

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

A research-based laboratory module

Duncan J. Wardrop

Department of Chemistry
University of Illinois at Chicago

233rd ACS National Meeting, 28 March 2007

Goals of this CASPiE Module

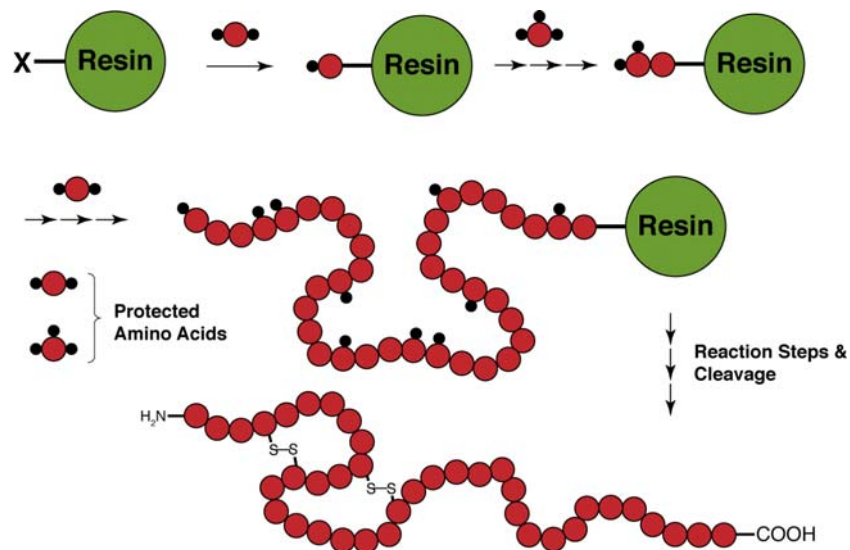
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- 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.

Why SPOS in an Undergraduate Lab?

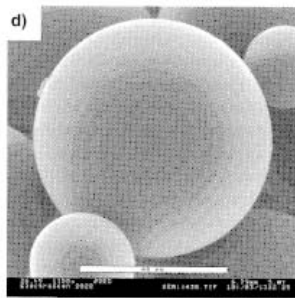
Despite its current importance in the fields of medicinal chemistry and chemical biology, the undergraduate experience of solid-supported synthesis is often limited to an in-class description of the Merrifield peptide synthesis.....



“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”

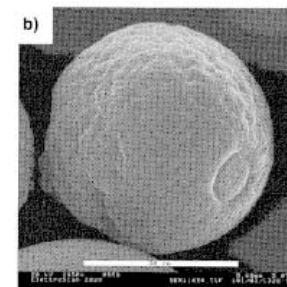
D. Hangauer, *Modern Drug Discovery*, **2001**, 4, 38

Practical Challenges of SPOS



200-400 mesh

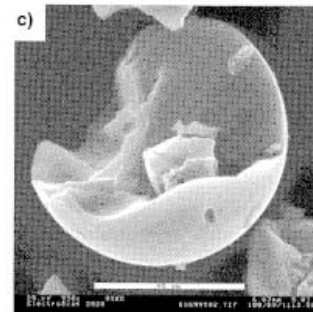
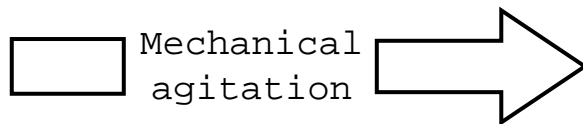
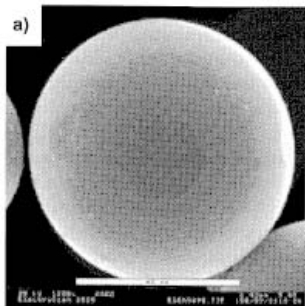
- Mass transfer in and out of bead
- Long reaction times
- Beads require extensive post-reaction washing
- Characterization of resin-bound intermediates
- Mechanical stability of resin beads



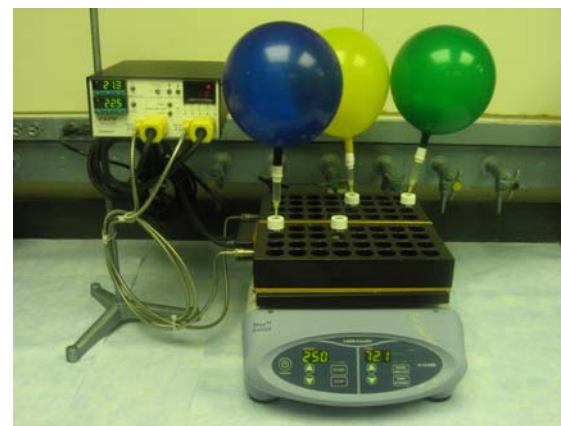
unswollen resin

Typical bead washing sequence: $\text{DMF} \rightarrow \text{H}_2\text{O} \rightarrow \text{THF}/\text{H}_2\text{O} \rightarrow \text{THF} \rightarrow \text{MeOH} \rightarrow \text{CH}_2\text{Cl}_2 \rightarrow \text{MeOH}$

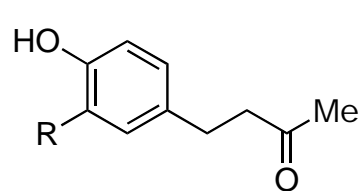
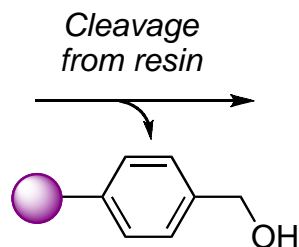
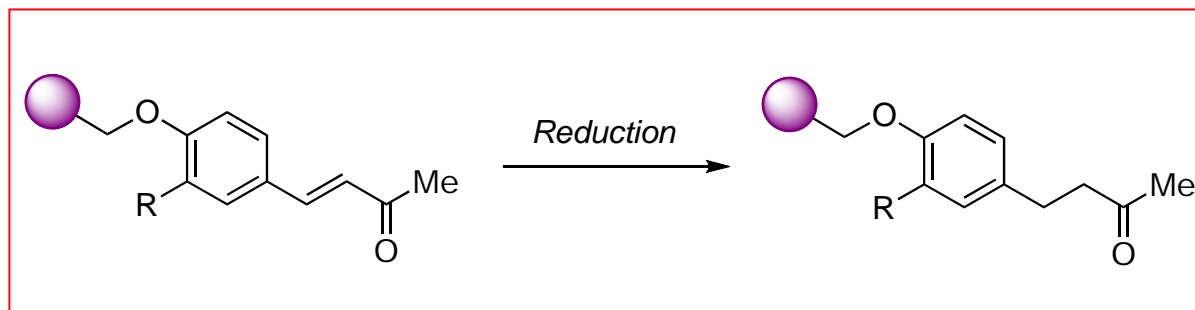
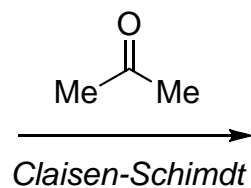
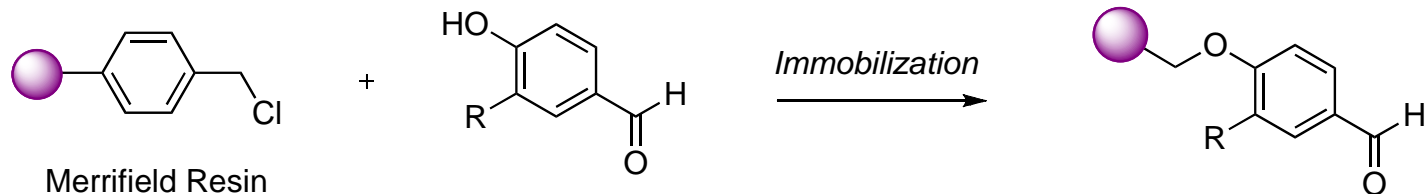
Shaken not Stirred!



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

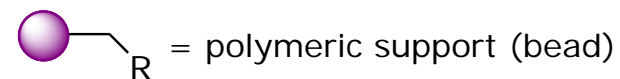


Module Overview

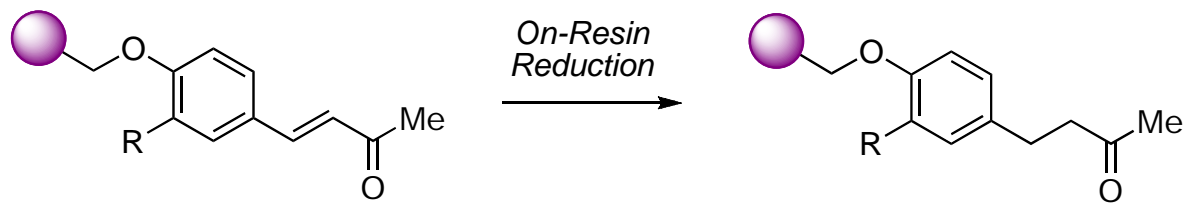


Zingerone (R = OMe)

Rheosmin (R = H)



An Authentic Scientific Problem?



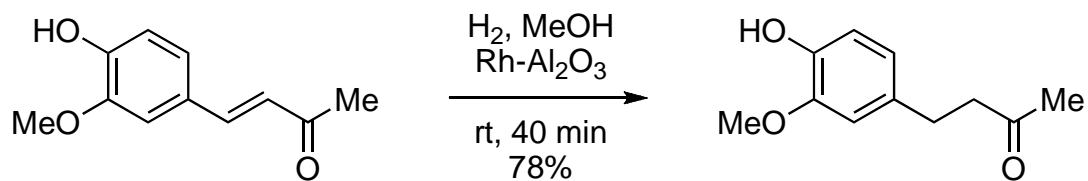
“...many synthetic reactions that work well under more standard conditions are not effective under the conditions that are used for diversity-oriented synthesis, particularly if the library components (or the reagents) are attached to a solid support. As a simple example, catalytic hydrogenation using 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*

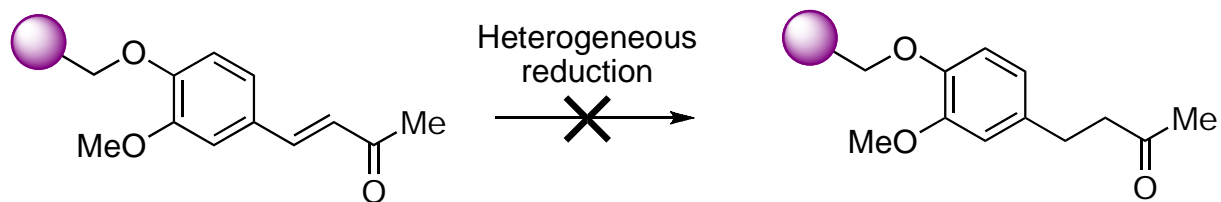
National Institute of General Medical Sciences (NIGMS)

A Three Phase Problem

2 Phase System



3 Phase System

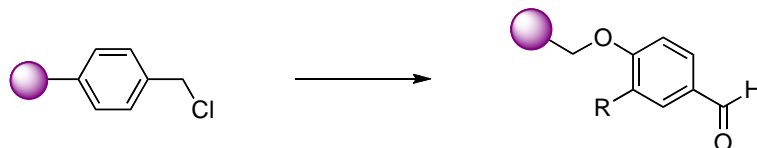


CASPiE Module Stats.

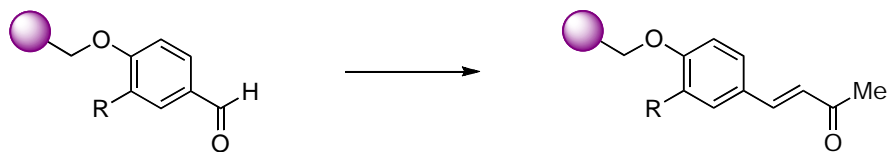
- Module developed through collaboration between graduate student and peer leaders
- Module integrated into CHEM 235 during spring and summer 2006
- Implemented in final six weeks of semester
- 4-5 students per research group
- Two peer leaders per class

Module Timeline

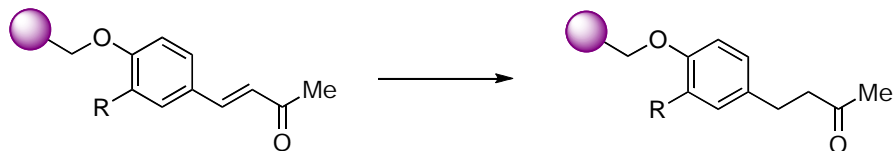
Week 1: Immobilization



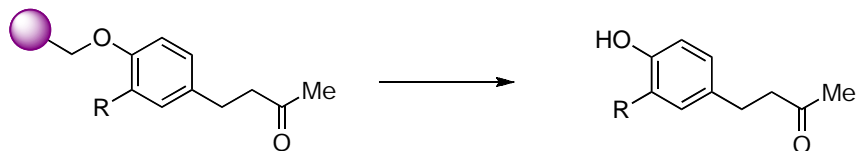
Week 2: Claisen-Schmidt Reaction



Weeks 3-4: Research Component



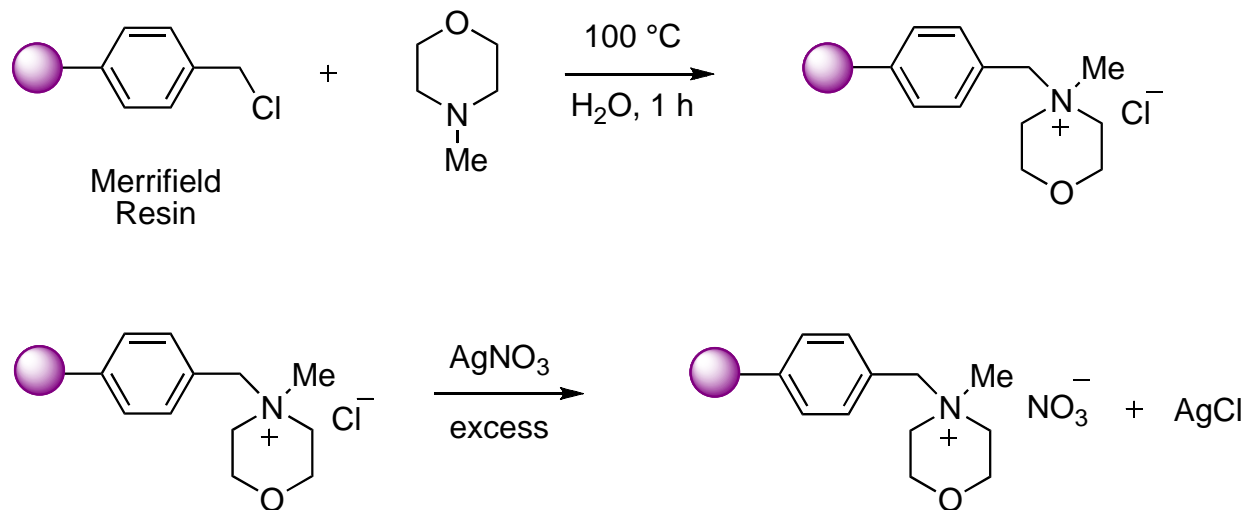
Week 5: Cleavage



Week 6: Student Poster Presentation

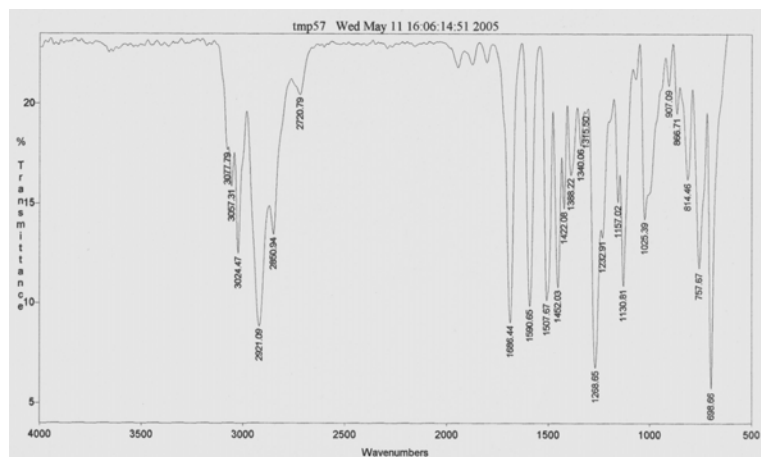
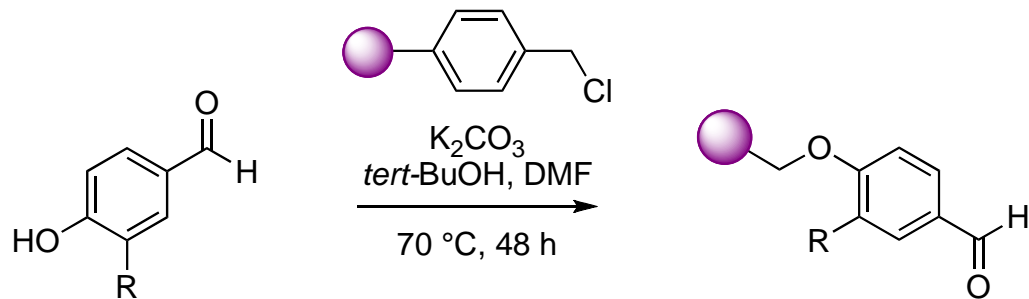
1 Week = 2 x 3 hour laboratory

Volhard Titration of Merrifield Resin



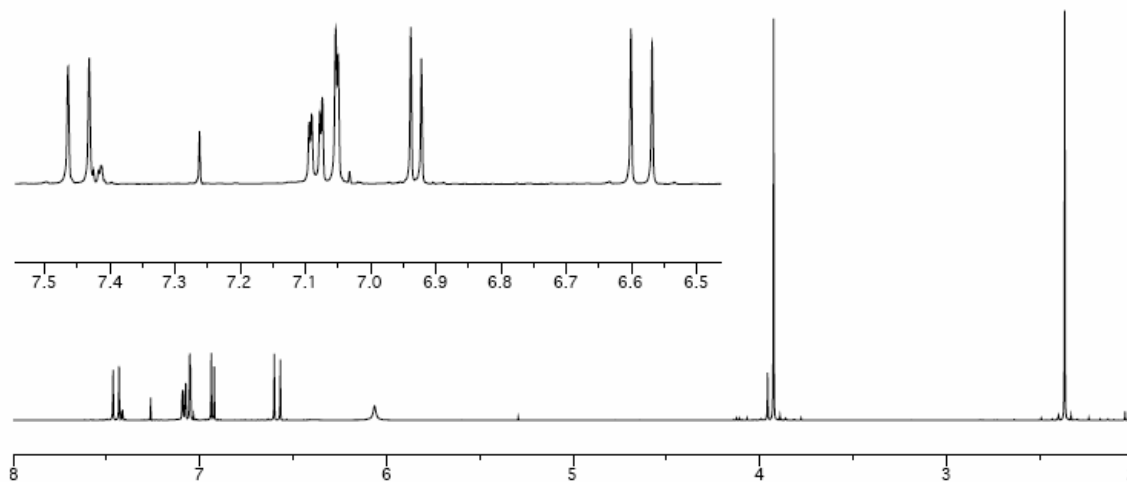
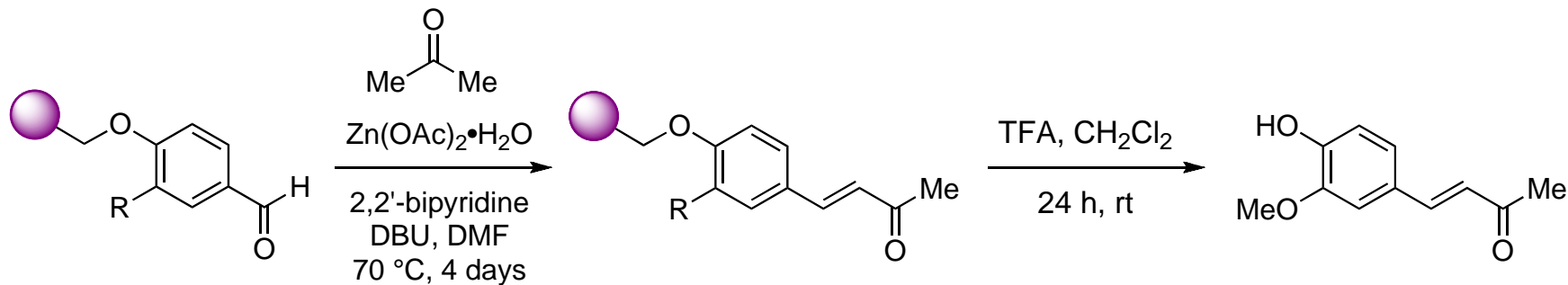
Chloromethyl(polystyrene) crosslinked with 1% DVB; ~1.7 mmol Cl/g resin

Immobilization & Characterization



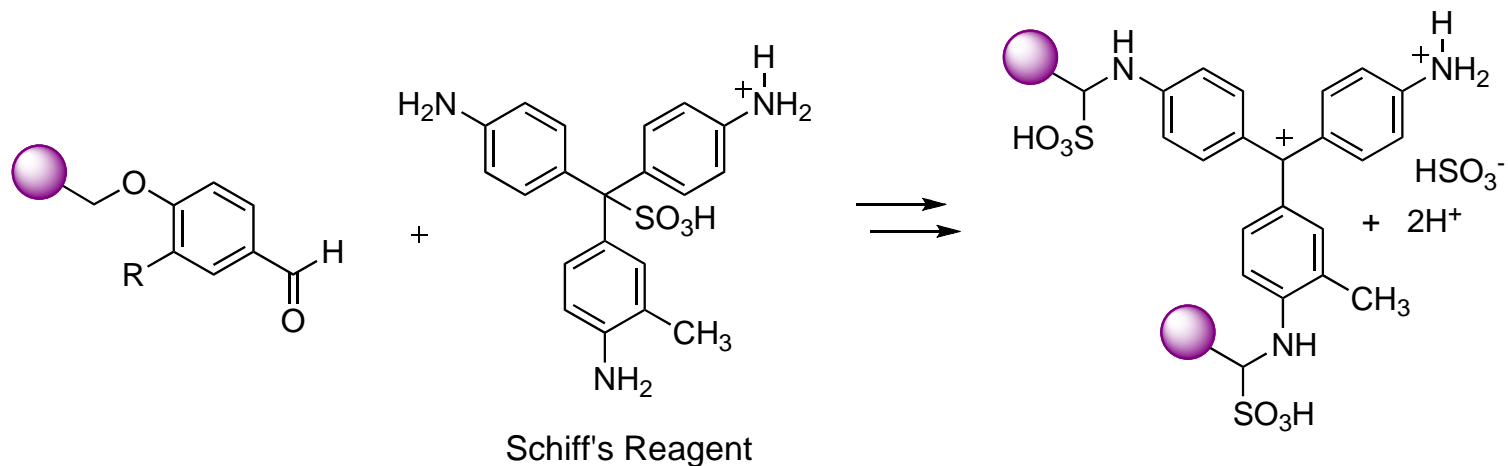
FTIR of immobilized aldehyde (powdered resin in KBr disc)

Claisen-Schmidt Condensation



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

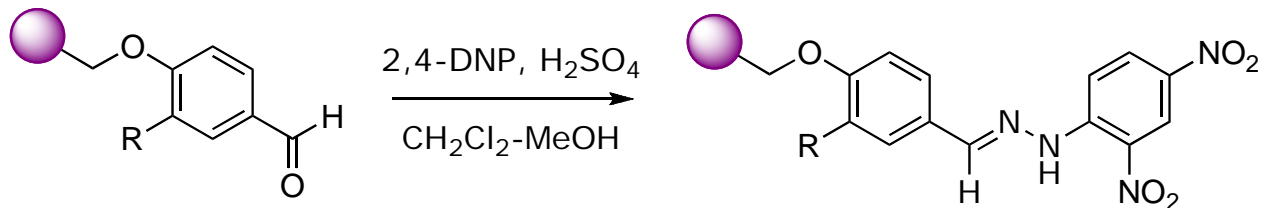
On-Resin Colorimetric Analysis

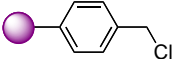



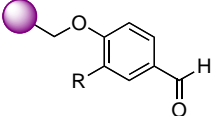



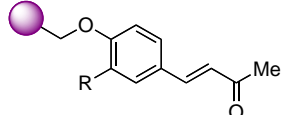





- Students found this color change difficult to identify on resin beads
- Presence of residual THF in bead causes false positives

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

A Colorimetric Research Project

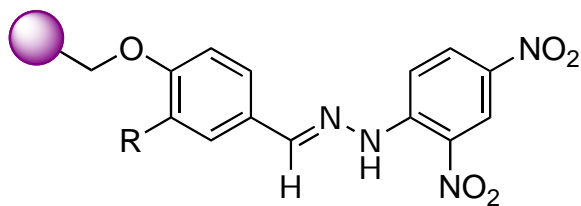


| Substrate | Group 1 | Group 2 | Group 3 |
|---|---|--|---|
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

DNP stain distinguishes between resin-bound aldehydes and unsaturated ketones

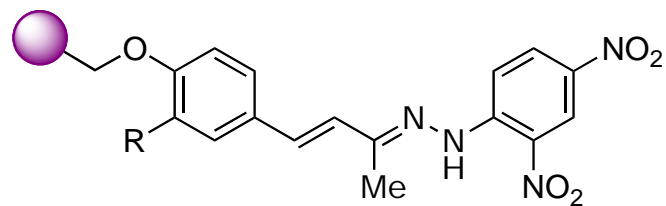
Color variations upon treating resins with 2,4-dinitrophenylhydrazine (2,4-DNP)

Origin of Differential Color Change



$\lambda_{\max} \sim 270 \text{ nm}$

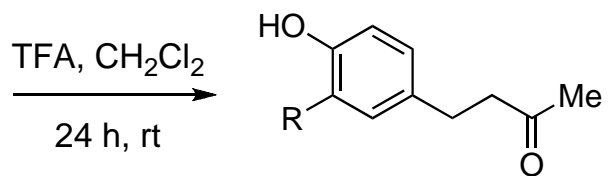
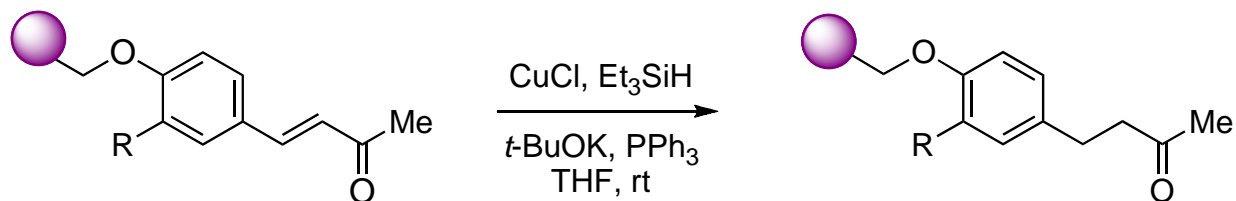
vs.



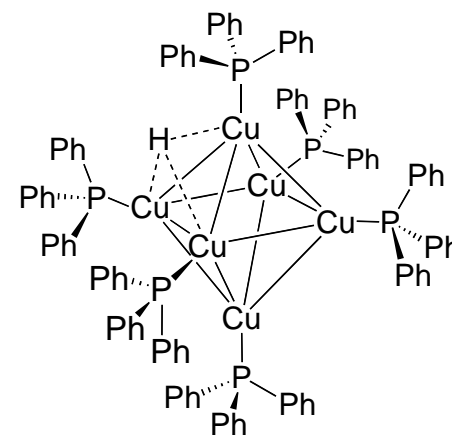
$\lambda_{\max} \sim 310 \text{ nm}$



Reduction with Stryker's Reagent

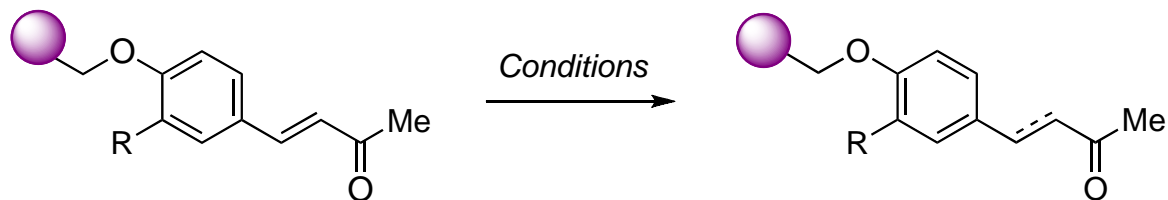


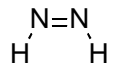
Zingerone ($\text{R} = \text{OMe}$)
Rheosmin ($\text{R} = \text{H}$)



Stryker's Reagent
 $[\text{Ph}_3\text{PCuH}]_6$

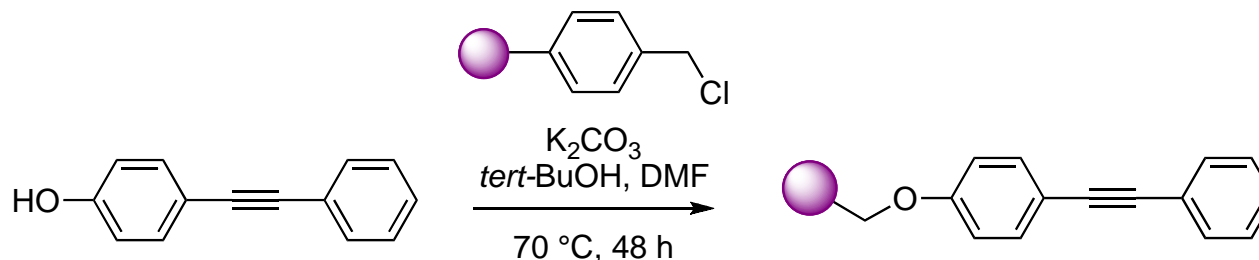
Reduction Results from CHEM 235



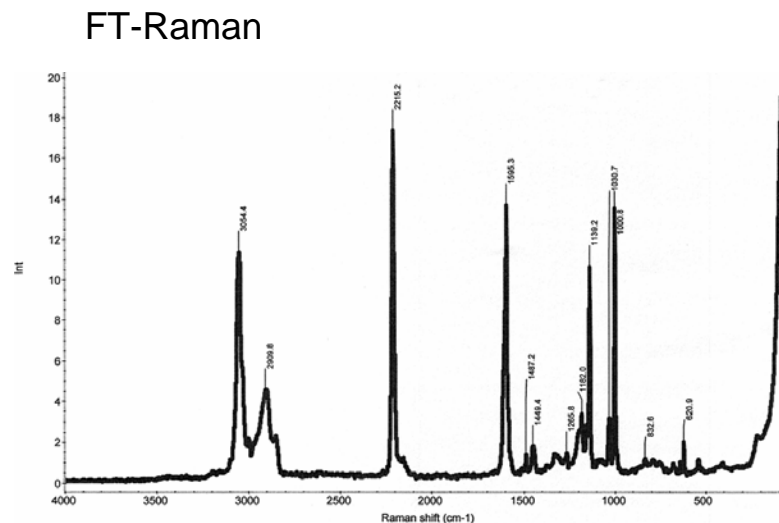
| Conditions | Result |
|---|----------------|
| $[\text{Ph}_3\text{PCuH}]_6$ | product + s.m. |
| $\text{PdCl}_2, \text{NaBH}_4$ PEG- CH_2Cl_2 | no reaction |
| $\text{Pd}(\text{OAc})_2, \text{PMHS}$ THF- H_2O | no reaction |
| $\text{NiCl}_2, \text{NaBH}_4$ MeOH, THF | no reaction |
|  | product + 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.....



IR spectra of immobilized alkyne has no stretch at 2215 cm⁻¹

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

Chad Landrie

Menaka Lunda

Nick Redder

Christine Toh

Debora Steffen

Gabriela Weaver

Donald Wink

Funding

National Science Foundation (CHE-0418902)
