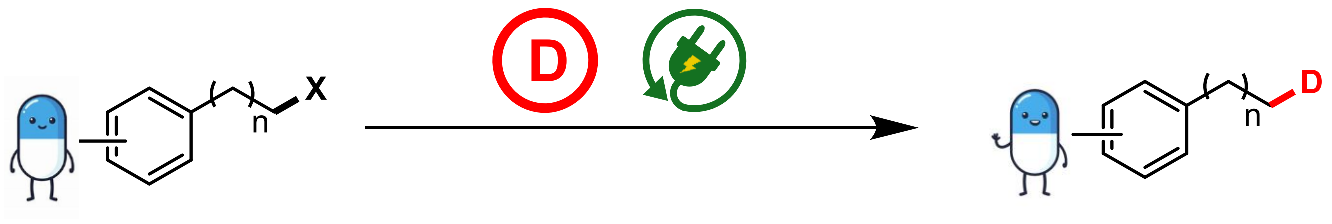
Electrochemical Deuteration Reaction



Reporter: Xu Song
Supervisor: Prof. Shengming Ma
2025-4-25 ***Seminar***

Outline

- ***Background***
- ***Electrochemical Hydrogen isotope exchange Reaction***
- ***Electrochemical Dearomative Deuteration***
- ***Electrochemical Olefin Deuteration***
- ***Electrochemical Dehalogenation Deuteration***
- ***Electrochemical Deoxygenative Deuteration***
- ***Summary and Outlook***

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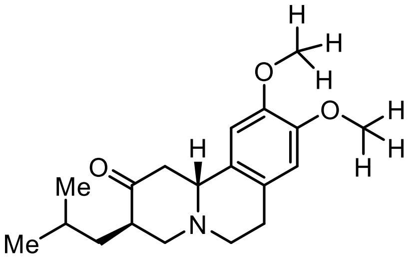
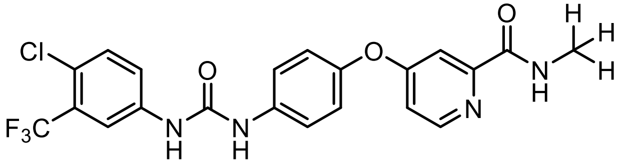
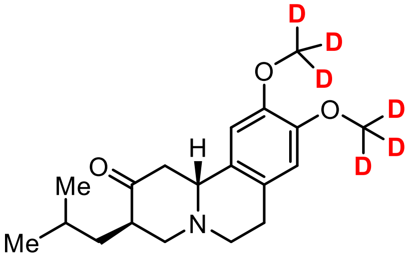
Deuterium modification of molecules and potential effects of precision deuteration



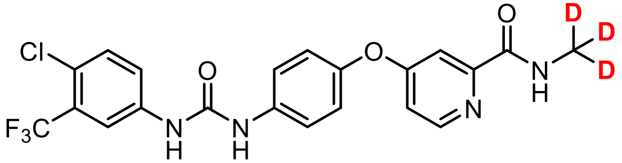
Tetrabenazine



Sorafenib



Austedo
(Huntington's chorea)
2017-FDA



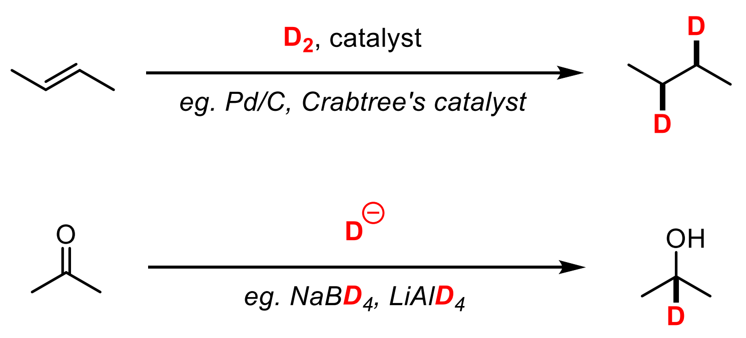
Donafenib
(liver cancer)
2021-NMPA

- *Improved drug selectivity*
- *Increased pharmacodynamic activity*
- *Reduced and less-frequent dosing*
- *Reduced toxicity*

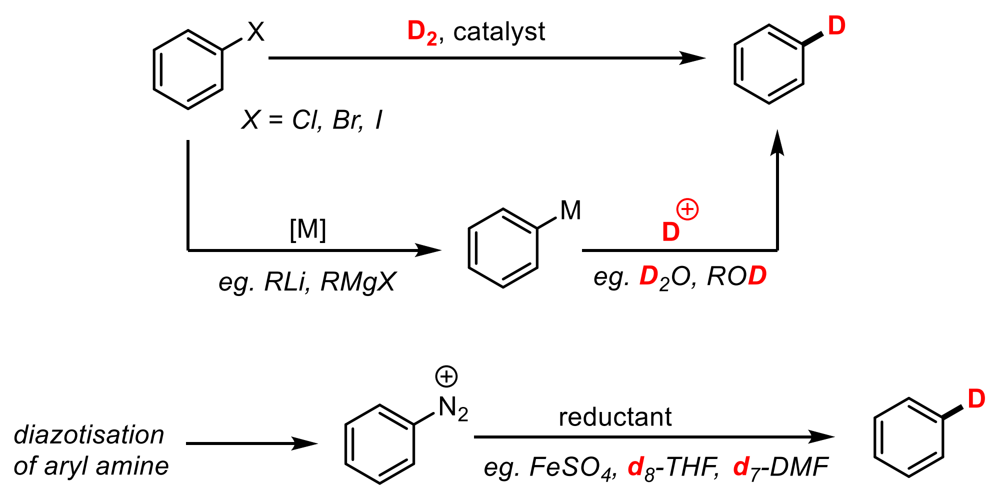
R. M. C. Di Martino, B. D. Maxwell, T. Pirali, *Nat. Rev. Drug Discov.* **2023**, *22*, 562–584.

Conventional methods for deuterium incorporation into organic molecules

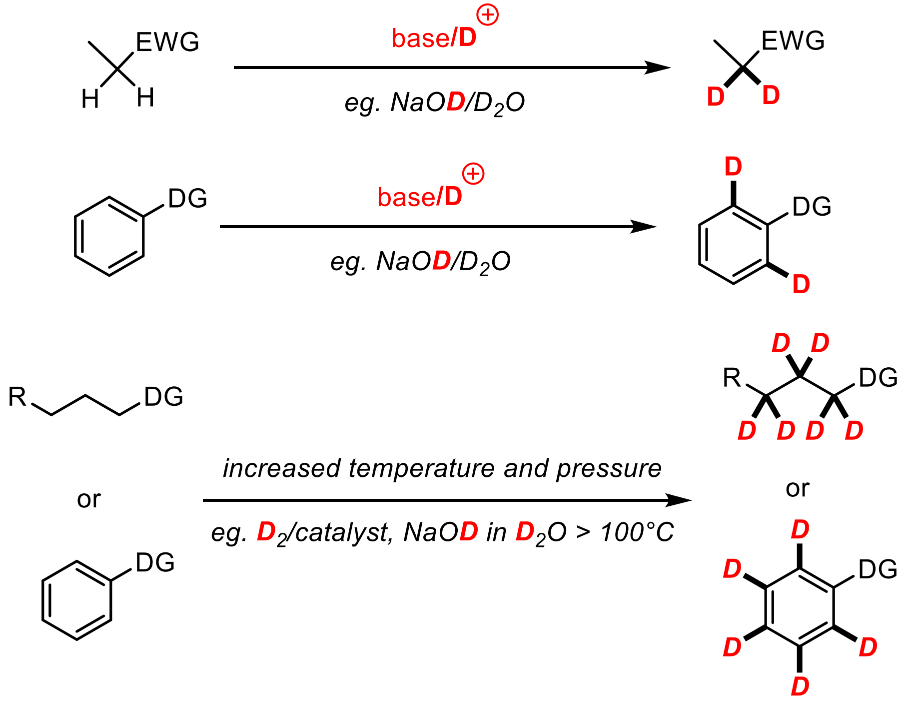
(a) addition of deuterium.



(b) substitution with deuterium.



(c) hydrogen isotope exchange (HIE).



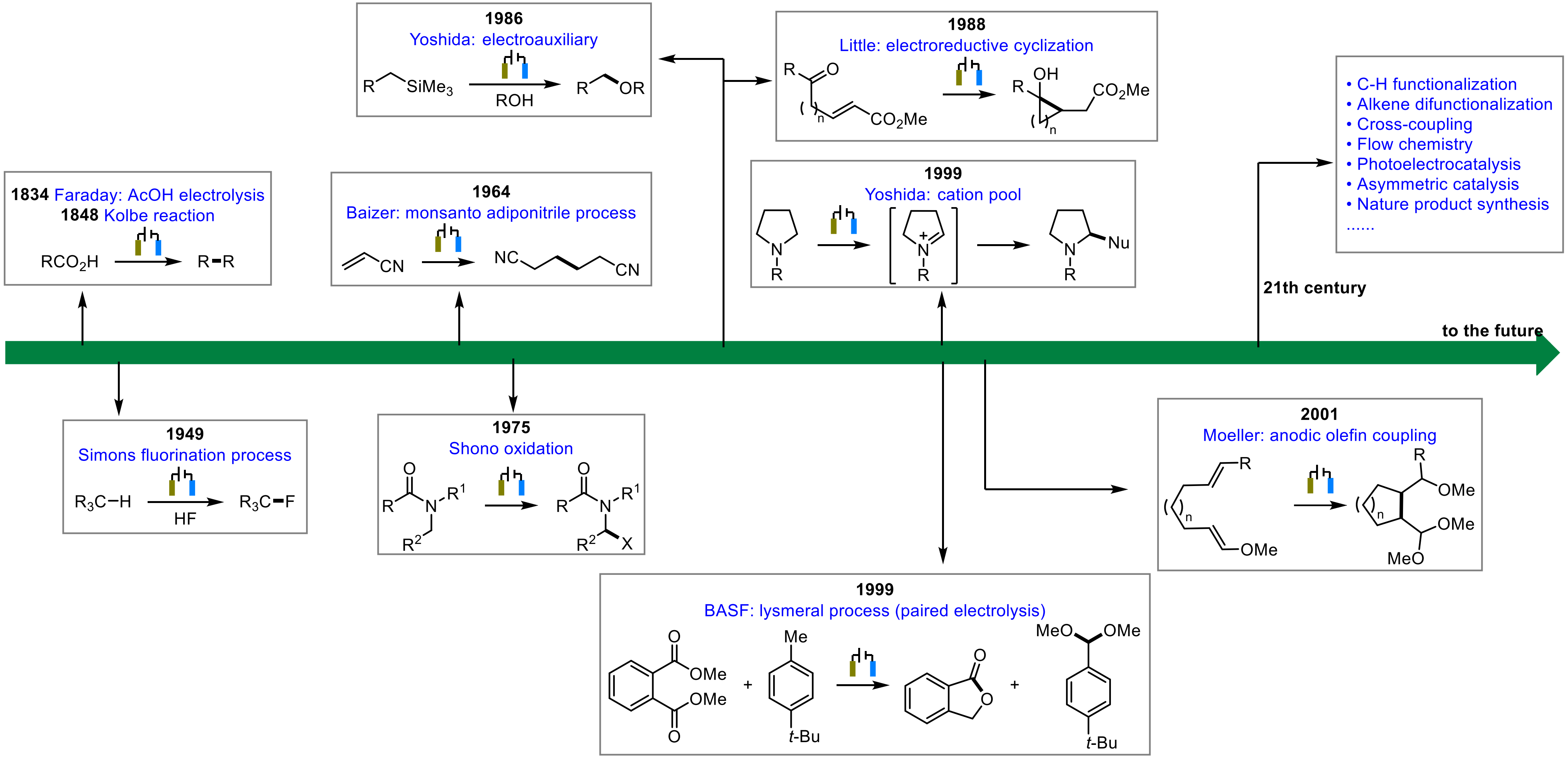
The use of D_2 as the deuterium source ✗

The requirement for air-sensitive reagents ✗

Challenges in achieving precise site-selectivity ✗

P. L. Norcott, *Chem. Commun.* **2022**, *58*, 2944–2953.

The development of organic electrochemistry



efficient ✓ economical ✓ widely used ✓

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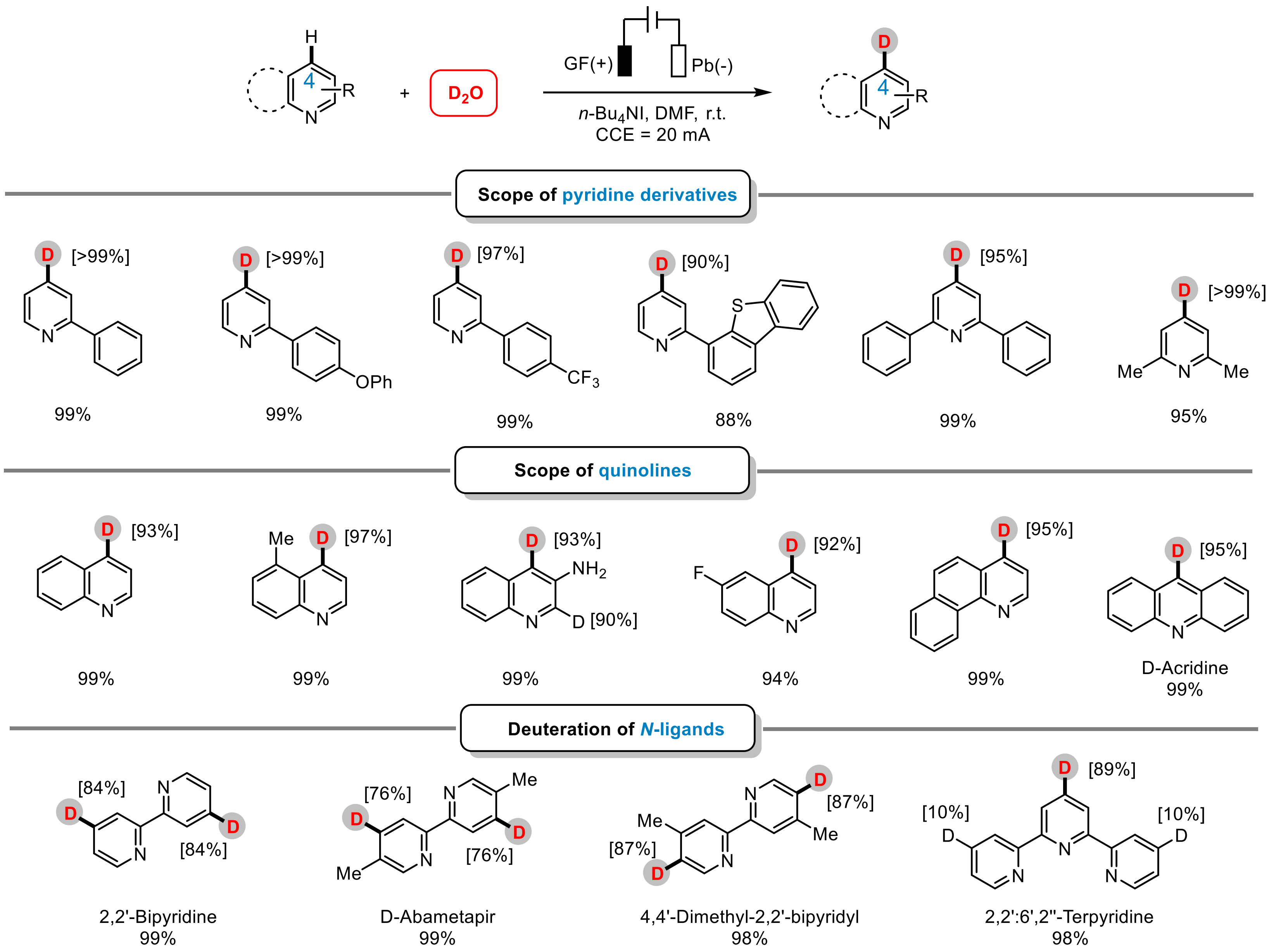
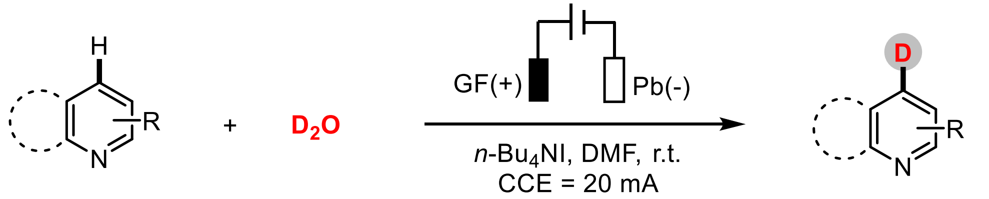
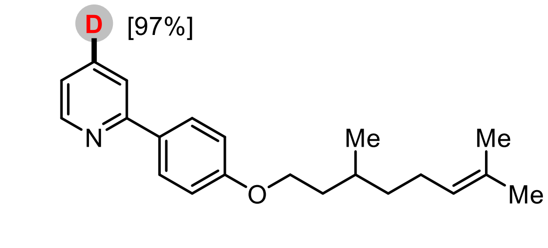


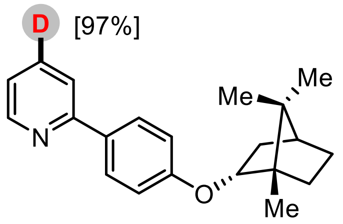
Z. Zhao, R. Zhang, Y. Liu, Z. Zhu, Q. Wang, Y. Qiu, *Nat. Commun.* **2024**, *15*, 3832.



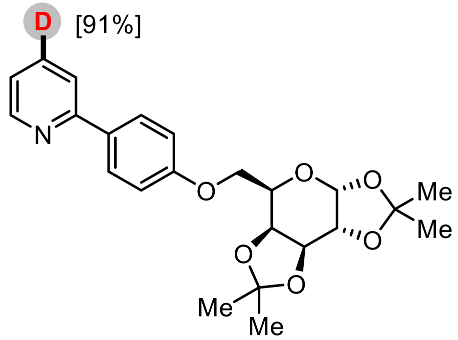
Late-stage modification of biorelevant compounds



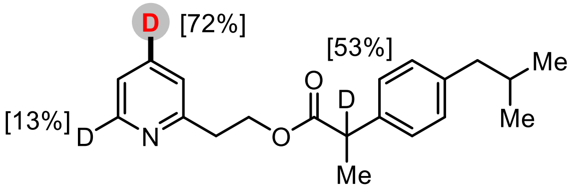
from Citronellol
99%



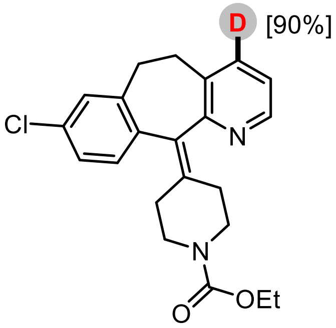
from Borneol
98%



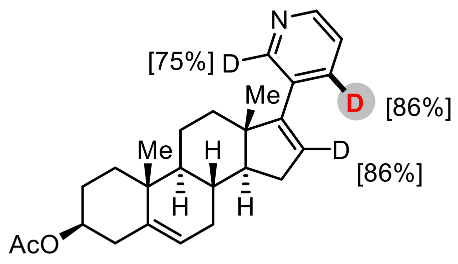
from D-galactopyranose
99%



from Ibuprofen
98%

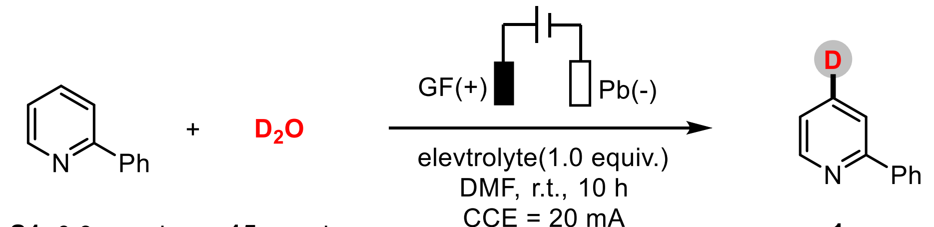


D-Loratadine (Claritin)
90%



D-Bisacodyl (Dulcolax)
92%

A. Effect of the electrolyte.

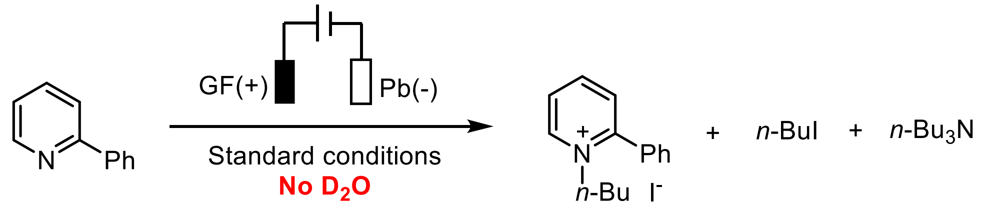


S1, 0.3 mmol   15 mmol   **1**

Entry	Electrolyte	Yield of **1** or recovered **S1** (%)	**1** (D%)
1	NaCl	99	0
2	$LiBF_4$	99	0
3	KPF_6	99	0
4	n-Bu_4NBr	93	99
5	n-Bu_4NCl	88	96
6	n-Bu_4NOAc	42	>99
7	n-Bu_4NPF_6	67	>99
8	n-Bu_4NHSO_4	76	>99
9	n-$Bu_4NH_2PO_4$	90	96

- the electrolyte tetrabutylammonium salt was crucial

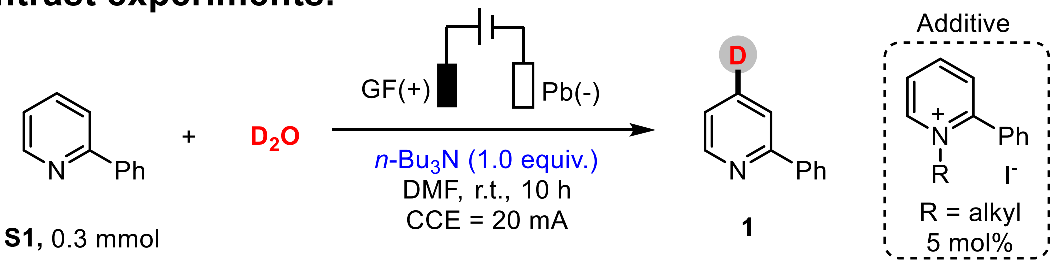
B. Observation of intermediate S1-a.



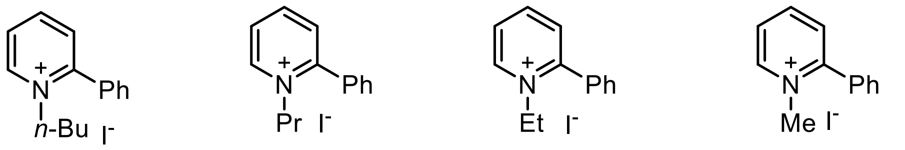
S1   **S1-a**

Detected by HRMS (212.1434)

C. Contrast experiments.



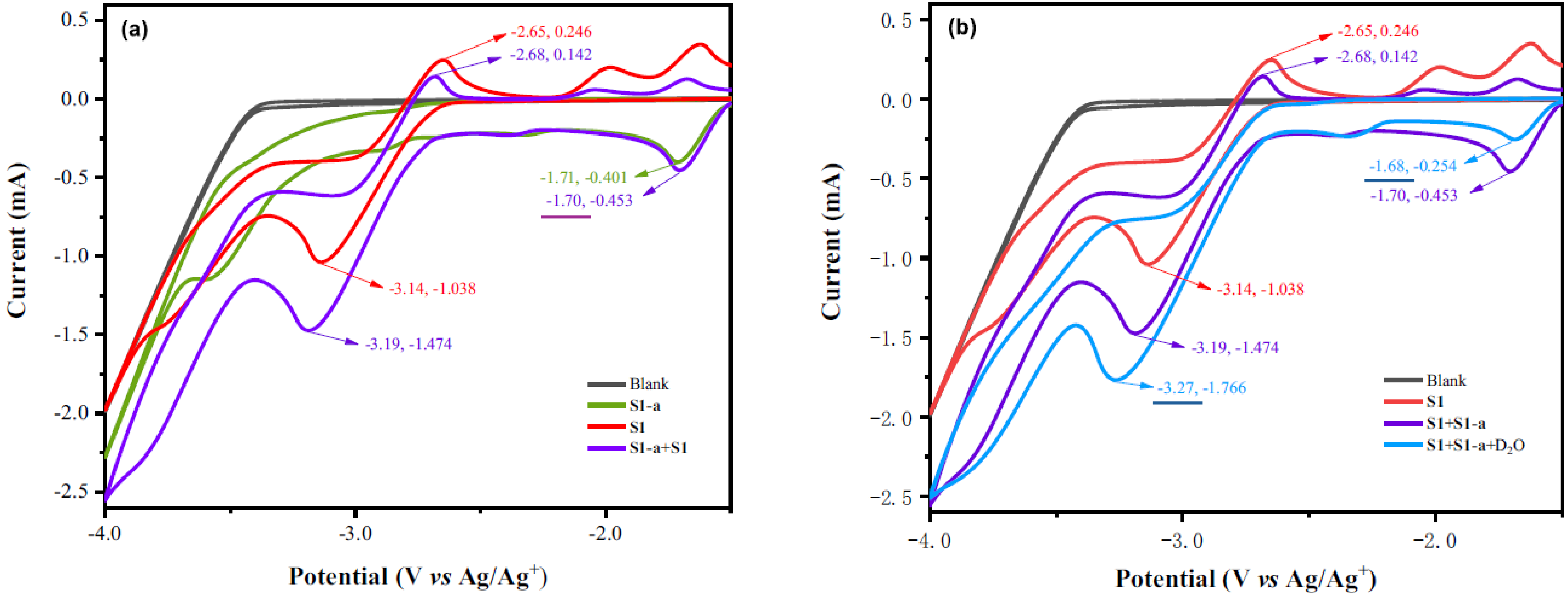
S1, 0.3 mmol   **1**

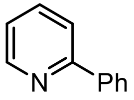


S1-a >99% D   **S1-b** 96% D   **S1-c** 90% D   **S1-d** 87% D

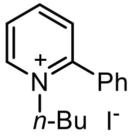
- S1-a may be the key intermediate in the reaction

D. Cyclic voltammetry studies.





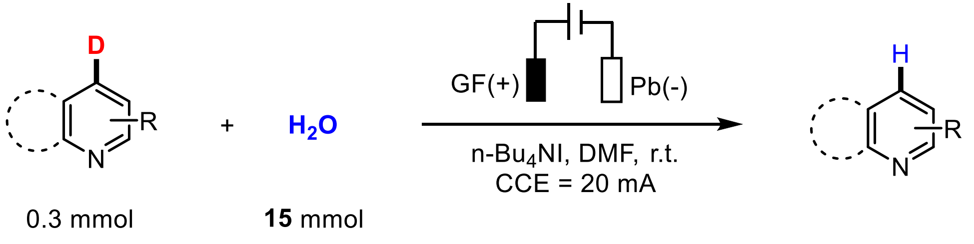
S1

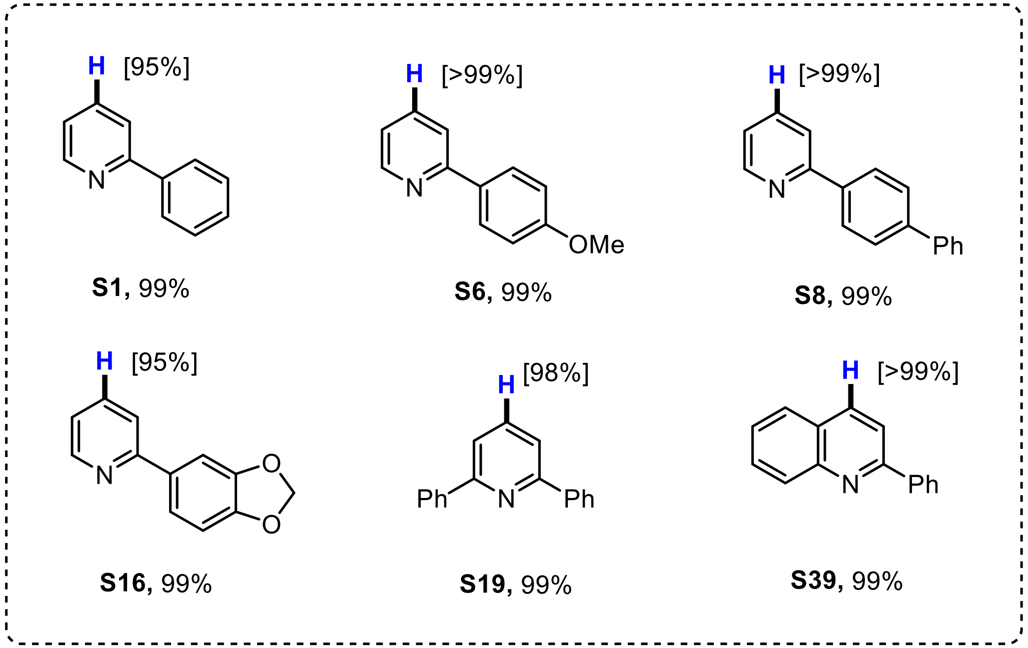


S1-a

- the catalytic current was generated because of S1-a
- the bifunctional participation of TBAI: the improvement of conductivity and the synthesis of S1-a

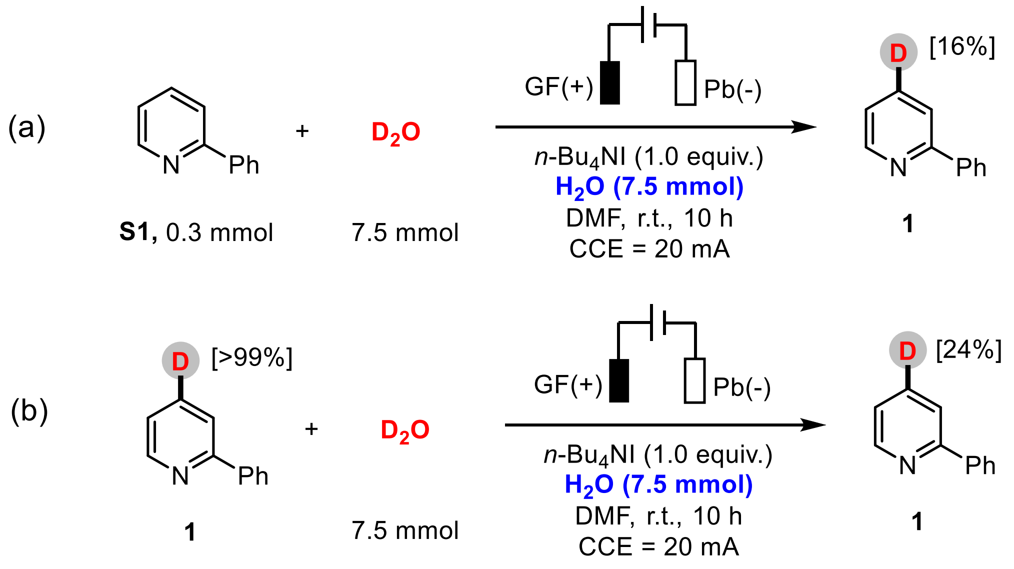
G. D/H exchange experiments.



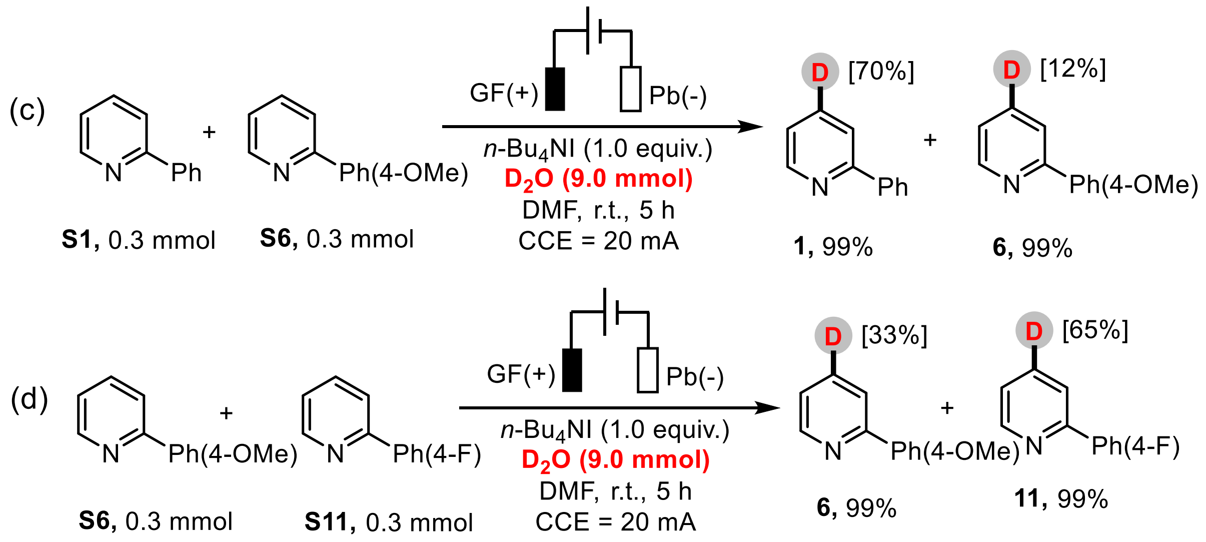


- this electrochemical deuteration reaction was reversible

H. Competition experiments.

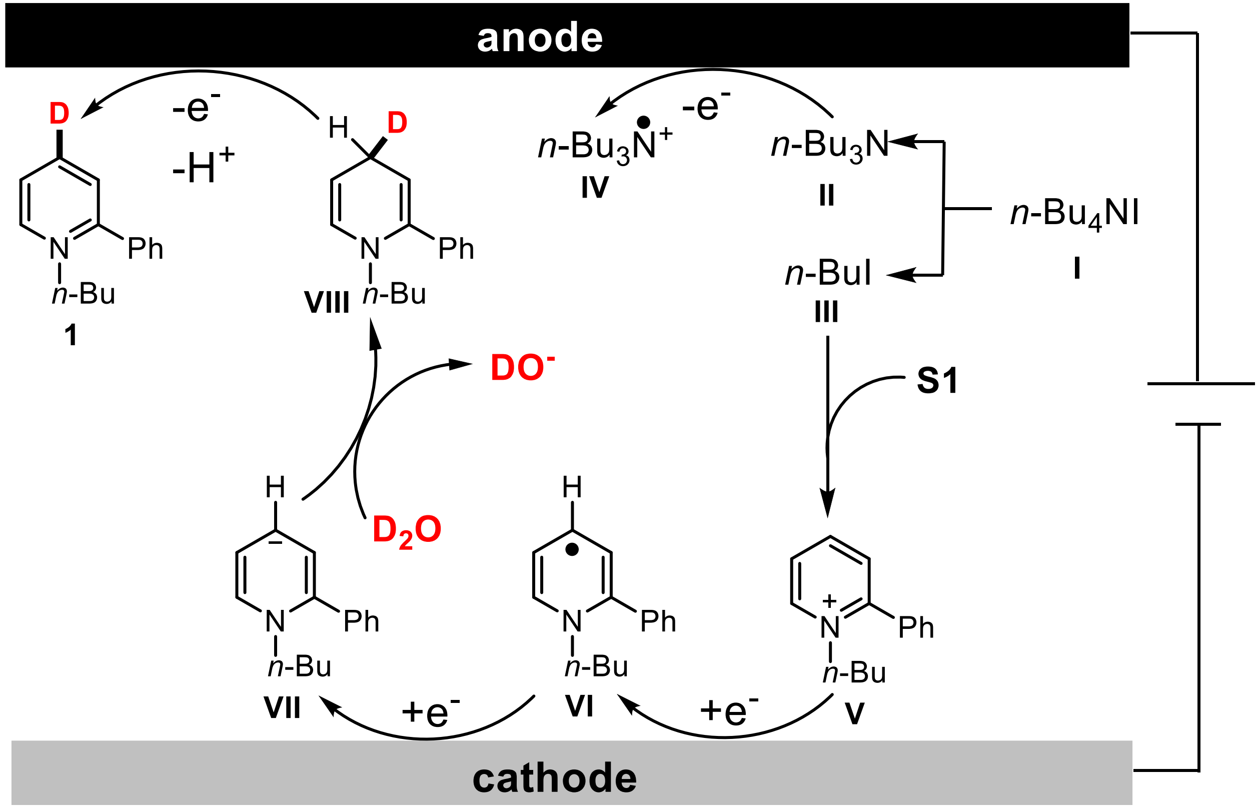


- the ability of pyridine anions to capture H+ is better than D+



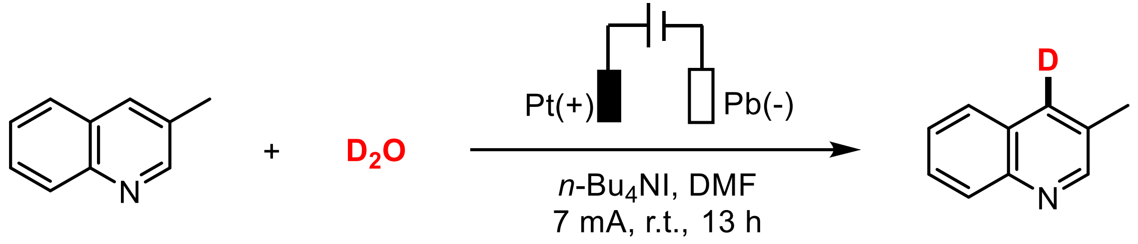
- the D% of products that bearing F was superior to that bearing OMe

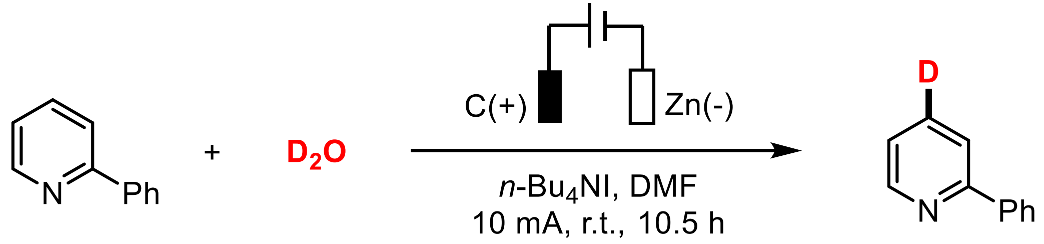
Proposed mechanism.



Electrochemical Hydrogen isotope exchange Reaction

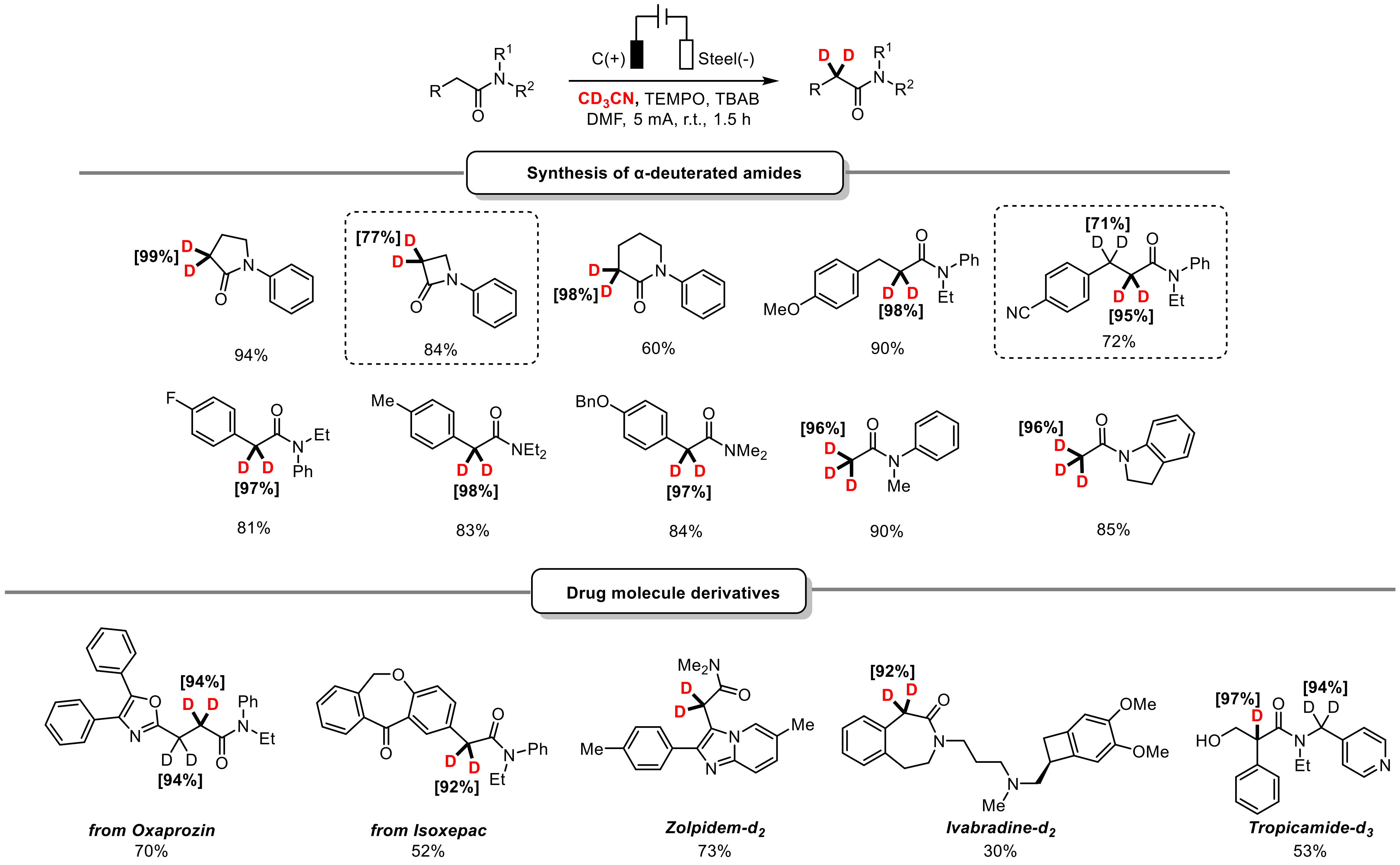
Other examples:





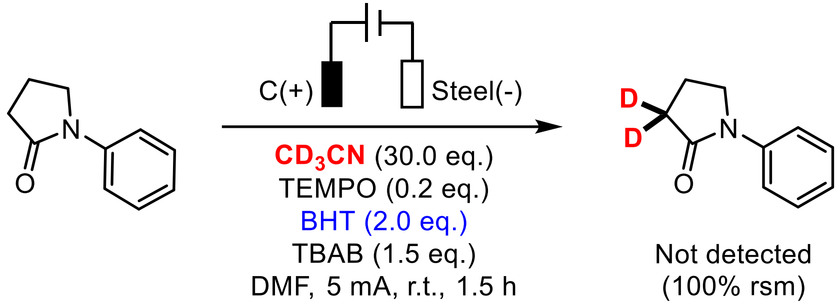
F. Qiu, Y. Chen, P. Liao, Y. Gao, M. Guo, H. Zhang, A. Lei, W. Li, Green Synth. Catal. **2024**, 10.1016/j.gresc.2024.06.003

L. Shi, M. Liu, L. Zheng, Q. Gao, M. Wang, X. Wang, J. Xiang, *Org. Lett.* **2024**, *26*, 4318–4322.

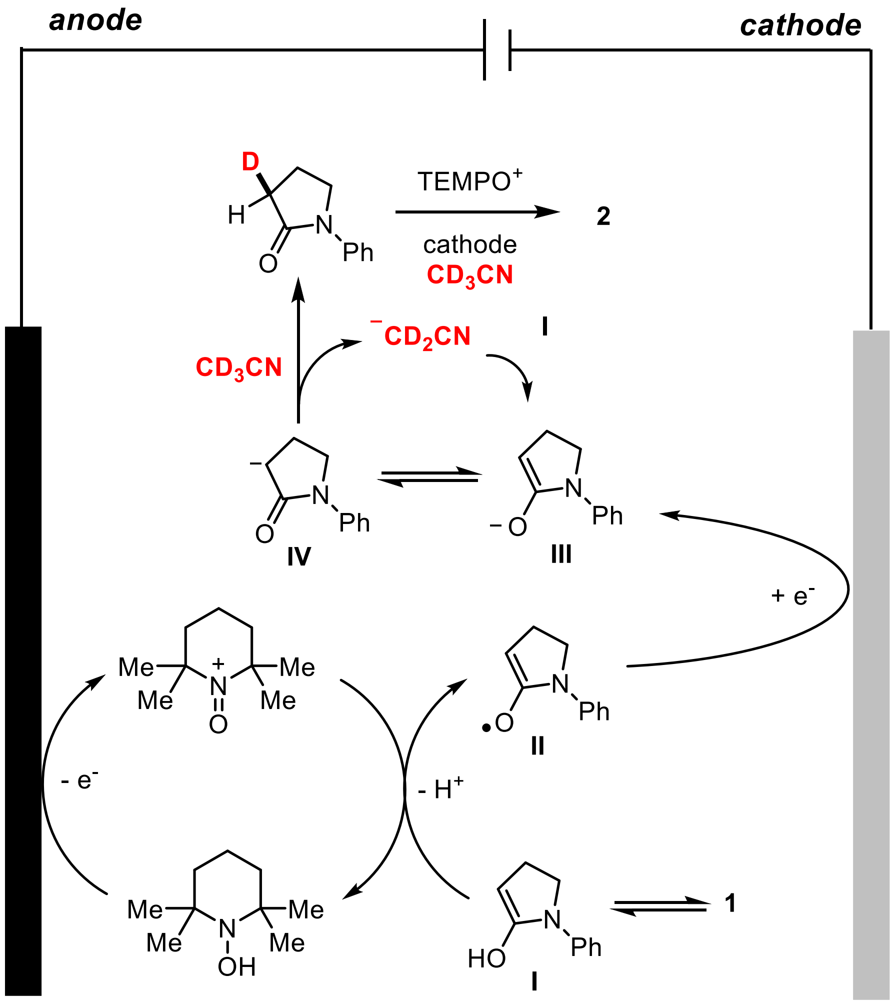


S. Ning, C. Wu, L. Zheng, M. Liu, Y. Zhang, X. Che, J. Xiang, *Green Chem.* **2023**, *25*, 9993–9997.

The radical-trapping experiment.



Proposed mechanism.



- a radical process should be involved in the electro-deuteration reaction

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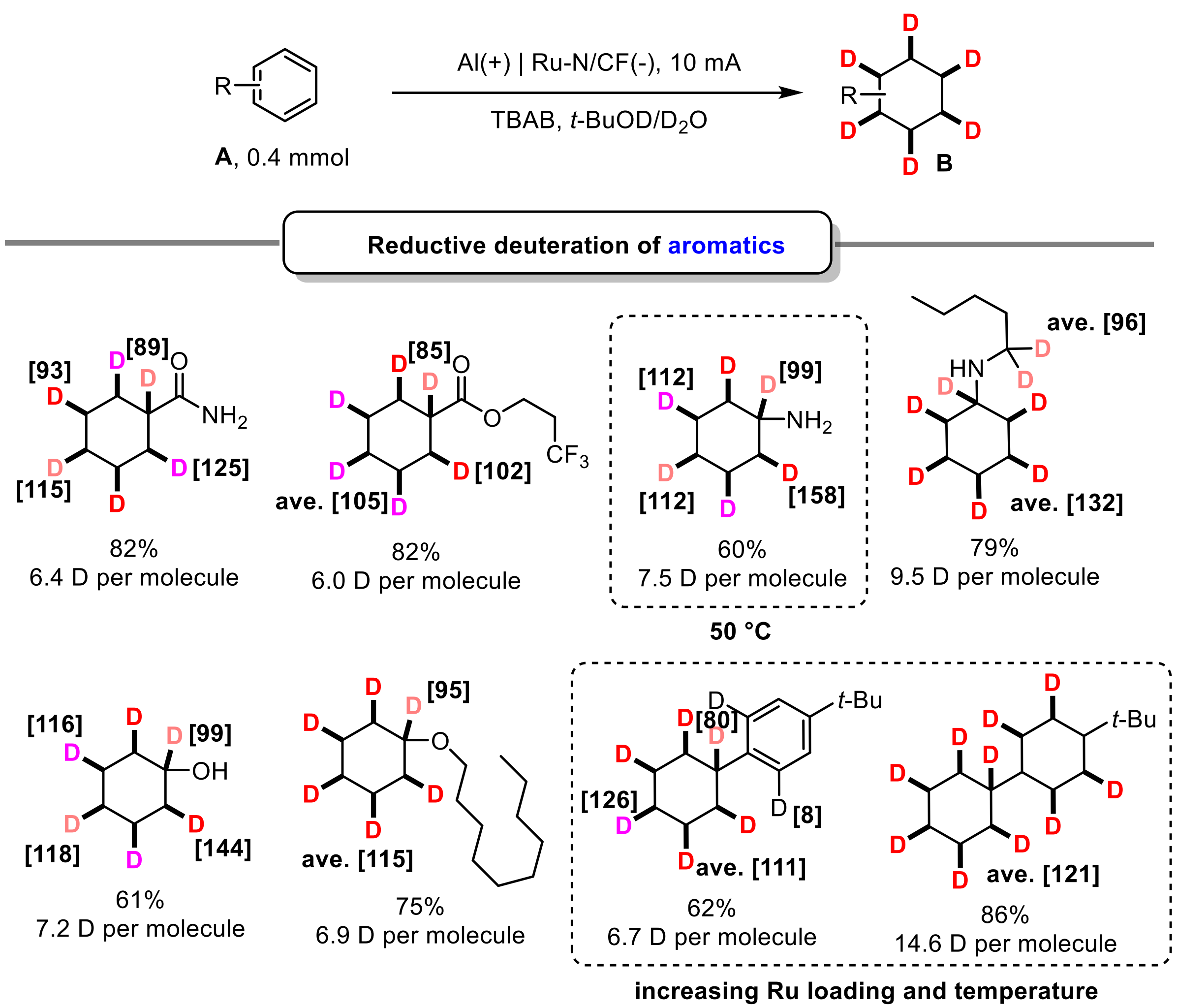
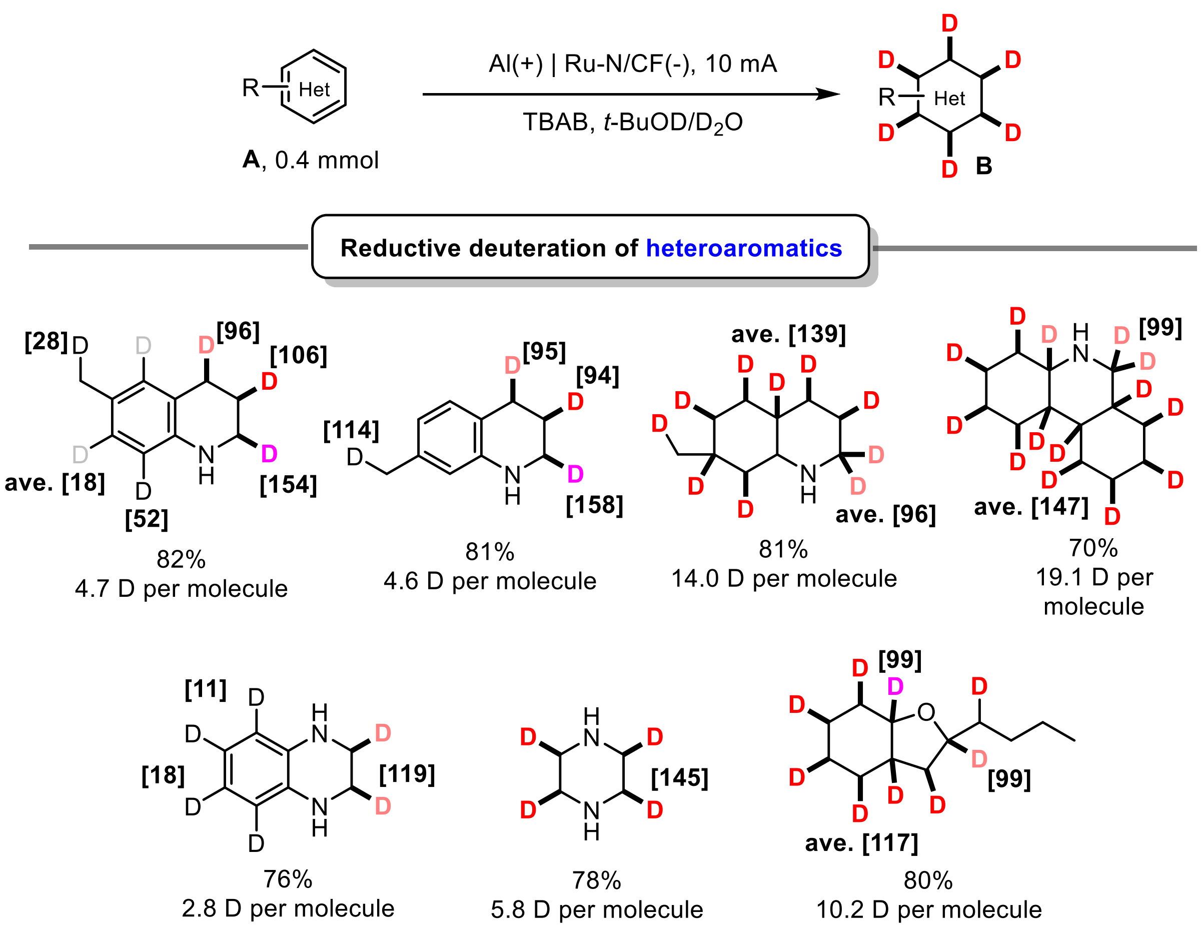
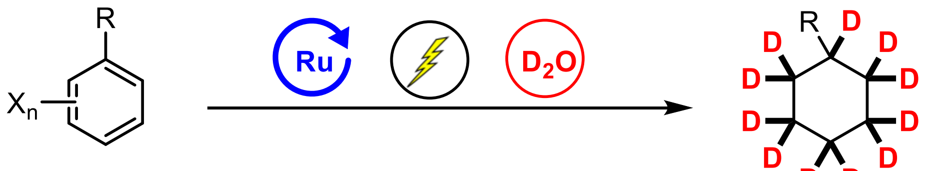


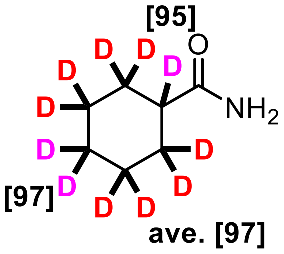


F. Bu, Y. Deng, J. Xu, D. Yang, Y. Li, W. Li, A. Lei, *Nature* **2024**, *634*, 592–599.

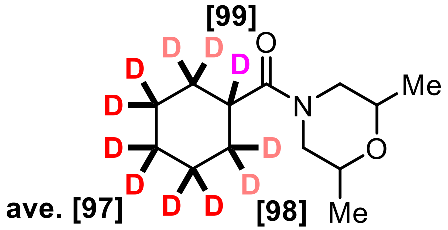


X = F, n = 1-10

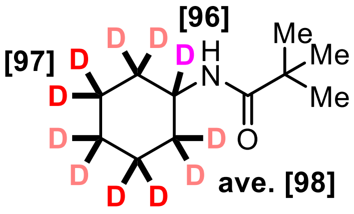
Defluorinated deuterated reaction



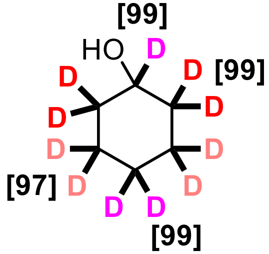
85%
10.7 D per molecule
X = F, n = 5



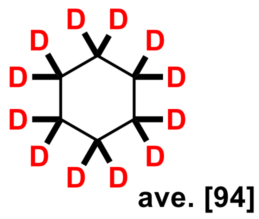
75%
10.7 D per molecule
X = F, n = 5



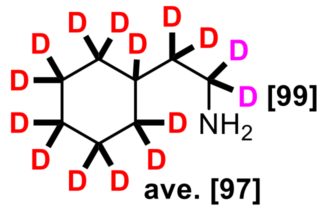
93%
10.8 D per molecule
X = F, n = 5



65%
10.8 D per molecule
X = F, n = 5

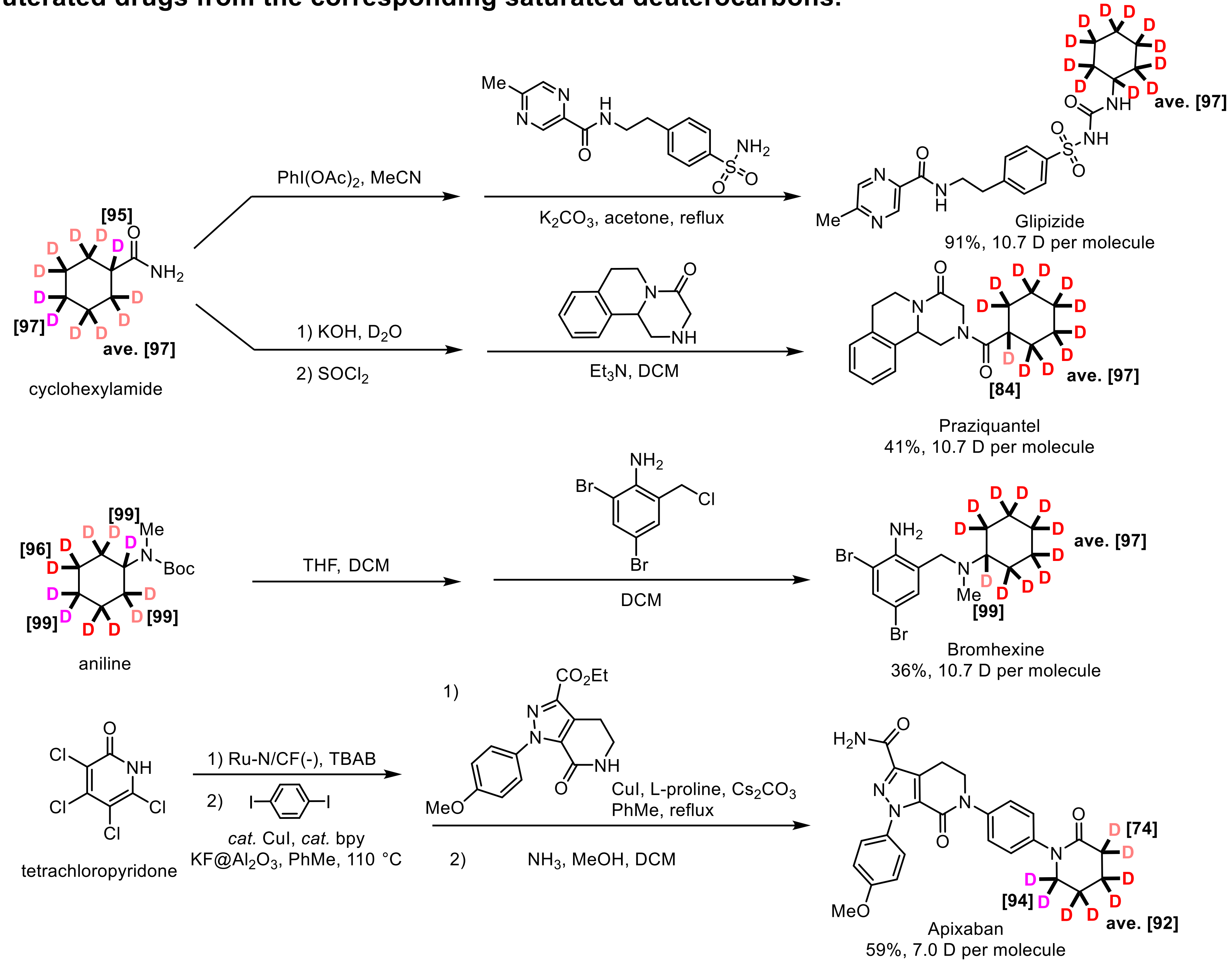


con > 99%
11.3 D per molecule
X = F, n = 6



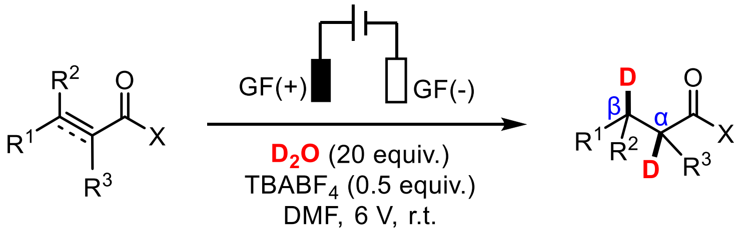
48%
14.6 D per molecule
X = F, n = 5

Preparation of deuterated drugs from the corresponding saturated deuterocarbons.

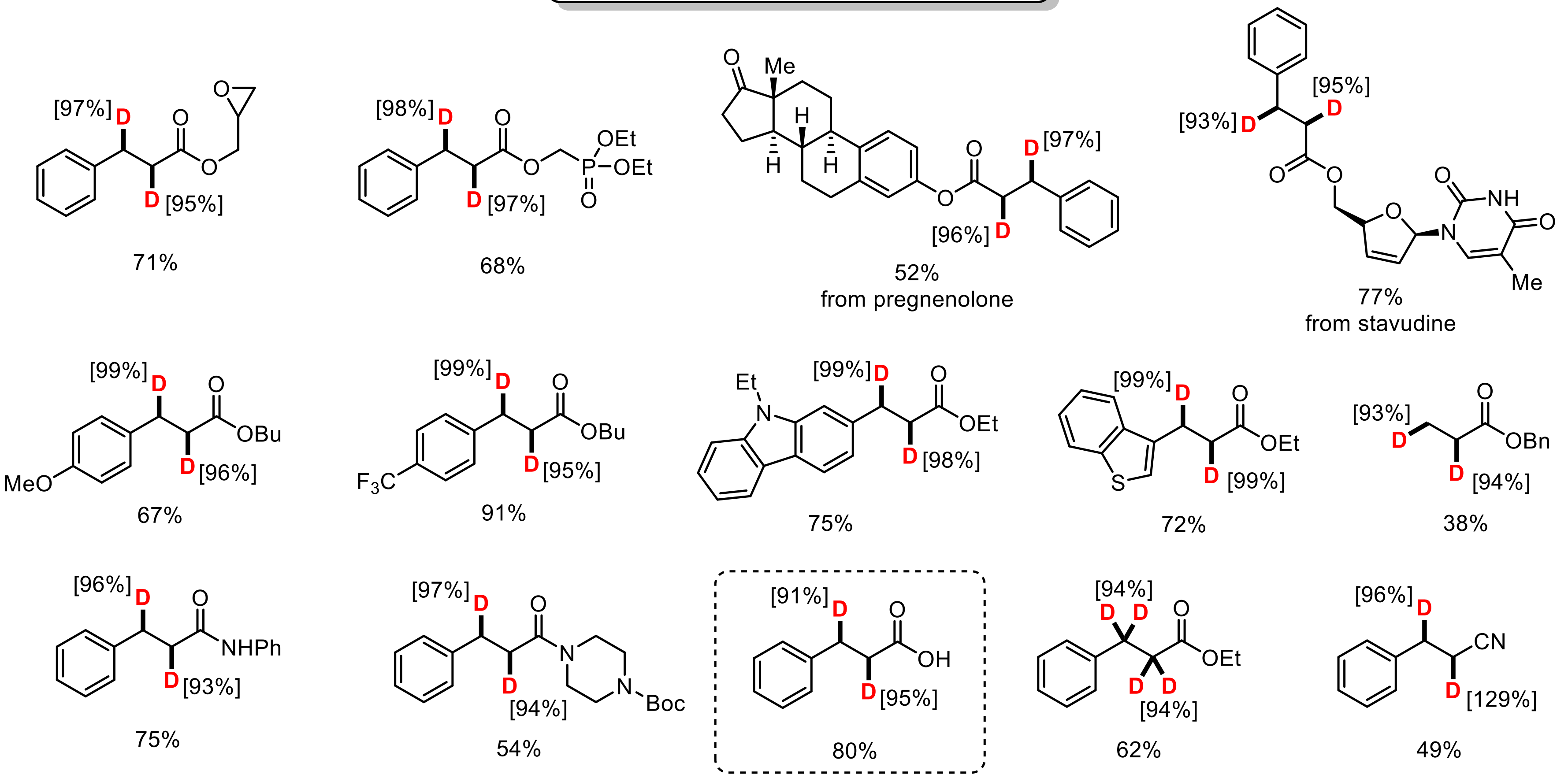


Outline

*Electrochemical **Active** Olefin Deuteration*

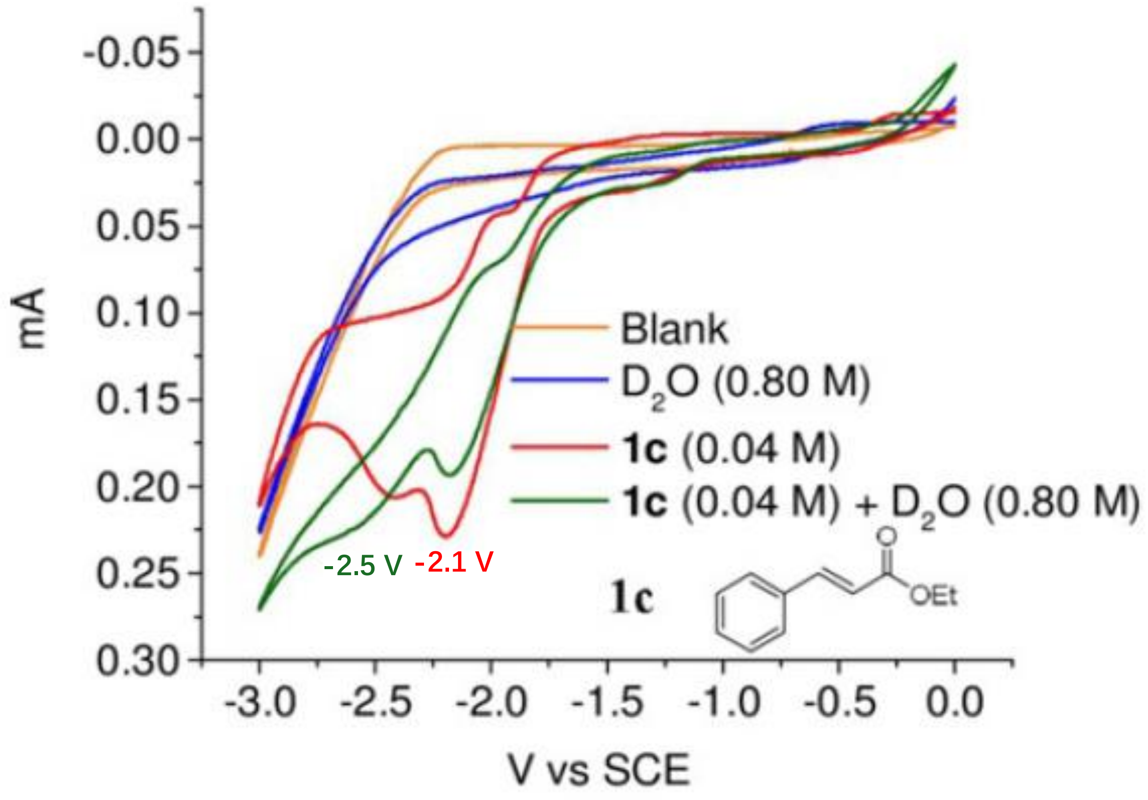


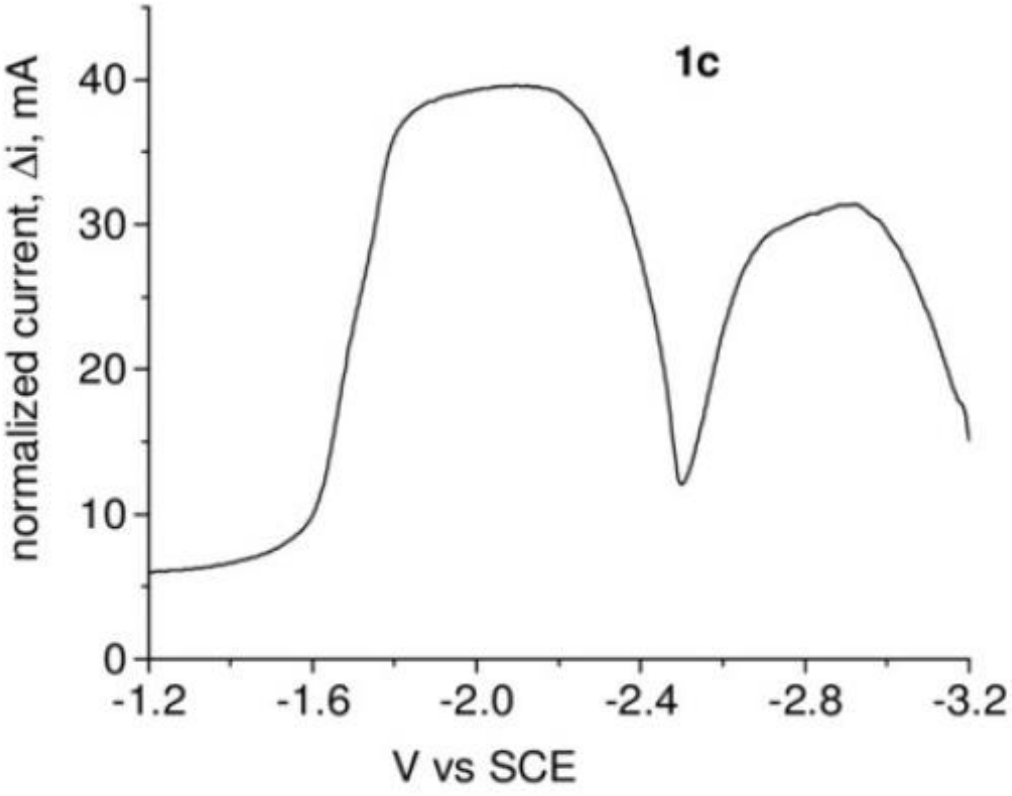
Scope of electrochemical deuteration



X. Liu, R. Liu, J. Qiu, X. Cheng, G. Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 13962–13967.

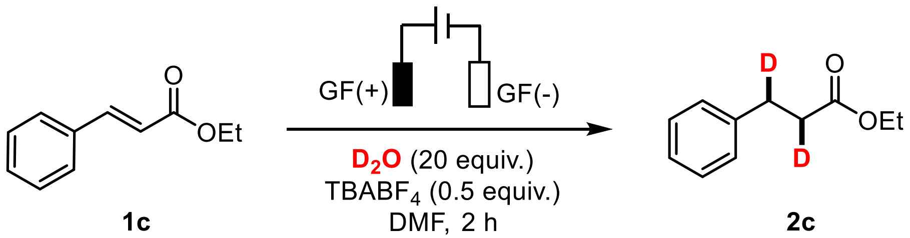
A. CV and SWV analysis of species in reaction.

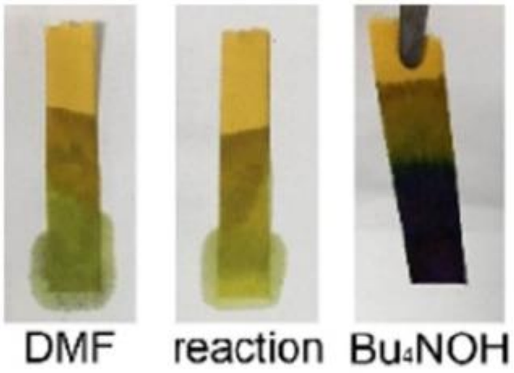




- the reaction is initiated by electron transfer to the substrate to yield an anionic radical
- there is an ECEC pathway in this reaction

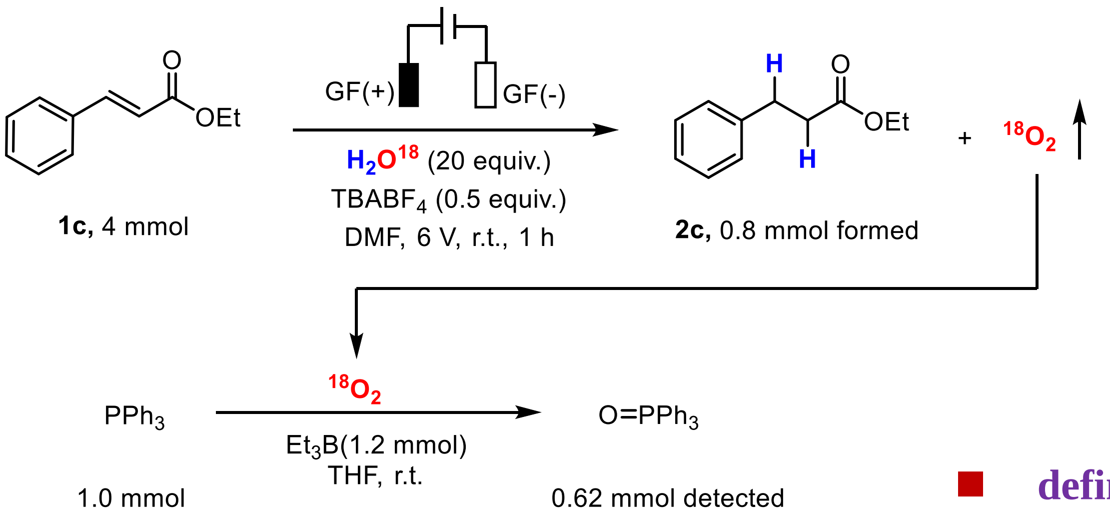
B. Measuring pH of the reaction.





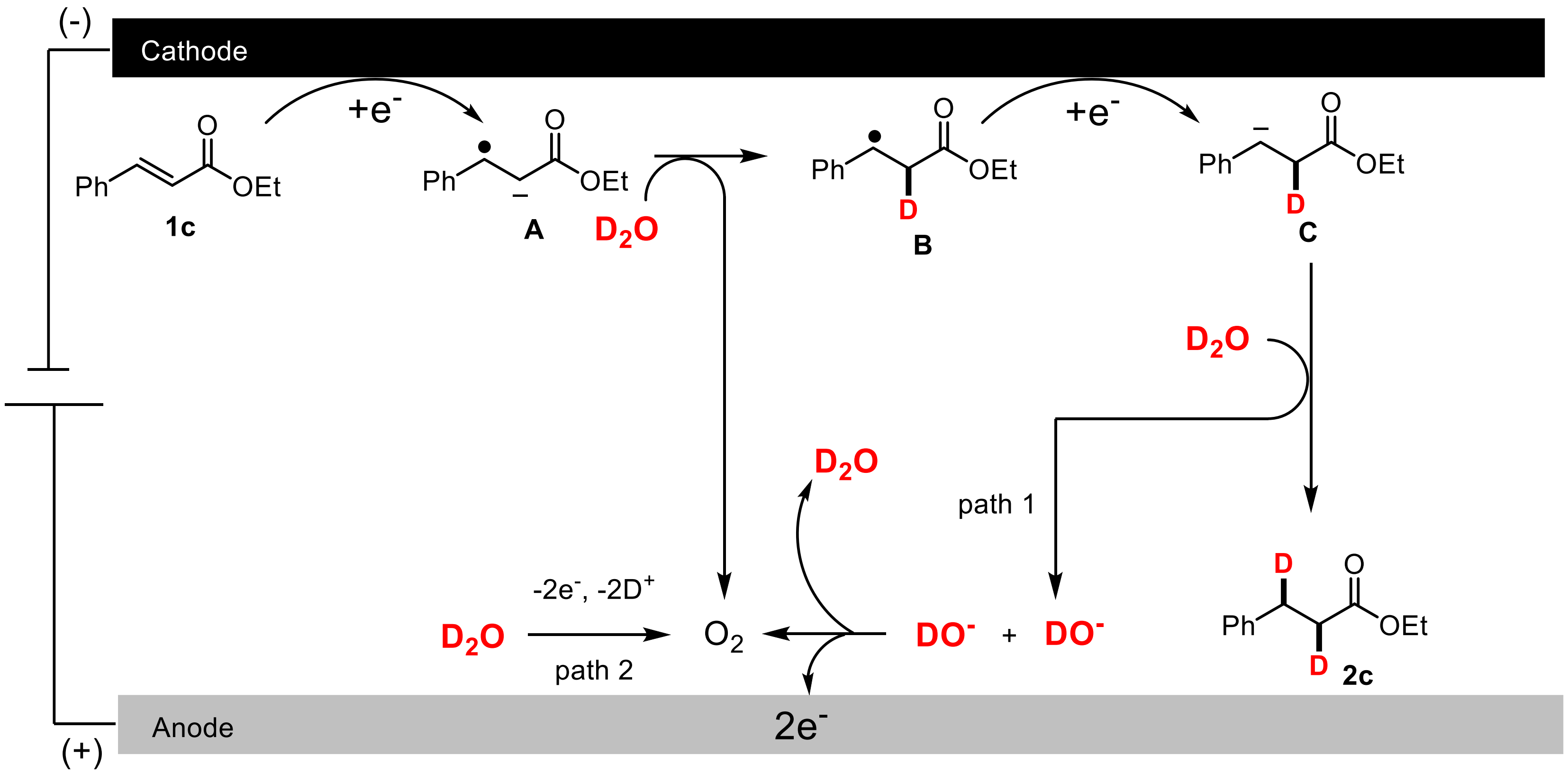
- the pH not vary significantly from neutral

C. Detection of oxygen generation in reaction.



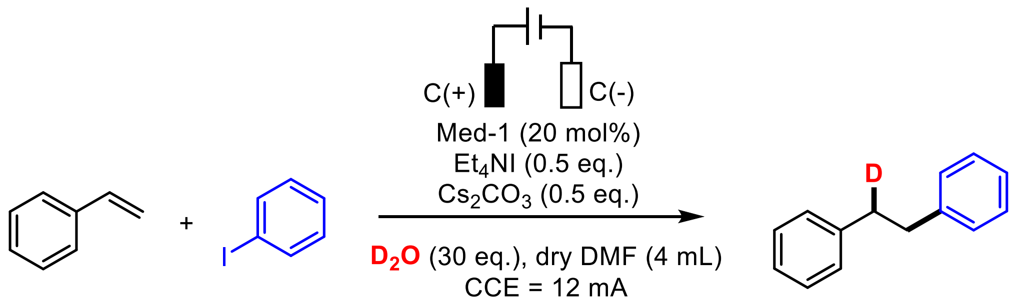
- definitely capture the $^{18}O_2$ as a triphenylphosphine oxide

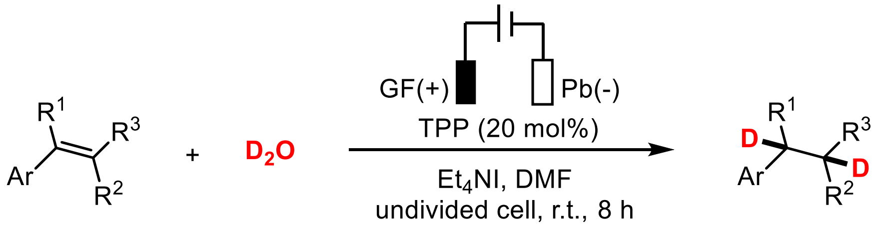
Proposed mechanism.

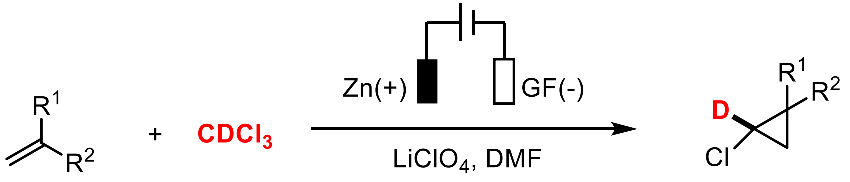


Electrochemical Active Olefin Deuteration

Other examples:





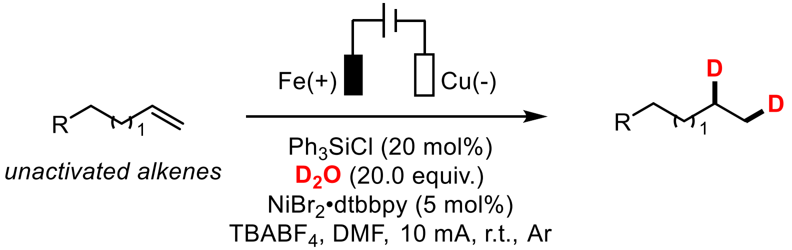


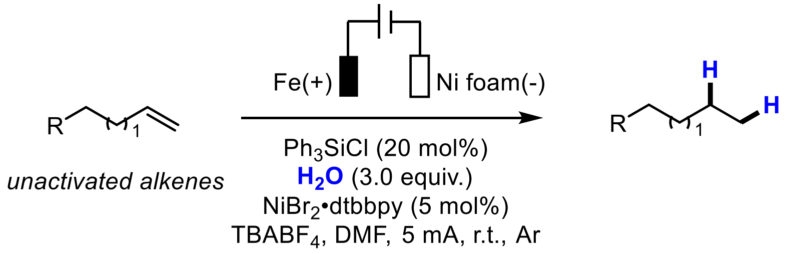
X. Li, J. Zhou, W. Deng, Z. Wang, Y. Wen, Z. Li, Y. Qiu, Y. Huang, *Chem. Sci.* **2024**, *15*, 11418–11427.

K. Yang, T. Feng, Y. Qiu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202312803.

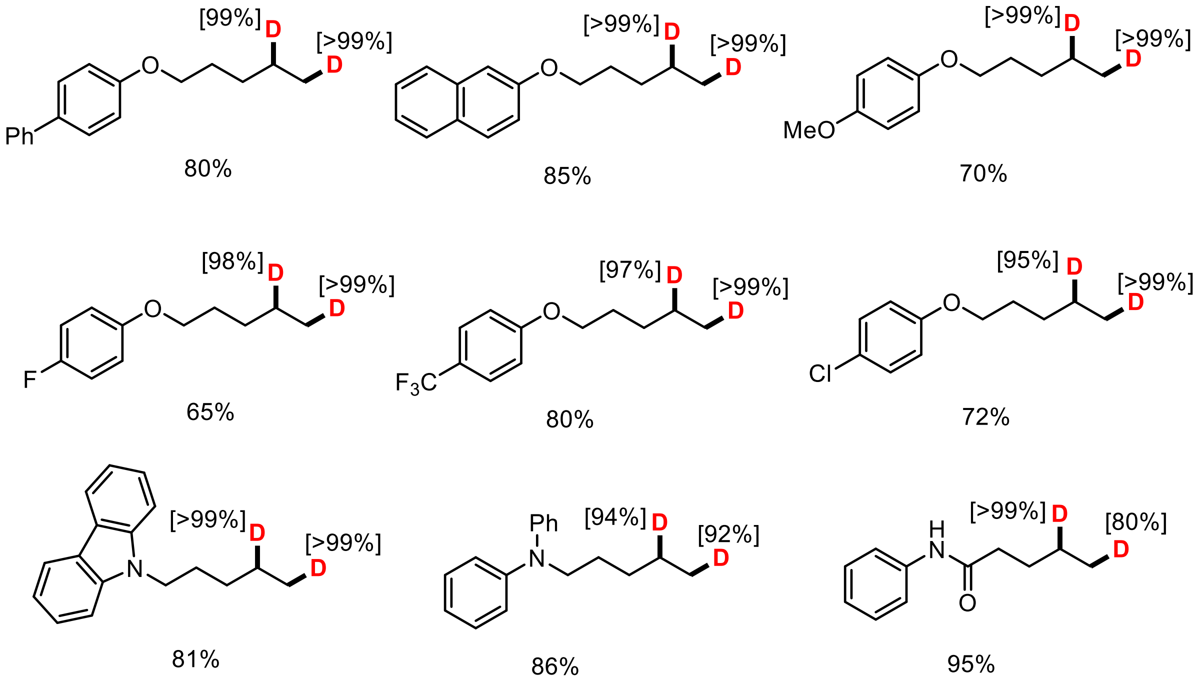
X. Zhang, X. Cheng, *Org. Lett.* **2022**, *24*, 8645–8650.

Electrochemical Non-active Olefin Deuteration

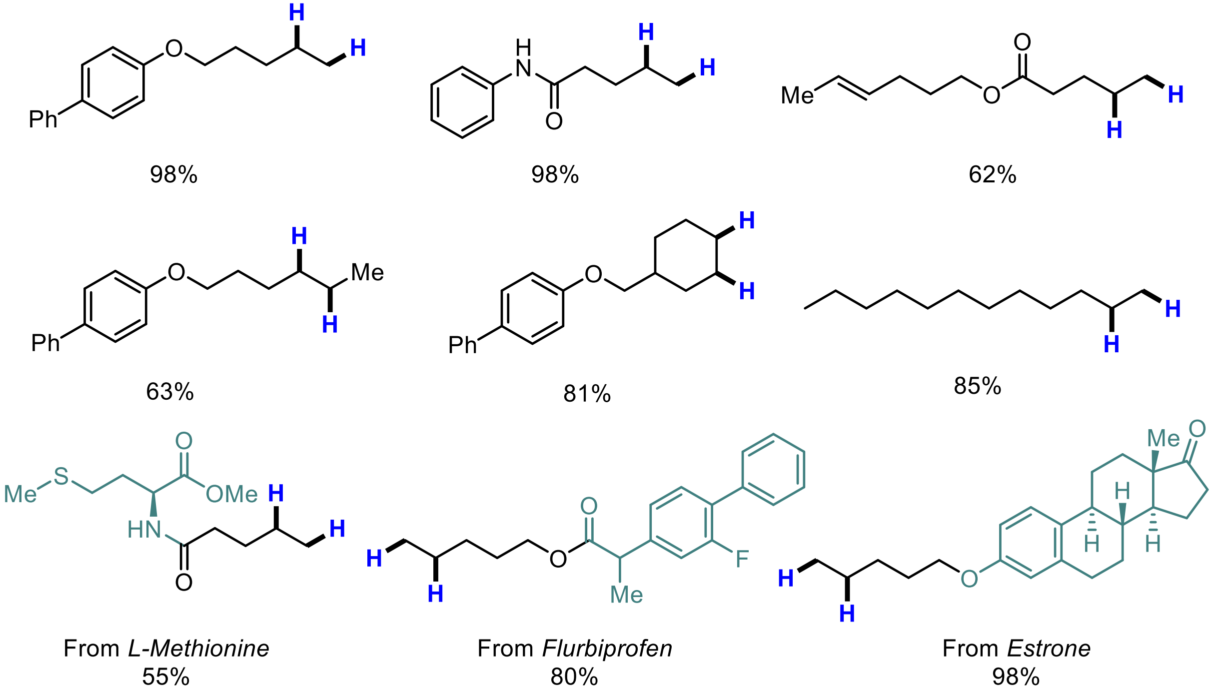




Scope of electroreductive deuteration



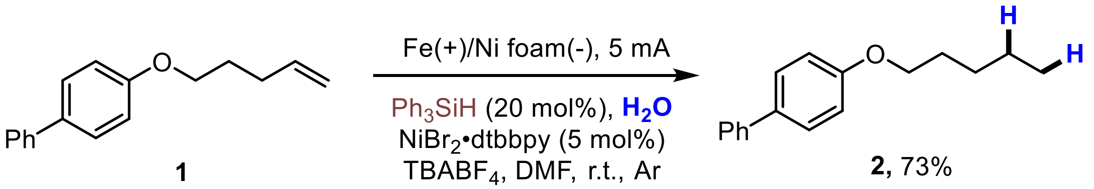
Scope of electroreductive hydrogenation



Y. Wang, Q. Wang, L. Wu, K. Jia, M. Wang, Y. Qiu, *Nat. Commun.* **2024**, *15*, 2780.

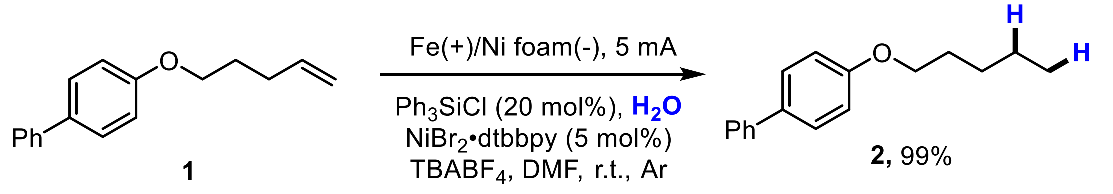
A. Investigation on the role of chlorosilane.

(a)



■ Ph_3SiH could catalysis the reaction

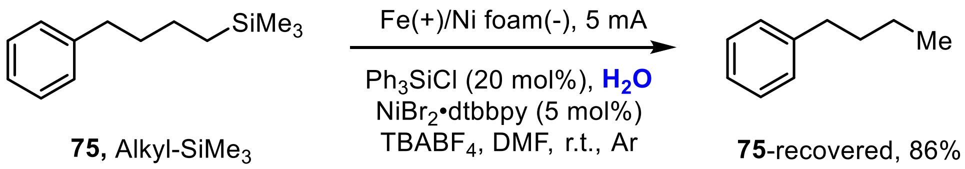
(b)



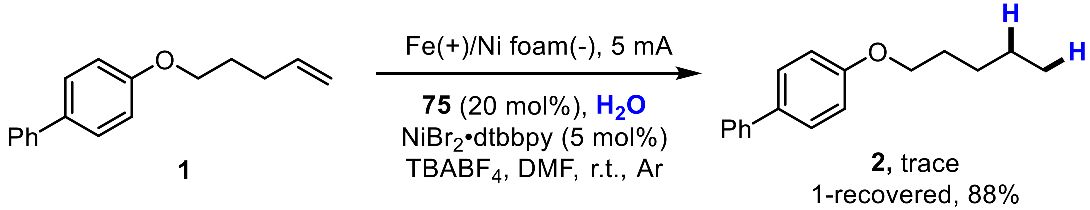
Ph_3SiH was detected by GC-MS

■ Ph_3SiH could be the key active specie

(c)

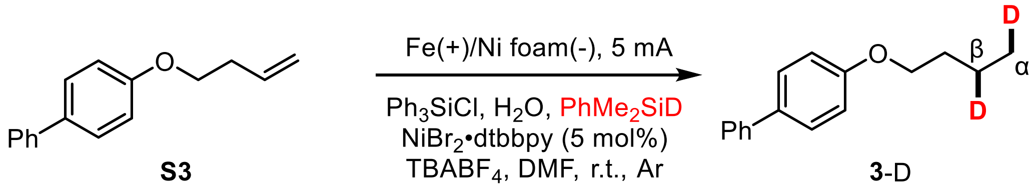


(d)



B. Deuteration experiments.

(e)

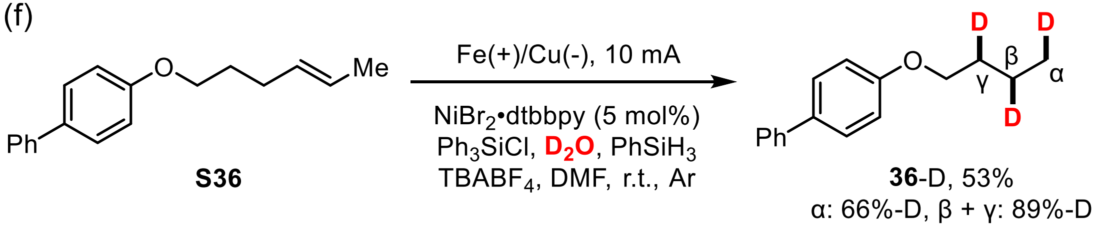


Entry	$PhMe_2SiD$	Yield%	D-inc.%(α/β)
1	5.0 equiv.	90	85/79
2[a]	5.0 equiv.	88	56/85

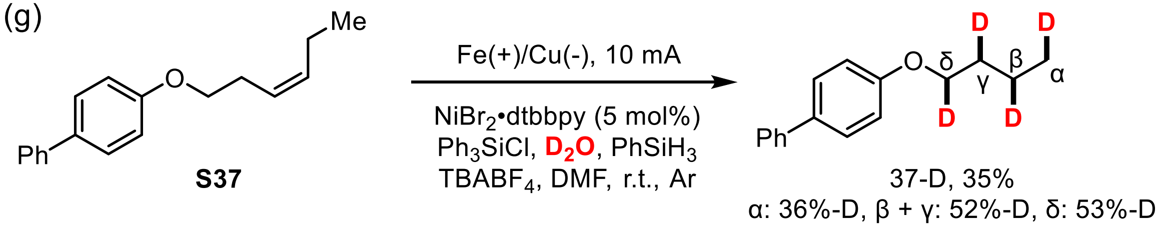
[a] w/o $NiBr_2$•dtbbpy

■ the hydrogen in the product was from silane

(f)

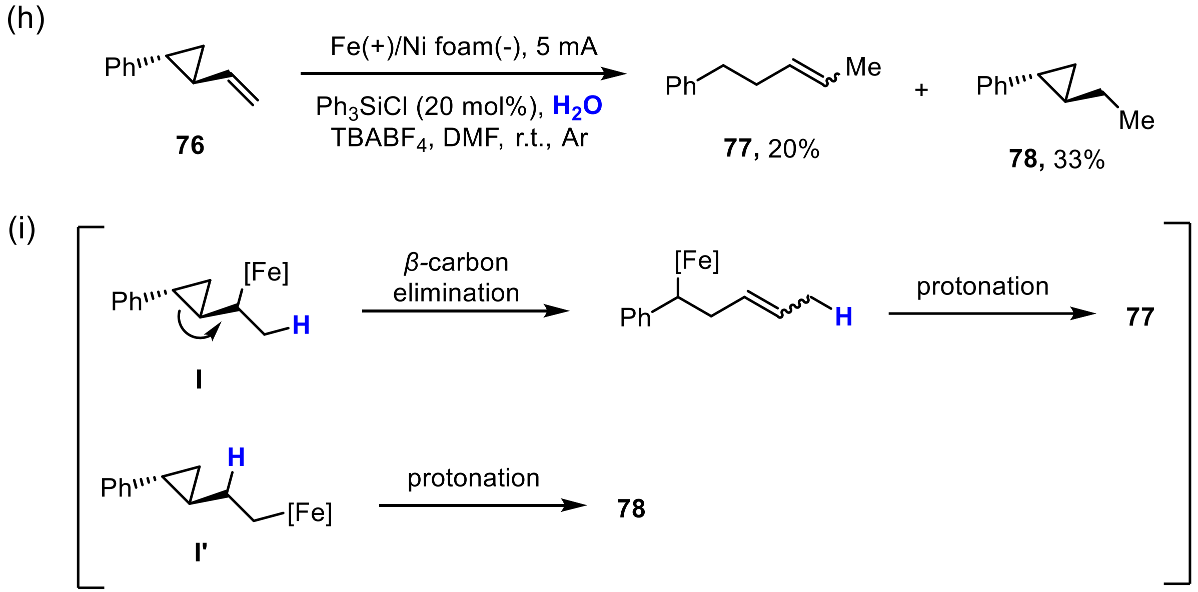


(g)

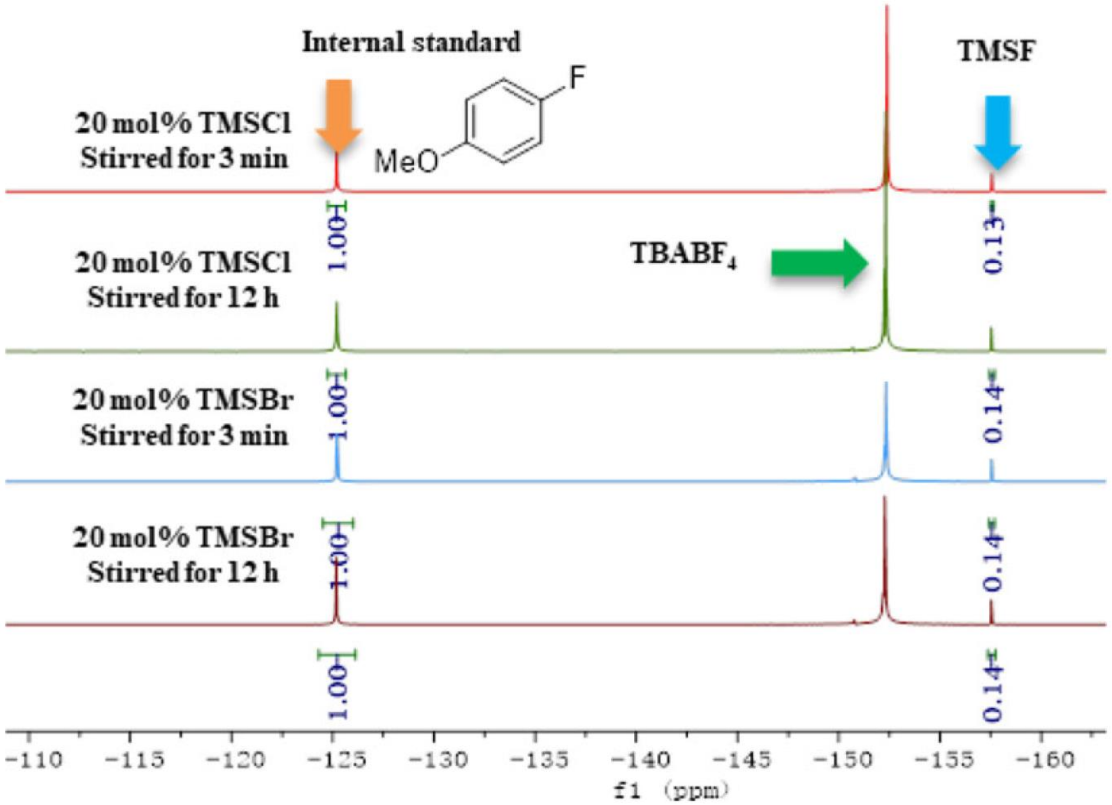


■ the double bond might migrate to the end first

C. Ring-opening experiments.

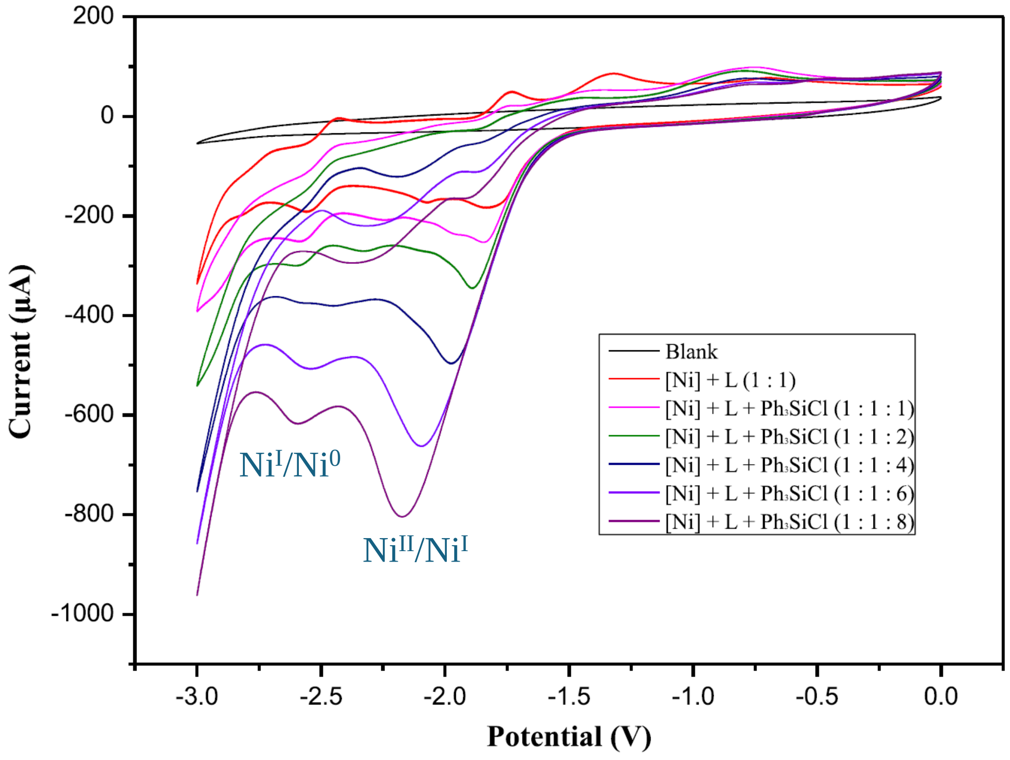


D. ^{19}F NMR spectroscopic evidence for the formation of fluorosilanes.

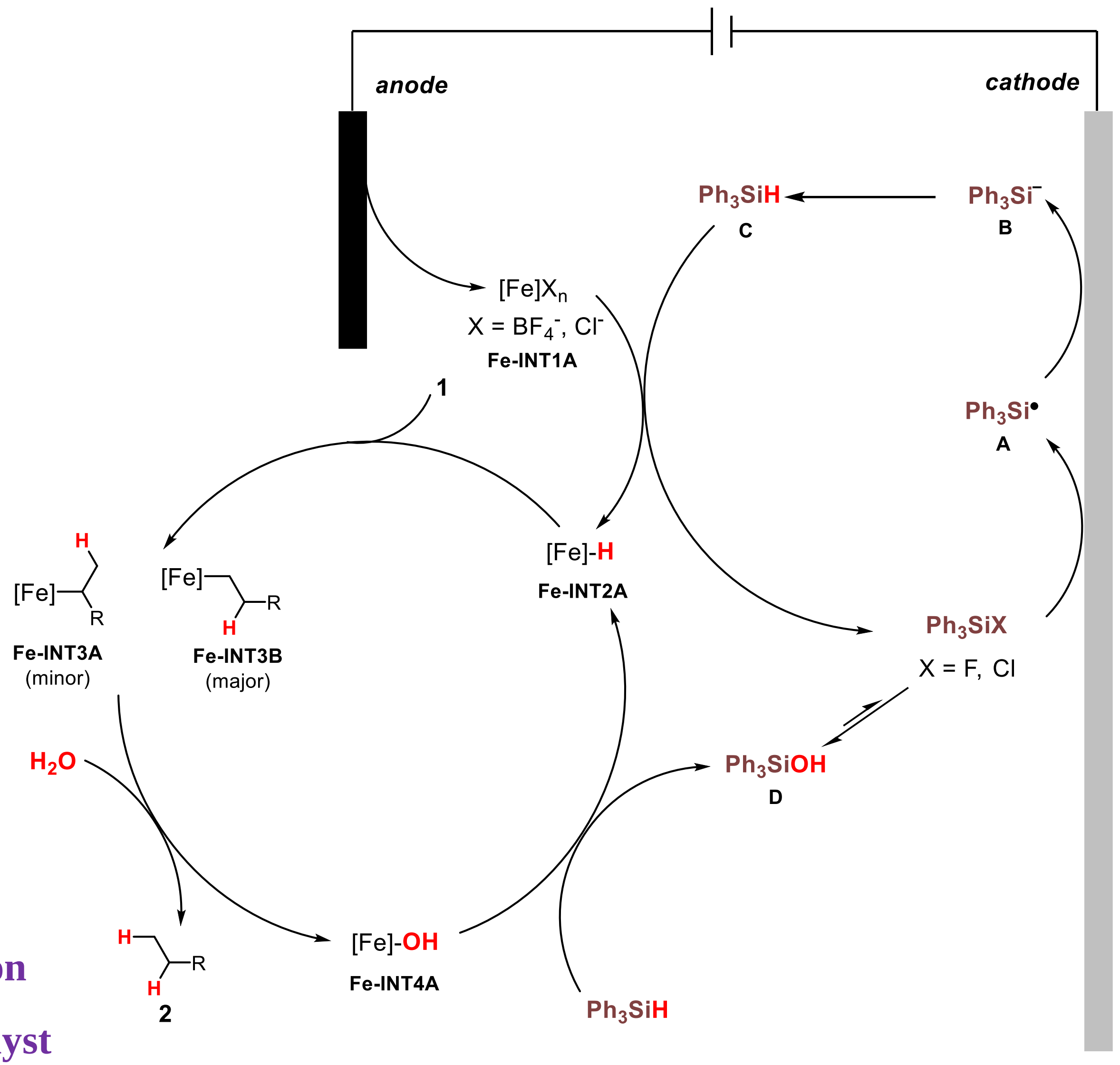


- **highly active chlorosilane or bromosilane could exist in the reaction system in the form of fluorosilane**

E. CV experiments.



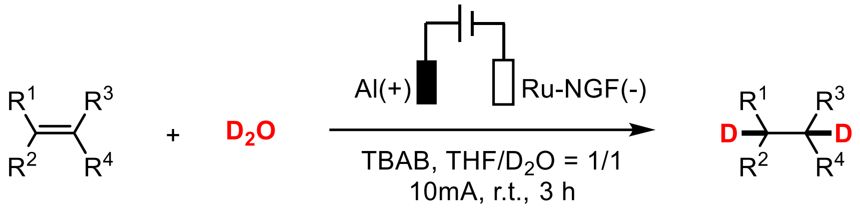
F. Proposed mechanism.

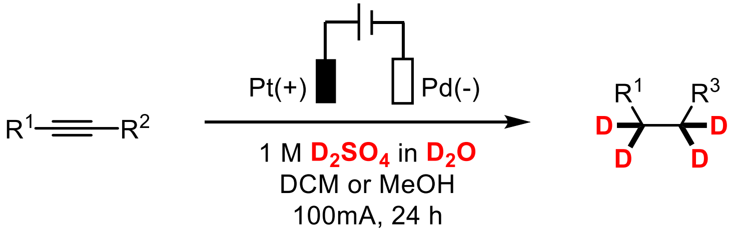


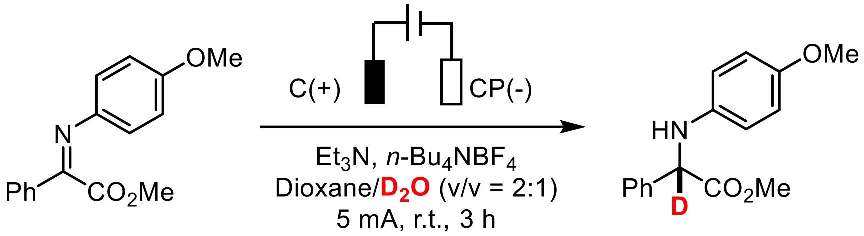
- both the Ni(II) ligand complex and Ph_3SiCl underwent reduction
- the in-situ generated Ni(0) complex appears to be the active catalyst

Electrochemical Non-active Olefin Deuteration

Other examples:







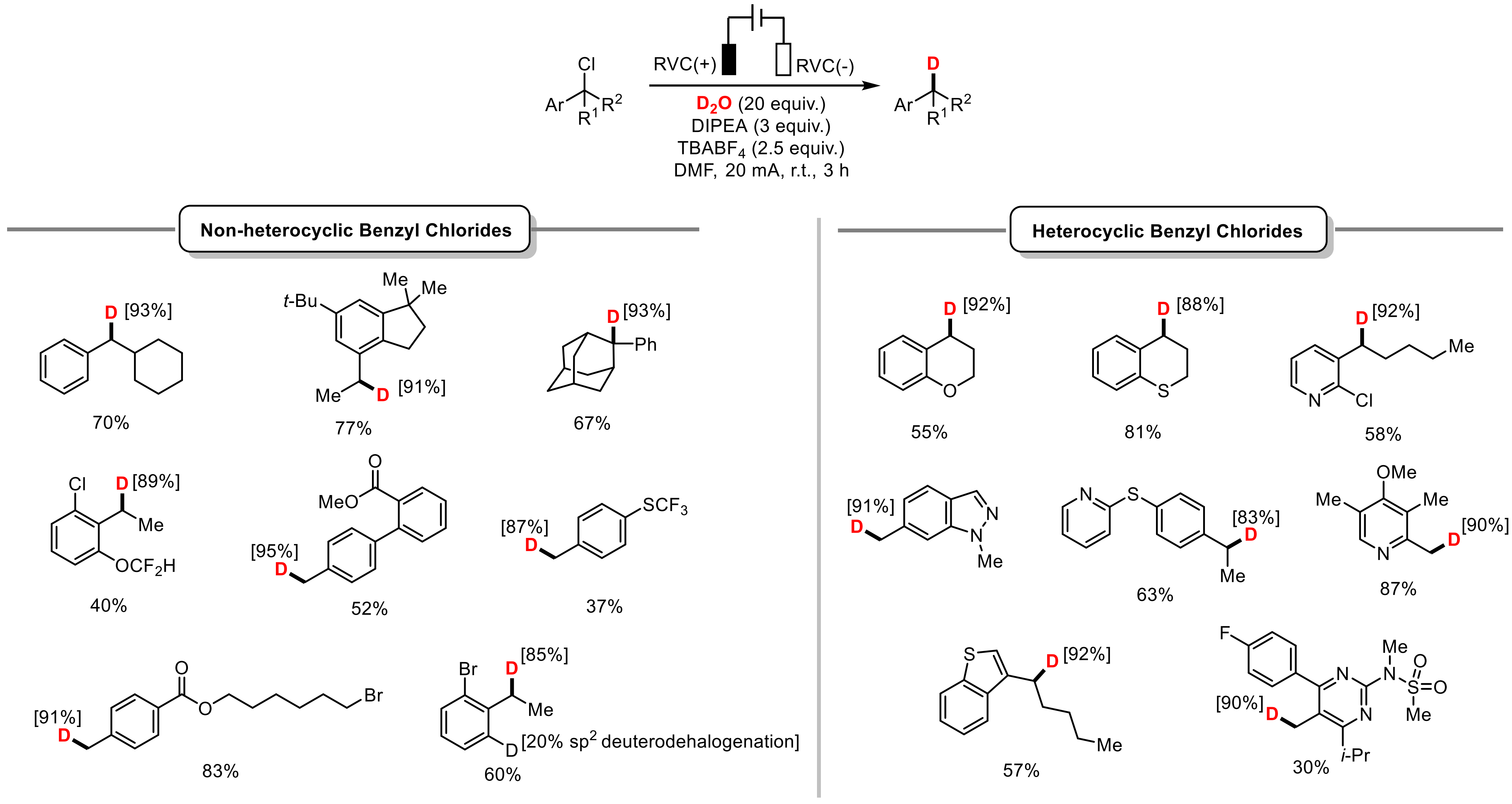
F. Bu, Y. Deng, L. Lu, Y. Li, W. Song, Z. Yang, X. Luo, X. Dong, R. Yi, D. Yang, S. Wang, A. Lei, W. Li, *J. Am. Chem. Soc.* **2025**, *147*, 5785–5795.

A. Kurimoto, R. S. Sherbo, Y. Cao, N. W. X. Loo, C. P. Berlinguette, *Nat. Catal.* **2020**, *3*, 719–726.

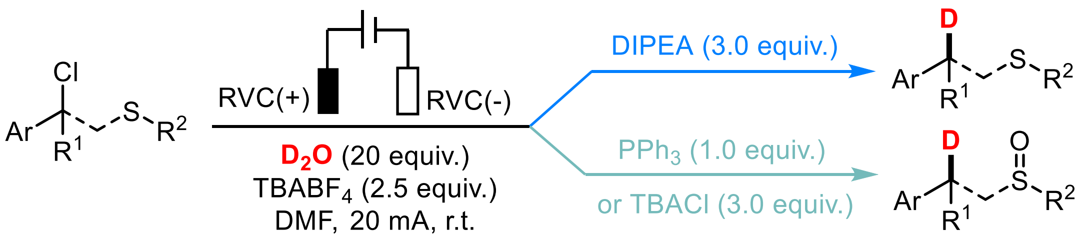
Y. Fan, W. Ou, M. Chen, Y. Liu, B. Zhang, W. Ruan, C. Su, *Org. Lett.* **2023**, *25*, 432–437.

Outline

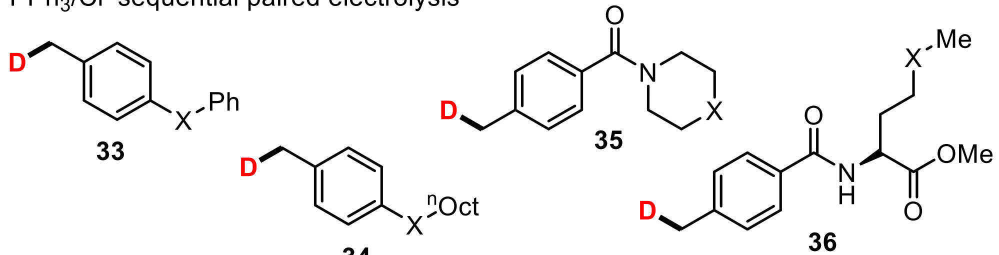
- ***Background***
- ***Electrochemical Hydrogen isotope exchange Reaction***
- ***Electrochemical Dearomative Deuteration***
- ***Electrochemical Olefin Deuteration***
- ***Electrochemical Dehalogenation Deuteration***
- ***Electrochemical Deoxygenative Deuteration***
- ***Summary and Outlook***



D. Wood, S. Lin, *Angew. Chem. Int. Ed.* **2023**, *62*, e202218858.

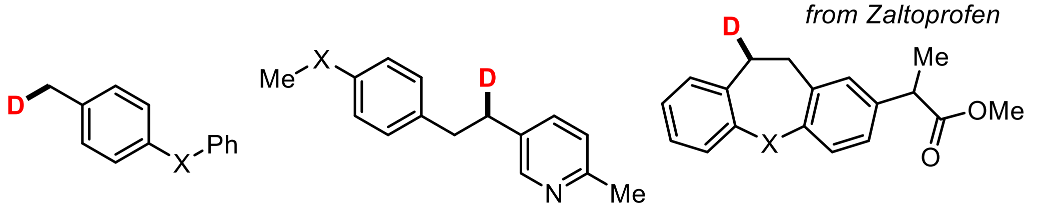


A. PPh_3/Cl^- sequential paired electrolysis



Substrate	Product	Reductant	X	Yield(%)	Deuterium(%)
sub-33	33	DIPEA	S	68	93
sub-34	34	DIPEA	S	72	80
sub-35	35	DIPEA	S	53	88
sub-36	36	DIPEA	S	68	80
sub-33	33-ox	PPh_3	S=O	74	97
sub-34	34-ox	PPh_3	S=O	53	97
sub-35	35-ox	PPh_3	S=O	53	94
sub-36	36-ox	PPh_3	S=O	52	96

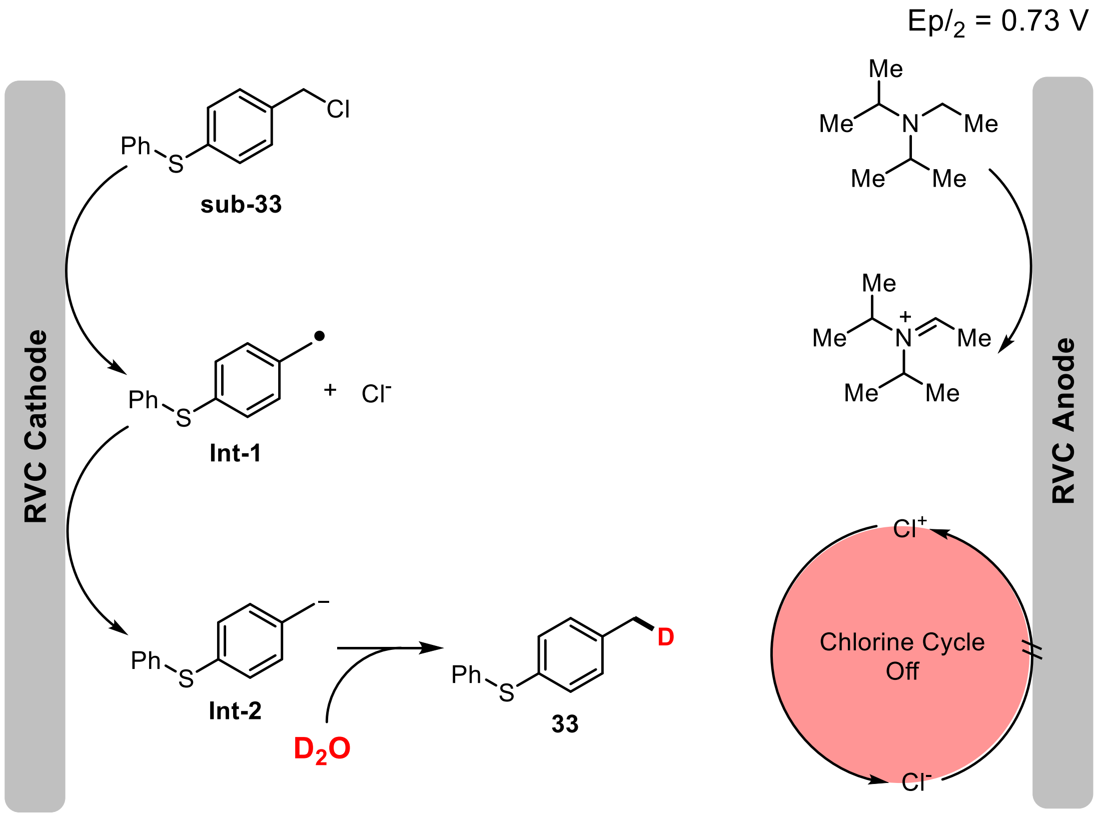
B. TBACl sequential paired electrolysis



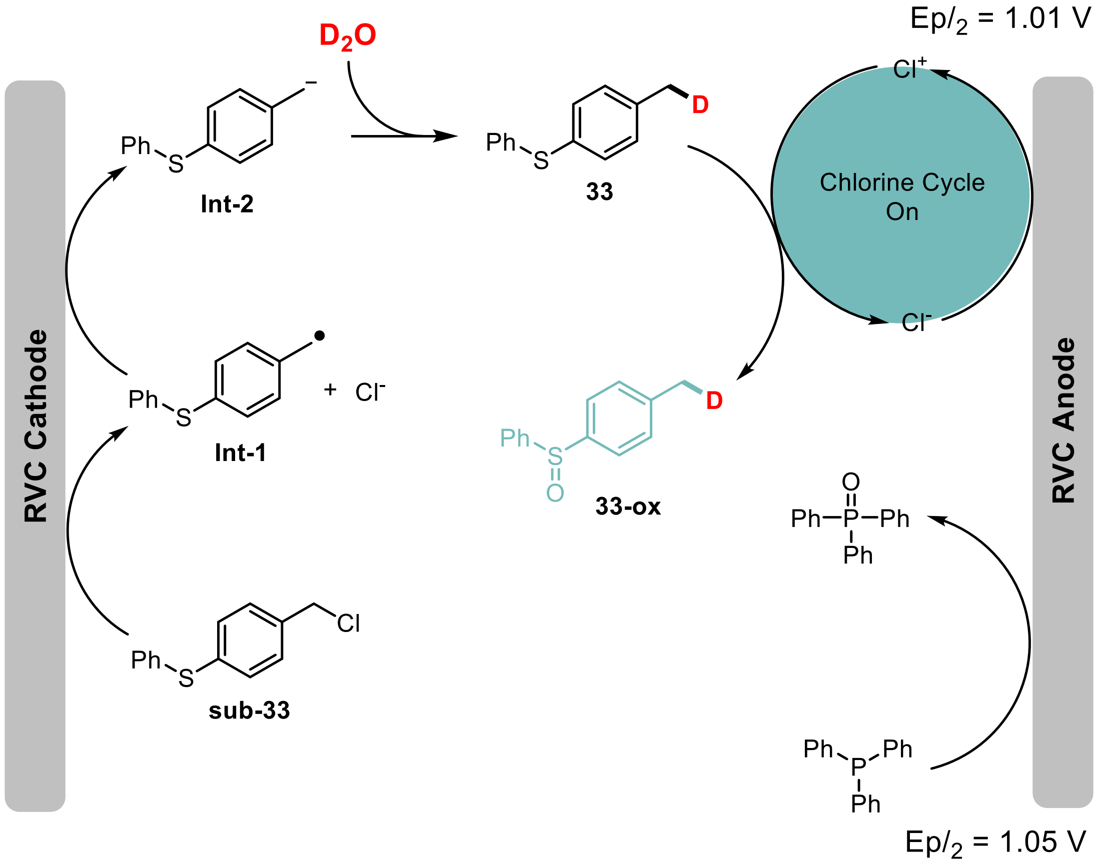
Substrate	Product	Reductant	X	Yield(%)	Deuterium(%)
sub-33	33	DIPEA	S	68	93
sub-37	37	DIPEA	S	44	88
sub-38	38	DIPEA	S	88	>99
sub-33	33-ox	TBACl	S=O	52	83
sub-37	37-ox	TBACl	S=O	30	88
sub-38	38-ox	TBACl	S=O	52	89

Proposed mechanism.

A. Net Reductive.

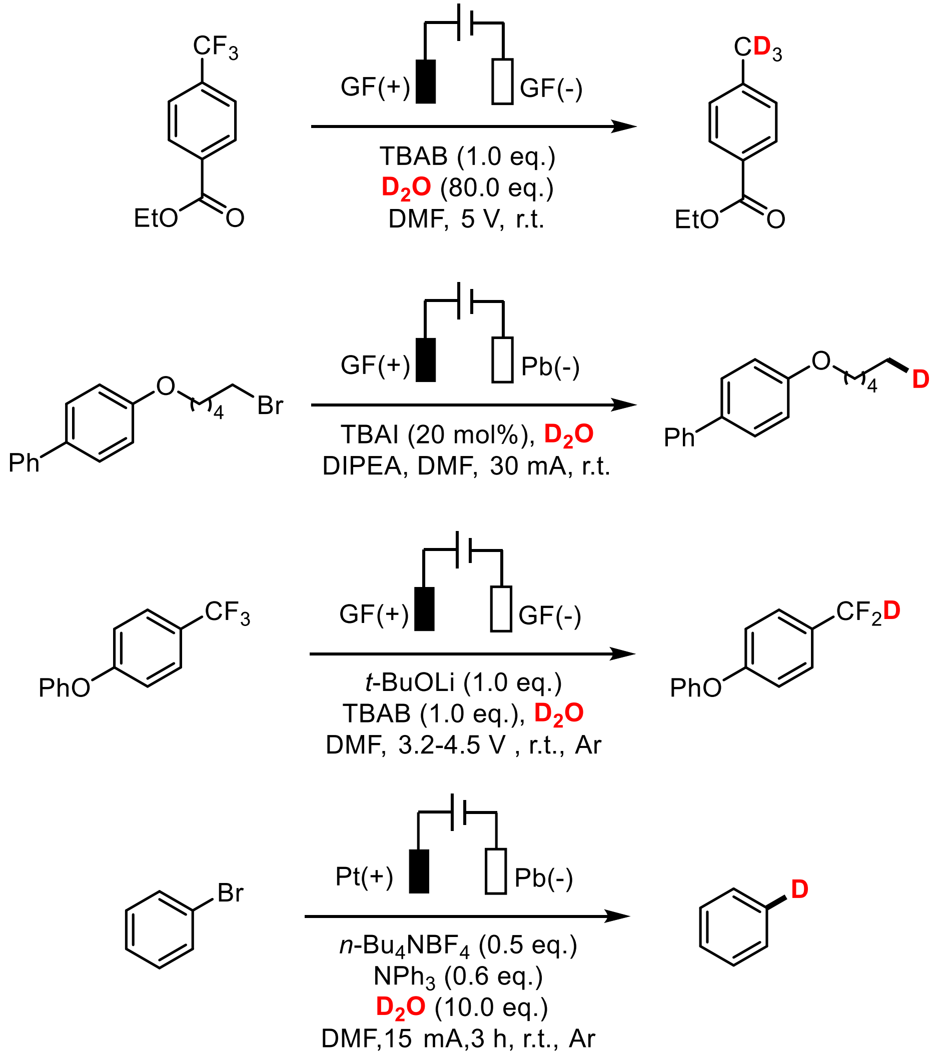


B. Redox-Neutral.



Electrochemical Dehalogenation Deuteration

Other examples:



J. Cheng, J. Sheng, X. Cheng, *Org. Lett.* **2023**, *25*, 5602–5607.

P. Li, C. Guo, S. Wang, D. Ma, T. Feng, Y. Wang, Y. Qiu, *Nat. Commun.* **2022**, *13*, 3774.

J. Sheng, X. Cheng, *CCS Chem.* **2024**, *6*, 230–240.

L. Lu, H. Li, Y. Zheng, F. Bu, A. Lei, *CCS Chem.* **2020**, *2*, 2669–2675.

Outline

- ■ *Background*
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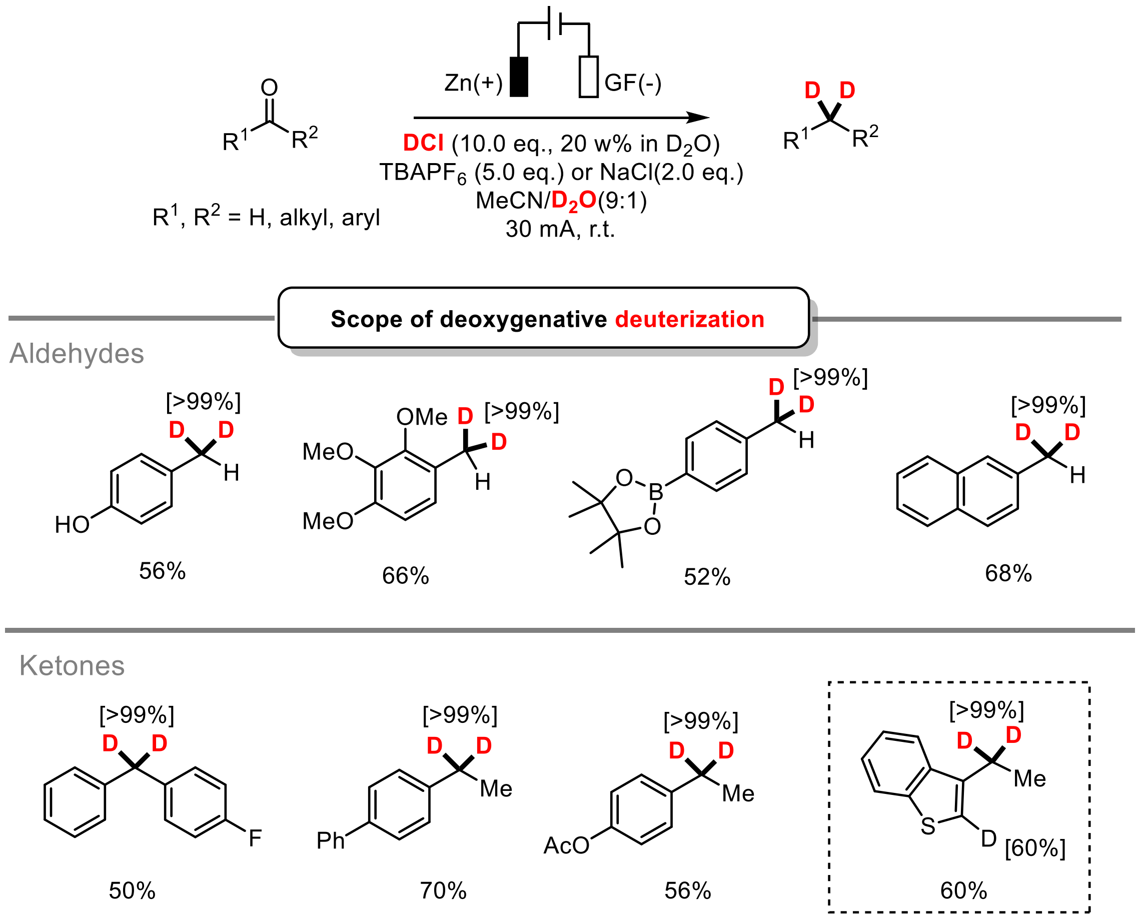
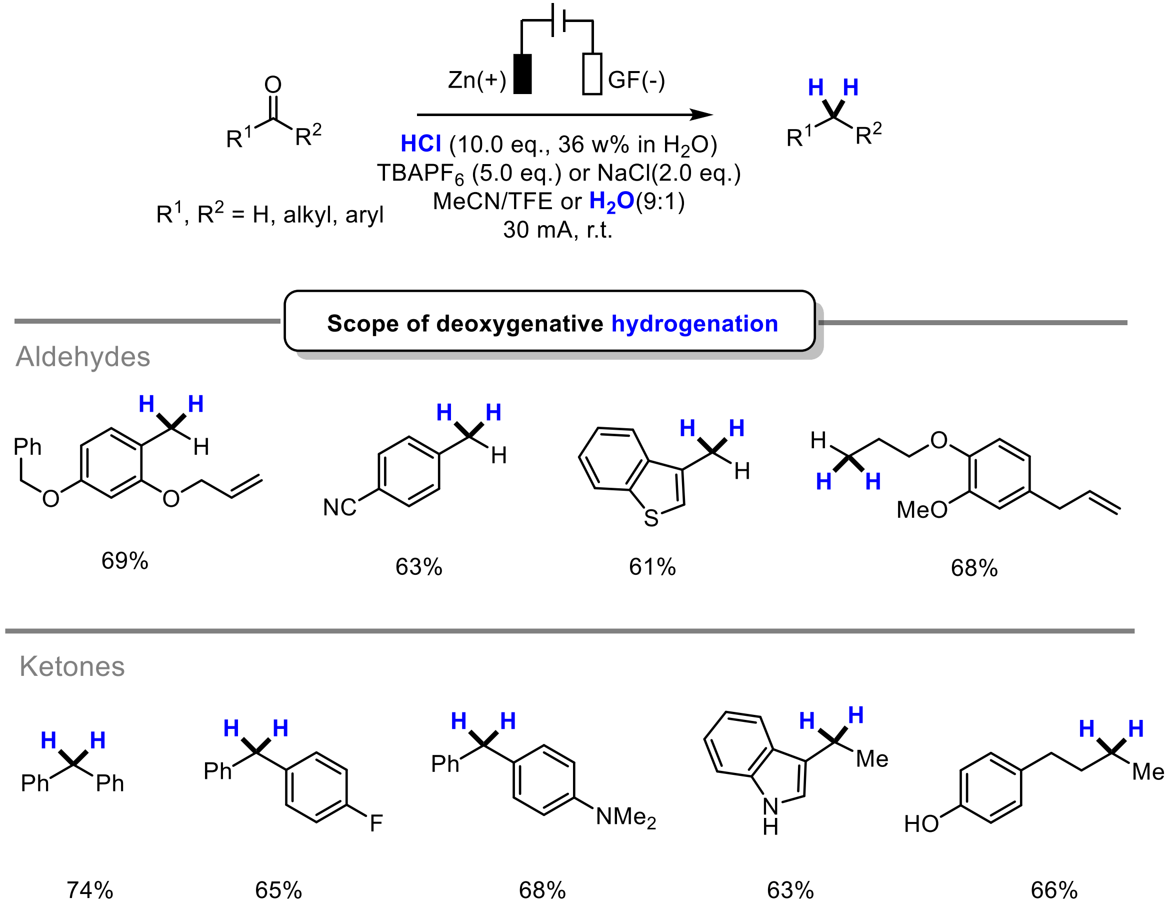
- ■ ***Electrochemical Deoxygenative Deuteration***
- ■ *Summary and Outlook*

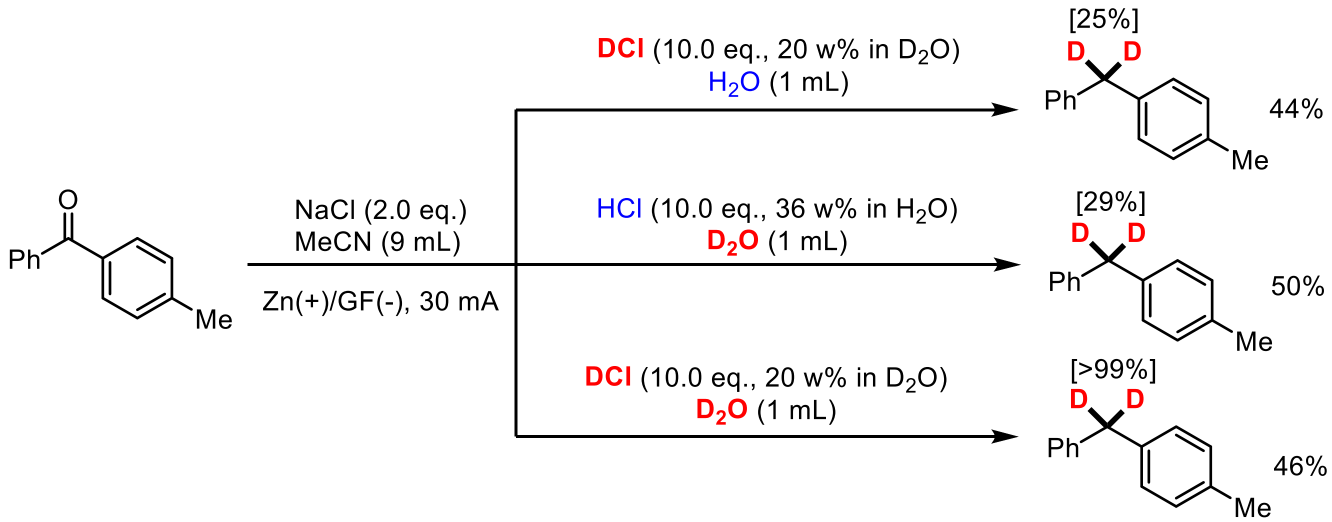
Electrochemical Deoxygenative Deuteration





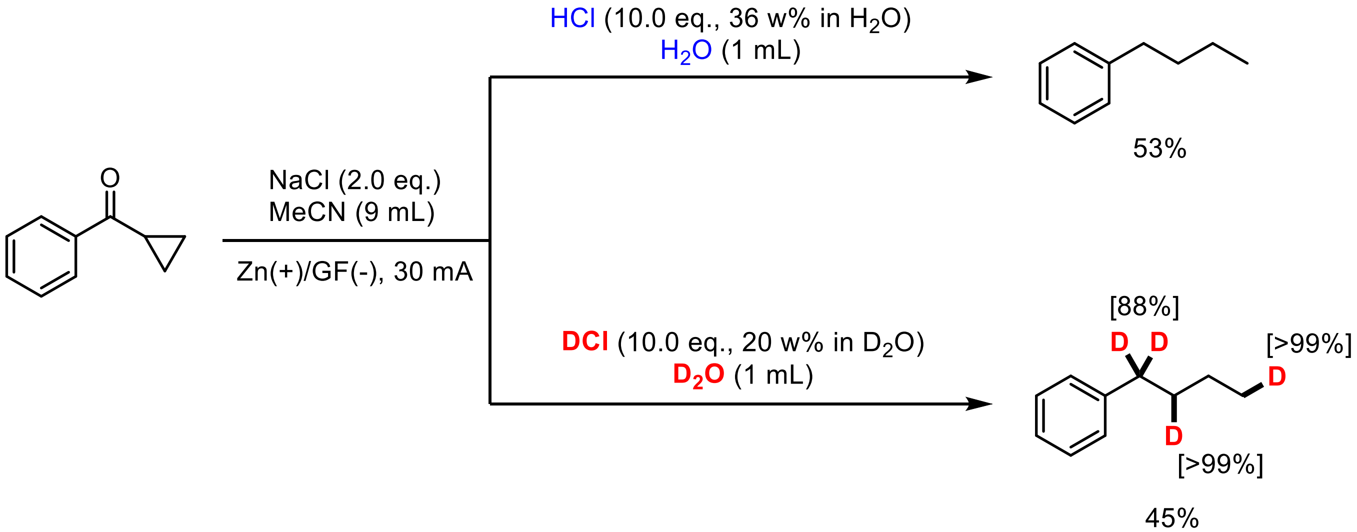
Z. Sun, R. Ji, J. Wu, J. Zhao, F. Fang, F. Wang, C. Jiang, Z. Q. Liu, Adv. Synth. Catal. **2023**, 365, 476–481.

A. Deuteration experiments.



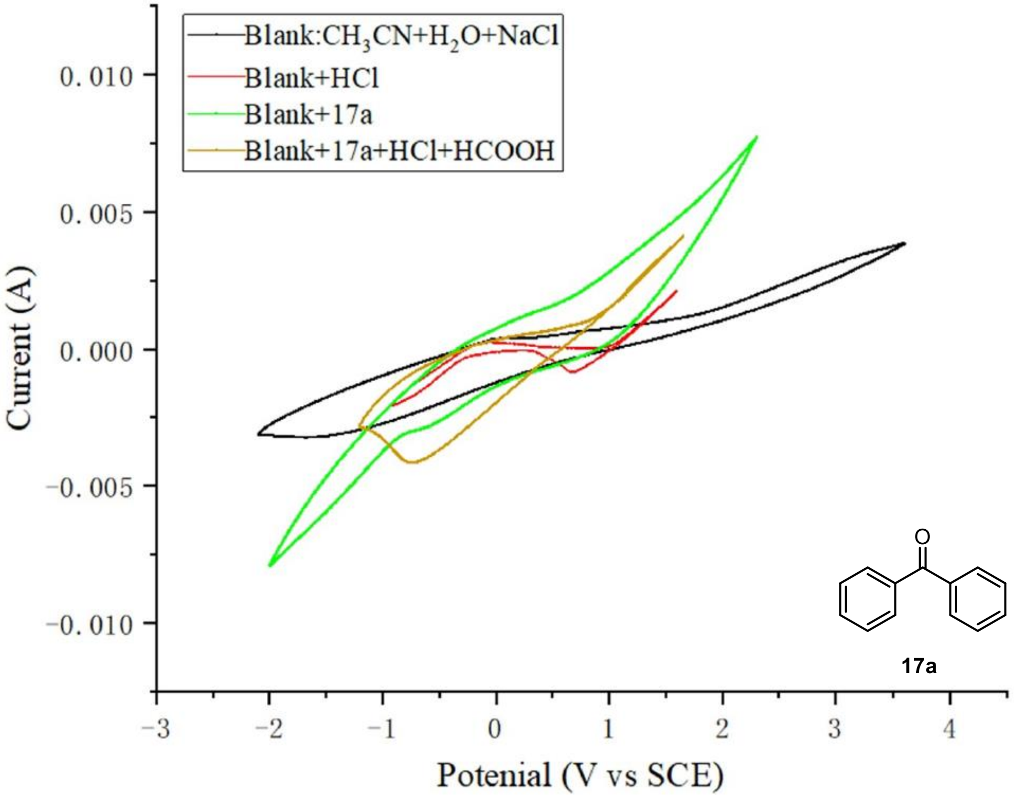
■ **both DCl and D_2O serve as sources of deuterium**

B. Radical clock experiments.

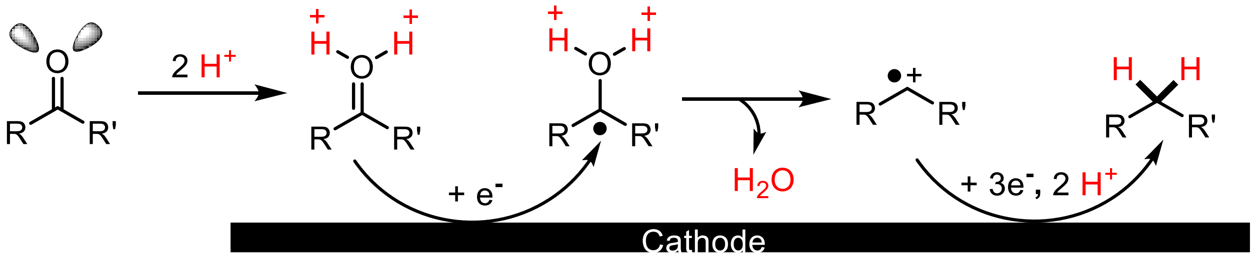


■ **a benzylic radical intermediate should be involved in the process**

C. CV experiments.



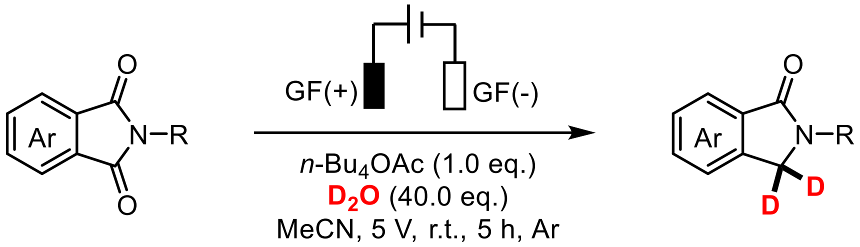
Proposed mechanism.



- the addition of protonate promotes electron transfer from the cathode to the C=O π* orbital

Electrochemical Deoxygenative Deuteration

Other example:



A. Qiu, J. Li, X. Zhang, P. Ran, W. Ding, X. Cheng, M. Ding, Adv. Synth. Catal. **2023**, 365, 2894–2899.

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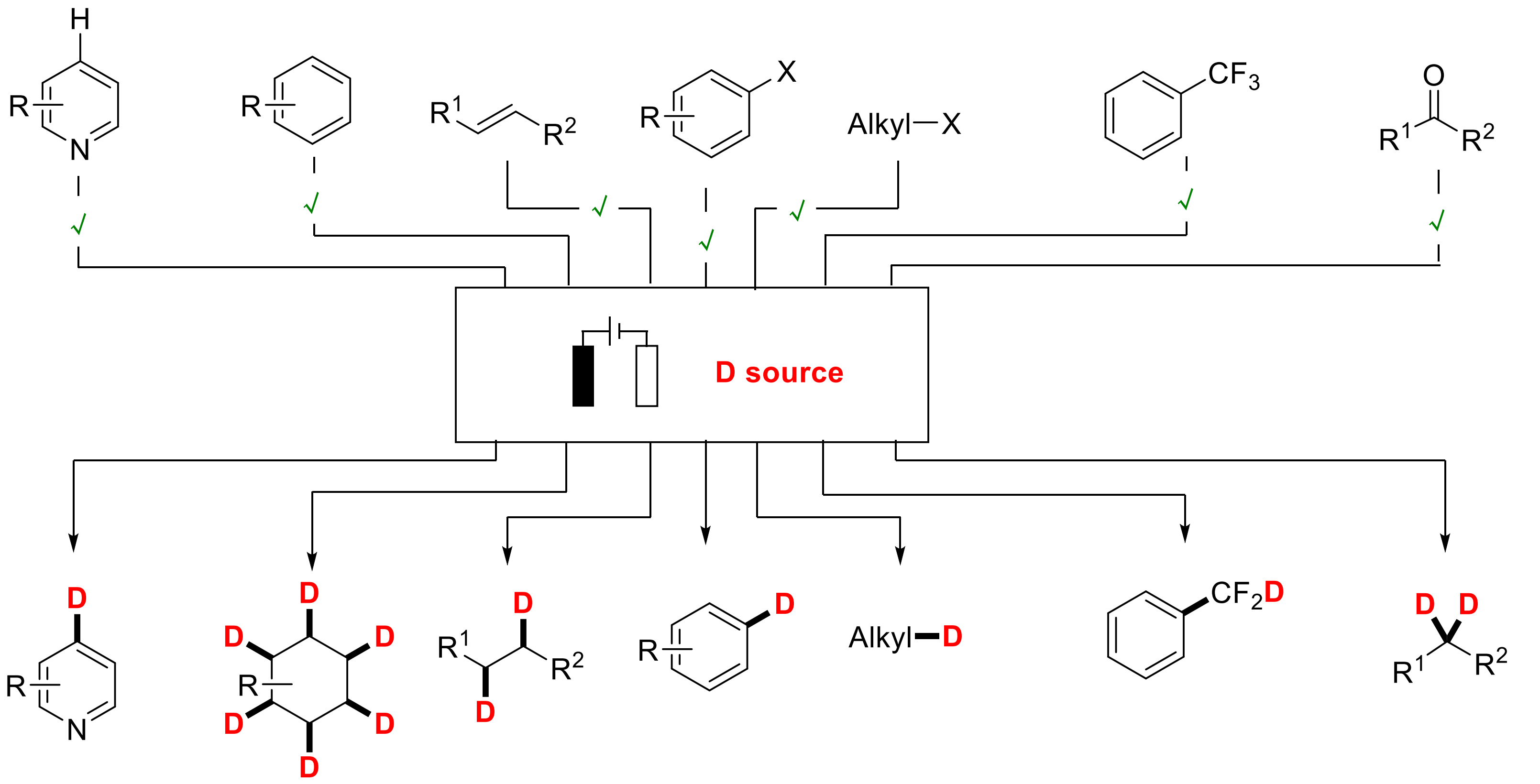
Summary

Electrochemical deuteration reaction

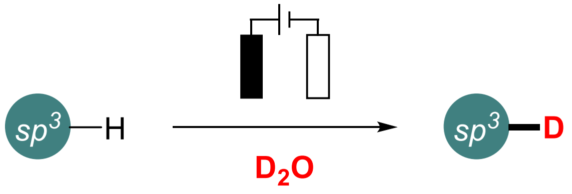


Advantages:

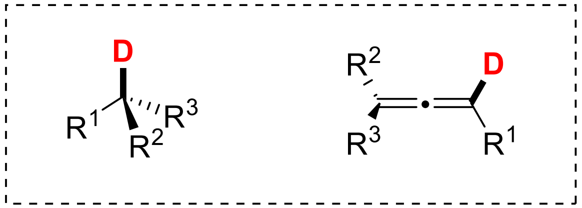
1) Proceed under mild reaction conditions.
2) Enable regioselectivity or chemoselectivity that is difficult or impossible to achieve with conventional methods.
3) Eliminate the need for stoichiometric redox reagents, thereby minimizing chemical waste.

Outlook

1. The direct and selective deuteration of inert C(sp^3)-H bonds

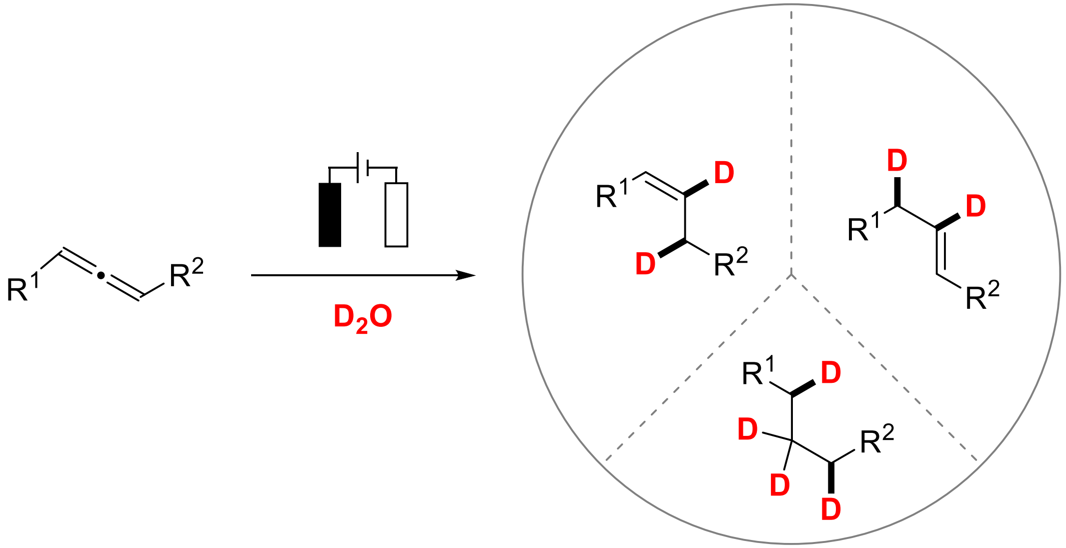


2. The asymmetric construction of C-D bonds



using the right metal catalysts and chiral ligands,
or even by bringing in chiral amino acids or NHC-based catalysts

3. The selective deuteration of allenes



Thanks for your listening ！

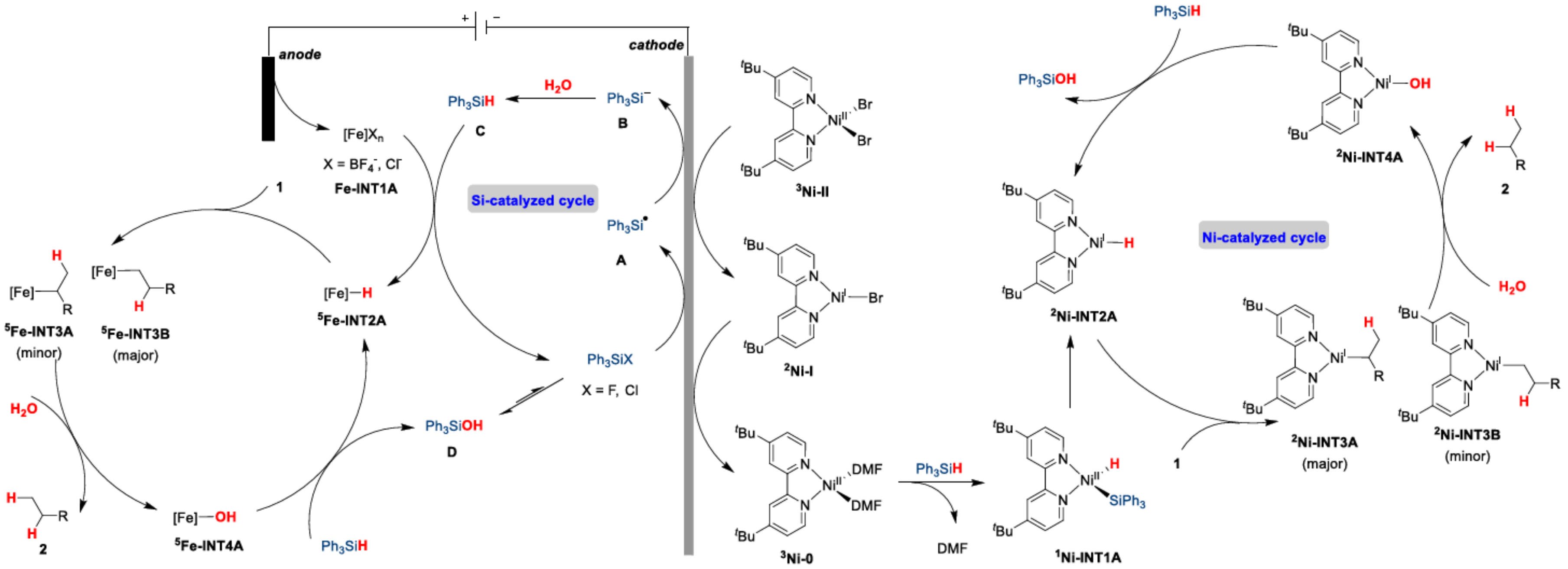
球磨法

Table 3. Scope of substrates used in the hydrogenation.[a]

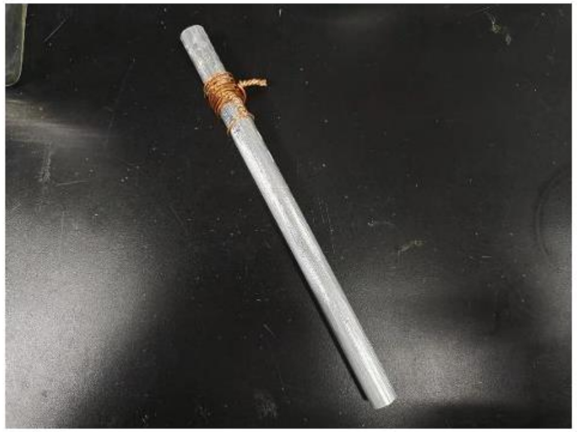
Substrate —[Fritsch Pulverisette 7, Classic Line Ball Mill (P-7), H_2O (30 equiv) / SUS 304 balls (50), Air, 800 rpm, in 12 mL SUS304 vessel]→ Product

electron transfer, electron transfer, chemical protonation, chemical protonation (EECC) mechanism

electron transfer, chemical protonation, electron transfer, chemical protonation (ECEC) mechanism



Supplementary Figure 11. The proposed catalytic cycle for the electroreduction of unactivated alkenes using H_2O as hydrogen source.

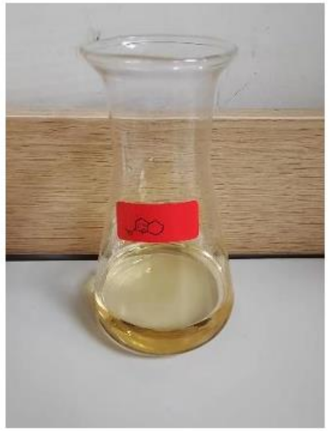


Zinc bar anode

R=2.0 cm, L=30.0 cm

Graphite felt cathode

20.0 cm*15.0 cm*0.5 cm



Reaction equipment