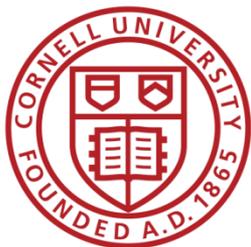


New Catalytic Strategies for Selective Organic Electrosynthesis

Song Lin
Cornell University

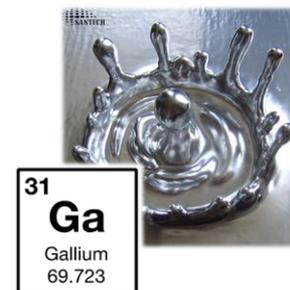
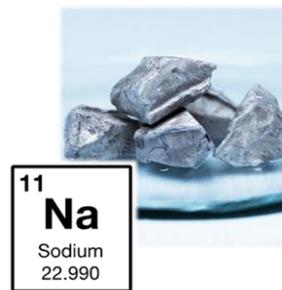
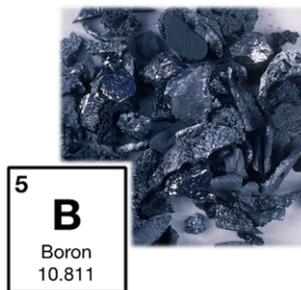
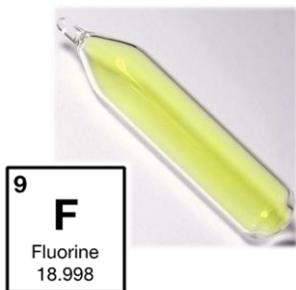
Chemical Sciences Roundtable Workshop
Washington, DC
November 18, 2019



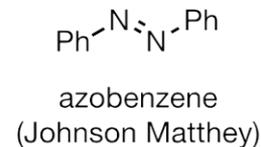
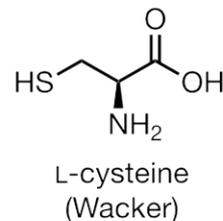
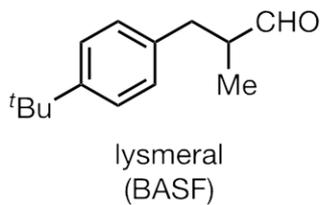
Brief History of Electrosynthesis

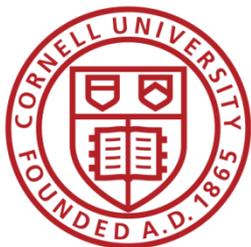
From element discovery to fine chemical synthesis

Examples of chemical elements discovered or isolated electrochemically:

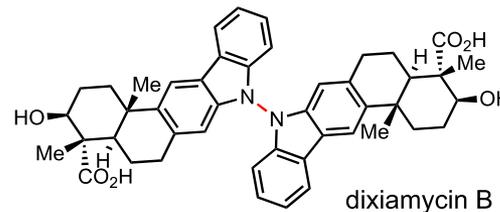
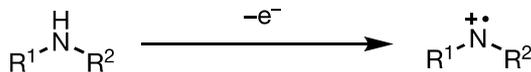
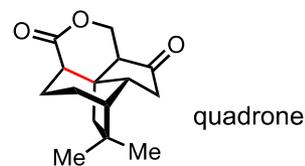
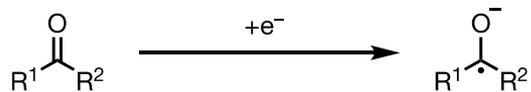
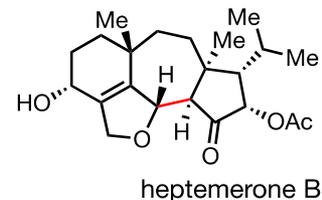
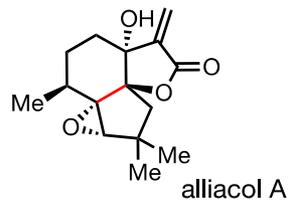
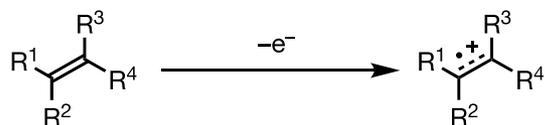
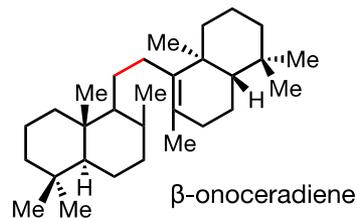
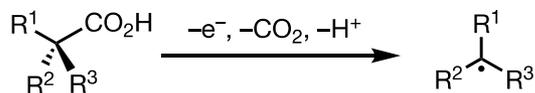


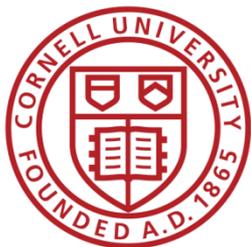
Examples of fine chemicals produced electrochemically:





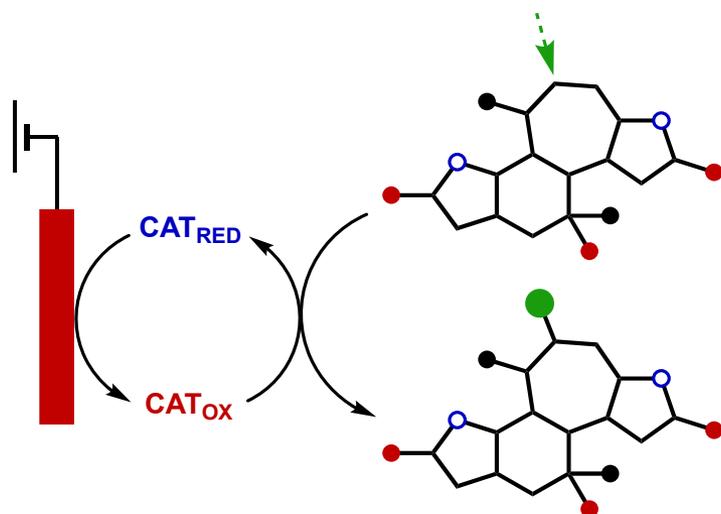
Application of Electrochemistry in Organic Synthesis

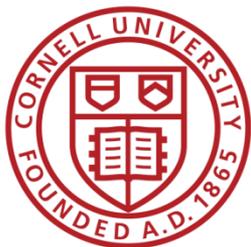




Overview of Research in the Lin Laboratory

Electrocatalysis as a new avenue for reaction discovery



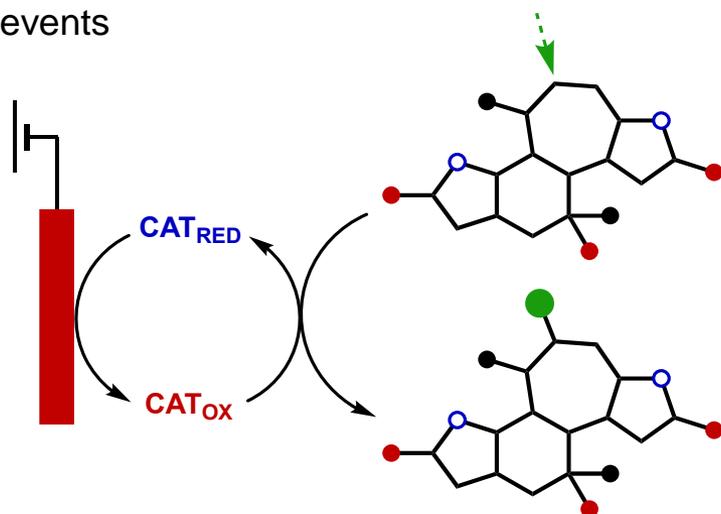


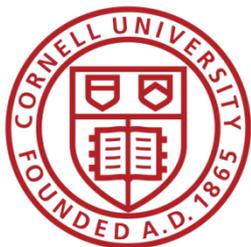
Overview of Research in the Lin Laboratory

Electrocatalysis as a new avenue for reaction discovery

Electrochemistry

- Precise potential control
- Direct generation of radical intermediates
- Integration of multiple redox events
- External temporal control



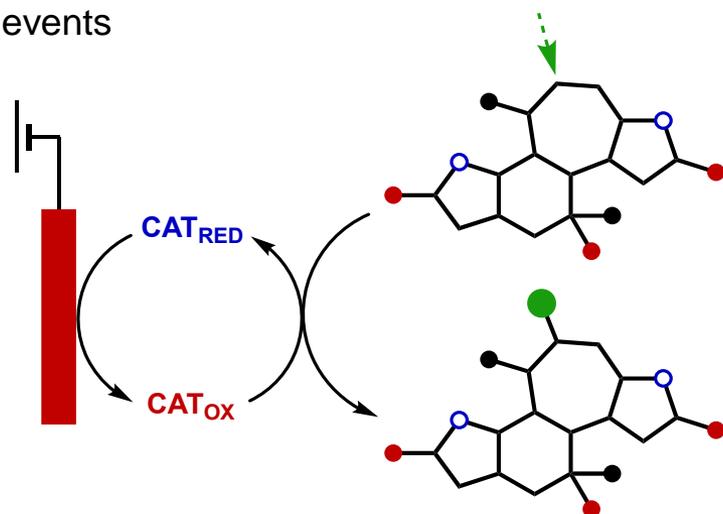


Overview of Research in the Lin Laboratory

Electrocatalysis as a new avenue for reaction discovery

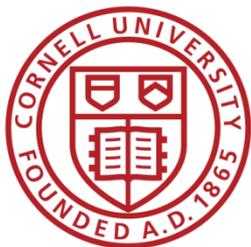
Electrochemistry

- Precise potential control
- Direct generation of radical intermediates
- Integration of multiple redox events
- External temporal control



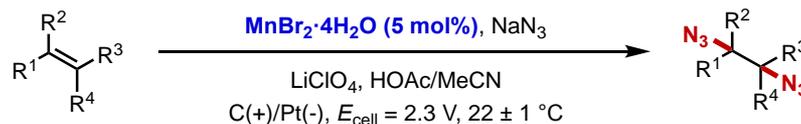
Catalysis

- Promote reaction kinetics
- Control chemoselectivity
- Impart stereoselectivity

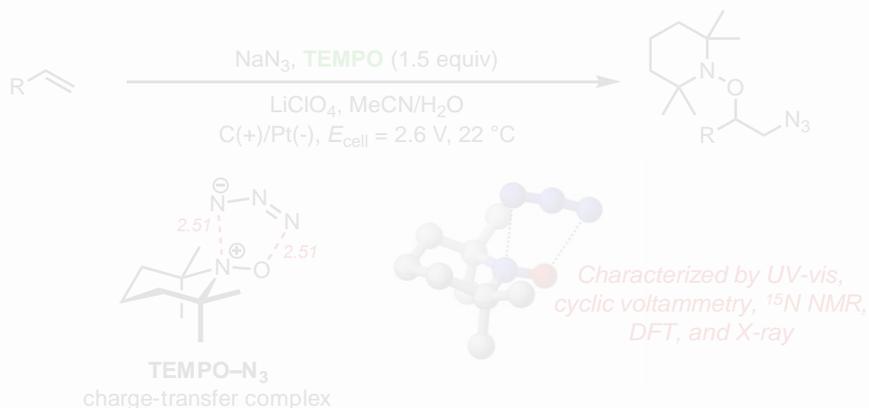


A Trilogy of Electrochemical Alkene Azidation

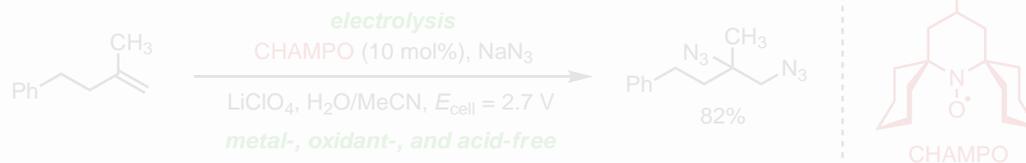
1st-Generation Alkene Diazidation: Mn Catalysis

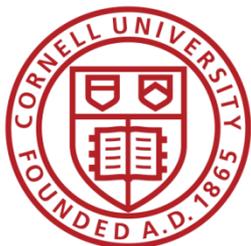


Electrochemical Azidoxygenation: Mechanistic Investigation



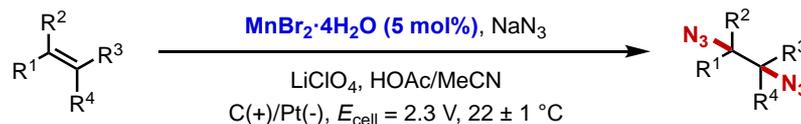
2nd-Generation Alkene Diazidation: Aminoxyl Catalysis



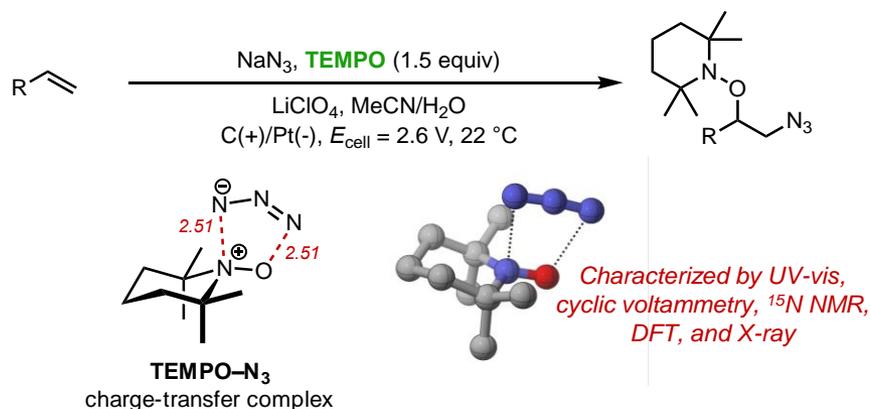


A Trilogy of Electrochemical Alkene Azidation

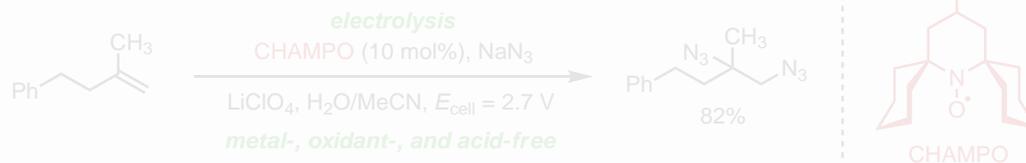
1st-Generation Alkene Diazidation: Mn Catalysis

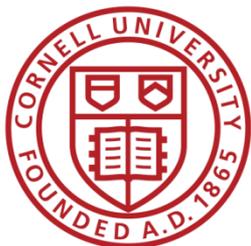


Electrochemical Azidoxygenation: Mechanistic Investigation



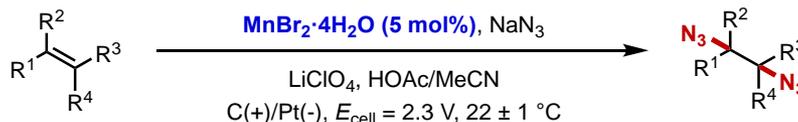
2nd-Generation Alkene Diazidation: Aminoxyl Catalysis



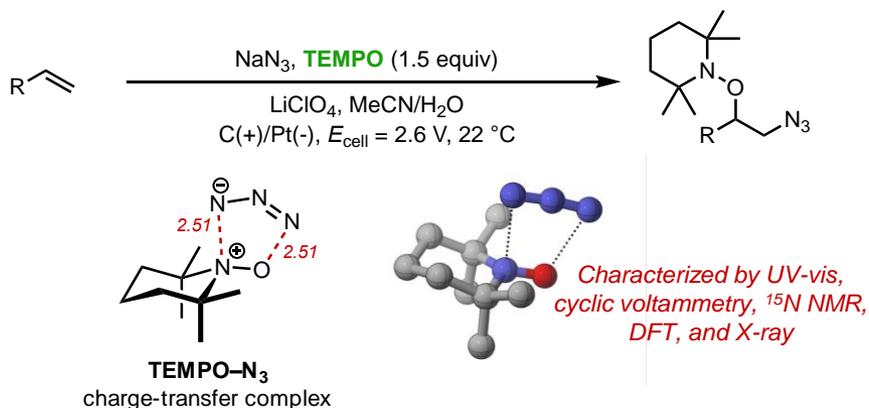


A Trilogy of Electrochemical Alkene Azidation

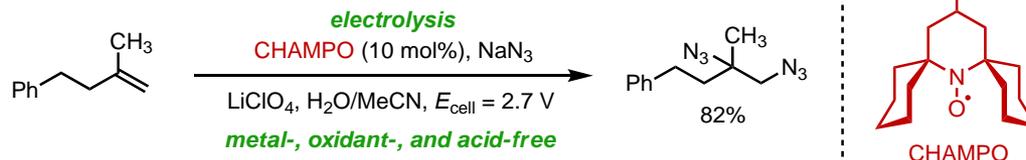
1st-Generation Alkene Diazidation: Mn Catalysis

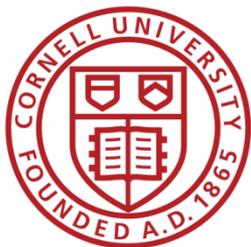


Electrochemical Azidoxygenation: Mechanistic Investigation



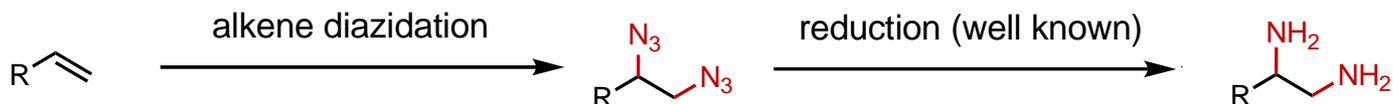
2nd-Generation Alkene Diazidation: Aminoxyl Catalysis



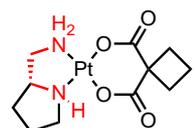


Research Problem: Synthesis of Vicinal Diamines

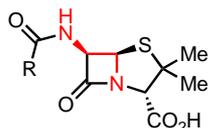
Diazidation-reduction provides a potentially general approach to diamines



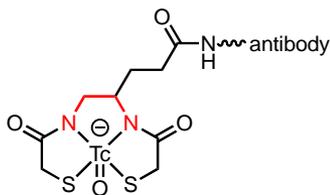
Medicinally relevant compounds



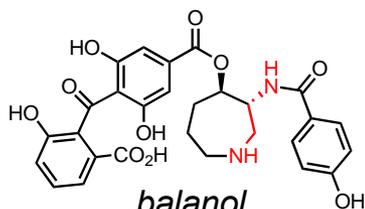
DWA 2114R
(anti-tumor)



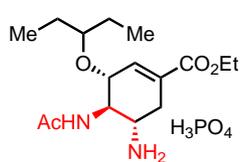
penicillins
(antibiotics)



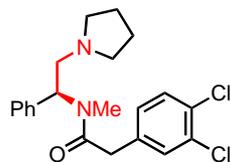
(radioactive imaging)



balanol
(anti-cancer)

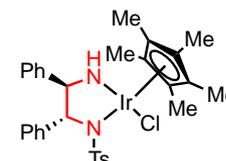
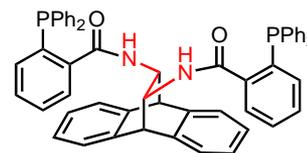
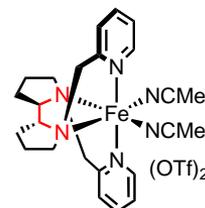
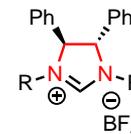
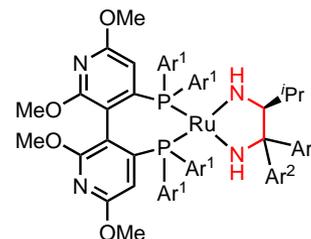
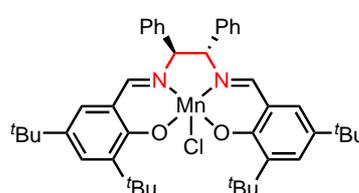


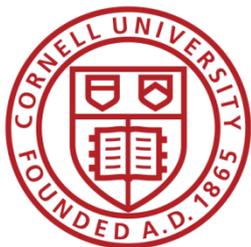
Tamiflu®
(anti-virus)



ICI-199,411
(k agonist)

Classic catalysts and ligands

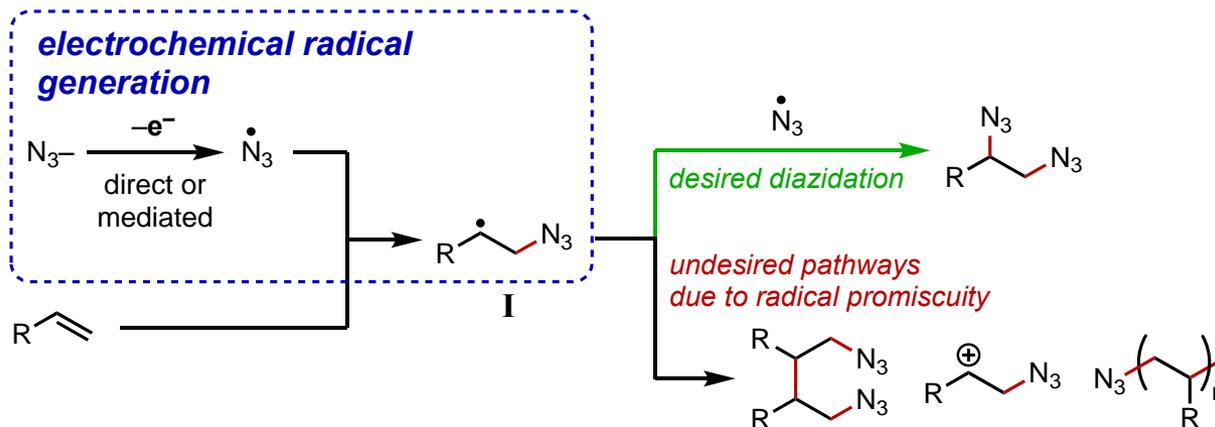


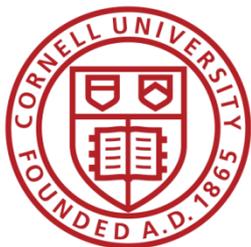


Initial Proof of Concept

An electrochemically driven radical pathway

Working hypothesis:

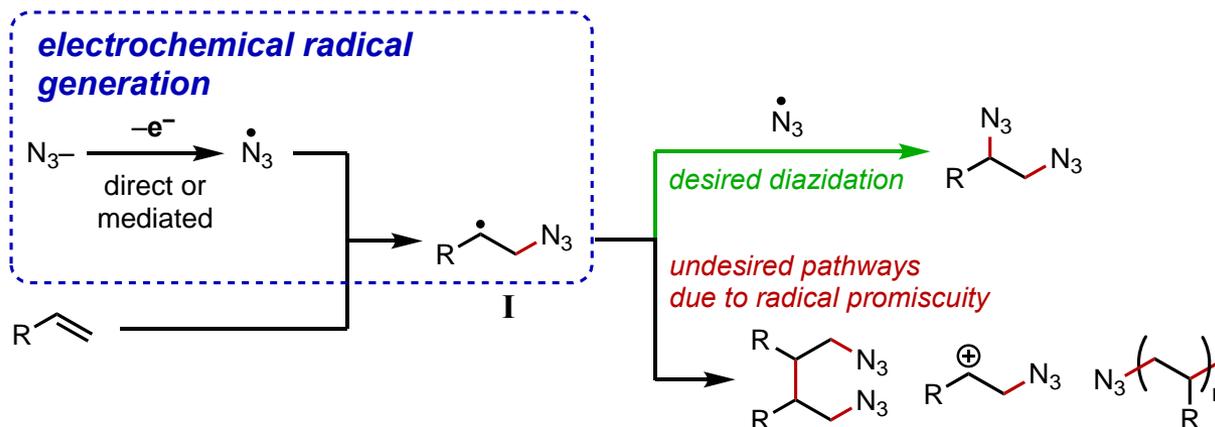




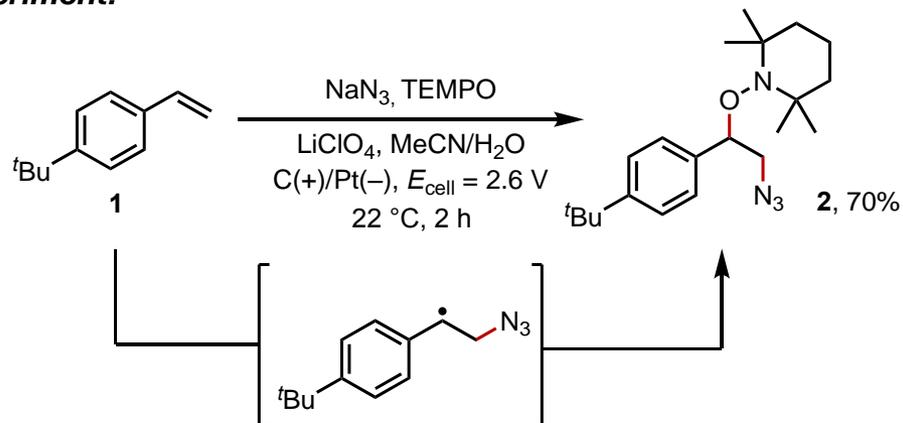
Initial Proof of Concept

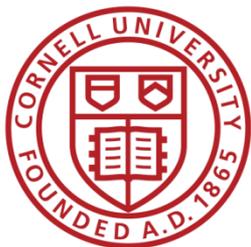
Control experiments shed light on key radical events

Working hypothesis:



Proof-of-concept experiment:

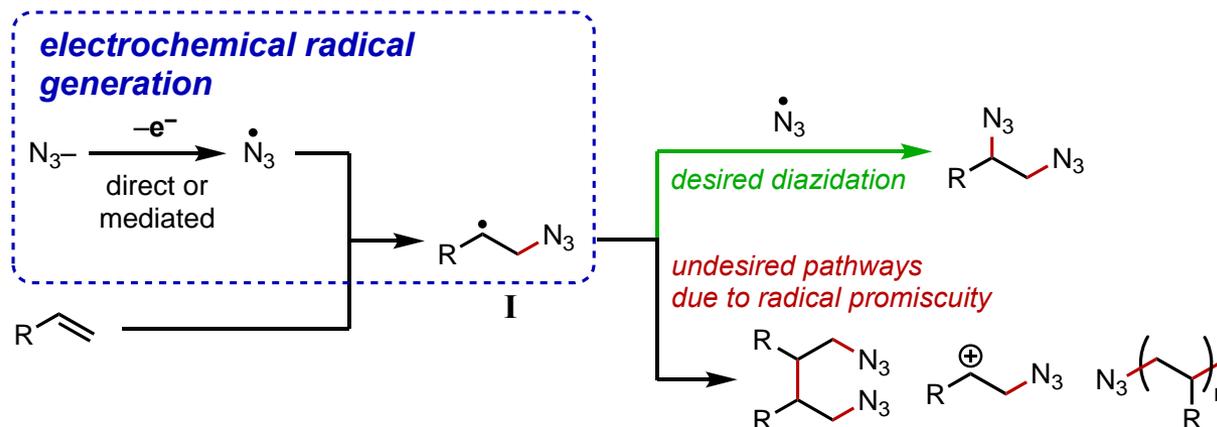




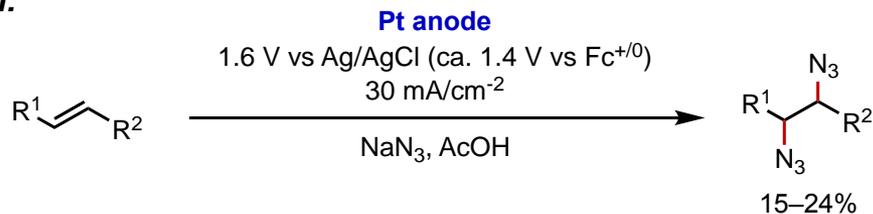
Initial Proof of Concept

Control experiments shed light on key radical events

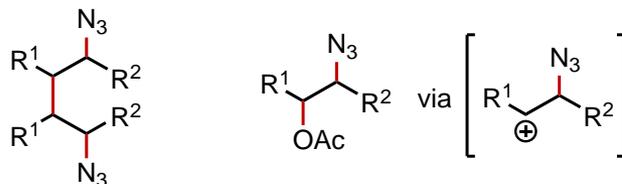
Working hypothesis:

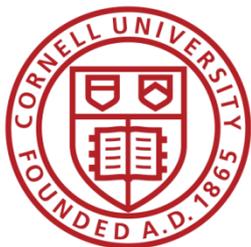


Literature information:



Major byproducts:

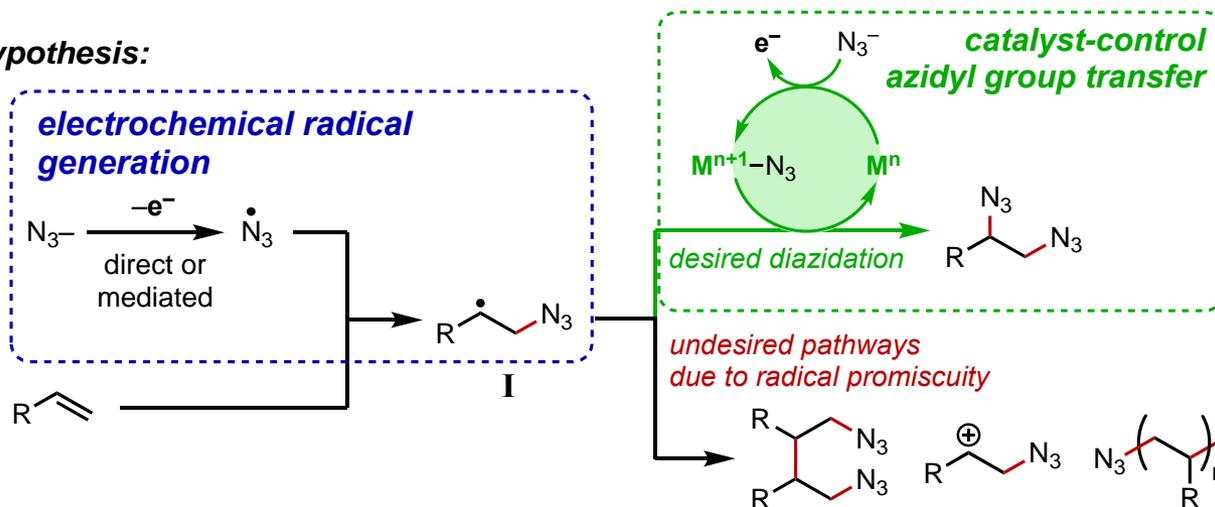


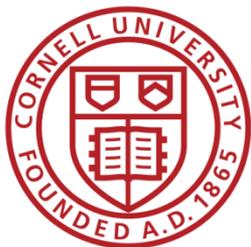


Initial Proof of Concept

Searching for an electrocatalyst to promote the diazidation

Working hypothesis:

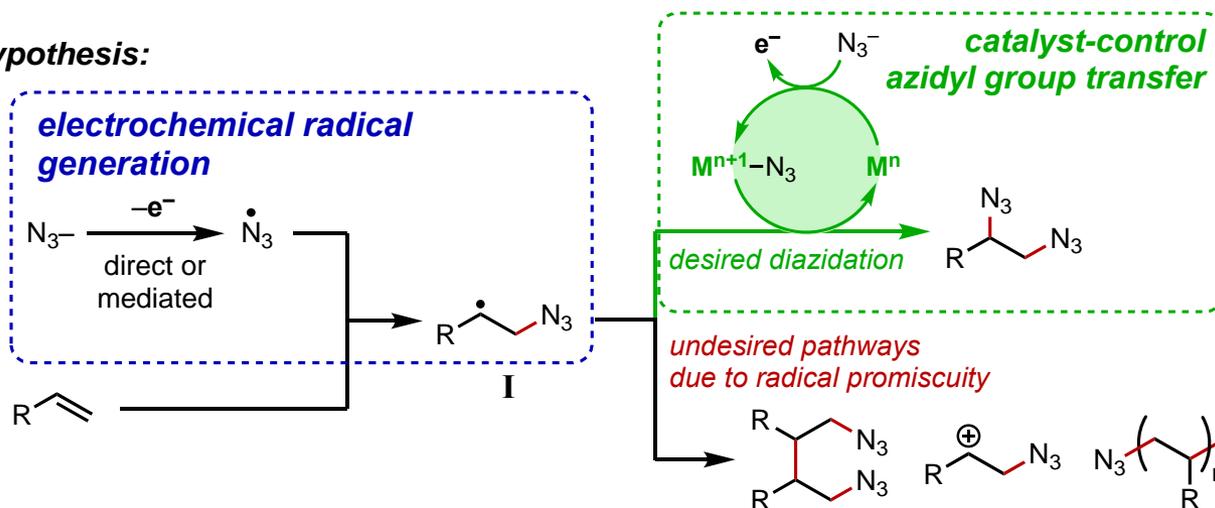




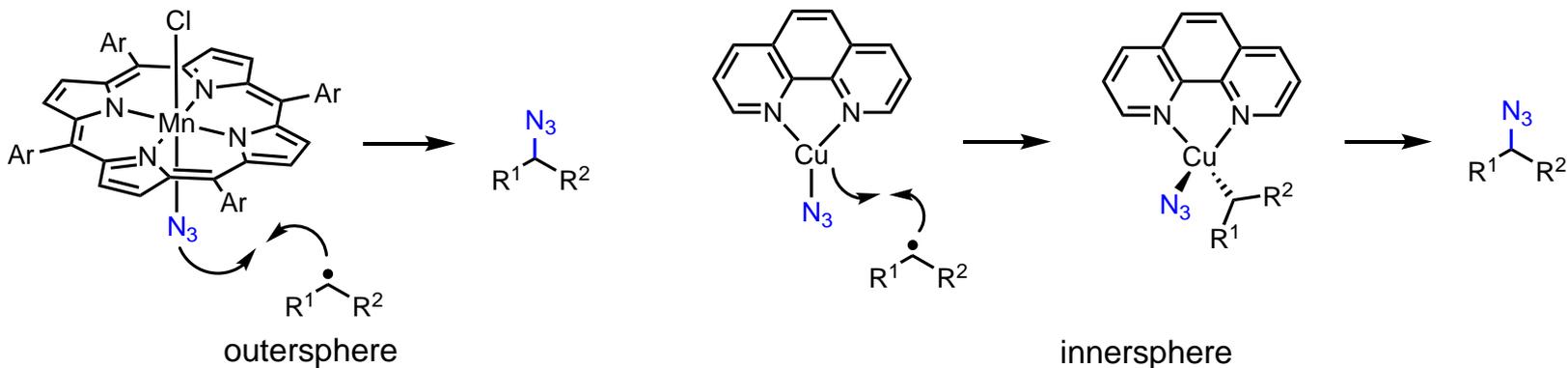
Initial Proof of Concept

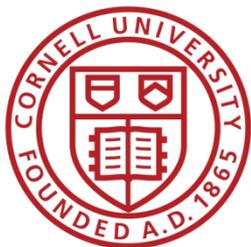
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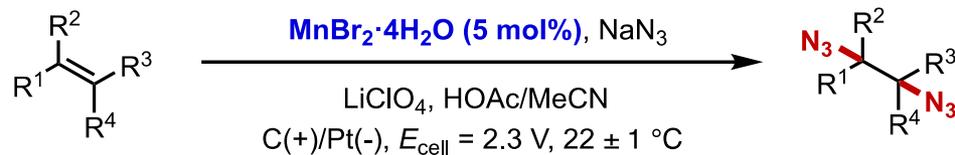
Literature information:





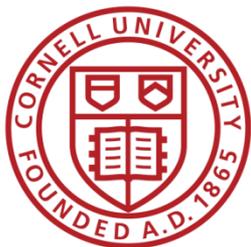
Reaction Discovery

Mn catalyst promotes highly efficient and selective alkene diazidation



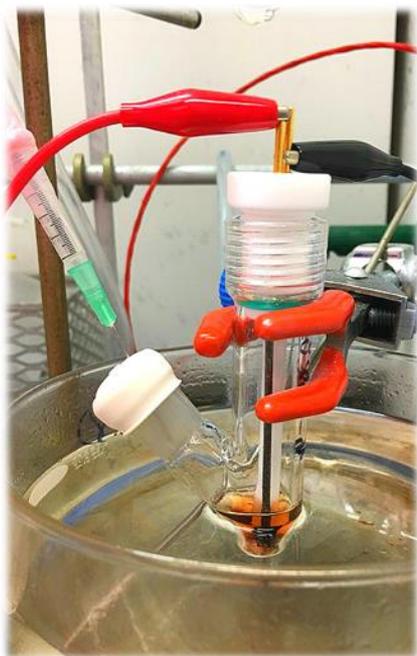
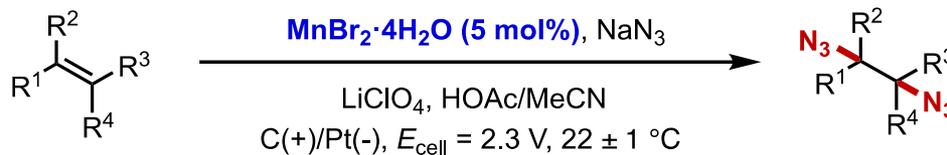
N Fu, GS Sauer, A Saha, A Loo, S Lin *Science* **2017**, *357*, 575–579

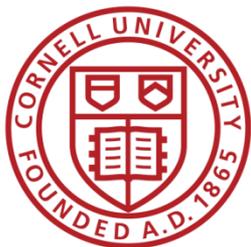
For an account: **JB Parry, N Fu, S Lin** *Synlett* **2018**, 257–265



Electrochemical Alkene Diazidation

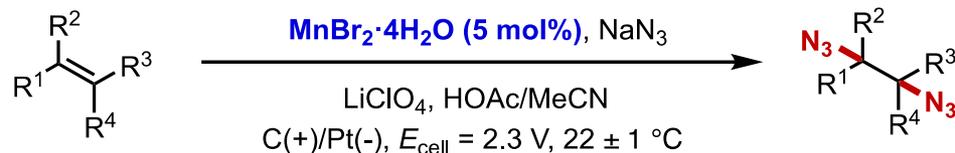
Reaction setups



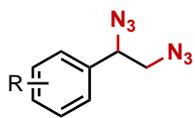


Reaction Discovery

Mn catalyst promotes highly efficient and selective alkene diazidation



Monosubstituted

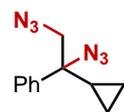


R = H (2b)	95%
4- <i>t</i> -Bu (1b)	90% (92%)
4-MeO (3b)	84%
4-F (4b)	85%
4-Cl (5b)	86%
3-MeO (6b)	66%
4-CN (7b)	70%
2,4,6-Me ₃ (8b)	88%

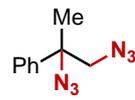
1,1-Disubstituted



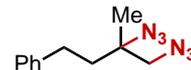
9b, 87%



13b, 86%

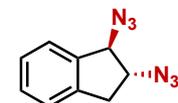


14b, 80%

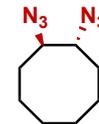


15b, 91%

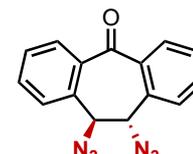
Disubstituted



22b, 82% (90%)
(dr > 19:1)

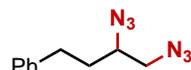


23b, 79%
(dr = 4:1)



24b, 62%
(dr = 2:1)

1,2-Disubstituted



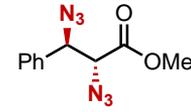
10b, 83%



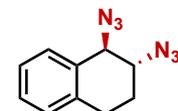
16b, 95%
(dr = 3:1)



17b, 73%
(dr = 2:1)

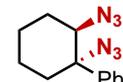


18b, 92%
(dr = 2:1)



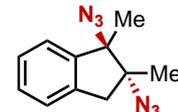
25b, 83%
(dr = 10:1)

Trisubstituted



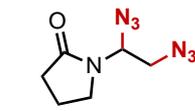
26b, 88%
(dr = 10:1)

Tetrasubstituted



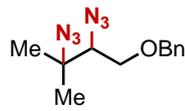
27b, 72% (75%)
(dr > 19:1)

Trisubstituted

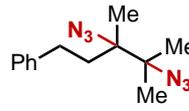


12b, 98%

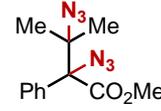
Tetrasubstituted



19b, 82%



20b, 68%

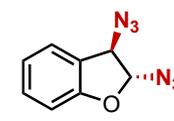


21b, 82%

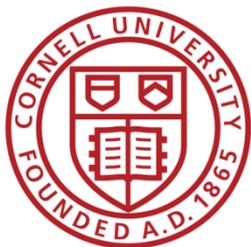
Electron-rich heterocycle



28b, 69% (dr = 10:1)

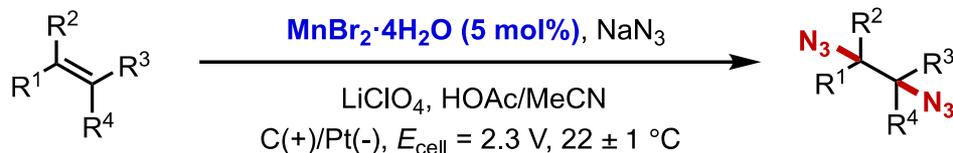


29b, 78% (dr = 9:1)



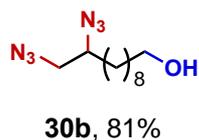
Functional Group Compatibility

Echem offers innate functional group selectivity

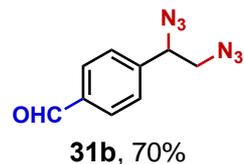


Functional groups sensitive to oxidation

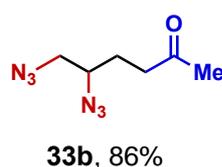
Alcohol



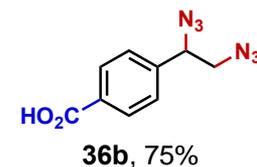
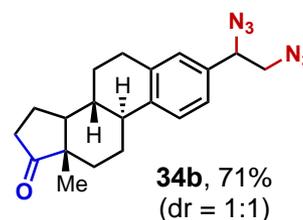
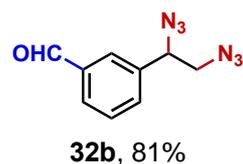
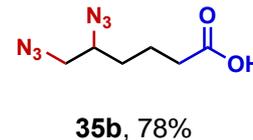
Aldehyde



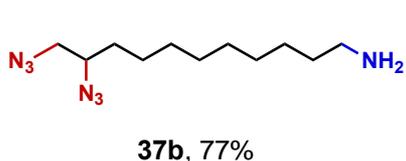
Enolizable ketone



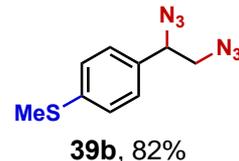
Carboxylic acid



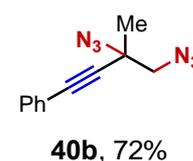
Amine



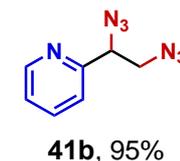
Sulfide



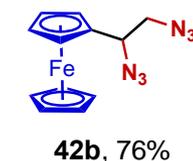
Alkyne



N-Heterocycle

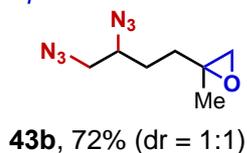


Organometallic

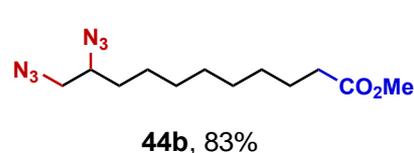


Functional groups sensitive to nucleophilic substitution

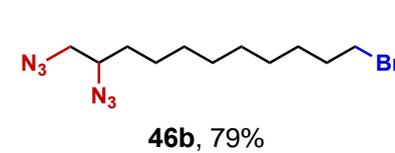
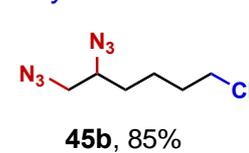
Epoxide

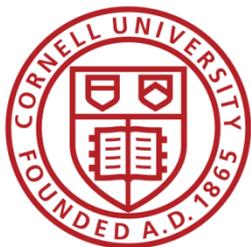


Ester



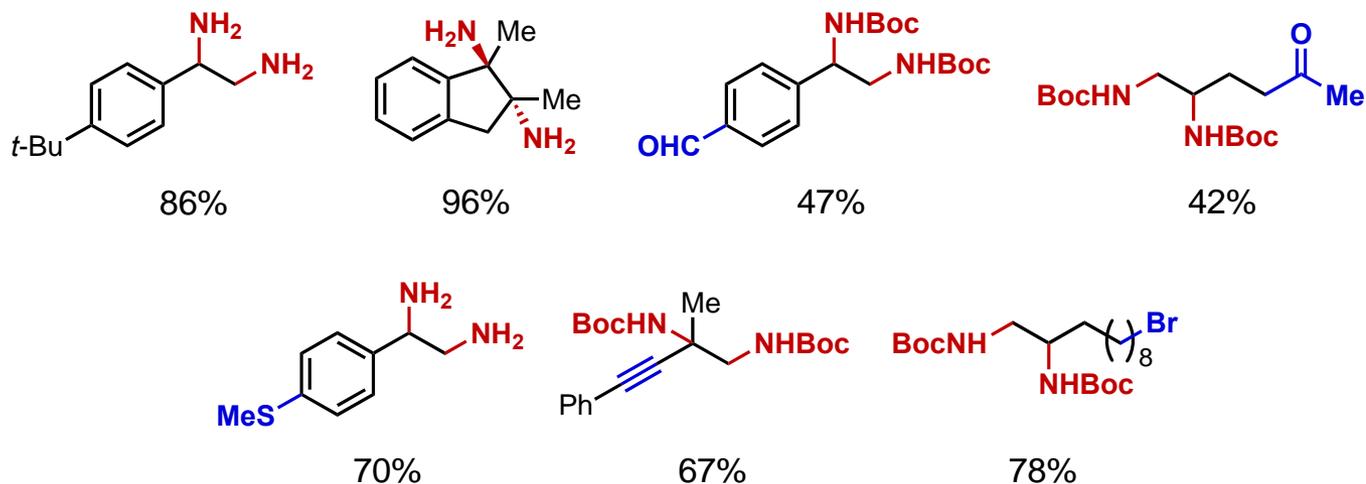
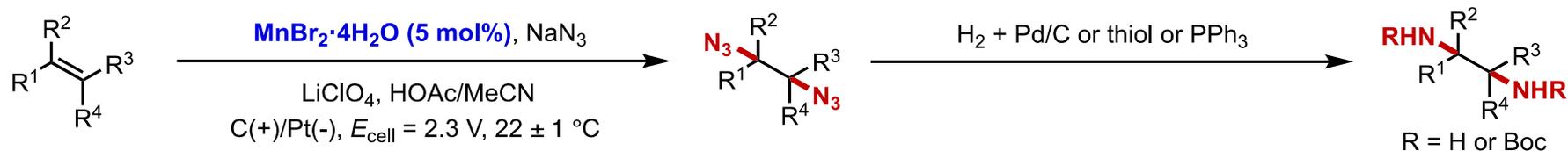
Alkyl halide

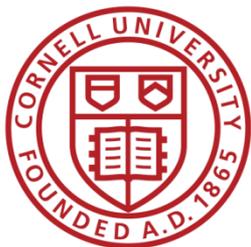




Tandem Diazidation–Reduction for Diamine Synthesis

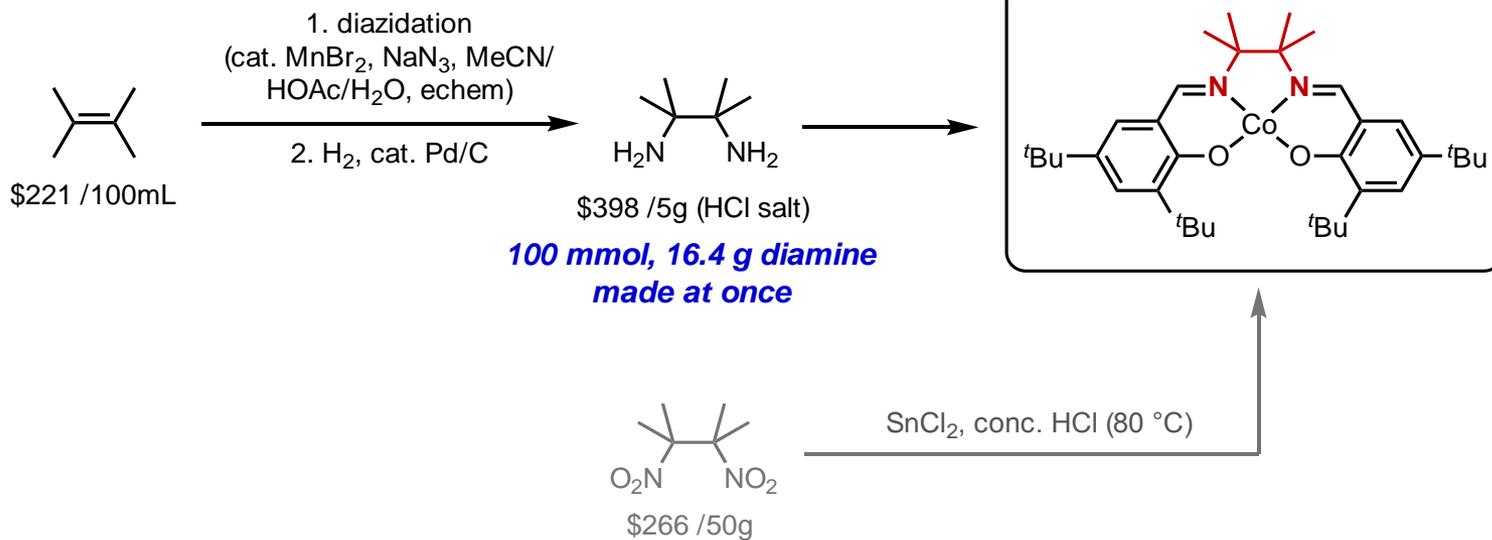
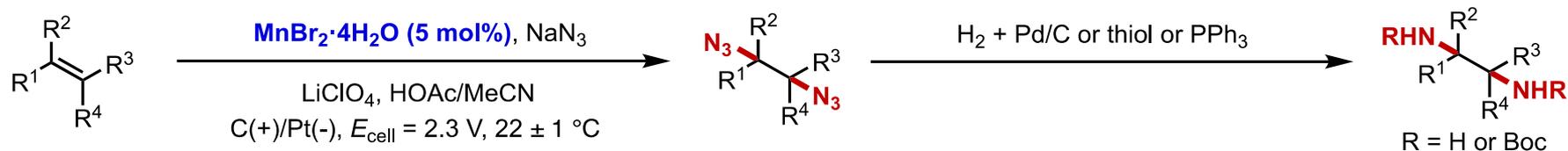
Toward a safer and more practical protocol for the synthesis of diamines

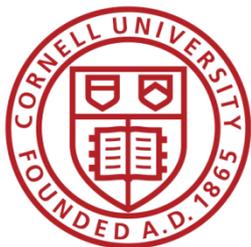




Tandem Diazidation–Reduction for Diamine Synthesis

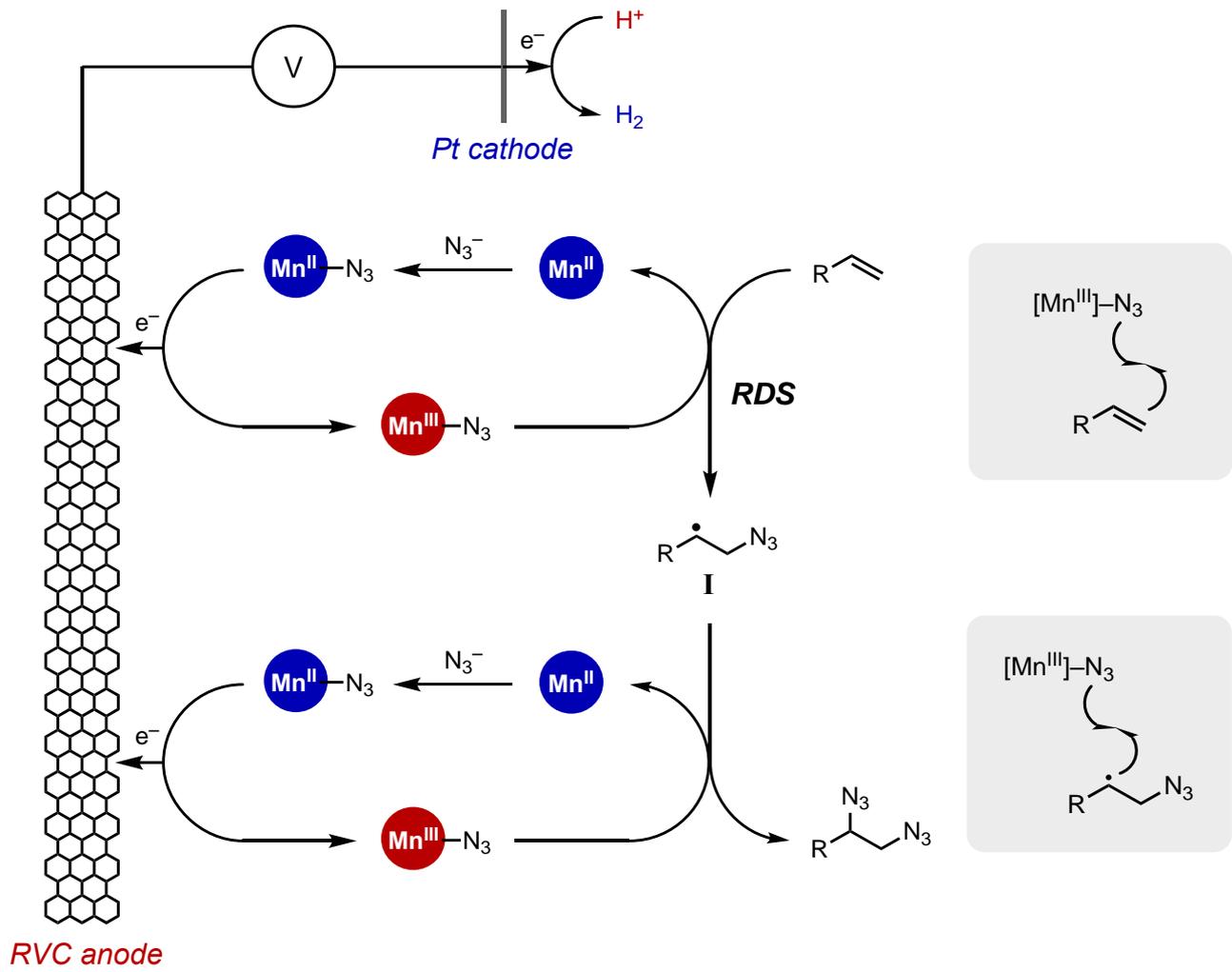
Toward a safer and more practical protocol for the synthesis of diamines

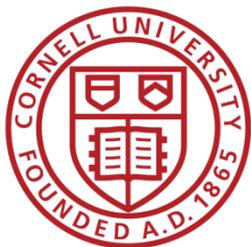




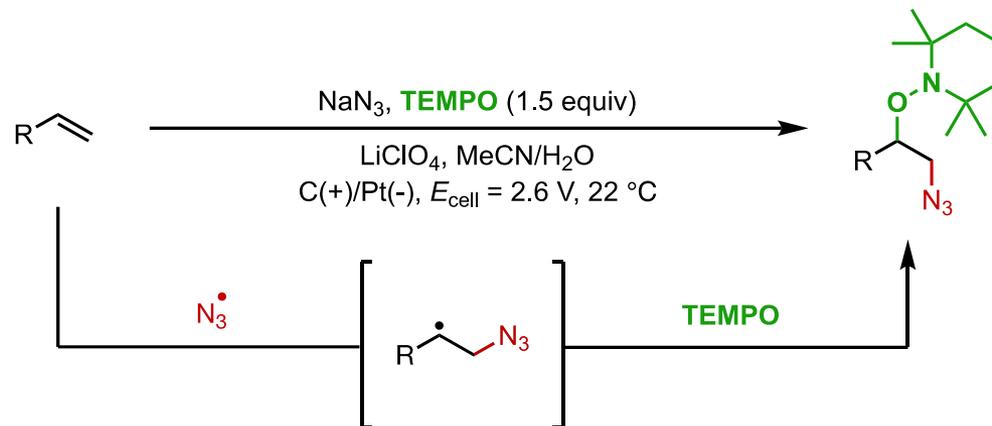
Proposed Reaction Mechanism

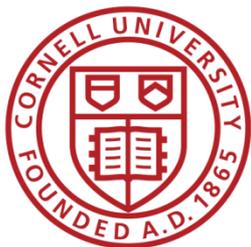
Mn-promotes the addition of both N_3 groups to the alkene



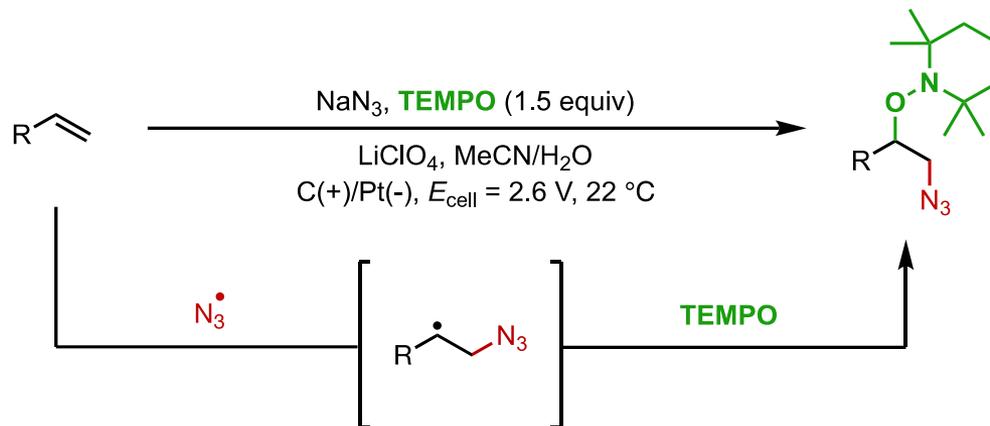


Electrochemical Azidooxygenations

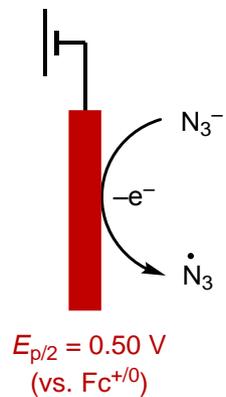




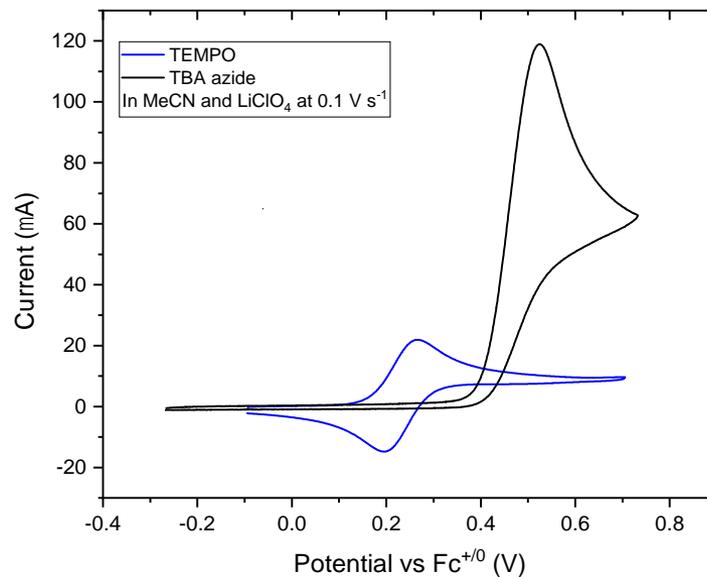
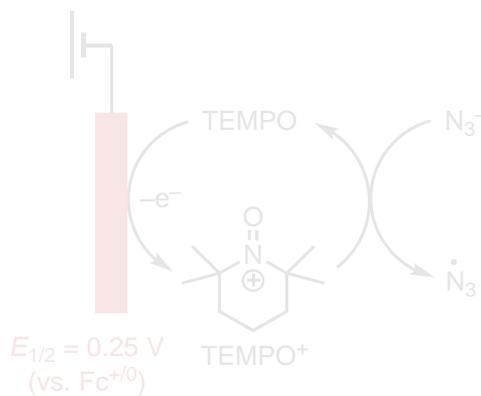
Electrochemical Azidooxygenations

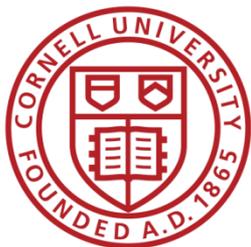


Pathway 1:
Direct anodic oxidation of N_3^-

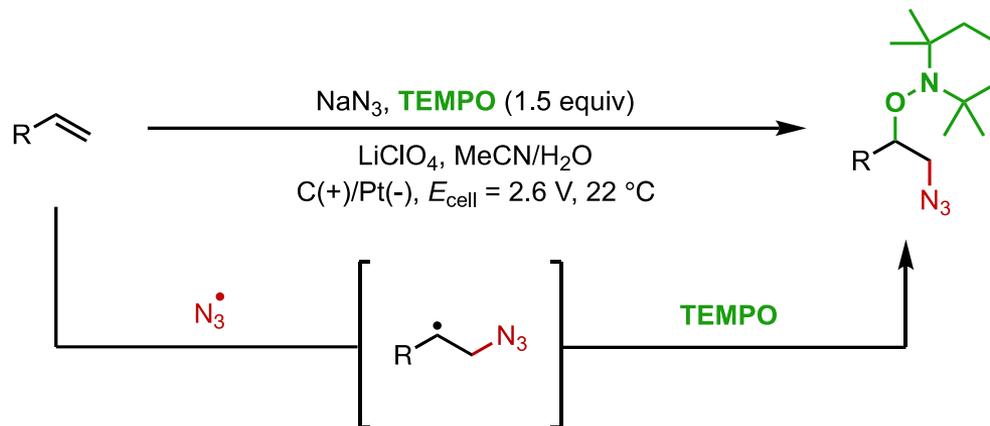


Pathway 2:
TEMPO-mediated oxidation of N_3^-

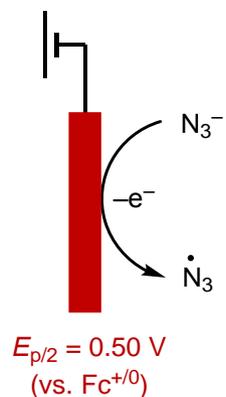




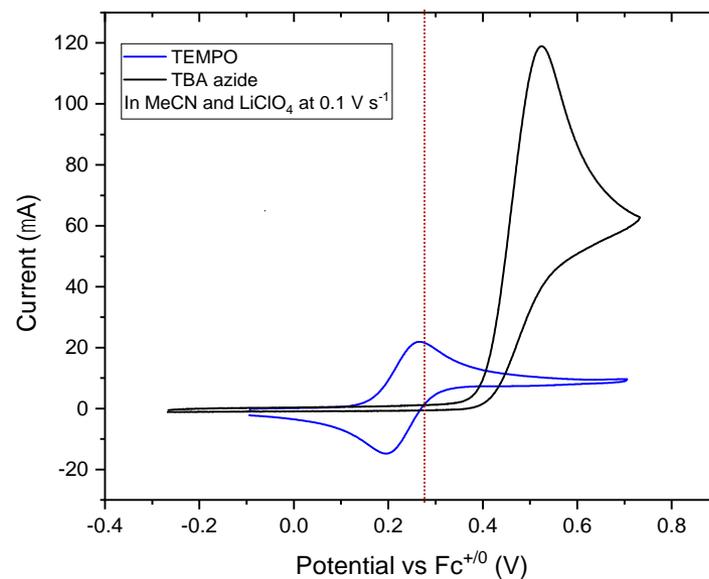
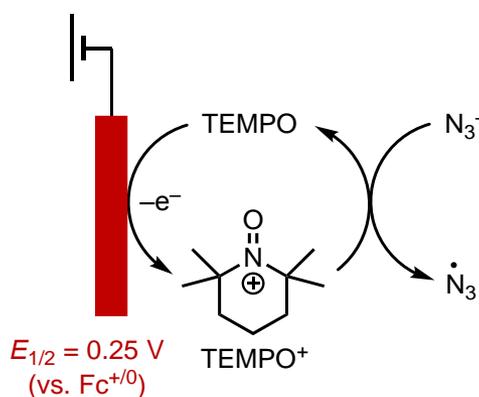
Electrochemical Azidooxygenations

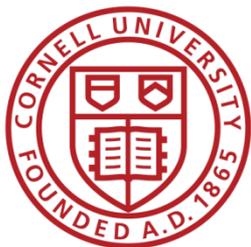


Pathway 1:
Direct anodic oxidation of N_3^-

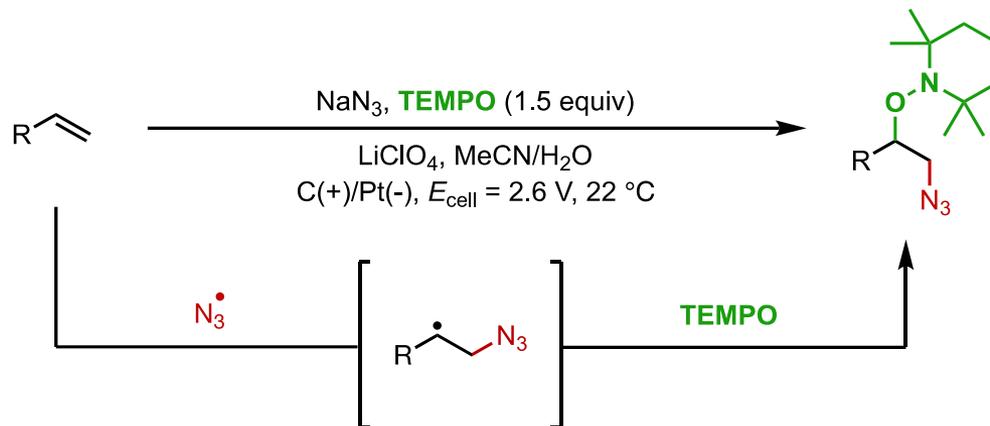


Pathway 2:
TEMPO-mediated oxidation of N_3^-

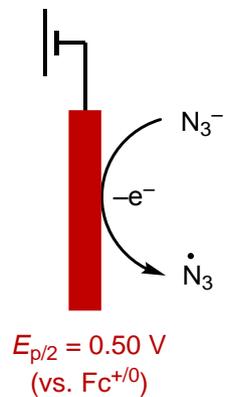




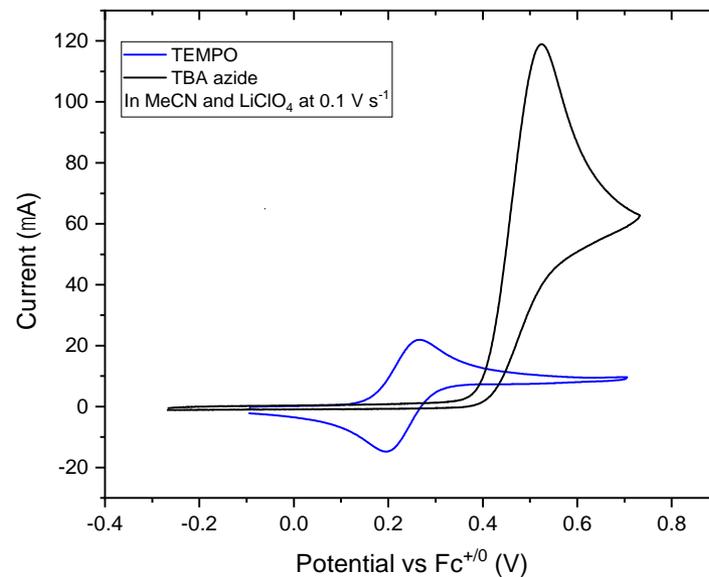
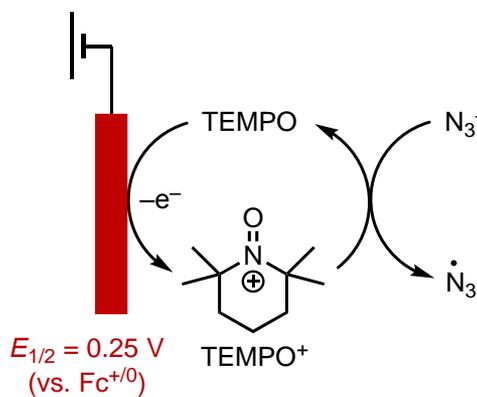
Electrochemical Azidooxygenations

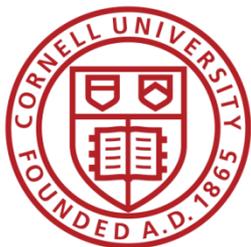


Pathway 1:
Direct anodic oxidation of N_3^-



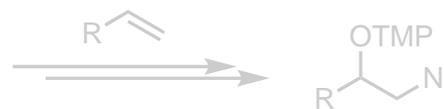
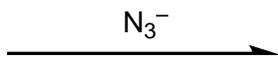
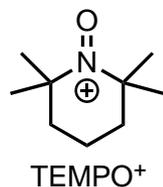
Pathway 2:
TEMPO-mediated oxidation of N_3^-



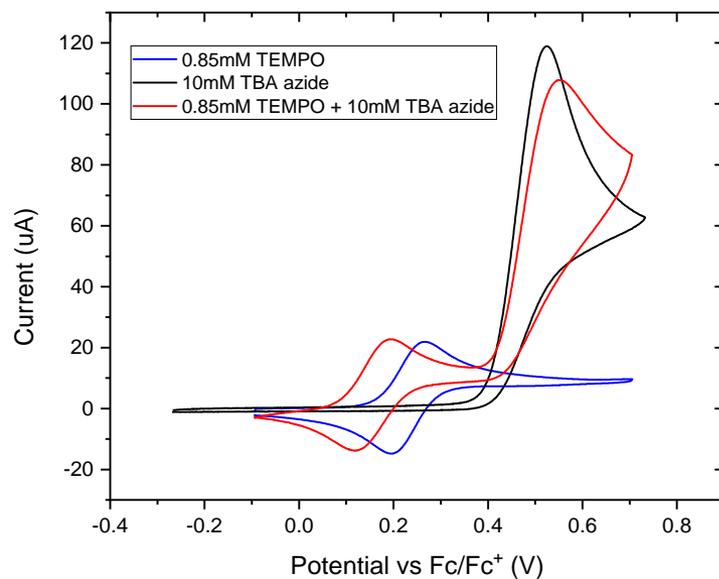
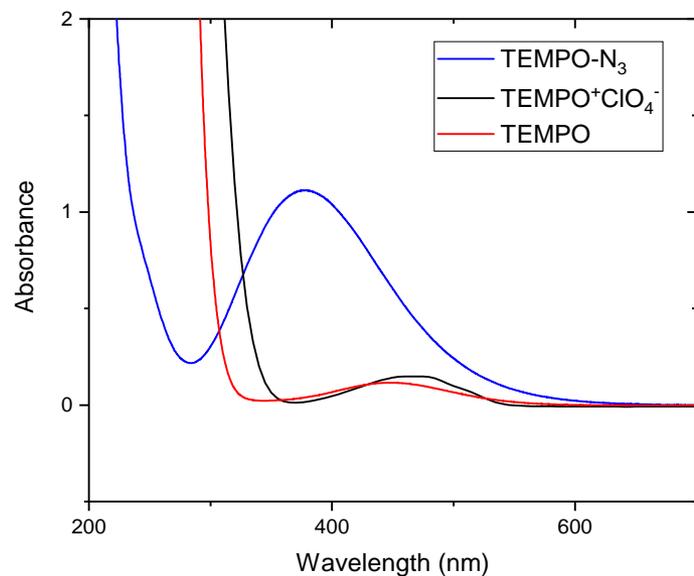


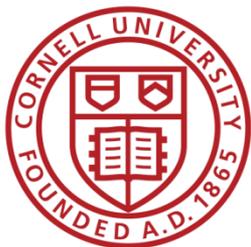
Oxidation of azide anion by TEMPO⁺

UV-vis and CV reveal the formation of a new charge-transfer adduct



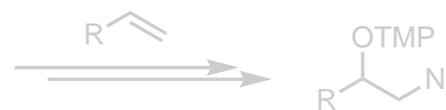
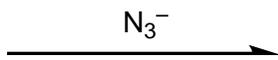
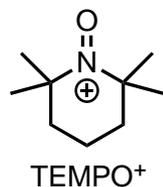
slowly decomposes, $t_{1/2} \sim 7$ min



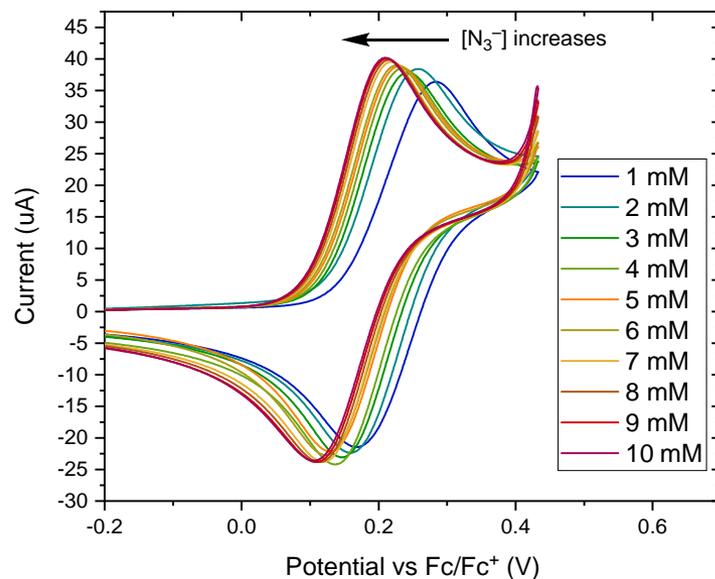
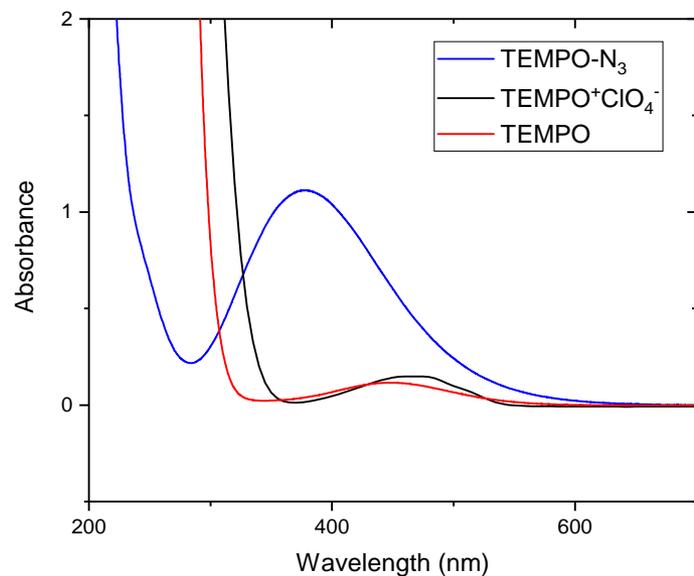


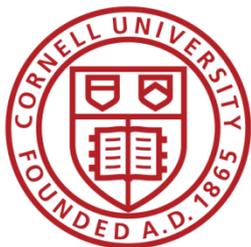
Oxidation of azide anion by TEMPO⁺

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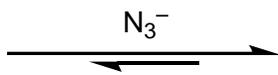
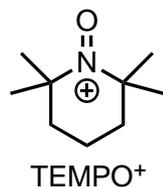
slowly decomposes, $t_{1/2} \sim 7$ min



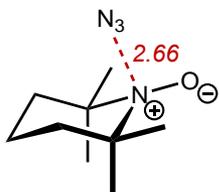
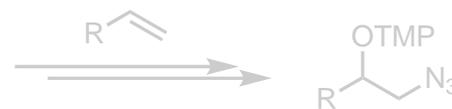


Identification of the TEMPO-N₃ Adduct

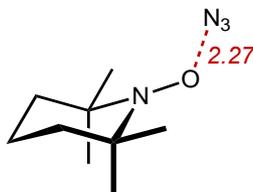
Computational data provides insights into the chemical structure



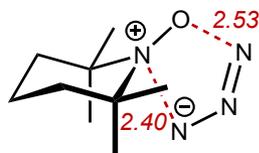
$\lambda_{\max} = 377 \text{ nm}$



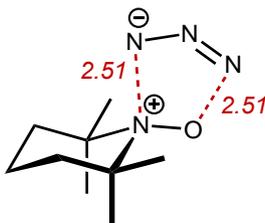
I₁, $E_{\text{rel}} = 2.71$
 $\lambda_{\max} = 607 \text{ nm}$



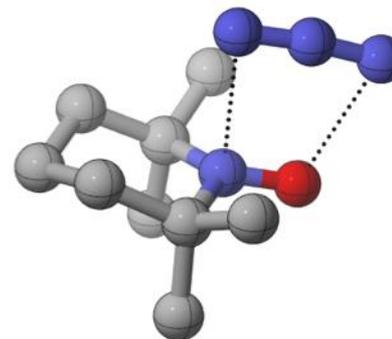
I₂, $E_{\text{rel}} = 6.32$
 $\lambda_{\max} = 455 \text{ nm}$



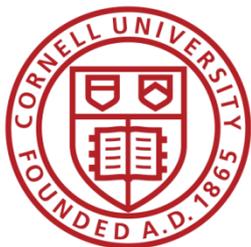
I₃, $E_{\text{rel}} = +3.08$
 $\lambda_{\max} = 331 \text{ nm}$



I₄, $E_{\text{rel}} = 0$
 $\lambda_{\max} = 350 \text{ nm}$

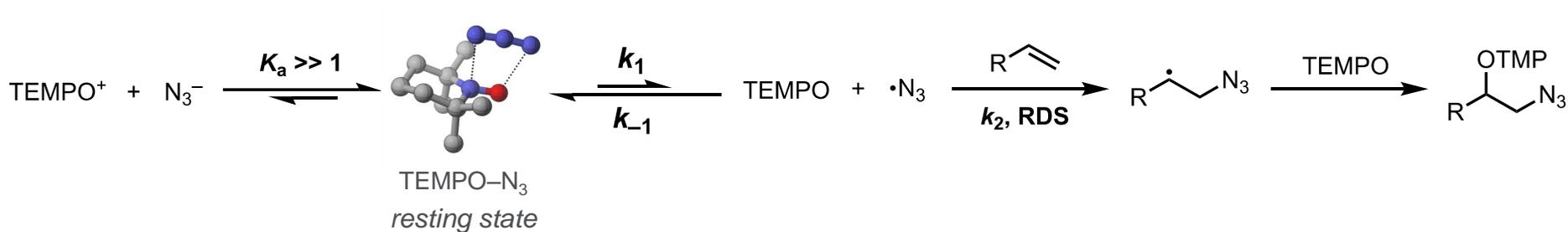


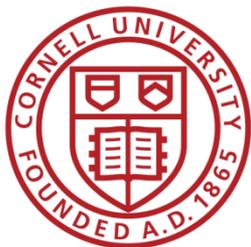
B3LYP/def2-TZVP/PCM = MeCN
Greg Sauer, Prof. Kyle Lancaster



Mechanism of the Electrochemical Azidooxygenation

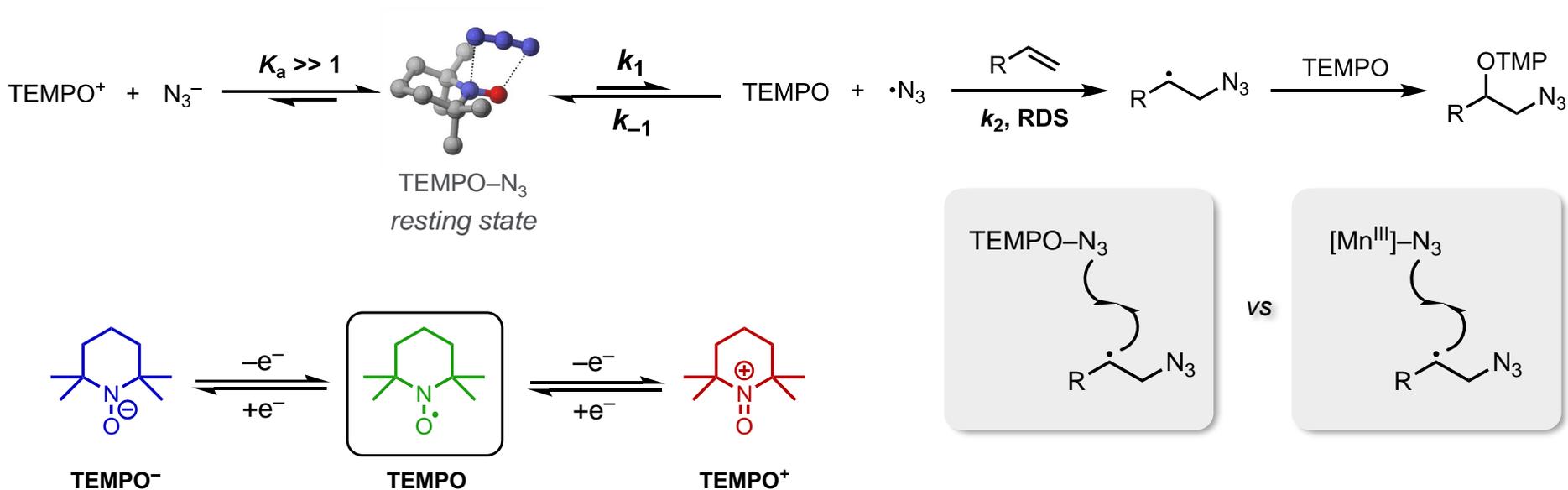
TEMPO-N₃ adduct plays a key role

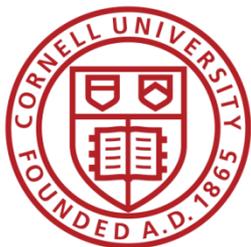




TEMPO-Catalyzed Alkene Diazidation

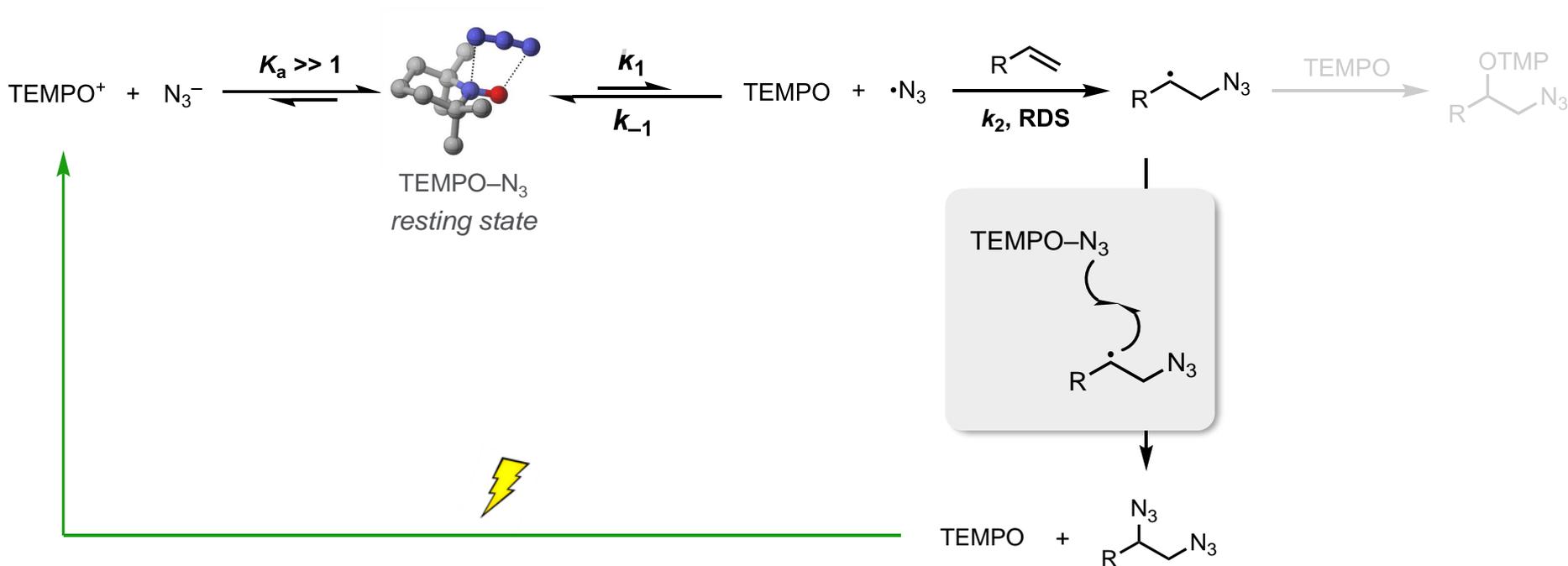
Mechanistic info guides the development of catalytic diazidation

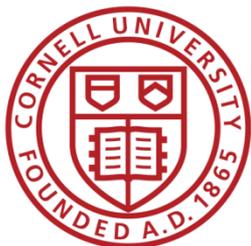




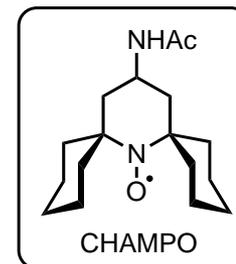
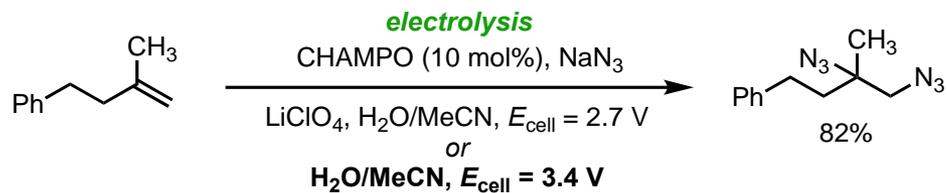
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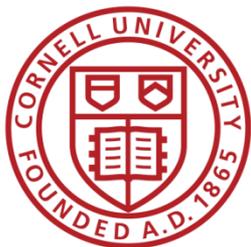
Mechanistic info guides the development of catalytic diazidation



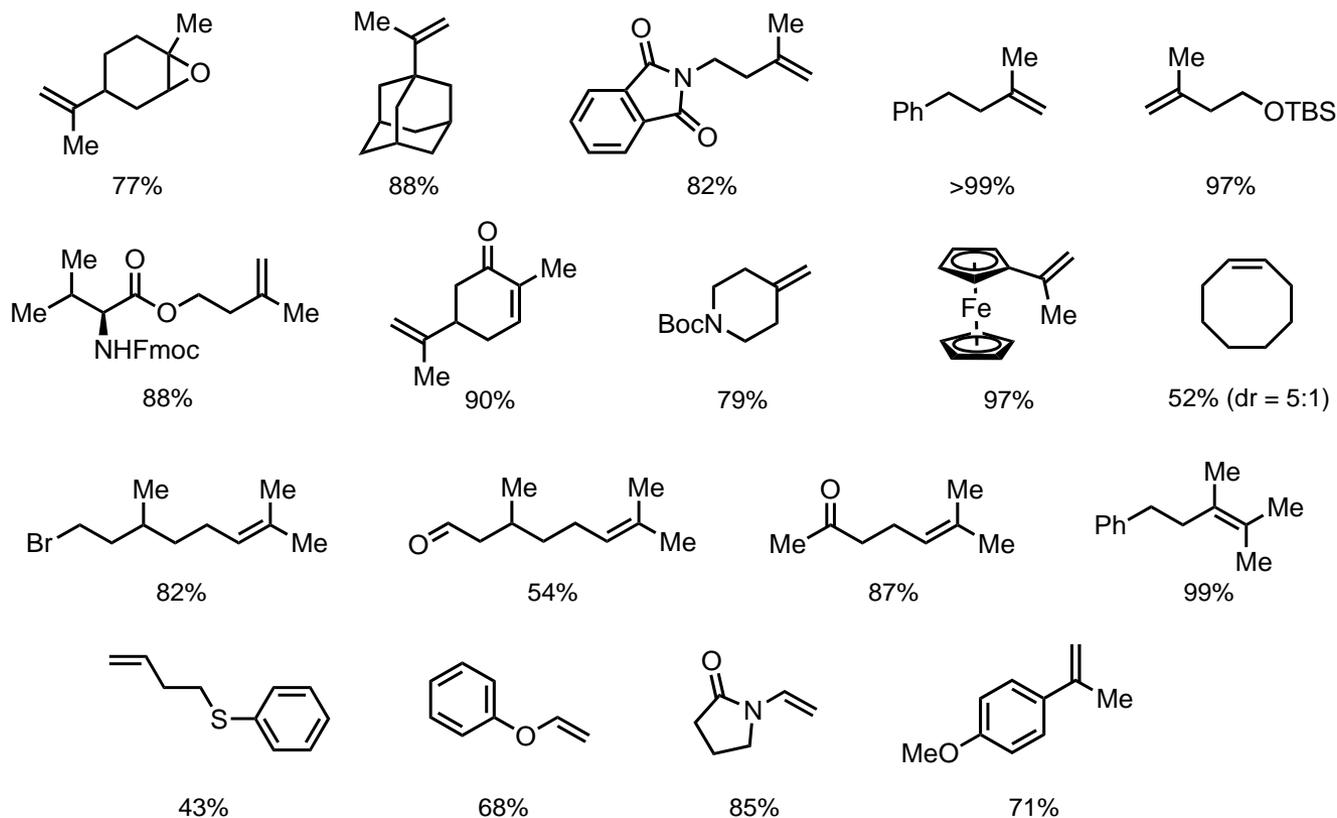
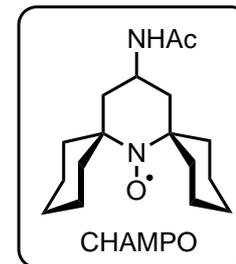
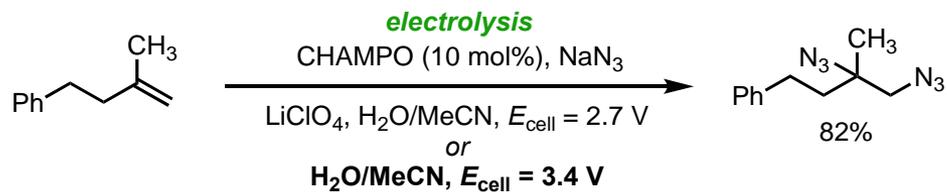


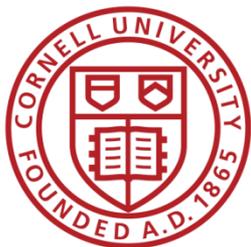
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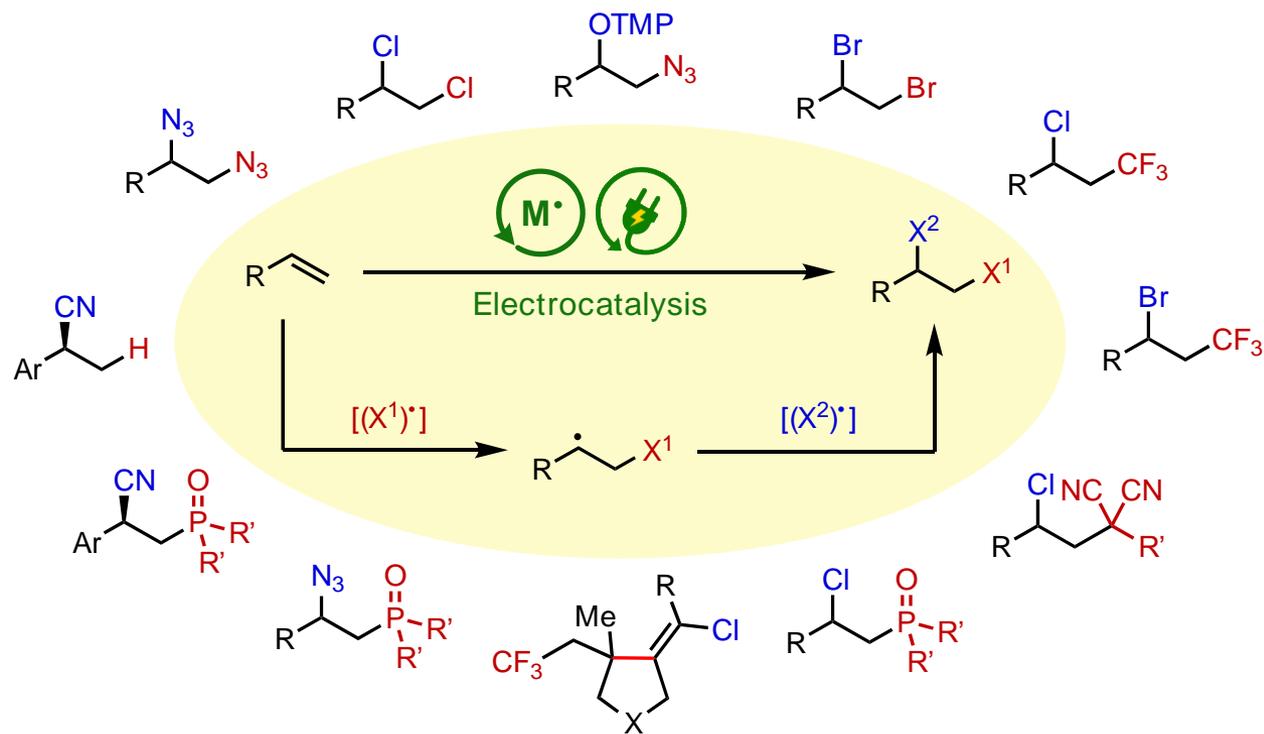


TEMPO-Catalyzed Alkene Diazidation





Diverse Electrocatalytic Alkene Difunctionalizations



MEDICINAL CHEMISTRY

Amping up the pharma lab: Drug companies explore the potential of electrochemistry

Medicinal and process chemists are starting to tap into the current trend

by *Bethany Halford*

NOVEMBER 4, 2019 | APPEARED IN **VOLUME 97, ISSUE 43**



Acknowledgements

Graduate students

Weiyang Guan
Justin Ho
Liat Kugelmass
Will Lee
Jinjian Liu
Lingxiang Lu
Jonas Rein
Yifan Shen
Juno Siu
Devin Wood
Xiangyu Wu

Postdoctoral scholars

Terry McCallum
Wen Zhang
Hyunwoo Kim
Luiz Novaes

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Geoff Coates
Brett Fors
Tristan Lambert
Kyle Lancaster
Tim Noël
Matt Sigman

Alumni

Postdoc, grad and undergrad students:

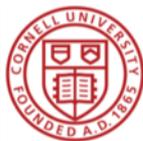
Wei Hao (now Scripps)
Lu Song (now ICCAS)
Kevin Ye (now Fuzhou Univ)
Niankai Fu (now ICCAS)
Keith Carpenter (now Buffalo)
Gregory Sauer
Joe Parry (now Cornell)
Jason Chari (now UCLA)
Sophia Lai (now Harvard)
Reed Macey (now Cambridge)
Ambarneil Saha (now UCLA)
Aaron Loo (now Columbia)

Visiting students:

Leonardo Melo (Univ. of Brasilia)
Anthony Allen (Oberlin; now UMich)
Gisselle Pombar (UCF; now Princeton)
Johannes Harenberg (Munich)
Atsushi Ozaki (Tokyo U of Sci and Tech)
Binyang Jiang (Nankai; now SIOC)
Ian Coates (Bucknell University)
Celeste Tobar (Mt. St. Mary's; now UCSB)

Funding

Cornell University (Start-up)
Howard and Abby Milstein (Start-up)
NIH (R01 GM130928; GM130928-S01)
NSF CAREER (CHE-1751839)
Office of Naval Research
Eli Lilly
Alfred P. Sloan Foundation
Atkinson Center for a Sustainable Future
ACS Green Chemistry Institute
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