Development of an old reagent for the reduction of solid-supported alkenes

A research-based laboratory module

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Goals of this CASPiE Module

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

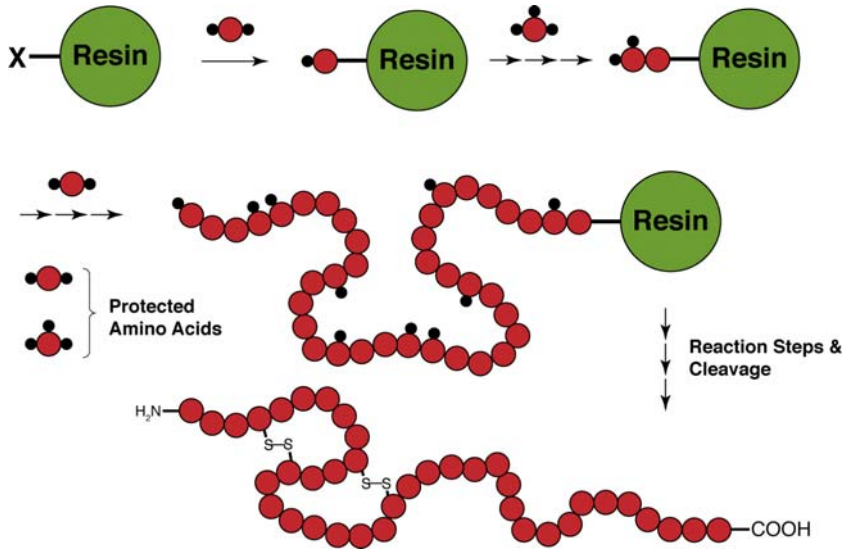
- Provide 2nd year students with an introduction to the concept and practice of solid-supported organic synthesis (SPOS)
- Investigate methods for the reduction of alkenes immobilized on solid support
- Utilize this method in a short synthesis of the natural products zingerone and rheosmin

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

CASPiE = Center for Authentic Science Practice in Education

Why SPOS in an Undergraduate Lab?

Despite its current importance in the fields of medicinal chemistry and chemical biology, the undergraduate experience of solid-supported synthesis is often limited to an in-class description of the Merrifield peptide synthesis…….

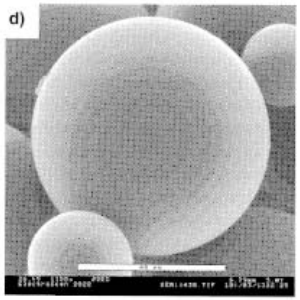


"Throughout the pharmaceutical and biotech industries, it has become increasingly clear in recent years that there just aren't enough chemists trained in combinatorial [solid-phase] chemistry"'

D. Hangauer, *Modern Drug Discovery,* **2001**, *4*, 38

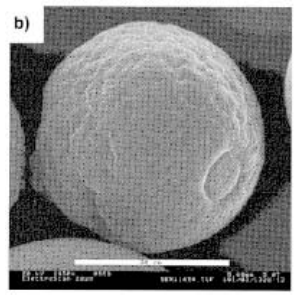
SPOS = Solid phase organic synthesis

Practical Challenges of SPOS



200-400 mesh

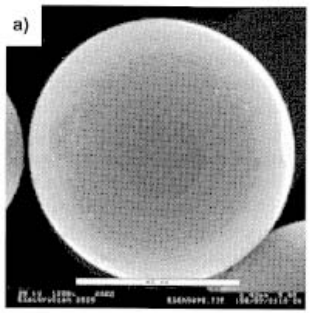
- Mass transfer in and out of bead
- Long reaction times
- Beads require extensive post-reaction washing
- Characterization of resin-bound intermediates
- Mechanical stability of resin beads



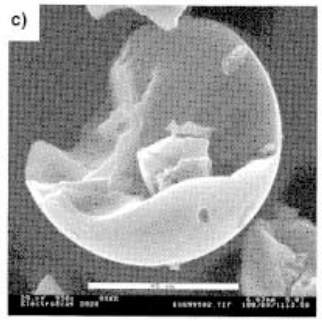
unswollen resin

Typical bead washing sequence: DMF$\rightarrow$$H_2O$$\rightarrow$THF/$H_2O$$\rightarrow$THF$\rightarrow$MeOH$\rightarrow$$CH_2Cl_2$$\rightarrow$MeOH

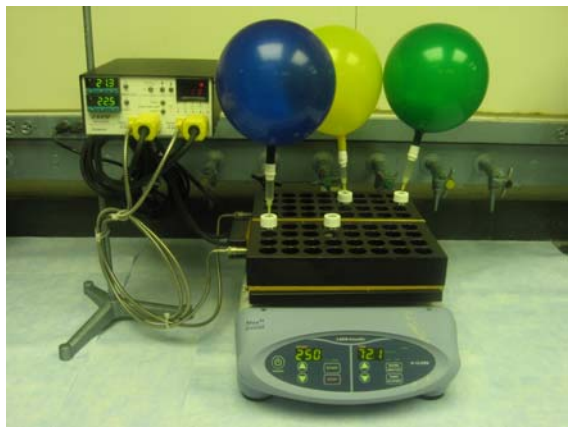
Shaken not Stirred!



Mechanical agitation

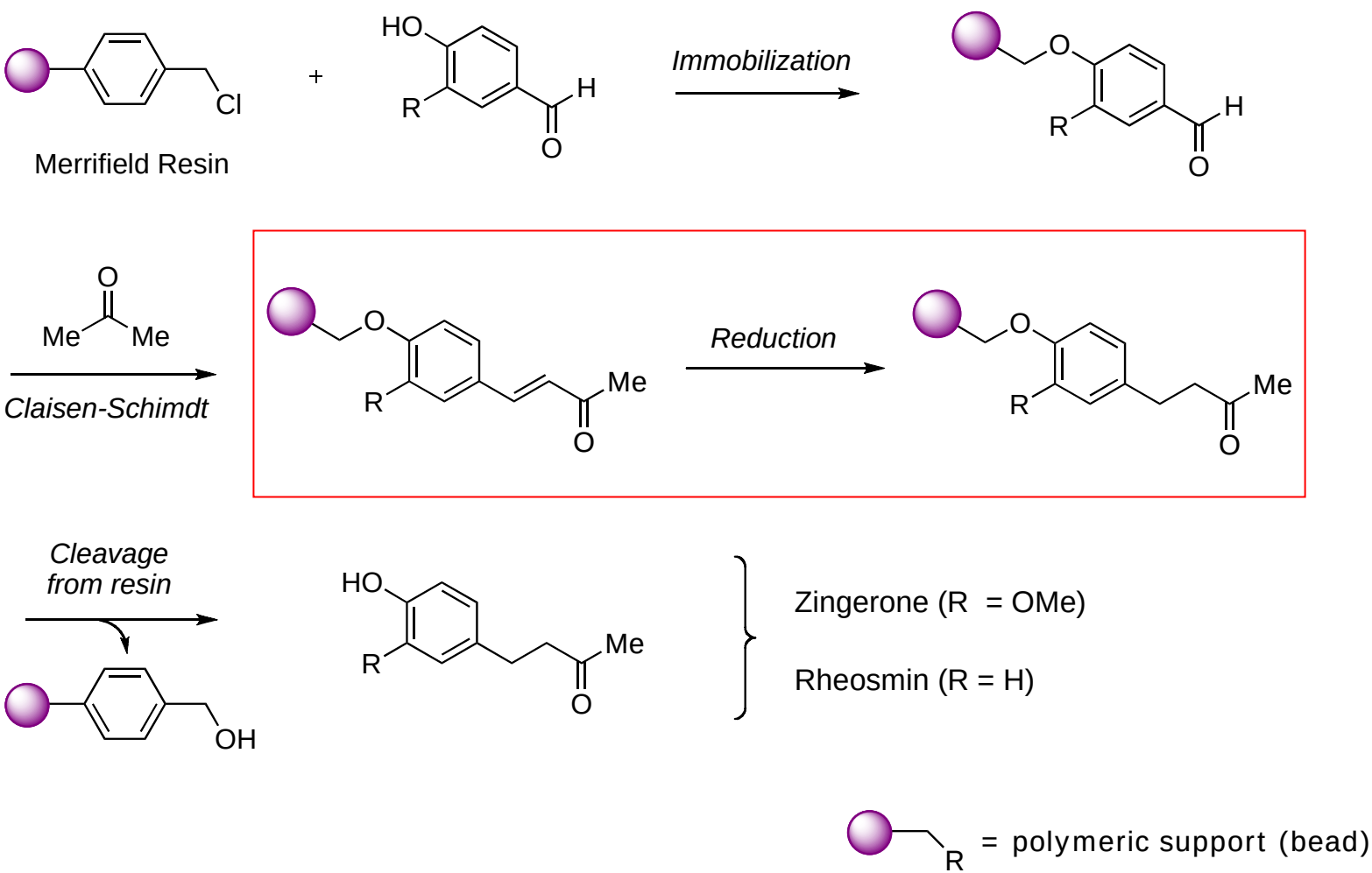


To prevent bead fragmentation, reactions were carried out in 10 mL screw-top vials with agitation provided by a bench-top shaker…



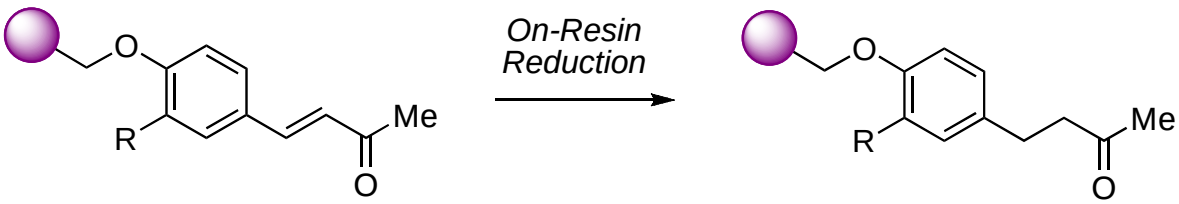
LAB-LINE® MaxQ™ 2000 bench-top shaker + 64-well heating block

Module Overview



L. R. Smith *The Chemical Educator* **1996**, *1*(3)

An Authentic Scientific Problem?



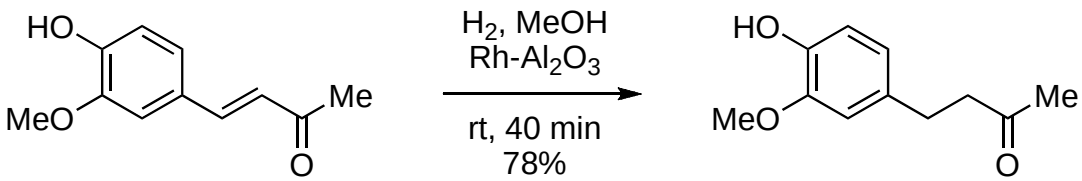
"…many synthetic reactions that work well under more standard conditions are not effective under the conditions that are used for diversity-oriented synthesis, particularly if the library components (or the reagents) are attached to a solid support. As a simple example, catalytic hydrogenation using palladium on charcoal is a common, high-yielding method for reducing olefins; however, catalytic hydrogenation does not work well if the olefin is attached to a solid support."

Centers of Excellence in Chemical Methodologies and Library Development

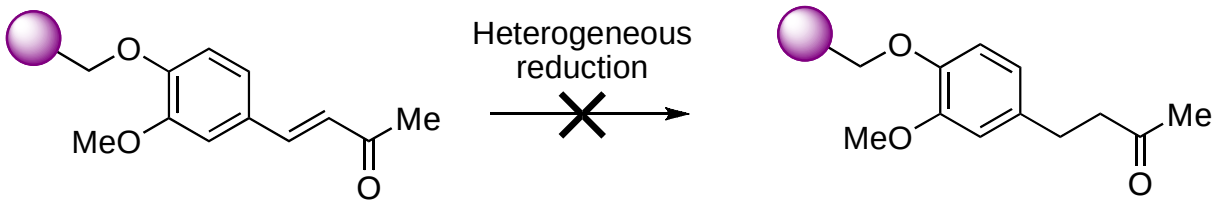
National Institute of General Medical Sciences (NIGMS)

A Three Phase Problem

2 Phase System



3 Phase System



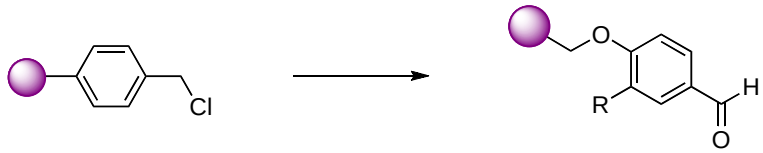
CASPiE Module Stats.

- Module developed through collaboration between graduate student and peer leaders
- Module integrated into CHEM 235 during spring and summer 2006
- Implemented in final six weeks of semester
- 4-5 students per research group
- Two peer leaders per class

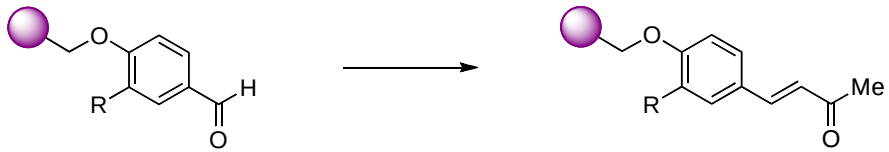
CHEM 235 = second semester organic laboratory

Module Timeline

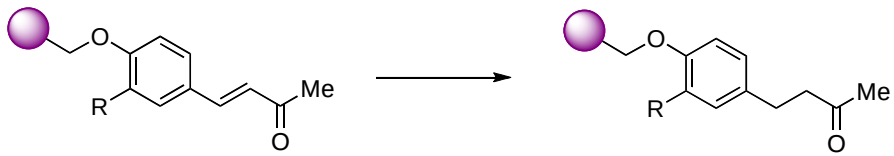
Week 1: Immobilization



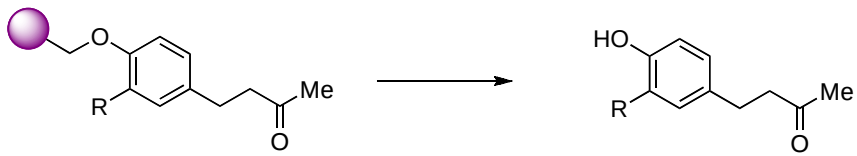
Week 2: Claisen-Schmidt Reaction



Weeks 3-4: Research Component



Week 5: Cleavage



Week 6: Student Poster Presentation

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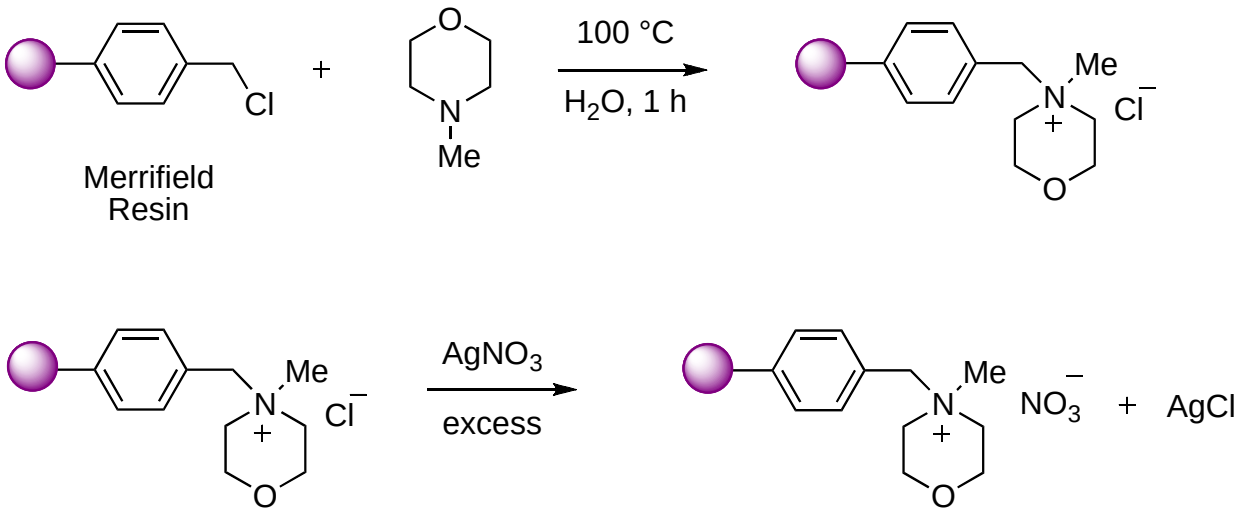
1 Week = 2 x 3 hour laboratory

Volhard Titration of Merrifield Resin

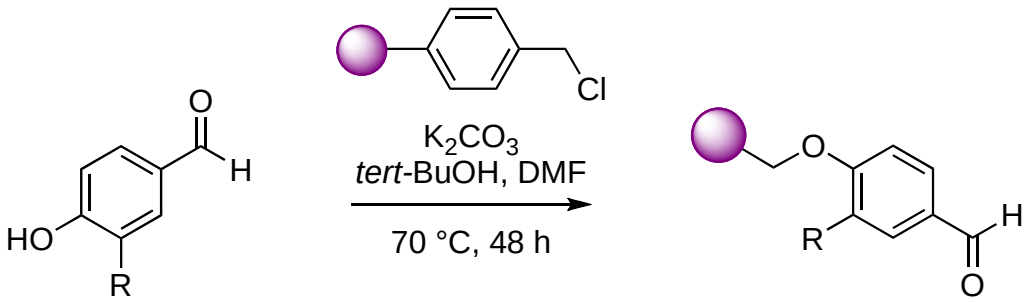


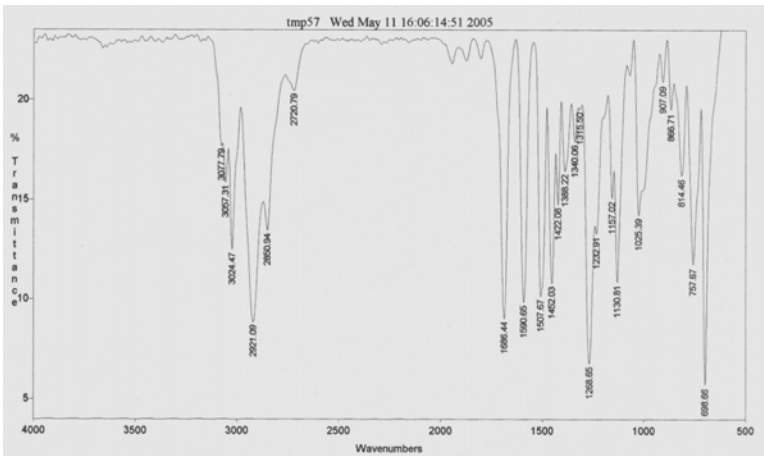
$AgNO_3$ (unreacted) + KSCN → AgSCN + KNO_3

KSCN + Fe_3^+ (indicator) → $[FeSCN]_2^+$

Chloromethyl(polystyrene) crosslinked with 1% DVB; ~1.7 mmol Cl/g resin

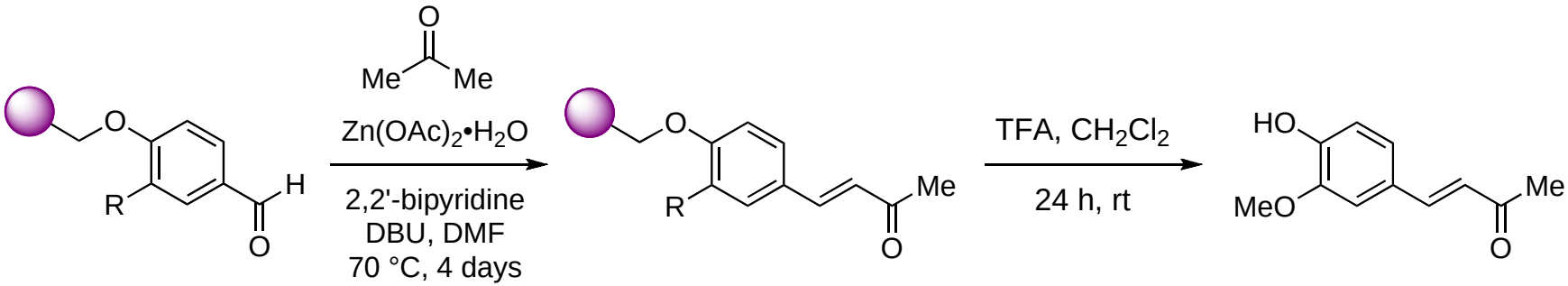
Immobilization & Characterization

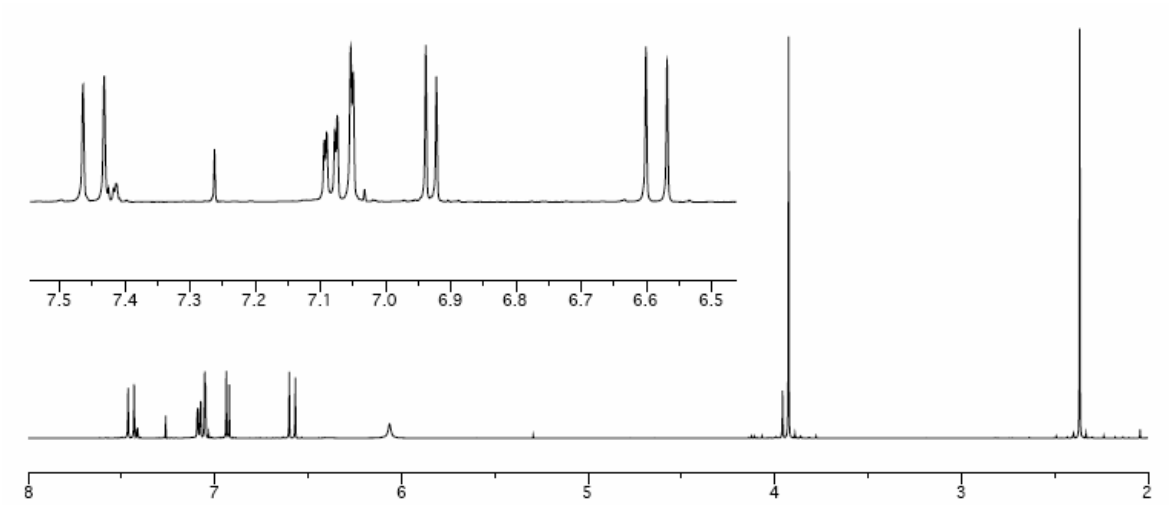




FTIR of immobilized aldehyde (powdered resin in KBr disc)

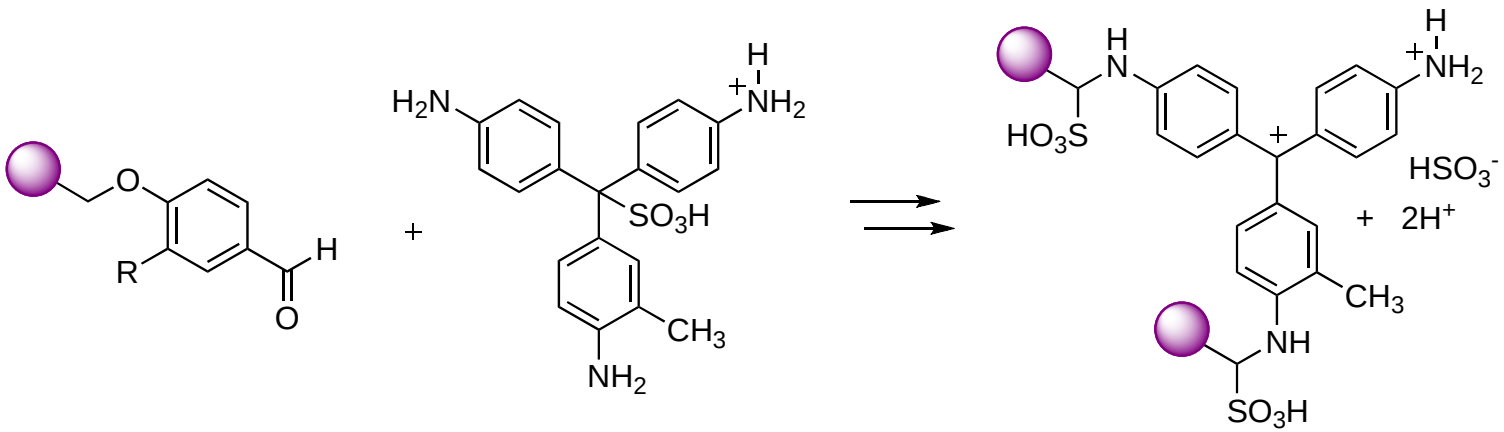
Claisen-Schmidt Condensation





^{1}H NMR spectra of Claisen-Schmidt product, after cleavage from resin

On-Resin Colorimetric Analysis

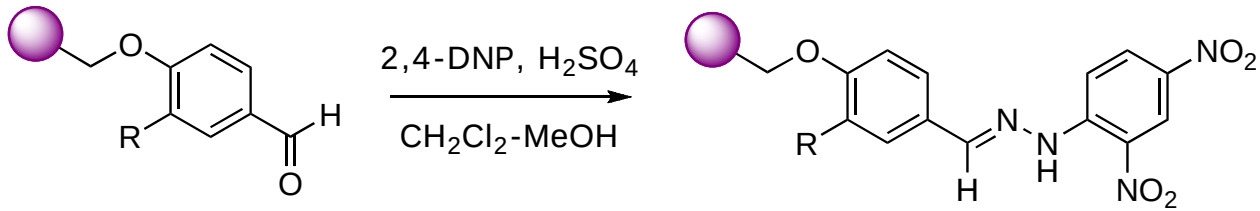


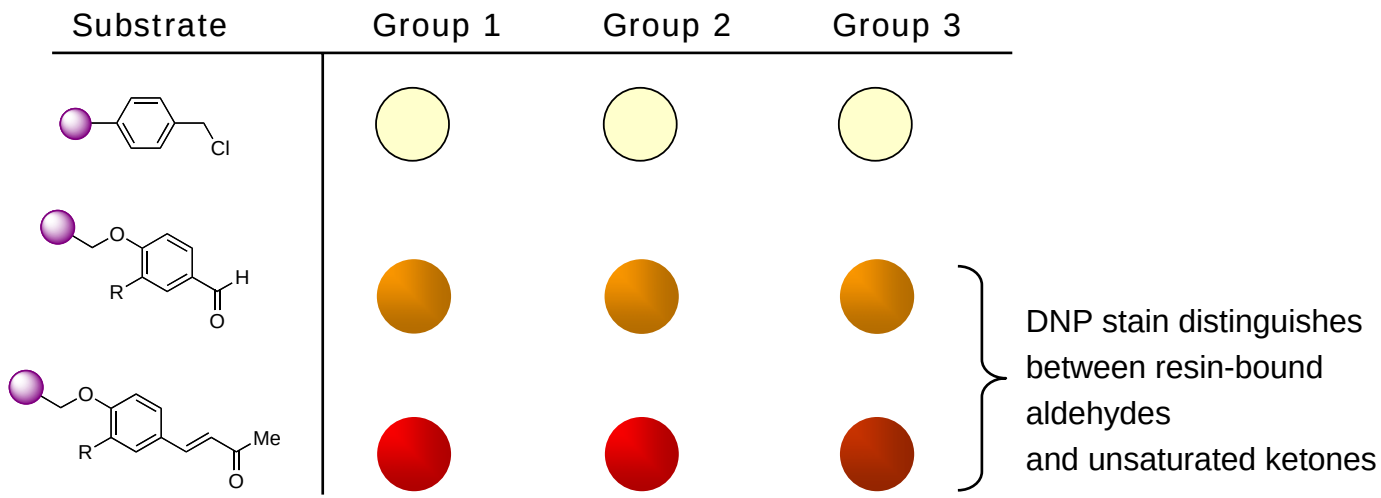
Schiff's Reagent

- Students found this color change difficult to identify on resin beads
- Presence of residual THF in bead causes false positives

b = Schiff's reagent; **c** Schiff's reagent + R-CHO

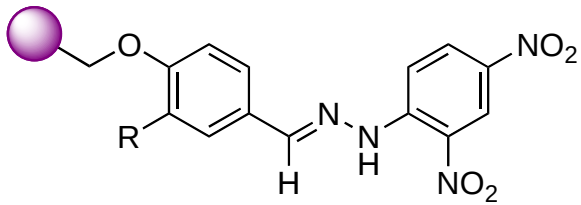
A Colorimetric Research Project





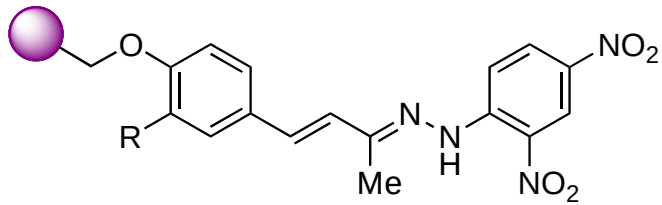
Color variations upon treating resins with 2,4-dinitrophenylhydrazine (2,4-DNP)

Origin of Differential Color Change



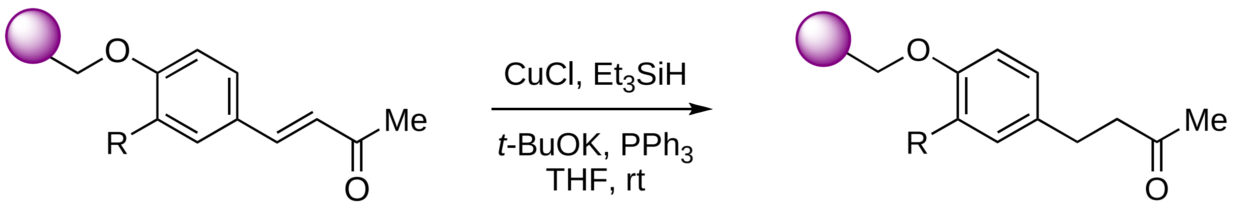
λ_{max} ~ 270 nm

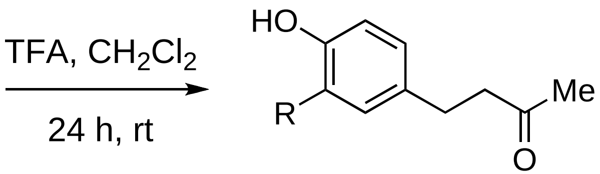
vs.



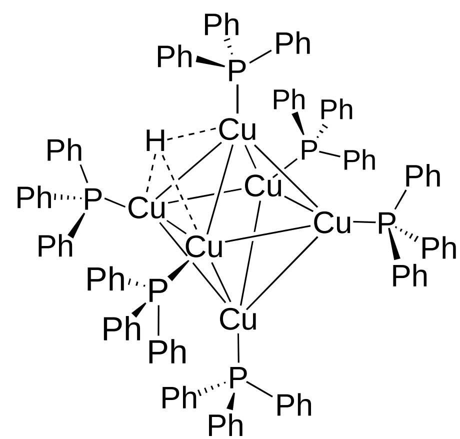
λ_{max} ~ 310 nm

Reduction with Stryker's Reagent



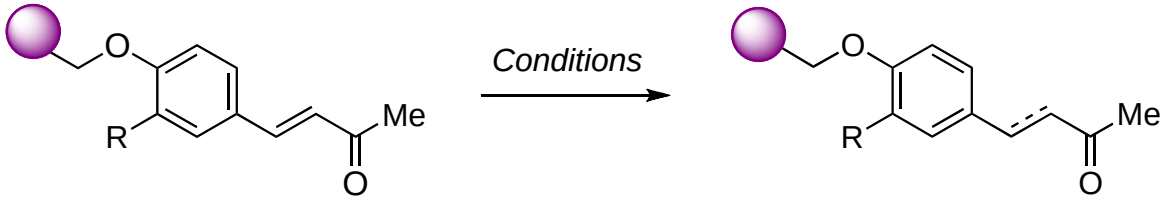


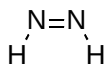
Zingerone (R = OMe)
Rheosmin (R = H)



Stryker's Reagent
$[Ph_3PCuH]_6$

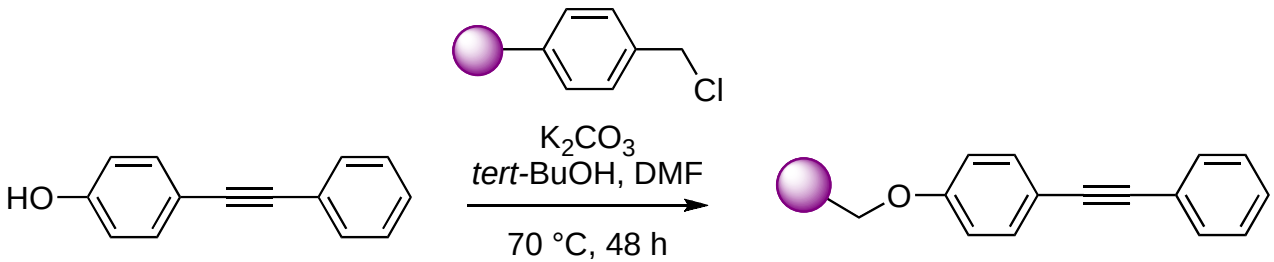
Reduction Results from CHEM 235



Conditions	Result
$[Ph_3PCuH]_6$	product + s.m.
$PdCl_2$, $NaBH_4$ PEG-CH_2Cl_2	no reaction
$Pd(OAc)_2$, PMHS THF-H_2O	no reaction
$NiCl_2$, $NaBH_4$ MeOH, THF	no reaction
	product + s.m.

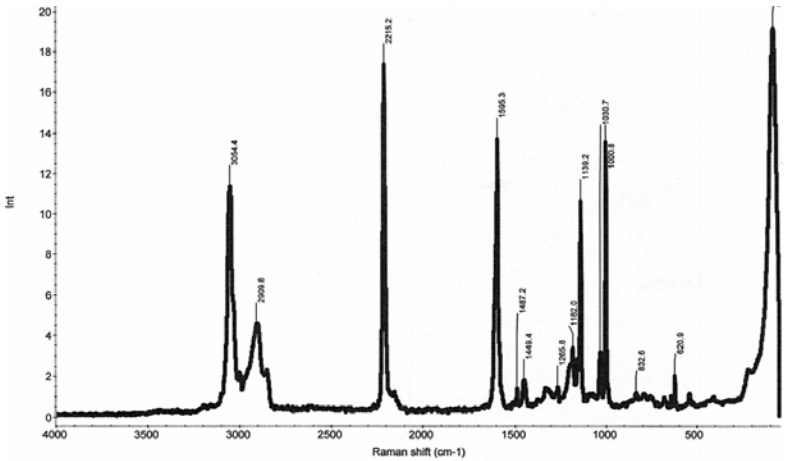
Stryker's reagent is highly sensitive to aerial oxidation!

An Alternative Substrate



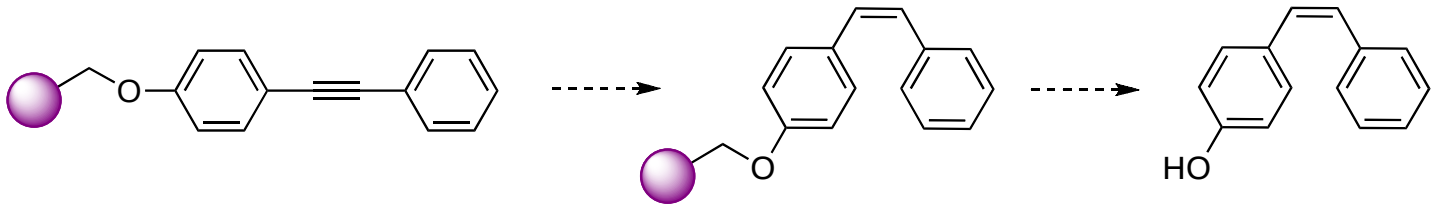
After shipping resin samples to Purdue University, FT-Raman spectra were collected by UIC students via remote access……

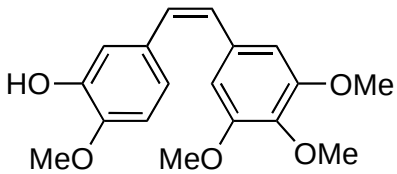
FT-Raman



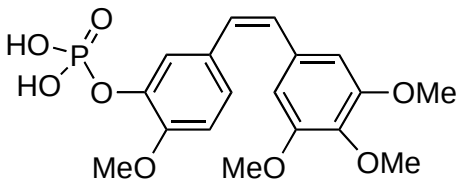
IR spectra of immobilized alkyne has no stretch at 2215 cm^{-1}

CASPiE as an Ongoing Process





CA-4



CA-4P

- Combretastatins (CA) are isolated from the South African bush willow tree
- Vascular targeting agents
- CA4P in phase II clinical trials for the treatment of solid tumors

Summary

- Successfully introduced the concept and practice of SPOS to the sophomore curriculum
- Developed a new CASPiE module that provides second year students with access to research experiences as part of the mainstream curriculum
- Incorporated a wide variety of analytical techniques, which UIC students were not previously exposed to
- Demonstrated the practicality of remote instrumentation

Acknowledgements

Development & Implementation

David Dickson

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Gabriela Weaver

Donald Wink

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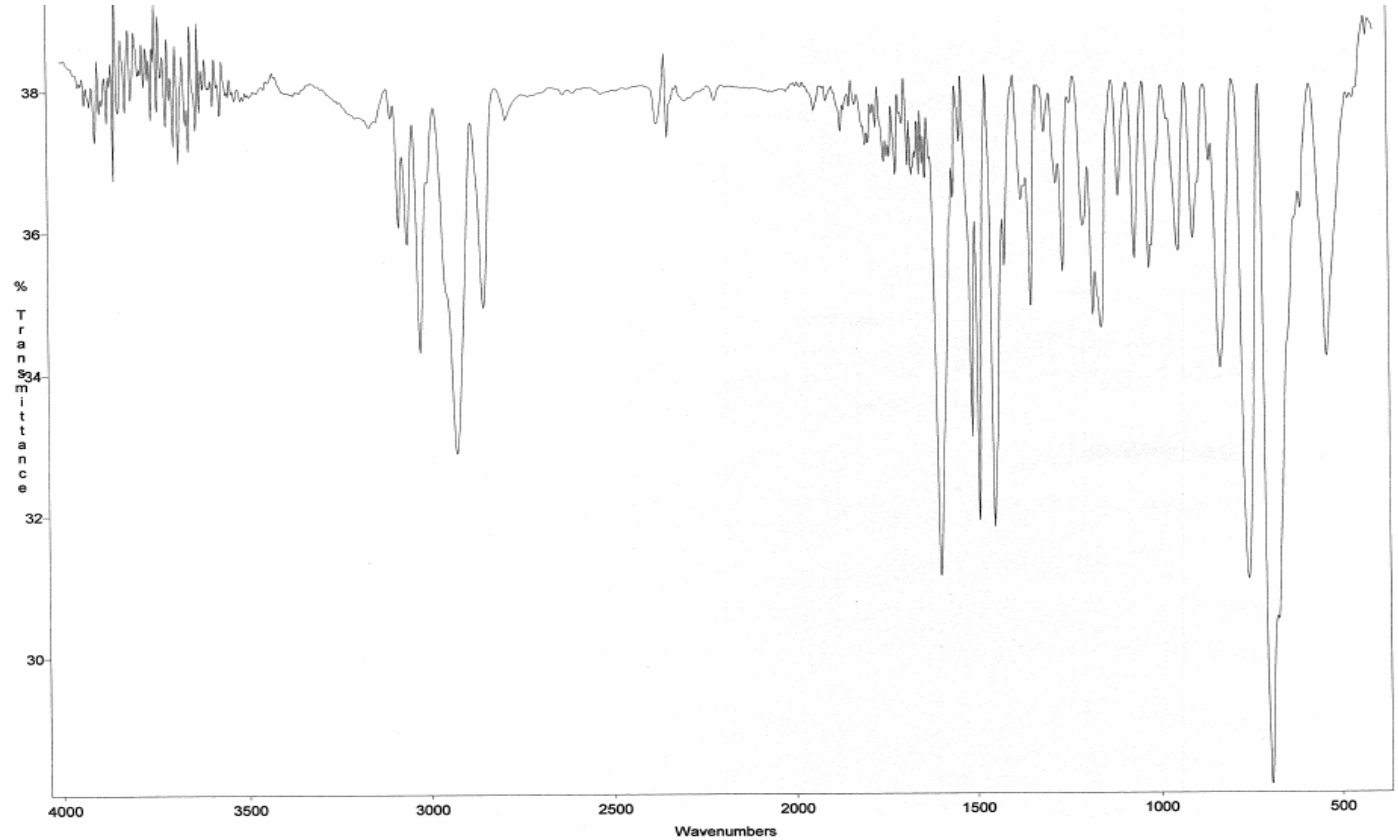
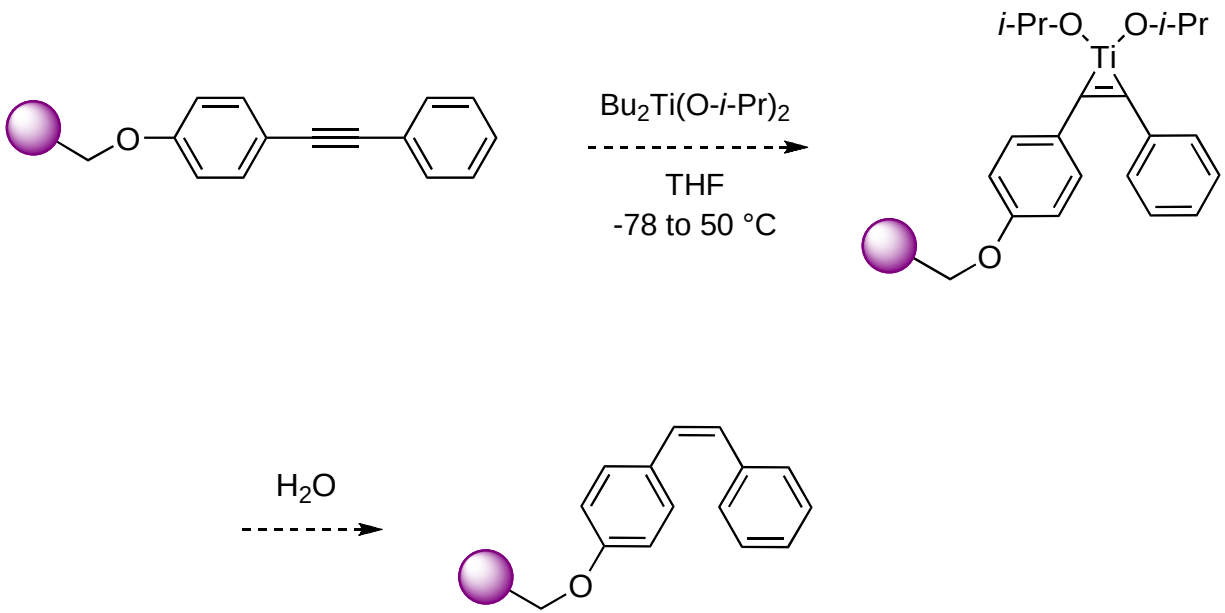
National Science Foundation (CHE-0418902)

IR of Immobilized Alkyne



Reduction of Immobilized Alkynes?



Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24