Universitat de Barcelona

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*The great metaphysician*
*Giorgio de Chirico, s XX*

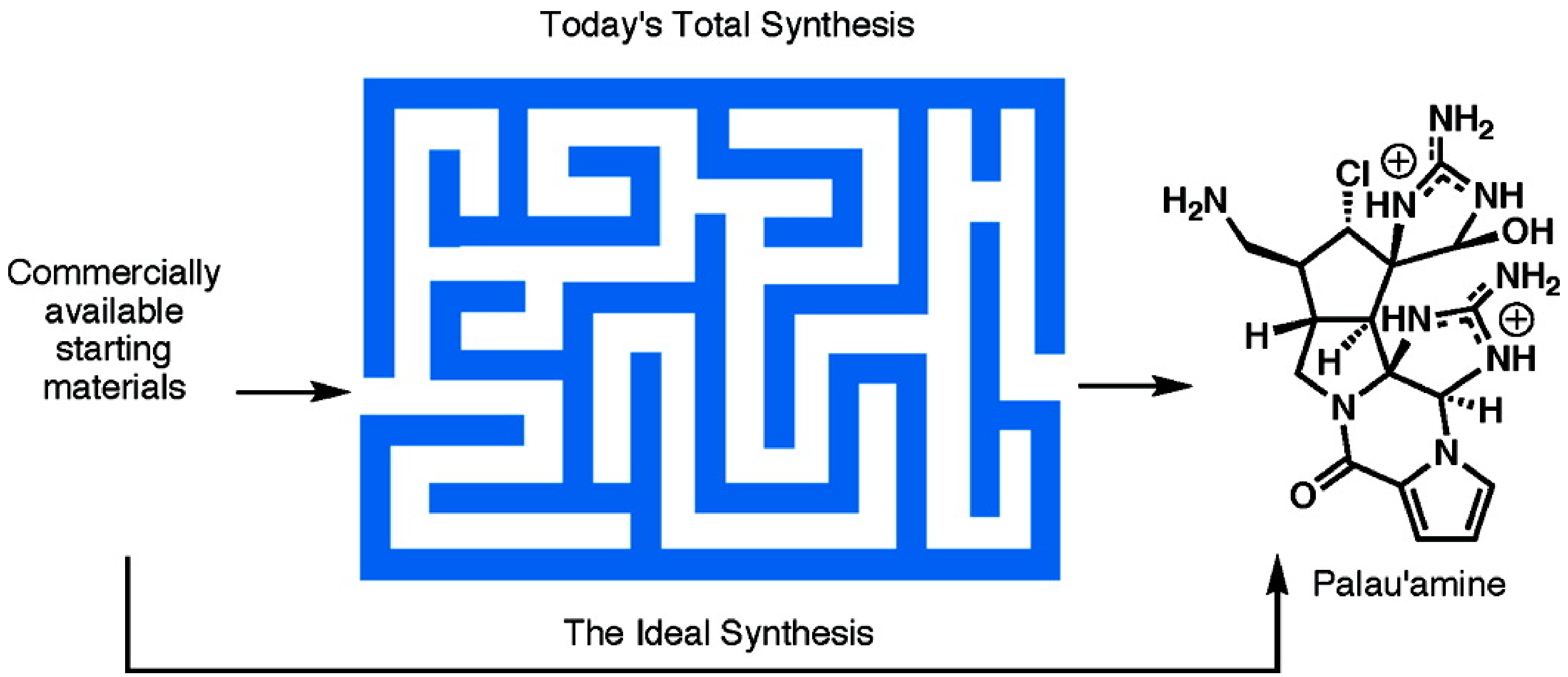
# 5. Intr. to Retrosynthetic Analysis

Organic Synthesis 2014-2015 Autumn

# The ideal synthesis

- *Irrespective of the target,*

  *there is a endless pursuit of the ideal synthesis*



*Aiming for the Ideal Synthesis*

*Gaich, T.; Baran, P. S. J. Org. Chem.* ***2010****, 75 4657*

# The ideal synthesis

## *Environmentally acceptable*

*avoidance of problematic waste (the greenest route)*
*avoidance of toxic intermediates (the healthiest route)*

## *Safe*

*avoidance of risking procedures (the safest route)*

## *Economically acceptable*

*cost of materials (the cheapest route)*
*novelty (the patent route)*

## *Robust*

*easily scale-up, reproduibility*

## *Ideal Synthesis*

## *Highly efficient*

*Simple, high yield, a few steps*

- *... sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality*

*Hendrickson, J. B. J. Am. Chem. Soc.* ***1975****, 97, 5784*

# Synthesis? How?

*The exercise of Organic Synthesis requires*

1. **Knowledge of Reactivity (Structure-Mechanism)**

2. **Design ability (Retrosynthetic Analysis)**

*The ultimate goal of Organic Synthesis is to assemble an organic compound (**target**) from readily available starting materials and reagents in the most efficient way. This process usually begins with the design of a synthetic plan (**Strategy**)*

# Retrosynthetic Analysis

*Retrosynthetic (or antithetic) analysis is a problem solving technique for transforming the structure of a synthetic target molecule (TGT) to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis.*

*The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a TGT.*

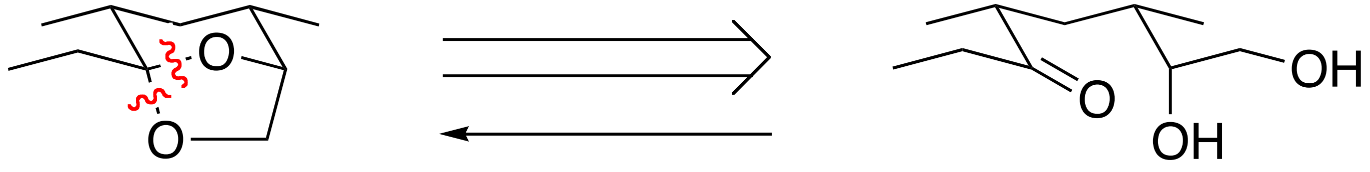
*Each structure derived antithetically from a target the itself becomes a TGT for a further analysis.*

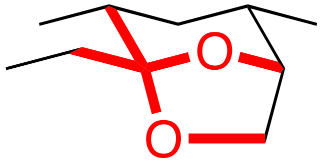
*Repetition of this process eventually produces a tree of intermediates having chemical structural as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TGT.*

## *Transform? What is it?*

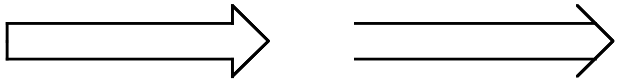
*The transformation of a molecule into a synthetic precursor is accomplished by application of a* ***transform,*** *the exact reverse of a synthetic reaction, to a target structure*

***Transform:*** *reverse reaction in retrosynthetic sense*



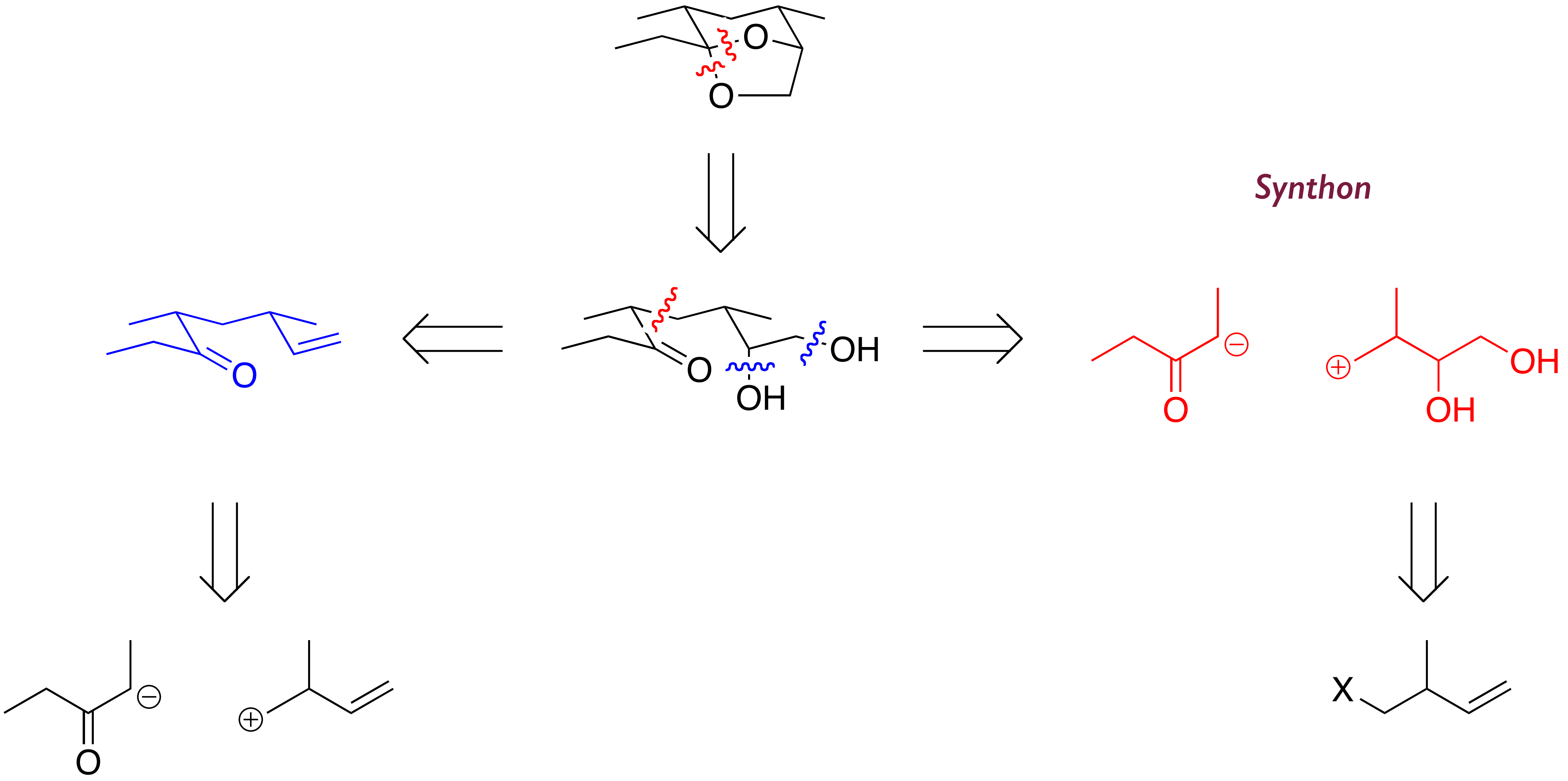


***Retron***



*Retrosynthetic arrows*

## Tree of intermediates? What is it?

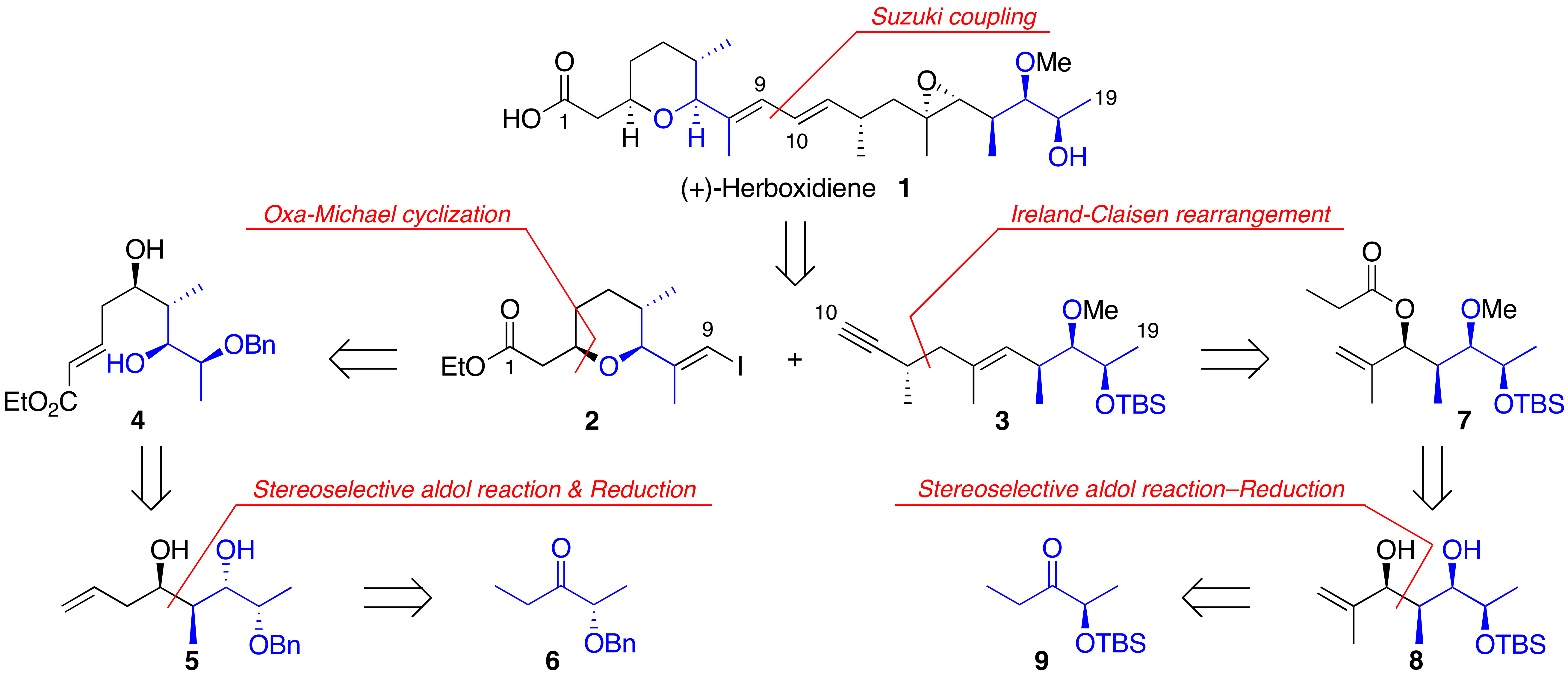


# Retrosynthetic Analysis

*Total Syntheses of (+)-Herboxidiene from Two Chiral Lactate-Derived Ketones*

*Romea, P.; Urpí, F.*

*Org. Lett.* ***2011***



Suzuki coupling

Oxa-Michael cyclization

Ireland-Claisen rearrangement

Stereoselective aldol reaction & Reduction

Stereoselective aldol reaction–Reduction

Universitat de Barcelona

# Strategy & Tactic

## *Strategy* ■

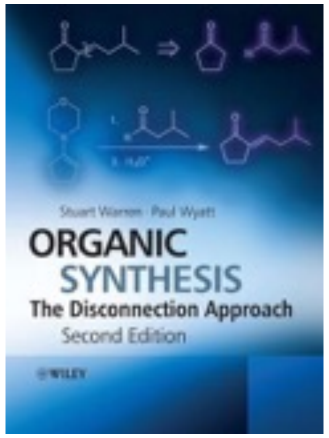
*Strategy refers to the general plan to synthesize the TGT*

*Retrosynthetic arrows should provide a clear idea of the strategy*

## *Tactic* ■

*Tactical issues deal with the actual execution of the plan*

*Tactic is closely associated with structure and reactivity*

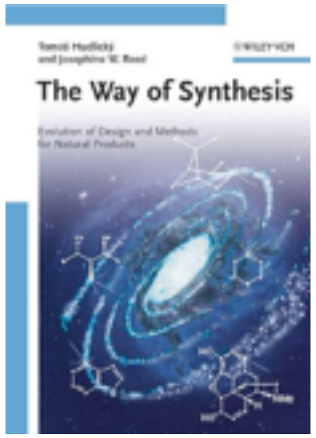

Stuart Warren · Paul Wyatt

ORGANIC SYNTHESIS

The Disconnection Approach

Second Edition

WILEY


The Way of Synthesis

# Strategy & Tactic

## LEFT BRAIN

*Logic*

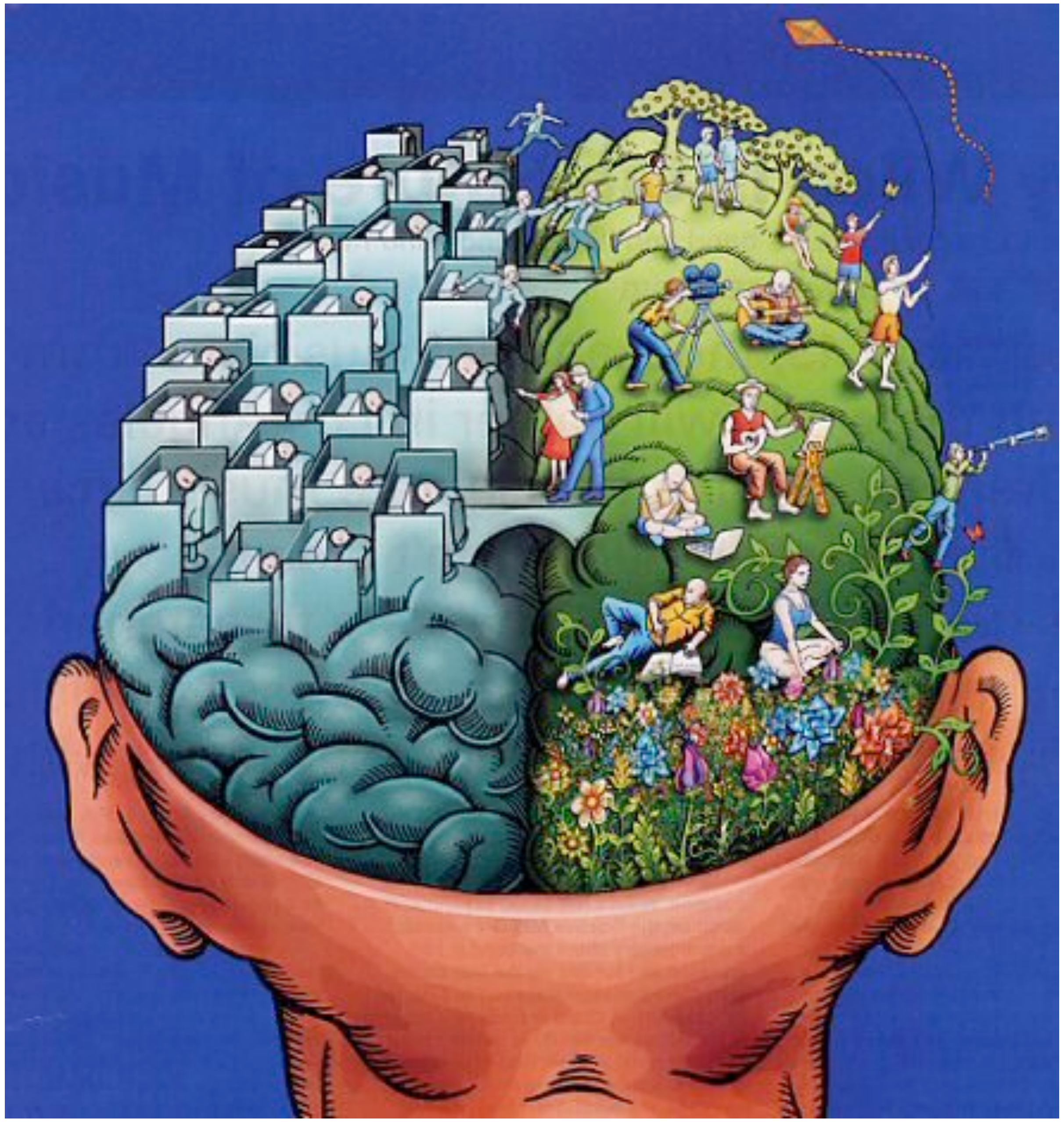
*Analysis*

*Organization*

*Knowledge /Facts*

*Detail*

*Maths & Science*



http://www.webdesignerdepot.com/2009/

## RIGHT BRAIN

*Intuition*

*Emotion*

*Spirituality*

*Belief*

*Big picture*

*Art / Music*

- *Tactic* ⇄ *Strategy*

*Is there any standard strategy to analyze any target ?*

*Is there any preferential manner to proceed ?*

*Not exactly,*

*Freedom, imagination, and risk are common words in synthesis*

*Organic Synthesis is a heuristic and somehow artistic activity*

*in which concepts as beauty or elegance often appears*

# Strategies for Retrosynthetic Analysis

*Keeping these ideas in mind, some general strategies can be recognized …*

*Building Block Oriented Synthesis* 🟥

*Functional Group Oriented Synthesis* 🟥

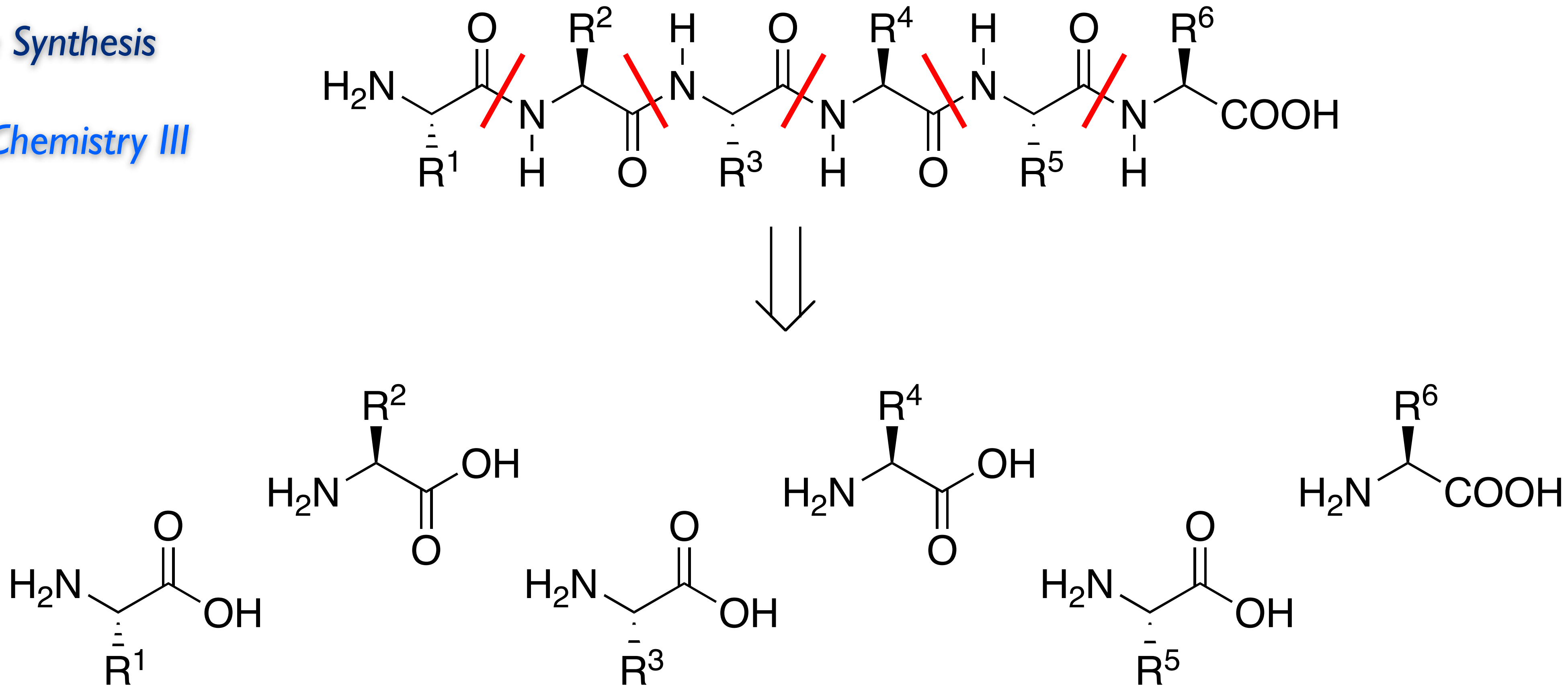
*Powerful Transformation Oriented Synthesis* 🟥

# Building Block Strategy

- *Based on the identification of certain structural unities (building block)*

*Peptide Synthesis*

*Organic Chemistry III*

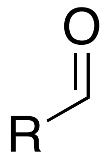


*Building blocks: amino acids*

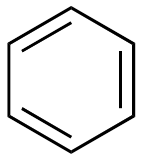
*Protecting groups? Starting building block?*

# Building Block Strategy

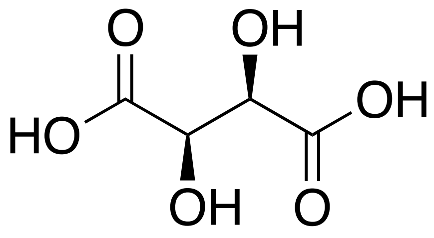
*Other common building blocks are easily recognized …*



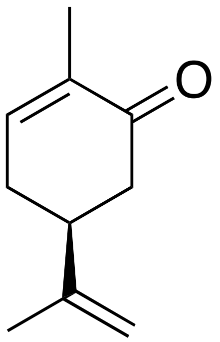
*Acyl group*



*Phenyl group*

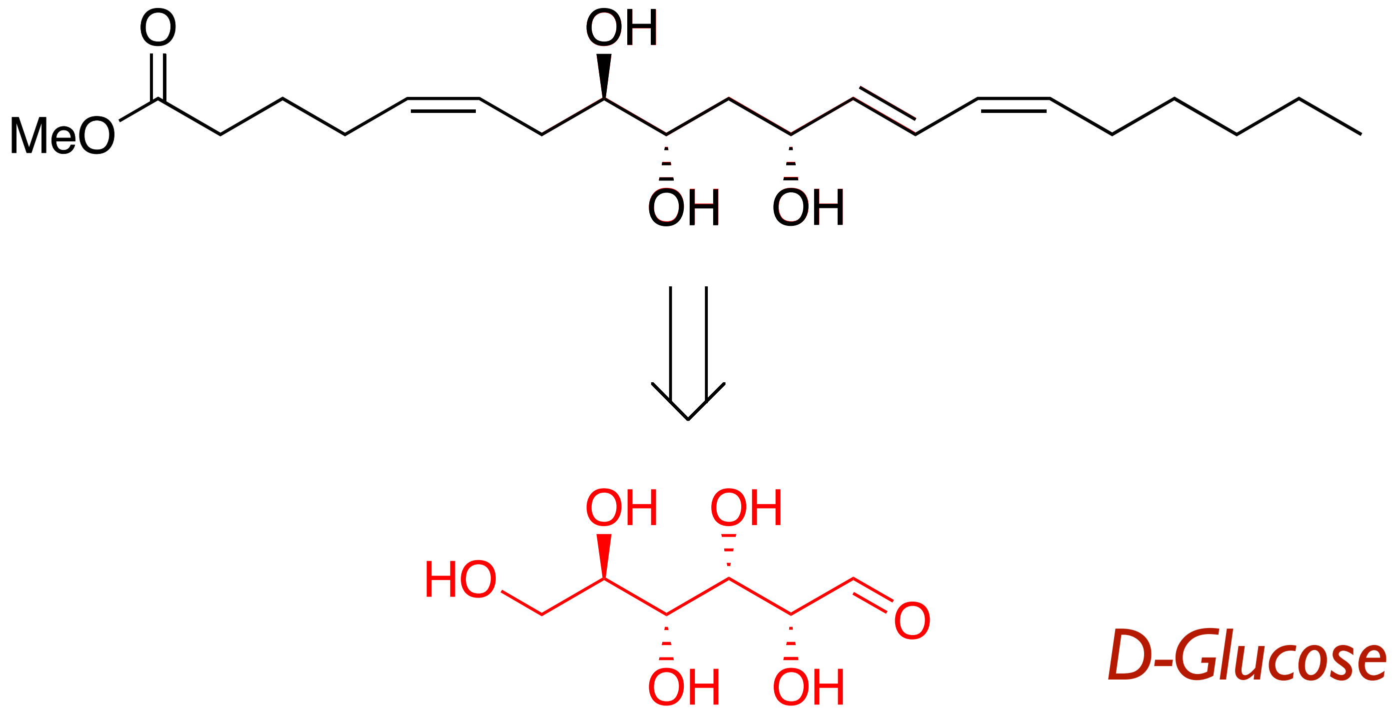


*Tartaric acid*



*Carvone*

***… but sometimes this is difficult***



*D-Glucose*

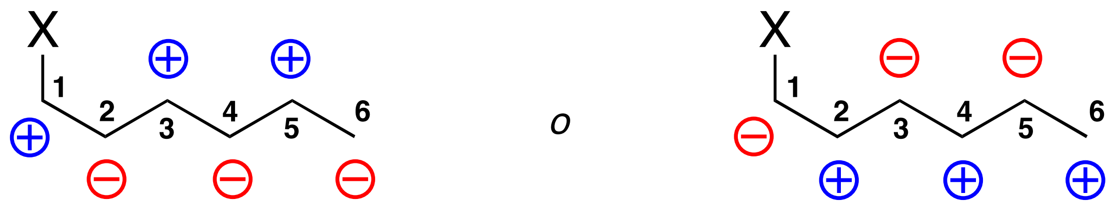
- *Based on the relationships between FG*

*Main ideas:*

*1. Any TGT is formed by a carbon backbone & FG (**heteroatom**)*

*2. The FG (**heteroatom**) polarizes the carbon backbone*

*3. Mainly applied to heterolytic mechanisms: nucleophile/electrophile*



*It might be useful to consider the carbon framework of any molecule as an ionic aggregate, whose origin relies on the presence of functional groups.*
*The symbol designations, + and –, simply denote potential electrophilic or nucleophilic site reactivity*

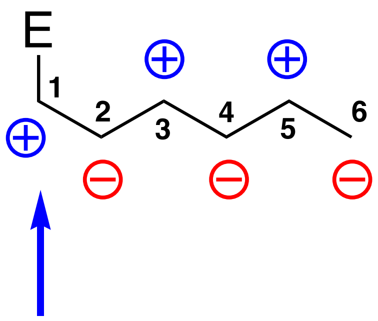
*Evans, D.A. Acc.Chem. Res.* ***1974****, 147.* *Seebach, D.ACIEE* ***1979****, 239*

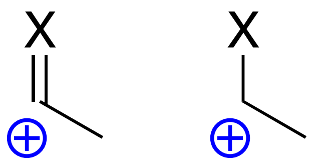
# Functional Group Strategy

*Depending on their nucleophilic / electrophilic role,*

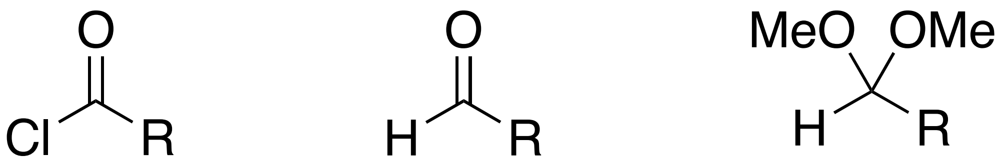
*synthons can be classified as* ***electron donors (d)*** *or* ***acceptors (a)*** *and*

*are accordingly numbered with respect to the relative positions of a FG and the reactive carbon atom*

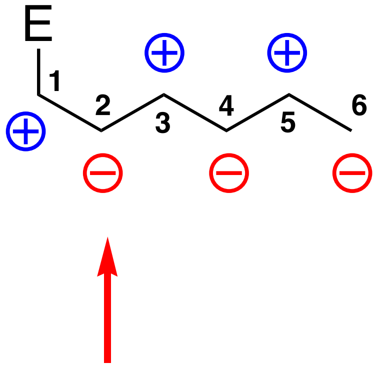


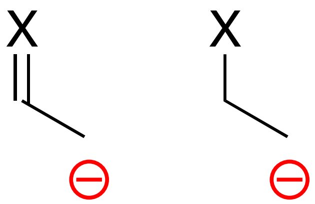


*Synthon $a^1$*

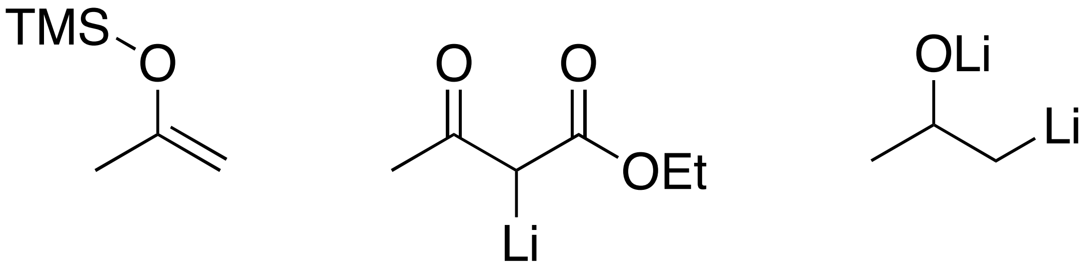


*Synthetic precursors*





*Synthon $d^2$*

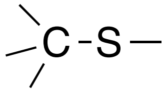


*Synthetic precursors*

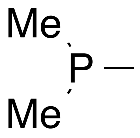
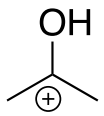
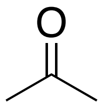
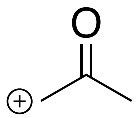
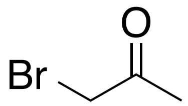
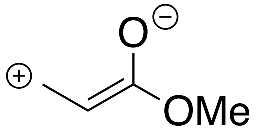
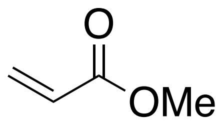
*Therefore, synthons can be* $\mathbf{a^0}$, $\mathbf{a^1}$, $\mathbf{a^2}$, $\mathbf{a^3}$, *... or* $\mathbf{d^0}$, $\mathbf{d^1}$, $\mathbf{d^2}$, $\mathbf{d^3}$, *...*

# Functional Group Strategy

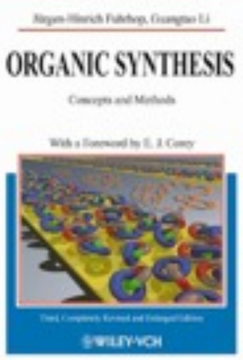
## *Synthons d*

| *Type* | *Example* | *Reacting materials* | *FG* |
|---|---|---|---|
| $d^0$ | $MeS^{\ominus}$ | MeSH |  |
| $d^1$ | $^{\ominus}C\equiv N$ | $KC\equiv N$ | $-C\equiv N$ |
| $d^2$ | $^{\ominus}CH_2CHO$ | $CH_3CHO$ | $-CHO$ |
| $d^3$ | $^{\ominus}C\equiv C-COOMe$ | $HC\equiv C-COOMe$ | $-CO_2Me$ |
| *Alkyl-d* | $Me^{\ominus}$ | MeLi | |

## *Synthons a*

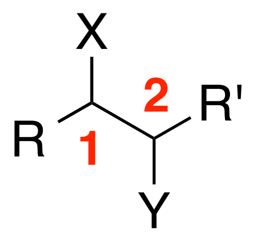
| *Type* | *Example* | *Reacting materials* | *FG* |
|---|---|---|---|
| $a^0$ | $^{\oplus}PMe_2$ | $ClPMe_2$ |  $Me_2P-$ |
| $a^1$ |  |  | $-CO-$ |
| $a^2$ |  |  | $-CO-$ |
| $a^3$ |  |  | $-CO_2Me$ |
| *Alkyl-a* | $Me^{\oplus}$ | MeI | |

*Chaps. 1.1-1.3*

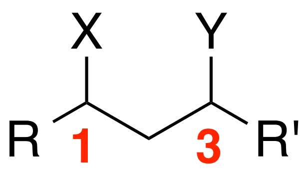


# Functional Group Strategy

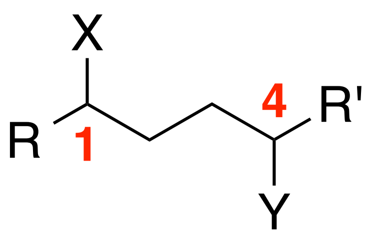
*The relationship between two FG depends on how distant they are …*



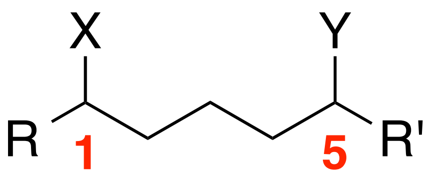
*1,2-Relationship*



*1,3-Relationship*

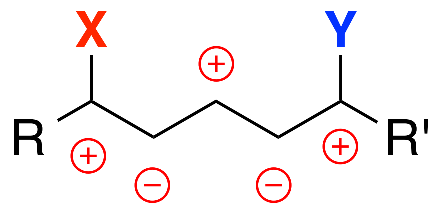


*1,4-Relationship*

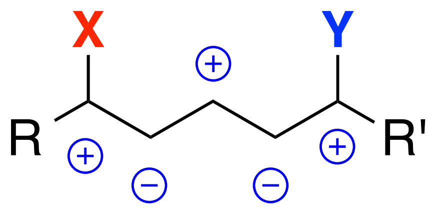


*1,5-Relationship*

*… and the polarization that they impart on the backbone*

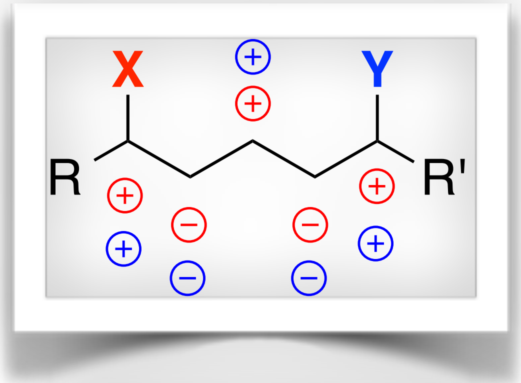


*polar arrangement by X*

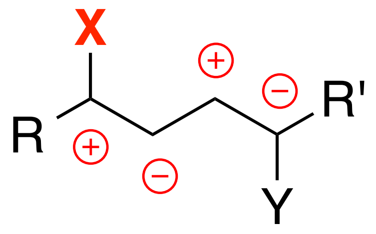


*polar arrangement by Y*

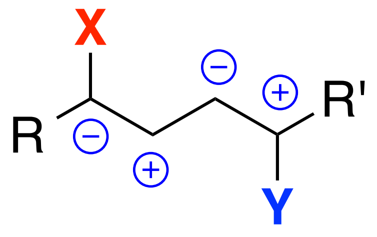
≡



*consonant (matched)*

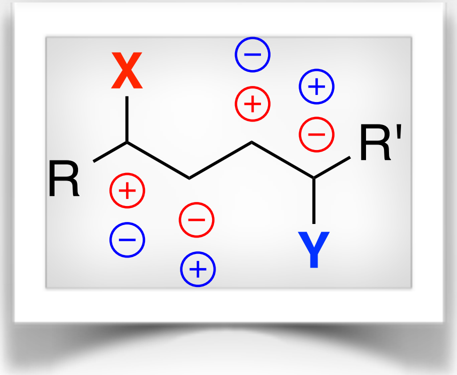


*polar arrangement by X*



*polar arrangement by Y*

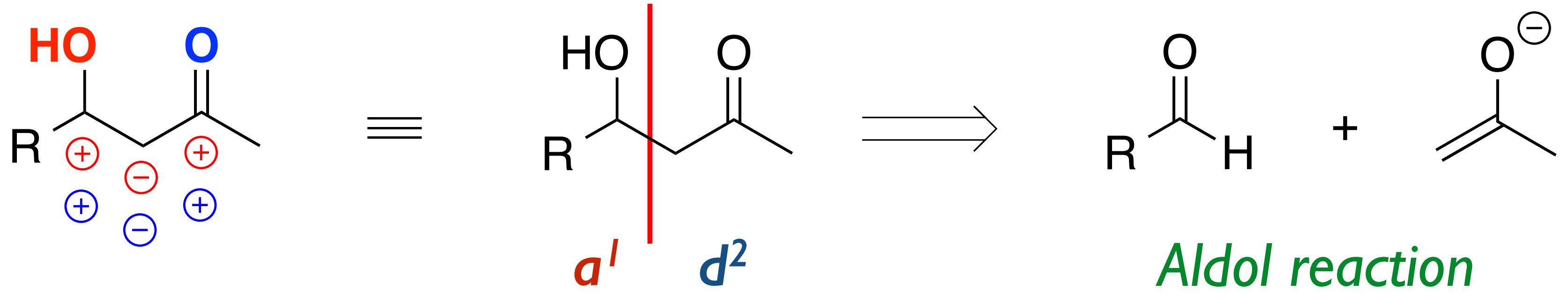
≡

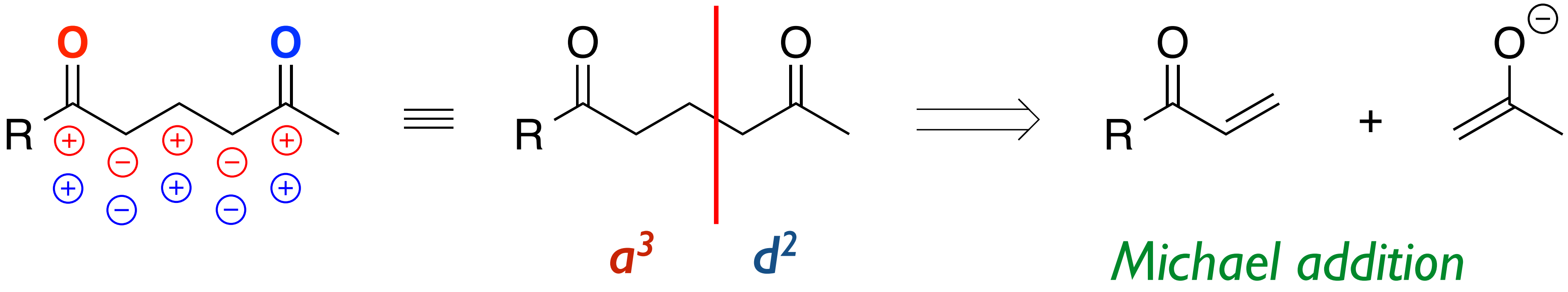


*dissonant (mismatched)*

# Functional Group Strategy

*Consonant (matched) relationships are quite easy to analyze …*





*Dissonant (mismatched) relationships are much more complicate and usually require the inversion on the polarity (UMPOLUNG) of one of the participants*

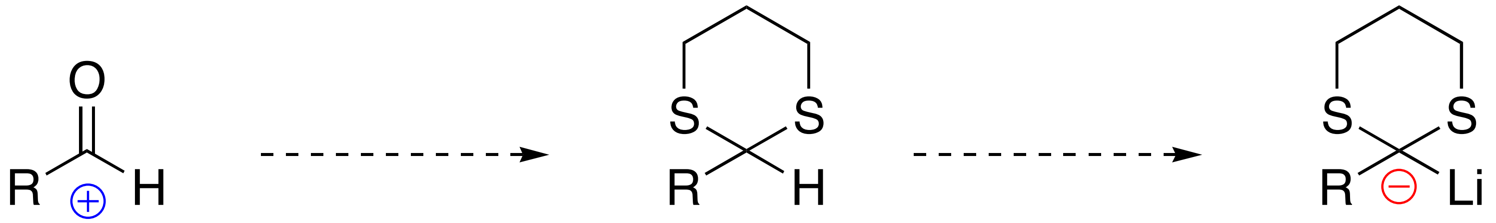
# Functional Group Strategy

## *UMPOLUNG refers to the change of the self-reactivity of a synthon*

*Acceptor, a$^1$*

*Donor, d$^1$*

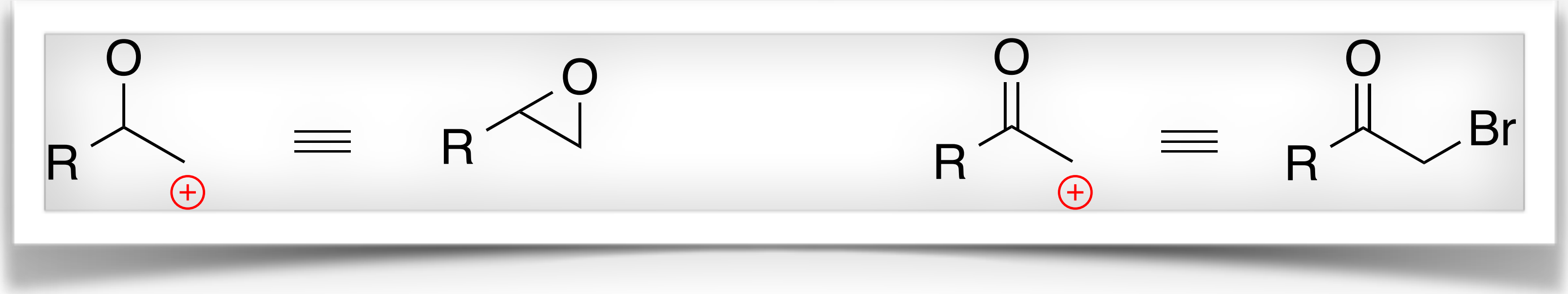
*Acceptor, a$^1$*



*Donor, d$^1$*

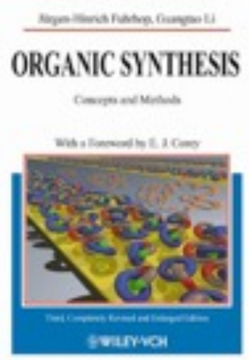
*Seebach, D. ACIEE* **1969**, *8, 639;* **1979**, *18, 239*
*For a seminal application, see Seebach, D.; Corey, E. J. JOC* **1975**, *40, 231*

## *Pay an especial attention to a$^2$ synthons*



*a$^2$ Synthons*

*Chaps. 1.1-1.3*



# Strategies for Retrosynthetic Analysis

*Unfortunately, FG strategy mostly applies for polar reactions,*

***so it does not cover other important transformations***

*Pericyclic reactions* 🟥

*Metathesis and Pd-based reactions* 🟥

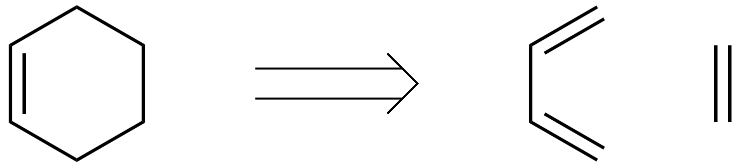
*Radical reactions* 🟥

*don’t fit in such a scheme and other disconnections must be implemented*

# Other disconnections: Olefins lead the way

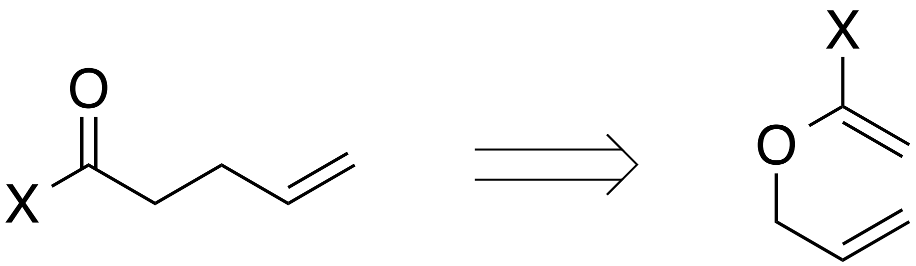
Chapter 2

Diels – Alder



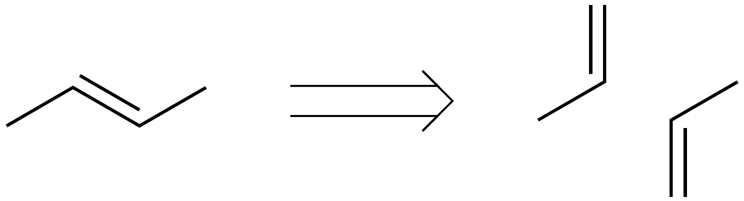
Claisen

Ireland – Claisen

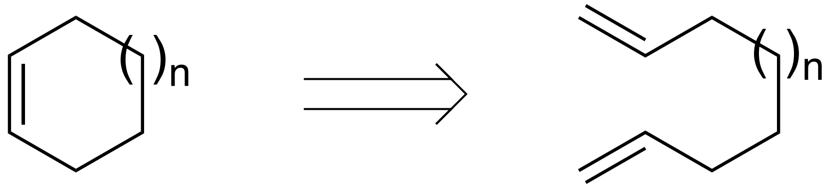


Chapter 3

Cross Metathesis

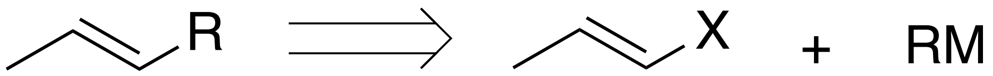


Ring Closing Metathesis



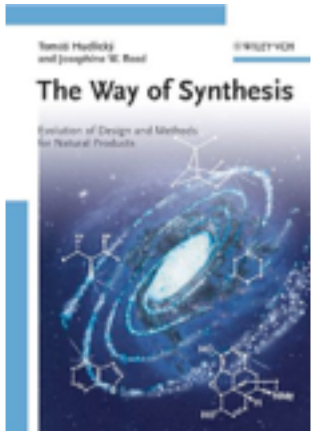
Chapter 4

Pd(0) Based Reactions



# Ranking of Syntheses?

Chapter 2.2



- *How good are the synthetic routes suggested by different retrosynthetic analyses of a TGT ?*
  - *Number of steps as low as possible (**Step Economy**)*
  - *Number of non-necessary redox steps as low as possible (**Redox Economy**)*
  - *Flexibility, easy scale-up, availability of starting materials, ...*
  - *Avoidance of toxic intermediates, side products, and waste*
  - *Convergent syntheses are used to be better than lineal syntheses*

*Lineal Synthesis*

$$\begin{tikzcd} A \arrow[r] & B \arrow[r] & C \arrow[r] & D \arrow[r] & E \arrow[r] & F \arrow[r] & \text{TGT} \end{tikzcd}$$

*Convergent Synthesis*

$$\begin{tikzcd} A \arrow[r] & B \arrow[r] & C \arrow[r, dash] & {} \arrow[r] & \text{TGT} \\ D \arrow[r] & E \arrow[r] & F \arrow[r] & G \arrow[u, dash] & \end{tikzcd}$$

# Useful Definitions

***Target molecule (TGT)***
*the molecule to be synthesized*

***Retrosynthetic analysis or retrosynthesis***
*the process of mentally breaking down a molecule into a starting material*

***Disconnection***
*an imaginary bond cleavage corresponding to a reverse of a real reaction*

***Transform***
*the exact reverse of a synthetic reaction*

***Retron***
*structural subunit on the target that enables a transform to operate*

***Synthon***
*idealized fragment resulting from a disconnection, which is related to possible synthetic operations*

***Umpolung***
*reversal of normal polarization of a molecule or synth*

***Reagent***
*a real chemical compound used as the equivalent of a synthon*

# Useful Definitions

***Synthesis tree***

*set of all the possible disconnections and synthons leading from the target to the starting materials of a synthesis*

***Total synthesis***

*the chemical synthesis of a TGT from relatively simple starting materials*

***Formal total synthesis***

*the chemical synthesis of an intermediate that has already been transformed into the desired target*

***Lineal synthesis***

*a synthesis of consecutive steps*

***Convergent synthesis***

*a synthesis involving the assembly of fragments*