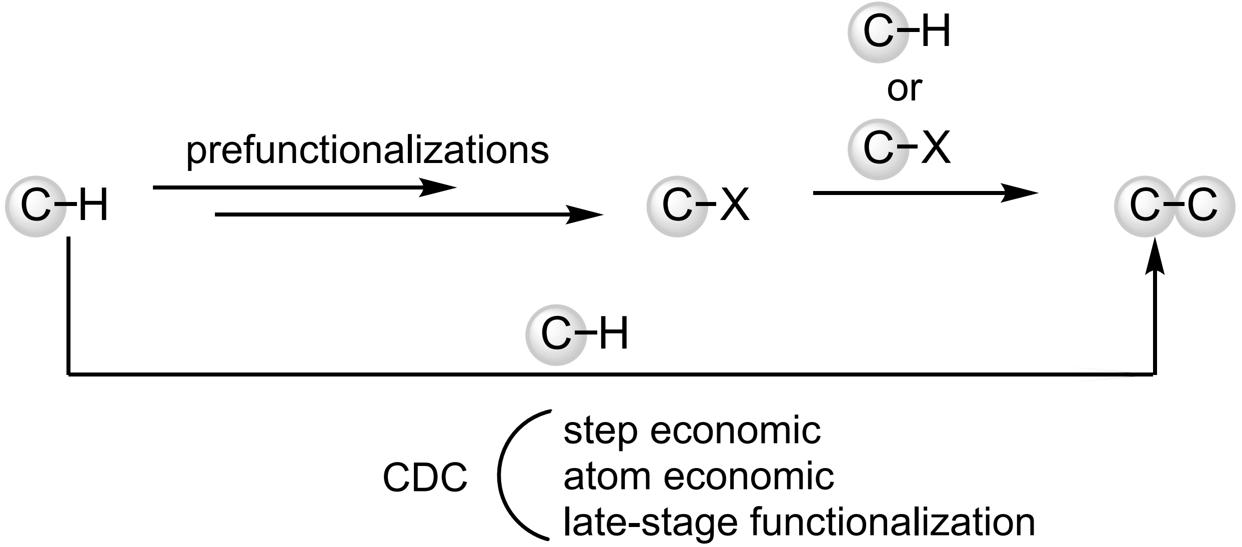
Rhodium-Catalyzed Cross-Dehydrogenative Coupling

Synthesis Club - May 2021

Veronica O'Connor

Cross-Dehydrogenative Coupling (CDC)

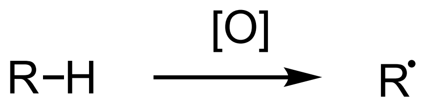
- Forms C-C bonds from C-H bonds.
- Removes need for prefunctionalization.
- Limits number of steps in synthesis.
- Allows for late-stage functionalization
- Green Chemistry
    - Produces H_2 as unharmful by-product.



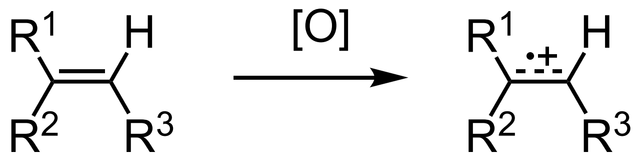
Huang, C. Y.; Kang, H.; Li, J.; Li, C. J. *J. Org. Chem.* **2019**, *84* (20), 12705–12721.

C-H Activation Strategies

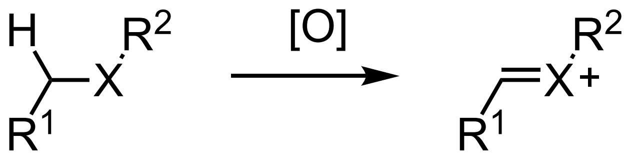
1. hydrogen atom abstraction



4. single-electron alkene/arene oxidation

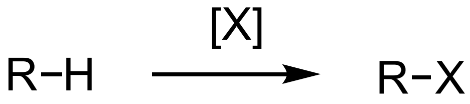


2.α-heteroatom-driven hydride removal

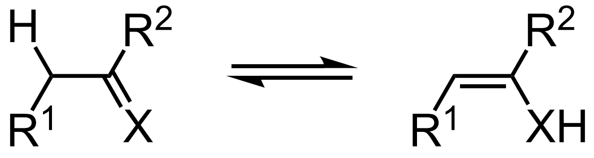


X = NR^3, O, S

5. in situ C-H functionalization

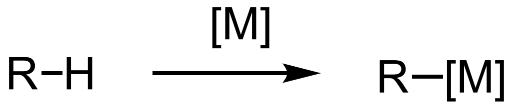


3. tautomerization



X = NR^3, O, S

6. metal-catalyzed C-H activation

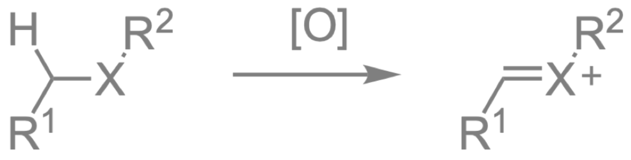


Huang, C. Y.; Kang, H.; Li, J.; Li, C. J. *J. Org. Chem.* **2019**, *84* (20), 12705–12721.

C-H Activation Strategies

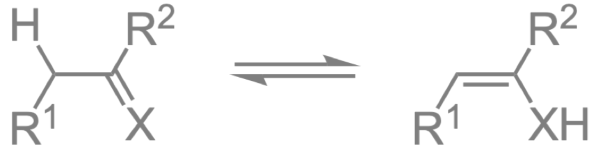
1. hydrogen atom abstraction

2. α-heteroatom-driven hydride removal



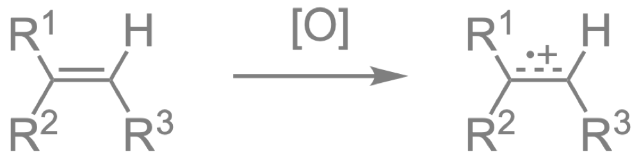
X = NR^3, O, S

3. tautomerization



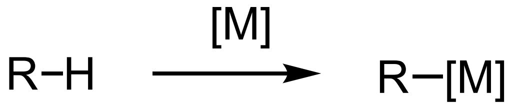
X = NR^3, O, S

4. single-electron alkene/arene oxidation



5. in situ C-H functionalization

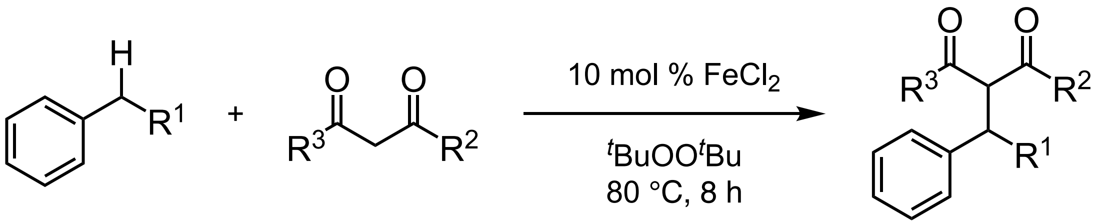
6. metal-catalyzed C-H activation



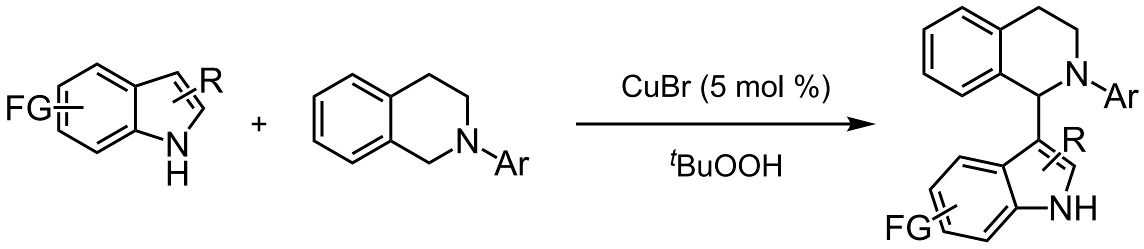
Huang, C. Y.; Kang, H.; Li, J.; Li, C. J. *J. Org. Chem.* **2019**, *84* (20), 12705–12721.

Metal-Catalyzed CDC Select Scope

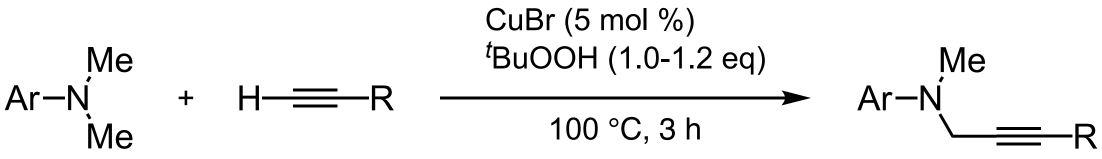
1. sp^3-sp^3



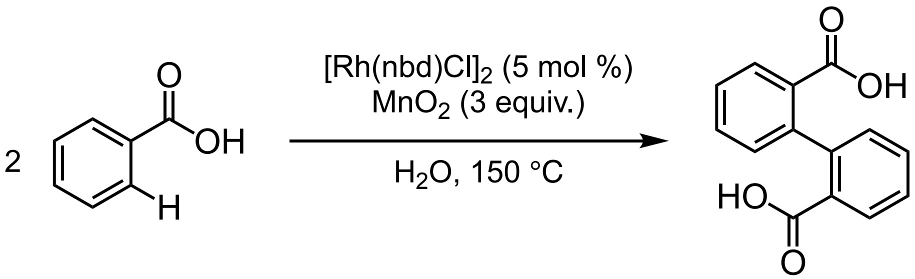
2. sp^3-sp^2



3. sp^3-sp



4. sp^2-sp^2



Li, C.-J. *Acc. Chem. Res.* **2009**, *42* (2), 335–344.
Gong, H.; Zeng, H.; Zhou, F.; Li, C. J. *Angew. Chemie - Int. Ed.* **2015**, *54* (19), 5718–5721.

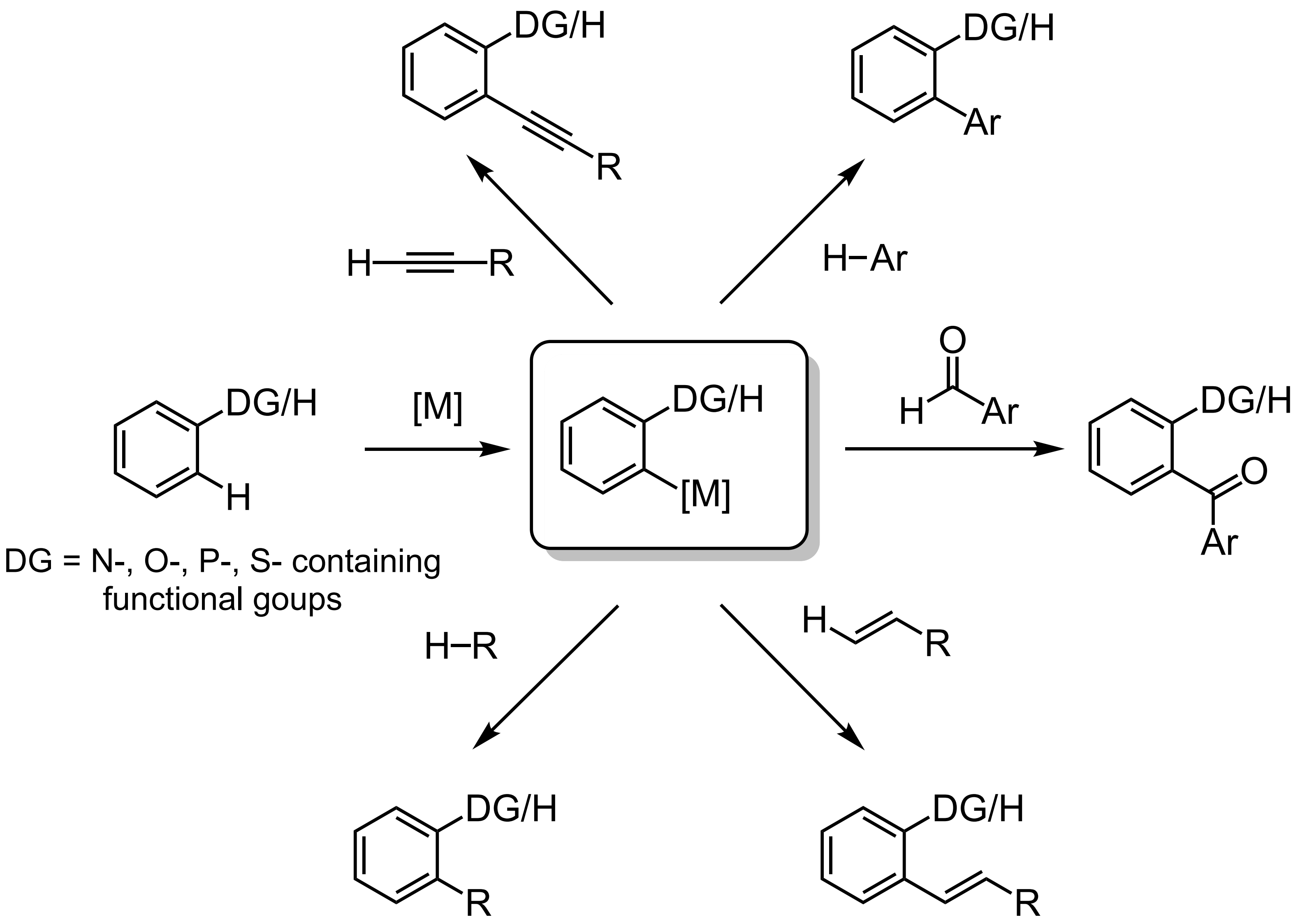
Challenges and Selectivity

Challenge: *How can we be selective with C-H Activation?*

Using directing groups!

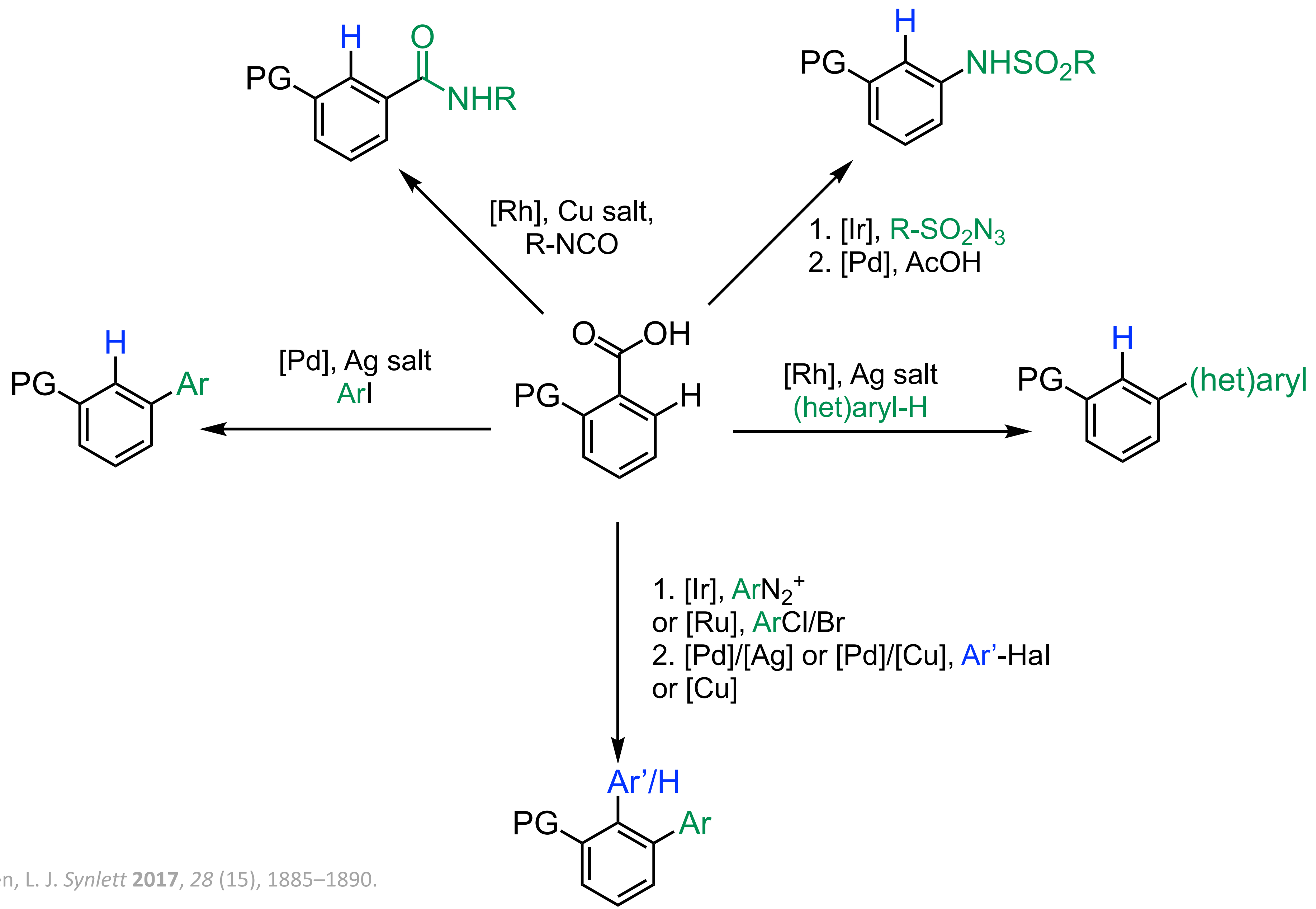
- Alcohol, ketones, and carboxylic acids, while more easily removable, are less coordinating than N, P, and S containing functional groups.

Directed Aryl C-H Activation



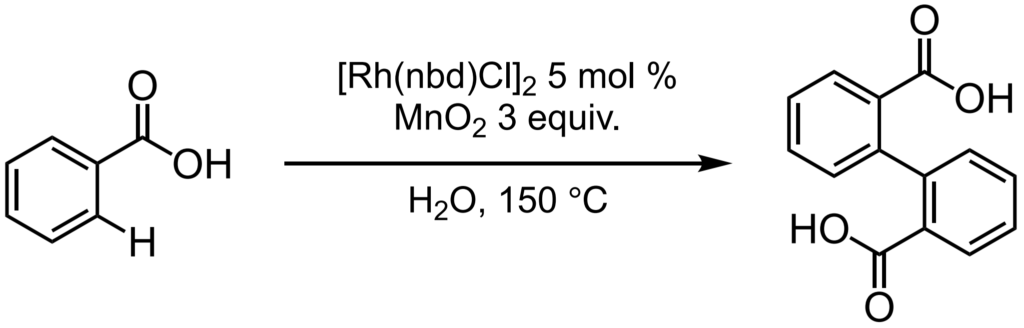
Huang, C. Y.; Kang, H.; Li, J.; Li, C. J. *J. Org. Chem.* **2019**, *84* (20), 12705–12721.

Carboxylic Acid Directing Groups



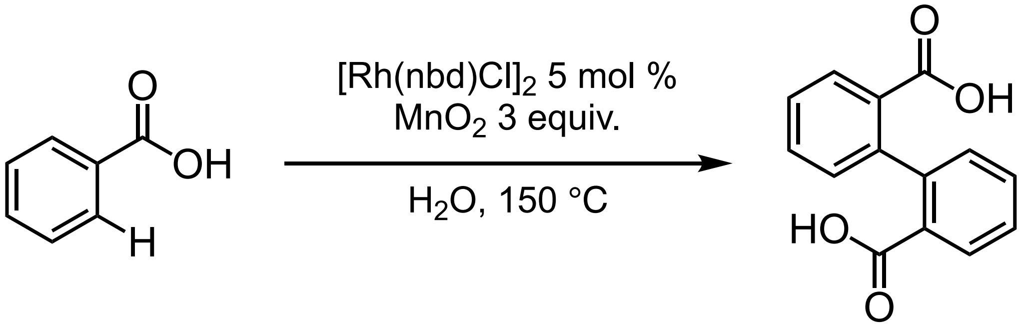
Biafora, A.; Gooßen, L. J. *Synlett* **2017**, *28* (15), 1885–1890.

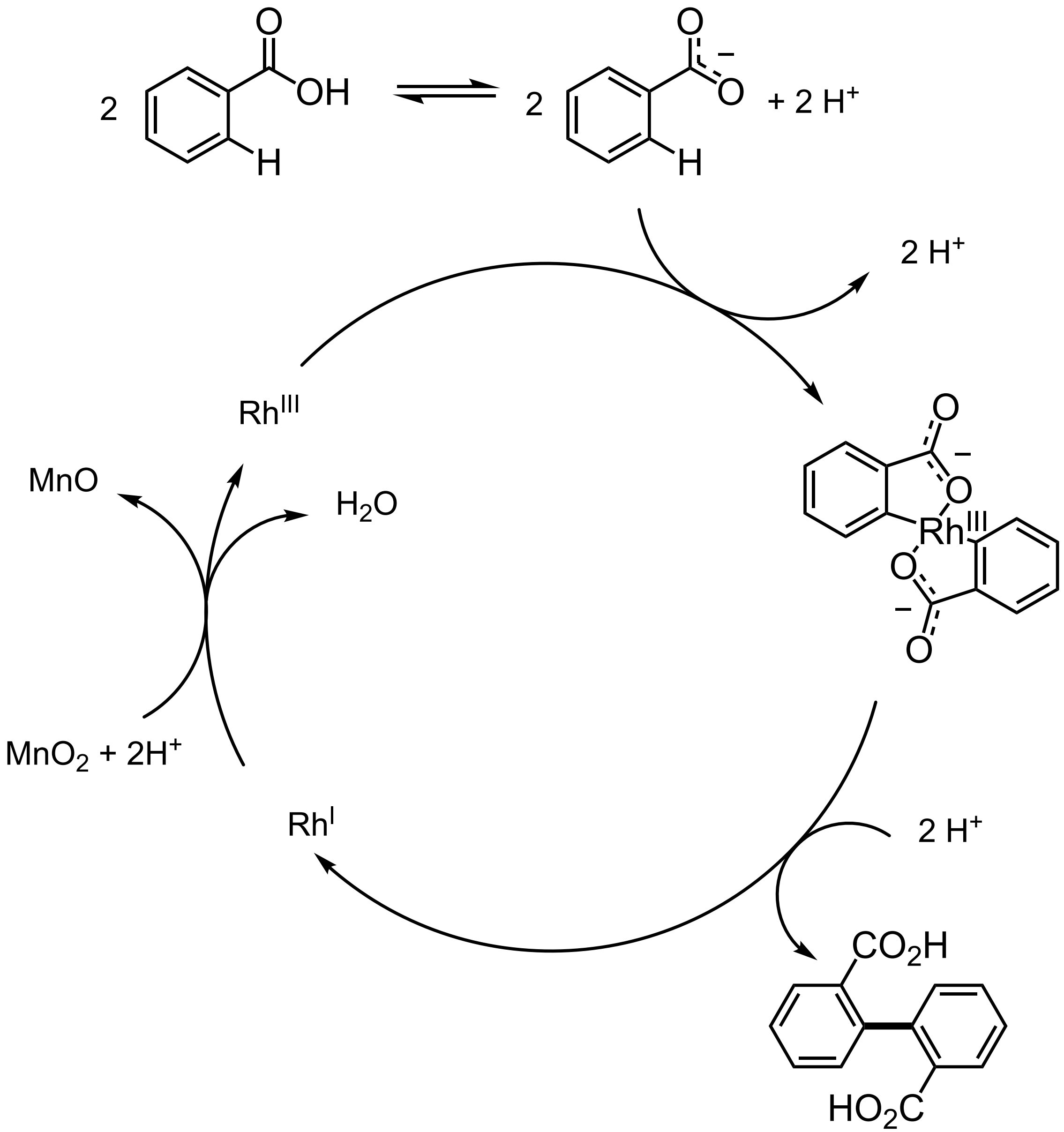
CDC Literature Example



Gong, H.; Zeng, H.; Zhou, F.; Li, C. J. *Angew. Chemie - Int. Ed.* **2015**, *54* (19), 5718–5721.

CDC Literature Example





Gong, H.; Zeng, H.; Zhou, F.; Li, C. J. *Angew. Chemie - Int. Ed.* **2015**, *54* (19), 5718–5721.

Why use Electrochemistry?

- Metal oxides are unwanted waste produced in traditional CDC reactions.
- Limited regioselectivity when relying on electronics or steric factors alone.

Solution: *Use electric current as an inexpensive and waste free oxidant!*

Combining CDC and Electrochemistry

ACS Catalysis

pubs.acs.org/acscatalysis Letter

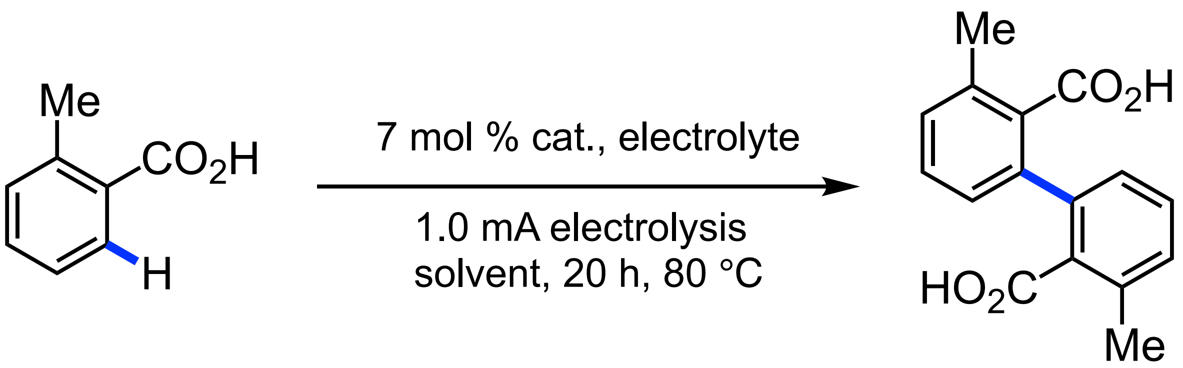
2,2′-Biaryldicarboxylate Synthesis via Electrocatalytic Dehydrogenative C–H/C–H Coupling of Benzoic Acids

Zhongyi Zeng, Jonas F. Goebel, Xianming Liu, and Lukas J. Gooßen*

Cite This: *ACS Catal.* 2021, 11, 6626–6632 Read Online

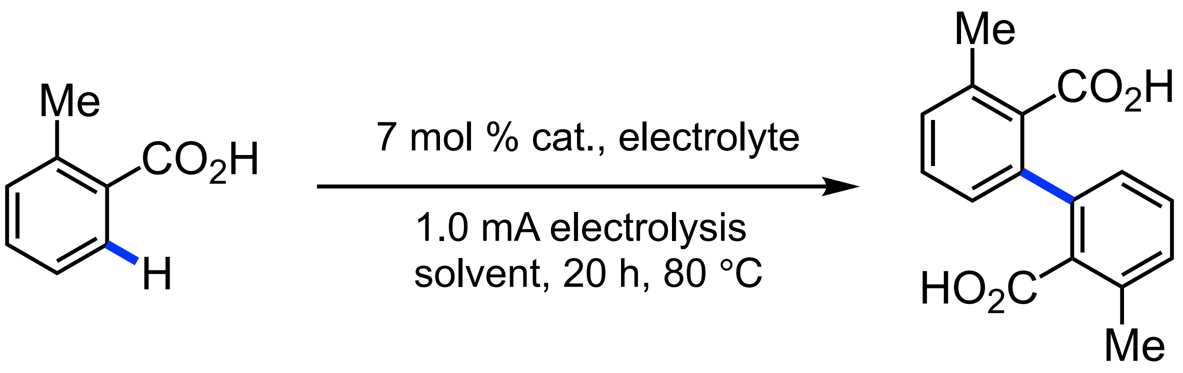
Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

Combining CDC and Electrochemistry



Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

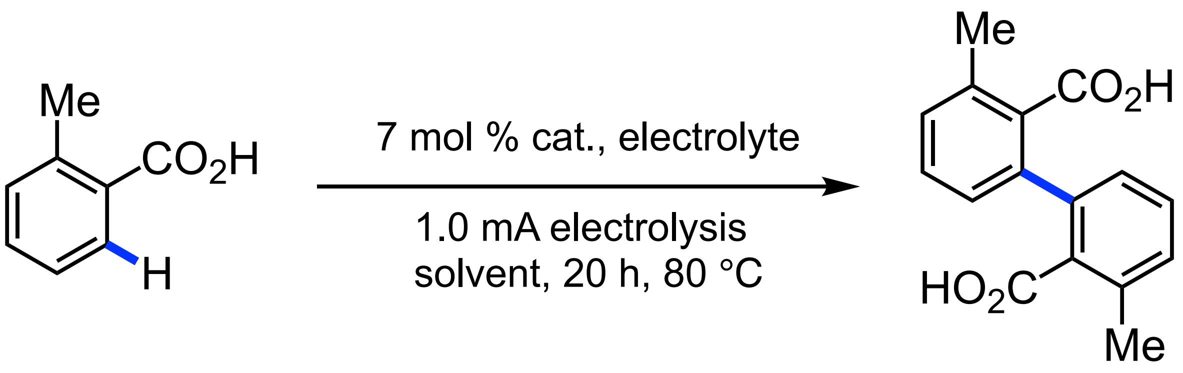
Combining CDC and Electrochemistry



no.	catalyst	solvent	electrode	conv. (%)	**2a** (%)
1	$[Cp^*IrCl_2]_2$	DMF	Pt(+)‖Pt(−)	46	<5
2	$Pd(OAc)_2$	DMF	Pt(+)‖Pt(−)	35	<5
3	$[RuCl_2(p\text{-cym})]_2$	DMF	Pt(+)‖Pt(−)	60	39
4	$[Rh(cod)Cl]_2$	DMF	Pt(+)‖Pt(−)	>95	81
5	$Rh_2(OAc)_4$	DMF	Pt(+)‖Pt(−)	83	71
6	$Rh(OAc)_3$	DMF	Pt(+)‖Pt(−)	75	69
7	$[Cp^*RhCl_2]_2$	DMF	Pt(+)‖Pt(−)	>95	71
8	$\mathbf{RhCl_3 \cdot 3H_2O}$	**DMF**	**Pt(+)‖Pt(−)**	**>95**	87 (77)
9	$RhCl_3 \cdot 3H_2O$	DMF	Ni(+)‖Pt(−)	70	6
10	$RhCl_3 \cdot 3H_2O$	DMF	graphite(+)‖Pt(−)	>95	26
11	$RhCl_3 \cdot 3H_2O$	DMF	RVC(+)‖Pt(−)	49	38
12	$RhCl_3 \cdot 3H_2O$	DMF	Pt(+)‖steel(−)	>95	78
13	$RhCl_3 \cdot 3H_2O$	DMAc	Pt(+)‖Pt(−)	77	72
14	$RhCl_3 \cdot 3H_2O$	DMSO	Pt(+)‖Pt(−)	33	18
15	$RhCl_3 \cdot 3H_2O$	^{n}BuOH	Pt(+)‖Pt(−)	42	24

Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

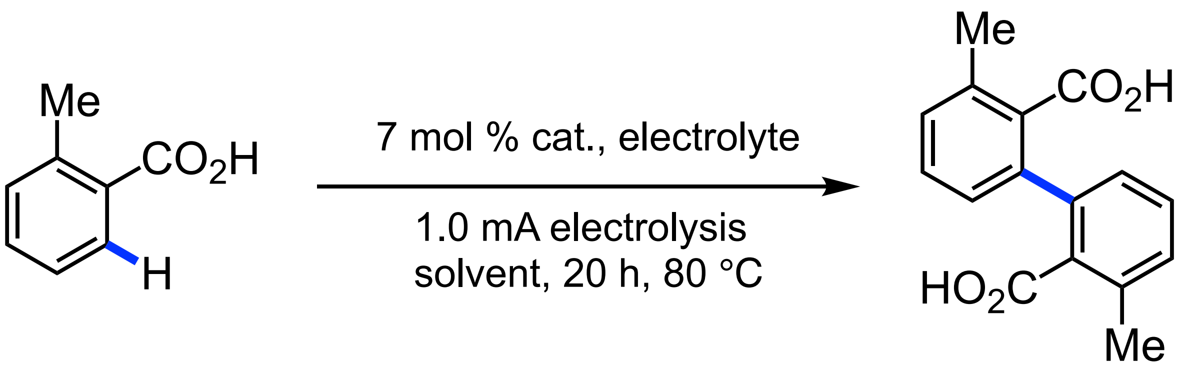
Combining CDC and Electrochemistry



further variation from optimal condition (entry 8)			
16	3 mol % $RhCl_3{\cdot}3H_2O$	91	74
17	$^nBu_4NPF_6$ instead of $^nBu_4NOAc$	9	trace
18	KOAc instead of $^nBu_4NOAc$	>95	86
19	electrolysis at 3.0 mA	>95	78
20	electrolysis at 0.5 mA	>95	86
21	run at 60 °C	89	66
22	no electricity	18	<5
23	no $RhCl_3{\cdot}3H_2O$	<5	trace
24	O_2 (balloon) instead of electricity	36	15
25	$NaClO_2$ (2 equiv) instead of electricity	42	19
26	Ag_2CO_3 (2 equiv) instead of electricity	>95	65
27	MnO_2 (2 equiv) instead of electricity	>95	60
28	CuO (2 equiv) instead of electricity	53	39

Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

Notable Reaction Conditions



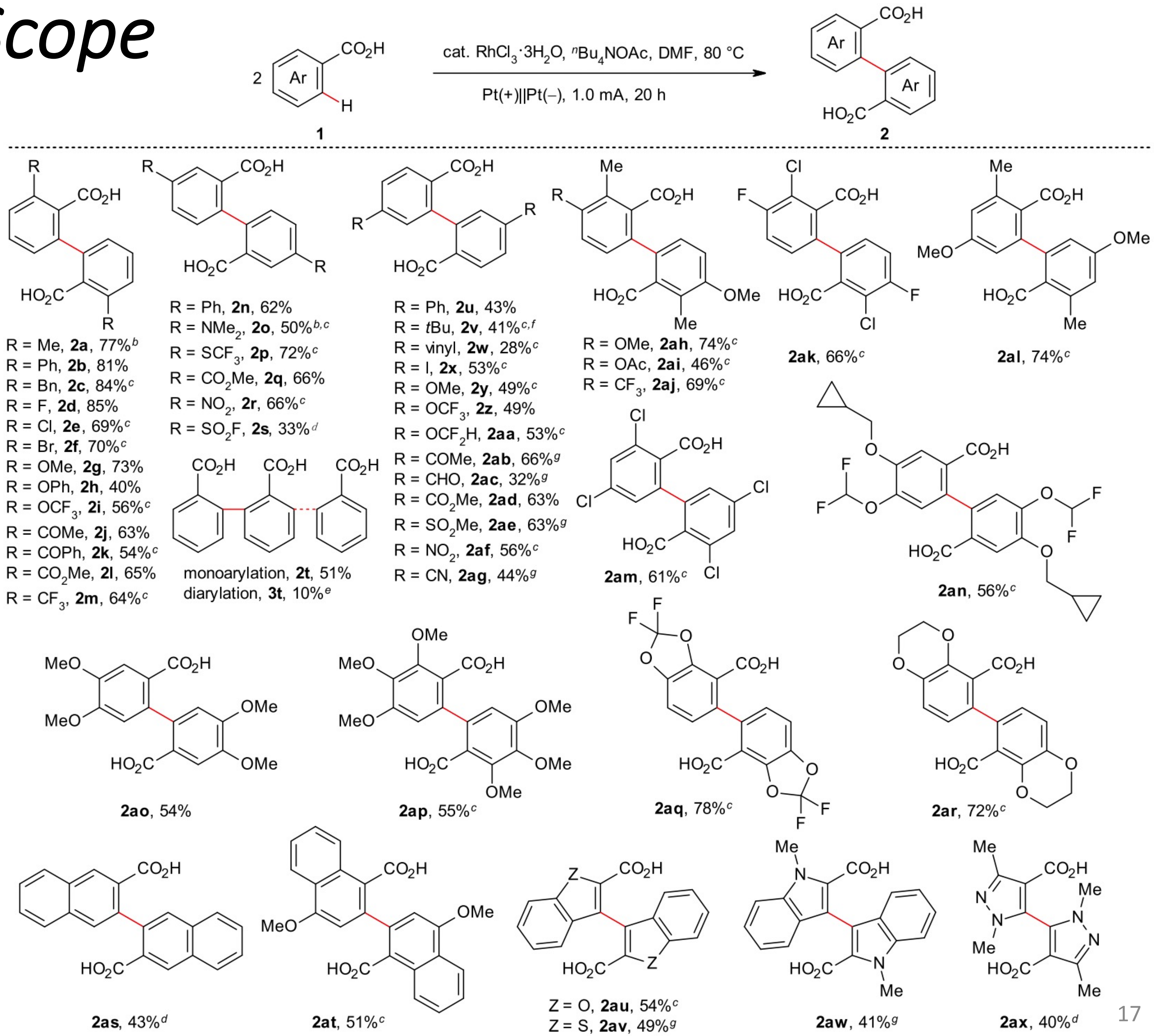
No.	Catalyst	Solvent	Electrode	Conv. (%)
8	$Rh^{III}Cl_3 \bullet 3H_2O$	DMF	Pt(+)||Pt(-)	>95

No.	Variation from No. 8	Conv. (%)
26	Ag_2CO_3 (rather than current)	>95
27	MnO_2 (rather than current)	>95

Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

Homocoupling Scope

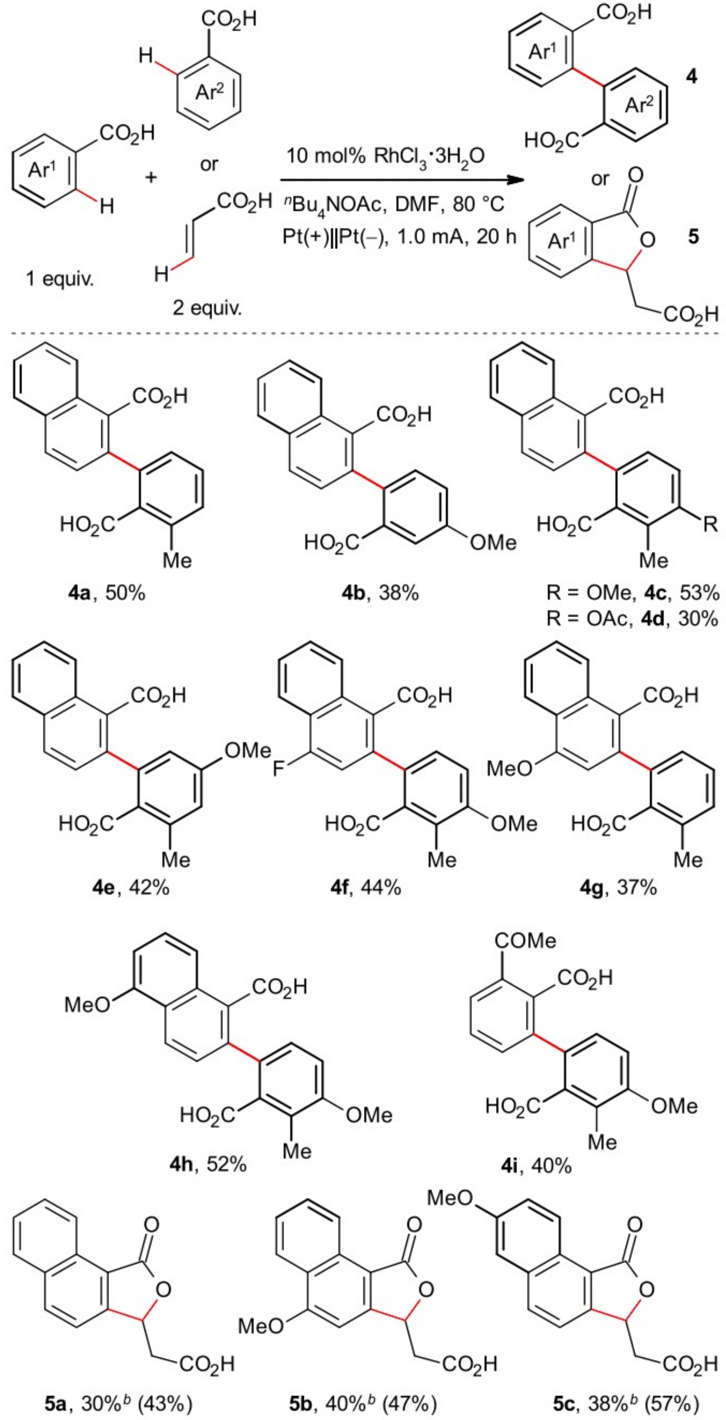
- Tolerates EWGs and EDGs.
- Tolerates ortho, meta, and para position substituents.



Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

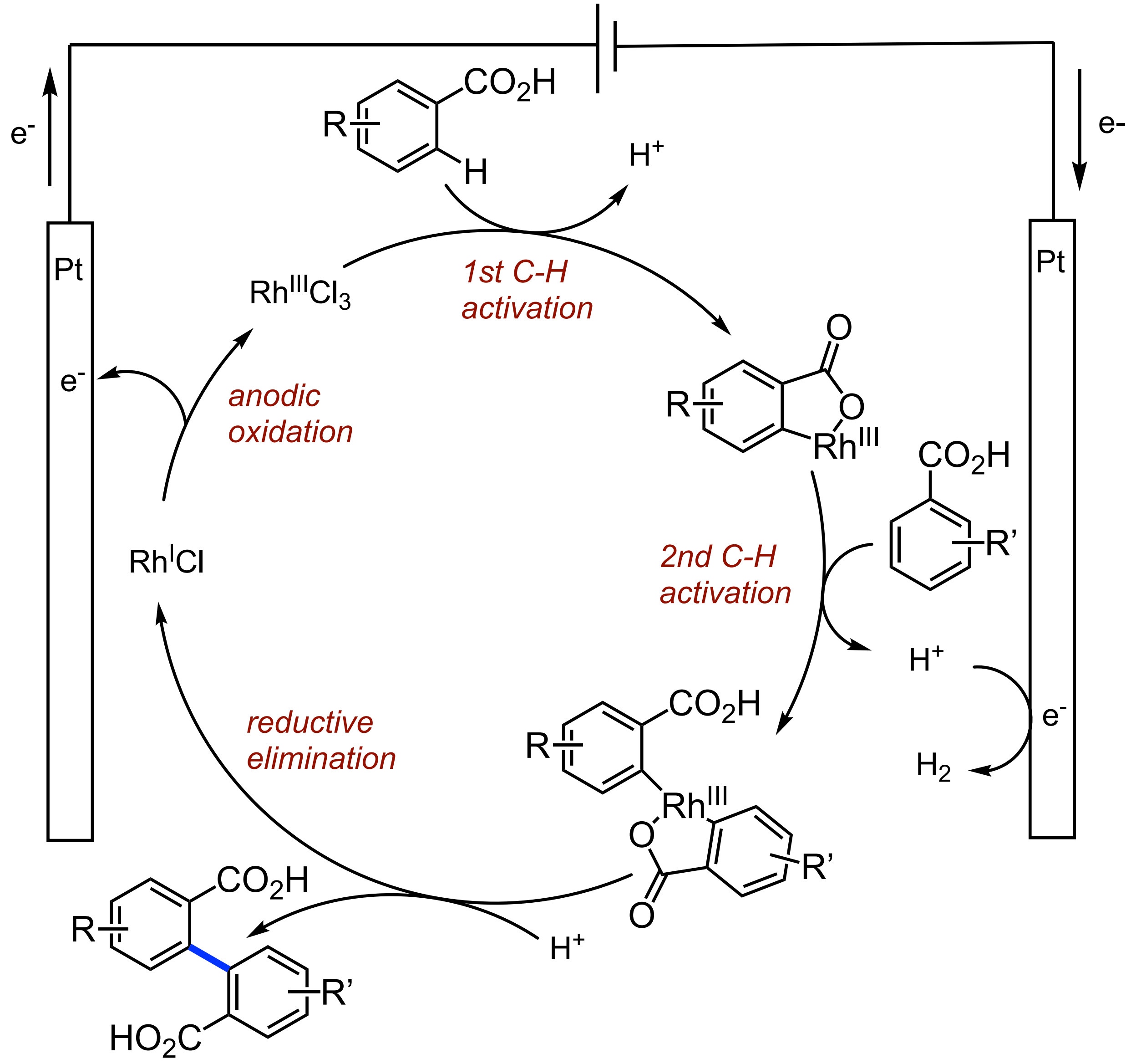
Expanded CDC Scope

- Experiences success with heterocoupling as well.
- Aryl rings are not required for CDC.



Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

Electrochemical Catalyst Cycle



Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).

General Electrochemical Setup

Figure S2. Detailed parts of cap.

Figure S3. Detailed view of cap.

Figure S4. Assembled cap.

Figure S5. undivide cell.

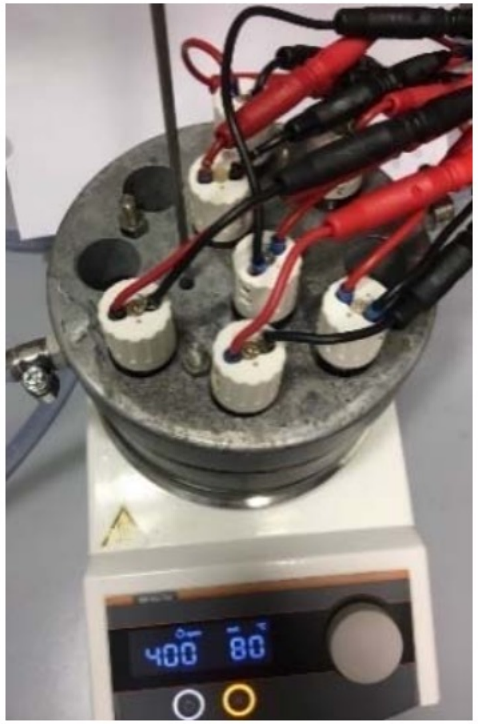


Figure S6. Running electrolytic reactions.

Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Cata.* **2021**, *19* (32).