Master Course
in Organic Chemistry

2018-19

methods **and design** in organic synthesis

Pere Romea

7.Cascade Reactions

Band of Brothers
HBO

From this day to the ending of the world,

But we in it shall be remembered—

We few, we happy few, we band of brothers

Henry V

William Shakespeare

Pot Economy

POT ECONOMY

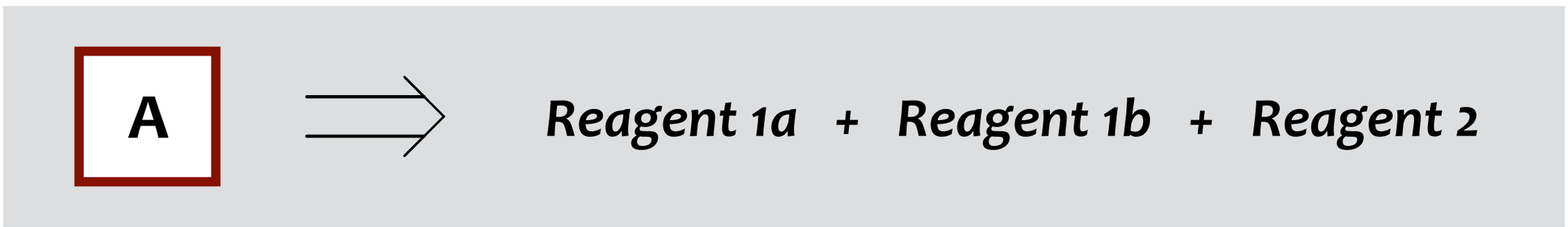
aim to complete an entire multi-step synthesis in a single pot
(see Chapter 5)

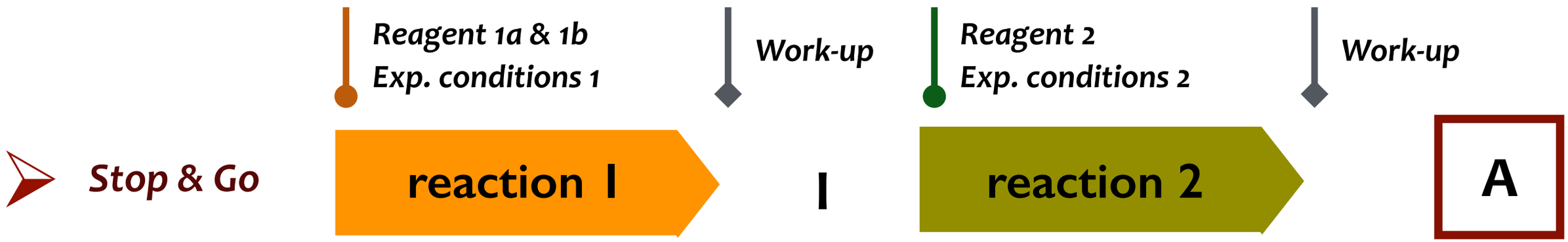
Guidelines Chapter 5

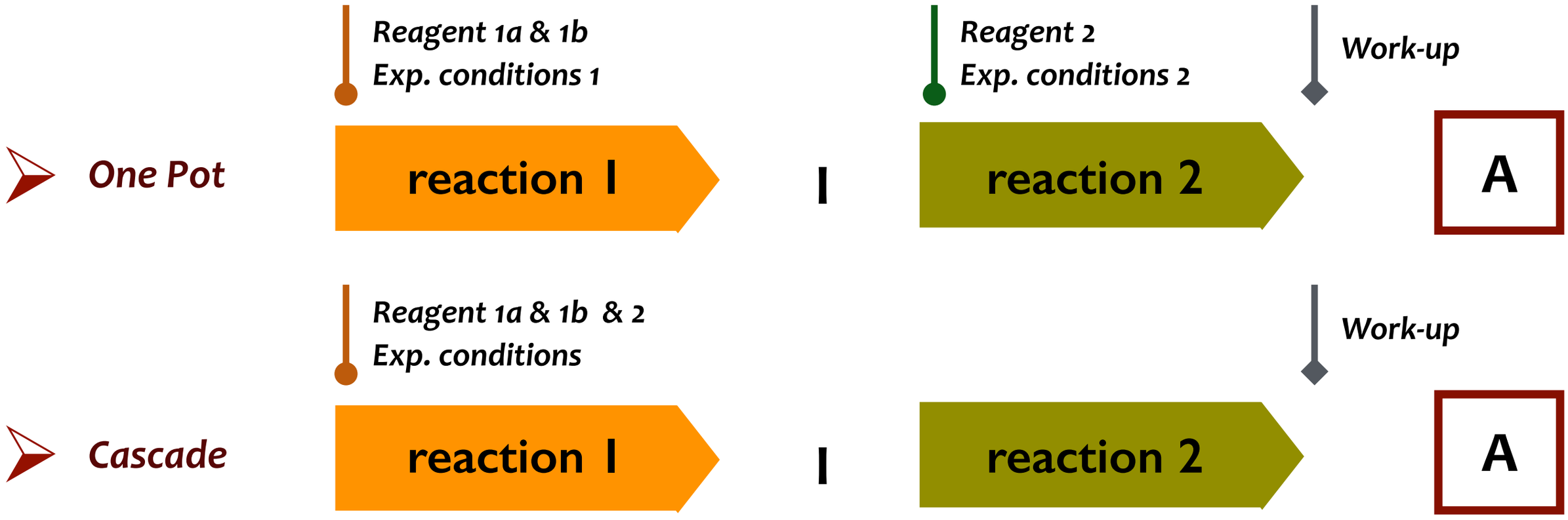
Pot Economy *strives to save time and resources by avoiding purifications between individual steps within a multistep synthesis, thus minimizing the transfer of material between vessels, which increases the overall efficiency. A procedure under* ***Pot Economy*** *premises can minimize chemical waste, save time, simplify practical aspects and increase the overall yield*

MacMillan, D. W. C. *Synlett* 2007, 1477; Clarke, P. A. *Green Chem.* **2007**, 9, 438; Christmann, M. *ACIE* **2011**, 50, 3605; Hayashi, Y. *CS* **2016**, 7, 866

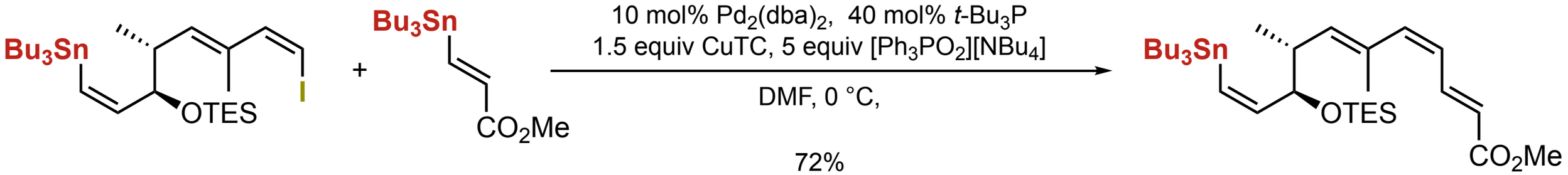
Pot Economy


A
Reagent 1a + Reagent 1b + Reagent 2


Reagent 1a & 1b
Exp. conditions 1
Work-up
Reagent 2
Exp. conditions 2
Work-up
Stop & Go
reaction 1
I
reaction 2
A

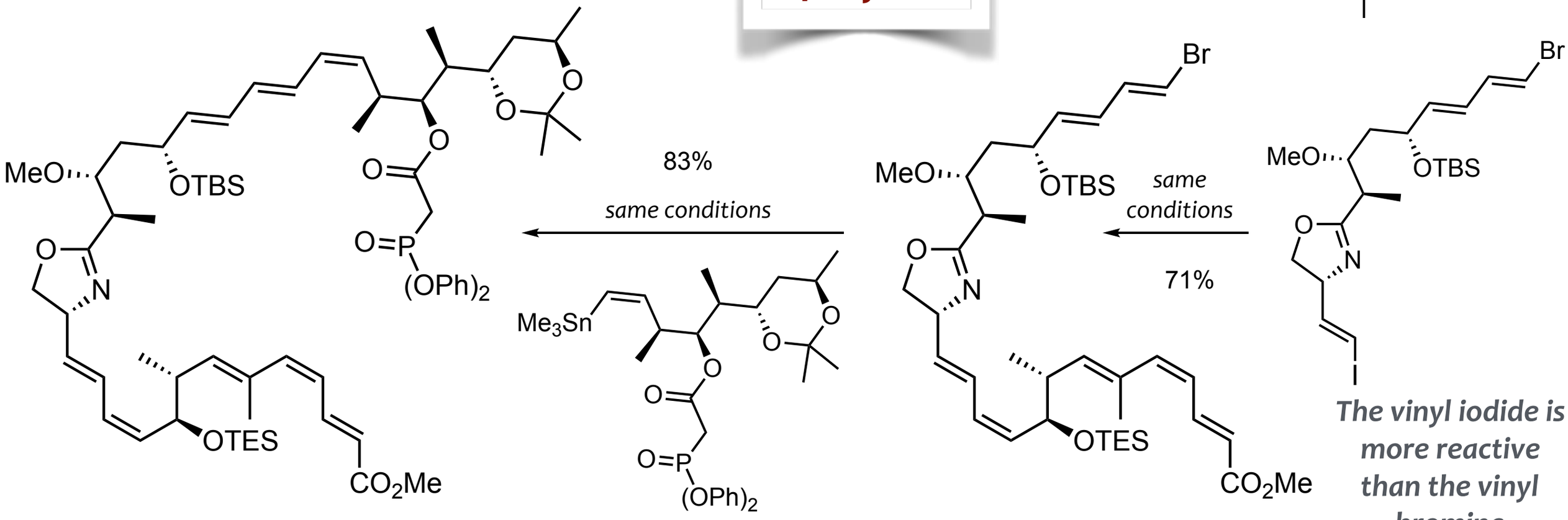

Reagent 1a & 1b
Exp. conditions 1
Reagent 2
Exp. conditions 2
Work-up
One Pot
reaction 1
I
reaction 2
A
Reagent 1a & 1b & 2
Exp. conditions
Work-up
Cascade
reaction 1
I
reaction 2
A

Stop&Go and One-Pot Procedures



The E vinyl stannane is more reactive than the Z vinyl stannane for steric reasons

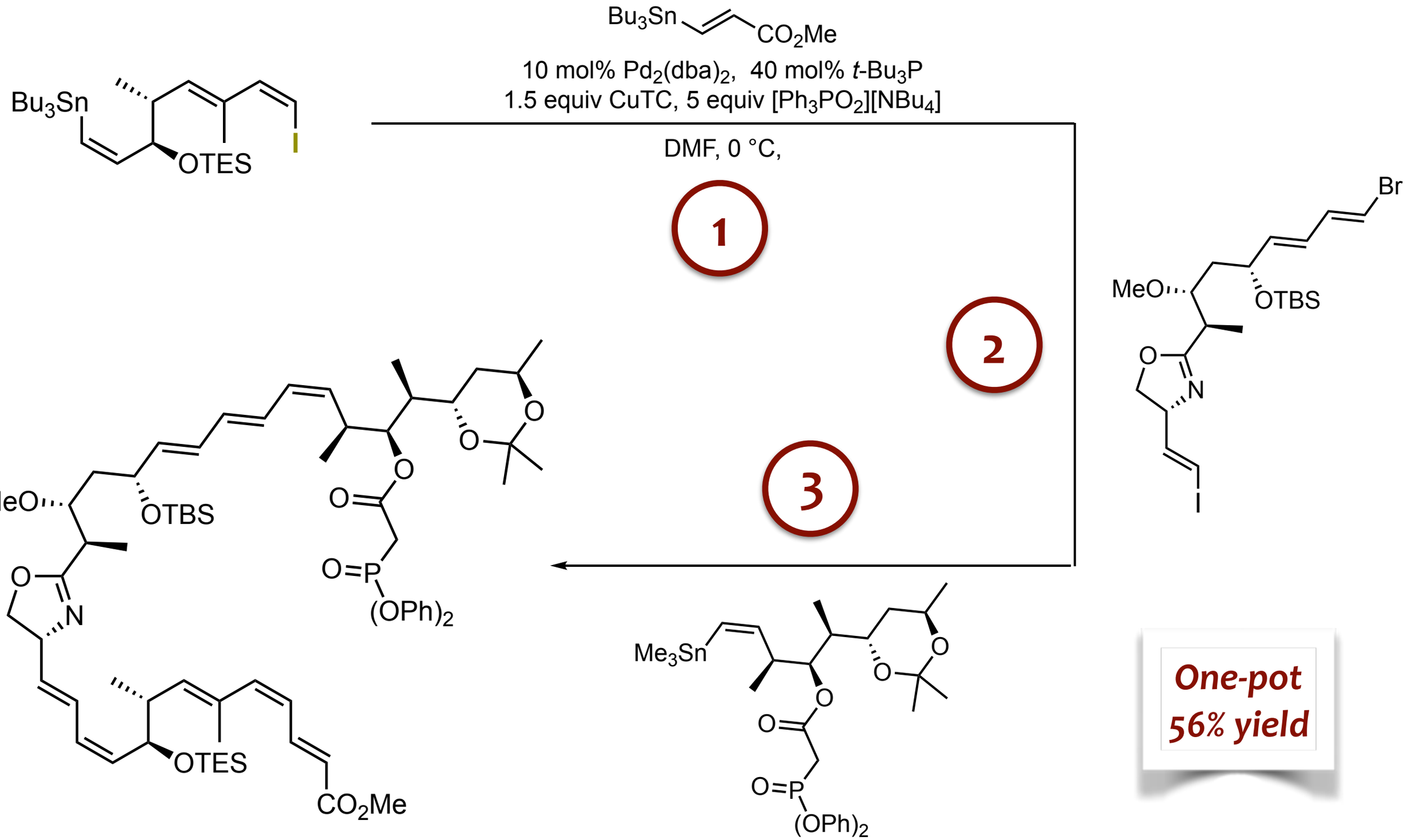
Three steps 40% yield



The vinyl iodide is more reactive than the vinyl bromine

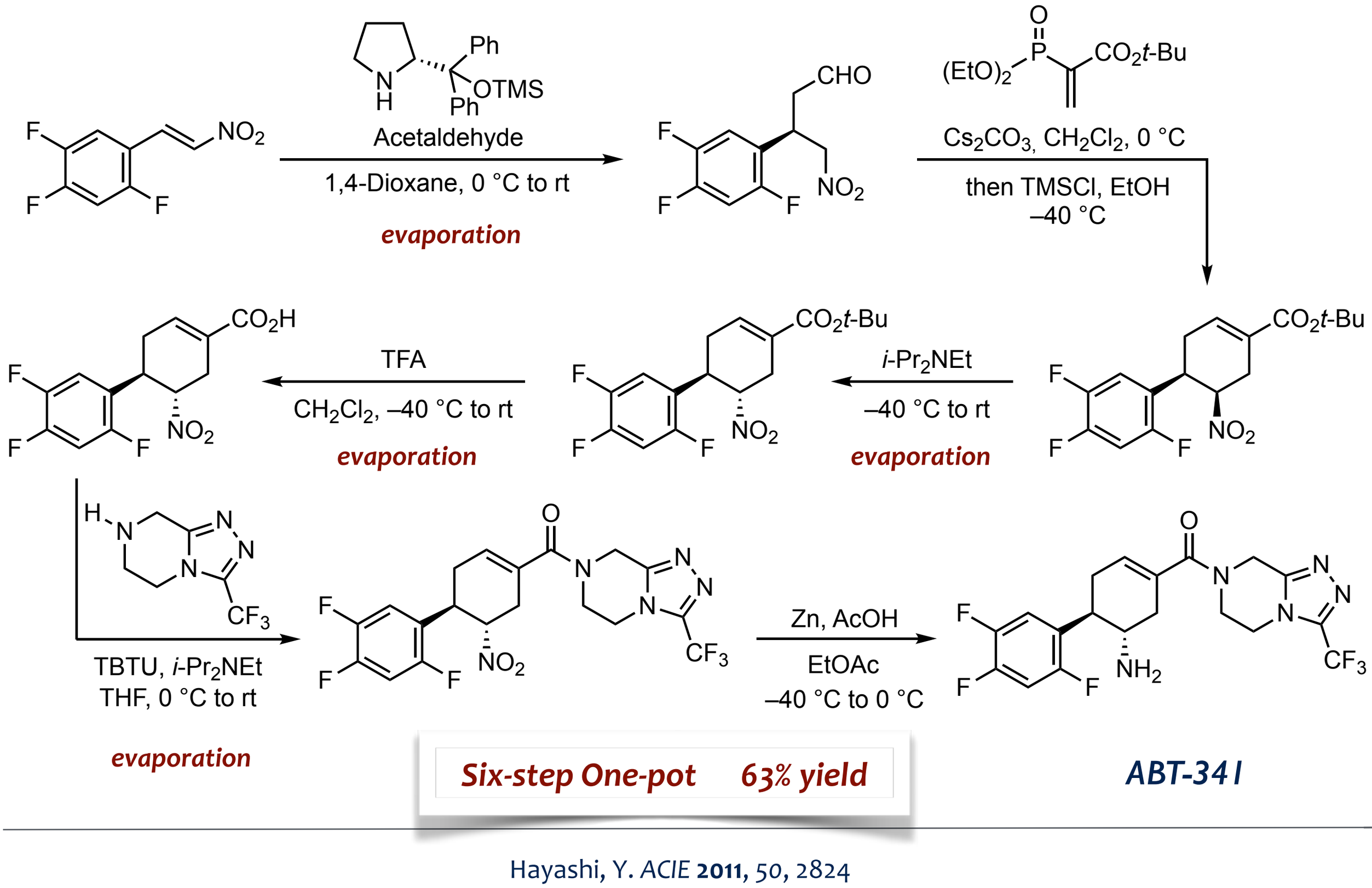
Paterson, I. *ACIE* **2017**, 56, 645

Stop&Go and One-Pot Procedures



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

Stop&Go and One-Pot Procedures



Hayashi, Y. *ACIE* **2011,** *50,* 2824

Concepts and Terminology

Today it is not only a question of what we can synthesize,
but ***how we do it****…*

The usual procedure for the synthesis of organic compounds
is the stepwise formation of the individual bonds in the target molecule.
However, it would be much more efficient if
one could form several bonds in one sequence without isolating the intermediates,
changing the reaction conditions, or adding reagents

Thus, these reactions would allow an ecologically and economically favorable production

We call this type of transformation a **DOMINO REACTION**
For this also the expression **CASCADE** *has been used*

Tietze, L. F. *CR* **1996**, 96, 115

Concepts and Terminology

Different authors use varying definitions as to
what constitutes a cascade process.
A variety of terms, including ***cascade***, ***domino***, ***tandem***, *and* ***sequential***,
are used in the literature, often seemingly
interchangeably and with liberal abandon …
For our subjective purposes, we shall employ
the term **CASCADE** *to encompass all of the above descriptors*

If further reagents are added at various points **ONE POT TRANSFORMATION**

Although often composed solely of intramolecular transformations,
cascade reactions can also occur intermolecularly,
in which case they also fall under the category of **MULTICOMPONENT REACTIONS**,
where three or more compounds react to form a single product that
retain majority of the atoms of the starting materials

Nicolaou, K. C. *ACIE* **2006**, *45*, 7134; *CSR* **2009**, *38*, 2993

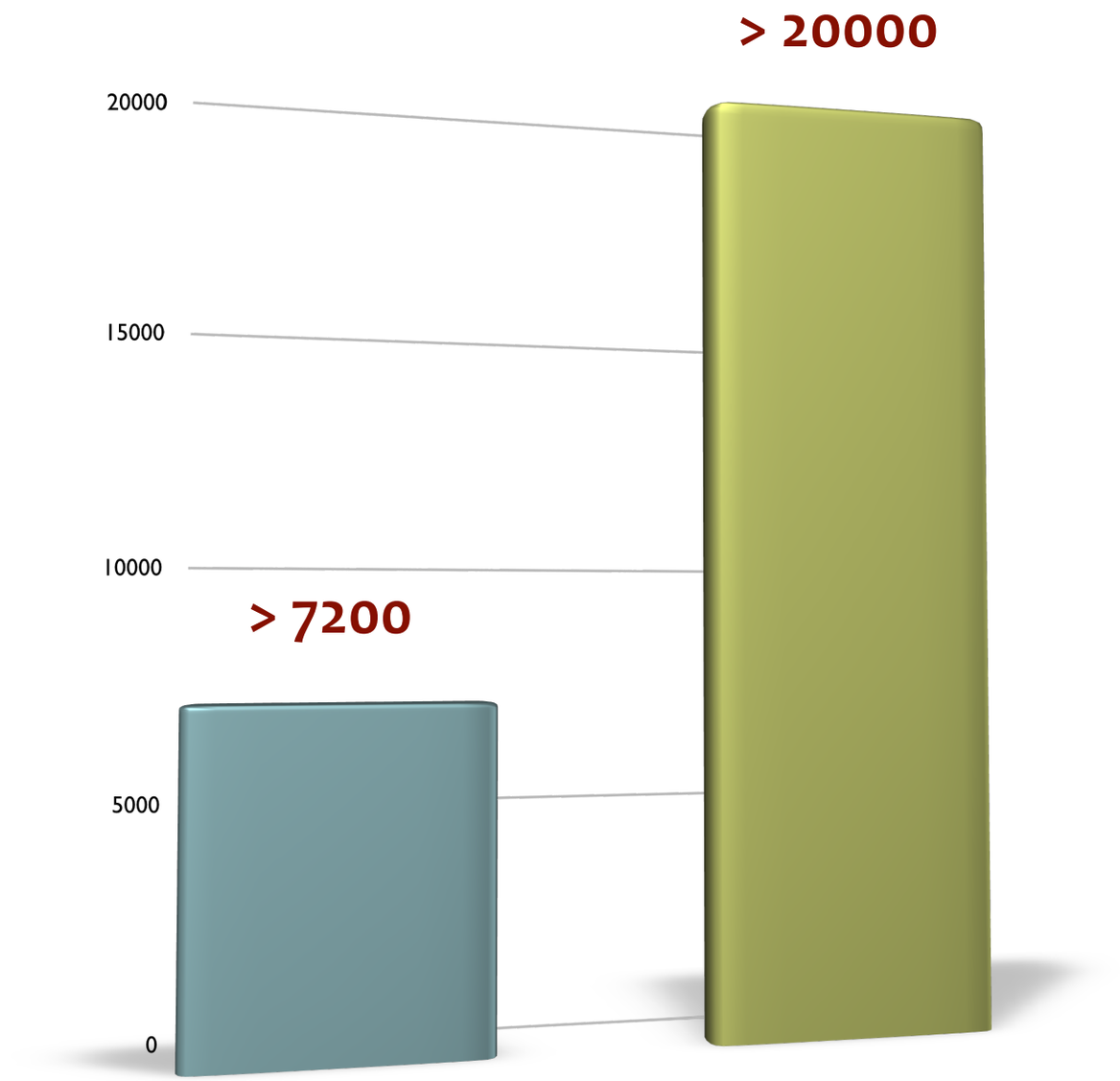
Concepts and Terminology

DOMINO

Tietze, L. F. *CR* **1996**, *96*, 115

CASCADE

Nicolaou, K. C. *ACIE* **2006**, *45*, 7134



Number of Articles Containing Term in the Title

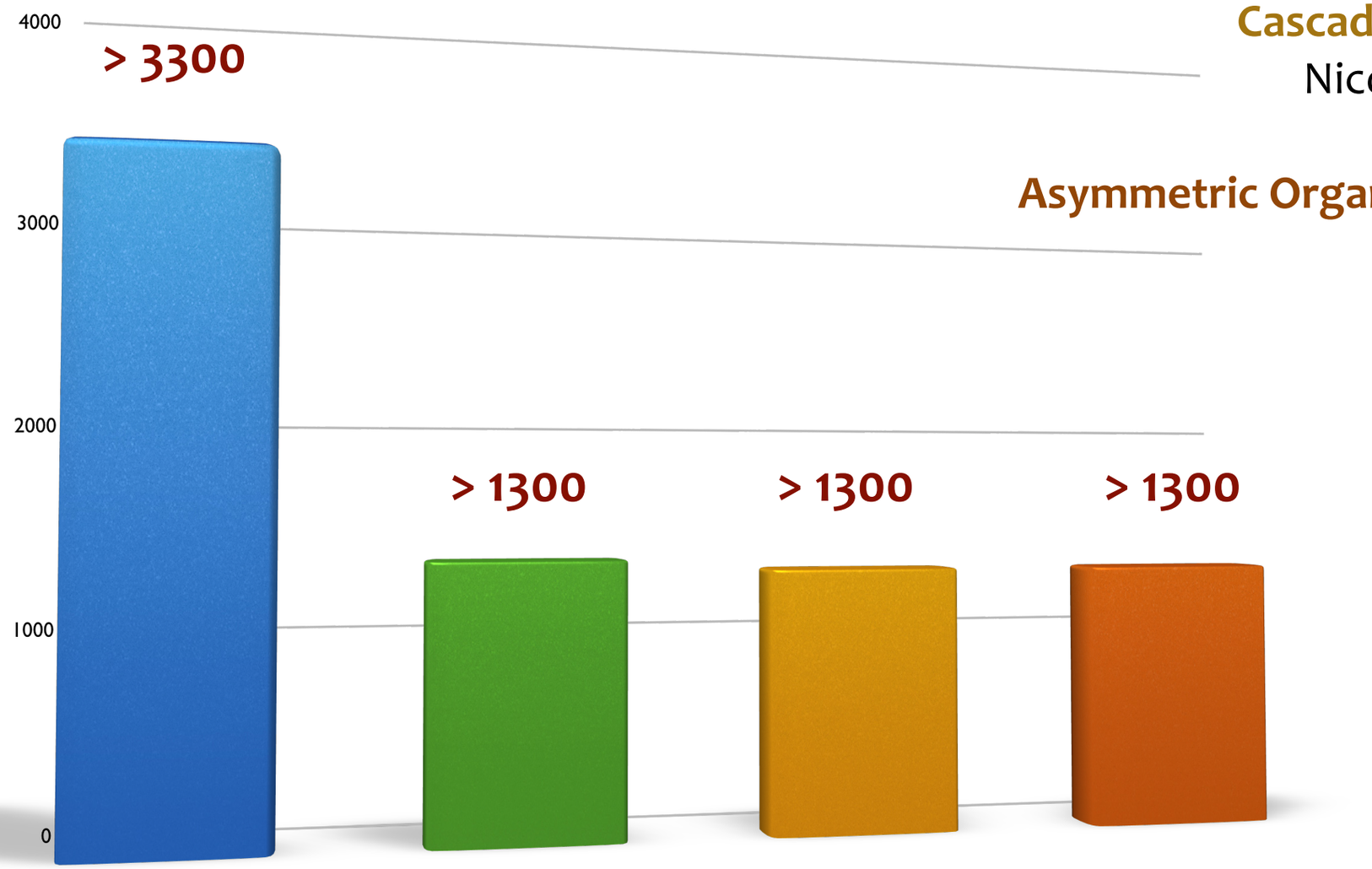
Concepts and Terminology

Domino Reactions in Organic Synthesis
Tietze, L. F. *CR* **1996**, *96*, 115

Asymmetric Multicomponent Reactions (AMCRs): The New Frontier
Yus, M. *ACIE* **2005**, *44*, 1602

Cascade Reactions in Total Synthesis
Nicolaou, K. C. *ACIE* **2006**, *45*, 7134

Asymmetric Organocatalytic Domino Reactions
Enders, D. *ACIE* **2007**, *46*, 1570



Concepts and Terminology

Domino *(or* ***Cascade****) reaction is a process involving two or more bond forming transformations (usually C–C bonds), which take place under the same reaction conditions without adding additional reagents and catalysts and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*

Tietze, L. F. *CR* **1996**, 96, 115

Concepts and Terminology

The rapid generation of molecular complexity from simple starting materials is of paramount importance in synthetic chemistry

The design of cascades to provide specific targeted molecules of considerable structural and stereochemical complexity poses a significant intellectual challenge and can be one of the most impressive activities in natural product synthesis.

Cascade reactions *contribute immeasurably to both the* ***science and art*** *of total synthesis, bringing not only improved* ***practical efficiency*** *but also enhanced aesthetic appeal to synthetic planning*

Although often composed solely of ***intramolecular transformations****, cascade reactions can also occur* ***intermolecularly***

According to the mechanism of the first step, one can distinguish between a ***nucleophilic, electrophilic, radical, pericyclic, transition-metal,*** *or* ***organocatalytic*** *cascades, which can be combined with reactions of the described type in a second, third, or fourth step*

Tietze, L. F. *CR* **1996**, *96*, 115. Nicolaou, K. C. *ACIE* **2006**, *45*, 7134; *CSR* **2009**, *38*, 2993; Anderson, E. A. *CSR* **2016**, *45*, 1557

Nucleophilic Cascades

Robinson Anullation

Mannich Reaction

See also Chapter 4 & 6

See also Multicomponent Reactions

2 new bonds & 1 stereocenter

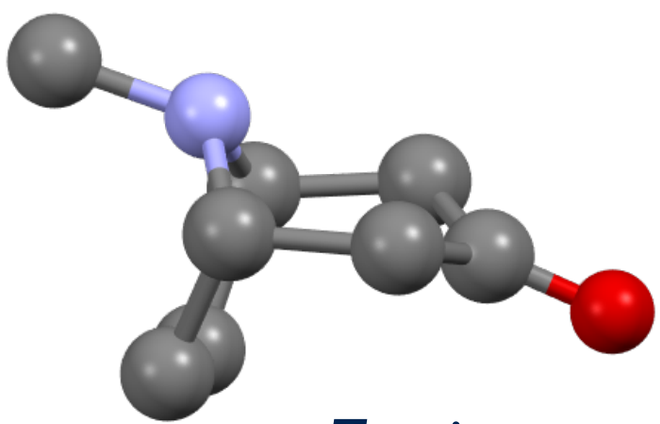
Nucleophilic Cascades

Robinson's landmark synthesis of tropinone

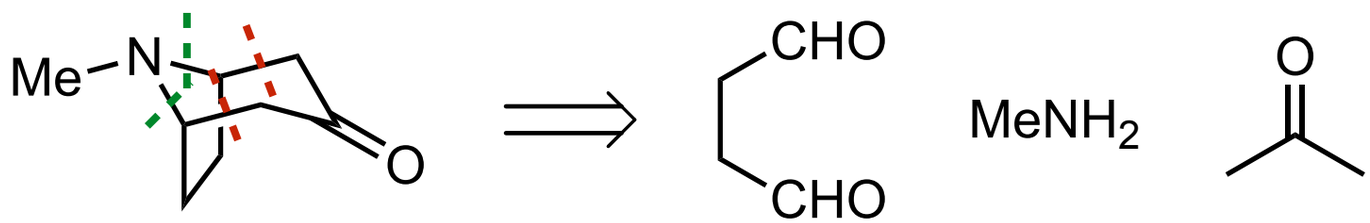
By imaging hydrolysis at the points indicated by the dotted lines,
the substance may be resolved into
succinaldehyde, methyl amine, and acetone,
and this observation suggested a line of attack of the problem
which has resulted in a ***direct synthesis***

Sir Robert Robinson
(1886-1975)

NOBEL PRIZE IN CHEMISTRY 1947



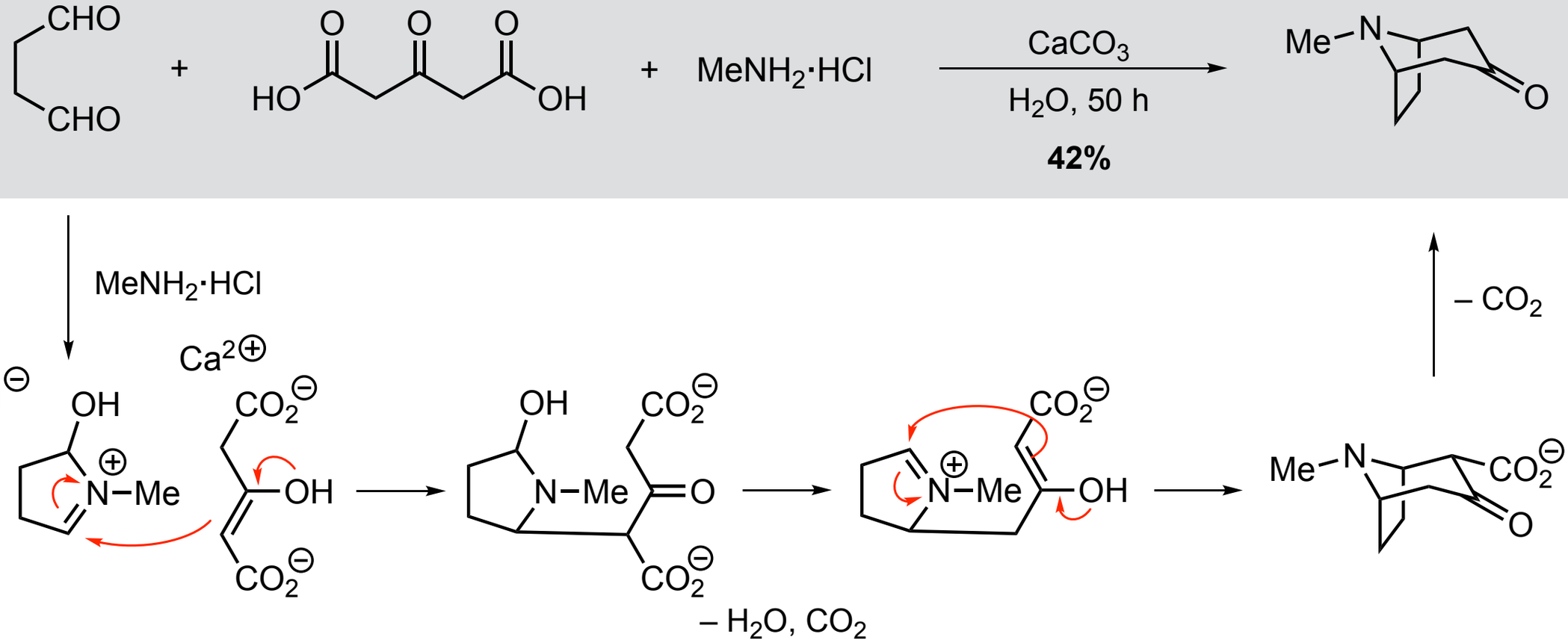
Tropinone



Robinson, R. *JCS Trans* **1917,** *111*, 762; *CC* **2013,** *49*, 10775

Nucleophilic Cascades

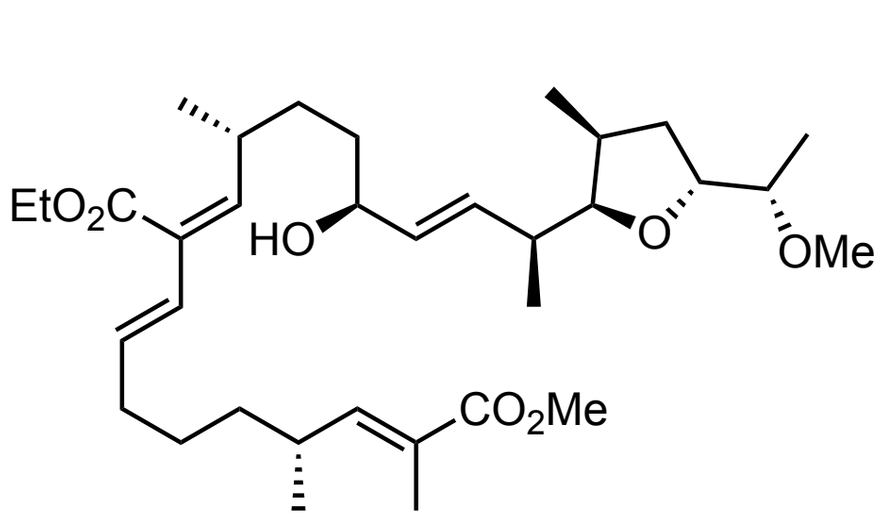
Robinson's landmark synthesis of tropinone



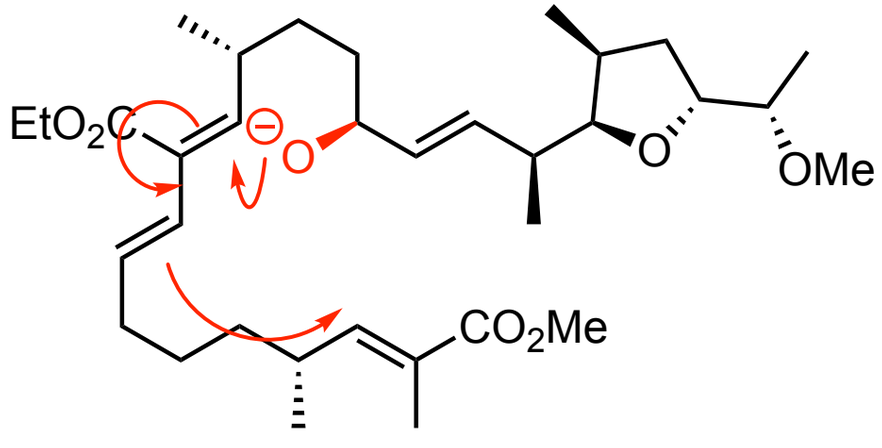
4 new bonds in a single step

Robinson, R. *JCS Trans* **1917,** *111*, 762; *CC* **2013,** *49*, 10775

Nucleophilic Cascades

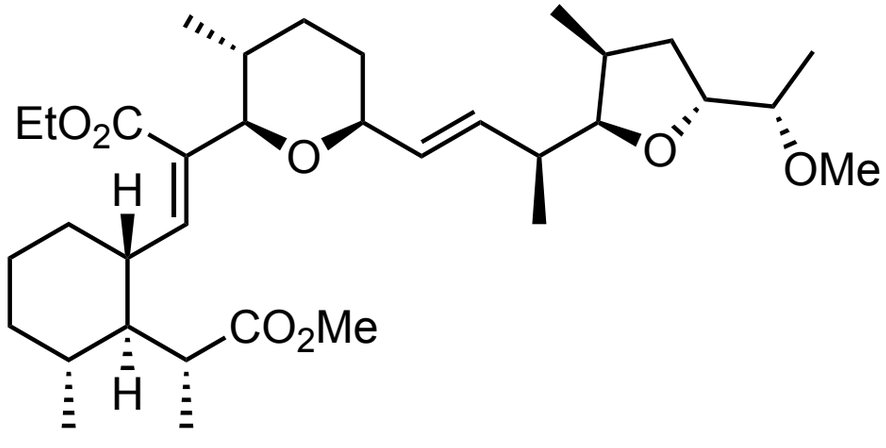


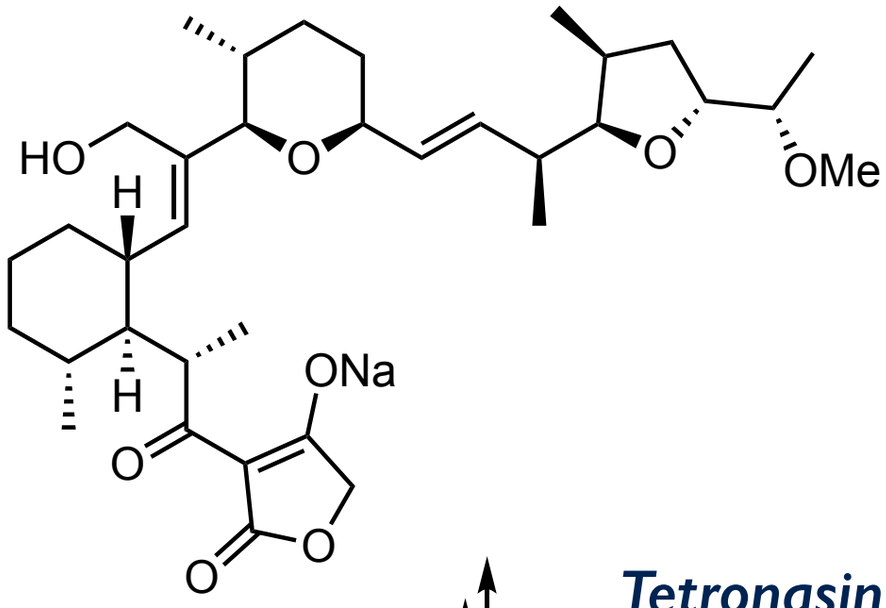
KHMDS, toluene, 0 °C



2 new bonds &
4 stereocenters

67%



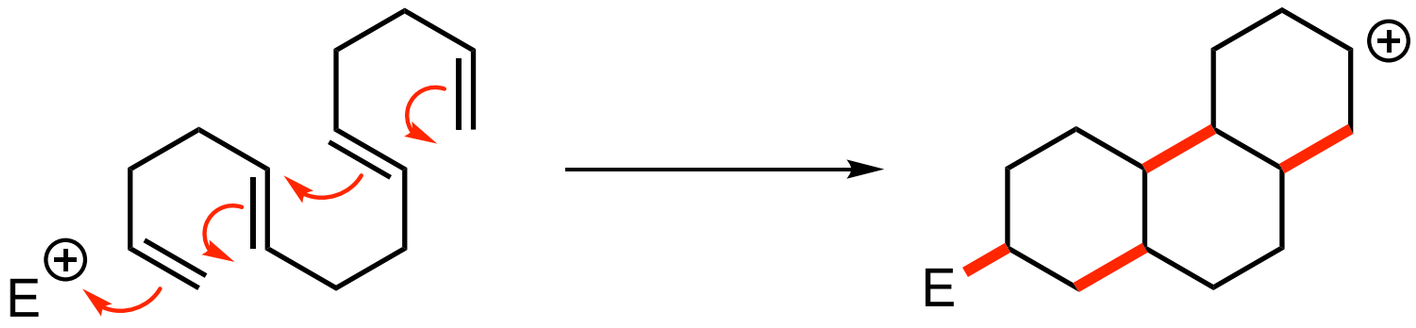


Tetronasin

Ley, S. V. *JCS Perkin Trans. 1* **1998,** 2259

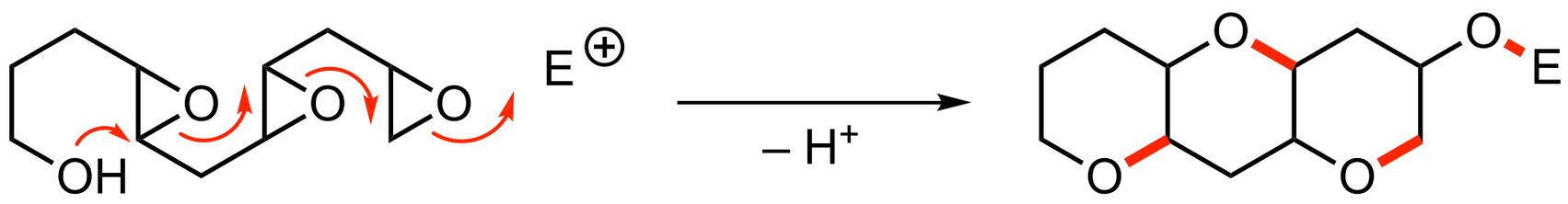
Electrophilic Cascades

Polyene Cyclizations



Tietze, L. F. *CR* **1996**, *96*, 115. Nicolaou, K. C. *ACIE* **2006**, *45*, 7134.
Johnston, J. N. *CR* **2005**, *105*, 4730. Barrett, A. G. M. *Synthesis* **2019**, *51*, 67

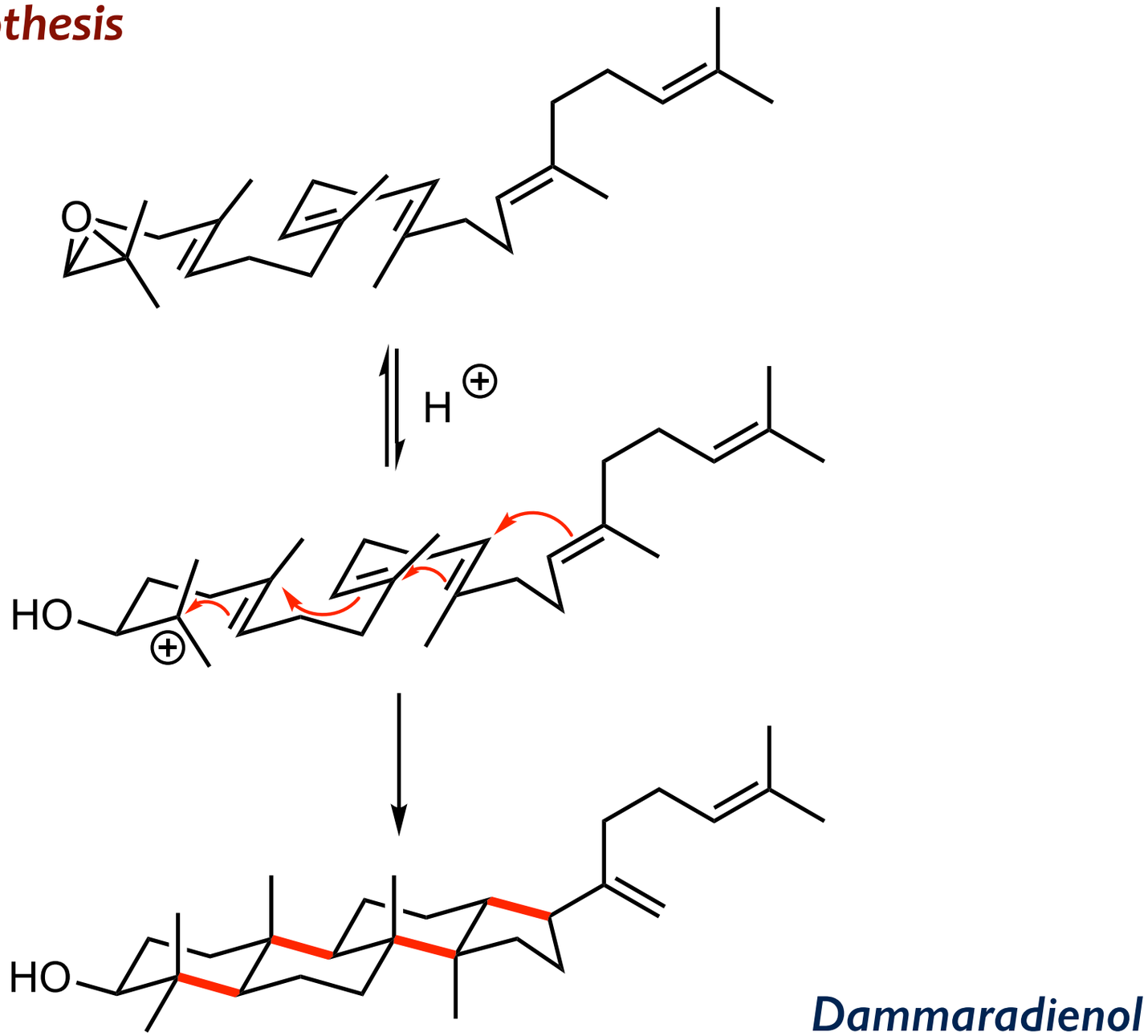
Epoxide-Opening Cascades



Jamison, T. F. *CSR* **2009**, *38*, 3175; *ACIE* **2009**, *48*, 5250; *Mar. Drugs* **2010**, *8*, 763

Electrophilic Cascades. Polyene Cyclizations

Stork-Eschenmoser hypothesis

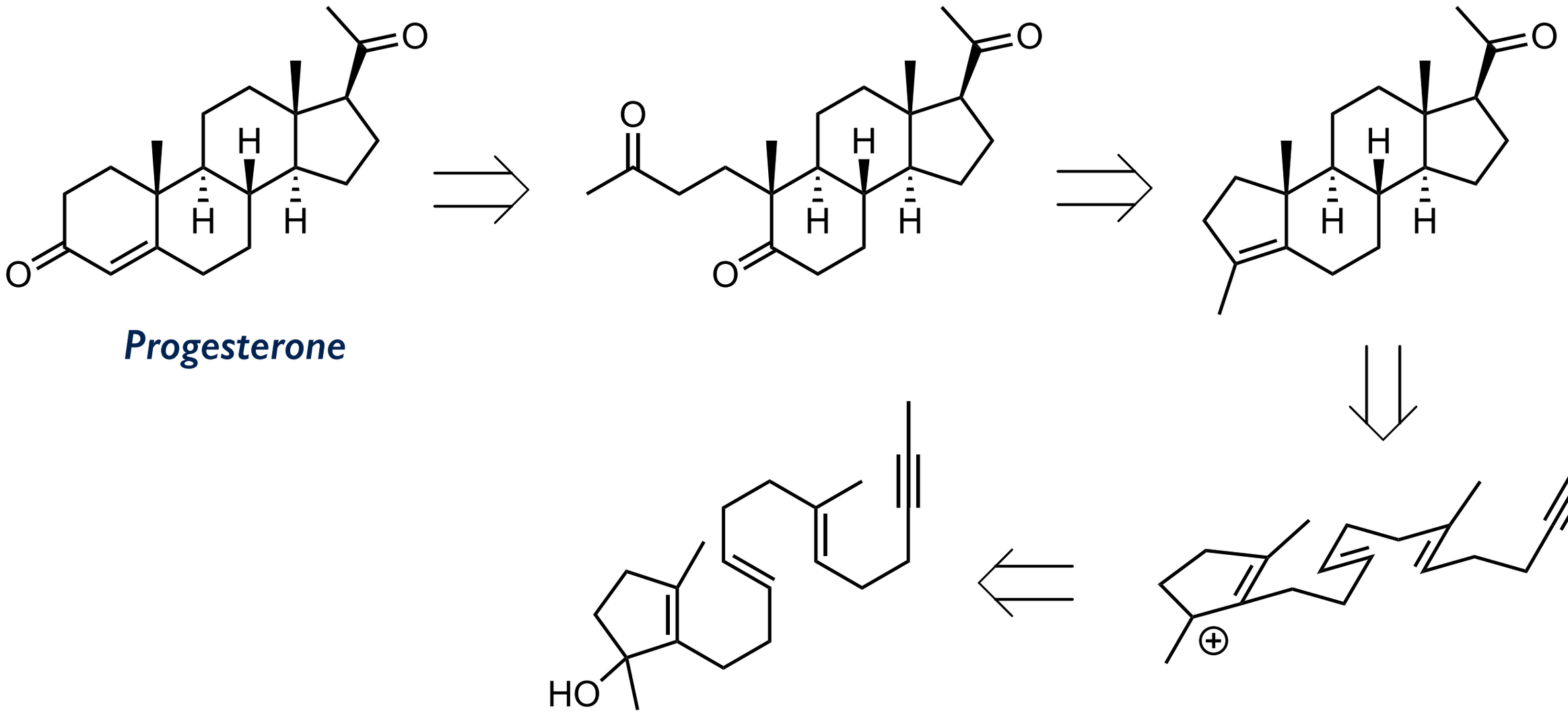


Dammaradienol

Stork, G. *JACS* **1955**, *77*, 5068; Eschenmoser, A. *HCA* **1955**, *38*, 1890 & **1957**, *40*, 2191

Electrophilic Cascades. Polyene Cyclizations

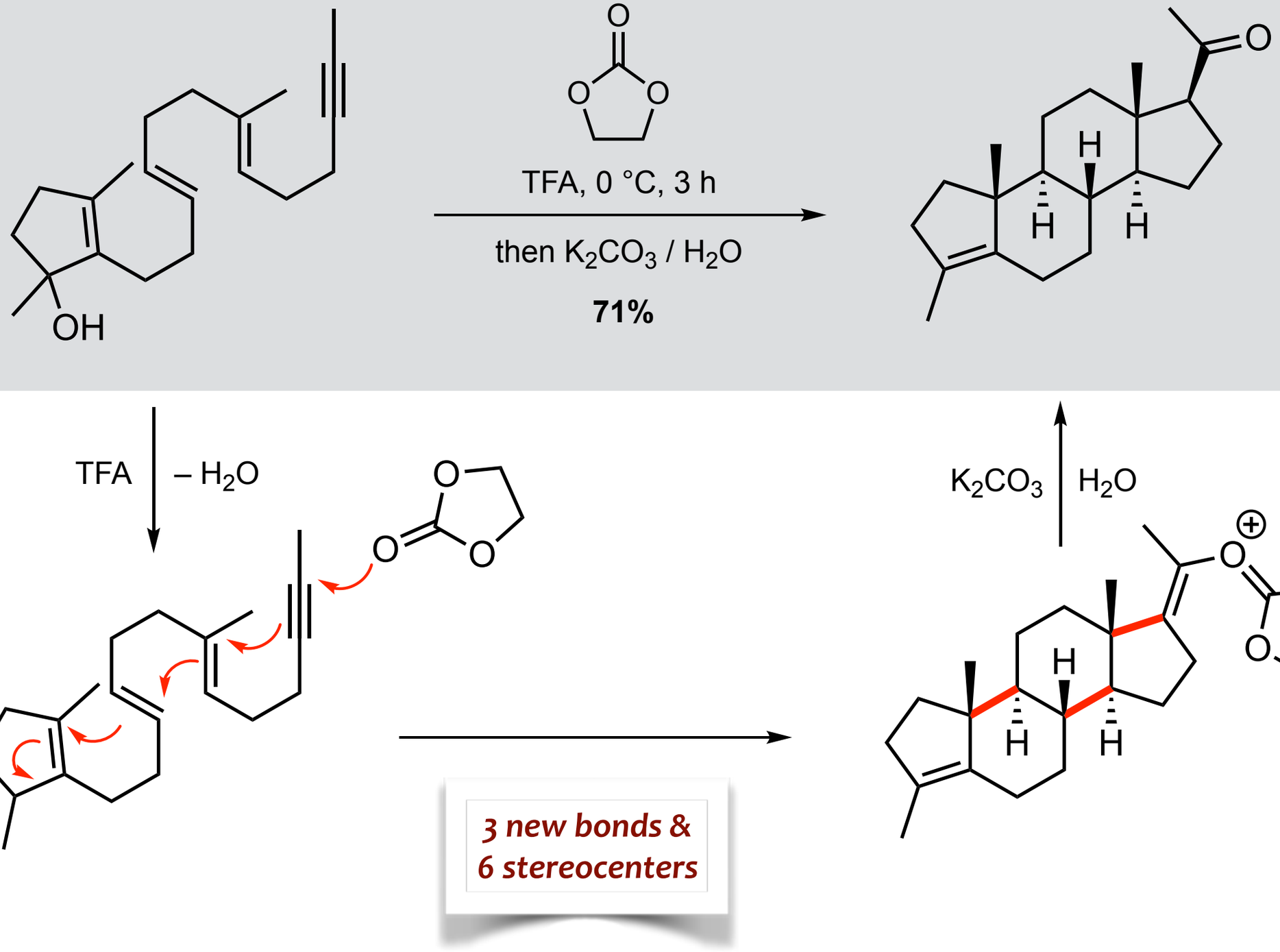
Johnson's landmark synthesis of progesterone



Progesterone

Johnson, W. S. JACS 1971, 93, 4332; *ACIEE* **1976**, *15*, 9; *JACS* **1978**, *100*, 4274

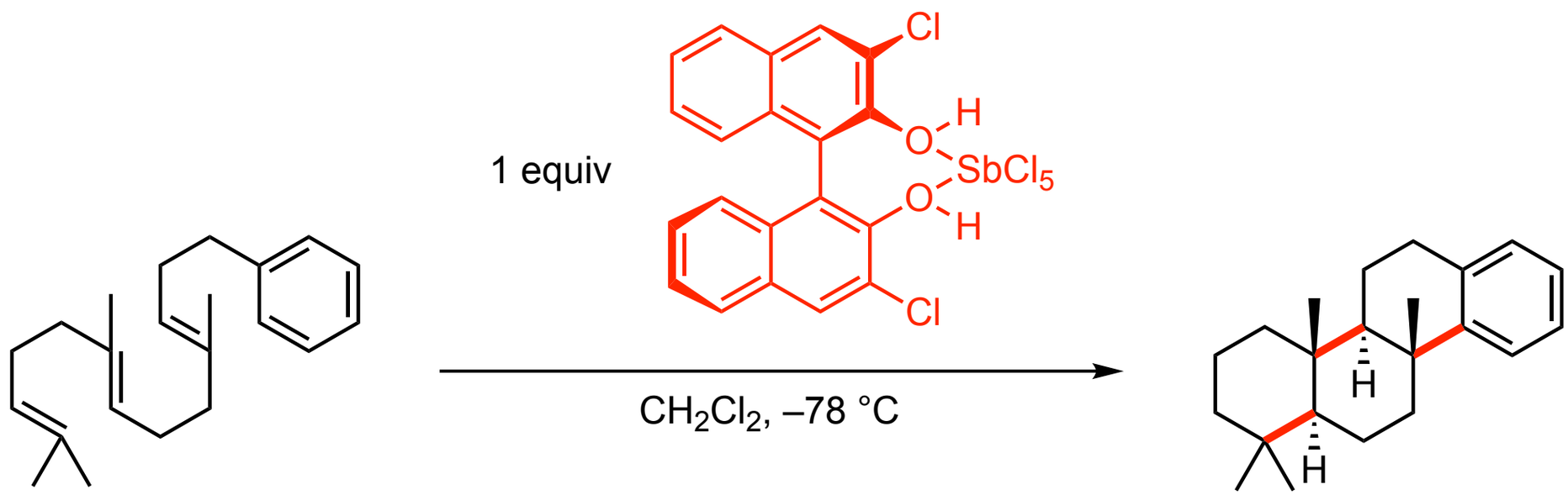
Electrophilic Cascades. Polyene Cyclizations

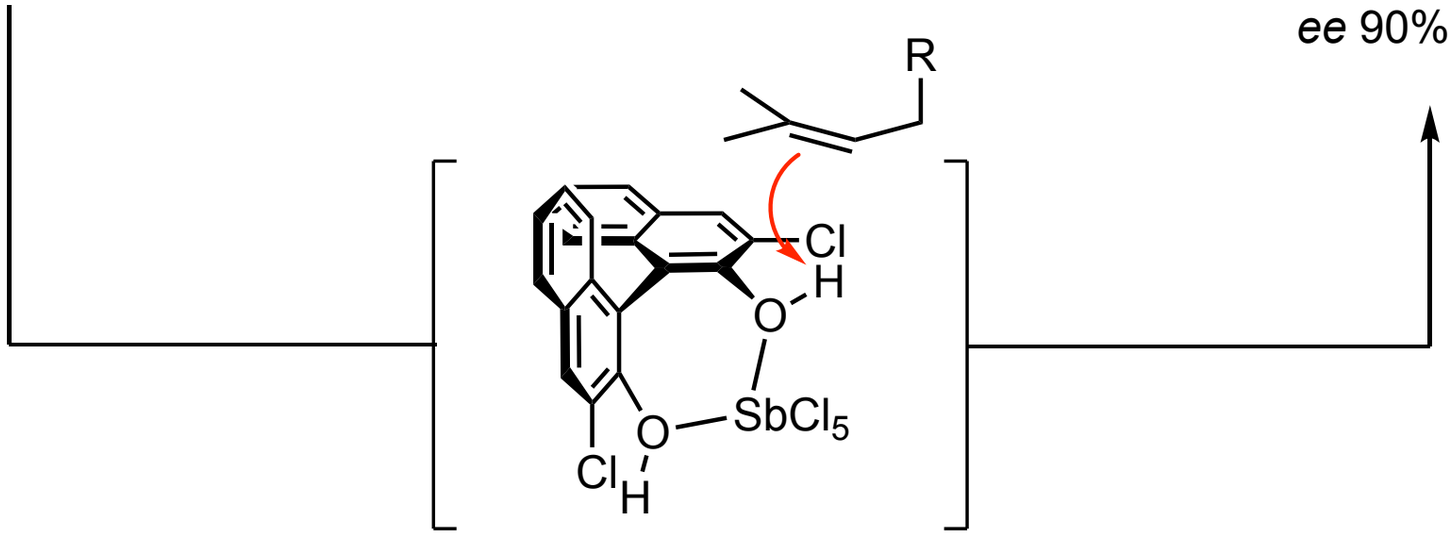


Johnson, W. S. *JACS* **1971**, *93*, 4332; *ACIEE* **1976**, *15*, 9; *JACS* **1978**, *100*, 4274

Electrophilic Cascades. Polyene Cyclizations

Polyene cyclizations controlled by chiral Lewis acid can be ***enantioselective***



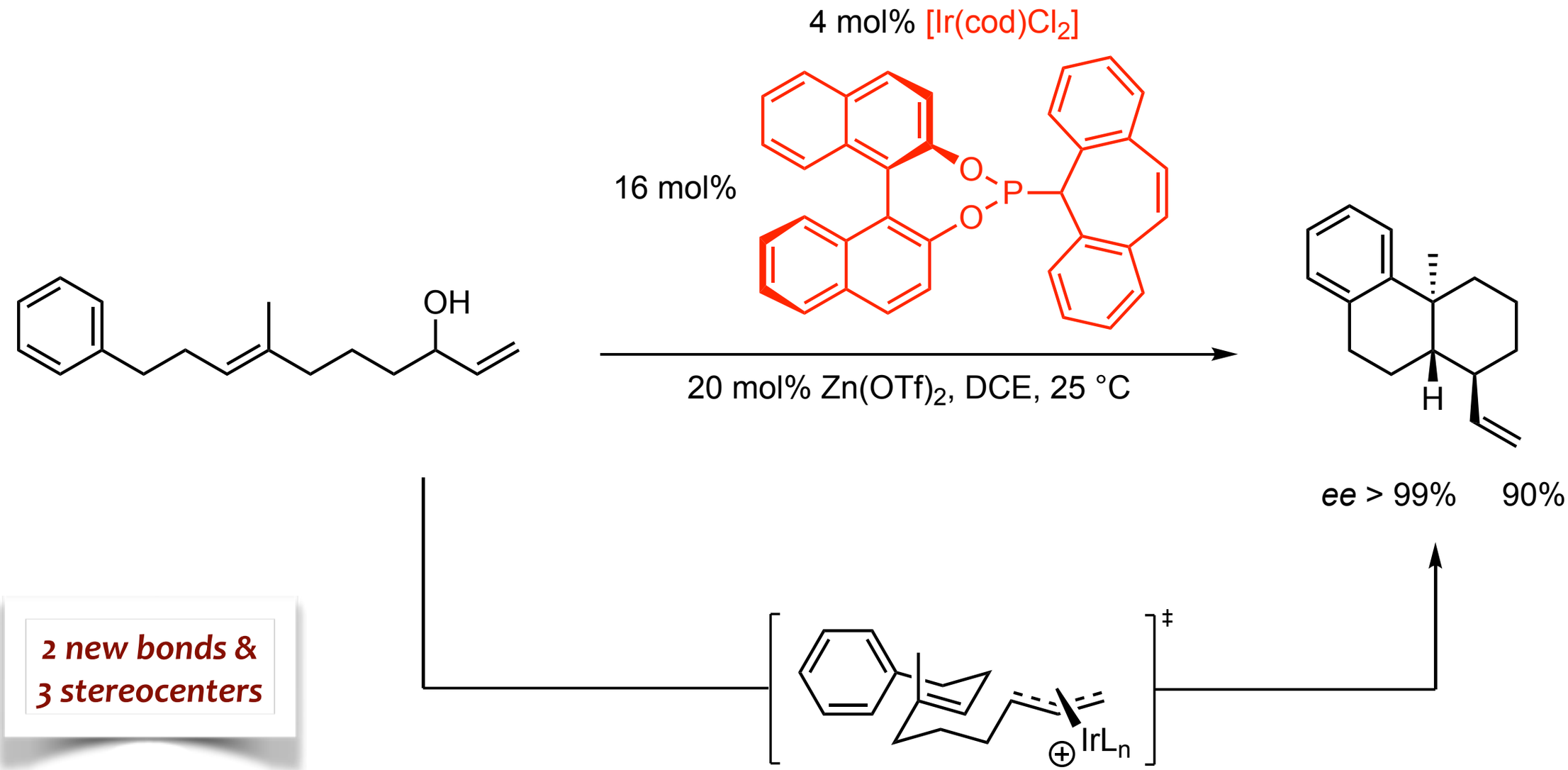


3 new bonds & 4 stereocenters

Corey, E. J. *JACS* **2012**, *134*, 11992

Electrophilic Cascades. Polyene Cyclizations

Polyene cyclizations controlled by chiral Lewis acid can be ***enantioselective*** *and* ***catalytic***

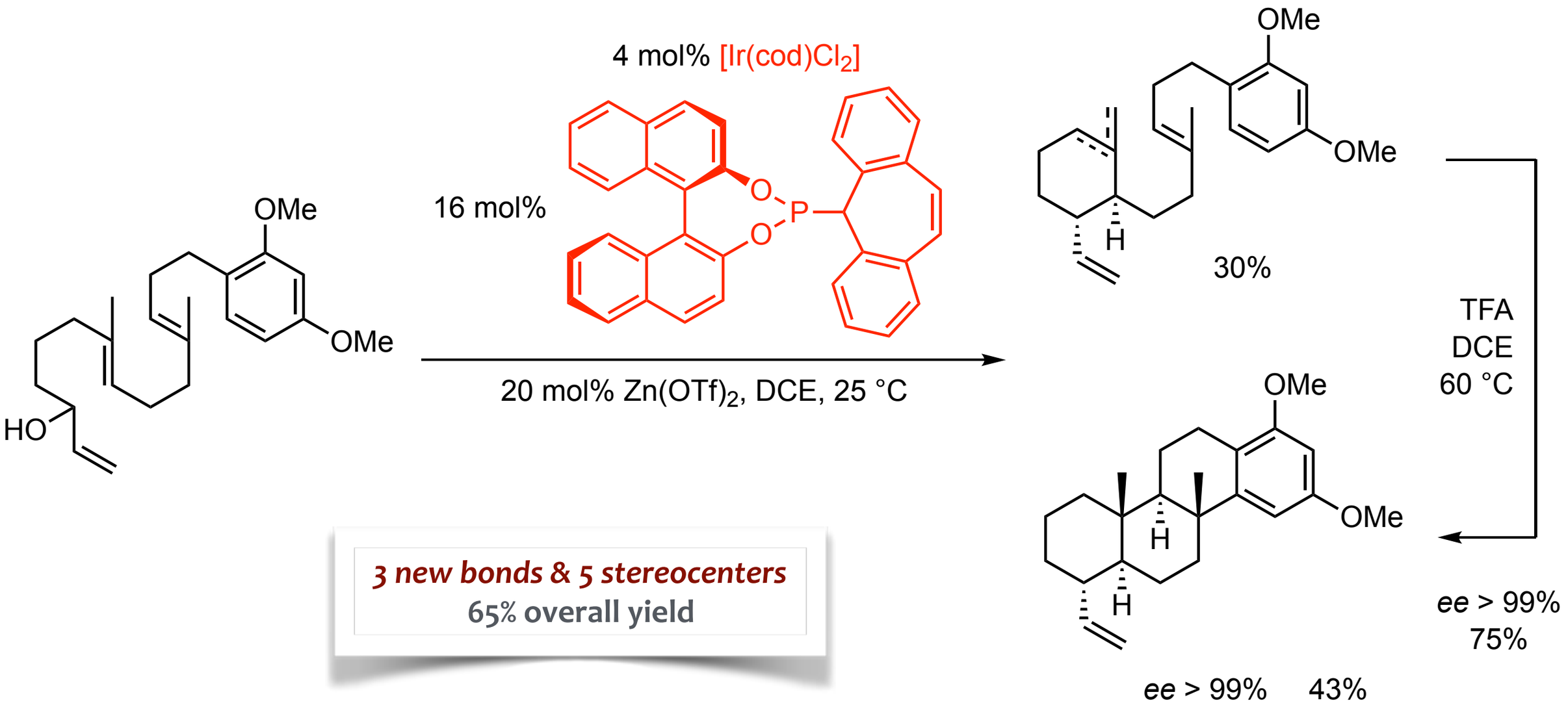


2 new bonds & 3 stereocenters

Carreira, E. M. *JACS* **2012**, *134*, 20276

Electrophilic Cascades. Polyene Cyclizations

*Polyene cyclizations controlled by chiral Lewis acid can be **enantioselective** and **catalytic***

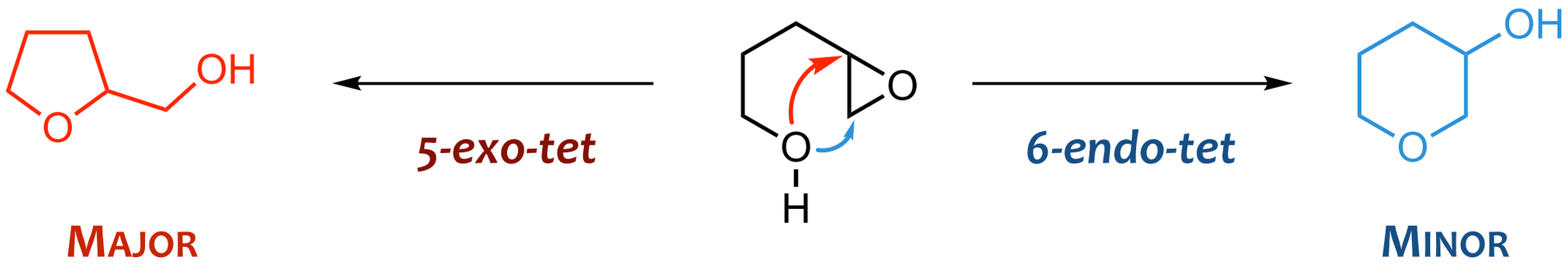


3 new bonds & 5 stereocenters
65% overall yield

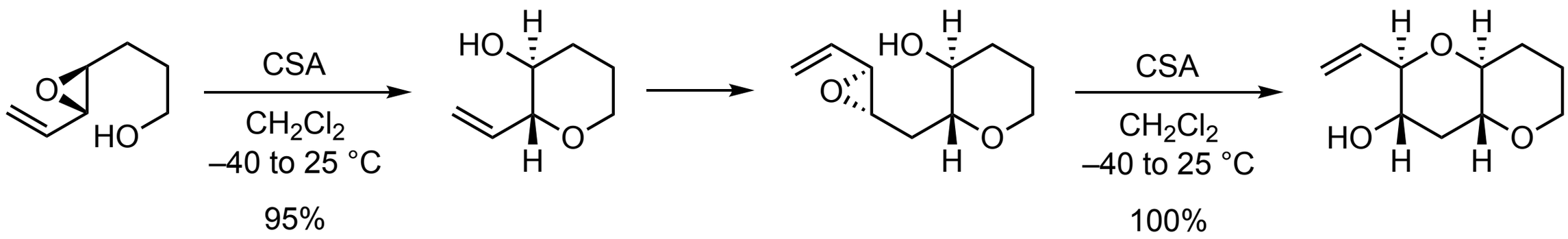
Carreira, E. M. *JACS* **2012**, *134*, 20276

Electrophilic Cascades. Epoxide Opening

*The cyclization of hydroxy epoxides often favors the **exo-tet** opening*

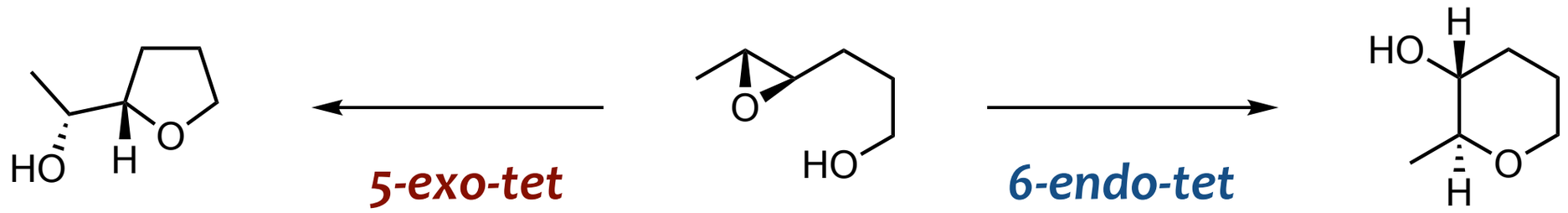


*Methods for **endo-cyclizations** rely on substituents that stabilize the partial positive charge or directing groups that deactivate the exo pathway*



Nicolaou, K. C. *JACS* **1989**, *111*, 5330; Jamison, T. F. *ACIE* **2009**, *48*, 5250, *Mar. Drugs* **2010**, *8*, 763

Electrophilic Cascades. Epoxide Opening

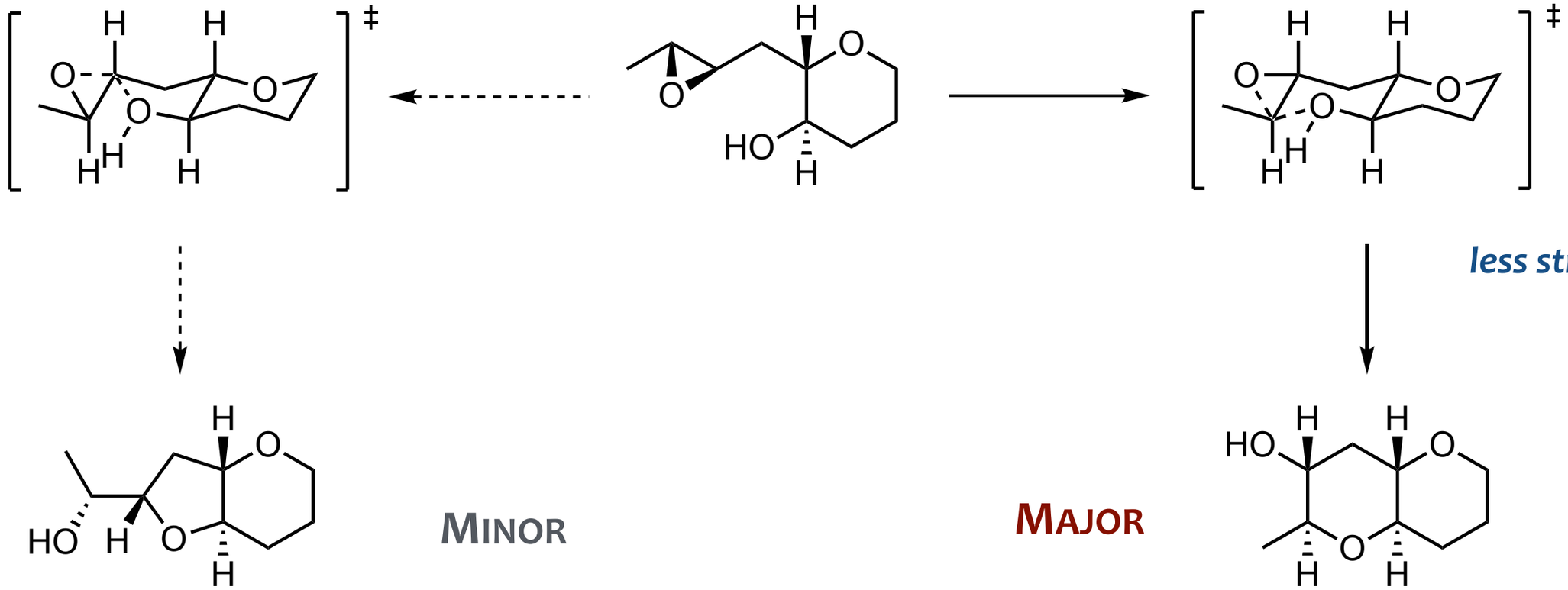


MAJOR

MINOR

attach template to preorganize the substrate

alter the approach of the nucleophile to the epoxide



MINOR

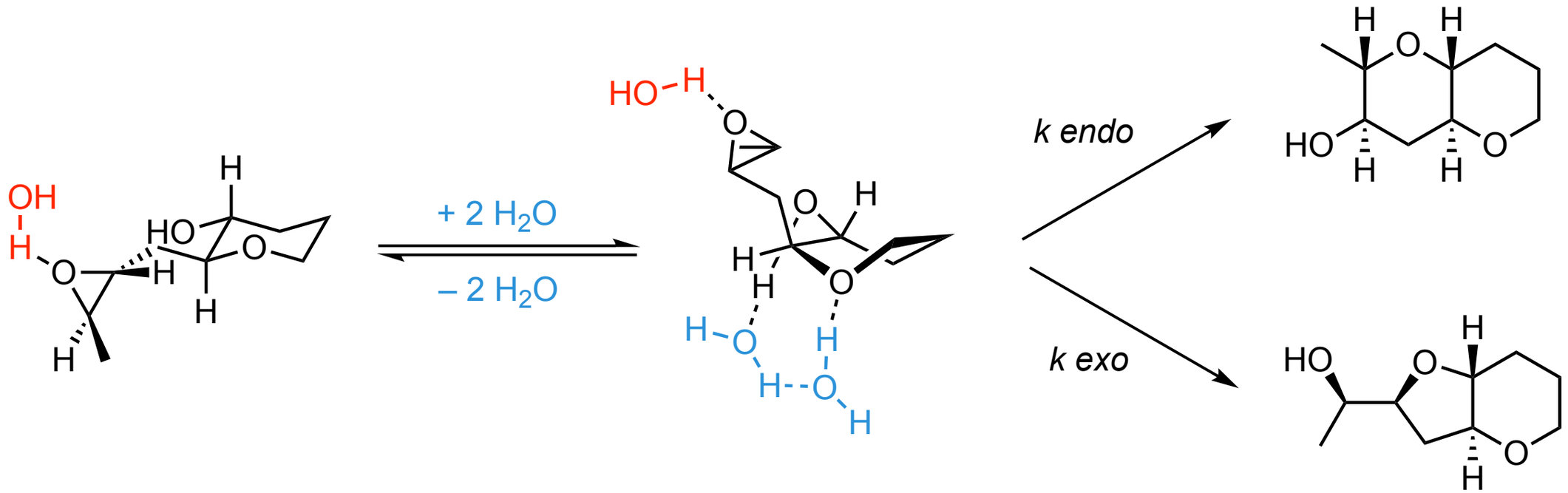
MAJOR

Jamison, T. F. *Science* **2007**, *317*, 1189

Electrophilic Cascades. Epoxide Opening

Water plays a crucial role both in the conversion and the selectivity

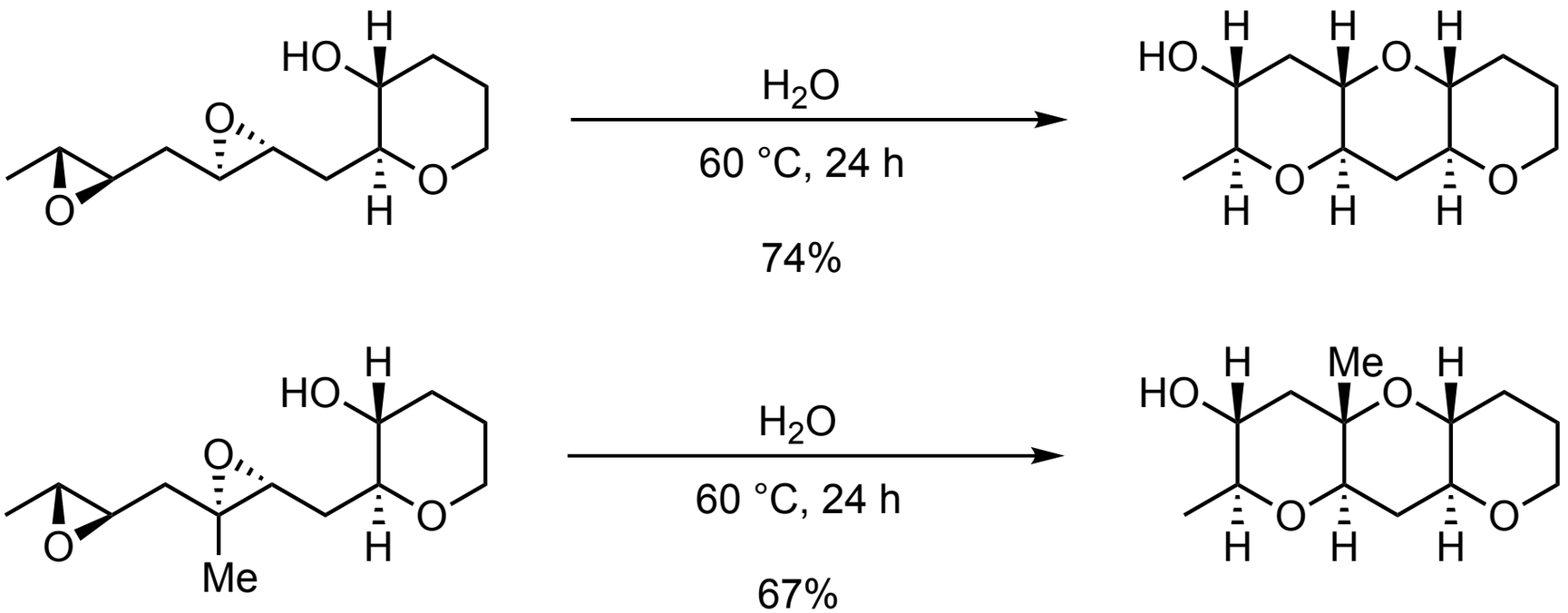
Jamison suggested that epoxy alcohol cyclizations in water occur for hydrated conformations with the appropriate geometry for the reaction



k endo >> k exo

Jamison, T. F. *Science* **2007**, *317*, 1189; *JACS* **2009**, *131*, 6383; *Mar. Drugs.* **2010**, *8*, 763

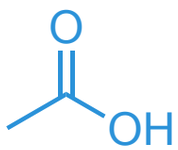
Electrophilic Cascades. Epoxide Opening



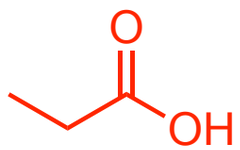
Jamison, T. F. *Science* **2007**, *317*, 1189; *JACS.* **2009**, *131*, 6678; *ACIE* **2009**, *48*, 4430

Electrophilic Cascades. Epoxide Opening

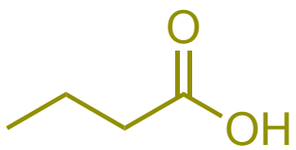
Cane-Celmer-Westley hypothesis on the polyether biogenesis



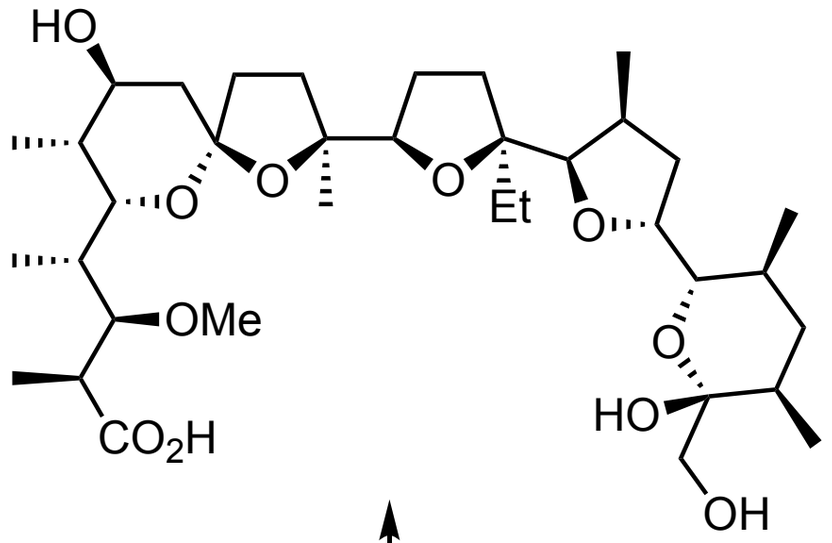
(5x)



(7x)

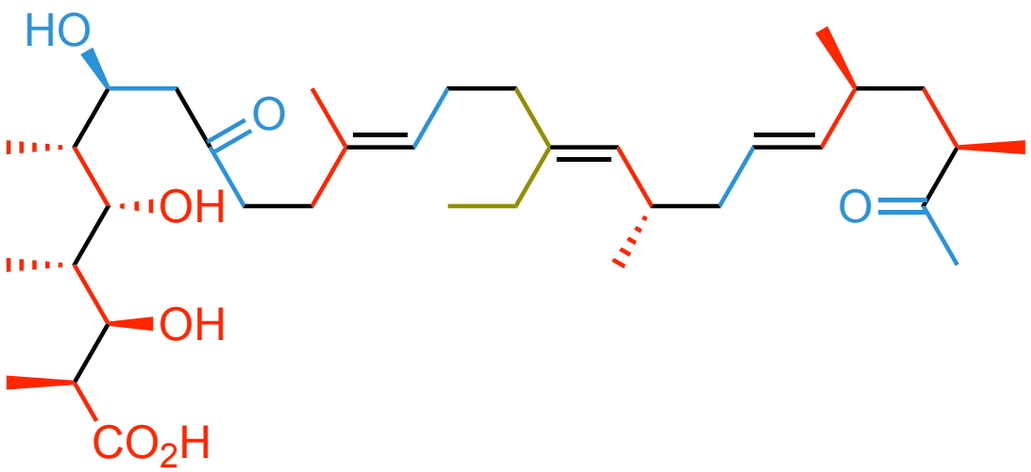


(1x)

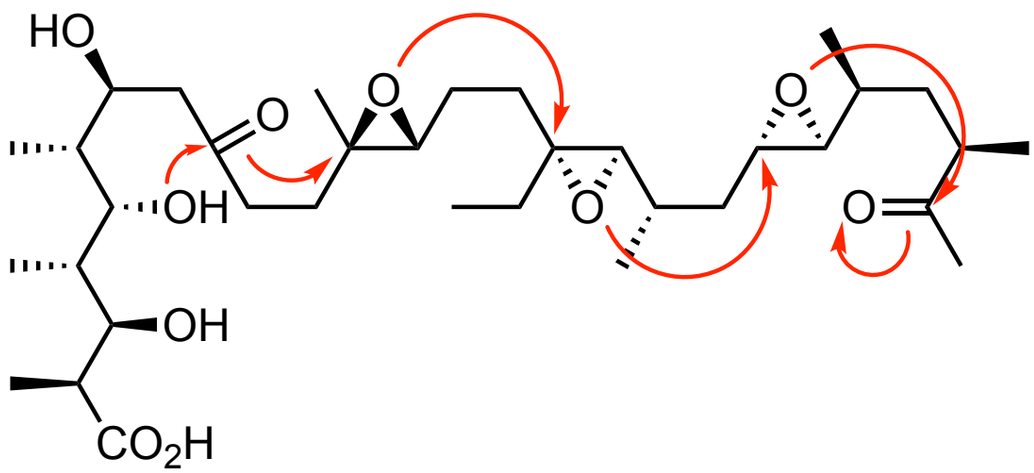


Monensin A

polyketide synthase



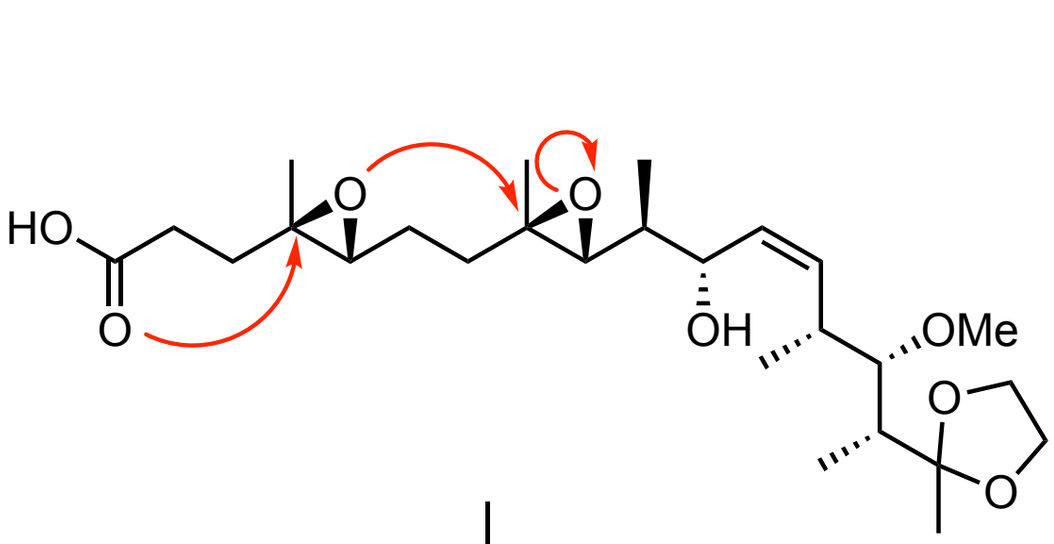
epoxidation



cyclization

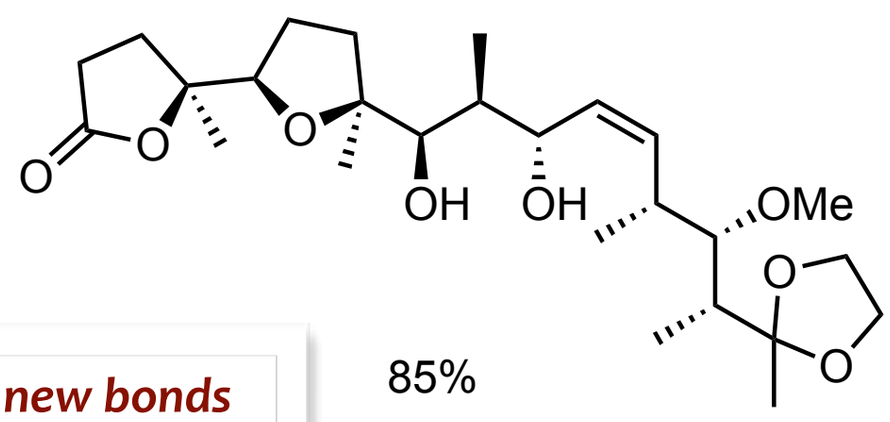
Cane, D. E.; Celmer, W. D; Westley, J. W. *JACS* **1983**, *105*, 3594

Electrophilic Cascades. Epoxide Opening



4 Å mol sieves

CH_2Cl_2, 23 °C



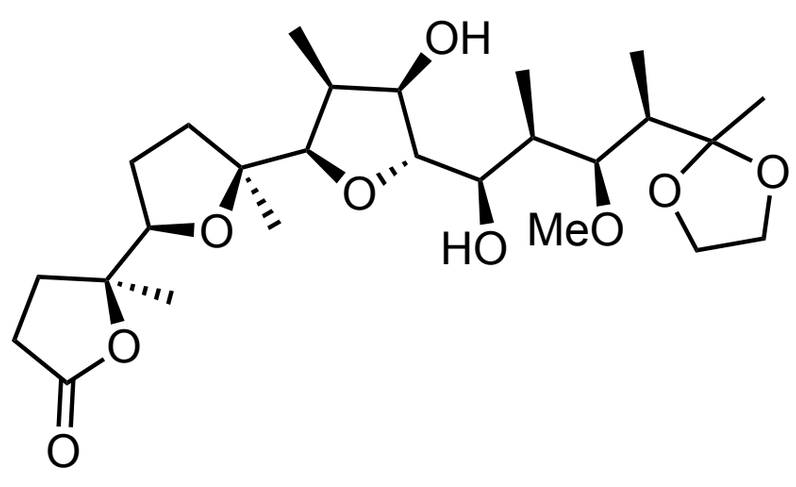
85%

2 new bonds

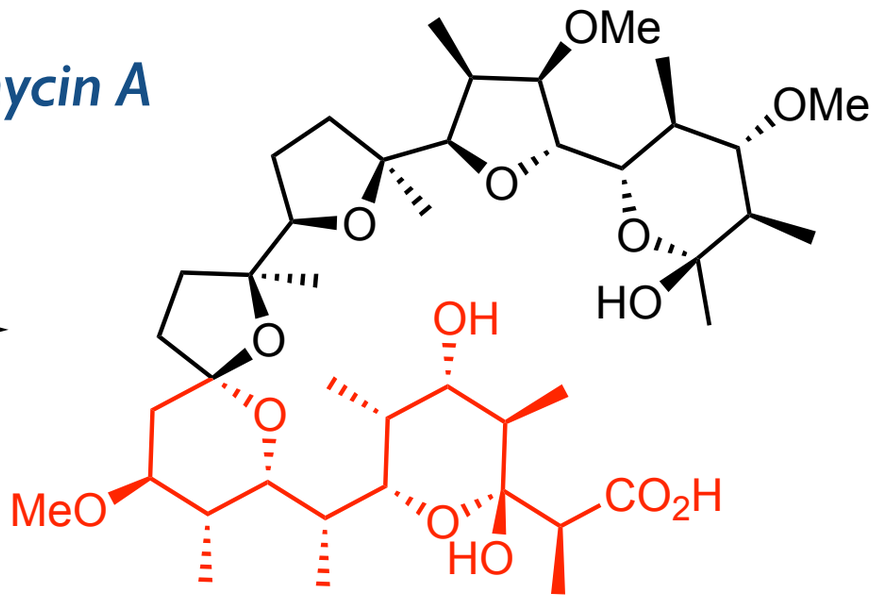
1) MMPP, CH_2Cl_2, 0 °C

2) AcOH, CH_2Cl_2, 23 °C

81%

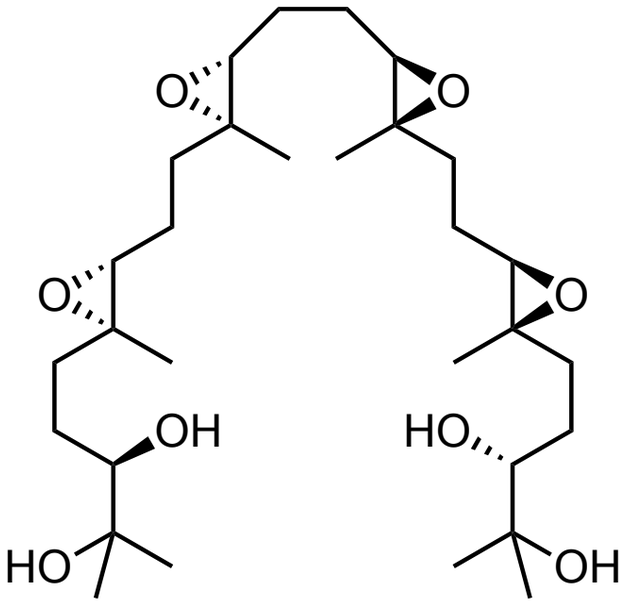


Lonomycin A



Evans, D. A. *JACS* **1995,** *117,* 3448

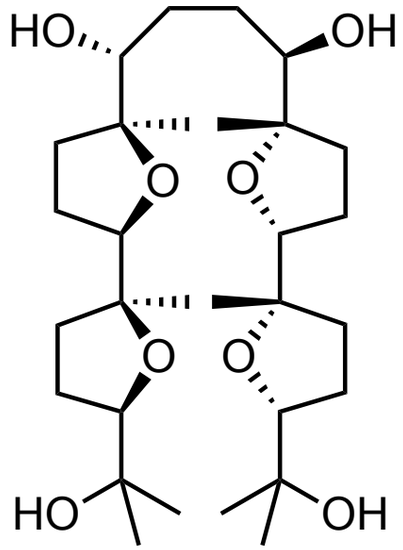
Electrophilic Cascades. Epoxide Opening



CSA

CH_2Cl_2, –94 °C

44%

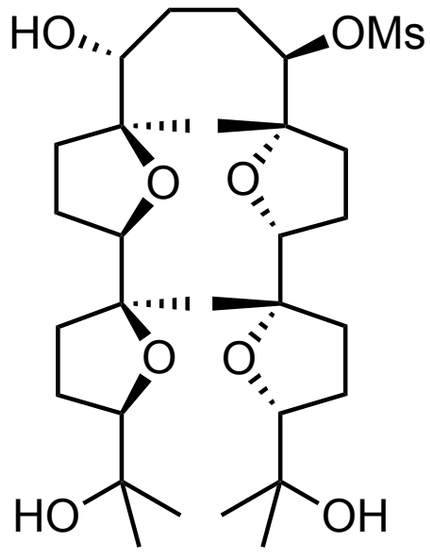


4 new bonds

Symmetry
Chapter 3

MsCl, DMAP
pyr
0 °C to rt

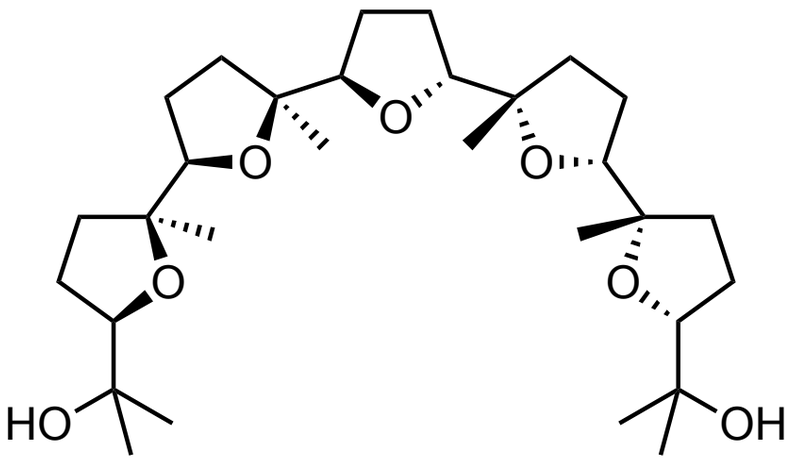
50%



NaOAc

AcOH, 40 °C

65%

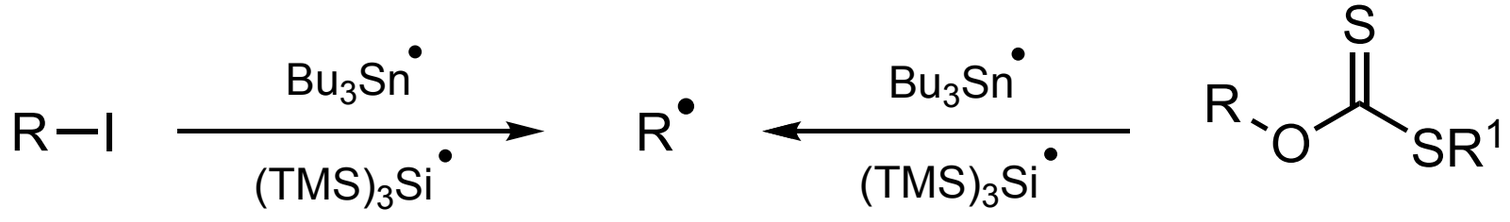


Glabrescrol

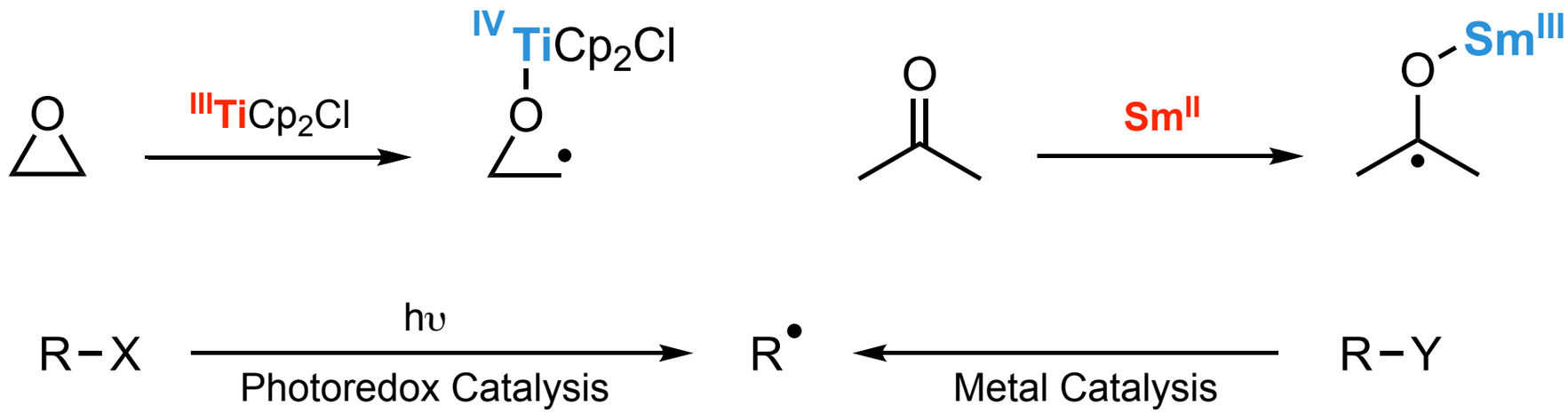
Corey, E. J. *JACS* **2000,** *122,* 9328

Radical Cascades

Tin & Silicon–mediated Cascades



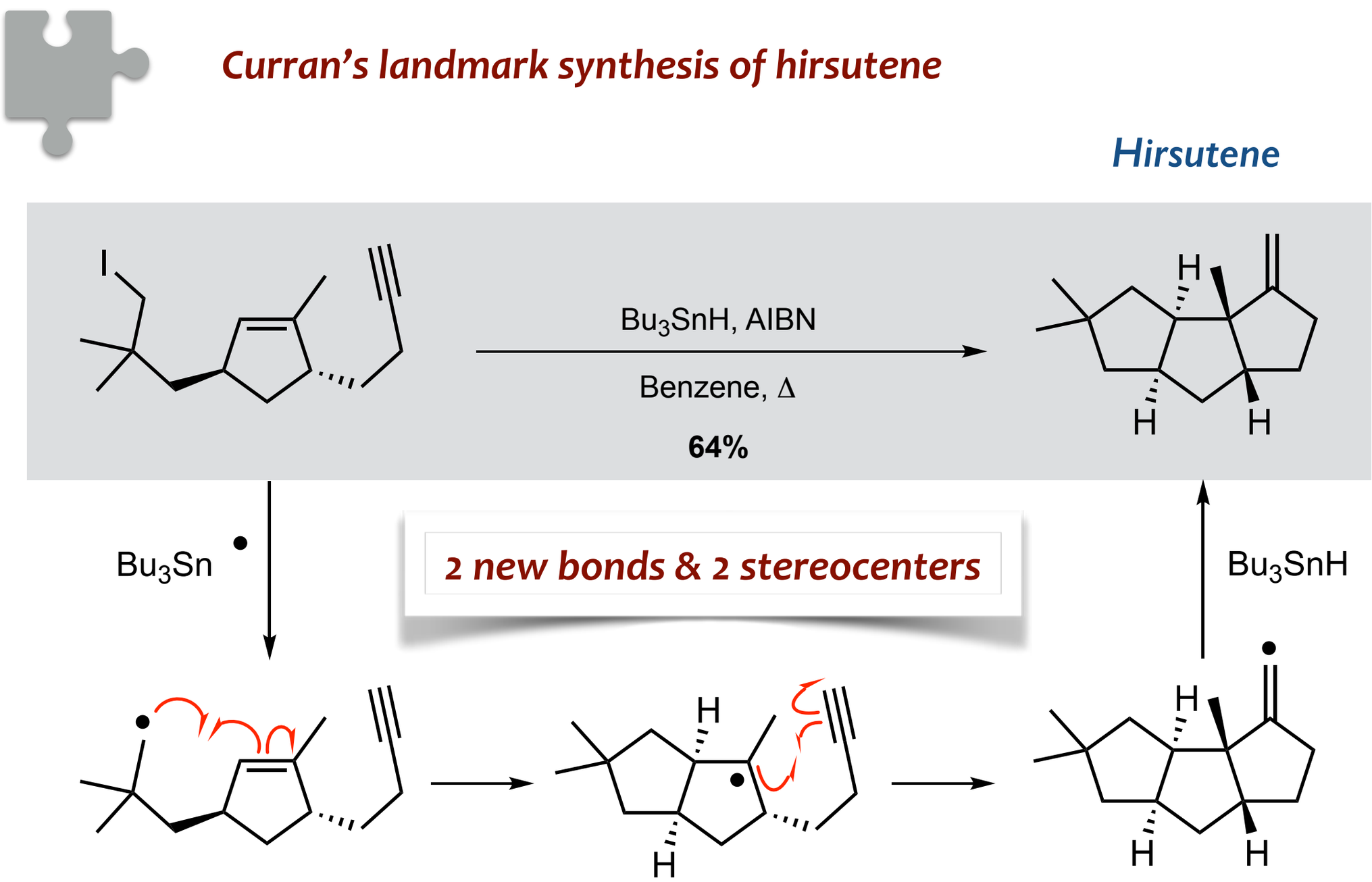
Transition metal-mediated Cascades (SET)



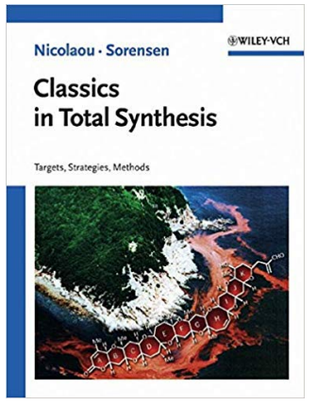
Nicolaou, K. C. *ACIE* **2006**, *45*, 7134; Stephenson, C. R. J. *ACS Catal* **2014**, *4*, 703;
Studer, A. & Curran, D. P. *Nat. Chem.* **2014**, *6*, 765; Procter, D. J. *Nat. Chem. Rev.* **2017**, *1*, 0077;
Barrett, A. G. M. *Synthesis* **2019**, *51*, 67

Radical Cascades. Tin Mediated

Curran's landmark synthesis of hirsutene



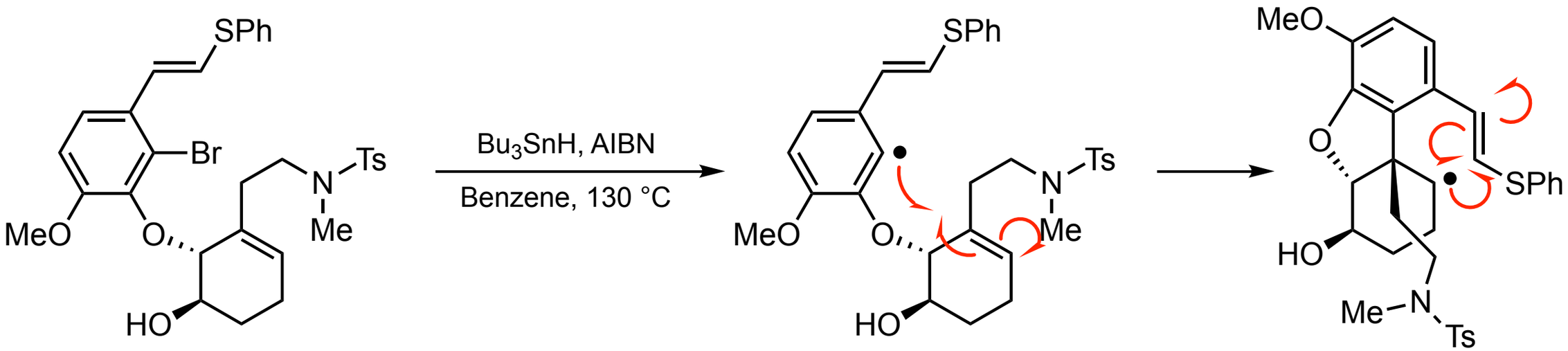
Cyclizations Chapter 6



For an account, see p 381

Curran, D. P. *JACS* **1985,** *107*, 1445

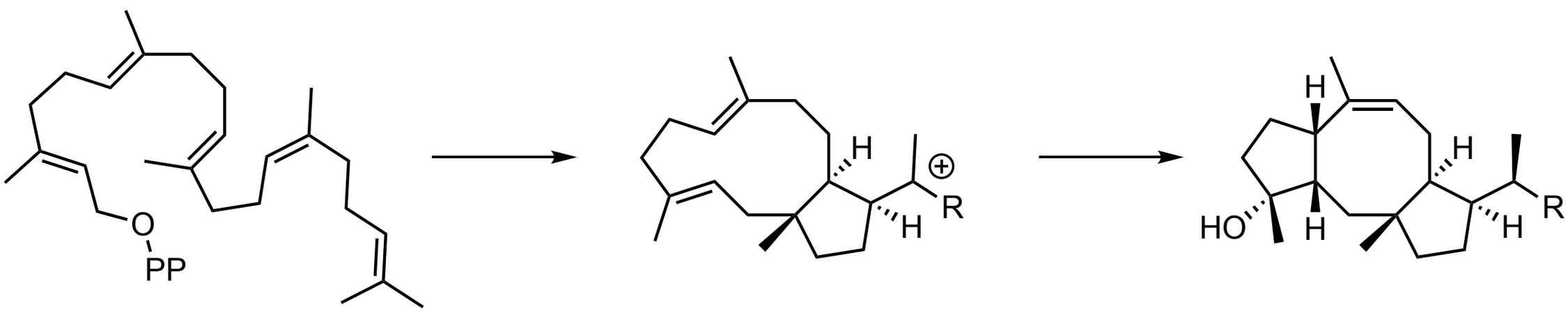
Radical Cascades. Tin Mediated



Parker, K. *JACS* **1992**, *114*, 9688; *JOC* **2006**, *71*, 449

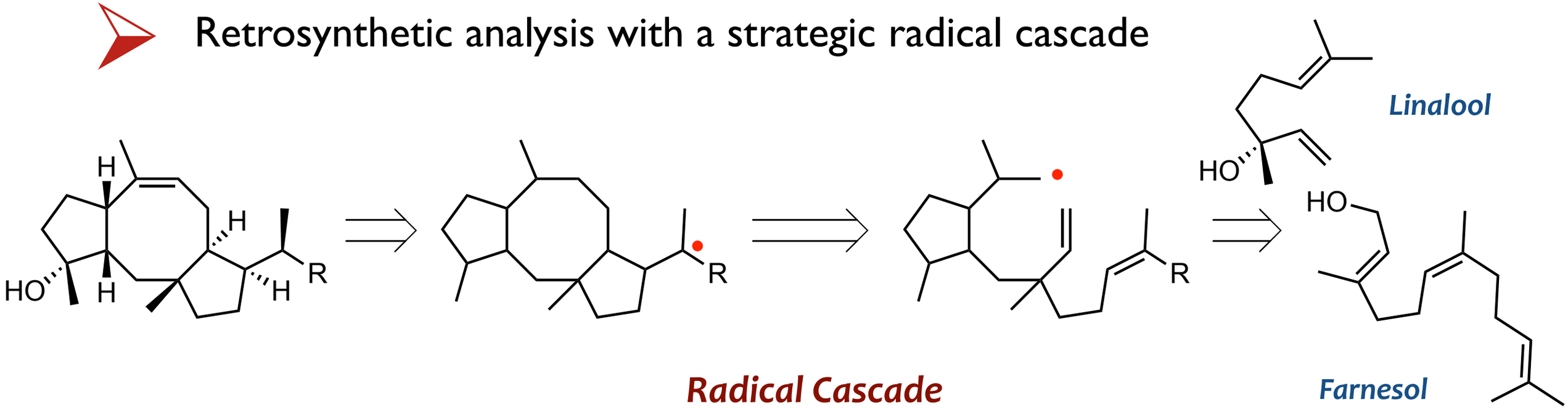
Radical Cascades. Silicon Mediated

Proposed biosynthesis of ophiobiolin sesterterpenes



Geranylfarnesyl

Retrosynthetic analysis with a strategic radical cascade



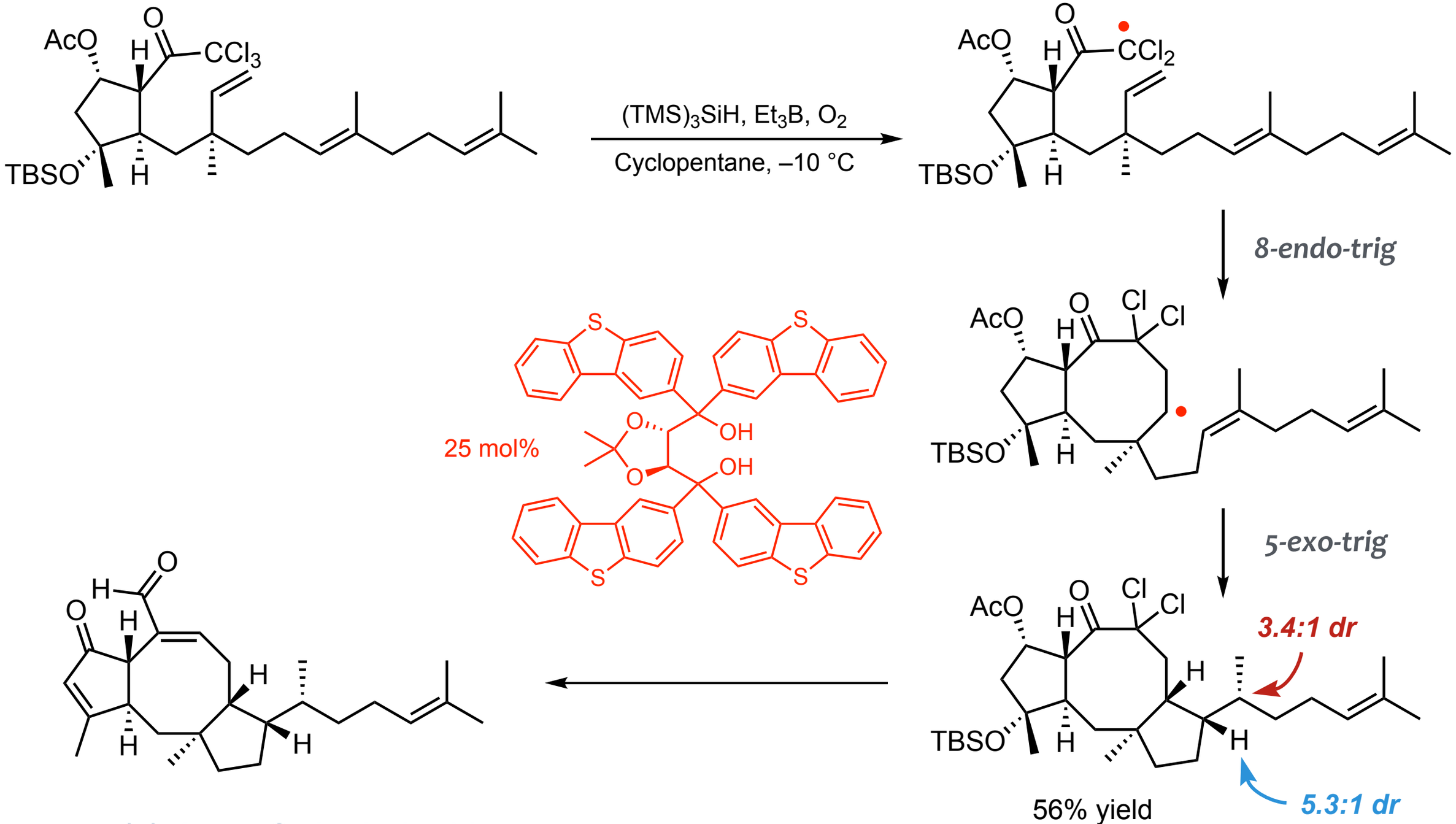
Radical Cascade

Linalool

Farnesol

Maimone, T. J. *Science* **2016**, 352, 1078

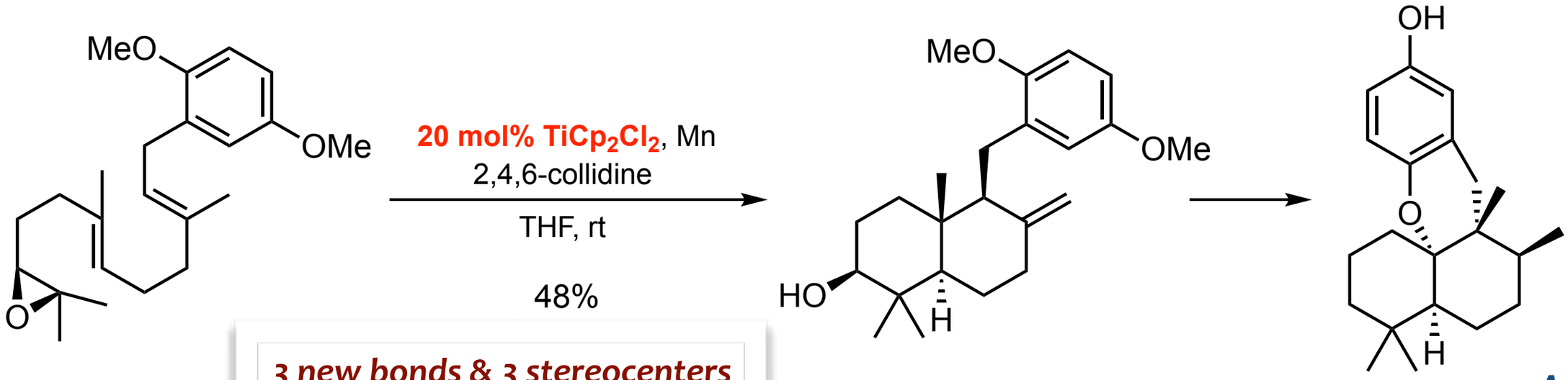
Radical Cascades. Silicon Mediated



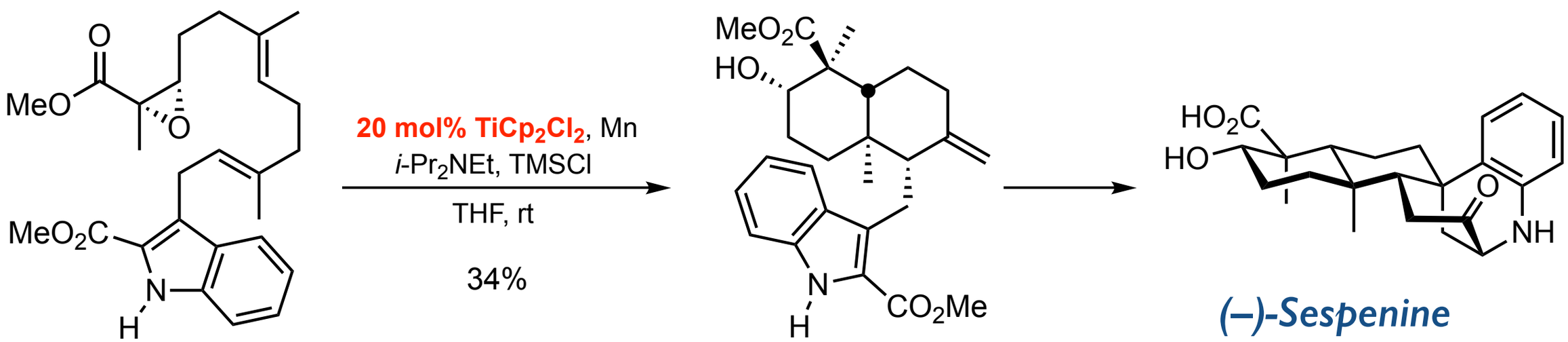
(–)-6-epi-Ophiobolin N

Maimone, T. J. *Science* **2016**, 352, 1078

Radical Cascades. Epoxide Opening

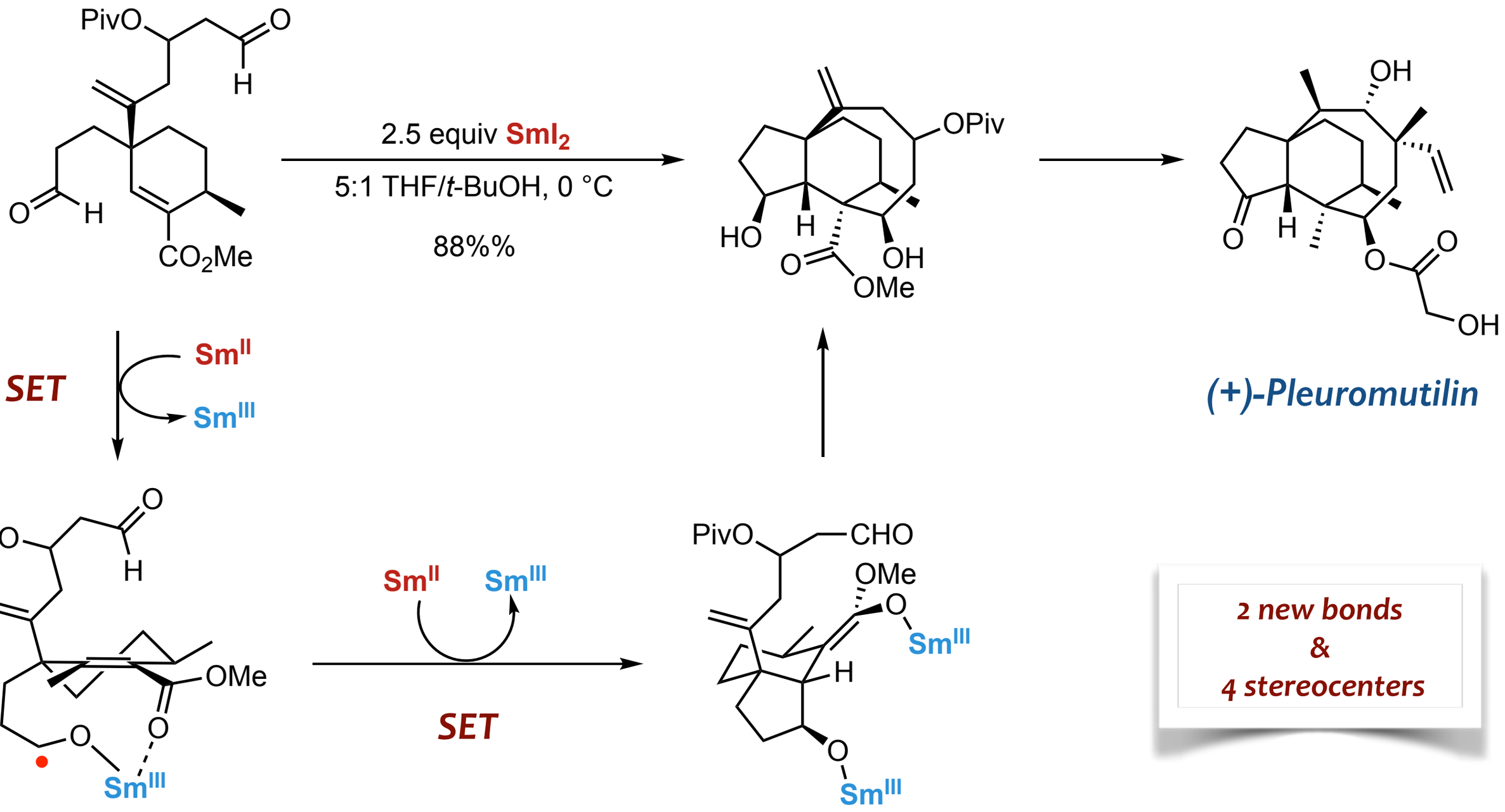


Rosales, A.; Oltra, J. E. *JOC* **2015**, *80*, 1866



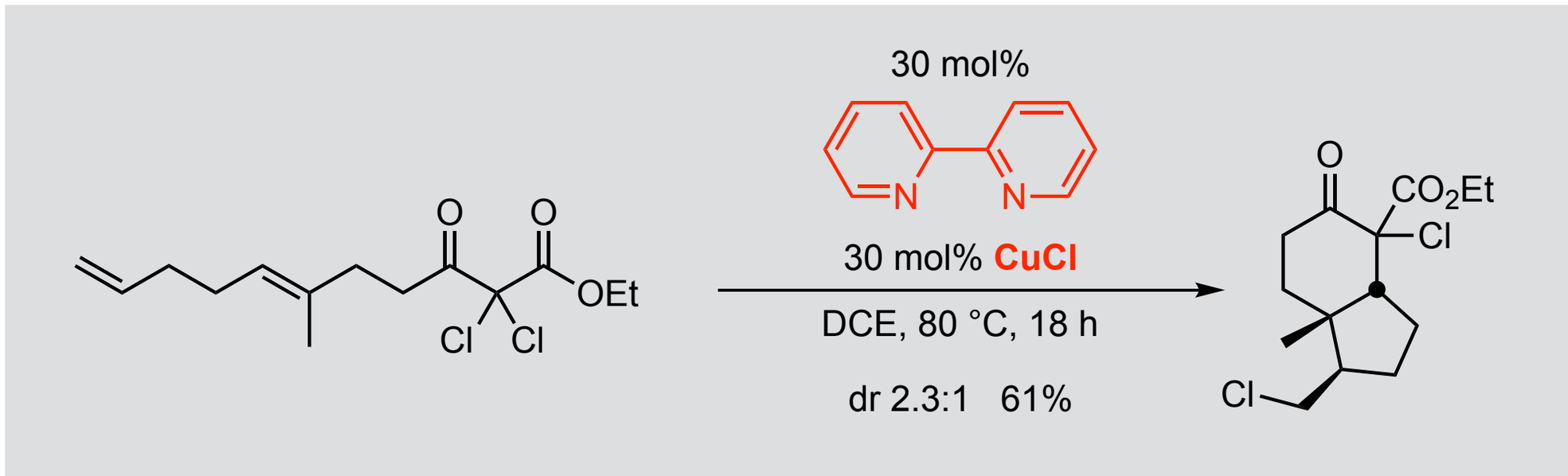
Li, A. *OCF* **2016**, *3*, 368

Radical Cascades. Samarium Mediated

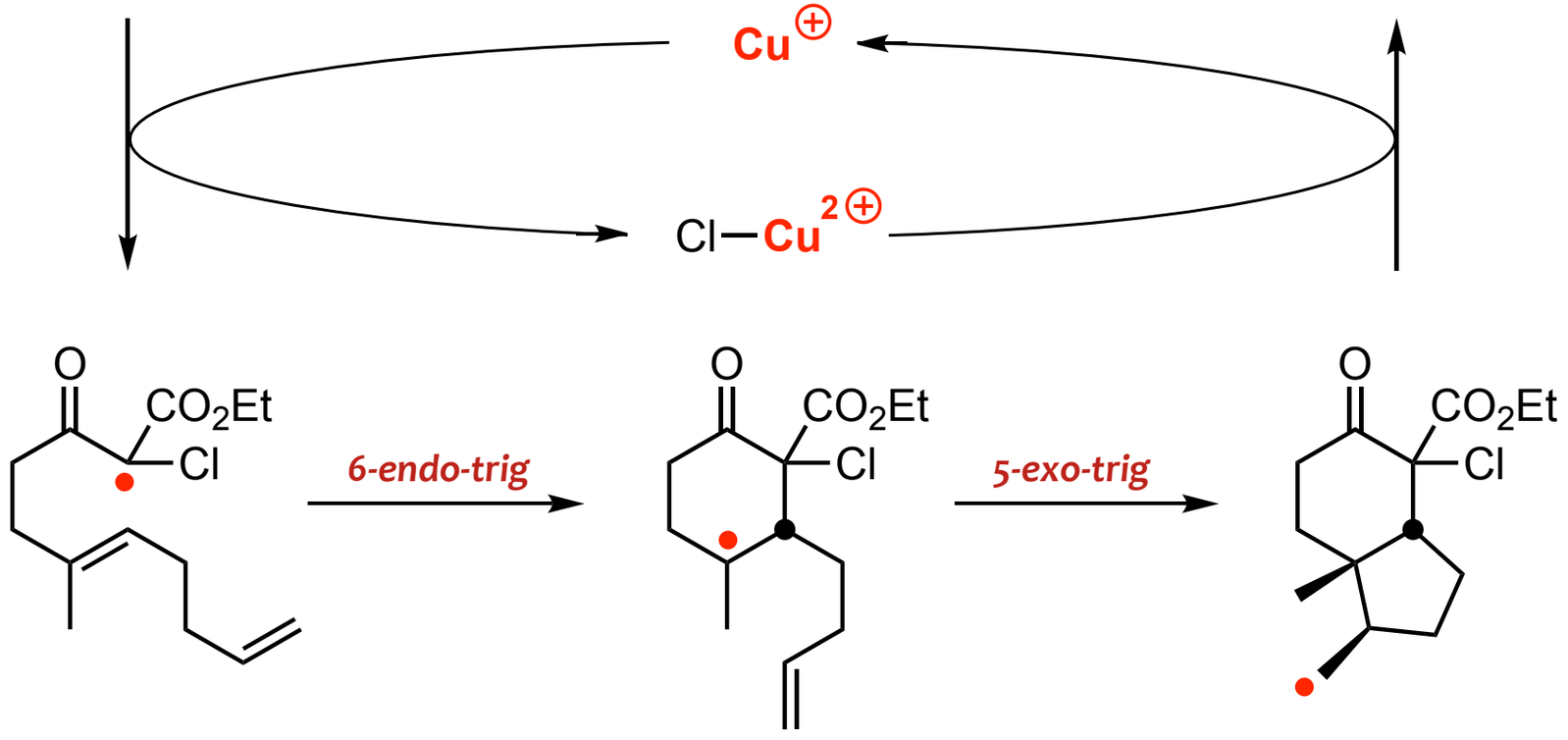


Procter, D. J. *ACIE* **2009,** *48*, 9315; *CEJ* **2013,** *19*, 6718

Radical Cascades. Copper Mediated

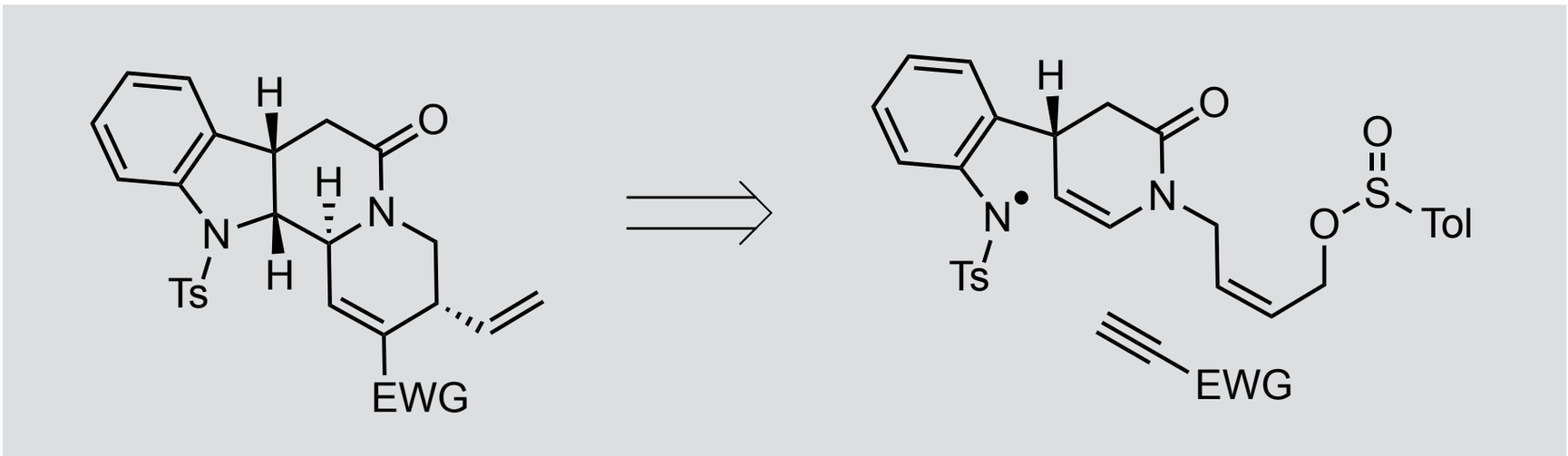


3 new bonds
&
3 stereocenters



Yang, D. *OL* **2006**, *8*, 5757. See also Maimone, T. J. *Science* **2016**, 352, 1078

Radical Cascades. Photoredox Catalysis



(+)-Cinchonidine

Qin, Y. *ACIE* **2018,** *57,* 12299; see also *OL* **2019,** *21,* 252

Pericyclic Cascades

Angewandte Reviews

A. C. Jones, B. M. Stoltz et al.

DOI: 10.1002/anie.201302572

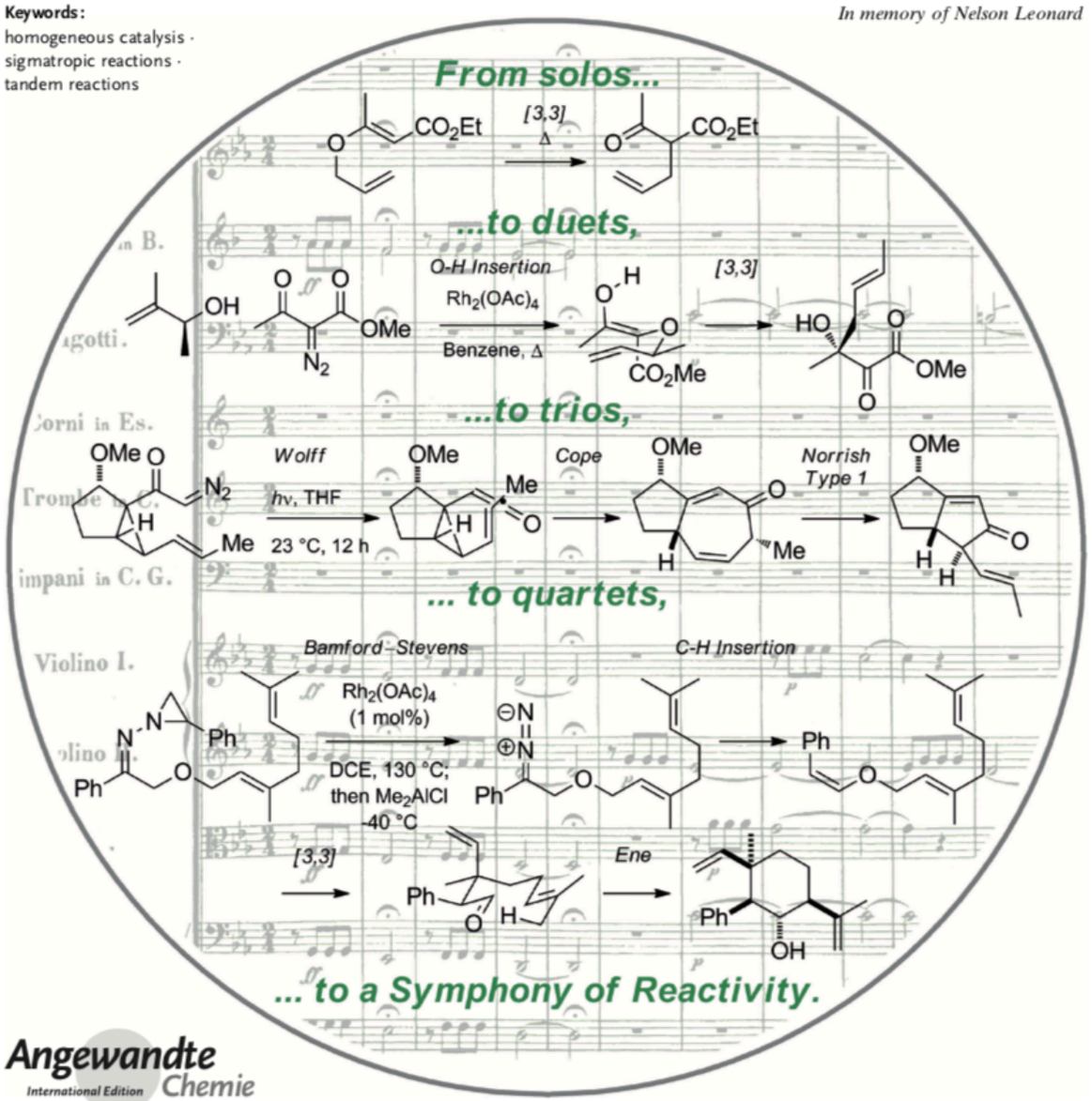
Molecules and Music

Toward a Symphony of Reactivity: Cascades Involving Catalysis and Sigmatropic Rearrangements

Amanda C. Jones, Jeremy A. May, Richmond Sarpong, and Brian M. Stoltz**

Keywords:
homogeneous catalysis · sigmatropic reactions · tandem reactions

In memory of Nelson Leonard



Angewandte International Edition Chemie

In many regards,

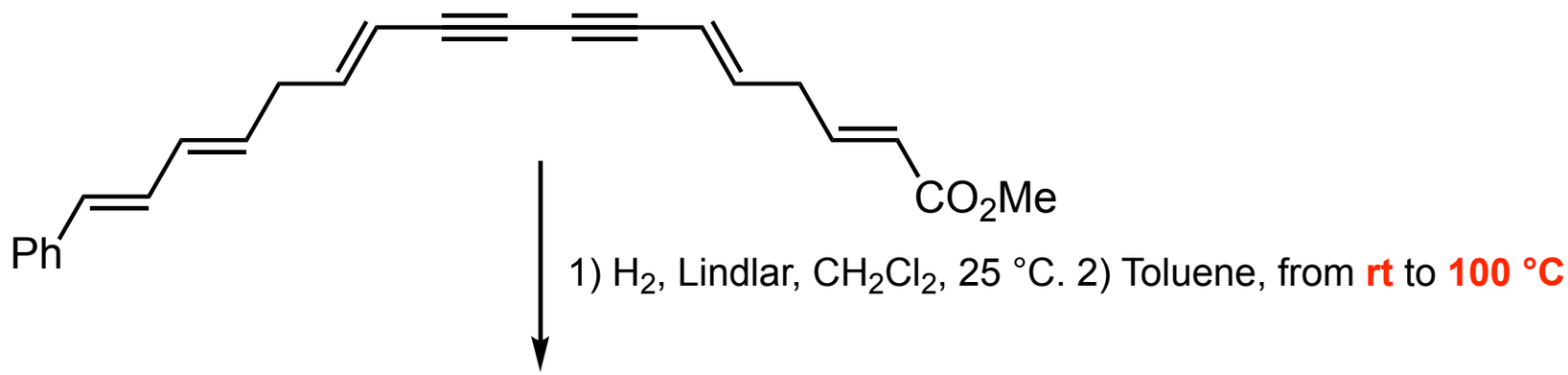
the ***inherent beauty*** *associated with a synthetic sequence can be linked to a certain combination of the creativity with which a sequence is designed and the overall efficiency with which the ultimate process is performed. In synthesis, as in other endeavors, beauty is very much in the eyes of the beholder*

Jones, A. C. ; Stoltz, B. M.

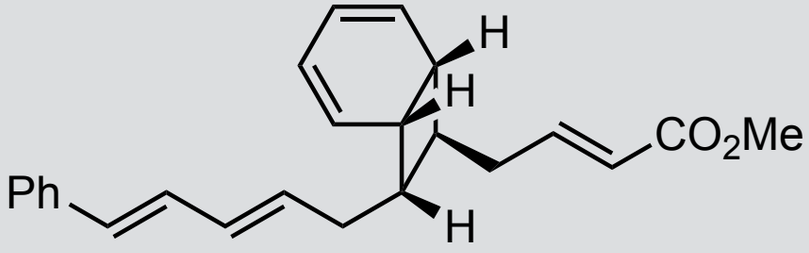
ACIE ***2014****, 53, 2556*

Electrocyclic Cascades

Nicolaou's landmark biomimetic synthesis of Endiandric Acid B, C, F, and G

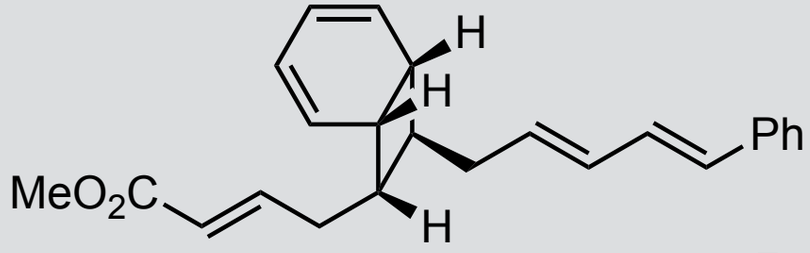


BEFORE HEATING



Endiandric Acid F Methyl Ester

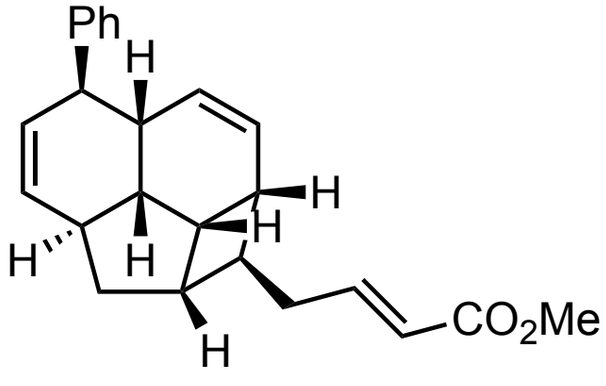
15%



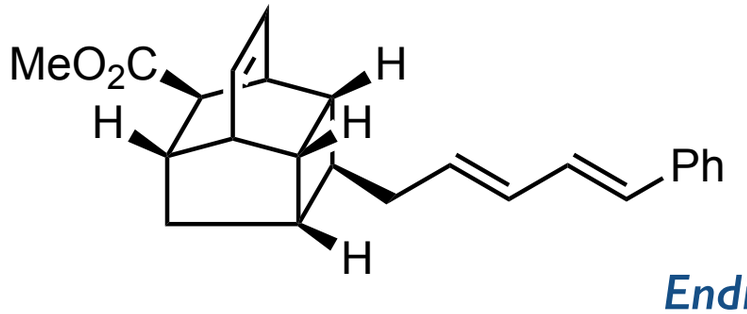
12%

Endiandric Acid G Methyl Ester

AFTER HEATING



Endiandric Acid B Methyl Ester



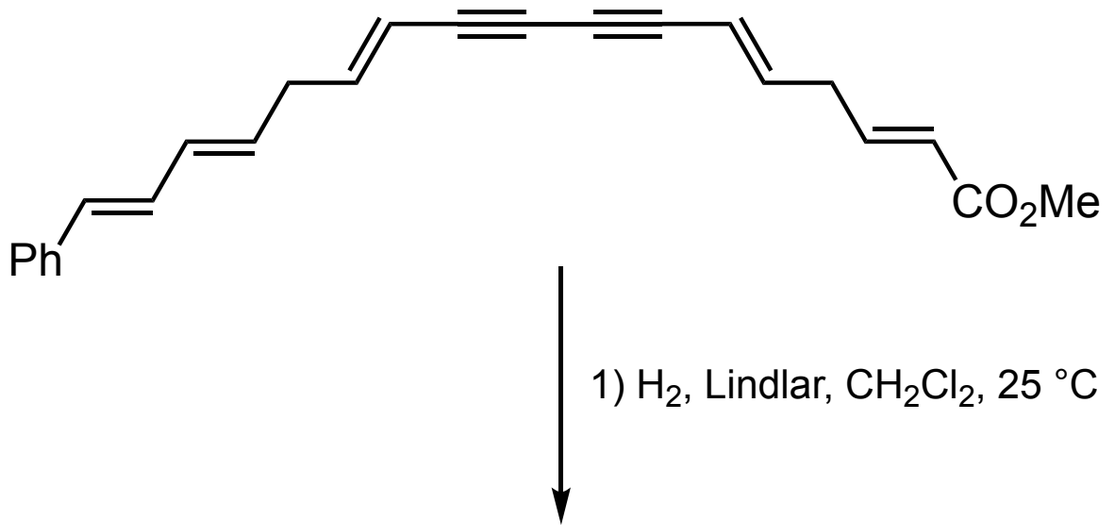
Endiandric Acid C Methyl Ester

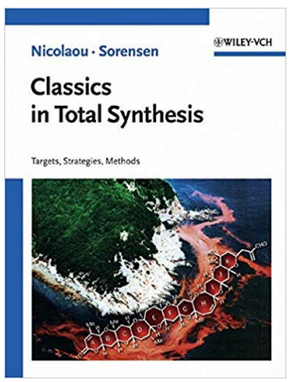
4.5:1 Overall yield 28%

Nicolaou, K. C. *JACS* **1982**, *104*, 5555, 5557, 5558, 5560

Electrocyclic Cascades

Nicolaou's landmark biomimetic synthesis of Endiandric Acid B, C, F, and G



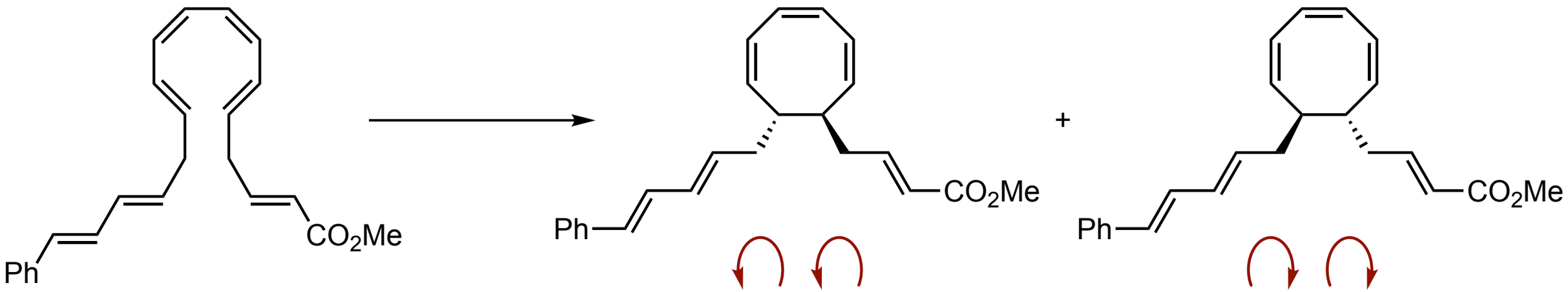


For an account, see p 265

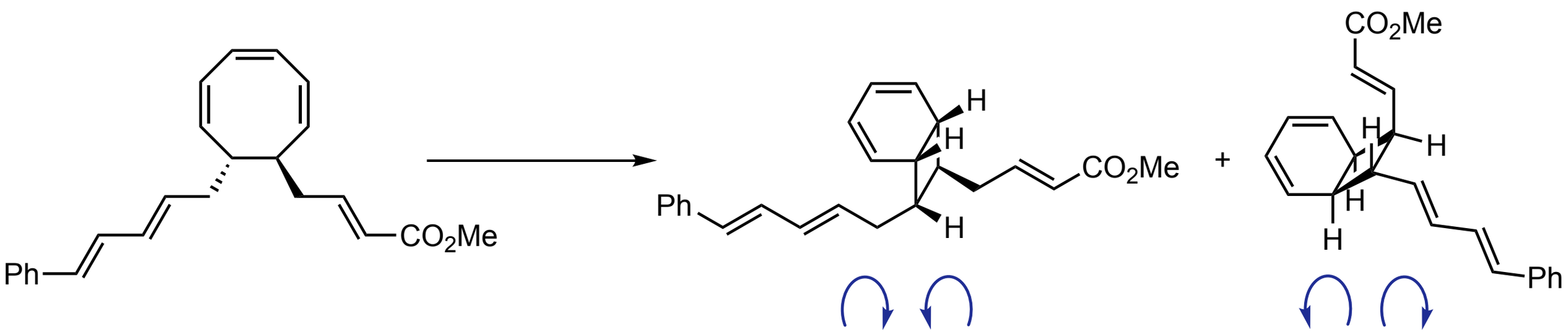
Nicolaou, K. C. *JACS* **1982**, *104*, 5555, 5557, 5558, 5560

Electrocyclic Cascades

Conrotatory 8π electron electrocyclic



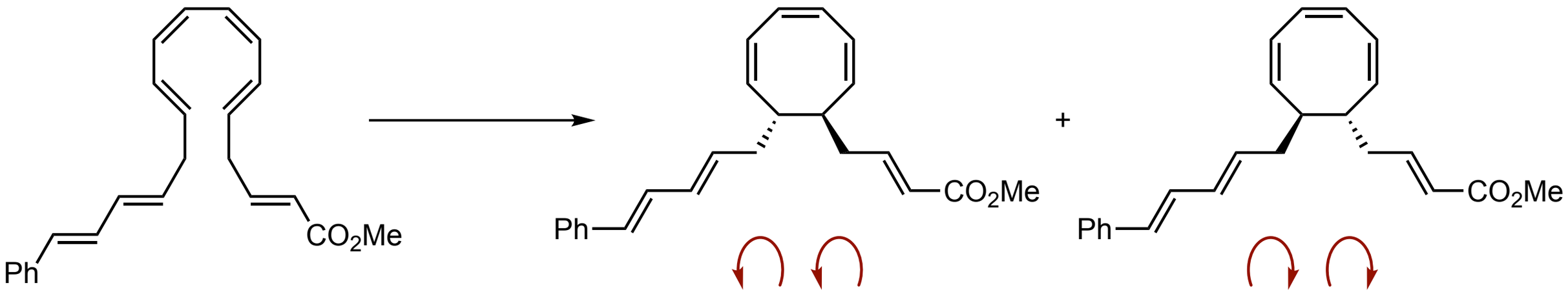
Disrotatory 6π electron electrocyclic



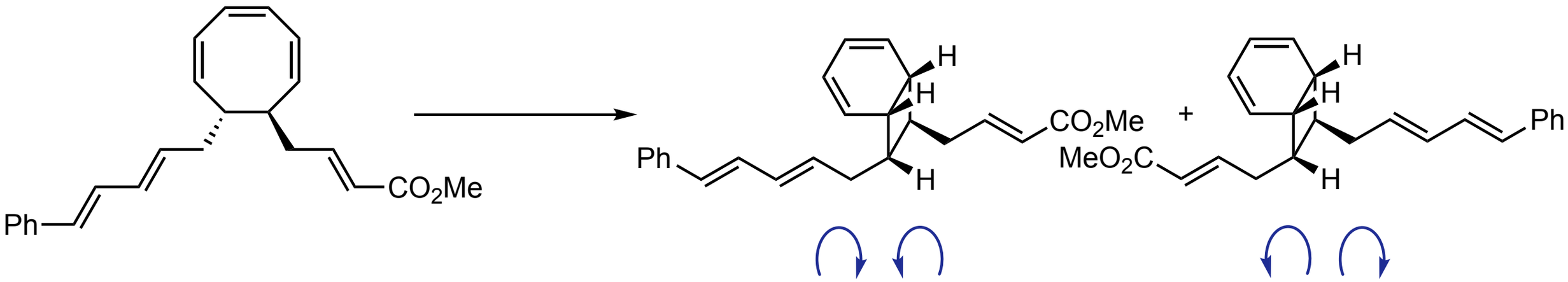
Nicolaou, K. C. *JACS* **1982**, *104*, 5555, 5557, 5558, 5560

Electrocyclic Cascades

Conrotatory 8π electron electrocyclic



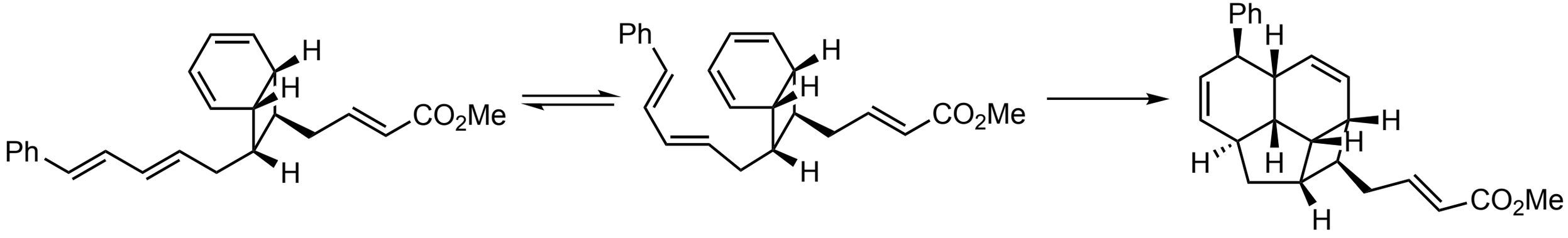
Disrotatory 6π electron electrocyclic



Nicolaou, K. C. *JACS* **1982**, *104*, 5555, 5557, 5558, 5560

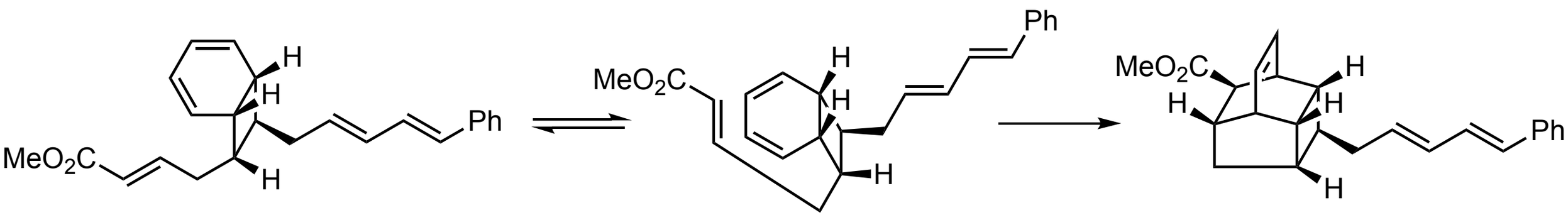
Electrocyclic Cascades

Intramolecular Diels Alder



diastereomers

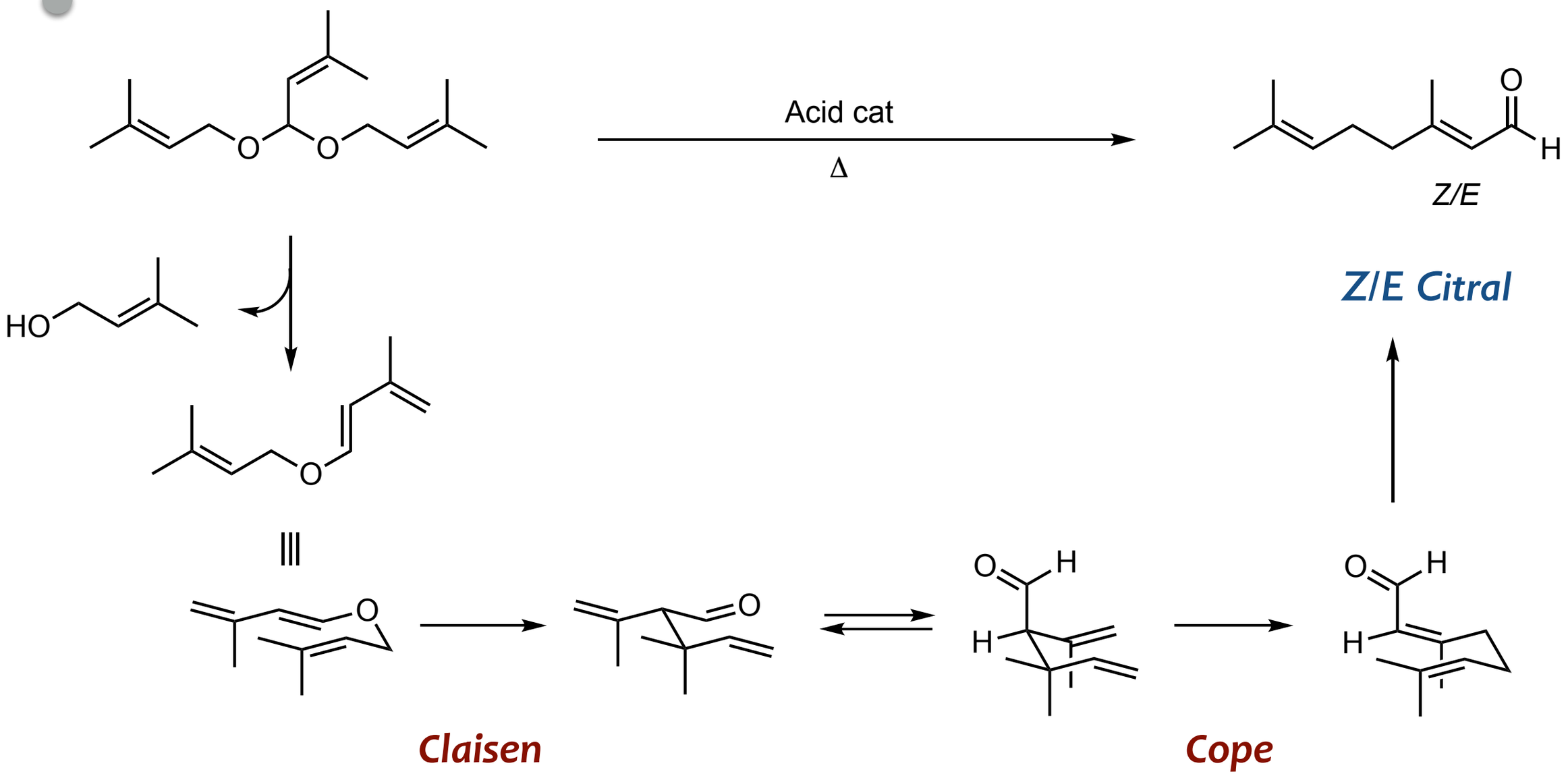
constitutional isomers



Nicolaou, K. C. *JACS* **1982**, *104*, 5555, 5557, 5558, 5560

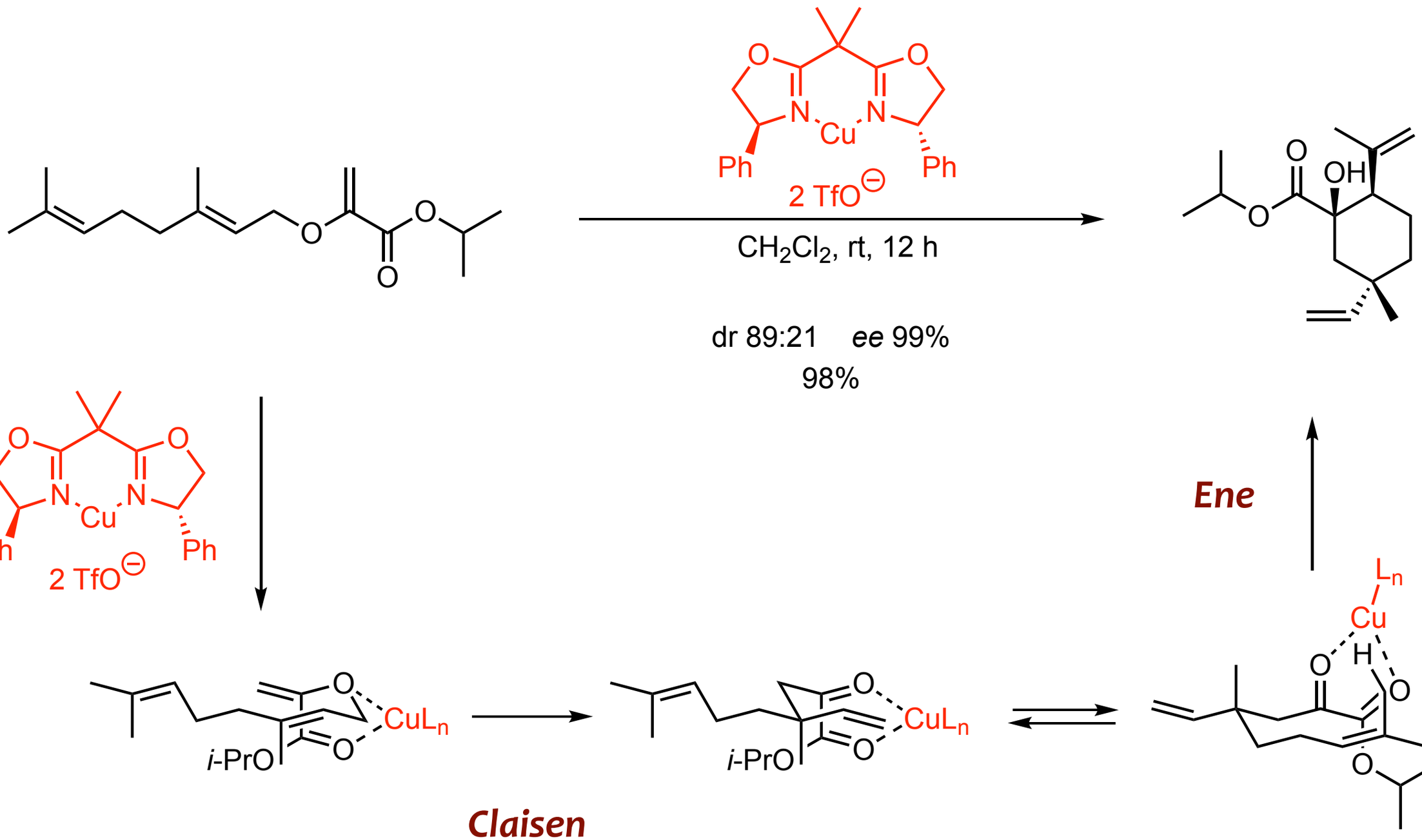
Sigmatropic Cascades

BASF Continous Citral Process



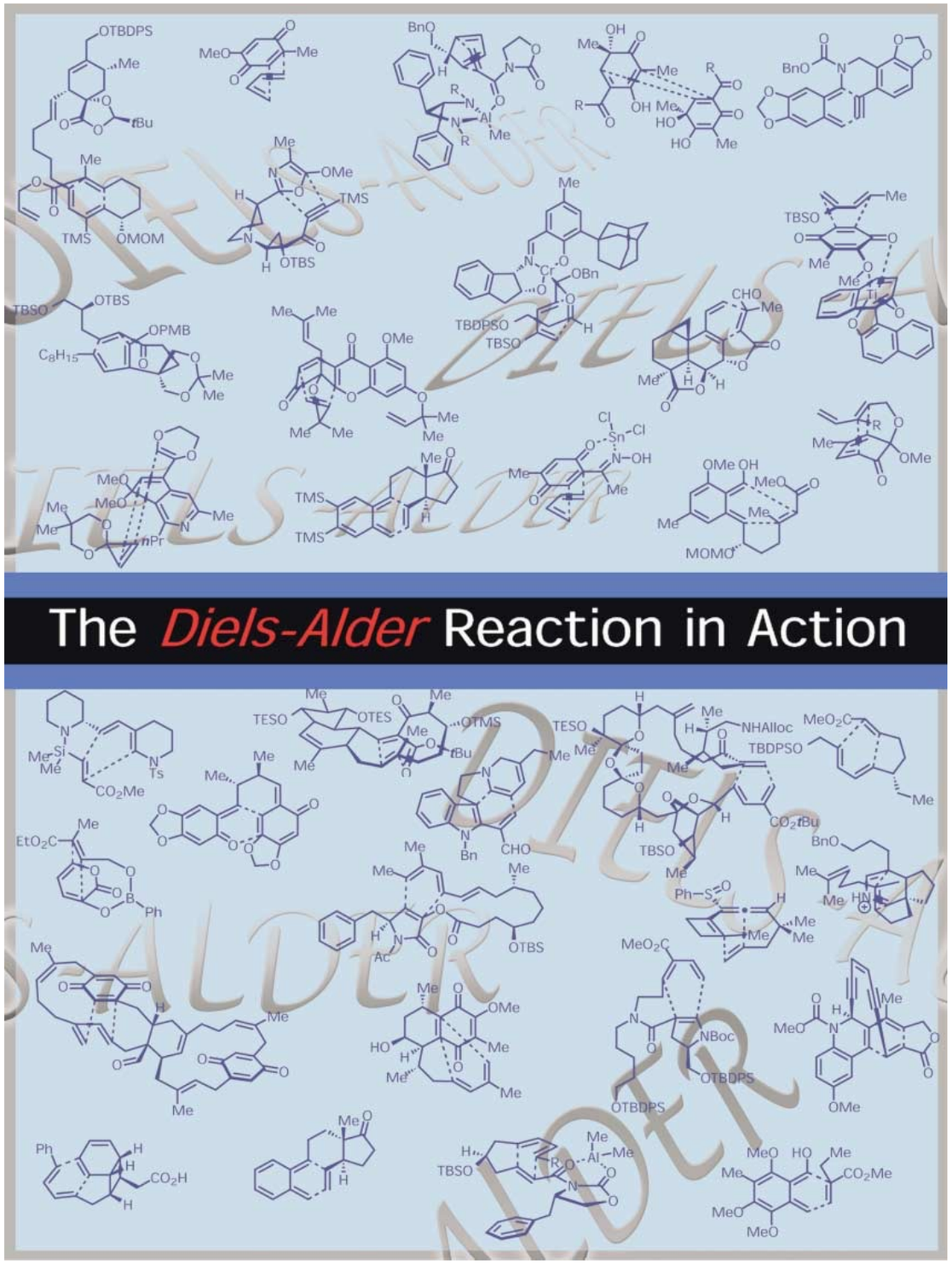
USA Patent 4288636 09/08, **1981**

Sigmatropic Cascades



Hieserman, M. *Synlett* **2002**, 1999

Diels Alder Cascades



The Diels-Alder reaction

has both enabled and shaped the art and science of total synthesis over the last few decades to an extent which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire.

With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and ***programmed cascade sequences*** *facilitating complex molecule con- struction, the Diels-Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products.*

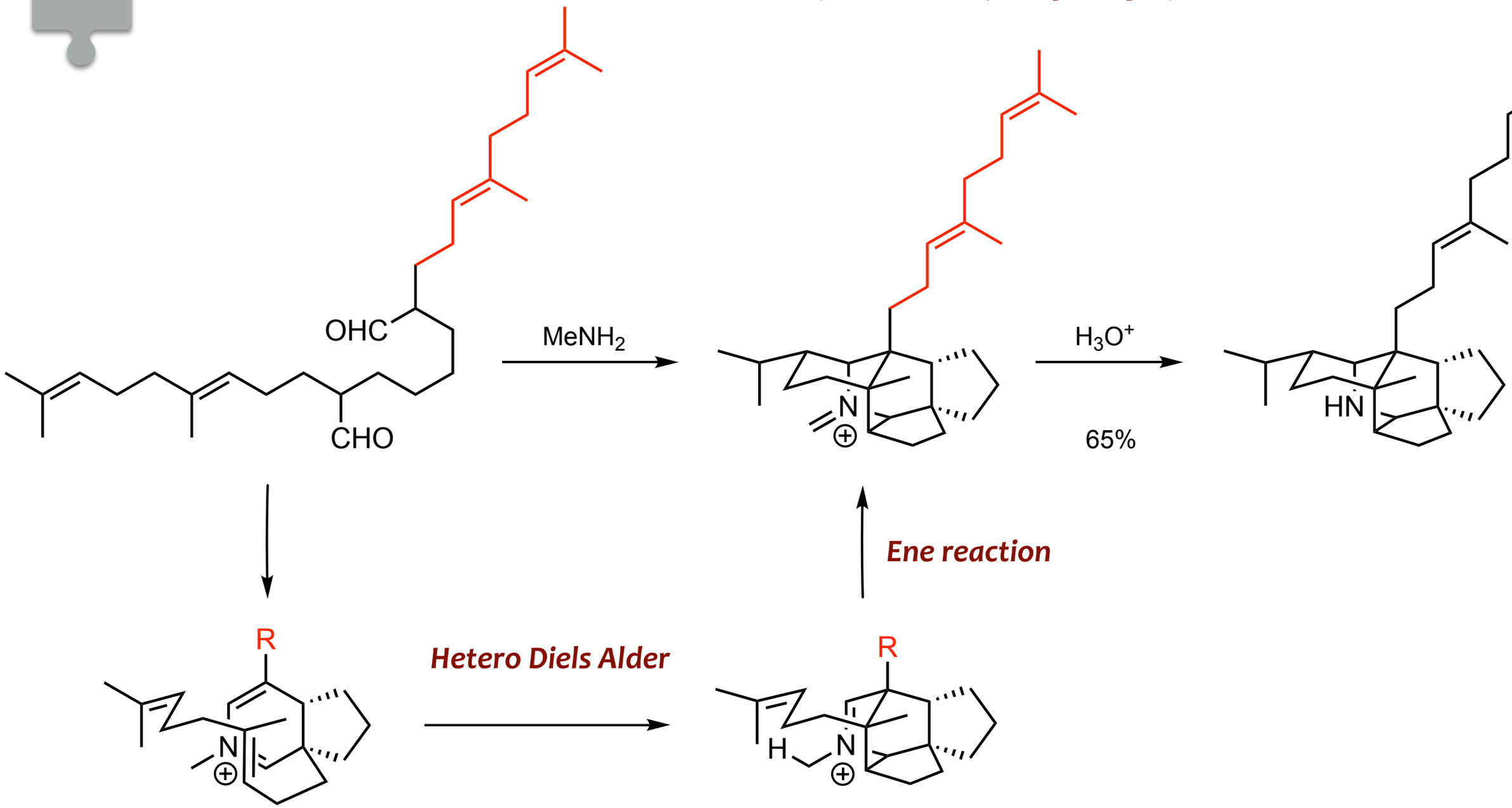
Nicolaou, K. C. ACIE **2002**, *41, 1668*

Cyclizations
Chapter 6

Remember!

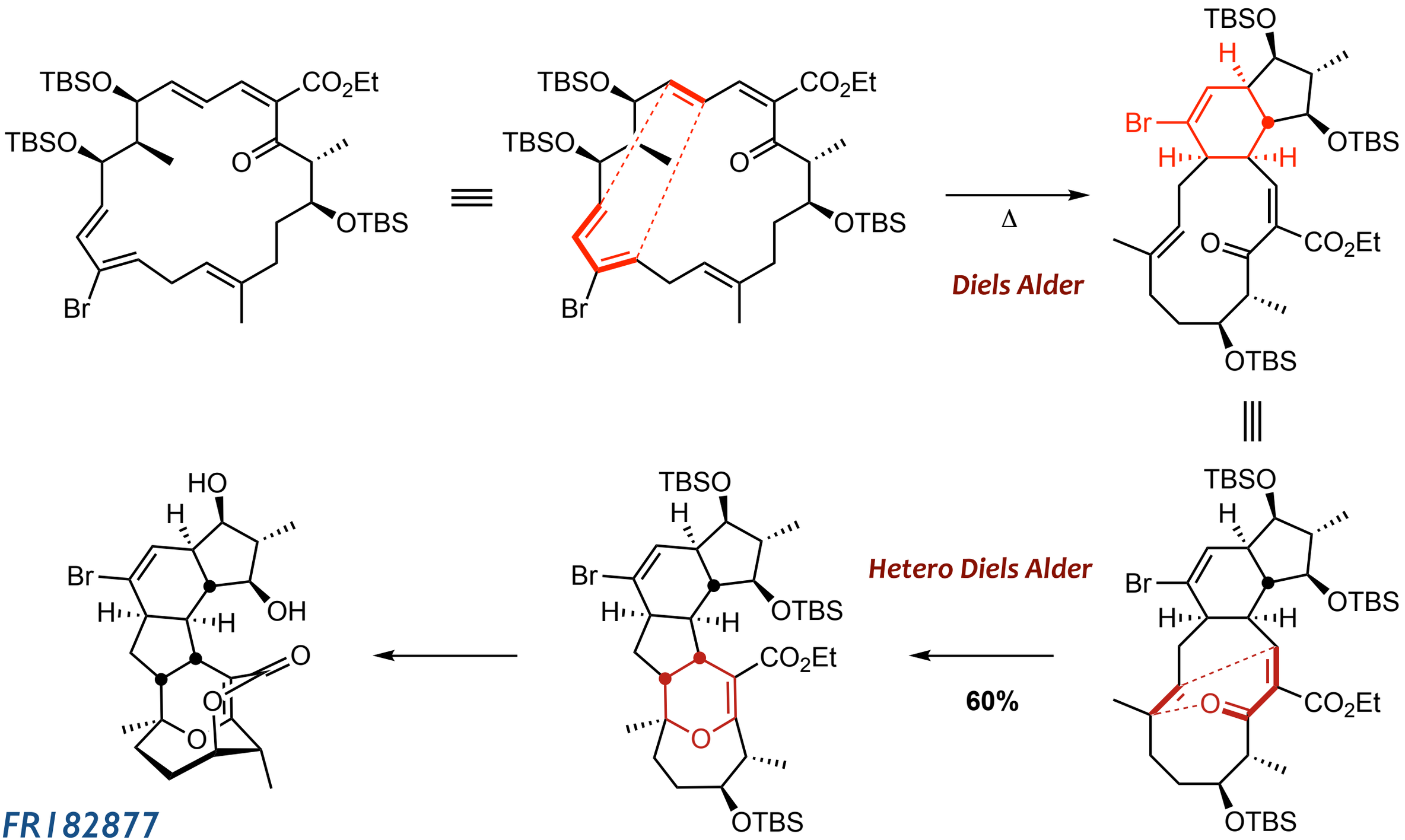
Diels Alder Cascades

Heathcock's landmark biomimetic synthesis of Daphniphylium alkaloids



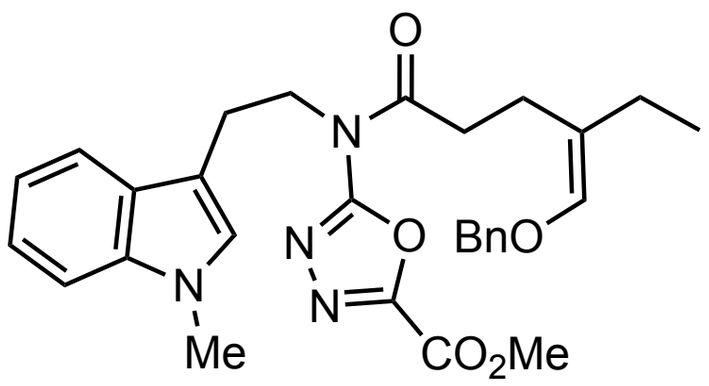
Heathcock, C. H. *Science* **1990**, *248*, 1532; *PNAS* **1996**, *93*, 14323; Tantillo, D. J. *OL* **2016**, *18*, 4482
Hanessian, S. *CR* **2017**, *117*, 4104

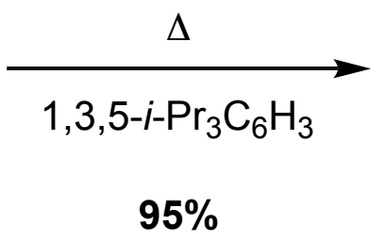
Diels Alder Cascades



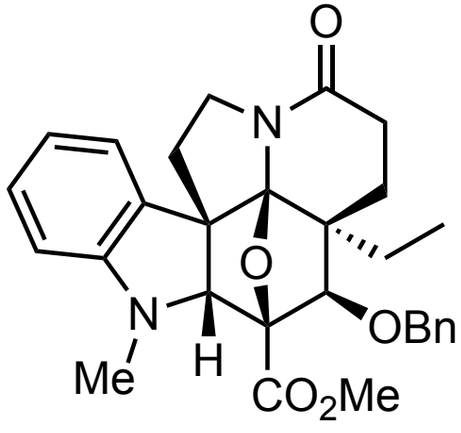
Evans, D. A. *ACIE* **2002**, 41, 1787

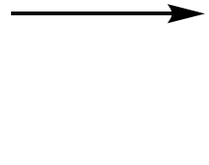
Diels Alder Cascades

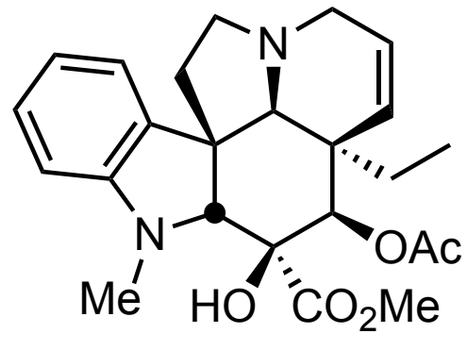




95%

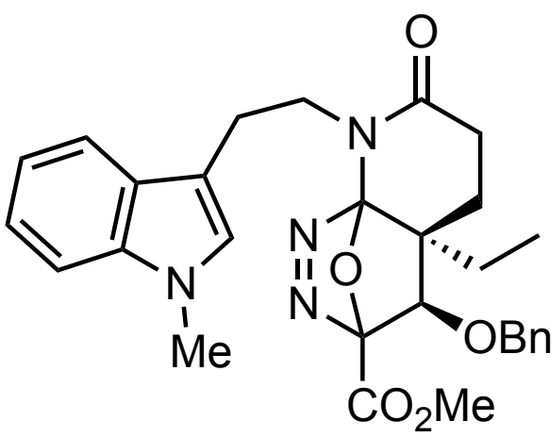


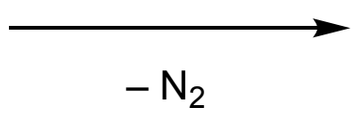


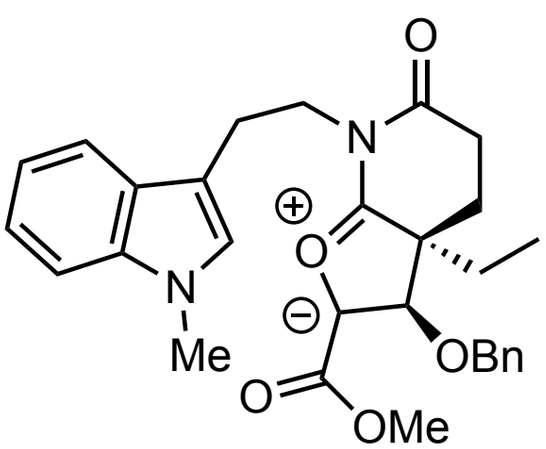


Vindorosine

Diels Alder ***[4πs + 2πs]***





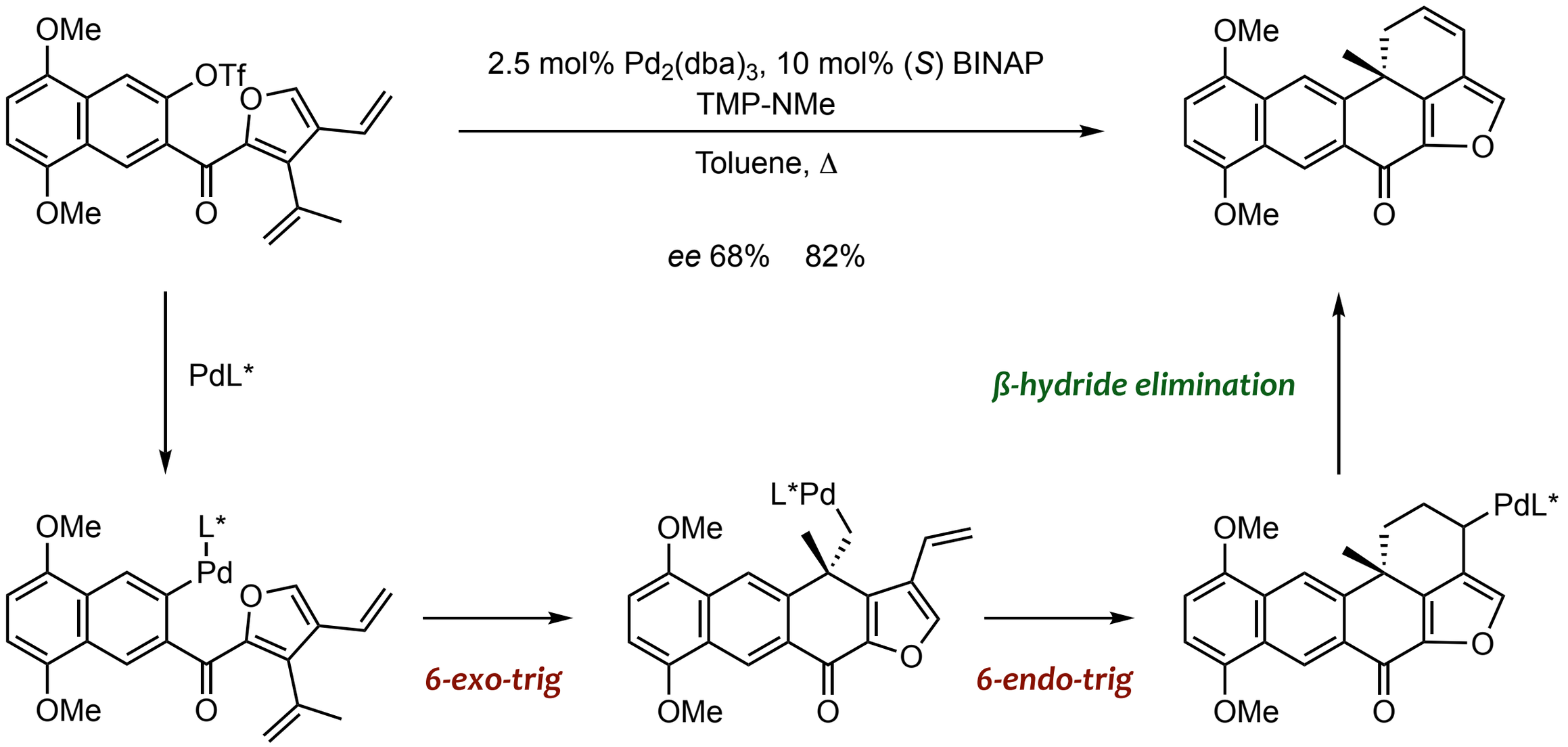


[4πs + 2πs] ***1,3-Dipolar cycloaddition***

Cyclizations
Chapter 6

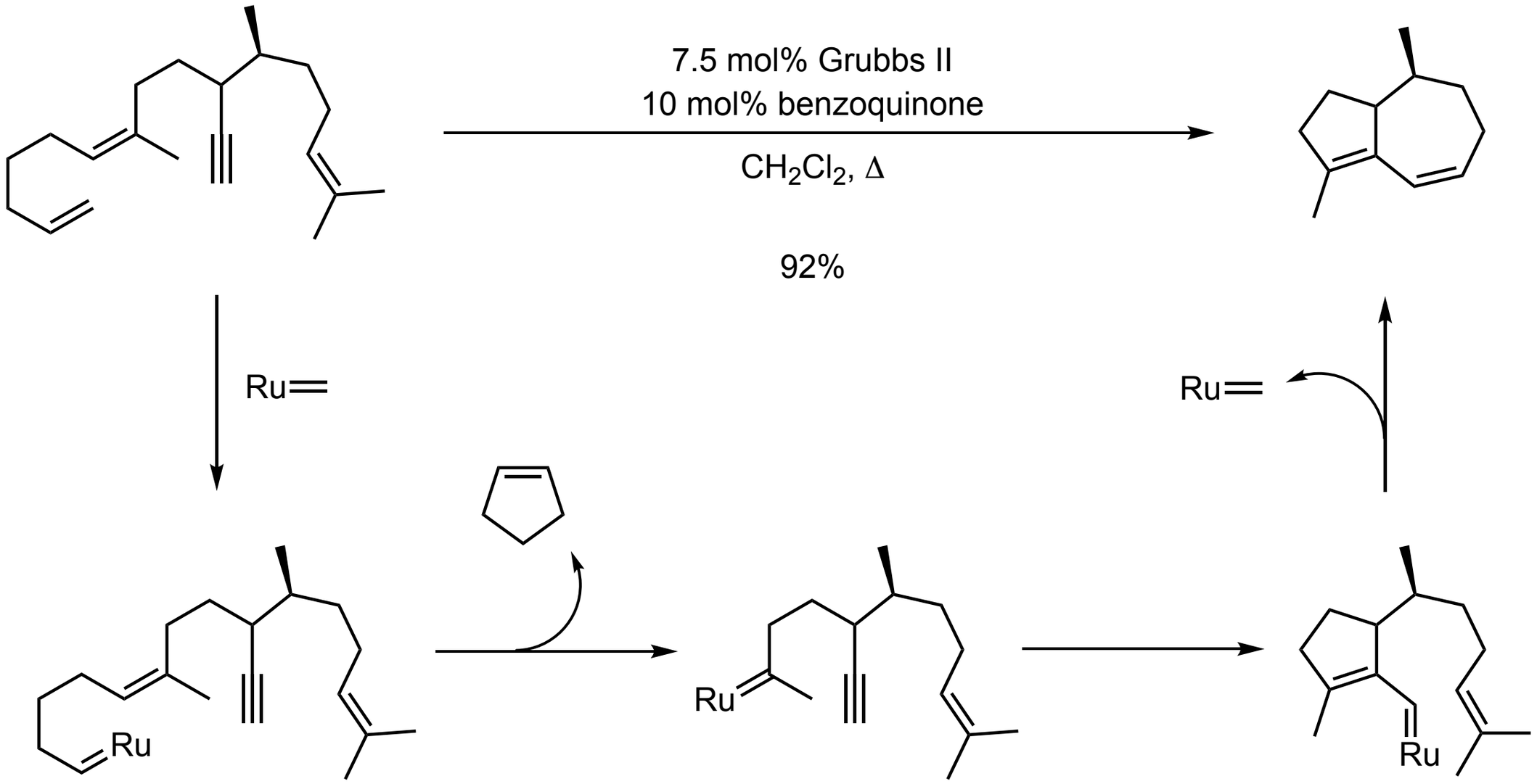
Boger, D. L. *ACIE* **2006**, 45, 620

Transition Metal Cascades. Heck



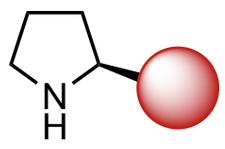
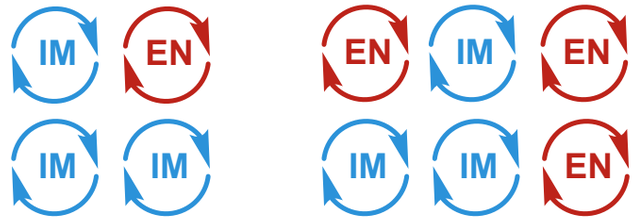
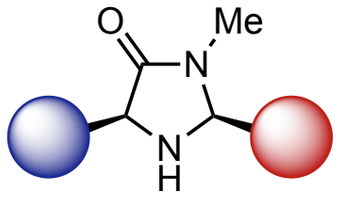
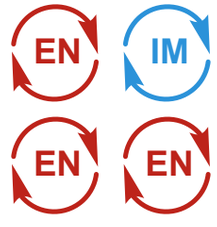
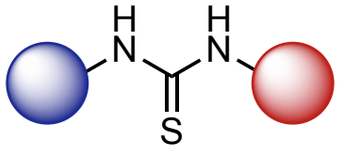
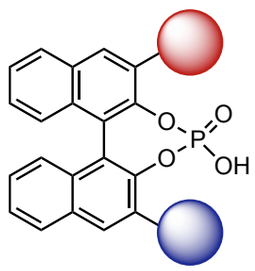
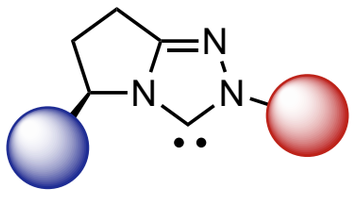
Keay, B. A. *JACS* **1996**, *118*, 10766

Transition Metal Cascades. Metathesis



Metz, P. *OL* **2016**, *18*, 3298

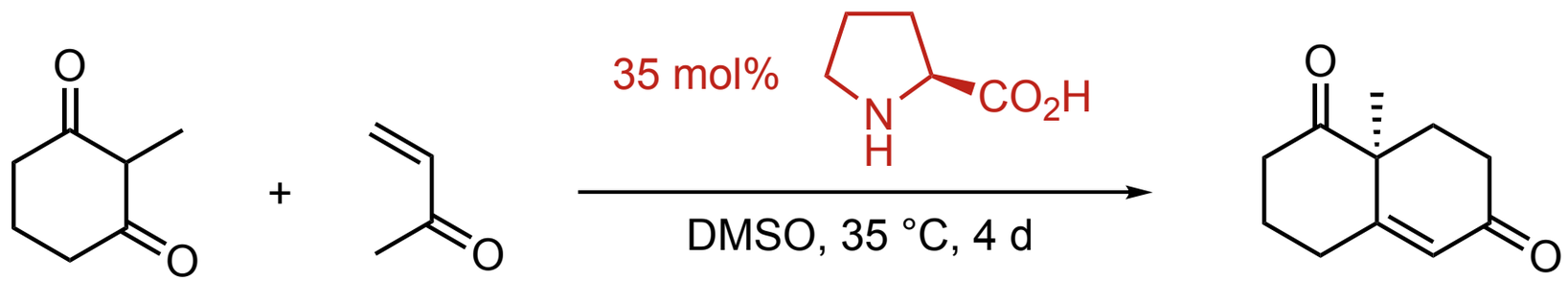
Organocatalytic Cascades

Catalyst	Activation mode	Typical reaction steps	Combination
	*Enamine activation of carbonyl compounds* ***(HOMO raising)***	EN: *Aldol reaction*, *Michael reaction*, *Mannich reaction*	
	*Iminium activation of unsaturated aldehydes* ***(LUMO lowering)***	IM: *Michael reaction*, *Diels-Alder reaction*, *Friedel-Crafts reaction*	
	*Hydrogen bonding* ***(LUMO lowering)***	HD: *Michael reaction*, *Henry reaction*, *Mannich reaction*	
	*Protonation* ***(LUMO lowering)***	H+: *Michael reaction*, *Mannich reaction*, *Friedel-Crafts reaction*, *Reduction*	
	*Umpolung*	NHC: *Nucleophilic acylation*, *Benzoin reaction*, *Stetted reaction*	

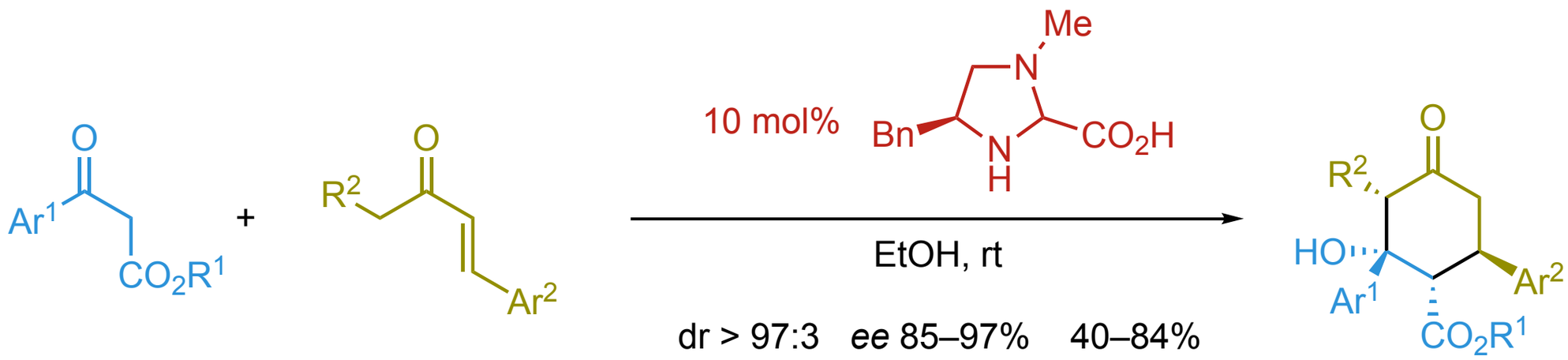
Enders, D. *Nat. Chem.* **2010**, 2, 167; Jørgensen, K. A. *ACIE* **2011**, 50, 8492; Rueping, M. *CR* **2014**, *114*, 2390

Organocatalytic Cascades

Inspirational organocatalytic cascades: Michael/Aldol reactions

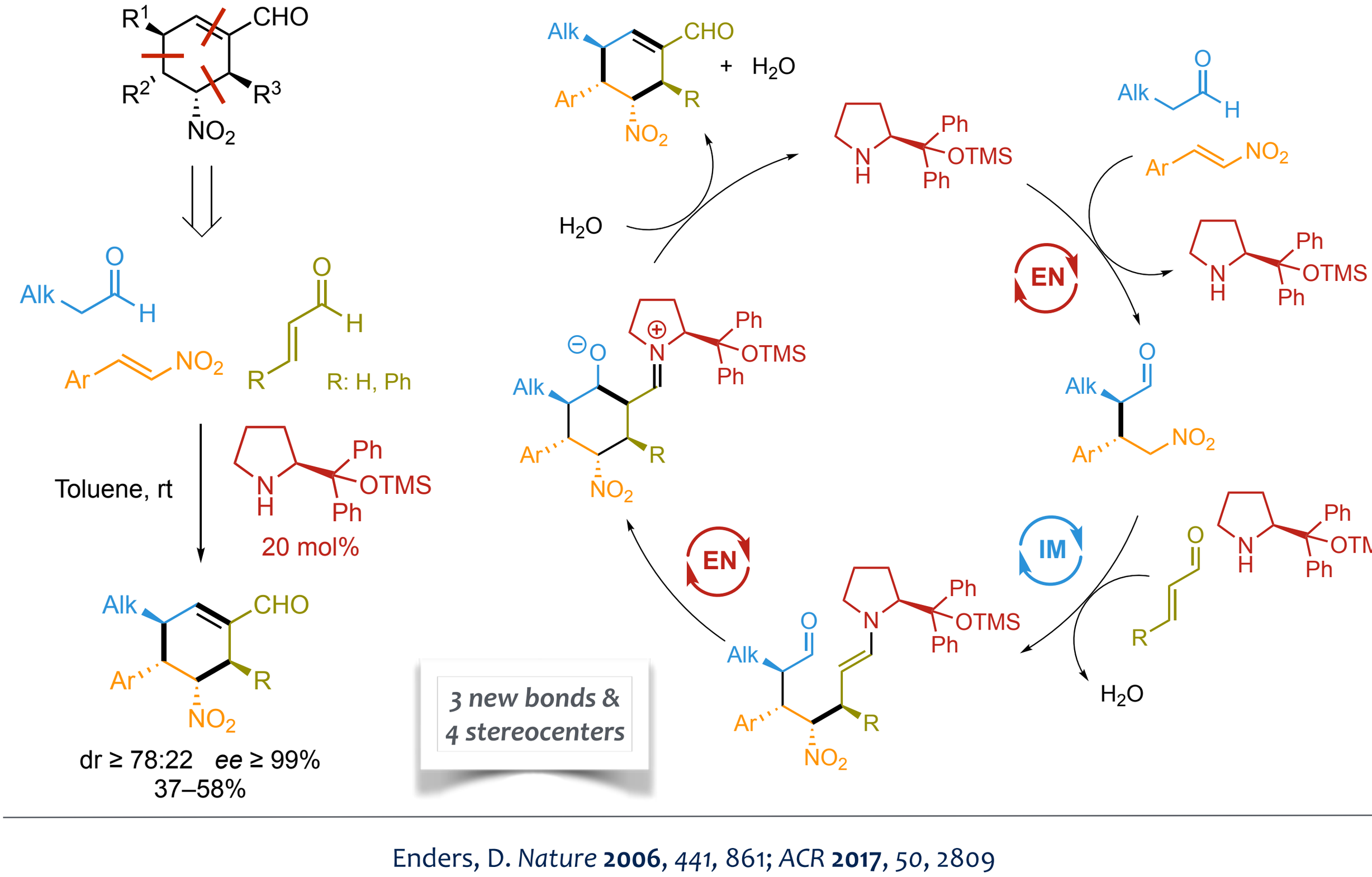


Barbas, C. *TL* **2000**, *41*, 6951



Jørgensen, K. A. *ACIE* **2004**, *43*, 1272

Organocatalytic Cascades

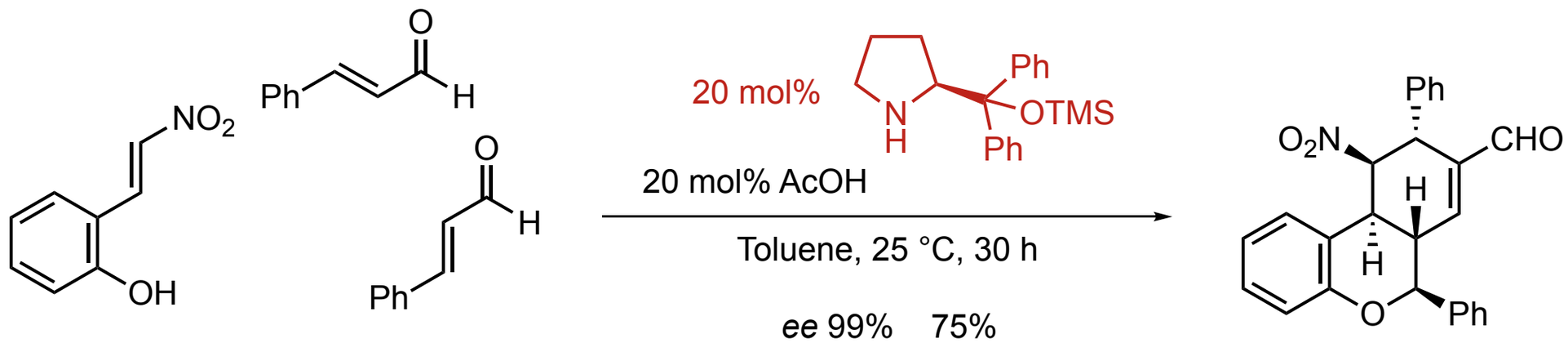


Enders, D. *Nature* **2006**, *441*, 861; *ACR* **2017**, 50, 2809

Organocatalytic Cascades

Oxa-Michael/Michael/Michael/Aldol condensation

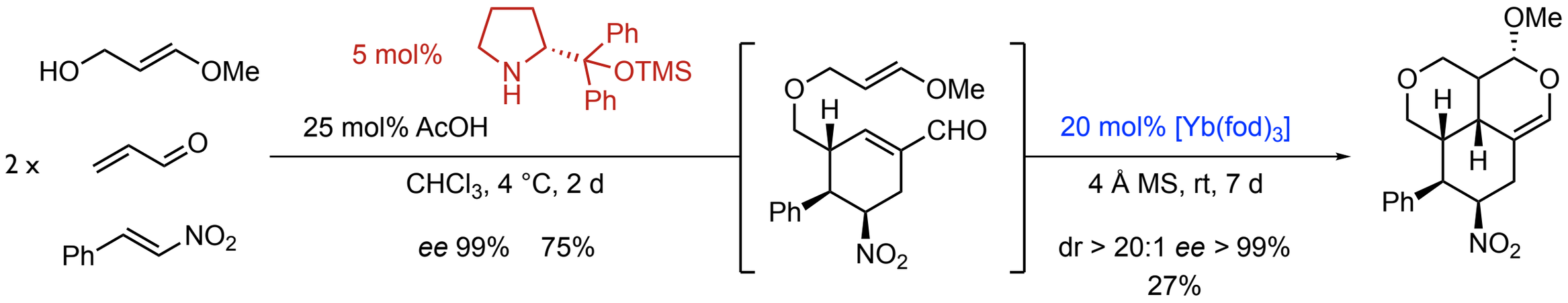
IM EN IM EN



Hong, J. E. *TL* **2009**, *80*, 1866

One pot Oxa-Michael/Michael/Michael/Aldol cond/Hetero Diels Alder

IM EN IM EN LA



Enders, D. *ACIE* **2016**, *55*, 16153

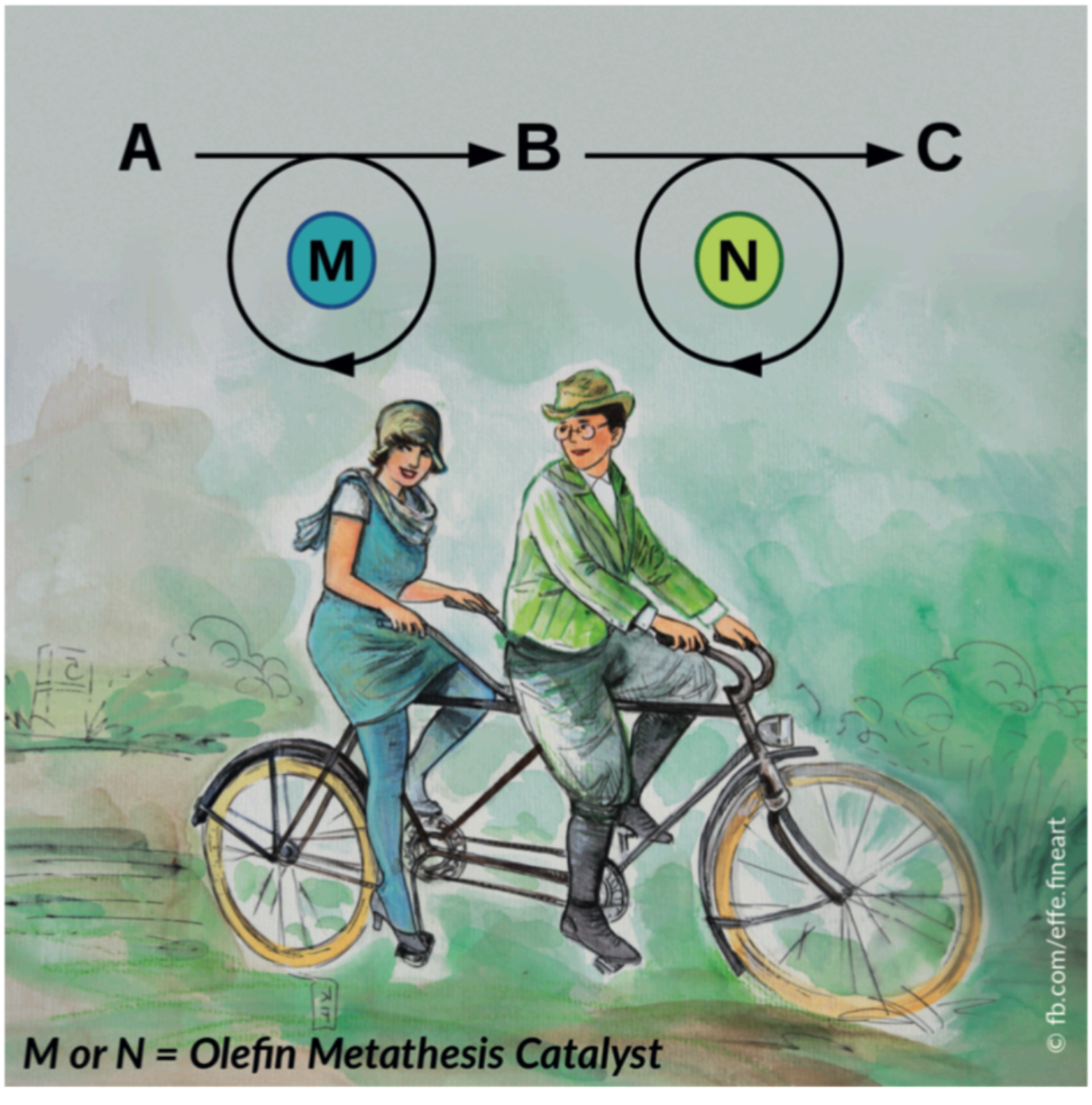
Merging Catalysts

Olefin Metathesis

Tandem Catalysis Utilizing Olefin Metathesis Reactions

Grzegorz K. Zieliński*[a] and Karol Grela*[a, b]

Dedicated to Professor Janusz Jurczak on the occasion of 75th birthday



Combination of catalysts
in a well orchestrated manner
produces highly efficient sequences

Fogg, D. E.; dos Santos, E. N.
Coord. Chem. Rev. **2004**, *248*, 2365

Menche, D. *Nat. Prod. Rep.* **2014**, *31*, 456

Marks, T. J. *Nature Chem.* **2015**, *7*, 477

Zielinski, G. K.; Grela, K. *CEJ* **2016**, 22, 9440

Enzymatic Cascade Reaction in Biosynthesis

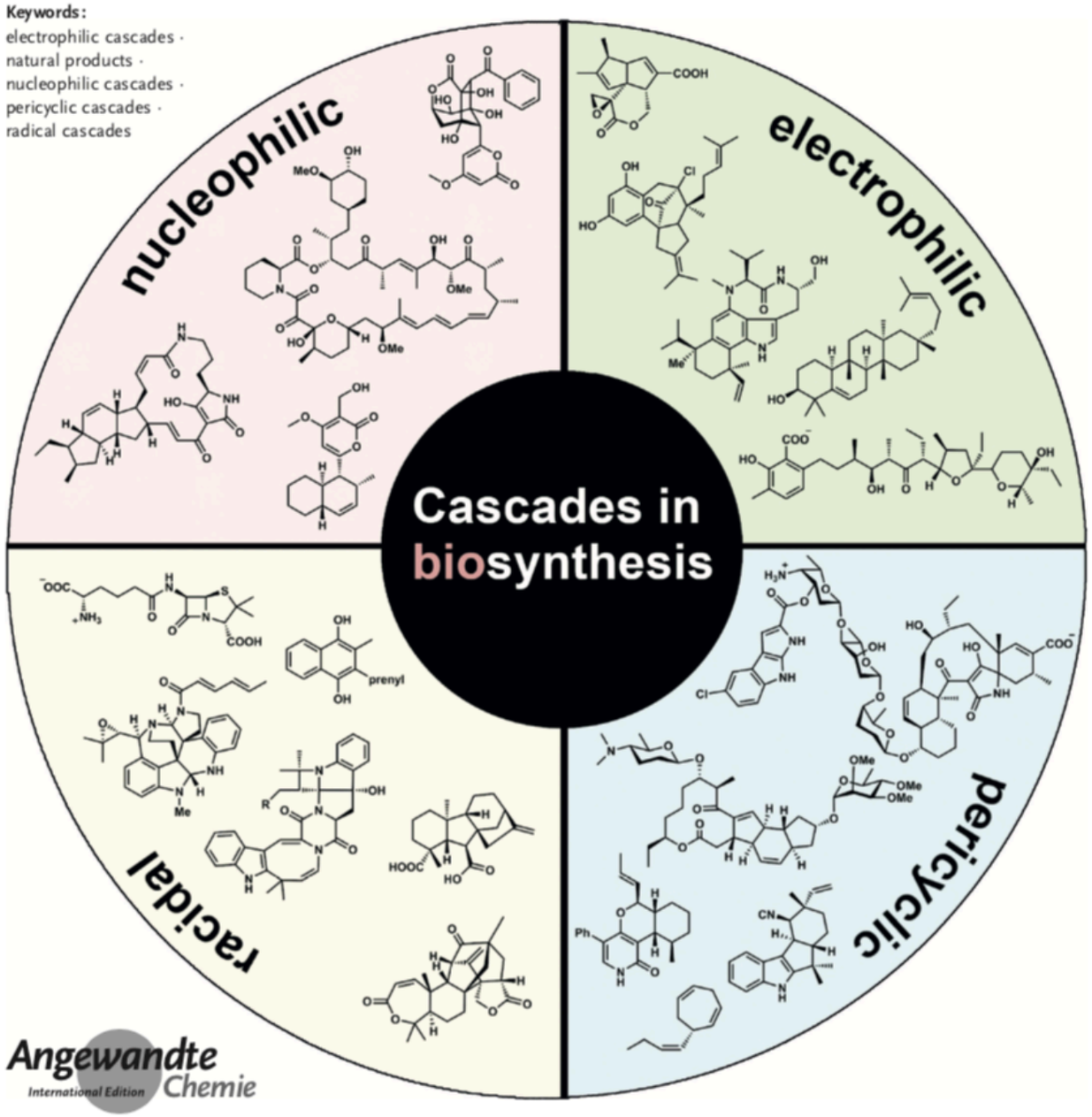
Biosynthesis

International Edition: DOI: 10.1002/anie.201807844
German Edition: DOI: 10.1002/ange.201807844

Enzymatic Cascade Reactions in Biosynthesis

*Christopher T. Walsh and Bradley S. Moore**

Keywords:
electrophilic cascades · natural products · nucleophilic cascades · pericyclic cascades · radical cascades



The use of enzymes may be an option to generate complex molecular architectures

Moore, B. S. *ACIE* **2019**, 58, 6846

Multicomponent Reactions

Multicomponent Reactions (MCRs) *are* ***one-pot reactions***
employing three or more reactants,
where most of the atoms the starting materials
are incorporated in the final product generating almost no by-products

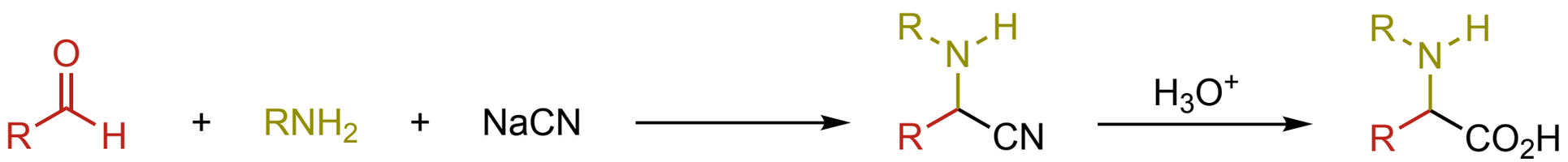
Mannich & ***Pauson-Khand*** *reactions*
are illustrative examples studied in former Chapters

See FG Strategies (Chap 4)
and Cyclizations (Chap 6)

Armstrong, R. W. *ACR* **1996**, *29*, 123; Enders, D. *ACIE* **2007**, *46*, 1570
Orru, R. V. A. *ACIE* **2011**, *50*, 6234; Dömling, A. *CR* **2012**, *112*, 3083

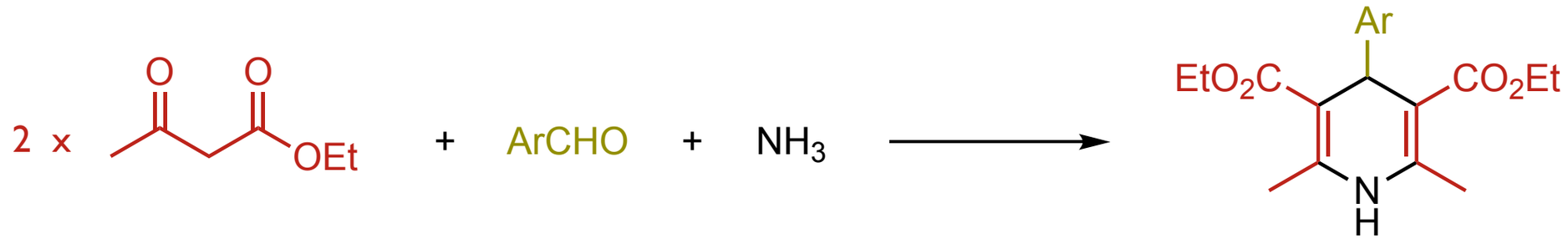
Multicomponent Reactions

Strecker



Strecker, A. *Liebigs Ann. Chem.* **1850,** *75,* 27

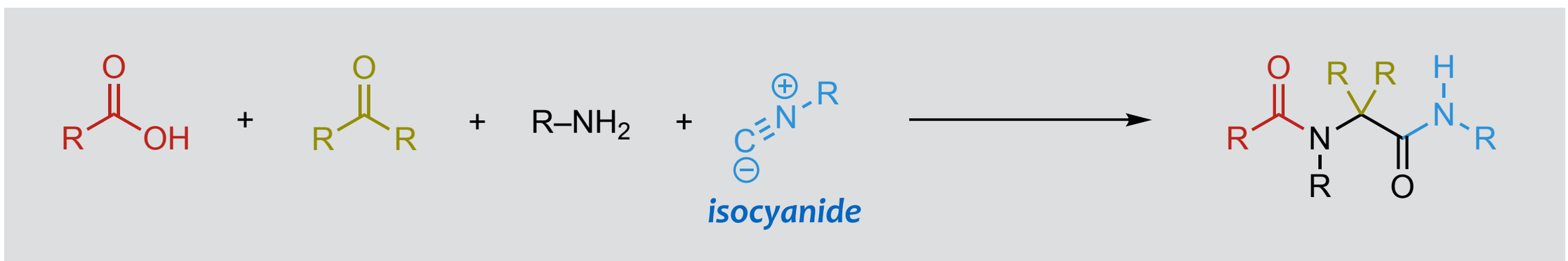
Hantzsch

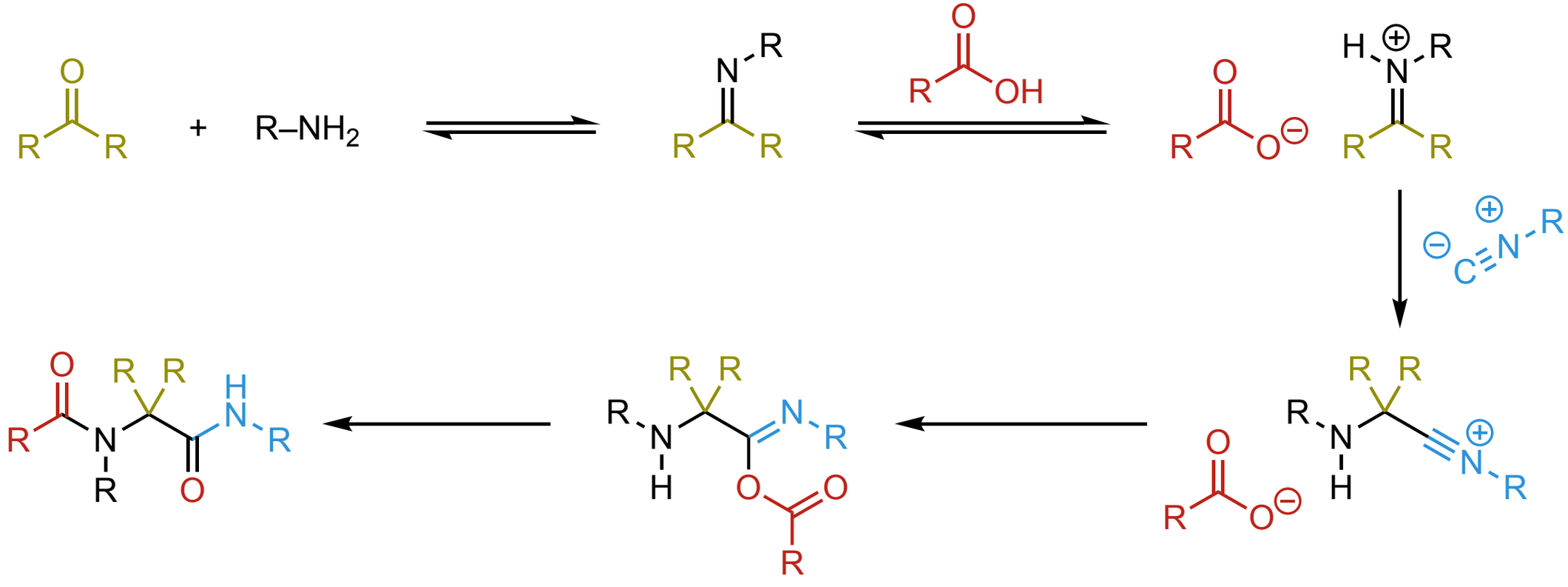


Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882,** *215,* 1

Multicomponent Reactions

Ugi





Ugi, I. *Angew. Chem.* **1959**, *71*, 386; *ACIEE* **1962**, *1*, 8