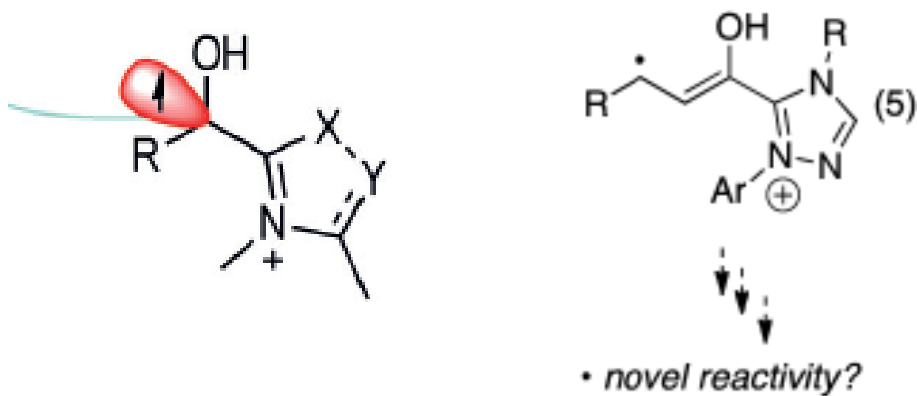


N-Heterocyclic Carbene Catalyzed Radical Reactions



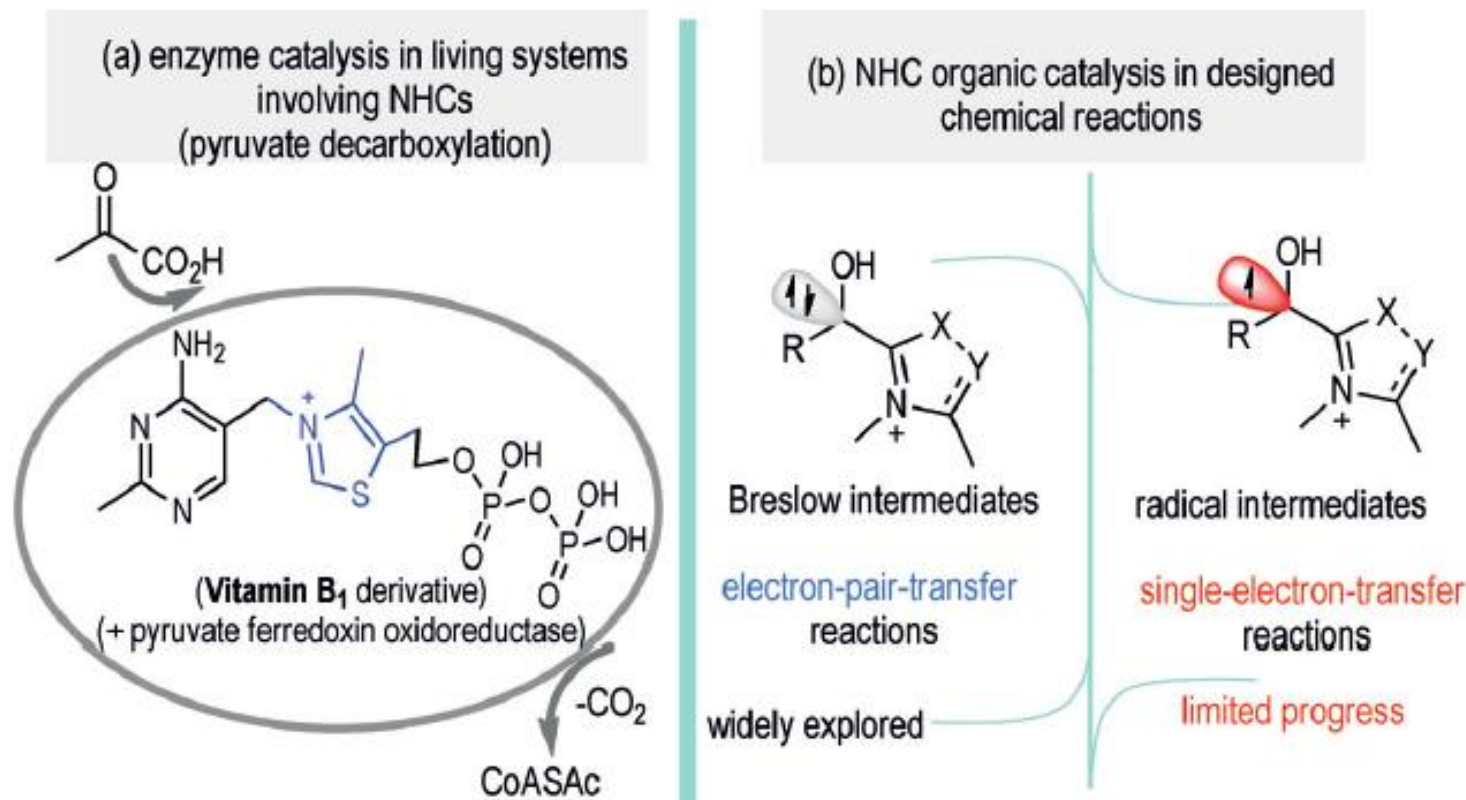
Reporter: Shi-Yong Chen
Supervisor: *Prof.* Yong Huang
Date: 6/10/2019

Table of Content

1. Background
2. Reactions of aldehyde carbonyl carbon centers
3. Reactions of β or γ -carbon centers
4. Reactions of aldehydes as the terminal reductants
5. Conclusions and outlook
6. Acknowledgement

1. Background

NHC-catalyzed reactions in living systems and organic synthesis:



- in enzymatic catalysis, both **electron-pair-transfer** and **single-electron-transfer** processes are involved
- in organic synthesis, most NHC-catalyzed reactions are designed based on **electron-pair-transfer** processes

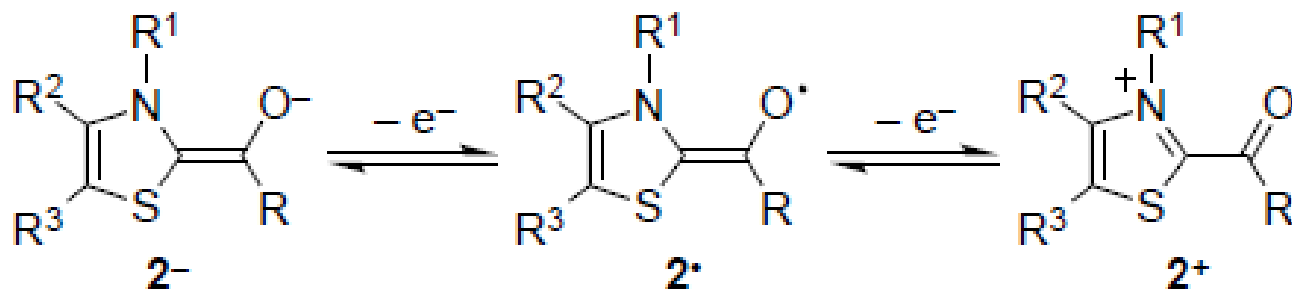
Angew. Chem. Int. Ed. **2019**, 58, 2–5

Angew. Chem. Int. Ed. **2017**, 56, 3754–3756

1. Background

Fukuzumi, 1998, *ACIE*

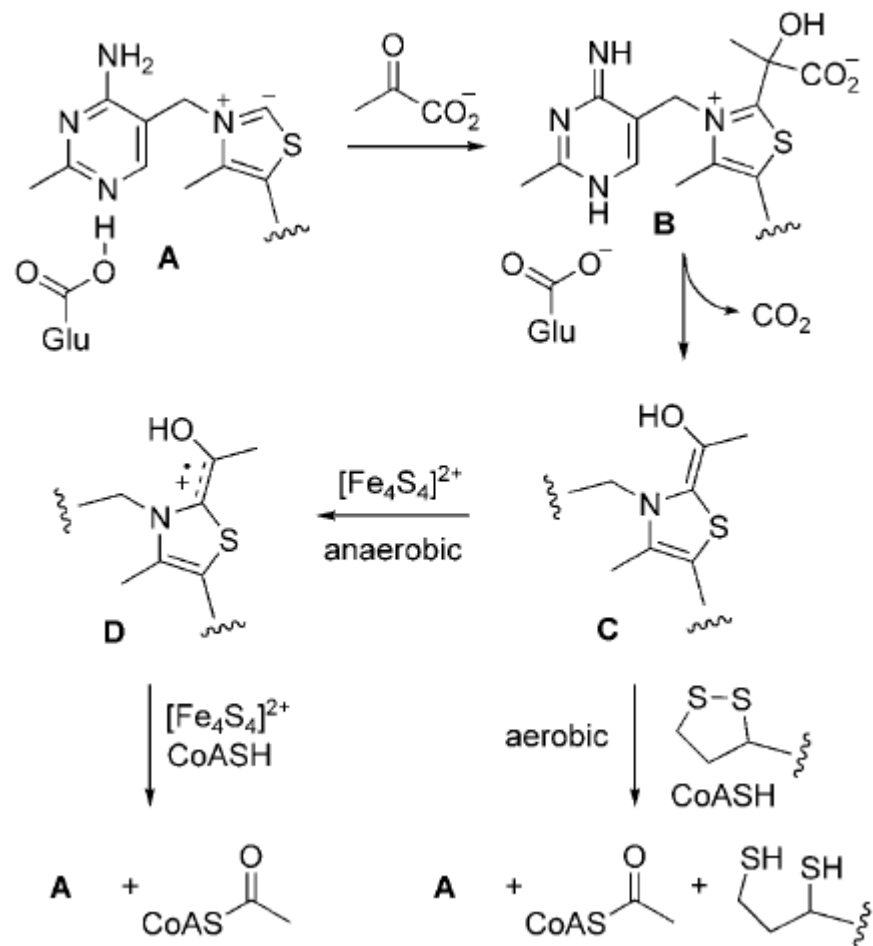
Direct observation of radical intermediates While Investigating the Redox Behavior of Thiamin Coenzyme Models:



- With low-temperature (233 K) cyclic voltammetry and EPR spectroscopy.
- The enolate form of Breslow intermediate has a strong reducing ability ($E^{\text{ox}} = -0.95 \sim -0.97$ V) and fast electron transfer property.

1. Background

NHCs catalyze the oxidative decarboxylation of pyruvate:

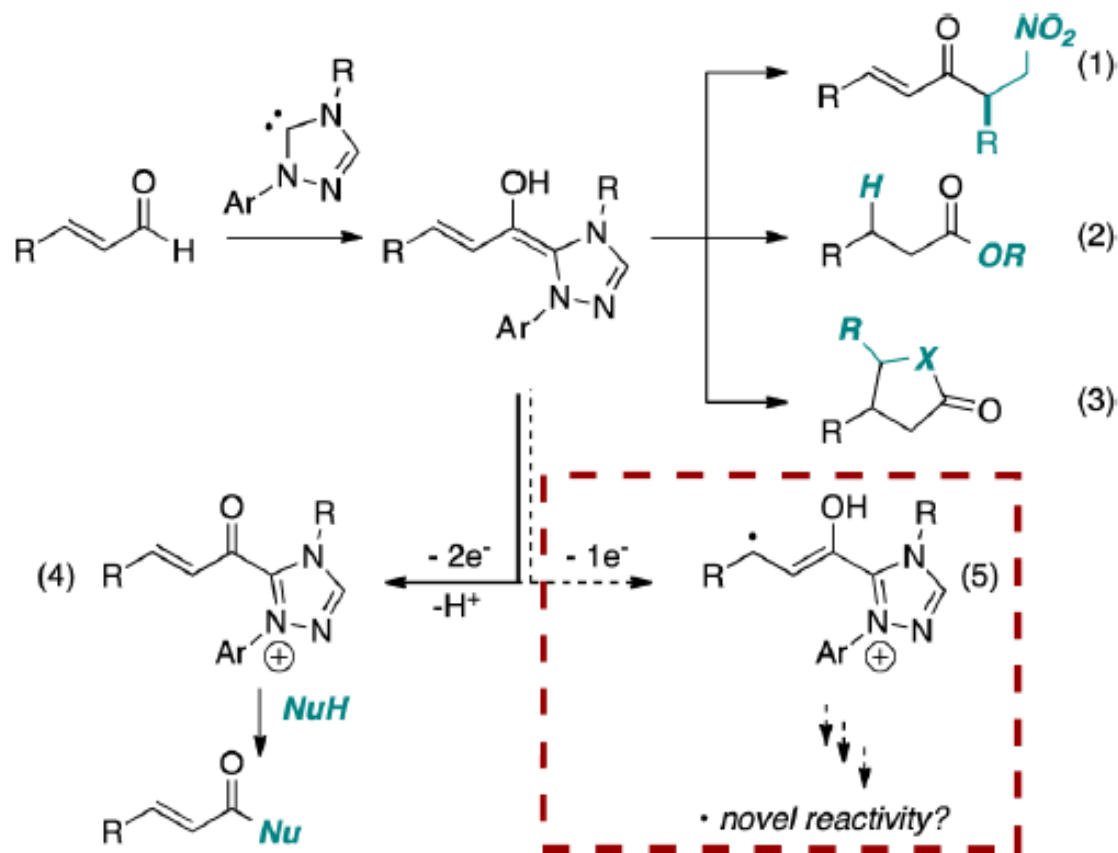


Science **2001**, 294, 2559

Angew. Chem. Int. Ed. **2008**, 47, 8727–8730

1. Background

The use of α,β -unsaturated aldehydes as substrates for NHC catalysis:



2. Reactions of aldehyde carbonyl carbon centers

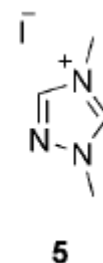
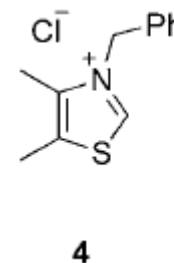
Studer, 2008, *ACIE*

Biomimetic carbene-catalyzed oxidations of aldehydes using TEMPO:



Table 1: NHC-catalyzed oxidation of various aldehydes with TEMPO (2 equiv) and DBU in THF at room temperature for 6–12 h.

Entry	Catalyst (mol%)	Product	R	Yield [%]
1 ^[a]	3 (10)	2a	C ₆ H ₅ CH=CH	87
2 ^[a]	4 (10)	2a	C ₆ H ₅ CH=CH	86
3 ^[a]	5 (10)	2a	C ₆ H ₅ CH=CH	85



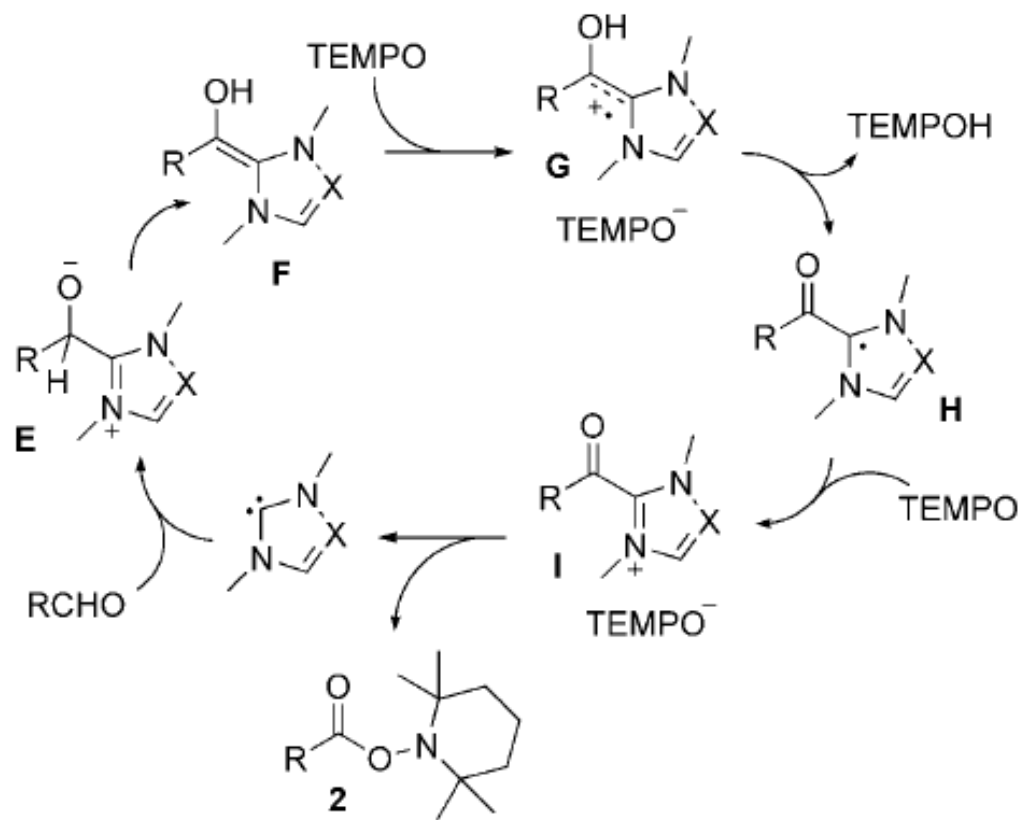
The carbene structure does not influence oxidation to a large extent.

2. Reactions of aldehyde carbonyl carbon centers

Studer, 2008, *ACIE*

Biomimetic carbene-catalyzed oxidations of aldehydes using TEMPO:

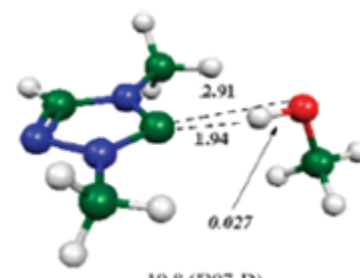
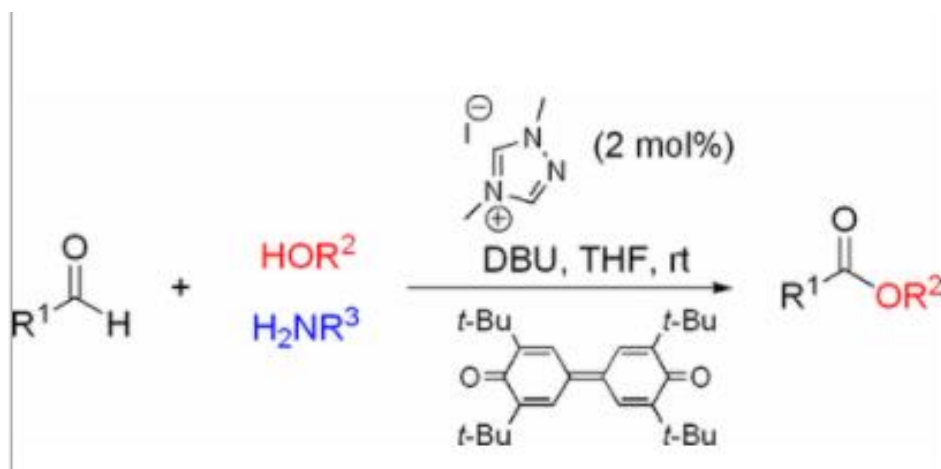
Suggested mechanism (X=N, CH)



2. Reactions of aldehyde carbonyl carbon centers

Studer, 2010, *JACS*

NHC catalyzed oxidations of aldehydes to esters: chemoselective acylation of alcohols in presence of amines:

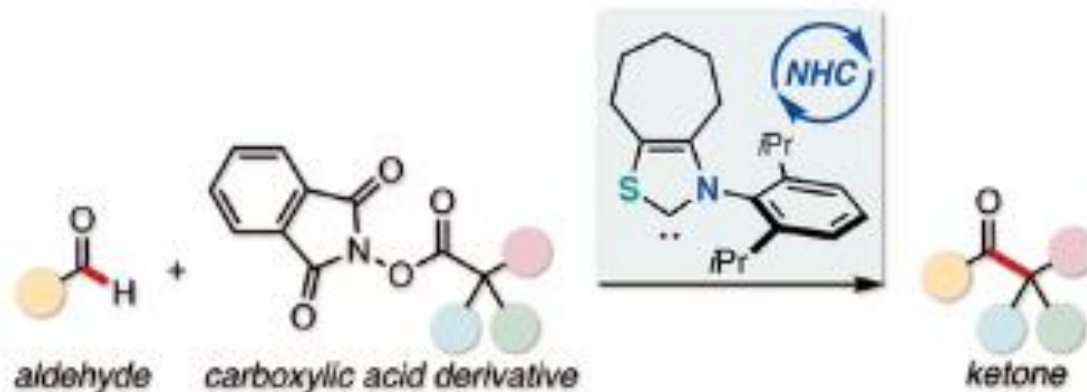


- The carbene has a dual role: (a) it catalyzes the oxidation and (b) it activates the alcohol.
- Preferable activation of the alcohol by H-bonding to the carbene thereby increasing the alcohol nucleophilicity.

2. Reactions of aldehyde carbonyl carbon centers

Ohmiya, 2019, *JACS*

N-heterocyclic carbene-catalyzed decarboxylative alkylation of aldehydes:

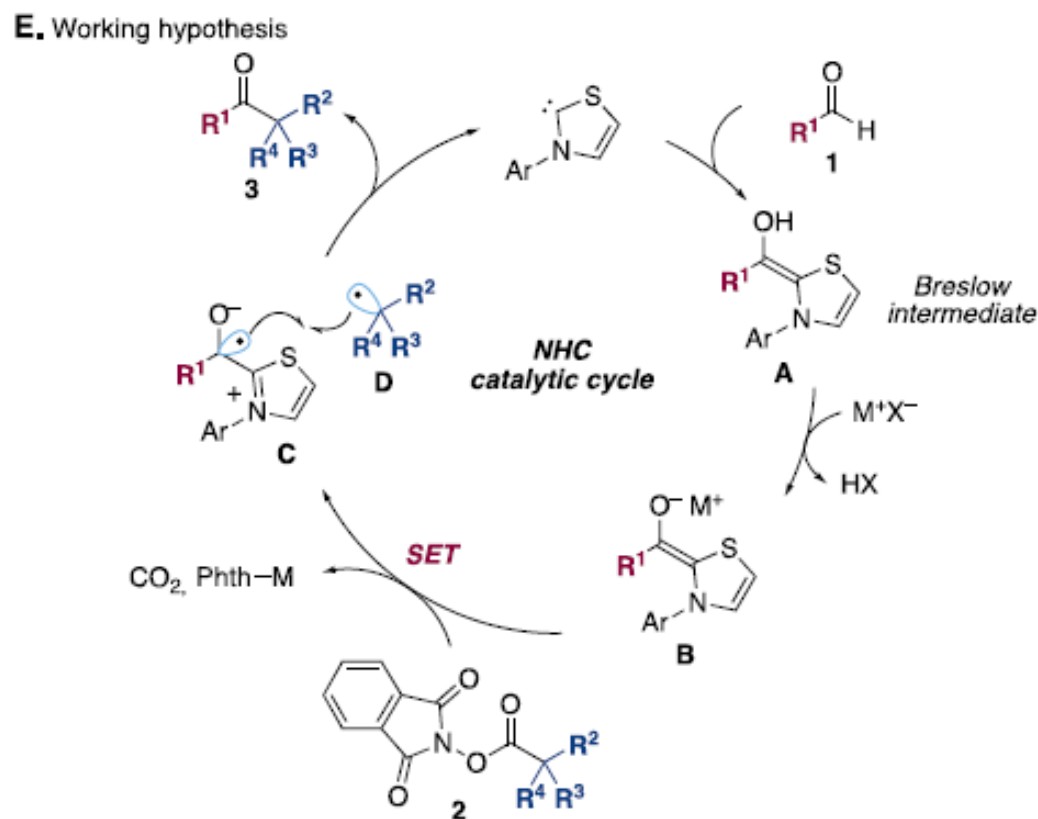


➤ Redox-active esters that can accept one electron and then liberate an alkyl radical.

2. Reactions of aldehyde carbonyl carbon centers

Ohmiya, 2019, *JACS*

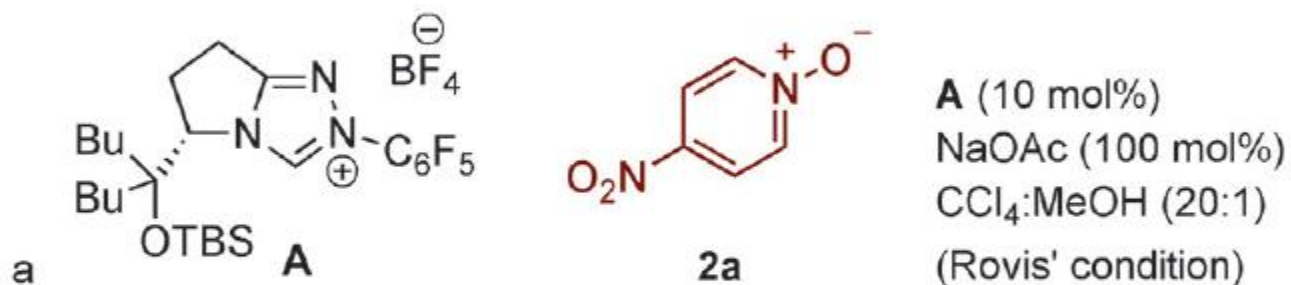
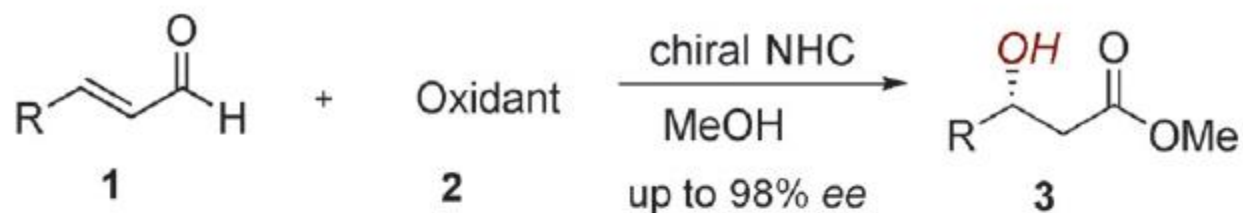
N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes:



3. Reactions of β -carbon centers

Rovis, 2014, *JACS*; Chi, 2015, *JACS*

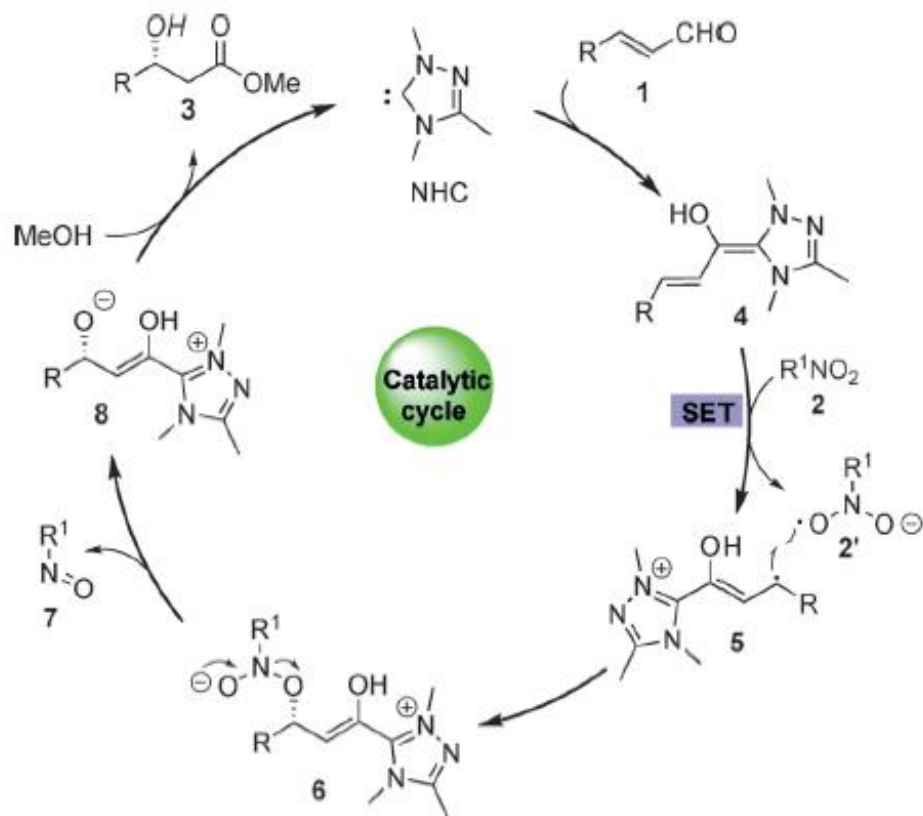
Enantioselective NHC-catalyzed β -hydroxylation of enals:



3. Reactions of β -carbon centers

Rovis, 2014, *JACS*; Chi, 2015, *JACS*

Enantioselective NHC-catalyzed β -hydroxylation of enals:



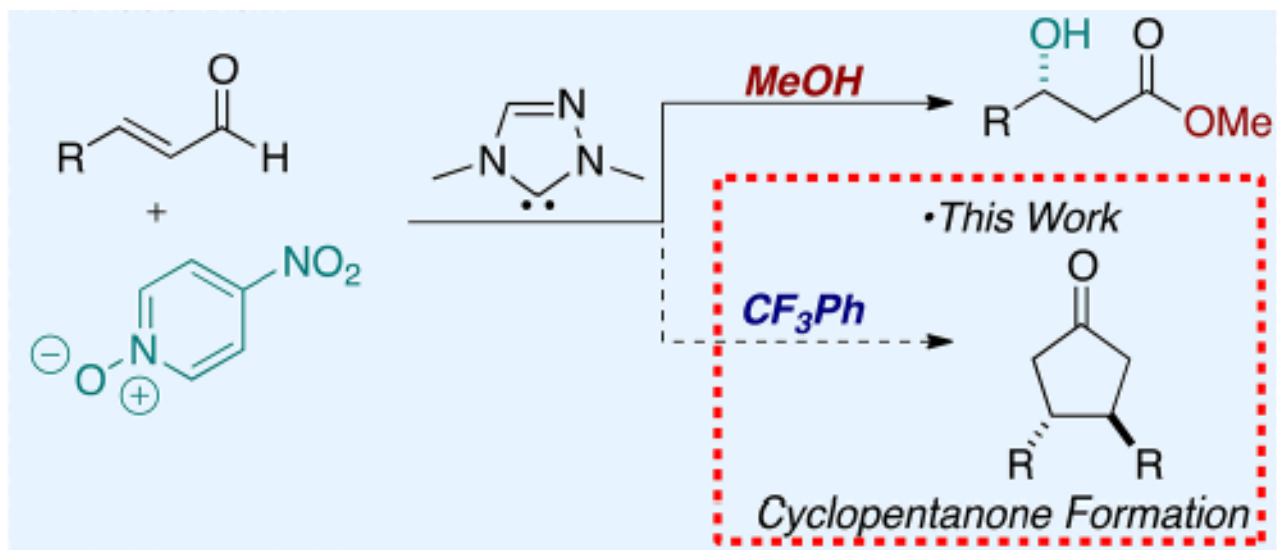
J. Am. Chem. Soc. **2014**, *136*, 14674–14677

J. Am. Chem. Soc. **2015**, *137*, 2416–2419

3. Reactions of β -carbon centers

Rovis, 2015, JACS

NHC-catalyzed enantioselective synthesis of 3,4-disubstituted cyclopentanones from enals:

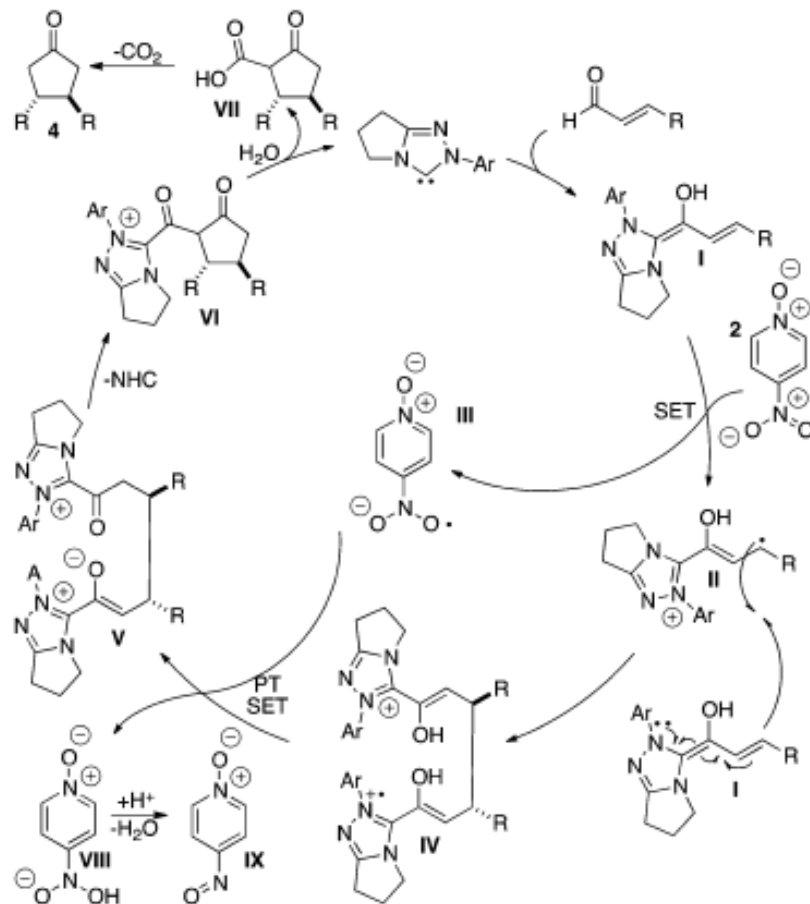


non-nucleophilic solvent

3. Reactions of β -carbon centers

Rovis, 2015, *JACS*

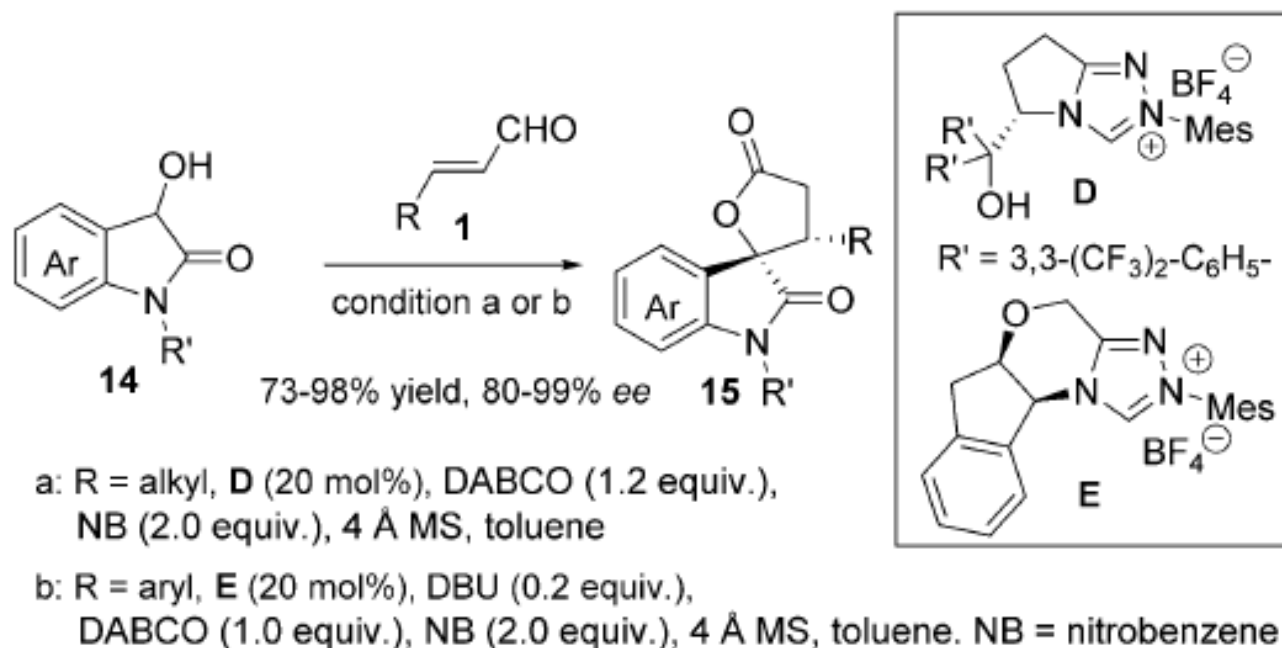
NHC-catalyzed enantioselective synthesis of 3,4-disubstituted cyclopentanones from enals:



3. Reactions of β -carbon centers

Ye, 2017, *Chem. Sci.*

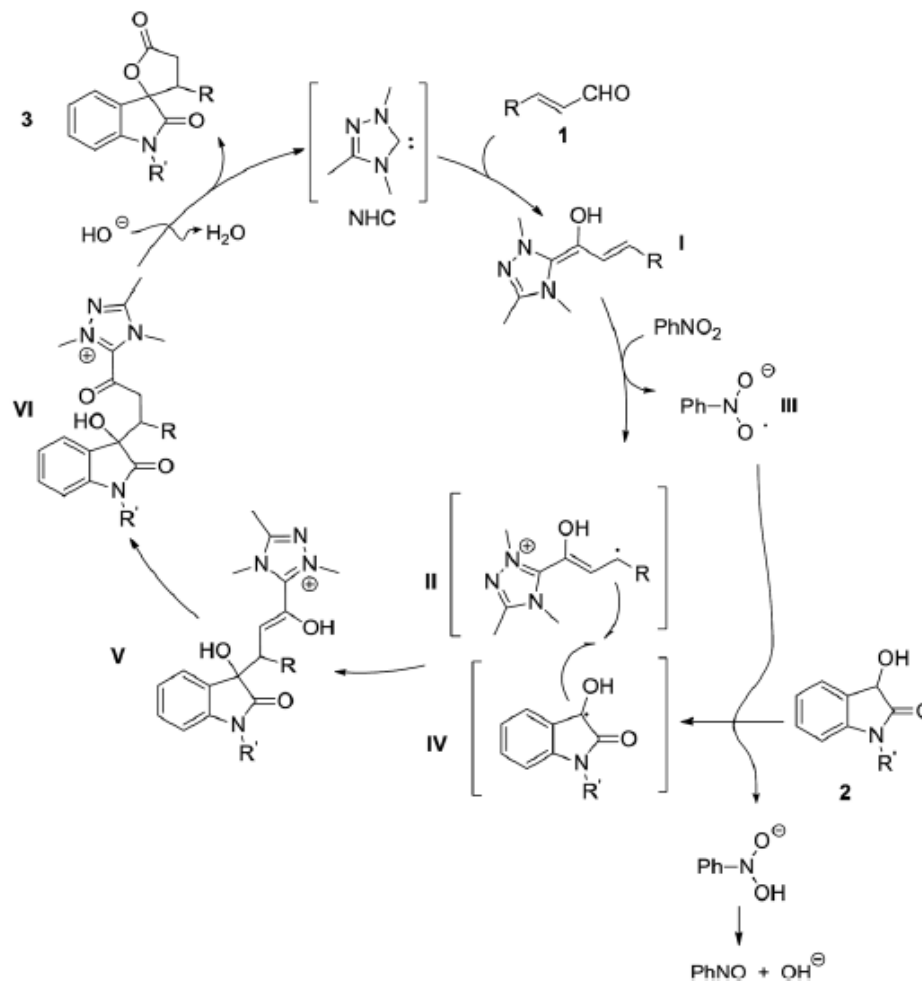
NHC-catalyzed oxidative [3 + 2] annulation of dioxindoles and enals:



3. Reactions of β -carbon centers

Ye, 2017, *Chem. Sci.*

NHC-catalyzed oxidative [3 + 2] annulation of dioxindoles and enals:

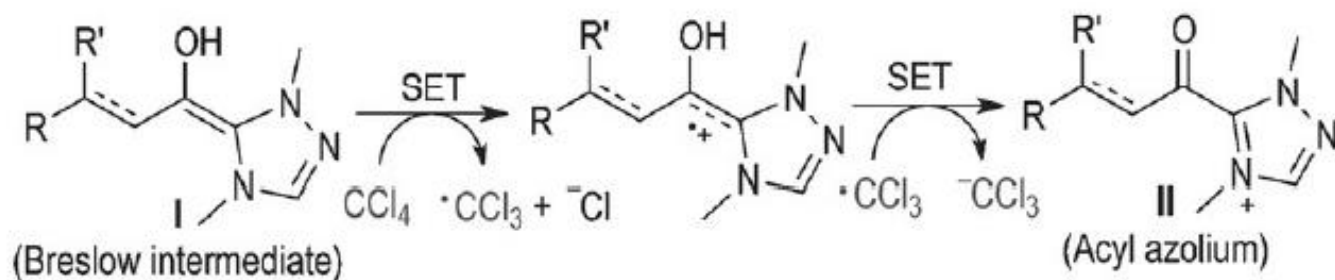


3. Reactions of β -carbon centers

Chi, 2017, *ACIE*

Polyhalides as efficient and mild oxidants for oxidative carbene organocatalysis by radical processes:

c) This work: Simple polyhalides as oxidants by a two-steps SET process.



CCl_4
typical organic
solvent

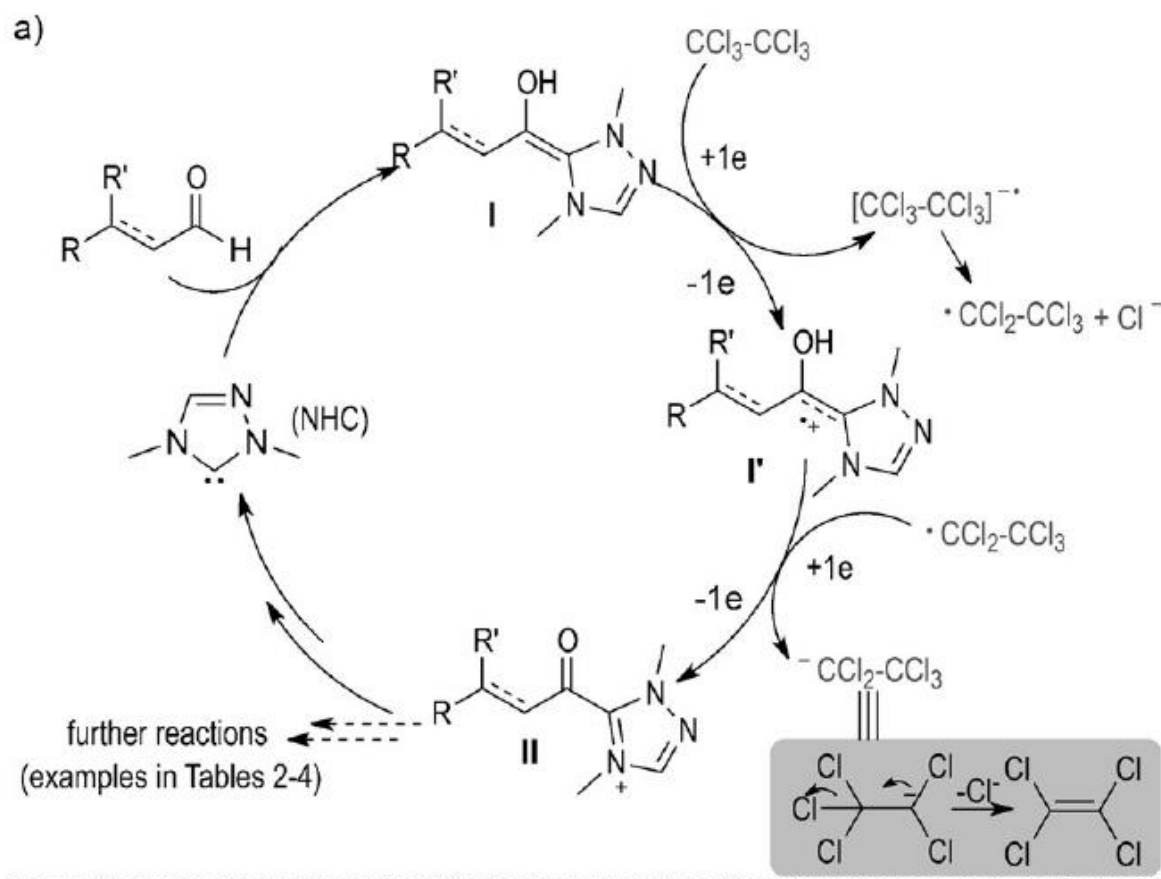
CCl_3CCl_3 (C_2Cl_6)
Sigma-Aldrich ~\$90/500g
Alibaba ~\$1.5/kg

- Simple and inexpensive oxidant
- Easily removable reductant
- Amenable for large-scale synthesis
- SET oxidative pathway

3. Reactions of β -carbon centers

Chi, 2017, *ACIE*

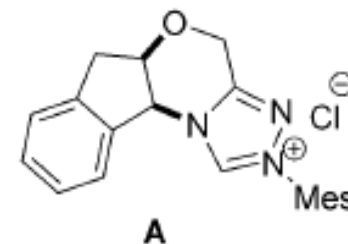
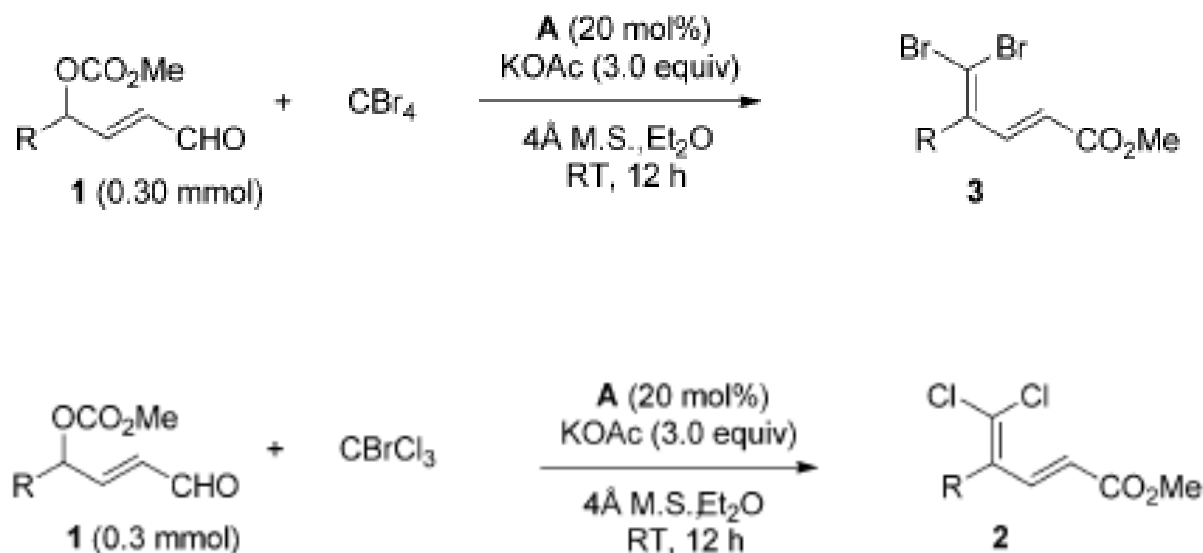
Polyhalides as efficient and mild oxidants for oxidative carbene organocatalysis by radical processes:



3. Reactions of γ -carbon centers

Sun, 2016, *ACIE*

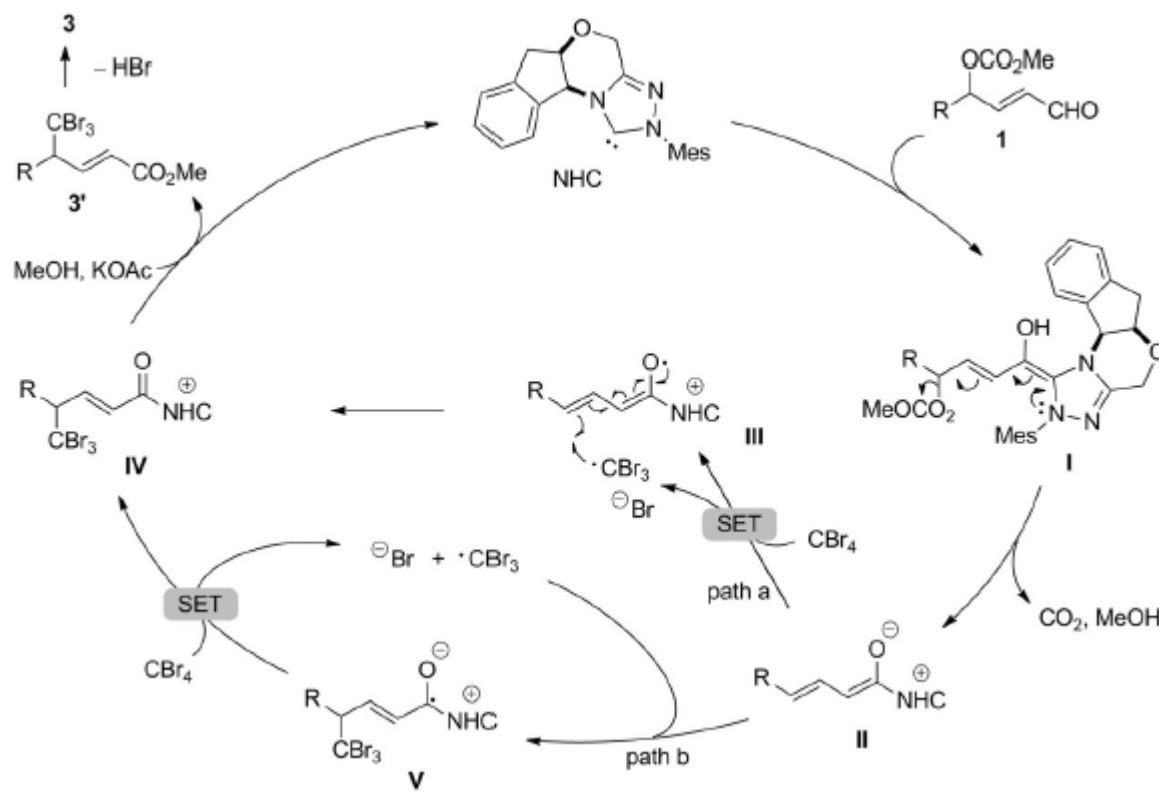
NHC-catalyzed γ -dihalomethylenation of enals by single-electron transfer:



3. Reactions of γ -carbon centers

Sun, 2016, *ACIE*

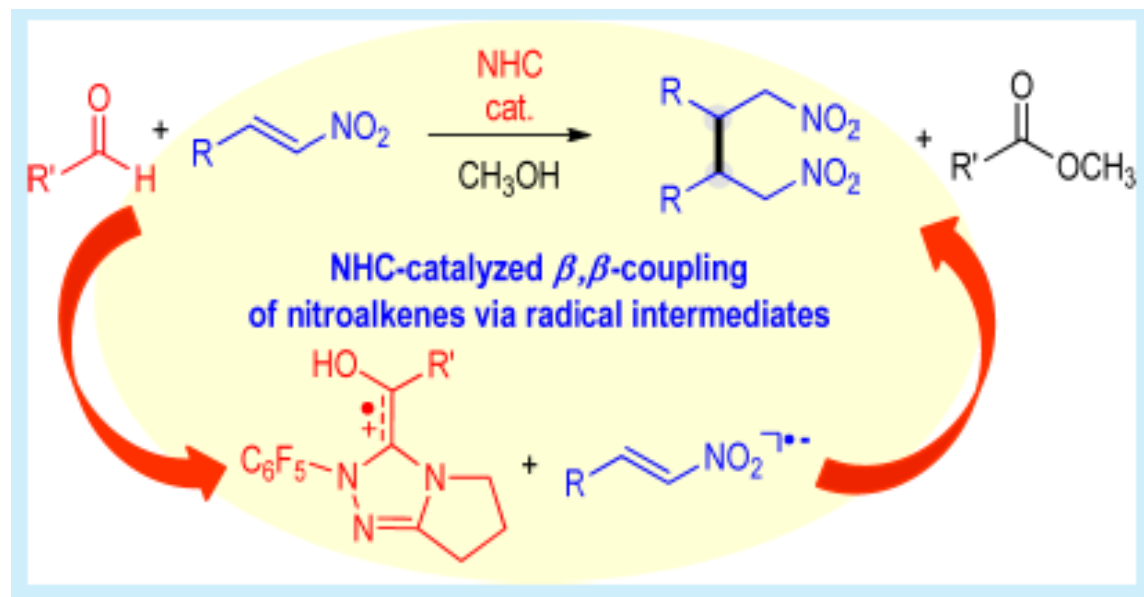
NHC-catalyzed γ -dihalomethylenation of enals by single-electron transfer:



4. Reactions of aldehydes as the terminal reductants

Chi, 2014, *OL*

N-Heterocyclic carbene organocatalytic reductive β,β -coupling reactions of nitroalkenes:

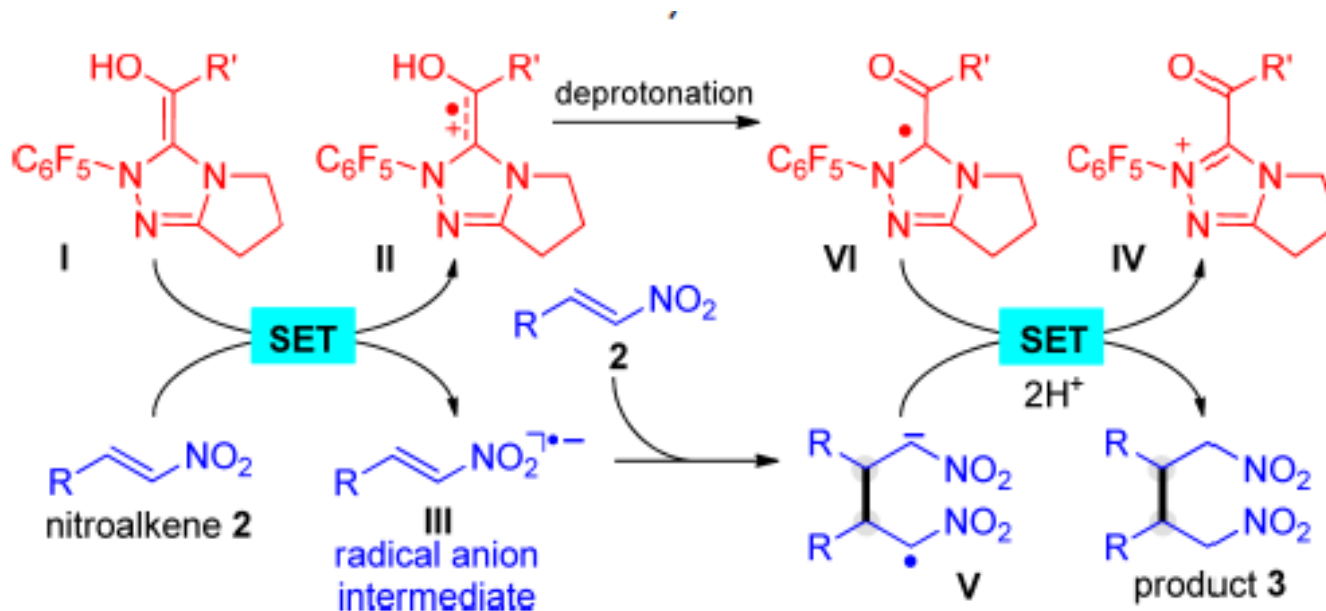


4. Reactions of aldehydes as the terminal reductants

Chi, 2014, *OL*

N-Heterocyclic Carbene Organocatalytic Reductive β,β -Coupling

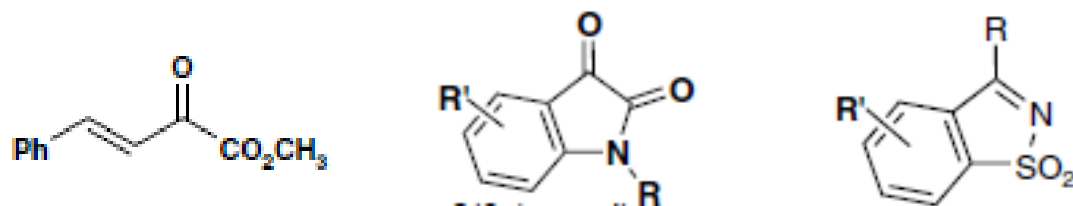
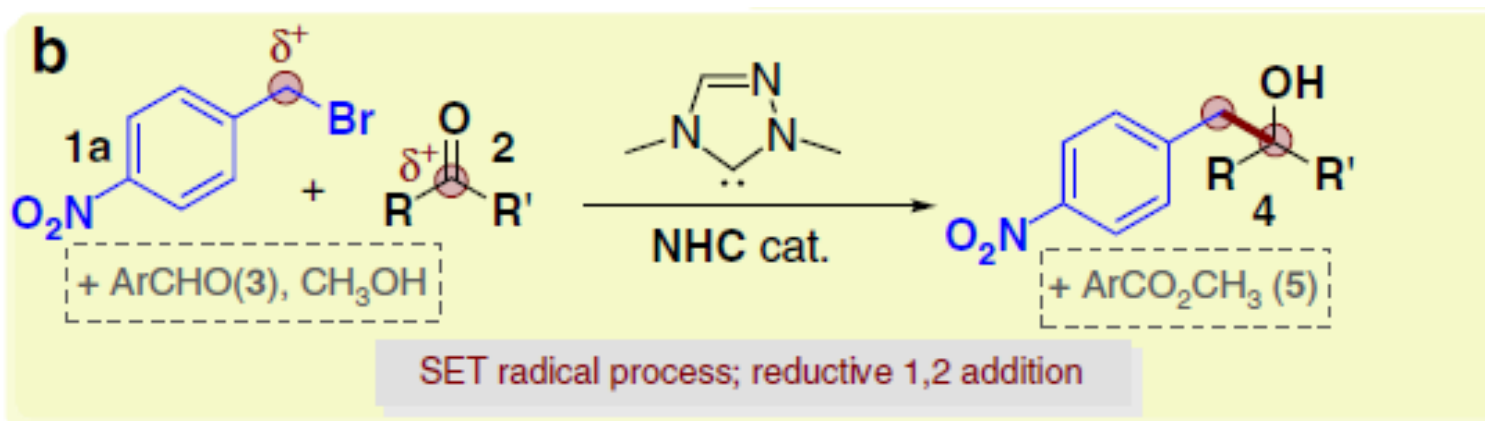
Reactions of Nitroalkenes:



4. Reactions of aldehydes as the terminal reductants

Chi, 2016, NC

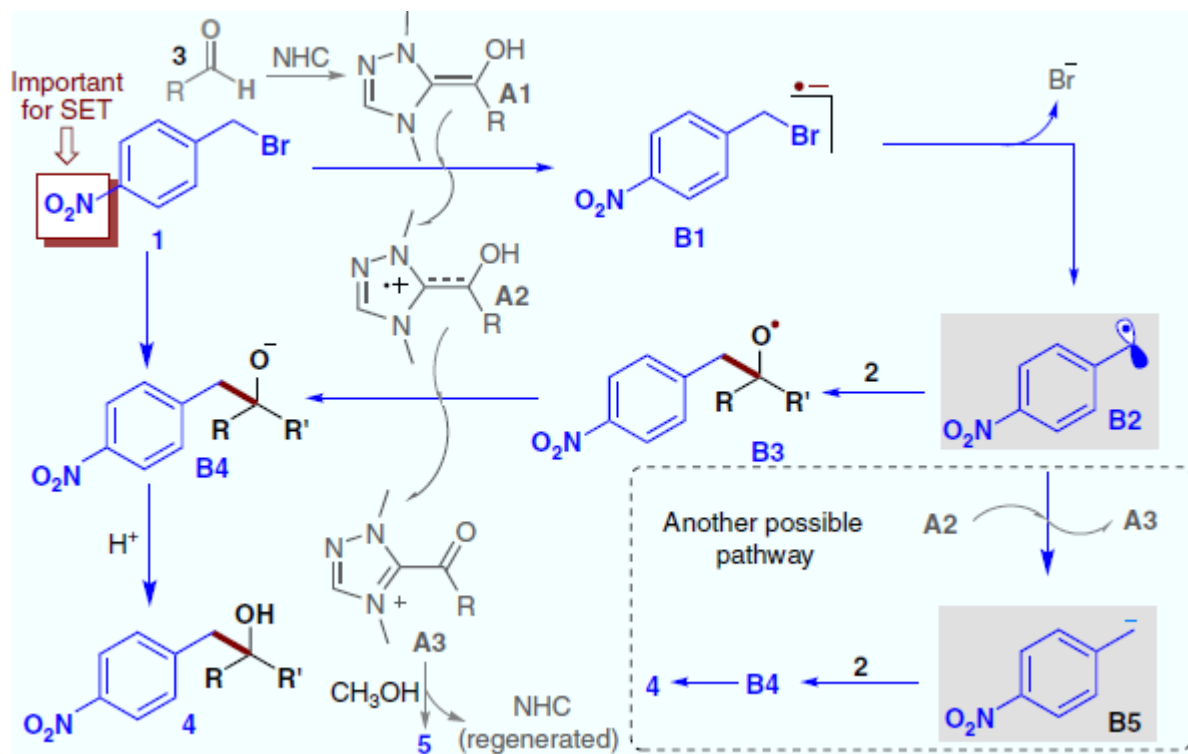
NHC-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines:



4. Reactions of aldehydes as the terminal reductants

Chi, 2016, NC

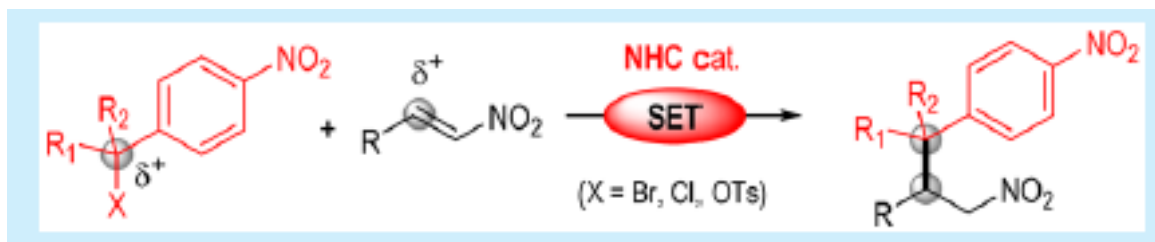
NHC-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines:



4. Reactions of aldehydes as the terminal reductants

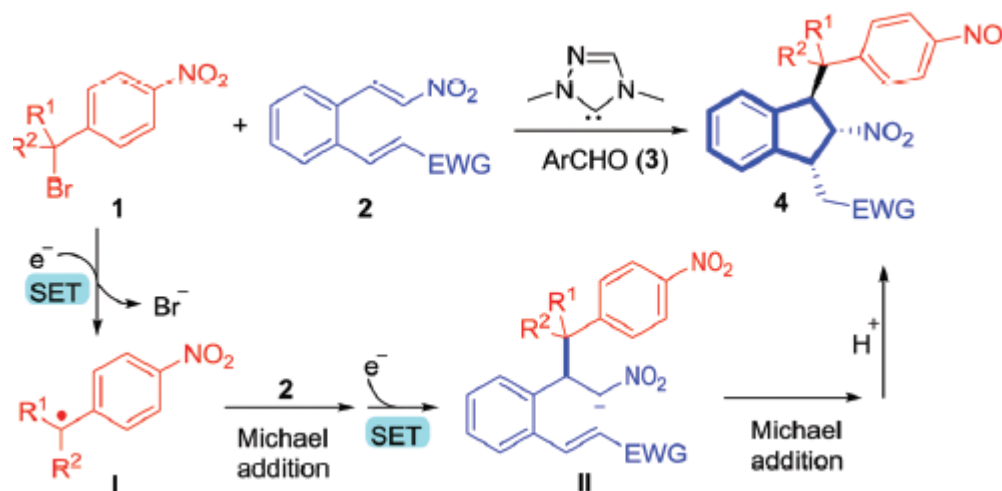
Chi, 2017, *OL*

NHC-catalysed reductive coupling of nitrobenzyl bromide and nitroalkene:



Chi, 2017, *CC*

Synthesis of indanes via NHC-catalyzed single-electron-transfer processes:

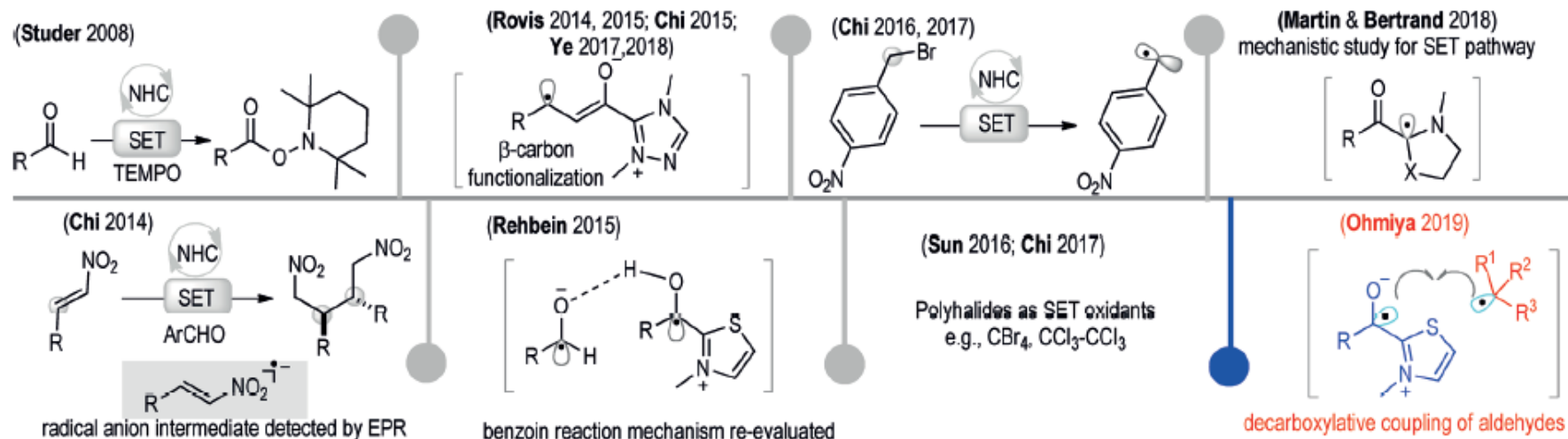


Org. Lett. **2017**, *19*, 632–635

Chem. Commun., **2017**, *53*, 11952--11955

5. Conclusions and outlook

➤ Summary of NHC-catalyzed SET reactions:



➤ Outlook

- ✓ Identification of new SET oxidants (and reductants)
- ✓ Design of new carbene catalysts
- ✓ Assembly of challenging products
- ✓ Mechanistic studies (*J. Am. Chem. Soc.* 2019, 141, 1109–1117)

6. Acknowledgement

Prof. Huang

Dr. Chen

All members in E201

All of you

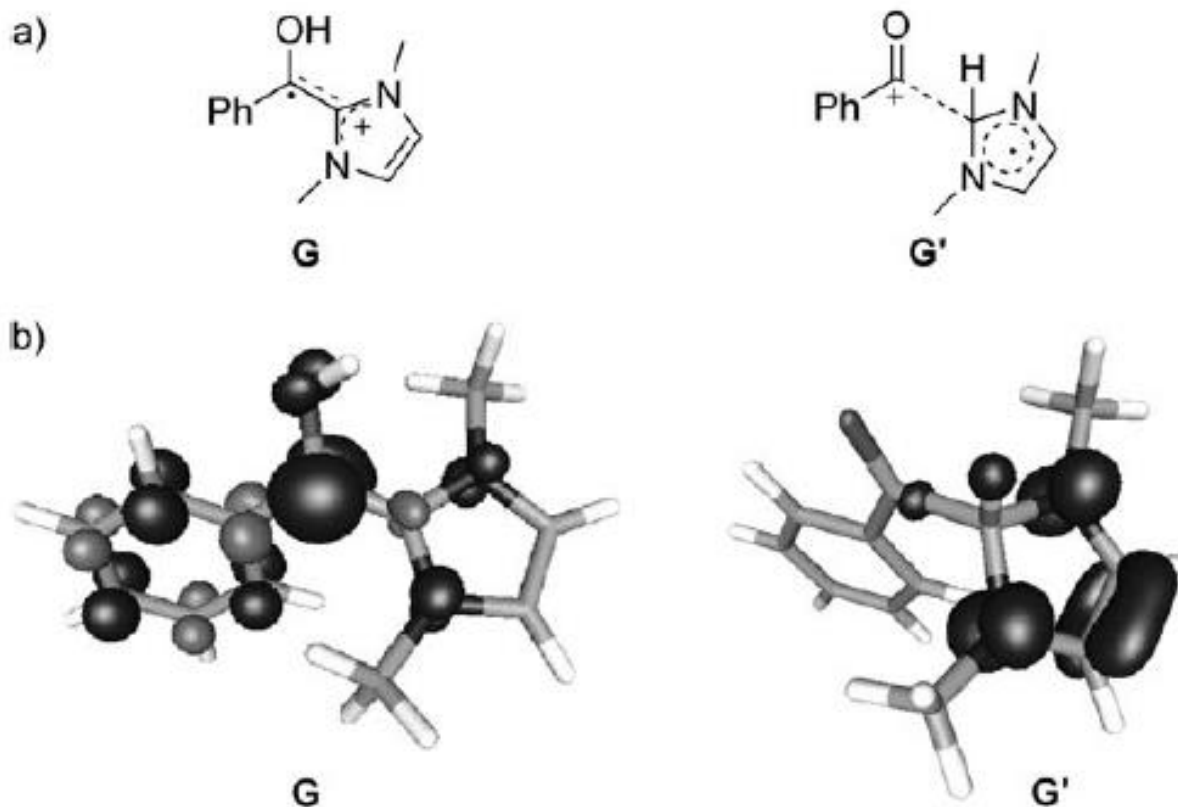


Figure 1. Lewis formulas and calculated structures (PBEh/TZVP) including a plot of the spin-density distribution (isosurface value of 0.01 a.u., positive values in black, negative values in gray) of the two tautomeric forms of the radical cation (**G** and **G'**).

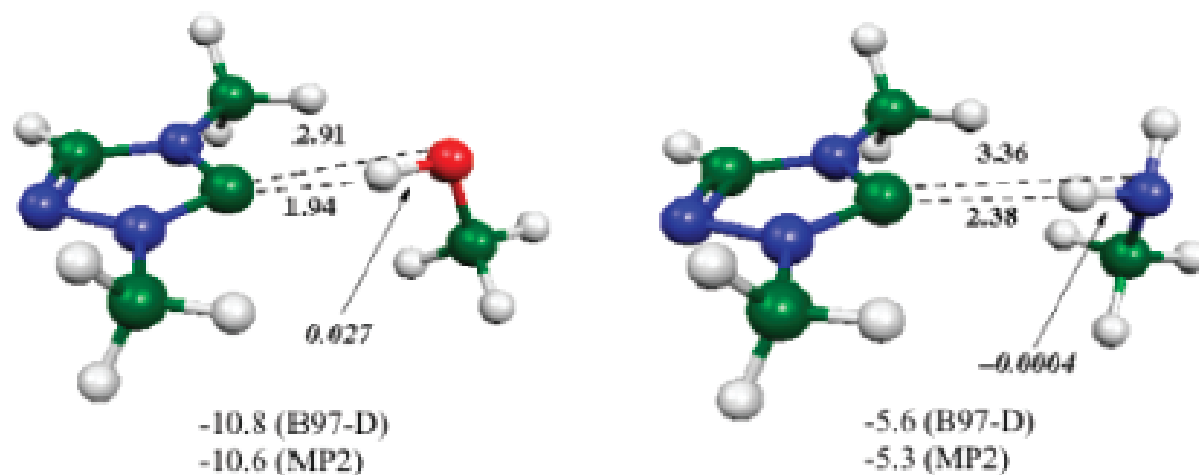


Figure 1. DFT structures (B97-D/TZVPP) of NHC–MeOH (left) and NHC–MeNH₂ complexes (right), and the binding energies (kcal/mol). Intermolecular CH, CO, CN distances in Å. Change of OH, NH lengths relative to free MeOH and MeNH₂ in italics (positive means elongation).

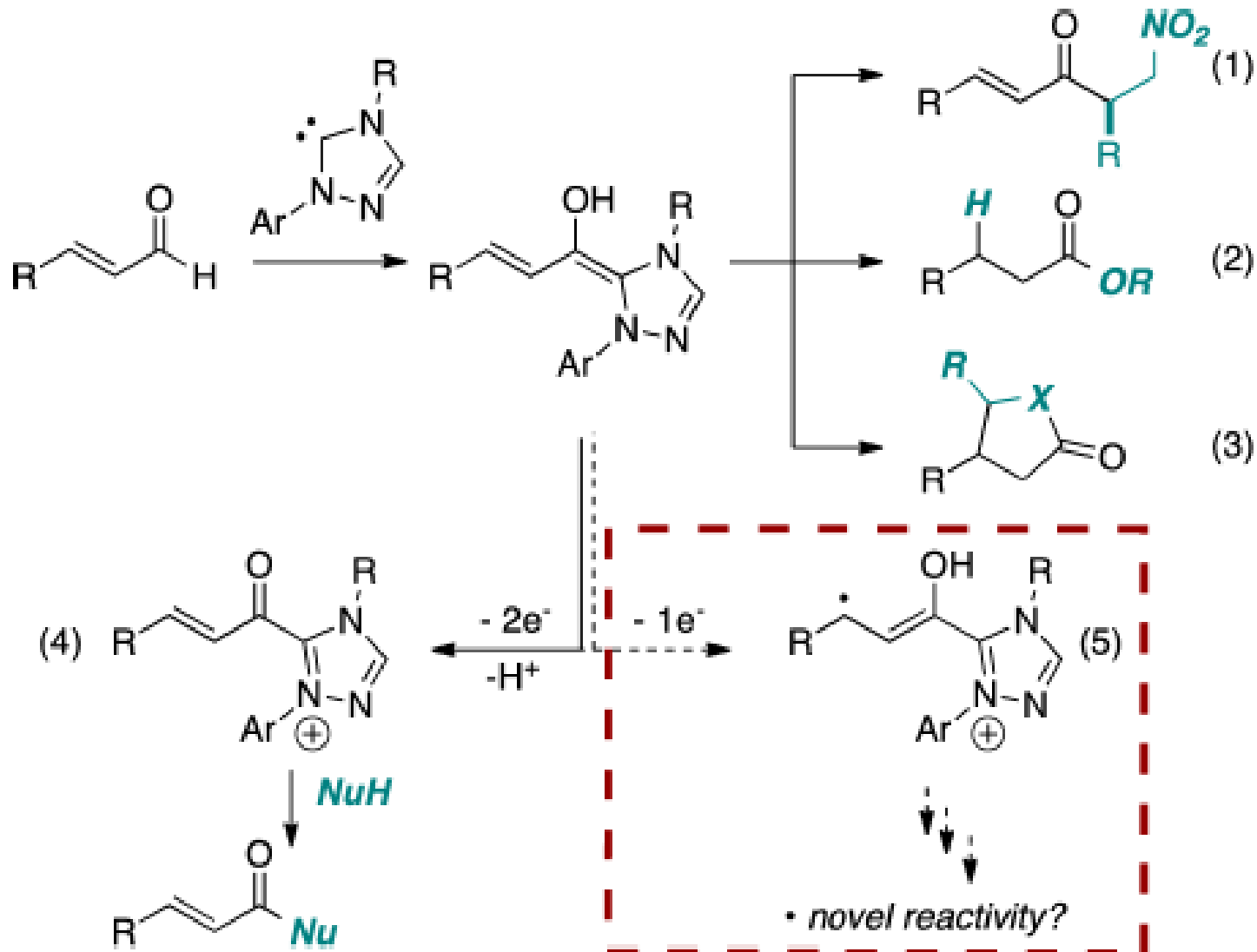


figure 1. Background.

Table 2. Scope of the Racemic Reaction^{a,b}

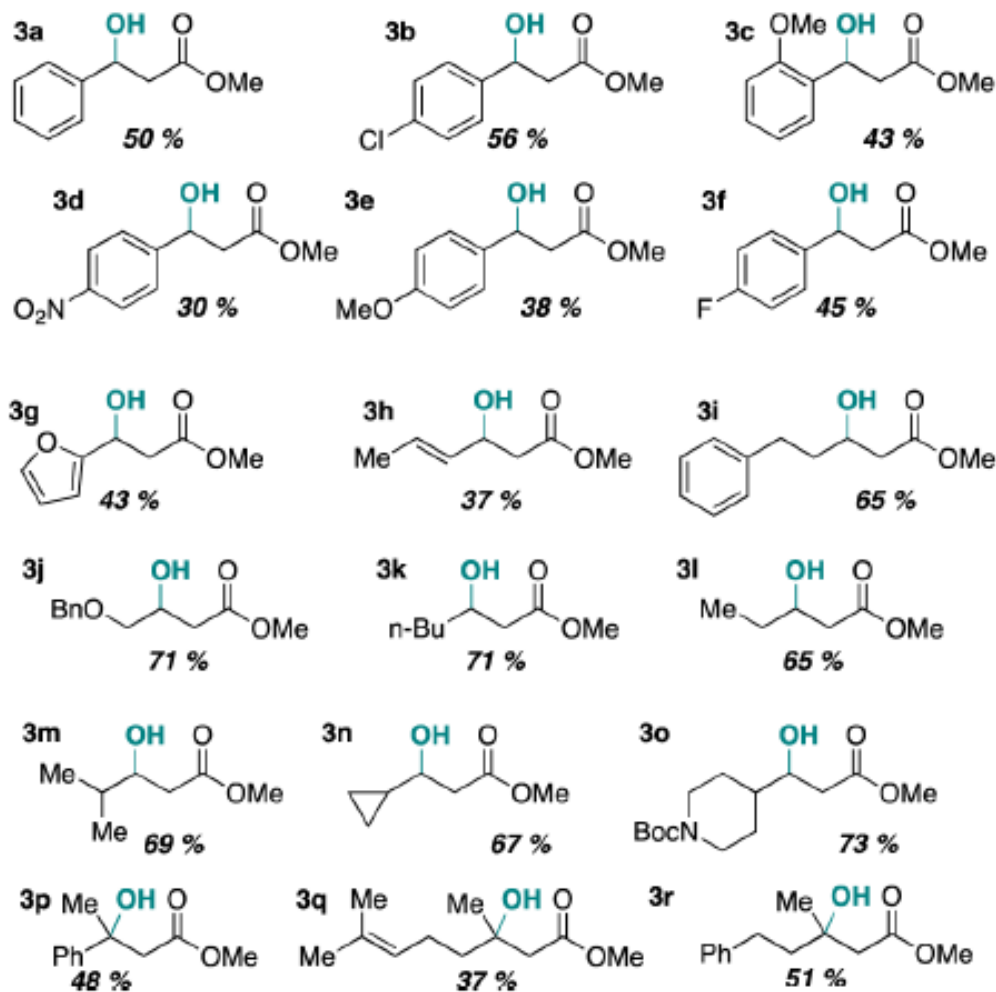
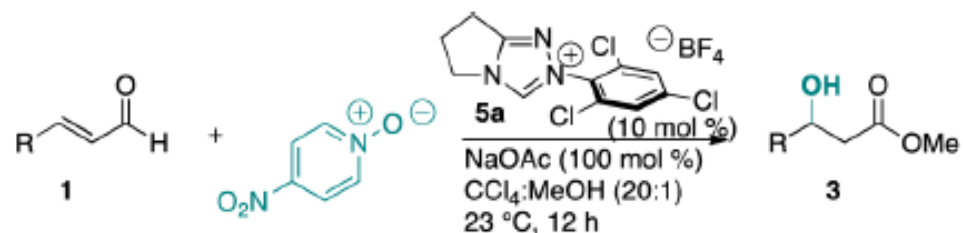
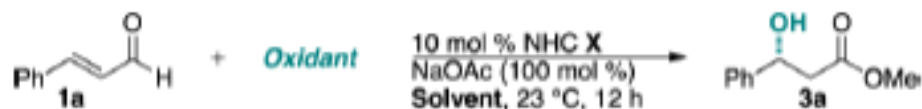


Table 3. Optimization of the Asymmetric Variant^a



entry	NHC	oxidant	solvent	yield (%) ^b	ee (%) ^c
1	5b	2a	MeOH	39	-25
2	5c	2a	MeOH	36	-7
3	5d	2a	MeOH	15	66
4	5e	2a	MeOH	22	0
5	5f	2a	MeOH	42	-8
6	5g	2a	MeOH	51	31
7	5g	2a	DCM/MeOH (20:1)	36	79
8	5g	2a	toluene/MeOH (20:1)	30	87
9	5g	2a	trifluorotoluene/MeOH (20:1)	44	88
10	5g	2a	CCl ₄ /MeOH (20:1)	45	92
11	5g	2d	CCl ₄ /MeOH (20:1)	34	84
12	5g	2e	CCl ₄ /MeOH (20:1)	32	76
13	5g	2f	CCl ₄ /MeOH (20:1)	12	16

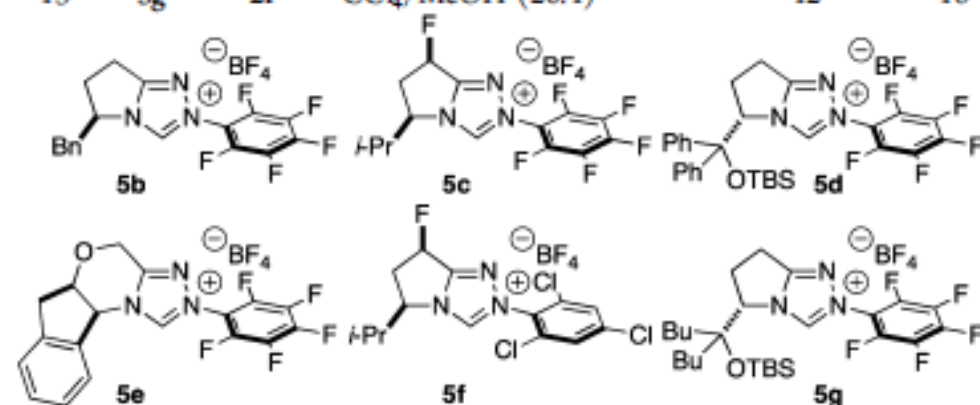
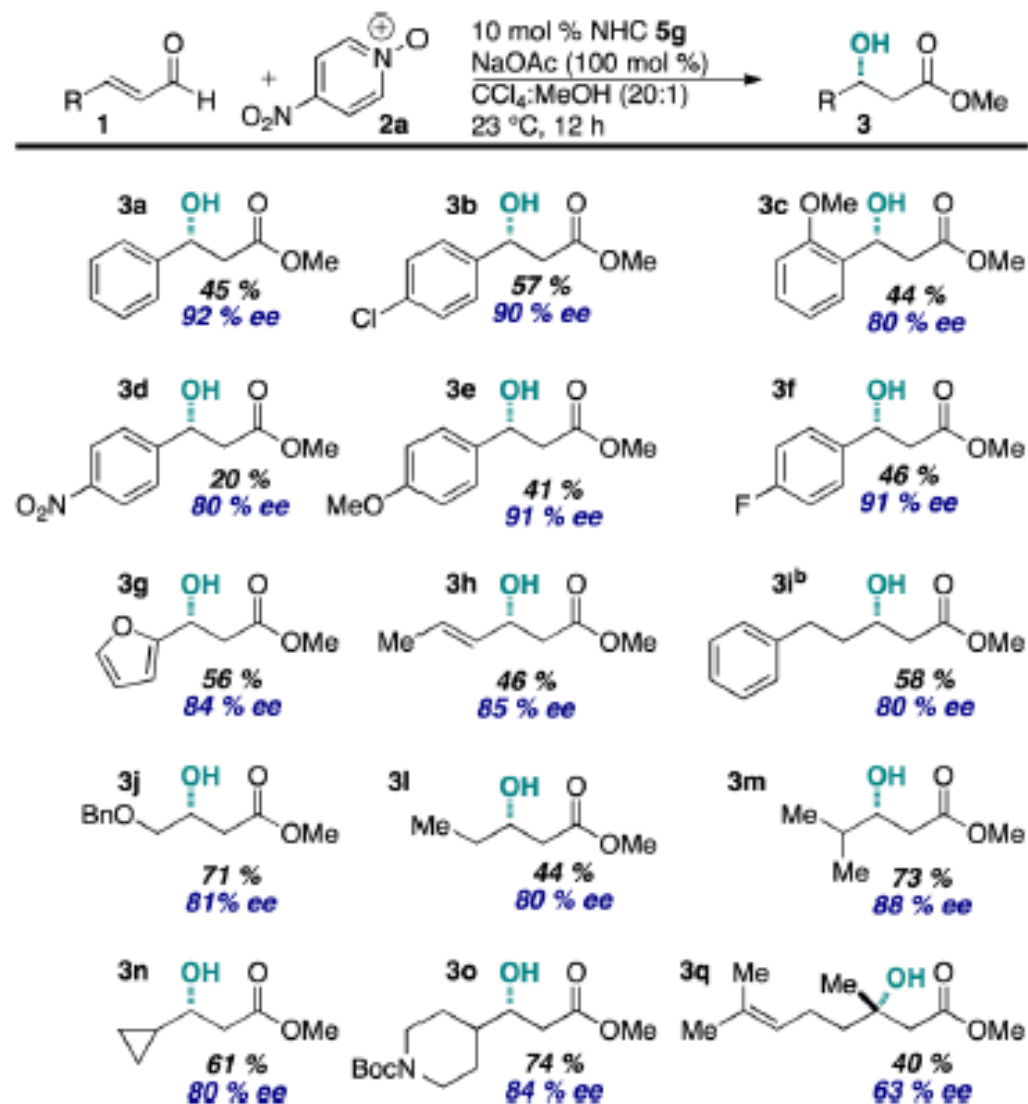


Table 4. Scope of the Asymmetric Reaction^a

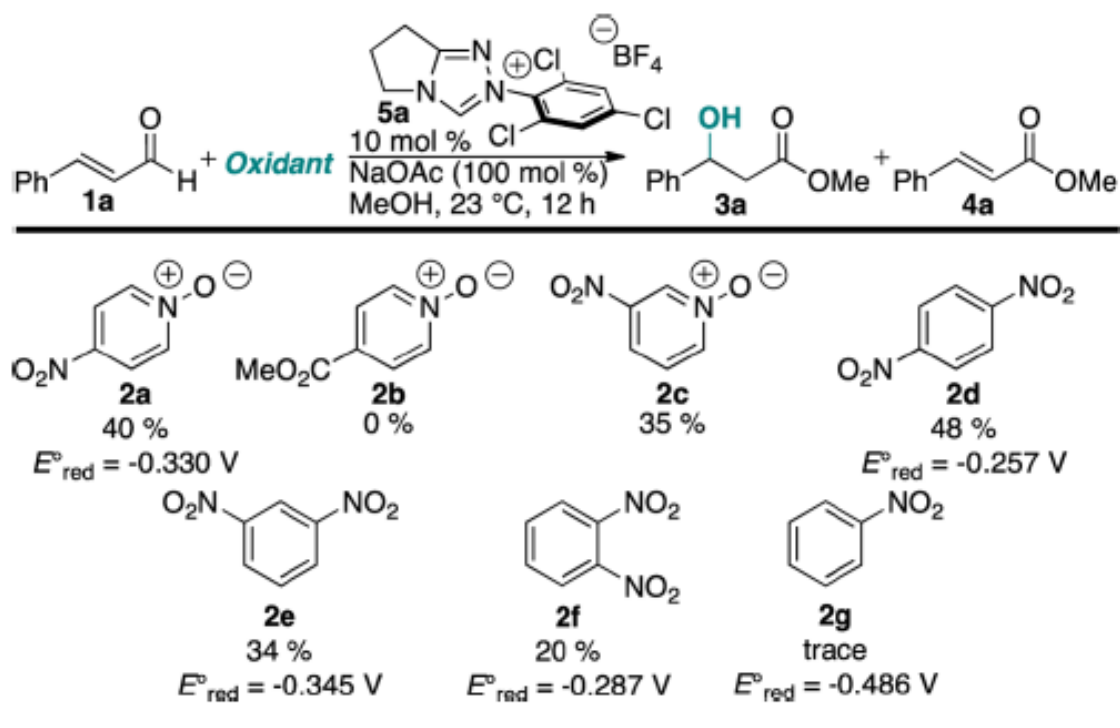


^aSee footnotes *a–c* in Table 3. ^bThe reaction was conducted in PhCF₃/MeOH (20:1).

3. Reactions of β -carbon centers

Rovis, 2014, *JACS*

Enantioselective NHC-catalyzed β -hydroxylation of enals using nitroarenes:

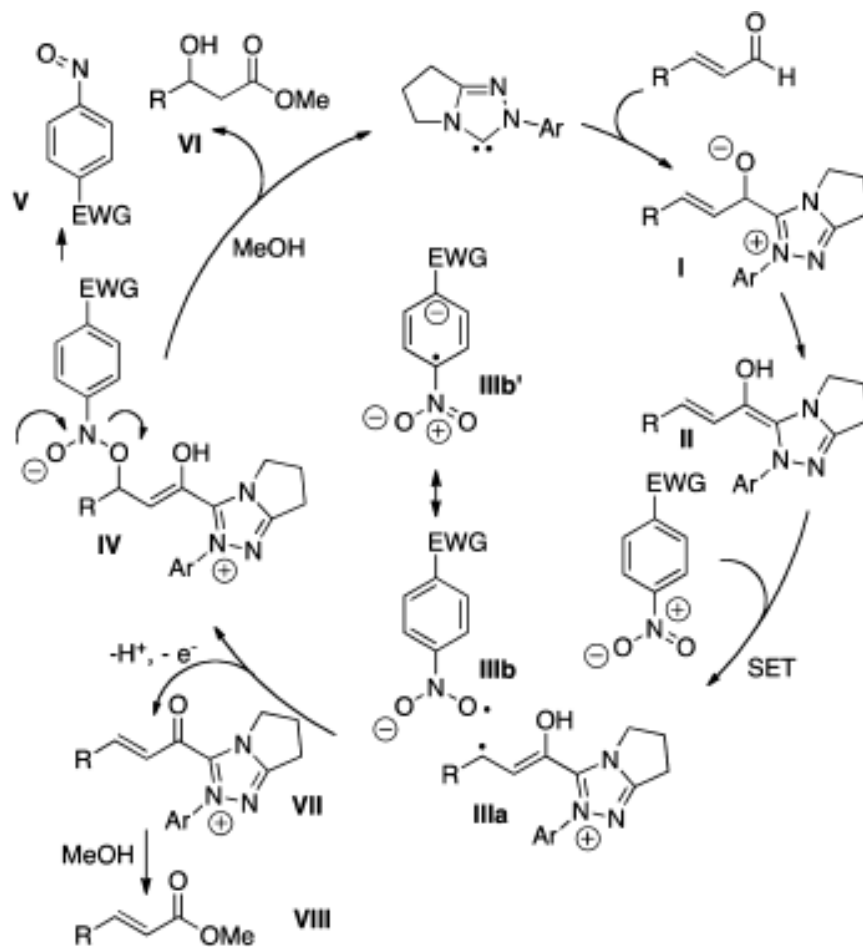


➤ The nitro group in the oxygen transfer step.

3. Reactions of β -carbon centers

Rovis, 2014, *JACS*

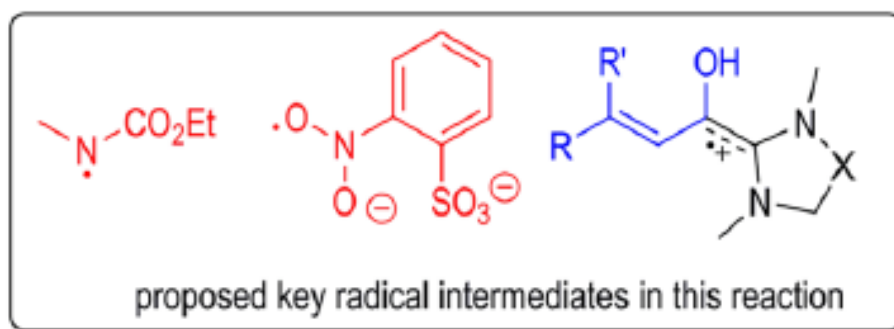
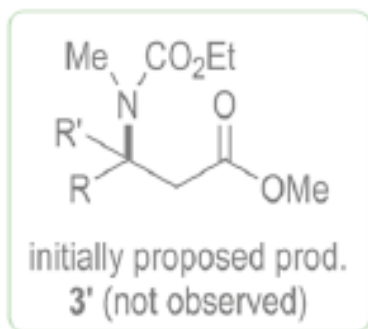
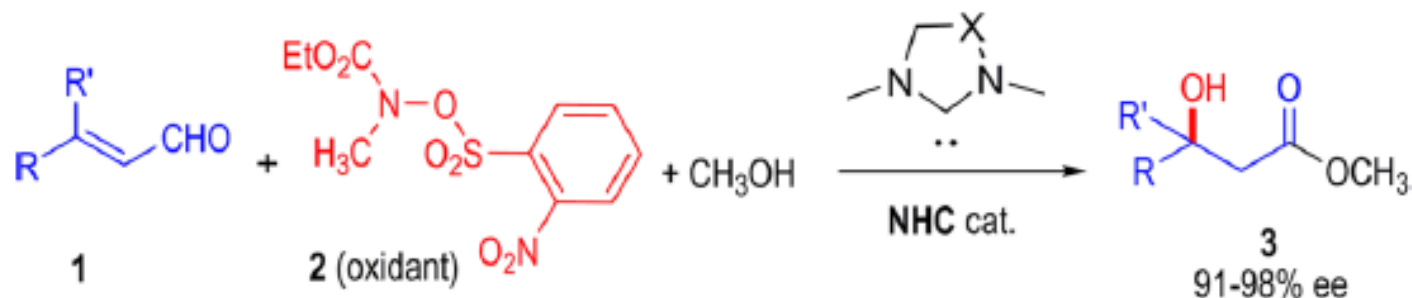
Enantioselective NHC-catalyzed β -hydroxylation of enals using nitroarenes:



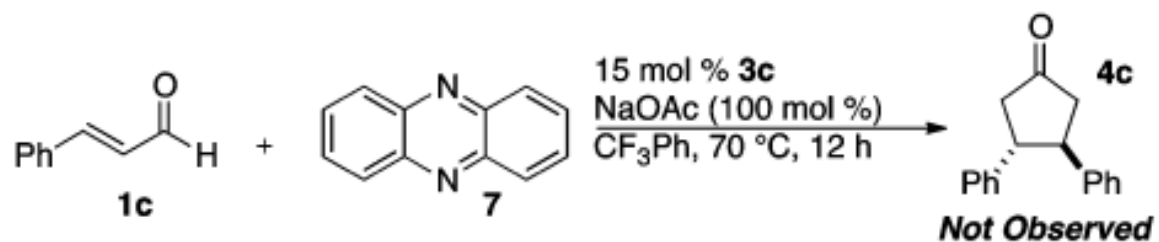
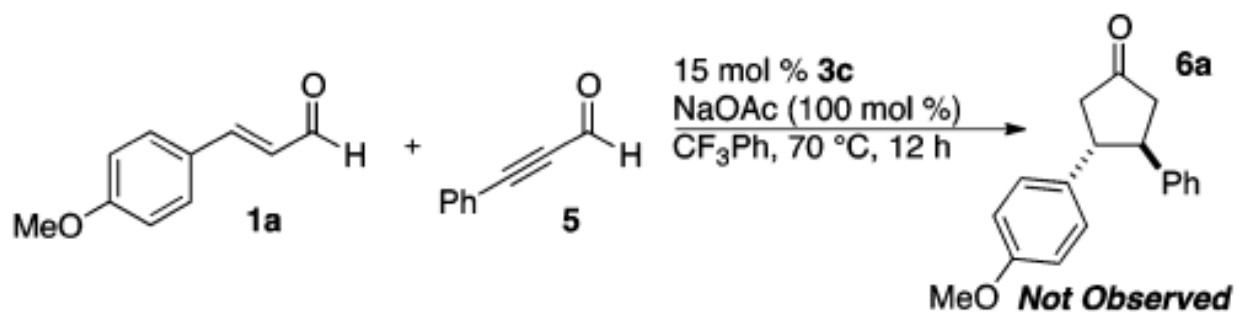
3. Reactions of β -carbon centers

Chi, 2015, *JACS*

N-heterocyclic carbene-catalyzed radical reactions for highly enantioselective β -hydroxylation of enals:



Scheme 2. Control Experiments



•Probing [1,4] Addition to Acyl Azolium

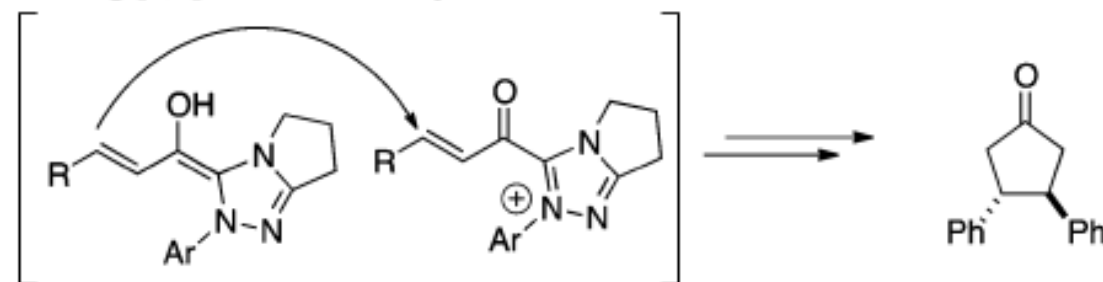
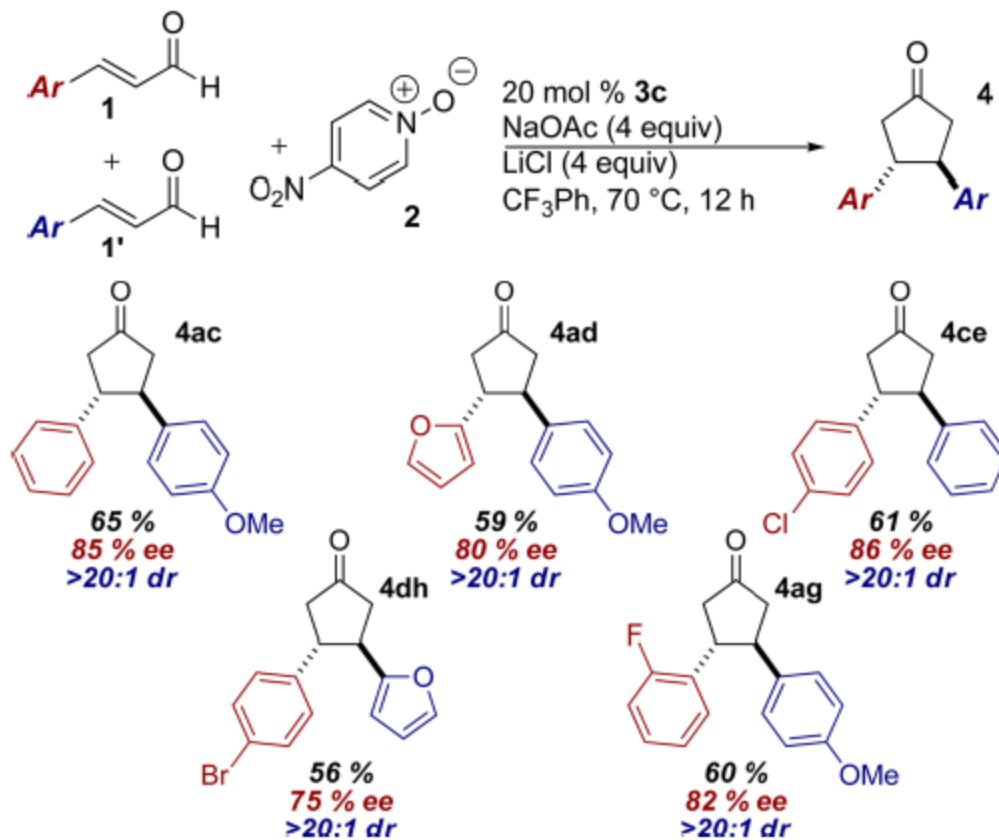


Table 3. Cross-Reaction^{a,b}



^aReactions were carried out with 1.0 equiv of **1**, 4.0 equiv of **1'**, and 4.0 equiv of **2**. ^bSee footnotes b–c in Table 1.