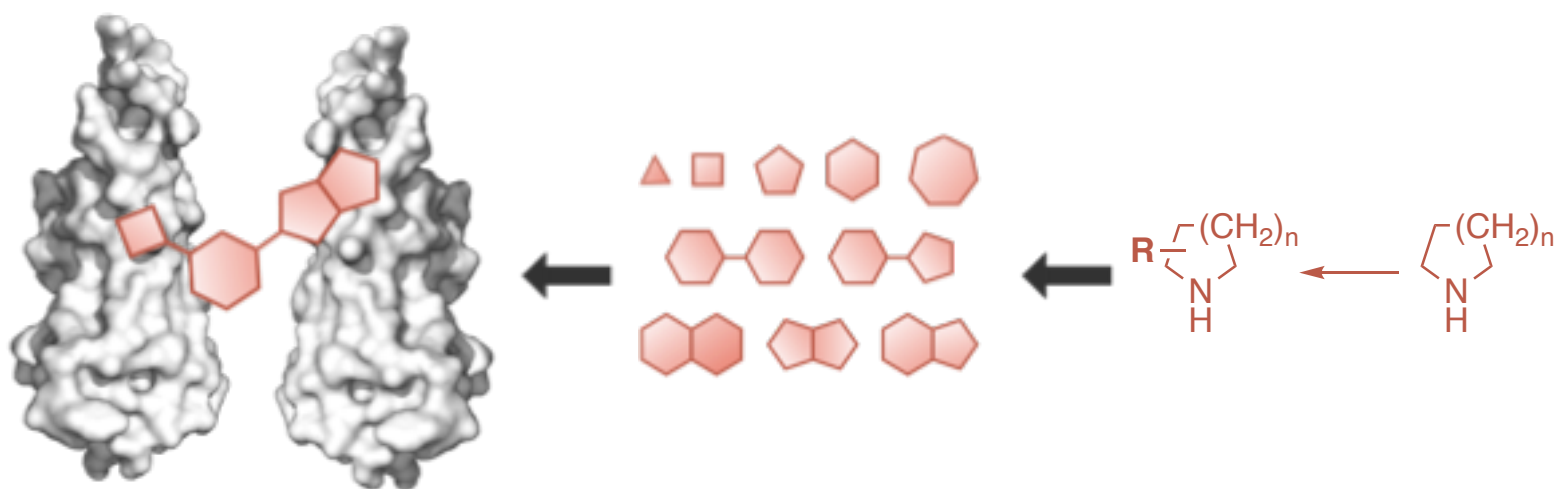


# Targeting Protein-Protein Interactions – the Pursuit of Asymmetric Direct Functionalization of Saturated N-Heterocycles for Efficient Development of Topologically Complex Chemical Fragments for Fragment-Based Drug Discovery

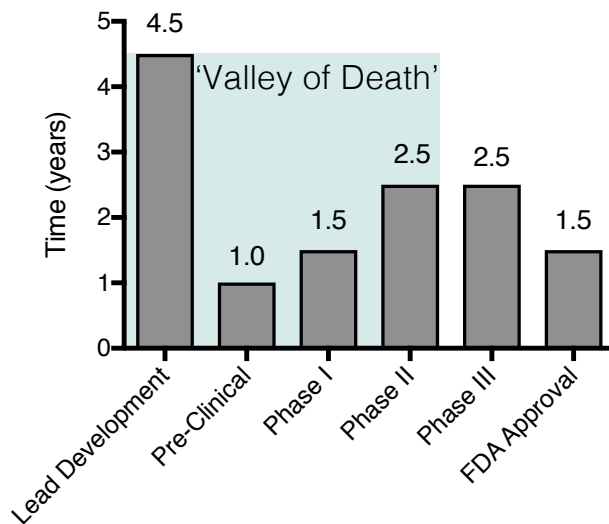
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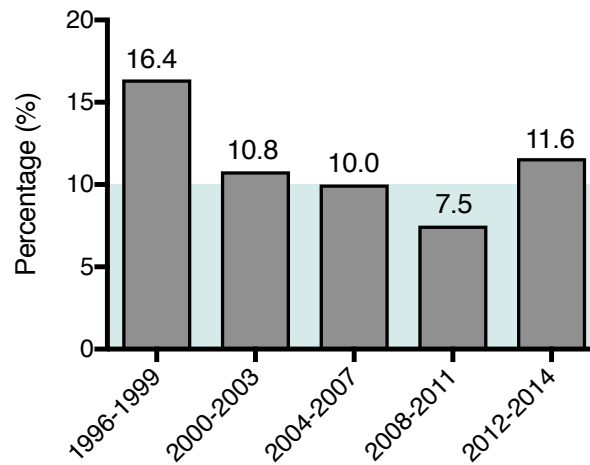
Evan Carder  
Wipf Group Frontiers Seminar  
September 30, 2017

# Part I. Current Reality of Drug Discovery

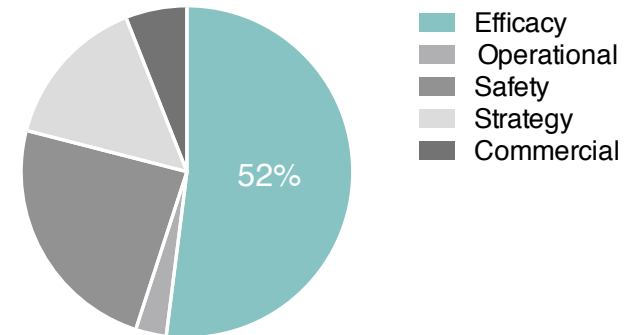
### Drug Development Timeline



### Cumulative Success Rate Phase I to Launch

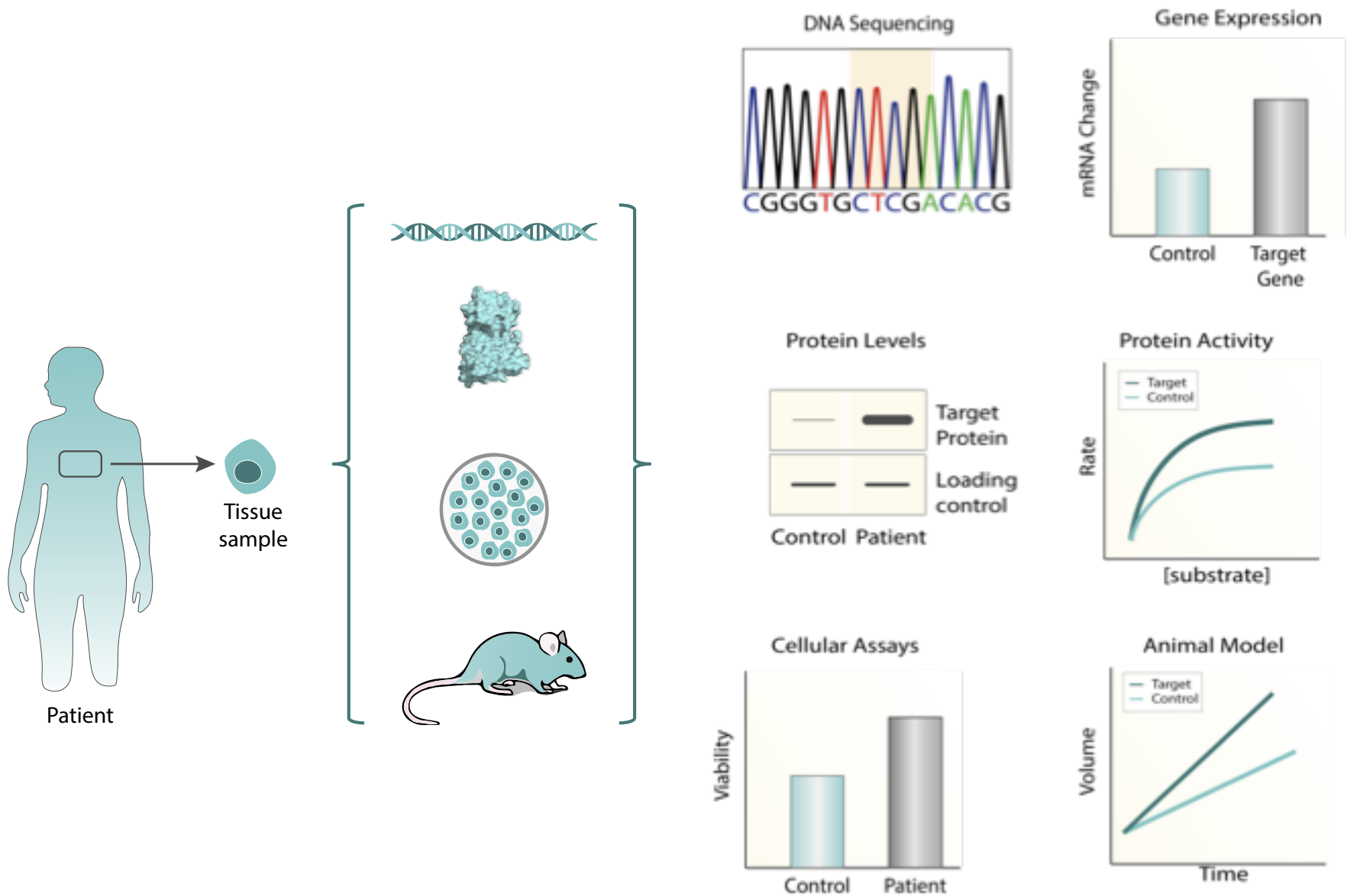


### Reason for Clinical Trial Failure 2013-2015



*Nat. Rev. Drug Disc.* **2015**, 14, 475.  
*Nat. Rev. Drug Disc.* **2016**, 15, 817.  
*Nat. Rev. Drug Disc.* **2016**, 15, 447.

# Lack of Clinical Efficacy – Poor Target Identification and Validation



*Brit. J. Pharm.* **2011**, 162, 1239.  
*Nat. Rev. Drug Disc.* **2013**, 12, 581.  
*Nat. Rev. Cancer* **2017**, 17, 441.

# Tractable Disease Targets

## I. Clinically Validated

### **Enzymes**

Oxidoreductases

Transferases

Proteases

Hydrolases

Isomerases

Ligases

### **Receptors**

GPCR

Cytokine receptor

Integrin receptor

Nuclear receptor

### **Ion-Channels**

Ca<sup>2+</sup> channels

K<sup>+</sup> channels

Na<sup>+</sup> channels

Cl<sup>-</sup> channels

### **Nucleic Acids and Ribosomes**

DNA

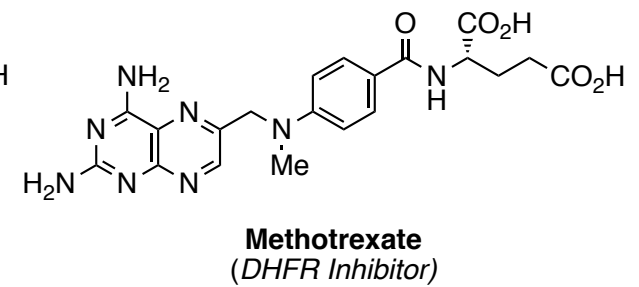
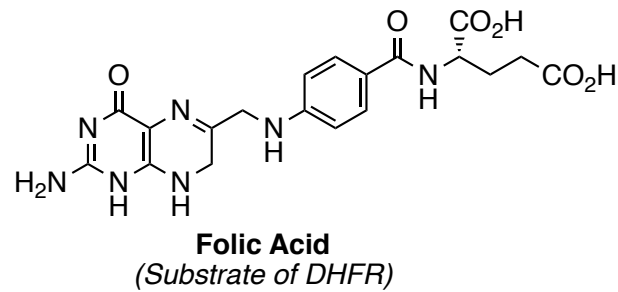
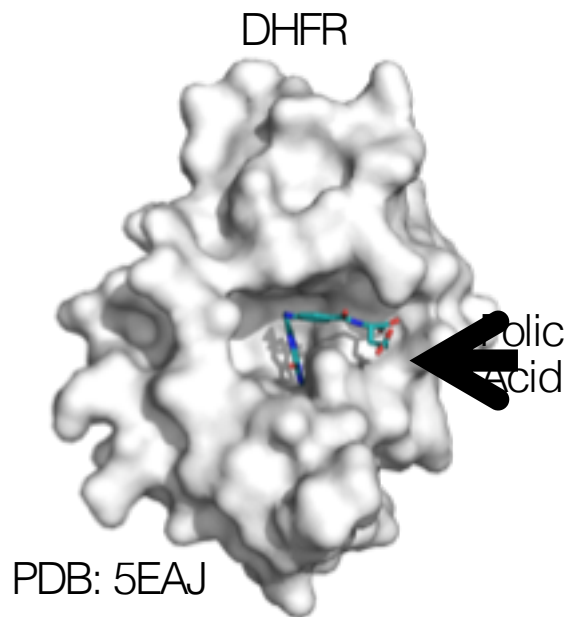
RNA

Spindle

Ribosomes

# Tractable Disease Targets

## II. Druggability

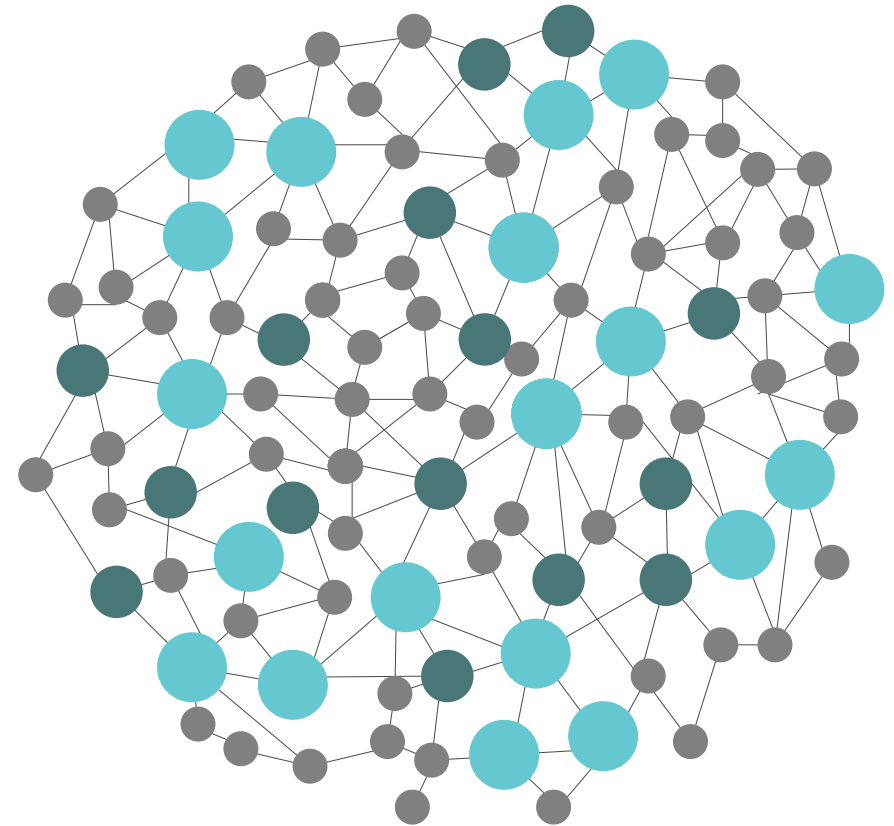


*"the most fruitful basis for the discovery of a new drug is to start with an old drug"*

– James Black

# New Drug Target Category

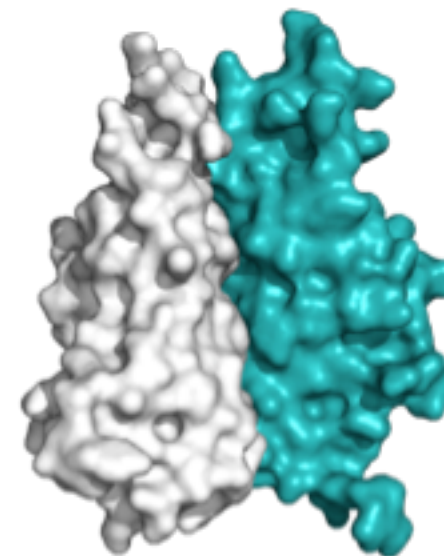
- There is an estimated 130,000 – 650,000 types of protein-protein interactions (PPI) in the human interactome.
- The interactome is very complex and diverse and their extensive network regulate most biochemical pathways involved in cell signaling, growth, and survival.
- Protein-protein interactions are now recognized as potential therapeutic targets
- Identifying therapeutically relevant PPIs is considerably difficult.



The Interactome - the extensive network of Protein-Protein Interactions

# Characteristics of Protein-Protein Interactions

- PPI display fewer well-defined concave binding sites than classical enzymes and receptors.
- Protein-protein interfaces tend to be flat with large surface area (1,500 – 3,000 Å<sup>2</sup>) and dominated by hydrophobic and complementary charge interactions.
- Not all residues at the protein-protein interface contribute equally toward binding. Only a small subset of contact residues contribute toward the binding free energy.
- “Hot spot” residues or regions are significantly responsible for the majority of the PPI binding free energy



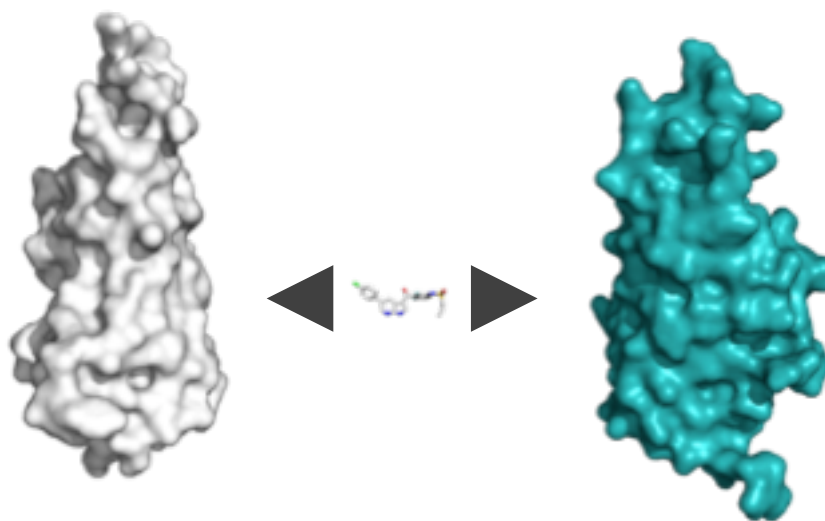
Side-view



Protein Interface

*Nat. Rev. Drug. Disc.* **2004**, 3, 301.  
*Annu. Rev. Pharmacol., Toxicol.* **2014**, 54, 435.  
*Chem. Biol.* **2014**, 9, 1102.  
*Bioorg. Med. Lett.* **2014**, 24, 2546.  
*Chem. Soc. Rev.* **2015**, 44, 8238.  
*Nat. Rev. Drug Disc.* **2016**, 15, 533.

# Strategies towards Modulating a Protein-Protein Interaction



## Hot spot identification

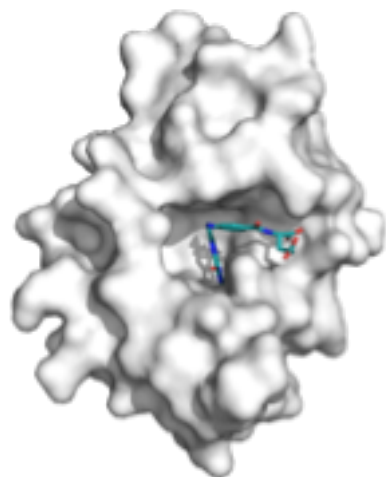
1. Alanine scanning mutagenesis
2. Nuclear magnetic resonance
3. X-ray crystallography

## Disrupting hot spot residues

1. Orthosteric inhibition
2. Allosteric regulation
3. Interfacial binding/stabilization



# Druggability: Challenges Developing PPI Inhibitor



## Classical Drug Target

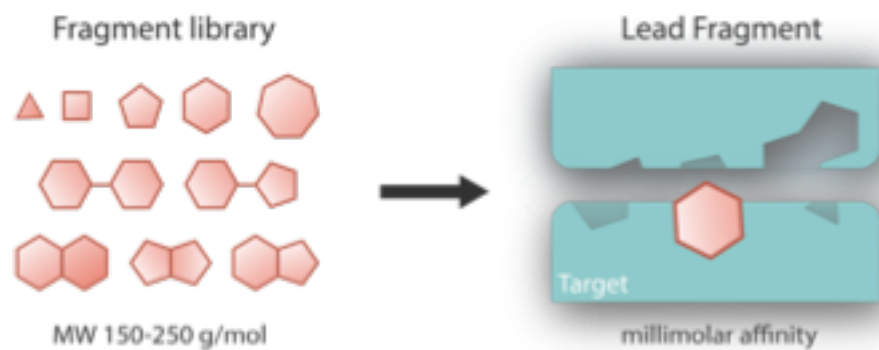
- Natural small molecule partners
- Well-defined binding sites
- Concavity
- Hydrogen-bond donors and acceptors



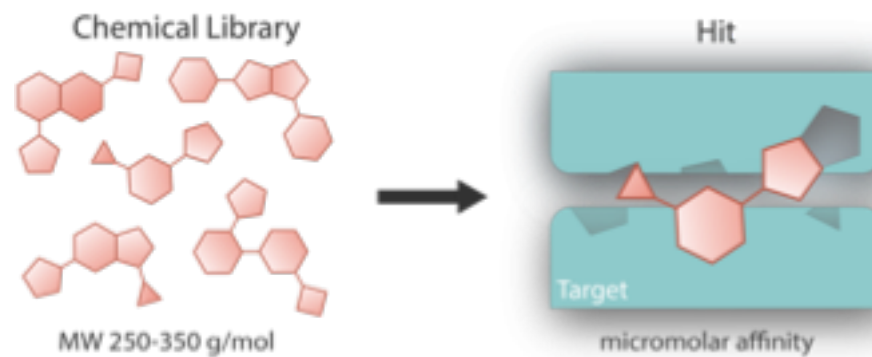
## Protein-Protein Interaction

- No natural small molecule partners
- Fewer well-defined binding sites
- Flat and featureless surface
- Lack of hydrogen-bond donors and acceptors
- Conformational plasticity

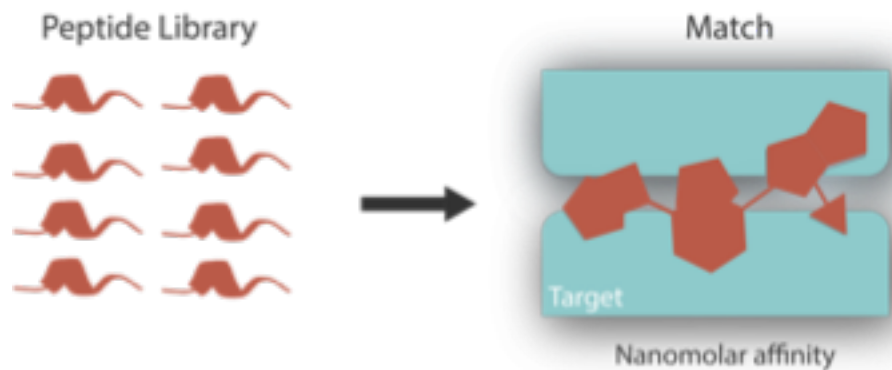
# Identification of PPI Inhibitors



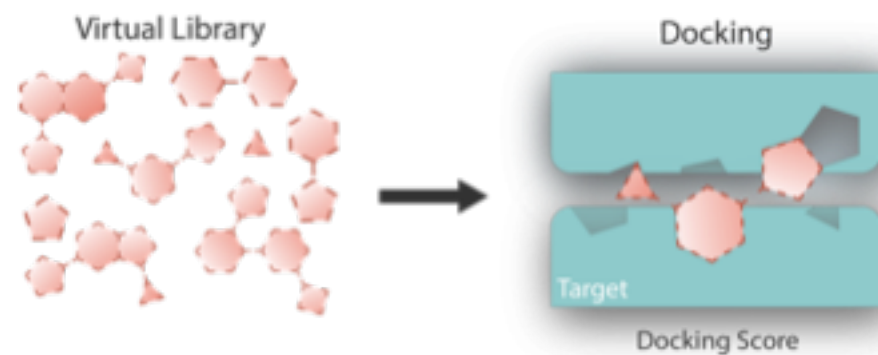
Fragment-based screening



High-throughput screening (HTS)

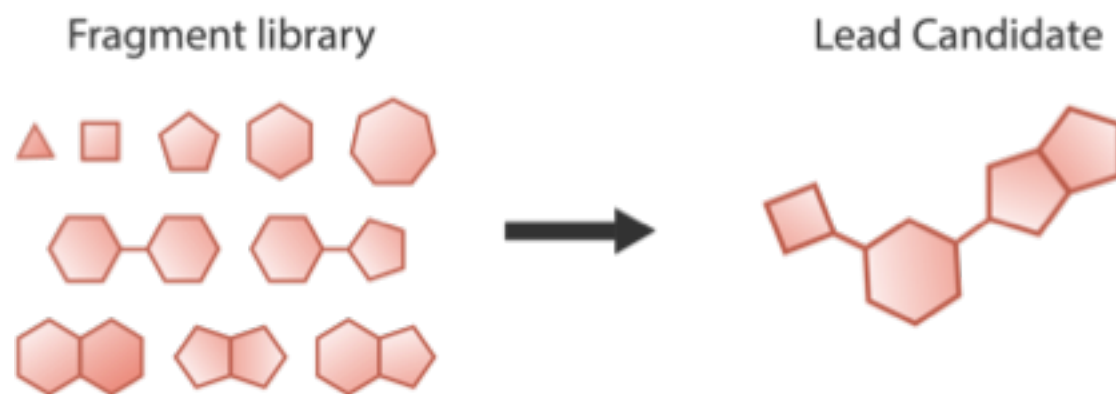


Peptide/Peptide mimics



Virtual screening

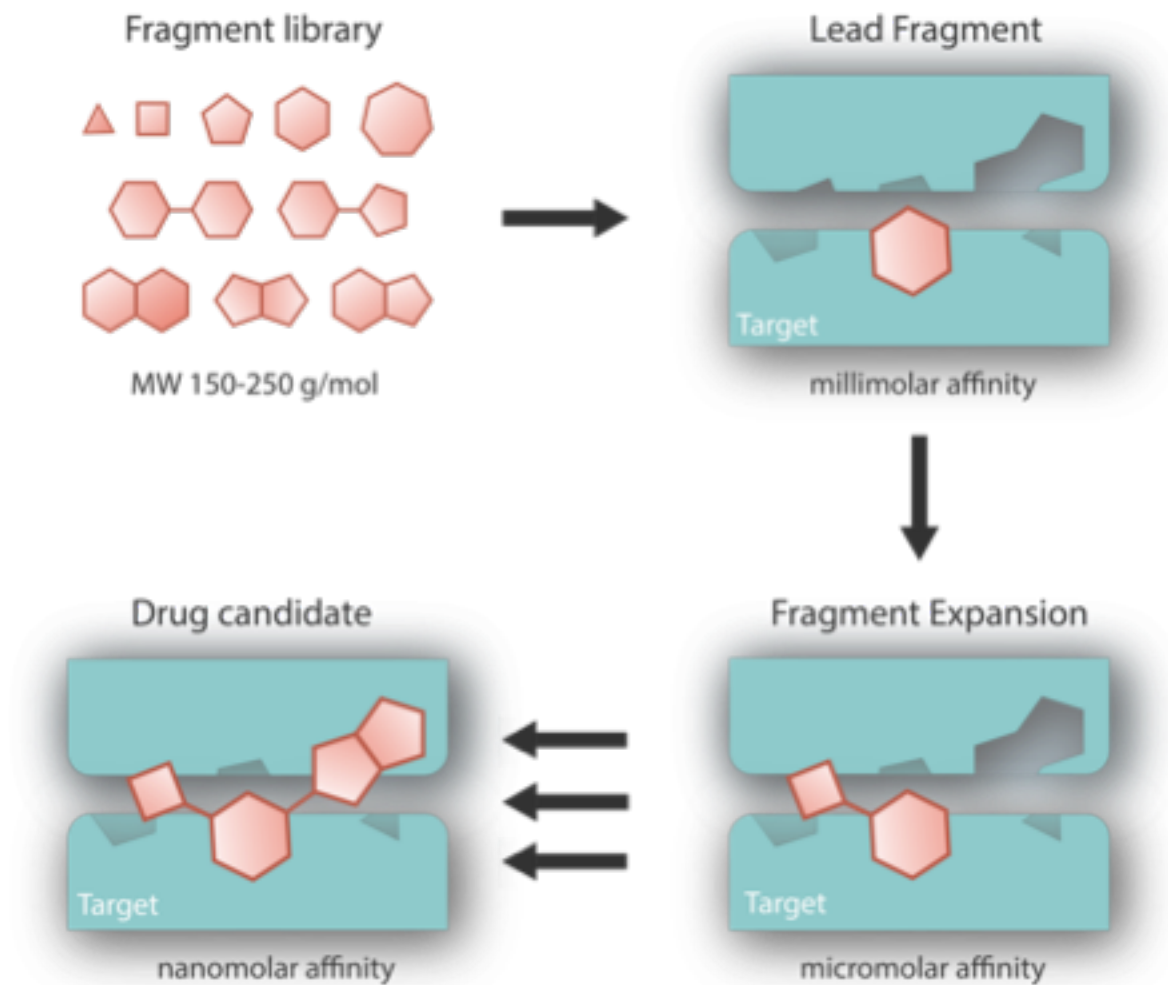
## Part II. Fragment-Based Drug Discovery (FBDD)



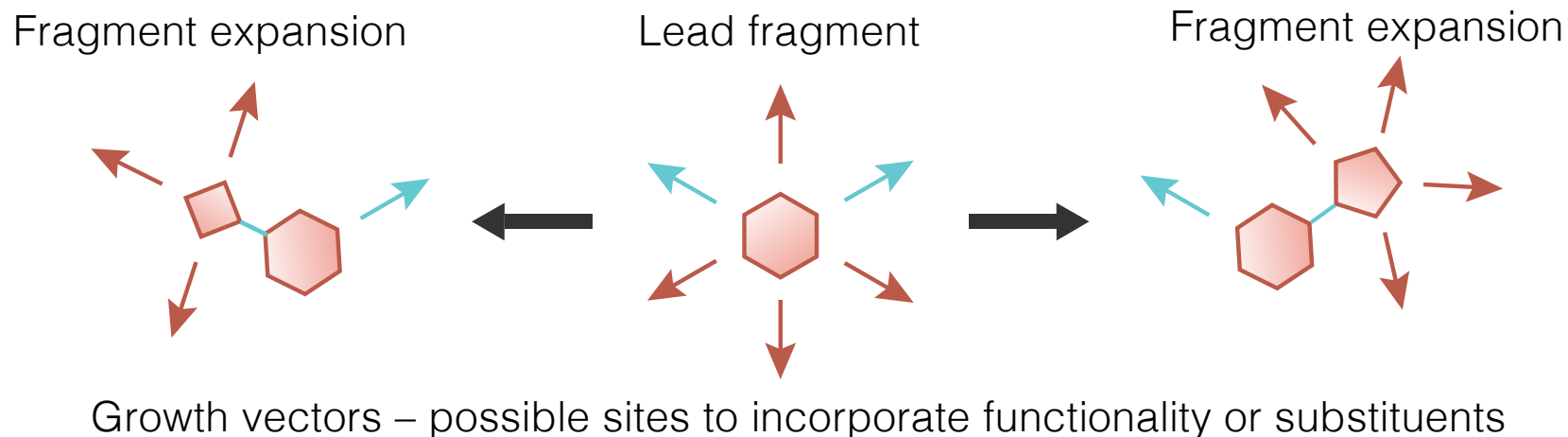
### Advantages of FBDD:

- Begin with low molecular weight subunits
- Greater diversity and complexity
- Access to more chemical space
- Better physiochemical properties
- High-quality intermolecular interactions
- Opportunity for novel intellectual property

# Fragment-Based Lead Development



# Greater Survey of Chemical Space



## Importance:

- Structural and stereochemical diversity
- Enhanced complexity
- High-quality intermolecular interactions

## Protein Interface:

- Fewer well-defined binding sites
- Flat and featureless surface
- Lack of hydrogen-bond donors and acceptors
- Conformational plasticity

# Success Story – Development of Navotoclax (ABT-263)

- B cell lymphoma 2 (BCL-2)

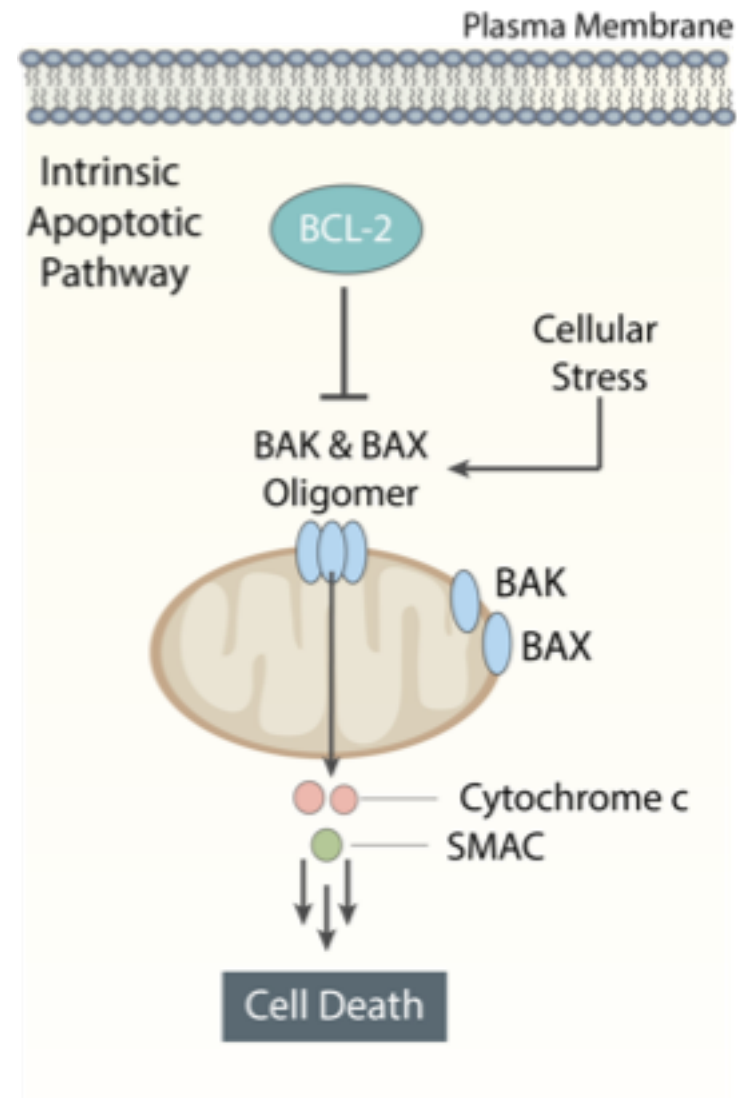
Regulate the intrinsic apoptotic pathway

Inhibit essential pro-apoptotic effectors BAK and BAX by binding to their BH3 domain and preventing oligomerization.

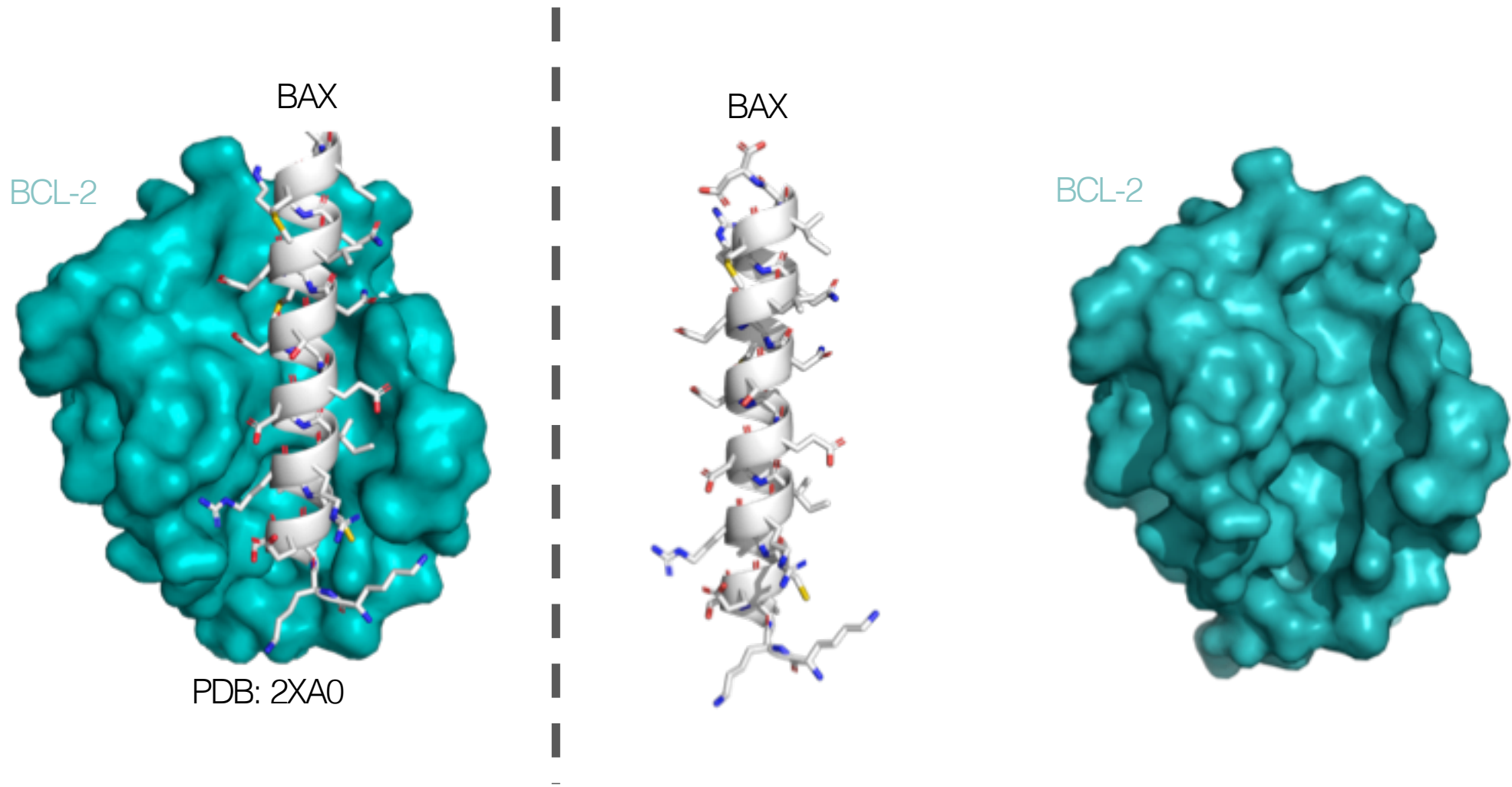
Upregulated in cancer

Associated with chemoresistance and cancer cell survival

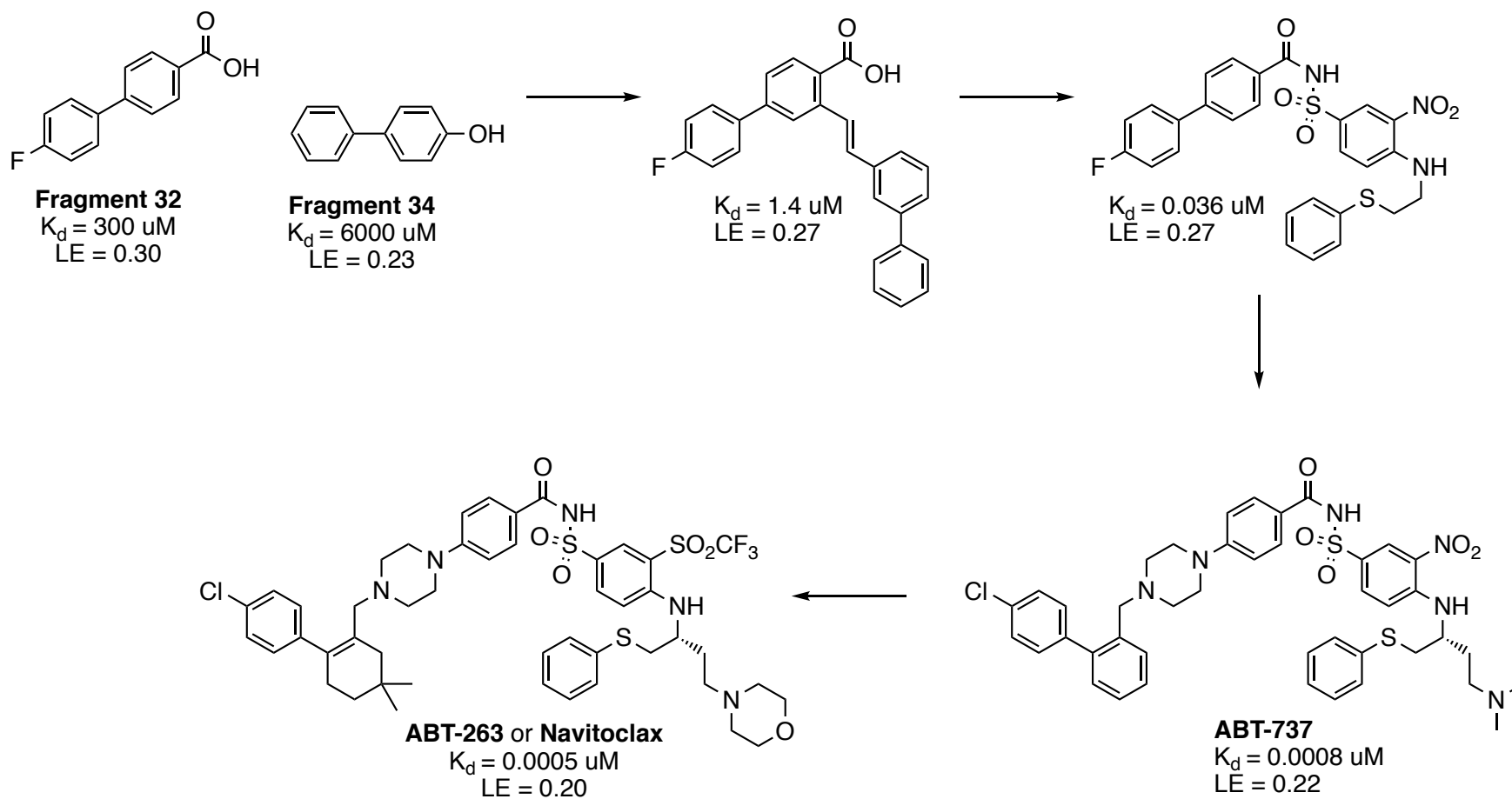
Targeting the anti-apoptotic BCL-2 protein is an attractive therapeutic strategy in cancer.



# BCL-2 and BAX Protein-Protein Interaction

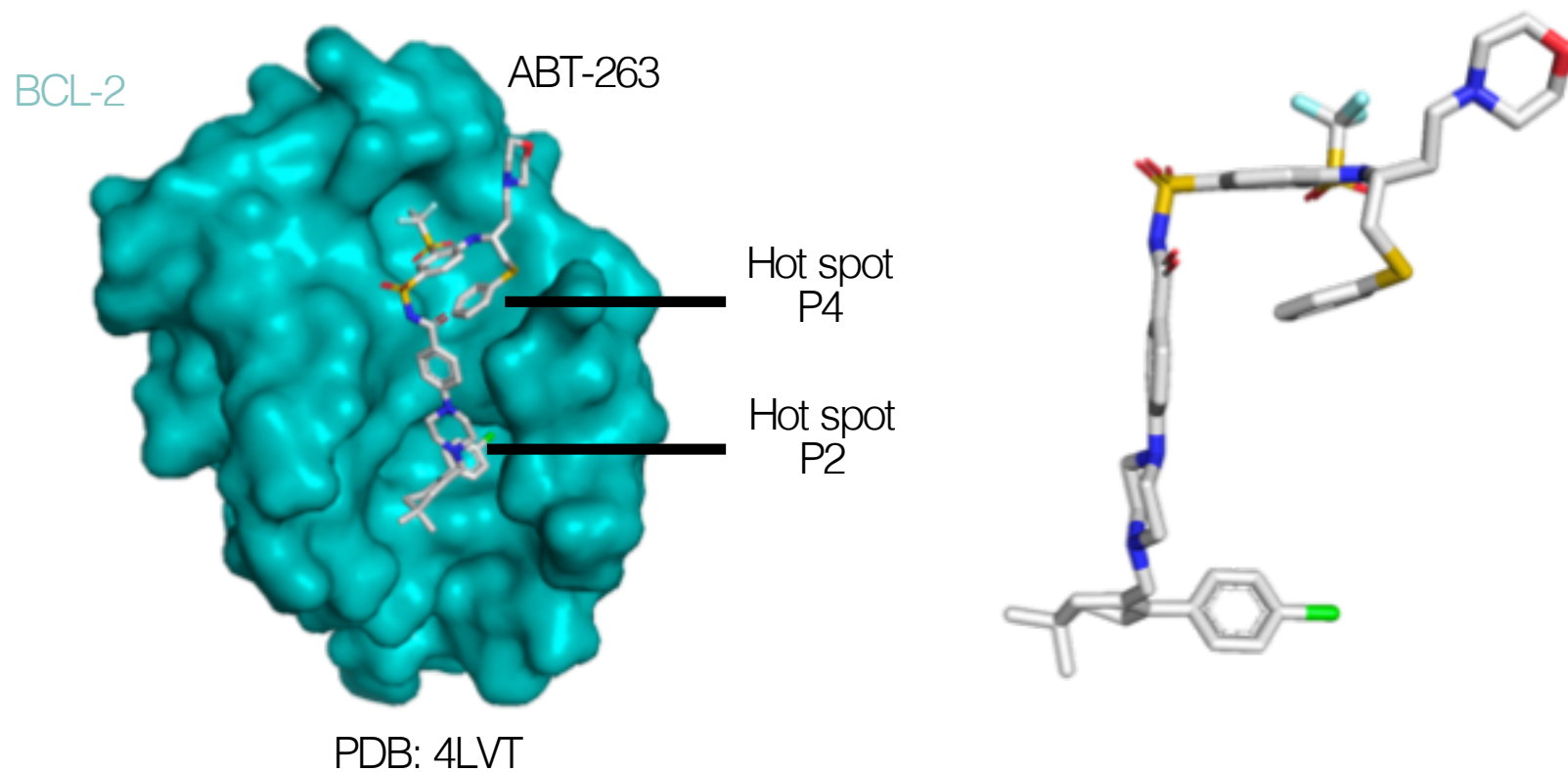


# Medicinal Chemistry Efforts of Navitoclax (ABT-263)

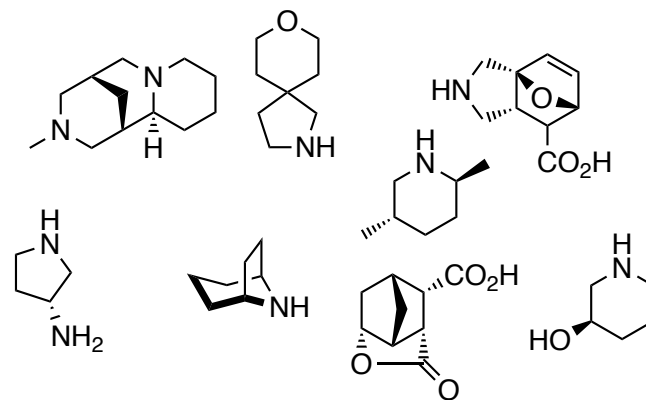
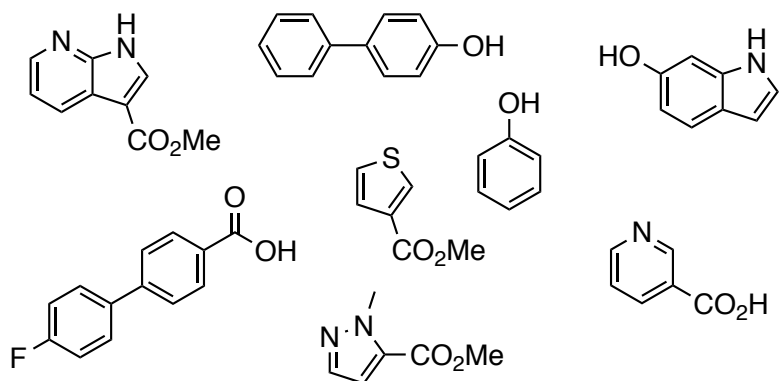




# Success Story – Development of Navotoclax (ABT-263)



# Challenges to FBDD – Escape from the Flatland



## Fragments libraries

- Commercially available
- Substantial  $sp^2$ -rich compounds
- Flat molecules lacking dimensionality
- Improve physiochemical properties to conserve drug-likeness

## Improve 3-Dimensionality

- Incorporate structural and stereochemical diversity
- Emulate natural product structural motifs
- $Sp^3$  carbons can increase the number and scope of vectors for fragment growth.
- “Chiral  $sp^3$ -rich heterocycles are greatly underrepresented”

*Angew. Chem. Int. Ed.* **2016**, 55, 488.

*Nat. Chem.* **2013**, 5, 21.

*Med. Chem. Commun.* **2013**, 4, 515.

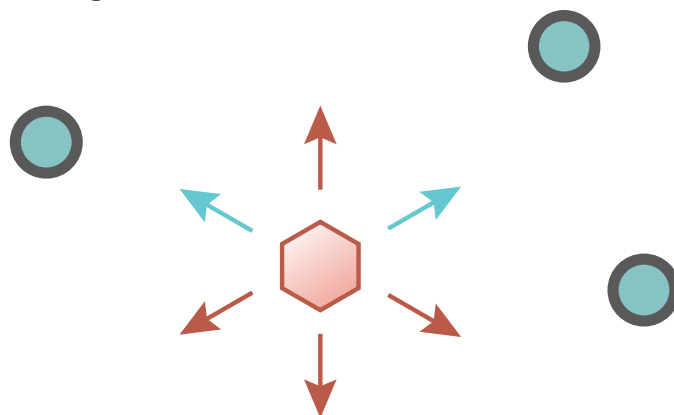
*PNAS* **2011**, 108, 6799.

*J. Med. Chem.* **2009**, 52, 6752.

# Challenges to FBDD – Efficient Synthetic Methodology

## Structure-guided medicinal chemistry

X-ray informed fragment-design requires tailor synthetic transformations to the central core of the fragment



## “Precision Synthesis”

- Synthetic vectors  
Methodology that allows synthetically accessible vectors to incorporate substituents
- Molecular recognition  
Methodology that enables incorporation of heteroatoms and tolerates polar H-bonding functionality.
- Shape  
Control of stereo- and regio-chemistry.
- Synthetic tractability  
Efficient synthesis (few steps) using commercially available reagents.

# Part III. Asymmetric Direct-Functionalization of Saturated N-Heterocycles

Saturated N-Heterocycles:

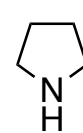
- Biologically relevant

Natural products  
Pharmaceuticals  
Agriculture

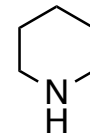
- Biological handle – hydrogen bonding capabilities

- Significant opportunity for growth vectors to enhance intermolecular interactions

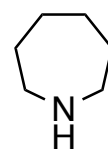
- Synthetically undeveloped



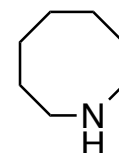
pyrrolidine



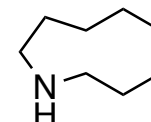
piperidine



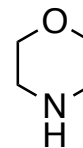
azepane



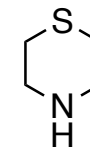
azocane



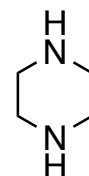
azonane



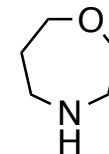
morpholine



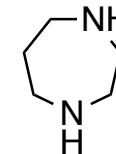
thiomorpholine



1,4-piperazine

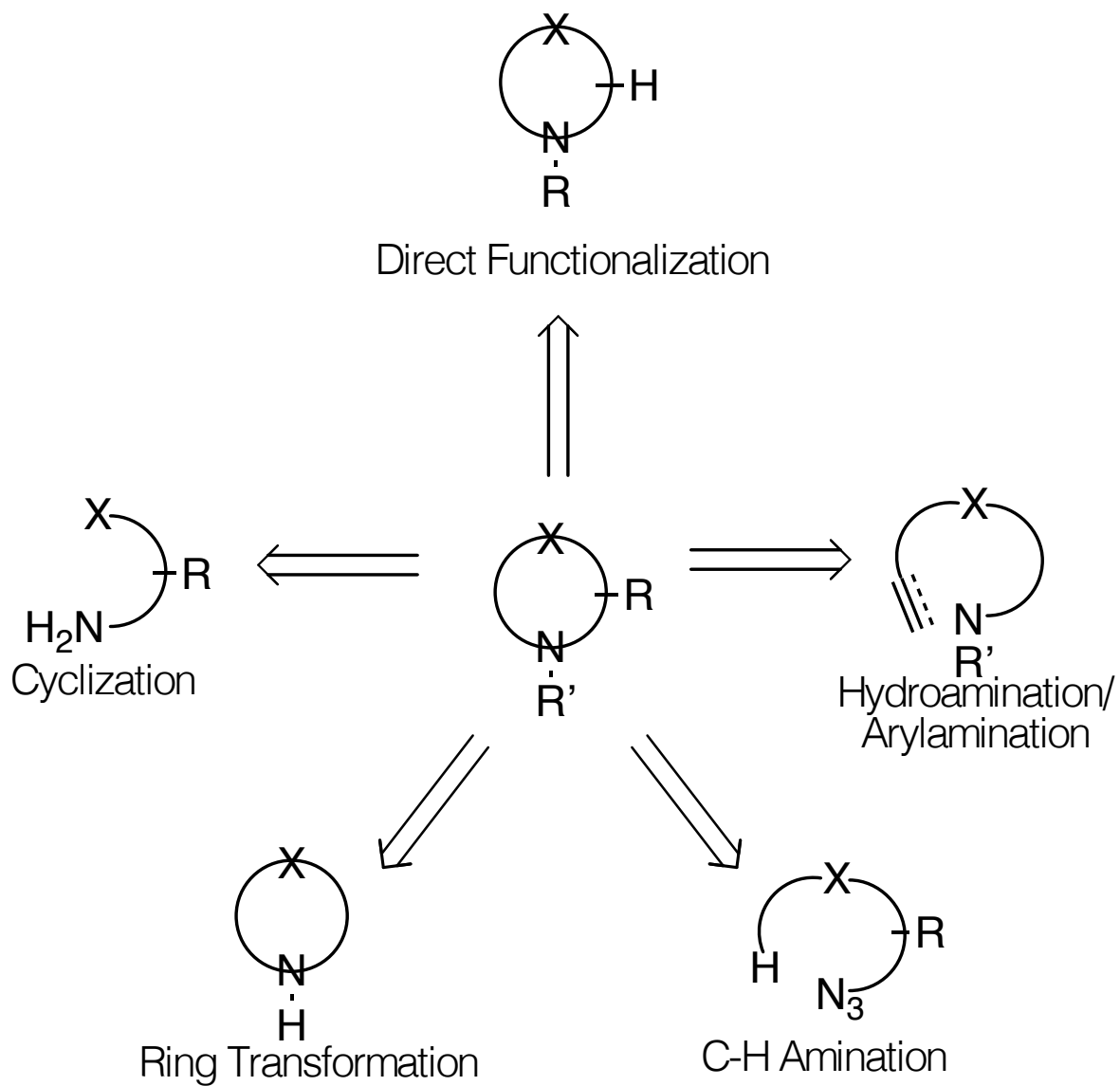


1,4-oxazepane



1,4-diazepane

# Synthesis of Saturated N-Heterocycles



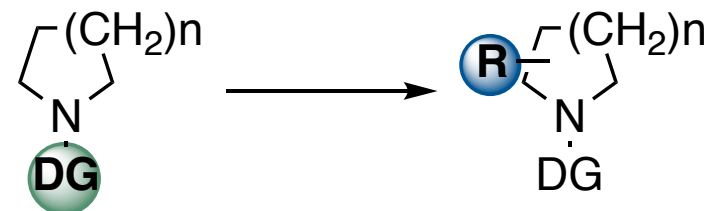
# Direct Functionalization

Not all C-H bonds are equal

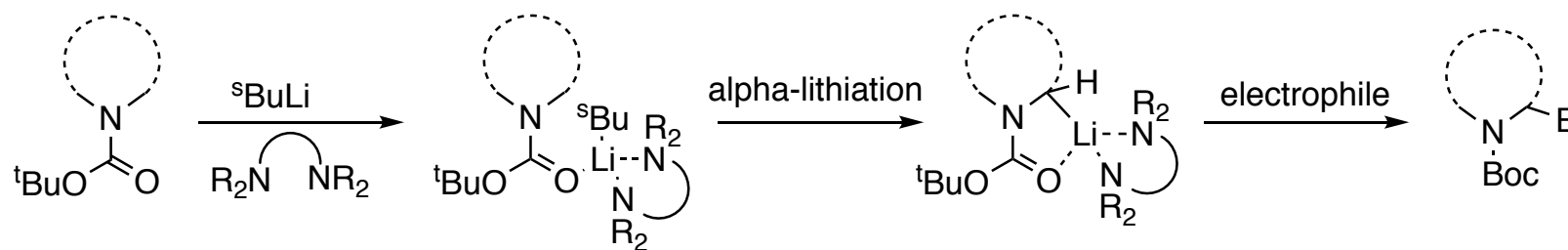
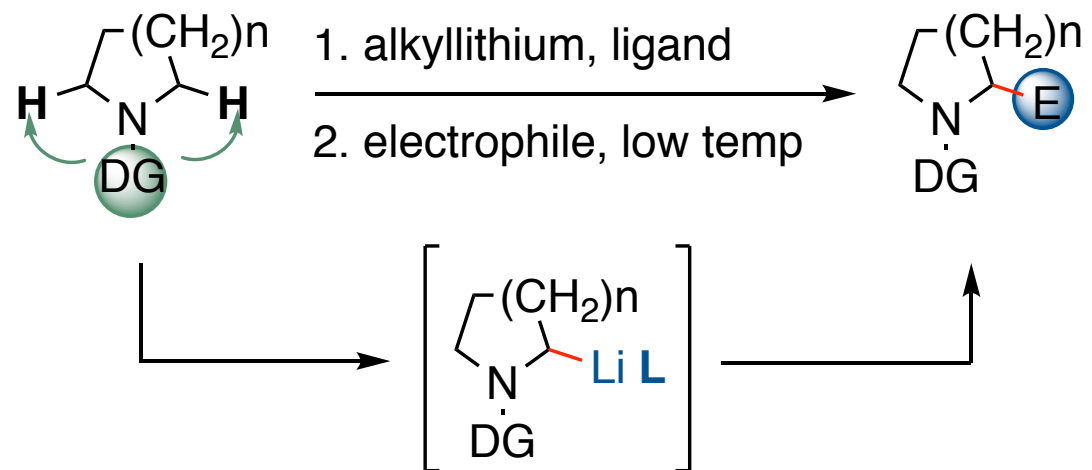
- Electronics
- Steric
- Stereoelectronics
- Directed-proximal effects – for site selectivity

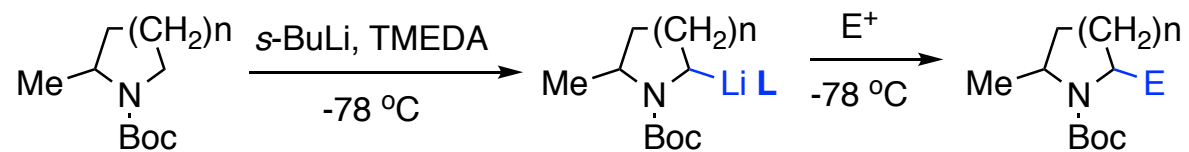
Saturated N-Heterocycles

- Alpha-Lithiation
- Cationic
- Radical
- Transition-metal



# Alpha-Lithiation



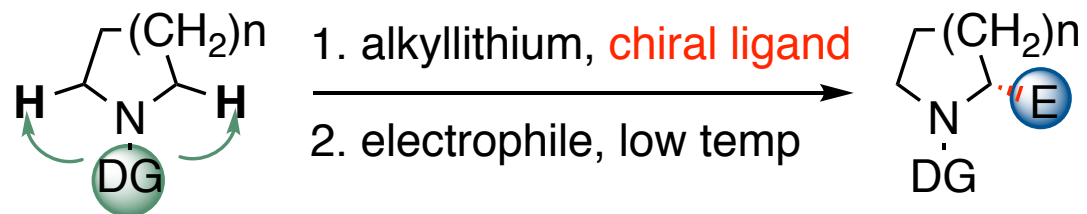


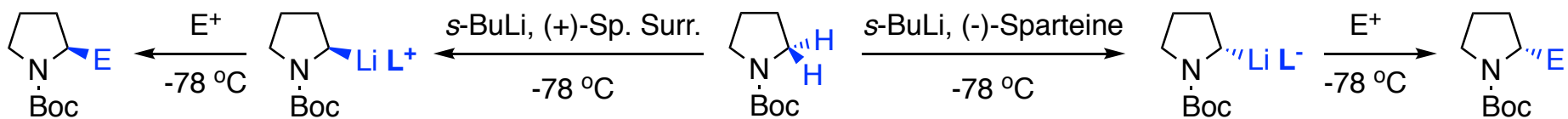
Substrate	Major product	E	% Yield
		Me	72%
		TMS	93%
		D	81%
		Me	71%
		PhCH(OH)	96%
		D	90%
		CHO	87%
		Me	83%

Substrate	Major product	E	% Yield
		SnBu <sub>3</sub>	83%
		Me	41%
		TMS	67%
		CHO	63%



# Asymmetric Alpha-Lithiation



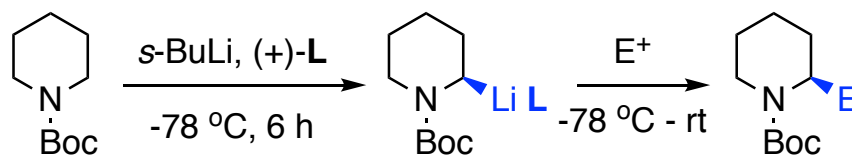


E	% Yield, ( <i>er</i> )
TMS	84%, (95:5)

(+)-Sparteine surrogate  
 (O'Brien 2002)

E	% Yield, ( <i>er</i> )
TMS	71%, (97:3)
CH <sub>3</sub>	76%, (98:2)
Bu <sub>3</sub> Sn	70%, (97:3)
CO <sub>2</sub> H	55%, (94:6)
Ph <sub>2</sub> C(OH)	75%, (95:5)

(-)-Sparteine  
 (Beak 1994)



E	% Yield, ( <i>er</i> )
( <i>R</i> )-TMS	73%, (86:14)
( <i>R</i> )-Bu <sub>3</sub> Sn	82%, (88:12)
( <i>S</i> )-CO <sub>2</sub>	92%, (88:12)
( <i>S</i> )-MeO <sub>2</sub> C	78%, (88:12)
( <i>R</i> )-PhMe <sub>2</sub> Si	85%, (73:27)
( <i>R</i> )-Me	45%, (64:36)

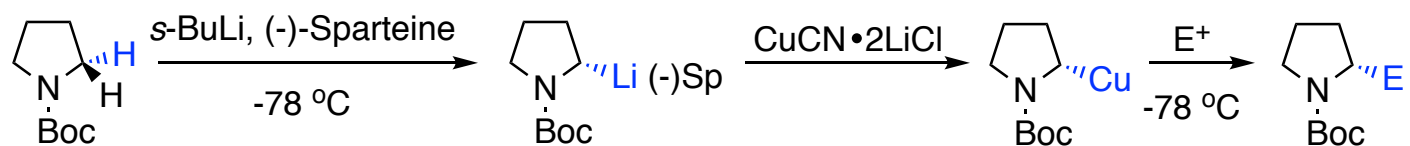
(+)-L

*J. Am. Chem. Soc.* **1994**, 3231.

*Acc. Chem. Res.* **1996**, 522.

*Tetrahedron: Asymmetry* **2005**, 661.

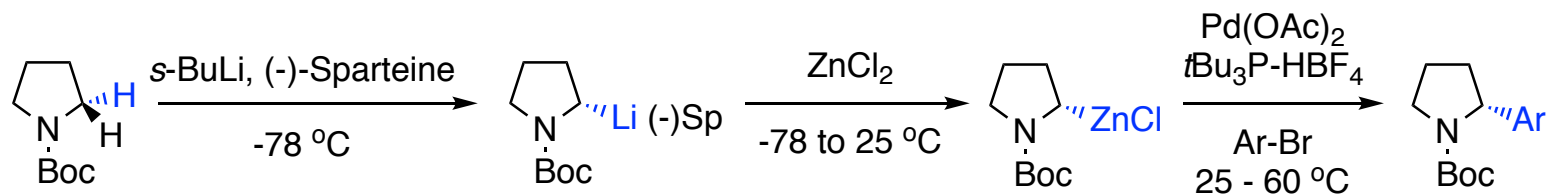
*J. Am. Chem. Soc.* **2010**, 132, 7260.



E <sup>+</sup>	Product	% Yield ( <i>er</i> )
		85%, (90:10)
		84%, (94:6)
		56%, (72:28) 65%, (94:6) 50%, (92:8)
		89%, (95:5) 53%, (91:9)

X = I  
 X = Tf  
 X = Nf  
 R = H  
 R = *n*-Bu

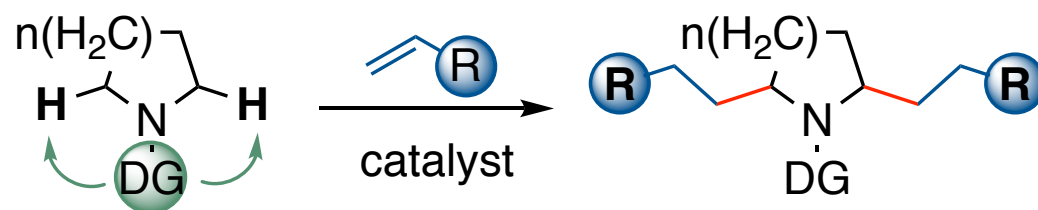
E <sup>+</sup>	Product	% Yield ( <i>er</i> )
		79% (80:20)
		95%, (50:50)
		56%, (72:28)
		87%, (85:15) <i>dr</i> (56:44)

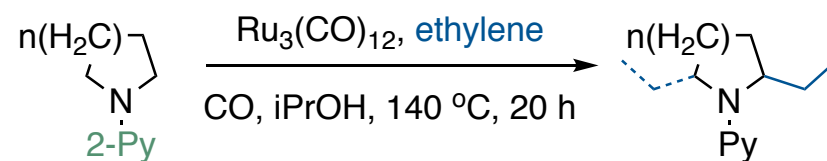
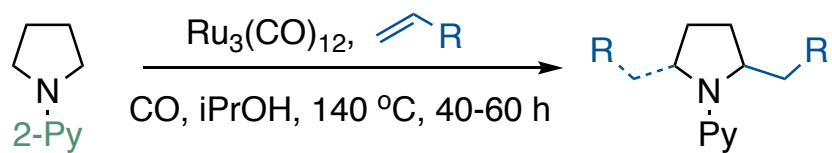


Ar-Br	Product	% Yield ( <i>er</i> )
	R: H	82%, (96:4)
	F	75%, (96:4)
	NMe <sub>2</sub>	78%, (96:4)
	CO <sub>2</sub> Me	81%, (96:4)
	SO <sub>2</sub> Me	87%, (97:3)
	CN	80%, (96:4)
	NH <sub>2</sub>	70%, (96:4)
	R: Me	71%, (96:4)
	OMe	72%, (96:4)
		78% (96:4)

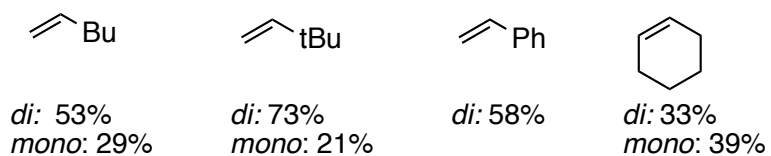
Ar-Br	Product	% Yield ( <i>er</i> )
		81% (96:4)
		77% (96:4)
		60%, (96:4)

## C-2 Direct Alkylation

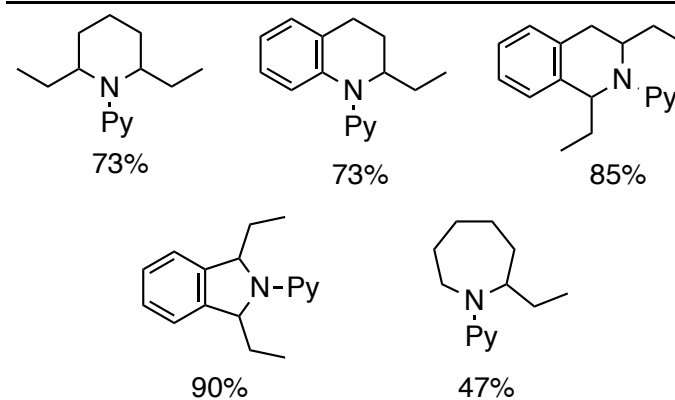


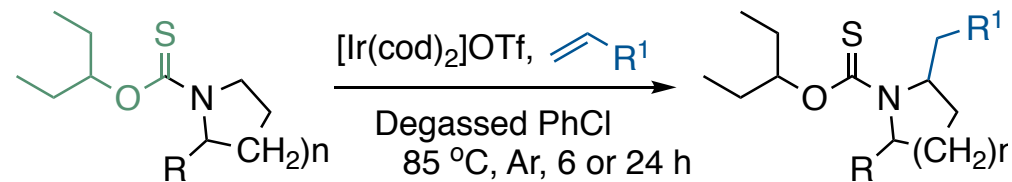
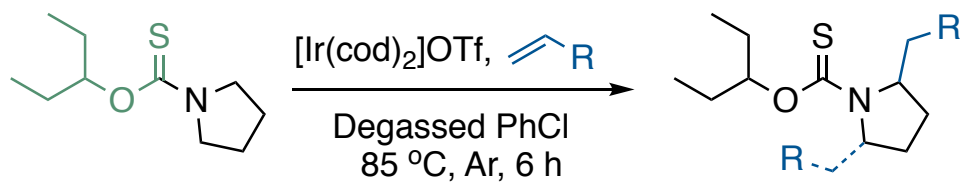


### Alkene

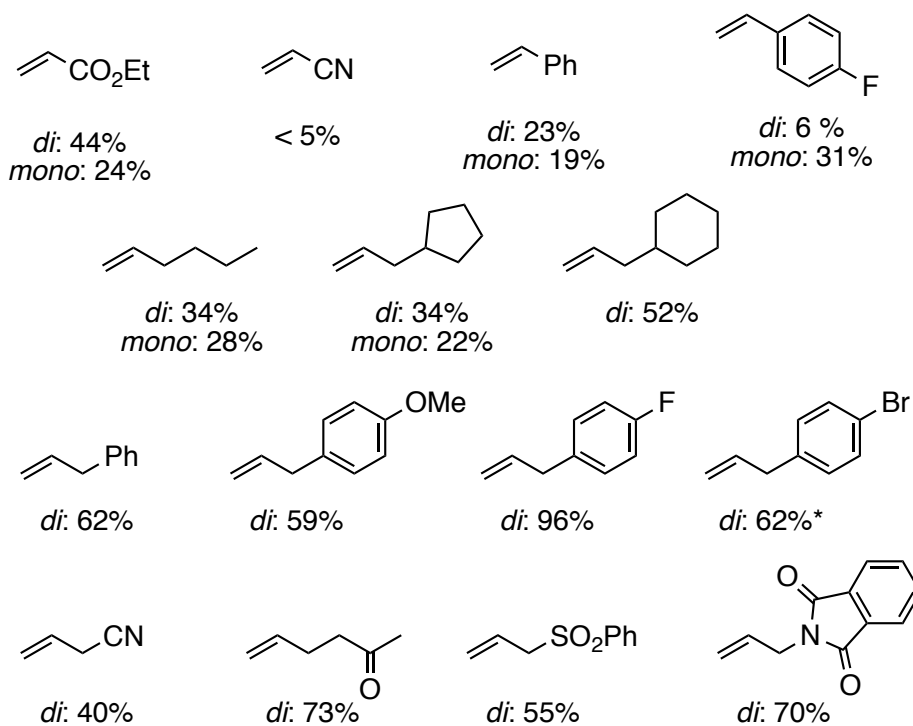


### Substrate scope

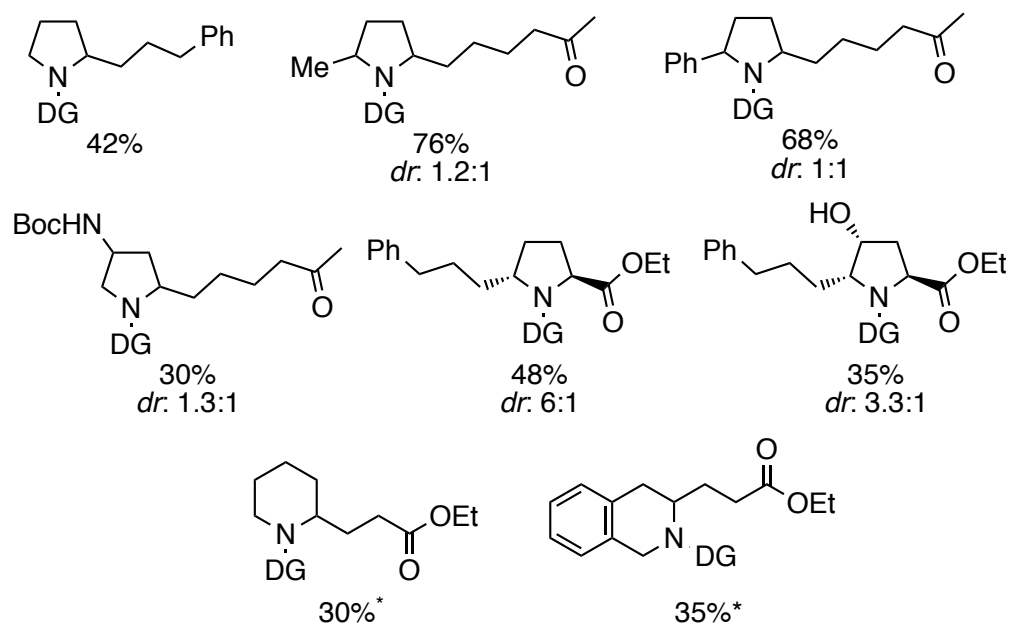




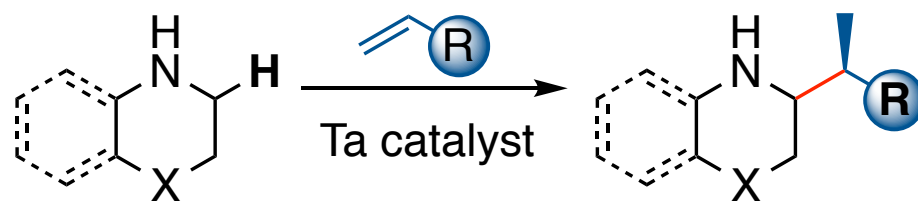
### Alkene



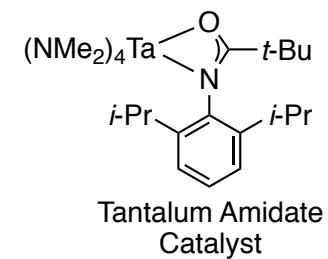
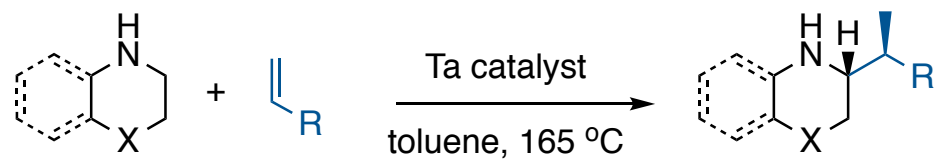
### Substrate Scope



## Directing Group Free Direct Alkylation

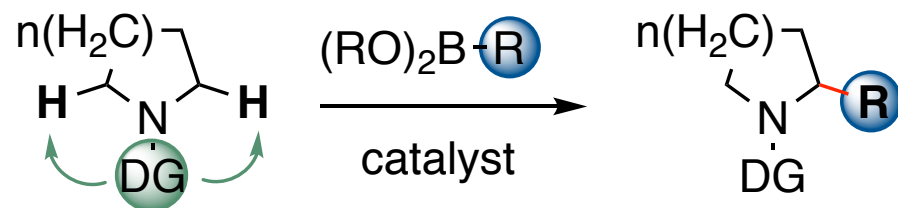


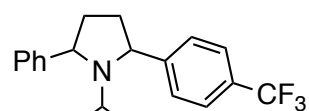
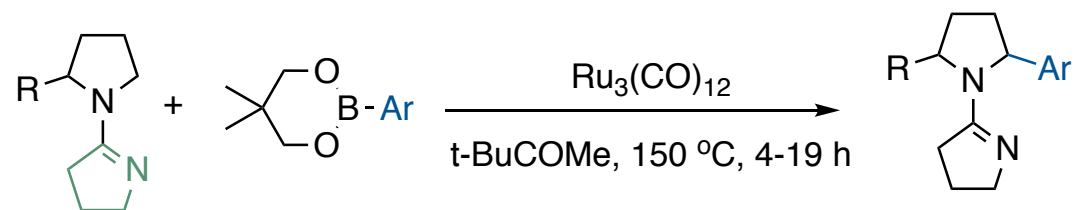




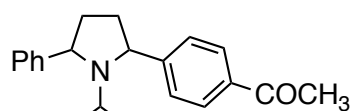
Product	t(h)	% Yield, <i>dr</i>	
	143 h	76%, >20:1	
	72 h	79%, >20:1	
	69 h	59%, >20:1	
	165 h	64%, >20:1	
	R = Me	72 h	43%, >20:1
	Ph	72 h	68%, >20:1
	PMP	72 h	84%, >20:1
	72 h	60%, 10:1	

## C-2 Direct Arylation

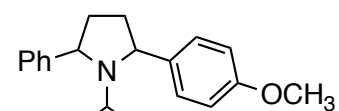




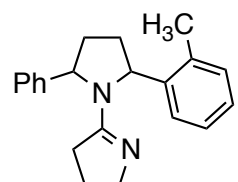
76%  
trans/cis = 3:1



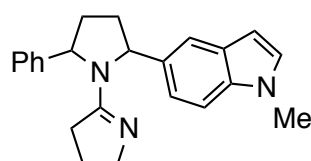
45%  
trans



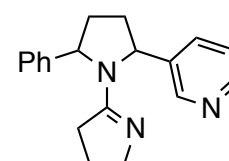
70%  
trans/cis = 4:1



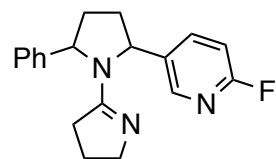
62%  
trans/cis = 6:1



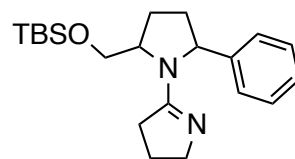
62%  
trans/cis = 5:1



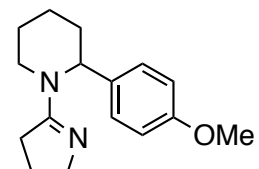
72%  
trans/cis = 3:1



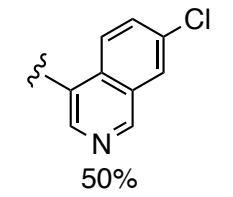
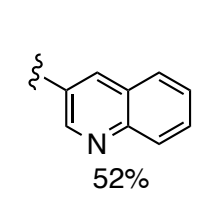
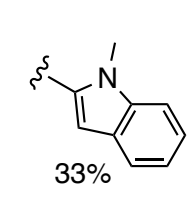
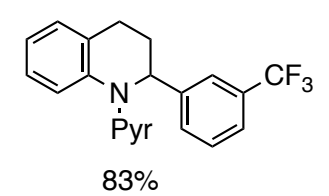
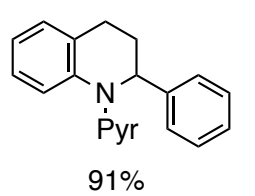
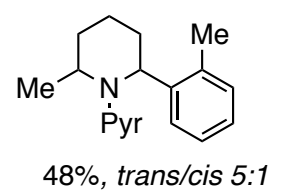
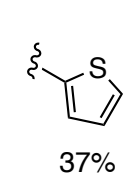
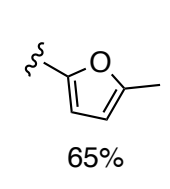
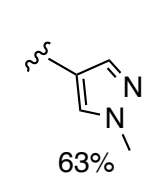
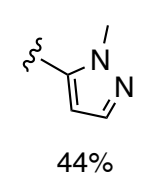
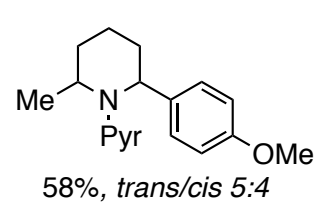
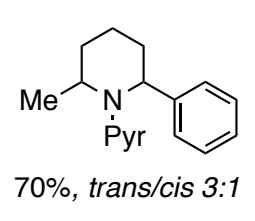
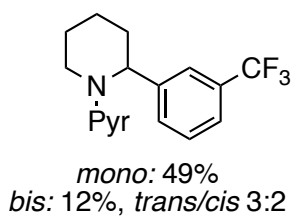
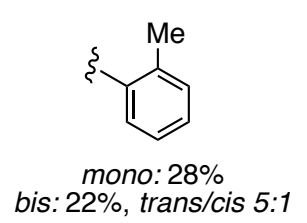
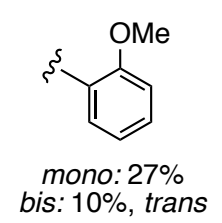
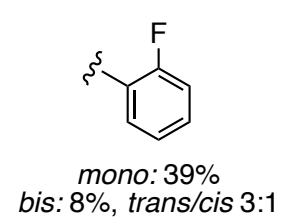
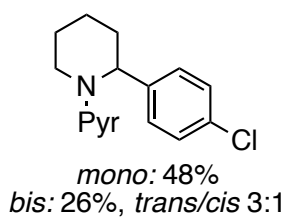
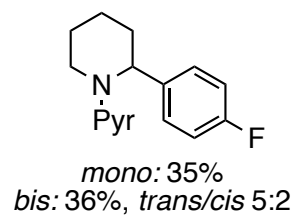
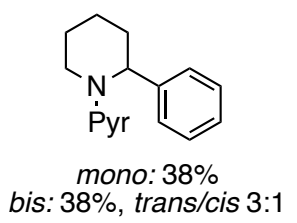
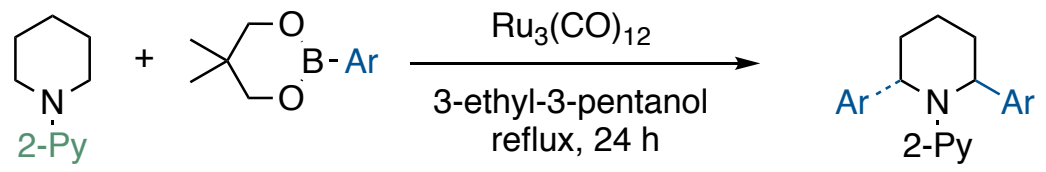
63%  
trans/cis = 3:1



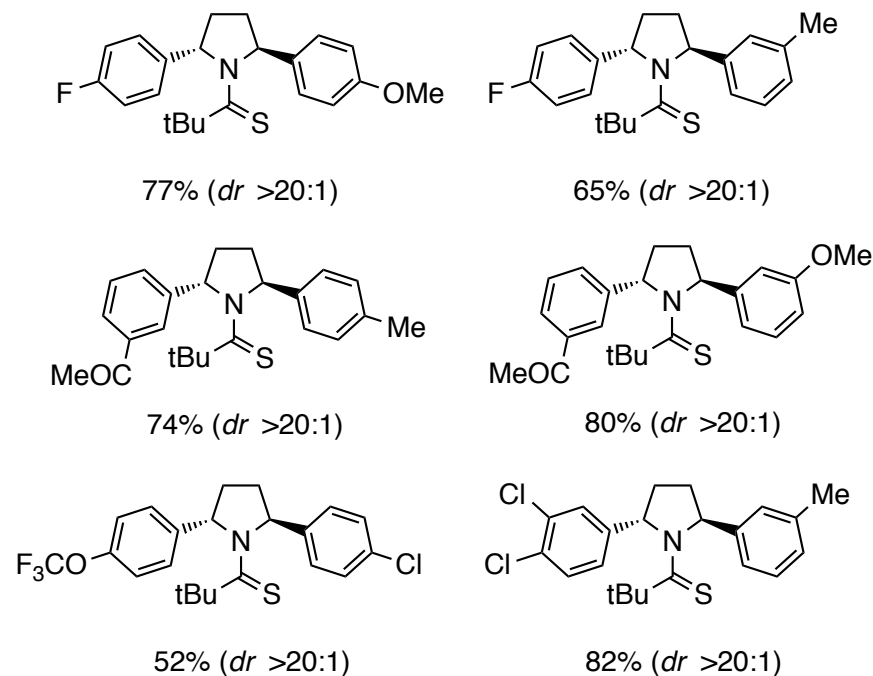
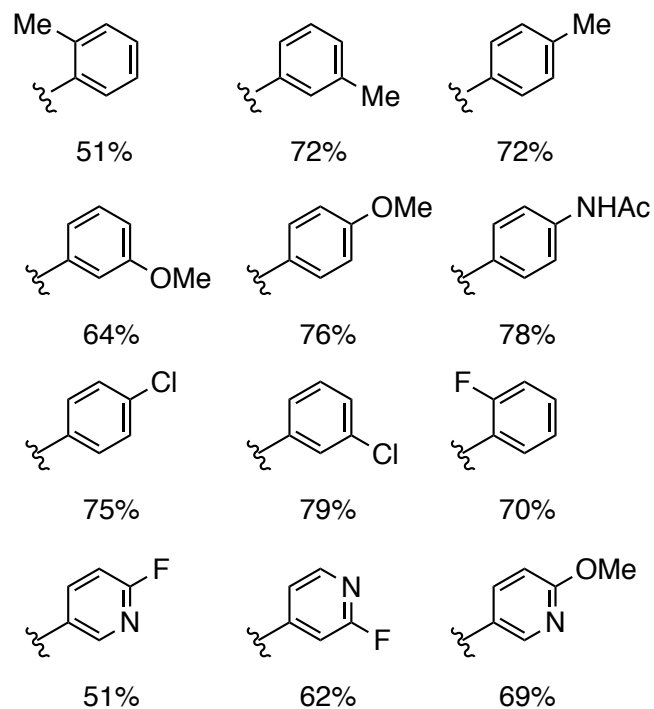
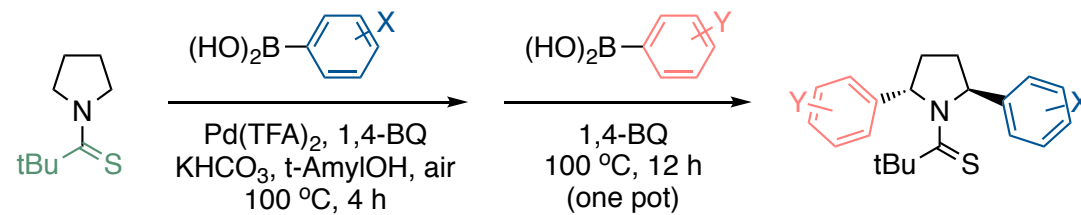
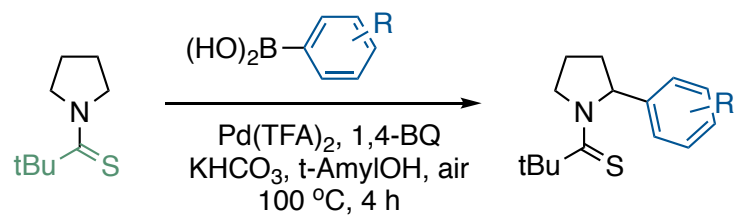
57%  
trans



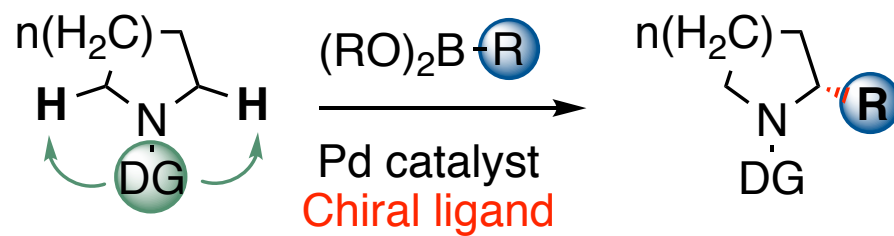
38%

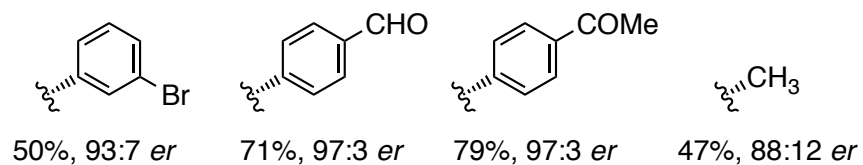
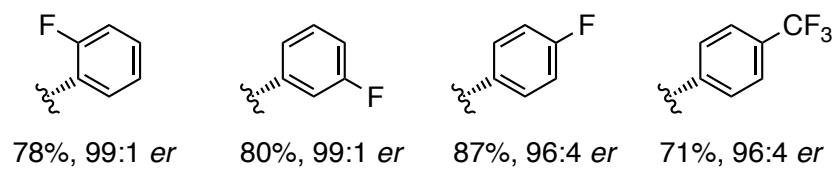
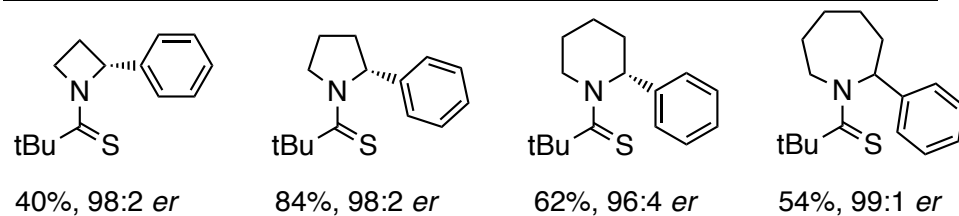
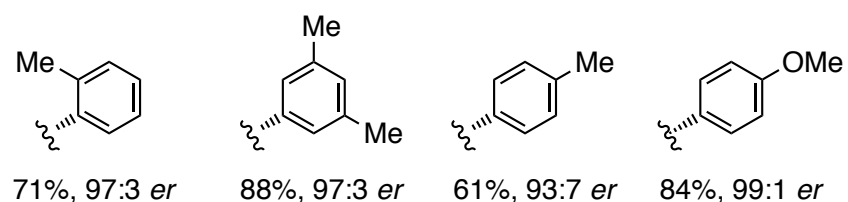
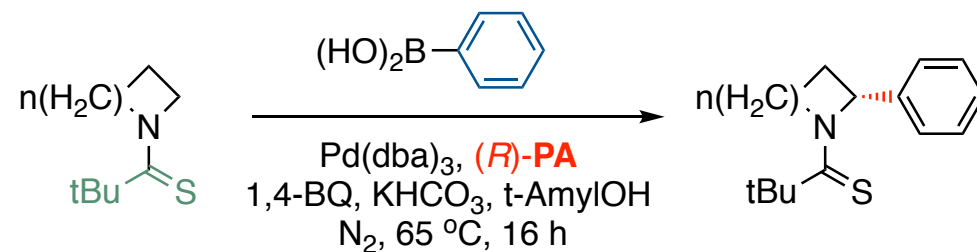
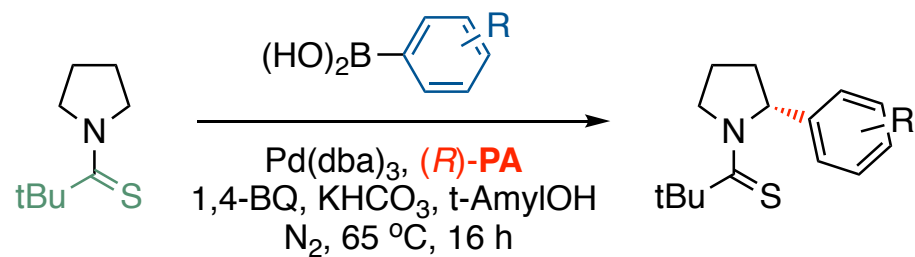


*Chem. Eur. J.* **2010**, 16, 13063.  
*Chem. Eur. J.* **2013**, 19, 10378.

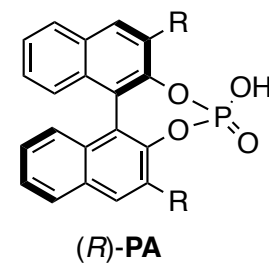


# Enantioselective C-2 Direct Arylation

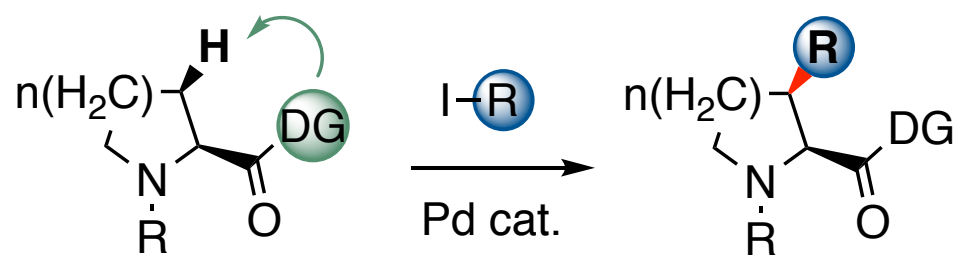




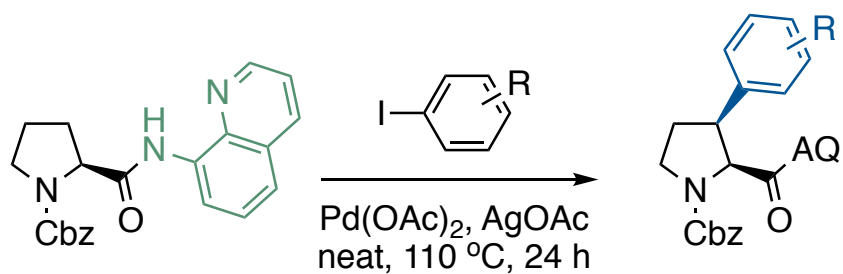
Nat. Chem. **2017**, 9, 140.



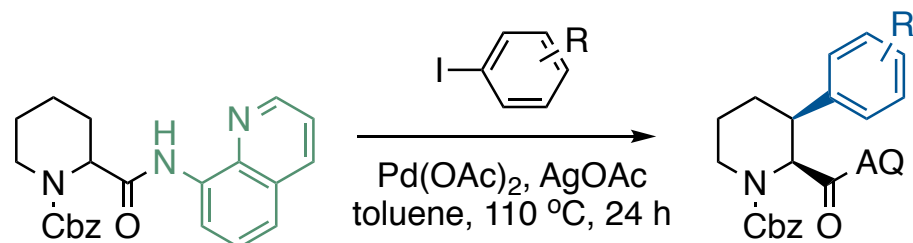
## Regio- and Stereospecific C-3 Functionalization







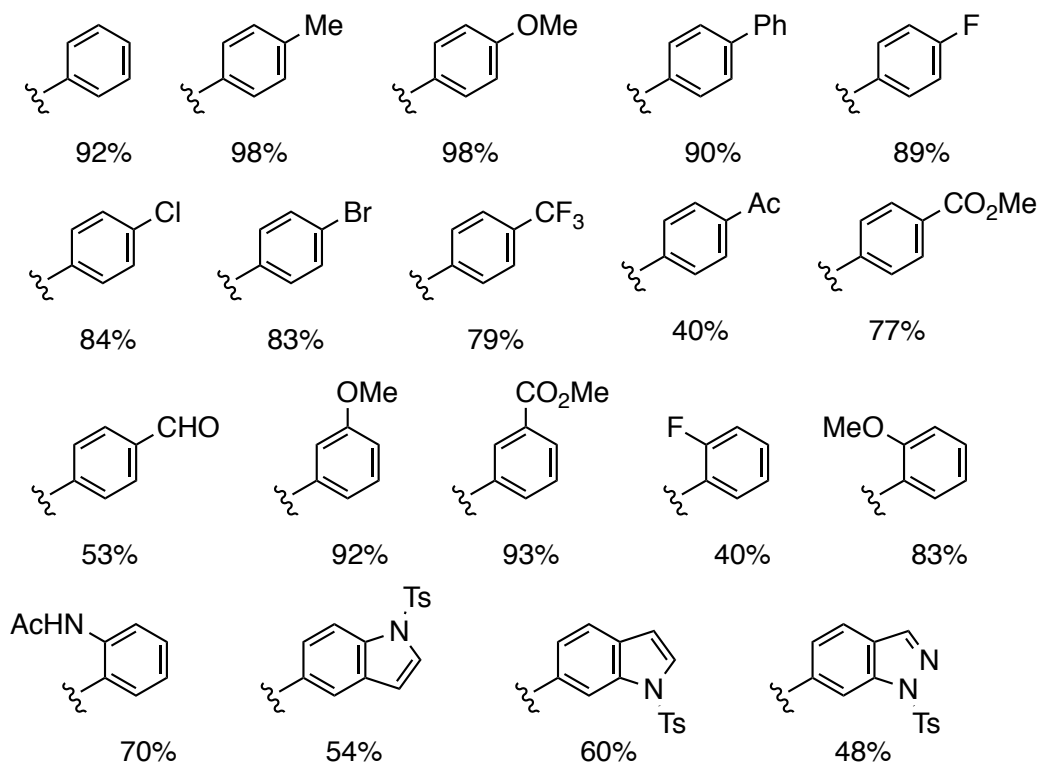
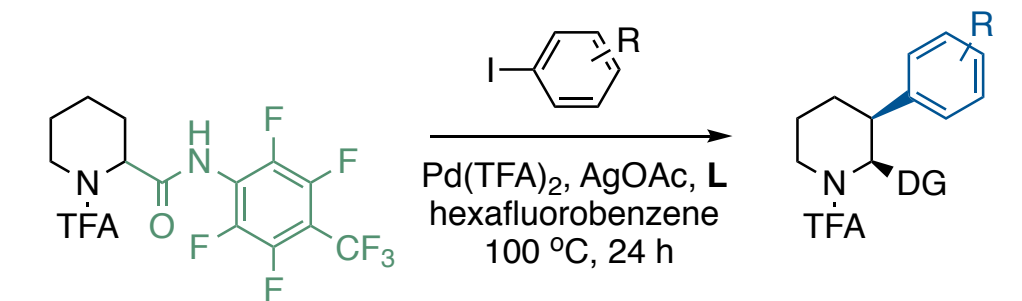
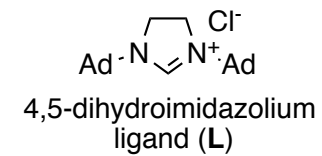
Ar-I	% Yield	Ar-I	% Yield
	86%		76%
	91%		45%
	88%		34%
	90%		34%
	22%		28%
	44%		87%



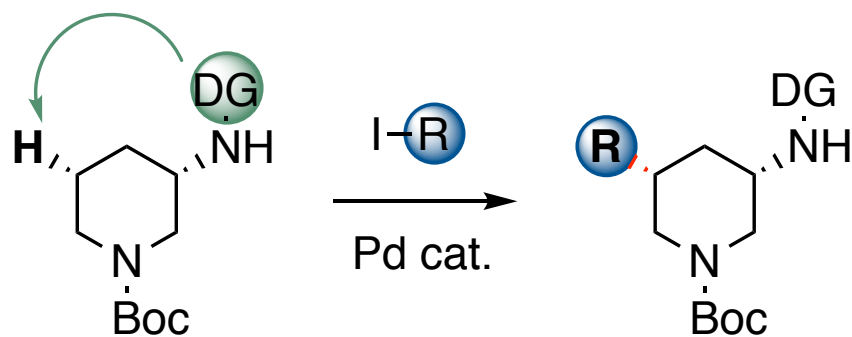
Ar-I	% Yield
	96%
	98%
	90%
	98%

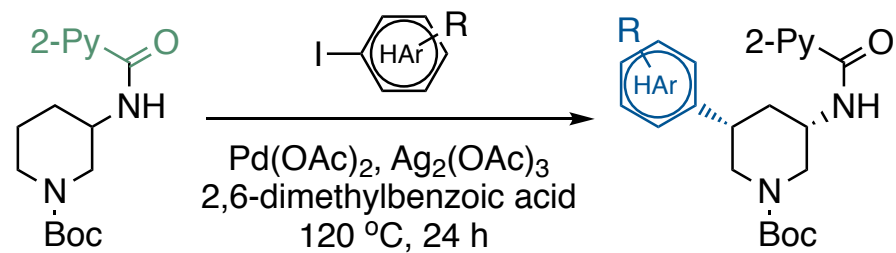
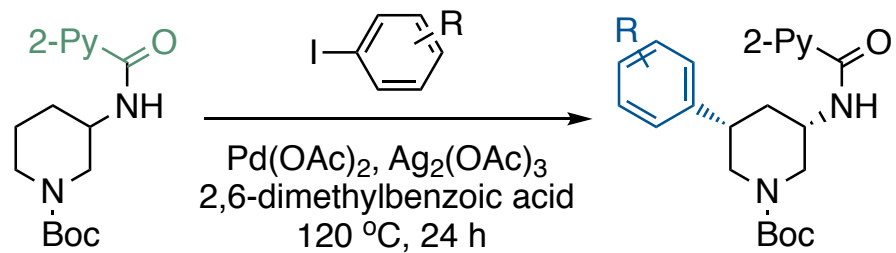
*Org. Lett.* **2014**, 16, 4956.

*Eur. J. Org. Chem.* **2016**, 139.



# Regio- and Stereospecific C-5 Functionalization of 3-Aminopiperidine

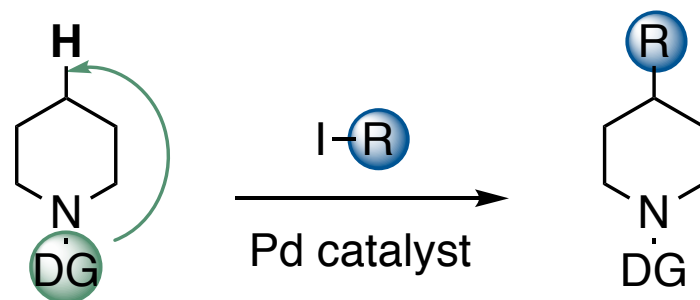


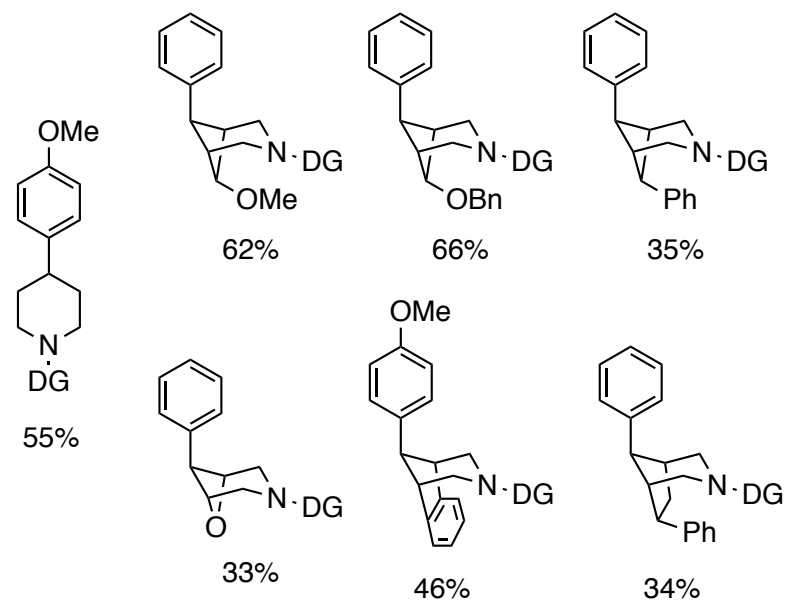
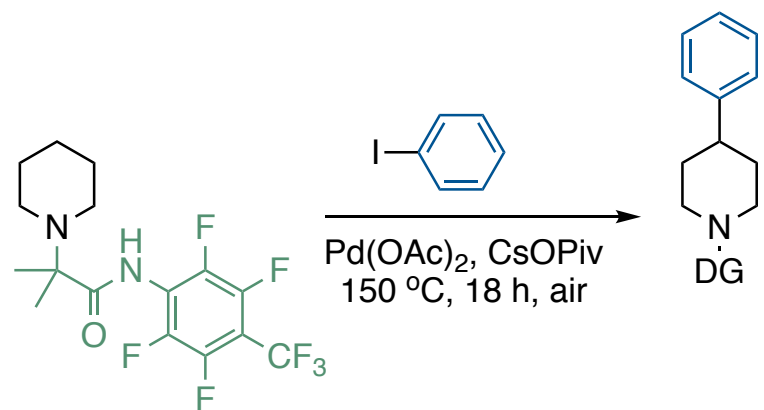


Ar-I	% Yield	Ar-I	% Yield
	71%		70%
	65%		68%
	78%		60%
	67%		62%
	72%		9%

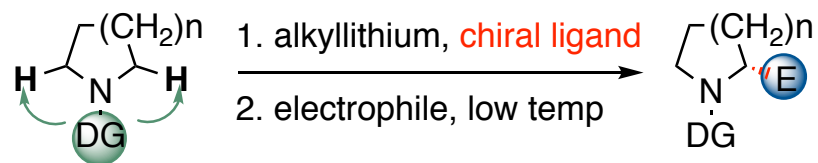
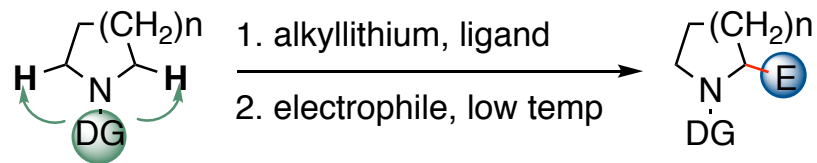
HAr-I	% Yield
	72%
	98%

## Regiospecific C-4 Direct Functionalization of Piperidine

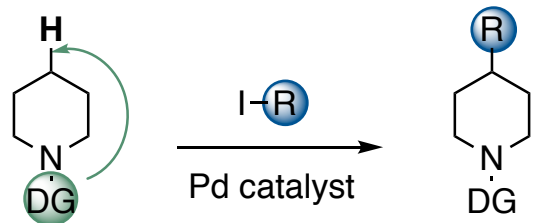
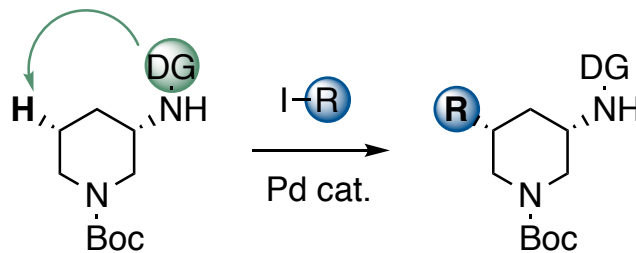
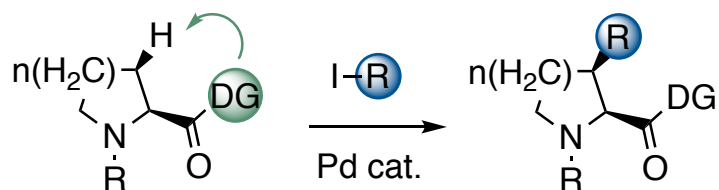
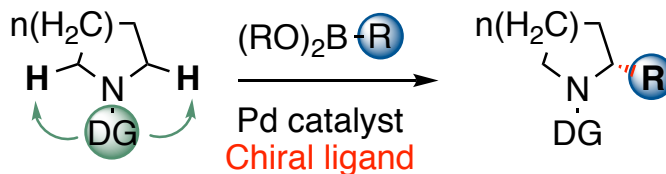
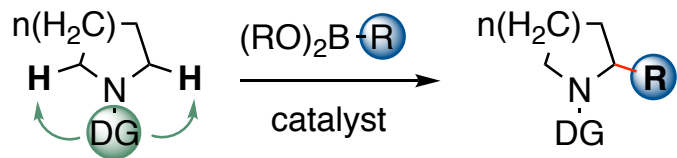
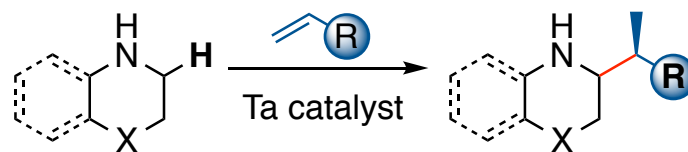
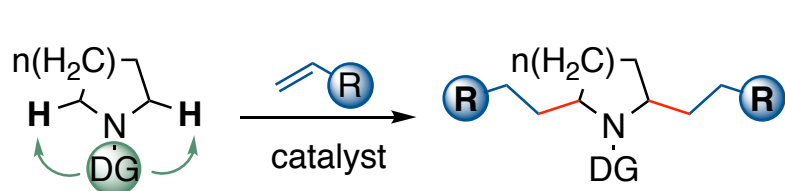




## Alpha-lithiation



## Transition metal-catalyzed



# Future Efforts

## I. Drug Development

- Lack of drug efficacy is a significant barrier towards advancing modern medicine.
- Protein-protein interactions offer a new category of possible drug targets; however, identifying therapeutically relevant PPIs is considerably difficult.
- Modulating a protein-protein interaction with a small molecule is feasible; however, the identification and development of such a molecule is rather difficult and requires the advancement in modern drug development.

## II. Fragment-Based Drug Development

- Improve 3-Dimensionality
- Incorporate structural and stereochemical diversity
- Emulate natural product structural motifs

## III. Asymmetric Direct Functionalization

- Enhance stereo- and regioselective control
- Expand scope and substitutional diversity
  - Scope: 2-atom heterocycles
  - Substitutions: heteroatoms
- Efficient and robust



# Thank you

Dr. Peter Wipf and Wipf group members

