ORGANIC ELECTROCHEMISTRY

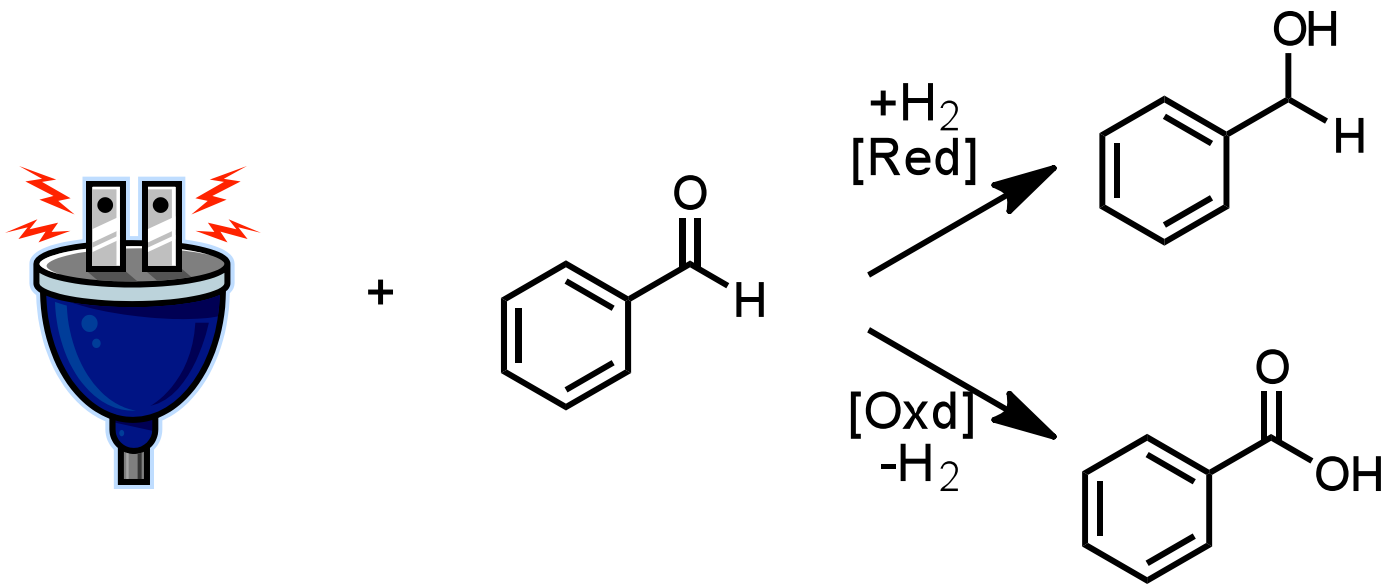
Zachery Matesich 18 June 2013

Roadmap

- Organic Electrochemistry
- Electrochemical Cell
- Radical Ions
- Anodic Oxidations
- Cathodic Reductions
- Conclusion

Organic Electrochemistry: What is it?

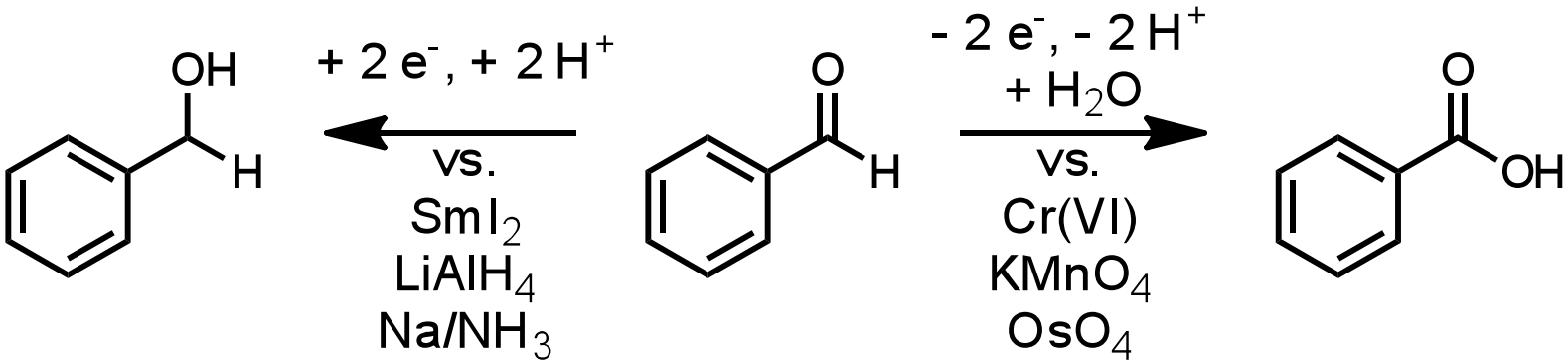
- Use of electrical current through a reaction to activate organic molecules through the addition or removal of electrons



Fry, A. *Electochem. Soc. Interface* **2009**, 28-33.

Organic Electrochemistry: Why?

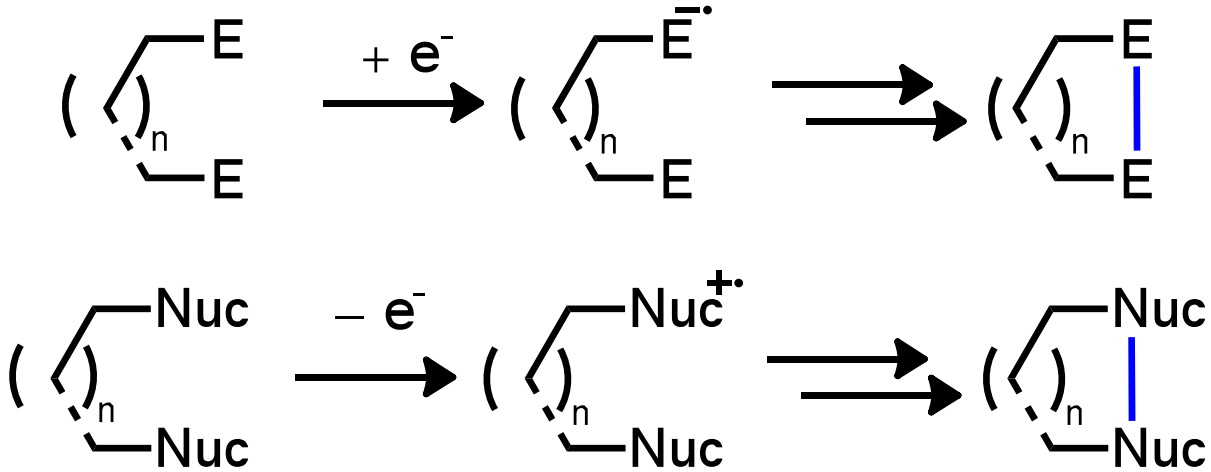
- Reaction economy
  - Direct control of electron energy via over potential
  - Electrons/protons are (typically) sole reagents



Frontana-Uribe, B.A. *et al Green Chem.* **2010,** *12,* 2099-2119.

Organic Electrochemistry: Why?

- Synthetic utility
  - Umpolung chemistry
  - High, typically predictable, tolerance of functional groups

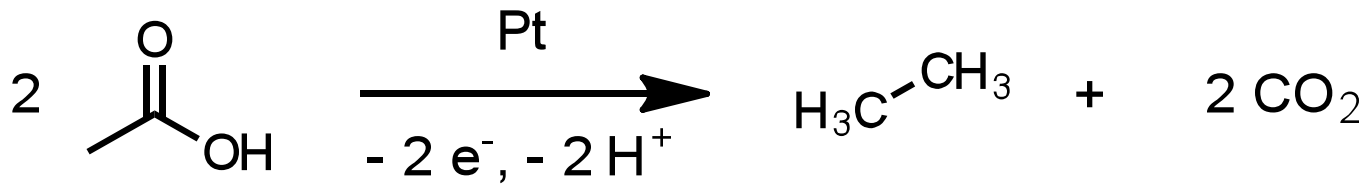


E = electrophile; Nuc = nucleophile

Frontana-Uribe, B.A. *et al Green Chem.* **2010,** *12,* 2099-2119.

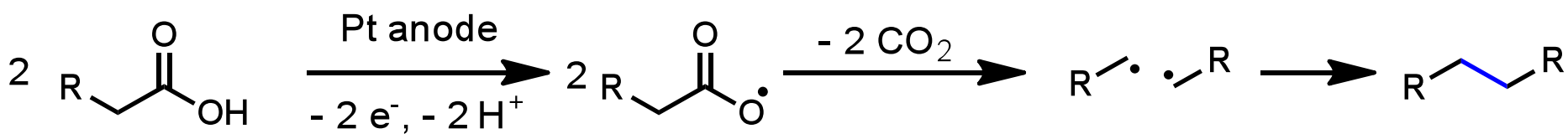
Organic Electrochemistry: Early Beginnings

- 1st example – Faraday (1834):



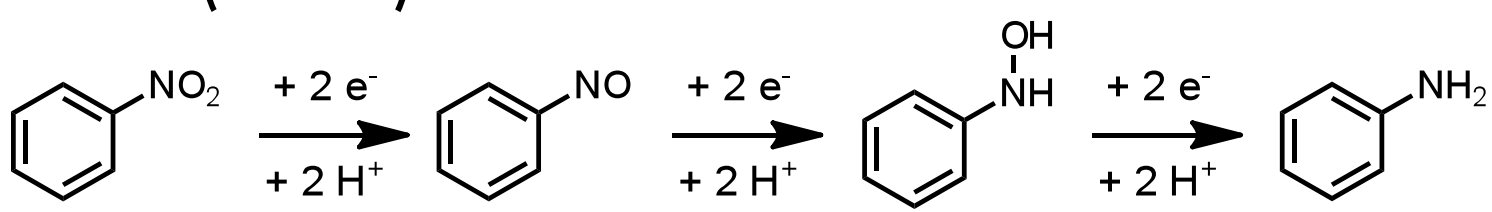
Farday, M. *Phil. Trans. R. Soc. Lond.* **1834,** 124, 77-122.

- Kolbe Electrolysis (1848):



Kolbe, H. *Justus Liebigs Ann. Chem.* **1848,** *69*, 257-372.

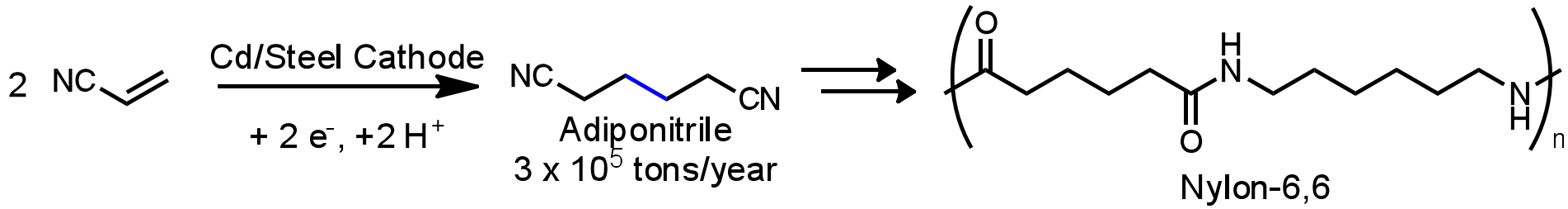
- Haber (1900):



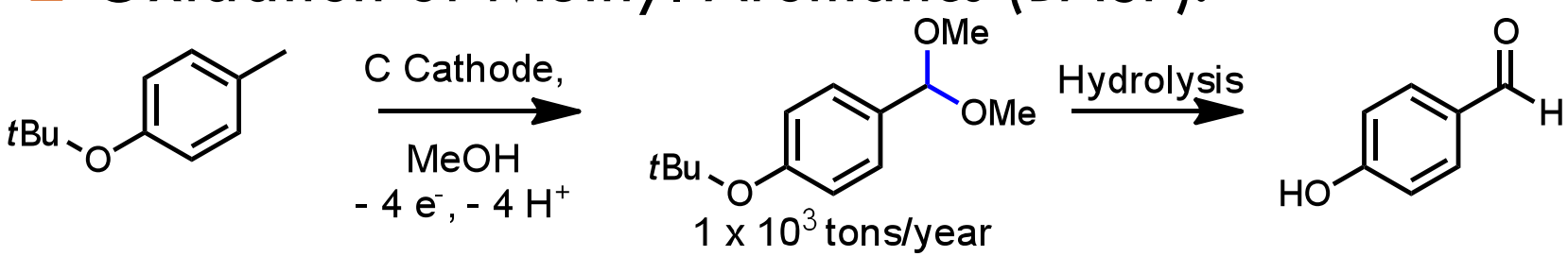
Haber, F. *et al. Z.Phys. Chem.* **1900,** *32*, 271.

Organic Electrochemistry: Use in industry

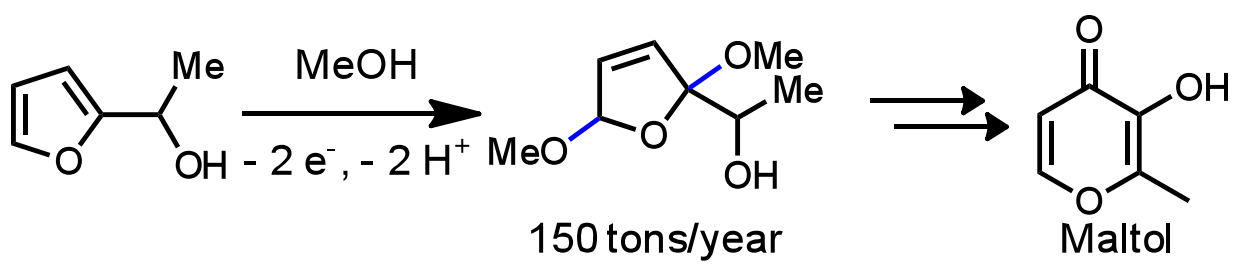
- Hydrodimerization of Acrylonitrile (Monsanto):



- Oxidation of Methyl Aromatics (BASF):



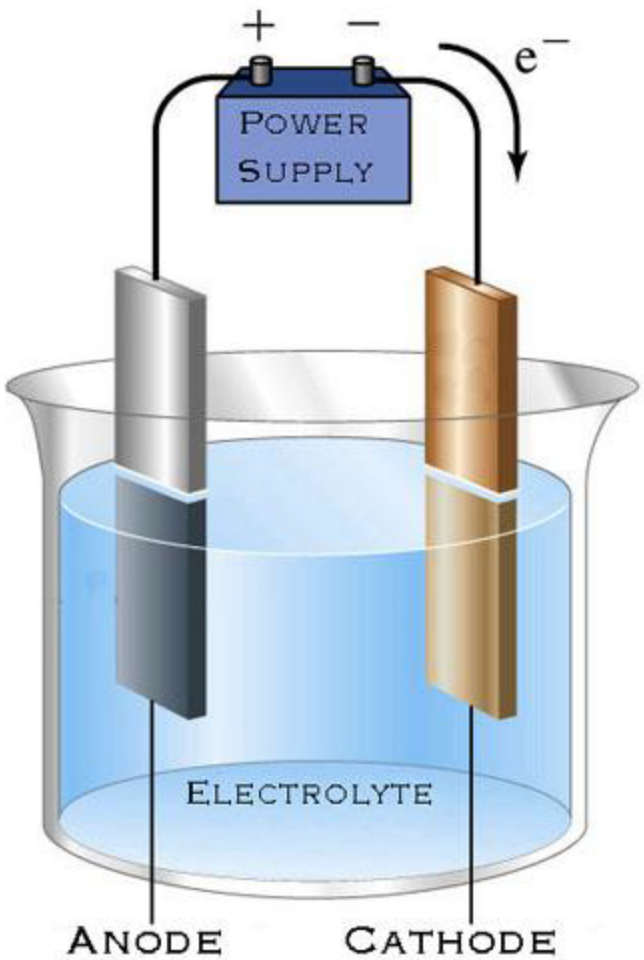
- Methoxylation (Otsuka):



Pletcher, D.; Walsh, F. C. Industrial Electrochemistry; Blackie Academic & Professional: Glasgow, 1993

Electrochemistry: Basics

- Electrolytic cell - electricity is applied

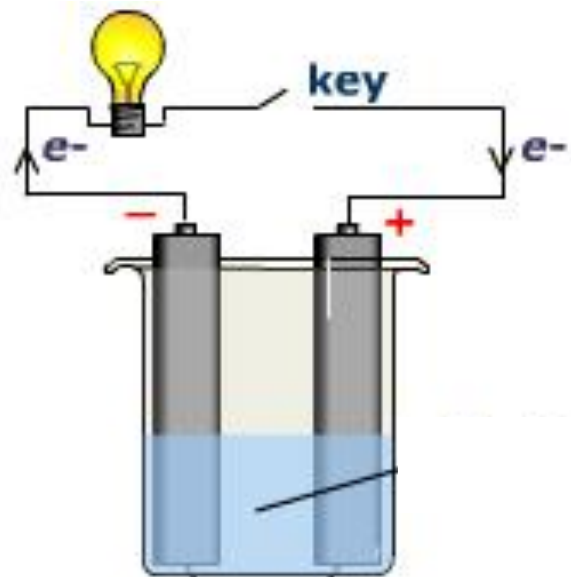


- Anode: Oxidation site
- Cathode: Reduction site
- Solvent: MeOH, CH_3CN, H_2O
- Electrolyte: Bu_4NBF_4, $LiClO_4$, Et_4NClO_4
- Two methods for actions:
  - Constant current
  - Constant potential
- $\Delta G = -n F E$

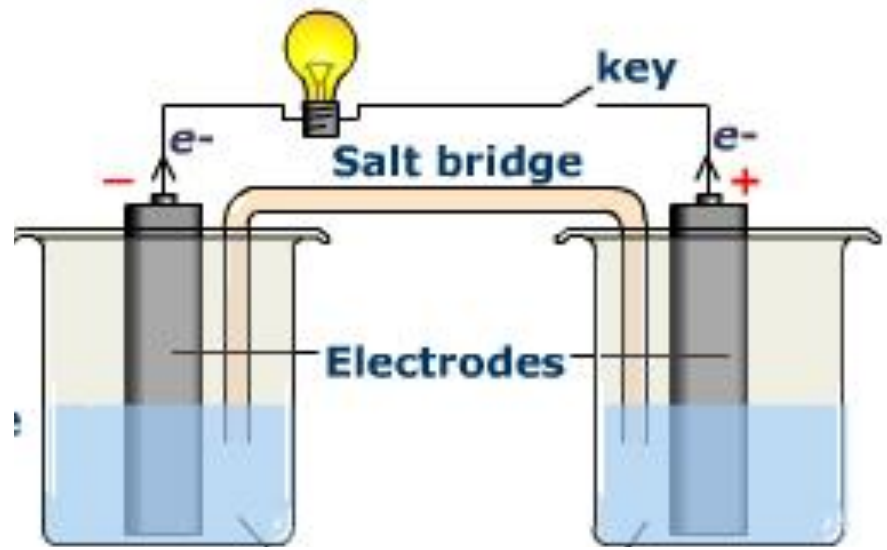
Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Electrochemical Cell: Design

- Two main types of cells:



Undivided



Divided

- Requires use of third electrode for reference for constant potential experiments

Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Electrochemical Cell: Design - Undivided

http://www.gamry.com/assets/Uploads/EuroCell-Kit.jpg

- Simplest design
- Must ensure compound compatibility
- Use of protic solvents aids in reaction mediation

Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Electrochemical Cell: Design - Divided

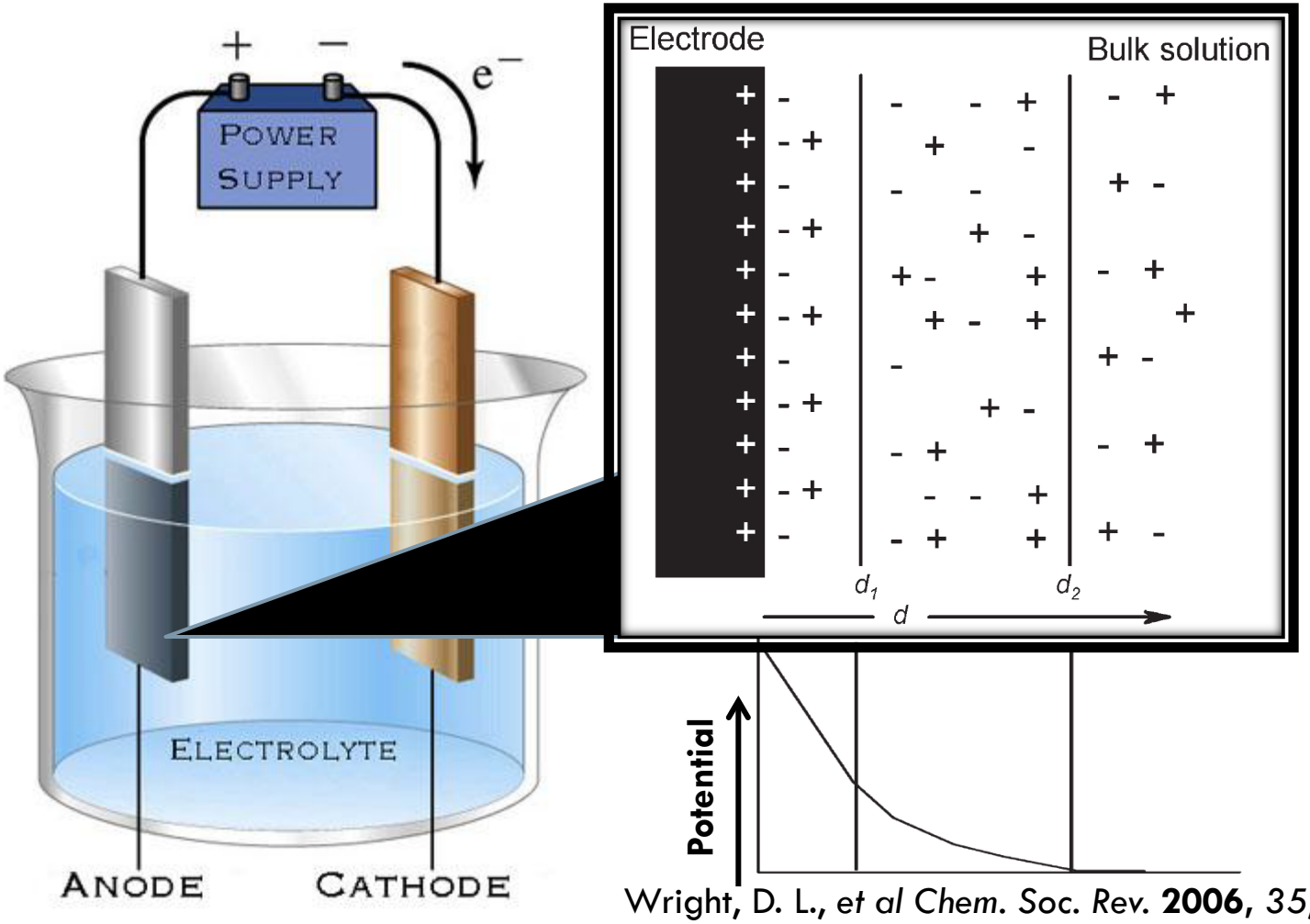
http://www.blogs.uni-mainz.de/fb09akwaldvogel/files/2010/09/oximered2a2.jpg

- More complex (and expensive)
- Avoids issue of compound compatibility
- Sacrificial metal or substrate in auxiliary electrode

Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Electrochemical Cell: Considerations

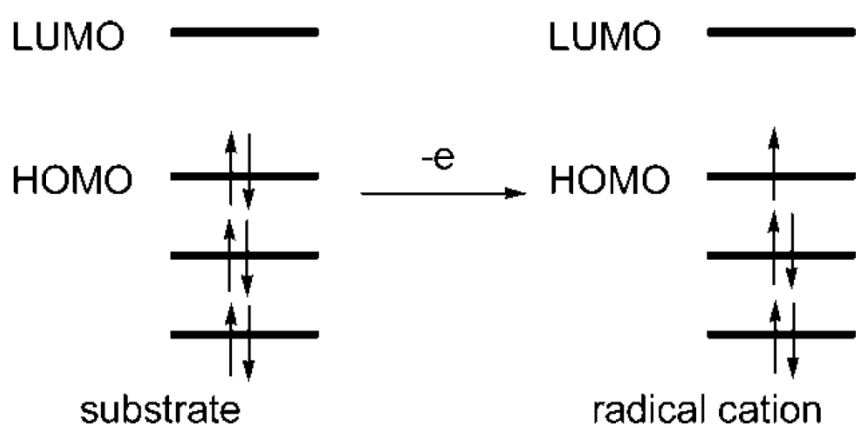
- Double-layer interface



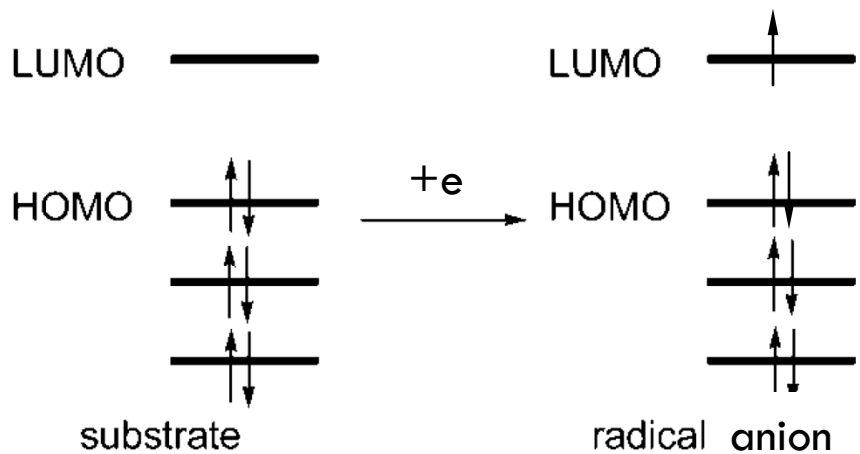
Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Radical Ions

- Oxidation



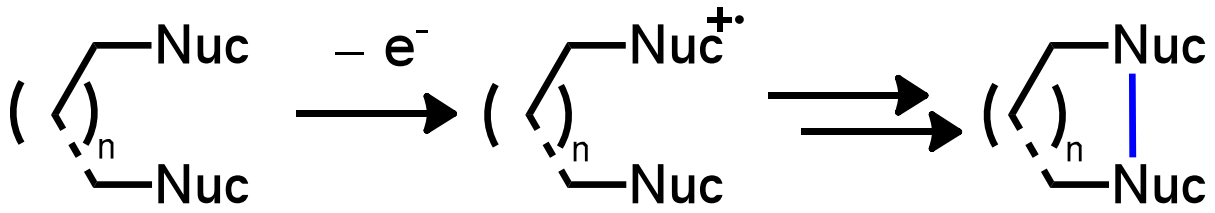
- Reduction



Yoshida, J. *et al Chem. Rev.* **2008**, *108*, 2265-2299.
Yoon, T. *Eur. J. Org. Chem.* **2012**, 3359–3372.

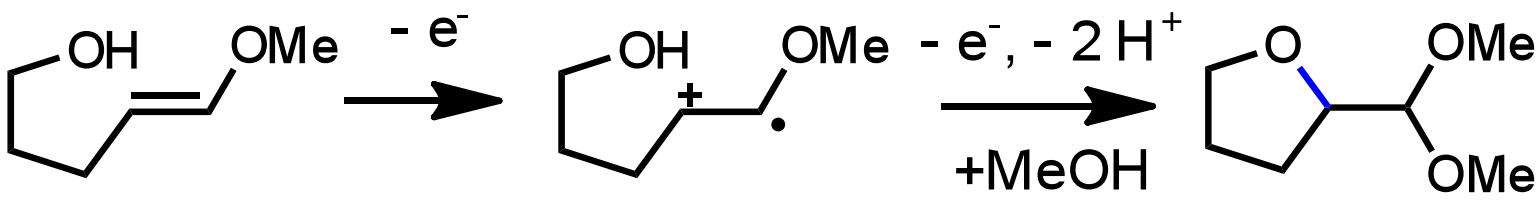
Anodic Oxidation

- Removal of electron from substrate



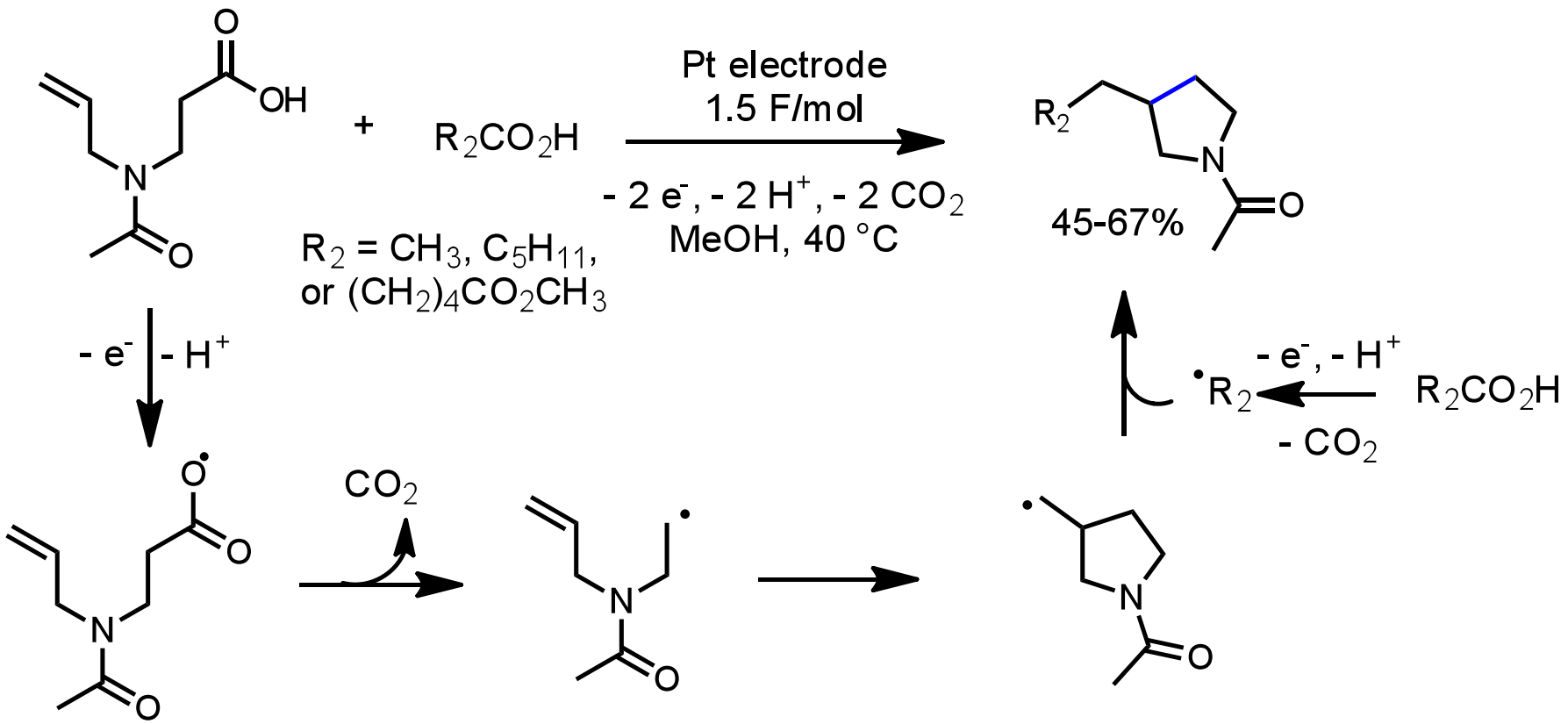
Nuc = nucleophile

- Generally highly reactive intermediates formed



Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Kolbe Oxidation

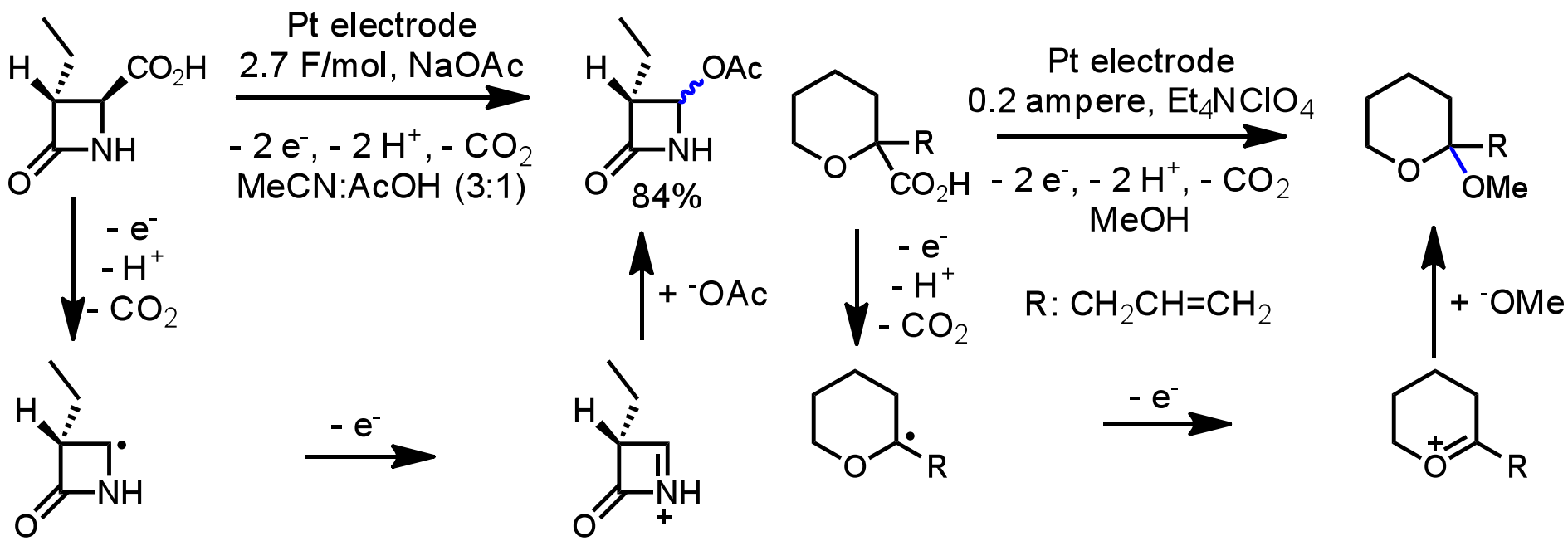


- Method to induce more control over intermediate?

Schäfer, H. J., *et al Tetrahedron Lett.* **1988**, *29*, 2797-2800.

Non-Kolbe Oxidation

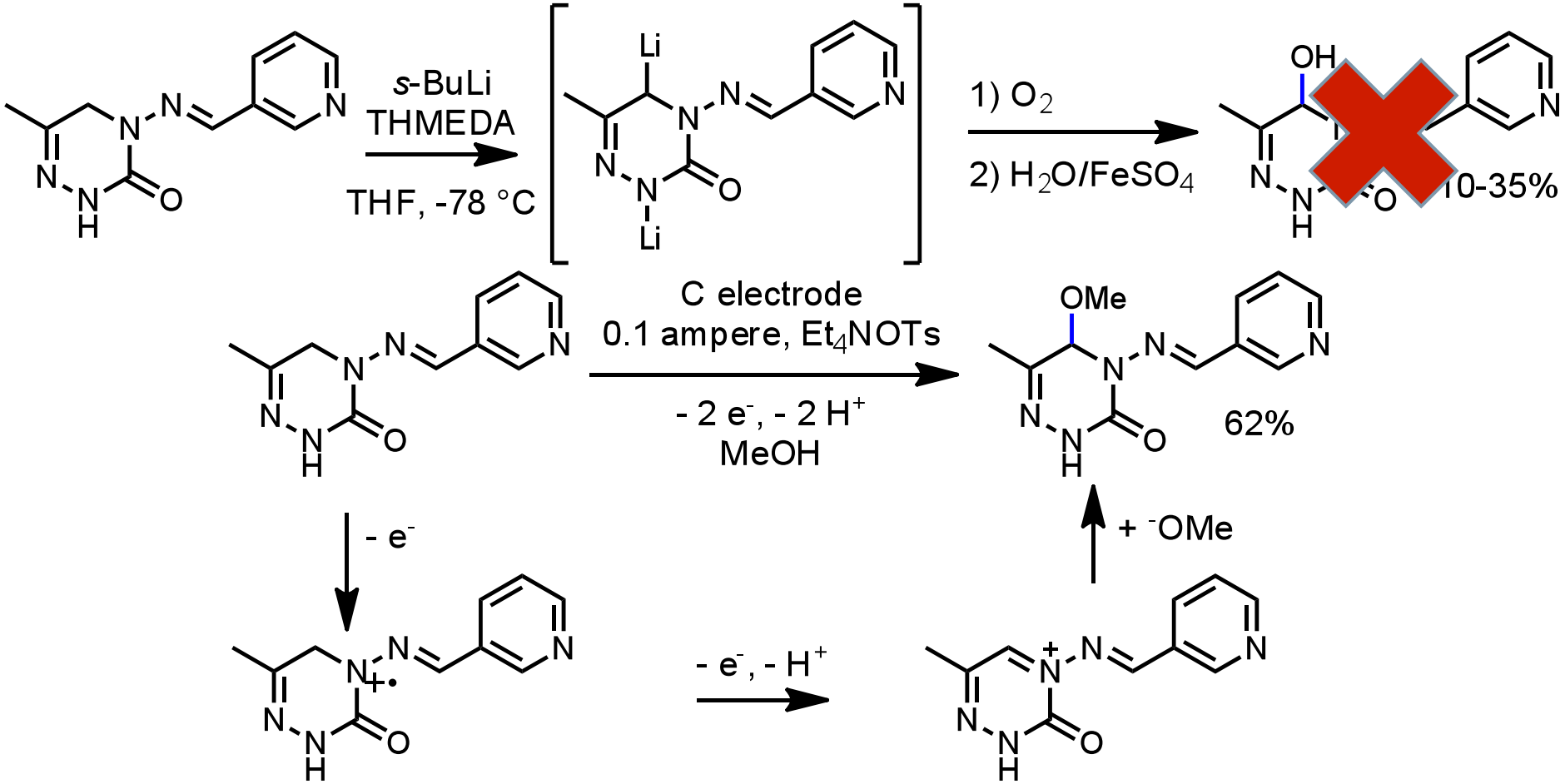
- Presence of a heteroatom α to carbonyl



- Stabilized carbocation formation inhibits dimerization

Shibasaki, M. *et al* Tetrahedron **1991**, *47*, 531-540.
Wuts, P. G. M. Tetrahedron Letters **1982**, *23*, 3987-3990.

Non-Kolbe Oxidation: Cautionary Tale

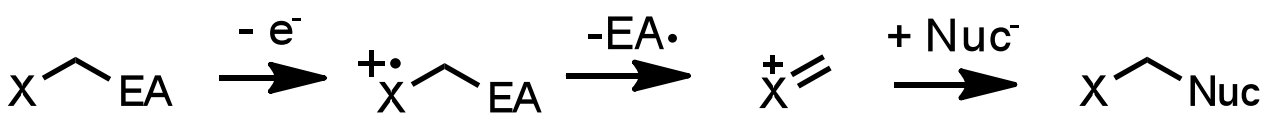


- Can non-solvent nucleophiles be employed?

Hudlicky, T. *et al J. Am. Chem. Soc.* **1997**, *119*, 7694-7701.

Use of Electroauxiliaries

- Introduction of a functional group that promotes electron transfer in a more selective manner



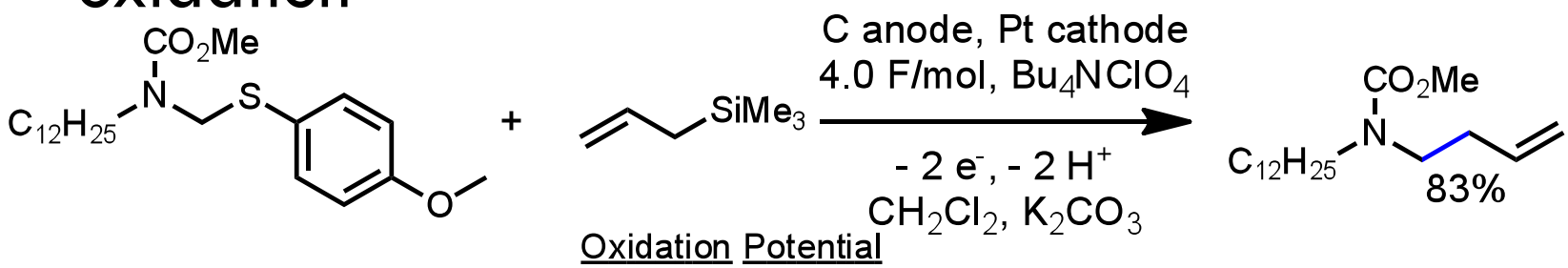
Compound	E (V)*	Compound	E (V)*
MeO C_7H_{15}	> 2.50	MeO C_7H_{15} $SiMe_3$	1.72
MeO $SiMe_3$	1.90	PhS $SiMe_3$	1.12
MeO SPh	1.40	PhS $SnBu_3$	0.69
MeO $SnBu_3$	0.91	PhS $SiMe_3$ $SnBu_3$	0.68

*vs. Ag/AgCl

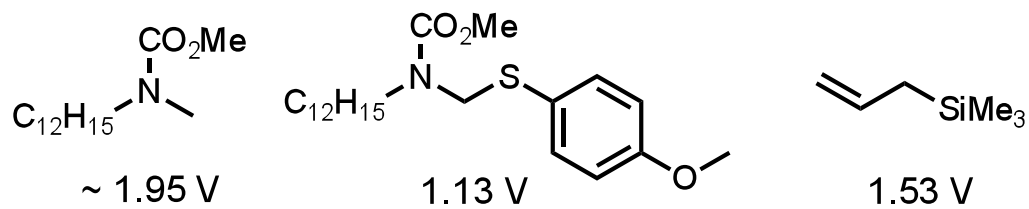
Yoshida, J. *et al Chem. Soc. Rev.* **2008**, *108, 2265-2299.*

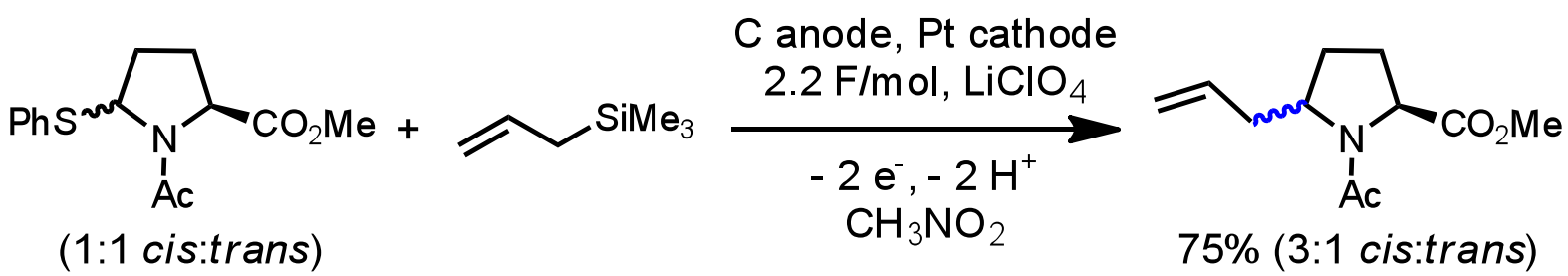
Electroauxiliaries: Non-solvent Nucleophile

- Electroauxiliary allow for preferential substrate oxidation



Oxidation Potential





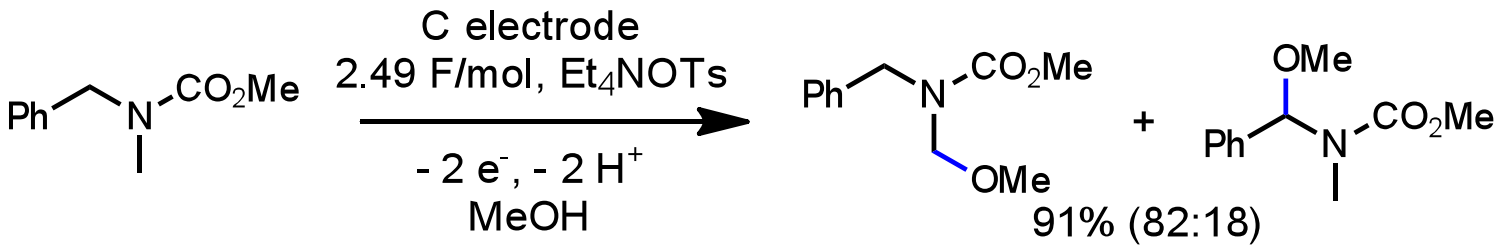
(1:1 *cis*:*trans*)

75% (3:1 *cis*:*trans*)

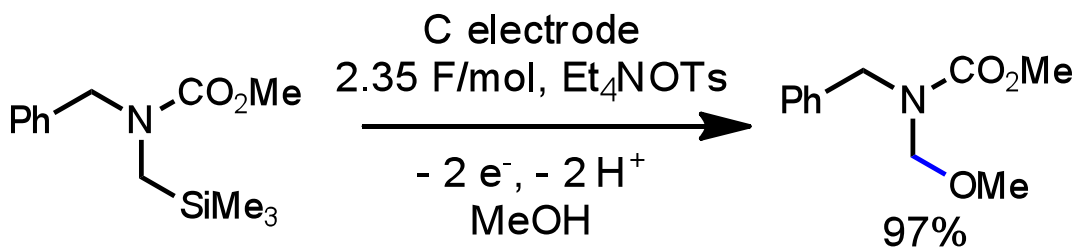
Yoshida, J. *et al Electrochim. Acta.* **1997**, *42*, 1995-2003.
Chiba, K. *et al Org. Lett.* **2002**, *4*, 3735-3737.

Electroauxiliaries: Regioisomer control

- Without electroauxiliary



- With electroauxiliary

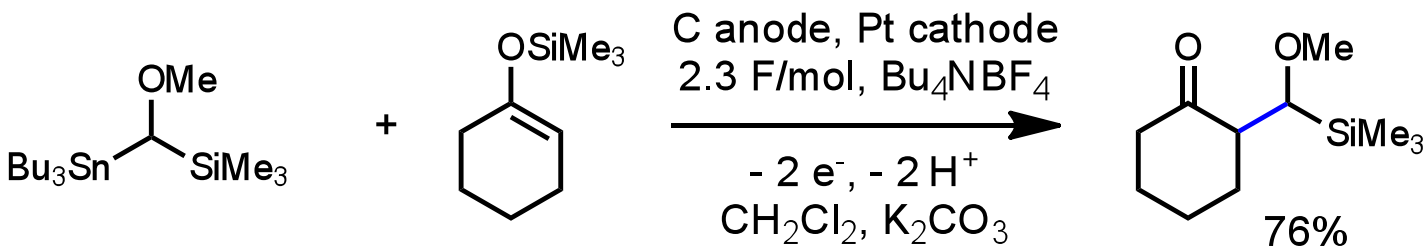


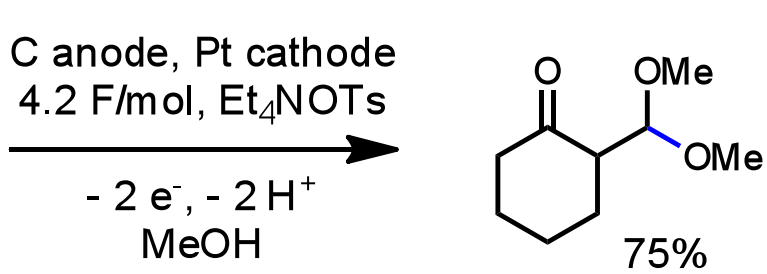
- Use of electroauxiliaries can give selective formation of single product in higher yield with less energy

Yoshida, J. *et al Tetrahedron Lett.* **1987**, *28, 6621-6624.*

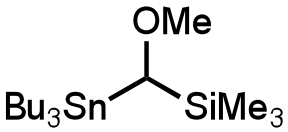
Electroauxiliaries: Selective Oxidation

- Use of two different electroauxiliaries

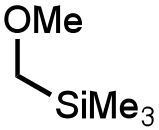




Oxidation Potential



0.9 V



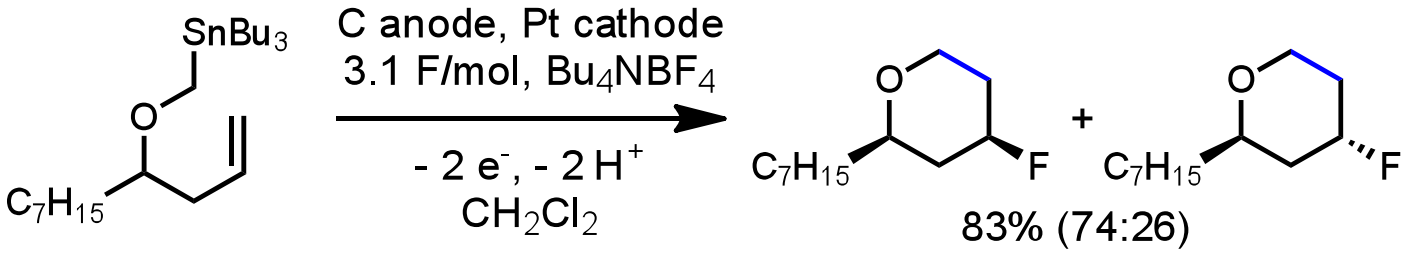
1.6 V

- Allows for sequential addition of nucleophiles

Yoshida, J. *et al Chem. Lett.* **1998**, *1011-1012.*

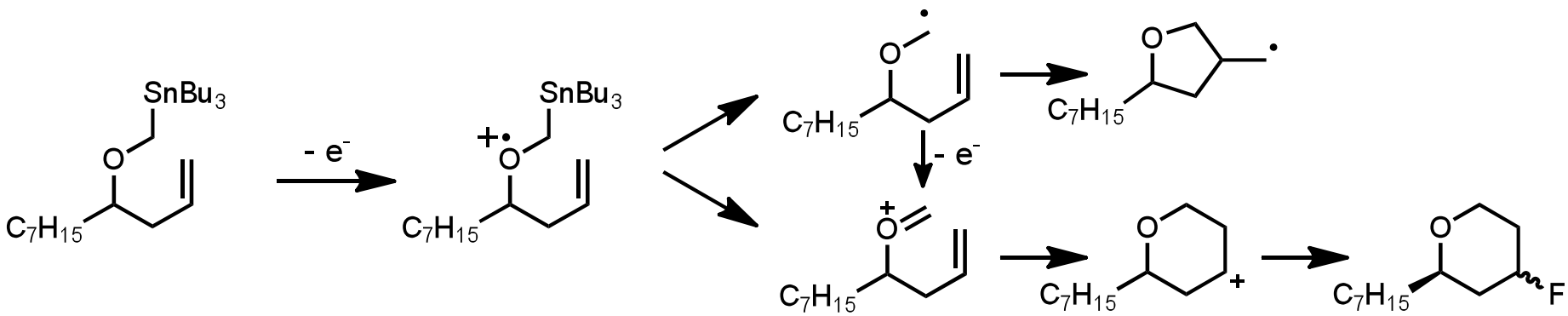
Electroauxiliaries: Cyclization Fluorination

- Inclusion of fluorine during cyclization



EA = $SiMe_3$ 68% (55:45)
= SMe 64% (87:13)

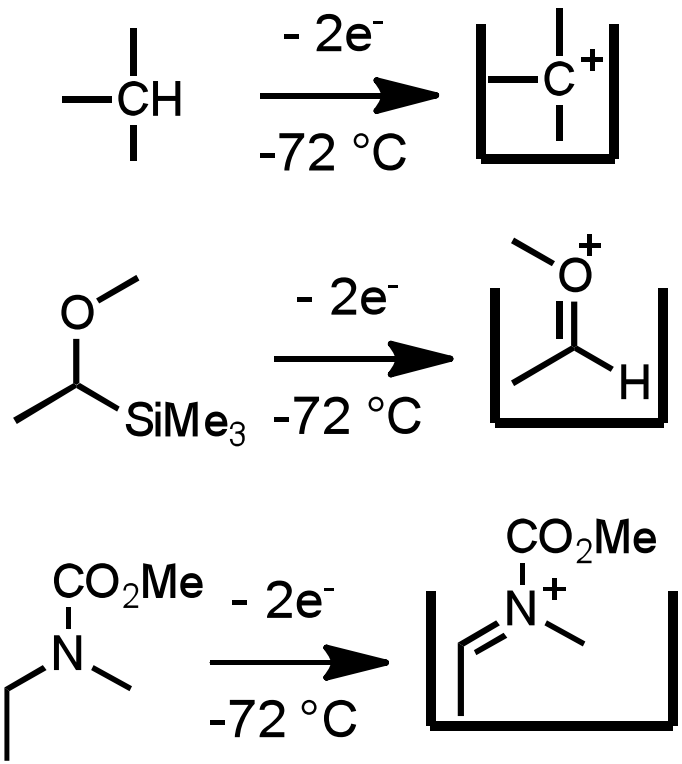
- Distinguish between radical and cation pathways

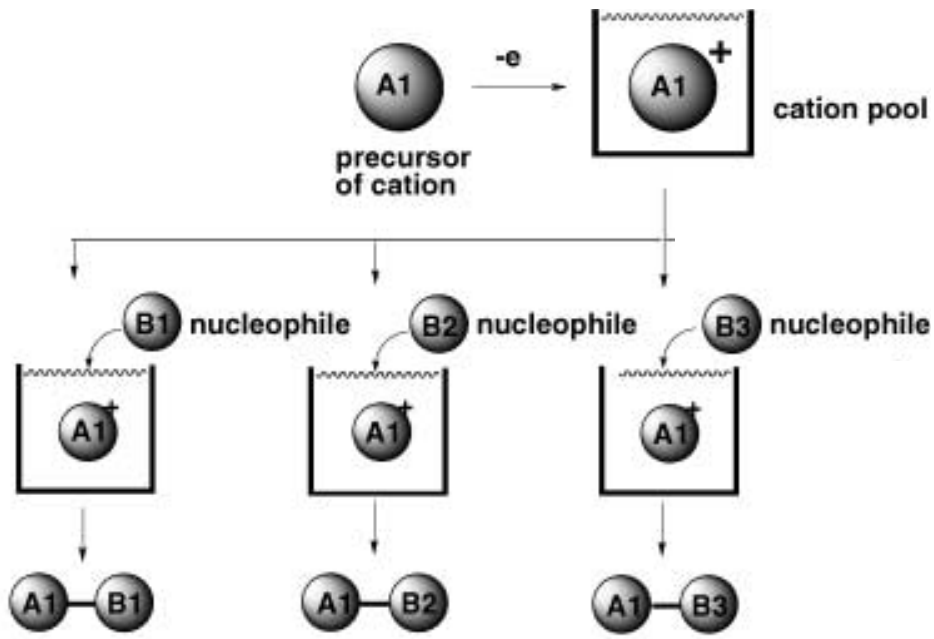


Yoshida, J. *et al J. Am. Chem. Soc.* **1992**, *114*, 7594-7595.

Cation Pool Methodology

- Generation of organic cations at low temp (~ -70°C)
- Use of CH_2Cl_2 and Bu_4NBF_4 allow favorable system

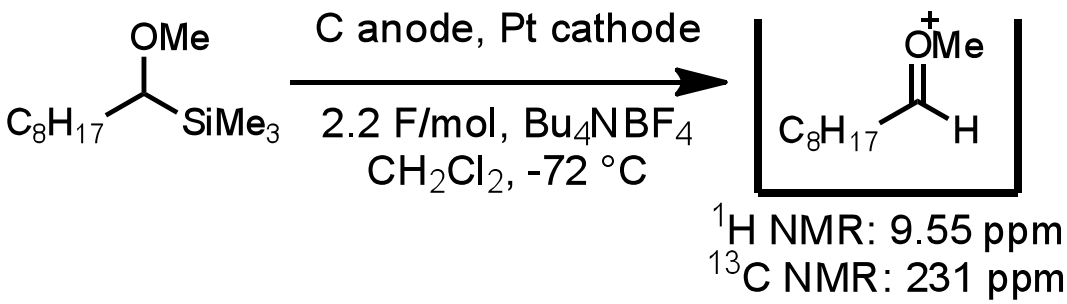


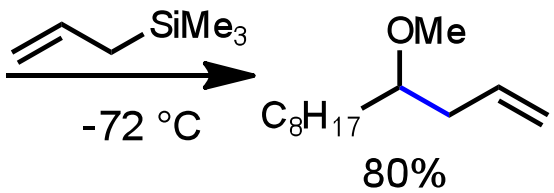


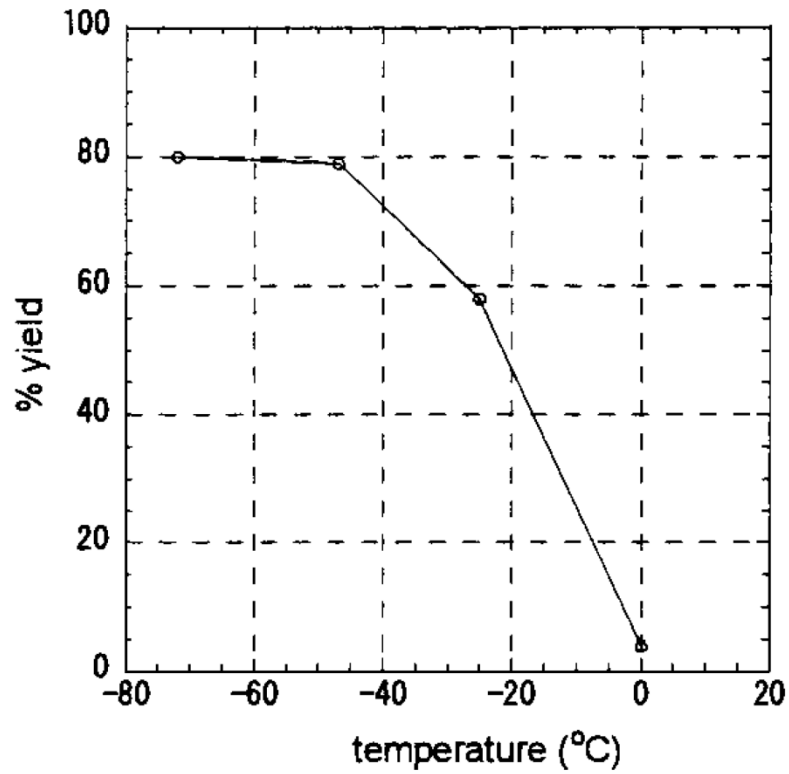
Yoshida, J. *et al Chem. Eur. J.* **2002,** *8,* 2650-2658.

Cation Pool: Alkoxycarbenium Ions

- Use of carbon nucleophiles





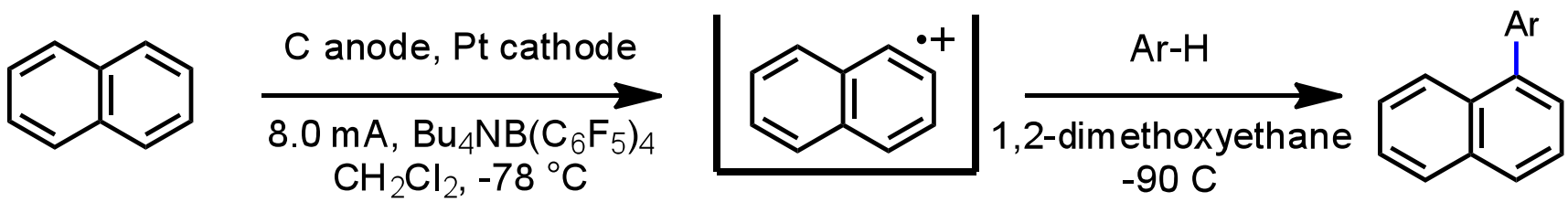


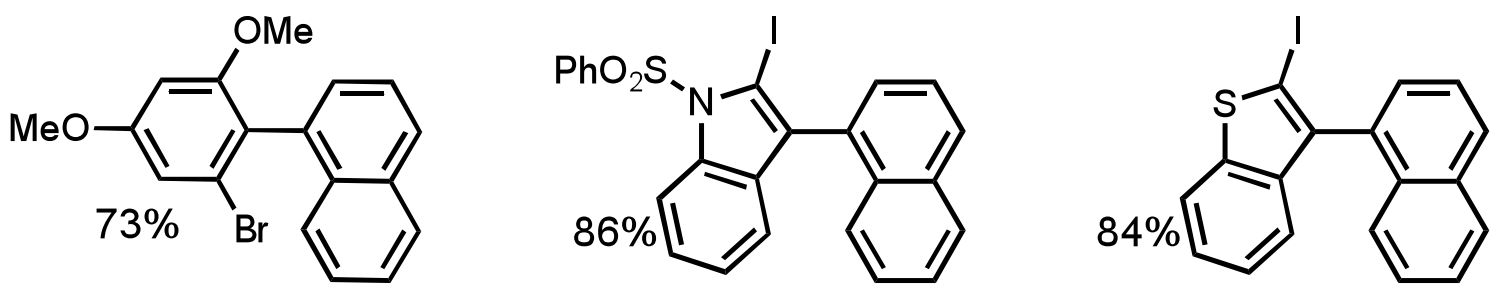
- Temperature dependence (< -50 °C)

Yoshida, J. *et al J. Am. Chem. Soc.* **2000**, *122*, 10244-10245.

Cation Pool: C-H Cross-coupling

- Cation pool methodology, but employing radical cations



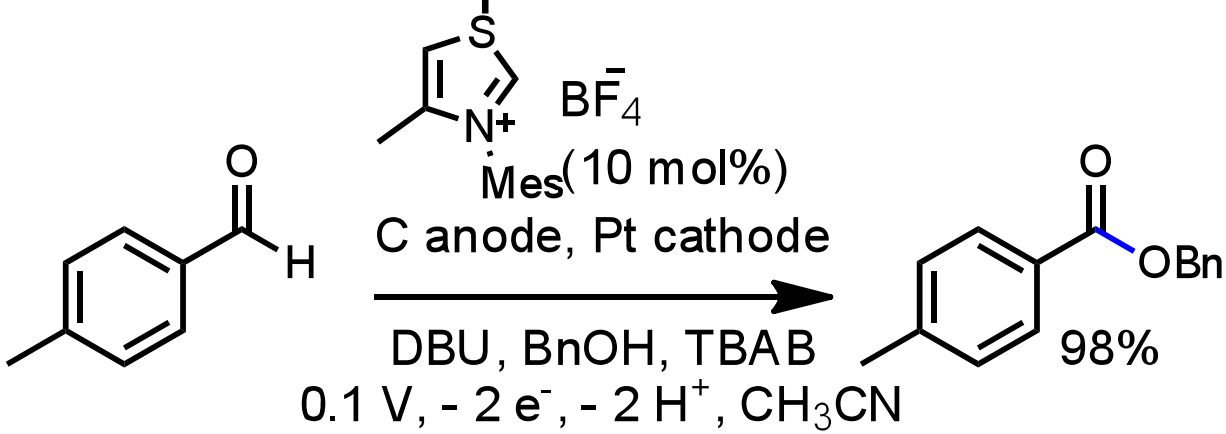


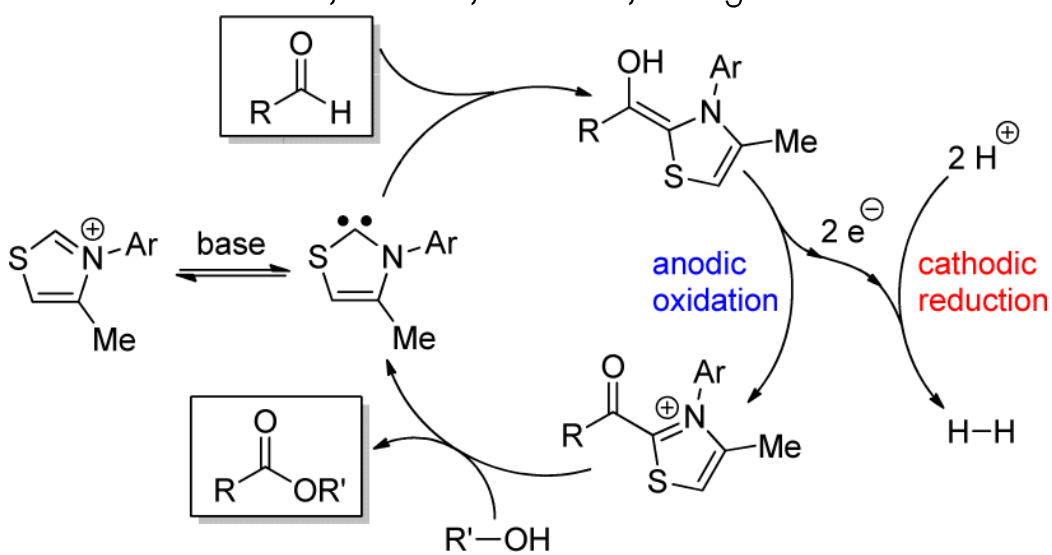
- Regioselectivity is typically high and predictable (DFT)

Yoshida, J. *et al Angew. Chem. Int. Ed.* **2012**, *51*, 7259-7262.

In situ electroauxiliaries

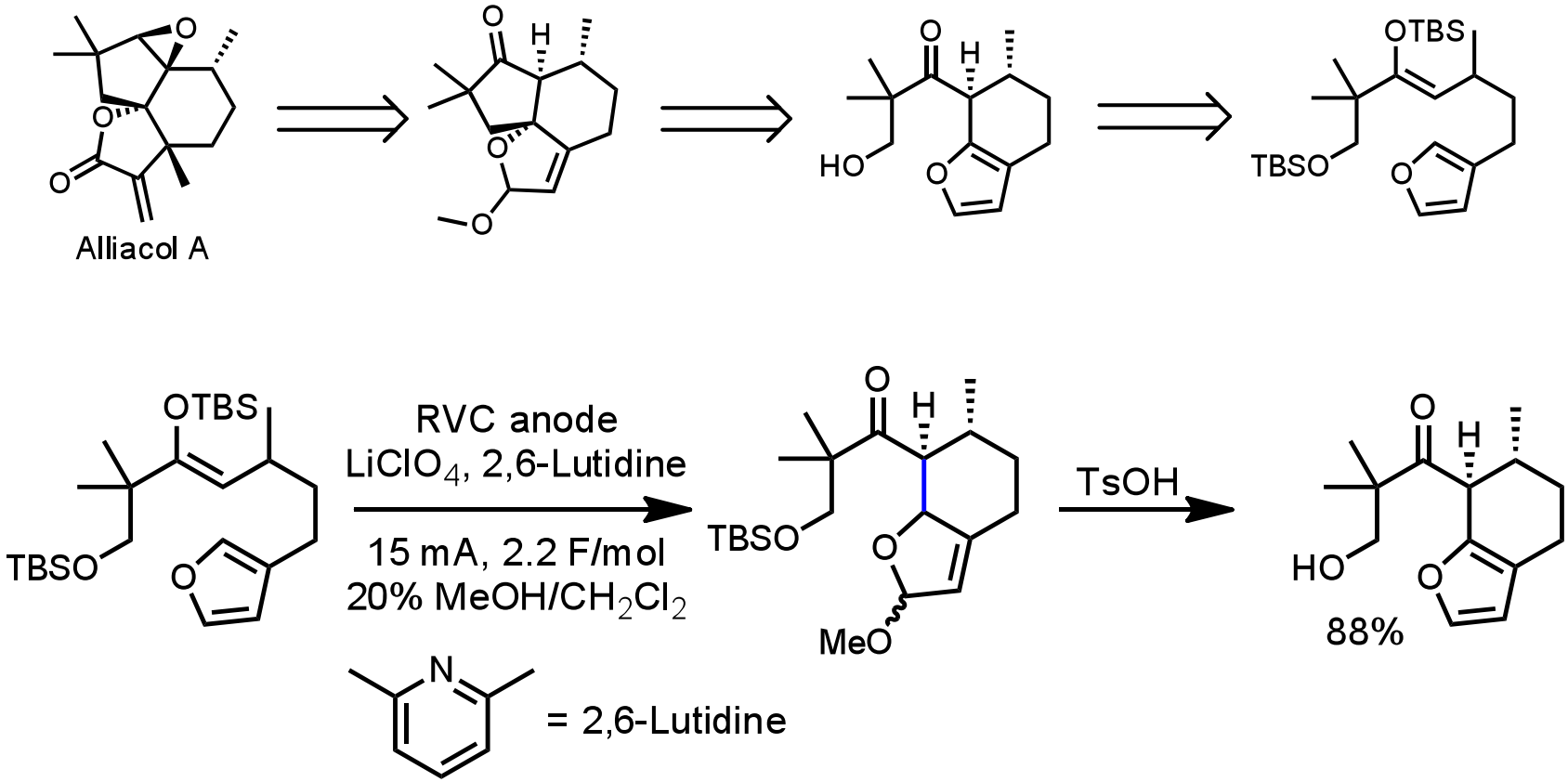
- Alleviates need for pre-installation of leaving groups





Boydston, A. J. *et al J. Am. Chem. Soc.* **2012,** *134,* 12374–12377.

Synthesis of Alliacol A

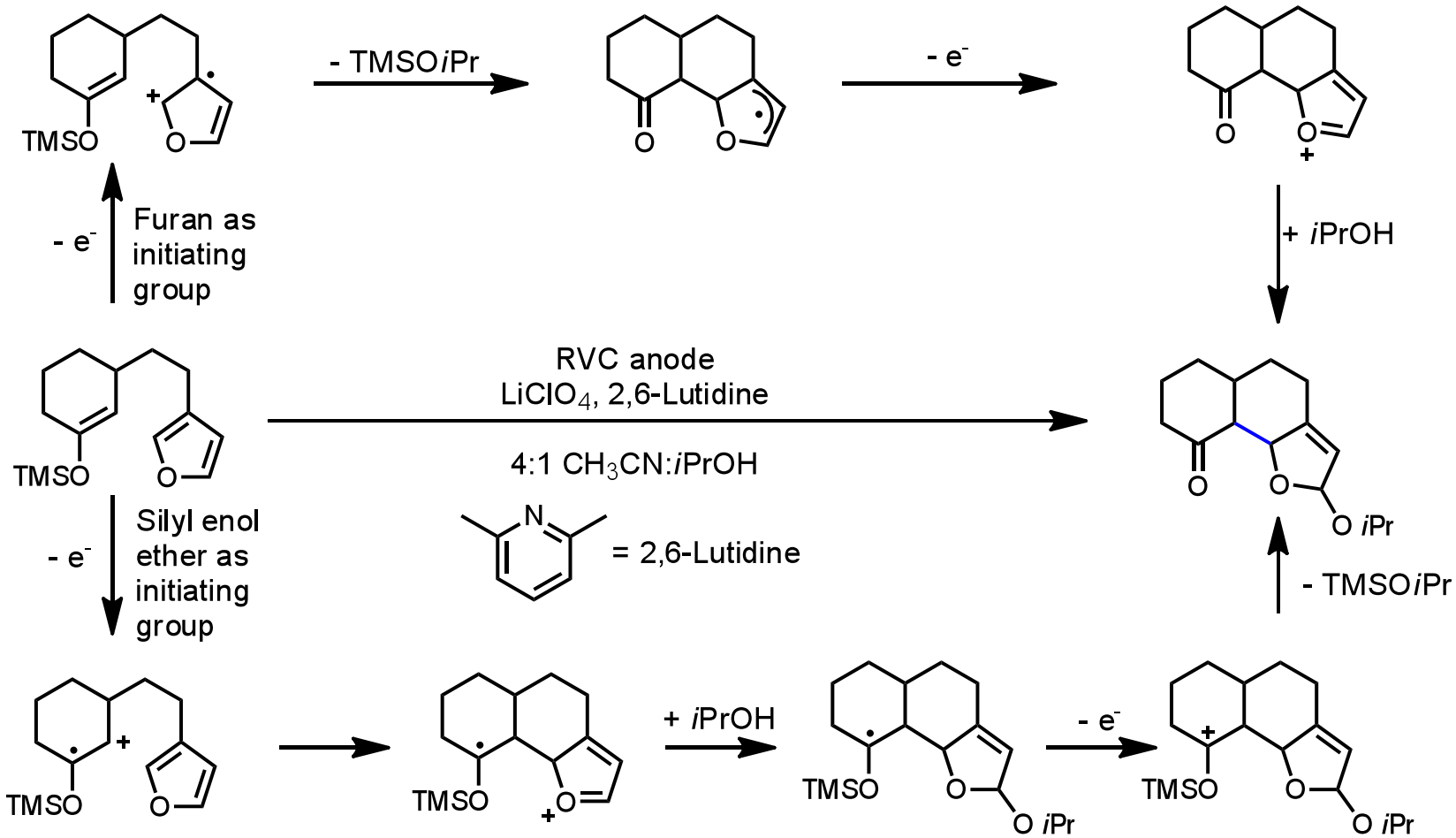


- Expedient bonding of two nucleophiles

Moeller, K. D. *et al J. Am. Chem. Soc.* **2003**, *125*, 36-37.

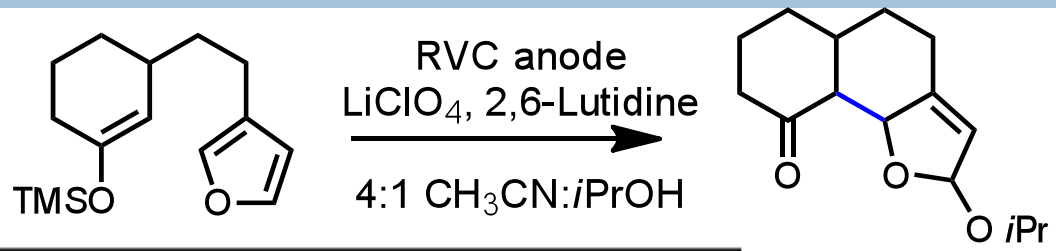
Group Problem

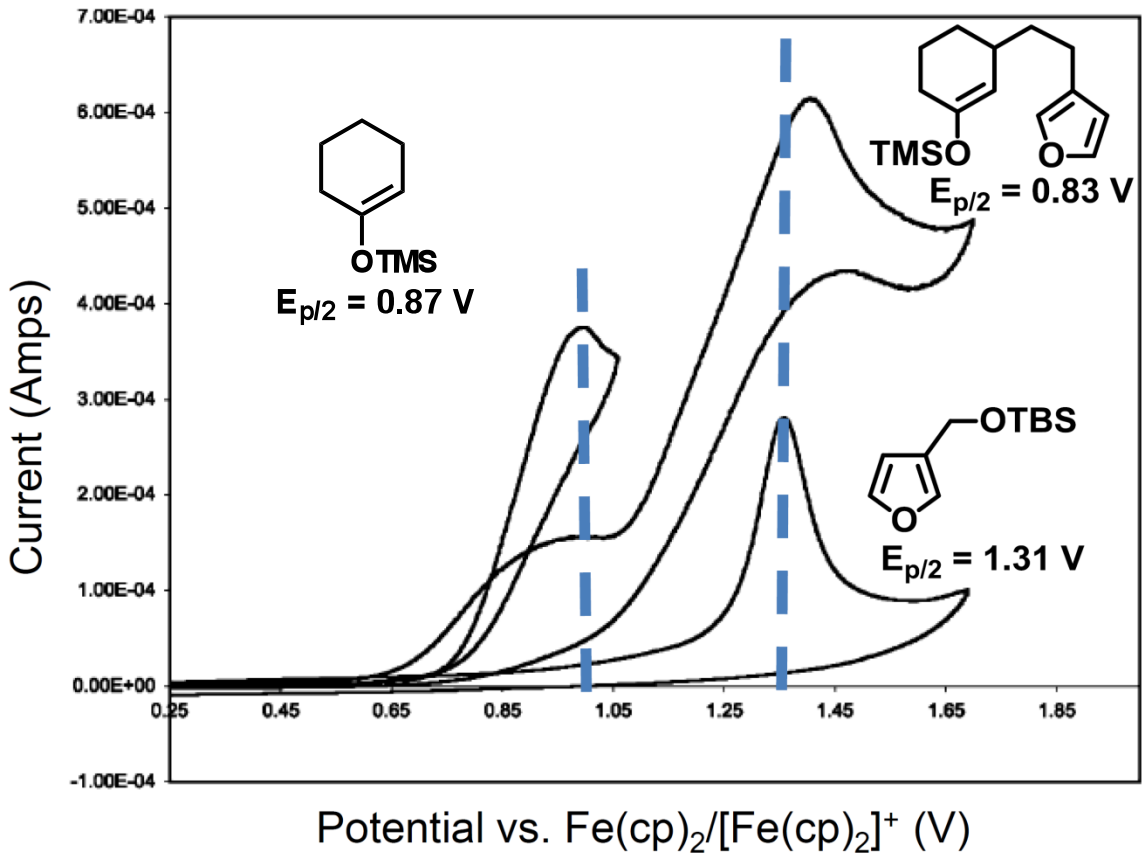
- At least two mechanisms for key anode oxidation step



Wright, D. L. *et al J. Org. Chem.* **2004**, *69*, 3726-3734.

Which functional group initiates?



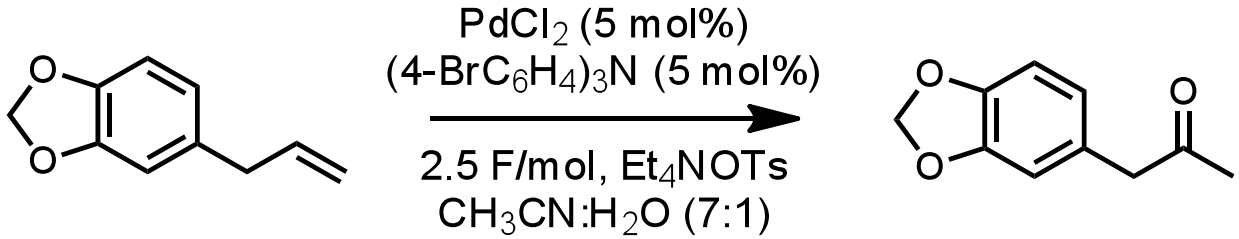


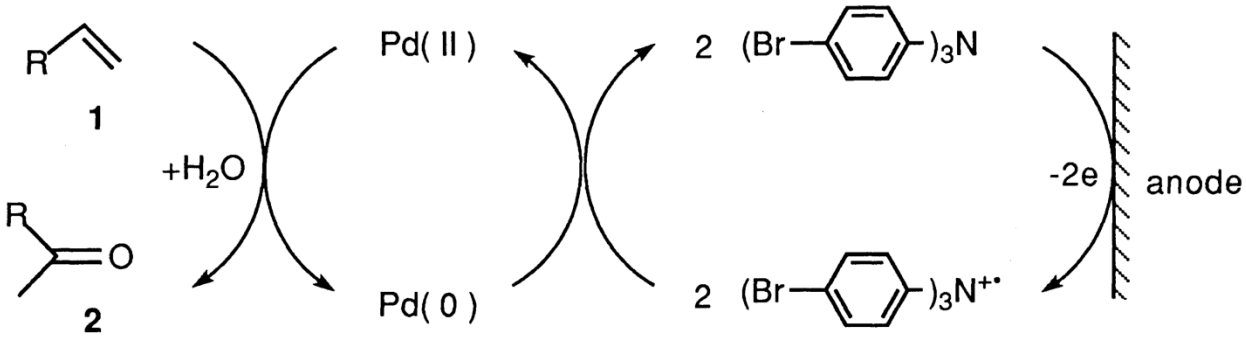
- Substrates subjected to cyclic voltammetric (CV) analysis
- Peak signifies oxidation potential
- Lack of negative peak reveals irreversible oxidation

Wright, D. L. *et al J. Org. Chem.* **2004**, *69*, 3726-3734.

Anodic Oxidation: Mediation of Pd

- Wacker oxidation of terminal alkenes

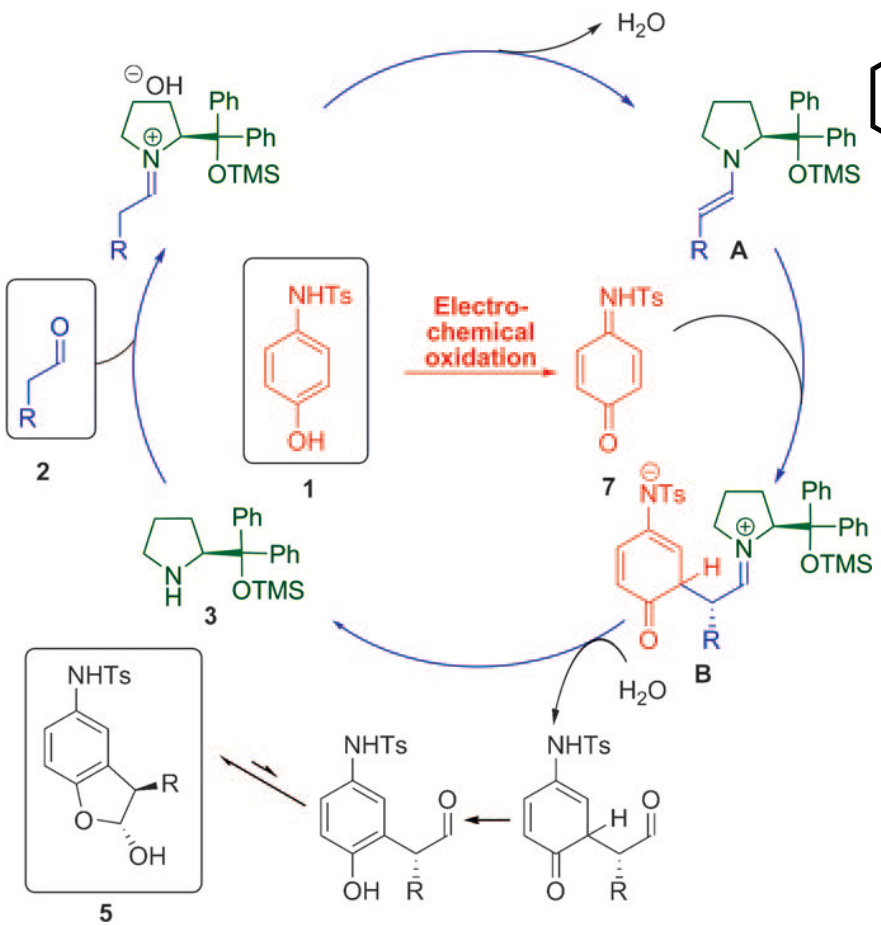


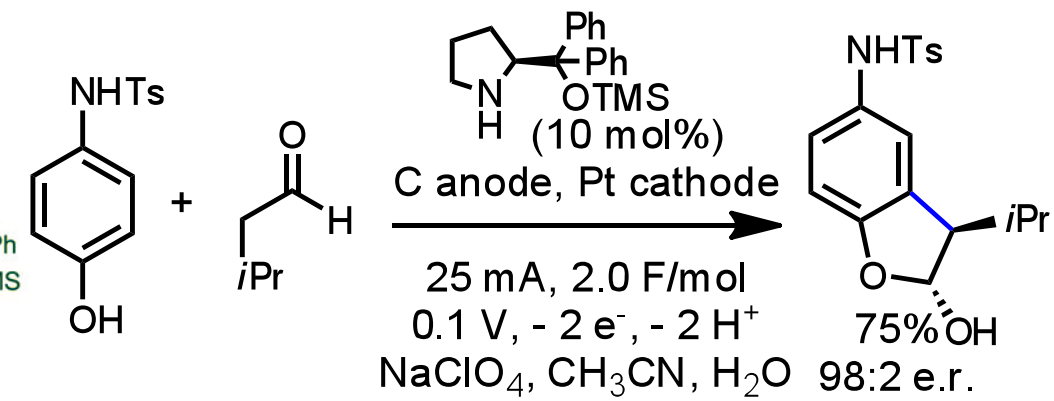


- Mediator allows reaction to take place in bulk solvent
- Alleviates the need for stoichiometric oxidants

Wright, D. L. *et al J. Org. Chem.* **2004**, *69*, 3726-3734.

Enantioselective Anodic Oxidation



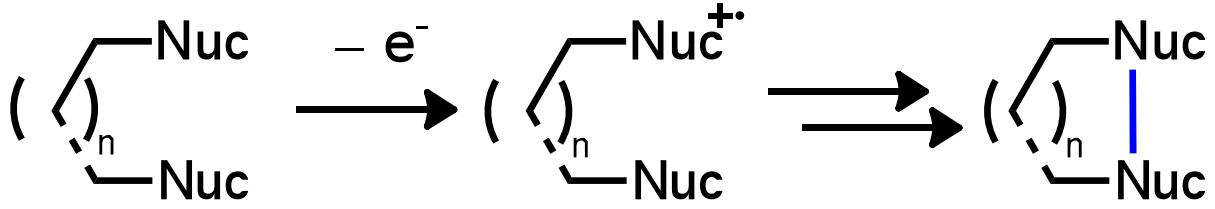


- Use of enamine catalysis to achieve high yields and e.r. (following $NaBH_4$ workup)
- Robust system, even with undivided cell

Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2010,** *49,* 129-133.

Anodic Oxidation: Summary

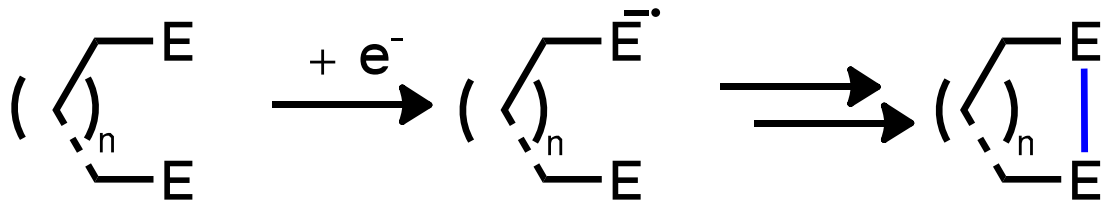
- Highly applicable to complex molecule synthesis
- Selective oxidation allows for stepwise reactions
- Use of electroauxiliaries allows for more precise control of substrate reactions
- Generation of reactive cation intermediates possible for use in diversified synthesis
- Progress in enantioselective reactions



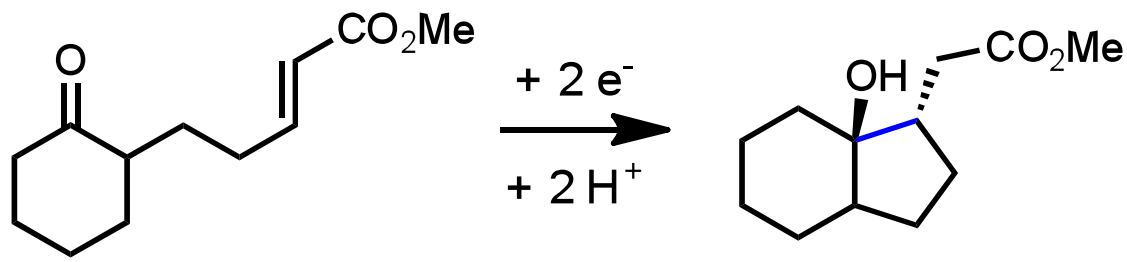
Nuc = nucleophile

Cathodic Reduction

- Addition of electron to substrate



E = electrophile



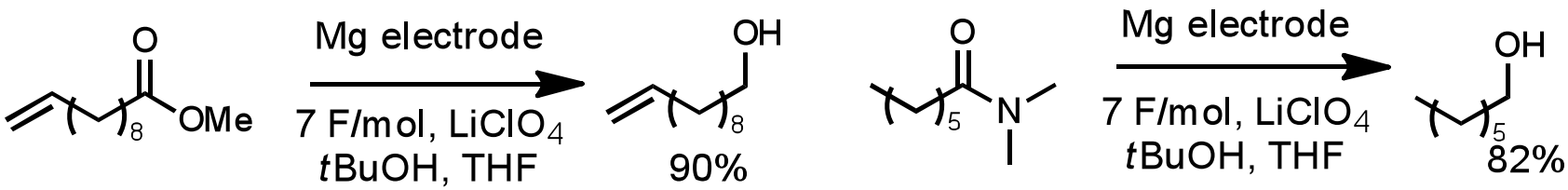
- Need to isolate oxygen from system

1.23 V

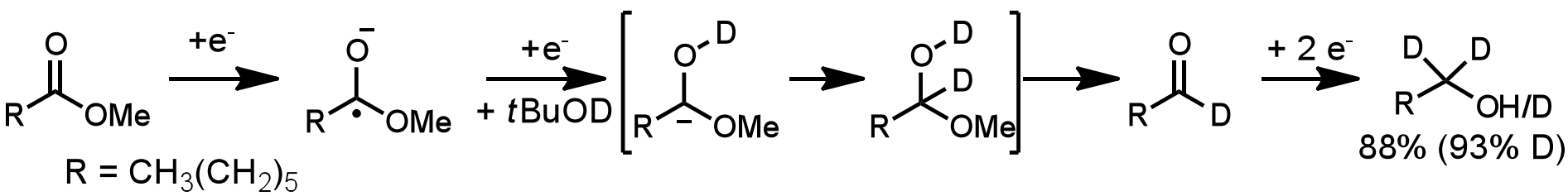
Wright, D. L., *et al Chem. Soc. Rev.* **2006**, *35*, 605-621

Electroreductive: Formation of 1° alcohols

- Challenging due to high reduction potentials of esters and amides



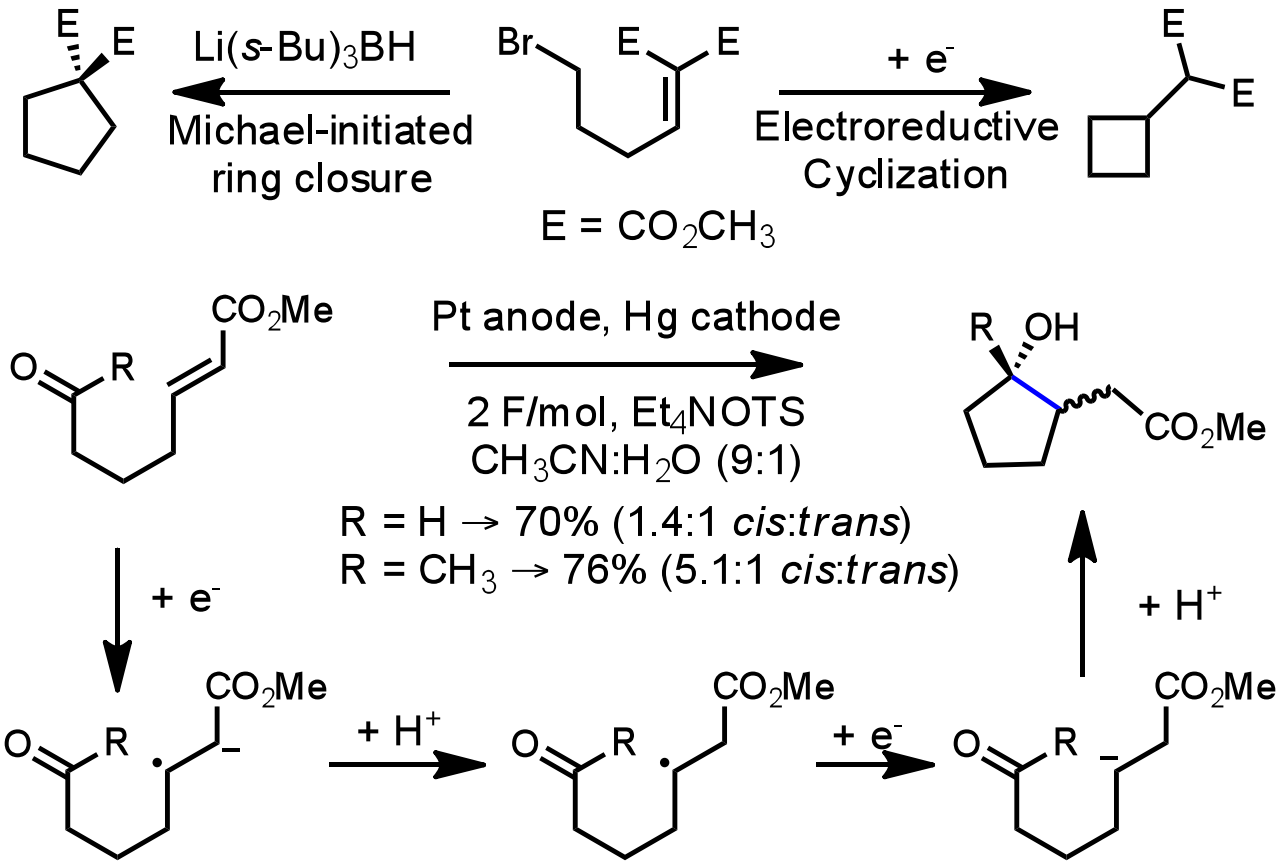
- Alcohol source of H^+ → deuterium incorporation



Shono, T. *et al J. Org. Chem.* **1992**, *57*, 1061-1063.

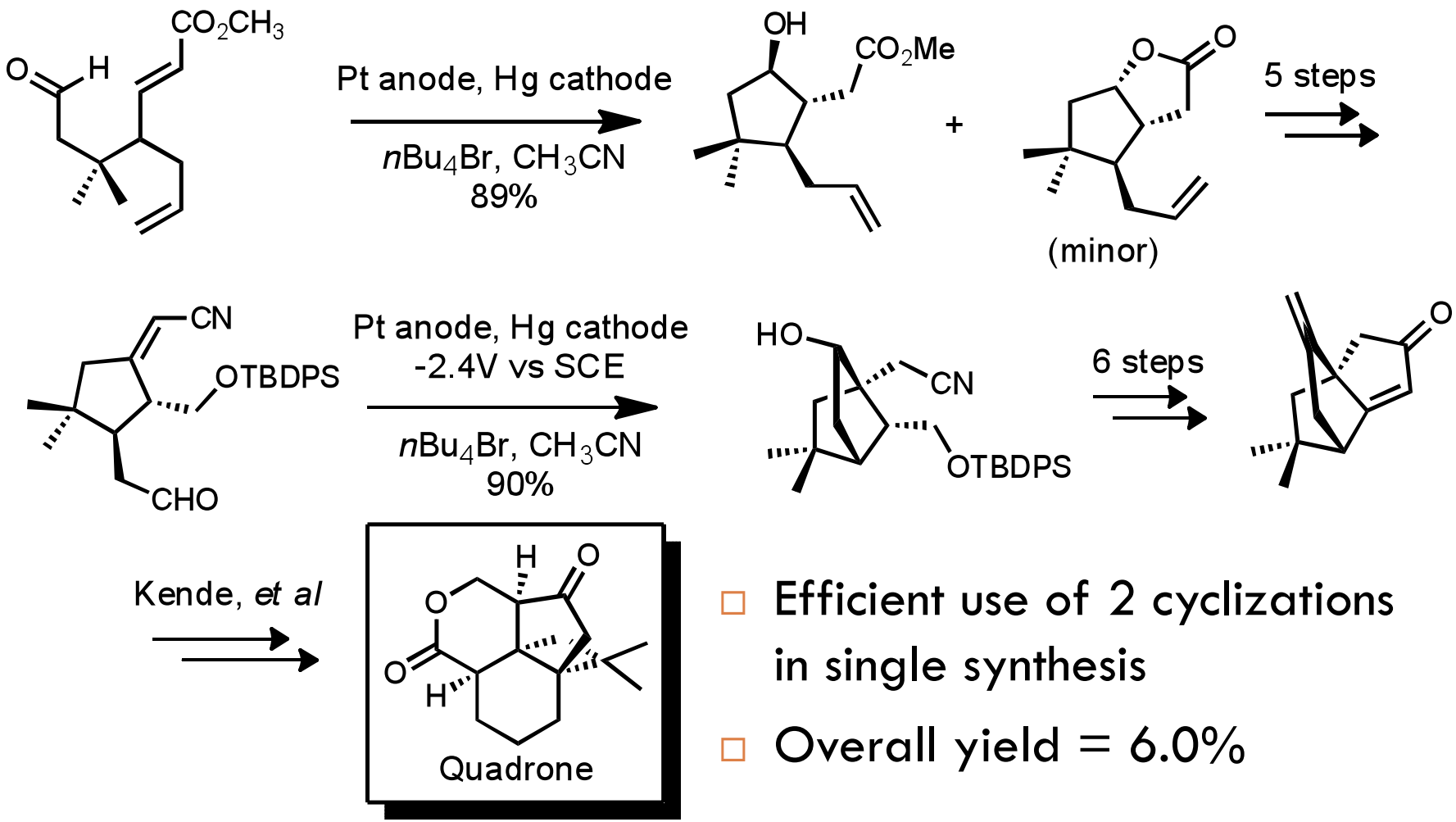
Electroreductive Cyclization

- Complementary reactivity



Little, R. D. *et al J. Org. Chem.* **1988**, *53*, 2287-2294.

Electroreductive Cyclization: Quadrone

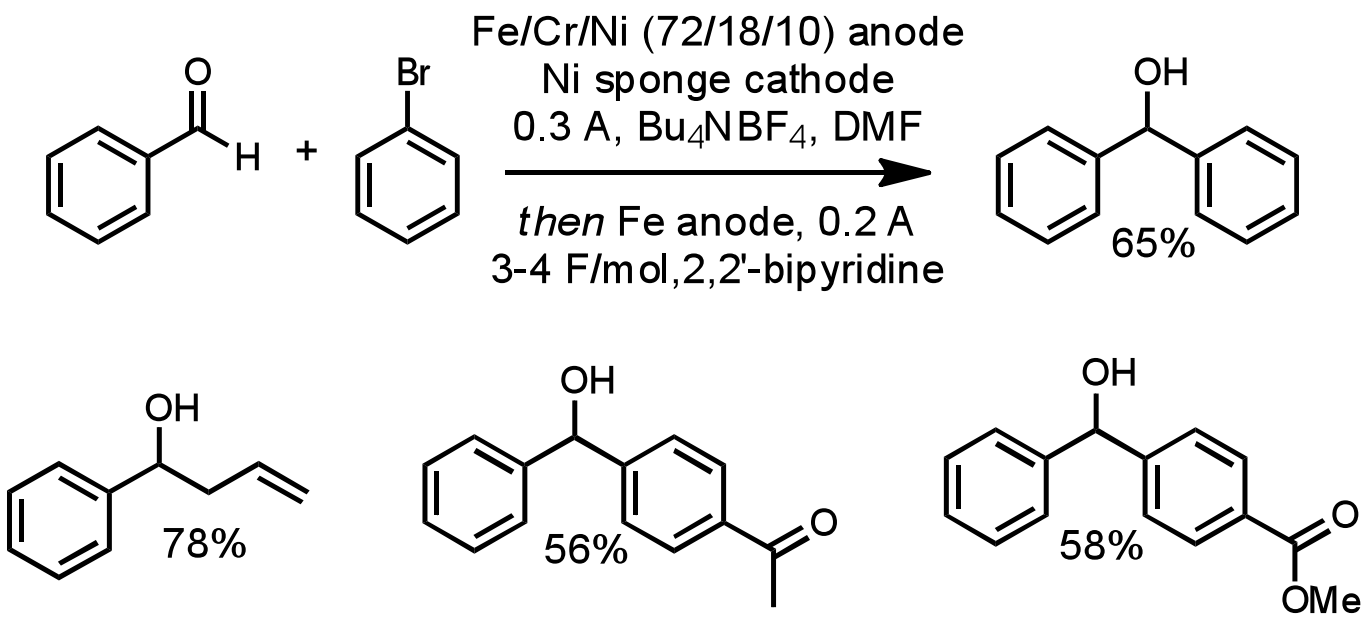


- Efficient use of 2 cyclizations in single synthesis
- Overall yield = 6.0%

Little, R. D. *et al Tetrahedron Lett.* **1990**, *31*, 485-488.
Kende, A. S. *et al J. Am. Chem. Soc.* **1982**, *104*, 5808-5810.

Electroreductive Cyclization: NHK Reaction

- Adaption of Nozaki-Hiyama-Kishi reaction

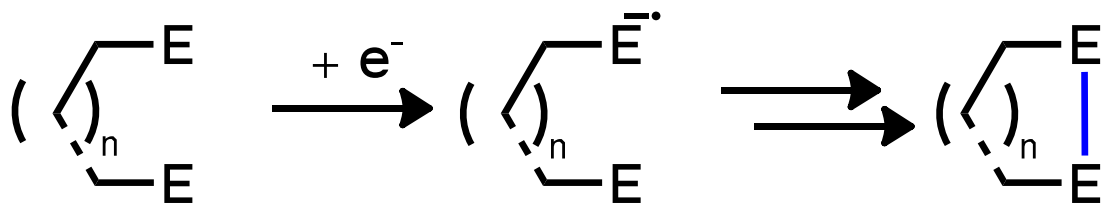


- Sacrificial anode allow for catalytic use of Cr(II) (7%)

Durandetti, M. *et al Org. Lett.* **2001**, *3*, 2073-2076.

Cathodic Reduction: Summary

- Umpolung chemistry allows for complementary cyclizations
- Ease in reduction of alcohol without use of hydride
- Possibility for incorporation of deuterium

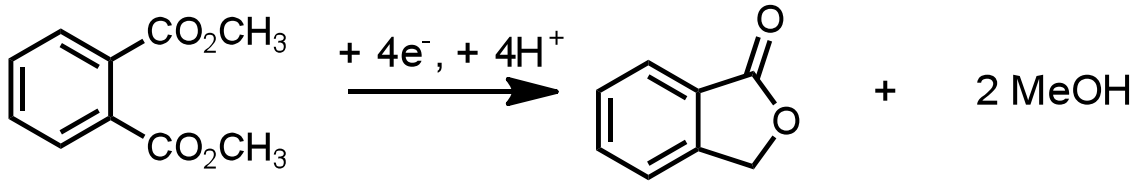


E = electrophile

Paired Electrosynthesis

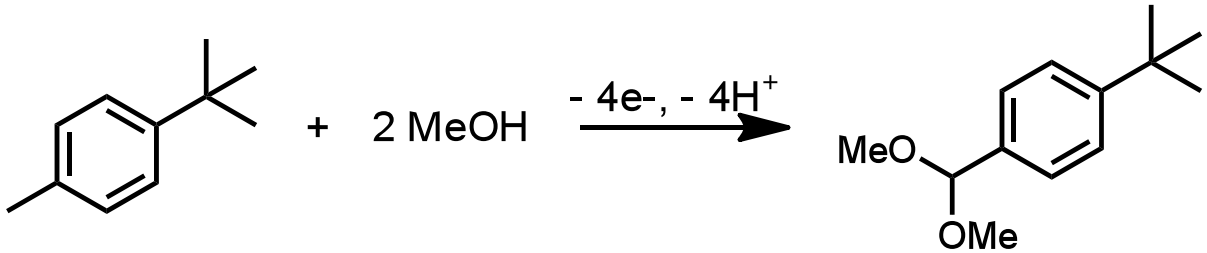
- "Holy Grail" of organic electrochemistry

Cathode Rxn



Phthalide (fungicide)

Anode Rxn



t-butylbenzaldehyde dimethylacetal
400 metric tons/year

- Near total atom economy

Frontana-Uribe, B.A. *et al Green Chem.* **2010,** *12,* 2099-2119.

Limitations

- Use in industry still restricted by mechanics of process – engineering problem
- Initial set up costs
- Few examples for enantioselective additions or cyclizations – general for radical chemistry

Conclusions

- Application of organic electrochemistry involves mild reaction conditions with very high tolerance for functional groups
- High atom economy and low waste lends process to be of an emerging push for "green chemistry"
- Analytical methods available to predict reactivity
- Has further application in metal mediated reactions

"While electrochemical techniques are still far from routine, the utility of simple reaction setups and the availability of commercial power supplies, electrodes, and reaction cells means that the majority of electrochemical synthetic methods are available to any chemist willing to peruse them."

-K. D. Moeller, 2000

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