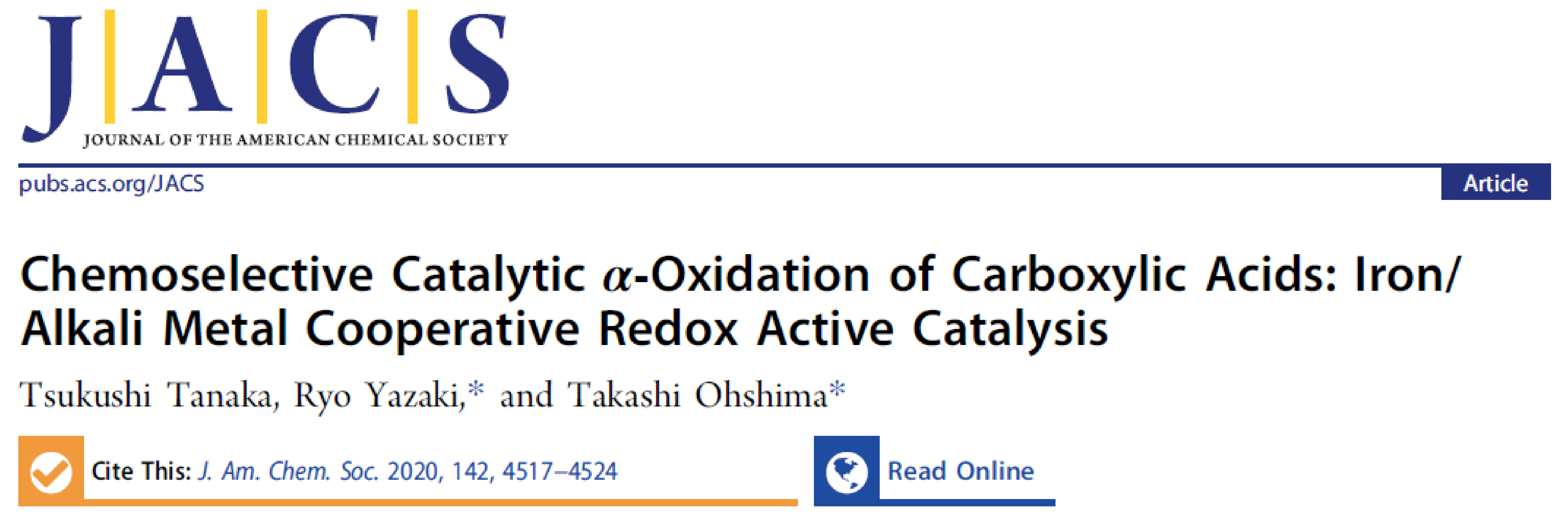

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Article

Chemoselective Catalytic α-Oxidation of Carboxylic Acids: Iron/Alkali Metal Cooperative Redox Active Catalysis

Tsukushi Tanaka, Ryo Yazaki,* and Takashi Ohshima*

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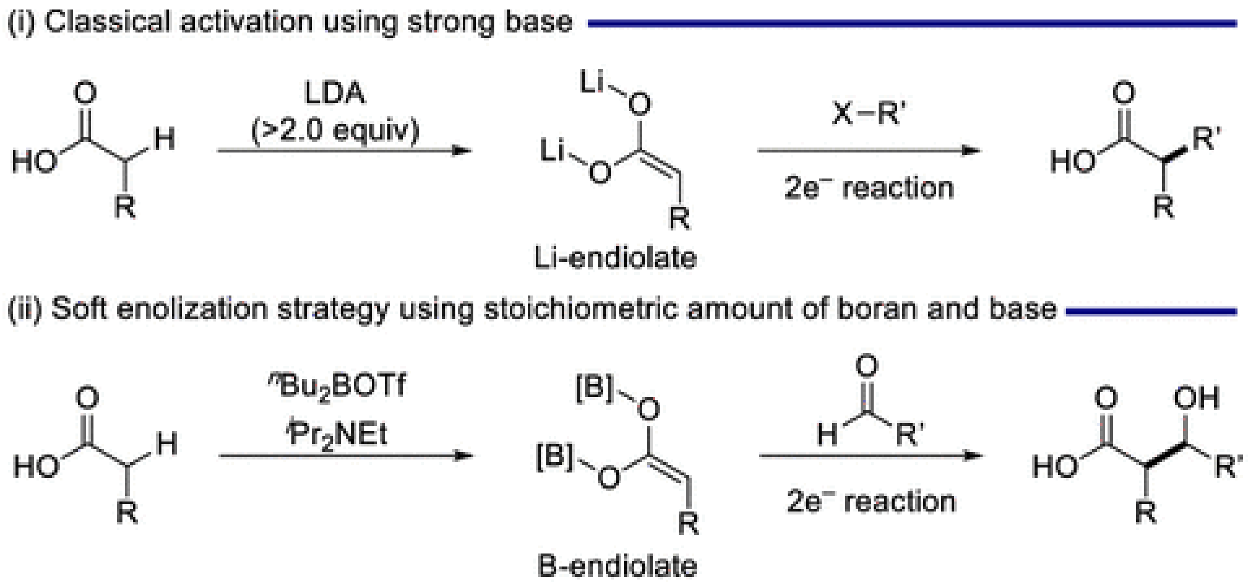
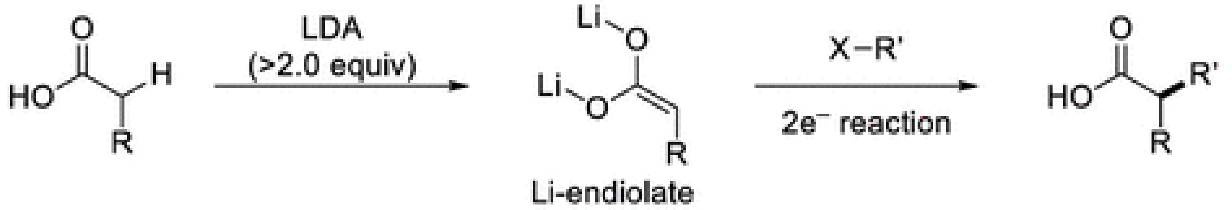


- Two equivalent of base for efficient enolization

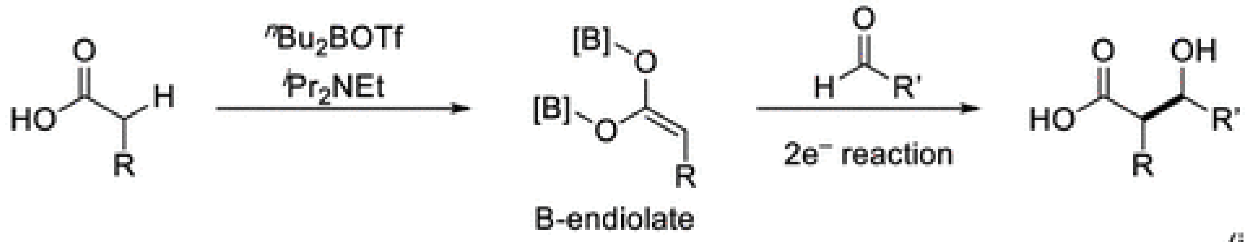
- Two equivalent of boron triflate and base to complete the direct aldol reaction

(i) Classical activation using strong base



- Two equivalent of base for efficient enolization

(ii) Soft enolization strategy using stoichiometric amount of boran and base

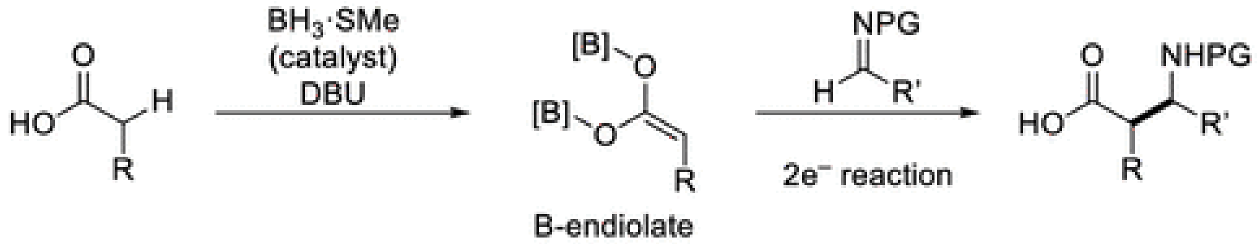


- Two equivalent of boron triflate and base to complete the direct aldol reaction

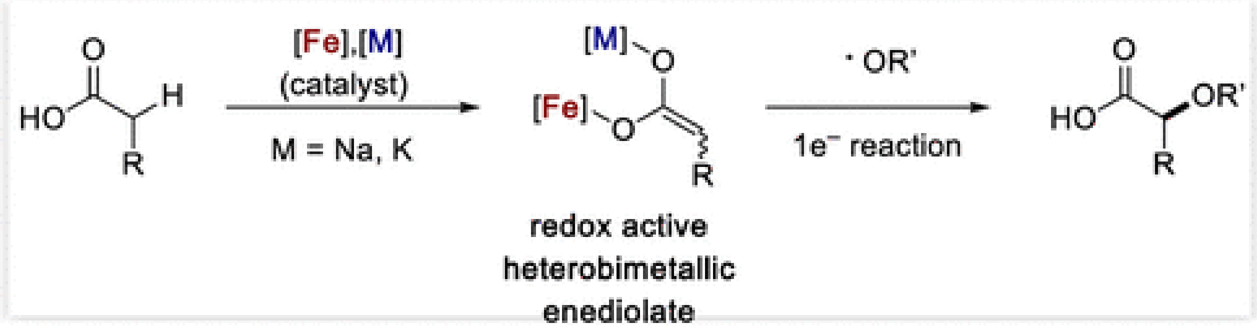
- Catalytic amount of borane and one equivalent of base

- One electron radical process, other functional group tolerance

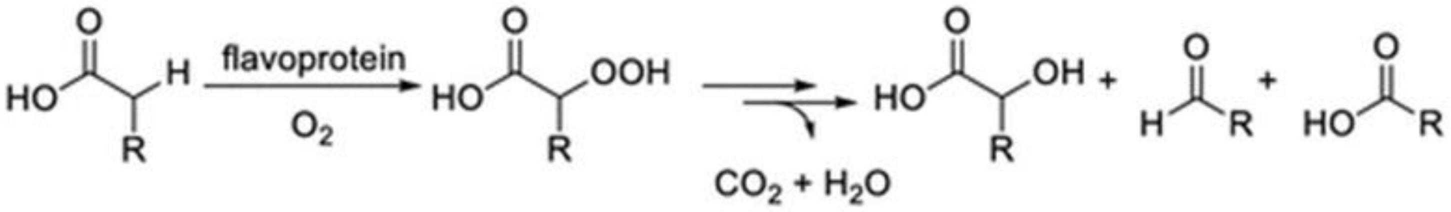
(iii) Boran-catalyzed reaction using stoichiometric amount of base



(iv) This work: redox active heterobimetallic enediolate generation strategy

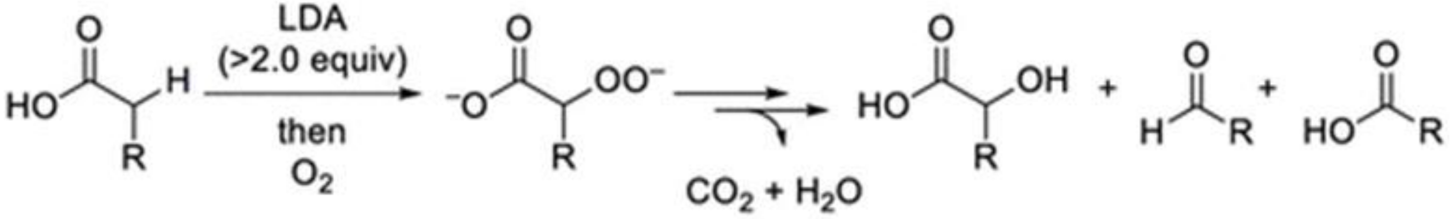


(i) Biochemical reaction in higher plant



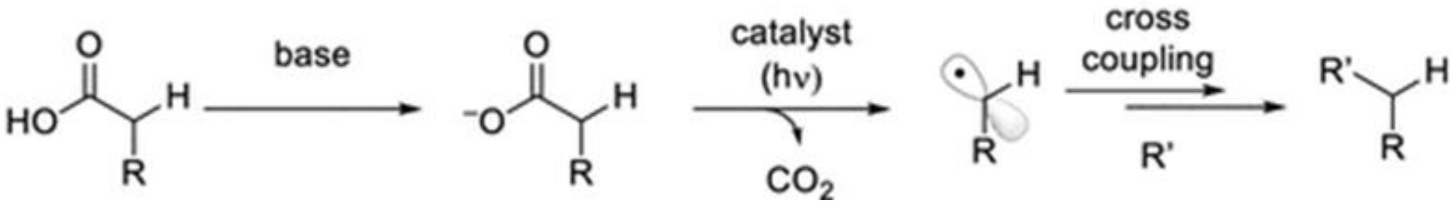
- Biochemical reaction tends to form preferentially aldehyde with dehydrative decarboxylation

(ii) Strong base-mediated reaction



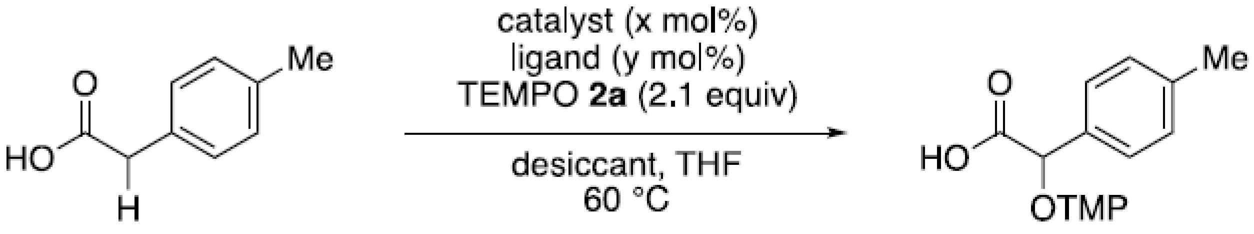
- Low yield for the α-hydroxy acids and non-functionalized

(iii) Transition metal, photoredox catalyst-mediated decarboxylative radical formation



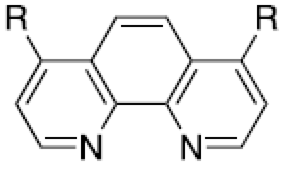
- Decarboxylation and alkyl radical formed

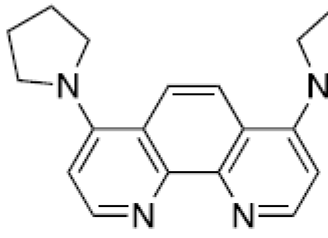
Optimization Study

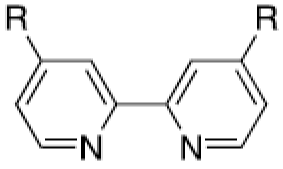

catalyst (x mol%)
ligand (y mol%)
TEMPO **2a** (2.1 equiv)
desiccant, THF
60 °C

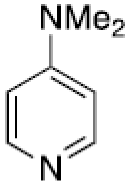
1a → **3aa**

entry	catalyst (x mol%)	ligand (y mol%)	desiccant	time (h)	yield (%)
1	$Fe(OAc)_2$ (20)	**L1** (20)	MS3A	3	53
2	$Fe(OAc)_2$ (20)	**L1** (20)	MS4A	3	75
3	$Fe(OAc)_2$ (20)	**L1** (20)	MS5A	3	37
4	$FeCl_2$ (20)	**L1** (20)	MS4A	3	10
5	$FeCl_3$ (20)	**L1** (20)	MS4A	3	trace
6	CuOAc (20)	**L1** (20)	MS4A	3	3
7	$Cu(OAc)_2$ (20)	**L1** (20)	MS4A	3	2

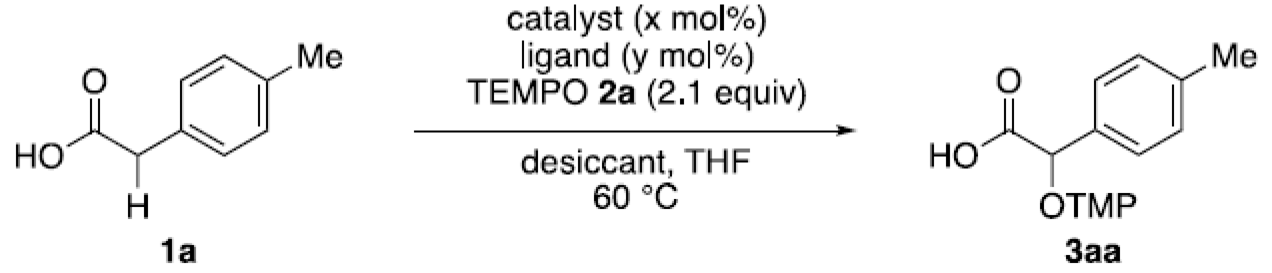

R = H (**L1**)
Ph (**L2**)
Cl (**L3**)
OMe (**L4**)
NMe_2 (**L5**)


L6

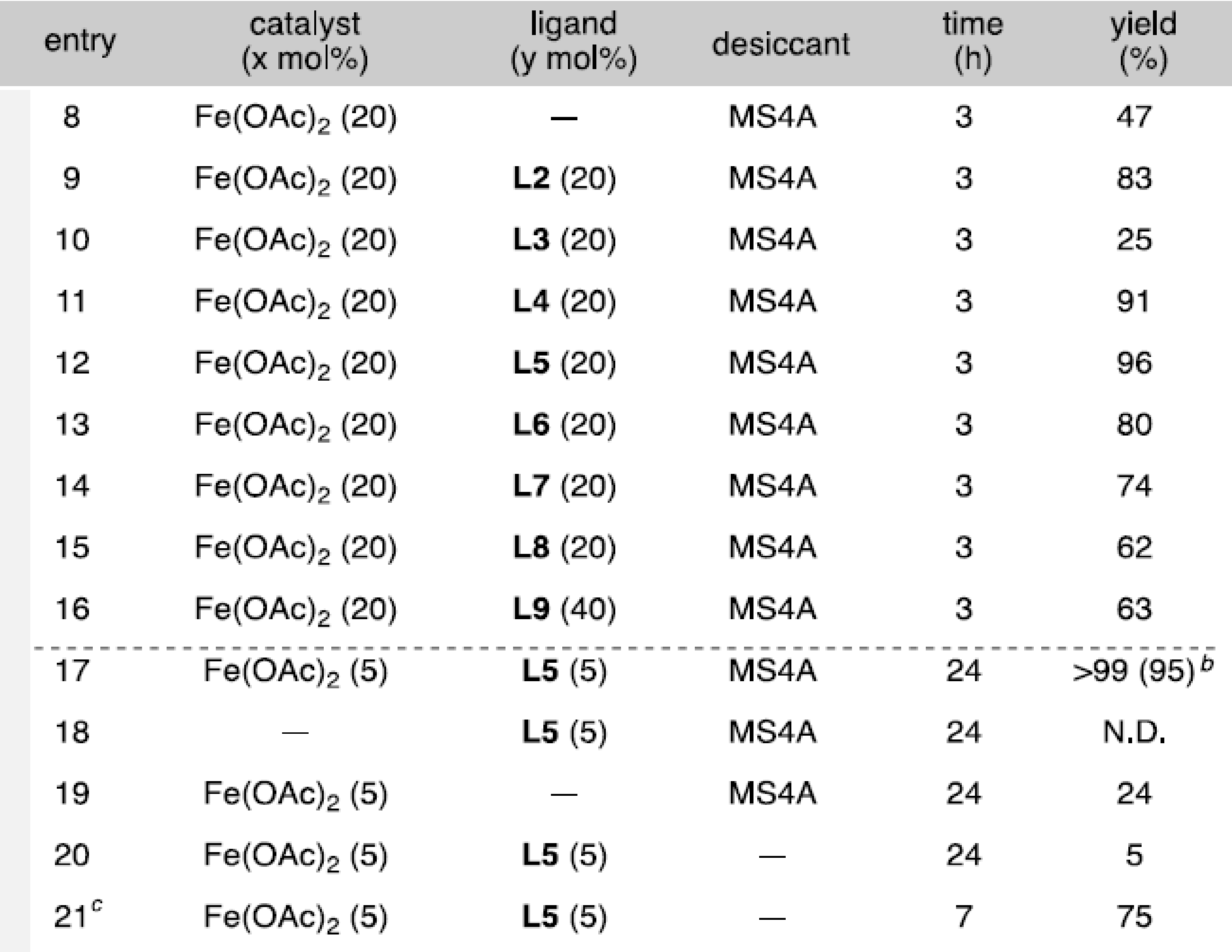

R = H (**L7**)
OMe (**L8**)


L9

Optimization Study

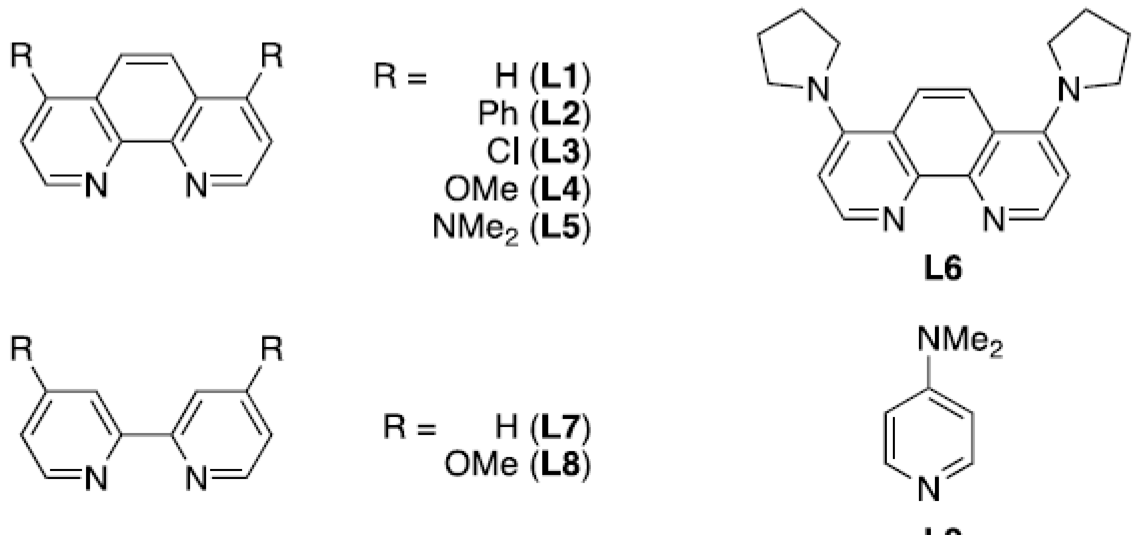


1a **3aa**



entry	catalyst (x mol%)	ligand (y mol%)	desiccant	time (h)	yield (%)
8	$Fe(OAc)_2$ (20)	—	MS4A	3	47
9	$Fe(OAc)_2$ (20)	**L2** (20)	MS4A	3	83
10	$Fe(OAc)_2$ (20)	**L3** (20)	MS4A	3	25
11	$Fe(OAc)_2$ (20)	**L4** (20)	MS4A	3	91
12	$Fe(OAc)_2$ (20)	**L5** (20)	MS4A	3	96
13	$Fe(OAc)_2$ (20)	**L6** (20)	MS4A	3	80
14	$Fe(OAc)_2$ (20)	**L7** (20)	MS4A	3	74
15	$Fe(OAc)_2$ (20)	**L8** (20)	MS4A	3	62
16	$Fe(OAc)_2$ (20)	**L9** (40)	MS4A	3	63
17	$Fe(OAc)_2$ (5)	**L5** (5)	MS4A	24	>99 (95)[b]
18	—	**L5** (5)	MS4A	24	N.D.
19	$Fe(OAc)_2$ (5)	—	MS4A	24	24
20	$Fe(OAc)_2$ (5)	**L5** (5)	—	24	5
21[c]	$Fe(OAc)_2$ (5)	**L5** (5)	—	7	75

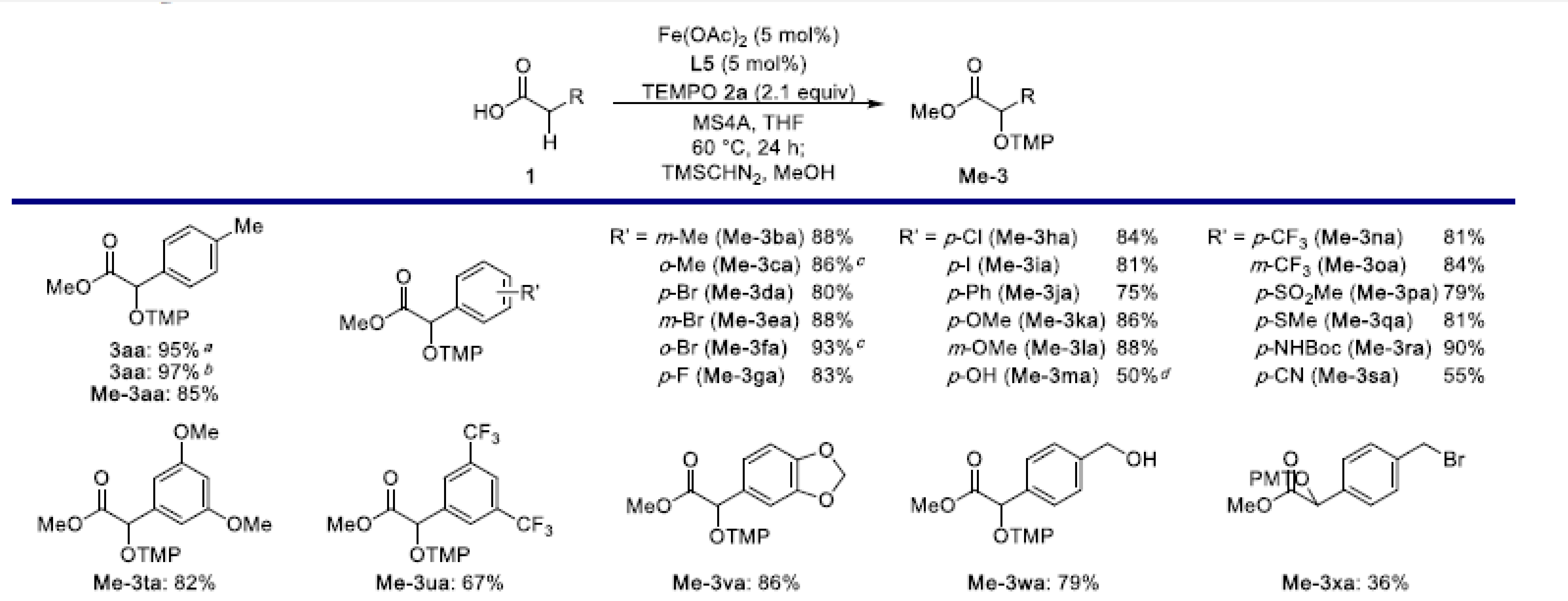
- All yields are determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard
- b : Isolated yield
- c : 100 °C in 1,4 dioxane



L6

L9

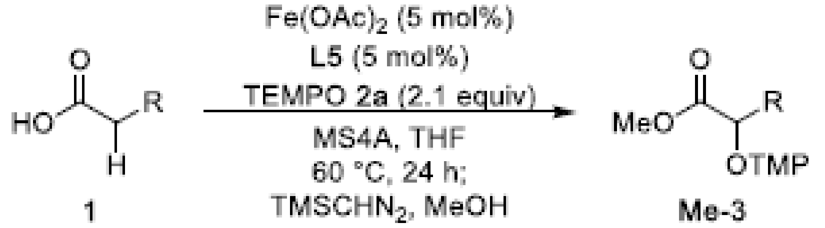
Substrate Scope

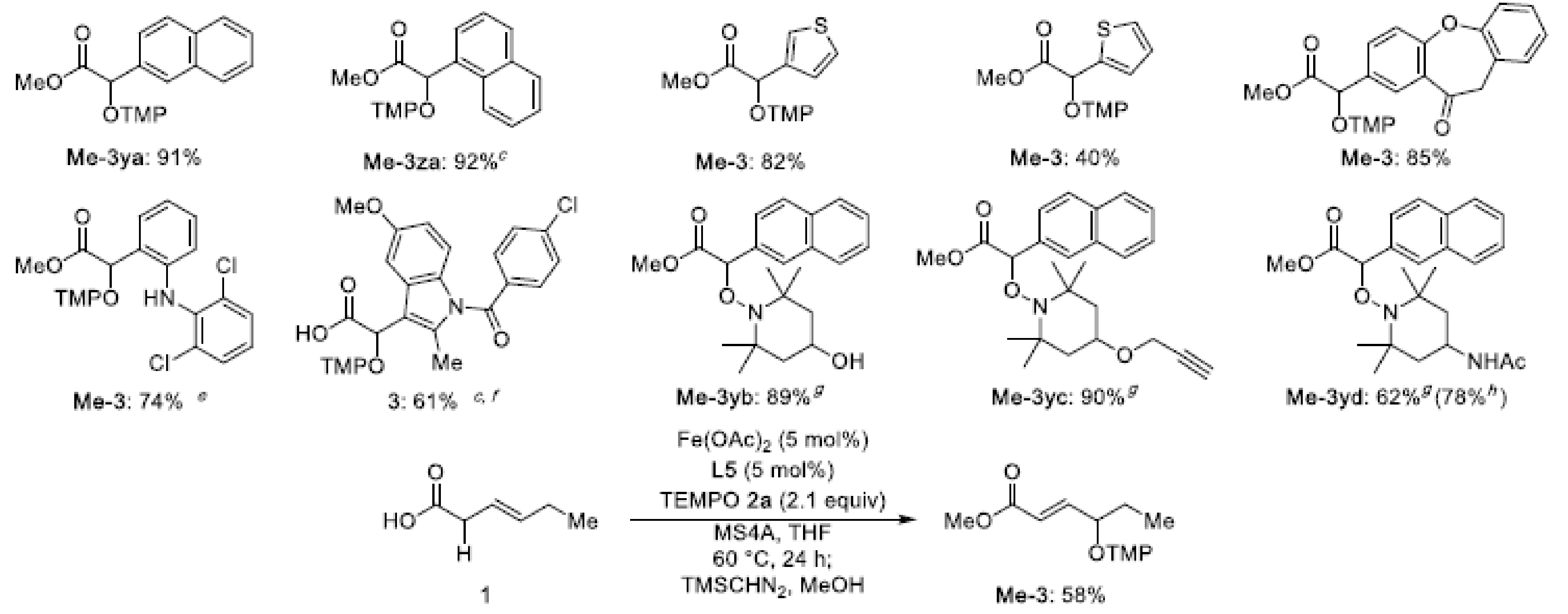


R'	Compound	Yield
m-Me	Me-3ba	88%
o-Me	Me-3ca	86%[c]
p-Br	Me-3da	80%
m-Br	Me-3ea	88%
o-Br	Me-3fa	93%[c]
p-F	Me-3ga	83%
p-Cl	Me-3ha	84%
p-I	Me-3ia	81%
p-Ph	Me-3ja	75%
p-OMe	Me-3ka	86%
m-OMe	Me-3la	88%
p-OH	Me-3ma	50%[d]
p-CF$_3$	Me-3na	81%
m-CF$_3$	Me-3oa	84%
p-SO$_2$Me	Me-3pa	79%
p-SMe	Me-3qa	81%
p-NHBoc	Me-3ra	90%
p-CN	Me-3sa	55%

[a] Isolated as carboxylic acid. [b] 1 mol % of Fe(OAc)$_2$ and L5 were used for 72 h. A 1.19 g amount of the product 3aa was isolated as carboxylic acid. [c] 4.0 equiv of TEMPO **2a** and 10 mol % of Fe(OAc)$_2$ and L5 were used. [d] 2-(4-Acetoxyphenyl)acetic acid (**1m-Ac**) was used as a substrate. [e] 4.0 equiv of TEMPO **2a** and 20 mol % of Fe(OAc)$_2$ and L5 were used. [f] Yield was determined by ^{1}H NMR analysis using dibenzyl as an internal standard. [g] 2.1 equiv of corresponding TEMPO derivatives (**2b**−**2d**) and 10 mol % of Fe(OAc)$_2$ and L5 were used. [h] Yield based on recovered esterified starting material (**Me-1y**) was shown.

Substrate Scope





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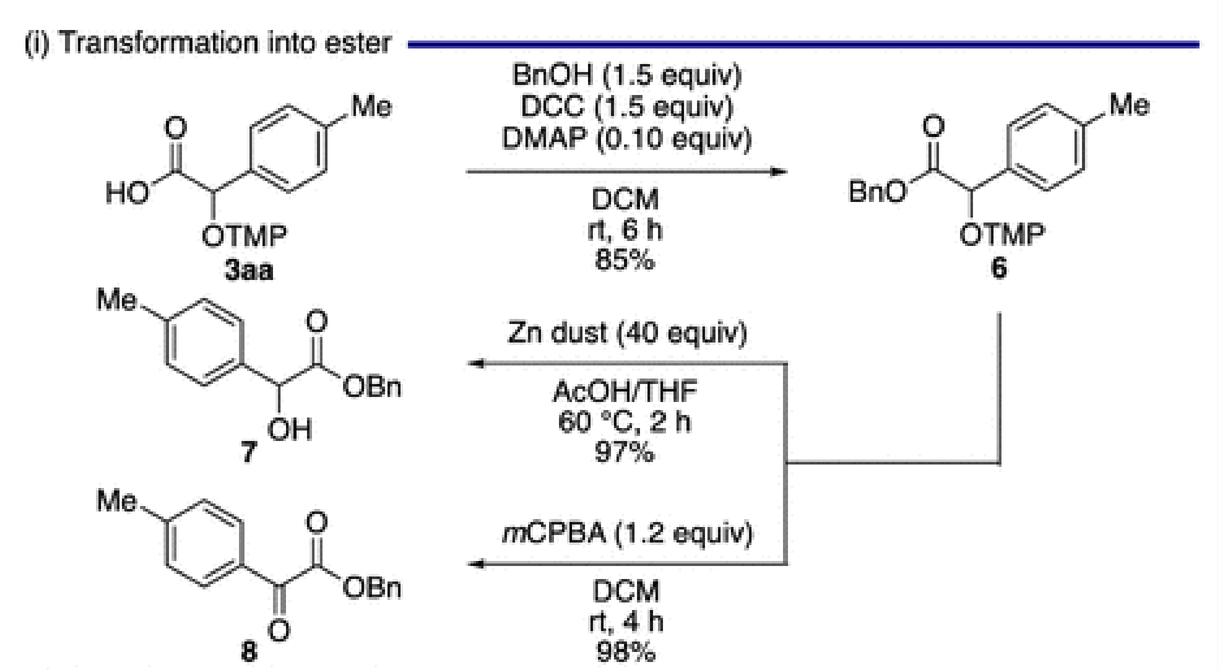
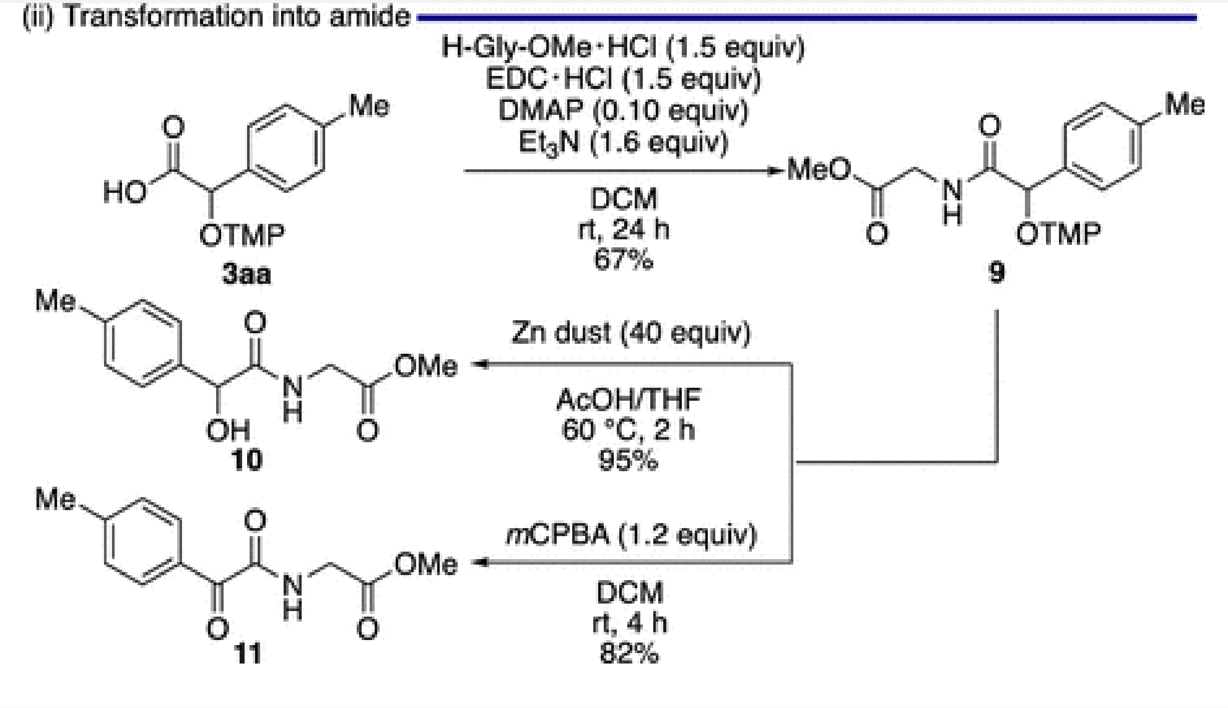
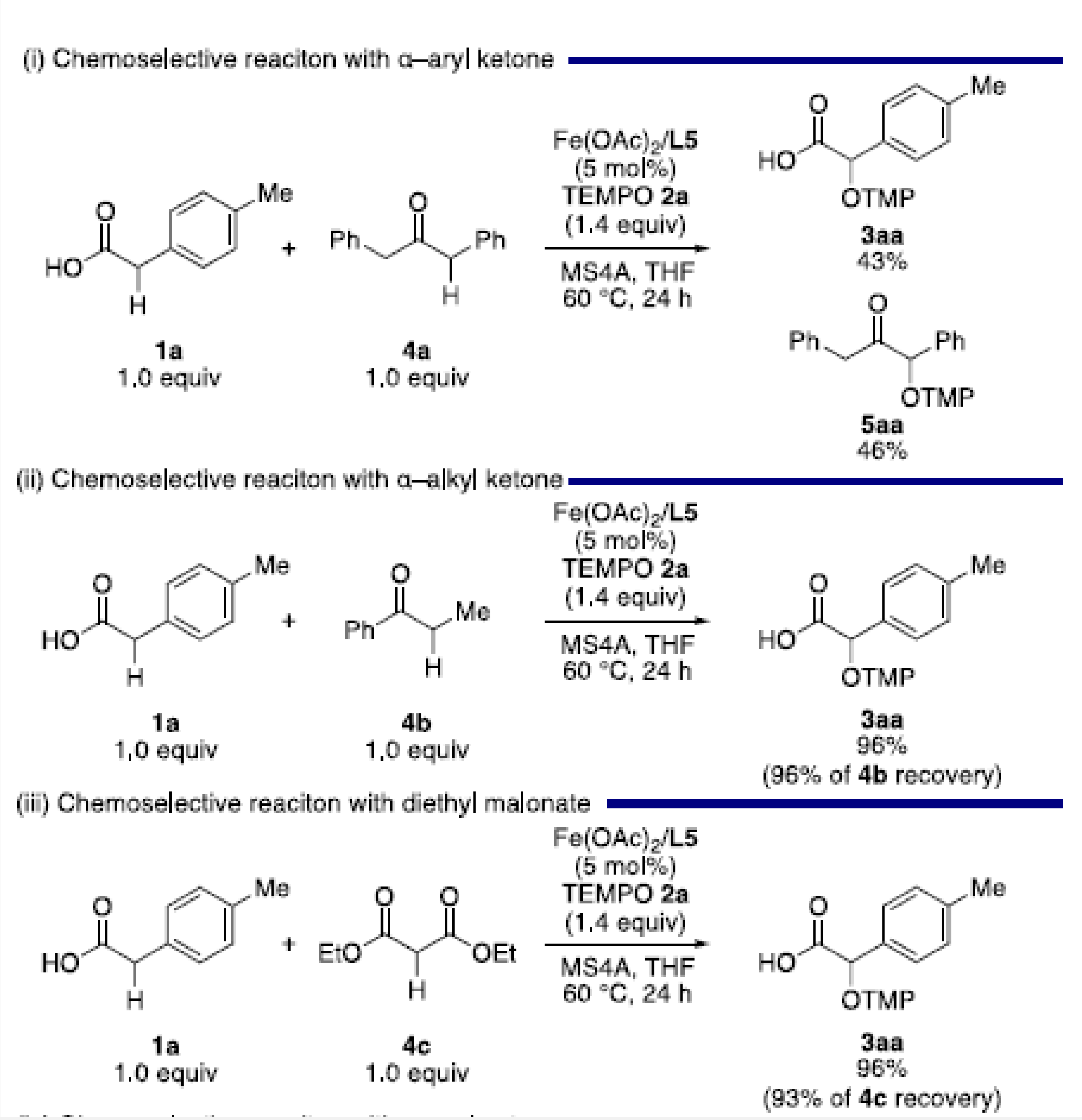
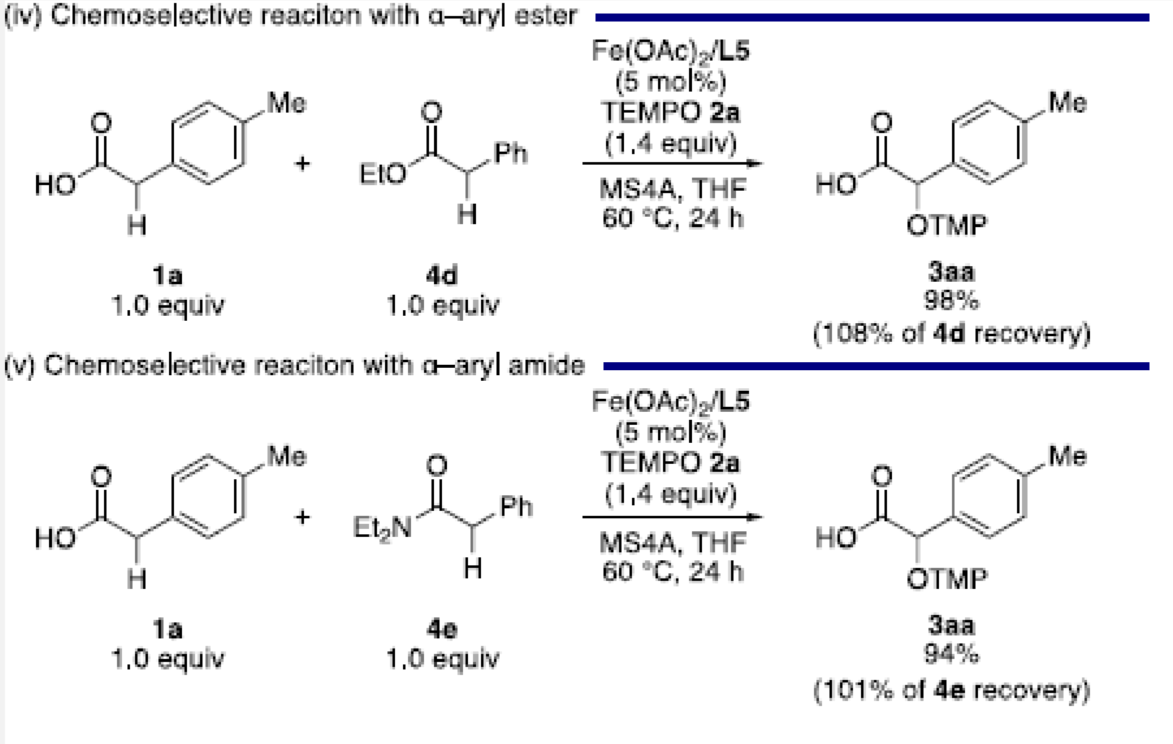
Transformation of the products





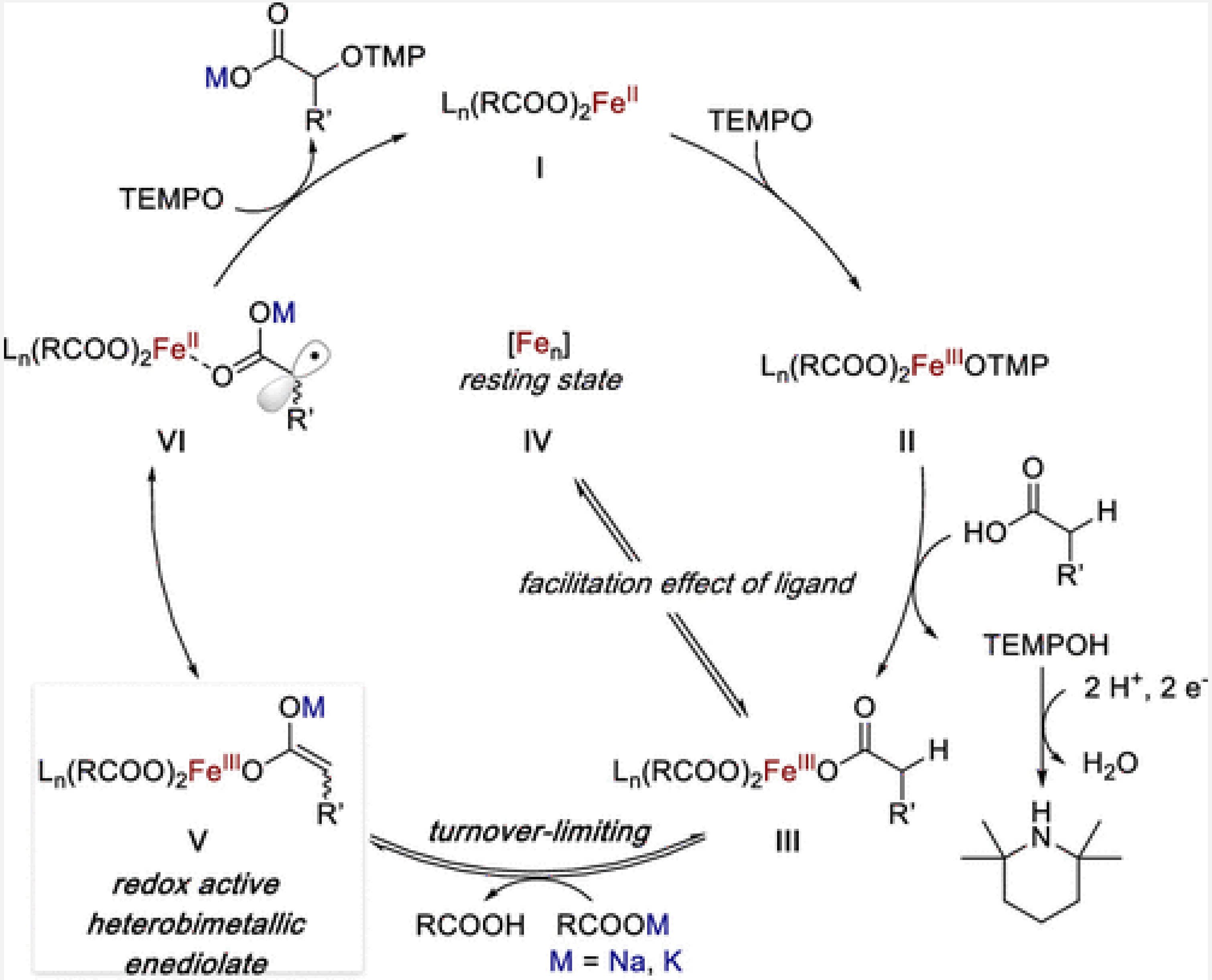
Chemoselective activation of carboxylic acids





- Not efficient with α-aryl ketone

Proposed catalytic cycle

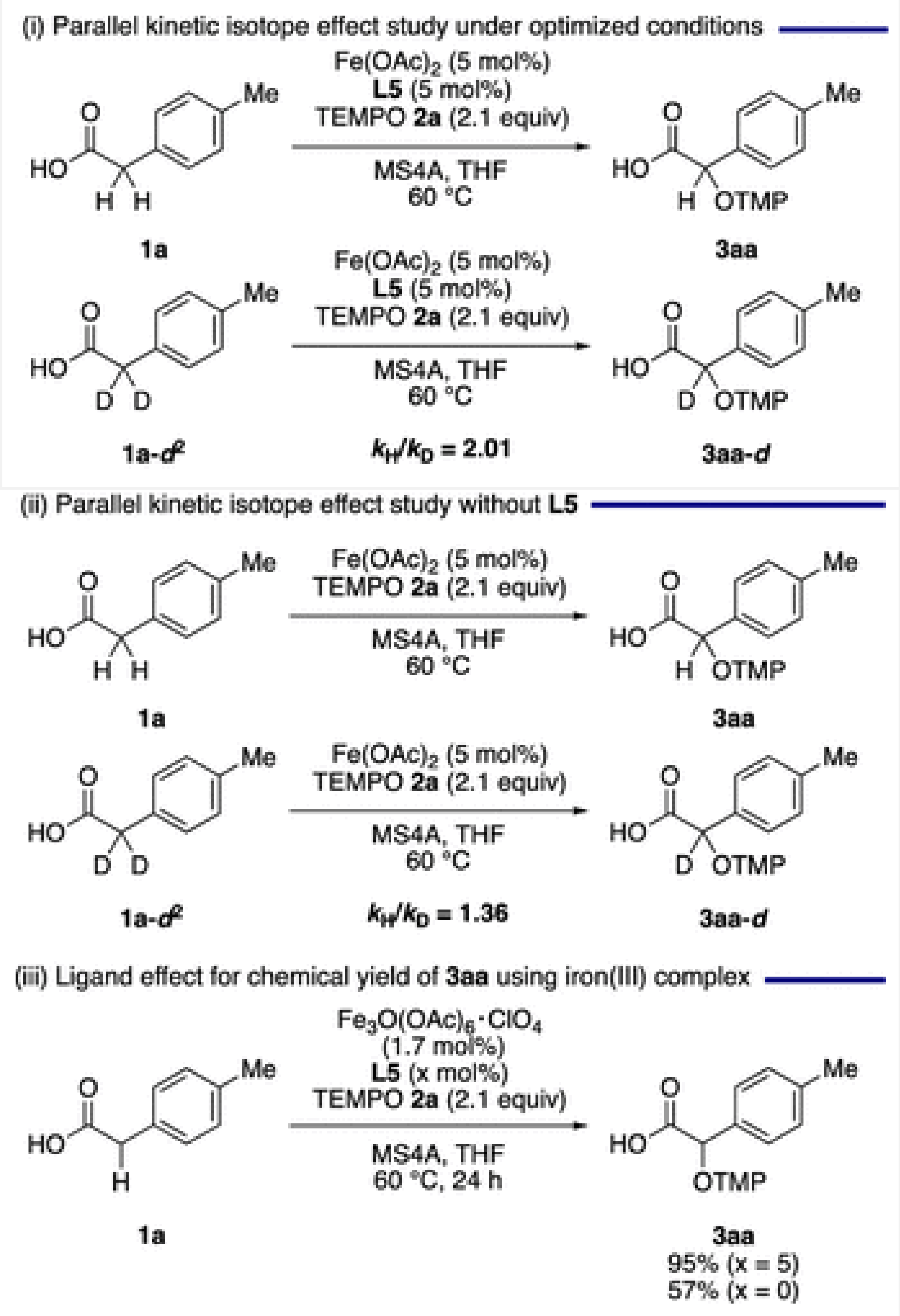


1: Oxydation of Iron(II) by TEMPO

2: Carboxylate exchange

3 : Deprotonative activation to form V

4 : Cross-coupling with TEMPO



Kinetic Isotope Effect study

- Enolization of carboxylic acid limit the turnover
- Formation of an active monomeric species from inactive multinuclear iron species

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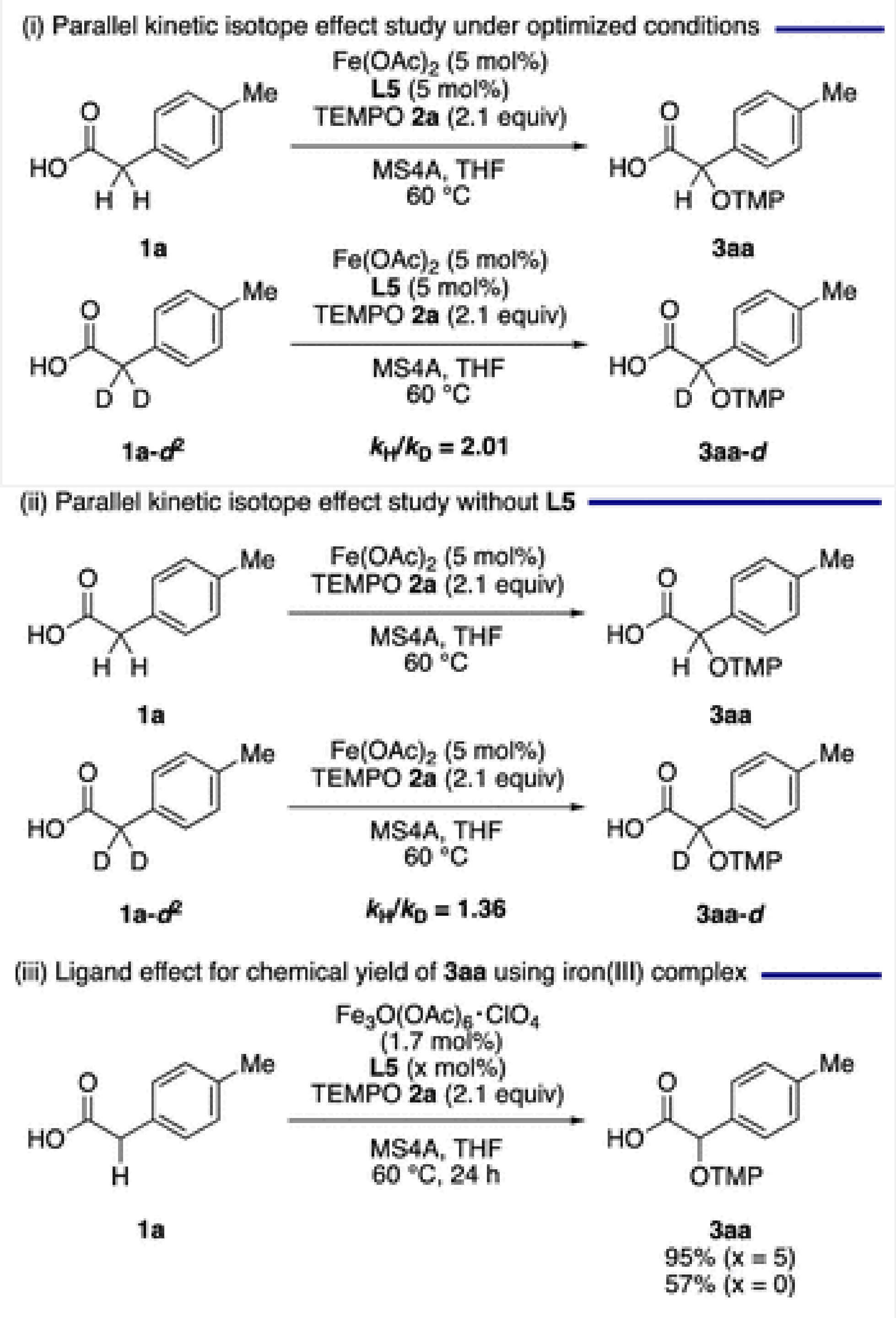
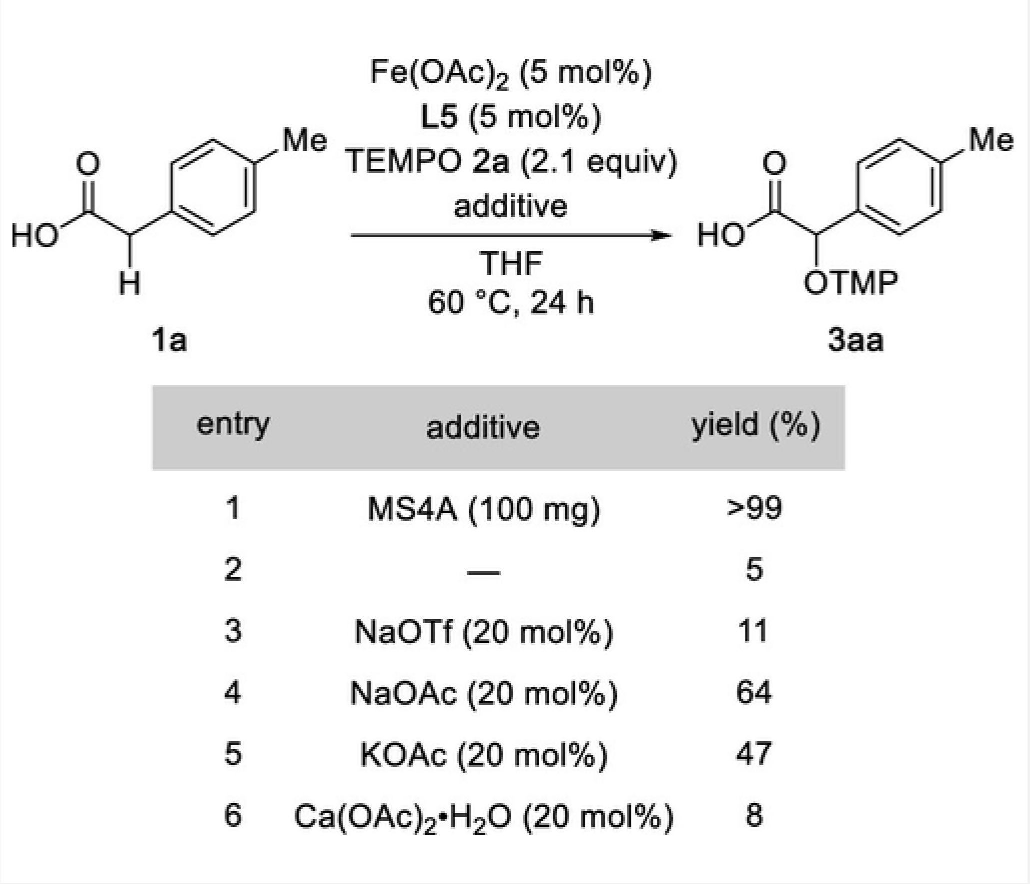
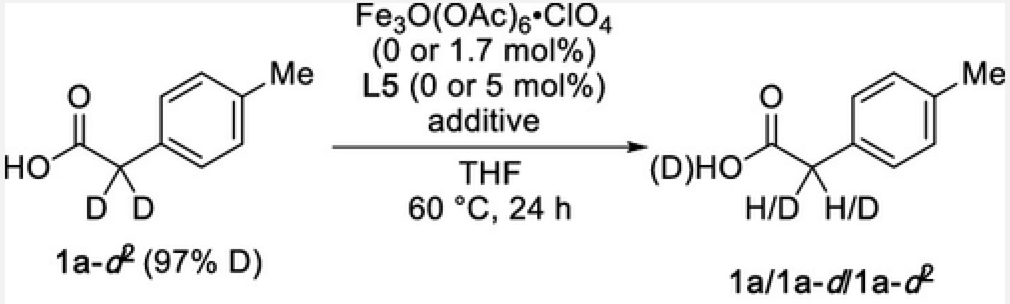




entry	additive	yield (%)
1	MS4A (100 mg)	>99
2	—	5
3	NaOTf (20 mol%)	11
4	NaOAc (20 mol%)	64
5	KOAc (20 mol%)	47
6	$Ca(OAc)_2 \cdot H_2O$ (20 mol%)	8

Effect of alkali Metal salt study

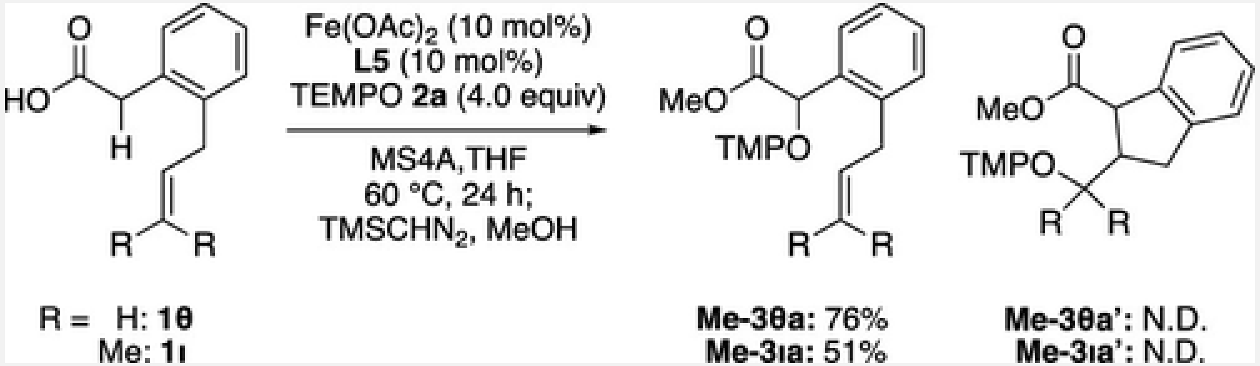
Effect of sodium ion for Enolization with Fe(III) complex



entry	catalyst	additive	(H/H+D %)
1	$Fe_3O(OAc)_6$•ClO_4/L5	MS4A (100 mg)	51
2	$Fe_3O(OAc)_6$•ClO_4/L5	—	6
3	—	MS4A (100 mg)	6
4	—	—	3
5	$Fe_3O(OAc)_6$•ClO_4/L5	NaOAc (20 mol%)	37
6	—	NaOAc (20 mol%)	4

- Proton exchange observed with moleular sieves and NaOAc
- Enolization probably achieved by bimetallic system

Radical Clock Experiments



- No observation of the formation of cyclized product
- α-radical species highly reactive and coupled with TEMPO

Thanks for your attention