

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

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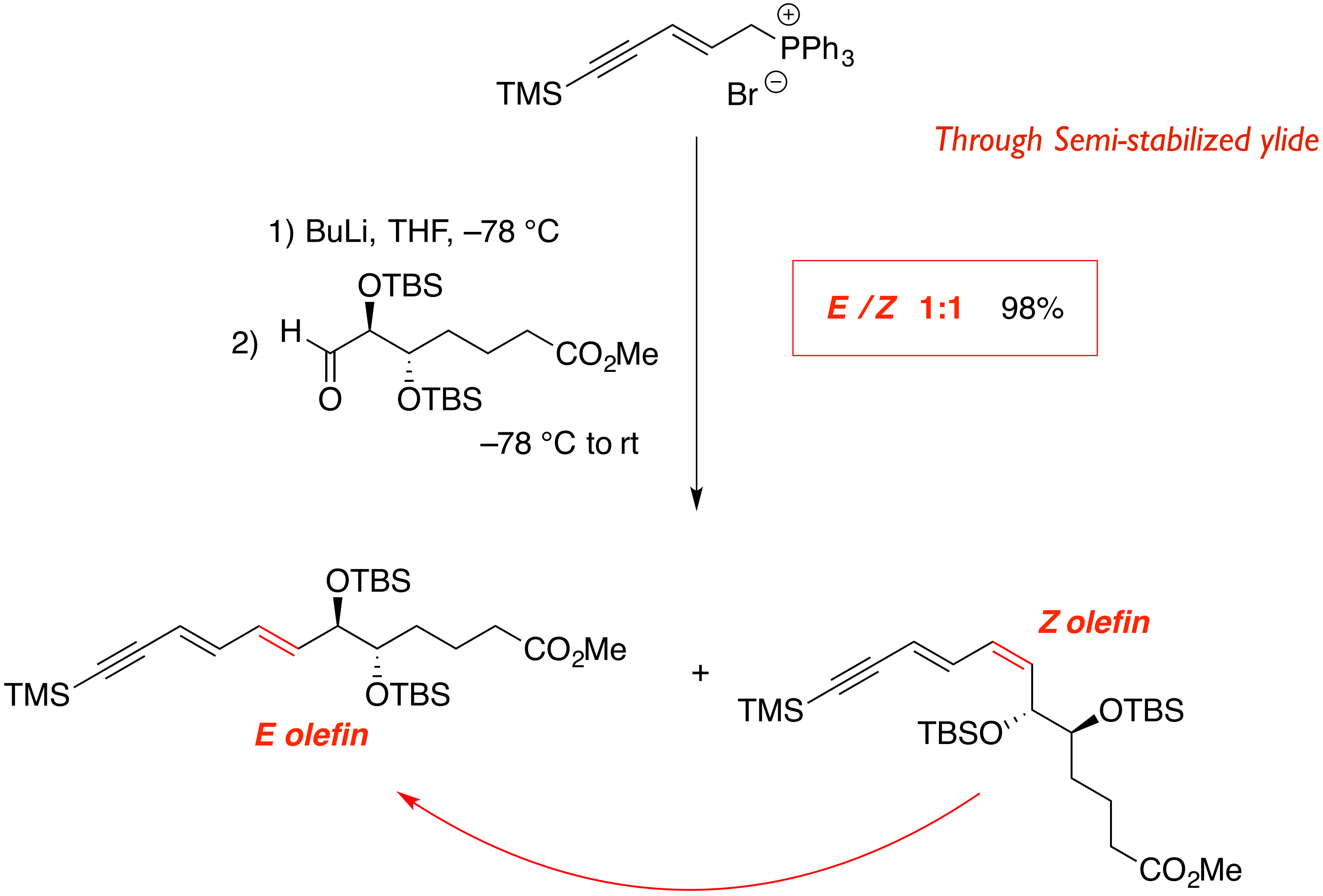
Wittig Reaction in Synthesis



Through Semi-stabilized ylide

1) BuLi, THF, –78 °C

2)

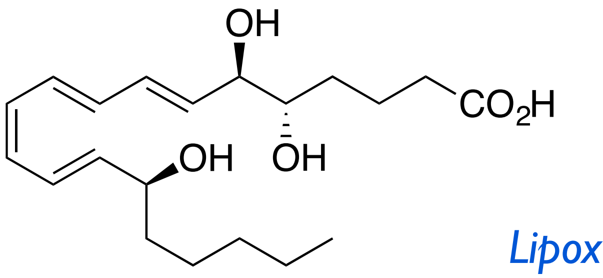
–78 °C to rt

E / Z 1:1 98%

E olefin

Z olefin

I_2 cat

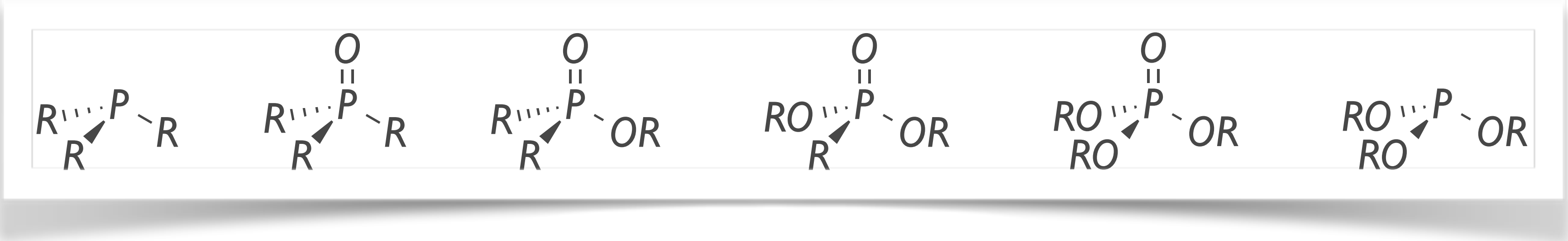


Lipoxin A

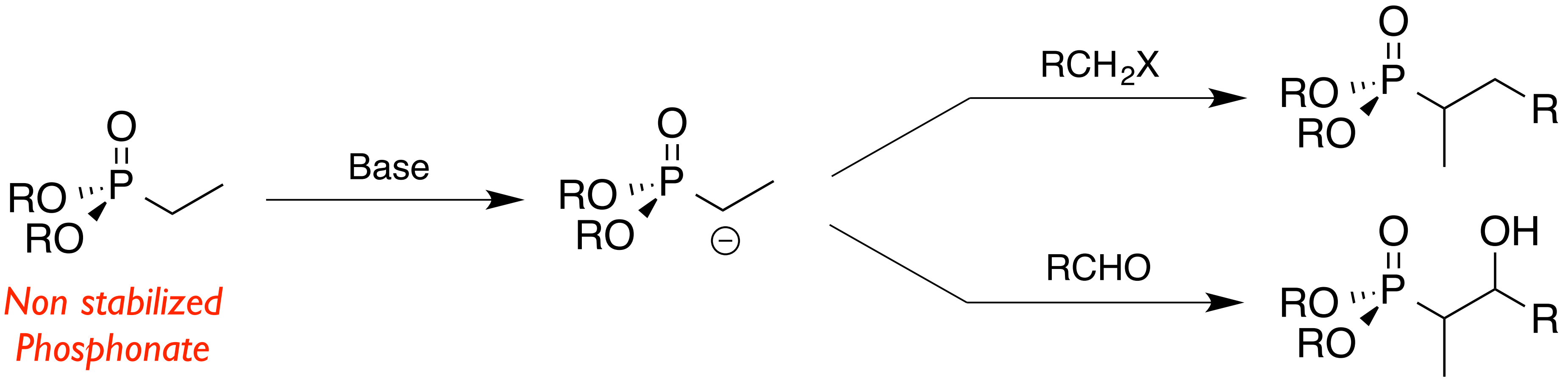
Nicolaou, K. C. *JACS* **1985**, *107*, 7515

Phosphonates: a new Source of Carbon Nucleophiles

Remember

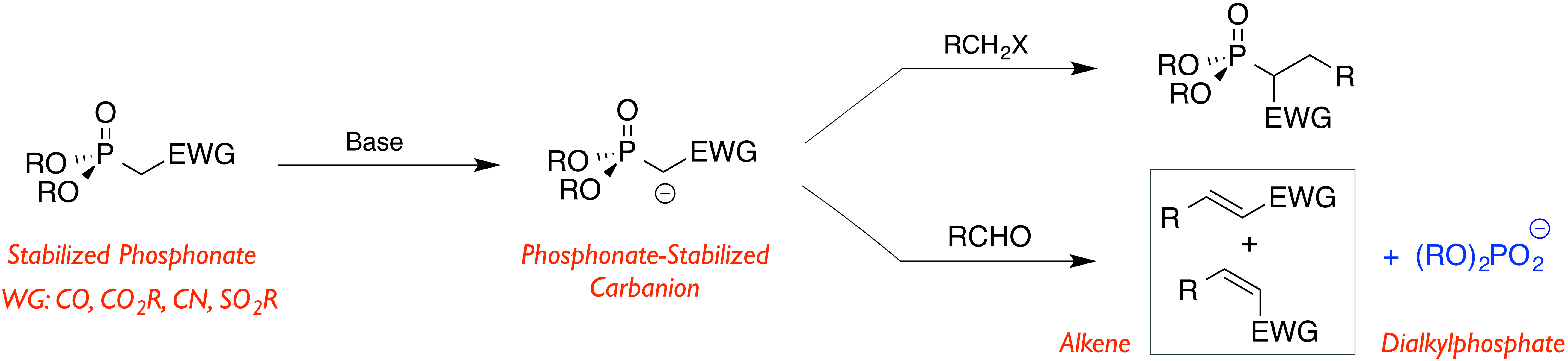


Phosphine · *Phosphine Oxide* · *Phosphinate* · *Phosphonate* · *Phosphate* · *Phosphite*



Non stabilized Phosphonate

β-Hydroxy Phosphonate



Stabilized Phosphonate

EWG: CO, CO_2R, CN, SO_2R

Phosphonate-Stabilized Carbanion

Alkene

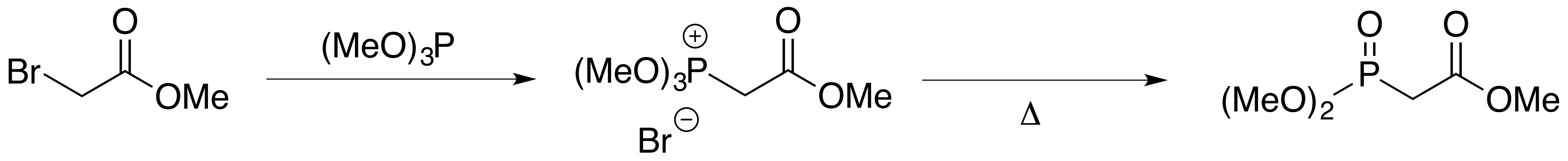
Dialkylphosphate salt

Phosphonate stabilized carbanions are more nucleophilic and basic than the corresponding phosphonium ylides

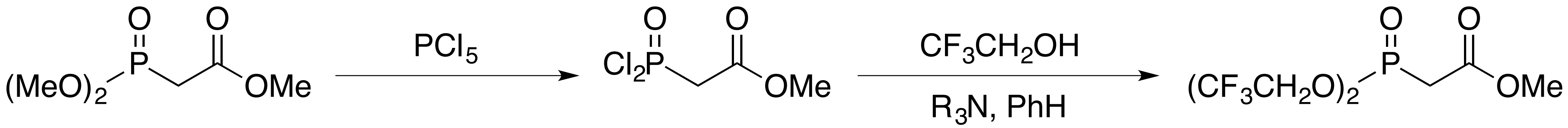
The by-product dialkylphosphate salt, $(RO)_2PO_2^-$, is readily removed by aqueous extraction

Phosphonates: Synthesis and Acidity

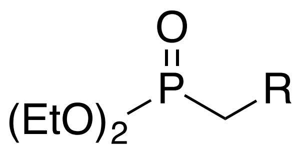
Synthetic approaches



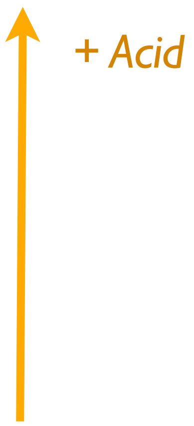
Michaelis Arbuzov



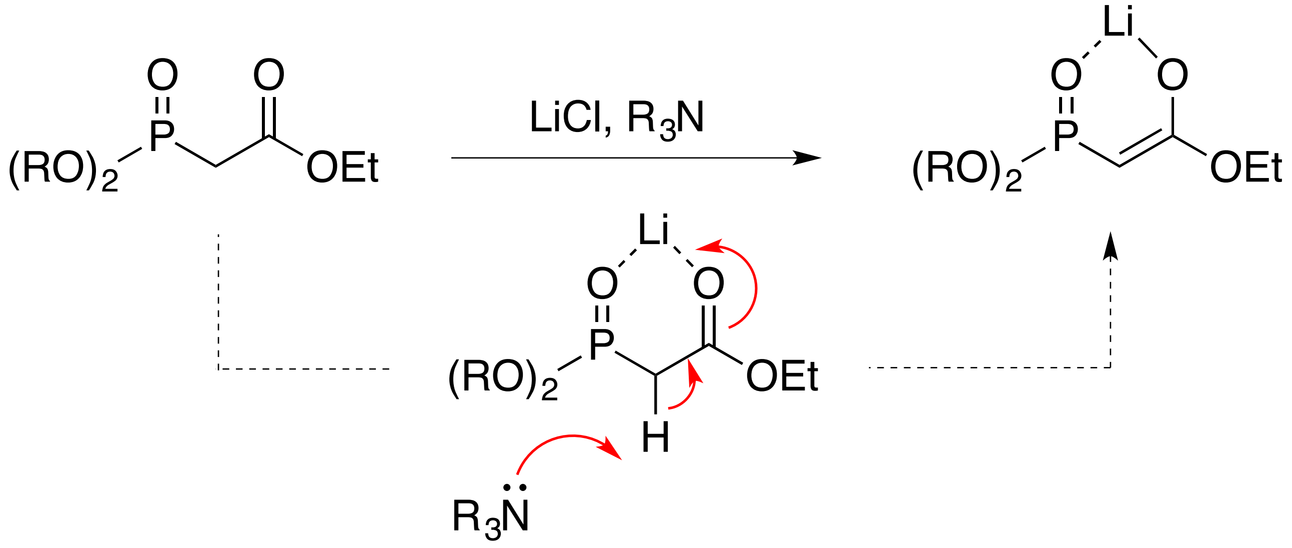
Acidity



R	*pK$_a$*
CN	*16.4*
CO$_2$Et	*18.6*
Cl	*26.2*
Ph	*27.6*
SiMe$_3$	*28.8*



Masamune-Roush Conditions

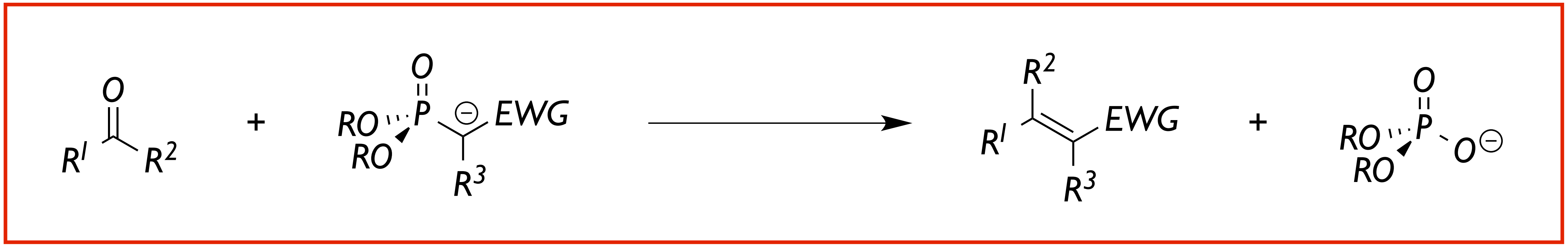


R$_3$N: i-Pr$_2$NEt, DBU

For nucleophilicity,
Mayr, H. *JACS* **2009**, *131*, 704

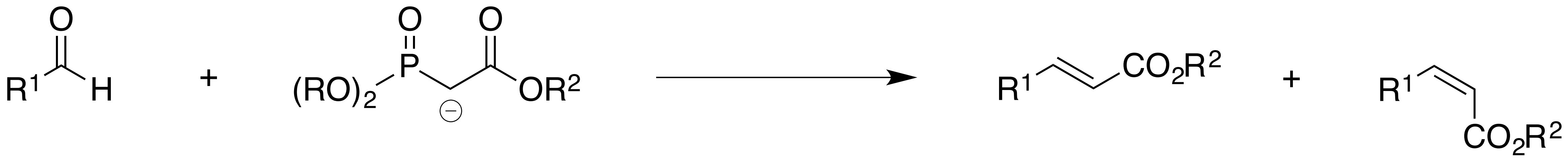
Wittig Variants: Concept

Wittig variants: addition of phosphonate carbanions to carbonyls



Phosphonate	
$(AlkylO)_2POCH_2CO_2R^2$	Horner-Wadsworth-Emmons
$(CF_3CH_2O)_2POCH_2CO_2R^2$	Still-Gennari
$(ArylO)_2POCH_2CO_2R^2$	Ando

HWE, Still-Gennari & Ando Reactions: Stereoselectivity



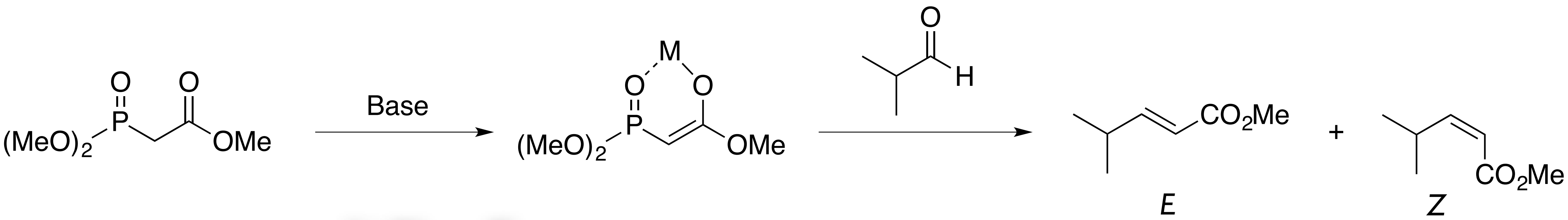
E

Z

Thermodynamically favored

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

Horner-Wadsworth-Emmons Reaction: Stereoselectivity

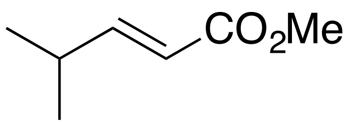


*Bu**Li**, **Na**H, **K**H*

For the use of LiOCH(CF$_3$)$_2$, Myers, A. G. *OL* **2005**, *7*, 4281

		E / Z ratio	
Temperature	*Cation*	*THF*	*DME*
–78 °C	*Li*	*1 / 3*	*1 / 1*
	Na	*1 / 1*	*1 / 1*
	K	*1 / 1*	*1 / 1*
23 °C	*Li*	*5.3 / 1*	*12 / 1*
	Na	*4.3 / 1*	*5.3 / 1*
	K	*4 / 1*	*4 / 1*

Major isomer: E



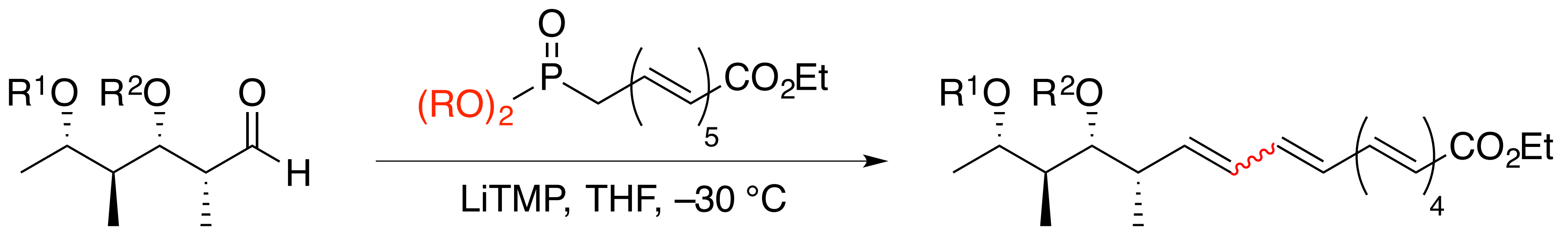
High T, Li > Na > K, DME > THF

Heathcock, C. H. *JOC* **1990**, *55*, 3386

Universitat de Barcelona

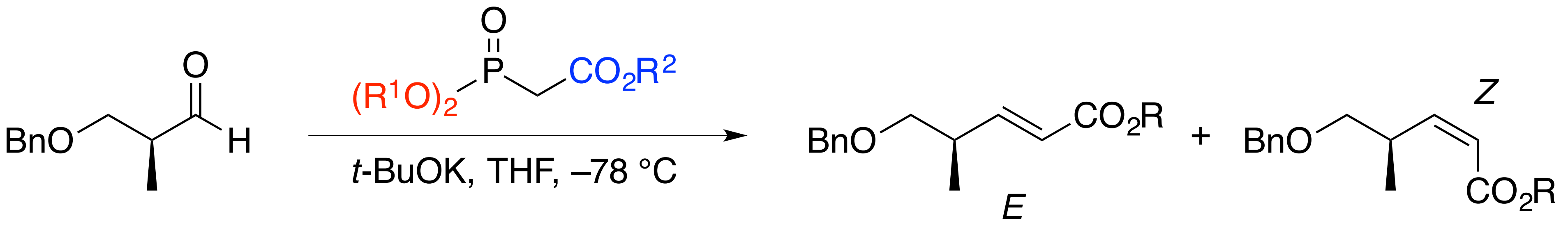
Horner-Wadsworth-Emmons Reaction: Stereoselectivity

However, sensitive substrates usually require mild conditions and the phosphonate becomes crucial ...



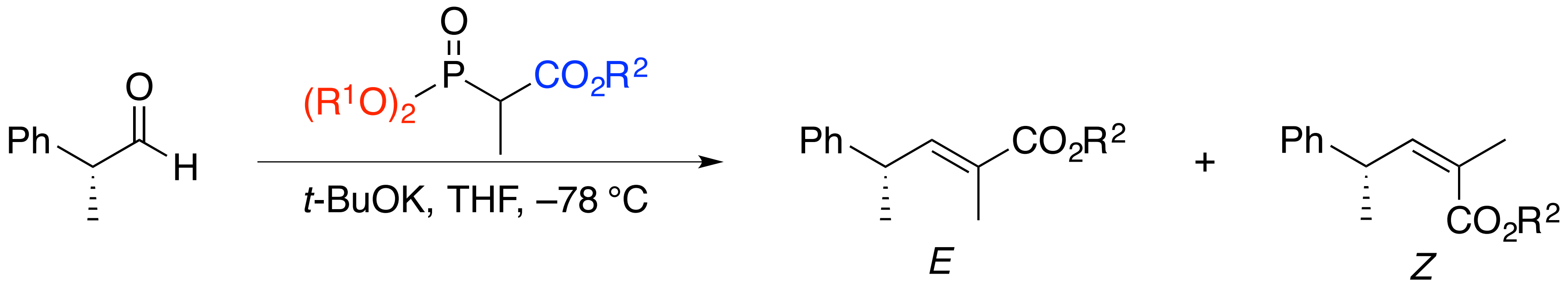
R	*E / Z*
Me	*1 : 1.2*
Et	*1.75: 1*
i-Pr	*E only*

More bulky *More E*



R1	*R2*	*E / Z*
Me	*Me*	*1 : 1.2*
i-Pr	*Et*	*95 : 5*

More bulky *More E*

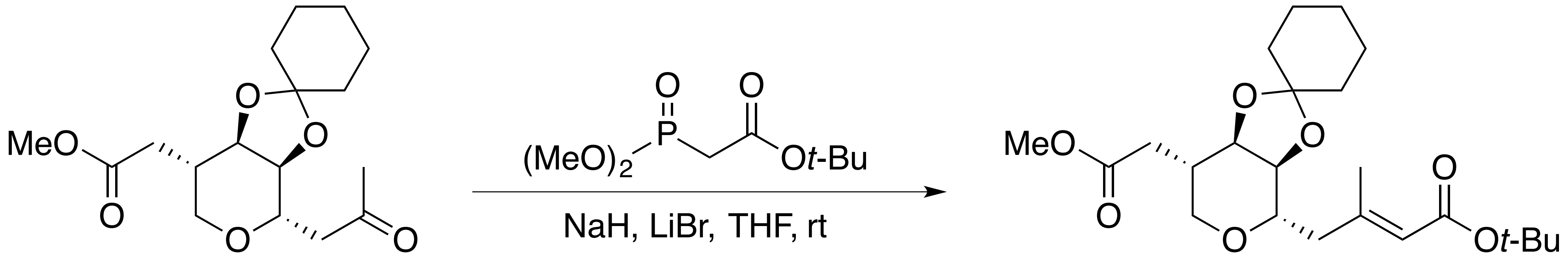


R1	*R2*	*E / Z*
Me	*Me*	*5 : 95*
Me	*Et*	*10 : 90*
Et	*Et*	*40 : 60*
i-Pr	*Et*	*90 : 10*
i-Pr	*i-Pr*	*95 : 5*

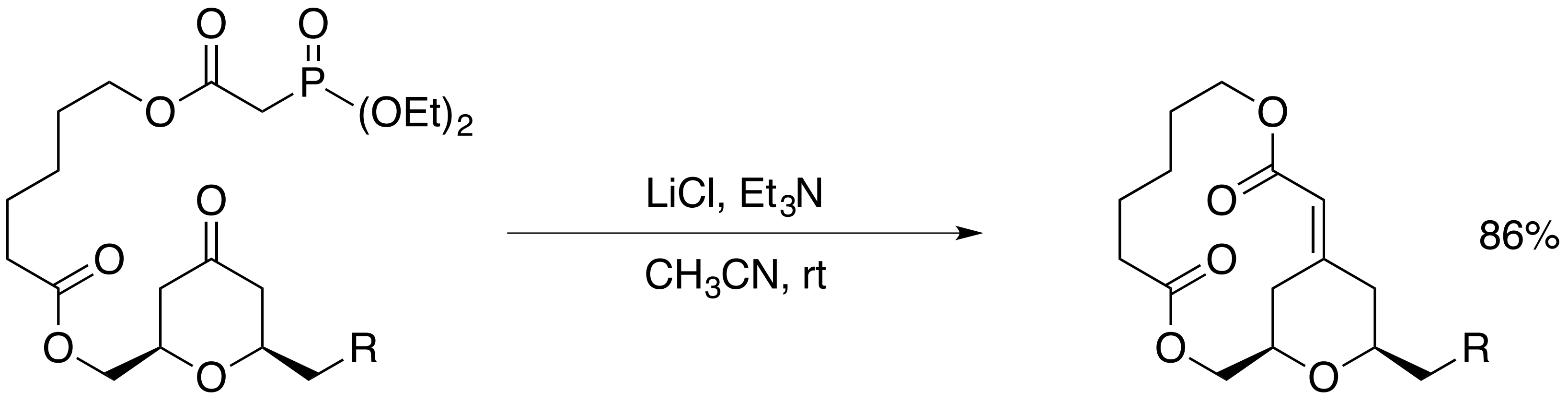
More bulky *More E*

Horner-Wadsworth-Emmons Reaction: Stereoselectivity

Ketones can be partners of phosphonates due to their high nucleophilicity ...



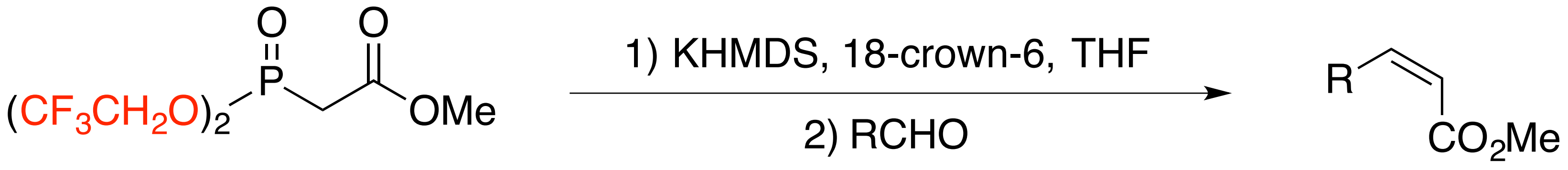
E / Z 7 : 1 77%

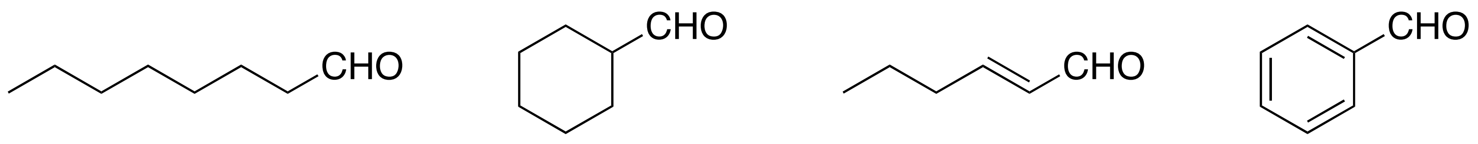


86%

Still-Gennari Reaction: Stereoselectivity

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



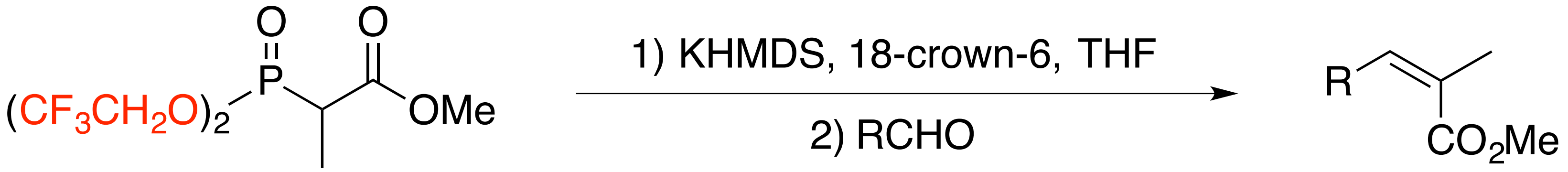


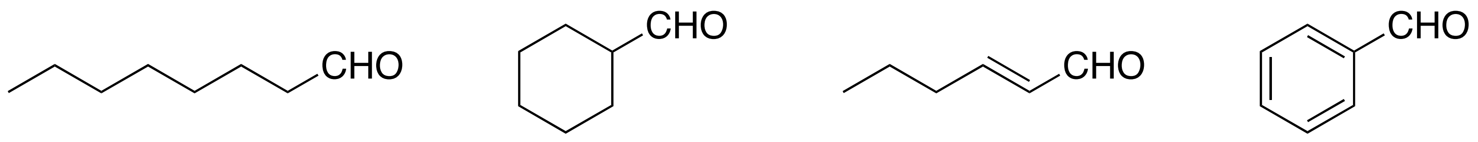
12:1 90%

4:1 74%

> 50:1 87%

> 50:1 95%





46:1 88%

50:1 80%

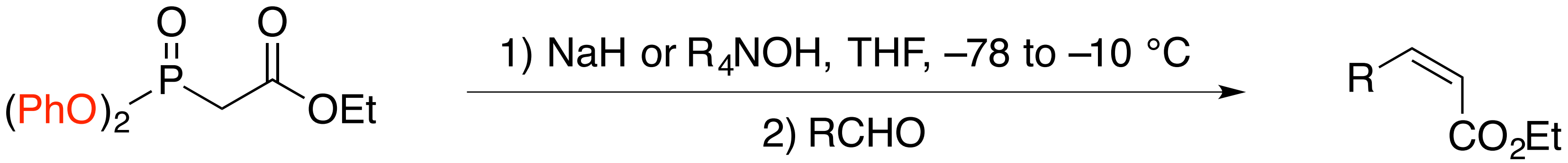
> 50:1 79%

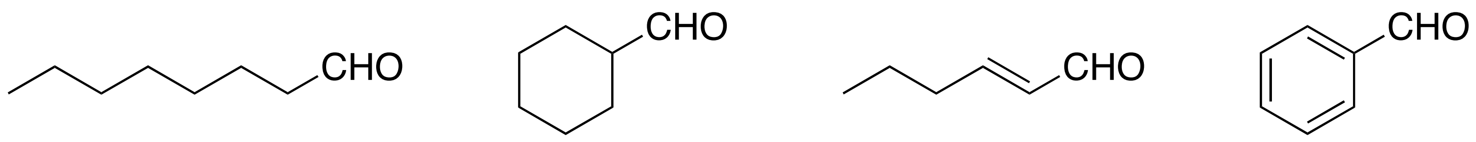
30:1 95%

Still, W. C. & Gennari, C. *Tetrahedron Lett.* **1983**, *23*, 4405

Ando Reaction: Stereoselectivity

Ando reaction also gives Z olefins …





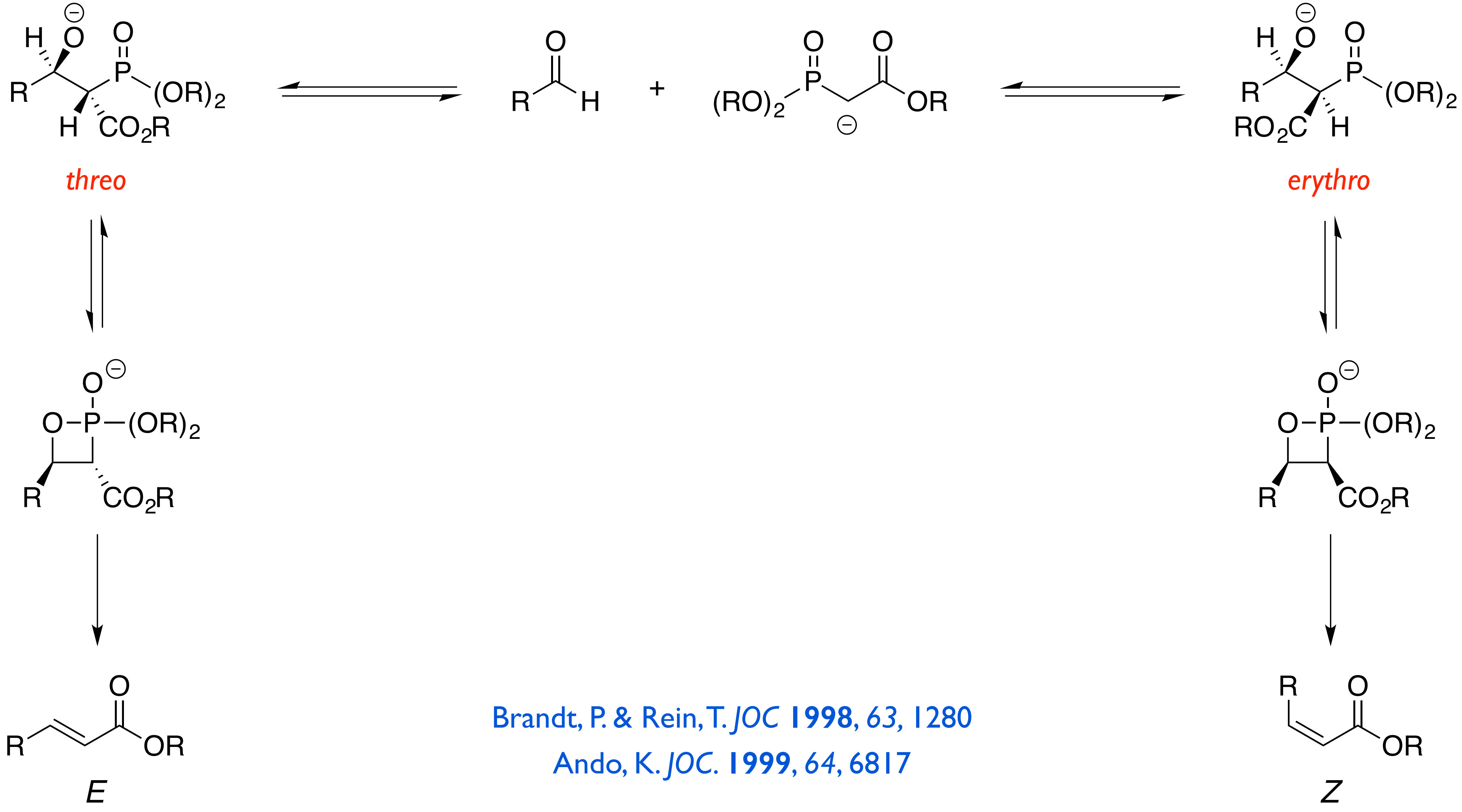
90:10 100% *91:9 98%* *89:11 97%* *93:7 98%*

Z / *E* 95:5 85%

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

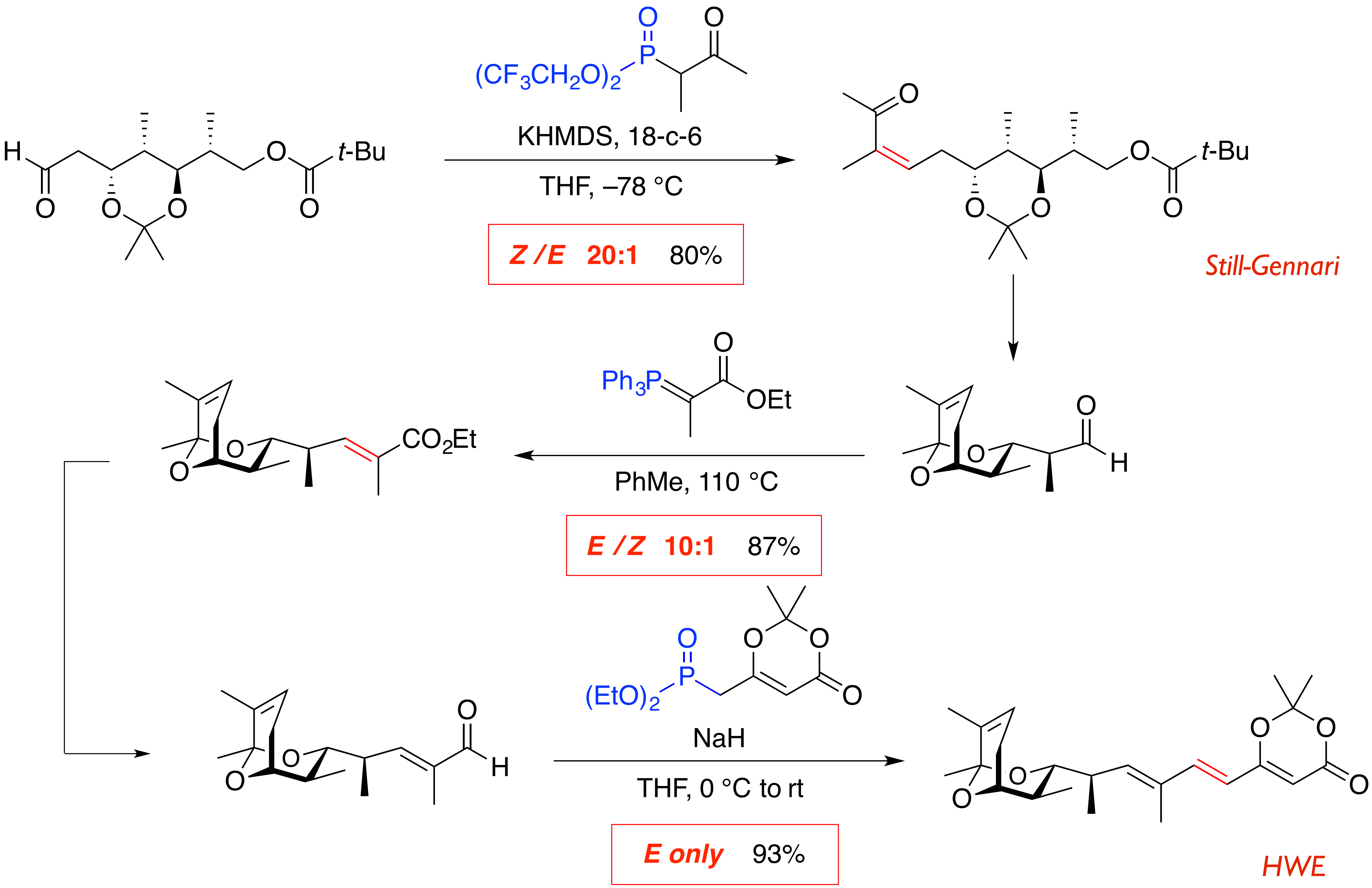
HWE & Variants: Mechanism

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

Wittig, HWE & Variants in Synthesis



KHMDS, 18-c-6

THF, –78 °C

***Z / E* 20:1** 80%

Still-Gennari

PhMe, 110 °C

***E / Z* 10:1** 87%

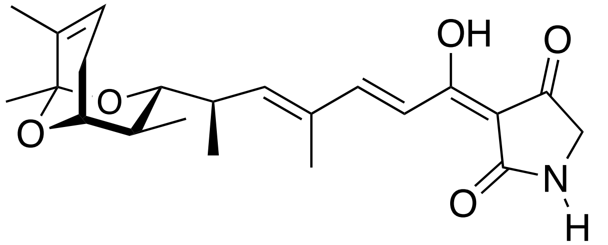
Wittig
Stabilized ylide

NaH

THF, 0 °C to rt

E only 93%

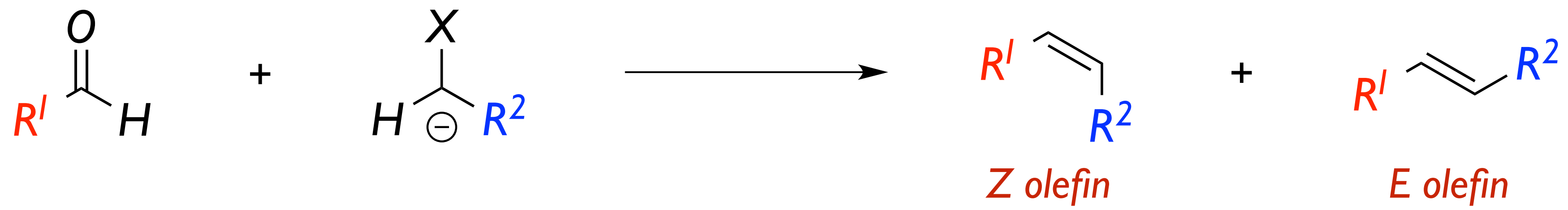
HWE



Tirandamycin C

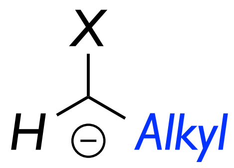
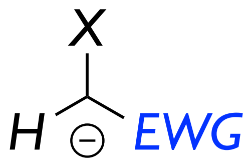
Yadav, J. S. *JOC* **2012**, *77*, 9628

Stereoselectivity of Wittig, HWE & Variants

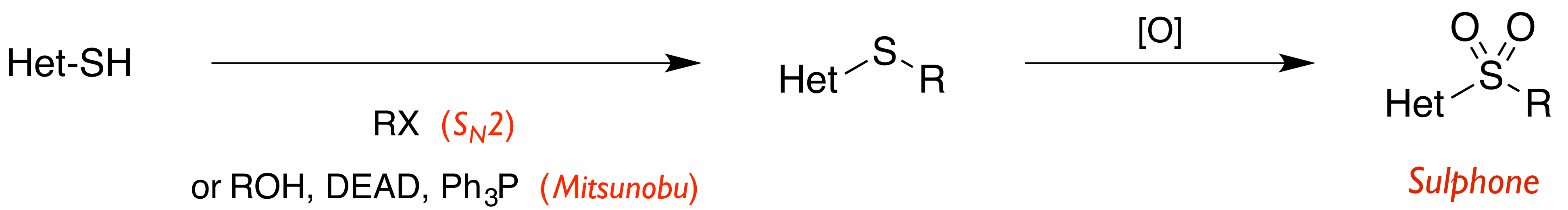


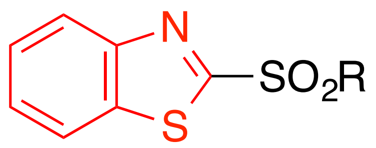
Regioselectivity ✓

Stereoselectivity (Z versus E) ?

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

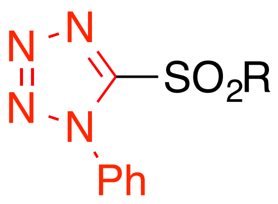
Julia-Kocienski Reaction: Concept





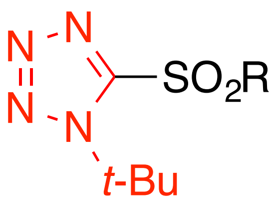
BT

Julia,1991



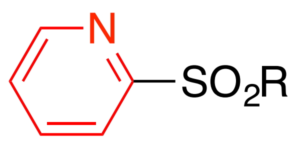
PT

Kocienski, 1998



TBT

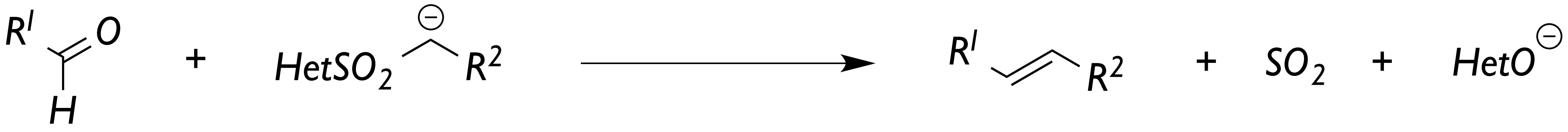
Kocienski, 2000



PYR

Julia,1993

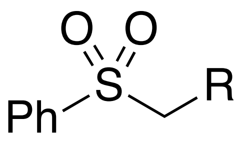
- *Julia-Kocienski reaction: addition of sulfone carbanions to aldehydes*



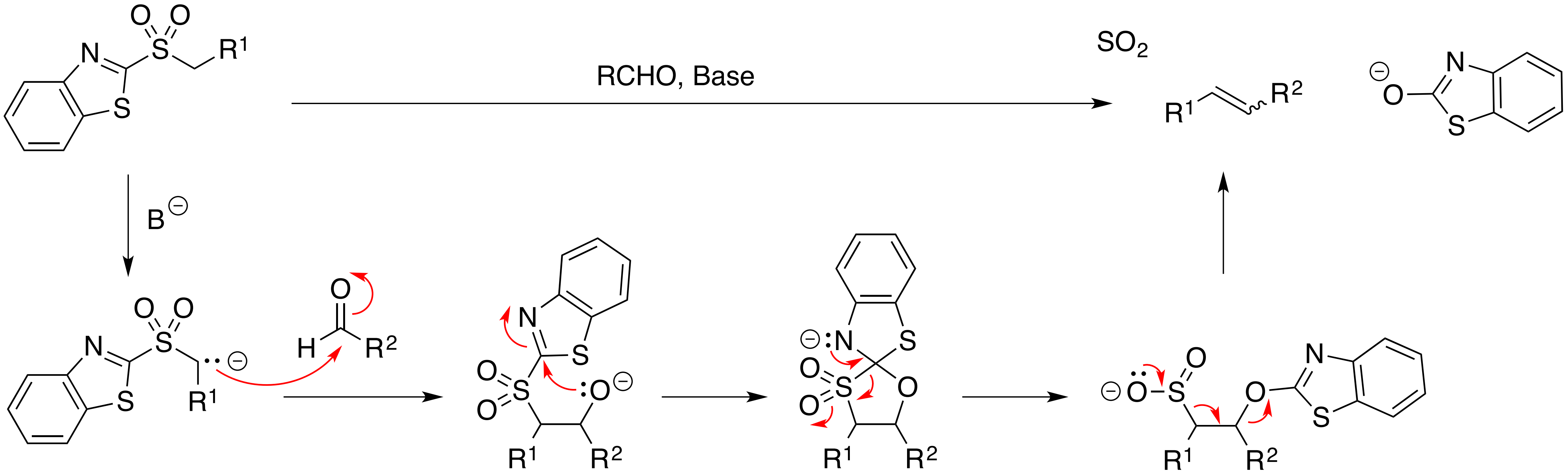
Blakemore, P. R. *JCS Perkin Trans 1* **2002**, 2563; Aïssa, C. *EJOC* **2009**, 1831

Julia-Kocienski Reaction: Mechanism

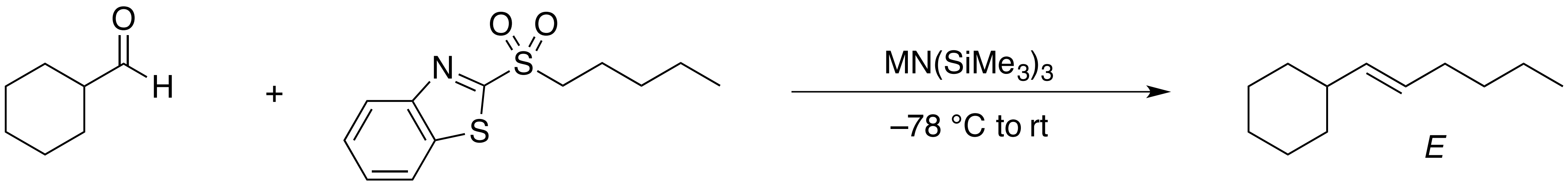
Sulfone acidity



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

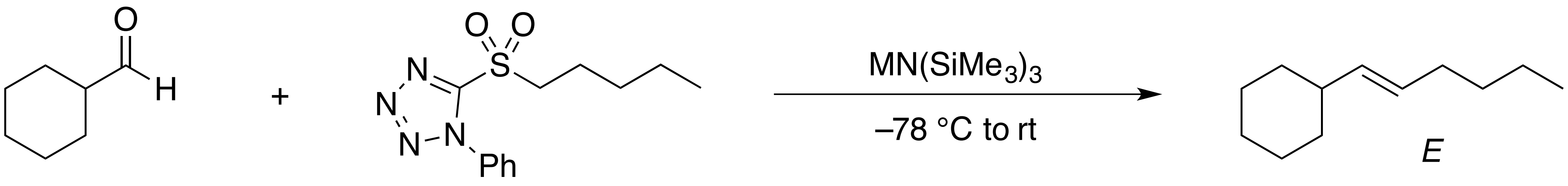


Julia-Kocienski Reaction: Stereoselectivity



More E

M	PhMe	Et$_2$O	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



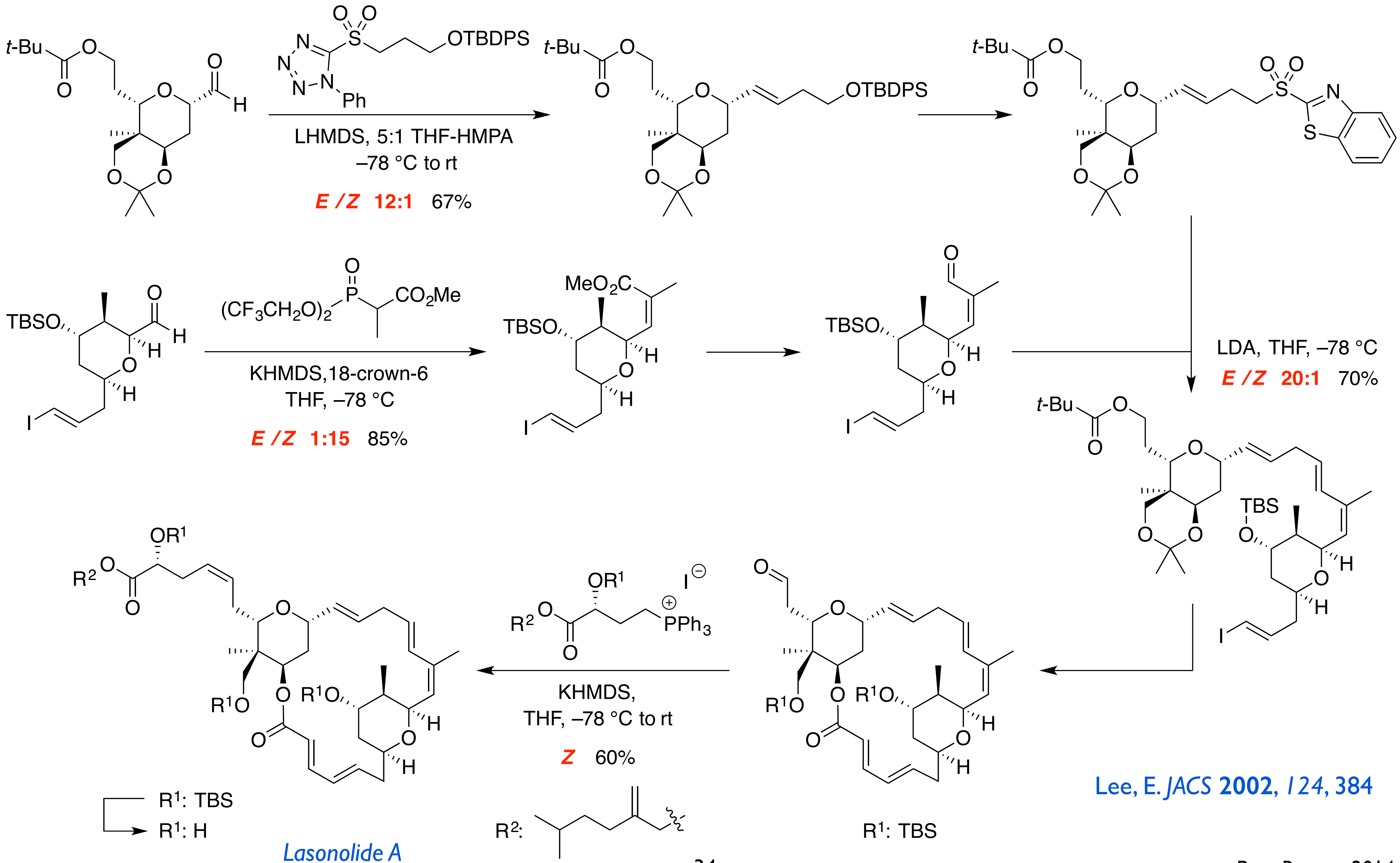
More E

M	PhMe	Et$_2$O	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

Synthesis of Natural Products



Lasonolide A

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

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.SCHROCK

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**, 4490

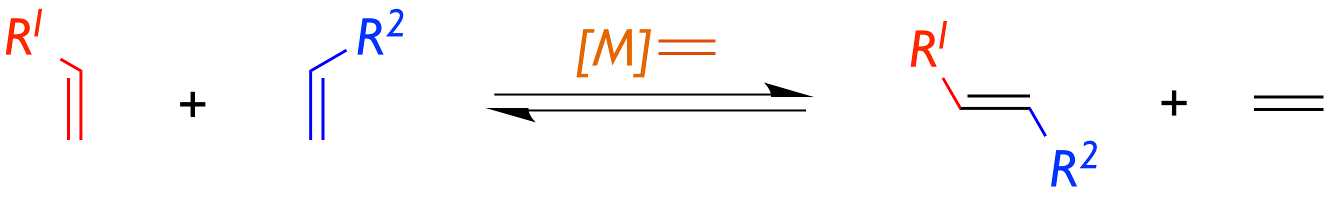
Robert H. Grubbs. *The Development of Olefin Metathesis Catalysts: An Organometallic Success Story, in ACR* **2001**, *34*, 18–29

Olefin Metathesis: Concept

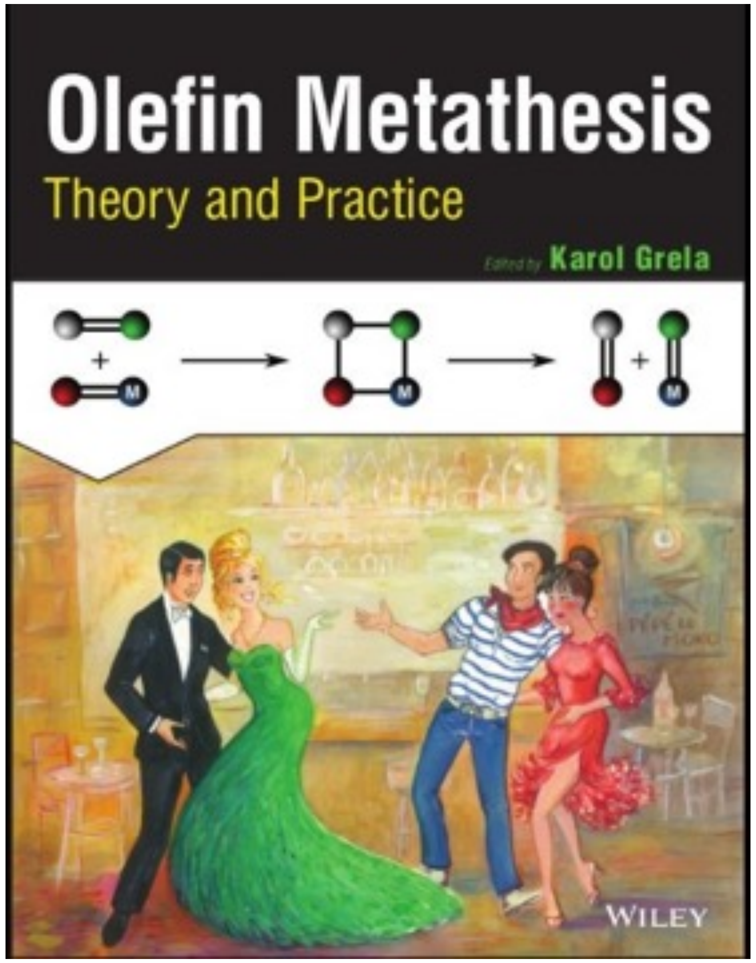
***Metathesis* = *Meta* (change) & *thesis* (position)**

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*

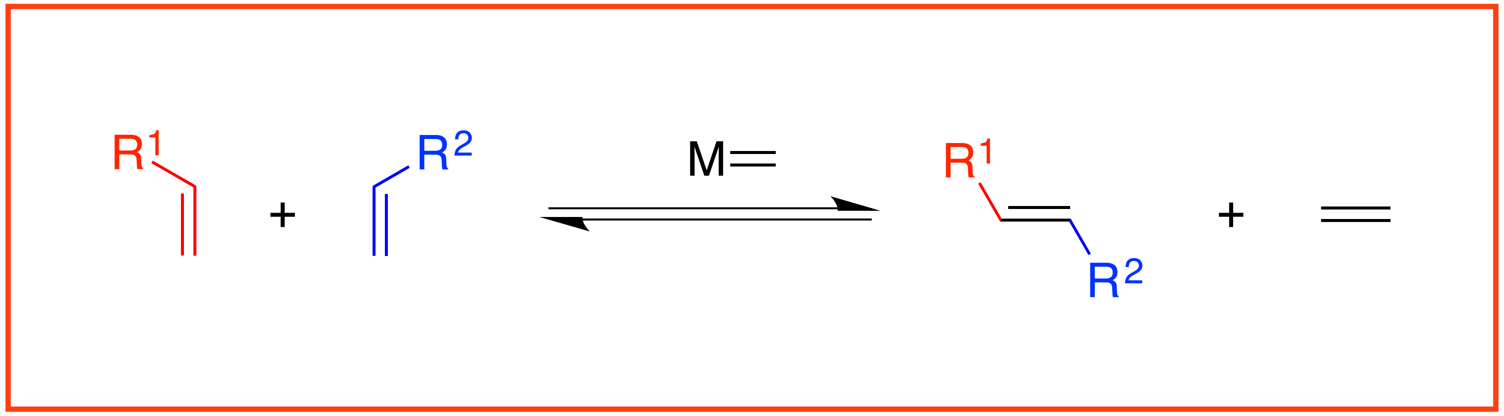


Nicolaou, K. C. *Classics in Total Synthesis II*. p. 162



Grela K. *Olefin Metathesis. Theory and Practice*. Wiley

Olefin Metathesis: Features & Mechanism



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,

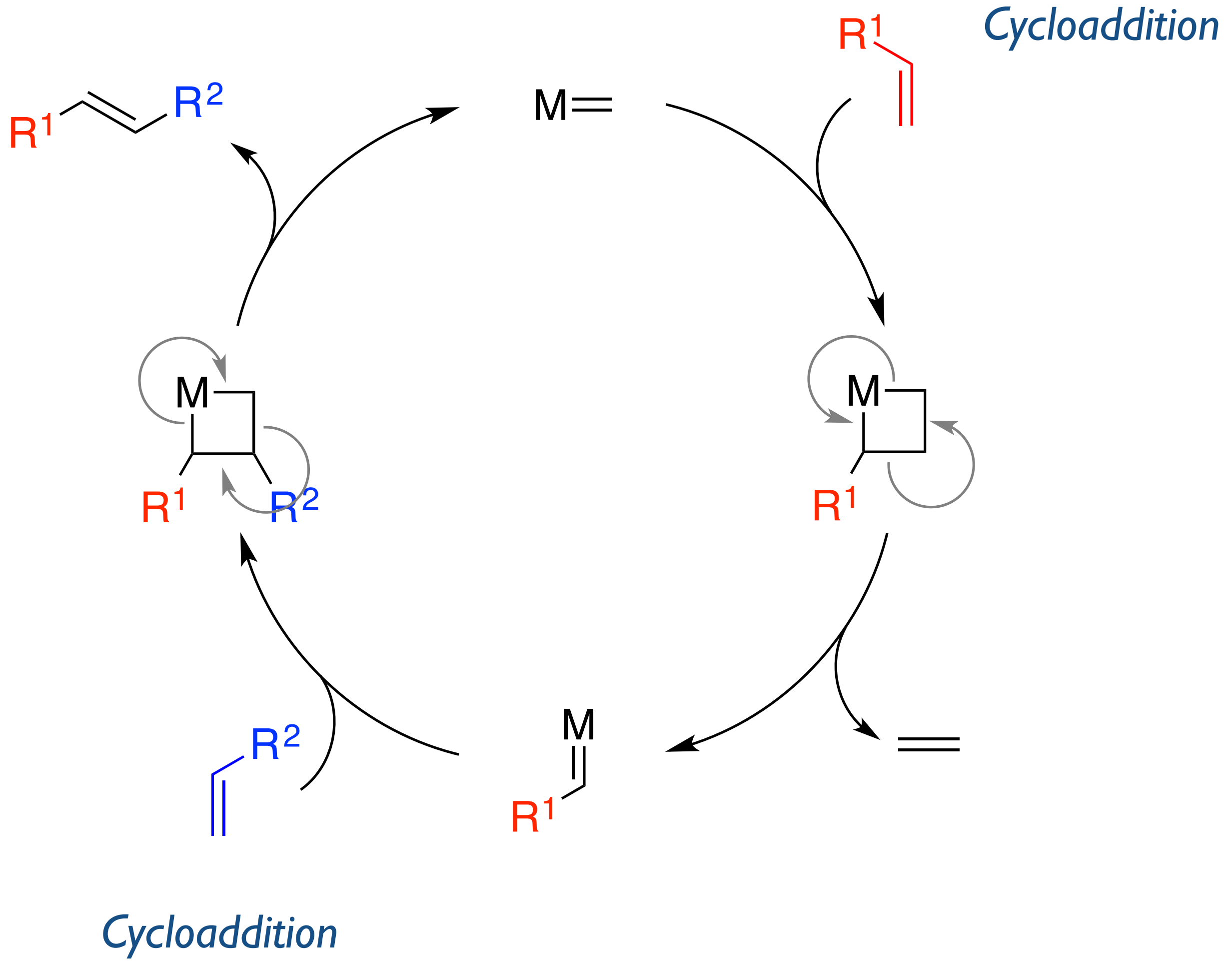
the reversible character of olefin metathesis usually

results in the formation

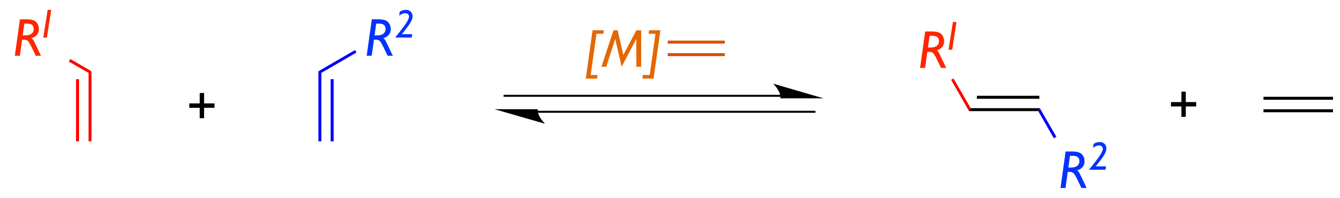
of the thermodynamically most favorable E product.

CURRENT CHALLENGE: KINETIC STEREOCONTROL

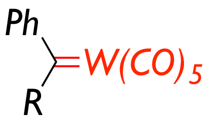
Fürstner, A, *Science* **2013**, *341*, 1357
Fischmeister, C. *ChemCatChem* **2013**, *5*, 3436
Grubbs, R. H. *Chem. Sci.* **2014**, 5, 501



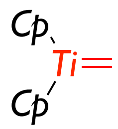
Olefin Metathesis: Catalysts



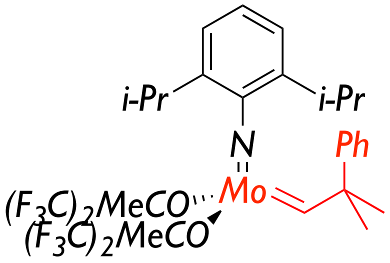
Ruthenium carbenes, [M]=, *are the most common catalysts used in olefin methathesis so far.*



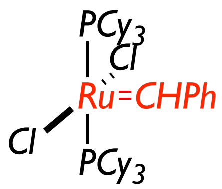
Katz 1976



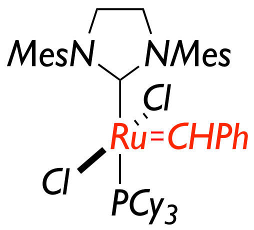
Tebbe 1978



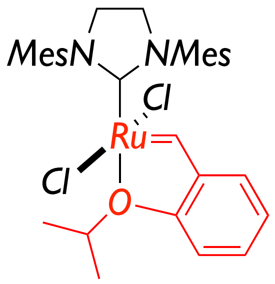
Schrock 1990



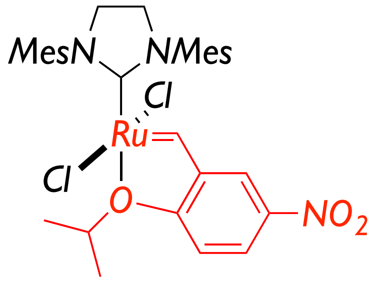
Grubbs I 1995



Grubbs II 1999



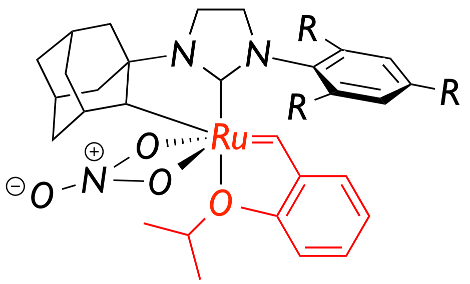
Hoveyda 2000



Grela 2002

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

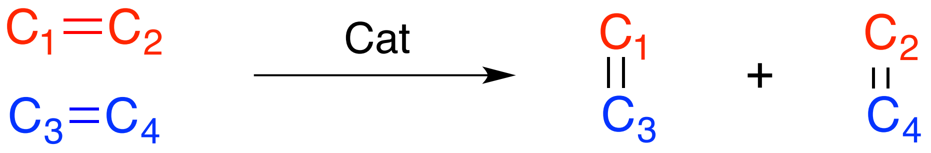
For a recent account of different ruthenium catalysts, Grela, K. *ASC* **2013**, *355*, 1997
For a recent perspective on Olefin Metathesis, Hoveyda, A. H. *JOC* **2014**, *79*, 4763



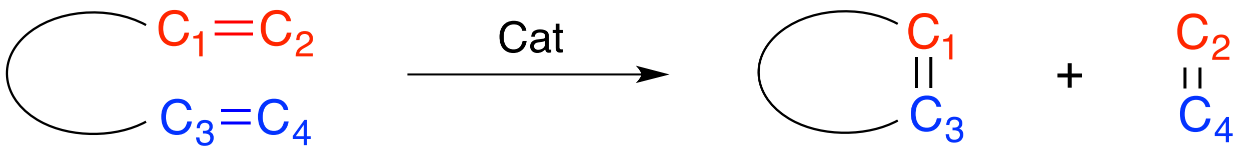
More complex ruthenium based complexes are being developed to achieve high Z stereoselectivity

Olefin Metathesis: A Powerful Synthetic Tool

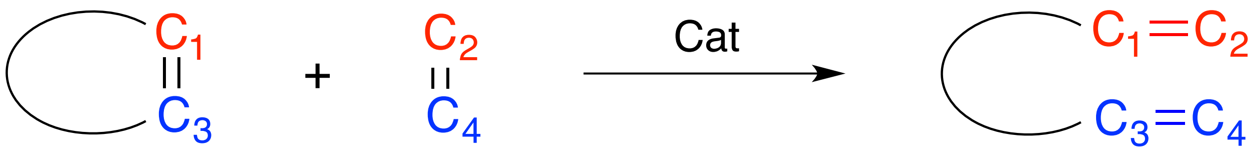
__Olefin metathesis__ is now widely considered as one of the most powerful synthetic tools in organic synthesis

🟩 

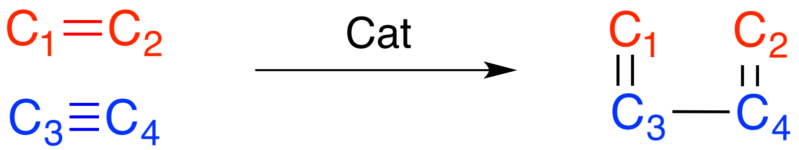
Cross Metathesis

🟩 

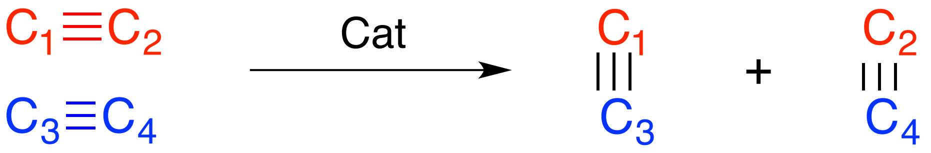
Ring-Closing Metathesis (RCM)

🟨 

Ring-Opening Metathesis

🟨 

Enyne Metathesis

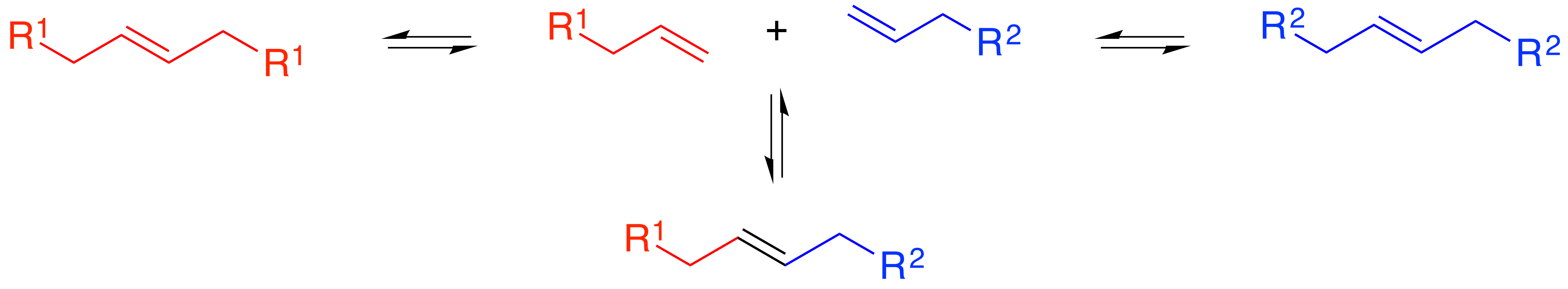
🟨 

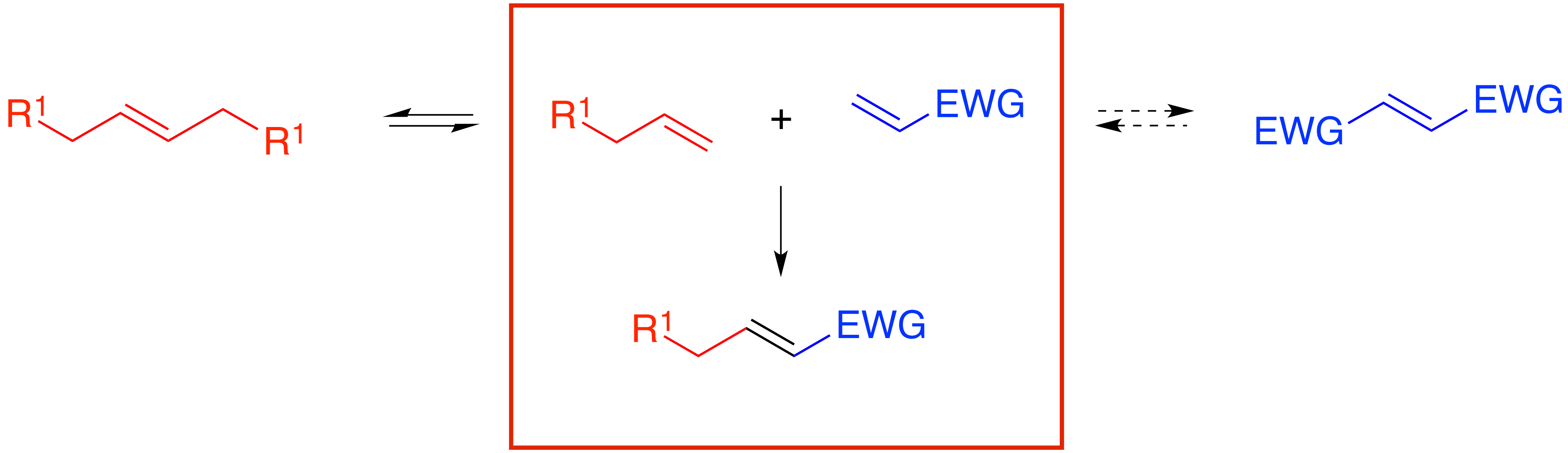
Alkyne Metathesis

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; Grela, K. *Chem. Rev.* **2009**, *109*, 3708;
Mori, M. *AS&C* **2007**, *349*, 121. Fürstner, A. *ACIE* **2013**, *52*, 2

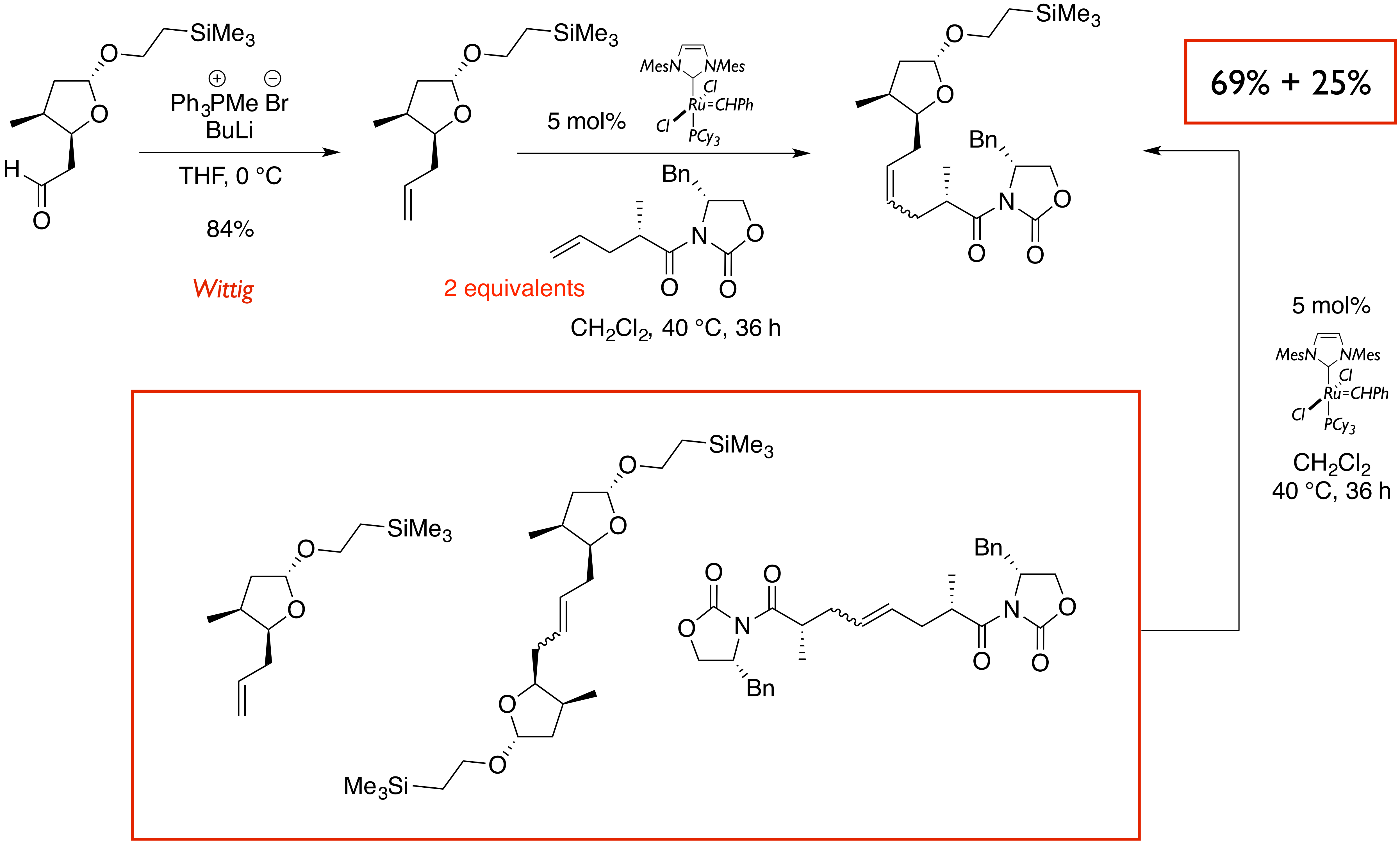
Cross Metathesis

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





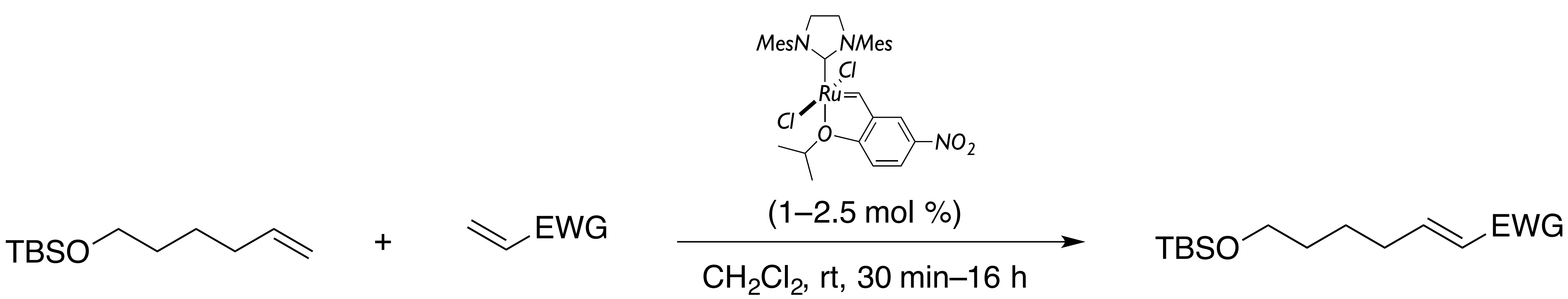
Cross Metathesis

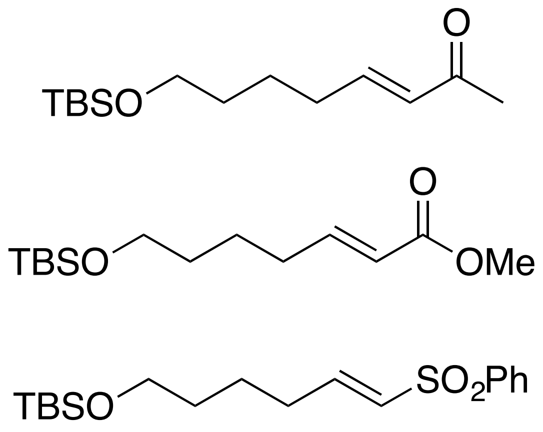


69% + 25%

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

Cross Metathesis



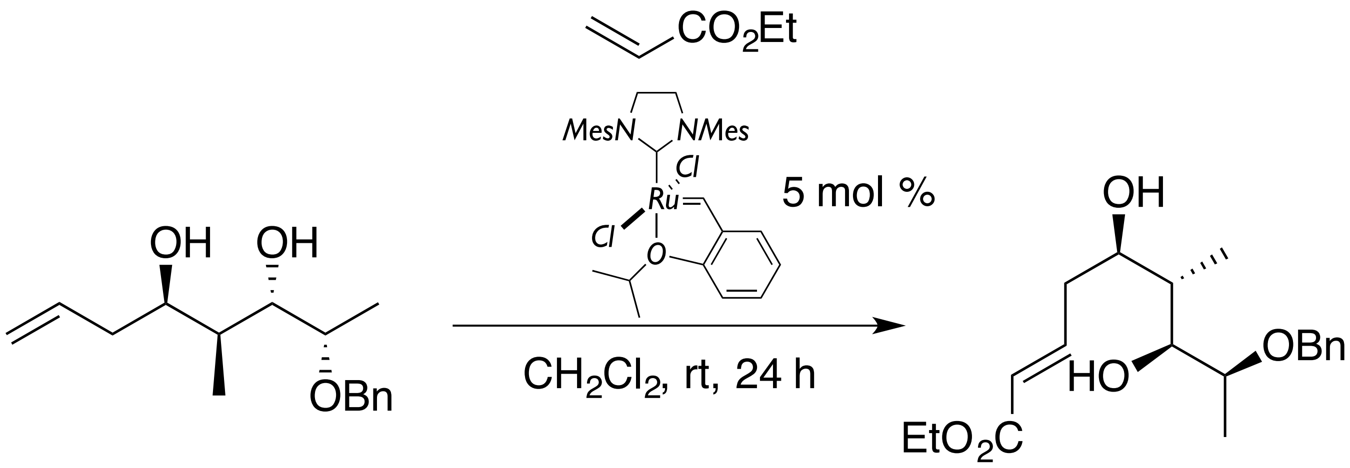


E/Z 99:1 82%

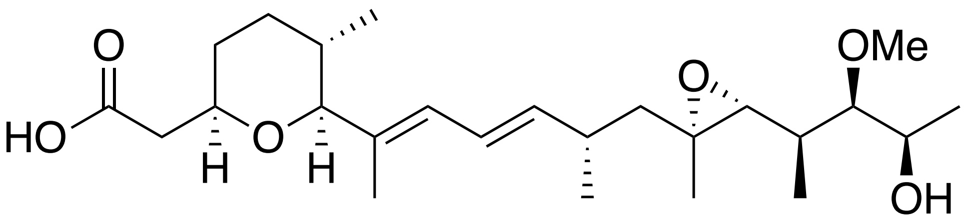
E/Z 95:5 95%

E only 90%

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



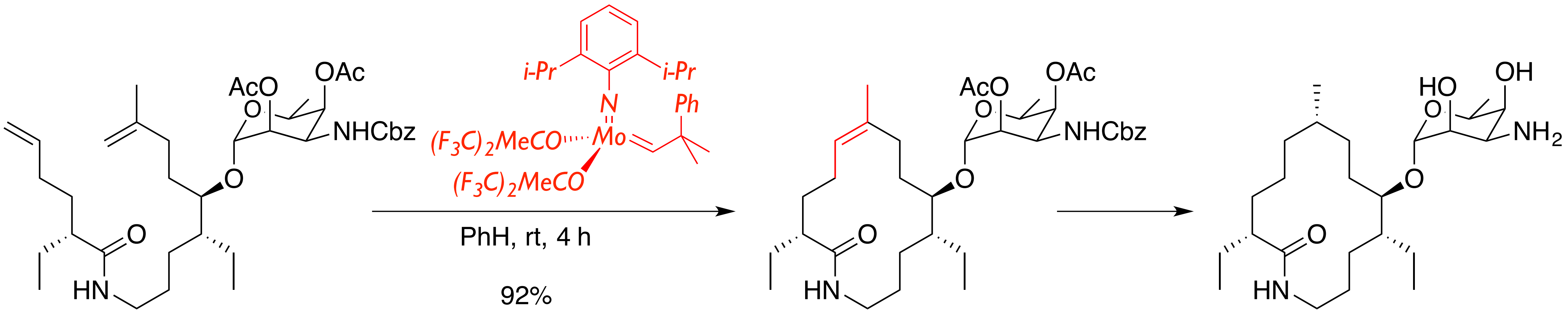
E/Z > 97:3 90%



Herboxidiè

Romea, P. & Urpí, F. *OL* **2011**, *13*, 5350

Ring-Closing Metathesis



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

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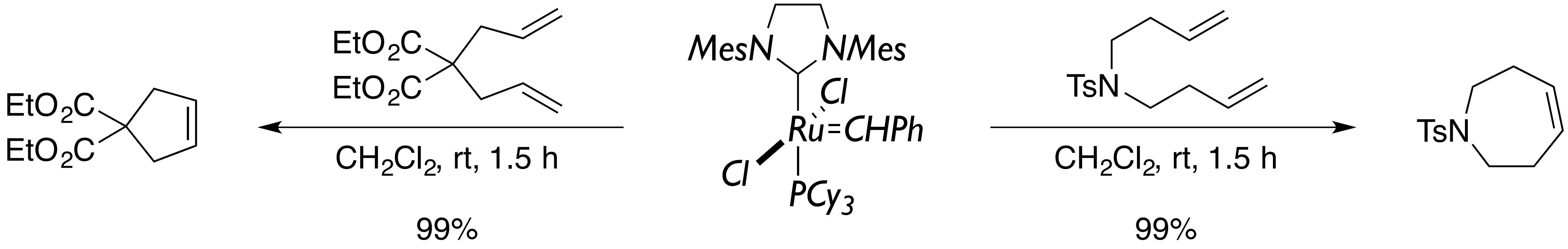
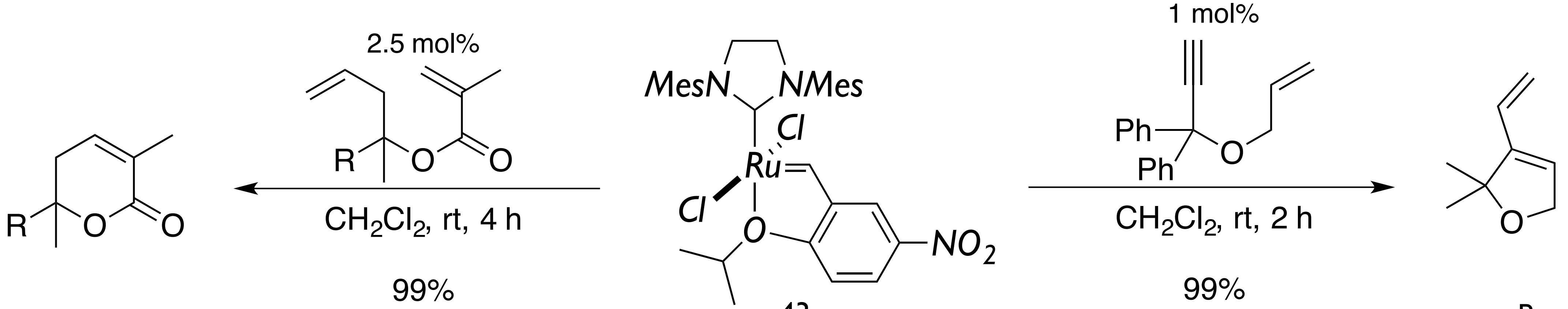
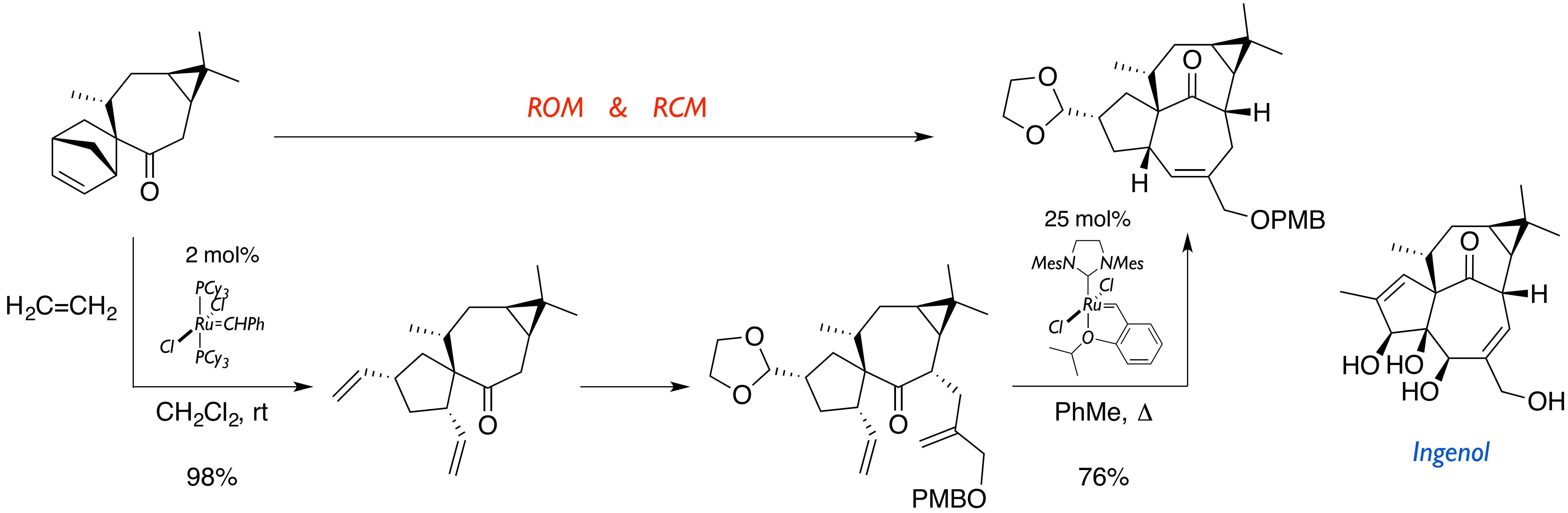




Ring-Closing Metathesis



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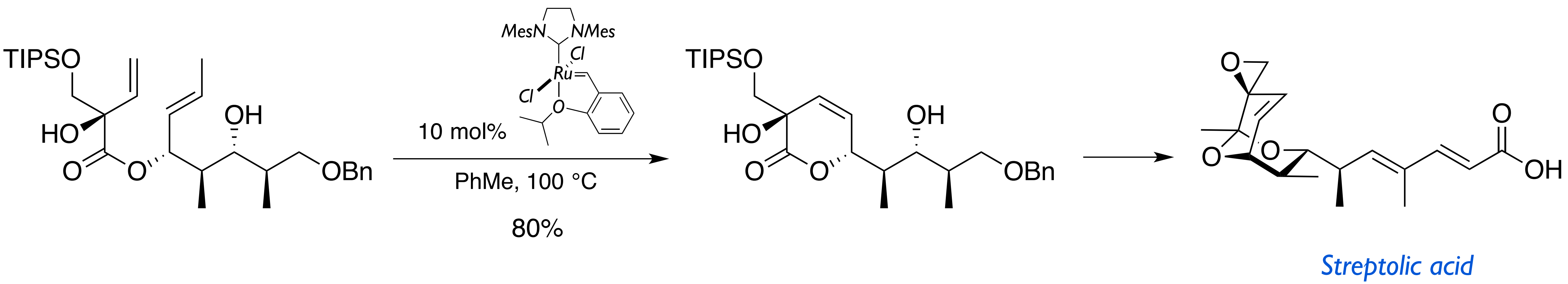

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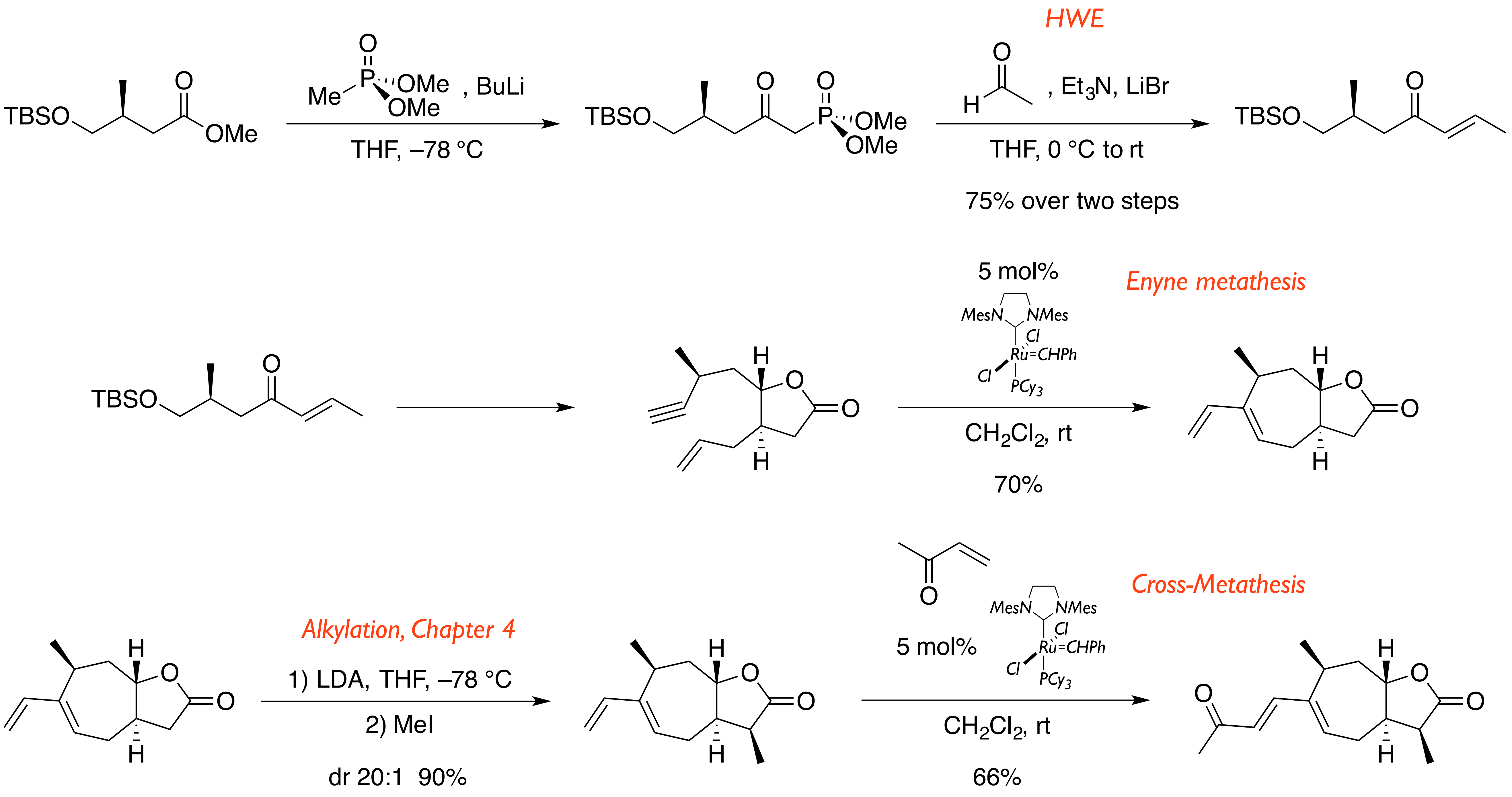
TOTAL SYNTHESIS of DIHYDROXANTHAIN: synthesis of C=C in action



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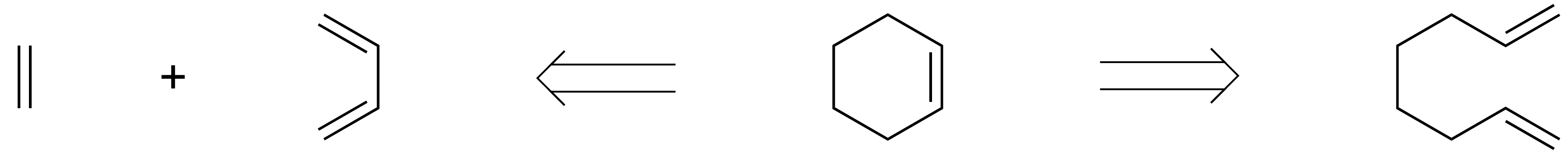
Diels-Alder and Ring-Closing Metathesis: two ways to cyclohexenes



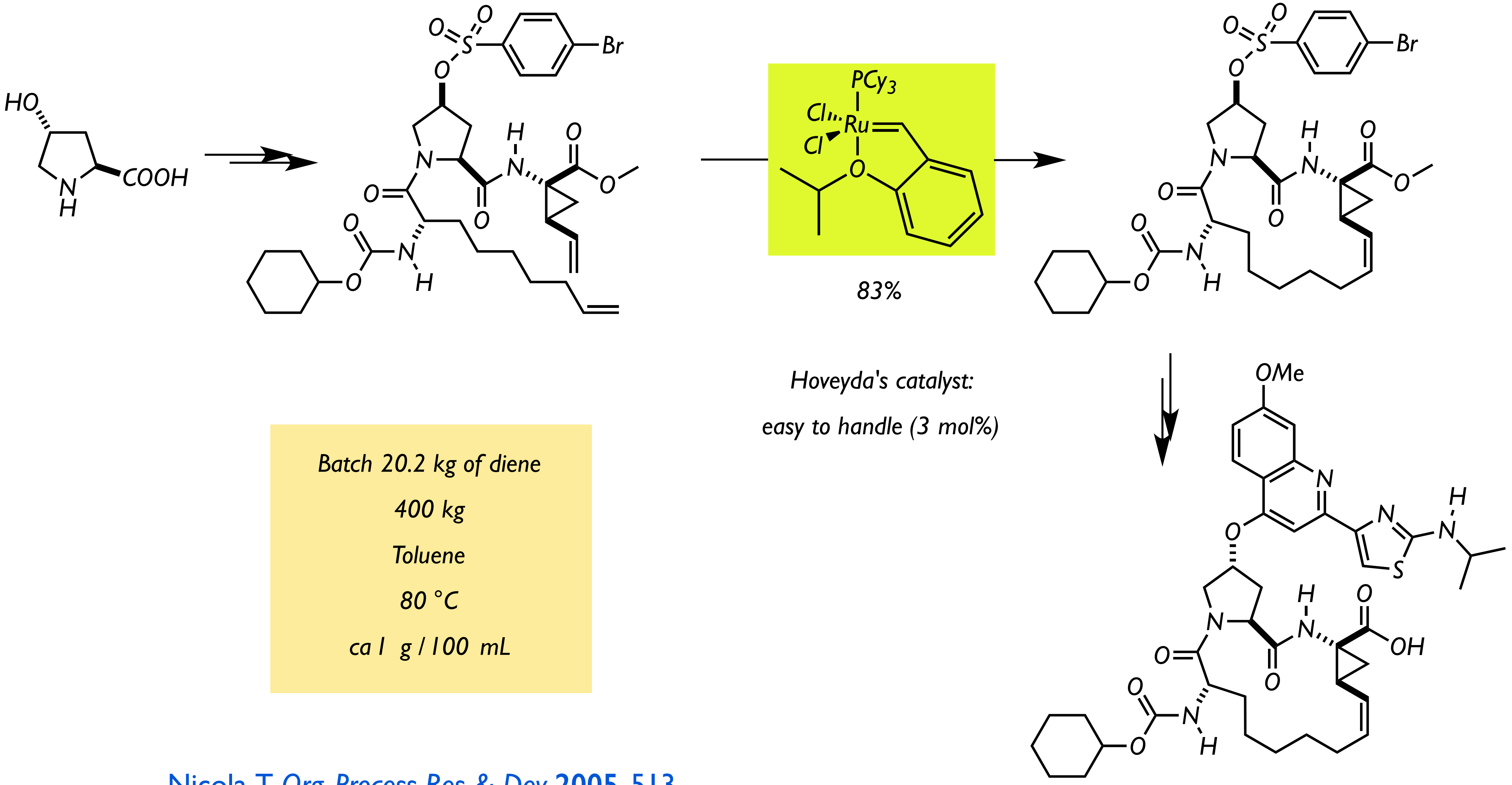
Diels-Alder

RCM

+ 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*

Ring-Closing Metathesis

Mature metathesis for scale-up: BILN 2061 ZW by Boehringer Ingelheim Pharma GmbH & Co



83%

Hoveyda's catalyst:

easy to handle (3 mol%)

Batch 20.2 kg of diene

400 kg

Toluene

80 °C

ca 1 g / 100 mL

BILN 2061 ZW

Nicola, T. *Org. Process Res & Dev* **2005**, 513