

Electrochemical Synthesis Utilizing Alternating Current

Literature Seminar

2023/12/16 Koichi Hagiwara

Contents

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1. Introduction of electrochemistry and alternating current

2. Electrochemical reactions utilizing rapid alternating polarity (rAP) by Prof. Baran group

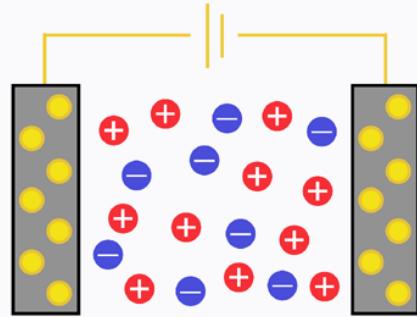
2-1. Reductive reaction

2-2. Oxidative reaction

Basics of Electrochemical Reaction

Electrochemical Cell

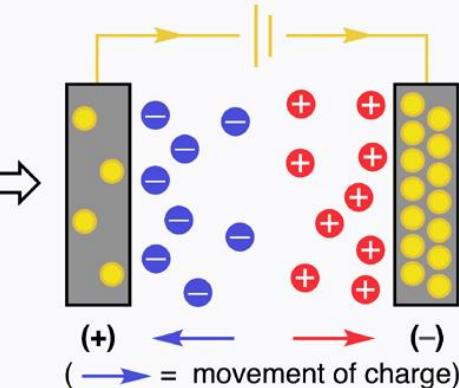
A power source (||) connects two electrodes sitting in a solution of electrolyte and substrate.



(● = electron, + ● = positive and negative charge carriers)

Current

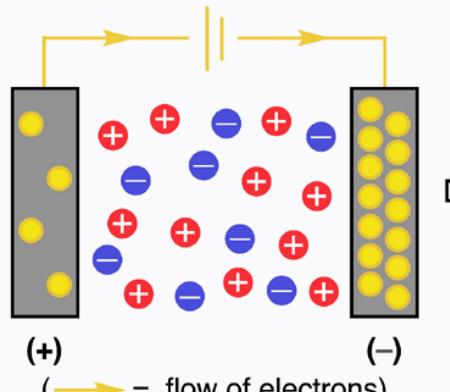
The electrode potential also causes movement of reagents and charged species in solution. This process, in combination with electron flow, is called the 'current'.



(→ = movement of charge)

Potential/Voltage

Electrons are pulled from the anode (+) and pushed into the cathode (-), generating a potential difference (or 'voltage') that forces electrons to flow in and out of the electrodes.



Substrate Oxidation/Reduction

Electrons do not pass through solution. Instead, reagents are oxidized and reduced on the surface of the electrodes to complete the circuit.

mode of electrolysis

1. constant current

potential drifts to maintain the current

a. easier set up

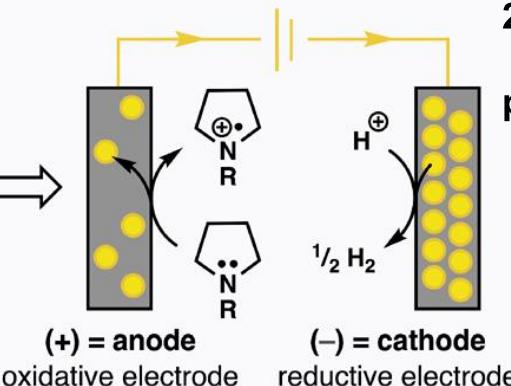
b. selectivity problem

(over-oxidation, reduction)

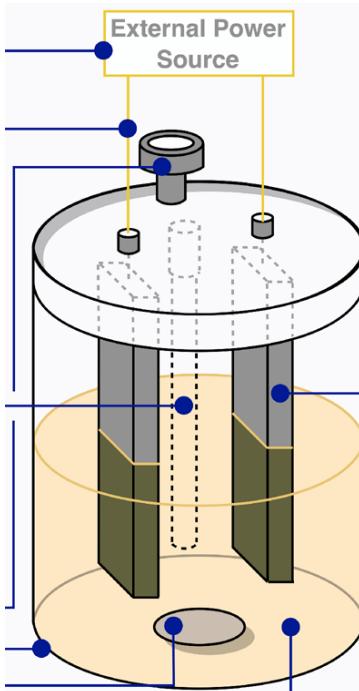
2. constant potential

current adjusts to maintain the cell potential

a. higher selectivity

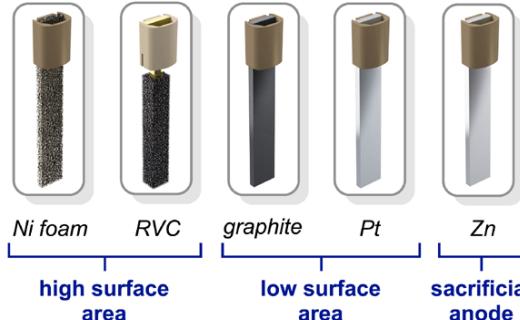


Electrodes and Electrolyte



Electrodes

- Electron transfer occurs on the electrode surface so the choice of material can affect reactivity/selectivity (a small selection is shown below).

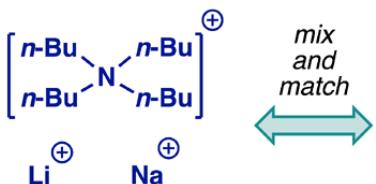


- The reaction of interest occurs on the 'working electrode', which is paired with a 'counter electrode'.
- Carbon-based materials are commonly used due to the low cost, stability, and wide potential range.
- Sacrificial anodes such as Zn, Ni, and Al are used when reduction is desired (see Figure 3).

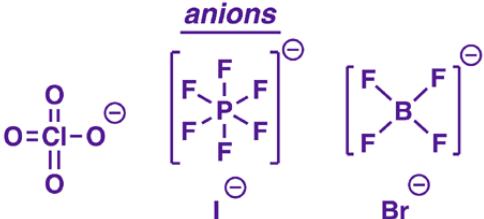
Electrolyte

- Electrolyte improves conductivity by providing a source of positive and negative ions which carry charge through the circuit and reduce resistance.
- Li⁺ and Bu₄N⁺ salts are commonly used because they are relatively inert and soluble in most organic solvents.
- The electrolyte coats the electrode surface (forming a 'double layer'), affecting diffusion of the substrate which can influence reactivity.

cations



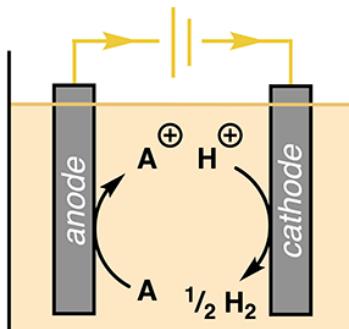
anions



Ideas for Successful Electrochemical Reaction

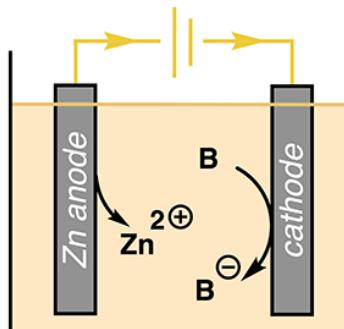
A. Oxidation is Desired

Anode = Substrate oxidation
Cathode = Proton reduction

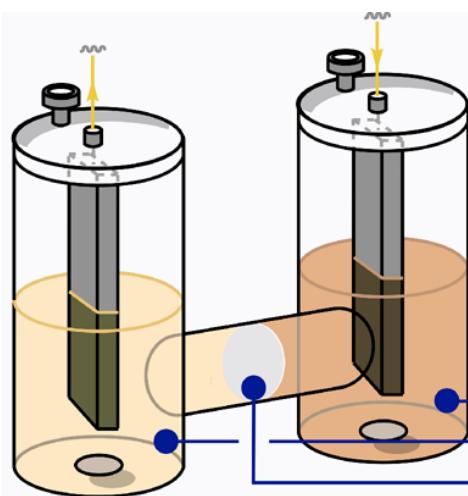


B. Reduction is Desired

Anode = Sacrificial electrode
Cathode = Substrate reduction



C. Both are Desired = 'Paired electrolysis'

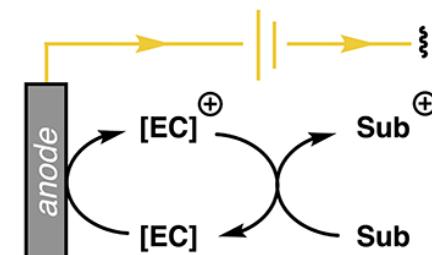


- Divided cells are composed of anodic and cathodic chambers separated by a frit or membrane.
 - A divided cell is used when a substrate, product, or reagent must be protected from the counter electrode.
 - The presence of the frit or membrane increases resistance and provides an added degree of difficulty in setup.
- cathodic chamber
anodic chamber
frit or permeable membrane

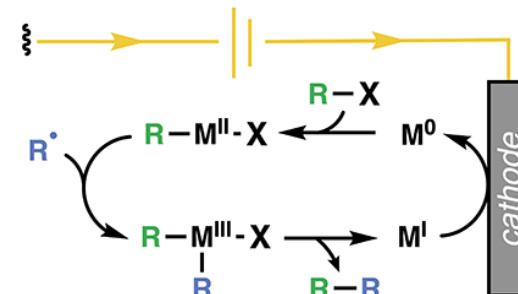
Electrocatalysts (EC)

'Electrocatalyst' encompasses the many types of catalytic species in electroorganic synthesis.

One type, called 'redox mediators', shuttles electrons between electrode and substrate.

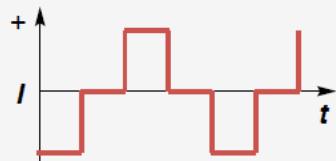


Other electrocatalysts include transition metal species that undergo electrolysis during the classic catalytic cycles.



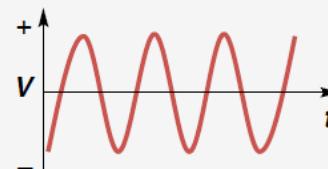
Classification of Alternating Current

(1) Switching polarity: Hilt, 2020

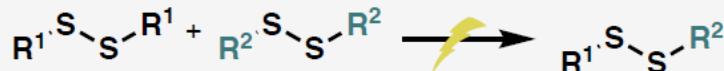


Current control, step current

(2) Sinusoidal alternating current (AC): Semenov, 2020

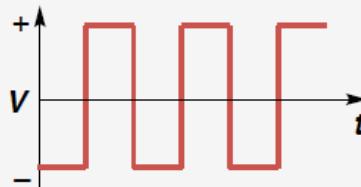


Potential control, sinusoidal wave



- Periodical polarity switch gave cleaner reaction over DC

(3) Bipolar square wave: Nguyen and Luo, 2020

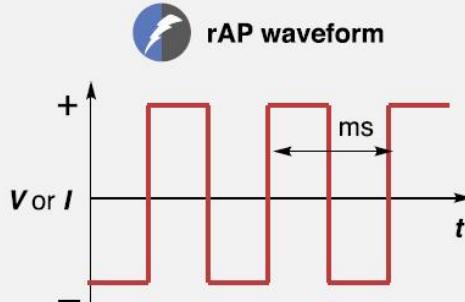


Potential control, square wave

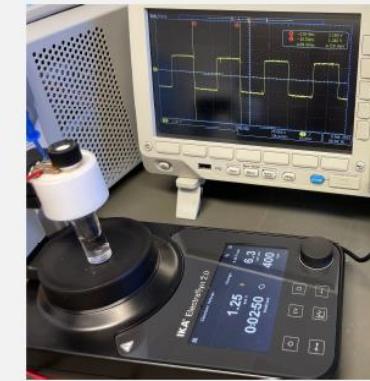


- AC gave improved yield over DC

B. Rapid alternating polarity (rAP)

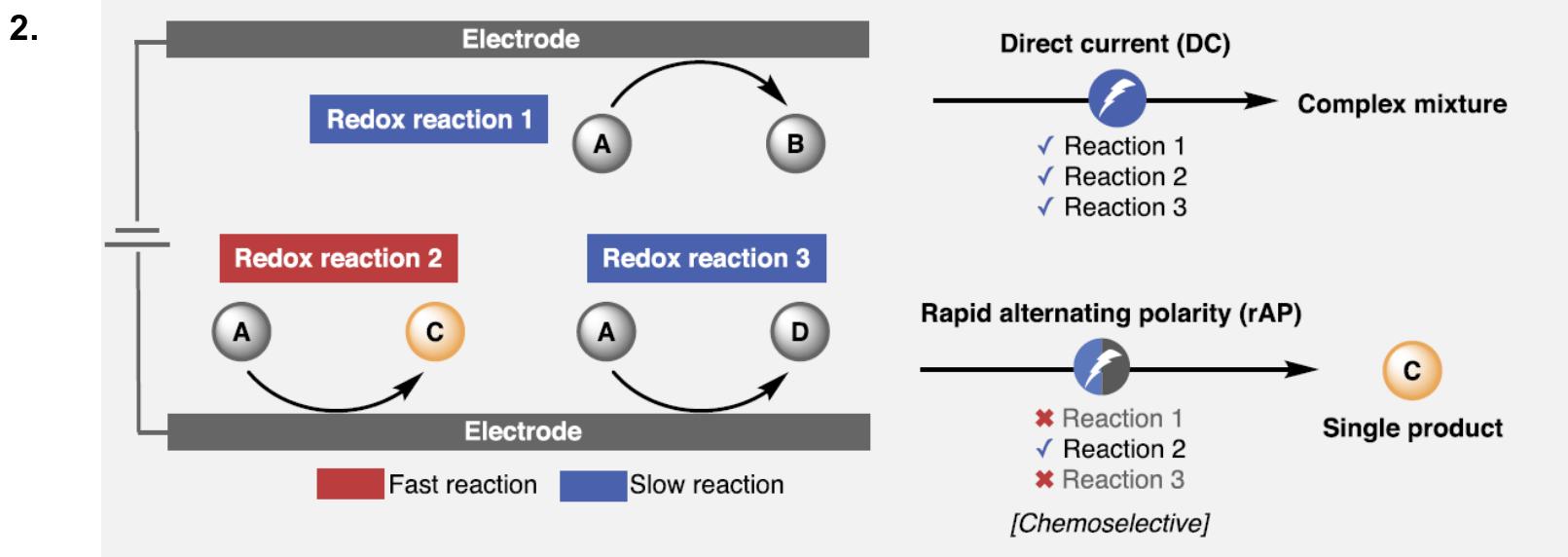
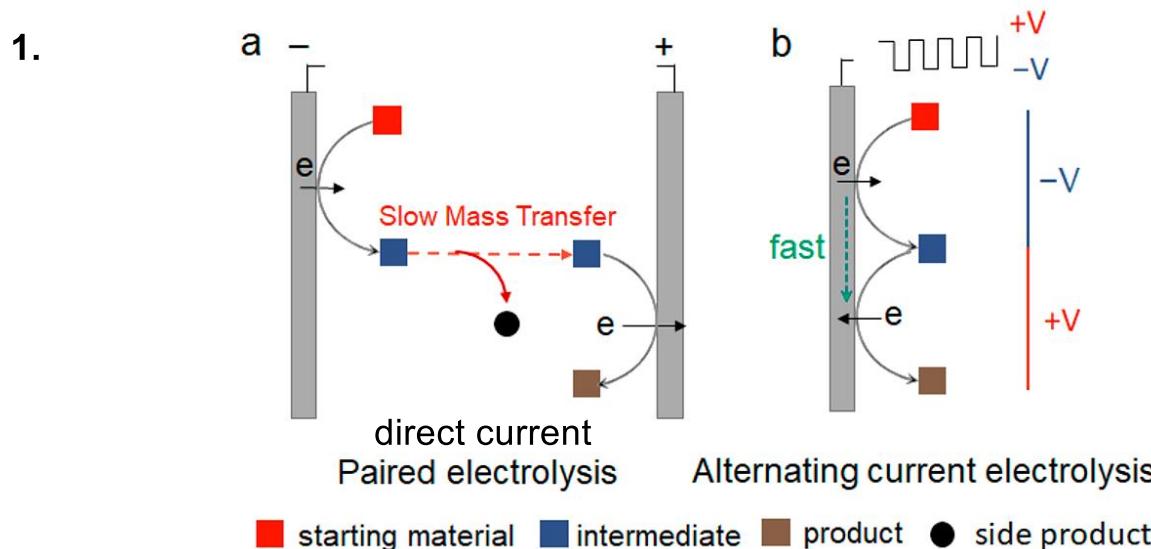


- Millisecond square waveform of AC
- Current- or potential-controlled wave



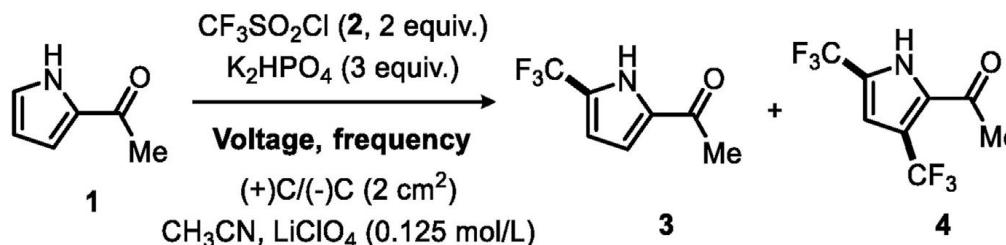
Implemented in a commercial device (oscilloscope depicts rAP output from an ElectraSyn 2.0)

Working Hypothesis

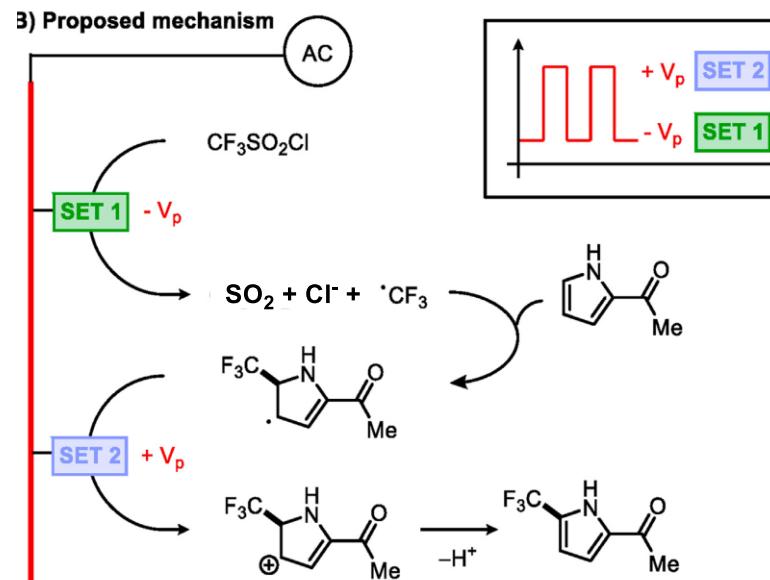


- 1) Rodrigo, S.; Um, C.; Mixdorf, J. C.; Gunasekera, D.; Nguyen, H. M.; Luo, L. *Org. Lett.* **2020**, *20*, 6719.
- 2) Kawamata, Y.; Hayashi, K.; Carlson, E.; Shaji, S.; Waldmann, D.; Simmons, B. J.; Edwards, J. T.; Zapf, C. W.; Saito, M.; Baran, P. S. *J. Am. Chem. Soc.* **2021**, *143*, 16580.

Paired Electrolysis by AC



Voltage (Vp)	Frequency (f)	Conversion	Yield (3:4)
4.4	100 Hz	100%	84% (19:1)
3.3	100 Hz	6%	-
4.4	10 Hz	21%	- (0.75:1)
4.4	1000 Hz	<1%	-



- 1) Rodrigo, S.; Um, C.; Mixdorf, J. C.; Gunasekera, D.; Nguyen, H. M.; Luo, L. *Org. Lett.* **2020**, *20*, 6719.
 2) Zhong, J.; Ding, C.; Kim, H.; McCallum, T.; Ye, K. *Green Synth. Catal.* **2022**, *3*, 4.

Contents

1. Introduction of electrochemistry and alternating current

2. Electrochemical reactions utilizing rapid alternating polarity (rAP) by Prof. Baran group

2-1. Reductive reaction

2-2. Oxidative reaction

Author Information



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1995–1997 B.S. with Honors in Chemistry, New York University
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1997–2001 Ph.D. in Chemistry, The Scripps Research Institute
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2001–2003 Postdoctoral associate, Harvard University
Advisor: Prof. E. J. Corey

2003–2006 Assistant professor of chemistry, The Scripps Research Institute

2006–2008 Associate professor of chemistry, The Scripps Research Institute

2008–present Professor of chemistry, The Scripps Research Institute

<https://baranlab.org/>

Reaction Setup

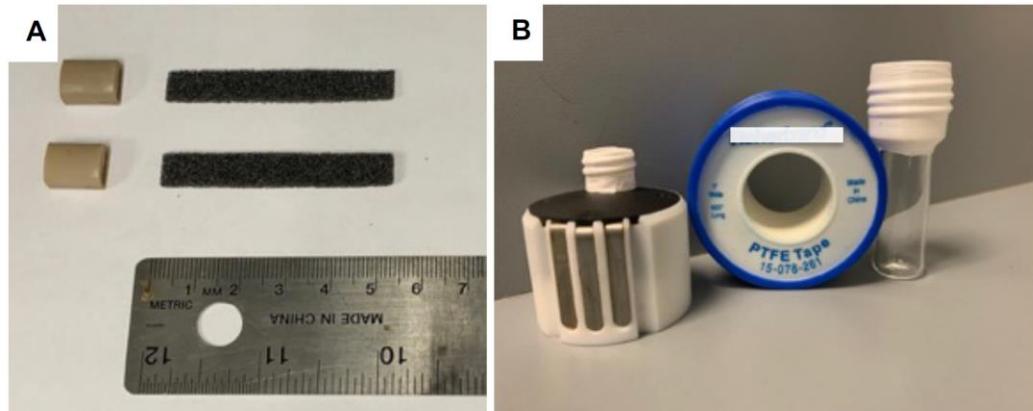
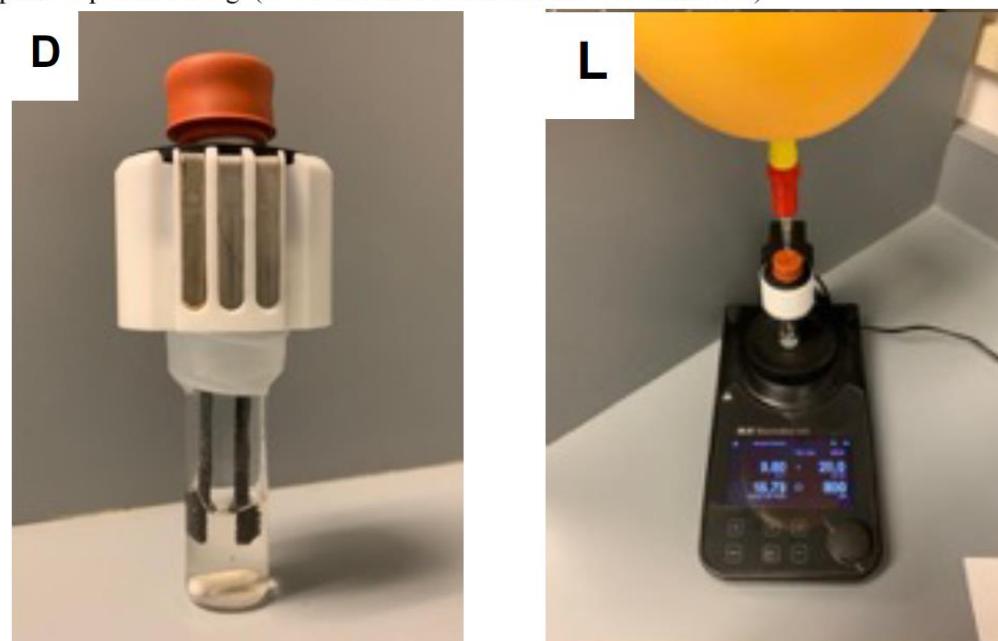


Figure S2. Equipment and setup for electrolysis: (A) RVC electrodes are cut into small blocks (approximate size: 1 mm x 5.5 cm x 0.75 cm). (B) IKA ElectraSyn cap and IKA ElectraSyn 5 mL vial are wrapped with PTFE tape to improve sealing. (Pro-Seal can be used without this treatment.)

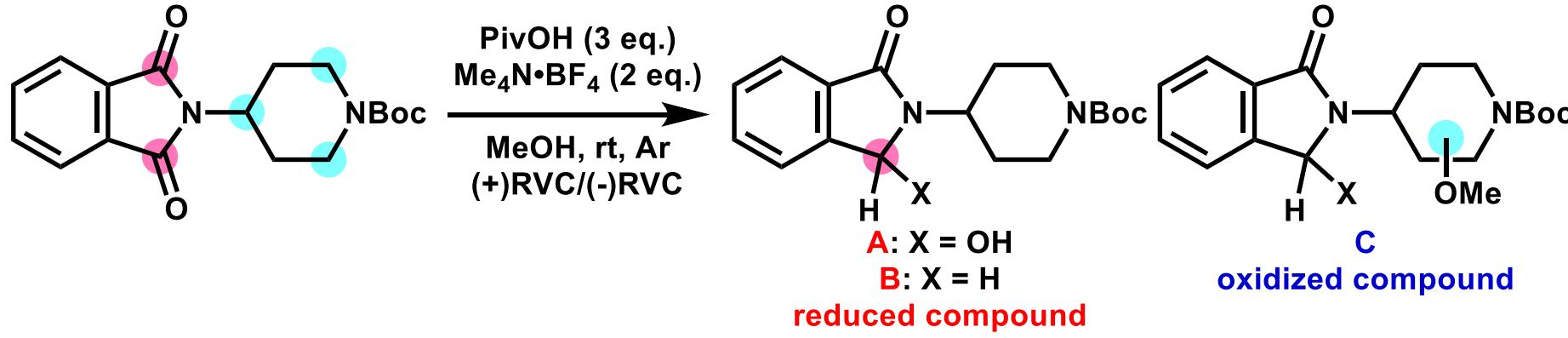
Permission granted by IKA.



- 1. set current (mA)**
- 2. set the amount of substrate (mmol)**
- 3. set the electron amount (F/mol)**
- 4. set frequency**

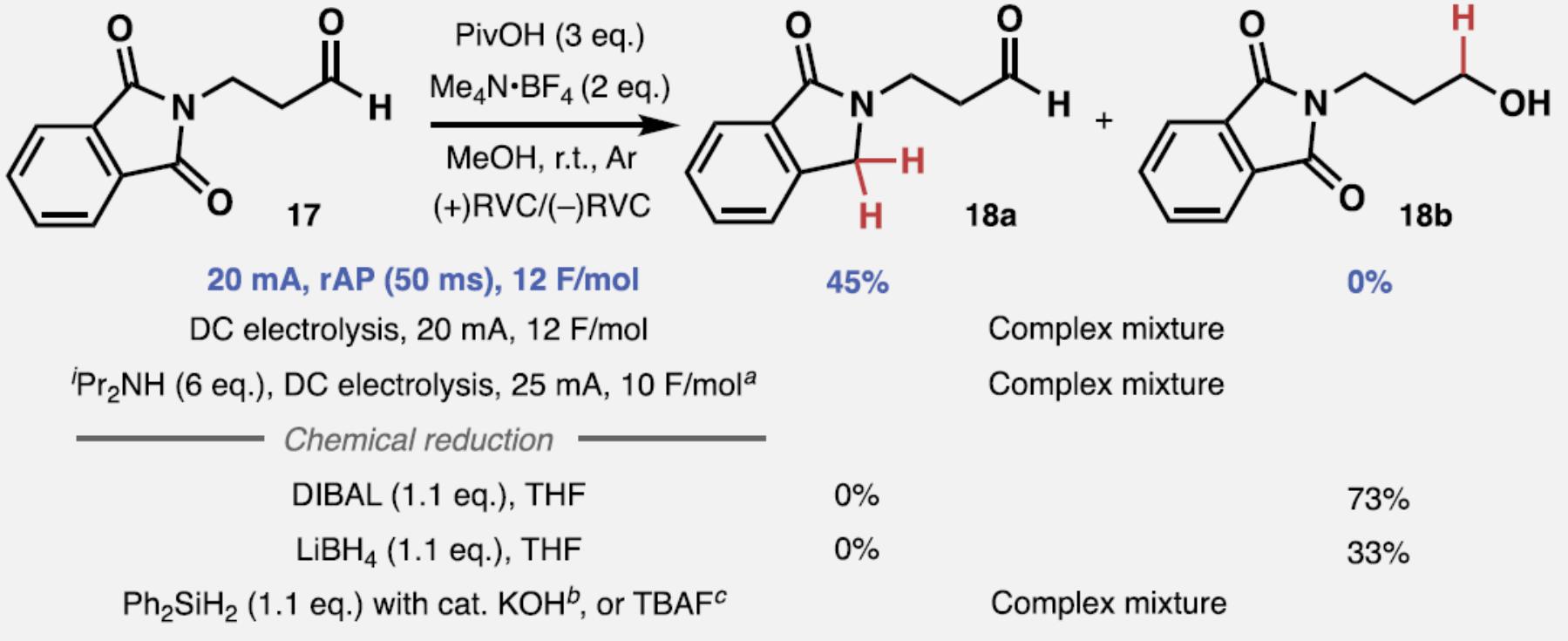
Chemosselective Reduction of Phthalimide

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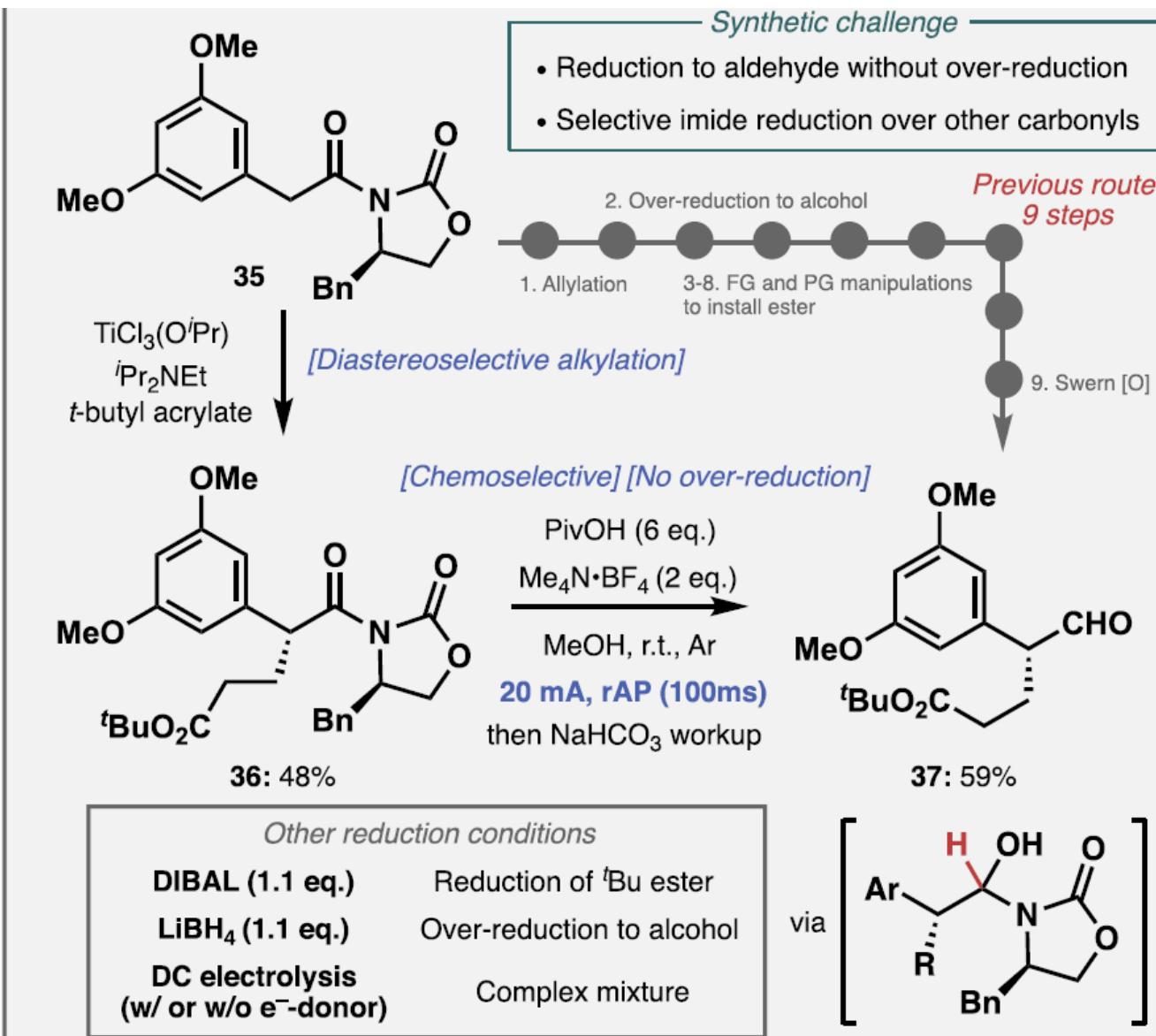


entry	electrolysis conditions	yield			
		A	B	C	SM
DC 1	20 mA, 20 F/mol	0%	0%	YES	0%
2	20 mA, 200 ms (2.5 Hz), 20 F/mol	0%	48%	YES	0%
3	20 mA, <u>100 ms (5 Hz)</u> , 20 F/mol	0%	60%	NO	0%
rAP 4	20 mA, <u>25 ms (20 Hz)</u> , 20 F/mol	82%	0%	NO	0%
5	<u>40 mA</u> , 25 ms (20 Hz), 20 F/mol	0%	69%	NO	0%
6	<u>10 mA</u> , 100 ms (5 Hz), 20 F/mol	69%	0%	NO	0%
DC 7	devided cell, 10 mA, 10 F/mol	7%	0%	NO	75%
8	Zn sacrificial anode, 5 mA, 20 F/mol	67%	0%	NO	11%

Reduction of Phthalimide in the Presence of Aldehyde

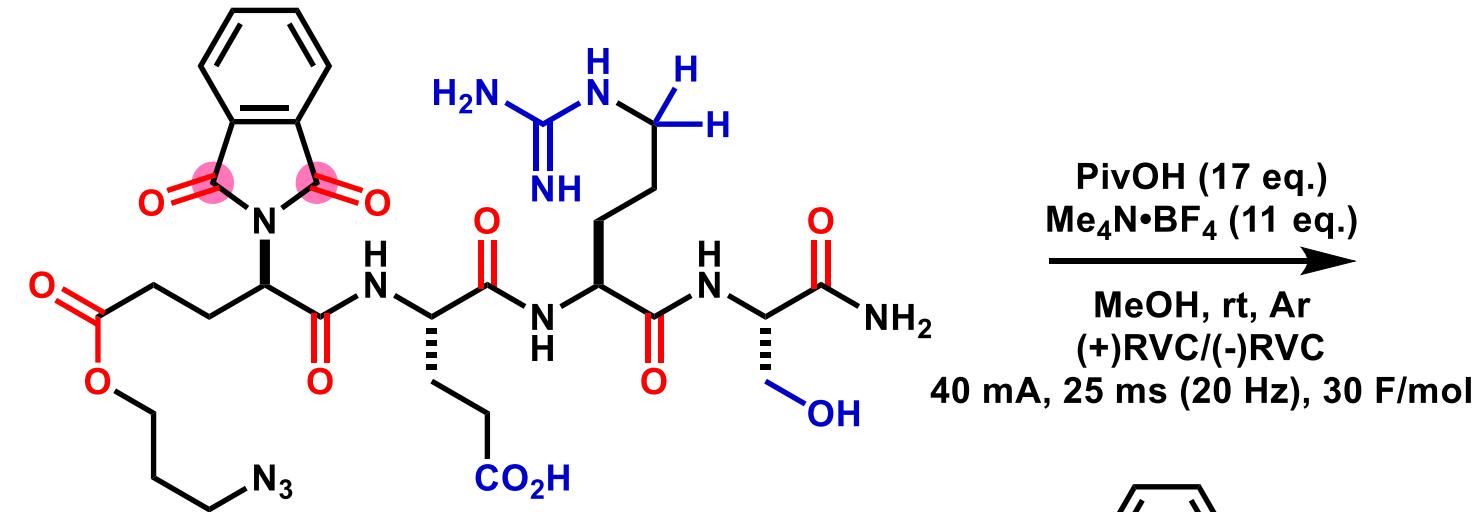


Reductive Cleavage of Chiral Auxiliary

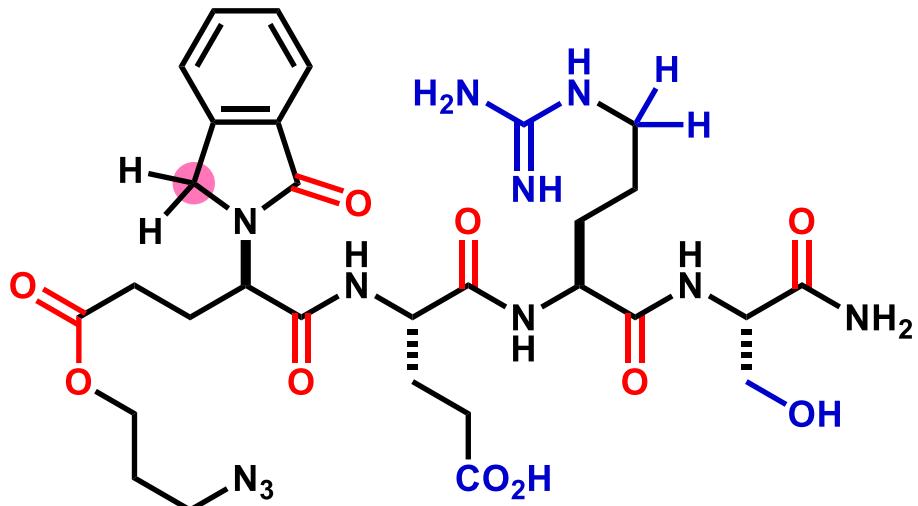


Chemoselectie Reduction of Phthalimide in Complex Tetrapeptide

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- possible reduction possible oxidation
- azide
 - ester
 - imide
 - amide
- alcohol
 - carboxylic acid
 - guanidine
 - α -C-H

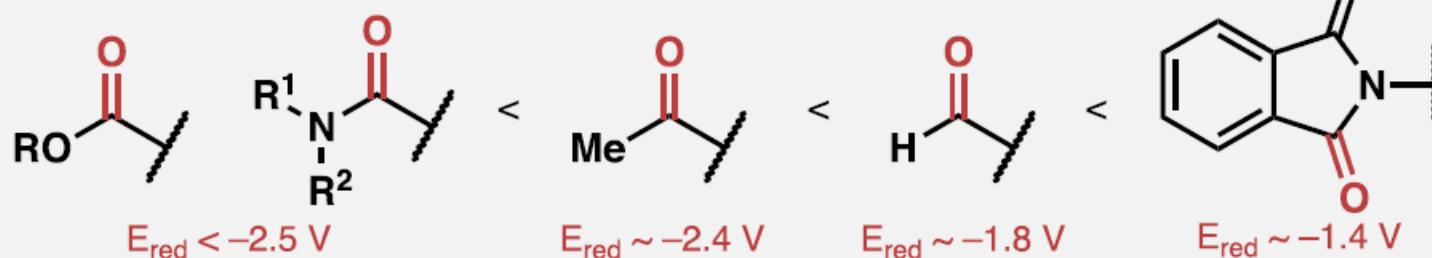


Rationale of Chemoselectivity

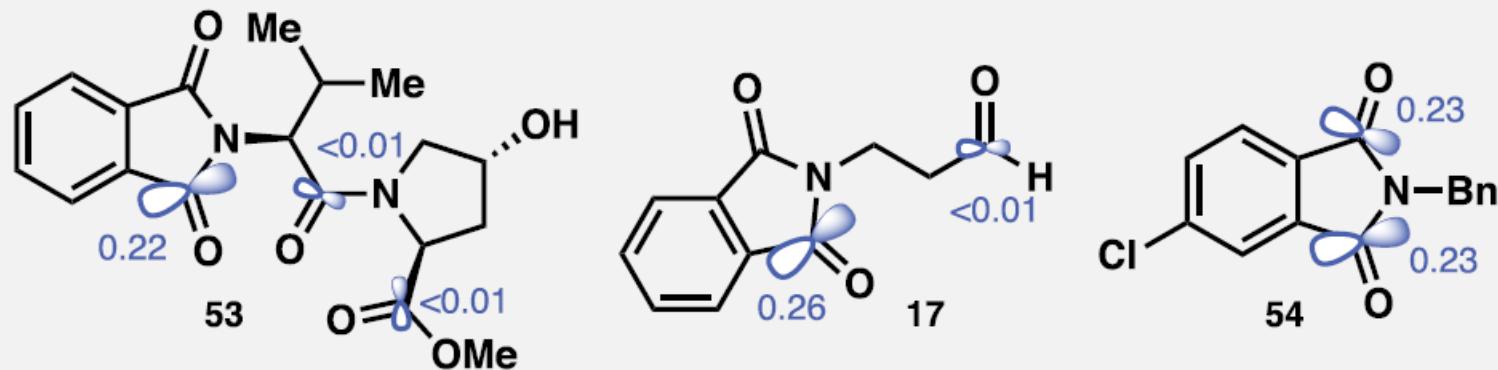
A. Rationale of chemoselectivity by E_{red} and LUMO coefficients

Reduction potential

thermodynamic parameter



LUMO coefficients ($2p_z$)



Exp. results

Reduction of phthalimide

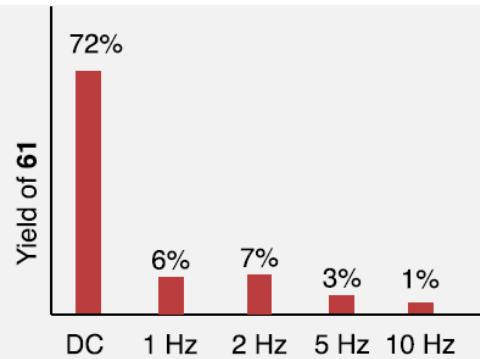
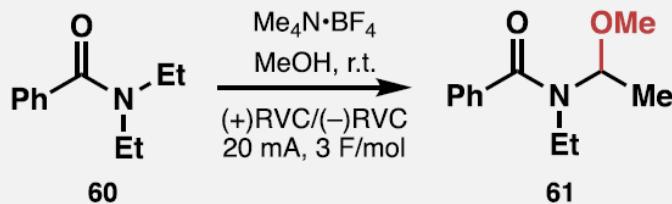
Reduction of phthalimide

Mixture of regioisomers

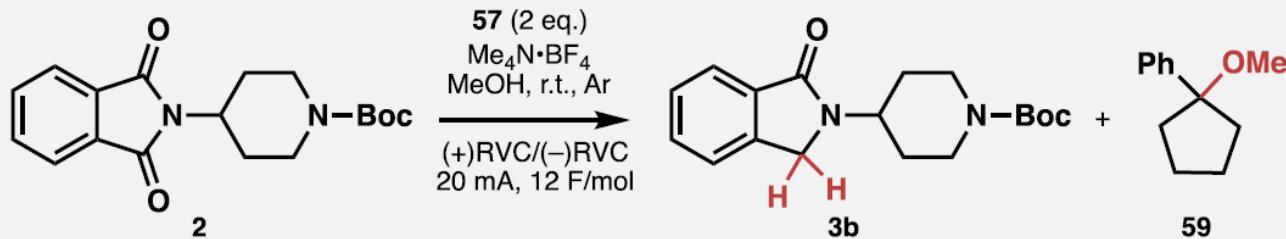
Effect of Frequency

17

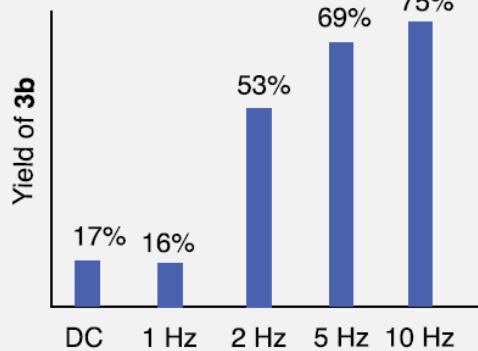
- Shono oxidation (side reaction)



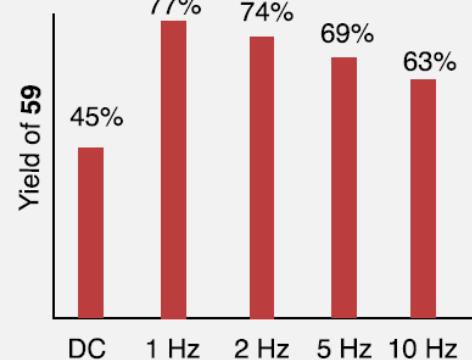
high overpotential



- *Imide reduction*



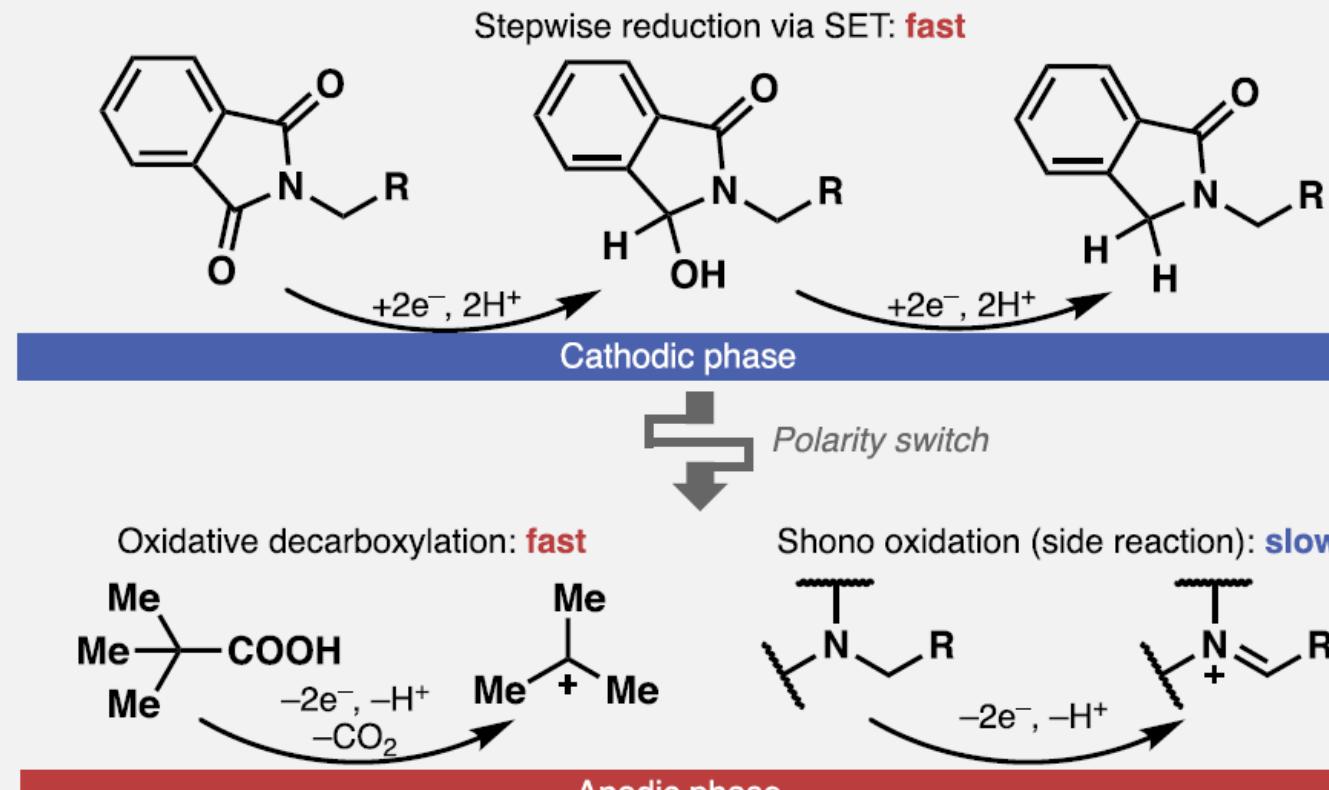
- *Decarboxylation*



Reaction Mechanism

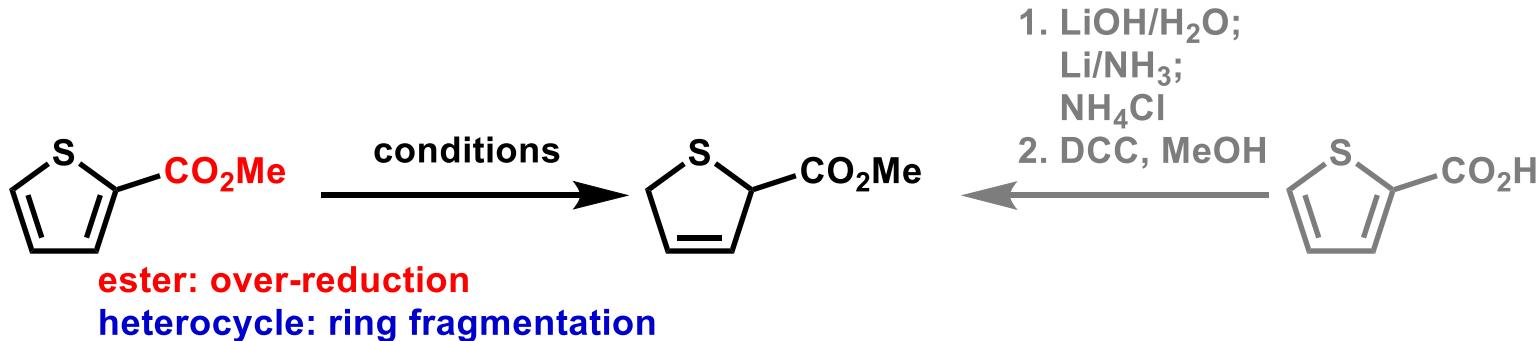
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E. Proposed mechanism



(Hetero)arene Reduction

- Optimization of Reaction Conditions -



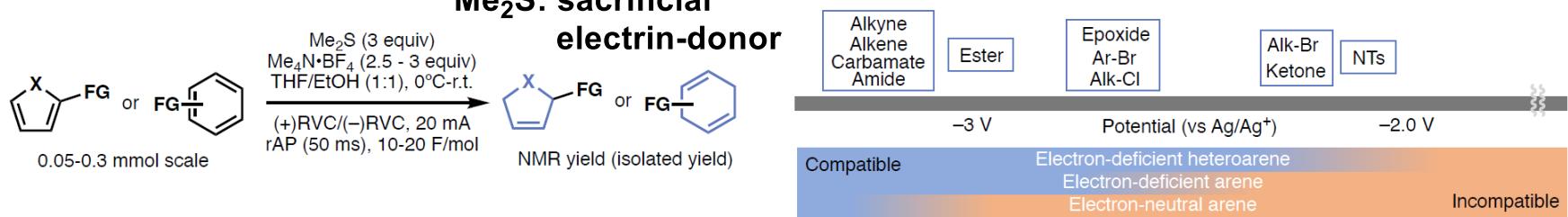
Entry	Chemical conditions	Yield
1	Li (5 eq), ^t BuOH, THF/NH ₃ , -78 °C; then NH ₄ Cl	0% (decomp.)
2	Li (3 eq), ethylenediamine (6 eq), ^t BuOH (2.5 eq), THF, 0 °C	0% (SM 8%)
3	LiDBB (4 eq), THF, (MeOCH ₂ CH ₂) ₂ NH (1.2 eq), -78 °C	39%
Electrochemical conditions		
4	LiBr (7.5 eq), DMU (3 eq), TPPA (10 eq), THF, rt, (+)-Mg/(-)-steel wire, 10 mA	0% (decomp.)
5	Me ₄ N ⁺ BF ₄ ⁻ (2.5 eq), THF/EtOH	[DC] <5% (decomp.)
6	(+)-RVC/(-)-RVC, 20 mA, 10 F/mol, r.t.	[rAP (50 ms)] 83% (isolated)

- 1) Hayashi, K.; Griffin, J.; Harper, K. C.; Kawamata, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2022**, *144*, 5762.
 2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.

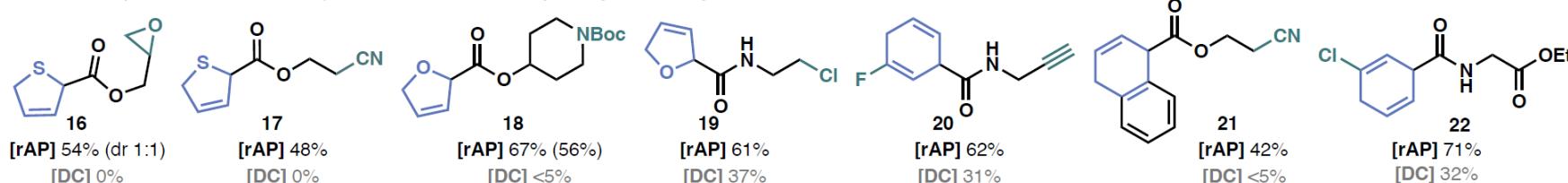
(Hetero)arene Reduction

- Substrate Scope -

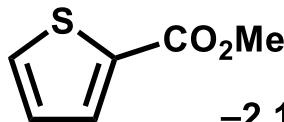
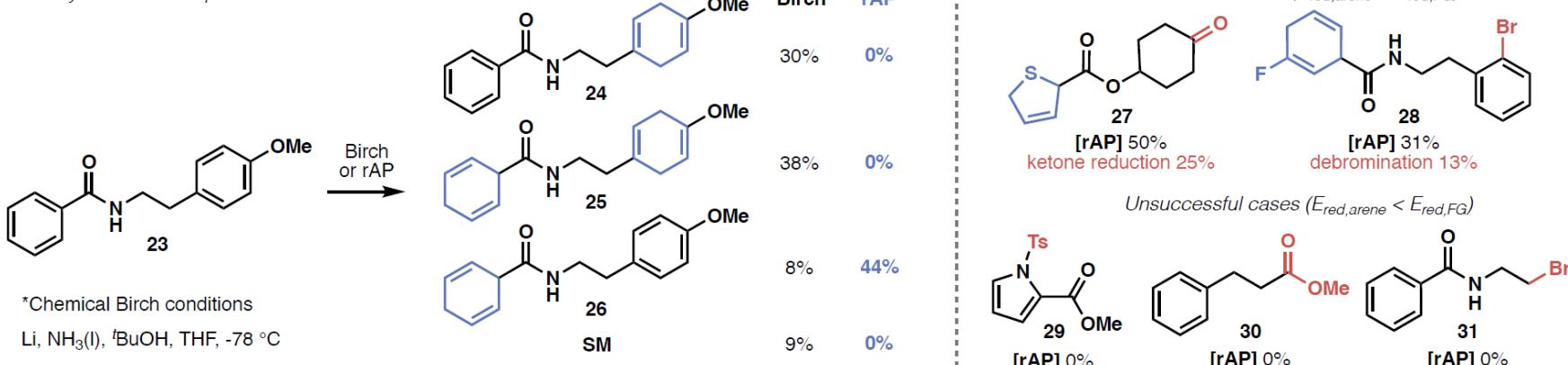
Me₂S: sacrificial electron-donor



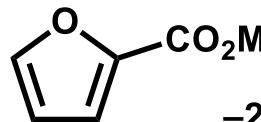
Selected examples



Selectivity between multiple arenes



-2.12 V

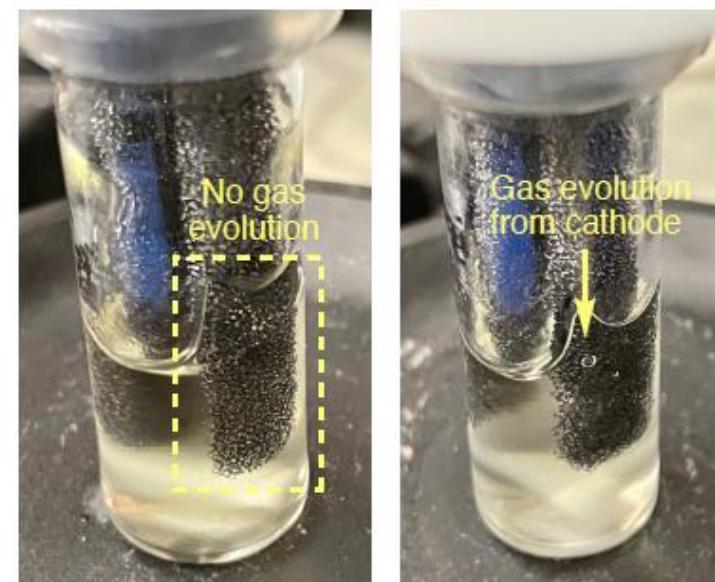
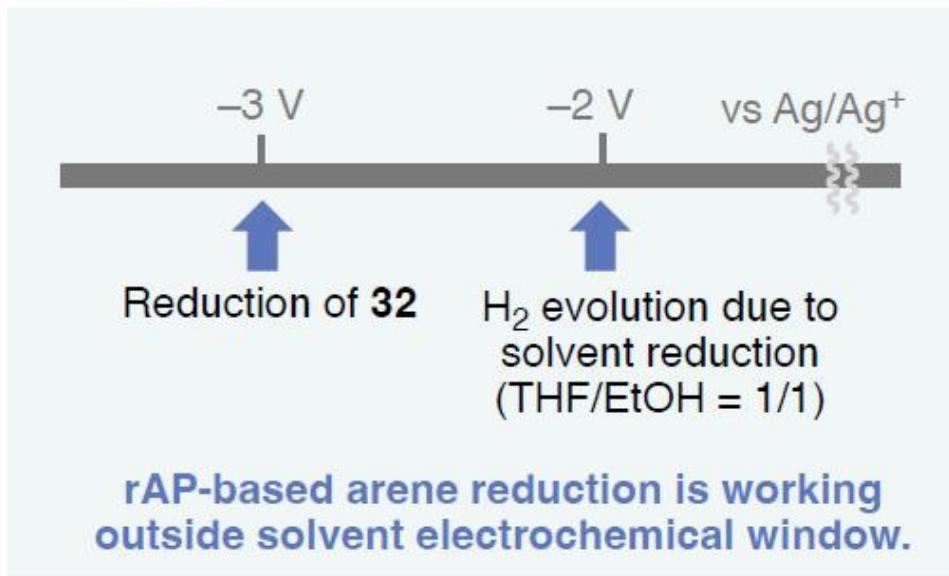
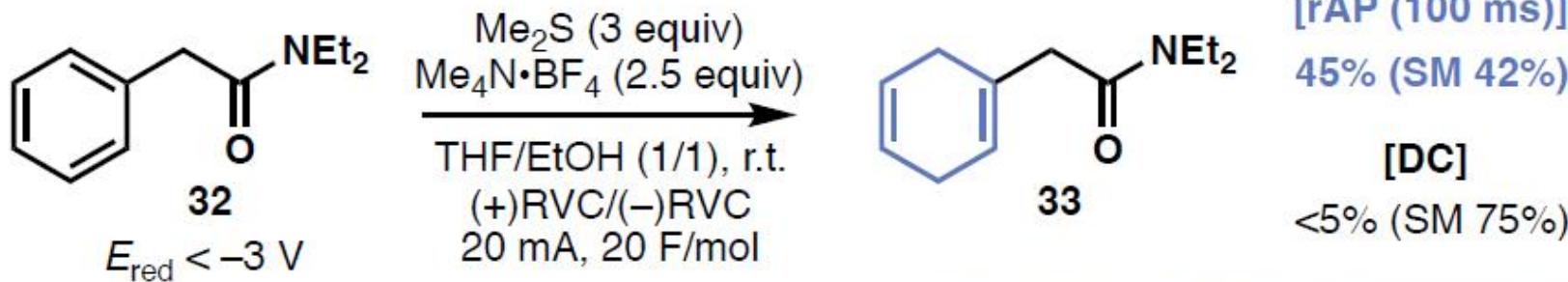


-2.37 V

1) Hayashi, K.; Griffin, J.; Harper, K. C.; Kawamata, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2022**, *144*, 5762.

2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.

Difference between rAP and DC in the (Hetero)arene Reduction



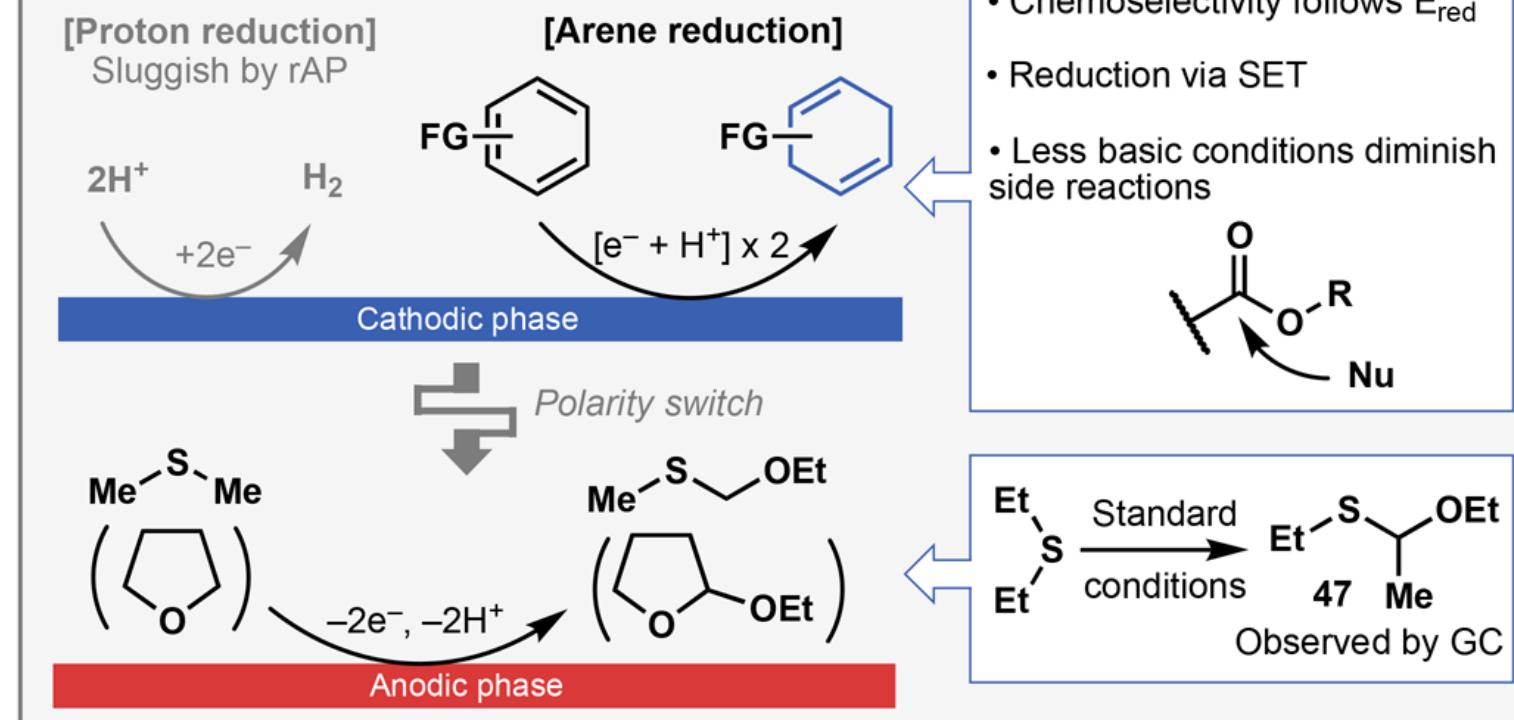
rAP **H₂ gas from cathode (reduction)** → **basic (EtO⁻)**

1) Hayashi, K.; Griffin, J.; Harper, K. C.; Kawamata, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2022**, *144*, 5762.

2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.

Plausinle Mechanism of (Hetero)arene Reduction

C. Overall mechanism



small amount of solvent would be oxidized at anode.

- 1) Hayashi, K.; Griffin, J.; Harper, K. C.; Kawamata, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2022**, *144*, 5762.
- 2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.

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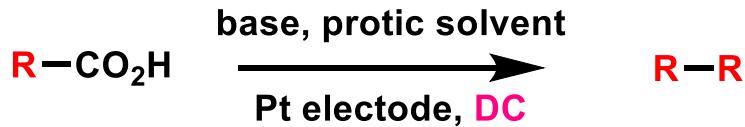
1. Introduction of electrochemistry and alternating current

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2-2. Oxidative reaction

Kolbe Coupling (Oxidative Coupling)

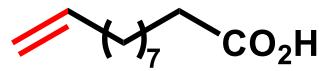
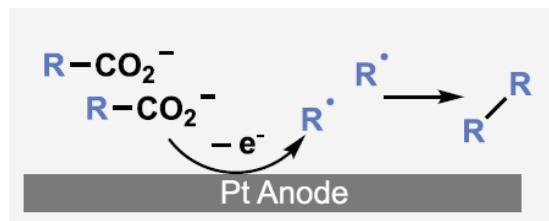


- Kolbe reaction

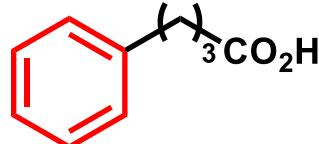
first described by Faraday in 1834, established by Kolbe in 1849

one of the oldest electrochemical reactions and C–C bond forming reactions

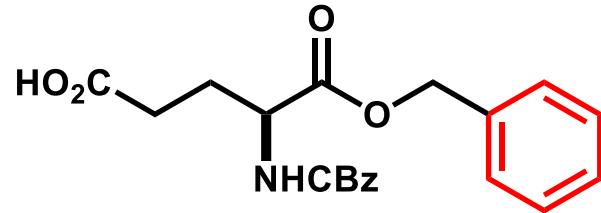
require high voltage, harsh oxidative conditions → low functional group compatibility



0%



0%



11%

Kolbe Coupling by rAP

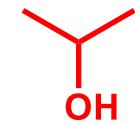
- Optimization of Reaction Conditions -



Entry	Conditions	GC Yield (%)
1	NaOMe (10 mol%), MeOH, (+)Pt/(-)Pt, 60 mA, DC	0
2*	NaOMe (10 mol%), MeOH, (+)Pt/(-)Pt, 10 V, AC (sinusoidal)	0
3	Me ₄ N•OH (10 mol%), acetone, (+)Pt/(-)Pt, 60 mA, DC	0
4	Me ₄ N•OH (10 mol%), acetone, (+)RVC/(-)RVC, 60 mA, DC	<5
5	Me ₄ N•OH (10 mol%), acetone, RVC/RVC, 60 mA, rAP(50ms, 10Hz)	72 (63) [†]
Effect of reaction parameters		
6	Entry 5 with KOH _{aq} (10 mol%) instead of Me ₄ N•OH (10 mol%)	59 [‡]
7	Entry 5 with Et ₃ N (10 mol%) instead of Me ₄ N•OH (10 mol%)	0
8	Entry 5 with MeCN instead of acetone	2
9	Entry 5 with MeOH instead of acetone	34
10	Entry 5 with rAP(100 ms) instead of rAP(50 ms)	55
11 [§]	Entry 5 with sinusoidal wave instead of rAP(50 ms) (10 V, 10 Hz)	27

amine was oxidized

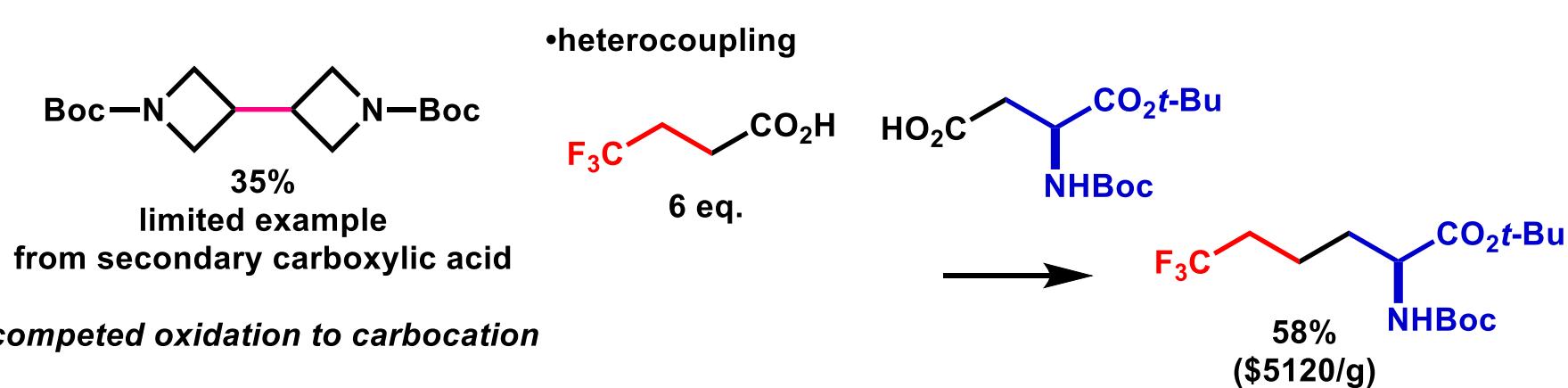
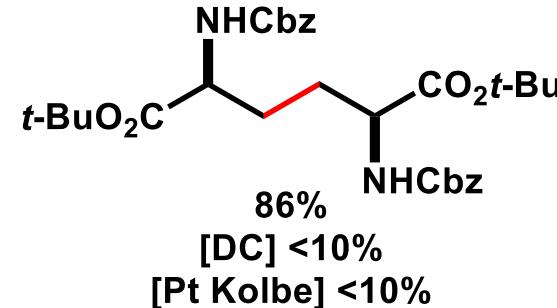
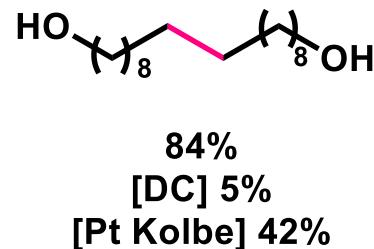
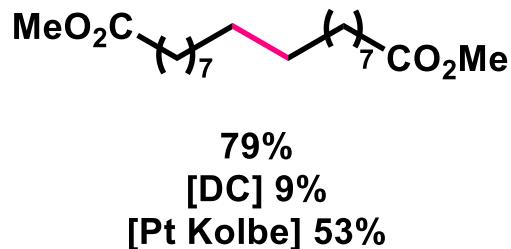
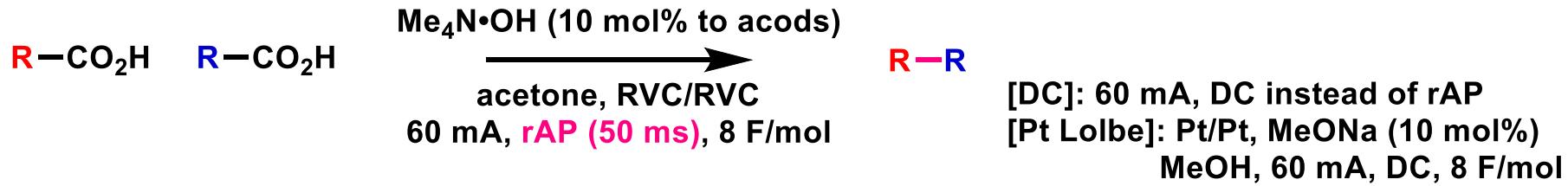
acetone was important


detected
→electron
and protone
acceptor

1) Hioki, Y.; Costantini, M.; Griffin, J.; Harper, K. C.; Merini, M. P.; Nissl, B.; Kawamata, Y.; Baran, P. S. *Science* **2023**, *380*, 81. 2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.

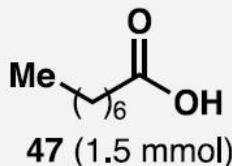
Kolbe Coupling by rAP

- Substrate Scope -

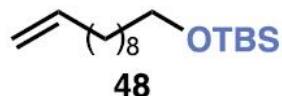


Kolbe Coupling by rAP

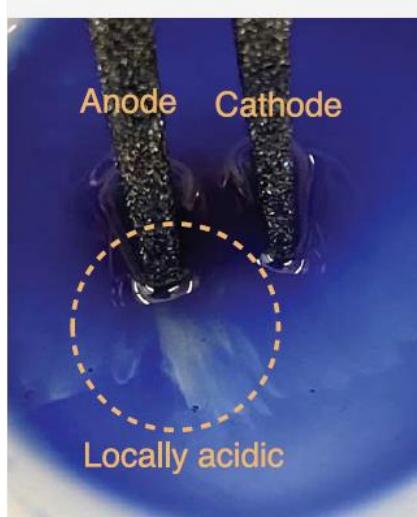
- Local Acidity -



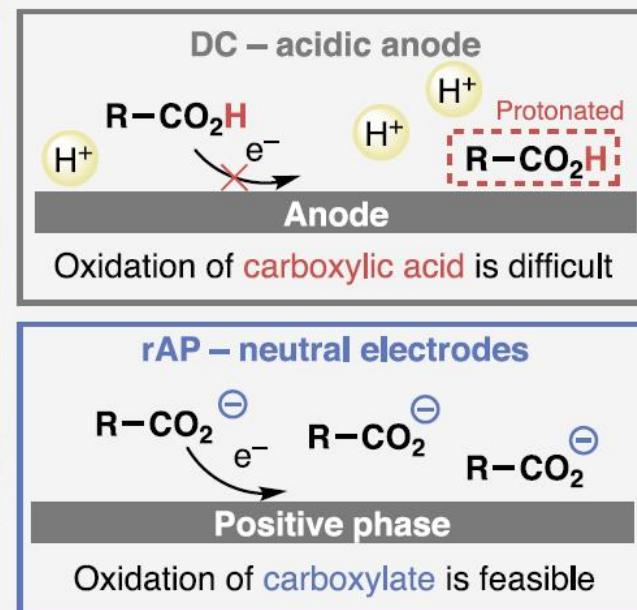
Acid-sensitive probe



	$\xrightarrow[\text{Acetone, RVC/RVC}]{\text{Me}_4\text{N}\cdot\text{OH (10 mol\%)}}$	 49 (Kolbe dimer)	 50 (Deprotection pdt)
		49	50 (remaining 48)
	60 mA, DC, 10 F/mol	37%	52% (48%)
	60 mA, rAP(50ms), 10 F/mol	71%	5% (95%)



Visualization of reaction pH (with bromophenol blue)



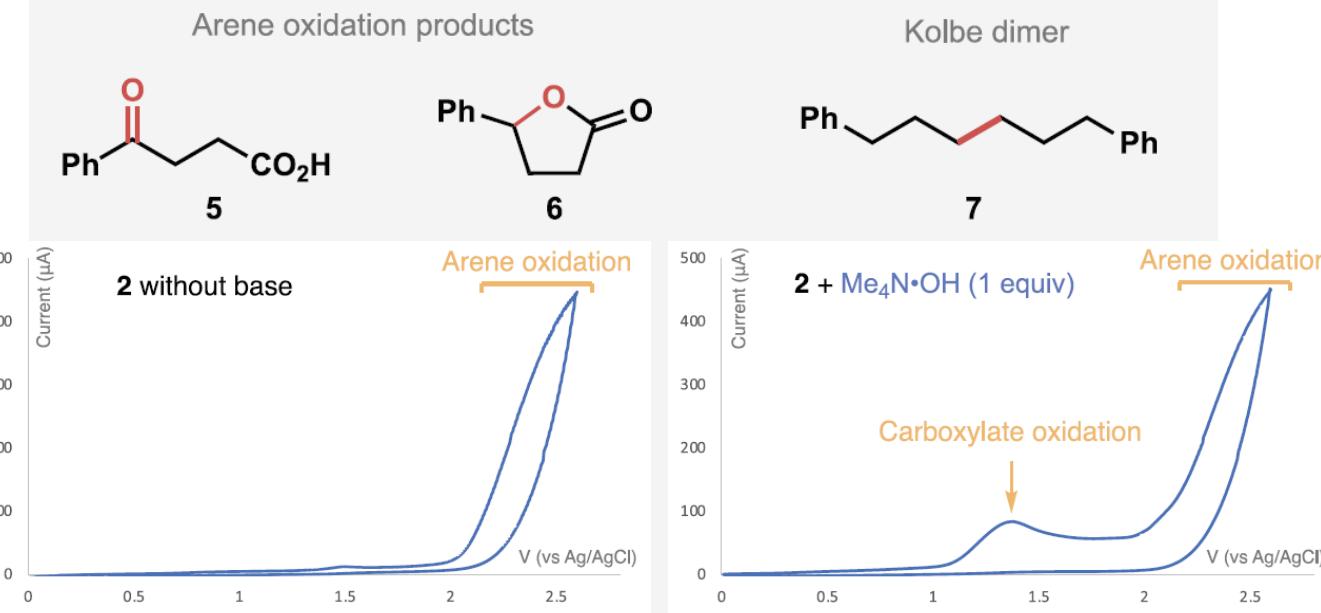
In DC conditions, electrogenerated acid was observed around anode through the oxidation of solvent, water, or substrate.³⁾

1) Hioki, Y.; Costantini, M.; Griffin, J.; Harper, K. C.; Merini, M. P.; Nissl, B.; Kawamata, Y.; Baran, P. S. *Science* **2023**, *380*, 81. 2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**. 3) Neison, M. F. *Encyclopedia of Electrochemistry* Wiley, 2007.

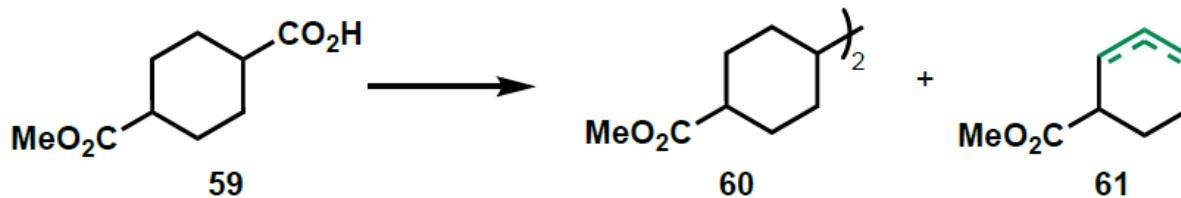
Waveform-Controlled Chemoslectivity

<chem>CC(Cc1ccccc1)CC(=O)O</chem> 2 (1.5 mmol)	$\xrightarrow[\text{Acetone, electrodesUnder Ar}]{\text{Me}_4\text{N}\cdot\text{OH (10 mol\%)}}$	Arene oxidation pdt (5 and 6)	Kolbe dimer (7)
Entry	Electrochemical parameters	Arene oxidation	Kolbe dimer
1	DC, (+)Pt/(-)Pt, 60 mA, 8 F/mol	n.d. [¶]	n.d. [¶]
2	DC, (+)RVC/(-)RVC, 60 mA, 8 F/mol	34% (5/6 = 1/1.3)	0%
3	DC, (+)RVC/(-)RVC, 6 mA, 8 F/mol	38% (5/6 = 1/1.4)	0%
4	rAP(50 ms), RVC/RVC, 60 mA, 12 F/mol	0%	70%

} locally acidic
→ exist as
carboxylic acids



Decarboxylative Olefination



Standard conditions

10 mol% $\text{Me}_4\text{N}\cdot\text{OH}$, acetone, RVC/
RVC, 60 mA, rAP (50 ms), 8 F/mol

16%

21%

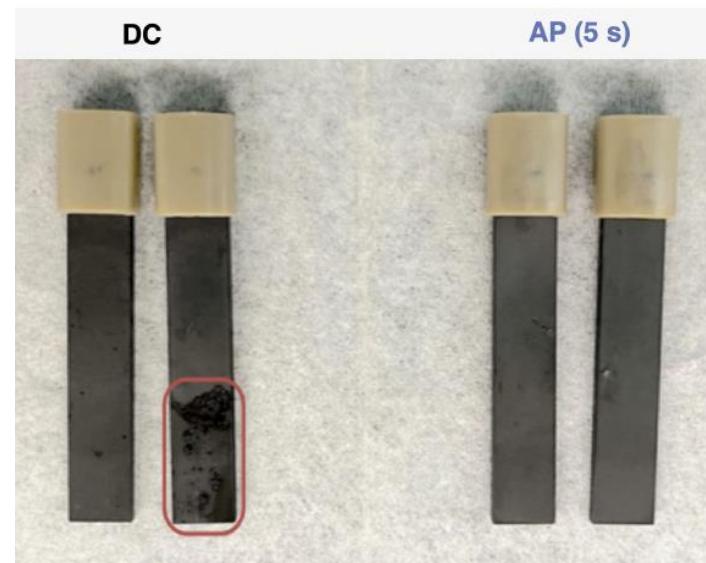
Modified conditions

30 mol% $\text{Me}_4\text{N}\cdot\text{OH}$, 20 mol% PivOH
acetone, **C/C, 60 mA (DC), 5 s AP**, 5 F/mol

0%

68% (11:1)

DC conditions: low conversion
anode (ox) fouling
due to electrogenerated acid



Necessity of Alternating Current

Electrode potential was swept back and forth between three windows:

0 – 3.0 V window

Decarboxylation at high end, **barely reductive** at low end

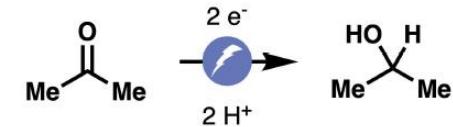
-1.0 – 3.0 V window

Decarboxylation at high end, **mildly reductive but no solvent reduction** at low end

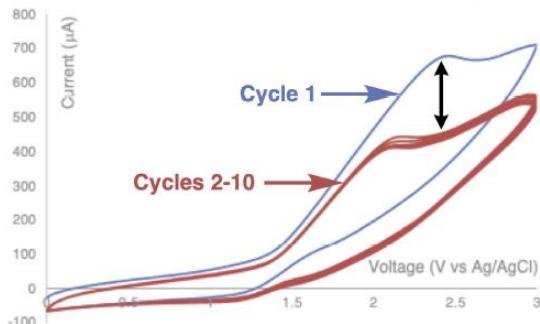
-2.5 – 3.0 V window

Decarboxylation at high end, **solvent reduction** at low end

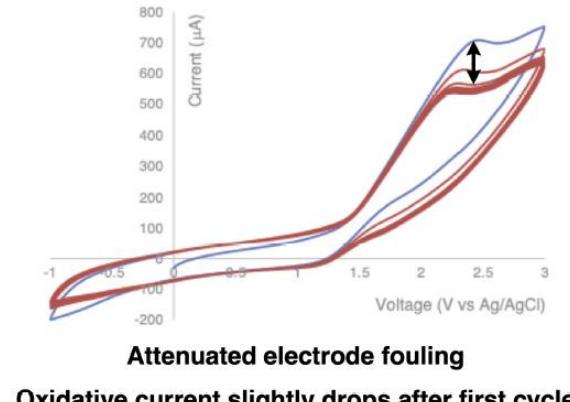
Acetone reduction consumes H⁺ and “resets” the electrode



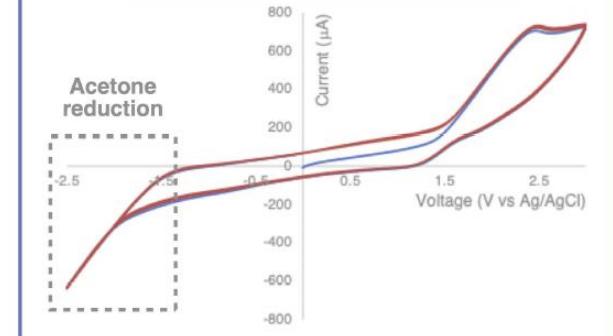
0 – 3.0 V window



-1.0 – 3.0 V window



-2.5 – 3.0 V window

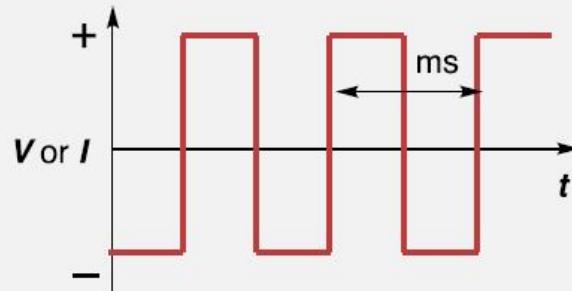


Summary

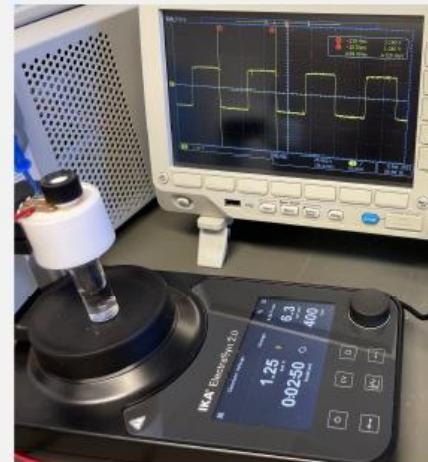
B. Rapid alternating polarity (rAP)



rAP waveform



- Millisecond square waveform of AC
- Current- or potential-controlled wave



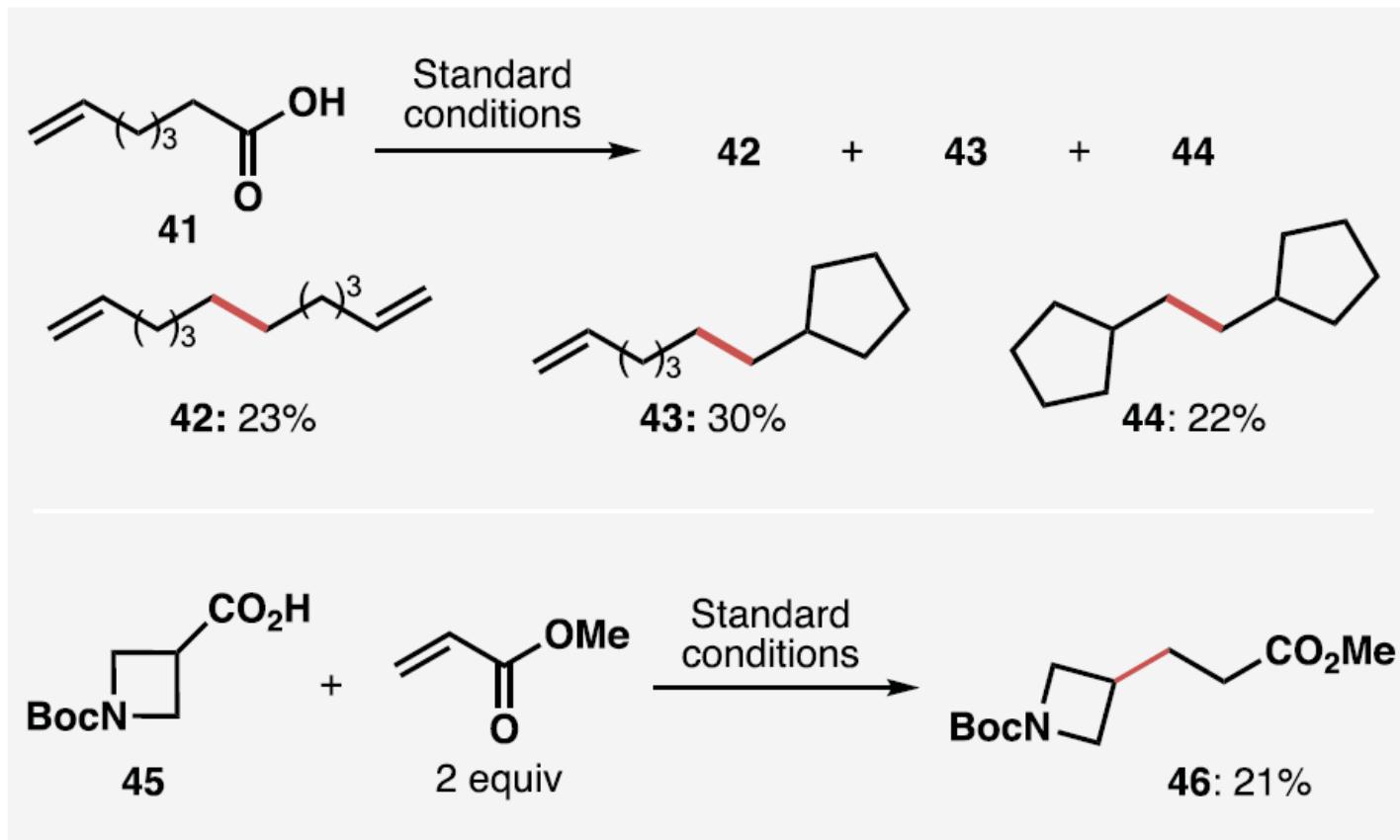
Implemented in a commercial device
(oscilloscope depicts rAP output from
an ElectraSyn 2.0)

unique effects of rapid alternating polarity (rAP)

1. simplify complex redox reactions by **suppressing slow redox processes**
2. **outcompete protone reduction** to enable Birch-type (hetero)arene reduction
3. **alter local pH environment around electrodes** to facilitate decarboxylation of carboxylic acids

Kolbe Coupling by rAP

- Evidence for Radical Generation -



1) Hioki, Y.; Costantini, M.; Griffin, J.; Harper, K. C.; Merini, M. P.; Nissl, B.; Kawamata, Y.; Baran, P. S. *Science* **2023**, *380*, 81. 2) Kawamata, Y.; Baran, P. S. *ChemRxiv* **2023**.