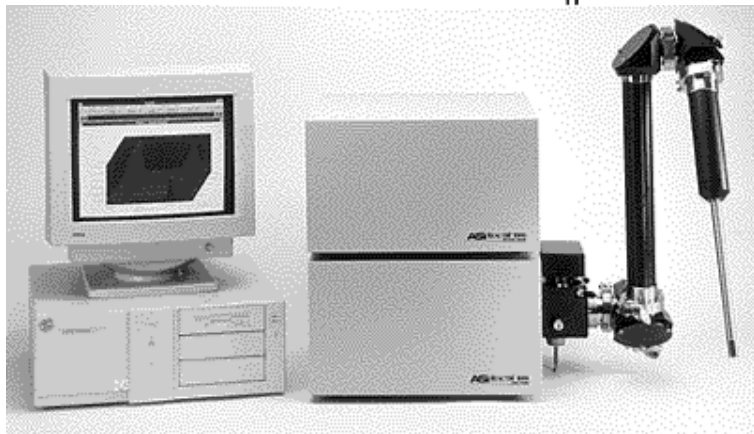
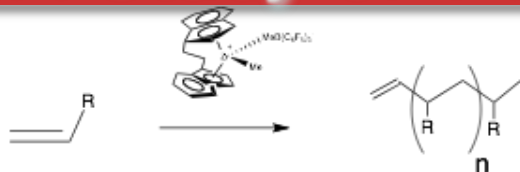


IR Study of 1-Hexene Polymerization

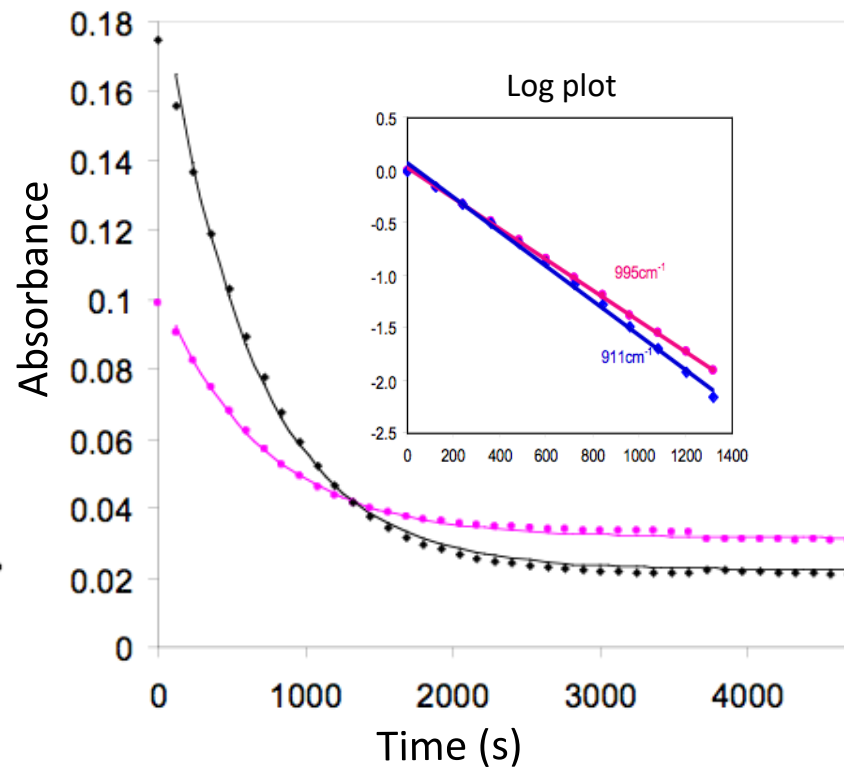
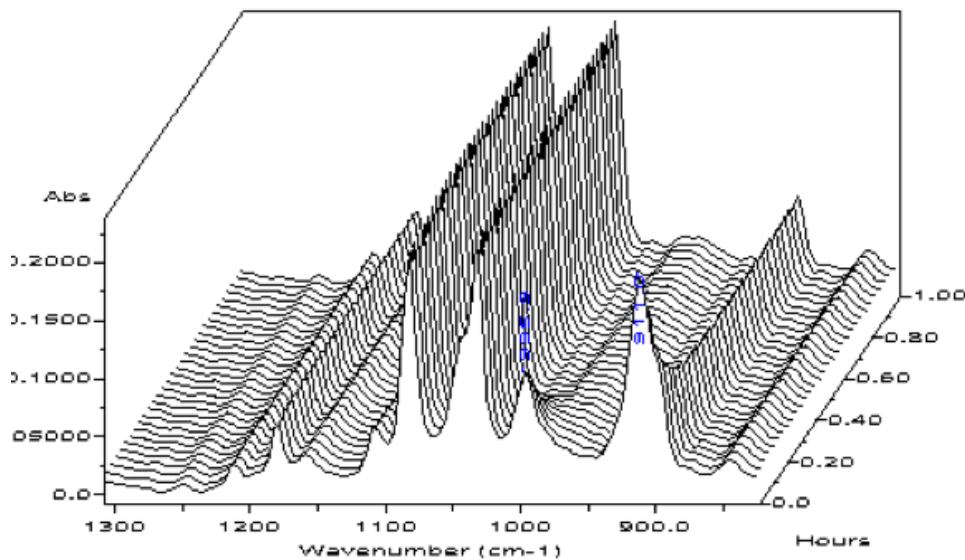


Reaction conditions:

$$[(\text{EBI})\text{Zr}(\text{CH}_3)_2] = [\text{B}(\text{C}_6\text{F}_5)_3] = 8.33 \times 10^{-4} \text{ M}$$

$$[1\text{-hexene}] = 1.0 \text{ M}$$

$$T = 0^\circ \text{C}$$

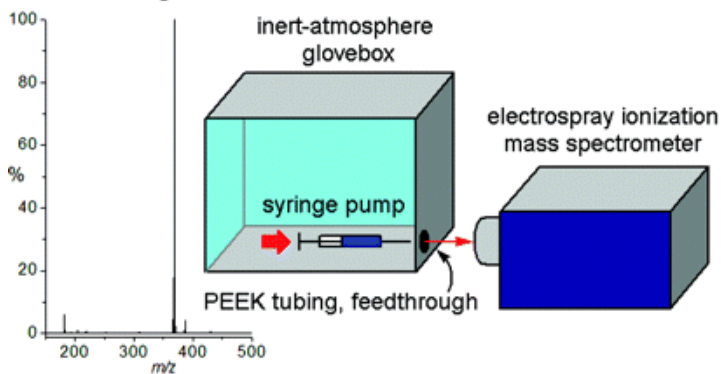


Measuring Catalytic Rates- Mass Spectrometry

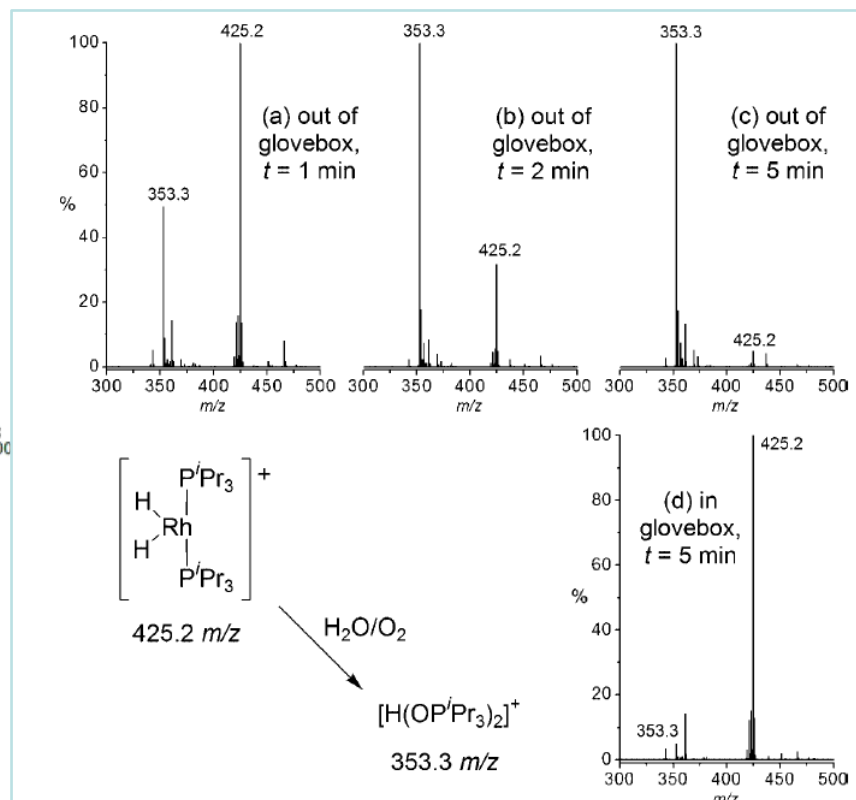
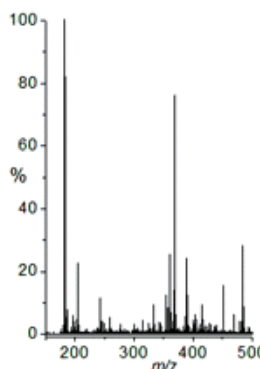
ElectroSpray Ionization (ESI) and Matrix Assisted Laser Desorption Ionization (MALDI) are “Soft” Ionization Methods

Interfacing with a glovebox enables clean spectra

ESI-MS with glovebox



...and without



Coupling an Electro-spray Ionization Mass Spectrometer with a Glovebox: A Straightforward, Powerful, and Convenient Combination for Analysis of Air-Sensitive Organometallics

Lubben, A. T.; McIndoe, J. S.; Weller, A. S.

Organometallics; **(Note)**; 2008; 27(13); 3303-3306.

Measuring Catalytic Rates - MALDI

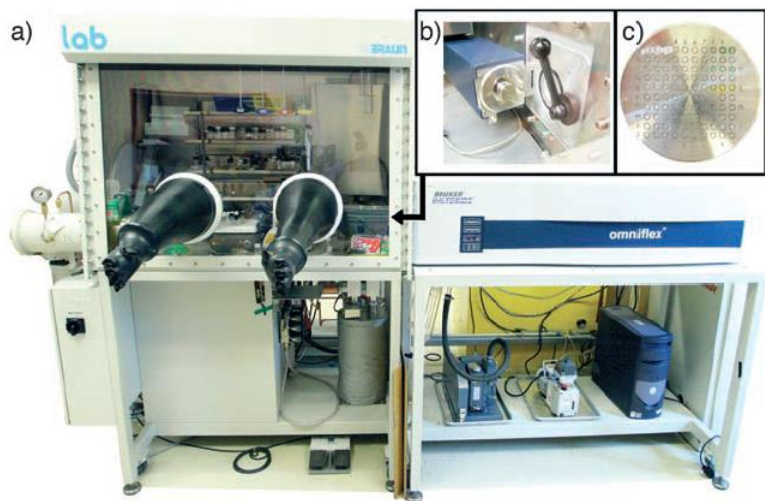


Figure 1. a) Inert-atmosphere MALDI-TOF mass spectrometer; b) open loading chamber projecting into the glovebox; c) target plate.

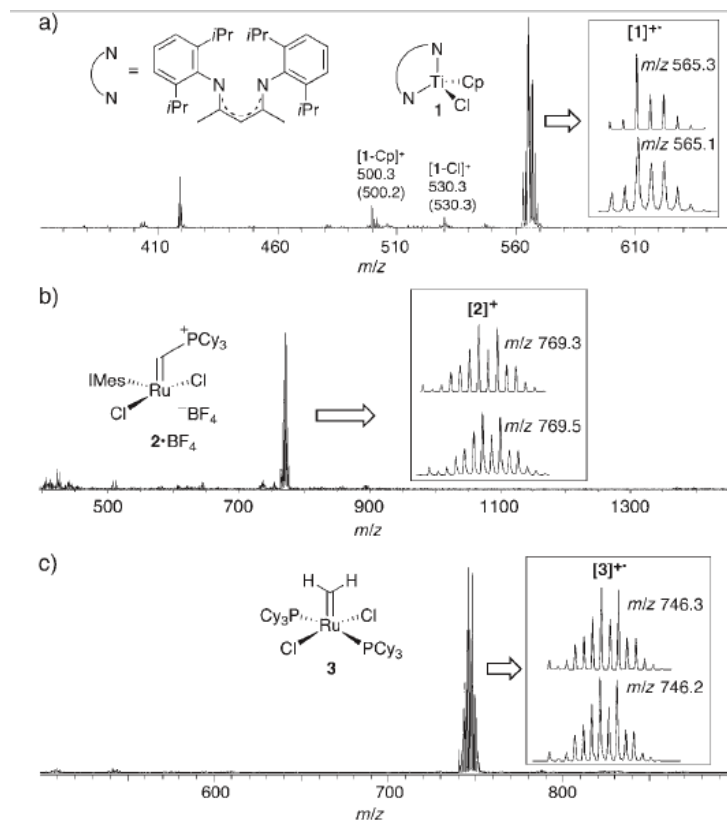
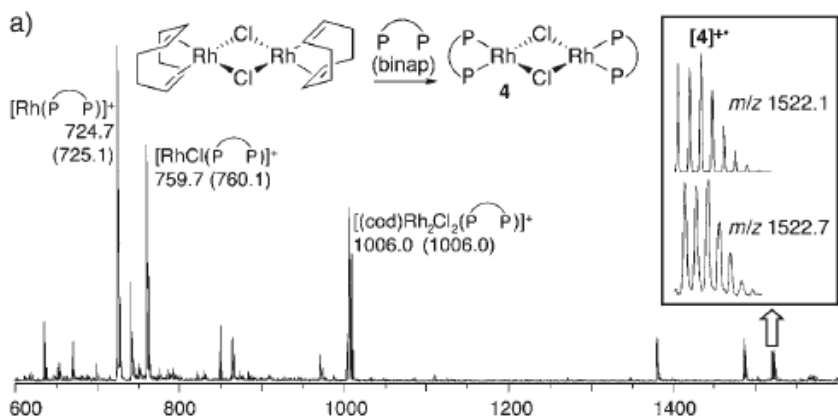


Figure 2. MALDI mass spectra of isolated complexes. a) An oxophilic Ti^{III} complex^[14] (pyrene matrix); b) the Piers metathesis catalyst 2-BF₄^[15] (pyrene); c) a first-generation Grubbs catalyst^[16] (anthracene). Labels give found (calculated) m/z values. Insets show isotope patterns for the molecular ions (top: simulated, bottom: observed). Cp = C₅H₅, IMes = *N,N'*-bis(mesityl)imidazol-2-ylidene, Cy = cyclohexyl.



A Gas Phase MS Reactor

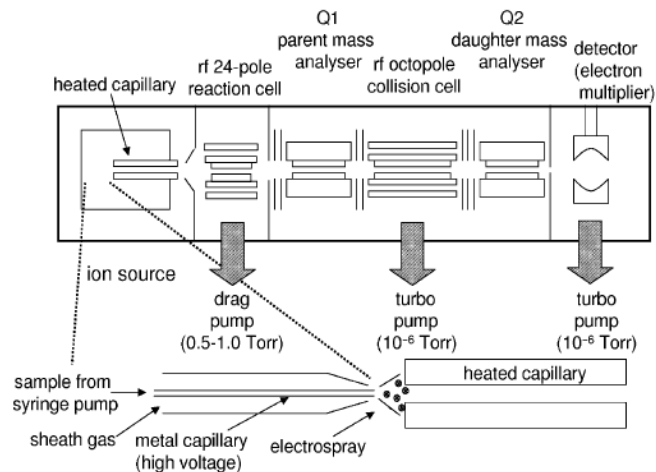
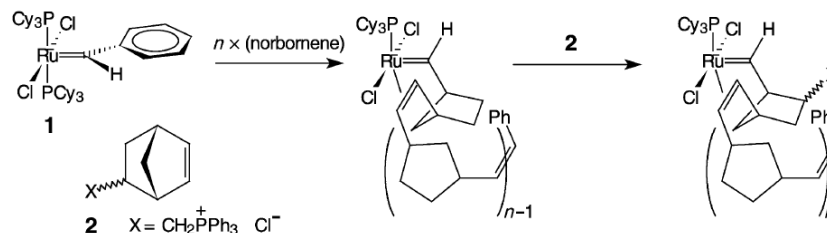


Figure 1. Schematic representation of the modified Finnigan MAT TSQ-700 ESI tandem mass spectrometer. Catalyst ions are sprayed from dilute solution in the ion source, desolvated, and transferred into the vacuum system through the heated capillary, after which the final desolvation or fragmentation occurs at the skimmer. The two radio-frequency (rf) multipoles serve as reaction “vessels” for collisions of the ions with neutral gaseous reagents. After each stage of reaction, product identification and/or selection is carried out in a quadrupole mass analyzer.



Scheme 1. Derivatization of ruthenium catalysts with cationic norbornene species enables detection by ESI-MS.

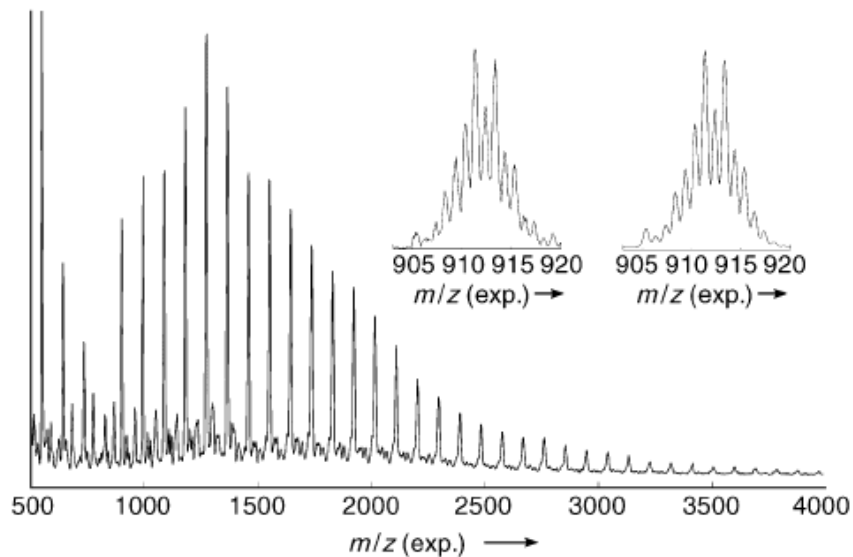


Figure 4. ESI-MS of the catalyst-bound ROMP oligomers obtained by reaction of $[(\text{Cp}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ with norbornene and a covalently functionalized norbornene derivative. Complexes that incorporated the functionalized norbornene are visible in the ESI-MS. The inset compares the isotope pattern of one oligomer against a computed distribution.

Measuring Catalytic Rates - NMR

NMR is an Information-Rich Technique
but we must consider time-scales

Traditional Rate Regime

- $t_{1/2} \geq 30 \text{ sec}$, $k \leq 0.01 \text{ s}^{-1}$
- Limited by mixing outside NMR probe
- Very minor linebroadening effects ($> 0.01 \text{ Hz}$)

Intermediate Rate Regime

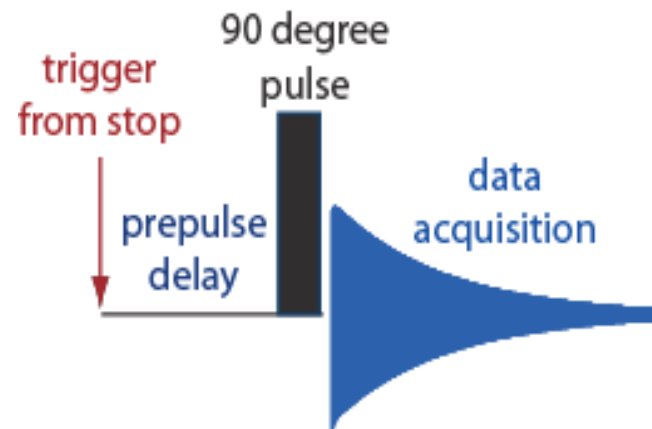
- $0.1 < t_{1/2} < 30 \text{ sec}$, $0.01 < k < 10 \text{ s}^{-1}$
- Requires mixing in or very near NMR probe
- Some linebroadening expected

Millisecond Rate Regime

- $t_{1/2} \leq 0.1 \text{ sec}$, $k \geq 10 \text{ s}^{-1}$
- Requires very short dead times
- Dispersive product signals expected

collect series of spectra
following single “shot”

multiple “shots” with
incremented prepulse delay
for faster reactions

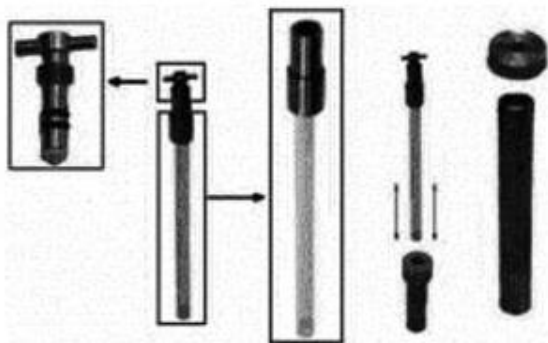


General Attributes

- Many useful nuclei (H, P, C, Si, Li, B, F, Co, etc.)
- Resonance intensity generally proportional to concentration
- Chemical shift related to structure
- Many methods for assignments

NMR at High Pressures

Sapphire Tubes (also PEEK)



I.T. Horváth and J.M. Millar. Chem. Rev. 91 (1991), p. 1339

C. Roe, J. Mag. Res. 63, 388 (1985)

Flow Cell

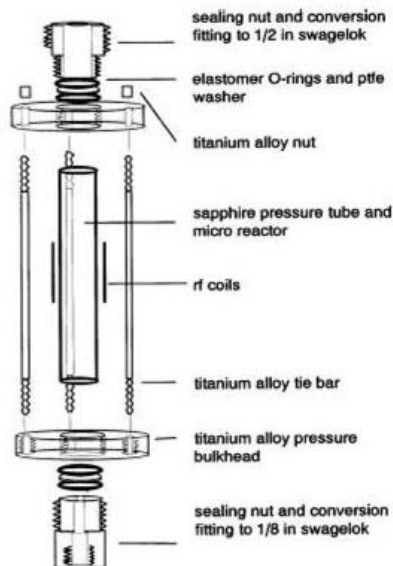
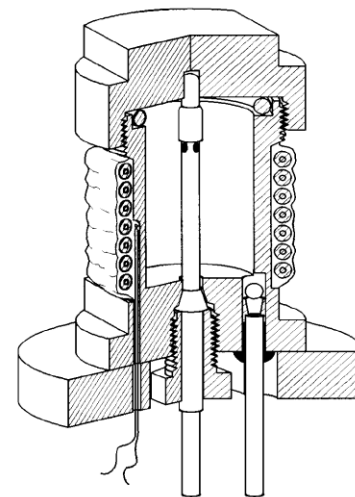


Figure 7.3 Exploded view of the high pressure in situ NMR flow cell. (From J. A. Iggo, D. Shirley, N. C. Tong, *New J. Chem.* 1998, 1043.)

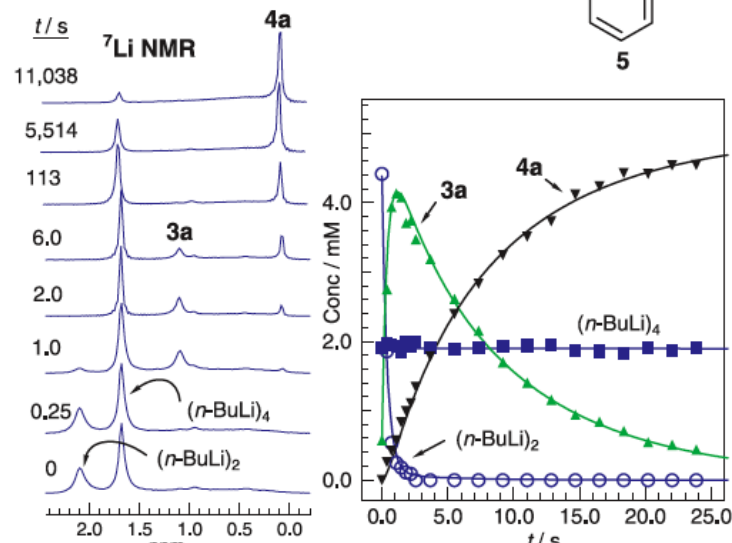
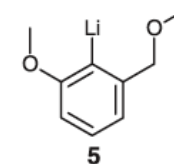
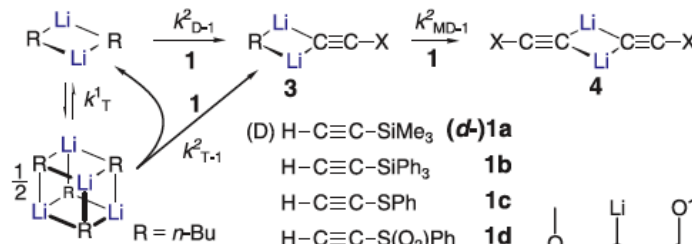
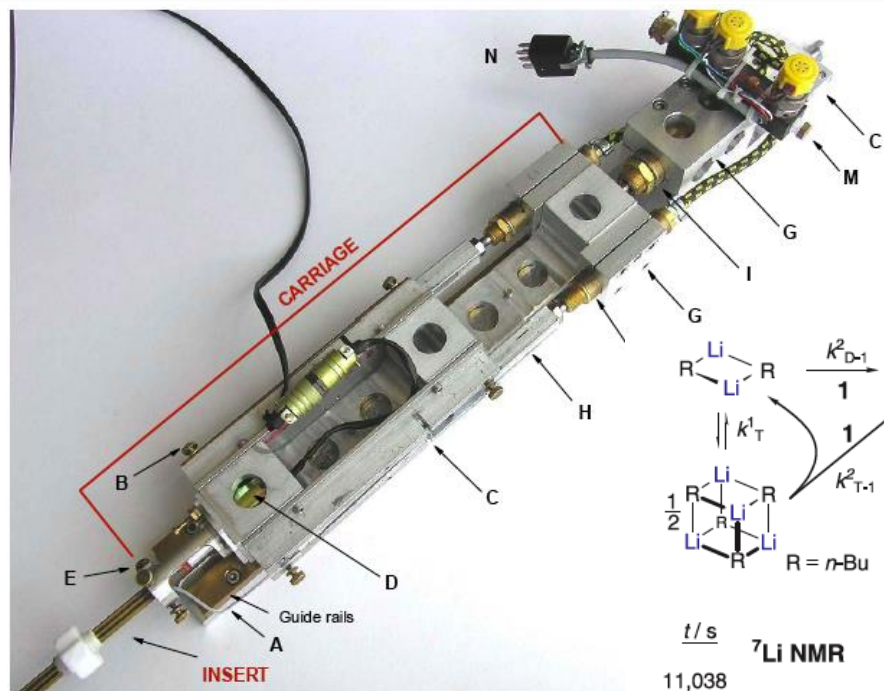
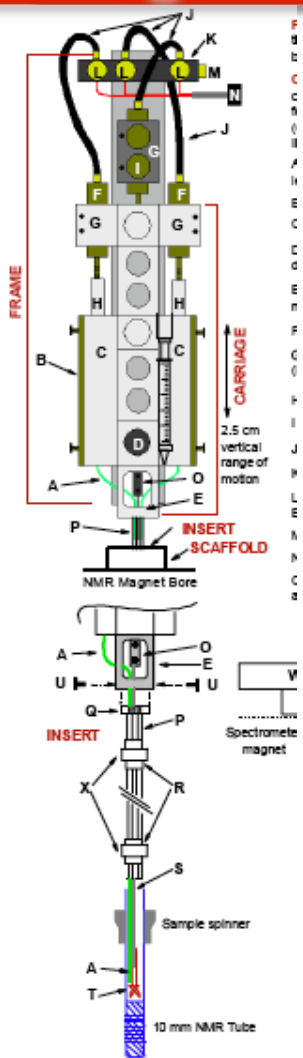
Toroidal Cavity Autoclave



Niessen, H.G.; Trautner, P.; Wiemann, S.; Bargon, J.; Woelk, K. *Rev. Sci. Instrum.* 2002, 73, 1259-1266.

Clark Landis - Modern Methods

Going Further - Rapid Injection NMR



Reactivity of the Triple Ion and Separated Ion Pair of

Tris(trimethylsilyl)methylithium with Aldehydes: A RINMR Study

Jones, A. C.; Sanders, A. W.; Sikorski, W. H.; Jansen, K. L.; Reich, H. J. *J. Am. Chem. Soc.* (**Communication**); **2008**; 130(19); 6060-6061.



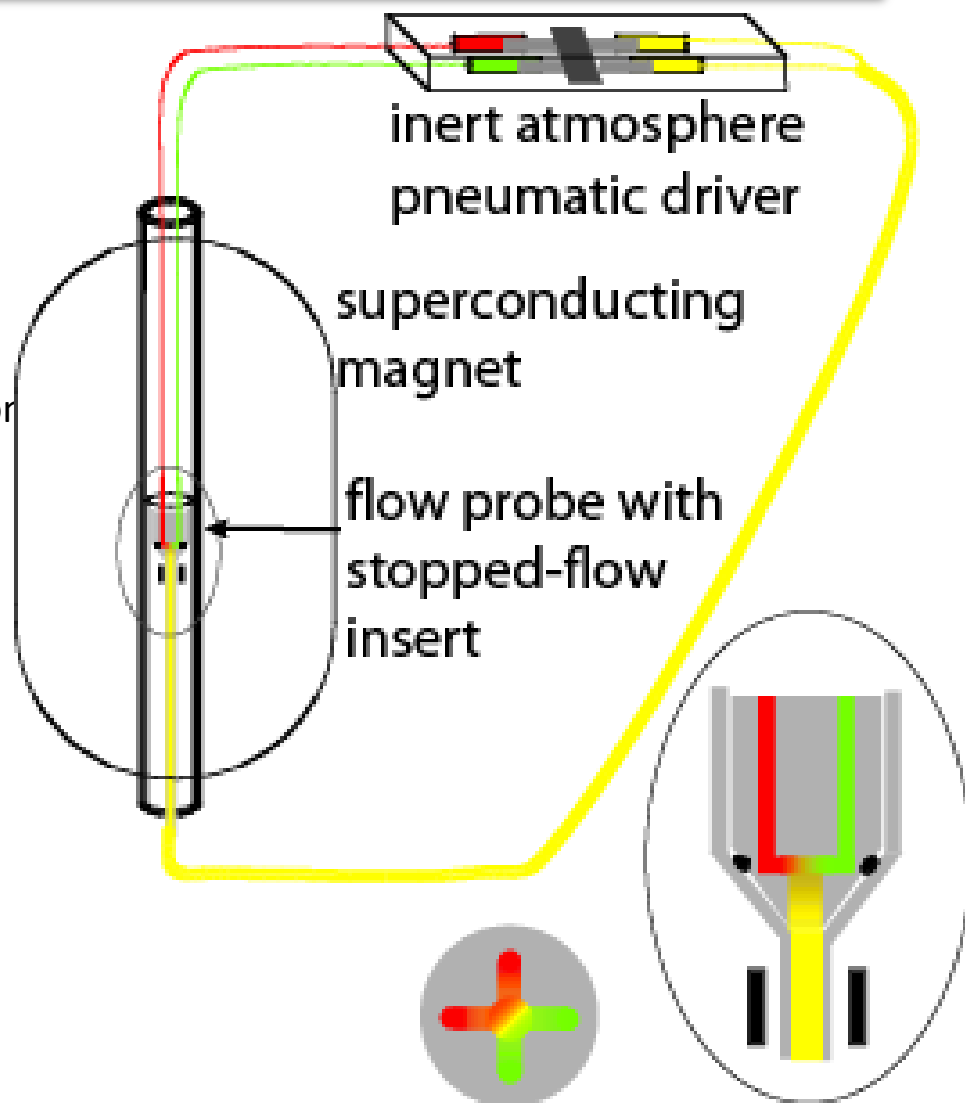
Stopped-Flow NMR Spectroscopy

Background

- Stopped-flow methods monitor very fast reactions
- NMR can monitor multiple species in solution simultaneously
- Ernst explored the effect of fast reactions on NMR lineshapes in 1979
- SF-NMR has not become a routine experiment

Our Project Goals

- Focus on developing practical instrumentation from commercially available parts
- For very fast reactions, can kinetics be determined from a single NMR spectrum?

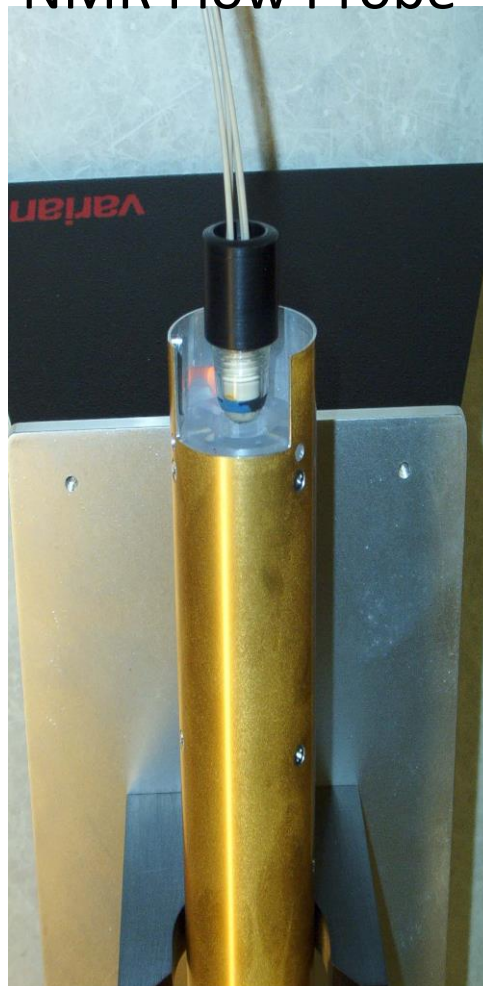


Stopped-Flow NMR: Mixer

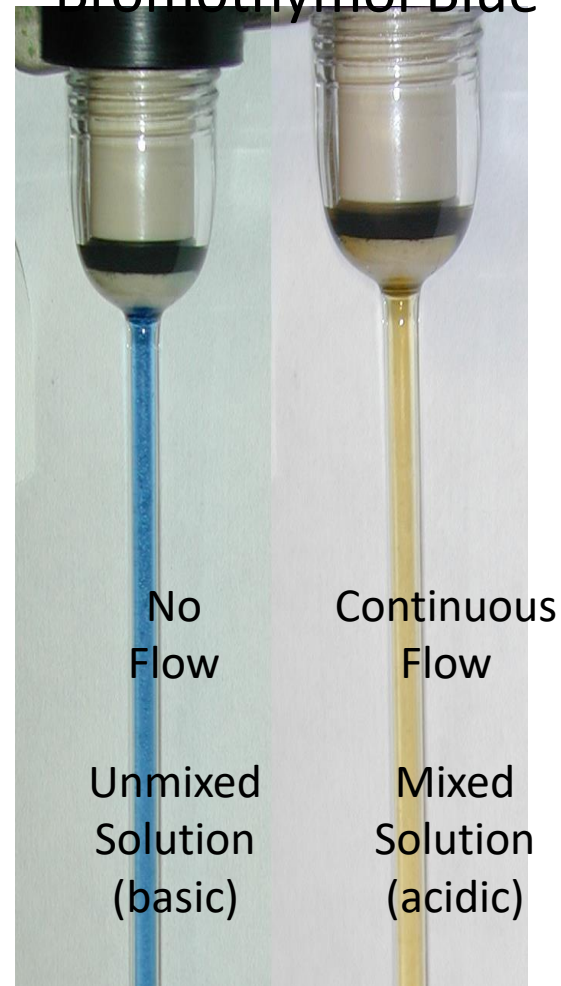
Disassembled Mixer



Mixer placed in
NMR Flow Probe



Mixing Tests with
Bromothymol Blue



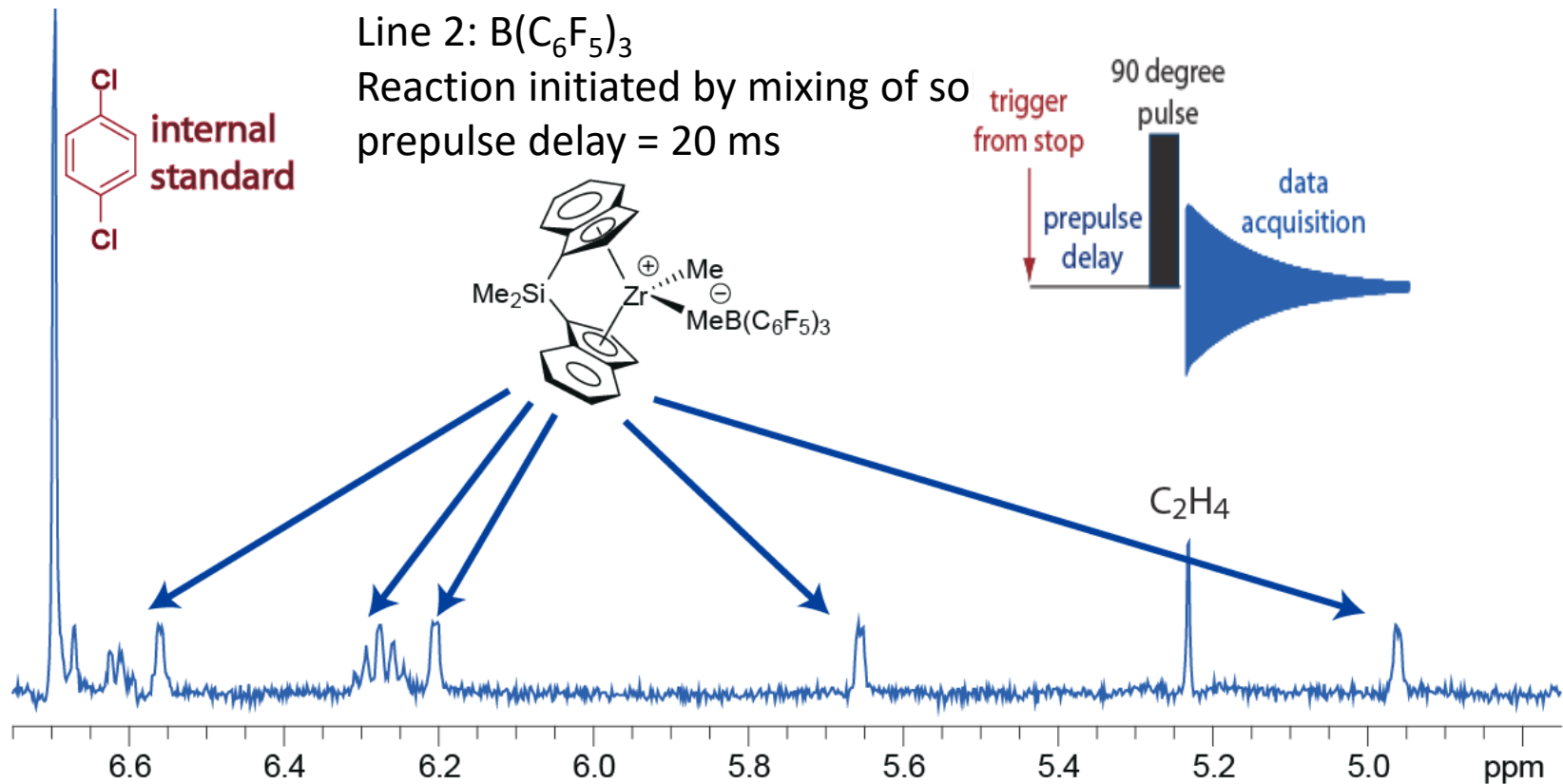
Ethene Polymerization 20 ms after Mixing

Experimental setup:

Line 1: zirconocene, internal standard, ethene

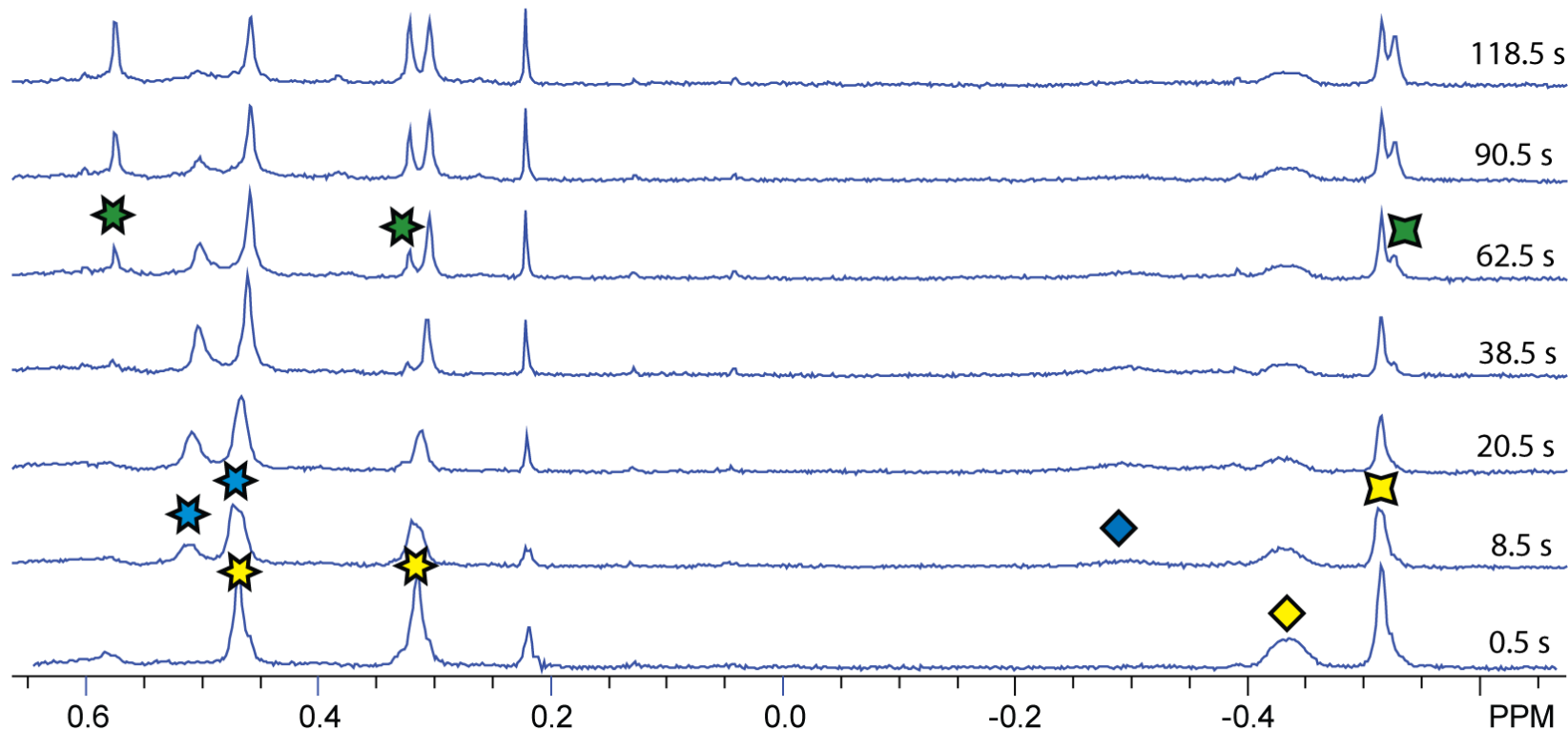
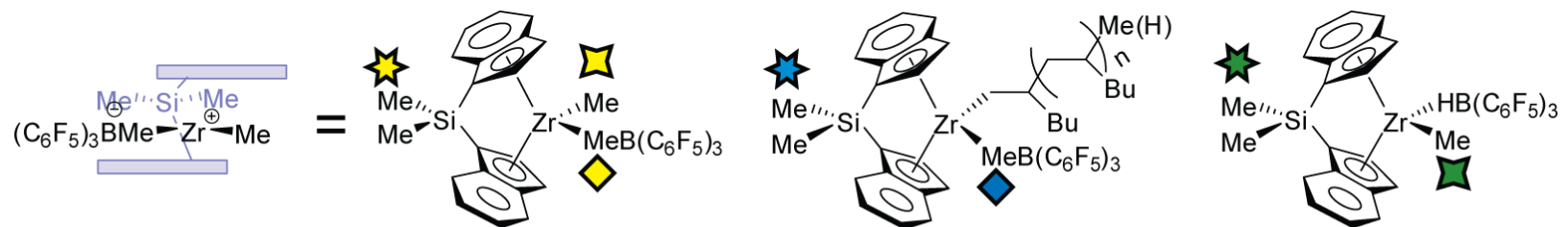
Line 2: $B(C_6F_5)_3$

Reaction initiated by mixing of so
prepulse delay = 20 ms



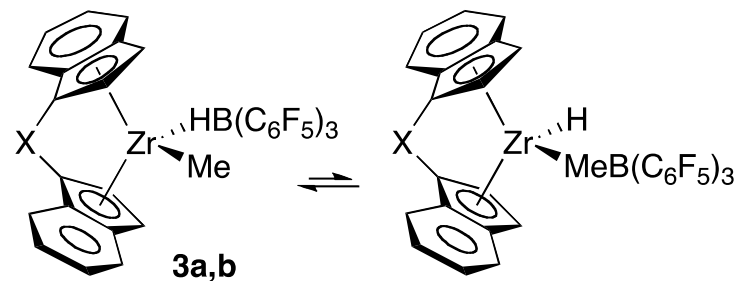
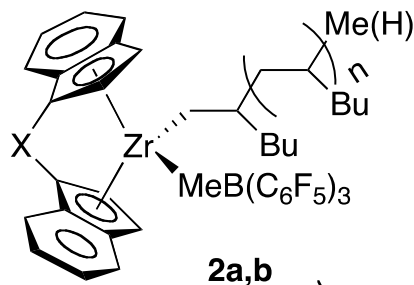
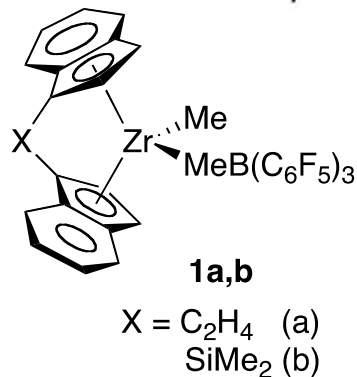
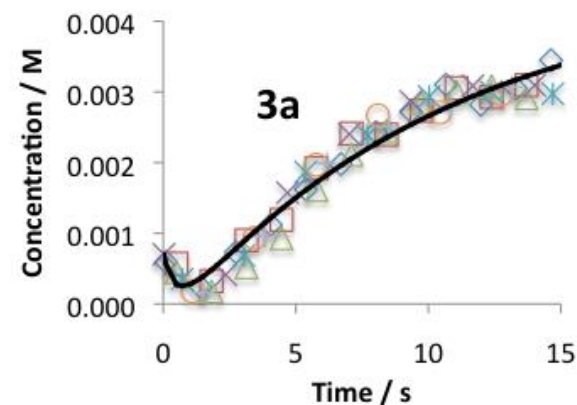
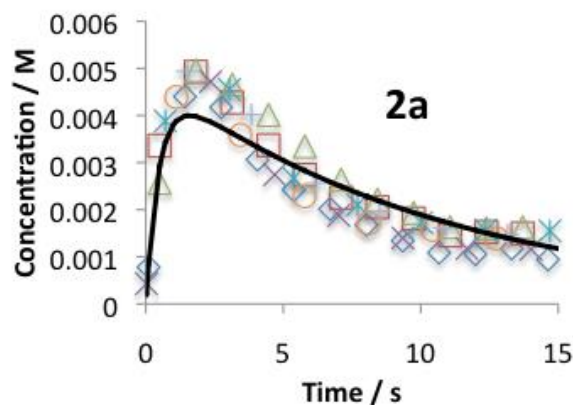
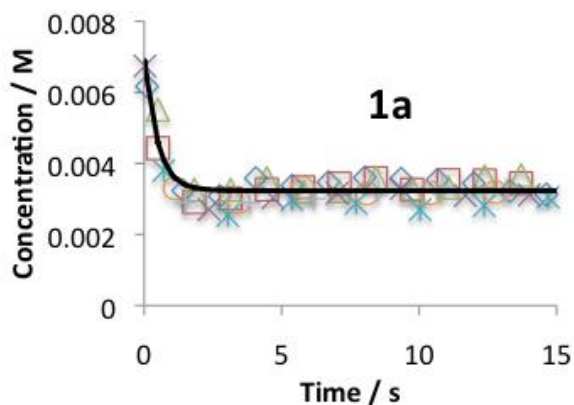
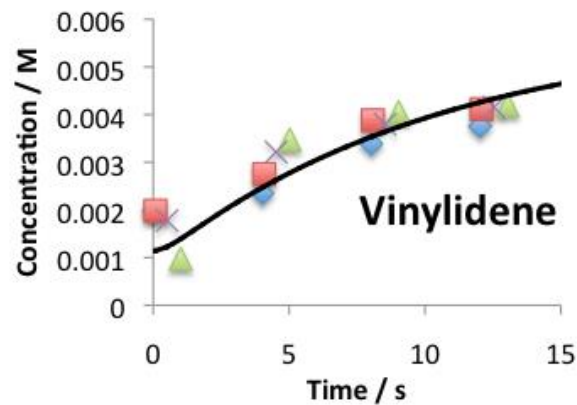
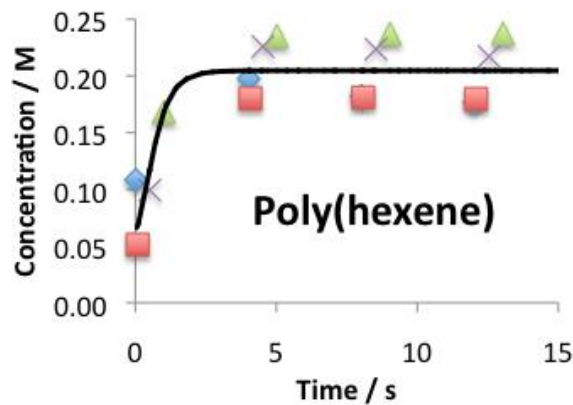
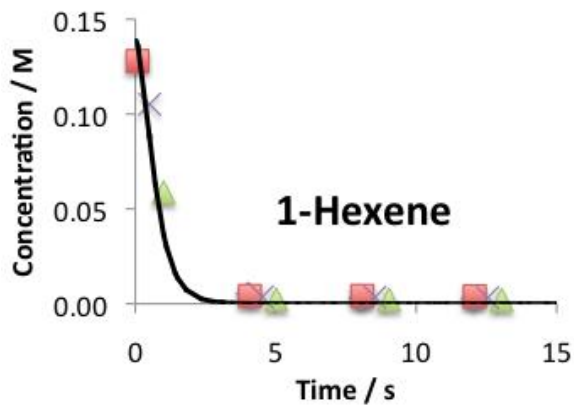
room temperature, single scan spectrum

Direct Observation of Catalyst Speciation at Room Temperature



$[Zr]_0 = 15 \text{ mM}$, $[1\text{-hexene}]_0 = 0.5 \text{ M}$, single-scan ^1H NMR spectra

SF-NMR with ^1H and ^{19}F Detection (Room T)



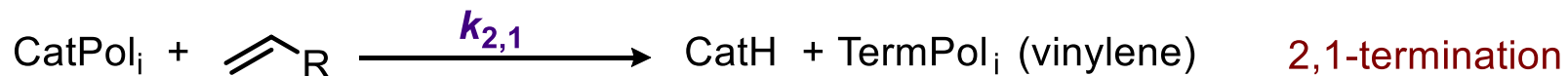
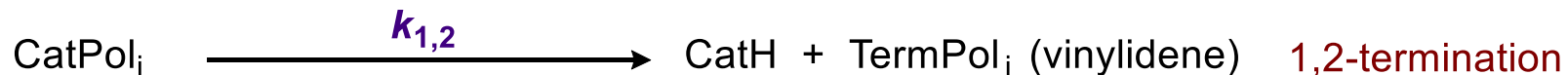
Analyzing Kinetic Data

- Fit Concentration vs. Time plots to Kinetic Model
- Reaction Progress Kinetics Analysis
- Variable Time Normalization Analysis

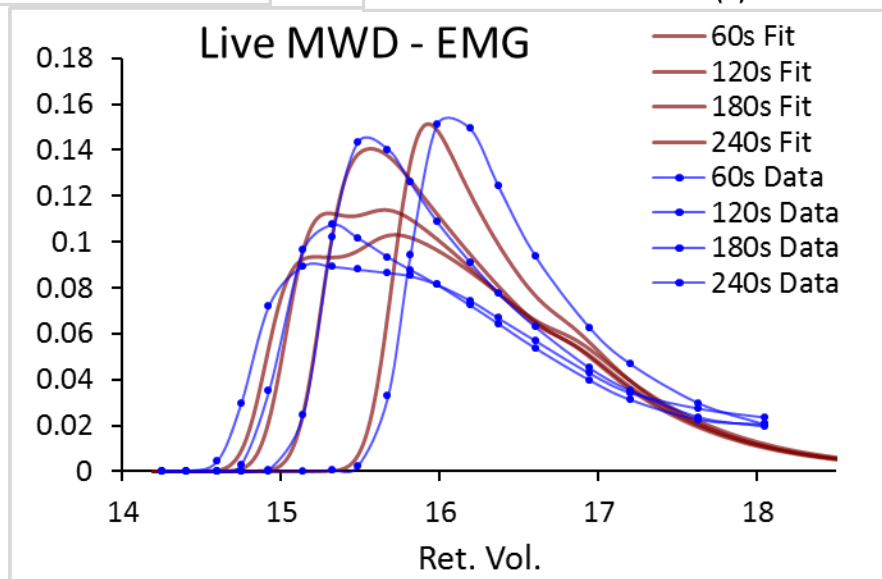
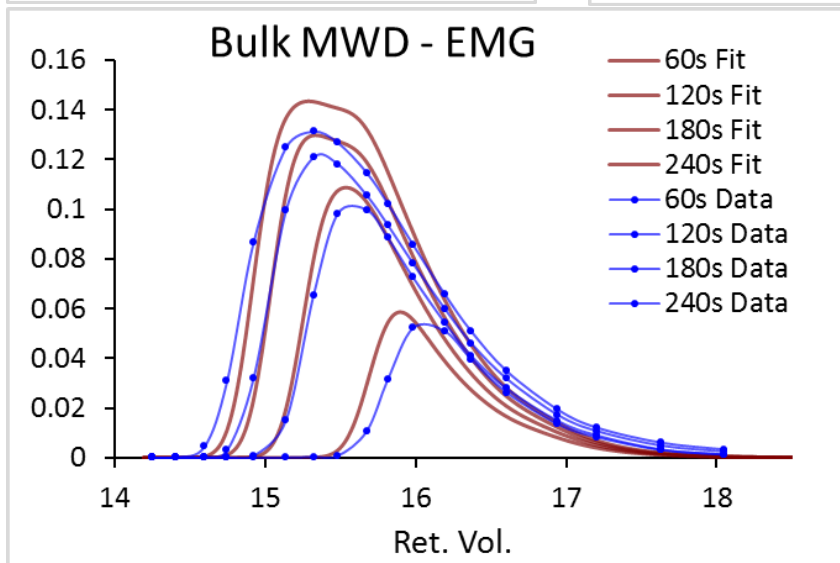
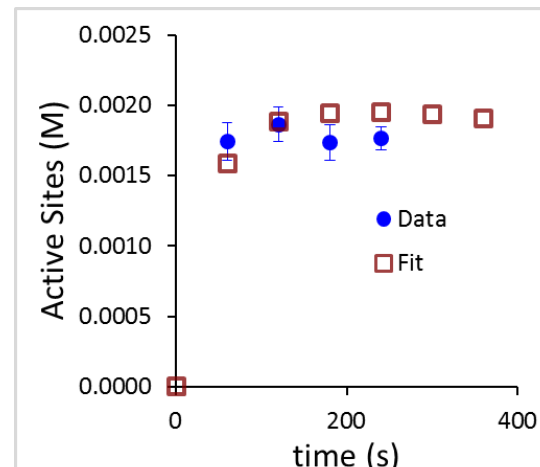
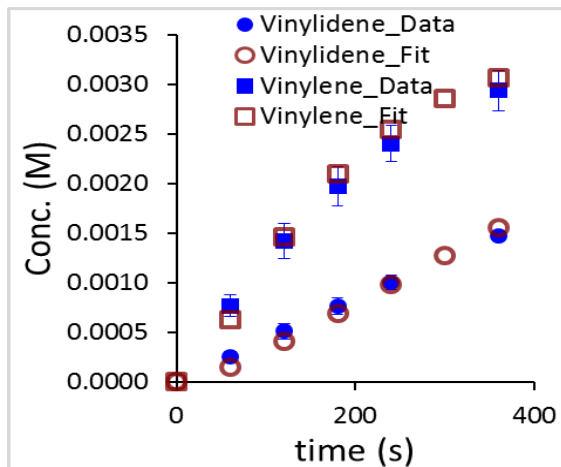
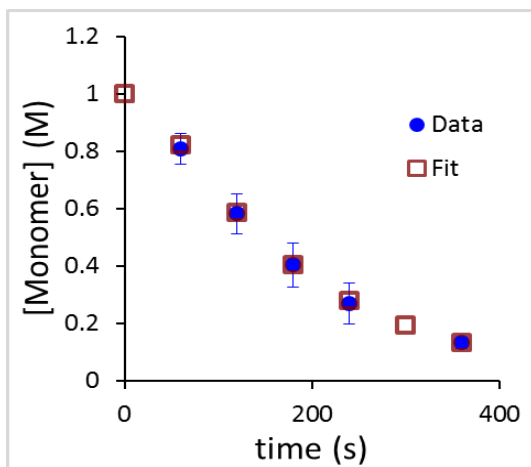
Hoops S., Sahle S., Gauges R., Lee C., Pahle J., Simus N., Singhal M., Xu L., Mendes P. and Kummer U. (2006). **COPASI: a Complex Pathway Simulator**. *Bioinformatics* 22, 3067-74.

Matlab, Mathematica, Kinsim, many others

Example Kinetic Model: Metallocene-Catalyzed Polymerization



Fit the rate constants to the observed data

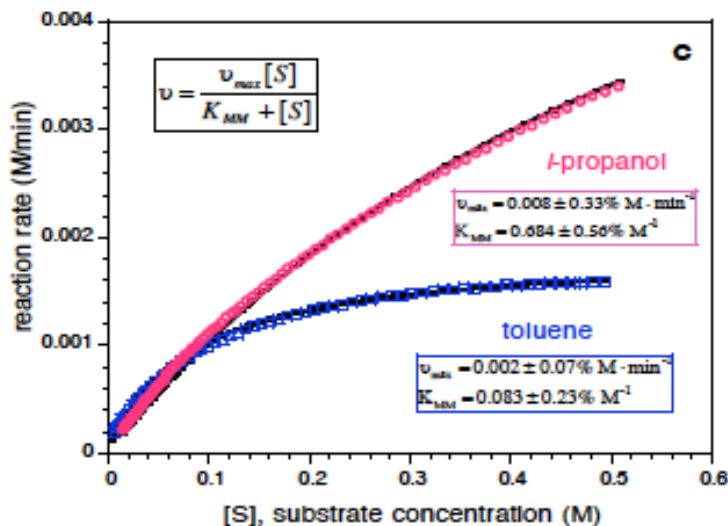


Reaction Progress Kinetic Analysis

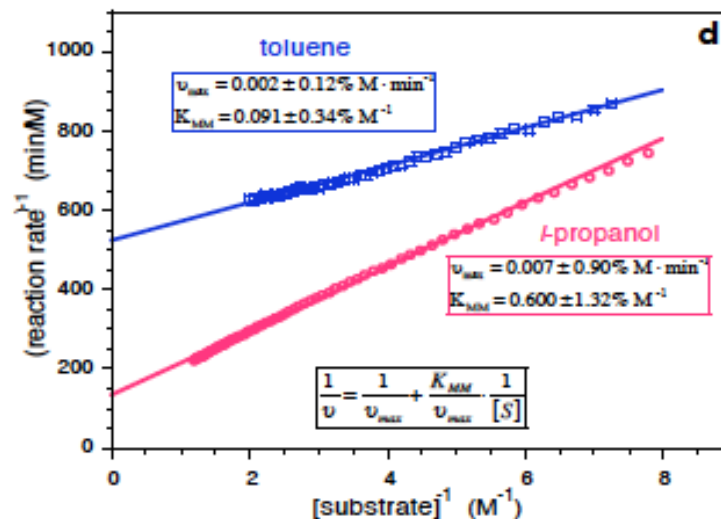
Blackmond, D. G., **Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions.** *Angew. Chem. Int. Ed.*, **2005**, *44*, 4302–4320.

- A kinetic rate law gives a relationship between **reaction rate** and **substrate concentration**.
- **Time** appears only implicitly in this expression.
- We need to combine our integral and differential forms of data collection to product a **graphical rate equation**.

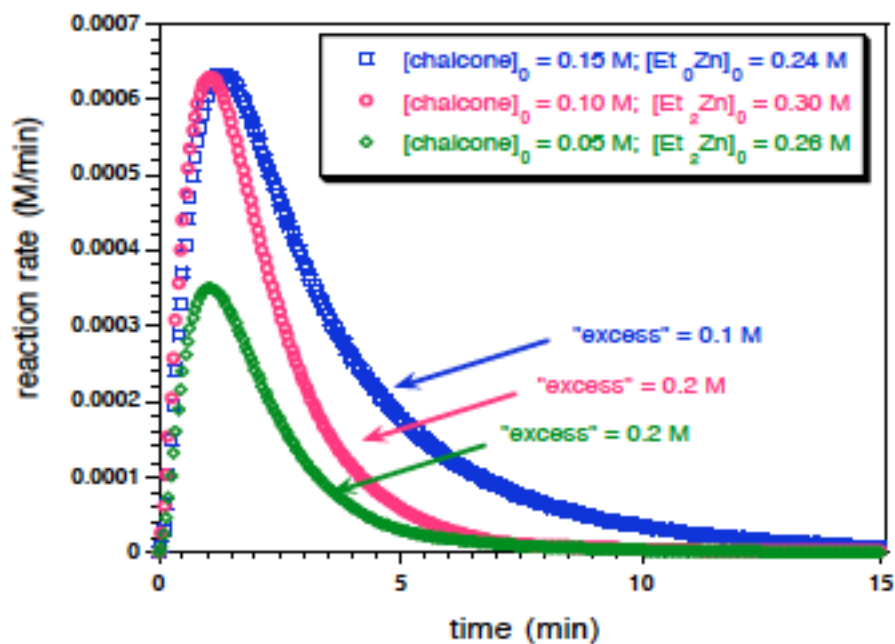
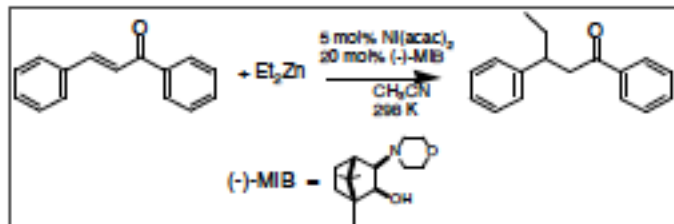
- Rate vs. substrate concentration



- Inverted form gives a **straight line**

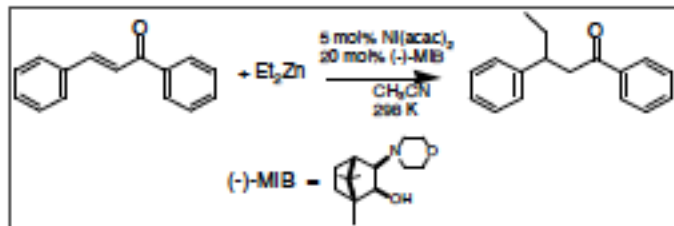


RPKA, "excess", and overlay



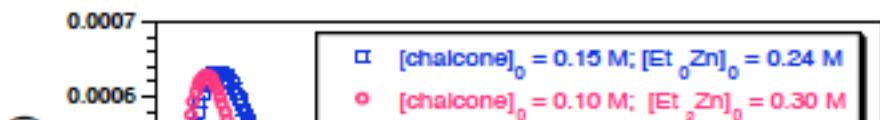
3 reactions 3 data sets

RPKA, "excess", and overlay



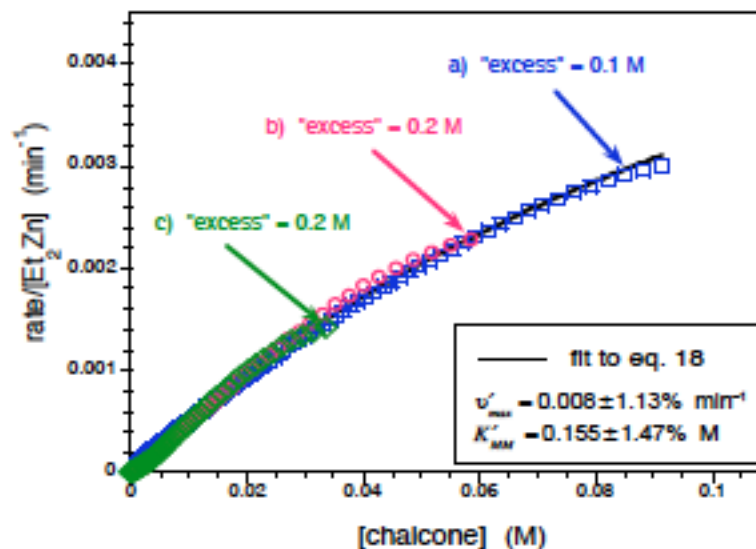
The overlay demonstrates that the **rate is 1st order in [Et₂Zn]**

The curvature suggests **saturation behavior in [Chalcone]**



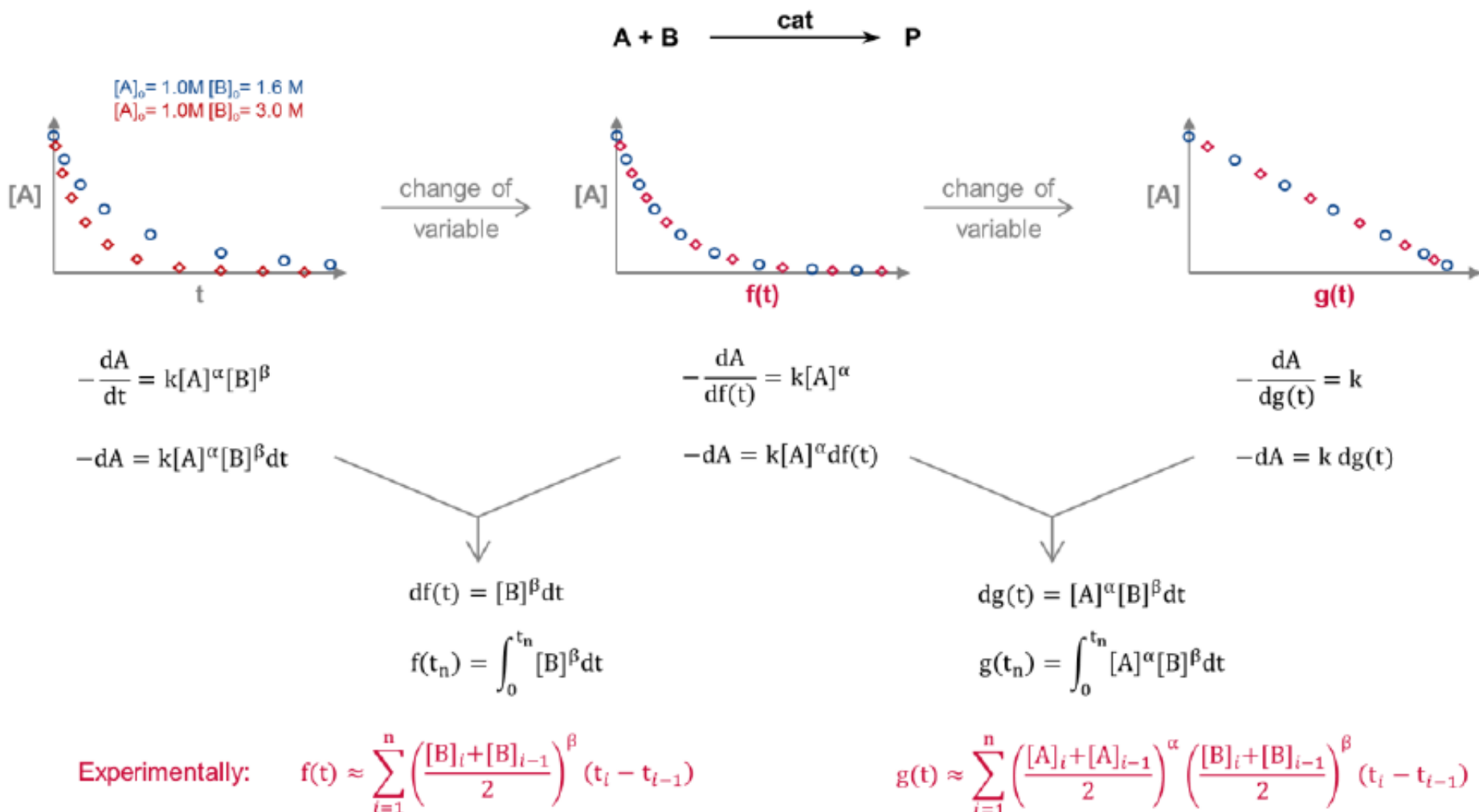
Rate/[2] vs. [1]
....Overlay!

This is a visual way to tease mechanistic information out of the data.



Variable Time Normalization Analysis

J. Burés, **Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles** *Angew. Chem. Int. Ed.* **2016**, *55*, 16084.



RPKA and VTNA are Complementary



Reaction Progress Kinetic Analysis

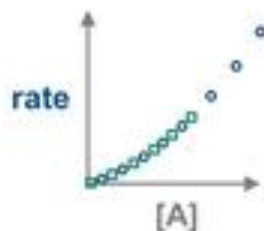
Rate profiles

(obtained by ITC)

Concentration profiles

(obtained by NMR, IR, UV, HPLC, GC,...)

a) same excess^[1]

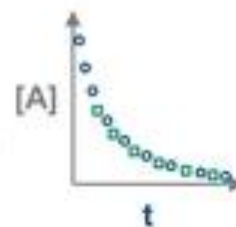


$$[e] = [A]_0 - [B]_0 = 0.5 \text{ M}$$

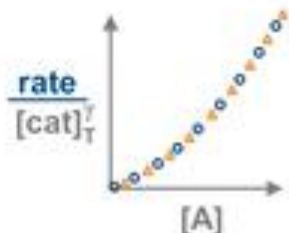
$$[A]_0 = 1.0 \text{ M} \quad [A]_0 = 0.6 \text{ M}$$

catalyst deactivation
product inhibition

d) time adjustment^[2]



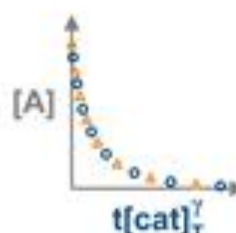
b) different catalyst loading^[1]



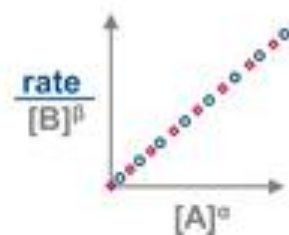
1 mol% cat
0.5 mol% cat

order in catalyst

e) normalized time scale^[3]



c) different excess^[1]

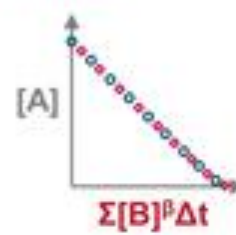


$$[e] = [A]_0 - [B]_0 = 0.5 \text{ M}$$

$$[e] = [A]_0 - [B]_0 = 1.0 \text{ M}$$

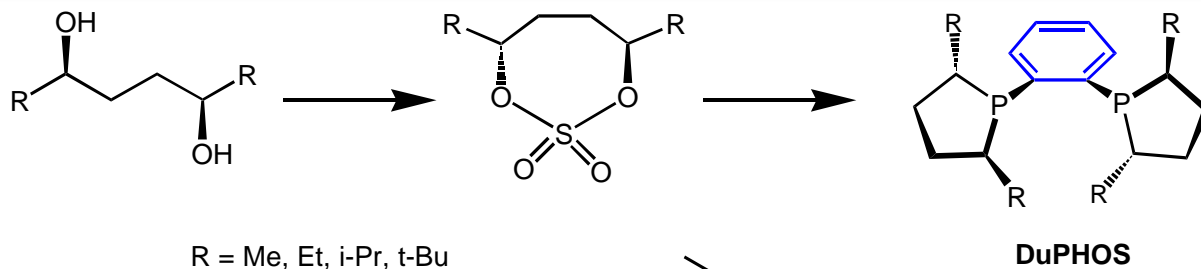
order in reagents

f) this work



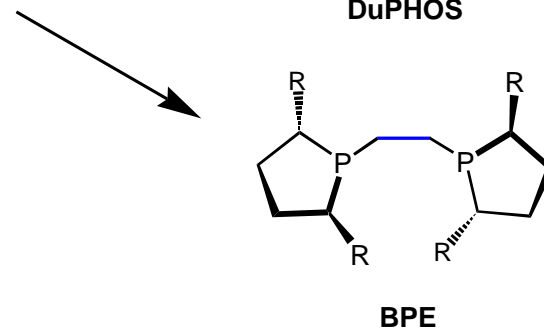
Phospholanes and BisDiazaphospholanes

DuPhos Synthesis

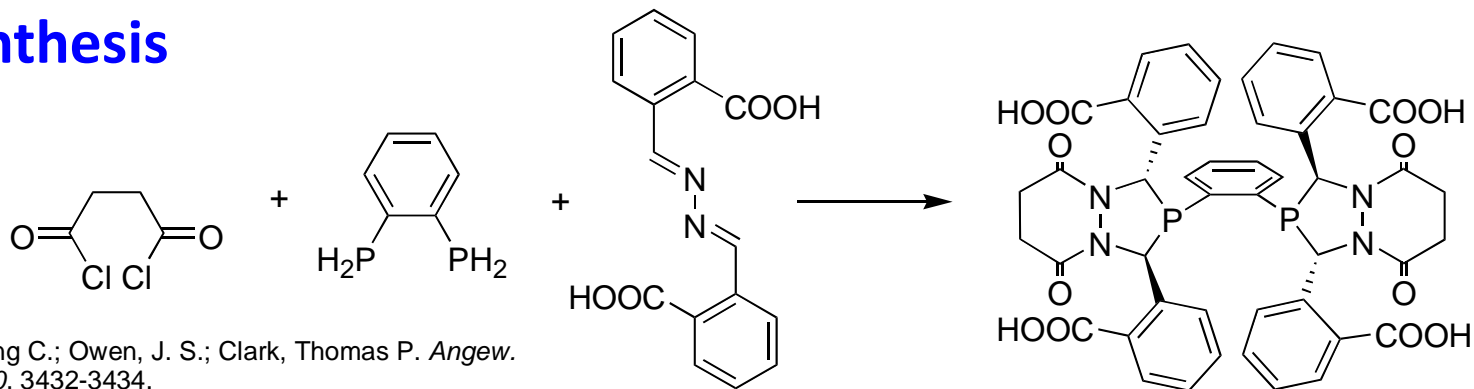


Burk, M. J.; Feaster, J. E.; Harlow, R. L.
Organometallics **1990**, *9*, 2653.

Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*,
8518.



DiazaPhos Synthesis

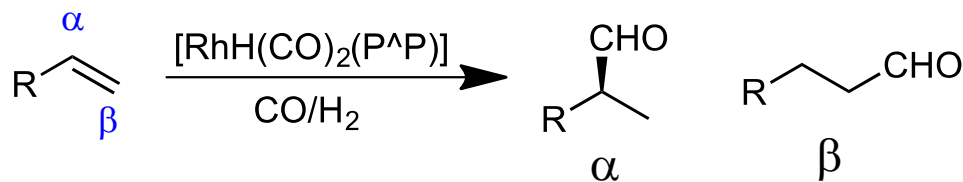


Landis, Clark R.; Jin, Wiechang C.; Owen, J. S.; Clark, Thomas P. *Angew. Chem. Int. Ed. Engl.*, **2000**, *40*, 3432-3434.

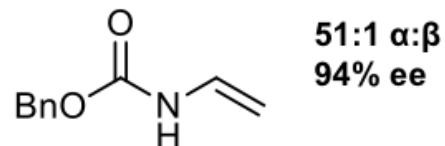
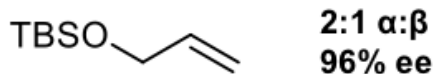
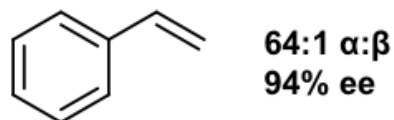
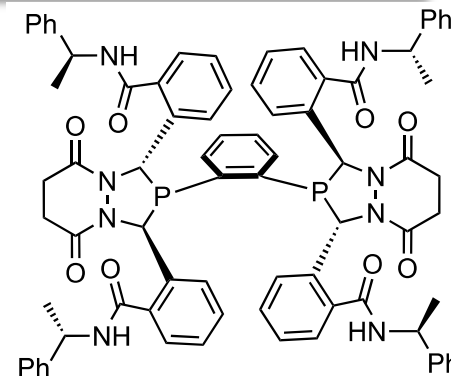
'Diazaphosphacycles' Clark R. Landis, Wiechang Jin, Jonathon Owen, Thomas Clark, US Patent Office, 2003/0055254 A1.

'Diazaphosphacycles' Landis, Clark R.; Jin, Wiechang, W.; Owen, J. S.; Clark, T. P. WO Patent 2003/010174 A1

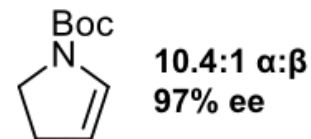
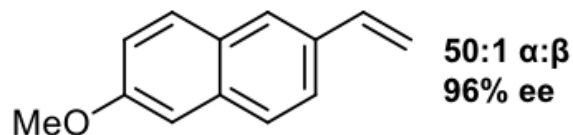
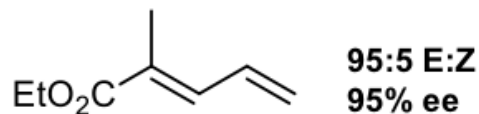
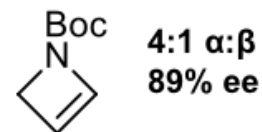
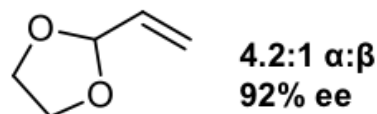
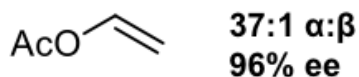
Enantioselective Hydroformylation



Substrate:catalyst loadings as high as 150,000:1
 Turnover frequencies as high as 20,000 per hour



Precursor to Roche Aldehyde

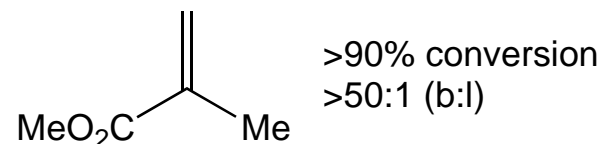
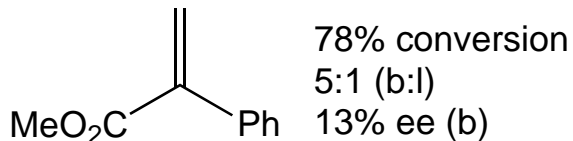
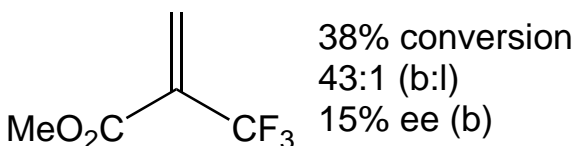
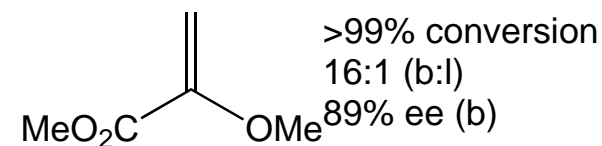
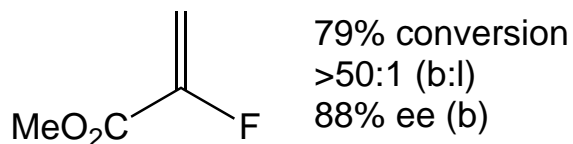
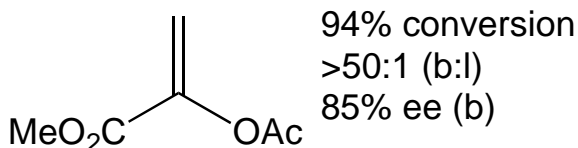
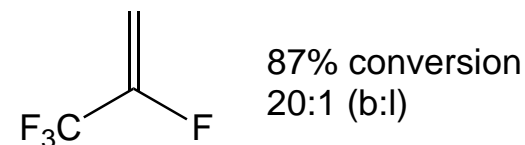
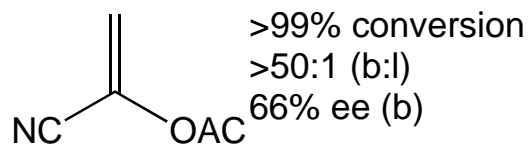
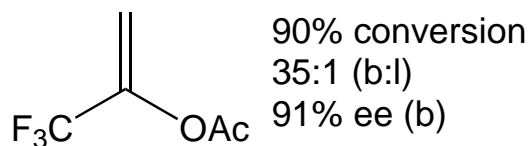
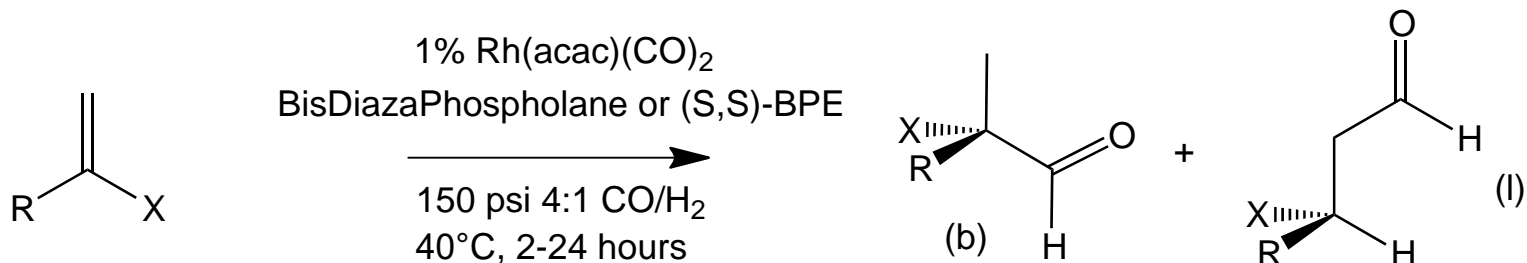


Precursor to Fragment in Lejimalide Total Synthesis

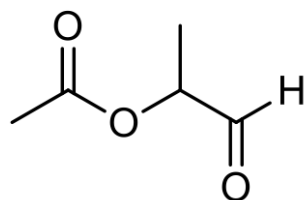
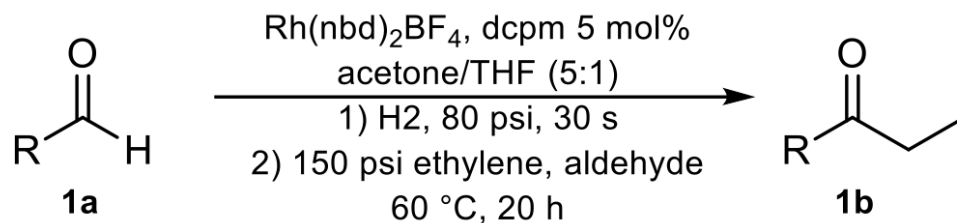
Precursor to Naproxen

Precursor to Proline

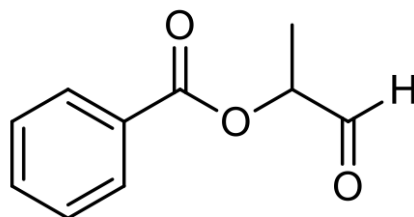
Making Tetrasubstituted Stereogenic Centers



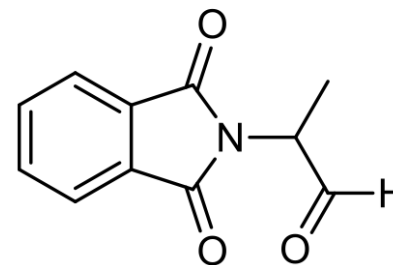
Hydroacylation of Aldehydes with Ethene



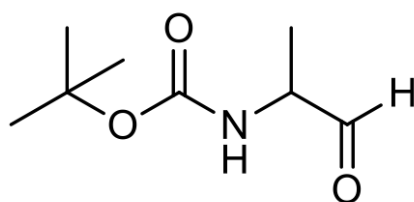
1a
>99%



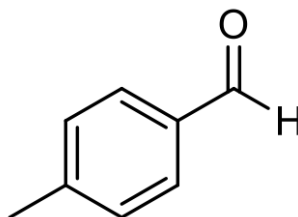
2a
26%



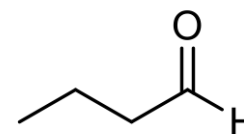
3a
97%



4a
>99%



5a
16%



6a
>99%^a

Enantiopure aldehydes give complete enantiospecificity

Oligoester and Oligopeptide Synthesis?

Is it possible to make short, chiral polyesters

- with control of sequence,
- catalytic introduction of all stereocenters (R or S),
- without using coupling agents,
- and with 100% atom economy ?

MAYBE....

