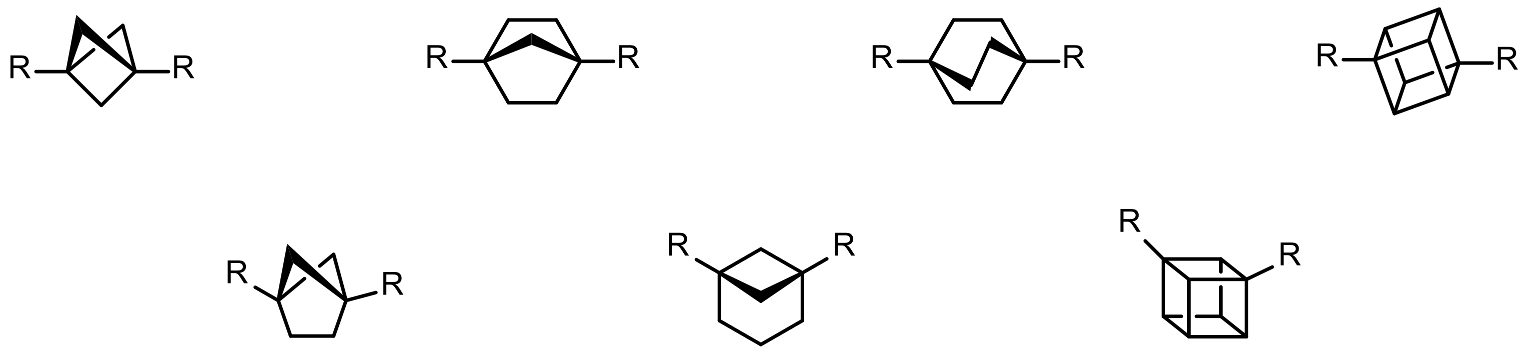
Bioisosteres for Benzene



Nick Wade
Denmark Group Meeting

July 29th, 2025

Form Follows Function

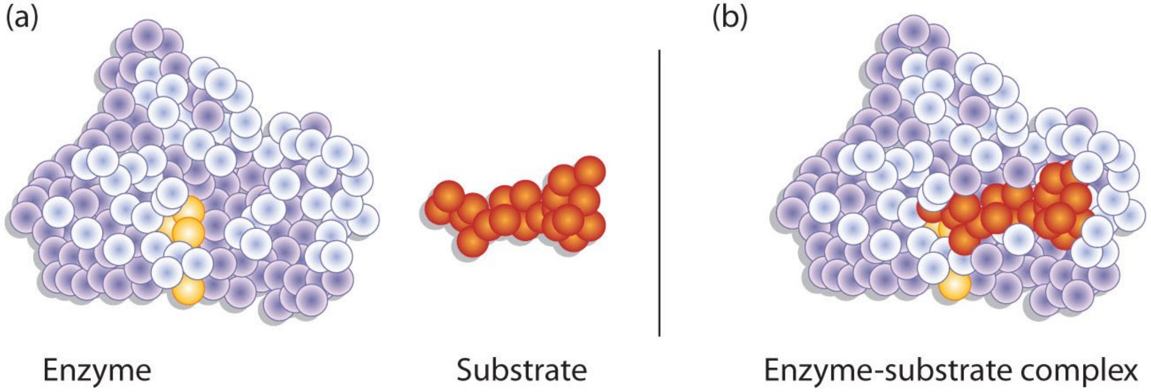
<u>On the macroscopic scale:</u> Giraffes, fish and sports cars

Giraffes wouldn't have long necks if they grazed on low-lying grasses

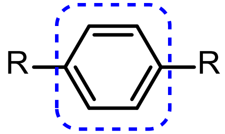
Fish wouldn't have gills and fins if they walked on land

SED's corvette wouldn't have a sleek design and a V8 engine if all he did was drive the speed limit

<u>On the microscopic scale:</u> Enzyme binding pockets



<u>Desired Function</u>:
Enzyme binding



Different form, similar function:
"Bioisostere"

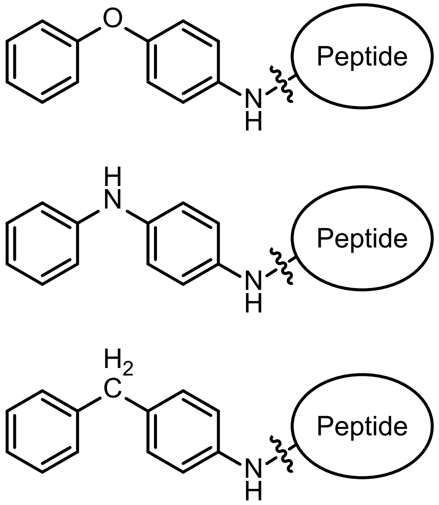
https://courses.lumenlearning.com/suny-orgbiochemistry/chapter/18-6-enzyme-action/

Bioisostere: Definition and Classical Examples

"Bio" = biological   "Iso" = same

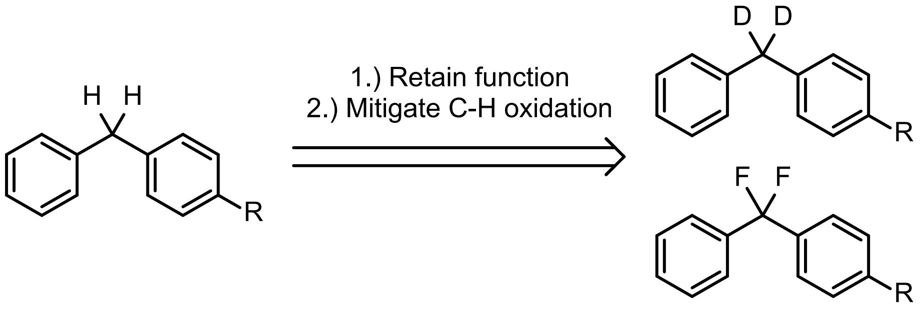
Thornber (1979): Groups or molecules which have chemical and physical similarities producing broadly similar biological effects.

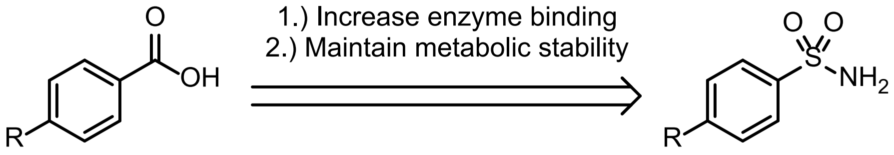
Hans Erlenmeyer (Grandson of Emil Erlenmeyer) in 1932 reported the first example of intentional isosterism:



All three species were indistinguishable in binding to antibodies and triggered similar immune responses

"Classical" Examples of Bioisosterism:
Functional group manipulation





What about large structural changes to carbocyclic backbones?

Thornber, C.W. Isosterism and molecular modification in drug design. *Chem. Soc. Rev.* **1979**, 8, 563., Erlenmeyer, H., Berger, E., Biochem Z. **1932**, 252, 22.

Presentation Outline: Nonclassical Bioisosteres

Why Use a Bioisostere?
When to and when not to replace an aromatic ring

General Synthetic Strategies:
two success stories, pilot scale synthesis
and modern methods

Conclusion and Outlook:
new isosteres and new methods

Tunable Parameters In Drug Discovery: Early *In-vitro* Studies

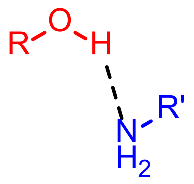
In vitro:
Lipinski's rule of 5: (For oral drugs)
-5 hydrogen-bond donors

-10 (5 × 2) hydrogen-bond acceptors

-a molecular weight greater than 500

-a calculated Log P (cLogP) greater than 5.

H bond donor



H bond acceptor

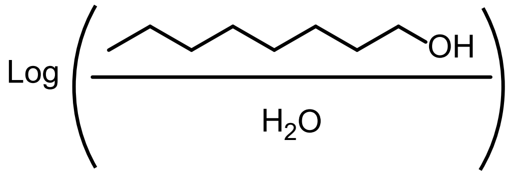
During SAR Studies:

-Conformational rigidity and enzyme binding
(Lower flexibility leads to lower promiscuity)

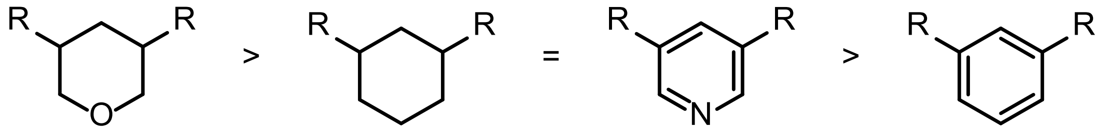
-Liver cell metabolism ($T_{1/2}$)

-Replacement of potentially problematic fragments

LogP = partition coefficient between octanol and water
(Higher value, more lipophilic, less water soluble)



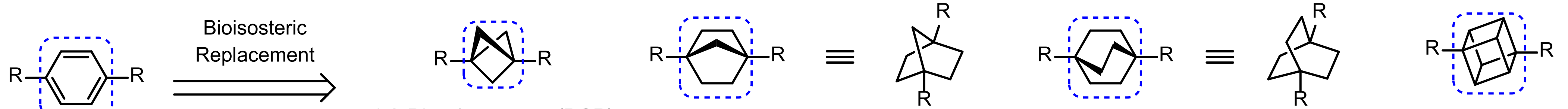
GSK's systematic analysis of trends
concerning solubility and bioavailability:



Drug Discov. Today, **2011**, 16, 164–171,

Common Isosteres for Disubstituted Benzenes

Copious Examples of Disubstituted Benzene Isosteres:

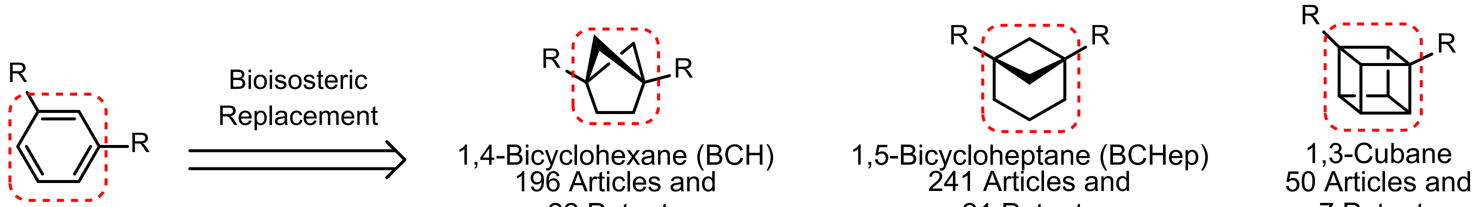


1,3-Bicyclopentane (BCP)
242 Articles and
424 Patents

1,4-Bicycloheptane (BCHep)
133 Articles and
120 Patents

1,4-Bicyclooctane (BCO)
524 Articles and
529 Patents

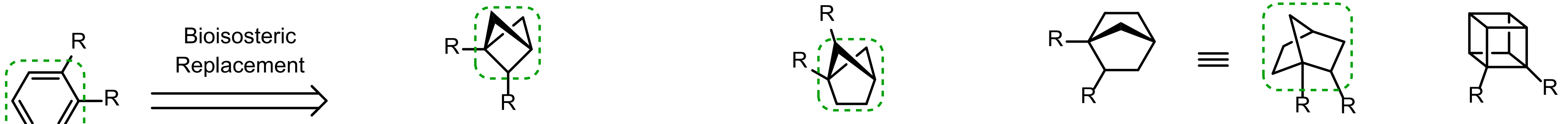
1,4-Cubane
196 Articles and
60 Patents



1,4-Bicyclohexane (BCH)
196 Articles and
22 Patents

1,5-Bicycloheptane (BCHep)
241 Articles and
21 Patents

1,3-Cubane
50 Articles and
7 Patents

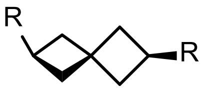


1,2-Bicyclopentane (BCP)
31 Articles and
7 Patents

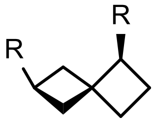
1,5-Bicyclohexane (BCH)
315 Articles and
11 Patents

1,6-Bicycloheptane (BCHep)
670 Articles and
157 Patents

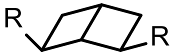
1,2-Cubane
48 Articles and
6 Patents



1,5-Spiro[3.3]heptane
57 articles and
87 Patents



1,4-Spiro[3.3]heptane
17 articles and
10 Patents



1,3-Ladderane
20 Articles and
3 Patents

Two Lingering Questions:
1.) What physical properties can be modulated with bioisosteric replacement?
2.) When can arenes become problematic?

Qin, T. et al. *Nat. Rev. Chem.* **2024**, 8, 605–627.

Design Principles – Size and Exit Vector Angles

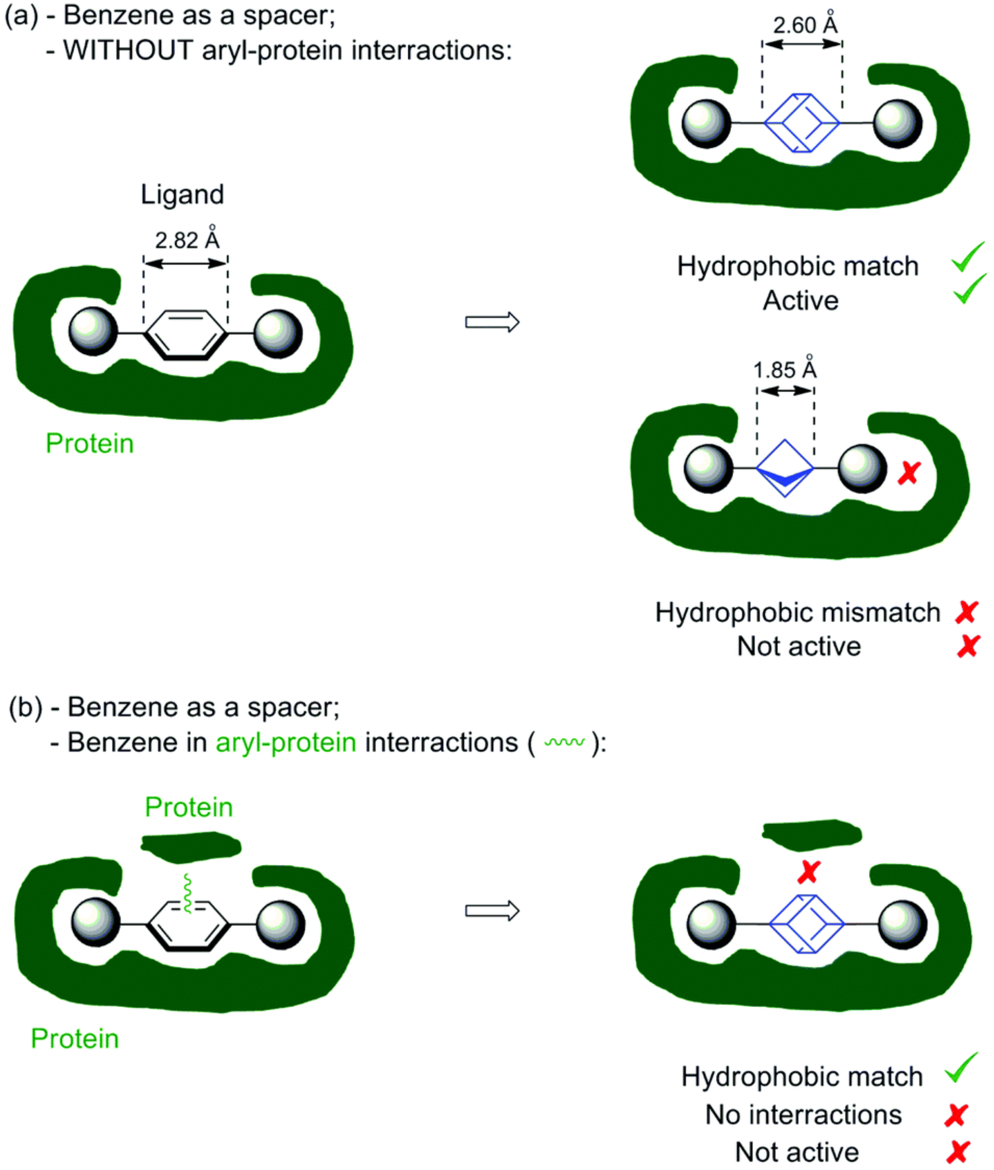
1.) The linker must structurally closely resemble the residue of benzene and have a similar physico-chemical profile.

2.) It must be conformationally rigid – bicyclic or polycyclic – to fix the positions of the substituents in space.

3.) The distance between the substituents must be similar to that in the disubstituted benzenes.

-Pavel K. Mykhailiuk, CSO of Enamine

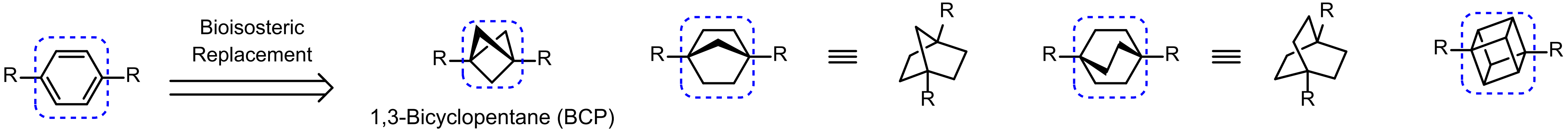
Enamine



Mykhailiuk, P. *Org. Biomol. Chem.* **2019**, 17, 2839

Design Principles – Modulation of cLogP and Solubility

Isosteres can be used to increase or decrease cLogP to help modulate solubility and lipophilicity:



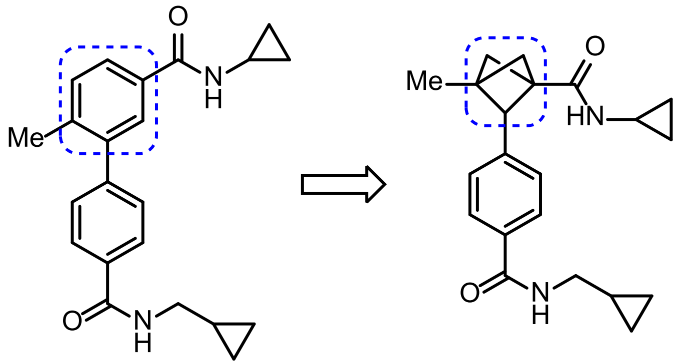
p-Benzene:
cLogP: 3.01*

1,3-Bicyclopentane (BCP)
cLogP: 2.35*

1,4-Bicycloheptane (BCHep)
cLogP: 3.19*

1,4-Bicyclooctane (BCO)
cLogP: 3.61*

1,4-Cubane
cLogP: 1.59*



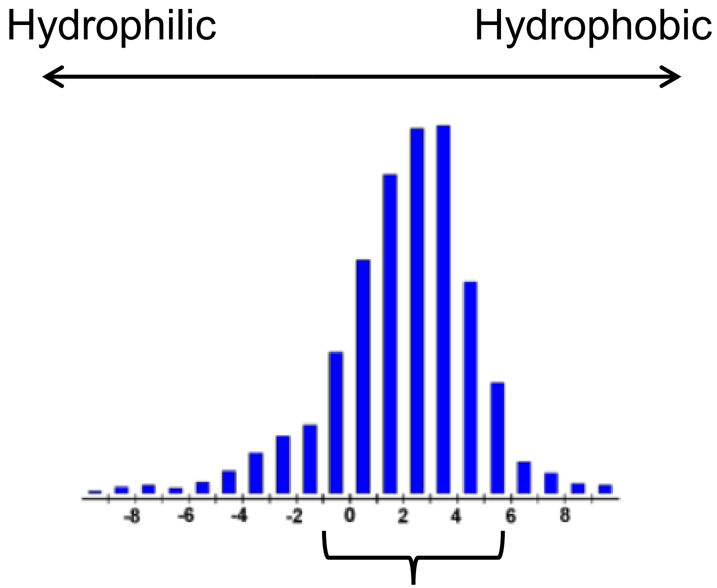
p38 Kinase Inhibitor:

LogP: 2.24
Solubility (H_2O, pH 7.4): 4 μM

BCP Analogue:

LogP: 1.95
Solubility (H_2O, pH 7.4): 174 μM
Similar cell permeability in test cell lines

p38 Kinase inhibitor vs BCP analogue



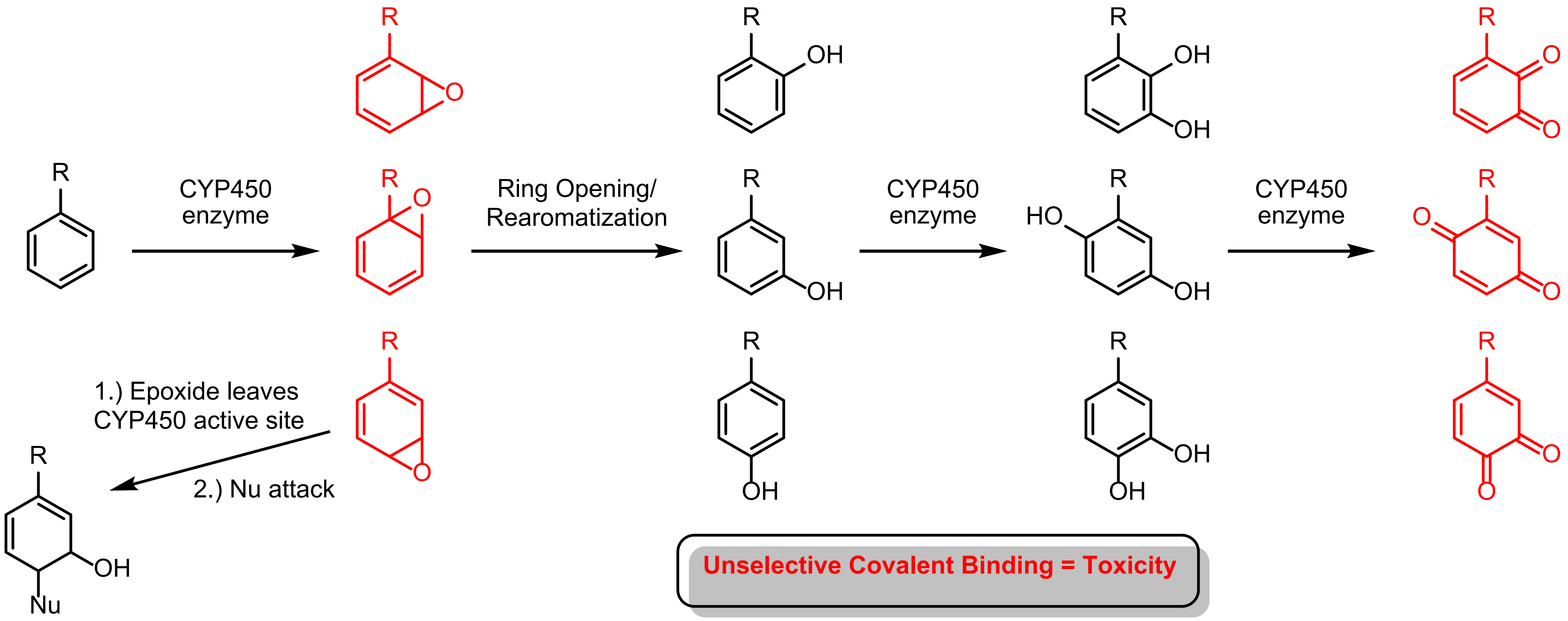
Sweet spot for small molecule drug design

*cLogP values of all scaffolds were calculated with all R groups set as methyl groups

Qin, T. et al. *Nat. Rev. Chem.* **2024**, 8, 605–627 and https://www.organic-chemistry.org/prog/peo/cLogP.html

Oxidation of Arenes by CYP450s

Arene oxidation can lead to cytotoxic byproducts:



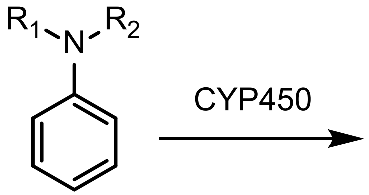
Well-designed arene replacement in some cases can mitigate undesired oxidation and reduce cytotoxicity *in vivo*

Meanwell, N and Subbaiah, M. *J. Med. Chem.* **2021**, 64, 14046−14128.

Mini Group Problem and Aniline Replacement

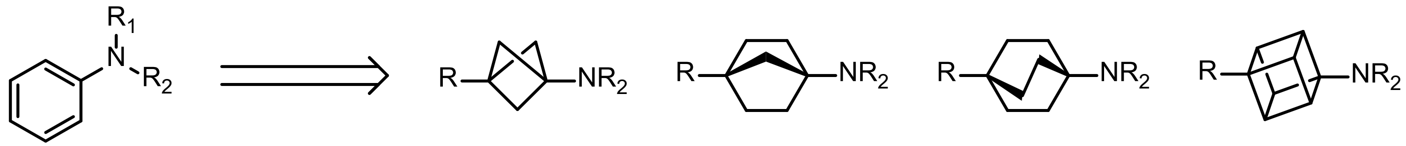
How can dialkyl anilines act as metabolic liabilities in drug molecules?

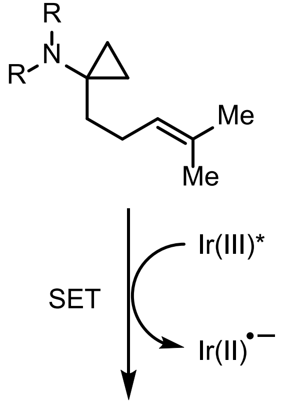
Draw the reactive/ cytotoxic species that will lead to undesired drug toxicity



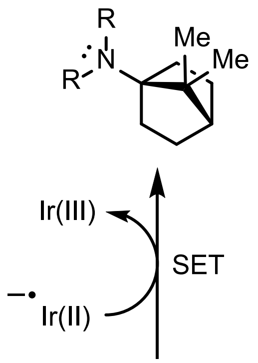
R= alkyl

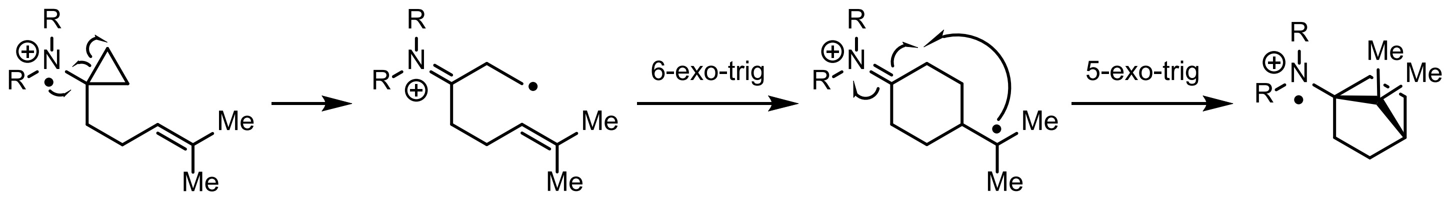
Electron rich arenes have a higher propensity for CYP450 oxidation





Corey Stephenson, University of British Columbia



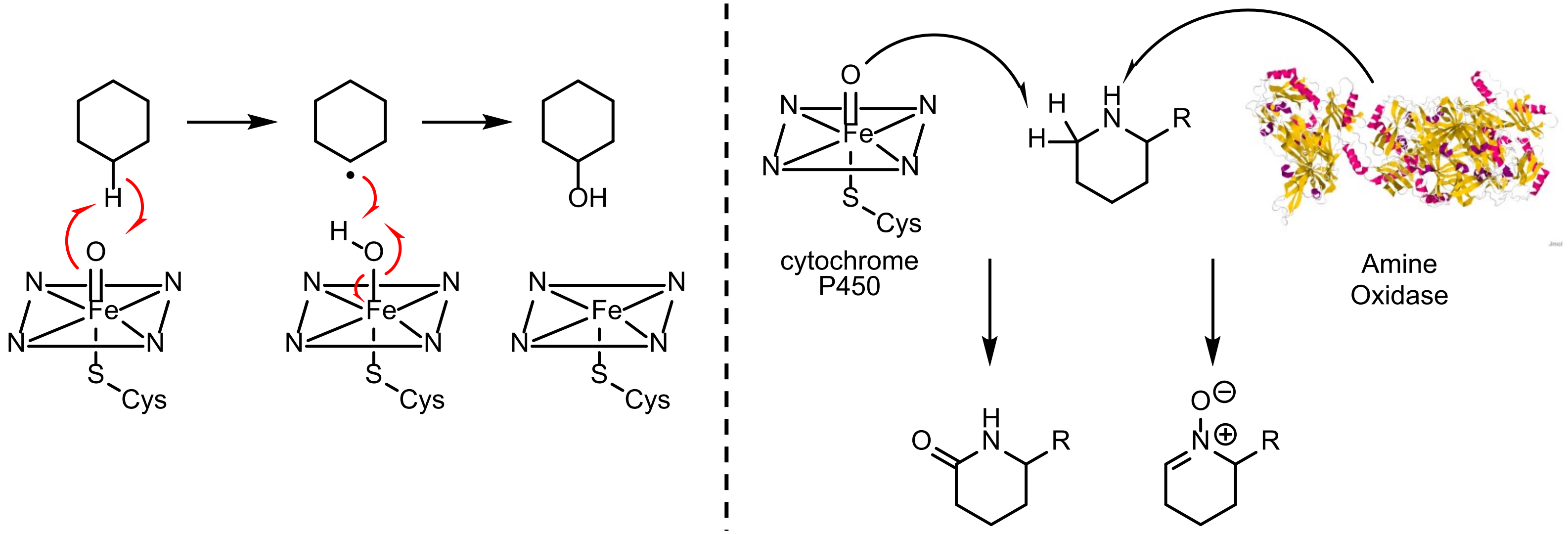


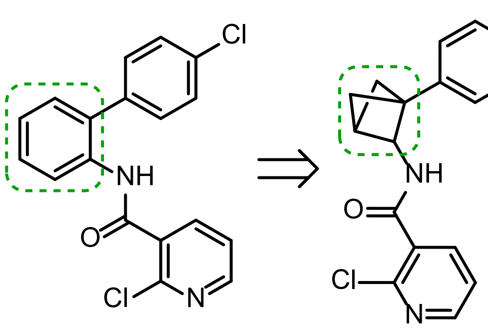
Stephenson and co. tested compounds versus human liver cell metabolism and found similar $T_{1/2}$ values but no electrophilic, potentially cytotoxic byproducts from metabolism

Stephenson et. al., *ACS Med. Chem. Lett.* **2020**, 11, 10, 1785–1788, Stephenson et. al., *Chem* **2019**, 5, 215–226

C-H and N oxidation – Drug Decomposition Pathways

CYP450 and oxidases can rapidly metabolize aliphatics and heteroaliphatics:





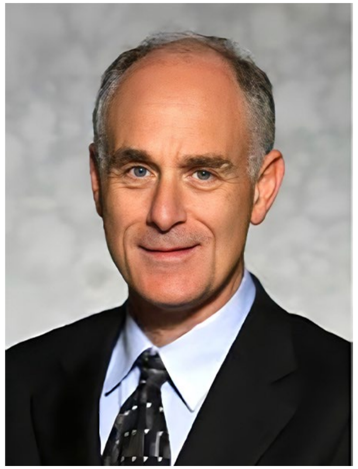
Boscalid

BCP-Boscalid

BCP-Boscalid solubility (aq, pH 7.4) was significantly improved

Liver cell metabolism: 3.5x shorter $T_{1/2}$

"In the iterative optimization of a lead molecule with a phenyl ring where bioisosteric replacement is contemplated, an important consideration is understanding whether the phenyl ring contributes to a liability that requires mitigation.
Care must be exercised in selecting an appropriate bioisostere when it has to simultaneously accommodate the role of the phenyl ring in drug–target interactions."
-Nicholas Meanwell, BMS, Head of Antiviral Discovery Chemistry (1993-2015)



Meanwell, N and Subbaiah, M. *J. Med. Chem.* **2021**, 64, 14046−14128.

Presentation Outline: Nonclassical Bioisosteres

Why Use a Bioisostere?
When to and when not to replace an aromatic ring

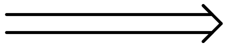
General Synthetic Strategies:
two success stories, pilot scale synthesis
and modern methods

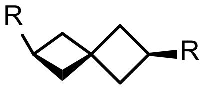
Conclusion and Outlook:
new isosteres and new methods

Bioisostere Preparation: Strain Driven Synthesis

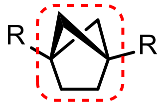
Benzene:
Ring Strain:
0 kcal/mol

Bioisosteric
Replacement

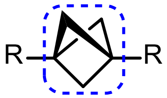




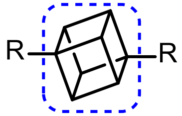
Spiro[3.3]heptane
Ring Strain:
~54 kcal/mol
over 7 atoms



BCH
Ring Strain:
~58 kcal/mol
over 6 atoms

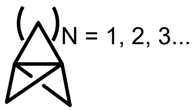


BCP
Ring Strain:
~60 kcal/mol
over 5 atoms

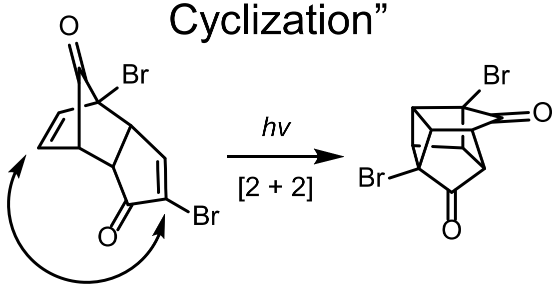


1,4-Cubane
Ring Strain:
~142 kcal/mol
over 8 atoms

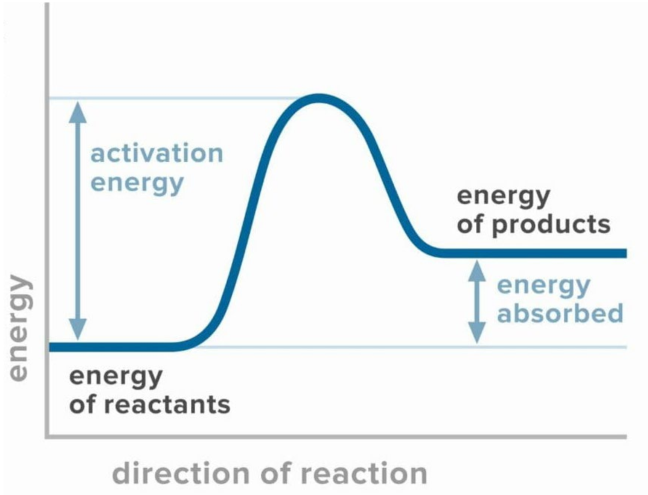
“[N.1.1]-Propellane difunctionalization”



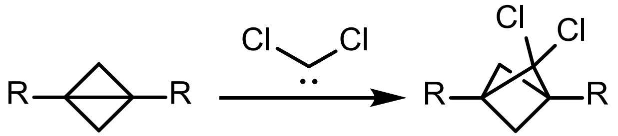
“Photochemical Cyclization”



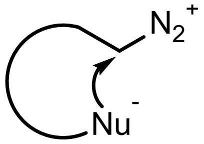
Only So Many Ways to Build In Strain:



“Breaking Weak C-C bonds”



“Strong Nucleophiles and Great Leaving Groups”



John D. Roberts and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* ISBN 0-8053-8329-8

Strategy #1: [N.1.1]-Propellane Difunctionalization

Multiple synthetic strategies and history covered by Kimberly's group meeting:

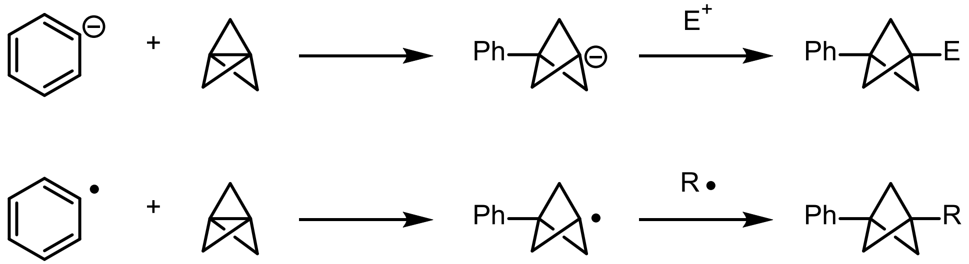
HISTORY OF [1.1.1]PROPELLANES AND BICYCLO[1.1.1]PENTANES

KIMBERLY HILBY

10/29/2019

https://denmarkgroup.web.illinois.edu/wp-content/uploads/2021/09/Kimberly-Hilby-Presentation-October-2019.pdf

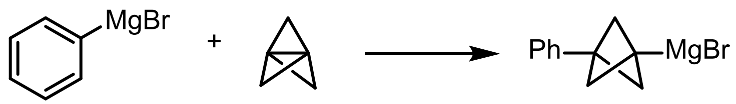
Extensive coverage of polar and radical reactivity of [1.1.1]-Propellane:



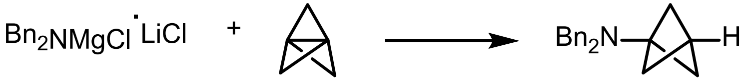
Modern strategy:

Addition of X-Y across internal bond of [1.1.1]-propellane:

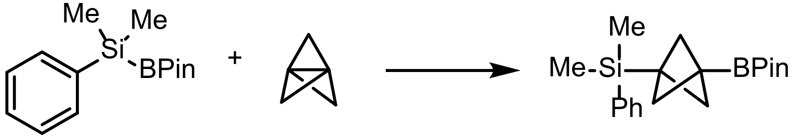
Wiberg, 1994:



Baran, 2016:



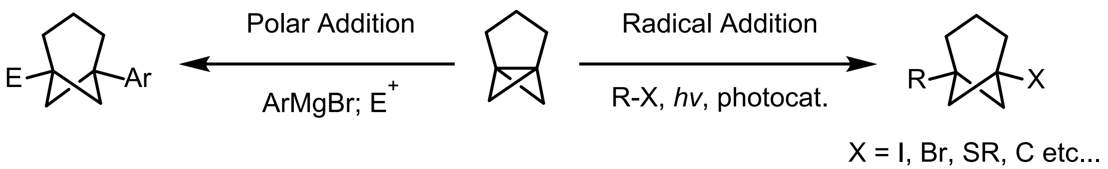
Uchiyama, 2020:



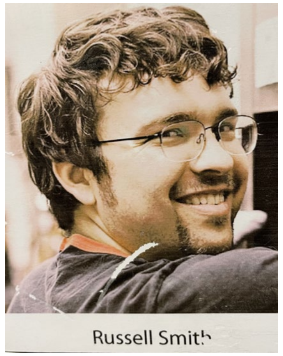
1.) Wiberg et. al., *J. Am. Chem. Soc.* **1994**, 112, 2194
2.) Baran et. al., *Science*, **2016**, 351, 241
3.) Uchiyama et. al., *Angew. Chem. Int. Ed.* **2020**, 59, 1970.

Strategy #1: Propellane Difunctionalization

Application to larger rings: [3.1.1]-Bicycloheptane as a *meta*-benzene isostere:



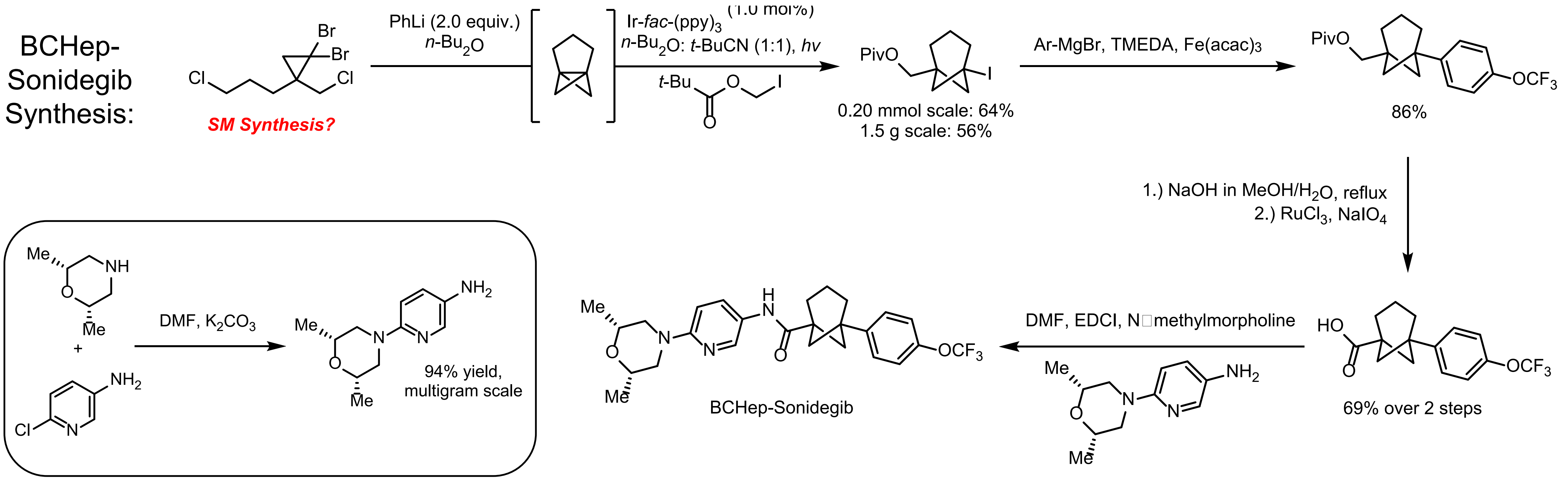
44 Examples, 31-90% yield
Multiple drug scaffolds
Comparison of biological activity



(AbbVie)

Ed Anderson
(Oxford)

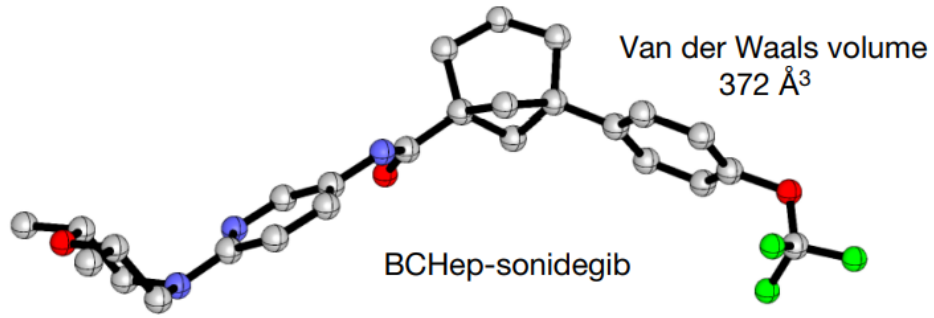
BCHep-Sonidegib Synthesis:

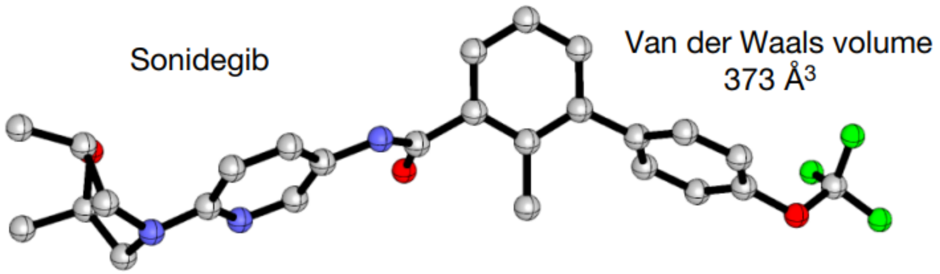


Anderson, E. et. al., *Nature* **2022**, 611, 721–726.

[3.1.1]-BCHep-Sonidegib: Physical and Biological Properties

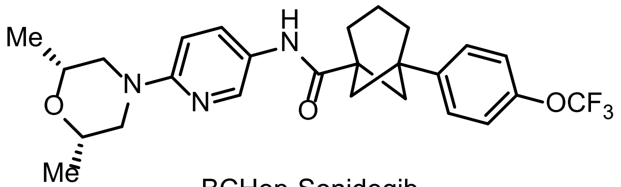
Bond angles and Volume:
Mimics a meta-substituted benzene closely



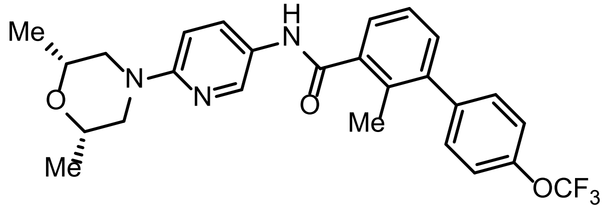


Similar bond angles and Van der Waals volume with minimal conformational flexibility in both cases!

Head-to-head comparison:



BCHep-Sonidegib



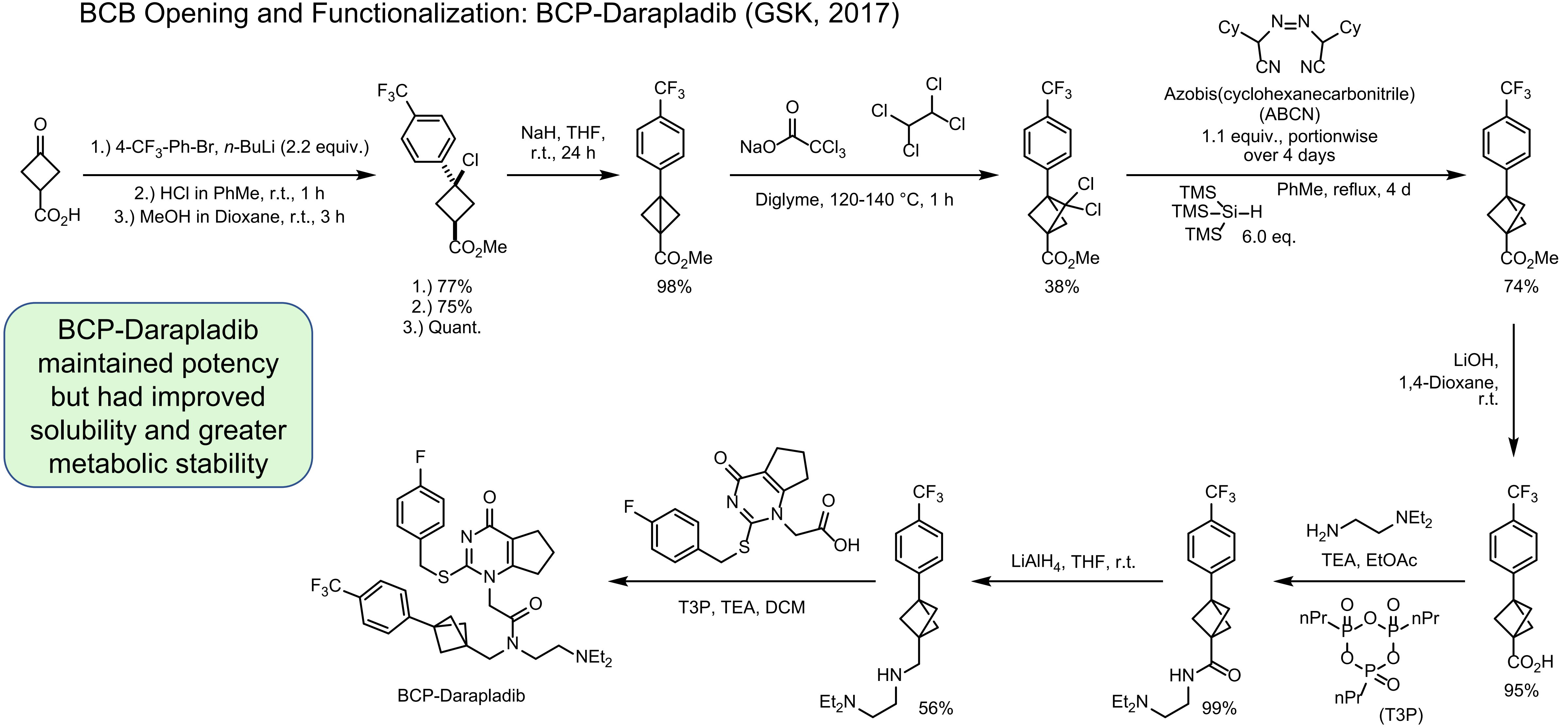
Sonidegib

	BCHep-Sonidegib	Sonidegib
cLogP	6.2	6.8
Caco-2 efflux ratio	0.7	1.1
Liver cell metabolic half life ($T_{1/2}$)	76	70
CYP2C9 Inhibition (μM)	18.5	4.2
CYP2C19 Inhibition (μM)	13.9	>50

New lead as a CYP2C19 inhibitor (used in combination therapeutics to slow oxidation of metabolically unstable compounds)

Strategy #2: Breaking Weak C-C bonds

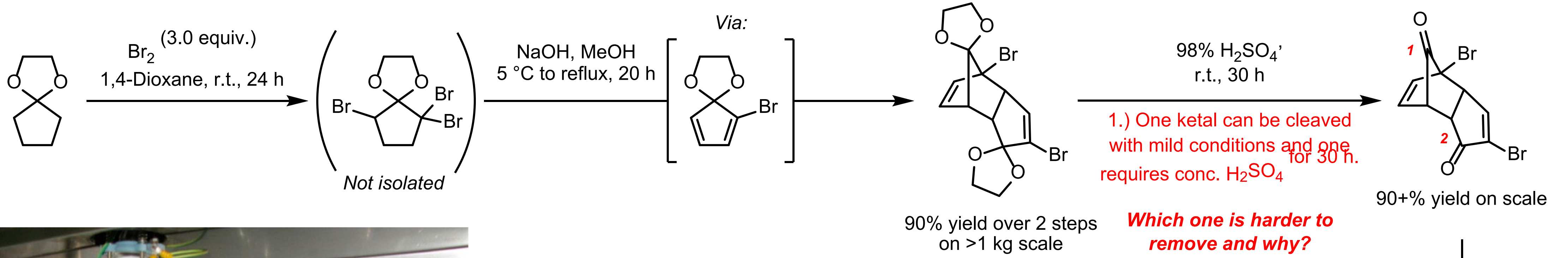
BCB Opening and Functionalization: BCP-Darapladib (GSK, 2017)

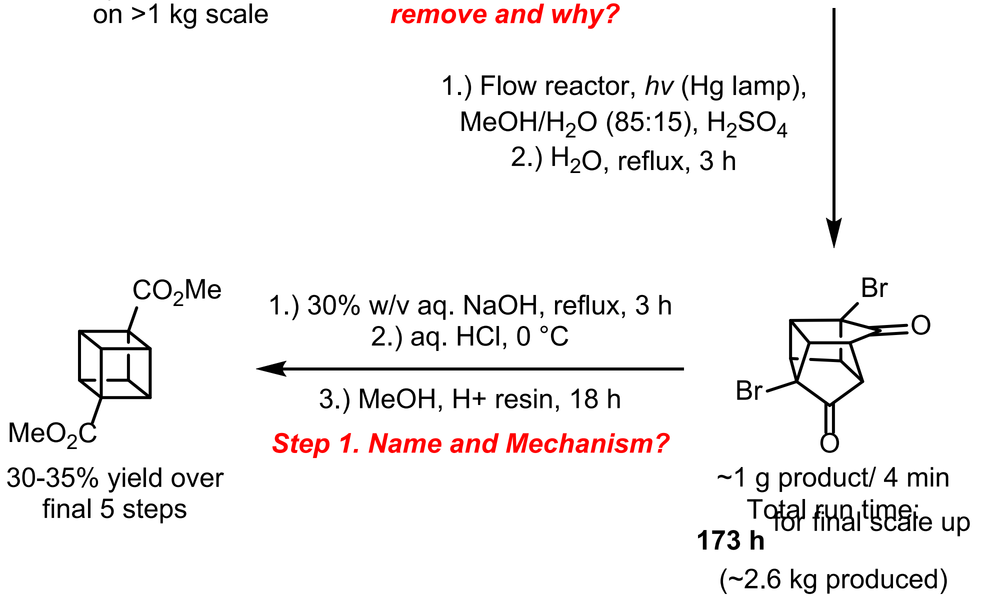


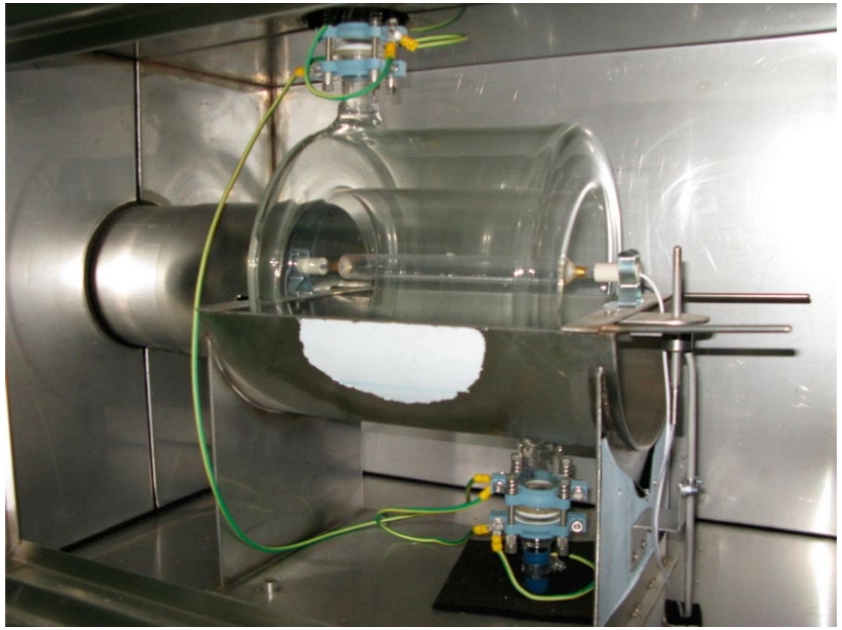
BCP-Darapladib maintained potency but had improved solubility and greater metabolic stability

Strategy #3: Photochemical Cyclization

Photochemical cyclization: Pilot Scale Synthesis of Cubane-1,4-biscarboxylic acid methyl ester (560 g scale)







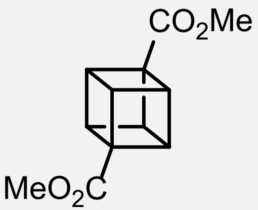
Flow photochemical reactor used for the [2 + 2] cycloaddition step

~560 g produced in an overall 20% yield

Tsanaktsidis, J. et. al., *Org. Process Res. Dev.* **2013**, 17, 1503−1509

Strategy #3: Photochemical Cyclization

Photochemical cyclization: Pilot Scale Synthesis of Cubane-1,4-biscarboxylic acid methyl ester (560 g scale)

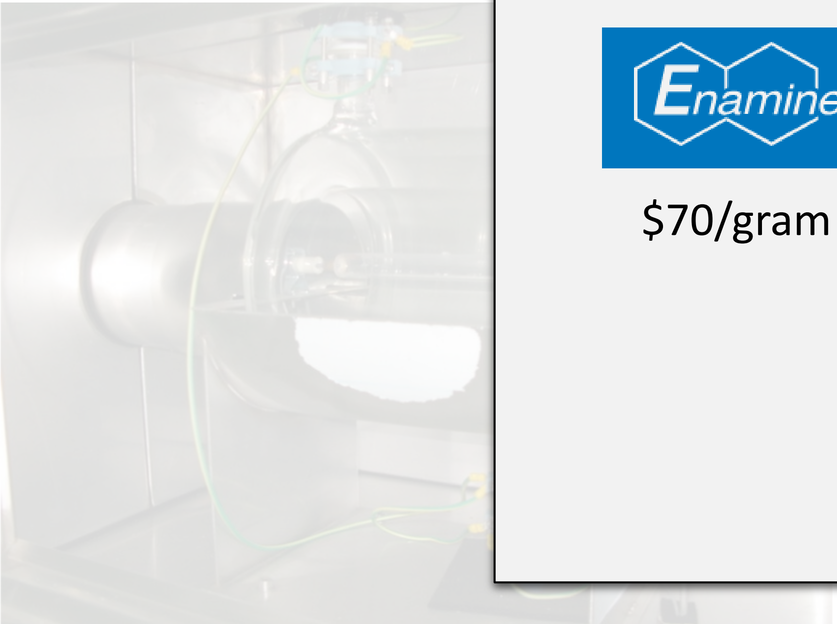


Enamine	Combi-Blocks	AmBeed (A Brand of Bepharm Scientific Inc.)
$70/gram	$105/gram	$90/gram

90+% yield on scale

~1 g product/ 4 min for final scale up

Total run time: 173 h (~2.6 kg produced)



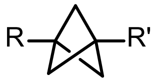
Flow photochemical reactor used for the [2 + 2] cycloaddition step

Tsanaktsidis, J. et. al., *Org. Process Res. Dev.* **2013**, 17, 1503−1509

Strategy #4: Strong Nucleophiles and Great Leaving Groups

Enamine

Pavel K. Mykhailiuk

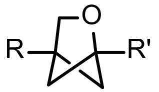


Still too nonpolar, poorly water soluble

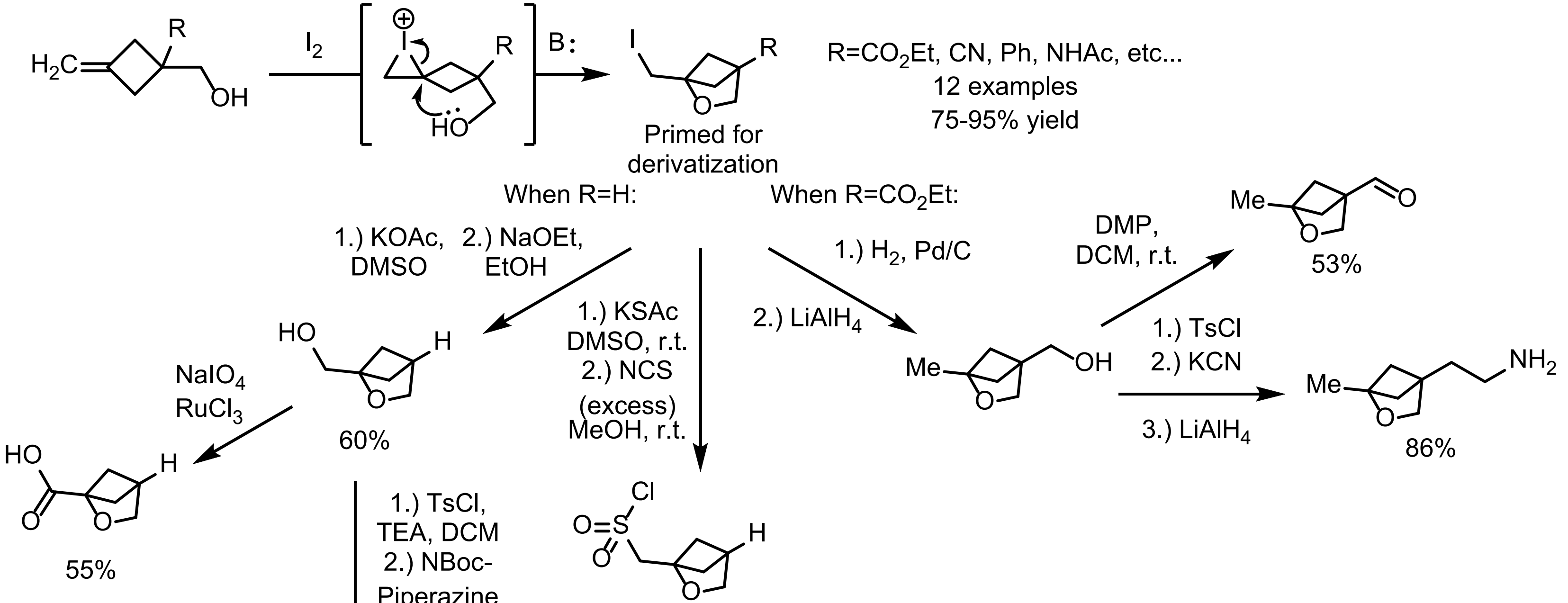
||

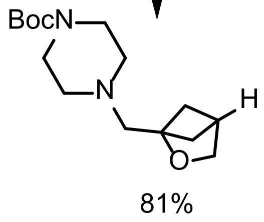
Improved Function

⇓

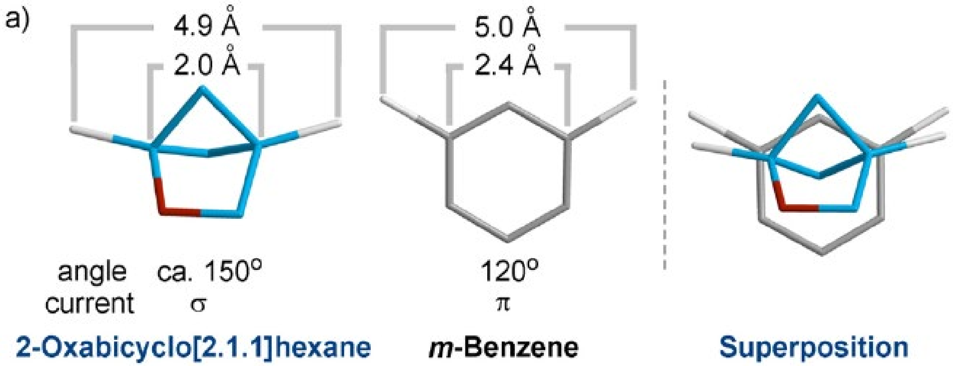


Oxa-[2.1.1]-BCH
More water soluble



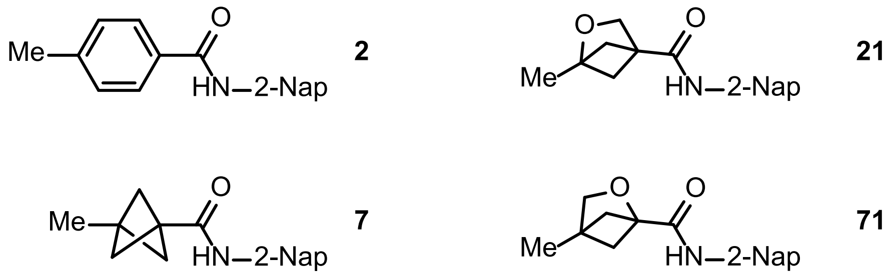


Meta-disubstituted benzene mimic:



Enhanced solubility:

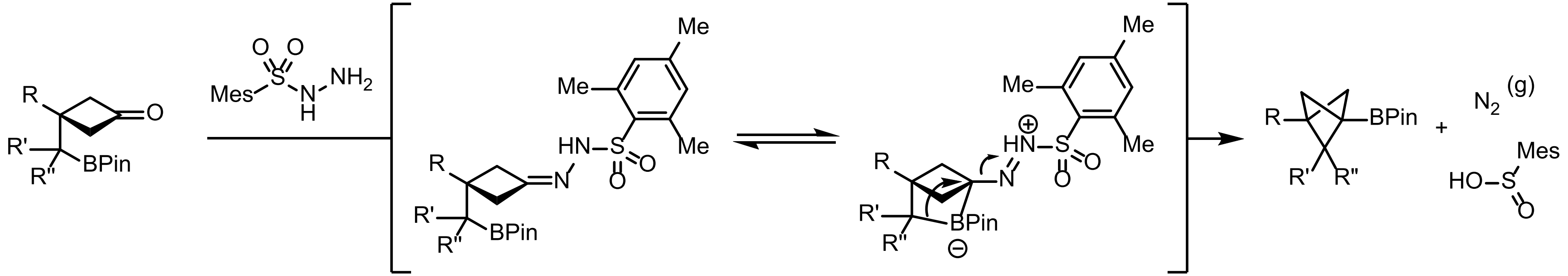
Water solubility, pH = 7.4 (μM)



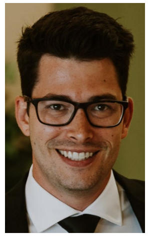
Mykhailiuk et. al., *Angew. Chem. Int. Ed.* **2020**, 59, 7161–7167

Strategy #4: Strong Nucleophiles and Great Leaving Groups

Forced ring closure via the ultimate leaving group: N_2

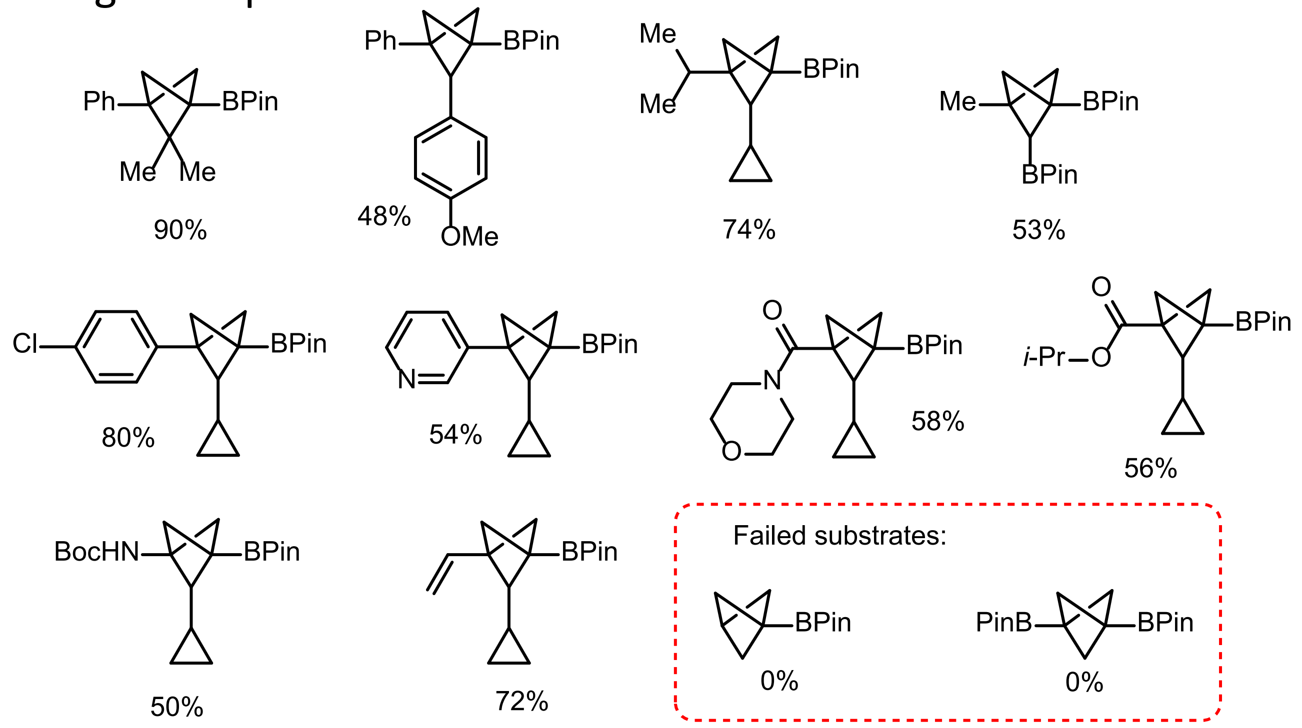


Tian Qin
UT Southwestern

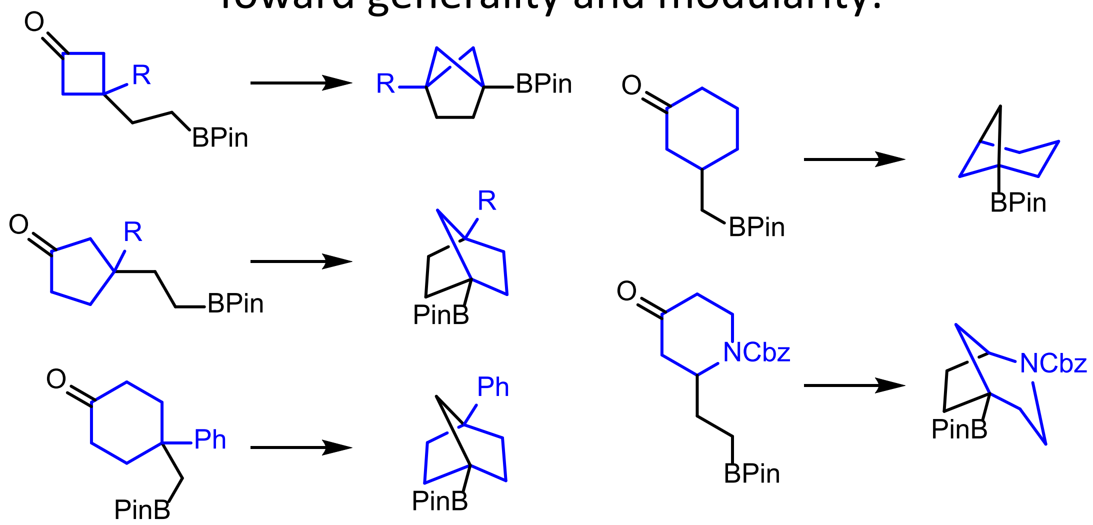


Jonathan Hughes
Merck – Process Division

Abridged Scope:



Toward generality and modularity:



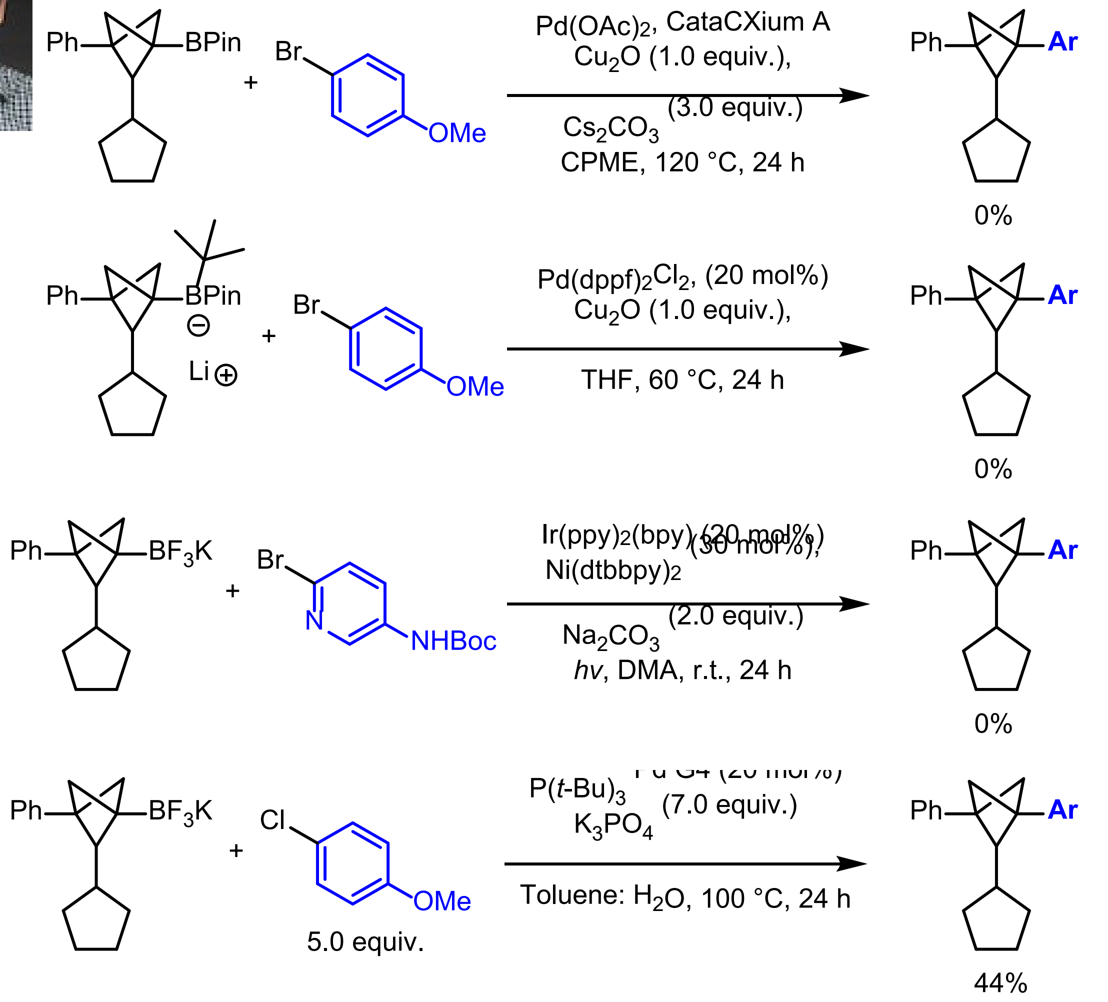
How did the 2-Sub-BCP-Bpin perform in Suzuki-Miyaura cross-coupling?

Qin, T., *Nat. Chem.* **2021**, 13, 950–955.

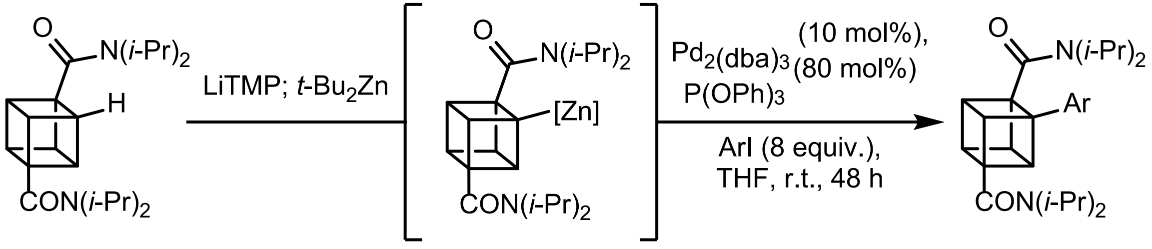
Synthetic Struggles: Lacking Direct, Modular C-C bond formation

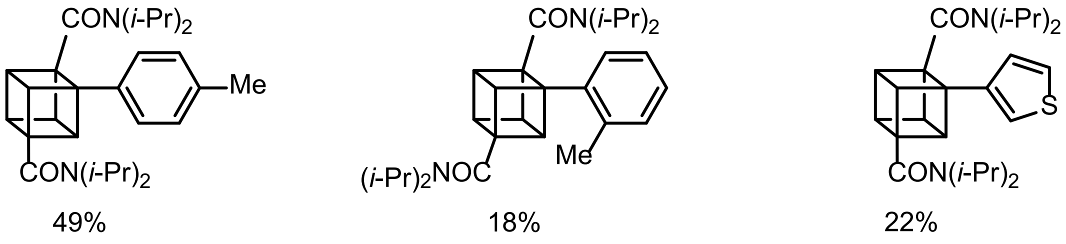
Current synthetic methods limit medicinal chemists in performing direct $C(sp^3)$-$C(sp^2)$ cross-couplings:

Testing previously reported BCP coupling conditions:



Cubane coupling:
limited synthetic utility





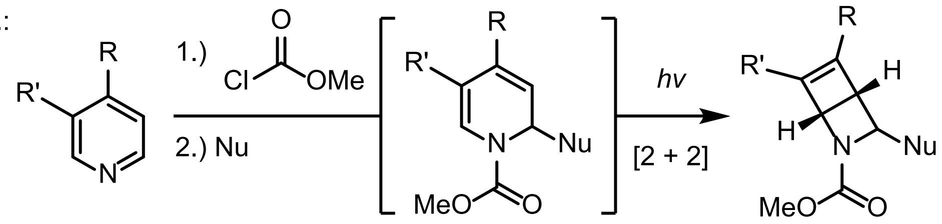
Current coupling methods fall short with complex substrates used in drug discovery

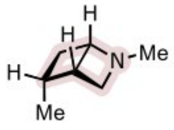
Qin, T., *Nat. Chem.* **2021**, 13, 950–955. Cubane Negishi coupling: *Chem. Sci.* **2020**, 11, 7672–7675.

Future Directions: New Isosteres and New Methods

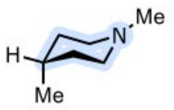
Expansion into heteroaliphatics: Dewar pyridine and Aza-BCHep

Sarlah and co.:

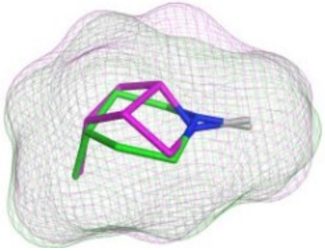




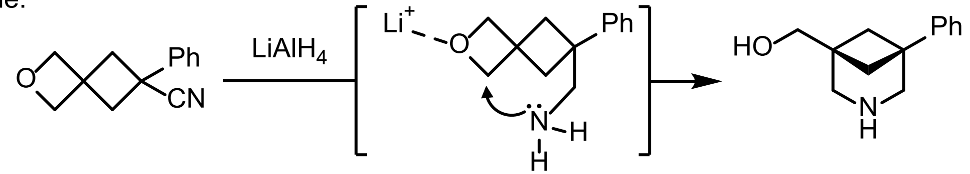
I (R_1, R_2 = Me)

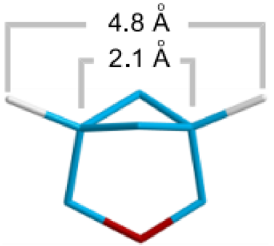


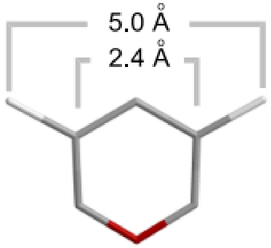
J (R_1, R_2 = Me)



Enamine:



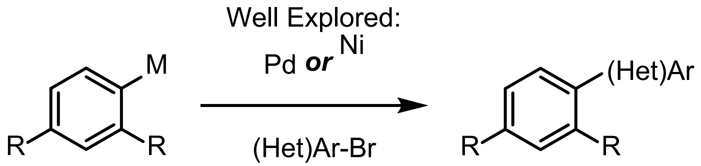


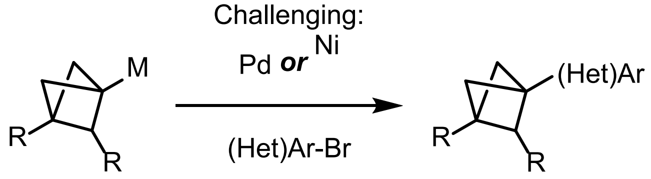


	3-Azabicyclo[3.1.1]heptane	m-Pyridine
angle	125°	125°
current	σ	π

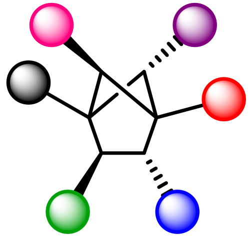
3-Azabicyclo[3.1.1]heptane ***m*-Pyridine**

Synthetic Accessibility:
Scalable synthesis for process routes and modular screening for discovery screening





Defined Exit Vectors:
Stereodefined synthesis



Dewar Pyridine: ChemRxiv. 2023; doi: 10.26434/chemrxiv-2023-jgr4j. Aza-BCHep: Mykhailiuk, P. et al. ChemRxiv 2023, doi: 10.26434/chemrxiv-2023-jbb0r

Additional Readings

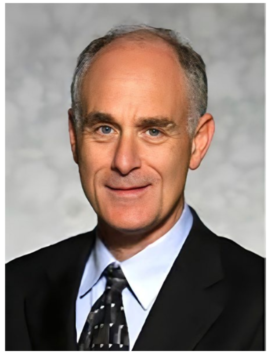
Journal of Medicinal Chemistry

pubs.acs.org/jmc   Perspective

Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design

Murugaiah A. M. Subbaiah* and Nicholas A. Meanwell*

Meanwell, N and Subbaiah, M.
J. Med. Chem. **2021**, 64, 14046−14128.



Mykhailiuk, P.
Org. Biomol. Chem. **2019**, 17, 2839

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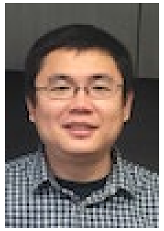
Saturated bioisosteres of benzene: where to go next?

Pavel K. Mykhailiuk [a,b]

Three-dimensional saturated C(sp^3)-rich bioisosteres for benzene

Jet Tsien [1], Chao Hu [1], Rohan R. Merchant [2] & Tian Qin [1]

Qin, T. et al. *Nat. Rev. Chem.* **2024**, 8, 605–627.



Questions?