

ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

September 19–23, 2024
Ischia (Napoli) Italy



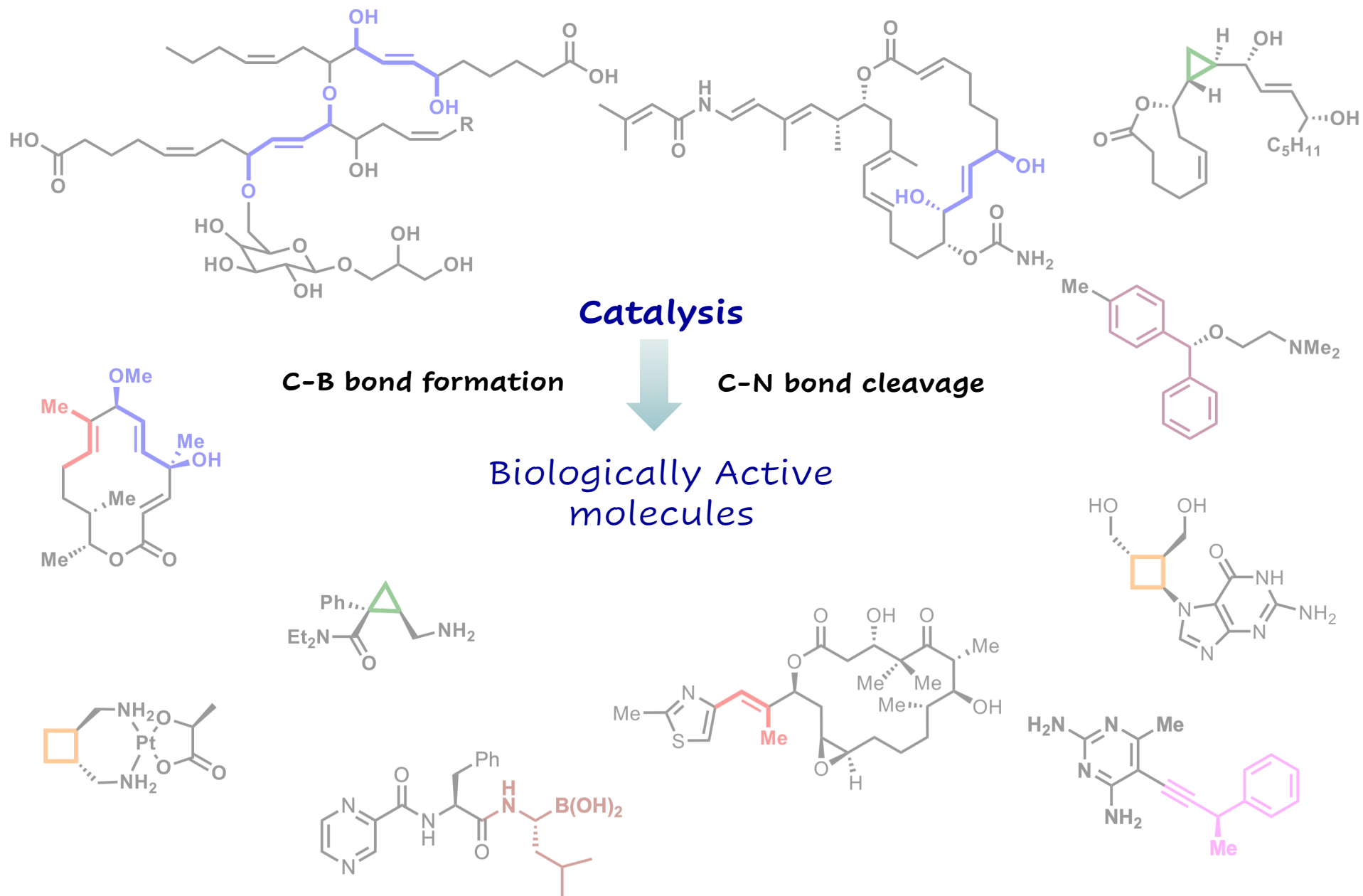
Catalysis to increase complexity:

stereoselective synthesis of sp^3 -rich building blocks

Mariola Tortosa

Universidad Autónoma de Madrid

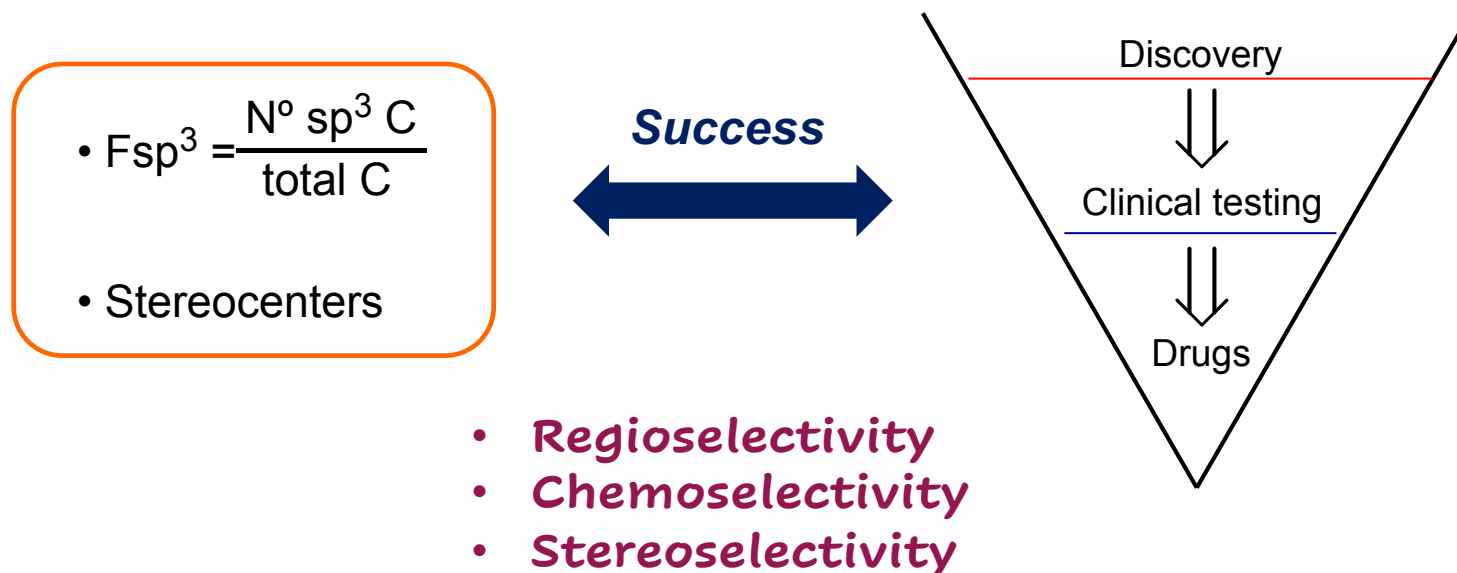
Catalysis to Increase Complexity



Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success

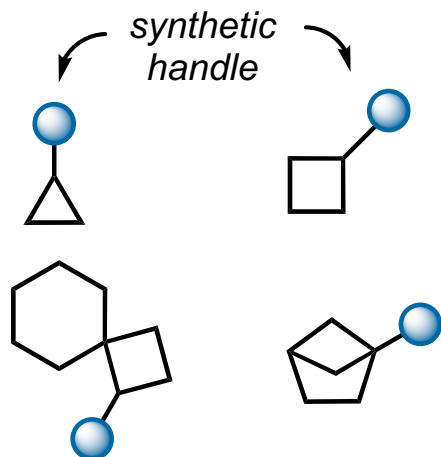
Frank Lovering,^{*,†} Jack Bikker,[‡] and Christine Humblet[§]

Wyeth Research, Chemical Sciences, [†]200 Cambridgepark Drive, Cambridge, Massachusetts 02140, [‡]401 North Middletown Road, Pearl River, New York 10965, and [§]865 Ridge Road, Monmouth Junction, New Jersey 08543

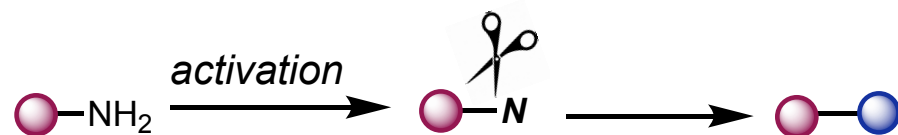
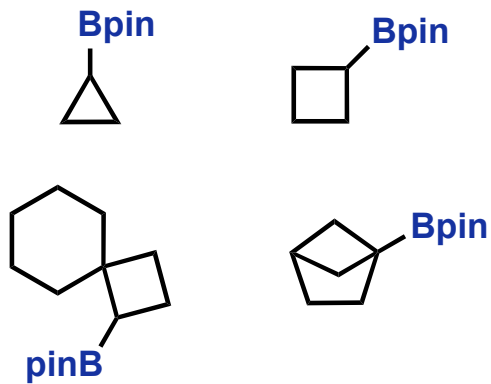
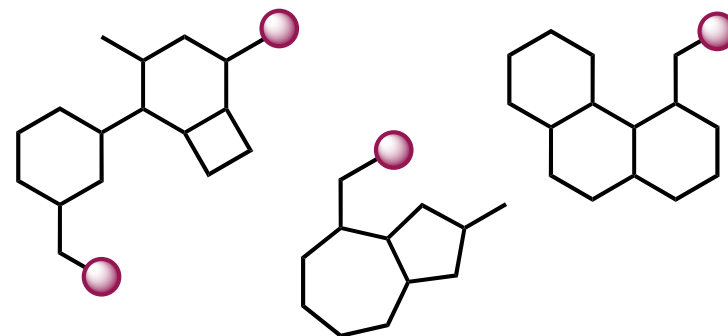


Catalysis to Increase Complexity

Synthesis of modifiable building blocks



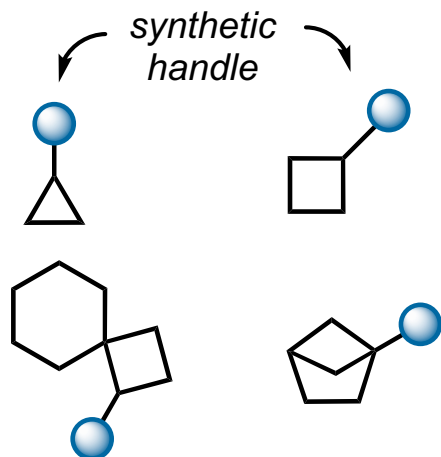
Selective modification of abundant functional groups



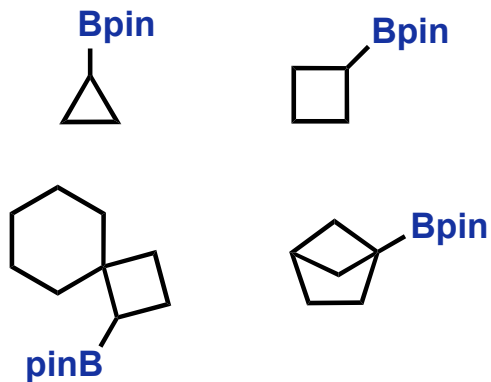
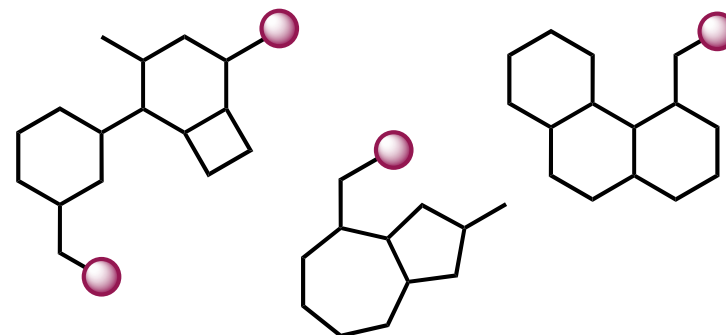
C-N cleavage

Catalysis to Increase Complexity

Synthesis of modifiable building blocks

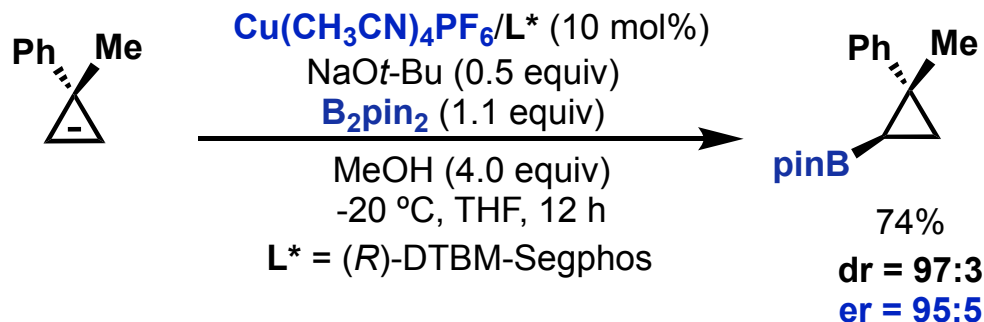


Selective modification of abundant functional groups

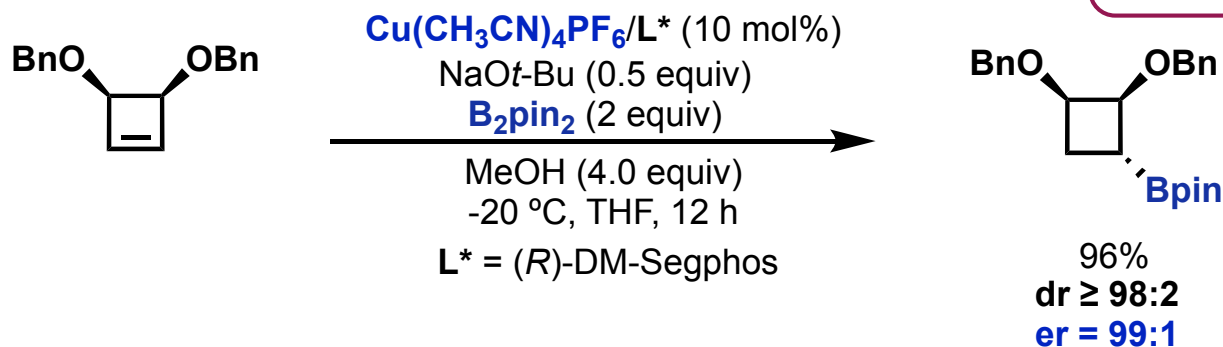


- *Versatile functional group*
- *Configurational stability C-B bond*
- *Few synthetic stereoselective methods*

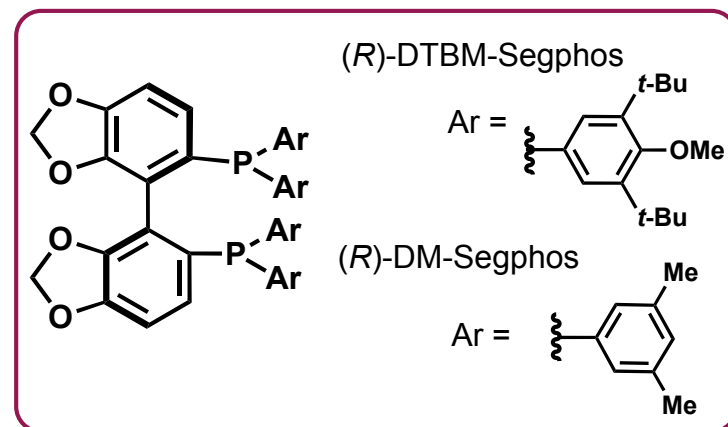
Copper-Catalyzed Desymmetrization



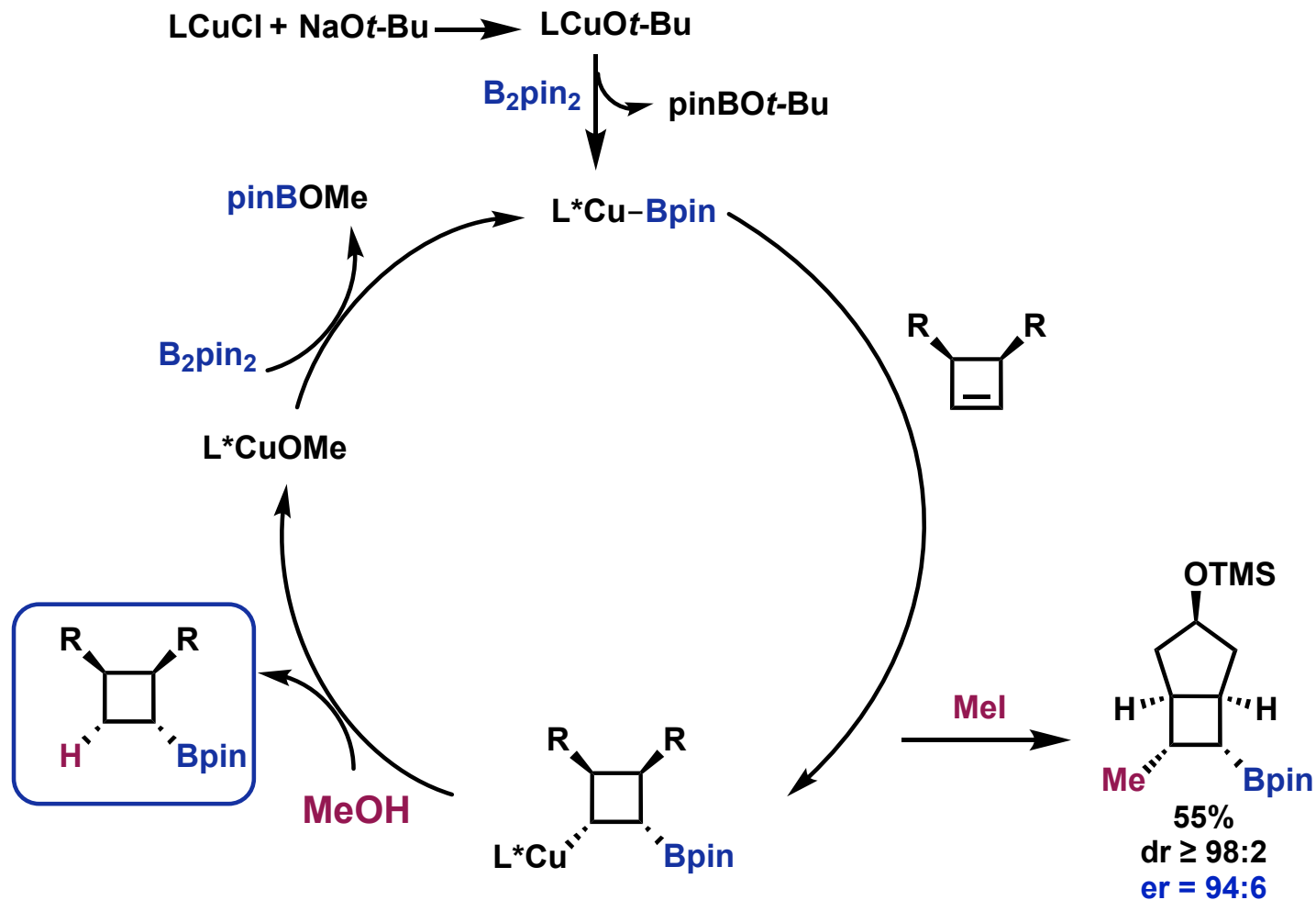
J. Am. Chem. Soc. **2014**, 136, 15833



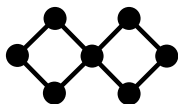
Angew. Chem. Int. Ed. **2016**, 55, 6969



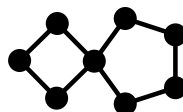
Cyclopropyl Amino-Boronic Esters



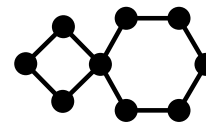
Cyclobutyl Spirocycles



Spiro[3,3]heptanes



Spiro[3,4]octanes



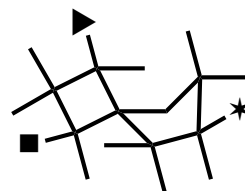
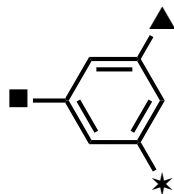
Spiro[3,5]nonanes

Poorly explored regions of chemical space

Expanded toolbox to modulate physicochemical properties

Well-defined exit vectors

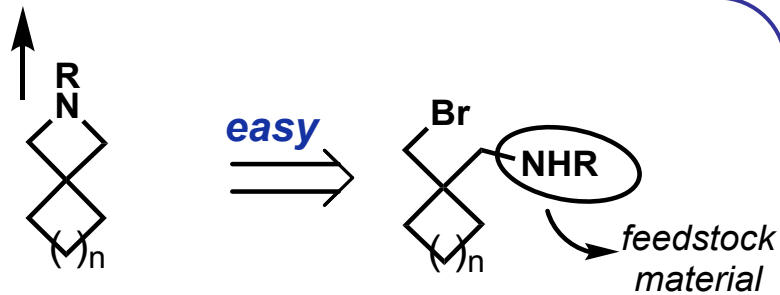
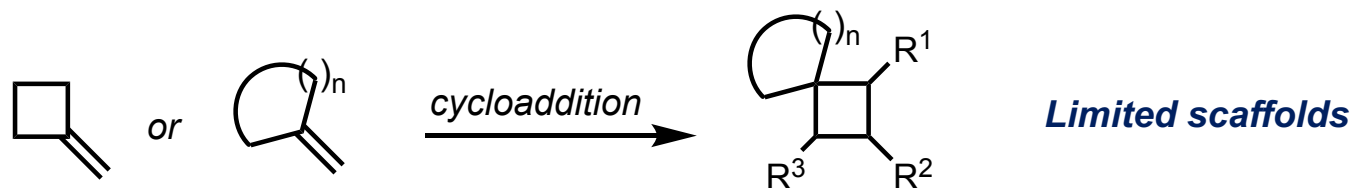
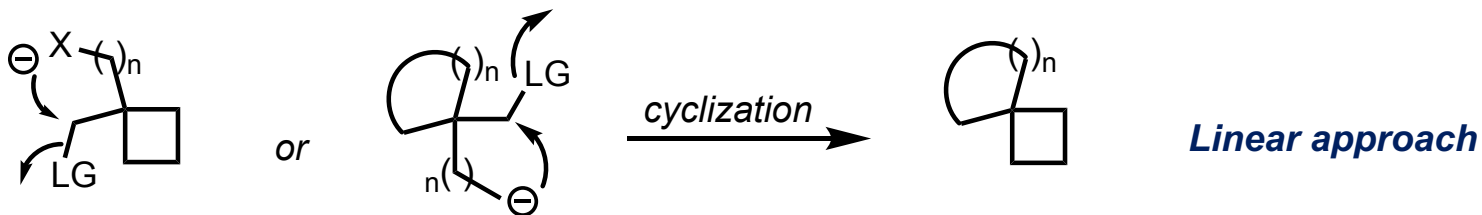
2D-exit vectors



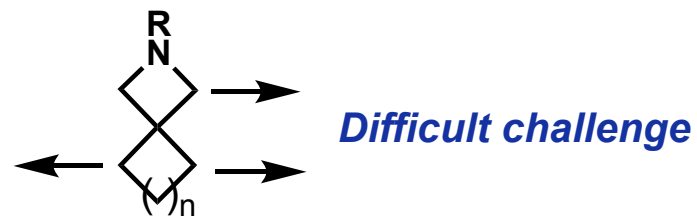
3D-exit vectors

Cyclobutyl Spirocycles

Common strategies



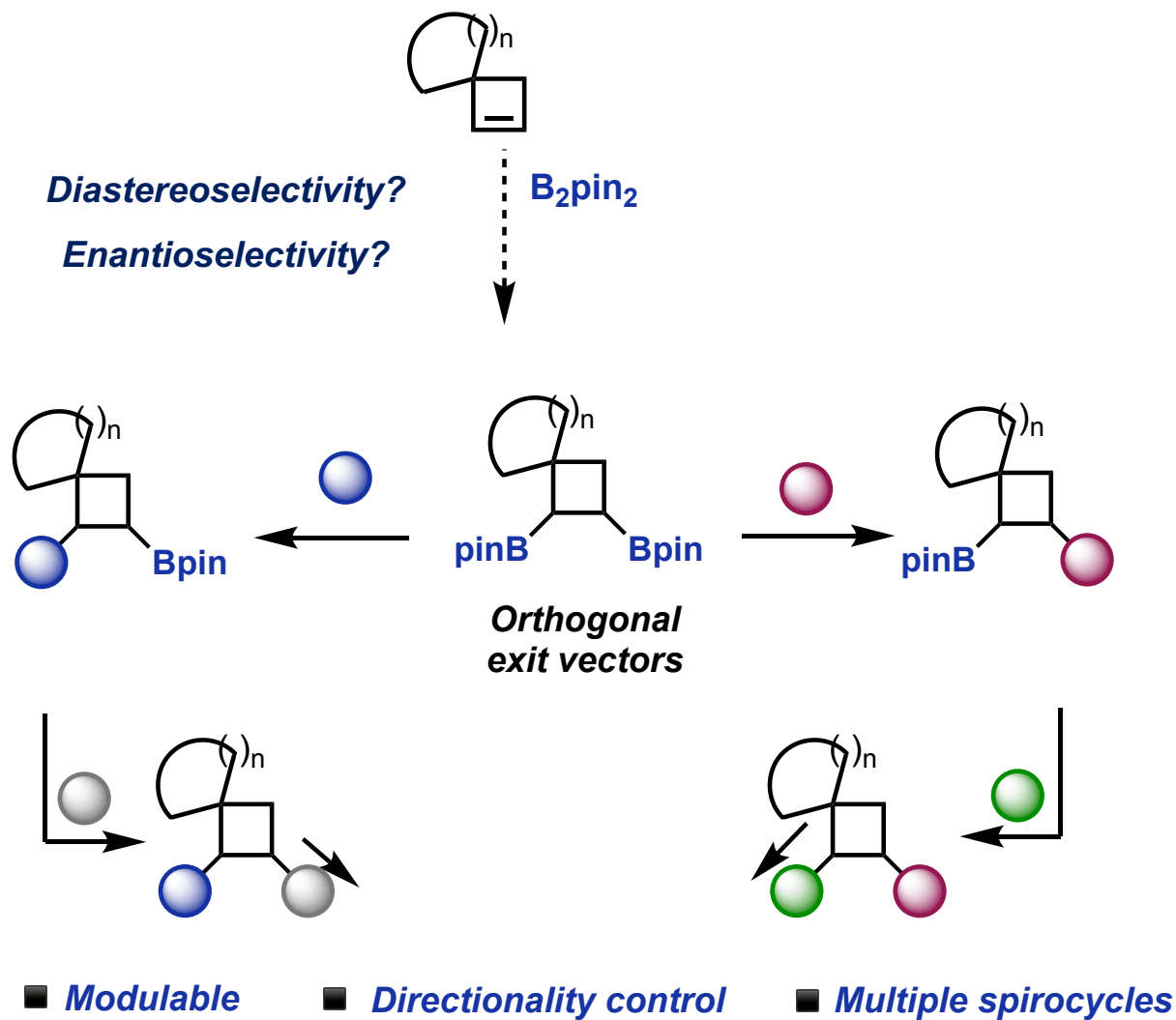
exit vectors on terminal heteroatoms



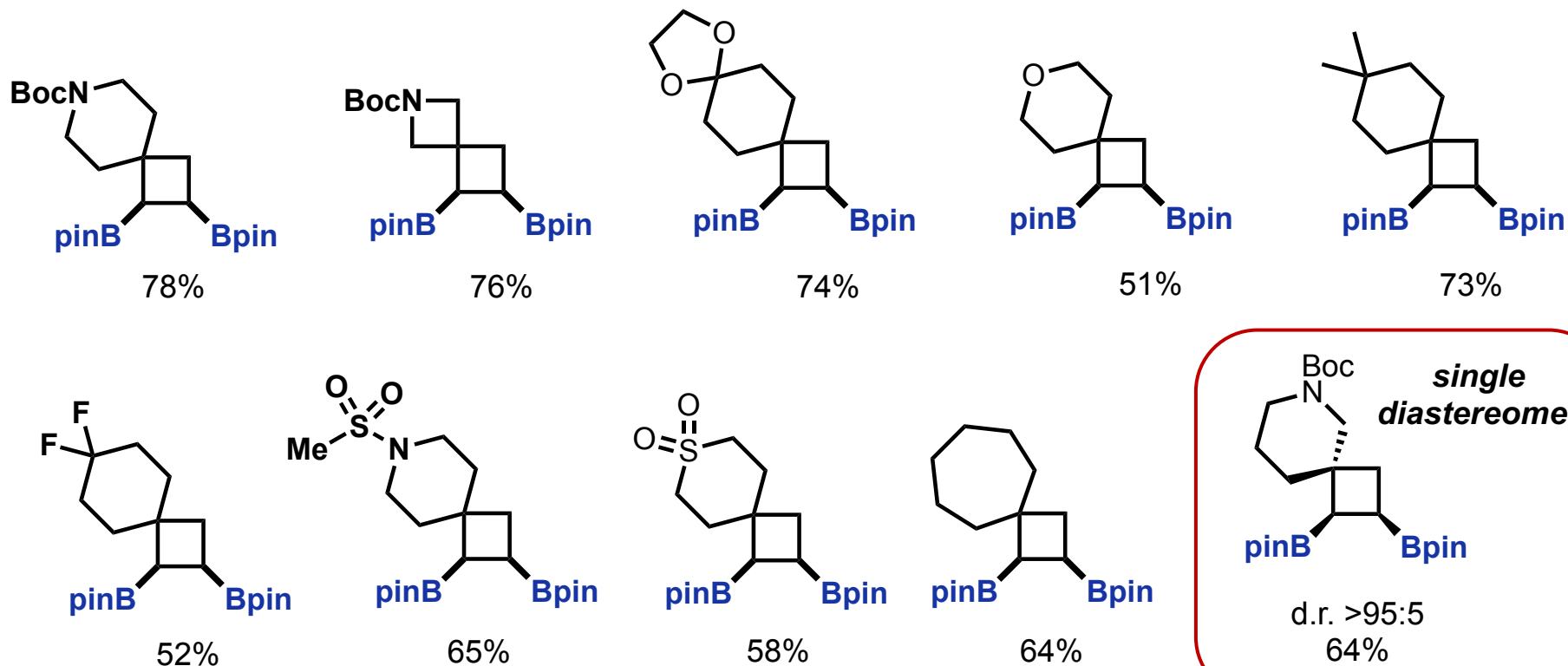
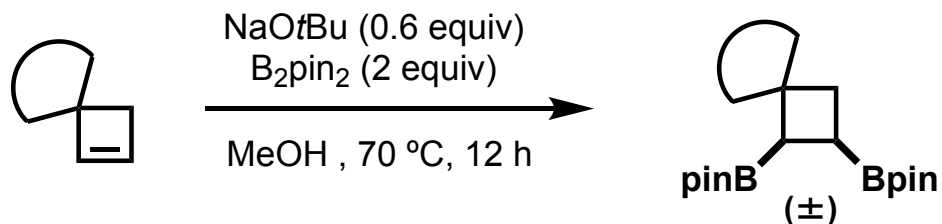
exit vectors on carbon orthogonal angles

Difficult challenge

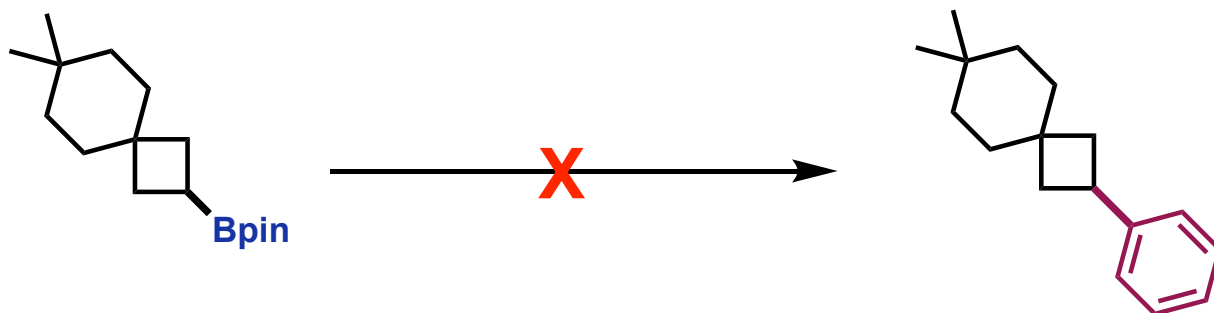
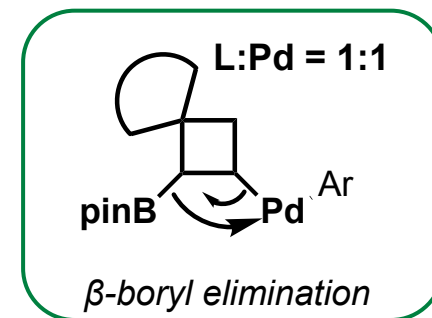
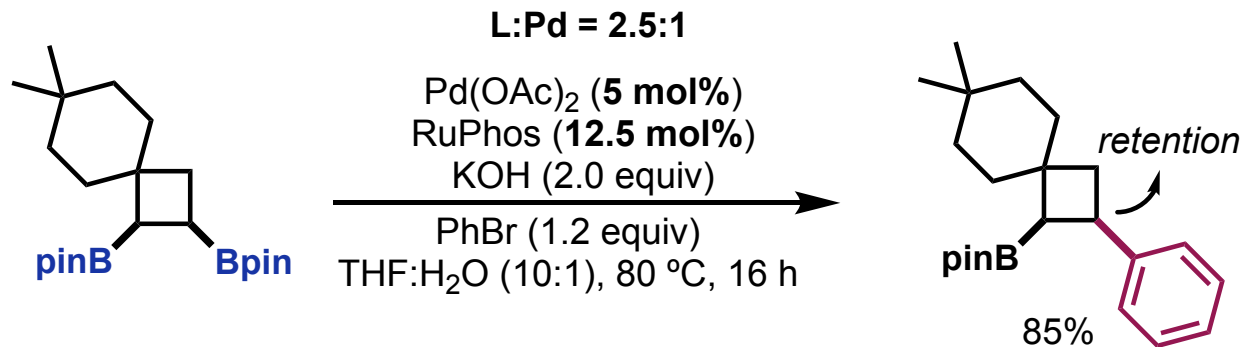
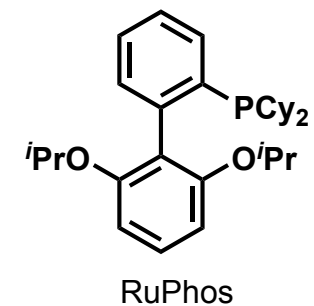
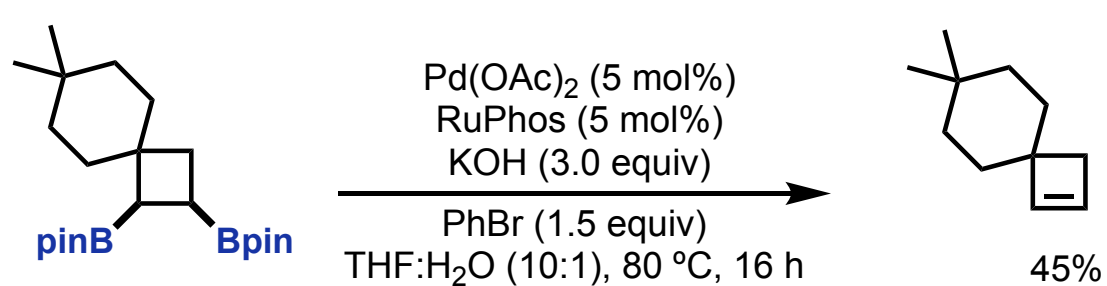
Spirocyclobutenes



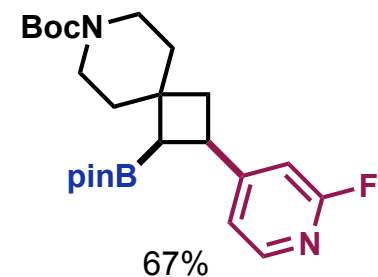
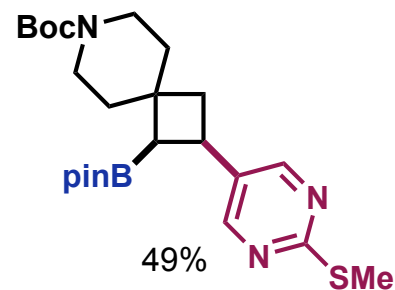
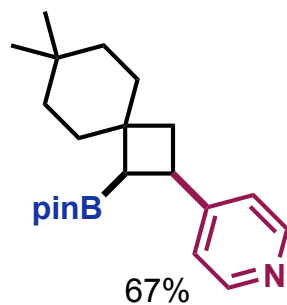
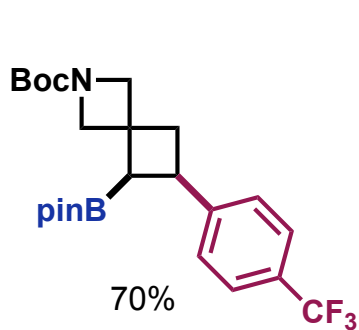
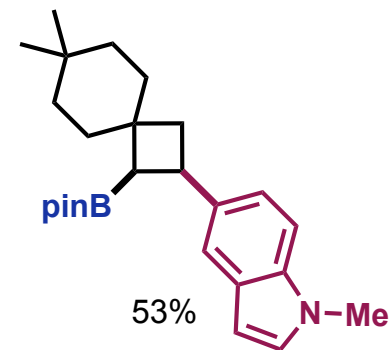
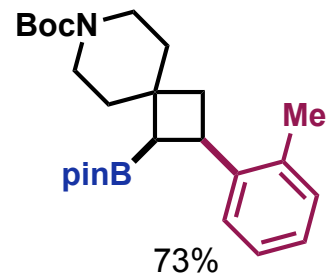
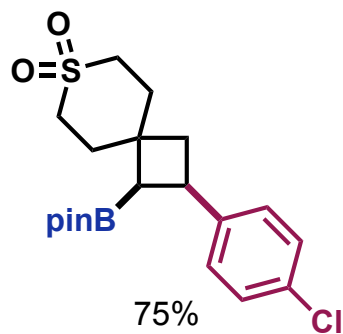
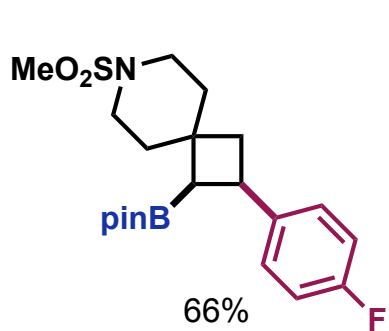
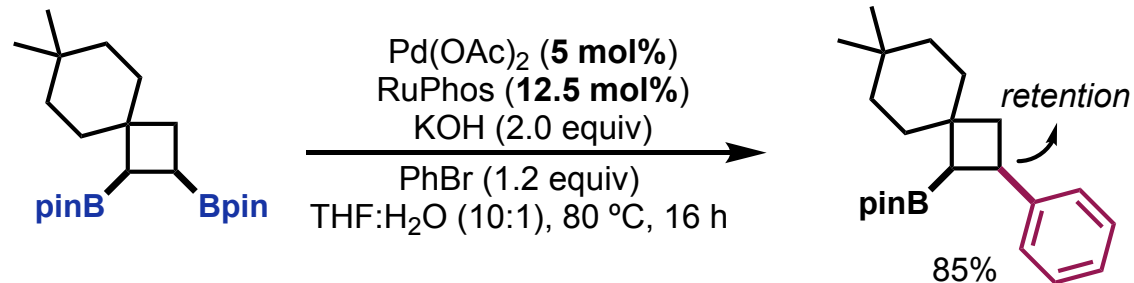
Cyclobutyl Spirocycles



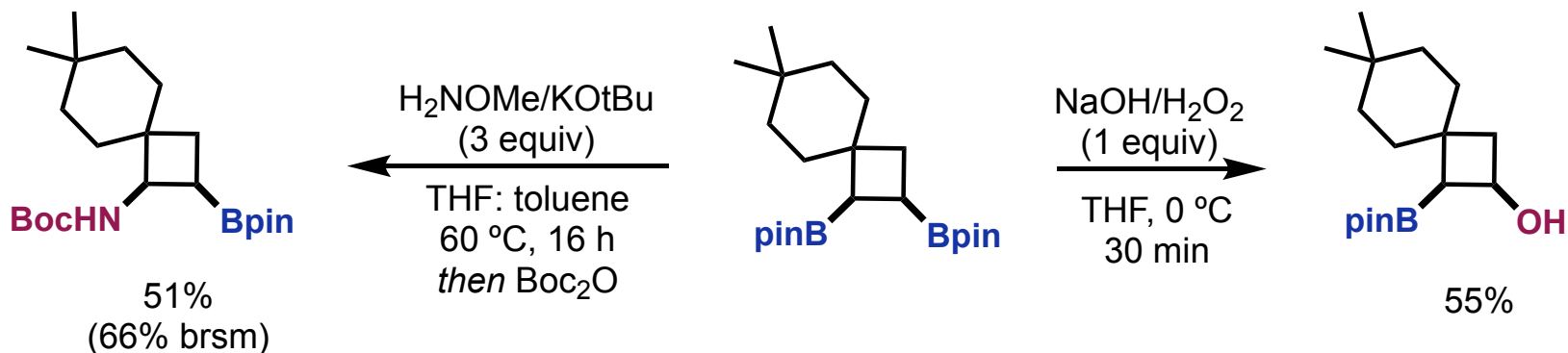
Selective Cross-Coupling



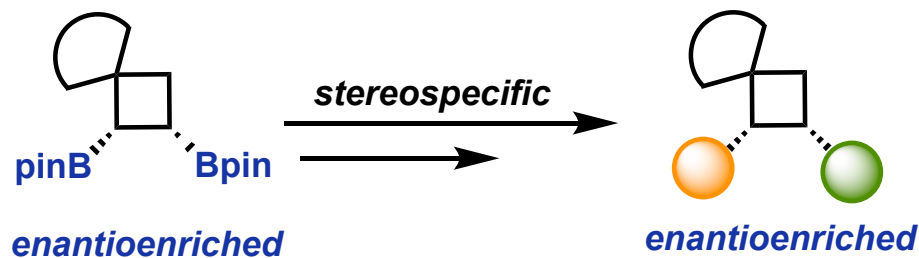
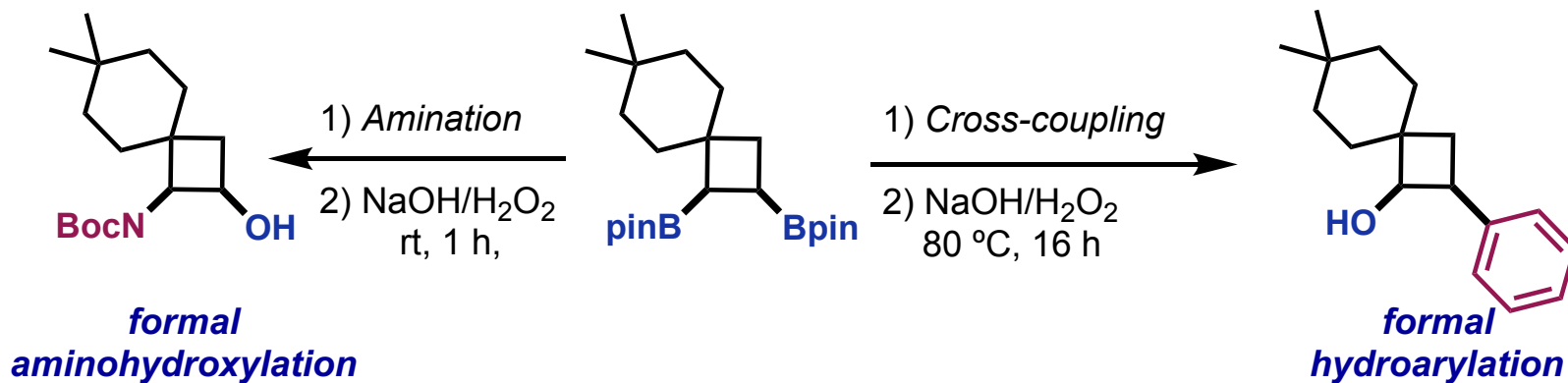
Selective Cross-Coupling



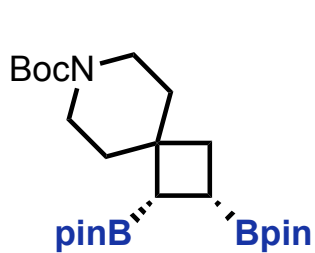
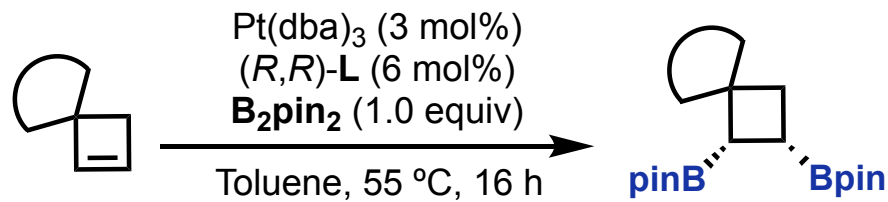
Selective Functionalization



Difunctionalizations

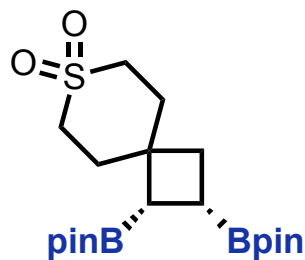


Enantioselective Diboration



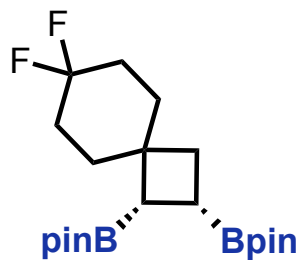
94%
er = 88:12

er = 98:2

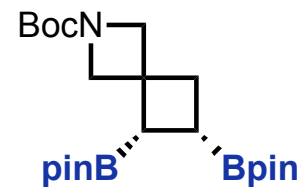


64%
er = 85:15

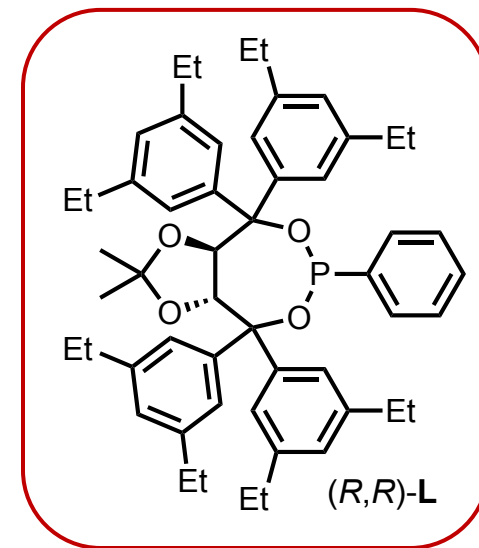
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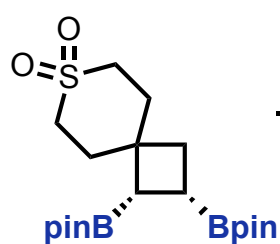
60%
er = 86:14



73%
er = 90:10

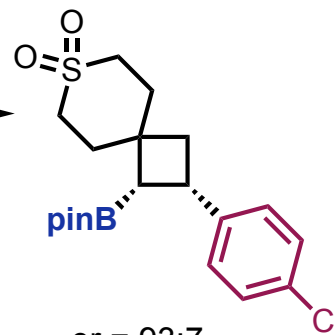


single recrystallization

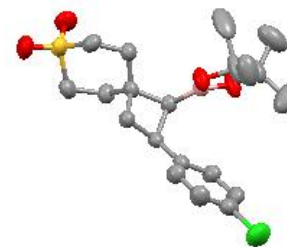


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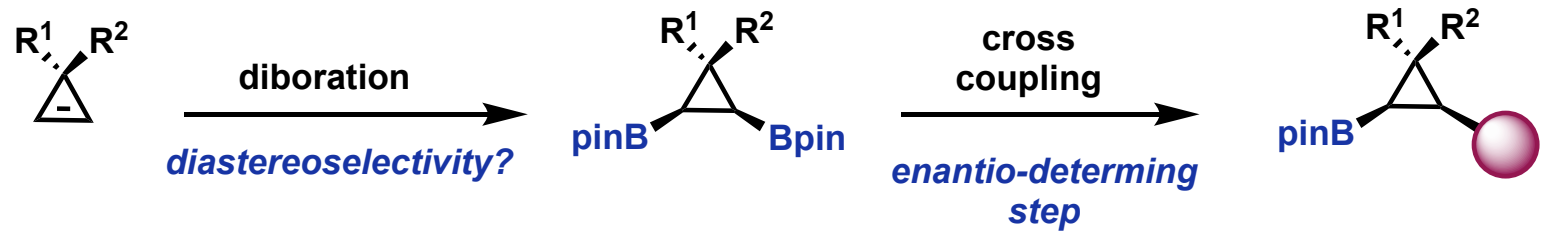
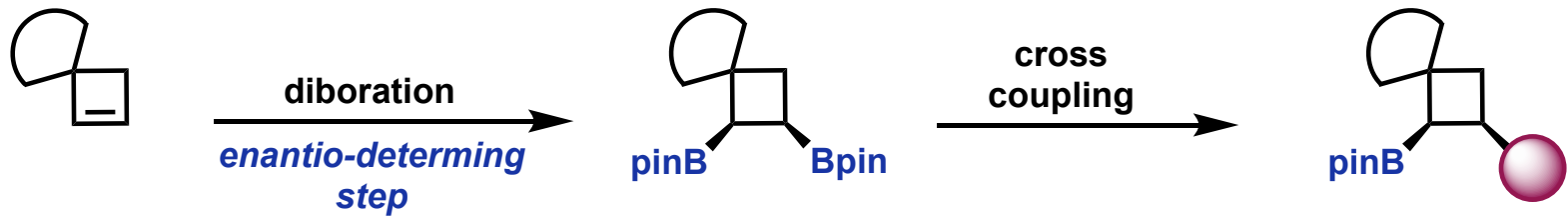
Selective
cross-coupling



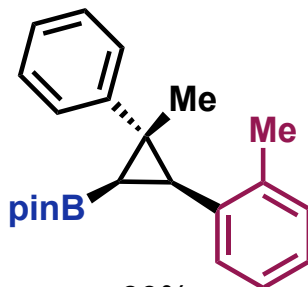
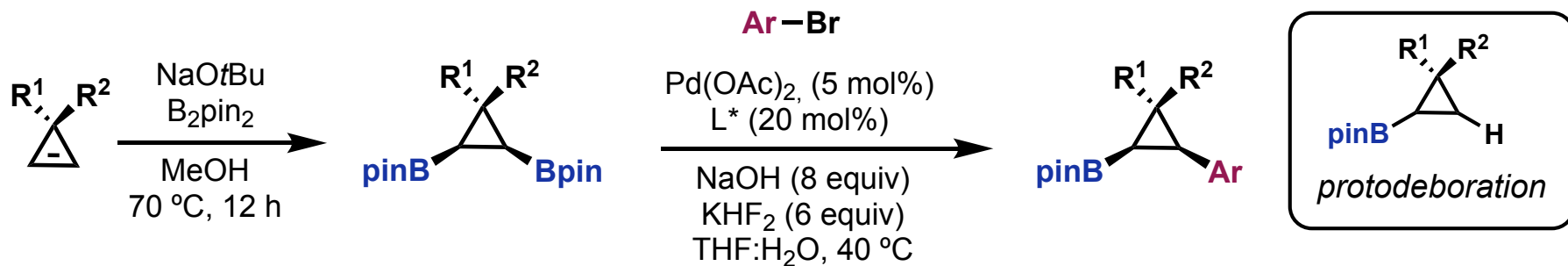
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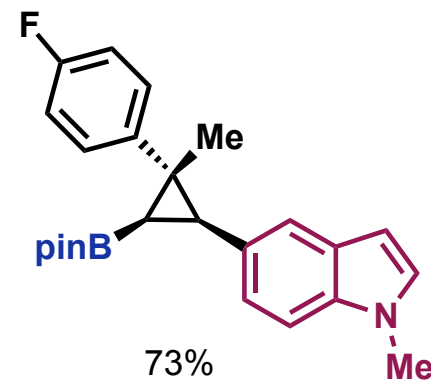
Diboration of cyclopropenes



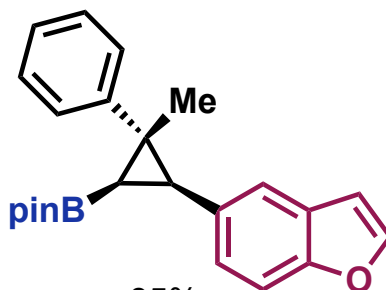
Enantioselective cross-coupling: challenges involved



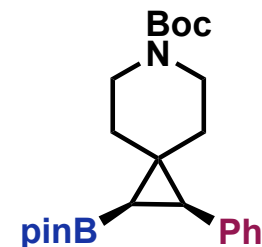
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er = 95:5



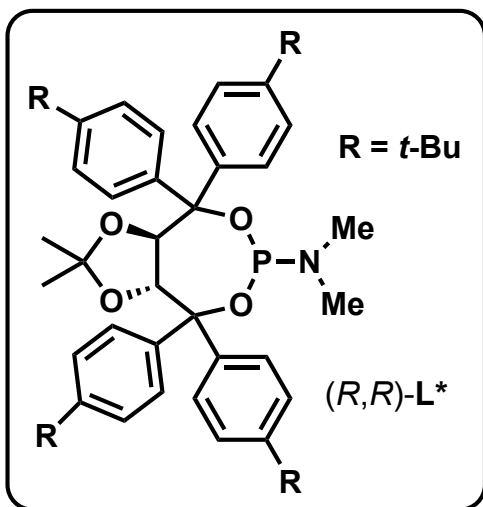
73%
er = 90:10



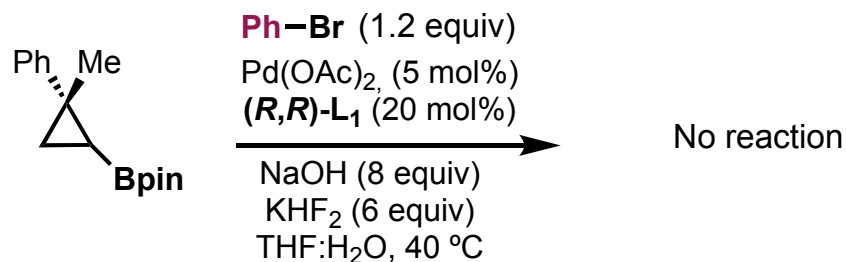
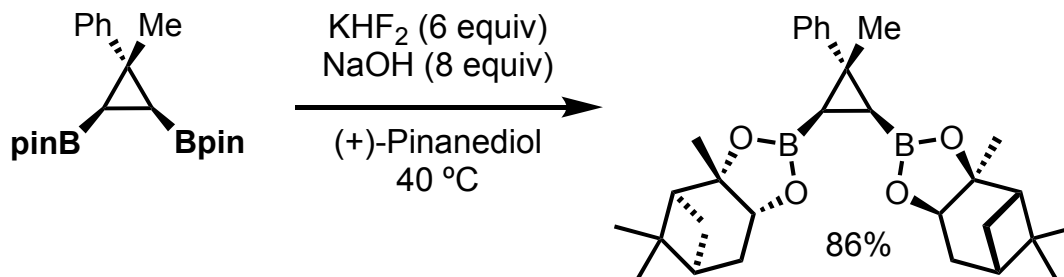
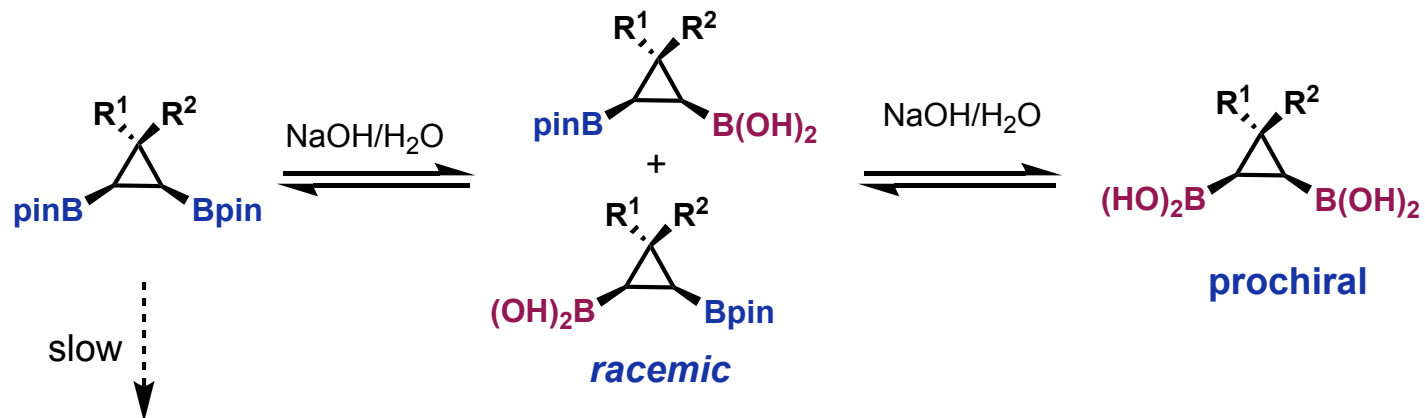
85%
er = 92:8



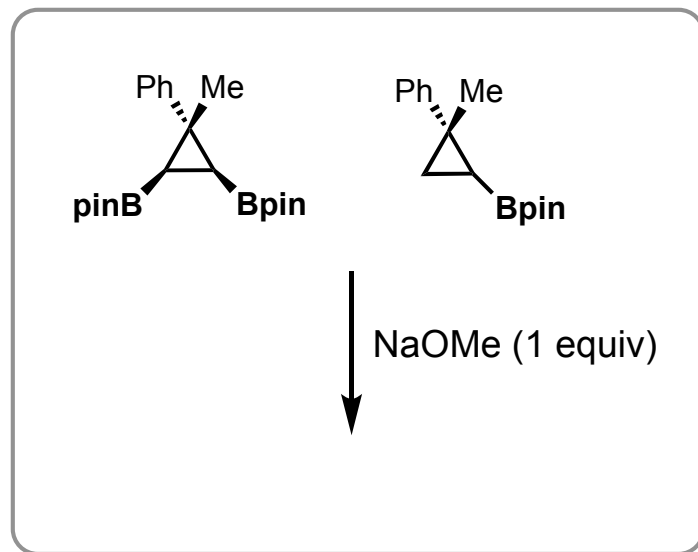
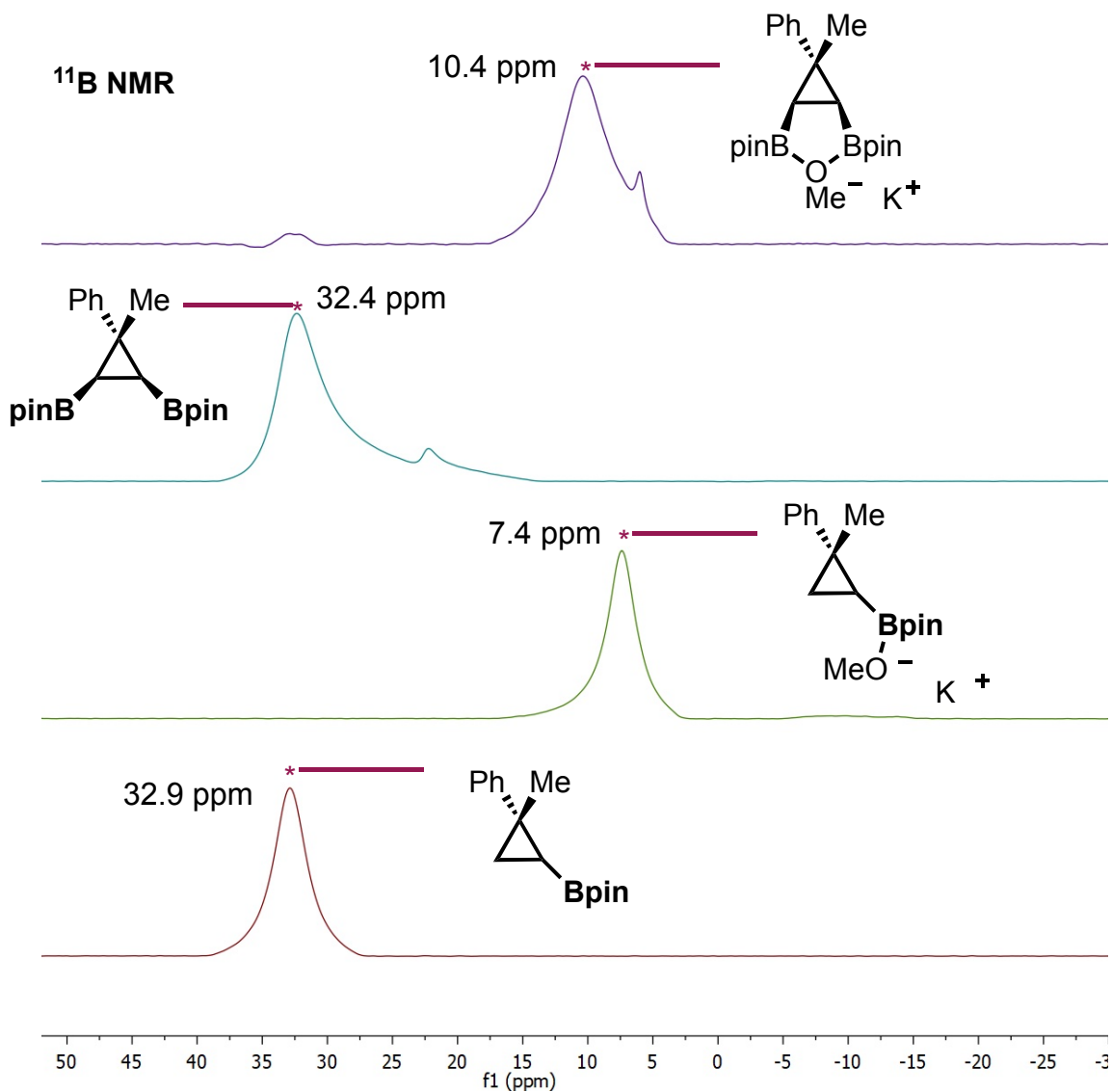
56%
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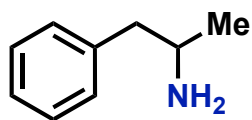
Enantioselective cross-coupling: challenges involved



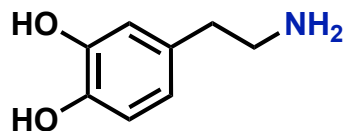
Enantioselective cross-coupling: challenges involved



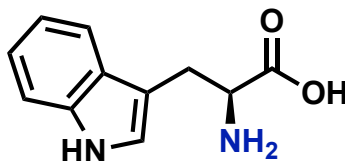
Amines as building blocks



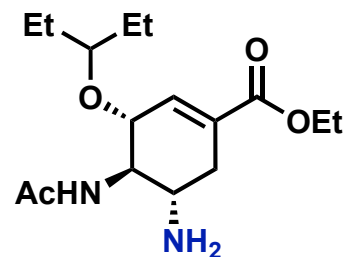
Amphetamine
(Adrenergic)



Dopamine
(Neurotransmitter)



Tryptophan
(Aminoacid)

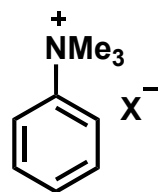
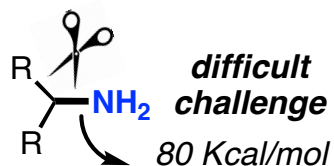


Oseltamivir
(Antiviral)

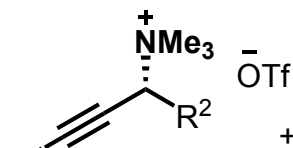
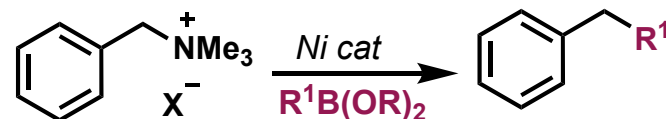
✓ Structural diversity

✓ Abundant

✓ Commercial



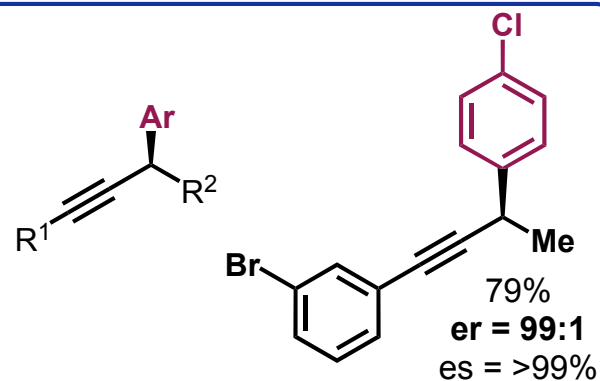
metal = Ni, Pd, Fe, Rh,
 $R^1M = MgX, ZnX, B(OR)_2$



$ArMgBr$
(1.1 equiv)

$[Cu(CH_3CN)_4]PF_6$
(5 mol%)

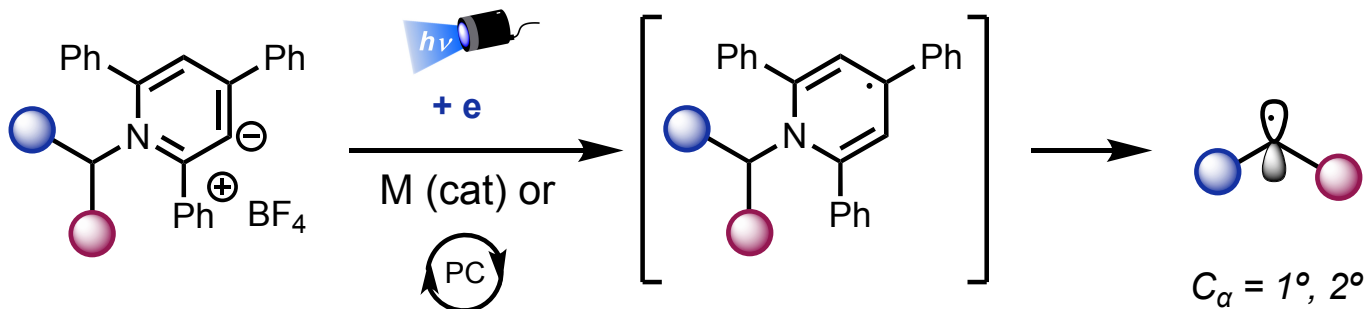
$CH_2Cl_2, -40\text{ }^\circ C$
5 min



J. Am. Chem. Soc. **2017**, *139*, 8448

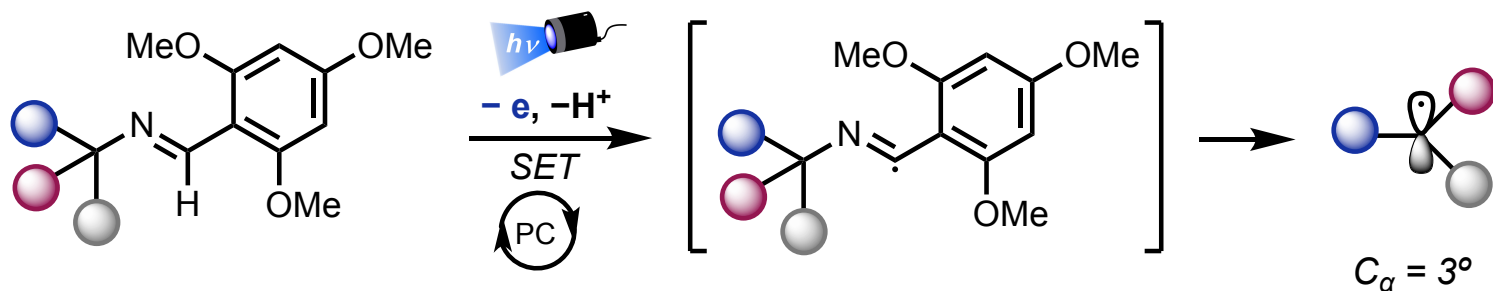
Light-mediated deaminations

Reduction of pyridinium salts



Watson: *J. Am. Chem. Soc.* **2017**, 139, 5313
Recent review, Wu: *ACS Catal.* **2019**, 9, 8943

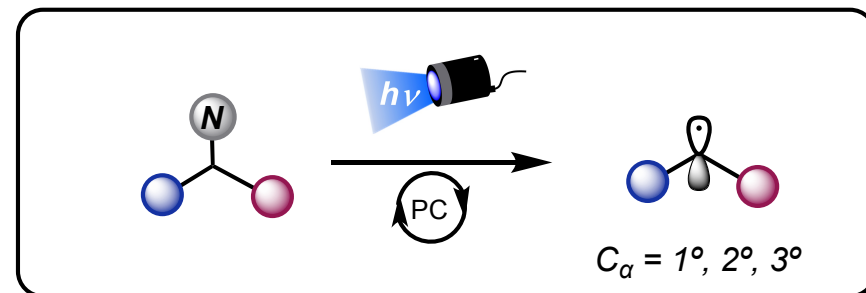
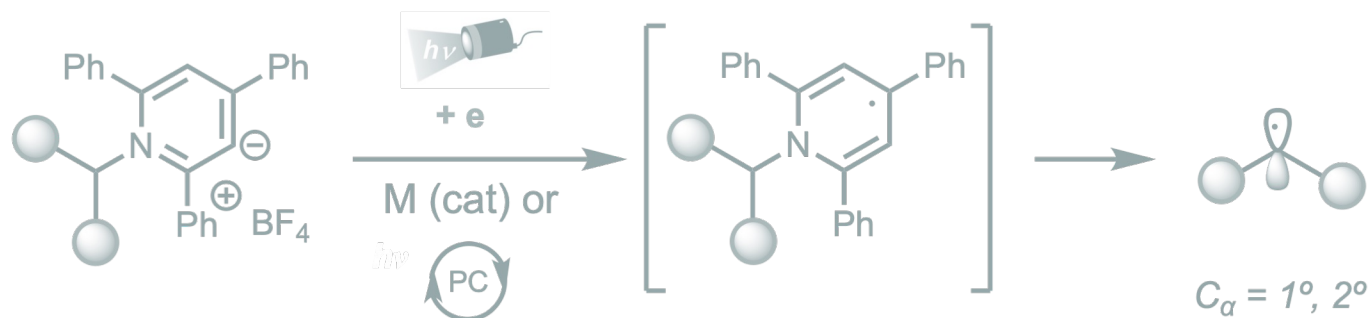
Oxidation of trimethoxybenzyl imines



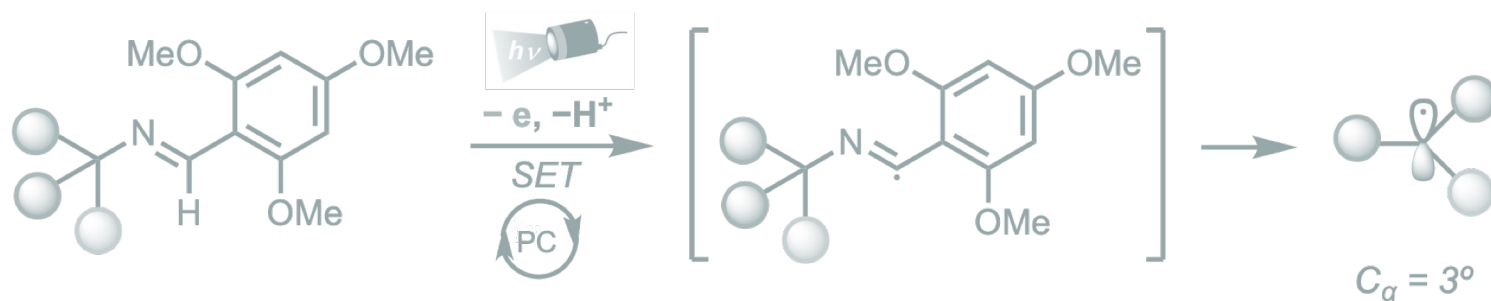
Rovis: *J. Am. Chem. Soc.* **2020**, 142, 18310

Light-mediated deaminations

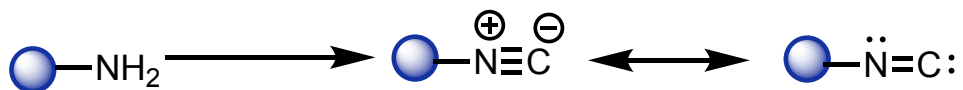
Reduction of pyridinium salts



Oxidation of trimethoxybenzyl imines

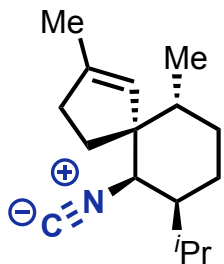


Isonitriles as radical precursors

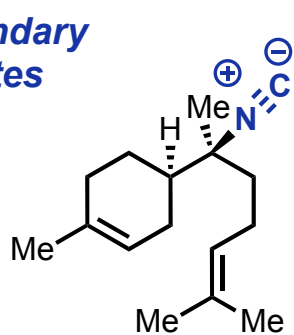


- *Hydrolysis*
- *Ugi reaction*
- *[4+1]-cycloaddition*
- *Polymerization*

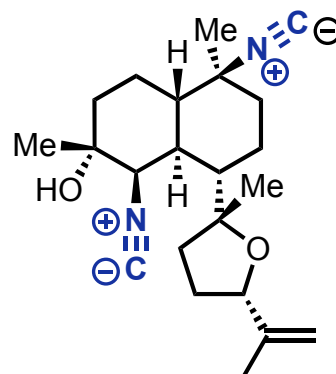
> 100 Secondary metabolites



Axisonitrile-3

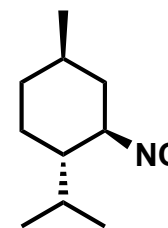


Isocyanobisabolene

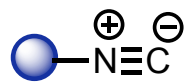


Kalihinol C

>C₁₀ alkyl isonitriles are odorless and chemically stable

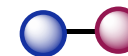


grapefruit odor



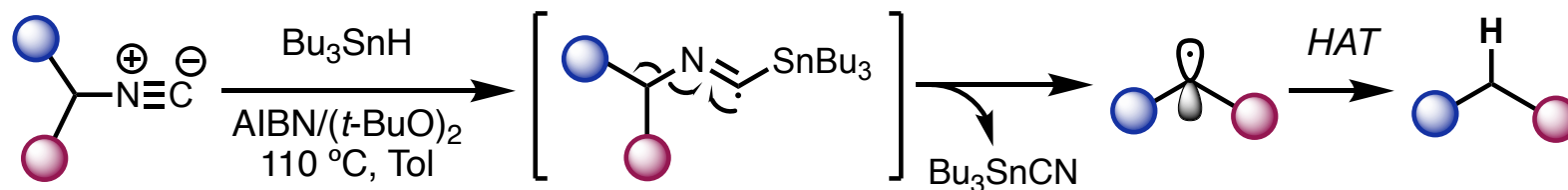
Unexplored

Cat



Isonitriles as radical precursors in light mediated reactions

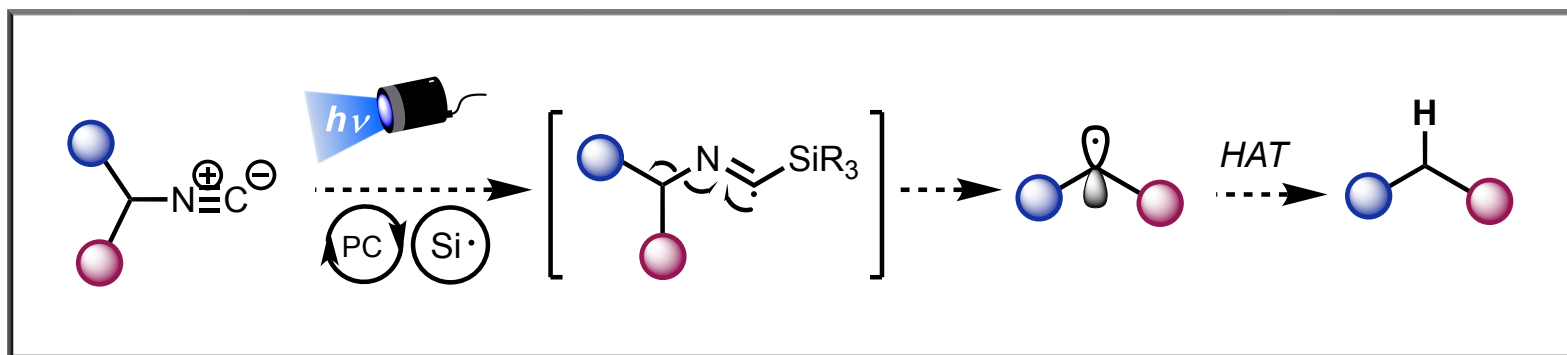
Barton-Saegusa radical hydro-deamination



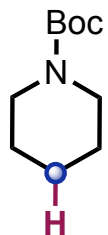
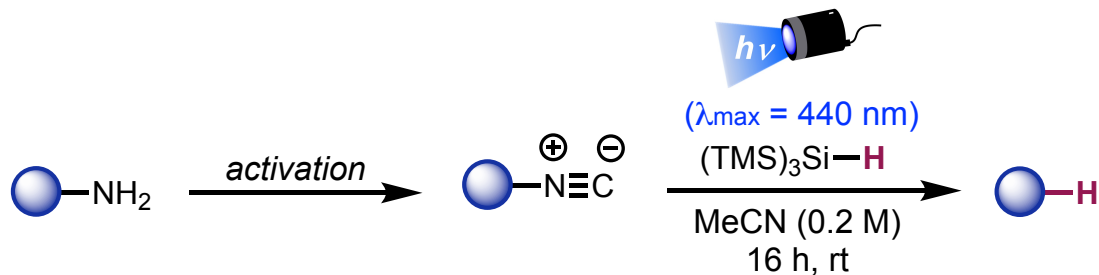
Saegusa: *J. Am. Chem. Soc.* **1968**, *90*, 4182

Barton: *Tetrahedron Lett.* **1979**, *20*, 2291–2294

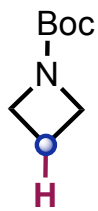
- X** High temperatures
- X** Bu_3SnH , radical initiator



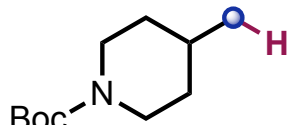
Light-mediated hydrodeamination



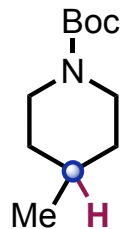
96%



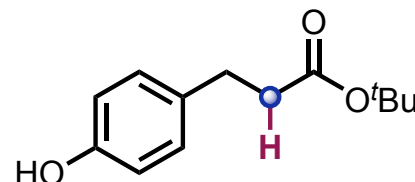
86%



85%

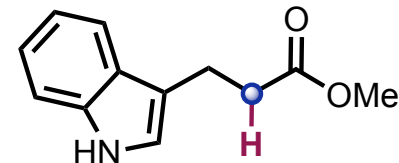


81%



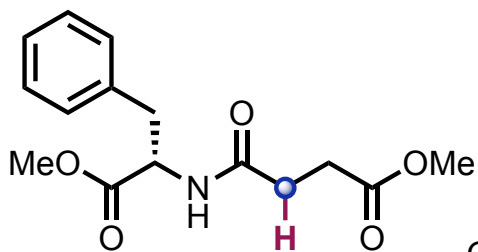
95%

from tyrosine



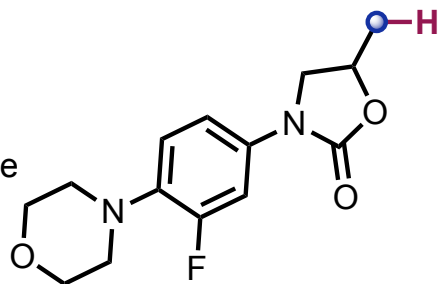
81%

from tryptophan



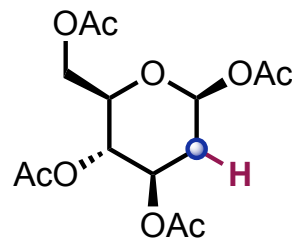
81%

from Asp-Phe



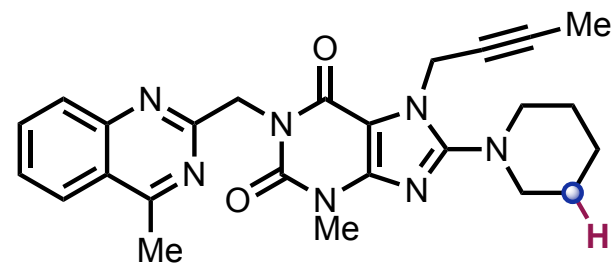
91%

from deacetyllinezolid



80%

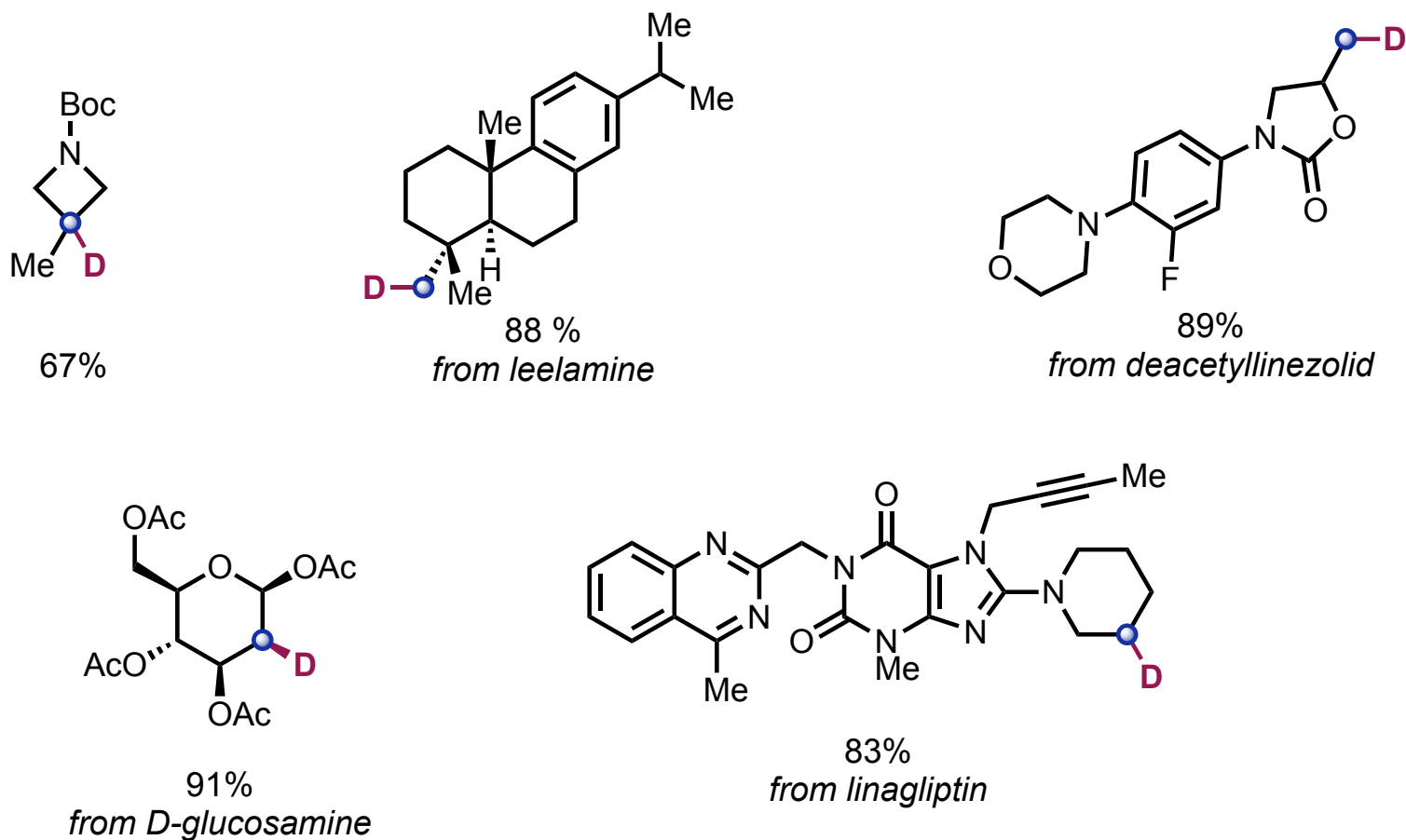
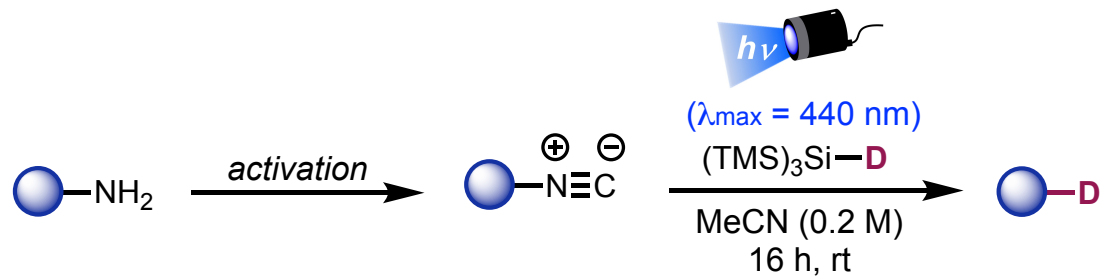
from D-glucosamine



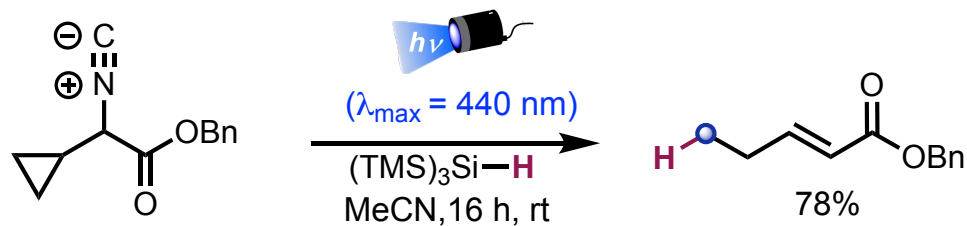
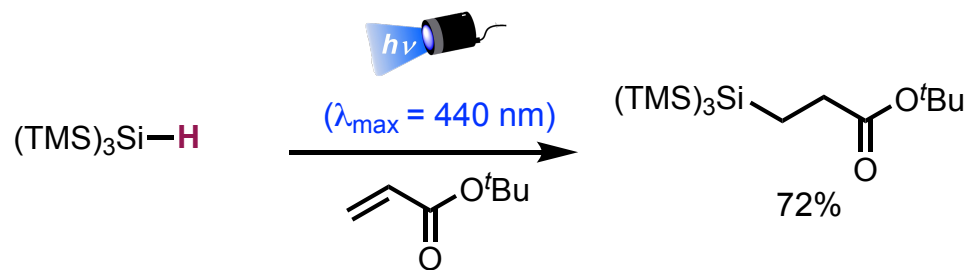
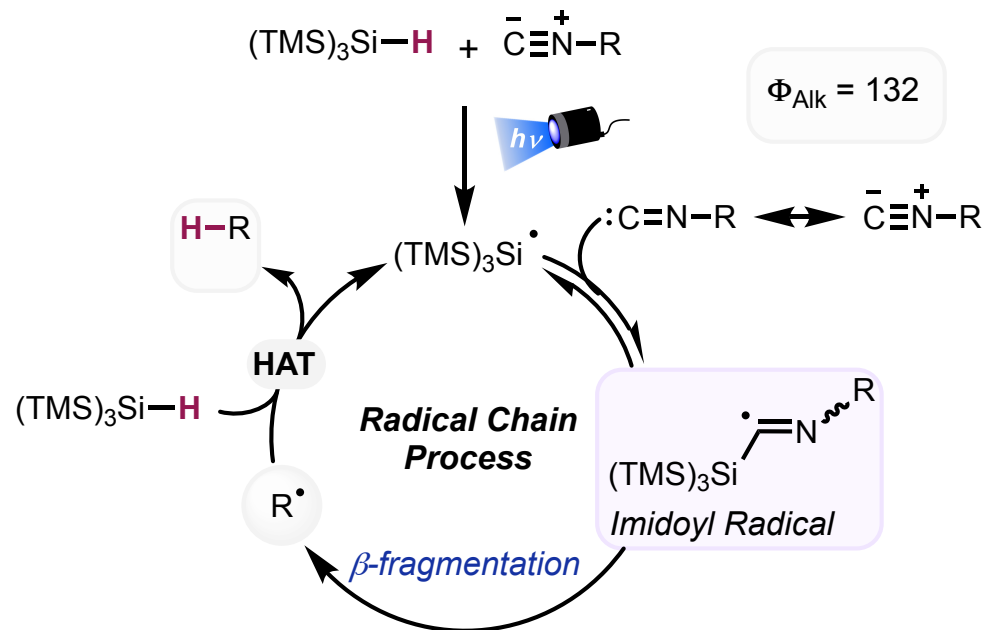
93%

from linagliptin

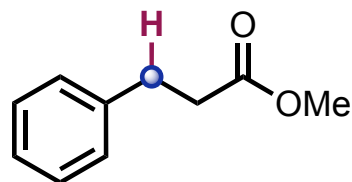
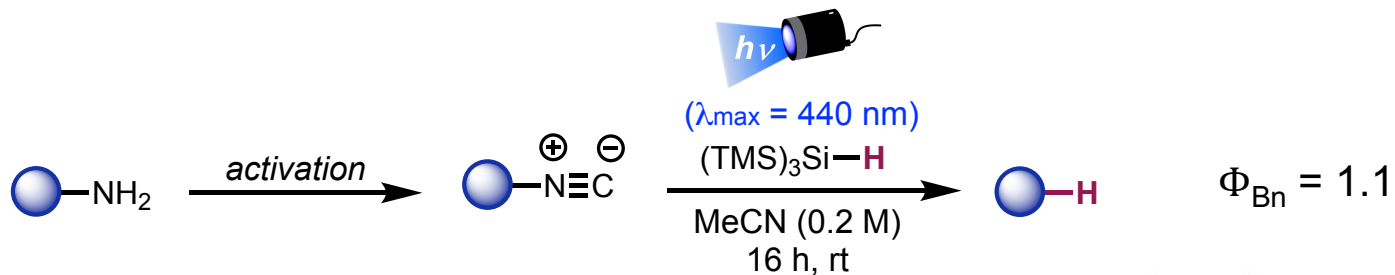
Light-mediated deutero-deamination



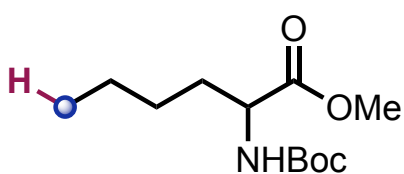
Light-mediated hydro and deuterio-deamination



Light-mediated hydrodeamination

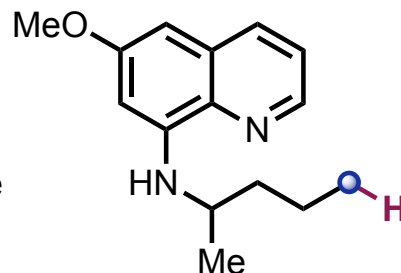


5%



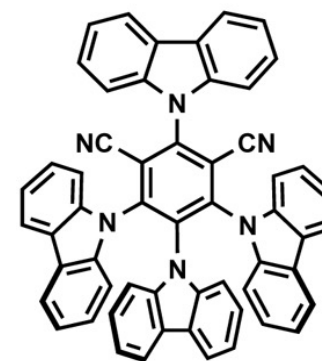
47%

from lysine



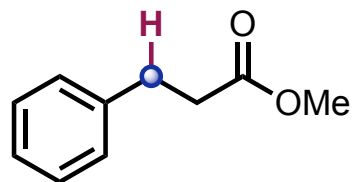
0%

from primaquine

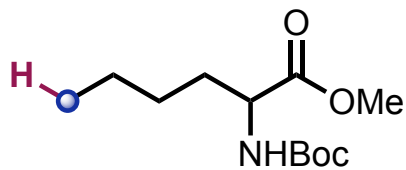


4CzIPN

(1 mol%)

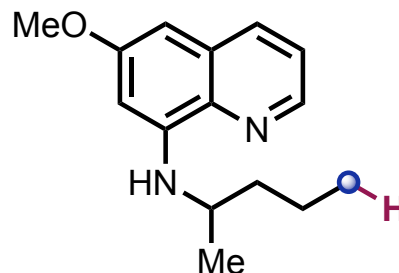


77%



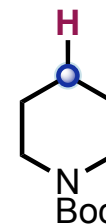
93%

from lysine



95%

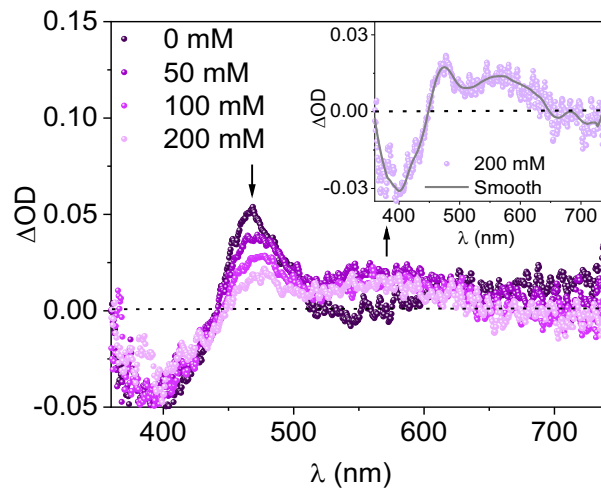
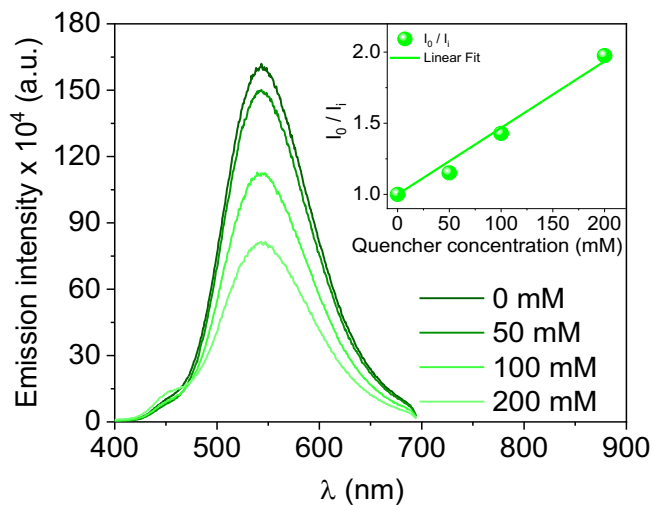
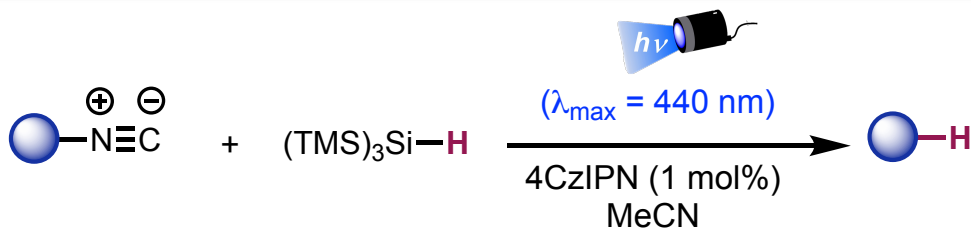
from primaquine



without 4CzIPN 99% 16 h

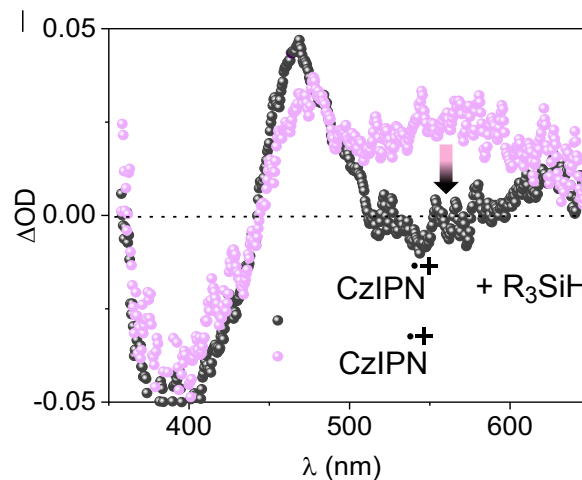
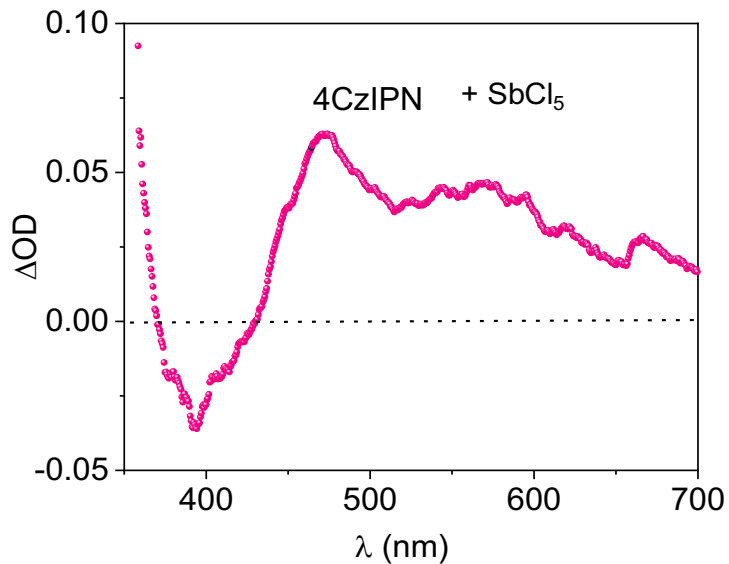
with 4CzIPN 83% 10 min

Light-mediated hydro and deuterio-deamination

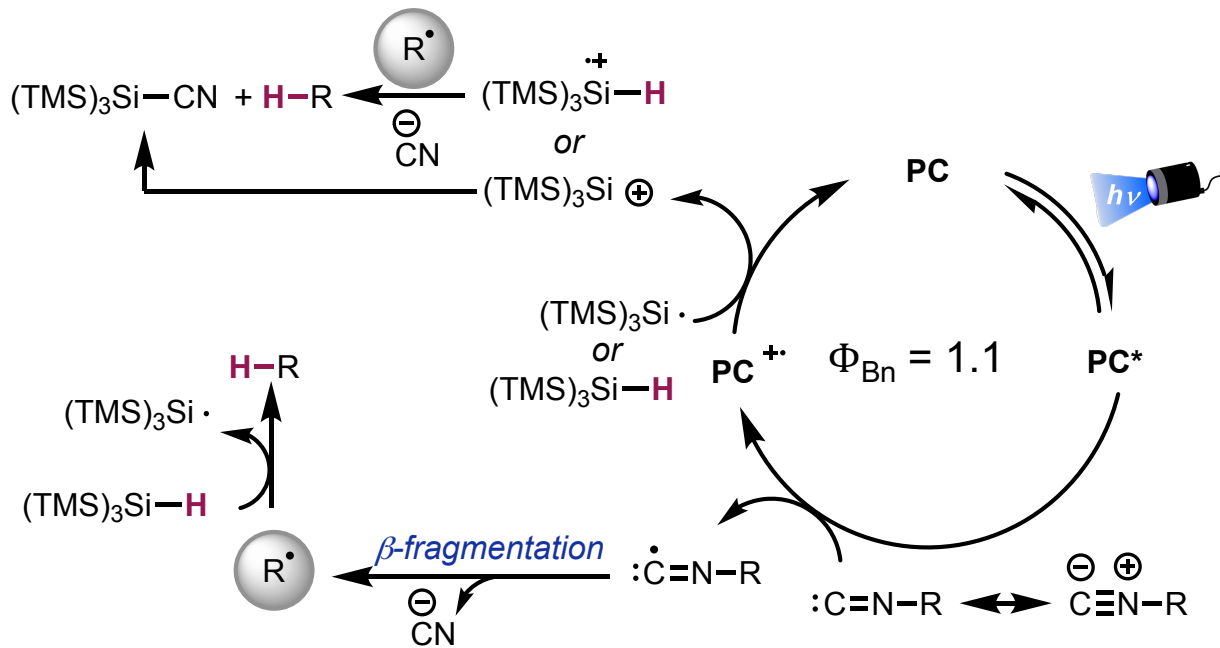


institute
IMdea
 energy

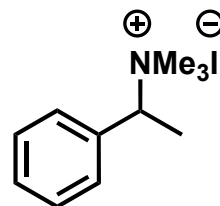
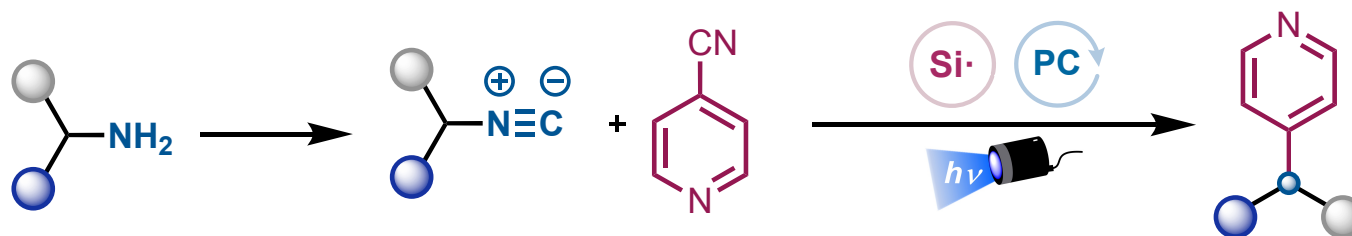
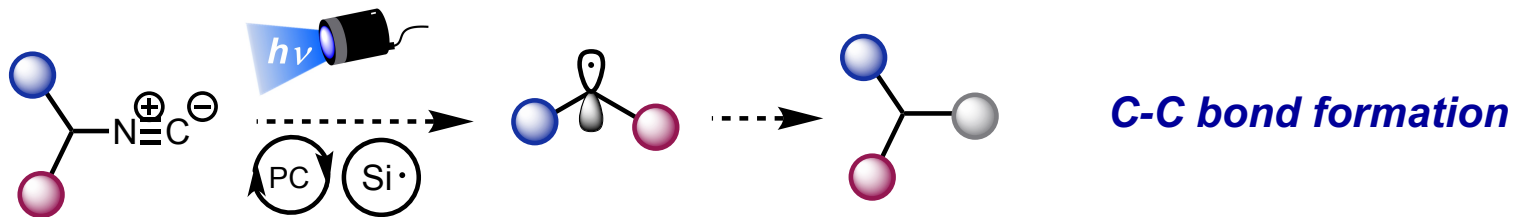
Transient Absorption Spectroscopy



Light-mediated hydro and deuterio-deamination



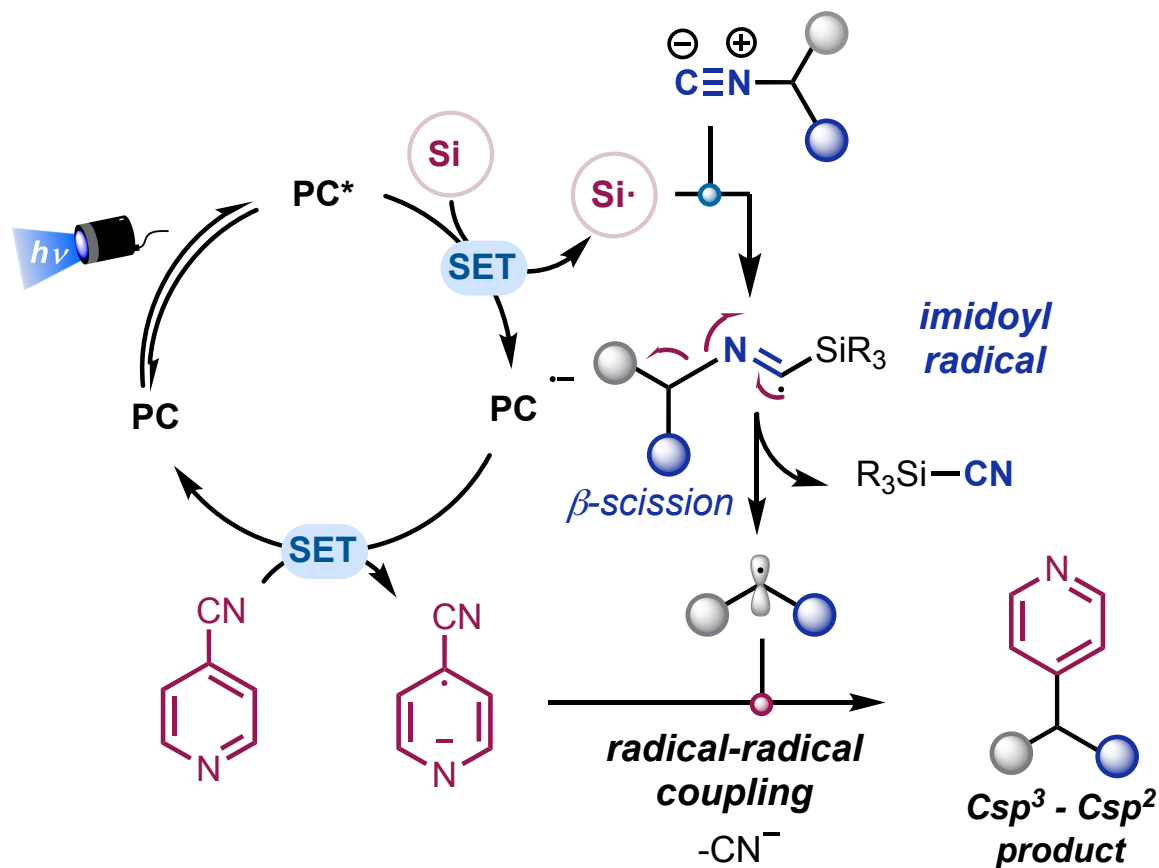
Isonitriles in light-mediated C-C bond formation



benzylic substrates

Yu, Zhou: *Sci. China Chem.* **2019**, 62, 1519

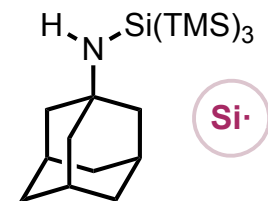
Isonitriles in light-mediated deamination



$(TMS)_3Si-H$ *not ideal reagent*

$BDE_{(Si-H)} = 84.7 \text{ Kcal/mol}$

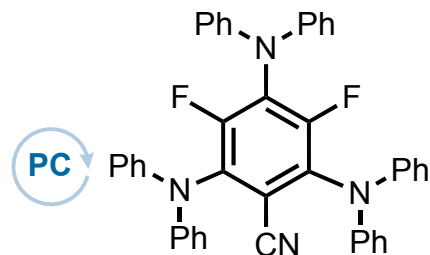
$E_{pa} = +1.67 \text{ V}$



✓ $> BDE_{(N-H)} (\sim 111 \text{ Kcal/mol})$

✓ *more nucleophilic silyl radical*

✓ *low oxidation potential ($E_{pa} = +0.75\text{V}$)*

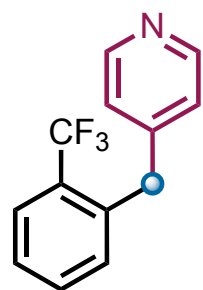
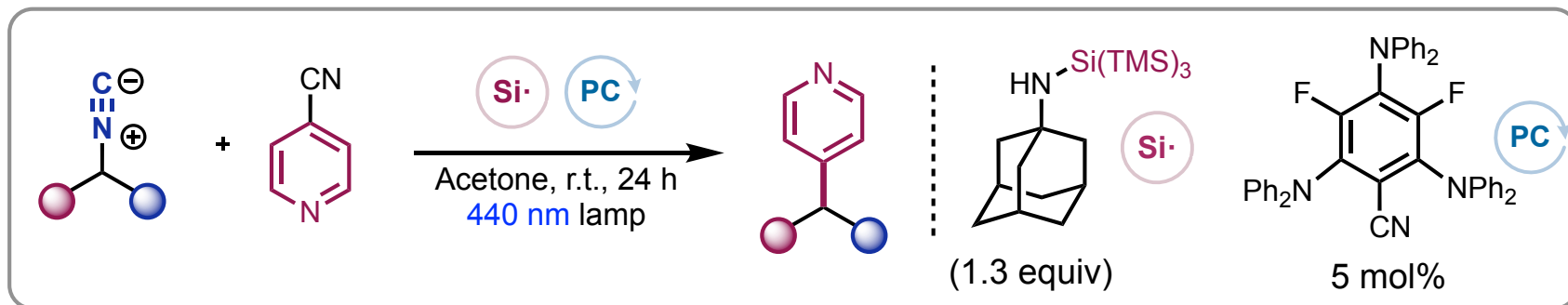


3DPA2FBN

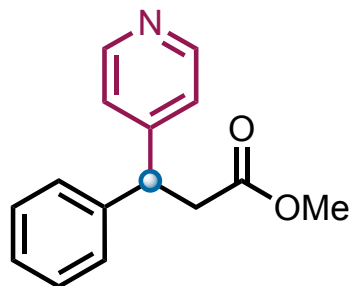
$E_{1/2}^{red} (PC^*/\bar{P}C) = +0.92 \text{ V}$

$E_{1/2}^{red} (PC/\bar{P}C) = -1.92 \text{ V}$

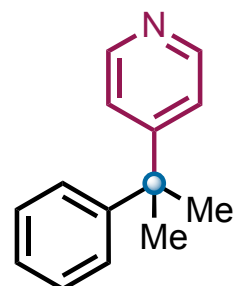
Isonitriles in light-mediated deamination



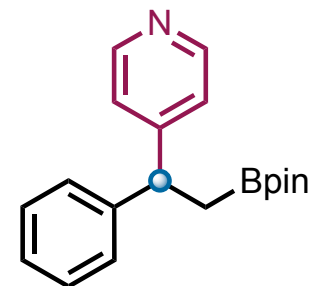
66%



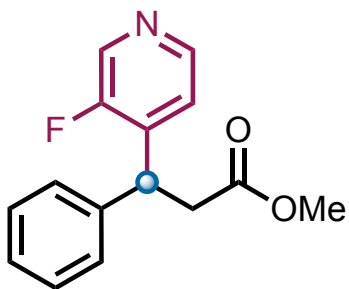
84%



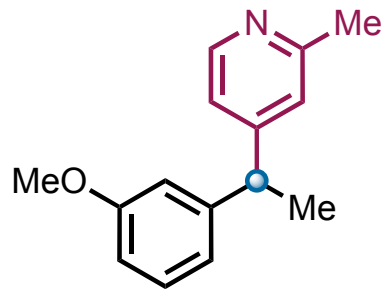
75%



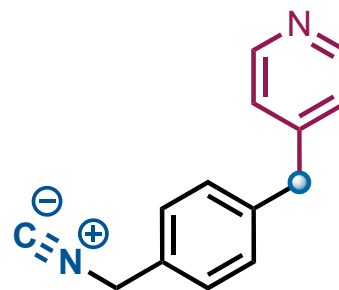
58%



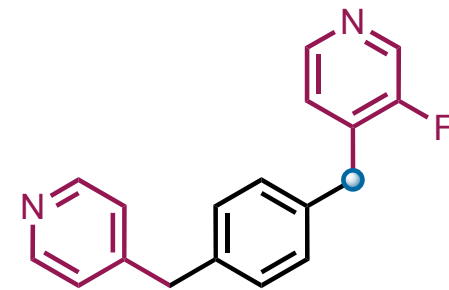
77%



70%

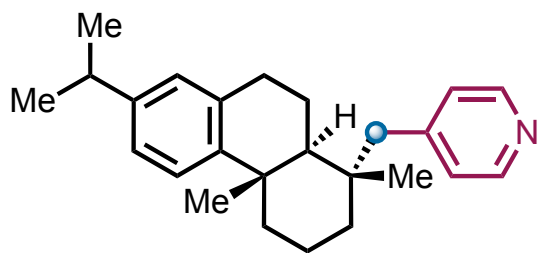
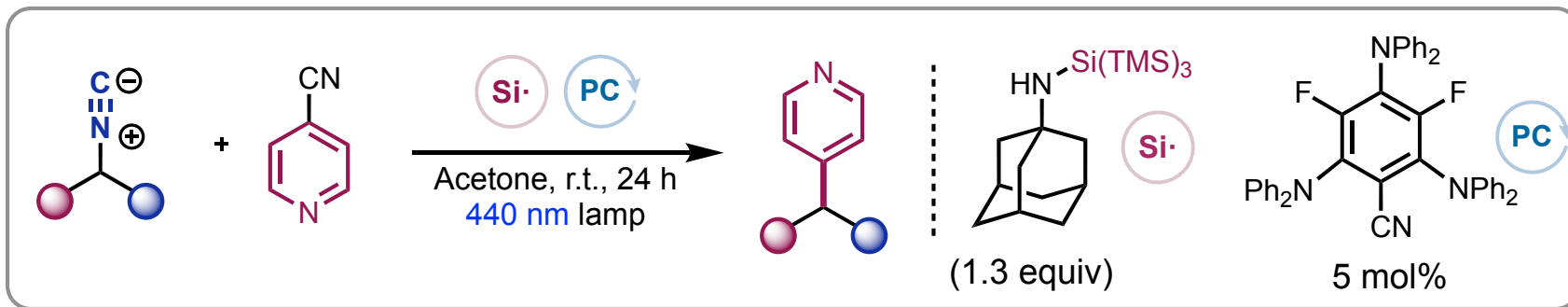


51%

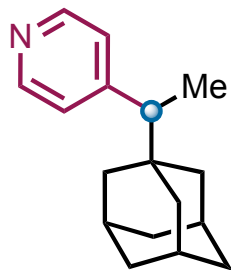


53%

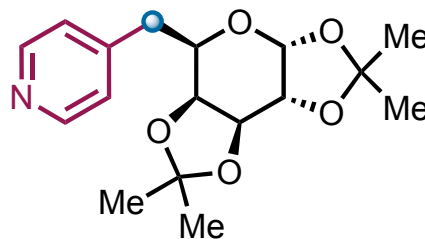
Isonitriles in light-mediated deamination



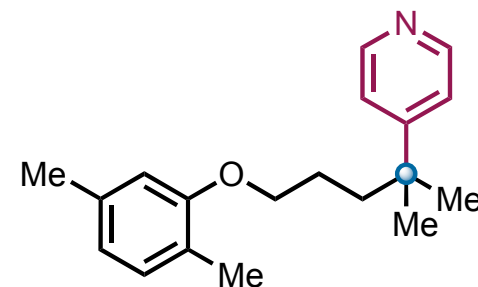
61%
from leelamine



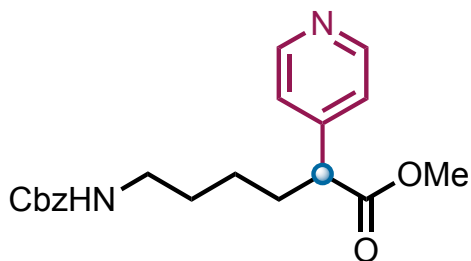
96%
from rimantadine



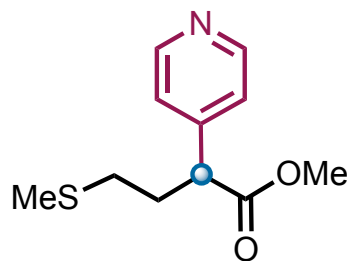
24%
from α -D-galactopyranose



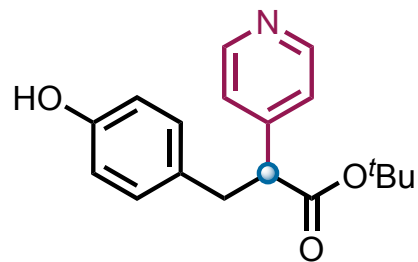
84%
from gemfibrozil



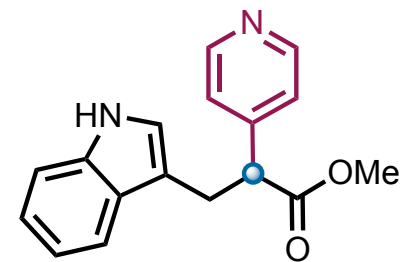
44%
from lysine



48%
from methionine

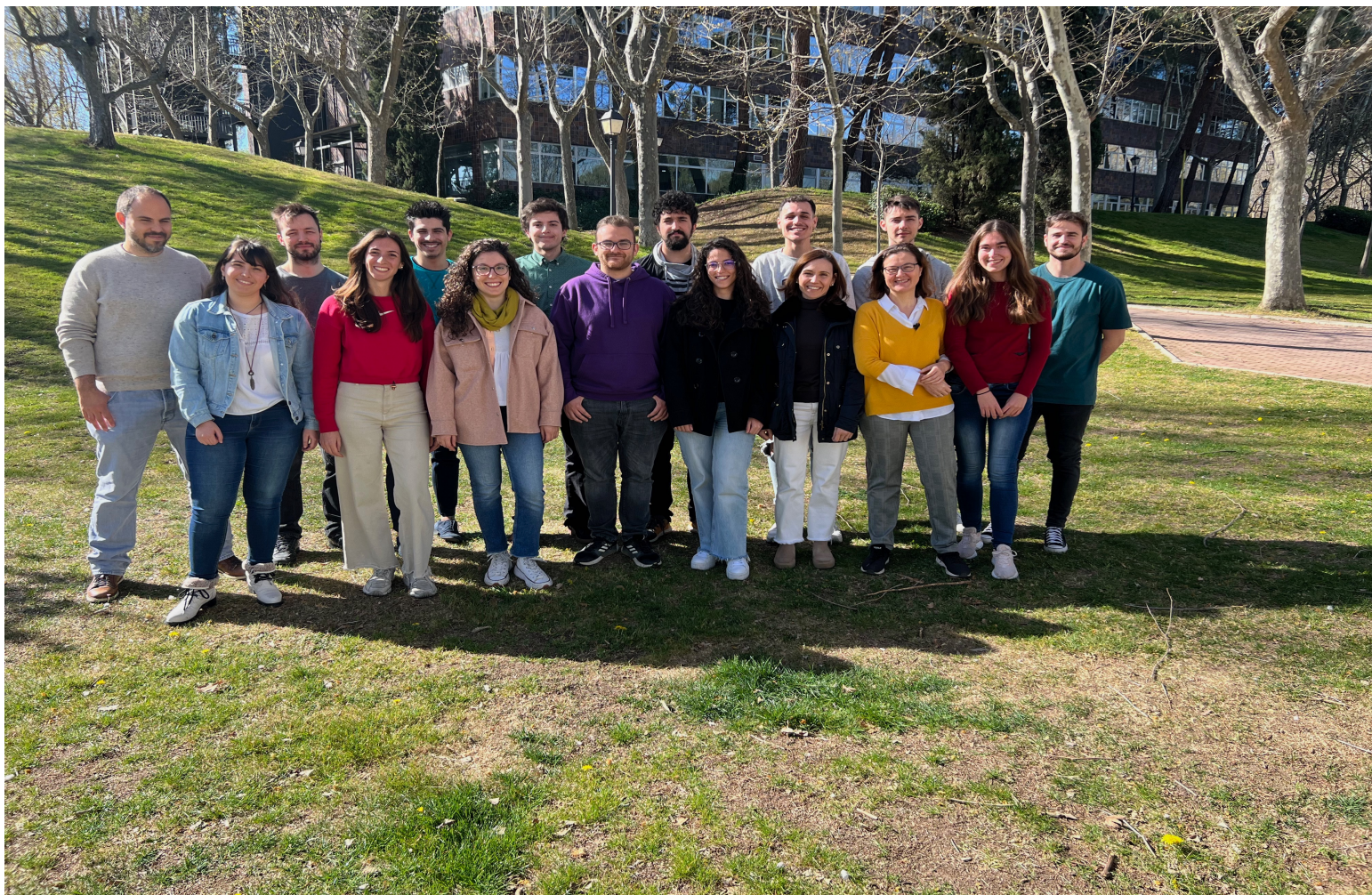


45%
from tyrosine



48%
from tryptophan

Acknowledgements



ERC-Starting Grant DAUBOR
ERC-Consolidator Grant SCAN

