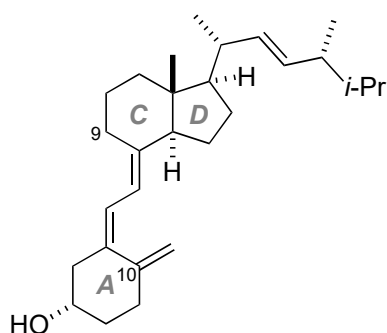


Problem Session (4) -Answer-

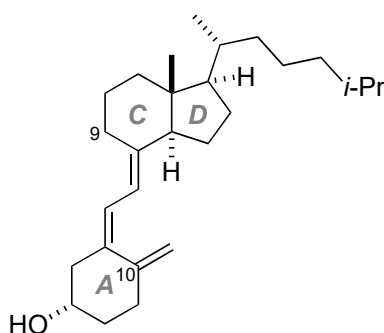
2024/01/20 Wataru Shigematsu

Topic: Total synthesis of (+)-calcipotriol and vitamin D analogs using electrochemical couplings

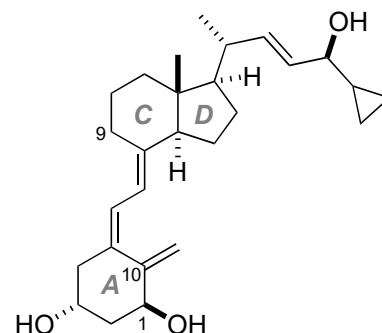
Introduction: Vitamin D analogs and (+)-calcipotriol



Vitamin D₂ (1)



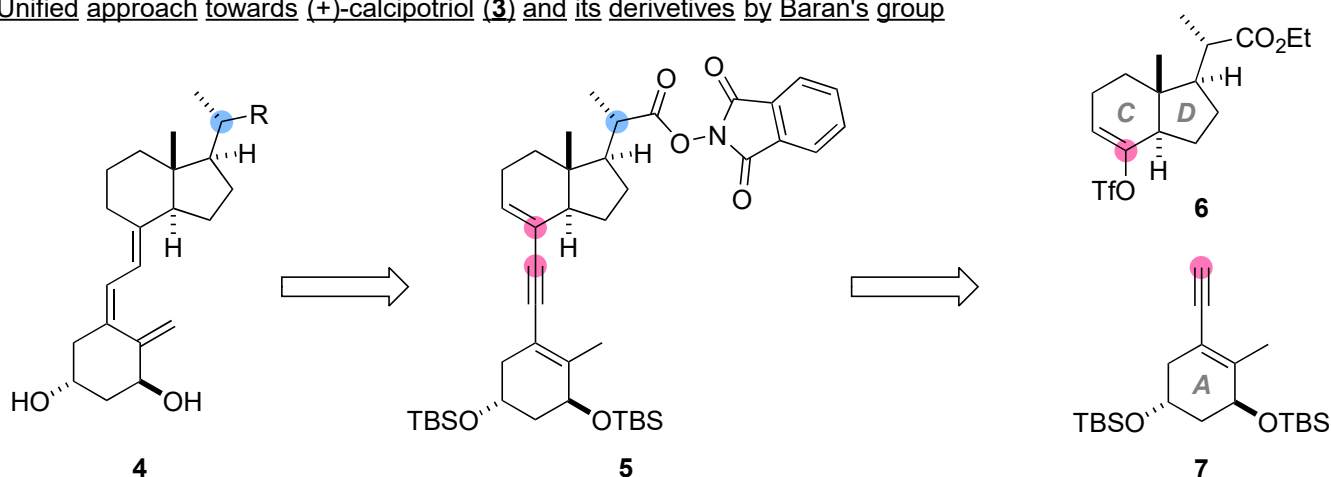
Vitamin D₃ (2)



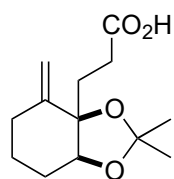
(+)-calcipotriol (3)

(+)-calcipotriol (3) : the drug of the treatment of psoriasis ^{ref 1)}

Unified approach towards (+)-calcipotriol (3) and its derivatives by Baran's group



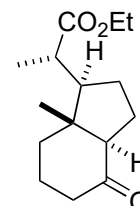
Please provide the reaction mechanisms.



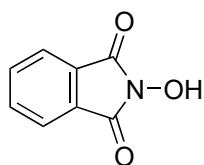
1-1

1. NHPI (1.25 equiv), DIC (1.1 equiv), THF, rt;
NiCl₂·6H₂O (10 mol%), 2,2'-bpy (10 mol%)
NaI (30 mol%), AgNO₃ (30 mol%),
1-3 (1.2 equiv), DMF, rt,
(+)Mg/(-)RVC, 120 mA, 3.3 F/mol, 63%

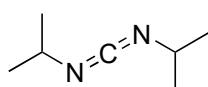
2. Fe(dpm)₃ (34 mol%), PhSiH₂(*Oi*-Pr) (3 equiv)
ClCH₂CH₂Cl, HOCH₂CH₂OH, 0 °C, 47%
3. AcOH/THF/H₂O (4:1:1, 65 mM), 40 °C
4. PPh₃ (2.5 equiv), C₂Cl₆ (2.5 equiv),
i-Pr₂NEt (5 equiv), MeCN, 0 °C to reflux,
44% (2 steps)



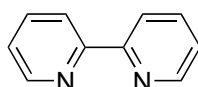
1-2



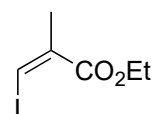
NHPI



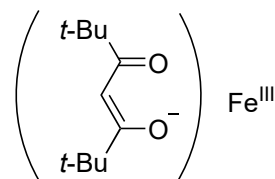
DIC



2,2'-bpy



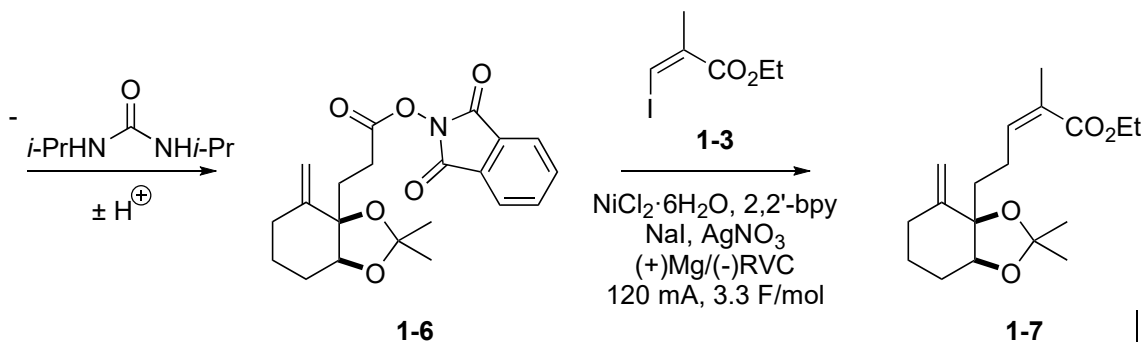
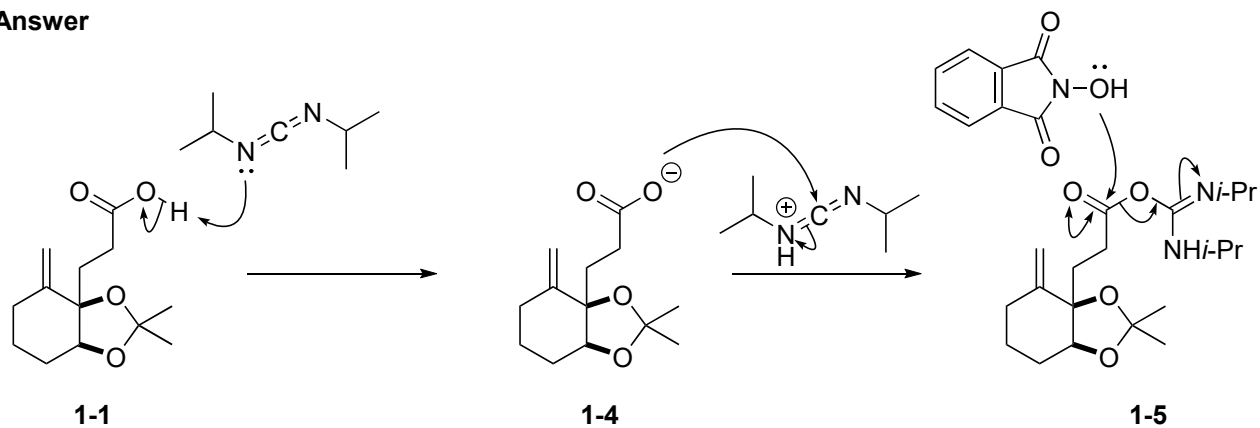
1-3



Fe(dpm)₃

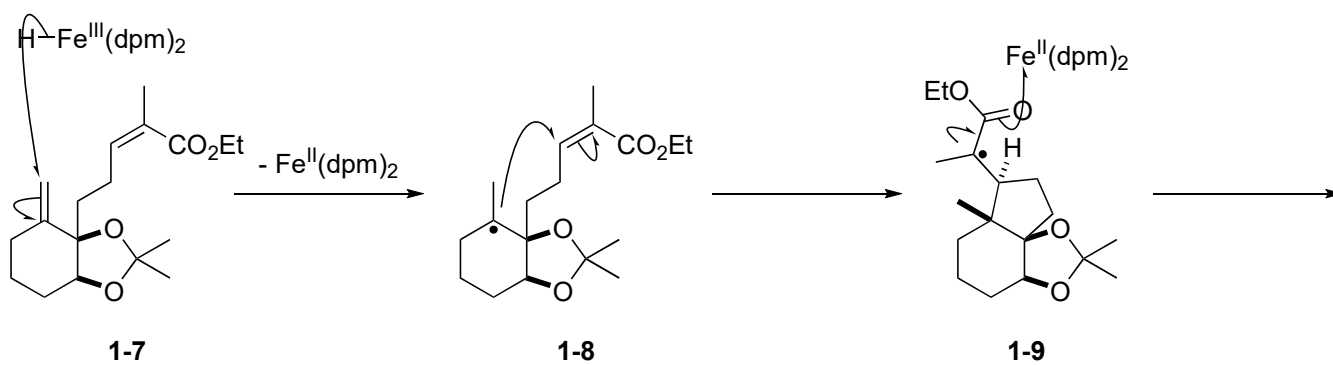
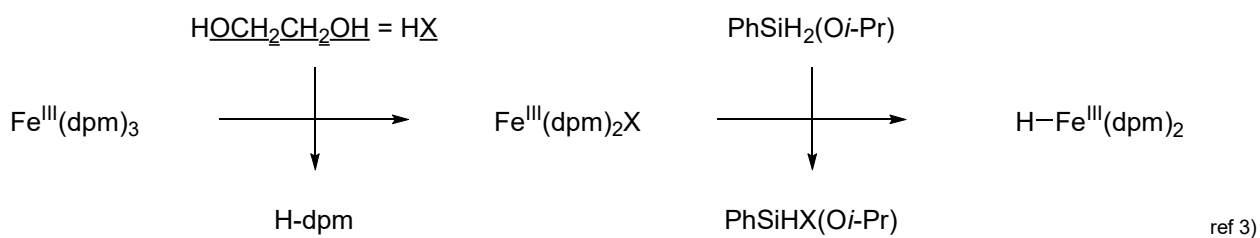
Gu, J.; Rodriguez, K. X.; Kanda, Y.; Yang, S.; Ociepa, M.; Wilke, H.; Abrishami, A. V.; Jørgensen, L.; Skak-Nielsen, T.; Chen, J. S.; Baran, P. S. *Proc. Nat. Acad. Sci.* **2022**, *119*, e22008141.

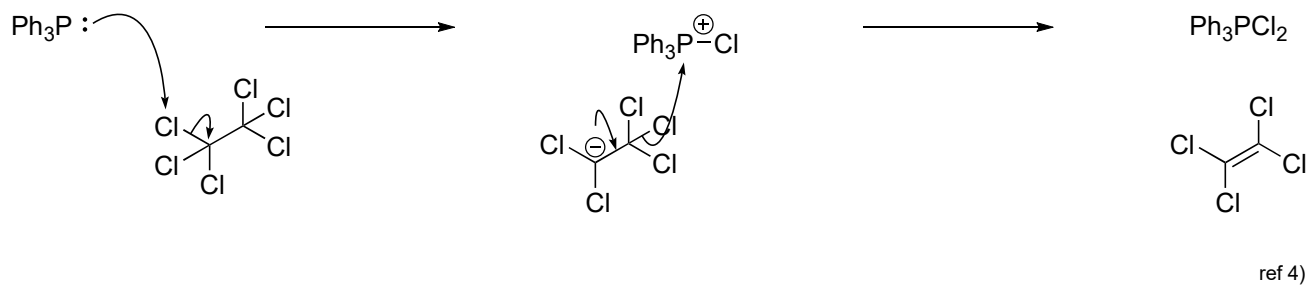
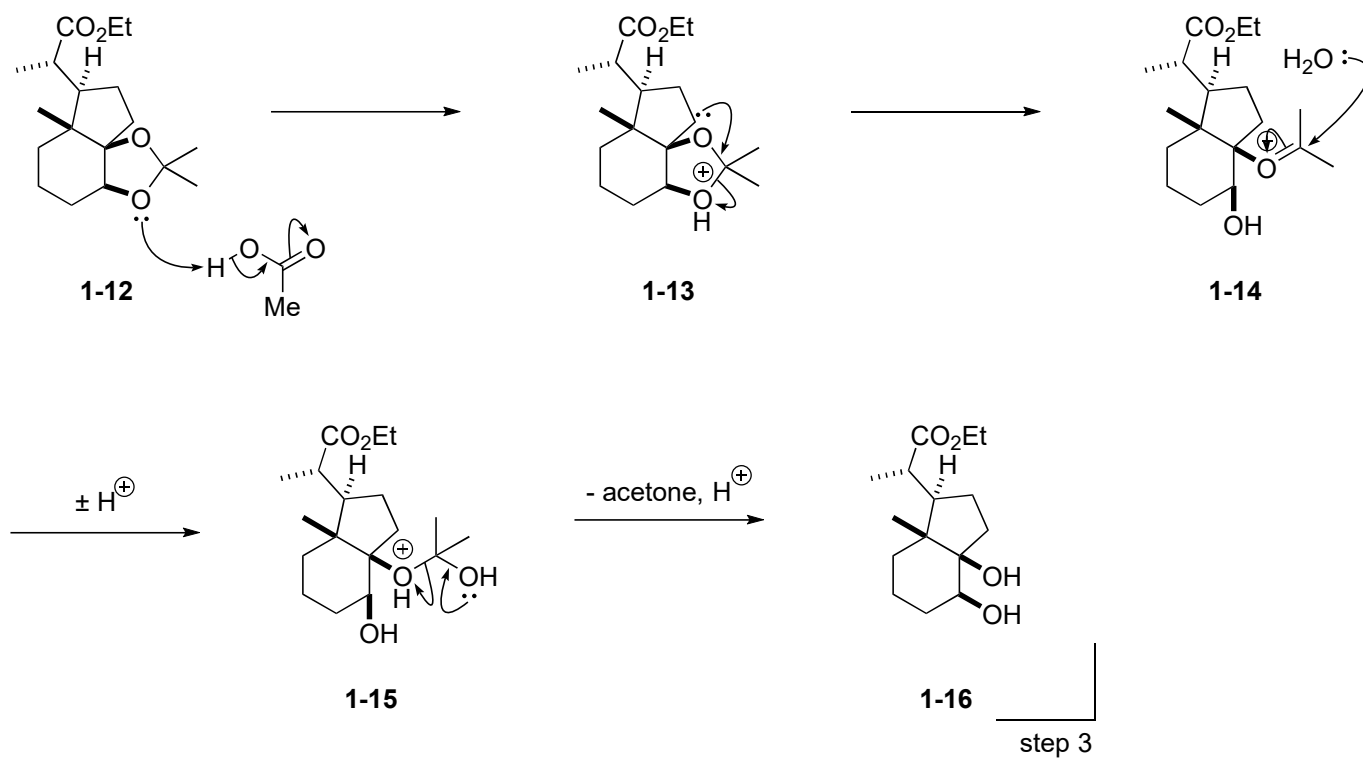
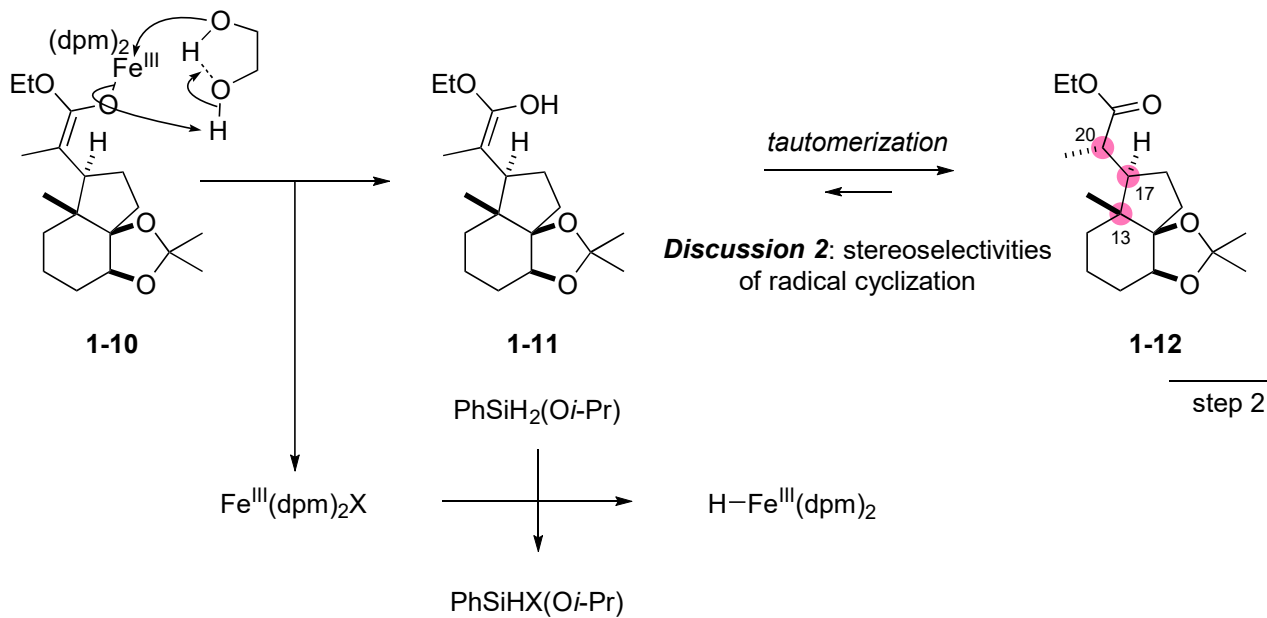
Answer

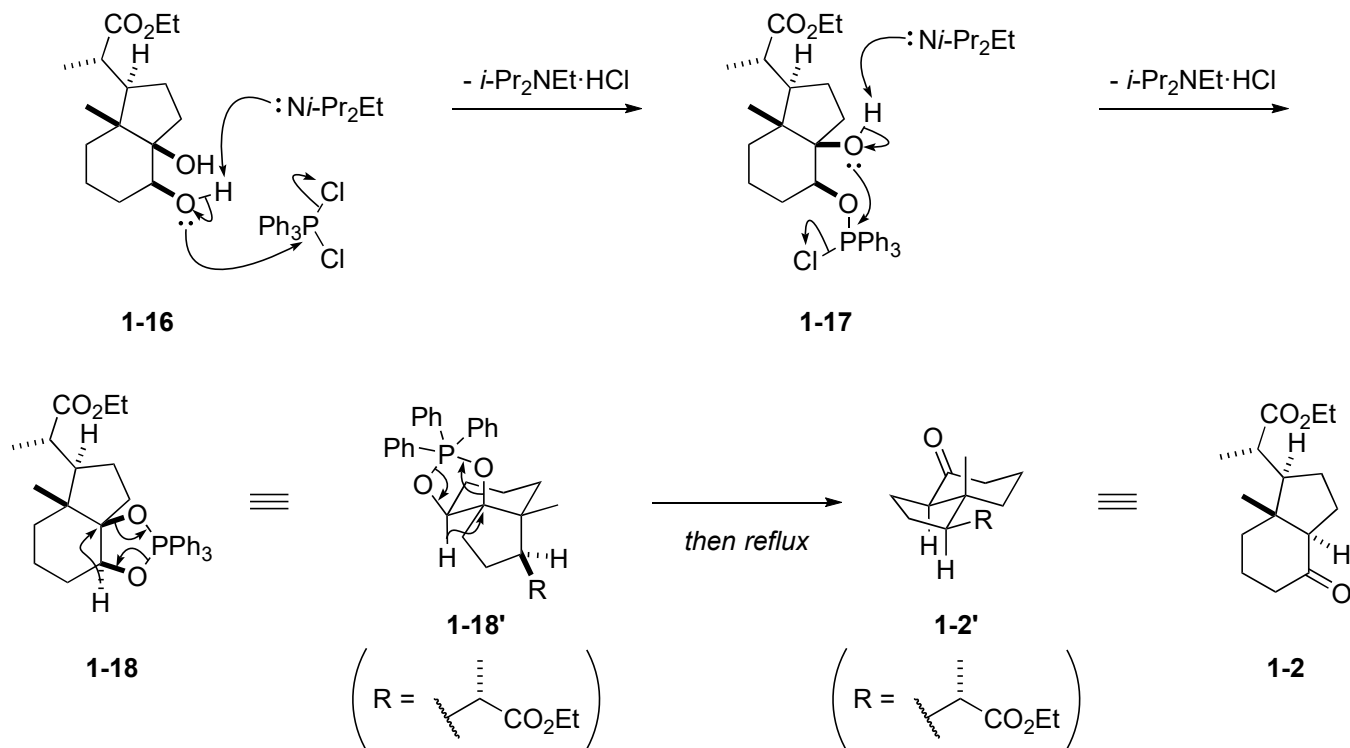


Discussion 1: electrochemical reductive cross-coupling ^{ref 2)}

step 1







Discussion 1: Electrochemical reductive cross-coupling ^{ref 2)}

1. The roles of the reagents

1-1. Experiments for original coupling ^{ref 2)}

1-1-1. Experiments for original coupling without LiCl

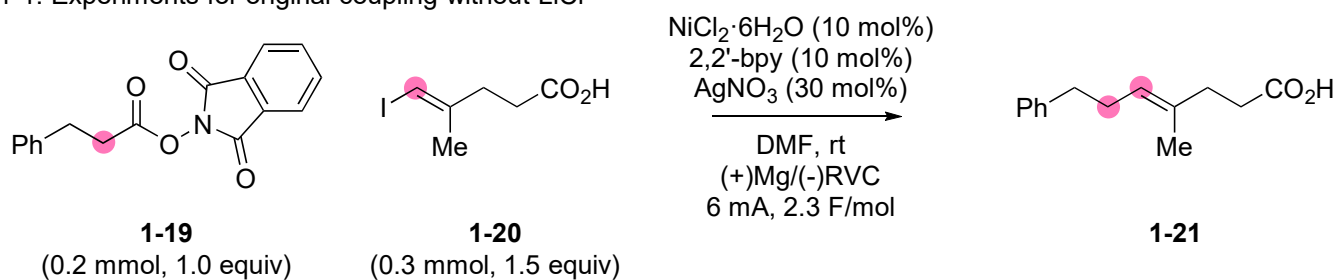


Table 1

entry	deviation from above	NMR yield of 1-21
1	none	52%
2	no NiCl ₂ ·6H ₂ O ^{a)}	0%
3	no 2,2'-bpy	0%
4	Ni(NO ₃) ₂ ·6H ₂ O instead of NiCl ₂ ·6H ₂ O	9%
5	Ni(NO ₃) ₂ ·6H ₂ O instead of NiCl ₂ ·6H ₂ O + LiCl (30 mol%)	40%
6	no AgNO ₃	20%
7	Ag(OCOCF ₃) instead of AgNO ₃	36%
8	CuCl ₂ instead of AgNO ₃	14%
9	NiCl ₂ ·6H ₂ O (20 mol%) 2,2'-bpy (20 mol%) no AgNO ₃	33%

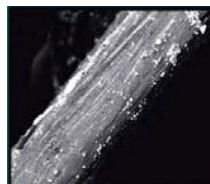
a) LiCl (30 mol%) was used as electrolyte.

In standard condition, cross-coupling proceeded in moderate yield (entry 1). Ni^{II}, ligand, and halide donor were necessary for this reaction (entries 2~5). Addition of Ag^I played an important role in this reaction. Cu^{II} instead of Ag^I wasn't effective in this reaction (entries 6~8).

In entry 1, in-situ deposition of Ag⁰-nanoparticles were observed on cathode (see below).



during the reaction



after the reaction

The cathode potential of the reaction in the presence of AgNO₃ was 510 mV more positive than the reaction without AgNO₃, which might prevent overreduction of nickel (Ni^{II} → Ni⁰, Ni^{III} → Ni^I) and the passivation of the cathode. In fact, without AgNO₃, the yield got better with doubled catalyst loading (entries 6 and 9).

1-1-2. Addition of LiCl as the electrolyte

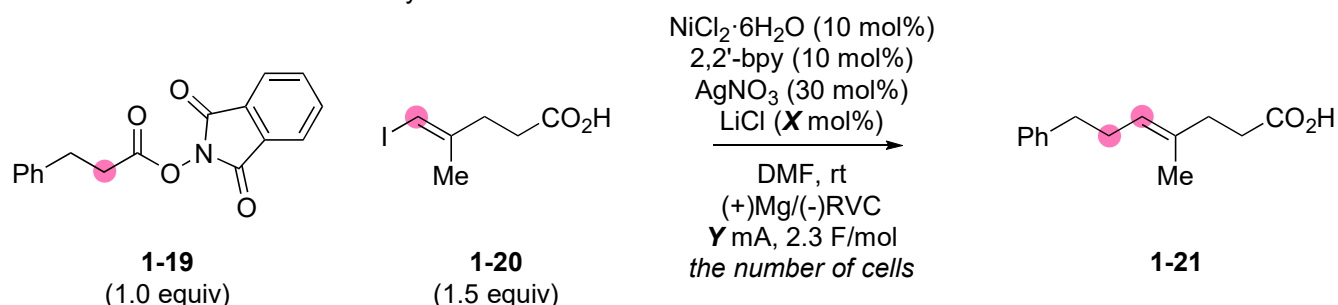


Table 2 (without LiCl)

entry	1-19	Y	<i>the number of cells (in series)</i>
1	0.2 mmol	6.0	1
2	3.3 mmol	100	1
3	20 mmol	100	6

Table 3 ^{a)}

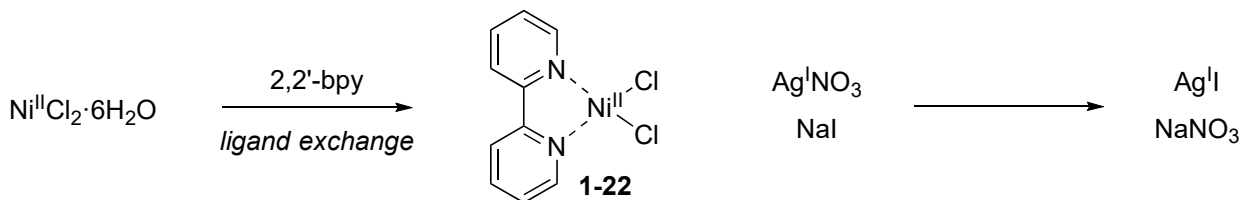
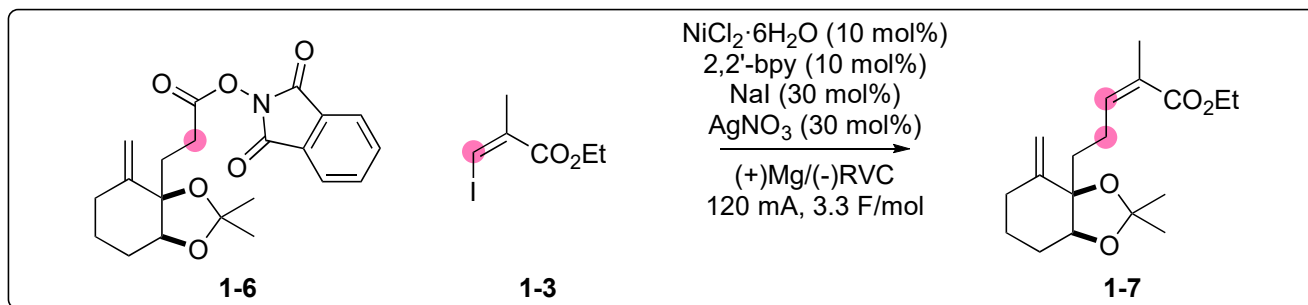
entry	X	yield
1	0	45%
2	30	45%

a) 0.2 mmol of **1-19** was used. The reactions were conducted in one cell. AgNO₃ (50 mol%), 6 mA, 2.5 F/mol

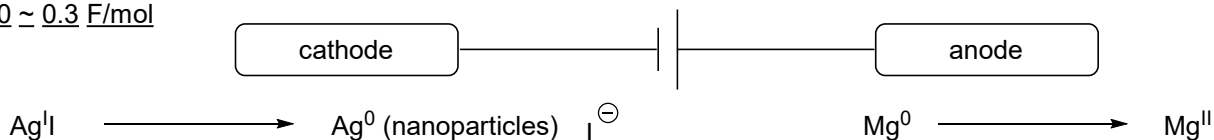
The electrochemical reactor (ElectraSyn 2.0) is factory limited at 100 mA and 30 V. As reaction scale increases, so too should current in the reaction. This means that there is an upper bound on the scale (Table 2, entry 2). This problem can be solved by using the "carousel" electrochemical reactor which allows current delivery, in series, for up to 6 cells (Table 2, entry 3).

However, in series, each vial can only have a 5 V potential on average to stay below the total 30 V limit of the reactor. To accomplish this, LiCl (0.3 equiv.) was added as a supporting electrolyte to lower the resistance of each cell to lower the required potential to below the 30 V limit. LiCl has no effect on the reaction (Table 3). NaI must have been used as the electrolyte instead of LiCl.

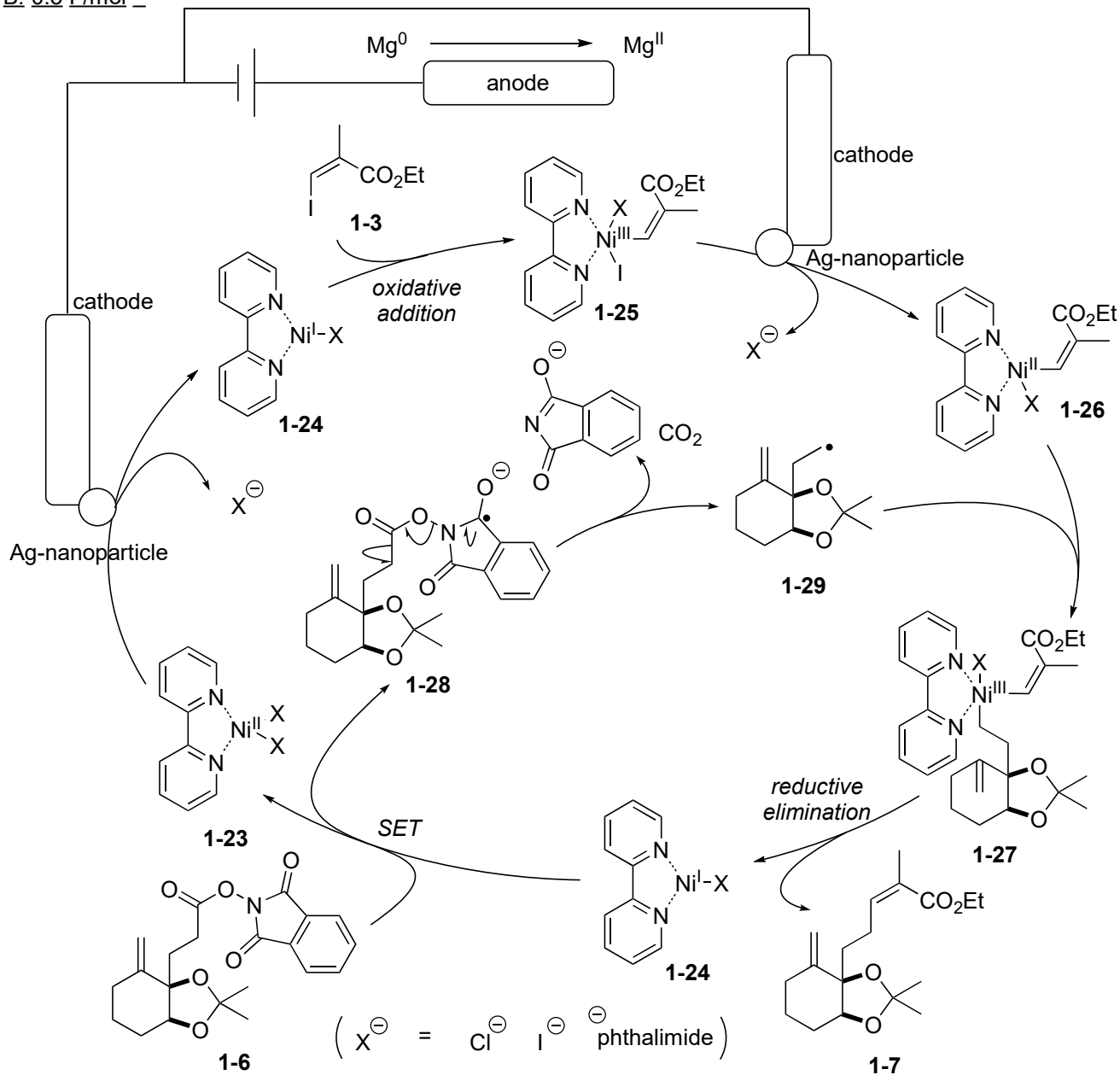
1-2. Reaction mechanism



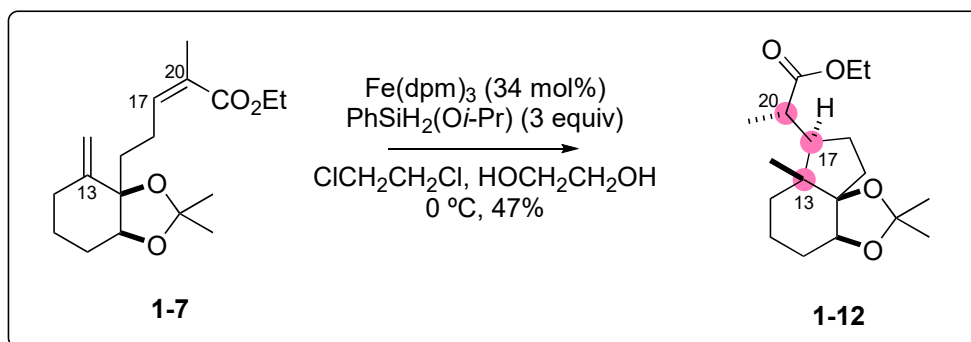
A. $0 \approx 0.3 \text{ F/mol}$



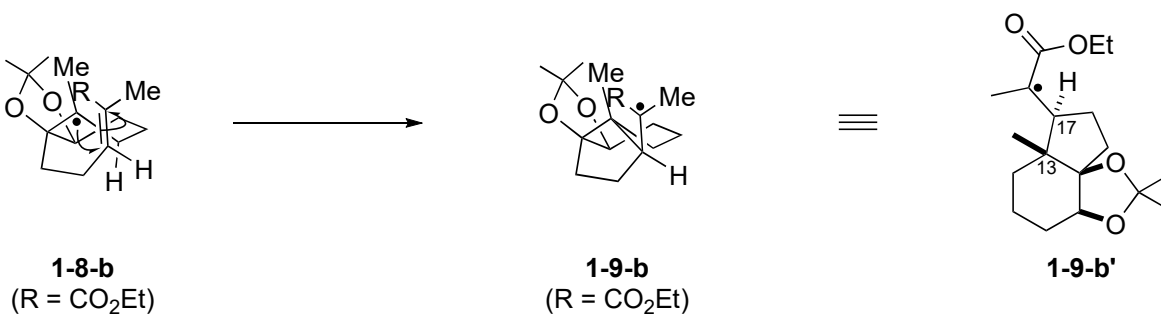
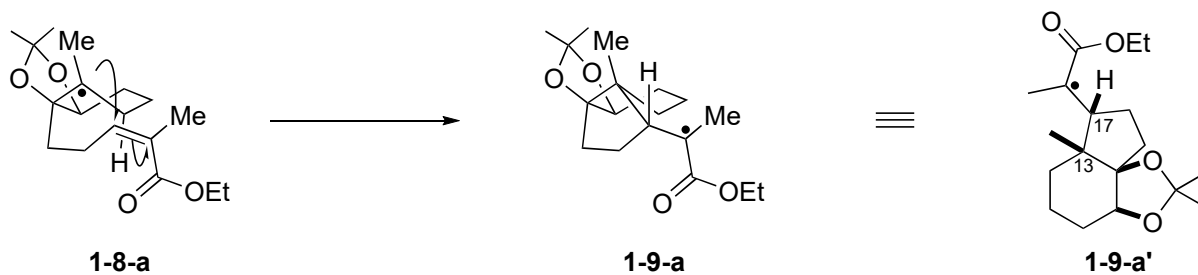
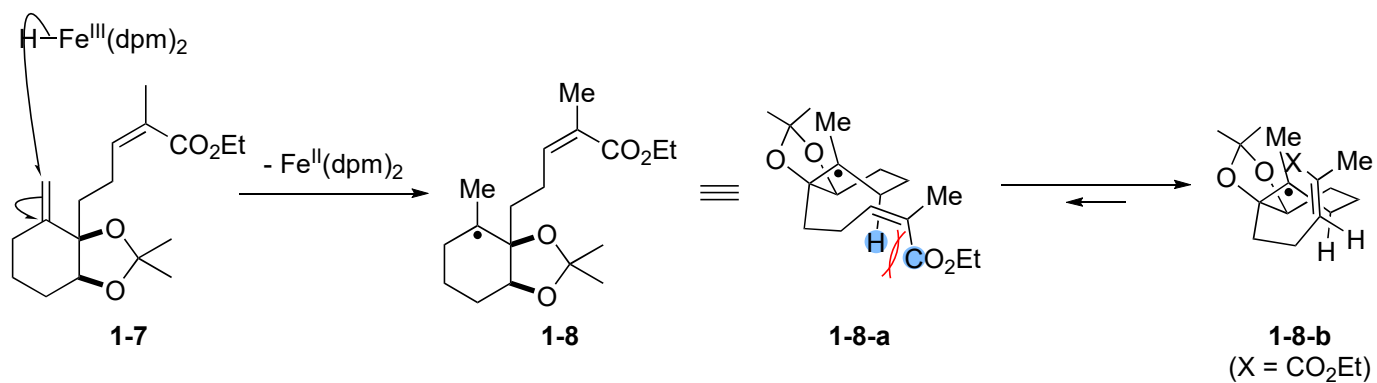
B. $0.3 \text{ F/mol} \approx$



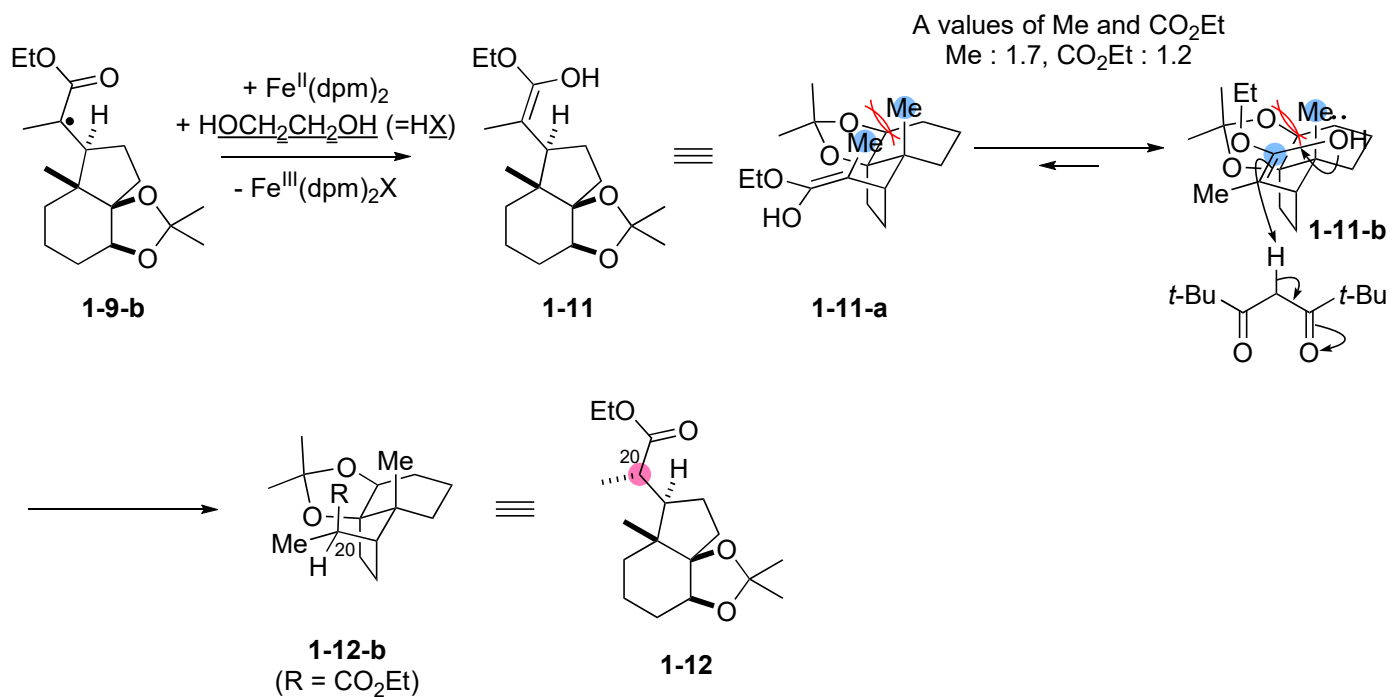
Discussion 2: Stereoselectivities of radical cyclization



2-1. C13 and C17 stereochemistry



2-2. C20 stereochemistry



References

- 1)a) Leysens, L.; Verlinden, L.; Verstuyl, A. *Front. Physiol.* **2014**, *5*, 122.
 b) Maestro, M. A.; Molnàr, F.; Carlberg, C. *J. Med. Chem.* **2019**, *62*, 6854.
- 2) Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. T.; Baran, P. S. *Science* **2022**, *375*, 745.
- 3) Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. *J. Am. Chem. Soc.* **2019**, *141*, 7473.
- 4) DeCamp, A. E.; Mills, S. G.; Kawaguuchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564.