

电催化C-H键胺化反应研究进展

汇报人：易小斐

导师：施章杰 教授

2024.9.27



目录

- 一、研究背景与意义
- 二、电催化的 sp^2 C-H胺化反应
- 三、电催化的 sp^3 C-H胺化反应
- 四、总结与展望

目录

一、研究背景与意义

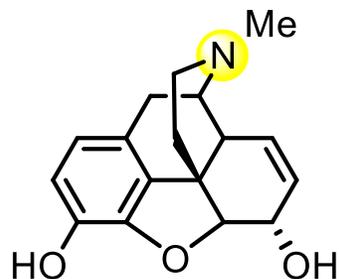
二、电催化的 sp^2 C-H胺化反应

三、电催化的 sp^3 C-H胺化反应

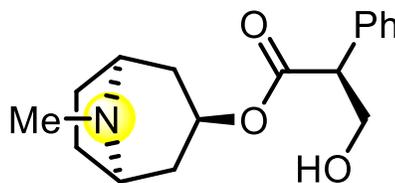
四、总结与展望

1.1 研究背景-含氮有机化合物的重要性

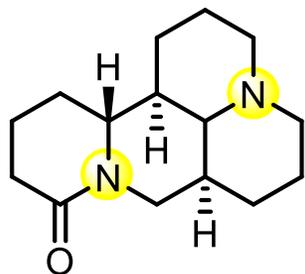
a) Natural Products



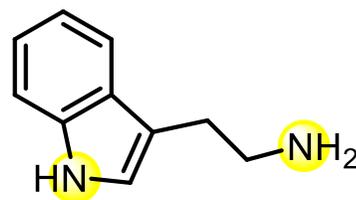
Morphine (吗啡)



Atropine (阿托品)

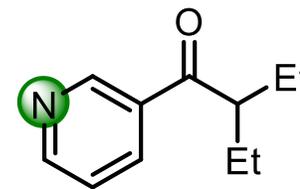


Matrine (苦参碱)

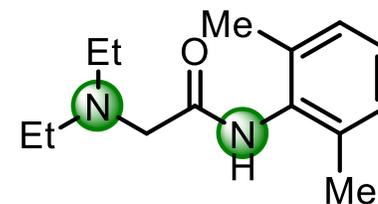


Tryptamine (色胺)

b) Emergency Medicines

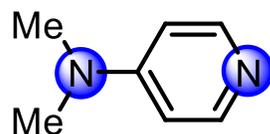


Coramine (可拉明)

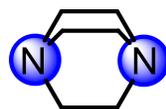


Lidocaine (利多卡因)

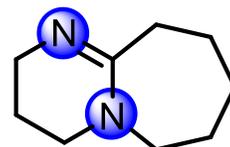
c) Catalysts



DMAP

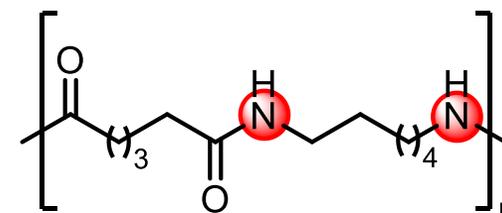


DABCO



DBU

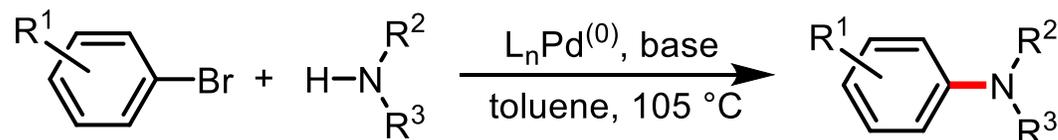
d) Materials



Polyadipohexylenediamine (尼龙-66)

1.2 研究背景-交叉偶联形成C-N键的方法

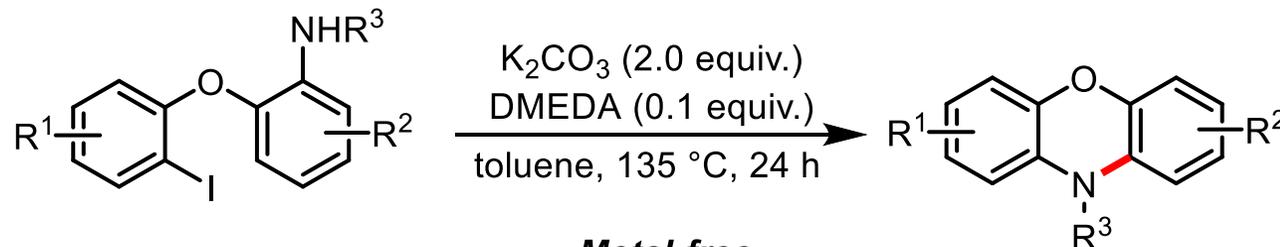
a) Buchwald-Hartwig coupling reaction



High chemo-selectivity
High reaction efficiency

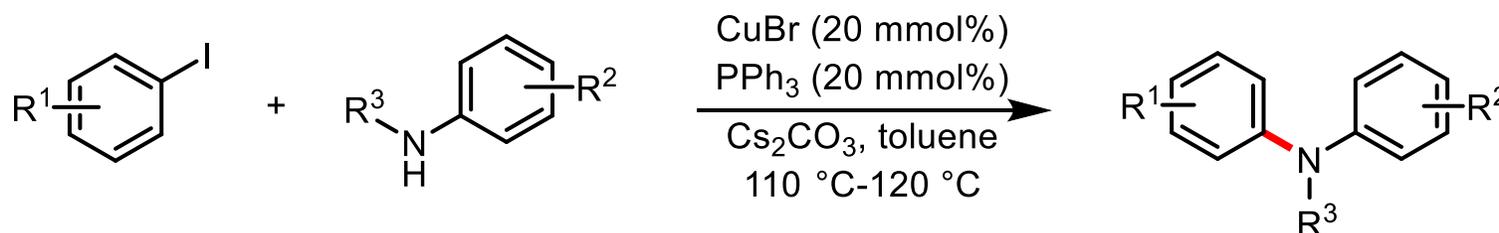
High cost
Potential toxicity
Activated substrates

c) Metal-free C-N bond formation



Metal-free
Harsh conditions
Activated substrates

b) Ullmann coupling reaction



High chemo-selectivity
High reaction efficiency

Potential toxicity
Activated substrates

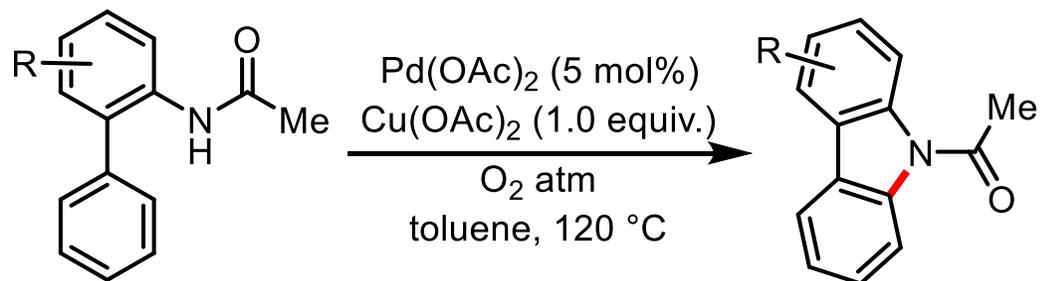
a) S. L. Buchwald, et al. *J. Am. Chem. Soc.* **1994**, *116*, 7901-7902

b) D. Venkataraman, et al. *Tetrahedron Lett.* **2001**, *42*, 4791-4793

c) C. Bolm, et al. *Org. Lett.* **2012**, *14*, 1892-1895

1.3 研究背景-C-H键直接胺化

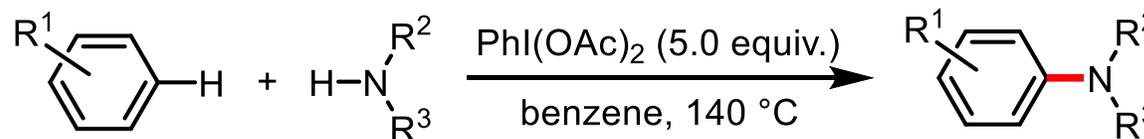
a) Buchwald's CDC amination reaction



High chemo-selectivity
High reaction efficiency

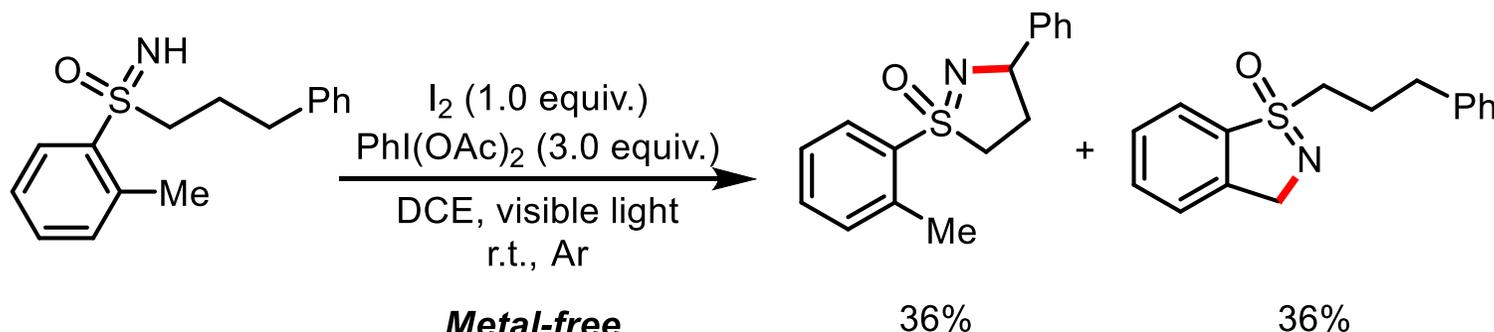
High cost
Potential toxicity
Directing-group

b) C-H Bond Oxidative Amination without Transition Metal



Metal-free
Harsh conditions
Excess amounts of oxidant

c) Hofmann-Löffler-Freytag (HLF) Reactions



Metal-free
Poor chemo-selectivity
Hard purification



Without Oxidant
Without Transition Metal
High Chemo-selectivity

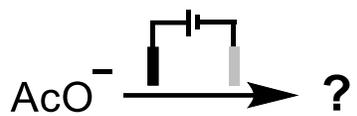
a) S. L. Buchwald, et al. *Angew. Chem. Int. Ed.* **2008**, 47, 1932-1934

b) S. H. Cho, S. Chang, et al. *J. Am. Chem. Soc.* **2011**, 133, 16382-16385

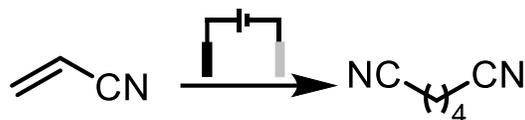
c) C. Bolm, et al. *Adv. Synth. Catal.* **2017**, 359, 4274-4277

1.4 有机电化学的发展

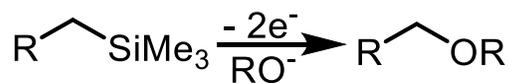
[1833]
Faraday's laws of
electrolysis



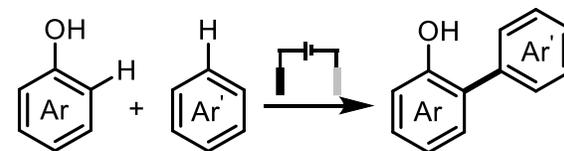
[1965]
Monsanto
adiponitrile process



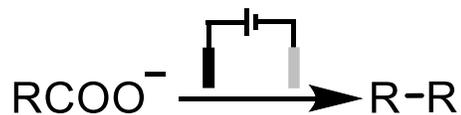
[1986]
Yoshida electroauxiliaries



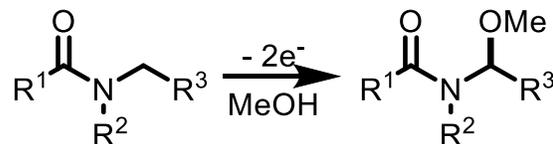
[2012]
Waldvogel Biaryl coupling



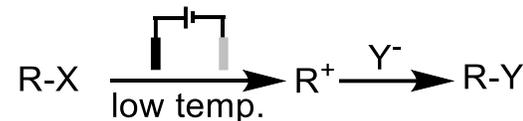
[1849]
Kolbe reaction



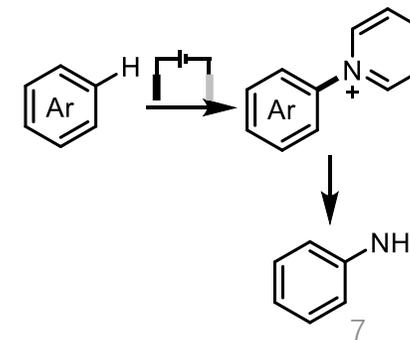
[1975]
Shono oxidation



[1999]
Yoshida's cation pool

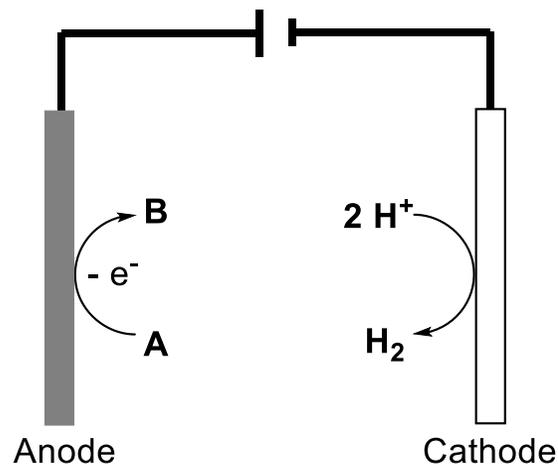


[2013]
Yoshida C-H amination

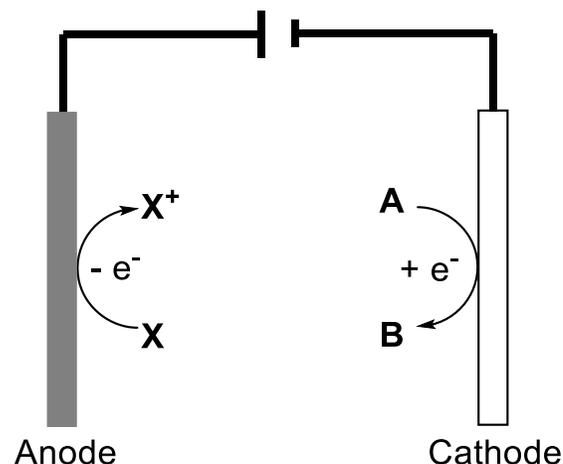


1.5 有机电化学反应简介

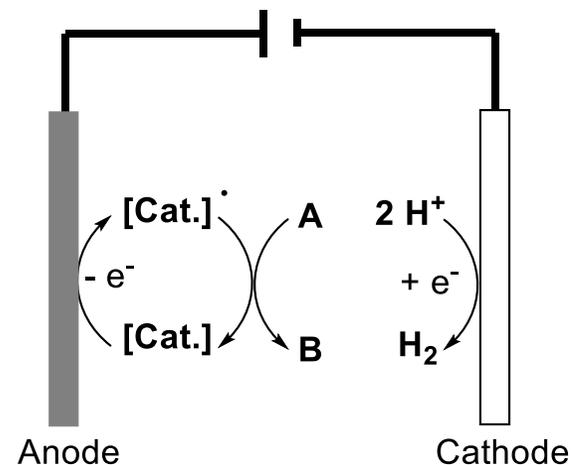
四种不同的反应类型



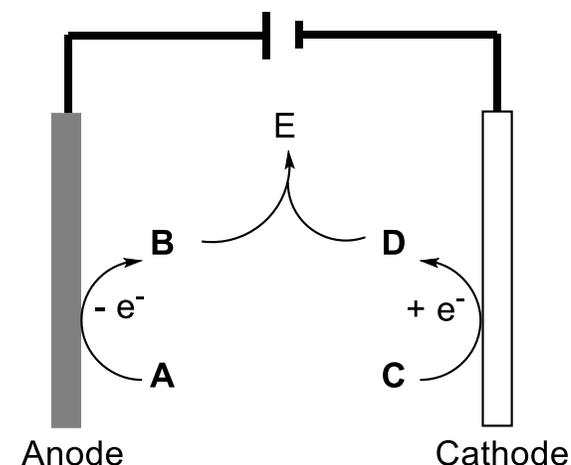
Anodic oxidation



Cathodic reduction



Oxidation by catalyst



Oxidation & reduction

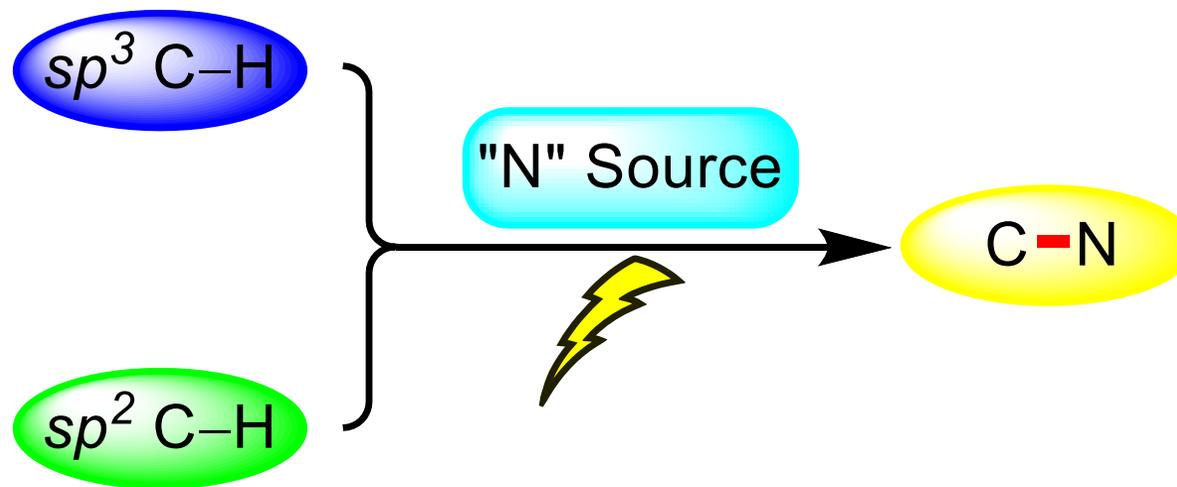
两种不同的电解模式

恒电流	恒电压
电势随反应进行增大	电流随反应进行变小
反应速度快, 转化率高	反应速度慢, 转化率低
反应选择性差	反应选择性好

有机电化学反应的优势

- 1) 底物在电极得失电子
- 2) 反应条件温和
- 3) 反应选择性高, 易于纯化

1.6 目标：实现C-H胺化与电催化结合



- ◆ *Without Oxidants*
- ◆ *Without Transition Metals*
- ◆ *High Chemo-selectivity*



目录

一、研究背景与意义

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三、电催化的 sp^3 C-H胺化反应

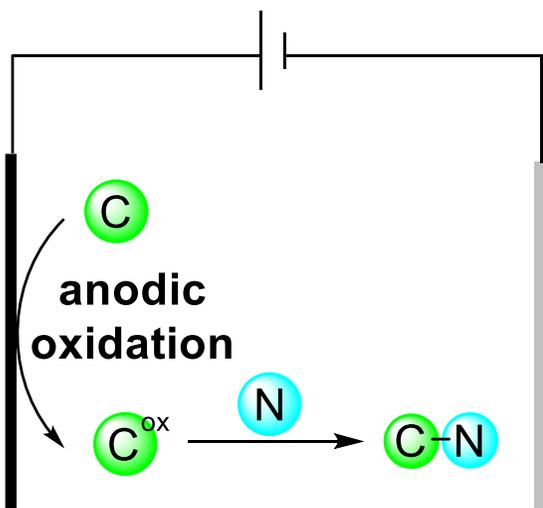
四、总结与展望

电催化 sp^2 C-H键胺化主要的四种类型

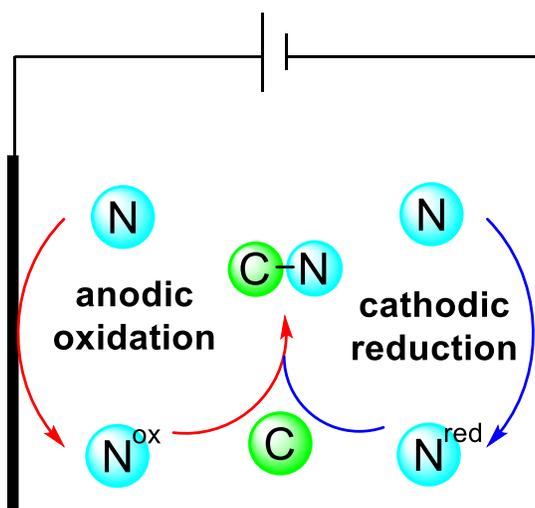
底物参与电极反应

底物不参与电极反应

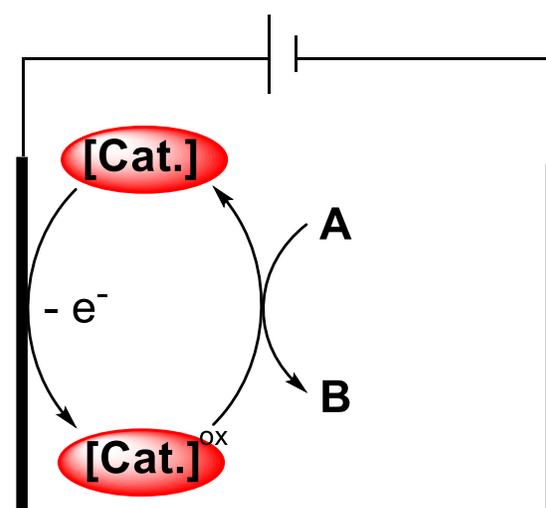
碳源启动的C-H键胺化



氮源启动的C-H键胺化



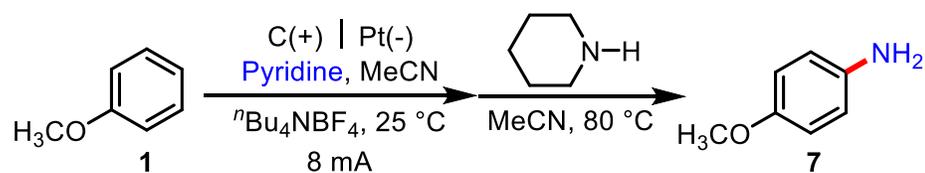
催化剂参与电极反应



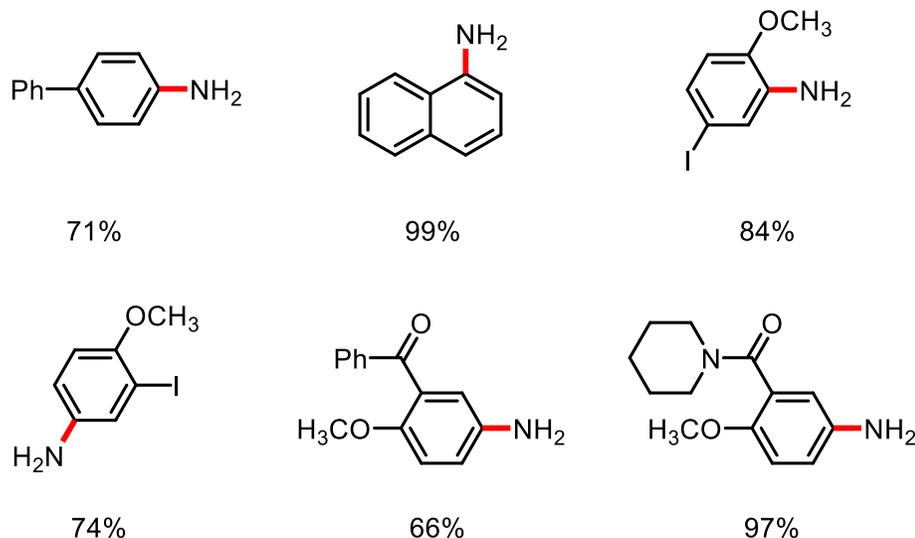
2.1 底物直接参与电极反应

2.1.1 碳源启动的C-H键氧化胺化

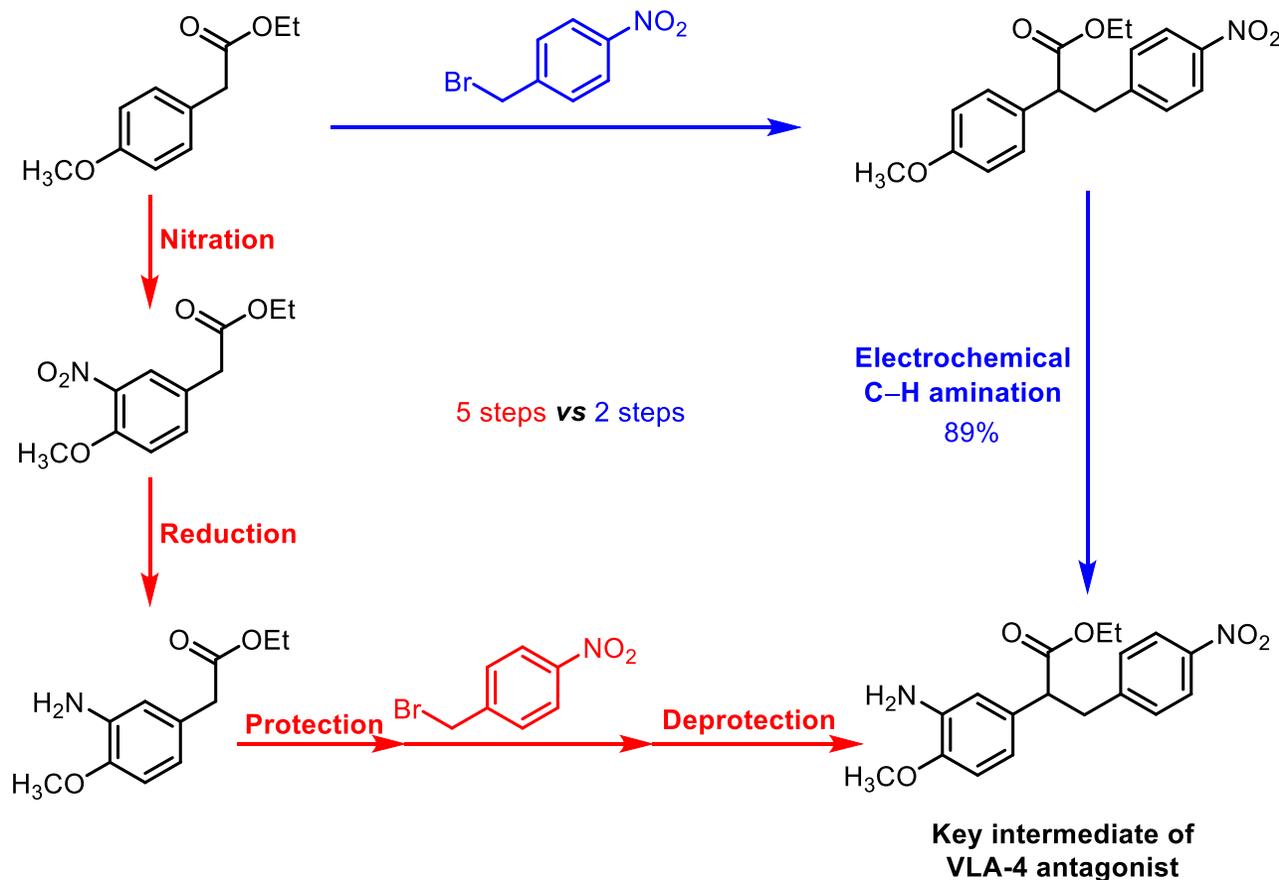
首例电催化 sp^2 C-H胺化



Representative products



Synthetic application

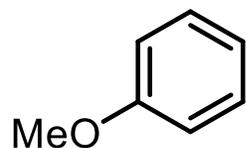
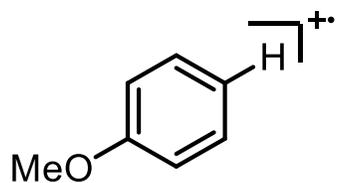
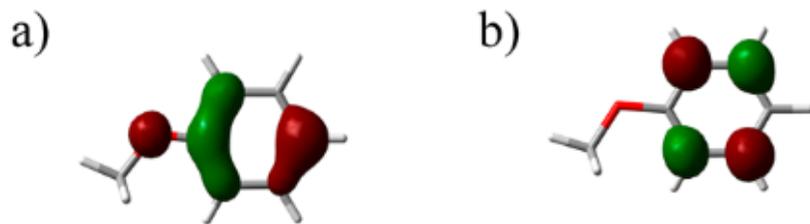


Jun-ichi Yoshida
Kyoto University
(1953-2019)

2.1 底物直接参与电极反应

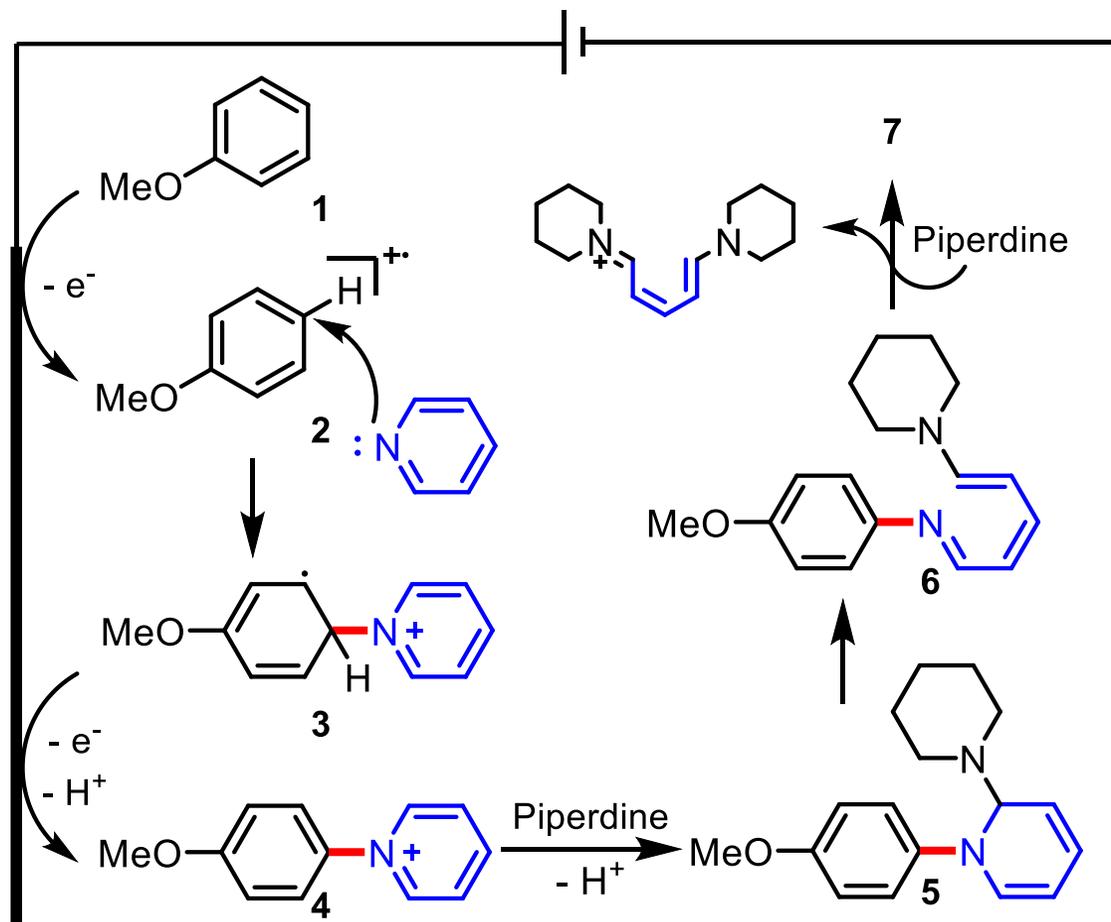
2.1.1 碳源启动的C-H键氧化胺化

DFT calculations



The lowest unoccupied molecular orbitals obtained by DFT calculations (B3LYP/6-31G*)

Proposed mechanism

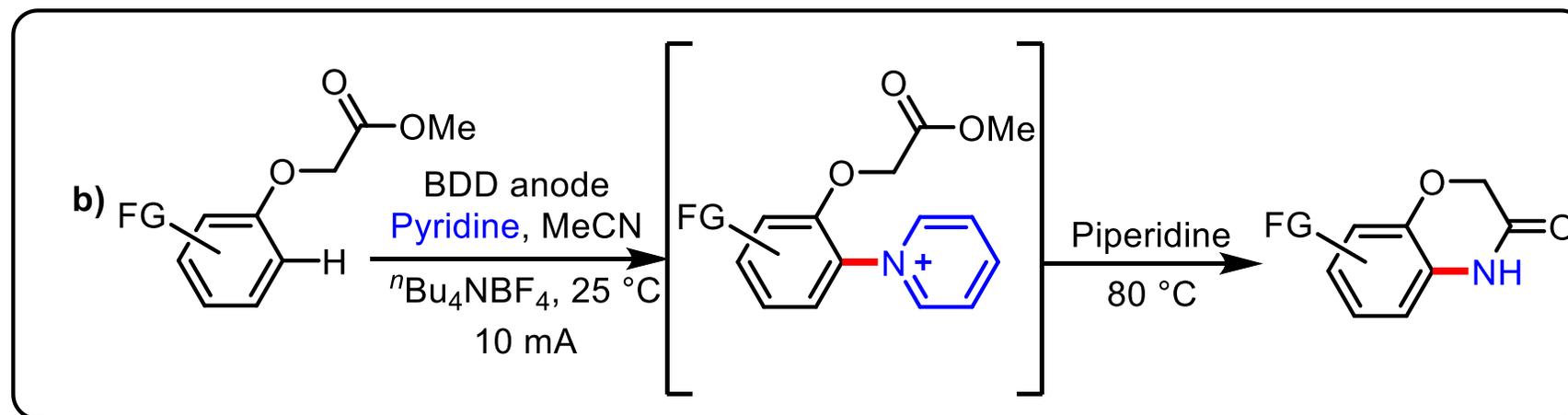
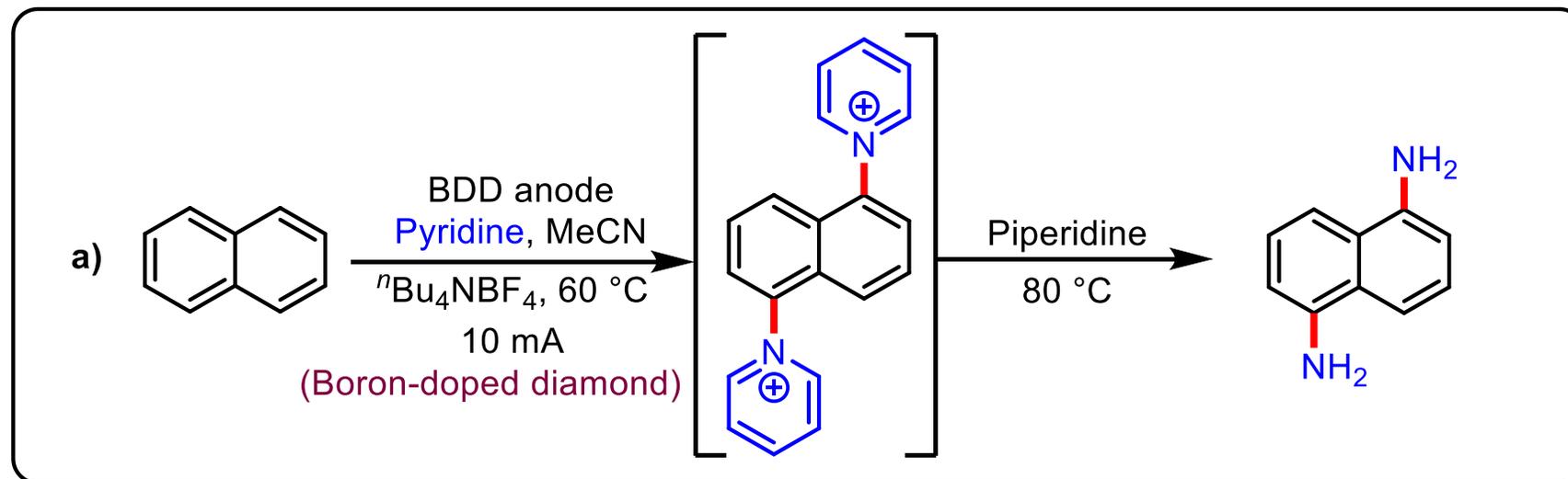


2.1 底物直接参与电极反应

2.1.1 碳源启动的C-H键氧化胺化

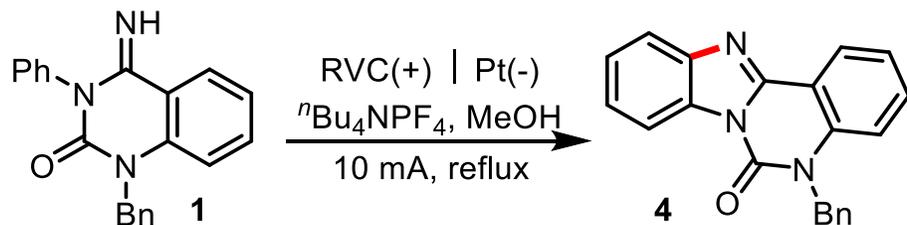


Siegfried R. Waldvogel
Johannes Gutenberg University of
Mainz

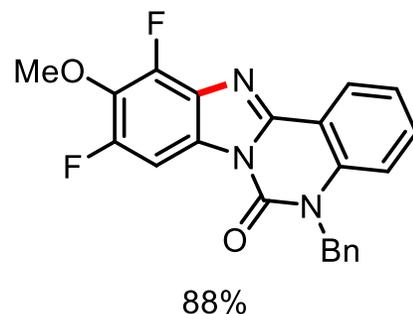
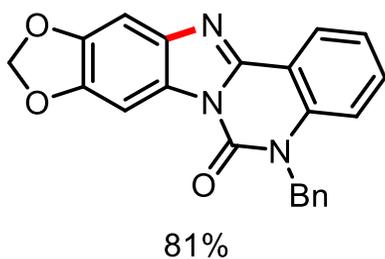
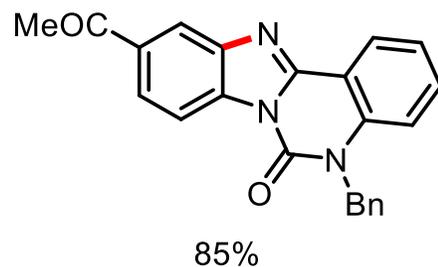
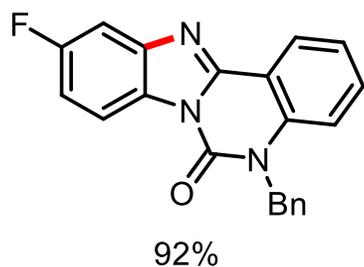


2.1 底物直接参与电极反应

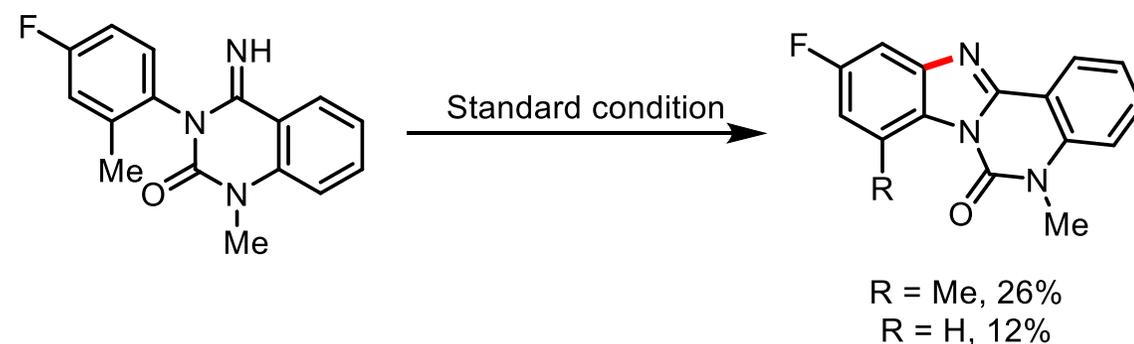
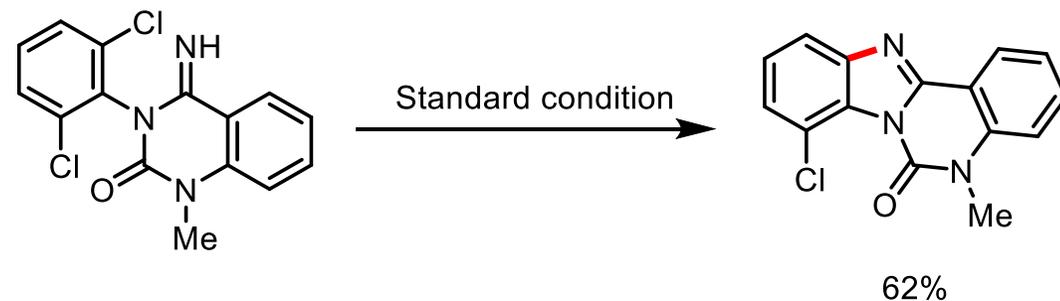
2.1.2 氮源启动的C-H键胺化



Representative products



Mechanistic studies

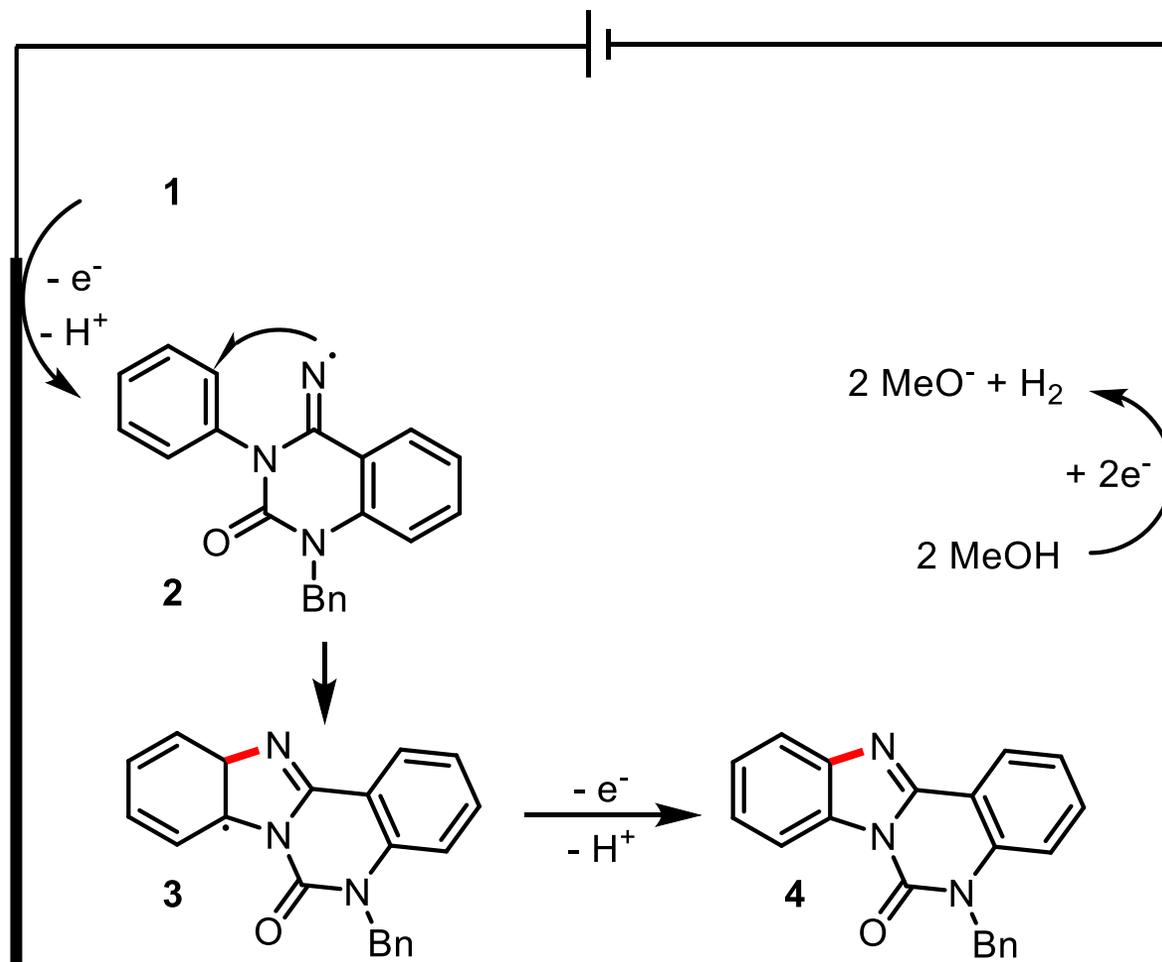


Hai-Chao Xu
Xiamen University

2.1 底物直接参与电极反应

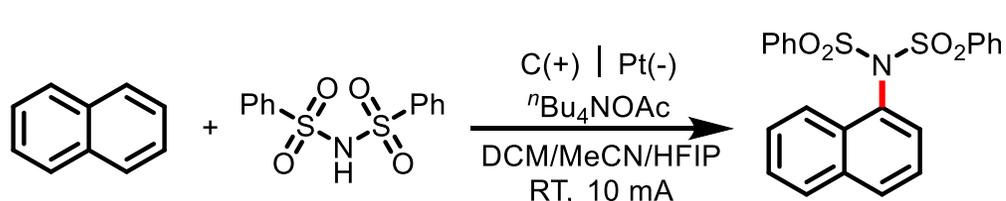
2.1.2 氮源启动的C-H键氧化胺化

Proposed mechanism

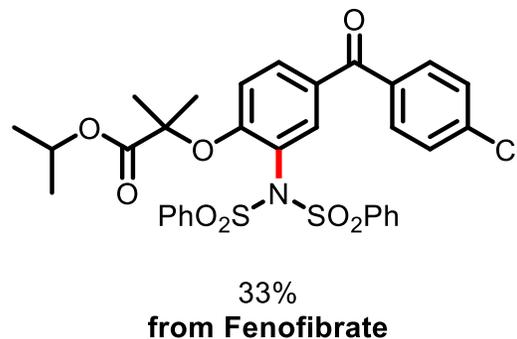
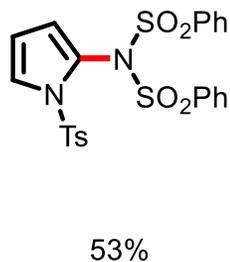
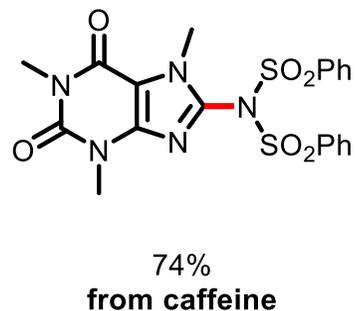
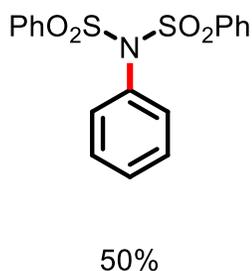


2.1 底物直接参与电极反应

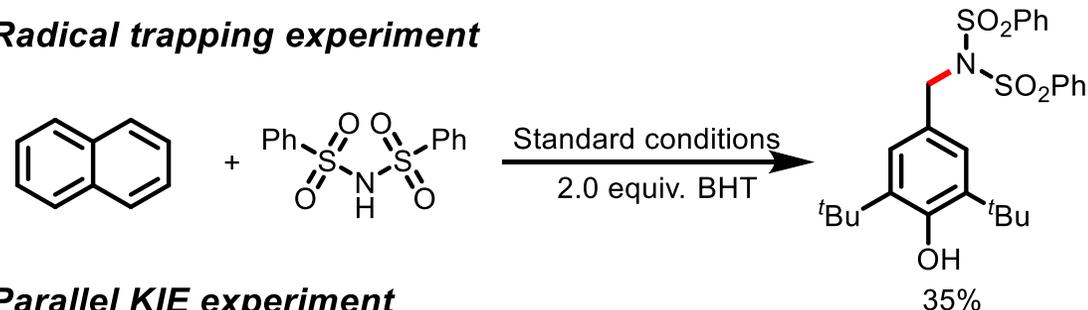
2.1.2 氮源启动的C-H键氧化胺化



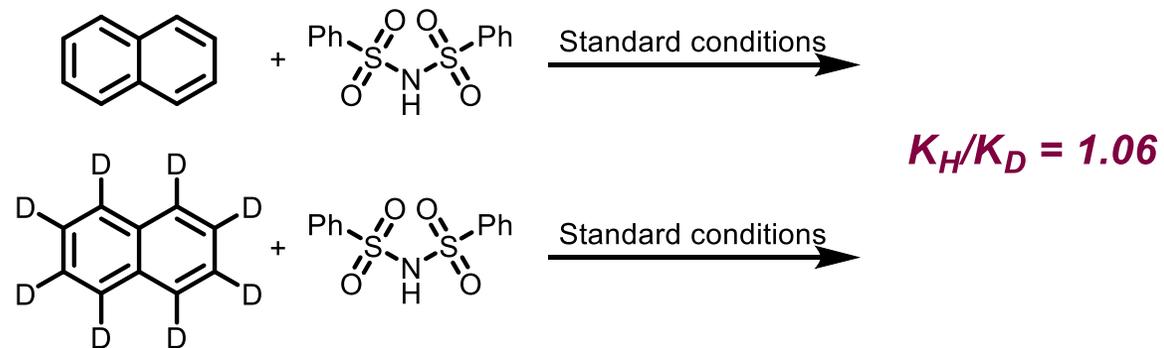
Representative products



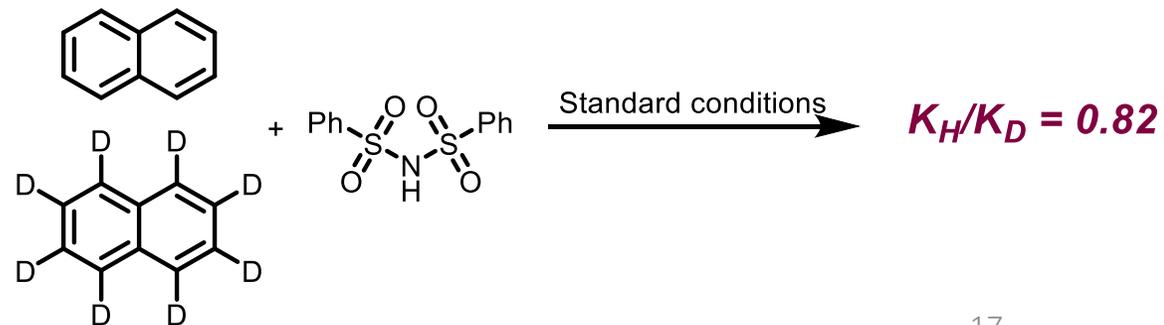
Radical trapping experiment



Parallel KIE experiment



Competition KIE experiment



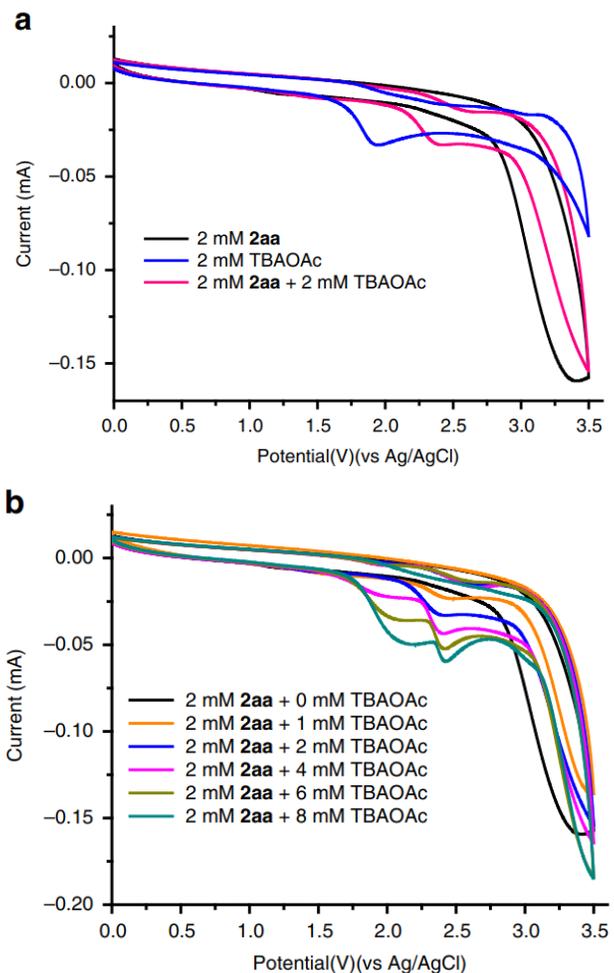
Aiwèn Lei

Wuhan University

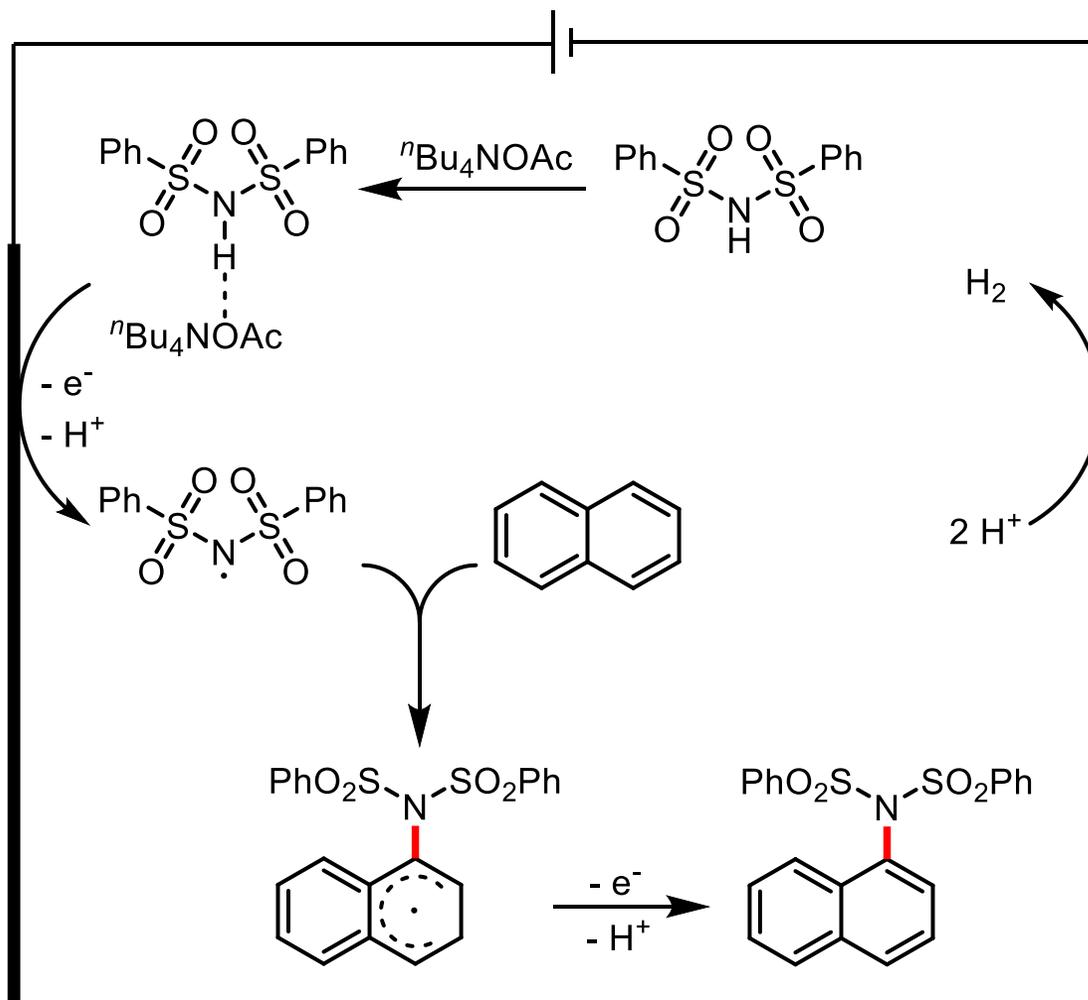
2.1 底物直接参与电极反应

2.1.2 氮源启动的C-H键胺化

Cyclic voltammetry experiments



Proposed mechanism

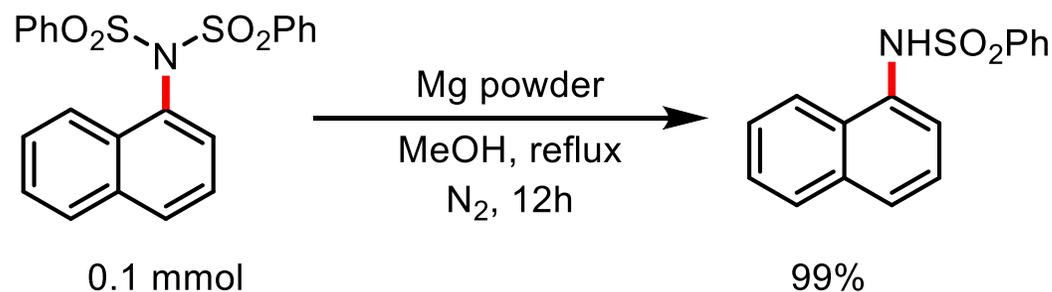


2.1 底物直接参与电极反应

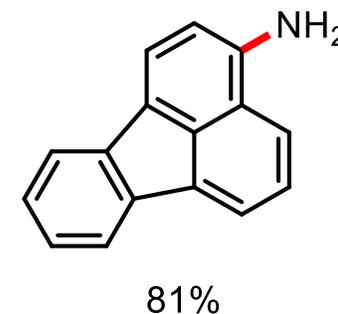
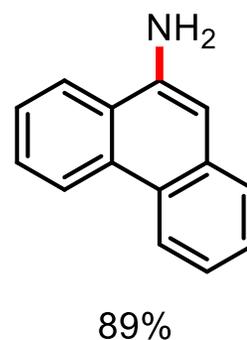
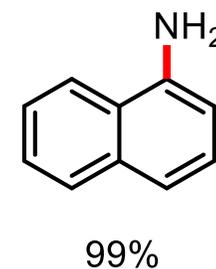
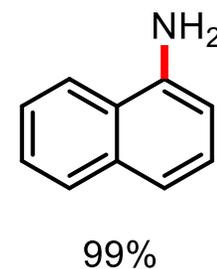
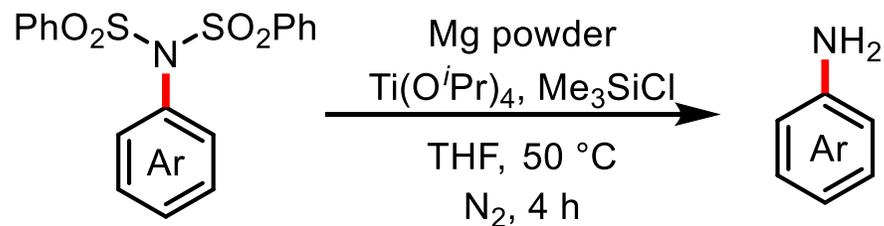
2.1.2 氮源启动的C-H键氧化胺化

Deprotection of arylimines

1) Mono-desulfonation of product



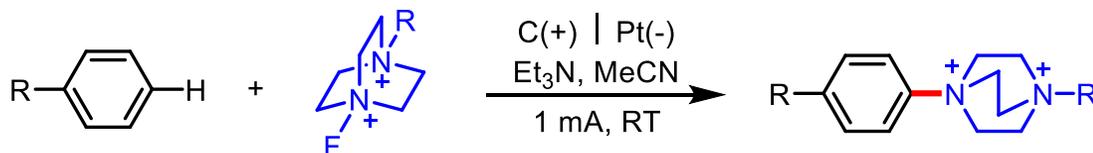
2) Double-desulfonation of product



2.1 底物直接参与电极反应

2.1.3 氮源启动的C-H键胺化

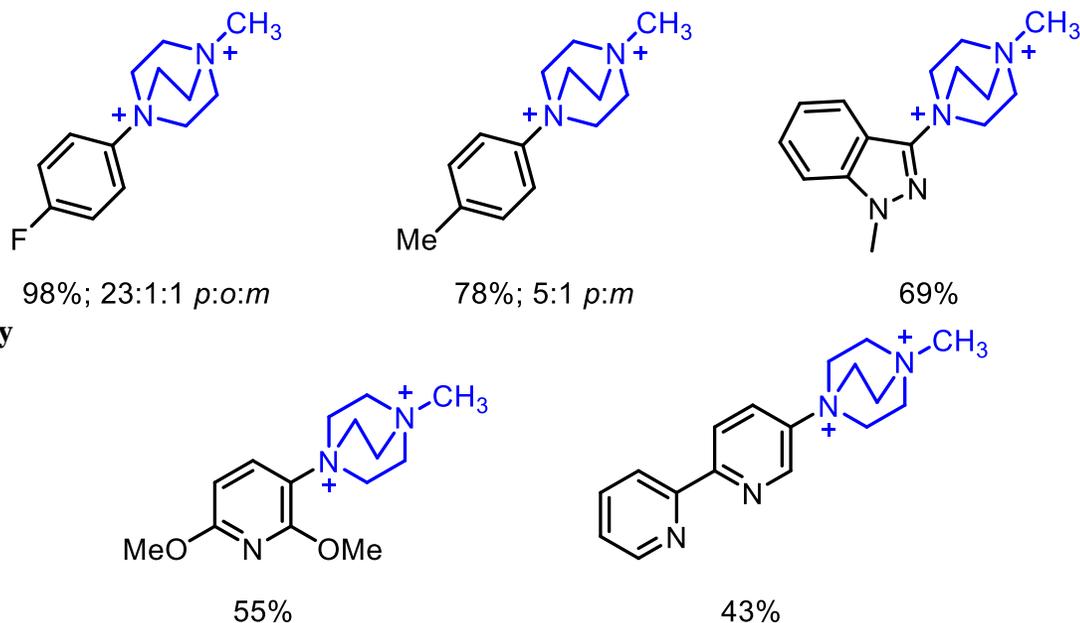
首例电催化氮源在阴极还原为活性中间体



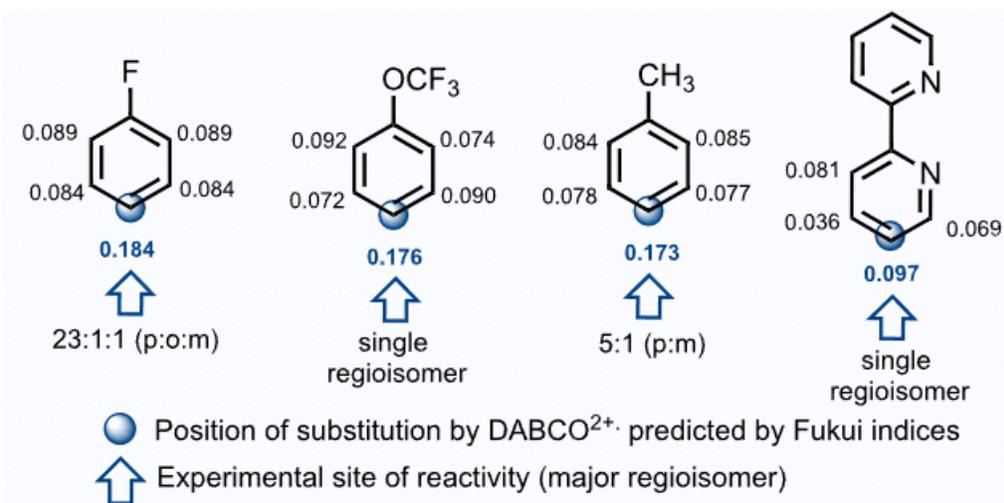
Representative products



Christian A. Malapit
Northwestern University



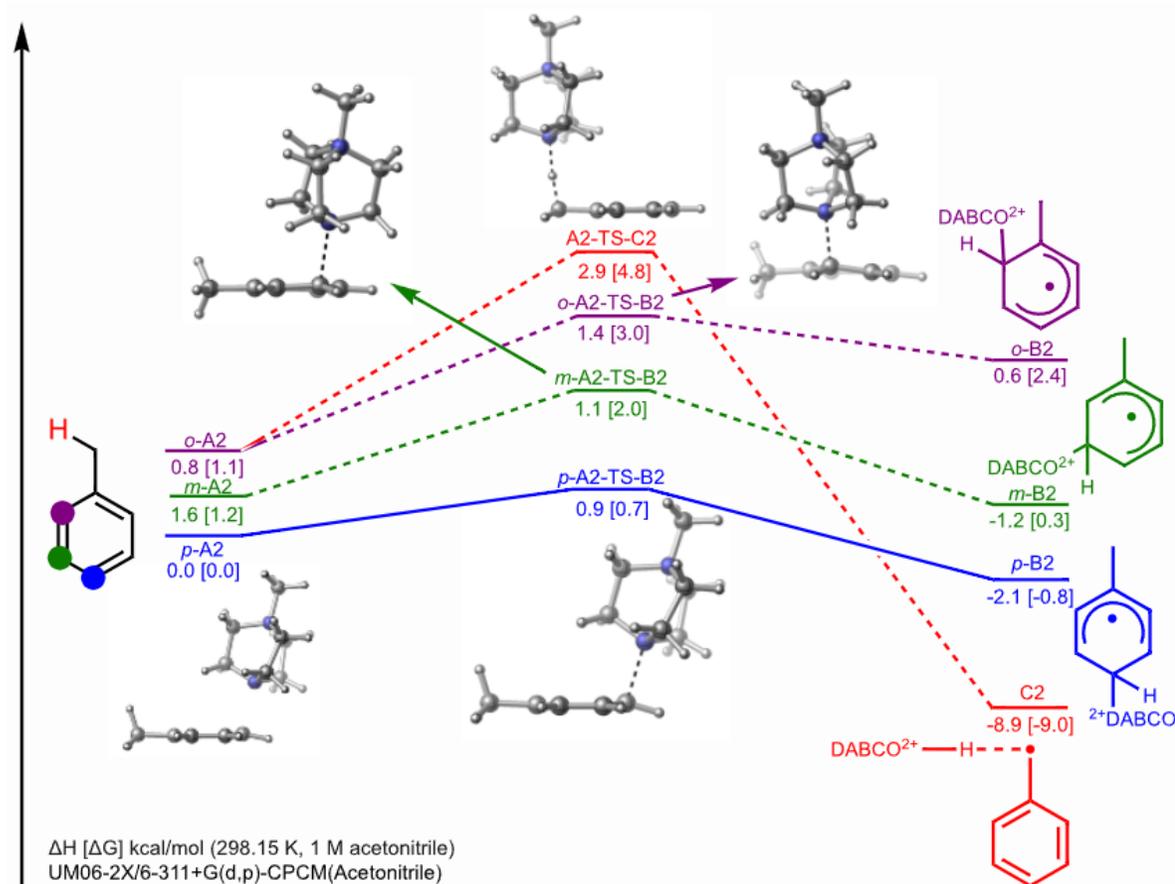
a) Calculated Fukui indices and experimental regioselectivity



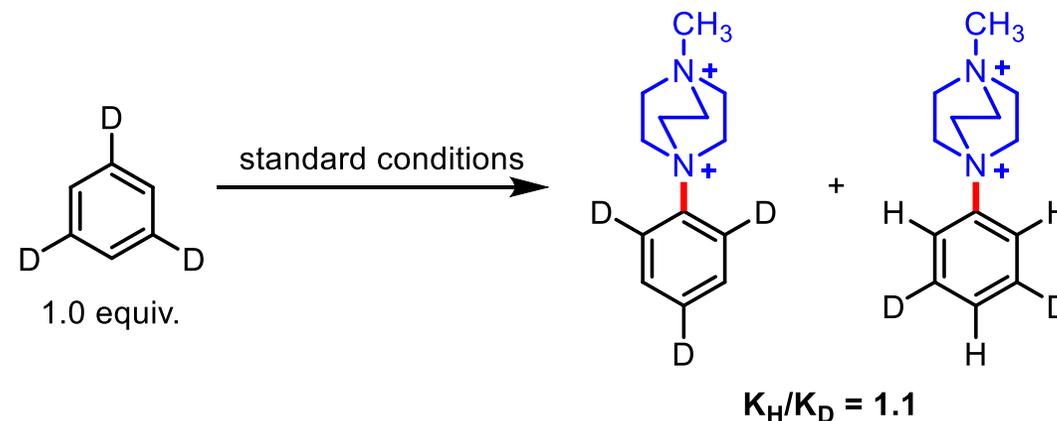
2.1 底物直接参与电极反应

2.1.3 氮源启动的C-H键胺化

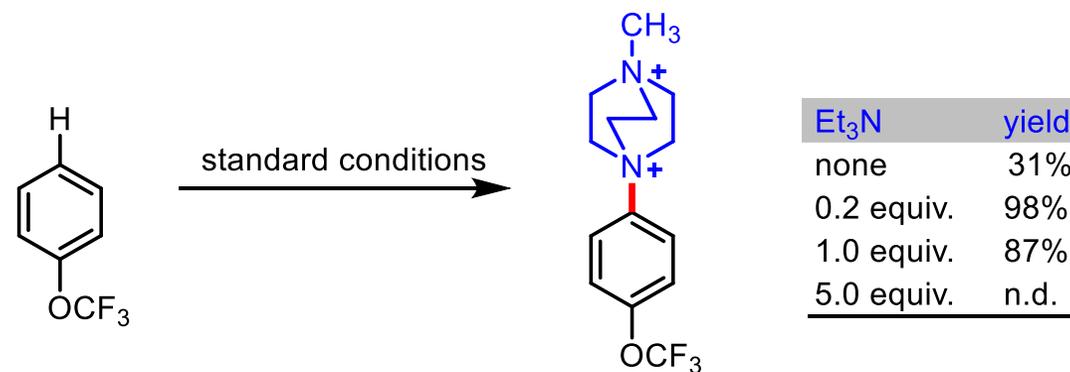
b) DFT studies on radical-cation – pi interaction vs HAT and observed regioselectivity



c) KIE studies



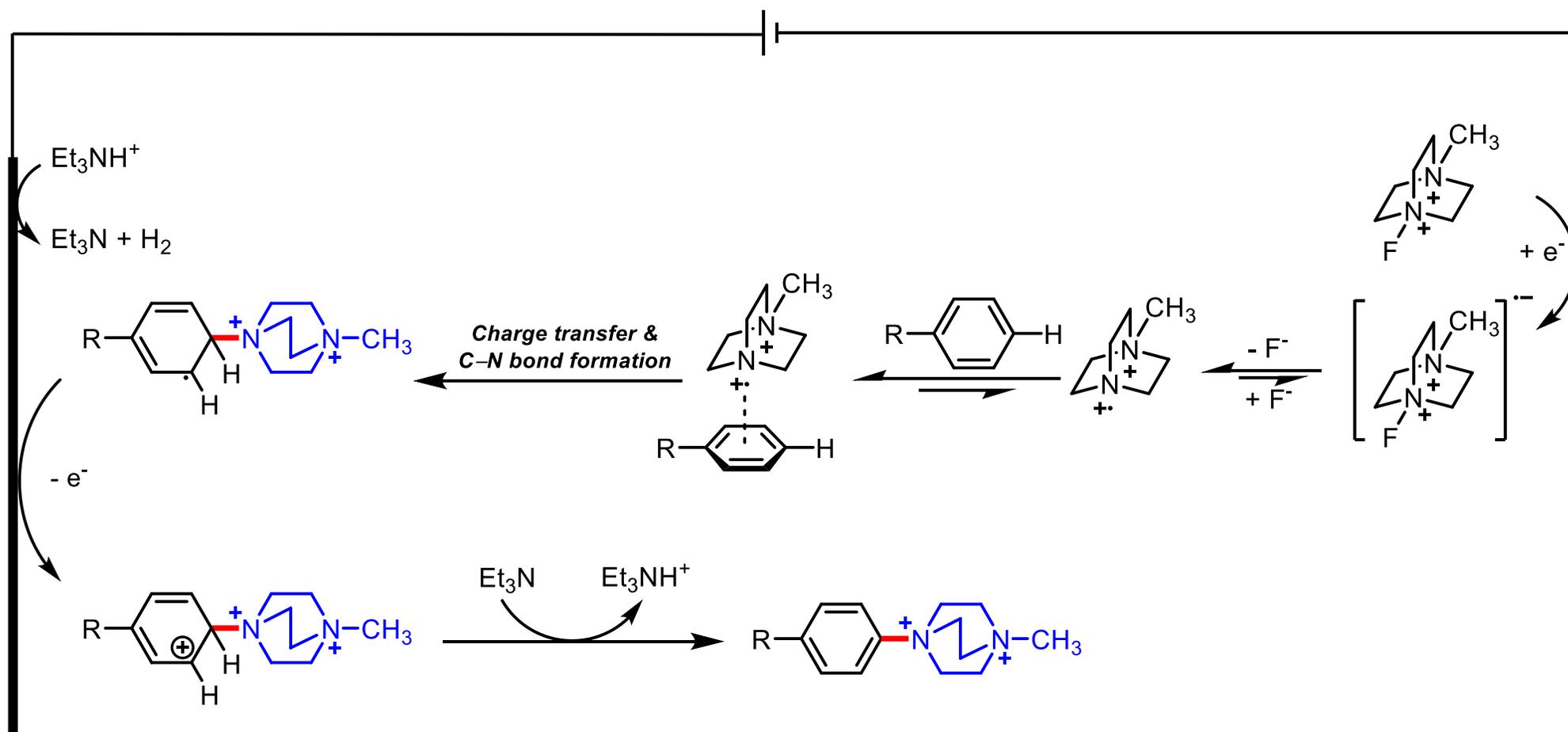
d) Role and effects of Et₃N



2.1 底物直接参与电极反应

2.1.3 氮源启动的C-H键胺化

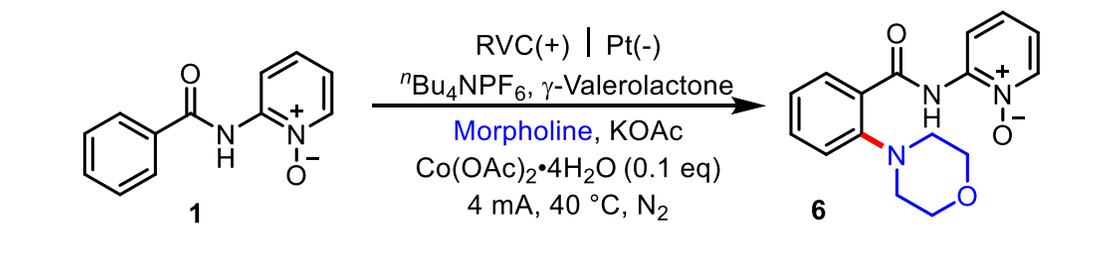
Proposed mechanism



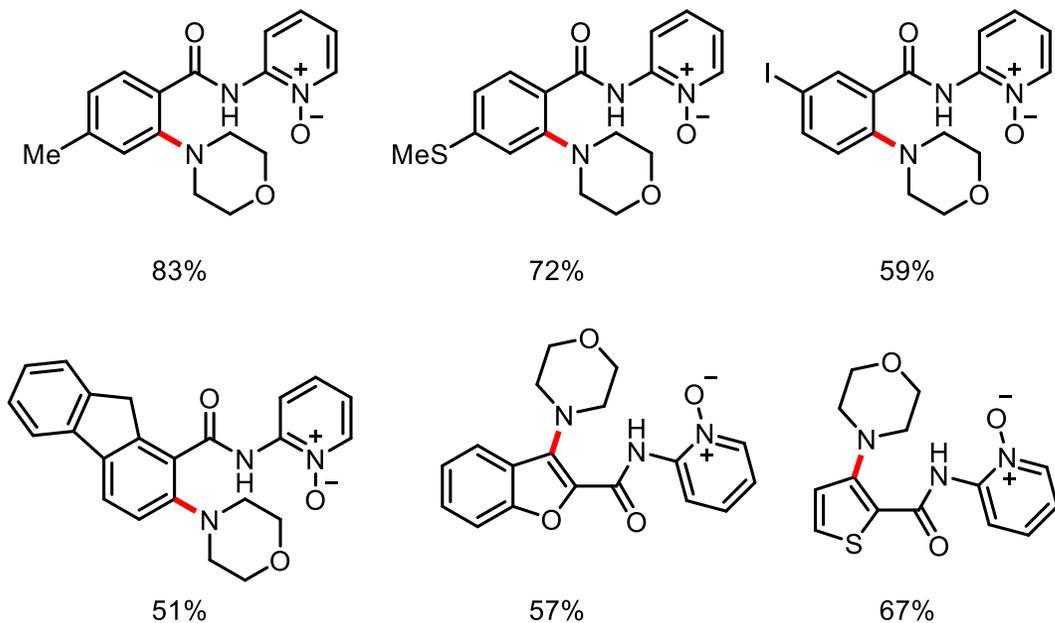
2.2 底物不参与电极反应

2.2.1 钴参与电极反应

Lutz Ackermann报道的首例过渡金属参与的电催化C-H胺化反应

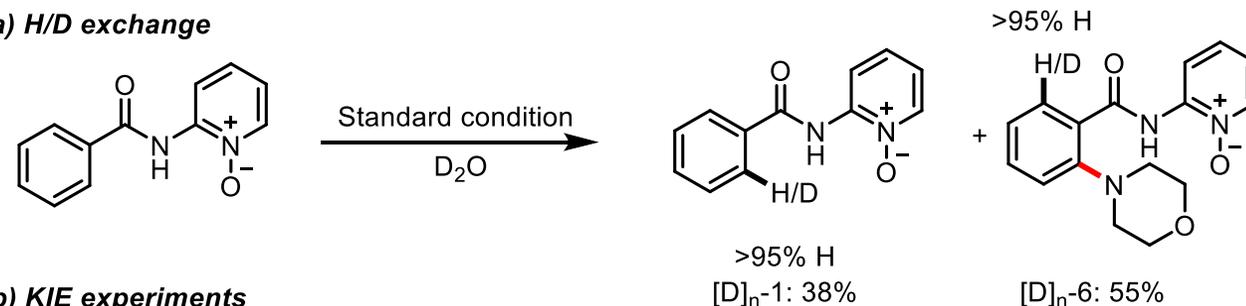


Representative products

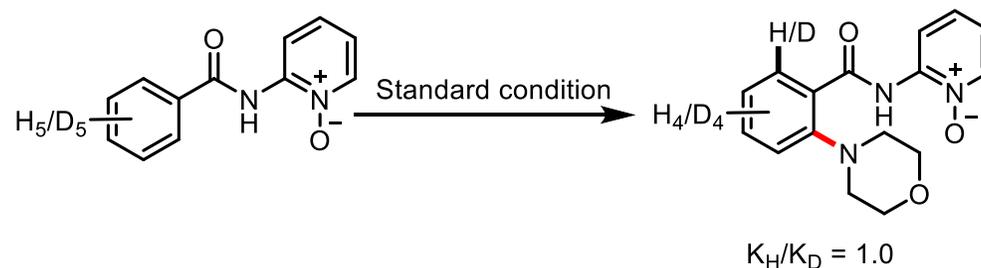


Control experiments

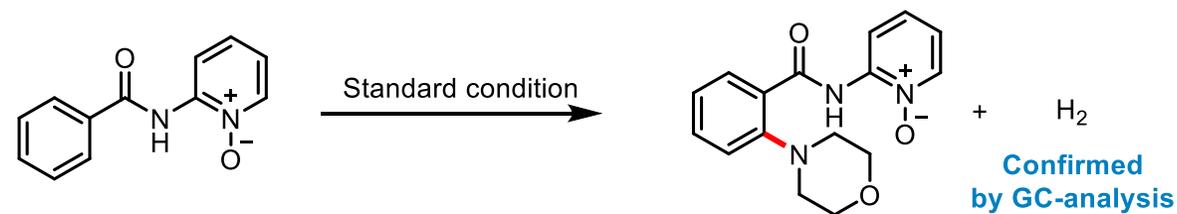
a) H/D exchange



b) KIE experiments



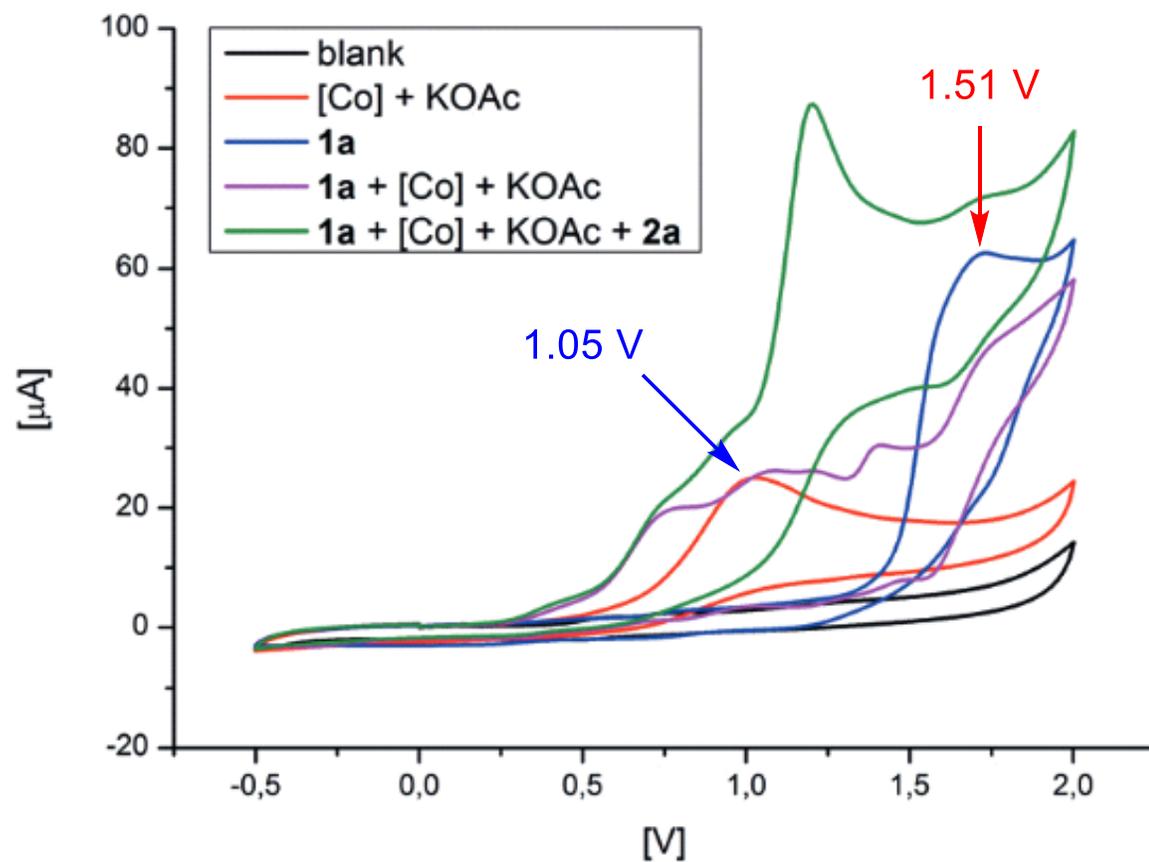
c) Headspace H_2 -analysis



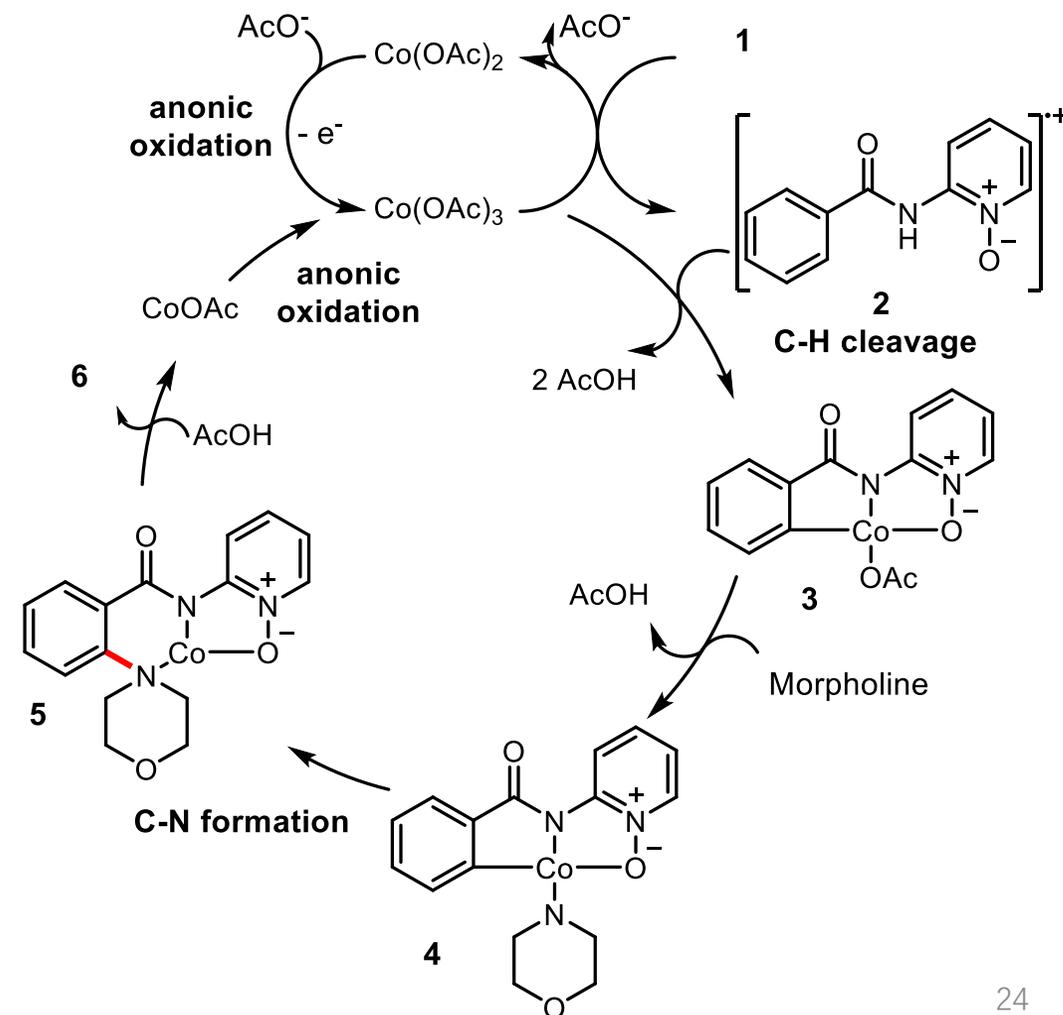
2.2 底物不参与电极反应

2.2.1 钴参与电极反应

Cyclic voltammetry experiments

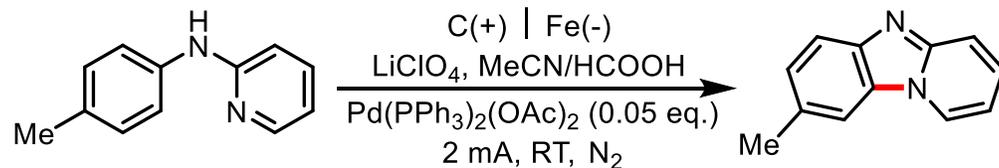


Proposed mechanism

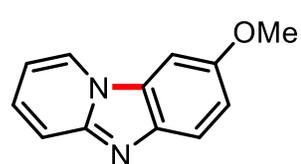


2.2 底物不参与电极反应

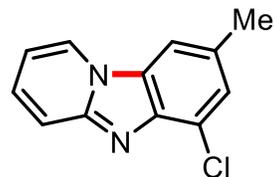
2.2.2 钯参与电极反应



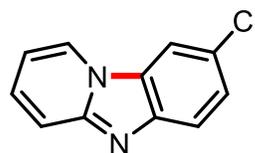
Representative products



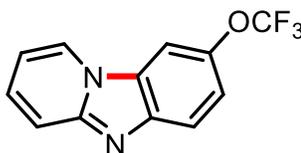
99%



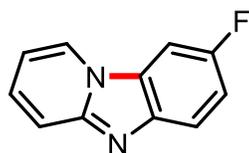
71%



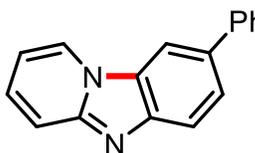
45%



62%



60%



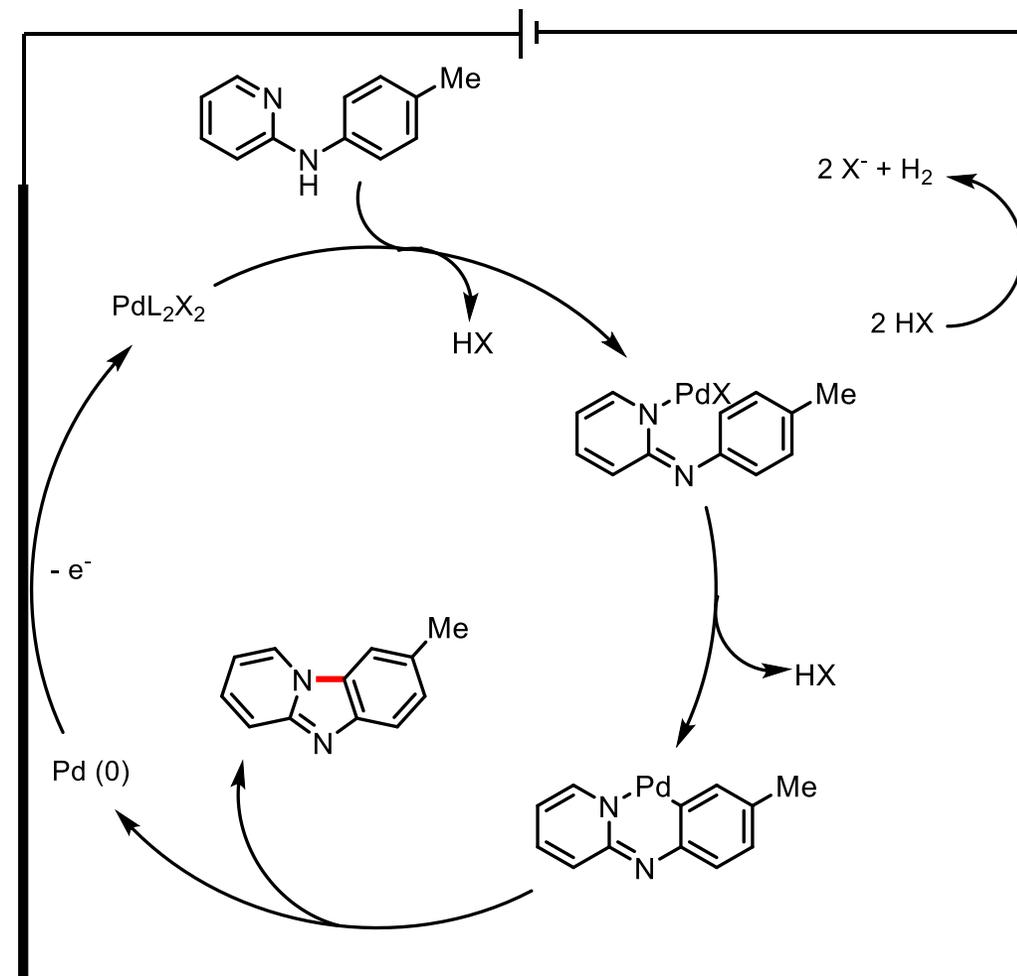
40%



Aiwèn Lei

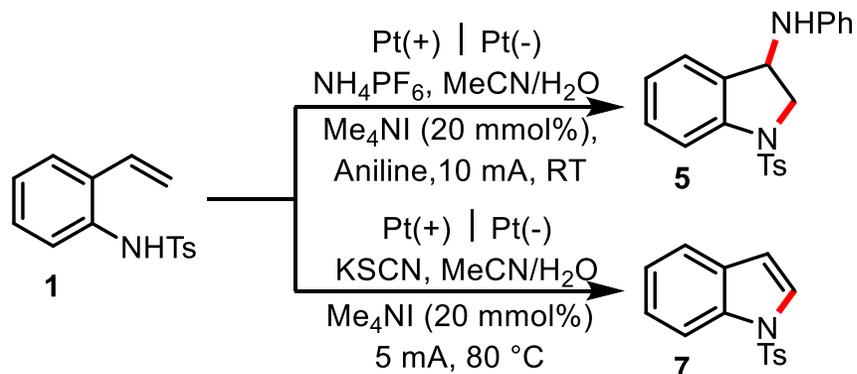
Wuhan University

Proposed mechanism



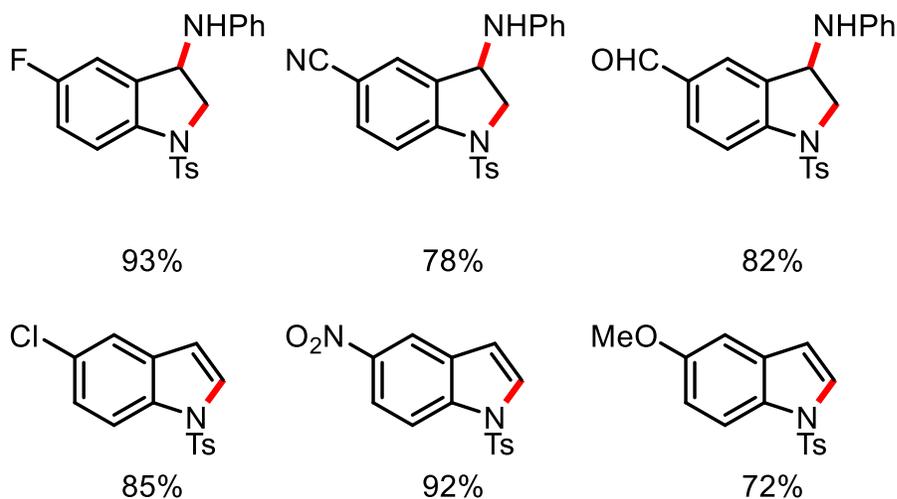
2.2 底物不参与电极反应

2.2.3 碘参与电极反应

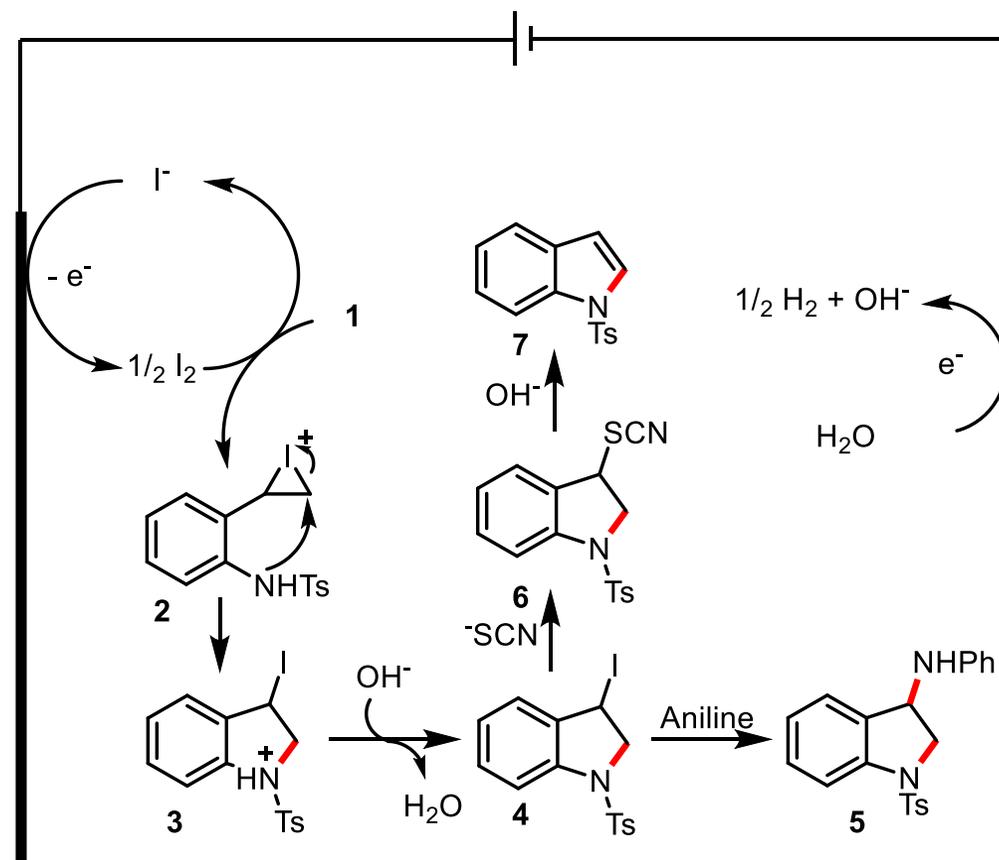


Zhiyong Wang
USTC

Representative products



Proposed mechanism

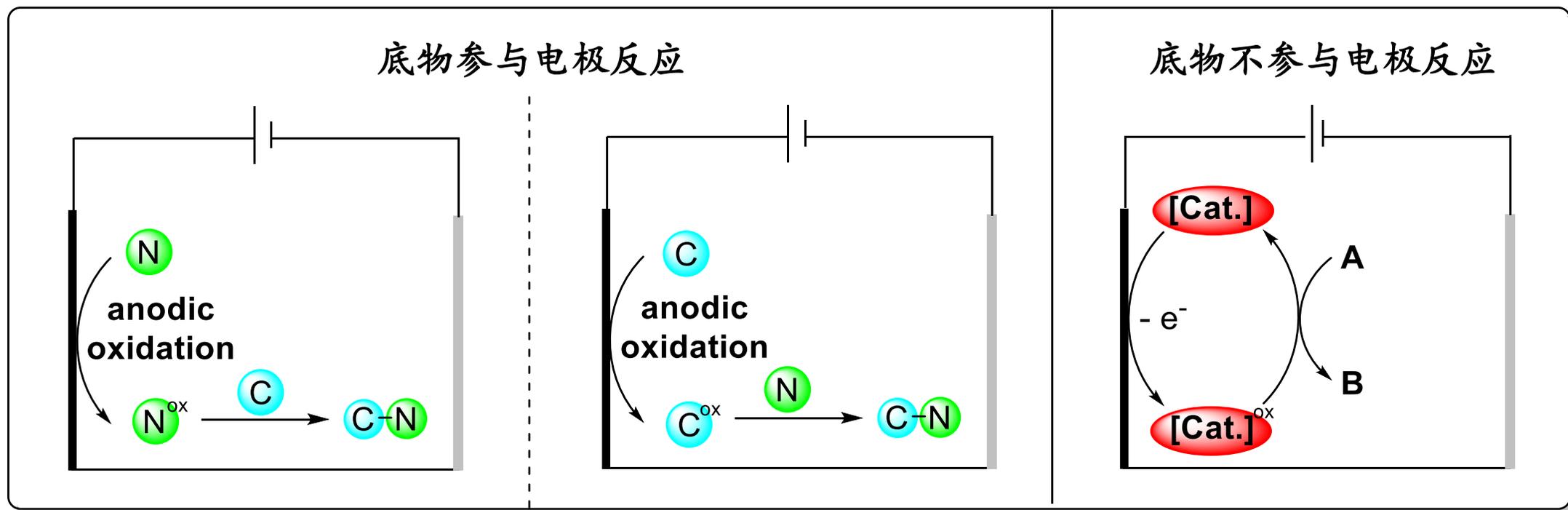




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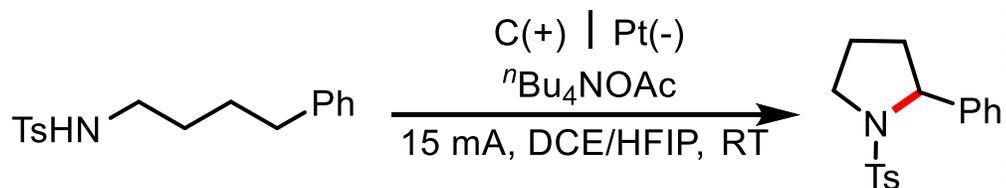
- 一、研究背景与意义
- 二、电催化的 sp^2 C-H胺化反应
- 三、电催化的 sp^3 C-H胺化反应
- 四、总结与展望

电催化的 sp^3 C-H胺化反应主要的三种类型

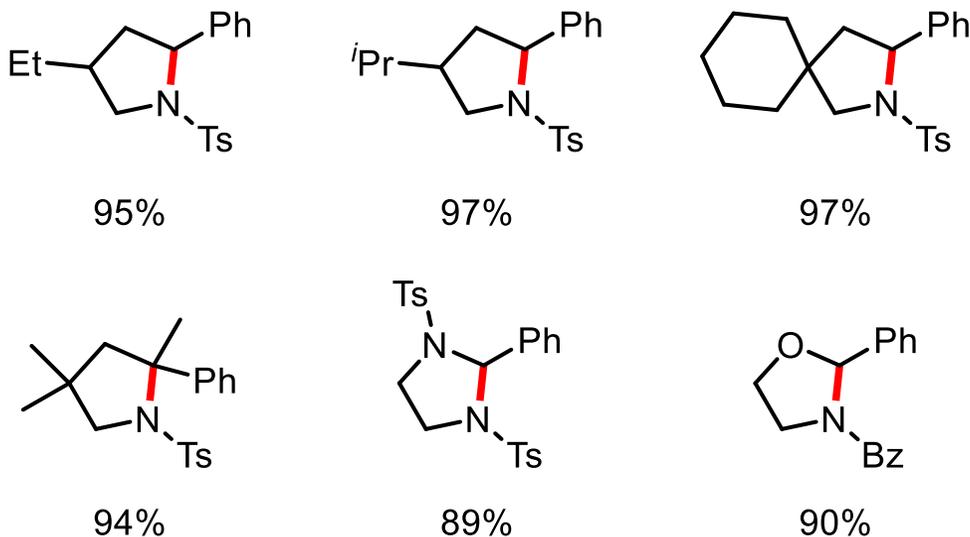


3.1 底物直接参与电极反应

3.1.1 氮源启动的C-H键氧化胺化

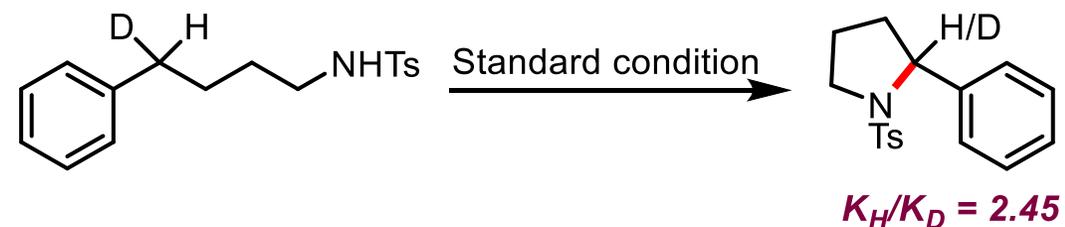


Representative products

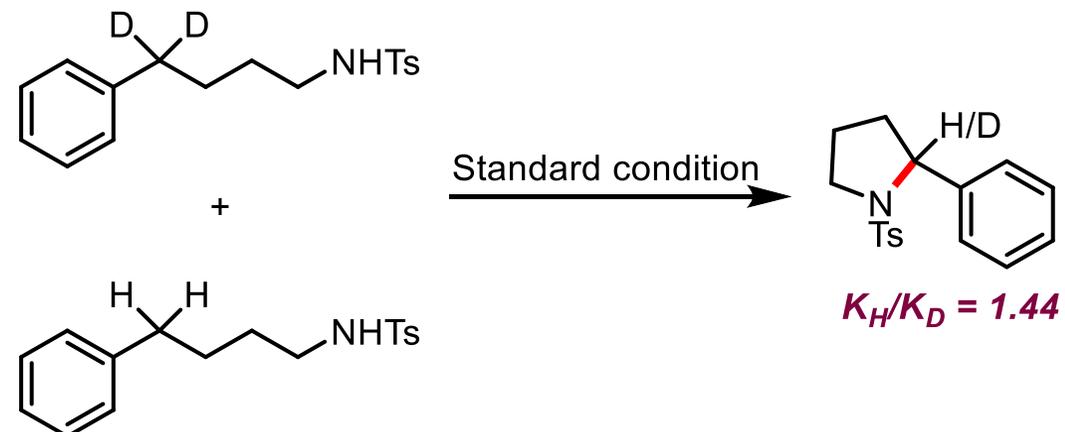


The control experiments

a) Intramolecular KIE experiment



b) Intermolecular KIE experiment



Aiwen Lei

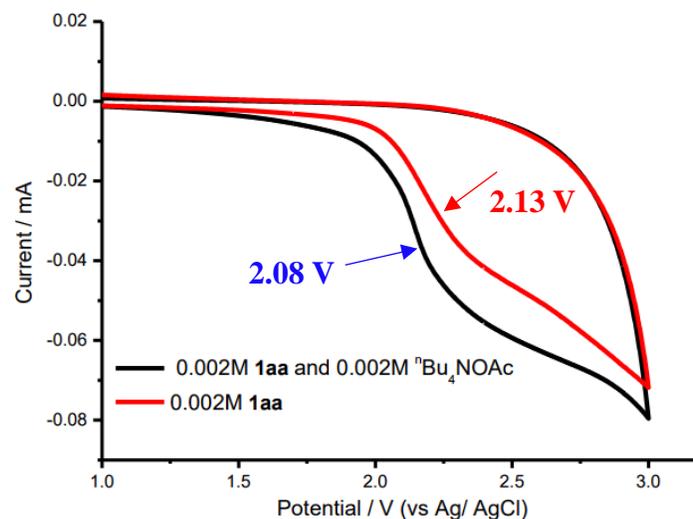
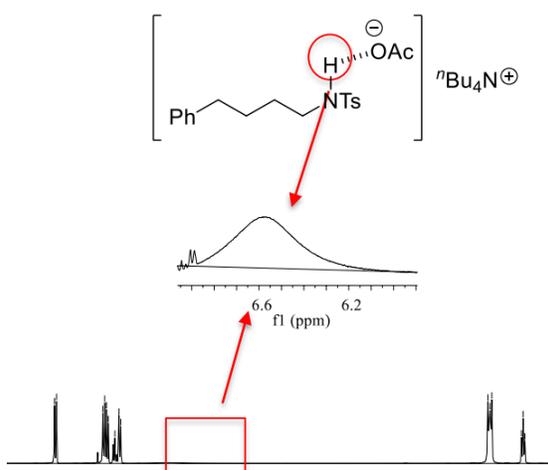
Wuhan University

3.1 底物直接参与电极反应

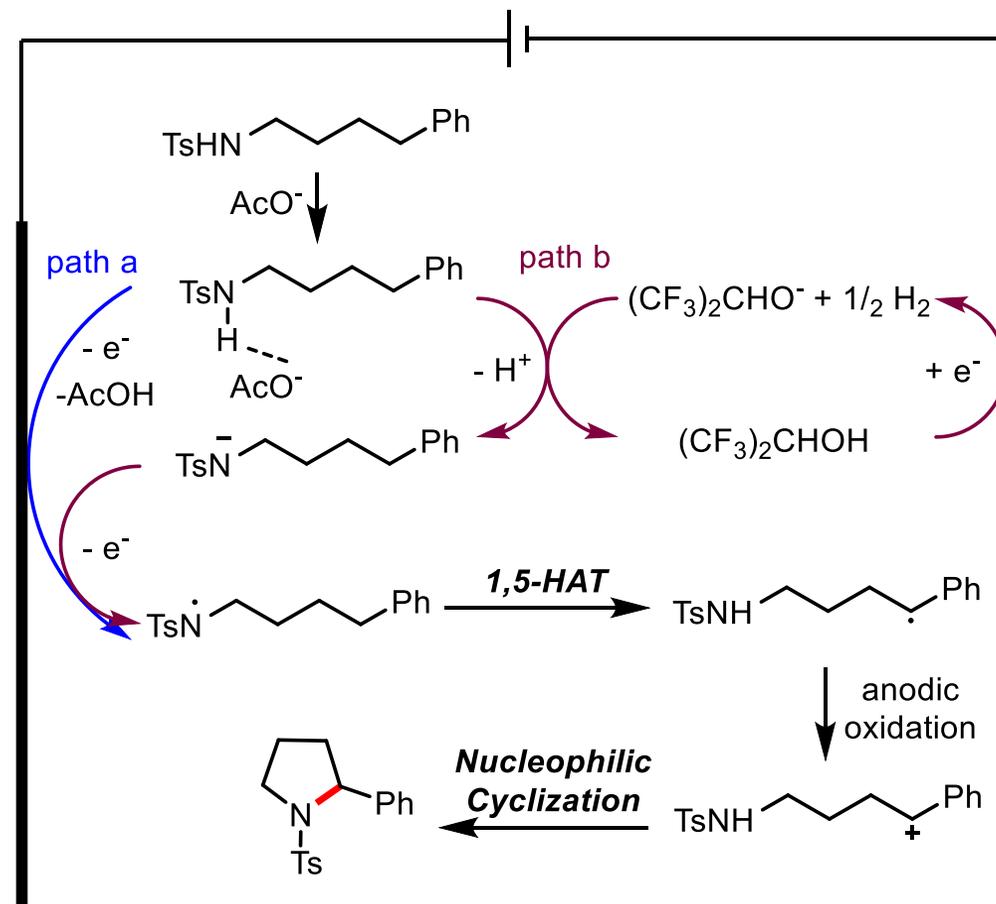
3.1.1 氮源启动的C-H键氧化胺化

The control experiments

c) ^1H NMR and CV studies



Proposed mechanism

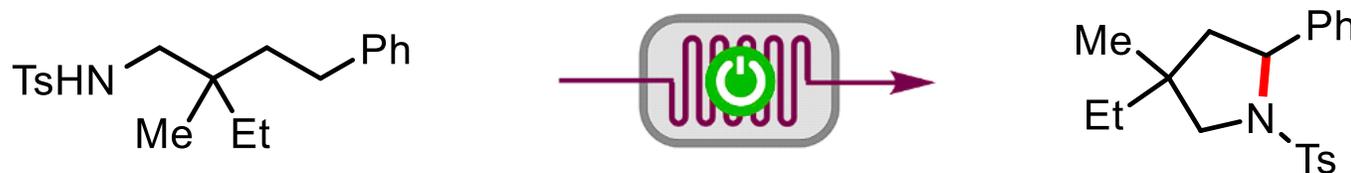


3.1 底物直接参与电极反应

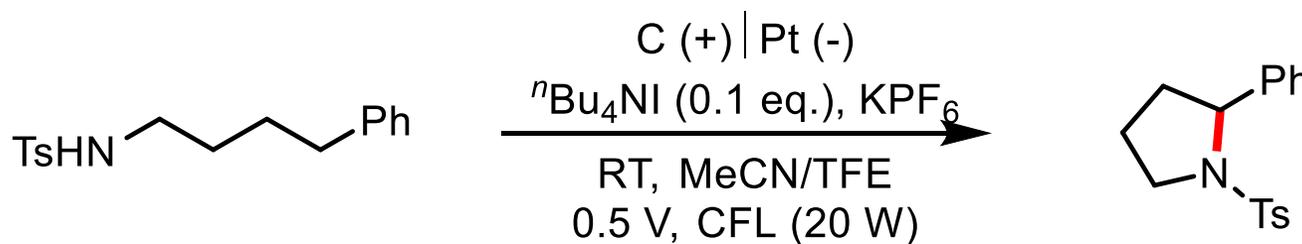
3.1.1 氮源启动的C-H键氧化胺化



Magnus Rueping
KAUST



Continuous Flow Electrosynthesis
Gram-scale synthesis



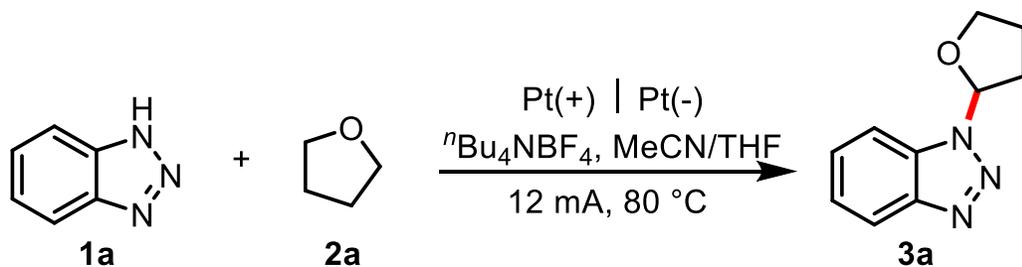
Photoelectrochemical synthesis



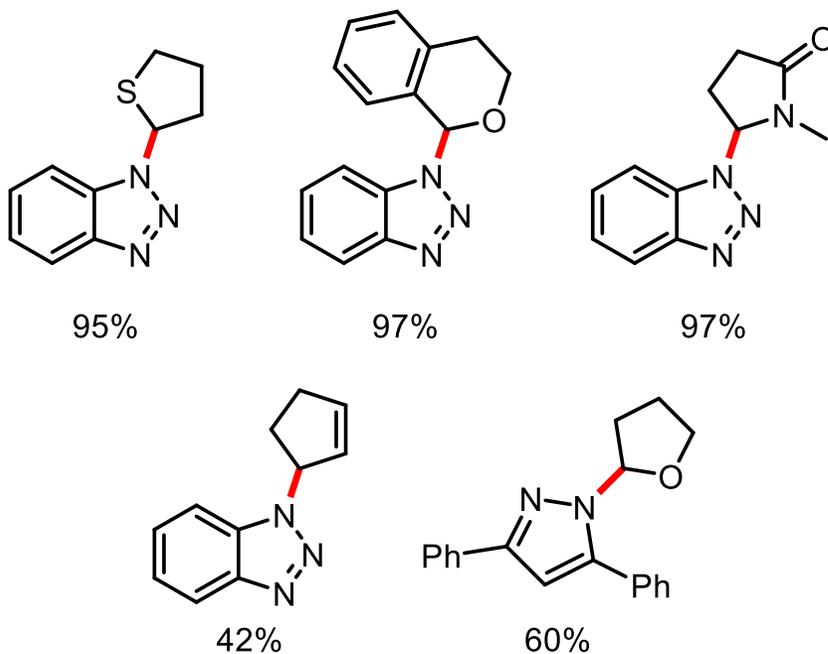
Shannon S. Stahl
University of Wisconsin-Madison

3.1 底物直接参与电极反应

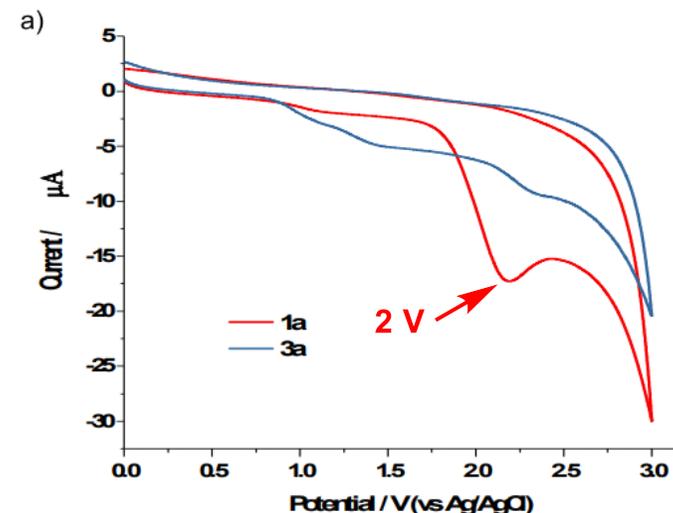
3.1.1 氮源启动的C-H键氧化胺化



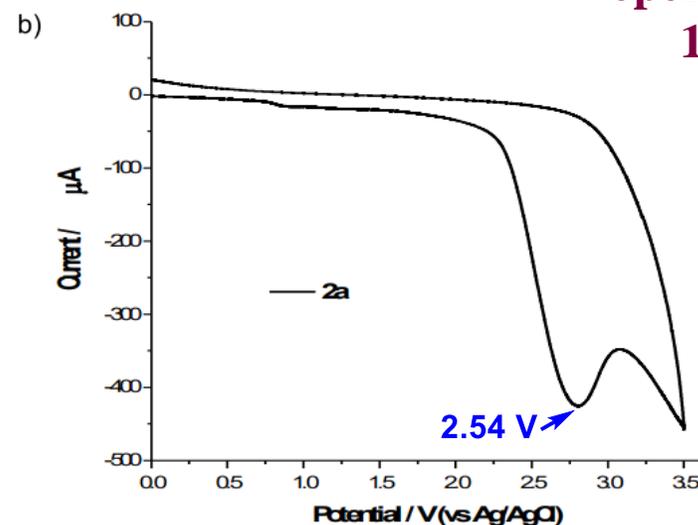
Representative products



Cyclic voltammetry experiments



operating voltage:
1.90-2.23 V



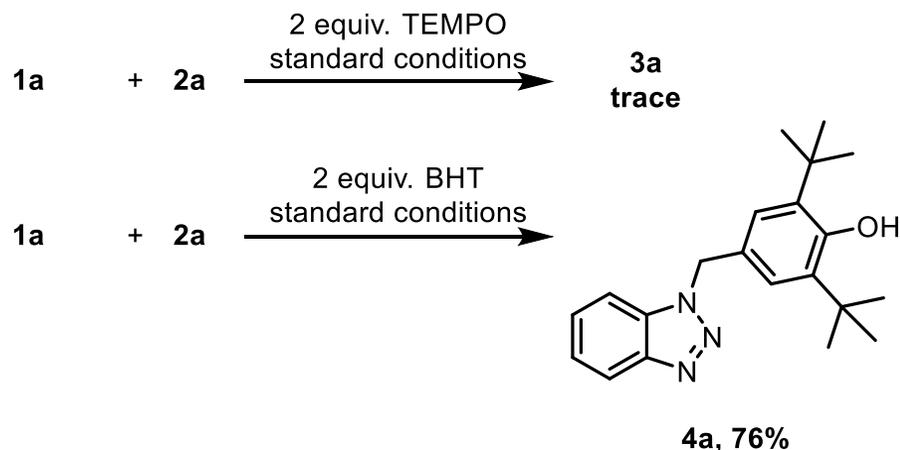
Aiwèn Lei

Wuhan University

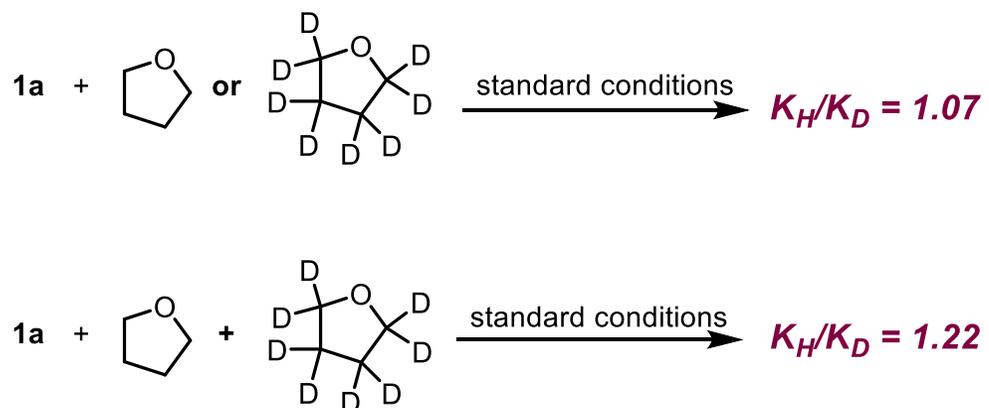
3.1 底物直接参与电极反应

3.1.1 氮源启动的C-H键氧化胺化

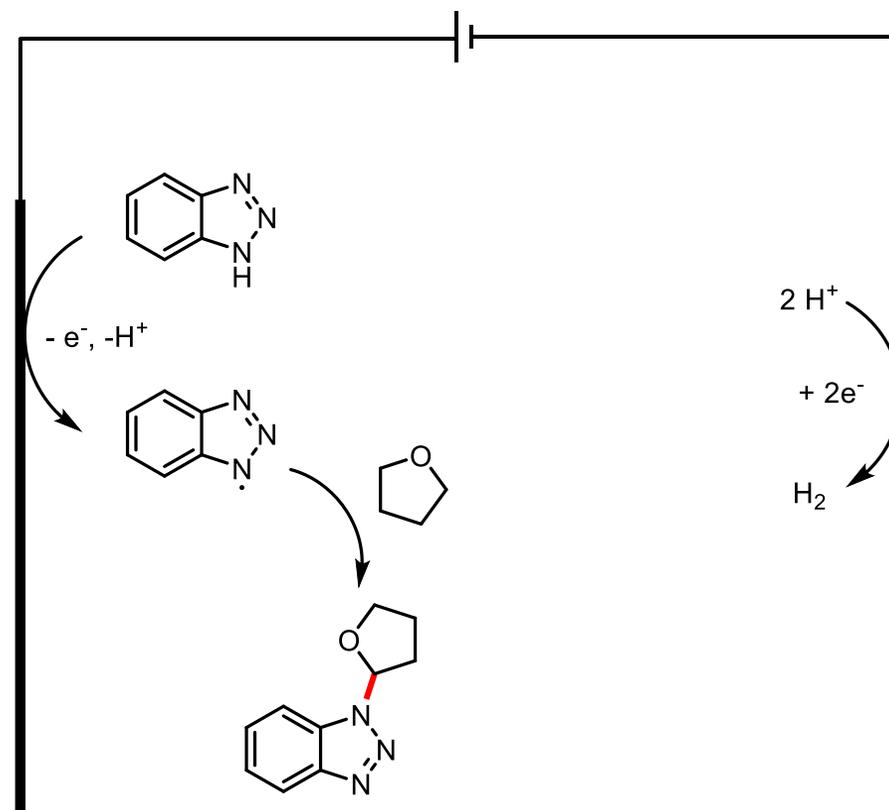
Radical trapping experiments



KIE experiments

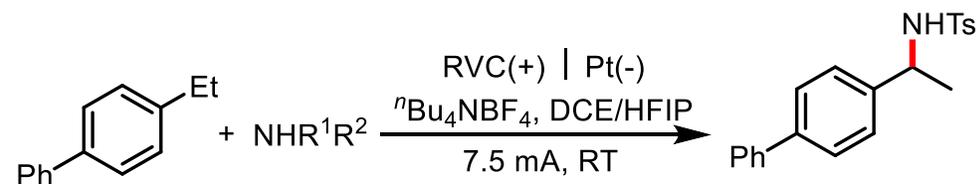


Proposed mechanism



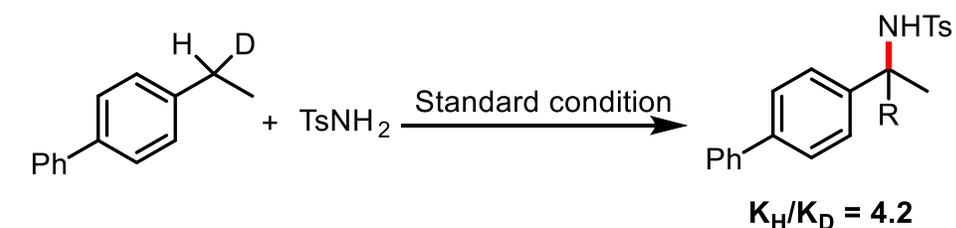
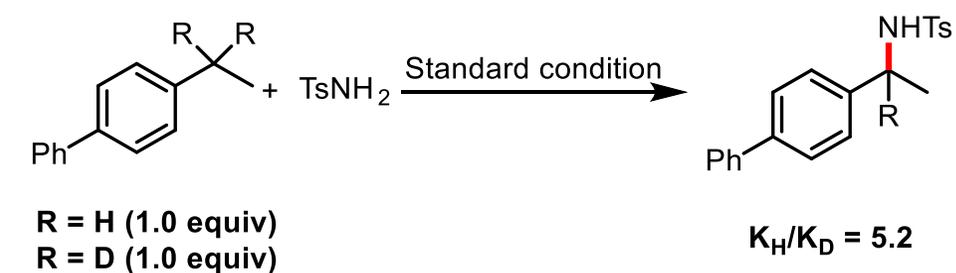
3.1 底物直接参与电极反应

3.1.2 碳源启动的C-H键氧化胺化

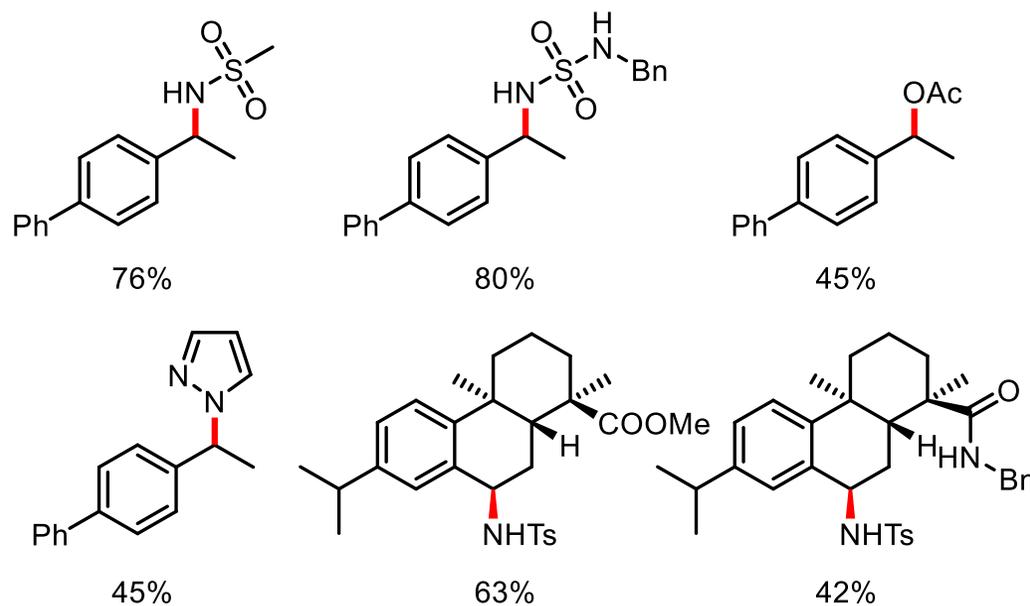


The control experiments

KIE experiments



Representative products

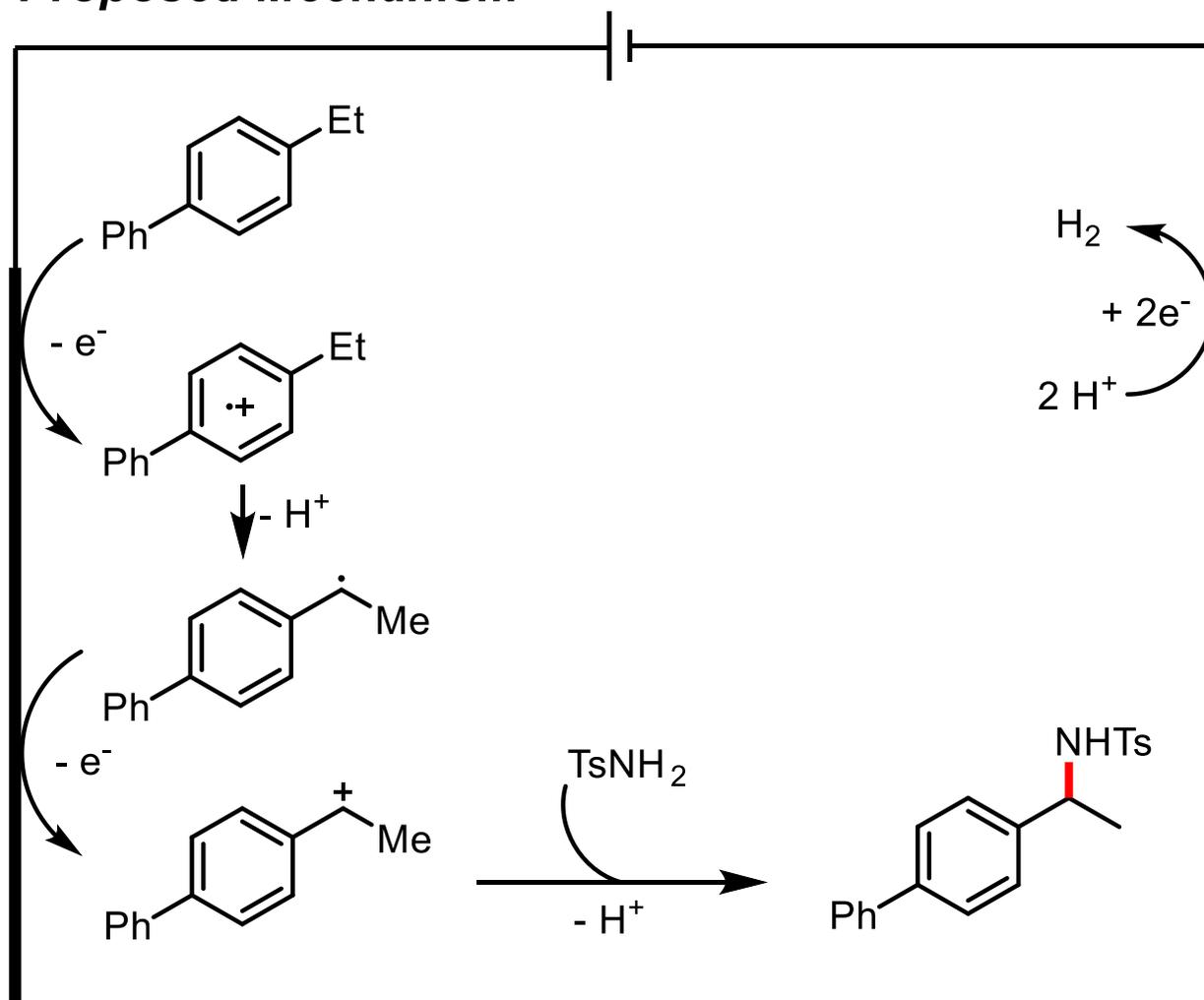


Hai-Chao Xu
Xiamen University

3.1 底物直接参与电极反应

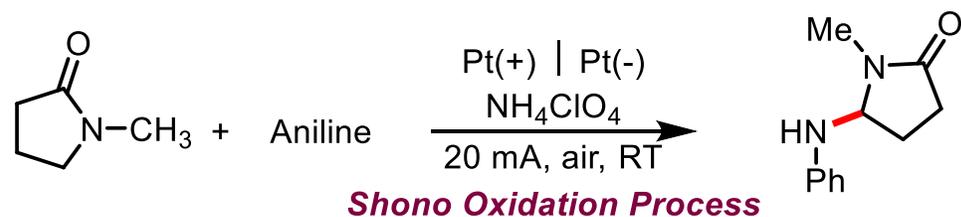
3.1.2 碳源启动的C-H键氧化胺化

Proposed Mechanism



3.1 底物直接参与电极反应

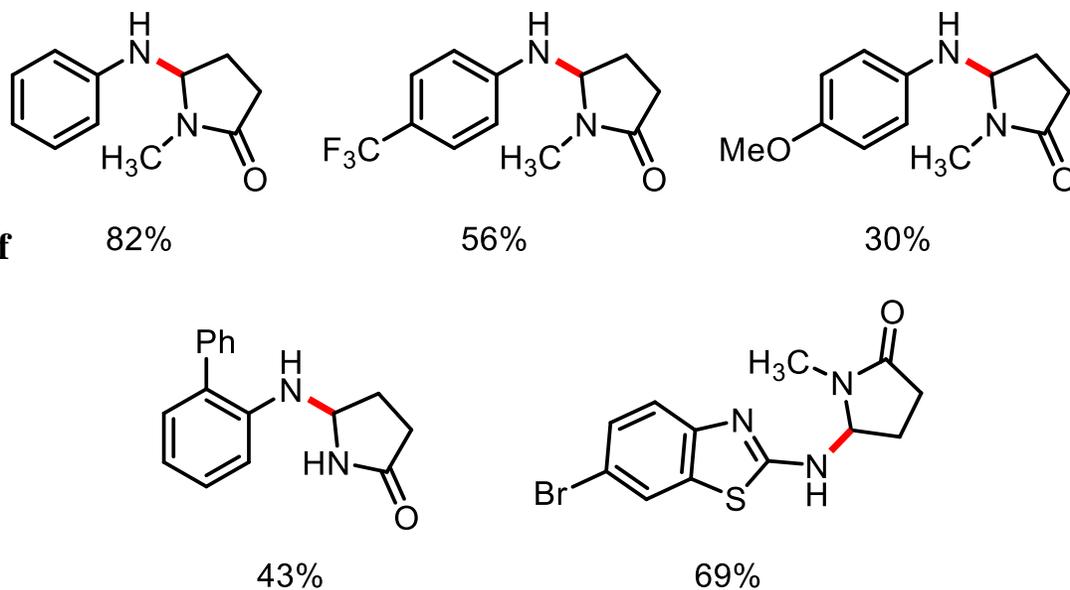
3.1.2 碳源启动的C-H键氧化胺化



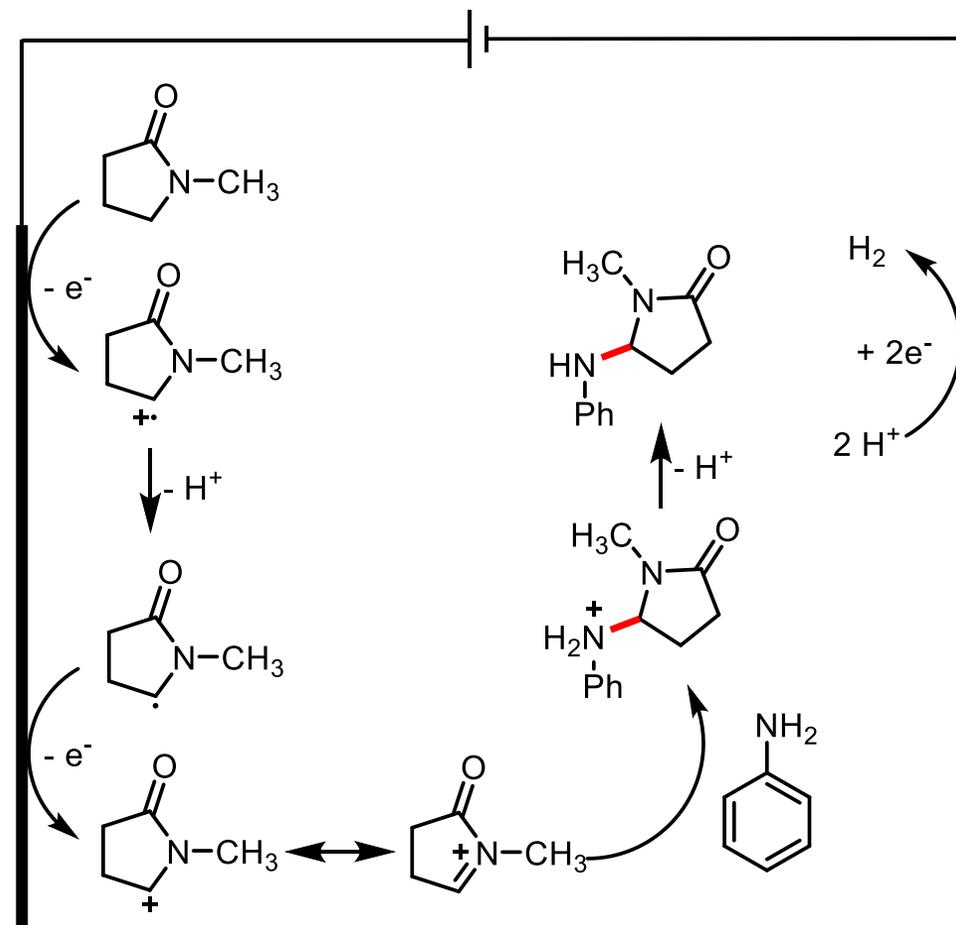
Jingmei Huang

South China University of Technology

Representative products

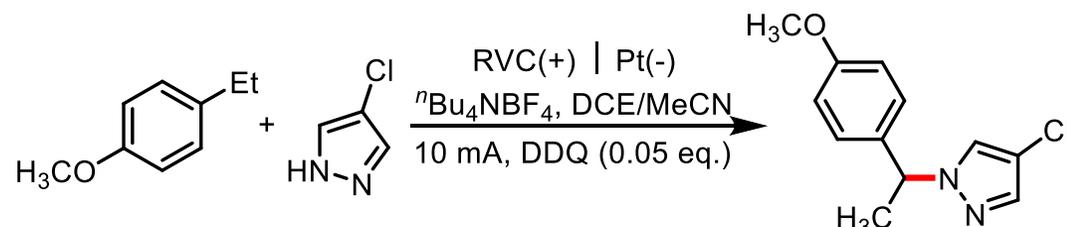


Proposed mechanism

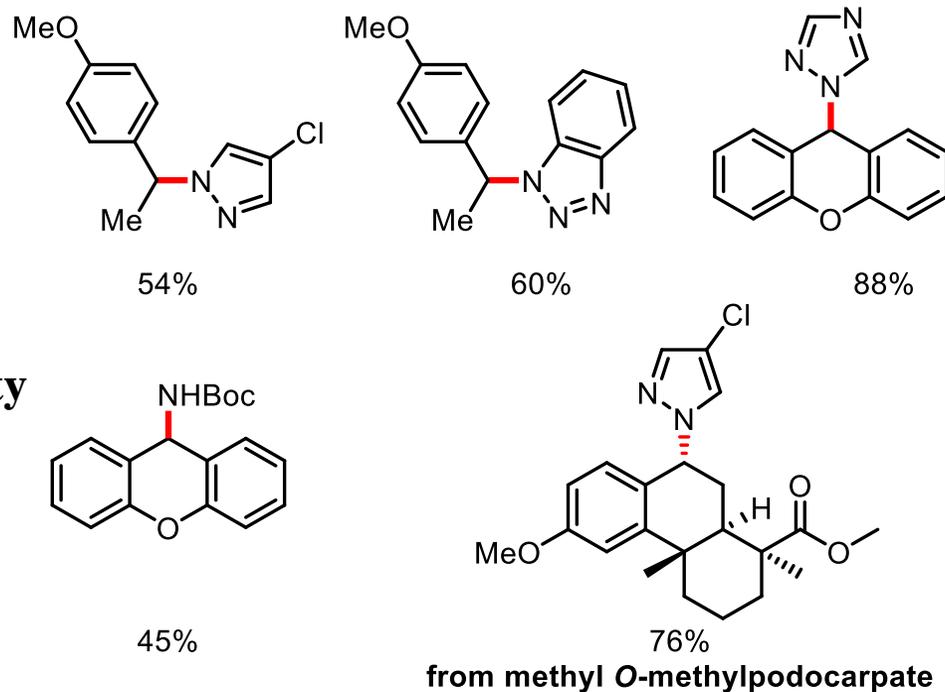


3.2 底物不参与电极反应

3.2.1 DDQ参与电极反应



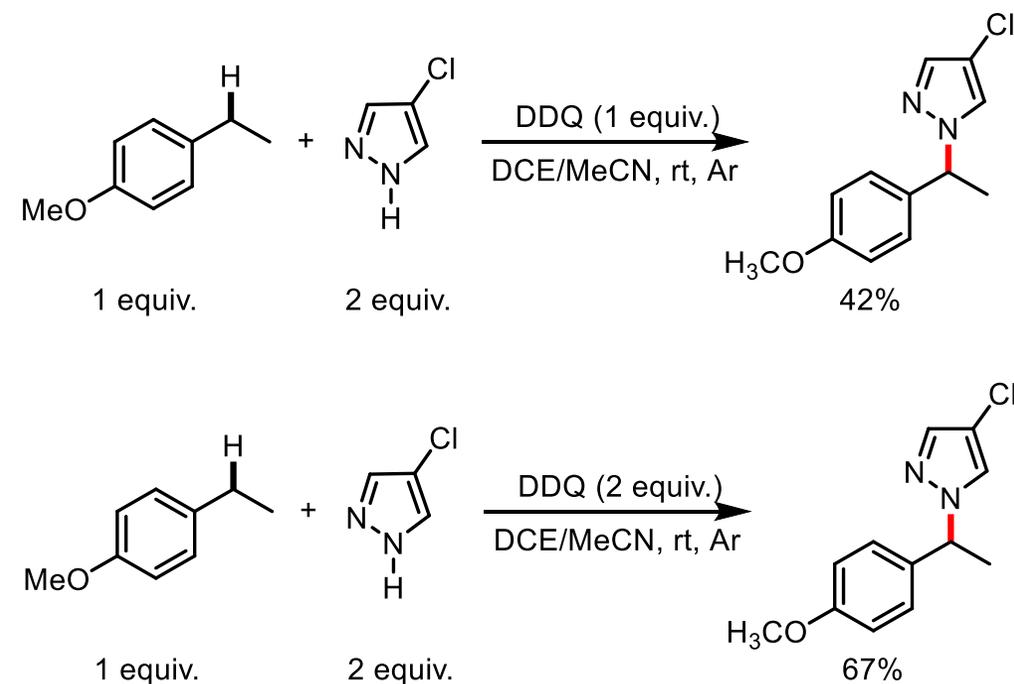
Representative products



Lei Wang

Taizhou University

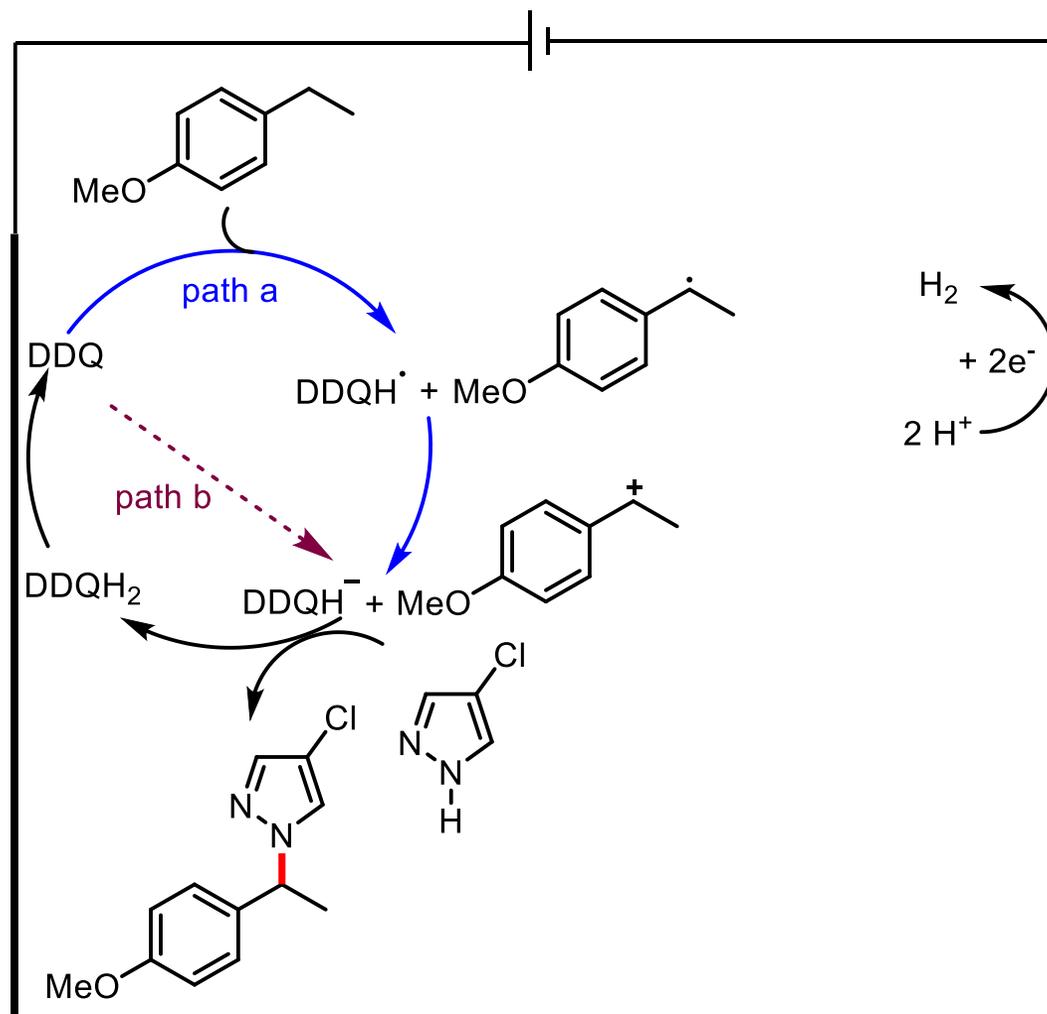
Control experiments



3.2 底物不参与电极反应

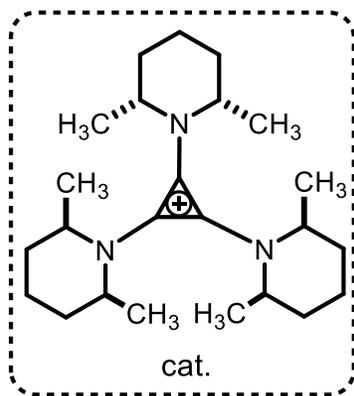
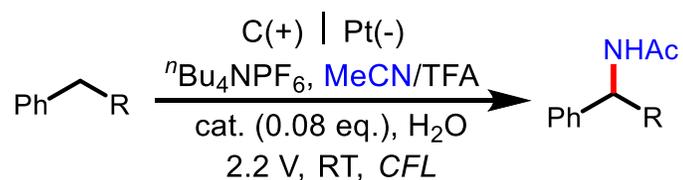
3.2.1 DDQ参与电极反应

Proposed Mechanism

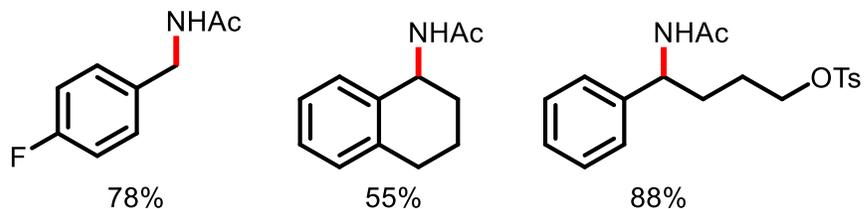


3.2 底物不参与电极反应

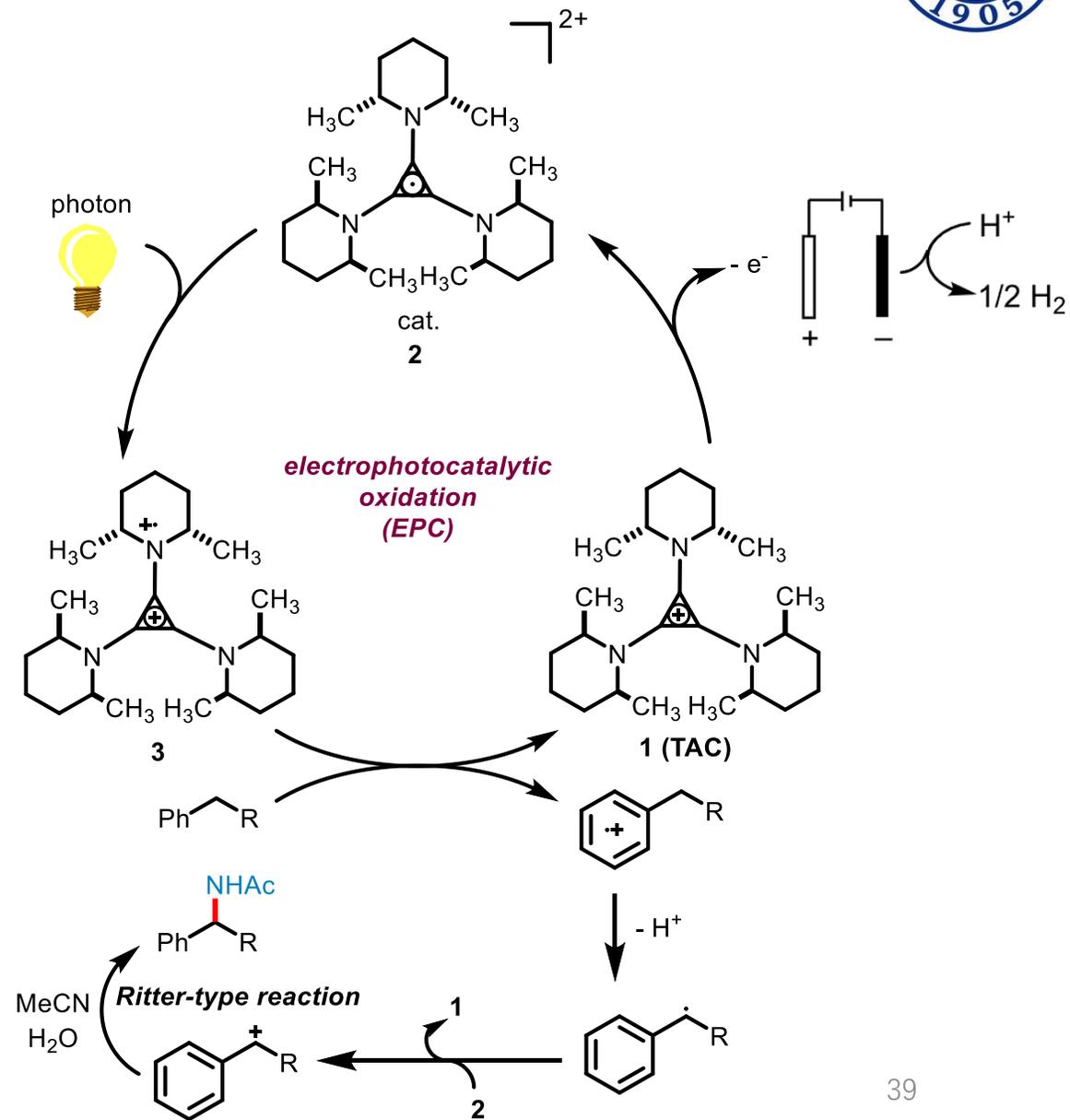
3.2.2 TAC光敏剂参与电极反应



Representative products

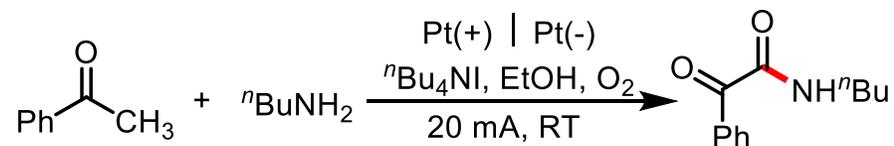


Tristan H. Lambert
Cornell University

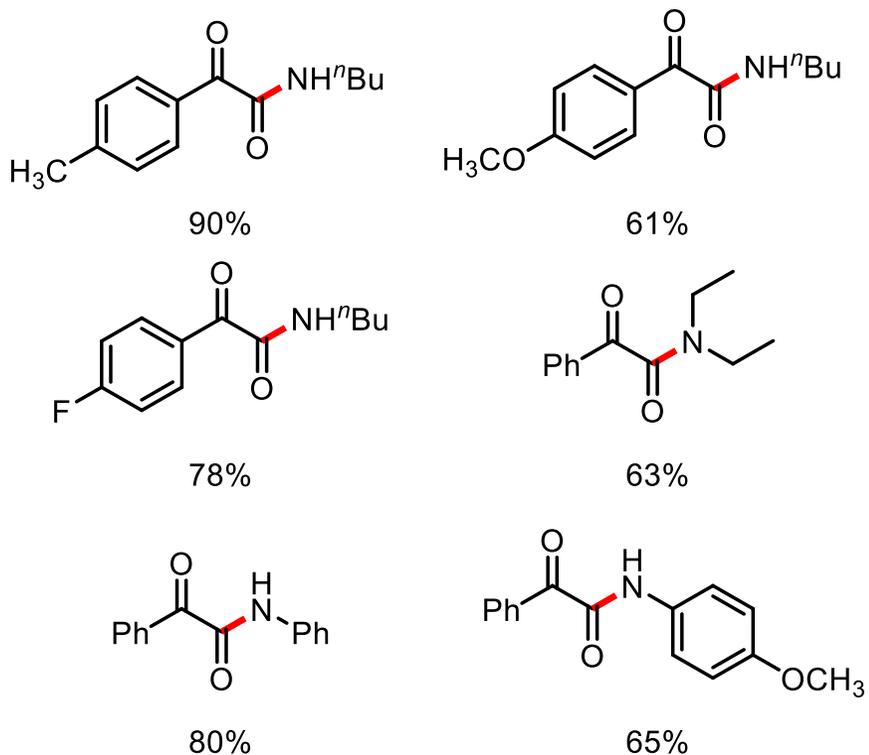


3.2 底物不参与电极反应

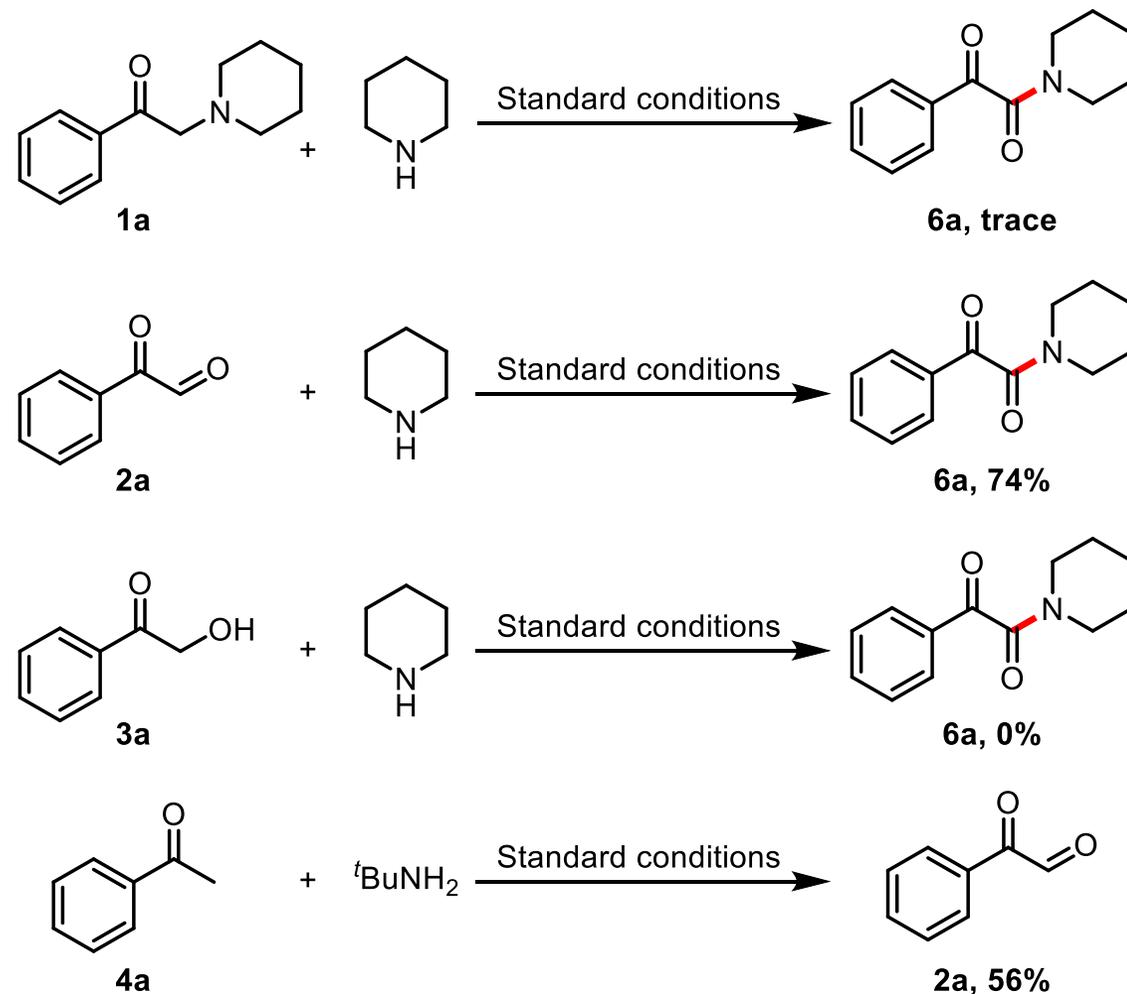
3.2.3 碘参与电极反应



Representative products



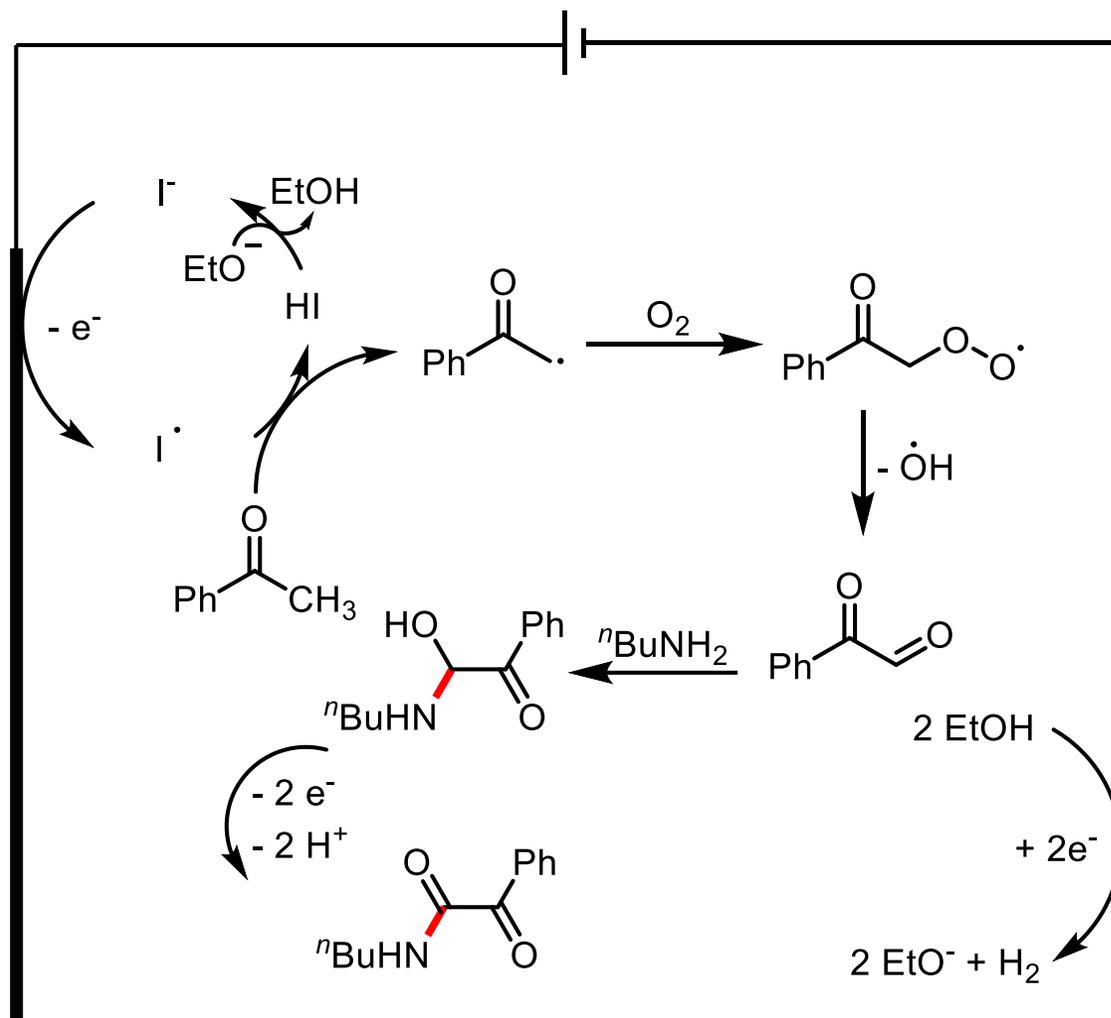
Control experiments



3.2 底物不参与电极反应

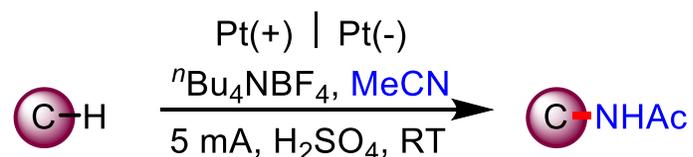
3.2.3 碘参与电极反应

Proposed mechanism



3.2 底物不参与电极反应

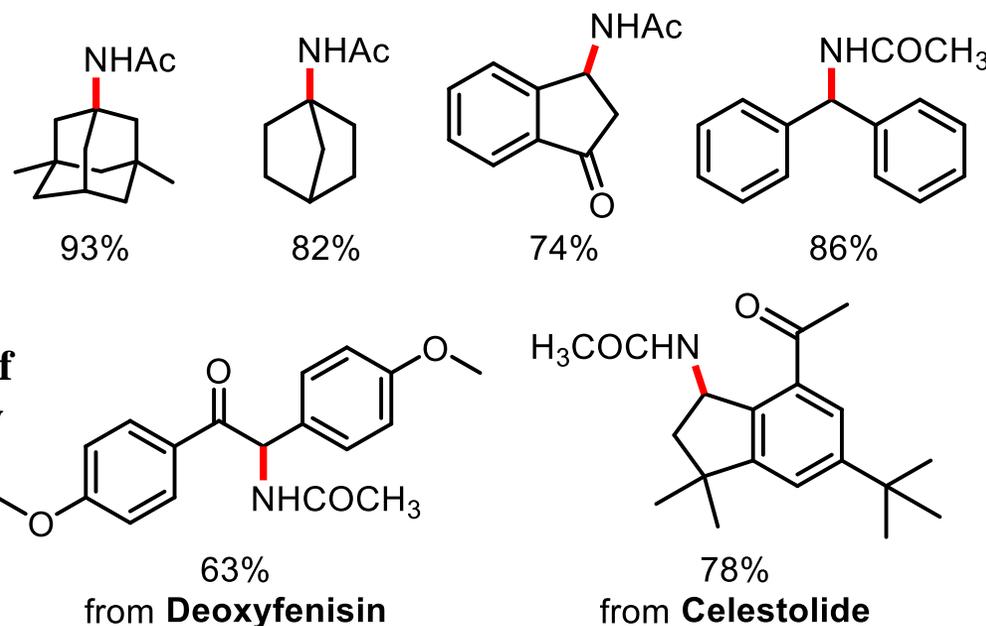
3.2.4 SO_4^{2-} 参与电极反应



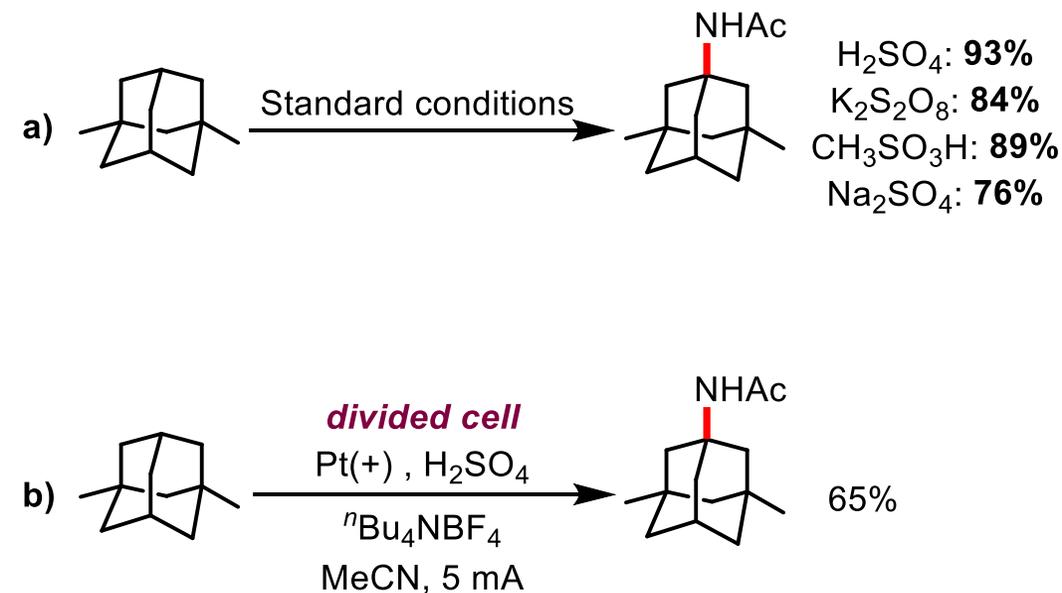
Jinxing Ye

East China University of
Science and Technology

Representative products



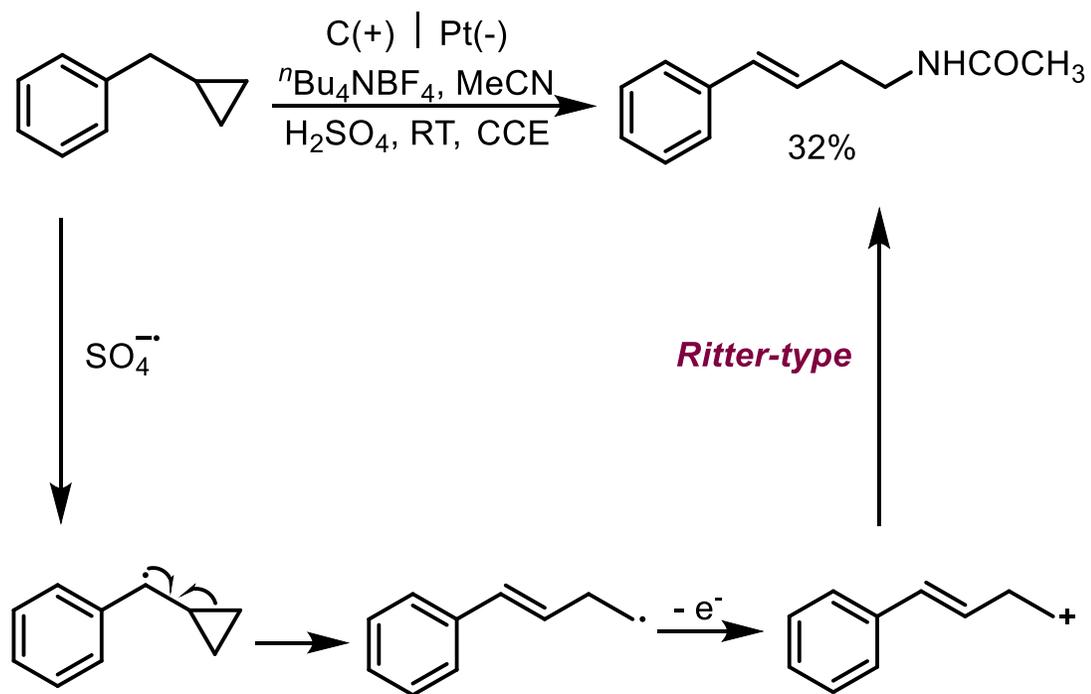
Control experiments



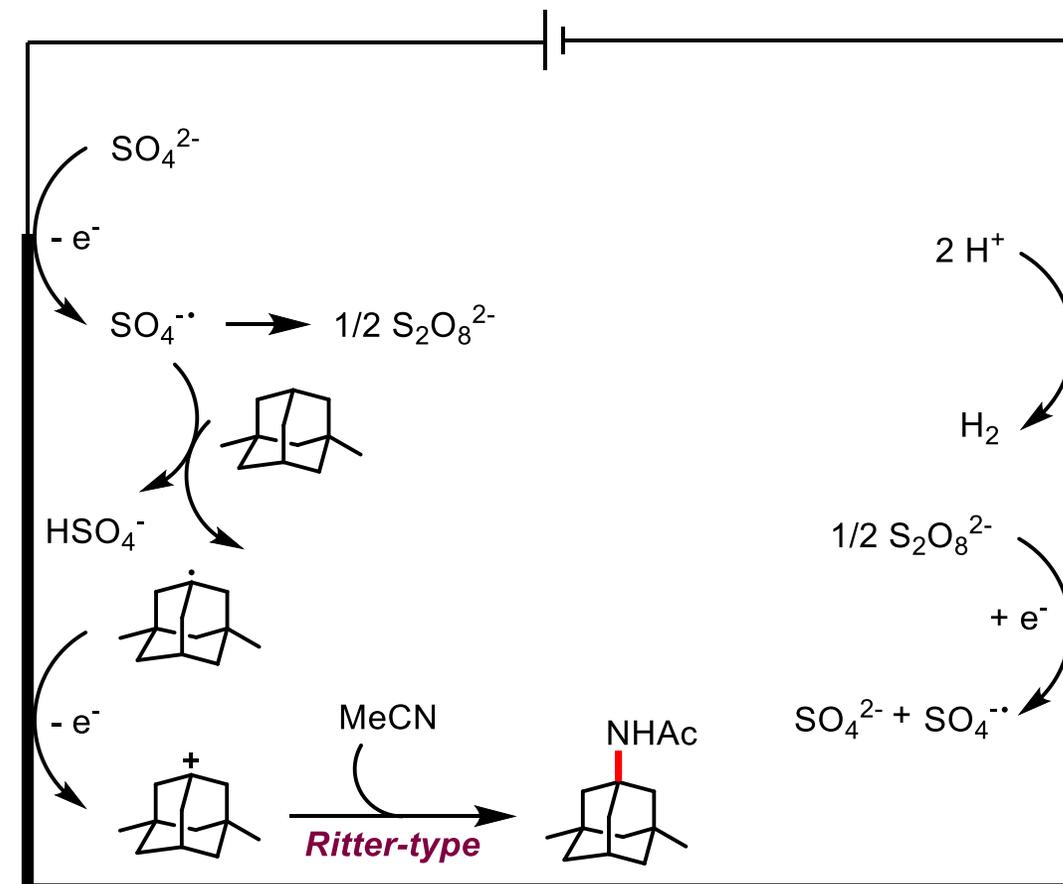
3.2 底物不参与电极反应

3.2.3 SO_4^{2-} 参与电极反应

Radical trapping experiments



Proposed mechanism



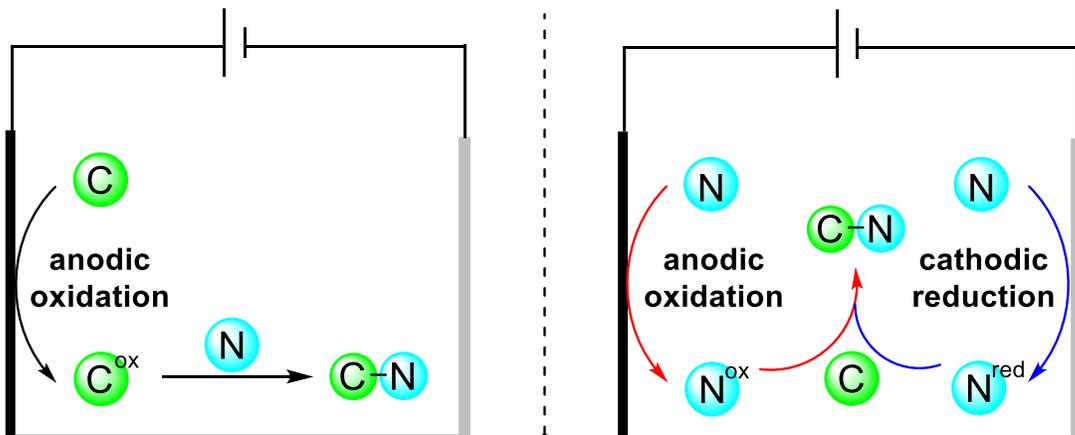


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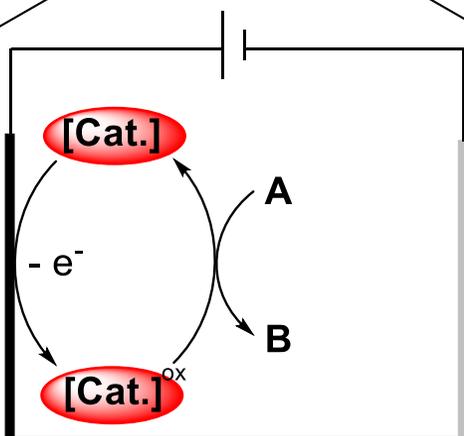
- 一、研究背景与意义
- 二、电催化的 sp^3 C-H胺化反应
- 三、电催化的 sp^2 C-H胺化反应
- 四、总结与展望

4. 总结与展望

底物参与电极反应



底物不参与电极反应

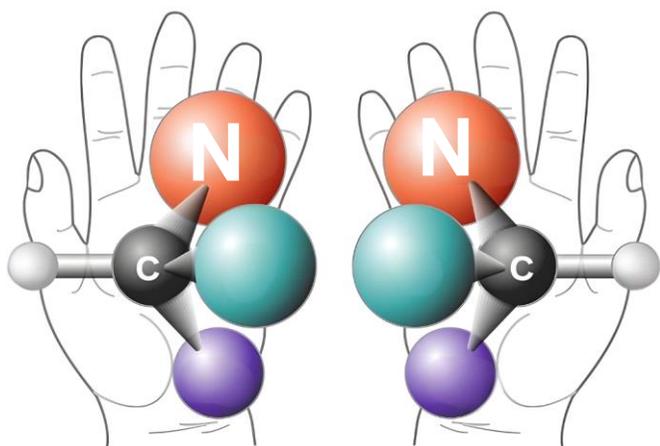


优势

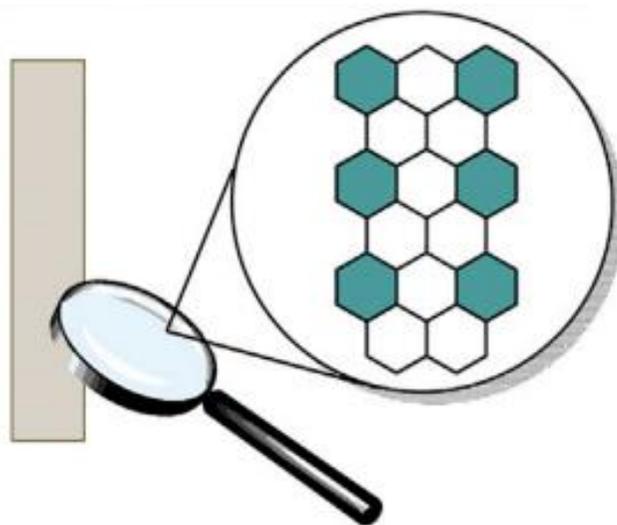
- 反应条件温和，更安全
- 在电极发生氧化/还原替代了传统氧化/还原剂的使用
- 电位可调，通过加入催化量的氧化剂、催化剂，可以在更低的电位下进行反应，较少副反应的发生

不足之处

- 惰性C-H键的活化在电催化中仍然难以进行
- 电催化的放大反应难以实现
- 电催化的反应类型不如传统化学广泛



不对称C-H键胺化



新型电极材料

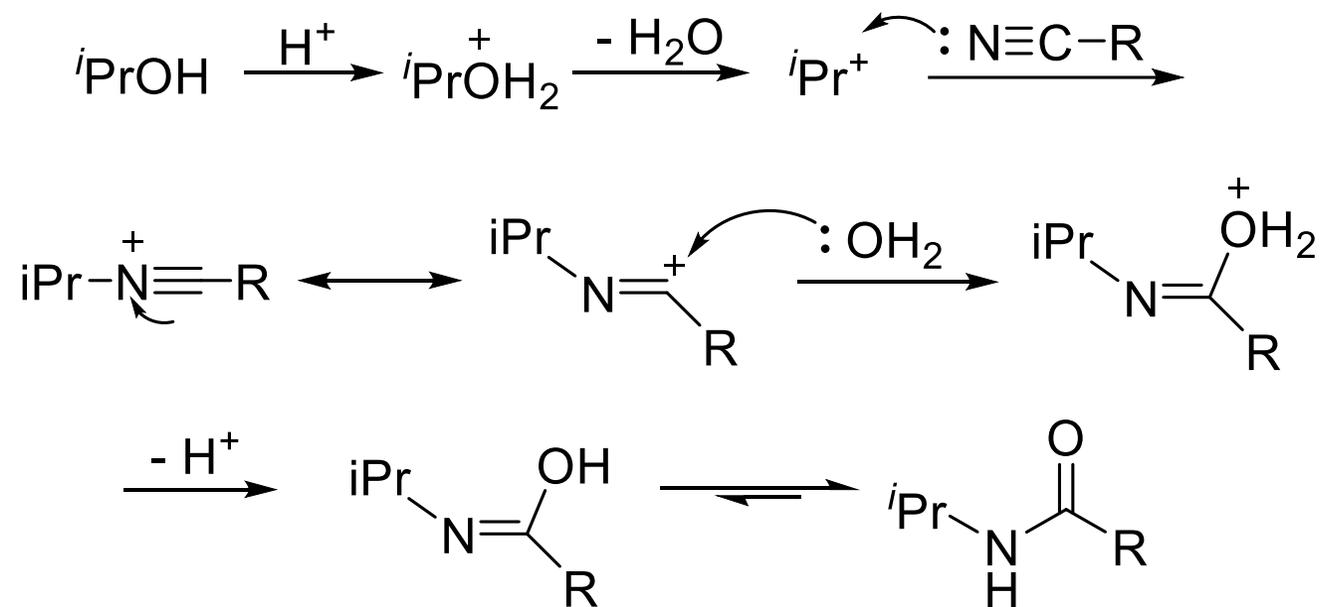


光电催化结合

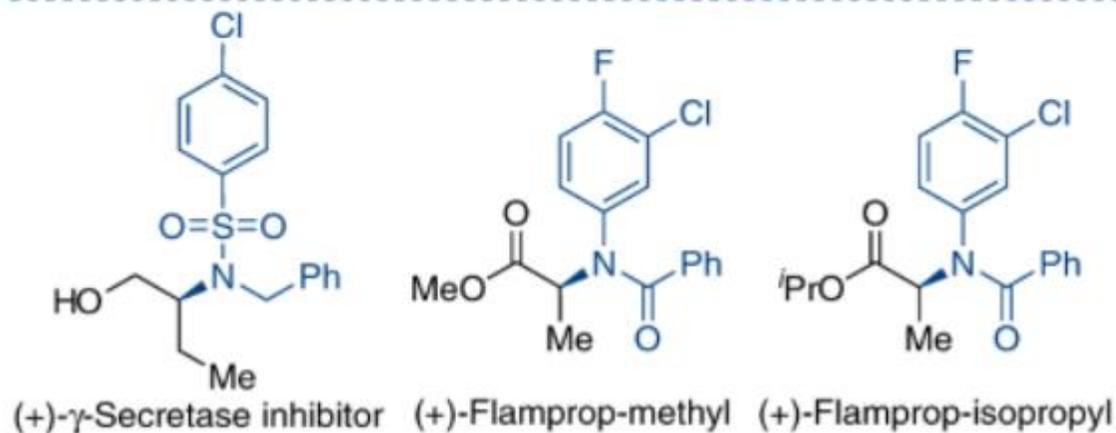
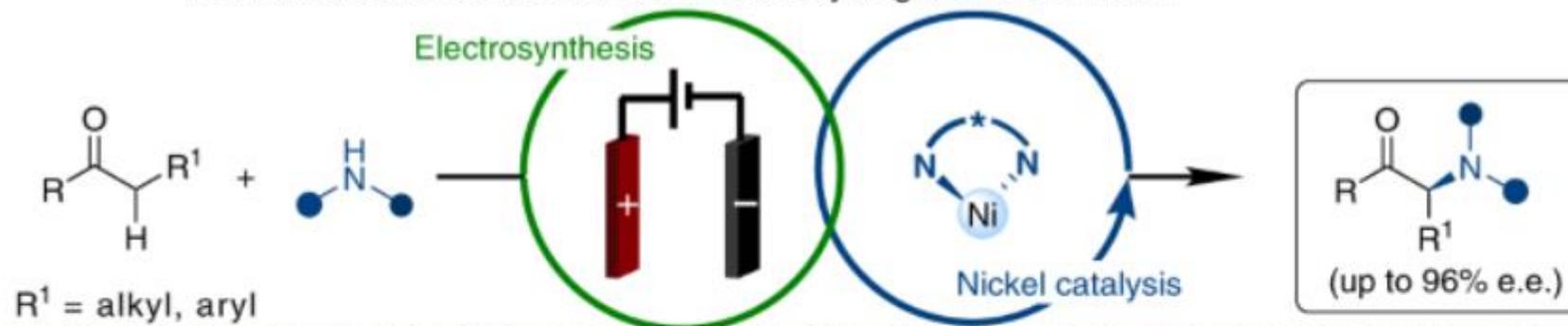


感谢倾听
请各位老师同学批评指正！

Ritter reaction



Enantioselective electrochemical cross-dehydrogenative amination



- Enantioselective electrosynthesis
- Cross-dehydrogenative amination
- Enantioselective (up to 96% e.e.)
- >70 examples
- Access to bioactive molecules