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Bellinzona,16 settembre 2011

Think Like a Chemist

Considerations of a Practitioner on the Nature of Chemistry and Its Relation to Other Sciences

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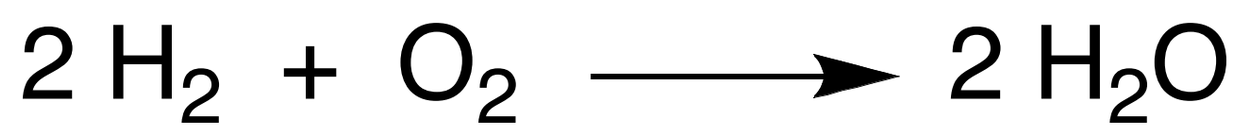
- **Some general concepts and a logical structure of chemistry**
- **The language of organic chemistry**
- **Qualitative concepts in chemistry**
- **Interdisciplinarity**

Terminology and General Concepts

1 Naming Elements



- Hydrogen reacts with oxygen. Water forms
- *Dihydrogen* reacts with *Dioxygen* ...
- Phosphorus, P_4: *Tetraphosphorus*; Sulfur, S_8: *Octasulfur*; Fullerene, C_{60}: *Hexadecacarbon*
- Such more precise designations are legitimate and correct but by no means necessary or mandatory, they just appear to be more rigorous
- The term "hydrogen" shall convey the notion that the elemental substance we call hydrogen exists under standard conditions as a molecular material to be formulated as H_2
- Theoretical knowledge and/or factual knowledge about substances must convey this notion

Dihydrogen Complexes

- "Dihydrogen" is an otherwise engaged notion
- It is commonly used when molecular hydrogen acts as a ligand in (transition) metal complexes (η^2-H_2)
- Analogous dioxygen (η^2-O_2, η^1-O_2) and diniztogen compounds (η^2-N_2, η^1-N_2, μ-N_2) are known
- A dihydrogen complexes constitute the prototypical σ complex (every σ bond may in priciple act as a two-electron donor for a metal center)

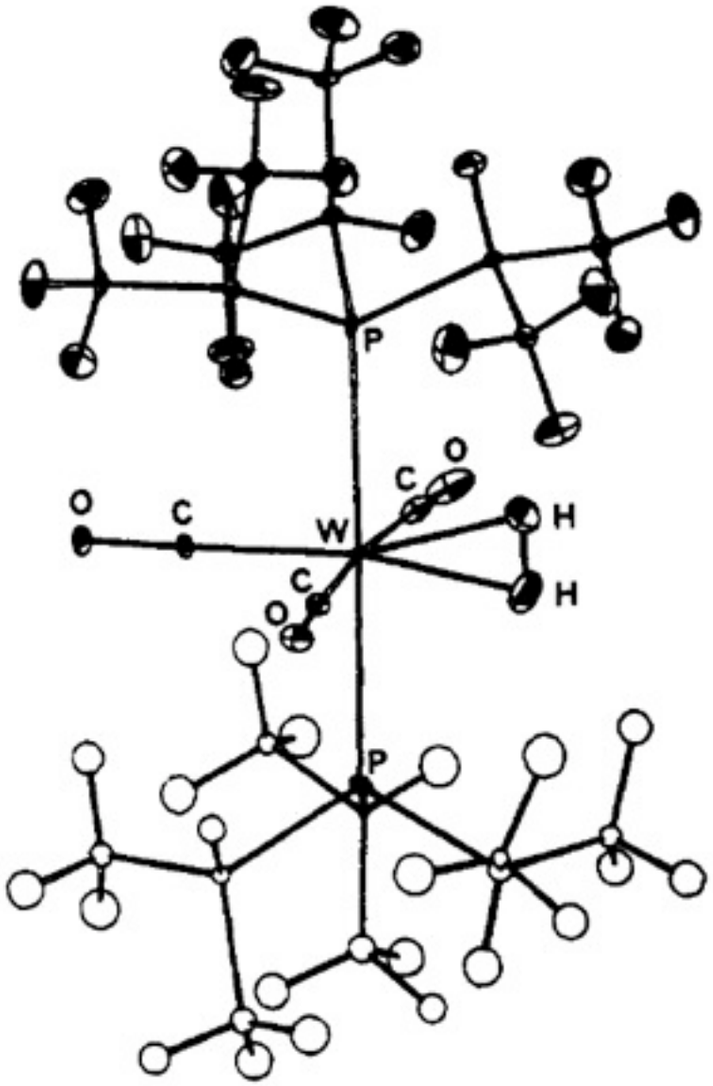


Figure 1. Structure of $W(CO)_3(PPr^i_3)_2(H_2)$ (neutron, 30 K). (Disorder is present in C–H positions of lower phosphine.)

a) G.J. Kubas, R.R. Ryan, B.I. Swanson, P.J. Vergamini, H.J. Wasserman, *J. Am. Chem. Soc.* **1984**, *106*, 451.
b) G.J. Kubas, *Acc. Chem. Res.* **1988**, *21*, 120.

Terminology and General Concepts

2 The Concept of the Pure Substance

- A pure substance is mostly defined according to atomic/molecular criteria. For example, it is said to be constituted by only one type of molecules
- 18.0153 g of pure water are composed by / comprise 6.022 10^{23} H_2O molecules

However:

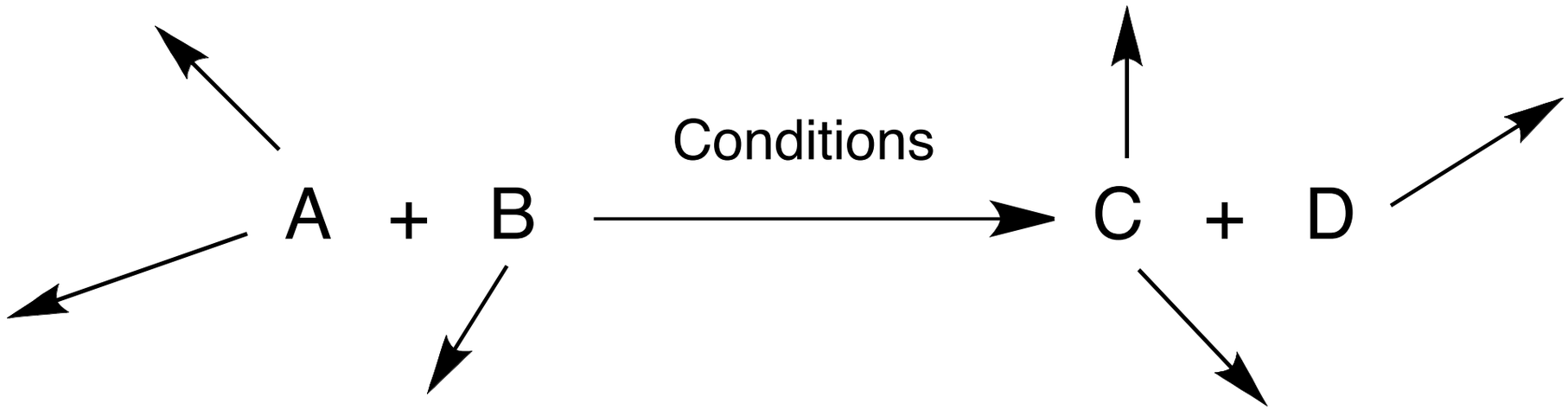
- The common material water does not only contain H_2O molecules but also HDO, D_2O, $H_2{}^{17}O$, $HD^{17}O$, $D_2{}^{17}O$, $H_2{}^{18}O$, $HD^{18}O$, $D_2{}^{18}O$ molecules
- The self-ionization of water generates H_3O^+, OH^- ions and the corresponding isotopomers
- Hydrogen bridging and self dissociation rapidly undo the identity / integrity of any individual water molecule

For a view of analytical philosophy, see: M. Weisberg, Water is *NOT* H_2O, in *Philosophy of Chemistry*, D. Baird et al. (Eds.), Springer, Dordrecht, **2006**, pp. 337-345.
See also: P. Needham, The Discovery that water is H_2O, *Int. Stud. Phil. Sci.* **2002**, *16*, 205-226; P. Needham, What is Water?, *Analysis* **2000**, *60*, 13-21.

The Operationalized Definition of a Pure Substance

- The pure substance is not a natural category (the material world cannot be described or conceived in terms of pure substances
- A separation / partition of the material world can be achieved *experimentally*
- Separation and purification operations usually include phase changes, such as in distillations, sublimations, crystallizations. A pure substance withstands changes of selected thermodynamic conditions
- A substance is then pure when a reiteration of experimental purification procedures no longer change its purity.
- A single molecule does not necessarily and adequately represent a corresponding pure substance
- The artificial and idealized concept of a pure substance does nevertheless fulfill a central role with respect to a systematic description of chemistry

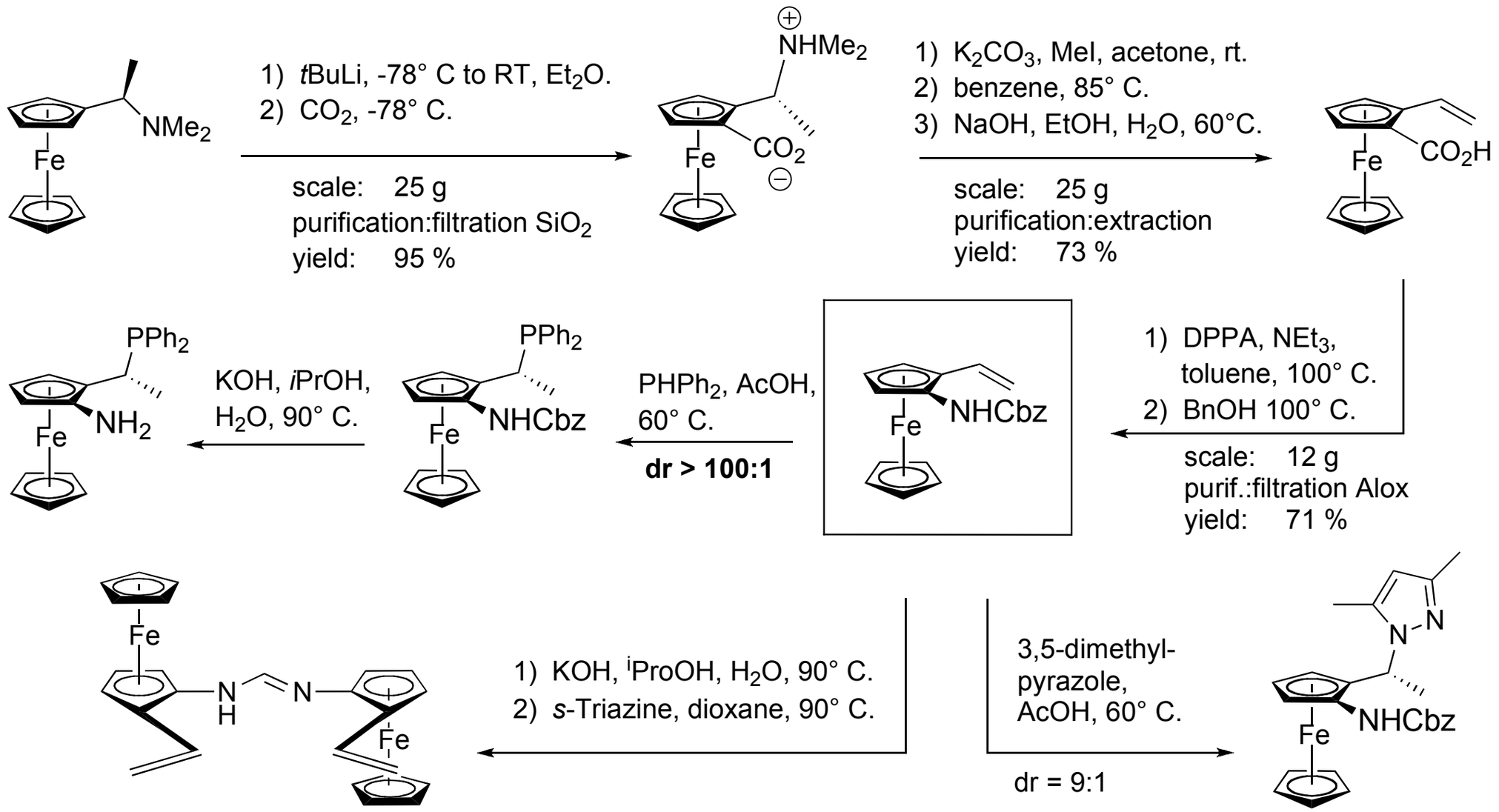
Pure Substances and a Logical Structure of Chemistry



- A chemical reaction equation establishes a relation between starting materials and products
- The interpretation of the reaction arrow as an equality sign is coercive, limiting and therefore problematic
- The reaction equation is the simplest form of a chemical network
- Such a network constitutes a logical structural starting point for a systematic organization of chemical knowledge

The Reaction Equation Does Not Need to Be an Equation...

- **A reaction equation can convey complete information about the participating species without explicitly taking into account complete and correct stoichiometry**



Reaction scheme taken from: A. Bertogg, A. Togni, *Organometallics* **2006**, *25*, 622-630.

The Classification of Substances

- **Classification fulfills a very important role in the natural sciences**
  - Philosophy, though, has for a long time mainly focussed on physics and its mathematical methods
- **The concept of pure substance allows for a classification of such complying substances. Similarities and differences in chemical behavior are the main criteria**
- **Similarity concept in chemistry:**

  Two substances belong to the same substance class in case they are chemically similar

  Two substances are chemically similar when, under the same conditions, they react to products belonging to the same class

Prediction Through Classification

- **Similar network relations are valid for classes of substances as for individual pure substances**
- **The affiliation of a substance to a certain class allows to predict which *new* substance will be synthetically accessible from it**
- **The classification of substances as typical for chemistry is fundamentally different from other types of classifications in the natural sciences. Its *predictive power* is higher**
- **The planning of multistep syntheses is most representative of this predictive power**

Predictive power, see: J. Schummer, *HYLE* **1998**, *4*, 129-162 (The Chemical Core of Chemistry I: A Conceptual Approach).
Predictive power must be interpreted as *enabling*. See, e.g.: B.M. Trost, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5348-5355.

The Language of Structural Formulas

- **The chemical sign language IS the language of organic chemistry !**

«[...] the chemical sign language is actually one of the most powerful predictive theories of science at all !»

J. Schummer, *HYLE* **1998**, *4*, 129-162 (The Chemical Core of Chemistry I: A Conceptual Approach)

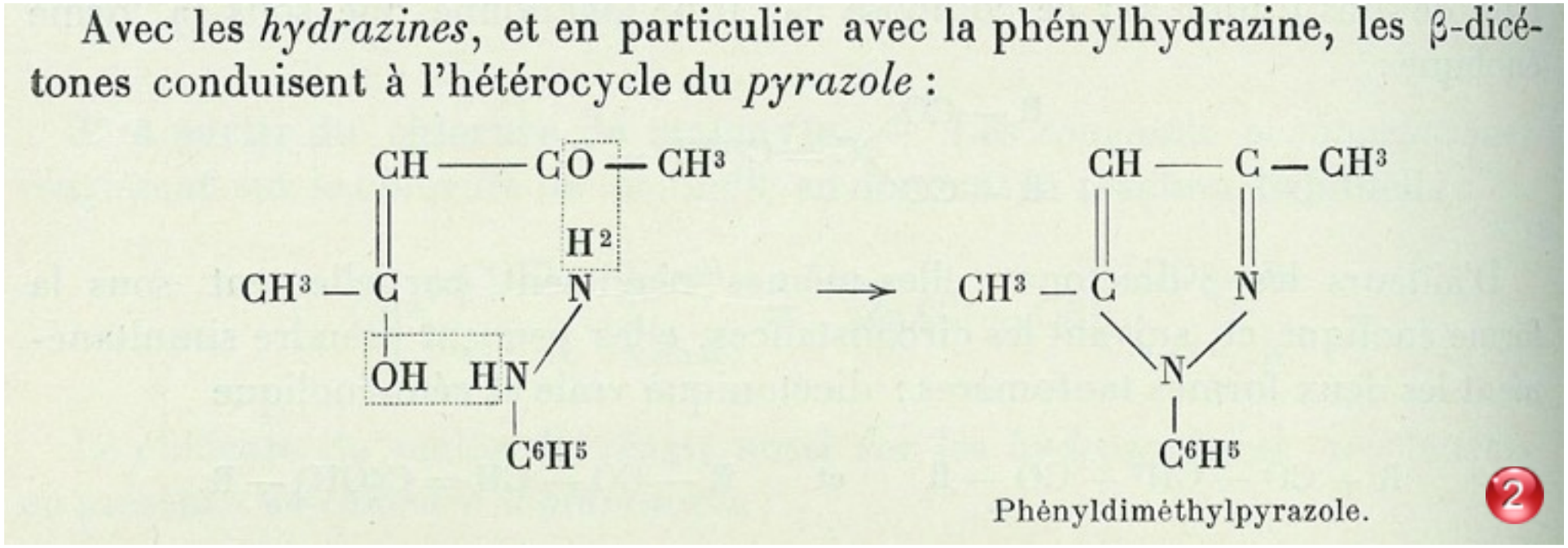
- **A structural formula is not only model-like representation and metaphor, it is primarily the expression of an advanced and highly developed theoretical thinking**

See also: a) R. Hoffmann, P. Laszlo, Darstellungen in der Chemie – die Sprache der Chemiker, *Angew. Chem.* **1991**, *103*, 1-16. b) R. Hoffmann, What might philosophy of science look like if chemists built it?, *Synthese* **2007**, *155*, 321-336.

Early Insight

Die Chemie ist zur "exakten" Wissenschaft nicht nur durch die ständige Verfeinerung ihrer Massmethoden geworden, sondern vor allem auch durch die Verschärfung dieses ihres gedanklichen Instruments, durch den Weg, den sie von der einfachen chemischen Formel bis zur *Strukturformel* durchmessen hat. Ganz allgemein besteht der wissenschaftliche Wert einer Formel nicht nur darin, dass sie gegebene empirische Tatbestände *zusammenfasst*, sondern dass sie neue Tatbestände gewissermassen *hervorlockt*. Sie stellt Probleme von Zusammenhängen, von Verknüpfungen und Reihenbildungen auf, die der unmittelbaren Beobachtung vorauseilen. So wird sie zu einem der hervorragendsten Mittel dessen, was Leibniz die "Logik der Entdeckung", die *logica inventionis*, genannt hat.

Ernst Cassirer: **1923**, *Philosophie der symbolischen Formen* [1]

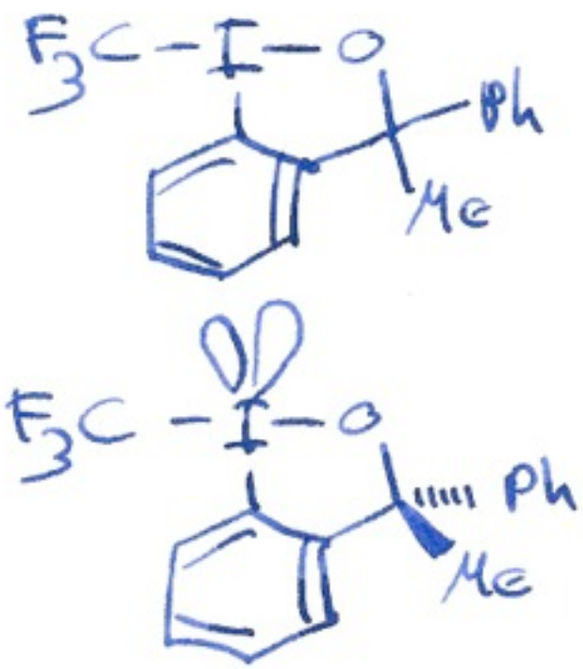


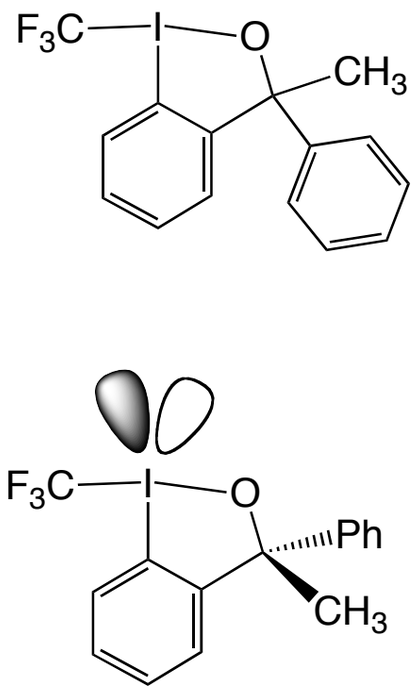
[2]

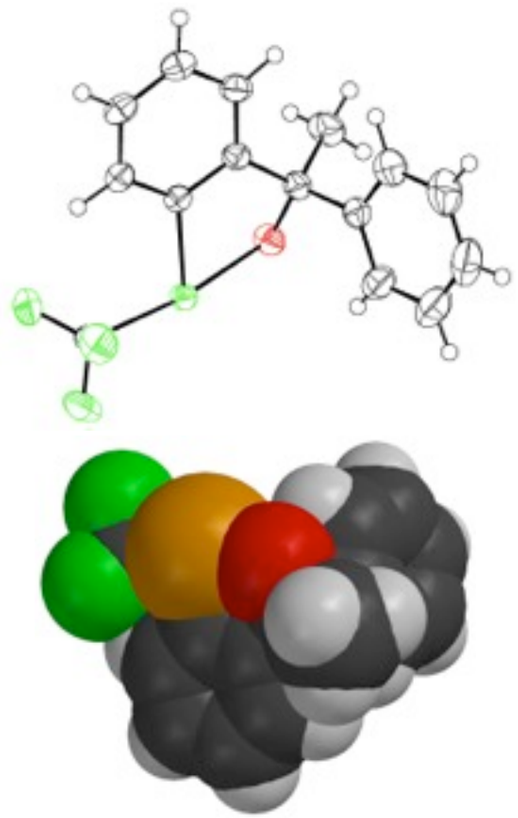
1. Ernst Cassirer, Gesammelte Werke, Hamburger Ausgabe: Band 13, *Philosophie der symbolischen Formen*, 3. Teil: *Phänomenologie der Erkenntnis*, Meiner Felix Verlag GmbH, Hamburg, **2002**, S. 509.
2. Victor Grignard, Précis de Chimie Organique, Masson, Paris, **1937**, p. 468.

Structural and Pictographic Representations

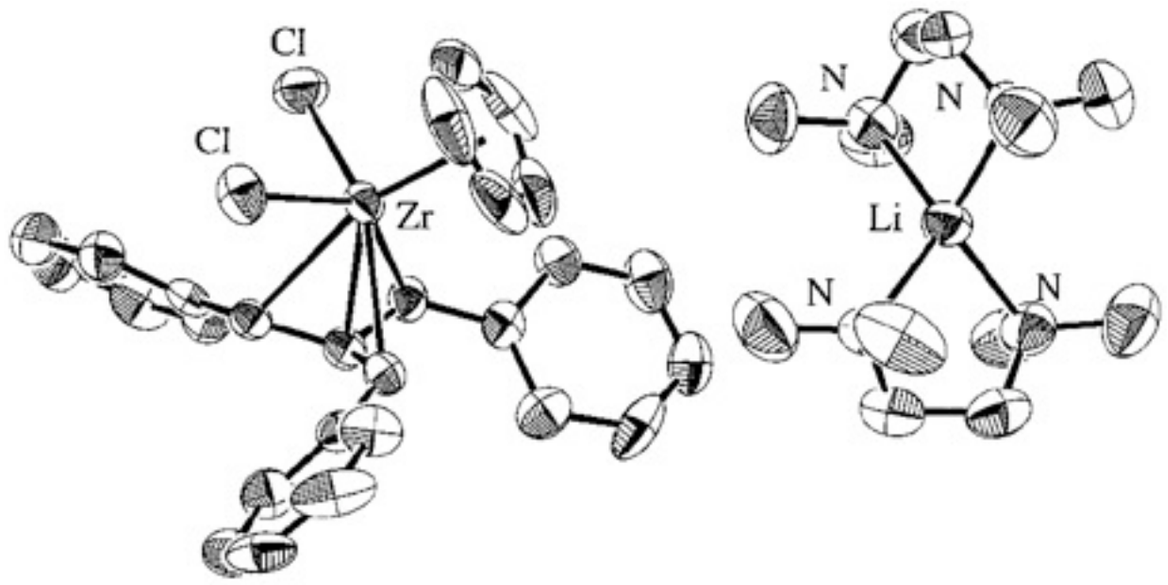
- A structural formula identifies a (pure) substance and is the basis for the prediction of its reactivity
- Thus, the structural formula conveys the position of the corresponding substance within the network of the known (and still unknown) substances
- A pictographic representation derives from measurements or quantum chemical calculations and plays a subordinate role in chemical communication



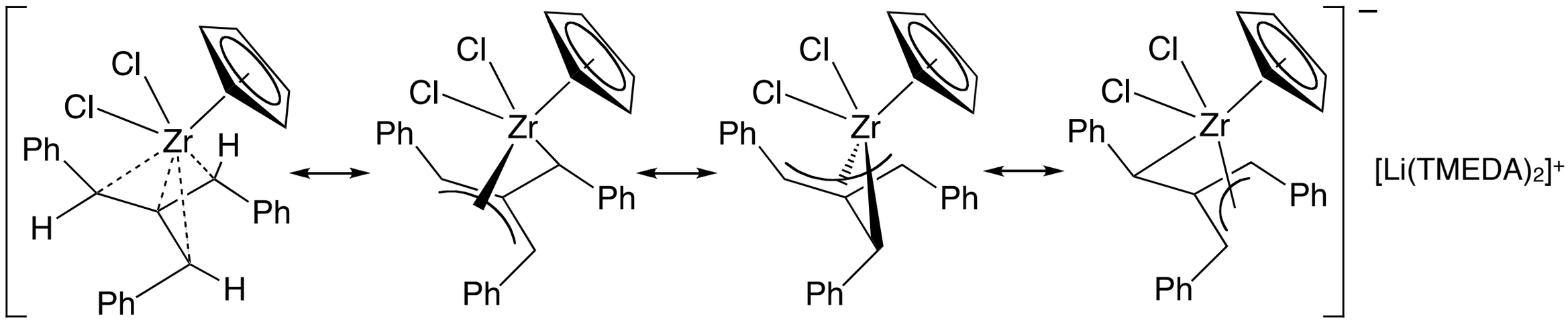




Translation and Interpretation



Understanding bonding relationships from crystallographic data is particularly important in organometallic chemistry



An η^4-Trimethylenemethane complex, derivative of $[C(CH_2)_3]^{2-}$

G. Rodriguez, G.C. Bazan, *J. Am. Chem. Soc.* **1997**, *119*, 343.

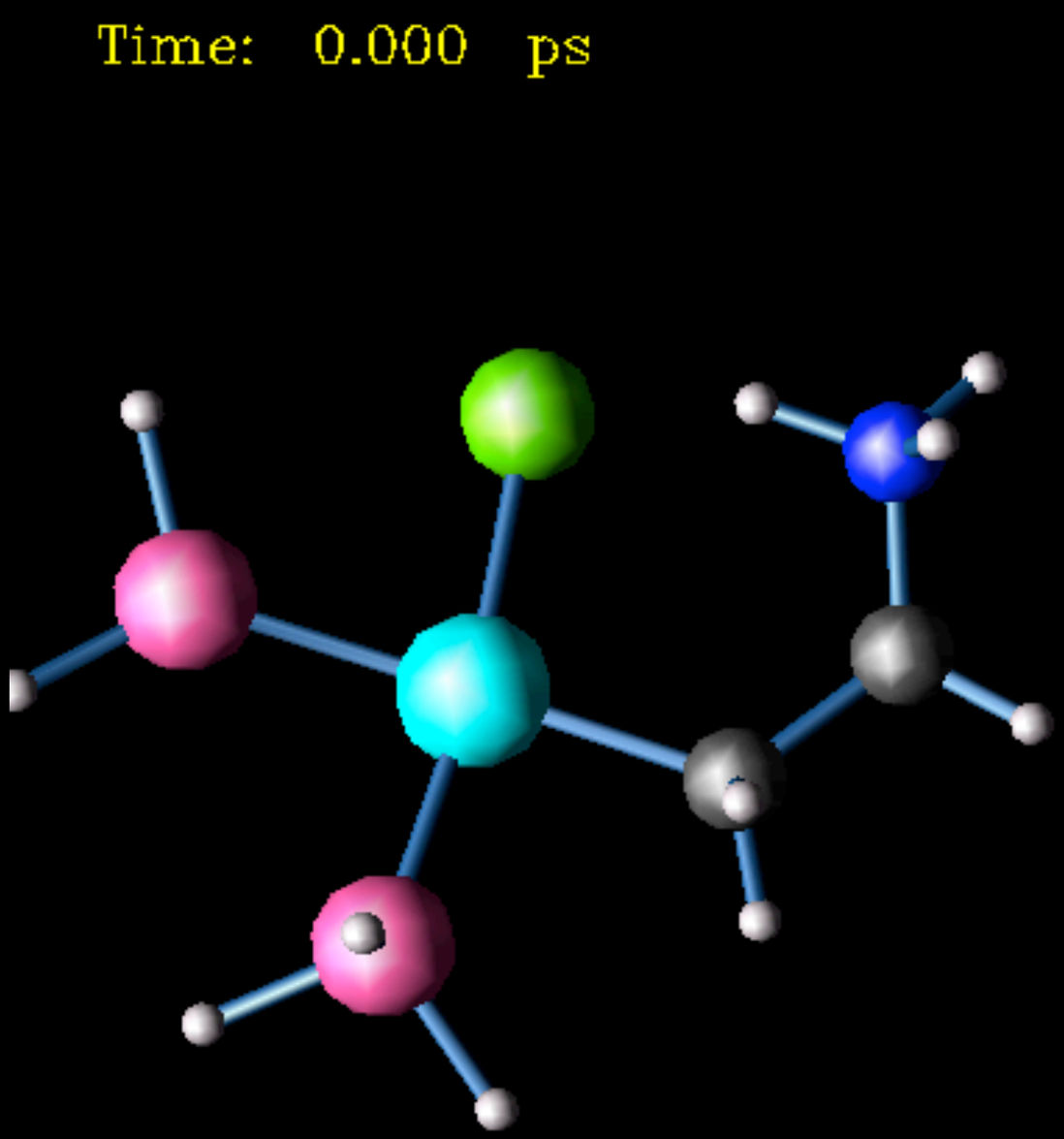
The Role of Quantum Chemistry

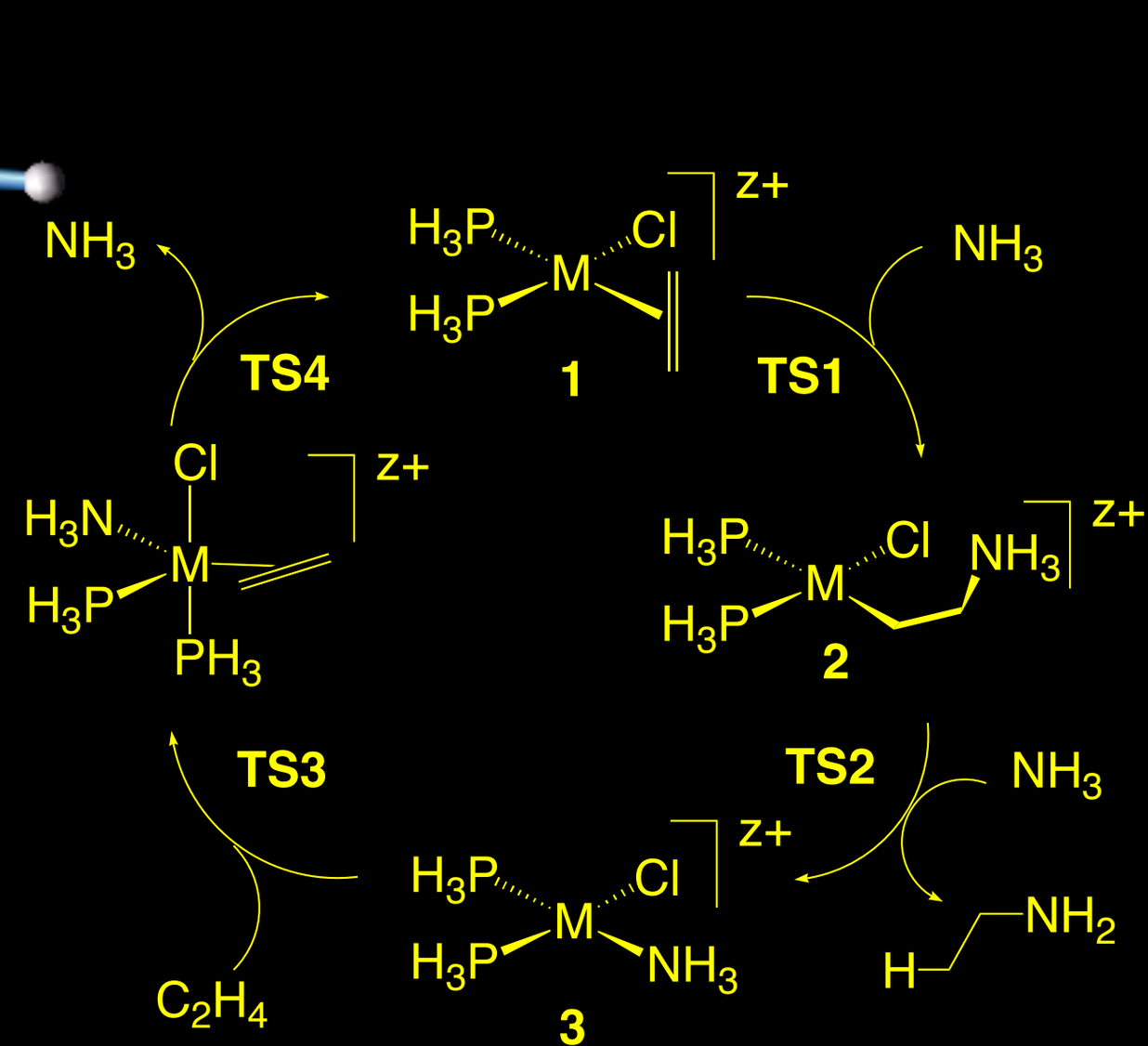
«The important concepts of chemistry have never been well-treated by ab-initio quantum chemistry so that quantum mechanics has *not* become the primary tool in the chemist's understanding of matter. Brute-force numerical quantum chemistry can hardly do justice to the qualitative features of chemistry. But without insight into qualitative concepts we are losing chemistry.»

H. Primas, *Chemistry, Quantum Mechanics and Reductionism*. *Perspectives in Theoretical Chemistry*, Springer, Berlin, **1981**

On the problem of a reduction of chemistry to physics, see: H. Primas, *Chemie in unserer Zeit* **1985**, *19*, 109-119 (Teil 1: Das molekulare Programm) und 160-166 (Teil 2: Die Chemie der Makrowelt)

Quantum Chemical Calculations and the Visualization of a Reaction Step

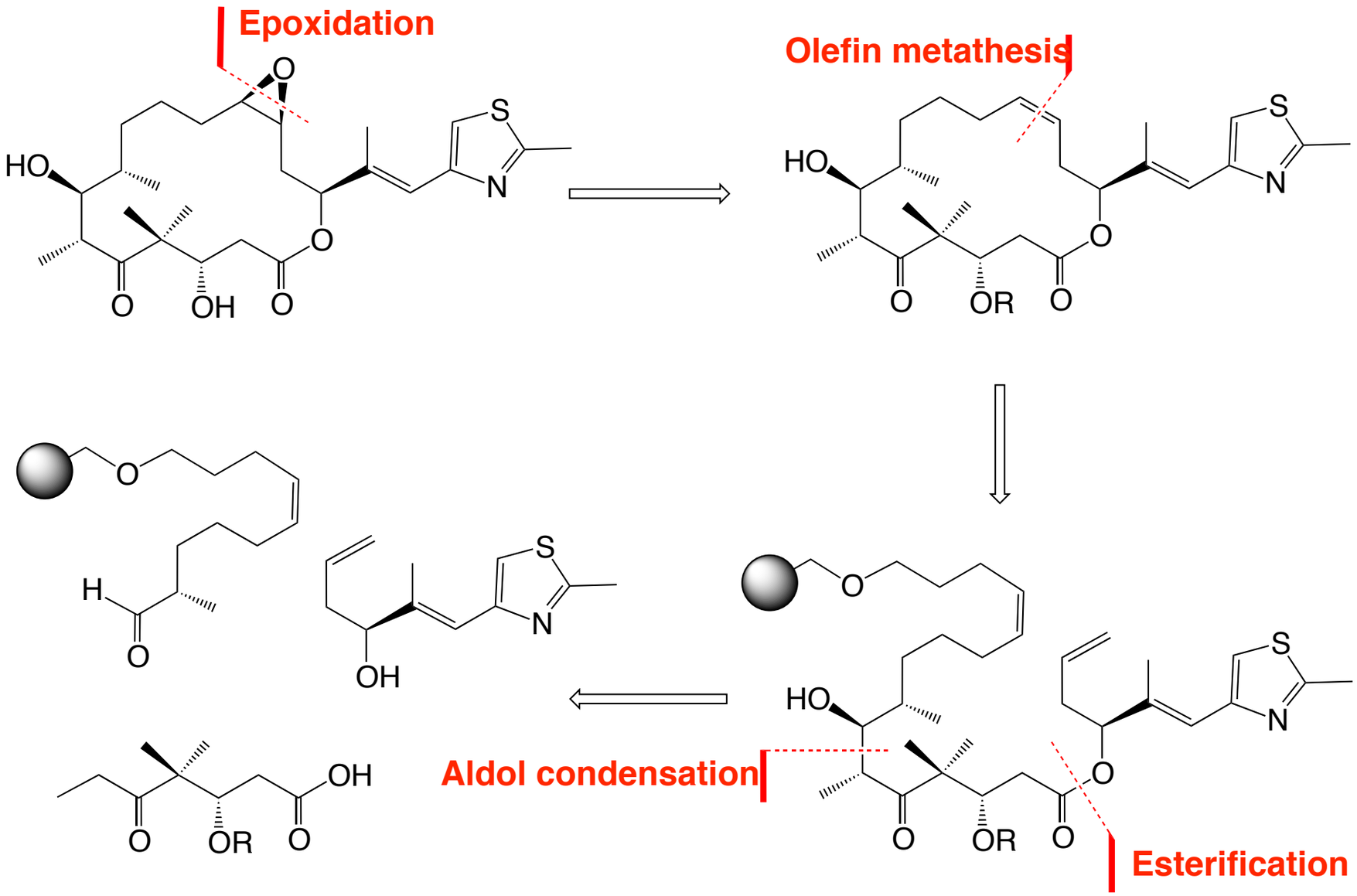




H.M. Senn, P. E. Blöchl, A. Togni, *J. Am. Chem. Soc.* **2000**, *122*, 4098

Retrosynthesis: A Theoretical Instrument

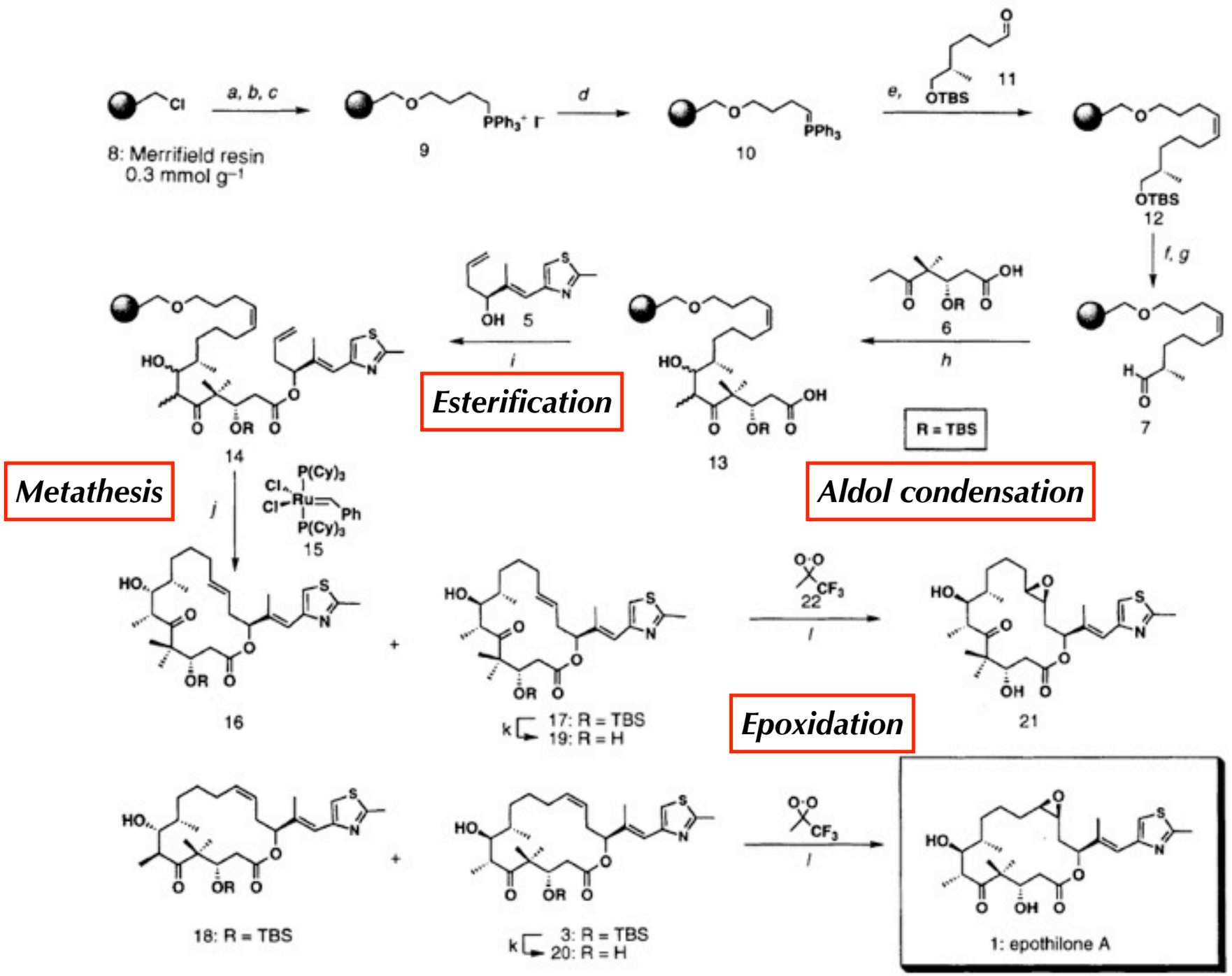
Example: The first total synthesis of Epothilone A and B



- A retrosynthesis is a special form of a synthesis plan
- The reaction steps in a retrosynthetic analysis may be ficticious and do not need to be accomplished experimentally in the given direction
- Retrosynthesis exemplifies how chemistry successfully escapes any attempt to reduce it to physics

K.C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268.

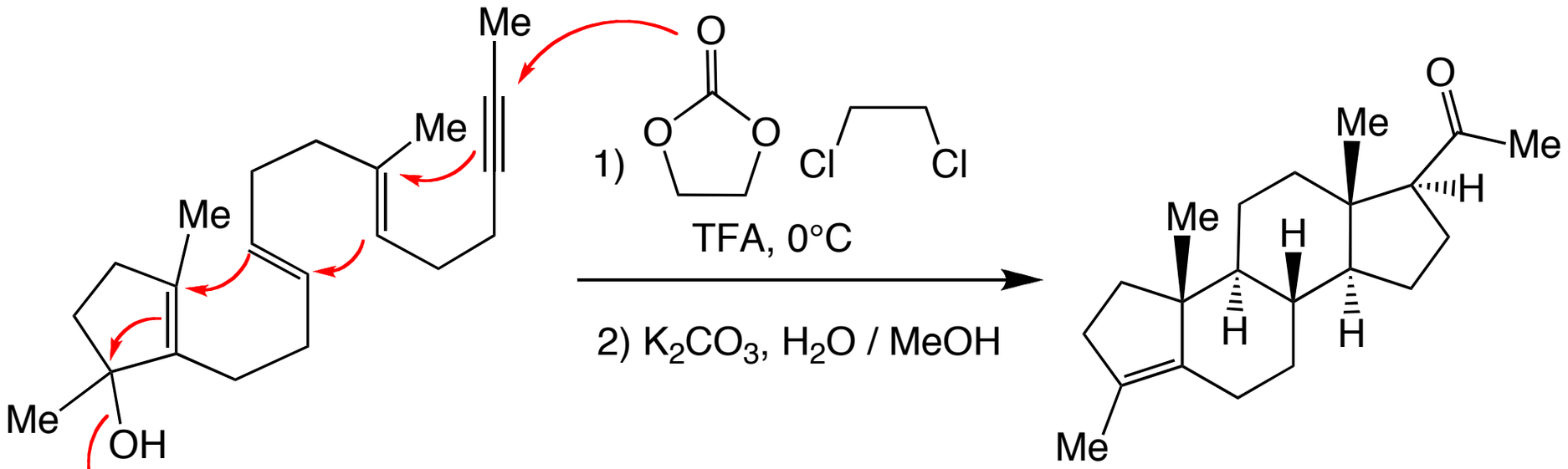
Synthesis as Implementation of Retrosynthesis



K.C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268.

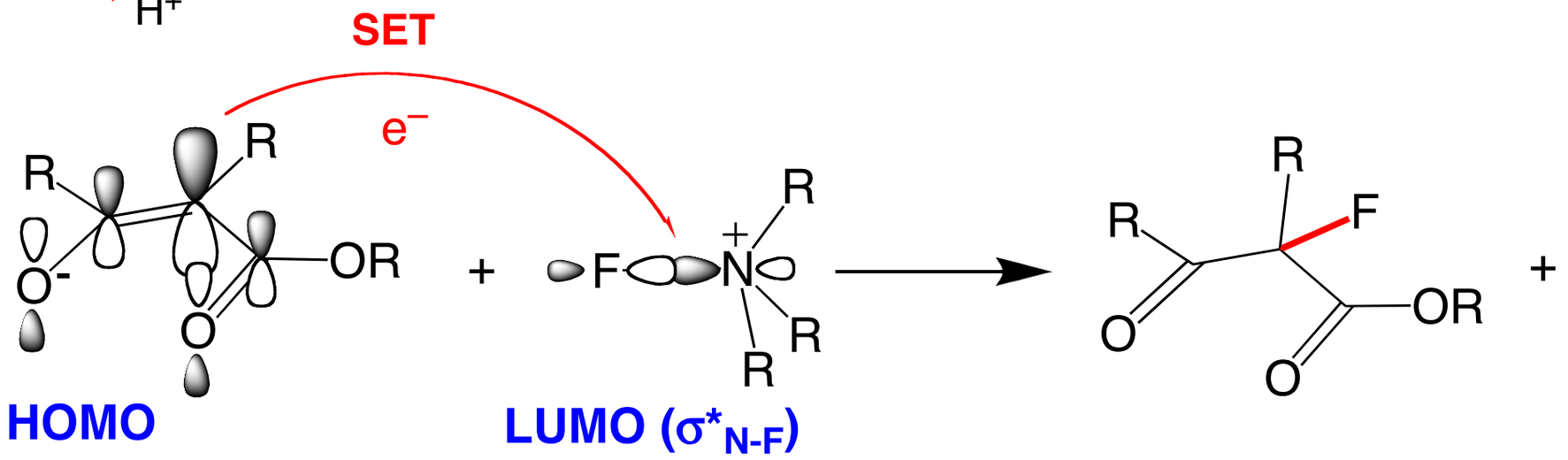
Reaction Mechanisms

- "*Pushing electrons*" und "*empty orbitals*" are common instruments in the discussion and interpretation of reaction mechanisms. They are totally extraneous to physics



1

The key polycyclization step in the Johnson biomimetic synthesis of progesterone



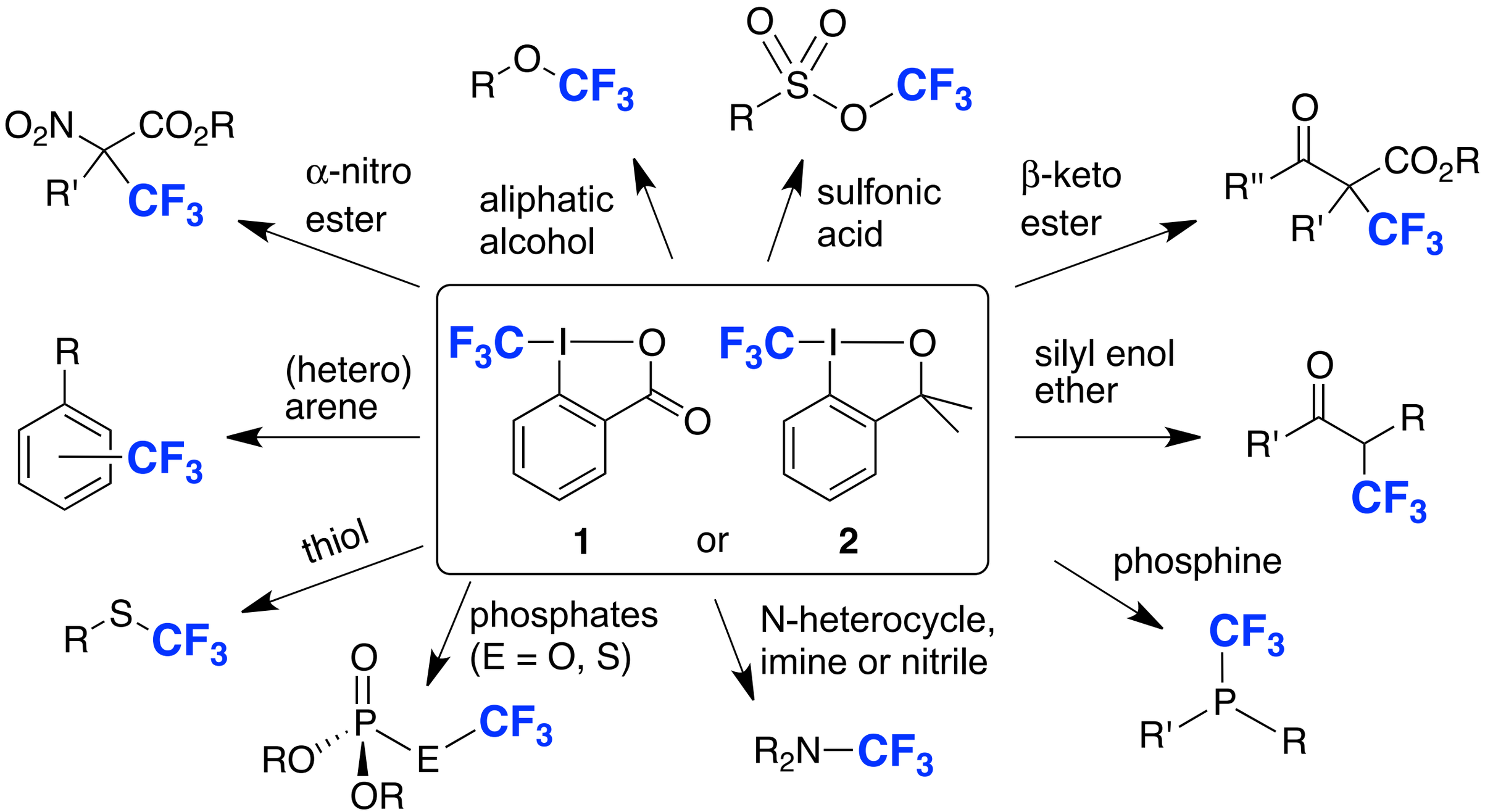
2

"Single-electron transfer" (SET) step in the catalytic electrophilic fluorination of 1,3-dicarbonyl compounds

1 M.B. Gravestock, W.S. Johnson, B.E. McCarry, R.J. Parry, B.E. Ratcliffe, *J. Am. Chem. Soc.* **1978**, *100*, 4274.

2 S. Piana, I. Devillers, A. Togni, U. Röthlisberger, *Angew. Chem. Int. Ed.* **2002**, *41*, 979.

Electrophilic Trifluoromethylation Reactions Using Iodane Reagents

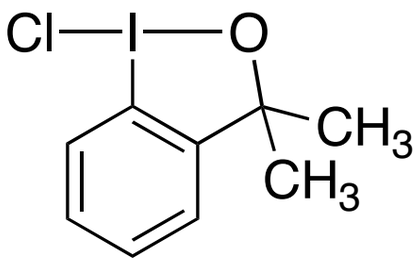


DSC Analysis of Hypervalent [I]-Cl and [I]-CF_3 Compounds

The Only Thermodynamic Data Available

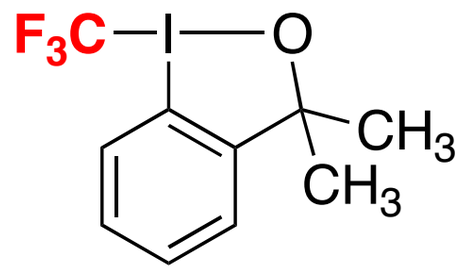
ΔH_{fus} =25.7 kJ·mol^{-1}

mp.: 148-151 °C



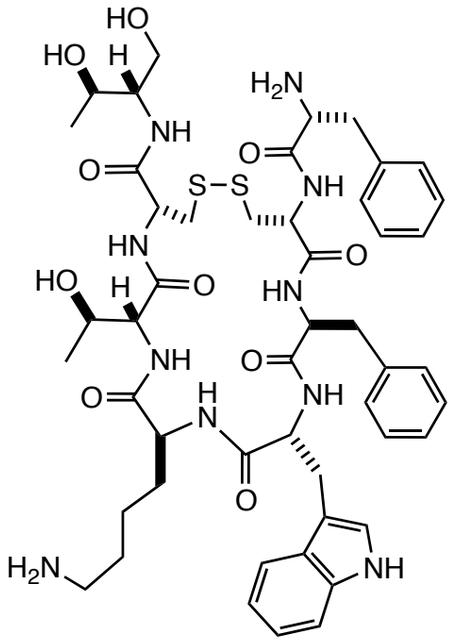
ΔH_{fus} =18.8 kJ·mol^{-1}

mp.: 76-79 °C



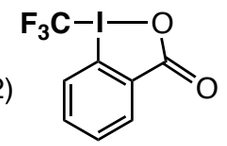
Trifluoromethylation of Sandostatin® and Coenzyme A

Link to Molecular Biology

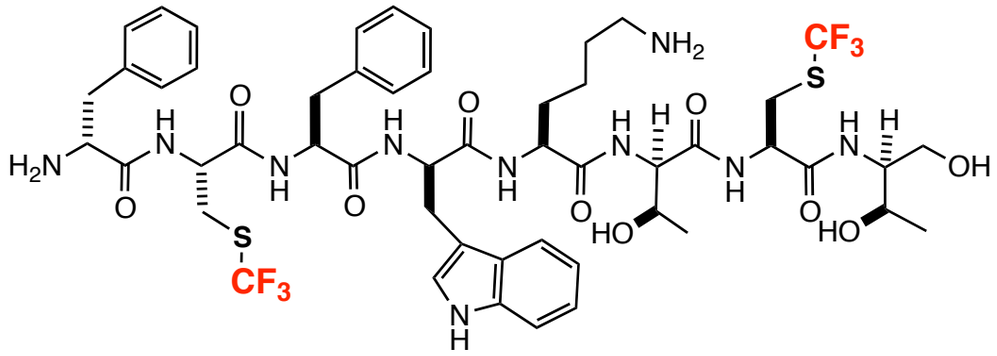


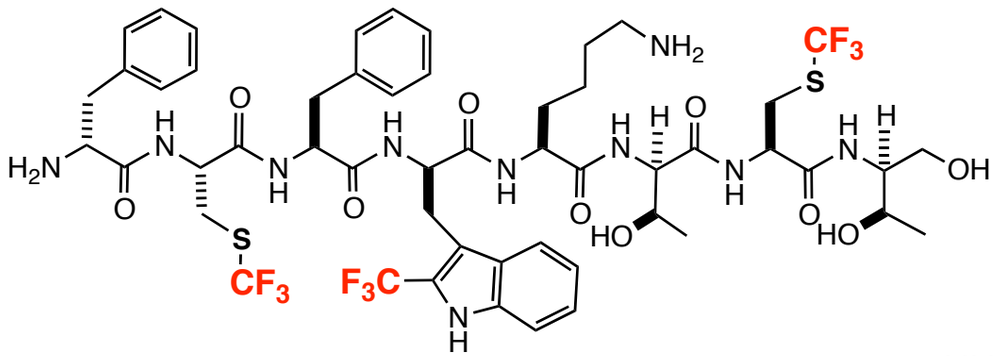
Octreotide (Sandostatin®)

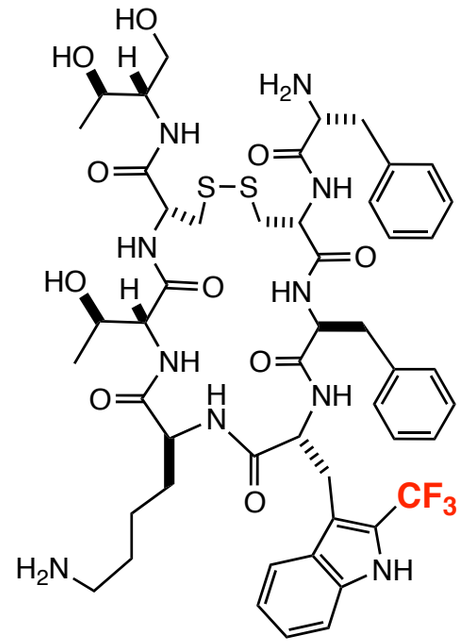
1) 1,4-Dithiothreitol, Phosphate buffer

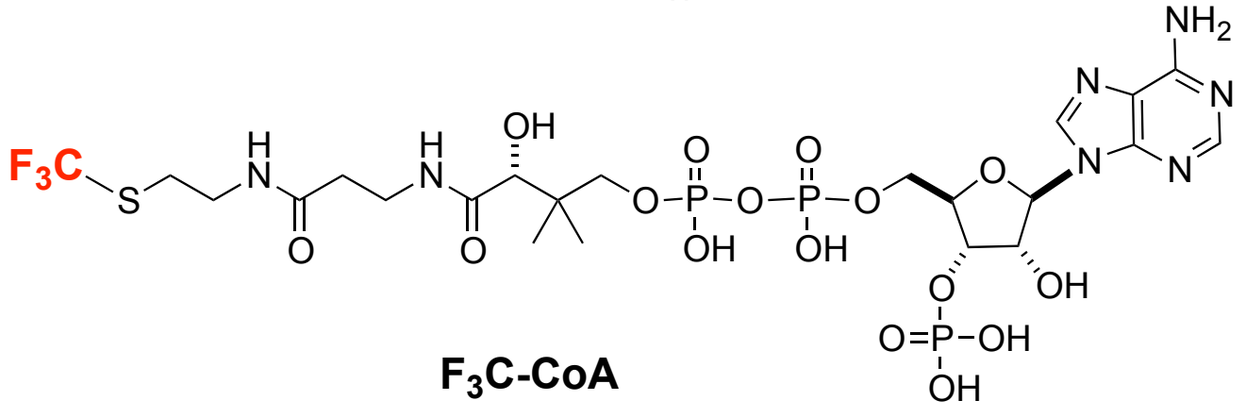
2) 

DBU / MeOH









F_3C-CoA

S. Capone, I. Kieltsch, O. Flögel, G. Lelais, A. Togni, D. Seebach, *Helv. Chim. Acta* **2008**, *91,* 2035.
D. Seebach, H. Widmer, S. Capone, R. Ernst, T. Bremi, I. Kieltsch, A. Togni, D. Monna, D. Langenegger, D. Hoyer, *Helv. Chim. Acta* **2009**, *92,* 2577.

For an analogous trifluoromethylation of **coenzyme A**, see: L. K. Charkoudian, C. W. Liu, S. Capone, D. E. Cane, A. Togni, D. Seebach, C. Khosla, *Protein Science* **2011**, *20*, 1244.

Concluding Comments

- A thorough understanding of chemistry – its quintessence, its way of thinking and its theory – can only be achieved via a disparate series of qualitative concepts
- However, the latter must be complemented by physics-derived quantitative concepts/theories (quantum mechanics, thermodynamics etc.)

- Thermodynamic data are very often just unavailable. This is the case for most new compounds in daily chemical research. Such data may be calculated via quantum chemical methods rather than by classical measurements

- Interdisciplinarity is not a discipline. Interdisciplinarity comes about when specialists of different disciplines learn to "talk to each other"

General Literature

Monographies

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- M. P. Crosland, *Historical Studies in the Language of Chemistry*, Dover Publications, Mineola, 1978, 2004 (ISBN 0-486-43802-3)
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