

The Isoinversion Principle

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Denmark group meeting

February 18, 2014

Selectivity in chemistry

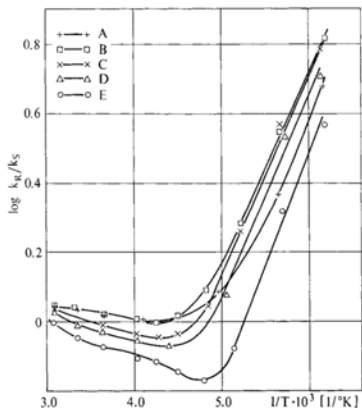
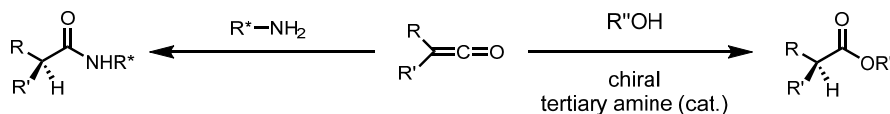
- Selection processes (**chemo-, site-, regio-, diastereo-, enantioselectivity**) play an important role in chemistry
- **Selectivity** is mainly a **kinetic phenomenon** (ratio of product formation rates)
- The discussion concerning selectivity is mainly focused on **steric and/or electronic features** of the catalyst/substrate
- Being a kinetic phenomenon, selectivity is also influenced by the reaction conditions

Selectivity as a function of temperature

DOGMA: *the lower the temperature, the higher the selectivity*

Pracejus (1960):

first report on a **non-linear relationship** between selectivity and temperature attributed to an interplay of enthalpy and entropy (addition of alcohols and amines to ketenes)



'Differences in enthalpy and entropy work in general in opposite directions; thus the reaction temperature determines which of the two factors dominates and decides the sign of the specificity. [...]

Clarification of the situation by extensive studies on the relations between reaction temperature and stereospecificity in asymmetric synthesis seems therefore urgently required.'

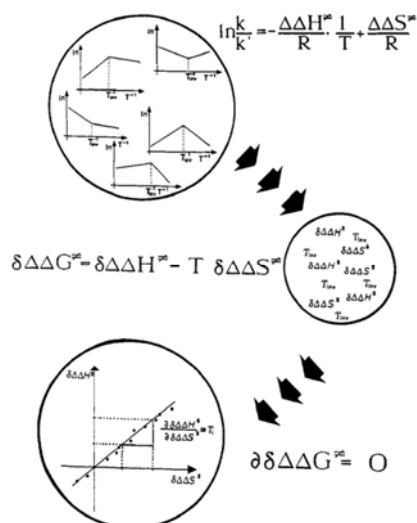
Pracejus, H. *Justus Liebigs Annalen der Chemie* **1960**, 634, 9
 Pracejus, H. *Justus Liebigs Annalen der Chemie* **1960**, 634, 23

Selectivity as a function of temperature

DOGMA: *the lower the temperature, the higher the selectivity*

Scharf (1989):

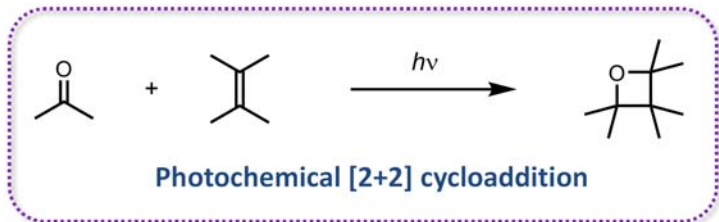
non-linear behaviors are explained as the **isoinversion principle** after systematic investigation of the **Paternò-Büchi reaction**



Hans-Dieter Scharf

Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, 111, 5367

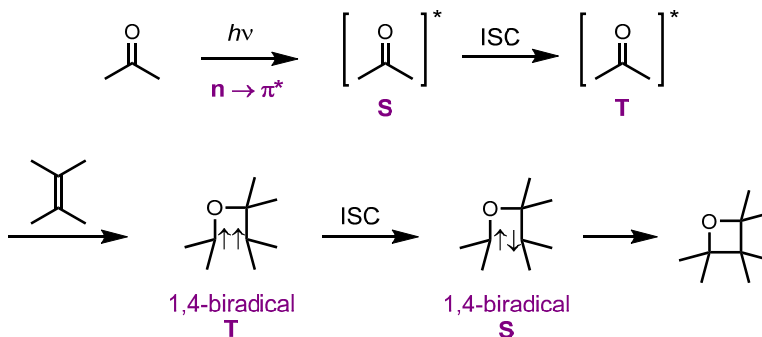
The Paternò-Büchi reaction



Emanuele Paternò

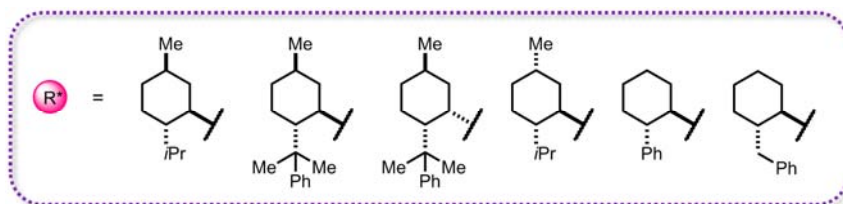
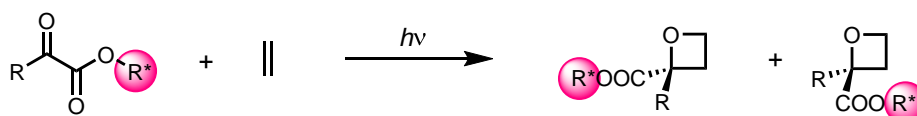


George Hermann Büchi



D'Auria, M.; Racioppi, R. *Molecules* **2013**, *18*, 11384

Stereoselective Paternò-Büchi reaction

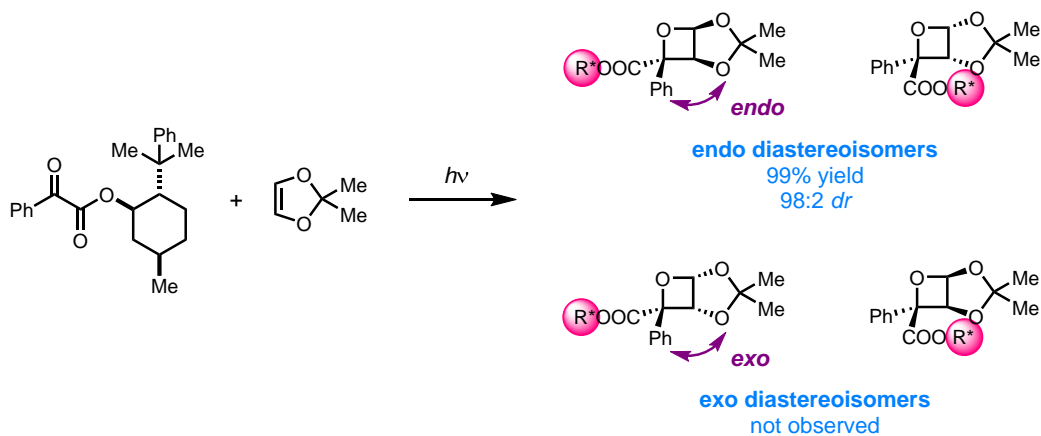


Diastereomeric ratio influenced by:

- Chiral auxiliary
- Olefin
- Ketone R group

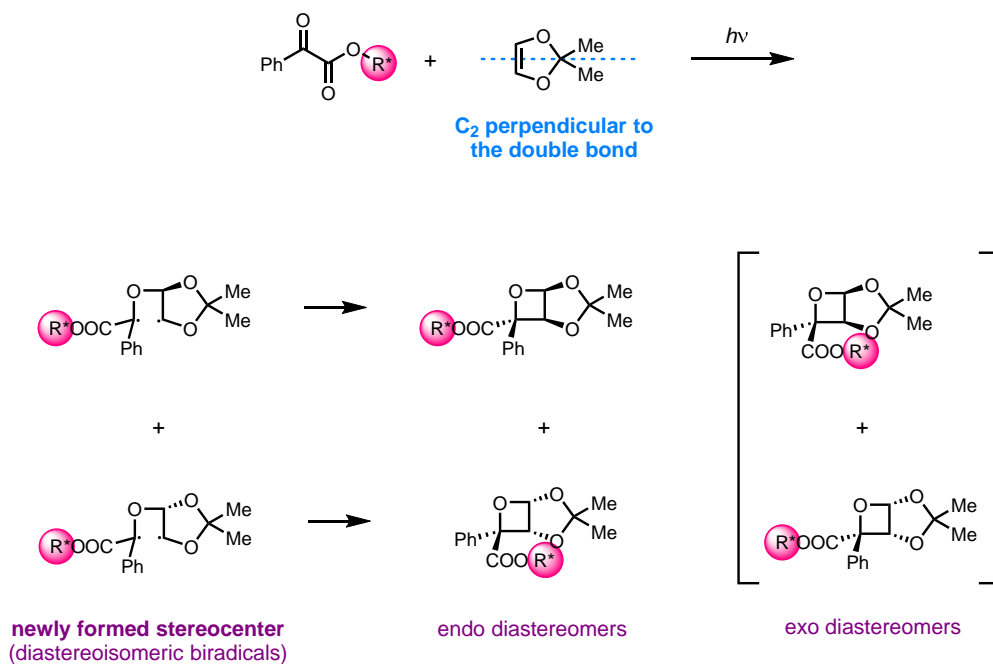
Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Endo selectivity



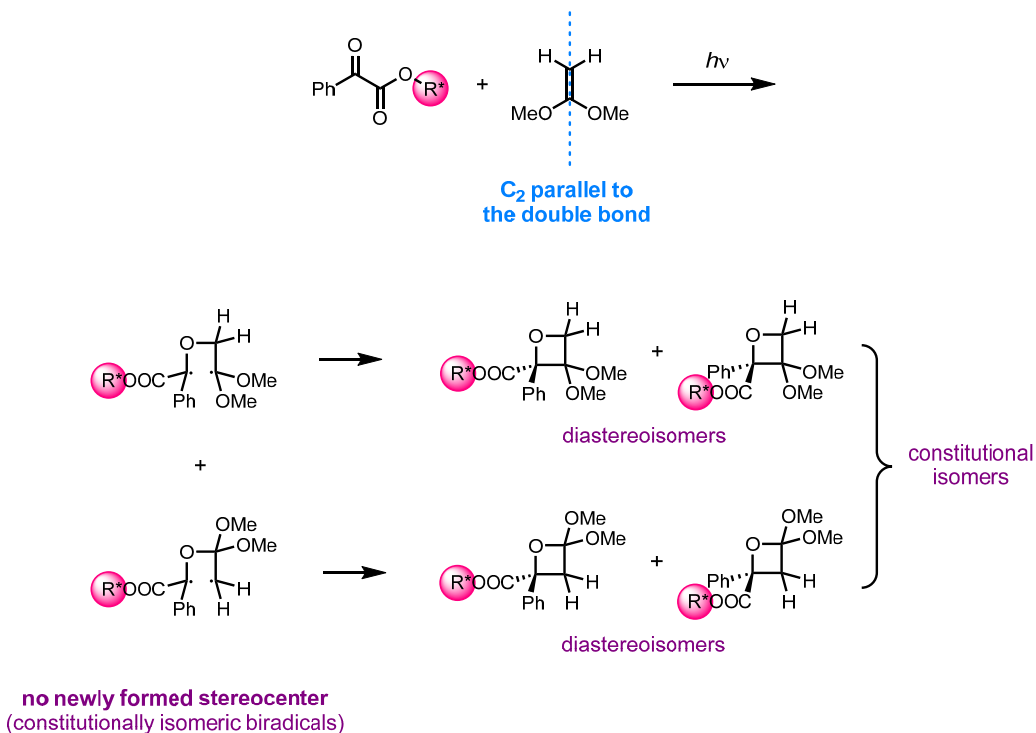
Nehring, A.; Scharf, H.-D.; Runsink, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 877

Olefin symmetry



Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Olefin symmetry



Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 477

Influence of the temperature

'The influence of temperature was not uniform on the regio- and diastereoselection. Diastereoselection may increase, but alternatively it may be constant or even decrease with decreasing temperature, contrary to common opinion.'

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} \quad (\text{Eyring equation})$$

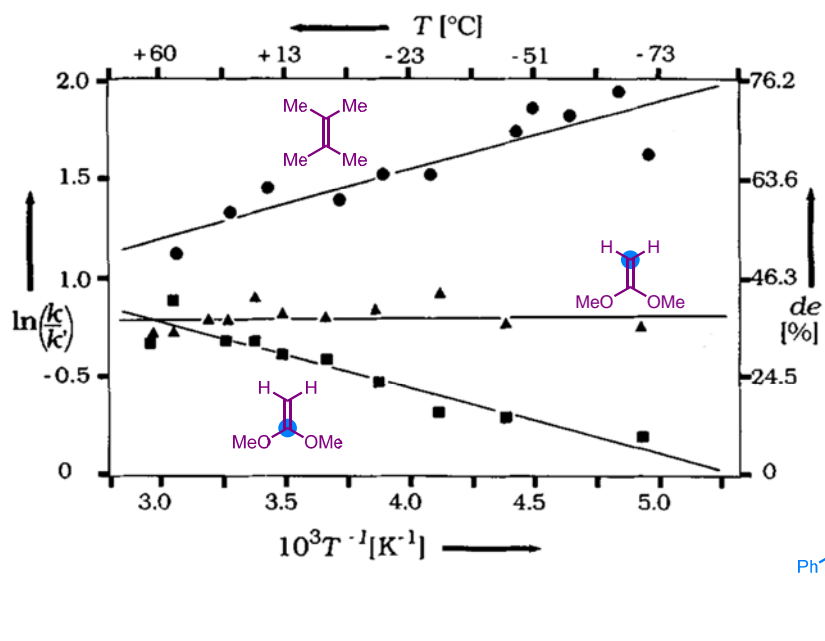
$$\frac{k_1}{k_2} = e^{-\frac{\Delta \Delta G^\ddagger}{RT}} \Rightarrow \ln \frac{k_1}{k_2} = -\frac{\Delta \Delta G^\ddagger}{RT}$$

$$\Delta G = \Delta H - T \Delta S \Rightarrow \ln \frac{k_1}{k_2} = -\frac{\Delta \Delta H^\ddagger}{R} \frac{1}{T} + \frac{\Delta \Delta S^\ddagger}{R}$$

k_1/k_2 is measured as the ratio of the intensities of selected signals in the ^{13}C NMR spectrum

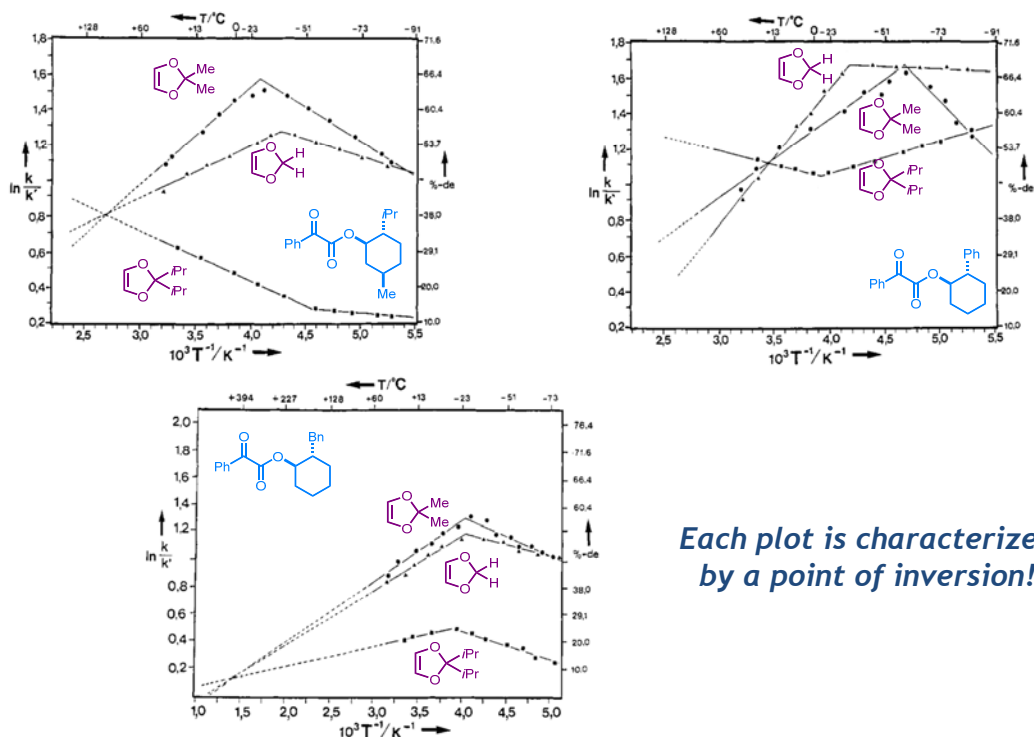
Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Plath, M. W.; Runsink, J. J. *Am. Chem. Soc.* **1989**, 111, 5367

Eyring diagrams



Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

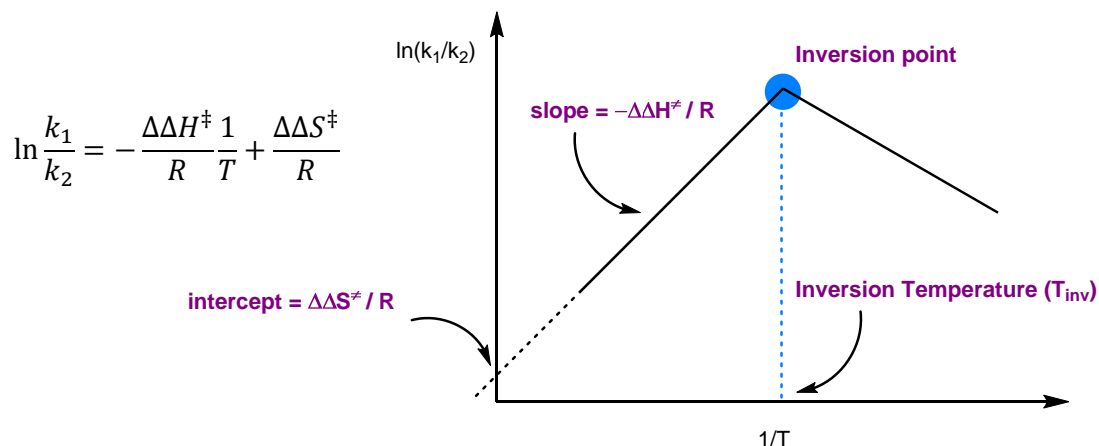
Eyring diagrams



Each plot is characterized by a point of inversion!

Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, *111*, 5367

Eyring diagrams



T_{inv} determines two distinct temperature regions, each with its own activation parameters:

$$\Delta\Delta H_1^\ddagger \text{ and } \Delta\Delta S_1^\ddagger \text{ (} T < T_{inv}\text{)}$$

$$\Delta\Delta H_2^\ddagger \text{ and } \Delta\Delta S_2^\ddagger \text{ (} T > T_{inv}\text{)}$$

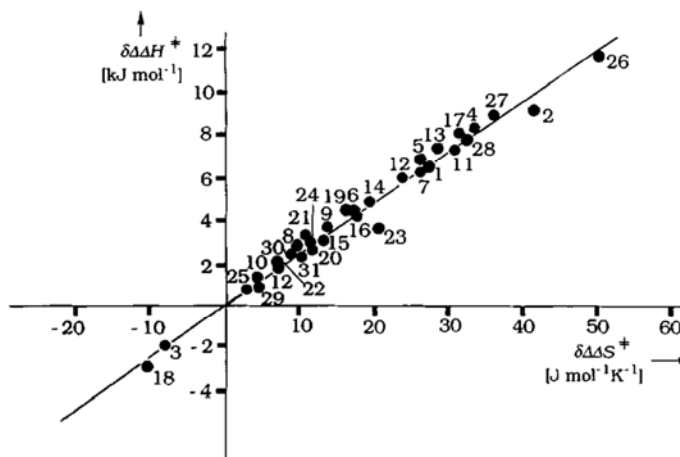
The isoinversion principle

$$\delta\Delta\Delta H^\ddagger = \Delta\Delta H^\ddagger_2 - \Delta\Delta H^\ddagger_1$$

$$\delta\Delta\Delta S^\ddagger = \Delta\Delta S^\ddagger_2 - \Delta\Delta S^\ddagger_1$$

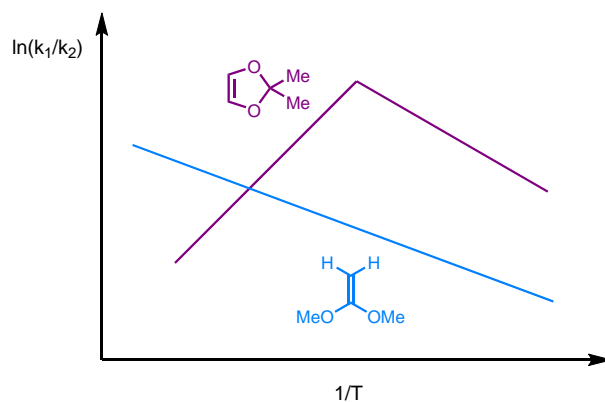
Linear correlation!

$$\delta\Delta\Delta S^\ddagger = T_i \delta\Delta\Delta H^\ddagger$$



- The **slope** has the dimensions of a temperature, defined as the **Isoinversion Temperature (T_i)**
- T_i is a characteristic **constant for the reaction studied** (for the Paternò-Büchi reaction, $T_i = 231 \text{ K}$)
- The **optimal value of selectivity** is expected at $T = T_i$ (debatable)

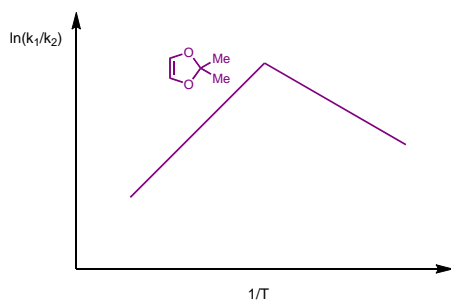
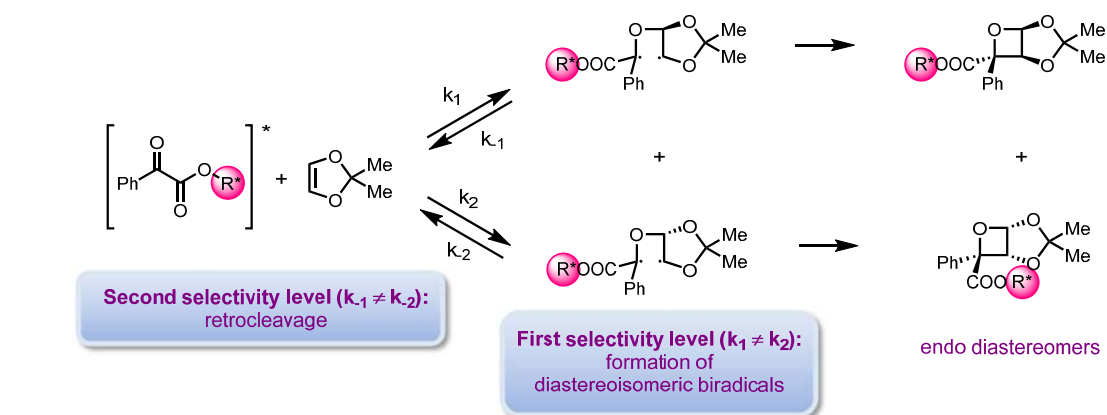
Why does T_{inv} occur?



Olefins with a C_2 axis perpendicular to the double bond display an inversion point

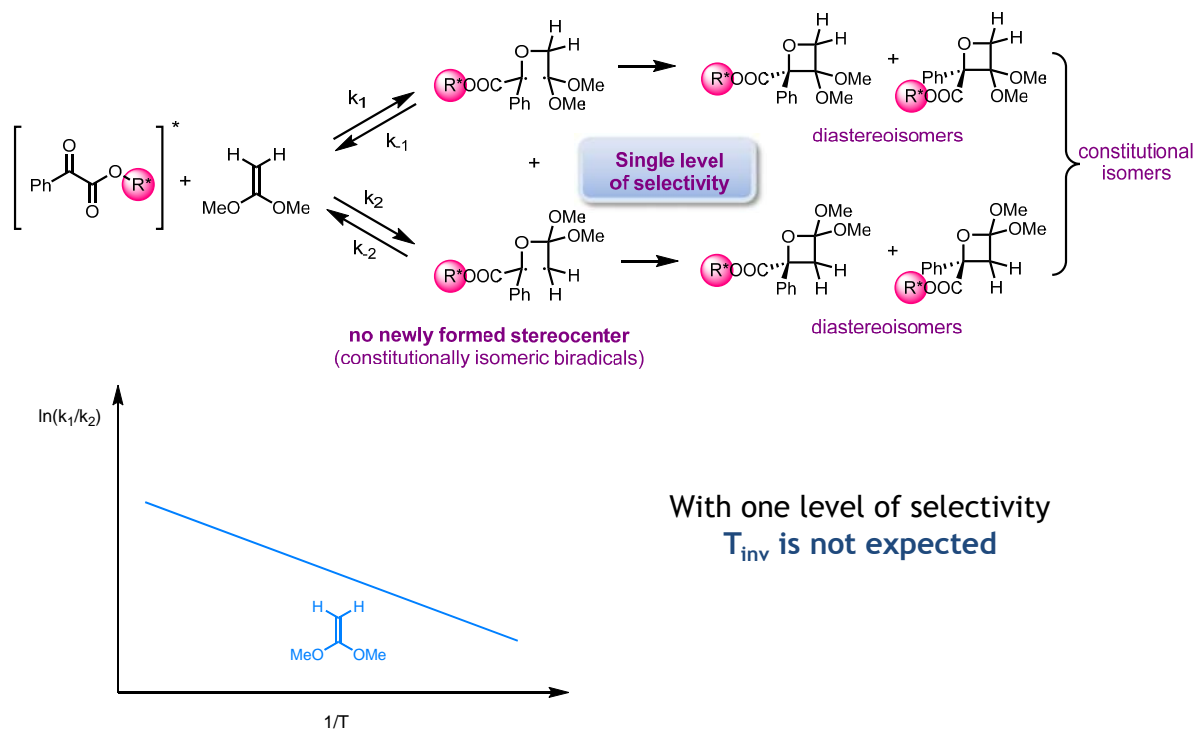
Olefins with a C_2 axis parallel to the double bond do not

Levels of diastereoselection



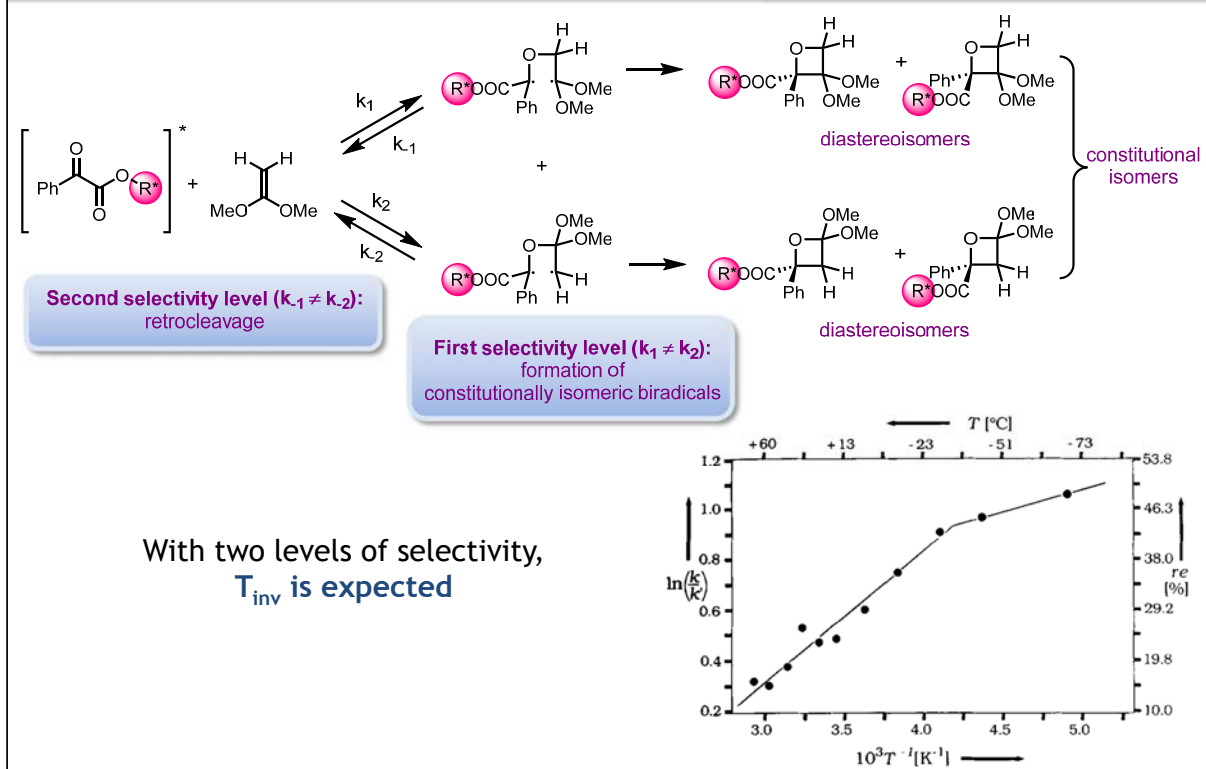
- The manifestation of T_{inv} implies a change in the selectivity-determining step
- At $T > T_{inv}$ ($\Delta\Delta H^\ddagger < 0$, $\Delta\Delta S^\ddagger < 0$) retrocleavage dominates
- At $T < T_{inv}$ ($\Delta\Delta H^\ddagger > 0$, $\Delta\Delta S^\ddagger \gg 0$) bond formation dominates

Levels of diastereoselection



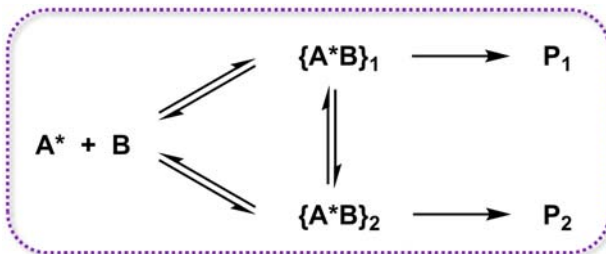
Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 477

Levels of regioselection



Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 477

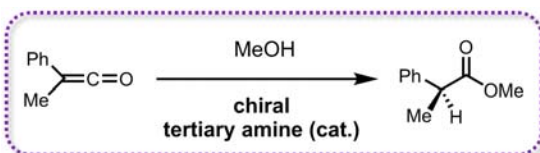
Generalization



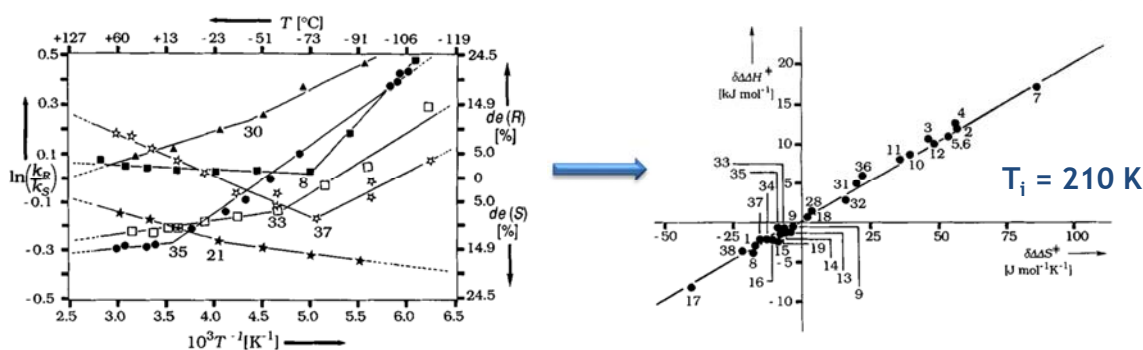
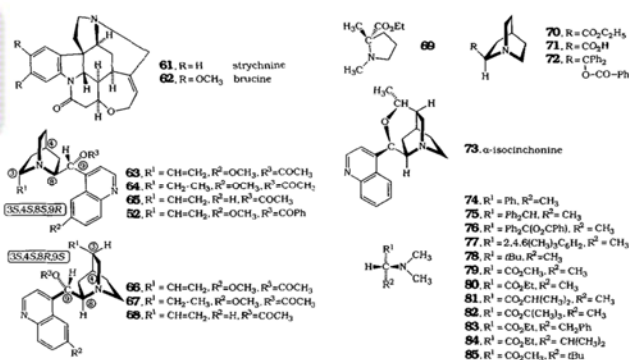
- Whenever **selectivity** is generated at two or more different levels, **inversion points** are expected in the Eyring diagram
- The isoinversion principle can be applied to **any kind of selective process** (stereo-, regio-, chemoselective)
- Stresses the **importance of temperature-dependent measurements of selectivity**
- Useful for the **optimization of reactions** and to **test mechanisms**

Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Reinterpreting Pracejus's results



Chiral amines:

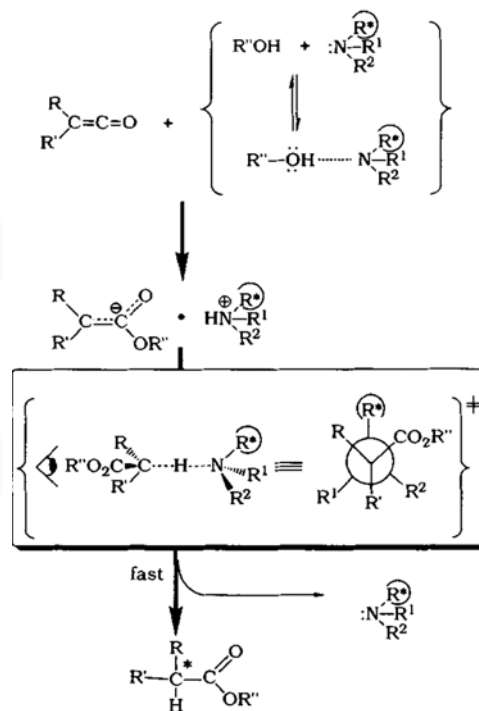


Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Reinterpreting Pracejus's results

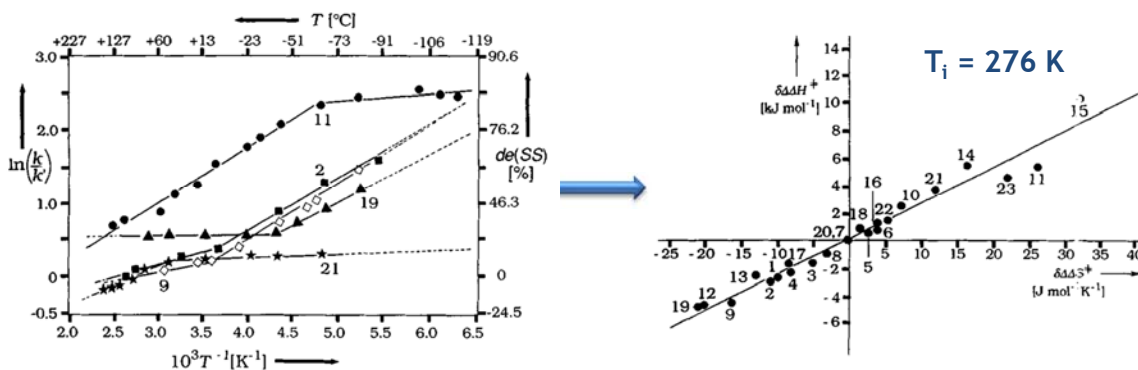
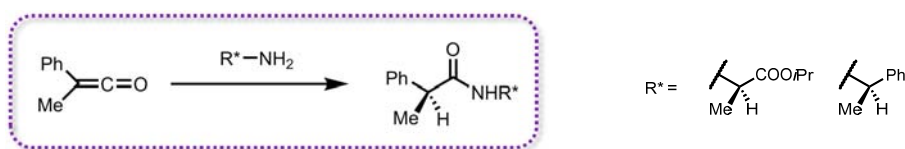
First selectivity level:
formation of a chiral adduct

Second selectivity level:
equilibration of conformers



Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Reinterpreting Pracejus's results

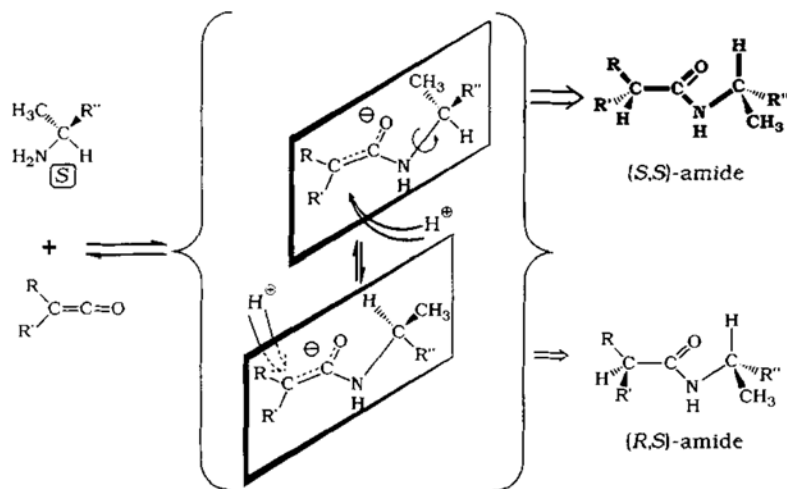


Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

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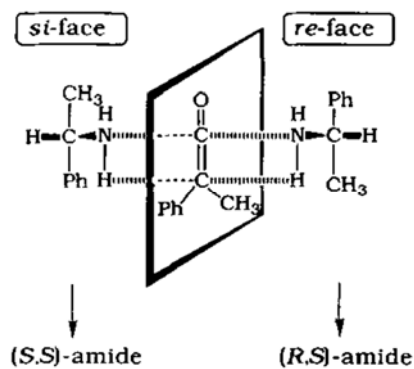
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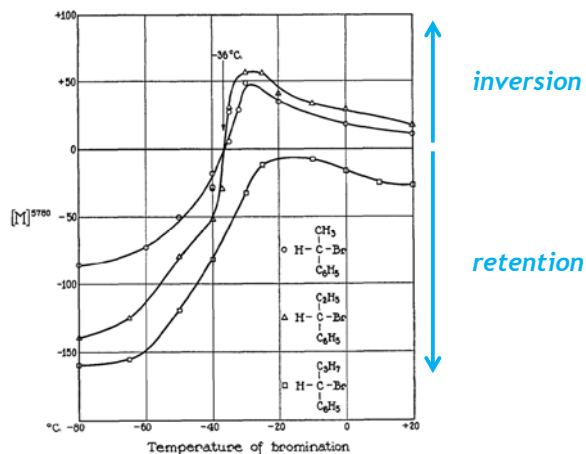
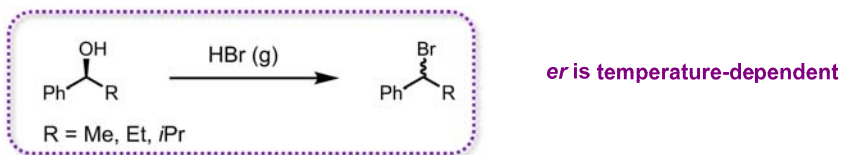
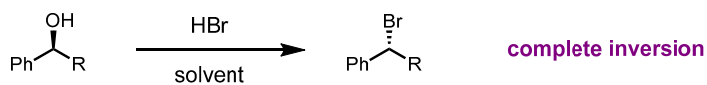
Reinterpreting Pracejus's results



*A concerted mechanism is ruled out
(no inversion point would be observed)*

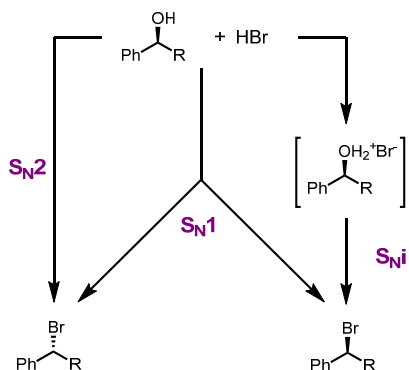
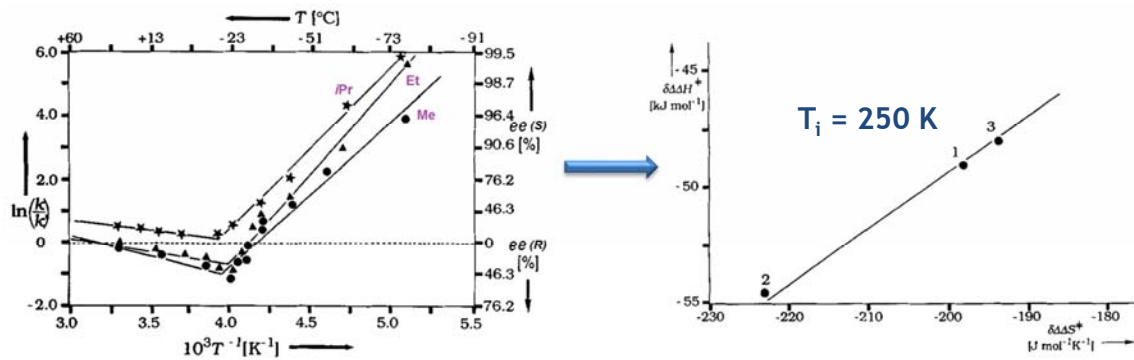
Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

Nucleophilic substitution



Levene, P. A.; Rothen, A. *J. Biol. Chem.* **1939**, *127*, 237

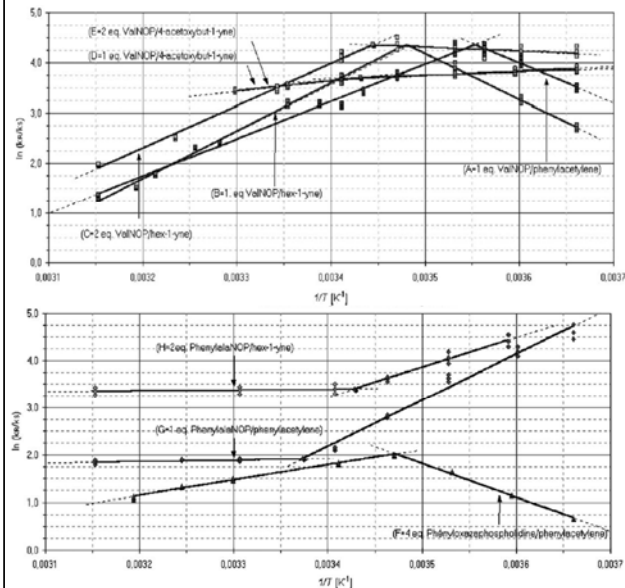
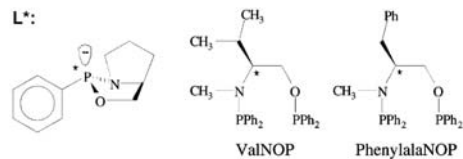
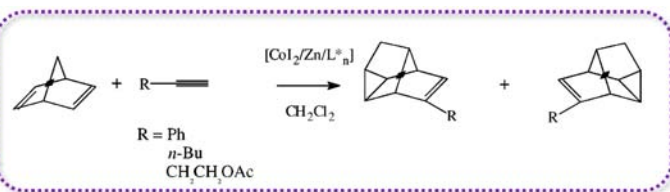
Nucleophilic substitution



Temperature-dependent interplay between competing reaction channels

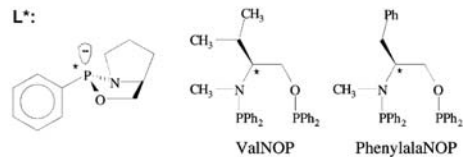
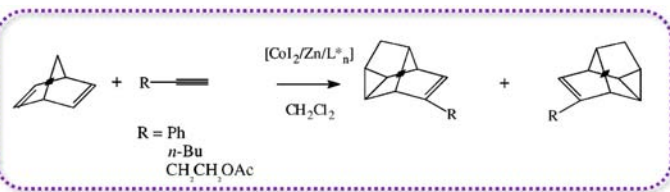
Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477

[2+2+2] cycloaddition - Group problem

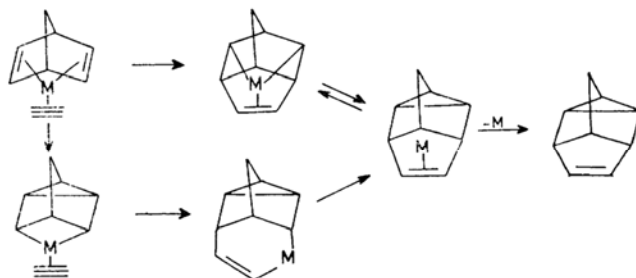


- Inversion points were found in all systems under examination ($T_{\text{inv}} = 8 - 23 \text{ }^\circ\text{C}$)
- The plot of $\delta\Delta\Delta H^\ddagger$ vs $\delta\Delta\Delta S^\ddagger$ furnished $T_i = 14 \text{ }^\circ\text{C}$

[2+2+2] cycloaddition - Group problem



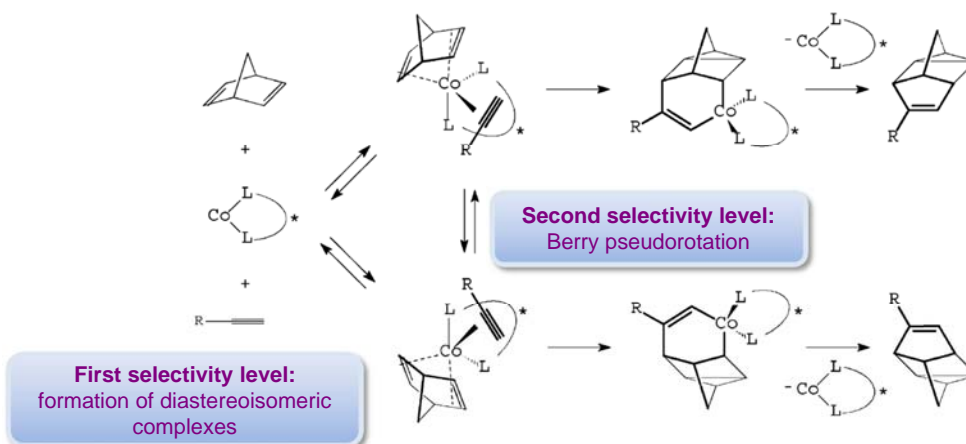
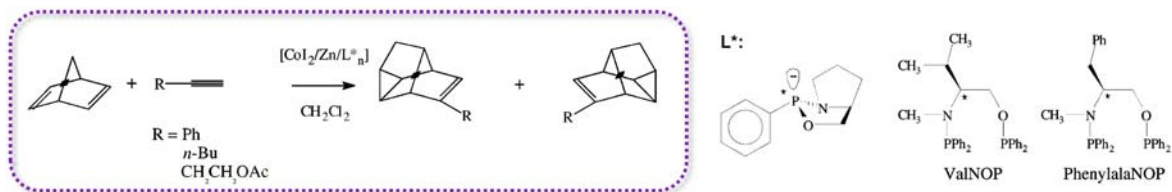
Plausible mechanisms:



Lyons, J. E.; Myers, H. K.; Schneider, A. J. *Chem. Soc., Chem. Commun.* **1978**, 636

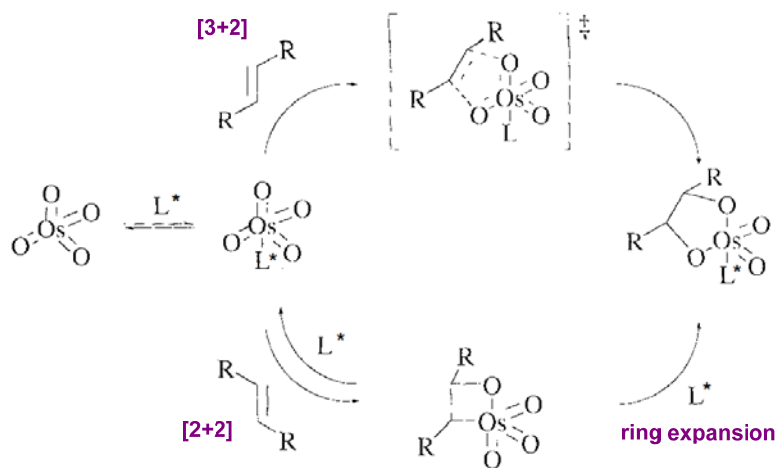
Explain the occurrence of inversion points.
Can either mechanism be ruled out?

[2+2+2] cycloaddition - Group problem



Pardigon, O.; Tenaglia, A.; Buono, G. *J. Mol. Catal. A: Chem.* **2003**, *196*, 157

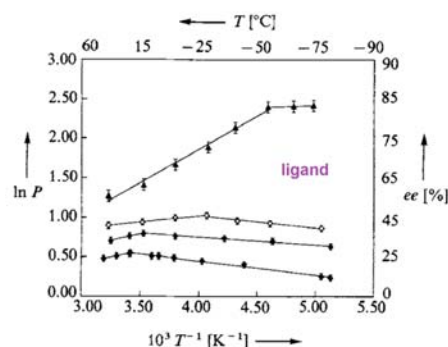
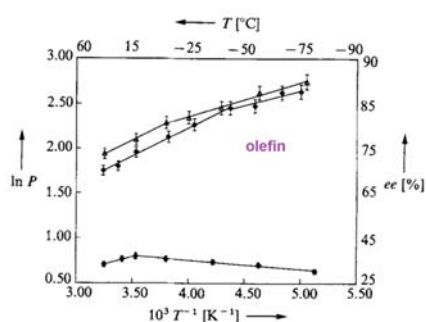
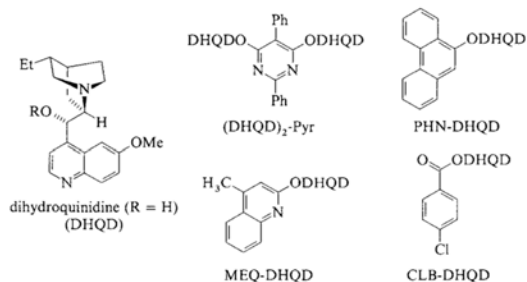
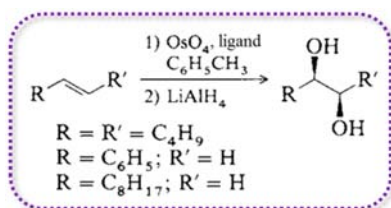
Sharpless asymmetric dihydroxylation



Concerted [3+2] or stepwise [2+2] and ring expansion?

Noe, M. C.; Letavic, M. A.; Snow, S. L. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004

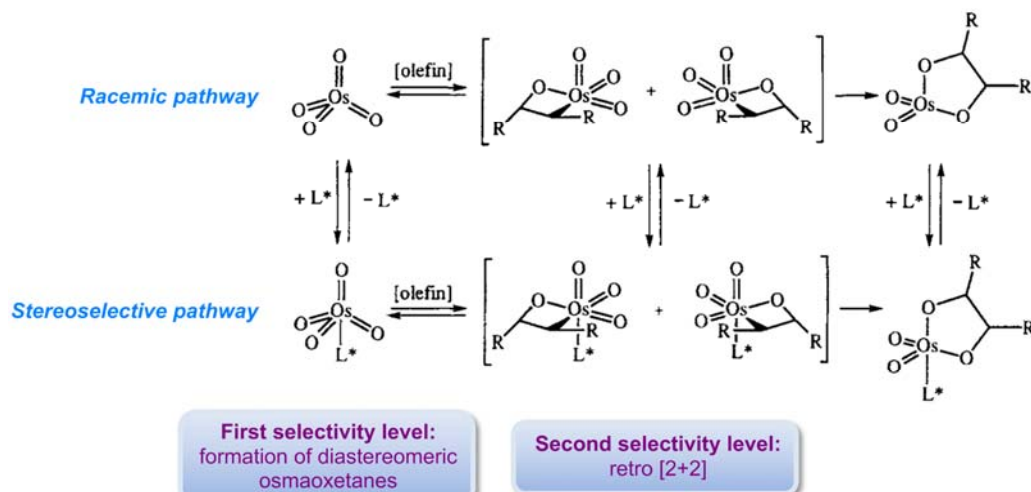
Sharpless asymmetric dihydroxylation



The occurrence of inversion points supports a stepwise mechanism

Göbel, T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1329

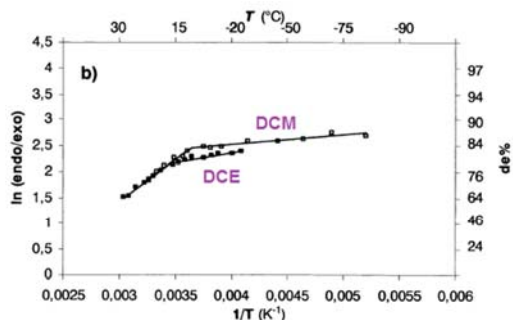
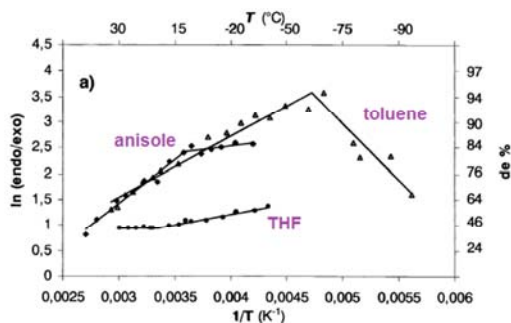
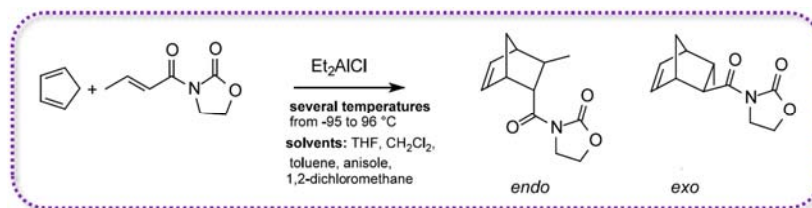
Sharpless asymmetric dihydroxylation



A stepwise [2+2] mechanism is in disagreement with more recent computational studies and KIE from natural abundance ¹³C NMR

Göbel, T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1329

Diels-Alder



CONTROVERSY!

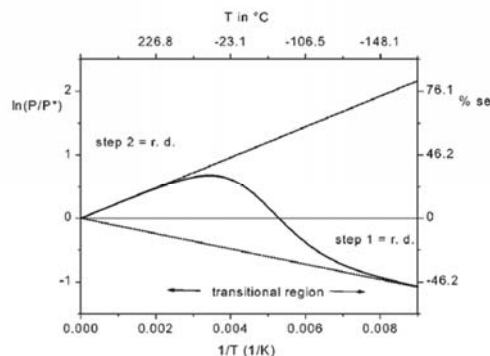
How to conciliate the existence of inversion points with the concerted mechanism of the Diels-Alder reaction?

Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* **2003**, 44, 93

Alternative interpretations

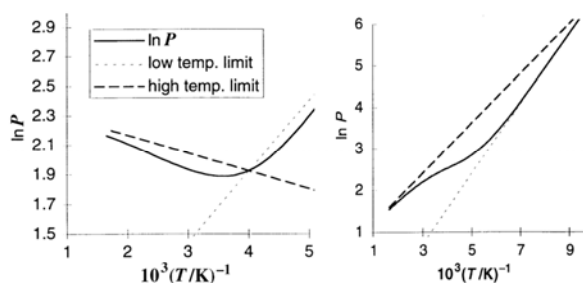
Ridd (1995):

- A sudden change in the dominance of selection levels is **unlikely**
- The inversion points are determined by the change from a rate-determining selection step to a **transitional region** where no single selection step is rate determining
- Plots of $\delta\Delta\Delta H^\ddagger$ vs $\delta\Delta\Delta S^\ddagger$ are necessarily linear and T_i has no simple physical meaning



Gypser (1997):

- Inversion points are physically significant only if the **inversion temperatures for the absolute rates are identical**
- If inversion points for the absolute rates differ, a formal inversion temperature can still be defined, but it has no physical meaning



Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1601
 Gypser, A.; Norrby, P.-O. *J. Chem. Soc., Perkin Trans. 2* **1997**, 939

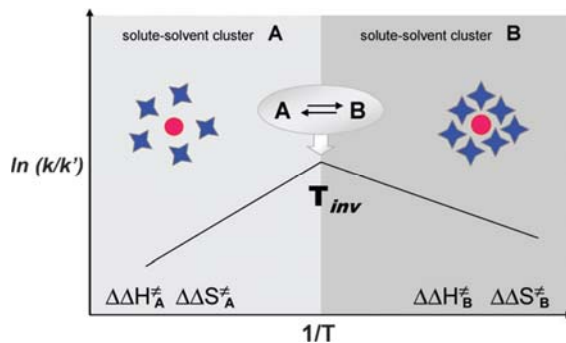
Alternative interpretations

Cainelli (1999):

- The models to rationalize stereoselectivity have a **limitation**: the reaction is considered to **occur in a vacuum**
- The **solvent effect** on stereoselectivity can be significant
- Even in the presence of weak solvation forces, the active chemical species is not the bare molecule, but **molecule-solvent clusters**
- T_{inv} constitutes a **transition between two different solute-solvent clusters**, which act as distinct species with different thermodynamic properties, reactivity and selectivity

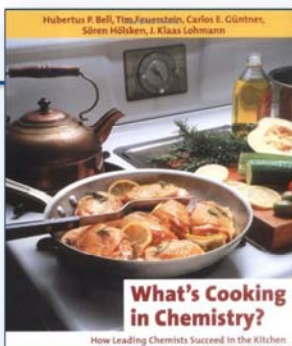


Gianfranco Cainelli



Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567
Cainelli, G.; Galletti, P.; Giacomini, D. *Chem. Soc. Rev.* **2009**, 38, 990

Alternative interpretations



What's Cooking in Chemistry?
How Leading Chemists Succeeded in the Kitchen

reactivity and

models to rationalize stereoselectivity have a **limitation**: the reaction is considered to **occur in a vacuum**

the **solvent effect** on stereoselectivity can be significant

Even in the presence of weak solvation forces, the active chemical species is not the bare molecule, but **molecule-solvent clusters**



Tagliatelle alla Bolognese

To make the pasta:

Starting materials (serves 4):

Pasta: 400 g flour pinch of salt
4 eggs
water

Sauce:

200 g peeled tomatoes
200 g minced meat
1 onion (not too large)
1 carrot
1 stalk of celery
5 tbsp white wine
extra virgin olive oil
salt, pepper

Knead 400 g flour, a pinch of salt, and 4 eggs with sufficient water to form a firm, smooth dough. Flour a worktop and, using a rolling pin and pasta maker, roll out until very thin. Roll up and cut into 10-mm wide strips of tagliatelle that should be as long as possible.

To make the sauce (ragù)

Concerning the meat, beef prevails, but also veal, pork, or turkey, and pancetta can be used.

Fry the finely chopped onion, carrot, and celery in a few tbsp of olive oil until brown.

Browning is the taste foundation of the ragù. Slow browning over low heat brings out the sweetness of the onion and carrot, while fast browning over high heat yields punchier, more robust flavors. Browning on medium heat strikes a balance between the two and is preferable.

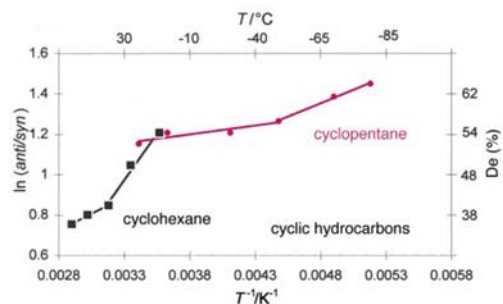
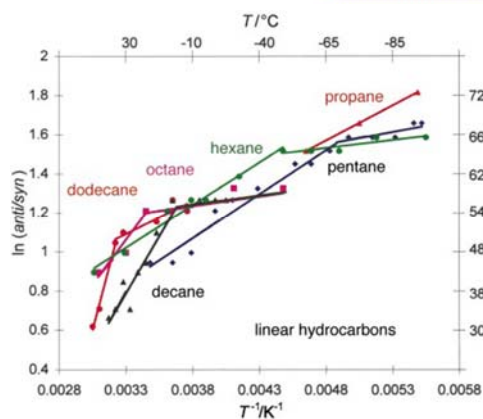
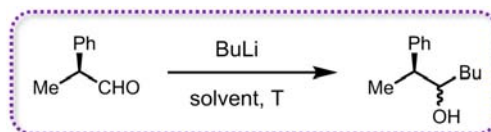
Once the onion begins to color, add the meat. Beef is often used by itself in Bologna, although it is frequently blended with veal, pork, turkey, and pancetta. After a few minutes pour in the wine. When evaporated, add the chopped tomatoes and season with salt and pepper. Cook over moderate heat for at least 2 hours. Cook tagliatelle in plenty of hot, salted water until "al dente" (in general, no more than 5 min). Drain tagliatelle, add the ragù, and serve with freshly grated parmesan cheese. Some people prefer the dish without.

«In Bologna alone, you will find hundreds of variations on the theme of ragù.»

«Tagliatelle are noodles about 10 mm wide. If the noodles are 5 mm wide, they are called fettuccine. Fettuccine are used in southern Italy, especially in Rome, but in northern Italy, and particularly in Bologna, the tagliatelle are much more common. The people of Bologna maintain that they are good only if they are prepared completely by hand, and all women, including most of the young ones, are capable of preparing tagliatelle using the rolling pin with masterly skill.»

Gianfranco Cainelli

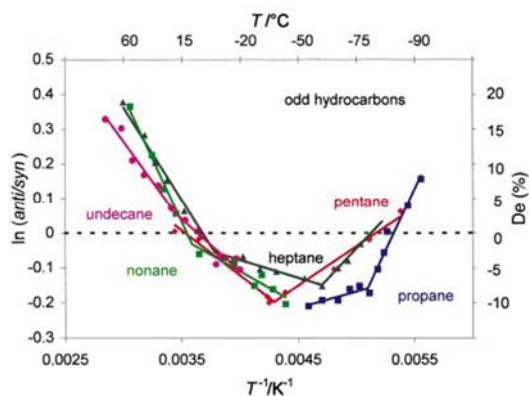
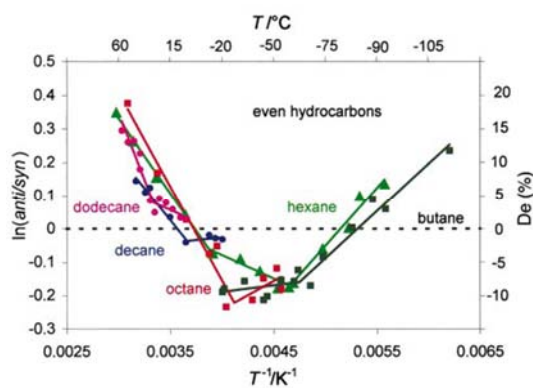
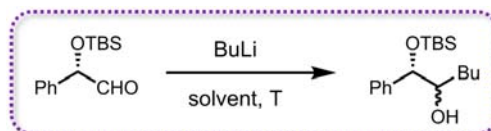
Effect of the solvent



- The longer the chain, the lower the d_r
- At low T , the facial selectivity is **entropy-driven** (flat line)
- At high T , the facial selectivity is **enthalpy-driven** (steep line)

Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2849

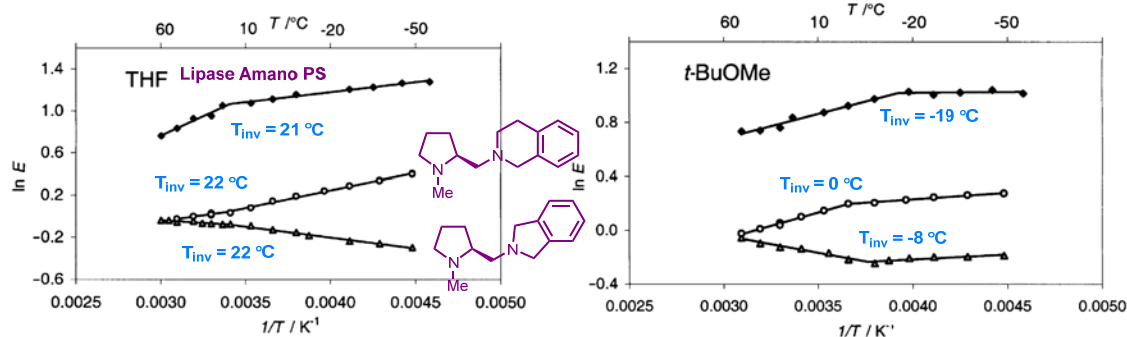
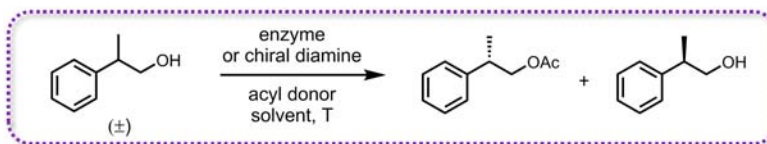
Effect of the solvent



- A temperature-dependent **reversal of selectivity** is observed
- **Multiple inversion points** are observed for hexane and heptane; it is unlikely that a double change in the mechanism or selectivity-determining step occurs

Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567

Effect of the solvent

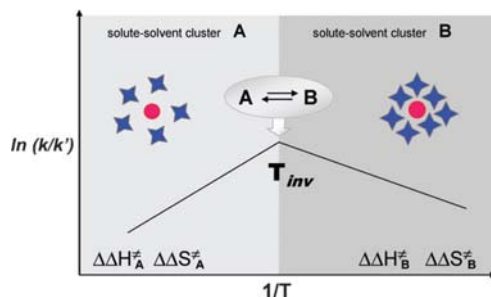


- In THF, T_{inv} values are similar for the bio- and chemo-catalyzed reaction
- T_{inv} is independent of the particular reaction system, but tightly related to the nature of the substrate-solvent pair

Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Quintavalla, A. *Helv. Chim. Acta* **2003**, *86*, 3548

Molecule-solvent clusters

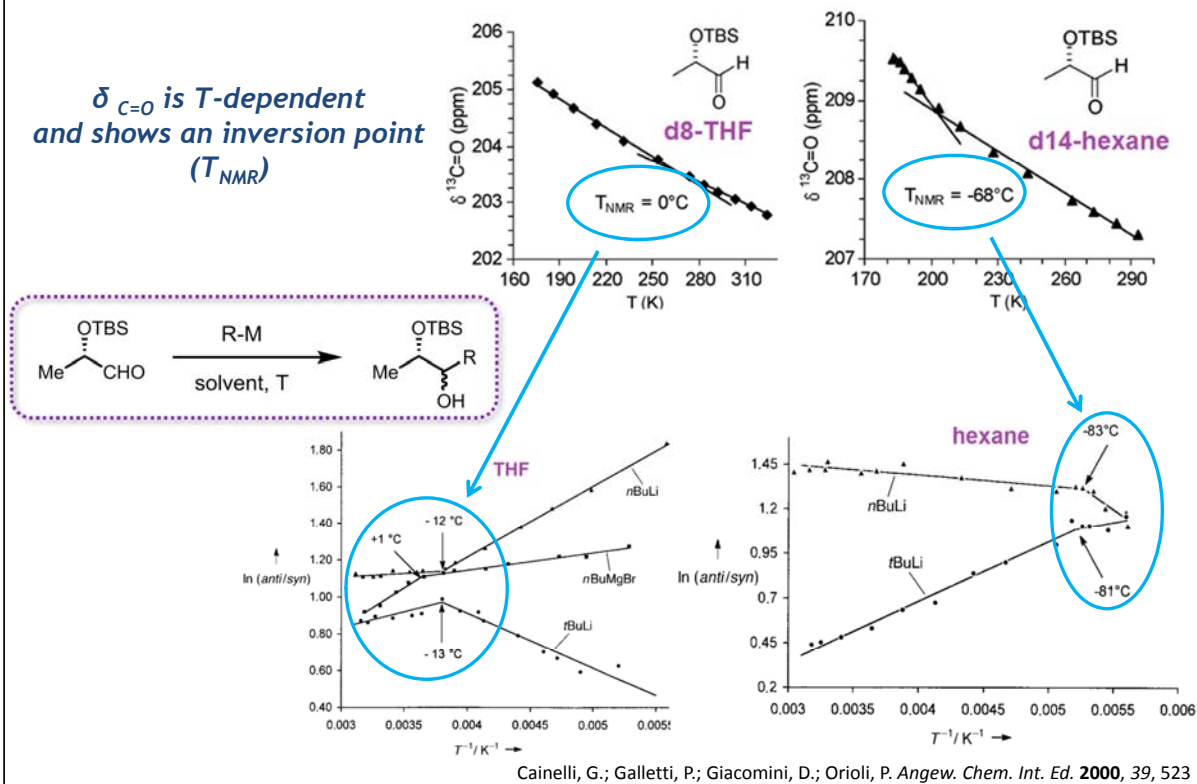
- Inversion points are due to the transition between two phases, represented by two distinct molecule-solvent clusters
- The interconversion of solvation clusters could involve an internal rearrangement or a solvent shell reorganization with transfer of solvent molecules to the medium
- Because of the complexity of the solvation process, it is difficult to formulate a detailed microscopic model of molecule-solvent clusters
- T_{inv} does not imply a change in the selectivity-determining step or in the reaction mechanism



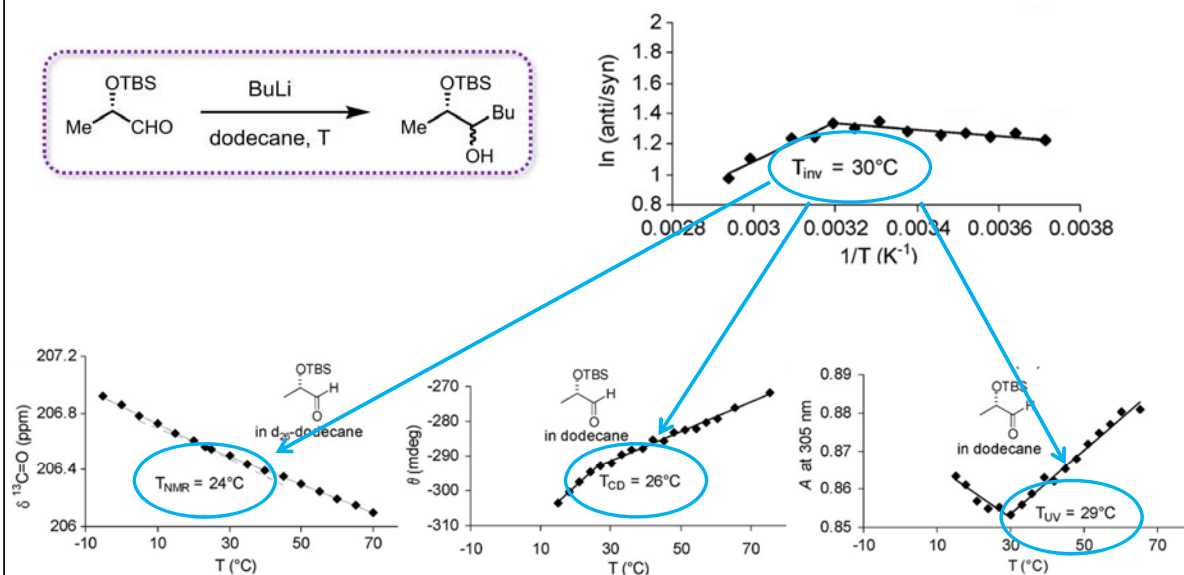
Cainelli, G.; Galletti, P.; Giacomini, D. *Chem. Soc. Rev.* **2009**, *38*, 990

Experimental evidence - NMR

$\delta_{C=O}$ is T -dependent
and shows an inversion point
(T_{NMR})



Experimental evidence - UV and CD



These results reinforce the hypothesis that T_{inv} corresponds to a transition between two different solvation states

Summary

- The occurrence of inversion points is **very common** through a variety of selective processes
- The phenomenon of inversion and its significance is still a **matter of debate** (change in the selectivity-determining step *vs* equilibrium of molecule-solvent clusters)
- Regardless of the physical meaning of T_{inv} , the optimization of a selective process **should always involve temperature-dependent studies**

References

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- *Solvent effects on stereoselectivity: more than just an environment*
Cainelli, G.; Galletti, P.; Giacomini, D. *Chem. Soc. Rev.* **2009**, *38*, 990
- *Selectivity from a kinetic point of view: nonlinear behavior of logarithmic product ratios as a function of the reciprocal temperature*
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