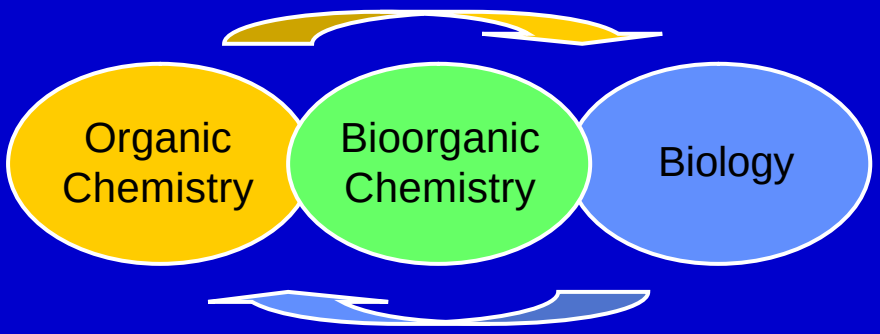
Bio-Organic Aspects of Catalysis

Understanding of biological phenomena at the precision level of organic-chemical methods



Inspiration for the design of biomimetic transformations and catalysts
- combinatorial methods -

Bio-Inspired Catalysis of Hydrogenation and Oxidation

Hydrogenation:

- The metal-free hydrogenase from methanogenic archaea and its mechanism of hydrogen activation
- The base-catalyzed hydrogenation of ketones

Oxidation:

- Recent news from the ruthenium porphyrin area
- On the mechanism of the Julià-Colonna epoxidation of enones

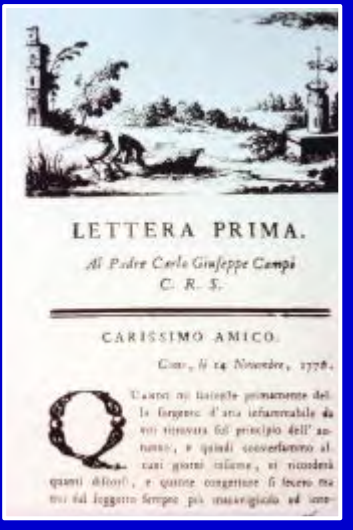
*See also posters by **Marc Andreae (no. 4)**, **Katja Glaubitz (no. 30)** and **Thomas Müller (no. 53)**!*

The metal-free hydrogenase from methanogenic archaea and its mechanism of hydrogen activation

The base-catalyzed hydrogenation of ketones

Biological Methanogenesis in Sweetwater Sediments

Annual production of CH_4 by methanogens : ca. 10^9 t



LETTERA PRIMA.

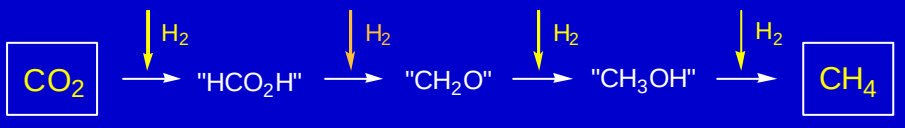
Al Padre Carlo Giuseppe Campi C. R. S.

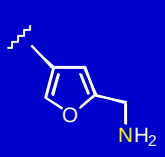
CARISSIMO AMICO.

Cons, li 14 Novembre, 1776.

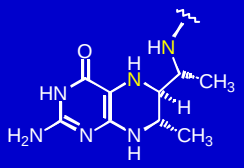
Q

Reduction of CO_2 by Methanogenic Archaea





Methanofuran

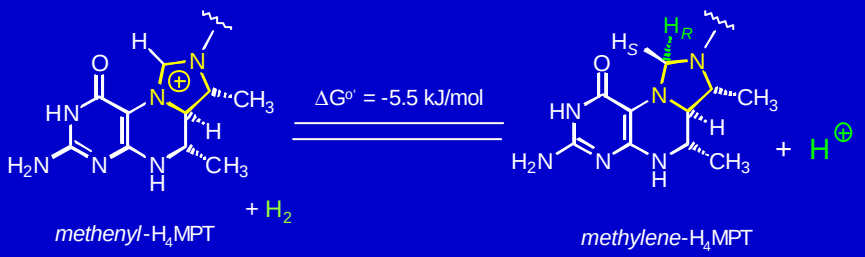


Tetrahydromethanopterin

Coemzyme M

The Metal-Free Hydrogenase from Methanogenic Archaea

„H_2-forming methylene tetrahydromethanopterin dehydrogenase“
„MFH“



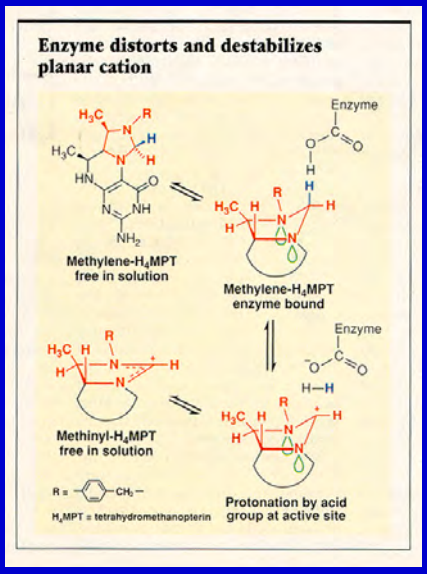
methenyl-H_4MPT

methylene-H_4MPT

- stereospecific addition/removal of hydride
- no transition metal involved in H_2-heterolysis

discovery: C. Zirngibl, R. Hedderich, R. K. Thauer, *FEBS Lett.* **1990**, *261*, 112-116;
reviews: R. K. Thauer, A. R. Klein, G. C. Hartmann, *Chem. Rev.* **1996**, *96*, 3031-3042;
A. Berkessel, *Curr. Opinion Chem. Biol.* **2001**, *5*, 1251-1257.

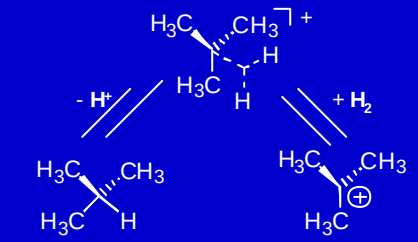
A First Mechanistic Proposal: Analogies to Carbocation Chemistry



A. Berkessel, R. K. Thauer,
Angew. Chem. **1995**, *107*, 2418;
Angew. Chem. Int. Ed. Engl. **1995**, *34*, 2247.

Hydrogenase catalyze proton mechanism

OCTOBER 30, 1995 C&EN 7



G. A. Olah, N. Hartz, G. Rasul, G. K. Surya Prakash,
J. Am. Chem. Soc. **1995**, *117*, 1336;
H. Hogeveen, C. J. Gaasbeek,
Rec. Trav. Chim Pays-Bas **1968**, *87*, 319.

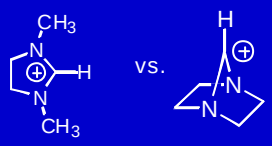
Theoretical Studies on the Mechanism of MFH

our study (1998)

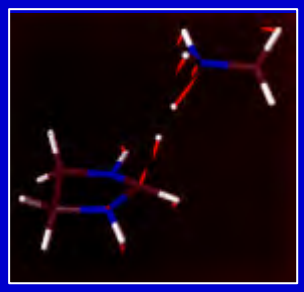
- Amine base as the primary and bulk water as the final proton acceptor
- Approximate thermoneutrality is reproduced
- Exp. activation barriers for MFH: 35-70 kJ/mol. Calculated: ca. 74 kJ/mol

Cioslowski, Boche (1997)

- Puckering of the five-membered ring as a possibility to tune the Lewis-acidity of the cation



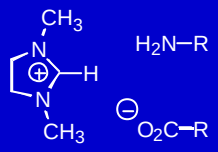
J. Cioslowski, G. Boche,
Angew. Chem. **1997**, *109*, 165-167,
Angew. Chem. Int. Ed. Engl. **1997**, *36*, 107-109



J. H. Teles, S. Brode, A. Berkessel,
J. Am. Chem. Soc. **1998**, *120*, 1345-1346

Scott, Golding, Radom (1998)

- Amines and carboxylates are equally well suited as primary proton acceptors.



A. P. Scott, B. T. Golding, L. Radom,
New J. Chem. **22**, 1171-1173 (1998)

The Walling-Bollyky Experiment...

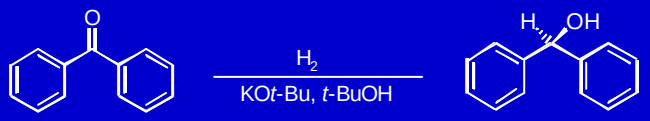
C. Walling, L. Bollyky, *J. Am. Chem. Soc.* **1961**, *83*, 2968-2969

BASE CATALYZED HOMOGENEOUS HYDROGENATION

Sir:

Although the reaction of molecular hydrogen with unsaturated organic molecules at moderate temperatures is generally energetically feasible, a potential barrier to the process exists which is only overcome by the use of heterogeneous catalysts or certain transition-metal complexes in homogeneous systems.[1]

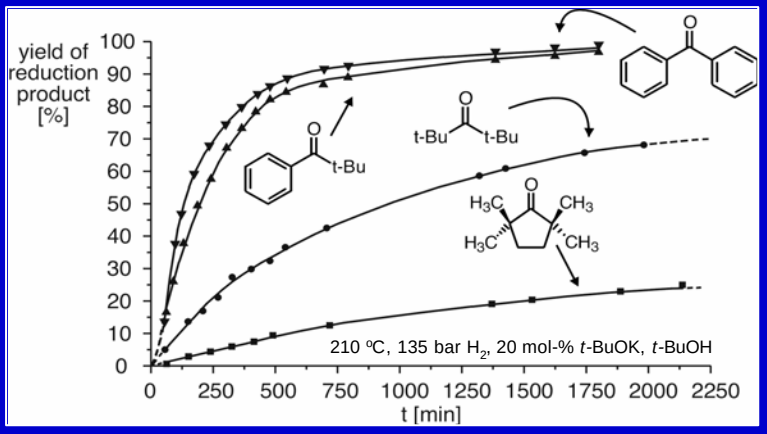
We now report such a base-catalyzed homogeneous hydrogenation, achieved by heating benzophenone in *tert*-butyl alcohol solution containing potassium *tert*-butoxide at 200° under 1300–2000 lb./in.² hydrogen pressure. Hydrogen is slowly absorbed and benzhydrol obtained in 40–60% yield, determined by gas chromatography, and identified by retention time, infrared spectra, and mixed melting point. No further reduction to diphenylmethane is detected.



In the base catalyzed reaction we believe it is the hydrogen which is activated by conversion to hydride ion.

Base-Catalyzed Hydrogenation of Ketones

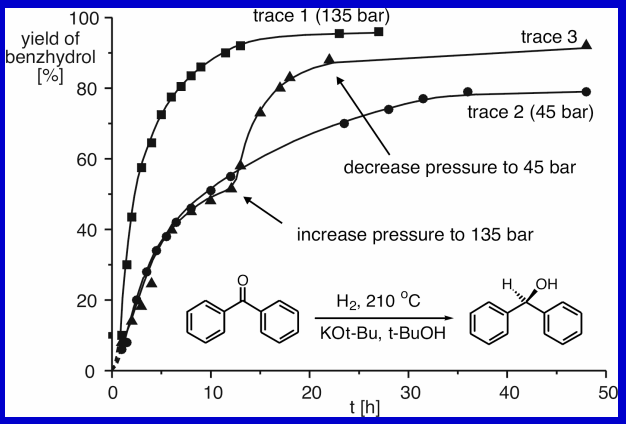
- substrates other than benzophenone -



A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc.* **2002**, *124* 8693-8698

Base-Catalyzed Hydrogenation of Ketones

- the reaction is irreversible....

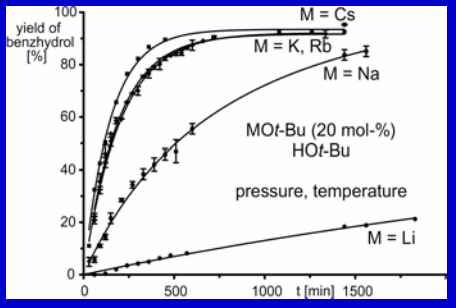


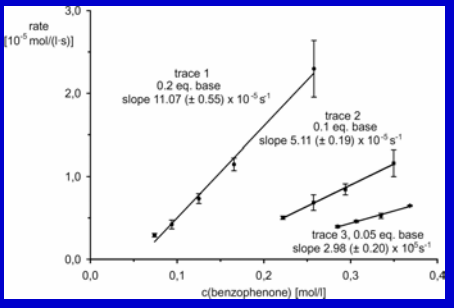
A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc.* **2002**, *124* 8693-8698

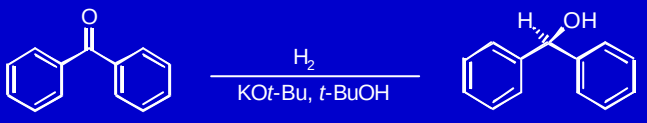
Base-Catalyzed Hydrogenation of Ketones

... the type of alkali ion strongly affords the the rate of reduction...

...and the reaction is first order both in substrate and base.



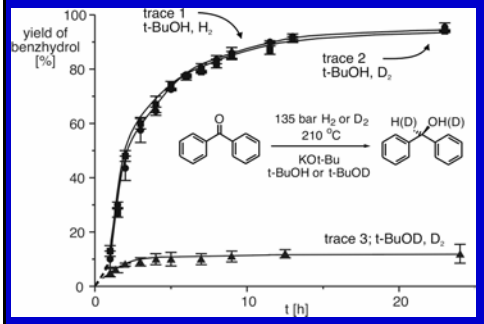


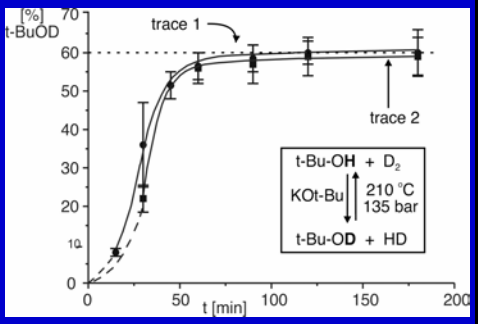


A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc.* **2002**, *124* 8693-8698

Base-Catalyzed Hydrogenation of Ketones

....deuterium vs. hydrogen...





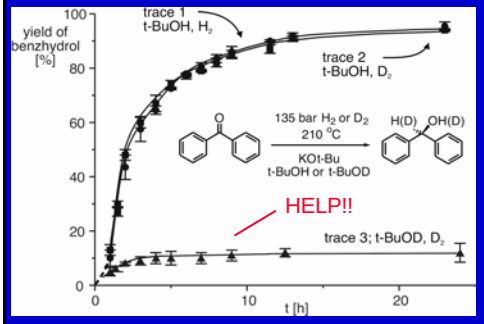
no difference in rate of H_2 vs. HD uptake

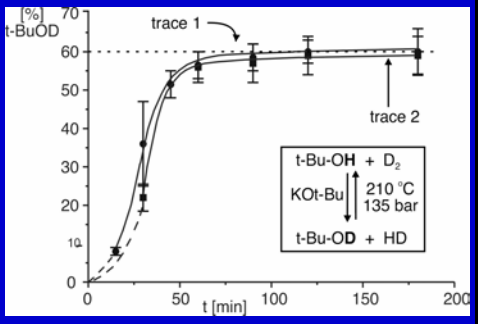
base-catalyzed isotope exchange between the gas phase and the solution

A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc*. **2002**, *124* 8693-8698

Base-Catalyzed Hydrogenation of Ketones

....deuterium vs. hydrogen...





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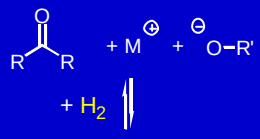
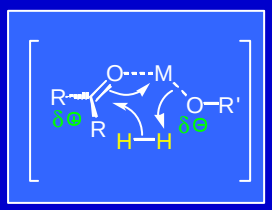
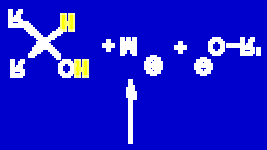
A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc*. **2002**, *124* 8693-8698

A mechanistic proposal.....

...for the base-catalyzed hydrogenation of ketones...

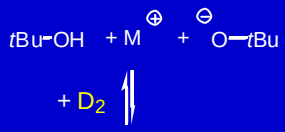


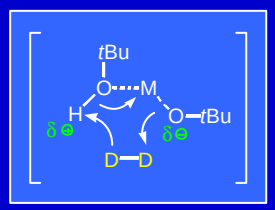


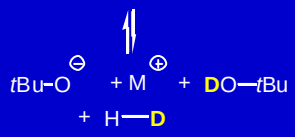


R': *t*Bu- or Ph_2CH-

...and the base-catalyzed isotope exchange with the solvent

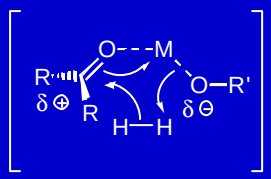




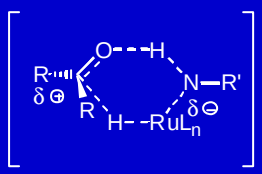


Base-Catalyzed Hydrogenation of Ketones

-analogies to ruthenium-catalyzed hydrogen transfer and hydrogenation -

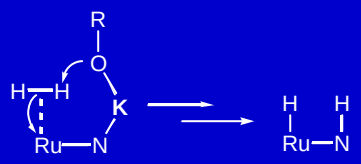


transition state proposed for the base-catalyzed hydrogenation of ketones



transition state proposed by *Noyori* for the transfer hydrogenation of ketones

e.g. R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2002**, *66*, 7931-7944



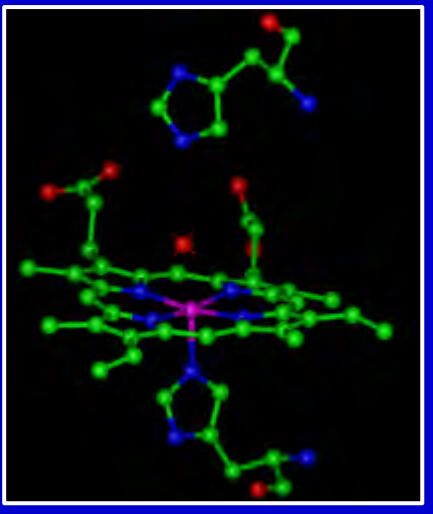
base-assisted heterolysis of hydrogen in the hydrogenation of ketones, as proposed by *Chen*

R. Hartmann, P. Chen, *Angew. Chem* **2001**, *113*, 3693-3697; *Angew. Chem. Int. Ed.* **2001**, *40*, 3581-3583.

Bio-inspired approaches
to novel catalysts for
asymmetric oxidations:

Recent news
from the ruthenium porphyrin field

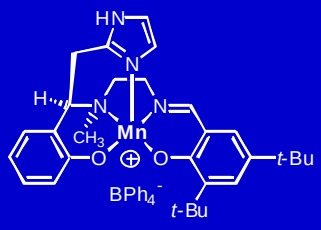
Cytochrome c Peroxidase from *Saccharomyces cerevisiae*

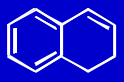


D. B. Goodin, D. E. McRee, *Biochemistry* **32**, 3313 (1993)

Models for Heme Peroxidases

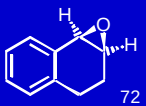
- pentadentate Mn-dihydrosalen complexes -





1 % aq. H_2O_2

10 mol-% catalyst



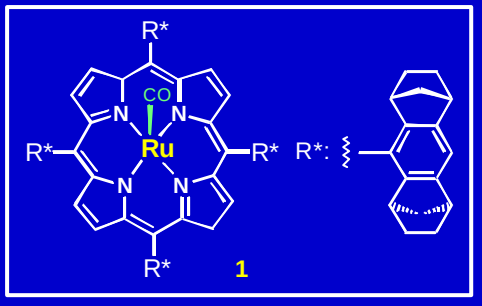
72 %, 66 % ee

A. Berkessel, M. Frauenkron, T. Schwenkreis, A. Steinmetz, G. Baum, D. Fenske, *J. Mol. Catal. A*, **113**, 321 (1996)

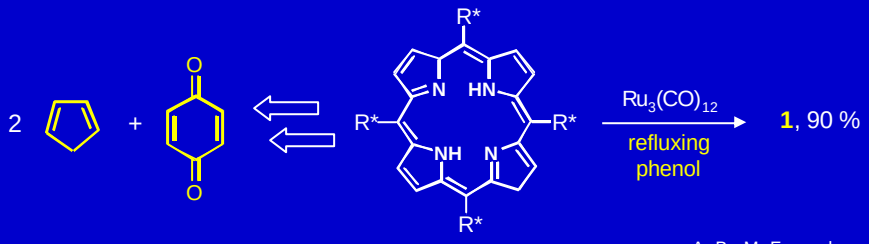
T. Schwenkreis, A. Berkessel, *Tetrahedron Lett.* **34**, 4785 (1993)

Asymmetric Catalysis with a Chiral Ruthenium Porphyrin

Synthesis of the catalyst...



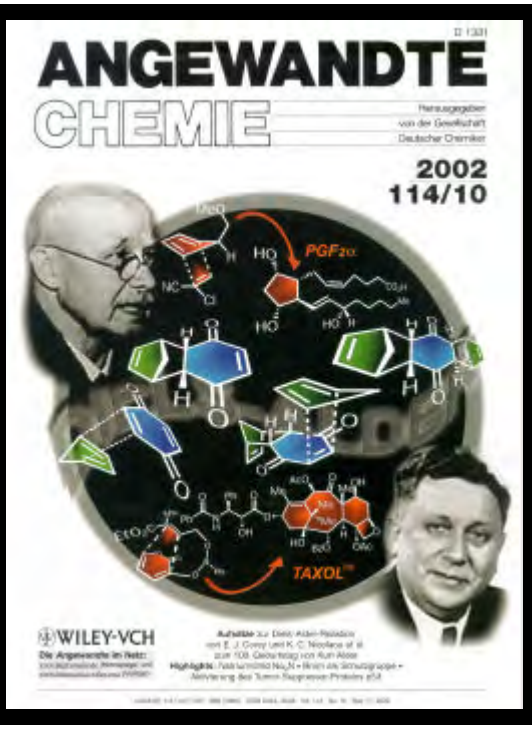
...poor (< 15 %) yields of Ru-insertion under standard conditions (e.g. benzene, toluene, decalin, diglyme...



W. Albrecht, *Liebigs Ann. Chem.* **348**, 31 (1906)

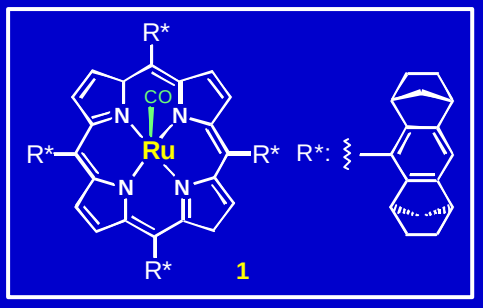
R. L. Halterman, S.-T. Jan, *J. Org. Chem.* **56**, 5253 (1991)

A. B., M. Frauenkron, *J. Chem. Soc. Perkin Trans. 1*, **1997**, 2265



Asymmetric Catalysis with a Chiral Ruthenium Porphyrin

Synthesis of the catalyst…



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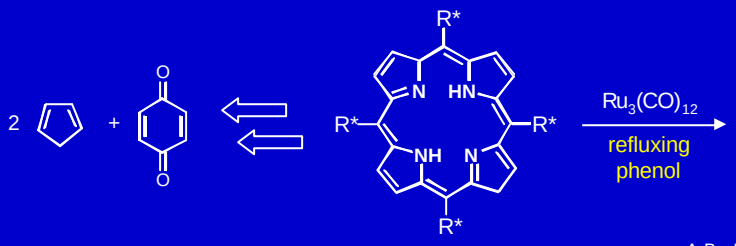
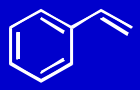
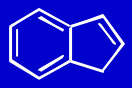
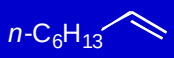


W. Albrecht, *Liebigs Ann. Chem.* **348**, 31 (1906)

R. L. Halterman, S.-T. Jan, *J. Org. Chem.* **56**, 5253 (1991)

A.B., M. Frauenkron, *J. Chem. Soc. Perkin Trans. 1*, **1997**, 2265

Asymmetric Epoxidation with a Chiral Ruthenium Porphyrin

olefin	yield [%]	ee [%]
	88	77 (1*R*,2*S*)
	79	70 (*S*)
	55	54 (1*R*,2*S*)
	5	5 (n.d.)
	5	0

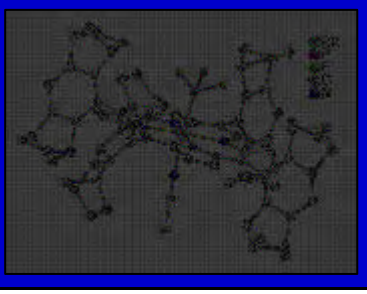
A. B., M. Frauenkron,
J. Chem. Soc. Perkin Trans. 1, **1997**, 2265

"Hirobe-conditions":

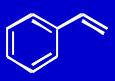
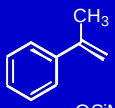
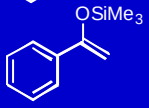
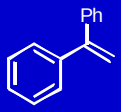
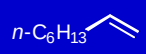
olefin (1000 eq.)
+
2,6-DCPNO, 1100 eq.
(2,6-dichloropyridine N-oxide)
+
Ru-porphyrin (1 eq.)

benzene, ca. 20 °C

M. Hirobe et al.,
e.g. *J. Am. Chem. Soc.* **114**, 10660 (1992)



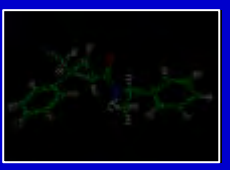
Asymmetric Cyclopropanation with a Chiral Ruthenium Porphyrin

olefin	yield of cyclopropanes [%]	*trans/cis*	ee *trans* [%]	ee *cis* [%]
	quant.	96:4	91 (1*S*,2*S*)	27 (1*S*,2*R*)
	quant.	66:34	90 (1*R*,2*R*)	38 (1*R*,2*S*)
	quant.	70:30	83	43
	60	- - -		95 (1*S*)
	42	99.5:0.5	82	6

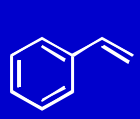
M. Frauenkron, A. B., *Tetrahedron Lett.* **38**, 7175 (1997)

olefin (1000 eq.)
+
ethyl diazoacetate, 1500 eq.
+
Ru-porphyrin (1 eq.)

1,2-dichloroethane,, 0 °C

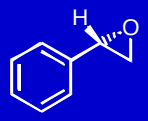


The Tetrakis-CF_3-Substituted Ruthenium Porphyrin....

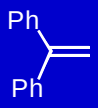


Hirobe-conditions

ca. 14.000 TTN
ca. 400 t.o./h

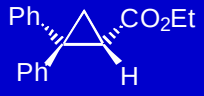


98 %, 83 % ee



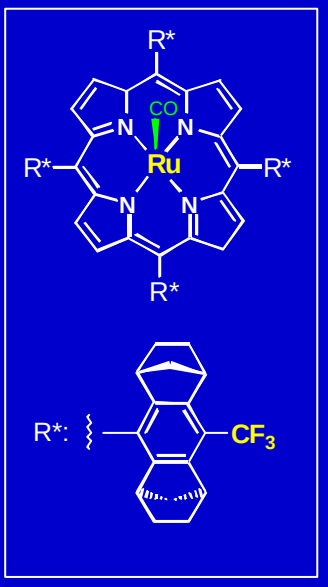
N_2CHCO_2Et
(1.1 eq.)

TTN ca. 7.500



94 %, 95 % ee

Patrick Kaiser



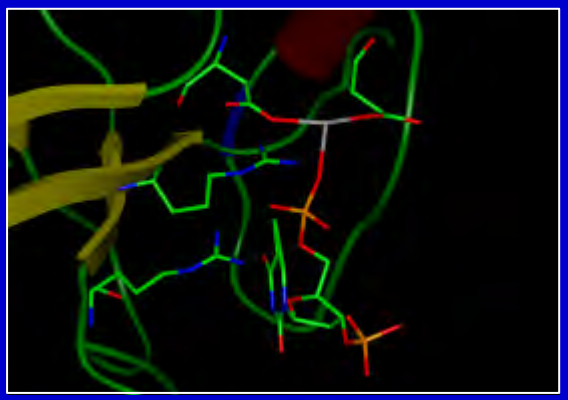
On the mechanism of the Juliá-Colonna-Roberts-epoxidation of enones

(first, a brief look at combinatorial approches to artificial hydrolase activity)

A Combinatorial Approach to Artificial Hydrolase Activity, I

- staphylococcal nuclease -

F. A. Cotton, E. E. Hazen, jr., M. J. Legg, *Proc. Natl. Acad. Sci. USA* **76**, 2551-2555 (1979)



- ion pairing of phosphate with guanidinium cations Arg 35, Arg 87

- coordination of phosphate to a *Lewis*-acidic metal ion (Ca^{2+}, coordinated by Asp 21, Asp 40)

- water molecule coordinated to the Ca^{2+}-ion

Reviews: e.g. N. Sträter, W. N. Lipscomb, T. Klabunde, B. Krebs, *Angew. Chem. Int. Ed. Engl.* **35**, 2024 (1996)

A Combinatorial Approach to Artificial Hydrolase Activity, I

- design and synthesis of an undecapeptide library -

X: Arg, His, Ser, Tyr, Trp $5^4 = 625$

P : TentaGel S-NH_2

HO_2C- - NH_2

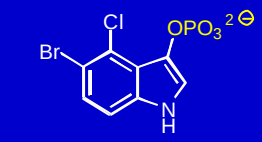
- split-mix-synthesis , Fmoc/PyBOP-protocol
- ca. 250 pmol peptide/bead

A. Berkessel, D. A. Hérault, *Angew. Chem. Int. Ed.* **38**, 102-105 (1999)

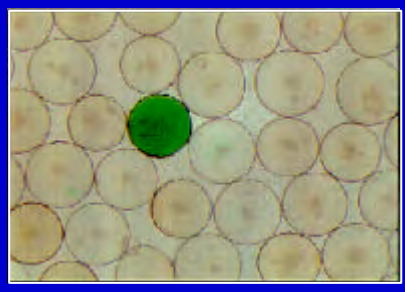
Bulk Screening of the Solid Phase-Bound Peptide Library

- incubation with transition metal ions and the test substrate -

- 10 mM EPPS-buffer, pH 5.6
- 1 mM indolyl phosphate
- 20 °C, 24 h



Insoluble indigo dye

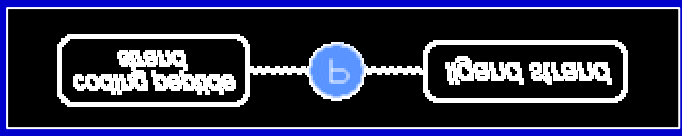


- 1 mM transition metal salts
- ratio peptide : metal ions ca. 1.2 : 1

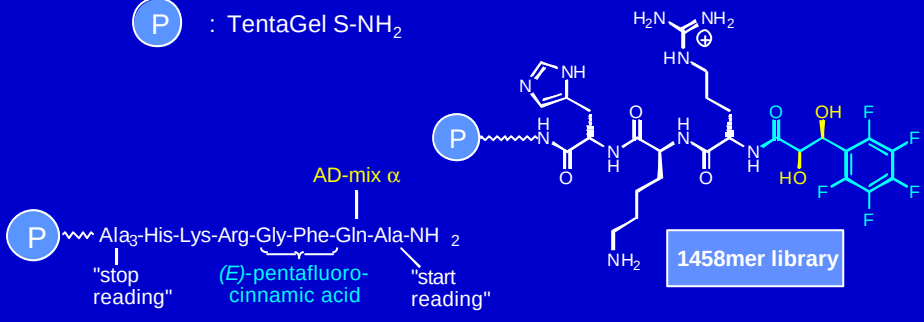
$CuCl_2$, $FeCl_3$•6 H_2O, $ZnCl_2$, $EuCl_3$•6H_2O, $ZrCl_4$, $(NH_4)_2Ce(NO_3)_6$, $Na_3[Co(NO_2)_6]$...

A Combinatorial Approach to Artificial Hydrolase Activity, II

- cleavage of phosphodiesters -



P : TentaGel S-NH_2

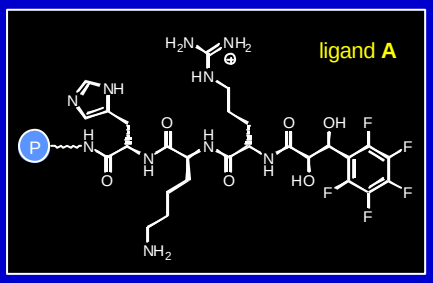


A. Berkessel, R. Riedl, *J. Comb. Chem.* **2**, 215-219 (2000)

Substructure-Activity-Analysis of the Ligands **A**,**B**

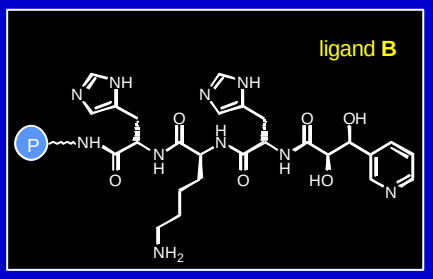
- the search for the minimal „catalophore“ -

...in the presence of Zn^{2+}...



Full length of ligand A required for activity; mutations /deletions are not tolerated

...in the presence of Eu^{3+}...



TentaGel-bound His is the minimal structural requirement!

Questions and opportunities:

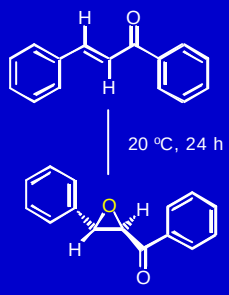
- Novel coordination chemistry with solid-phase bound ligands?
- Novel „entatic states“, catalysts resulting from solid-phase attachment (as opposed to the immobilization of e.g. known TM complexes)
- Minimal „catalophore“ of established oligomeric catalysts?

The Juliá-Colonna-Roberts-Epoxidation of Chalcones

- an amazingly simple and efficient protocol -

Triphasic system, composed of

- 30 % H_2O_2, NaOH
- organic solvent, e.g. toluene, DCM
- poly-amino acid, e.g. poly-*L*-Ala, *L*-Leu



85 %, 93 % ee
[(2*R*,3*S*) for poly-*L*-Ala]

Discovery:

S. Juliá et al., *Angew. Chem. Int. Ed. Engl.* **19**, 929 (1980);
S. Colonna et al., *J. Chem. Soc., Perkin Trans. I,* **1982**, 1317

Poly-Amino Acid-Catalyzed Epoxidation of Chalcones

- further development of the Julià-Colonna-method -

Empirical improvement of preparative aspects :

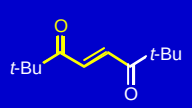
- Immobilisation of the poly-amino acid catalysts on solid supports (e.g. polystyrene, silica gel) results in easy separation of the catalyst, recycling is possible. Poly-amino acids are statistic mixtures with a maximum population typically at the 20-25 mers.
- Biphasic conditions allow for much shorter reaction times (= 1h): urea - H_2O_2 - 1,8-diazabicyclo[5.4.0]undec-7-ene (stoich.) - THF, or sodium percarbonate as the source of oxygen.

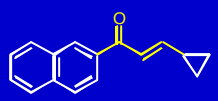
Recent Reviews :

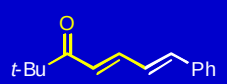
L. Pu, *Tetrahedron: Asymmetry* **9**, 1457 (1998);
M. J. Porter, J. Skidmore, *J. Chem. Soc., Chem. Commun.* **2000**, 1215.

Poly-Amino Acid-Catalyzed Epoxidation of Chalcones

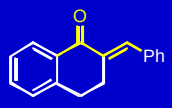
- current limitations of the Juliá-Colonna-Roberts-method -

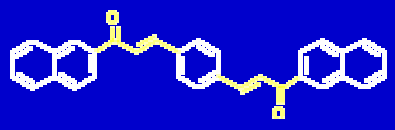


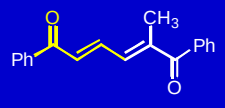




excellent yields and ees...



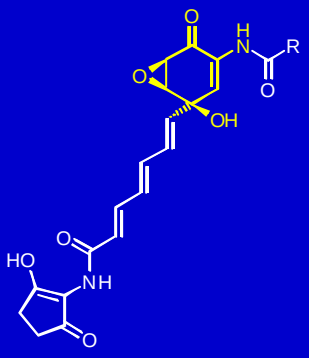




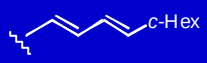
- despite extensive empirical optimization, the method is still applicable *only* to *E*-chalcones and related substrates.
- in particular, no *Z*-enones or cyclic enones can be used.
- a catalyst with a broader substrate spectrum is highly desirable.....

...e.g. for the synthesis of biologically active quinone epoxides in enantiomerically pure form...

R. J. K. Taylor,
see e.g.
J. Org. Chem. **63**,
3526 (1998)

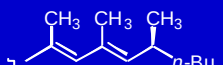


R:



Alisamycin

R:



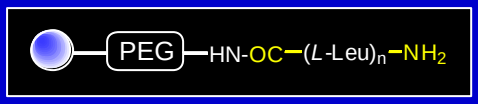
Manumycin

ras-farnesyltransferase inhibitors

„Understanding the mechanism of the Juliá-Colonna oxidation is the key to the application of the methodology to a broader range of substrates“, S. Roberts, *Chem. Comm.* **1998**, 1159.

Epoxidation of Chalcone with Polymer-Bound *L*-Leu

- effect of chain length on rate and enantiomeric excess -

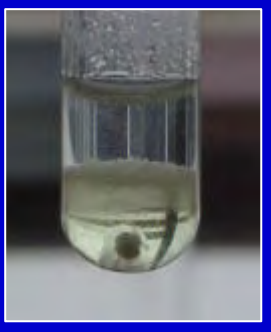


n = 1-20

peptide synthesis
on solid phase by
Fmoc/PyBOP protocol

Reaction conditions:

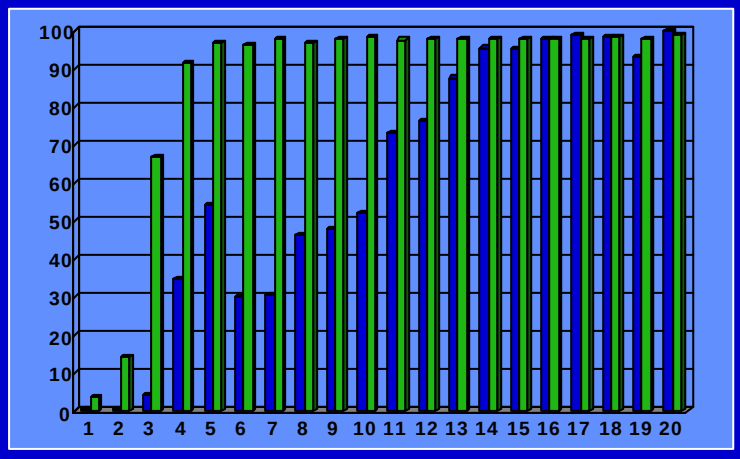
- 2.0 ml of 20 % aq. H_2O_2 / 2.6 M NaOH
- 40 mg (192 µmol) chalcone in 1.6 ml of dichloromethane
- TentaGel-bound peptide (21.9 µmol peptide)
- thermostatted at 20 °C, constant stirring rate
- analysis by HPLC on Whelk O-1



Epoxidation of Chalcone with Polymer-Bound *L*-Leu

- effect of chain length on rate and enantiomeric excess -

oligo-*L*-Leu bound to TentaGel S-NH_2

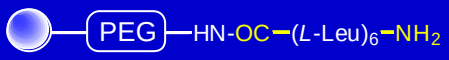


Epoxidation of Chalcone with Polymer-Bound *L*-Leu

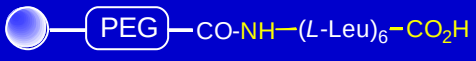
Whatever determines enantioselectivity does not require more than 5 amino acids, but the fraction of „active state" of the peptide increases with increasing chain length and levels off at n ca. 12.

The question of N- vs. C-terminus:

„normal" hexamer: 98 % ee, 38 % yield after 24 h



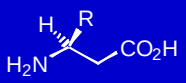
„inverse" hexamer: 12 % ee, ca. 1 % yield after 24 h



N-terminal region - and one loop of the helix seems to be sufficient....

Oligomers of β-Amino Acids

- β-Leu and *trans*-2-aminocyclohexane carboxylic acid -



β-Leu, R = *i*-Bu

Seebach et al., e.g.
Helv. Chim. Acta **81**,
932, 2218 (1998)

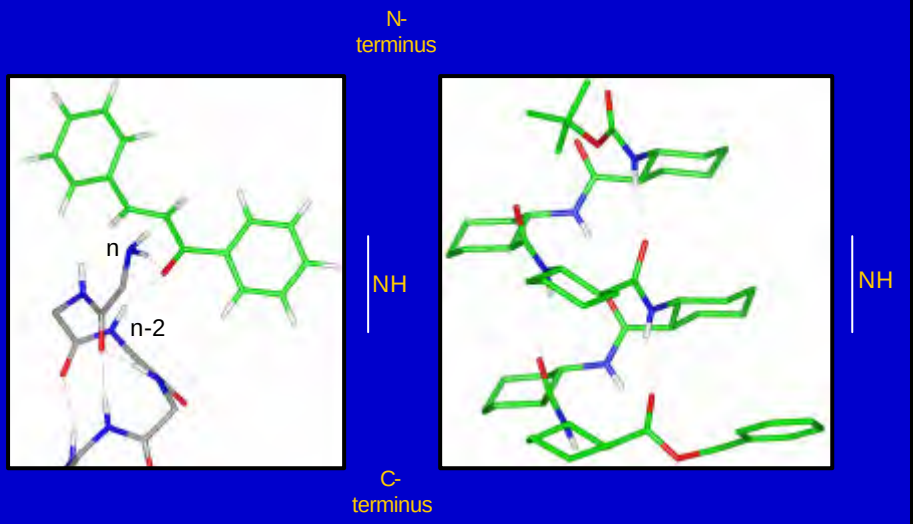
„ACHA"

e.g. Gellman et al.,
J. Am. Chem. Soc. **121**, 6206 (1999)
Acc. Chem. Res. **31**, 173 (1998)

A.Berkessel, K. Glaubitz, J. Lex,
Eur. J. Org. Chem. **2002**

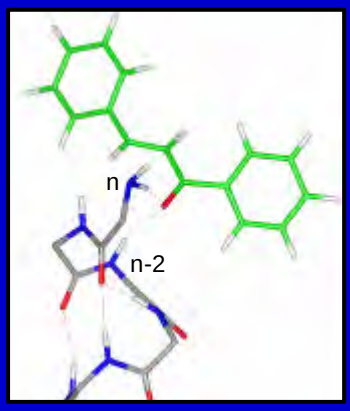
- β-Leu and in particular ACHA are known to form helices (3 AS per turn) much more readily than α-amino acids.
- however, the 1-5-mers of β-Leu and ACHA are catalytically inactive.

Comparison of Oligopeptide Helices



opposite orientation of the NH-bonds in 3.6_{12} and 3_{14} helices formed by α- and β-amino acids

Modelling Chalcone Binding to the N-Terminus

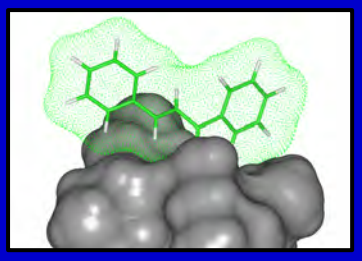


side-chains omitted for clarity

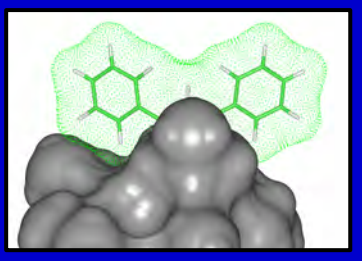
- „helix 8“ of myoglobin from X-ray structure
- replace side chains by *i*-Bu to mimic oligo-*L*-Leu, minimize
- docking of chalcone to the N-terminus of the α-helix
- MacroModel 6.0, Monte-Carlo-search
- invariably, binding occurs by H-bonding of the carbonyl-O to N_n and N_{n-2}

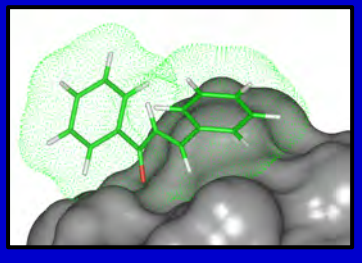
Modelling the Interaction of Chalcone with the N-Terminus

- docking before and after 180 ° rotation of the chalcone moiety -



3-si shielded



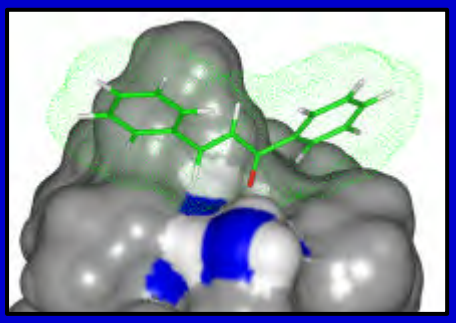


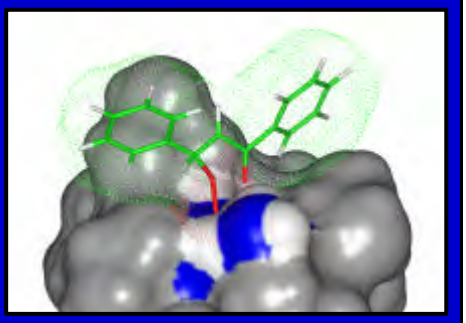
3-re shielded

...according to the modelling study, both binding modes of chalcone are equally well possible...

Stereoselective Addition of Hydroperoxide

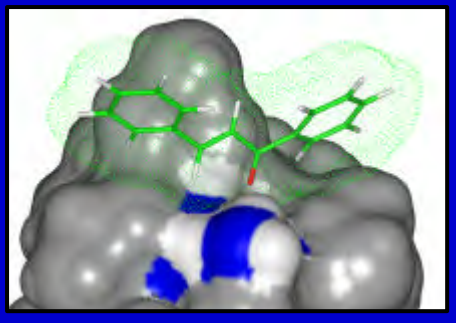
- the role of N_{n-1} -

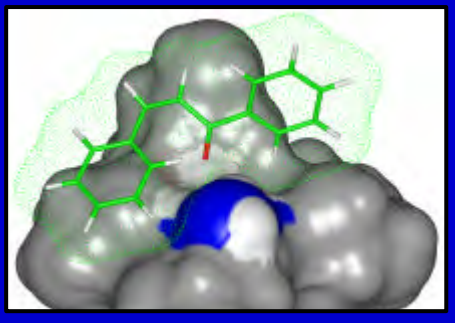




- NH of the penultimate amino acid is ideally positioned for steering a hydroperoxy anion into the β-position of the enone
- this intramolecular delivery of the nucleophile can not take place in the other possible docking mode of chalcone (rotated by 180 °)

trans- vs. *cis*-Chalcone...





trans-chalcone

cis-chalcone

- activation of the substrate chalcone is effected by H-bonding to the N-terminus of the helix
- enantioselectivity results from face-selective delivery of the nucleophile

Facit:
„mini-enzyme“

Conditions for extending the substrate spectrum :

- uncatalyzed background reaction must be slow
- proper positioning of the binding site for hydroperoxide („engineered“ amino acid)

Base-catalyzed hydrogenation of ketones

Thomas Schubert, Thomas Müller

Peroxidase models, ruthenium porphyrins

Thomas Schwenkreis, Matthias Frauenkron, Patrick Kaiser

Asymmetric enone epoxidation, peptide catalysts

Norbert Gasch, Katja Glaubitz, Christoph Koch

Combinatorial approaches to artificial hydrolase activity

David Hérault, Rainer Riedl

- DFG, SPP 462 „Peroxide Chemistry“
- EU Research Training Network „Combinatorial Catalysis“
- BASF AG
- Fonds der Chemischen Industrie