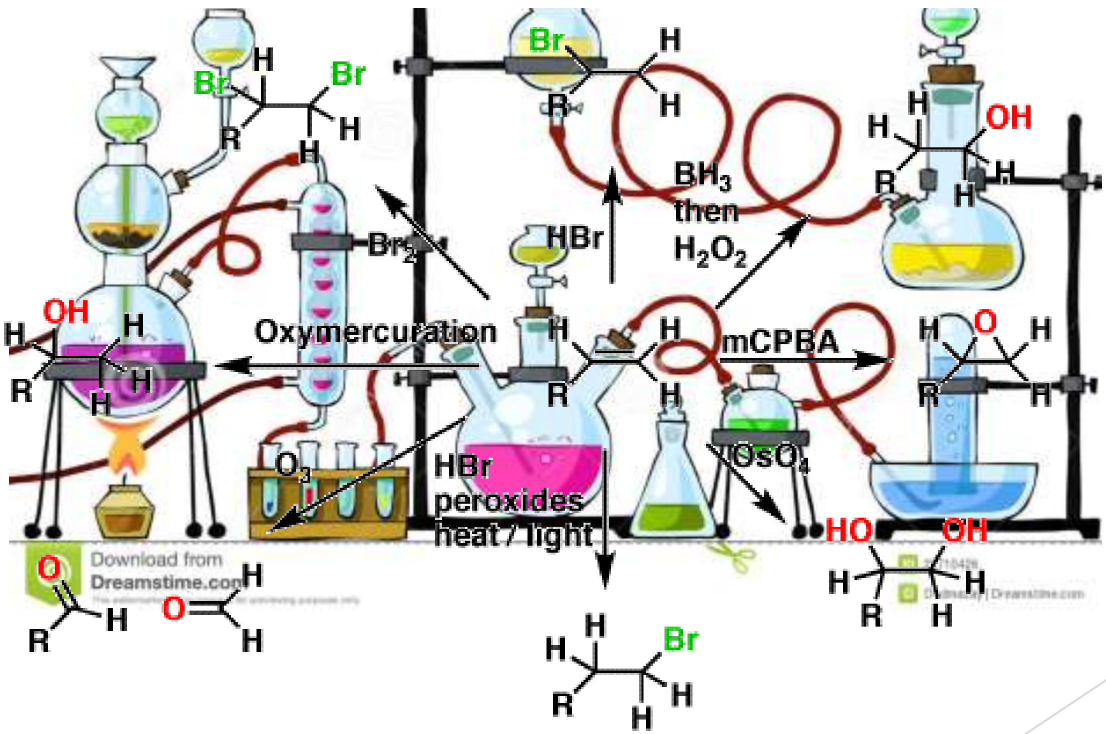
Hinkle Research Labs

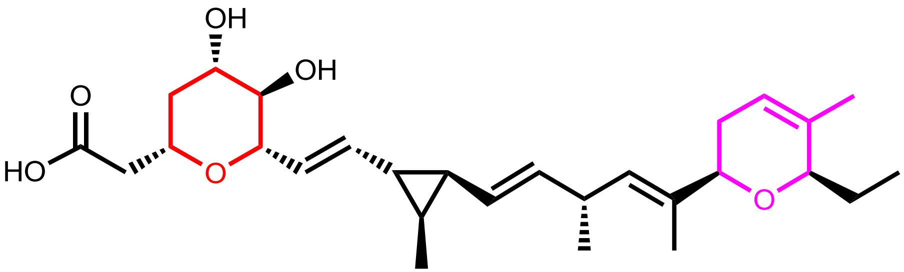
- *Synthetic and Physical Organic Chemistry*
  - *-- Reactive Intermediates -- Cascade Sequences to Aromatics*
  - *--Iodonium Salts -- ABE Chemicals (GreenBiologics)*



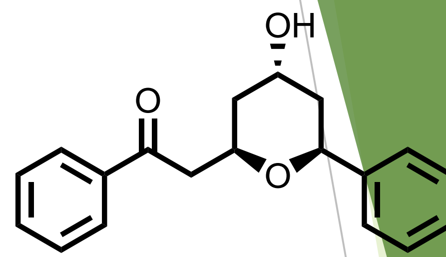
rjhink@wm.edu • 1-1501 • ISC 1039A

http://11452-presscdn-0-51.pagely.netdna-cdn.com/wp-content/uploads/2013/06/5-blankcanvas-4.png

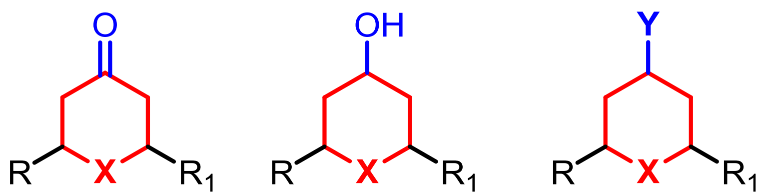
Heterocyclic Molecule Synthesis via Electrophilic Activation



Abruticine 1

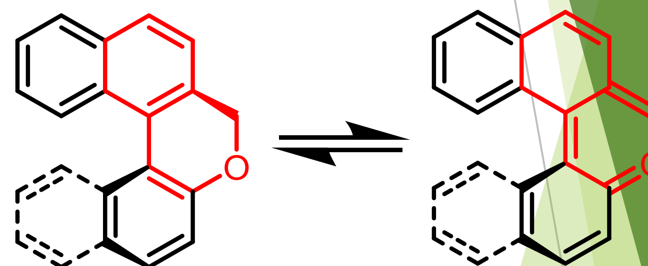


(-)-diospongin A

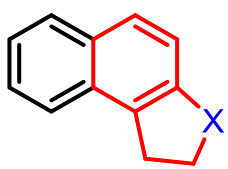


X = O, S, NR_2 **Y** = halide, H, etc.

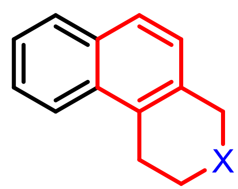
tetrahydropyrans, thiopyrans & piperidines



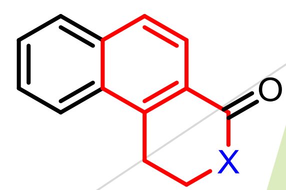
Photochromics?



dihydronaphthofurans & benzoindoles



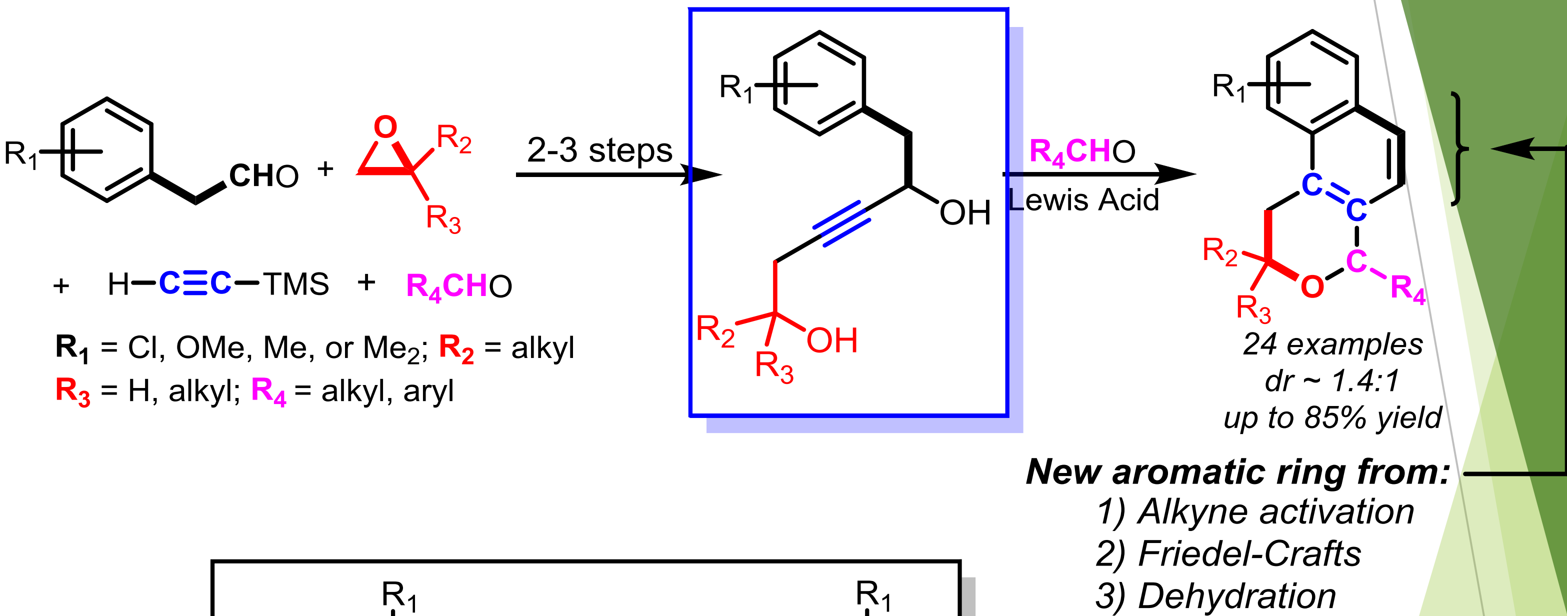
dihydronaphthopyrans & benzoisoquinolines

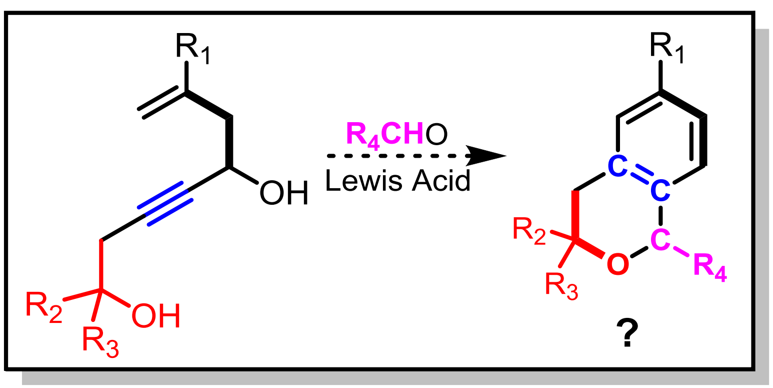


isochromenones & isoquinolinones

X = O, S, NR, etc.

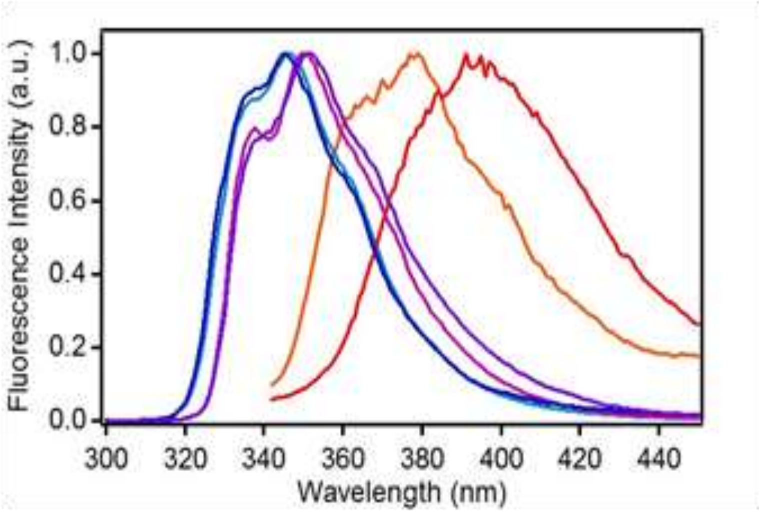
Alkynediols as Precursors to Polycyclic Compounds with New Aromatic Rings





Chen, Nofi, Lewis & Hinkle, *Org. Biomol. Chem*. **2017,** 15, 7584-7593 Doi: 10.1039/C7OB01412K

Examine Fluorescence in Benzo[f]isochromene series



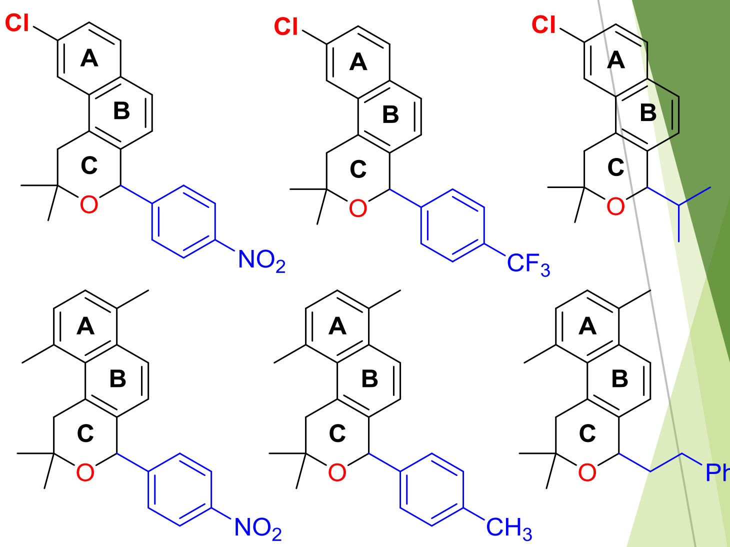
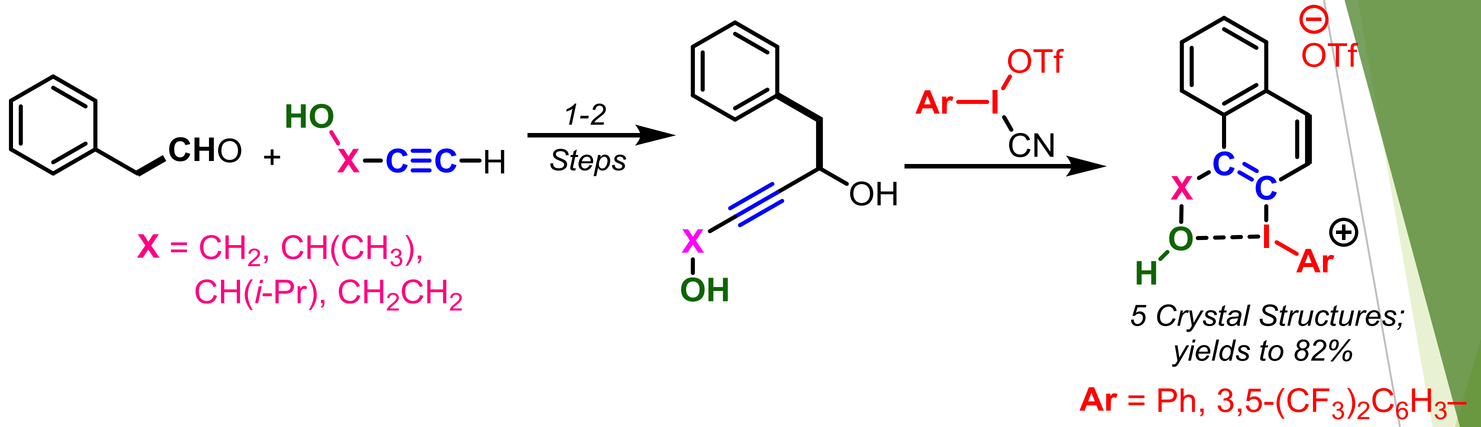


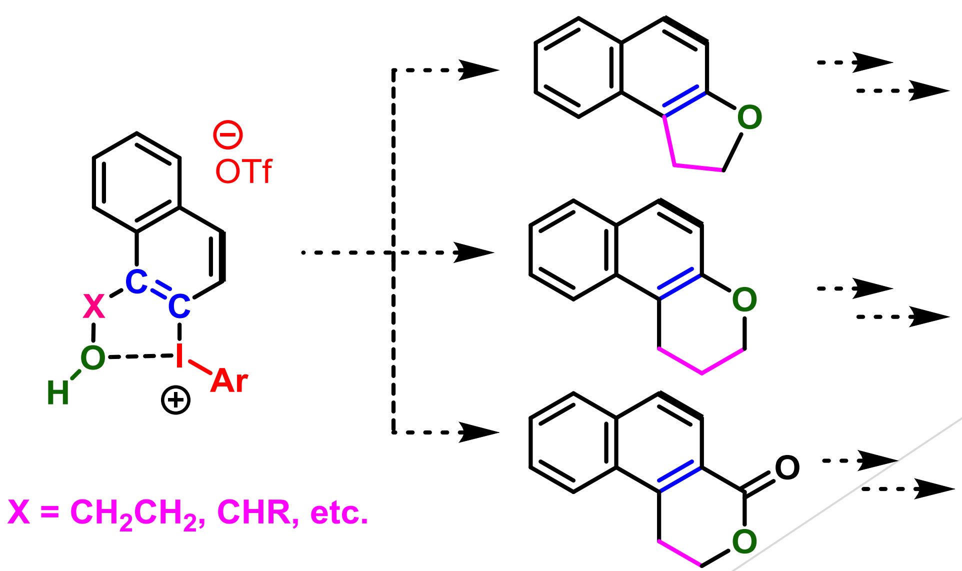
Figure 1. *Normalized* fluorescence maxima for six benzo[*f*]isochromenes.The two curves with maxima at ~375 and ~390 nm are for *p*-nitrophenyl derivatives.

Yuzhou Chen, *unpublished results.*

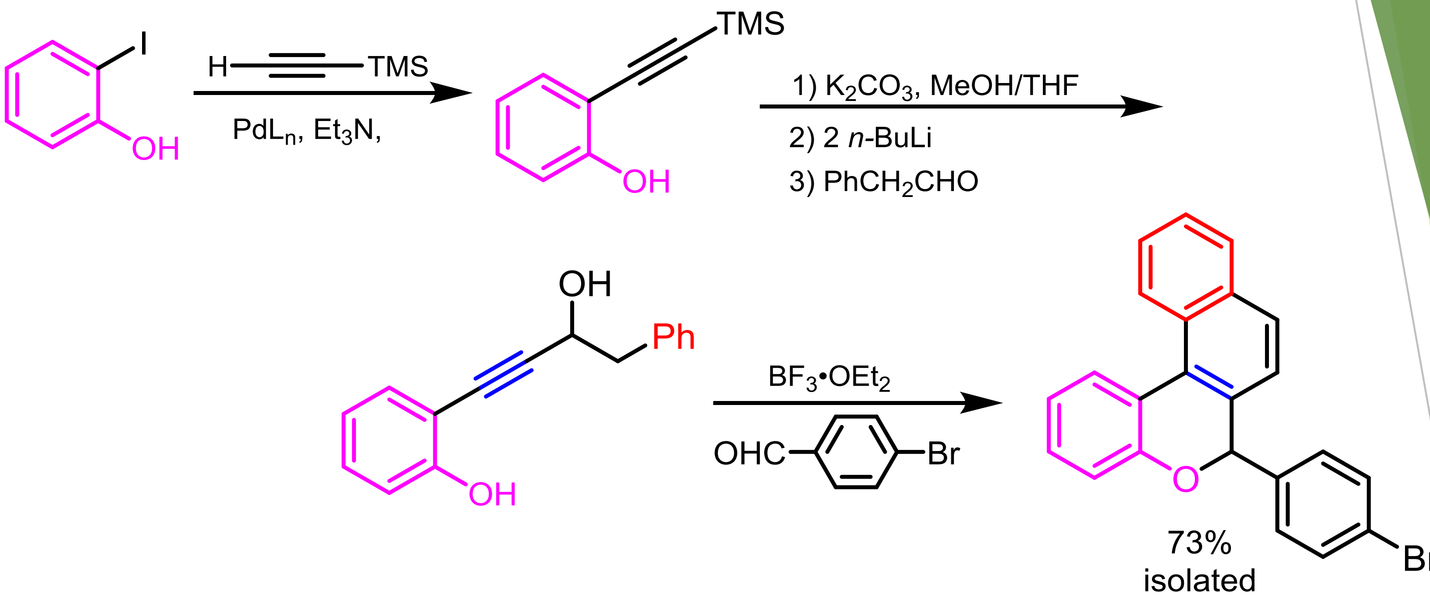
Alkynediols as Precursors to Naphthyl(aryl)iodonium Salts

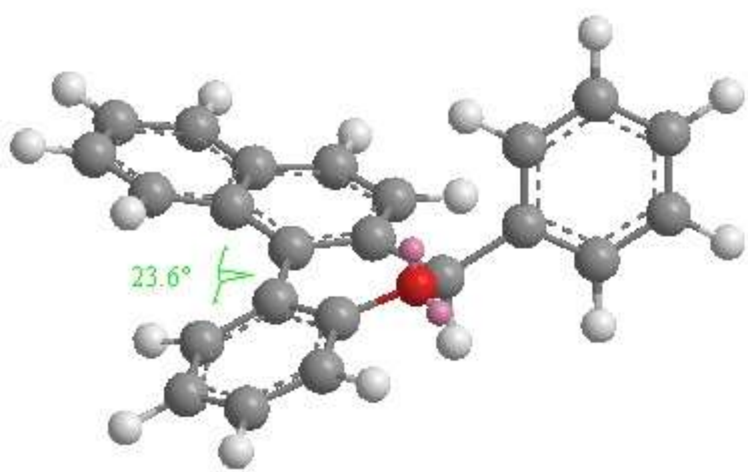


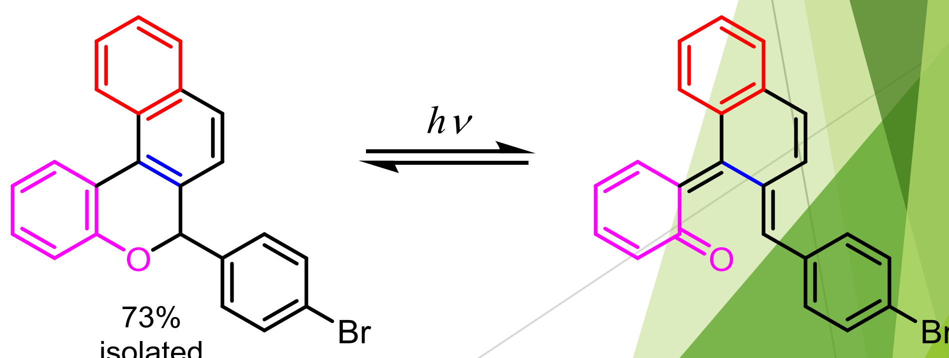
Hinkle , Bredenkamp, Pike & Cheon, *J. Org. Chem.* **2017**, Doi: 10.1021/acs.joc.7b01619



Alkynediols as Precursors to Naphthopyrans



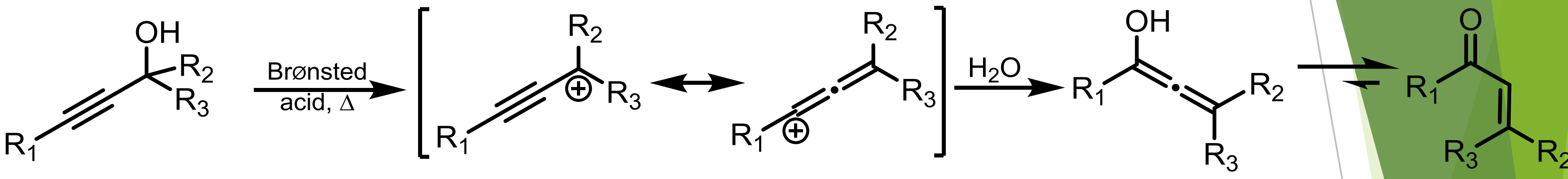




Either species fluorescent?
dihedral angle dependent?

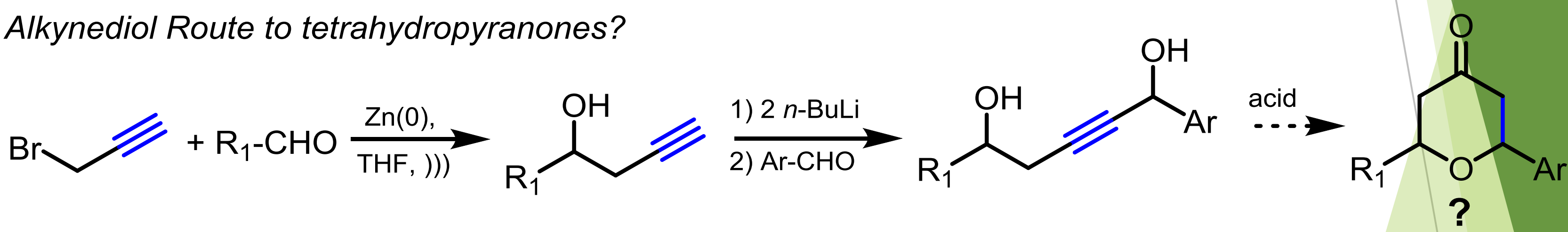
Alkynediols as Simple, Rapidly-Synthesized THP Precursors?

Meyer-Schuster Rearrangement:

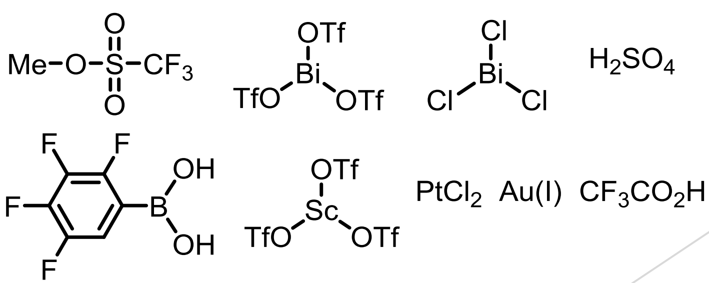


Either R_1 or R_2/R_3 has to help stabilize the putative allenyl-cation

Alkynediol Route to tetrahydropyranones?



Acids known to promote the rearrangement:



Discussion of Agreement Details in Progress

Dr. Lee Colyer Speight
Manager – Product Development & Business Analytics

Sales and Marketing Overview
August, 2016

Case Study: Beyond Ethanol

Historically significant

- ABE products and derivatives have strong historical significance:
  - Acetone was the solvent of choice for cordite production – high purity of ABE material ensured smokeless performance
  - *n*-butanol was used a fuel for British spitfire planes flown in WWII
  - *n*-butyl acetate enabled solvency of robust nitrocellulose lacquers for automobiles and led to development of spray guns for paint
- High purity of ABE solvents was key to these developments

Cordite image: https://en.wikipedia.org/wiki/Cordite#/media/File:Brisanzgranate_1_db.jpg
Spitfire image: https://g.foolcdn.com/editorial/images/156653/020_spitfire_abe_wiki_large.jpg
Automotive painting: http://images.wisegeek.com/person-applying-red-auto-paint.jpg

Strategic overview

Current and potential high value markets

Initial Identified High Value Markets

Additional Markets to Explore

- Small engine fuels
- Lubricants
- Cooking fuels
- Fragrance carriers
- Dry cleaning chemicals
- Novel green solvents
- Indoor smokeless fireplace fuels
- Fuel additives
- Pigment dispersions
- Stain removers
- Pest control products
- Degreasers

Current identified high value opportunities of $3.2 billion out of a $450 billion global specialty chemicals market

High value market potential

Focus on high potential – non-commodity applications

 Cosmetics	 Shampoo & Conditioners	 Soaps & Shower Gels	 Nail Polish Remover
 Food Ingredients	 Specialty Coatings	 Fragrances	 Flavourings
 Lab Chemicals	 Household Cleaners	 Performance Lubricants	 Retail Acetone
 Consumer Fuels	 Electronic Chemicals	 Plastics	 Hand Sanitizers

Things Students do in my Lab:

Projects for 2018-2019 might involve:

1) Expanding the scope of the benzo[*f*]isochromene syntheses.
   -studying electronic effects on spectrophotometric properties
2) Expanding the scope of naphthy(aryl)iodonium reaction
3) Utilizing naphthyl(aryl)iodonium salts for conversion to:
   -napthofurans
   -naphthopyrans
   -naphtholactones
4) Using the cylization cascade for photochromic molecules.
   -studying electronic effects on spectrophotometric properties.
5) Utilize Bio-based chemicals for making non-commodity compounds.

Lab Activities:
- Chemical synthesis
- Chromatographic purification
- High-Field NMR spectrometry, *including 2D NMR*
- Gas Chromatograpy and Mass Spectrometry
- Kinetic analysis

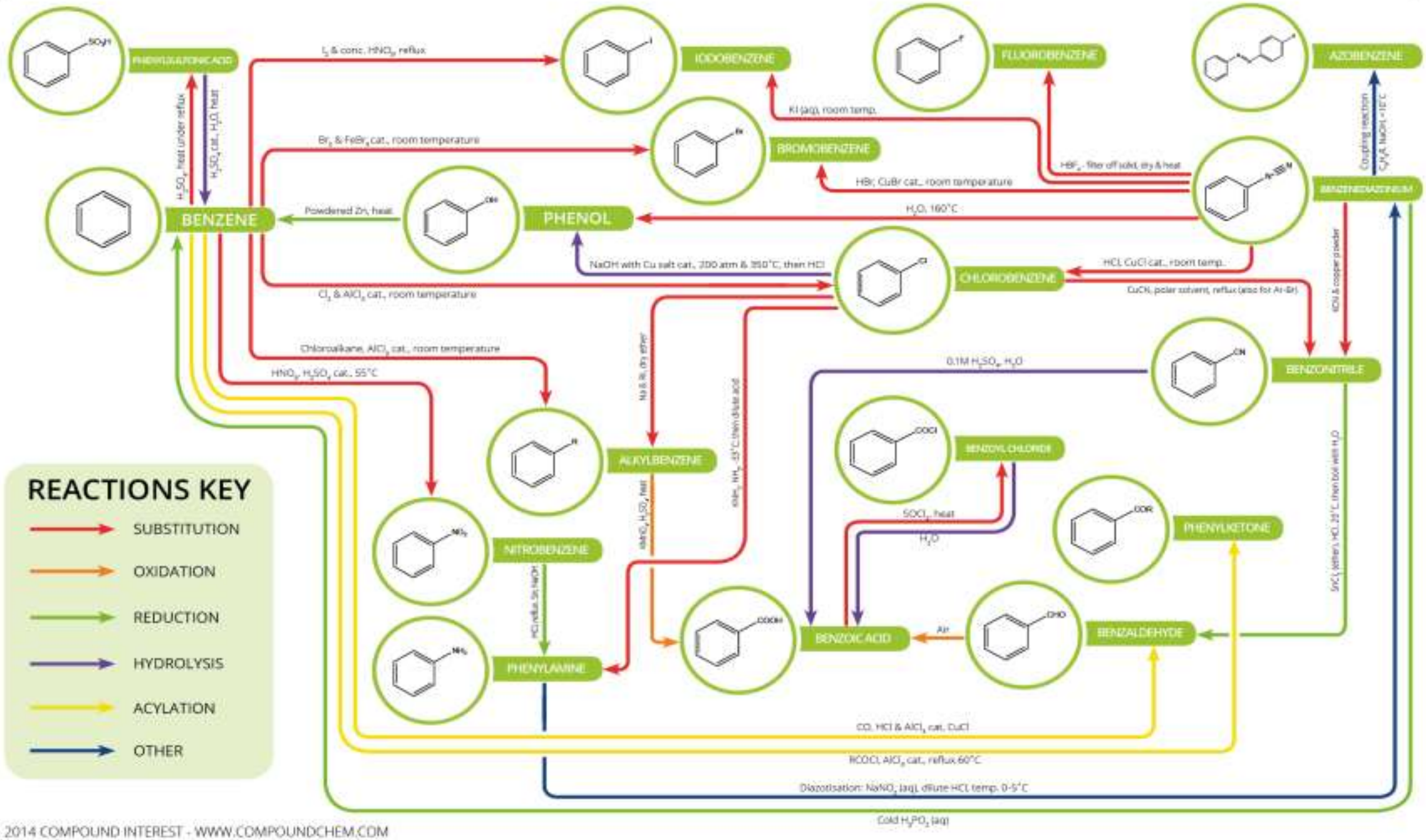
Positions Open:
- ~2-3 positions in summer 2018 (1 from GreenBiologics?).
- 1 or 2 additional positions possible with summer internship proposals.

***Current* Funding:** *Dean's Office*

***Anticipated Proposal Applications*:** *National Institutes of Health (NIH)*
National Sciene Foundation (NSF)

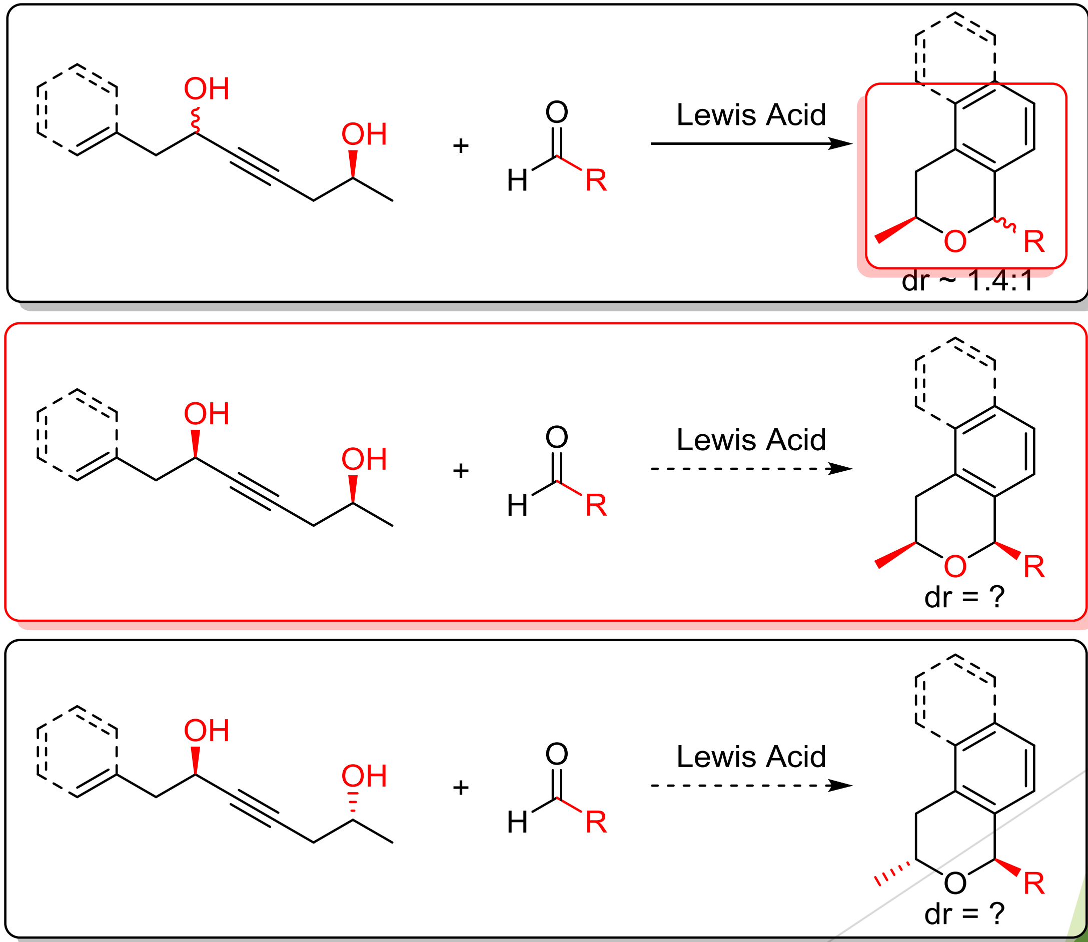
Rob Hinkle, ISC 1039-A
rjhink@wm.edu, 1-1501

AROMATIC REACTIONS MAP

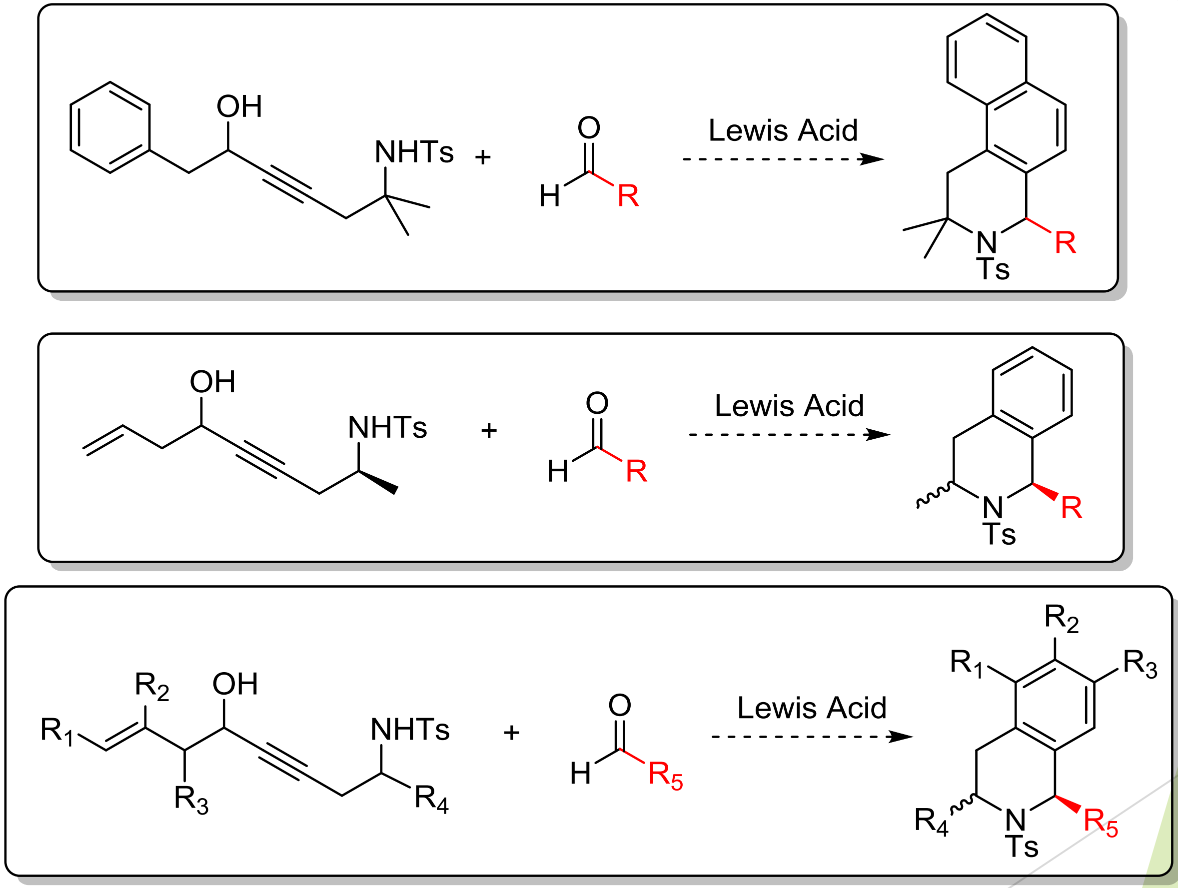


http://www.compoundchem.com/wp-content/uploads/2014/02/Aromatic-Chemistry-Reactions-Map1.png

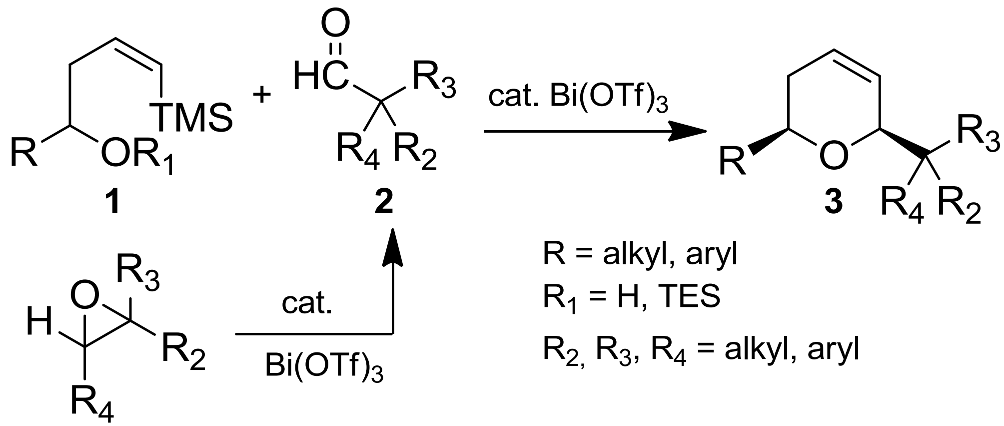
Reactions Toward Substituted 2,4-Dihydro-1H-benzo[f]isochromenes and Isochromenes : Stereochemical Effects?

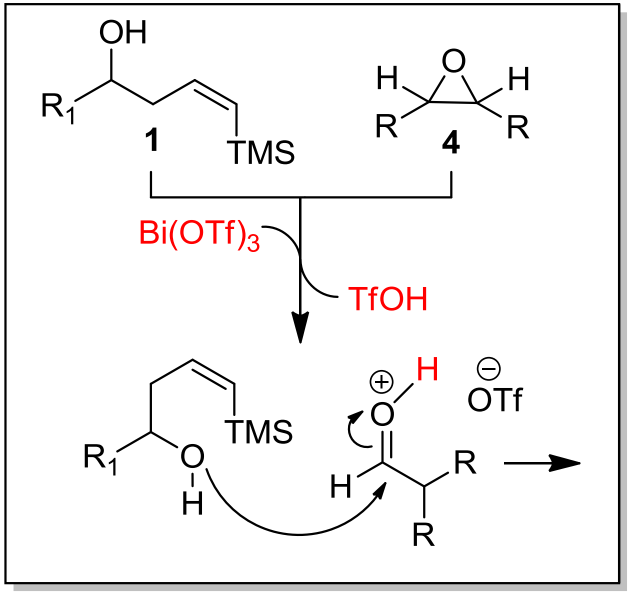


Tandem addition/Prins/Friedel-Crafts/dehydration reactions toward 2,2,4-trisubstituted-2,4-dihydro-1H-[f]isoquinolines



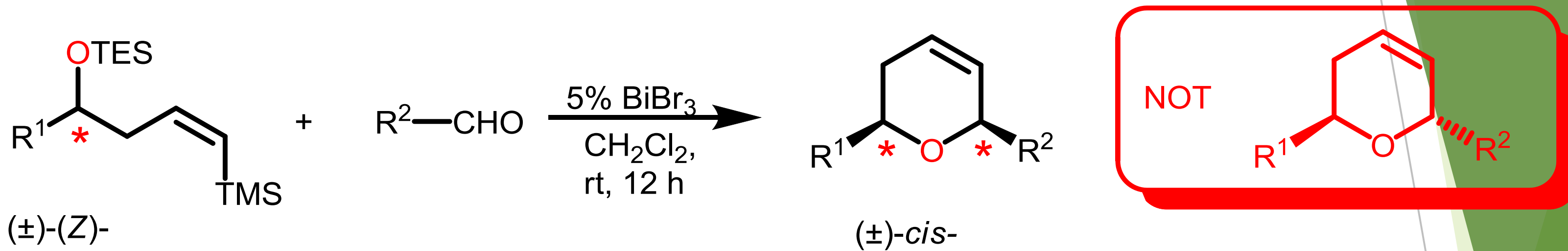
Role of Bi(III)





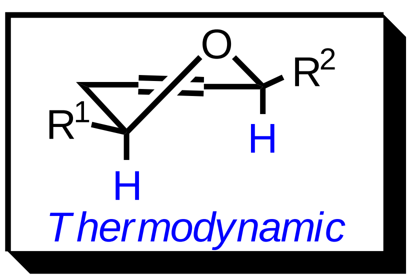
R. Frederick Lambert, Robert J. Hinkle,* **Stephen E. Ammann**, Yajing Lian, Jia Liu, Shane E. Lewis and Robert D. Pike, *J. Org. Chem.* 2011, **2011**, *76*, 9269-9277.

Bi(III) Mediated Reactions



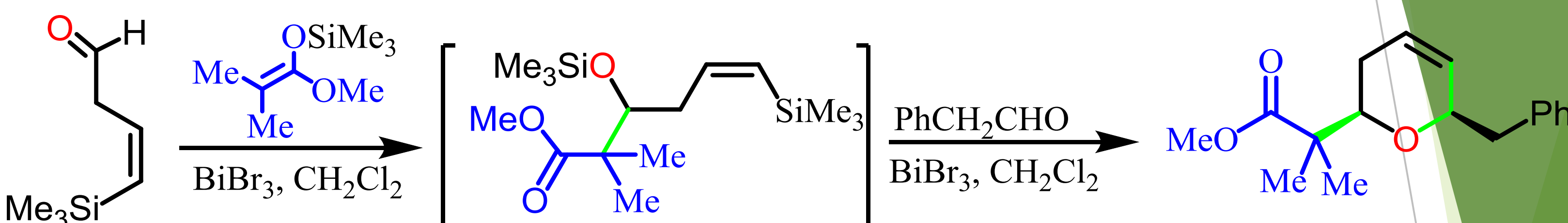
47-97%

R^1 = H, CH_3, Ph, *n*-C_5H_{11}
R^2 = Ph, $PhCH_2$-, 4-$(CF_3)C_6H_4$-, 4-$(CH_3O)C_6H_4$-



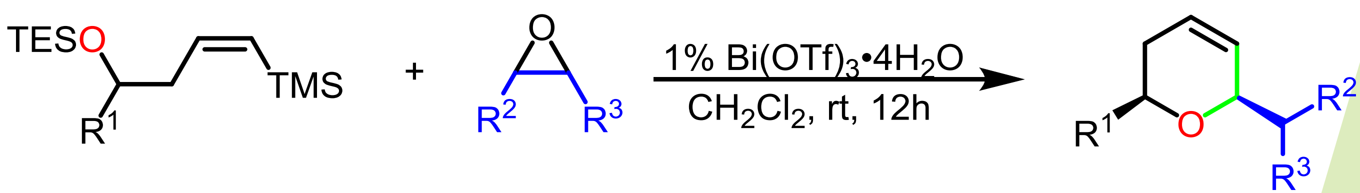
Lian, Y.; Hinkle, R. J., "$BiBr_3$-Initiated Tandem Addition/Silyl-Prins Reactions to 2,6-Disubstituted Dihydropyrans," *J. Org. Chem.* **2006**, *71*, 7071-7074.

Dihydropyrans



64 % as a single diastereomer

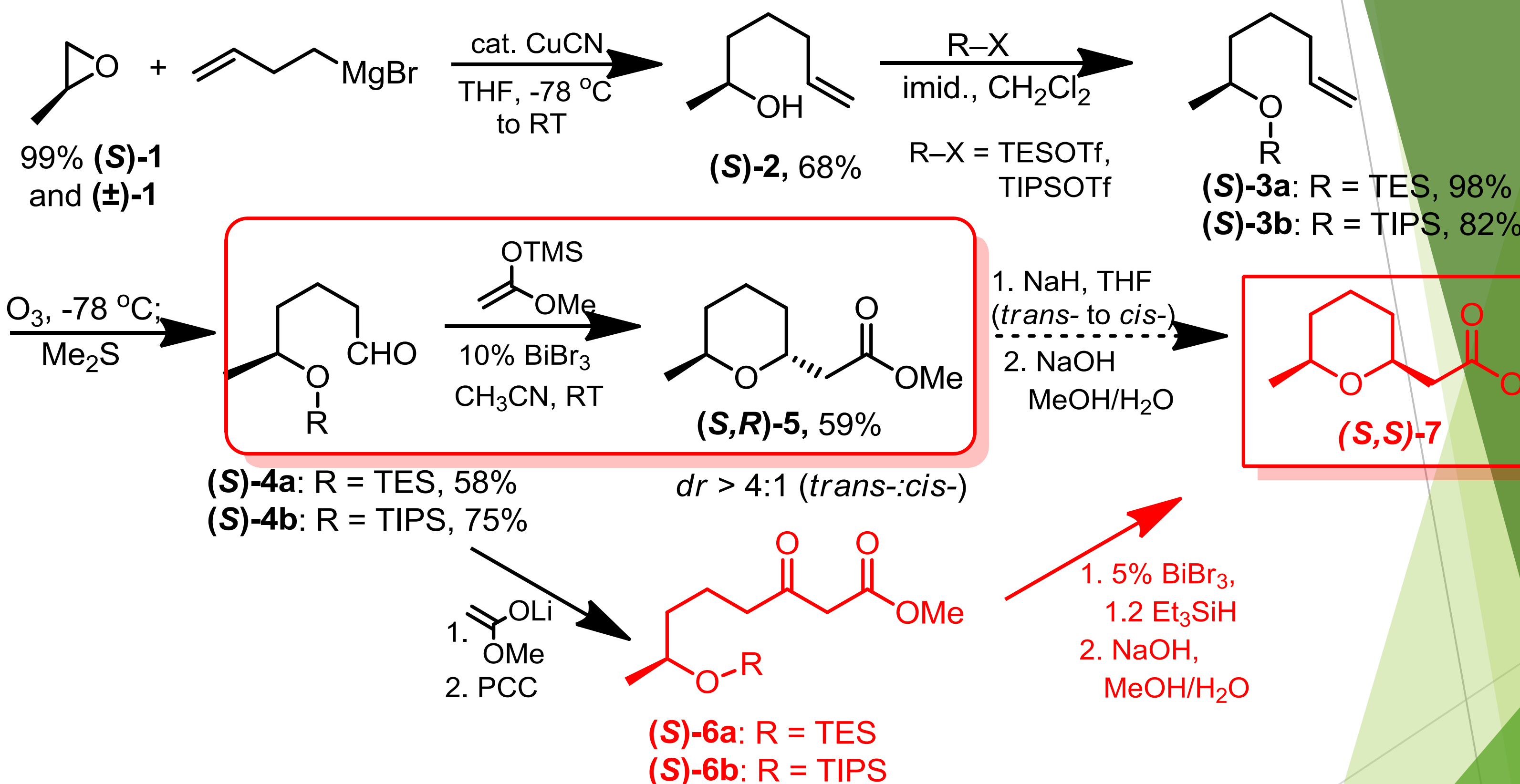
Natural Product with similar structure



- **Nitrogen instead of Oxygen?**
- **Enantiomerically-enriched substrates?**
- **Larger ring systems?**

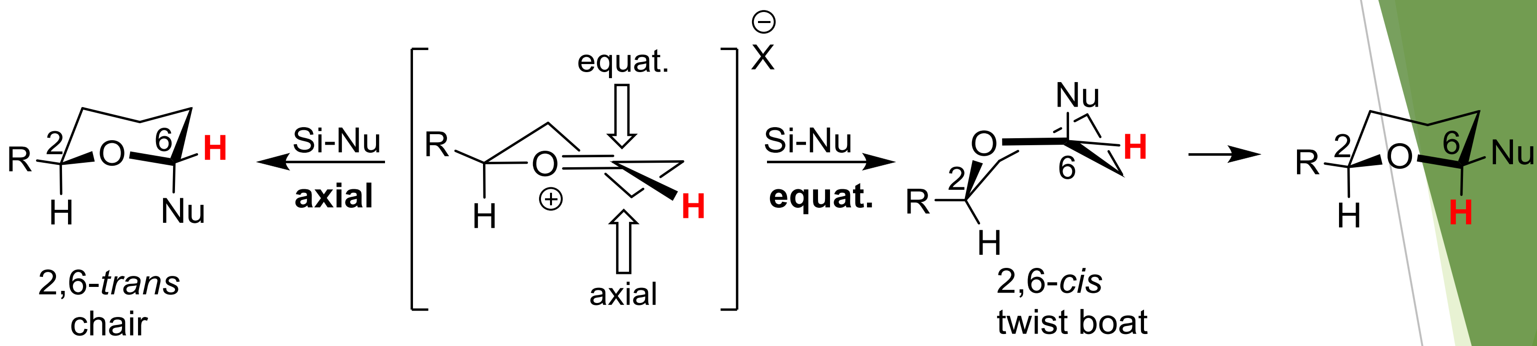
Robert J. Hinkle *, Yajing Lian, **Lee C. Speight, Heather E. Stevenson, Melissa M. Sprachman, Lauren A. Katkish, M. Christa Mattern**, *Tetrahedron* **2009**, *65*, 6834–6839.

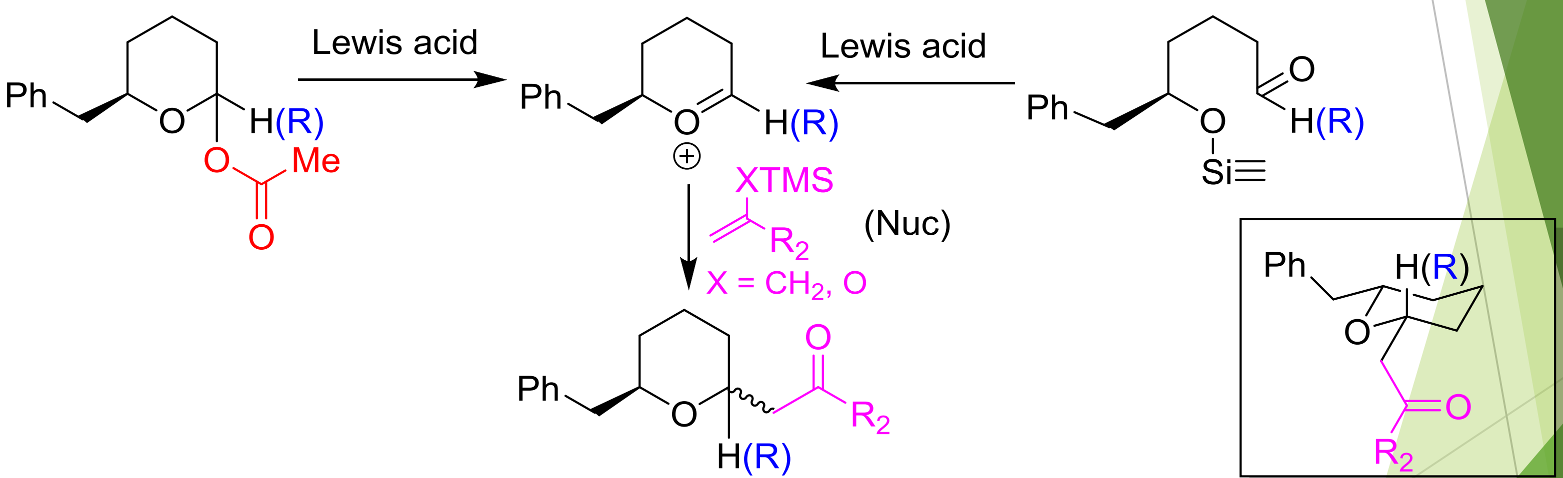
Stereocontrol in the Synthesis of Civet Component



Hinkle, R. J., Lian, Y.**; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C**.
Tetrahedron, **2005**, *61*, 11679-11685.

Stereoelectronic Model for Nucleophilic Addition





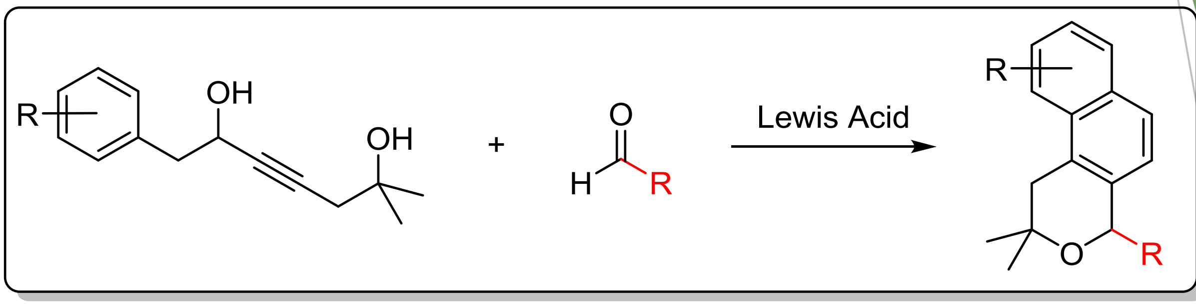
Stereselectivity depends upon acetate sterechemistry, Leaving Group ability (i.e., -OAc vs. -OTf) and nucleophile--Examining Electronic Effects

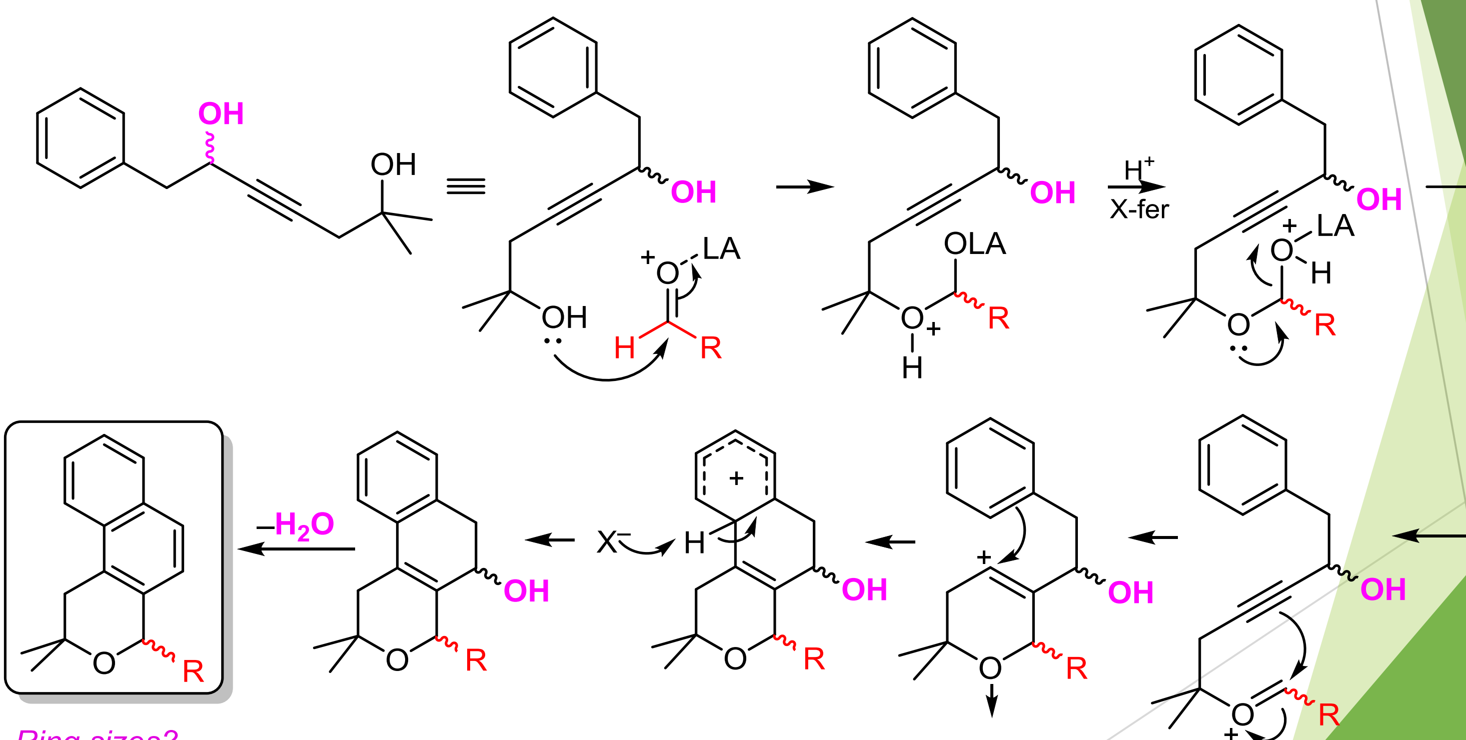
Woerpel and co-workers, *J. Org. Chem.* **2009,** *74,* 8039-8050.

Hinkle et al., *Tetrahedron* **2005,** *61,* 11679-11685.

Rahman, A. A.; Hinkle, R. J.; **Lambert, R. F.; Ammann, S. E.**; *manuscript in preparation.*

Tandem addition/Prins/Friedel—Crafts/dehydration reactions toward 2,2,4-trisubstituted-2,4-dihydro-1H-benzo[f]isochromenes





Ring sizes?
Asymmetric?

Hinkle, R. J.; Lewis, S. E., *Org. Lett.* **2013**, *15,* 4070-4073.