REACTIVITY EXPLORATION OF ALKYNE-FUNCTIONALIZED BICYCLOBUTANES: ACCESS TO MEDICINALLY RELEVANT MULTICYCLIC COMPOUNDS

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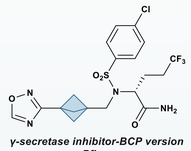
INTRODUCTION

A C_{sp3}-rich bioisosteres of aromatics

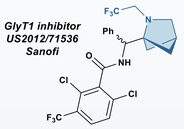
- Preserves spatial features
- Improved metabolic stability
- Enhanced binding selectivity
- Three-dimensional structure with substituents in a defined orientation
- Fully saturated and highly strained

B Bioisosteres – Escape from Flatland

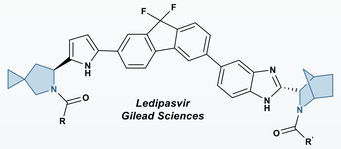


γ-secretase inhibitor-BCP version
Pfizer

GlyT1 inhibitor
US2012/71536
Sanofi

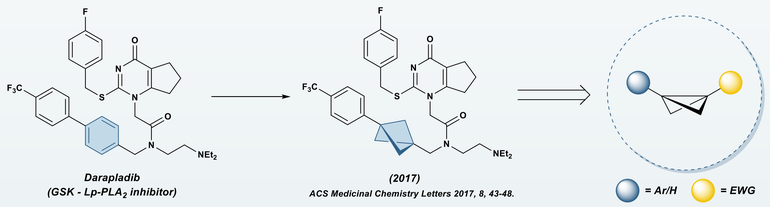


J. Med. Chem. 2012. 55.7. 3414-3424: Med. Chem. 2014.57.5. 2033-2046

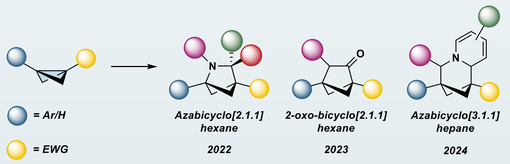


Ledipasvir
Gilead Sciences

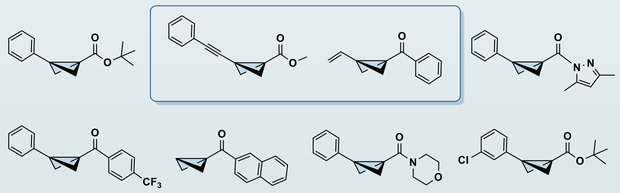
- sp^3-rich hybridized carbons
- Conformational rigidity
- Higher number of chiral centres



C Our Previous Work: Synthesis and exploring reactivity of bicyclobutanes

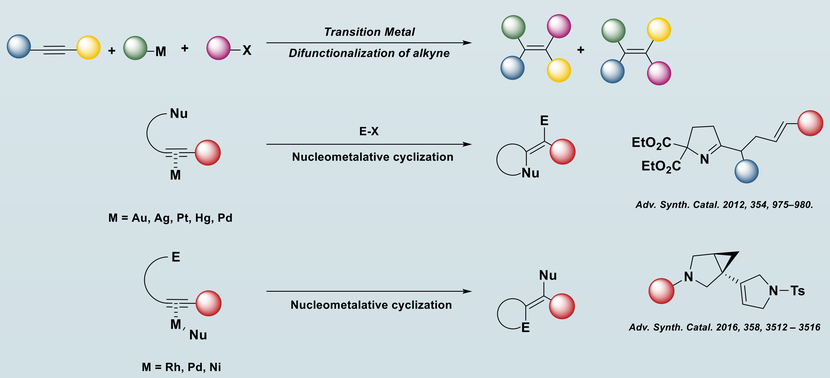


- Substituents stabilize the strained ring
- Facilitates certain transformations
- Limited in reactivity
- Unstable under most organometallic conditions



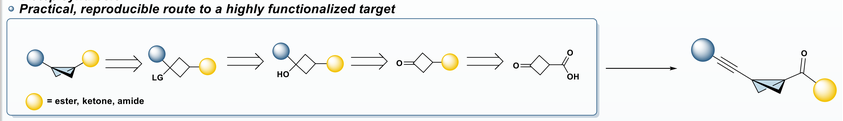
- Limited examples
- Lengthy, low-yielding synthetic routes
- Organometallic chemistry underexplored
- Offers unique reactivity

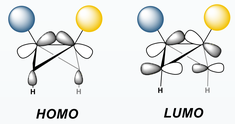
D Transition Metal-Catalyzed Functionalization of Alkynes



PROJECT OBJECTIVE

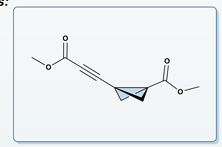
- 4-step synthesis
- Practical, reproducible route to a highly functionalized target

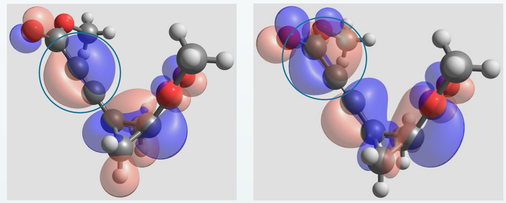




- Strain alters electron distribution
- More nucleophilic in certain contexts
- Strain and orbital alignment also activates toward ring-opening or cycloaddition

Bicyclobutane used for calculated molecular orbitals:



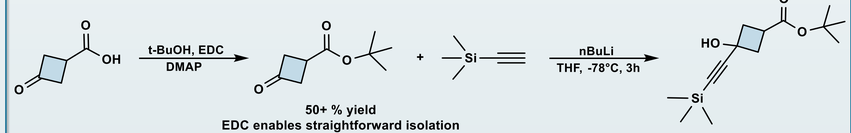


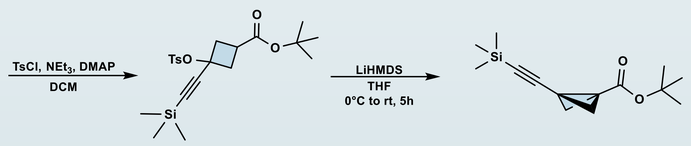
Alkyne adds further complexity by allowing reactivity at:

- The alkyne
- The strained ring
- Both the alkyne and strained ring

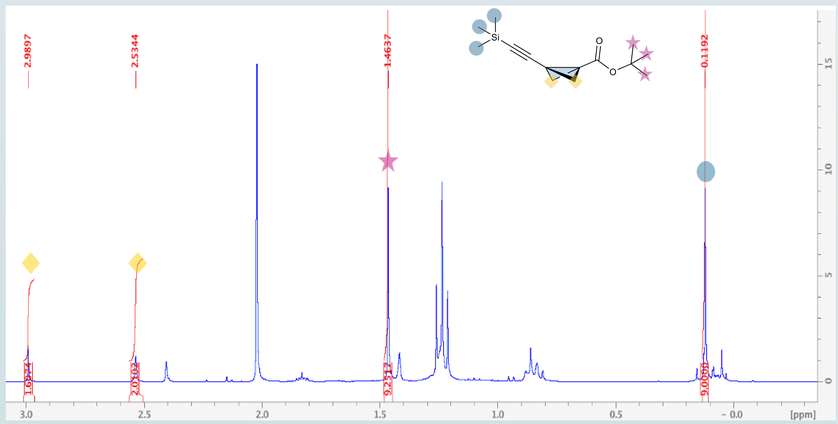
RESULTS

Synthesis route to alkynyl bicyclo[1.1.0]butanes



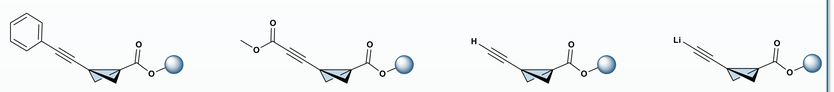


Characterization

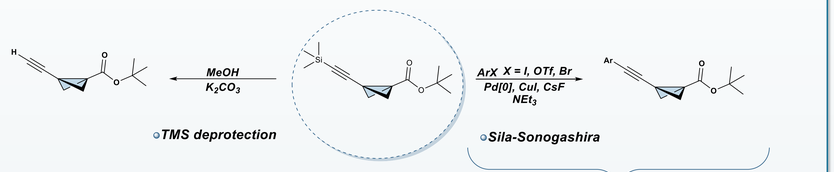


FUTURE WORK

Expansion of the Alkynyl Bicyclobutane Library

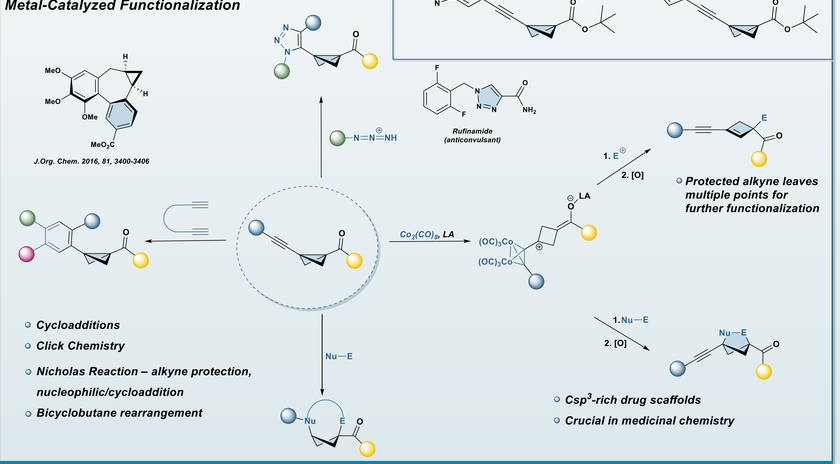


Reactivity Prospects of the TMS Acetylene Derivative



- TMS deprotection
- Sila-Sonogashira
- One alkynyl bicyclobutane allows access to a wide variety of more

Metal-Catalyzed Functionalization



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ACKNOWLEDGEMENTS

This research was supported by the Jamie Cassels Undergraduate Research Awards, University of Victoria
Spring 2026