Precise Determination of Reaction Rate Constants by Combining Reactions and Separations: New Routes in the High-Throughput Screening of Catalysts

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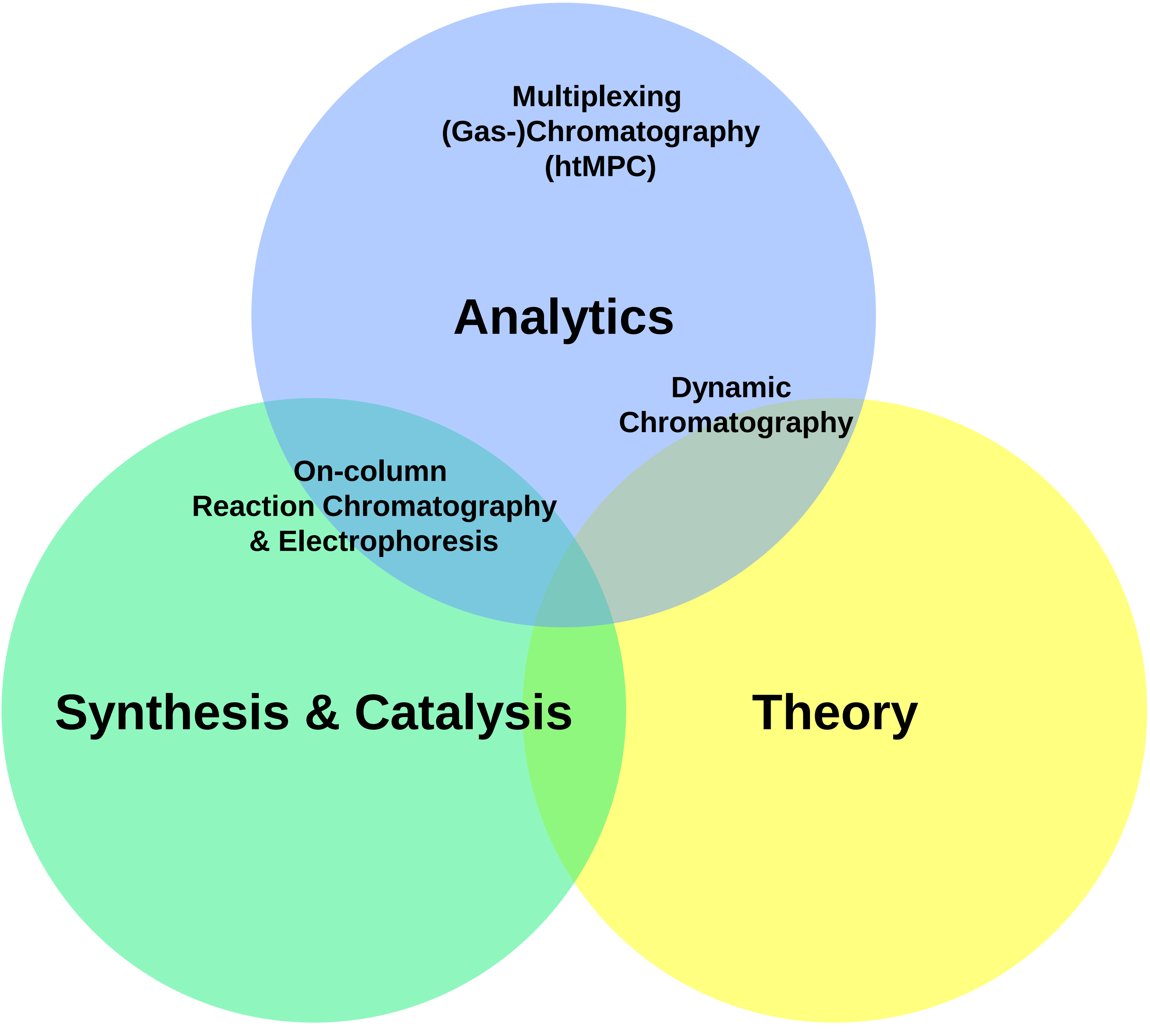
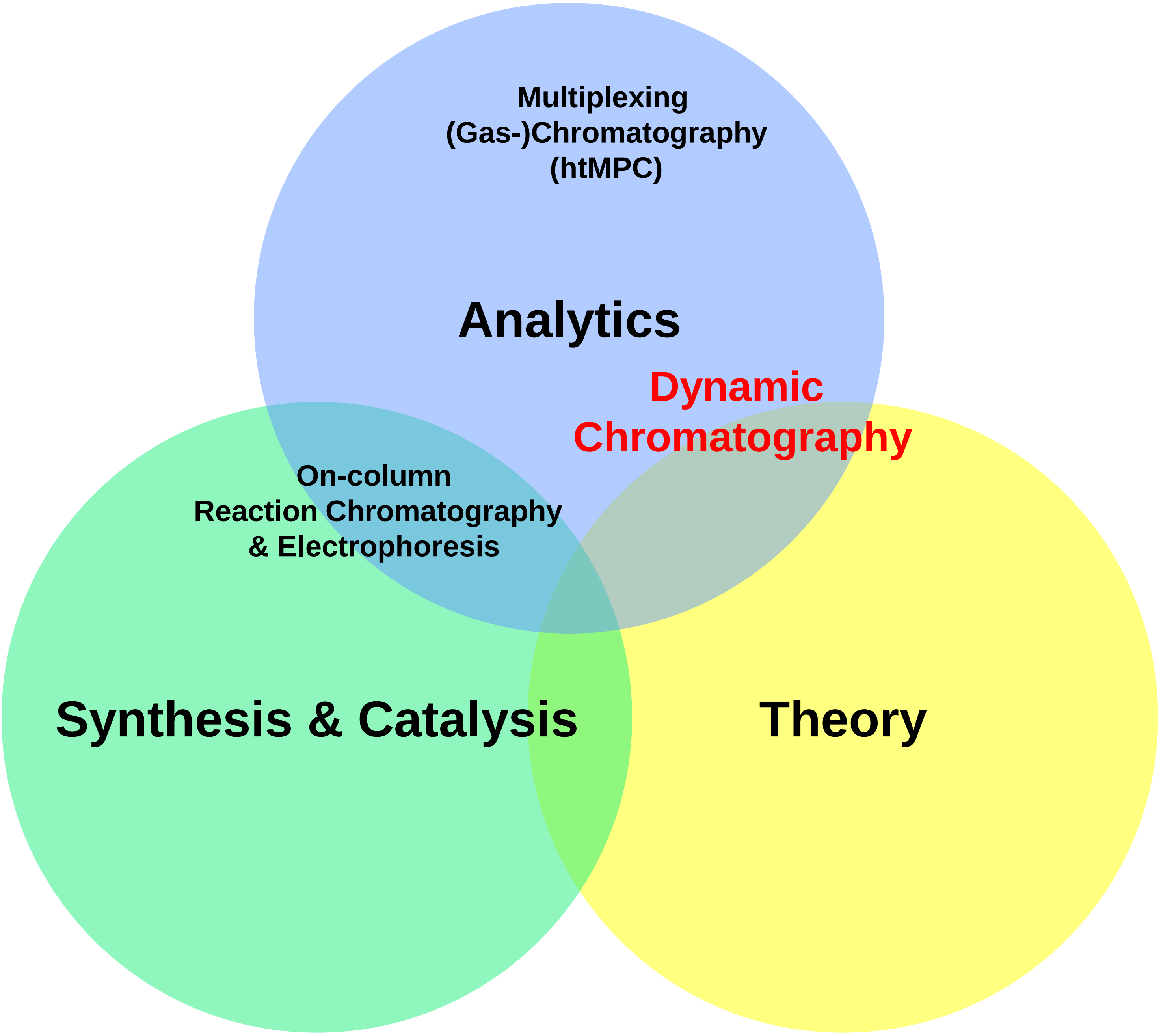

Multiplexing
(Gas-)Chromatography
(htMPC)
Analytics
Dynamic
Chromatography
On-column
Reaction Chromatography
& Electrophoresis
Synthesis & Catalysis
Theory


Multiplexing
(Gas-)Chromatography
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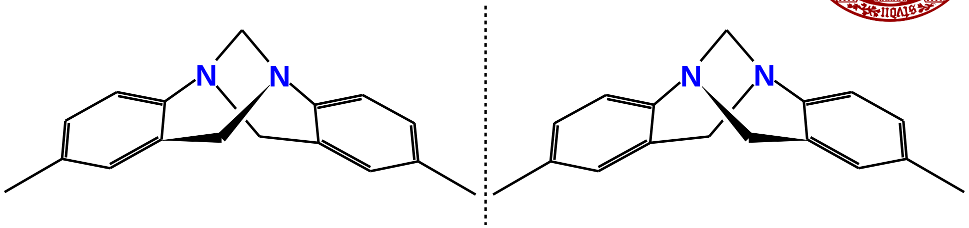
Analytics
Dynamic
Chromatography
On-column
Reaction Chromatography
& Electrophoresis
Synthesis & Catalysis
Theory

Pyramidal Chiral Nitrogen

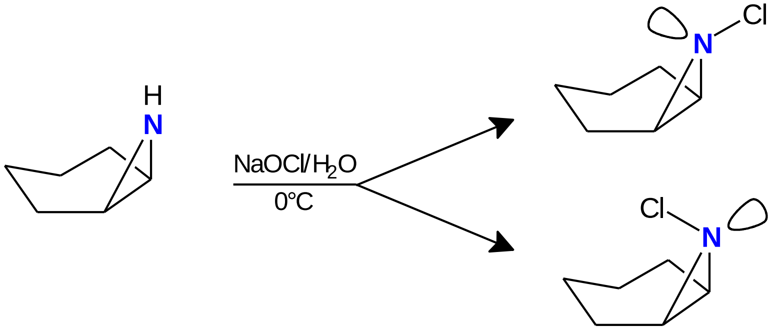
1944 V. Prelog et al.

Separation of Tröger's Base



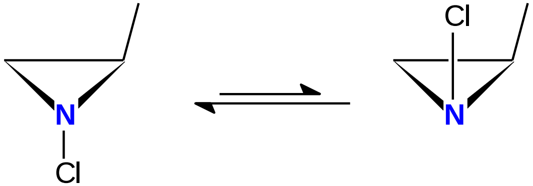
1968 A. Eschenmoser et al.

Isolation of N-Chloro-7-azabicyclo[4.1.0]heptane



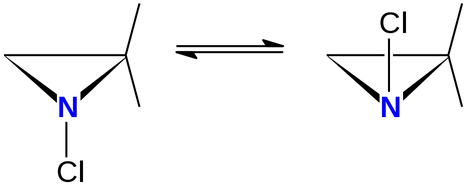
1968 J.-M. Lehn

N-Chloro-2-methylaziridine

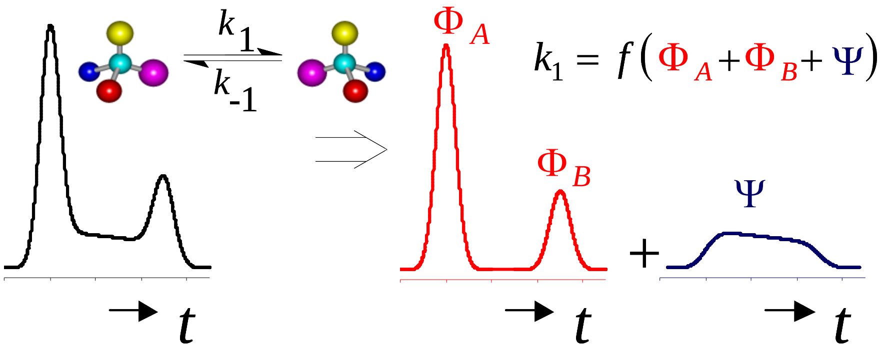


1977 R.G. Kostyanovsky et al.

Isolation of (+)-N-Chloro-2,2-dimethylaziridine

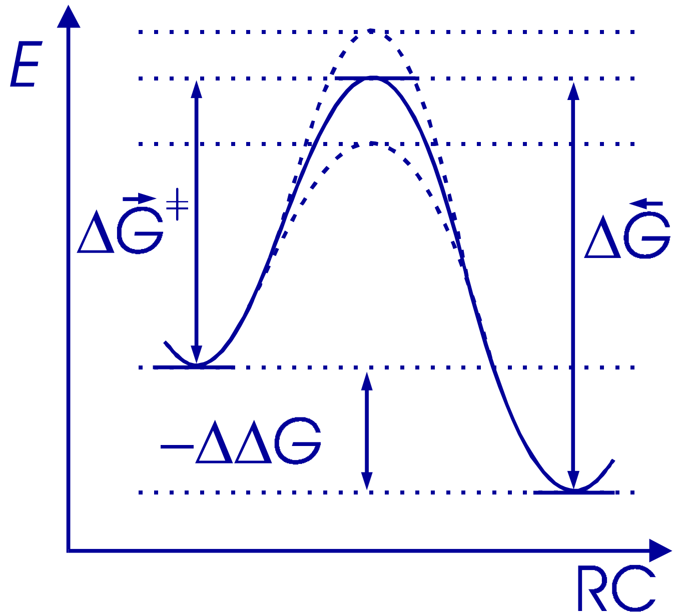


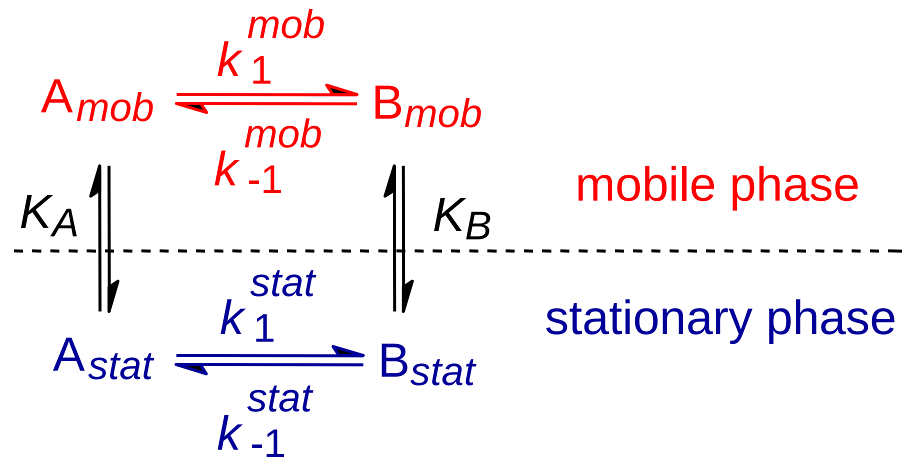
Molecular Dynamics: Interconversion



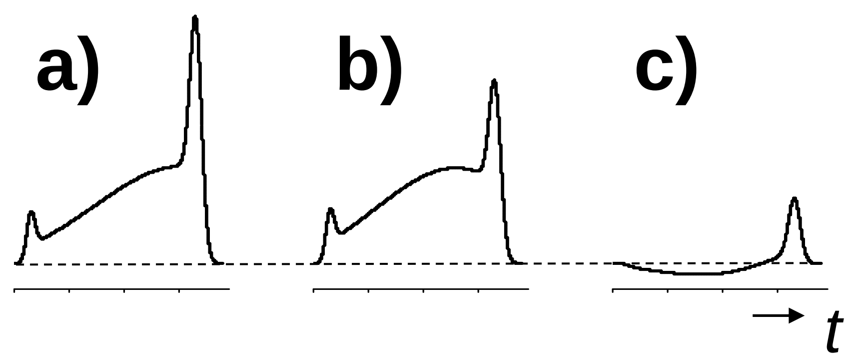
- Determination of reaction rate constants
- In the past long calculation times
- Precise determination of activation parameters
- Elucidation of reaction mechanisms

Rate Constants

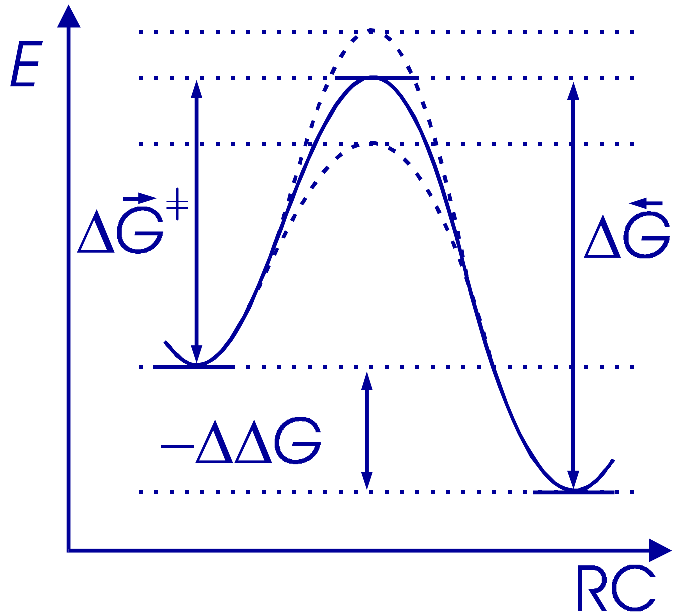


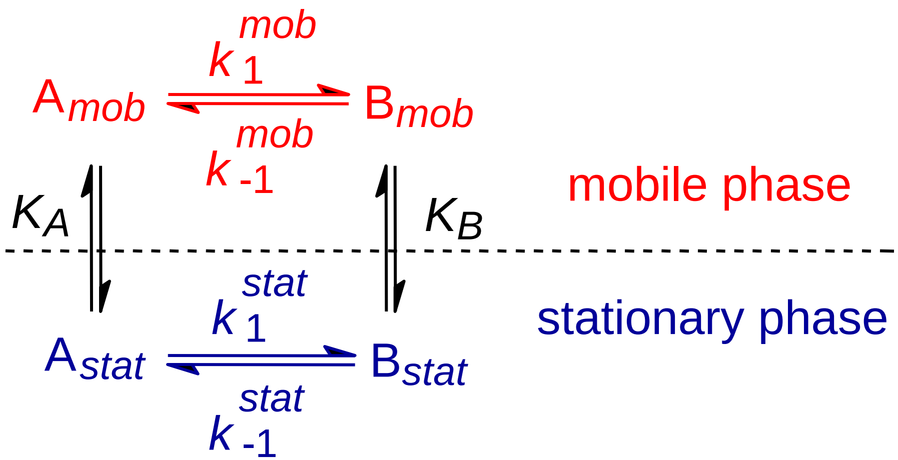


$$K^{stat} = \frac{K'_B}{K'_A} = \frac{k'_B}{k'_A} = \frac{k_1^{stat}}{k_{-1}^{stat}}$$



Rate Constants

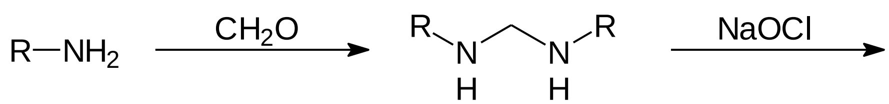


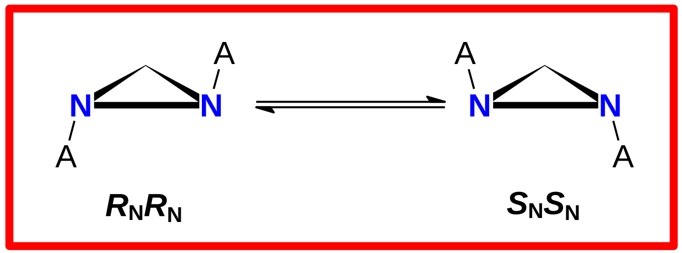


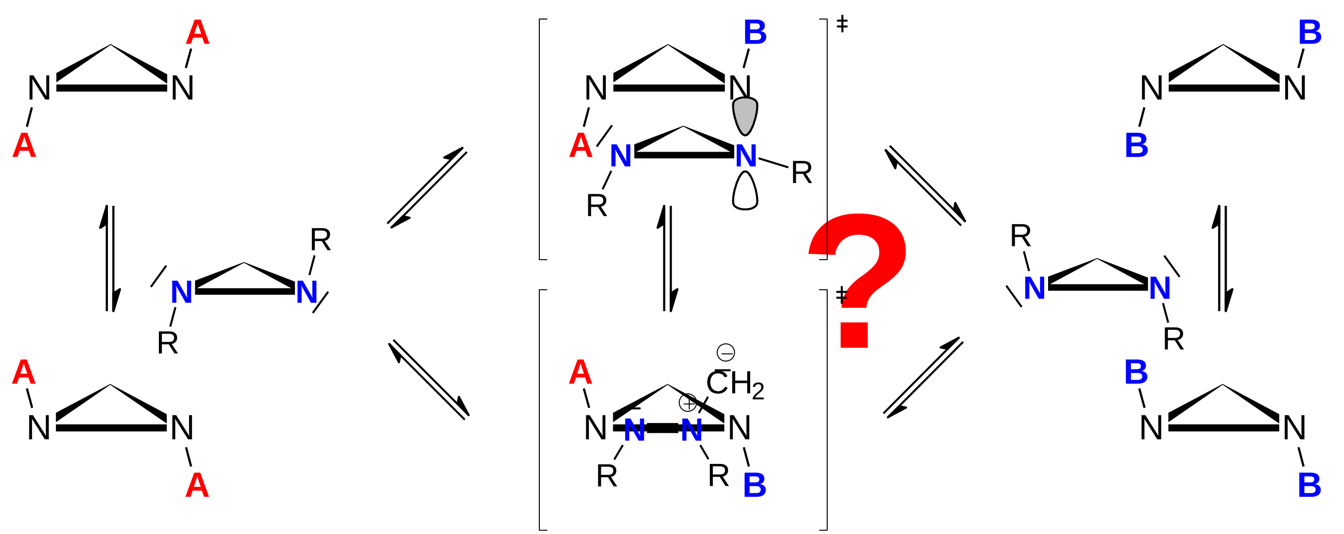
$$k_1^{app} = \frac{1}{1+k'_A} k_1^{mob} + \frac{k'_A}{1+k'_A} k_1^{stat}$$

$$k_{-1}^{app} = \frac{1}{1+k'_B} k_{-1}^{mob} + \frac{k'_B}{1+k'_B} k_{-1}^{stat} = \frac{A_\infty}{B_\infty}\left(\frac{1}{1+k'_B} k_1^{mob} + \frac{k'_B}{1+k'_B} \frac{k'_A}{k'_B} k_1^{stat} \right)$$

Molecular Dynamics: Interconversion

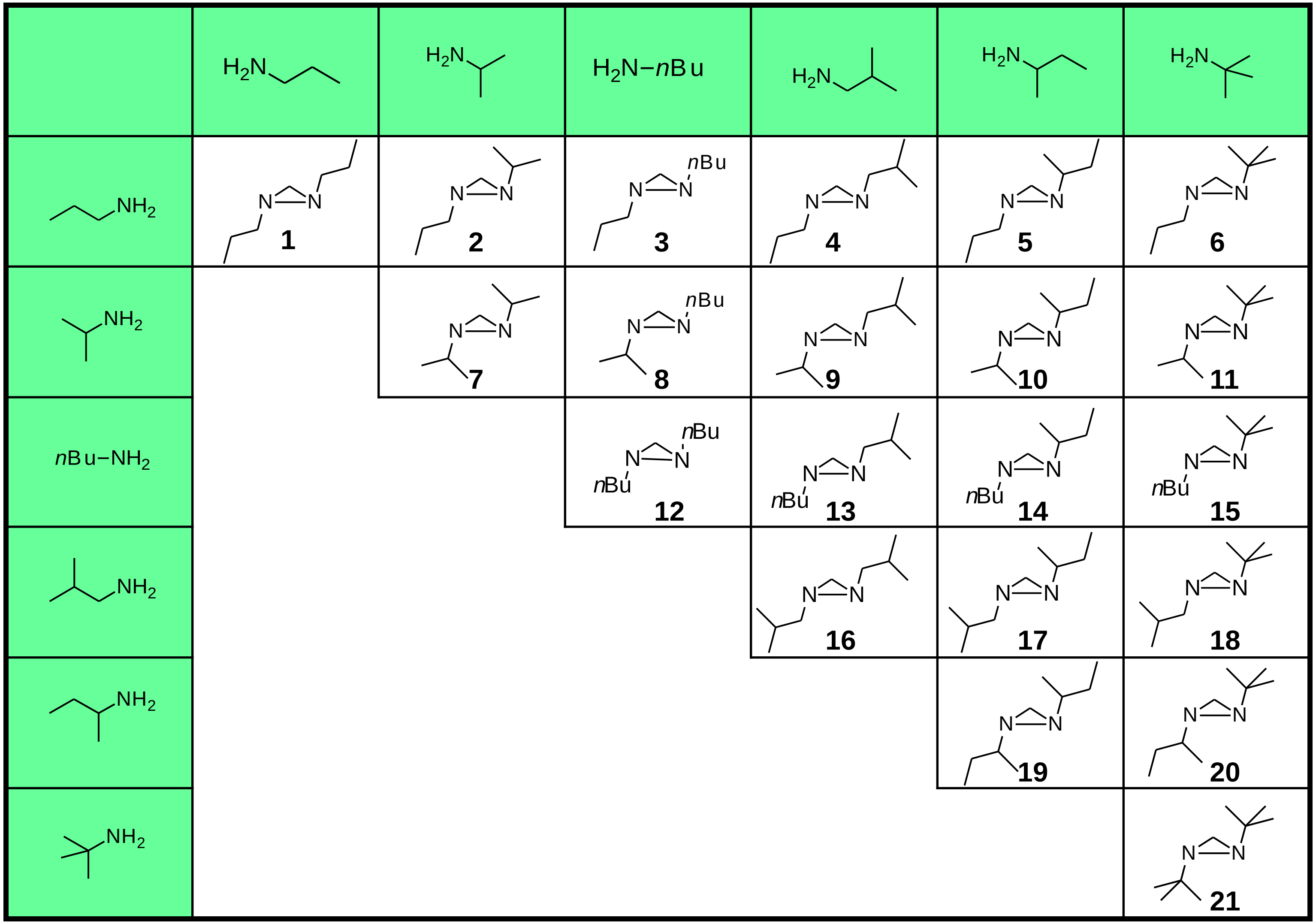




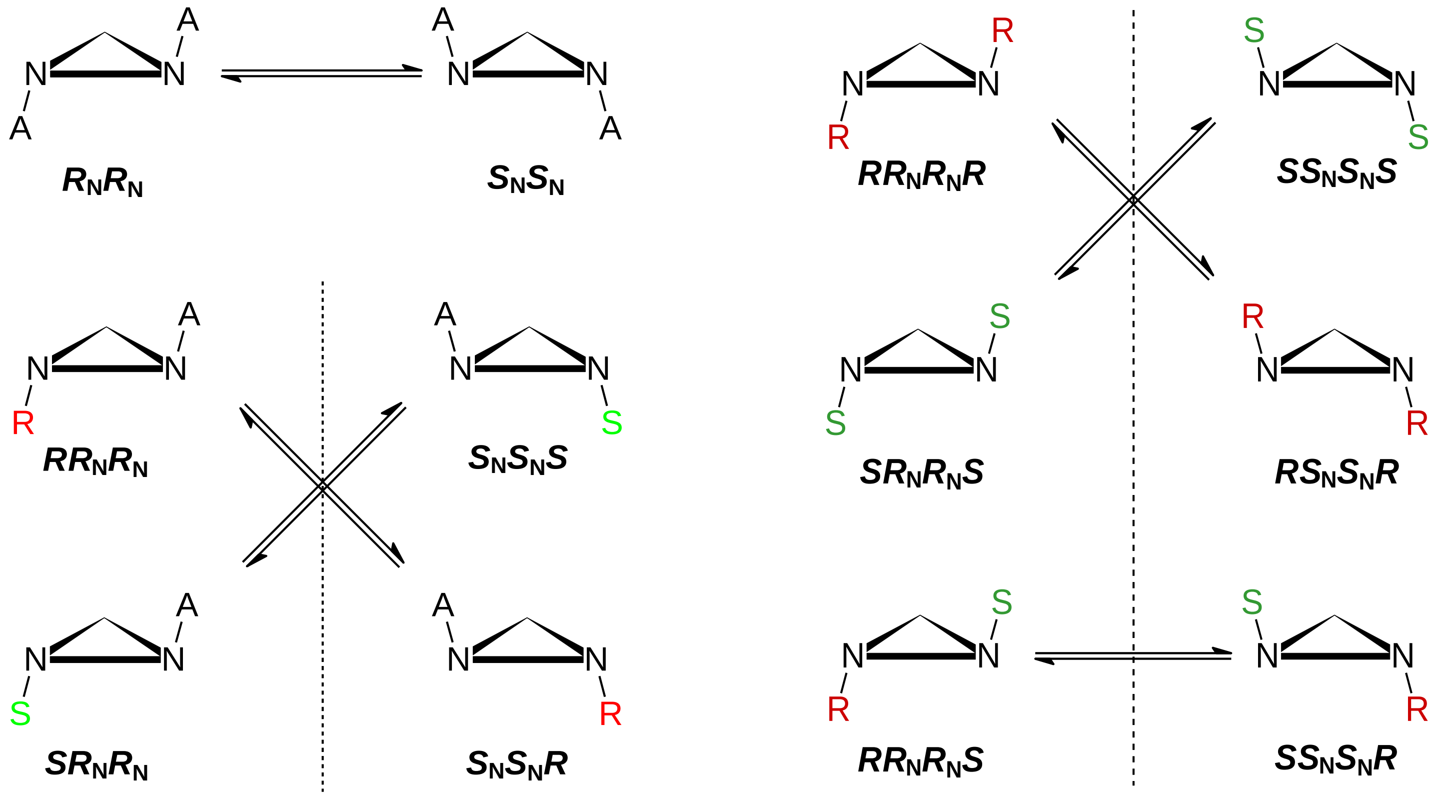


$\Delta G^{\#}_{AA}$ $\Delta G^{\#}_{AB}=(\Delta G^{\#}_{AA}+\Delta G^{\#}_{BB})/2$ $\Delta G^{\#}_{BB}$

Diaziridines



Diaziridines: Stereoisomers

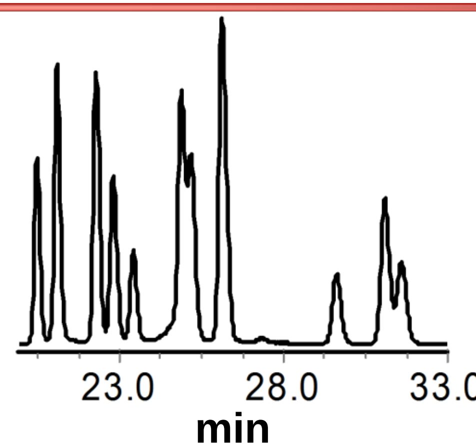


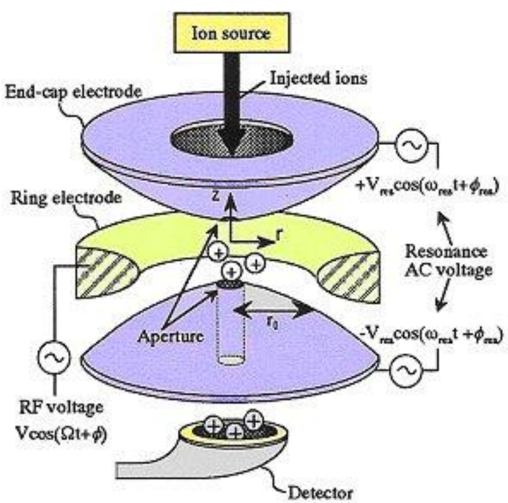
Statistical synthesis of mixed 1,2-substituted diaziridines:

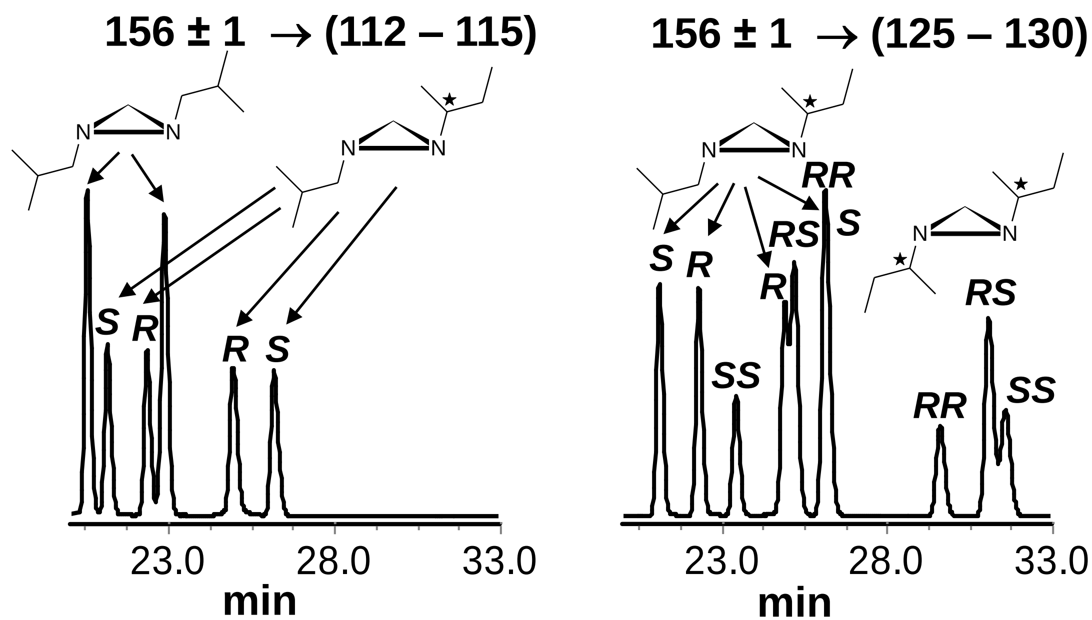
Constitutional isomers, stereoisomers (32 enantiomers, 24 epimers)

Separation of Constitutional Isomers

Multiple
Reaction
Monitoring







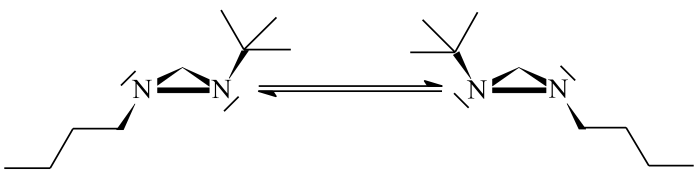
PolarisQ GC-MS
25 m Chirasil-ß-Dex 500 nm
120°C, 40 kPa He

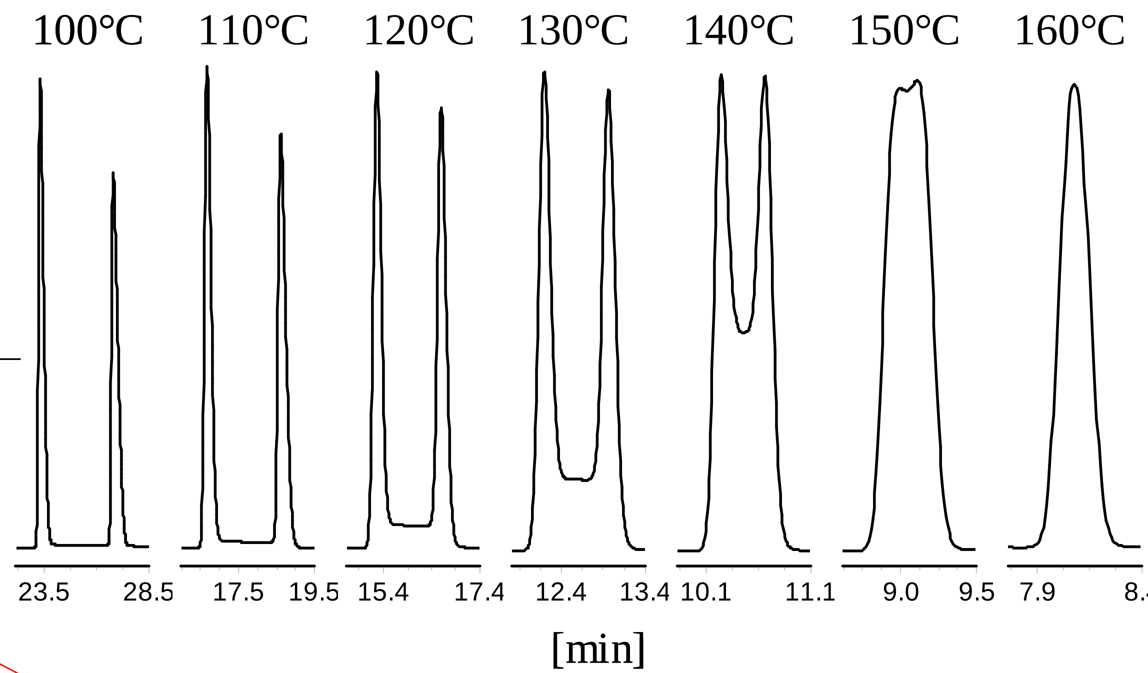
O. Trapp, *J. Chromatogr. A* ***2010****, 1217, 1010-1016.*

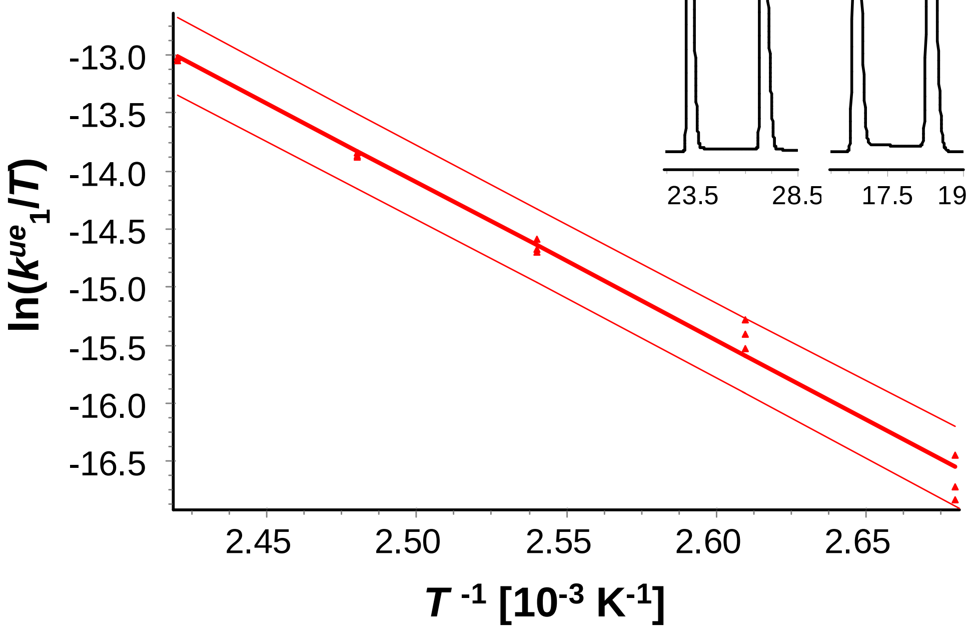
1-*n*-Butyl-2-*tert.*-butyldiaziridine

DGC Experiment

25 m Chirasil-ß-Dex 500 nm





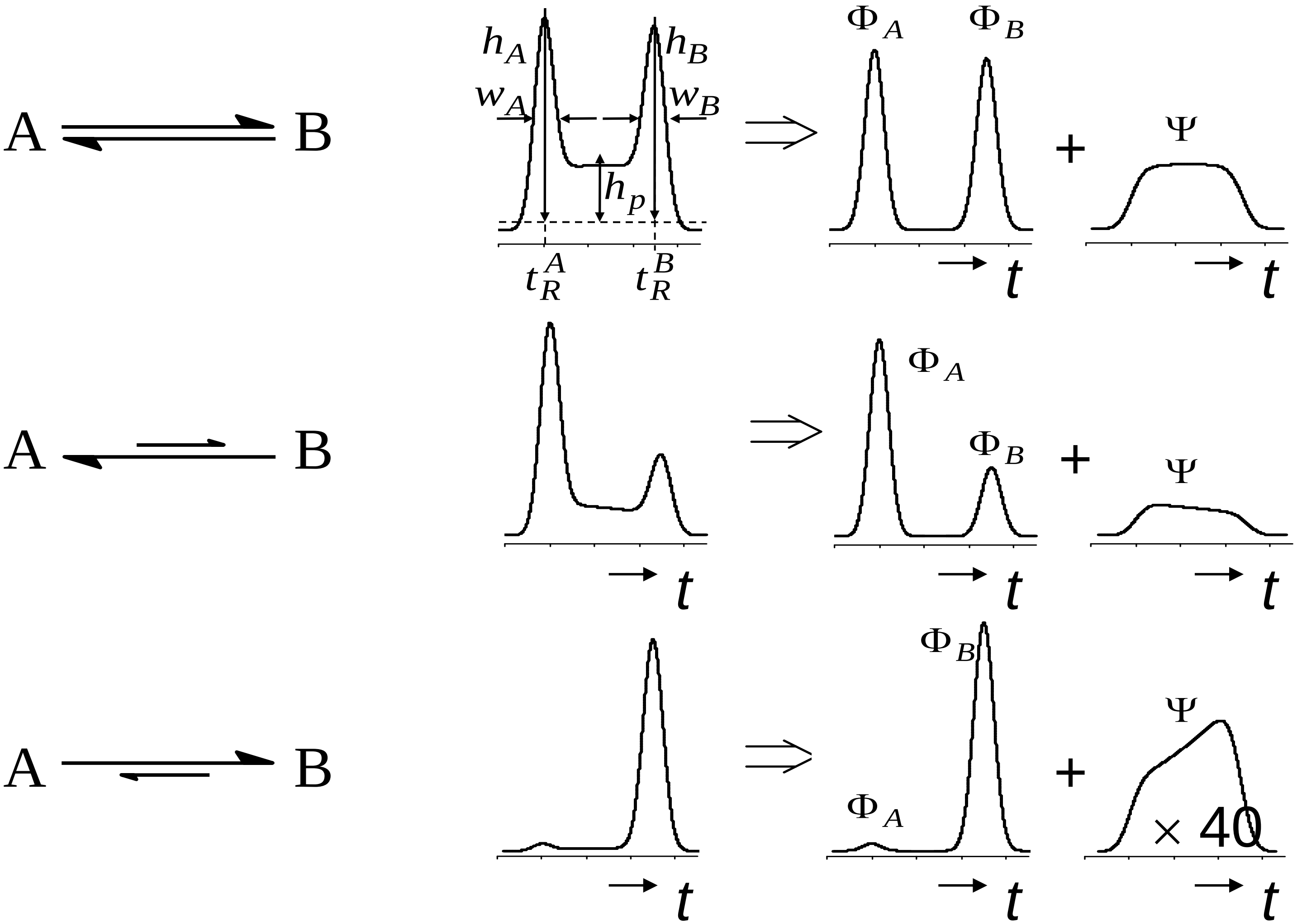


$\Delta H^{\ddagger}$ = 112.6 ± 2.5 kJ/mol

$\Delta S^{\ddagger}$ = -27 ± 2 J/(K mol)

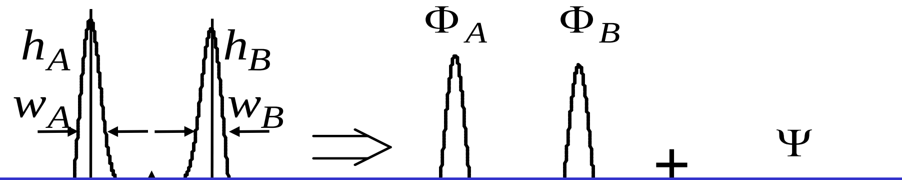
O. Trapp, Chirality **2006**, *18*, 489-497.

Mathematical Separation of Elution Profiles



Mathematical Separation of Elution Profiles

A ⇌ B

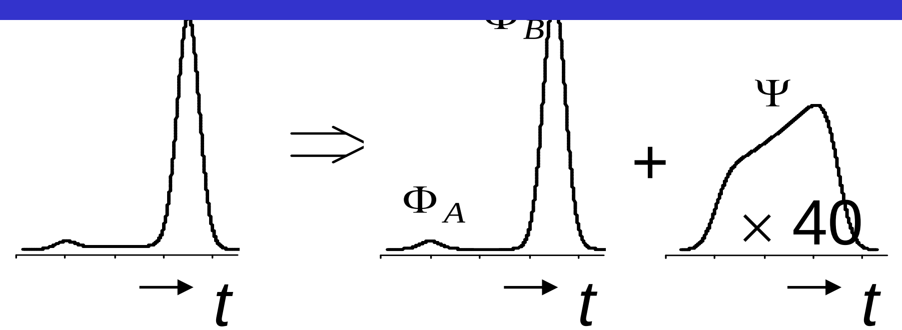


$$k_1^{ue} = f(\Phi_A(t), \Phi_B(t), \Psi_{ue}(t))$$

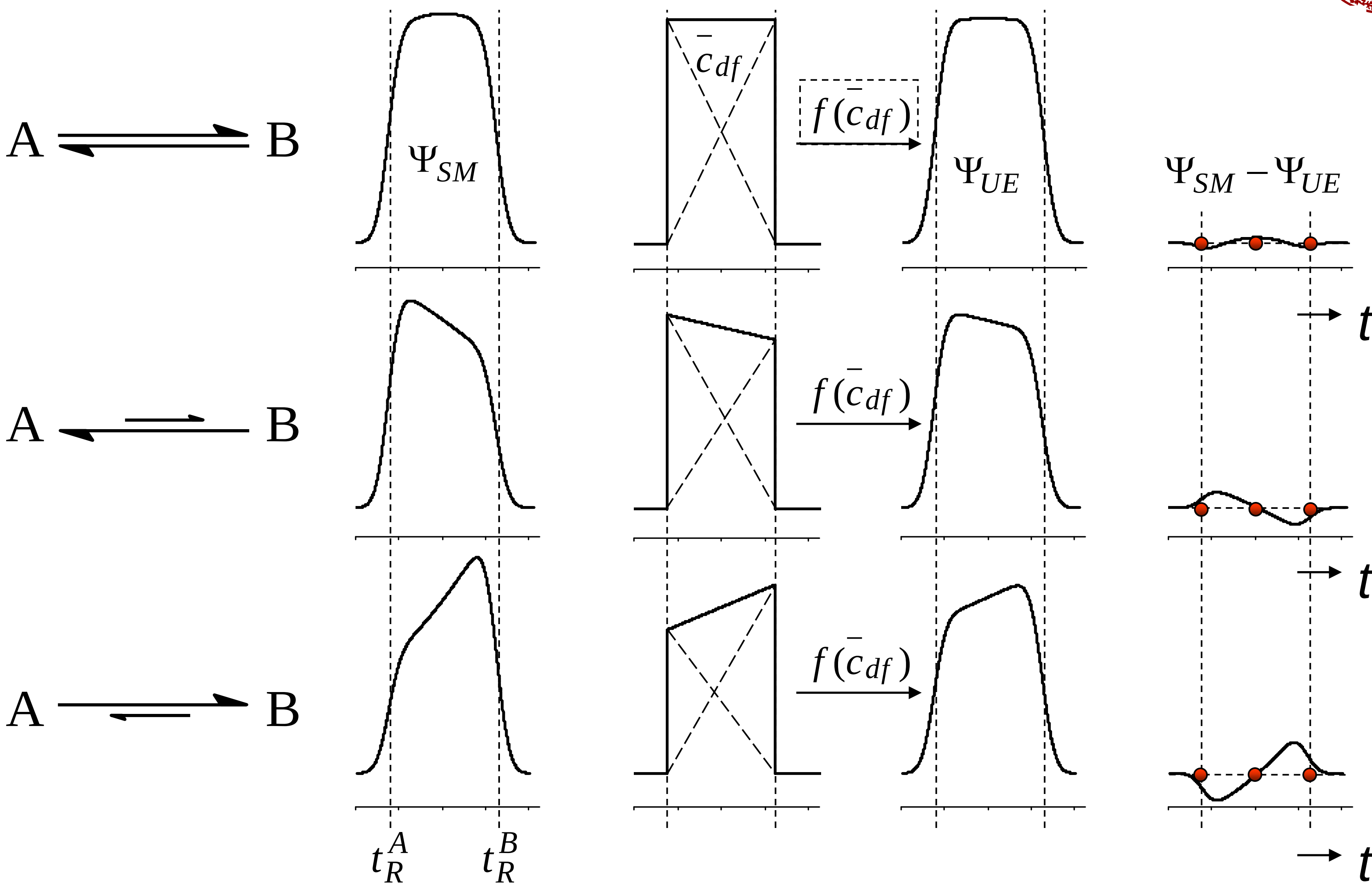
$$= f([A],[B],[A_0],[B_0],K_{A/B},t_R^A,t_R^B,w_A,w_B,h_p)$$

A

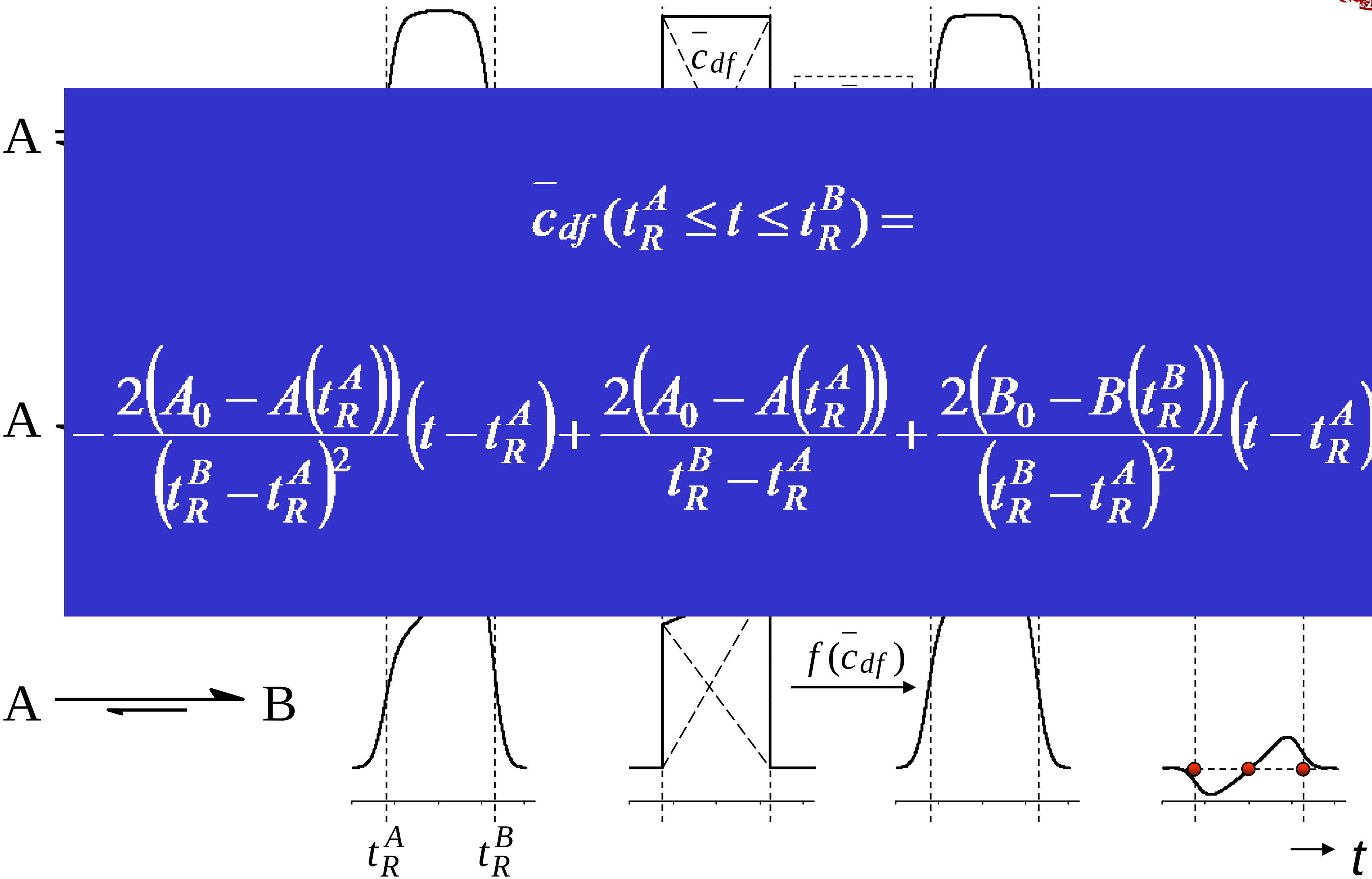
A ⇌ B



Stochastic Distribution Function $\Psi(t)$



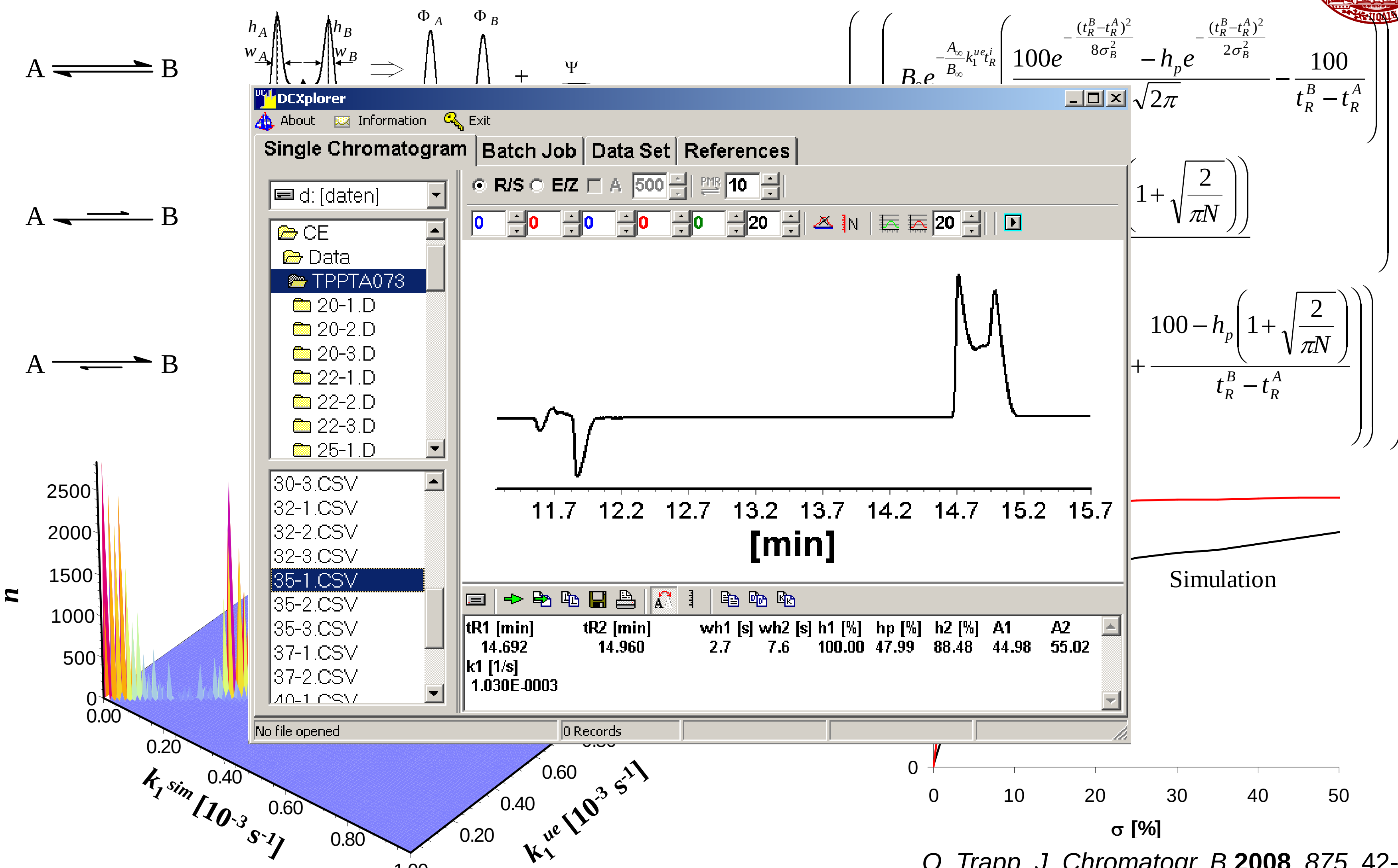
Stochastic Distribution Function $\Psi(t)$



$$\bar{c}_{df}(t_R^A \le t \le t_R^B) =$$

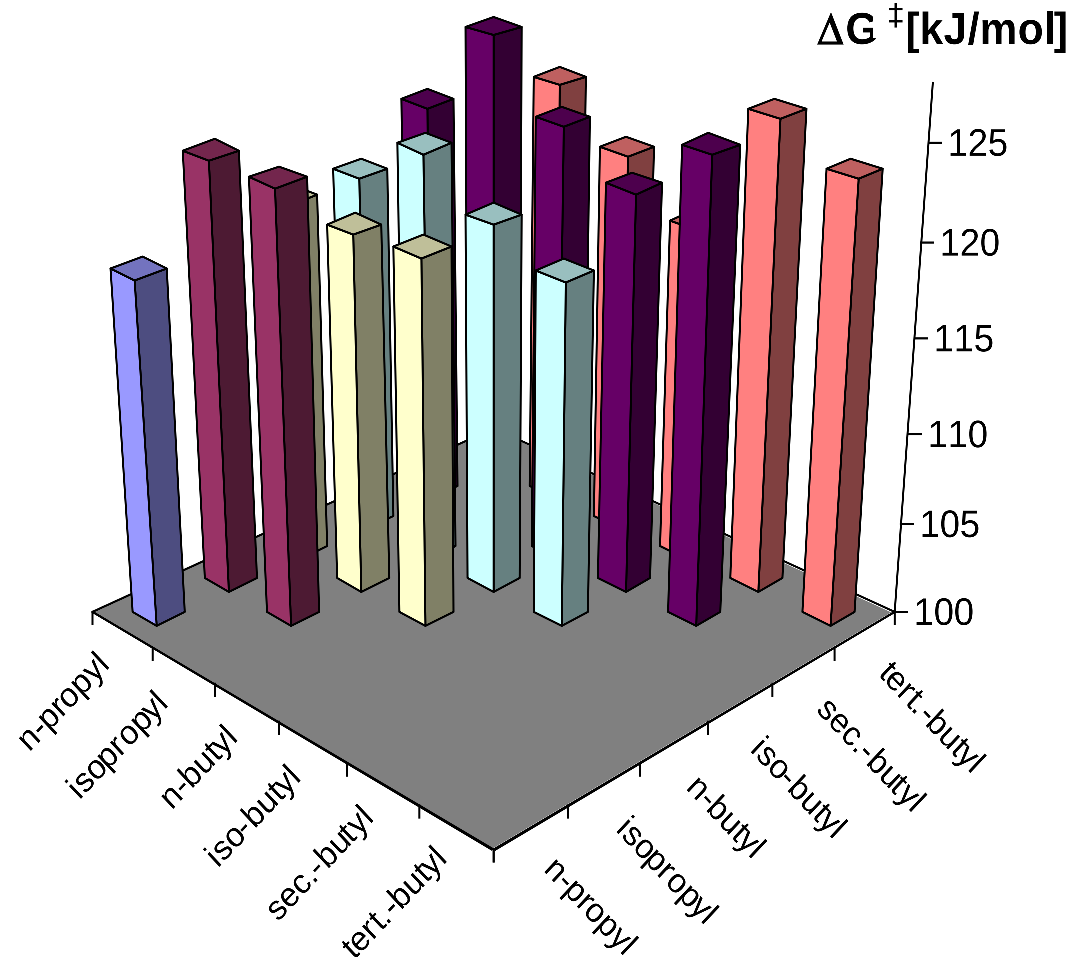
$$-\frac{2\left(A_0 - A\left(t_R^A\right)\right)}{\left(t_R^B - t_R^A\right)^2}\left(t - t_R^A\right) + \frac{2\left(A_0 - A\left(t_R^A\right)\right)}{t_R^B - t_R^A} + \frac{2\left(B_0 - B\left(t_R^B\right)\right)}{\left(t_R^B - t_R^A\right)^2}\left(t - t_R^A\right)$$

Unified Equation



O. Trapp, *J. Chromatogr. B* **2008**, *875*, 42-47.

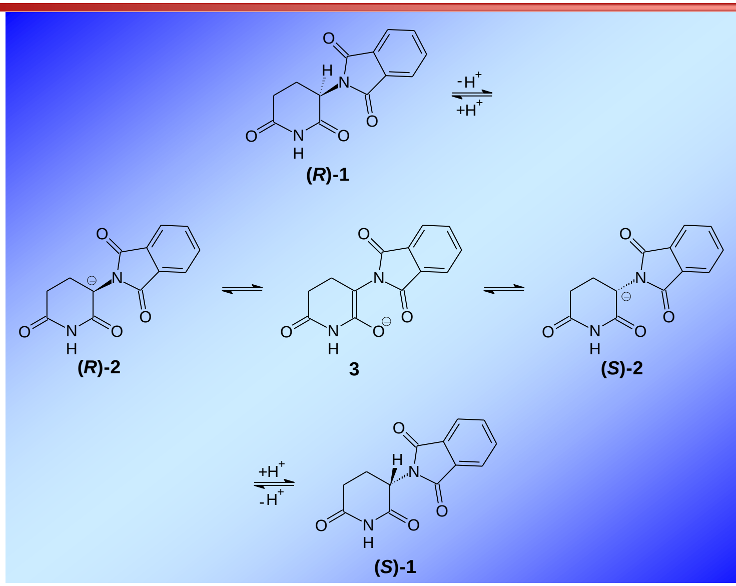
ΔG$^{\#}$ of 1,2-Substituted Diaziridines

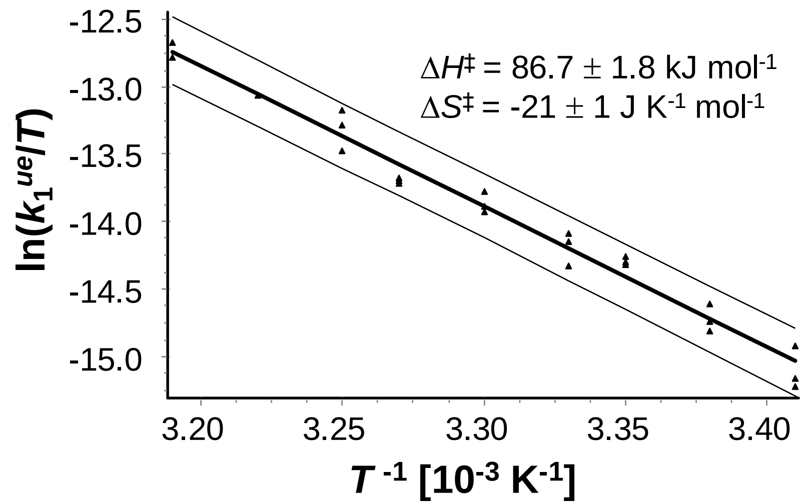


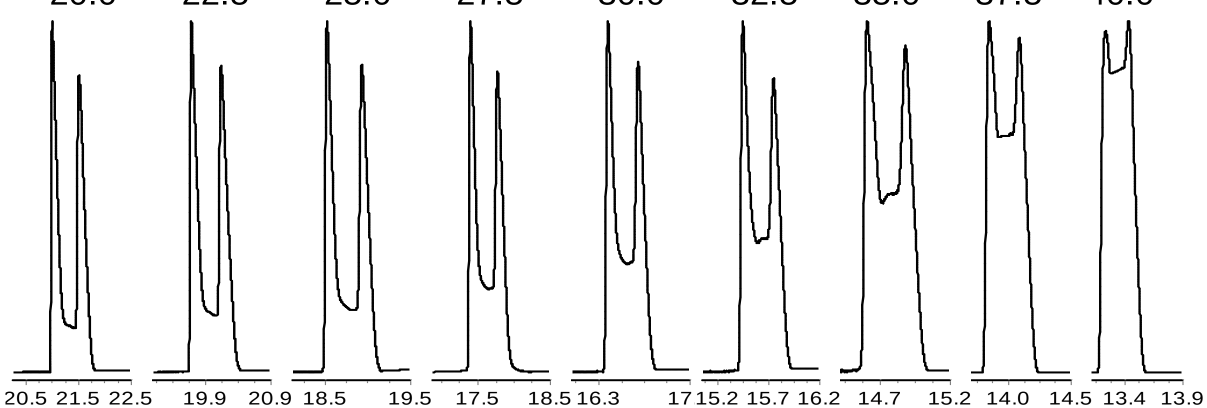
409 Experiments considered

Dipropydiaziridines: O. Trapp, L. Sahraoui, W. Hofstadt, W. Könen, *Chirality* **2010**, *22*, 284-291.
M. Kamuf, O. Trapp, *manuscript submitted*

Enantiomerization of Thalidomide







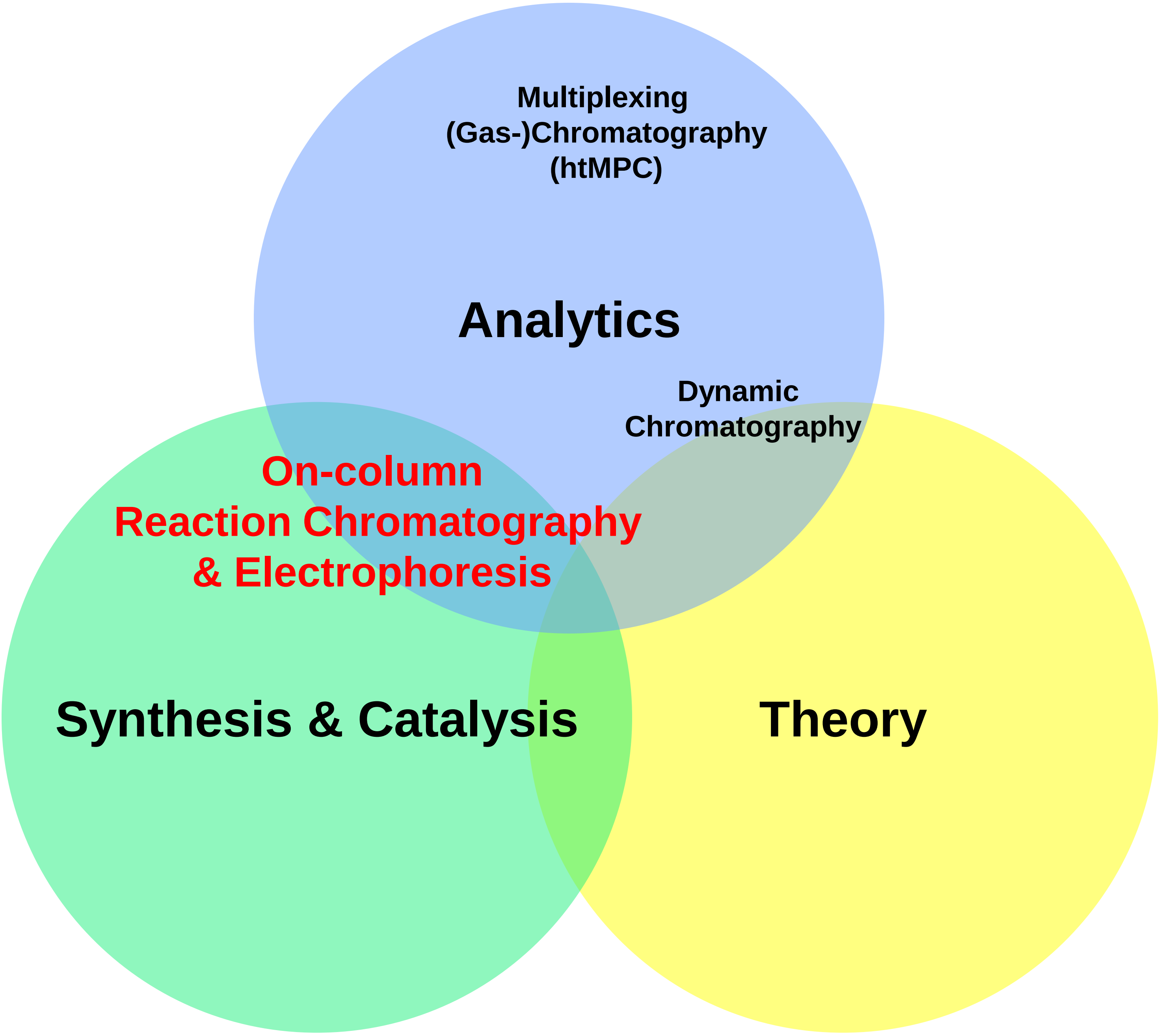
89 cm (effective length) fused-silica capillary (I.D. 50 µm), 50 mM sodium borate buffer, pH 9.3, 20 mg/ml carboxymethyl-β-cyclodextrin, U = +25 kV, λ = 214 ± 2 nm.

O. Trapp, *Electrophoresis* **2006**, *27*, 2999-3006.

Dynamic Chromatography: Summary

- Stereodynamics of molecules
  - stereochemical integrity
  - pharmaceuticals
  - peptides, proteins
- Precise determination of reaction rate constants
- Evaluation in real-time with Unified Equation
- High-throughput possible
- Separation and identification of complex mixtures by Multiple-Reaction-Monitoring MS

O. Trapp, *Electrophoresis* **2006**, *27*, 534-541.
O. Trapp, *Electrophoresis* **2006**, *27*, 2999-3006.
Heegaard & Trapp, *Anal. Chem.* **2006**, *78*, 3667-3673.



Multiplexing
(Gas-)Chromatography
(htMPC)
Analytics
Dynamic
Chromatography
On-column
Reaction Chromatography
& Electrophoresis
Synthesis & Catalysis
Theory

Catalysis

- Matching catalyst and reaction
- How fast?
- Kinetics, selectivity
- Activation parameters
- Mechanism
- Understanding → rational design
- High-throughput screening: large data sets
- Economic use of resources

Modes to Integrate Catalysis and Separation

Microreactor/ Flow-Reactor Approach

→ Reactor →

- ✓ Offline analysis
- ✓ Preparative mode

S.V. Ley, K.F. Jensen, A. Kirschning, P. Seeberger
G. Jas, A. Kirschning, *Chem. Eur. J.* **2003**, *9*, 5708-5723.

Chromatographic Microreactor Approach

→ Reactor → Separation →

- ✓ Online analysis, online kinetics
- ✓ Easy to couple with analytical techniques
- ✓ Ideal to study fast processes ($k > 10^{-2}\ s^{-1}$)

On-column Reaction Chromatography

→ Reaction & Separation Integrated →

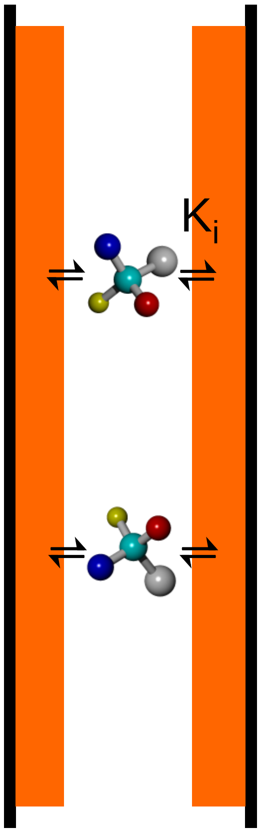
- ✓ Online analysis, online kinetics
- ✓ Selectivity of stationary phase
- ✓ Easy to couple with analytical techniques
- ✓ Ideal to study slower processes ($k < 10^{-2}\ s^{-1}$)
- ✓ Unified equation

- ➢ Reactant purity
- ➢ Kinetics
- ➢ Thermodynamics
- ➢ No competing reactions
- ➢ Reactant libraries
- ➢ High-throughput possible

O. Trapp, *J. Chromatogr. A* **2008**, *1184*, 160-190.

Thermodynamics & Kinetics

Thermodynamics



k', K
Van-Deemter-Golay
(Diffusion)

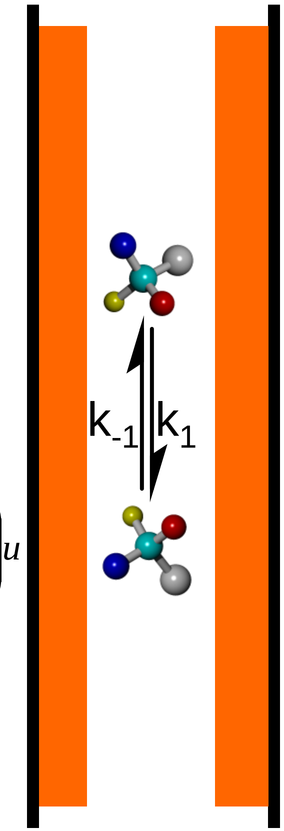
$$H = A + \frac{B}{u} + Cu$$

$$H = \frac{B}{u} + (C_M + C_S)u$$

$$H = \frac{2D_M}{u} + \left(\frac{1+6k'+11k'^2}{96(1+k')^2} \cdot \frac{d_c^2}{D_M} + \frac{2k'}{3(1+k')^2} \cdot \frac{d_f^2}{D_S} \right) u$$

Retention increment
($\Delta\Delta G$, $\Delta\Delta S$, $\Delta\Delta H$)

Kinetics

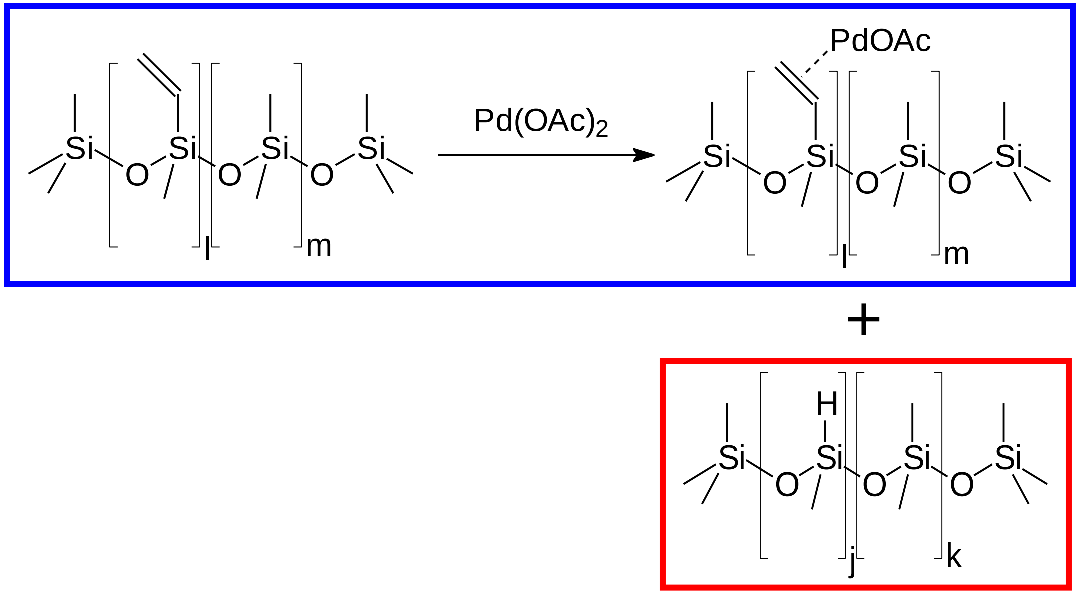


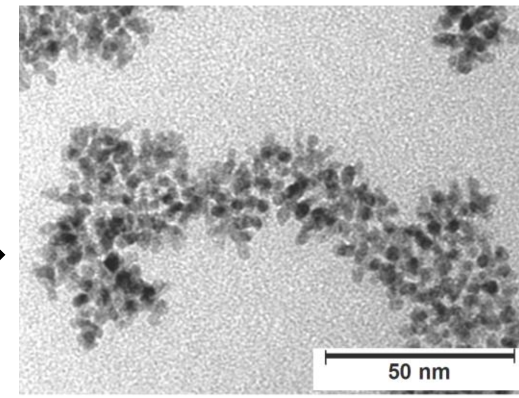
$k(T)$, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$
Unified Equation

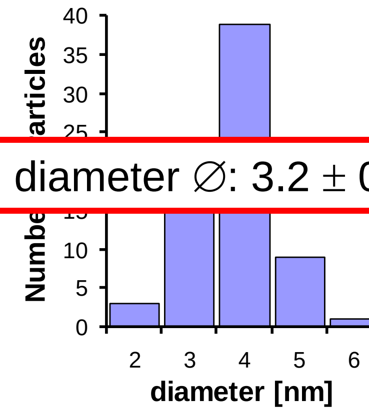
→**Interconversions**
(Dynamic Chromatography)

→**Conversions**
(on-column Reaction Chromatography)

Pd Nanoparticles







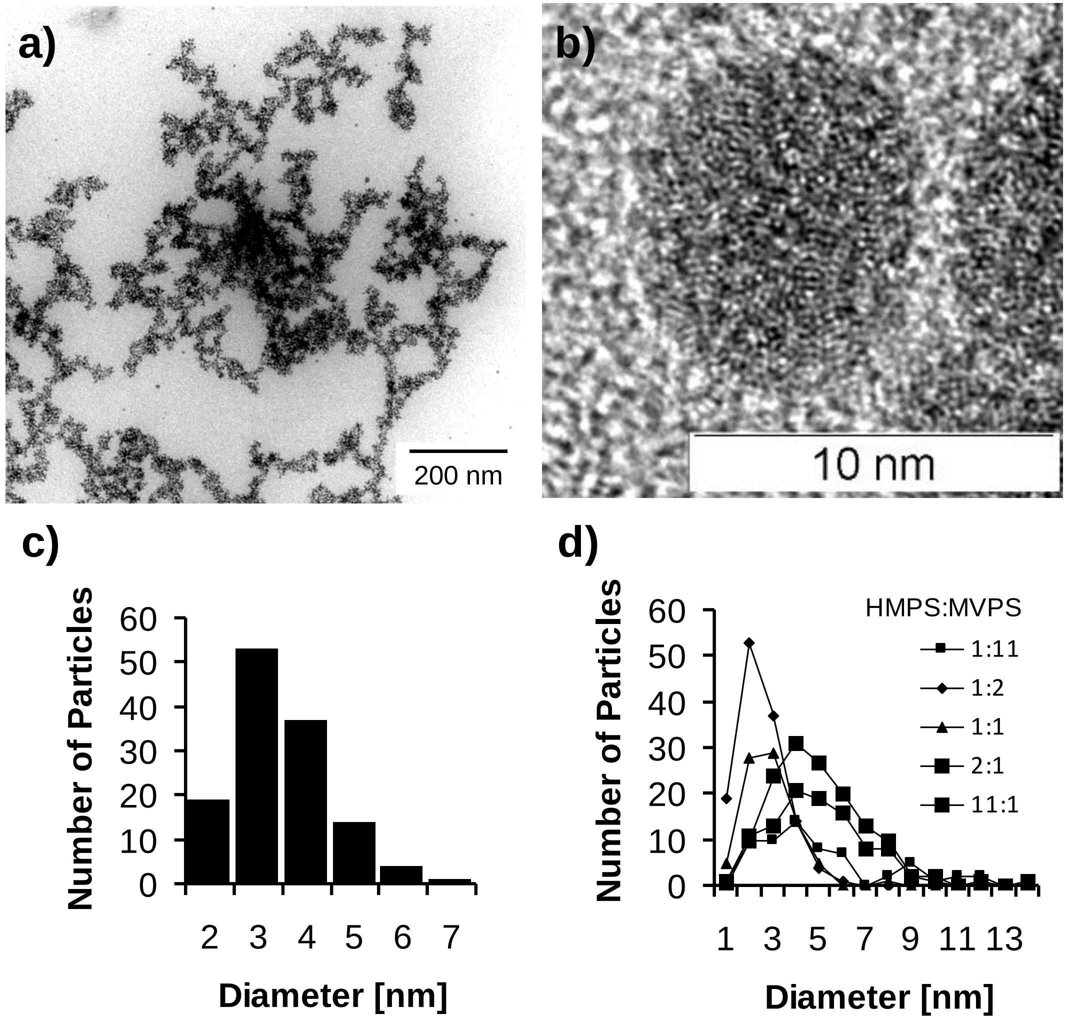
Mean diameter ∅: 3.2 ± 0.7 nm

- Reduction to Pd nanoparticles by Si-H
- Hydrosilylation → cross-linking of polysiloxanes
- Stabilization of particles by polysiloxane matrix
- free Si-OH groups on glass surfaces react with Si-H groups

  → permanently bonded

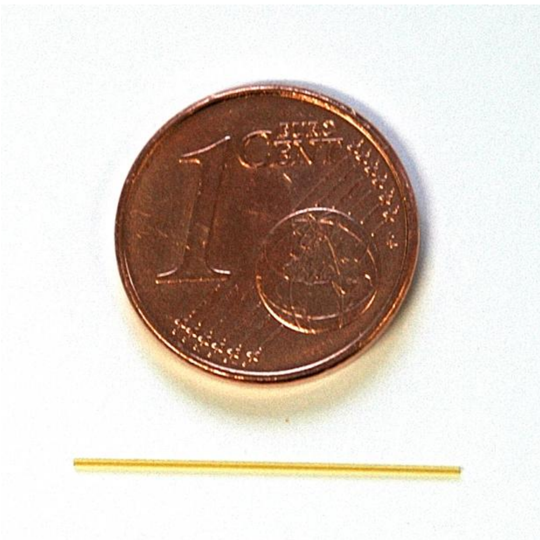
O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

Tuning of Pd Nanoparticles



O. Trapp, S.K. Weber, S. Bauch, T. Bäcker, B. Spliethoff, *Chem. Eur. J.* **2008,** *14*, 4657-4666.

Hydrogenations with Pd Nanoparticles in a Capillary

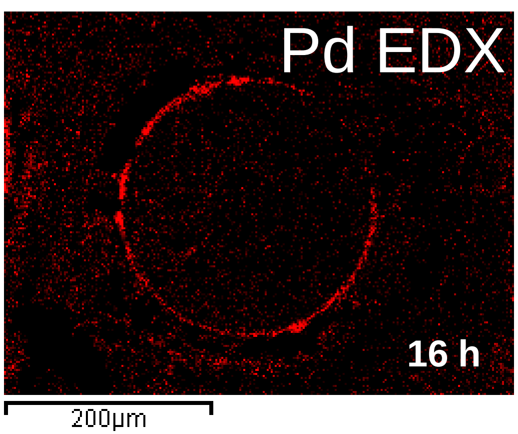


Length: 2 cm fused-silica column

i.d. 250 µm, 250 nm film thickness

7.8 ng Pd/ cm → 0.73 pmol/ cm

= 26.6 billions Pd-nanoparticles/ cm



Coupled to a separation column:

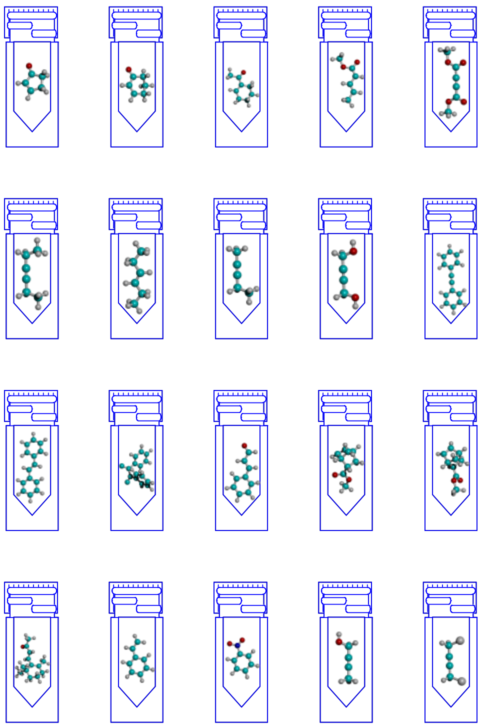
25 m GE SE-52 250 nm film thickness

(Poly(95%-dimethyl 5%-diphenyl)siloxane)

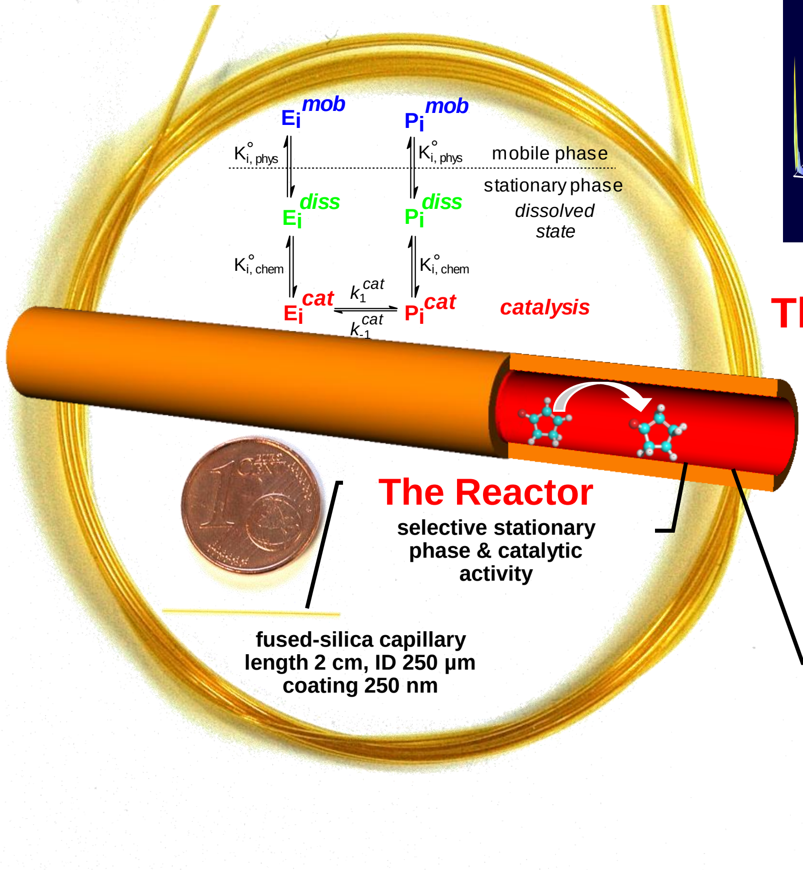
Carrier gas: H_2

On-column Reaction Chromatography

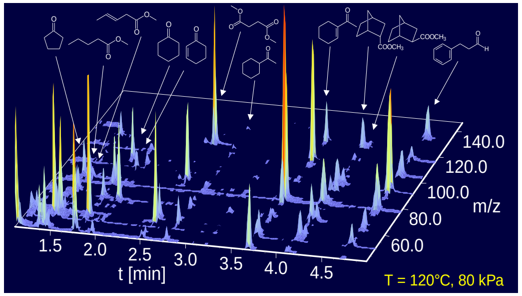
Reaction Library



On-column Synthesis & Separation



GC-MS Measurements

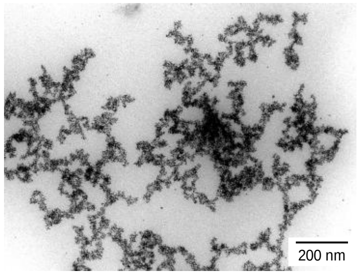


Thermodynamics & Kinetics

k, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$

Structure Correlation

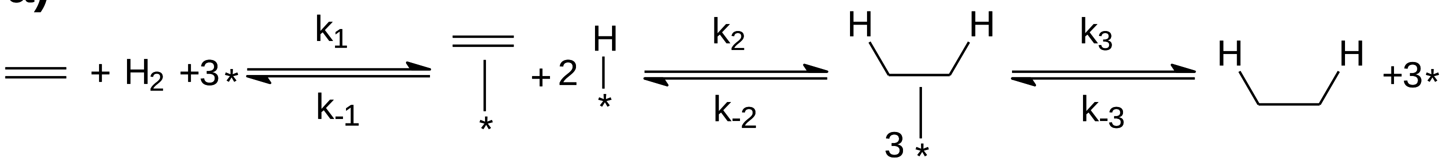
Characterization



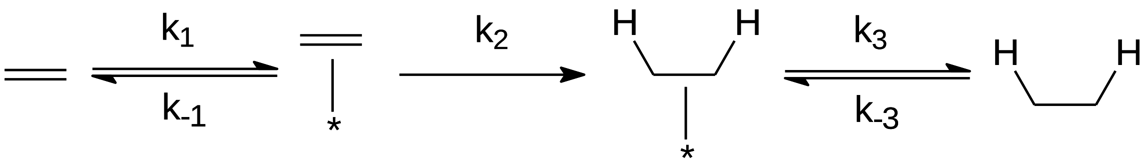
O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

Mechanism: Langmuir-Hinshelwood in a Chromatographic Reactor

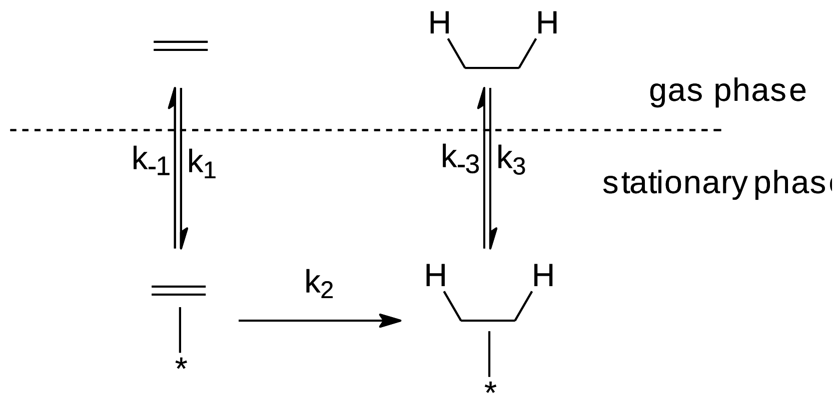
a)



b)

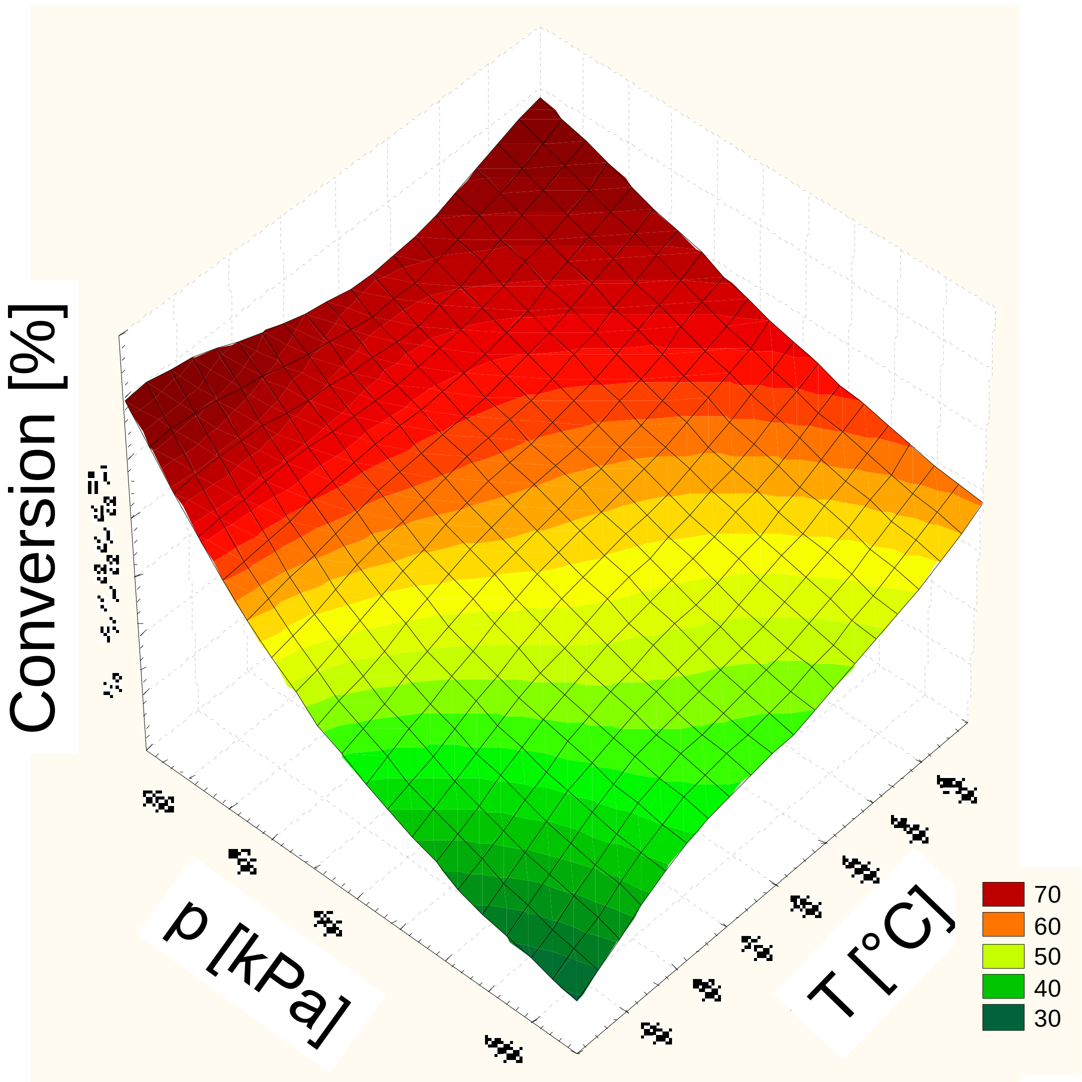


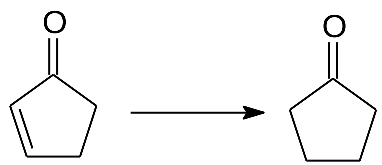
c)



O. Trapp, S.K. Weber, S. Bauch, T. Bäcker, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008,** 14, 4657-4666.

Hydrogenation of 2-Cyclopentenon

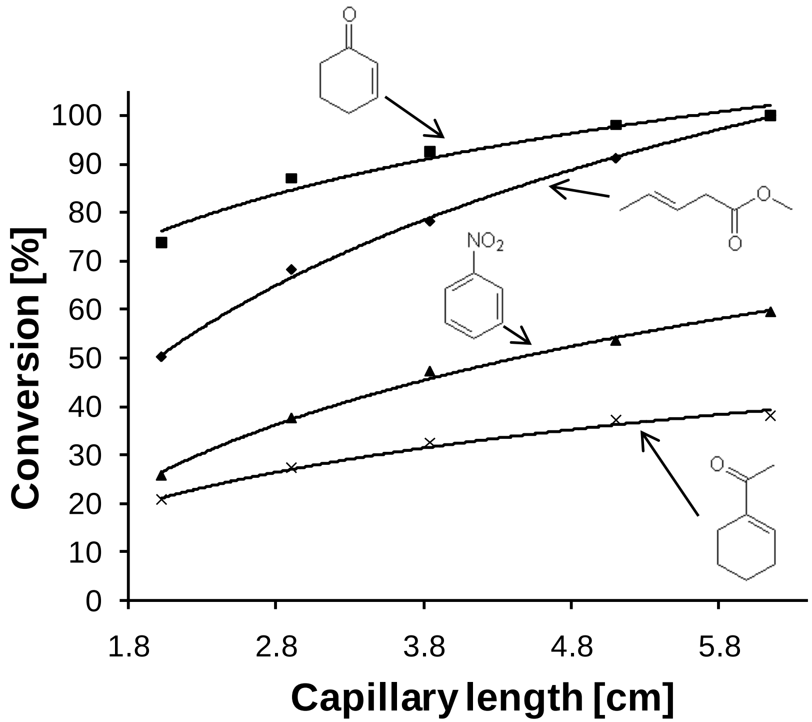


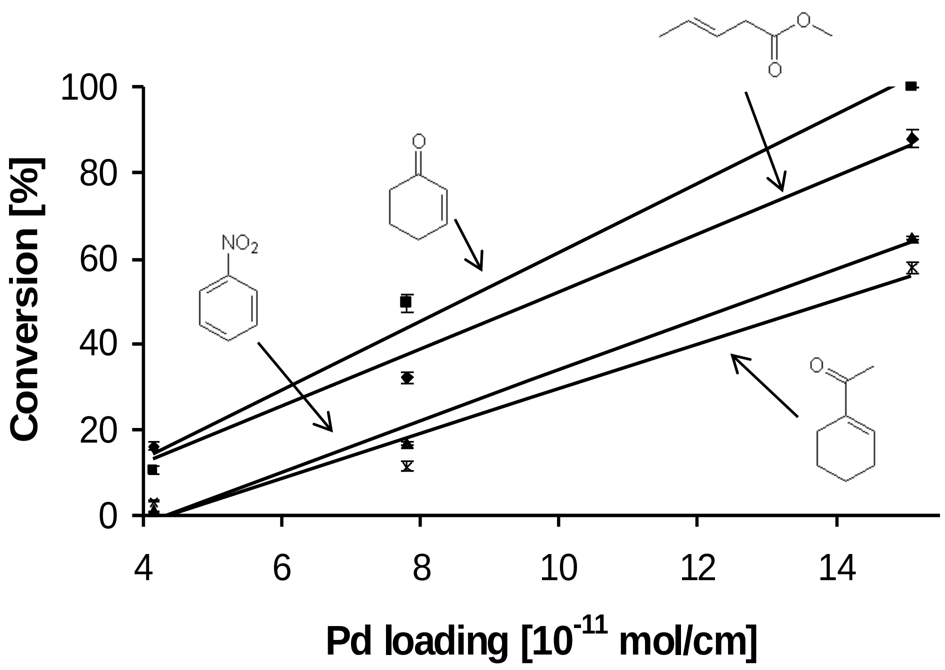


- Kinetics
- Diffusion
- Activation parameters

k = 8.9 s^{-1} (80°C)

Hydrogenations in a Capillary

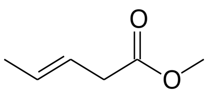
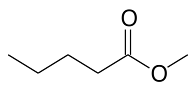
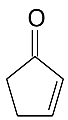
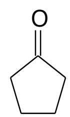
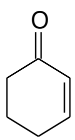
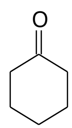
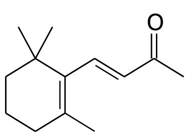
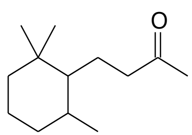
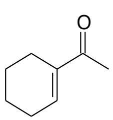
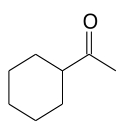
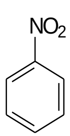
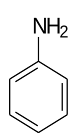




trans-methylpent-3-enoate (♦)
cyclohex-2-enone (■)
nitrobenzene (▲)
1-acetylcyclohexene (×)

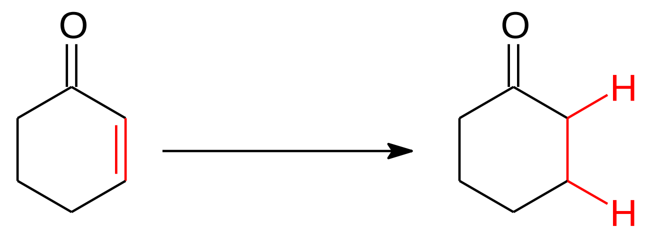
O. Trapp, S.K. Weber, S. Bauch, T. Bäcker, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008,** 14, 4657-4666.

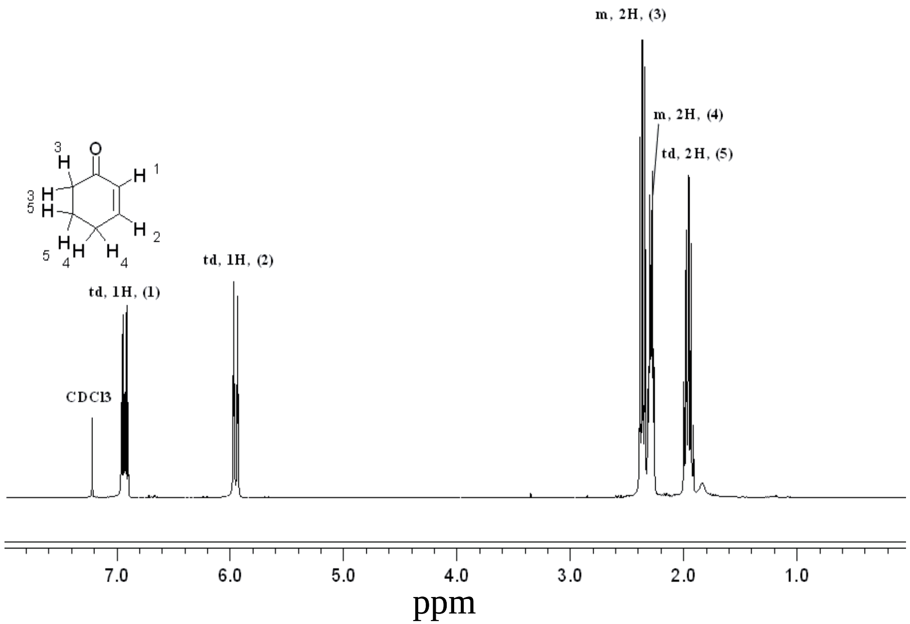
Activation Parameters

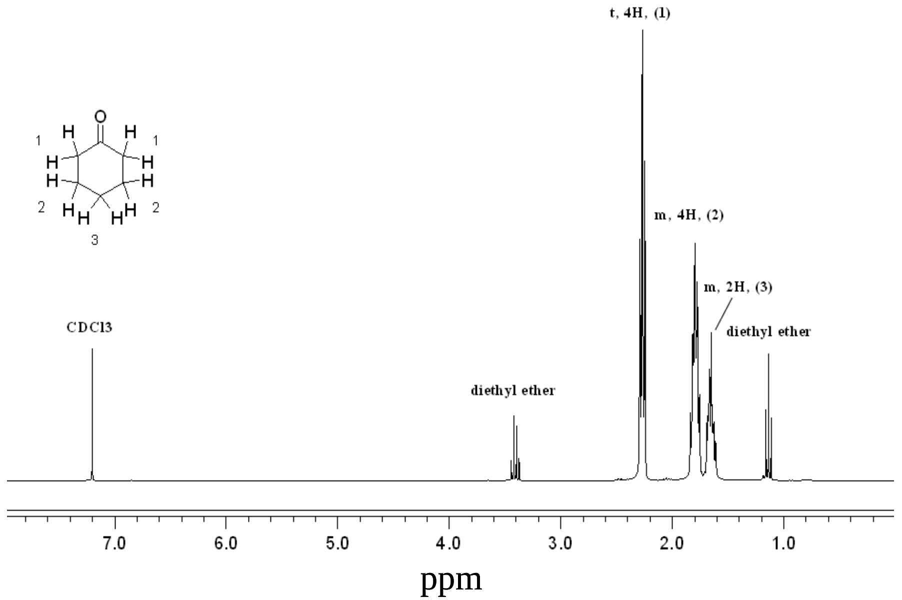
	Substrate	Produkte	C [%]	k [1/s]	$\Delta G^{\#}_{25°C}$ [kJ/mol]	$\Delta H^{\#}$ [kJ/mol]	$\Delta S^{\#}$ [J/K·mol]	r	s.d.
1			11	194.1	67.8	30.1 ± 0.5	-126 ± 3	0.997	0.057
2			62	42.1	70.4	25.2 ± 0.5	-152 ± 4	0.996	0.052
3			47	36.4	71.4	27.2 ± 0.7	-148 ± 6	0.996	0.046
4			22	3.7	82.3	56.0 ± 1.0	-94 ± 2	0.998	0.020
5			13	43.9	73.4	37.5 ± 0.6	-121 ± 3	0.999	0.025
6			36	23.0	75.3	38.3 ± 1.5	-124 ± 7	0.985	0.116

O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

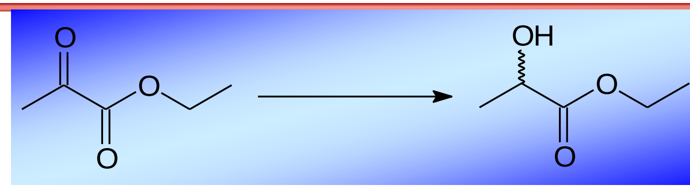
‘Lab-in-a-Capillary‘: Preparative Hydrogenations





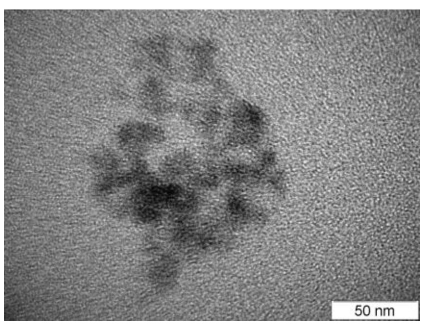


Enantioselective Hydrogenation

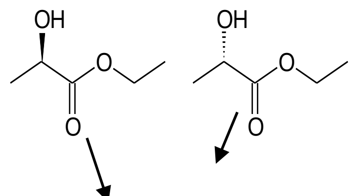


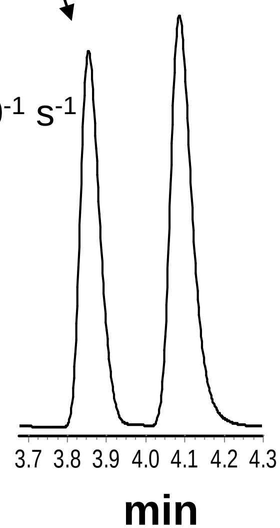
Hydrogenation over Pt-Nanoparticles

Reactor:
10 cm fs-capillary
i.d. 250 µm, 250 nm film thickness



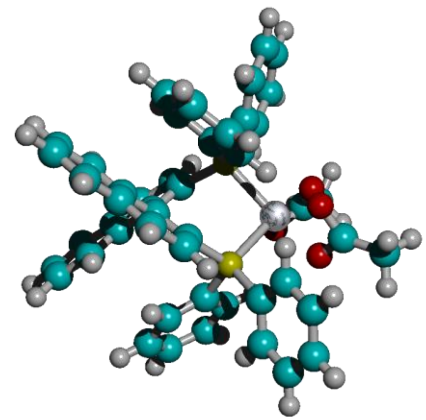
k = 1.4 10^{-1} s^{-1}





PolarisQ GC-MS
7.5 m 50% 6-TBDMS-2,3-di-Me-ß-CD
in PS086 250nm, 70°C, 40 kPa H_2

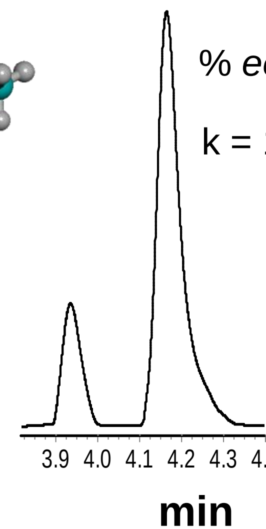
Noyori's Catalyst



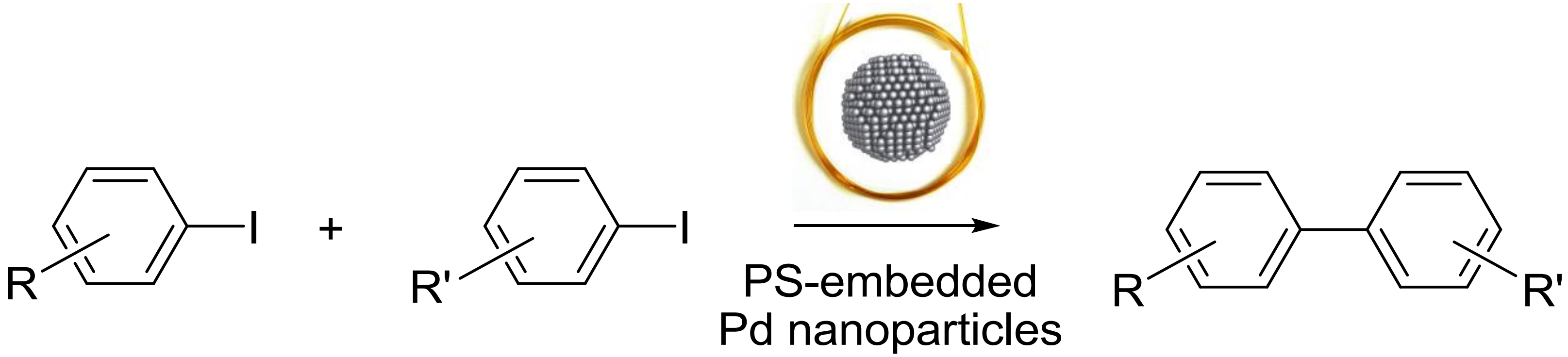
(R)-BINAP-Ru(II)-diacetate in SE30
Reactor:
20 cm fs-capillary
i.d. 250 µm, 250 nm film thickness

% *ee* = 59

k = 1.6 10^{-3} s^{-1}



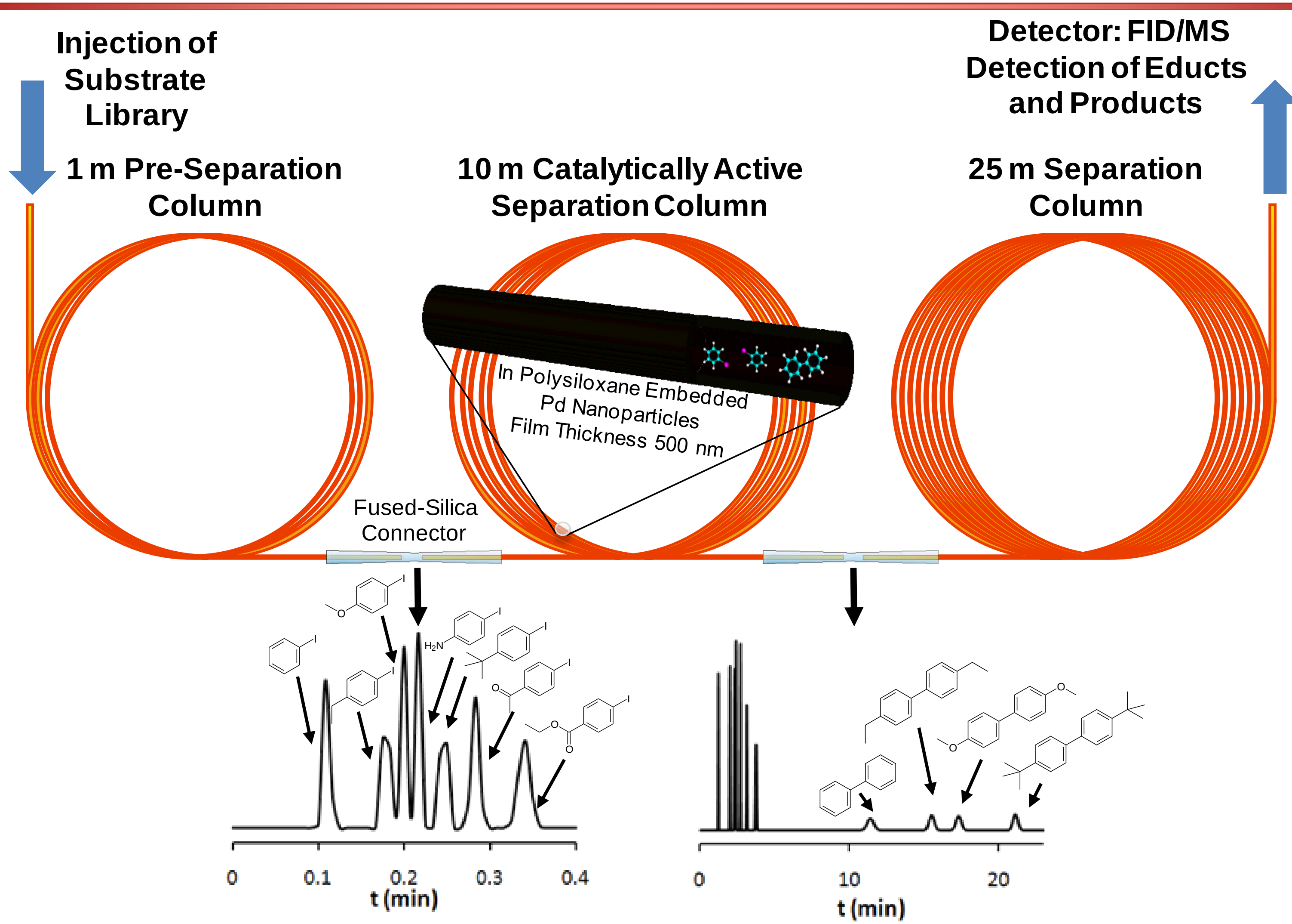
C-C Coupling Reactions



R = R' = H, Et, OMe, *t*Bu, COMe, COOEt, NH_2

S.K. Weber, S. Bremer, O. Trapp, *J. Chem. Eng. Sci.* **2010**, *65,* 2410-2416.

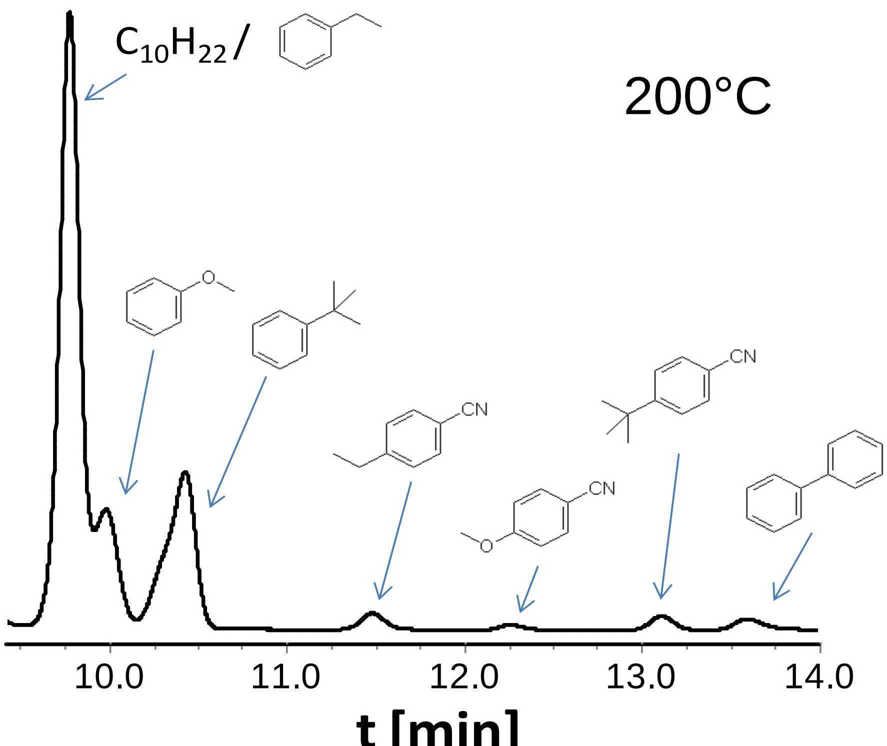
C-C Coupling Reactions

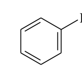
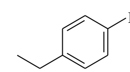
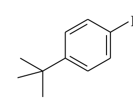
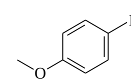


S.K. Weber, S. Bremer, O. Trapp, *J. Chem. Eng. Sci.* **2010**, *65,* 2410-2416.

Cyanation of Aryliodides

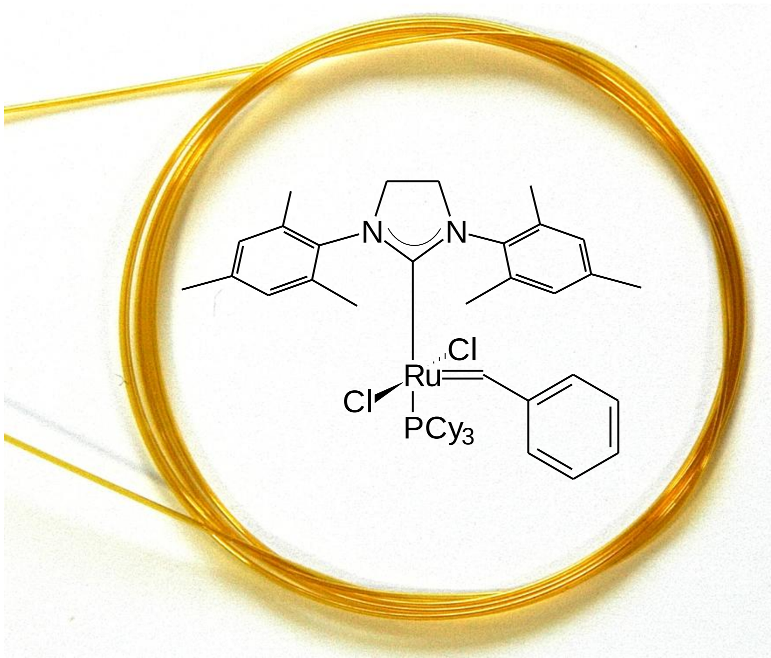
R = H, C_2H_5, $C(CH_3)_3$, OCH_3



Entry	Substrate	p [kPa]	Yield Ar-H [%]	Yield Ar-Ar [%]	Yield Ar-CN [%]
1		100	83.5	13.9	2.4
		60	83.6	13.4	2.7
		40	80.3	15.3	4.4
2		100	88.8	5.9	5.3
		60	94.2	4.5	1.3
		40	83.2	10.9	5.9
3		100	75.3	-	24.7
		60	69.1	-	30.9
		40	67.6	-	32.4
4		100	79.1	1.8	19.1
		60	77.5	-	22.5
		40	63.5	-	36.5

S.K. Weber, S. Bremer, O. Trapp, *J. Chem. Eng. Sci.* **2010**, *65*, 2410-2416.

Ring Closing Metathesis (RCM)



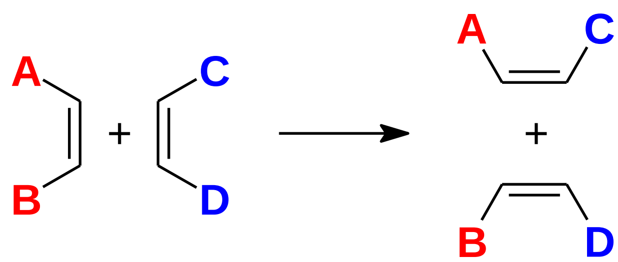
Combination of separation selectivity and catalytic activity

Length: 10 m fs-capillary

I.D. 250 µm, 500 nm film thickness

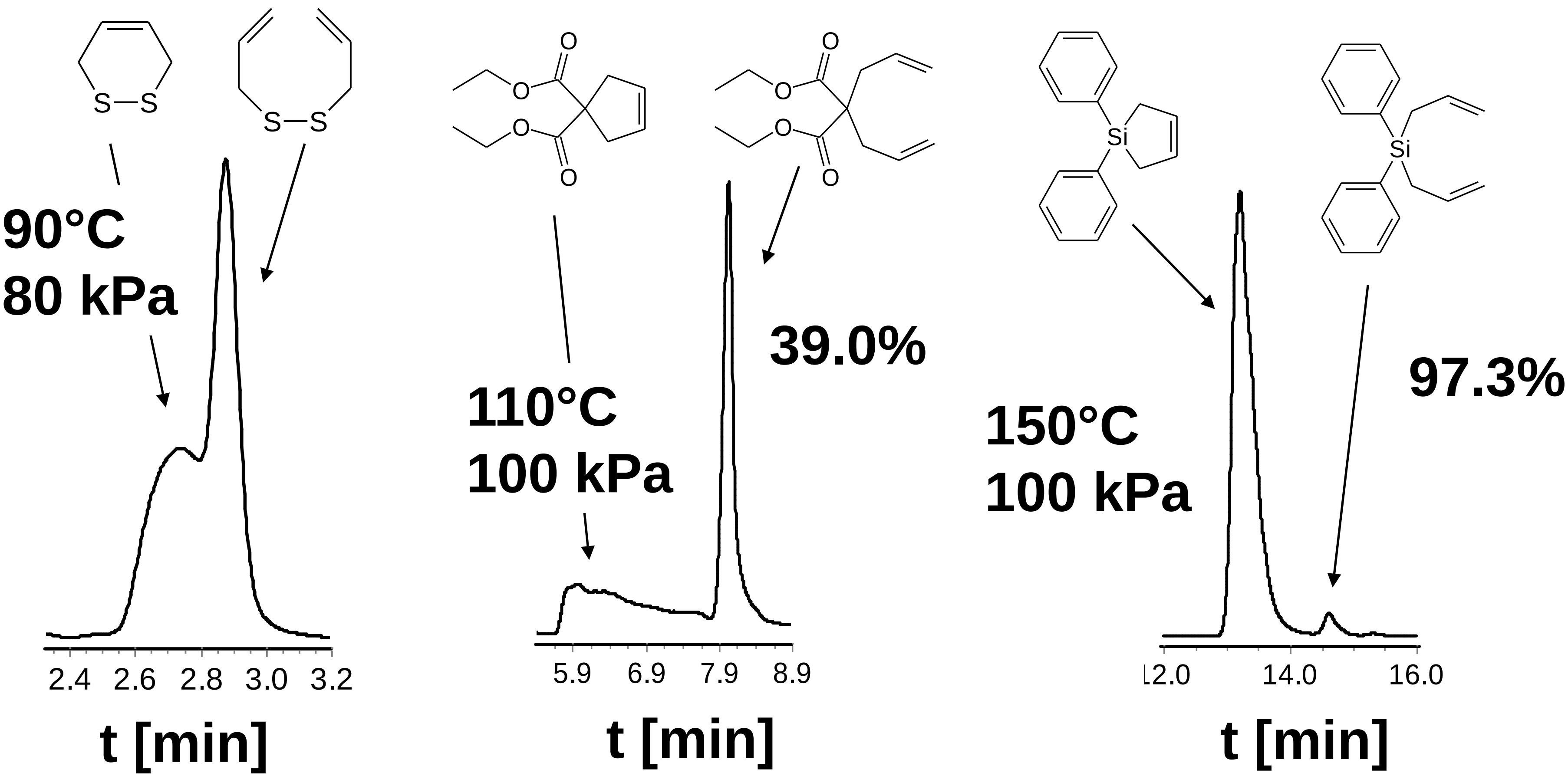
Grubbs 2nd generation catalyst dissolved in GE SE-30

1.6 µg catalyst/ m → 1.9 nmol/ m



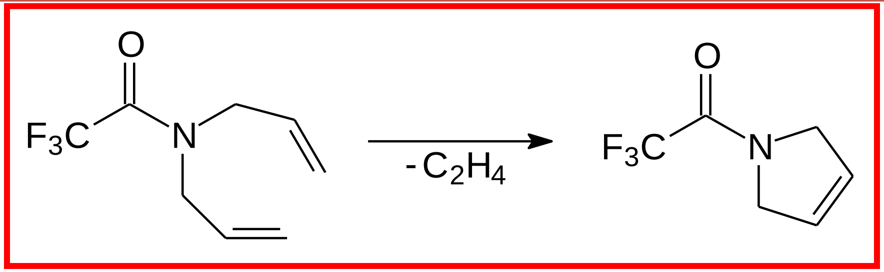
O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

Metathesis: Conversion Profiles

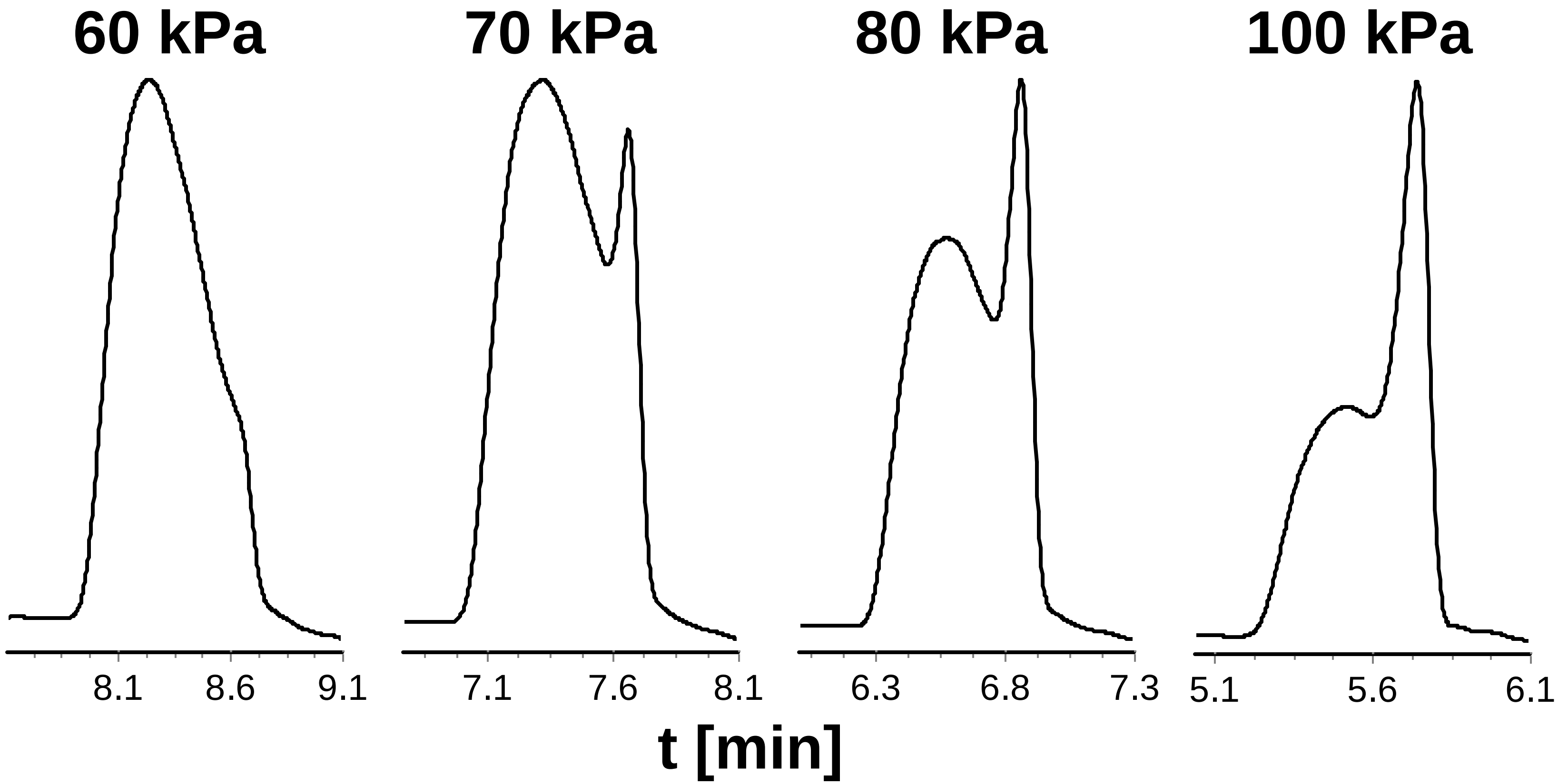


O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

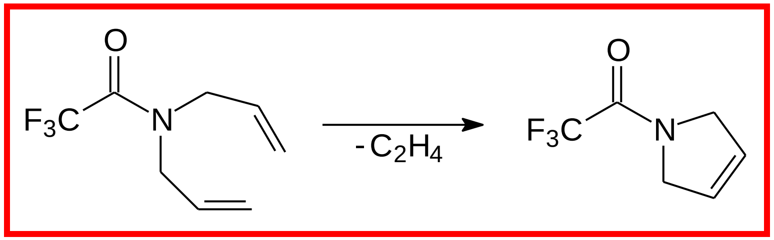
Metathesis – Contact Time Variation



50°C

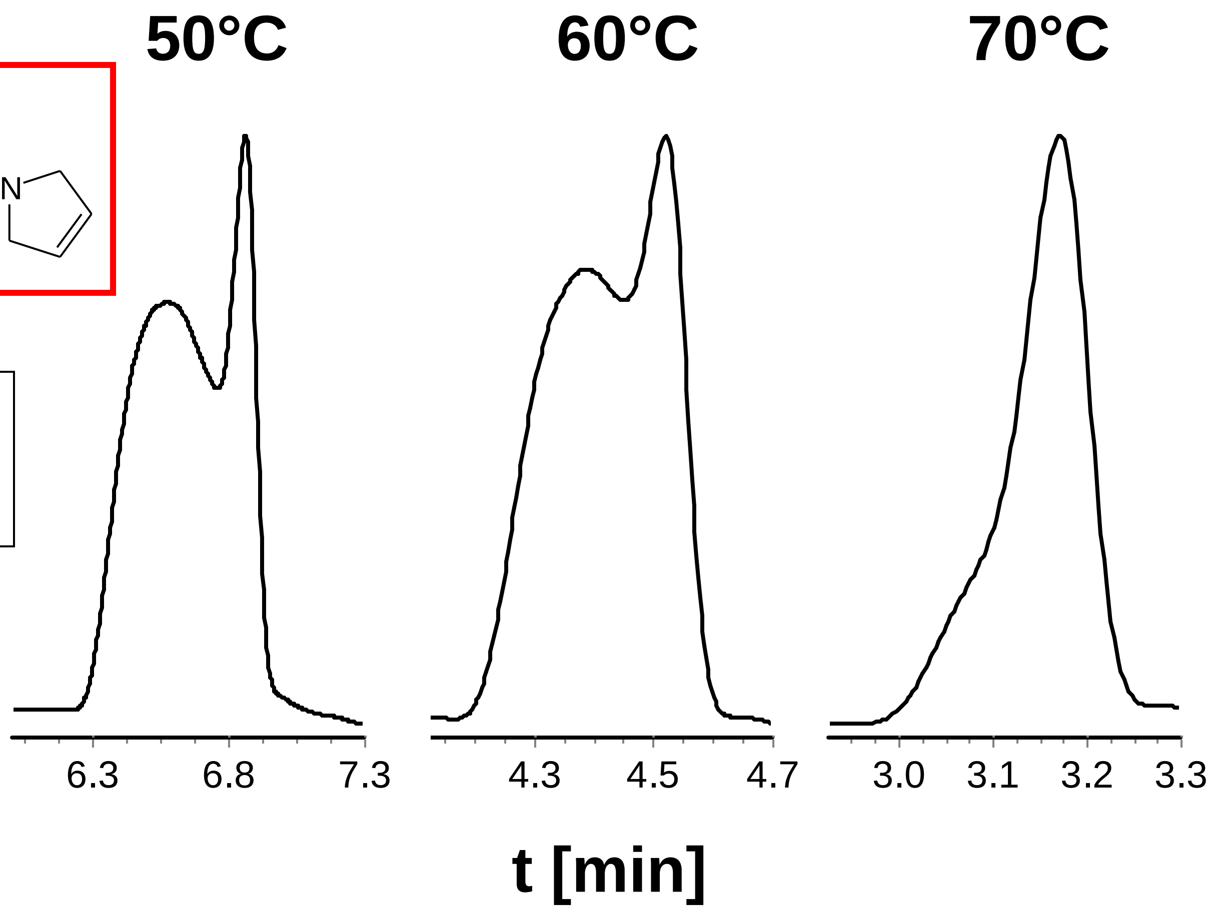


Metathesis – Activation Parameters



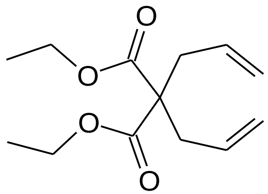
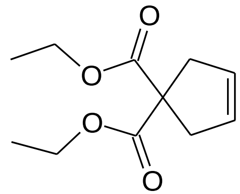
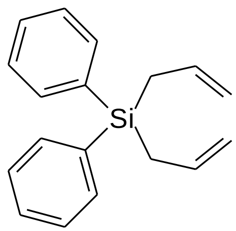
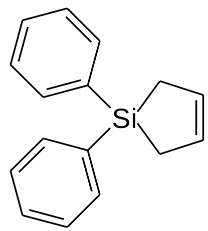
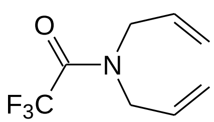
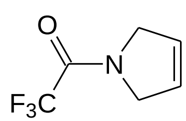
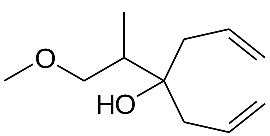
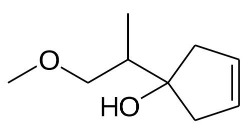
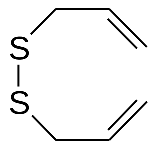
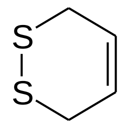
$\Delta H^{\ddagger}$ = 15.5 kJ/mol
$\Delta S^{\ddagger}$ = -230 J/(Kmol)

80 kPa



O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.
O. Trapp, S. Bremer, S.K. Weber, *Anal. Bioanal. Chem.* **2009**, *395,* 1673-1679.

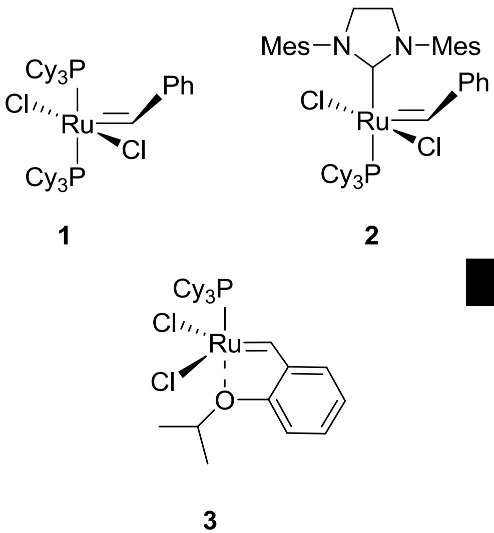
Activation Barriers

	Substrate	Product	T [°C]	C [%]	k [1/s]	$\Delta G^{\#}$ [kJ/mol]
1			110.0	39.0	$2.2 \cdot 10^{-3}$	114.1
2			150.0	97.3	$3.4 \cdot 10^{-3}$	124.9
4			50.0	62.5	$8.6 \cdot 10^{-3}$	89.8
5			120.0	59.5	$7.7 \cdot 10^{-3}$	113.1
6			90.0	51.0	$4.9 \cdot 10^{-3}$	105.6

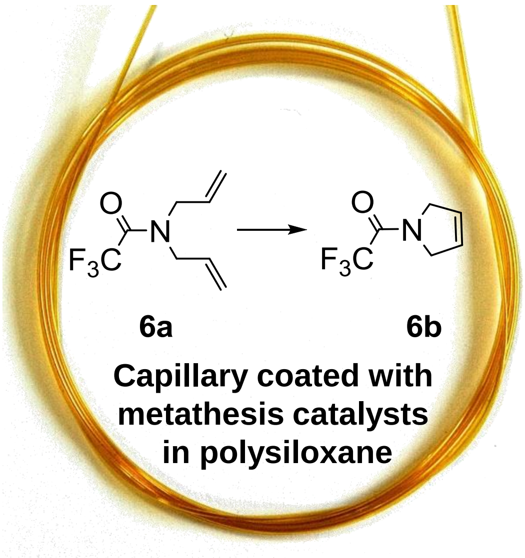
O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

In-depth Screening of Metathesis Catalysts

Catalysts

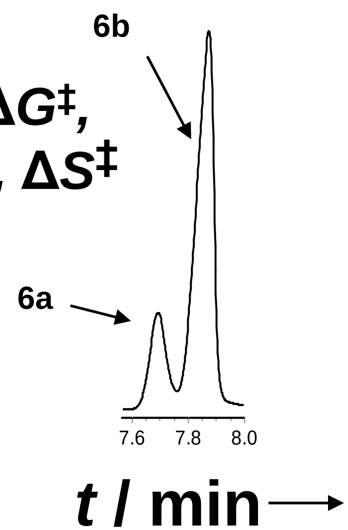


On-Column Ring Closure Metathesis



Thermodynamics & Kinetics

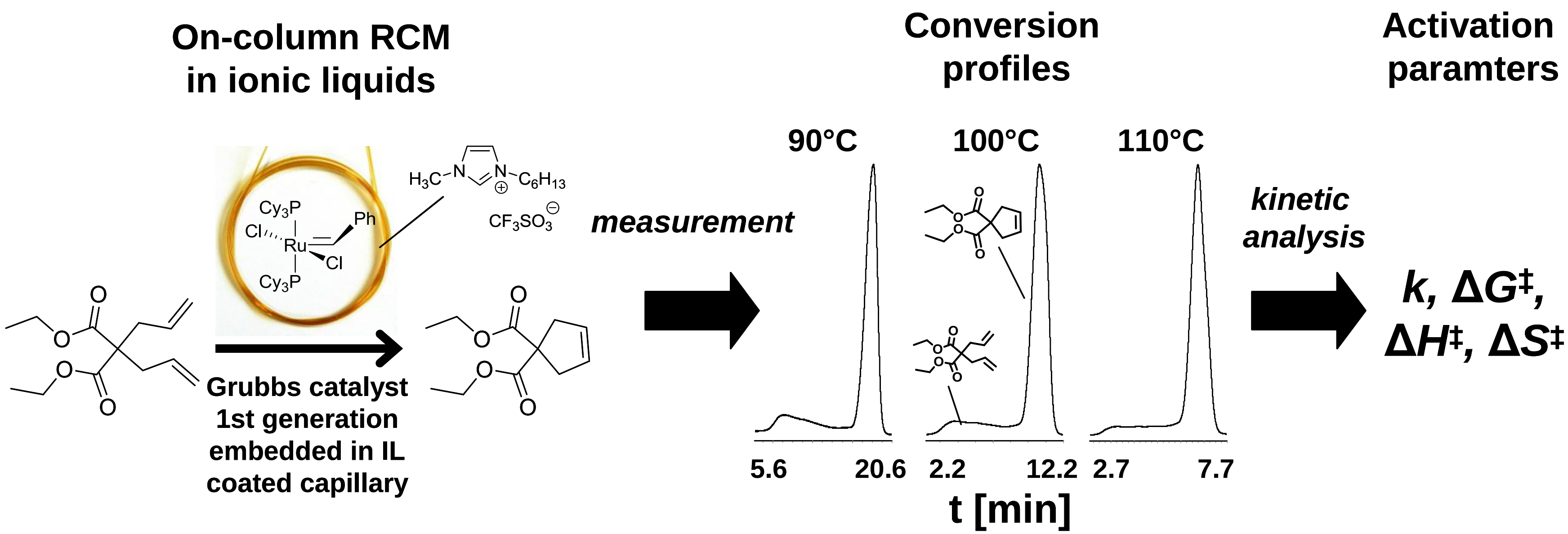
***k*, Δ*G*‡, Δ*H*‡, Δ*S*‡**



Chromatographic reactor coupled with separation column:
- 1-3 m reactor column
- Higher catalyst loading

S.K. Weber, S. Bauch, M. Spallek, O. Trapp, *submitted*

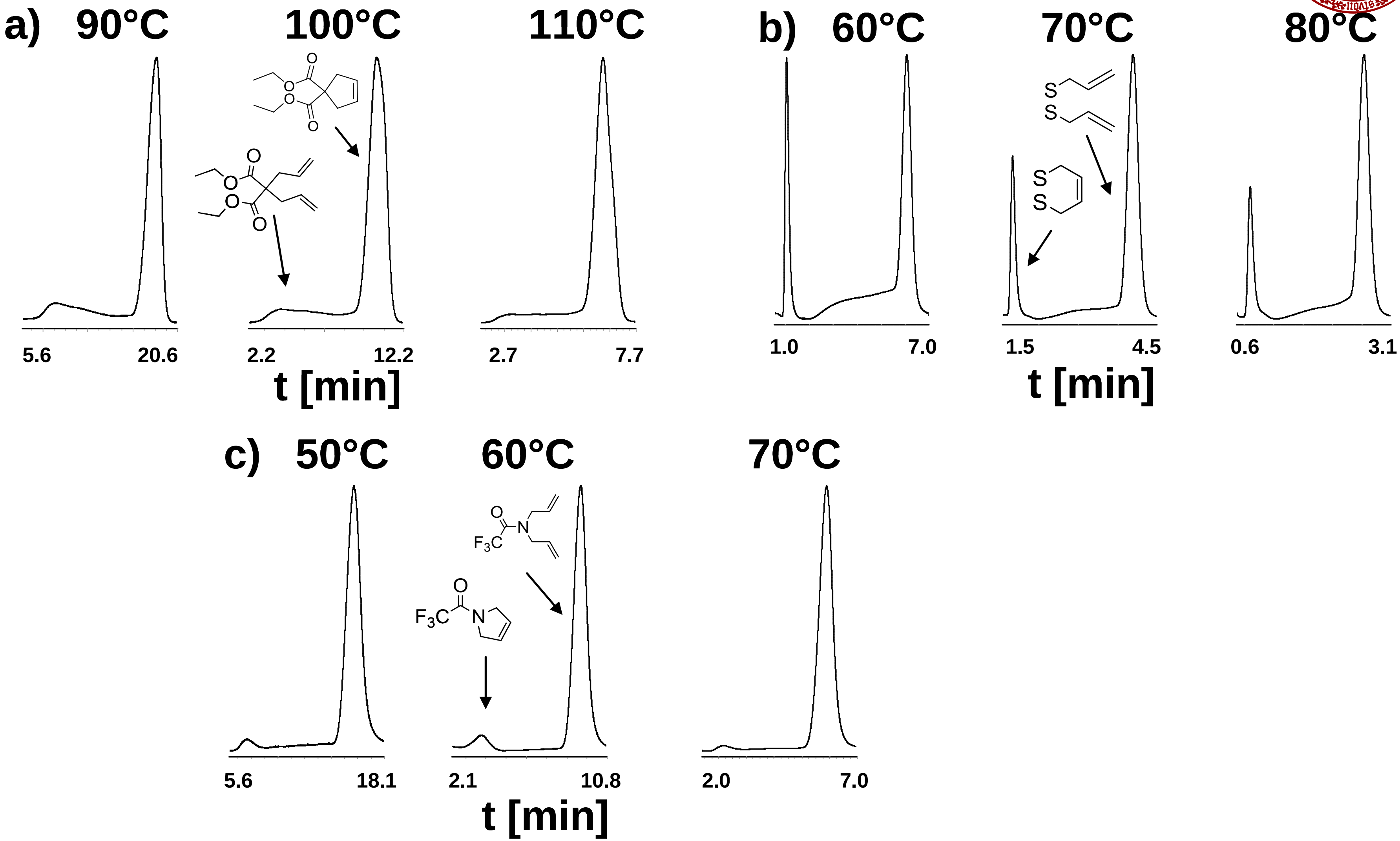
Metathesis in Room Temperature Ionic Liquids



Challenging tasks

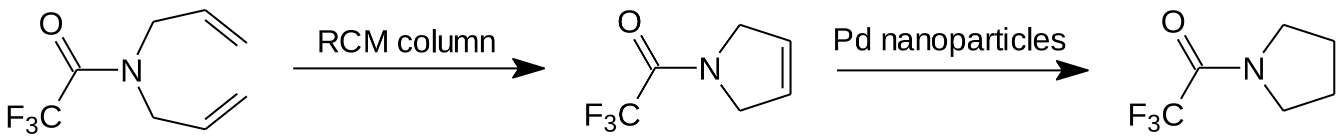
- Analytics of reaction educts and products in ionic liquids
- Time dependent measurements

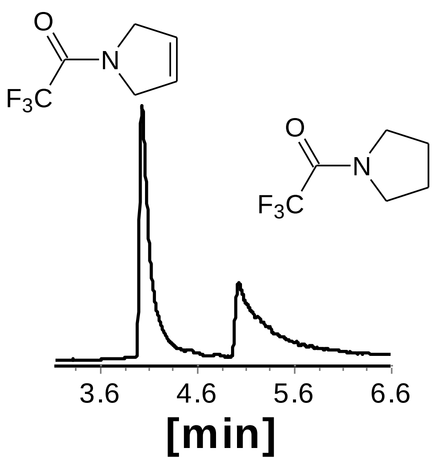
Measurement of Kinetic Data

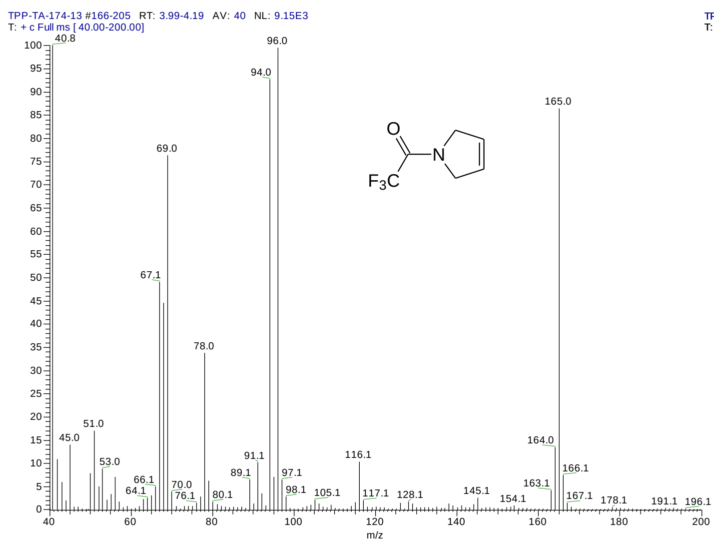


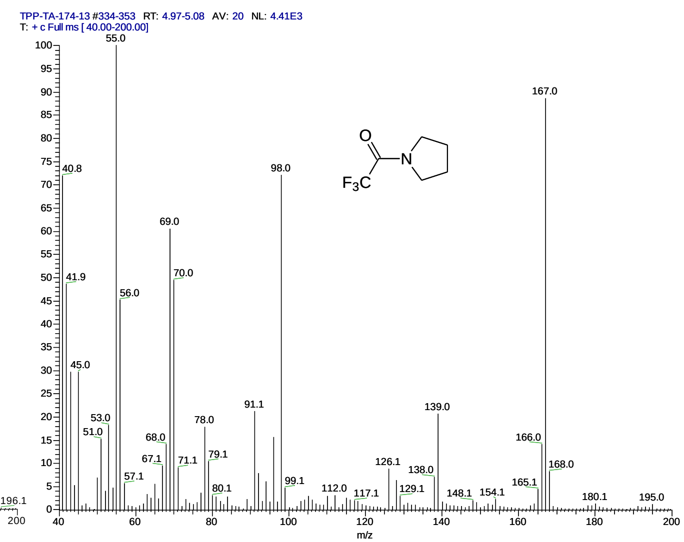
Reaction Cascades

<6 min



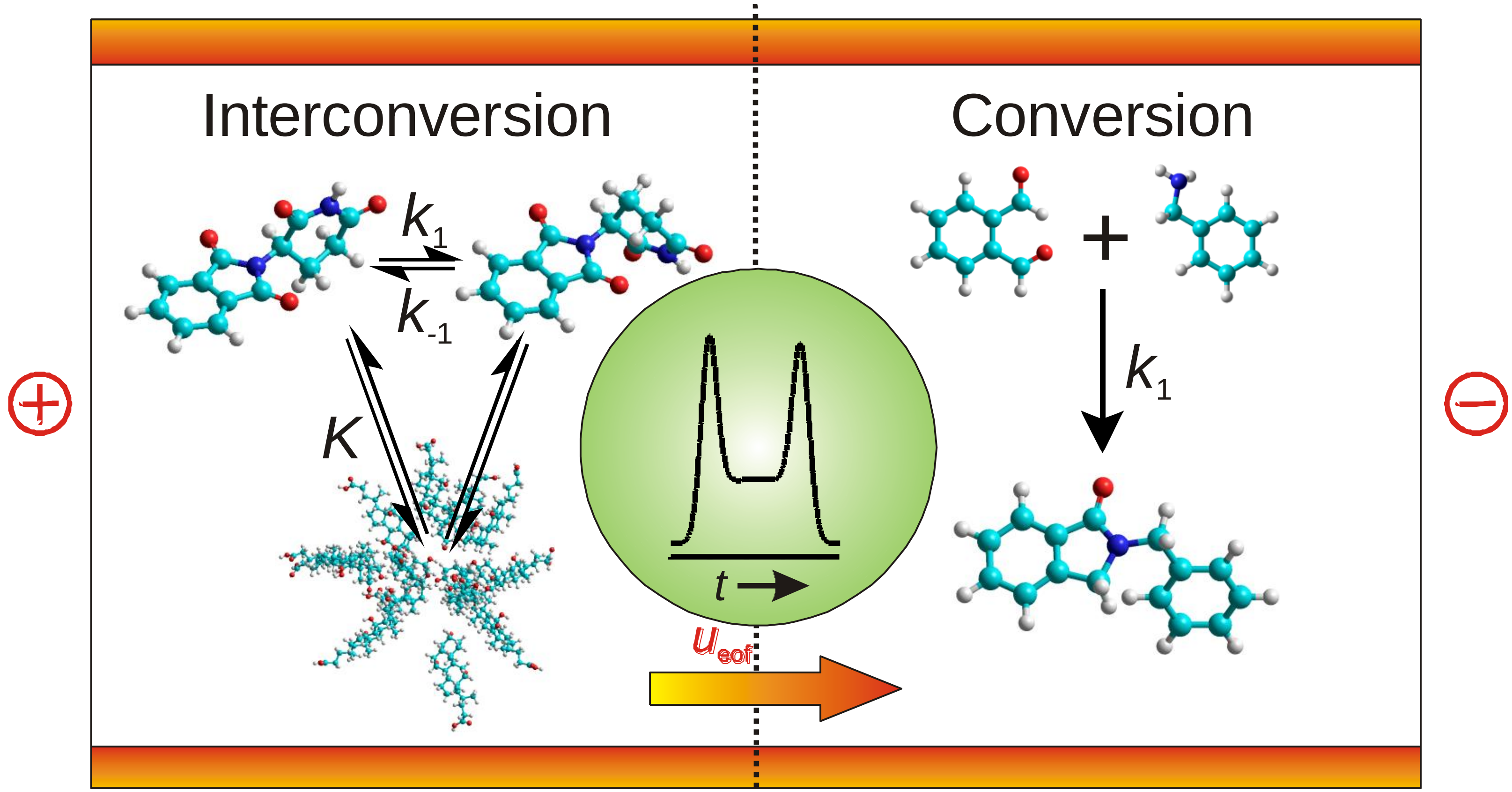






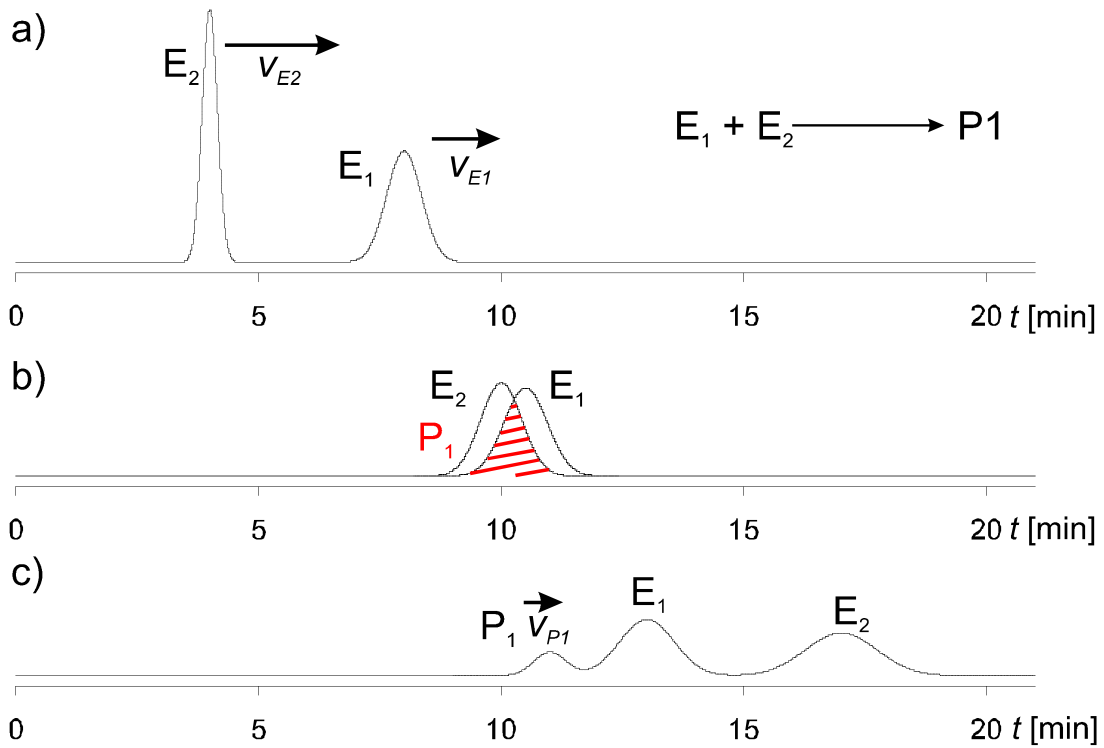
O. Trapp, S.K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem.* **2007**, *119*, 7447-7451.

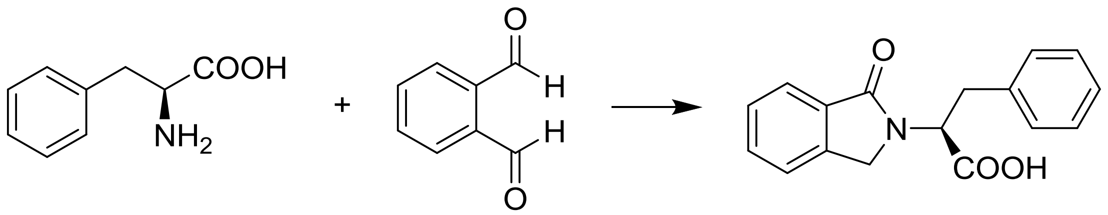
Higher-order Reactions



O. Trapp, *Electrophoresis* **2010**, *31*, 786-813.

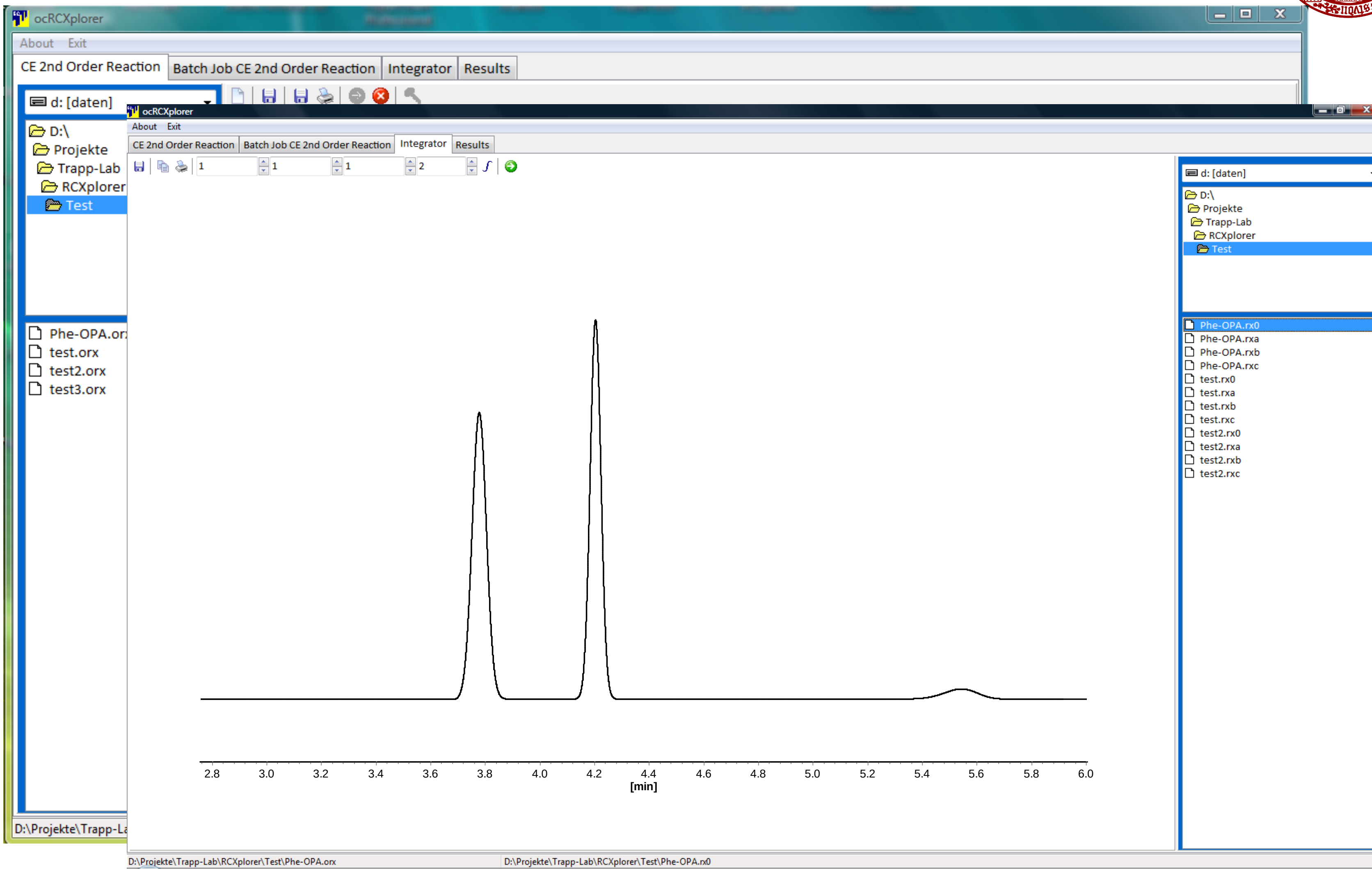
Higher-order Reactions



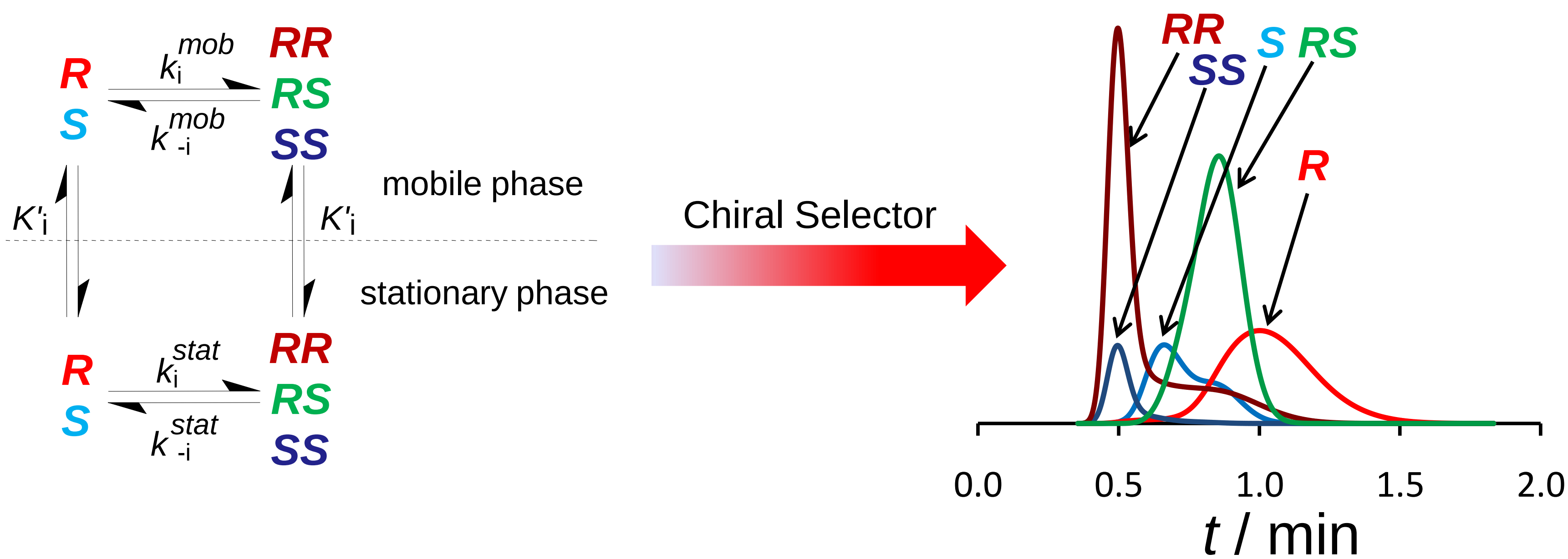


E1 E2 P

Evaluation of 2nd-order Reactions



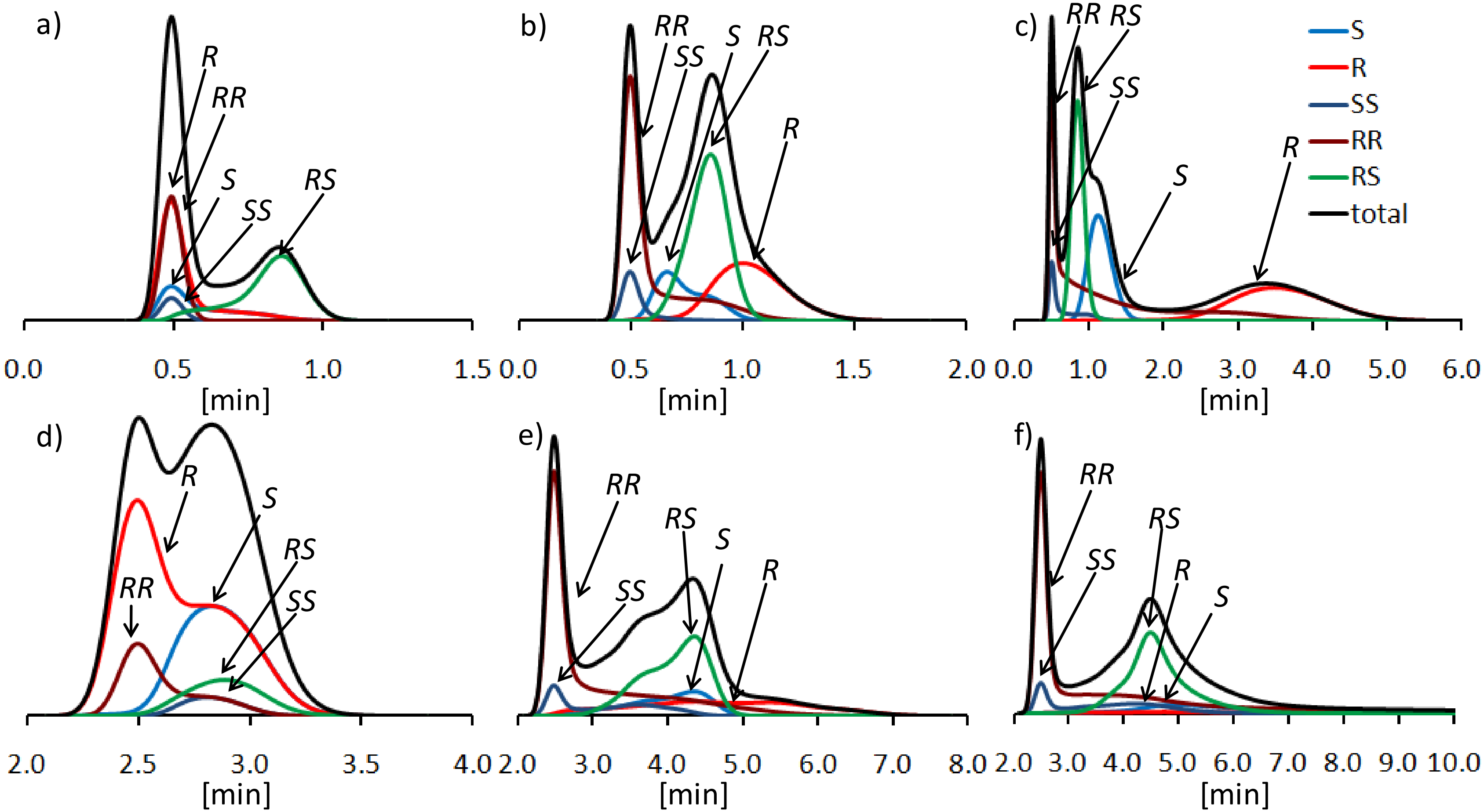
Nonlinear Effects in Enantioselective Chromatography



Prediction of unusual elution profiles of enantiomers in non-racemic mixtures on an achiral stationary phase doped with small amounts of a chiral selector

O. Trapp, V. Schurig, *Tetrahedron: Asymmetry* **2010**, 21, *in press.*

Nonlinear Effects

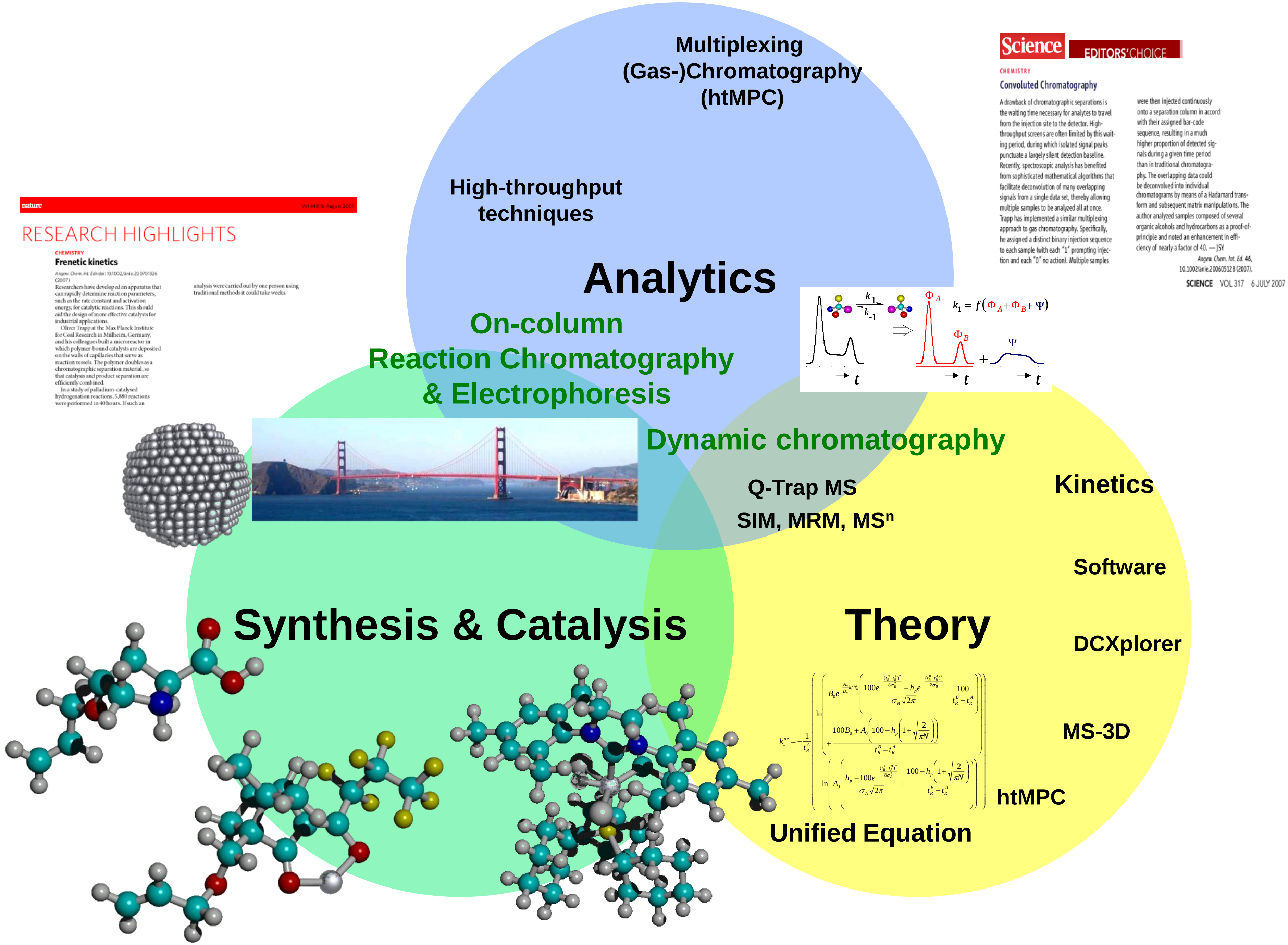


O. Trapp, V. Schurig, *Tetrahedron: Asymmetry* **2010**, 21, *in press.*

Conclusions & Outlook

- Combining separation selectivity & (enantioselective) catalysis
- High-throughput screening of catalysts and reactions
  → currently 5880 reactions in 40 h!
- Minute substrate consumption
- Continuous tuning of solvent properties
- Preparative synthesis possible (20 mg/ h) – micro plants
- Combinatorial catalyst preparation
- Catalyst by the 'meter'

→ **(R)evolution of chemist's toolkit**



Multiplexing
(Gas-)Chromatography
(htMPC)
High-throughput
techniques
Analytics
On-column
Reaction Chromatography
& Electrophoresis
Dynamic chromatography
Q-Trap MS
SIM, MRM, MSn
Kinetics
Software
DCXplorer
MS-3D
htMPC
Unified Equation
Theory
Synthesis & Catalysis
k1 = f(ΦA+ΦB+Ψ)
Science
EDITORS' CHOICE
CHEMISTRY
Convoluted Chromatography
A drawback of chromatographic separations is the waiting time necessary for analytes to travel from the injection site to the detector. High-throughput screens are often limited by this waiting period, during which isolated signal peaks punctuate a largely silent detection baseline. Recently, spectroscopic analysis has benefited from sophisticated mathematical algorithms that facilitate deconvolution of many overlapping signals from a single data set, thereby allowing multiple samples to be analyzed all at once. Trapp has implemented a similar multiplexing approach to gas chromatography. Specifically, he assigned a distinct binary injection sequence to each sample (with each "1" prompting injection and each "0" no action). Multiple samples were then injected continuously onto a separation column in accord with their assigned bar-code sequence, resulting in a much higher proportion of detected signals during a given time period than in traditional chromatography. The overlapping data could be deconvolved into individual chromatograms by means of a Hadamard transform and subsequent matrix manipulations. The author analyzed samples composed of several organic alcohols and hydrocarbons as a proof-of-principle and noted an enhancement in efficiency of nearly a factor of 40. — JSY
Angew. Chem. Int. Ed. 46, 10.1002/anie.200605128 (2007).
SCIENCE VOL 317 6 JULY 2007
nature
Vol 448|16 August 2007
RESEARCH HIGHLIGHTS
CHEMISTRY
Frenetic kinetics
Angew. Chem. Int. Edn doi: 10.1002/anie.200701326 (2007)
Researchers have developed an apparatus that can rapidly determine reaction parameters, such as the rate constant and activation energy, for catalytic reactions. This should aid the design of more effective catalysts for industrial applications.
Oliver Trapp at the Max Planck Institute for Coal Research in Mülheim, Germany, and his colleagues built a microreactor in which polymer-bound catalysts are deposited on the walls of capillaries that serve as reaction vessels. The polymer doubles as a chromatographic separation material, so that catalysis and product separation are efficiently combined.
In a study of palladium-catalysed hydrogenation reactions, 5,880 reactions were performed in 40 hours. If such an analysis were carried out by one person using traditional methods it could take weeks.

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Nordrhein-Westfälische Akademie der Wissenschaften
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MaCKiE International Workshop 2011

University of Heidelberg

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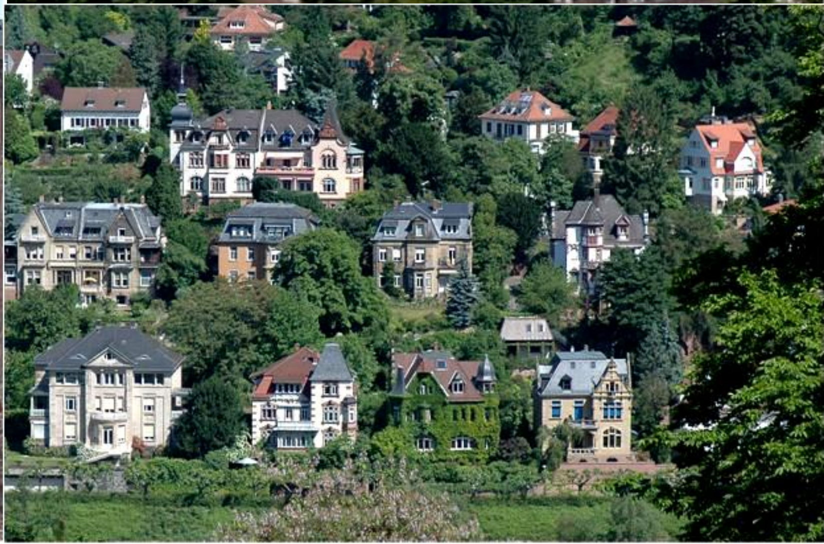

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Highlights:

- 625th Anniversary of the

Welcome you all to Heidelberg