Organic Electrosynthesis

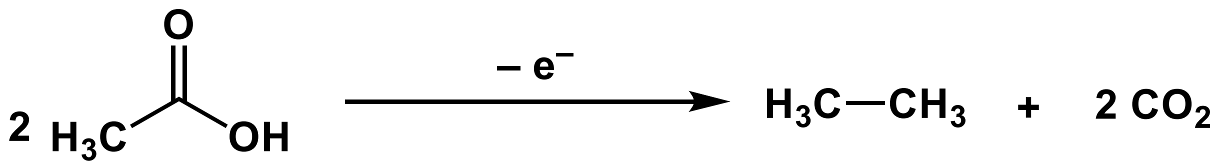
M1 Toyama

2019/07/25

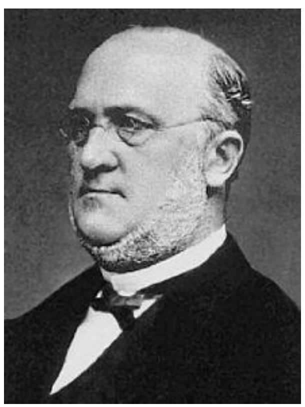
Contents

Introduction: Organic Electrosynthesis

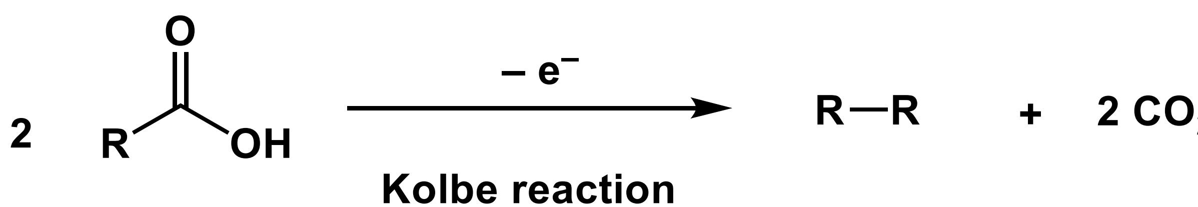
Faraday showed first example of organic electrosynthesis (1834) :



Michael Faraday
1791-1867

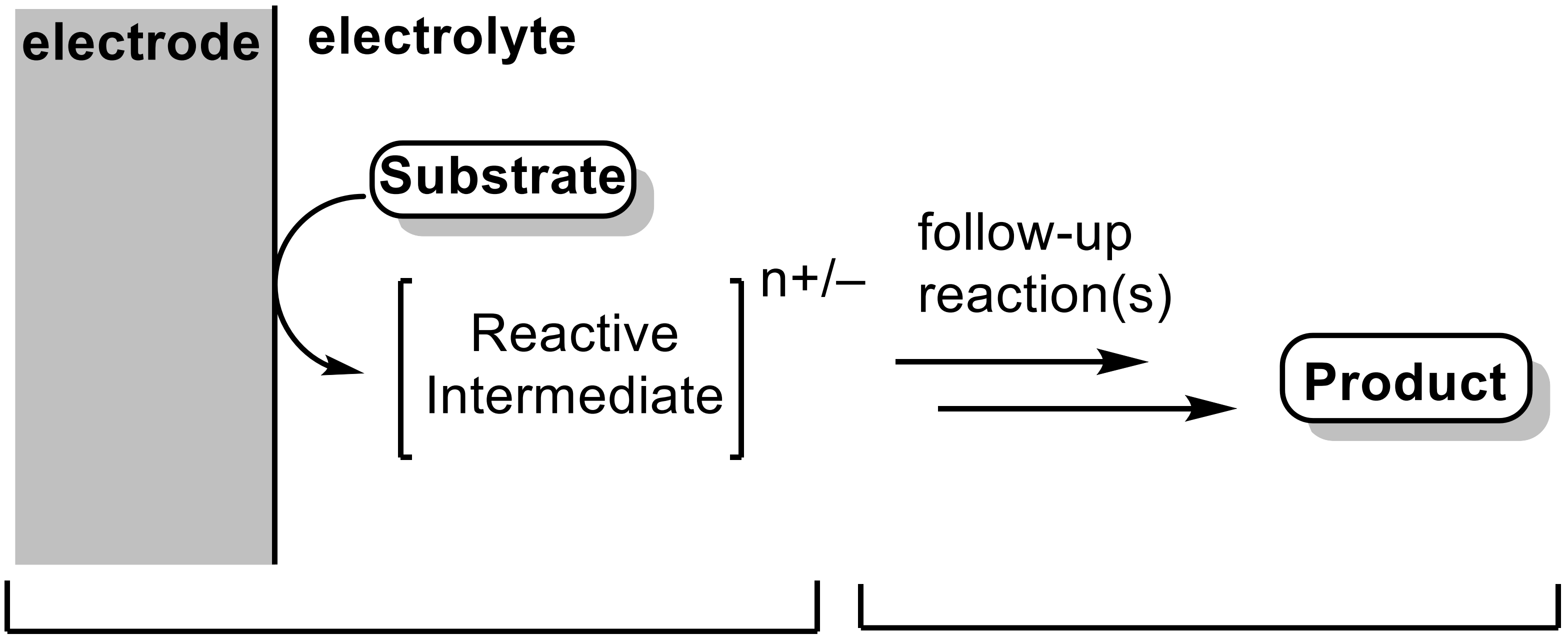


Kolbe generalized Faraday's discovery (1849) :



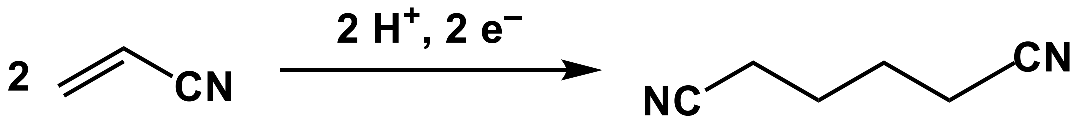
Hermann Kolbe
1818-1884

Overview of Organic Electrosynthesis

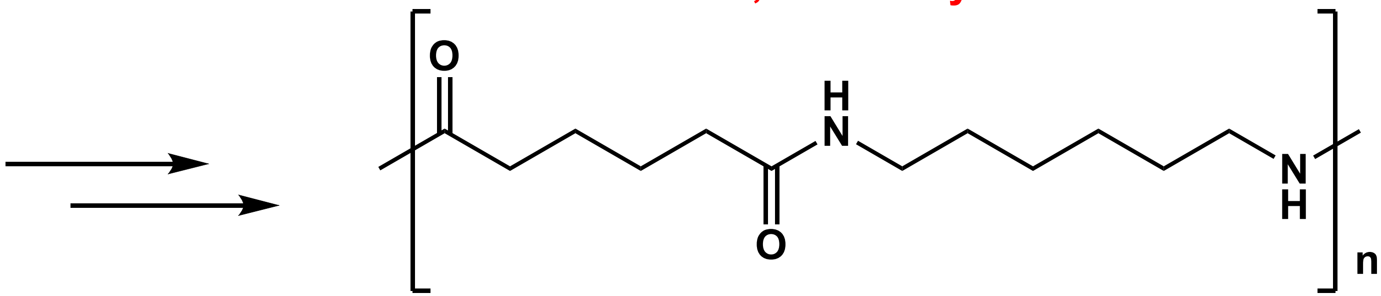


Electrochemical Process	**Chemical Process**
• electrode material	• supporting electrolyte
• constant voltage / current	• solvation
• over-potential	• temperature
• electrode adsorption	• kinetics
• electroric charge	• convection

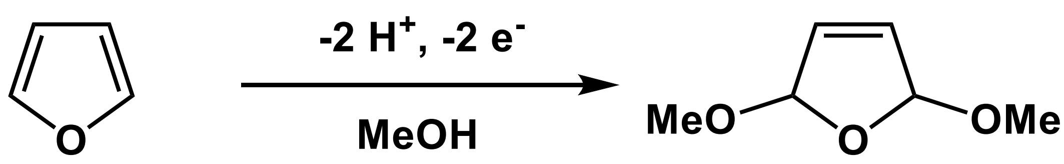
Examples of Organic Electrosynthesis



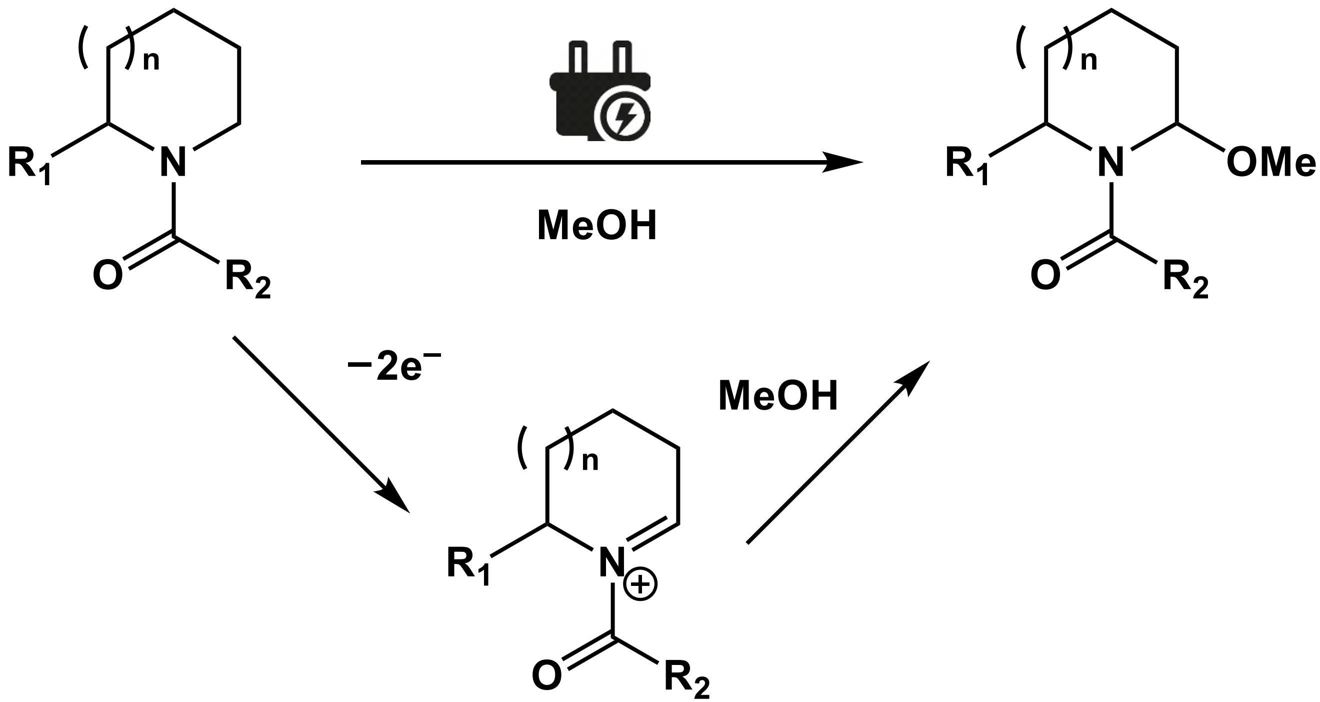
>200,000 tons/year



nylon-66



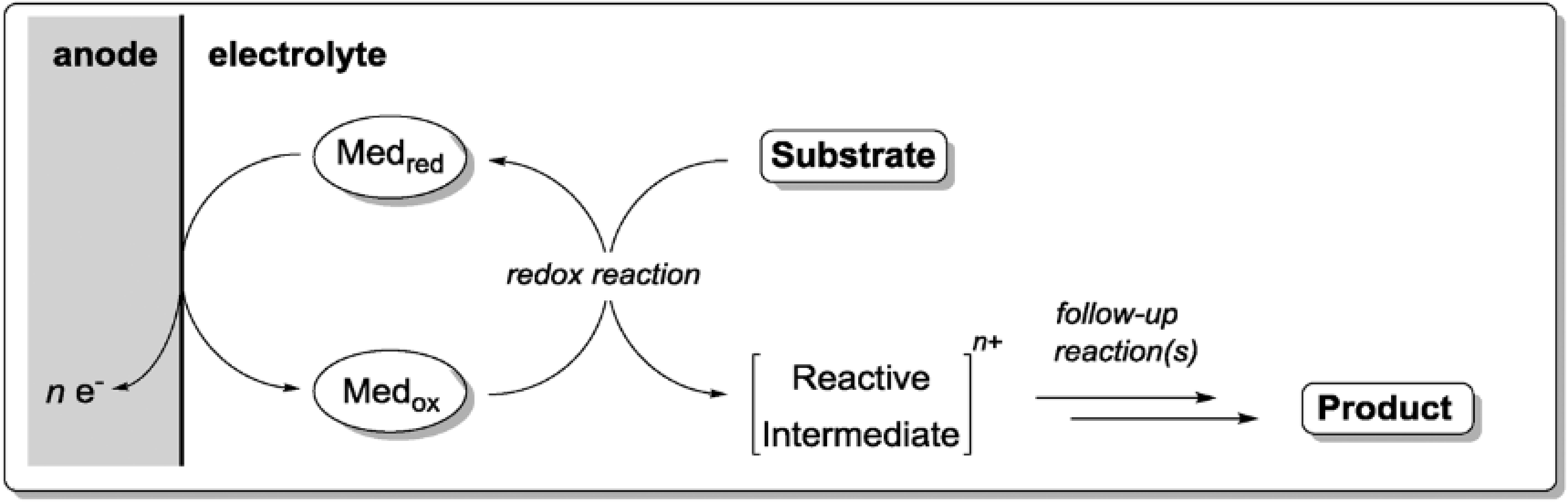
Shono Oxidation



✔ Functionalization of α position of amine

Shono, T.; Hamaguichi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

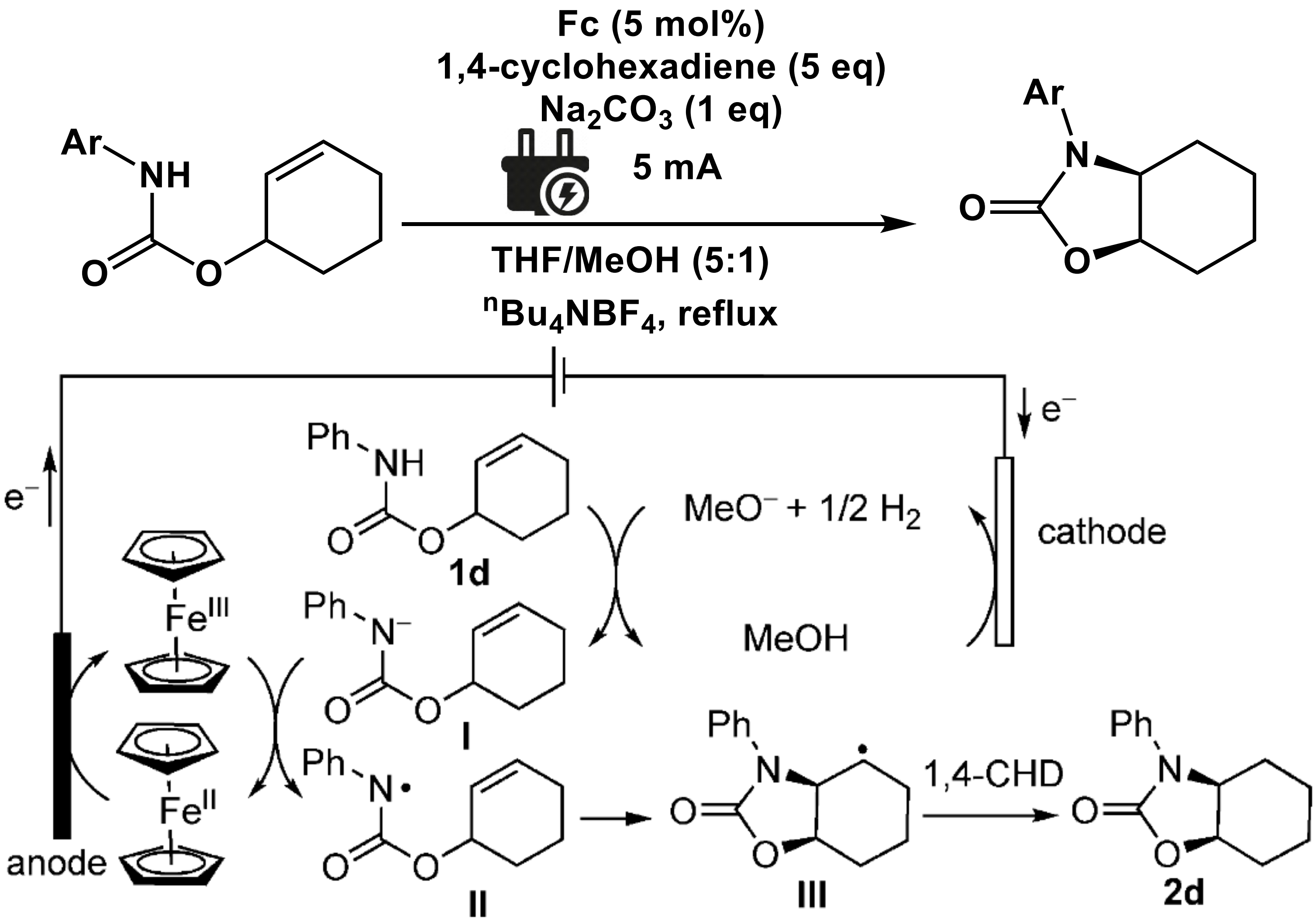
Mediator



- ✔ Avoid over-potential
- ✔ Mild conditions
- ✔ Different selectivity
- ✔ Avoid passivation of electrode

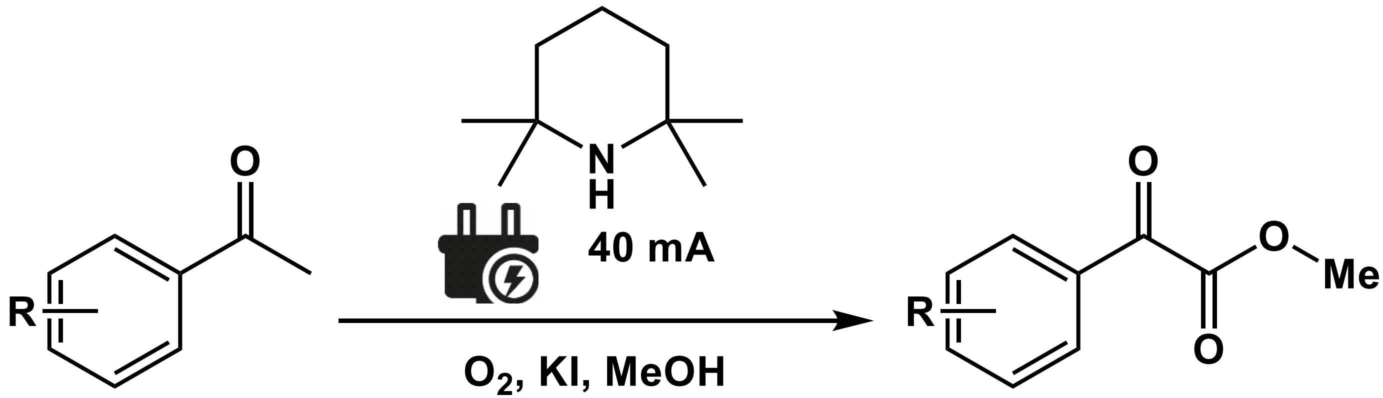
R. Francke and R. D. Little. *Chem. Soc. Rev.*, **2014**, *43*, 2492.

Examples of Mediator (1)

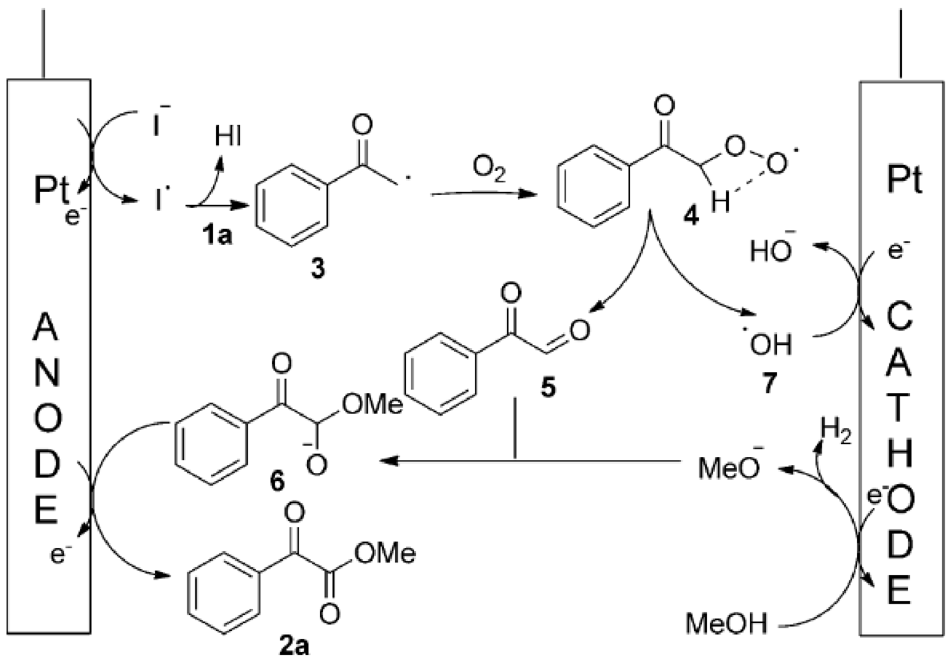


L. Zhu, P. Xiong, Z.-Y. Mao, Y.-H. Wang, X. Yan, X. Lu and H.-C. Xu, *Angew. Chem. Int. Ed.*, **2016**, *55*, 2226.

Examples of Mediator (2)



二電子的な
酸化還元反応と
一電子的な
酸化還元反応は
どうやって制御しているの？

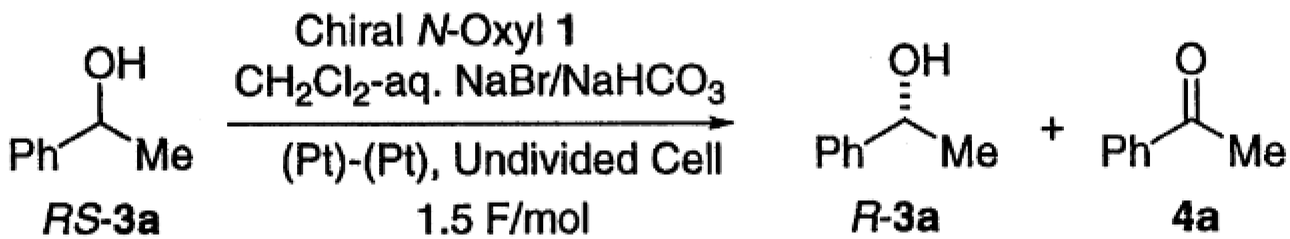


ヒドロキシラジカル出
せる
▶この方法機構解析に
使えるか？

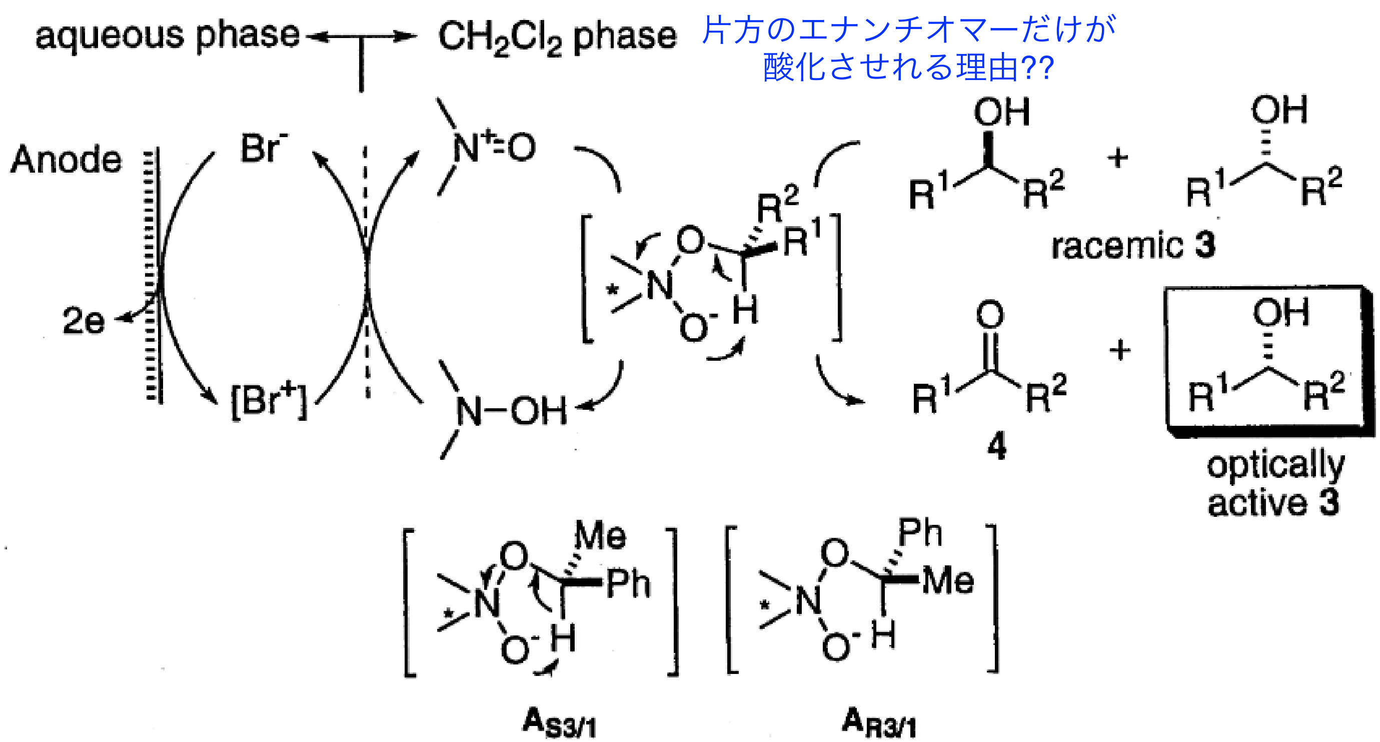
ヒドロキシラジカルだけを
出す方法があるか？

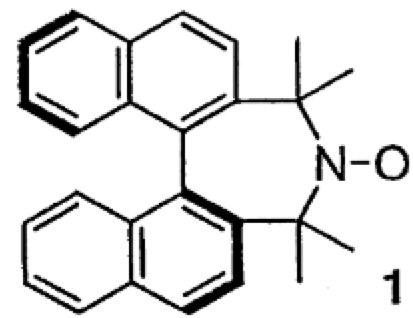
Z. Zhang, J. Su, Z. Zha and Z. Wang, *Chem. Eur. J.*, **2013**, *19*, 17711.

Examples of Mediator (3)



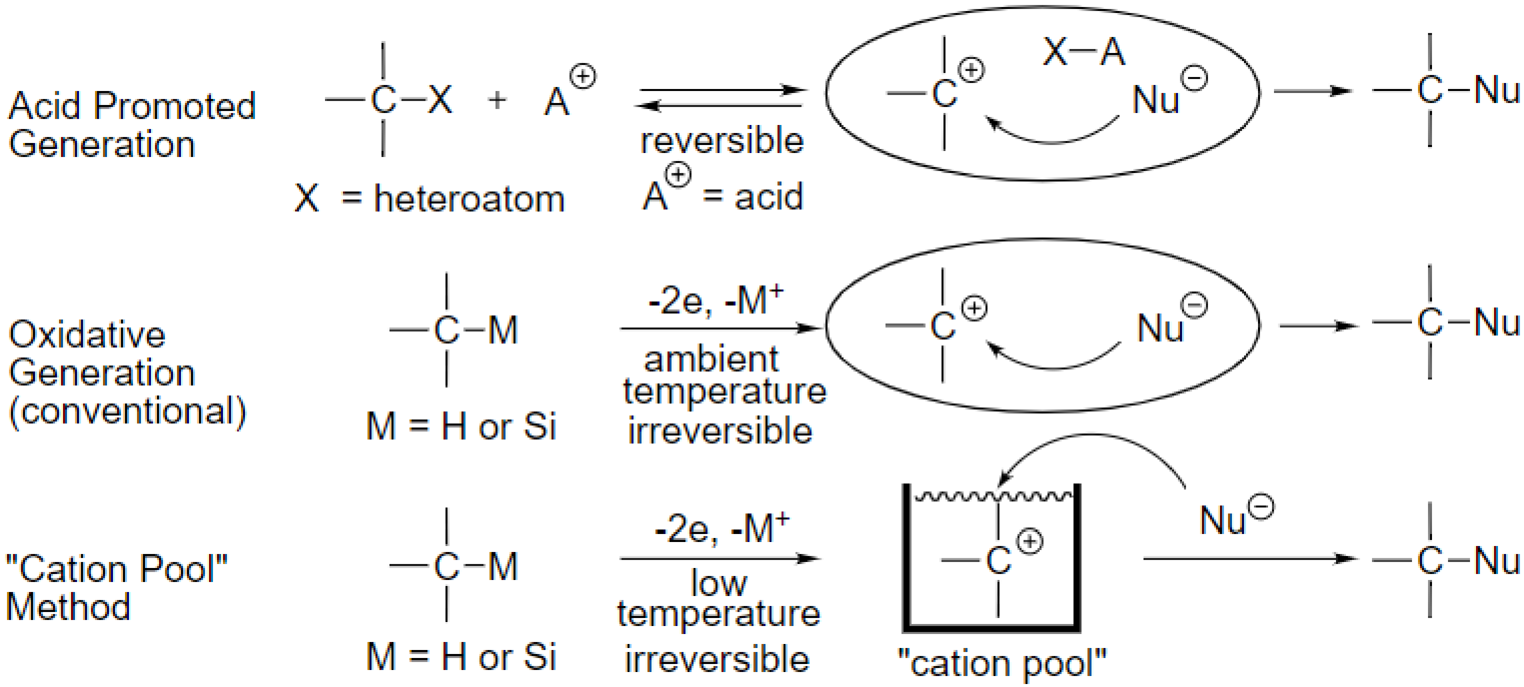
片方のエナンチオマーだけが
酸化させれる理由??





M. Kuroboshi, et al., *Tetrahedron Lett.*, **2000**, *41*, 8131.

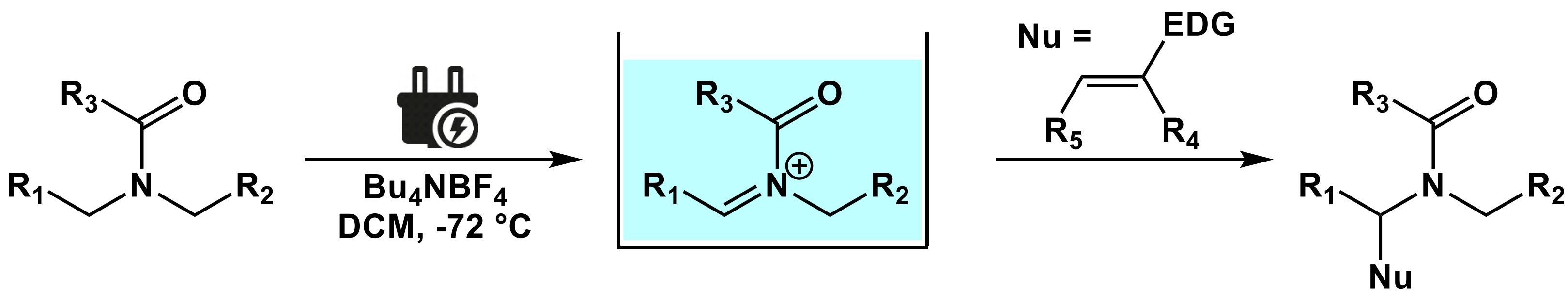
Cation Pool Method

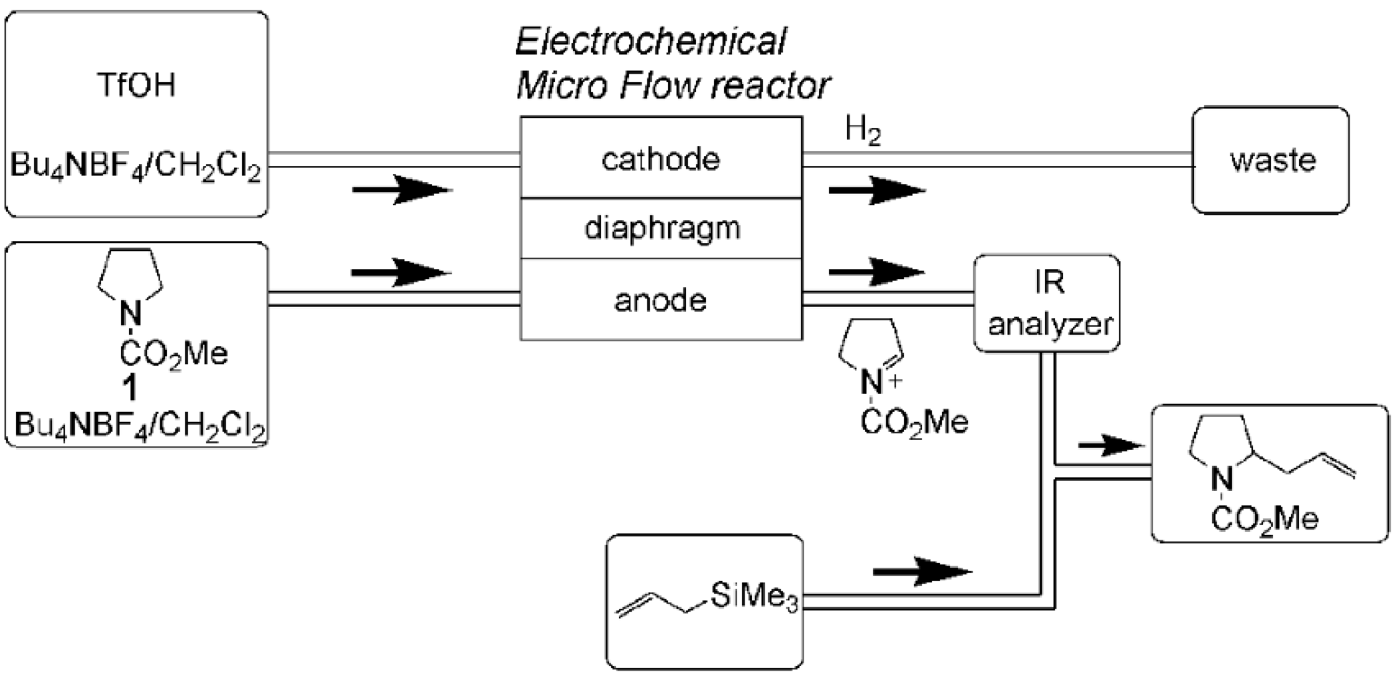


- Cation intermediate accumulation
- Various nucleophile can be introduced

J. –I. Yoshida, *Chem. Eur. J.*, **2002**, *12*, 2650.

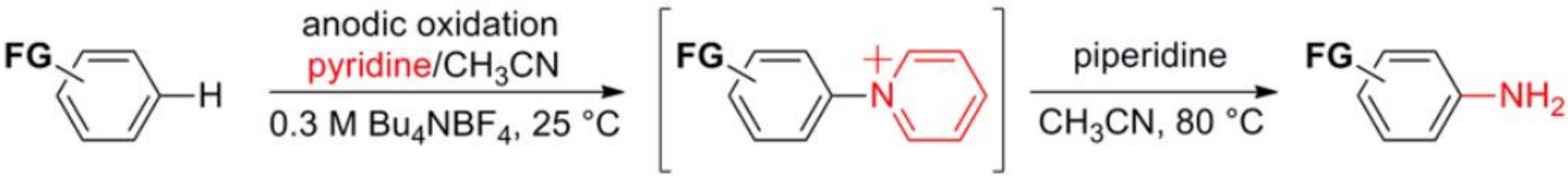
Examples of Cation Pool Method (1)

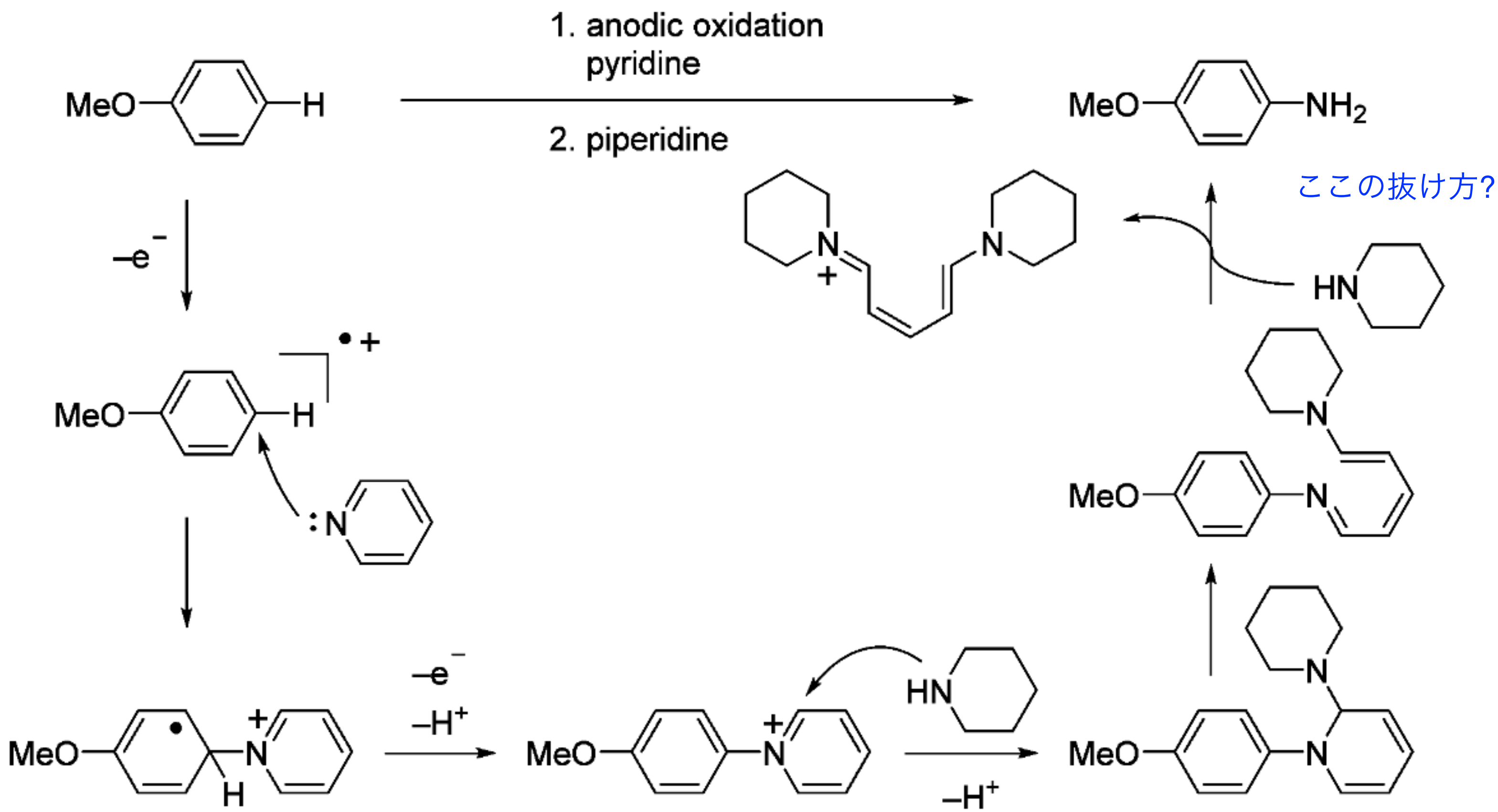




S. Suga, M. Okajima, K. Fujiwara and J.-I. Yoshida, *J. Am. Chem. Soc.*, **2001**, *123*, 7941.

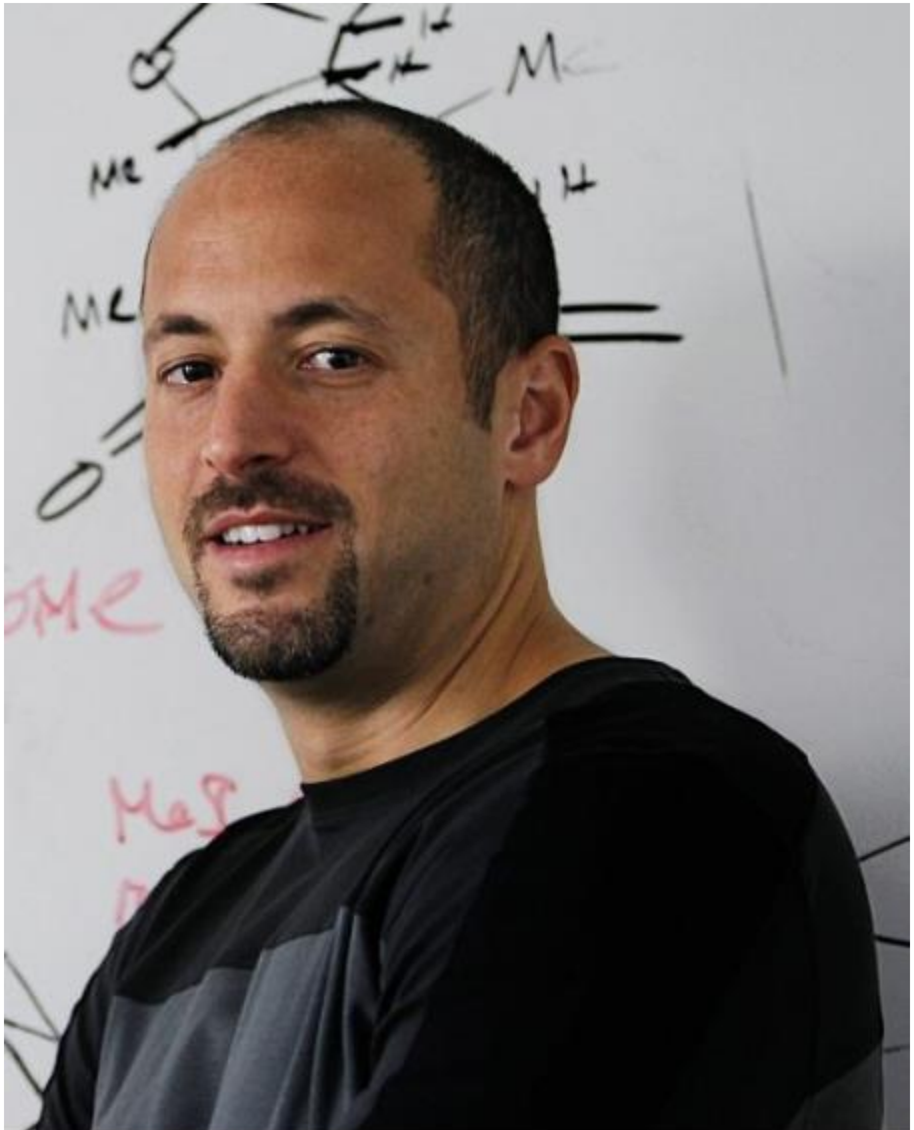
Examples of Cation Pool Method (2)





T. Morofuji, A. Shimizu and J.-I. Yoshida, *J. Am. Chem. Soc.*, **2013**, *135*, 5000.

Phil S. Baran

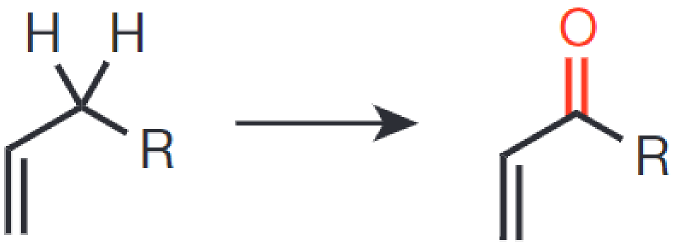


Phil S. Baran (born 1977) is a Professor in the Department of Chemistry at the Scripps Research Institute and Member of the Skaggs Institute for Chemical Biology. He received his B.S. in chemistry from New York University in 1997 and his Ph.D. from The Scripps Research Institute in 2001, under the supervision of K.C. Nicolaou. He did his postdoctoral fellowship in the laboratory of Nobel Laureate E. J. Corey at Harvard University.

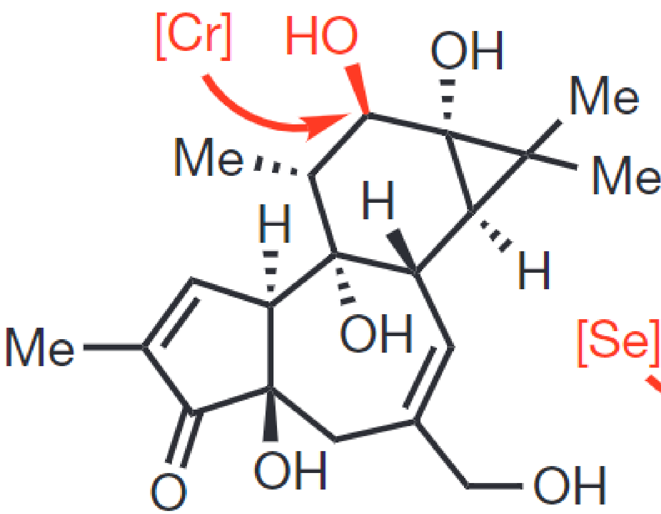
His work is focused on synthesizing complex organic compounds, the development of new reactions,and the development of new reagents.

Contents

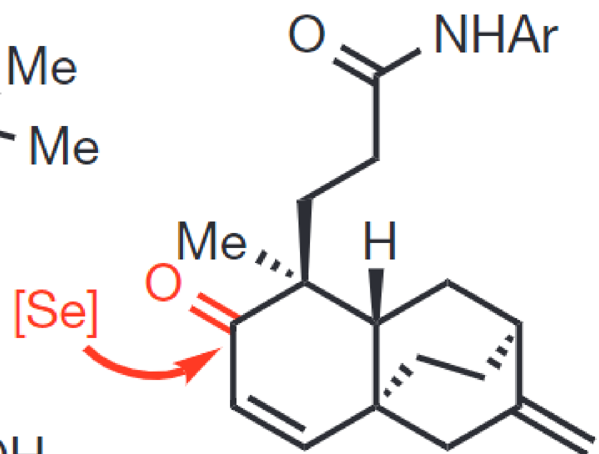
Allylic C-H Oxidation



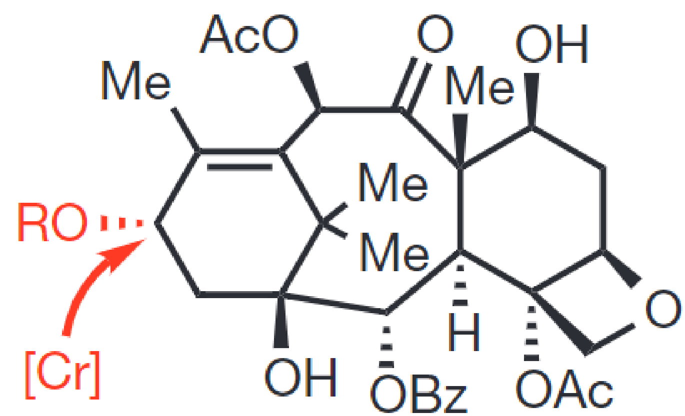
- Fundamental organic transformation
- Featured in >100 natural product syntheses
- About 80% use Cr, Se, Pd or Rh reagents



Phorbol



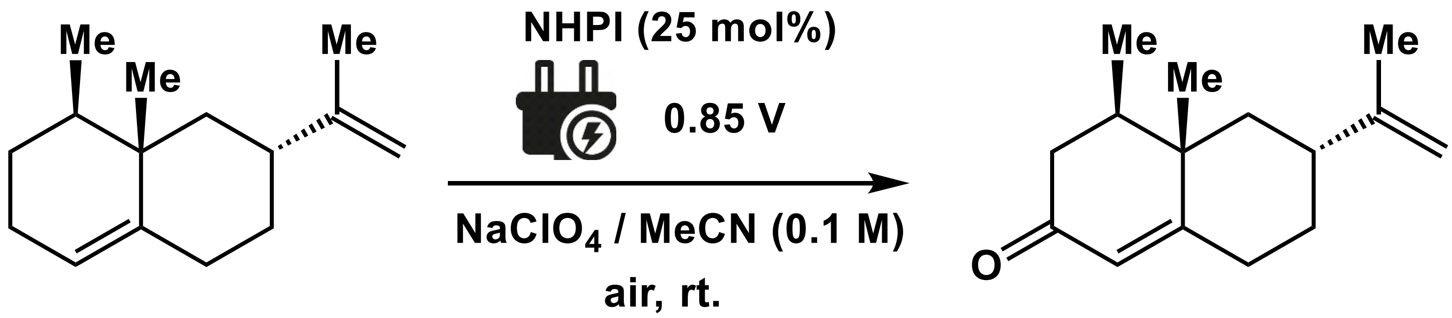
Platencin



Paclitaxel

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

Initial Trial

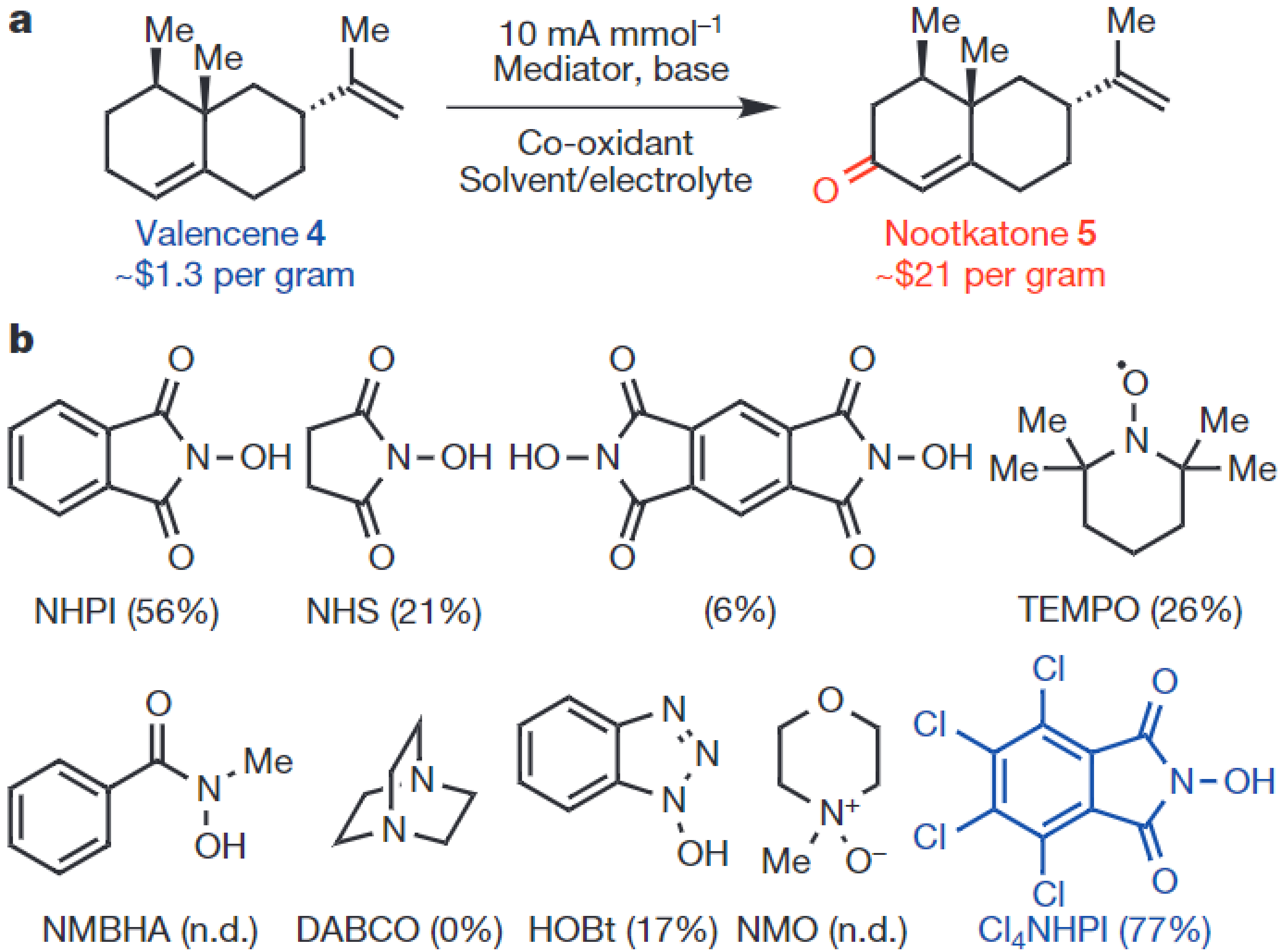


O source	yield
air	6%
O_2 bubbling	18%
^tBuOOH	51%

Masui, M., Hosomi, K., Tsuchida, K. & Ozaki, S. *Chem. Pharm. Bull*. **1985** *33*, 4798.

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

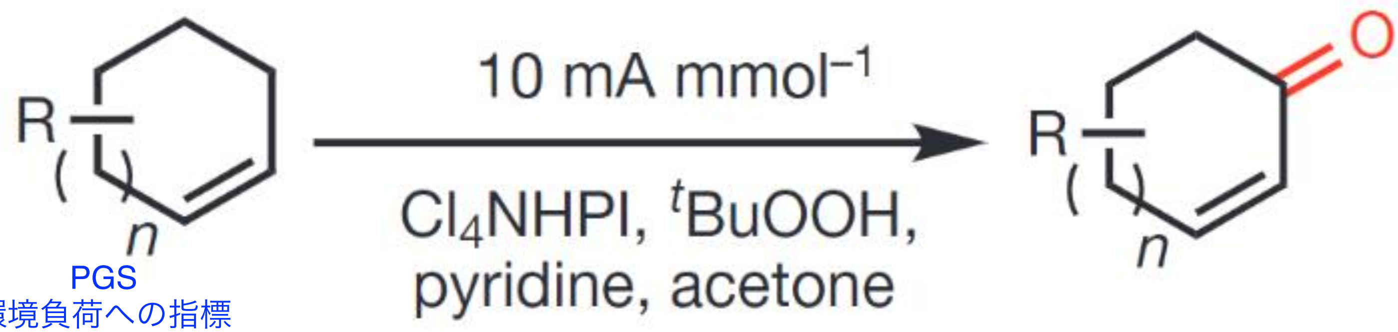
Screening of Mediator



メディエーター分子
どんな指針で決められているのか？

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

Electrochemical Allylic C-H Oxidation



PGS
環境負荷への指標
% 表記
高いほど環境への負荷が小さい

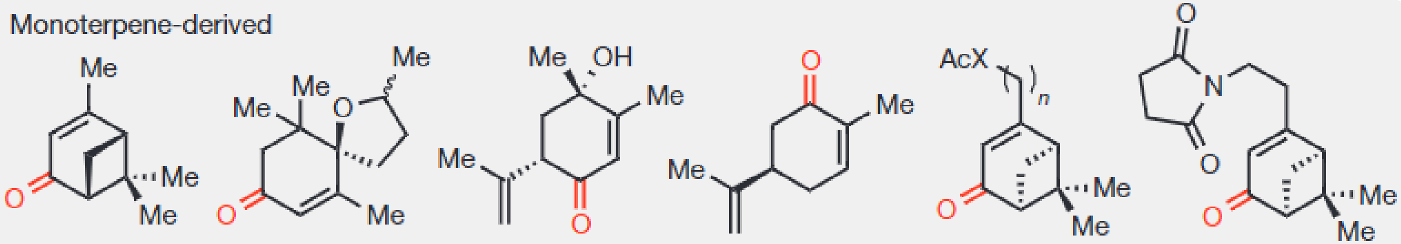
Crなど ca 37 %
本反応 ca 58 %

- 40 examples
- 15 natural products
- Sustainable
- Scalable
- Inexpensive carbon electrodes
- Inexpensive reagents
- Open flask

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

Substrate Scope (1)

Monoterpene-derived



3; 67%* (Verbenone) [Cr]; 49%‡ [Mn]; 63%‡

19 (α-Me); 63% (*cis*-Theaspirone) **20** (β-Me); 49% (*trans*-Theaspirone)

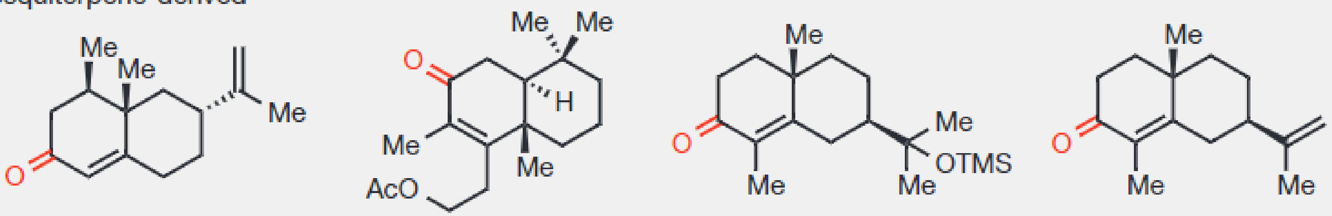
21; 47%

22; 42% (Carvone) [Cr]; 21%‡ [Rh]; 44%‡

23 (X = O, *n* = 1); 64% **24** (X = O, *n* = 2); 43% **25** (X = NH, *n* = 2); 42%

26; 53% (+about 12% s.m.)

Sesquiterpene-derived

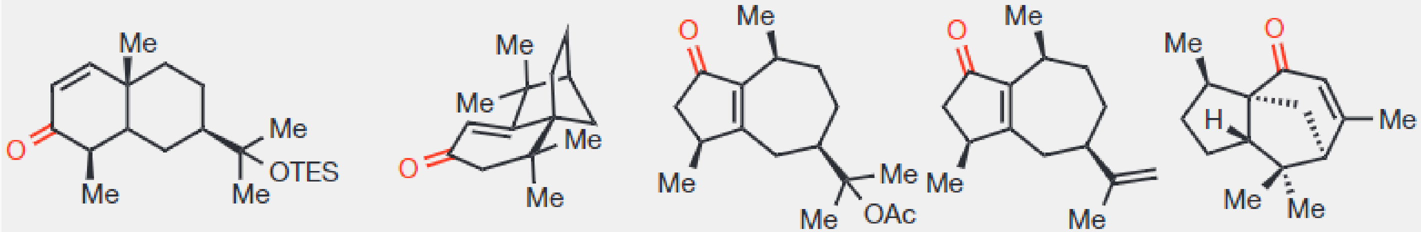


5; 77% (Nootkatone) 15 equiv. CrO_3•pyr; 80%‡ NHPI, cat. [Co]; 68%‡

27; 75% 4 equiv. Na_2CrO_4; 60%‡

28; 54% (Carissone silyl ether)

29; 51% (+about 15% s.m.) (Cyperone)



30; 67% (Epi-aubergenone silyl ether)

31; 91% (Isolongifolenone) 0.5 equiv. $Cr(CO)_6$; 82%‡

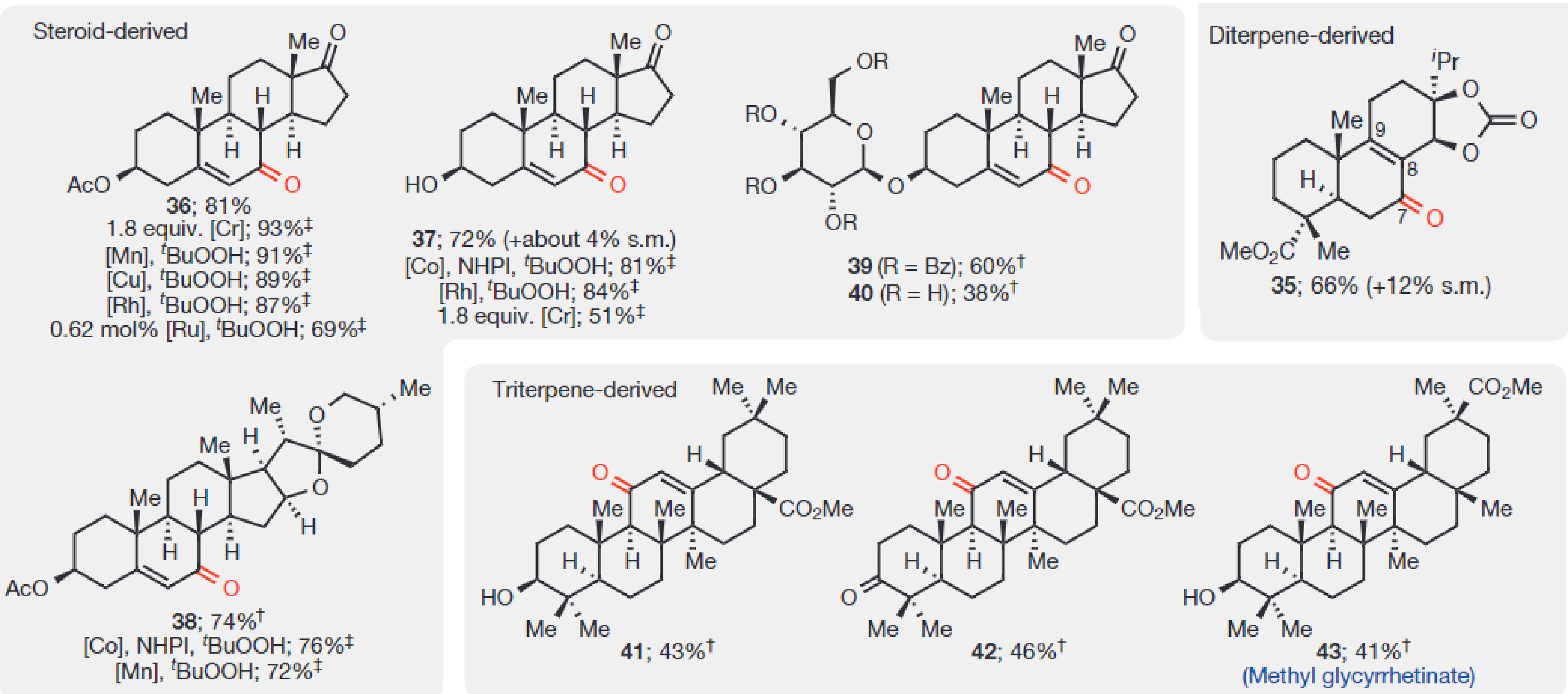
32; 41%* (Pancherione acetate)

33; 44% (+about 6% s.m.) (Rotundone)

34; 53% (Cedrene-10-one)

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

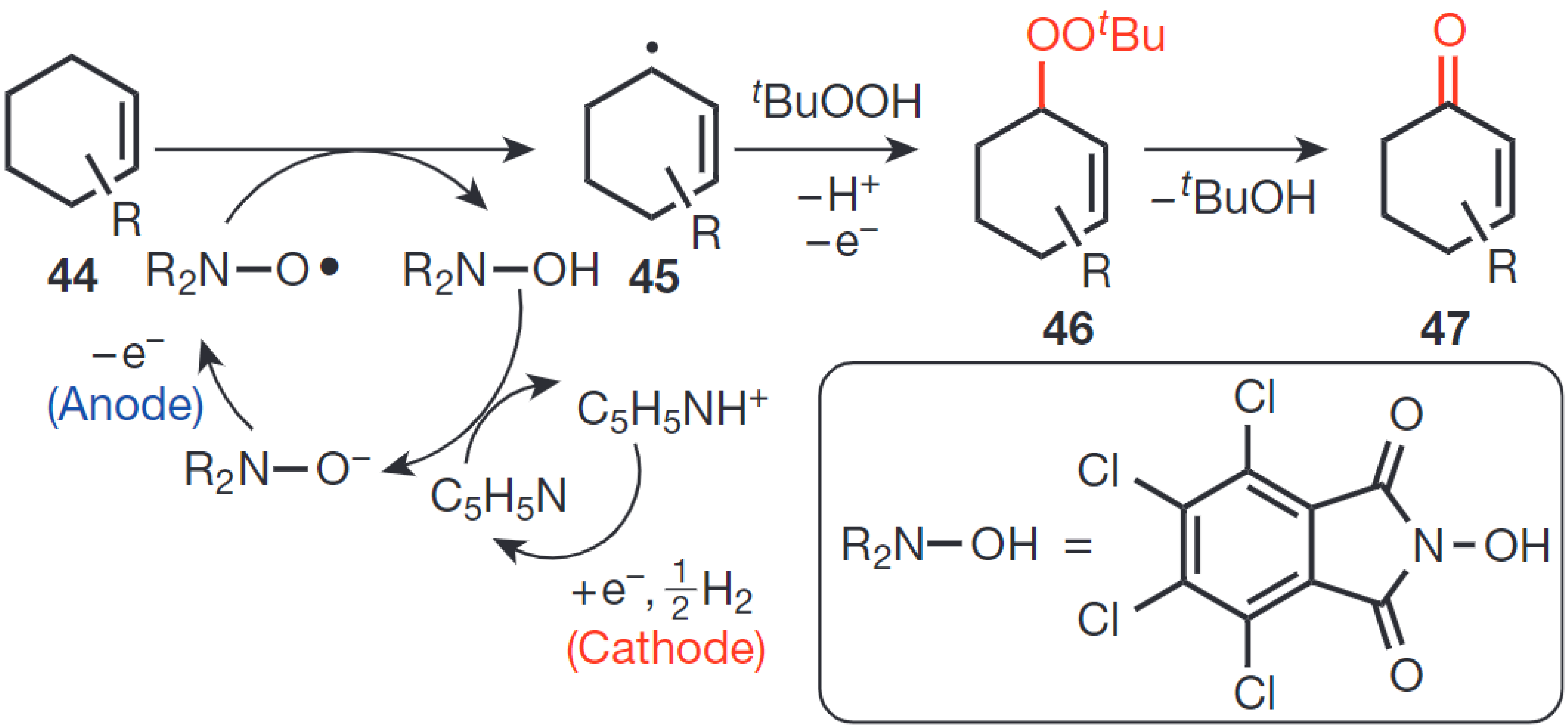
Substrate Scope (2)



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

Reaction Mechanism

ここは容易に
脱プロトン化進むの??



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

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1. Introduction

2. Electrochemical Allylic C-H Oxidation

3. Electrochemical Birch Reduction

4. Summary

Birch Reduction

Birch, *1946:* [undivided cell, NH_3/EtONa/EtOH, -78 °C]
- **R = hydrocarbon only**
- **Cryogenic temperatures required**
- **Ammonia condensation required**

Benkeser, *1963 & 1964:* [undivided cell, $MeNH_2$/LiCl, Pt(+)/Pt(-), 0 °C]
- **R = hydrocarbons only**
- **Solvent-quantity amine**
- **Precious metal electrodes**

Kariv-Miller, *1983 & 1984:* [divided cell, H_2O/THF/TBAOH, Pt(+)/Hg(-)]
- **R = ethers only**
- **Precious metal anode**
- **Unsafe mercury cathode**
- **Inconvenient divided cell**

Kashimura, *2003:* [undivided cell, ^{t}BuOH/THF, $LiClO_4$, Mg(+)/Mg(-)]
- **R = ethers and hydrocarbons only**
- **Continuous sonication required**
- **Dangerous and toxic perchlorate salts**

✗ Low chemo-selectivity

✗ Not Scalable

P. S. Baran *et al. Science*, **2019**, *363*, 838.

Screening

電極の選び方
・化合物の吸着能
・酸化還元電位
・陰極は水素を発生しやすさ

Commercial electrodes and potentiostat

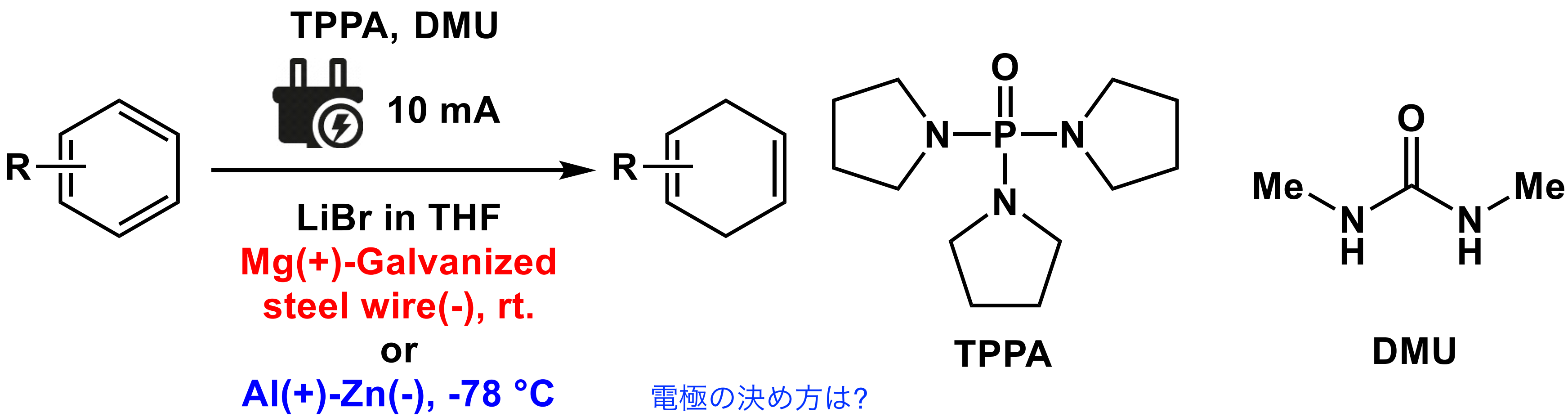
Entry	Ref	Electrodes	Conditions	Yield	By-prod.
1	13, 37	Pt(+)/Pt(-)	$MeNH_2$, LiCl	<5%	-
2	12, 44	SS(+)/Hg(-)	THF/H_2O, TBAOH	<5%	-
3	38	C(+)/Al(-)	HMPA/EtOH, LiCl, divided cell	<5%	-
4	15	Mg(+)/Mg(-)	THF/^{t}BuOH, $LiClO_4$, sonication	<5%	-
5	-	Al(+)/Zn(-)	THF, ^{t}BuOH, LiBr	<5%	-
6	-	Al(+)/Zn(-)	THF, ^{t}BuOH, LiBr, TPPA	50%	30%
7	-	Al(+)/Zn(-)	THF, DMU, LiBr, TPPA	65%	14%
8	-	Al(+)/Zn(-)	THF, DMU, LiBr, TPPA, -78 °C	74%	<5%
9	-	Mg(+)/GSW(-)	THF, DMU, LiBr, TPPA	70%	<5%

過充電により
Li が析出してしまう。
これはリチウムイオン電池の開発
でも見られる現象

Li イオンのトラップ剤 TPPA

P. S. Baran *et al. Science*, **2019**, *363*, 838.

Electrochemical Birch Reaction



電極の決め方は?
電圧などによる？？
なん電子か？

- Safe
- Ammonia / amine free
- Improved substrate scope
- Scalable (batch and flow)

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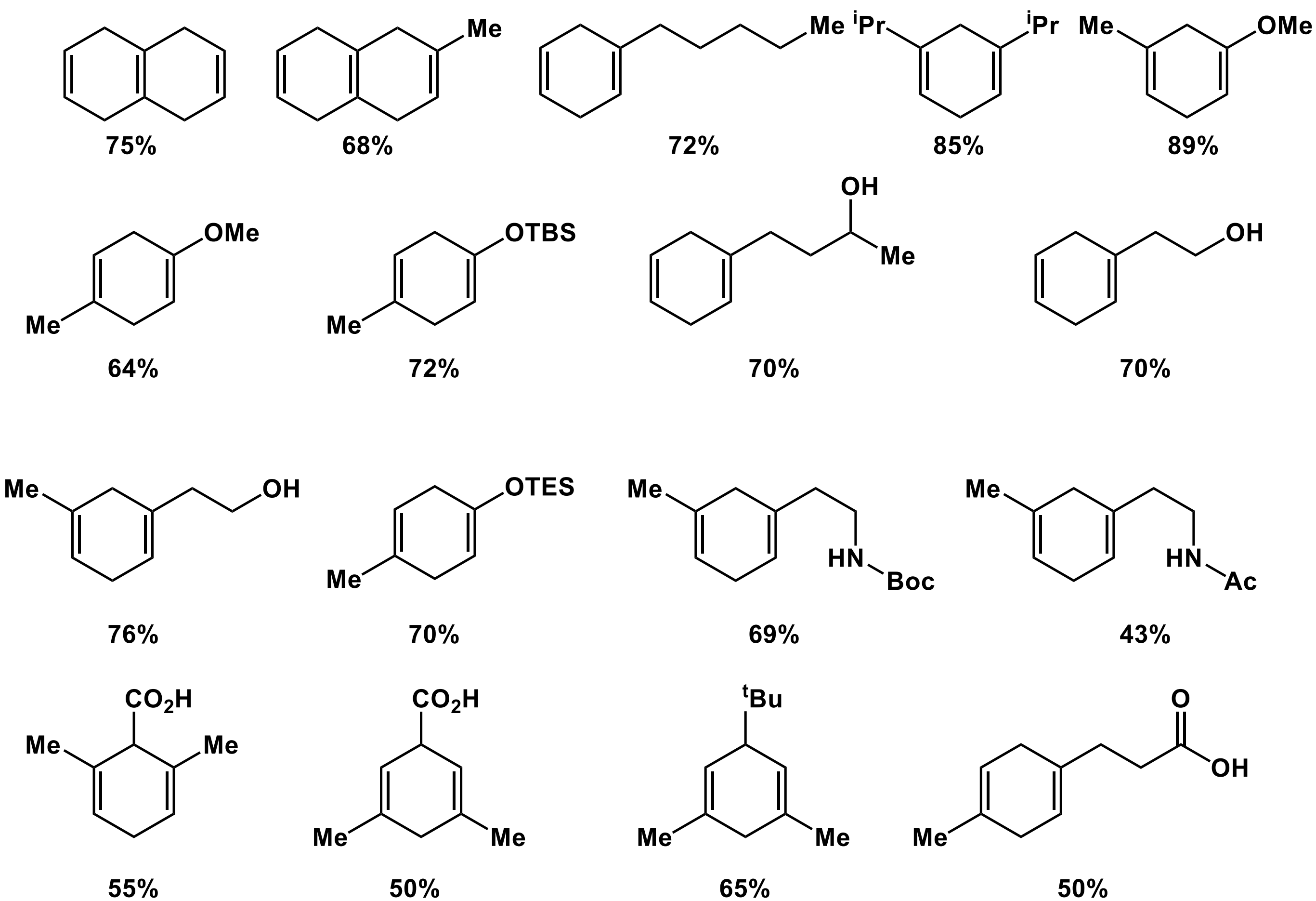
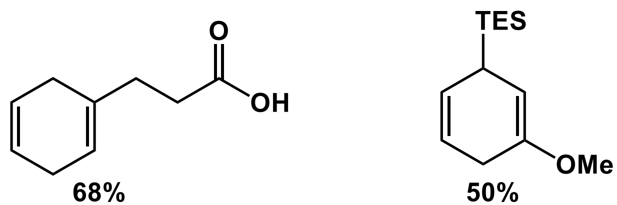
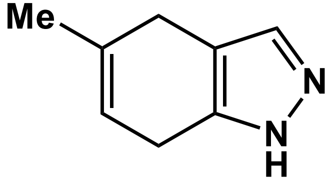
Substrate Scope (1)





P. S. Baran *et al. Science*, **2019**, *363*, 838.

Substrate Scope (2)



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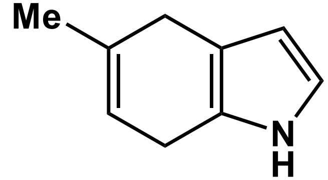
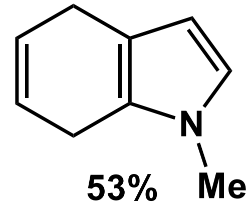


76%



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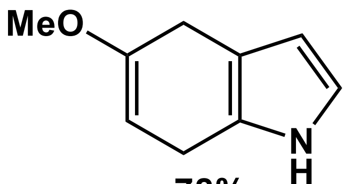
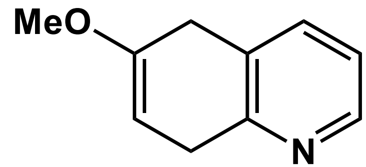
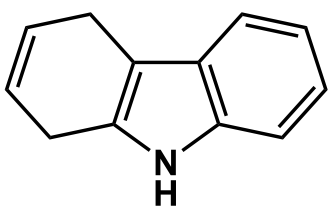


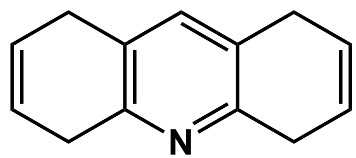
78%



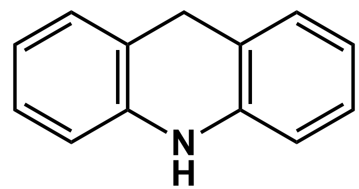
40%



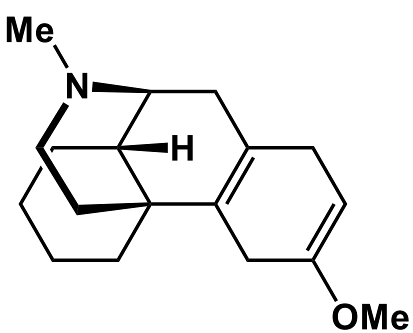
39%



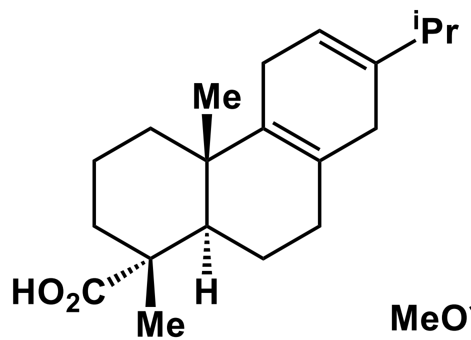
39%



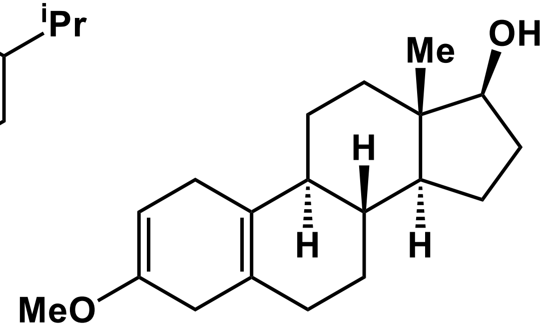
45%



59%



60%



65%

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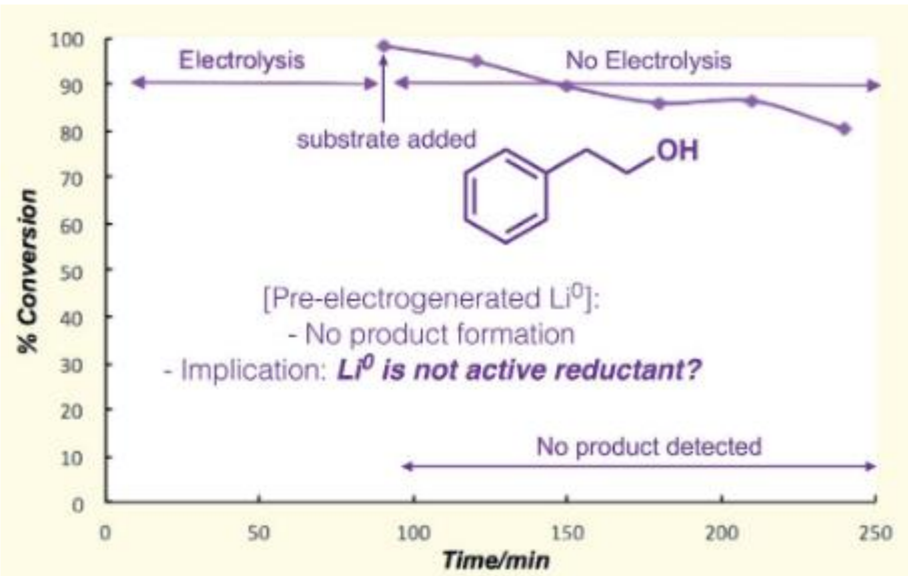
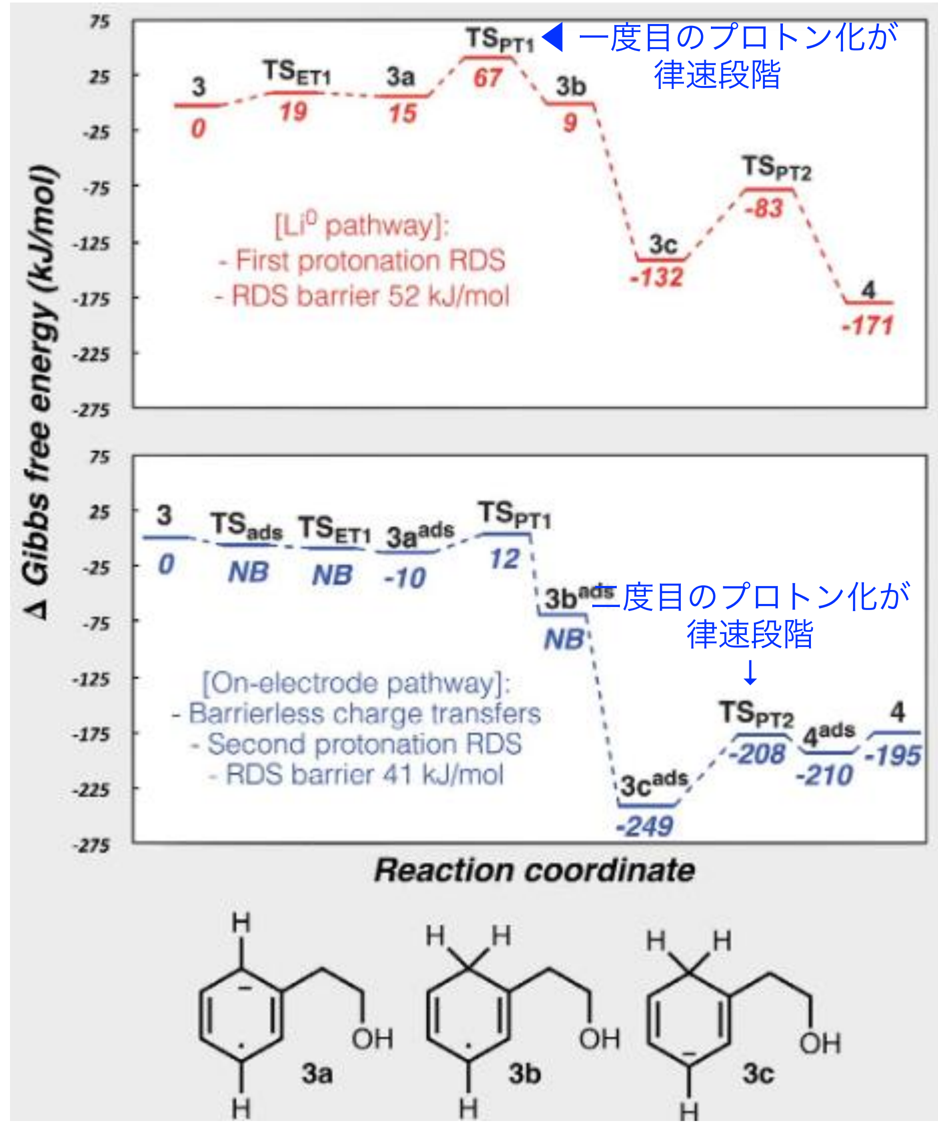
Li^0 pathway vs On-electrode pathway

Li0 は実験からも計算からも否定的





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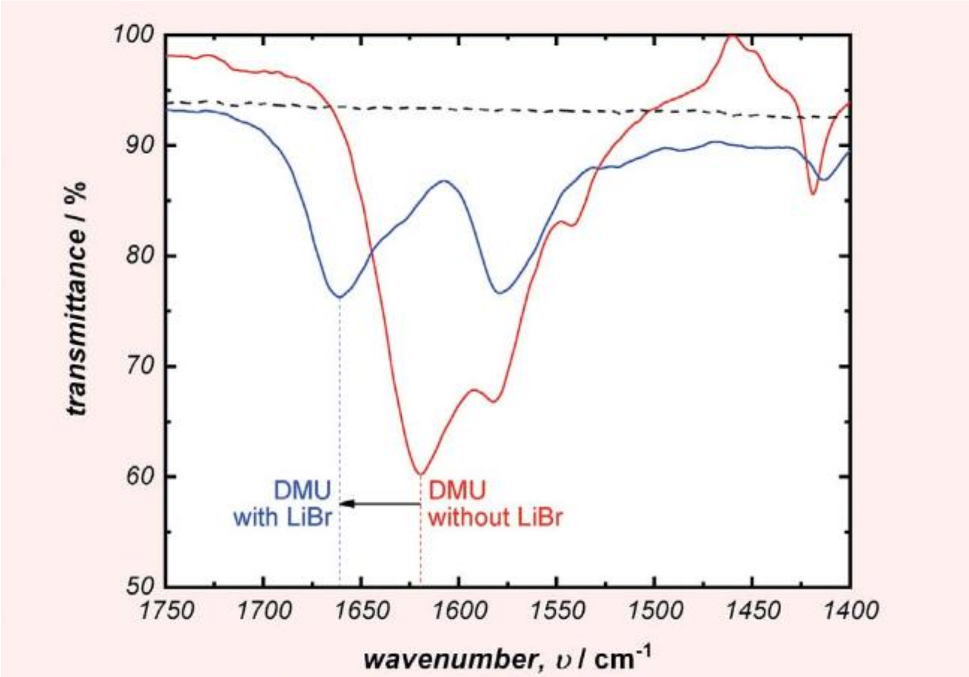
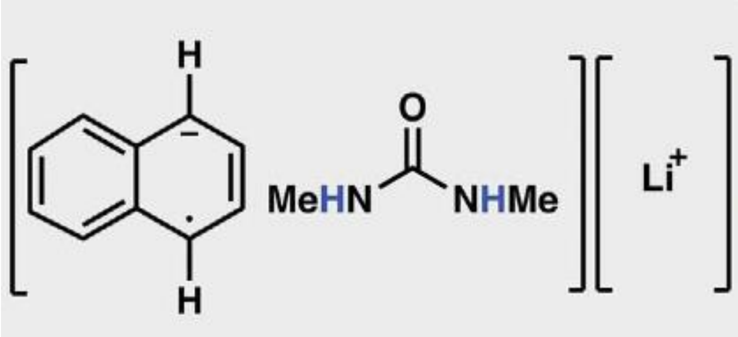
Role of DMU and LiBr

ATR IR of DMU with / without LiBr





- Proposed constituents of complex

- DMU has an integral role in stabilization

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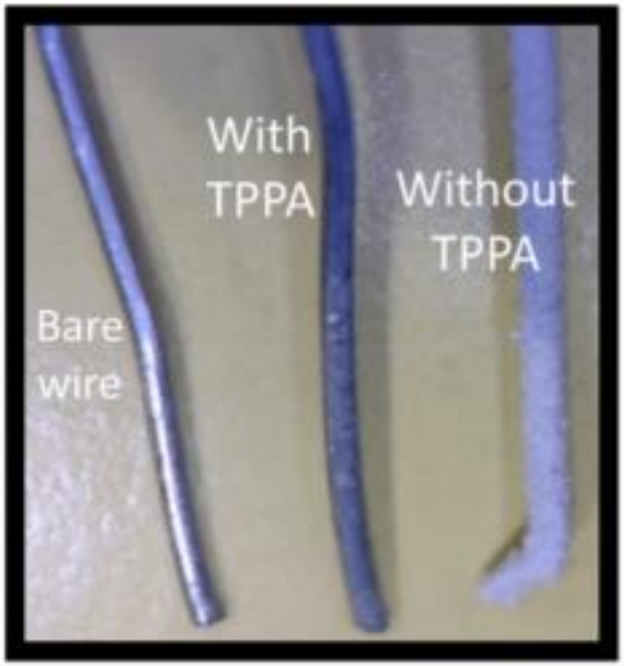
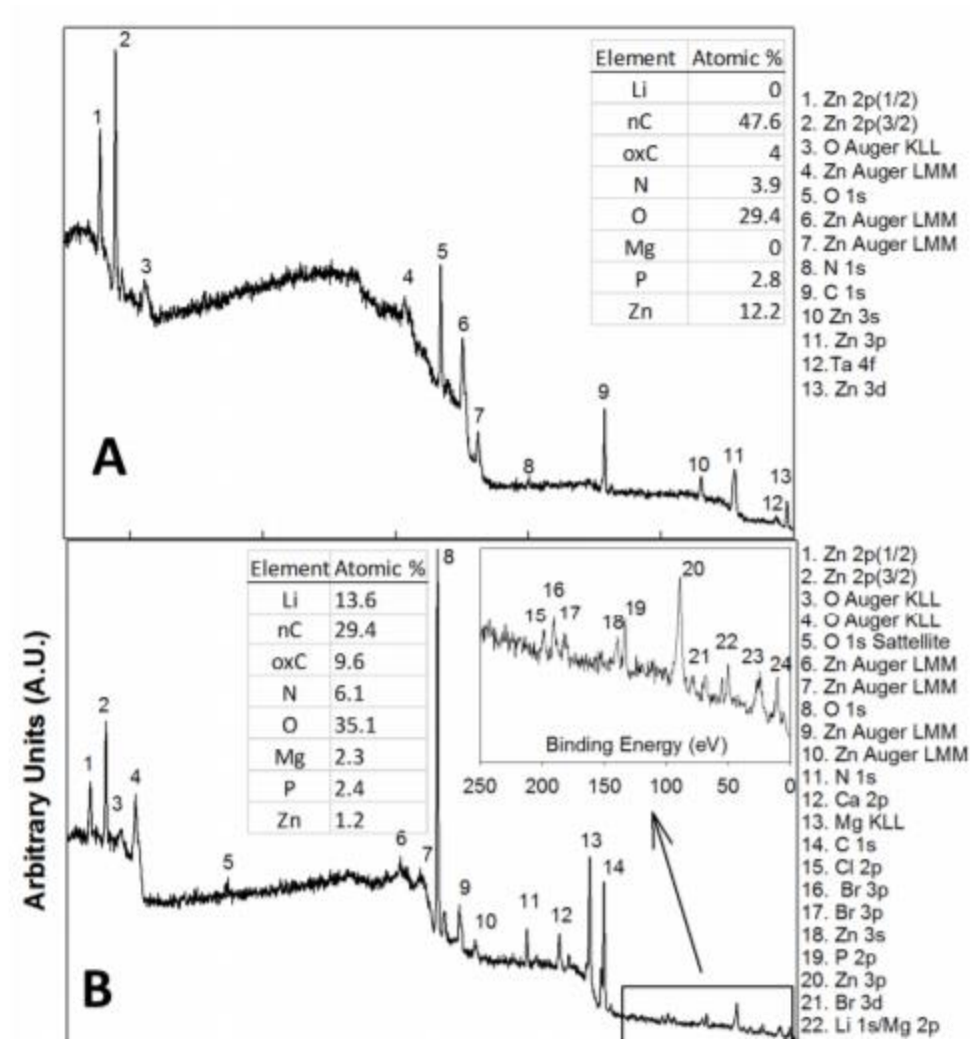
Role of TPPA



With TPPA, Zn electrode was still accessible.



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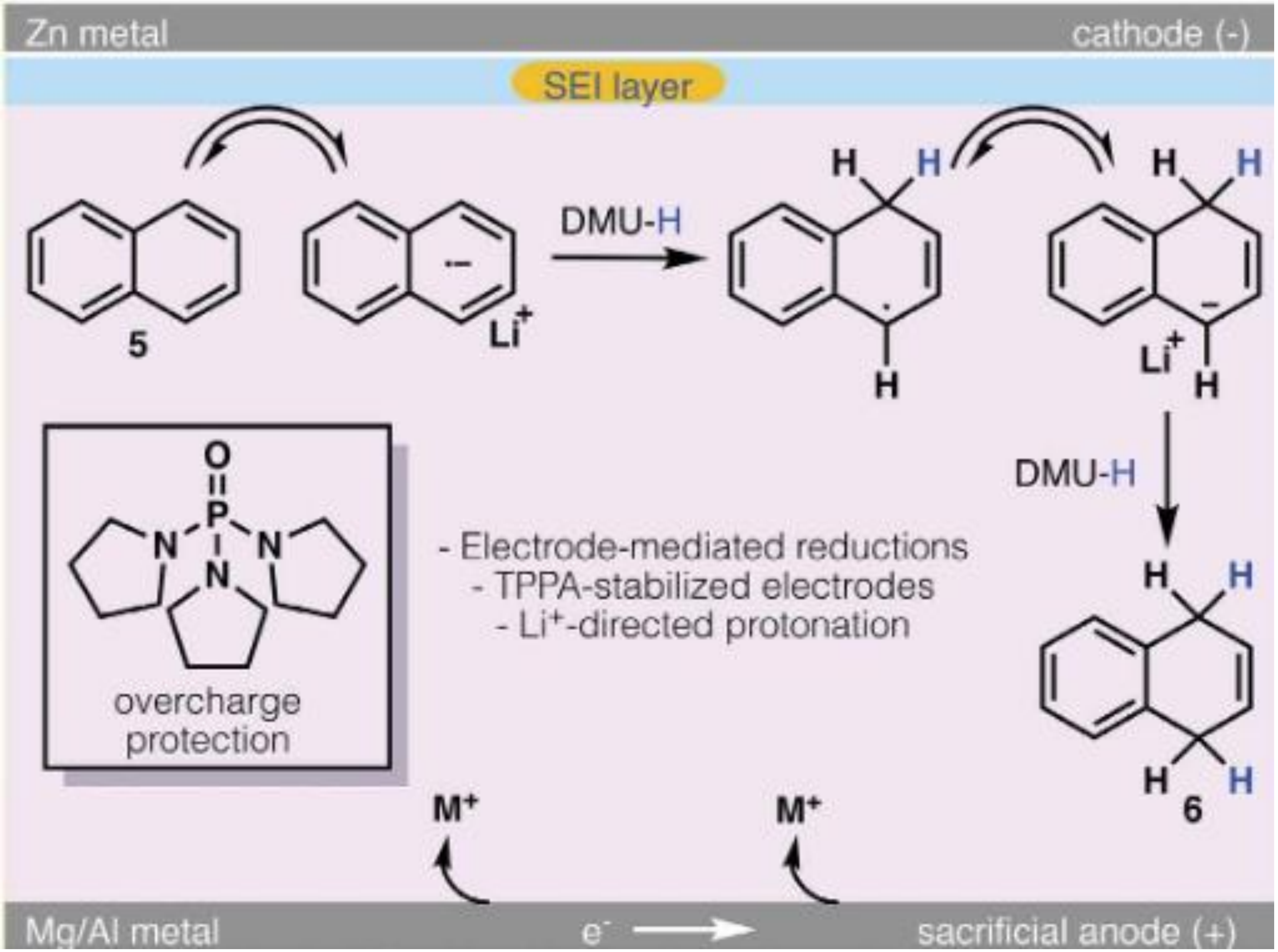
Reaction Mechanism



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Contents

Summary

- Organic electrosynthesis can avoid toxic oxidant / reductant.

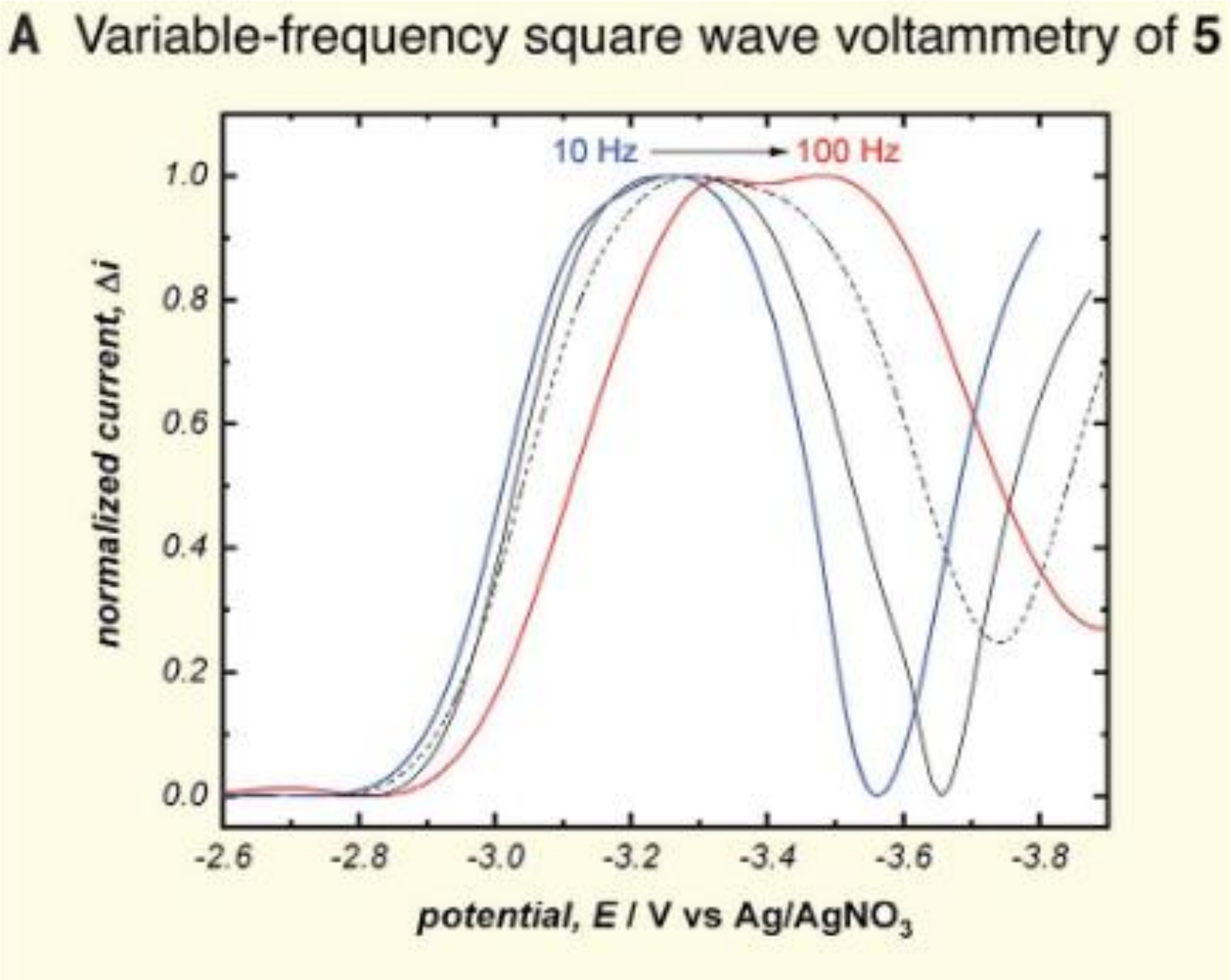
- Redox potential can be easily tunable.

- Chemoselectivity can be tunable by mediator and cation pool method.

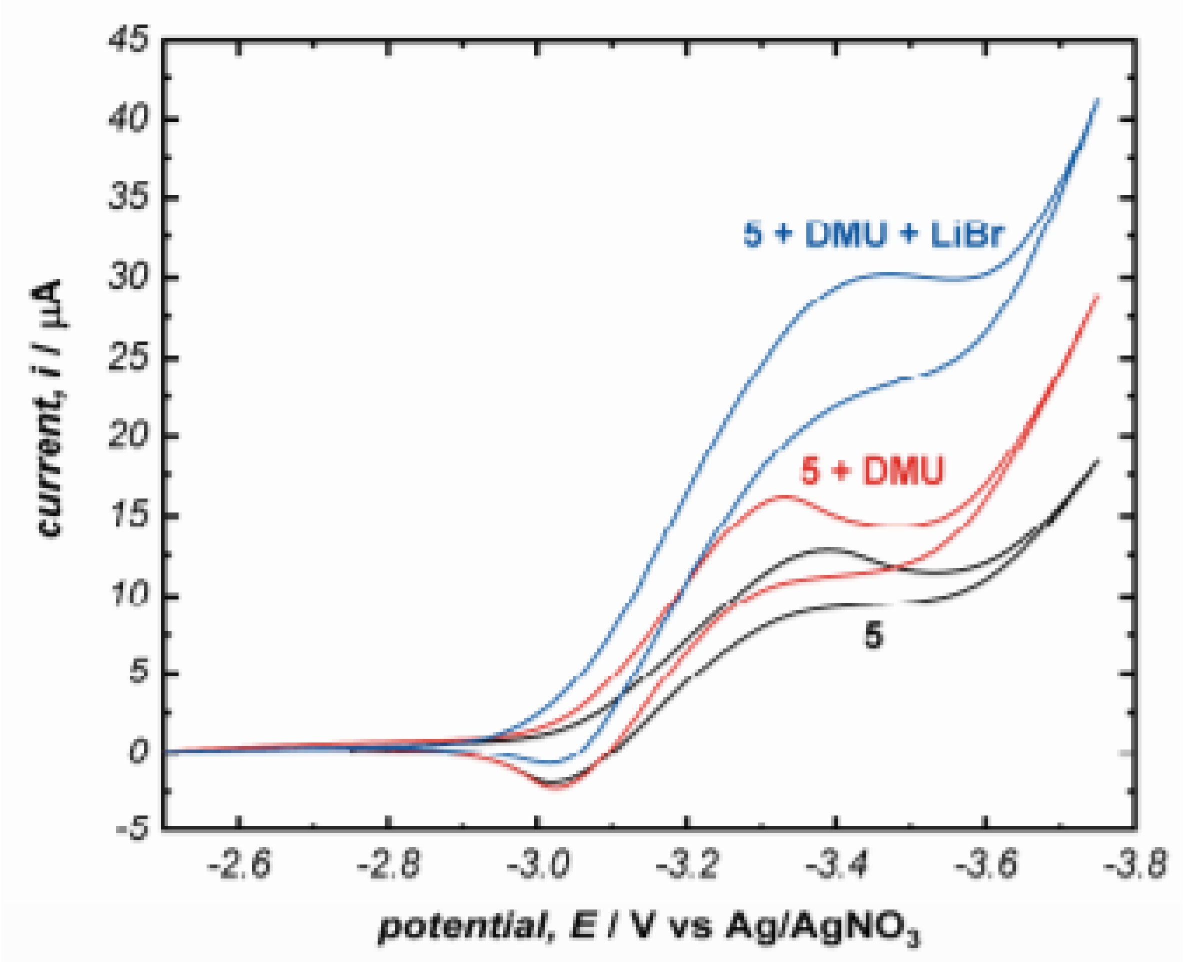
- Mild allylic C-H bond oxidation was developed using Cl_4-NHPI mediator.

- Mild electrochemical Birch reduction was developed with LiBr, DMU, TPPA

Appendix: square wave voltammetry



Appendix: Cyclic voltammetry



Appendix: Cyclic voltammetry