

Making Synthetic Organic Electrochemistry Mainstream

Chemical Sciences Roundtable



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

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Heterocyclic Chemistry website: www.scripps.edu/chem/baran/heterocycles/

Baran Lab Blog: openflask.blogspot.com; Twitter @baranlabreads

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 **Scripps
Research**

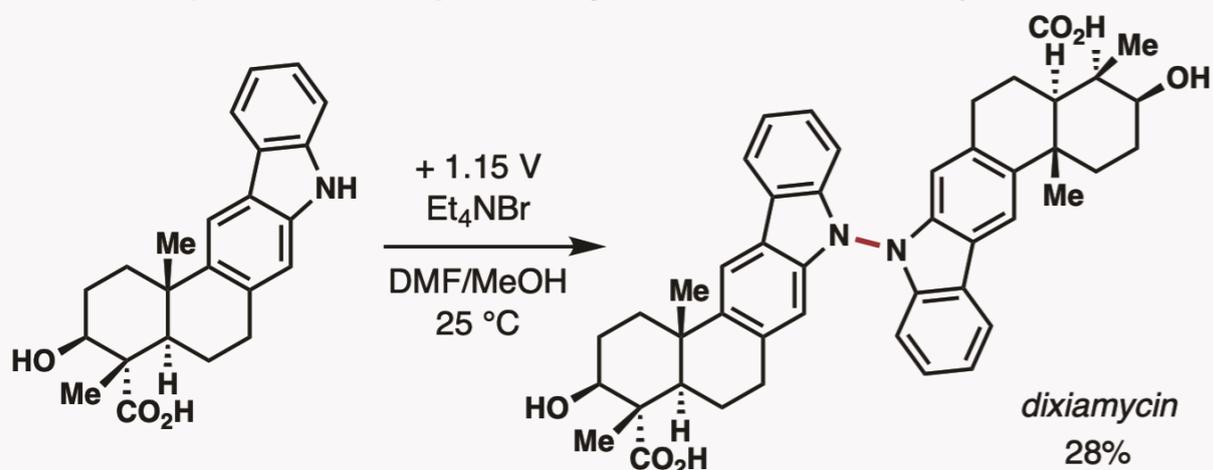
Science Changing Life

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]

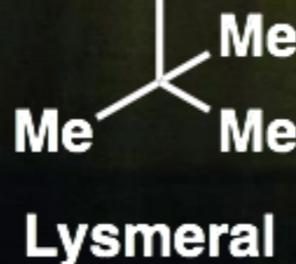
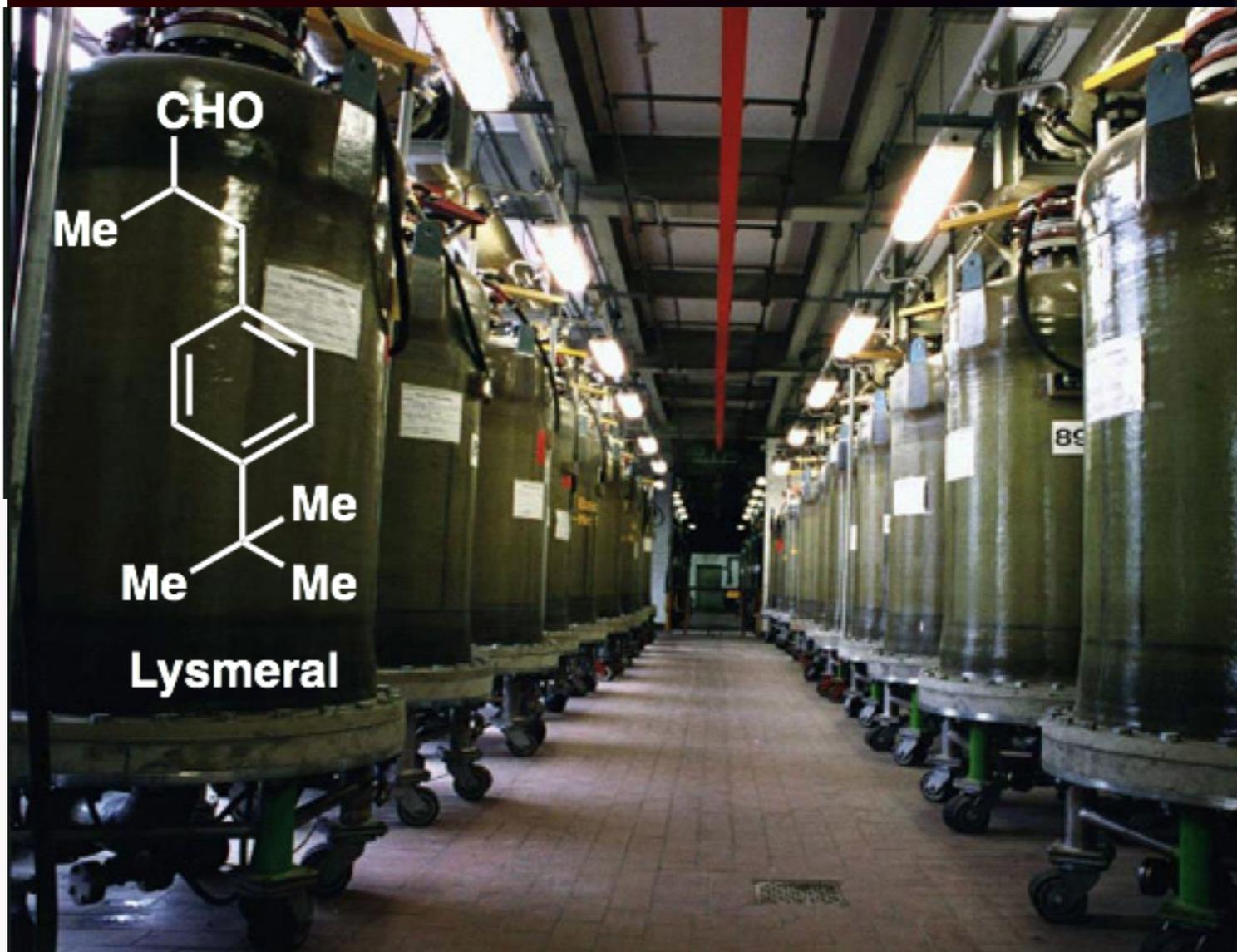
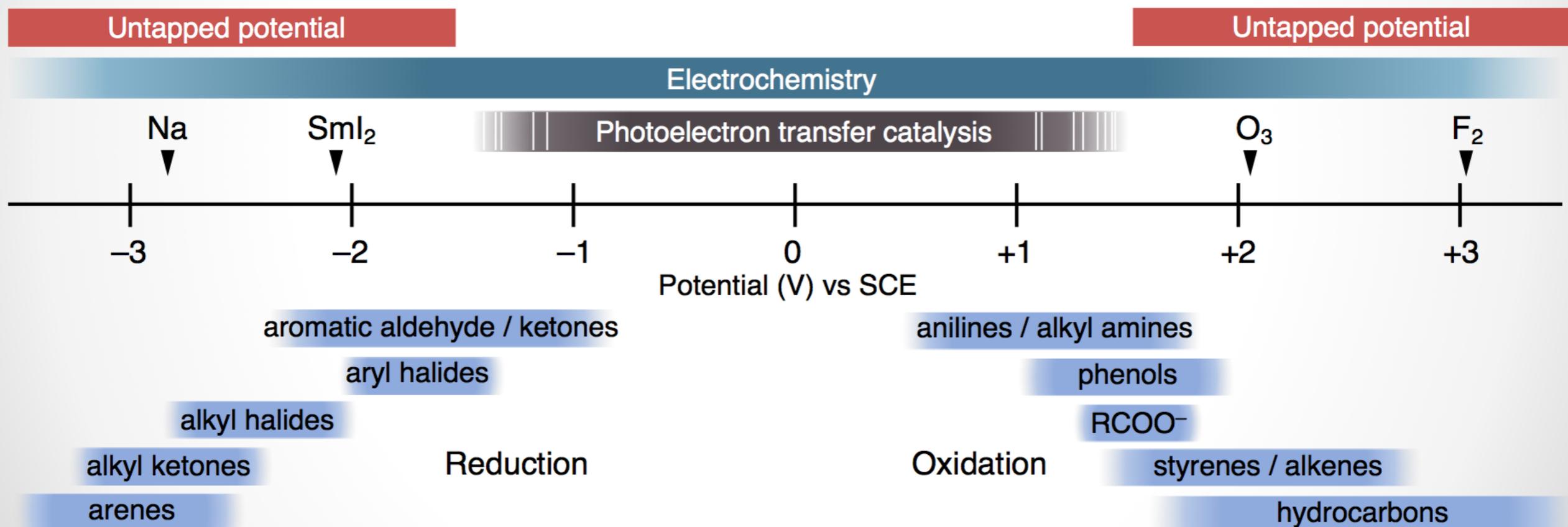
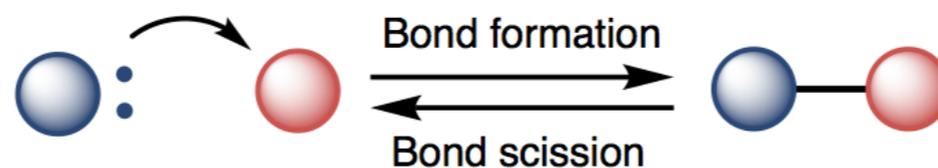


Image courtesy of Prof. Sigi Waldvogel

Why Electrochemistry?

Chemical reaction requires the **reorganization of electrons**



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

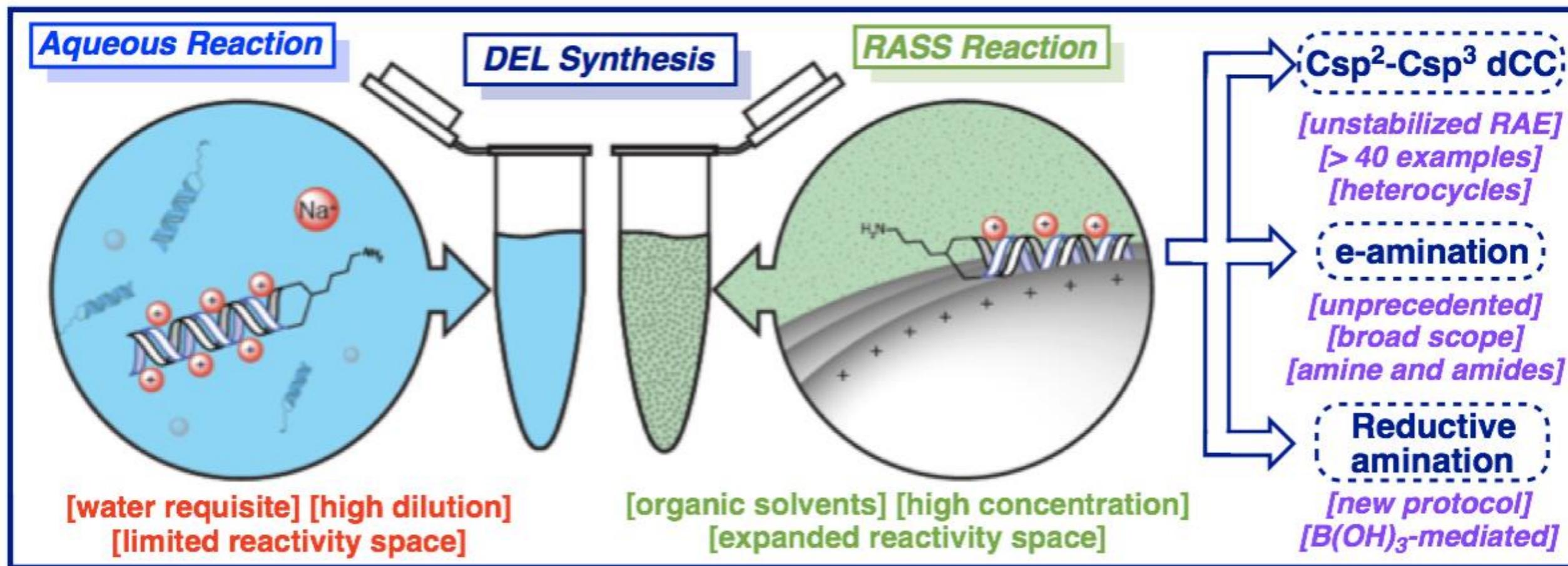
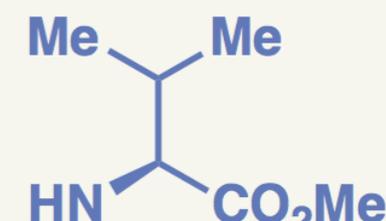
100g e-*A*

Br

Me

O

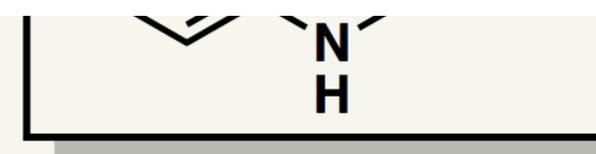
Ni(bpy)₃Br₂ (10 mol%)
nBu₄N⁺Br⁻ (0.2 M)



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

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

^a LiBr (0.89 M), DMA (0.1 M), 100 mA, 7 h.

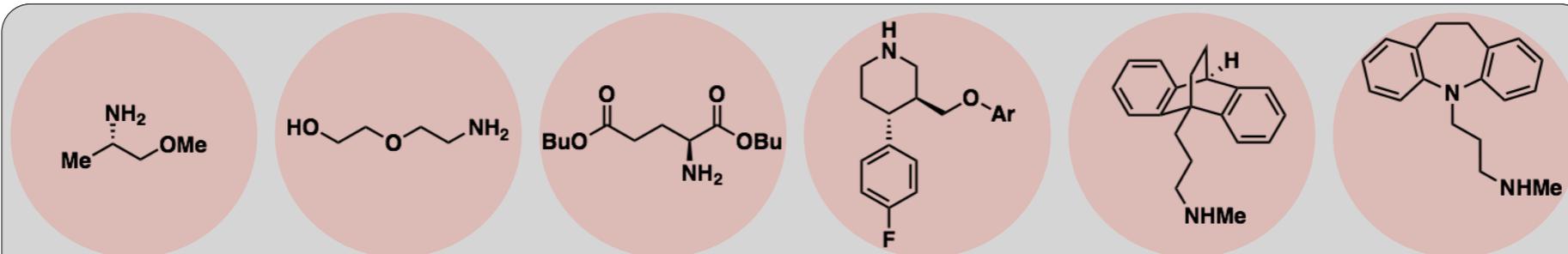


11-Step Synthesis of Teleocidins featuring E-amination, with H. Nakamura: *J. Am. Chem. Soc.* 2019, 141, 1494

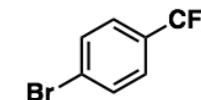
With Y. Kawamata, J. Vantourout, D. Hickey, H. Nakamura, Pfizer, Asymchem, NSF E-chem Cent, M. Neurock, H. White, S. Minter, *J. Am. Chem. Soc.* 2019, 141, 6392.

1st
generation^[1]

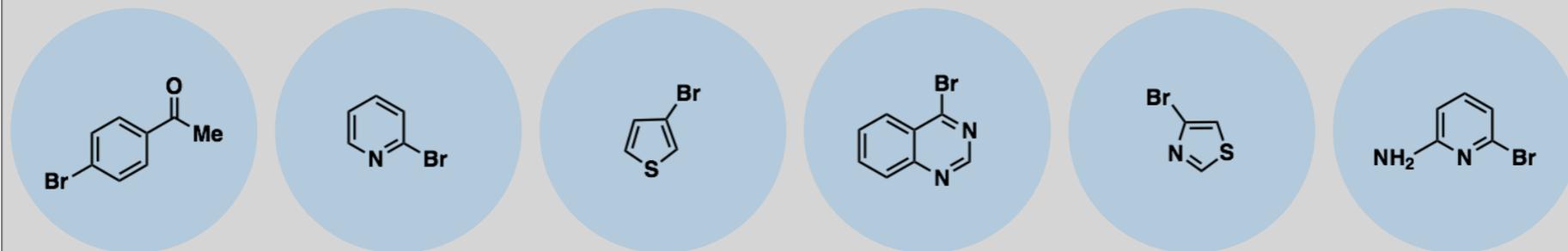
A



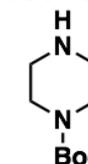
different amines
with



B

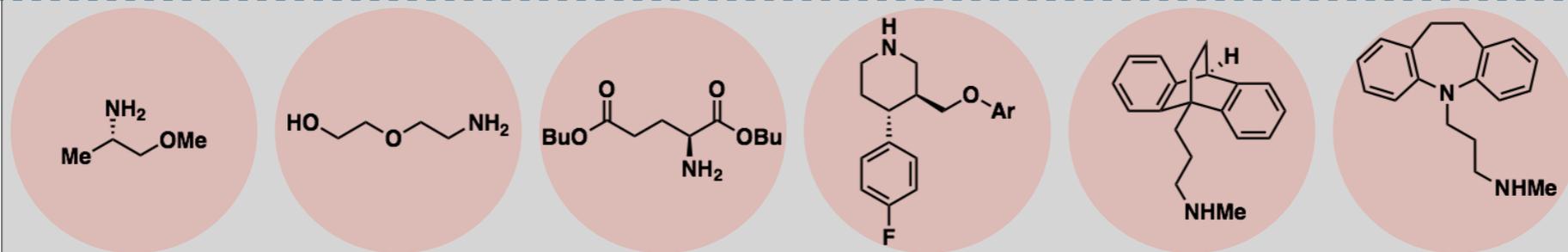


different ArBr
with

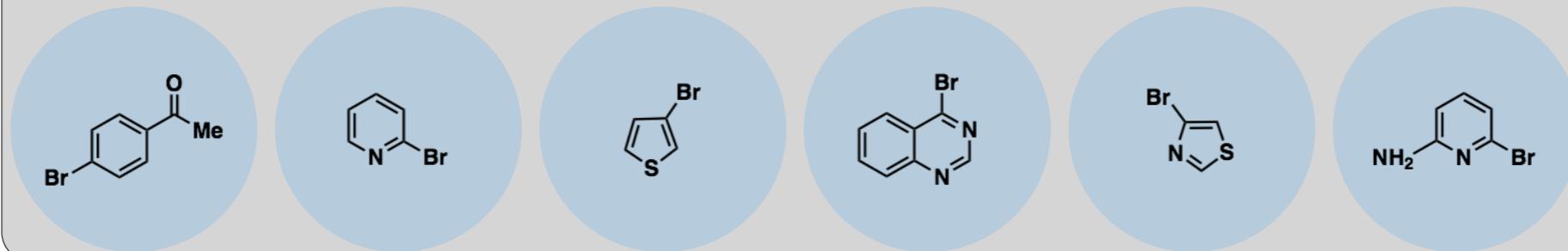


2nd
generation^[2]

C



D



1

2

3

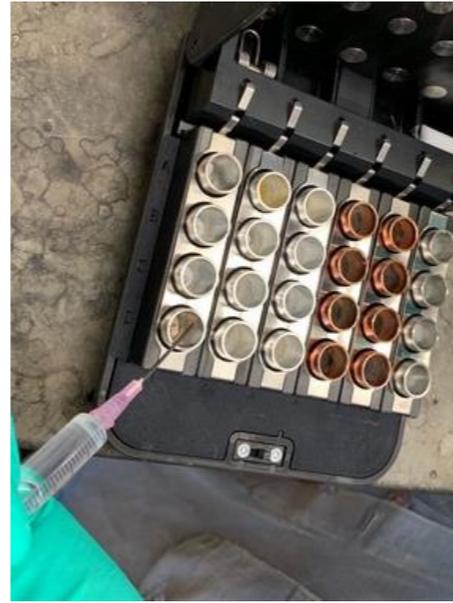
4

5

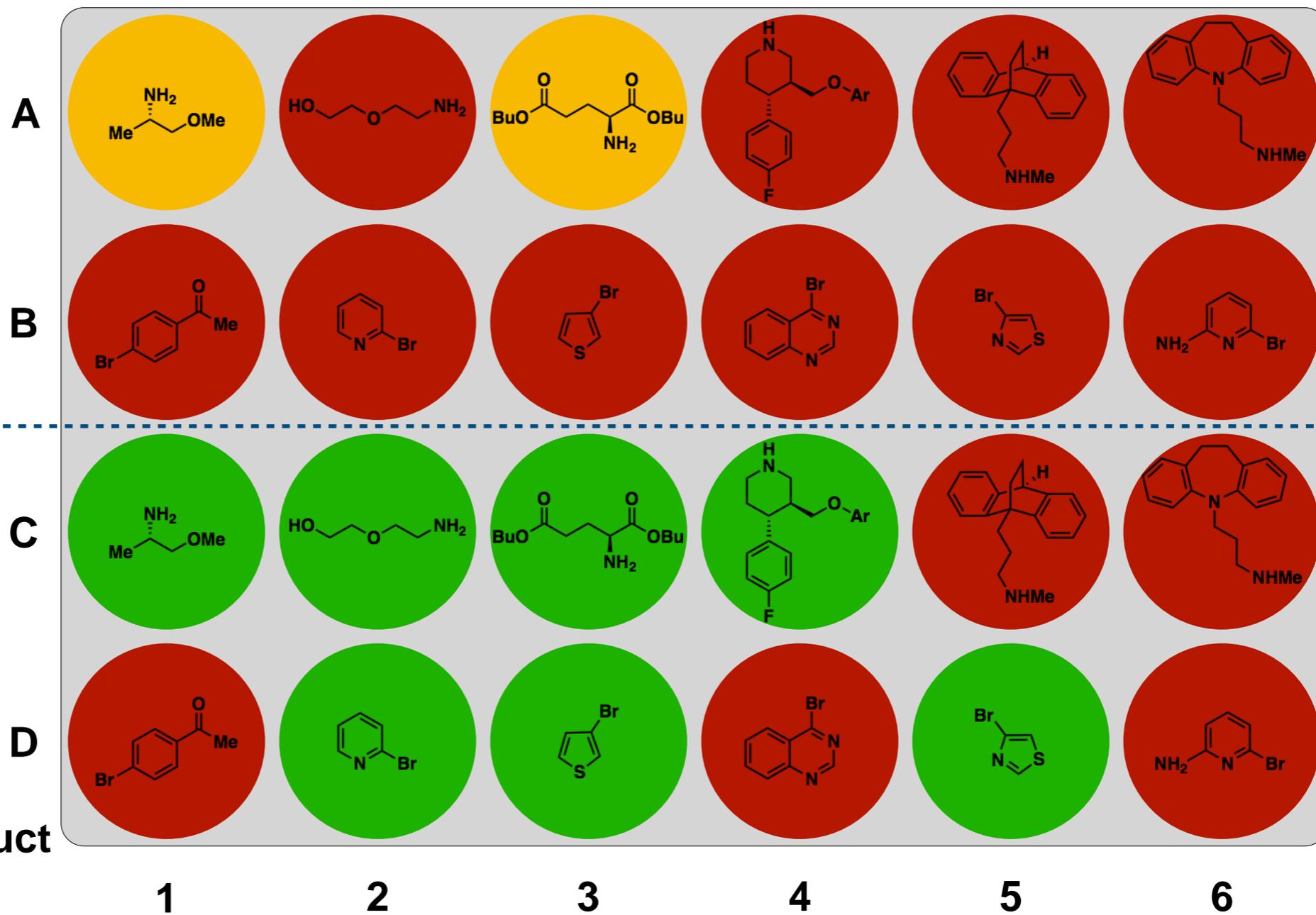
6

[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!*



1st
generation^[1]



● 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

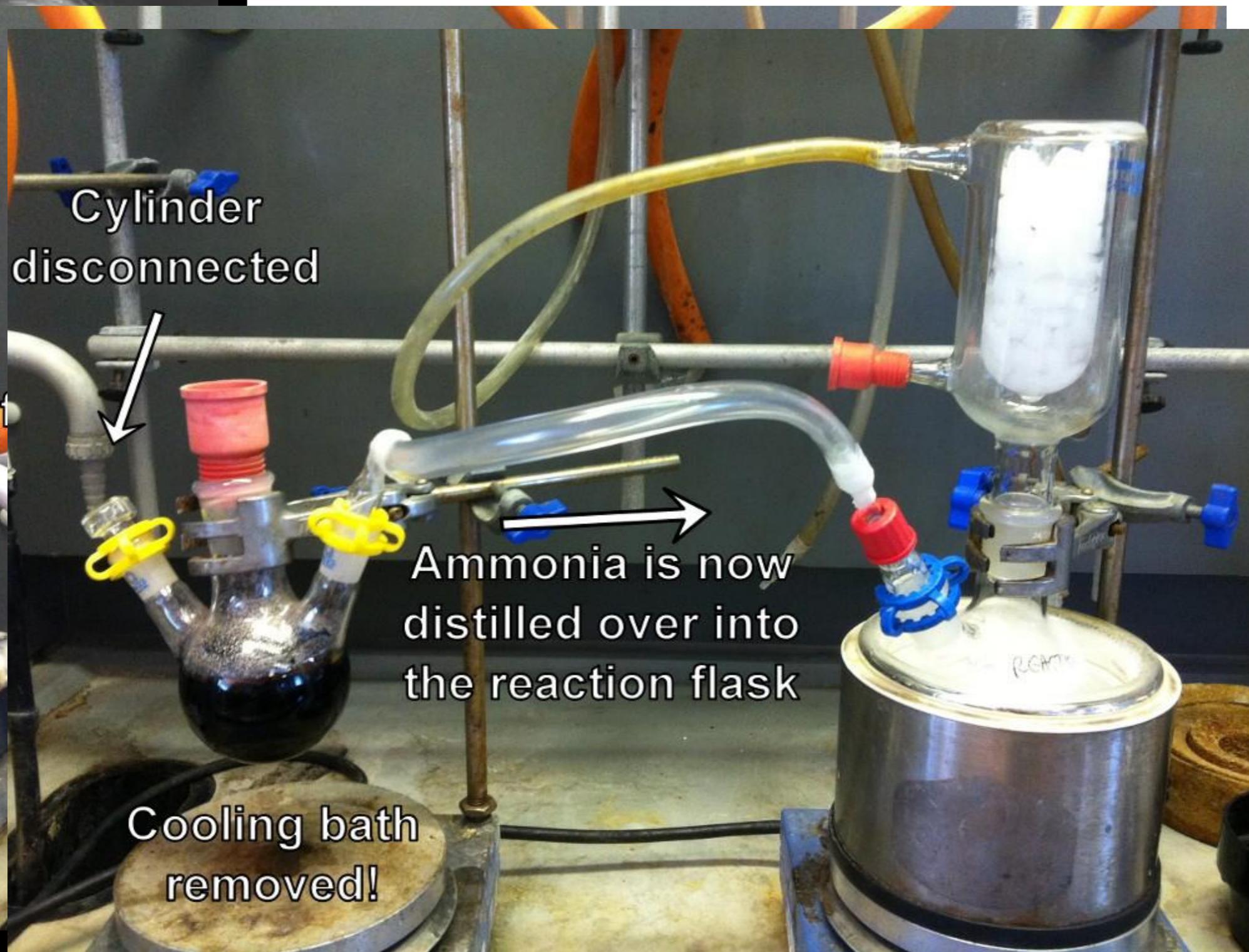
26%

426 votes · Final results

Electrifying a Classic Organic Reaction: Birch

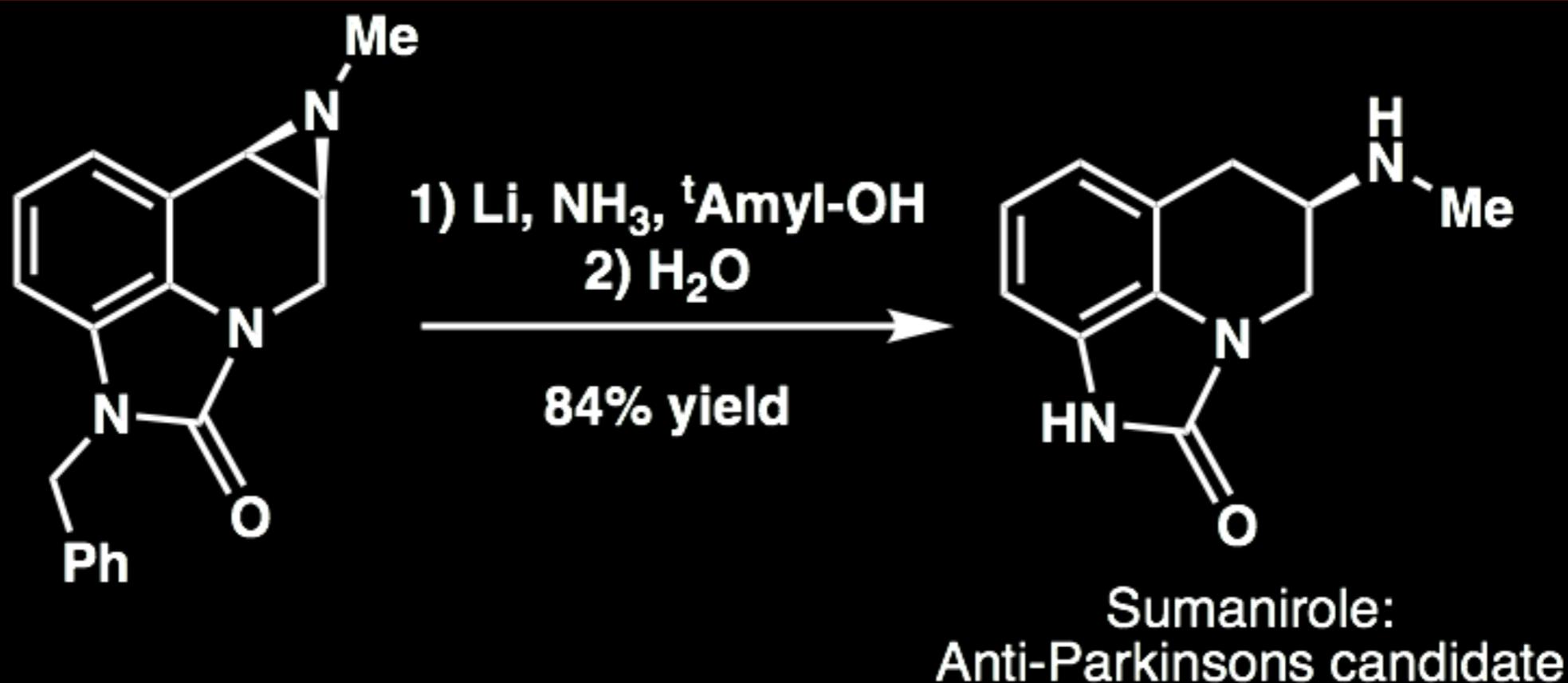
Birch reduction

From Wikipedia, the free encyclopedia



action was reported by R. B. Woodward at Oxford,^{[1][2][3][4]} which converted a five-membered ring into a propanone. The Birch reduction is a classic organic reduction. This reaction is of great importance in the discovery of that literature of organic chemistry.





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

**53 Kg batch, 2500 L of NH₃,
7 Kg Lithium**

- Enough NH₃ to fill three Boeing 747's at STP
- Equivalent to one 50 L tank (200 bar) of H₂ generated from quench of excess Li

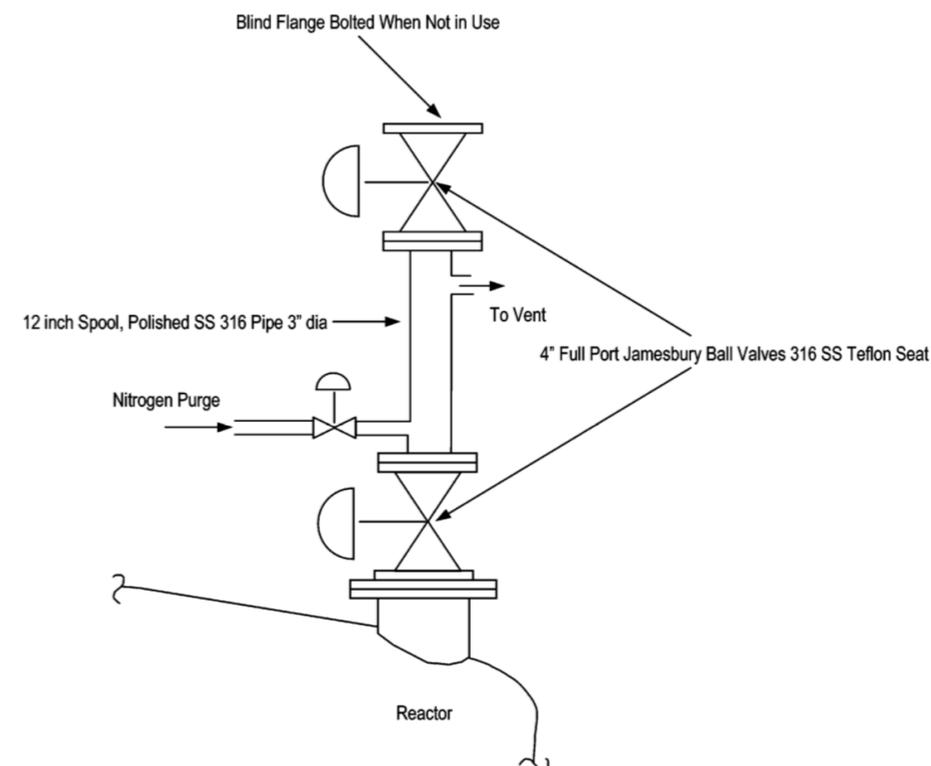
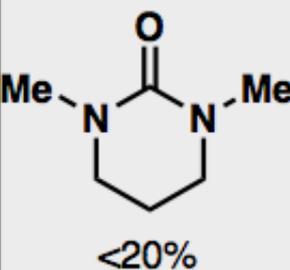
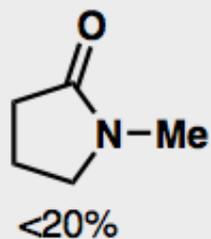


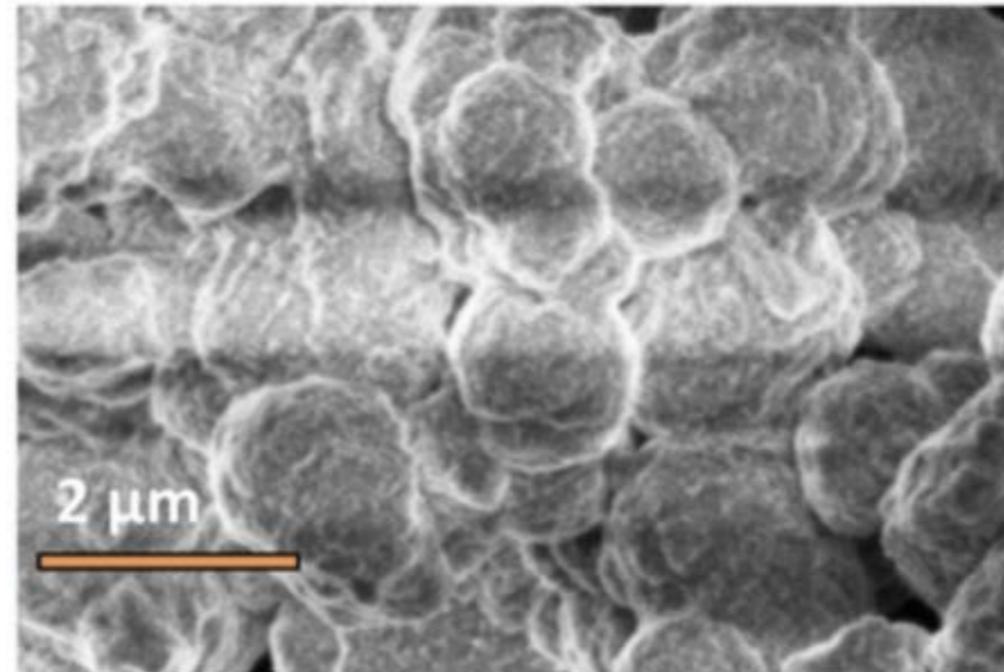
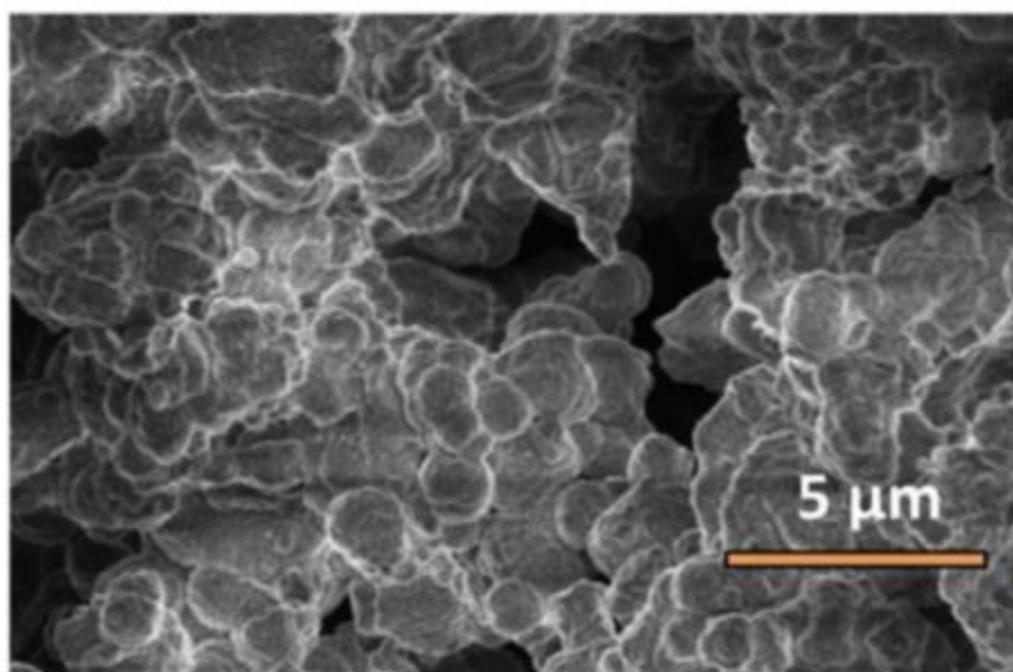
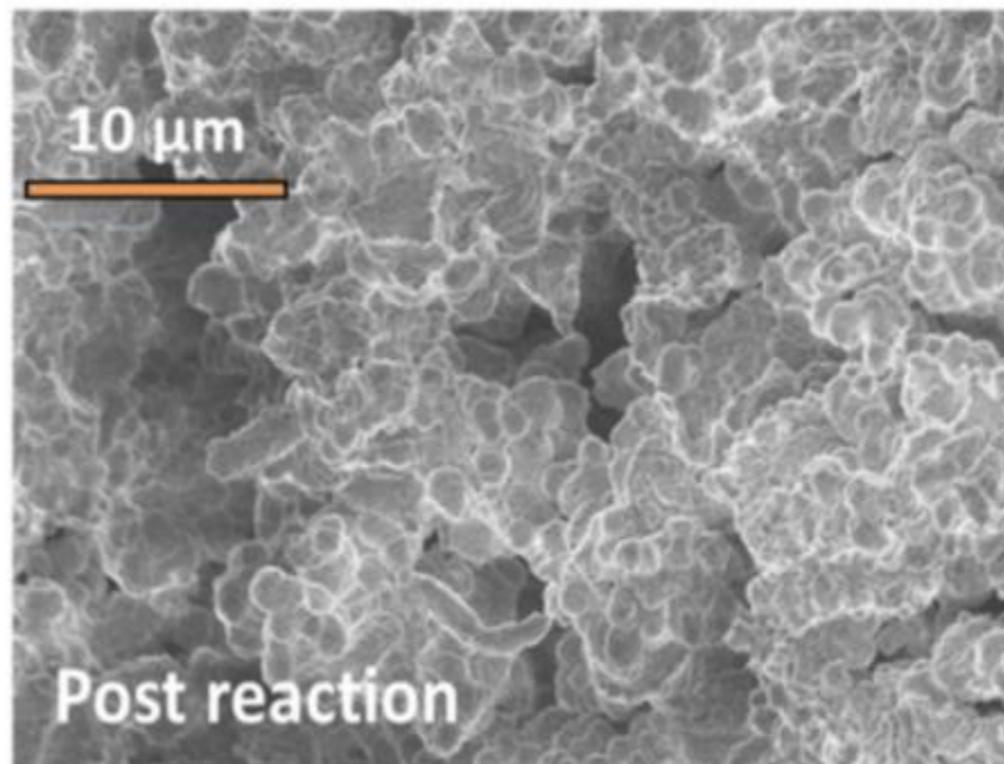
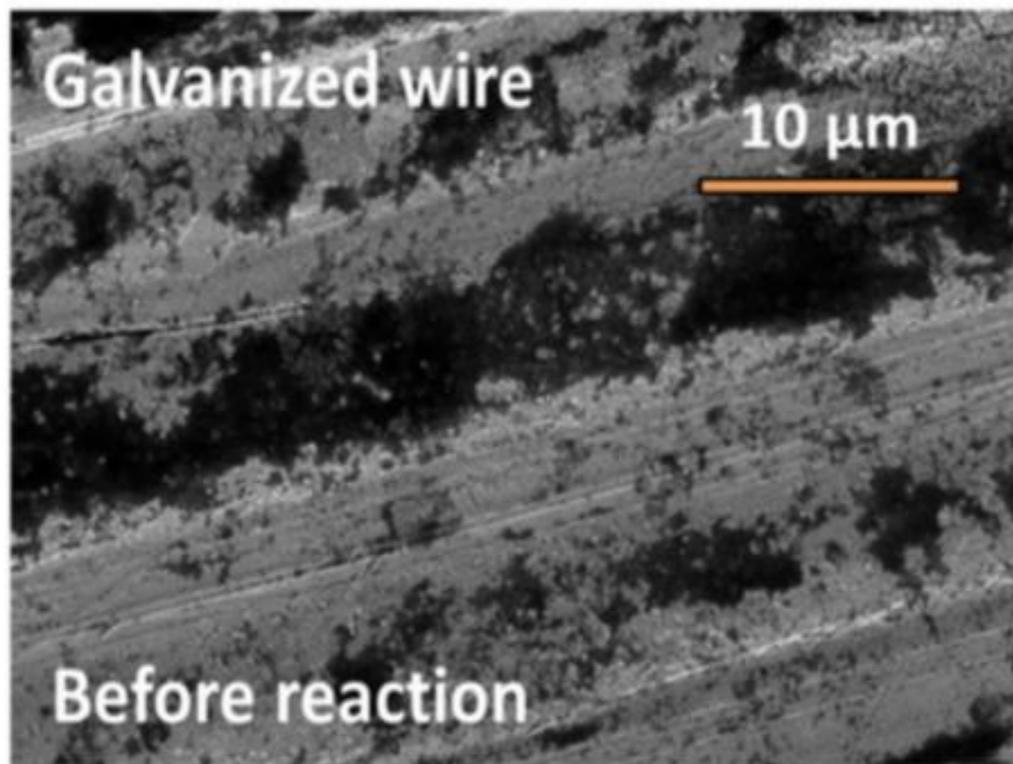
Figure 1. Schematic diagram for the lithium charging apparatus.

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

Li-ion battery additives



SEM Analysis



SEI: Solid Electrolyte Interface

ion
ntial
from
e
node

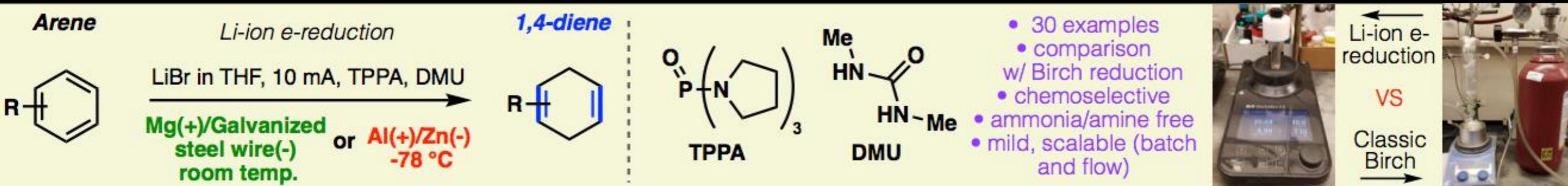
Commercial
electrodes
potentiostat

	By-prod.
0%	-
0%	-
0%	-
0%	-
0%	-
0%	-
0%	-
0%	30%
0%	14%
0%	<5%
0%	<5%

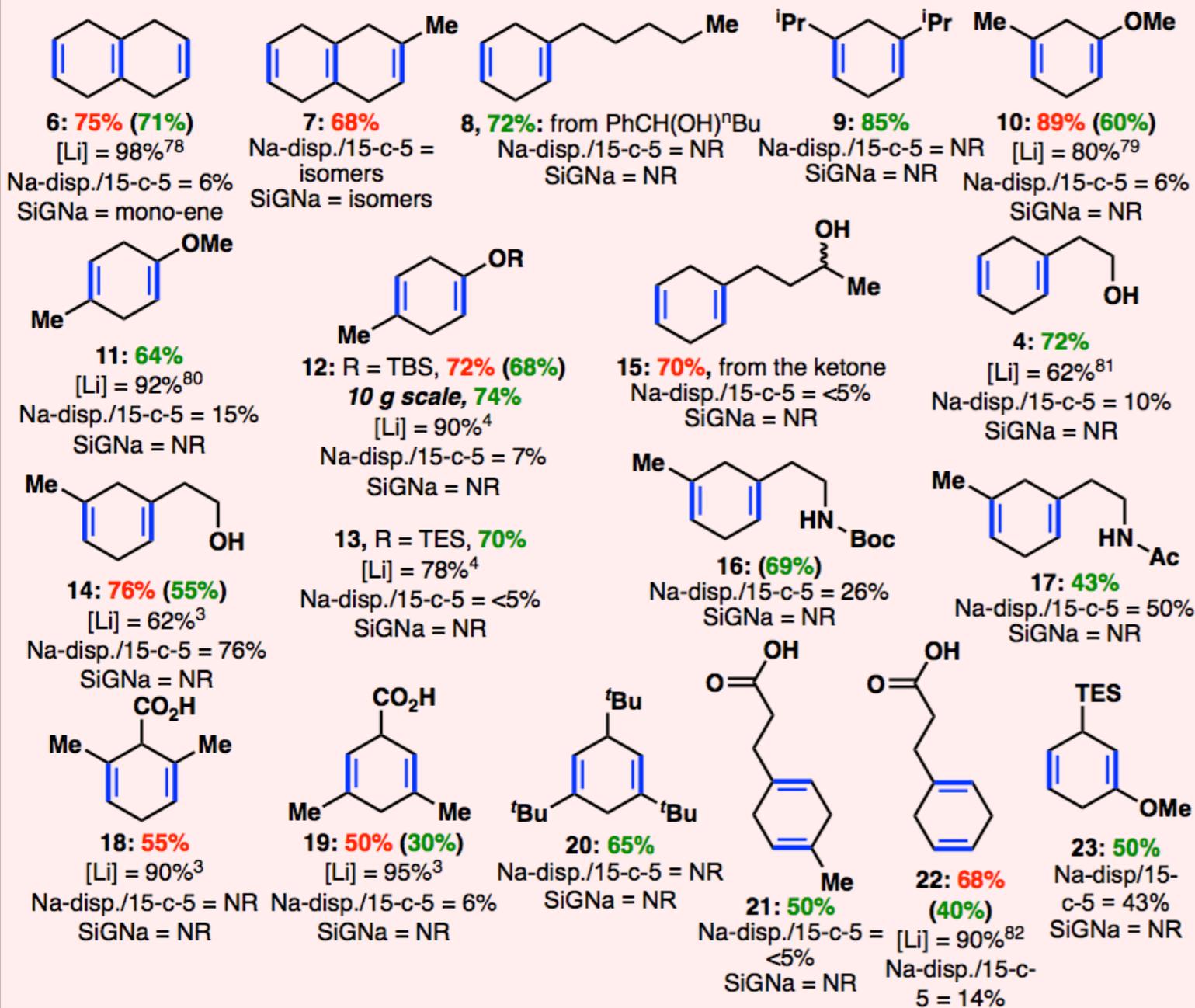
9 - 100% (+)/100% (-) 100% DMU, LiCl, TFA

IV H⁺ H⁻

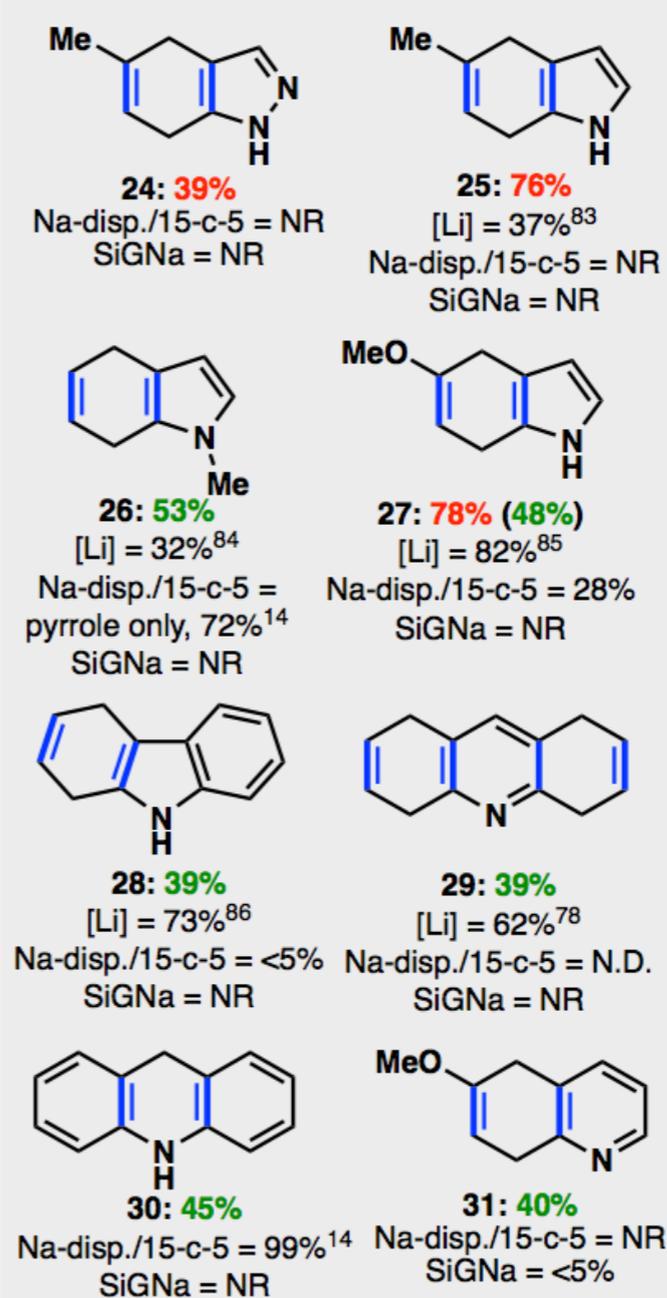
Li-Ion Electroreduction: Simple, Sustainable, Safe



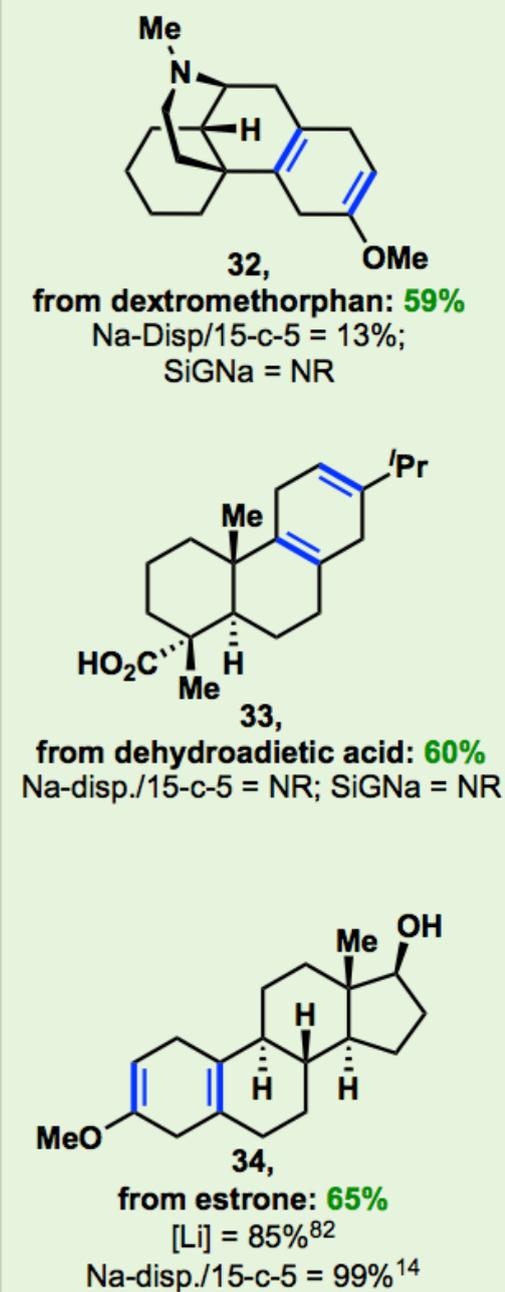
Carbocycles



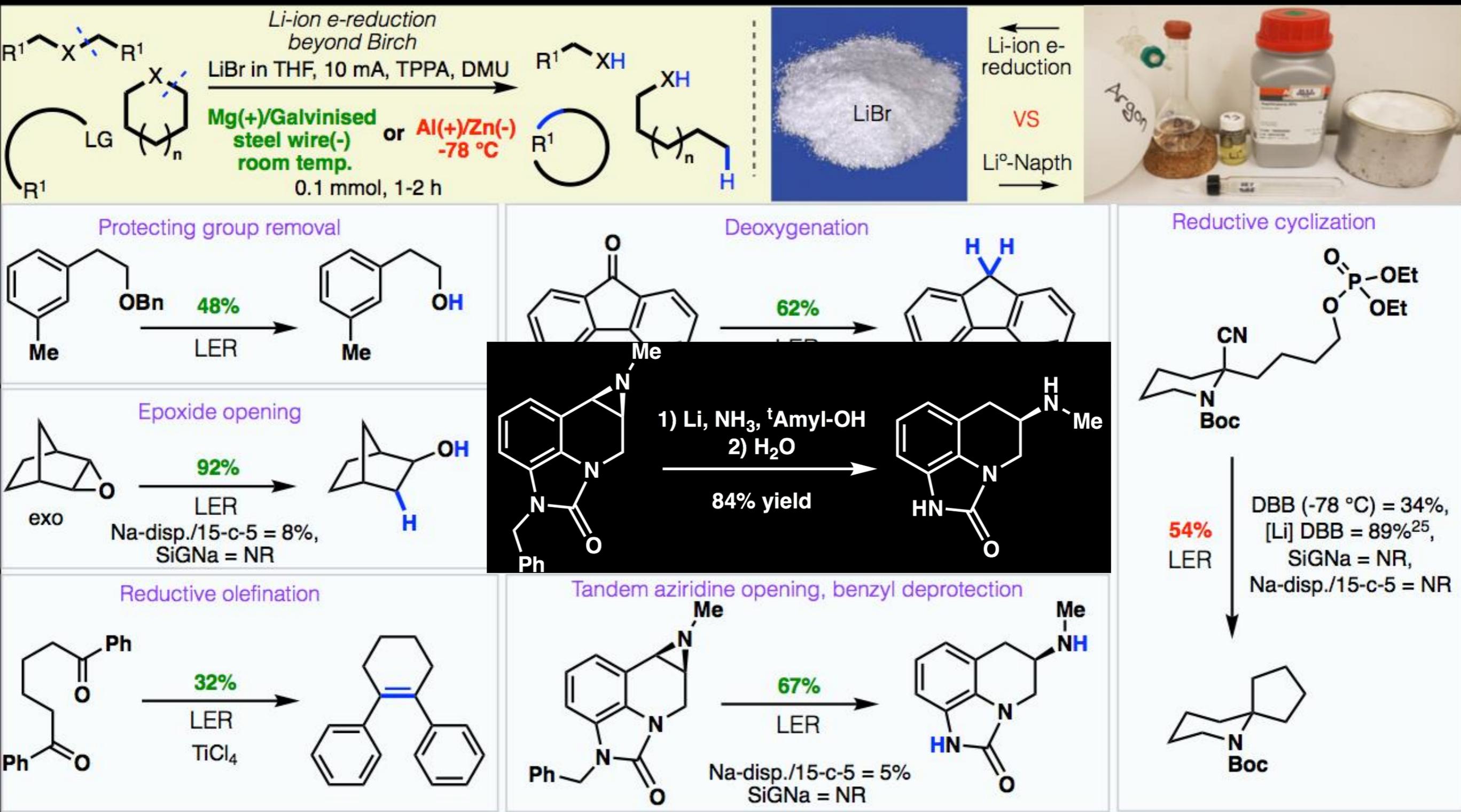
Heterocycles



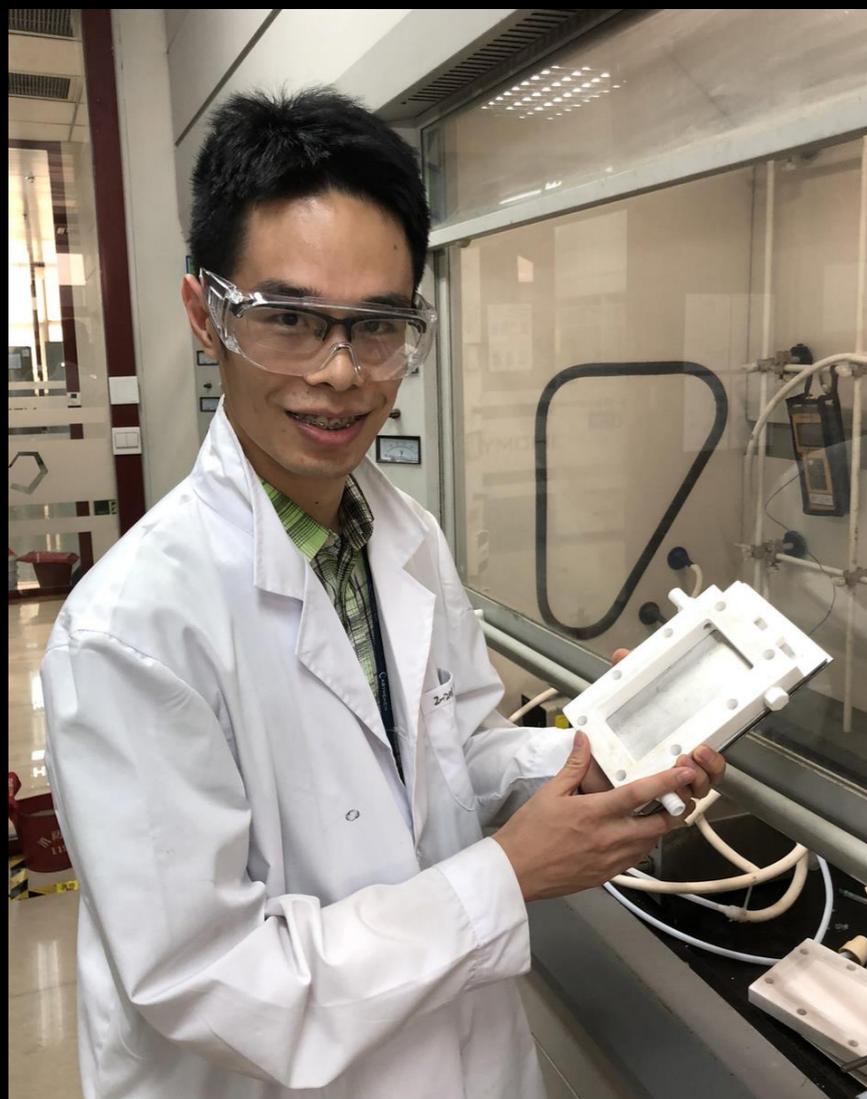
Natural product derivatives



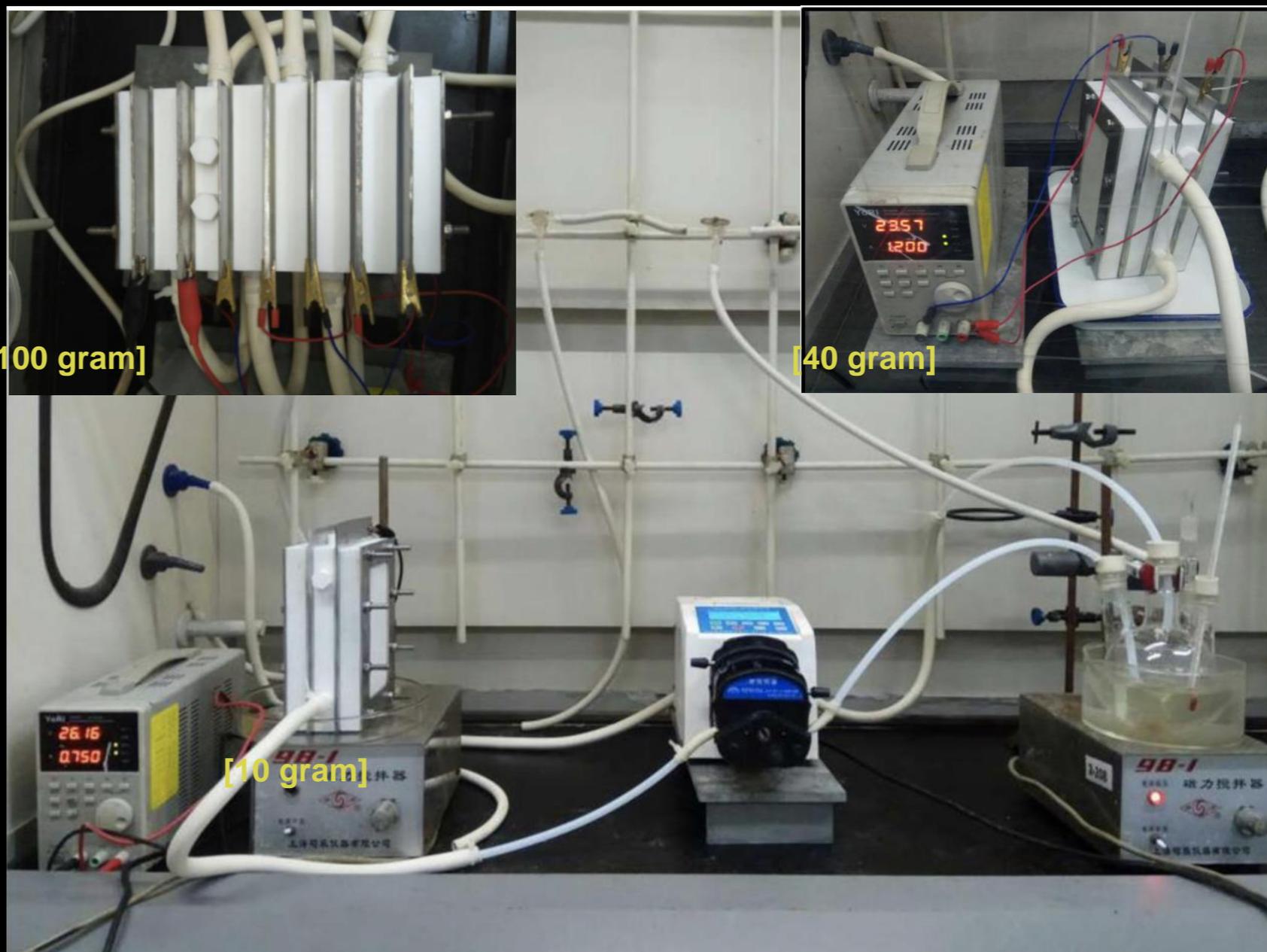
Li-Ion Electroreduction: Simple, Sustainable, Safe



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



Longrui Chen

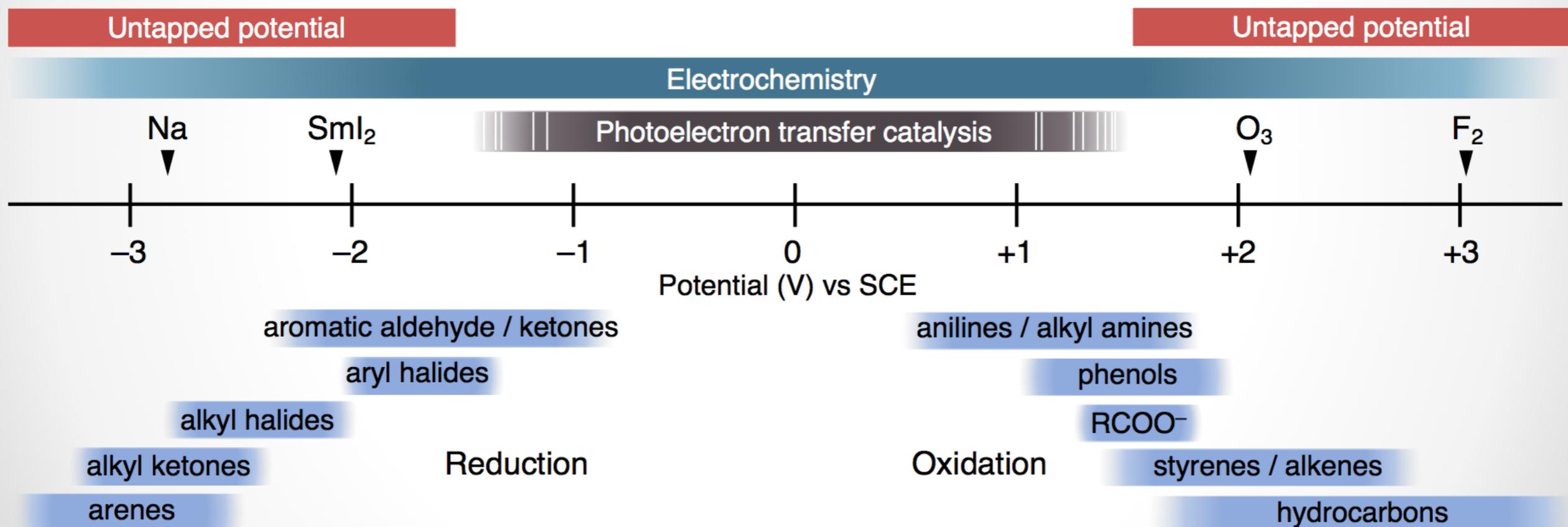
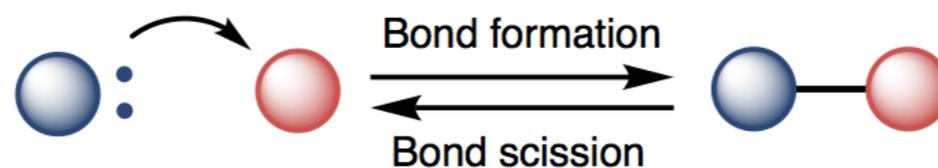


Modular flow setup gram to kilogram scale!!

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

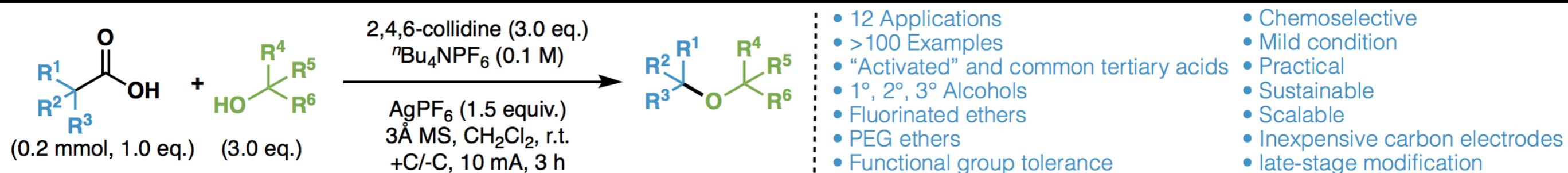
tBu **tBu** **tBu**
65%
Na-disp./15-c-5 = NR
SiGNa = NR

Me **iPr**
HO₂C **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

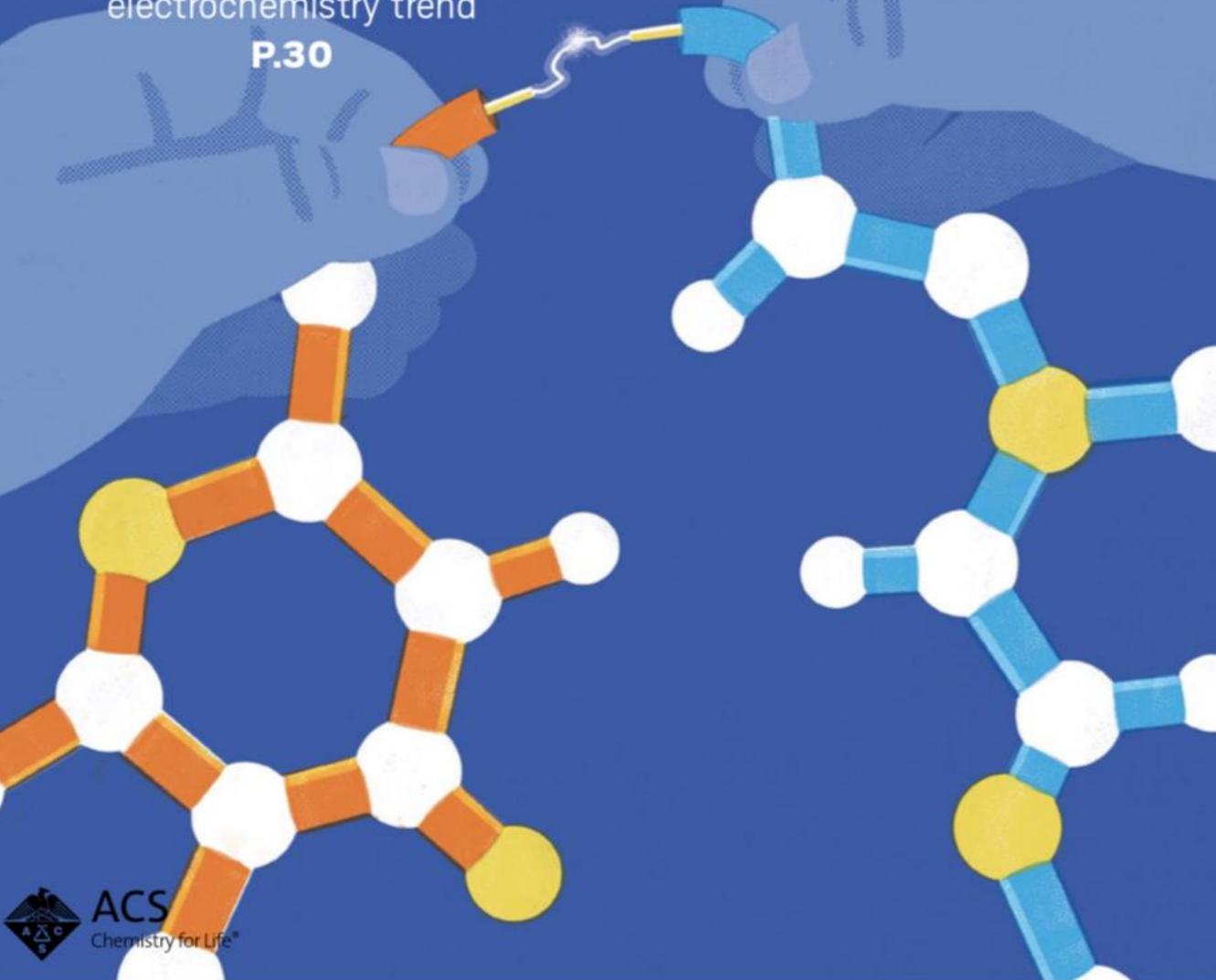
How does your salary compare? ACS survey returns **P.18**

Reining in science's plastic habit **P.22**

Pharma powers up

Medicinal and process chemists tap into the current electrochemistry trend

P.30

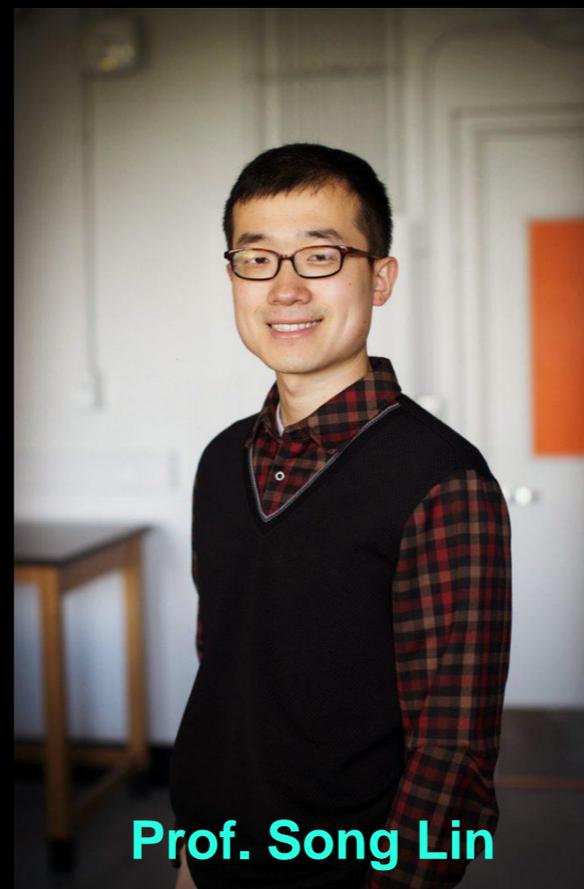


Cover story, Nov. 4, 2019

- Education
- Equipment



- Enablement
- Collaboration is key!**

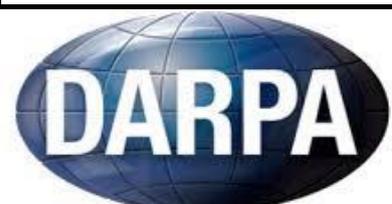


Prof. Song Lin



Prof. Kevin Moeller

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Current group members as of November, 2019:

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Staff Scientist: Julien Vantourout

-Postdoctoral Associates and Visiting Investigators-

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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)**