Making Synthetic Organic Electrochemistry Mainstream

Chemical Sciences Roundtable


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Book: portablechemistsconsultant.com
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

\[
\text{CHO} + 1.15 \text{ V} \text{ Et}_2\text{NBr} \rightarrow \text{dixiamycin} \quad 28\%
\]

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

Image courtesy of Prof. Sigi Waldvogel
Why Electrochemistry?

Chemical reaction requires the reorganization of electrons

- Bond formation
- Bond scission

Untapped potential

Electrochemistry

Potential (V) vs SCE

-3  -2  -1  0  +1  +2  +3

- Na  Sml₂  Photoelectron transfer catalysis  O₃  F₂

- aromatic aldehyde / ketones
- aryl halides
- alkyl halides
- alkyl ketones
- arenes

- Reduction

- anilines / alkyl amines
- phenols
- RCOO⁻
- styrenes / alkenes
- hydrocarbons

Chemical Space (molecular diversity)
What’s Holding Back Electrochemistry in Mainstream Synthesis?

Perception: “Alien Reactivity”

Perception and Partial Reality: Lack of Compelling Reactivity

• Same transforms, more sustainable (Process/Academic interest)
• New transforms (if powerfully enabling, everyone wants these)
• New selectivity (everyone wants these for truly useful reactions)


Yu Kawamata

ElectraSyn 2.0

With C. Li, Y. Kawamata, A. Manwama, G. Ontzourou, J. Stabler (Pfizer), and M. Chen (Pfizer), Q. Hu (Asymchem), D. Bao (Asymchem), M.


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Electrochemical Amination: A Useful Tool for Green Aryl Amination


1st generation[1]

2nd generation[2]


* The reactions are run under air!
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
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
**Birch reduction**

From Wikipedia, the free encyclopedia

The Birch reduction is a classical organic reaction for reducing ketones to alcohols using lithium or sodium metal in liquid ammonia. The reaction was discovered by Arthur Birch in the 1950s and is widely used in organic synthesis.

Ammonia is now distilled over into the reaction flask.

Cooling bath removed!
Resurrecting “Lost” Reductive Chemistry

53 Kg batch, 2500 L of NH$_3$, 7 Kg Lithium

- Enough NH$_3$ to fill three Boeing 747's at STP
- Equivalent to one 50 L tank (200 bar) of H$_2$ generated from quench of excess Li

Sumanireole: Anti-Parkinsons candidate

Translating Lessons from Li-Ion Batteries for Organic Synthesis

Li-ion battery additives

SEM Analysis

Before reaction

Post reaction

Galvanized wire

Li-Ion Electroreduction: Simple, Sustainable, Safe

Li-Ion Electroreduction: Simple, Sustainable, Safe

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

Longrui Chen

Modular flow setup gram to kilogram scale!!

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- Na

- aromatic aldehyde / ketones
- aryl halides
- alkyl halides
- alkyl ketones
- arenes

- anilines / alkyl amines
- phenols
- RCOO⁻
- styrenes / alkenes
- hydrocarbons

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

**Strongly reducing:**

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

**Strongly oxidizing:**

- 12 Applications
- >100 Examples
- “Activated” and common tertiary acids
- 1°, 2°, 3° Alcohols
- Fluorinated ethers
- PEG ethers
- Functional group tolerance
- Chemoselective
- Mild condition
- Practical
- Sustainable
- Scalable
- Inexpensive carbon electrodes
- late-stage modification

Parting Thoughts

• Education
• Equipment
• Enablement

Collaboration is key!

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