# Enantioselective Total Synthesis of (–)-Napyradiomycin A1 via Asymmetric Chlorination of an Isolated Olefin

Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745.

# Tandem Asymmetric Aza-Darzens/Ring-Opening Reactions: Dual Functionality from the Silane Lewis Acid

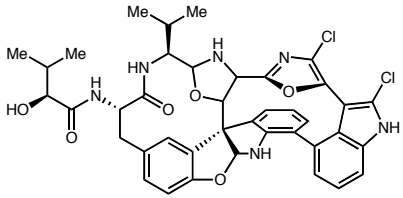
Valdez, S. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 14638–14639.

Mike Karney
Short Literature Presentation
Group Meeting 6-14-2010

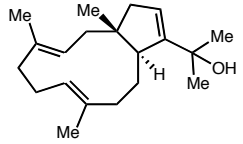
# *Profs. Scott A. Snyder and James L. Leighton*

## Scott A. Snyder

- **Undergraduate, Williams, 1995-1999 (Markgraf)**
  - **-Hetero Diels–Alder routes to Carboline Alkaloids**
- **Ph. D, Scripps, 1999-2004 (Nicolaou)**
  - **-Synthesis of diazonamide A**
  - **-19 publications**
  - **- Co-author of *Classics in Total Synthesis II***
- **Post-doc, Harvard, 2004-2006, (Corey)**
  - **-Worked on dollabellane family**
- **Assistant Prof, Columbia, 2006-present**



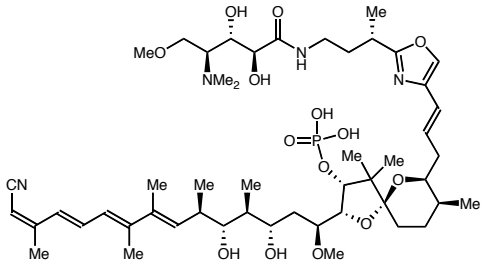
**diazonamide A**



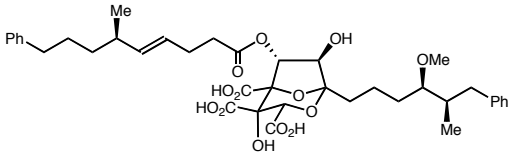
**palominol**

## James L. Leighton

- **Undergraduate, Yale, 1983-1987 (Danishefsky)**
- **Ph. D, Harvard, 1989-1994 (Evans)**
  - **-Syntheses of calyculin A and zaragozic acid C**
  - **-5 publications**
- **Post-doc, Harvard, 1994-1996, (Jacobsen)**
  - **-Enantioselective epoxide opening**
- **Assistant Prof, Columbia, 1996-1999**
- **Associate Prof, Columbia, 1999-2004**
- **Professor, Columbia, 2004-present**

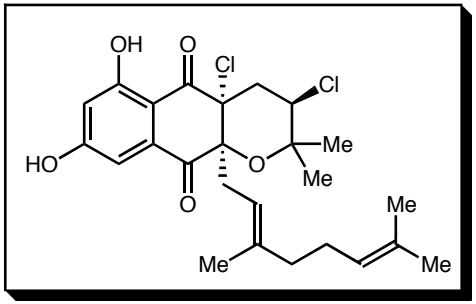


**calyculin A**

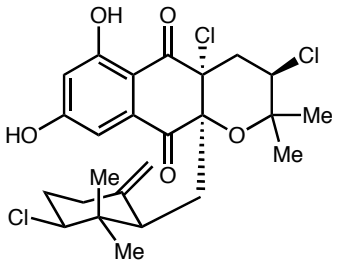


**zaragozic acid C**

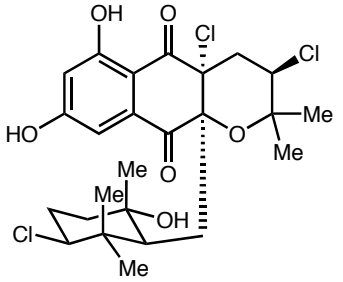
# *The Napyradiomycins*




**napyradiomycin A1**




**napyradiomycin B1**




**napyradiomycin B4**

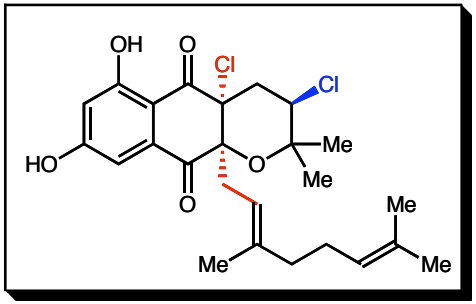
- **Isolated from a strain of *Streptomyces* bacteria**
- **Demonstrate antibacterial properties and activity as a nonsteroidal estrogen antagonist**
- **Structurally similar compounds have shown antitumor potency against colon carcinoma cells**

## Napyradiomycin A1

- **Three stereocenters**
- **Tricyclic core with small aliphatic chain**


Shiomi, K.; Iinuma, H.; Hamada, M.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H. *J. Antibiot.,* **1986**, *39*, 487–493
Hori, Y.; Abe, Y.; Shigematsu, N.; Goto, T.; Okuhara, M.; Kohsaka, M. *J. Antibiot.,* **1993**, *46*, 1890–1893

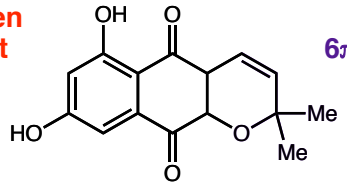
# *Napyradiomycin A1*



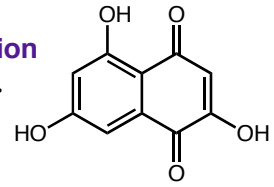

napyradiomycin A1

**Johnson-Claisen rearrangement**

**Asymmetric chlorination**



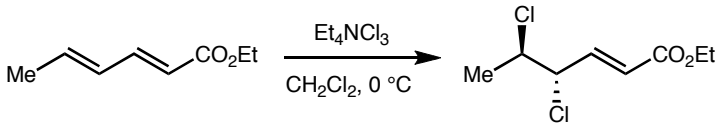

**Tandem Knovenagel/ 6π-electrocyclization**



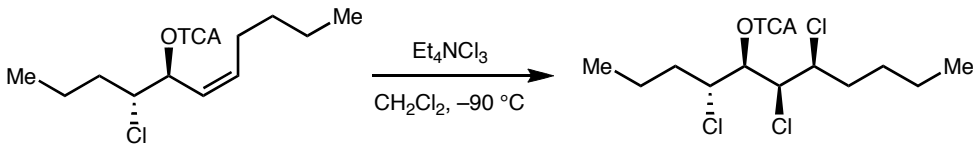

## Key Transformation

- **Enantioselective chlorination to direct stereochemistry of geranyl side chain and set contiguous stereocenter**

# *Stereoselective Chlorination of Natural Products*




***68% yield***
***racemic***



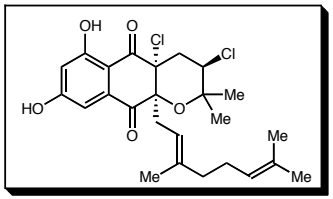

***76% yield***
***10.5:1 dr***


Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature,* **2009**, *457*, 573–576

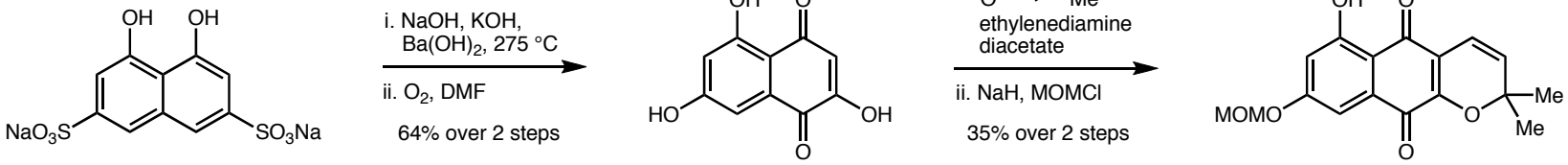
Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.,* **2008**, *130*, 12514–12518

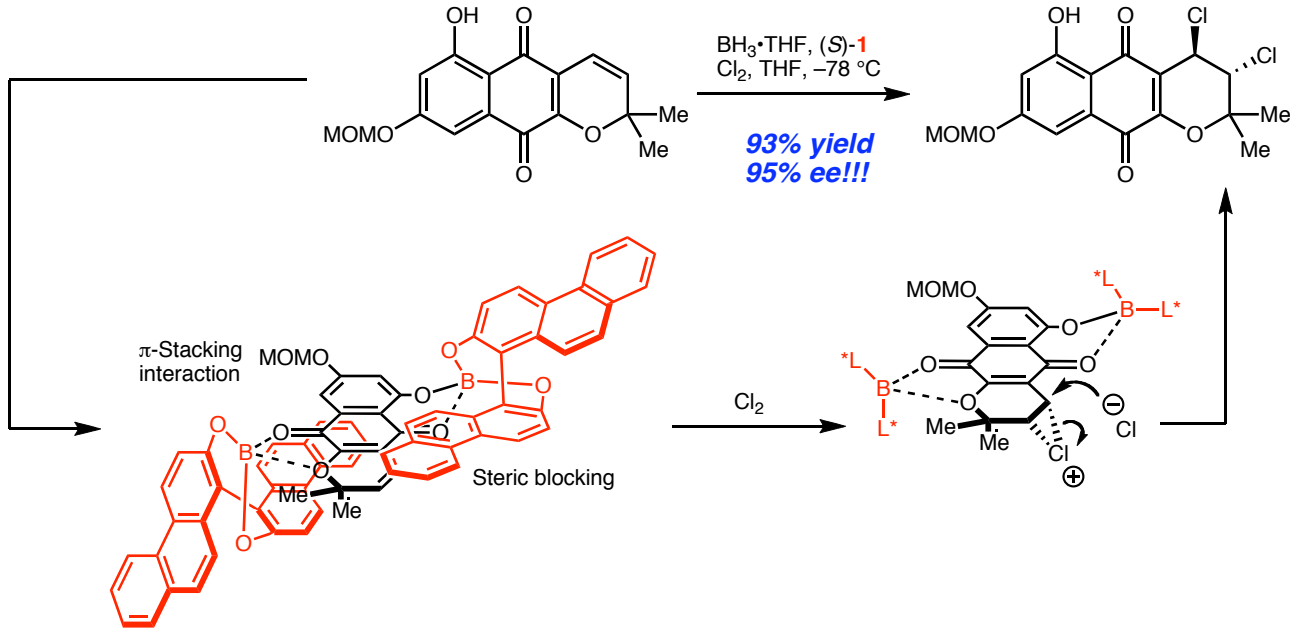
Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem. Int. Ed.,* **1997**, *36*, 2342–2344

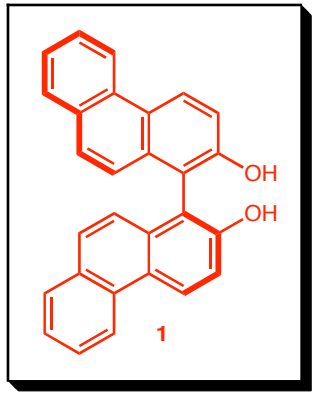
# *Building the Core*



**napyradiomycin A1**

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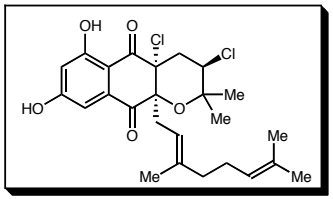
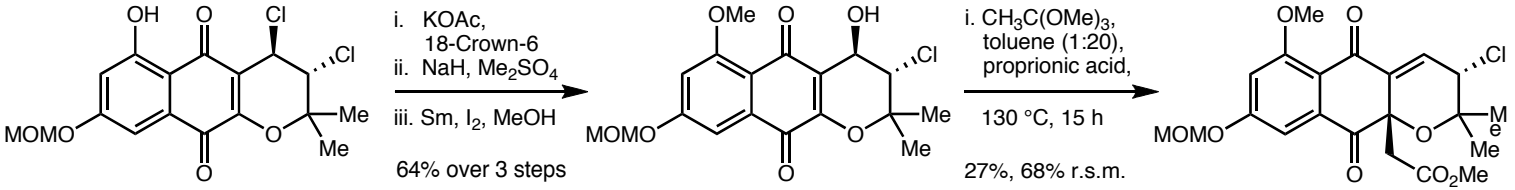
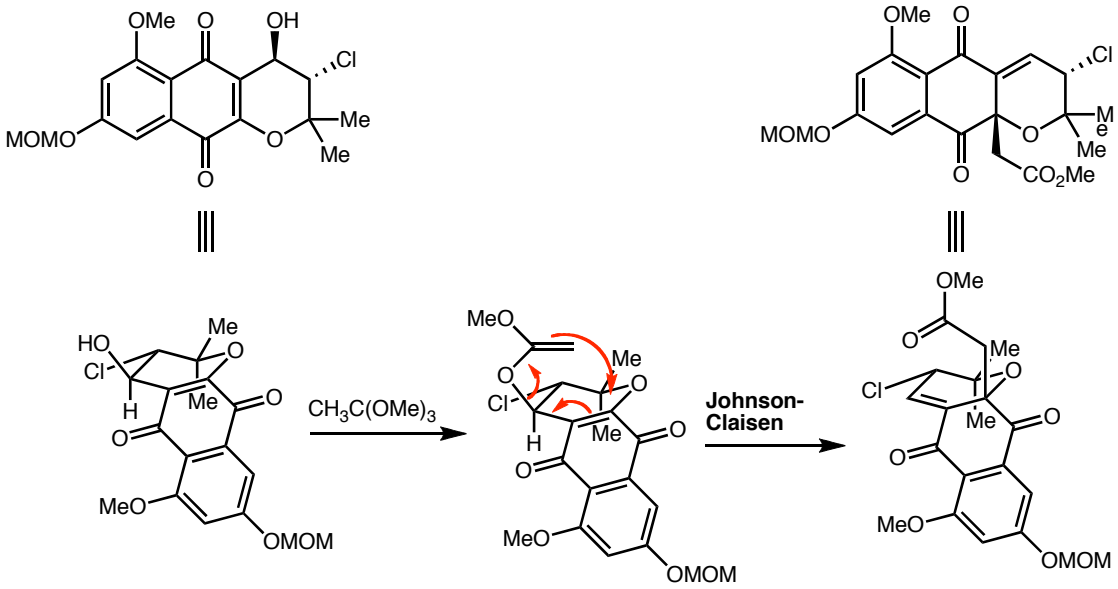
# *Johnson-Claisen*



**napyradiomycin A1**




# *OVER THE TOP!*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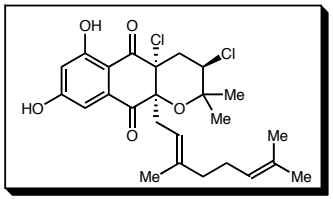
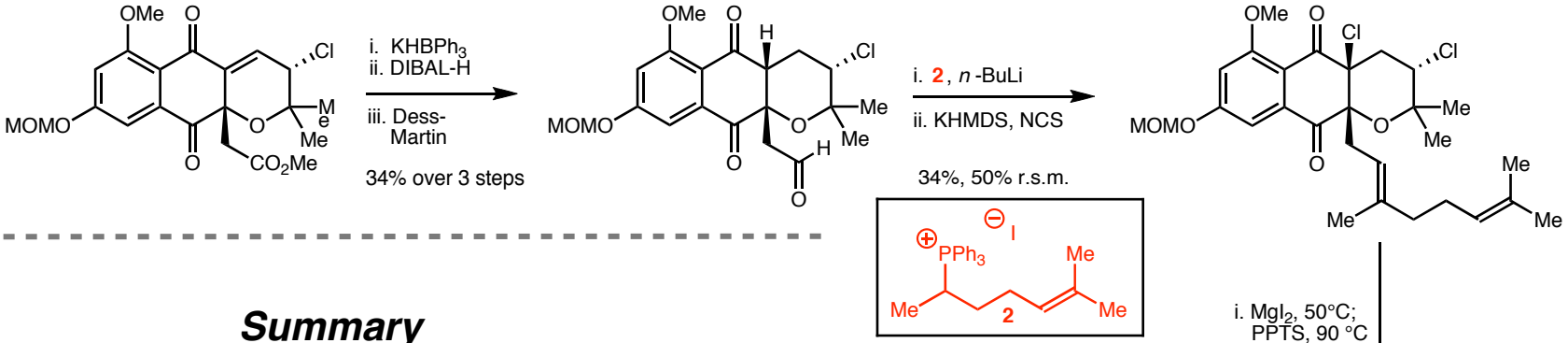
# Endgame



napyradiomycin A1

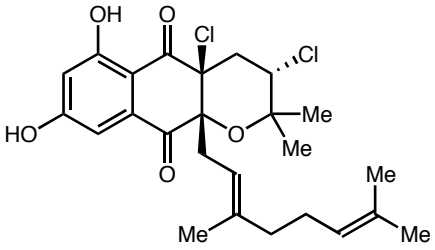





2

# Summary

- **First asymmetric total synthesis of any member of the napyradiomycin family**
  - **15 linear steps; 0.014% overall yield**
- **Key Transformations**
  - **2-step flaviolin synthesis, highly asymmetric chlorination , Johnson-Claisen rearrangement**
- **Future Directions**
  - **Asymmetric chloronium-induced cation-π cyclization**
  - **Catalytic, enantioselective chlorination**



**(–)-napyradiomycin A1**

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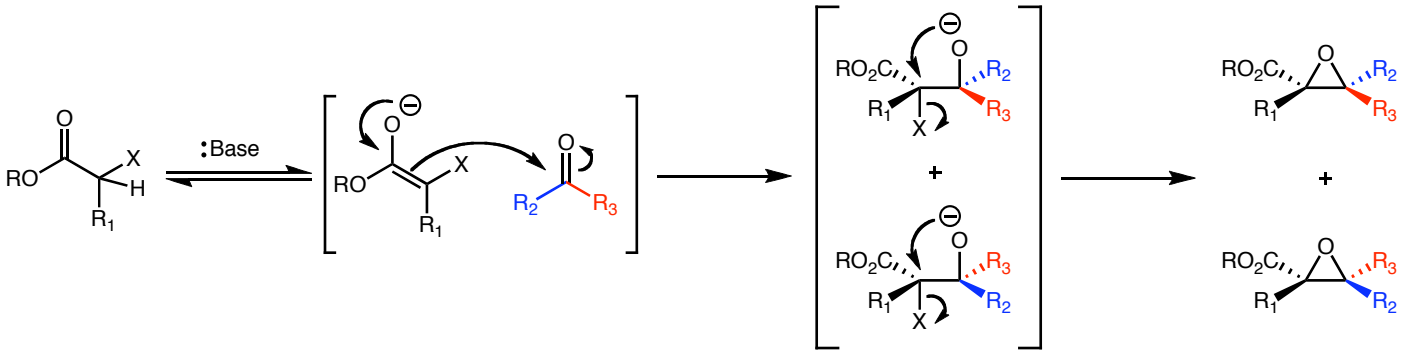
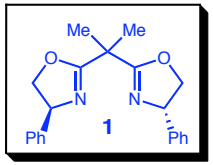
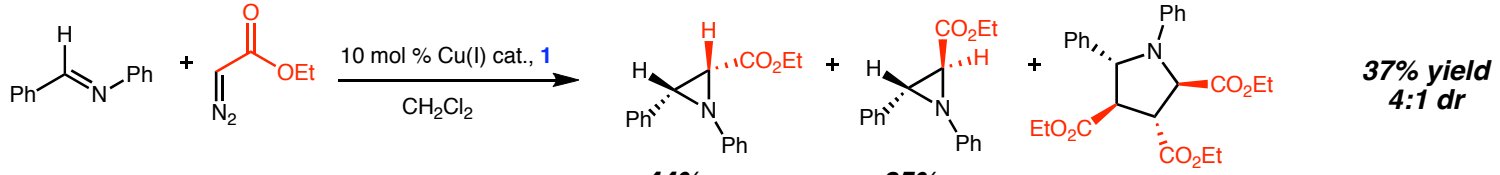
# Darzens Reaction

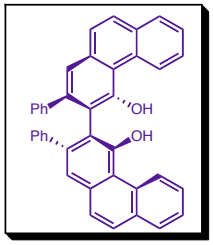


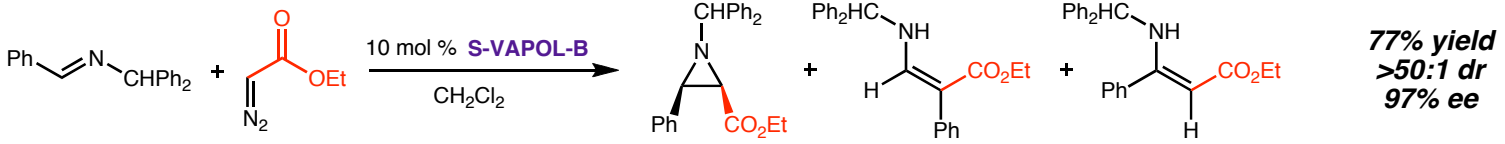

# Aza-Darzens Variants




*37% yield*
*4:1 dr*

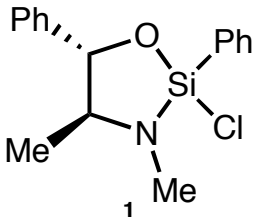



*77% yield*
*>50:1 dr*
*97% ee*


Darzens, G. *Compt. rend.,* **1911**, *151*, 883–884
Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 676–678
Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.*, **1999**, *121*, 5099–5100

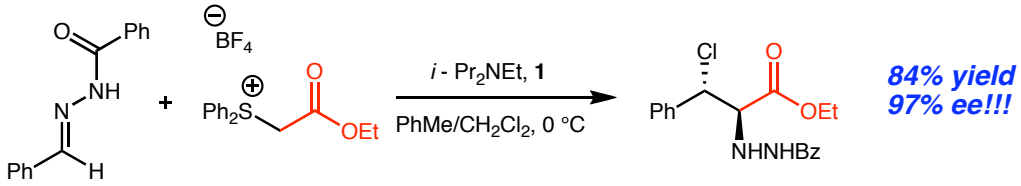
# *Leighton's Approach*




**1**

- **Chiral silane Lewis acid previously used in a number of acyl hydrazone nucleophilic addition manifolds**
  - **Mannich-type reactions with silyl enol ethers**
  - **[3+2] cycloadditions**
  - **Friedel–Crafts alkylations**
  - **Allylations**

**What other nucleophiles can be added to hydrazones??**

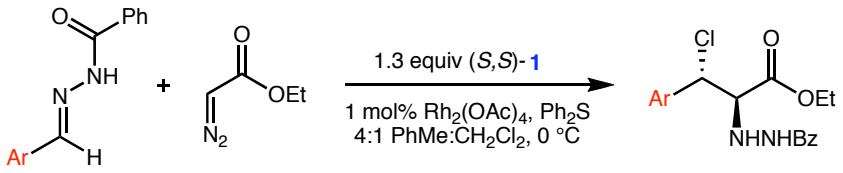


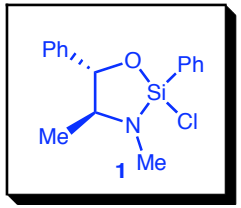

***84% yield***
***97% ee!!!***

- **Ring opened product obtained as single regioisomer and diastereomer**

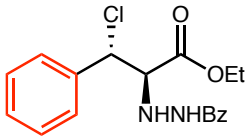

Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.,* **2004**, *126*, 5686–5687
Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.,* **2005**, *127*, 2858–2859
Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.,* **2005**, *127*, 9974–9975
Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.*, **2008**, *130*, 6676–6677

# *One-Pot Procedure*

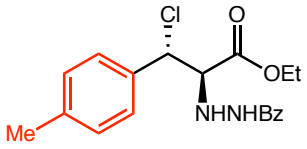


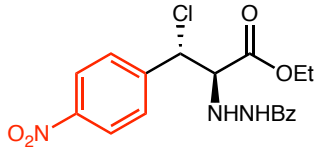

**Two equiv of ethyl diazoacetate and diphenyl sulfide needed because of dimerization**



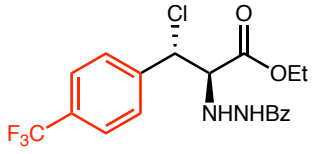
***88% yield***
***>20:1 rr***
***95% ee***



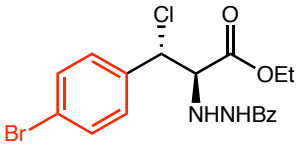
***76% yield***
***>20:1 rr***
***94% ee***



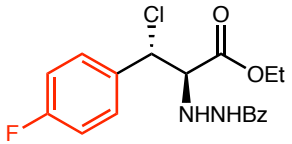
***82% yield***
***6:1 rr***
***94% ee***



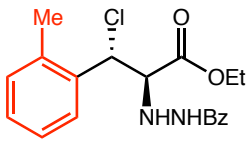
***83% yield***
***9:1 rr***
***97% ee***



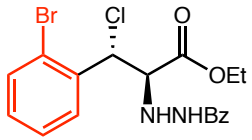
***85% yield***
***17:1 rr***
***91% ee***



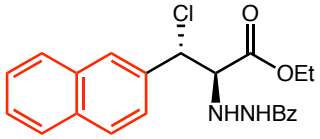
***81% yield***
***11:1 rr***
***91% ee***



***84% yield***
***10:1 rr***
***93% ee***



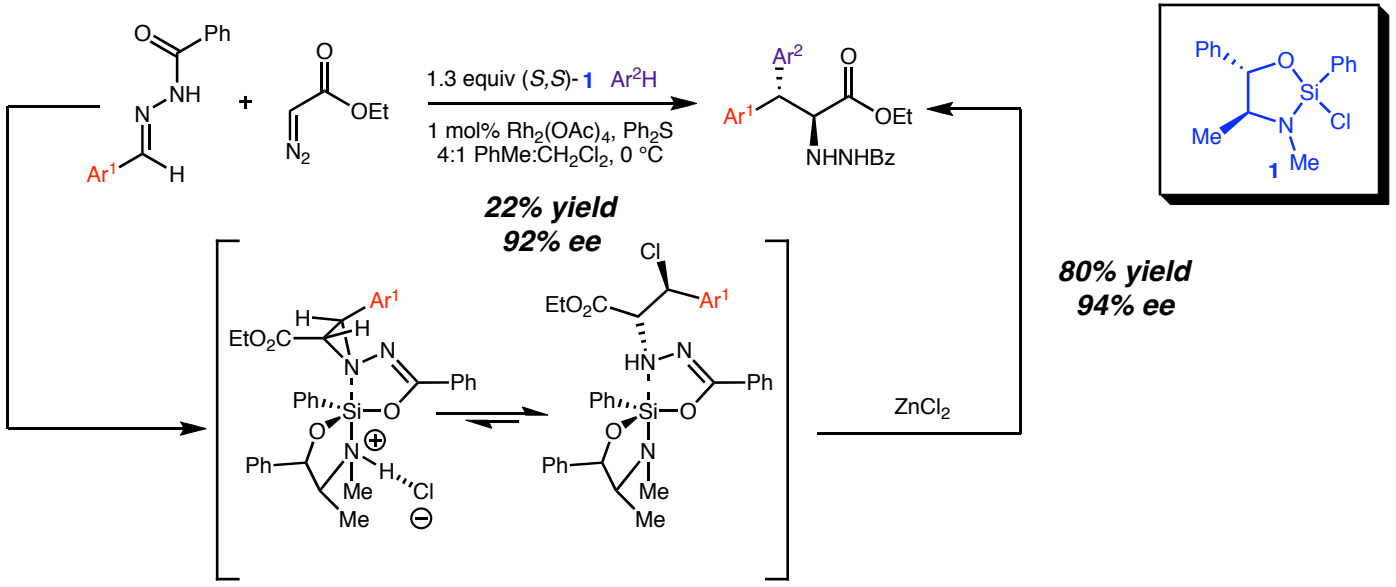
***81% yield***
***6:1 rr***
***86% ee***



***82% yield***
***7:1 rr***
***89% ee***

Valdez, S. C.; Leighton, J. L. *J. Am. Chem. Soc.*, **2009**, *131*, 14638–14639

# *Alternate Ring-Opening Nucleophiles*




- **Addition of electron rich arenes sluggish (72 h reaction times) and low yielding**
  - **Diastereochemical outcome implied equilibrium between two intermediates**
  - **Addition of a Lewis acid should favor aziridine intermediate**

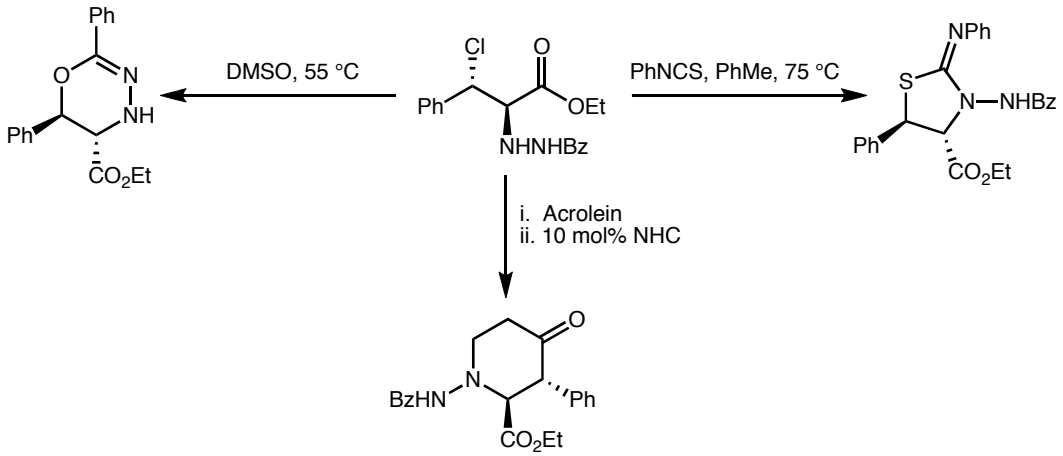
- **Brief survey of substrates showed good scope**
  - **Products obtained in good to moderate (50–80%) yields**
  - **Single regioisomers and diastereomers obtained with excellent enantioselectivity (>90% ee)**


Valdez, S. C.; Leighton, J. L. *J. Am. Chem. Soc.*, **2009**, *131*, 14638–14639

# *Applications and Conclusions*

- **General and highly efficient procedure to access β-chloro-α-hydrazido esters through an activated aziridine intermediate**

  **- One step to densely functionalized heterocycles**




- **Treatment with secondary nucleophiles access differentially substituted amino acid derivatives**

- **Future Directions**

  **- Expanding nucleophile scope**