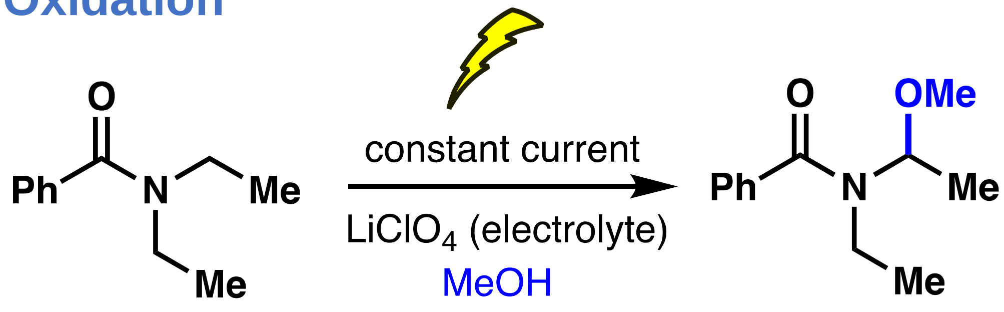
Electrochemistry: An Old Field for A New Era

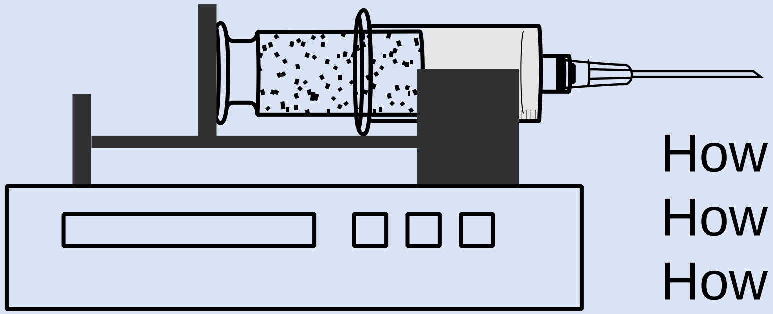
Yu Kawamata

The Scripps Research Institute

Basic Principle of Electrochemistry

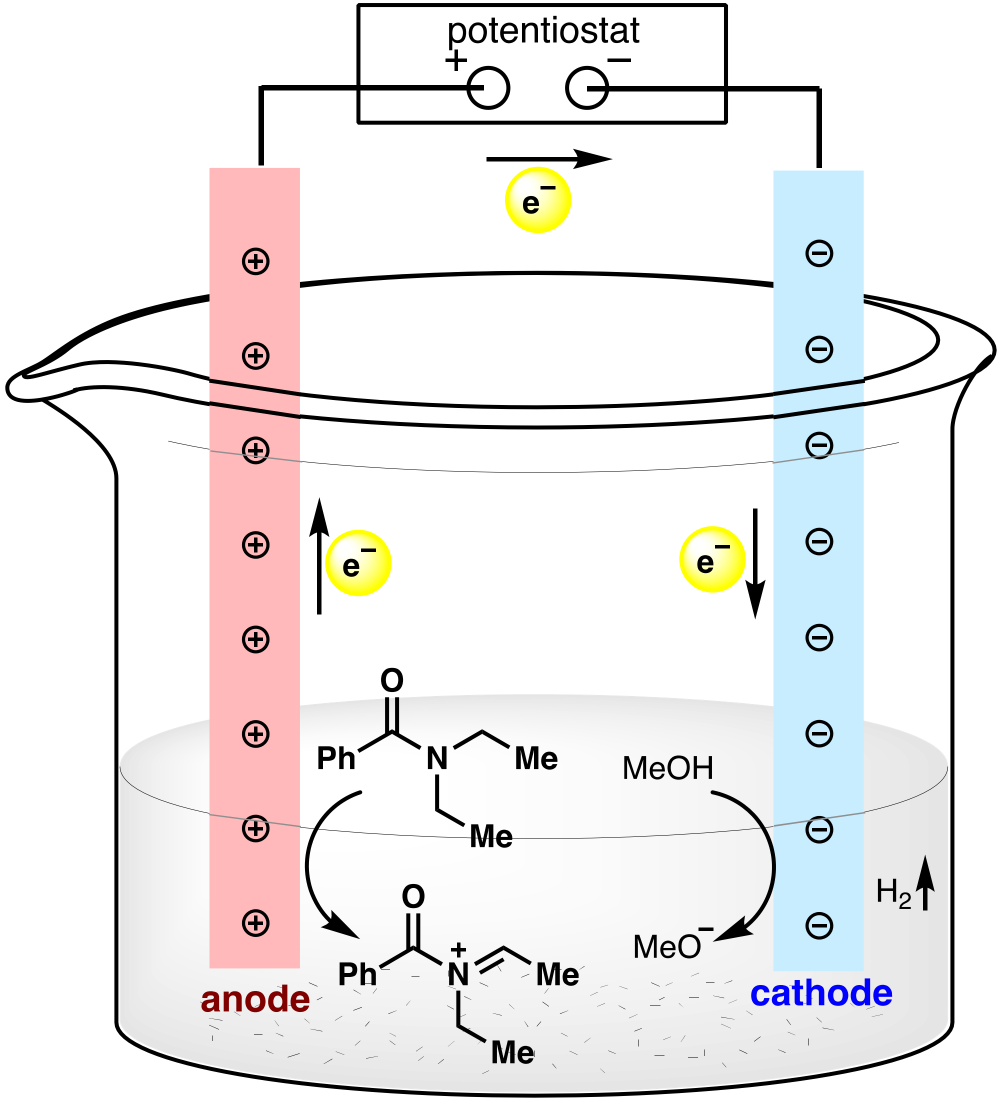
Shono Oxidation





How fast = current (A)
How strong = potential (V)
How much = total charge (Q)

Electrochemistry is a syringe pump of electron

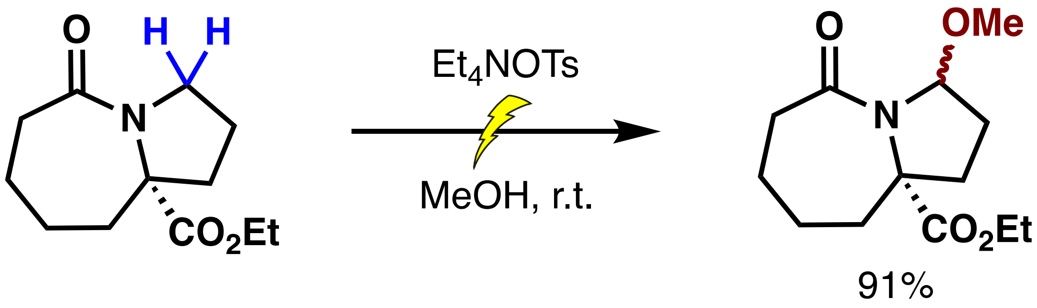


M. Yan, Y. Kawamata, P. S. Baran, Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev*. **2017**, *117*, 13230-13319.

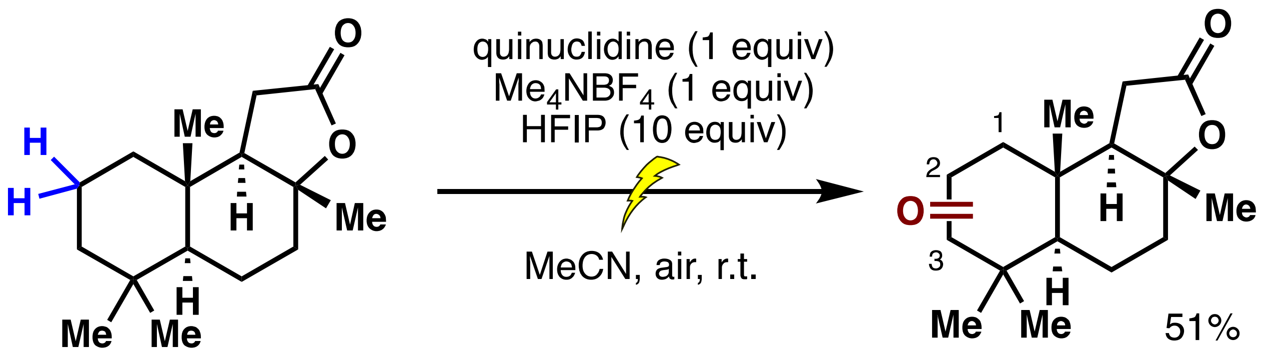
When to Use Electrochemistry

Electrochemistry is useful when:

- Appropriate redox reagents are not easily accessible.



Jeffery Aube *et al.*, *Angew. Chem. Int. Ed*. **2015**, *54*, 10555 –10558.



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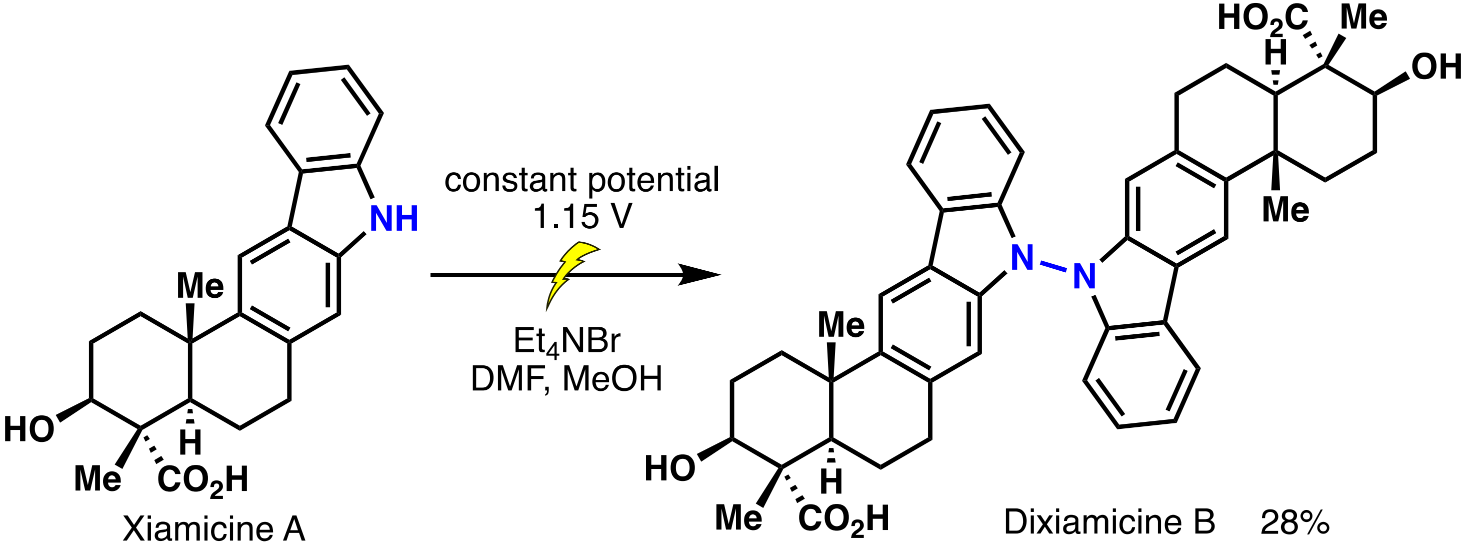
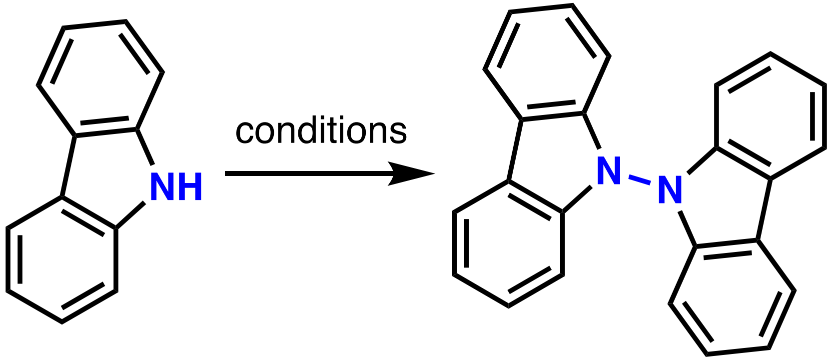
When to Use Electrochemistry

Electrochemistry is useful when:

- Appropriate redox reagents are not easily accessible.
- Reactivity needs to be “dialed-in”.



P. S. Baran *et al.*, *J. Am. Chem. Soc*. **2014**, *136*, 5571-5574.

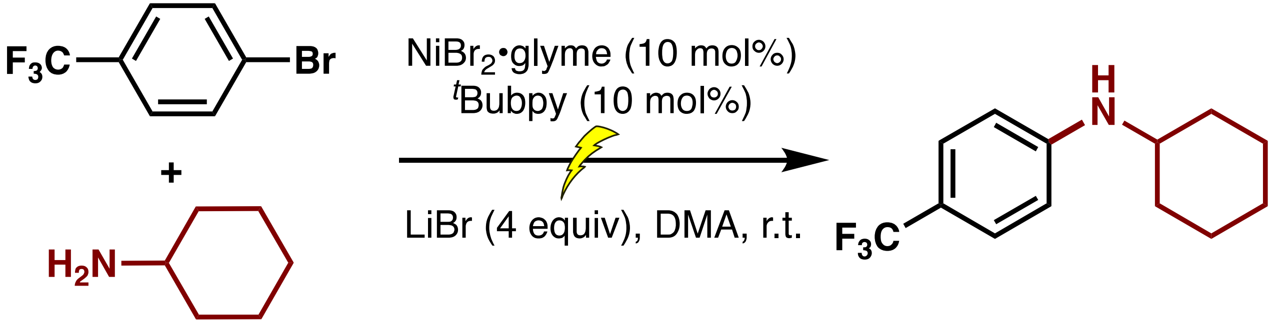


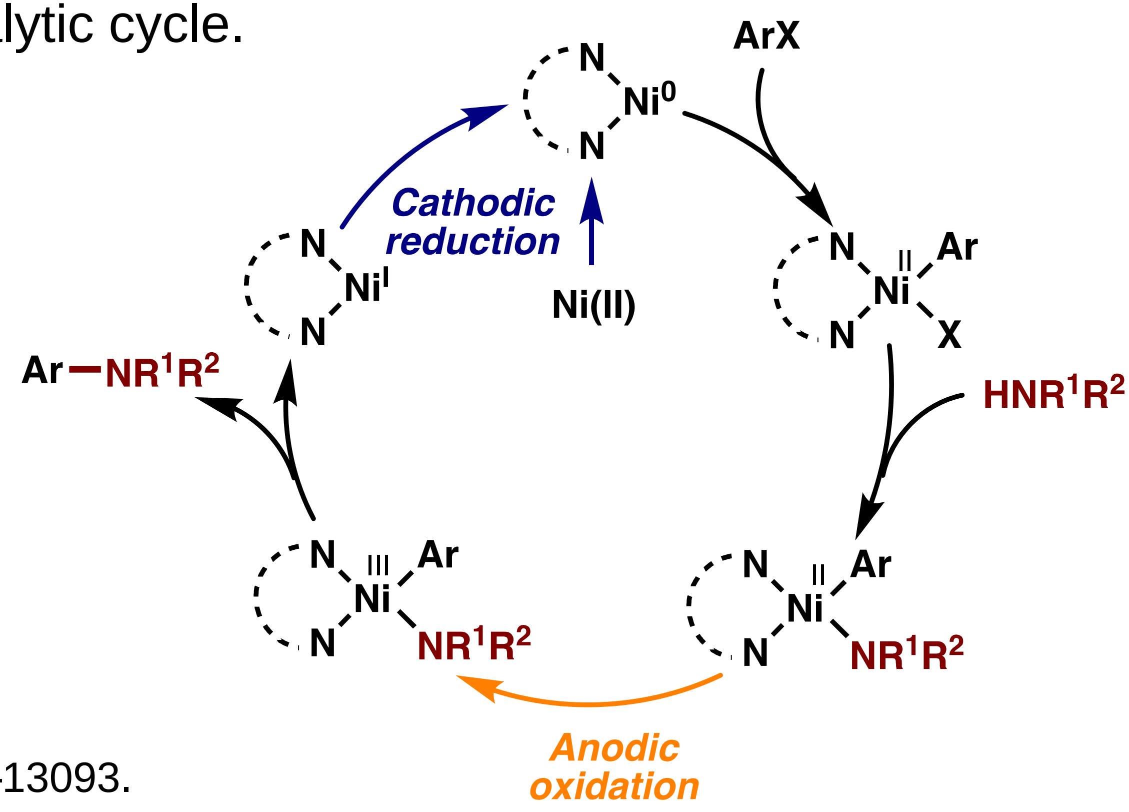
$KMnO_4$, acetone, Δ	< 20%
LDA, then [Cu]	no reaction
$PhI(TFA)_2$, CH_2Cl_2	no reaction
$KO^tBu/^tBuOCl$	trace
+1.2 V, DMF(5% MeOH)	60%

When to Use Electrochemistry

Electrochemistry is useful when:

- Appropriate redox reagents are not easily accessible.
- Reactivity needs to be “dialed-in”.
- Acceleration of redox steps in a complex catalytic cycle.



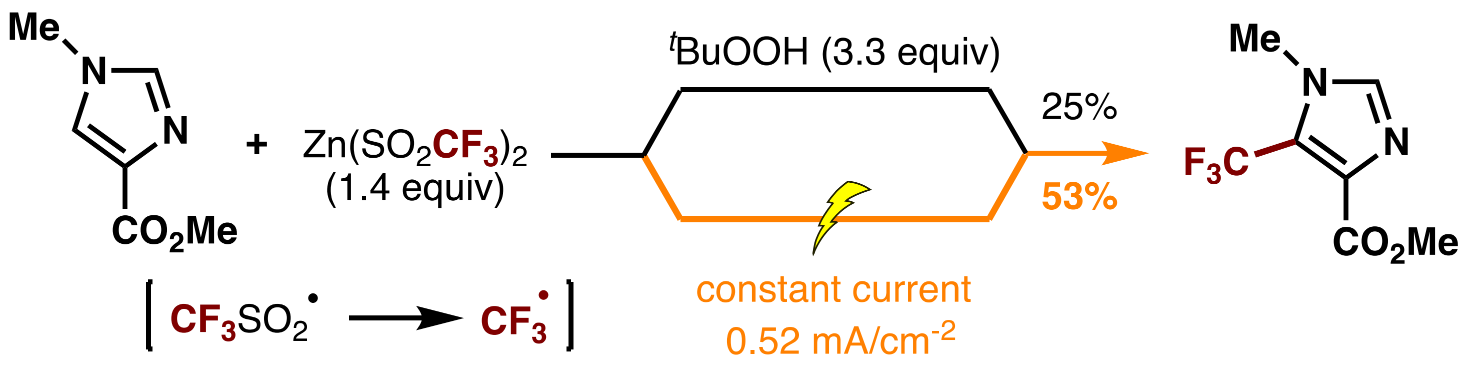


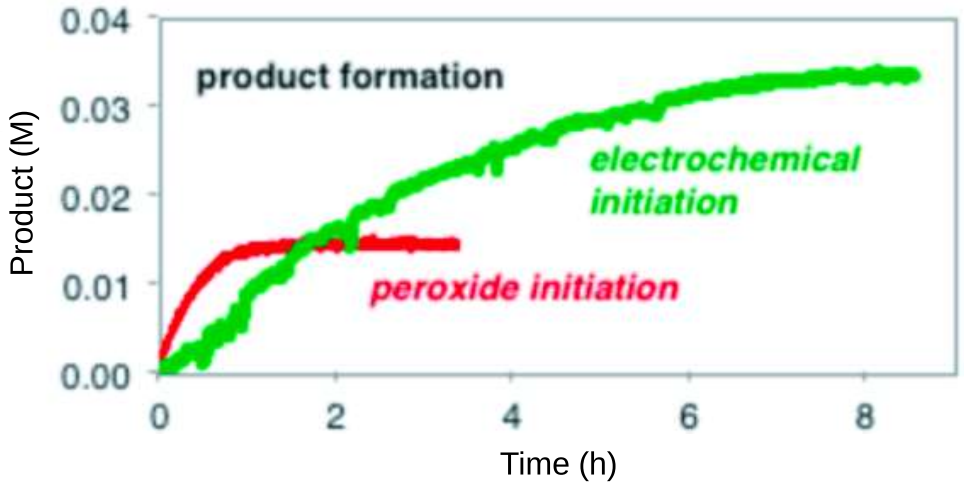
P. S. Baran *et al.*, *Angew. Chem. Int. Ed.* **2017**, *56*, 13088 –13093.

When to Use Electrochemistry

Electrochemistry is useful when:

- Appropriate redox reagents are not easily accessible.
- Reactivity needs to be “dialed-in”.
- Acceleration of redox steps in a complex catalytic cycle.
- Redox reactions with bad kinetics.

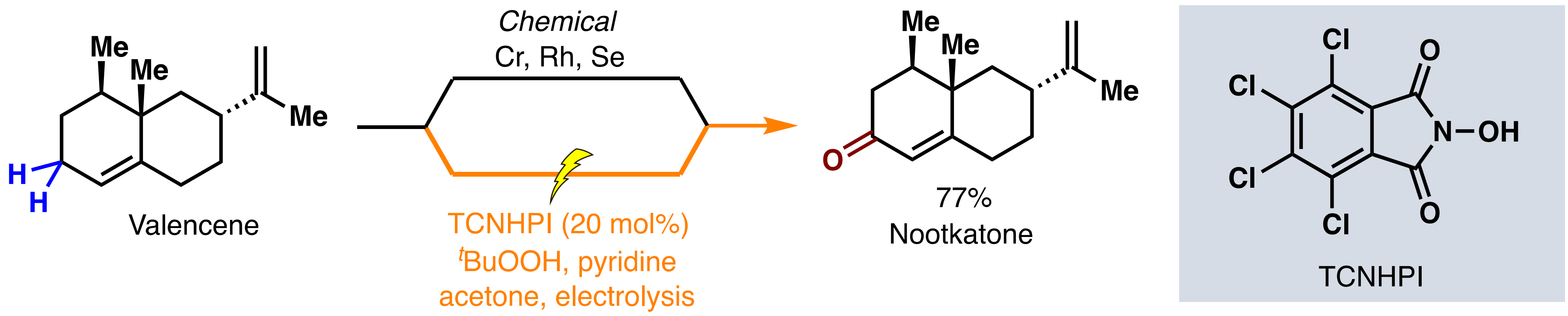




P. S. Baran, D. G. Blackmond *et al.*, *Angew. Chem. Int. Ed*. **2014**, *53*, 11868-11871.

Potential Application in Process Chemistry

- Toxic and hazardous reagents could be removed entirely or replaced with more benign reagents.



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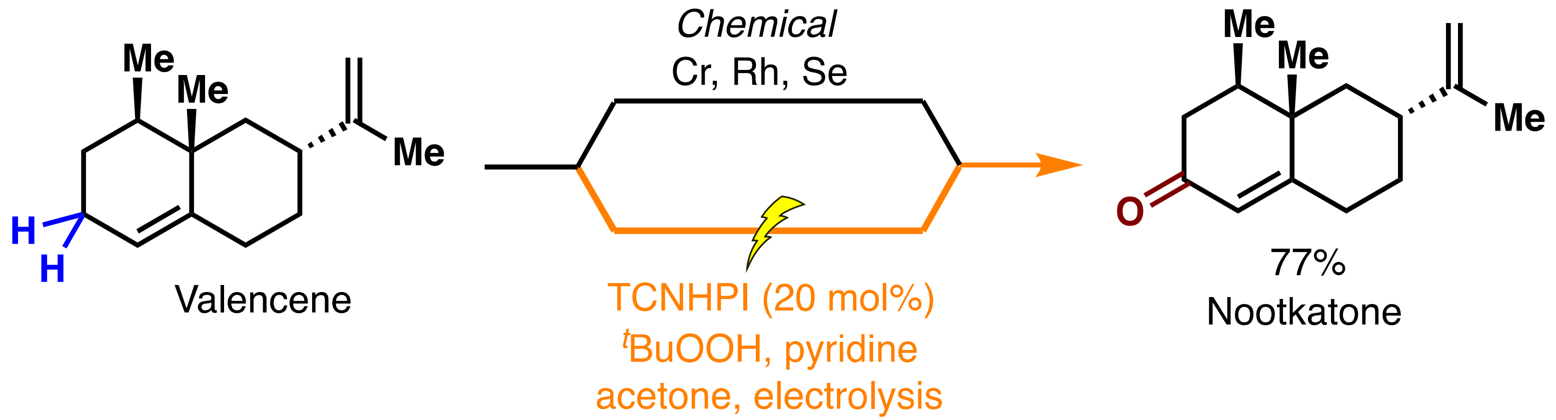
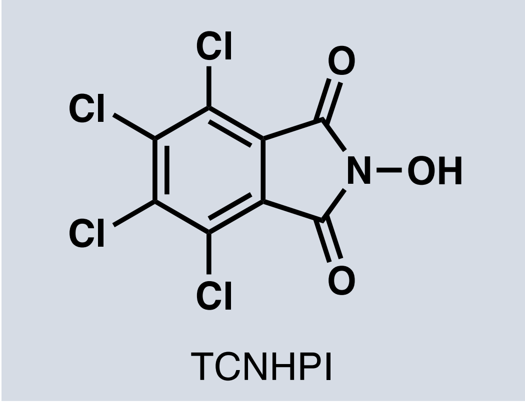
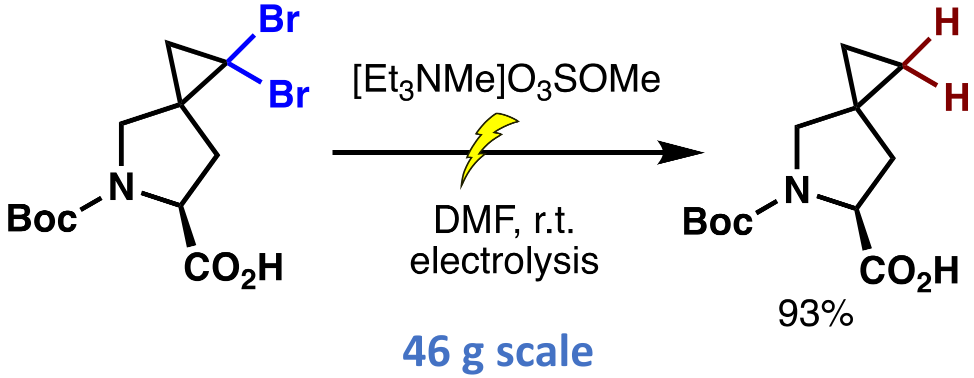
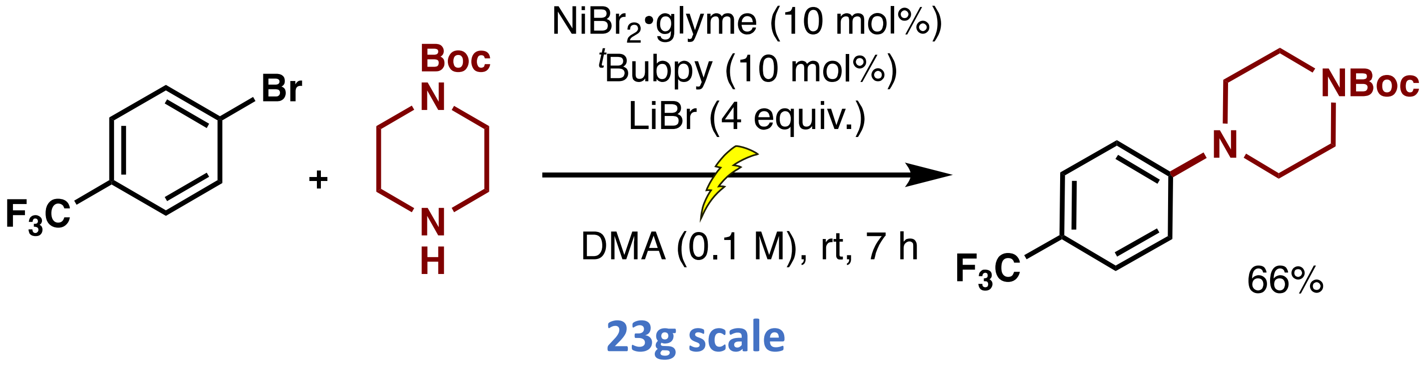




P. S. Baran *et al*., *Nature*, **2016**, *533*, 77-81.

- Scalable





S. R. Waldvogel *et al*., *Org. Process Res. Dev*. **2015**, *19*, 1428−1433.

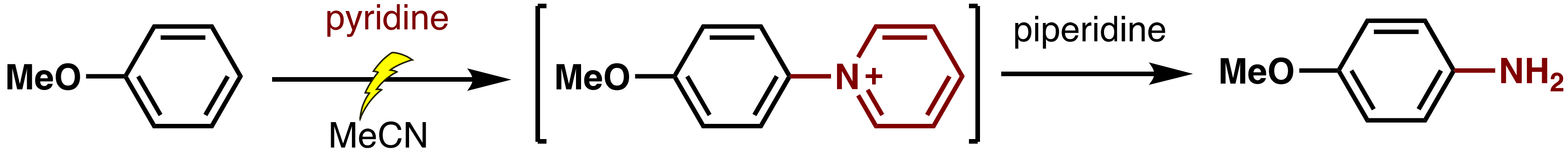
P. S. Baran *et al*., *Angew. Chem. Int. Ed*. **2017**, *56*, 13088 –13093.

Recent Application of Electrochemistry

C-N bond formation

Review: P. S. Baran *et al*., *Chem. Rev*. **2017**, *117*, 13230-13319.

C-H amination



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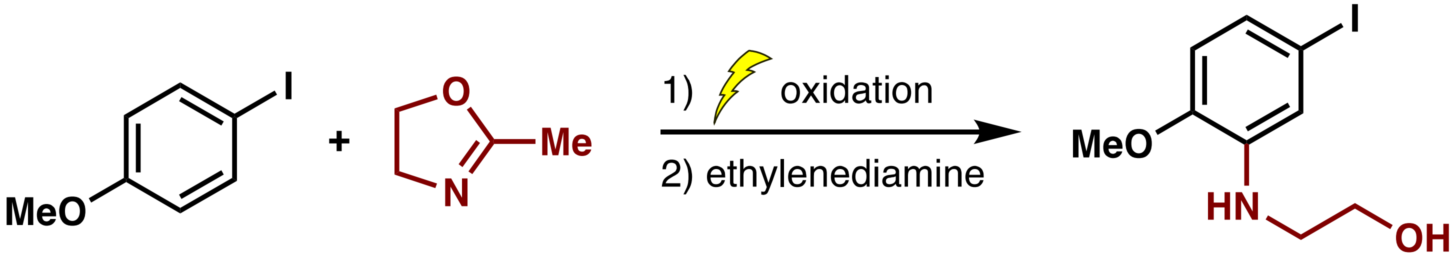
J. Yoshida *et al*, *J. Am. Chem. Soc*. **2013**, *135*, 5000-5003.



65%

J. Yoshida *et al*, *J. Am. Chem. Soc*. **2015**, *137*, 9816-9819.

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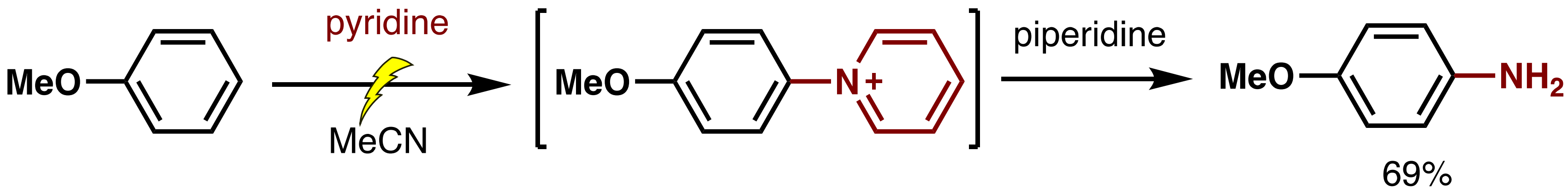

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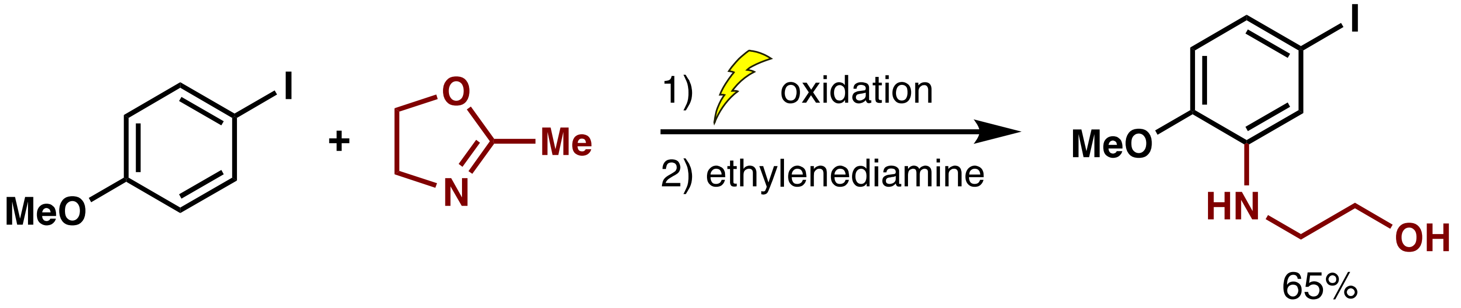
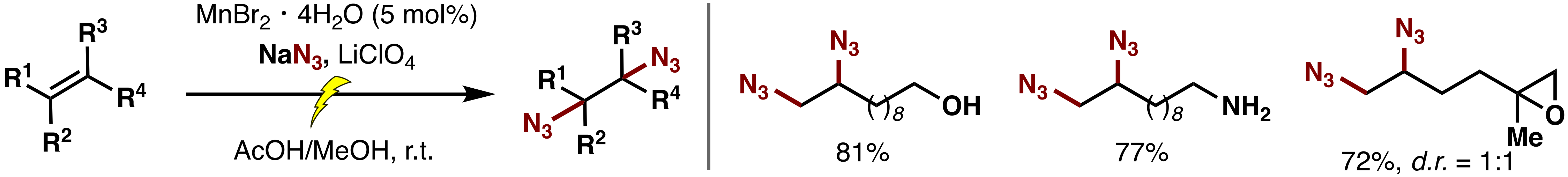


J. Yoshida *et al*, *J. Am. Chem. Soc*. **2015**, *137*, 9816-9819.

Diazidation



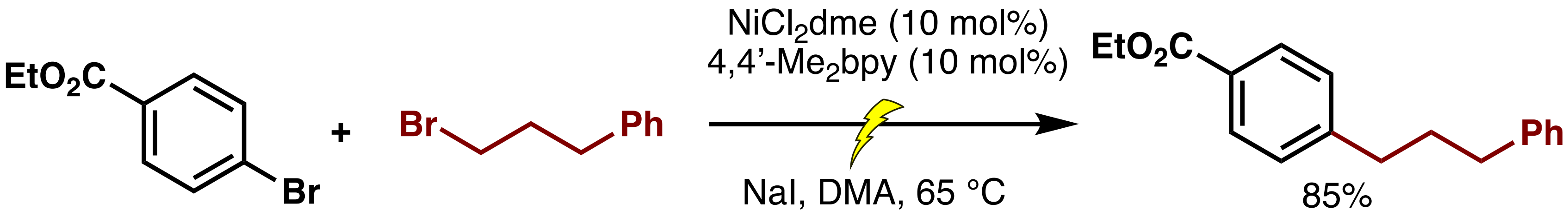
S. Lin *et al*, *Science* **2017**, *357*, 575-579.

Recent Application of Electrochemistry

C-C bond formation

Review: P. S. Baran *et al*., *Chem. Rev*. **2017**, *117*, 13230-13319.

Cross electrophile coupling



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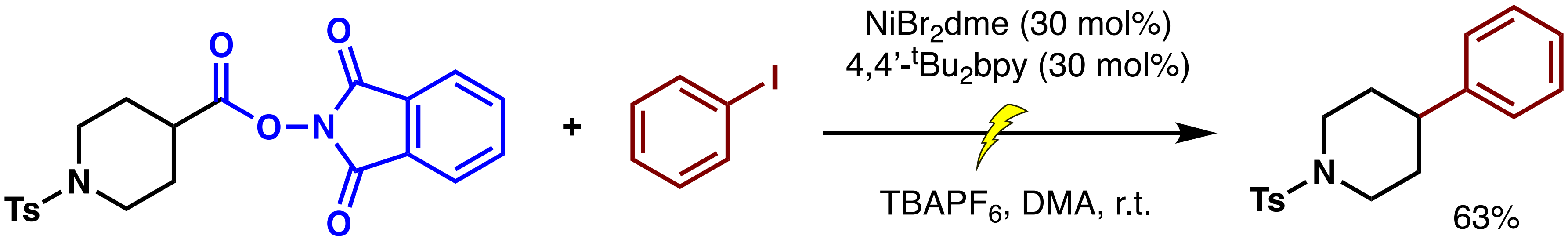

T. F. Jamison *et al*., *Org. Lett*. **2018**, *20*, 1338-1341.

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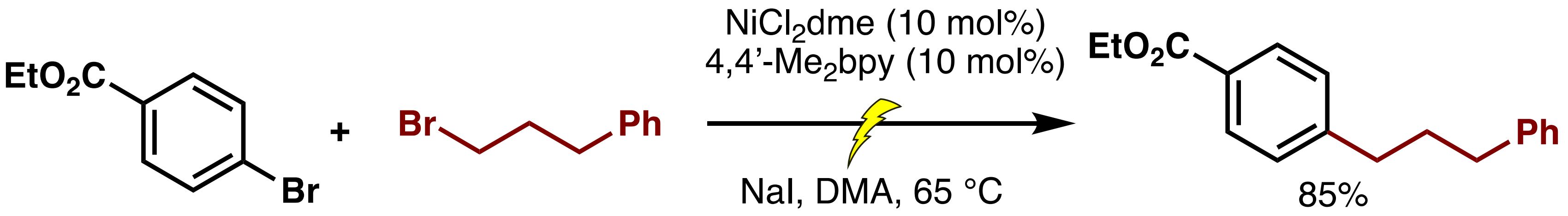

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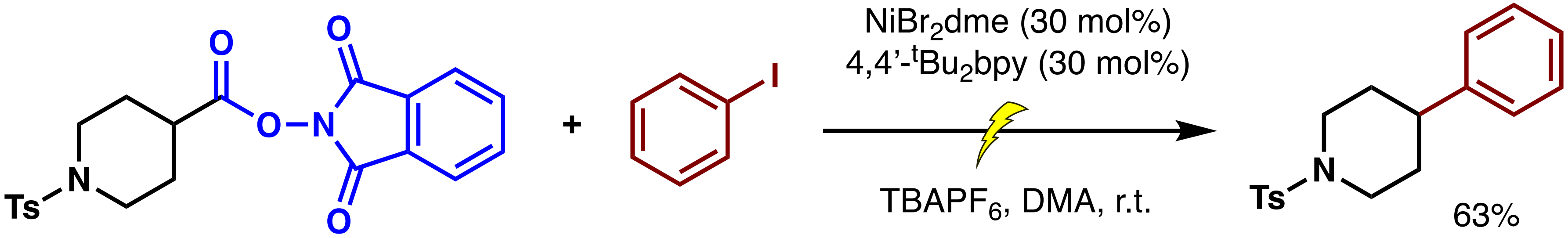
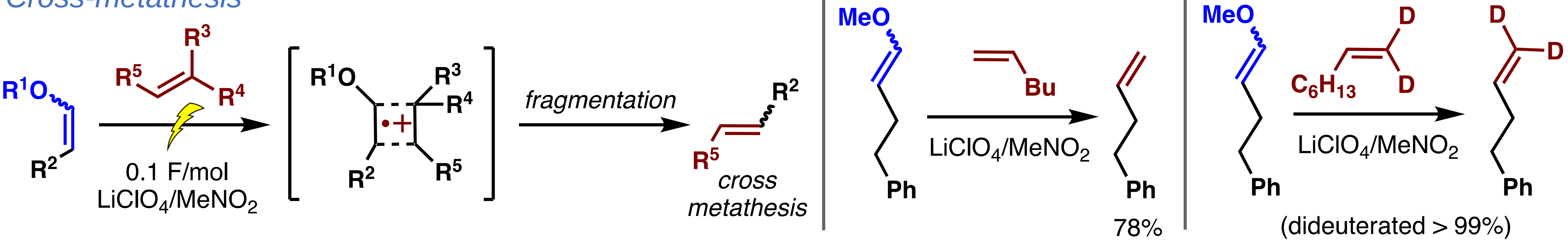


T. F. Jamison *et al*., *Org. Lett*. **2018**, *20*, 1338-1341.

Cross-metathesis



K. Chiba *et al*., *Angew. Chem. Int. Ed*. **2006**, *45*, 1461 –1463.

Electrochemical Parameters

Chemical reaction

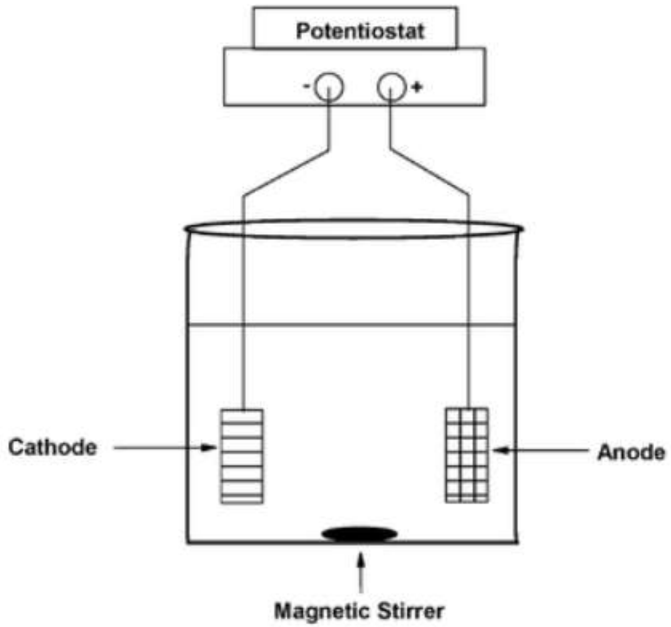
- Substrate
- Redox reagent
- Solvent
- (Catalyst)
- Flask

Electrochemical reaction

- Substrate
- Electricity
- Solvent
- (Mediator)
- Electrodes
- Electrolyte
- Constant current or constant potential
- Divided or undivided cell

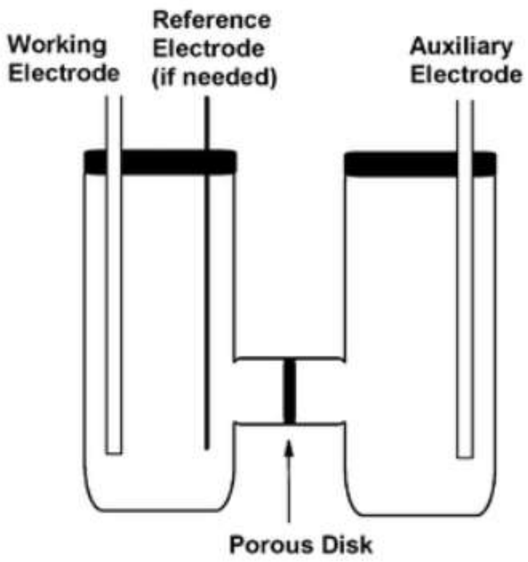
Divided or Undivided?

Undivided cell



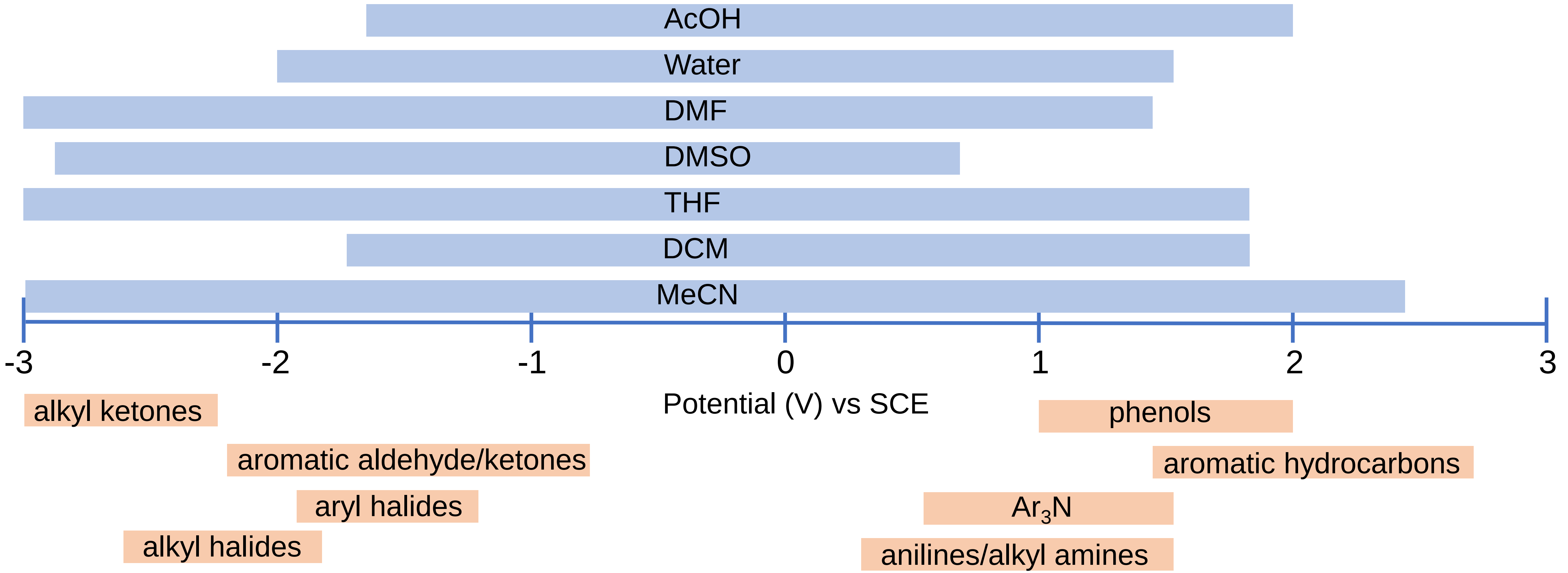
- Easy to set up
- First choice

Divided cell



- Higher resistance
- Less convenient than undivided cell
- Useful when a product reacts at the opposite electrode in undivided cell

Selection of Solvent



Oxidation: MeCN, acetone, $MeNO_2$, acetic acid, DCM, MeOH

Reduction: DMF, DMA, THF, MeCN, DMSO

Impractical solvent: benzene, toluene, hexane

D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723.

Selection of Electrodes

Anode

Anode for reduction									**Anode for oxidation**		
Mg	Al	Fe	Ni	Sn	Pb	Cu	Hg	Ag	Au	Pt	Carbon-based material

Sacrificial anode (Dissolve when used as anode)

Non-sacrificial anode

Carbon-based material: graphite, glassy carbon, RVC*, boron-doped diamond (BDD)

*RVC (Reticulum Vitreous Carbon) is porous glassy carbon

Selection of Electrodes

Anode

Anode for reduction									Anode for oxidation		
Mg	Al	Fe	Ni	Sn	Pb	Cu	Hg	Ag	Au	Pt	Carbon-based material
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Carbon-based material: graphite, glassy carbon, RVC*, boron-doped diamond (BDD)

*RVC (Reticulum Vitreous Carbon) is porous glassy carbon

Cathode

Cathode for reduction							Cathode for oxidation			
Mg	Al	Fe	Sn	Pb	Hg	carbon-based material	Fe	Au	Ni	Pt
Good for reduction of organic compounds							**When H_2 evolution is needed**			

Other Parameters

Electrolyte

- Ionic salt
- Good solubility to organic solvents
- Inert during a reaction
- Concentration: 0.1-0.5 M

Common electrolyte

Cation: Li^+, R_4N^+

Anion: BF_4, PF_6 , ClO_4 , triflate, halide

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Reaction mode

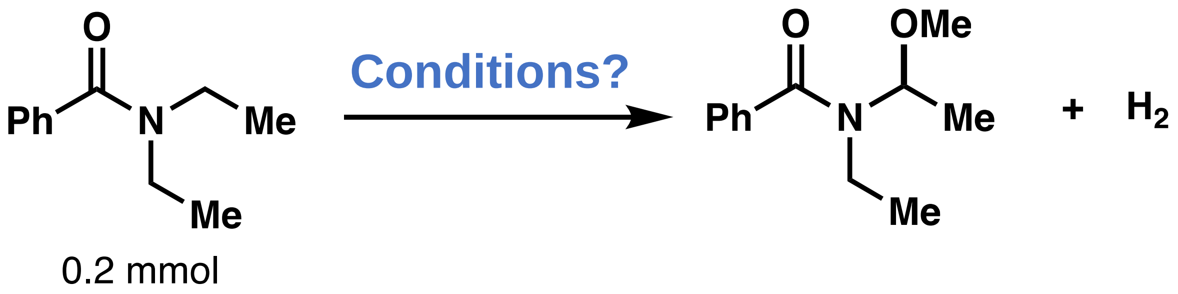
<u>Constant current</u>

- First choice
- Conversion is better than constant potential
- Current value: 2-10 mA, 2-4 F/mol
  (0.1-0.3 mmol reaction)

<u>Constant potential</u>

- Lower conversion, but higher selectivity than constant current
- Cyclic voltammetry helps to determine reaction potential that needs to be applied.
- For an instruction of cyclic voltammetry, see
  Go to Youtube → Search for ElectraSyn CV

Case Study 1: Finding the Right Conditions to Start



	Selection	Reason
Anode	RVC	Non-sacrificial anode
Cathode	Fe	Material with facile H_2 evolution
Electrolyte	$LiClO_4$	
Solvent	MeOH	Product is methanol adduct
Cell type	Undivided cell	
Reaction mode	Constant current (5 mA)	

Optimization

Initial conditions

(+)RVC/(−)Fe
$LiClO_4$
MeOH
Undivided cell
Constant current
5 mA

Was desired product obtained?

Yes → **Good yield?**

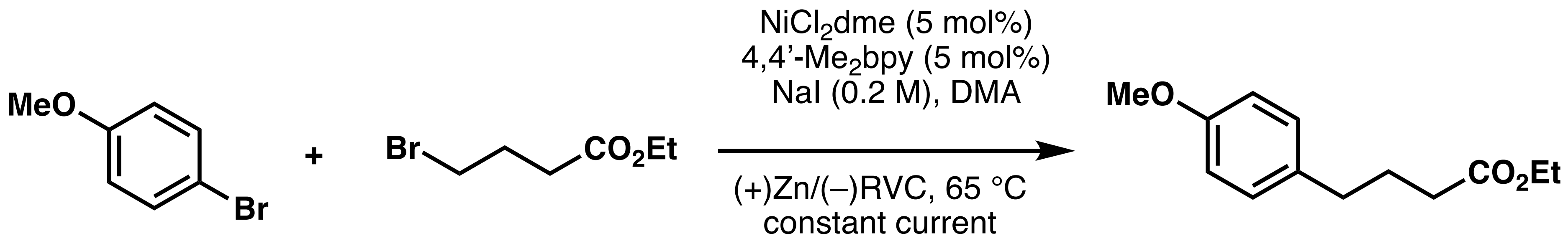
- Yes → Optimization completed!
- No →
  - (1) Change current with the same F/mol
  - (2) Change electrode
  - (3) Change solvent
  - (4) Change electrolyte

No → **No reaction?**

- Yes → Increase current
- No → Identify side reactions and modify conditions to avoid them.

Case Study 2: Scaling

E. C. Hansen *et al*., *Org. Lett*. **2017**, *19*, 3755-3758.



1.3 mmol 1.7 mmol 65%

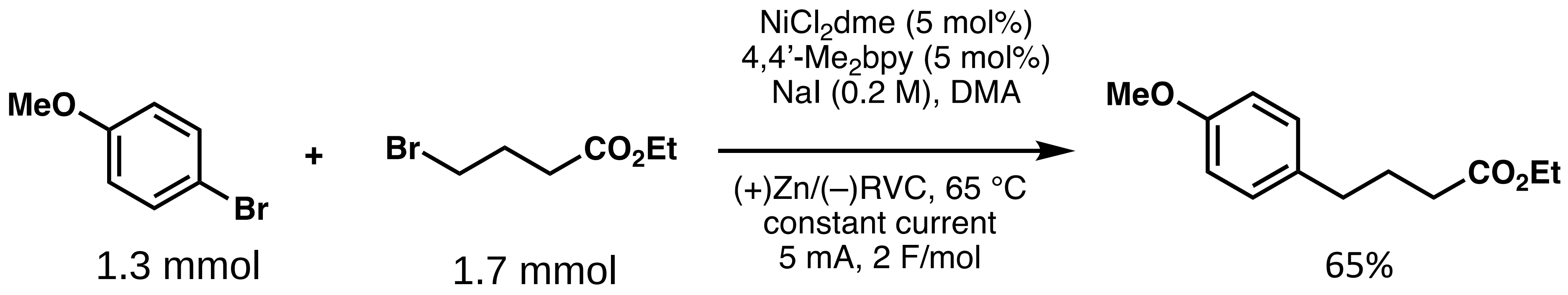
Case Study 2: Scaling

E. C. Hansen *et al*., *Org. Lett*. **2017**, *19*, 3755-3758.

0.33 mmol 0.43 mmol

Scale down

Constant current
1.3 mA, 2 F/mol



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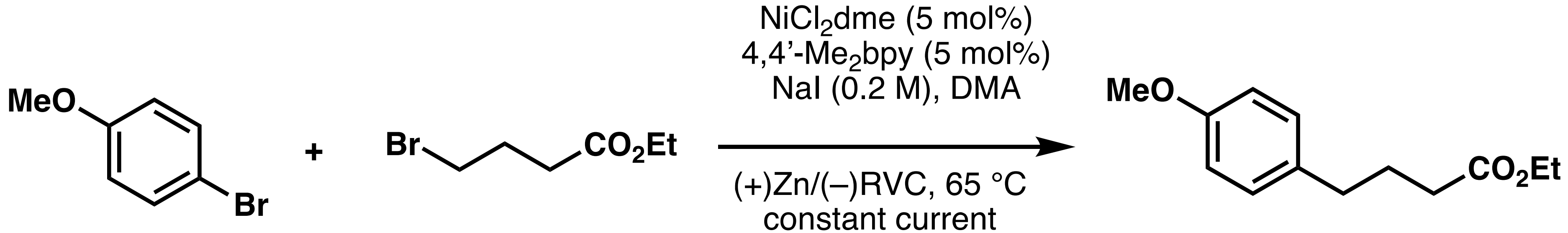

1.3 mmol 1.7 mmol 65%

Scale up

Constant current, **5 mA , 2 F/mol**

2.6 mmol 3.4 mmol

(To avoid high current density)

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0.33 mmol 0.43 mmol

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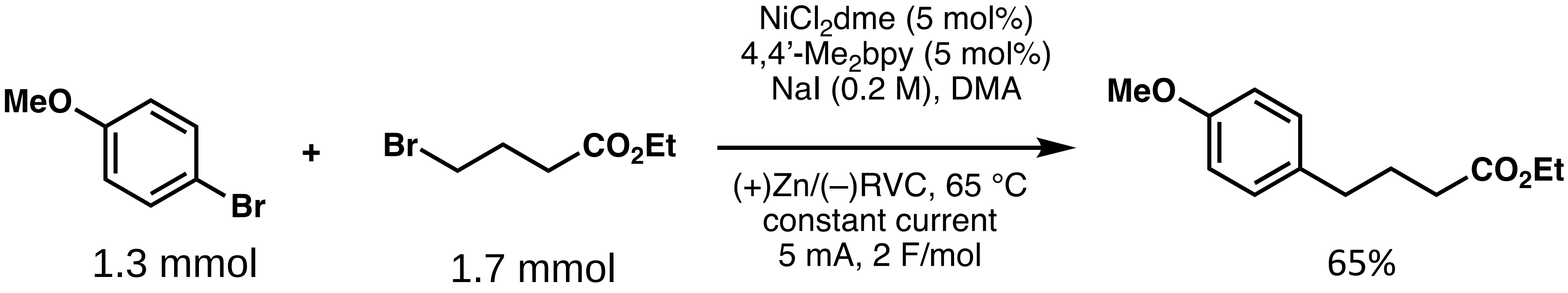
Constant current
1.3 mA, 2 F/mol



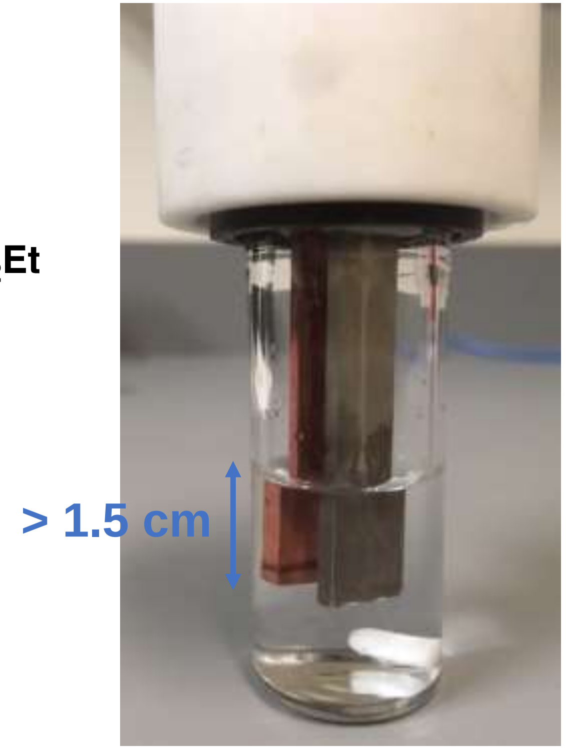
Scale up

Constant current, **5 mA , 2 F/mol**

2.6 mmol 3.4 mmol

(To avoid high current density)

Amount of solvent
& Vial size



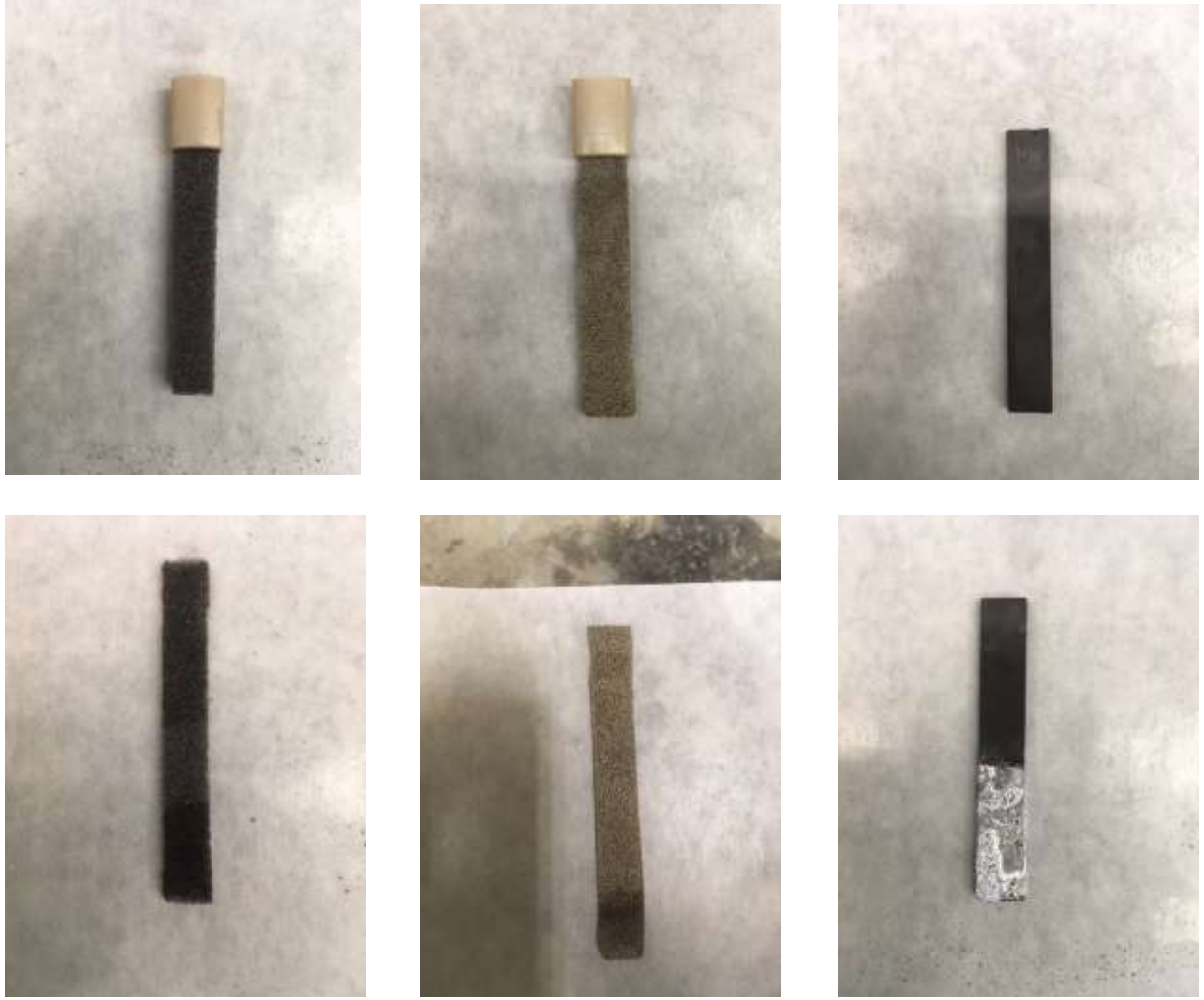
Troubleshooting

Problem	Possible cause	Solution
Voltage is too high (> 20 V without reference)	Bad connection between an electrode and a cap (corrosion, loose contact etc.)	Clean up and secure the connection.
	Electrode passivation	Wash or polish electrode.
	Low concentration of electrolyte	Add more electrolyte.
	Inappropriate solvent (low dielectric constant)	Change solvent or add more electrolyte.
Voltage is too low (<0.5 V without reference)	Short circuit	Make sure both electrodes are completely separated.

Electrode Maintenance and Cleaning

Good

Bad



Color change/fauling

Deposit

Cleaning of Electrode

1) Acetone wash to remove organic

2) 1 M HCl wash, then water rinse

3) Acetone wash again

If the above method is not enough:

4) Sonication

5) Scrape off deposit

Coming Soon

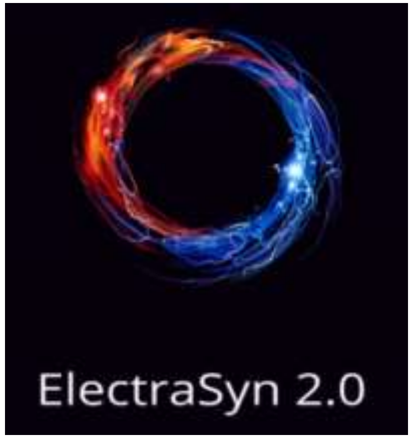
6-Reaction Carousel

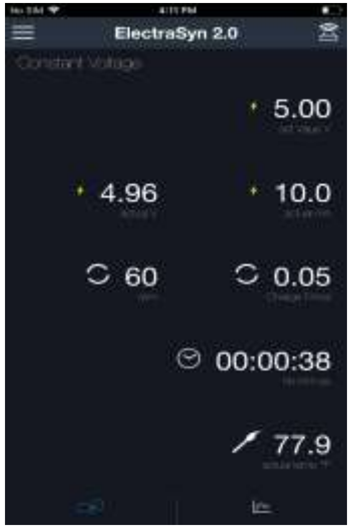
ElectraSyn Extension

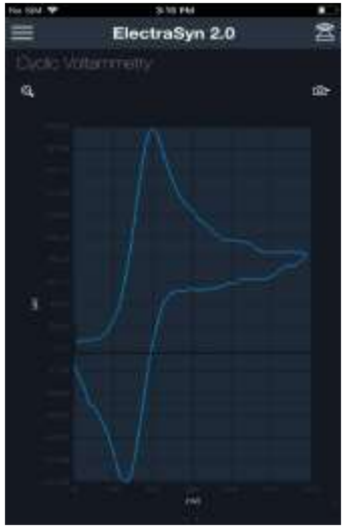
Microelectrodes

1 -2 mL vials

ElectraSyn App







Available from Testflight

YOUR CHEMISTRY HAS POTENTIAL

Summary: Preferred Selections

	Oxidation	Reduction	Net redox neutral
Anode	Pt or carbon-based	Sacrificial anode (Mg, Zn, Al, Fe, Sn, etc.)	Pt or carbon-based
Cathode	Various materials	Zn, Sn, Pb, carbon-based	Various materials
Electrolyte	Various Li or tetraalkylammonium salts		
Solvent	MeCN, acetone, $MeNO_2$, DCM, MeOH	DMF, DMA, THF, DMSO	MeCN, acetone, $MeNO_2$, DCM, MeOH
Cell type	Undivided cell		
Reaction mode	Constant current at 5 mA		

Summary: Default Conditions

	Oxidation	Reduction	Net redox neutral
Anode	Graphite or RVC	Zn	Graphite or RVC
Cathode	Ni foam	Zn	Ni foam
Electrolyte	$LiClO_4$ or $TBABF_4$		
Solvent	MeCN	DMF	MeCN
Cell type	Undivided cell		
Reaction mode	Constant current at 5 mA		