Topic

Electrochemically Driven Radical Reactions

汇报人：张丹　　2024年4月19日

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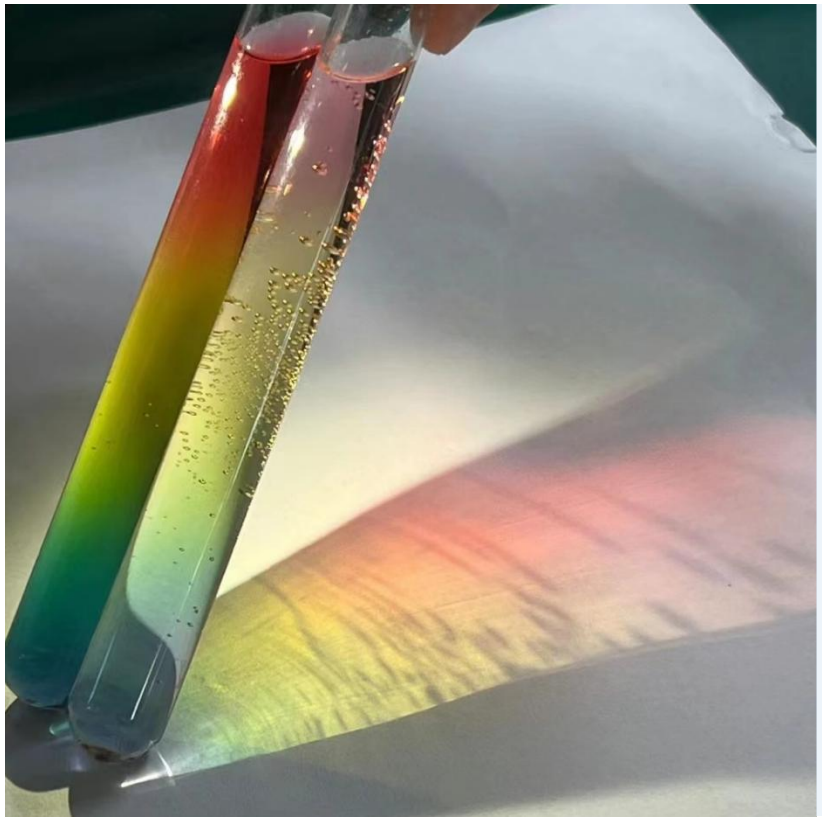

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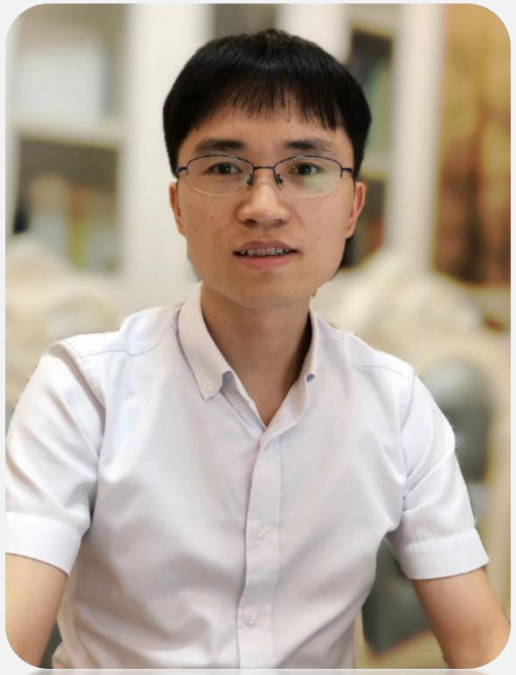
1. Author introduction



Hai-Chao Xu, Ph. D.

- **Education and research experience**

2002-2006	**B.S.** Xiamen University, China
2006-2010	**Ph.D.** Washington University in St. Louis, USA
2011-2013	**Postdoctoral Fellow.** Yale University, USA
2013-2014	**Assistant Professor.** Xiamen University
2014 – Present	**Professor.** Xiamen University

Research field

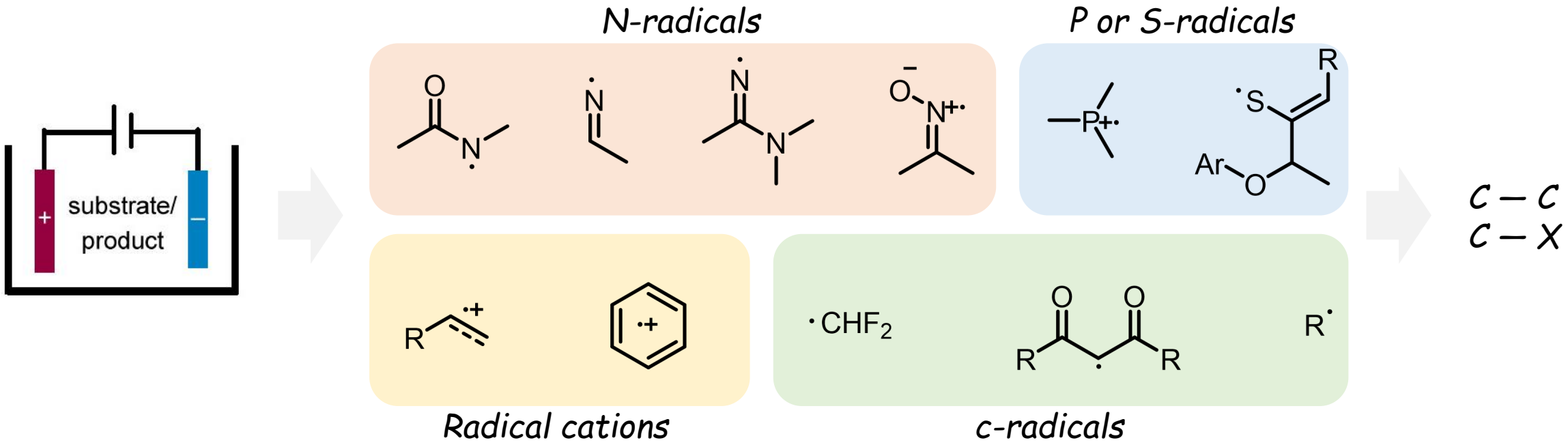
I. Molecular electrocatalysis
II. Molecular photoelectrocatalysis
III. Continous flow electrosynthesis

2. Background information

➢ **电化学优势（促进SET的有力工具）：**

a) 电极电势可持续性&可调谐性

b) 避免使用额外的化学氧化试剂（降低成本，绿化环境）

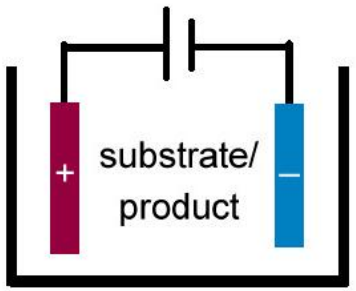


活性中间体

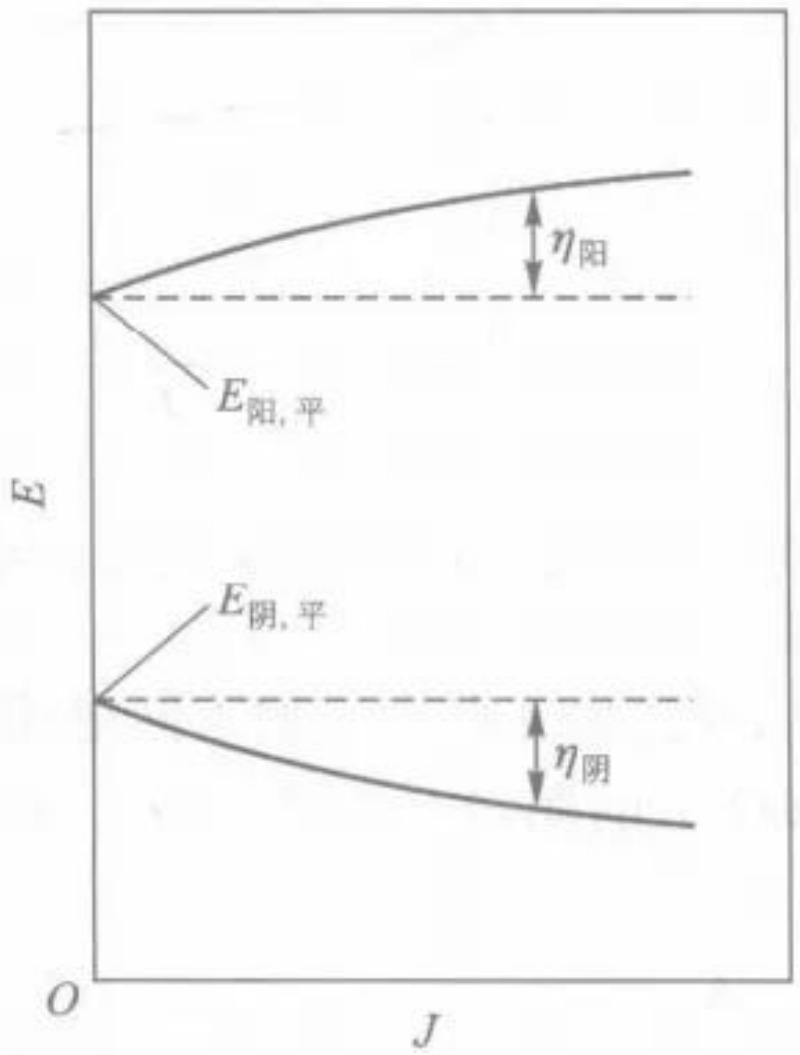
2. Background information

➢ Bactch Reactor

挑战：$E_{原料}$与$E_{产物}$相差较小时，可能造成底物过氧化



瓶式反应：搅拌后整个反应溶液本体中物质的分布是**均匀**的。在恒流电解过程中，原料浓度降低，电极电势会呈现增大的趋势，电解尾声可能会**发生很多副反应**，反应**选择性**进而**降低**。

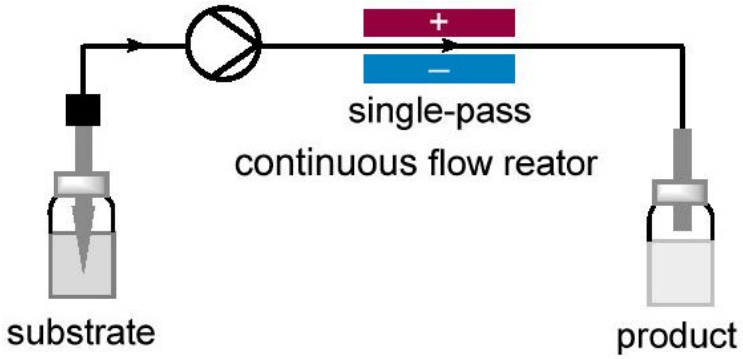


(a) 电解池

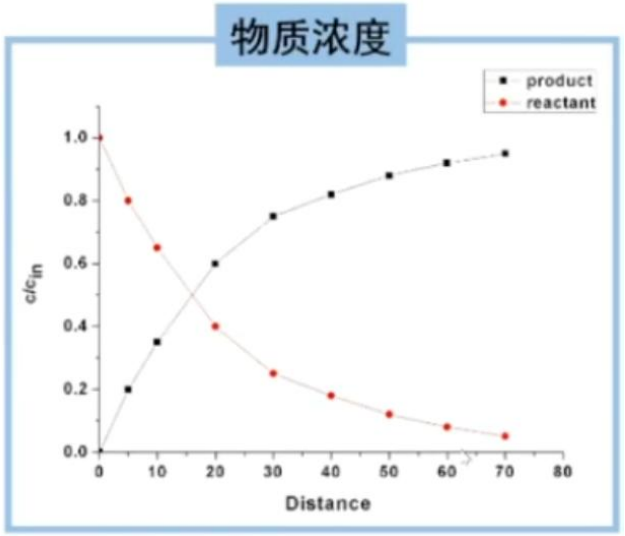
2. Background information

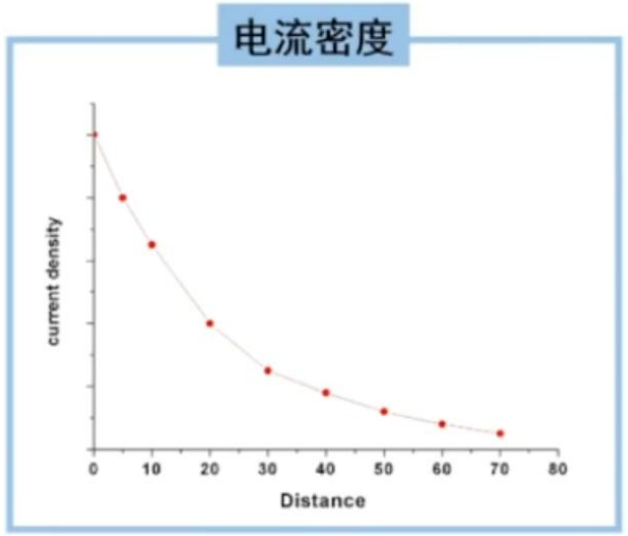
➢ **Flow Reactor 持续流动电合成装置**

成功解决：$E_{原料}$与$E_{产物}$相差较小造成底物过氧化



- ✓ **导电效果好，可减少使用电解质，提升反应选择性：**电极间距小
- ✓ **转化率增加：**电极比表面积大
- ✓ **易手动操作和反应规模的放大**

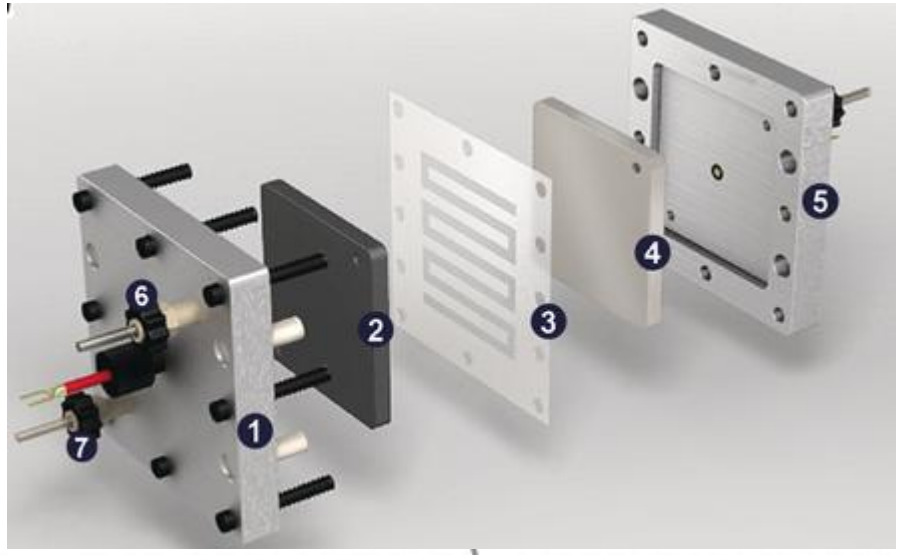




Flow反应：流动通道，入口进原料，出口出产物。整条通道**物质分布不均匀**，浓度逐渐降低，电流密度也逐渐降低，导致整条通道**电流密度不一致，避免副反应发生，提升反应选择性**。

2. Background information

➢ **Flow Reactor**

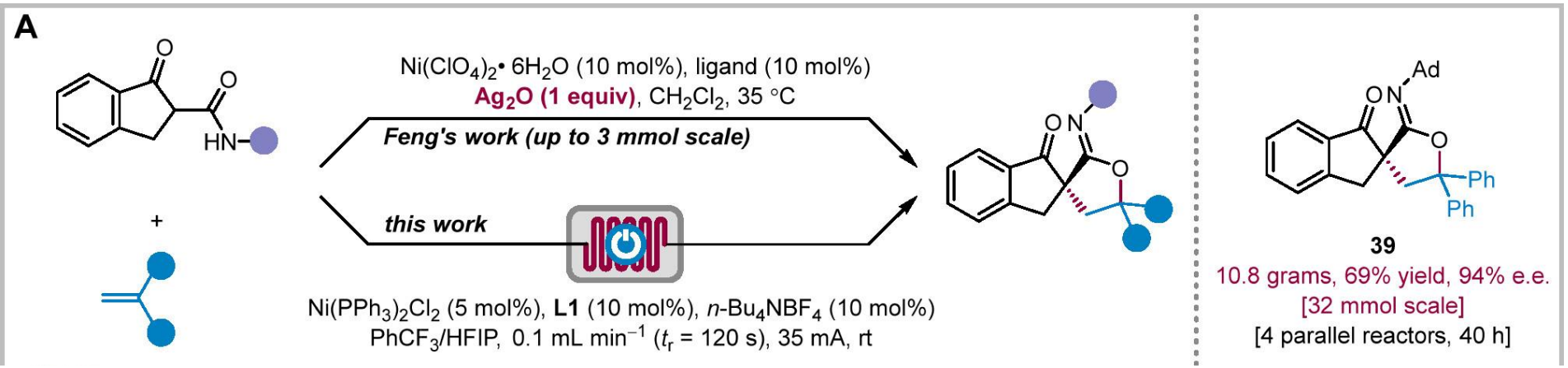


设计

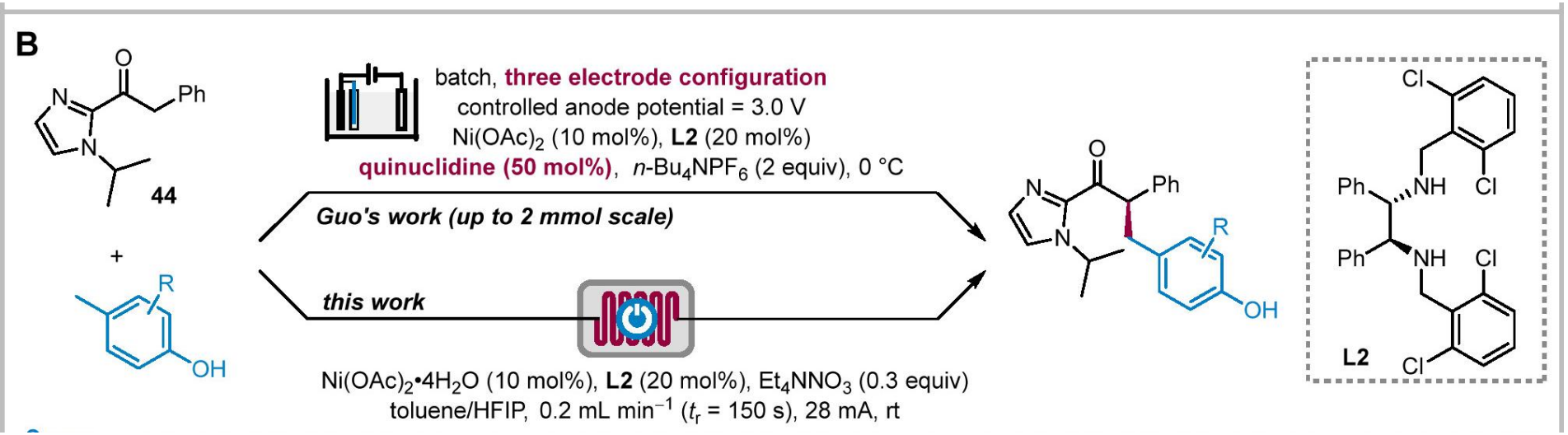
多流动线路并联以实现大规模合成

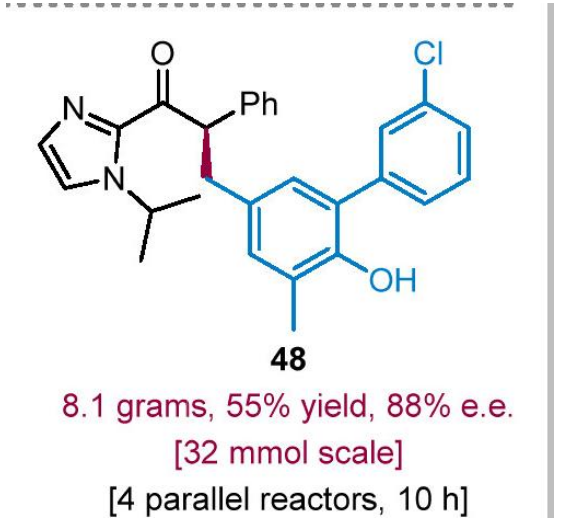
2. Background information

➢ Flow Reactor

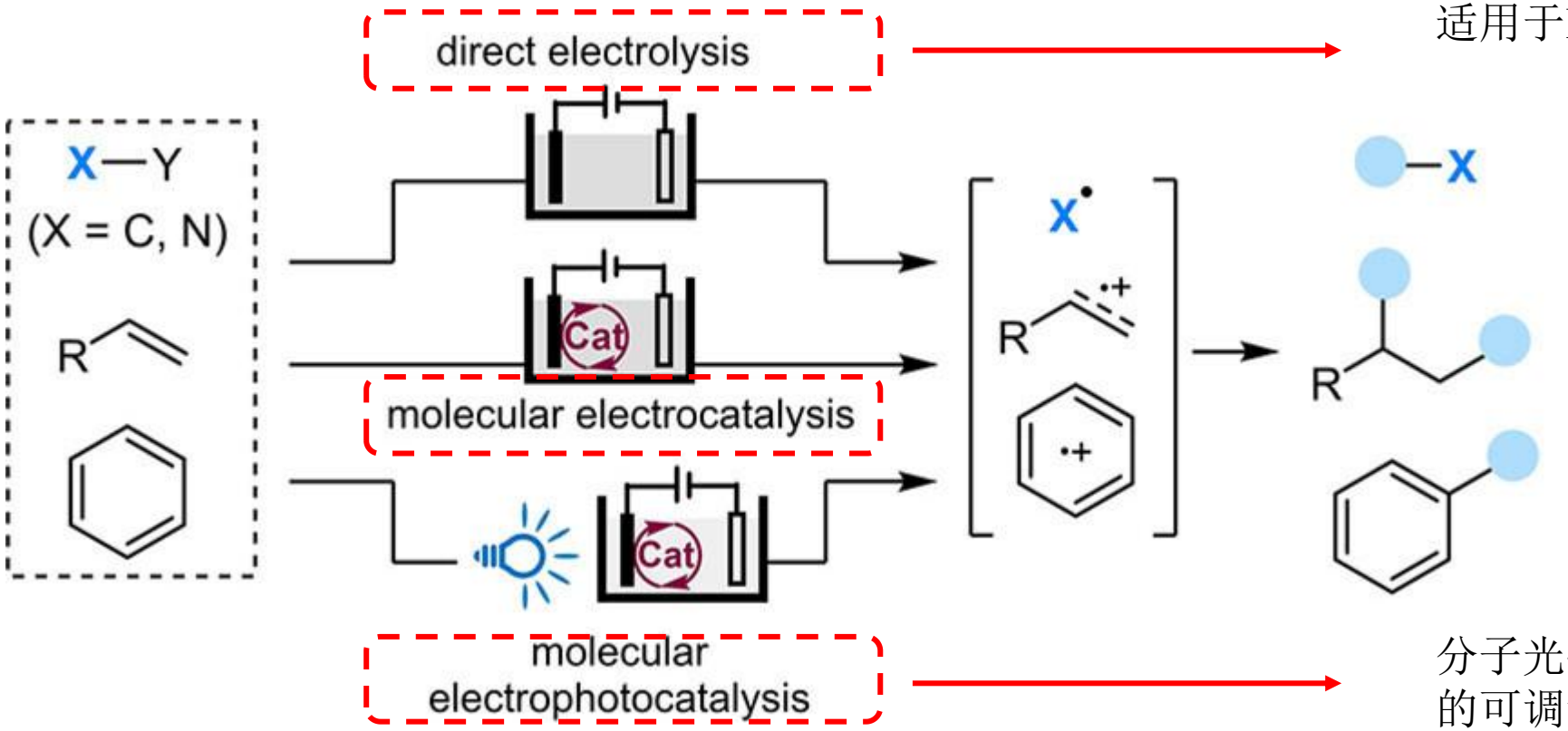


多流动线路并联以实现大规模合成





3. Electrochemically driven radical reactions



适用于$E_{原料}$与$E_{产物}$相差较大

间接电解：通过催化剂与有机分子之间的电子相互作用，降低反应活化能，加快有机物转化。促使自由基在电极电势较低的情况下生成。

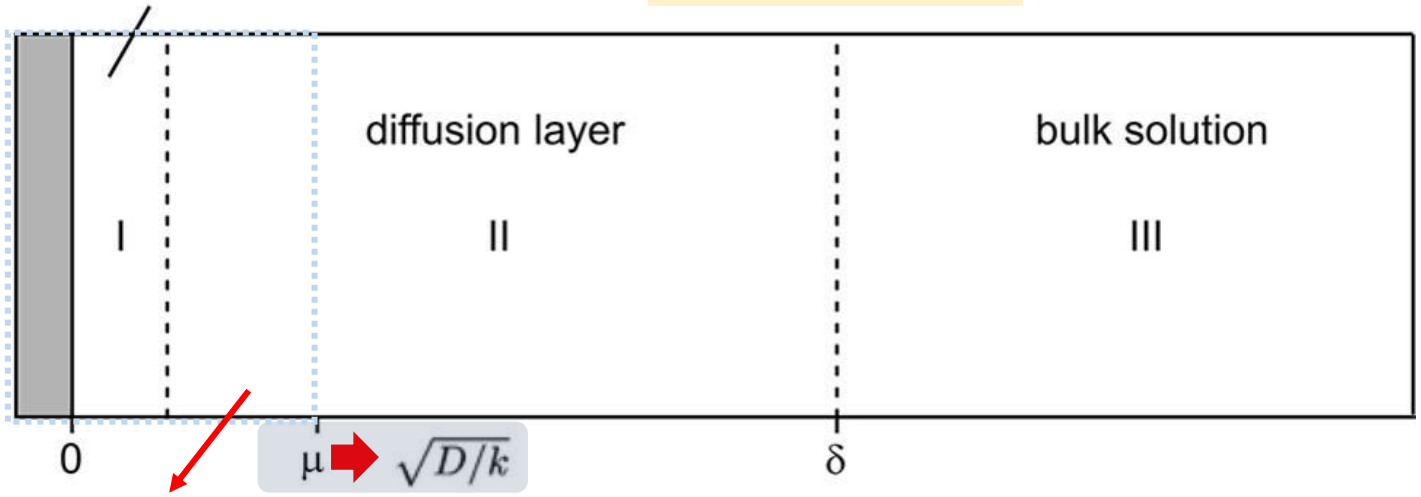
分子光化学独特的选择性和反应性&电化学的可调谐性和无试剂性相结合

3.1 Direct electrolysis

Challenge： 足够的选择性以实现所需的自由基反应

电极电解过程本质上是不均匀的！

electrical double layer (EDL) → 发生电子转移



反应物种高浓度聚集

$$A - e^- \rightleftharpoons B \xrightarrow{k} C$$

制定策略

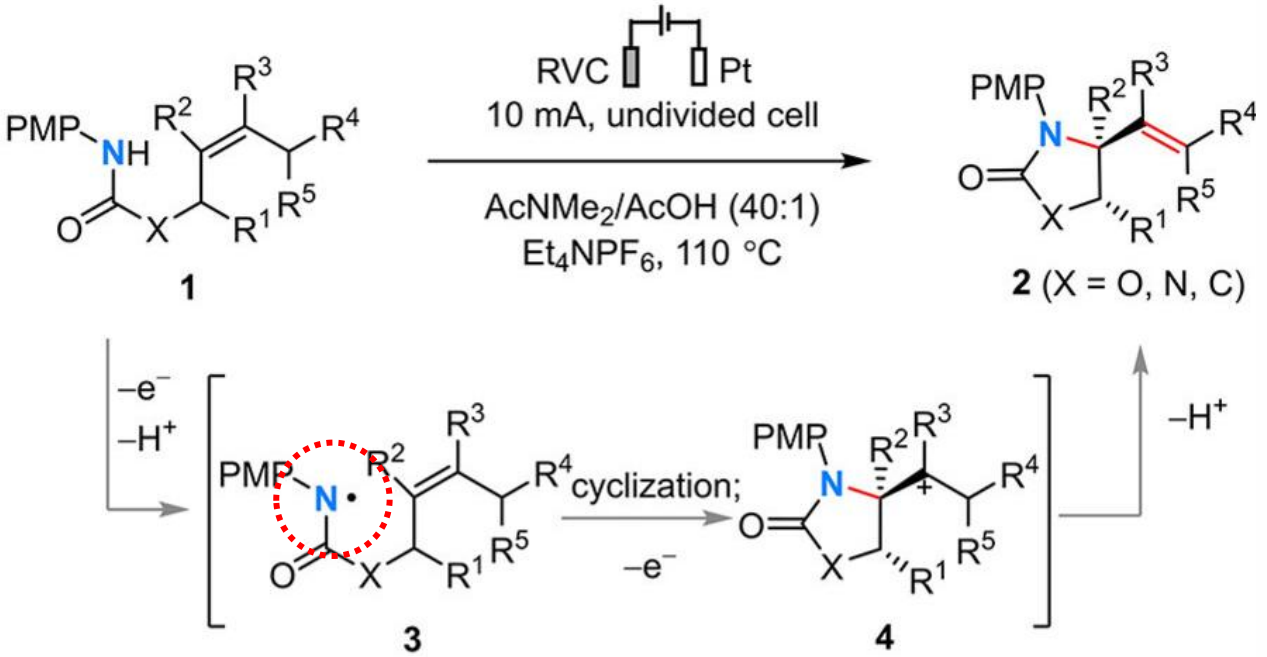
设计反应

抑制副产物生成

- k：一阶速率常数，D：扩散系数。
- 反应层厚度 μ 比扩散层薄得多，但比EDL厚得多。
- 在电极上产生的反应物种通常被限制在具有高局部浓度的扩散层中，会促进自由基二聚化、产物过氧化或与电极反应以引起电极钝化。

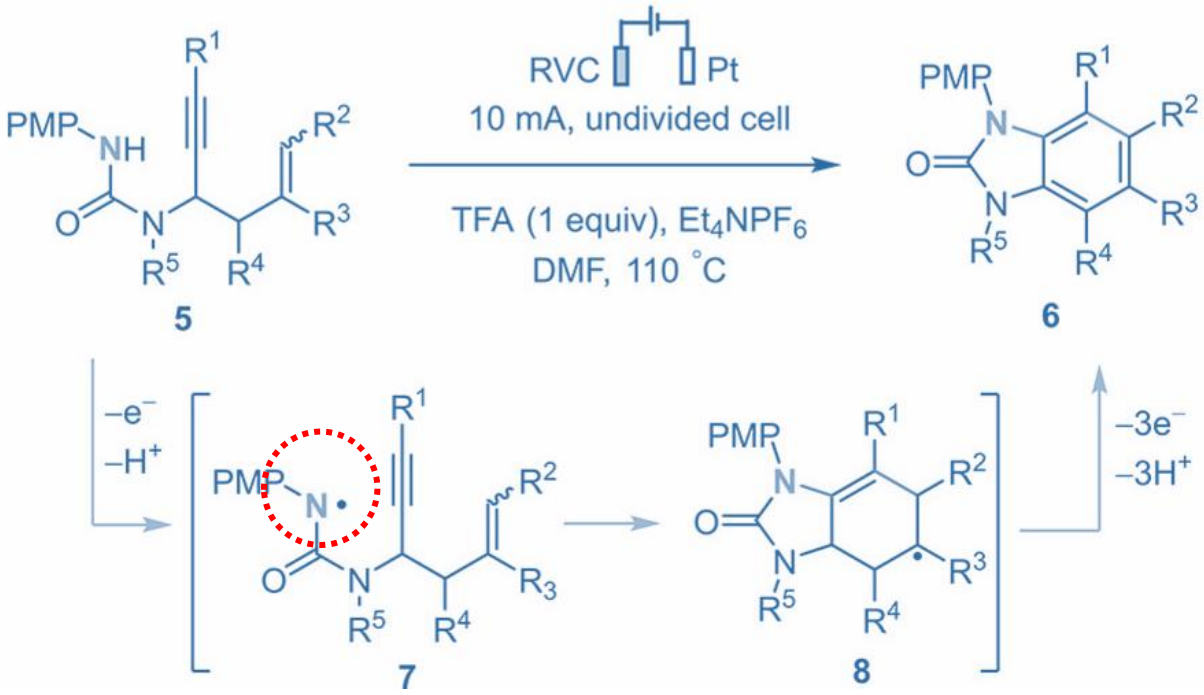
3.1.1 Radical Cyclization Reactions

Electrochemical intramolecular amination of tri- and tetrasubstituted olefins



J. Am. Chem. Soc. **2017**, *139*, 2956.

Electrochemical dehydrogenative cyclization cascade

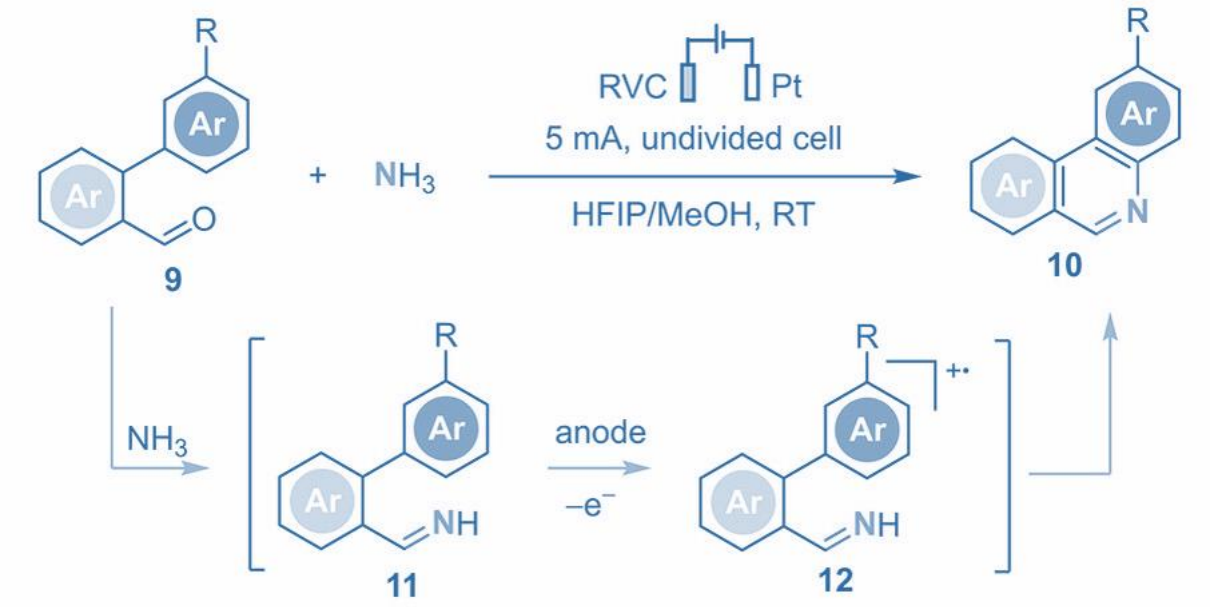


Sci. China Chem. **2019**, *62*, 1501-1503.

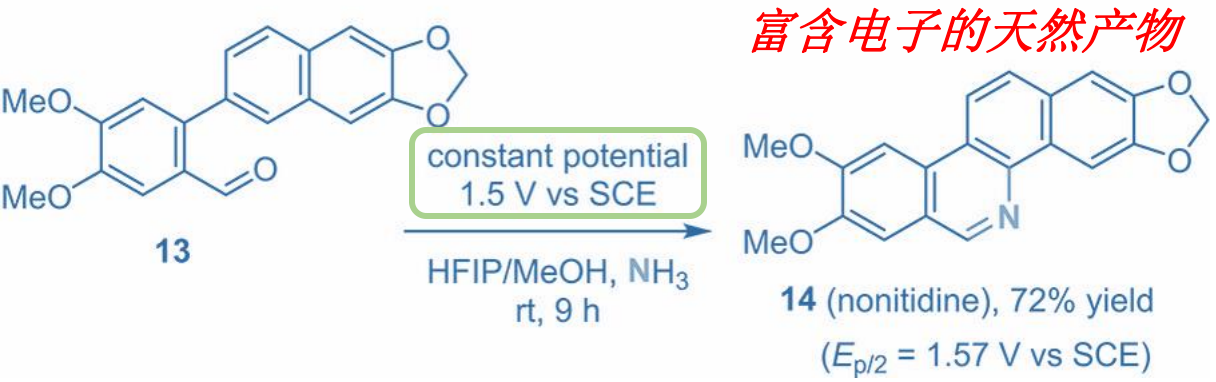
产物 **2,6***的氧化电位高于底物* **1,5***：避免产物过氧化！*

3.1.1 Radical Cyclization Reactions

A. Synthesis of *N*-heteroaromatics via cyclization of iminyl radical cations

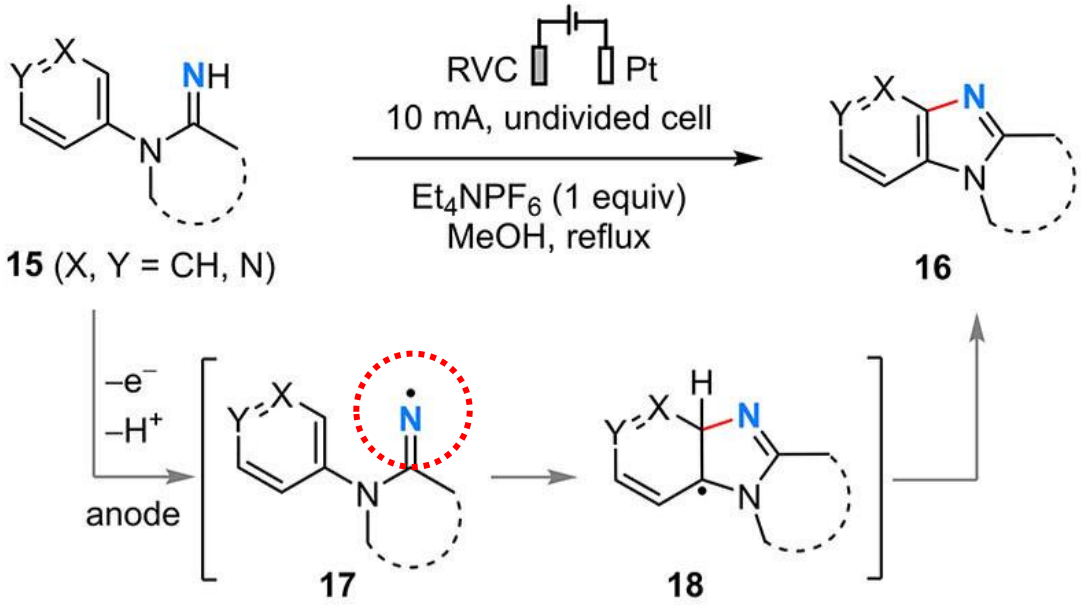


B. Avoiding overoxidation by controlled potential electrolysis

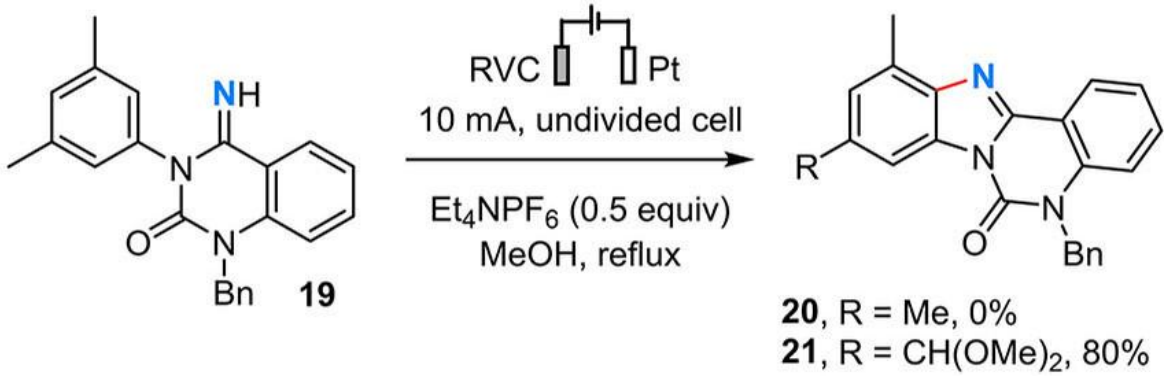


Angew. Chem. Int. Ed. **2017**, *56*, 12732.

A. Aromatic C–H/N–H coupling via amidinyl radicals

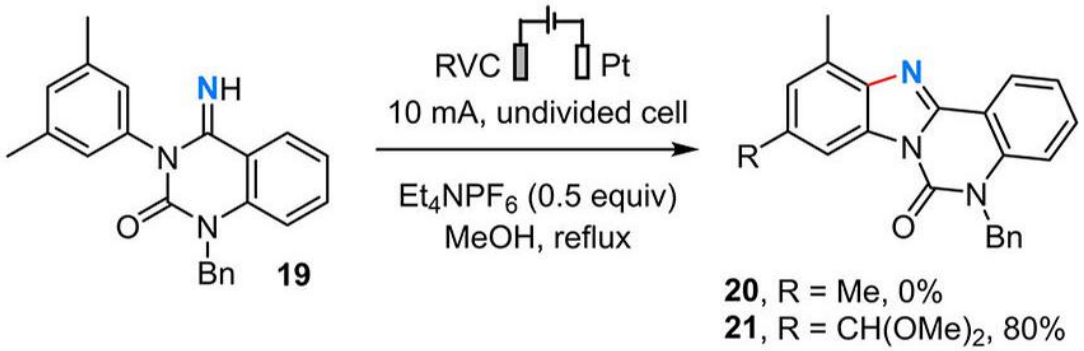


B. Cascade electrochemical cyclization/Me oxidation

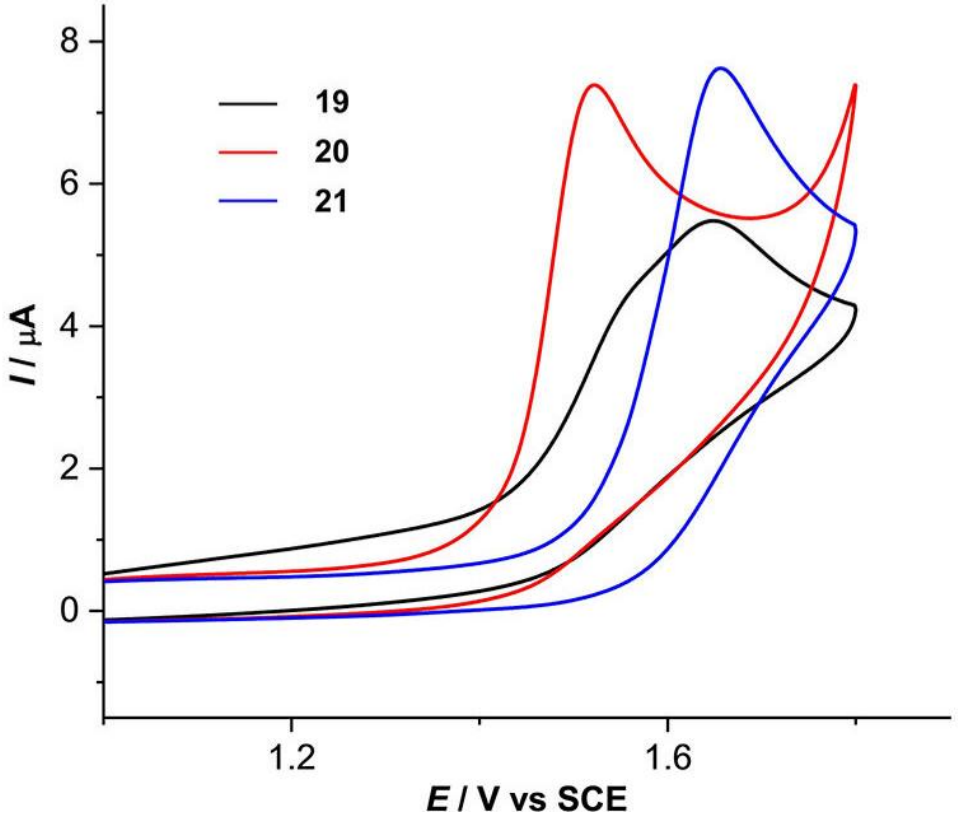


Angew. Chem. Int. Ed. **2017**, *56*, 587.

3.1.1 Radical Cyclization Reactions



C. Cyclic voltammograms



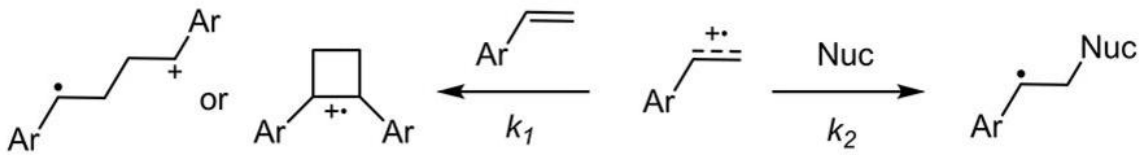
底物19

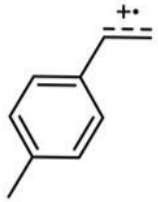
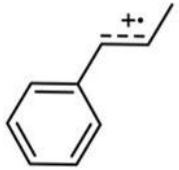
产物20

产物过氧化21

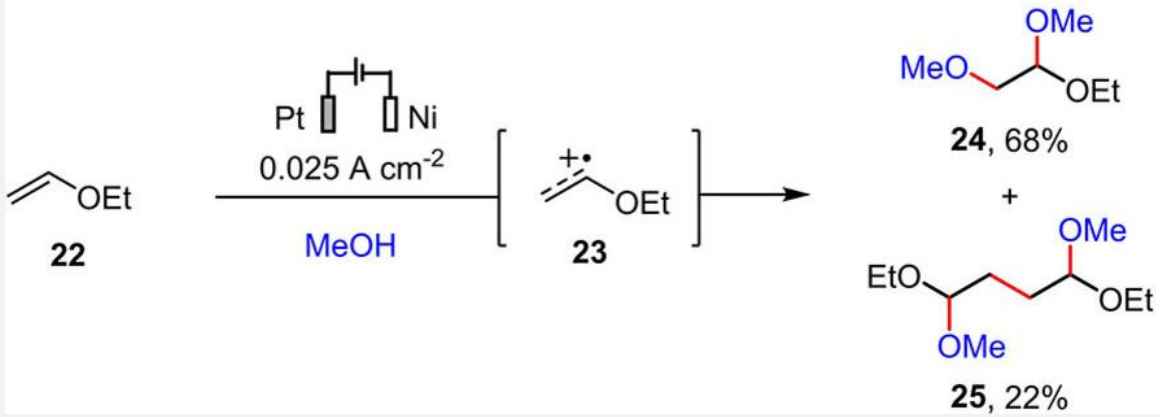
3.1.2 Intermolecular Radical Reactions

Reactivities of alkene radical cations



Radical cation	k_1/M^{-1} s^{-1}	k_2/M^{-1} s^{-1}		
	Alkene precursor	N_3^-	Cl^-	MeOH
	2.9×10^9	1×10^{10}	8.9×10^9	5.9×10^6
	1.4×10^9	1×10^{10}	6×10^9	9.7×10^6

Electrolysis of vinyl ether in MeOH



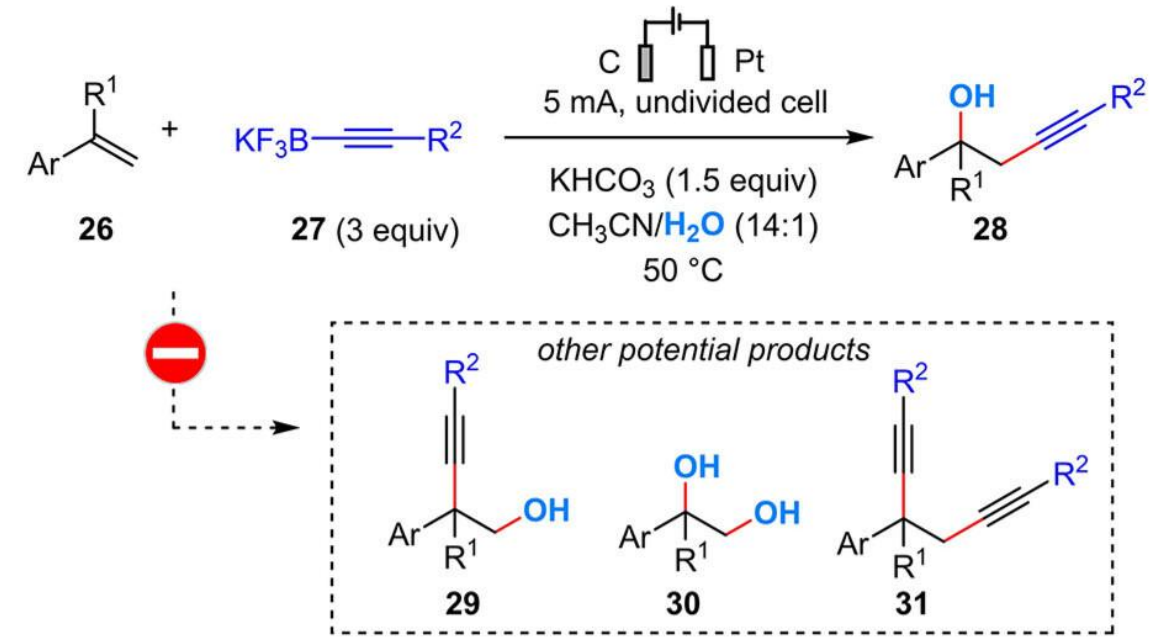
烯烃自由基阳离子：

✓ *高反应活性：为更具挑战的转化提供机会。*

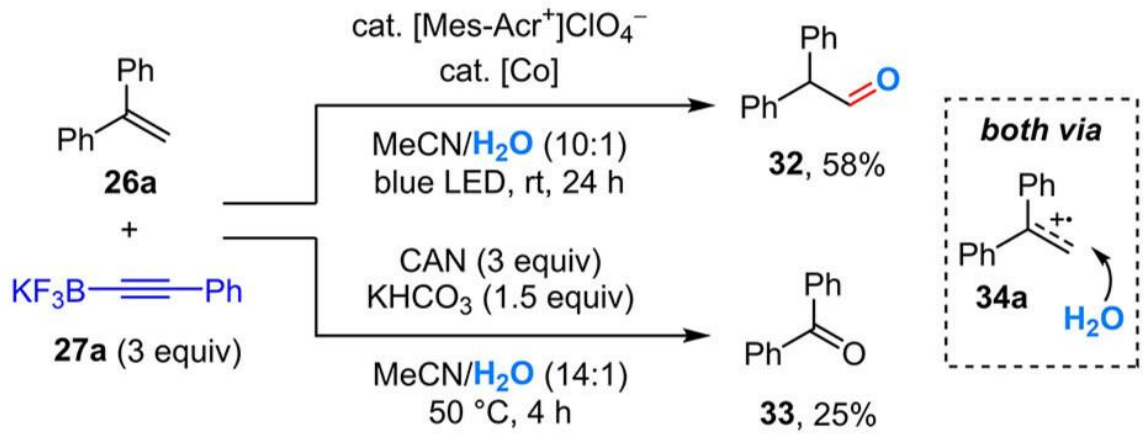
☐ ***Challenge**：其按照特定反应途径发生反应.。*

3.1.2 Intermolecular Radical Reactions

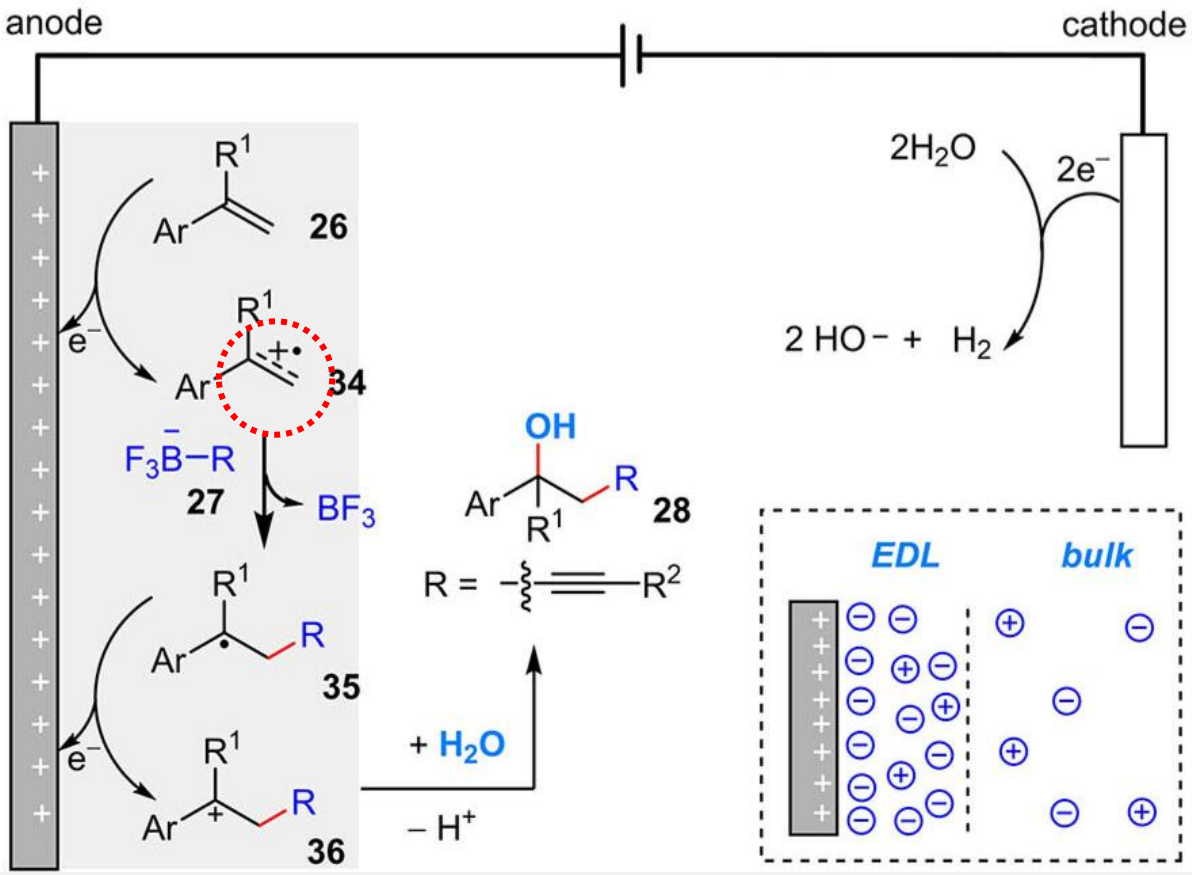
A. Electrochemical alkene carbohydroxylation with organotrifluoroborates and H_2O



B. Comparision with homogenous conditions



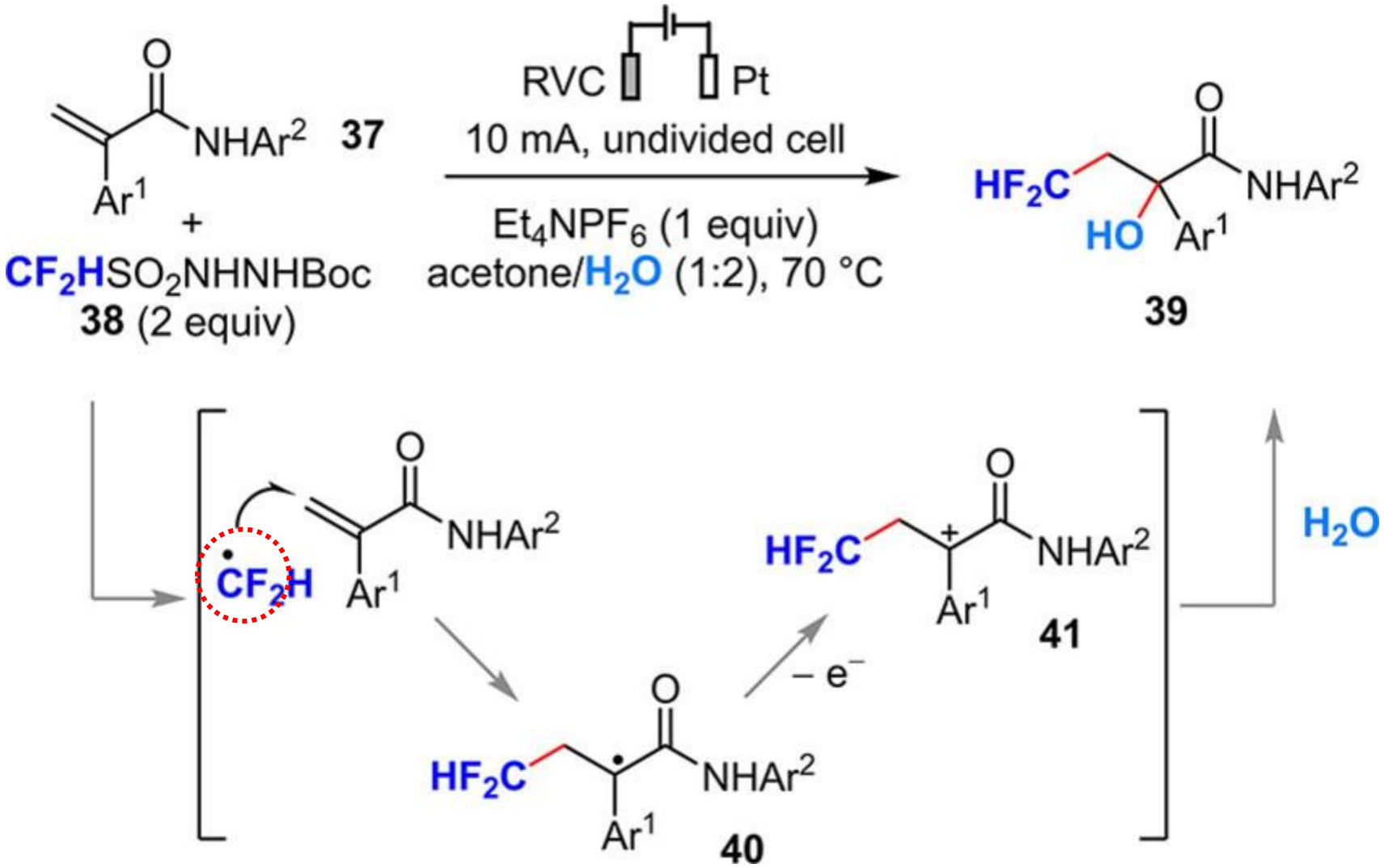
Proposed Mechanism



J. Am. Chem. Soc. **2018**, *140*, 16387.

利用电极表面的独特特性实现有趣和不同寻常的选择性！

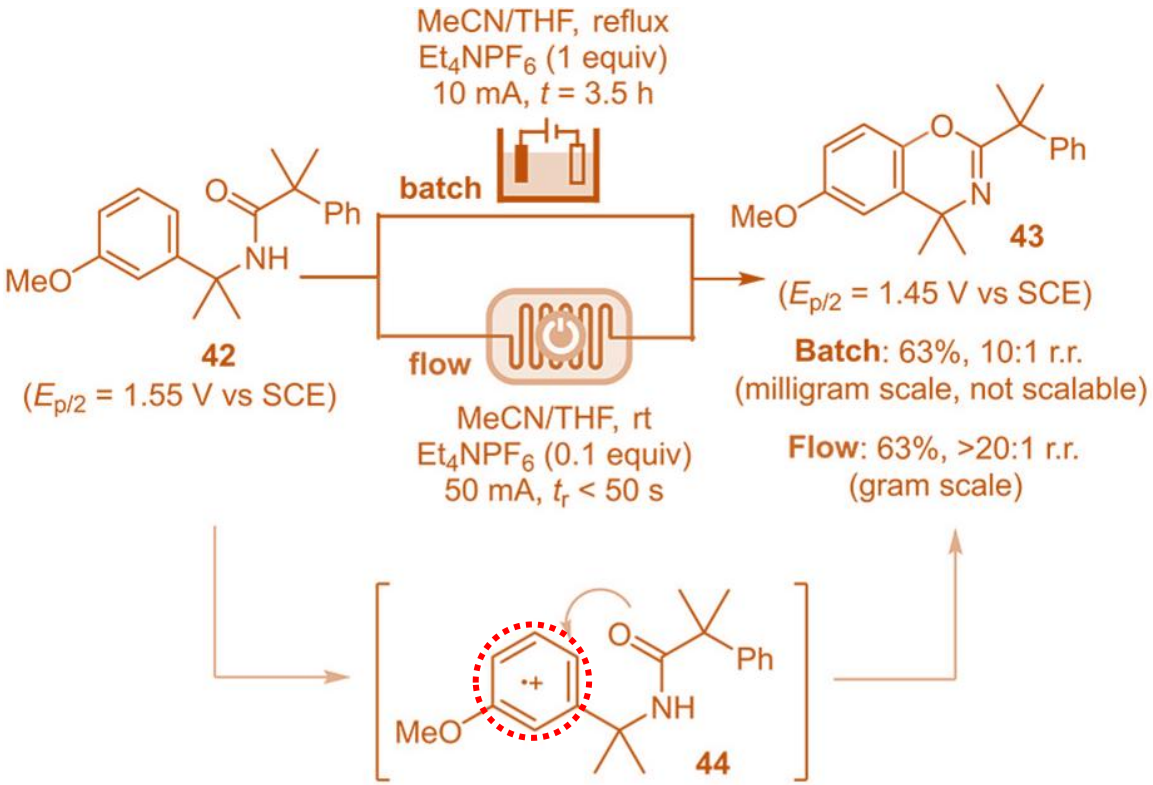
3.1.2 Intermolecular Radical Reactions



ChemSusChem. **2019**, *12*, 3060.

3.1.3 Electrolysis in Continuous

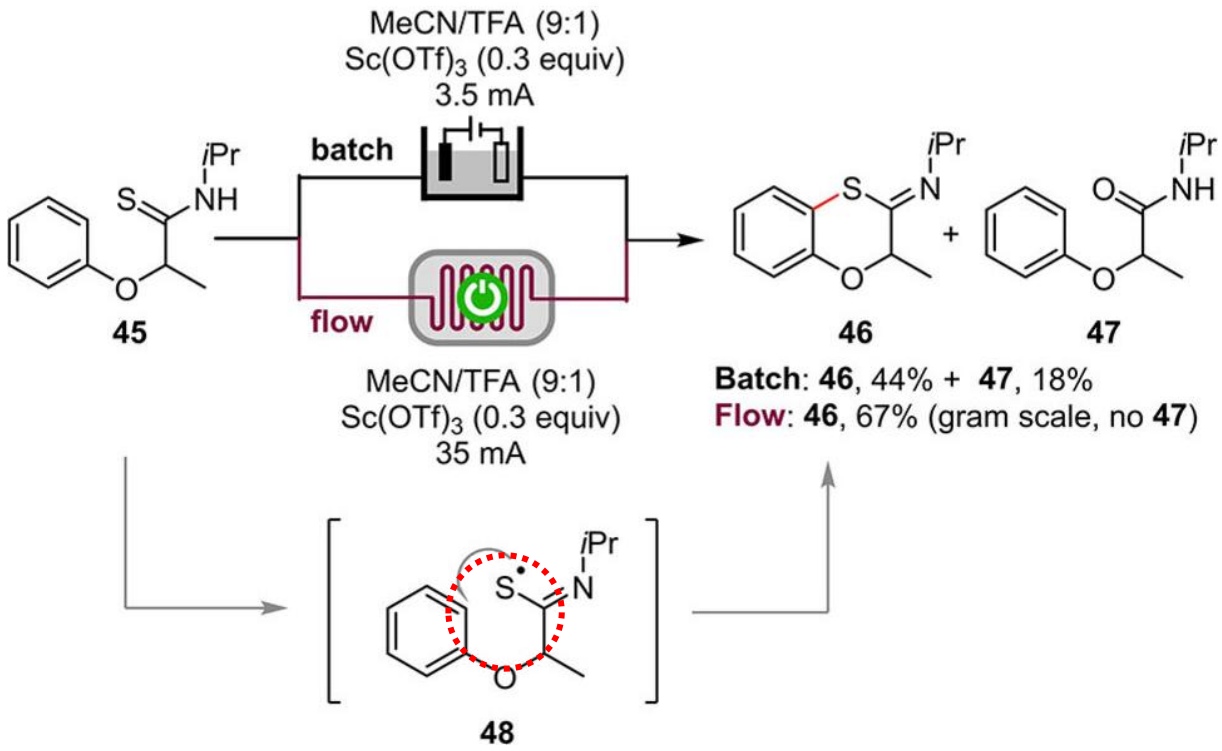
Dehydrogenative cyclization via arene radical cation



Org. Lett. **2017**, *19*, 6332.

底物与产物电极电势接近

Dehydrogenative cyclization of thioamidyl radical

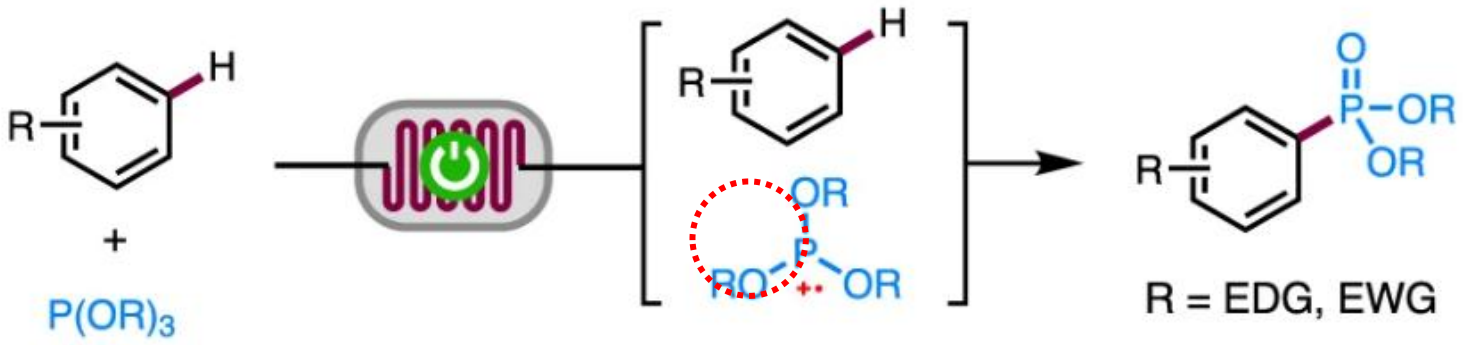


Angew. Chem. Int. Ed. **2019**, *58*, 6650.

硫代酰胺（尤其烷基硫代酰胺）：易发生脱硫副反应

3.1.3 Electrolysis in Continuous

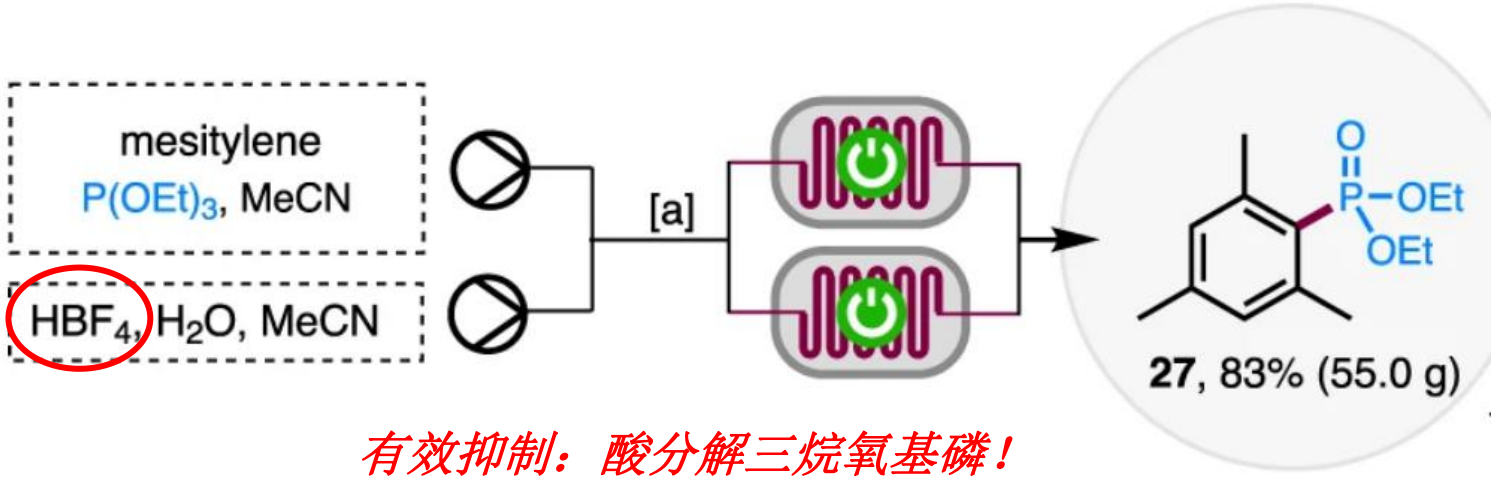
Dehydrogenative cyclization via arene radical cation



原位混合

持续流动电合成t<75 s

e-rich and -deficient arenes catalyst- and oxidant-free easy scale-up



稳定运行10 day!

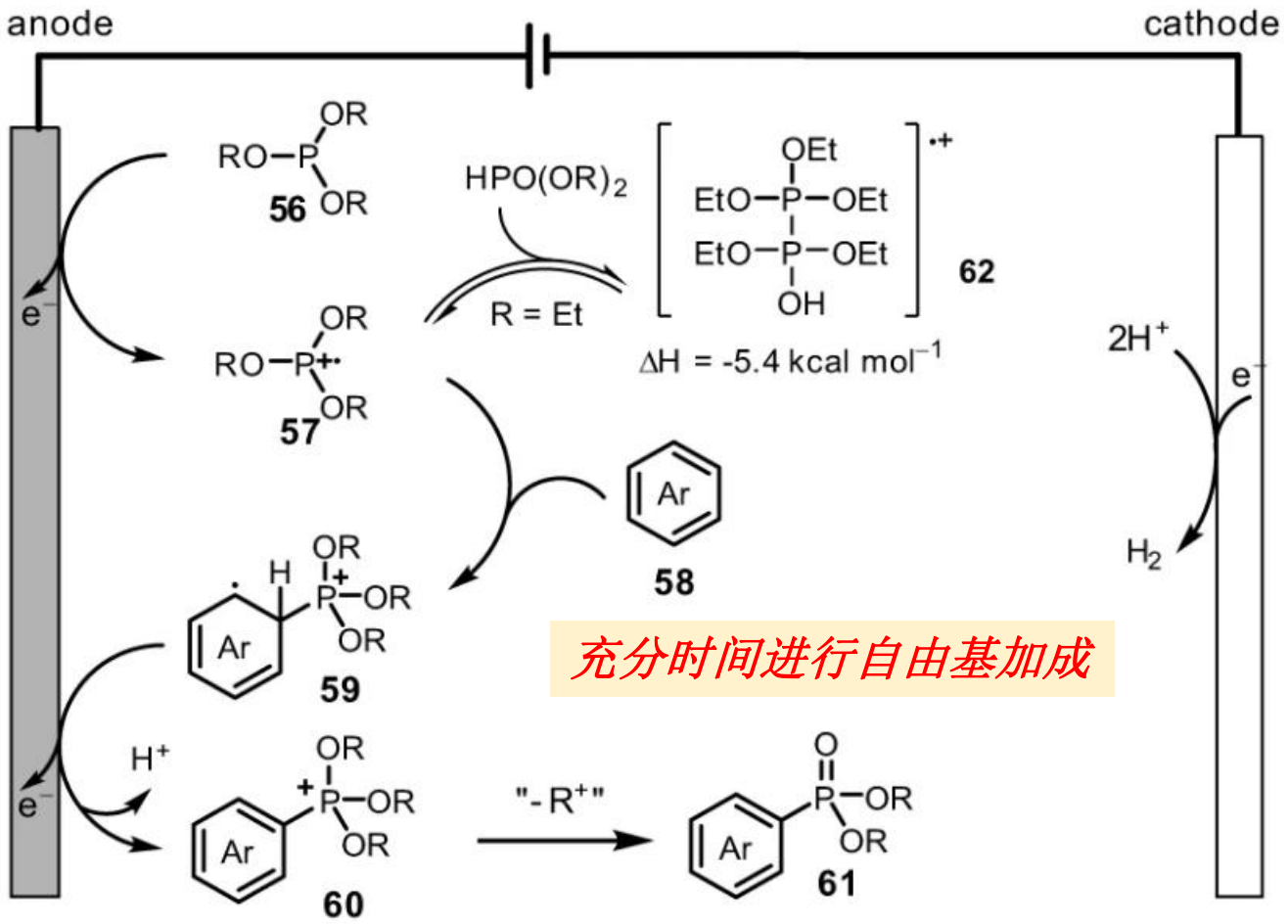
有效抑制：酸分解三烷氧基磷！

Angew. Chem. Int. Ed. **2019**, *58*, 6650.

3.1.3 Electrolysis in Continuous

少量H_2O：促进反应发生！

Conditions	NMR Yield of **2**
Standardconditions:$P(OEt)_3$ (5 equiv) + H_2O (2 equiv)	78%
Conditions I: $P(OEt)_3$ (5 equiv)	0%
Conditions II: $P(OEt)_3$ (3 equiv) + $HPO(OEt)_2$ (2 equiv)	58%
Conditions III: $P(OEt)_3$ (3 equiv) + $HPO(OEt)_2$ (0.2 equiv)	79%



少量H_2O：与三烷氧基磷形成亚磷酸酯

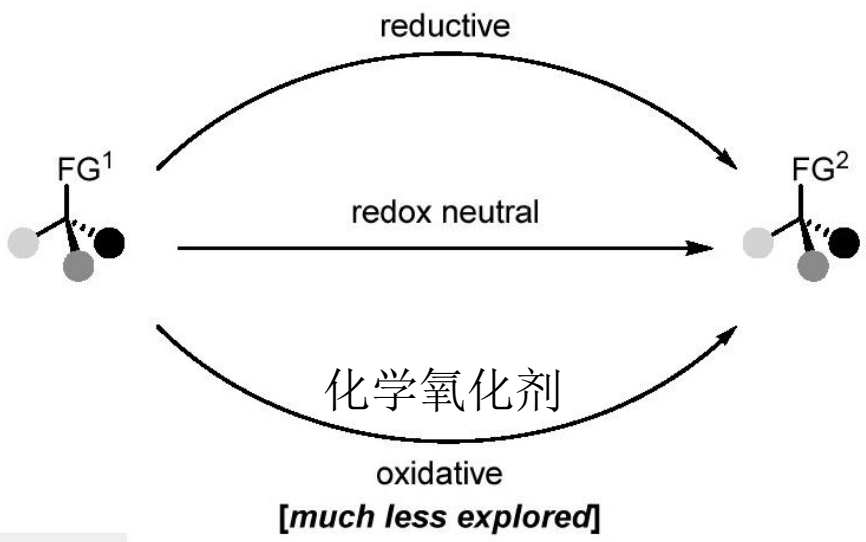
三烷氧基磷自由基阳离子：活性高，烷基易脱

亚磷酸酯：与三烷氧基磷自由基阳离子可逆结合将其稳定

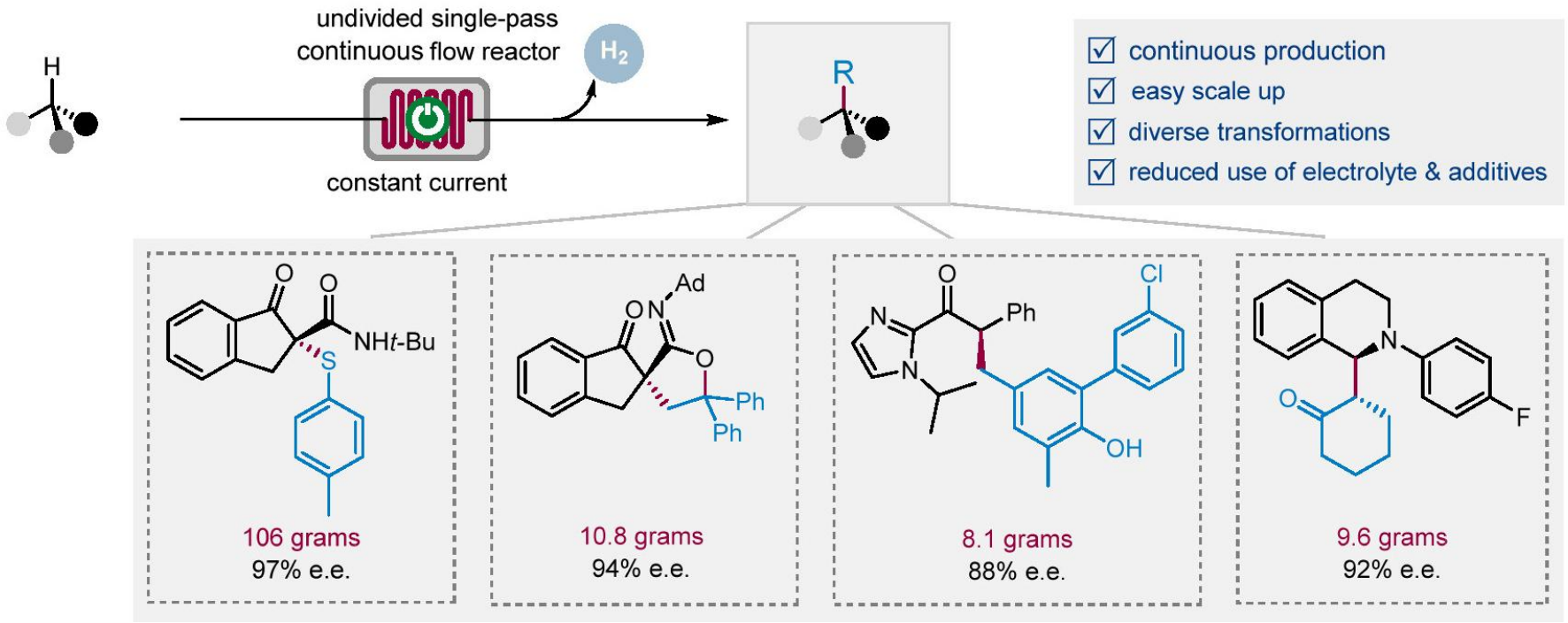
充分时间进行自由基加成

3.1.3 Electrolysis in Continuous

Unlocking the Potential of Oxidative Asymmetric Catalysis with Continuous Flow Electrochemistry

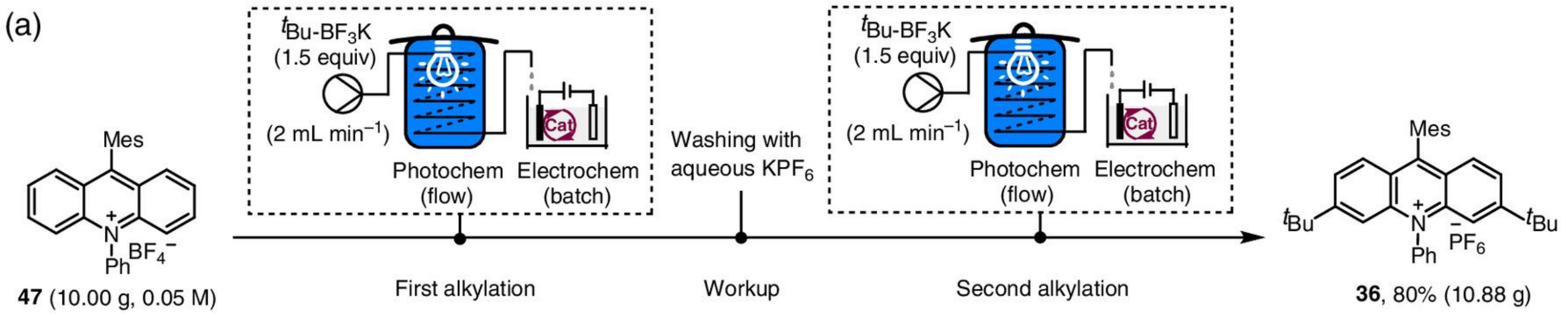


持续流动电合成装置的发现推动了“不对称催化合成”的发展！

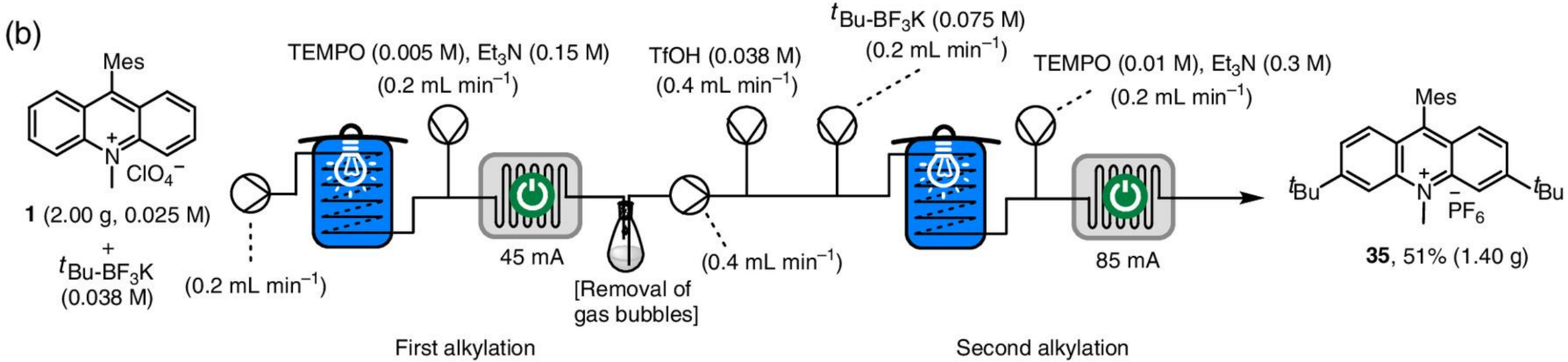


J. Am. Chem. Soc. **2024**, *146*, asap.

3.1.3 Electrolysis in Continuous



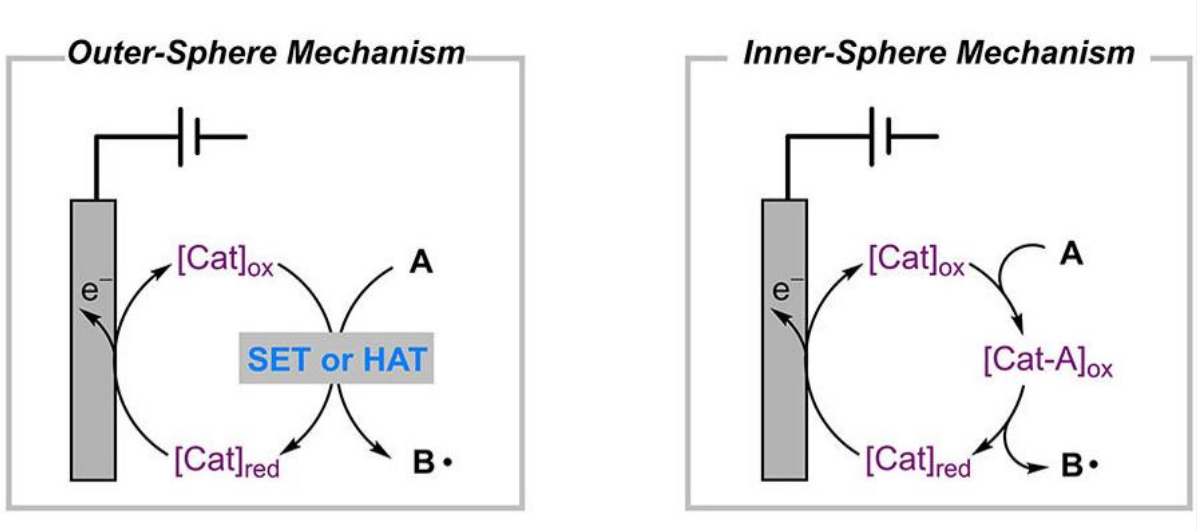
*持续流动电合成装置使得**Fukuzumi光催化剂**的合成更加容易！*



3.2 Molecular Electrocatalysis

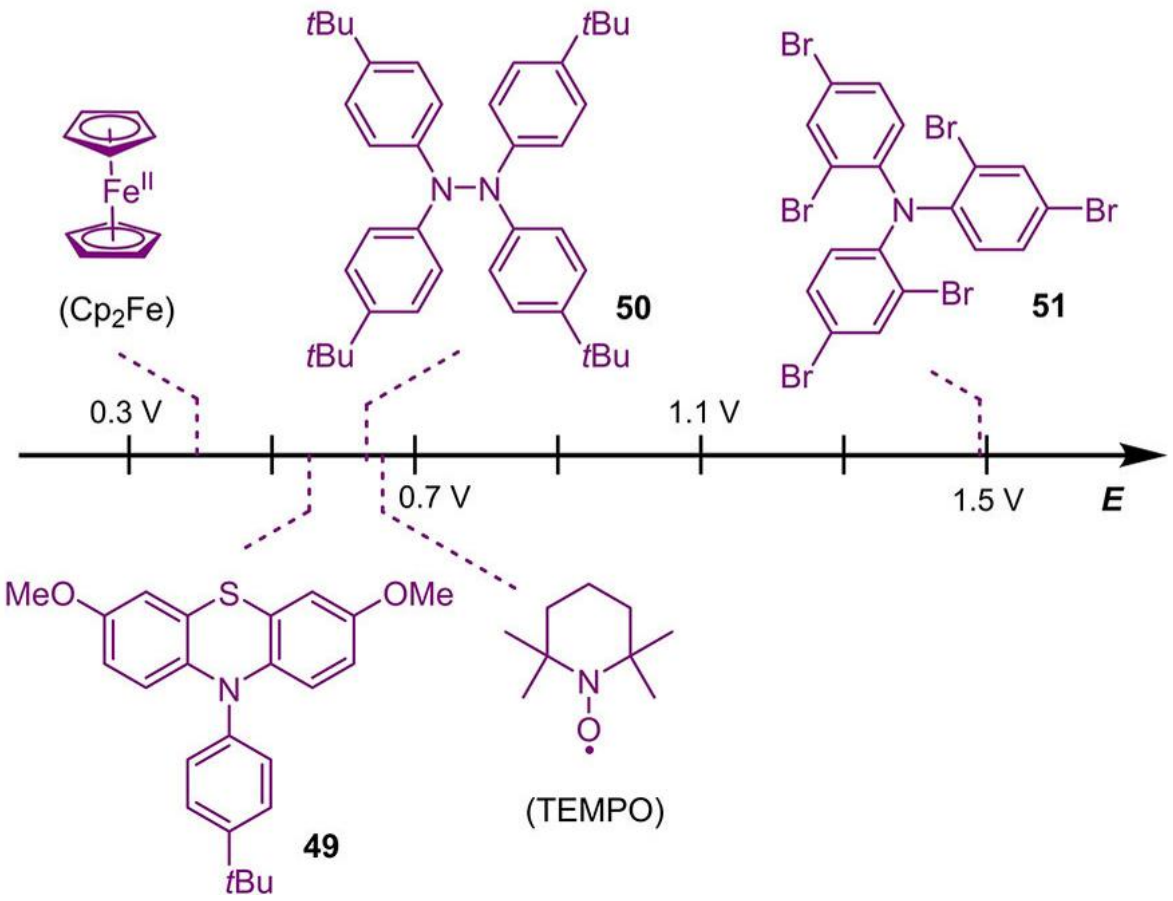
Mechanisms for molecular electrocatalysis

允许在远离电极的地方产生自由基中间体，局部浓度降低，副反应被抑制。同时，电极电势的降低，提供更好的化学选择性与立体选择性。

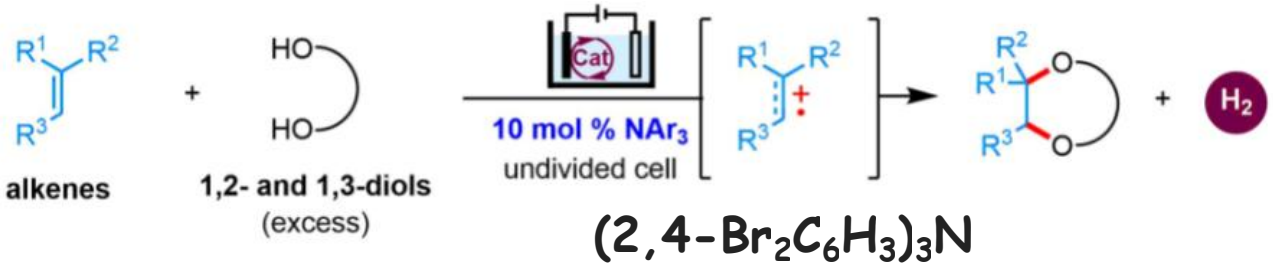


- 外球催化机制：催化剂与底物之间的电位间隙必须适当
- 内球催化机制：克服了催化剂与底物之间因大电位间隙导致无法有效反应的困难

Electrocatalysts employed in Xu's studies

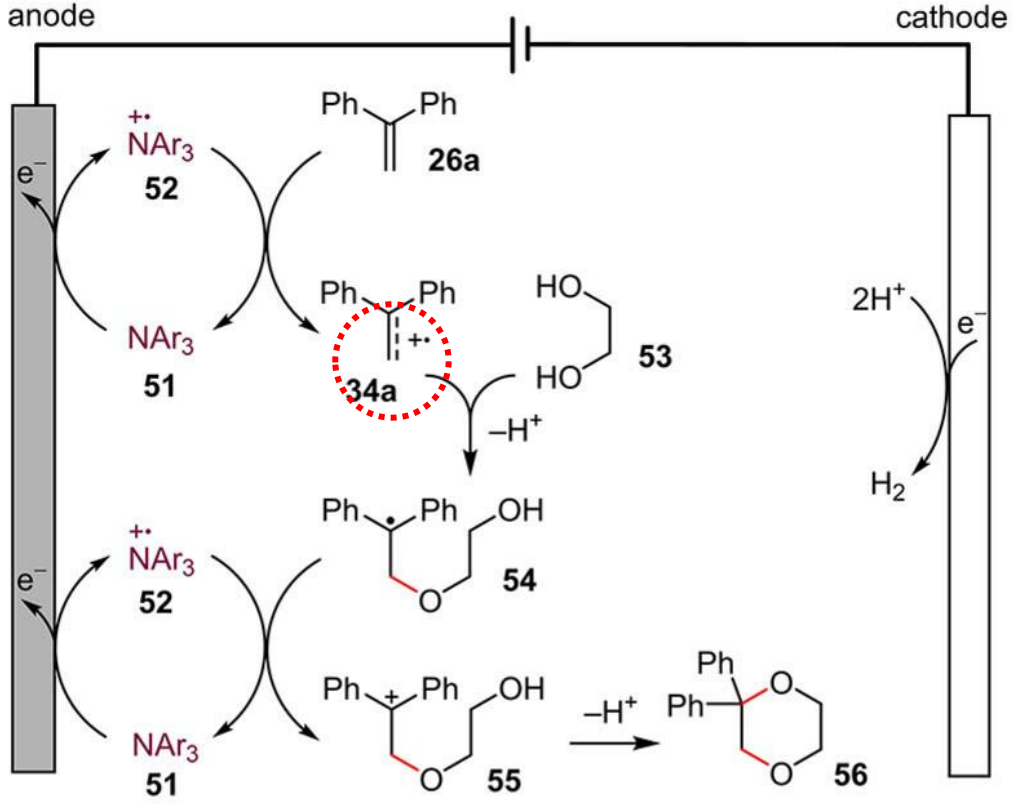


3.2.1 Radical Formation via Outer-sphere Mechanism

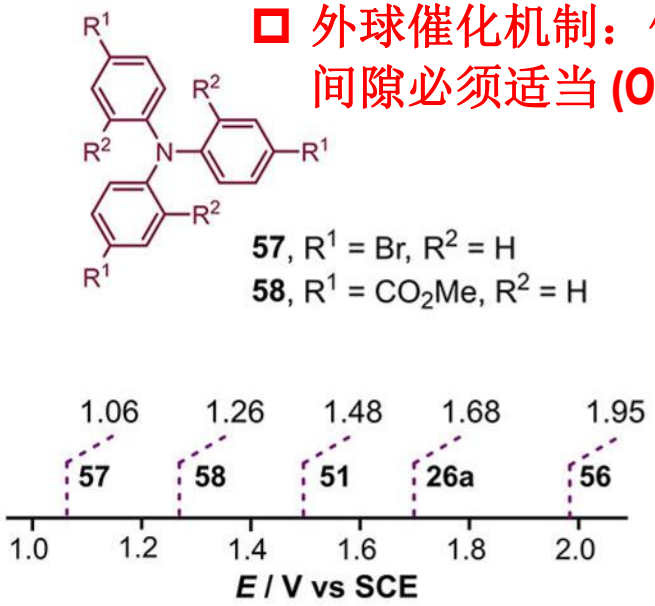


$(2,4\text{-}Br_2C_6H_3)_3N$

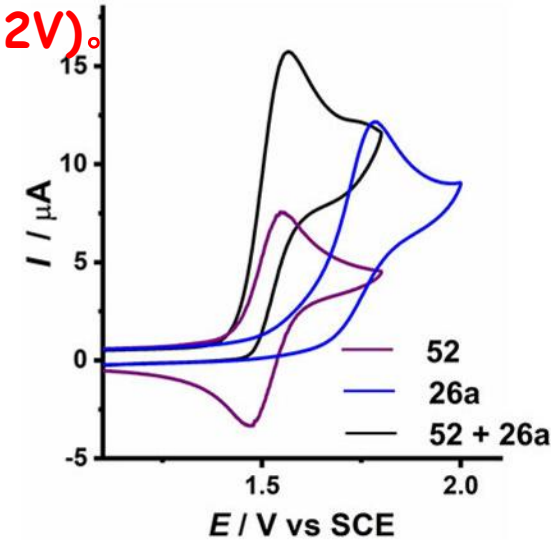
A. Mechanism for the electrocatalytic dehydrogenative alkene annulation with diols



B. Oxidation potentials

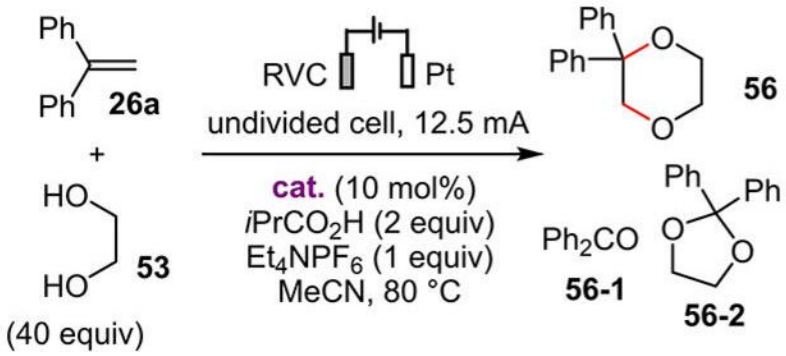


C. Cyclic voltammetry



- 外球催化机制：催化剂与底物之间的电位间隙必须适当 (0.2V)。

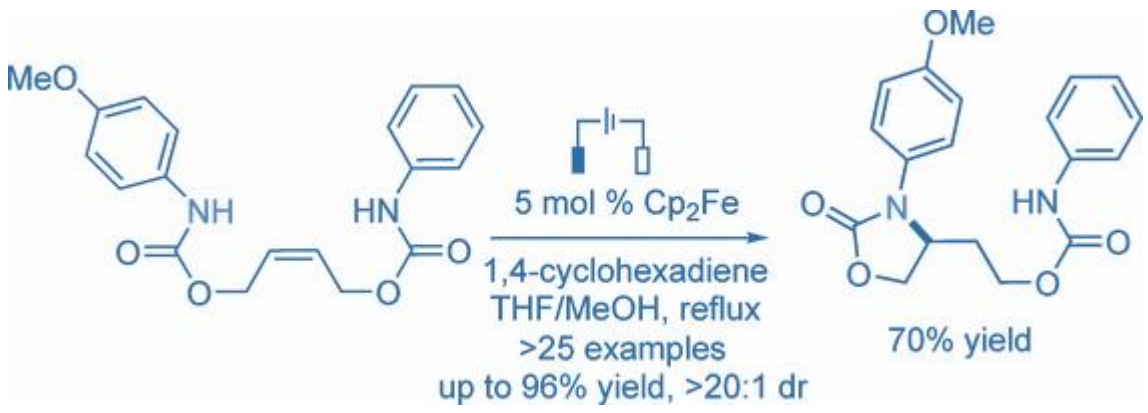
D. Electrocatalytic dehydrogenative alkene annulation with diols



cat.	yield% of 56
51	91
none	58 (6% of 56-1 and 16% of 56-2)
57	5 (65% of 26a)
58	44 (38% of 26a)

Nat. Commun. **2018**, *9*, 3551.

3.2.1 Radical Formation via Outer-sphere Mechanism

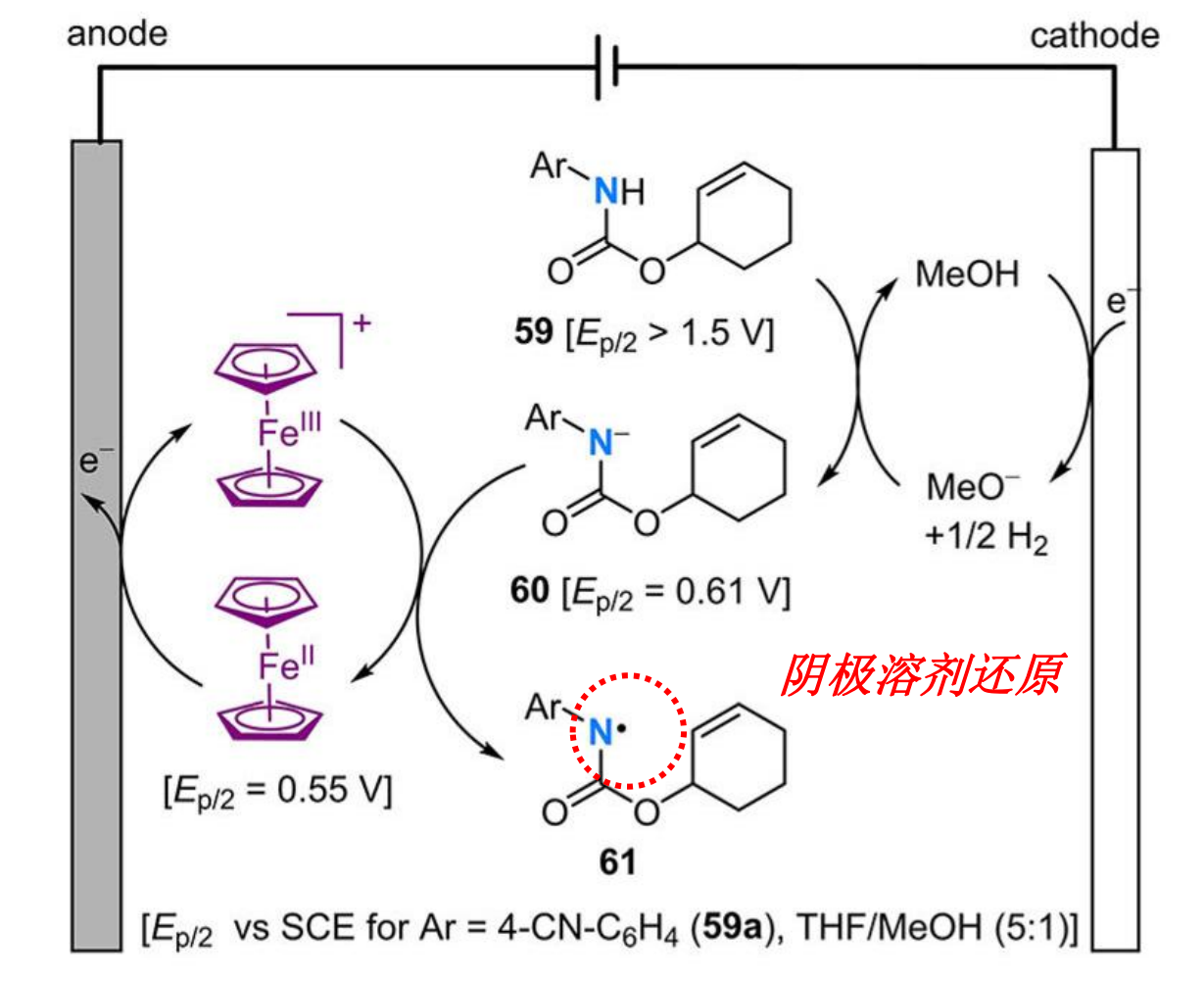


对于给定的X-H物种，通过X-H前体促进中性自由基形成所需的电势：

顺序质子/电子转移 < 反向电子/质子转移 < 质子耦合电子转移 (PCET)

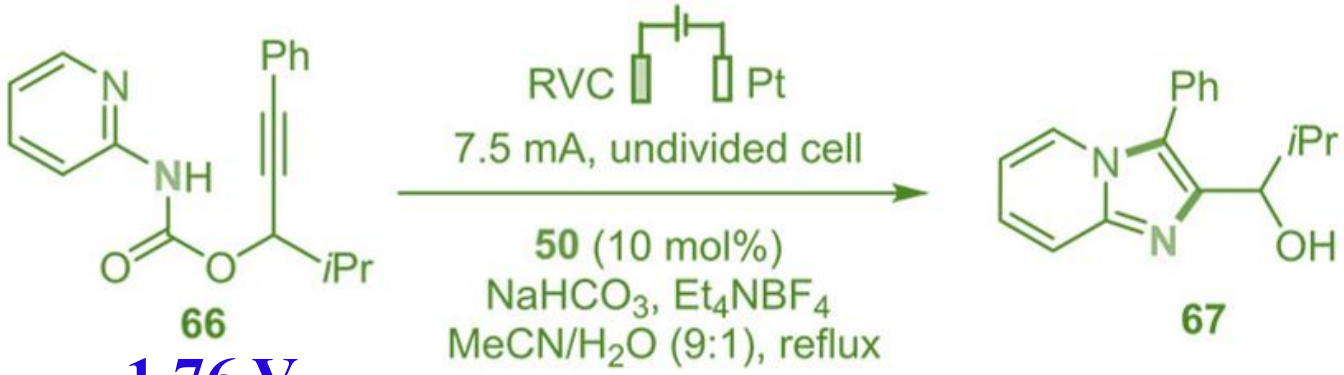
优选途径：电极电势温和，增加了官能团的耐受性

Proposed Mechanism



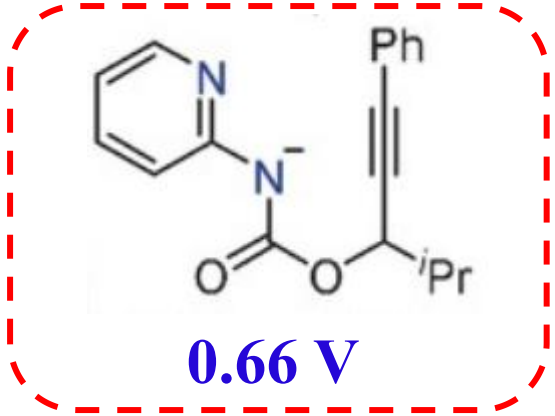
Angew. Chem. Int. Ed. **2016**, *55*, 2226.

3.2.1 Radical Formation via Outer-sphere Mechanism

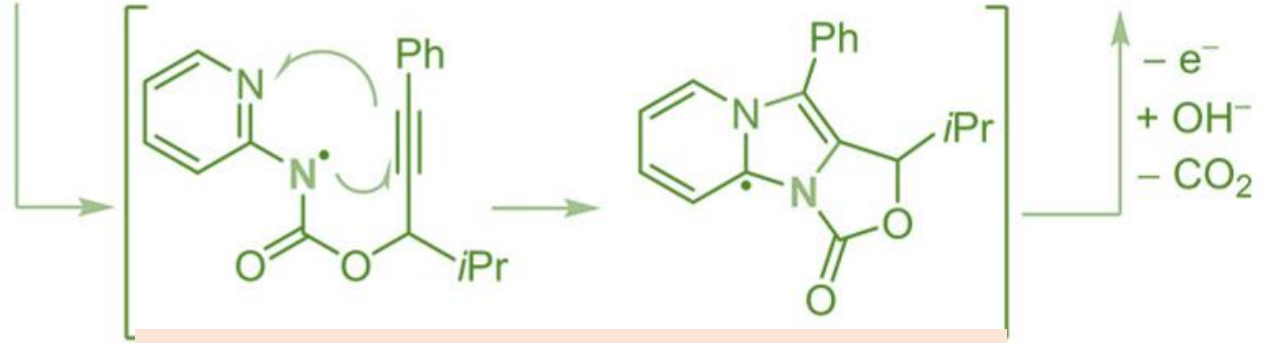


1.76 V

imidazo-fused heteroaromatics



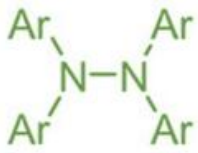
0.66 V



Cp_2Fe—0.55 V

✗

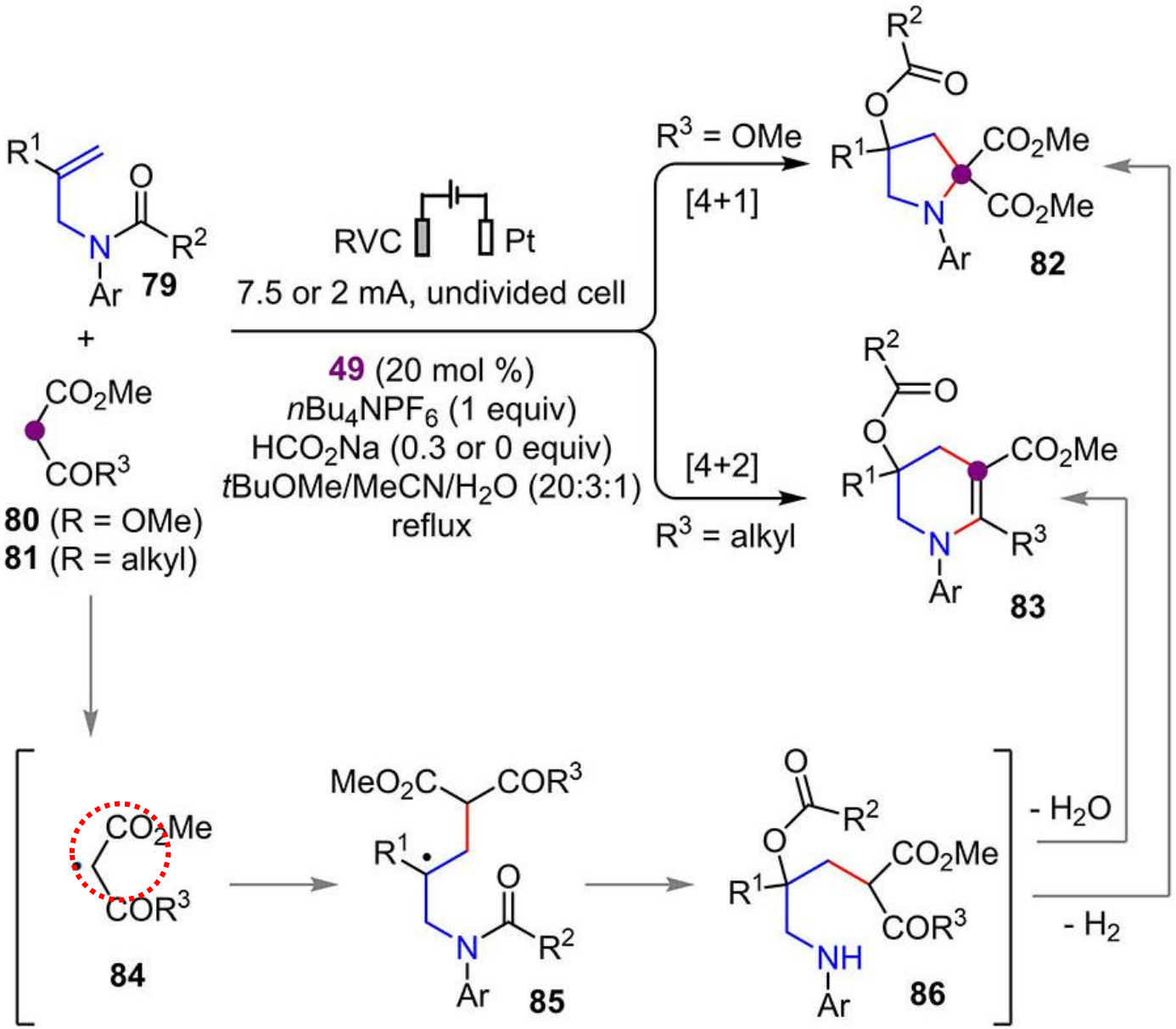
开发可进行结构改性的催化剂非常重要！



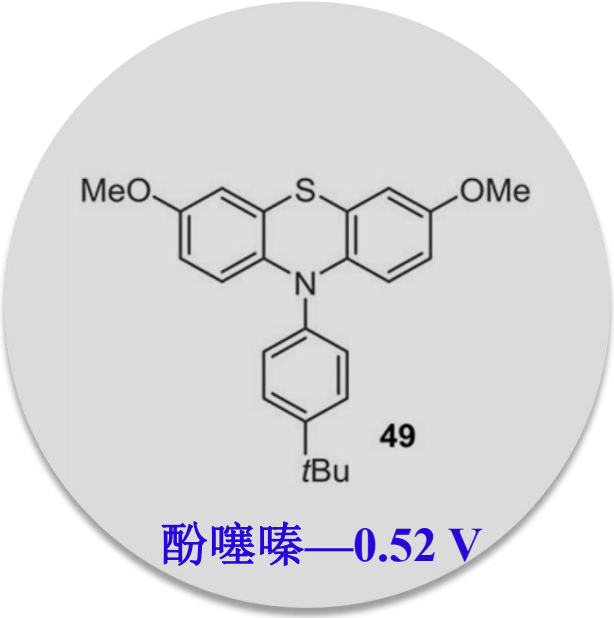
cat.	**50**, Ar = 4-*t*Bu-C_6H_4 [$E_{p/2}$ = 0.68 V vs SCE, MeCN/H_2O (9:1)]	**70**, Ar = 4-Me-C_6H_4 [$E_{p/2}$ = 0.64 V vs SCE, MeCN/H_2O (9:1)]
	67, 89% yield	**67**, 69% yield

Angew. Chem. Int. Ed. **2018**, *57*, 1636.

3.2.1 Radical Formation via Outer-sphere Mechanism

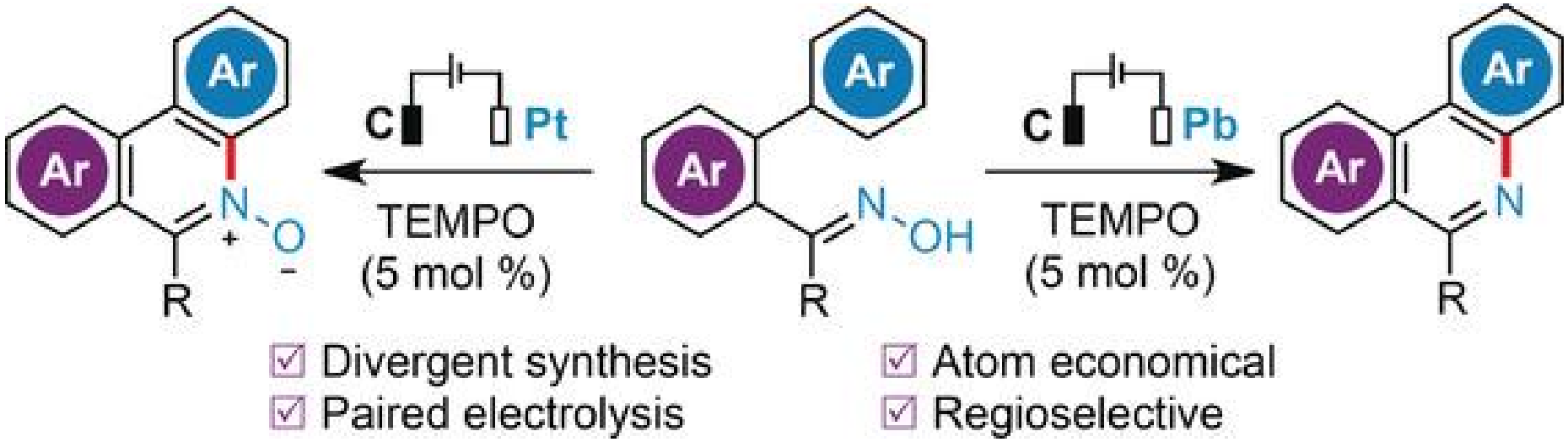


Electrocatalytic synthesis of N-heterocycles via dehydrogenative annulation



Angew. Chem. Int. Ed. **2018**, *57*, 14070.

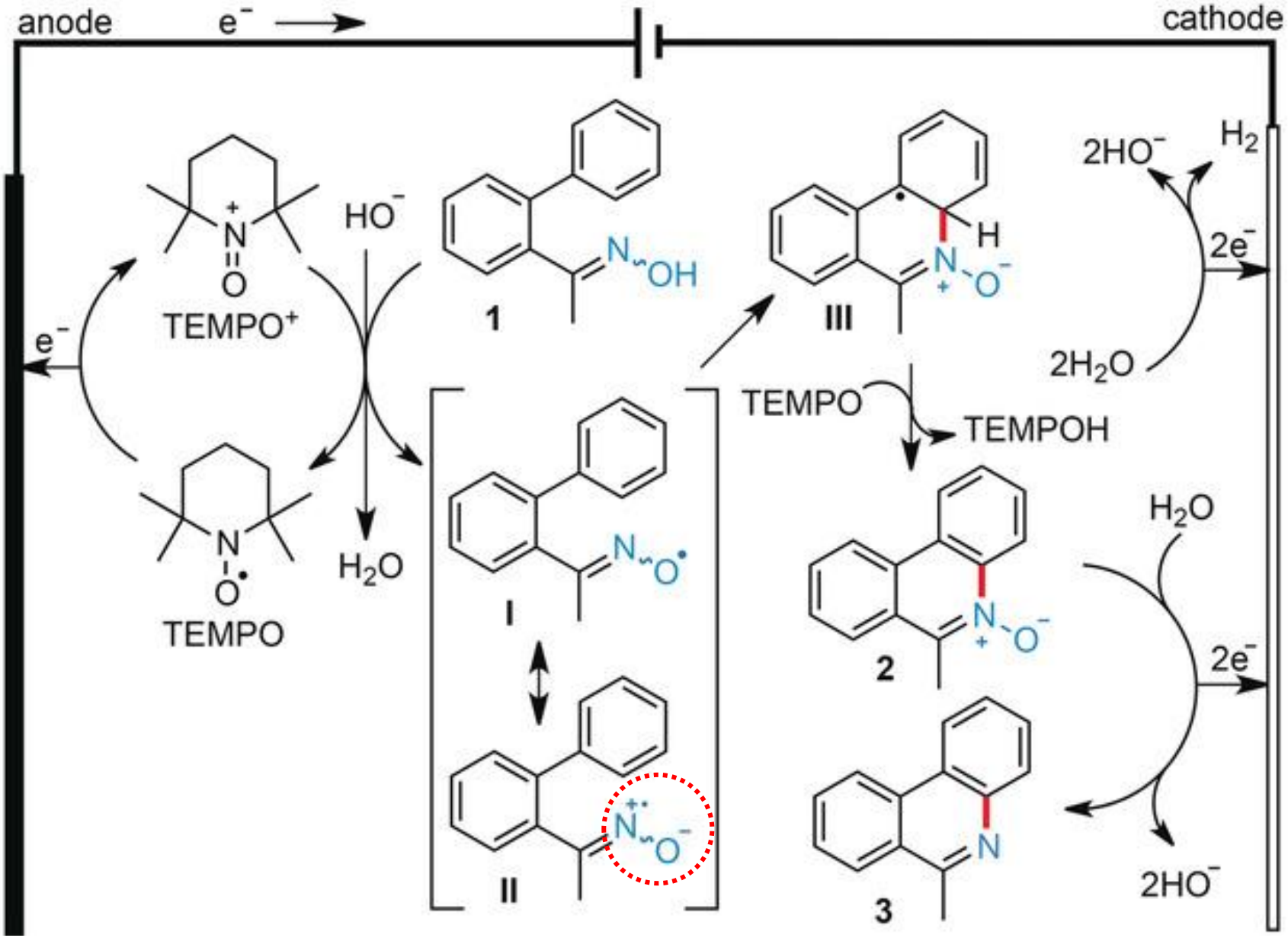
3.2.1 Radical Formation via Outer-sphere Mechanism



Angew. Chem. Int. Ed. **2018**, *57*, 14070.

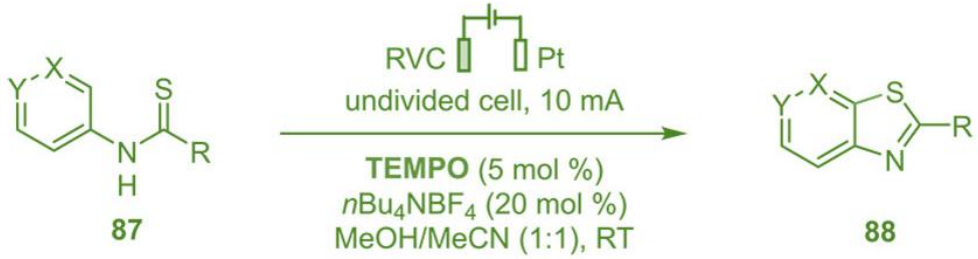
阴极材料可以有选择性：从易得“联芳酮肟底物”选择性生成C-H官能团化产物！

3.2.1 Radical Formation via Outer-sphere Mechanism

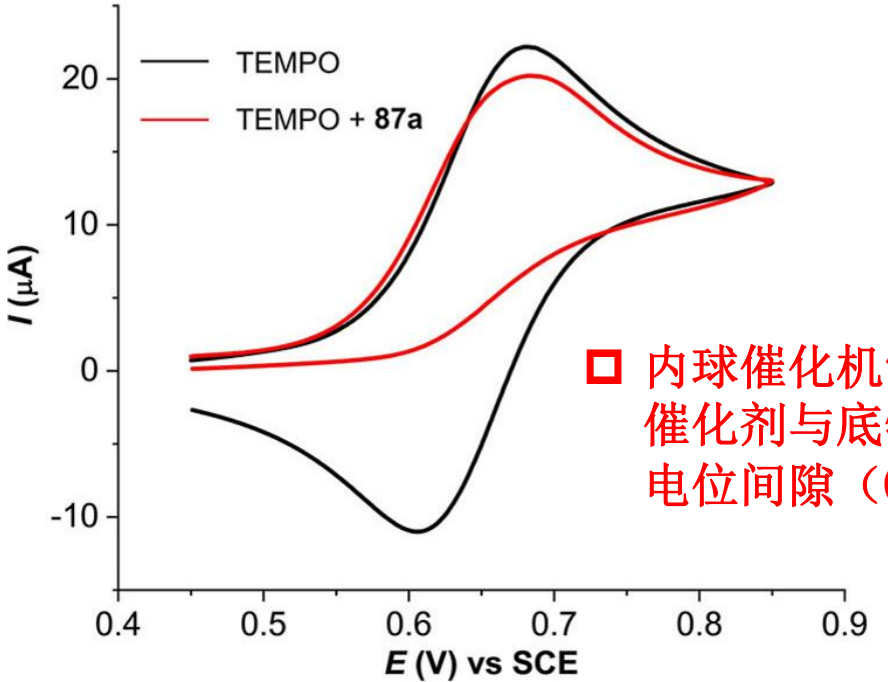


3.2.2 Radical Formation via Inner-sphere Mechanism

Electrocatalytic cyclization of N-aryl thioamides

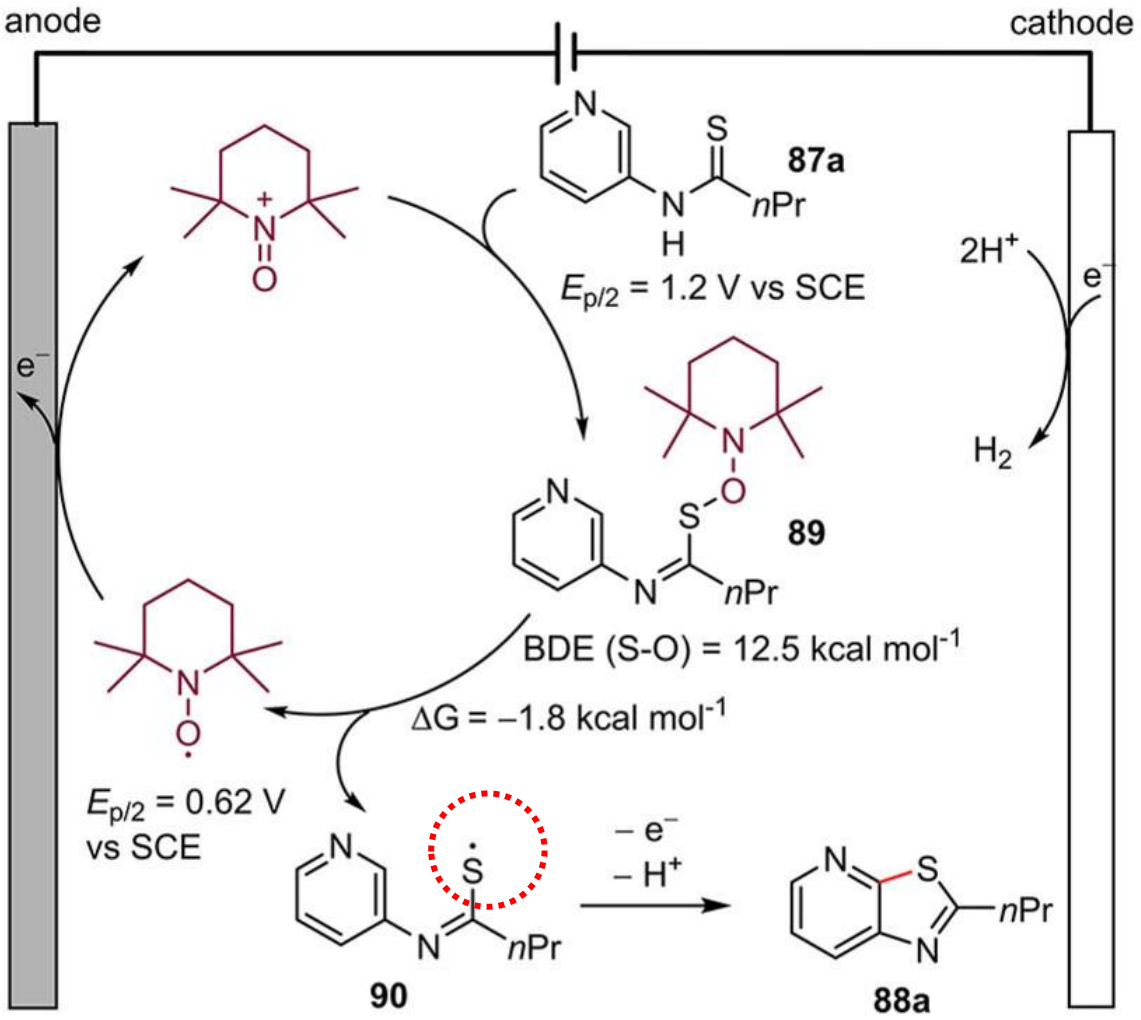


B. Cyclic voltammograms of TEMPO



- 内球催化机制：克服了催化剂与底物之间大的电位间隙（**0.58V**）。

Proposed mechanism



ACS Catal. **2017**, *7*, 2730.

3.3 Molecular electrophotocatalysis

能够触及更加广泛的氧化还原电势，可以在温和的电极电势下实现强氧化或还原能力

Electrocatalysis

可调谐性&无试剂性

Photoredox Catalysis

独特的选择性&反应性

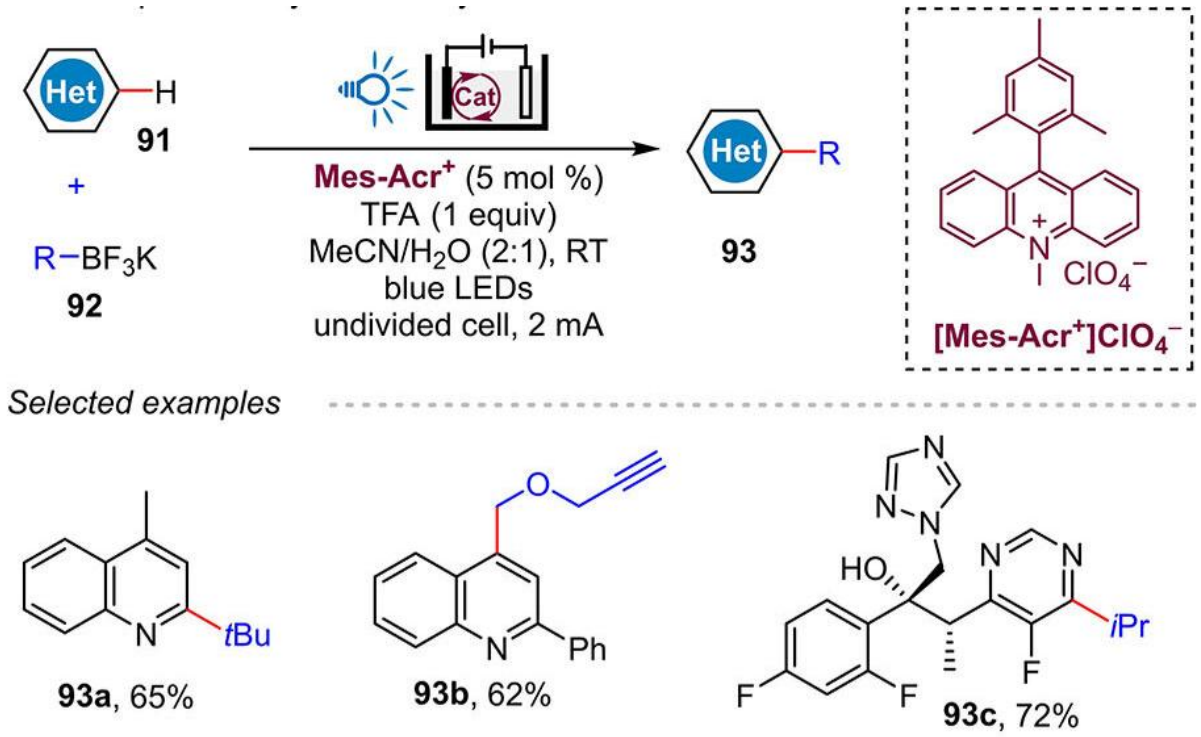
→ ***Remarkably effective “ 1 +1 >2 ”***

Advantage：

- ✓ 利用催化剂可以在**电极电势较低的条件下**去氧化底物**产生自由基物种**。
- ✓ 独特**瞬态激发态**特性，可以氧化**氧化电位更高的底物**，瞬态的性质避免产物发生过氧化，为反应的发现提供了非常大的机会。

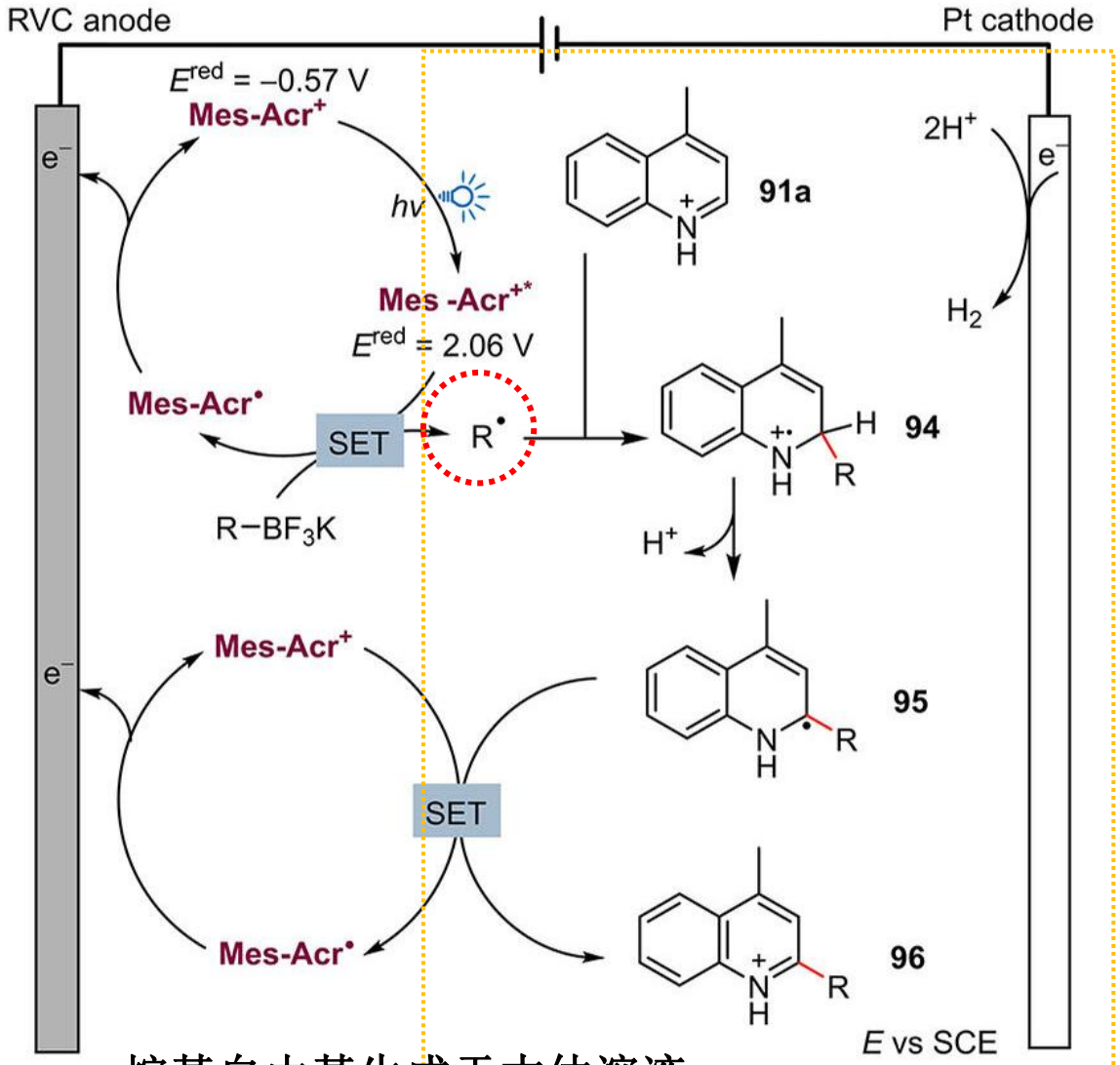
3.3 Molecular electrophotocatalysis

Electrophotocatalytic C-H alkylation of heteroarenes



Angew. Chem. Int. Ed. **2019**, *58*, 4592.

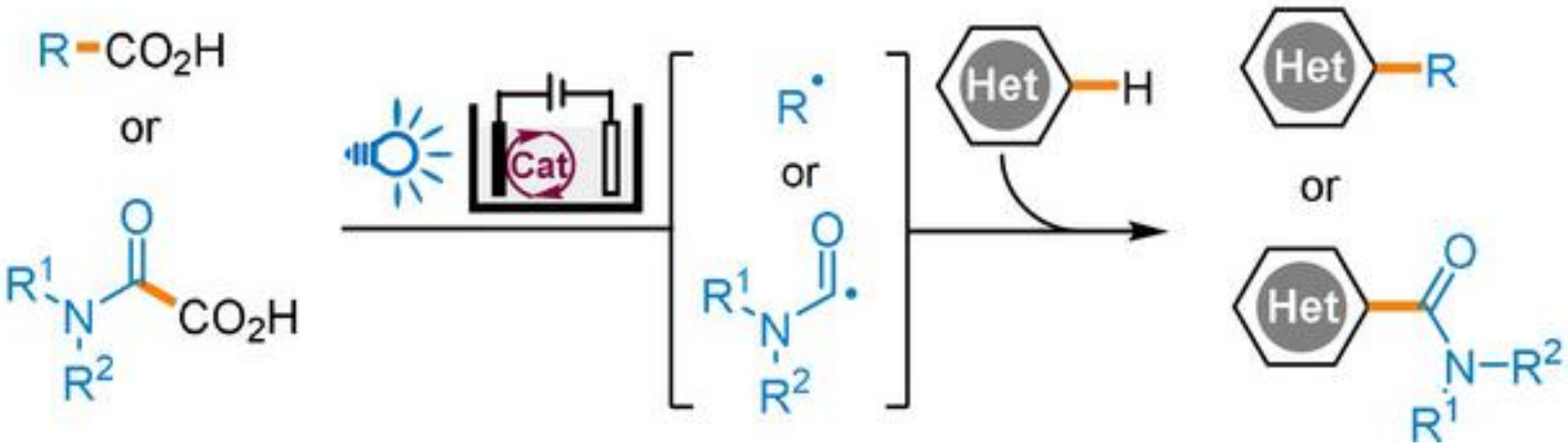
B. Mechanism for electrophotocatalytic C-H alkylation of heteroarenes



烷基自由基生成于本体溶液

3.3 Molecular electrophotocatalysis

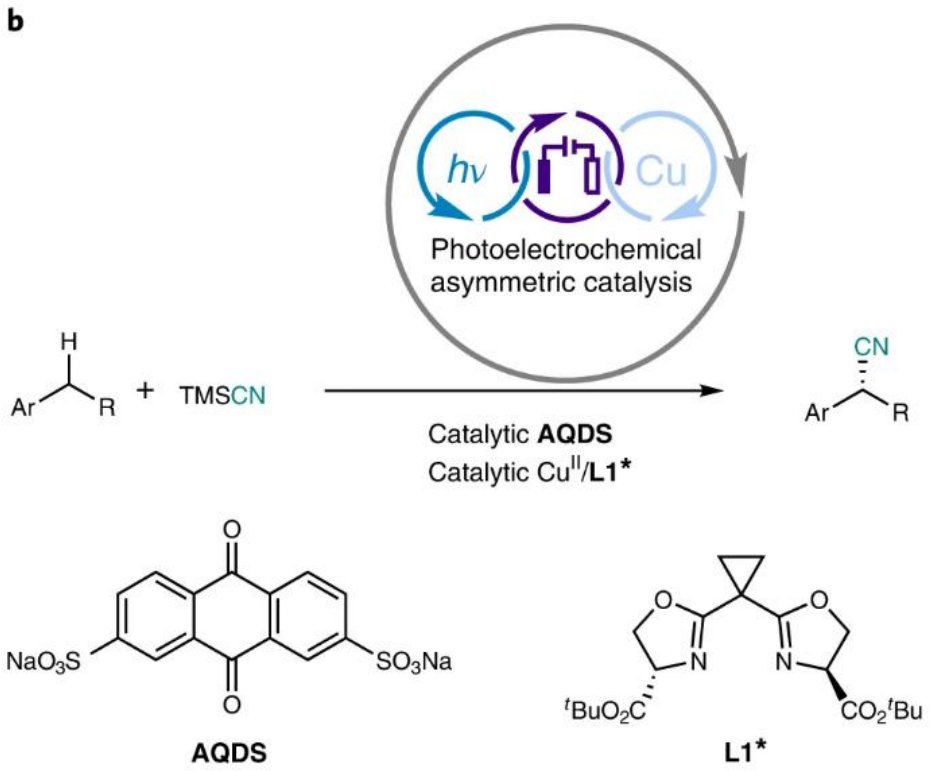
Electrophotocatalytic Decarboxylative C−H Functionalization of Heteroarenes

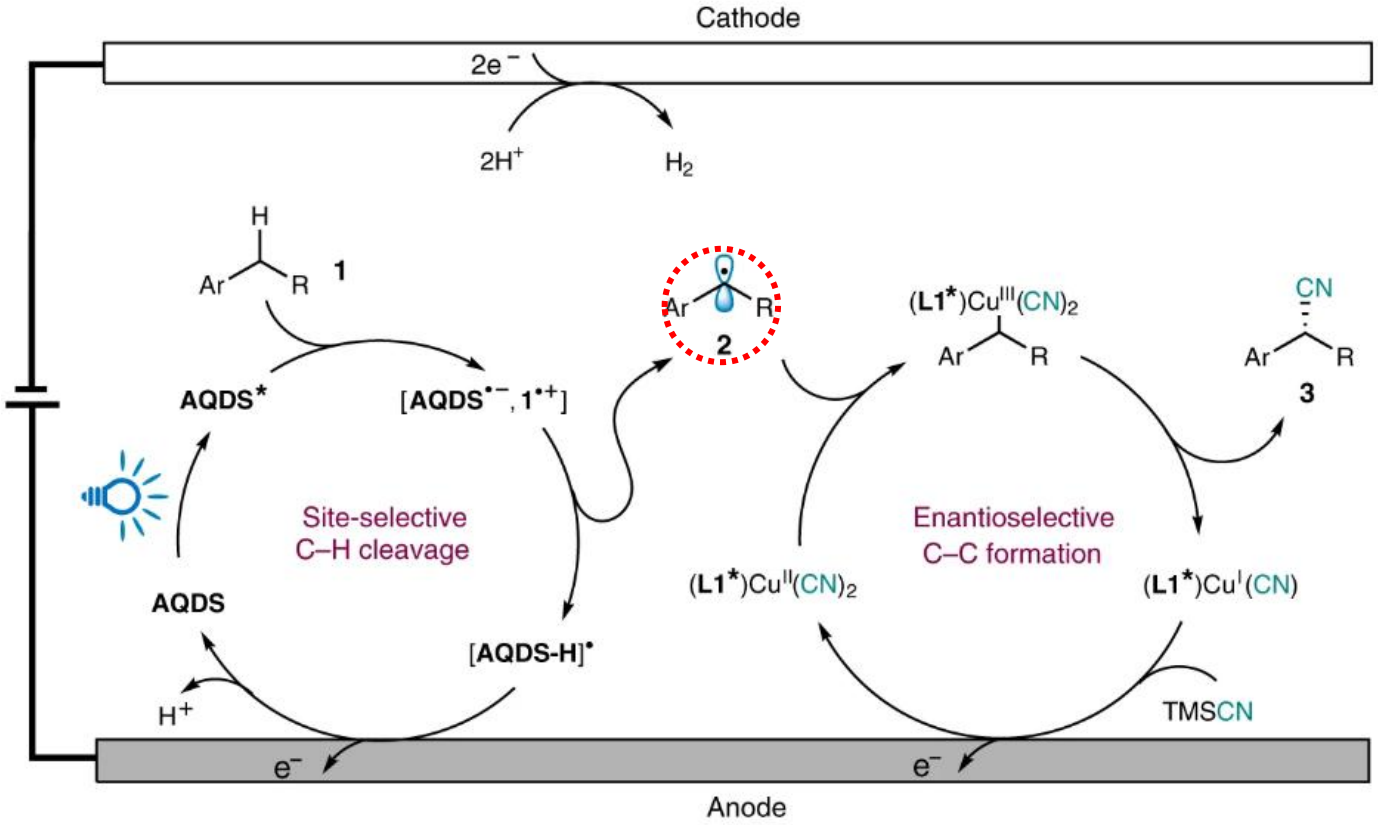


Angew. Chem. Int. Ed. **2020**, *59*, 10626.

3.3 Molecular electrophotocatalysis

Photoelectrochemical asymmetric catalysis enables site- and enantioselective cyanation of benzylic C–H bonds

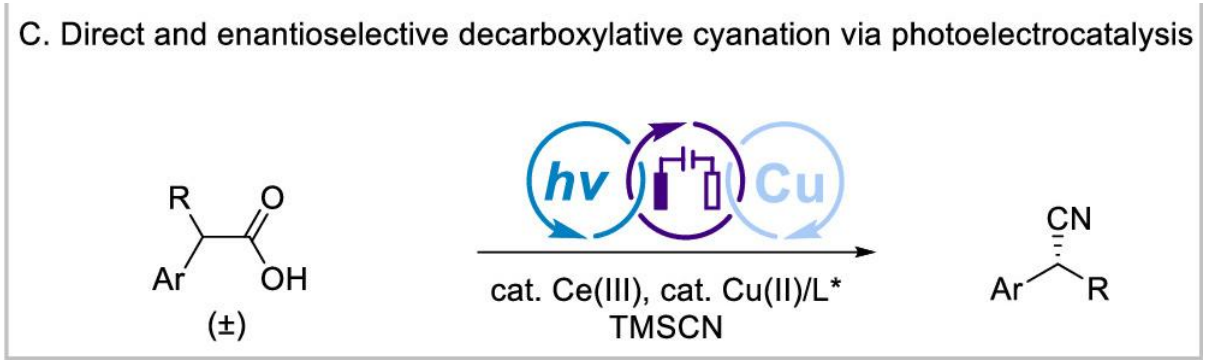


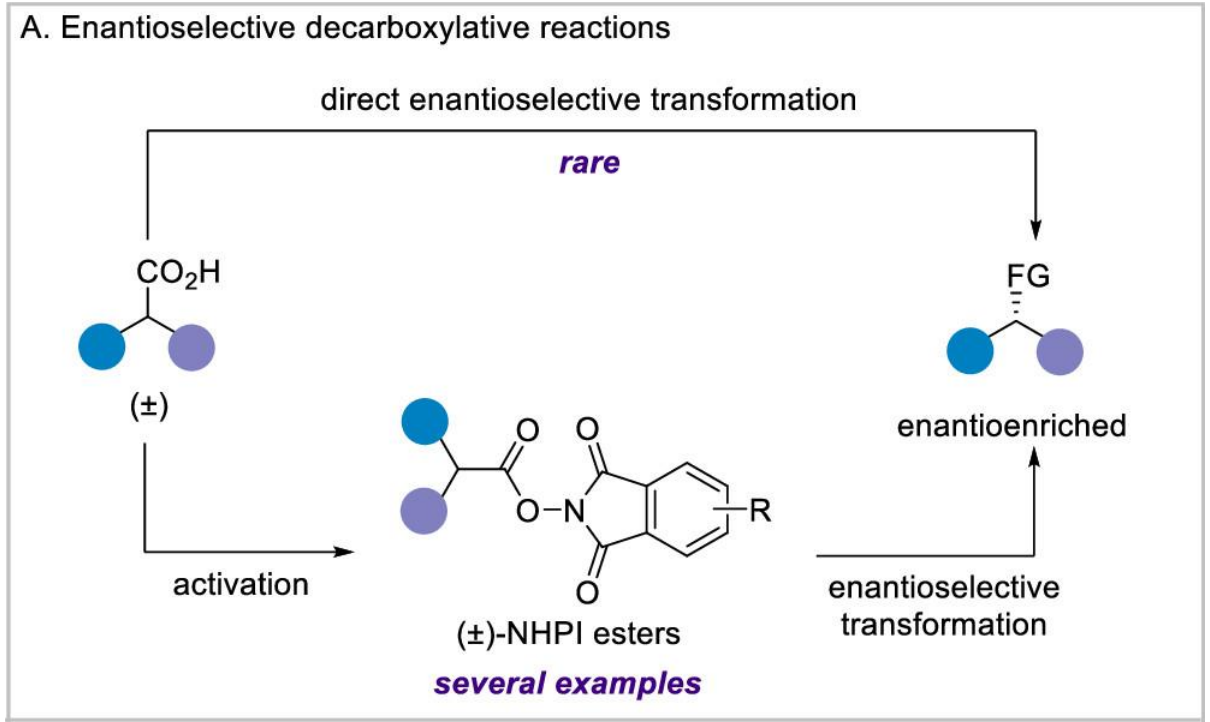


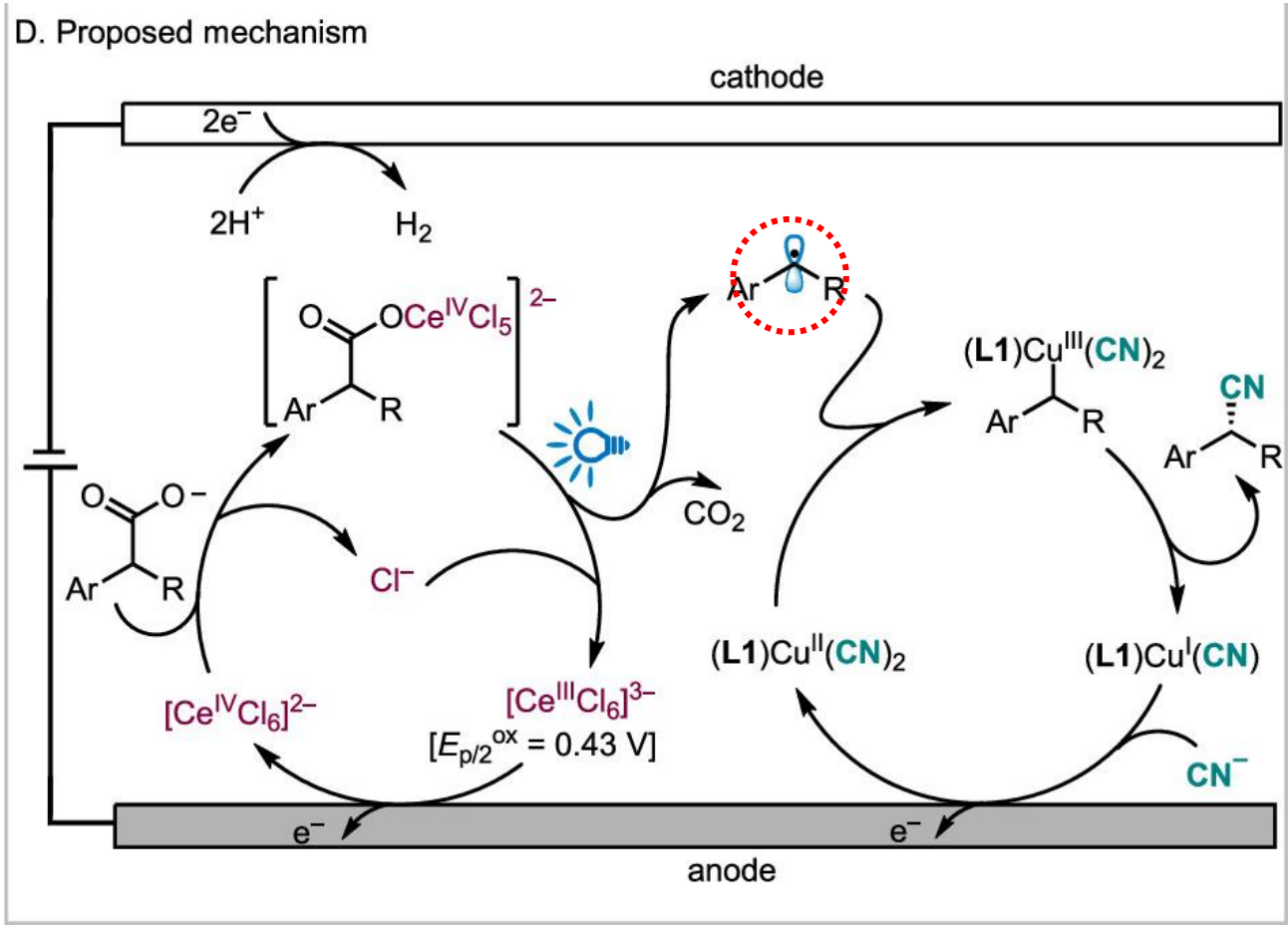
Nat. Catal. **2022**, *5*, 943-951.

3.3 Molecular electrophotocatalysis

Photoelectrochemical asymmetric catalysis enables direct and enantioselective decarboxylative cyanation

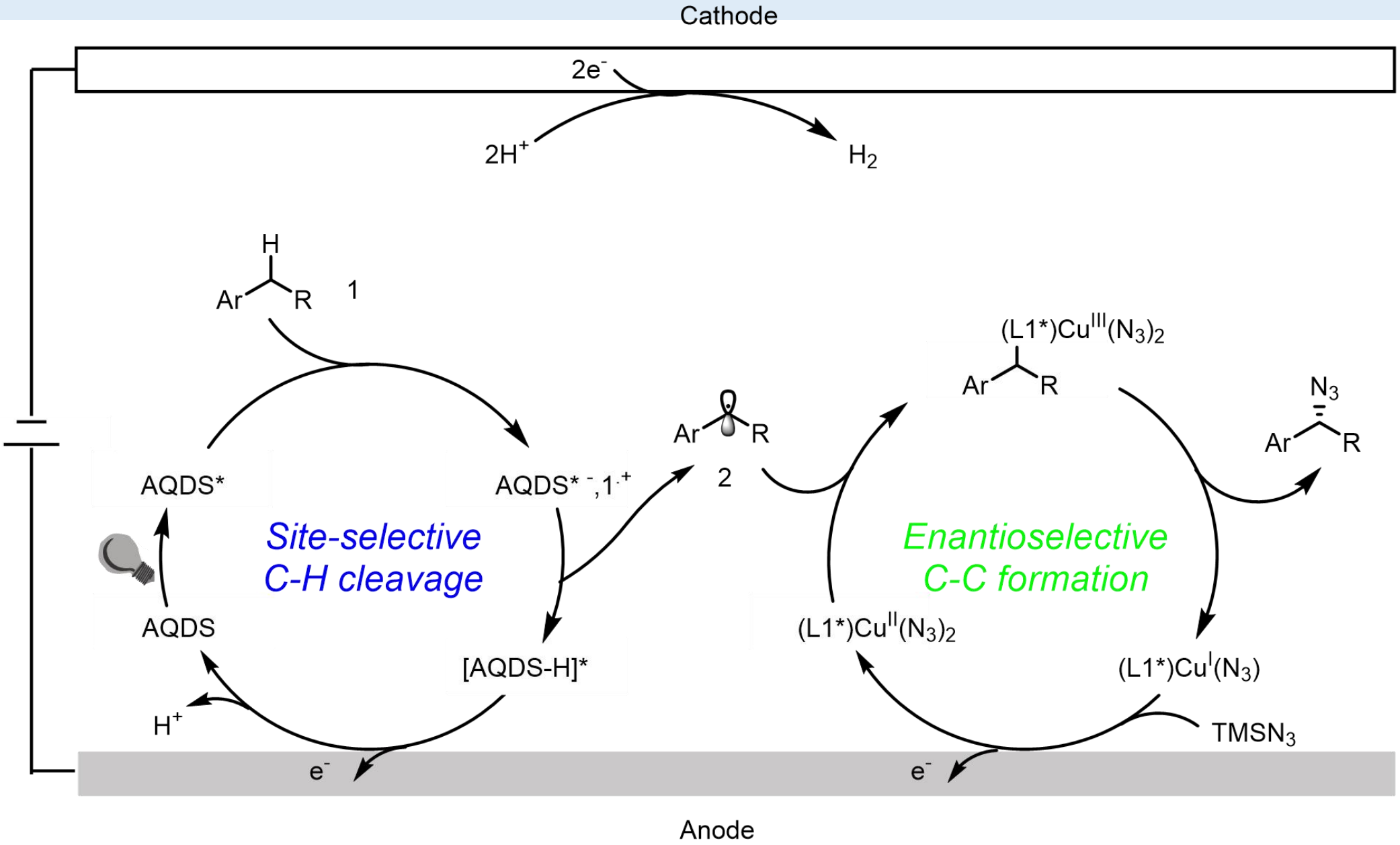






J. Am. Chem. Soc. **2022**, *144*, 20201-20206.

4. Proposal


Cathode
2e⁻
2H⁺
H2
H
Ar
R
1
AQDS*
AQDS* ⁻,1·⁺
Site-selective
C-H cleavage
AQDS
[AQDS-H]*
H⁺
e⁻
Ar
R
2
(L1*)Cu^III(N3)2
Ar
R
N3
Ar
R
Enantioselective
C-C formation
(L1*)Cu^II(N3)2
(L1*)Cu^I(N3)
TMSN3
e⁻
Anode

Thanks for you listening!