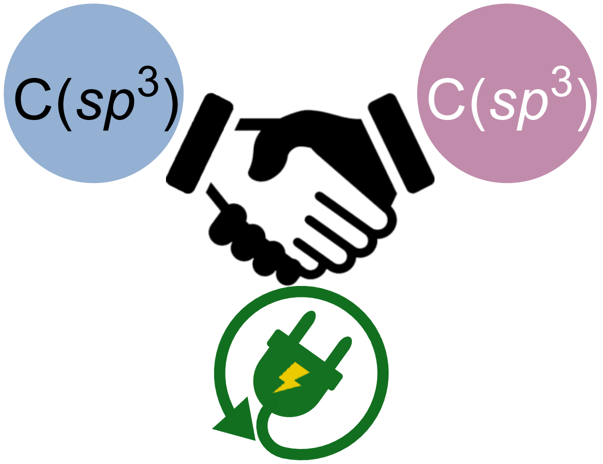
Recent advances in electrochemical $C(sp^3)$–$C(sp^3)$ cross-coupling



Seminar

May 10th, 2024

Dong Huang

Shengming Ma group

Outline

- *Introduction*
- *Dehalogenative C(sp^3)–C(sp^3) cross-coupling*
- *Decarboxylative C(sp^3)–C(sp^3) cross-coupling*
- *Summary and Outlook*

Outline

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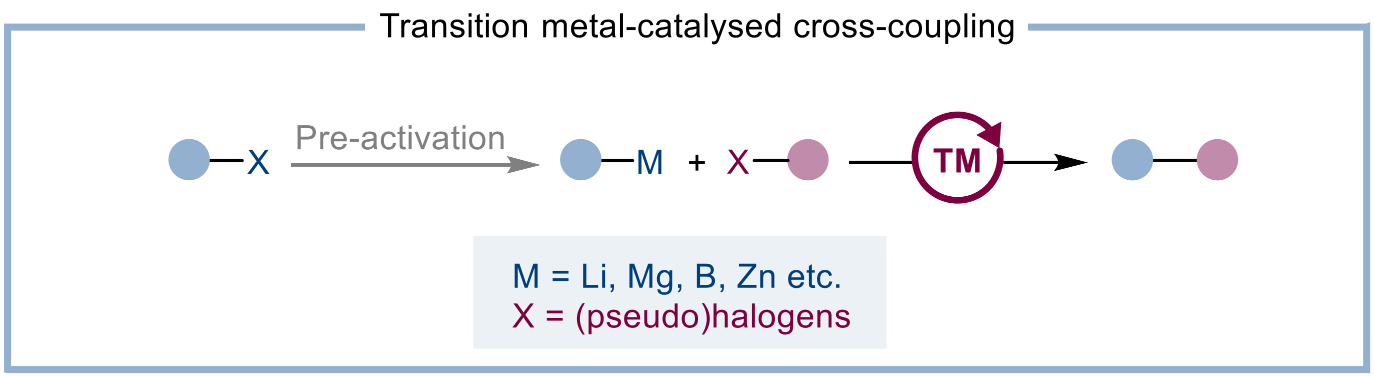
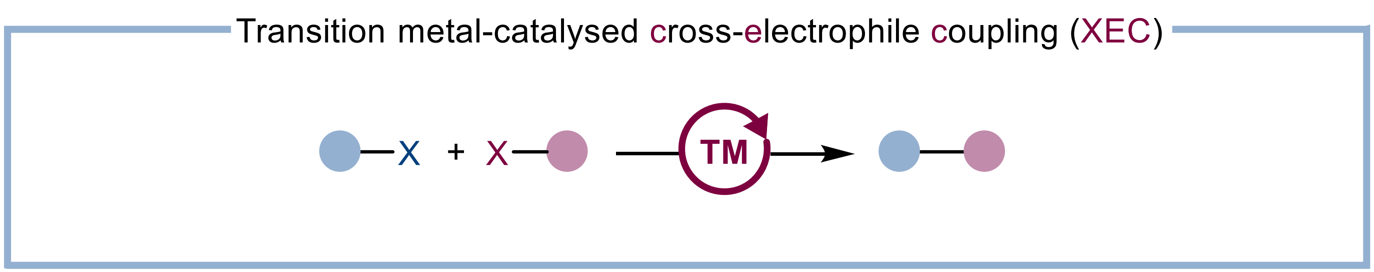
C–C cross-coupling

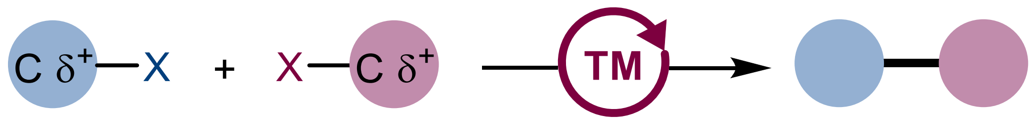
The construction of C–C bonds is a constant topic in organic chemistry





Weix, D. J. et al. *J. Org. Chem.* **2014**, *79*, 4793.
Jarvo, E. R. et al. *Nat. Rev. Chem.* **2017**, *1*, 0065.

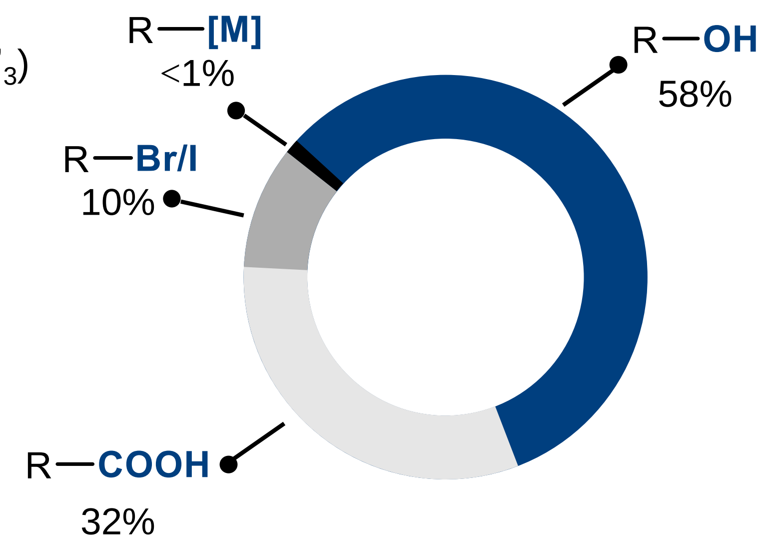
Cross-electrophile coupling (XEC)



XEC advantages:

- Cuts down one step (making nucleophile)
- Safety (avoids pyrophoric e.g. RMgX, or toxic e.g. $RSnR'_3$)
- Easier to handle
- Increased stability/easier storage
- More commercial availability
- Better FG compatibility

Commercial availability of C(*sp*^{3}) conjugate reagents



Definition of modern XEC:

- No *in situ* formation of nucleophile
- Reductant acts on catalyst
- No addition into polar π systems (e.g. NHK)
- Will not be discussed in electrochemical methods

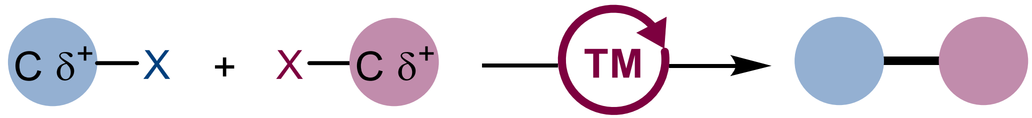
This topic:

- if discussed, termed as:

  electrochemical cross-electrophile coupling (eXEC)

Weix, D. J. et al. *J. Org. Chem.* **2014**, *79*, 4793.
Jarvo, E. R. et al. *Nat. Rev. Chem.* **2017**, *1*, 0065.
MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2016**, *138*, 8084.

Challenges and strategies in XEC



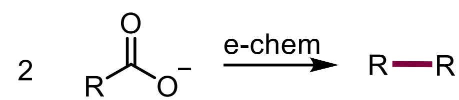
Issue: electrophile coupling discovered for a long tme achieving homocouling

Challenge: achieving cross-selectivity

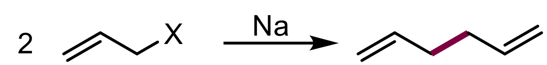
C(sp^2)–C(sp^3) (well-developed)

C(sp^2)–C(sp^2) / C(sp^3)–C(sp^3) (underdeveloped)

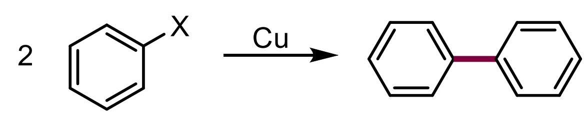
- ☐ Kolbe homocoupling (1847)



- ☐ Wurtz homocoupling (1855)



- ☐ Ullman homocoupling (1904)



XEC strategies

- ☐ Excess of one electrophile—in statistics

$$R^1\text{—X} + R^2\text{—X} \xrightarrow{\text{Cat}} R^1\text{—}R^1 + R^1\text{—}R^2 + R^2\text{—}R^2$$

1 equiv. n equiv. 1 : 2n : n^2

n	cross yield	cross/homo
1	50%	1/1
2	67%	1/1.25
3	75%	1/1.67

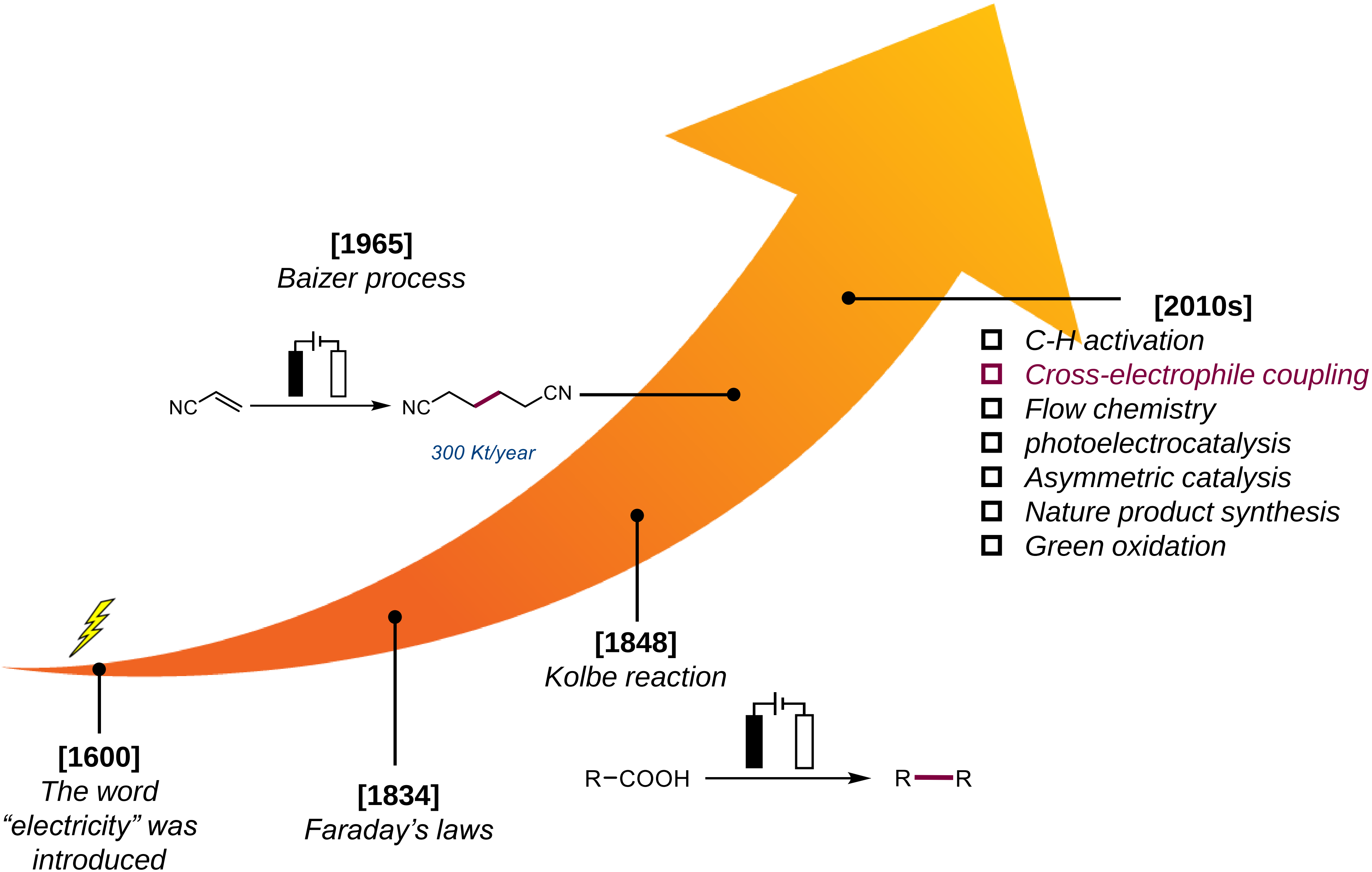
XEC strategies

- ☐ Electronic differentiation/matching
- ☐ Steric differentiation/matching

Core: Identify and distinguish two electrophiles (Distinct reactivity)

Weix, D. J. et al. *J. Org. Chem.* **2014**, *79*, 4793.
Jarvo, E. R. et al. *Nat. Rev. Chem.* **2017**, *1*, 0065.

A timeline of the development of organic electrochemistry



What electrochemistry can do in cross-electrophile coupling?
$C(sp^3)$–$C(sp^3)$ cross-coupling as example in this seminal

Lin, S. et al. *Chem. Soc. Rev.* **2021**, *50,* 7941.

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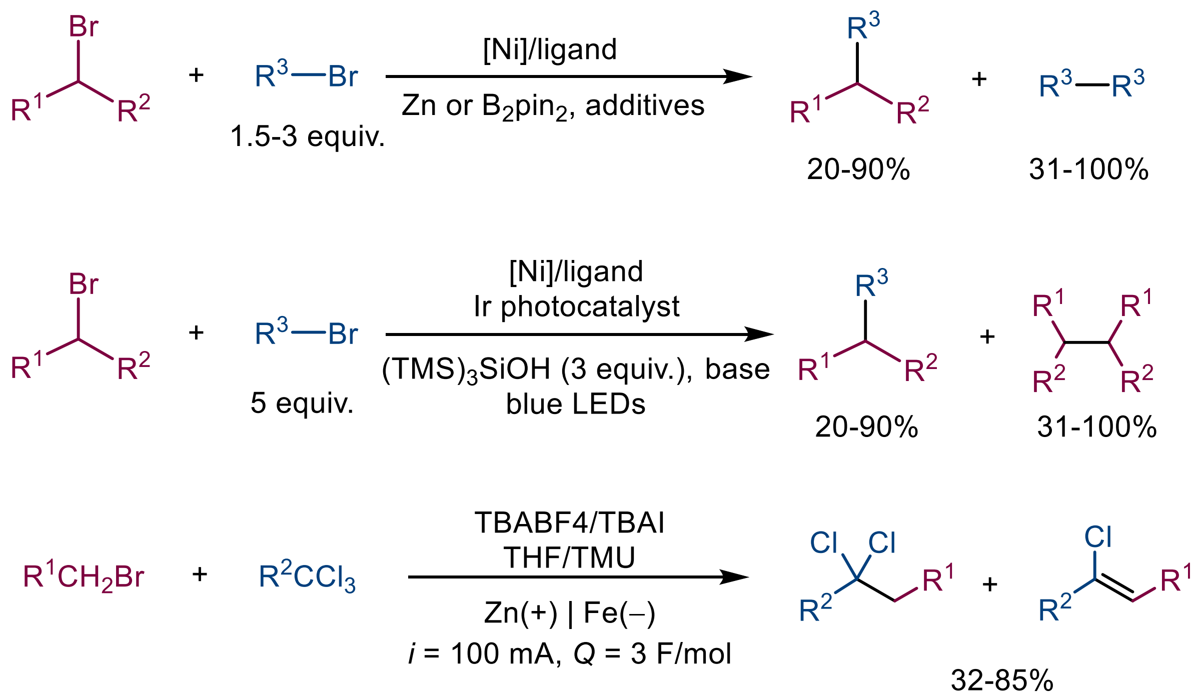
Dehalogenative C(sp³)–C(sp³) cross-coupling

Dehalogenative C(*sp*³)–C(*sp*³) cross-coupling

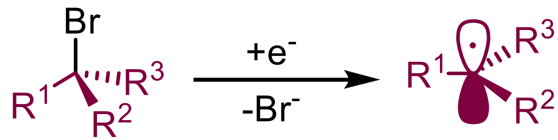


- ☐ Stoichiometric amounts of reductants and wastes
- ☐ Expensive halogen abstracters

- ☐ Only strongly activated alkyl halides in early example

Perichon, J. et al. *J. Org. Chem.* **1988**, *53*, 4720.; Gong, H. et al. *Org. Lett.* **2011**, *13*, 2138.; MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* **2018**, *140*, 17433.

Dehalogenative C(sp³)–C(sp³) cross-coupling



More subsituted
Better 1e⁻ electrophile

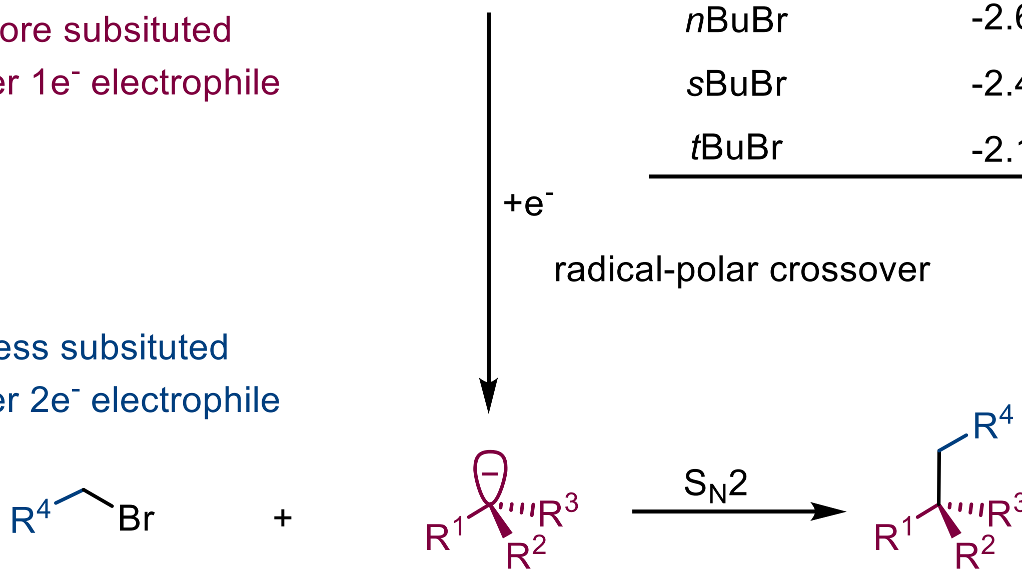
Reduction potential

R-X	E_{red} (vs. Ag wire)
*n*BuBr	-2.69 V
*s*BuBr	-2.42 V
*t*BuBr	-2.13 V

+e⁻

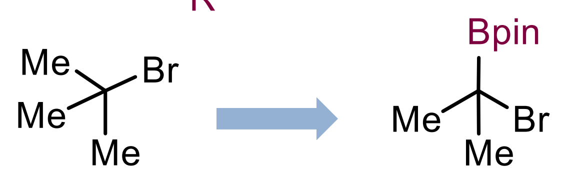
radical-polar crossover

Less subsituted
Better 2e⁻ electrophile



require the second reduction event to take place at a fast rate:

- ◻ minimize the diffusion of radical away from cathode
- ◻ inhibit dimerization and HAA of radical

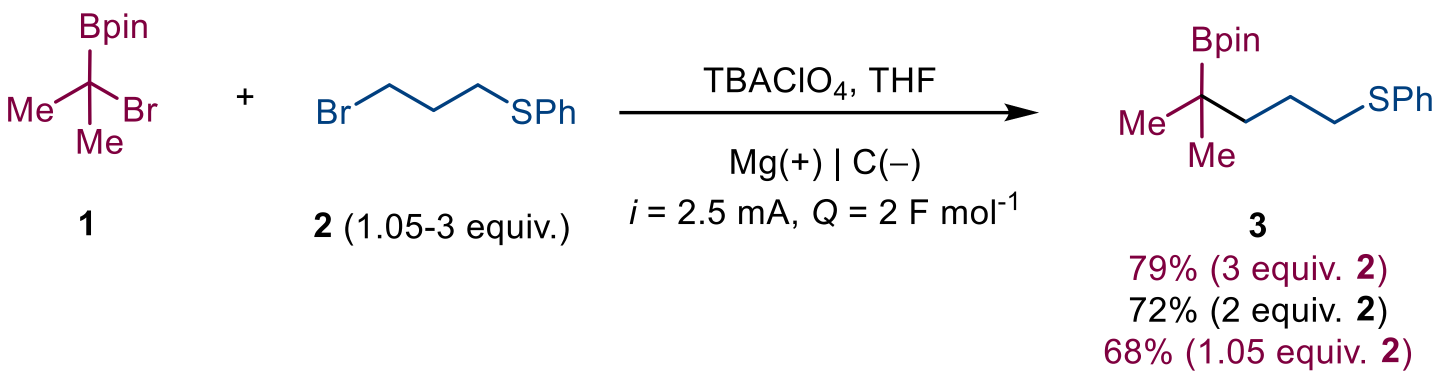


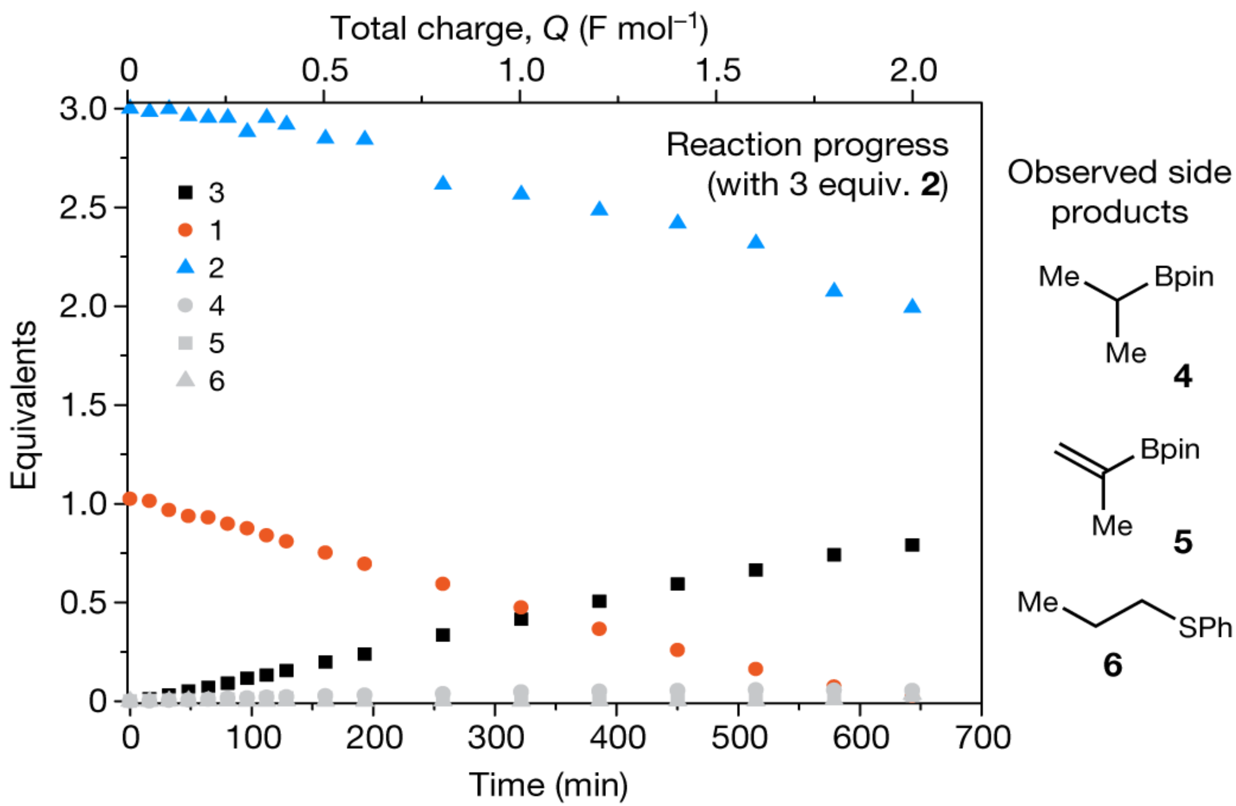
E_1° = -2.13 V
E_2° = -3.30 V

E_1° = -1.73 V
E_2° = -2.74 V

Lin, S. et al. *Nature* **2022**, *604,* 292.

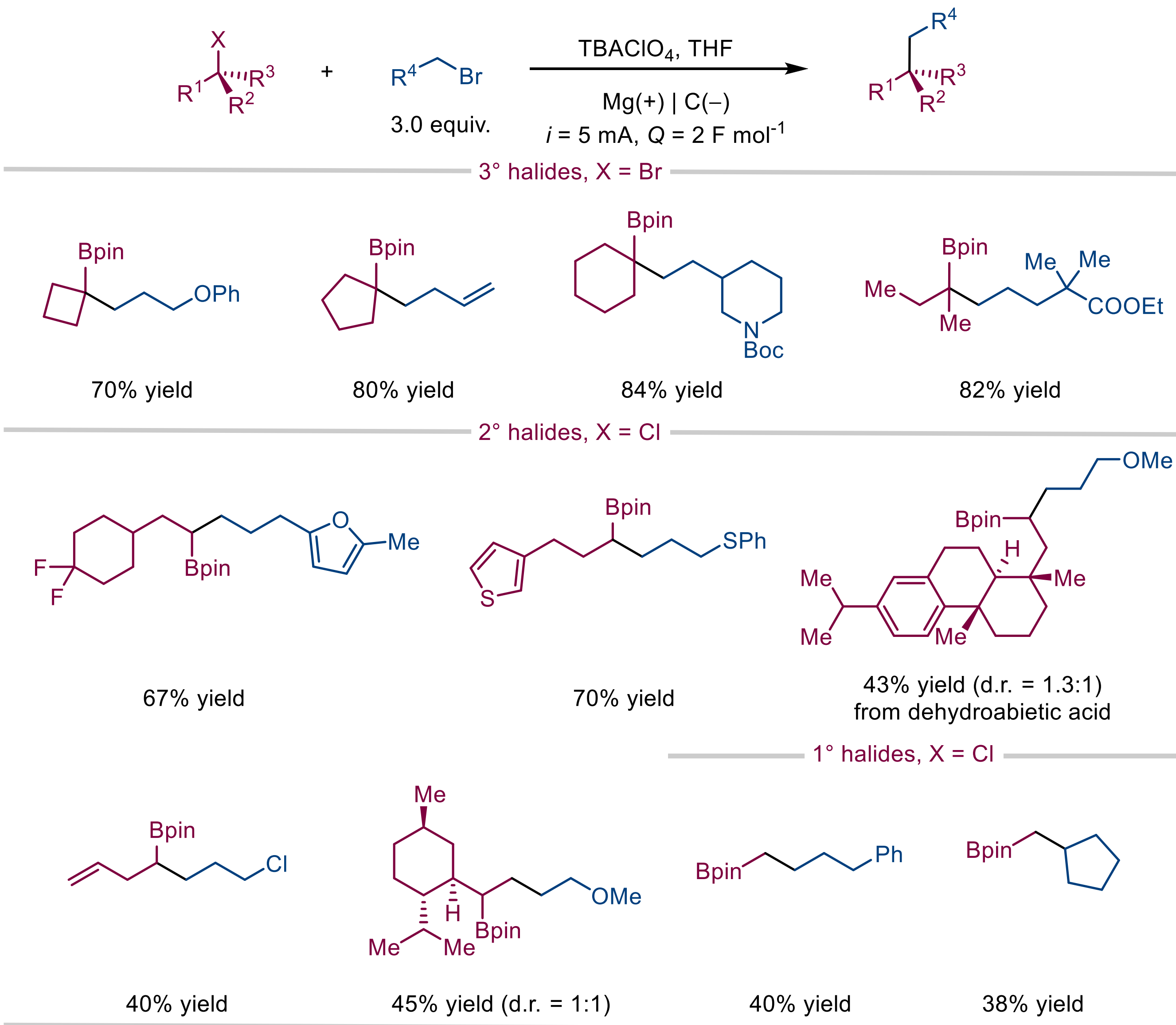
Dehalogenative C(sp^3)–C(sp^3) cross-coupling





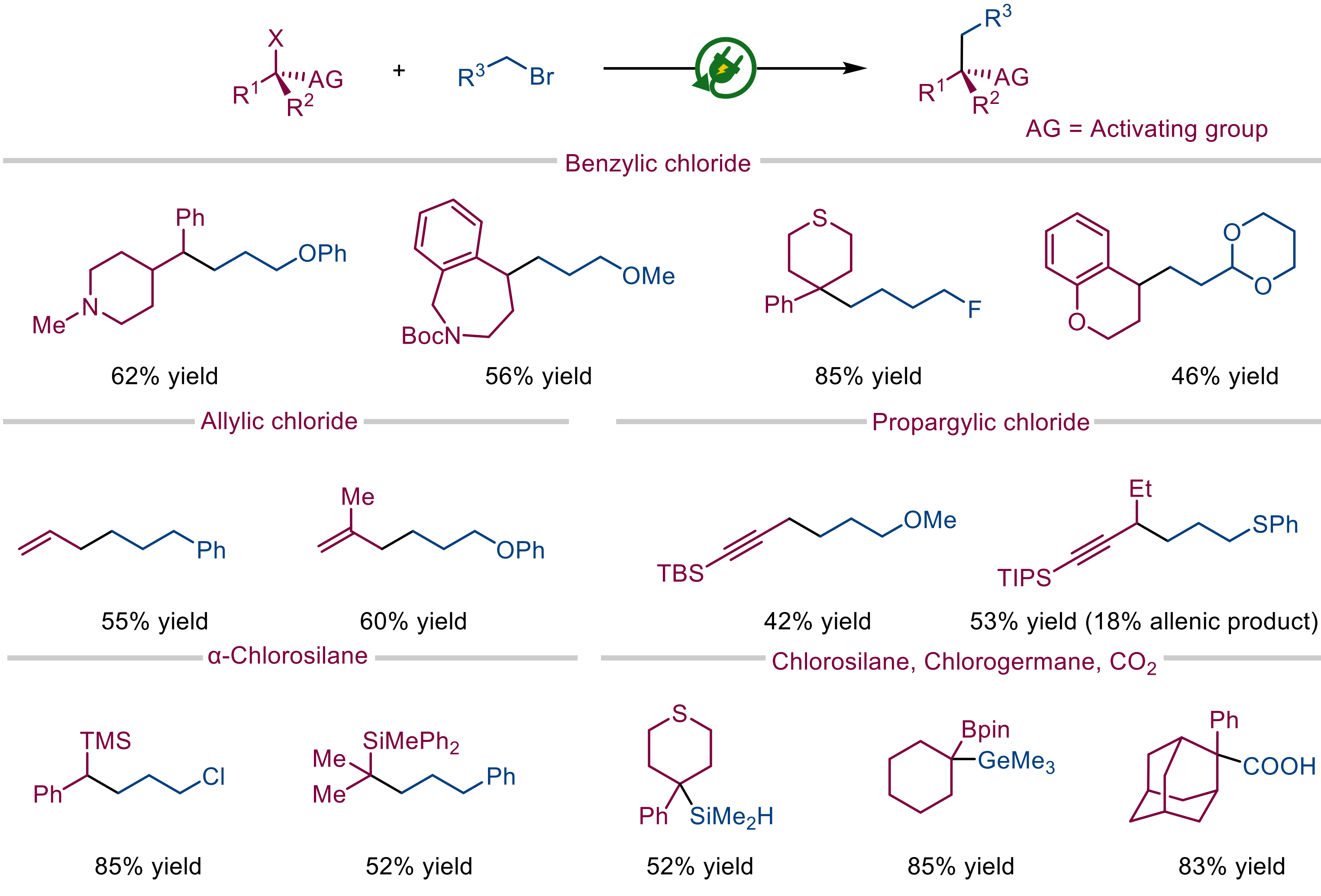
Lin, S. et al. *Nature* **2022**, *604*, 292.

Dehalogenative C(sp³)–C(sp³) cross-coupling



Lin, S. et al. *Nature* **2022**, *604,* 292.

Dehalogenative C(sp^3)–C(sp^3) cross-coupling



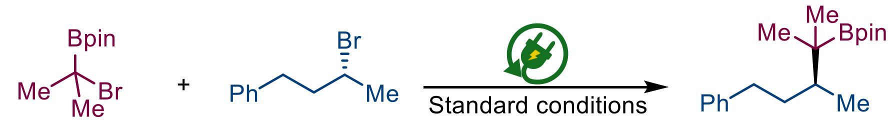
Lin, S. et al. *Nature* **2022**, *604,* 292.

Dehalogenative C(sp3)–C(sp3) cross-coupling

☐ Radical trapping experiment

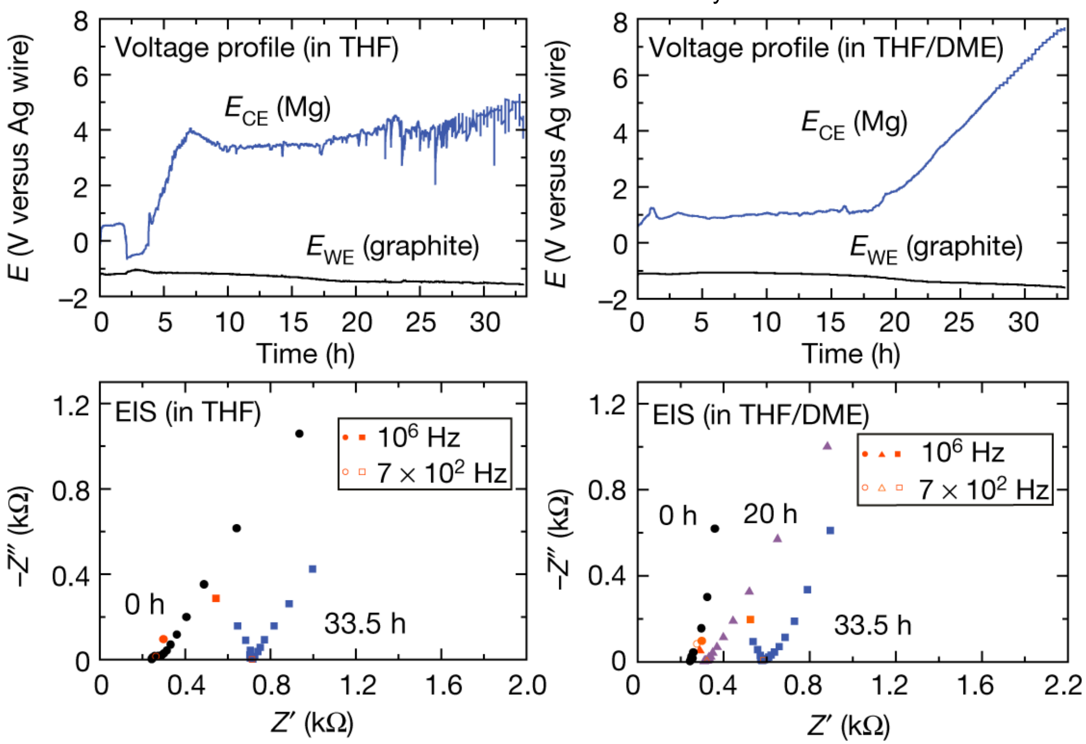
35% yield

☐ Stereocemistry test (S_N2 probe)



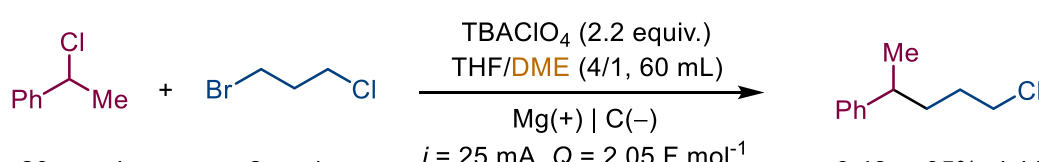
99% ee

30%, 92% ee



THF THF/DME

☐ Scale-up after additon of DME



20 mmol

2 equiv.

3.48 g, 95% yield

Lin, S. et al. *Nature* **2022**, *604*, 292.

C(sp³)–C(sp³) cross-coupling of unactivated alkyl halides

□ eXEC via S_N2

AG— C(*sp*³) —X + X— C(*sp*³) via AG— C(*sp*³)⊖

activating group attached

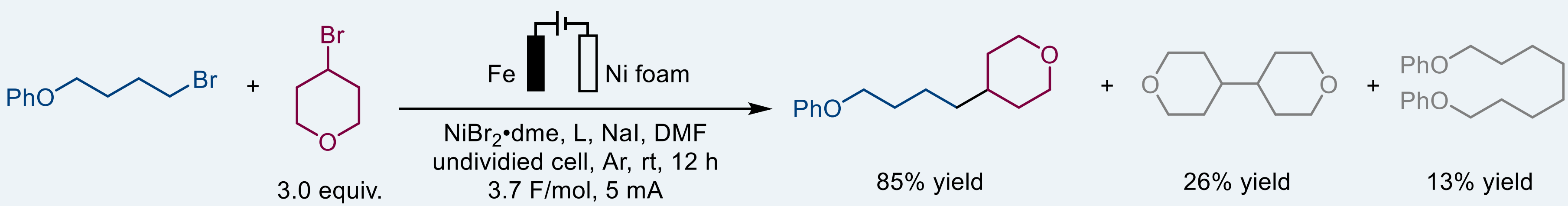
Examples:

□ Nickel-catalysed eXEC of unactivated alkyl halides

C(*sp*³) —X + X— C(*sp*³)

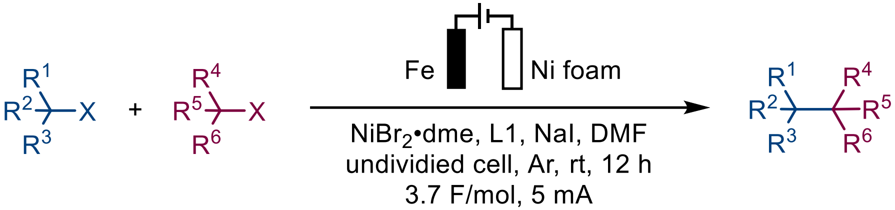
unactivated alkyl halides

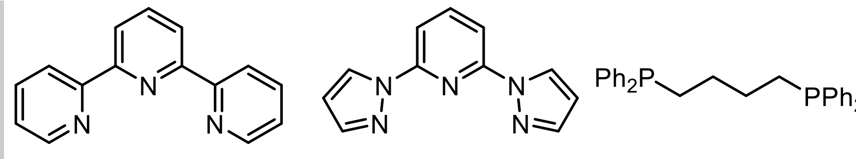
Examples:



Qiu, Y. et al. *Nat. Catal.* **2024**, *7*, 412.

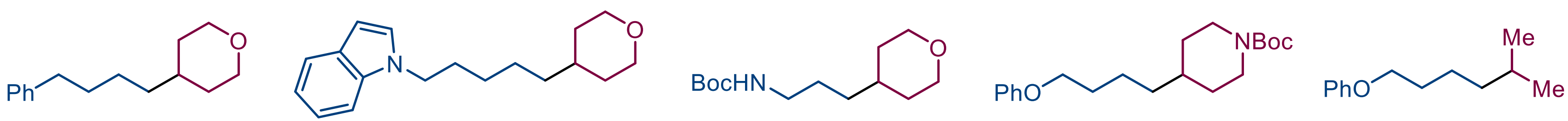
C(sp³)–C(sp³) cross-coupling of unactivated alkyl halides





L1 for 1°–2°/1°–1° halides coupling
L2 for 2°–2° halides coupling
L3 for 3°–1° halides coupling

1°–2° halides coupling

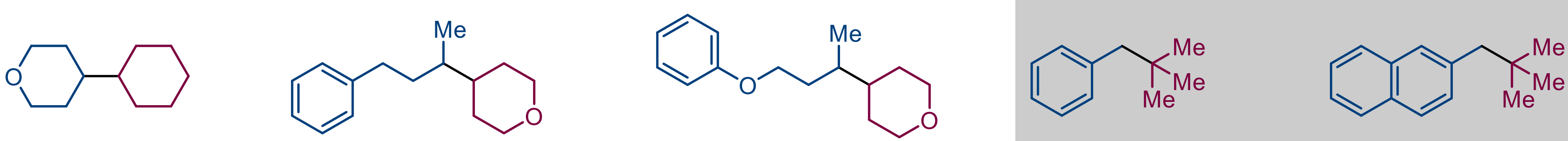


83% yield | 78% yield | 86% yield | 78% yield | 76% yield

1°–1° halides coupling

72% yield | 58% yield | 77% yield | 44% yield

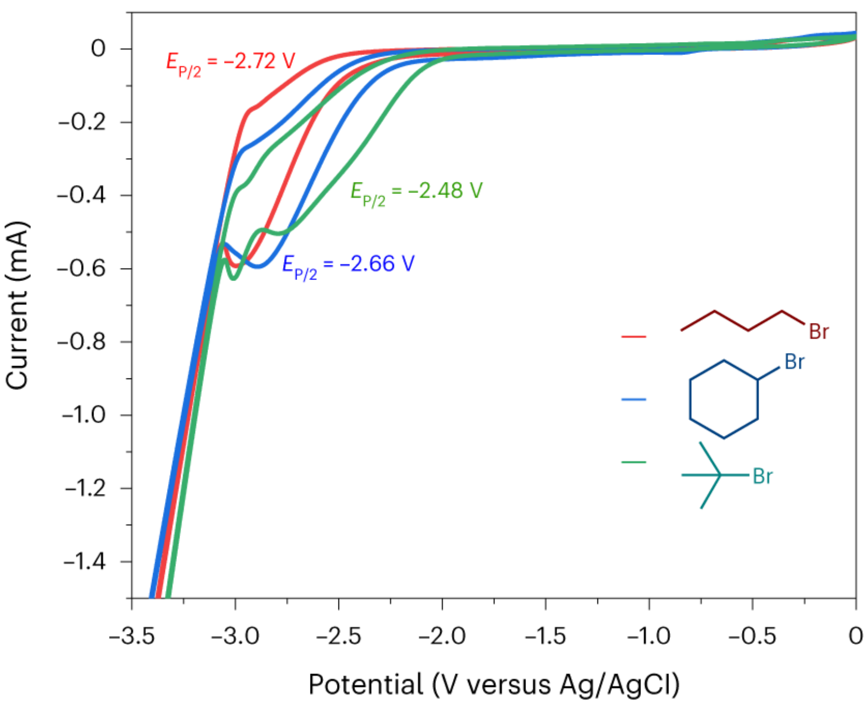
2°–2°/1°–3° halides coupling

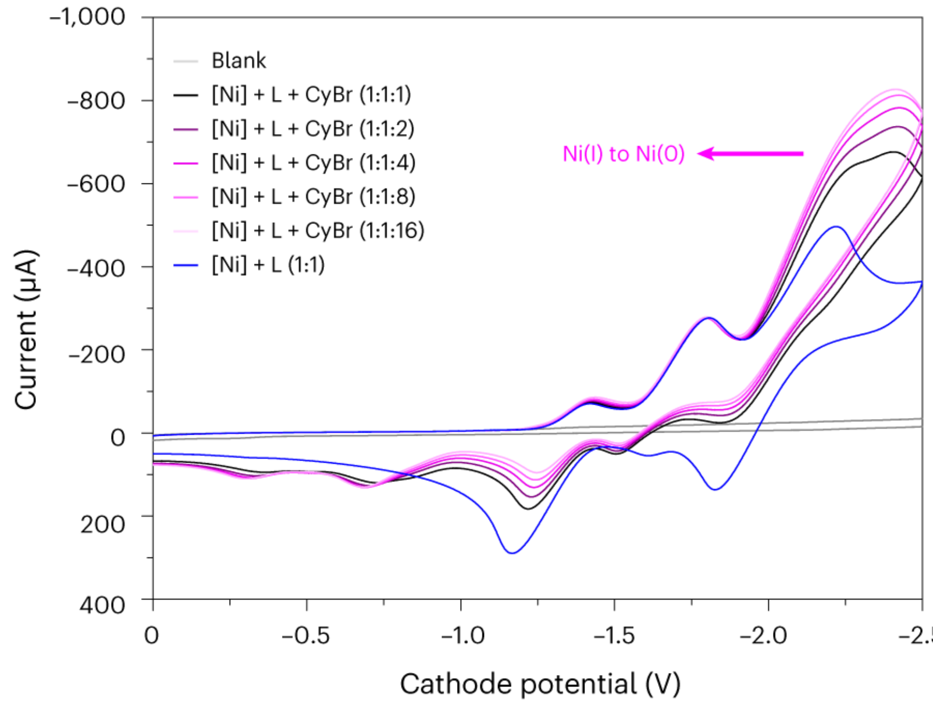


62% yield | 61% yield | 53% yield | 47% yield | 42% yield

Qiu, Y. et al. *Nat. Catal.* **2024**, *7*, 412.

C(sp³)–C(sp³) cross-coupling of unactivated alkyl halides





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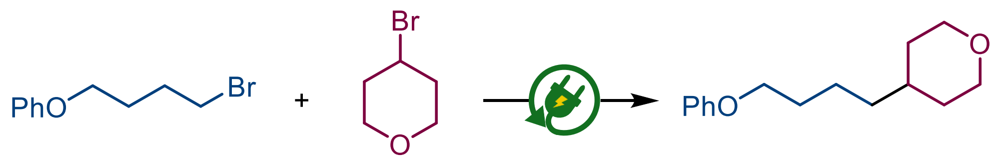
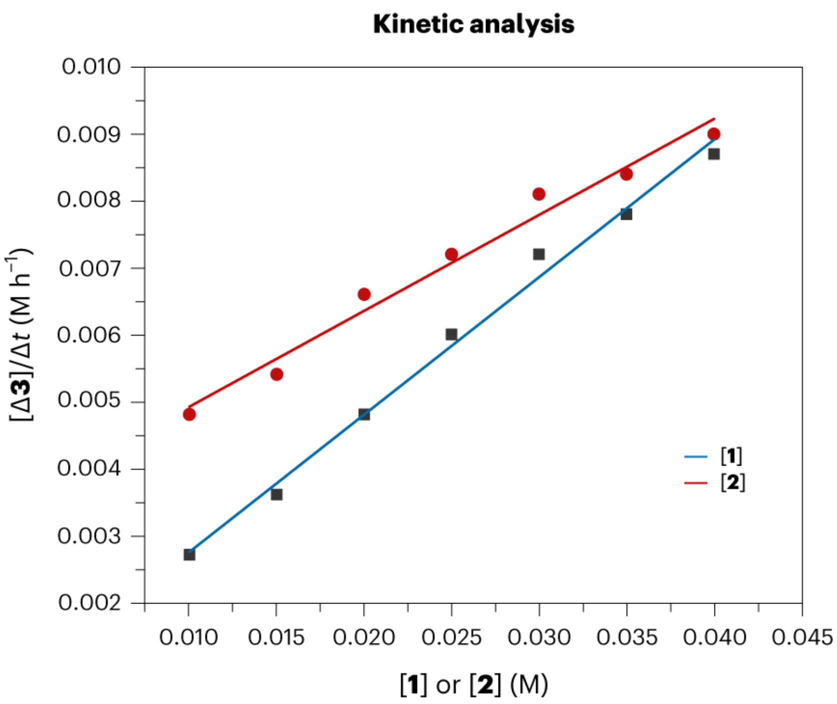
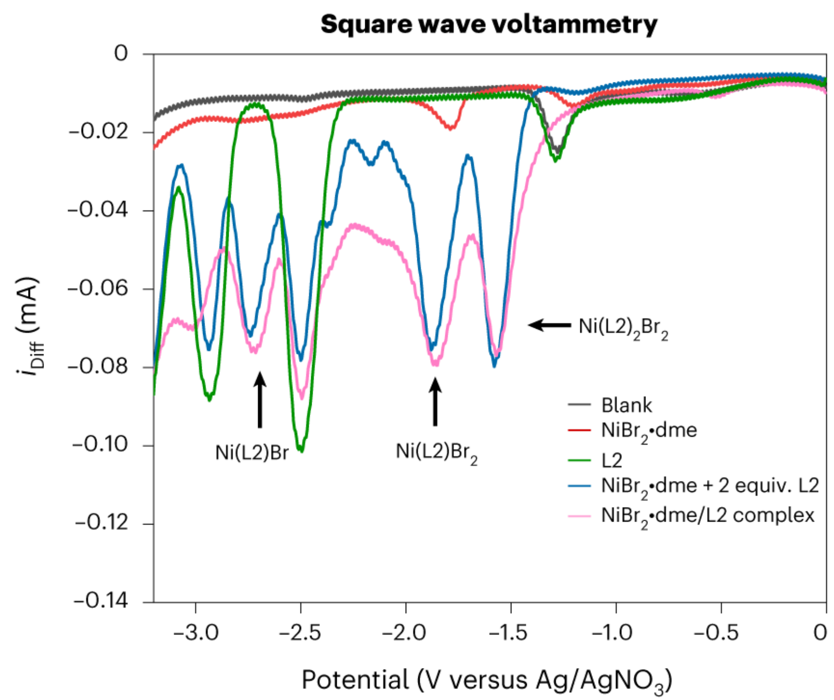
C(sp³)–C(sp³) cross-coupling of unactivated alkyl halides







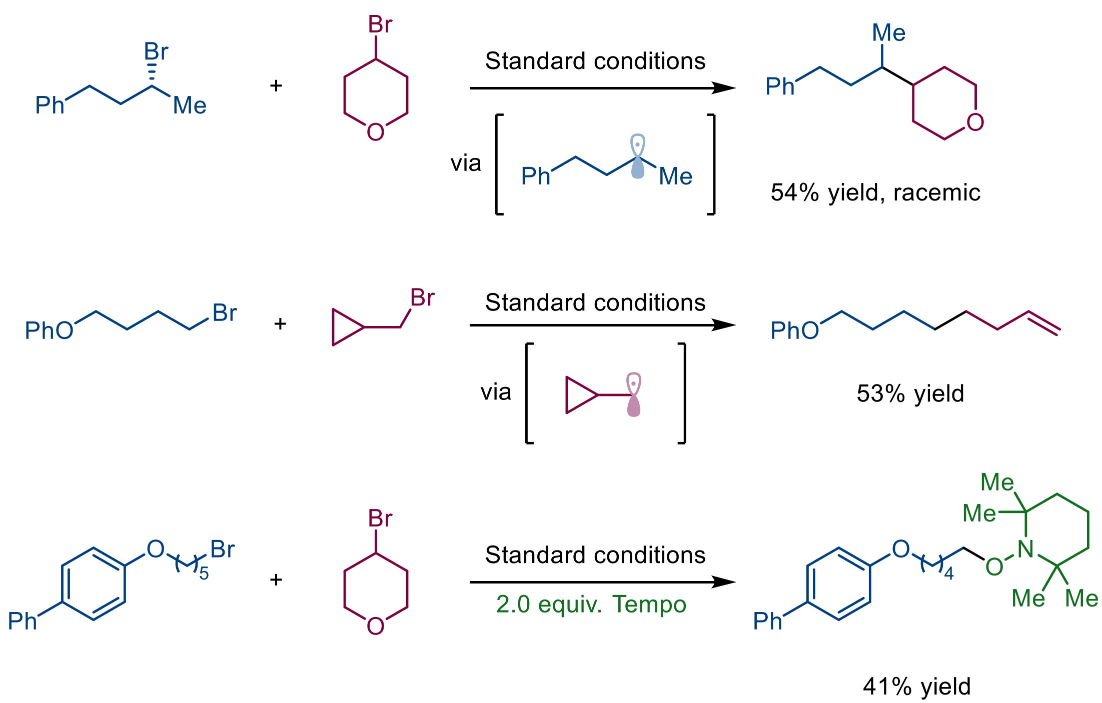
Qiu, Y. et al. *Nat. Catal.* **2024**, *7*, 412.

C(sp3)–C(sp3) cross-coupling of unactivated alkyl halides

☐ Control experiment of [Ni]

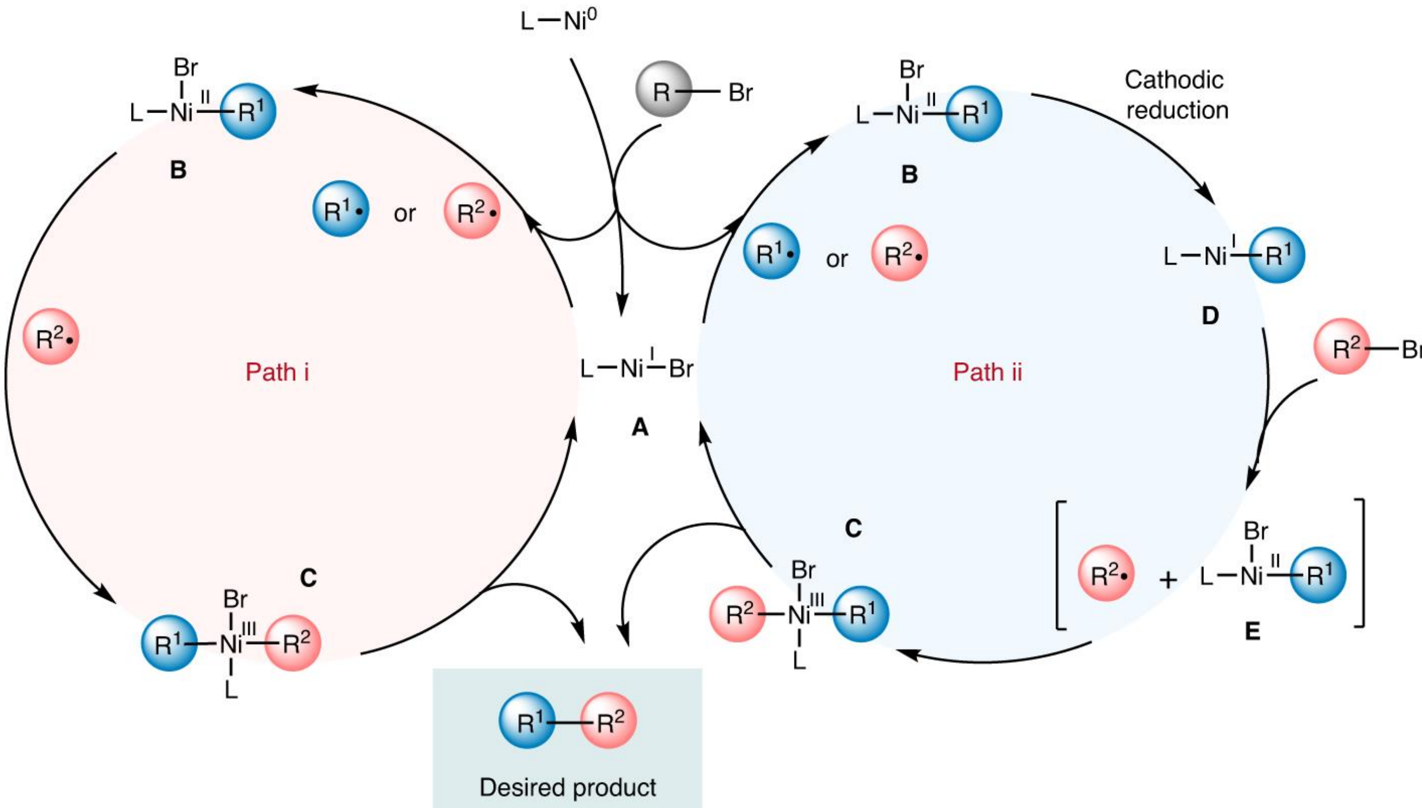
			No current	
No [Ni and L]	0.1 equiv. [Ni/L]	0.1 equiv. Ni^0	1 equiv. Ni^0	1 equiv. Ni^{II}
6% yield	83% yield	74% yield	9% yield	n.d.

☐ Radical-trapping experiments



Qiu, Y. et al. *Nat. Catal.* **2024**, *7*, 412.

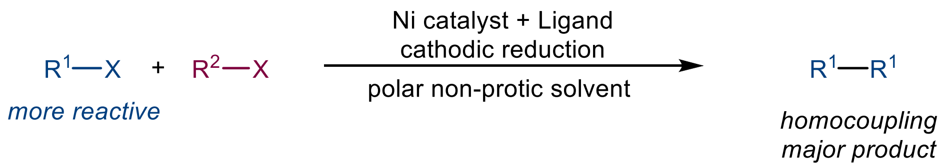
$C(sp^3)$–$C(sp^3)$ cross-coupling of unactivated alkyl halides

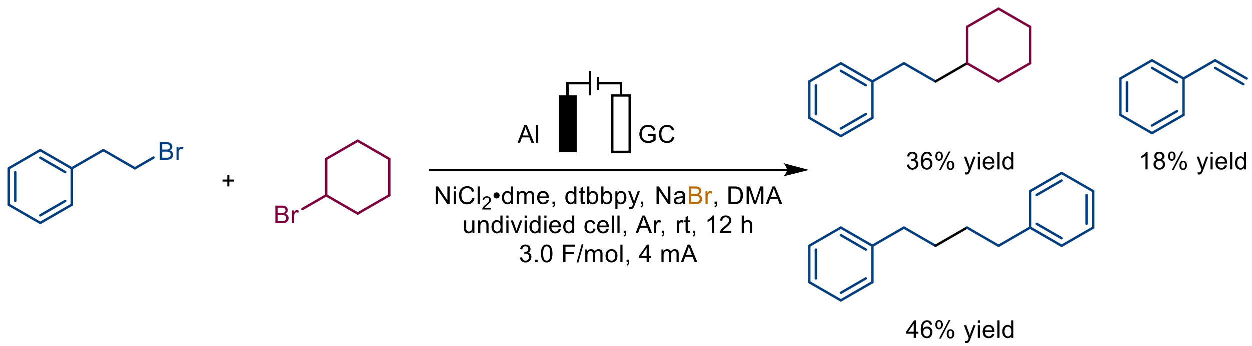


Qiu, Y. et al. *Nat. Catal.* **2024**, *7,* 412.

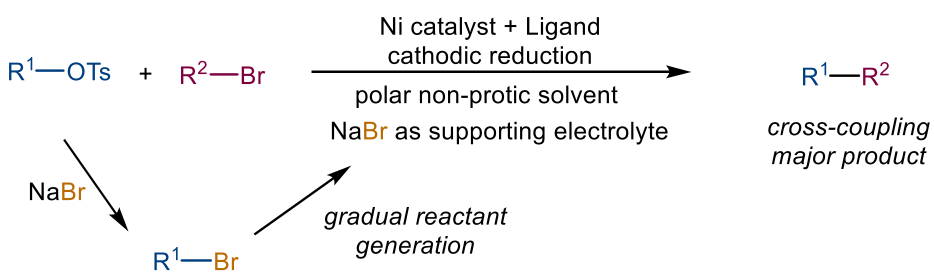
Reaction kinetics controls cross-selectivity

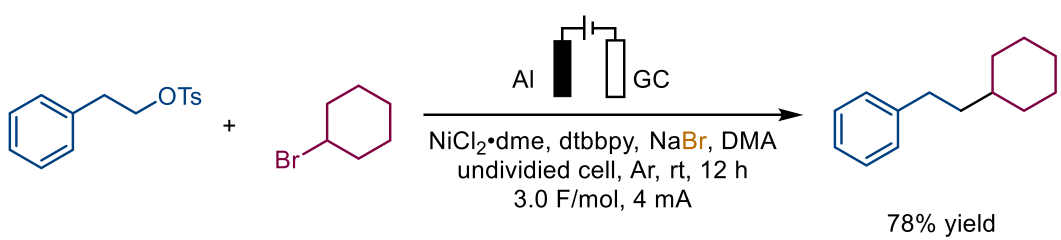
- ☐ reactivity mis-matched lead to homocoupling





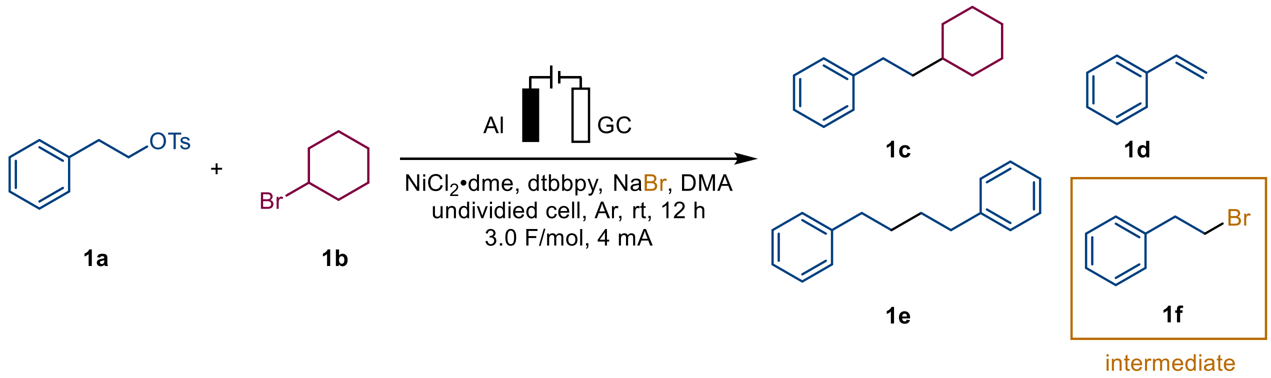
- ☐ reactive intermediate gradually generated

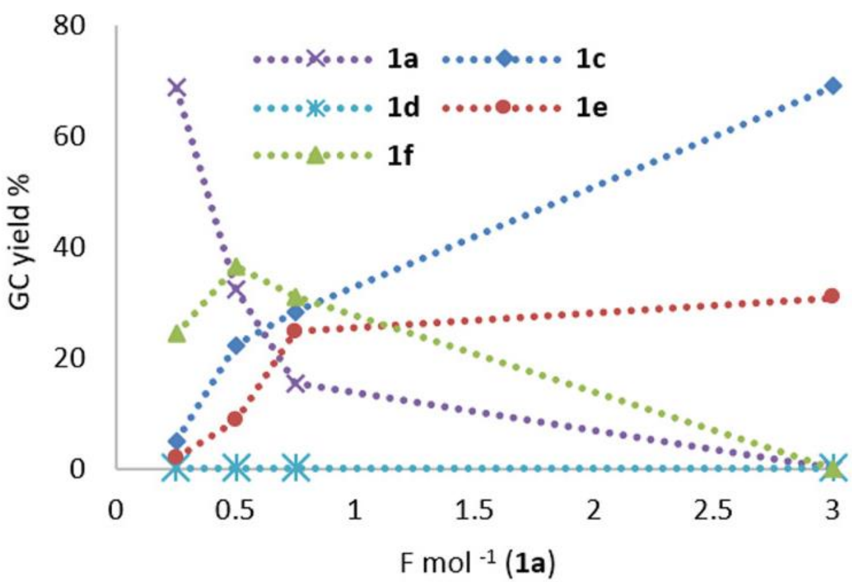


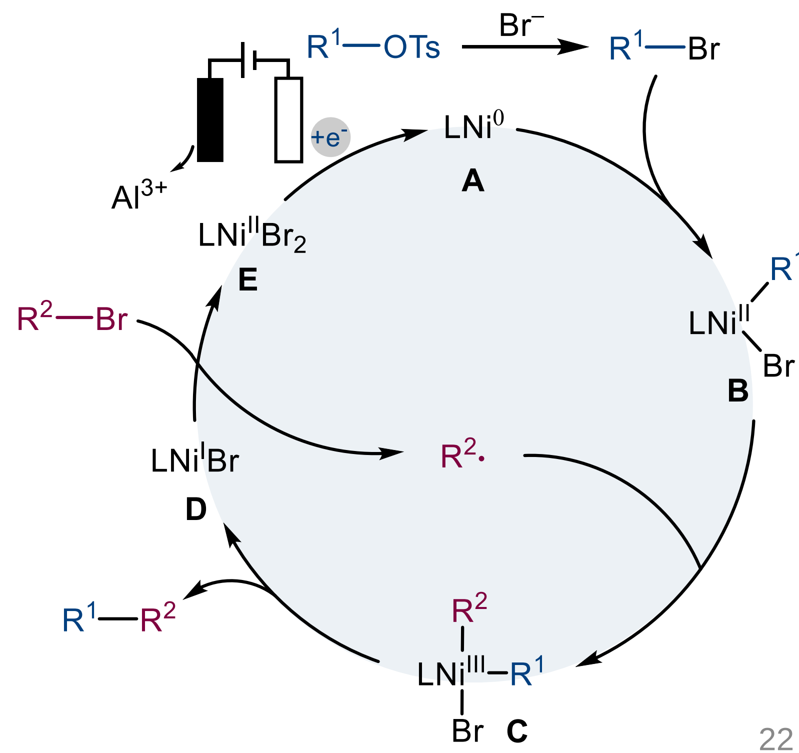


Cantillo, D. et al. *J. Am. Chem. Soc.* **2023**, *145,* 17023.

Reaction kinetics controls cross-selectivity

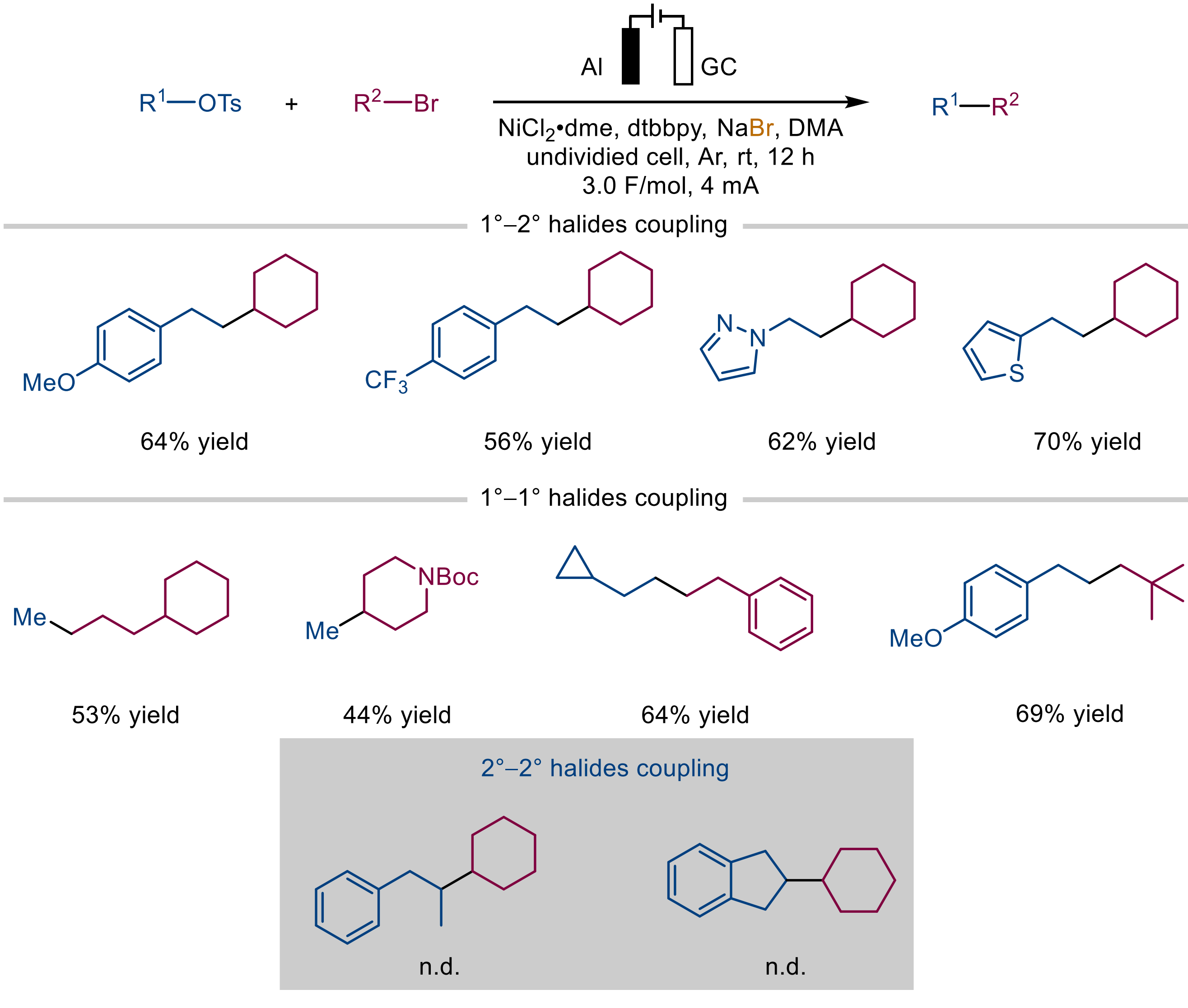






Cantillo, D. et al. *J. Am. Chem. Soc.* **2023**, *145,* 17023.

Dehalogenative C(sp³)–C(sp³) cross-coupling



Cantillo, D. et al. *J. Am. Chem. Soc.* **2023**, *145,* 17023.

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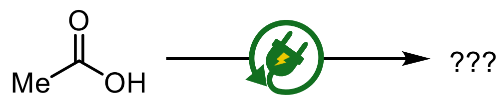
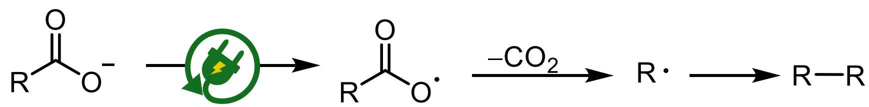
Early example of Decarboxylative C(sp^3)–C(sp^3) homocoupling

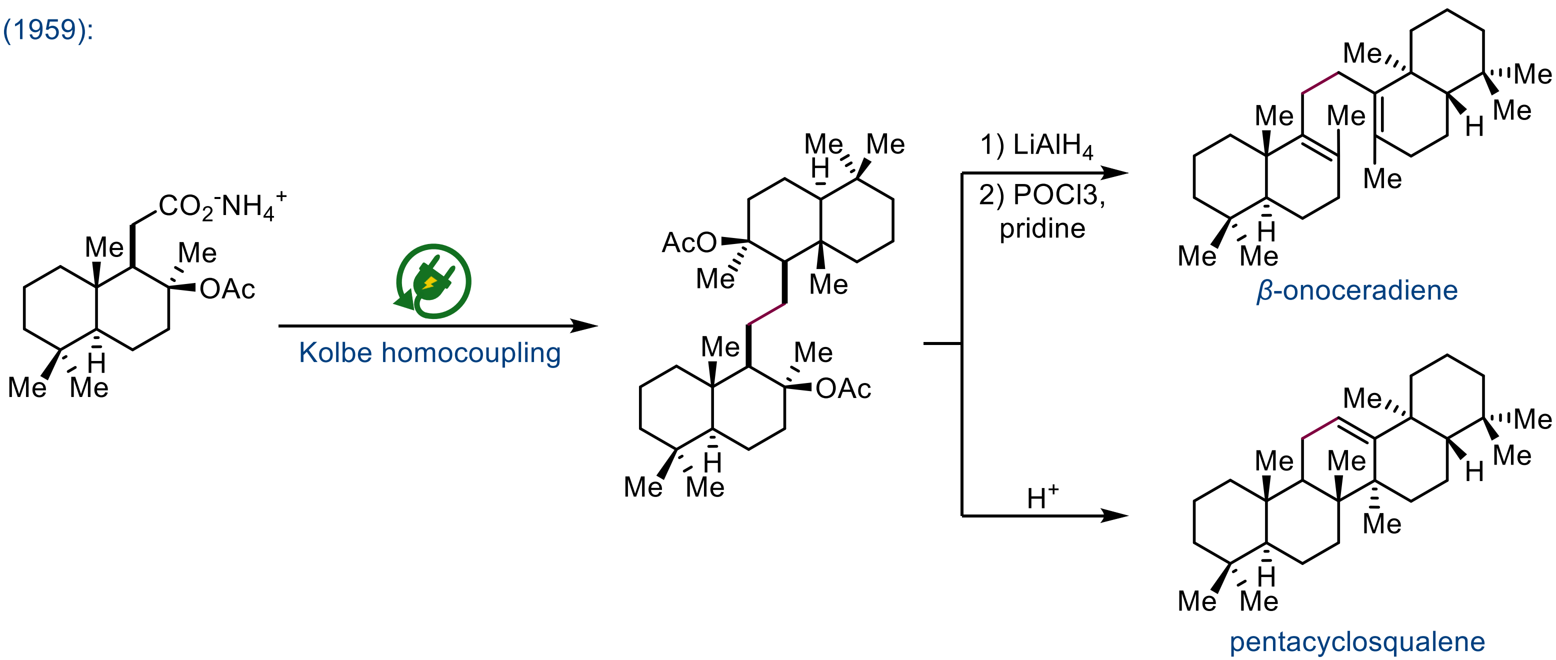


-Michael Faraday (1834)



-Hermann Kolbe (1847) homocoupling

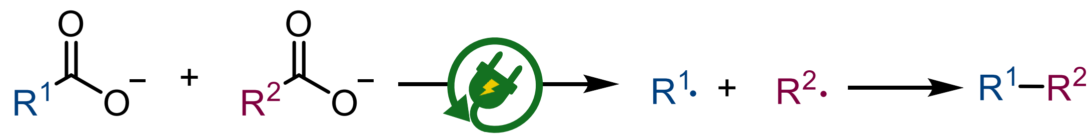
E. J. Corey (1959):

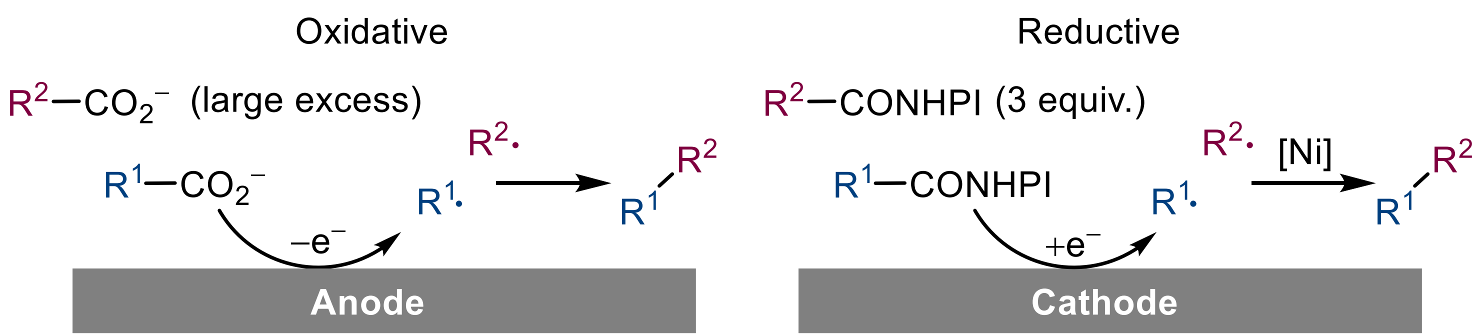


Corey, E. J. et al. *J. Am. Chem. Soc.* **1959**, *81*, 1739.

Doubly decarboxylative C(sp³)–C(sp³) cross-coupling

Kolbe cross-coupling: an unexplored opportunity

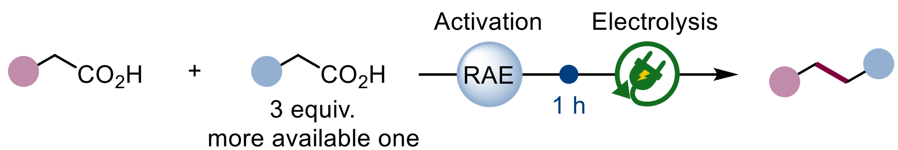




	Kolbe oxidative approach			Baran reductive approach		
Class of acids	1-1°	1-2°	2-2°	1-1°	1-2°	2-2°
Hydrocarbons	✓	limited	unknown	✓	✓	✓
N-containing	✓	limited	unknown	✓	✓	✓

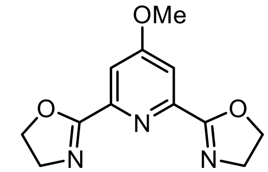
Baran, P. S. et al. *Nature* **2022**, *606*, 313.

Doubly decarboxylative coupling (dDCC)

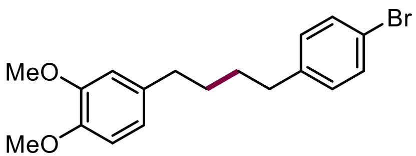


Activation
DIC (1.1 equiv.)
NHPI (1.1 equiv.)
DMAP (10 mol%)
DCM, rt, 1 h

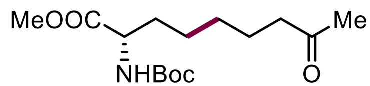
Electrolysis
$NiCl_2$•dme (20 mol%)
Ligand (20 mol%)
NaI (0.2 M), DMF, rt
Zn(+) | Ni foam (–)
4 mA, 4 F/mol



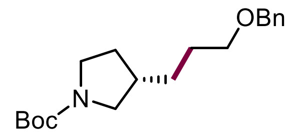
1°–1° coupling



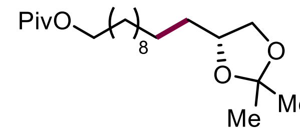
64% yield
(previous) 6 steps



65% yield
(previous) 7 steps

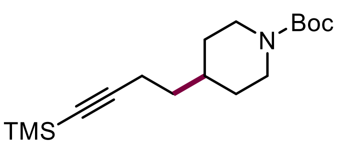


48% yield
(previous) 8 steps

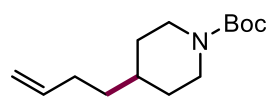


34% yield
(previous) 7 steps

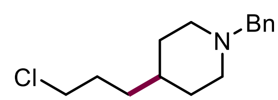
1°–2° coupling



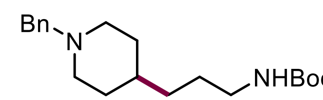
41% yield
(previous) 6 steps



60% yield
(previous) 4 steps

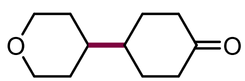


37% yield
(previous) 6 steps

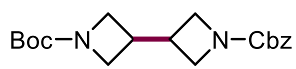


43% yield
(previous) 6 steps

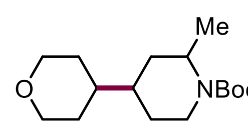
2°–2°/3°–1° coupling



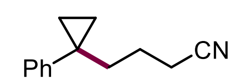
48% yield
(previous) 4 steps



40% yield
(previous) 7 steps



34% yield
dr = 2:1

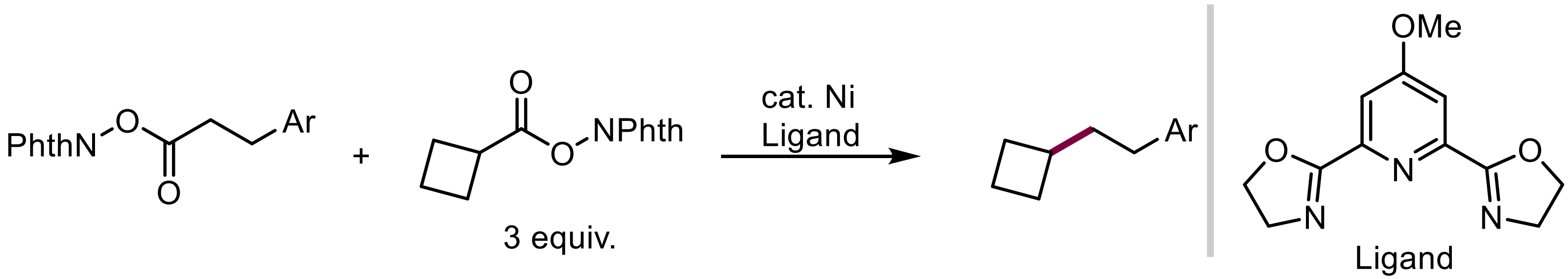


53% yield
(previous) 7 steps

Baran, P. S. et al. *Nature* **2022**, *606*, 313.

electrochemistry vs. photochemistry

☐ Comparison with photoredox conditions



Entry	Conditions	Yield
1		51%
2	Ir(ppy)3, NiCl•dme (5 mol%), Ligand (6 mol%), quinuclidine (1.2 equiv.), DMSO, violet LEDs (400 nm), rt	2%
3	Ir(ppy)3, NiCl•dme (5 mol%), Ligand (6 mol%), $^{i}Pr_2NEt$ (2 equiv.), DMA, blue LEDs (450 nm), rt	trace
4	Ir(ppy)3, NiCl•dme (20 mol%), Ligand (22 mol%), $^{i}Pr_2NEt$ (4 equiv.), DMA, blue LEDs (450 nm), rt	Quantitative dimerization

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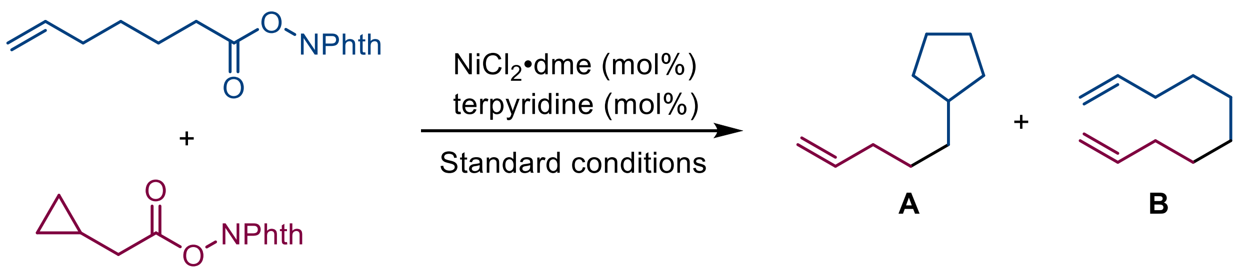
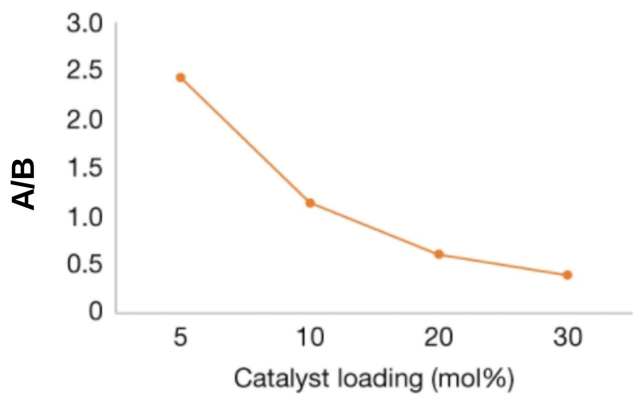
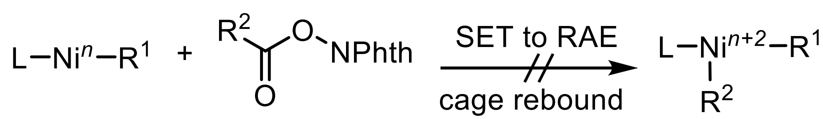
Doubly decarboxylative C(sp^3)–C(sp^3) cross-coupling

☐ Radical-clock experiments



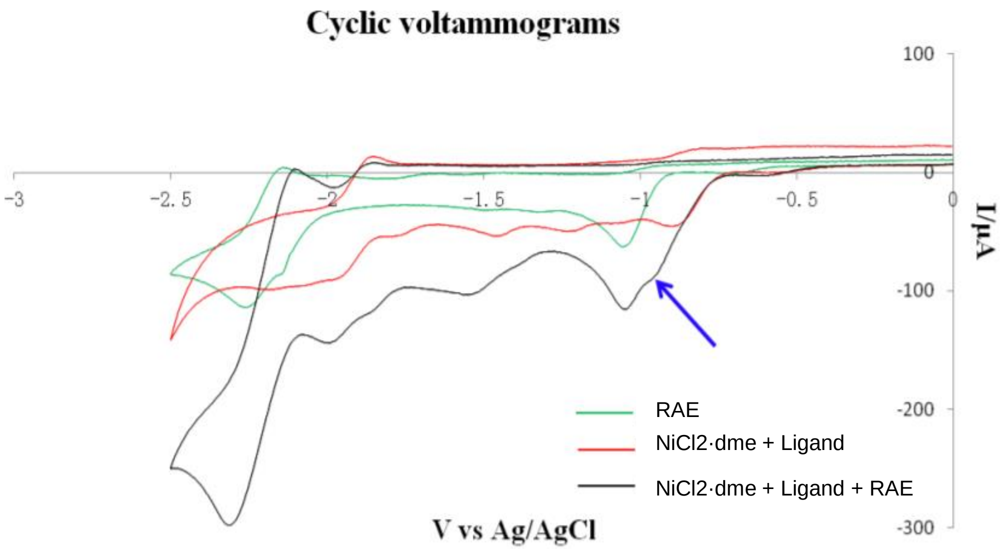


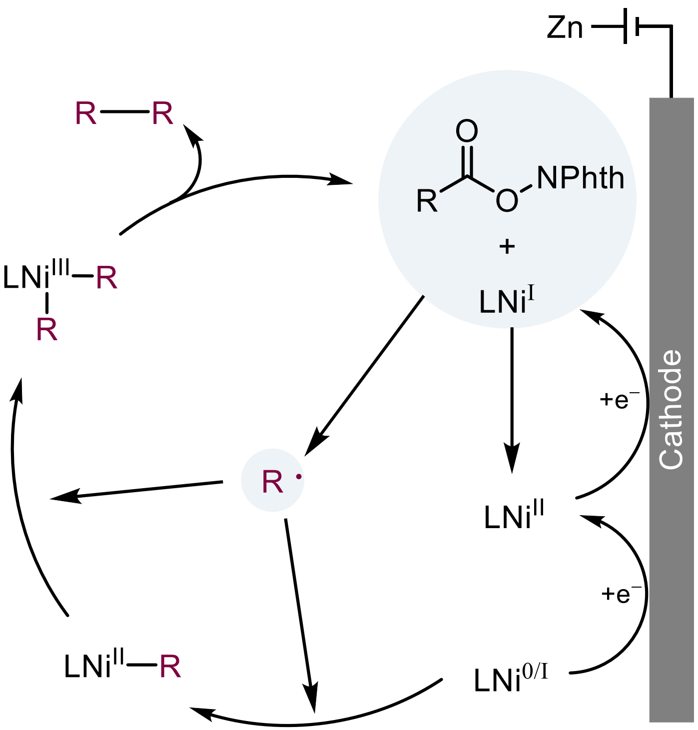


☐ the ratio of **A** and **B** is dependent on Ni catalyst concentration, indicating that cage-escaped radical might be involved for Ni–C bond formation

Baran, P. S. et al. *Nature* **2022**, *606,* 313.

Doubly decarboxylative C(sp³)–C(sp³) cross-coupling



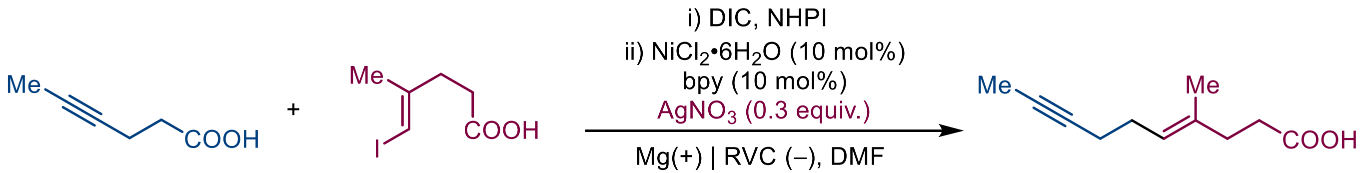


- RAE is reduced by Ni(I)
- Directly cathodic reduction is also possible

Baran, P. S. et al. *Nature* **2022**, *606,* 313.

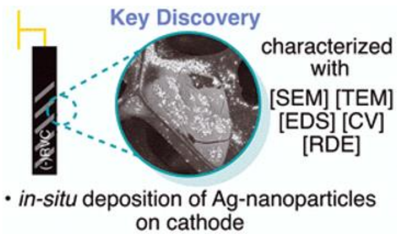
2nd generation dDCC: Ag-NPs-promoted dDCC

- Baran's previous work—Ag/Ni-catalysed alkenylation



1.5 equiv.

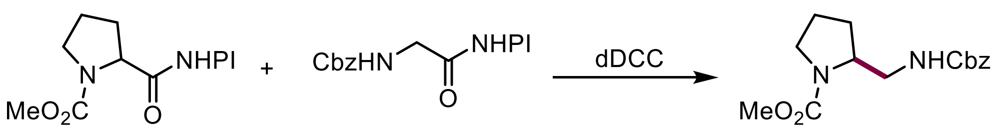
50% yield



Ag-NP's effects on the reaction

- extend catalyst lifetime
- prevent background decomposition of the RAEs
- lower the required overpotential to improve FG compatibility

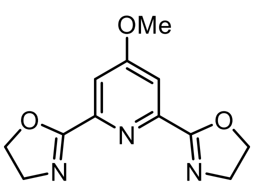
When $AgNO_3$ incorporated in C(sp^3)–C(sp^3) dDCC



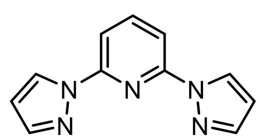
3.0 equiv

1st generation: 8% (with **L1**)
2nd generation: 67% (with **L2**)

1st generation	2nd generation
$NiCl_2$•dme (20 mol%)	$NiCl_2$•dme (20 mol%)
L1 (20 mol%)	**L1** or **L2** (20 mol%)
NaI (0.2 M), DMF, rt	$AgNO_3$ (50 mol%)
Zn(+) | Ni foam(–)	NBu_4•BF_4 (0.2 M), NMP
4 mA, 4 F/mol	Mg(+) | RVC(–)
	4 mA, 4.5 F/mol



L1

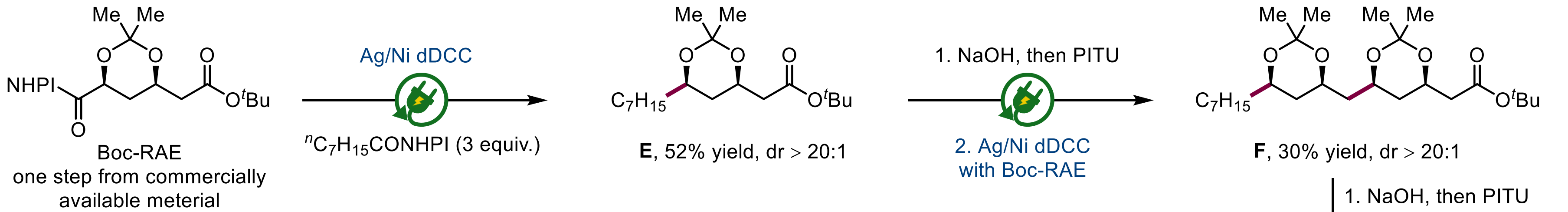


L2

2nd generation dDCC makes complex molecules synthesis possible

Baran, P. S. et al. *Science* **2022**, *375,* 745.
Baran, P. S. et al. *Nature* **2023**, *623,* 745.

2nd generation dDCC: a example of synthesis of Polyrhacitide A

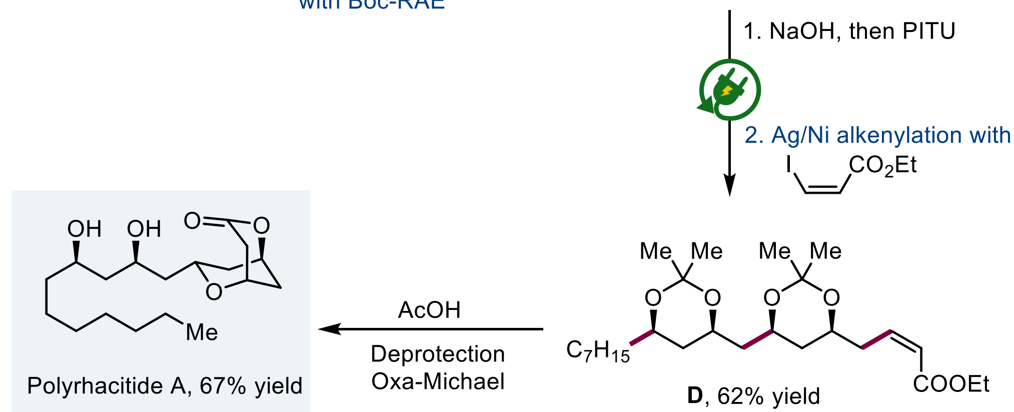


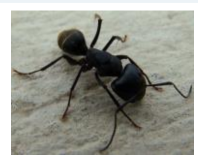
Conventional 2e⁻ synthesis--12 steps

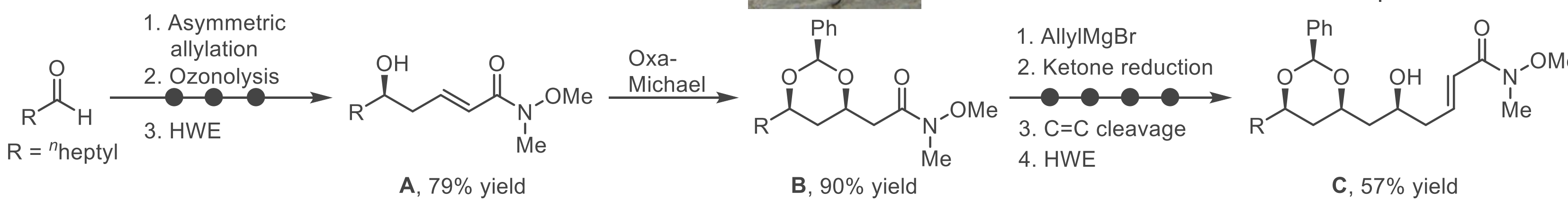
- ☐ Iterative sequence of olefin/carbonyl chemistry
- ☐ Many concession steps for FG and redox operations

1e⁻ radical disconnection--5 steps

- ☐ three directly electrochemical C-C bond formation
- ☐ Minimal concession steps

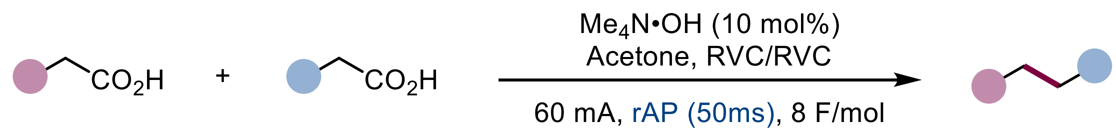






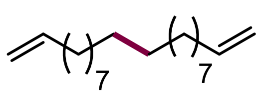
Baran, P. S. et al. *Nature* **2023**, *623*, 745.

rAP dDCC of unactivated Carboxylic acids



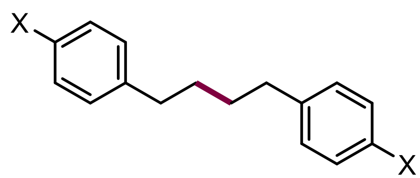
homocoupling | **cross-coupling**

Bio-derived



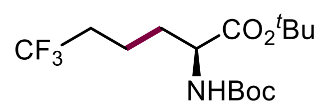
63%
[DC]: <5%
[Pt Kolbe]: 0%
200 mmol: 65%

Bio-derived



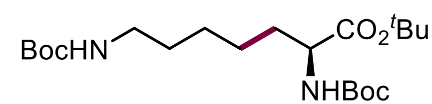
X = Br, 49%; OAc, 42%
[DC]: 0%
[Pt Kolbe]: 0%

Trifluoronorleucine



58%[a]
25 gram scale: 53%

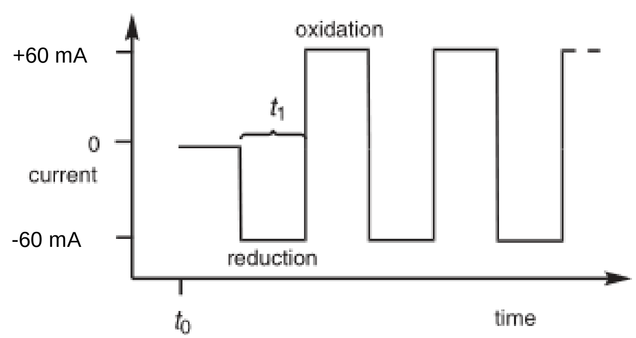
Lipidic amino acid



47%[b]

[DC]: the same conditions at 60mA (DC) 8 F/mol instead of rAP. **[Pt Kolbe]**: Pt/Pt electrodes, 10 mol% MeONa, MeOH, 60mA (DC) 8 F/mol

[a]Asp (0.1 mmol,1 equiv.), the second carboxylic acid (6 equiv.). [b]Asp (0.1 mmol,1 equiv.), the second carboxylic acid (3 equiv.)



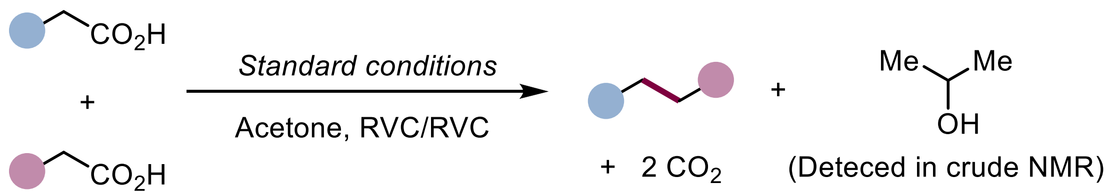
rapid alternating polarity (rAP)

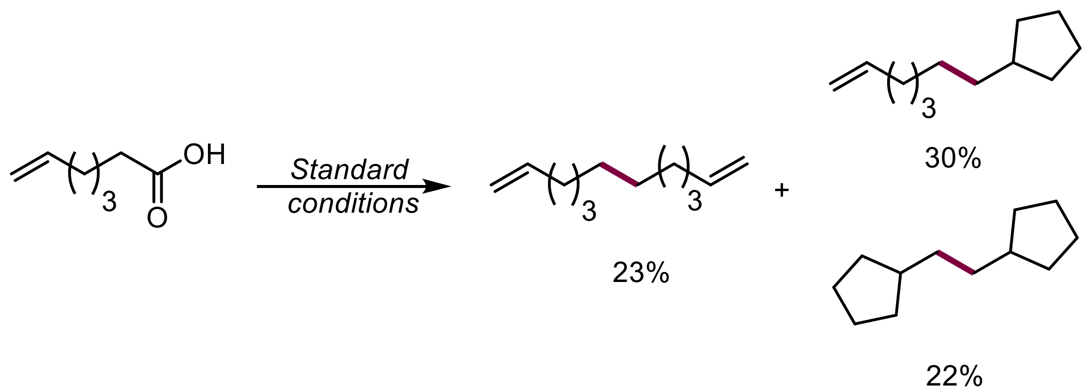
- ☐ No activation of carboxylic acids
- ☐ No expensive Pt electrode
- ☐ Upconversion of bio-derived carboxylic acids

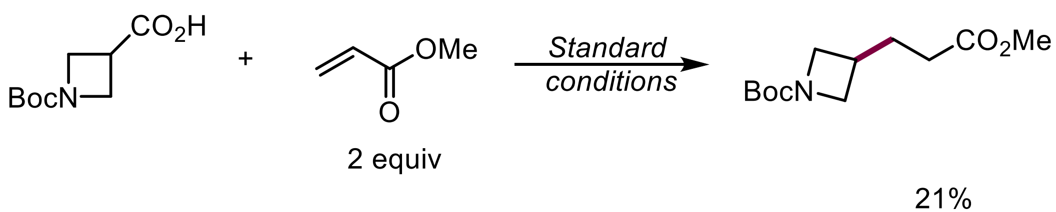
Baran, P. S. et al. *Science* **2023**, *380,* 81.

rAP dDCC of unactivated Carboxylic acids

Overall reaction and proof of free radical generation



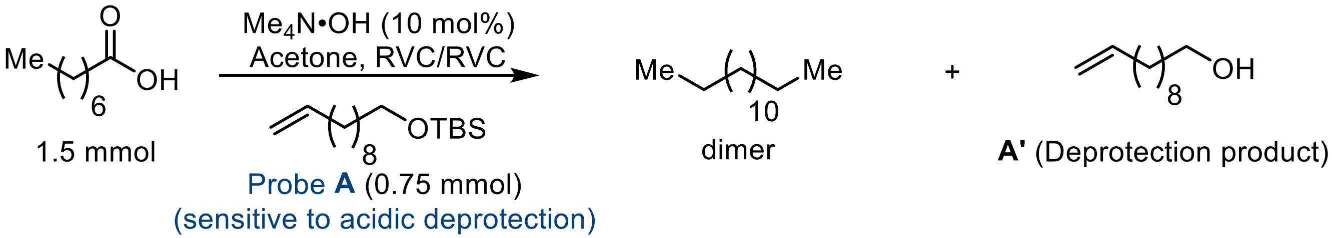




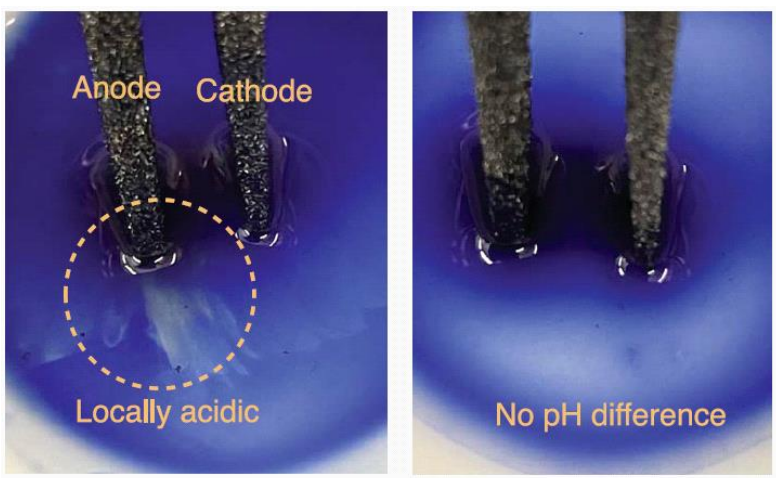
Baran, P. S. et al. *Science* **2023**, *380,* 81.

rAP dDCC of unactivated Carboxylic acids

DC vs. rAP: Differing pH surrounding the electrodes drives reactivity enhancement

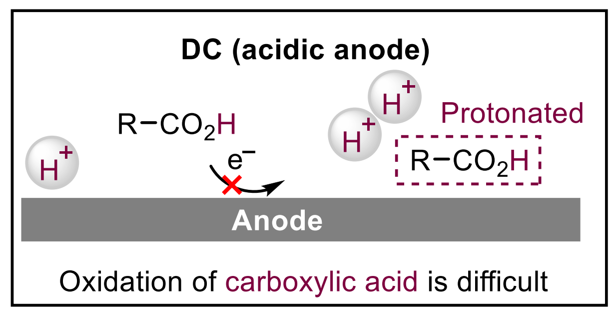


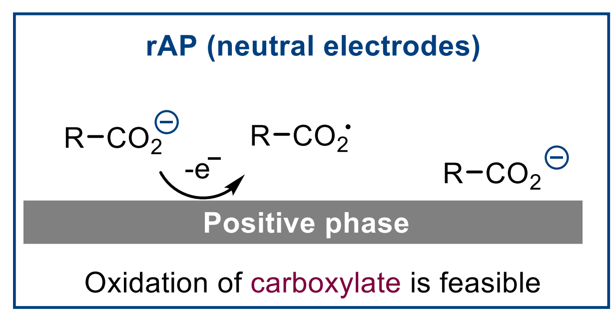
electrolysis conditions	dimer	**A'** (remaining **A**)
60 mA, DC, 10 F/mol	37%	52% (48%)
60 mA, rAP (50ms), 10 F/mol	71%	5% (95%)



DC (electrogenerated acid) **rAP**

Visualization of reaction pH (with bromophenol blue)



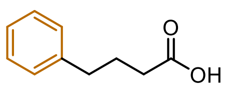


Baran, P. S. et al. *Science* **2023**, *380,* 81.

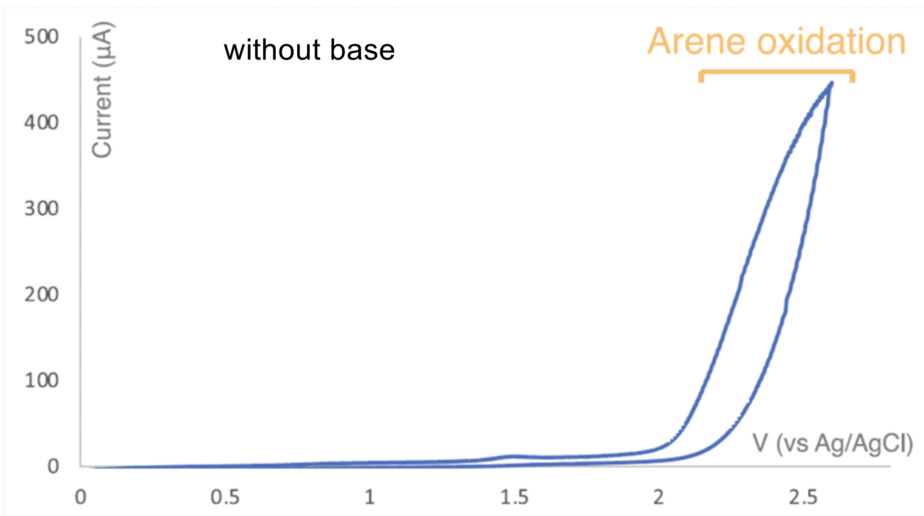
rAP dDCC of unactivated Carboxylic acids

Local pH difference lead to CV difference

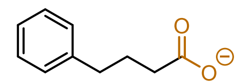
Under DC



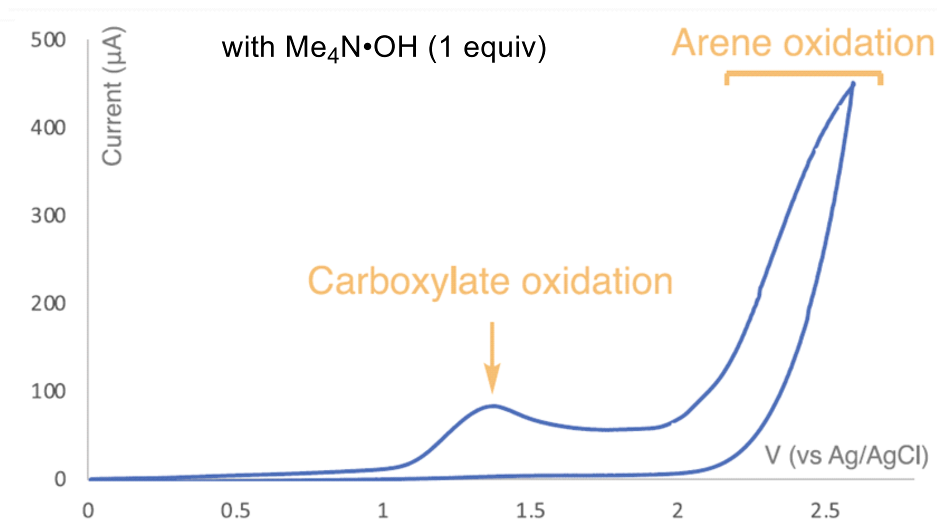
Benzylic oxidation product



Under rAP



Kolbe coupling



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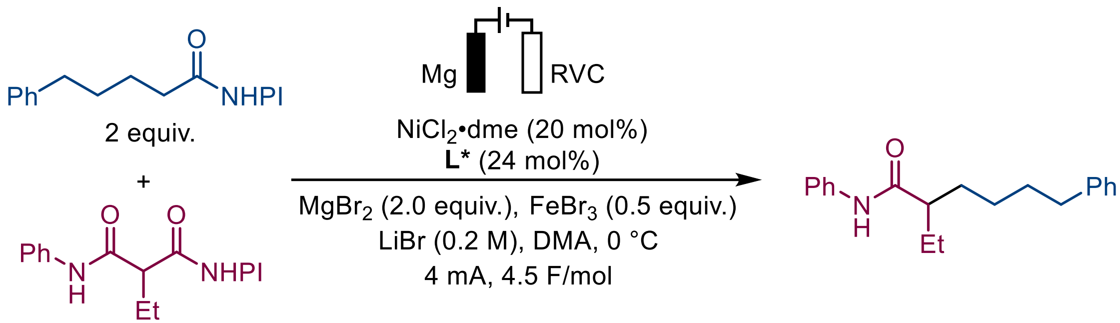
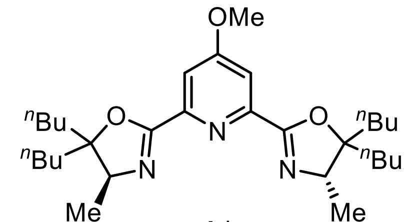
Enantioselective dDCC

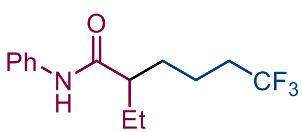




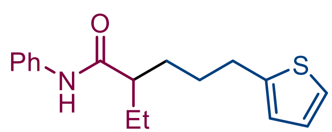
L*

entry	variation from above	yield (%)	ee (%)
1	none	54	90
2	1st generation Ni dDCC	3	16
3	2nd generation Ag/Ni dDCC	15	77

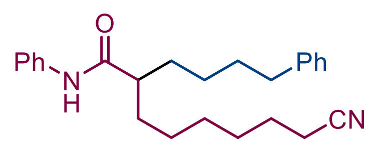
1°–2° coupling



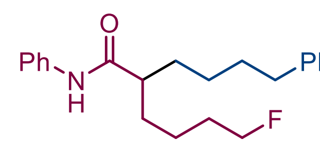
41%, 80% ee



52%, 91% ee

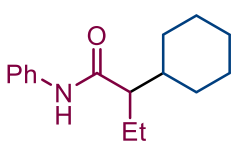


61%, 86% ee

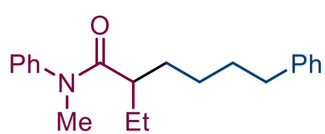


59%, 84% ee

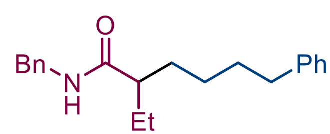
Limitation



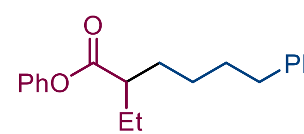
< 5% yield (2°–2° coupling)



< 5% yield (Free N-H required)



< 5% yield (Anilide required)



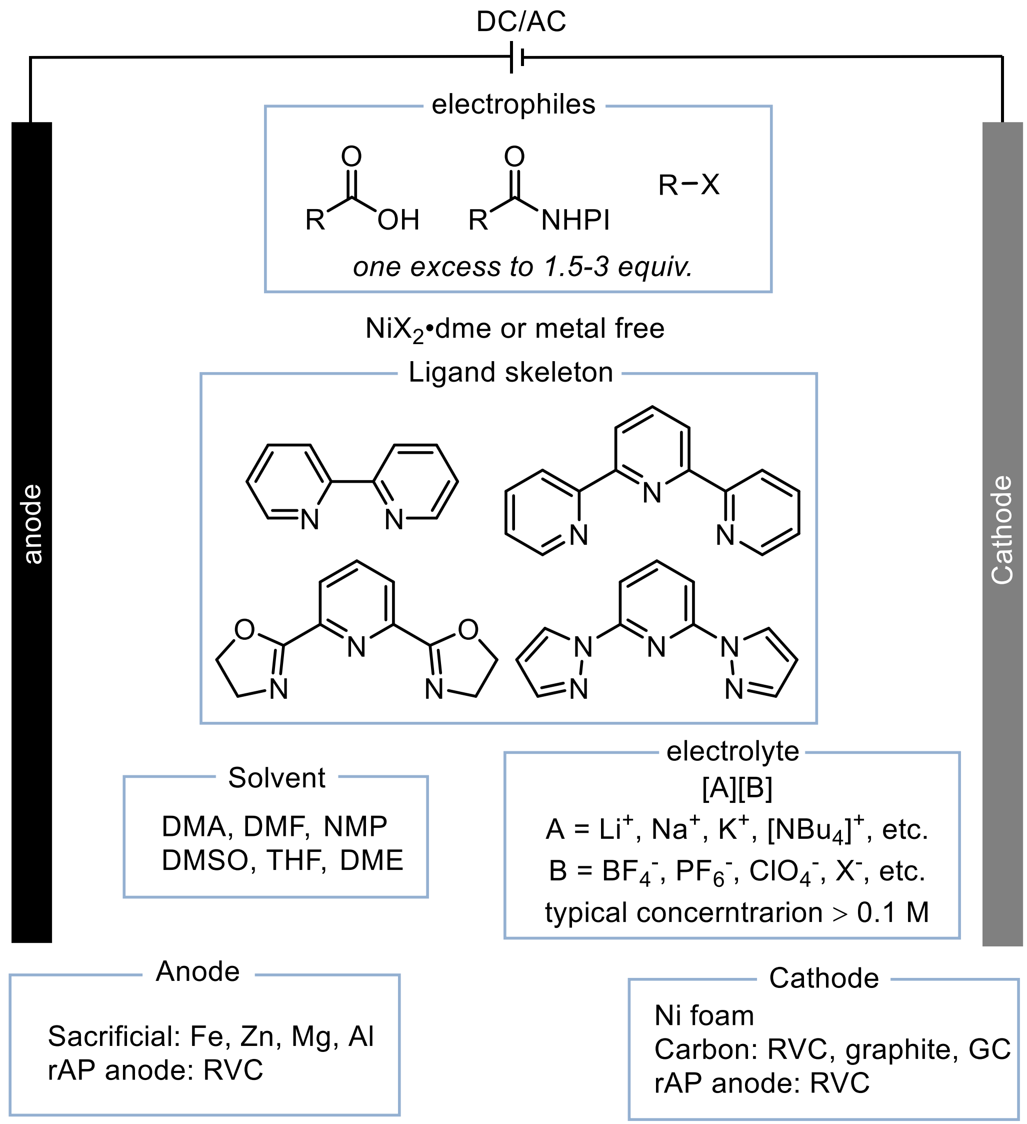
< 5% yield (Esters not competent)

Baran, P. S. et al. *J. Am. Chem. Soc.* **2023**, *145,* 17023.

Outline

- *Introduction*
- *Dehalogenative $C(sp^3)$–$C(sp^3)$ cross-coupling*
- *Decarboxylative $C(sp^3)$–$C(sp^3)$ cross-coupling*
- *Summary and Outlook*

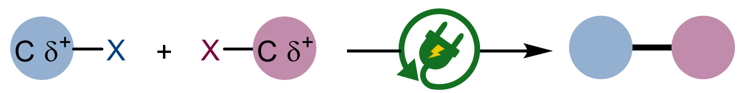
Summary

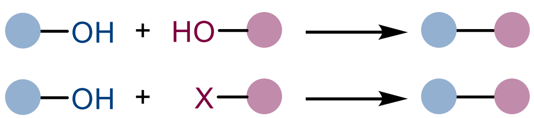


- ☐ Substrate induction
- ☐ Metal/Ligand regulation
- ☐ Potential-driven

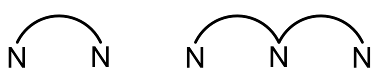
- ☐ Avoid using stoichiometric reductant/R-M
- ☐ Easy to scale-up
- ☐ Improve functional group compatibility

Outlook



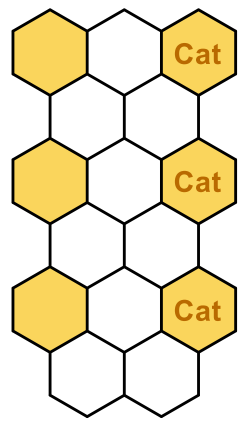


Other transition metal: Fe, Co, Cr etc.



new nitrogen chiral ligands
need to be designed

enrich reactivity
asymmetry electrosynthesis



modified electrode
more stable
recycle

photoelectrocatalysis
lower potential
better FG compatibility

Thanks for your listening