



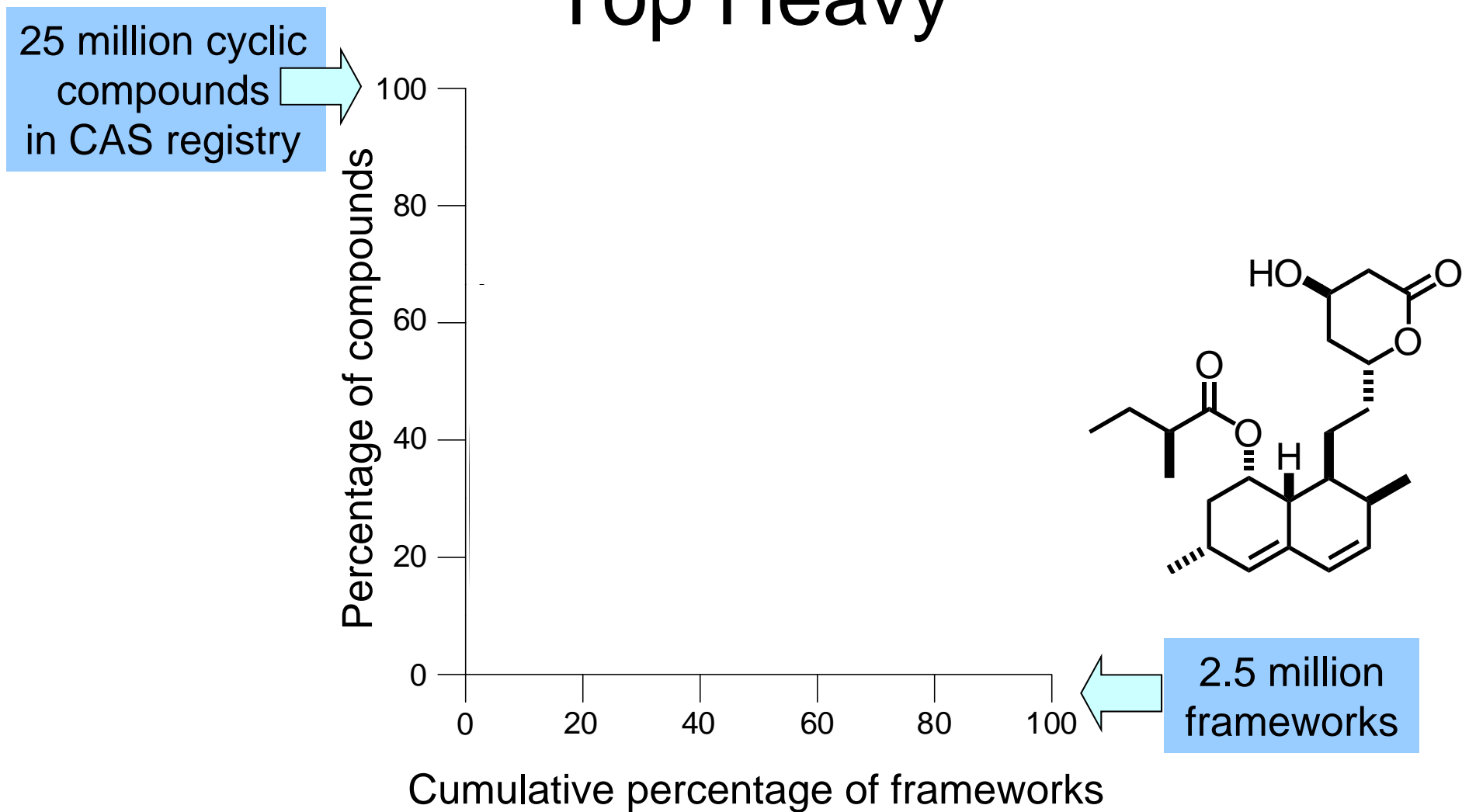
# The Development of Synthetic Approaches that Allow the Systematic Exploration of Chemical Space



[www.asn.leeds.ac.uk](http://www.asn.leeds.ac.uk)

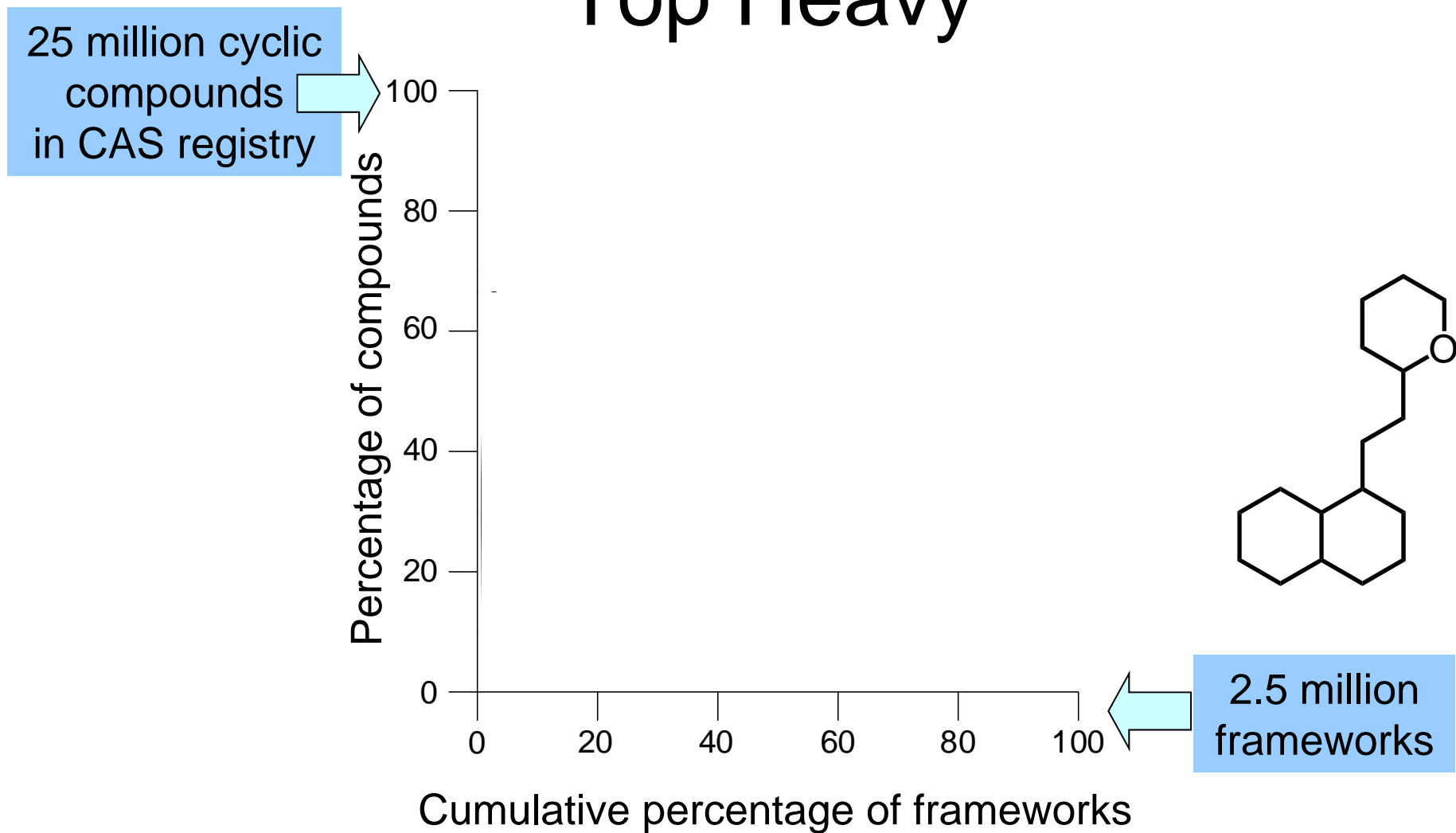
Prof. Adam Nelson  
School of Chemistry, University of Leeds, UK  
[a.s.nelson@leeds.ac.uk](mailto:a.s.nelson@leeds.ac.uk)

# The Organic Chemistry Universe is “Top Heavy”



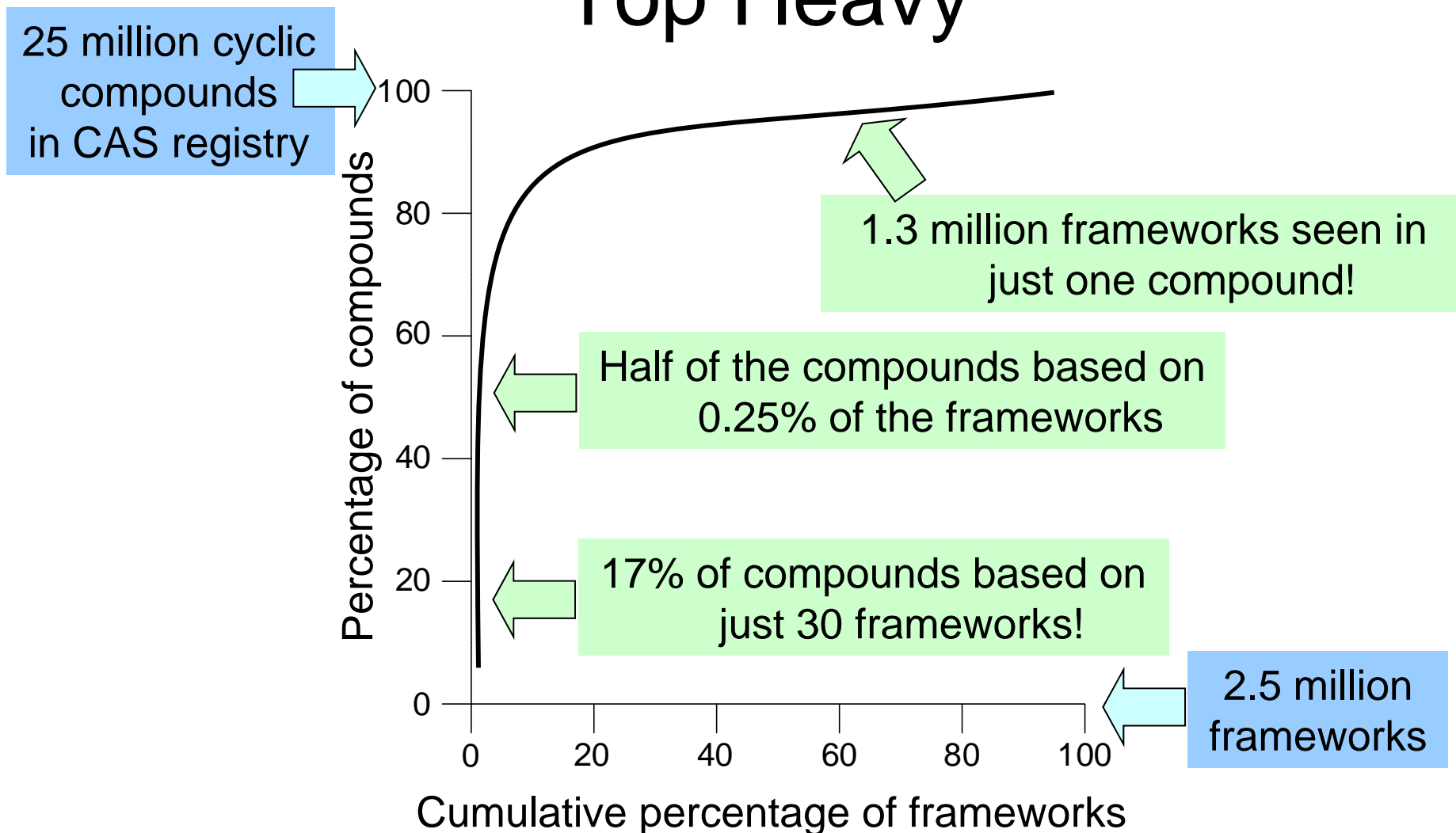
See A. H. Lipkus *et al*, *J. Org. Chem.* 2008, **73**, 4443

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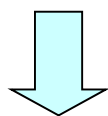
# The Organic Chemistry Universe is “Top Heavy”



See A. H. Lipkus *et al*, *J. Org. Chem.* 2008, **73**, 4443

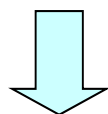
# HTS collections focus on a narrow range of cores

Commercial HTS collection  
( $\sim 10^6$  compounds)



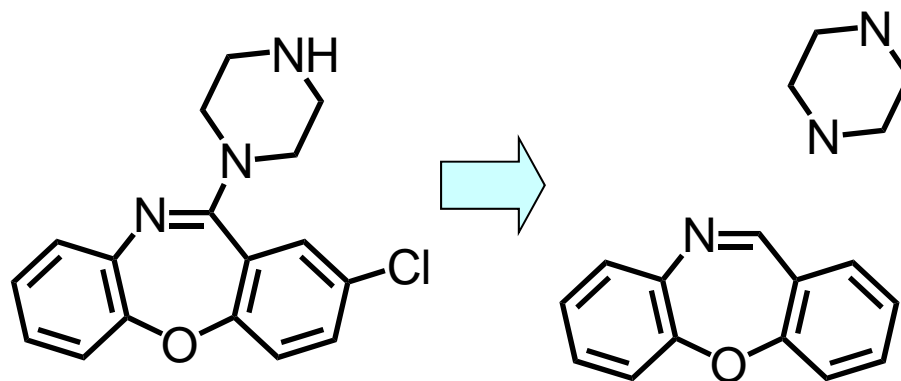
random selection

$\sim 10^4$  compounds



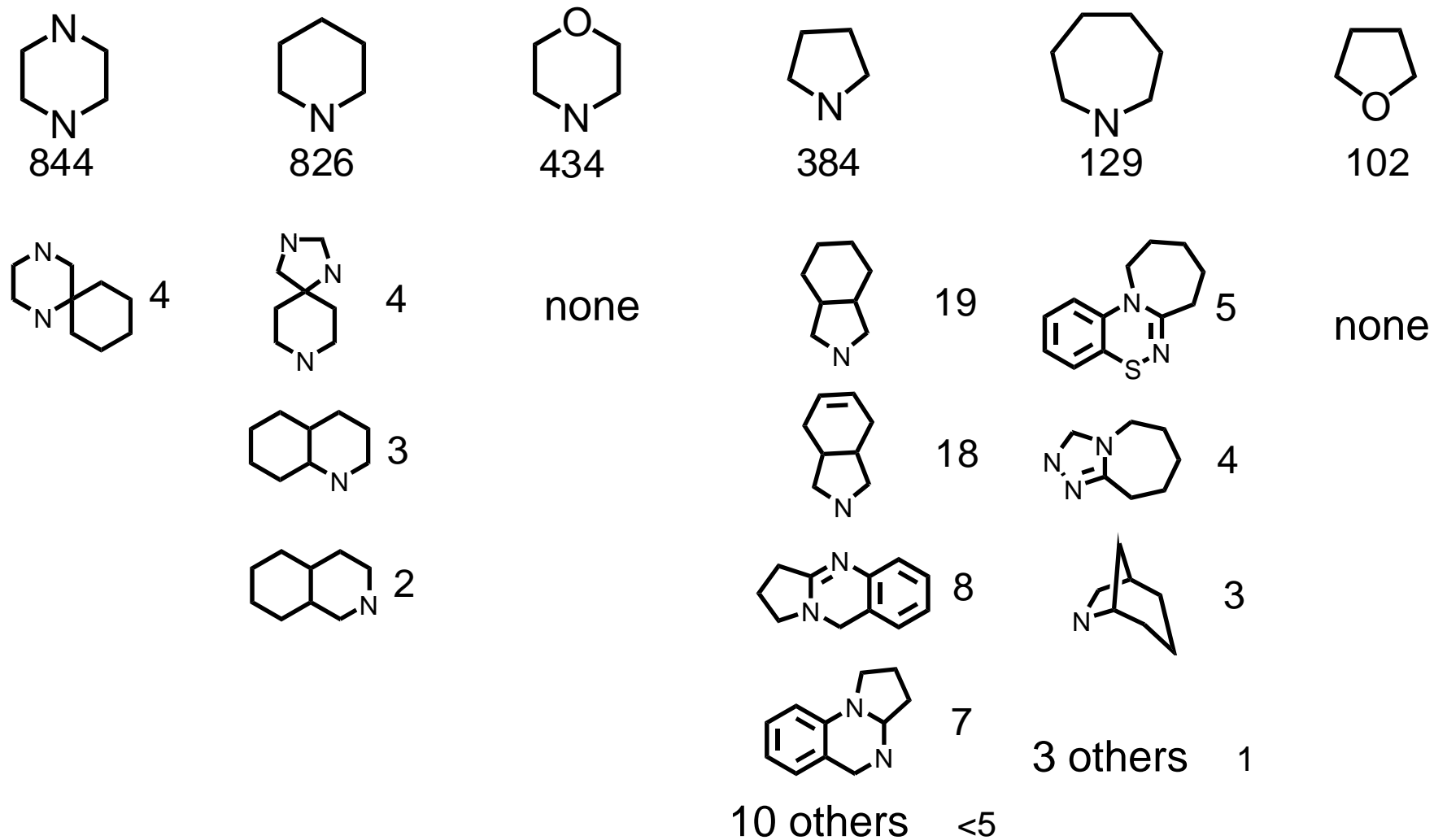
core analysis

Distribution of ring systems



With Stuart Warriner

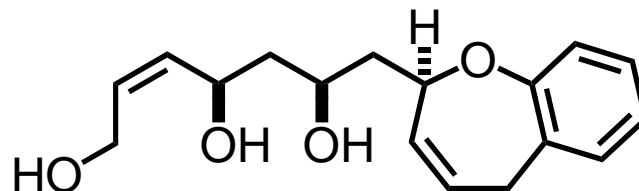
# Most common saturated ring systems in a commercial HTS library



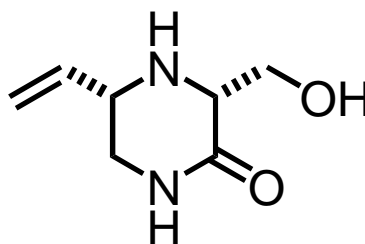
With Stuart Warriner

# Synthetic approaches to skeletally-diverse small molecules

1. Natural product-like molecules of unprecedented scaffold diversity



2. Scaffold diverse drug like cores

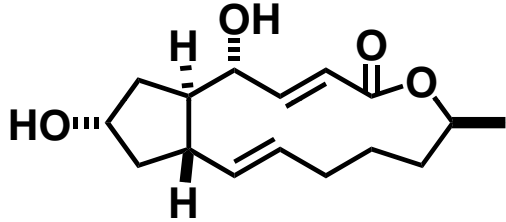


Designed to retain lead-like properties after derivatisation

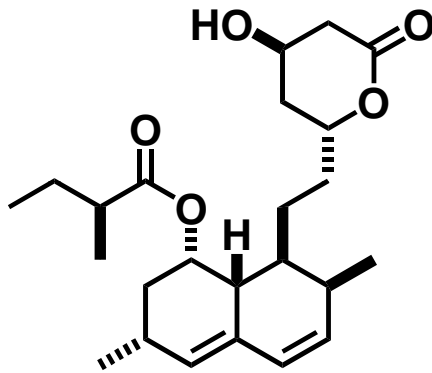
Natural Products: Inspiration for  
libraries of useful ligands?



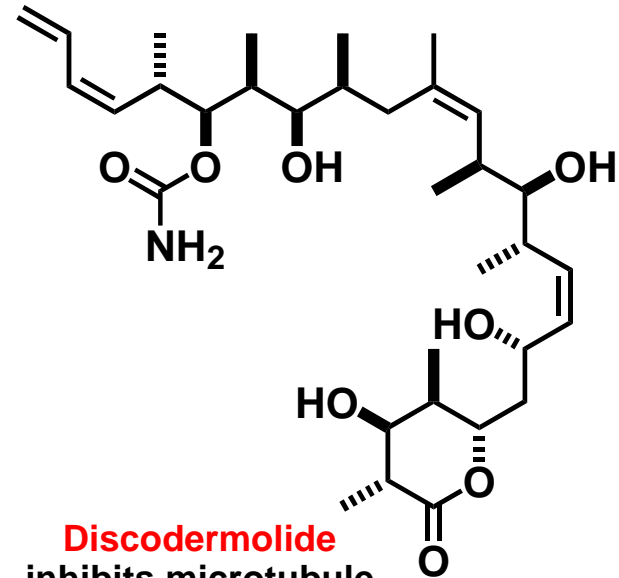
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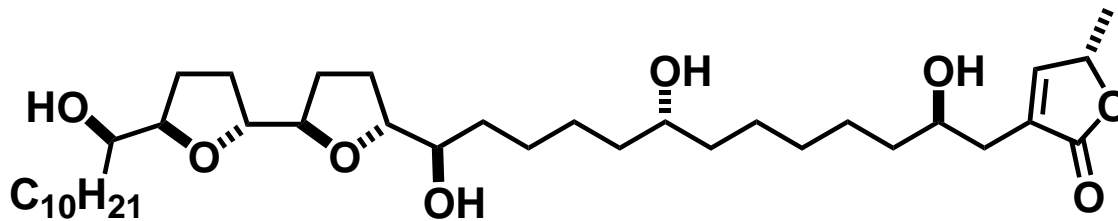
**(+)-Brefeldin A**  
inhibits Arf1p and, hence,  
protein trafficking  
from ER to Golgi



**Lovastatin** inhibits  
HMG-CoA reductase  
(anticholesterol agent)

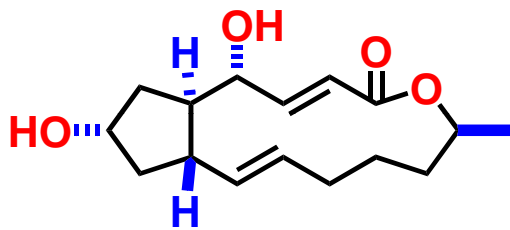


**Discodermolide**  
inhibits microtubule  
polymerisation

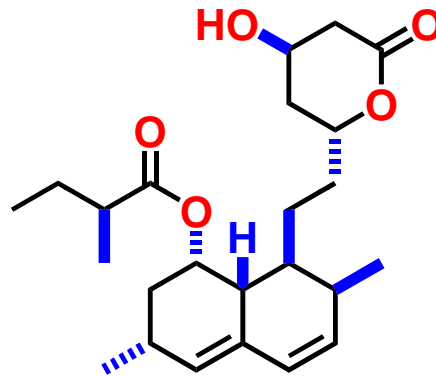


**10-Hydroxyasimicin**  
binds to mitochondrial complex I  
(fungicide and anti-tumour agent)

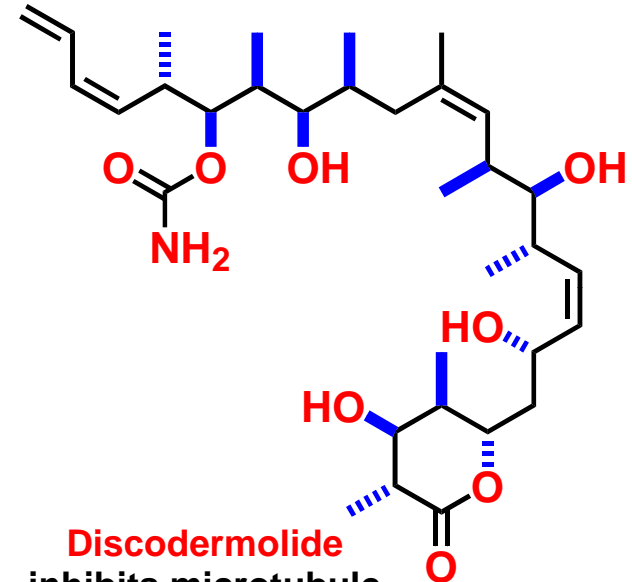
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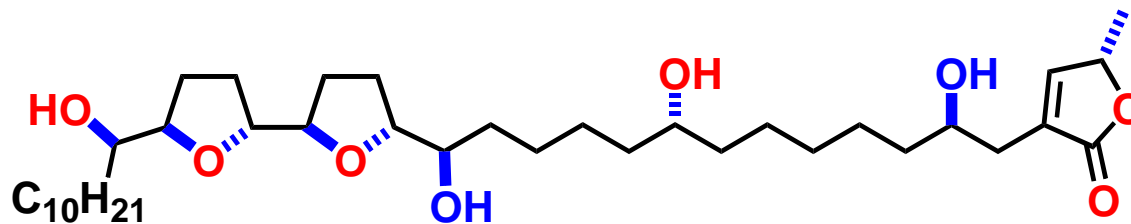
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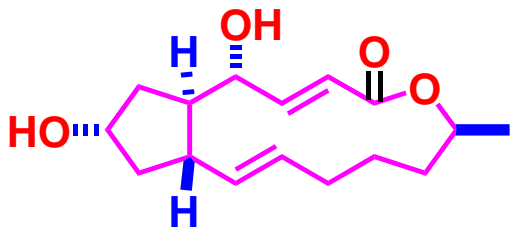


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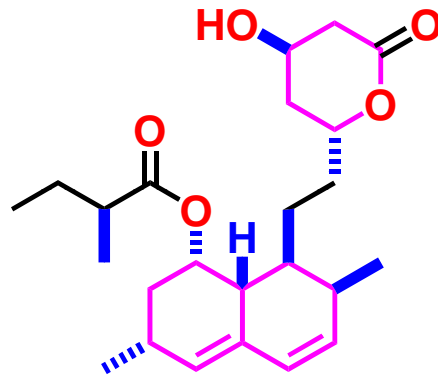


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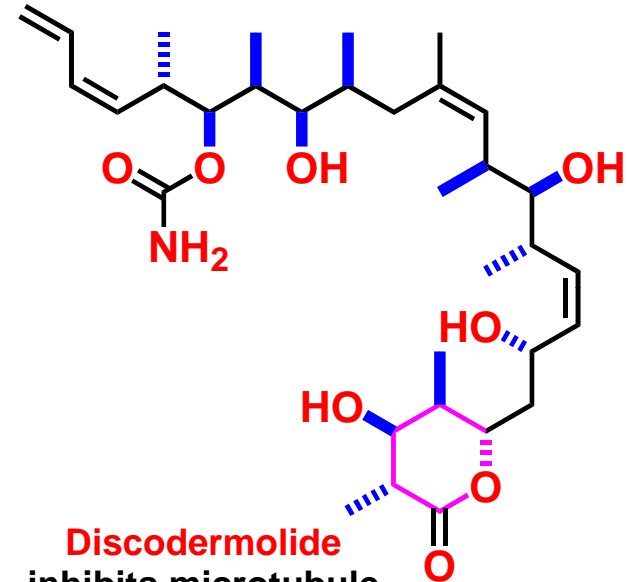
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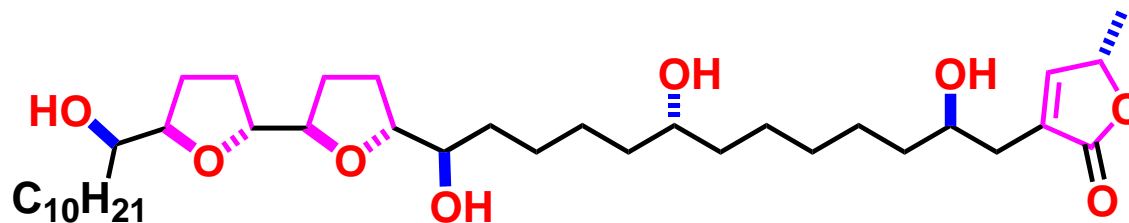
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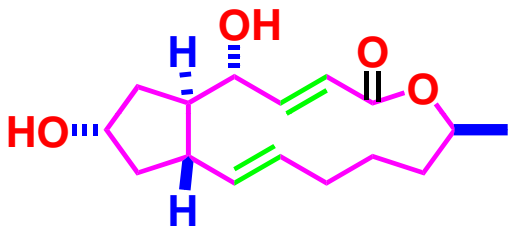


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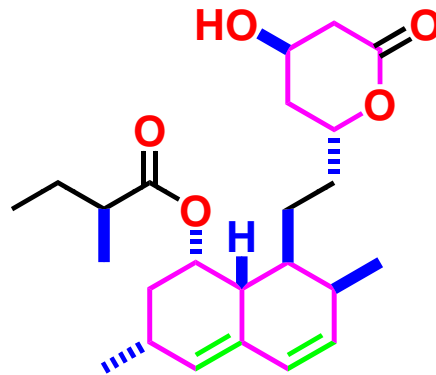


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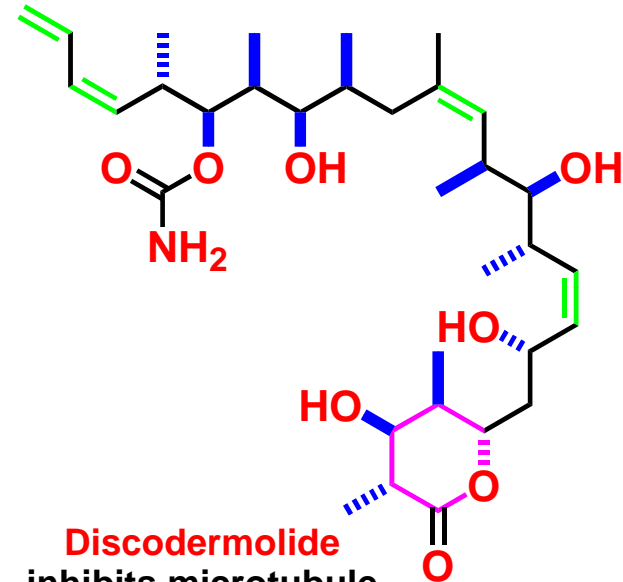
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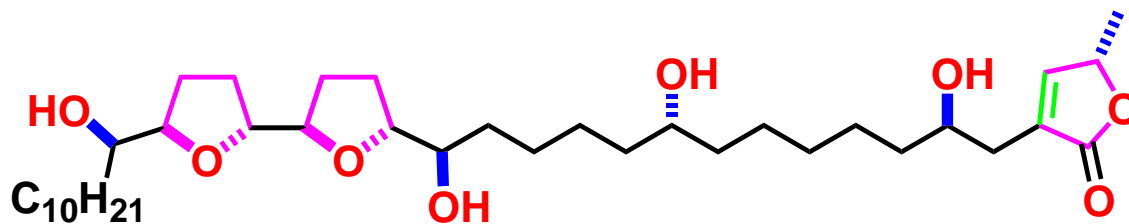
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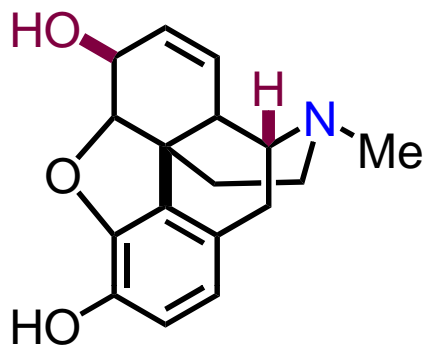


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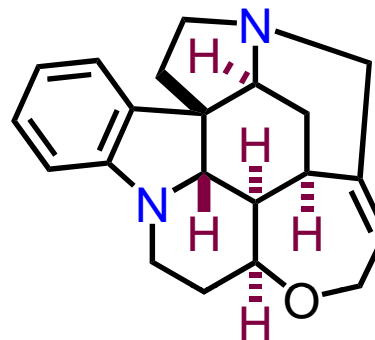


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# Inspiration from Alkaloid Natural Products



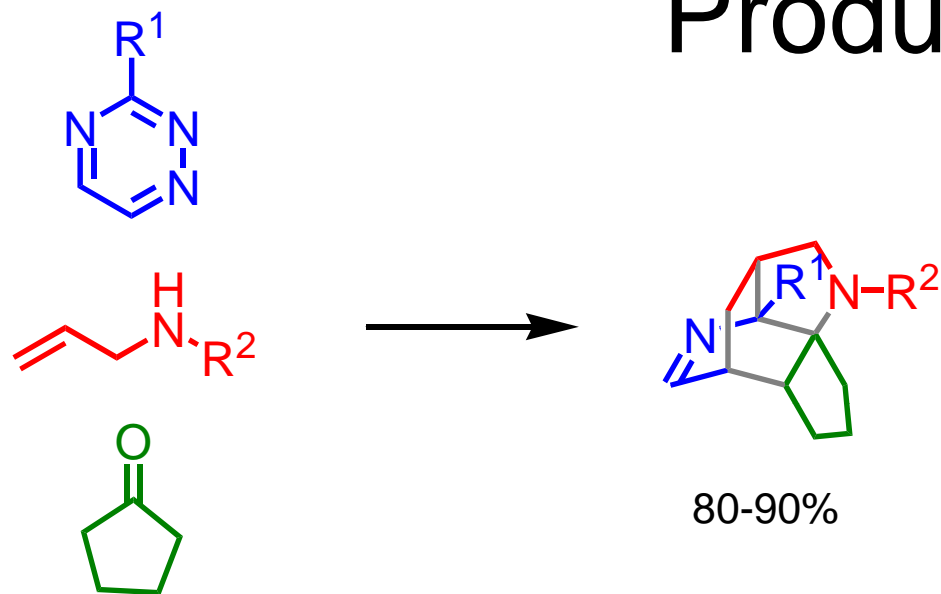
Morphine



Strychnine

with Sarah Murrison, Christian Einzinger, Steve Bartlett and Dan Tetlow

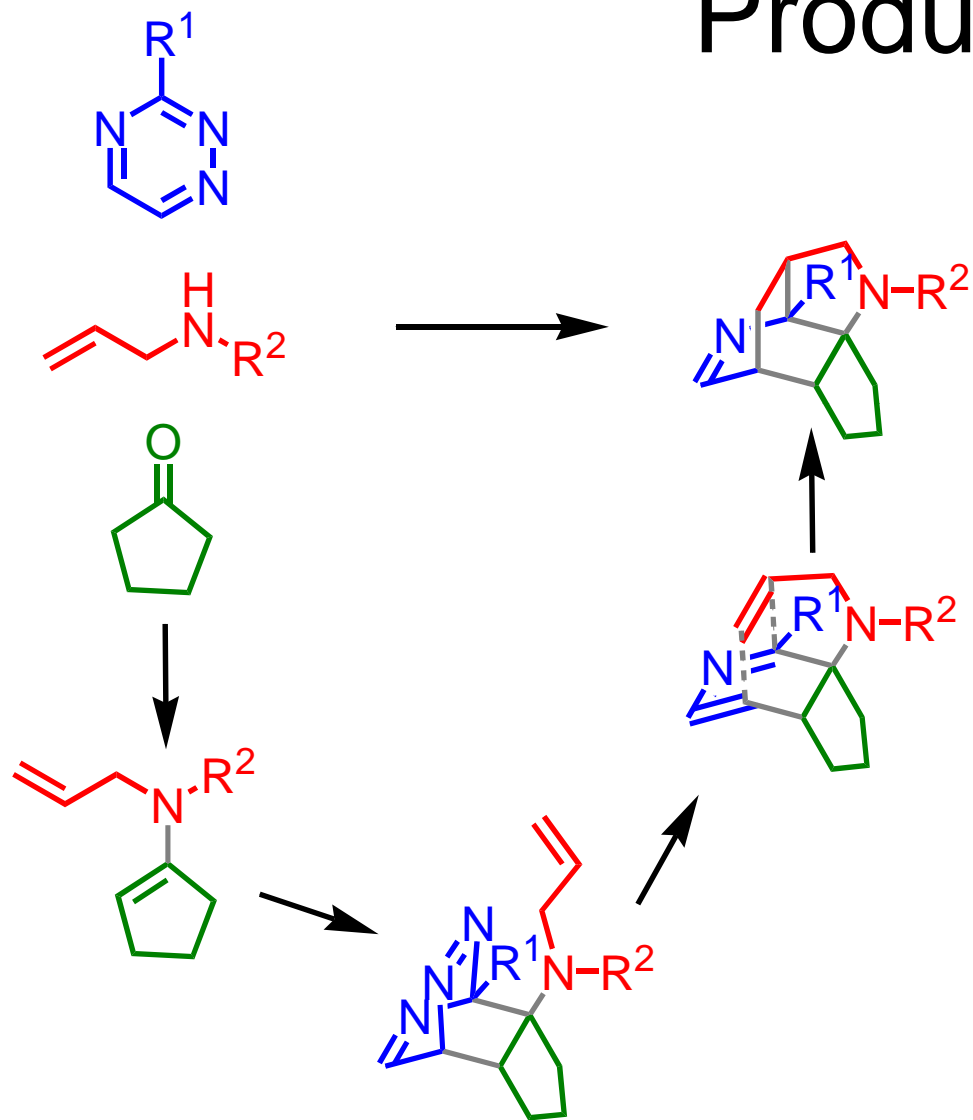
# Inspiration from Alkaloid Natural Products



For similar cascades, see: S. A. Raw and R. J. K. Taylor,  
*J. Am. Chem. Soc.* 2004, 126, 12260.

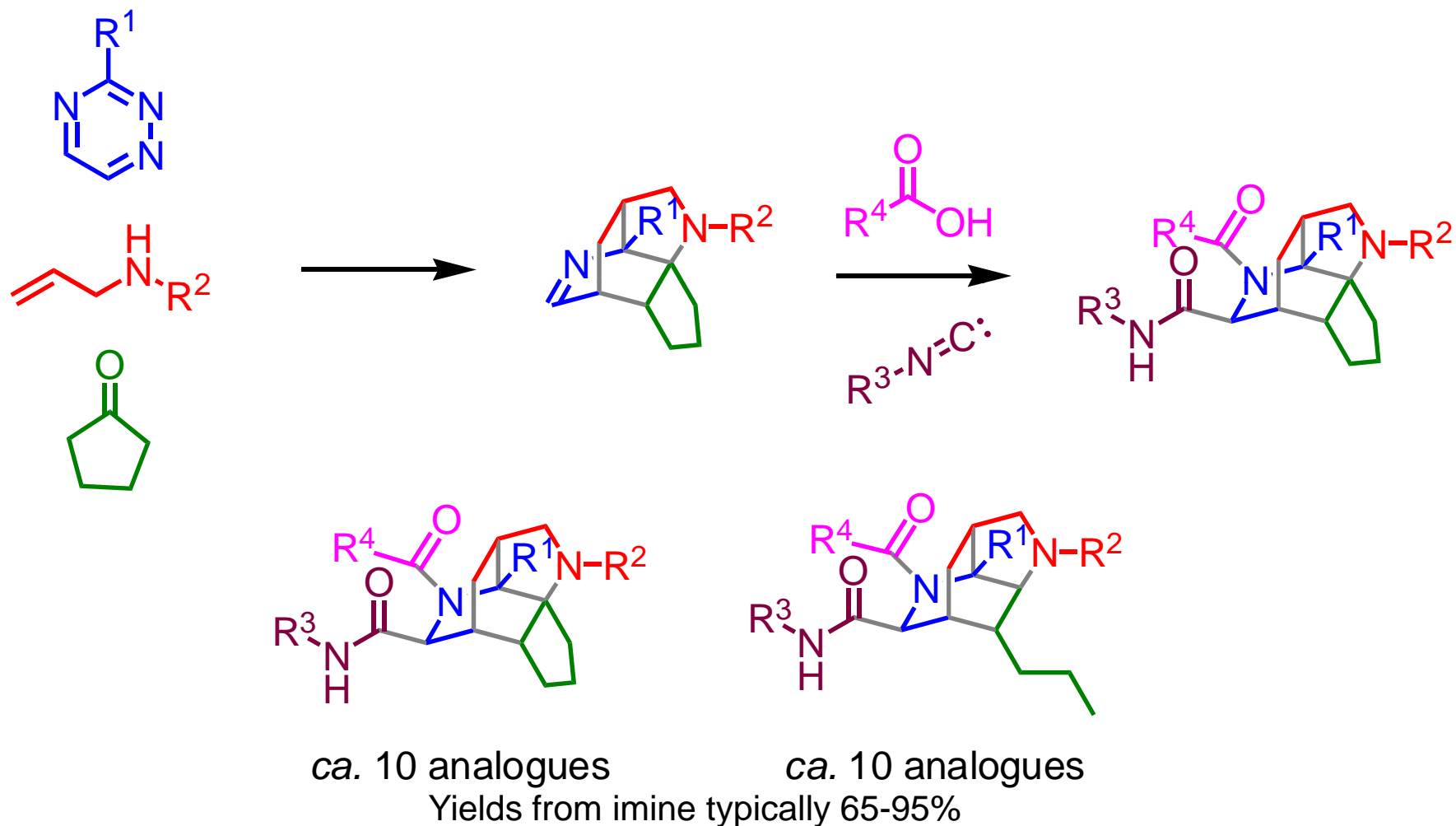
with Sarah Murrison, Christian Einzinger, Steve Bartlett and Dan Tetlow

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with Sarah Murrison, Christian Einzinger, Steve Bartlett and Dan Tetlow

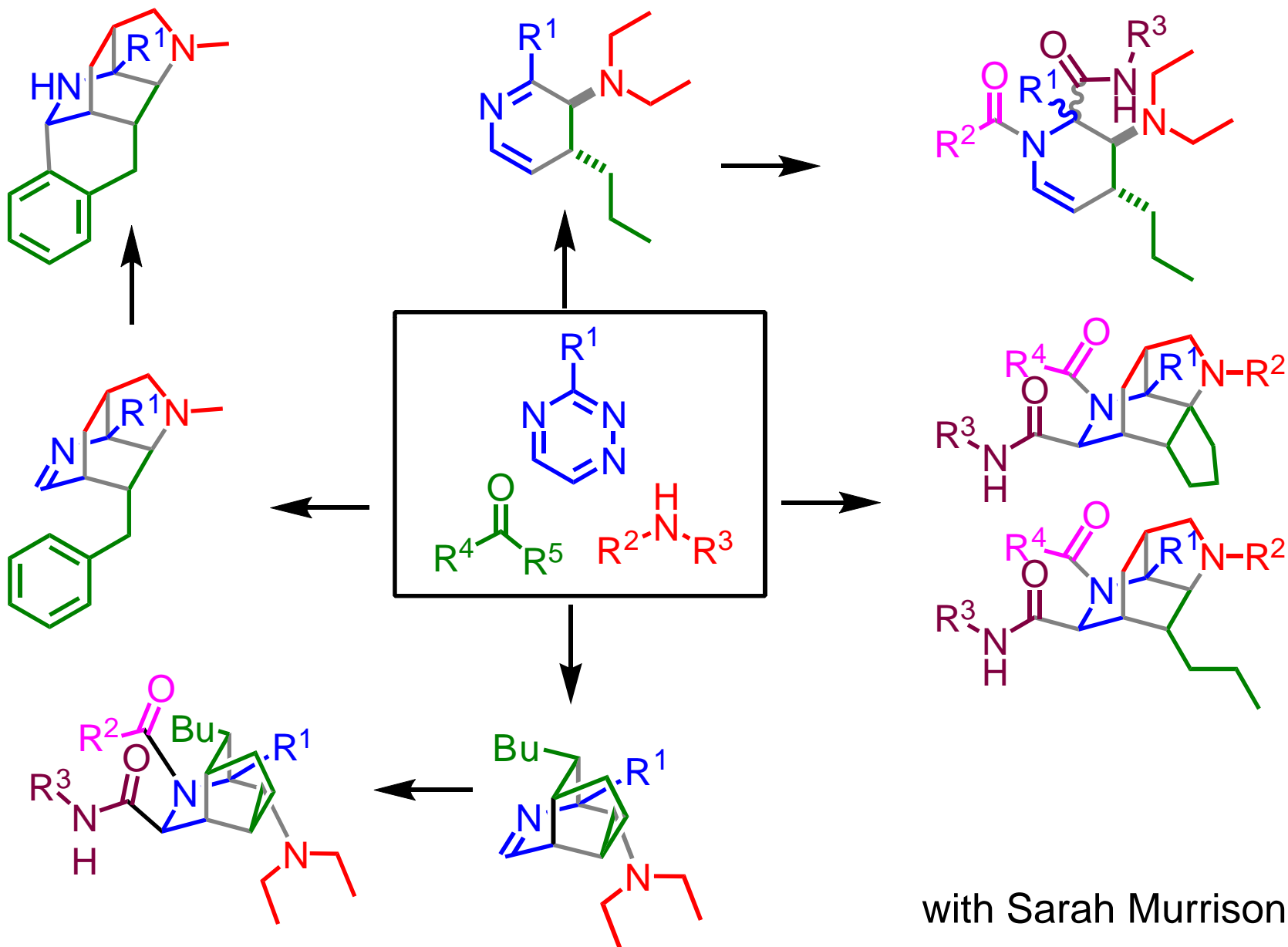
# Inspiration from Alkaloid Natural Products



with Sarah Murrison, Christian Einzinger, Steve Bartlett and Dan Tetlow



# Substituents can control the scaffold



with Sarah Murrison

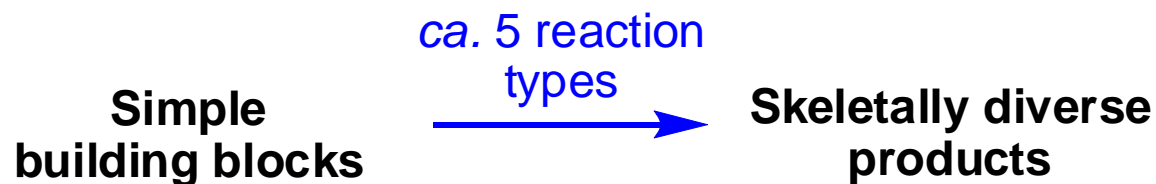
# Aim

To develop reliable methodology for the diversity-oriented synthesis of 'natural product-like' molecules

Important guiding features:

- broadly similar structural features to natural products but targeting different regions of biologically-relevant chemical space
- high skeletal, stereochemical and substitutional diversity
- amenable to parallel synthesis

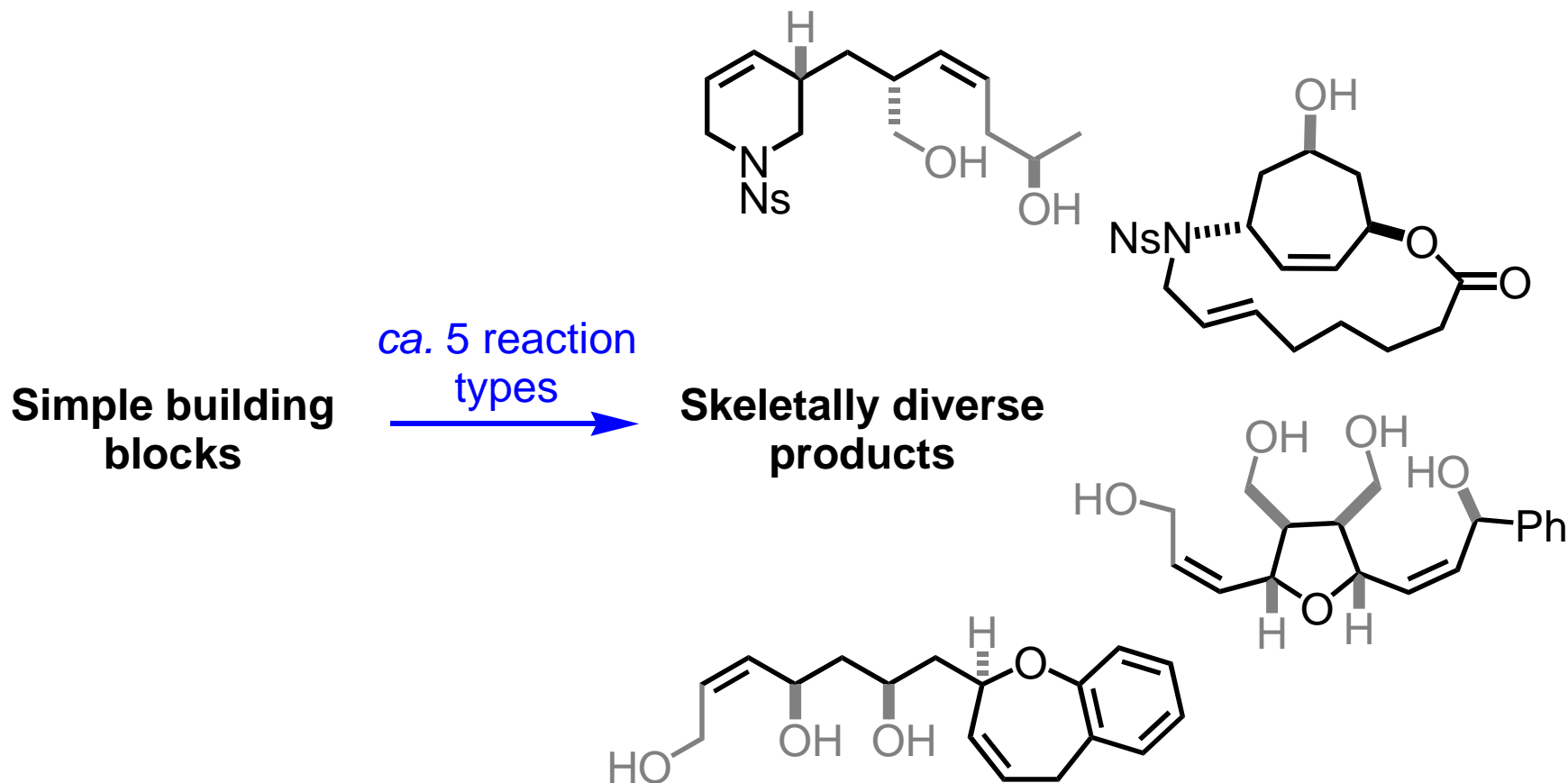
# Aim



*Angew. Chem. Int. Ed.* 2009, **48**, 104 (VIP article)

See also following News and Views articles in *Nature* (Schreiber), *Nature Chem. Biol.* (Waldmann); Highlights in *Angew. Chem.* (Spring) and *Nature Chem*; follow-up articles in *C&E News* and *Science* (editors' choice); and selection by Biology Faculty of 1000.

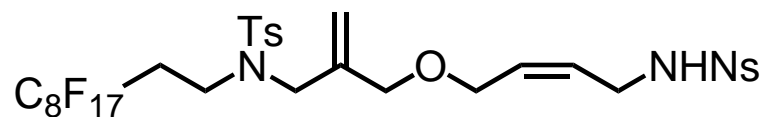
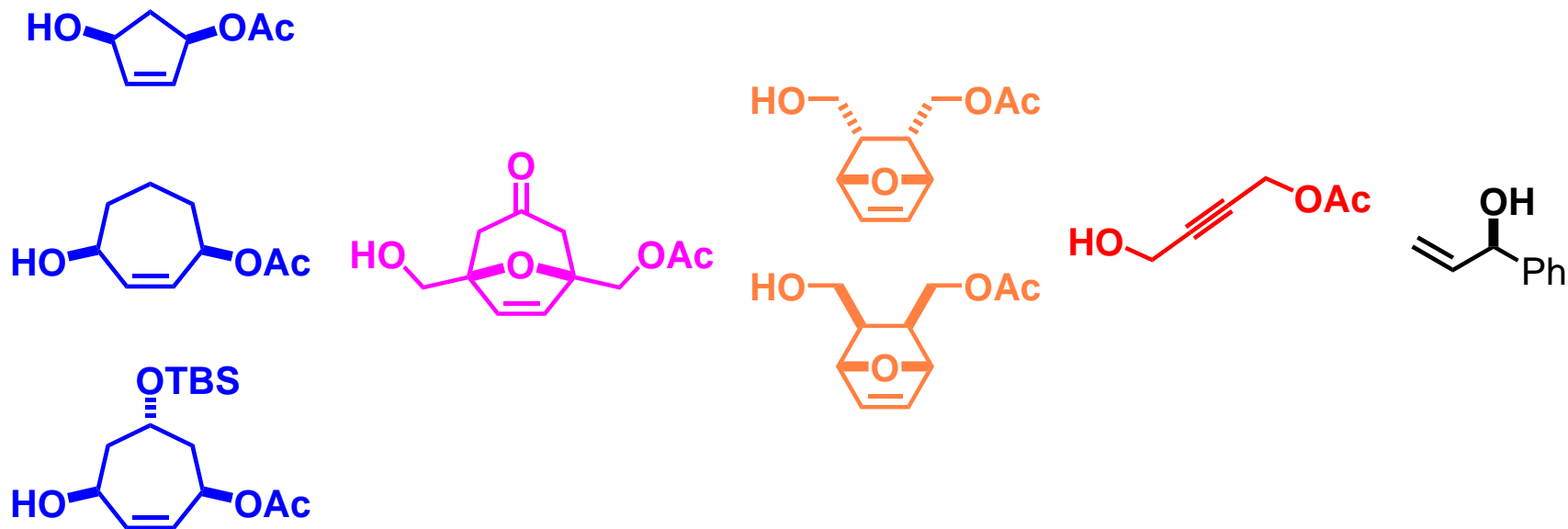
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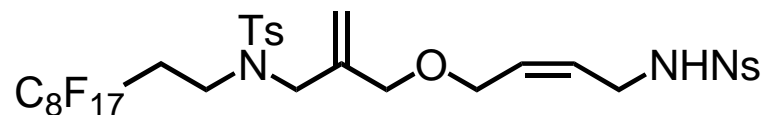
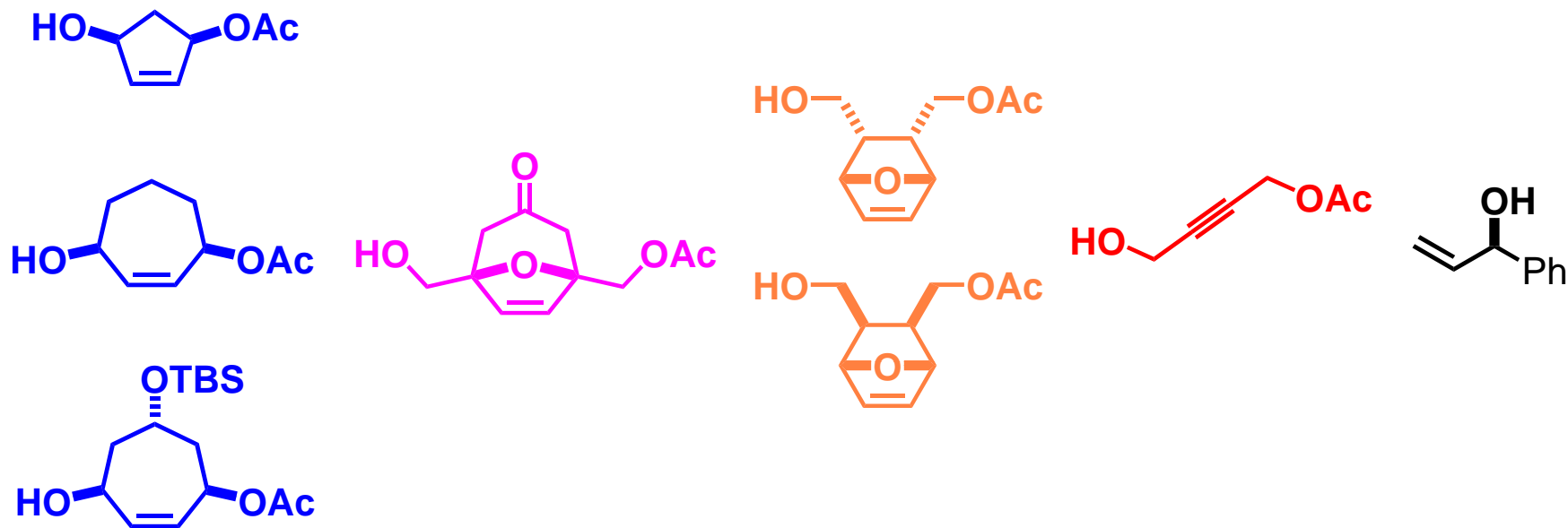
# An iterative DOS approach



Linker and Mitsunobu reactions: *J. Org. Chem* 2008, **73**, 2752

Silaketel formation: *Org. Biomol. Chem.* 2008, **6**, 1734

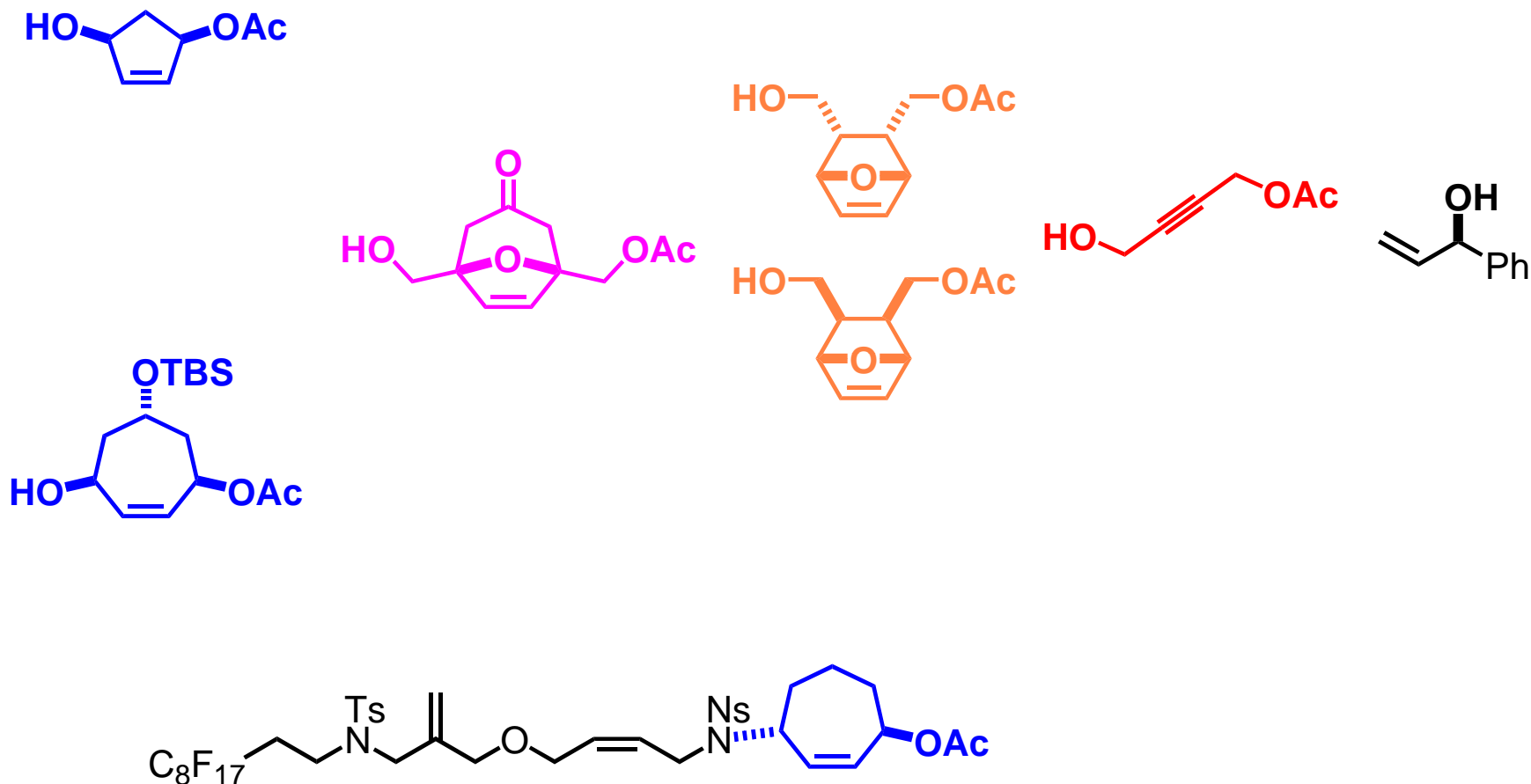
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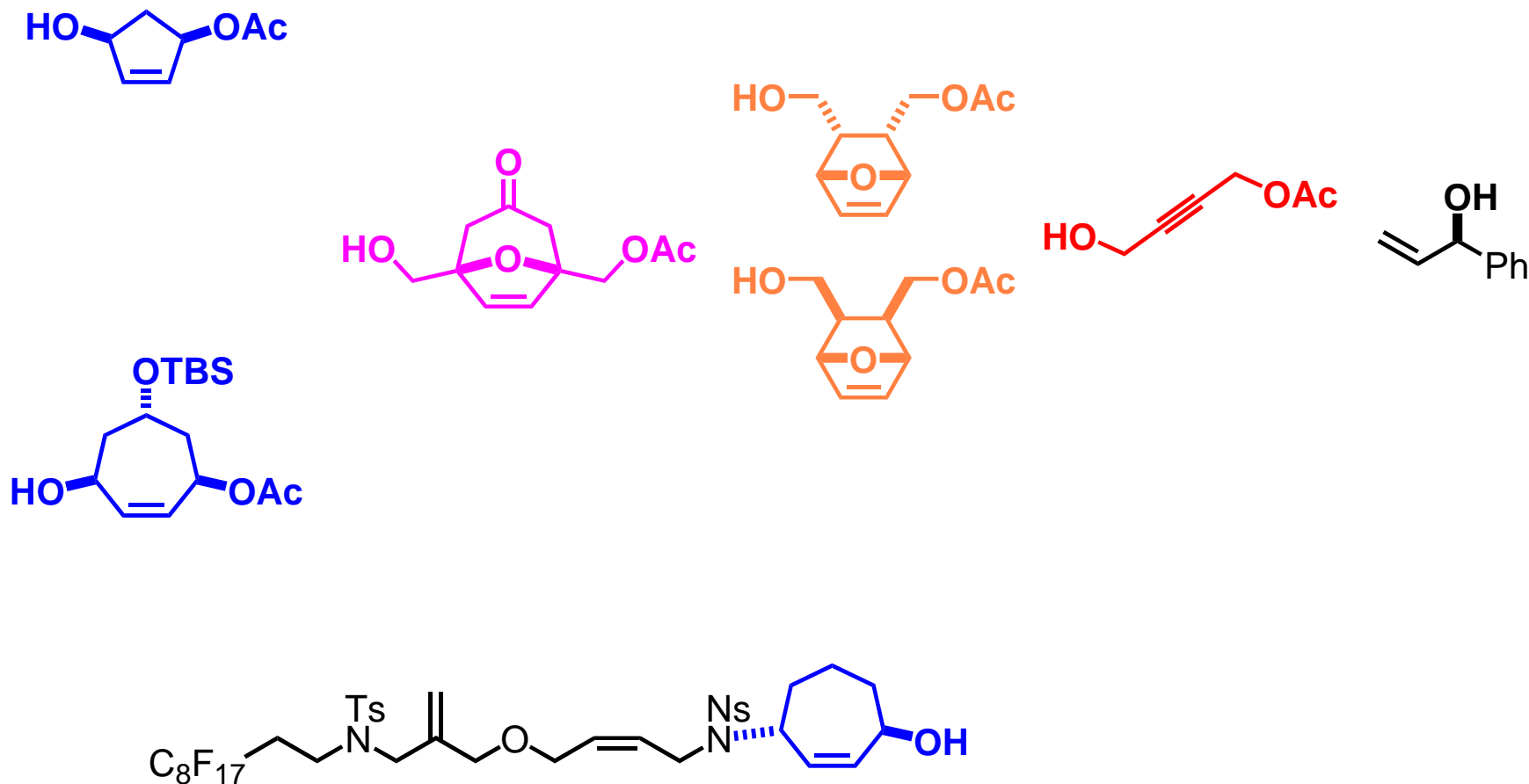
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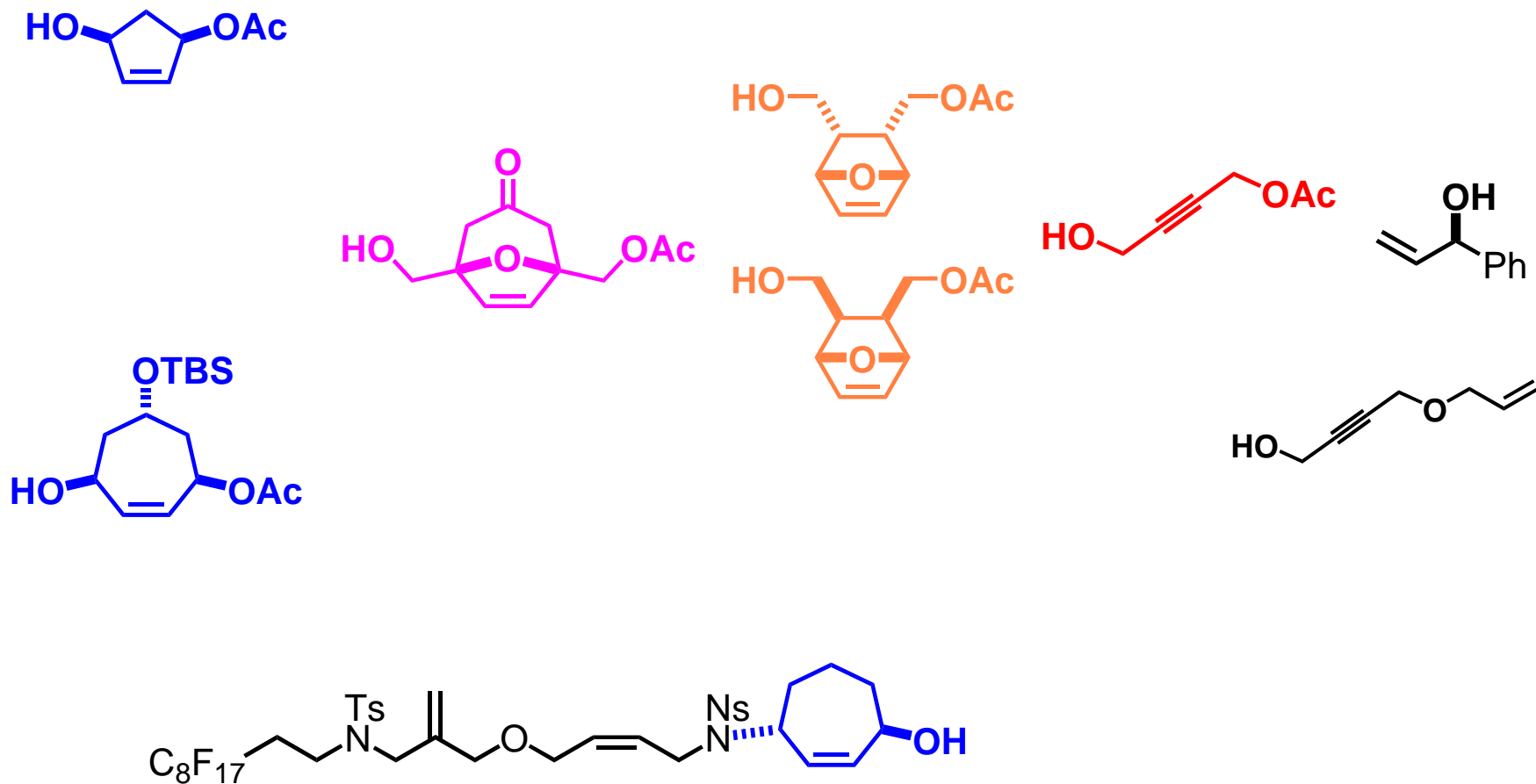


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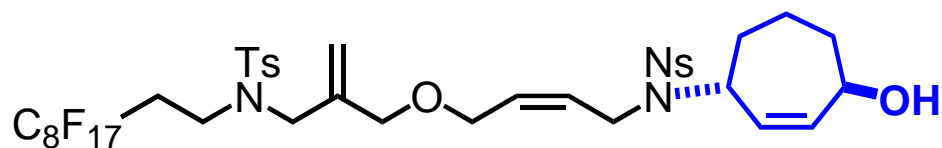
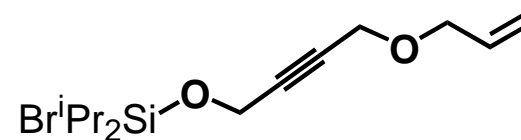
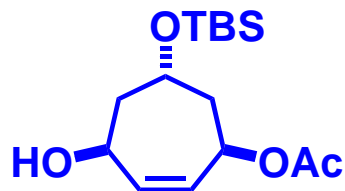
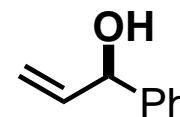
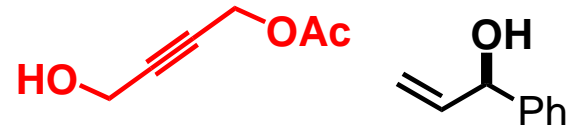
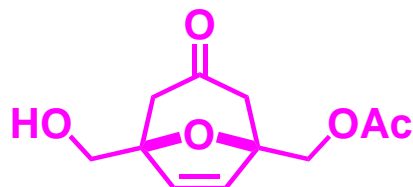


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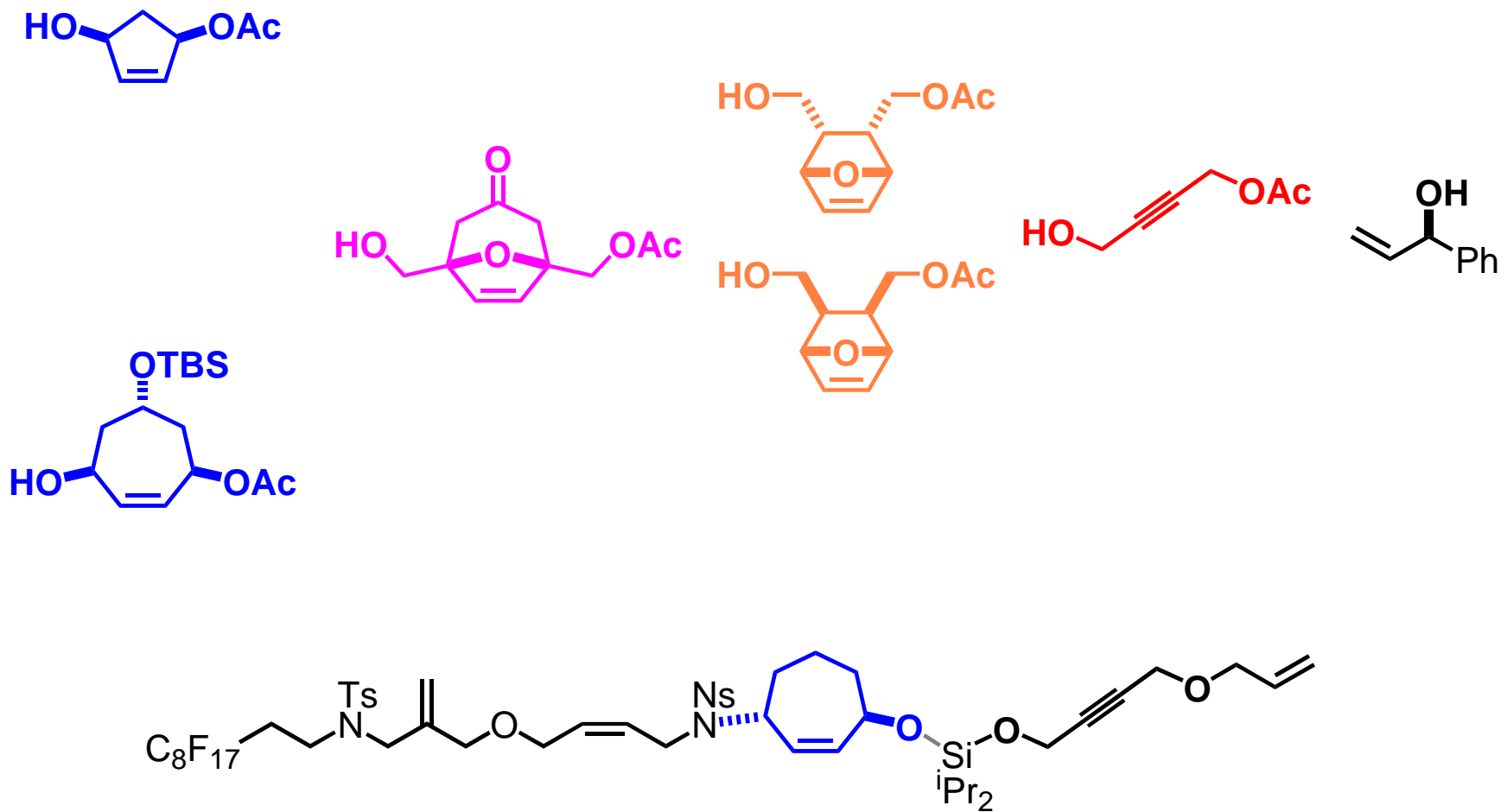
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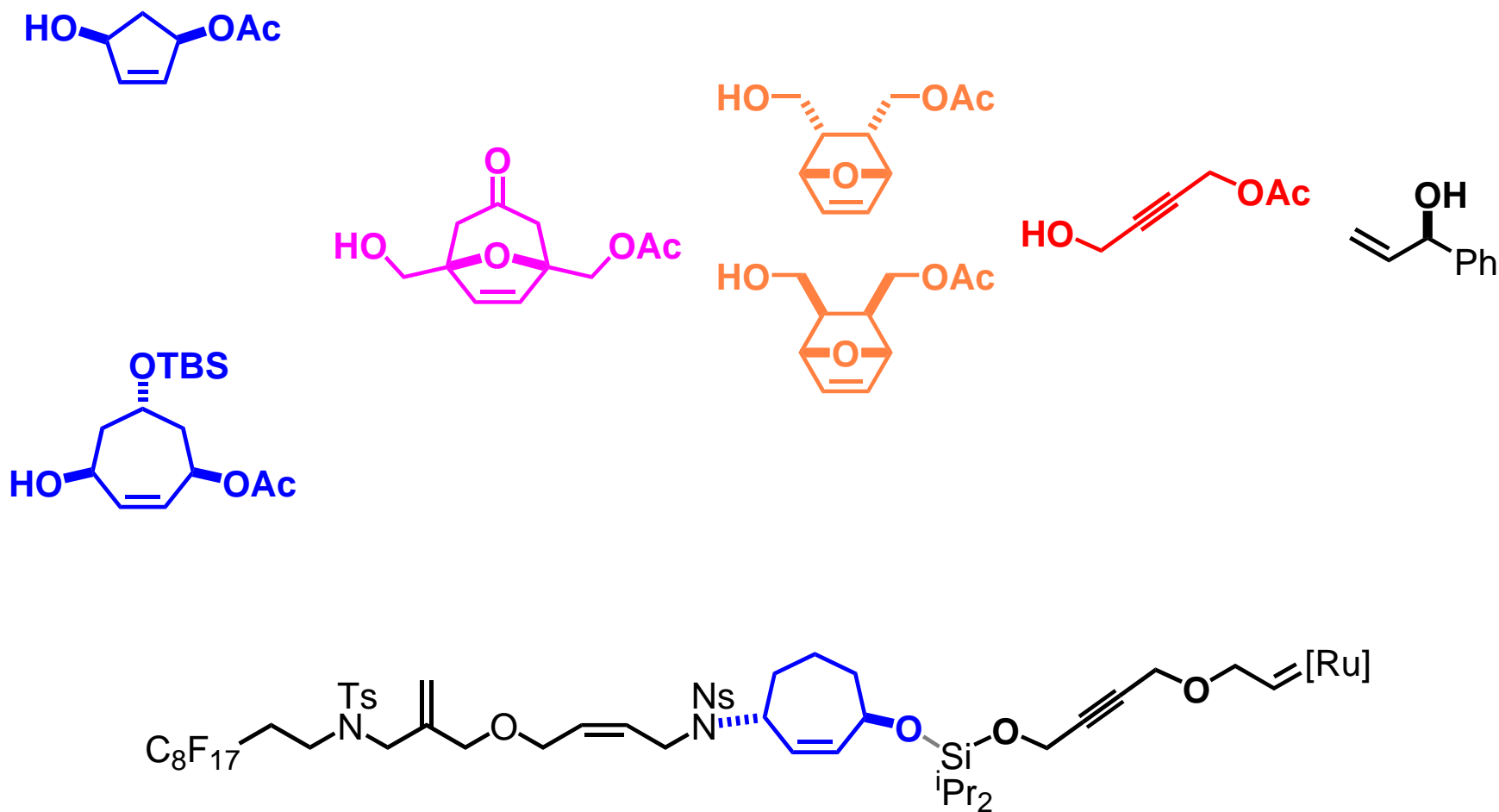
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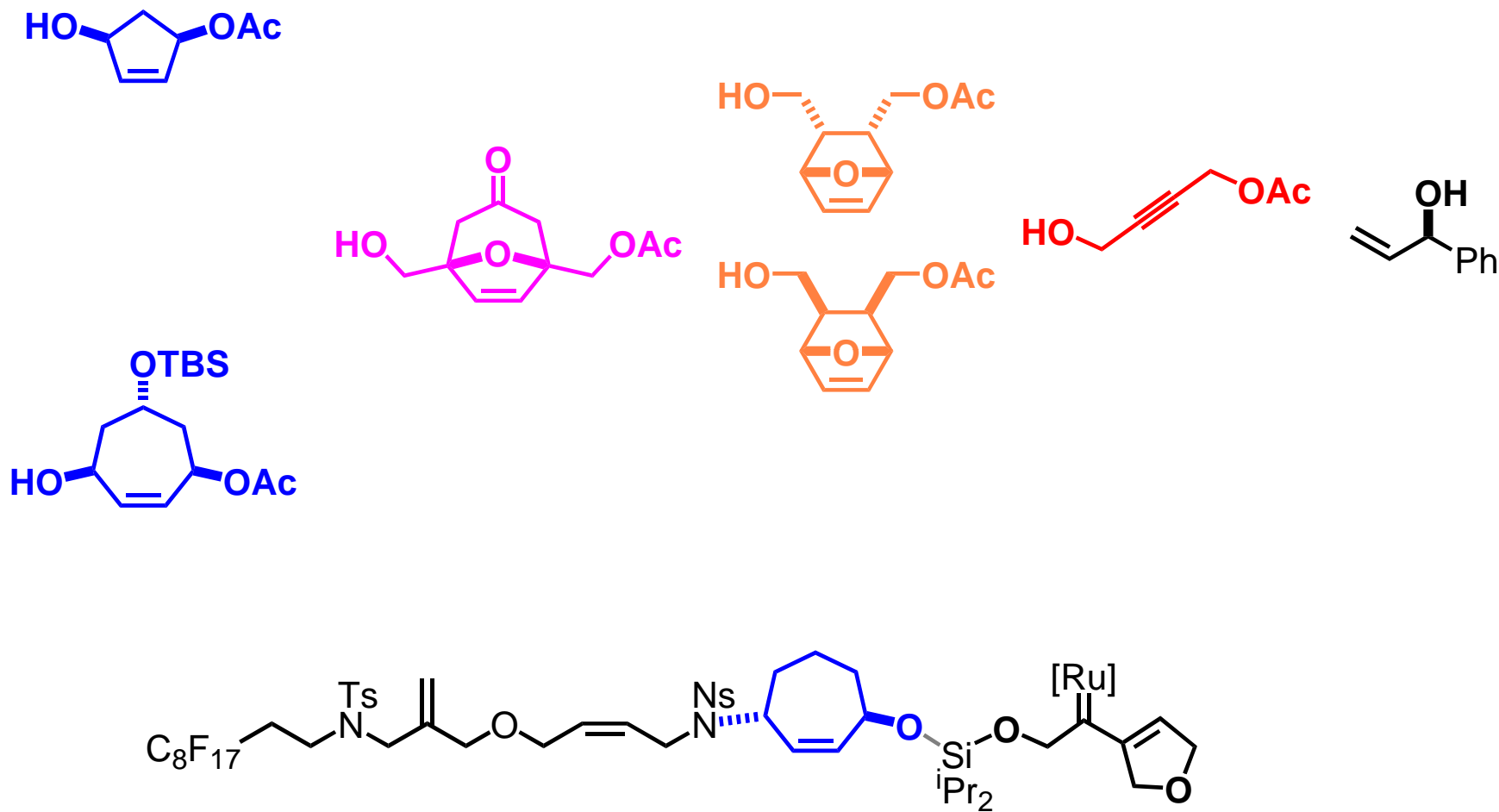
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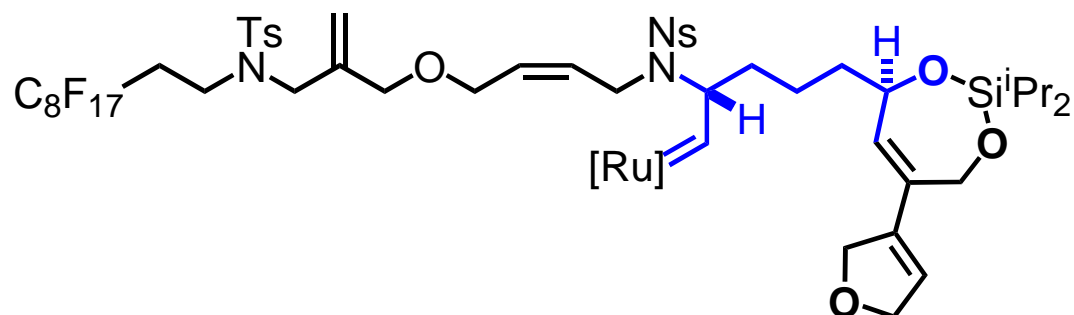
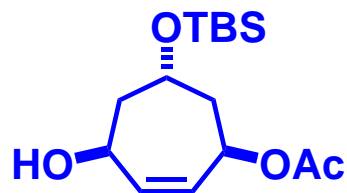
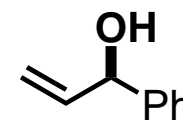
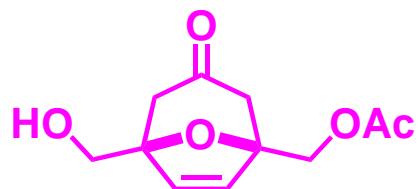
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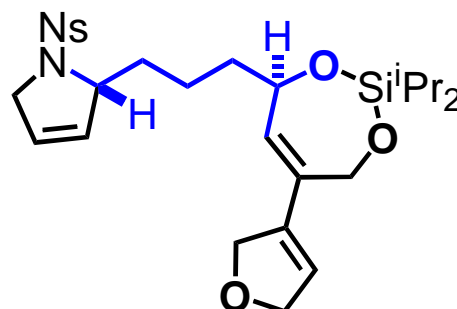
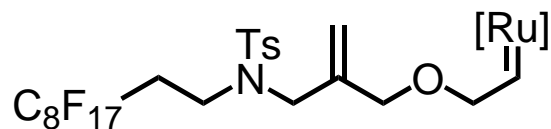
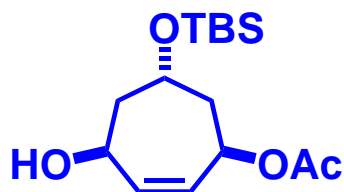
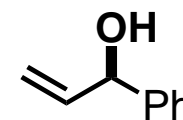
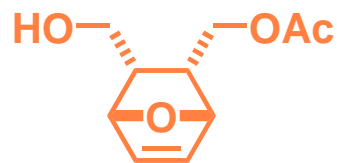
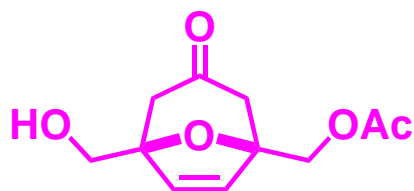
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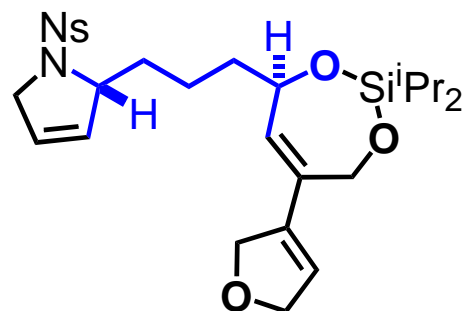
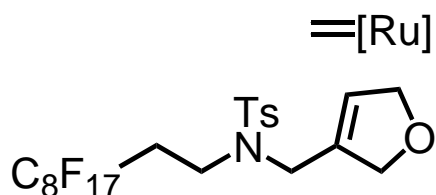
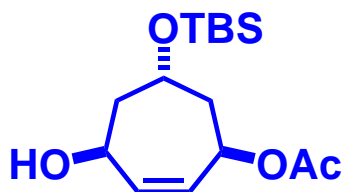
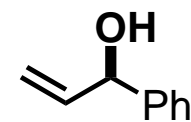
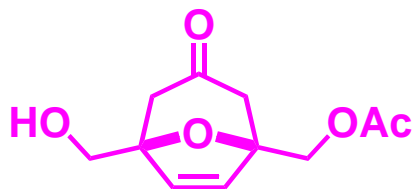
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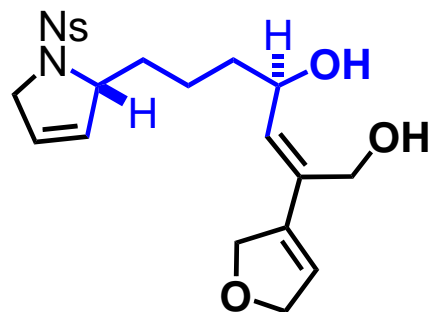
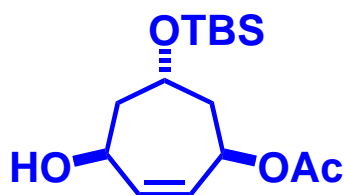
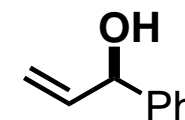
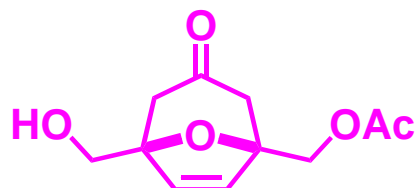


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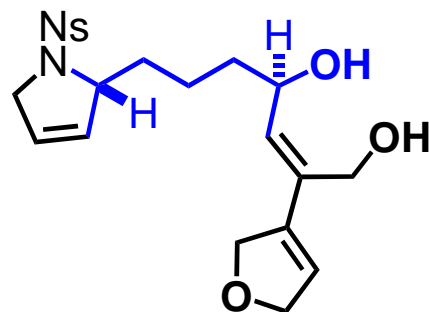
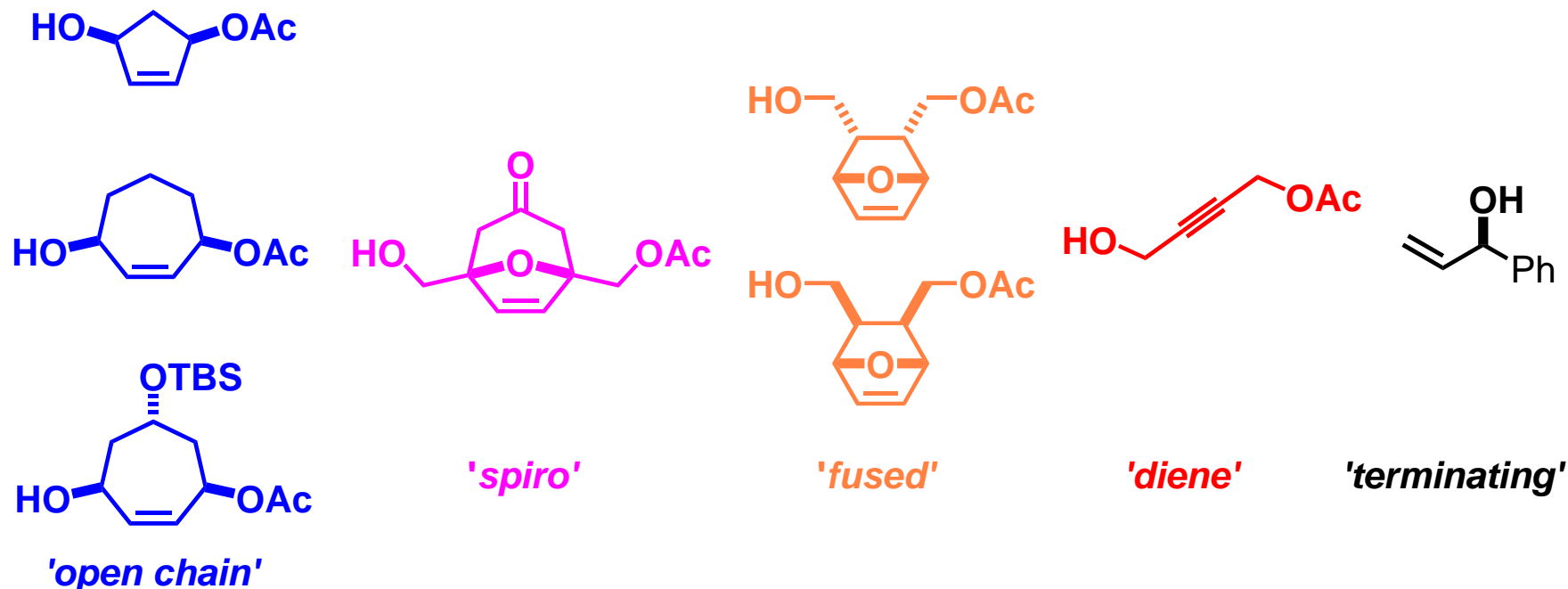
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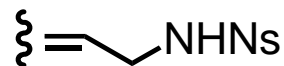
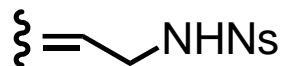
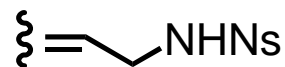
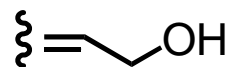
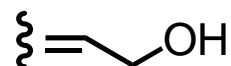
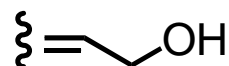
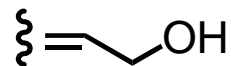
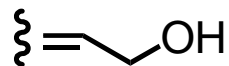
# An iterative DOS approach



Linker and Mitsunobu reactions: *J. Org. Chem* 2008, **73**, 2752

Silaketals formation: *Org. Biomol. Chem.* 2008, **6**, 1734

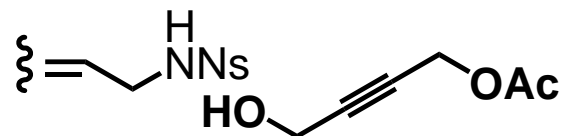
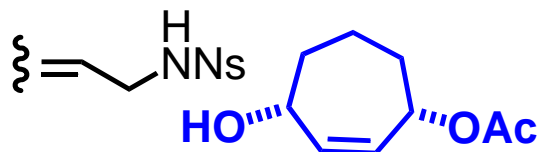
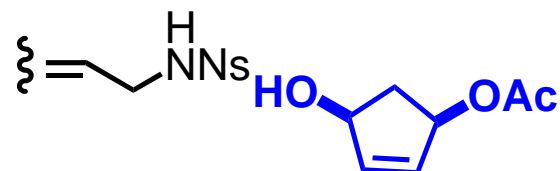
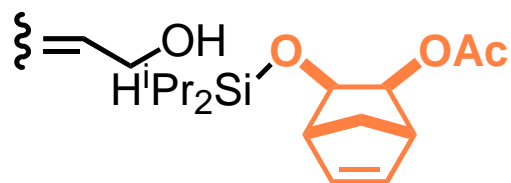
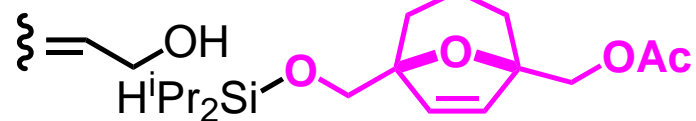
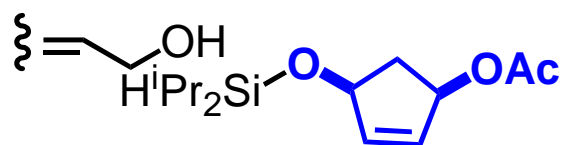
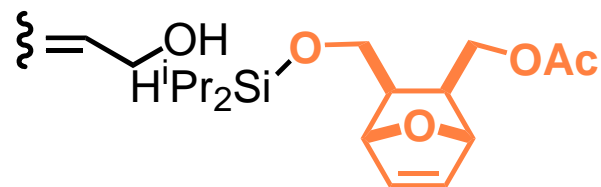
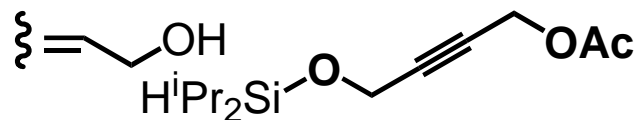
# Skeletally diverse natural product-like compounds: Iteration 1



Linker and Mitsunobu reactions: *J. Org. Chem* 2008, **73**, 2752

Silaketal formation: *Org. Biomol. Chem.* 2008, **6**, 1734

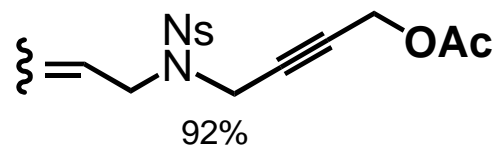
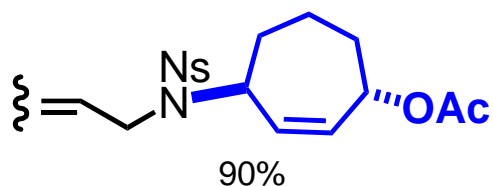
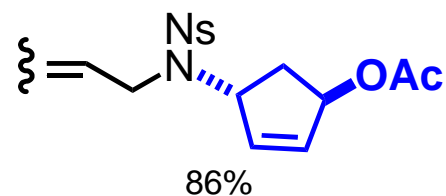
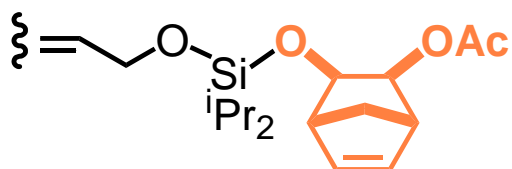
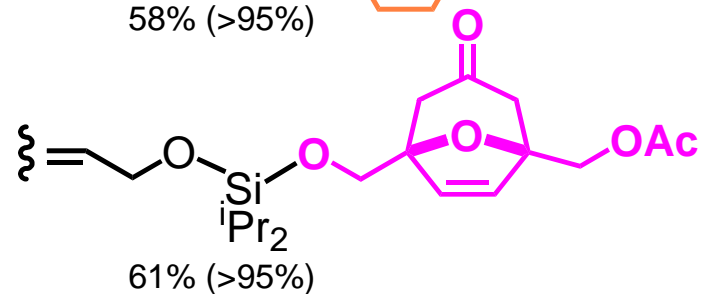
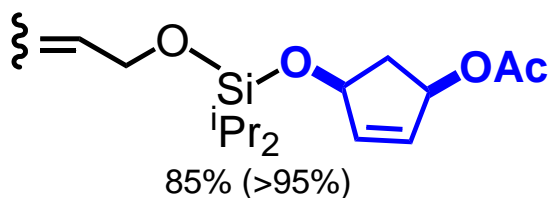
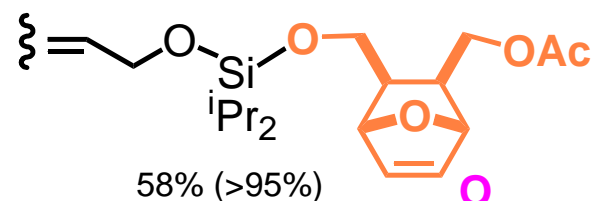
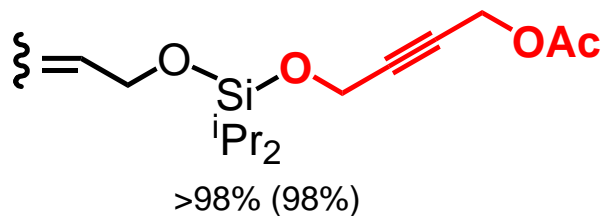
# Skeletally diverse natural product-like compounds: Iteration 1



1. Mitsunobu or silyl ether formation; 2. FSPE

with Chris Cordier, Stuart Leach and Daniel Morton

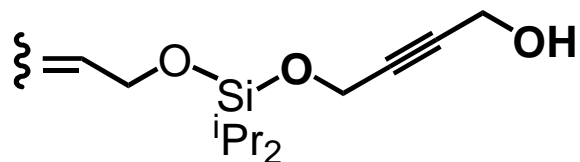
# Skeletally diverse natural product-like compounds: Iteration 1



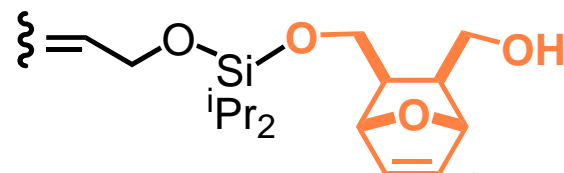
1. Mitsunobu or silyl ether formation; 2. FSPE

with Chris Cordier, Stuart Leach and Daniel Morton

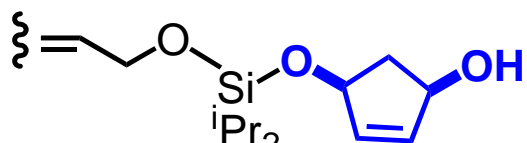
# Skeletally diverse natural product-like compounds: Iteration 1



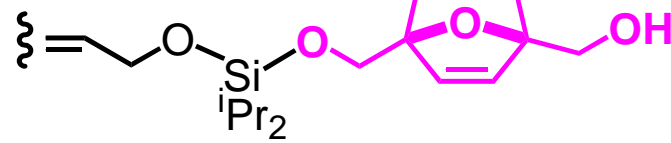
>98% (>95%) [4 h]



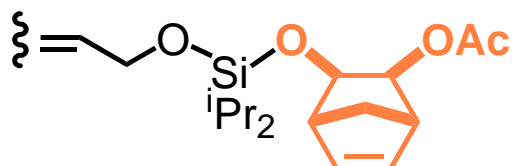
>98% [48 h]



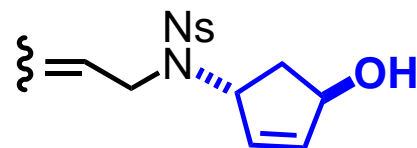
>98% [52 h]



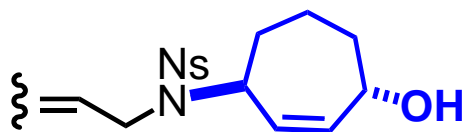
>98% [10 h]



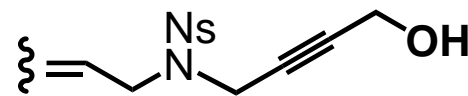
[no reaction after 100 h]



96%



>95%

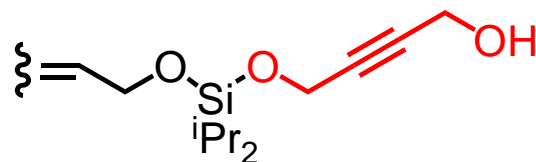
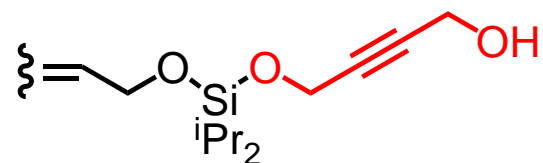
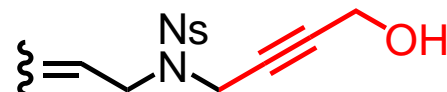
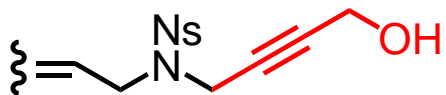
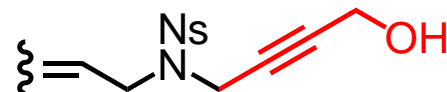
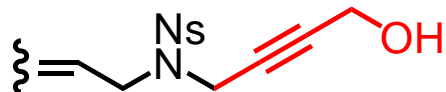
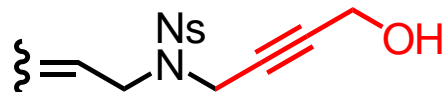
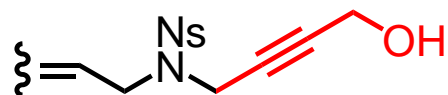


98%

1. NH<sub>3</sub>, MeOH; 2. FSPE

with Chris Cordier, Stuart Leach and Daniel Morton

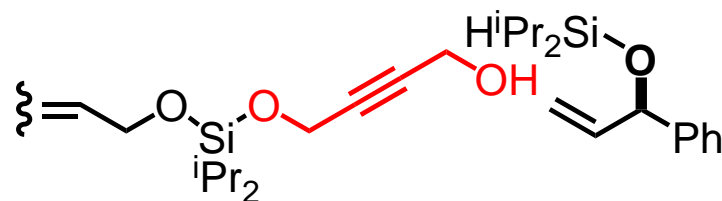
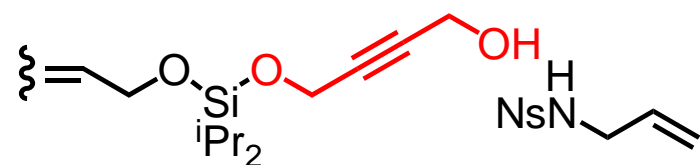
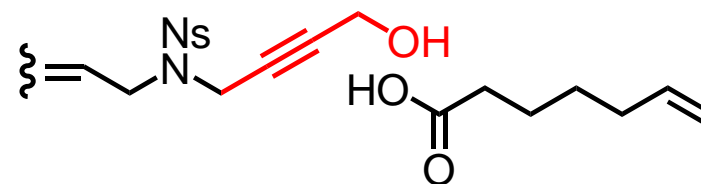
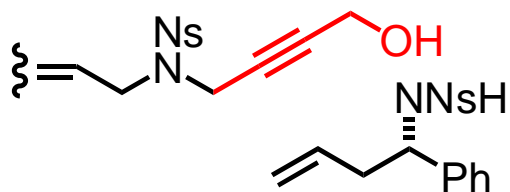
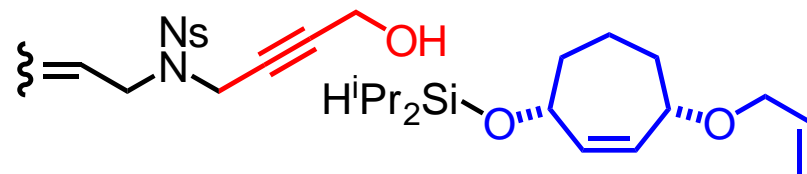
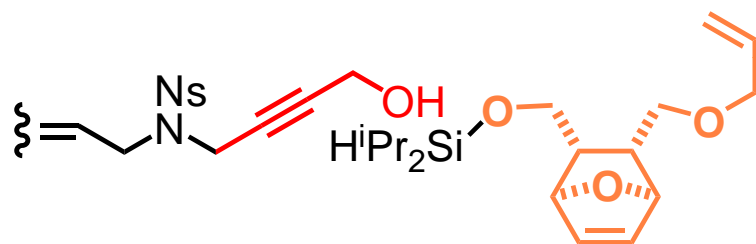
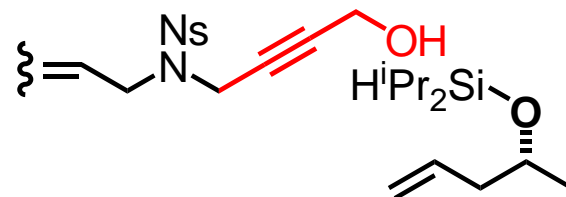
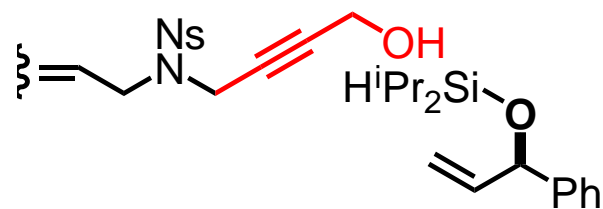
# Skeletally diverse natural product-like compounds: Iteration 2



Linker and Mitsunobu reactions: *J. Org. Chem* 2008, **73**, 2752

Silaketals formation: *Org. Biomol. Chem.* 2008, **6**, 1734

# Skeletally diverse natural product-like compounds: Iteration 2

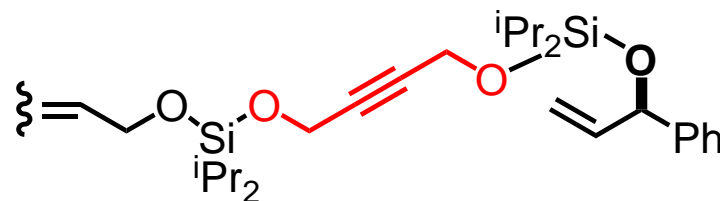
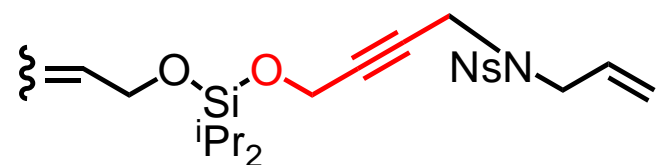
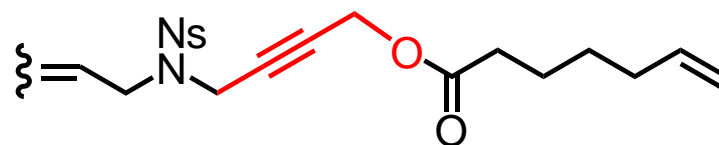
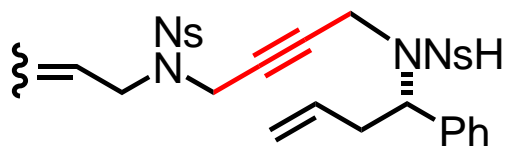
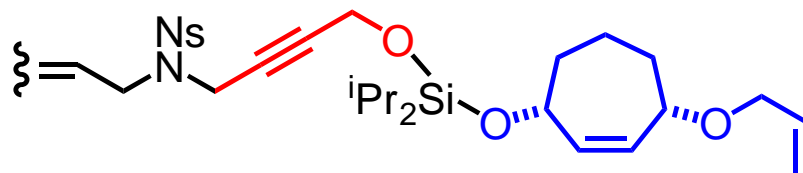
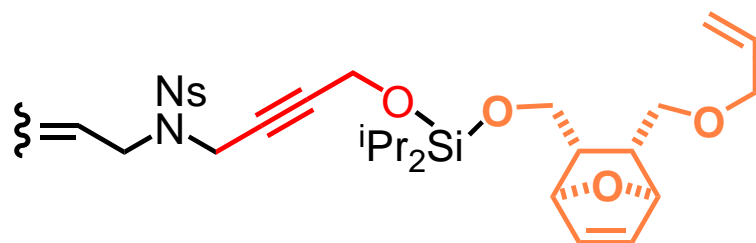
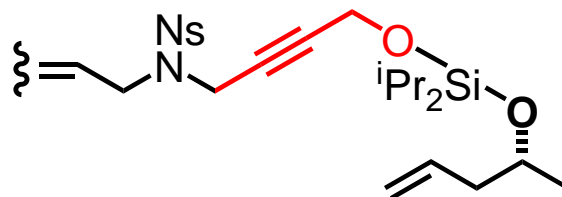
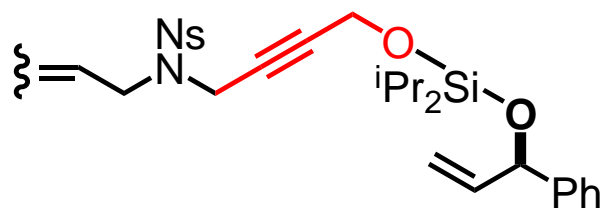


1. Mitsunobu or silyl ether formation; 2. FSPE

with Chris Cordier, Stuart Leach and Daniel Morton



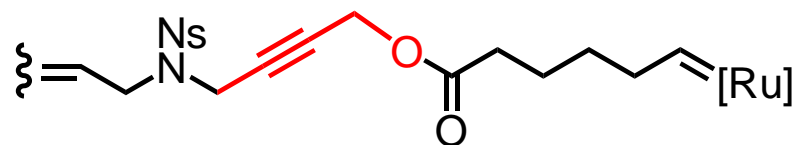
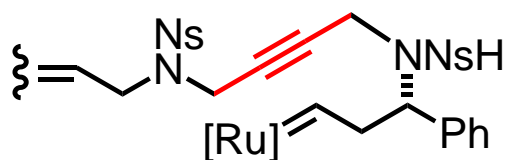
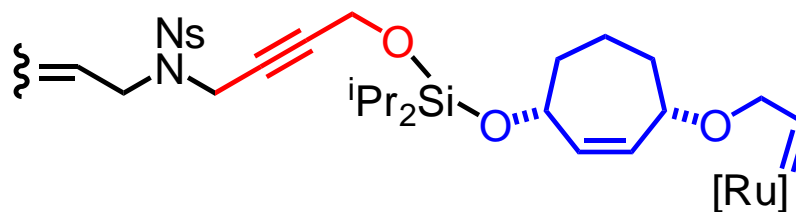
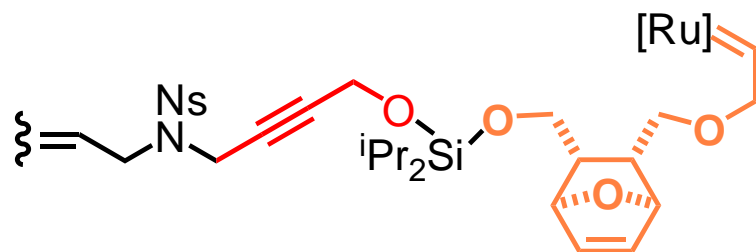
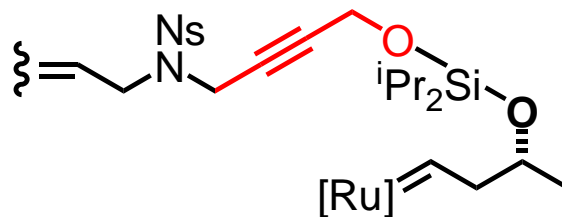
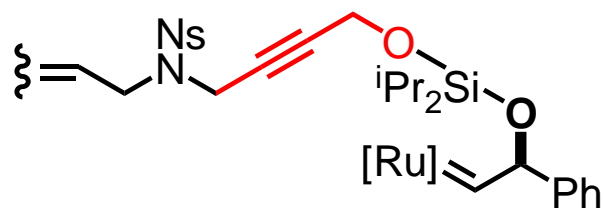
# Skeletally diverse natural product-like compounds: Iteration 2



1. Mitsunobu or silyl ether formation; 2. FSPE

with Chris Cordier, Stuart Leach and Daniel Morton

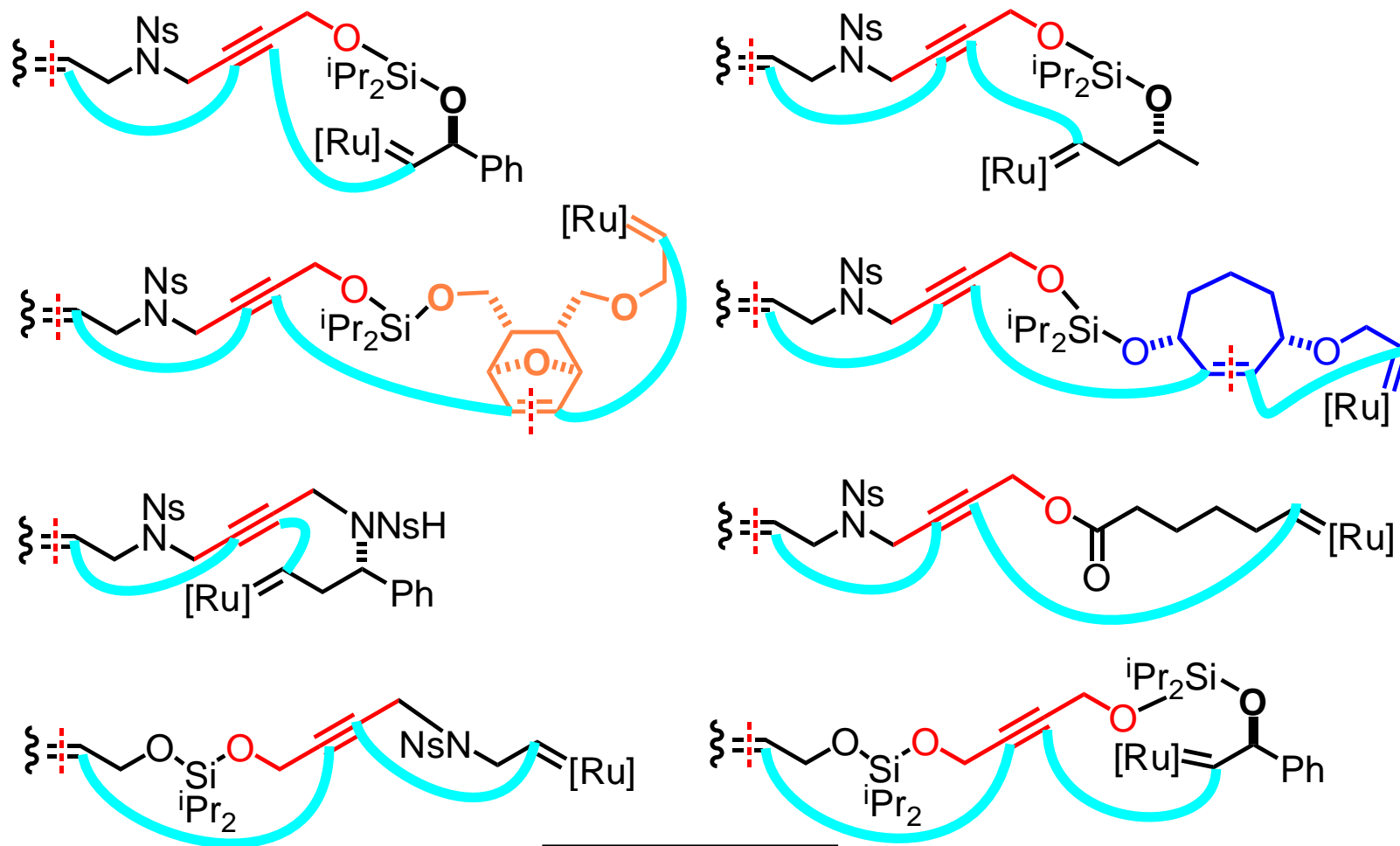
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Chris Cordier, Stuart Leach and Daniel Morton

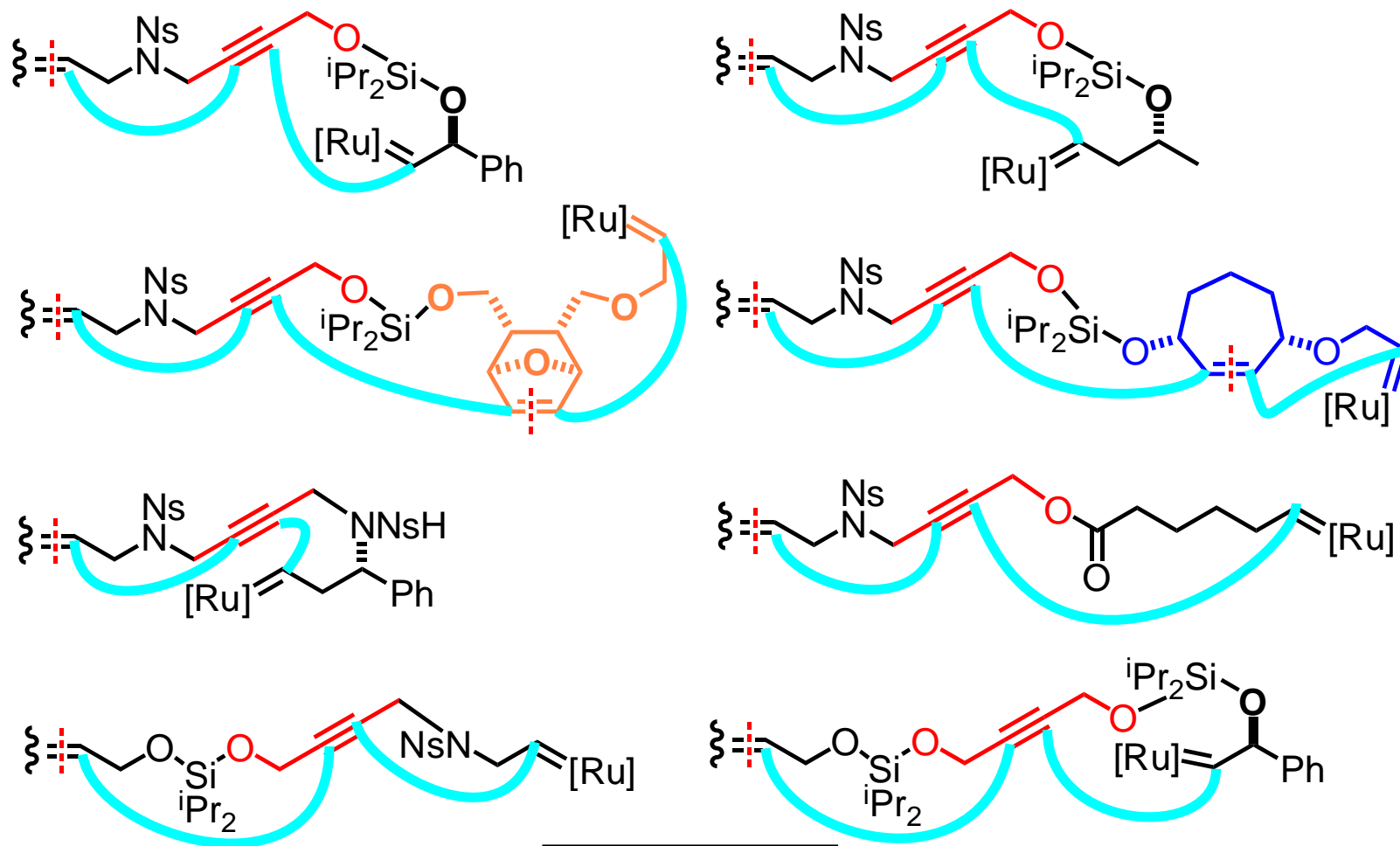
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Chris Cordier, Stuart Leach and Daniel Morton

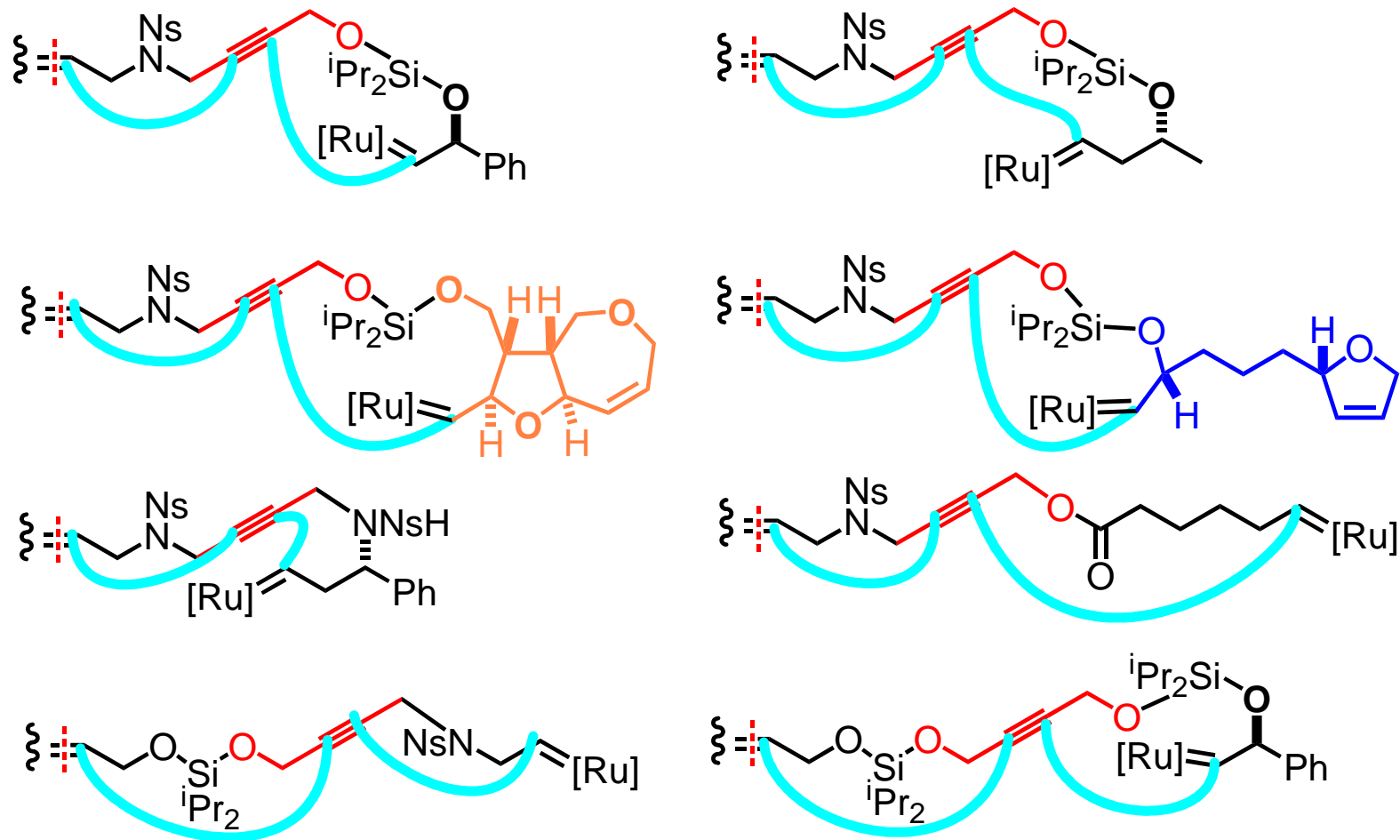
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Chris Cordier, Stuart Leach and Daniel Morton

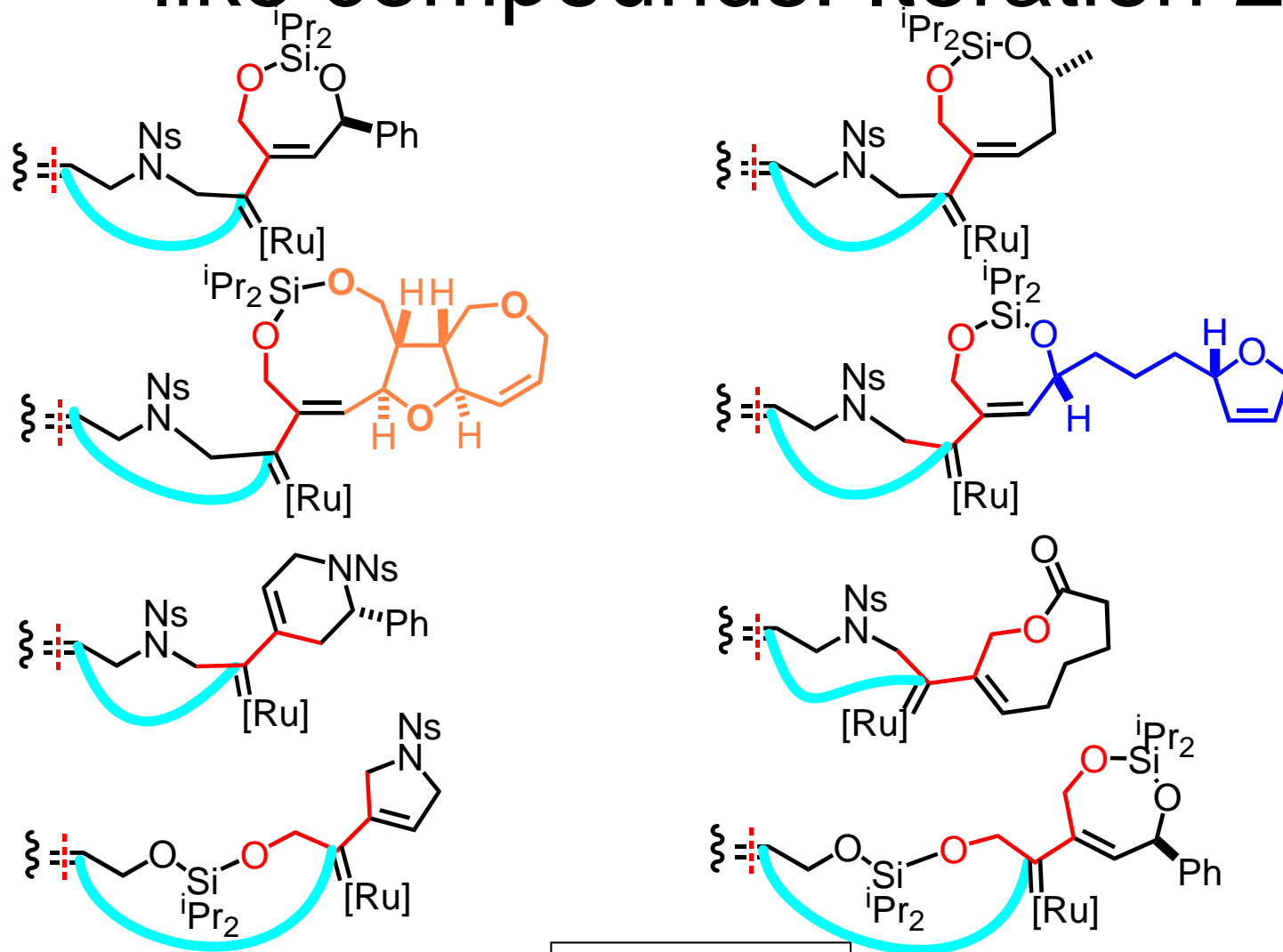
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Chris Cordier, Stuart Leach and Daniel Morton

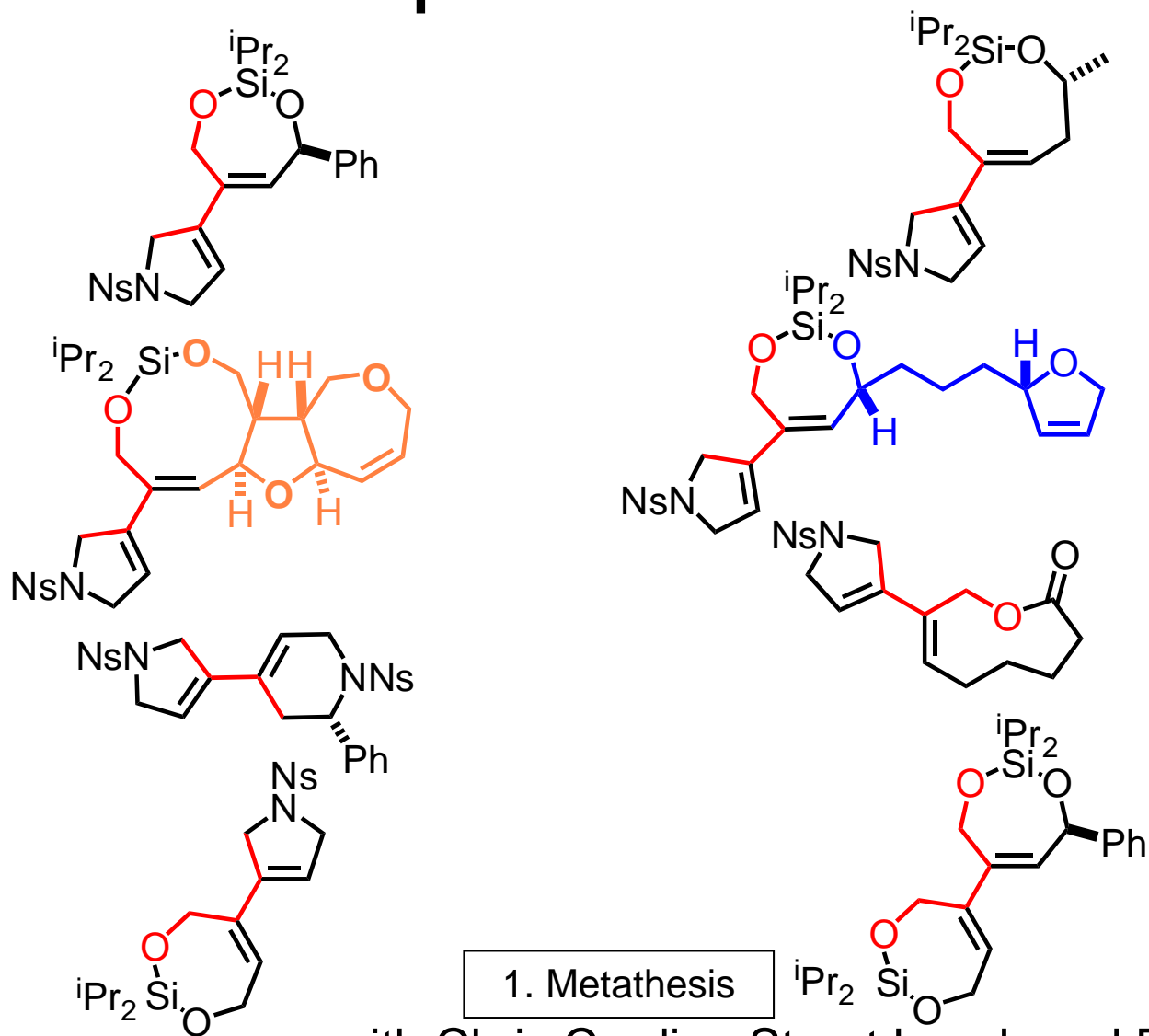
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

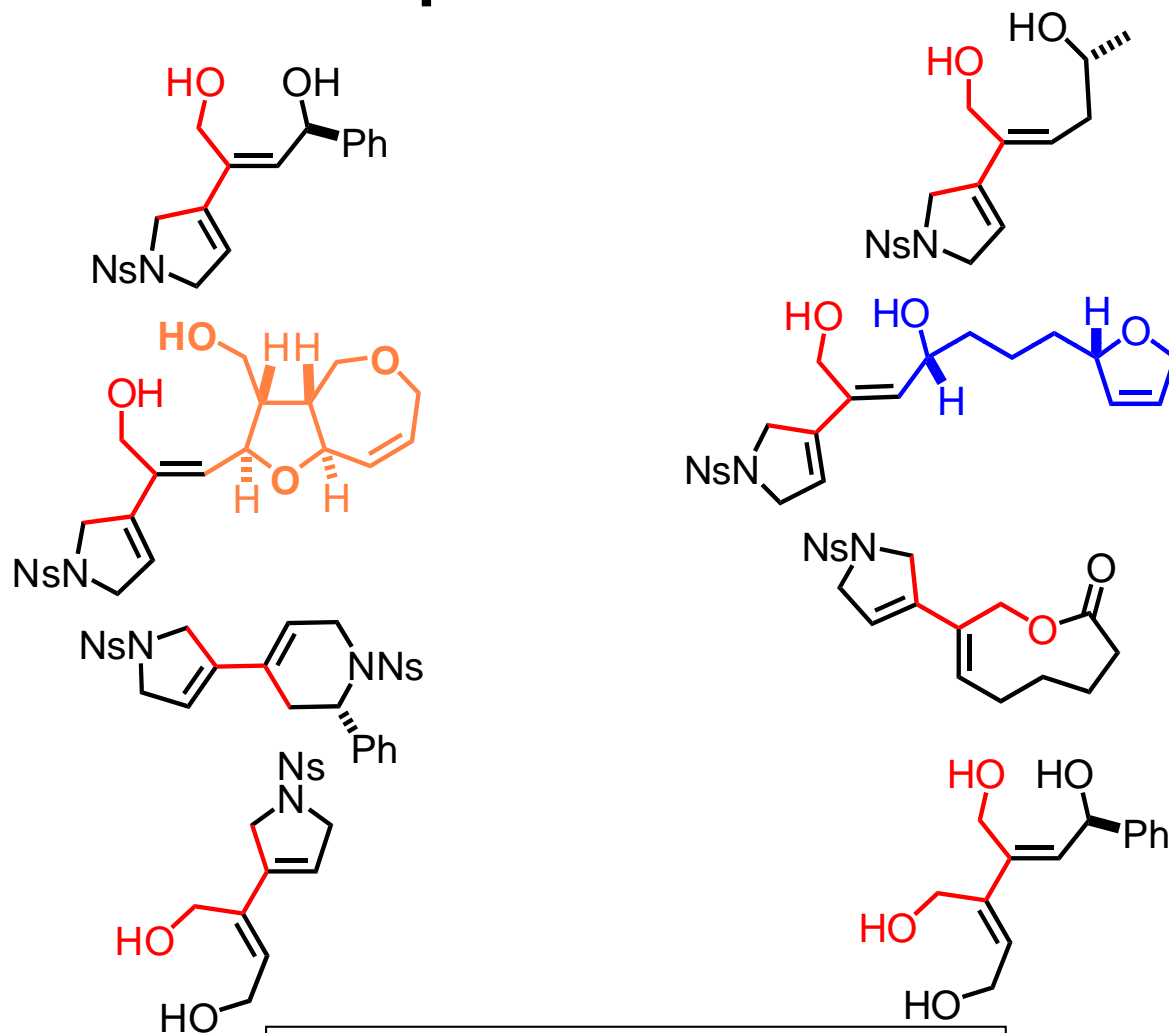
with Chris Cordier, Stuart Leach and Daniel Morton

# Skeletally diverse natural product-like compounds: Iteration 2



with Chris Cordier, Stuart Leach and Daniel Morton

# Skeletally diverse natural product-like compounds: Iteration 2



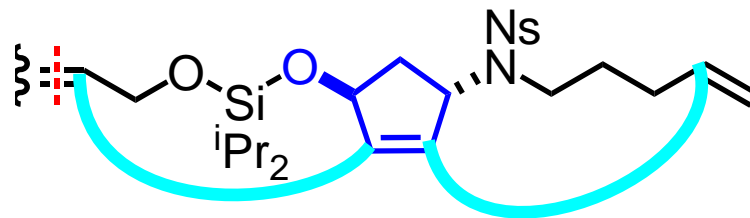
1. HF, pyridine; 2. FSPE; 3. purify

with Chris Cordier, Stuart Leach and Daniel Morton



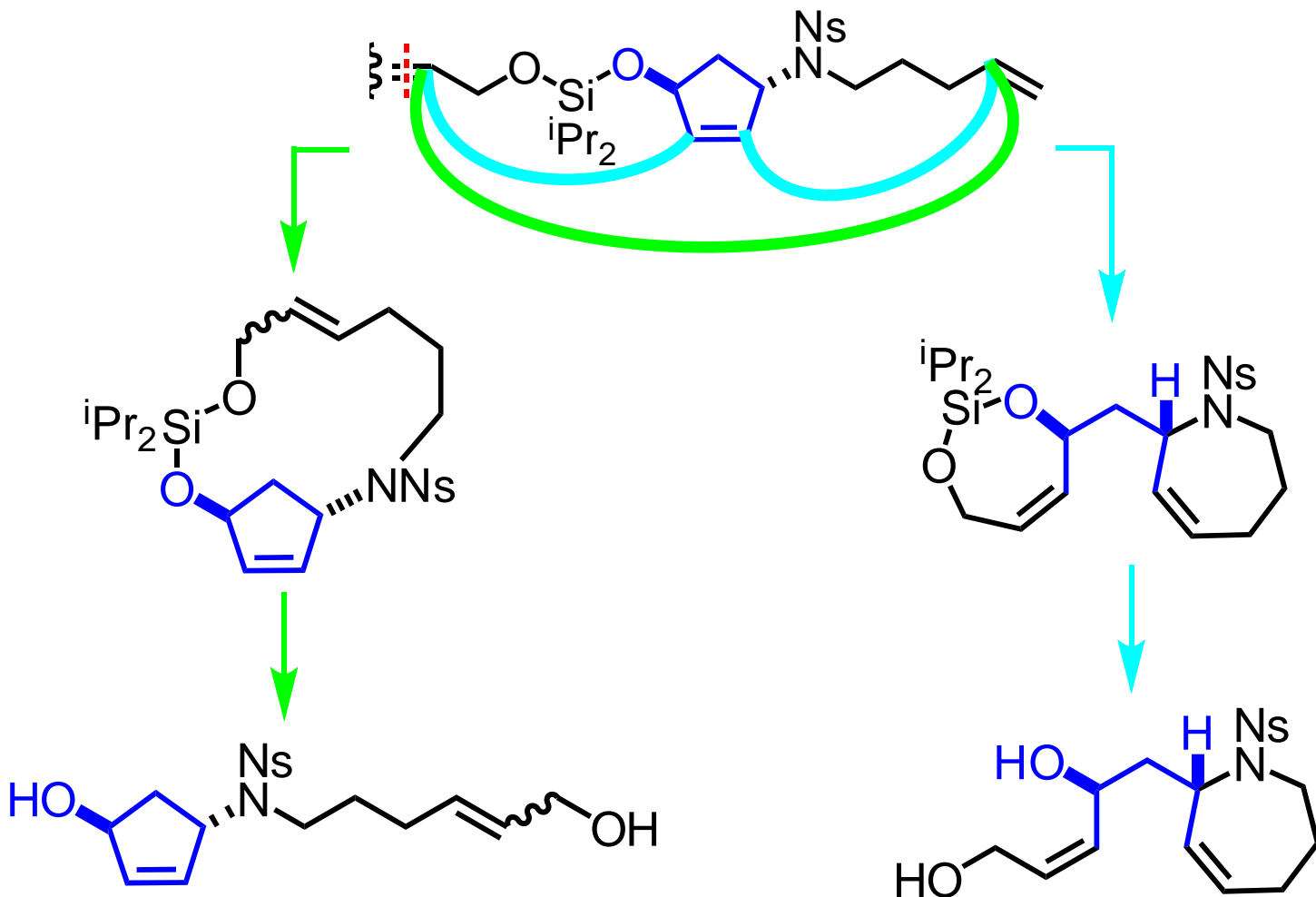
# What can go 'wrong'?

## Competitive cyclisations



# What can go 'wrong'?

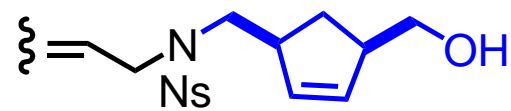
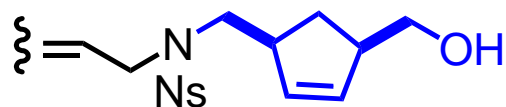
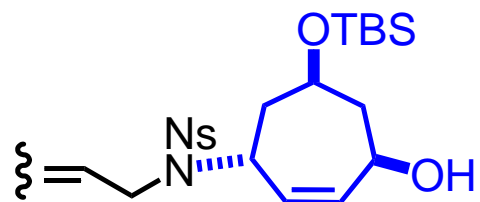
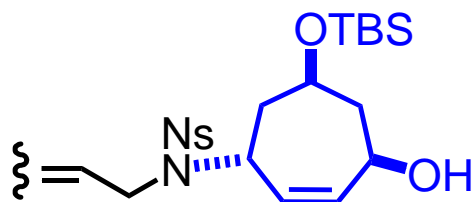
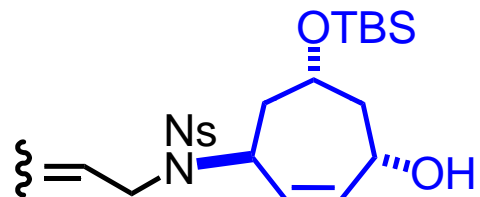
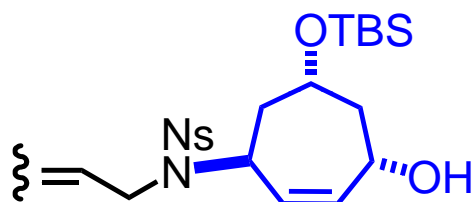
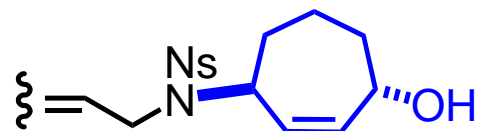
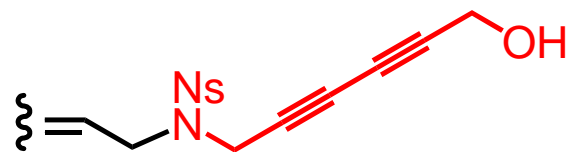
## Competitive cyclisations



Macrocyclic-tethered cross-metathesis

i.e. first building block sometimes skipped

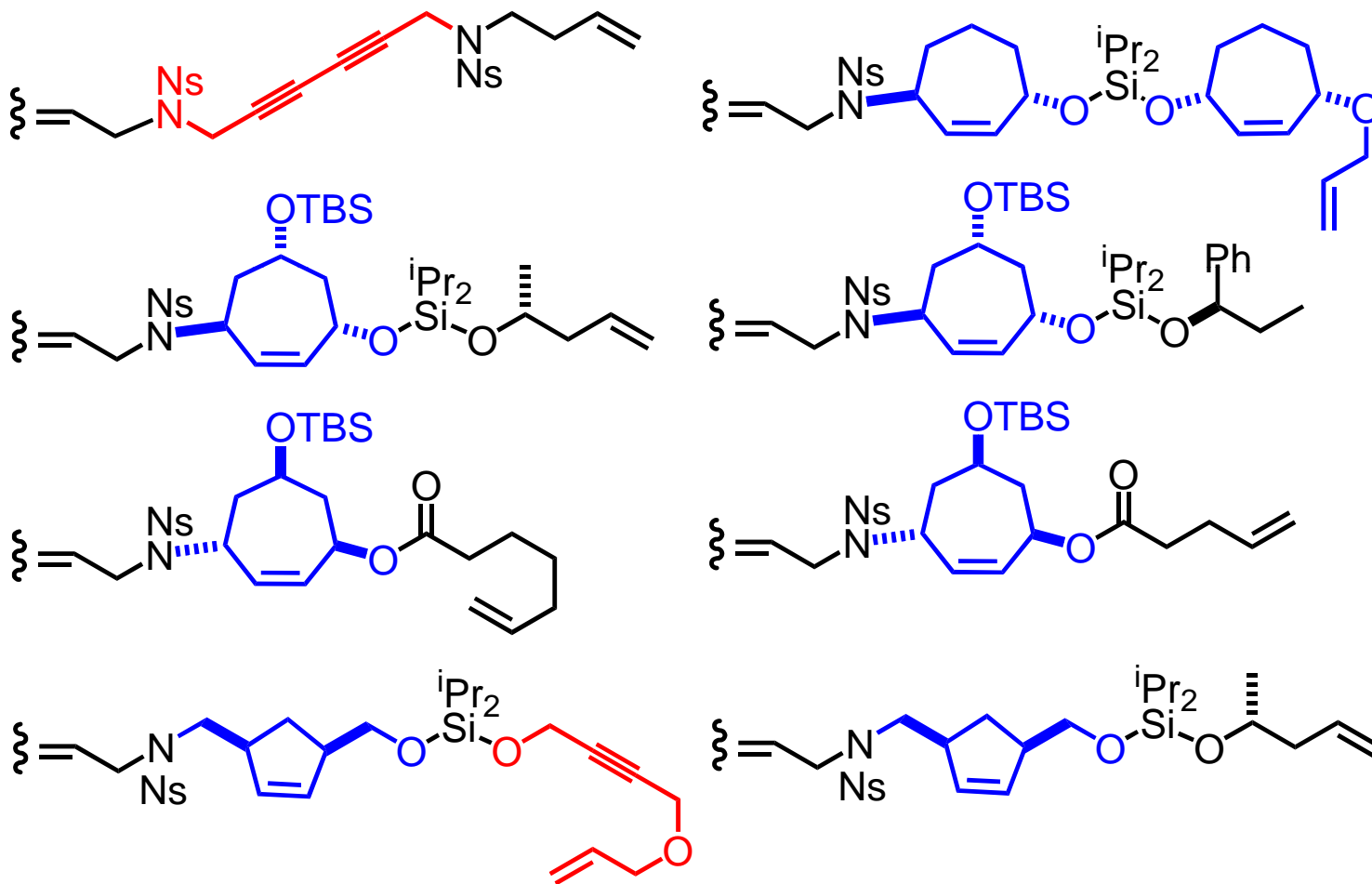
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Stuart Leach, Chris Cordier and Daniel Morton

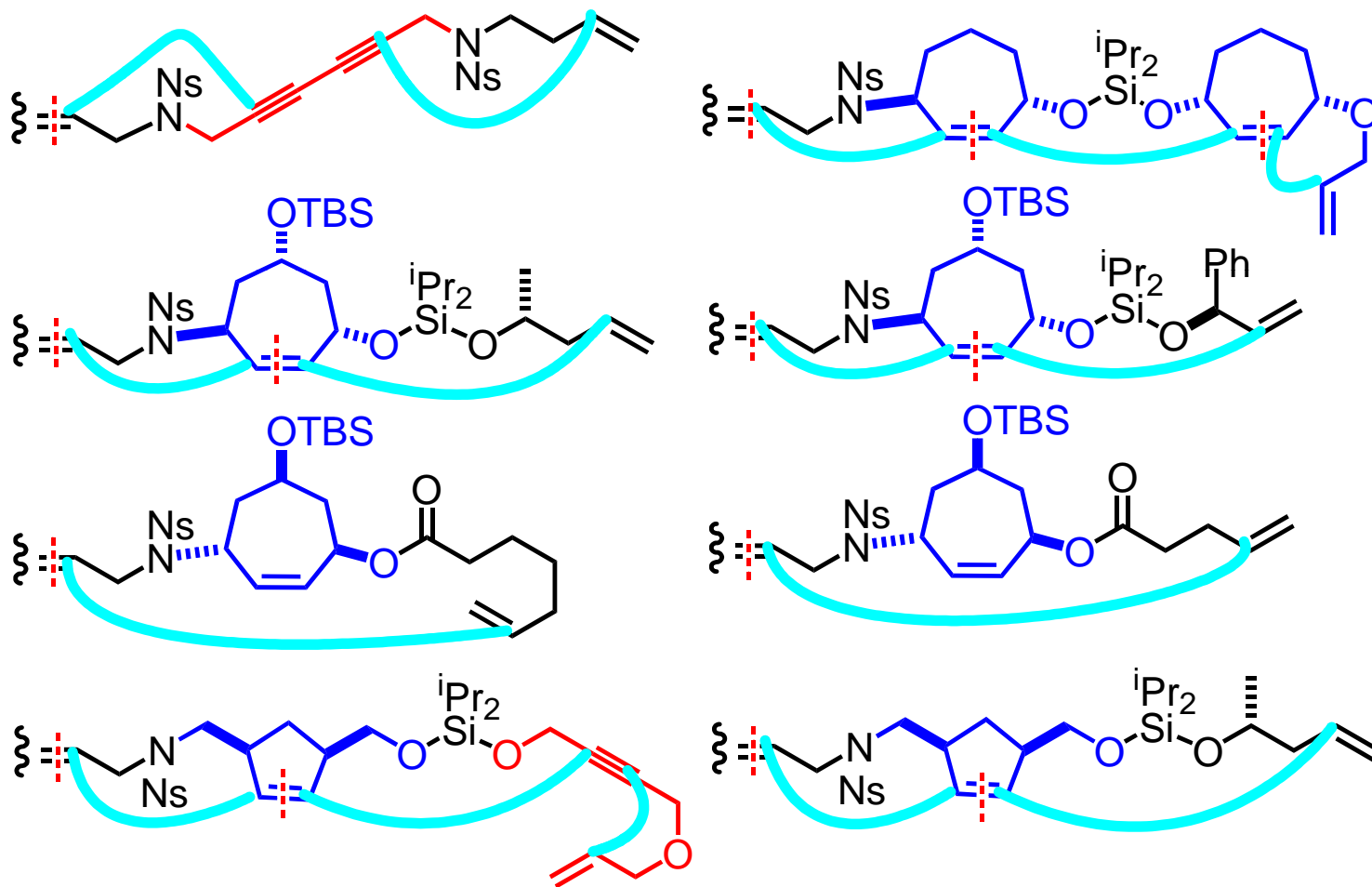
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Stuart Leach, Chris Cordier and Daniel Morton

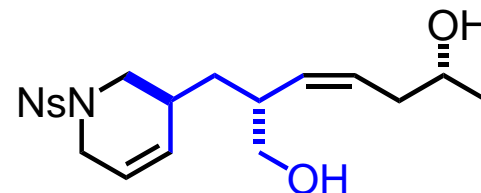
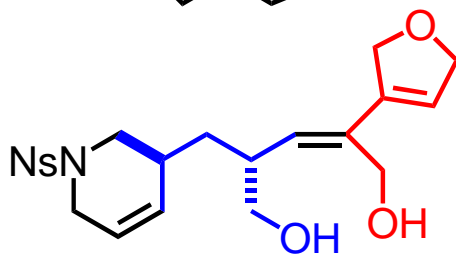
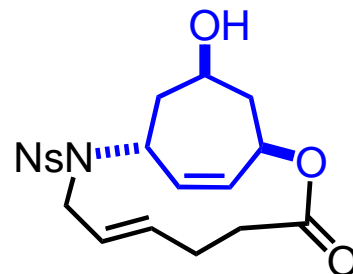
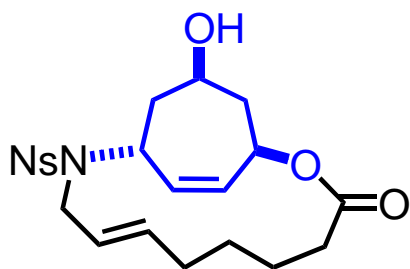
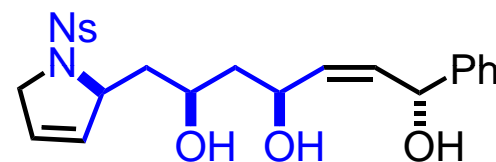
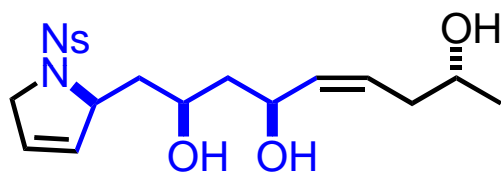
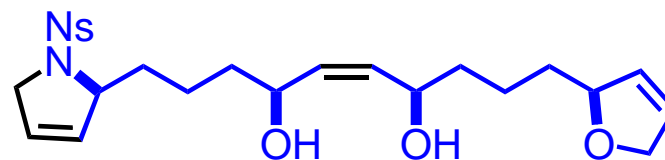
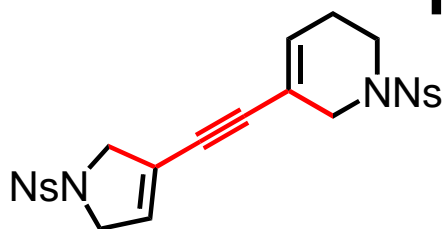
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Stuart Leach, Chris Cordier and Daniel Morton

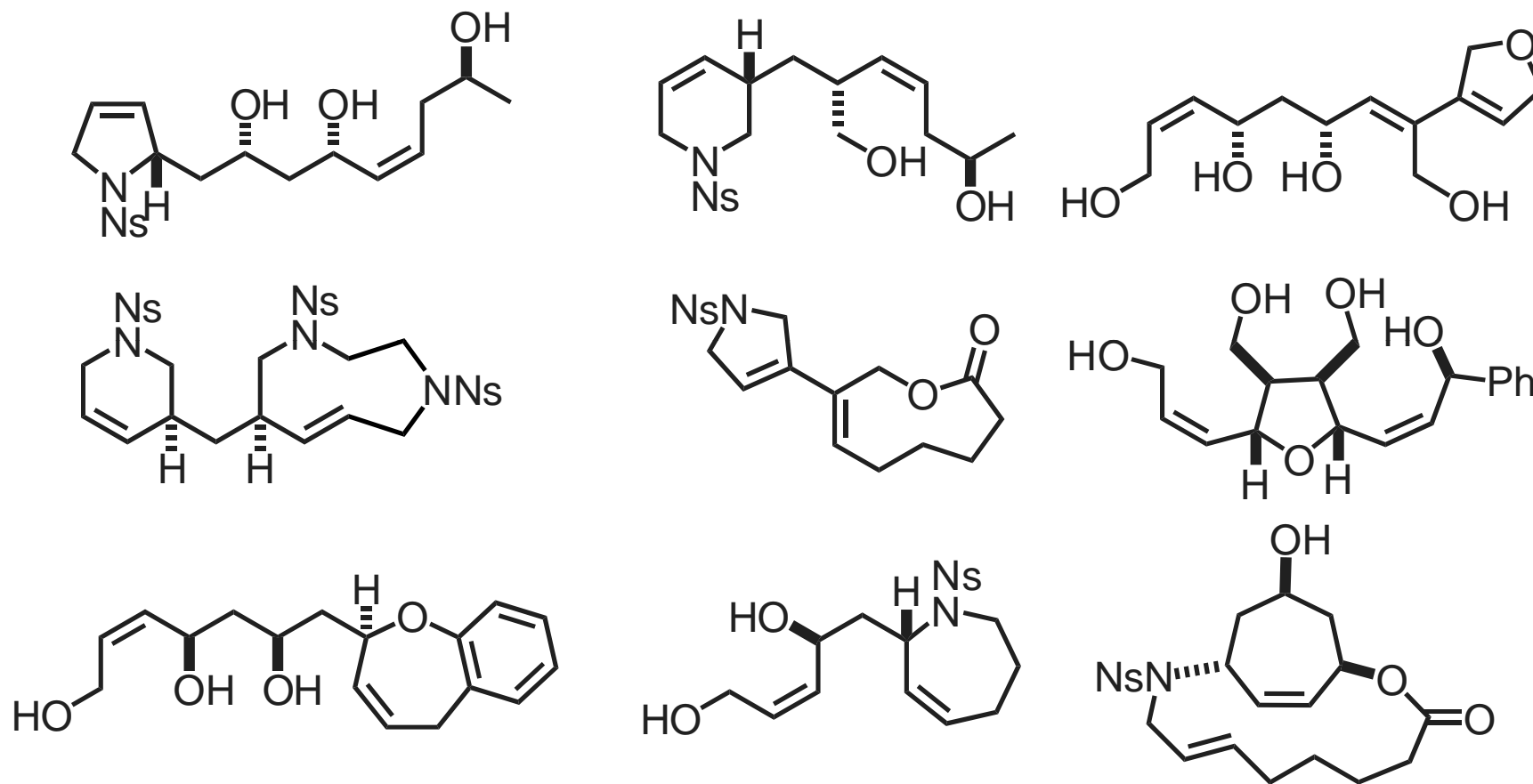
# Skeletally diverse natural product-like compounds: Iteration 2



1. Metathesis

with Stuart Leach, Chris Cordier and Daniel Morton

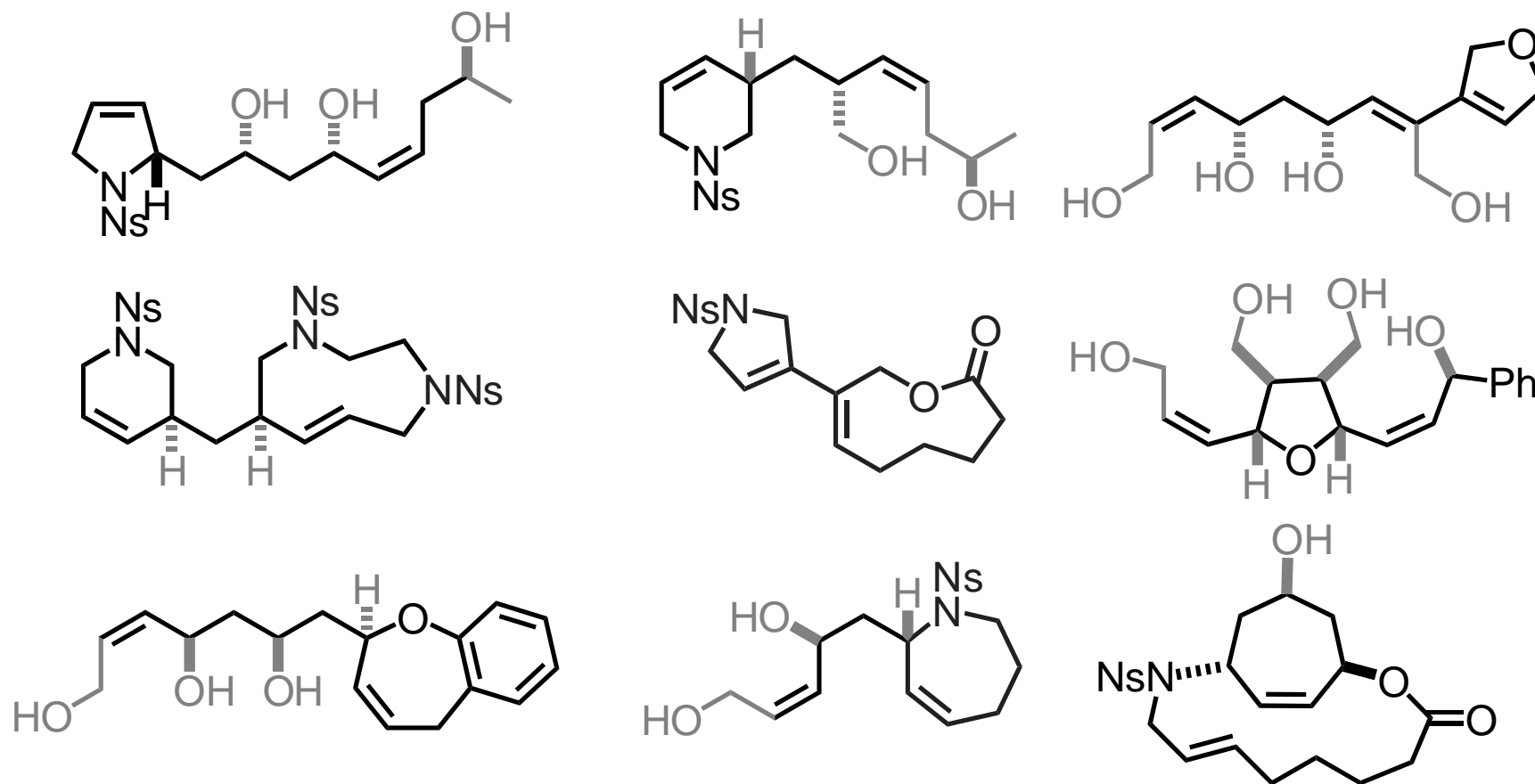
# Classification of product scaffolds



For an hierarchical scaffold classification, see: Waldmann *et al*,  
*J. Chem. Inf. Model.*, 2007, **47**, 47

For the natural product scaffold 'tree': *Proc. Natl. Acad. Sci.* 2006, 103, 10606

# Classification of product scaffolds

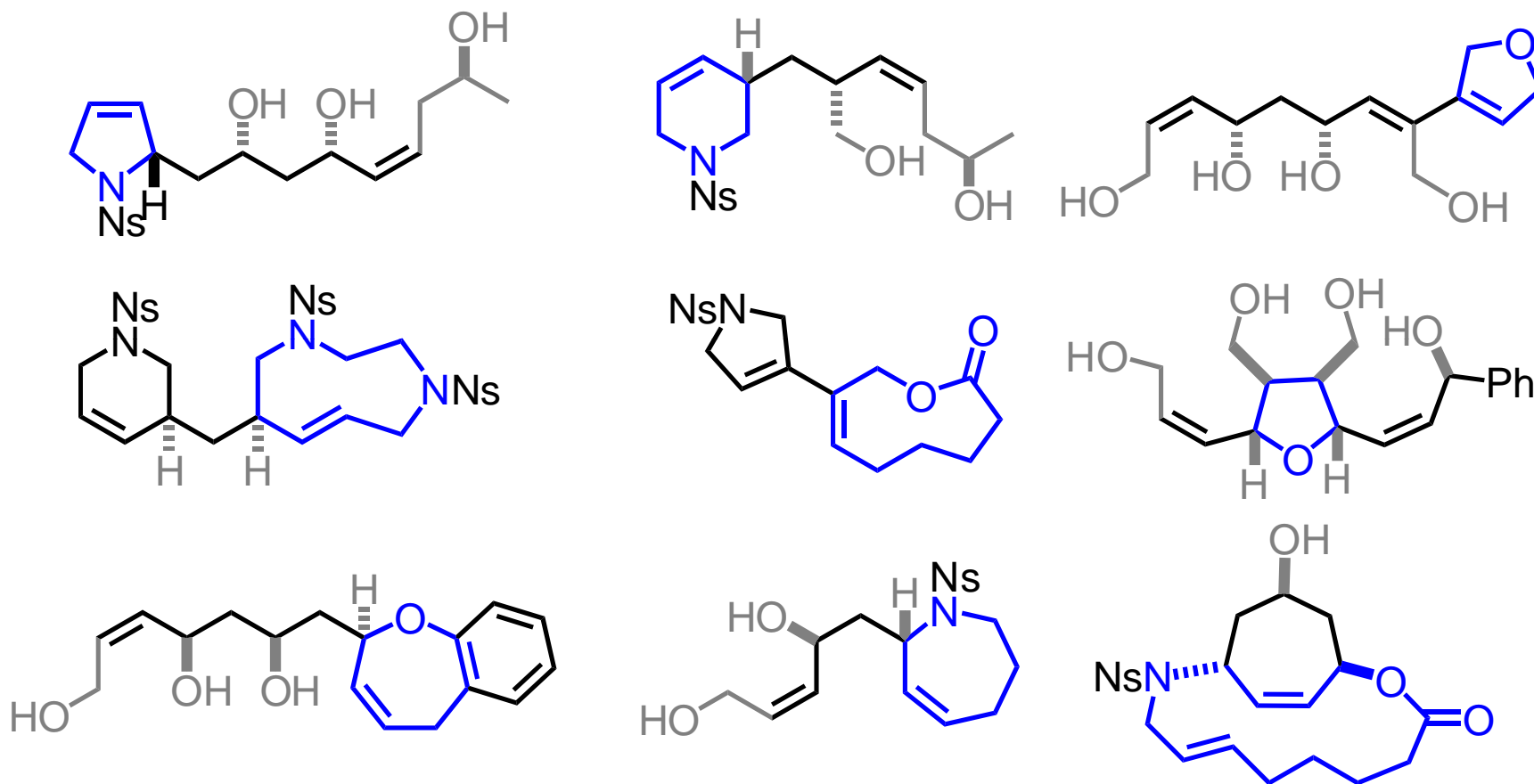


For an hierarchical scaffold classification, see: Waldmann *et al*,  
*J. Chem. Inf. Model.*, 2007, **47**, 47

For the natural product scaffold 'tree': *Proc. Natl. Acad. Sci.* 2006, 103, 10606



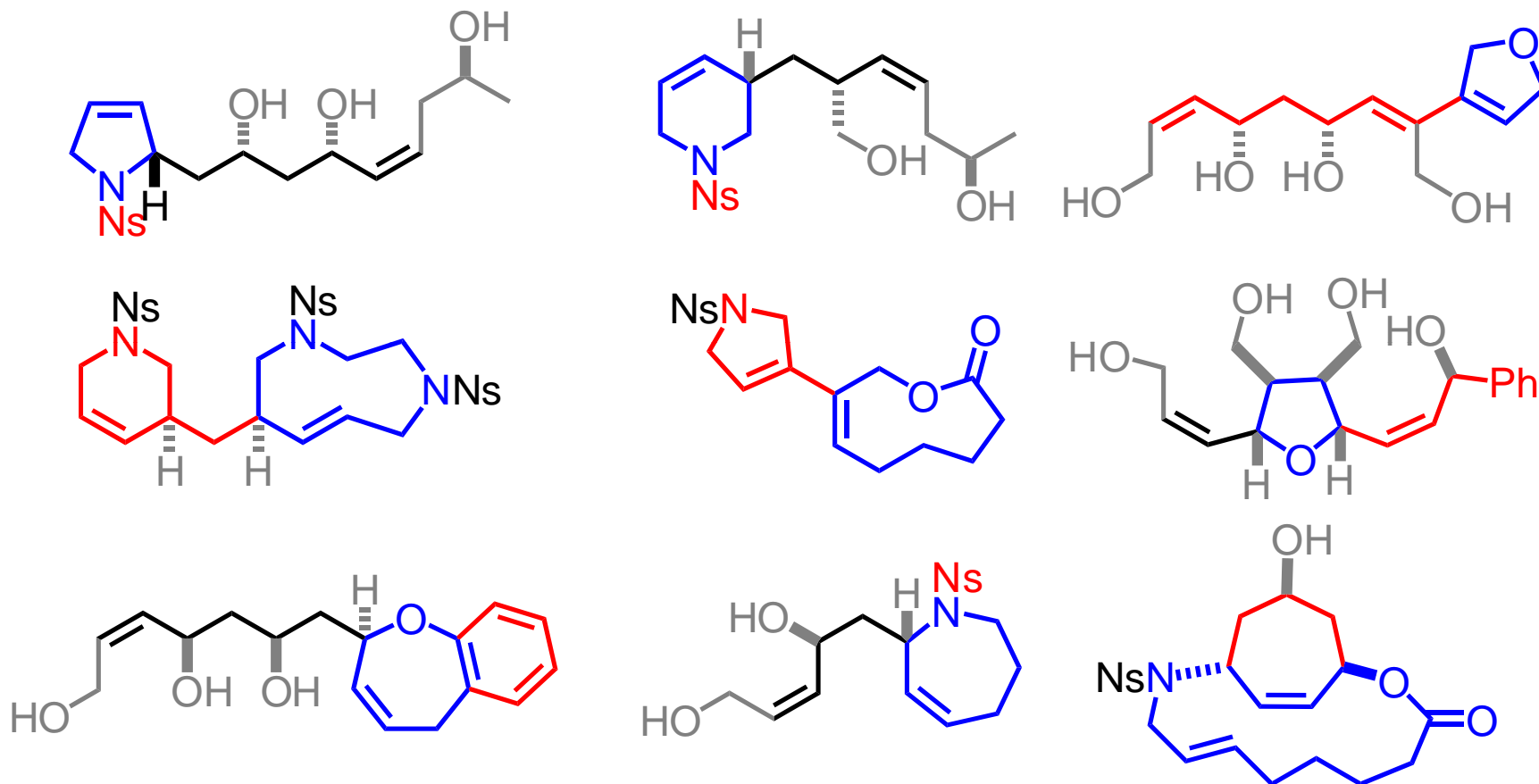
# Classification of product scaffolds



For an hierarchical scaffold classification, see: Waldmann *et al*,  
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For the natural product scaffold 'tree': *Proc. Natl. Acad. Sci.* 2006, 103, 10606

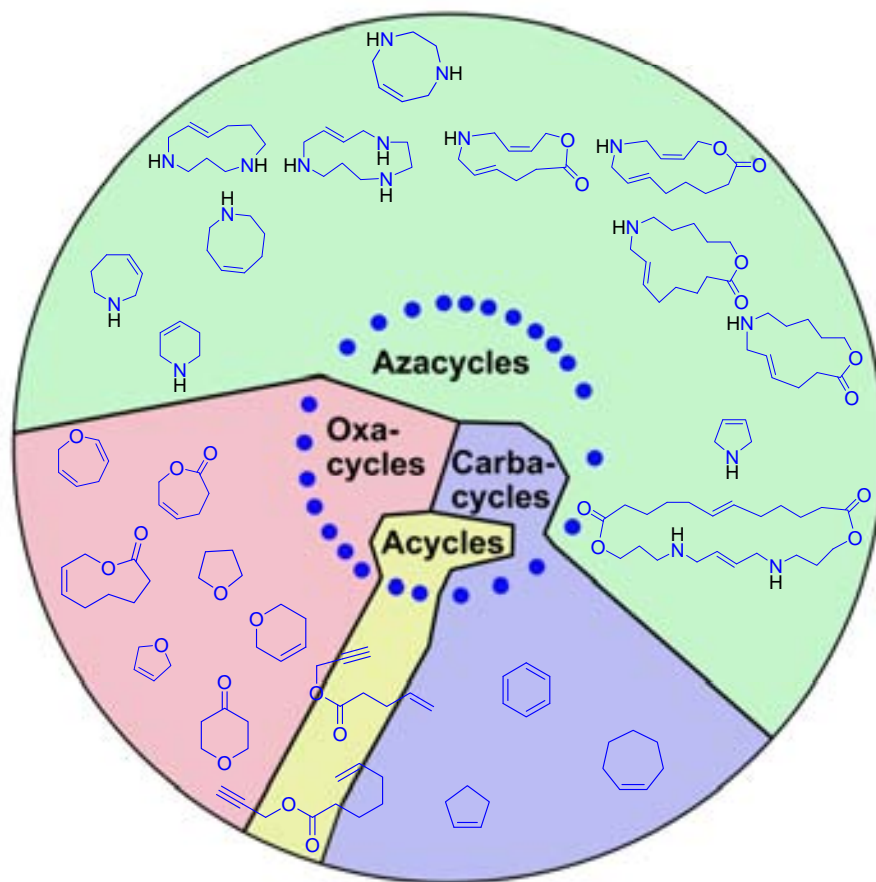
# Classification of product scaffolds



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For the natural product scaffold 'tree': *Proc. Natl. Acad. Sci.* 2006, 103, 10606

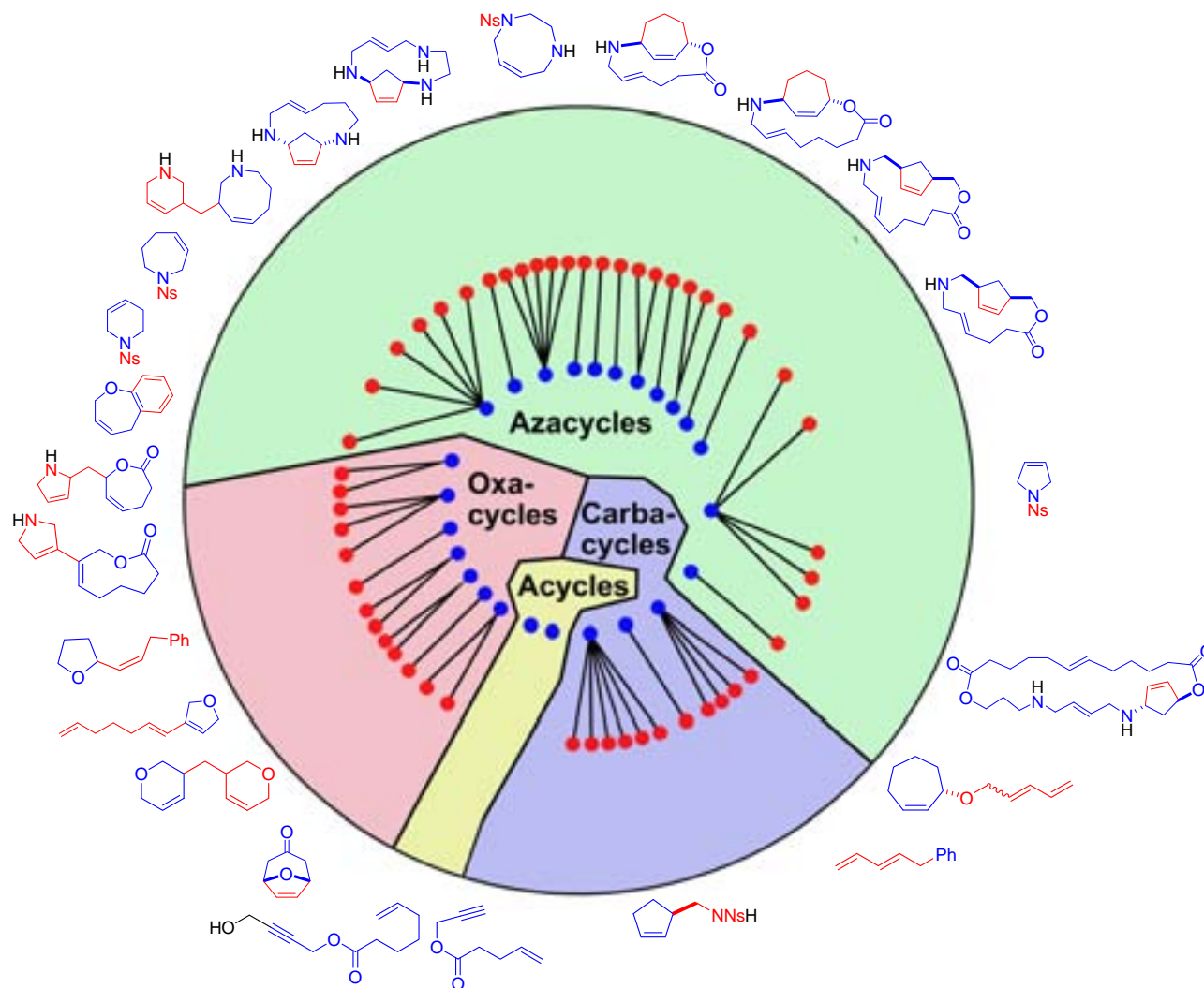
# Classification of product scaffolds



For an hierarchical scaffold classification, see: Waldmann *et al*,  
*J. Chem. Inf. Model.*, 2007, **47**, 47

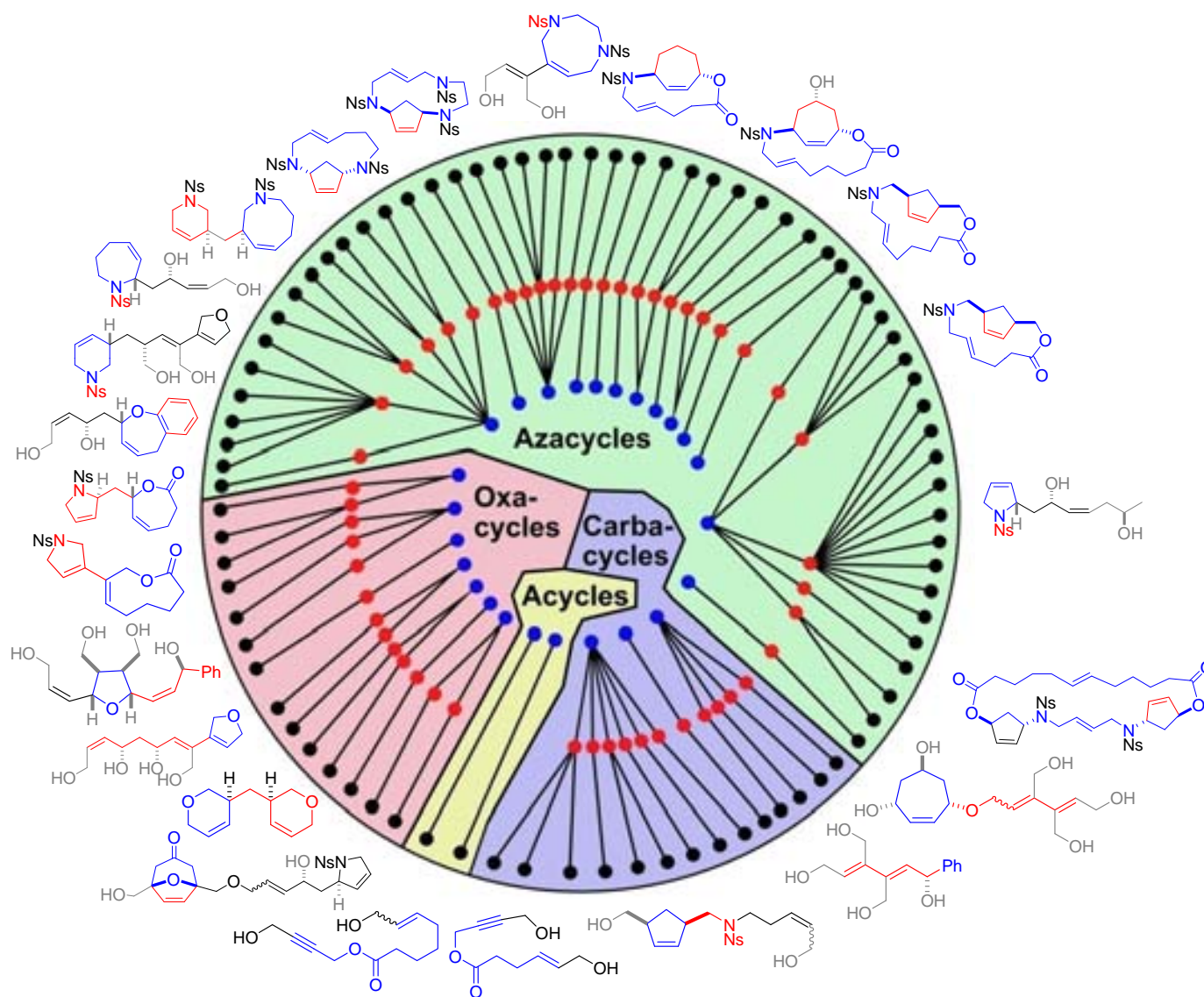
For the natural product scaffold 'tree': *Proc. Natl. Acad. Sci.* 2006, 103, 10606

# Classification of product scaffolds



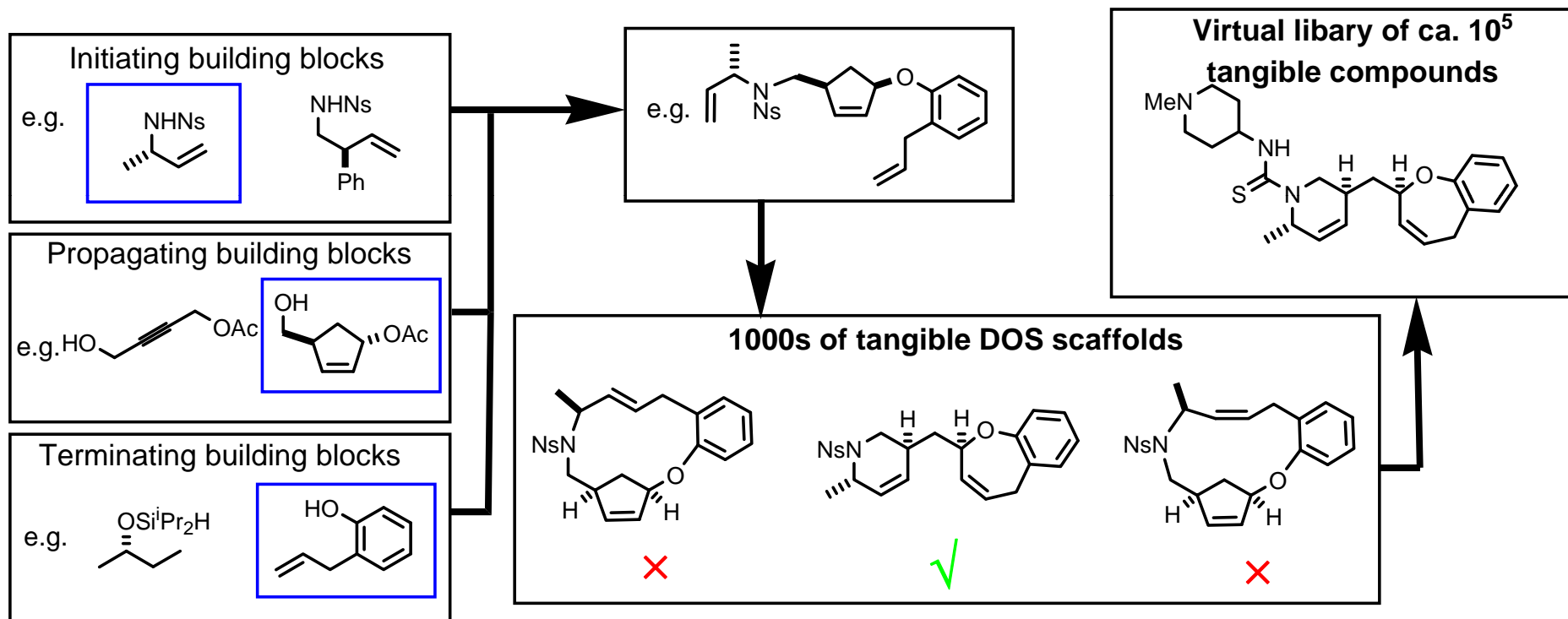
*Angew. Chem. Int. Ed.* 2009, **48**, 104

# Classification of product scaffolds



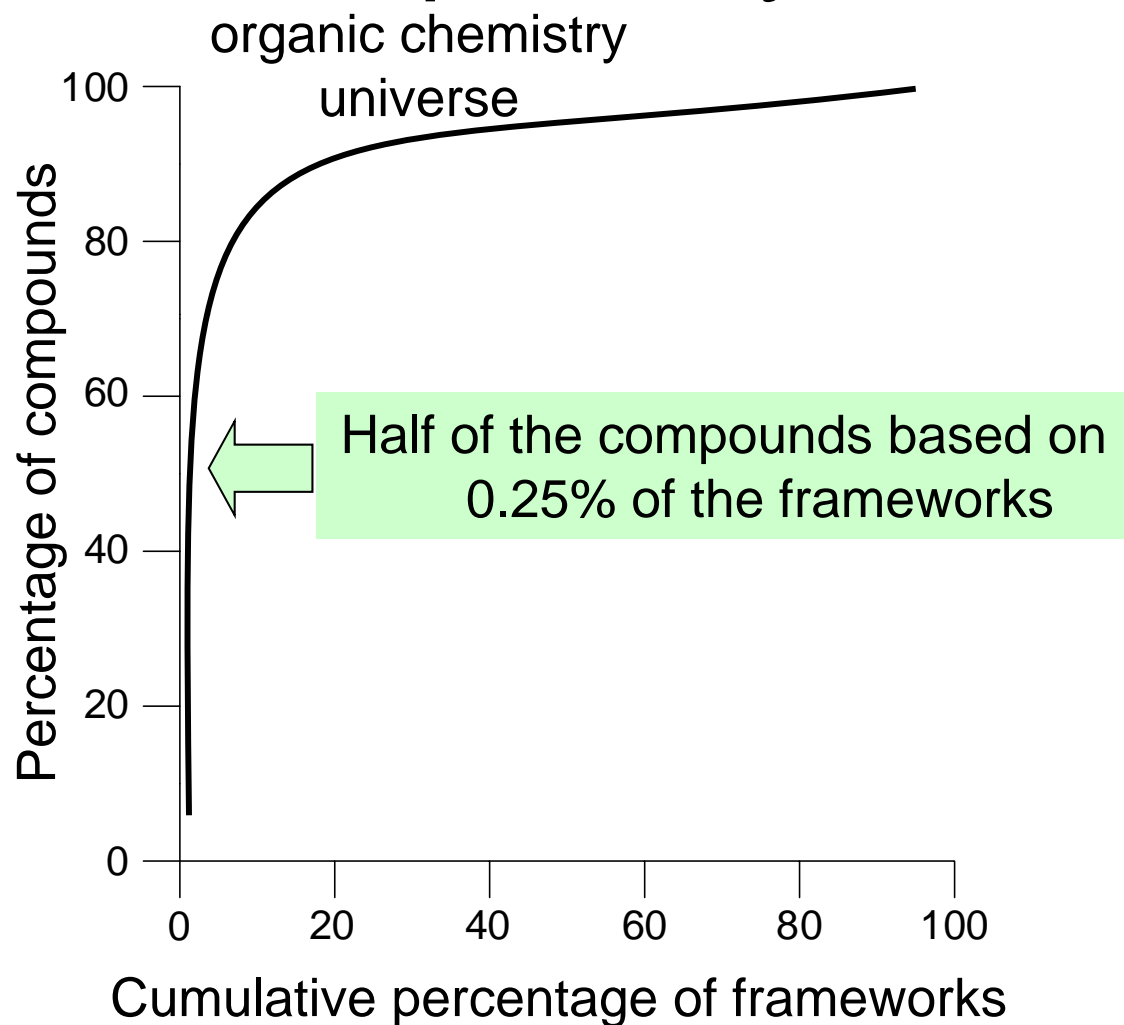
*Angew. Chem. Int. Ed.* 2009, **48**, 104

# Determining the likely scope of the synthetic approach



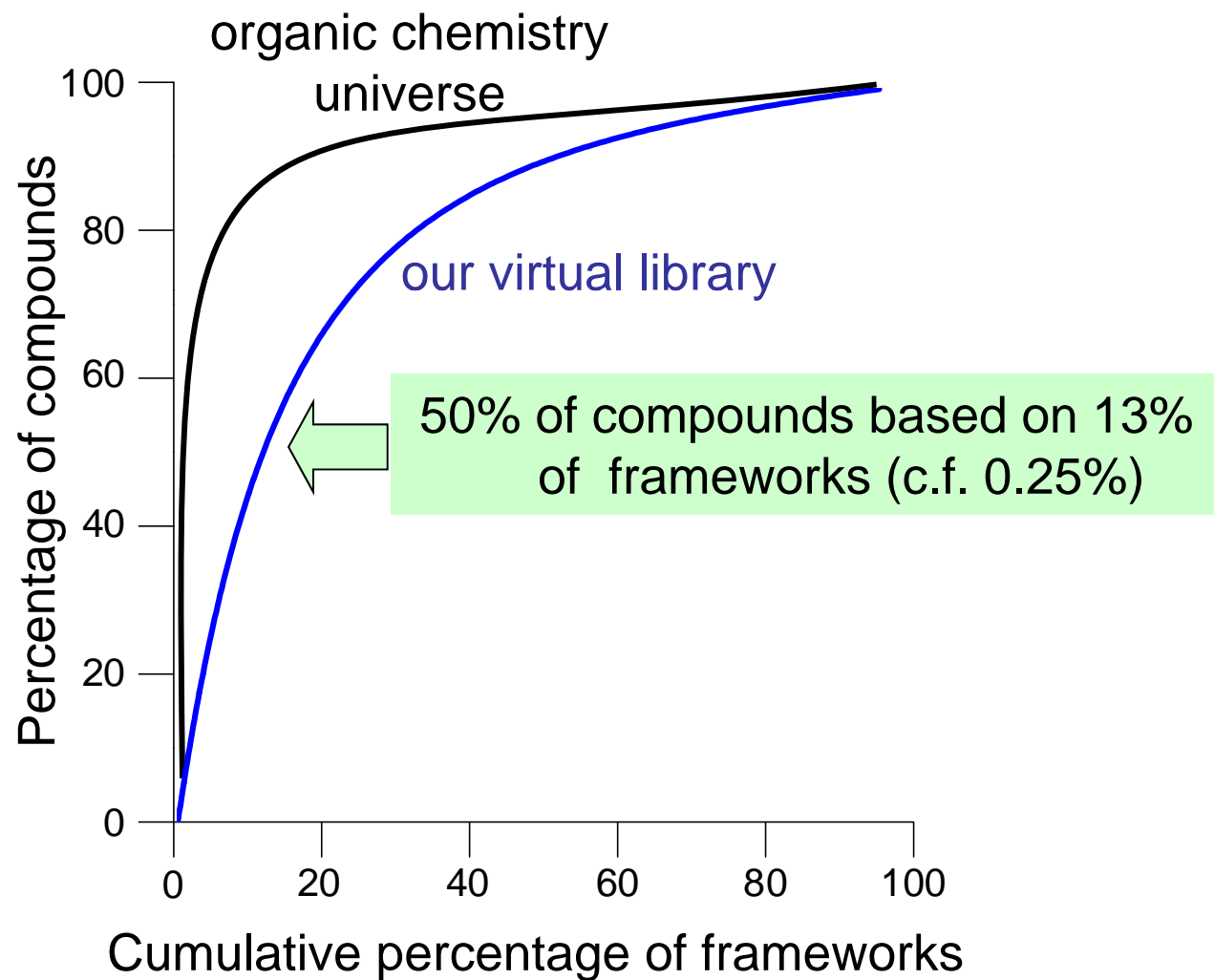
With Stuart Warriner

# The Organic Chemistry Universe is “Top Heavy”



See A. H. Lipkus *et al*, *J. Org. Chem.* 2008, **73**, 4443

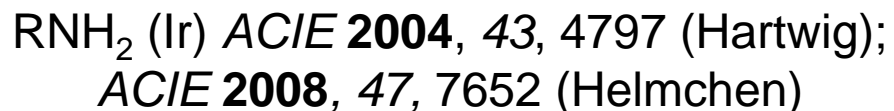
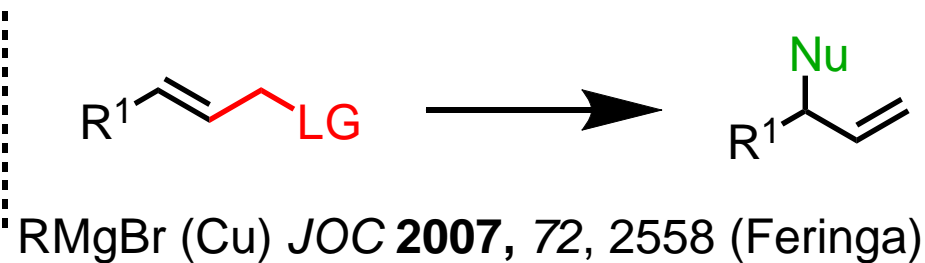
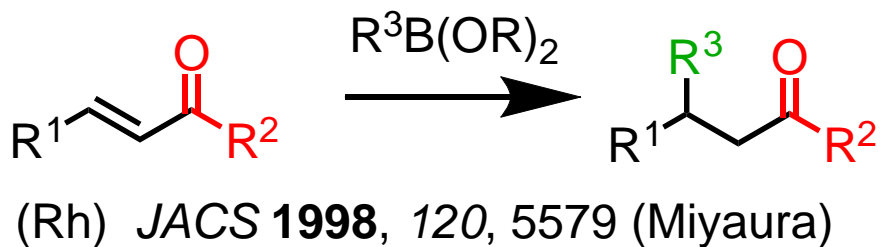
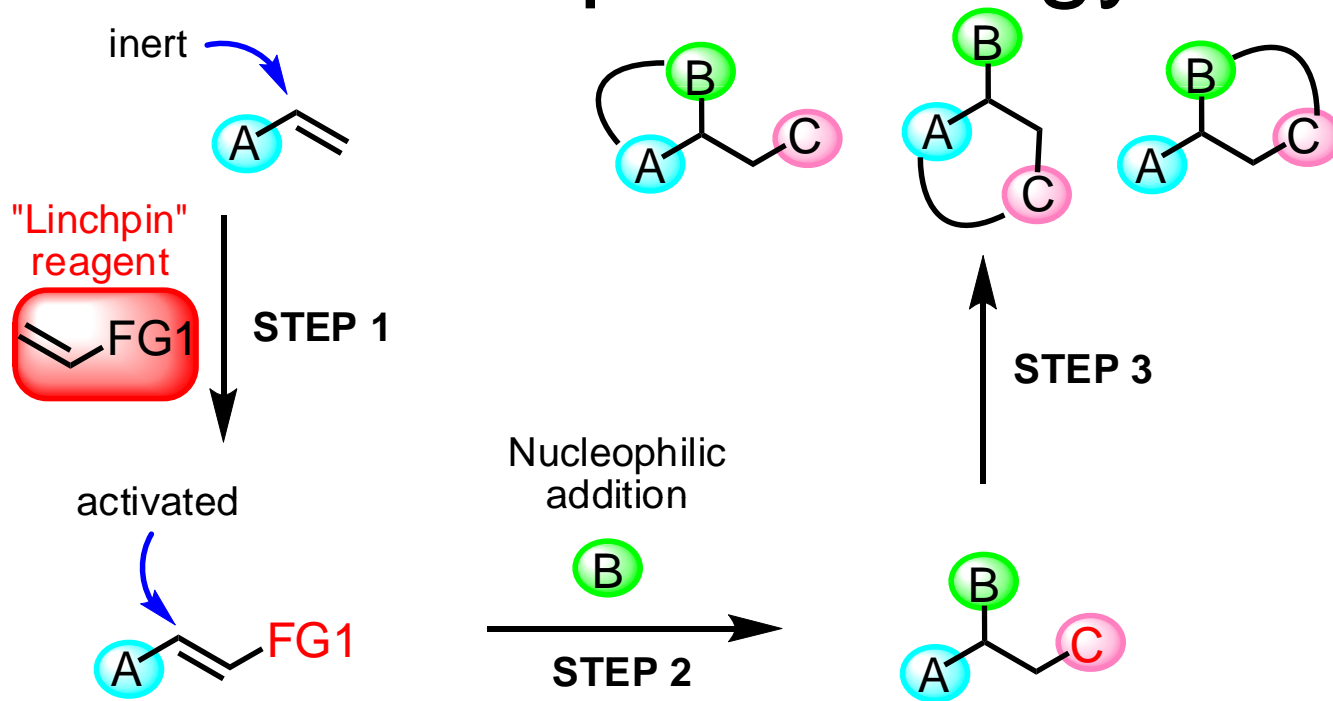
# Towards more even coverage of chemical space



With Stuart Warriner

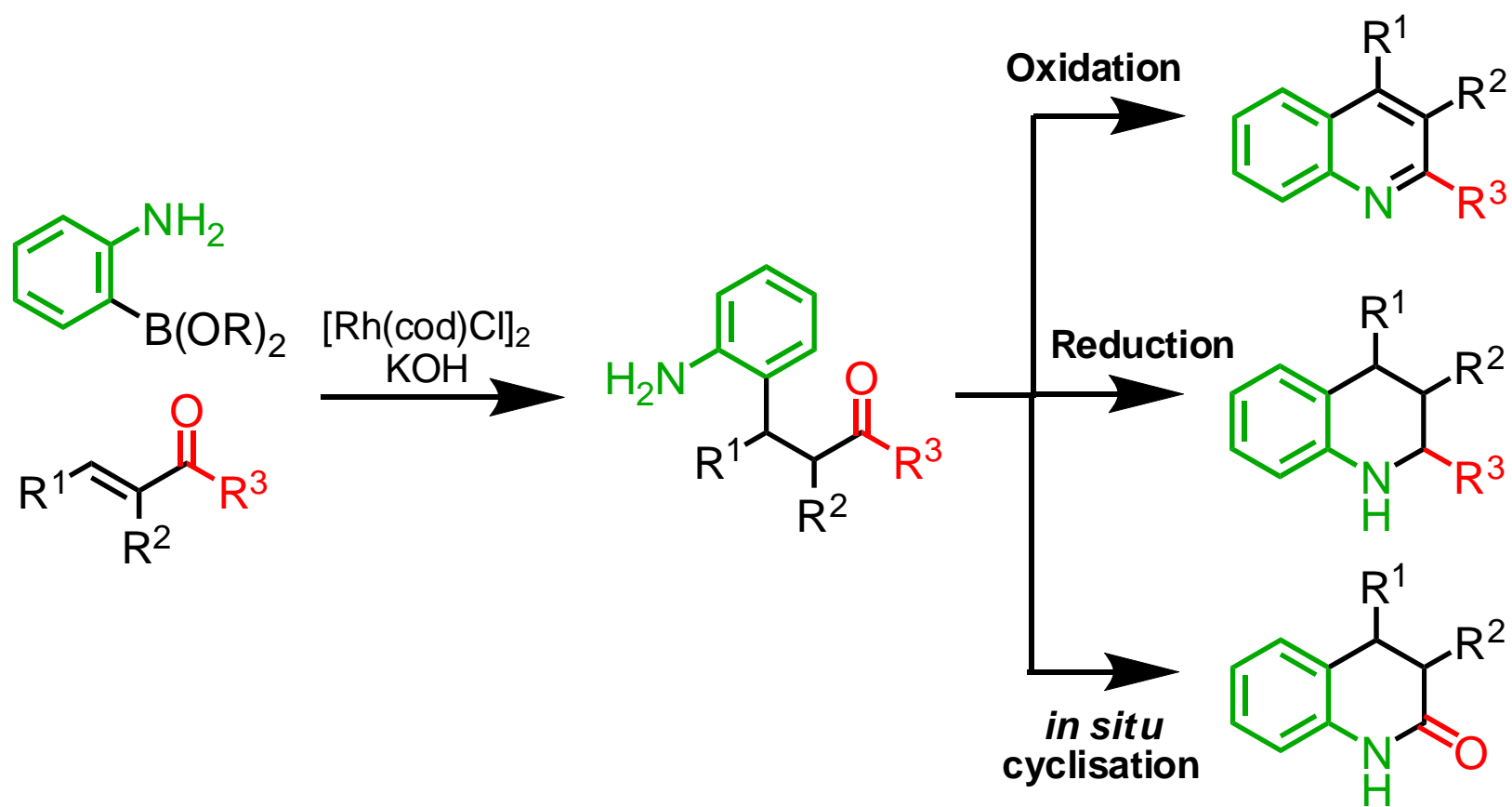


# The Linchpin Strategy

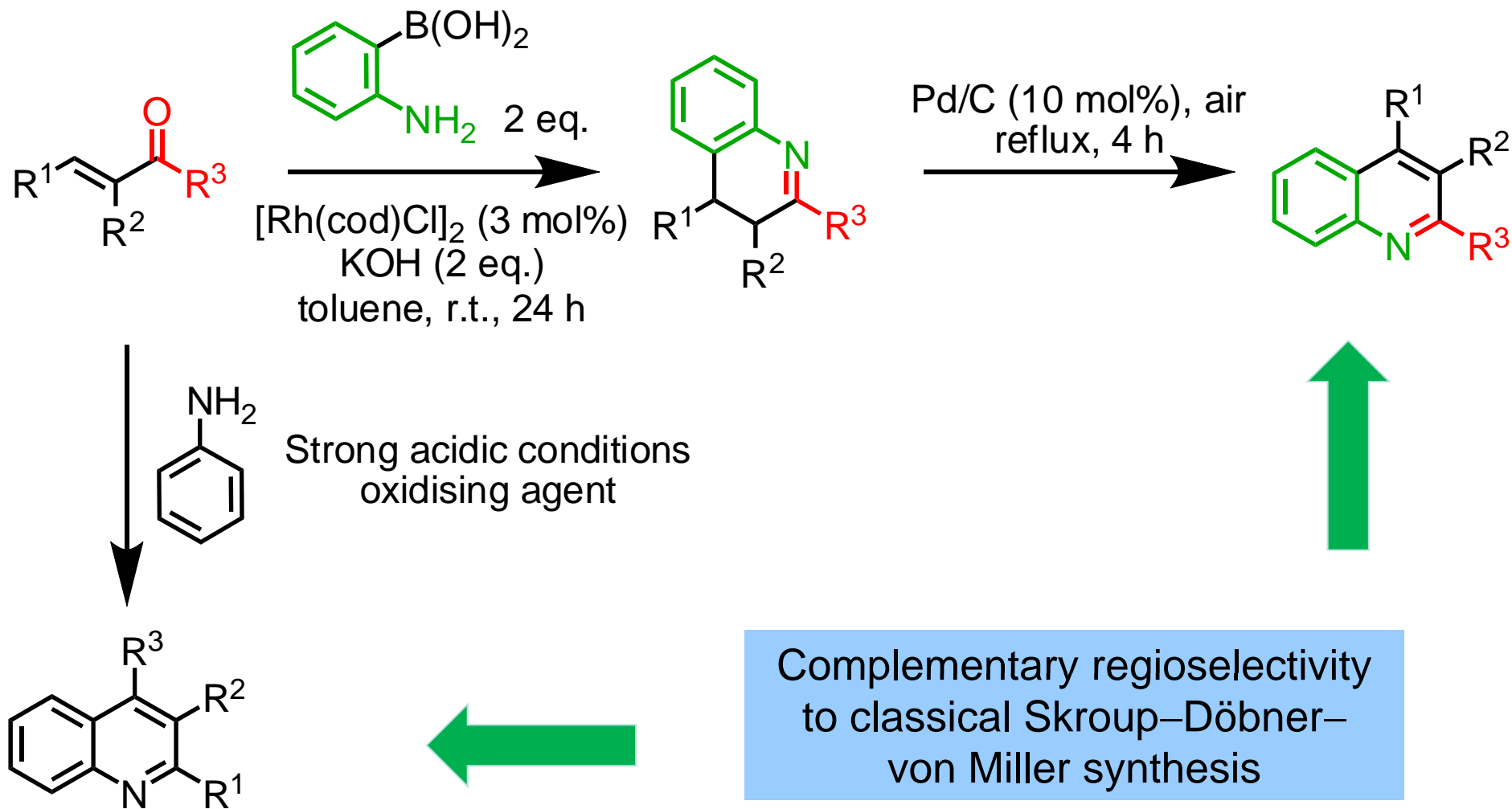


with Steve Marsden (Leeds), David House, Gordon Weingarten and Amanda Campbell (GSK)

# Application of the Linchpin Strategy in the Synthesis of Heterocycles



# One-Pot Synthesis of Quinolines

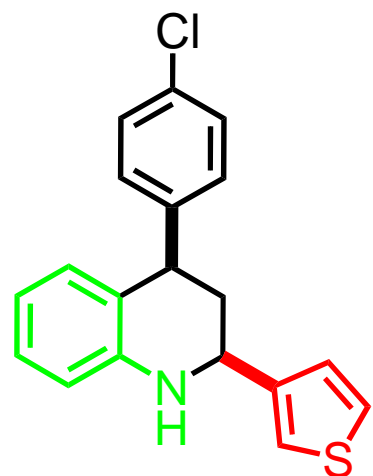
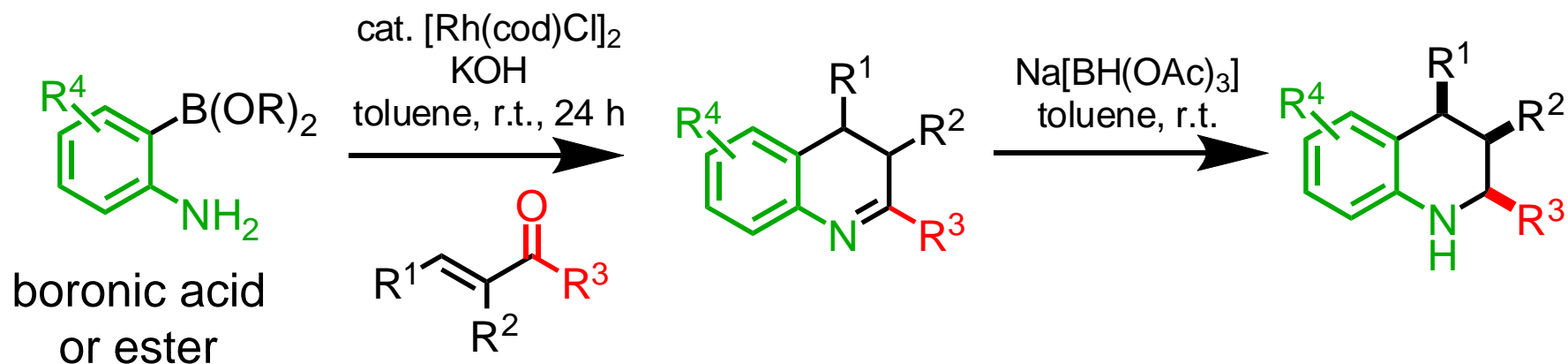


ca. 12 examples with aryl and aliphatic  $\text{R}^1\text{-R}^3$

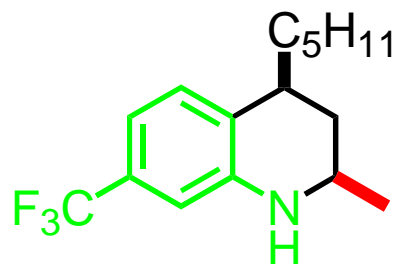
Pinacol boronic esters, prepared from 2-bromoanilines, are also substrates. This allows substitution of the benzenoid ring

Jo Horn

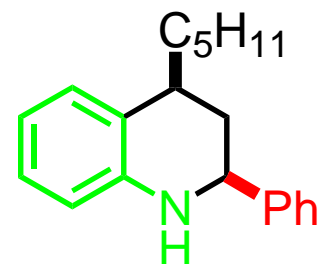
# One-Pot Synthesis of Quinolines



81%, d.r. > 95:5



73%, d.r. 89:11



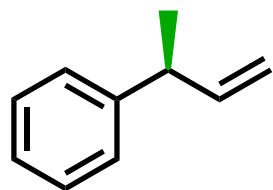
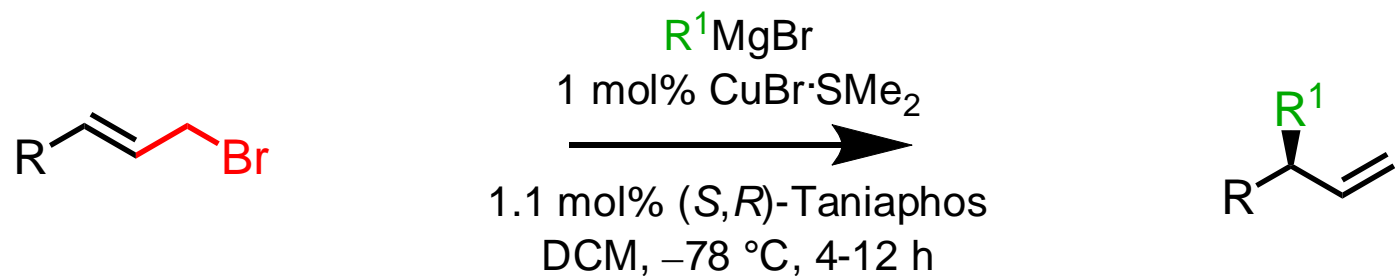
76%, d.r. 95:5

ca. 12 examples with aryl and aliphatic  $R^1$ - $R^3$

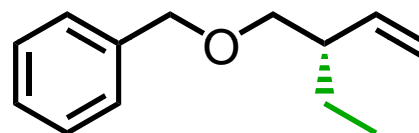
Up to >99% ee possible with 2-NHBoc boronic esters (cat. DuanPhos)

Jo Horn and John Li

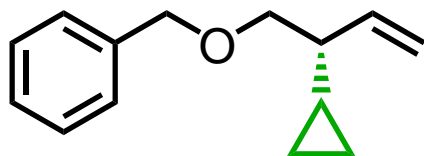
# Cu-catalysed asymmetric alkylation



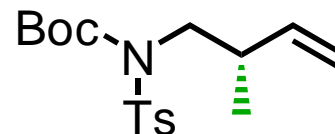
61%,  $S_N2'/S_N2$  92:8



97%,  $S_N2'/S_N2 > 95:5$ , ee 91%



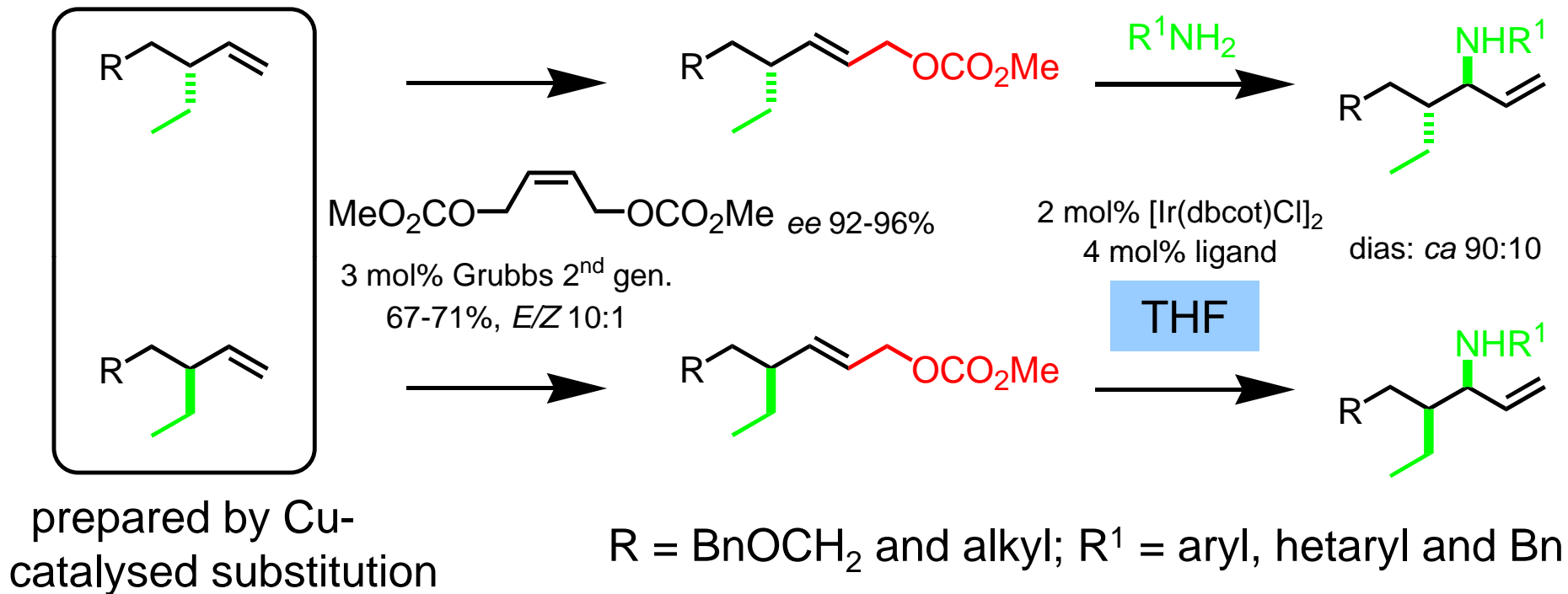
24%,  $S_N2'/S_N2 = 75:25$



86%,  $S_N2'/S_N2 > 95:5$ , ee 90%

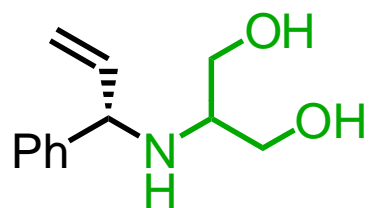
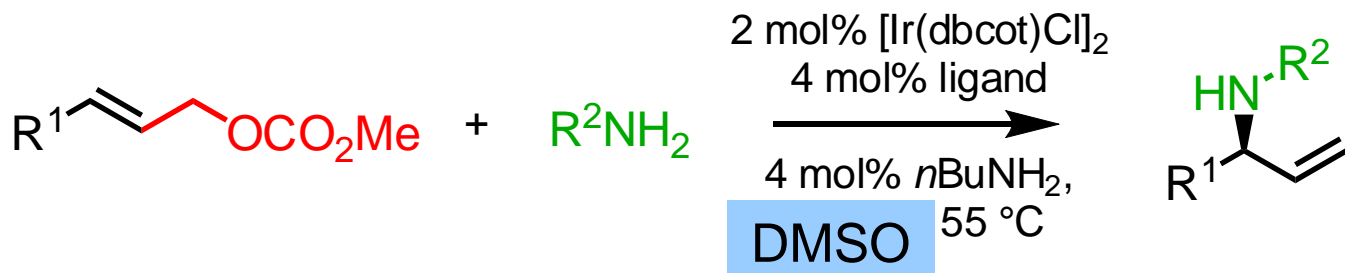
The reaction is possible with many different substituents

# The approach may be used iteratively

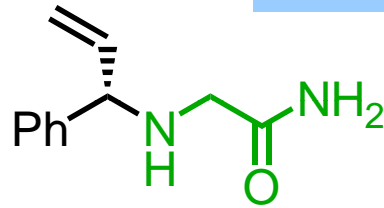


Virtually no match/mismatch effects are observed. The Ir-catalysed substitution proceeds under catalyst control

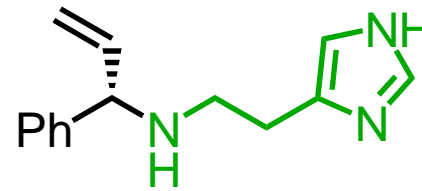
# The Ir-catalysed substitution may be extended to polar amines



85%, 93% ee



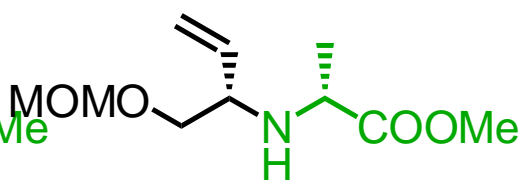
83%, 69% ee



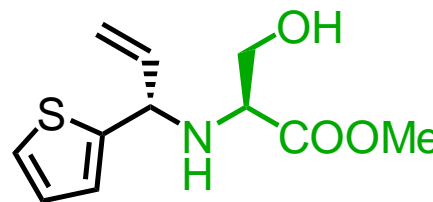
66%, 97% ee



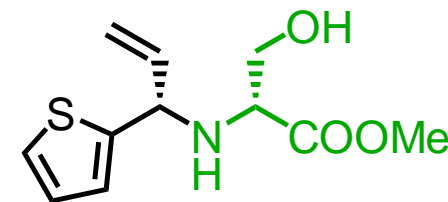
74%, d.r. 92:8  
**Matched**



74%, d.r. 90:10  
**Mismatched**



84%, d.r. 88:12  
**Matched**

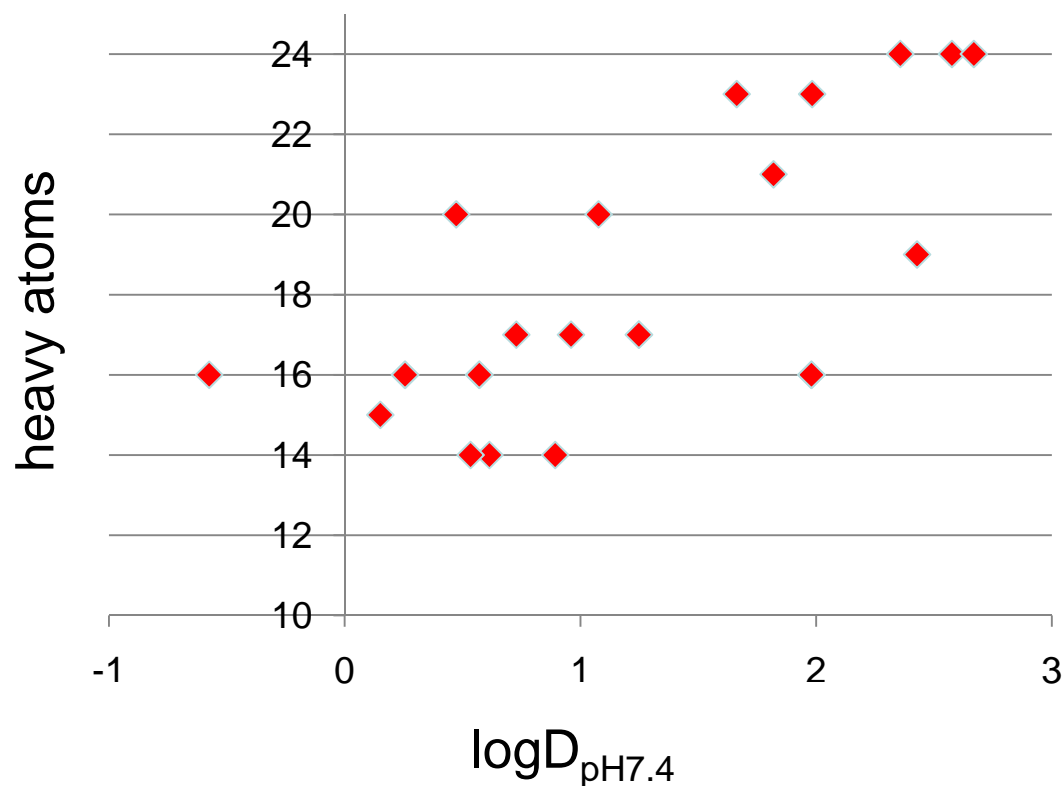
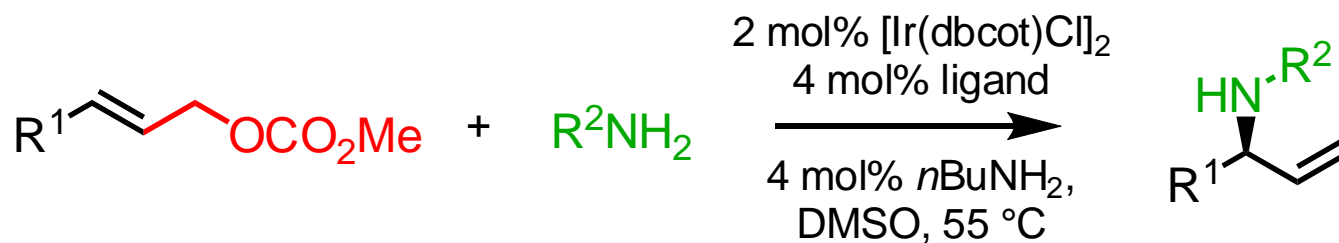


74%, d.r. 69:31  
**Mismatched**

High levels of catalyst control are observed

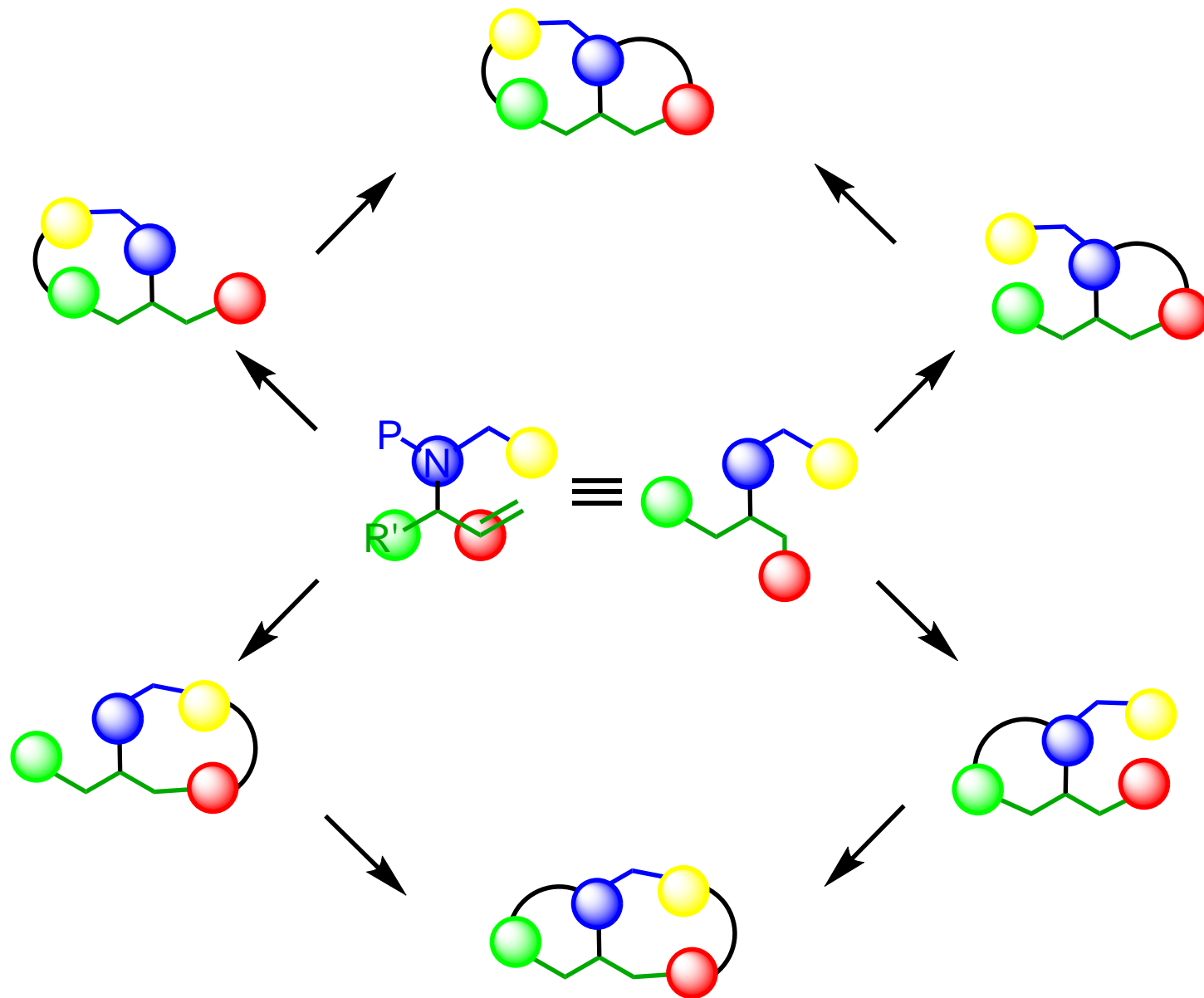
Paolo Tosatti

# The Ir-catalysed substitution may be extended to polar amines





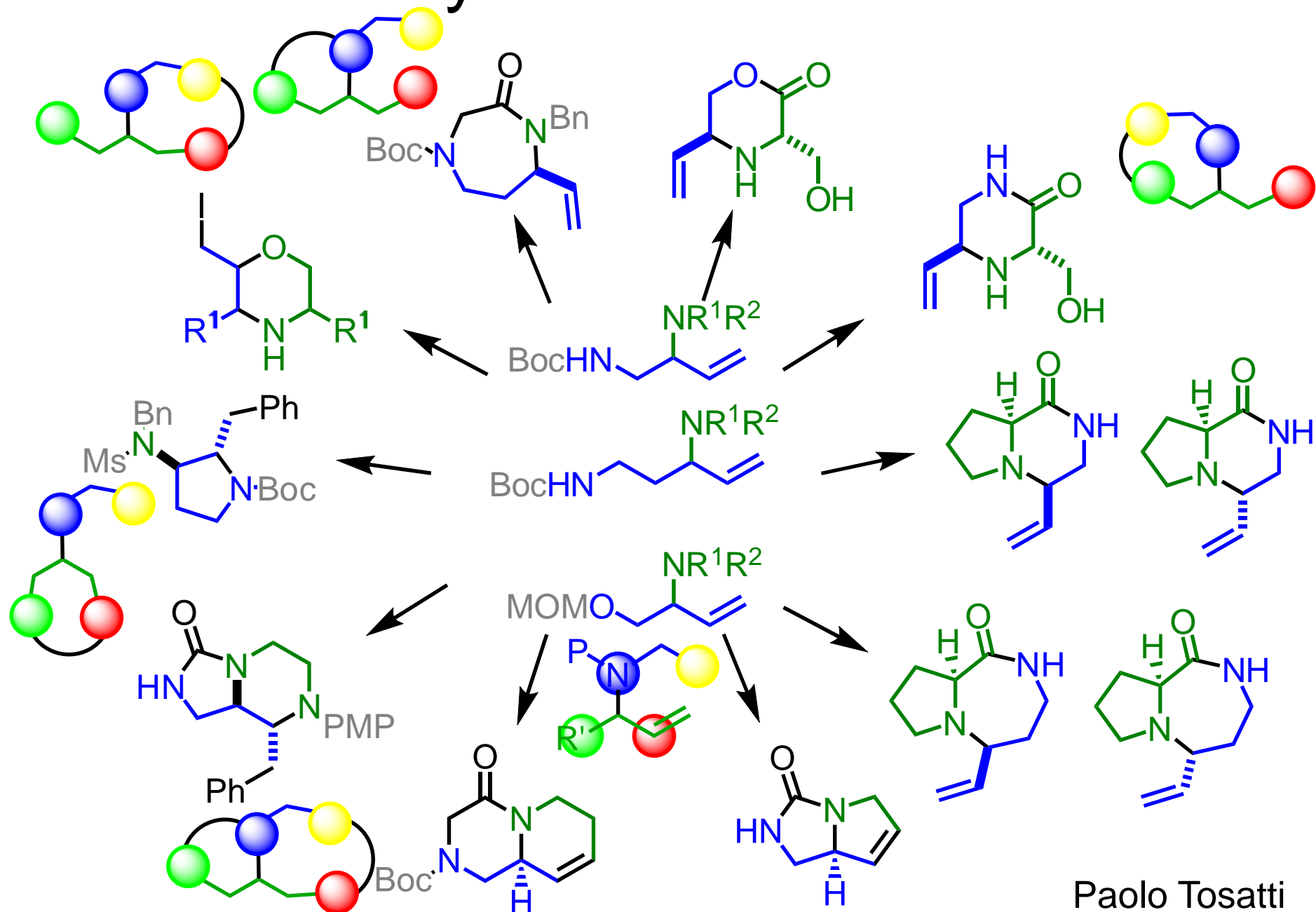
# Ir-enabled synthesis of lead-like cores



# Ir-enabled synthesis of lead-like cores



# Ir-enabled synthesis of lead-like cores



Paolo Tosatti



# Acknowledgments

## PhD students

Robert Hodgson

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