Master Course
in Organic Chemistry

2018-19

methods **and design** in organic synthesis

Pere Romea

Visione metafísica di New York
Giorgio De Chirico, *1975*

5. New approaches

Building Block Strategy

based on the recognition of structural units

Functional Group Strategy

based on the FG relationships

rational

reliable

robust

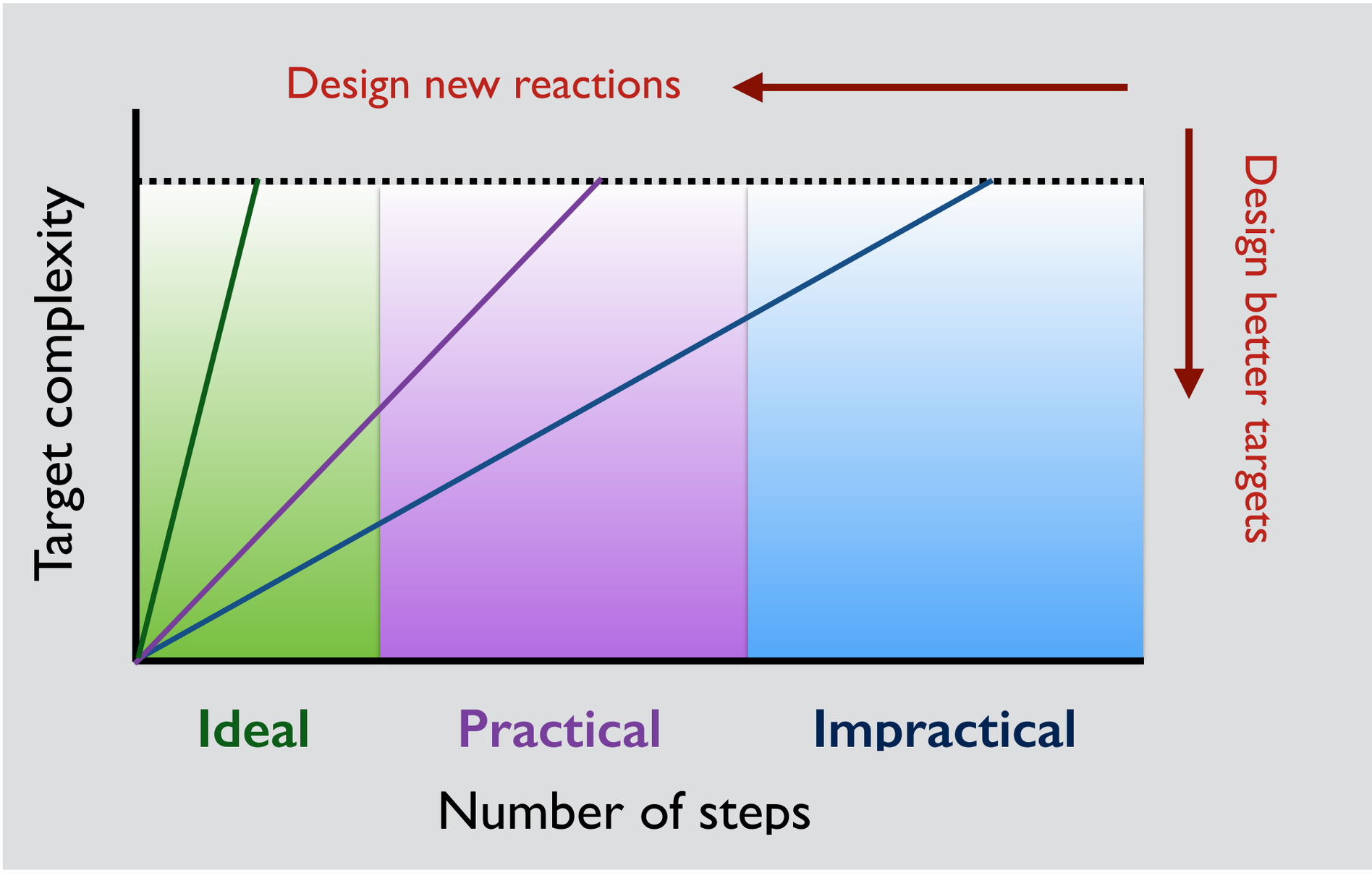
restricted to heterolytic mechs

radical reactions? pericyclic reactions?

reactivity and selectivity as problems

protecting groups? changes/adjustments of FGs?

An efficient synthesis should not contain more than 20 steps



Wender, P. A. *ACR* **2008**, *41*, 40; Nature **2009**, *460*, 197

STEP ECONOMY

as least steps as possible

Fürstner, A. *Synlett* **1999**, 1523
Wender, P. A. *Tet* **2006**, *62*, 7505; *Tet* **2013**, *69*, 7529; *NPR* **2014**, *31*, 433

REDOX ECONOMY

avoidance of redundant redox steps

Baran, P. S.; Hoffmann, R. W. *ACIE* **2009**, *48*, 2854

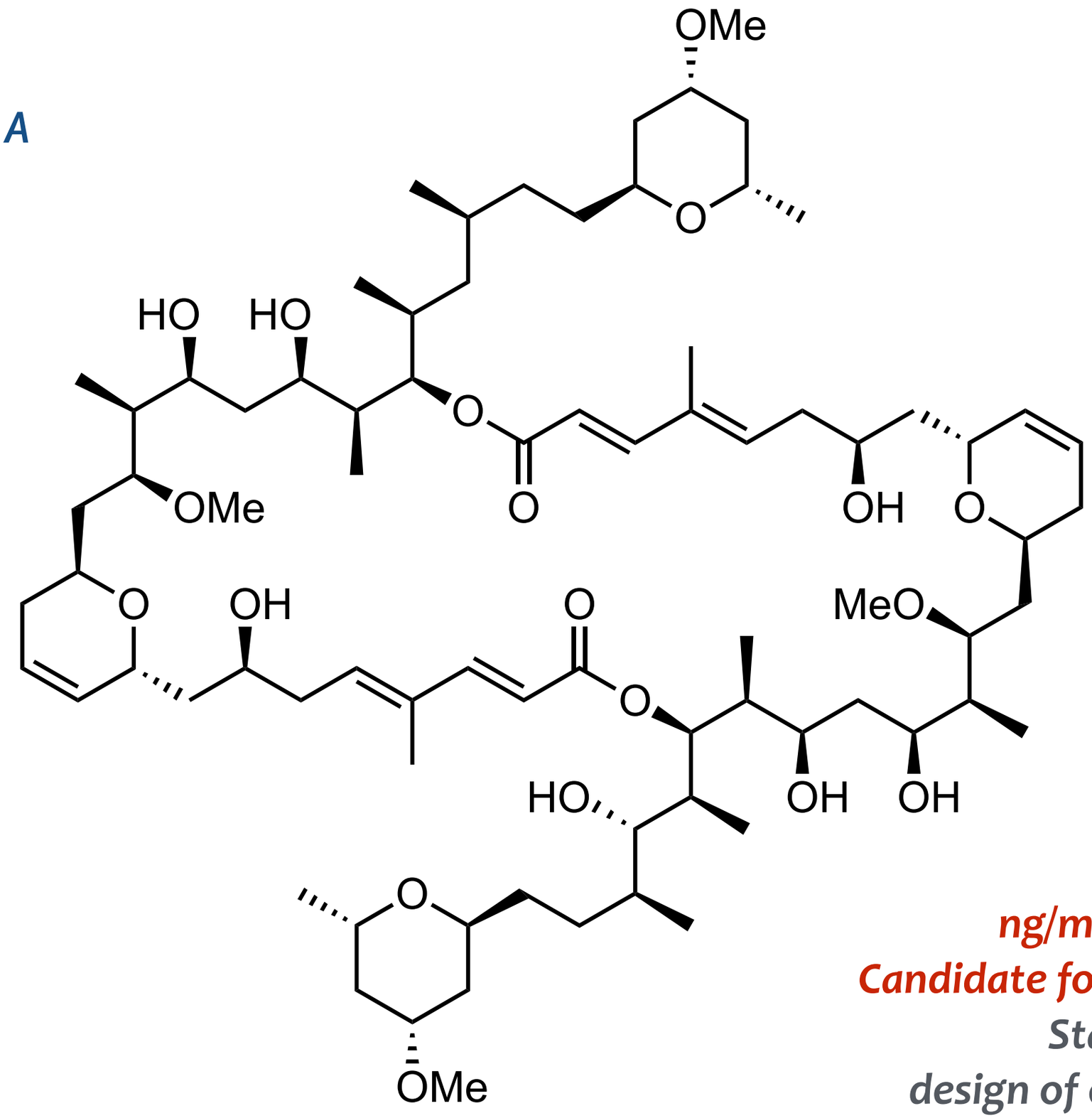
For *The Economies of* Synthesis, see: Baran, P. S.; Hoffmann, R. W. *CSR* **2009**, *38*, 3010

POT ECONOMY

aim to complete an entire multi-step synthesis in a single pot
(see Chapter 7)

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

Swinholide A

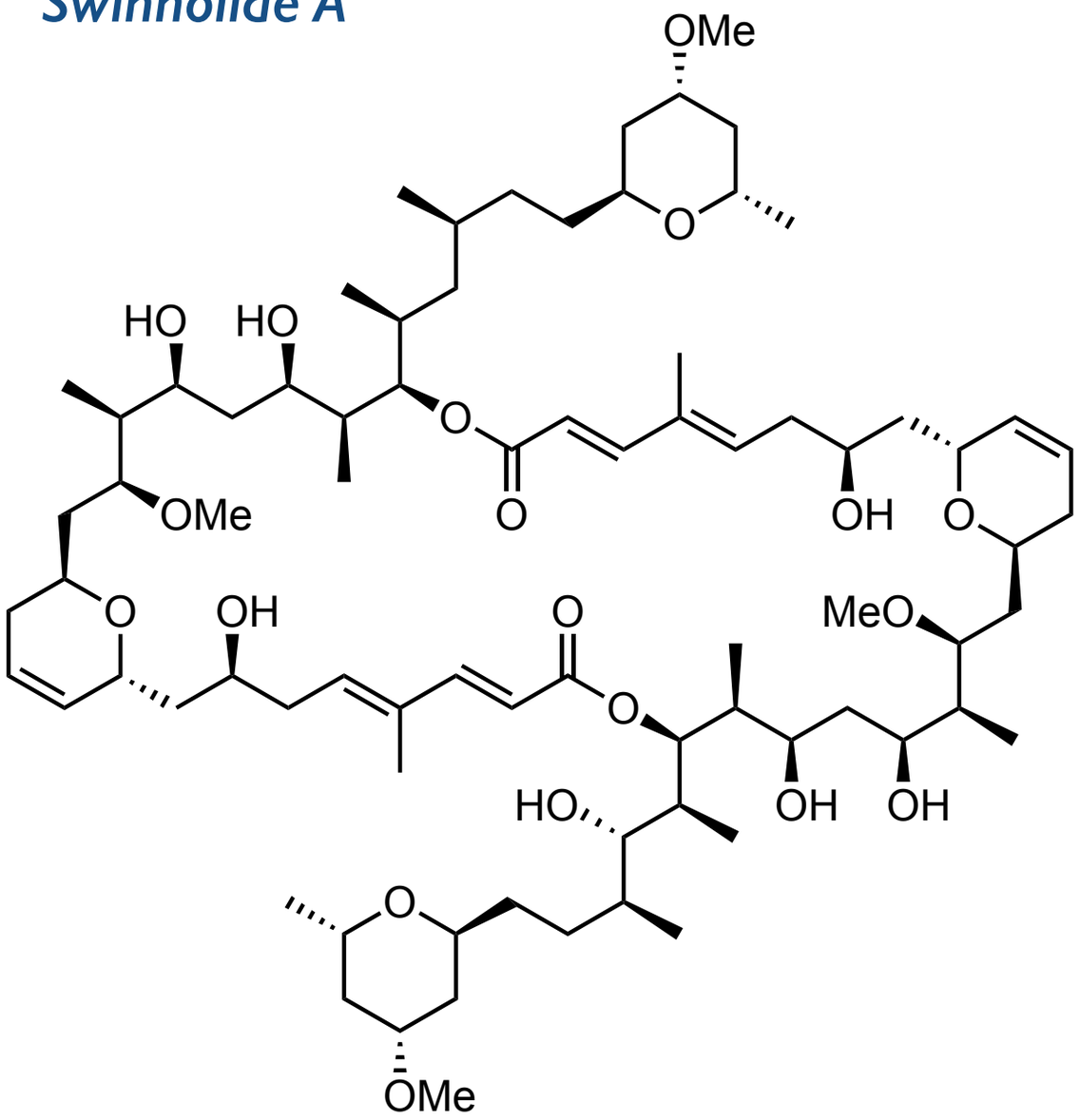


ng/mL cytotoxic activity

Candidate for cancer treatment

Starting point for the design of clinical candidates?

Swinholide A



Three Total Syntheses

Paterson, I. *JACS* **1994**, *116*, 9391
Tet **1995**, *51*, 9393, 9413 9437, 9467

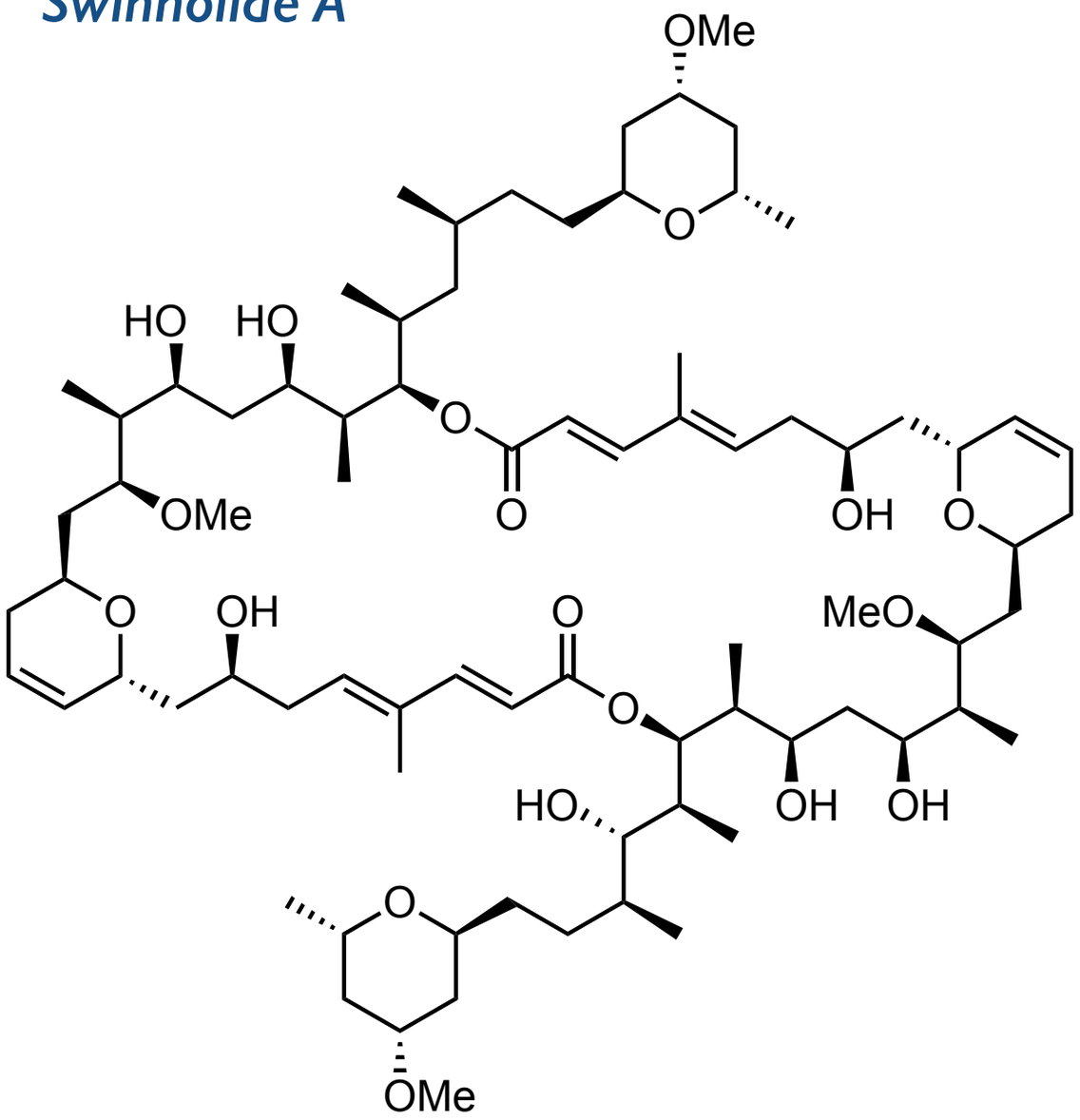
+ 1 year

Nicolaou, K. C. *JACS* **1995**, *118*, 3059
CEJ **1995**, 2, 847

+ 21 years

Krische, M. J. *JACS* **2016**, *139*, 14246

Swinholide A



THREE TOTAL SYNTHESES

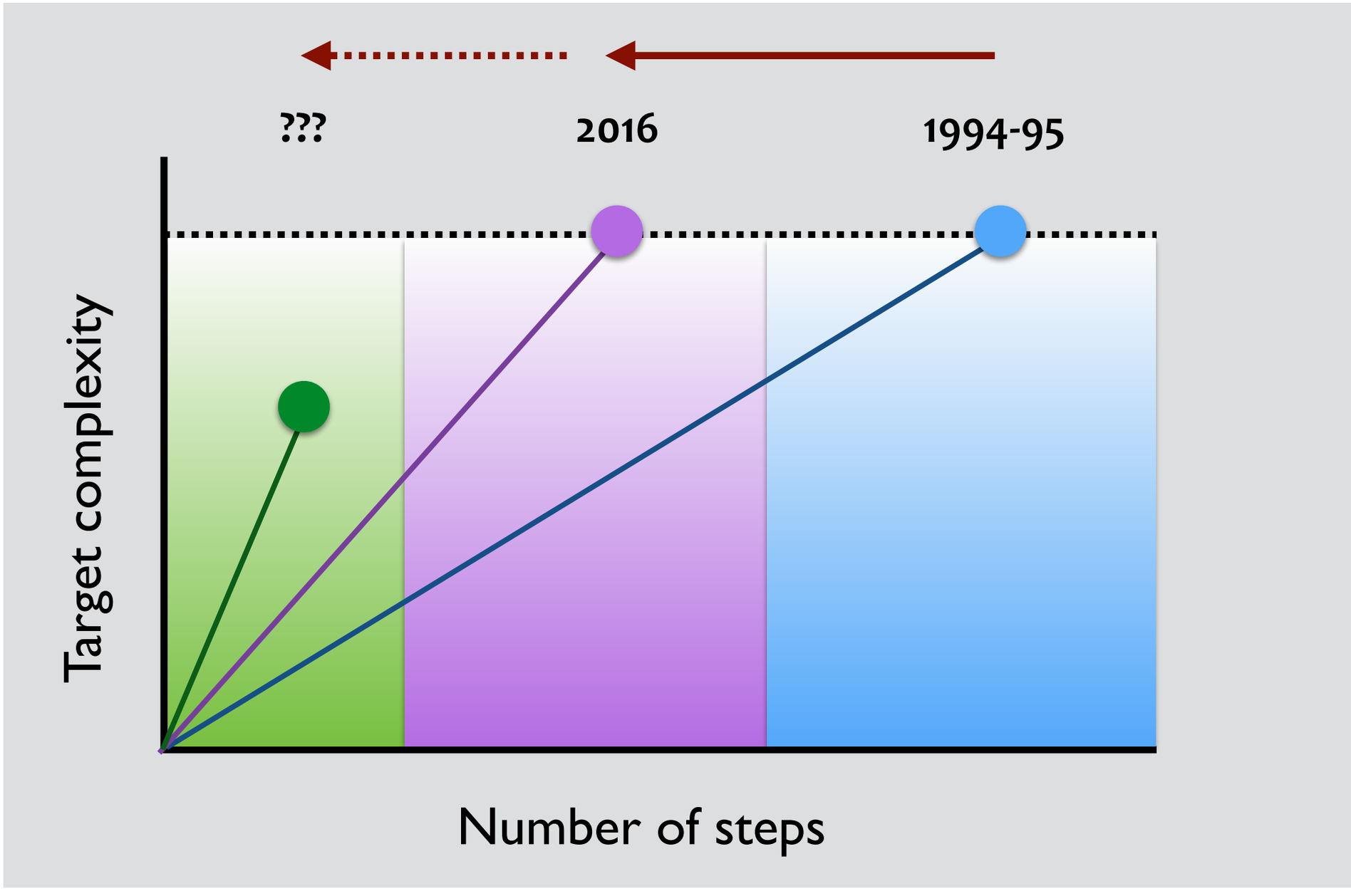
Paterson, I.
27 Longest Lineal Synthesis ; 50 Total Steps

Nicolaou, K. C. *JACS* **1995**, *118*, 3059
35 Longest Lineal Synthesis ; 59 Total Steps

Rh-Catalyzed reductive aldol reaction
Ru-Catalyzed Metathesis
Ir-Catalyzed Alcohol Allylation

Krische, M. J. *JACS* **2016**, *139*, 14246
15 Longest Lineal Synthesis ; 30 Total Steps

More simple TGT ***More efficient reactions and strategies: CATALYSIS***



New Operational Strategies

Computational support

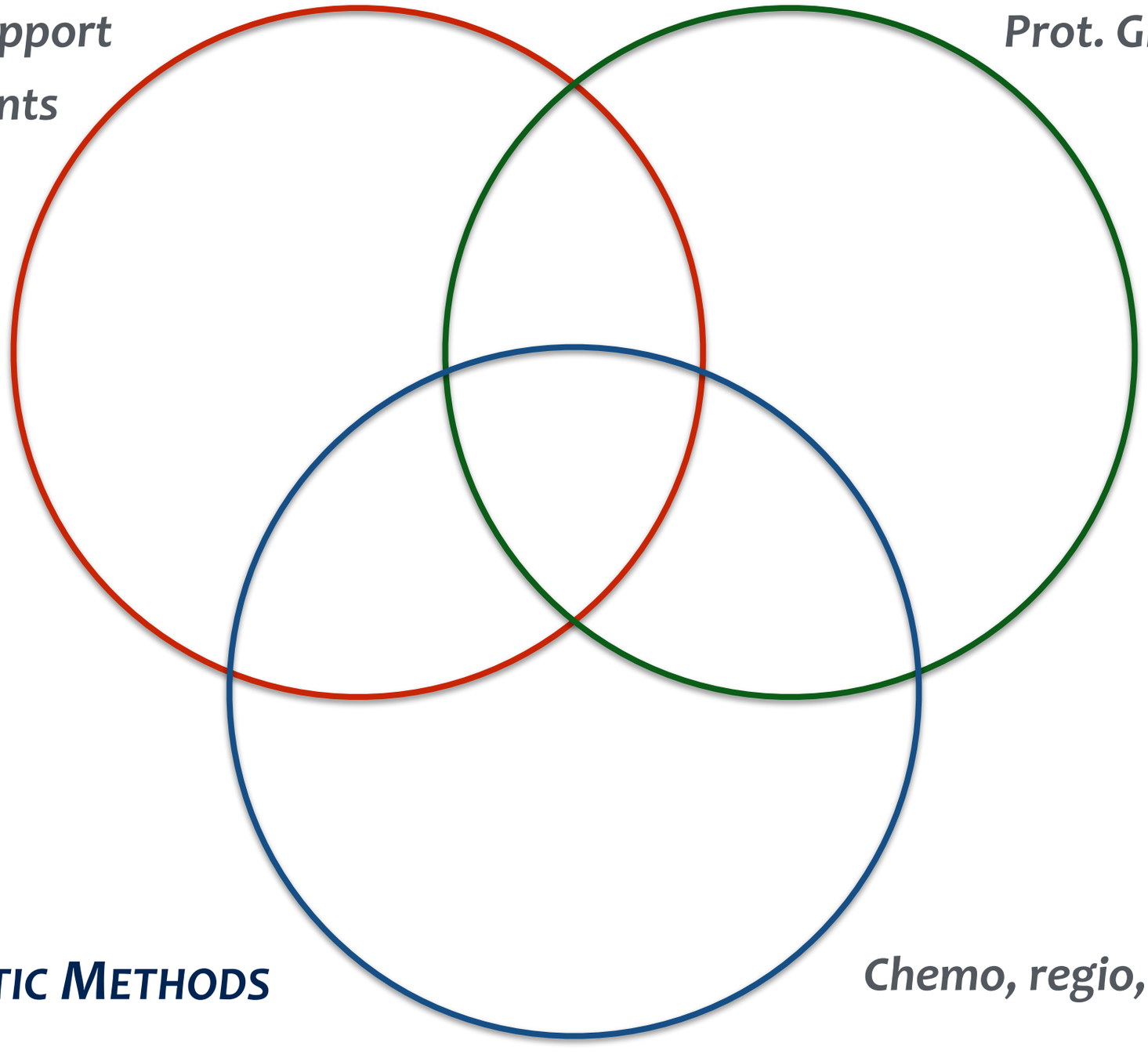
Solid phase reagents

Scavengers

New Synthetic Strategies

Prot. Group free sequences

Tandem sequences

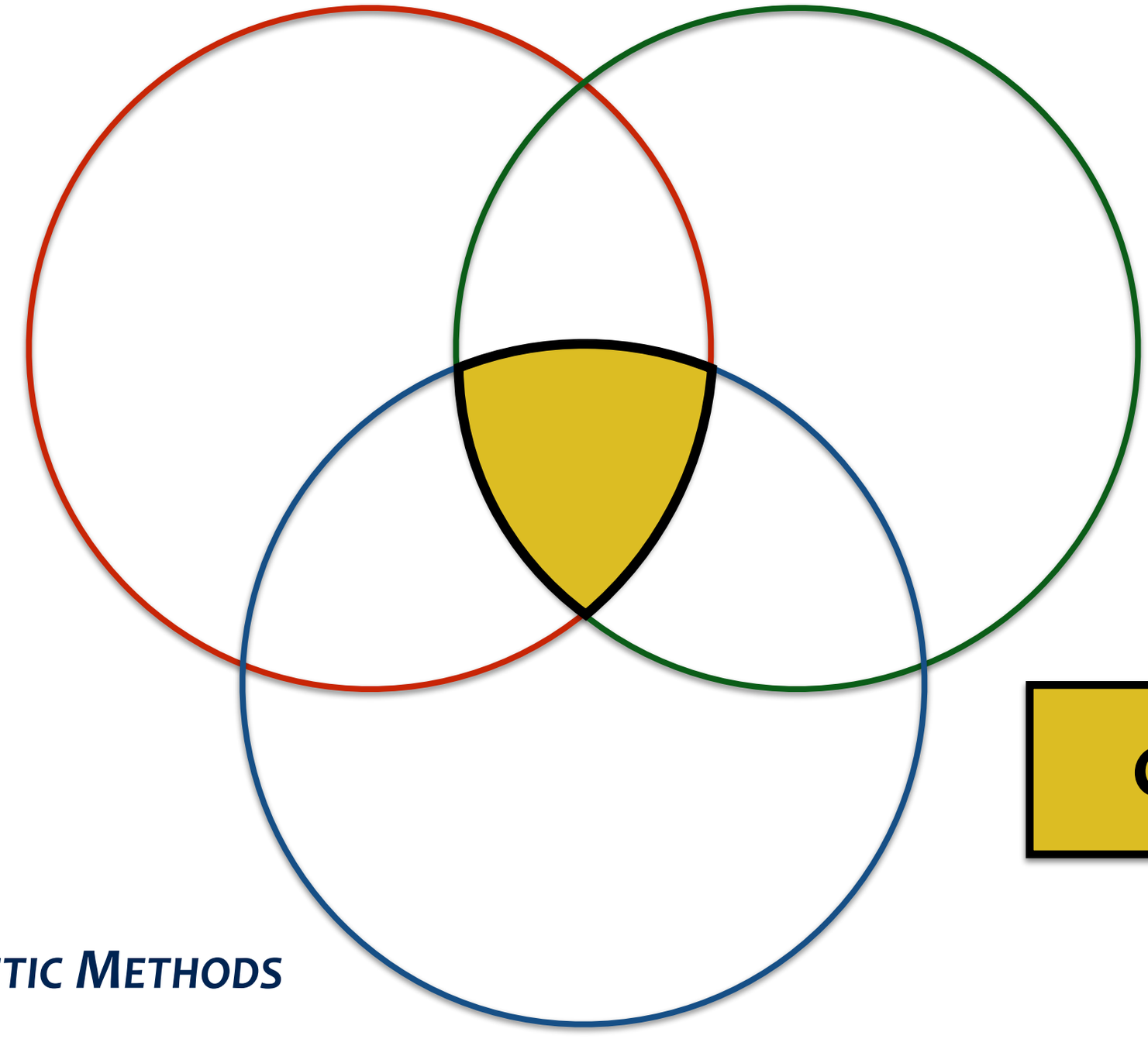


New Synthetic Methods

Chemo, regio, and stereoselective reactions

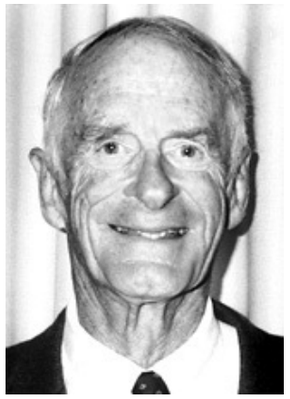
NEW OPERATIONAL STRATEGIES

NEW SYNTHETIC STRATEGIES



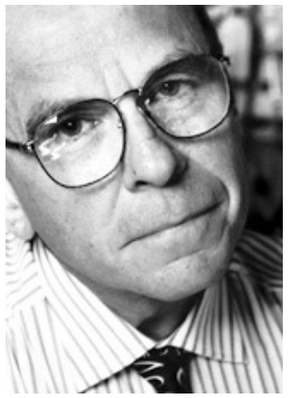
Catalysis

NEW SYNTHETIC METHODS



W. S. Knowles

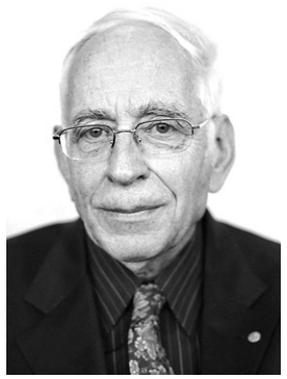
R. Noyori



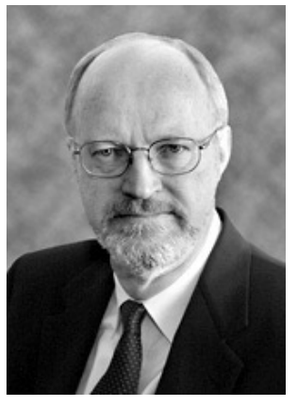
K. B. Sharpless

2001

for their work on chirally catalyzed hydrogenation and oxidation reactions



Y. Chauvin



R. H. Grubbs

R. R. Schrock

2005

for the development of the metathesis method in organic synthesis

R. F. Heck

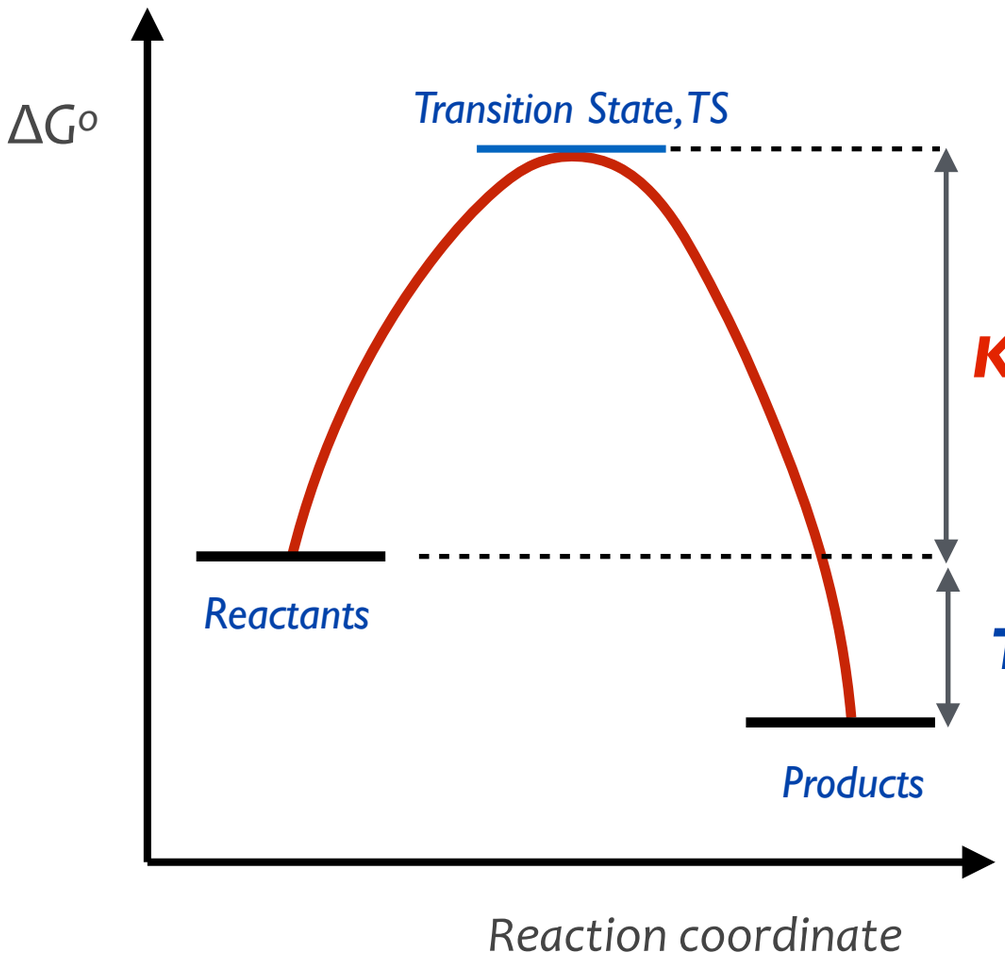
E-i-. Negishi

A. Suzuki

2010

for palladium-catalyzed cross couplings in organic synthesis

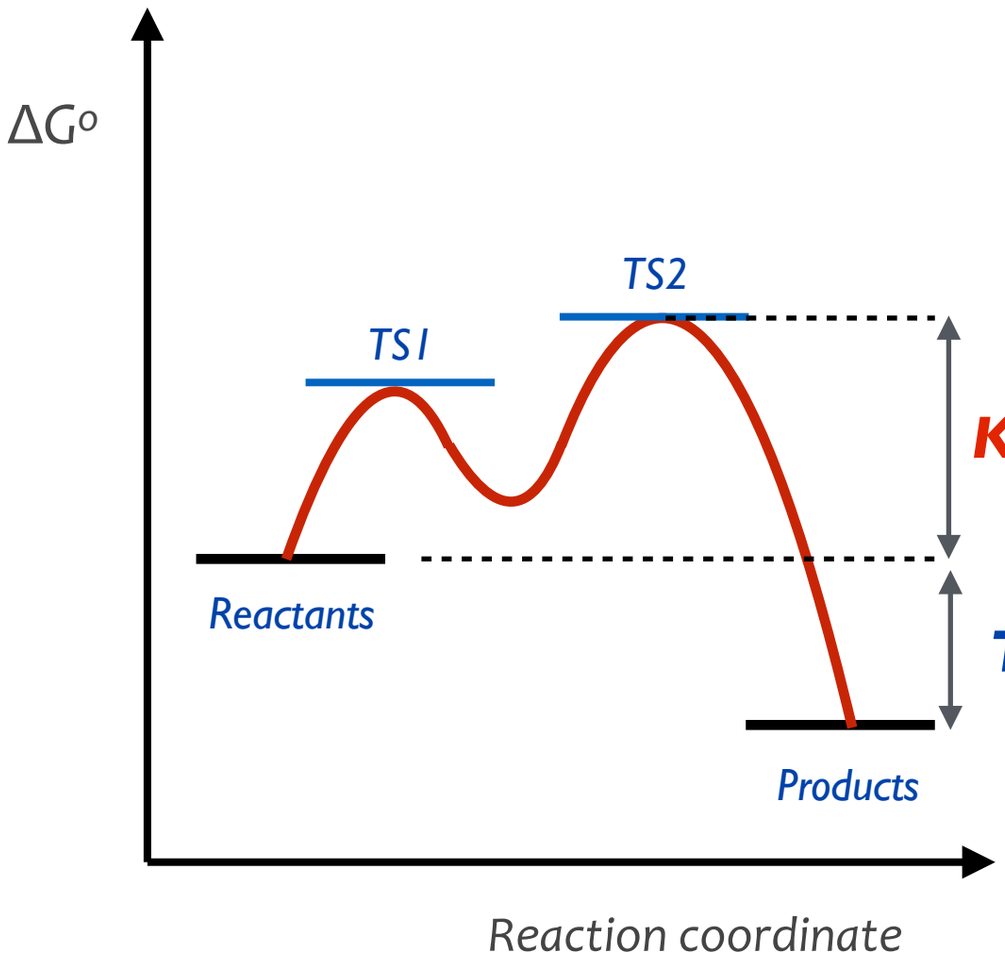
A catalyst is a substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction. The process is called catalysis

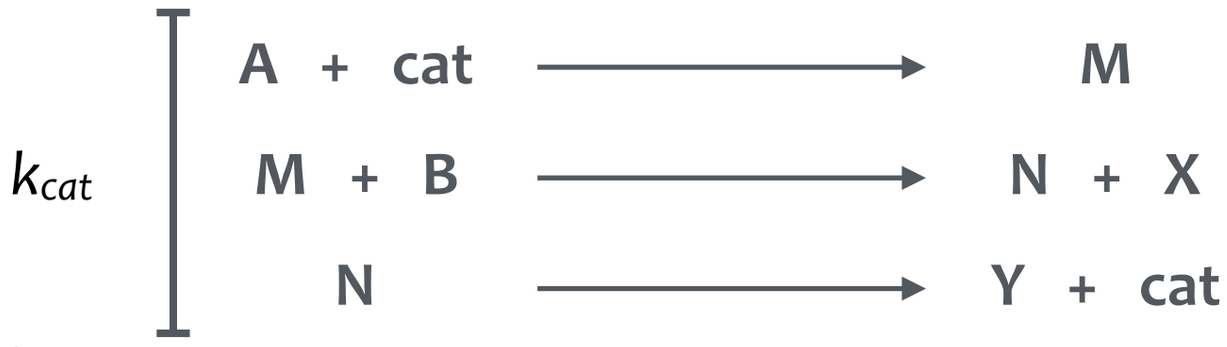


$$A + B \xrightarrow{k_{background}} X + Y$$

A non-catalyzed process

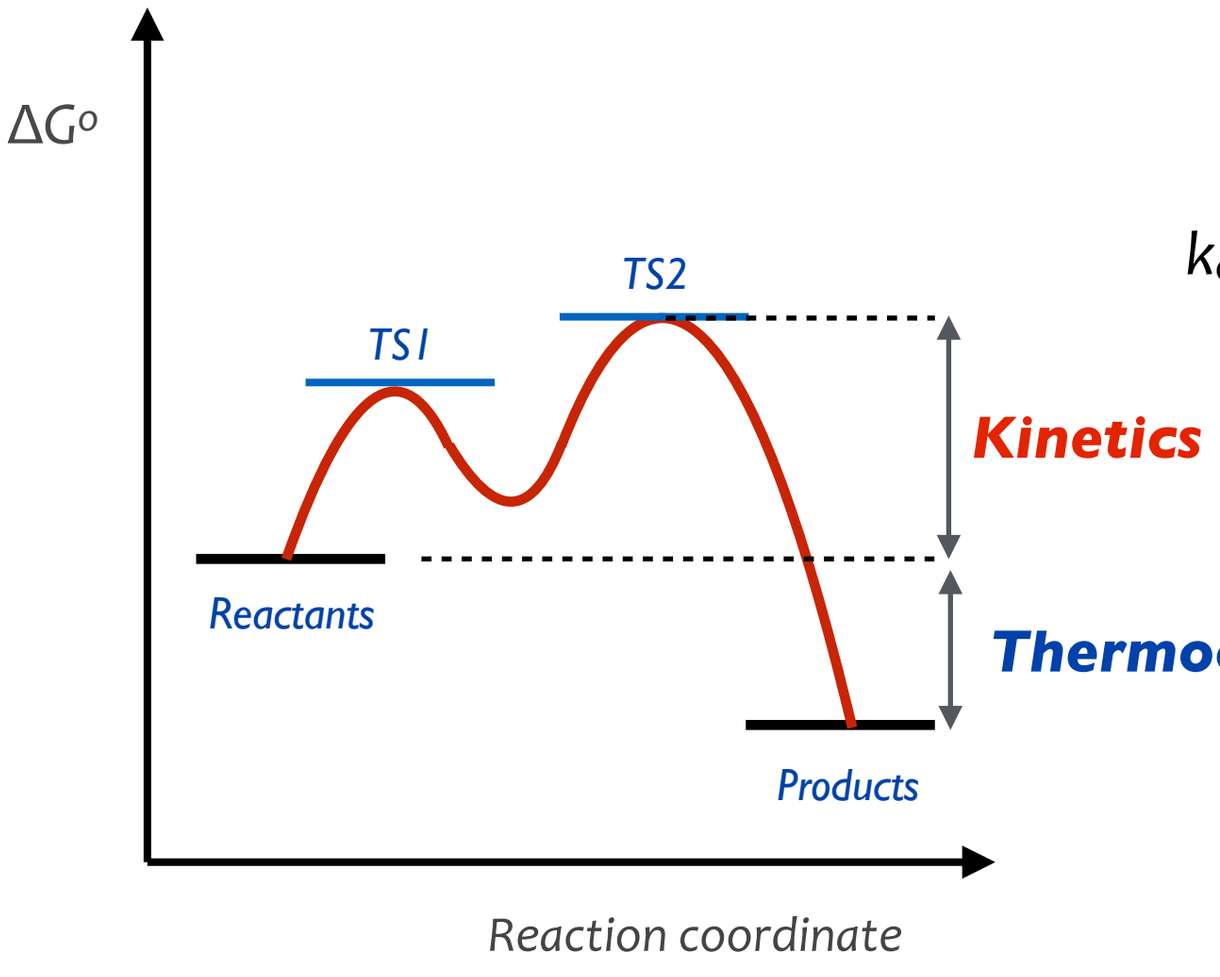
A catalyst is a substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction. The process is called catalysis

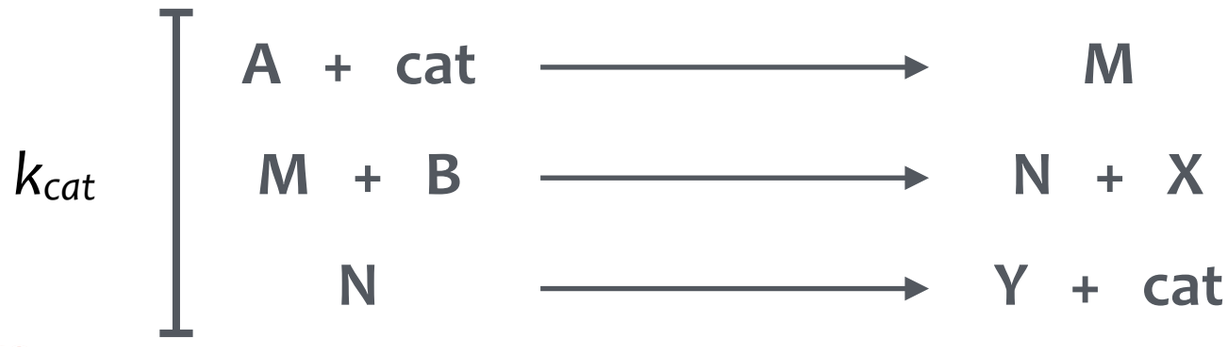




This definition is sufficiently broad to encompass catalysts used in both small (substoichiometric) and large (stoichiometric and superstoichiometric) quantities as well as relatively complicated ($[Ir(PCy_3)_3]^+BPh_4$) and simple (H^+) catalysts

Jones, A. C.; Stoltz, B. M. ACIE 2014, 53, 2556

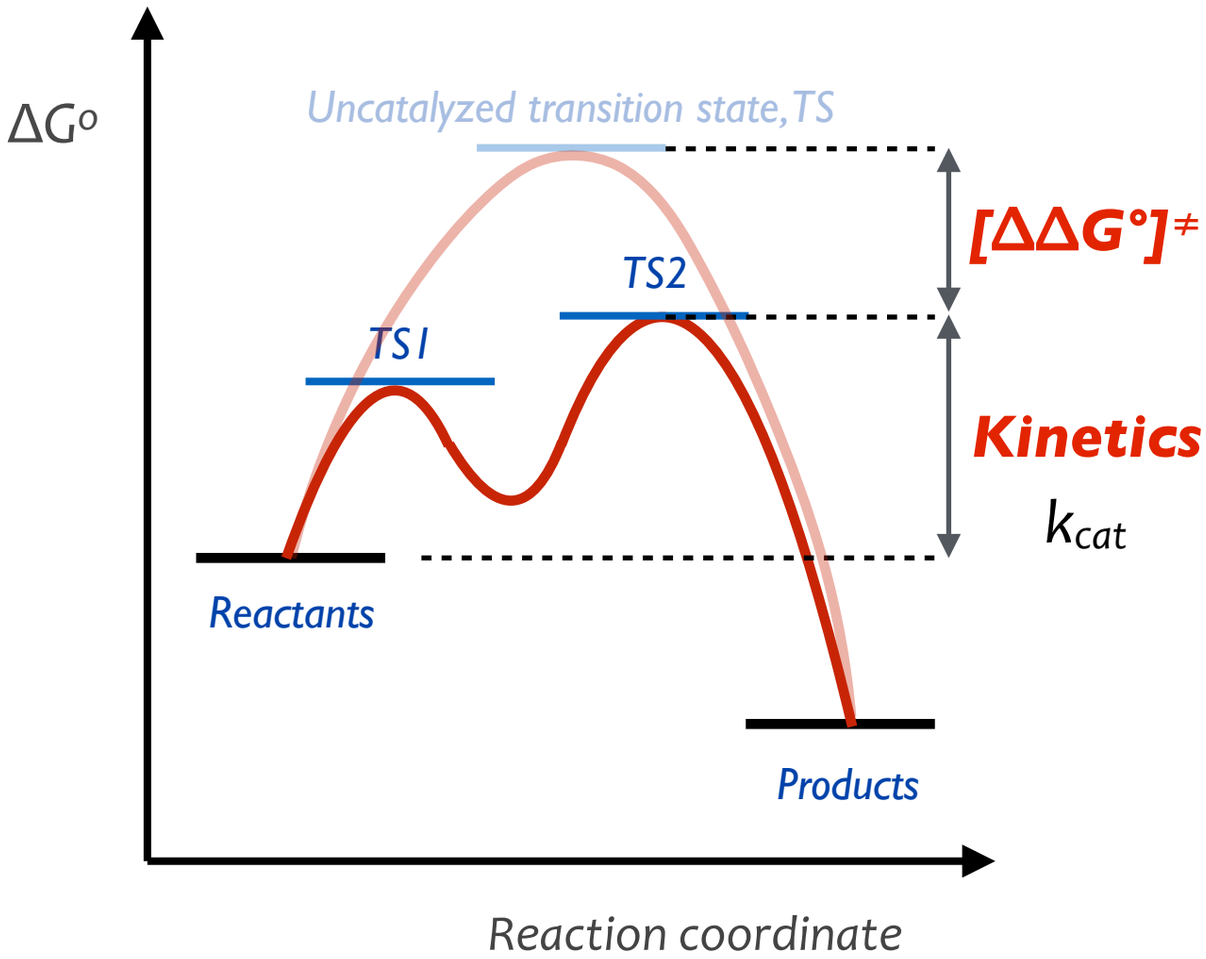




A catalyzed process

This definition is sufficiently broad to encompass catalysts used in both small (substoichiometric) and large (stoichiometric and superstoichiometric) quantities as well as relatively complicated ($[Ir(PCy_3)_3]^+BPh_4$) and simple (H^+) catalysts

Jones, A. C.; Stoltz, B. M. ACIE 2014, 53, 2556



Activation mode

A catalyzed process

$[\Delta\Delta G^\circ]^\neq$ as higher as possible

$$k_{cat} >> k_{background}$$

Organometallic Catalysis: Few Activation Concepts

Lewis Acids Catalysts

Mukaiyama
Corey
Evans
Shibasaki

Atom Transfer Catalysts

Sharpless
Jacobsen
Shi

Olefin Metathesis

Grubbs
Schrock
Hoveyda
Fürstner

σ-bond insertion
C–C bond coupling

Suzuki
Stille
Negishi
Kumada

σ-bond insertion
C–N, O, S bond coupling

Buchwald
Hartwig

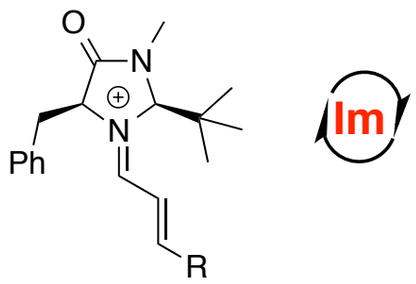
π-bond insertion

Trost
Noyori
Heck
Krische

Relatively few activation modes have resulted in a large number of chemical reactions

Organocatalysis Has Added More Activation Concepts

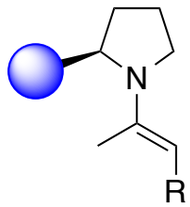
Iminium Catalysis



Im

MacMillan

Enamine Catalysis

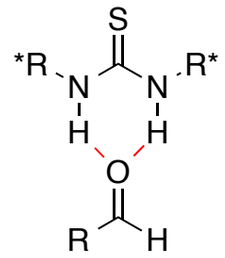


En

List

Jorgensen

H-Bond Catalysis

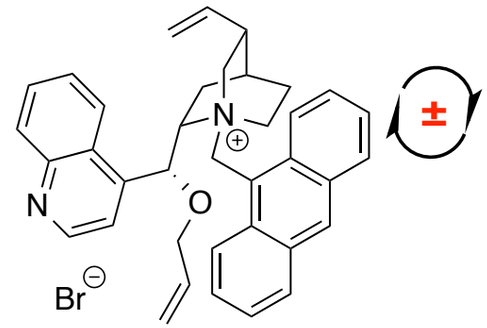


H+

Jacobsen

Rawal

Ion-pairing Catalysis



±

O'Donnell

Maruoka

Two new modes of catalyst activation have recently been devised

SOMO Catalysis

So

Photoredox Catalysis

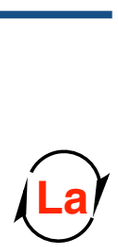
±e

MacMillan, Stephenson, Nicewicz, Yoon, Bach, Rueping

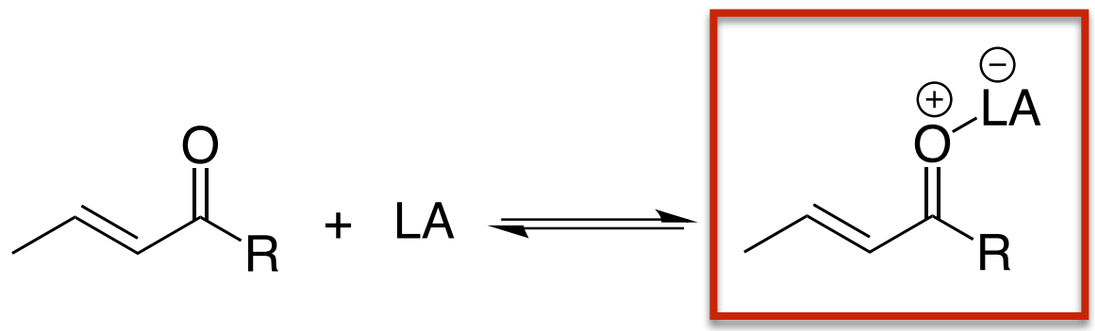
See Synthesis handouts (Chapter 2)

Lewis Acids Catalysts

Mukaiyama
Corey
Evans
Shibasaki



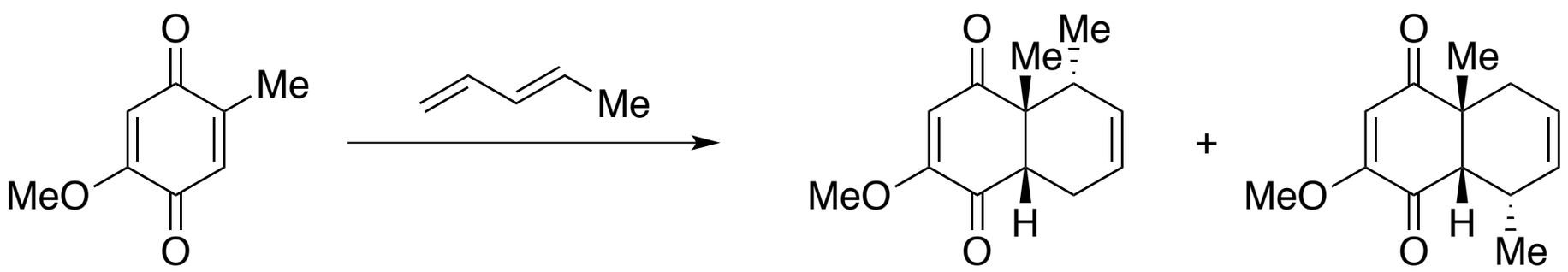
Diels-Alder: one of the most important pericyclic reactions



better dienophile

milder experimental conditions:

better selectivity

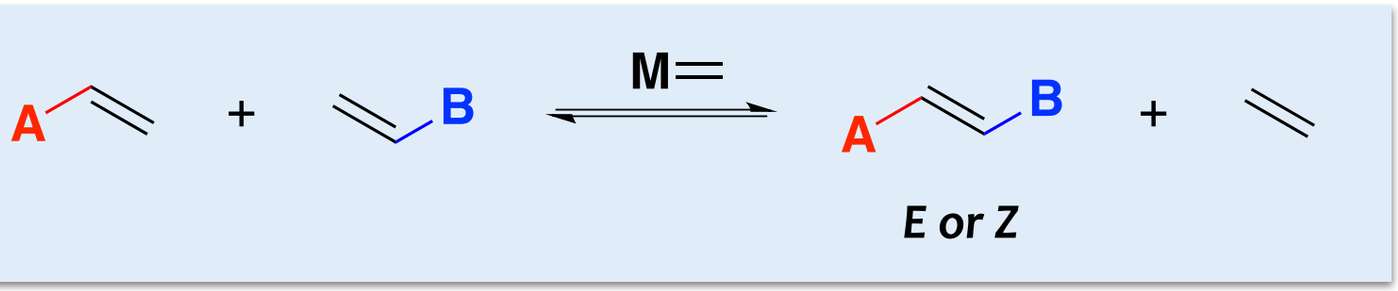


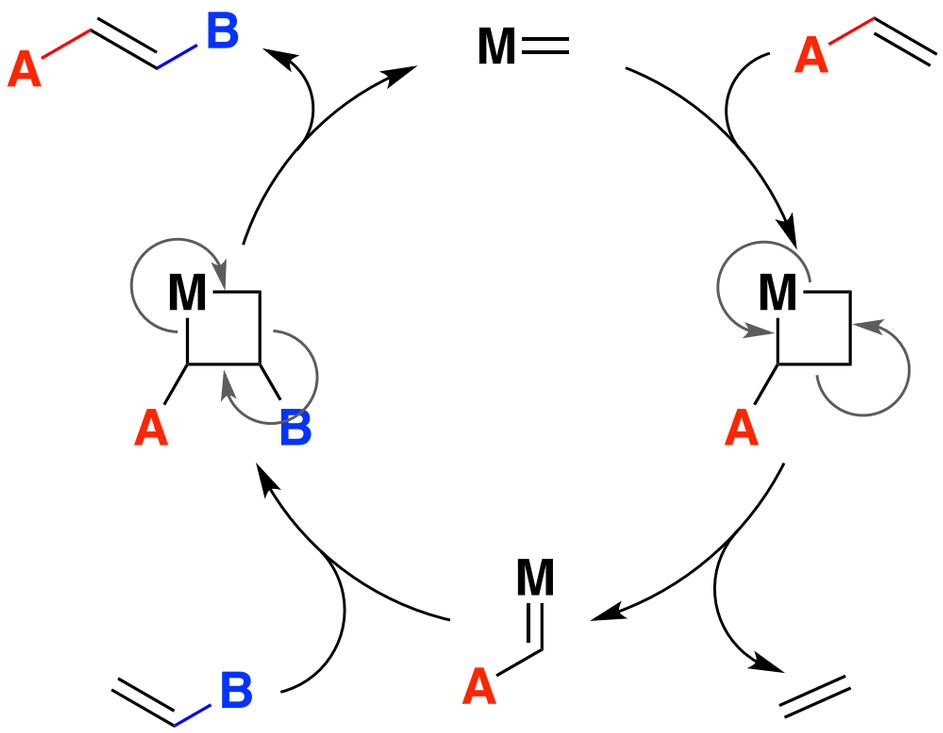
Conditions	Ratio
Without LA (100 °C)	*50 : 50*
BF3·OEt2 (–20 °C)	*80 : 20*
SnCl4 (–20 °C)	*5 : 95*

regioselectivity?

Reusch, W. *JOC* **1980**, *45*, *5012*

Metathesis: a key reaction for the formation of alkenes



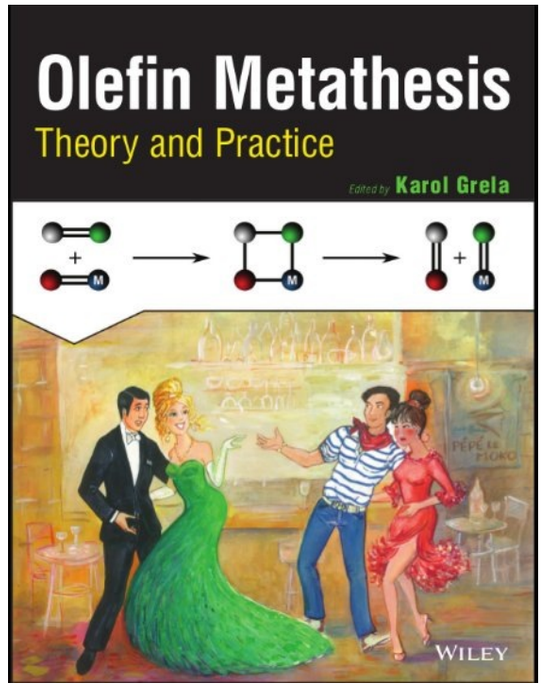


Metathesis can also involve alkynes

See Synthesis handouts (Chapter 3)

Olefin Metathesis

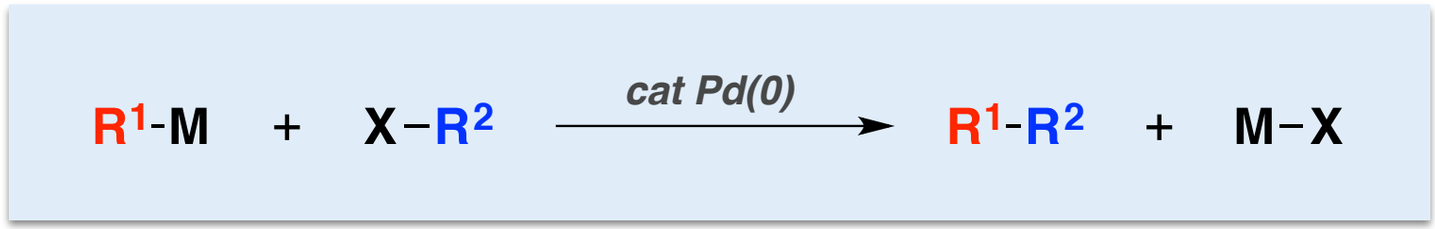
Grubbs
Schrock
Hoveyda
Fürstner

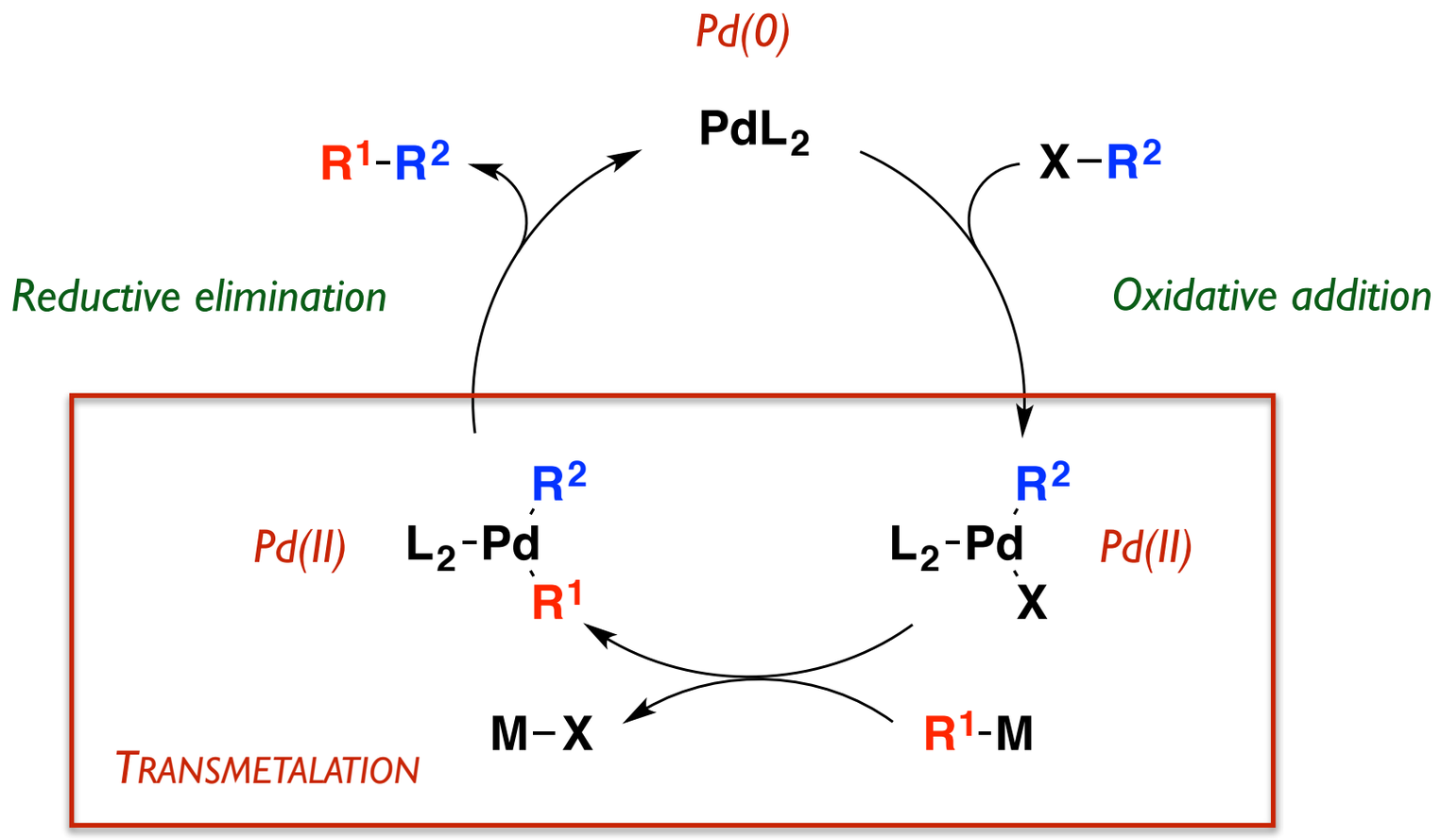


Grela K.
Olefin Metathesis. Theory and Practice. Wiley

Pd-Coupling reactions: a new way to construct C–C bonds

See Synthesis handouts (Chapter 4)





σ-bond insertion
C–C bond coupling

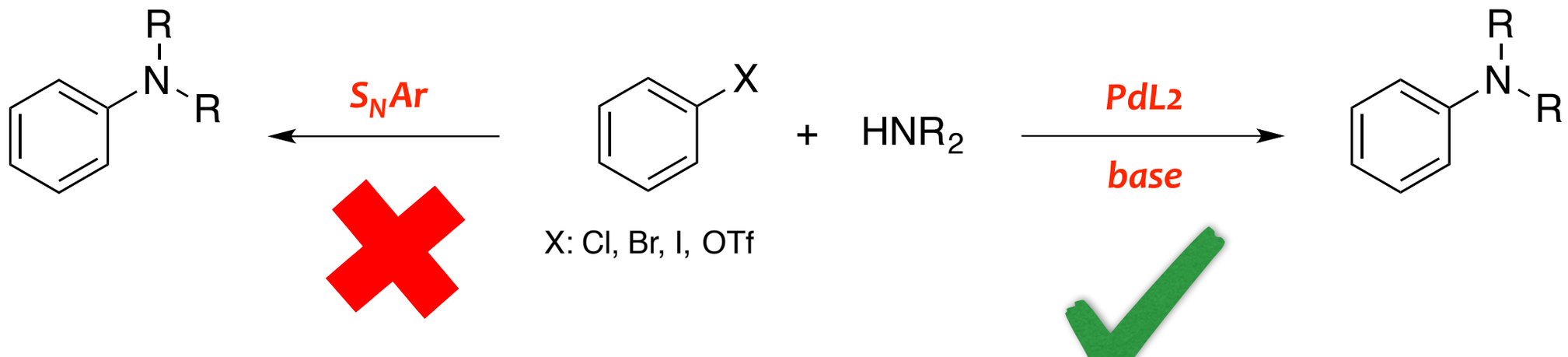
Suzuki
Stille
Negishi
Kumada

σ

Fürstner, A. *ACIE* **2005,** *44,* 674

R^1: alkyl, alkenyl, alkynyl, aryl R^2: better no beta H
X: I, Br, Cl, OTf

Pd-Coupling reactions: C–X bonds now available



σ-bond insertion
C–N, O, S bond coupling

Buchwald
Hartwig

Buchwald,S. *ACR* **1998**, *31*, 805
Hartwig, J. *ACR* **1998**, *31*, 852

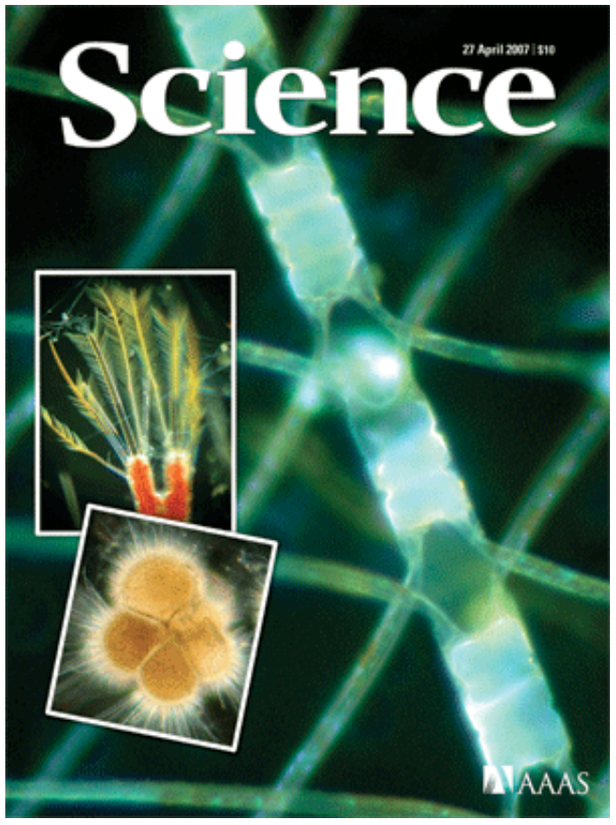
*In the **Buchwald-Hartwig reaction**,*
Pd(0) insertion into an aryl halide bond
in an oxidative step
is followed by the coordination
of an amine (or other nucleophiles)
to yield the substitution product

A new way to build structures

SOMO Catalysis | **Photoredox Catalysis**

MacMillan, Stephenson, Nicewicz, Yoon, Bach, Rueping

A New Concept: SOMO Catalysis



Science **2007**, *316*, 582

David W. C. MacMillan

Enantioselective Organocatalysis Using SOMO Activation

Teresa D. Beeson,[1,2] Anthony Mastracchio,[1,2] Jun-Bae Hong,[1,2] Kate Ashton,[1,2] David W. C. MacMillan[1,2]*

The asymmetric α-addition of relatively nonpolar hydrocarbon substrates, such as allyl and aryl groups, to aldehydes and ketones remains a largely unsolved problem in organic synthesis, despite the wide potential utility of direct routes to such products. We reasoned that well-established chiral amine catalysis, which activates aldehydes toward electrophile addition by enamine formation, could be expanded to this important reaction class by applying a single-electron oxidant to create a transient radical species from the enamine. We demonstrated the concept of singly occupied molecular orbital (SOMO) activation with a highly selective α-allylation of aldehydes, and we here present preliminary results for enantioselective heteroarylations and cyclization/halogenation cascades.

Over the past four decades, the capacity to induce asymmetric transformations with enantioselective catalysts has remained a focal point for extensive research efforts in both industrial and academic settings. During this time, thousands of asymmetric catalytic reactions have been invented (*1*), in accord with the increasing need for enantiopure medicinal agents and the rapid advancement of the field of asymmetric synthesis. Most catalytic enantioinductive processes are derived from a small number of long-established activation modes. Activation modes such as Lewis acid catalysis (*2*), σ-bond insertion (*3*), π-bond insertion (*4*), atom transfer catalysis (*5*), and hydrogen bonding catalysis (*6*) have each spawned countless asymmetric reaction classes, thereby dramatically expanding the synthetic toolbox available to researchers in the physical and biological sciences. A necessary objective, therefore, for the continued advancement of the field of chemical synthesis is the design and implementation of distinct catalytic-activation modes that enable previously unknown transformations.

Over the past 8 years, our laboratory has been involved in the development of the field of organocatalysis, a research area that relies on the use of small organic molecules as catalysts for enantioselective transformations. As part of these studies, we introduced the concept of iminium catalysis (*7*): an enal or enone activation mode that lowers the energy of the substrate's lowest unoccupied molecular orbital, facilitating enantioselective C–C and C–N conjugate additions, cycloadditions, hydrogenations, and Friedel-Crafts alkylations (*8*). Simultaneously, Barbas and List (*9*) brought to fruition the concept of enamine catalysis (Fig. 1), which raises the energy of the highest occupied molecular orbital (HOMO) in aldehydes and ketones to promote enantioselective α-carbonyl functionalization with a large range of electrophiles (*10*). These two modes of catalyst activation (iminium and enamine) have provided, in total, more than 60 asymmetric methodologies over the past 7 years.

[1]Merck Center for Catalysis, Department of Chemistry, Princeton University, Princeton, NJ 08544, USA. [2]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

*To whom correspondence should be addressed. E-mail: dmacmill@princeton.edu

The frontier disconnections involve **C–H activation**

C–H activation is associated with a bond functionalization in which a carbon–hydrogen bond is cleaved and replaced with a carbon-X bond (where X is usually carbon, oxygen, or nitrogen)

The term usually implies that a transition metal is involved in the C–H cleavage process

A large variety of transforms are available, so many options can be considered

If C–H Bonds Could Talk: Selective C–H Bond

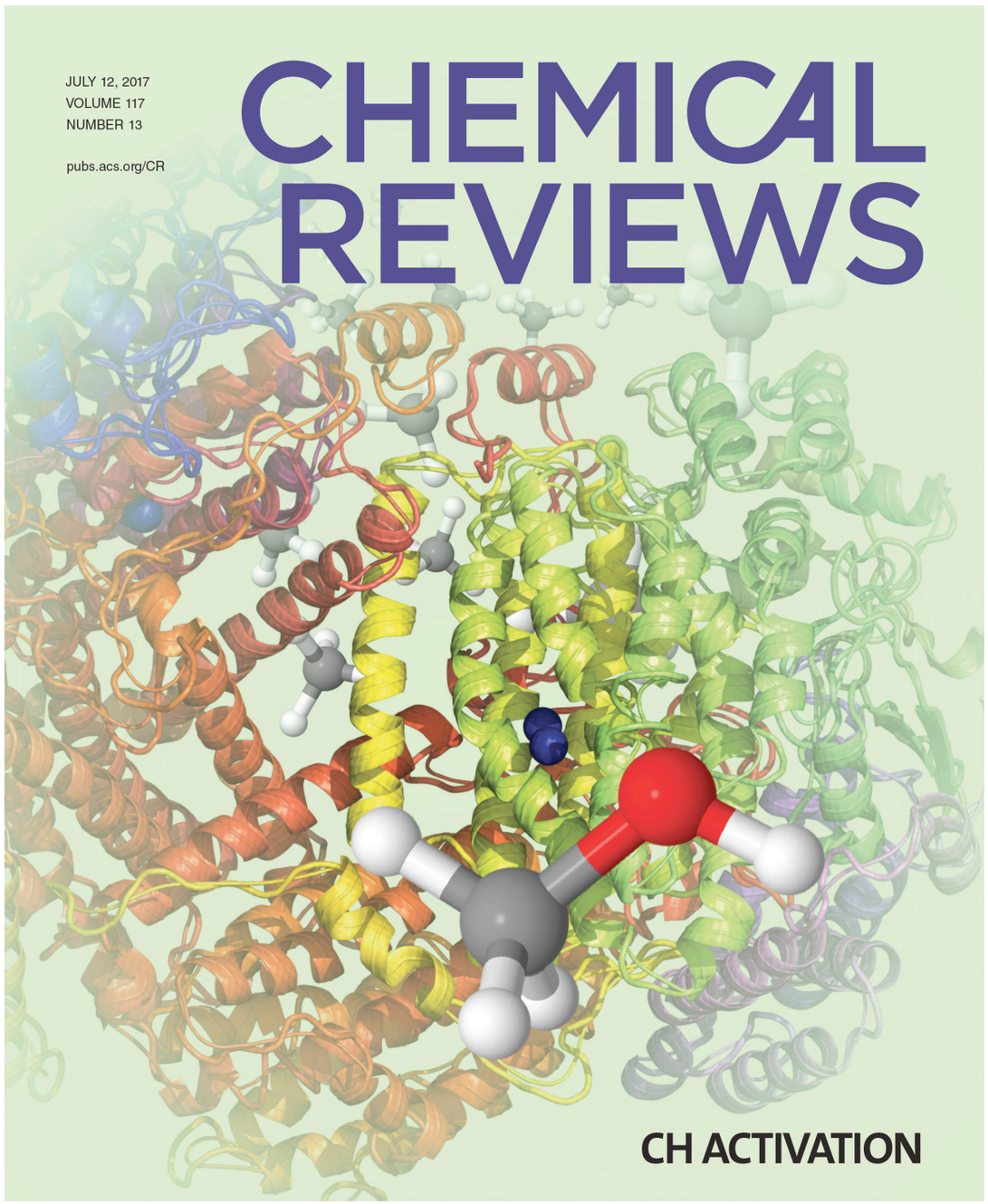
Let the molecule do the talking:

If C–H bonds could talk, they would tell stories of ***inductive effects, conjugation, hyperconjugation, steric hindrance, and strain release.***
These stories are told from the perspective of synthetic planning and draw from the immense body of literature on the topic

Baran, P. *Nature* **2009**, *459*, 824; *ACIE* **2011**, *50*, 3362

See also, Baran, P. *CSR* **2011**, *40*, 1976

For further comments, see Chapter 8



Chemistry Reviews

July **2017,** Issue 13

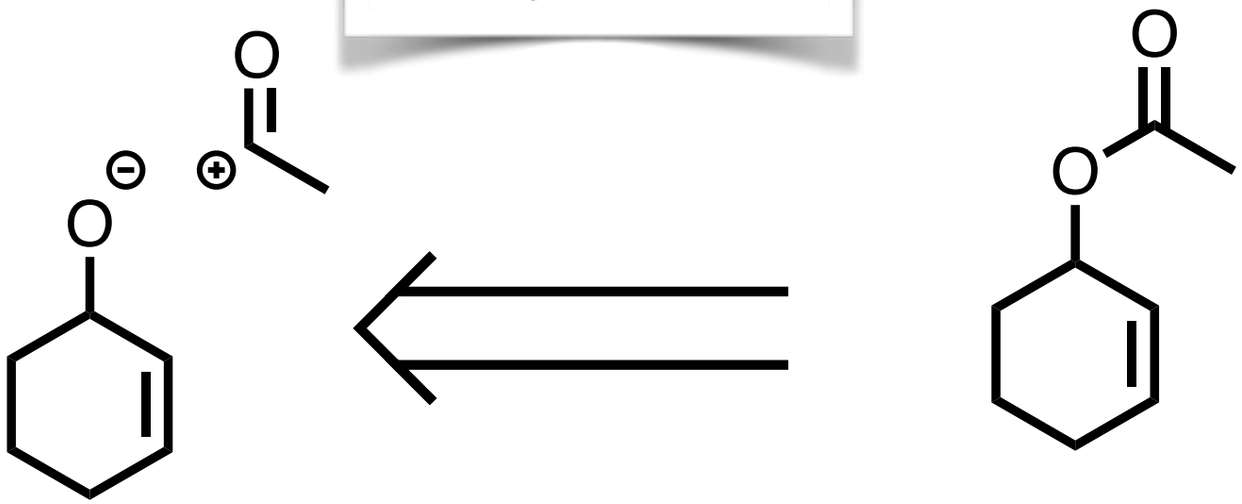
A comprehensive knowledge of
the structure of organic molecules,
mechanisms of reactions,
and reactivity
is nowadays essential
to design and carry out organic synthesis

The retrosynthetic analysis
could be based on the recognition
of the most appropriate transforms
However, …

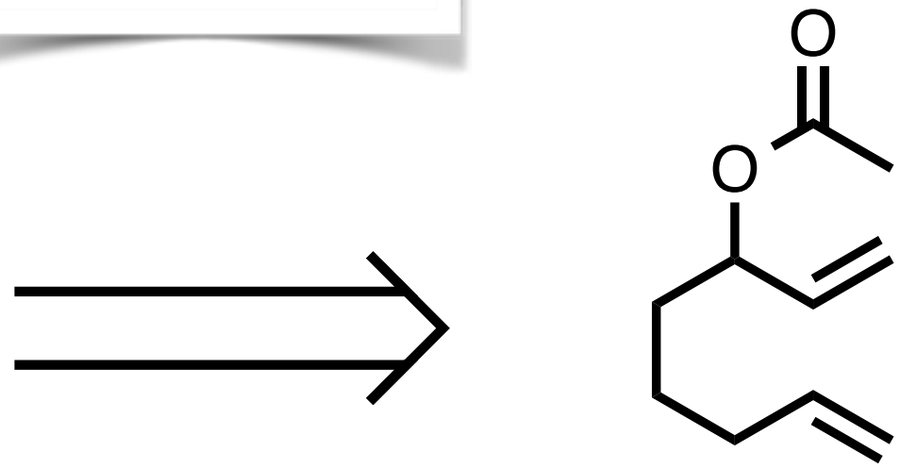
there are many thousands of transforms which are potentially useful in retrosynthetic analysis, just as there are very many known and useful chemical reactions

Elias J. Corey

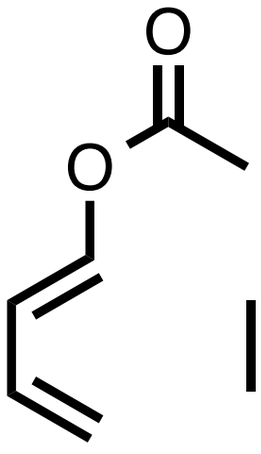
Acylation



Metathesis



Diels-Alder



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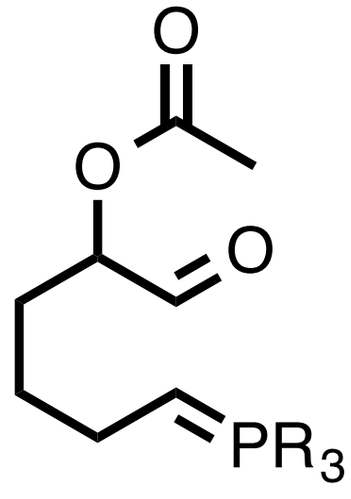
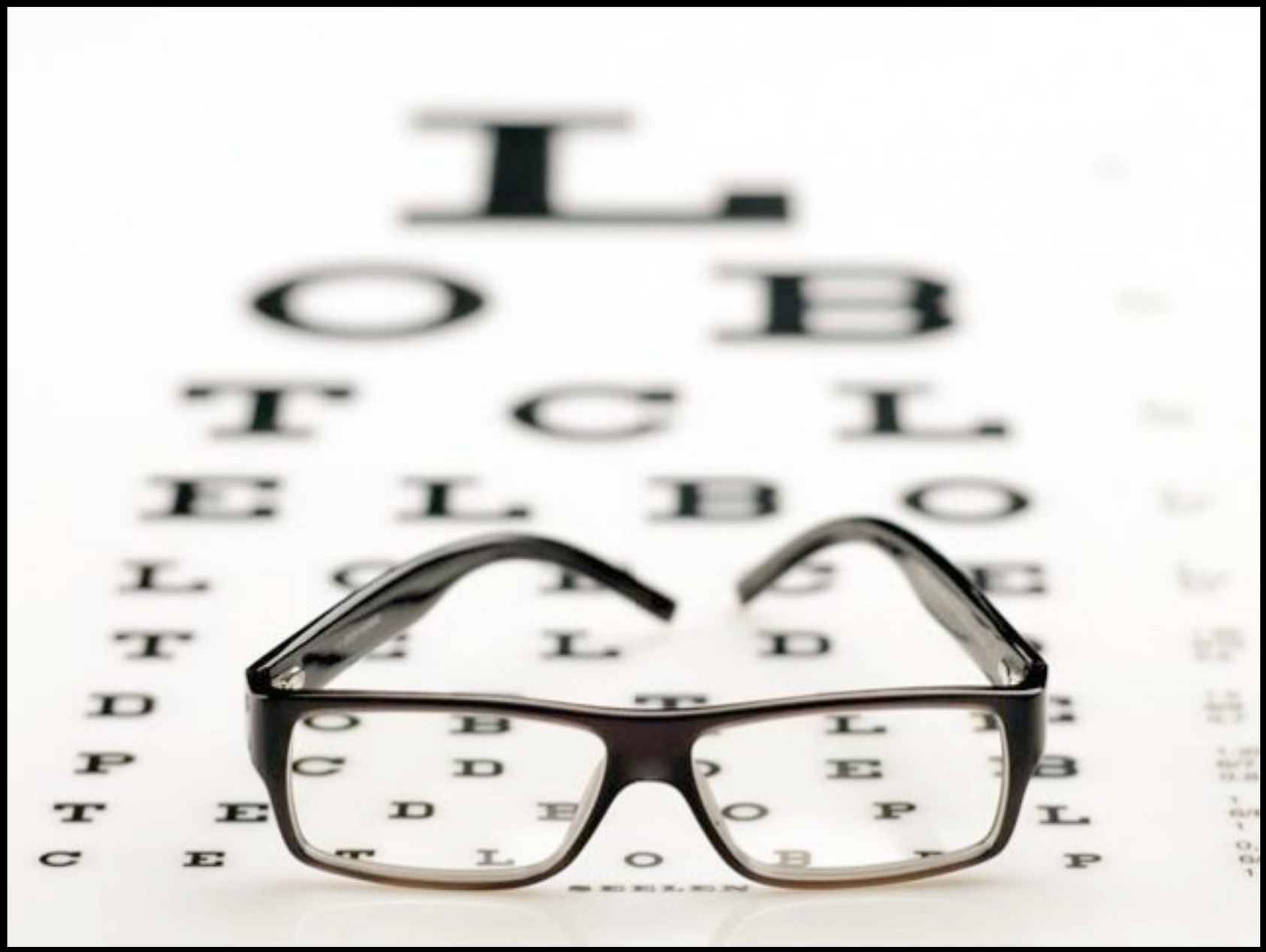




educate your **eyes**

sight needs KNOWLEDGE

for the proper recognition of potential

RETRONS / TRANSFORMS

Building Block-Based Strategy

recognition of structural units

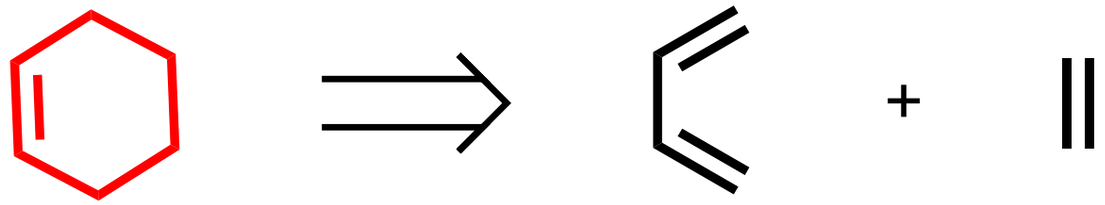
Functional Group-Based Strategy

analysis of the FG relationships

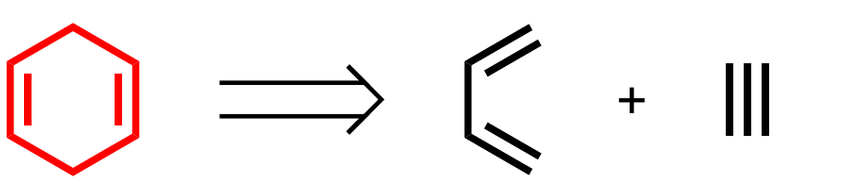
Transform-Based Strategy

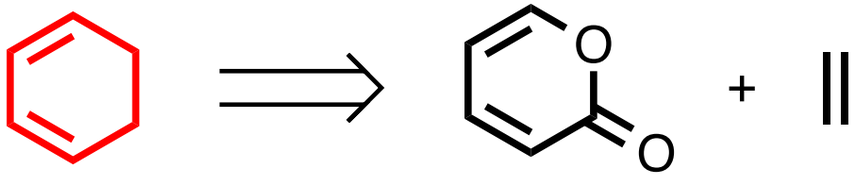
identification of suitable returns and
look ahead for a powerfully simplifying transform

Retron: *molecular substructure that enables certain transformations*

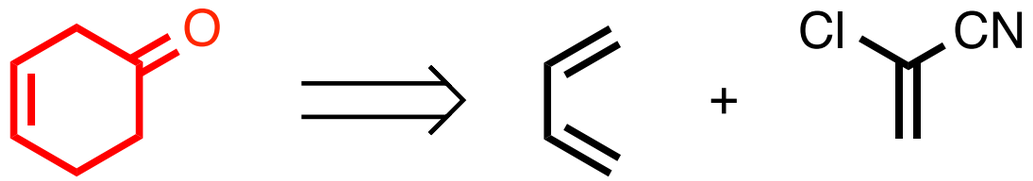


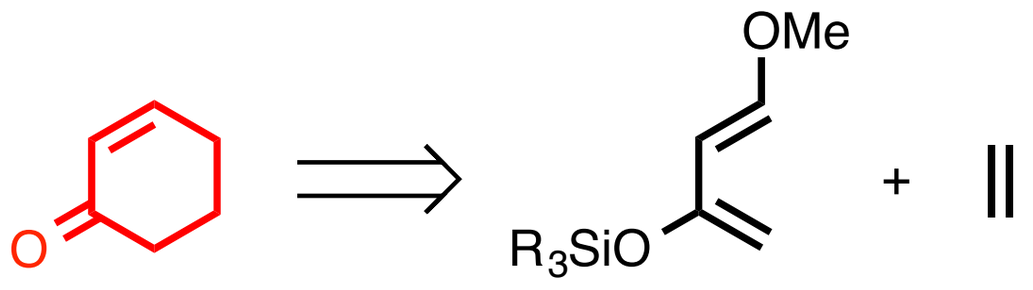
Supra Retron: *molecular substructure that can be associated with a variant of a general* ***transform***





α-pyrone



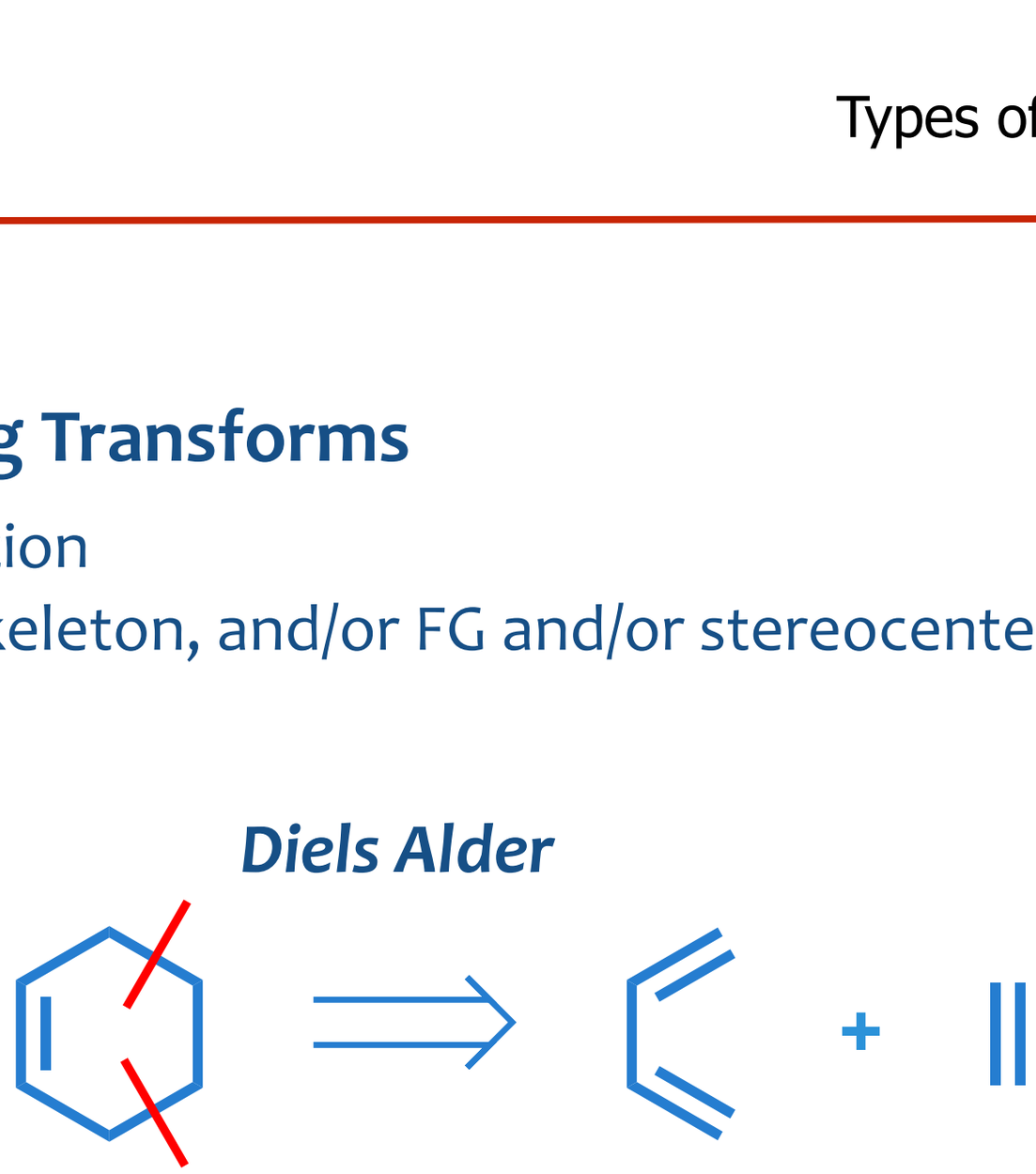


Danishefsky's diene

1. Structurally Simplifying Transforms

Effect molecular simplification
by disconnecting carbon skeleton, and/or FG and/or stereocenters

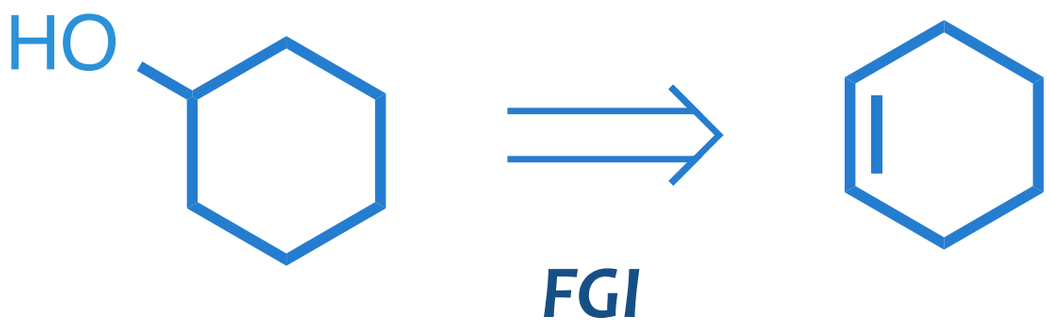
Diels Alder



Corey, E. J. *Logical of Chemical Synthesis*

2. Neutral Transforms

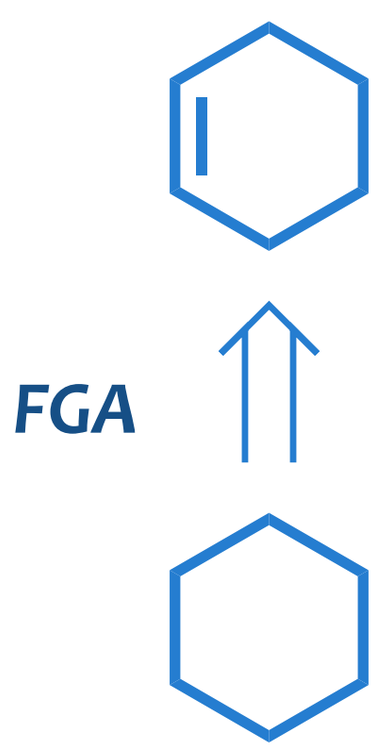
No essential change in molecular complexity, but which can be useful because they modify a TGT to allow a subsequent application of type 1
They include rearrangements of carbon backbone,
functional group interchange (FGI) and inversion/transfer of stereocenters



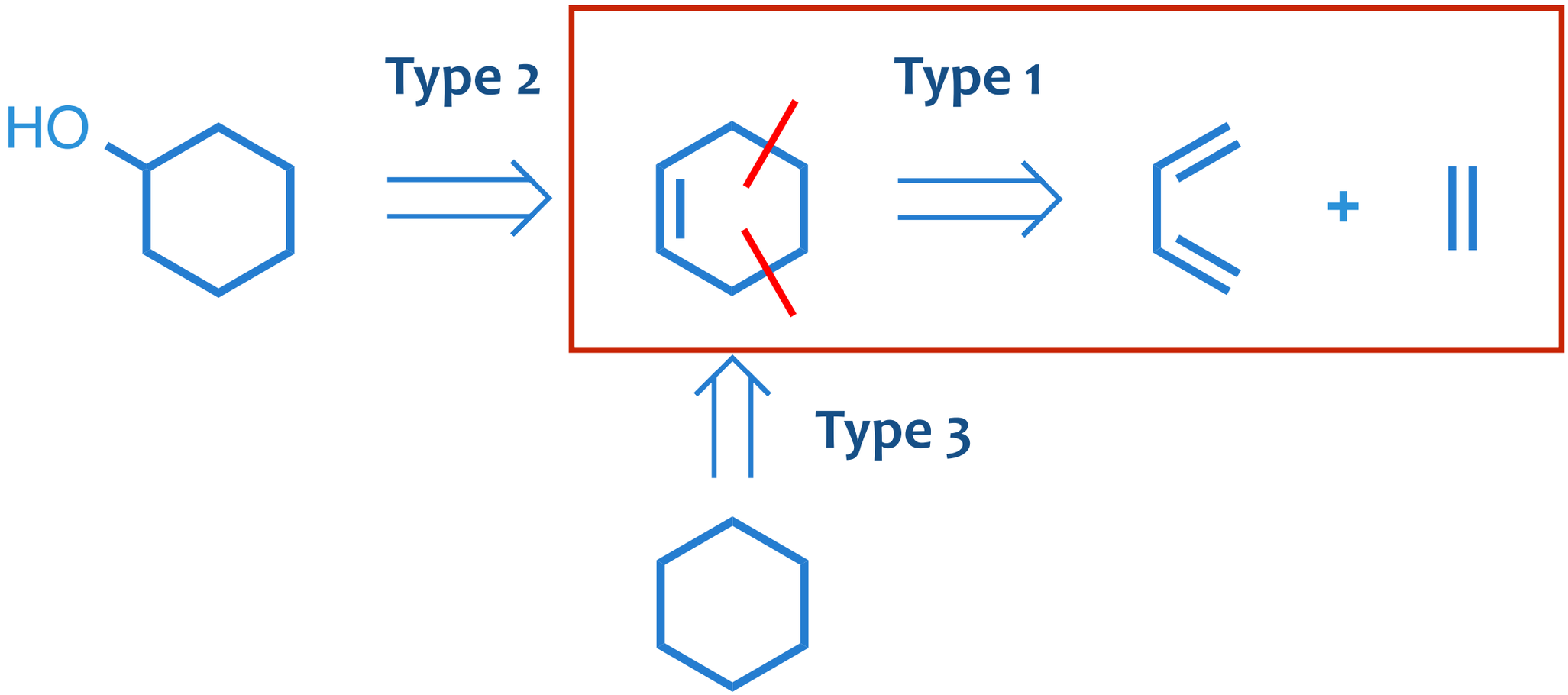
Corey, E. J. *Logical of Chemical Synthesis*

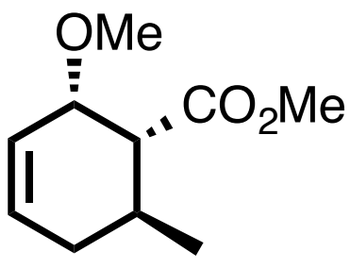
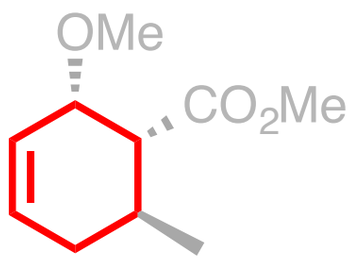
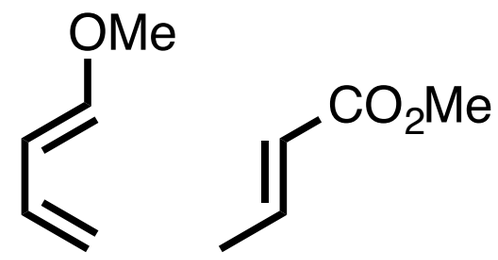
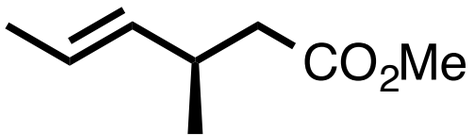
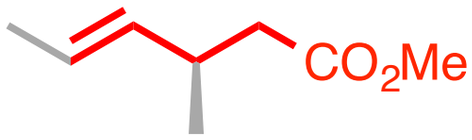
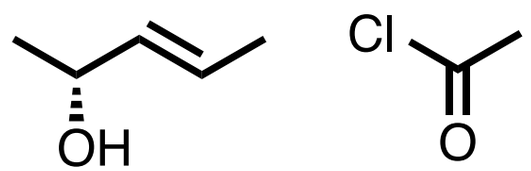
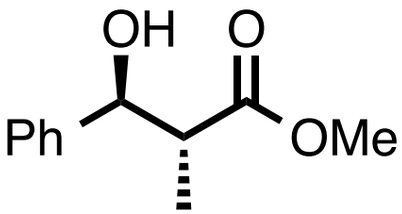
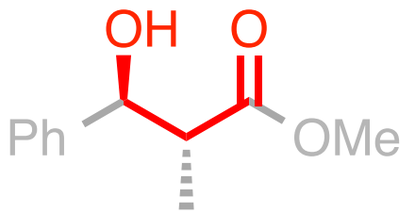
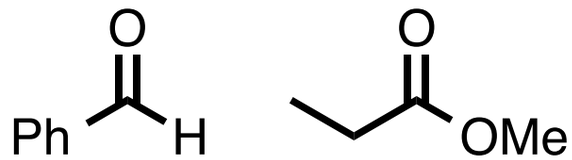
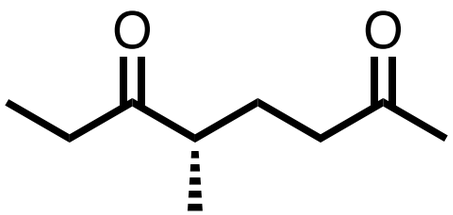
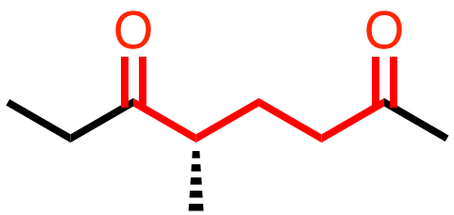
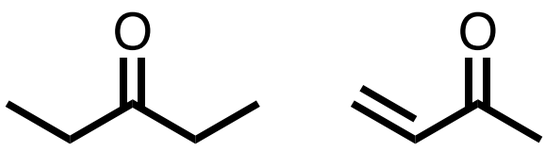
3. Structurally Increasing Complexity Transforms

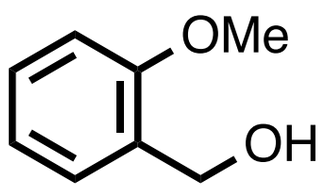
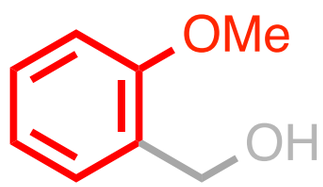
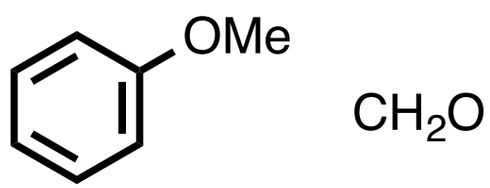
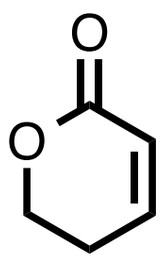
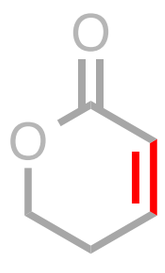
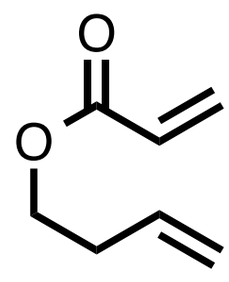
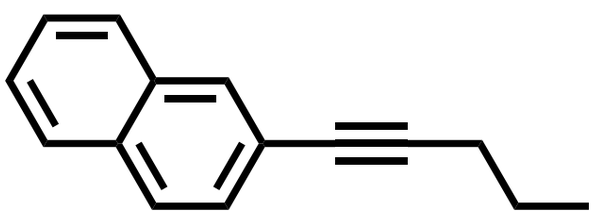
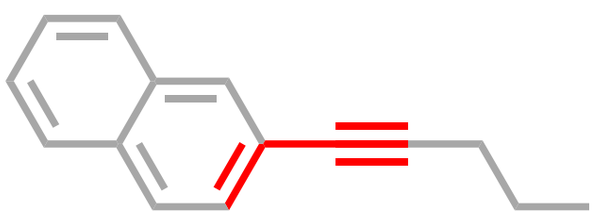
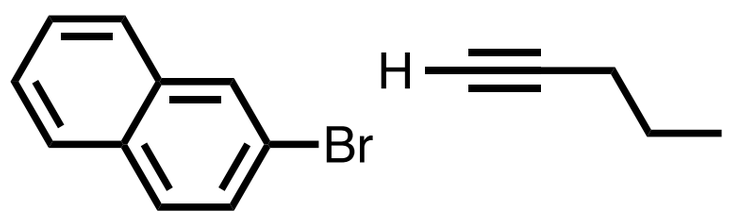
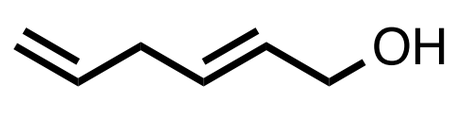
Include addition of rings, **functional groups (FGA)**, or stereocenters



Corey, E. J. *Logical of Chemical Synthesis*


HO
Type 2
Type 1
+
Type 3

Target	Retron	Transform	Precursors
		*Diels Alder*	
		*Ireland Claisen rearrangement*	
		*Aldol reaction*	
		*Michael reaction*	

Target	Retron	Transform	Precursors
		*Ortho-Li*	
		*Metathesis*	
		*Sonogashira coupling*	
		*Sharpless epoxidation*	

One feature of major significance is the overall effect of transform on **MOLECULAR COMPLEXITY**

Molecular size

Cyclic connectivity or topology

Functional Group (FG) content

Stereocenter content

Centers of high chemical reactivity

Kinetic (thermal) stability

Anales de Química

Eficiencia en la síntesis total de productos naturales

Ben Bradshaw y Josep Bonjoch

Resumen: La síntesis total de productos naturales ha entrado en una nueva era en la que la eficiencia del proceso asume un papel preponderante, a fin de poder acceder de manera escalable a moléculas con potencial impacto en la sociedad. Se presenta un panorama general de propuestas para alcanzar una síntesis ideal, tales como las estrategias de diseño de síntesis (uso de reacciones tándem, reducción de etapas no productivas) y nuevos procedimientos operacionales (uso de reactivos anclados, agentes secuestradores y economía de recipiente / pot-economy).

Palabras clave: eficiencia sintética, diseño de síntesis, economía de recipiente, síntesis total, productos naturales.

Abstract: The total synthesis of natural products is entering a new era in which efficiency is playing a central role in order to enable scalable syntheses of molecules with a potentially beneficial impact on society. An overview of proposals to reach an ideal synthesis, such as synthetic design strategies (using tandem reactions, cutting non-productive steps) and operational procedures (use of supported reagents and scavengers, and pot economy), is presented.

Keywords: synthetic efficiency, synthesis design, pot economy, total synthesis, natural products.

INTRODUCCIÓN

La síntesis total de productos naturales[1] a lo largo del siglo xx acometió el acceso a compuestos cada vez más complejos, auspiciada por motivos estructurales o de actividad biológica de los mismos. Un ejemplo emblemático, desarrollado en el grupo de Kishi,[2] es la síntesis de la palitoxina (Figura 1), cuya estructura contiene 71 elementos estereoquímicos ($5{,}4x10^{20}$ estereoisómeros posibles). El resultado global de esta actividad fue el descubrimiento de modos de reactividad, la génesis de nuevos catalizadores y la validación de métodos de síntesis en entornos estructurales exigentes, consolidando así el avance de la síntesis orgánica. Esta actividad fecunda permitió el crecimiento de las interacciones con la biología[3] y la química médica.[4] Sin embargo, el optimismo derivado de los hitos sintéticos alcanzados no despejaba las dudas acerca de la traducción de los logros sintéticos en beneficios reales para la sociedad. La síntesis total del taxol (Figura 1b) puso de manifiesto que el estado del arte en la síntesis de compuestos de alta complejidad no era eficiente desde un punto de vista práctico.[5] A pesar de los esfuerzos de diversos grupos de investigación, la síntesis total tan solo pudo proporcionar pequeñas cantidades de este valioso compuesto. Con la entrada del nuevo milenio, nuevas metodologías y tecnologías, y un enfoque holístico de la síntesis han convergido para dar un paso adelante al reto de la eficiencia. Así, algunos fármacos basados en productos naturales complejos se sintetizan a escala industrial[6,7] (p. ej. el agente antimitótico Halaven®,[8] Figura 1c), demostrando que el acceso a la complejidad estructural no está fuera del alcance de la síntesis total.

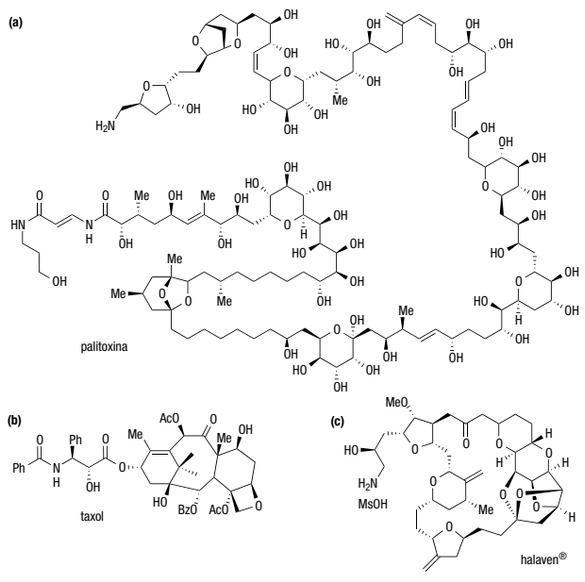


Figura 1. (a) Palitoxina; (b) Taxol; (c) Halaven®

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