

# Making Synthetic Organic Electrochemistry Mainstream

## Chemical Sciences Roundtable



*“Life science needs an Organic Chemistry that remains strong.” – Albert Eschenmoser (2008)*

*Phil S. Baran*

*Department of Chemistry*

*The Scripps Research Institute*

*Visit our website at: [www.scripps.edu/chem/baran](http://www.scripps.edu/chem/baran)*

*Heterocyclic Chemistry website: [www.scripps.edu/chem/baran/heterocycles/](http://www.scripps.edu/chem/baran/heterocycles/)*

*Baran Lab Blog: [openflask.blogspot.com](http://openflask.blogspot.com); Twitter @baranlabreads*

*Book: [portablechemistsconsultant.com](http://portablechemistsconsultant.com)*

 **Scripps  
Research**

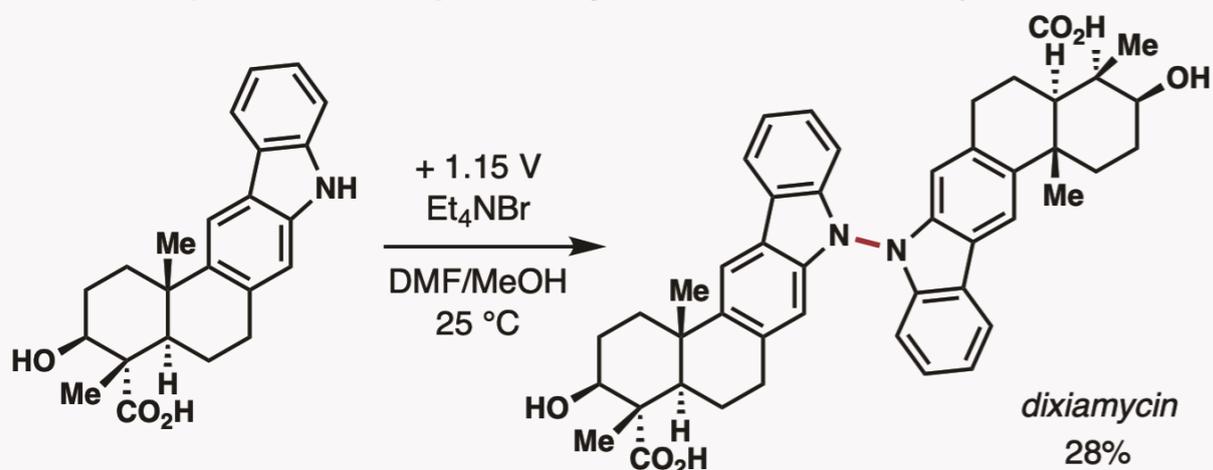
Science Changing Life

# Electrochemistry is Synonymous with Sustainability

## Electroorganic Chemistry: Solving Synthetic Problems

### A. Enabling Complex Synthesis

- > Oxidative dimerization offered the most ideal route to dimeric indole alkaloids
- > **Chemical oxidants** afforded little to no conversion on a model substrate
- > **Constant potential electrolysis** cleanly afforded the dimerized product



[fixed potential promotes selective dimerization] [scalable + reproducible]

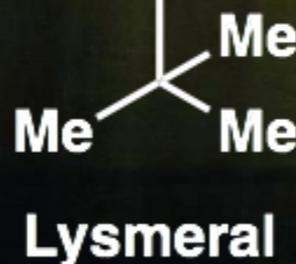
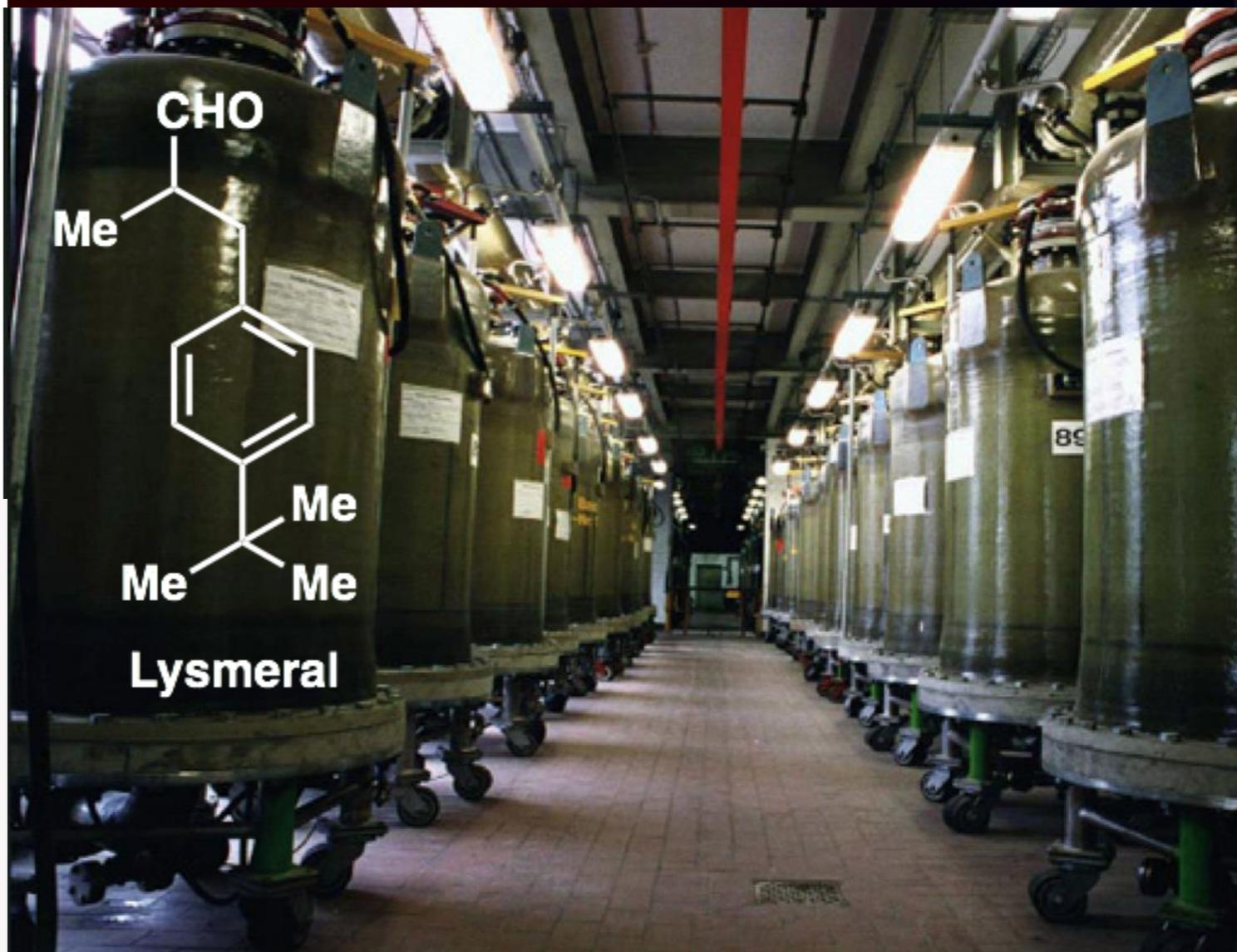
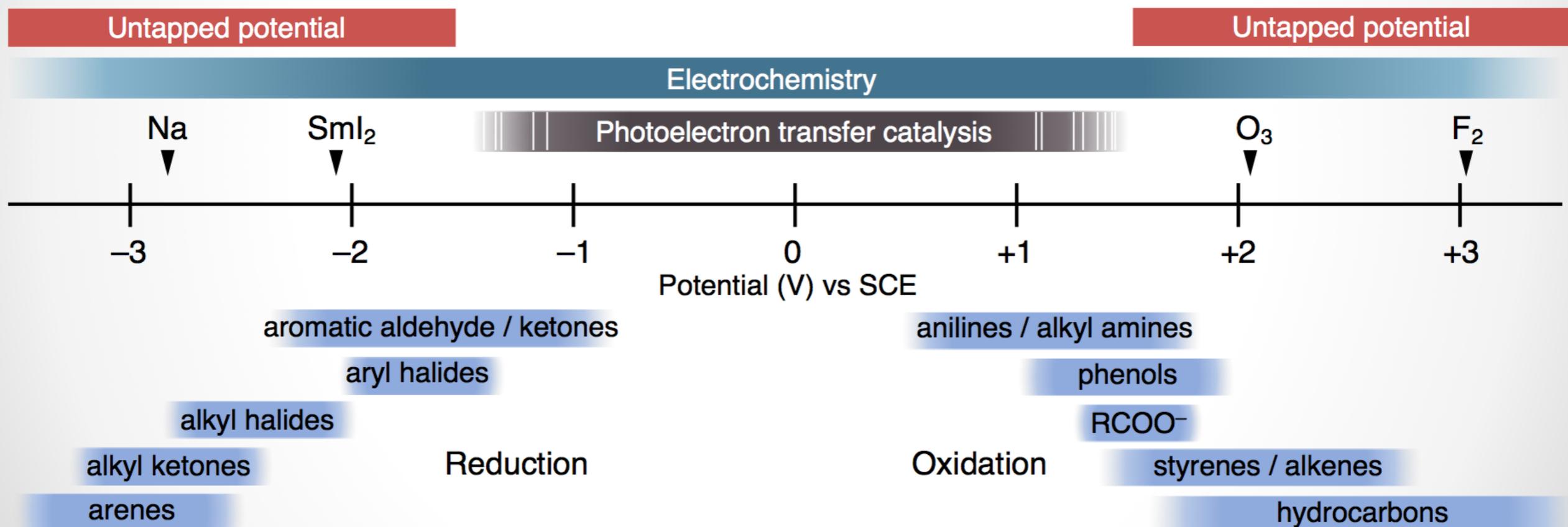
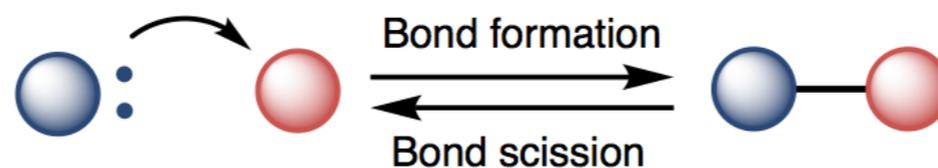


Image courtesy of Prof. Sigi Waldvogel

## Why Electrochemistry?

Chemical reaction requires the **reorganization of electrons**





# Electrochemical Amination: A Useful Tool for **Green Aryl Amination**

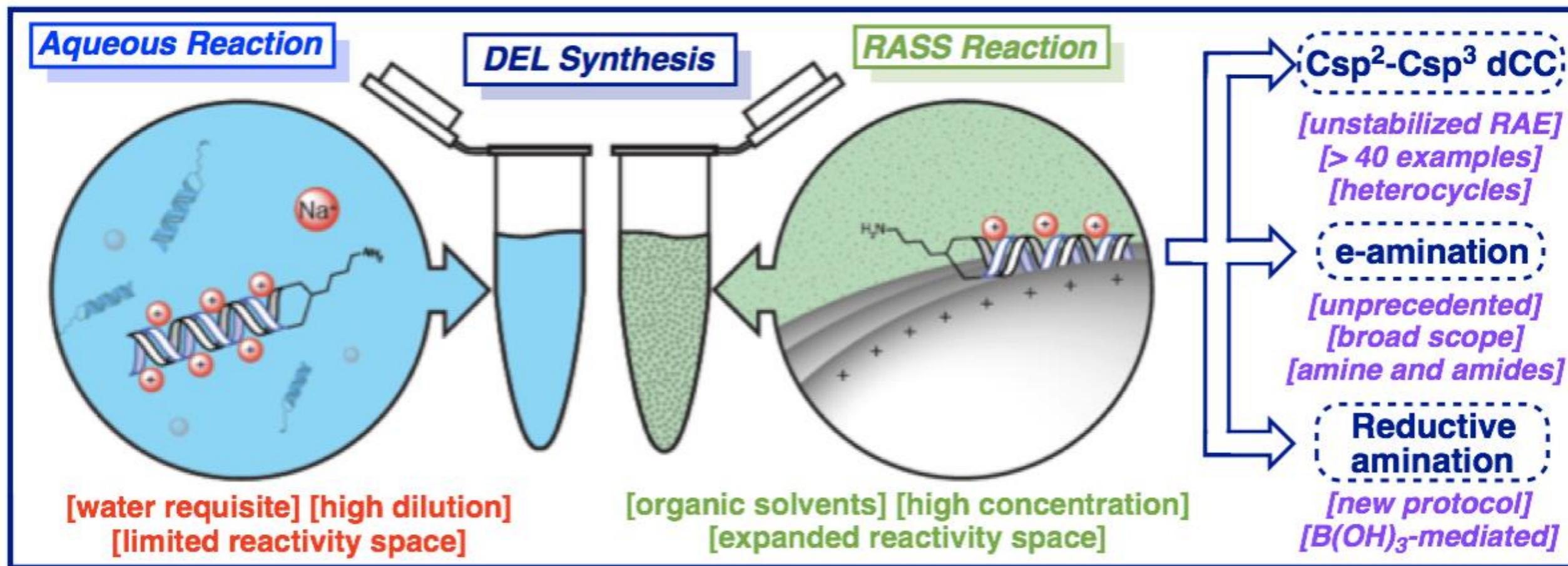
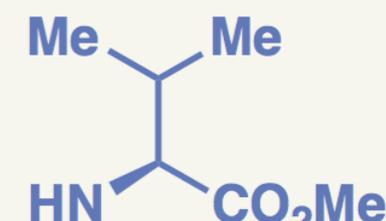
100g e-*A*

Br

Me

O

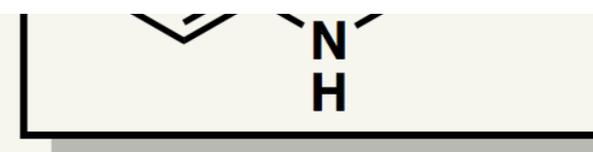
Ni(bpy)<sub>3</sub>Br<sub>2</sub> (10 mol%)  
nBu<sub>4</sub>N<sup>+</sup>Br<sup>-</sup> (0.2 M)



With Dawson group, Pfizer, *J. Am. Chem. Soc.* 2019, 141, 9998-10006.

and **A** (75 mol%) (88% ee)

<sup>a</sup> LiBr (0.89 M), DMA (0.1 M), 100 mA, 7 h.

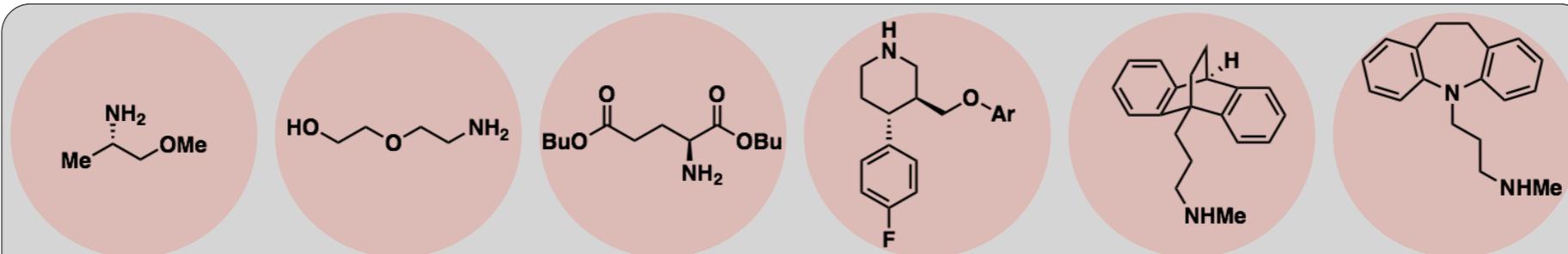


11-Step Synthesis of Teleocidins featuring E-amination, with H. Nakamura: *J. Am. Chem. Soc.* 2019, 141, 1494

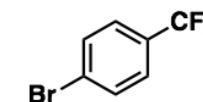
With Y. Kawamata, J. Vantourout, D. Hickey, H. Nakamura, Pfizer, Asymchem, NSF E-chem Cent, M. Neurock, H. White, S. Minter, *J. Am. Chem. Soc.* 2019, 141, 6392.

1<sup>st</sup>  
generation<sup>[1]</sup>

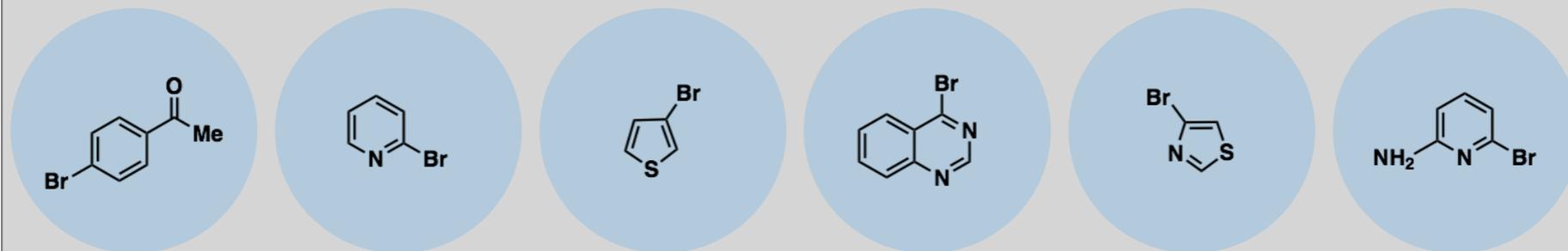
**A**



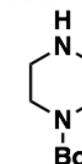
different amines  
with



**B**

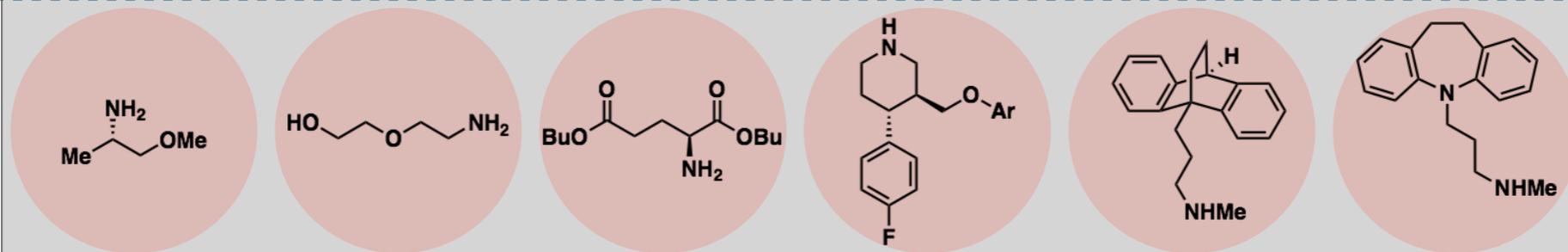


different ArBr  
with

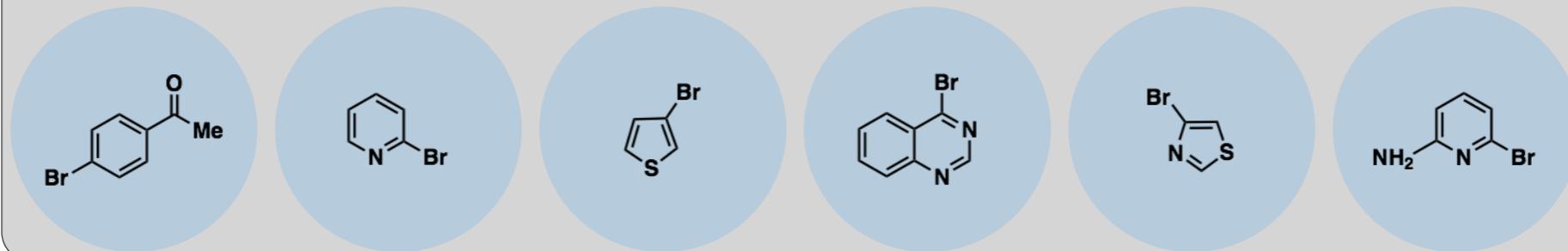


2<sup>nd</sup>  
generation<sup>[2]</sup>

**C**



**D**



**1**

**2**

**3**

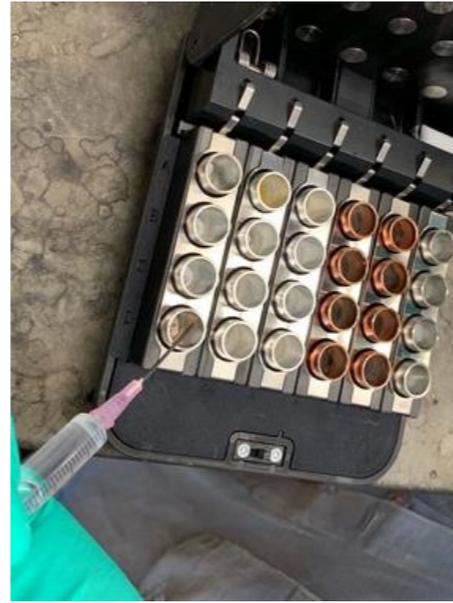
**4**

**5**

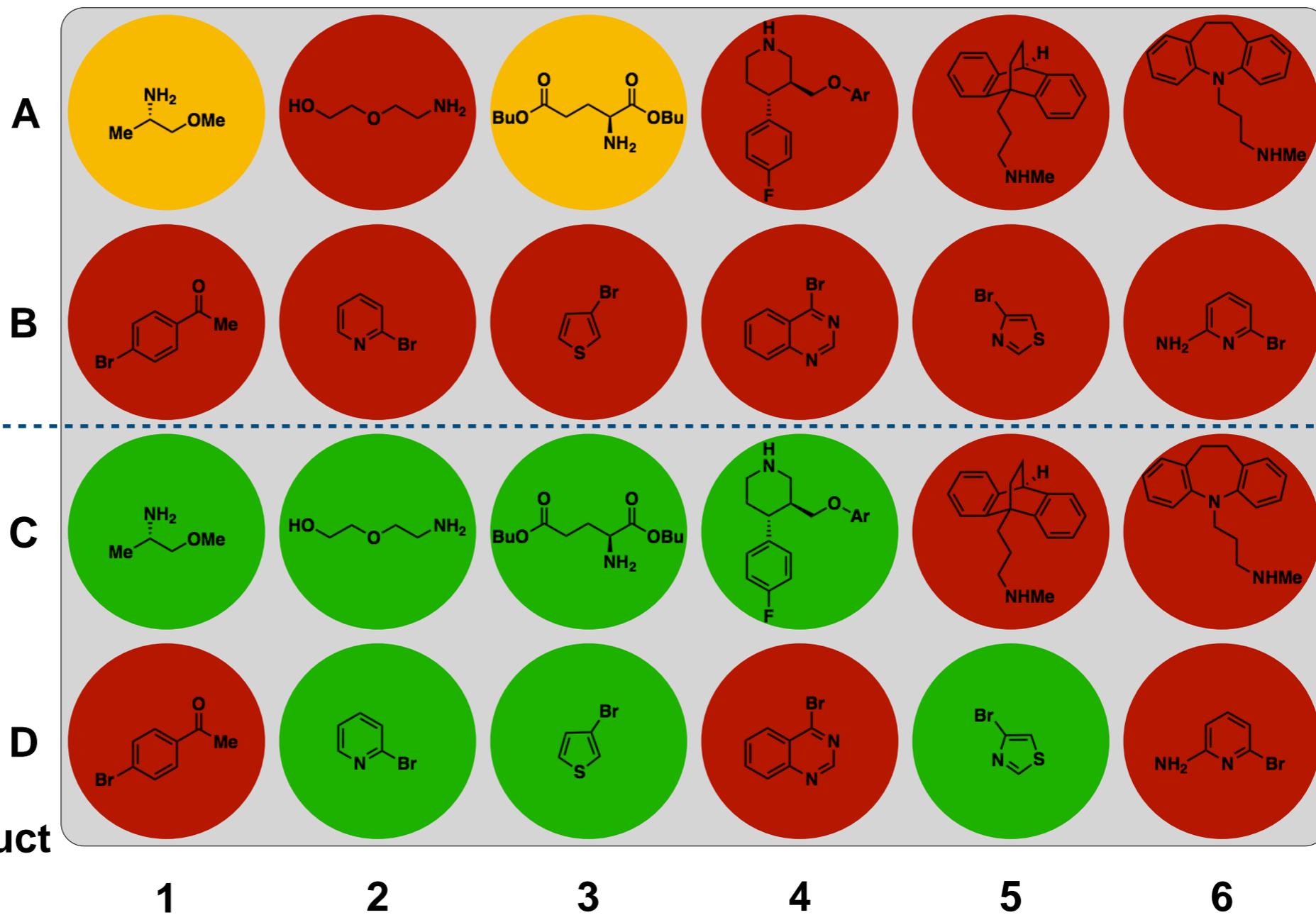
**6**

[1]Li, C. et al. *Angew. Chem. Int. Ed.* **2017**, 56, 13088. [2]Kawamata, Y. et al. *J. Am. Chem. Soc.* **2019**, 141, 6392.

\* *The reactions are run under air!*



1<sup>st</sup>  
generation<sup>[1]</sup>



● No desired product

● Trace amount

That amination is such a game changer. I tried 16 different Buchwald conditions and it didn't work. Never even a trace. With your amination 2.0 protocol it worked the first time in 67% yield. Both coupling partners are crazy as well. I wish you could have seen it. They have multiple acidic NH and basic heterocyclic N. Looks like explosives essentially. The fact that it worked so well is a bloody miracle! Please send my most sincere compliments to the team! I am going to do all my aminations now this way.

Regards,  
Art



**Baran Lab**

@BaranLabReads

Dear Industrial Colleagues, Which of these Named reactions are you most likely to avoid if possible?

Arndt-Eistert

15%

Balz-Schiemann

11%

**Birch**

**48%**

Wolf-Kishner

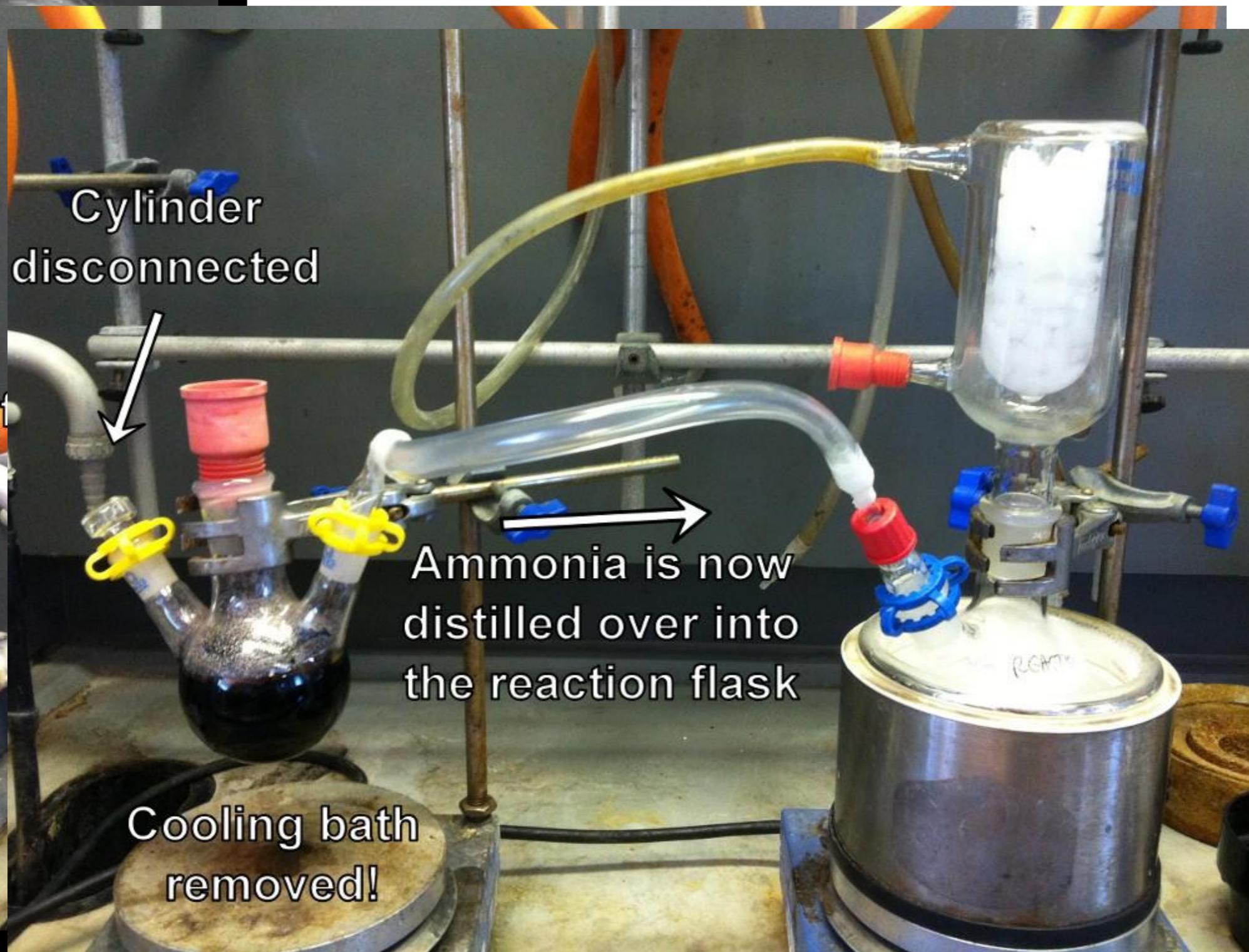
26%

426 votes · Final results

# Electrifying a Classic Organic Reaction: Birch

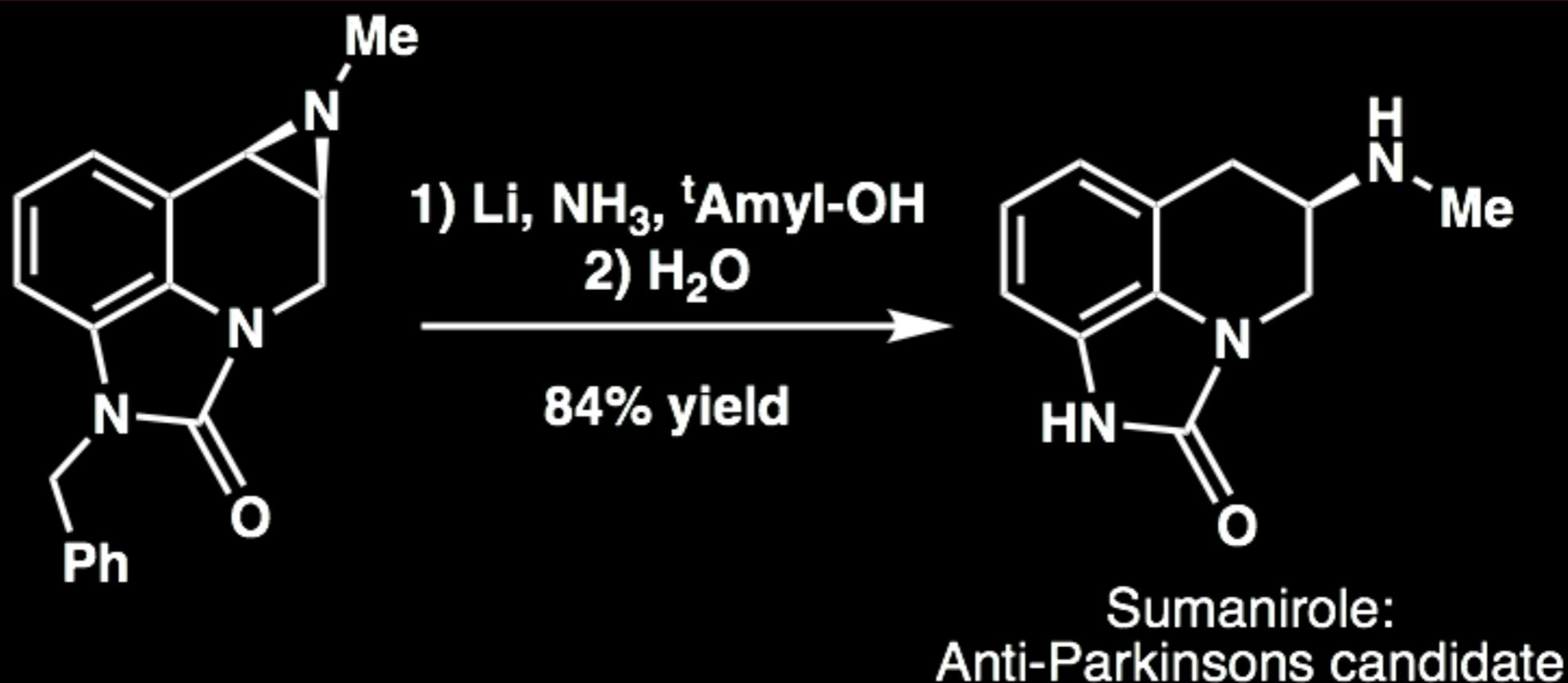
## Birch reduction

From Wikipedia, the free encyclopedia



action was reported by R. B. Woodward at Oxford,<sup>[1][2][3][4]</sup> which converted a five-membered ring into a propanone. The organic reduction of alkenes by this reaction is called Birch reduction. It was discovered that lithium is a powerful organic chemist.





Pfizer, *Org. Proc. Res. Dev.*, 2005, 9, 997

**53 Kg batch, 2500 L of NH<sub>3</sub>,  
7 Kg Lithium**

- Enough NH<sub>3</sub> to fill three Boeing 747's at STP
- Equivalent to one 50 L tank (200 bar) of H<sub>2</sub> generated from quench of excess Li

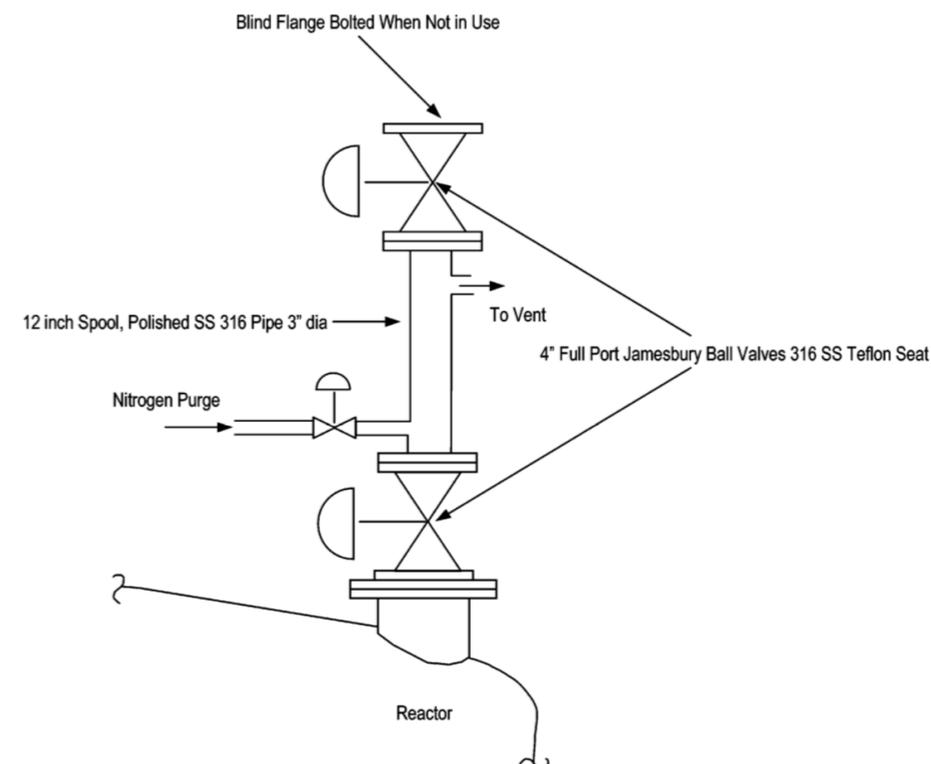
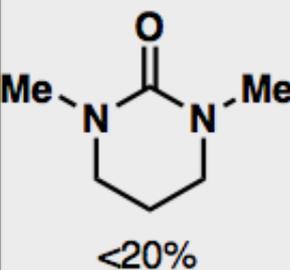
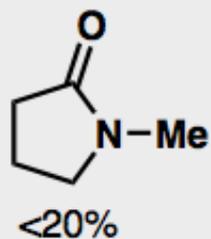


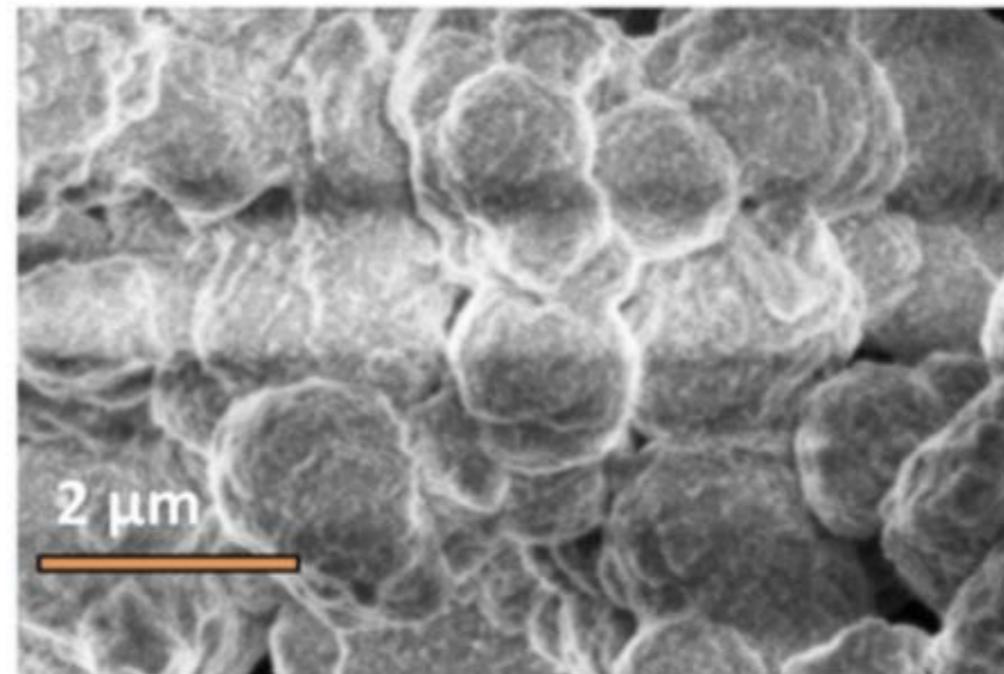
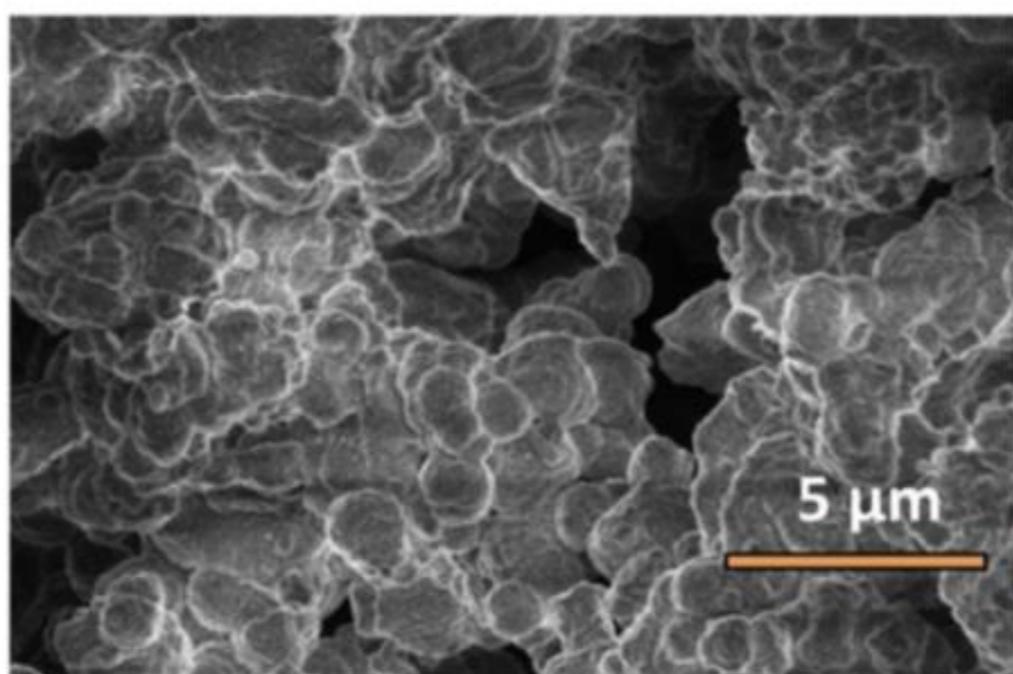
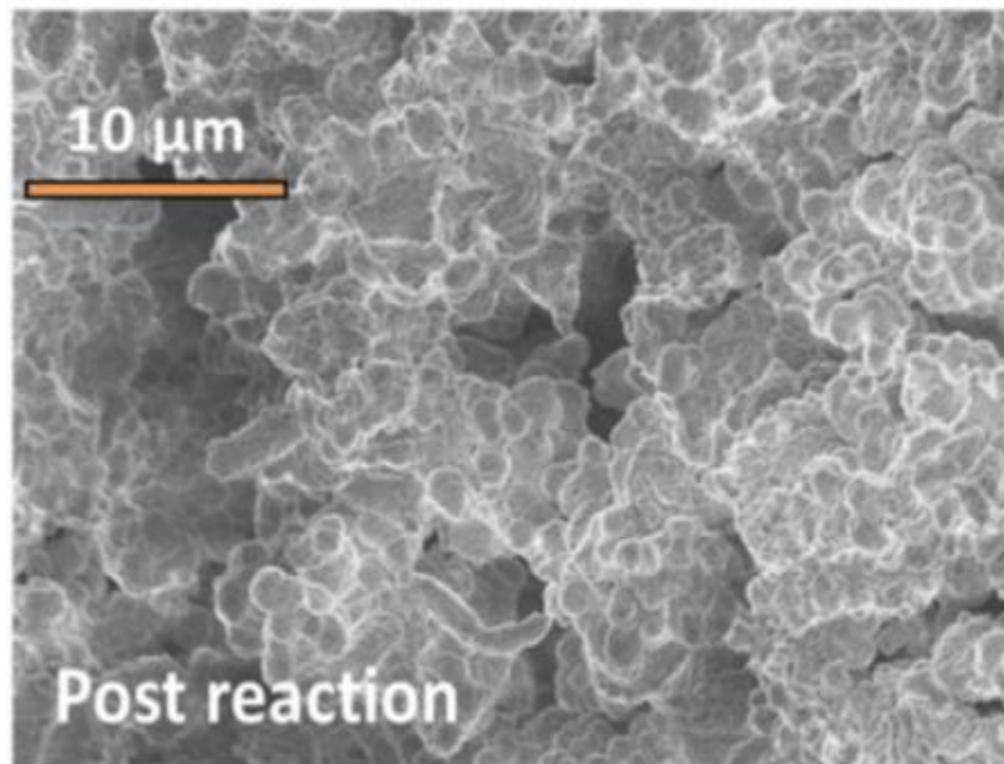
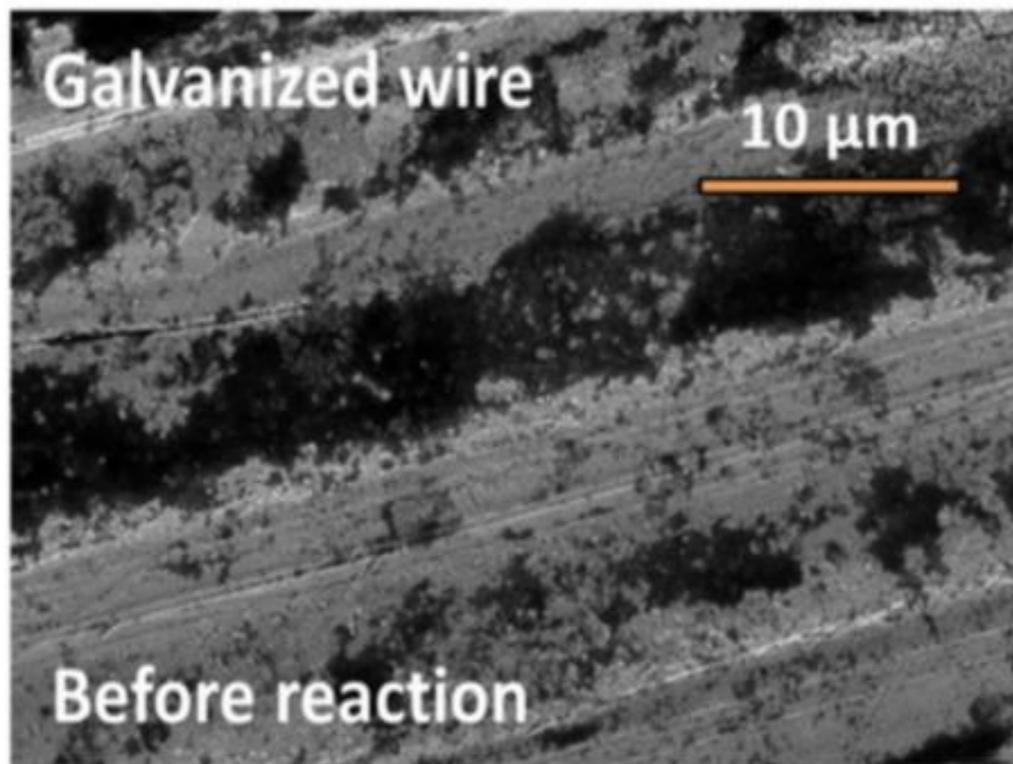
Figure 1. Schematic diagram for the lithium charging apparatus.

# Translating Lessons from **Li-Ion Batteries** for Organic Synthesis

Li-ion battery additives



## SEM Analysis



SEI: Solid Electrolyte Interface

ion

ntial

from  
e

node

Commercial  
electrodes  
potentiostat

d By-prod.

0%	-
0%	-
0%	-
0%	-
0%	-
0%	-
0%	-
0%	30%
0%	14%
0%	<5%
0%	<5%

9 - 100 mg(+) / 100 μm(-)

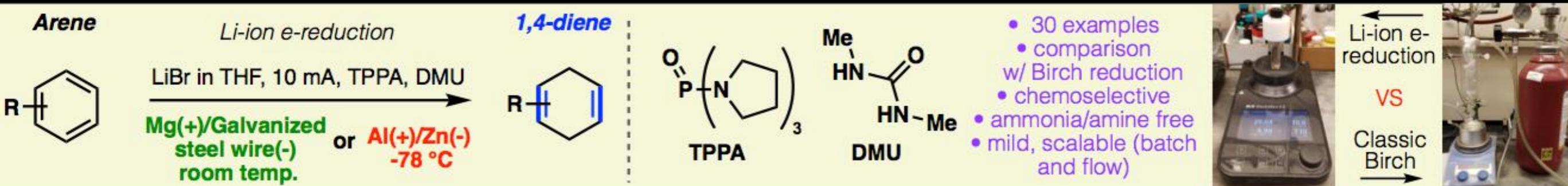
100 mg, DMU, LiClO<sub>4</sub>, TFA

100%

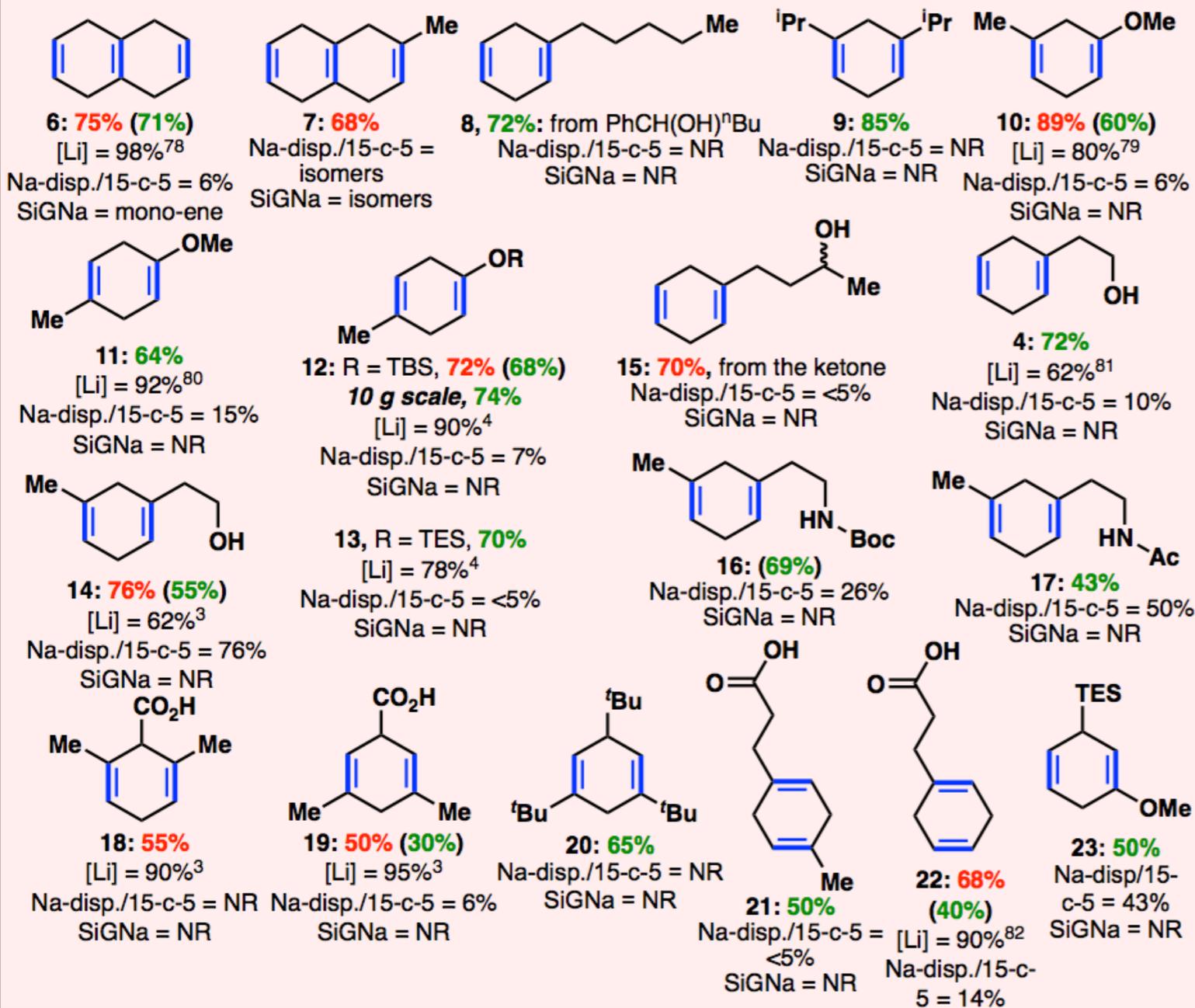
IV

H<sup>+</sup> H<sup>-</sup>

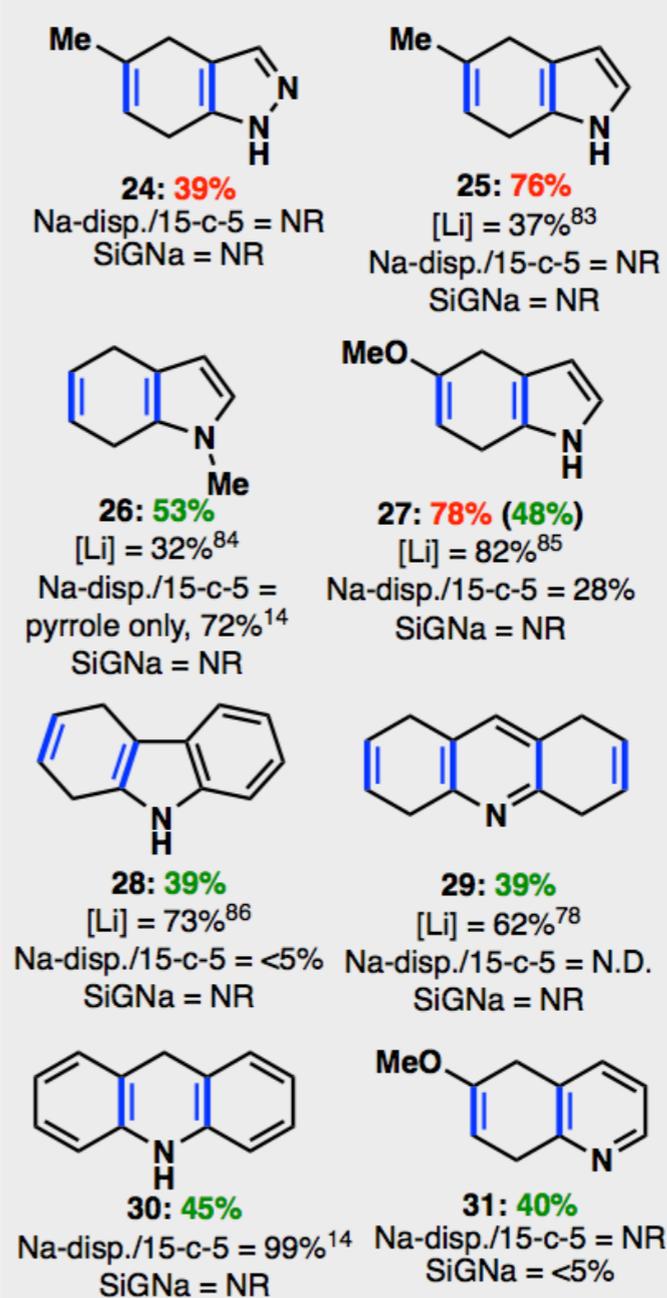
# Li-Ion Electroreduction: Simple, Sustainable, Safe



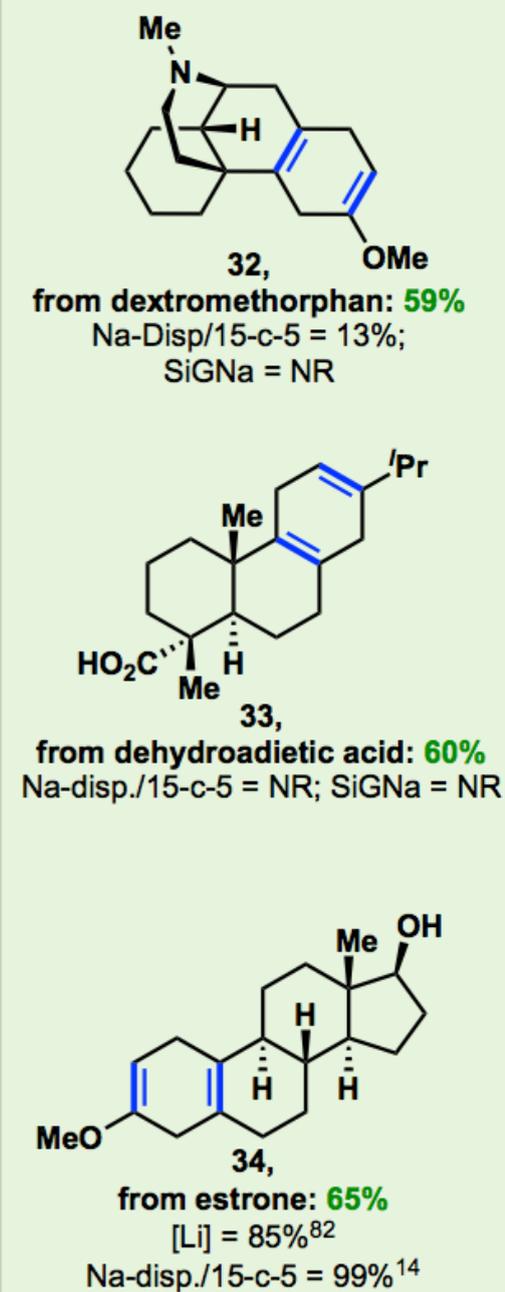
## Carbocycles



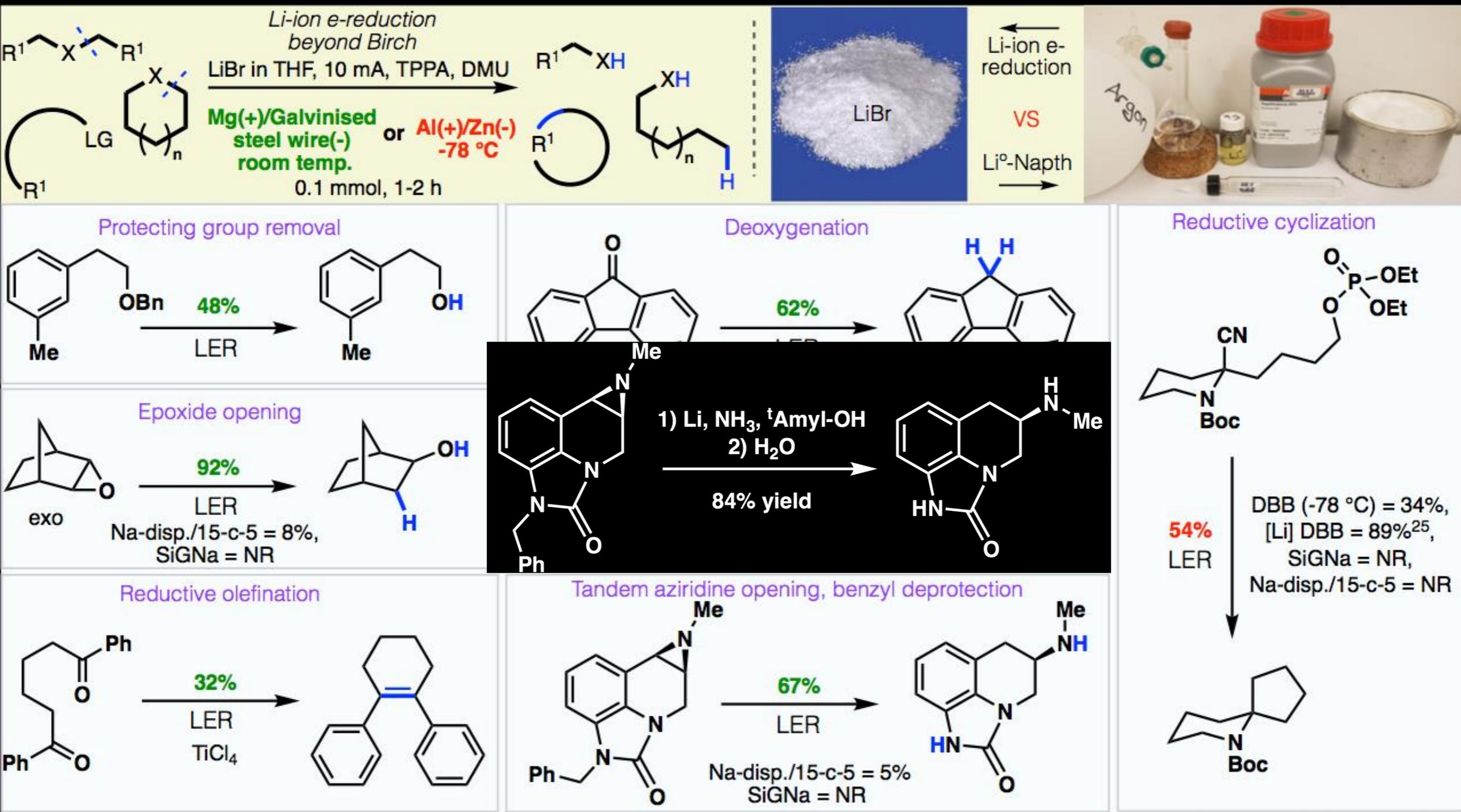
## Heterocycles



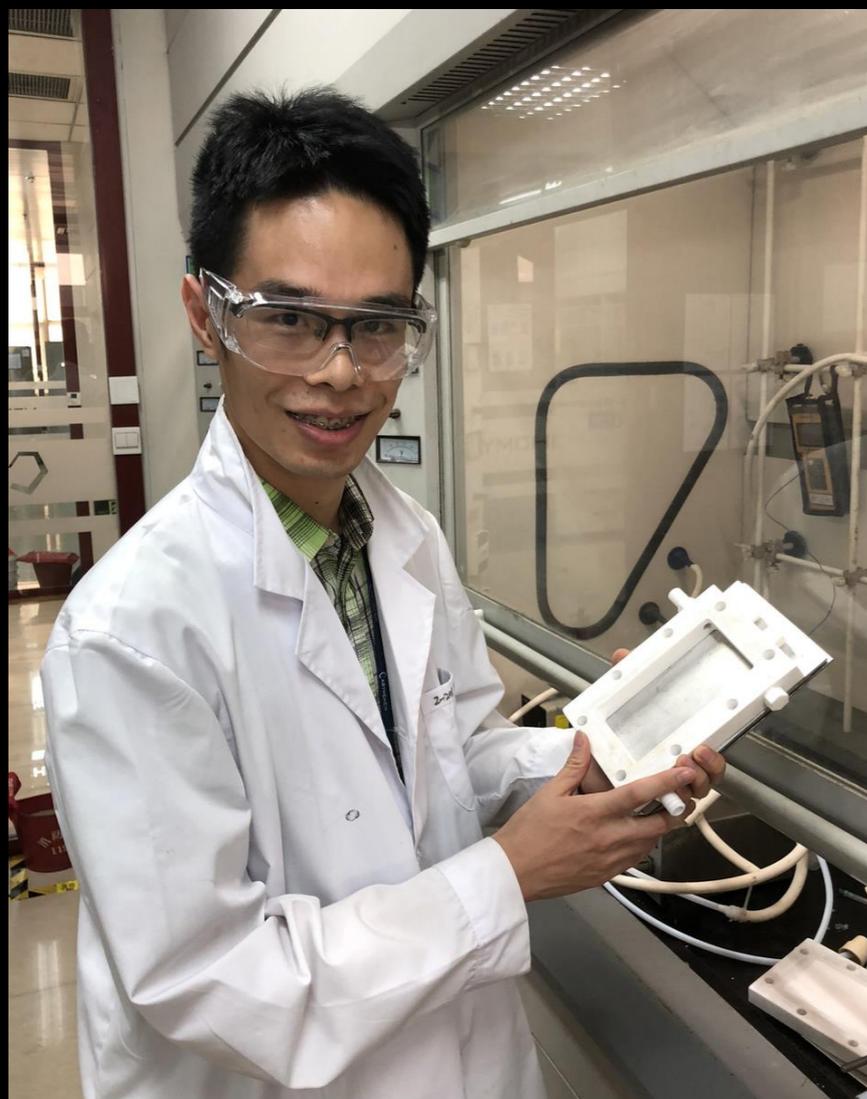
## Natural product derivatives



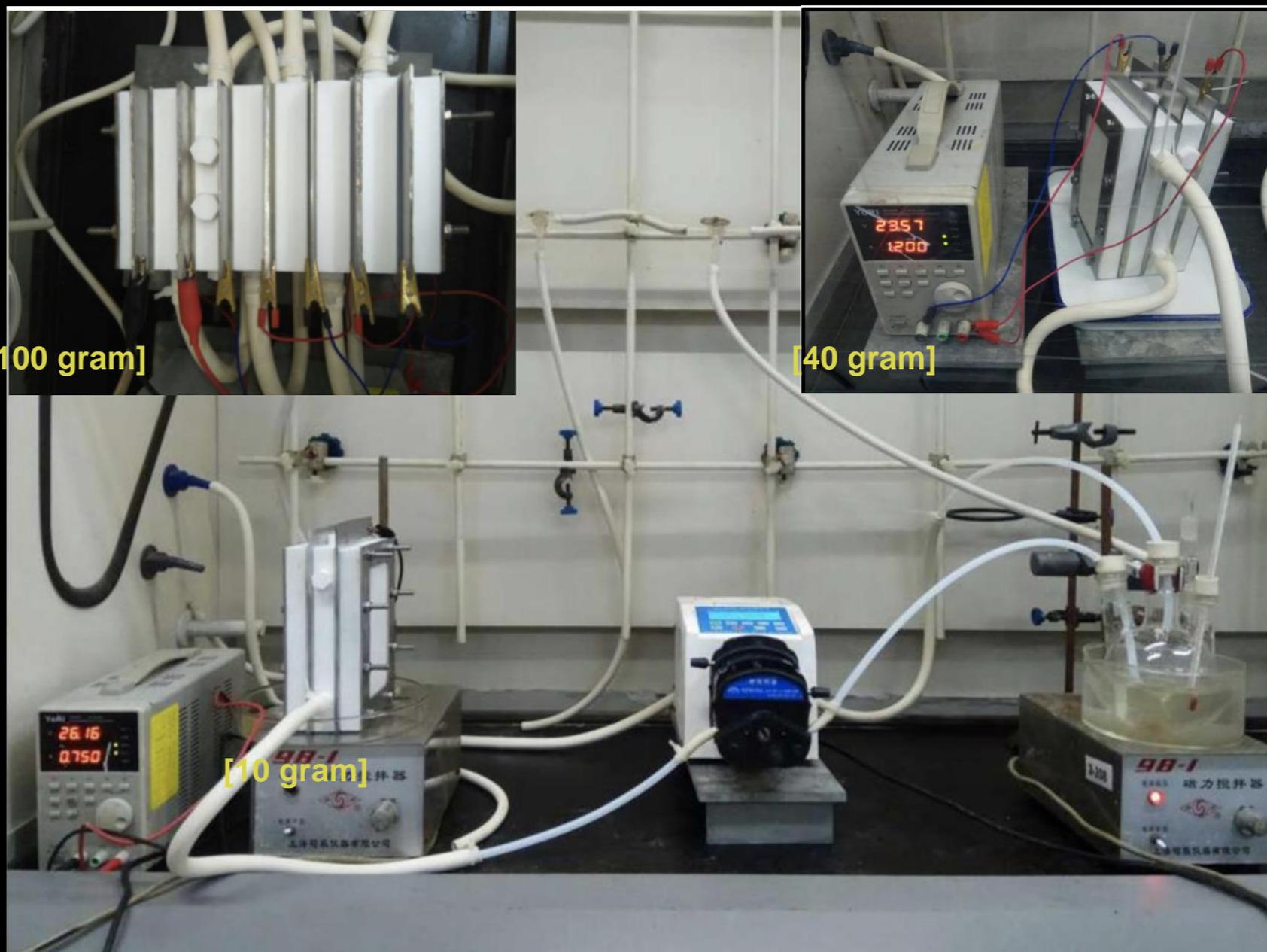
# Li-Ion Electroreduction: Simple, Sustainable, Safe



# Li-Ion Electroreduction: Simple, Sustainable, Safe, **Scalable**



Longrui Chen

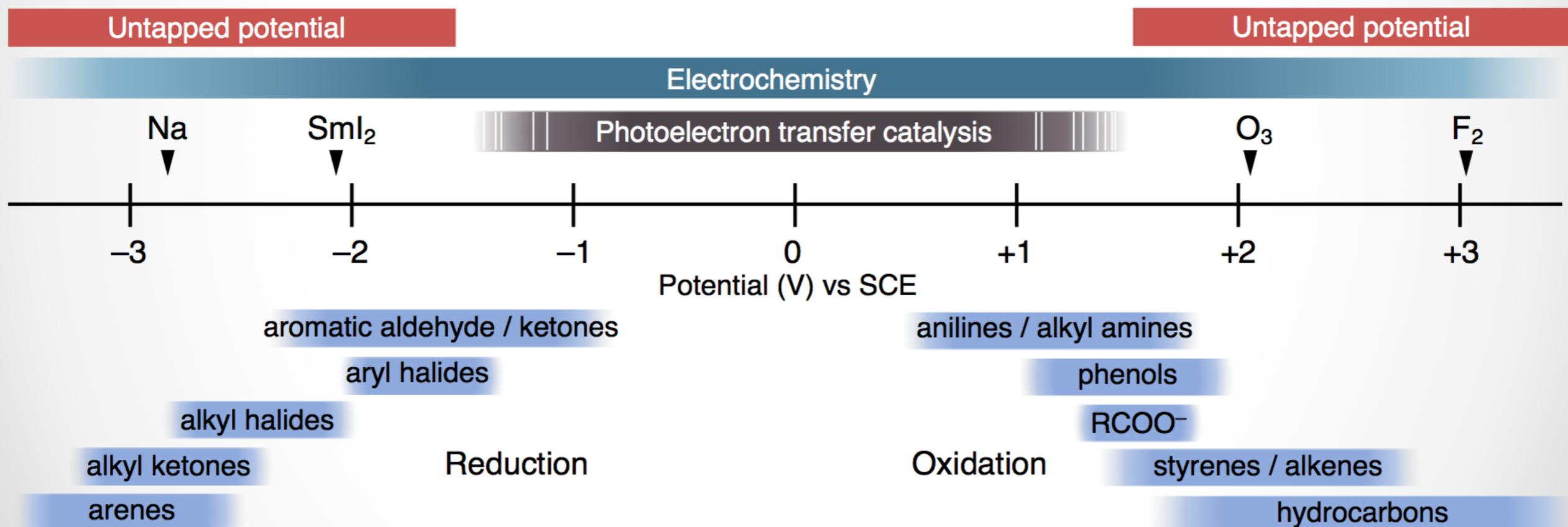
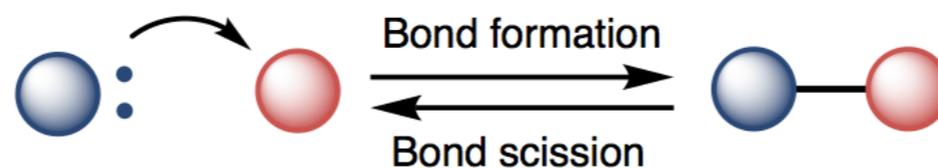


Modular flow setup gram to kilogram scale!!

# Li-Ion Electroreduction: Simple, Sustainable, Safe

## Why Electrochemistry?

Chemical reaction requires the reorganization of electrons



<https://cci.utah.edu>

Kevin Klunder

Jeremy Starr

Mike Collins

David Hickey

## Two new “forcing functions” for the use of e-chem in synthesis (because sustainability is not enough):

### Strongly reducing:

**Me** - comparison w/ Birch reduction  
- mild, scalable (batch and flow)  
- ammonia/amine free  
- chemoselective  
- 30 examples

from dextromethorphan: **59%**  
Na-disp./15-c-5 = 13%;  
SiGNa = NR

**tBu** **tBu** **tBu**  
**65%**  
Na-disp./15-c-5 = NR  
SiGNa = NR

**Me** **iPr**  
**HO<sub>2</sub>C** **Me** **H**  
from dehydroabiatic acid: **60%**  
Na-disp./15-c-5 = NR; SiGNa = NR



Li-ion e-reduction

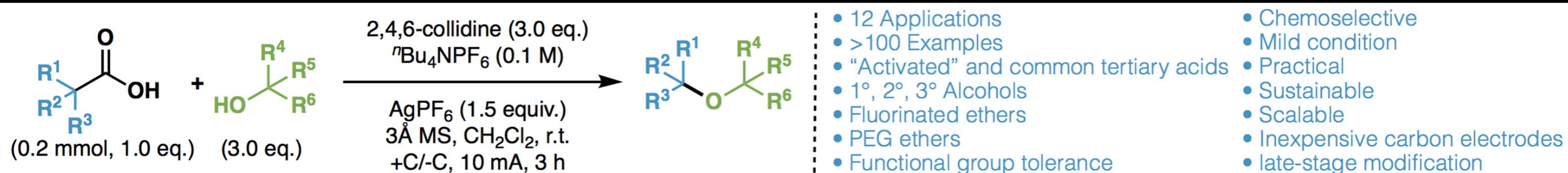
VS

Classic Birch



With B. Peters, S. Beil, Y. Kawamata, K. Rodriguez, S. Reisberg, *Pfizer*, Asymchem, **NSF E-chem Cent**, *Science* 2019, 363, 838.

### Strongly oxidizing:



With J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. Reisberg, P. Mykhailiuk, BMS, *Pfizer*, D. Blackmond, 2019, *Nature*, 573, 398.

# Parting Thoughts

# C&EN

CHEMICAL & ENGINEERING NEWS

NOVEMBER 4, 2019

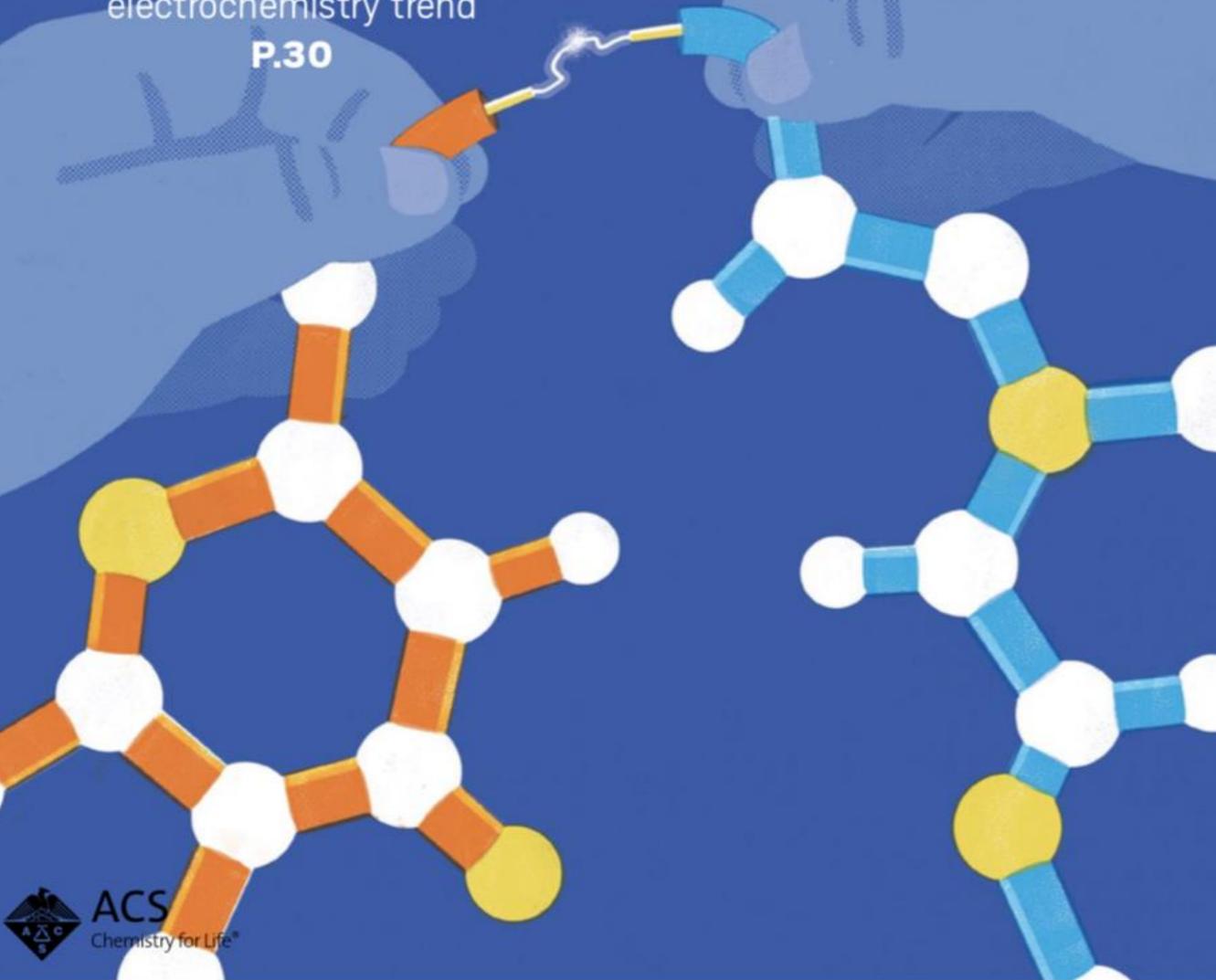
How does your salary compare? ACS survey returns P.18

Reining in science's plastic habit P.22

## Pharma powers up

Medicinal and process chemists tap into the current electrochemistry trend

P.30



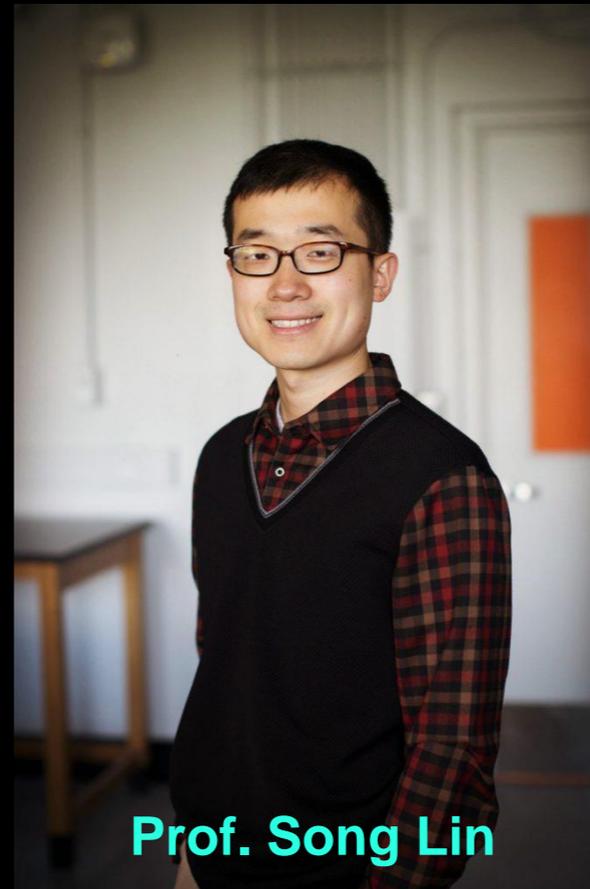
ACS  
Chemistry for Life®

Cover story, Nov. 4, 2019

- Education
- Equipment



- Enablement
- Collaboration is key!

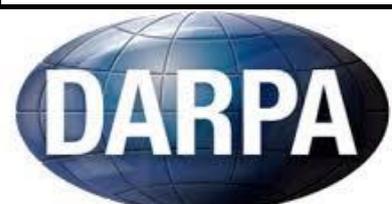
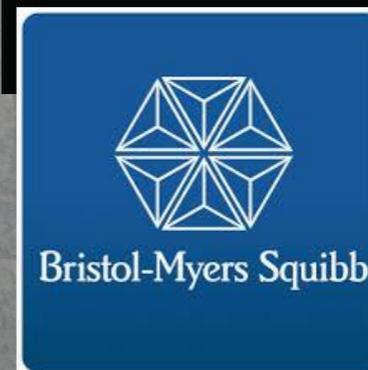


Prof. Song Lin



Prof. Kevin Moeller

# Acknowledgements



Current group members as of November, 2019:

## -Graduate Students-

Lisa Barton • Cheng Bi • Kelly Eberle • Jesse Gu • Stephen Harwood • Yuzuru Kanda • Kyle Knouse • Kyle McClymont • Max Palkowitz • David Peters • Sol Reisberg • Brendyn Smith • Tom Stratton • Junchen Tang • Dongmin Xu

**Staff Scientist:** Julien Vantourout

## -Postdoctoral Associates and Visiting Investigators-

Tie-Gen Chen • Yang Gao • Chi He • Guangke He • Gary Hermann • Cian Kingston • Yu Kawamata • Hugh Nakamura • Natalia Padiál • Byron Peters • Cody Pitts • Kevin Rodriguez • Masato Saito • Ming Shang • Yusuke Takahira • Johannes Teske • Jin-Xin Zhao

**Collaborators:** Dr. Jesse Sabatini (ARL), Donna Blackmond, Asymchem, Aldrich, BMS, IFF, IKA, Chemveda, Merck, Minakem, Pfizer, Eisai, Syngenta, Vividion, LEO Pharma, **Dr. Jason Chen (Scripps Automated Synthesis Facility)**