



Seminar

Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes

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Supervisor: Prof. Junliang Zhang

2024.3.29

1. Introduction
2. Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes
 - 2.1 Redox-neutral dialkylation of unactivated alkenes
 - 2.2 Reductive dialkylation of unactivated alkenes
3. Summary and Outlook

1. Introduction

2. Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes

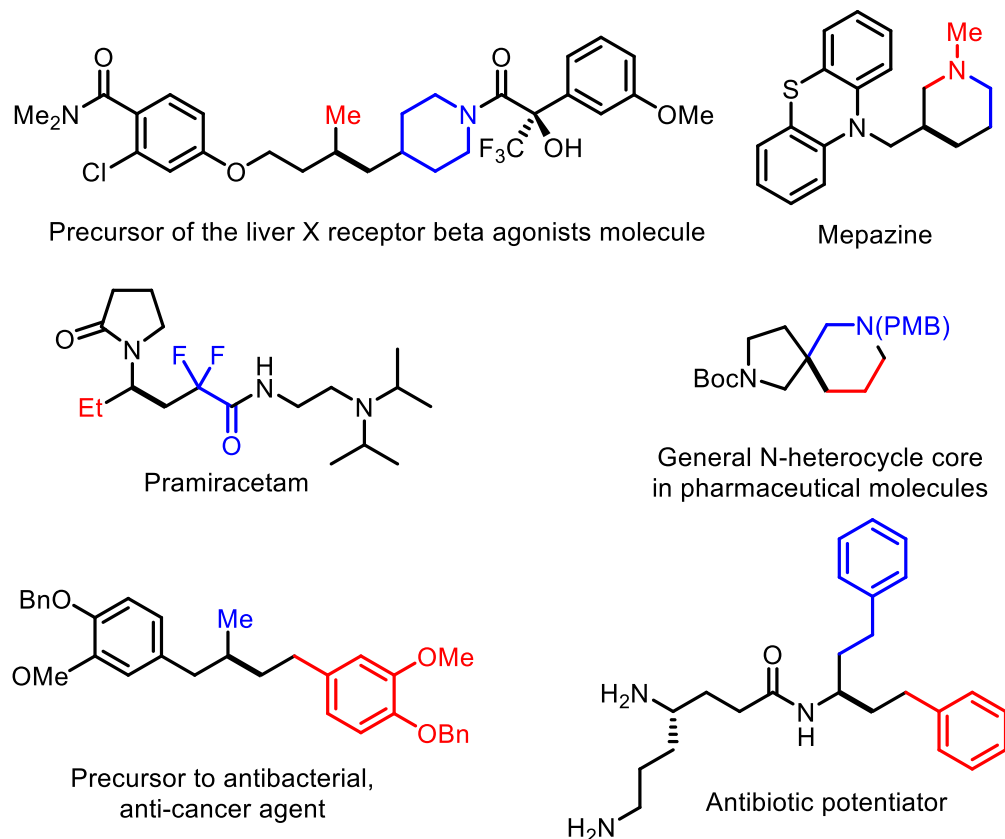
2.1 Redox-neutral dialkylation of unactivated alkenes

2.2 Reductive dialkylation of unactivated alkenes

3. Summary and Outlook

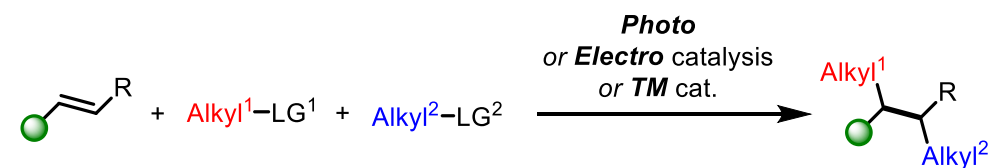
1.1 Three-component dialkylation of alkenes

Bioactive molecular framework

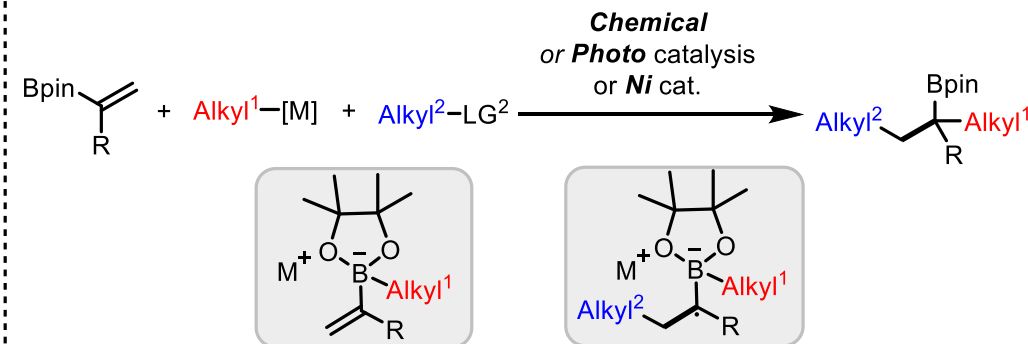


General strategies

Three-component dialkylation of alkenes with differential alkylation reagents



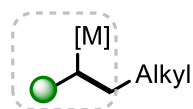
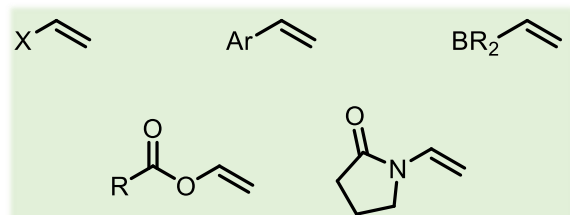
1,2-Migrations of vinylboron ate complexes



presynthesis of vinylboron ate complexes

1.1 Three-component dialkylation of alkenes

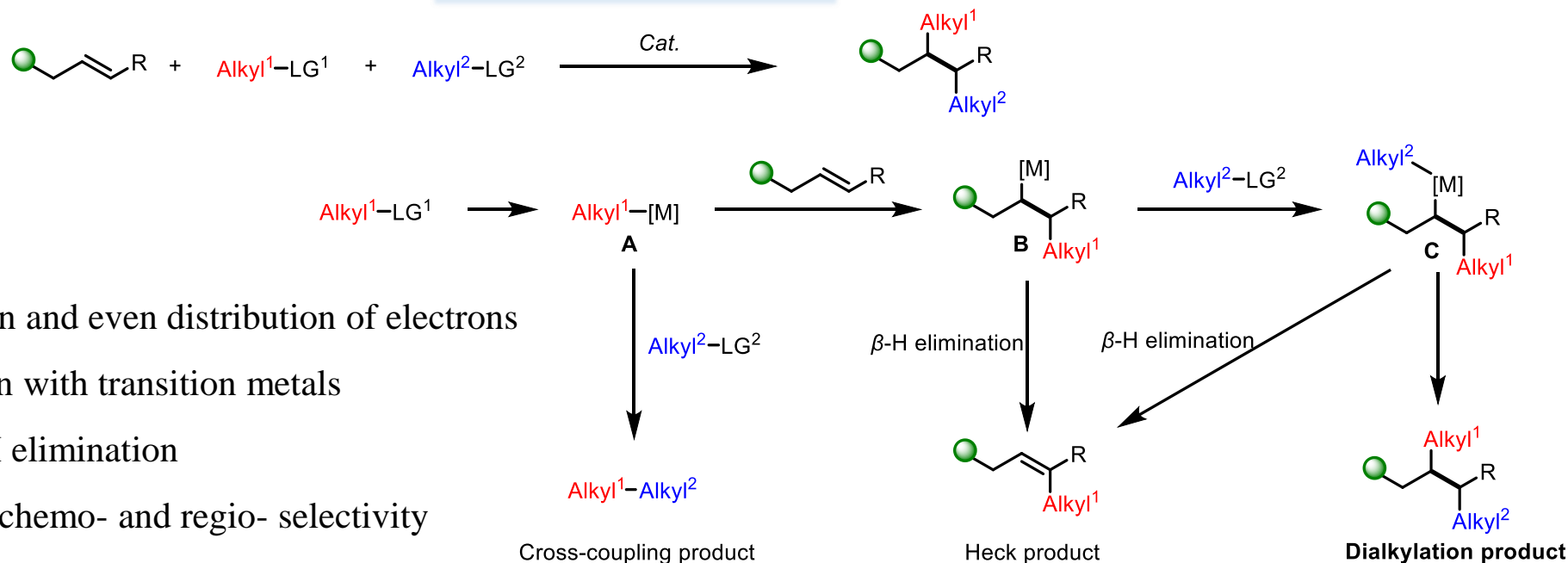
Activated alkenes



Conjugated-stabilized C-[M]

- High polarization
- Good reactivity and regioselectivity
- Be not prone to β -H elimination

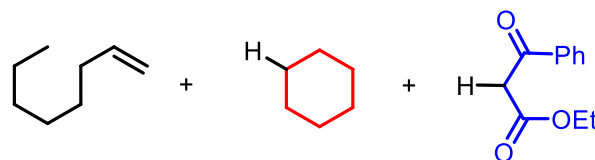
Unactivated alkenes



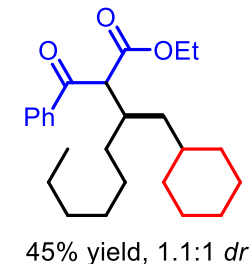
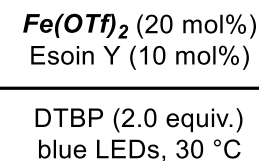
1.2 Three-component dialkylation of unactivated alkenes

The first example catalyzed by Ni
The development: **Seminar content**

Li group (2019)



Only one example

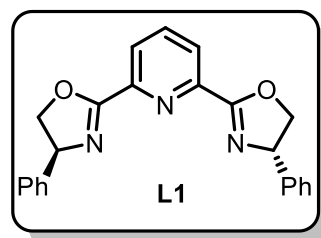
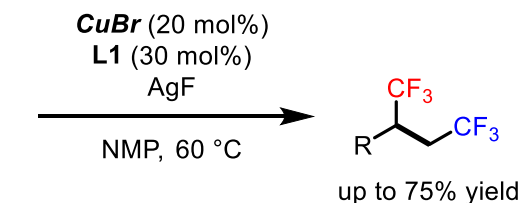
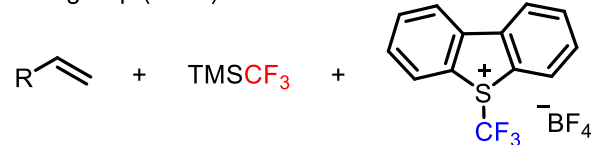


2018
Ni catalysis

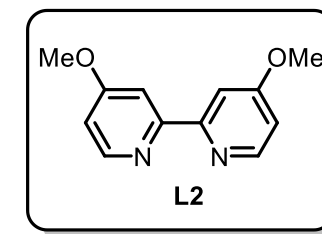
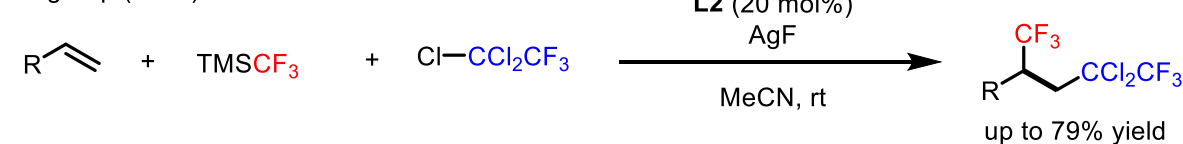
2019
Fe catalysis

2019
Cu catalysis

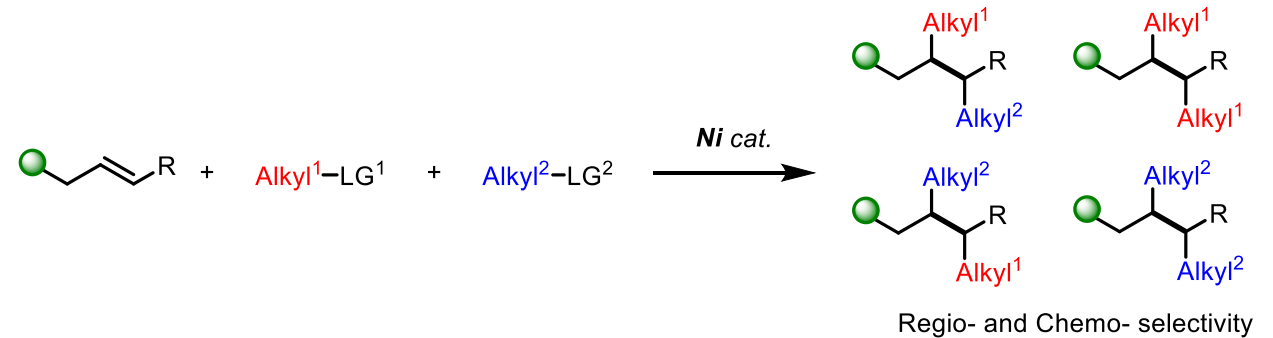
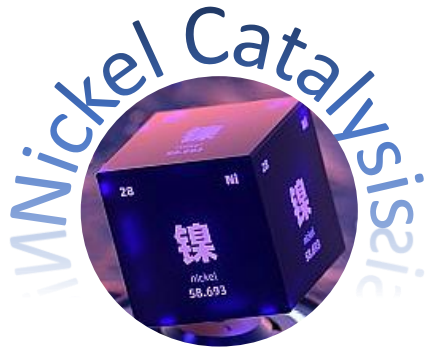
Lee group (2019)



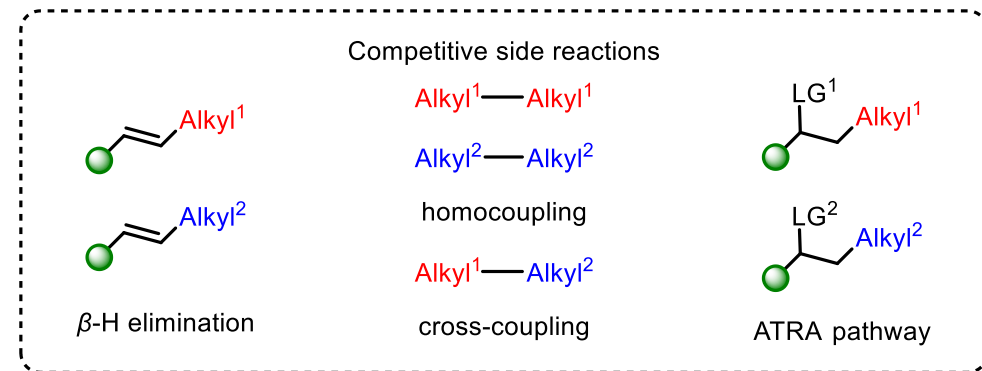
Li group (2019)



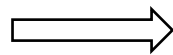
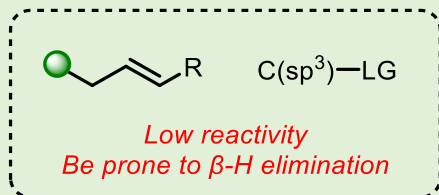
1.3 Ni-catalyzed three-component dialkylation of unactivated alkenes



- Earth-abundant
- Multiple oxidation states (Ni⁰-Ni^{IV})
- Excellent coordination ability
- Relatively slow β -H elimination process



Major difficulties are from:



Challenges:

- Low reactivity and poor catalytic efficiency
- Competitive side reactions via β -H elimination, atom transfer radical addition and homocoupling
- Hard to control regio- and chemo- selectivity

1. Introduction

2. Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes

2.1 Redox-neutral dialkylation of unactivated alkenes

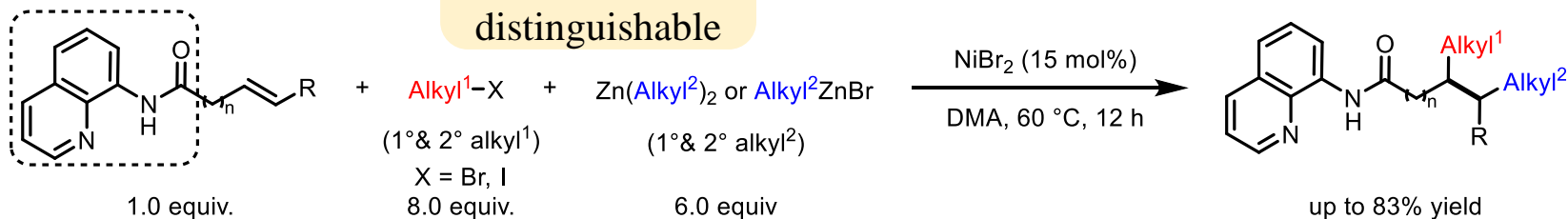
2.2 Reductive dialkylation of unactivated alkenes

3. Summary and Outlook

2.1 Redox-neutral dialkylation of unactivated alkenes

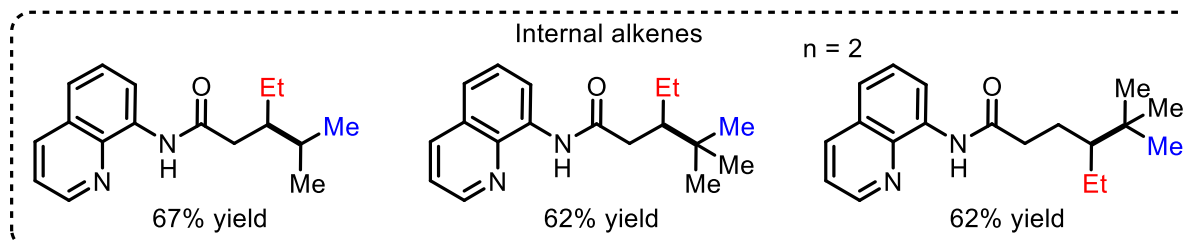
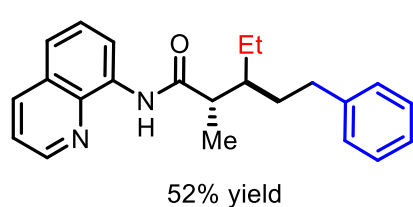
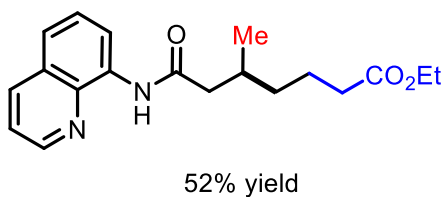
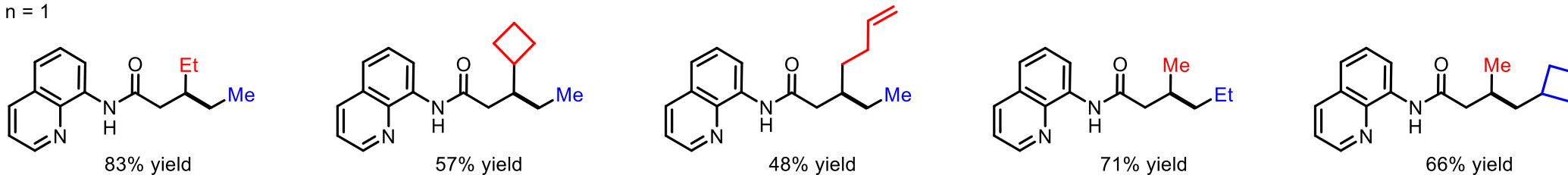
Engle group (2018)

electronically distinguishable

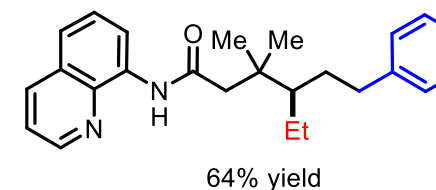
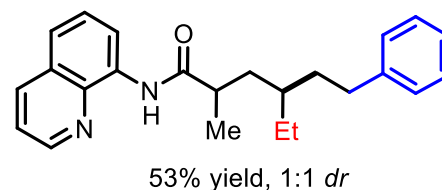
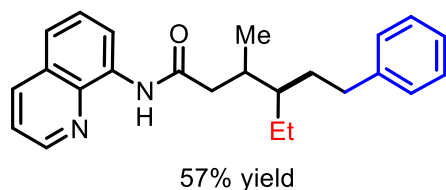
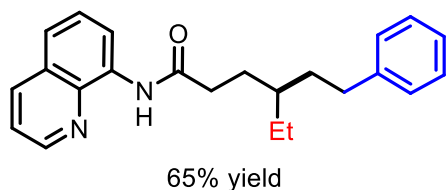


Selected examples

n = 1

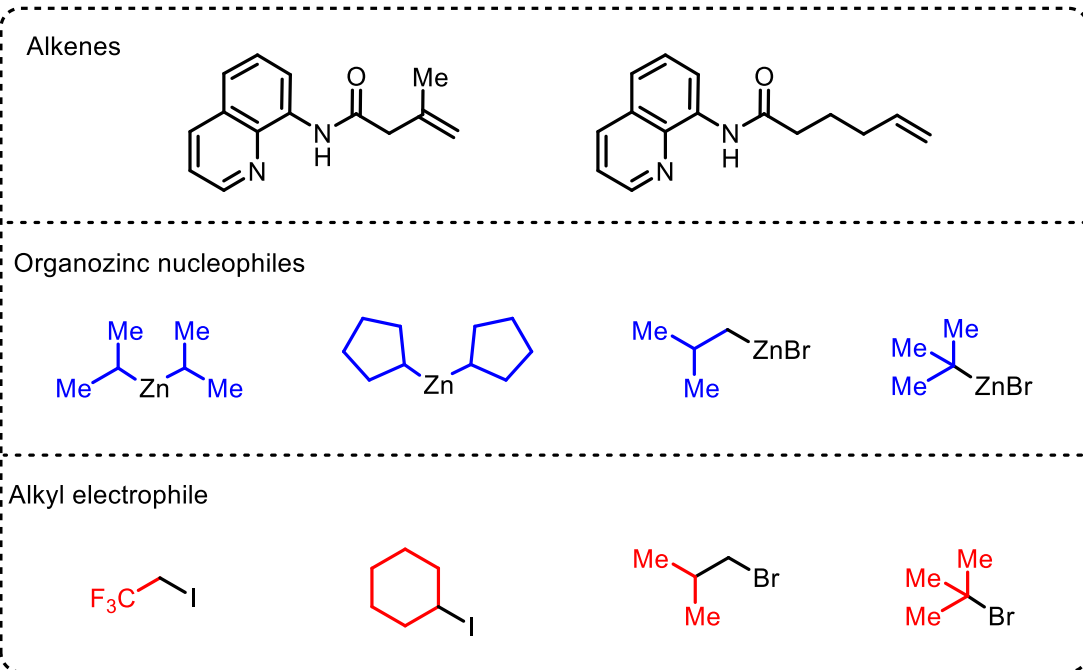


n = 2



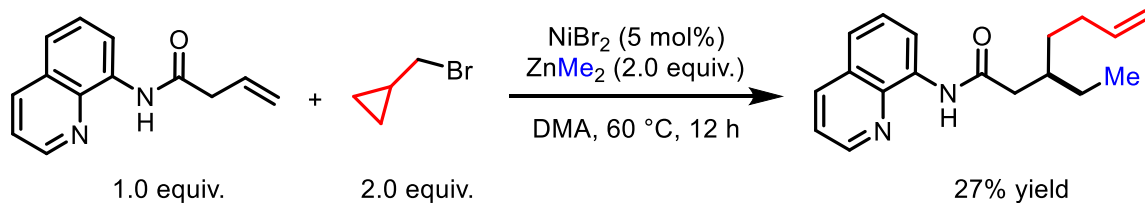
2.1 Redox-neutral dialkylation of unactivated alkenes

Unsuccessful examples

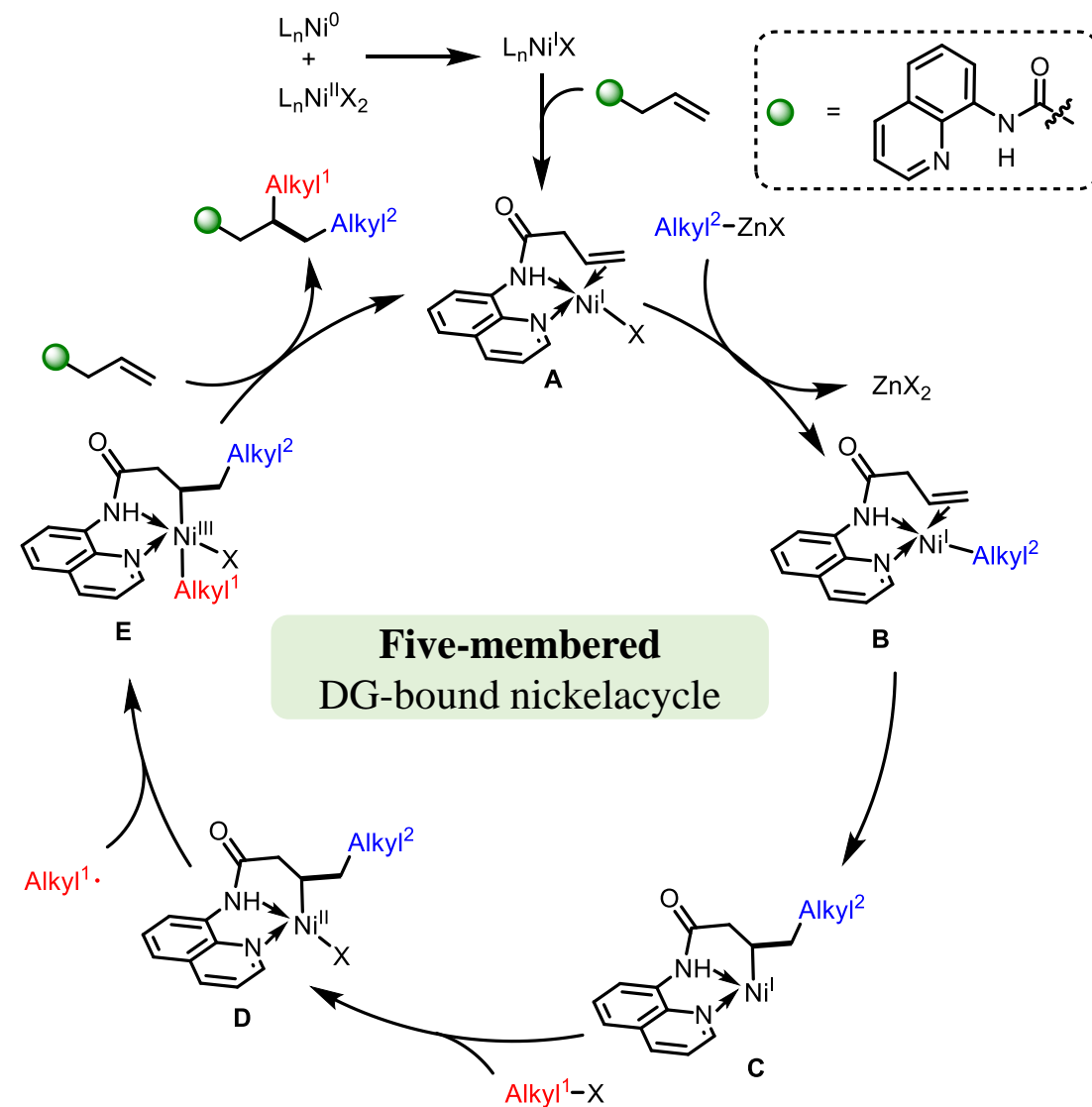


The Mechanistic Experiments

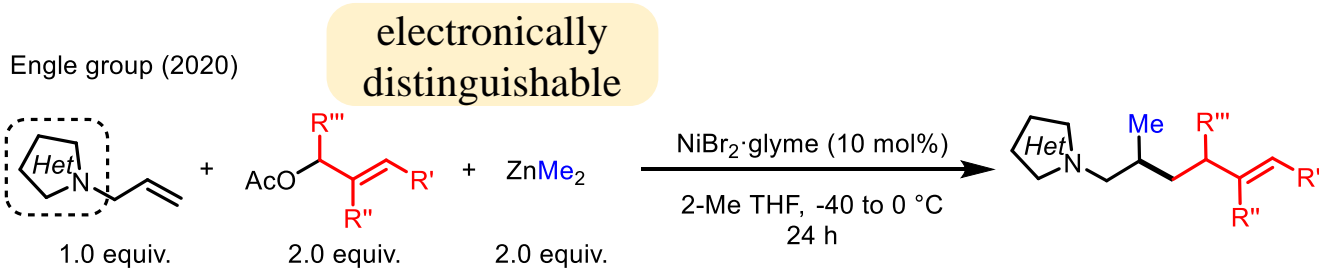
Radical clock experiment



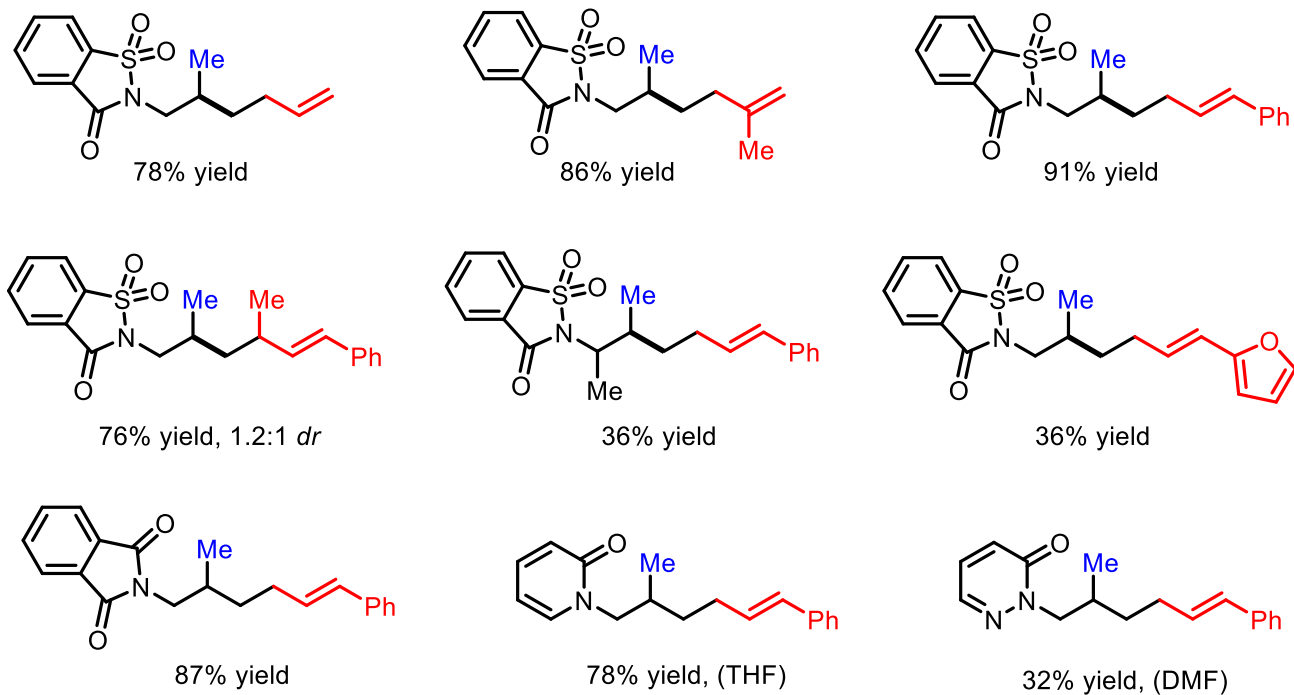
Proposed Mechanism



2.1 Redox-neutral dialkylation of unactivated alkenes

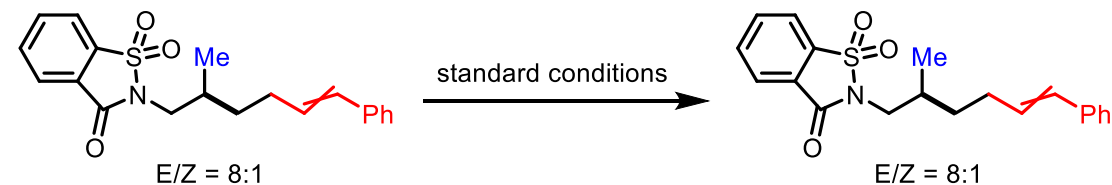
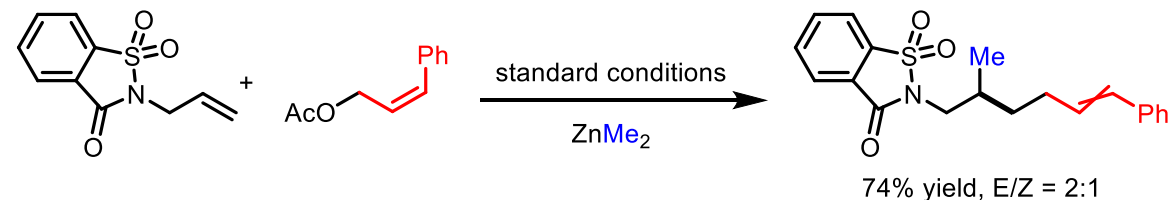


Selected examples

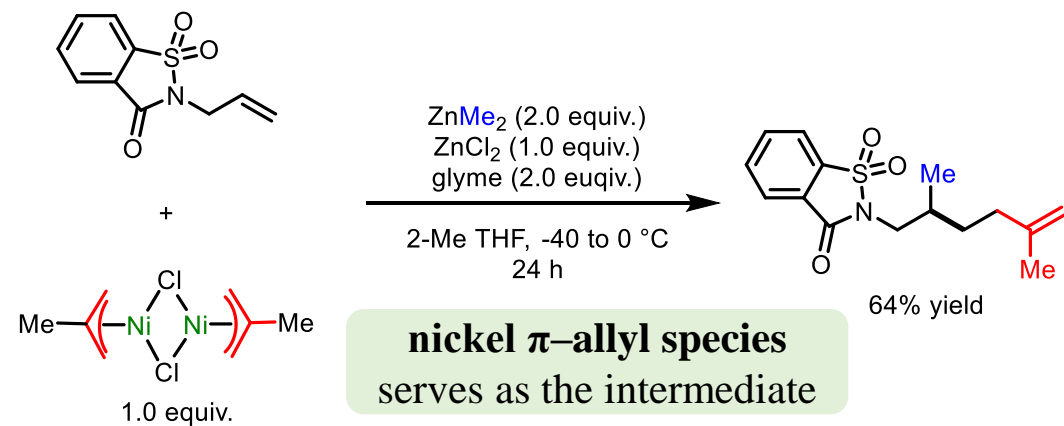


The Mechanistic Experiments

Probing isomerization

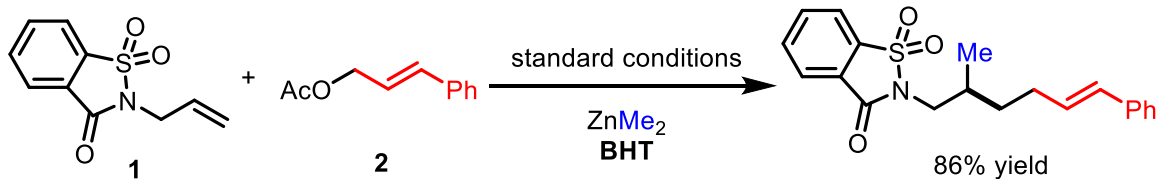


Reactivity of stoichiometric π -allyl complex

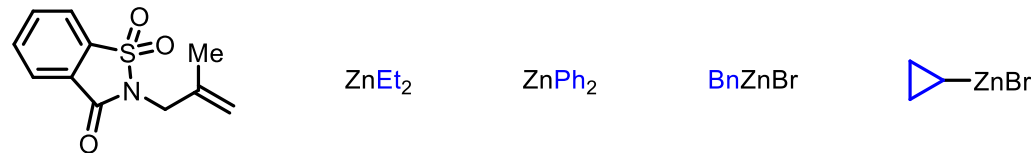


2.1 Redox-neutral dialkylation of unactivated alkenes

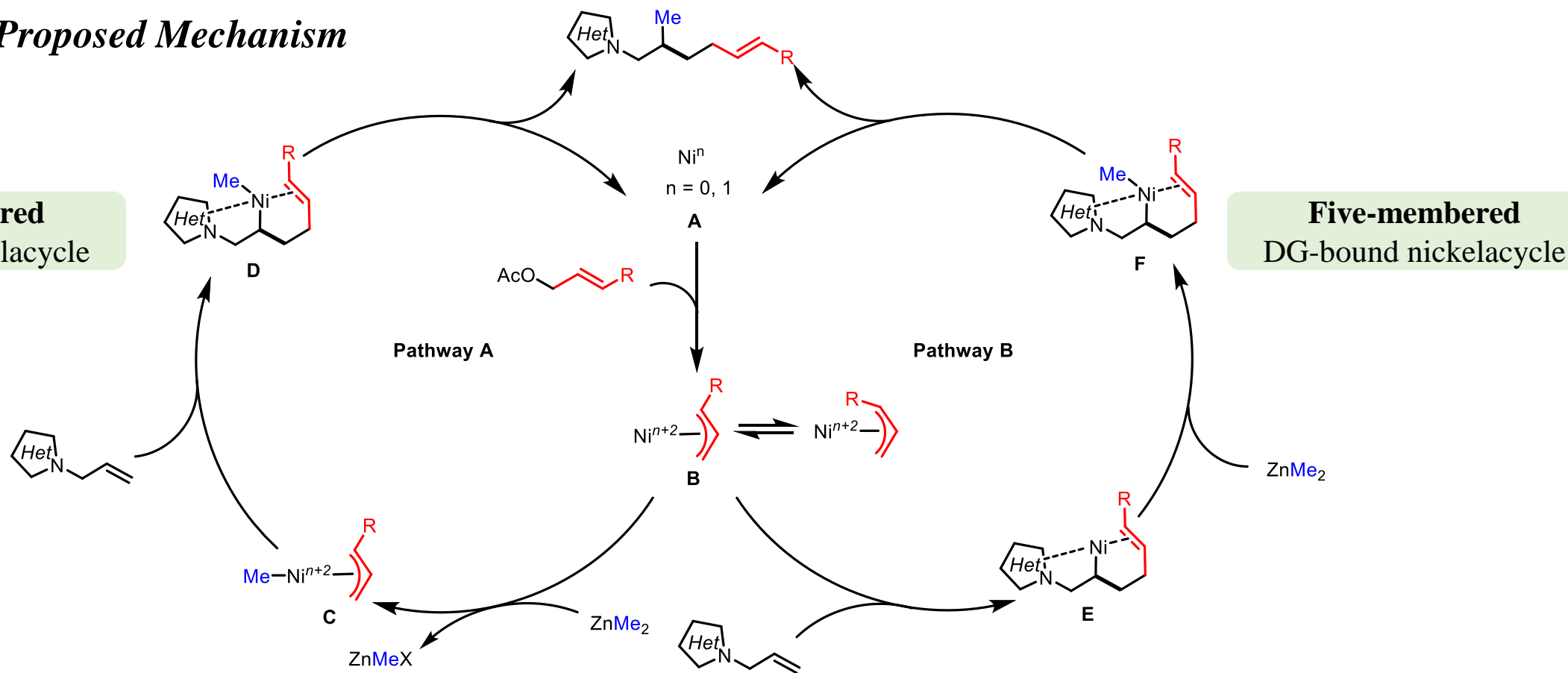
Radical trap experiment



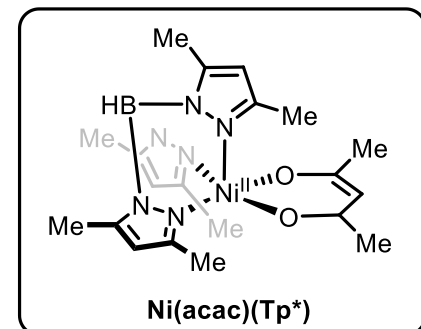
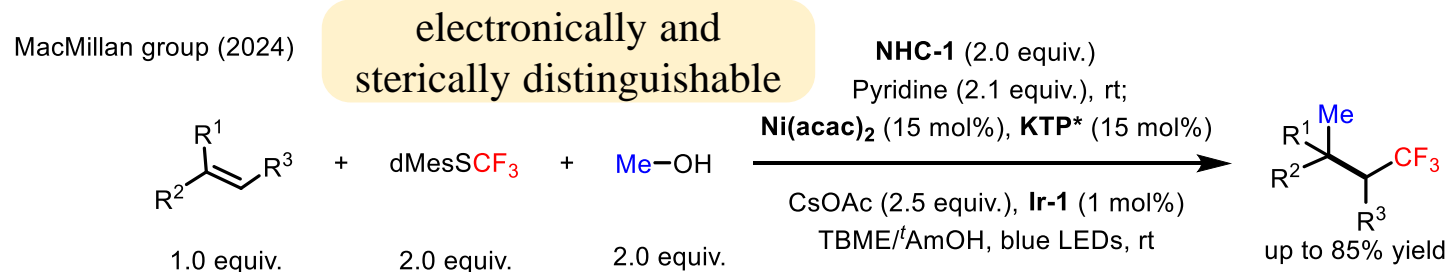
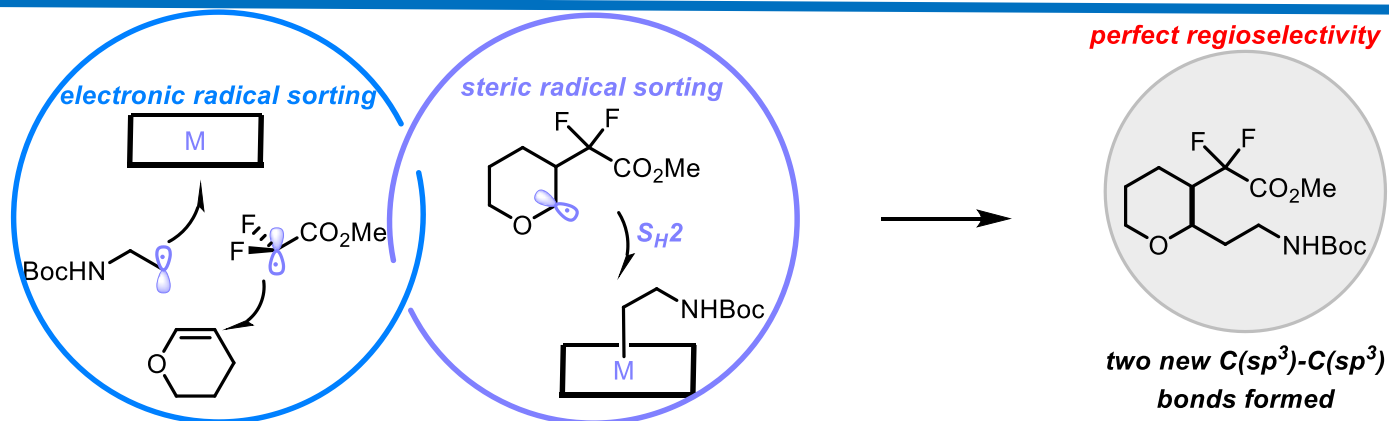
Unsuccessful examples



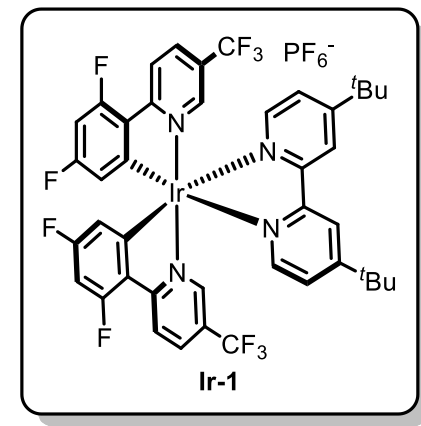
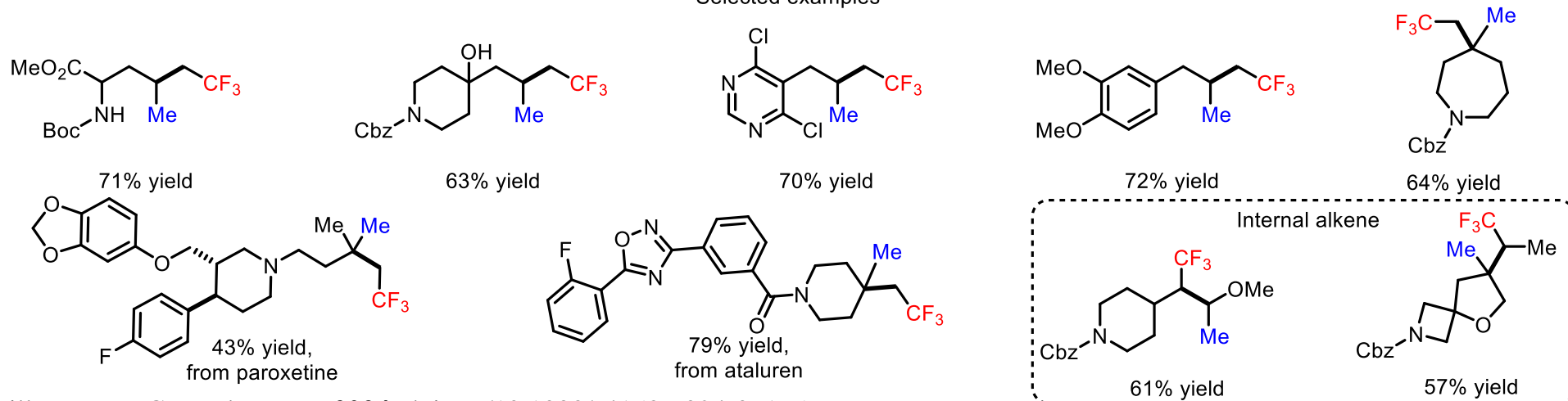
Proposed Mechanism



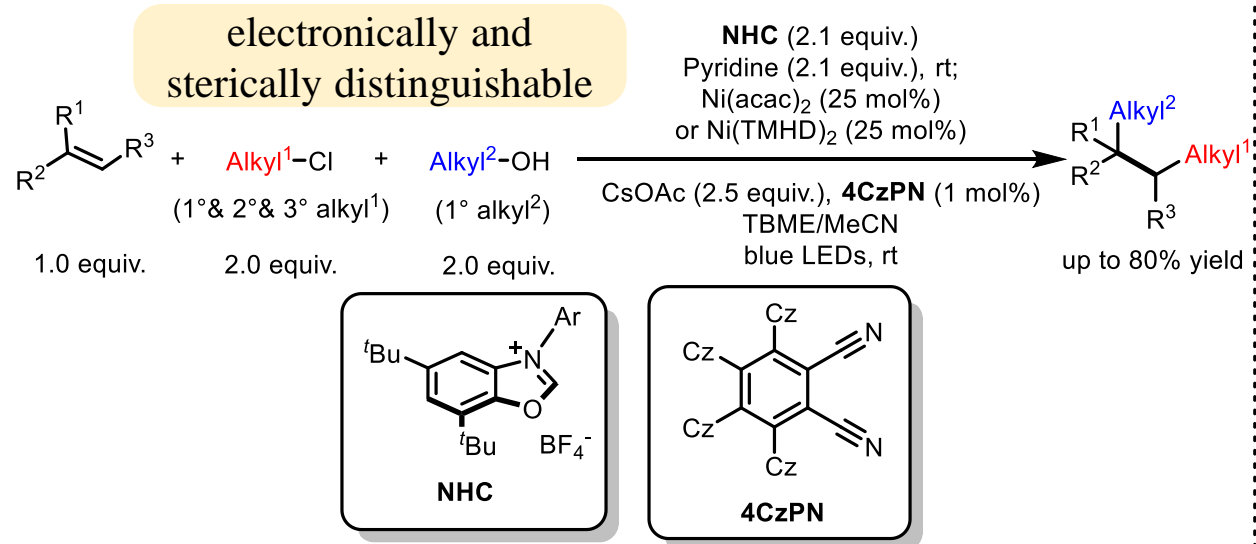
2.1 Redox-neutral dialkylation of unactivated alkenes



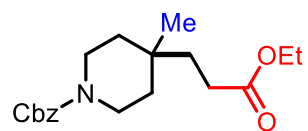
Selected examples



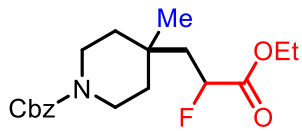
2.1 Redox-neutral dialkylation of unactivated alkenes



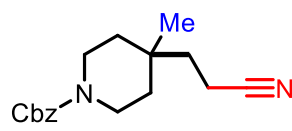
Selected examples



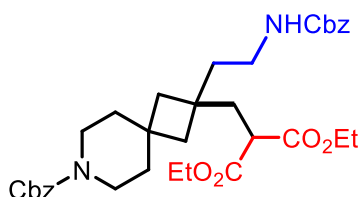
70% yield



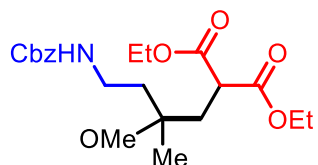
61% yield



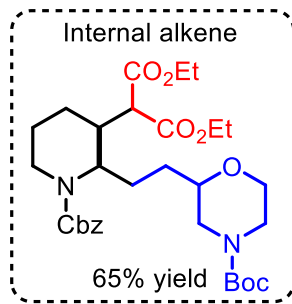
74% yield



53% yield

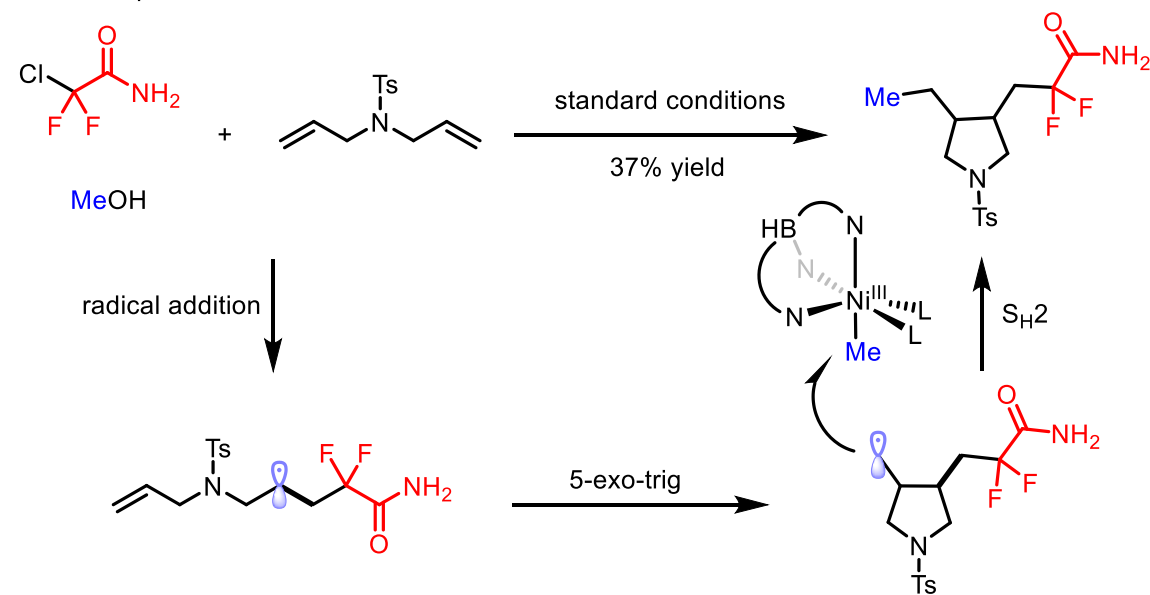


59% yield

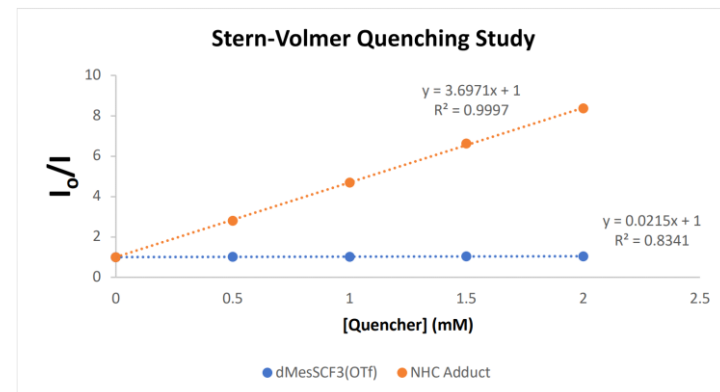


The Mechanistic Experiments

Radical clock experiment



Stern-Volmer quenching study

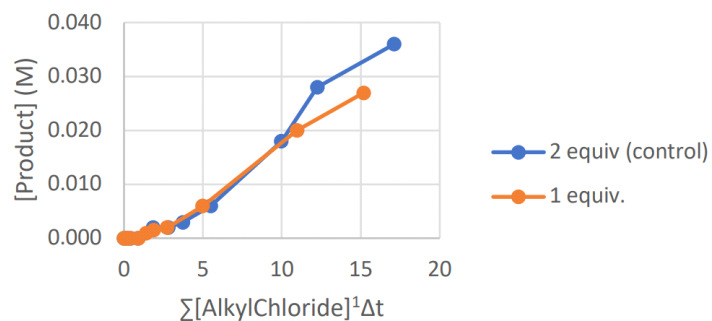


2.1 Redox-neutral dialkylation of unactivated alkenes

Kinetic Order (VTNA)

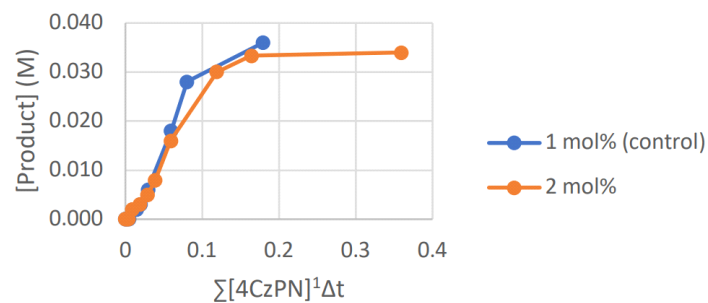
Alkyl Chloride VTNA

First Order



4CzPN VTNA

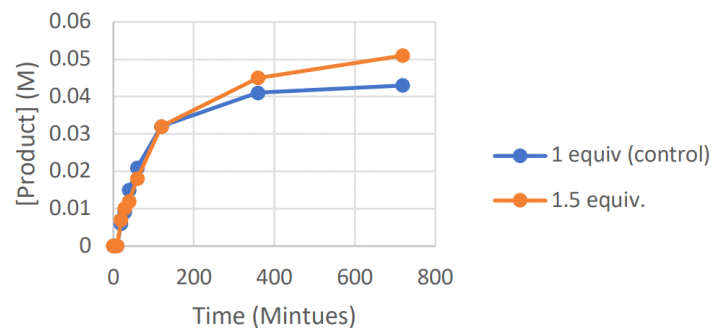
First Order



The rate-determining step:
The reaction of alkyl chloride
with photocatalyst

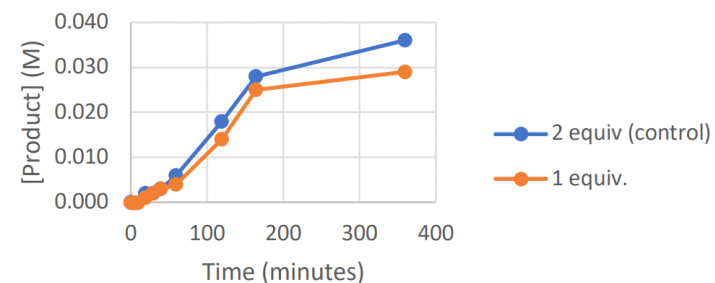
Alkene VTNA

Zero Order



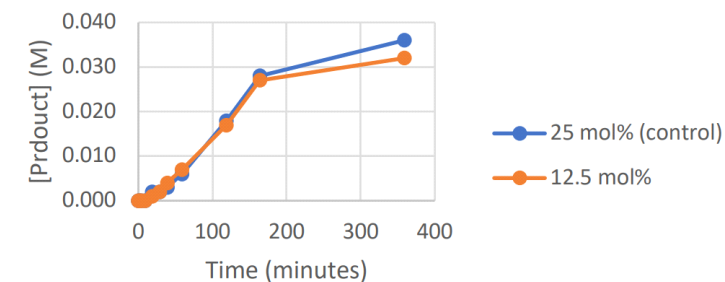
MeOH-NHC adduct VTNA

Zero Order



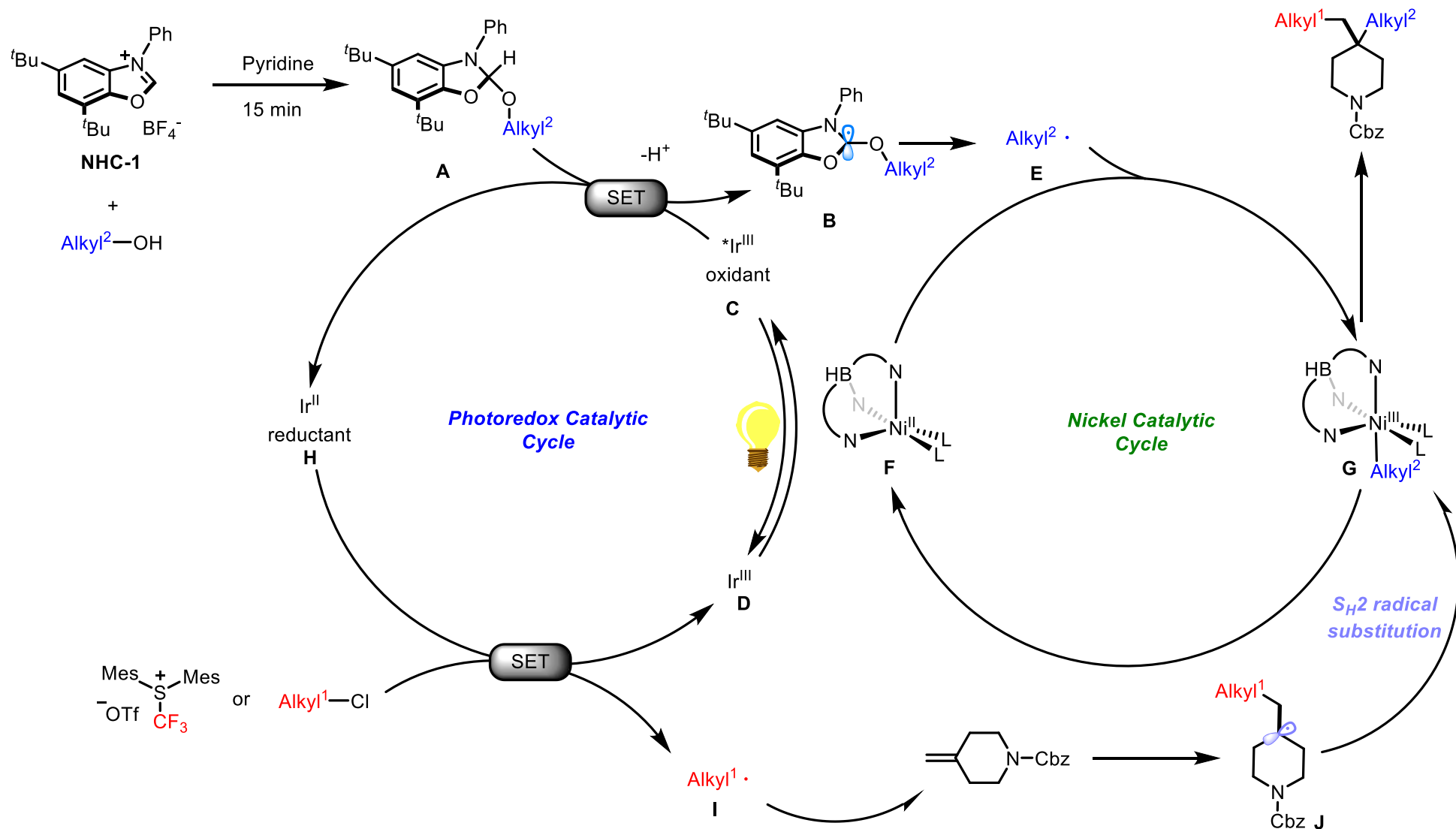
Ni(acac)₂ VTNA

Zero Order



2.1 Redox-neutral dialkylation of unactivated alkenes

Proposed Mechanism



1. Introduction

2. Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes

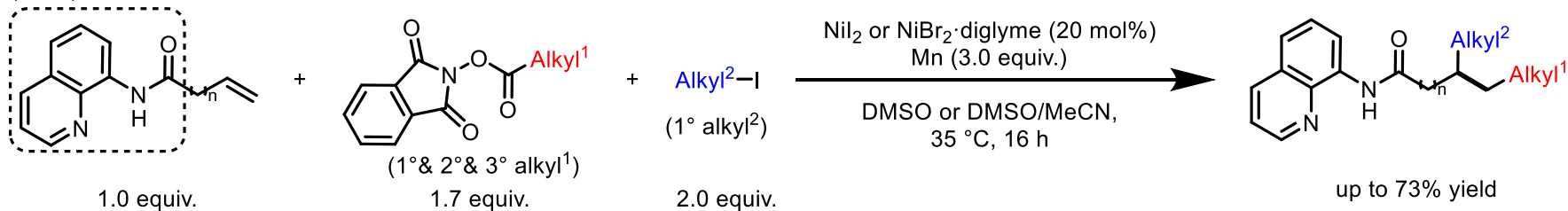
2.1 Redox-neutral dialkylation of unactivated alkenes

2.2 Reductive dialkylation of unactivated alkenes

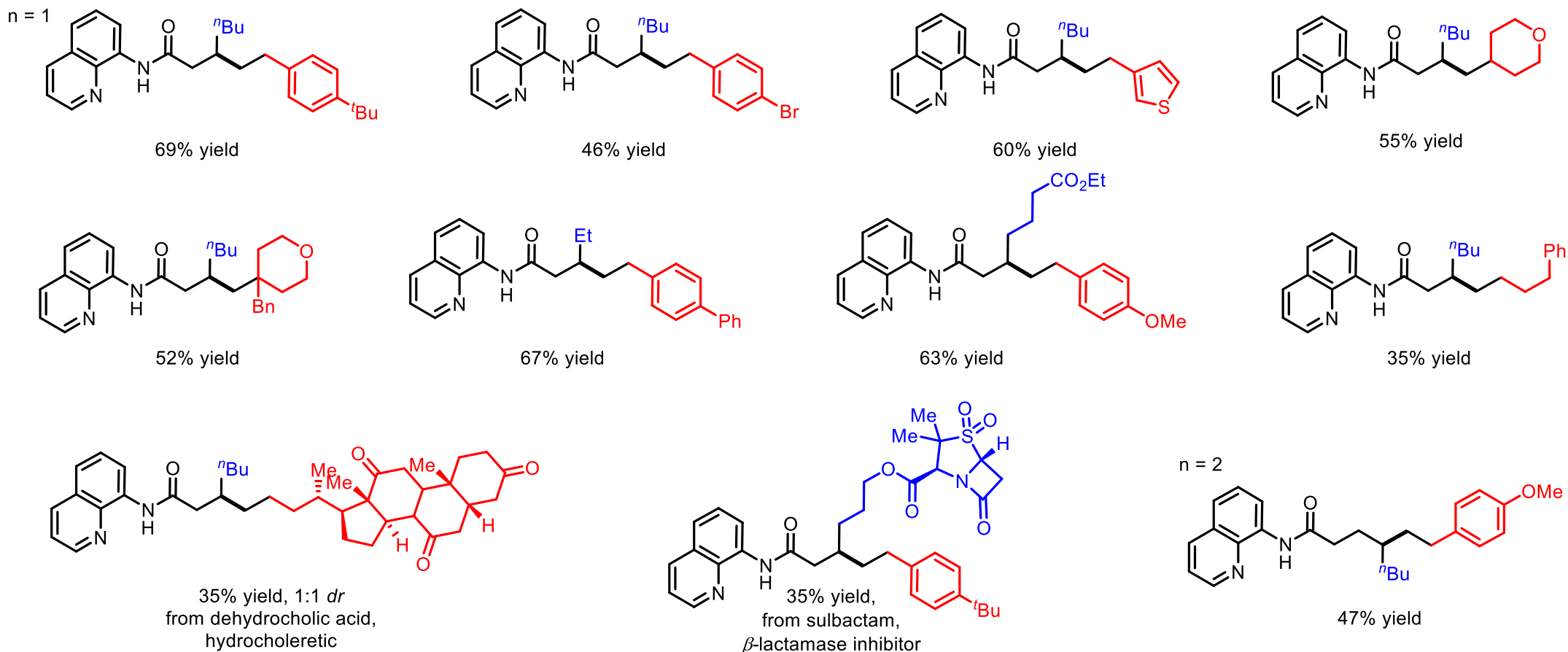
3. Summary and Outlook

2.2 Reductive dialkylation of unactivated alkenes

Koh group (2020)



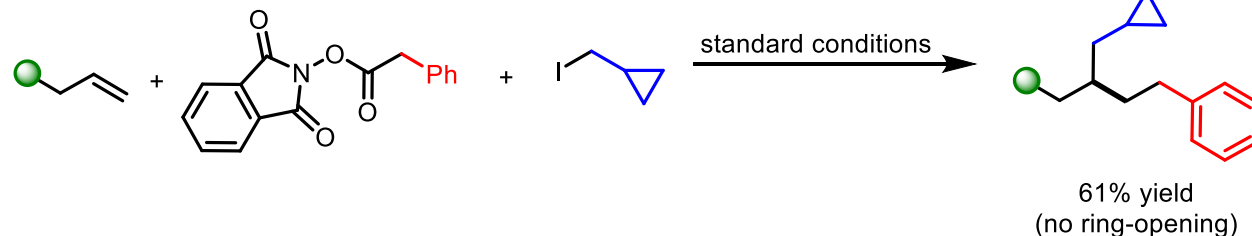
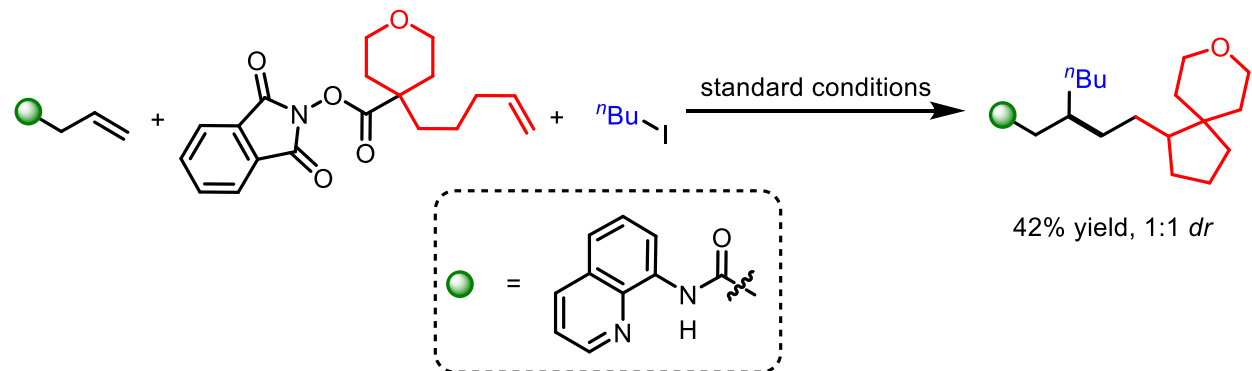
Selected examples



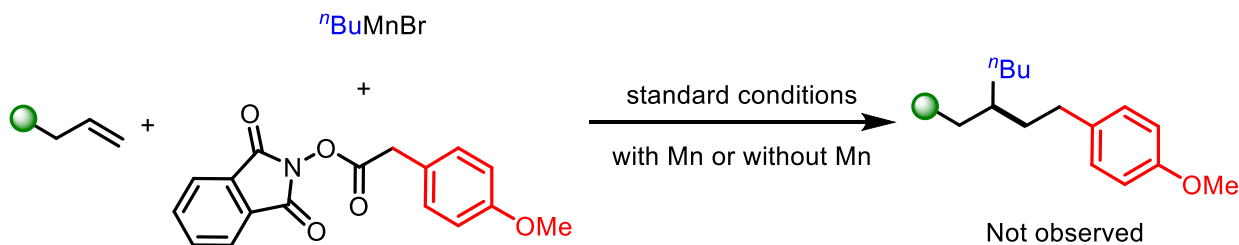
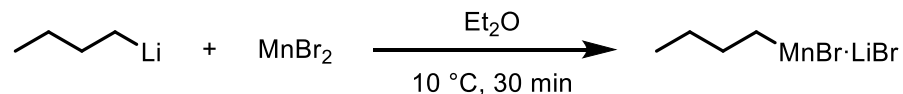
2.2 Reductive dialkylation of unactivated alkenes

The Mechanistic Experiments

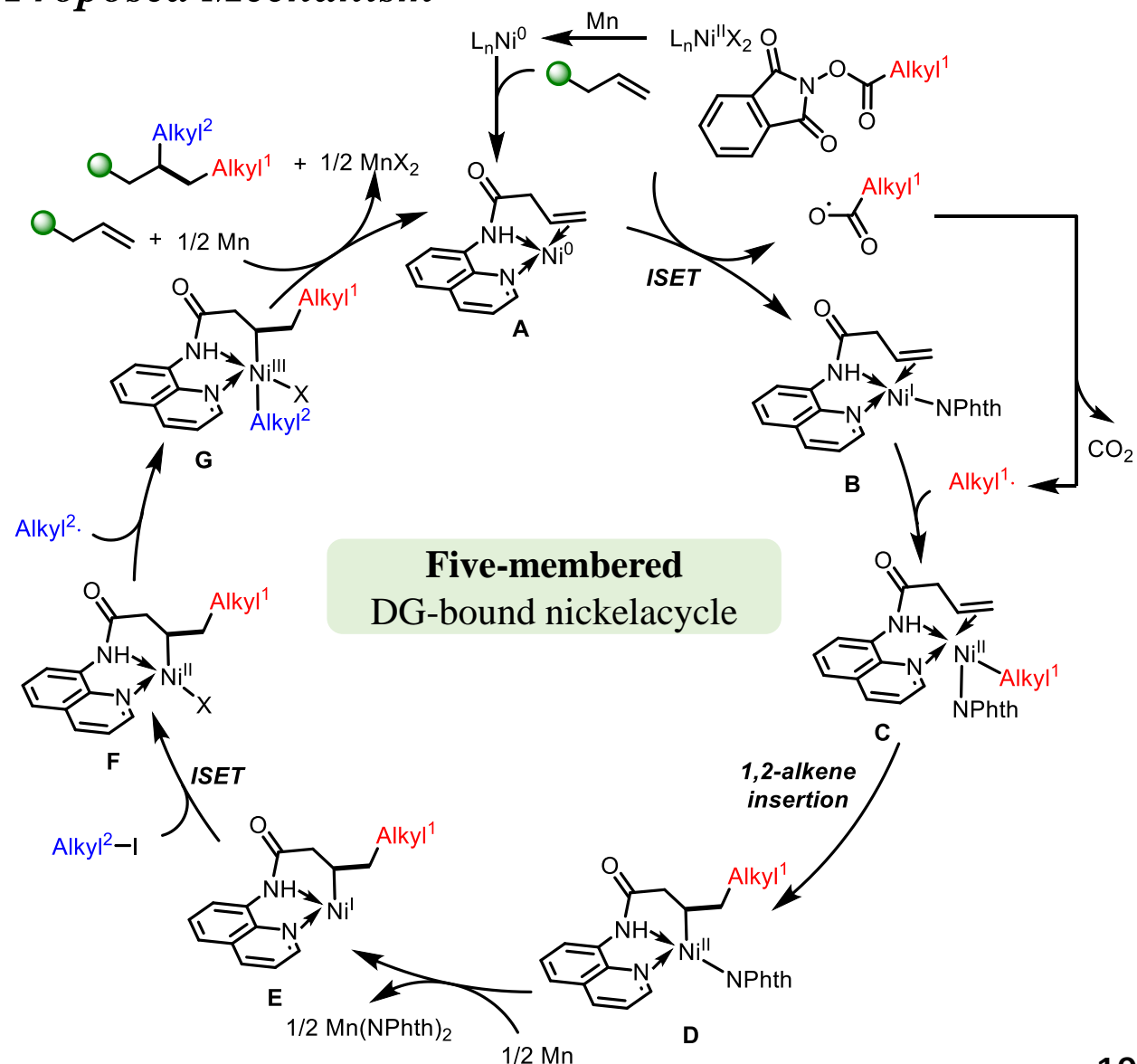
Radical clock experiments



Reaction with manganese(II) complex

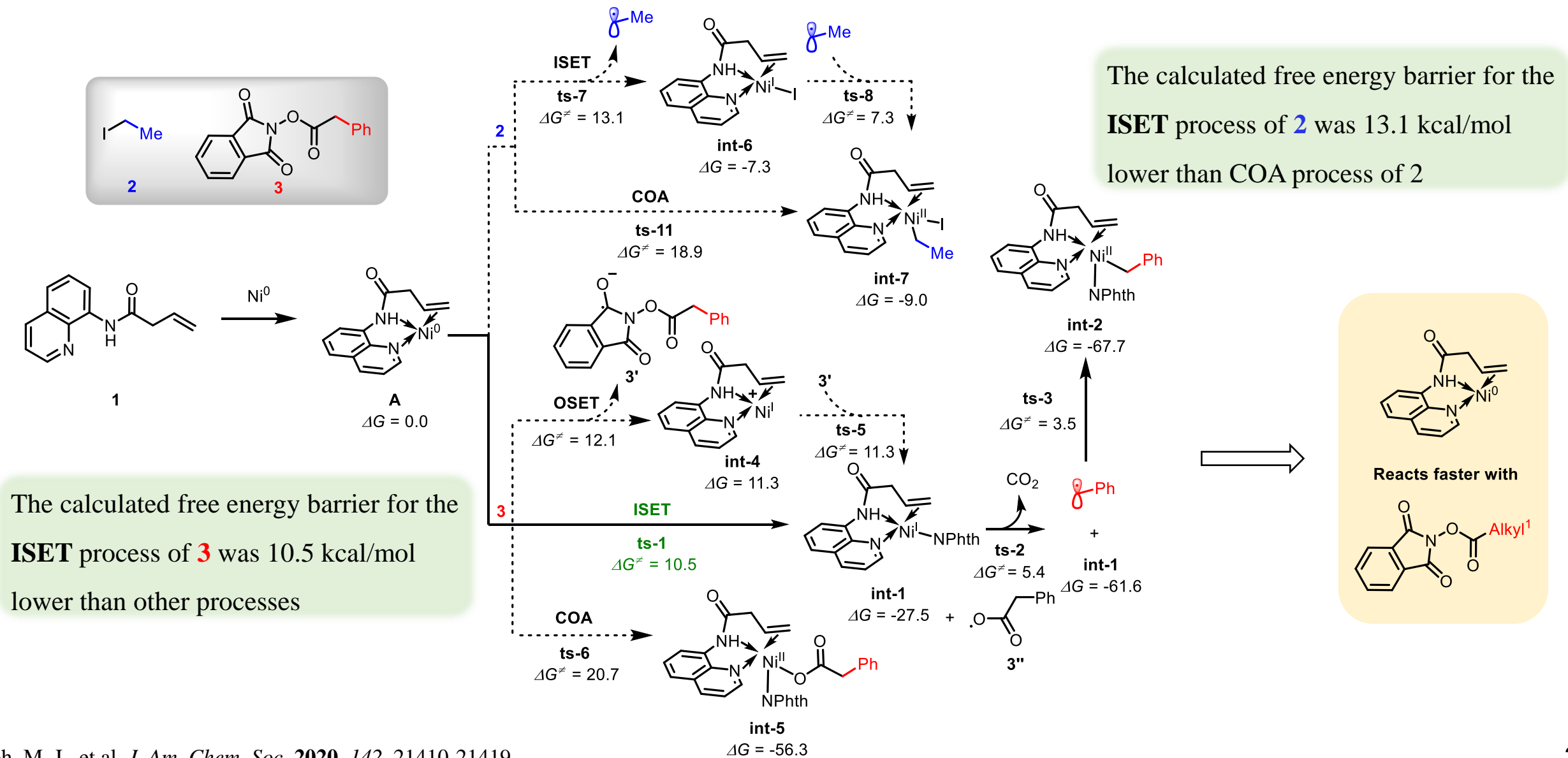


Proposed Mechanism



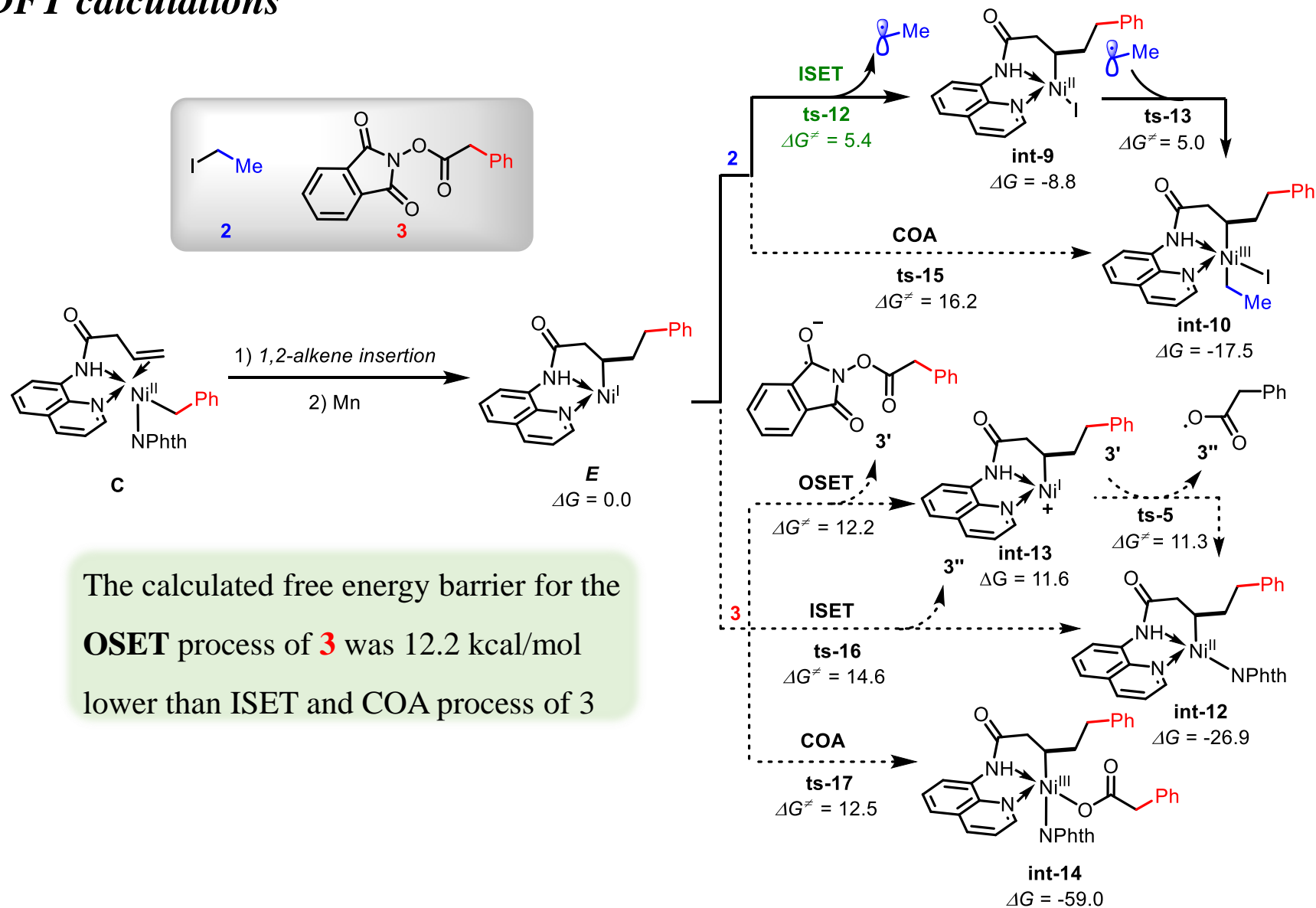
2.2 Reductive dialkylation of unactivated alkenes

DFT calculations



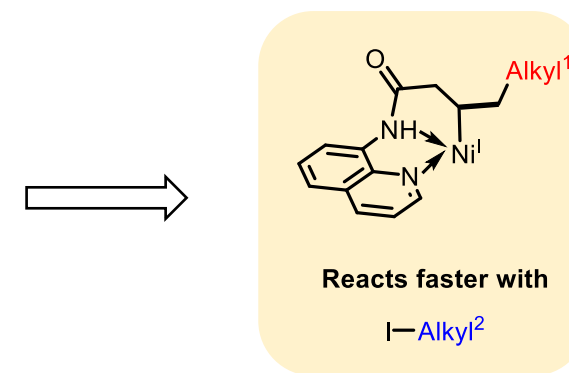
2.2 Reductive dialkylation of unactivated alkenes

DFT calculations



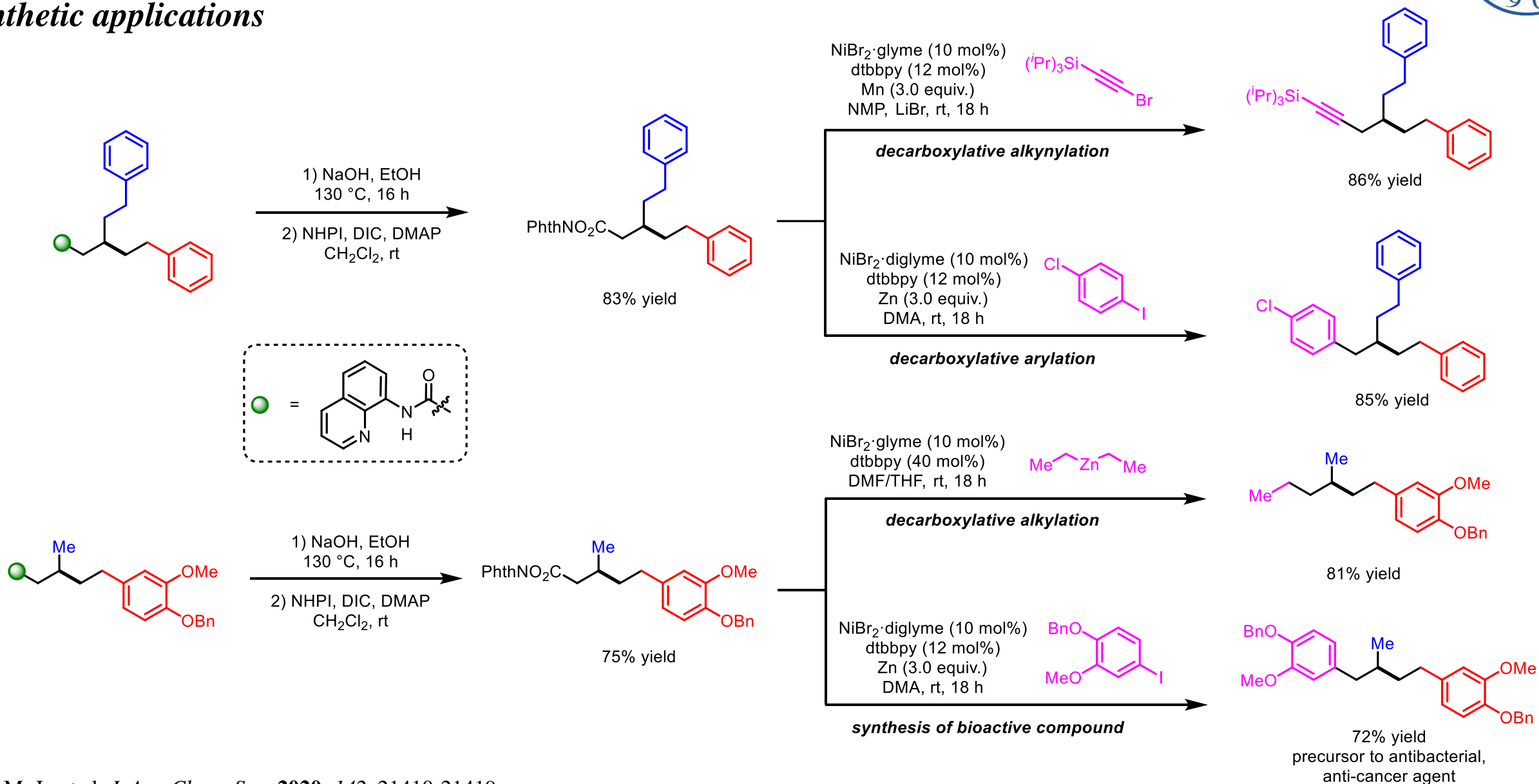
The calculated free energy barrier for the **ISET** process of **2** was 5.4 kcal/mol lower than other processes

The calculated free energy barrier for the **OSET** process of **3** was 12.2 kcal/mol lower than ISET and COA process of **3**



2.2 Reductive dialkylation of unactivated alkenes

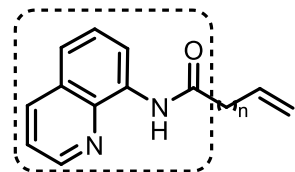
Synthetic applications



2.2 Reductive dialkylation of unactivated alkenes

Koh group (2020) & Yang group (2024)

sterically
distinguishable



1.0 equiv.

+ Alkyl¹-I
(2° alkyl¹)

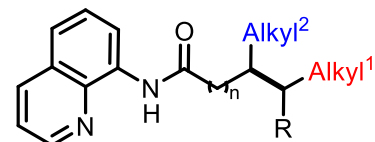
1.5 equiv.

+ Alkyl²-X
(1° alkyl²)
X = OTs, Br, I

2.0 equiv.

NiI₂ or Ni(acac)₂ (10 mol%)
Mn (2.5 equiv.)

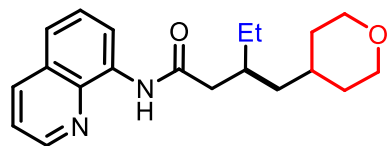
DMF, 50 °C, 12 h



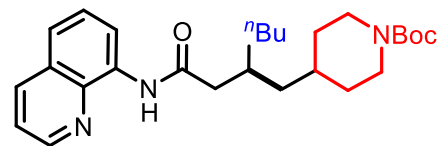
up to 88% yield

Selected examples

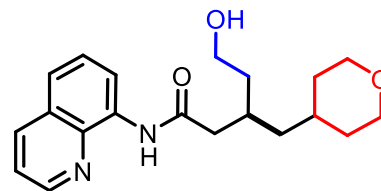
n = 1



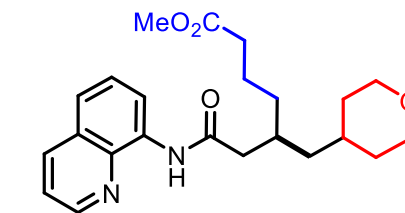
72% yield



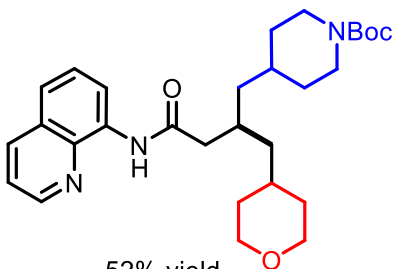
66% yield



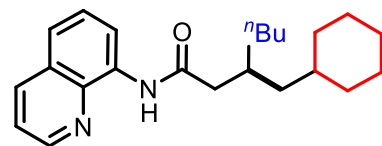
49% yield



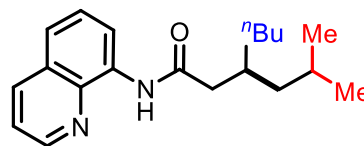
53% yield



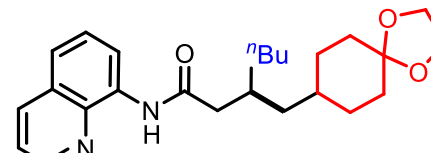
52% yield



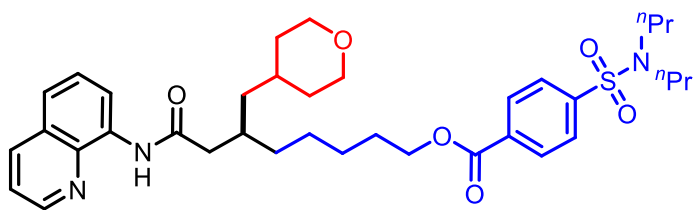
70% yield



82% yield

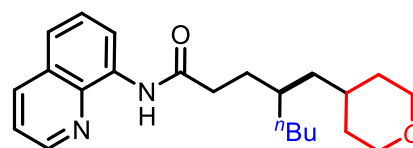


51% yield

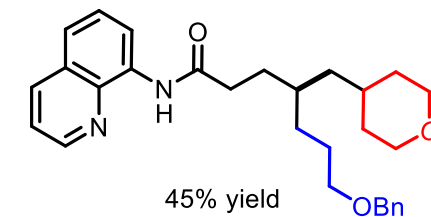


73% yield

n = 2

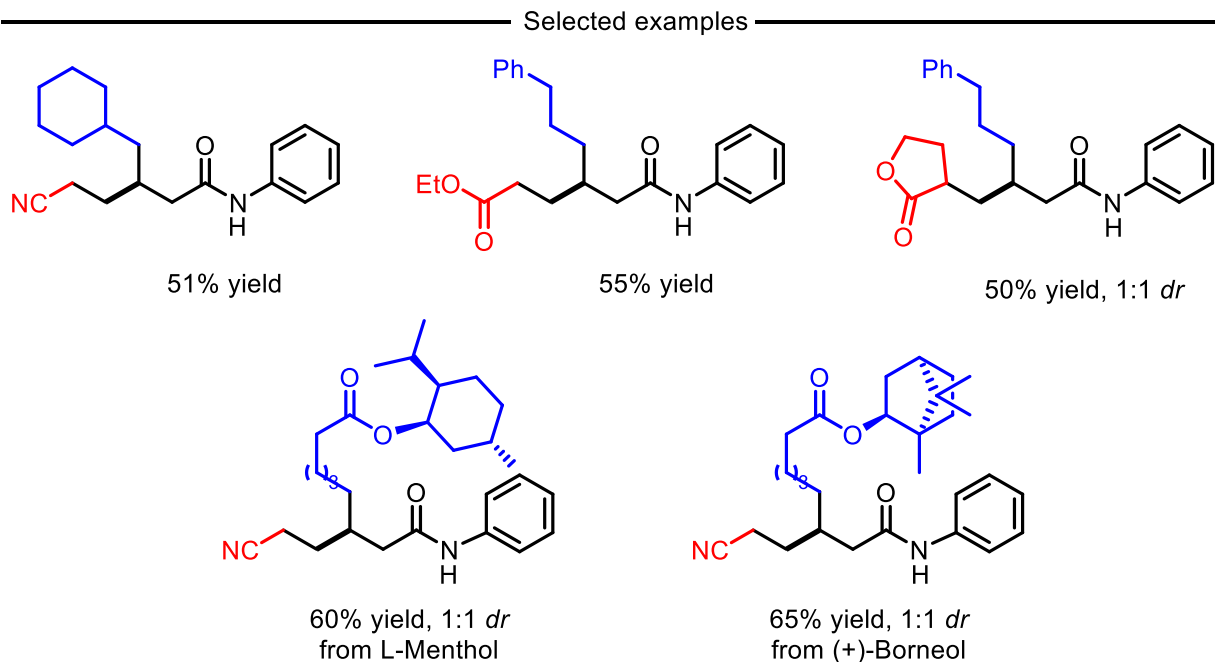
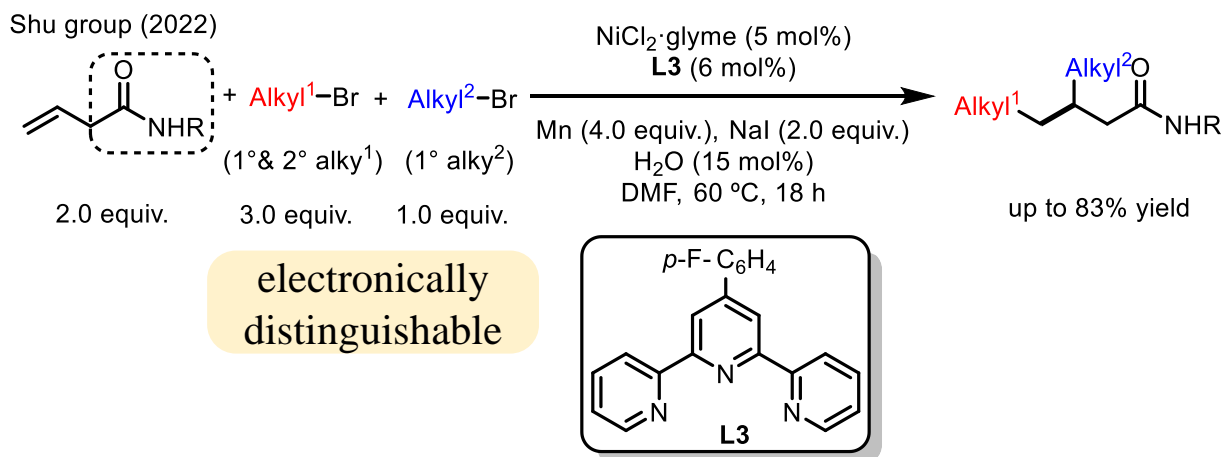


52% yield



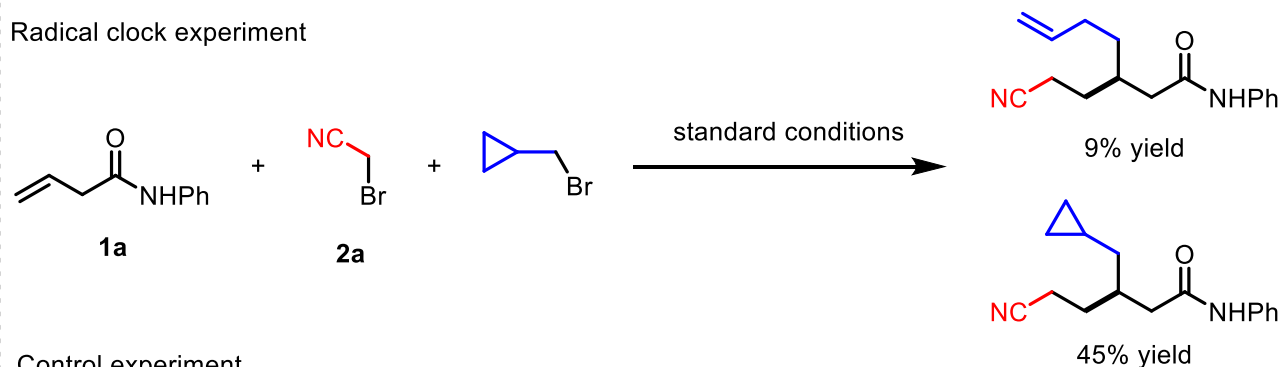
45% yield

2.2 Reductive dialkylation of unactivated alkenes

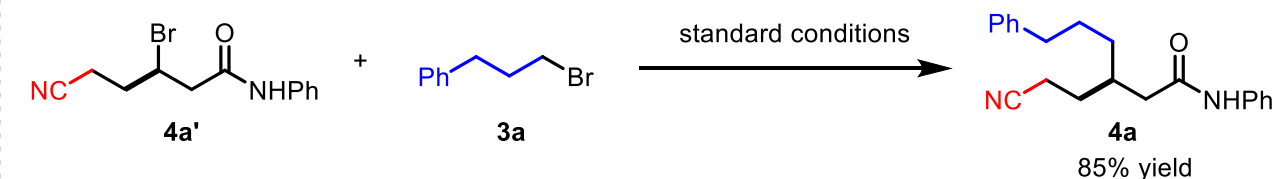


The Mechanistic Experiments

Radical clock experiment

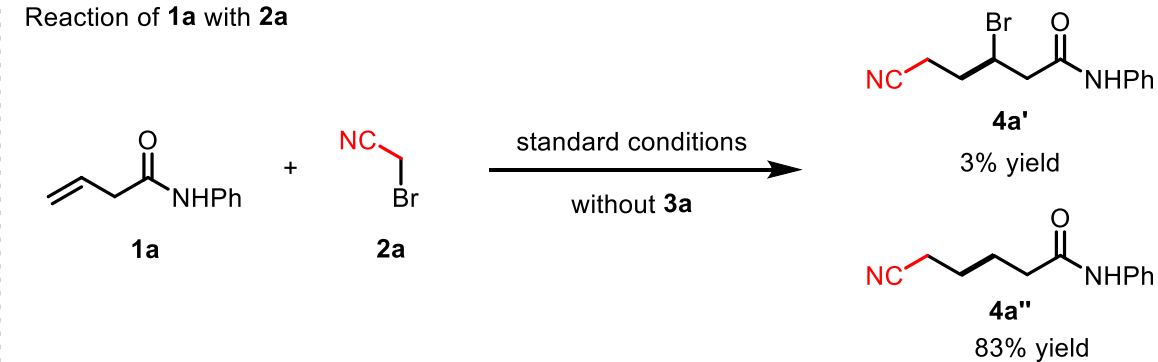


Control experiment



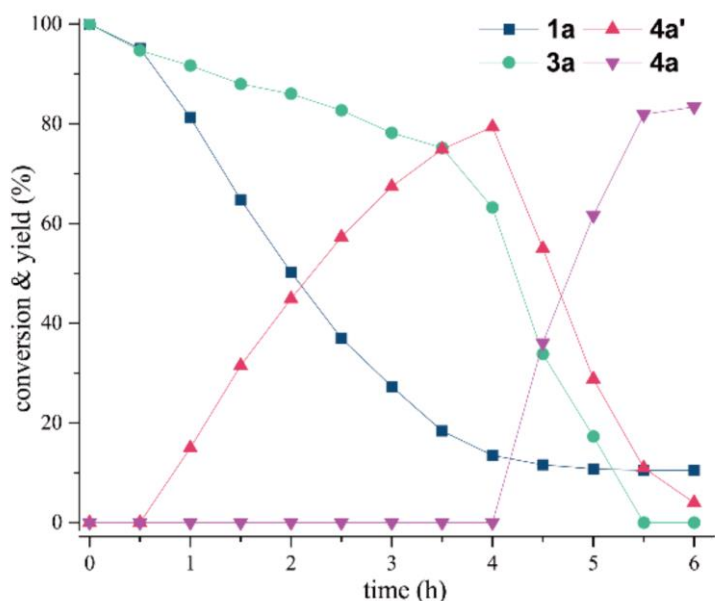
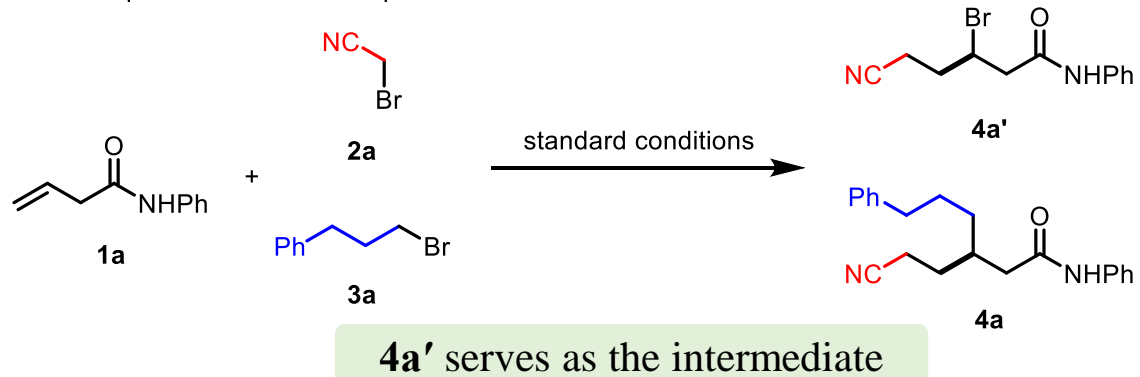
4a' serves as the intermediate

Reaction of 1a with 2a

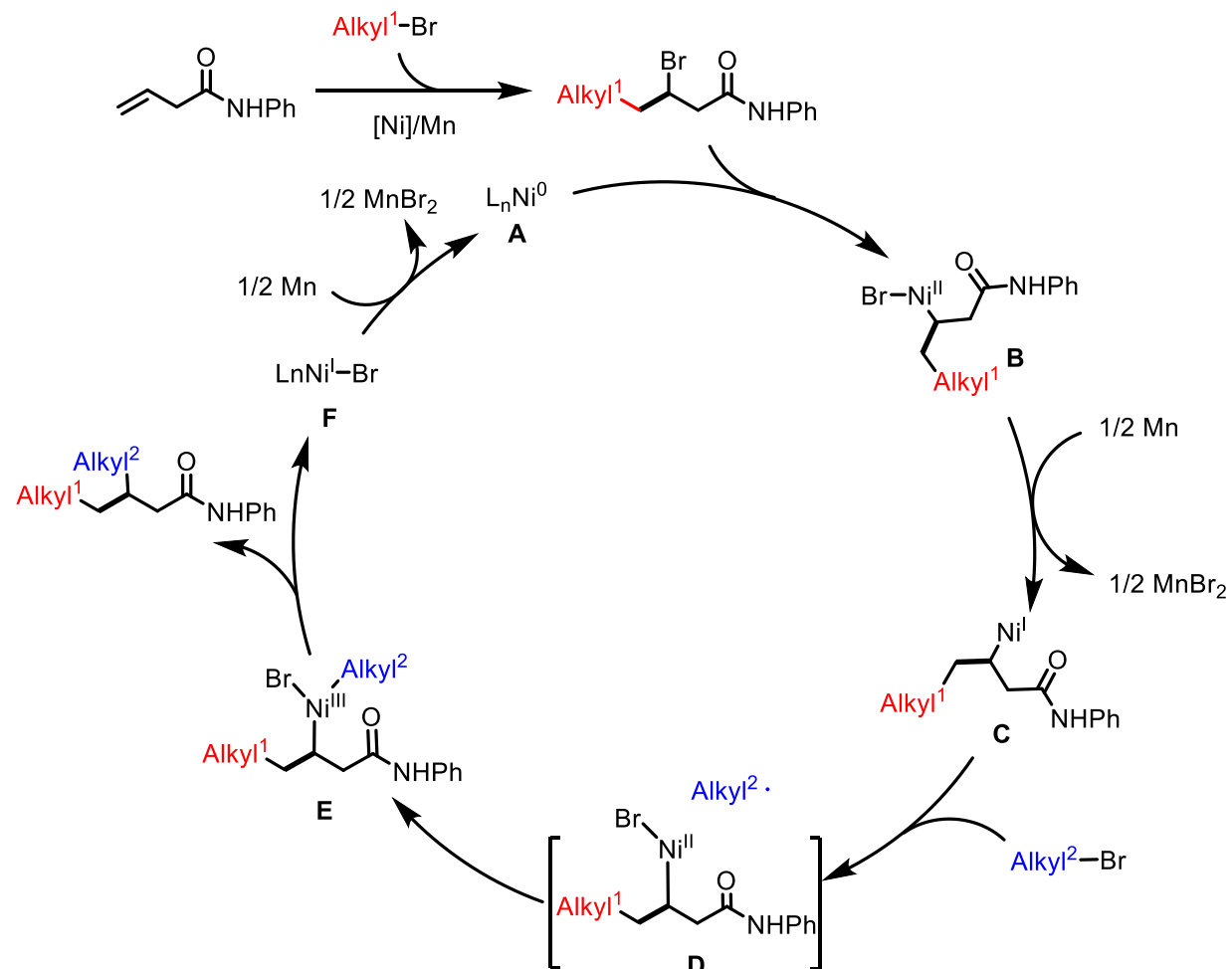


2.2 Reductive dialkylation of unactivated alkenes

Reaction profile of the reaction process

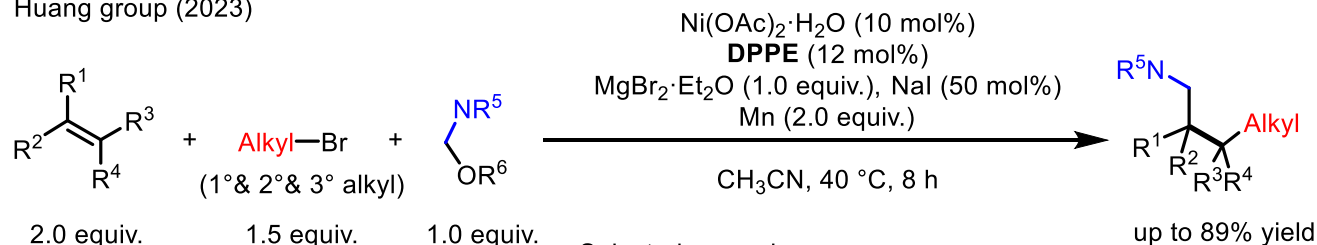


Proposed Mechanism

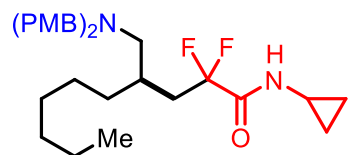


2.2 Reductive dialkylation of unactivated alkenes

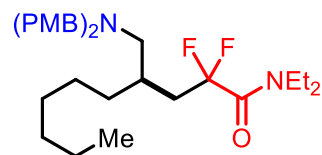
Huang group (2023)



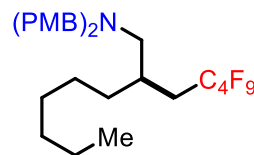
Selected examples



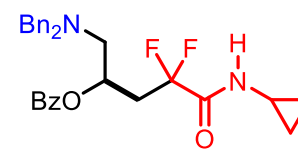
82% yield



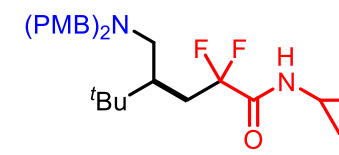
83% yield



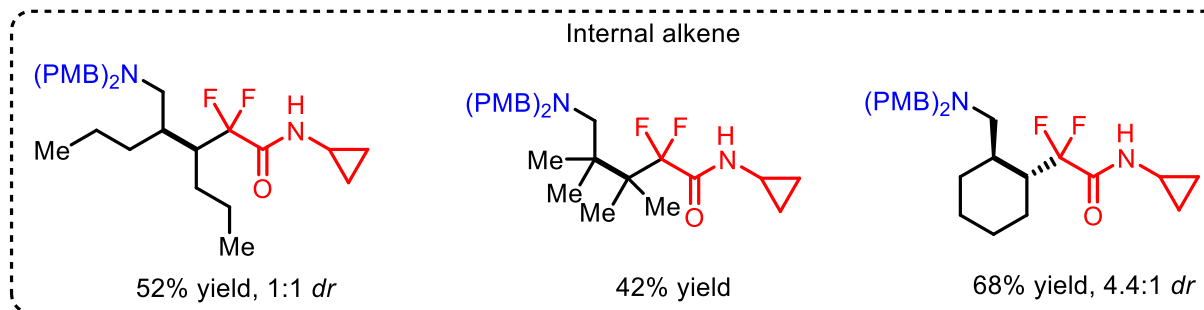
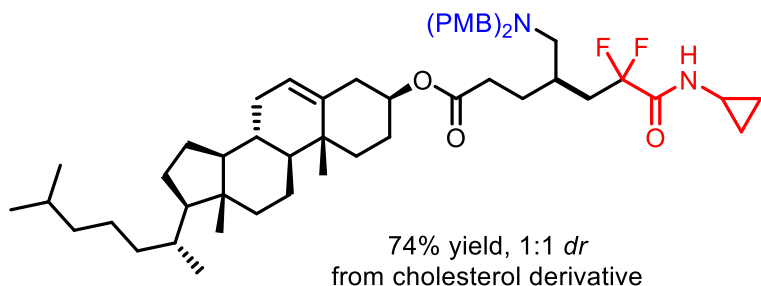
63% yield



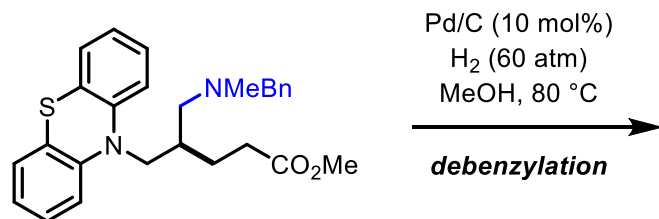
68% yield



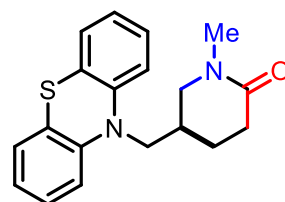
67% yield



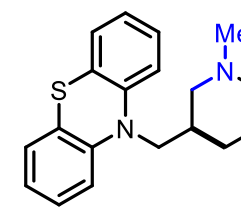
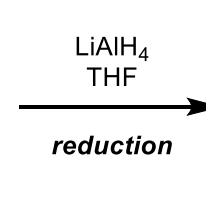
Synthesis of bioactive compounds



45% yield



80% yield

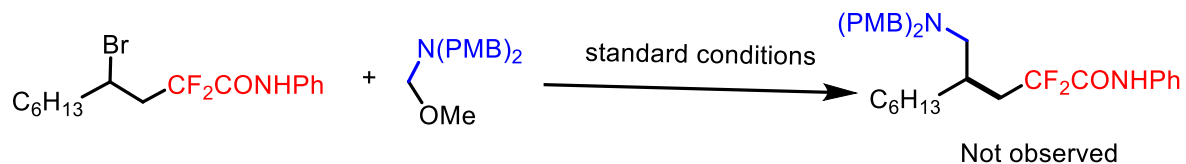


90% yield (mepazine)

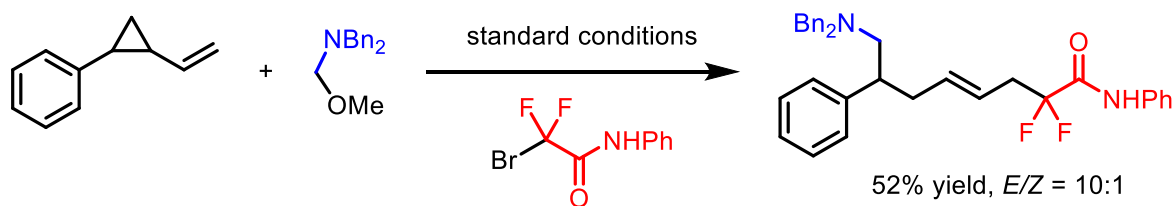
2.2 Reductive dialkylation of unactivated alkenes

The Mechanistic Experiments

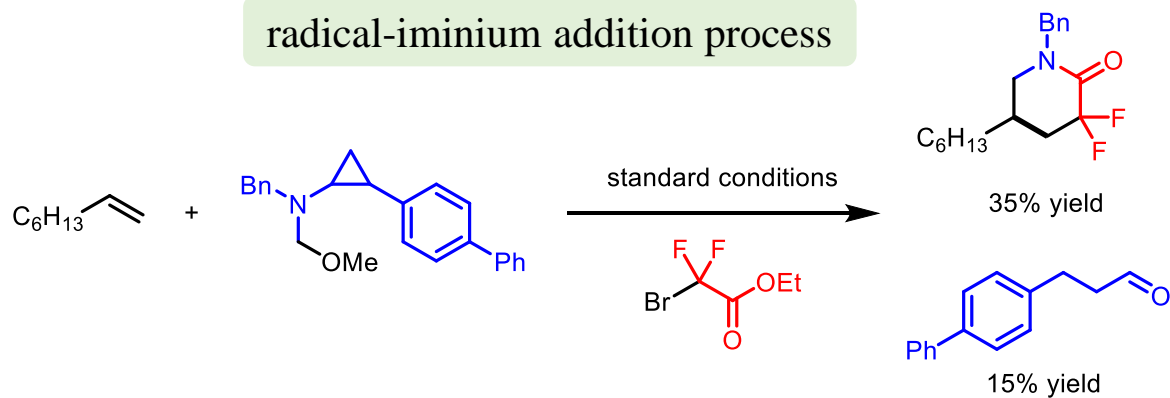
Reaction with ATRA product



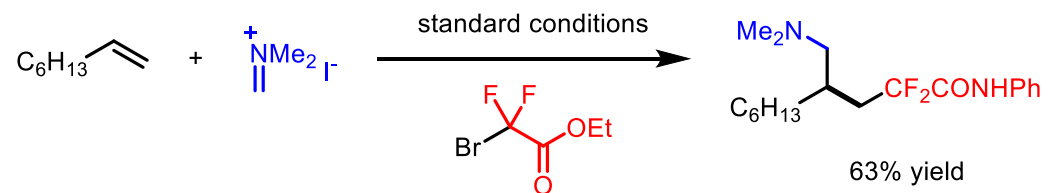
Radical clock experiments



radical-iminium addition process

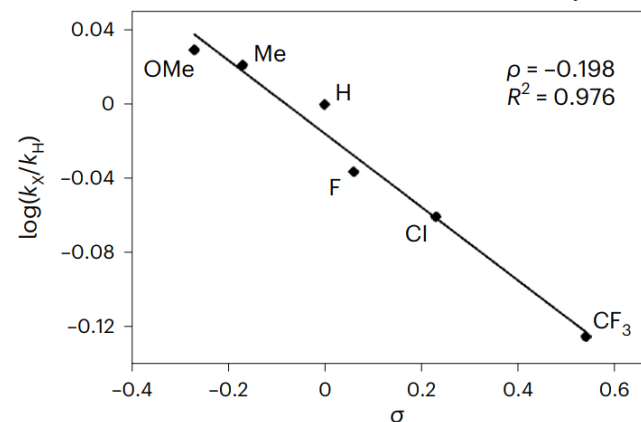
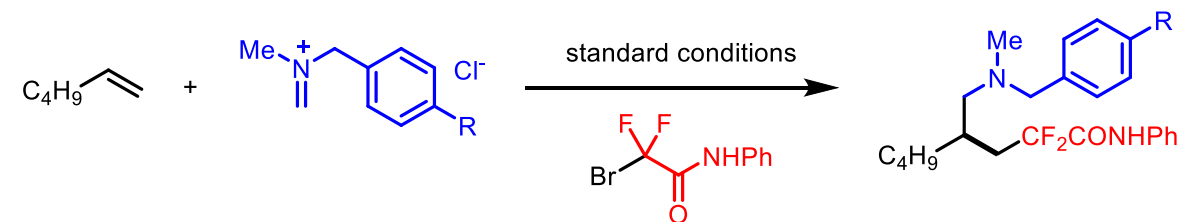


Reaction with iminium ion



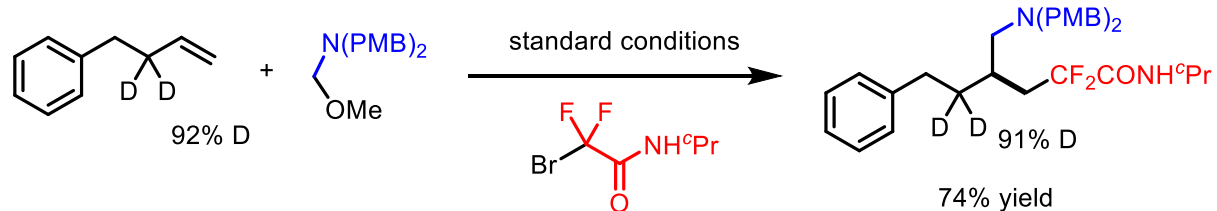
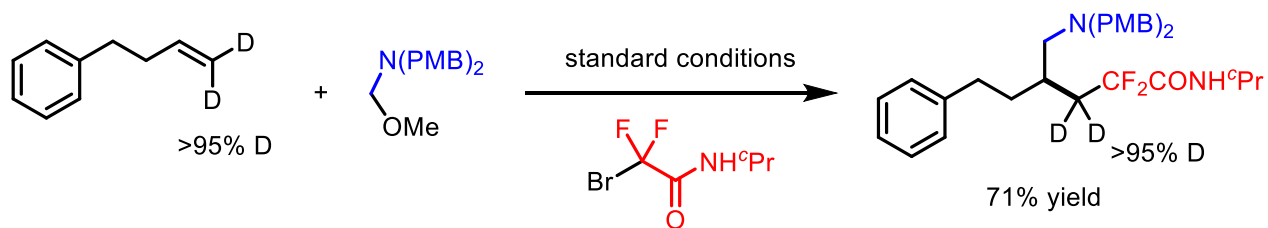
iminium ion serves as the intermediate

Hammett studies



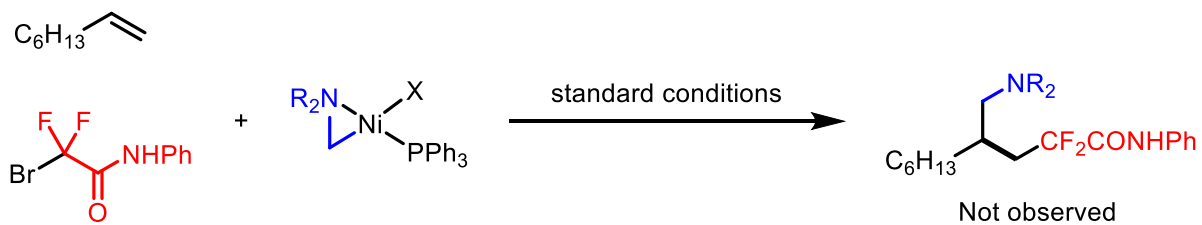
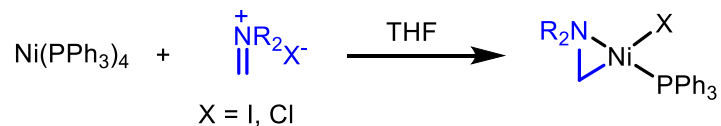
2.2 Reductive dialkylation of unactivated alkenes

Isotopic-labeling experiments

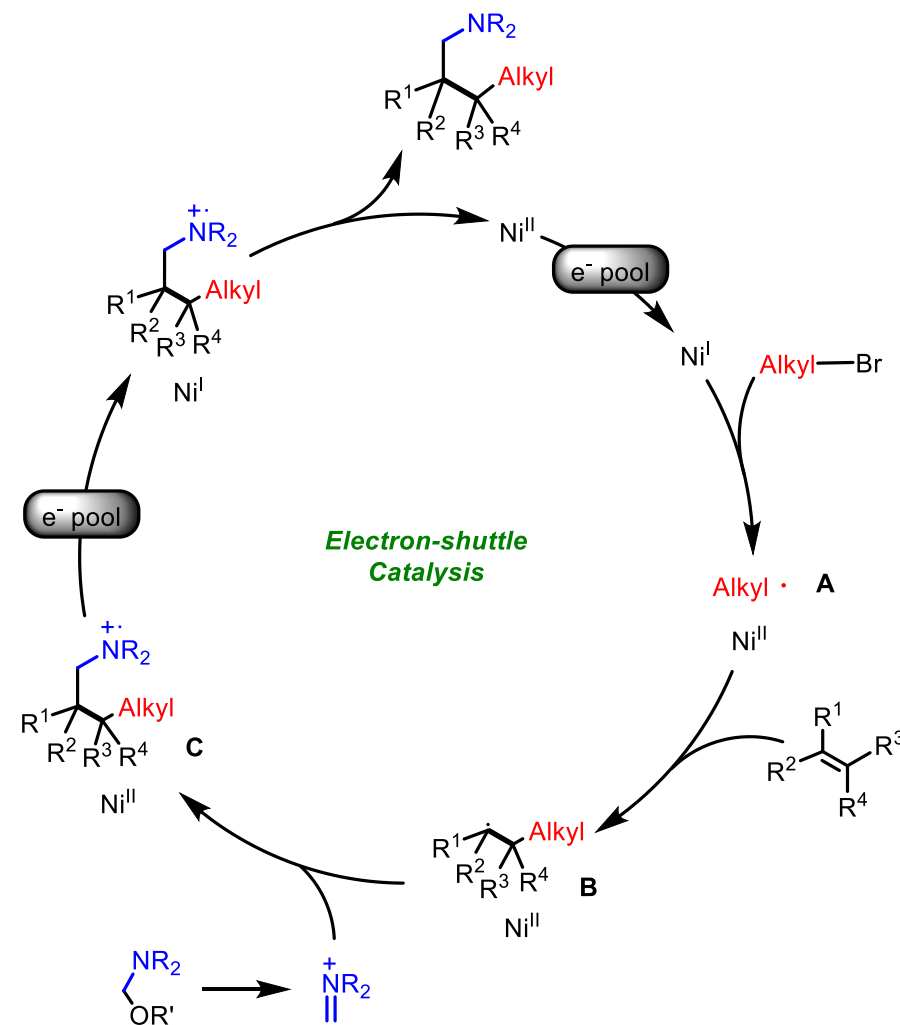


rule out the alkyl-nickel species

Reaction with nickel-iminium ion complex



Proposed Mechanism



1. Introduction

2. Nickel-Catalyzed Three-Component Dialkylation of Unactivated Alkenes

2.1 Redox-neutral dialkylation of unactivated alkenes

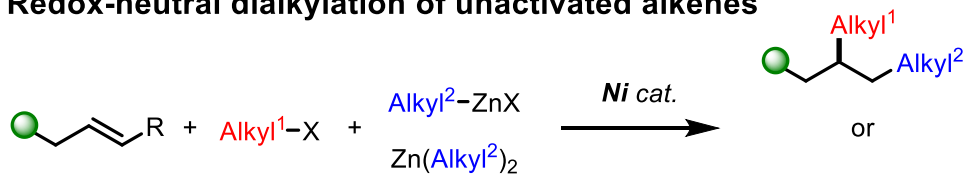
2.2 Reductive dialkylation of unactivated alkenes

3. Summary and Outlook

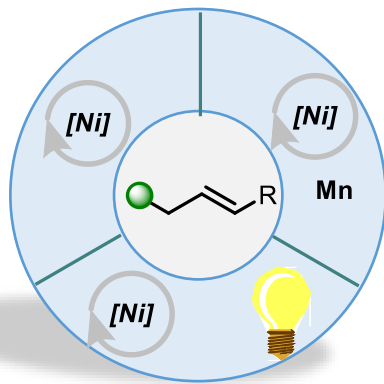
3. Summary and Outlook

Summary:

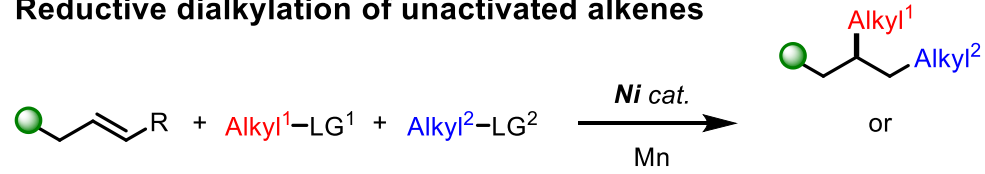
Redox-neutral dialkylation of unactivated alkenes



Sensitive alkylmetallic reagents

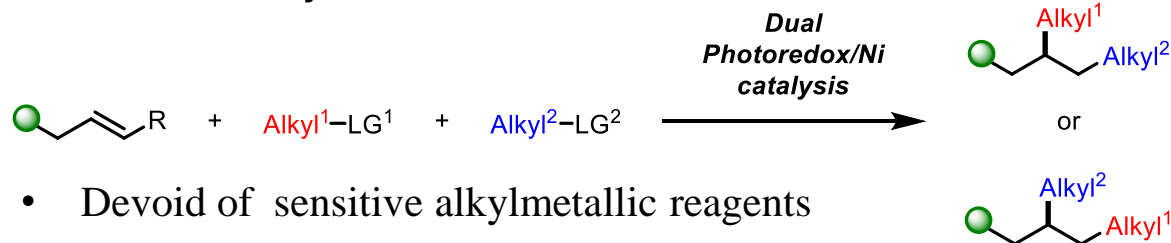


Reductive dialkylation of unactivated alkenes

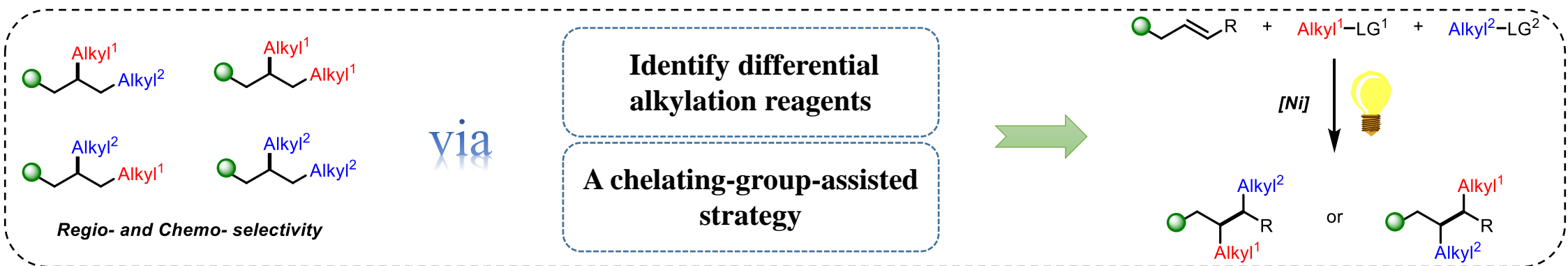


Stoichiometric metal reductant

Redox-neutral dialkylation of unactivated alkenes



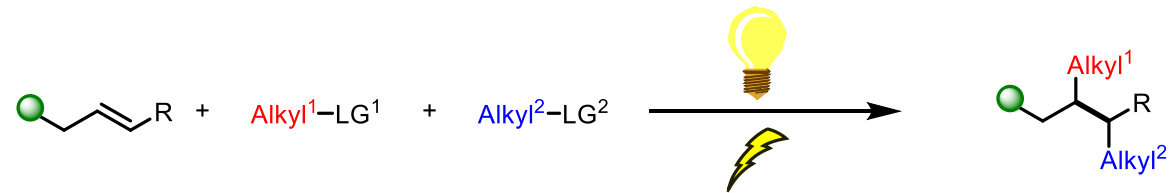
- Devoid of sensitive alkylmetallic reagents
- Devoid of stoichiometric metal reductant



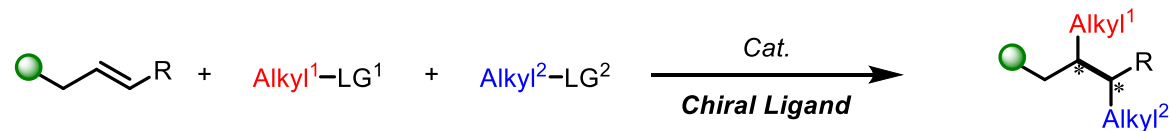
3. Summary and Outlook

Outlook:

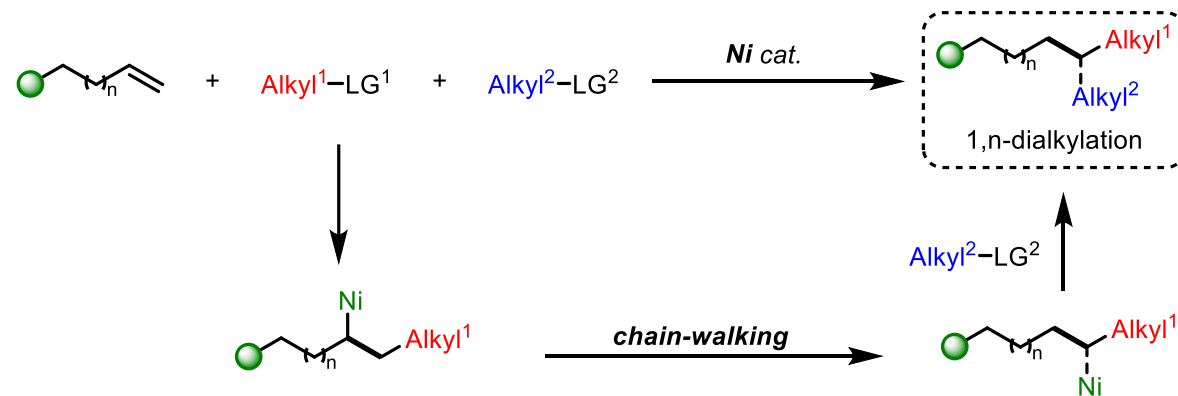
- The development of green and efficient photocatalysis/electrocatalysis



- The construction of an asymmetric dialkylation reaction



- The construction of 1,n-dialkylation of unactivated alkenes



Seminar



Thanks for your attention!

2024.3.29