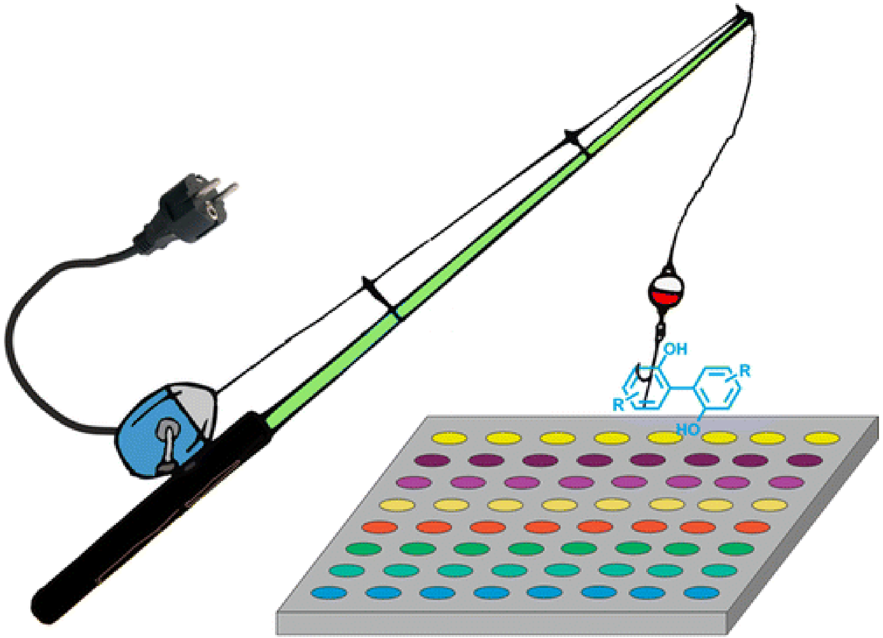
中国科学院上海有机化学研究所
Shanghai Institute of Organic Chemistry, CAS

Organic Electrochemical Synthesis



Jian Rong（荣 健）

Hu Group Meeting

Oct 31 , 2016

Outline

- ✓ **Introduction**

  — *History and Fundamental Information*

- ✓ **Organic Electrochemical Synthesis**

  — *General Organic Electrochemical Synthesis*
    - — Anode (阳极) oxidation
    - — Cathode (阴极) redution
    - — Paired organic electrosynthesis

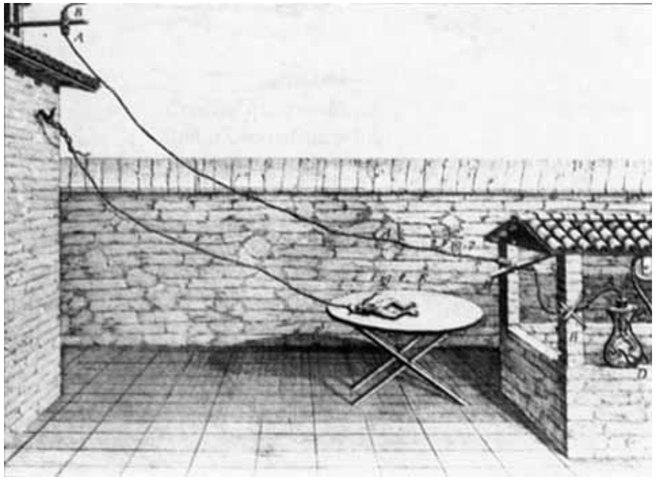
  — *Organic Electrosynthesis in Fluorine Chemistry*

  — *Organic Electrosynthesis in Natural Product Synthesis*

- ✓ **Summary**

  — *Advantages and Challenges*

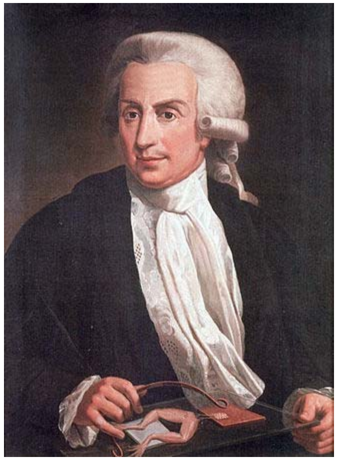
Introduction —— Electrochemistry



Galvani's experiment on frog(青蛙) legs

In 1791, the Italian physician and physicist Luigi Galvani found effect of electricity on muscular motion. (Essay *"De Viribus Electricitatis in Motu Musculari Commentarius"* in Latin)

This marked the birth of electrochemistry by establishing a bridge between chemical reaction and electricity.



Luigi Galvani （伽伐尼）

Electrochemistry is a branch of physical chemistry that studies the relationship with electricity and **Electrochemistry** is the only branch which is based on industry.

Analytical Electrochemistry

BioElectrochemistry

Synthetic Electrochemistry (include **Organic Electrosynthesis**)

Electrochemical Energy Conversion and Storage

Electrochemical Materials Science

Electrochemical Process Engineering and Technology

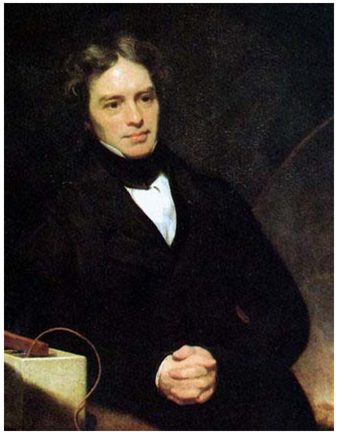
……

Introduction —— Organic Electrosynthesis

Early and famous example — the Kolbe reaction

In 1834, British physicist and chemist **Michael Faraday** observed the formation of a gaseous hydrocarbon, but he did not identify the products and missed the Kolbe Reaction. (Faraday's experiments led him to state his two Faraday‘s laws of electrolysis (电解))

$$2\ CH_3COO^- \xrightarrow{-2\ e^-} H_3C{-}CH_3 + 2\ CO_2$$



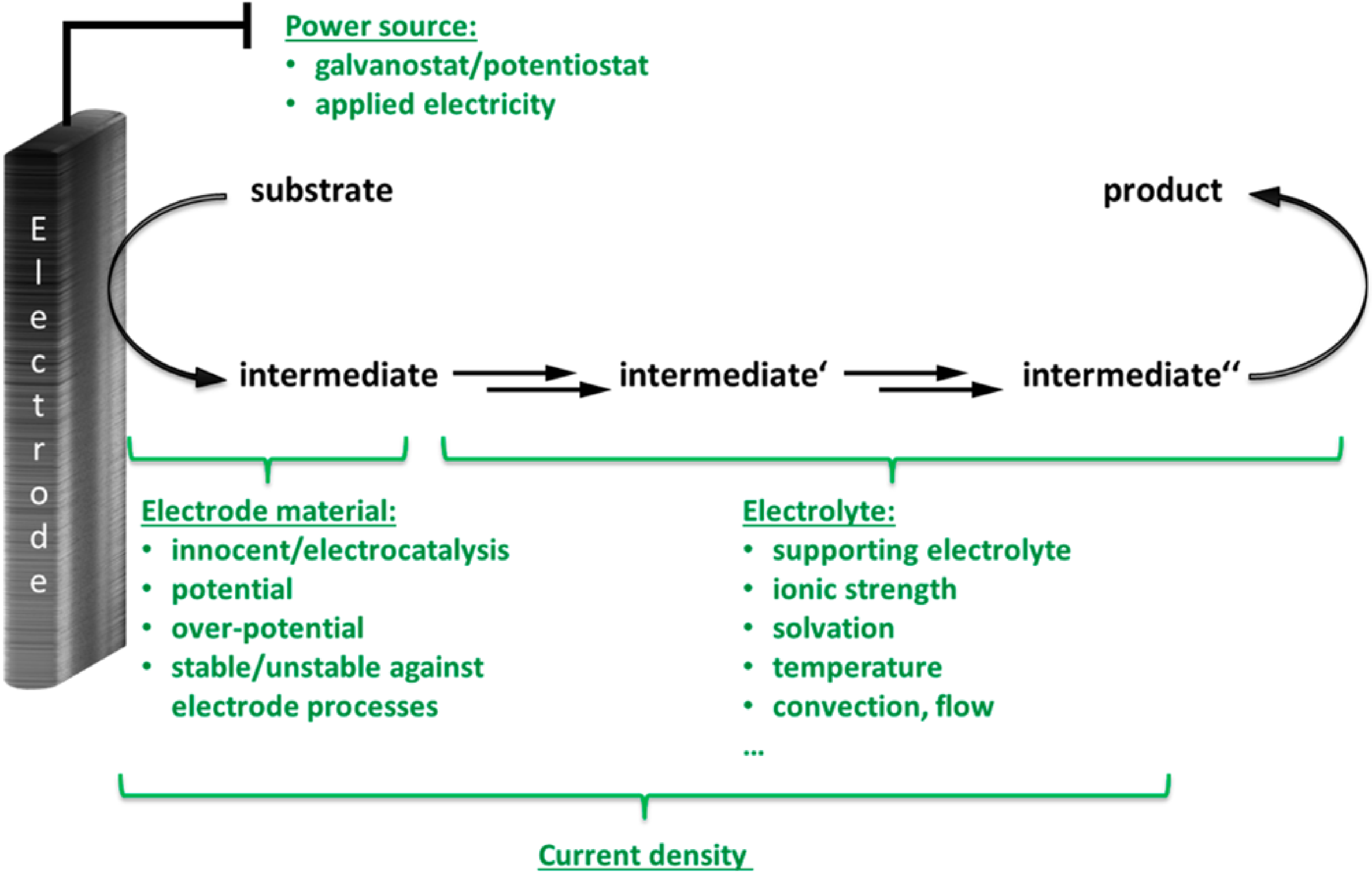
Michael Faraday

In 1849, **Hermann Kolbe**, however, did go much further and developed **the Kolbe reaction** which is one of the widely used in organic electrosynthesis, namely the oxidation at platinum of carboxylates to hydrocarbons (oxidative decarboxylation):

$$2\ RCOO^- \xrightarrow{-2\ e^-} R{-}R + 2\ CO_2$$

Hermann Kolbe

Overview of significant parameters



Power source:
- galvanostat/potentiostat
- applied electricity

substrate

product

intermediate

intermediate‘

intermediate“

Electrode material:
- innocent/electrocatalysis
- potential
- over-potential
- stable/unstable against electrode processes

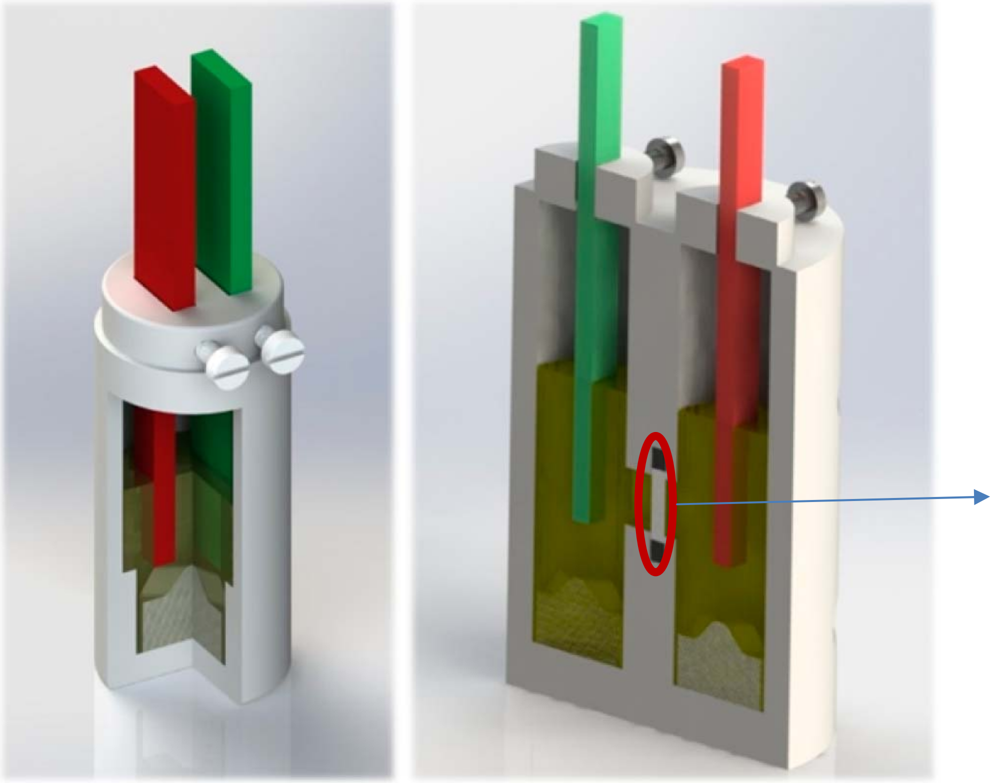
Electrolyte:
- supporting electrolyte
- ionic strength
- solvation
- temperature
- convection, flow

…

Current density

The parameters in organic electrosynthesis may be complex.

Reactor (Electrolytic cell)

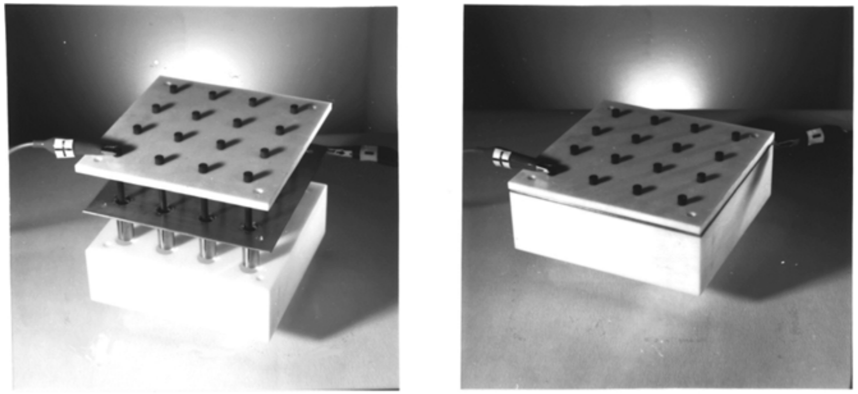


undivided cell (left) and **divided cell** (right)

They may have cathode and anode compartments separated by membranes or microporous materials (divided cells), or be single compartment (undivided cells).

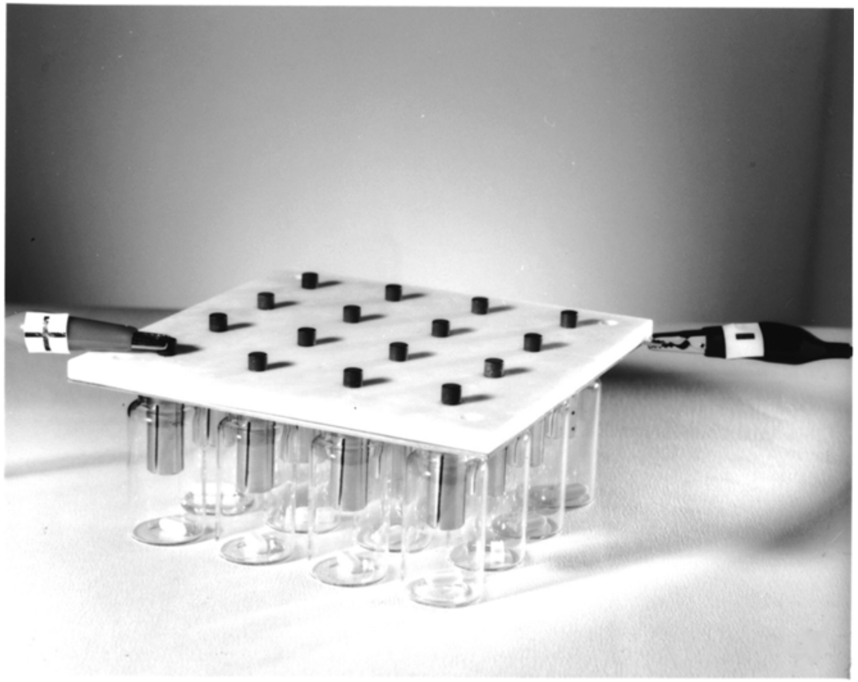
Reactor (Electrolytic cell)

single compartment (undivided cells)

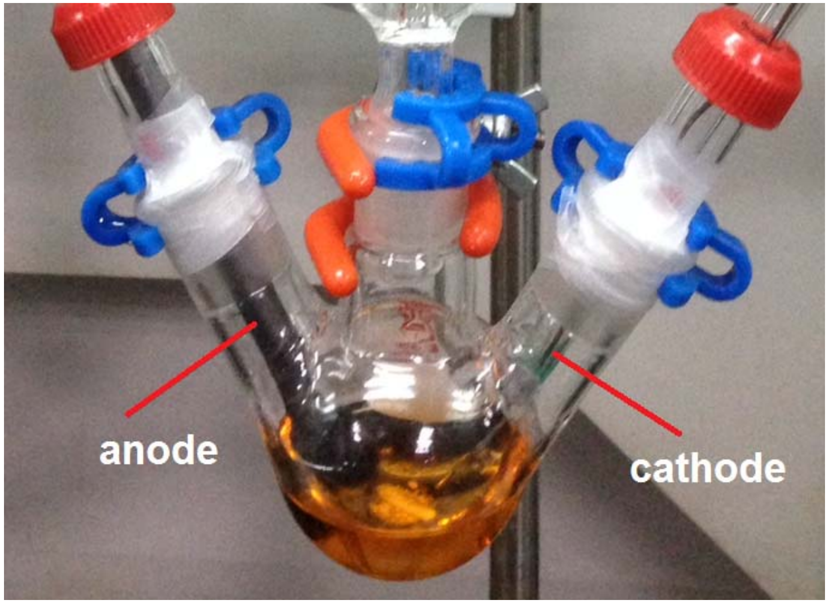


(a)

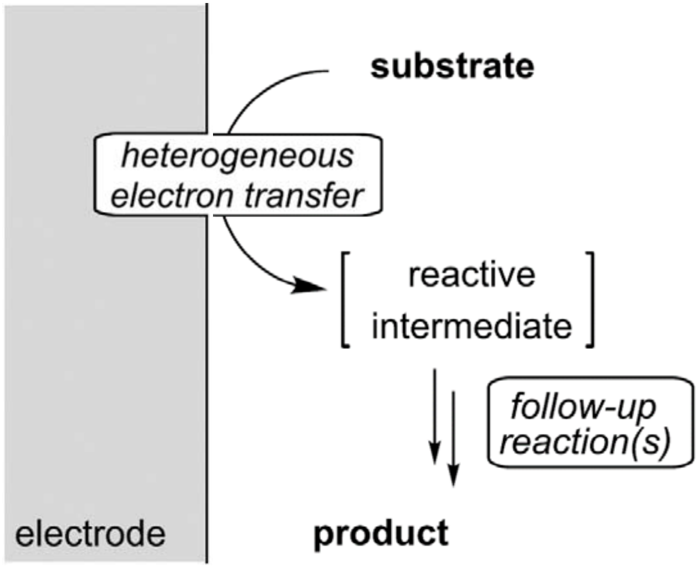
(b)



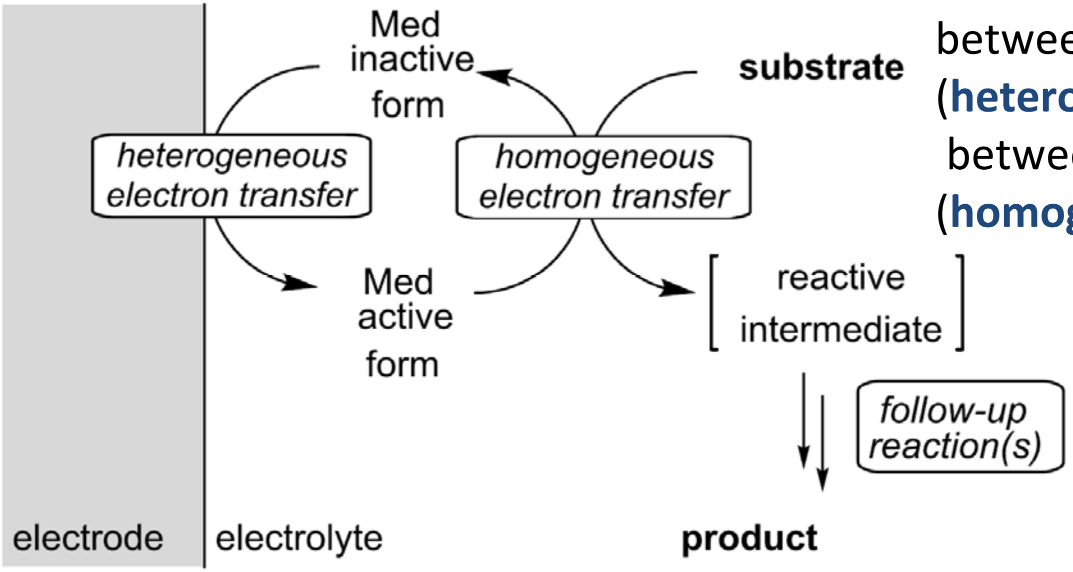
(c)



Direct electrolysis and indirect electrolysis

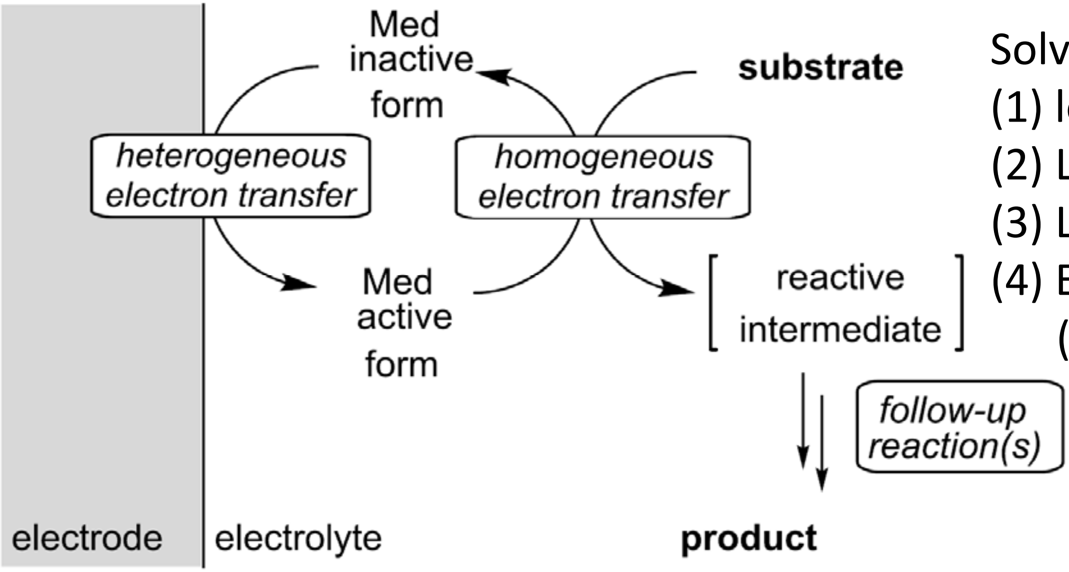


Electron transfer
between **electrode** and **substrate**
(**heterogeneous, kinetic inhibition**)



Electron transfer
between **electrode** and **redox mediator**
(**heterogeneous**)
between **redox mediator** and **substrate**
(**homogeneous**)

Advantages of indirect electrolysis



Solving these problems
(1) low solubility of substrate in electrolyte
(2) Low concentration needed in reaction
(3) Low reaction rate
(4) Electrode passivation (钝化)
(pollute the electrode)

(1) By shifting away from a heterogeneous electron transfer to a **homogeneous process**, **higher rate** can be achieved, which means that **overpotential (overoxidation/-reduction) can be avoided**, and this is particularly significant for large biomolecules that exhibit strong kinetic inhibition due to steric shielding of their redox centers.

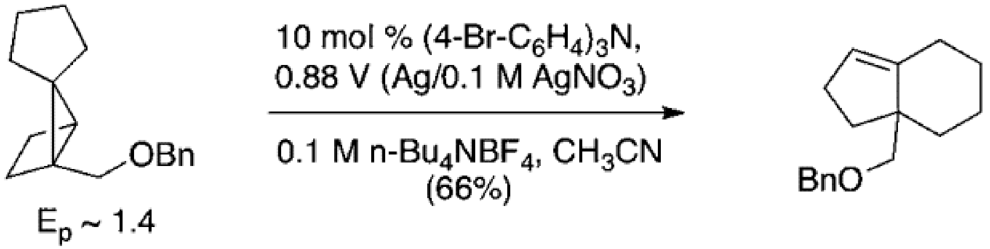
(2) Electron transfer mediators can **exhibit higher or totally different selectivity**.

(3) **Electrode passivation (钝化)** (that may result by the formation of a polymer film on the electrode surface) **can be avoided** with the employment of a mediator.

(4) Electrolysis is conducted **at lower potentials** (**even lower than the redox potential of the starting material**), the reaction can be carried out **under milder conditions** and **side reactions can be avoided**. This can be particularly significant when sensitive functional-groups, which are not intended to react, are present.

Advantages of indirect electrolysis

(4) Electrolysis is conducted **at lower potentials** (**even lower than the redox potential of the starting material**), the reaction can be carried out **under milder conditions** and **side reactions can be avoided**. This can be particularly significant when sensitive functional-groups, which are not intended to react, are present.



～520 mV easier to oxidize than the substrate

Avoiding an Impasse and Catalysis

$$\mathbf{M} \underset{+e}{\overset{-e}{\rightleftharpoons}} \mathbf{M}^{\bullet+} \qquad (1)$$

$$\mathbf{M}^{\bullet+} + \mathbf{Sub} \rightleftharpoons \mathbf{M} + (\mathbf{Sub})^{\bullet+} \qquad (2)$$

$$(\mathbf{Sub})^{\bullet+} \longrightarrow \text{toward product, } \mathbf{P} \qquad (3)$$

irreversible step

This apparent thermodynamic challenge can be overcome by shifting the equilibrium away from it (eq. 3).

N. Zhang, C. Zeng, C. M. Lam, R. K. Gbur, R. D. Little, *J. Org. Chem.* **2013**, *78*, 2104

Two different electrolytic modes

Controlled-potential electrolysis (恒电压电解):

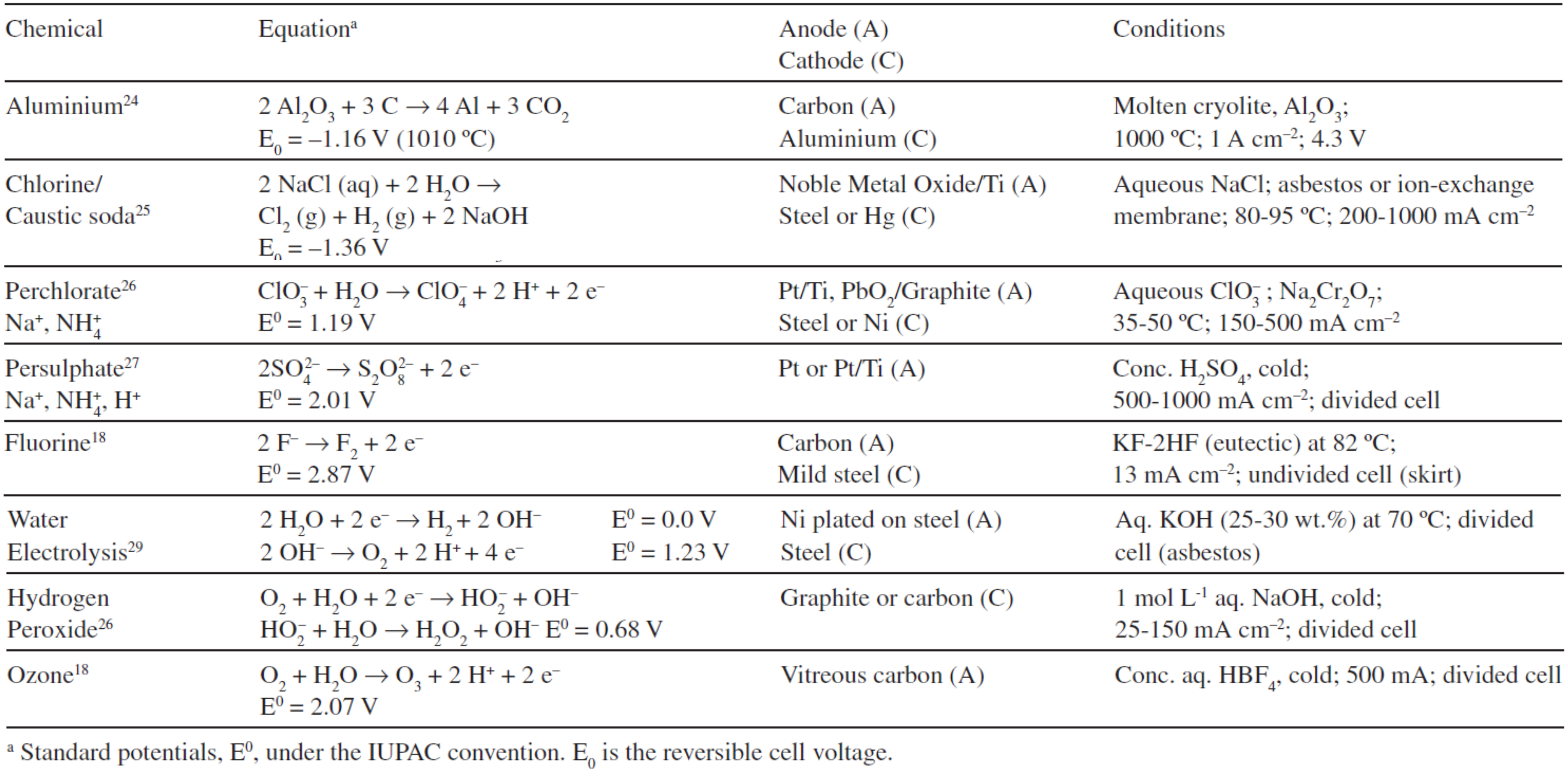
1. Three electrodes (a **working electrode (工作电极)**, a **counter electrode (对电极)** and a **reference electrode (参比电极)** (used to accurately maintain the voltage (电压) of the working electrode)
2. The important parameter is the **voltage (电压)**.
3. The **decrease in substrate concentration** is accompanied by a **decrease in the passing current** and therefore **reaction rate**.

Constant-current electrolysis (恒电流电解):

1. Two electrodes (a **working electrode (工作电极)**, a **counter electrode (对电极)**)
2. The important parameter is the **current density (电流)**, which describes the concentration of reactive intermediates formed and also determines the reaction pathway.
3. The **voltage is gradually increased (for oxidations)** to compensate (补偿) for the depleting (消耗) concentration of substrate. Since the **current remains constant**, **the rate of substrate consumption can also be maintained** provided all electron flow is associated with the desired electrolysis reaction.
4. This mode can be **easily used for scale-up.**

Electrochemistry based on industry

Inorganic electrochemical processes



Chemical	Equation[a]	Anode (A) Cathode (C)	Conditions
Aluminium[24]	$2\ Al_2O_3 + 3\ C \rightarrow 4\ Al + 3\ CO_2$ $E_0 = -1.16$ V (1010 ºC)	Carbon (A) Aluminium (C)	Molten cryolite, Al_2O_3; 1000 ºC; 1 A cm^{-2}; 4.3 V
Chlorine/ Caustic soda[25]	$2\ NaCl\ (aq) + 2\ H_2O \rightarrow$ $Cl_2\ (g) + H_2\ (g) + 2\ NaOH$ $E_0 = -1.36$ V	Noble Metal Oxide/Ti (A) Steel or Hg (C)	Aqueous NaCl; asbestos or ion-exchange membrane; 80-95 ºC; 200-1000 mA cm^{-2}
Perchlorate[26] Na^+, NH_4^+	$ClO_3^- + H_2O \rightarrow ClO_4^- + 2\ H^+ + 2\ e^-$ $E^0 = 1.19$ V	Pt/Ti, PbO_2/Graphite (A) Steel or Ni (C)	Aqueous ClO_3^- ; $Na_2Cr_2O_7$; 35-50 ºC; 150-500 mA cm^{-2}
Persulphate[27] Na^+, NH_4^+, H^+	$2SO_4^{2-} \rightarrow S_2O_8^{2-} + 2\ e^-$ $E^0 = 2.01$ V	Pt or Pt/Ti (A)	Conc. H_2SO_4, cold; 500-1000 mA cm^{-2}; divided cell
Fluorine[18]	$2\ F^- \rightarrow F_2 + 2\ e^-$ $E^0 = 2.87$ V	Carbon (A) Mild steel (C)	KF-2HF (eutectic) at 82 ºC; 13 mA cm^{-2}; undivided cell (skirt)
Water Electrolysis[29]	$2\ H_2O + 2\ e^- \rightarrow H_2 + 2\ OH^-$ $E^0 = 0.0$ V $2\ OH^- \rightarrow O_2 + 2\ H^+ + 4\ e^-$ $E^0 = 1.23$ V	Ni plated on steel (A) Steel (C)	Aq. KOH (25-30 wt.%) at 70 ºC; divided cell (asbestos)
Hydrogen Peroxide[26]	$O_2 + H_2O + 2\ e^- \rightarrow HO_2^- + OH^-$ $HO_2^- + H_2O \rightarrow H_2O_2 + OH^-$ $E^0 = 0.68$ V	Graphite or carbon (C)	1 mol L^{-1} aq. NaOH, cold; 25-150 mA cm^{-2}; divided cell
Ozone[18]	$O_2 + H_2O \rightarrow O_3 + 2\ H^+ + 2\ e^-$ $E^0 = 2.07$ V	Vitreous carbon (A)	Conc. aq. HBF_4, cold; 500 mA; divided cell

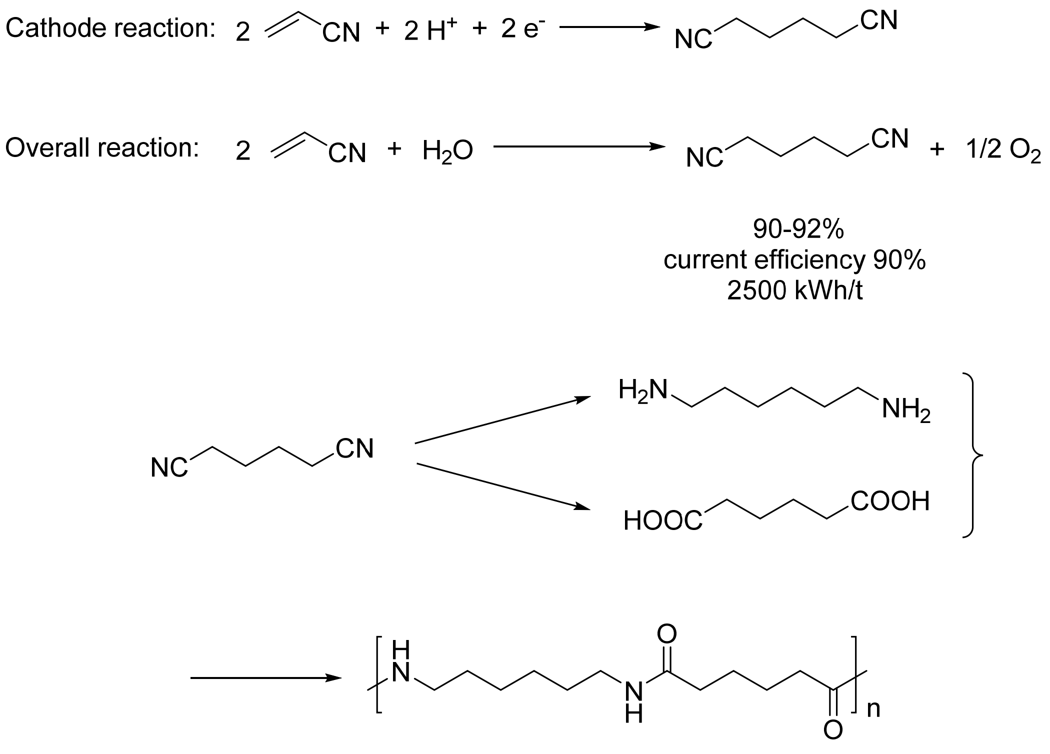
[a] Standard potentials, E^0, under the IUPAC convention. E_0 is the reversible cell voltage.

Al, H_2, O_2, O_3, H_2O_2, F_2, Cl_2, NaOH, $MClO_4$, MS_2O_8, etc.

Application of Organic Electrosynthesis

Electrochemical hydrodimerization of acrylonitrile

Anode reaction: $H_2O \longrightarrow 1/2\ O_2 + 2\ H^+ + 2\ e^-$



90-92%
current efficiency 90%
2500 kWh/t

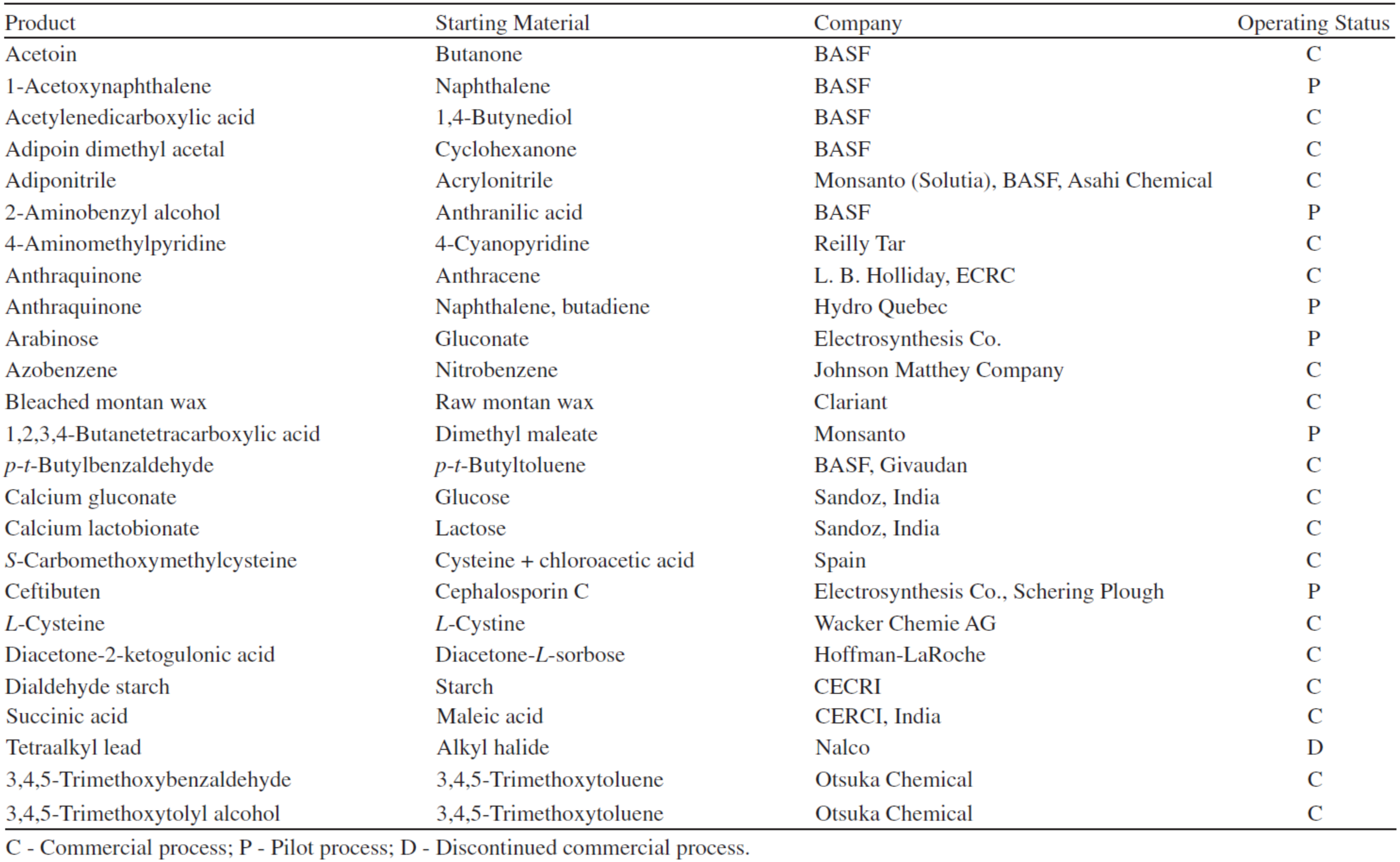
nylon-66

Nylon-66
2 million tons in 2015

developed in 1963, production in industry by Monsanto in 1965

Electrochemistry based on industry

Organic electrochemical processes

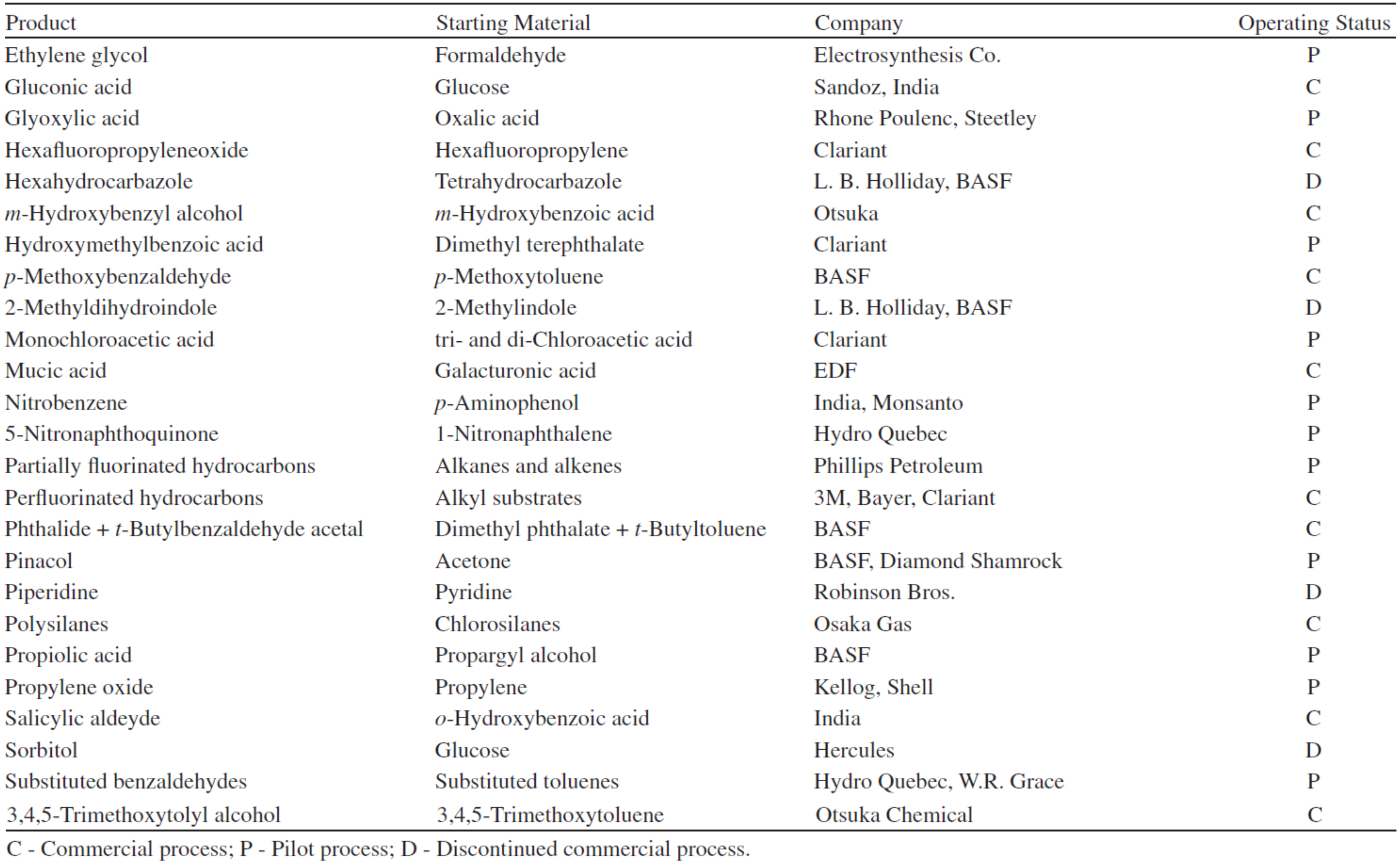


Product	Starting Material	Company	Operating Status
Acetoin	Butanone	BASF	C
1-Acetoxynaphthalene	Naphthalene	BASF	P
Acetylenedicarboxylic acid	1,4-Butynediol	BASF	C
Adipoin dimethyl acetal	Cyclohexanone	BASF	C
Adiponitrile	Acrylonitrile	Monsanto (Solutia), BASF, Asahi Chemical	C
2-Aminobenzyl alcohol	Anthranilic acid	BASF	P
4-Aminomethylpyridine	4-Cyanopyridine	Reilly Tar	C
Anthraquinone	Anthracene	L. B. Holliday, ECRC	C
Anthraquinone	Naphthalene, butadiene	Hydro Quebec	P
Arabinose	Gluconate	Electrosynthesis Co.	P
Azobenzene	Nitrobenzene	Johnson Matthey Company	C
Bleached montan wax	Raw montan wax	Clariant	C
1,2,3,4-Butanetetracarboxylic acid	Dimethyl maleate	Monsanto	P
p-t-Butylbenzaldehyde	*p-t*-Butyltoluene	BASF, Givaudan	C
Calcium gluconate	Glucose	Sandoz, India	C
Calcium lactobionate	Lactose	Sandoz, India	C
S-Carbomethoxymethylcysteine	Cysteine + chloroacetic acid	Spain	C
Ceftibuten	Cephalosporin C	Electrosynthesis Co., Schering Plough	P
L-Cysteine	*L*-Cystine	Wacker Chemie AG	C
Diacetone-2-ketogulonic acid	Diacetone-*L*-sorbose	Hoffman-LaRoche	C
Dialdehyde starch	Starch	CECRI	C
Succinic acid	Maleic acid	CERCI, India	C
Tetraalkyl lead	Alkyl halide	Nalco	D
3,4,5-Trimethoxybenzaldehyde	3,4,5-Trimethoxytoluene	Otsuka Chemical	C
3,4,5-Trimethoxytolyl alcohol	3,4,5-Trimethoxytoluene	Otsuka Chemical	C

C - Commercial process; P - Pilot process; D - Discontinued commercial process.

Electrochemistry based on industry

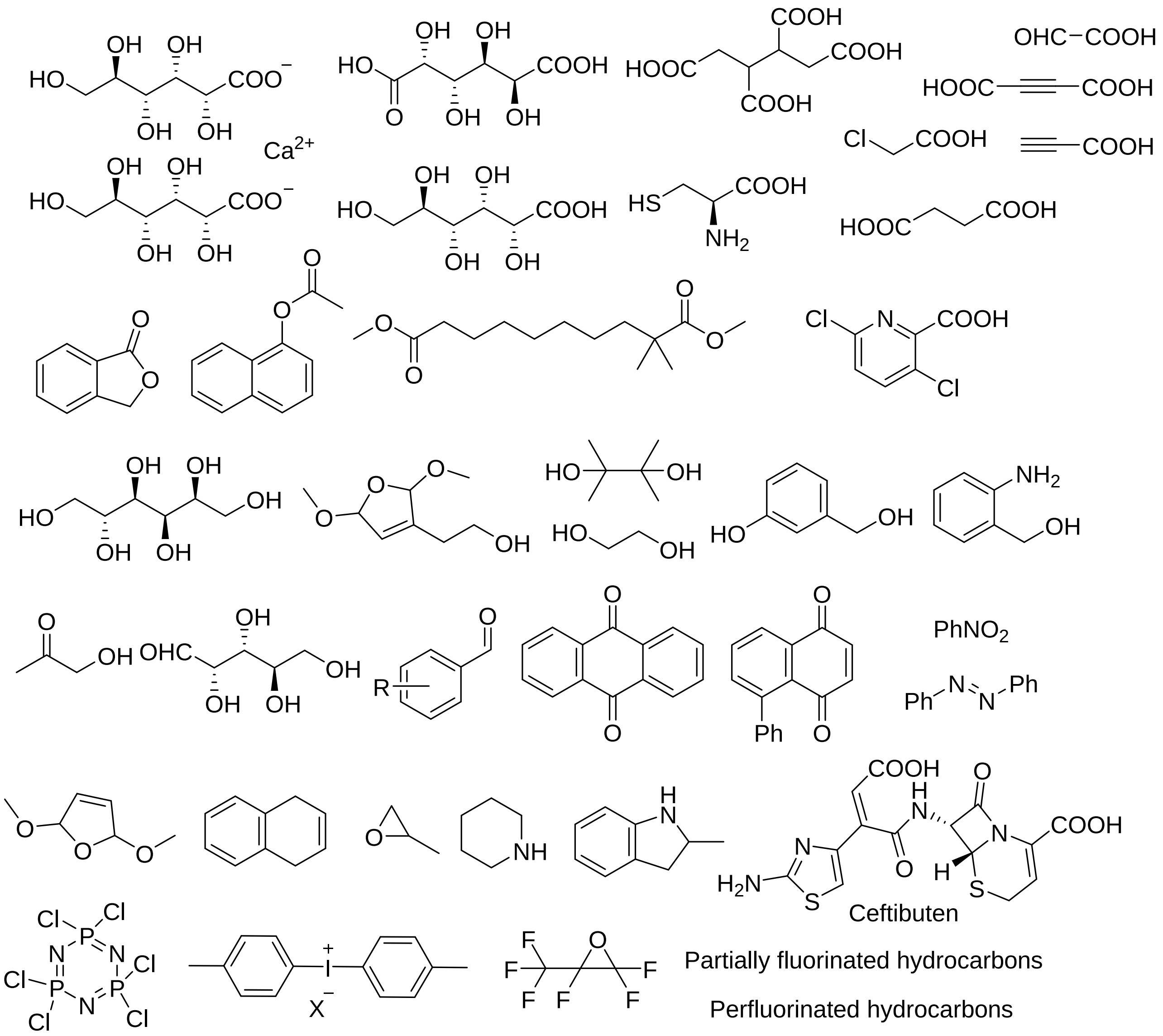
Organic electrochemical processes



Product	Starting Material	Company	Operating Status
Ethylene glycol	Formaldehyde	Electrosynthesis Co.	P
Gluconic acid	Glucose	Sandoz, India	C
Glyoxylic acid	Oxalic acid	Rhone Poulenc, Steetley	P
Hexafluoropropyleneoxide	Hexafluoropropylene	Clariant	C
Hexahydrocarbazole	Tetrahydrocarbazole	L. B. Holliday, BASF	D
m-Hydroxybenzyl alcohol	*m*-Hydroxybenzoic acid	Otsuka	C
Hydroxymethylbenzoic acid	Dimethyl terephthalate	Clariant	P
p-Methoxybenzaldehyde	*p*-Methoxytoluene	BASF	C
2-Methyldihydroindole	2-Methylindole	L. B. Holliday, BASF	D
Monochloroacetic acid	tri- and di-Chloroacetic acid	Clariant	P
Mucic acid	Galacturonic acid	EDF	C
Nitrobenzene	*p*-Aminophenol	India, Monsanto	P
5-Nitronaphthoquinone	1-Nitronaphthalene	Hydro Quebec	P
Partially fluorinated hydrocarbons	Alkanes and alkenes	Phillips Petroleum	P
Perfluorinated hydrocarbons	Alkyl substrates	3M, Bayer, Clariant	C
Phthalide + *t*-Butylbenzaldehyde acetal	Dimethyl phthalate + *t*-Butyltoluene	BASF	C
Pinacol	Acetone	BASF, Diamond Shamrock	P
Piperidine	Pyridine	Robinson Bros.	D
Polysilanes	Chlorosilanes	Osaka Gas	C
Propiolic acid	Propargyl alcohol	BASF	P
Propylene oxide	Propylene	Kellog, Shell	P
Salicylic aldeyde	*o*-Hydroxybenzoic acid	India	C
Sorbitol	Glucose	Hercules	D
Substituted benzaldehydes	Substituted toluenes	Hydro Quebec, W.R. Grace	P
3,4,5-Trimethoxytolyl alcohol	3,4,5-Trimethoxytoluene	Otsuka Chemical	C

C - Commercial process; P - Pilot process; D - Discontinued commercial process.

Organic chemicals from electrochemical industry



Ceftibuten

Partially fluorinated hydrocarbons

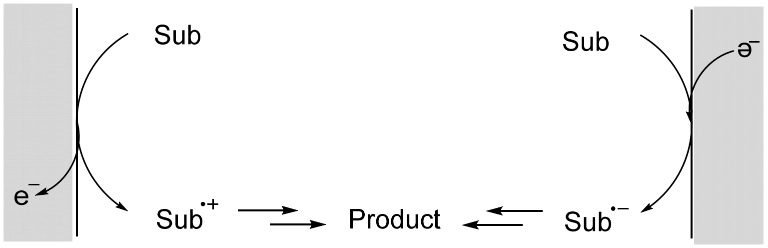
Perfluorinated hydrocarbons

Reaction types

Direct electrolysis

Anode oxidation

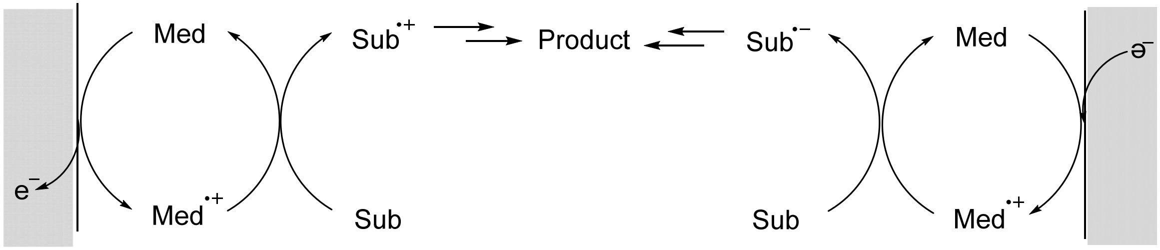
Cathode reduction



Indirect electrolysis

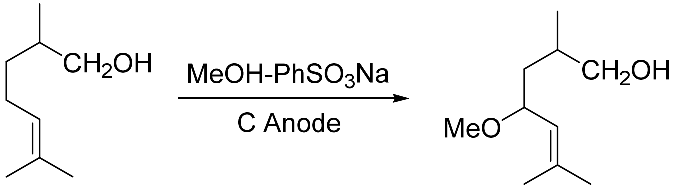
Anode oxidation

Cathode reduction



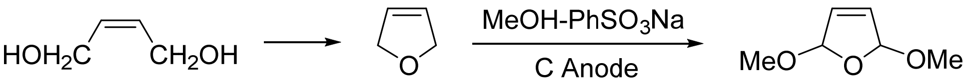
Anode oxidation

Methoxylation



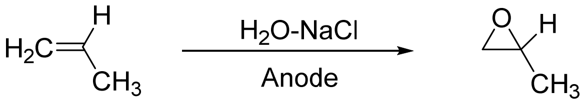
Citronellol (香茅醇)

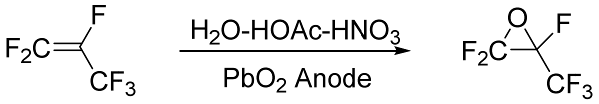
56%



70%
Production in industry by BASF

Epoxidation

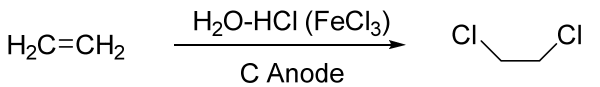




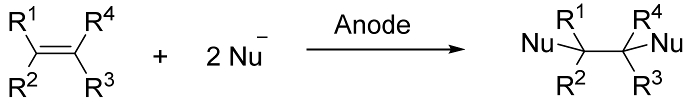
65-75%, current efficiency: 65%
Production in industry by Hoechst

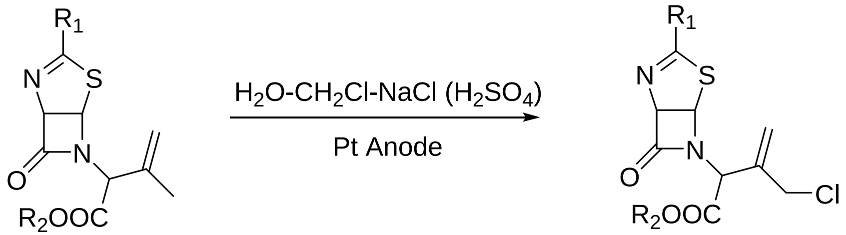
Anode oxidation

Halogenation

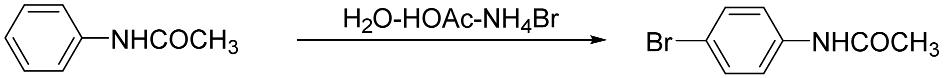


97%, current efficiency: >95%

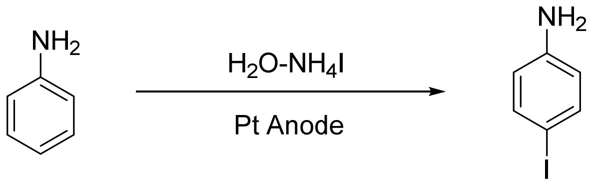




93%



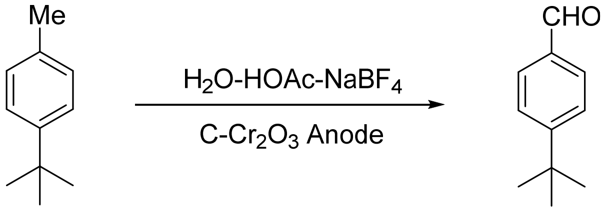
99%



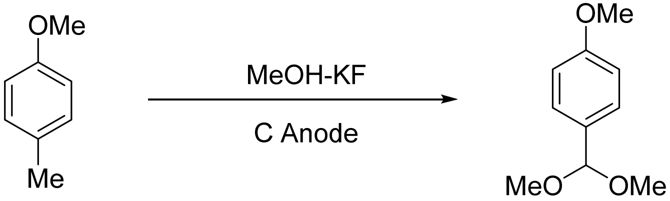
current efficiency: 91%
p:*o* = 96:4

Anode oxidation

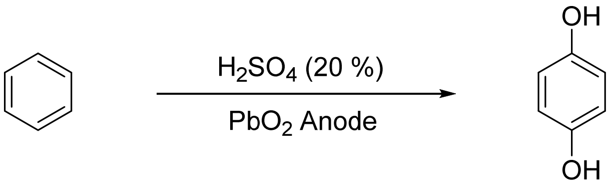
Oxidation of aromatics



87%
current efficiency: 67%



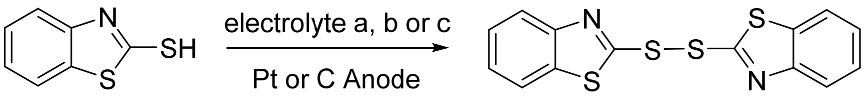
85%
Production in industry by BASF



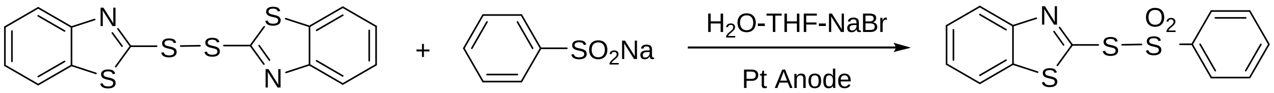
80%, very pure
production in industry

Anode oxidation

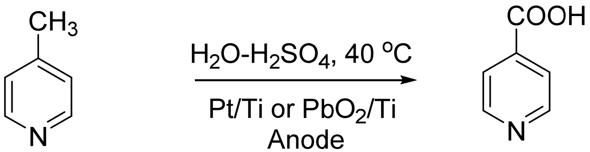
Oxidation of heteroaromatics



electrolyte a: Et_3N-MeOH 99%
b: MeOH-NaBr 99%
c: H_2O-KOH 98%



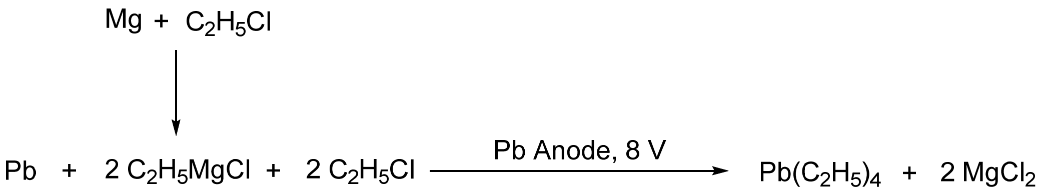
92%



65%, current efficiency: 68%

Anode oxidation

Synthesis of metal complex



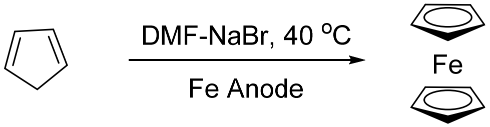
$$\mathrm{Pb} + 2\,\mathrm{C_2H_5MgCl} + 2\,\mathrm{C_2H_5Cl} \xrightarrow{\text{Pb Anode, 8 V}} \mathrm{Pb(C_2H_5)_4} + 2\,\mathrm{MgCl_2}$$

$$\mathrm{Mg} + \mathrm{C_2H_5Cl} \longrightarrow \mathrm{C_2H_5MgCl}$$

4000-5000 kWh/t

$5\text{x}10^5$ t/year

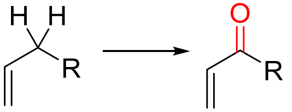
The latest standard in China: Pb% < 5 mg/L in gasoline(汽油)



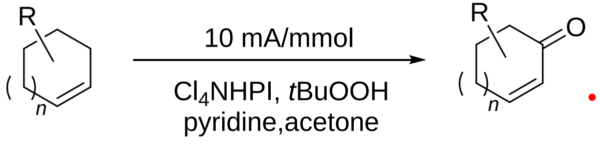
80%
current efficiency: 75%

Anode oxidation —— Recent example

Scalable and sustainable electrochemical allylic C–H oxidation



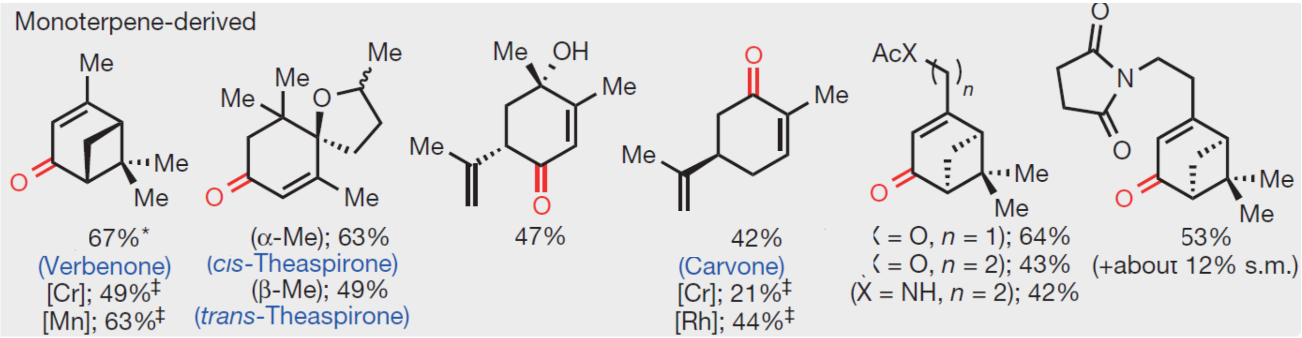
- Fundamental organic transformation
- Featured in >100 natural product syntheses
- About 80% use Cr, Se, Pd or Rh reagents



10 mA/mmol

Cl_4NHPI, *t*BuOOH
pyridine,acetone

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



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

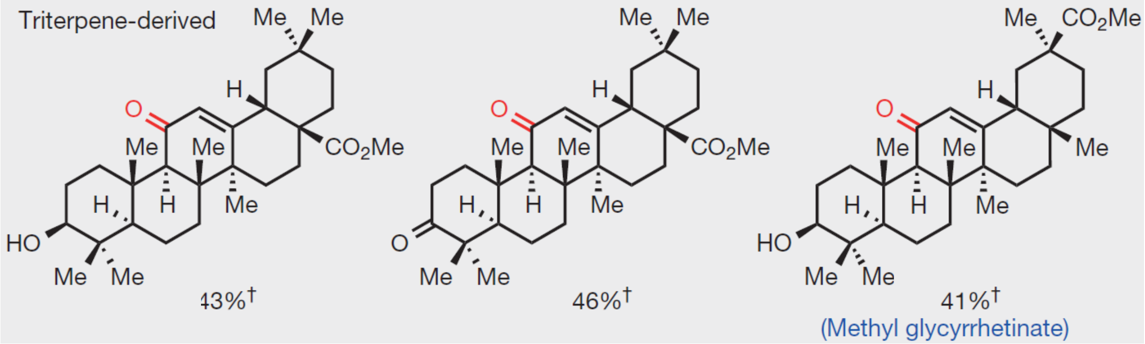
(α-Me); 63% (*cis*-Theaspirone) (β-Me); 49% (*trans*-Theaspirone)

47%

42% (Carvone) [Cr]; 21%‡ [Rh]; 44%‡

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

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



43%†

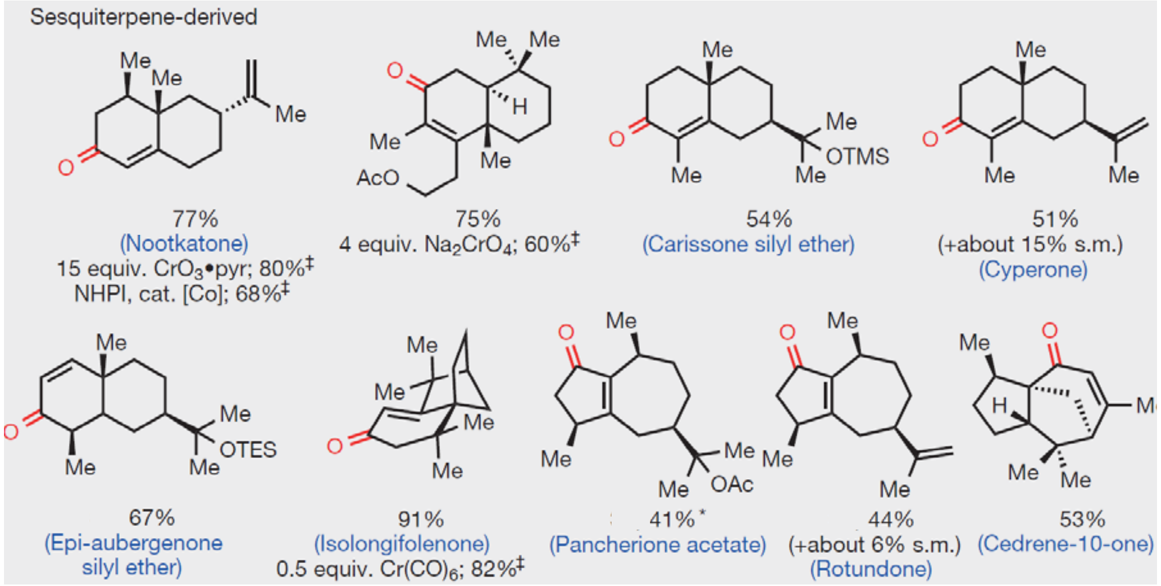
46%†

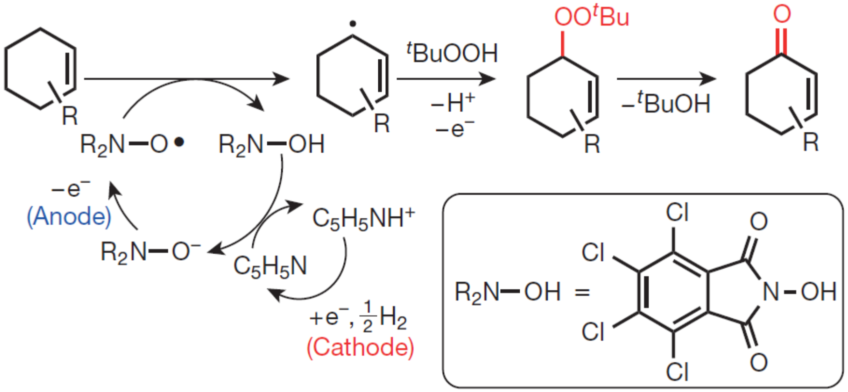
41%† (Methyl glycyrrhetinate)

E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 79.

Anode oxidation —— Recent example

Scalable and sustainable electrochemical allylic C–H oxidation

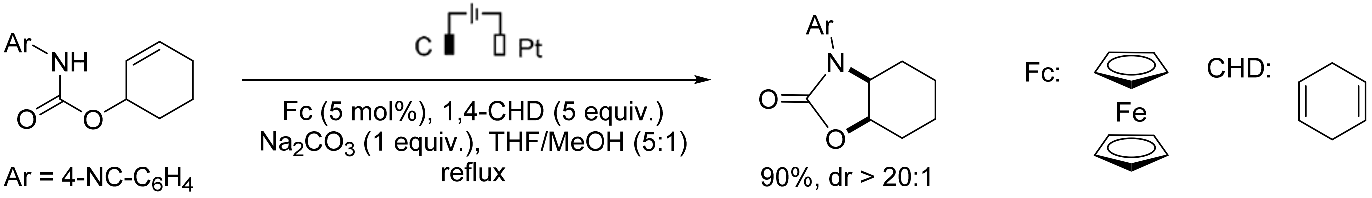


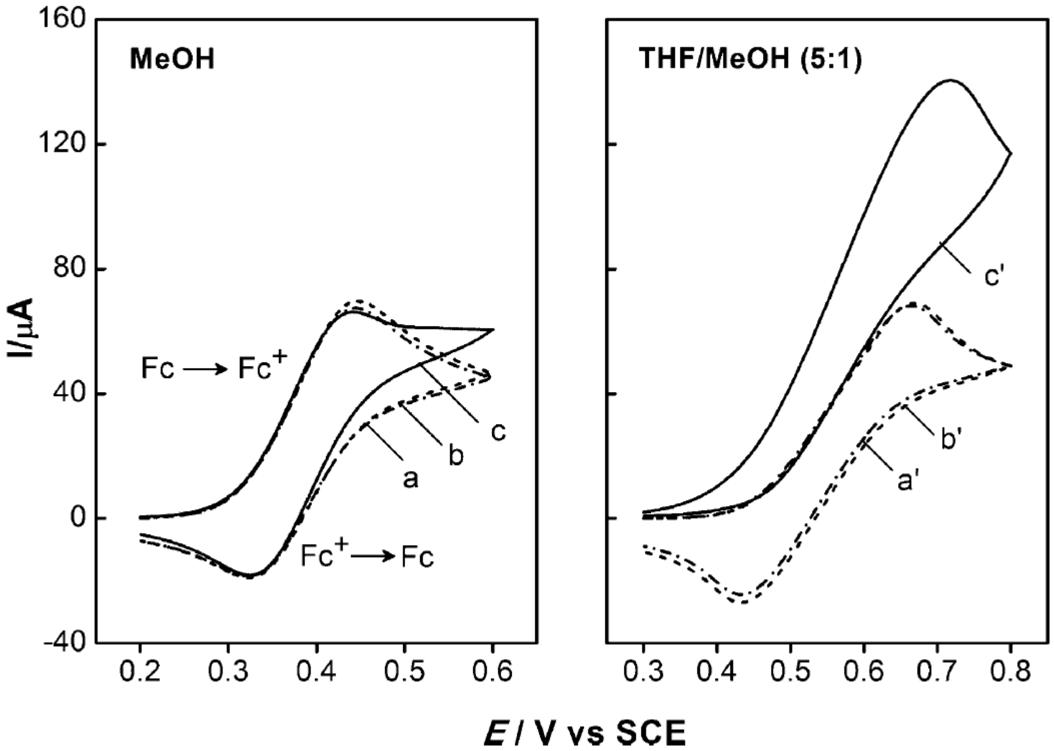


E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 79.

Anode oxidation —— Recent example

Electrocatalytic olefin hydroamidation



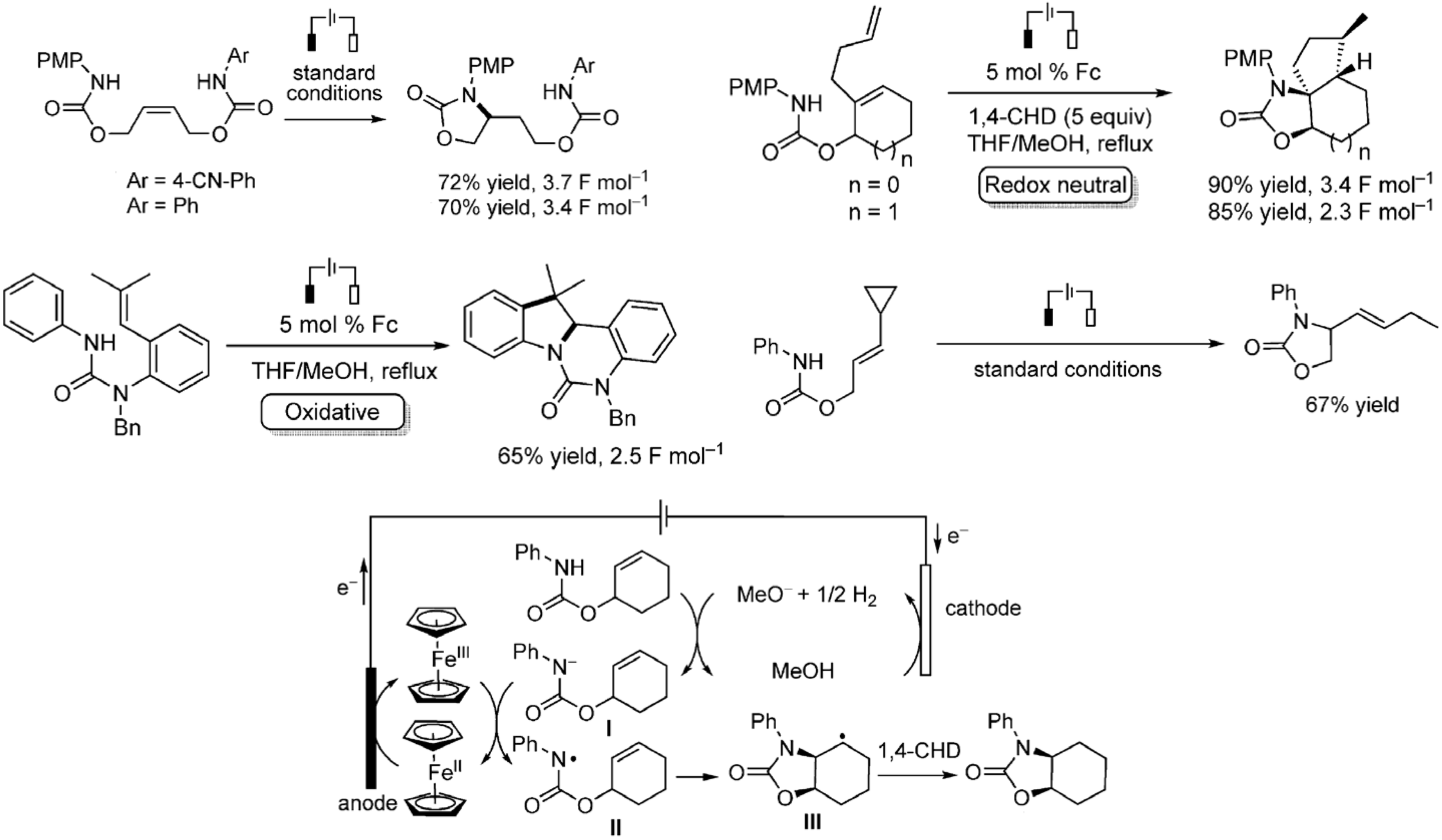


a/a': Fc
b/b': Fc + alkene
c/c': Fc + alkene + NaOMe

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

Anode oxidation —— Recent example

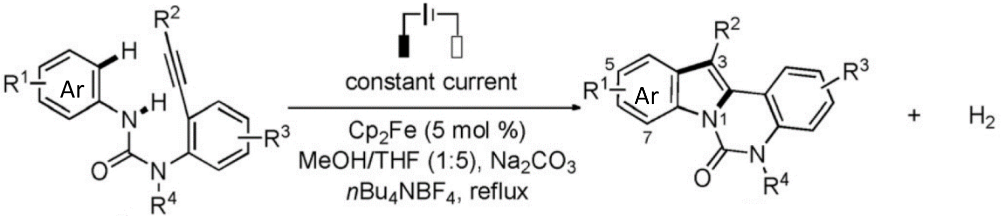
Electrocatalytic olefin hydroamidation



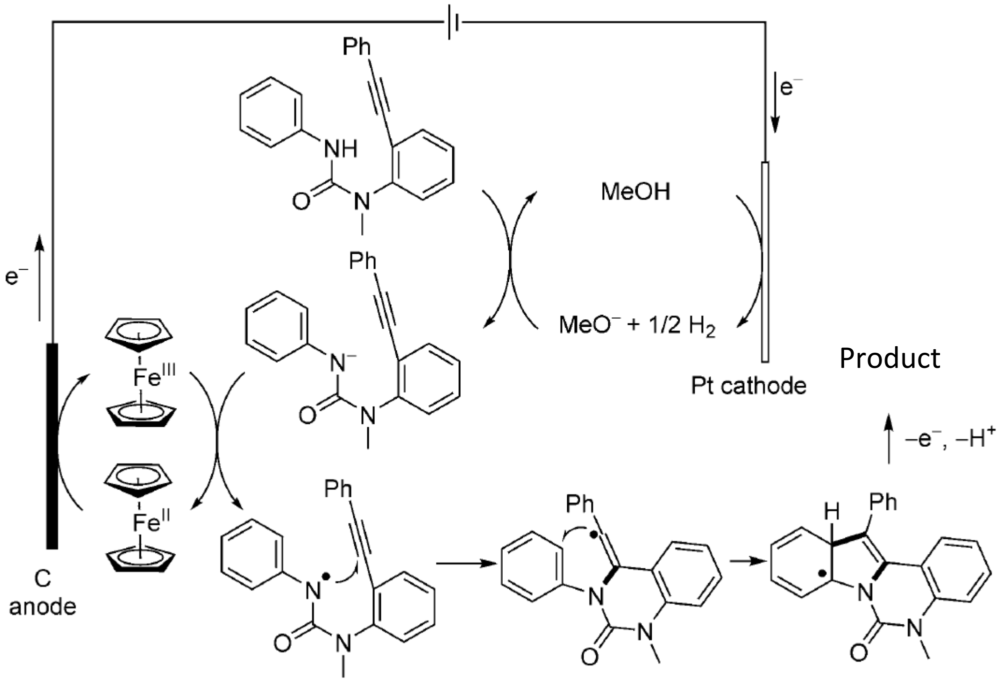
L.Zhu, P. Xiong, Z.-Y. Mao, Y.-H. Wang, X. Yan, X. Lu, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2226.

Anode oxidation —— Recent example

Electrochemical C-H/N-H functionalization for the synthesis of highly functionalized (aza)indoles

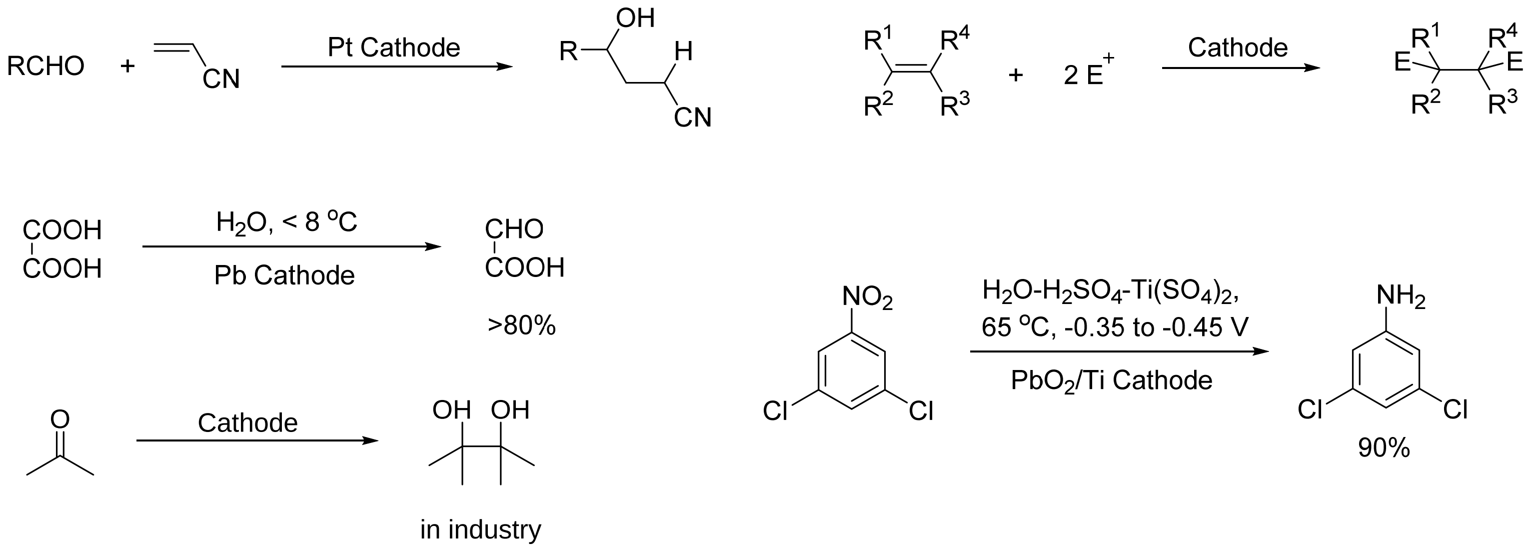


44 examples, 45-94%

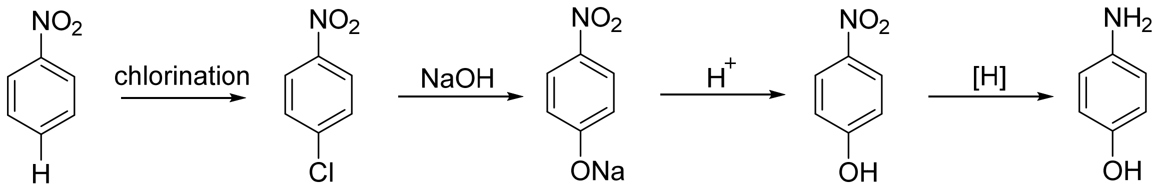


Z.-W. Hou, Z.-Y. Mao, H.-B. Zhao, Y. Y. Melcamu, X. Lu, J. Song, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9168.

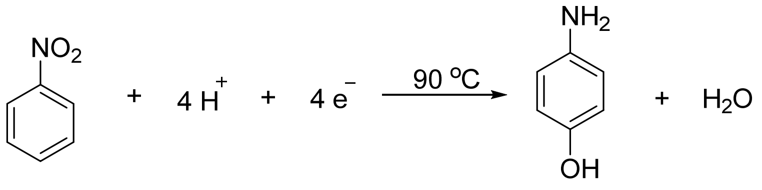
Cathode reduction



Traditional chemical method

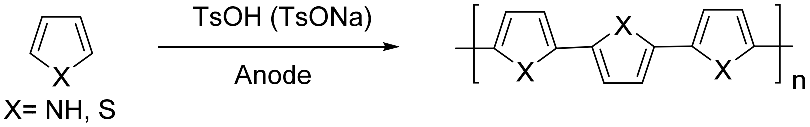


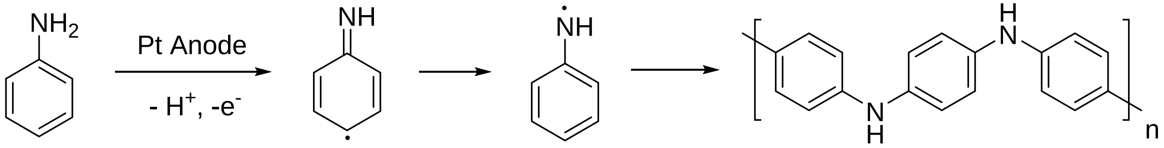
Electrochemical method

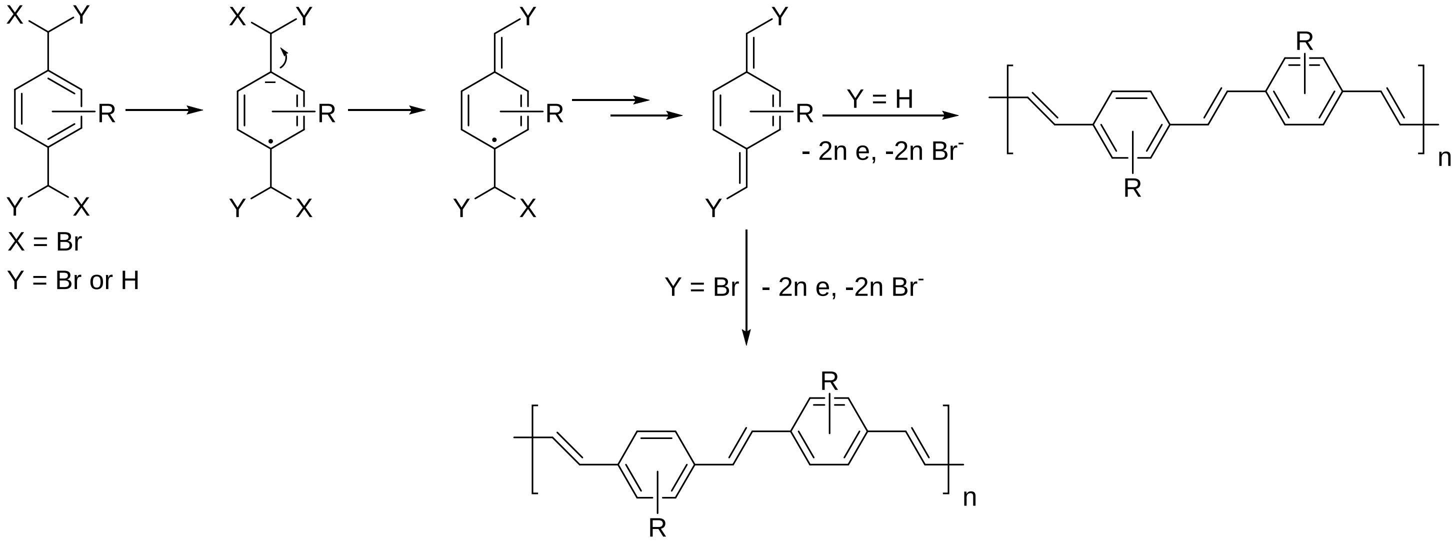


70 %, 7350 kWh/t

Polymerization







Paired organic electrosynthesis

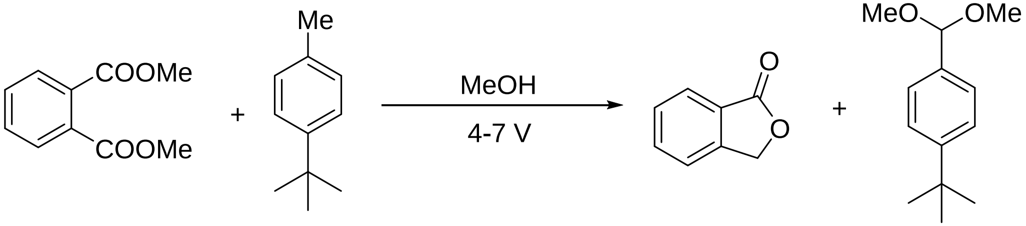
Three modes

$S^1 \xrightarrow{-n\,e} P^1,\ \ S^2 \xrightarrow{+n\,e} P^2$

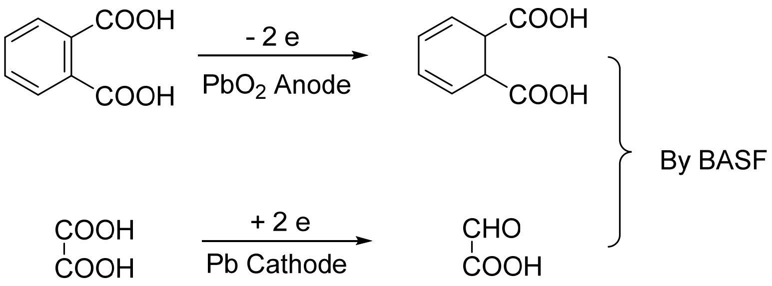
$P^1 \xleftarrow{-n\,e} S \xrightarrow{+n\,e} P^2$

$S \xrightarrow{\pm n\,e} P^1 \xrightarrow{\mp n\,e} P^2$

$S^1 \xrightarrow{-n\,e} P^1,\ \ S^2 \xrightarrow{+n\,e} P^2$



The first commercial example of paired organic electrosynthesis
(useful products are produced both on the anode and on the cathode)



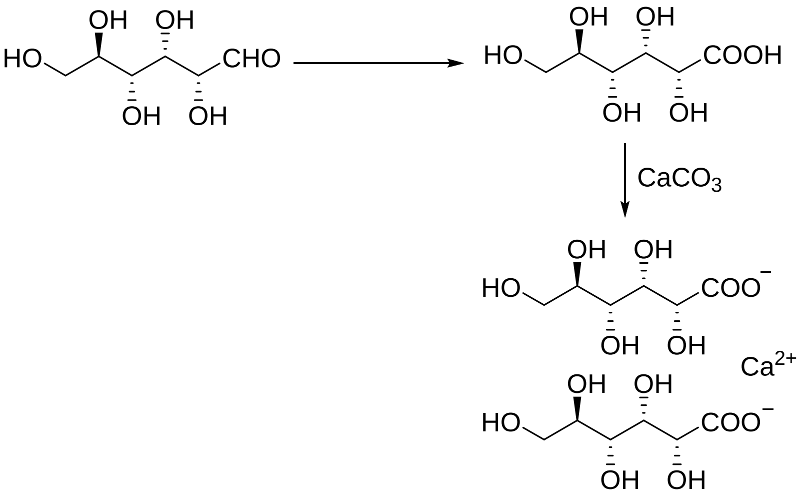
Paired organic electrosynthesis

$$P^1 \xleftarrow{-n\ e} S \xrightarrow{+n\ e} P^2$$

Anode reaction

$$2\ Br^- \longrightarrow Br_2 + 2\ e^-$$

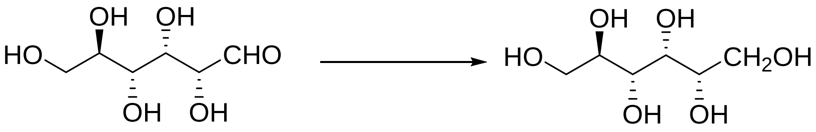
$$Br_2 + H_2O \longrightarrow HOBr + HBr$$



94%

Calcium Gluconate
(葡萄糖酸钙)

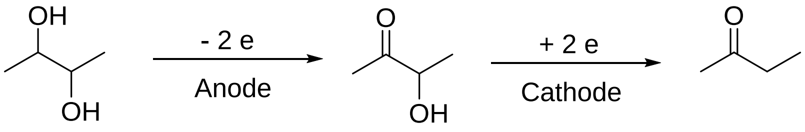
Cathode reaction



74%

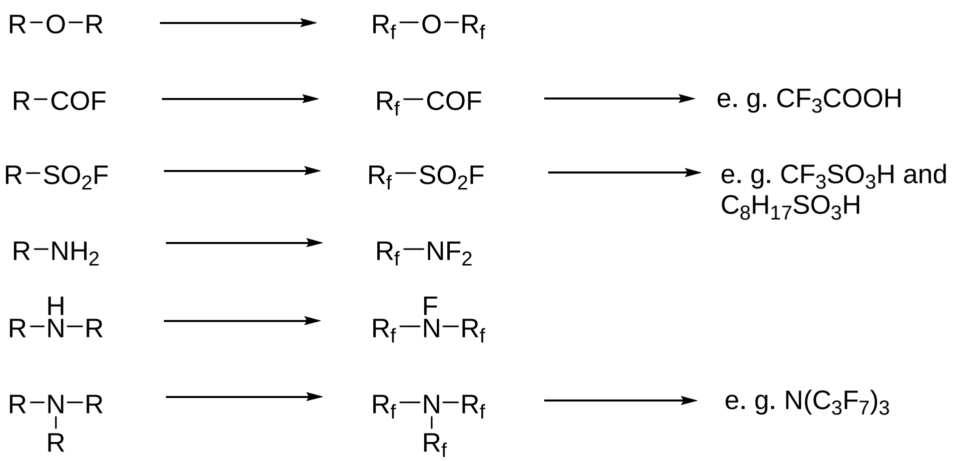
Sorbitol (山梨糖醇)

$$S \xrightarrow{\pm n\ e} P^1 \xrightarrow{\mp n\ e} P^2$$



Organic Electrosynthesis in Fluorine Chemistry

Perfluorination



$$R{-}O{-}R \longrightarrow R_f{-}O{-}R_f$$

$$R{-}COF \longrightarrow R_f{-}COF \longrightarrow \text{e. g. } CF_3COOH$$

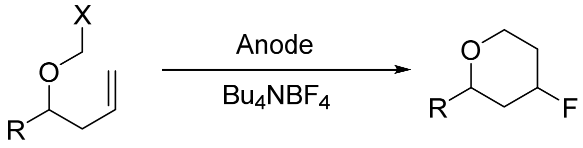
$$R{-}SO_2F \longrightarrow R_f{-}SO_2F \longrightarrow \text{e. g. } CF_3SO_3H \text{ and } C_8H_{17}SO_3H$$

$$R{-}NH_2 \longrightarrow R_f{-}NF_2$$

$$R{-}\overset{H}{N}{-}R \longrightarrow R_f{-}\overset{F}{N}{-}R_f$$

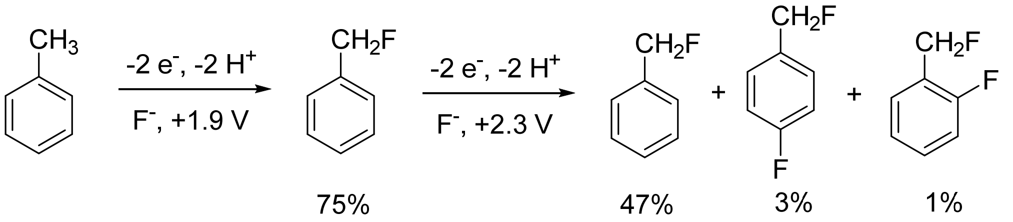
$$R{-}\underset{R}{N}{-}R \longrightarrow R_f{-}\underset{R_f}{N}{-}R_f \longrightarrow \text{e. g. } N(C_3F_7)_3$$

Selective fluorination



$R = C_7H_{15}$
$X = SMe, SnBu_3, SiMe_3$

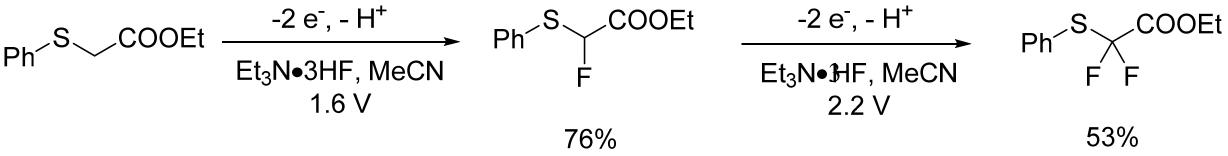
50-98%



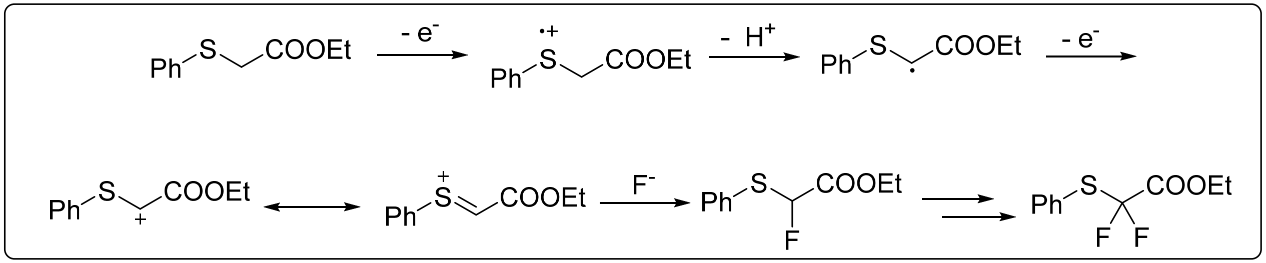
P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd Ed., Wiley-VCH, Weinheim, **2013.**

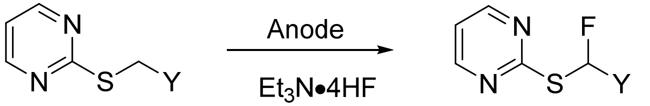
Organic Electrosynthesis in Fluorine Chemistry

Selective fluorination

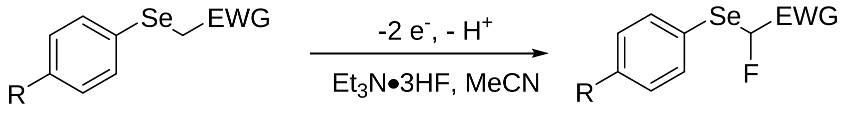


Proposed meachnism





Y = COOEt, 98%
Y = COOMe, 81%
Y = H, 63%

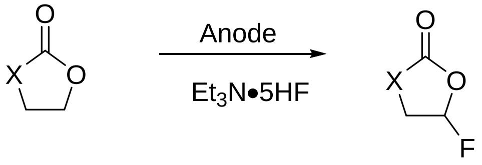


R = H, Cl, OMe
EWG = CN, COOEt

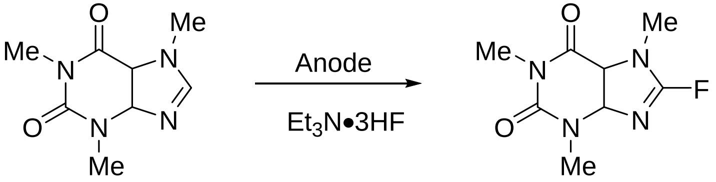
51-81%

Organic Electrosynthesis in Fluorine Chemistry

Selective fluorination

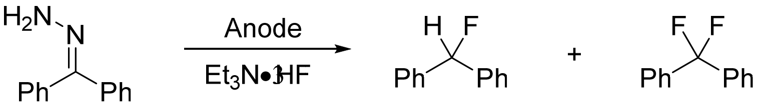


X = CH_2 75%
X = O 87%



Caffeine

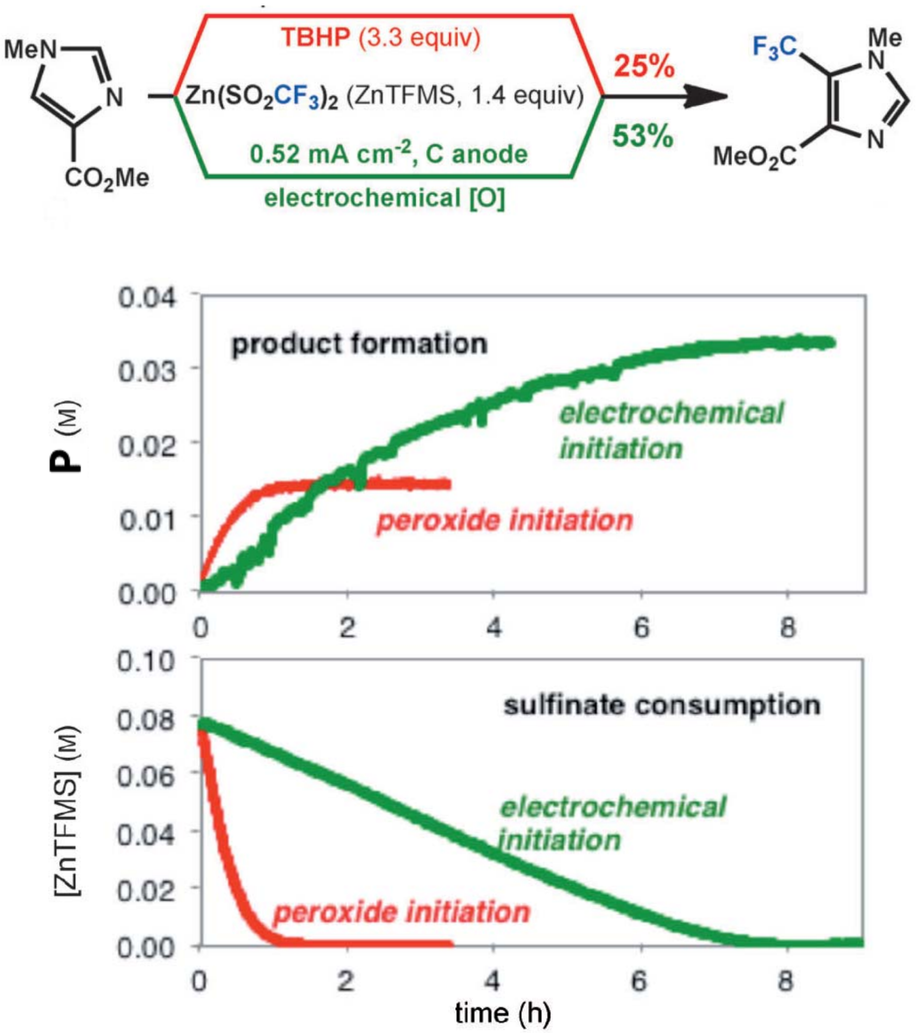
42%



95% 3%

Organic Electrosynthesis in Fluorine Chemistry

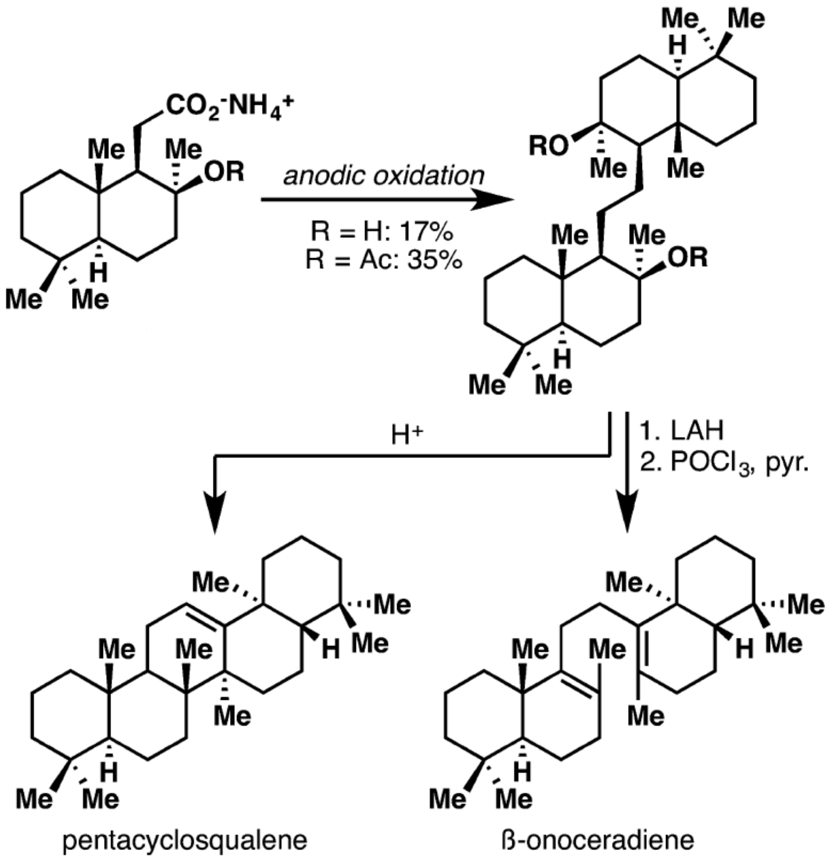
Radical C-H functionalization of heteroarenes under electrochemical control —— recent example



A. G. O’Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2014**, *53*, 11868.

Organic Electrosynthesis in Natural Product Synthesis

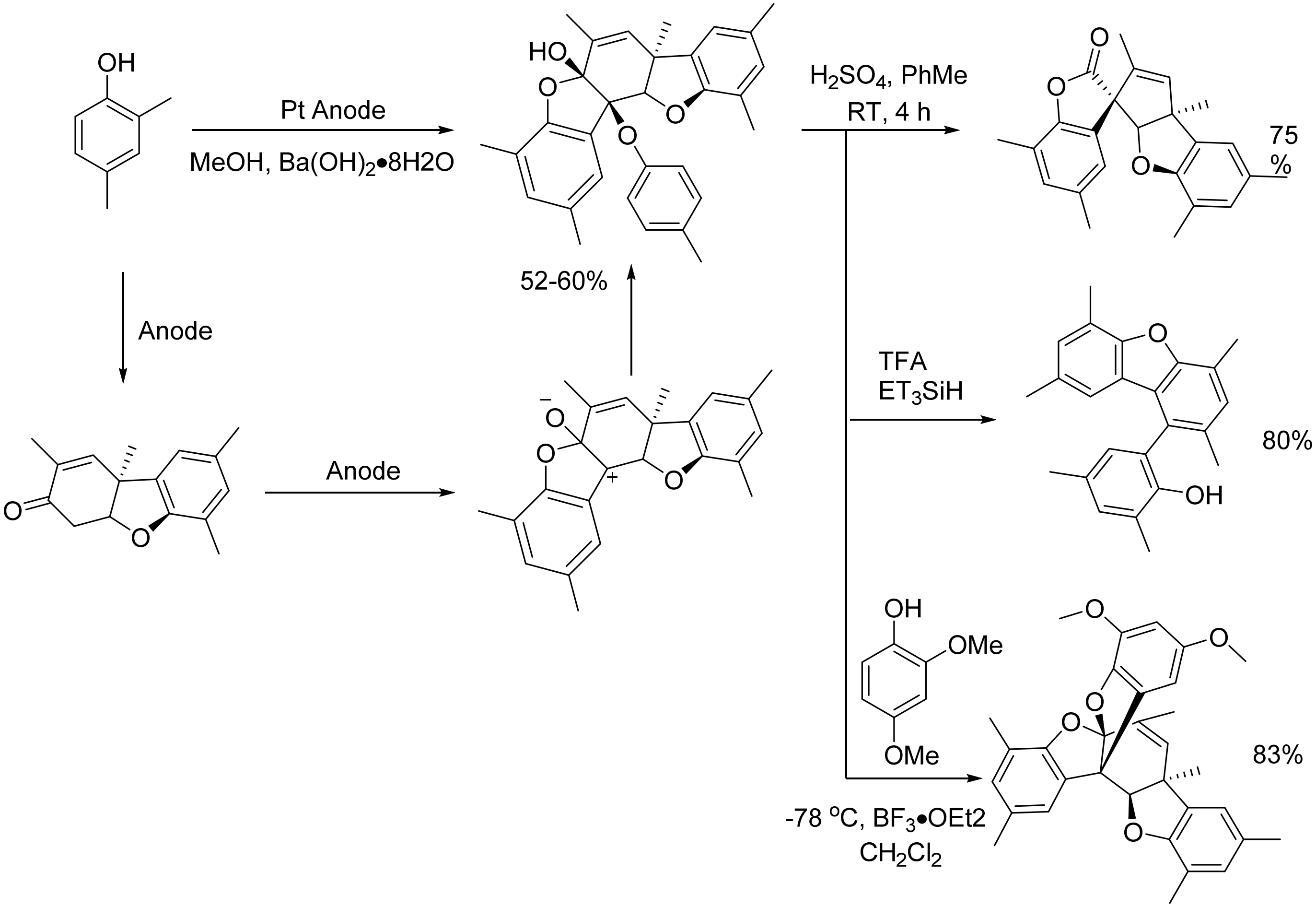
The synthesis of pentacyclosqualene (8,8′-cycloönocerene) and the α- and β-onoceradienes



E. J. Corey, R. R. Sauers, *J. Am. Soc. Chem.* **1959**, *81*, 1739.

Organic Electrosynthesis in Natural Product Synthesis

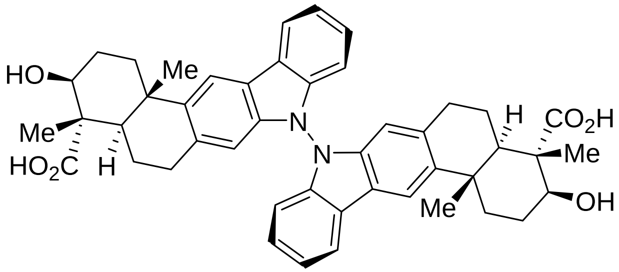
Anode oxidation of 2,4-dimethylphenol —— recent example



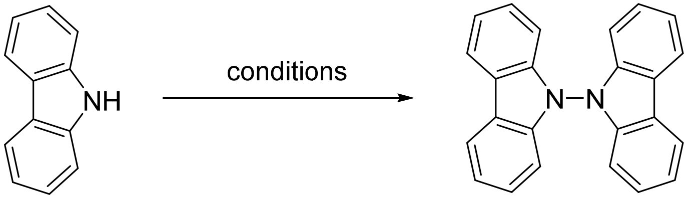
I. M. Malkowsky, C. E. Rommel, R. Fröhlich, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Chem.* **2006**, *12*, 7482.
I. M. Malkowsky, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Org. Chem.* **2006**, 4569.

Organic Electrosynthesis in Natural Product Synthesis

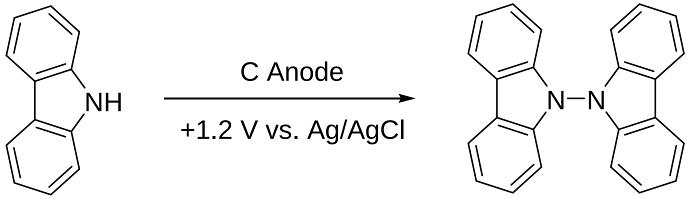
Total synthesis of Dixiamycin B by electrochemical oxidation



Dixiamycin B



entry	conditions	result
1	$KMnO_4$, acetone, heat	< 20% yield
2	LDA, then [Cu]	no reaction
3	$PhI(OCOCF_3)_2$, DCM	no reaction
4	KO*t*Bu/*t*BuCl	trace product



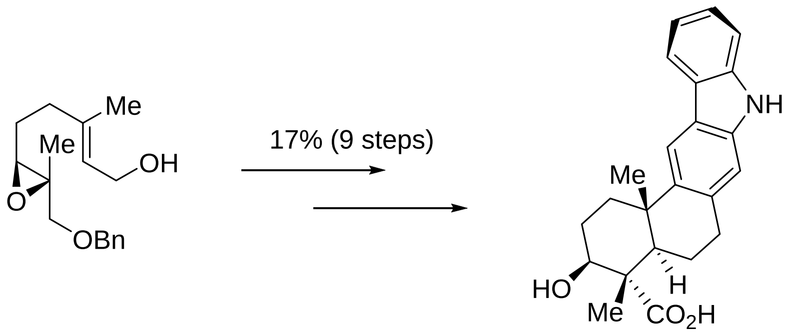
1 **2**

entry	solvent	time	result (**1**:**2** ratio)
1	DMF	3 h	15:1
2	DMF	3 h	10:1
3	DMF:MeOH (5:1)	3 h	10:1
4	DMF:MeOH (20:1)	3 h	5:1
5	DMF:MeOH (5:1)	18 h	0:1 (60%)

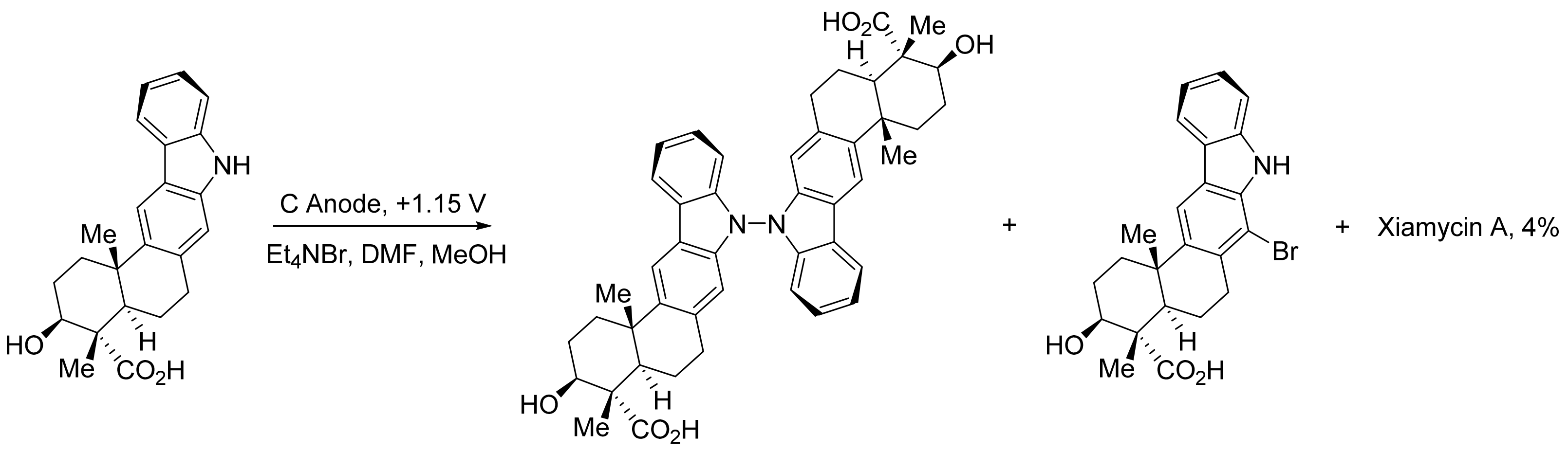
B. R. Rosen, E. W. Werner, A. G. O'Brien, P. S. Baran, *J. Am. Soc. Chem.* **2014**, *136*, 5571.

Organic Electrosynthesis in Natural Product Synthesis

Total synthesis of Dixiamycin B by electrochemical oxidation



Xiamycin A
> 1 gram prepared



Xiamycin A
> 1 gram prepared

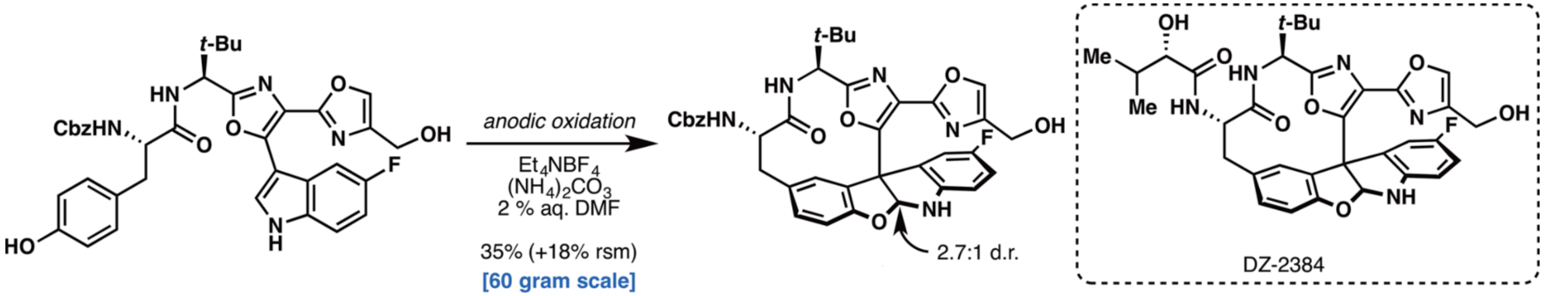
Dixiamycin B, 28%
Theoretical yield, 50%

Bromoia
mycin,
17%

B. R. Rosen, E. W. Werner, A. G. O’Brien, P. S. Baran, *J. Am. Soc. Chem.* **2014**, *136*, 5571.

Organic Electrosynthesis in Natural Product Synthesis

Electrolytic macrocyclizations: scalable synthesis of a diazonamide-based drug development candidate



H. Ding, P. L. DeRoy, C. Perreault, A. Larivée, A. Siddiqui, C. G. Caldwell, S. Harran, P. G. Harran, *Angew. Chem. Int. Ed.* **2015**, *54*, 4818.

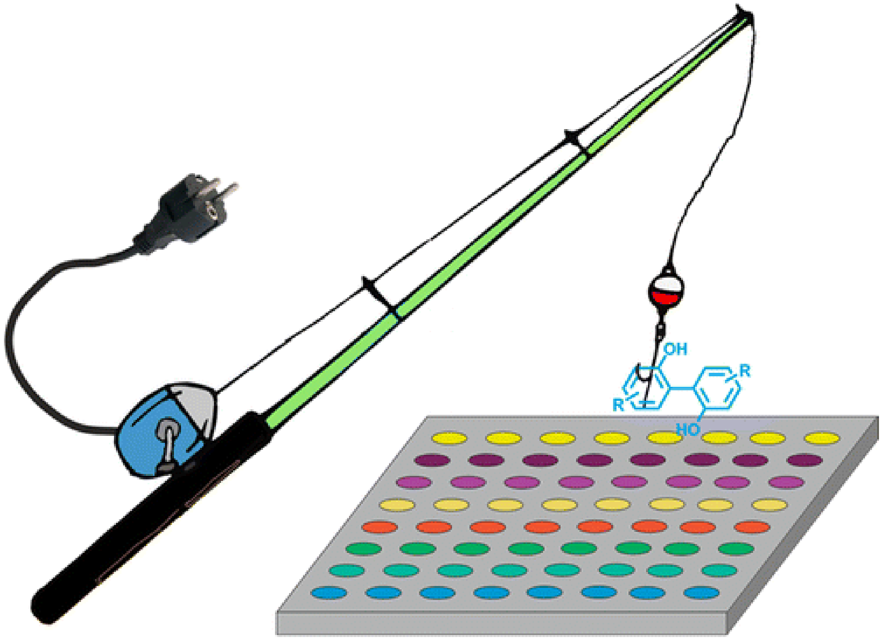
Summary

Advantages of organic electrochemical synthesis

1. **Avoiding the use of toxic or dangerous oxidants and reducants**, largely **minimising pollution problems** and **increasing sustainability**.
2. Electricity has a minor value compared to other reagents. Most reactions are conducted at RT and in the air (1 atm) and **lower energy cost** is needed. (**high innately scalability**)
3. **Redox potential (or voltage)** can be **tunable**, and this provides **more mild conditions** and **high functional group tolerance** which are more desirable for a complicated molecule. (**higher selectivity**)
4. Reaction rate can be controlled easily (by changing the current or voltage) and reaction can start and stop at any time you want (switch on/off).

Challenges remained

1. Compared to the highly developed organic catalytic synthesis, **basic research** in organic electrochemical synthesis is still **underdeveloped**. (Historical reasons: (1) Organic catalytic synthesis has dominated the center of organic synthesis. (2) Thermodynamics theory (such as, Nernst equation) was widely accepted long ago and research of the electrochemical theory was far behind.)
2. **More parameter** should be considered.(current, voltage, electrode and so on)
3. Electrochemists are traditionally educated in analytical chemistry and synthetic organochemists are traditionally educated in organic chemistry.



Thanks for your attention!