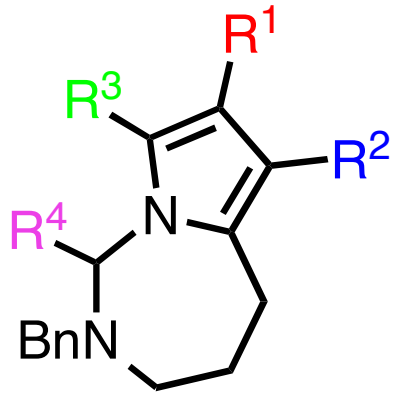
Oxidative C-H Bond Functionalization and Development of a Dynamic Combinatorial Library Using Pyrrolo[1,3]-Diazepines



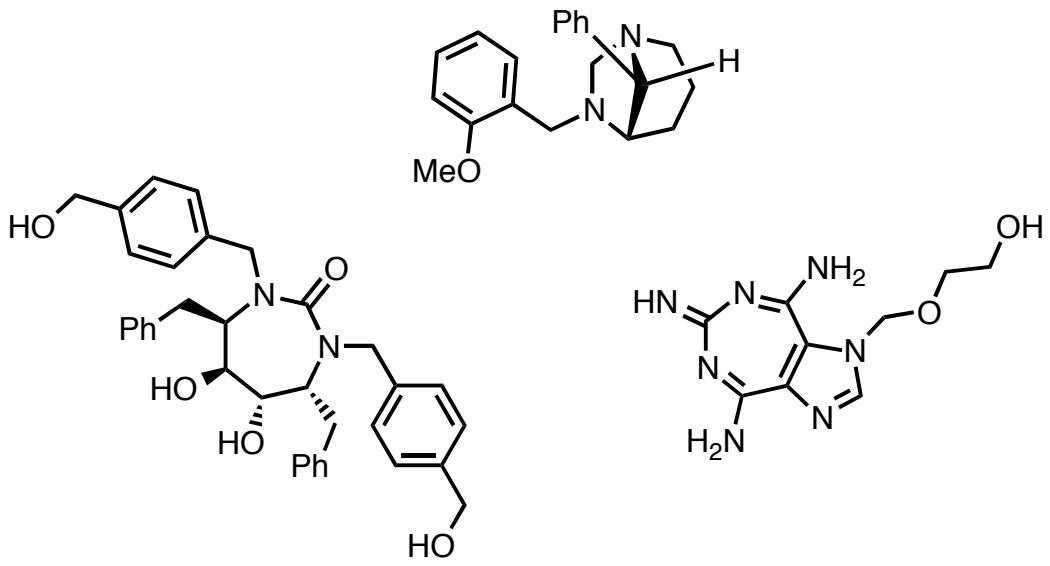
Brandon Parks

Wipf Group Topic Seminar

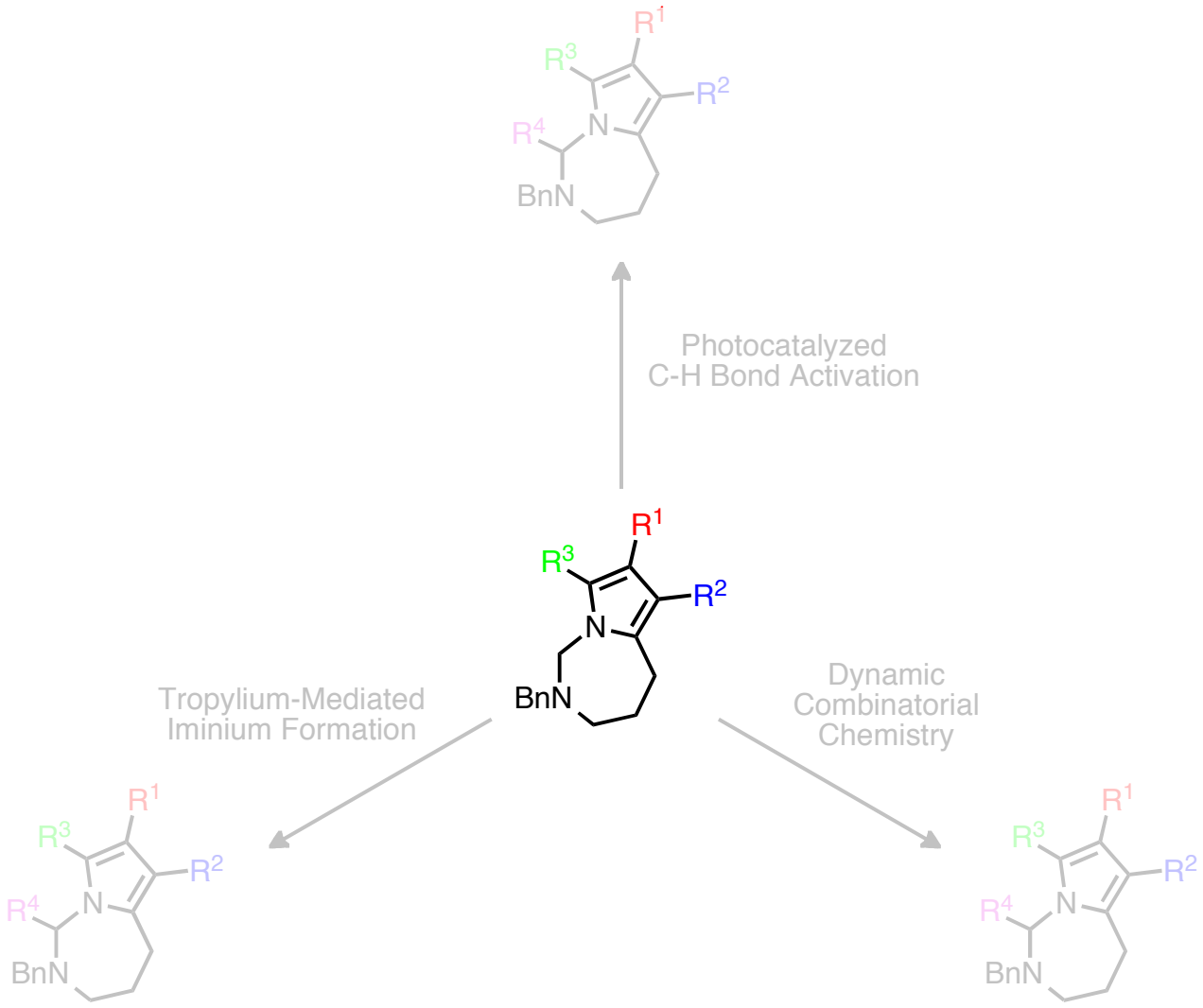
March 17th, 2012

Why 1,3-Diazepines?

- Relatively unstudied scaffold
- Potential biological activity



Boks, G. J.; Tollenaere, J. P.; Kroon, J. *Bioorg. Med. Chem.*, **1997**, *5*, 535.
Wang, L; Hosmane, R. S.; *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2893.
Dieltiens, N.; Claeys, D. D.; Allaert, B.; Verpoort, F.; Stevens, C. V. *Chem. Commun.*, **2005**, 4477.

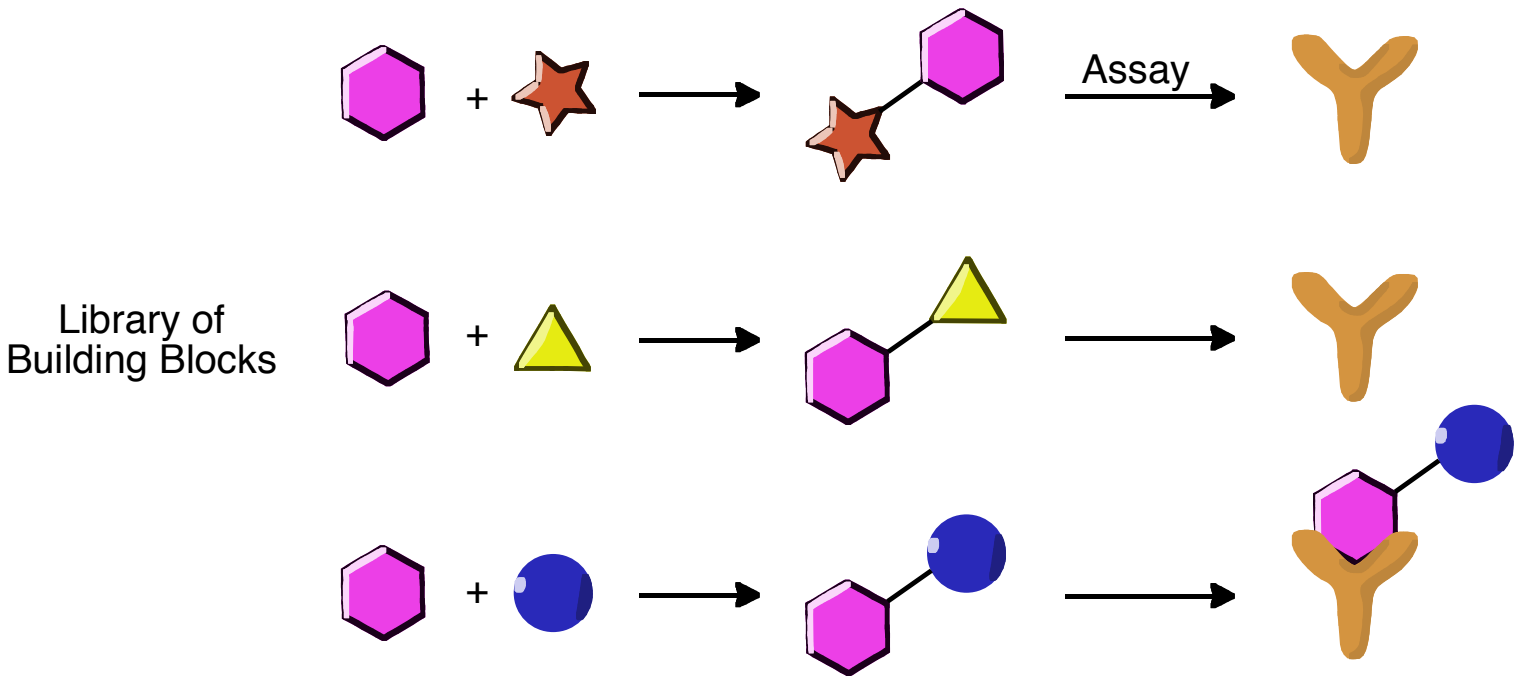

R1
R3
R2
R4
N
BnN
Photocatalyzed
C-H Bond Activation
Tropylium-Mediated
Iminium Formation
Dynamic
Combinatorial
Chemistry

Traditional Combinatorial Chemistry

- Each library member must be individually synthesized and purified
- Time-consuming and costly
- High-throughput processes help speed-up this process

Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Drug Discov. Today*, **2002**, *7*, 1117.
Potyrailo, R.; Rajan, K.; Stoewe, K.; Takeuchi, I.; Chisholm, B.; Lam, H. *ACS Comb. Sci.*, **2011**, *13*, 579.

Traditional Combinatorial Chemistry

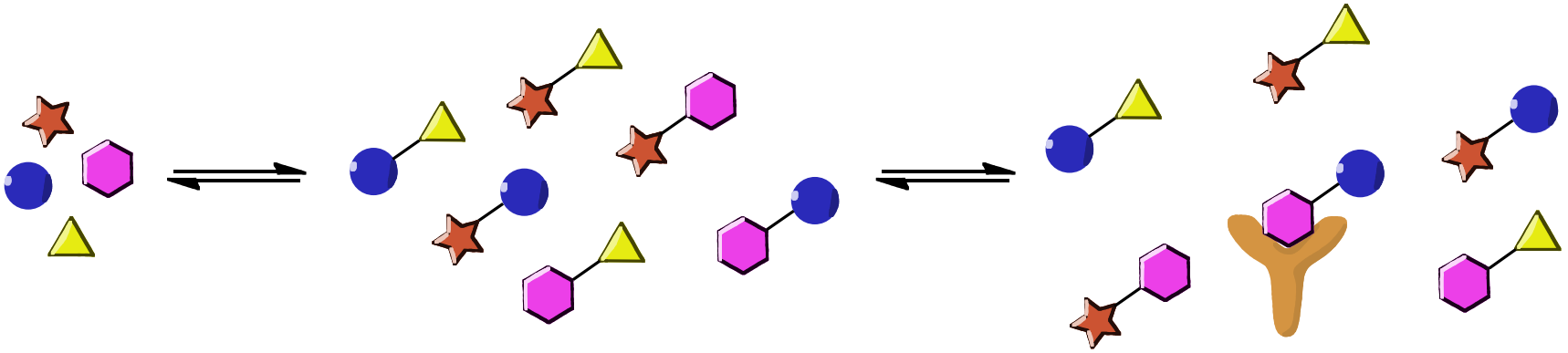


Dynamic Combinatorial Chemistry

- Building blocks are linked using reversible chemistry
  - "Theoretical" library
- Library composition governed by thermodynamics, not kinetics
- "Dynamic" library may respond to external influences

For Comprehensive Reviews:
Corbett, P. T.; Lecalire, J.; Vial, L.; West, K. R.; Wietor, J. L.; Sanders, J.K. M.; Otto, S. *Chem. Rev.*, **2006**, *106*, 3652.
Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Drug Discov. Today*, **2002**, *7*, 1117.
Ladame, S. *Org. Biomol. Chem.*, **2008**, *6*, 219.
Ludlow, R. F.; Otto, S. *Chem. Soc. Rev.*, **2008**, *37*, 101.
Cougnon, F. B. L.; Sanders, J. K. M. *Acc. Chem. Res.*, **2011**, ASAP.

Dynamic Combinatorial Chemistry



Thermodynamic Equilibrium

Library Re-Equilibrates Based On Le Châtelier's Principle!!

Traditional vs Dynamic Combinatorial Chemistry

Traditional

- Each library member must be individually synthesized
- Irreversible reactions
- Solubility doesn't affect library

Dynamic

- "Theoretical" library
- Reversible reactions
- All library members must be soluble
- Template effect affords amplification

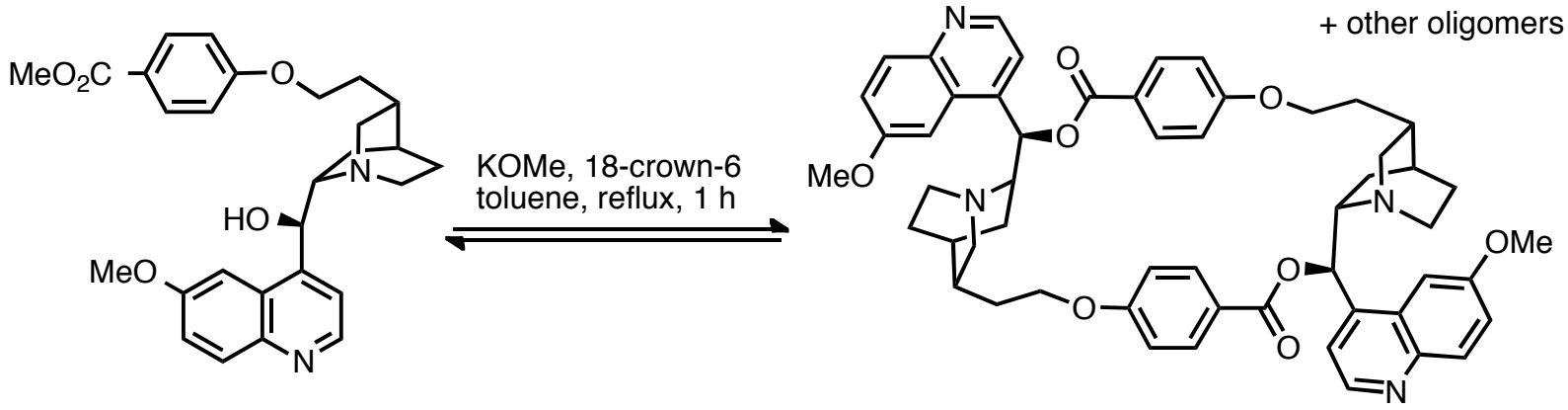
Corbett, P. T.; Lecalire, J.; Vial, L.; West, K. R.; Wietor, J. L.; Sanders, J.K. M.; Otto, S. *Chem. Rev.*, **2006**, *106*, 3652.
Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Drug Discov. Today*, **2002**, *7*, 1117.
Potyrailo, R.; Rajan, K.; Stoewe, K.; Takeuchi, I.; Chisholm, B.; Lam, H. *ACS Comb. Sci.*, **2011**, *13*, 579.

Examples of Dynamic Combinatorial Libraries

- Covalent:
  - Transesterfication
  - Transamidation
  - Acetal Exchange
  - Thioacetal Exchange
  - Transimination
  - Hydrazone
- Non-Covalent:
  - H-Bonding
  - Metal/Ligand Interactions

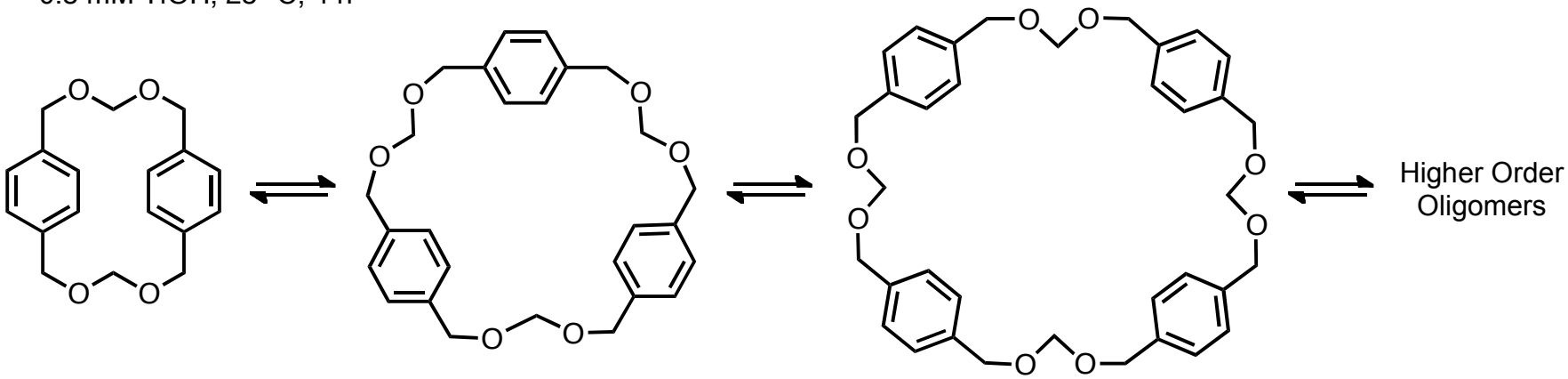
Corbett, P. T.; Lecalire, J.; Vial, L.; West, K. R.; Wietor, J. L.; Sanders, J.K. M.; Otto, S. *Chem. Rev.*, **2006**, *106*, 3652.

Transesterfication



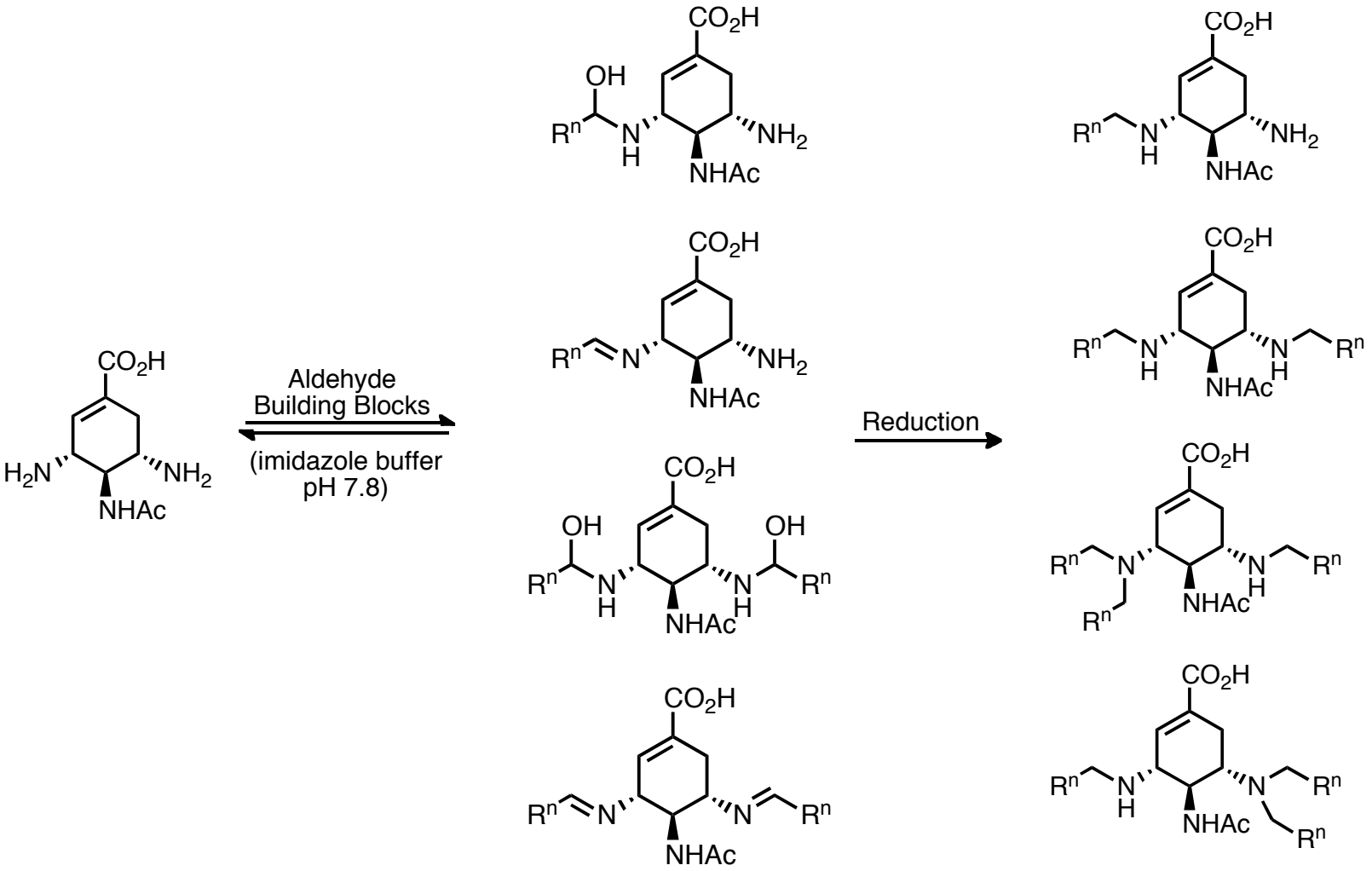
Acetal Exchange

Conditions:
0.5 mM TfOH, 25 °C, 4 h



Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2143.
Brady, P. A.; Bonar-Law, R. P.; Rowan, S. J.; Suckling, C. J.; Sanders, J. K. M. *Chem. Commun.*, **1996**, 319.
Rowan, S. J.; Sanders, J. K. M. *Chem. Commun,.* **1997,** 1407.
Cacciapaglia, R.; Stefano, S. D.; Mandolini, L. *J. Am. Chem. Soc.*, **2005**, *127*, 13666.

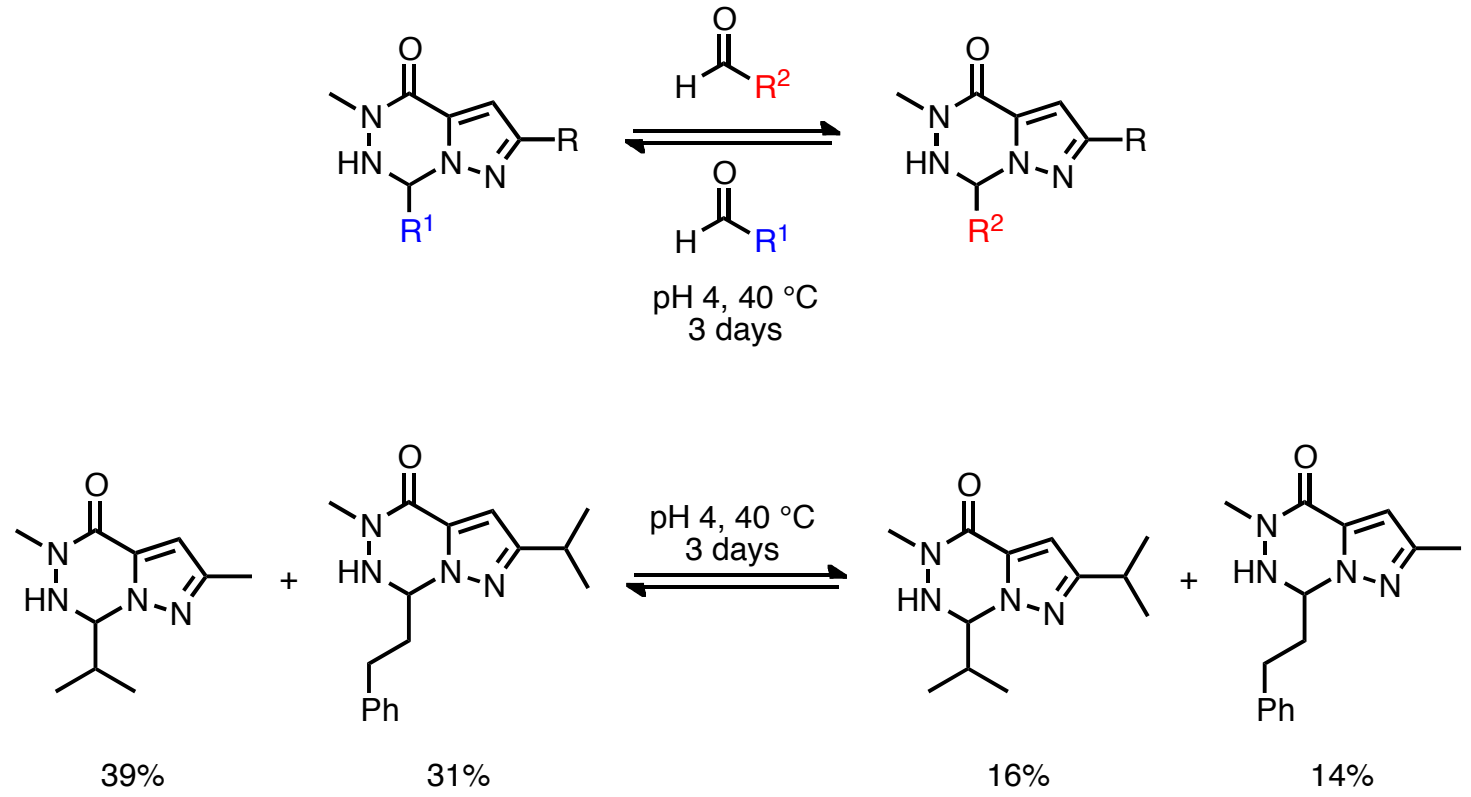
Identification of Neuraminidase Inhibitors



Hochgürtel, M.; Kroth, H.; Piecha, D.; Hofmann, M. W.; Nicolau, C.; Krause, S.; Schaaf, O.; Sonnenmoser, G.; Eliseev, A. V. *Proc. Natl. Acad. U. S. A.*, **2002**, *99*, 3382.
Matrosovich, M. N., Matrosovich, T. Y.; Gray, T.; Roberts, N. A.; Llenk, H-N. *J. Virol.*, **2004**, *78*, 12665.

Previous Work in the Wipf Group

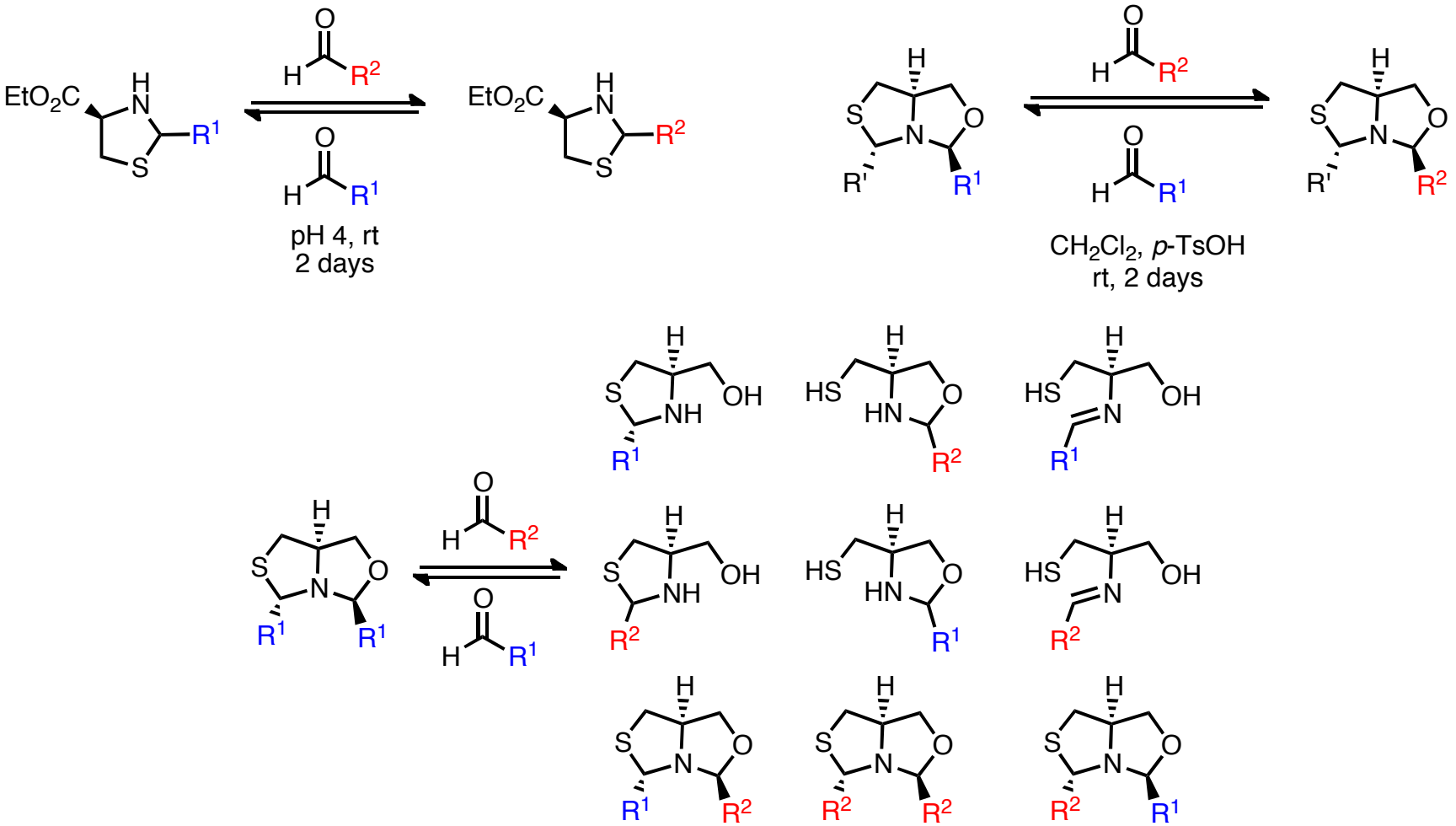
- Pyrazolotriazinone Exchange:



Wipf, P.; Mahler, S. G.; Okumura, K. *Org. Lett.*, **2005**, *7*, 4483.

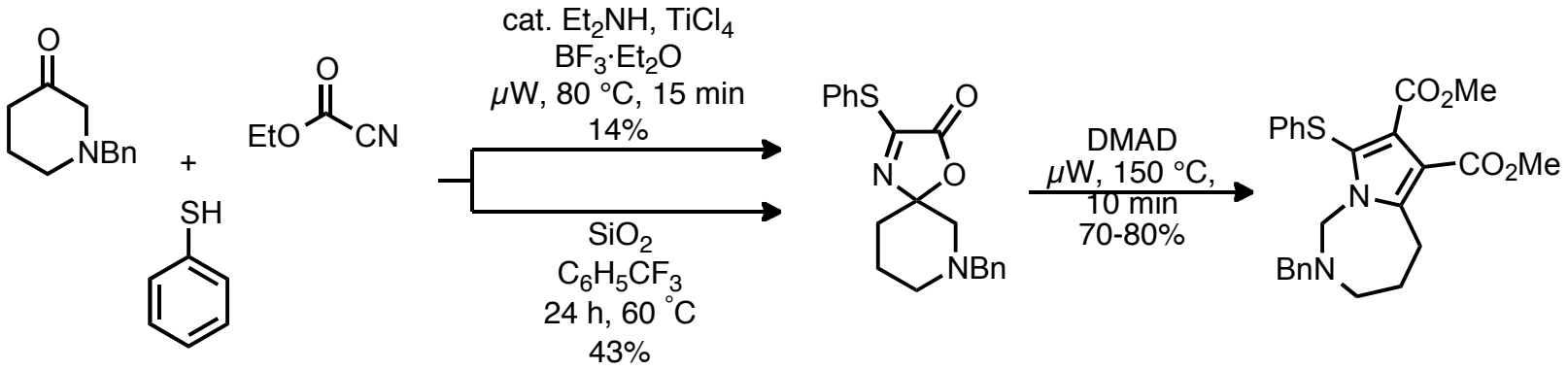
Previous Work in the Wipf Group

- Thiazolidine Exchange:



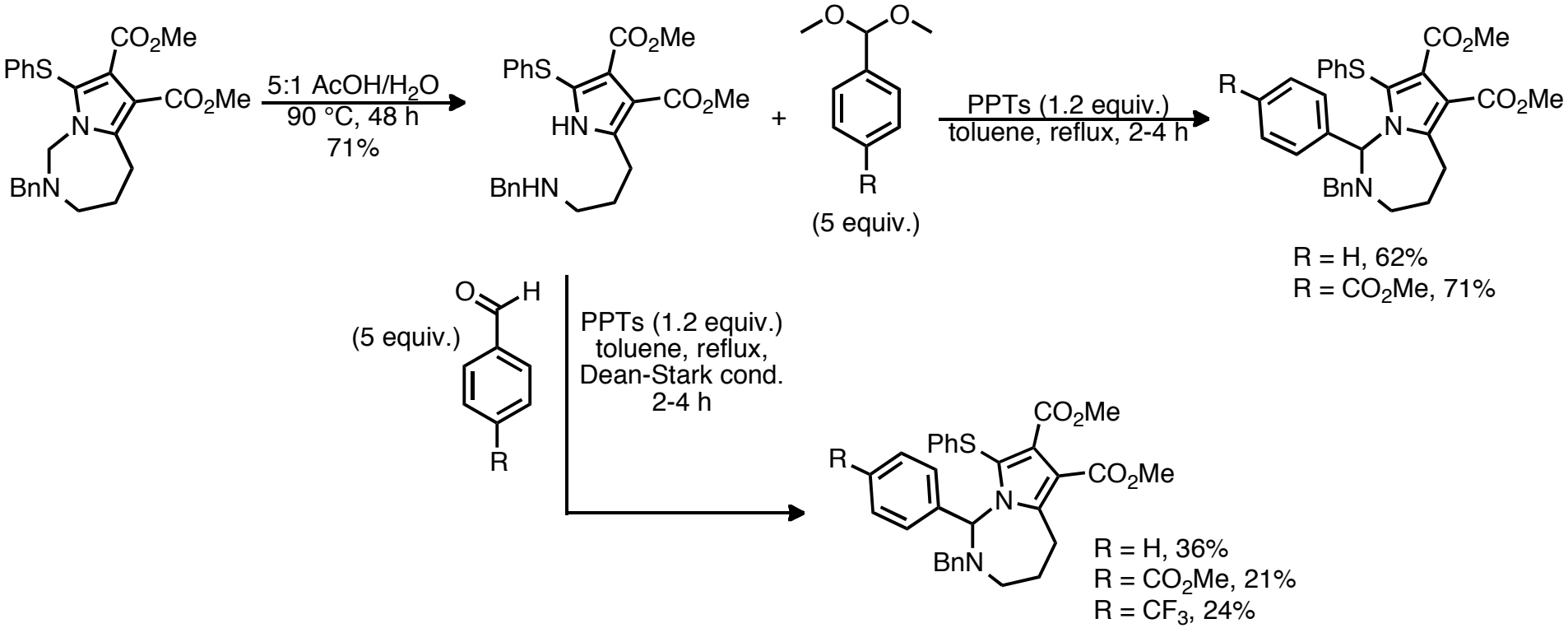
Saiz, C.; Wipf, P.; Manta, E.; Mahler, G. *Org. Lett.*, **2009**, *11*, 3170.

Synthesis of Pyrrolo[1,3]Diazepines



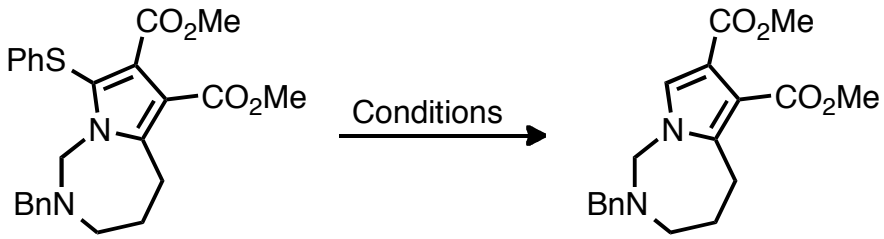
Liang, M.; Saiz, C.; Pizzo, C.; Wipf, P. *Tetrahedron Lett.* **2009**, *50*, 6810.
Boonya-udtayan, S.; Wipf, P. Unpublished Results.

Diazepine Exchange Chemistry



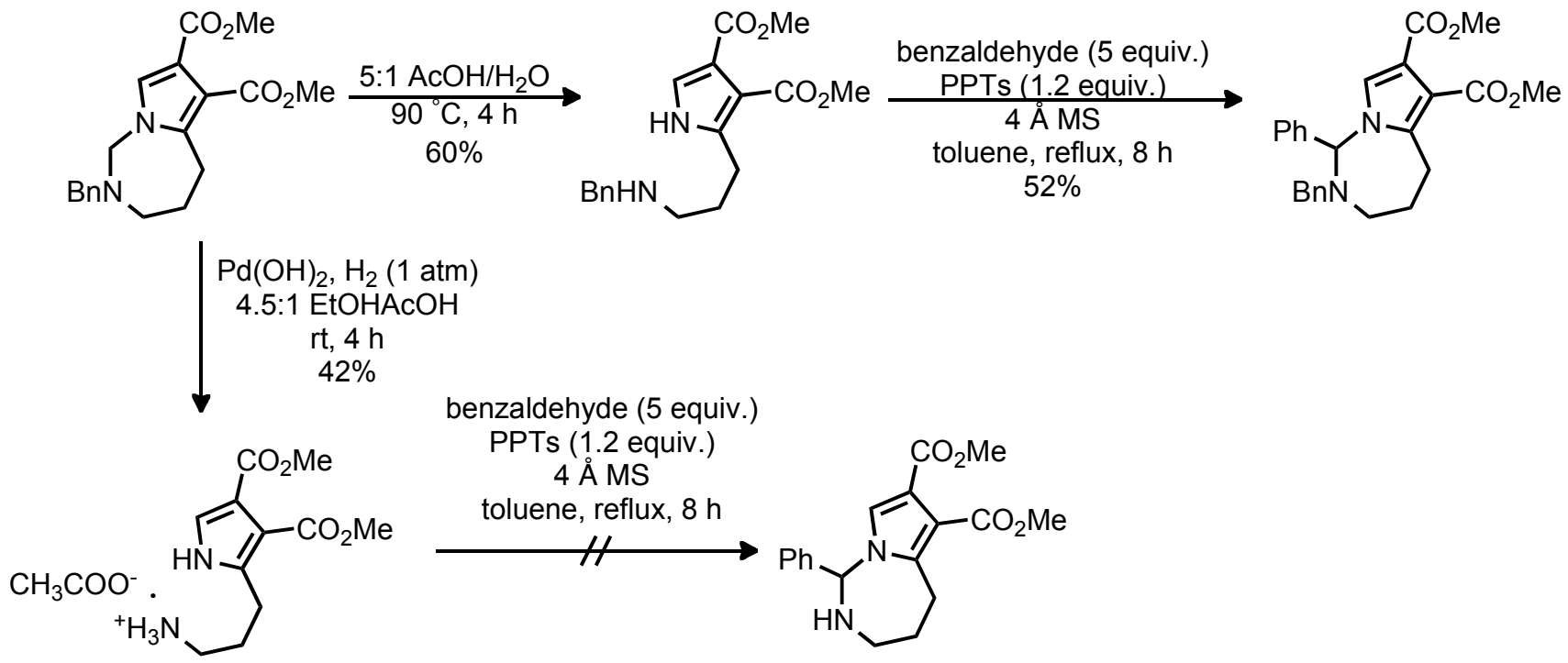
Liang, M.; Saiz, C.; Pizzo, C.; Wipf, P. *Tetrahedron Lett.* **2009**, *50*, 6810.
Pizzo, C.; Wipf, P. Unpublished Results.

Reductive Desulfurization Optimization

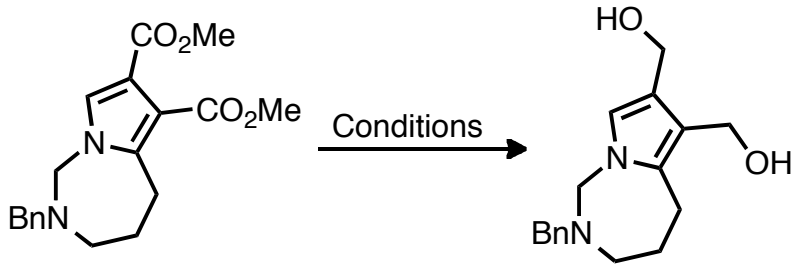


Entry	Condition	Time (h)	Result
1	Raney-Ni (11 equiv.), EtOH 60 °C	2	Desired Mass Observed
2	Raney-Ni (96 equiv.), EtOH, 60 °C	2.5	20% (by-product observed)
3	Raney-Ni (97 equiv.), THF, rt	3	69% (by-product observed)
4	Raney-Ni (129 equiv.), THF, 0 °C	6	85%
5	Raney-Ni (150 equiv.), THF, 0 °C	4	92%

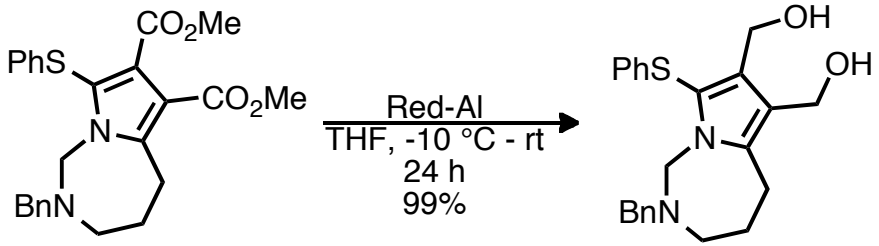
Diazepine Exchange Chemistry



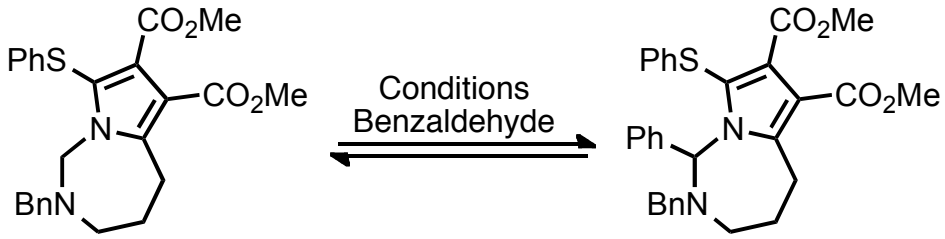
Pyrrole Ester Reduction



Entry	Condition	Time (h)	Result
1	$LiBH_4$ (2 equiv.), THF, 0 °C	2	NR
2	DIBALH (1.2 equiv.) CH_2Cl_2, 0 °C	2	44%
3	Red-Al (10 equiv.), THF -10 °C to rt	24	>99%



Diazepine Dynamic Exchange

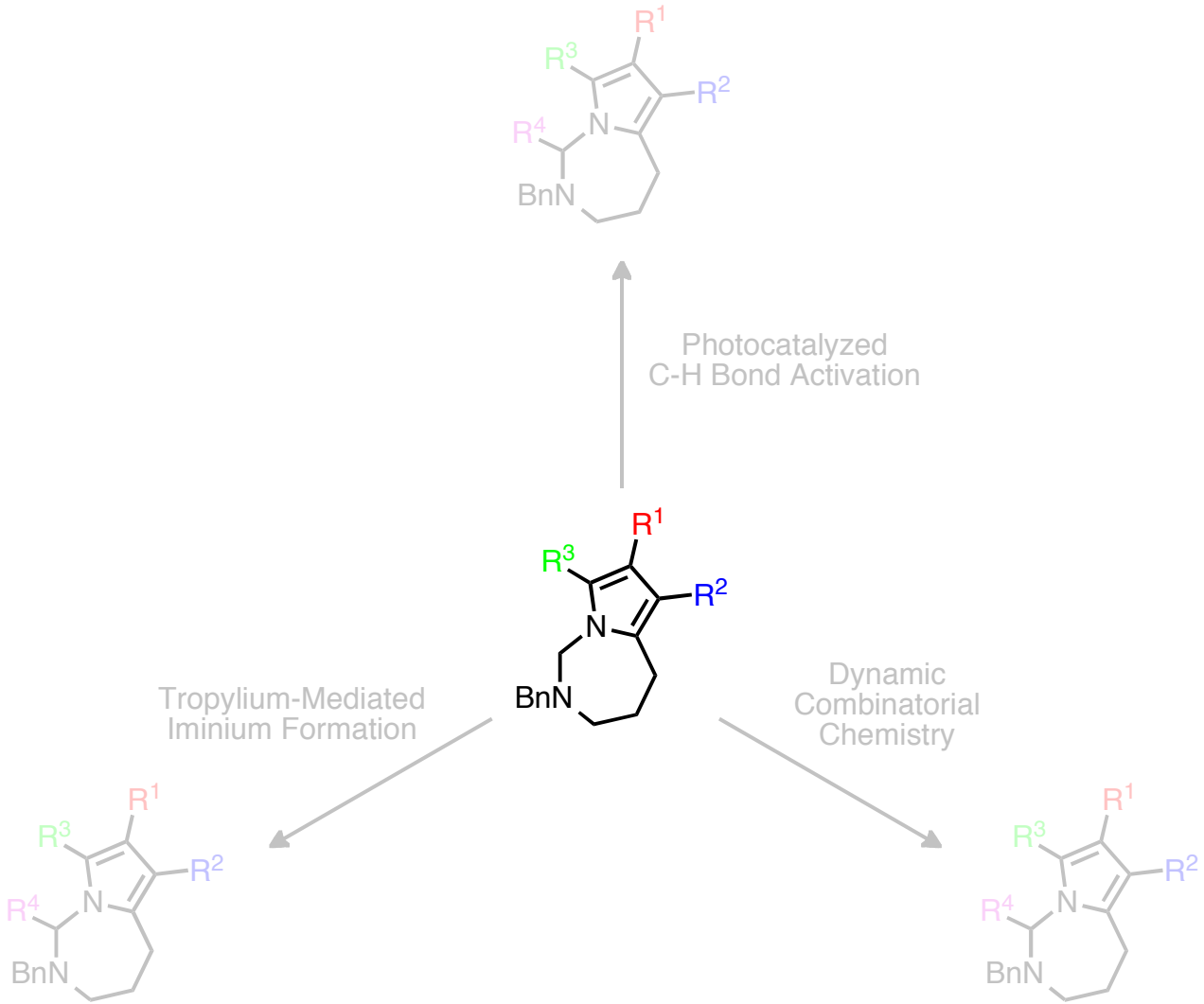


Entry	Condition	Time	Result
1	0.1 M phosphate-citrate buffer, pH 4, rt & 40 °C	48-72 h	no reactivity
2	0.1 M acetate buffer, pH 4, rt & 40 °C	48-72 h	no reactivity
3	0.1 M acetate buffer/methanol (7:3), pH 4, rt	24-48 h	some hydrolysis, no product obs.
4	PPTs (0.5 equiv.), CH_2Cl_2, rt	24-48 h	no reactivity
5	TsOH (0.5 equiv.), CH_2Cl_2, rt	24-48 h	no reactivity
6	TsOH (5 equiv.), CH_2Cl_2, rt	24-48 h	some hydrolysis, no product obs.
7	CF_3SO_3H (5 equiv.), CH_2Cl_2, rt	24-48 h	some hydrolysis, no product obs.
8	5:1 AcOH/H_2O, rt	24-48 h	hydrolysis, no product obs.
9	3:1 methanol/1M $HCl_{(aq)}$, rt & 40 °C	24-48 h	hydrolysis, no product obs.
10	Amberlite, MeOH, rt & 40 °C	24-48 h	no reactivity
11	SiO_2, CH_2Cl_2, rt	24-48 h	no reactivity
12	PPTs (1.2 equiv.) benzaldehyde (5 equiv.) 0.1 M, toluene, 80 °C	67 h	hydrolysis and desired product observed

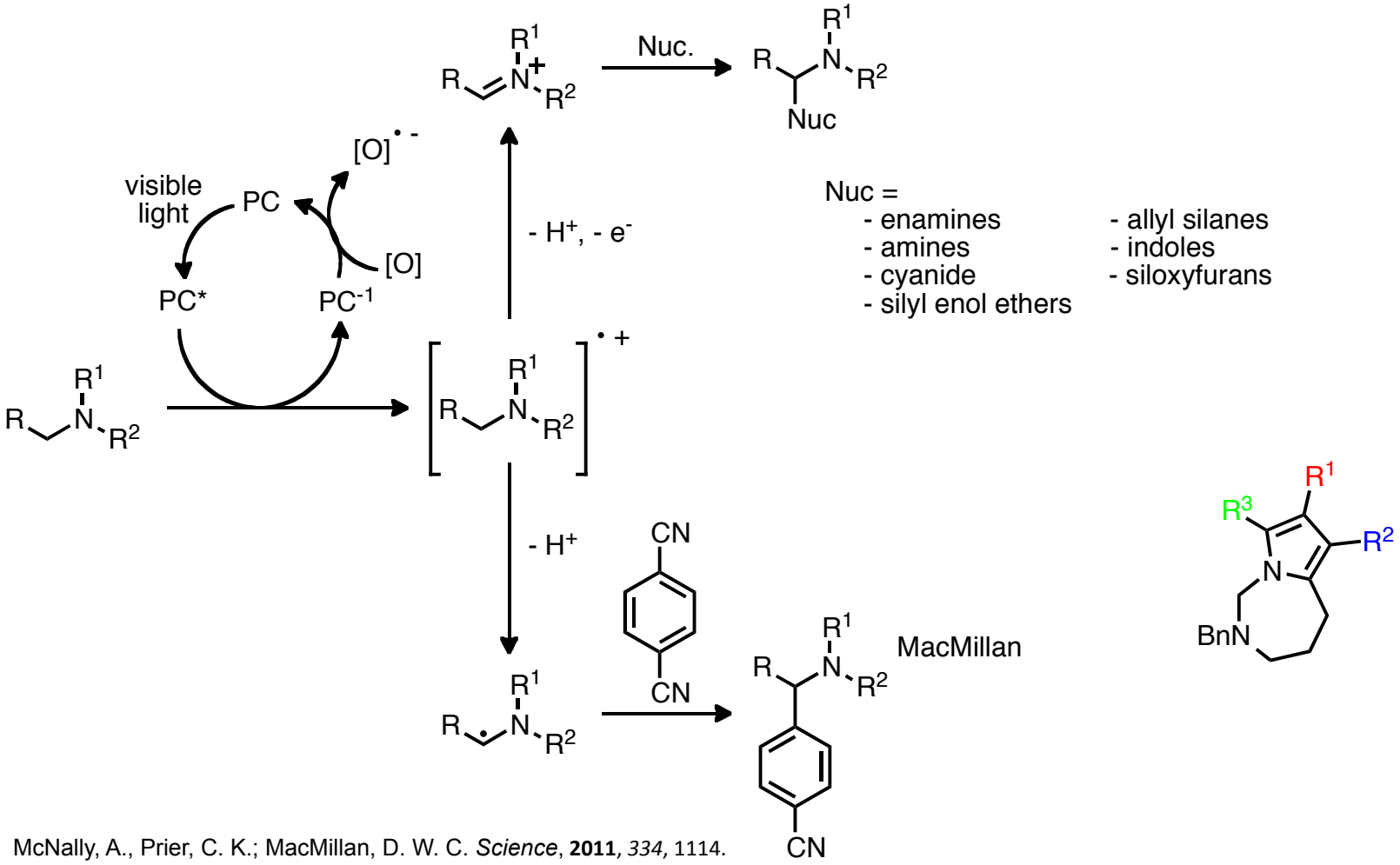
* All reactions were run with benzaldehyde (1 mM, 1 equiv.) and diazepine (1 mM, 1 equiv.) except entry 12

Future Directions

- Optimize dynamic exchange chemistry
  - Time, catalyst, temperature, concentration
- Analyze “dynamic combinatorial library” using HPLC and LC-MS
- Apply exchange chemistry to a “library” of aldehyde building blocks
  - Aryl, alkyl, heterocyclic, etc…
  - Ketones?

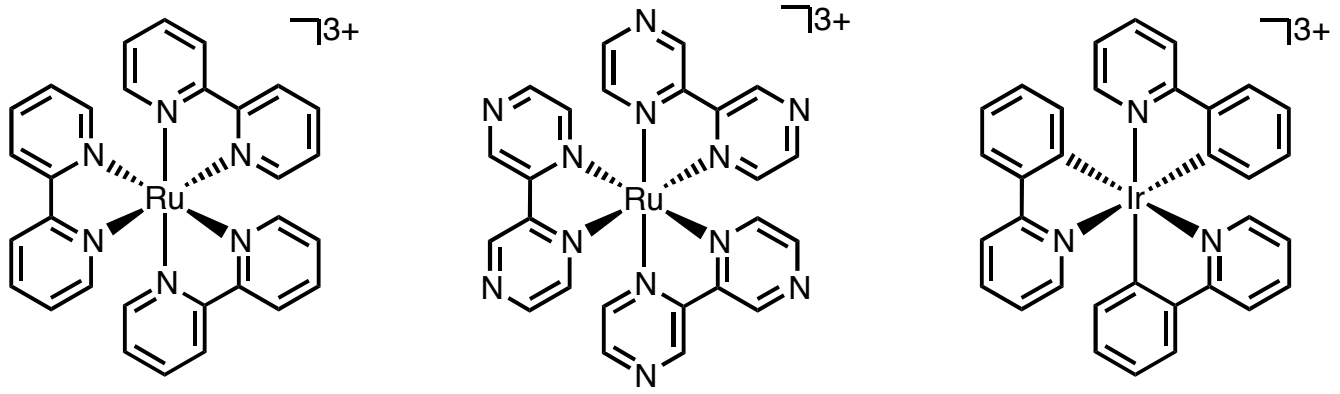

R1
R3
R2
R4
N
BnN
Photocatalyzed
C-H Bond Activation
Tropylium-Mediated
Iminium Formation
Dynamic
Combinatorial
Chemistry

Photocatalyzed Tertiary Amine C-H Bond Functionalization



McNally, A., Prier, C. K.; MacMillan, D. W. C. *Science*, **2011**, *334,* 1114.
For Comprehensive Reviews See:
Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem*., **2012**, *77,* 1617.
Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.*, **2011**, *40*, 102.

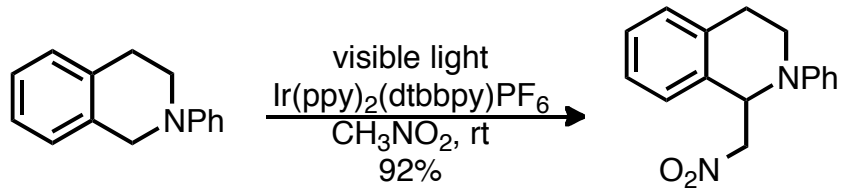
Popular Photocatalysts

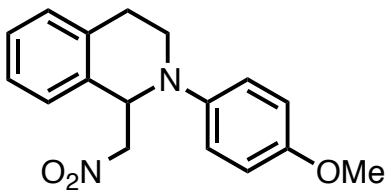


- Photocatalyst properties are extremely “tunable”

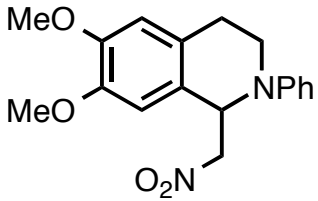
Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem*., **2012**, *77,* 1617.
Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.*, **2011**, *40*, 102.

Photoredox Catalyzed Iminium Formation

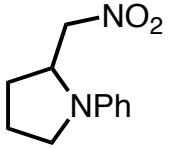




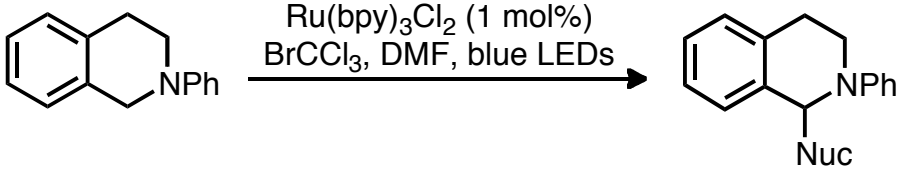
96%

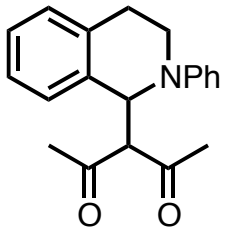


92%

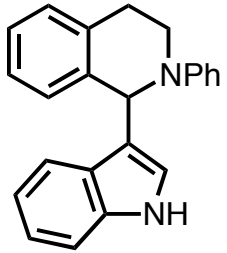


27% (72 h)

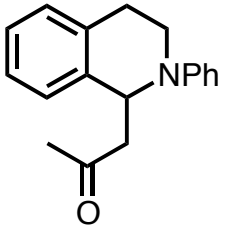




68%



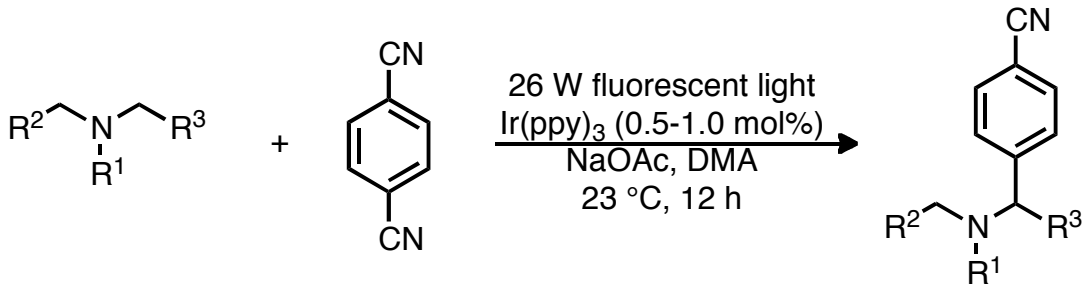
83%

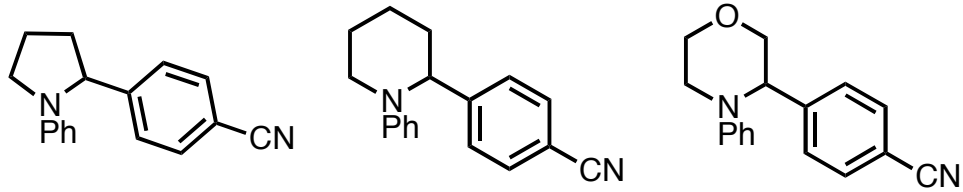


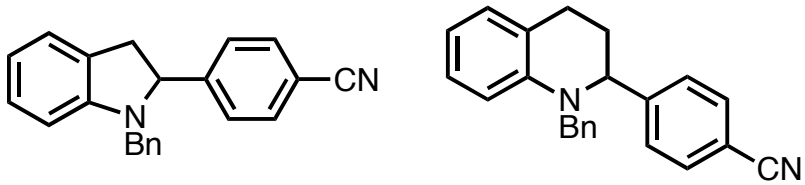
59%

Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.*, **2009**, *132*, 1464.
Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.*, **2012**, *14*, 94.

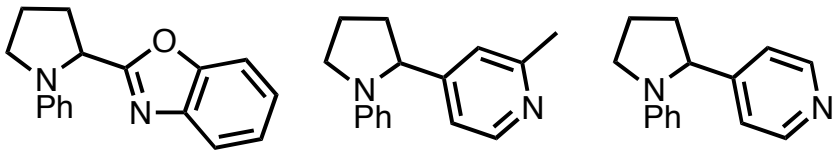
Oxidative α-Amino C-H Bond Arylation





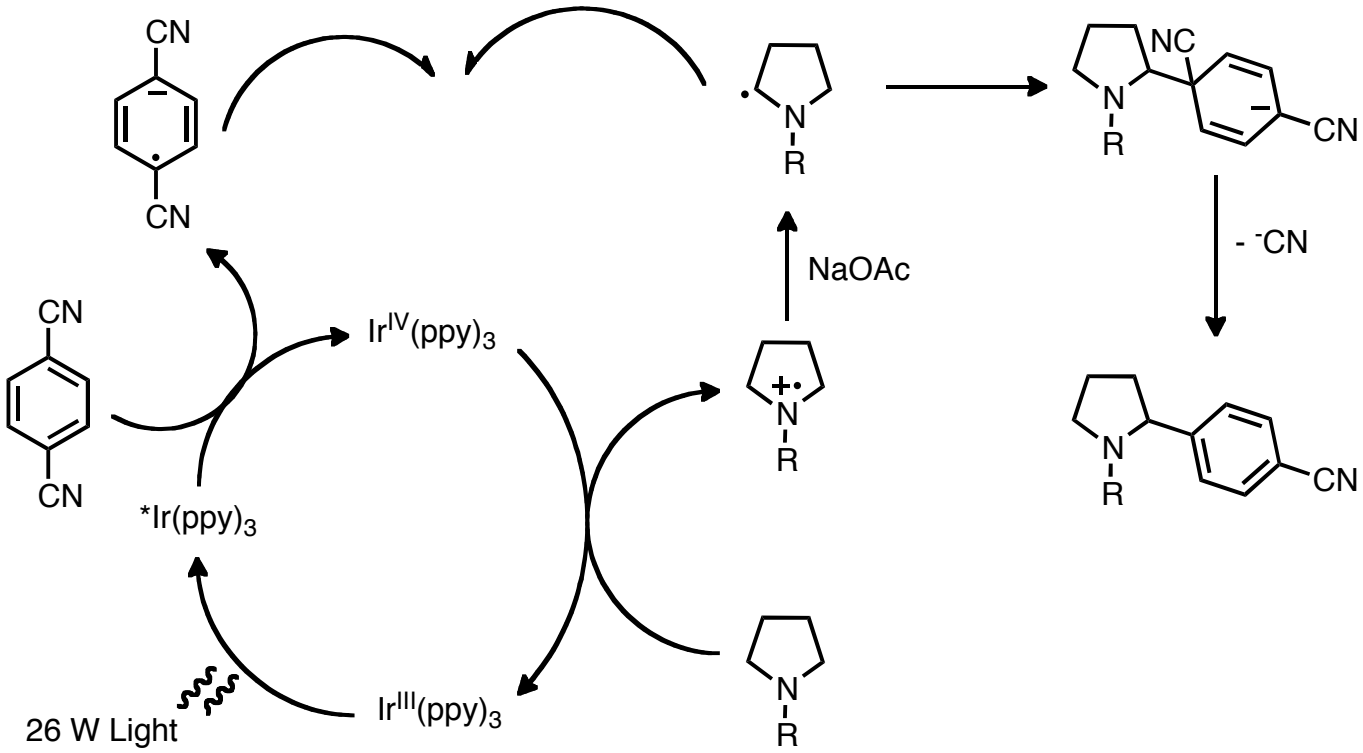


(12-24 h)



McNally, A., Prier, C. K.; MacMillan, D. W. C. *Science*, **2011**, *334,* 1114.

Proposed Mechanism



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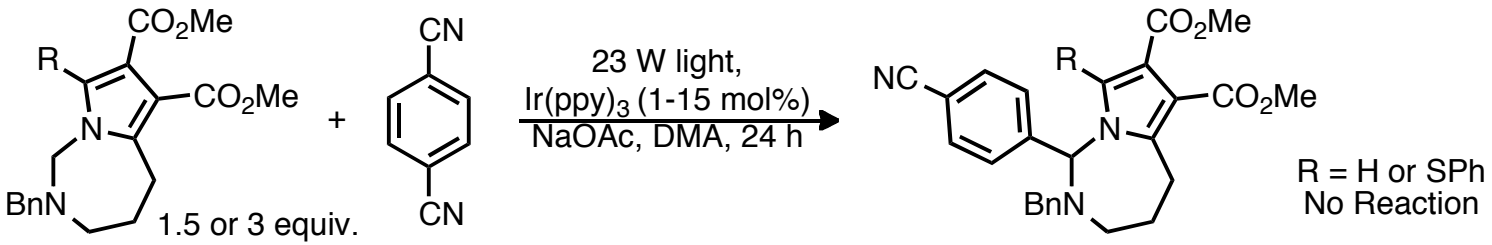
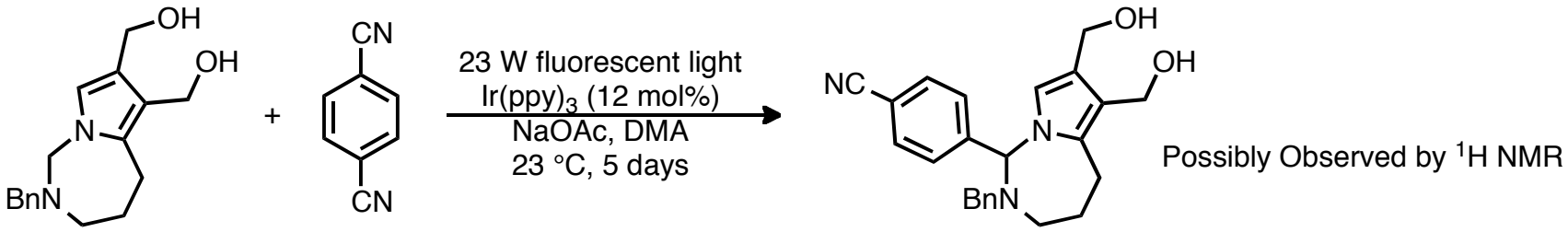
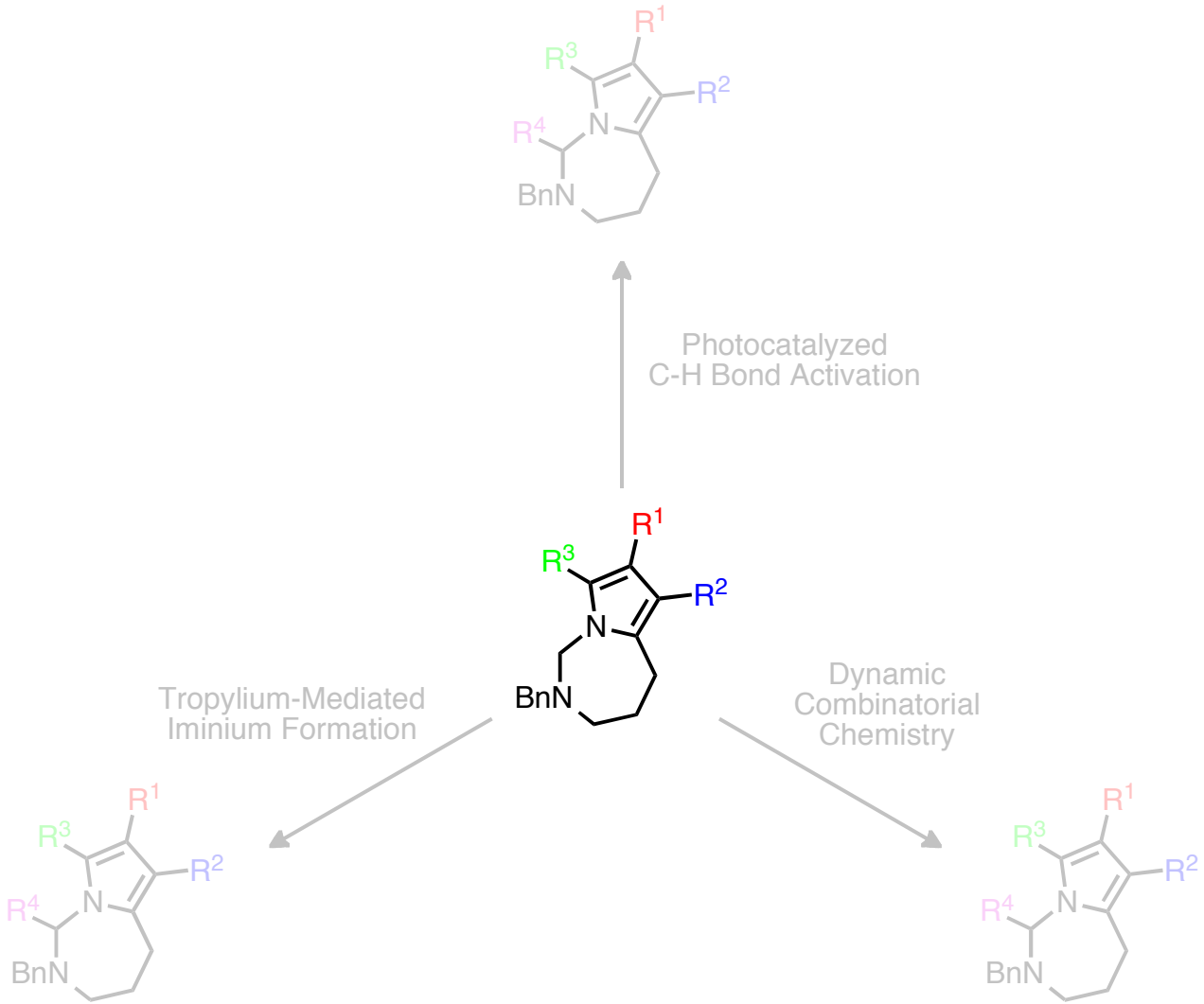
Oxidative α-Amino C-H Bond Arylation of Pyrrolo[1,3]-Diazepines



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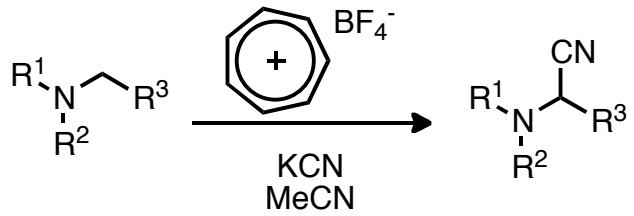
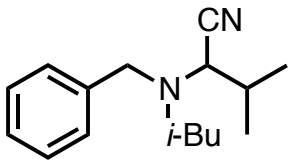
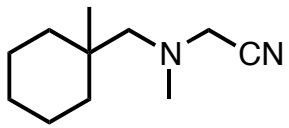
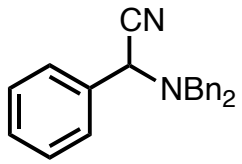




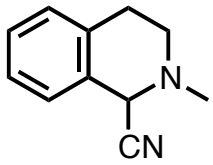
120 °C, 12 h
78%
5.9:1 r.r.



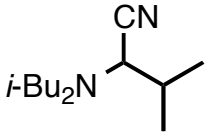
23 °C, 2 h
90%



80 °C, 12 h
42%



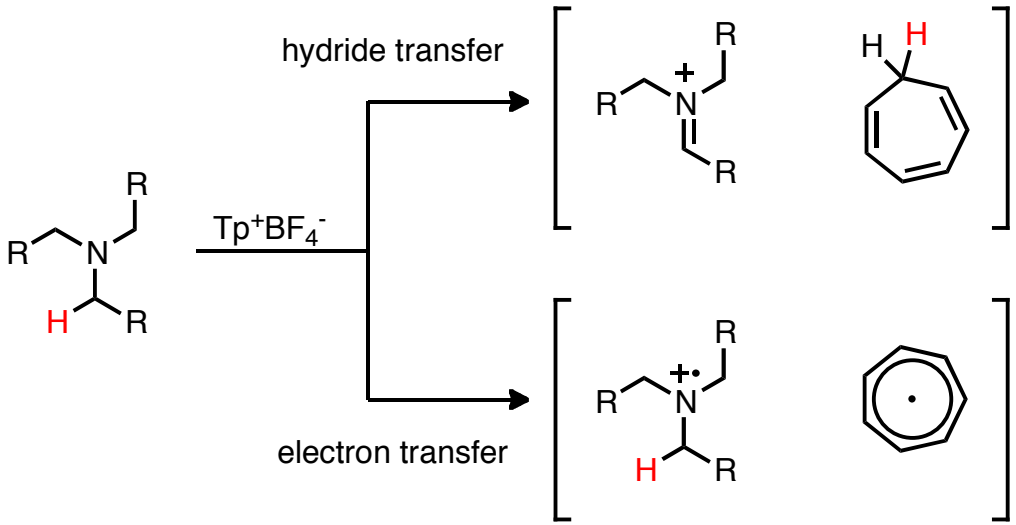
80 °C, 2 h
62%



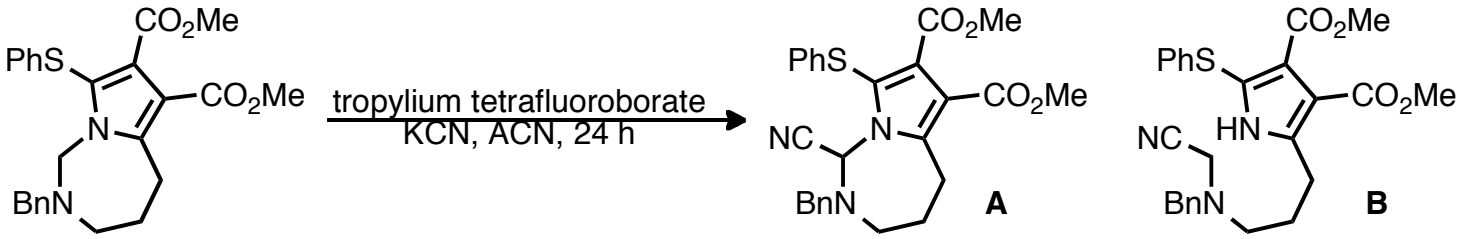
81%

Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.*, **2011**, *133*, 1260.

Proposed Mechanism



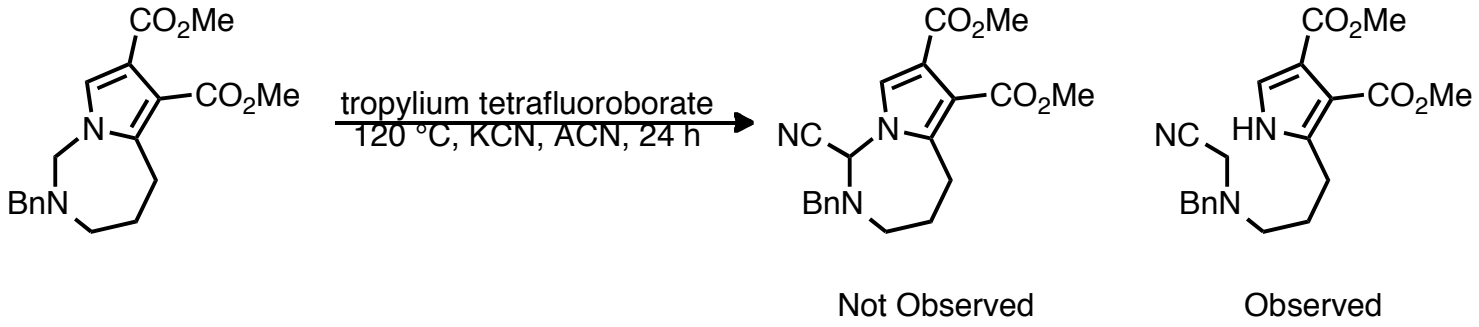
Tropylium-Mediated Cyanation of Pyrrolo[1,3]-Diazepine



Entry	Conditions	Result
1	rt	no reaction
2	80 °C	**B** observed by ^{1}H NMR
3	120 °C	**B** observed by ^{1}H NMR
4	1.5 equiv. tropylium tetrafluoroborate 120 °C	**B** observed by ^{1}H NMR
5	3.0 equiv. tropylium tetrafluoroborate 120 °C	**B** observed by ^{1}H NMR
6	no tropylium tetrafluoroborate 120 °C	27% **B**
7	no tropylium tetrafluoroborate 18-crown-6 ether, 120 °C	61% **B**

* All reaction were performed using 2 equiv. KCN with a diazepine concentration of 0.17 M

Tropylium-Mediated Cyanation of Pyrrolo[1,3]-Diazepine



Future Directions

- Utilize other more reactive photocatalysts
- Utilize other diazepine derivatives to promote reactivity
- Similar oxidative reactions could provide opportunities for functionalization

Acknowledgements

- Dr. Wipf
- Wipf Group Members – Past and Present
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