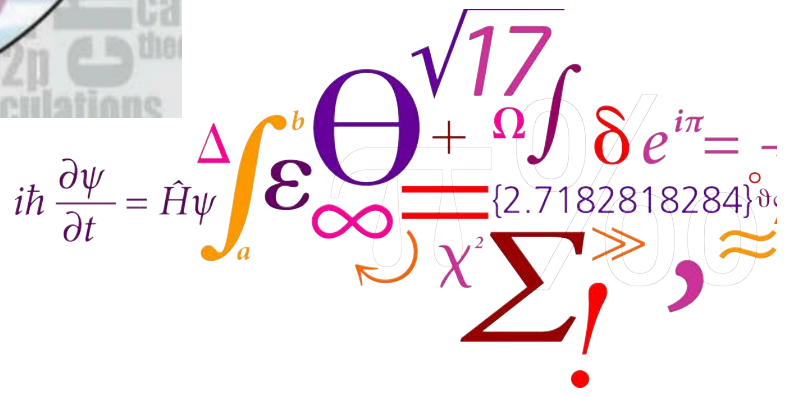
Development of the Molybdenum-catalyzed Deoxydehydration

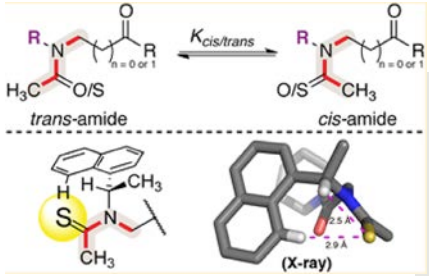
– an example of synergistic use of both experimental and theoretical tools

Peter Fristrup, ISOC 2017, September 3rd
DTU Chemistry
Department of Chemistry



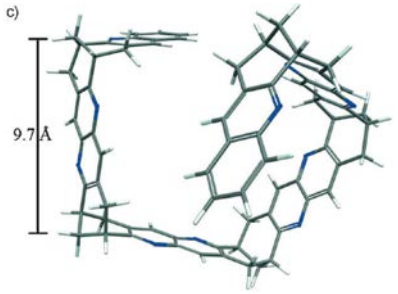
Research Overview– Fristrup

Structural properties



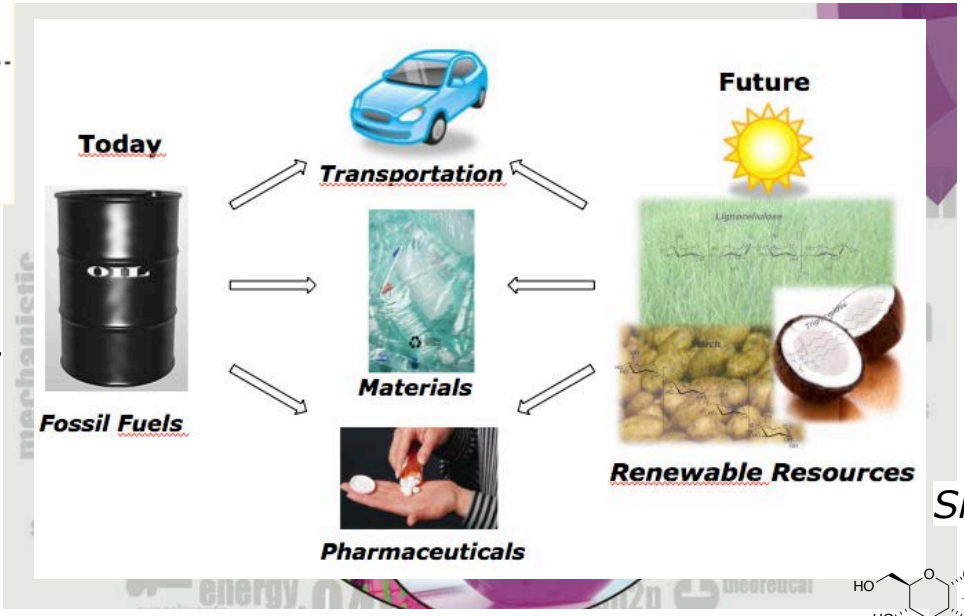
JACS **2013**, *135*, 2835.
Nature Comm. **2015**, *6:7013.*

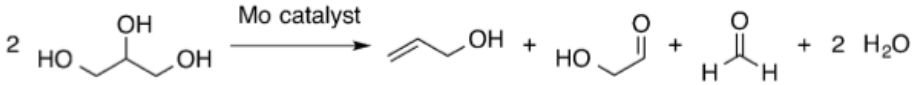
Chiroptical properties



Chem. Eur. J. **2013**, 19, 14963.
Org. Biomol. Chem. **2014**
J. Org. Chem. **2015**, *80*, 8142

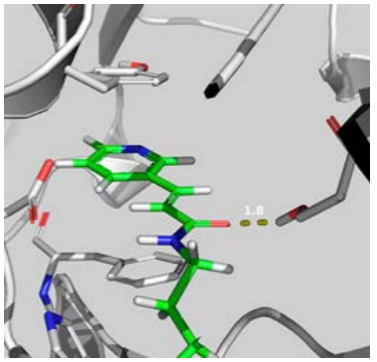
Biomass Conversion





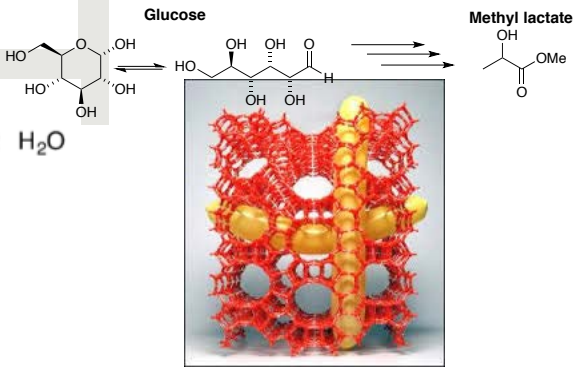
ChemSusChem **2014**, *7*, 425
ChemCatChem **2015**, *7*, 1184-1196.
Chem. Eur. J. **2015**, *21*, 3435-3432.
ChemSusChem **2015**, *8*, 767 (mini-review)
ACS Catalysis **2015**, *5,* 3638-3647
WO2015028028 A1

Chemistry/Biology



J. Med. Chem **2013**, *56*, 9071.
J. Med. Chem. **2014**, *57*, 9644.
J. Biol. Chem. ***2016*** *10.1074/jbc.M115.668699*

Sn-beta catalysis



J. Mater. Chem. A, 2014, 2, 20252.
ChemSusChem **2015**, *8*, 613
Green Chem **2016** 10.1039/C5GC02840J

Overview

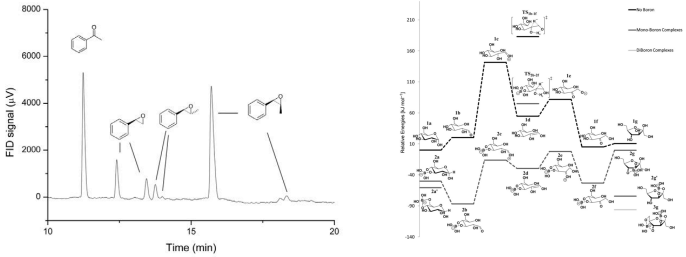
- Theoretical and Experimental methods are complementary
- When used together the information is more than the sum ☺

- I will highlight this approach using two examples:
  - Ruthenium-catalysed Amidation of Alcohols
  - Rhenium and Molybdenum-catalyzed Deoxydehydration

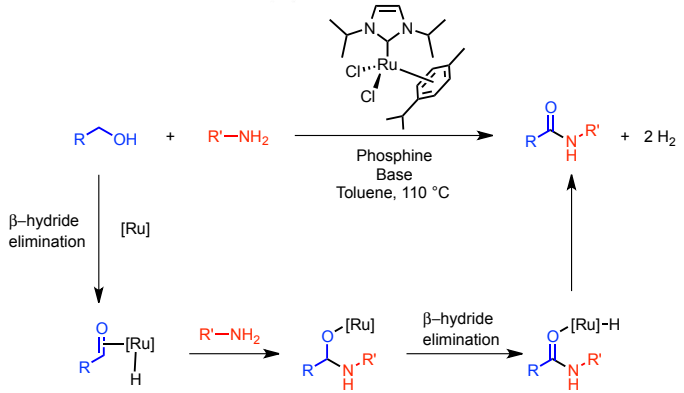
D. Lupp, N. J. Christensen, P. Fristrup *Dalton Trans.*, **2014**, *43,* 11093–11105.

Plan for todays lecture

- The toolbox of the organometallic chemist
  - Both experimental and theoretical

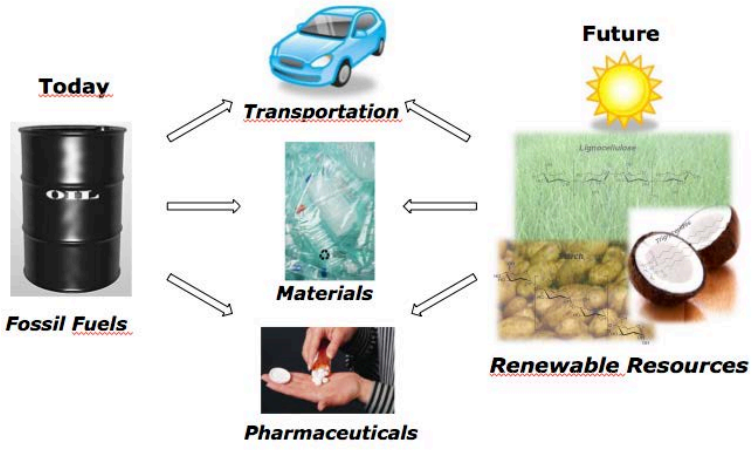


- Ruthenium catalyzed amide formation



- Conversion of diol to alkenes using

Rhenium or Molybdenum



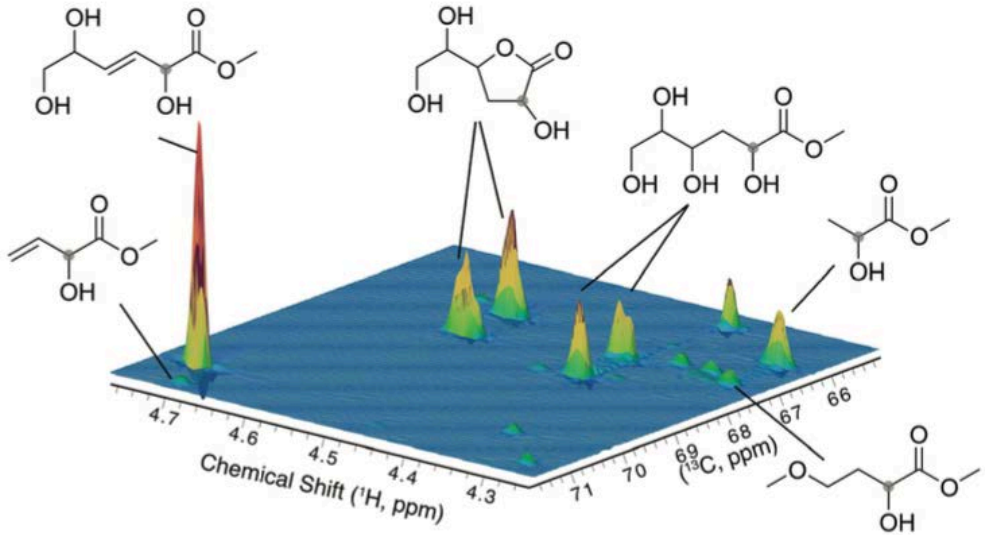
In the toolbox: Analytical Chemistry

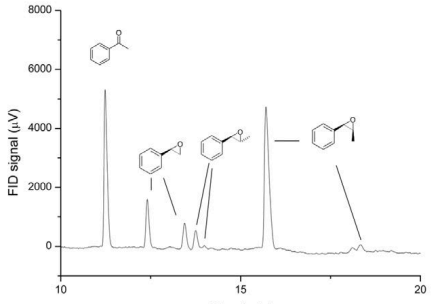
- Chromatography (GC, GC-MS, HPLC, LC-MS)

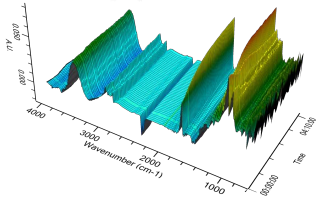
  Applications within catalysis, biomass conversion, also chiral analysis

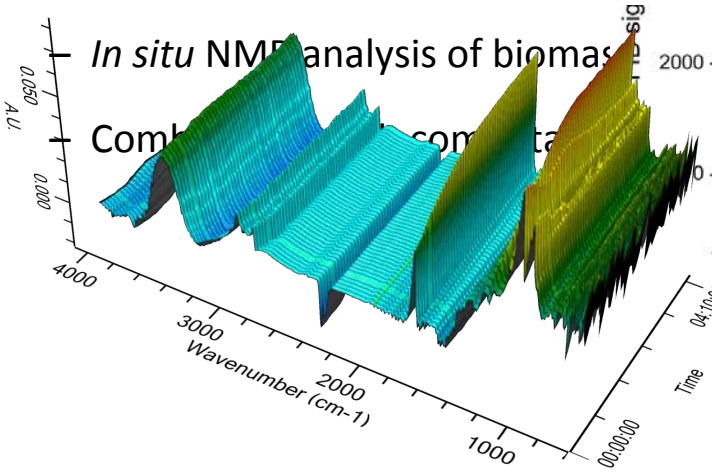
- *In situ* NMR analysis of biomass

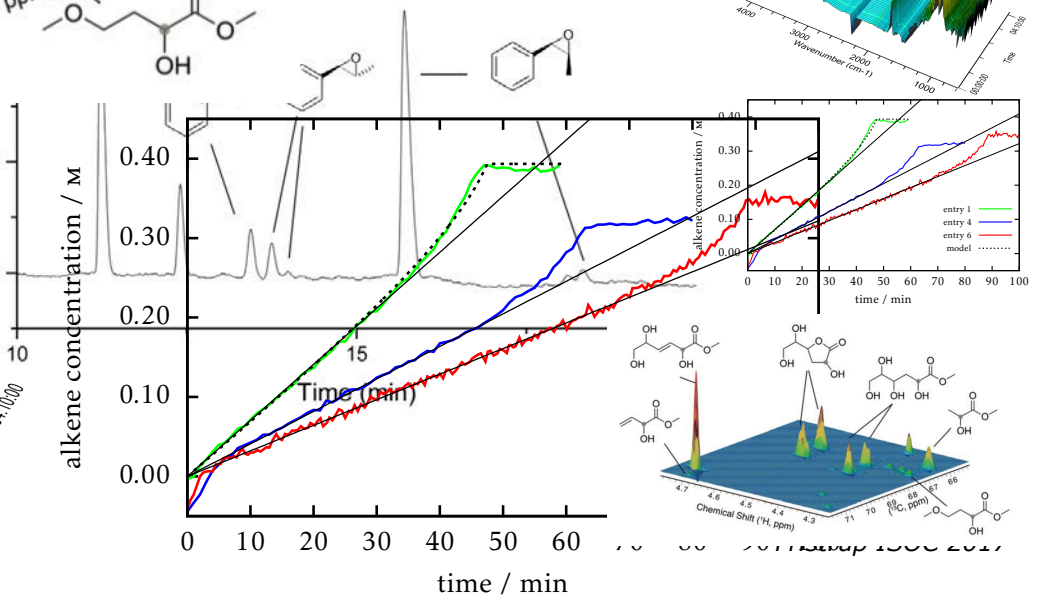
- Combined computational





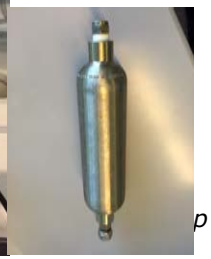






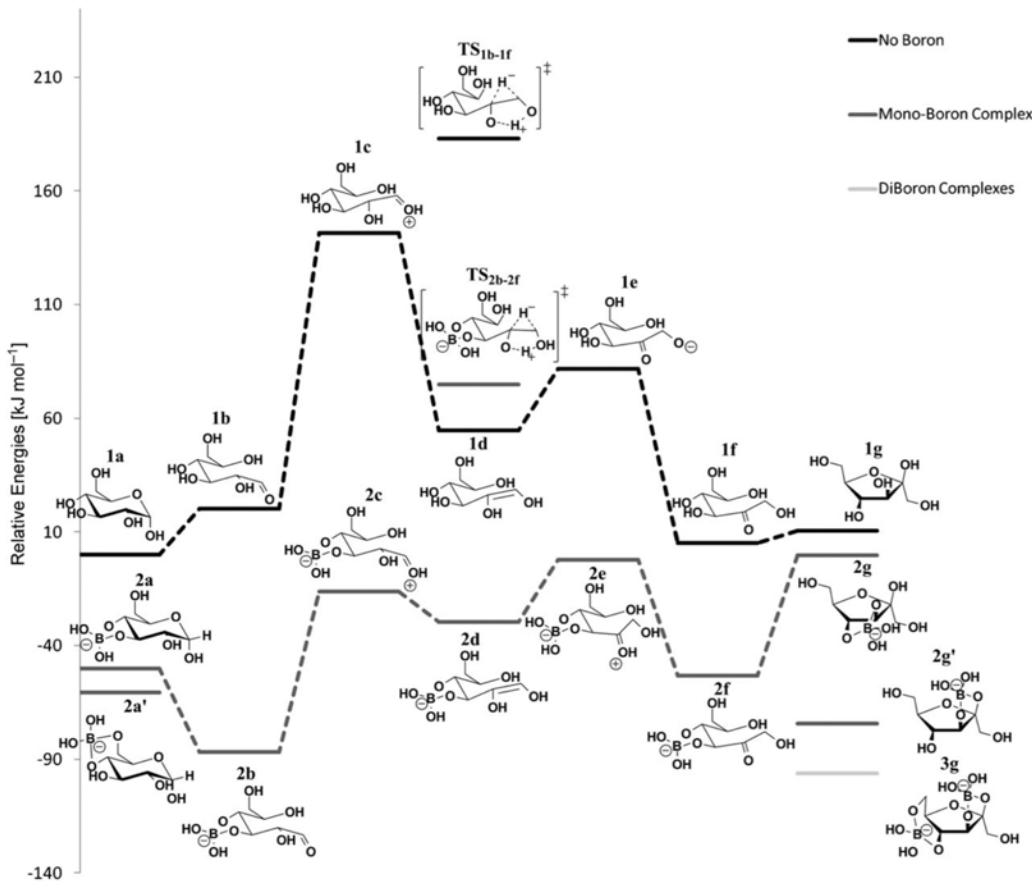
In the toolbox: Special Equipment

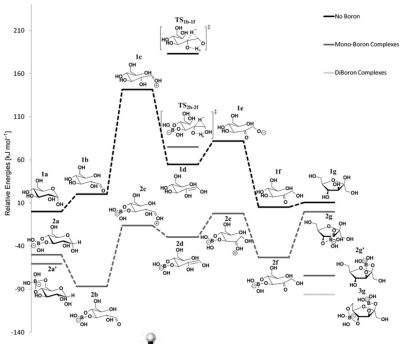
- Autoclaves for high-temperature, high-pressure reactions
  - Purchase, installation
  - Used routinely for reaction conducted at up to 250 °C/80 bar.
  - Sample extraction for off-line analysis
  - Adaptation to *in-situ* IR probe
- MW reactor with auto-sampler
  - Used routinely for reactions conducted at up to 300 °C/30 bar.
- Design of Swagelok equipment:
  - high-pressure reactor, relief valves
  - aluminum heating blocks

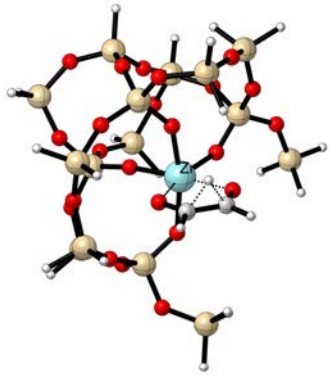


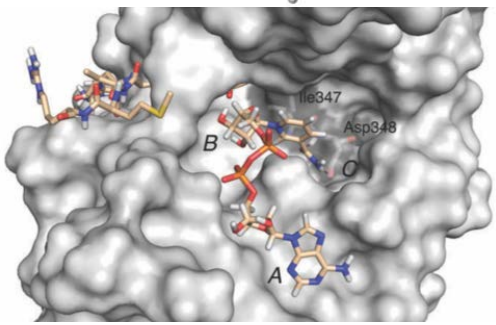
In the toolbox: Molecular Modelling

- [illegible]
- [illegible] y (DFT).
- [illegible] alysis
- (molecular
- [illegible])

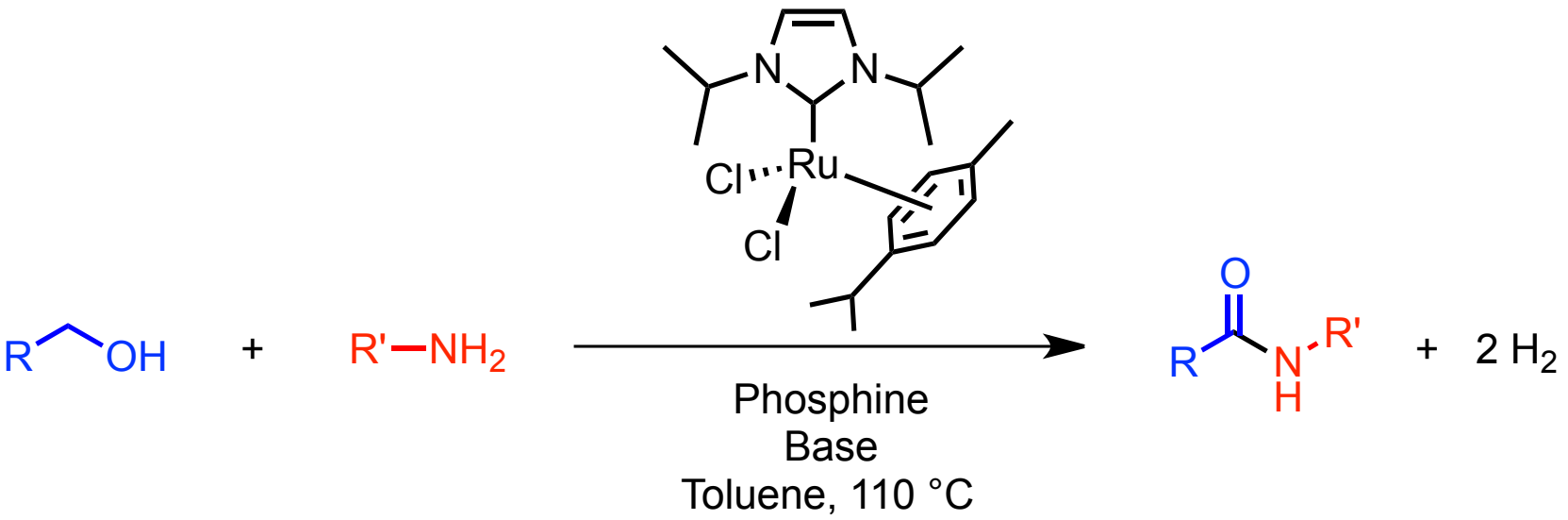








Ru-NHC catalyzed Amidation of Alcohols



- Amides are formed in high yields after 24 hours
- Both aromatic and aliphatic alcohols can be used
- Stereogenic centers are preserved during the reaction
- Primary amines react successfully

Ilya Makarov

Robert Madsen

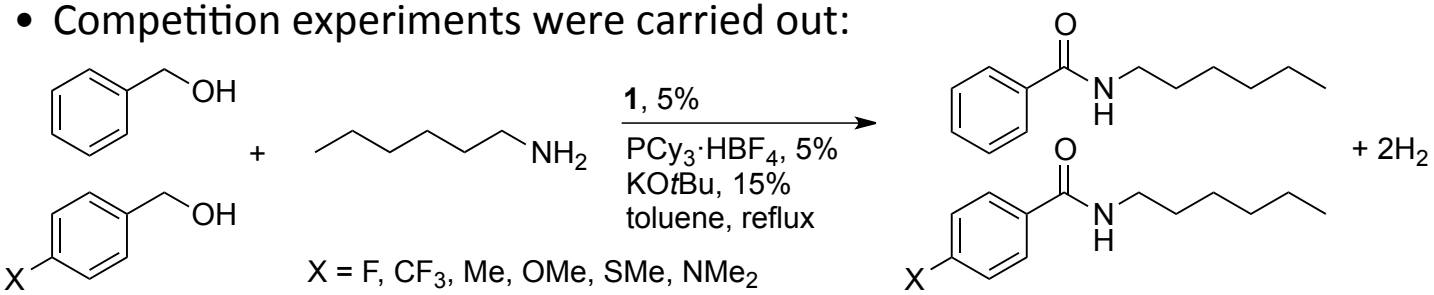
I. S. Makarov, P. Fristrup, R. Madsen, *Chem Eur. J.* **2012**, 18, 15683 – 15692 .

Classical Hammett study

- In 1937 Hammett worked on the acidity of substituted benzoic acids and found a connection between the acidity and the electronic nature of the substituent.

L. P. Hammett (1894-1987)

- Competition experiments were carried out:



Other examples include:

Heck reaction: P. Fristrup, S. Le Quement, D. Tanner, P.-O. Norrby, *Organometallics* **2004**, *23*, 6160.

Allylzinc additions to imines: L. Keinicke, P. Fristrup, P.-O. Norrby, R. Madsen, *J. Am. Chem. Soc.* **2005**, *127*, 15756.

Rh-cat. Decarbonylation: P. Fristrup, M. Kreis, A. Palmelund, P.-O. Norrby, R. Madsen *J. Am. Chem. Soc.* **2008**, *130*, 5206-5215.

Gold-nanoparticle catalyzed oxidations: P. Fristrup, L. B. Johansen, C. H. Christensen, *Chem. Commun.* **2008**, *24*, 2750-2752.

Iridium-catalyzed alkylation: P. Fristrup, M. Tursky, R. Madsen, *Org. Biomol. Chem.* **2012**, *10*, 2569-2577.

A little bit of math

- In a competition experiment the following rate expression exists for substrates (A,B):

$$d[A]/dt = k_A*[cat]*[A]$$

$$d[B]/dt = k_B*[cat]*[B]$$

- Division of one with the other gives:

$$d[A]/d[B] = k_A/k_B * [A]/[B]$$

- Separation of the variables (A,B) on each side gives:

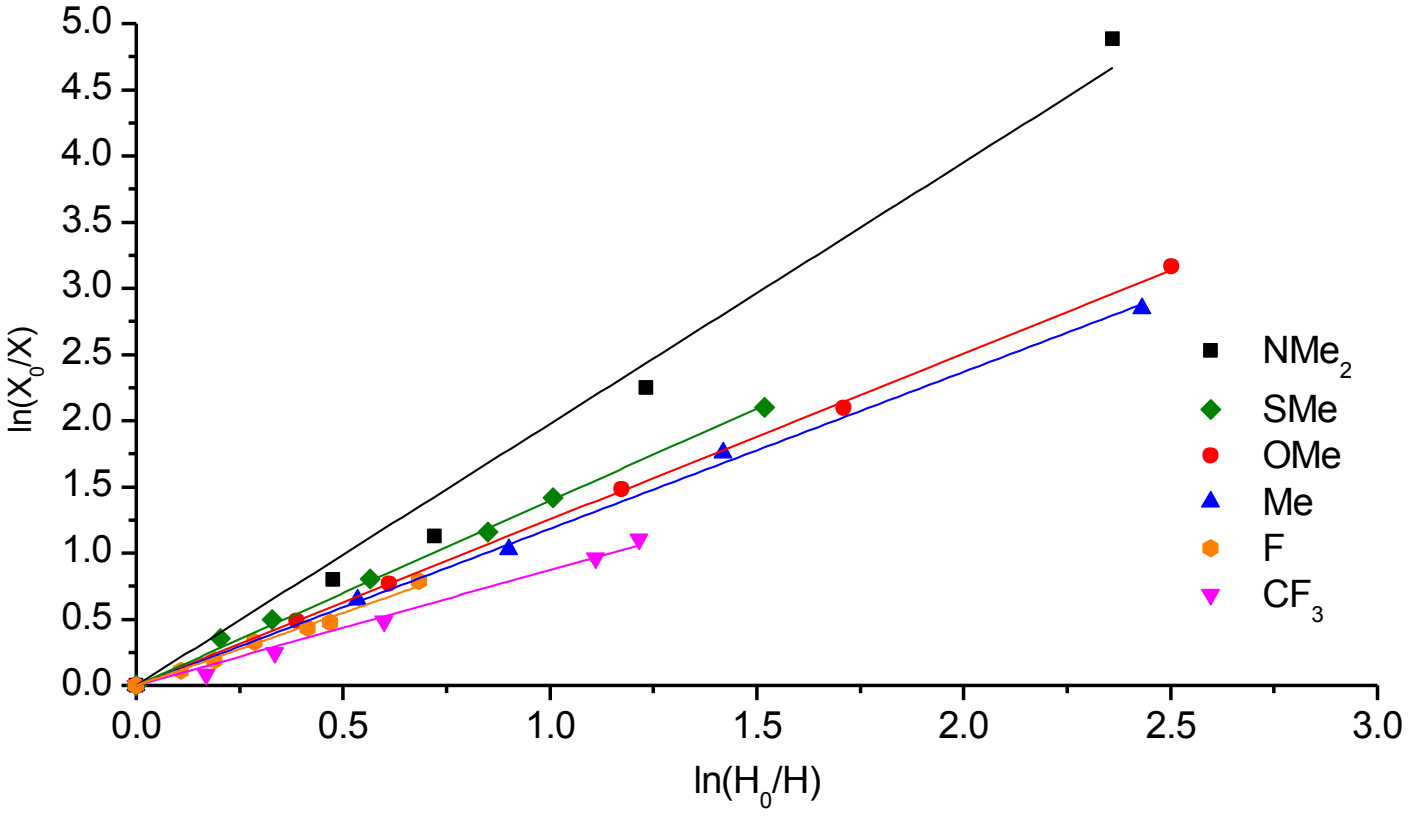
$$d[A]/[A] = k_A/k_B * d[B]/[B]$$

- Integration from initial concentration $[A]_0$, to actual concentration [A] we get

$$\ln([A]/[A]_0) = k_A/k_B * \ln([B]/[B]_0)$$

y-axis **slope** **x-axis**

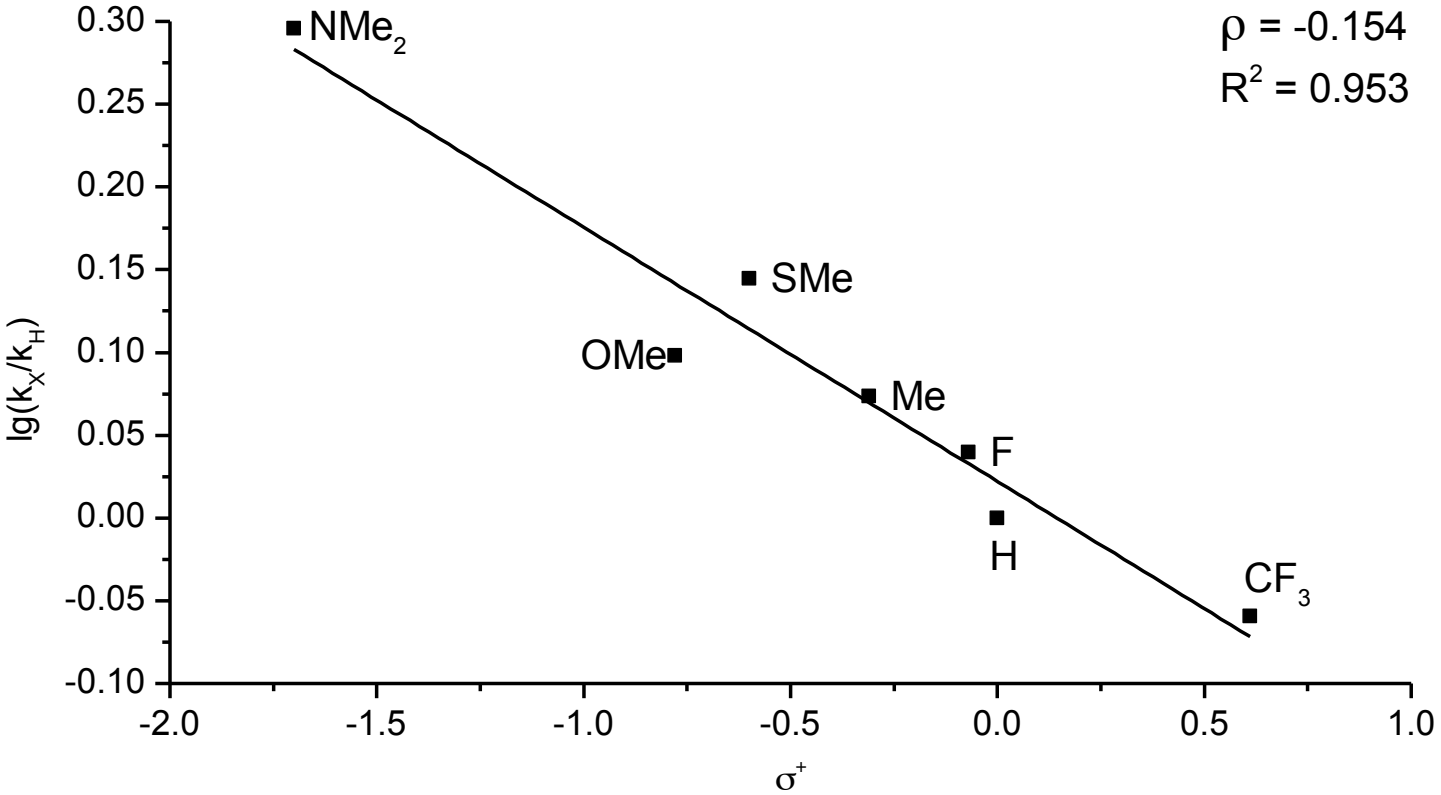
Competition Experiments



I. S. Makarov, P. Fristrup, R. Madsen, *Chem Eur. J.* **2012**, 18, 15683 – 15692 .

Hammett Plot

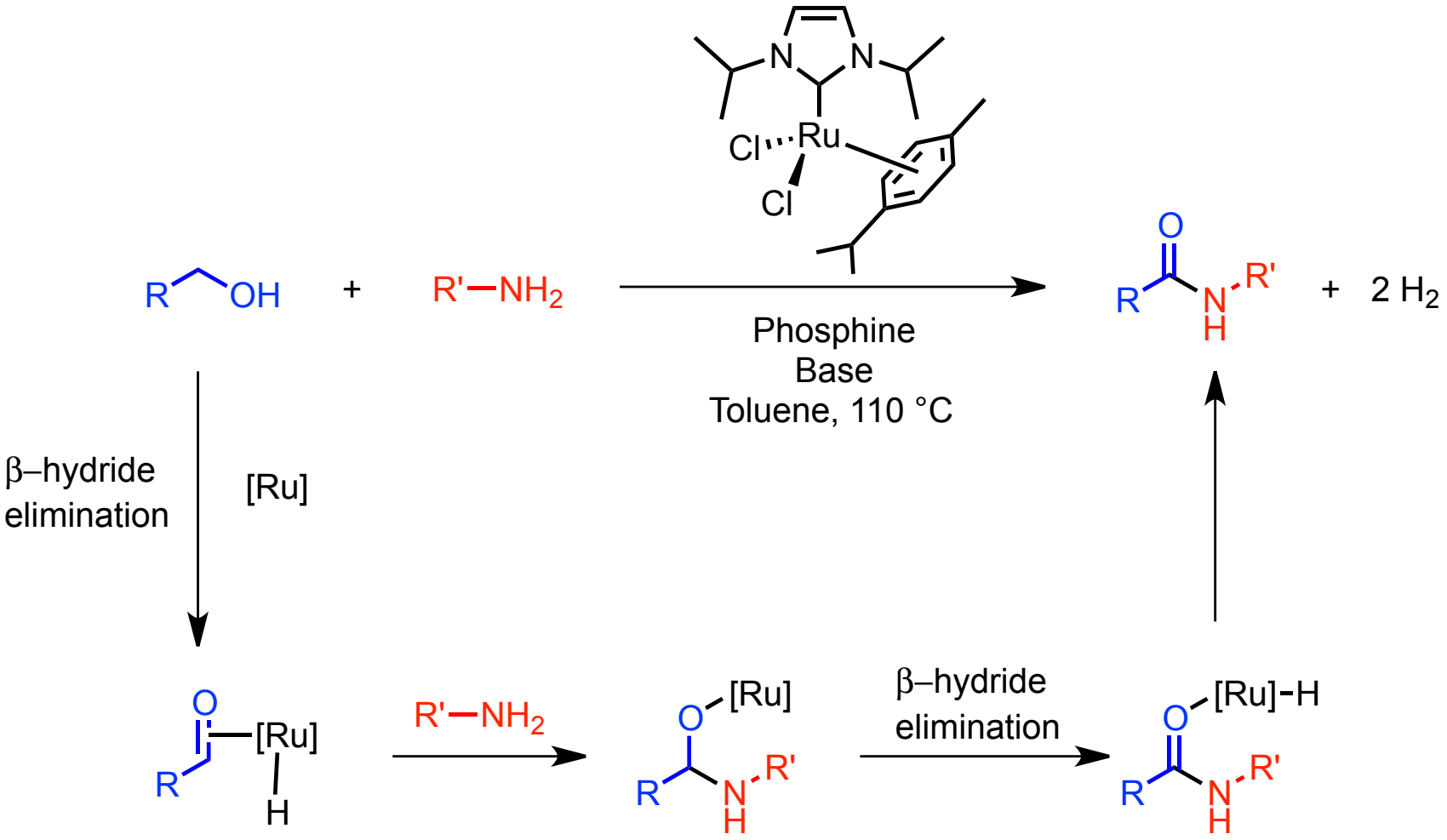
- No radicals involved. Development of a partial positive charge.



- Could be indicative of a β-hydride elimination.

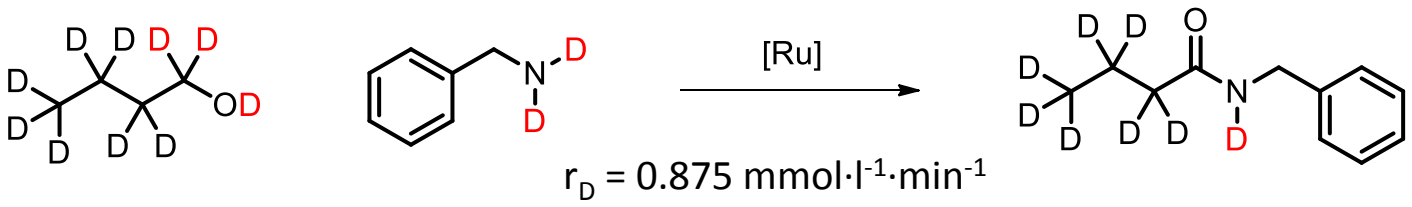
I. S. Makarov, P. Fristrup, R. Madsen, *Chem Eur. J.* **2012**, 18, 15683 – 15692 .

Simplified mechanism of the reaction

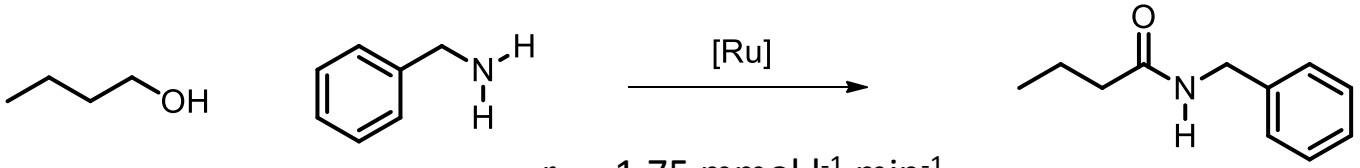


Kinetic Isotope Effect

- Due to scrambling the KIE had to be determined as two separate reactions



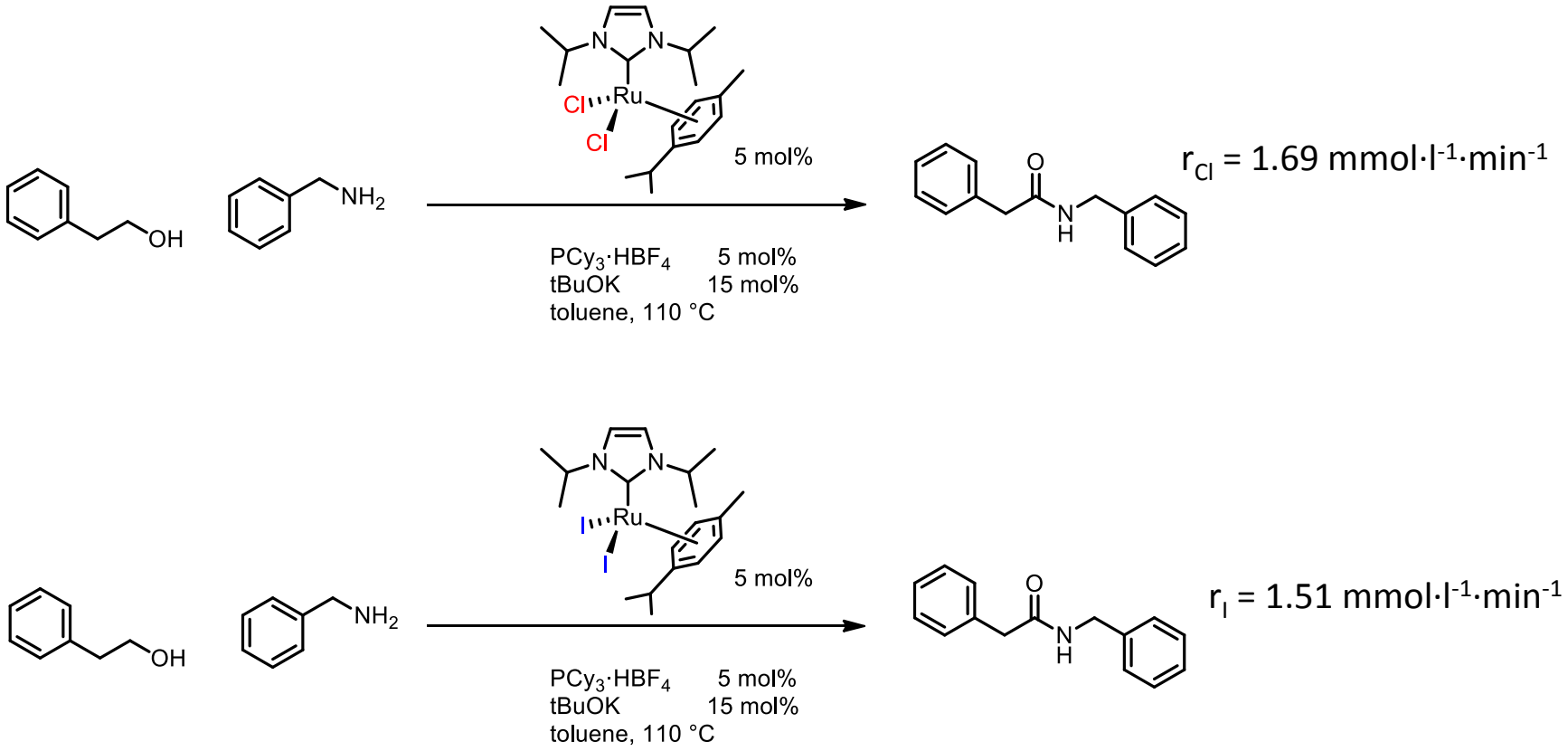
$r_D = 0.875\ mmol \cdot l^{-1} \cdot min^{-1}$



$r_H = 1.75\ mmol \cdot l^{-1} \cdot min^{-1}$

$KIE = r_H/r_D = 2$

Dichloride vs. diiodide complex

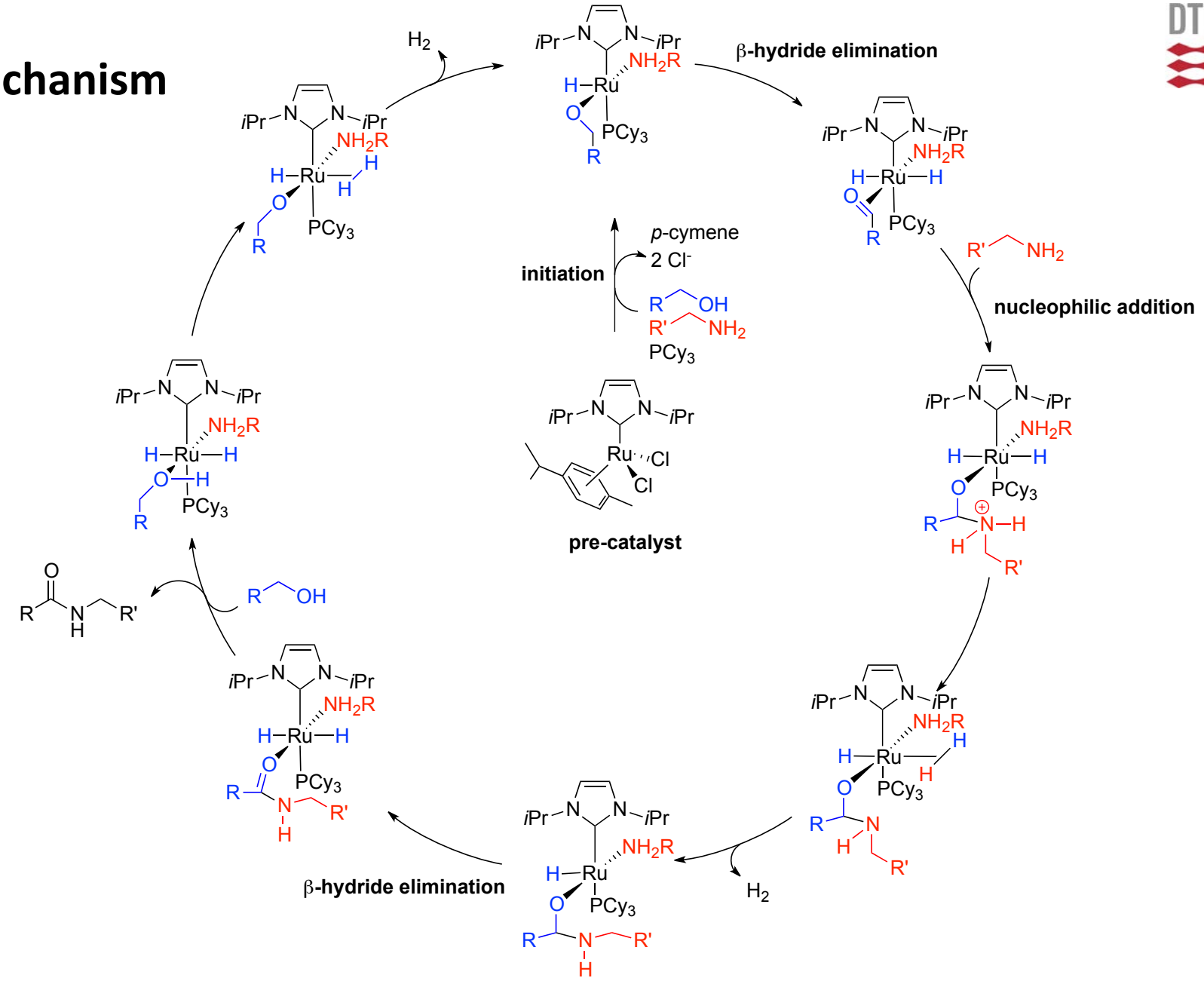


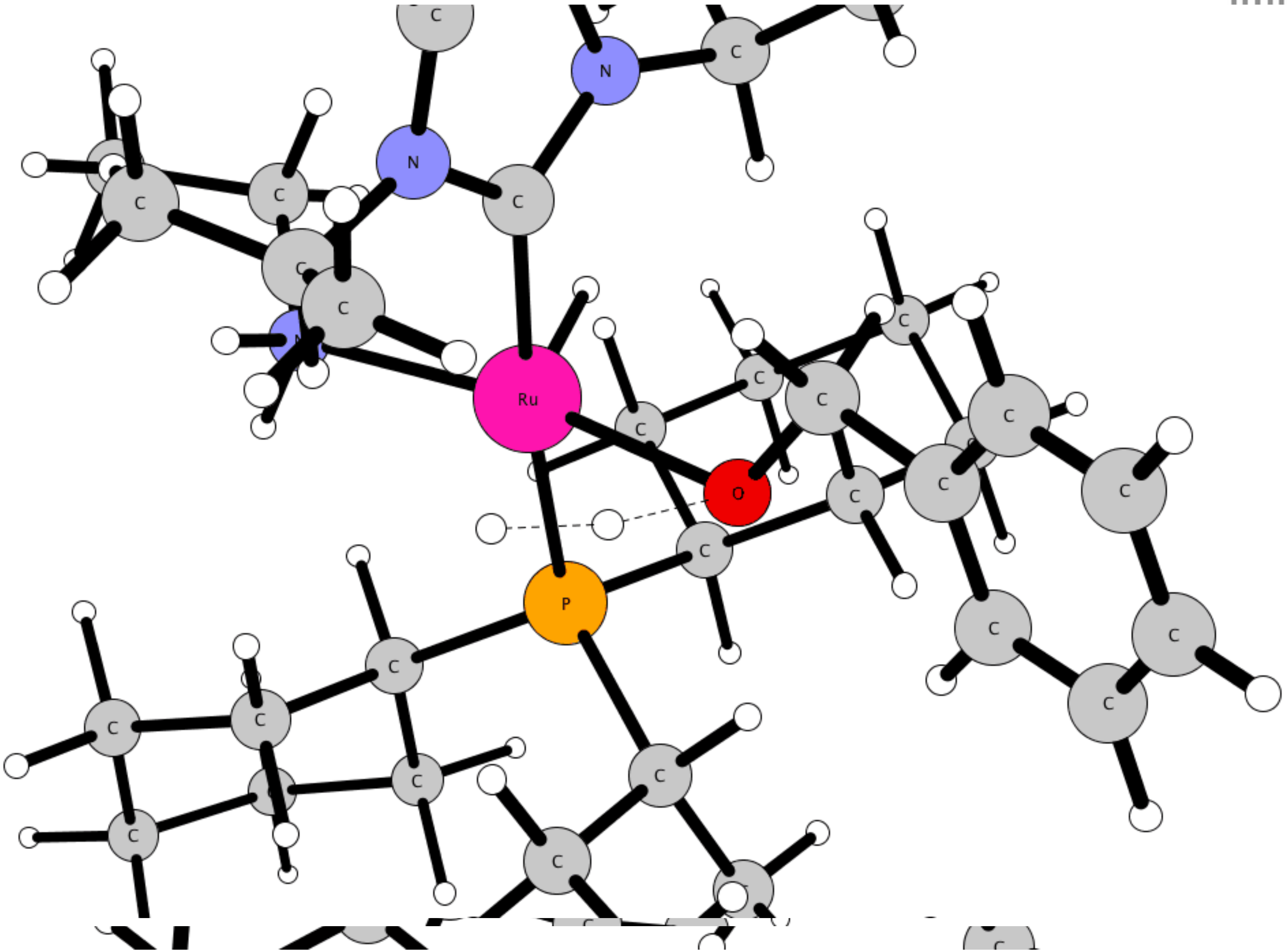
- The similar rates indicate that *neither* Cl or I stays coordinated and that the active catalyst instead is a dihydride.

Computational method

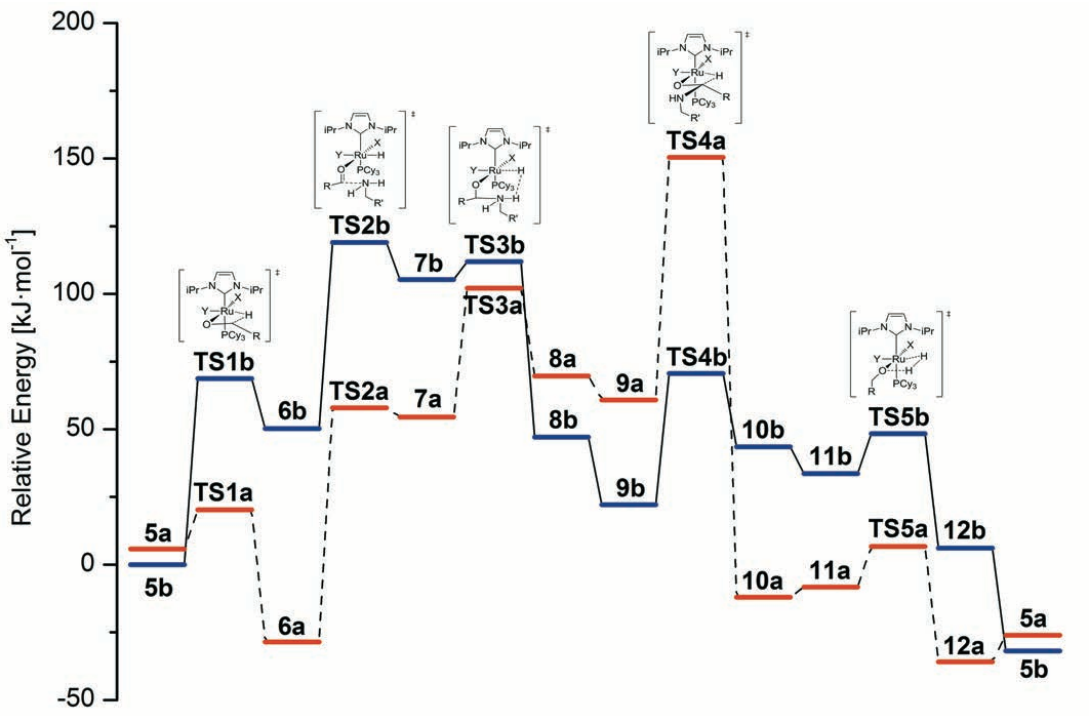
- Density functional theory (DFT)
- For many years B3LYP but now M06 and/or B3LYP-D3 functional (to get vdW part)
- 6-31G* or 6-31G** basis set
- Effective core potential on transition metals
- Solvation model (important!), Polarized Continuum Model
- We normally use “composite” energies consisting of:
  - Solvation energy (either fully optimized or single-point)
  - Gas phase entropic contributions (since freq-calcs in solvent are slow and error-prone)
- Why does it work so well?
- Cancellation of errors!!, comparison of similar intermediates in a catalytic cycle or even diastereomeric transition states in an enantioselective reaction

Mechanism


β-hydride elimination
nucleophilic addition
β-hydride elimination
H2
initiation
p-cymene
2 Cl-
PCy3
pre-catalyst


Ru
P
O
N
C

Experimental vs. Theoretical Results

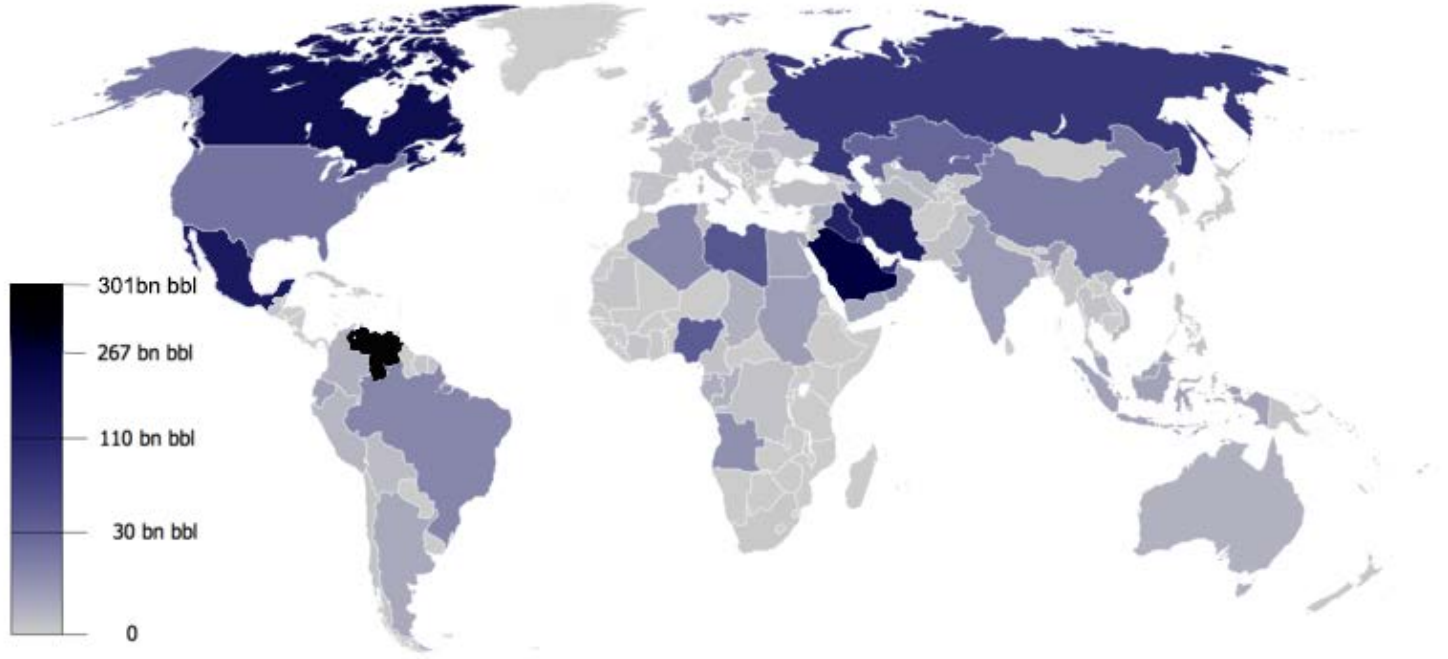


- TOF for trans-dihydride pathway (blue) was 0.74 h^{-1} (experiment 0.8 h^{-1})
- TOF for cis-dihydride pathway was 6 orders of magnitude smaller.

AUTOF software: A. Uhe, S. Kozuch, S. Shaik, *J. Comput. Chem.* **2011**, *32*, 978–985.

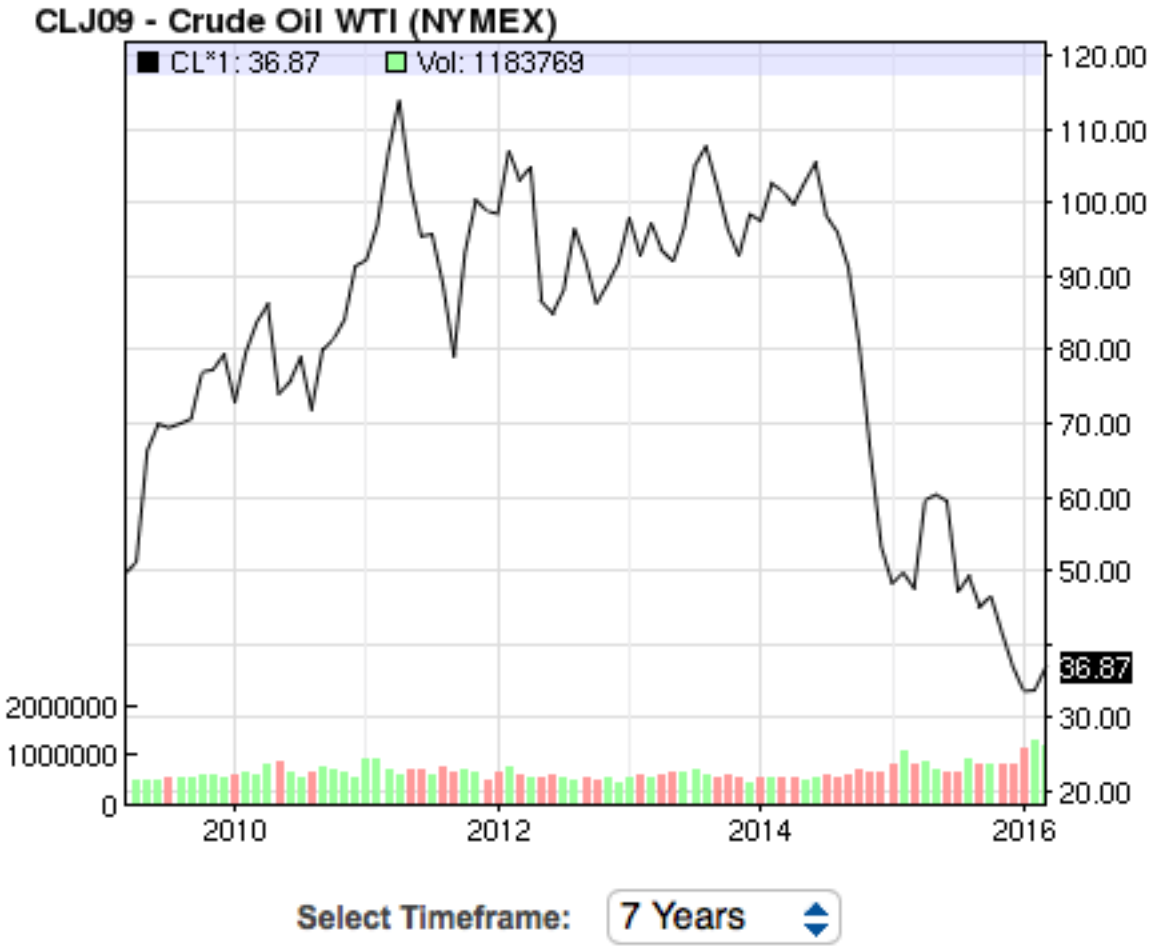
Motivation

- Our society is very dependent on fossil fuels, which are the main source of energy, materials and chemicals. A transition to renewable resources is challenging!



- In addition the oil reserves are distributed unevenly (main reserves are in Saudi Arabia, Russia, Venezuela, Canada).

CO_2 emissions, temperature increase

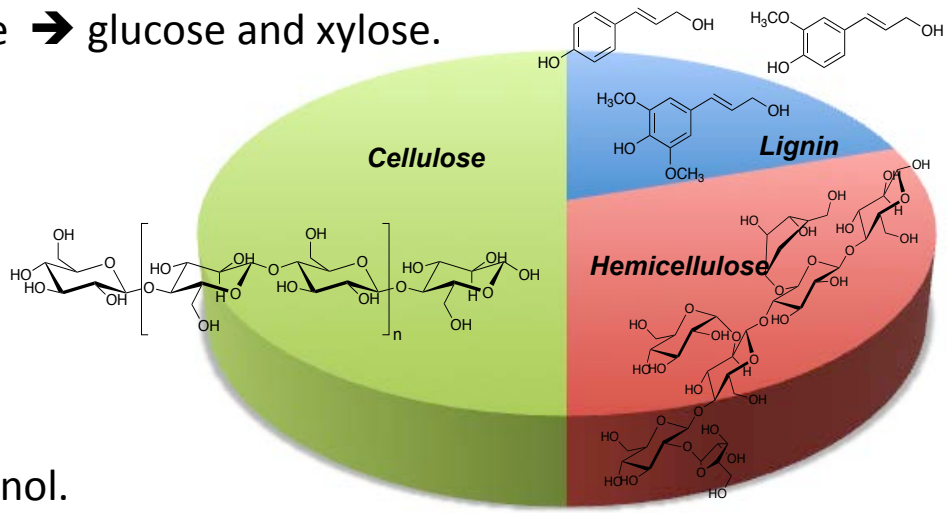


Chemical composition of biomass

Three main fractions:

1) Lignocellulose: cellulose, hemicellulose ➔ glucose and xylose.

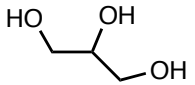
lignin ➔ aromatics?



2)

Carbohydrates: starch, sucrose ➔ ethanol.

3) Plant oils: Triglycerides ➔ biodiesel (FAME) + **waste glycerol**.



All have a high oxygen:carbon ratio compared to fossil resources.

Strateg

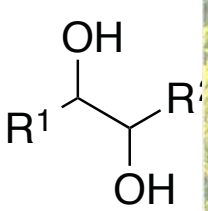
Dehydratic

Deoxygena

Deoxydeh

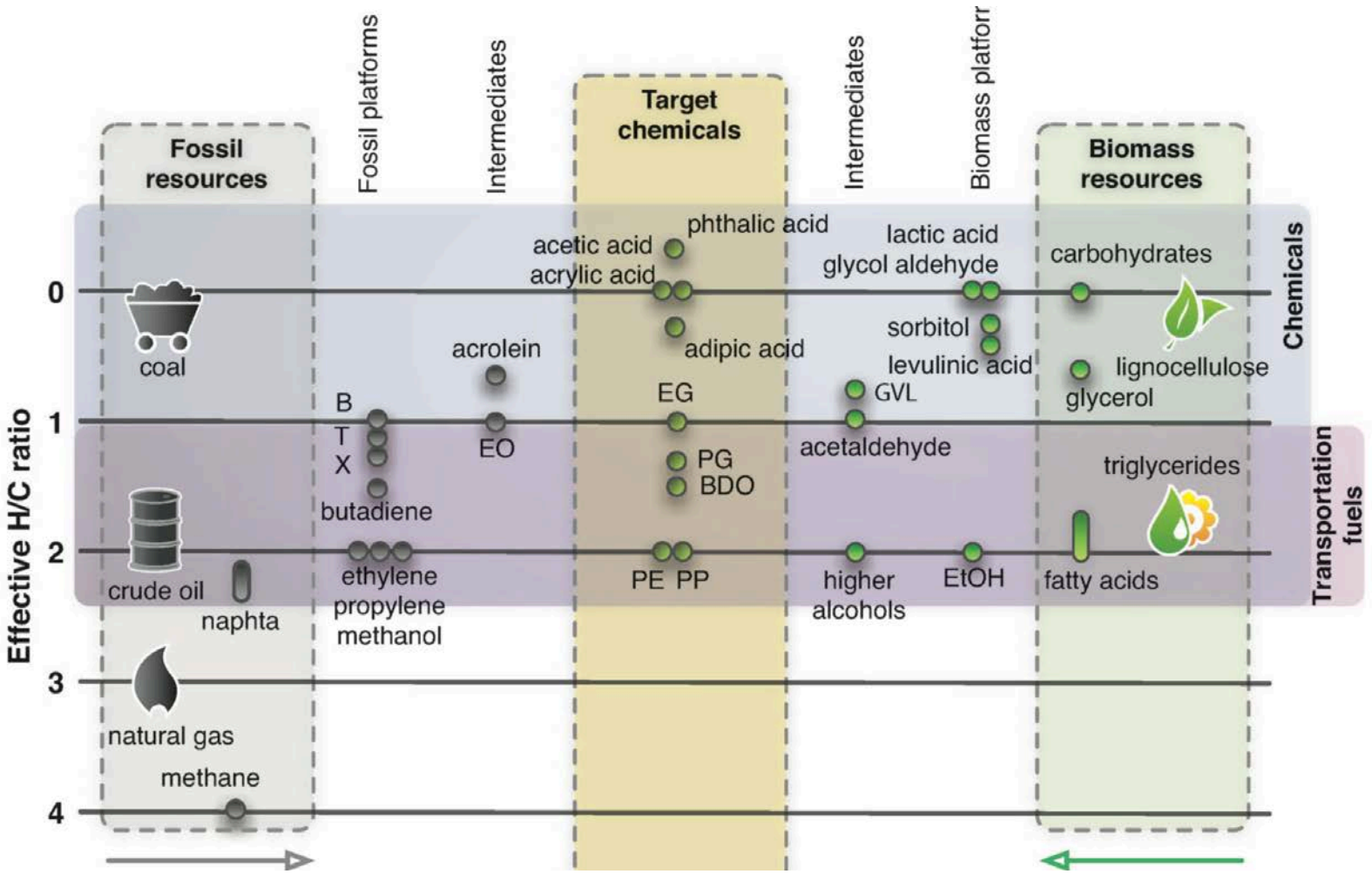
A unique c

diol into ar



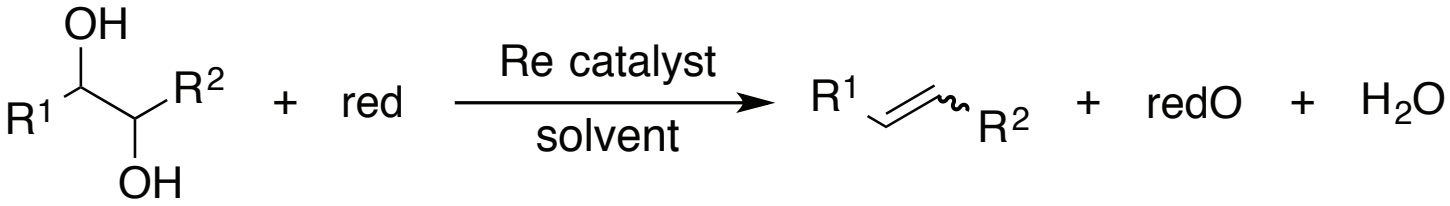
Dethlefsen, J.

Chemical building blocks from *either* oil or biomass



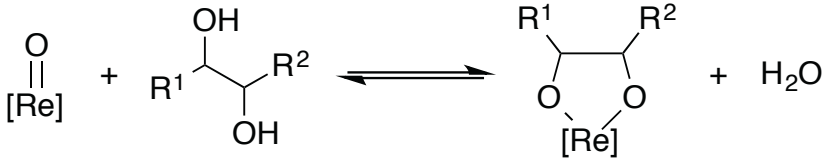
P. N. R. Vennestrøm, C. M. Osmundsen, C. H. Christensen, E. Taarning *Angew. Chem.* **2011**, *50*, 10502.

Rhenium-Catalyzed DODH – fundamental steps



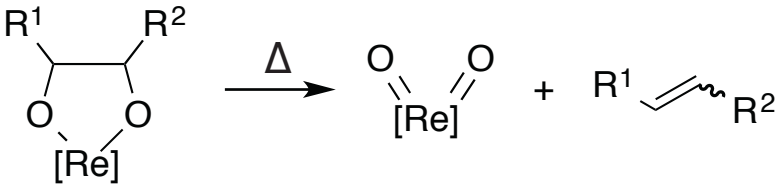
1. Condensation between diol

and Re^{VII}=O or Re^{V}=O:[1]

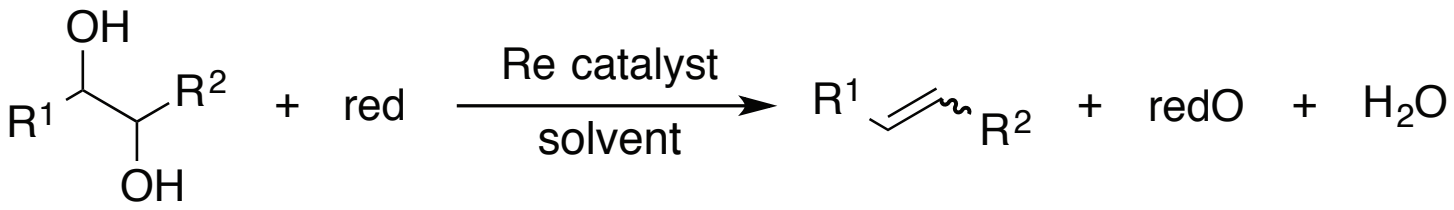


2. Reduction of Re^{VII} to Re^{V}.

3. Extrusion of alkene from ReV diolate:[2,3]



[1] Herrmann *Chem. Ber.* **1991**, *124*, 1101. [2] Herrmann *ACIE* **1987**, *26*, 462; [3] Gable *JACS* **1994**, *116*, 833; Gable *JACS* **1995**, *117*, 955; Gable *JACS* **1996**, *118*, 2625; Gable *JACS* **2002**, *124*, 3970.



Catalyst	Reductant	Solvent	Substrate	Ref.
Cp^*ReO_3	PPh_3	PhCl	styrenediol	[1]
CH_3ReO_3	H_2	THF	1,2-hexanediol	[2]
Bu_4NReO_4	Na_2SO_3	benzene, THF, CH_3CN	various	[3]
$Re_2(CO)_{10}$	2° alcohol	2° alcohol	aliphatic diols	[4]
CH_3ReO_3	glycerol	glycerol	glycerol	[5]
CH_3ReO_3	2° alcohol	2° alcohol	glycerol, sorbitol	[6]
$Cp^{ttt}ReO_3$	PPh_3	PhCl	aliph./benz. diols	[7]

[1] Cook and Andrews *JACS* **1996**, *118*, 9448.

[2] Abu-Omar *Inorg. Chem.* **2009**, *48*, 9998.

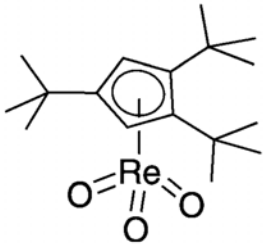
[3] Nicholas *Inorg Chem.* **2010**, *49*, 4744.

[4] Ellman and Bergman *JACS* **2010**, *132*, 11408.

[5] Abu-Omar *ChemSusChem* **2012**, *5*, 1401.

[6] Toste *ACIE* **2012**, *51*, 8082.

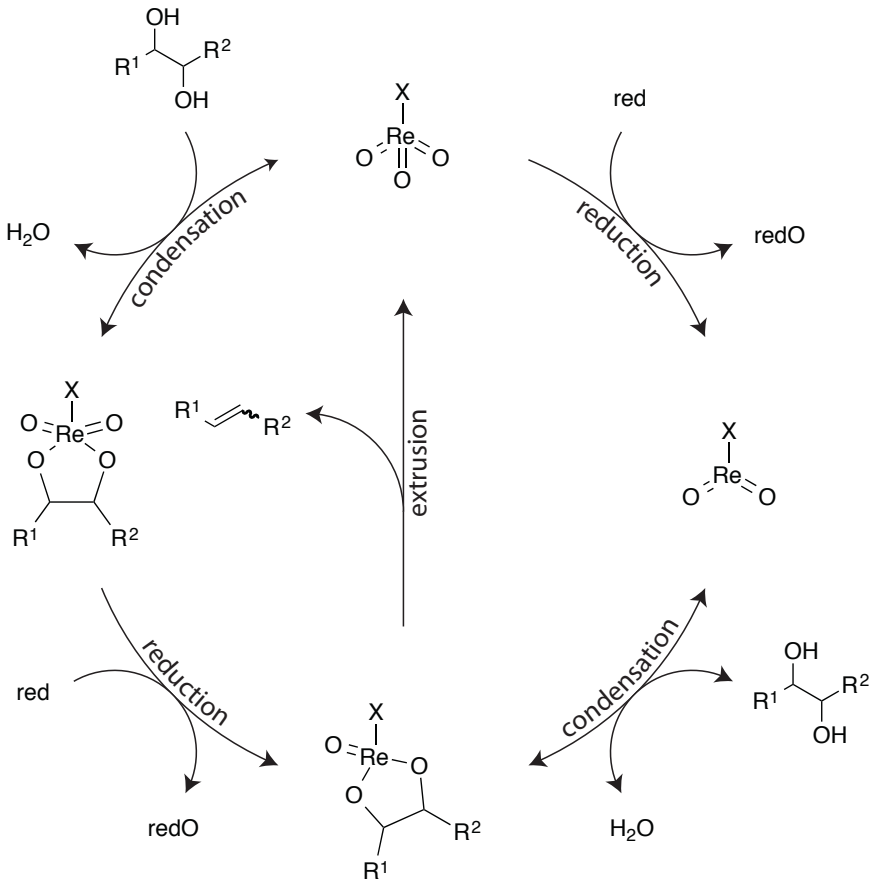
[7] Klein Gebbink *ChemSuschem* **2013**, *6*, 1673.



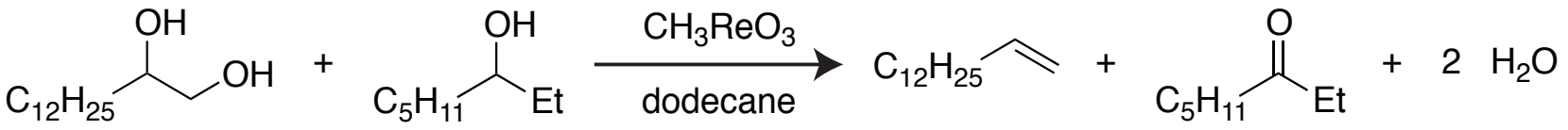
Dethlefsen and Fristrup *ChemSusChem* **2015**, *8*, 767 (minireview)

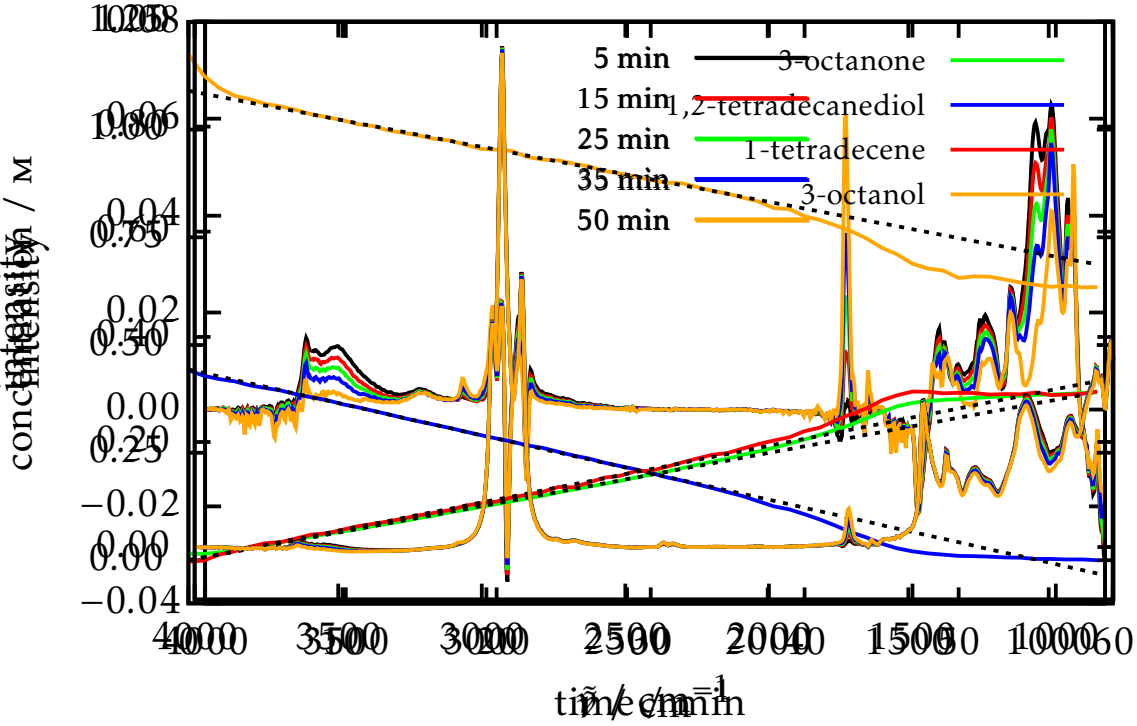
Mechanism of Rhenium-Catalyzed DODH

The order of the Condensation, the Reduction, and the Extrusion



In Situ Spectroscopic Investigation of the Rhenium-Catalyzed Deoxydehydration of Vicinal Diols





Dethlefsen, J. R. and Fristrup, P. ChemCatChem **2015**, *7*, 1184-1196

Kinteics of Rhenium-Catalyzed DODH

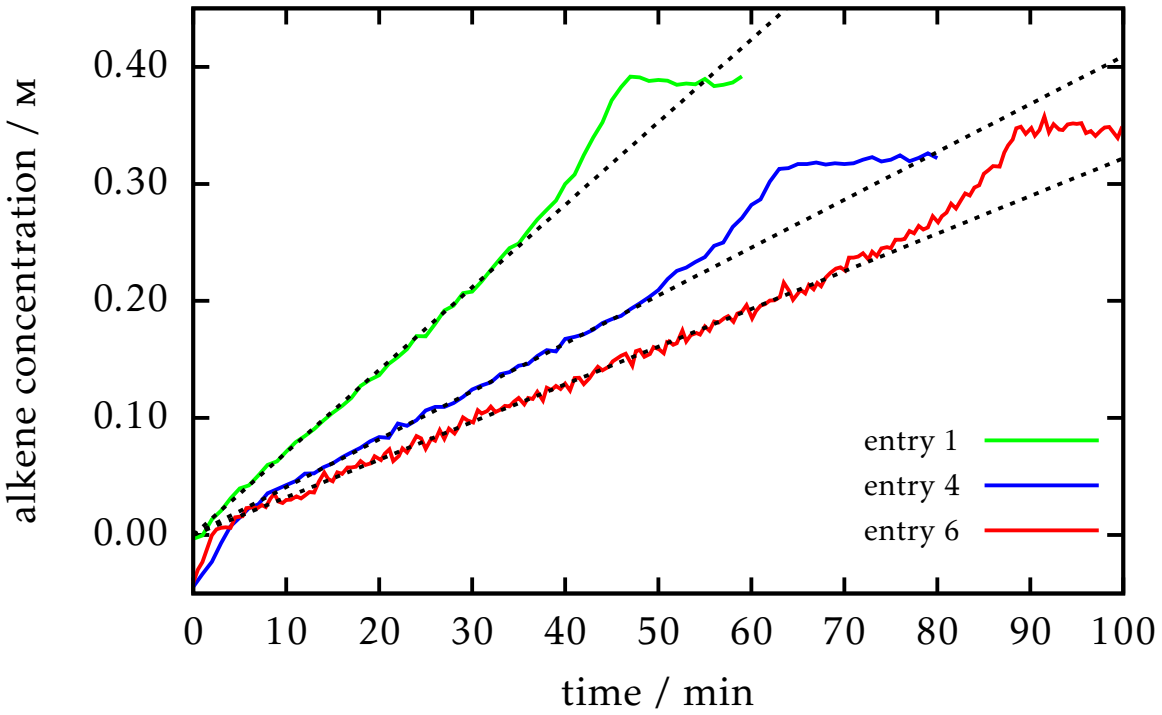
Standard experiment: **GREEN** Rate ≈ constant ⇒ zeroth-order reaction

Less catalyst: **RED** Rate ∝ $c(CH_3ReO_3)$ ⇒ first-order reaction in [cat.]

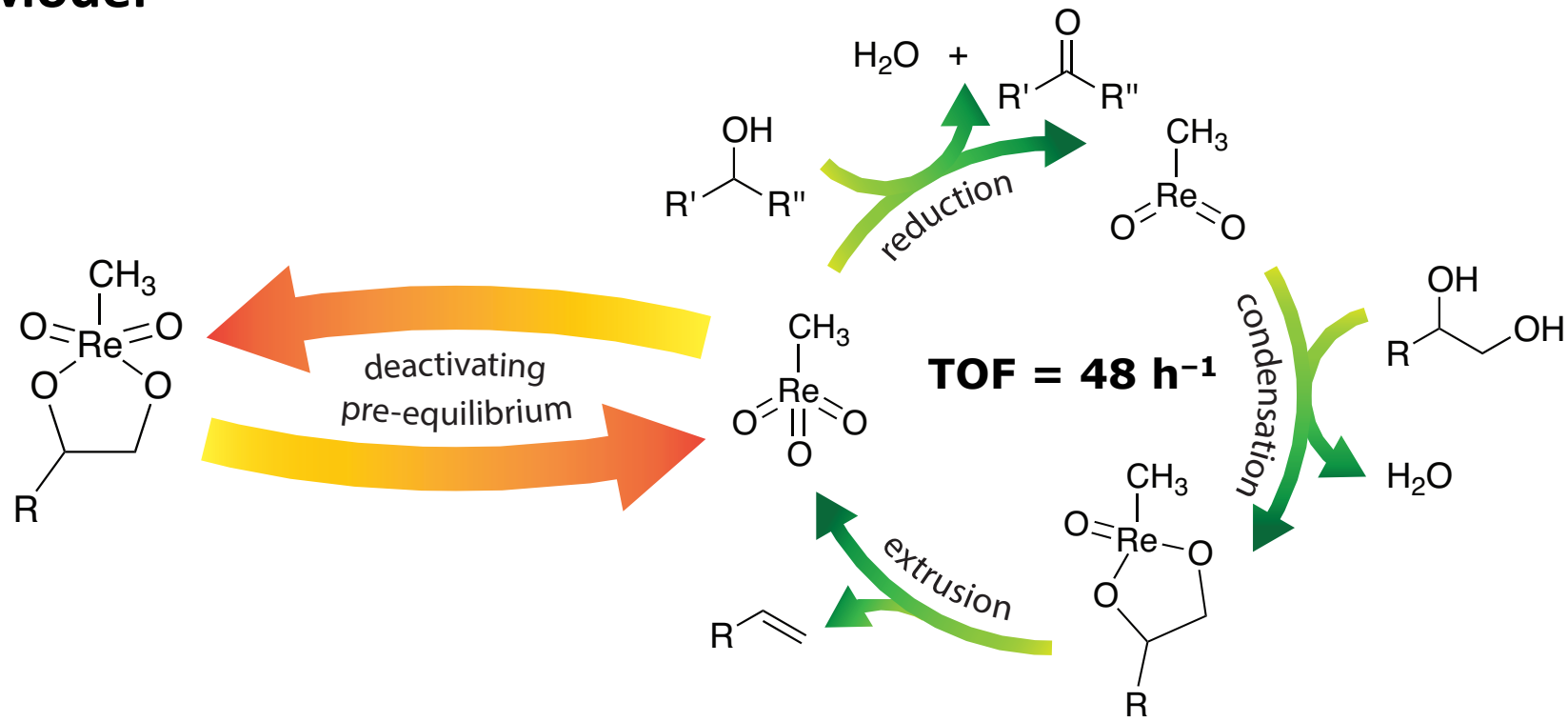
Less reductant: **BLUE** Rate ∝ $[red.]_0$ ⇒ first-order reaction in [red.]

KIE = 2.1 for $C_5H_{11}CD(OH)C_2H_5$ ⇒ rate dependent on [red.]

CONTRADICTION



Model

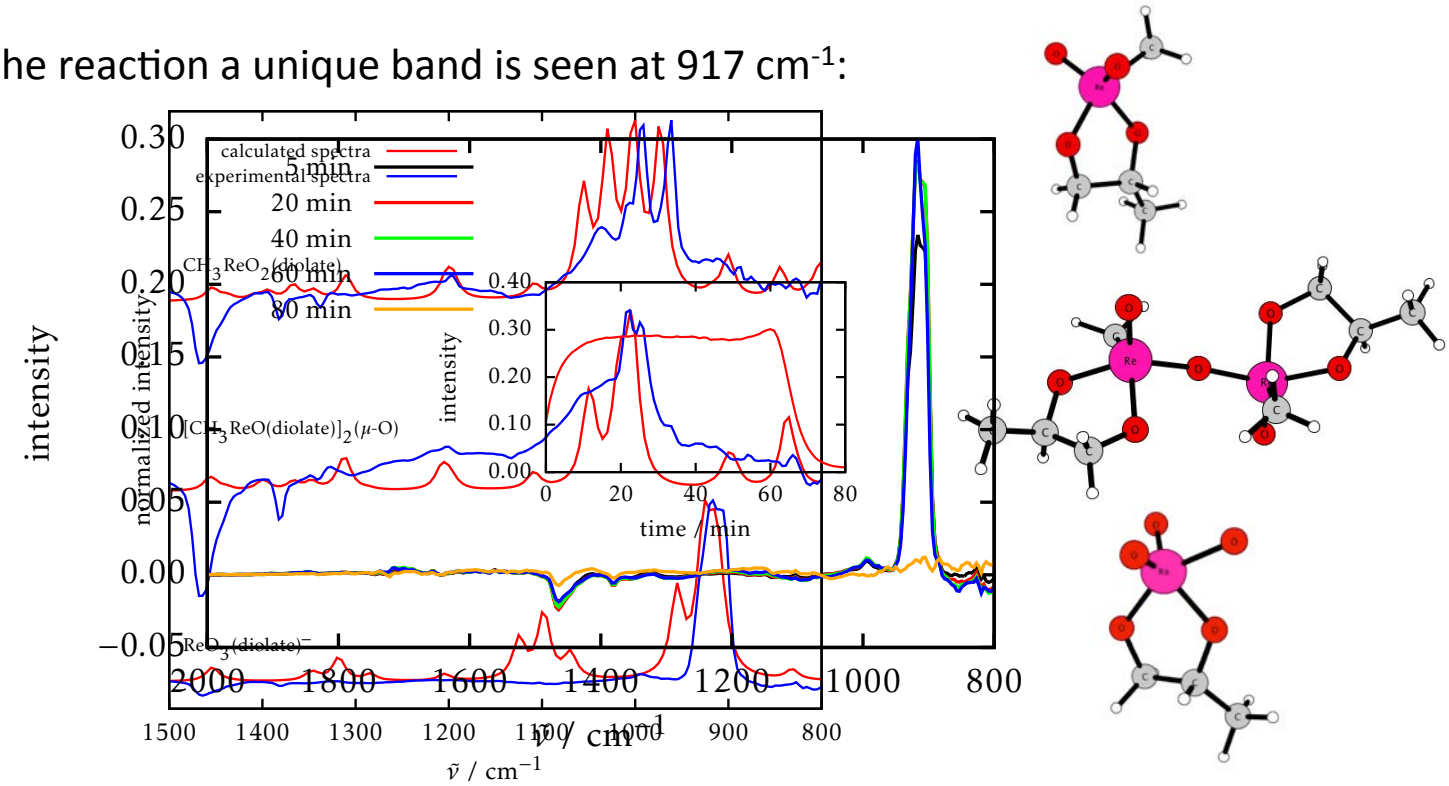


$$\frac{\mathrm{d[alkene]}}{\mathrm{d}t} = \frac{k\, c_{\mathrm{Re}}\, [\mathrm{red}]^2}{K\, [\mathrm{diol}] + [\mathrm{red}]}$$

Dethlefsen, J. R. and Fristrup, P. ChemCatChem **2015**, *7*, 1184-1196

Additional Mechanistic Details

- CH_3ReO_3 is hydrolyzed to ReO_4^-
- IR-spectra of intermediates; DFT calculations and 18O-labelling confirm assignment.
- CH_3ReO_2(diolate) and Re(VI) dimer are hidden by other bands.
- Under the reaction a unique band is seen at 917 cm^{-1}:



- ReO_3(diolate)$^-$ has a very strong band at a unique wavenumber (917 cm^{-1}).

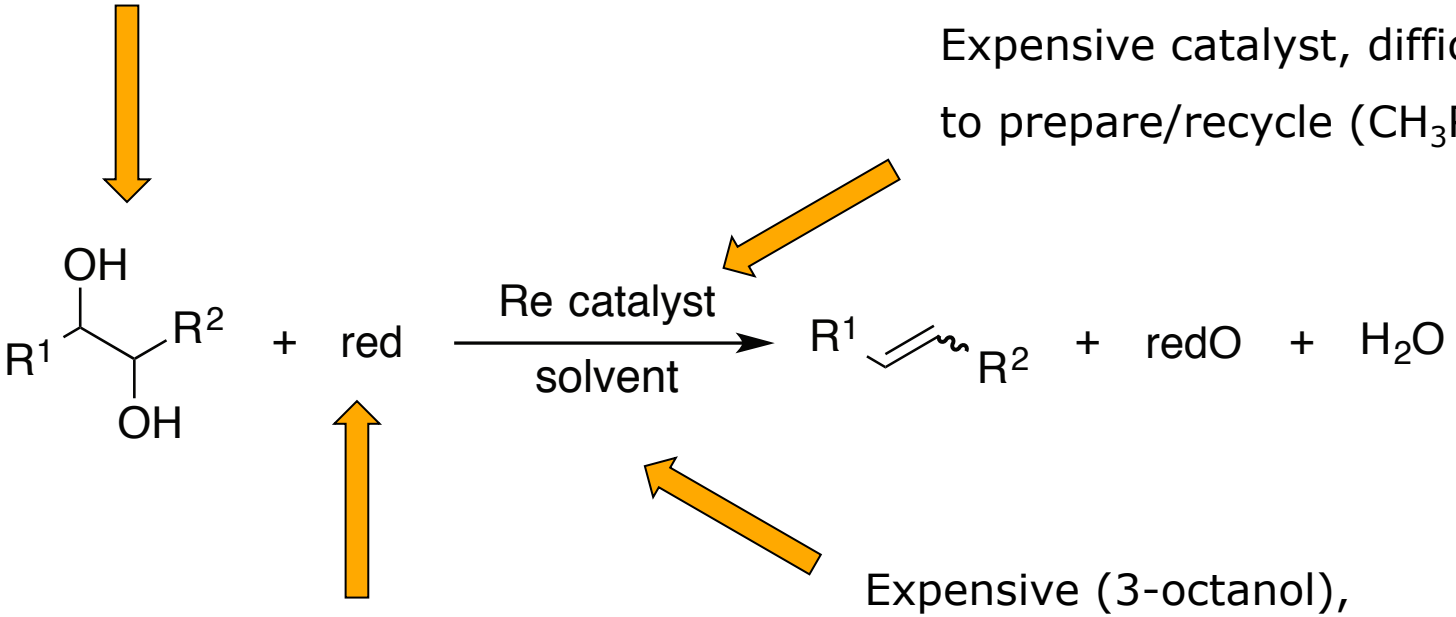
Summary Rhenium-DODH kinetics

- Surprising kinetics revealed by in situ spectroscopy:
  - Reversible deactivation of catalyst by substrate.
  - Acceleration (when substrate is nearly consumed)
  - Hydrolysis of CH_3ReO_3 to ReO_4^-
- Yield and selectivity are good; TOF is low.
- Mechanistic proposal explains all experimental observations and is supported by DFT calculations of the IR spectra of intermediates.

Dethlefsen, J. R. and Fristrup, P. ChemCatChem **2015**, *7*, 1184-1196

Challenges for *sustainable* deoxydehydration

Often model substrate (stilbene diol, long aliphatic diols)



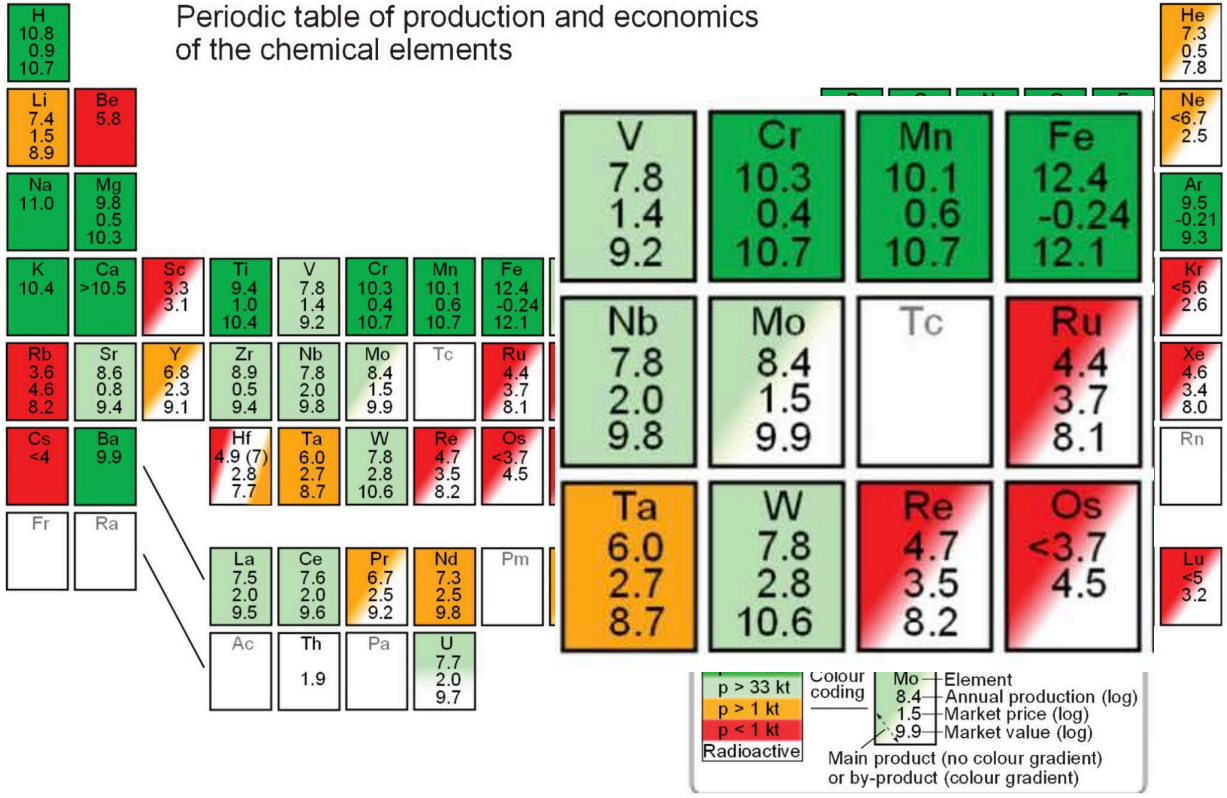
Expensive catalyst, difficult to prepare/recycle (CH_3ReO_3)

Expensive (PPh_3, 3-pentanol), "too" efficient (H_2)

Expensive (3-octanol), toxic (benzene), unable to dissolve biomass (3-pentanol)

“Terawatt challenge”

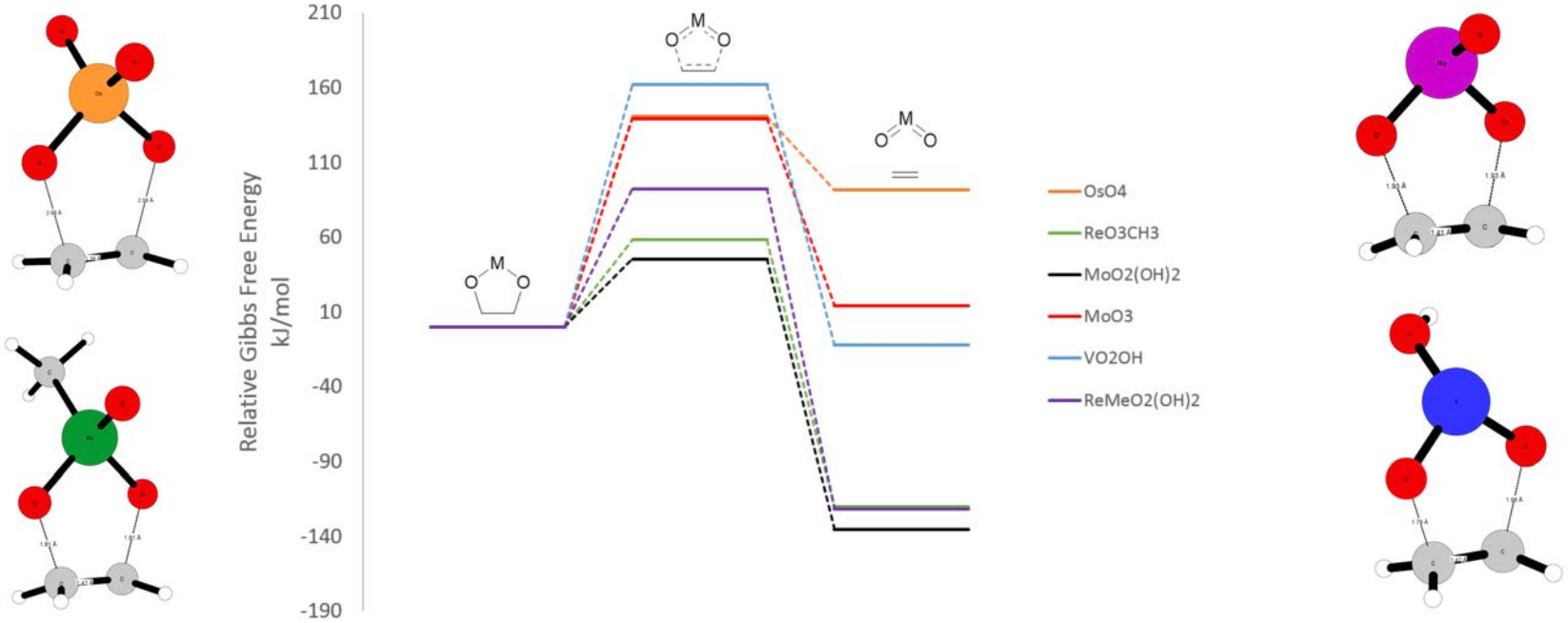
- Current global power consumption is 16 TW and fossil fuels contribute 87%.
- Which elements are available in sufficient amounts? Price? Availability? Geopolitics?



Vesborg and Jaramillo, RSC *Advances*, **2012**, *2*, 7933–7947.

Simplistic DFT study of alkene extrusion

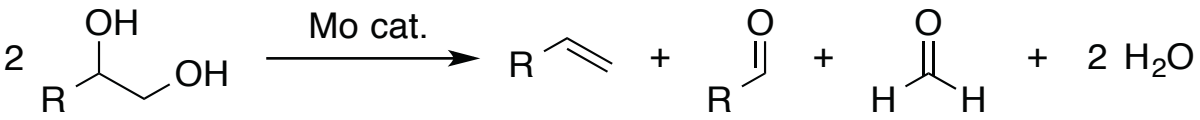
- Ethylene glycol as the diol, simple oxo or methyl ligands, “usual” oxidation states



- For osmium the diolate is favoured, for rhenium the alkene is favoured. MoO_3 initially looks impossible, but simple hydrolysis $MoO_2(OH)_2$ improves the energetics dramatically.

For technetium, see Pearlstein and Davison, *Polyhedron* **1988**, *7*, 1981-1989.

Molybdenum-Catalyzed Disproportionation of Diols



Highest alkene yield: 43% (1,2-tetradecanediol)

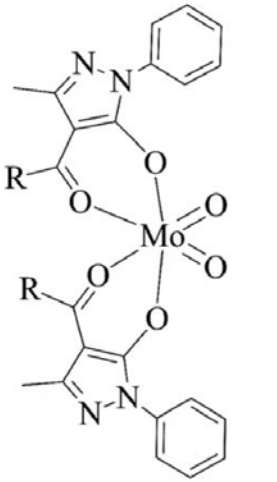
Catalysts:

$MoO_2X_2(bipy)$, X = Cl, Br, CH_3

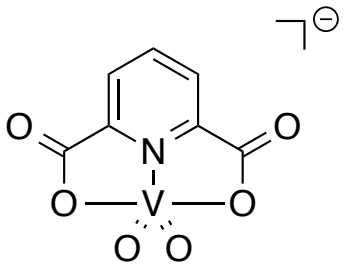
$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$

$Mo(CO)_6$

L. Hills et al.



Nicholas



$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$

WO2015028028 A1

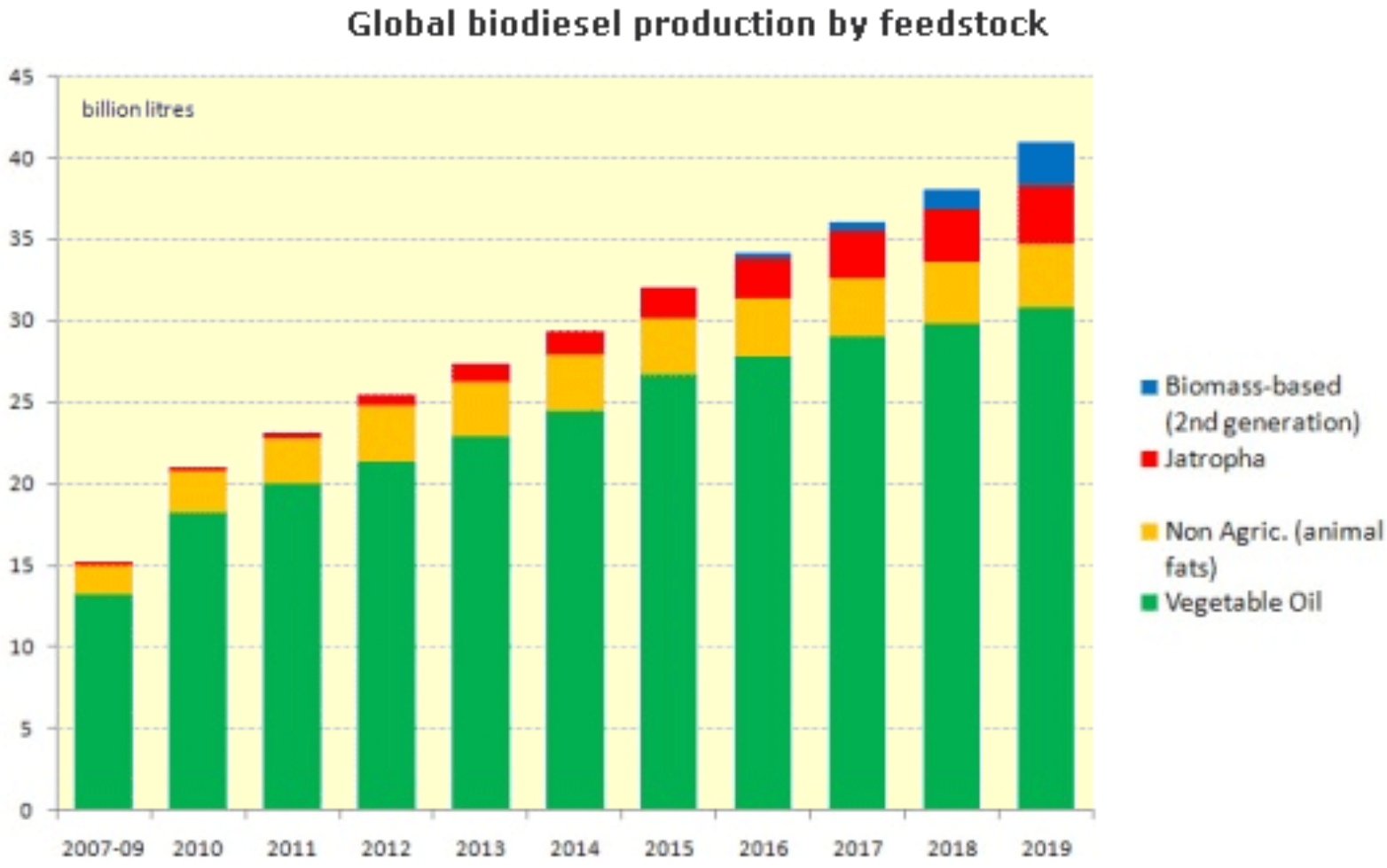
Re: Abu-Omar *ChemSusChem* **2012**, *5*, 1401.

Mo: L. Hills et al. *Eur. J. Inorg. Chem.* **2013**, 3352

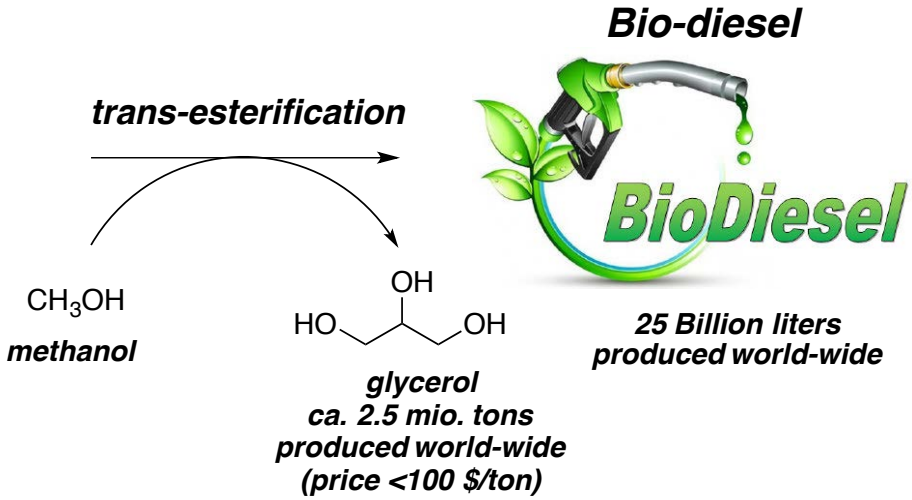
V: Chapman Jr. and Nicholas, *Chem. Commun.*, **2013**, *49*, 8199

Mo: Dethlefsen, Lupp, Oh, Fristrup *ChemSusChem* **2014**, *7*, 425

Biodiesel – a CO_2 neutral fuel



More biodiesel -> more glycerol

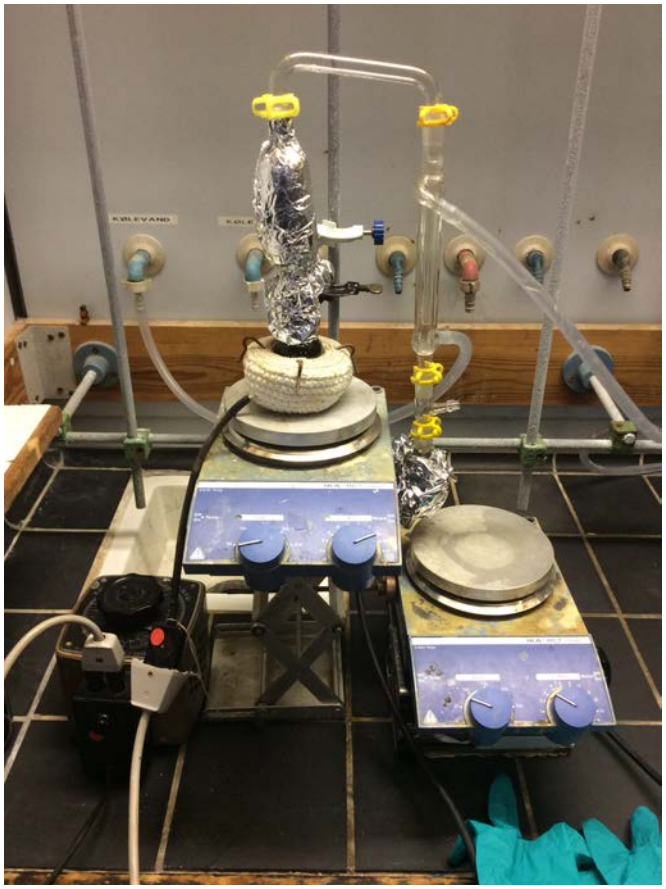


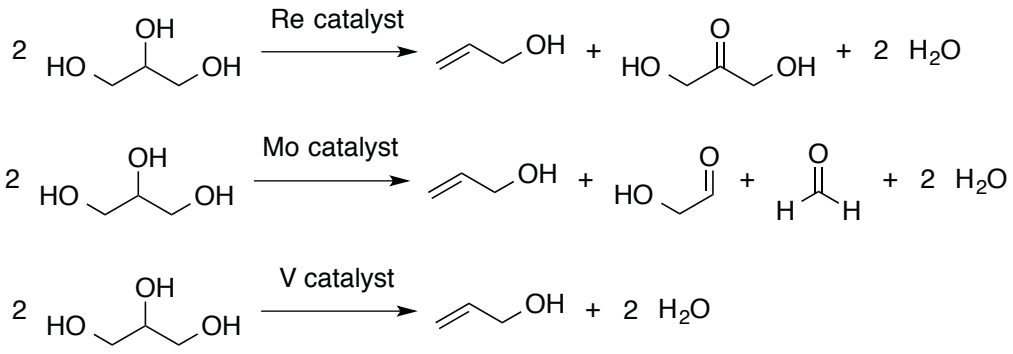
Glycerol is a cheap resource!

Conventional Uses:
Cosmetics, personal care
Beverages, food
Explosives
Paper, printing
Surface coating, textiles

Emerging uses:
Production of epichlorohydrin
Production of propylene glycol
Production of glycerol carbonate
All three are chemistry-driven!

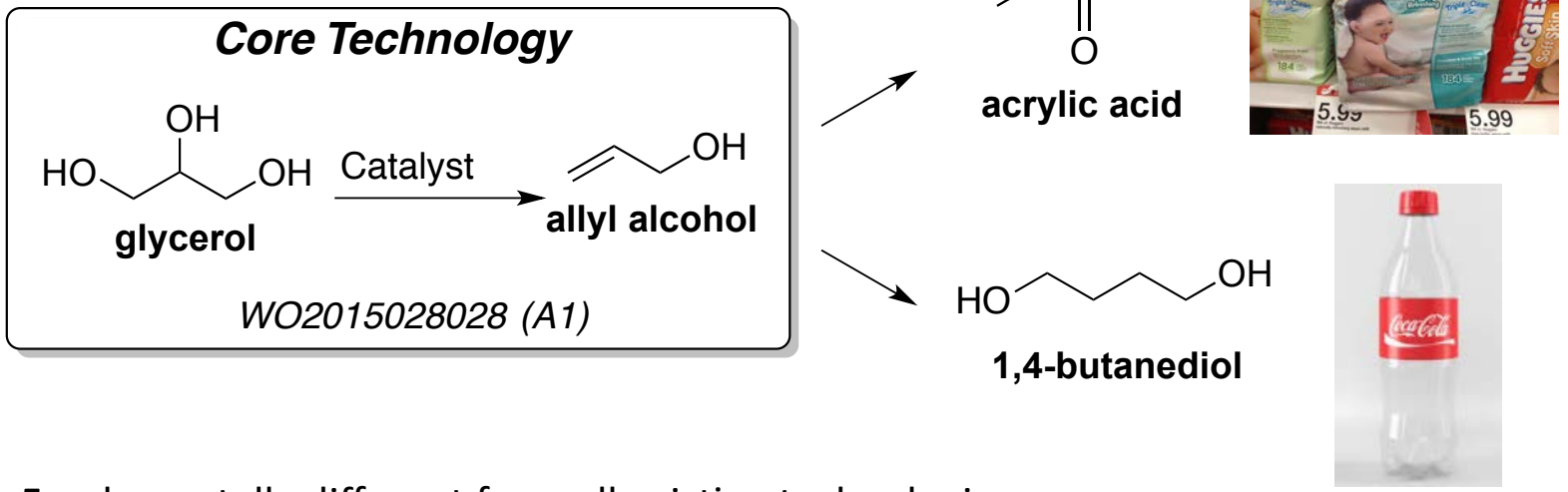
DODH of glycerol to allyl alcohol - Distillation setup





Catalyst	Yield of allyl alcohol	Yield of cond. prod.	Temp. and time
CH_3ReO_3 or NH_4ReO_4	27%	55wt%	175 °C 1 h
AHM	9%	69 wt%	≤230 °C 1.5 h
NH_4VO_3, V_2O_5, $V(acac)_3$	22%	65 wt%	250 °C 2–5 h

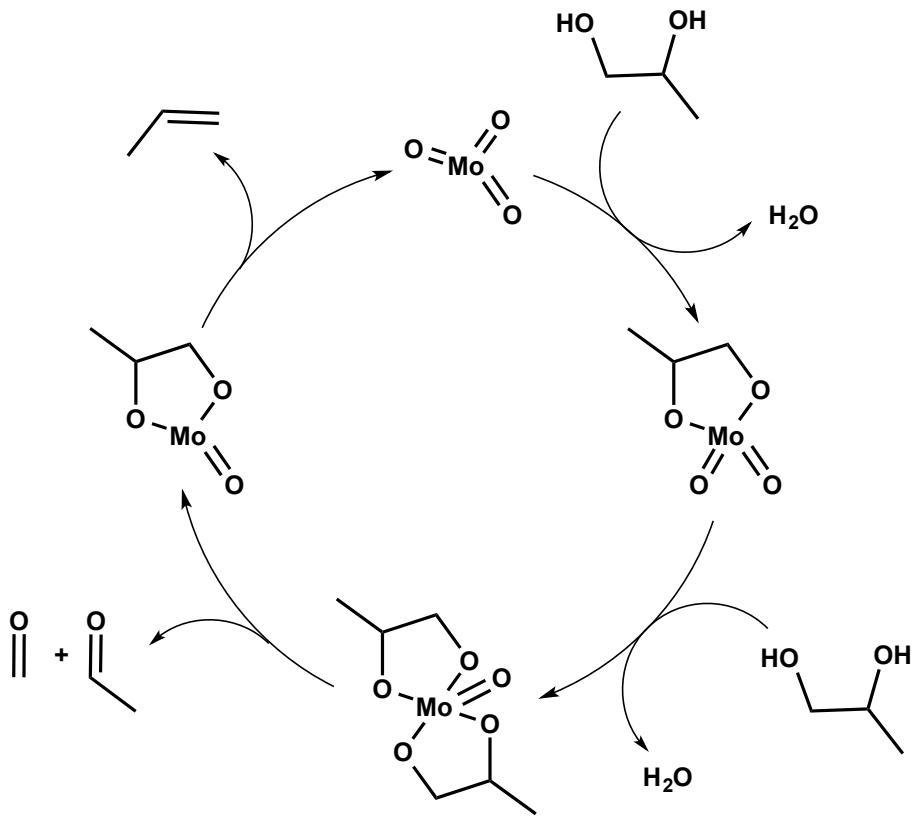
Allycerol – green, biobased allyl alcohol



- Fundamentally different from all existing technologies
- Changes glycerol from “water-like” to “oil-like”
- The reaction works with waste glycerol from enzymatic biodiesel process
- Chemical processes to convert allyl alcohol to large markets with rapid growth (5% annually) acrylic acid (5 mio. tons) and 1,4-butane diol (1.2 mio. tons) are known.

Tentative catalytic cycle

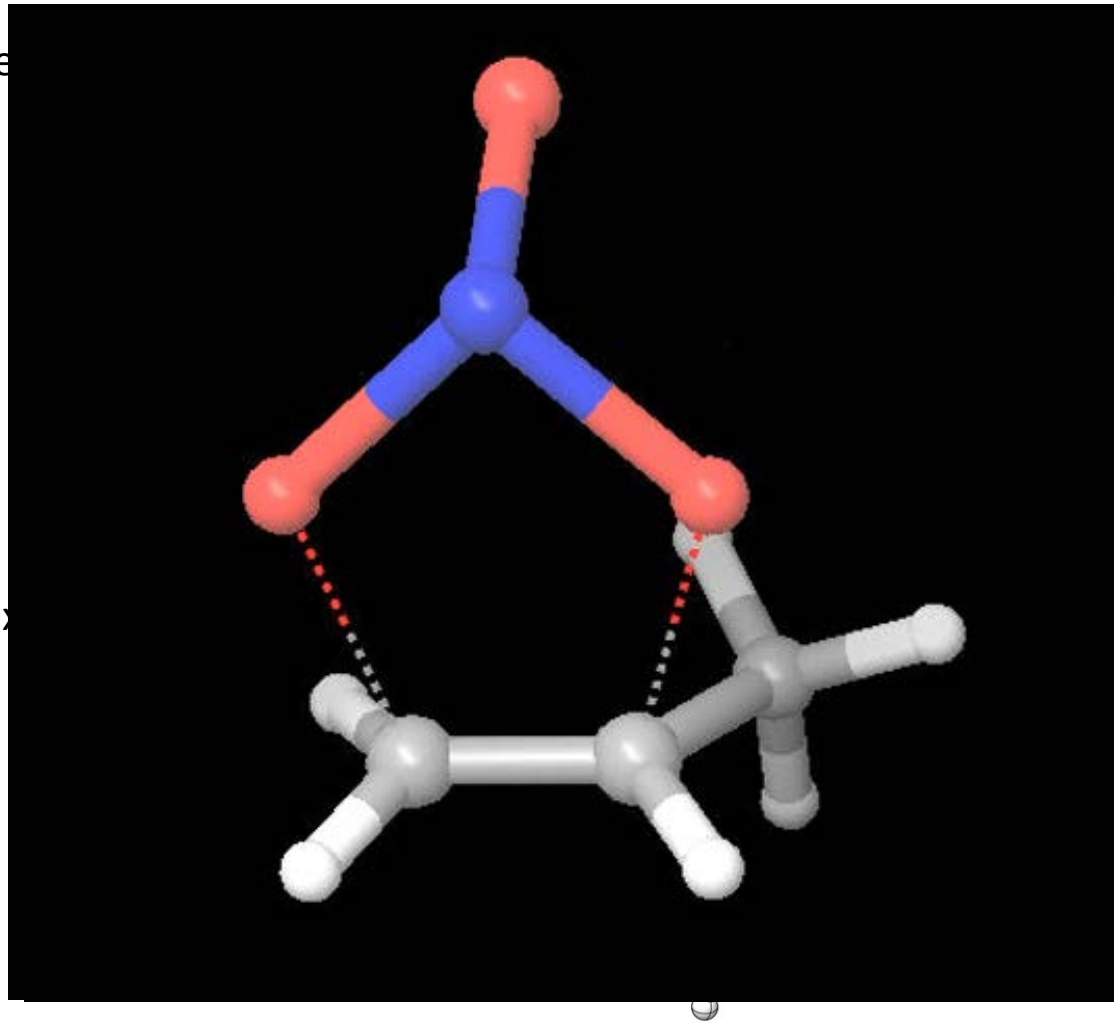
- Experimental results suggests coordination of diol, oxidative cleavage and alkene extrusion as the main steps in the catalytic cycle:



Lupp, Christensen, Dethlefsen, Fristrup *Chem. Eur. J.* **2015**, *21*, 3435-3432.

Oxidative cleavage and alkene extrusion

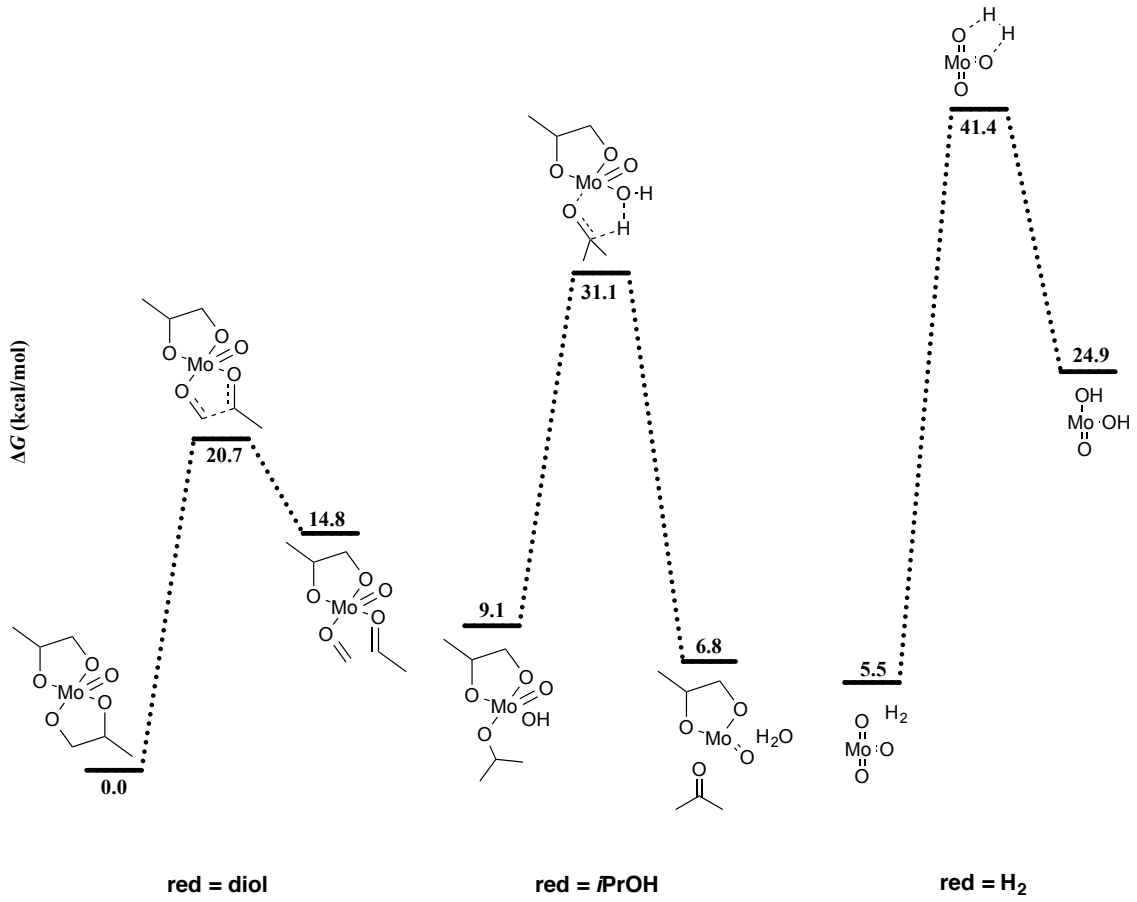
- TS for oxidative
- TS for alkene ex



Lupp, Christensen, Dethlefsen, Fristrup *Chem. Eur. J.* **2015**, *21*, 3435-3432.

Can we avoid diol oxidation?

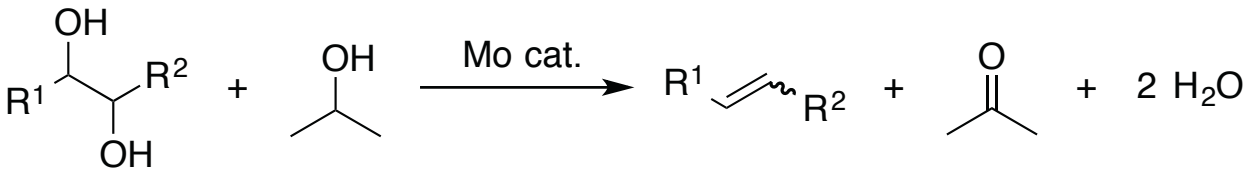
- Comparison of reductants (diol, hydrogen, iPrOH) using DFT calculations:



Dethlefsen, Lupp, Teshome, Nielsen, Fristrup *ACS Catalysis* **2015**, *5*, 3638-3647

New Strategy – avoid diol oxidation

- Catalyst: $(NH_4)_6Mo_7O_{24}$.
- Solvent: Cheap and green solvent miscible with carbohydrates (*i*PrOH).
- Reductant: *i*PrOH, oxidized to acetone.
- Substrate: Model compounds and glycerol.



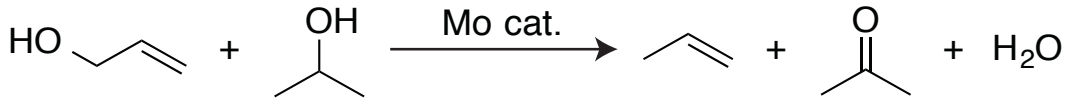
Conditions:

12 h at 250 °C

Approx. 80 bar

Alkene yield: **77%** (from 1,2-hexanediol)

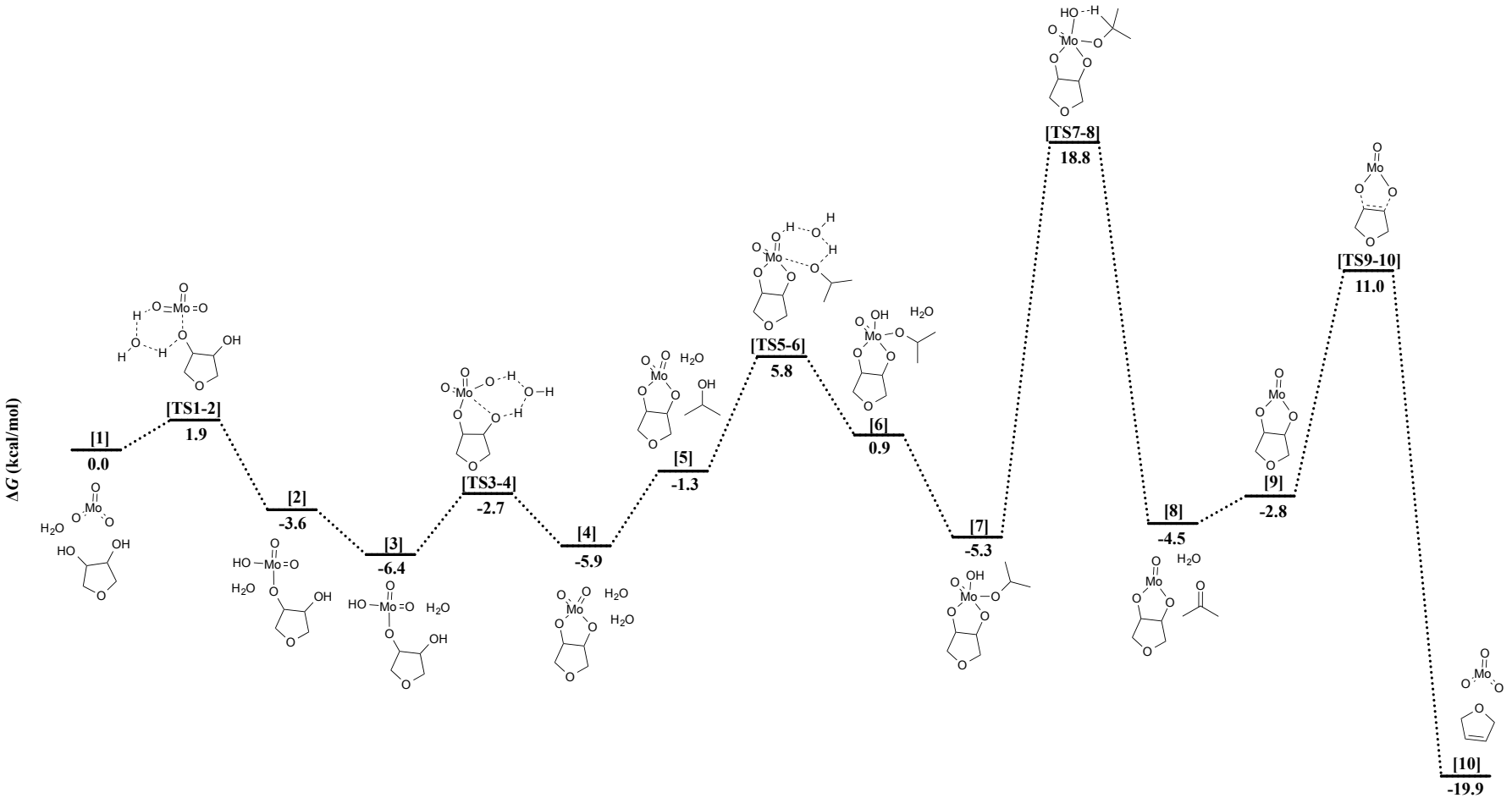
Yield of reduced species: **92%** (from 1,2-cyclohexanediol)



Propylene yield: at least 28% (difficult to quantify)

Dethlefsen, Lupp, Teshome, Nielsen, Fristrup *ACS Catalysis* **2015**, *5*, 3638-3647

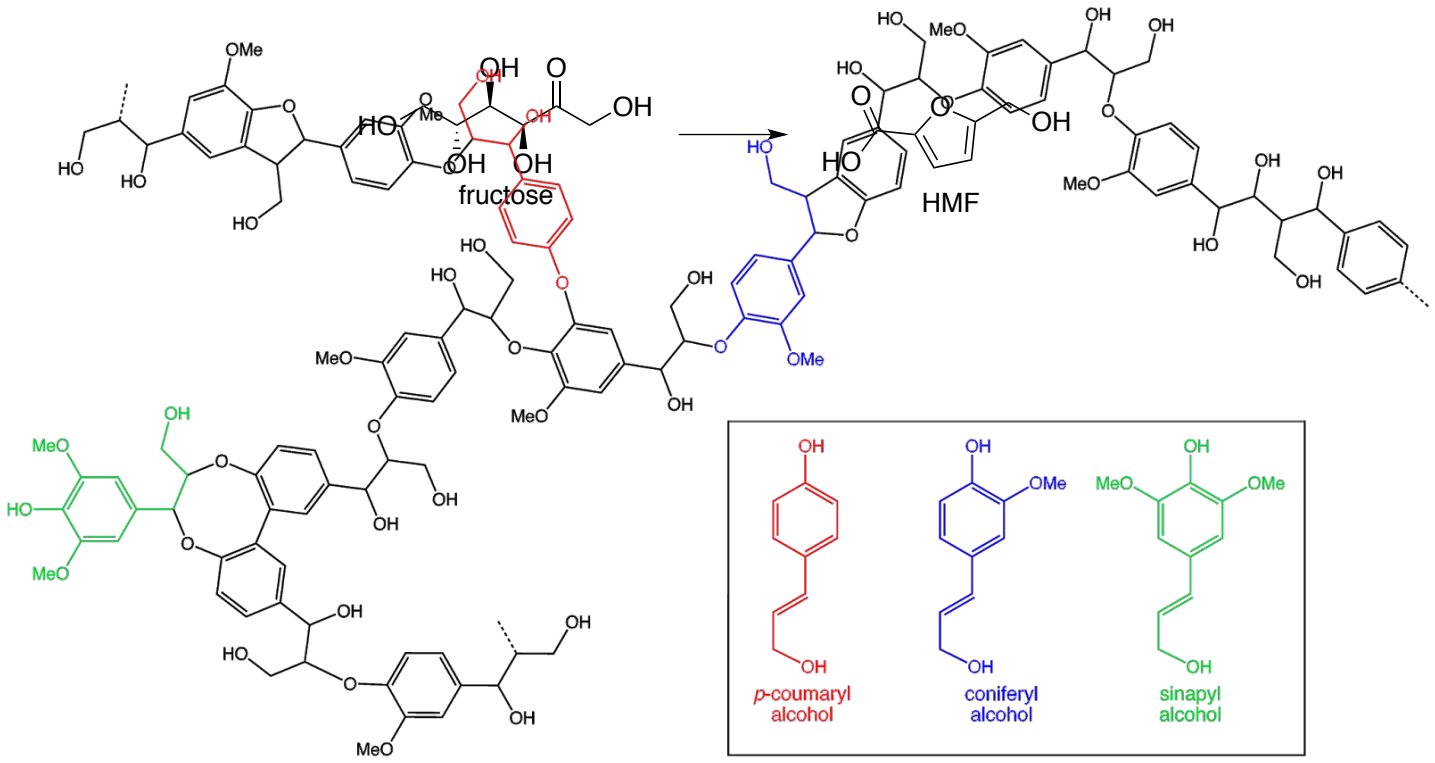
Full catalytic cycle



Dethlefsen, Lupp, Teshome, Nielsen, Fristrup *ACS Catalysis* **2015**, *5*, 3638-3647

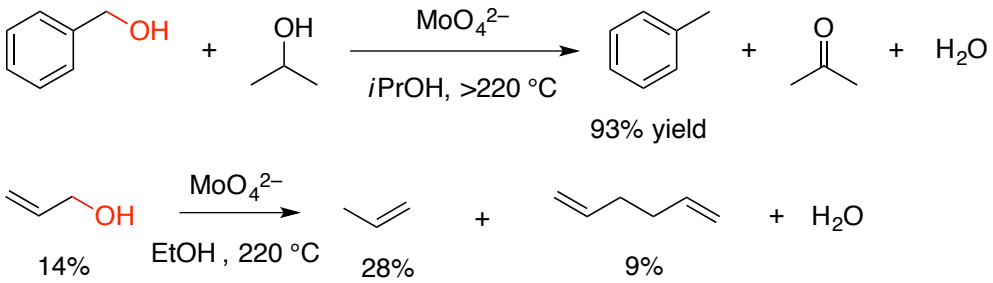
Deoxygenations of other alcohols

- The DODH reaction requires vicinal diols but biomass also contains “isolated” alcohols, for instance phenols or allylic alcohols in lignin or the hydroxymethyl group in HMF

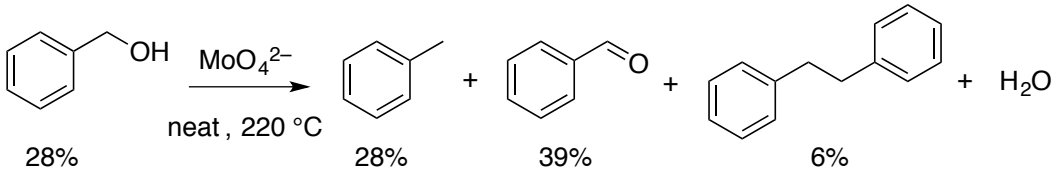


Deoxygenation of activated alcohols

- Allyl alcohol and benzyl alcohol can be deoxygenated:

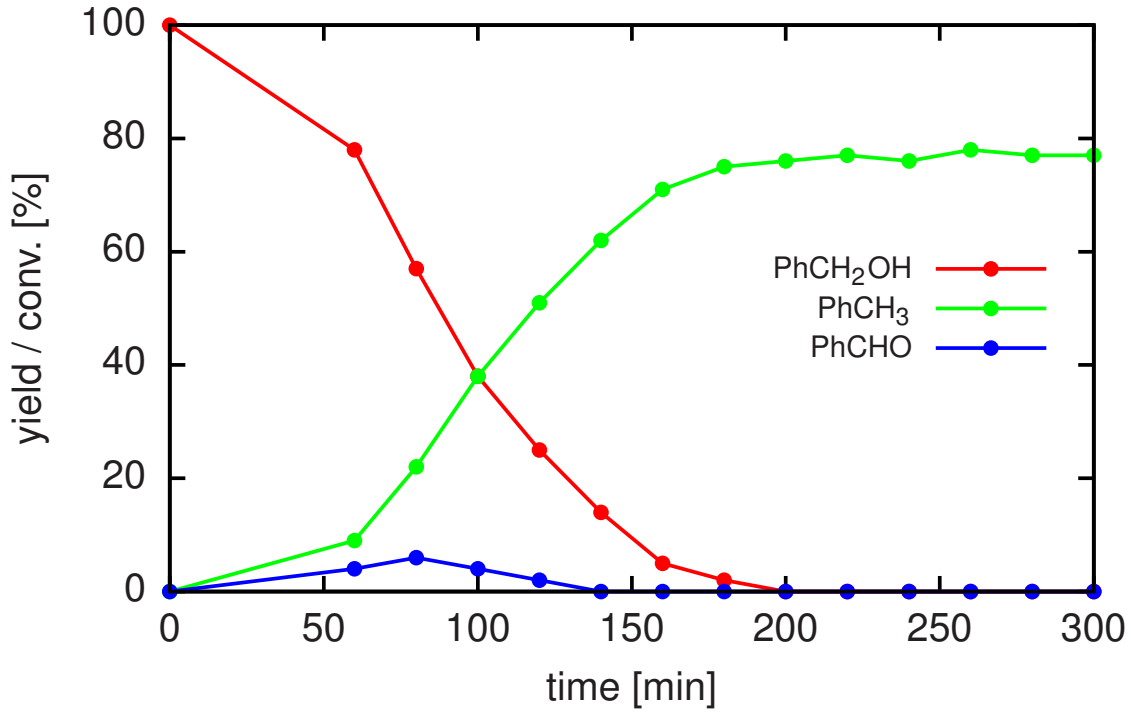


- In neat conditions dimerization is also observed for benzyl alcohol:



D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

Even in *i*PrOH Benzyl alcohol disproportionates

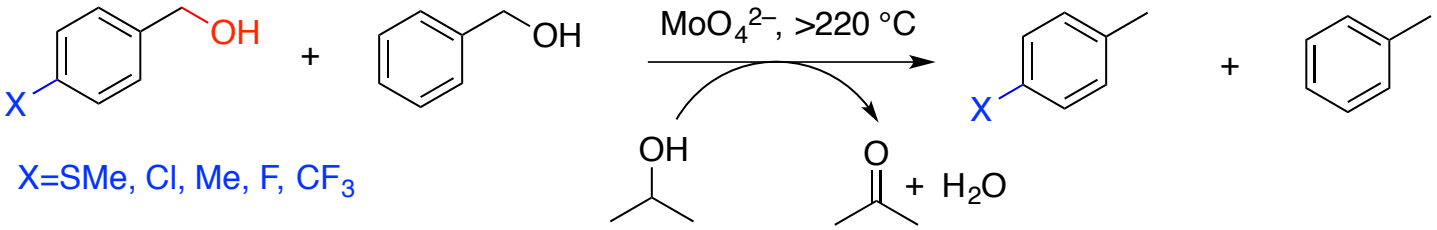


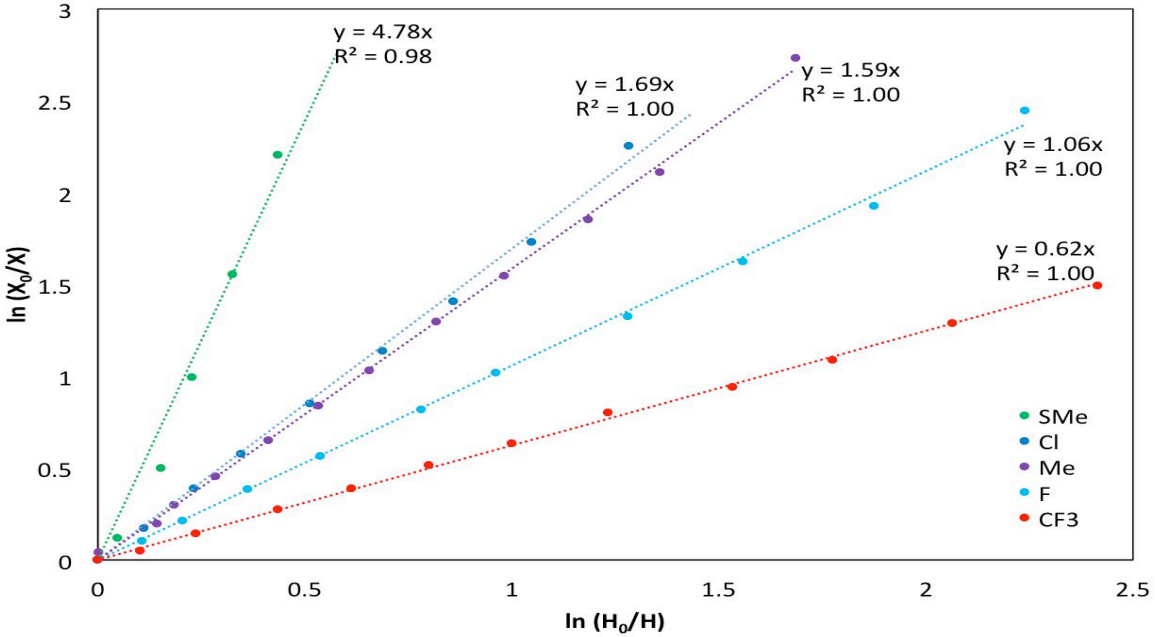
- BnOH is a better reductant than iPrOH.

D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

Hammett study

- Carried out as competition studies:

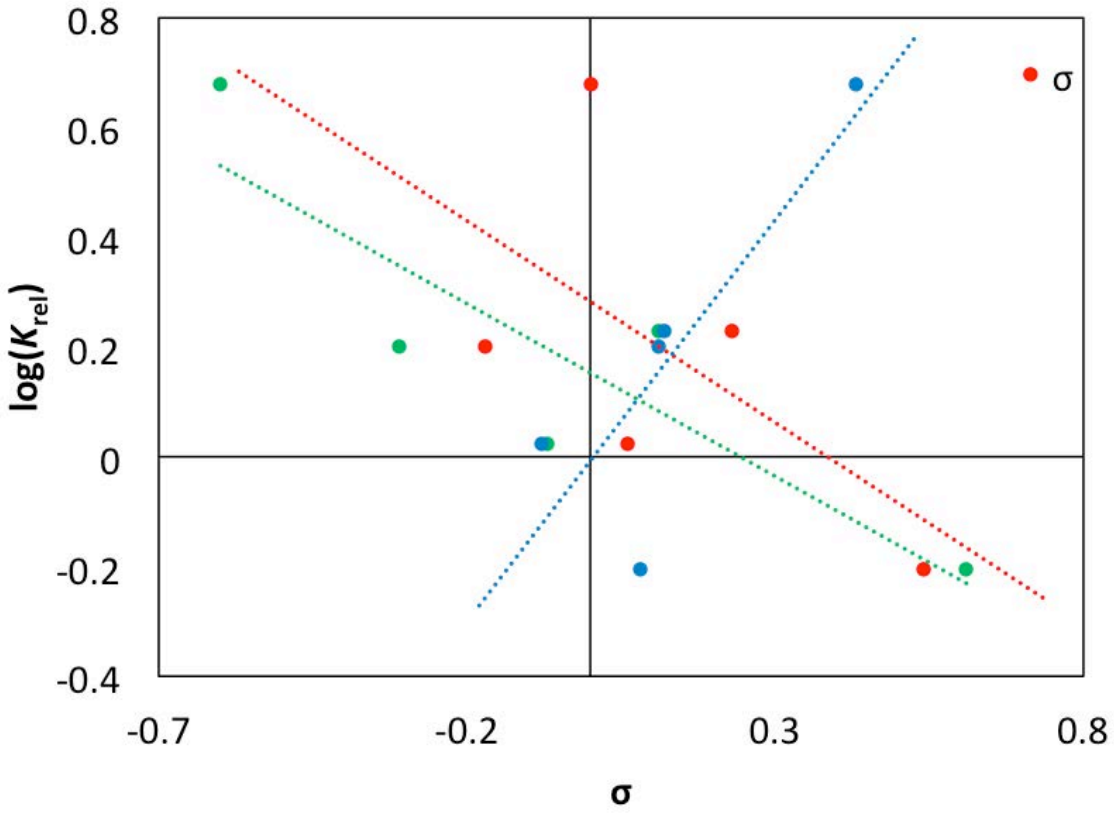




For earlier Hammett studies, see: JACS **2005**, *127, 15756; JACS* **2008**, *130, 5206; Chem. Eur. J.* **2012**, *18, 15683; Catal. Today* **2013**, *203, 211; Org. Biomol. Chem.* **2012**, *10, 2569; ACS Catal.* **2013**, *3, 294.*

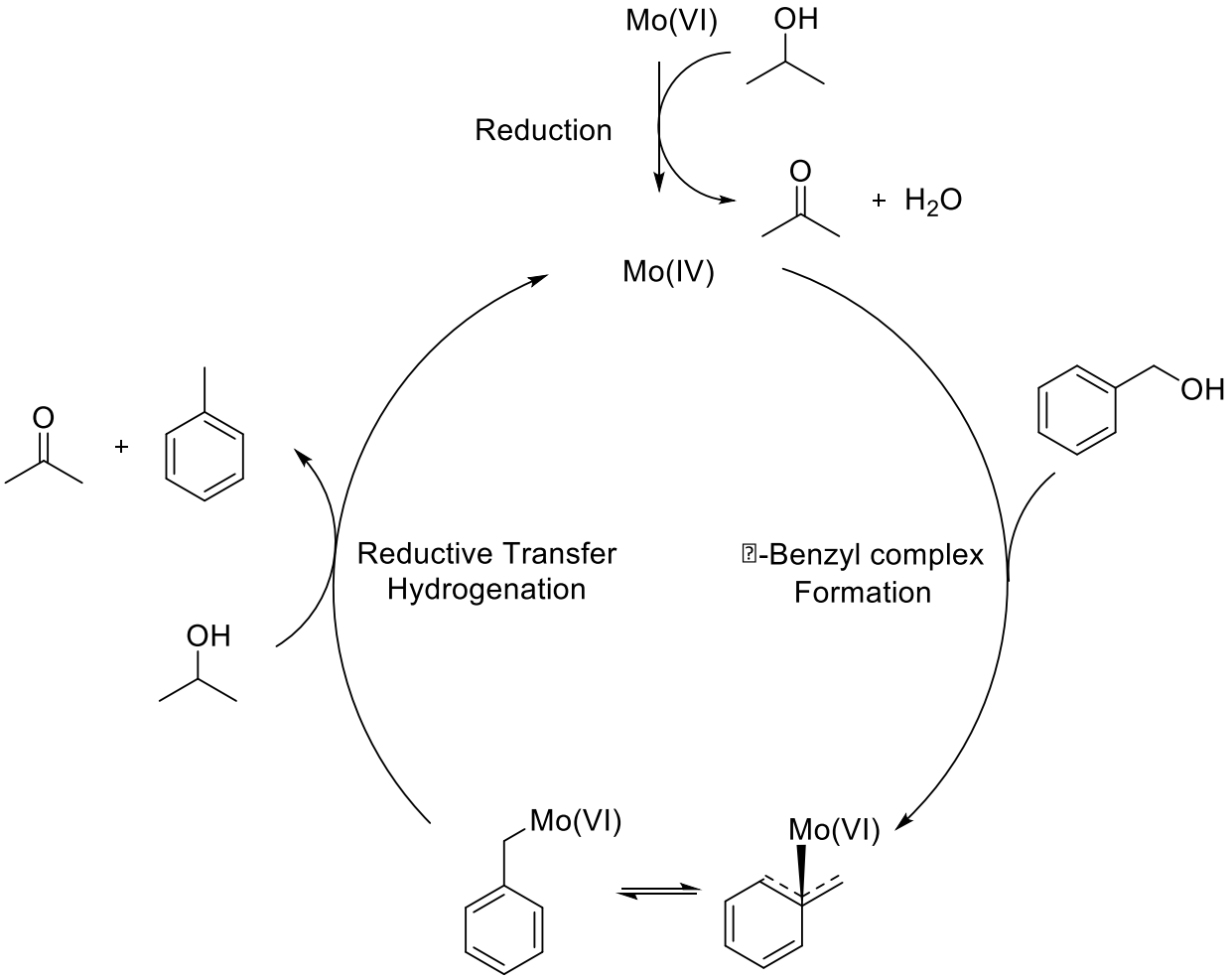
Hammett plot

- Not linear for any set of σ-values (σ, σ^+, $\sigma^\bullet$):



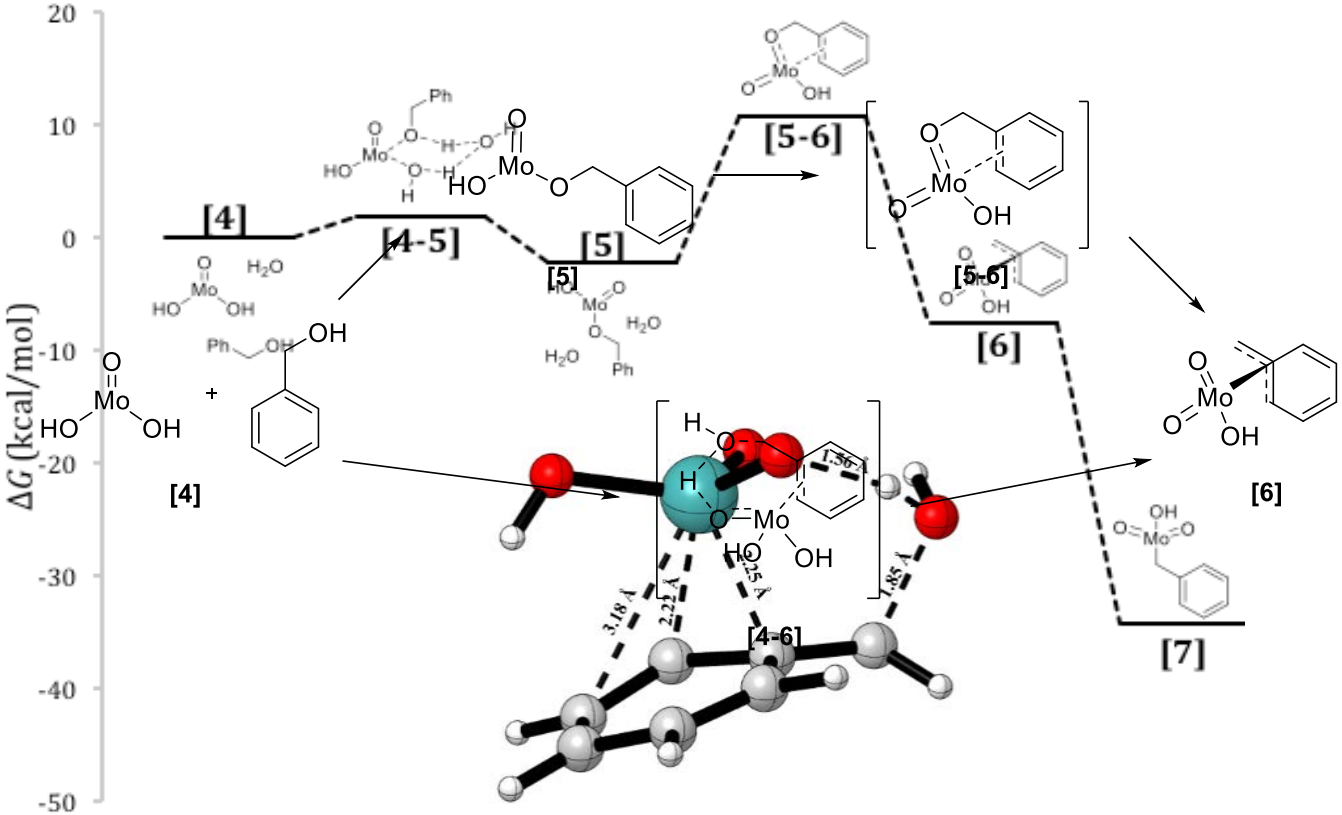
D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

DFT studies



D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

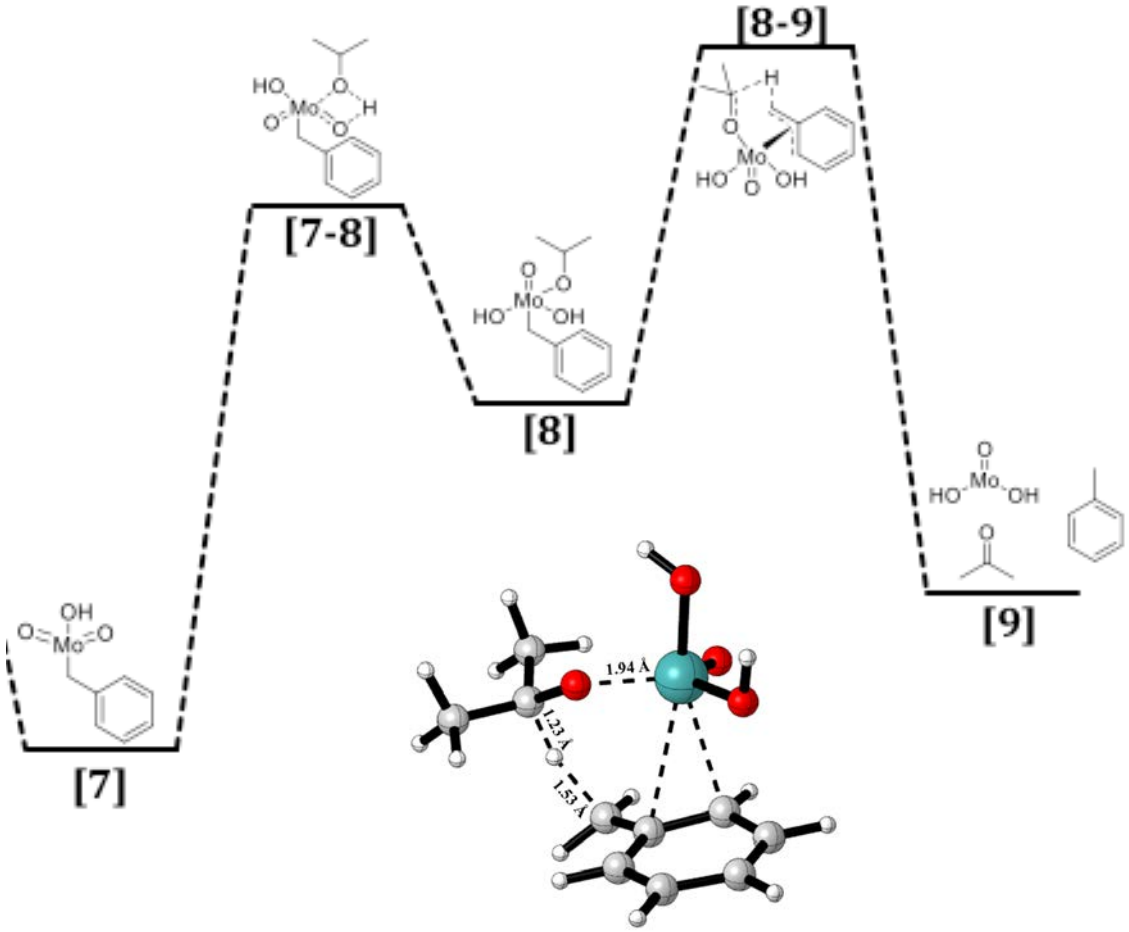
Mechanism for generation of π-benzyl molybdenum complex



The favoured TS **[5-6]**.

D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

Reductive elimination of toluene

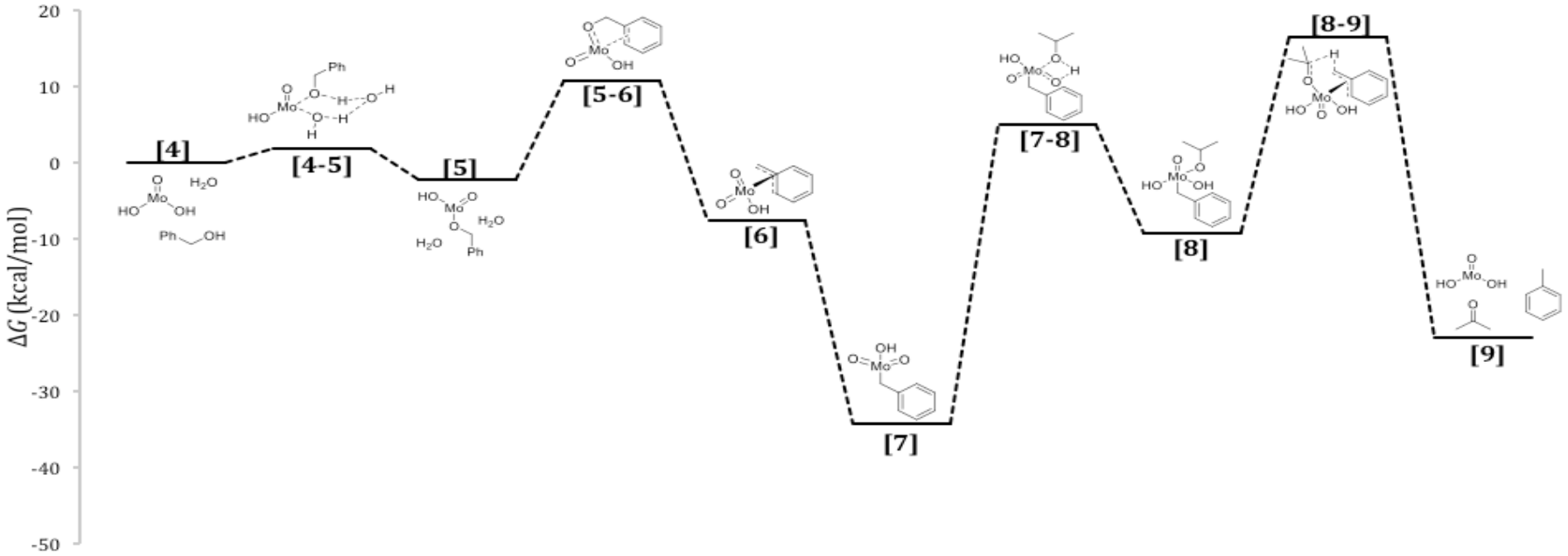


TS **[8-9]**.

D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

Overall energy profile

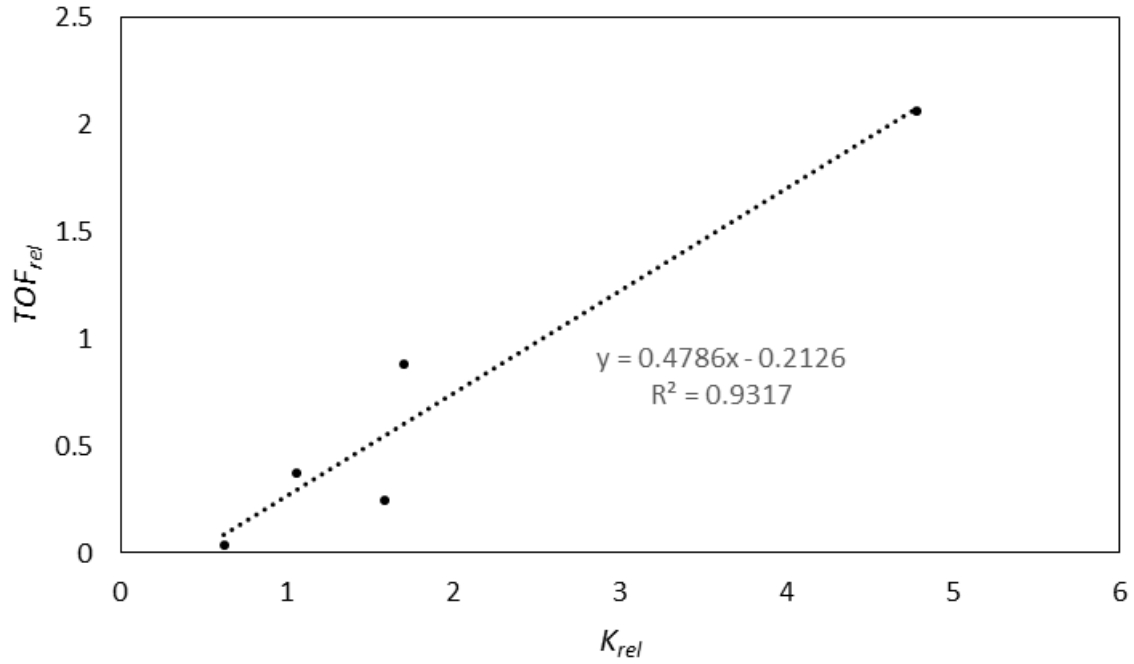
- Exergonic by 37 kcal/mol



- Largest barrier (**7 -> 7-8**) is 31 kcal/mol and the energetic span (**7 -> 8-9**) 51 kcal/mol.

D. B. Larsen, A. R. Petersen, J. R. Dethlefsen, A. Teshome, P. Fristrup *Chem. Eur. J.* **2016**, *22*, 16621-16631.

Comparison of exp. vs. theoretical rates

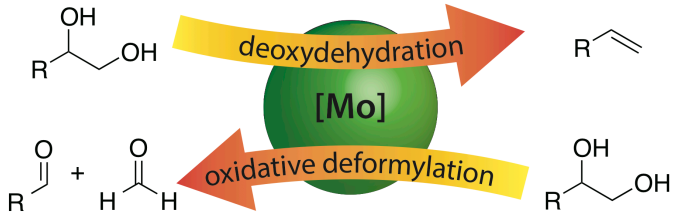


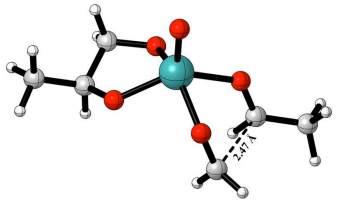
- Correlation of calculated, relative TOF values with relative reactivities determined in the competition experiments (Hammett study).

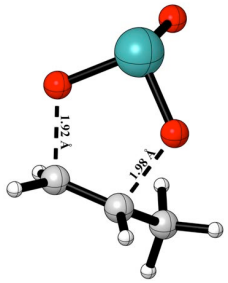
Dalton Trans. **2014**, *43*, 11093.
Synlett **2015**, *26*, 508.

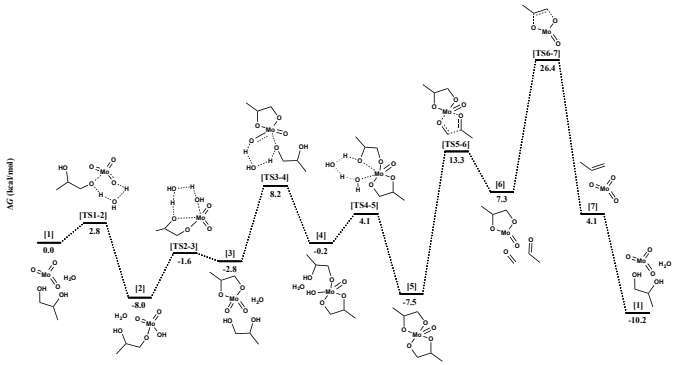
Conclusions

- Molybdenum-catalyzed DODH has been developed:
  - 1st generation process: diol is used as reductant
  - 2nd generation process: iPrOH as both solvent and reductant
  - DFT calculations were crucial in understanding the reactivity

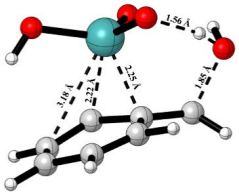


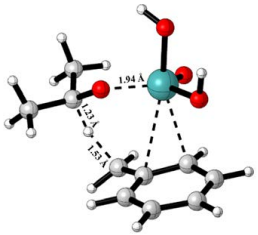


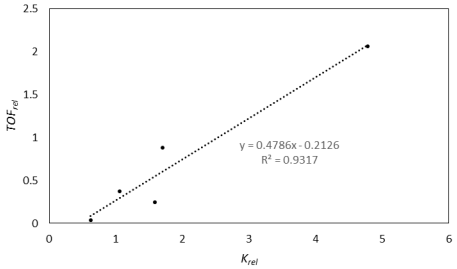




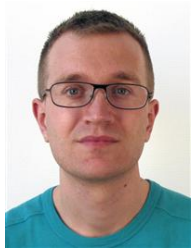
- Mechanistic study of Molybdenum-catalyzed transfer-HDO protocol
  - Overall good agreement between exp. and theoretical rates







Acknowledgements


Johannes R. Dethlefsen


Niels J. Christensen


Allan R. Petersen

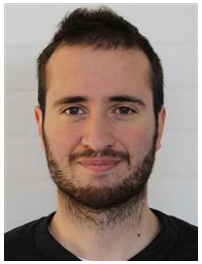

Ayele T. Gorfo


Daniel Lupp


Lasse Bo Nielsen


Søren Tolborg


Rita Coláco


Giuseppe Antonacci


Daniel Bo Larsen

THANK YOU FOR THE ATTENTION!

CARISMA

BIOVALUE SPIR

DTU Chemistry
Department of Chemistry

Sapere Aude