

Literature Report 4

Site- and Enantioselective Cross-Coupling of Saturated N-Heterocycles with Carboxylic Acids by Cooperative Ni/Photoredox Catalysis

Reporter: Jian Chen

Checker: Qing-Xian Xie

Shu, X.; Huo, H.* *et al.* *Nat. Commun.* **2023**, *14*, 125

2023-05-08

CV of Prof. Haohua Huo

Background:

- **2005-2012** B.S. & M.S., Xiamen University
- **2012-2016** Ph.D., Philipps-Universität Marburg
- **2016-2019** Postdoc., California Institute of Technology
- **2019-Now** Professor, Xiamen University



Research:

- Visible-light-driven enantioselective radical C(sp³)–H functionalization (photoredox and transition metal-catalyzed enantioselective C(sp³)–H cross-coupling reactions)

Contents

1

Introduction

2

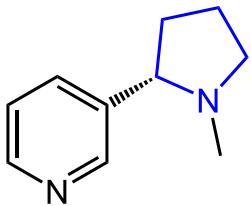
Site- and Enantioselective α -Acylation of Azacycles

3

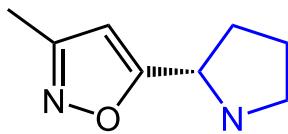
Summary

Introduction

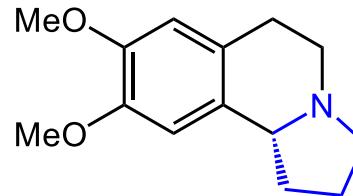
Chiral α -Functionalized Azacycles in Bioactive Compounds



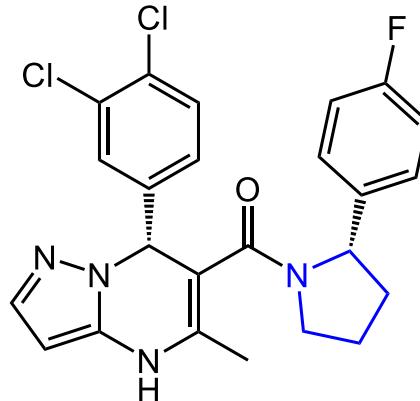
nicotine



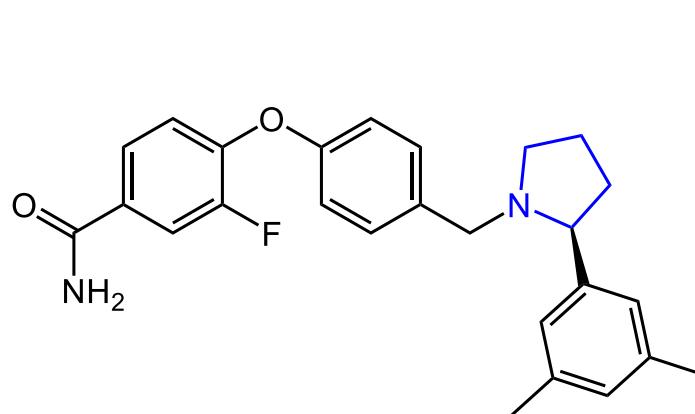
(S)-ABT-418



(+)-crispine A



BMS-394136

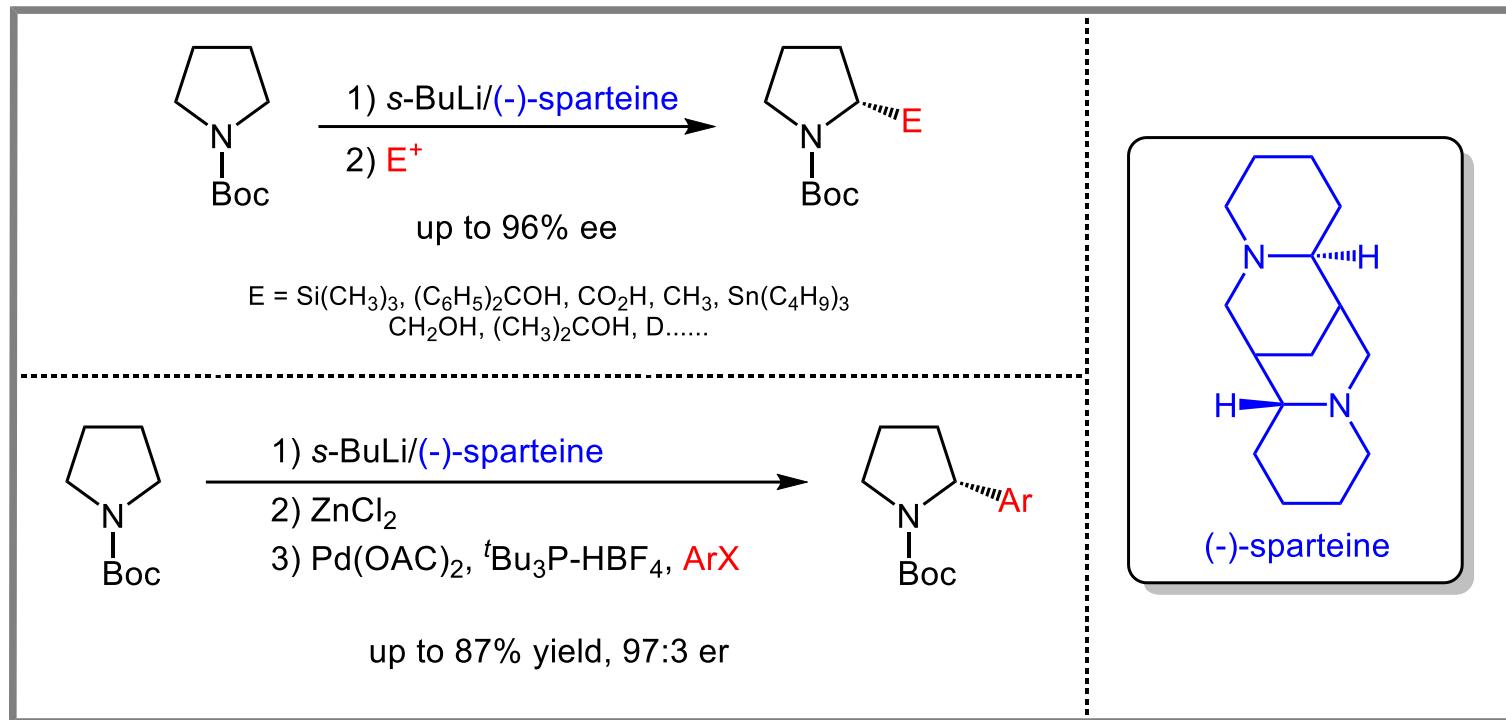


(S)-CERC-501

Qin, J.; Meggers, E.* *et al. Chem. Sci.* **2019**, *10*, 3202

Introduction

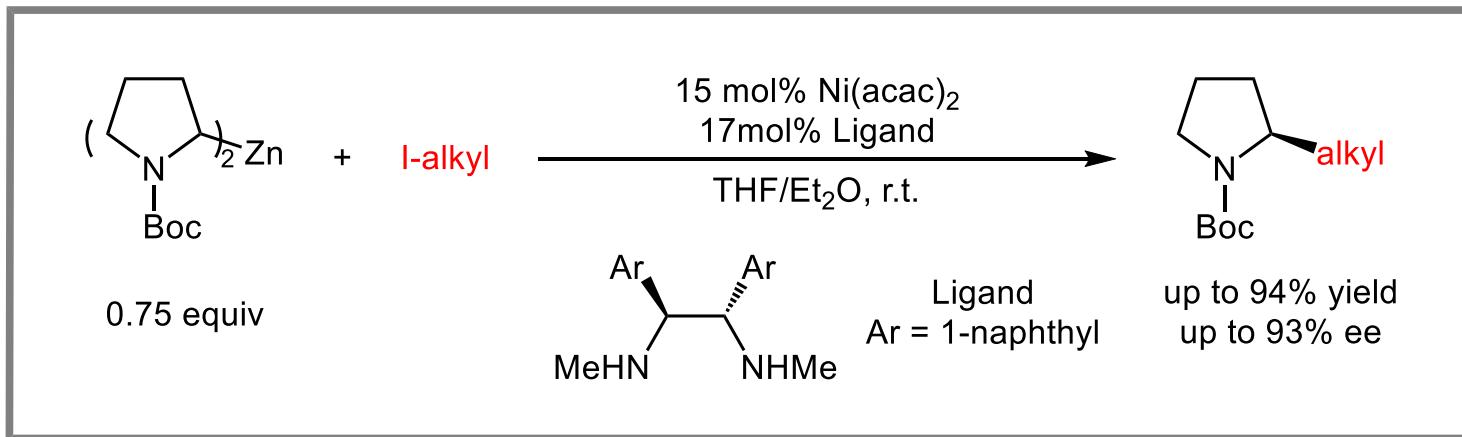
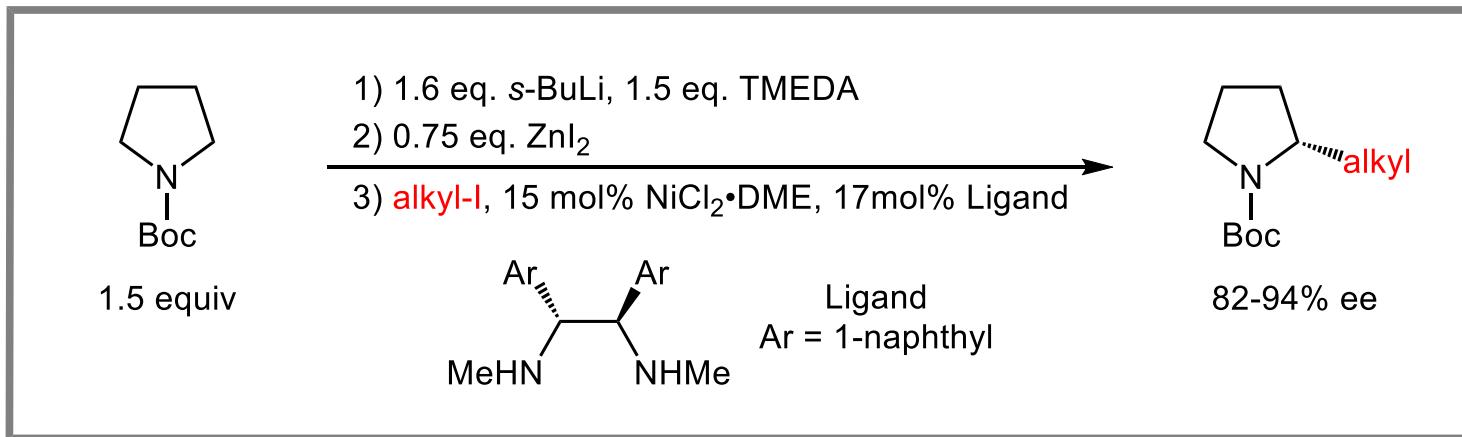
(-)-Sparteine Mediated Asymmetric α -Functionalization



Beak, P.* et al. *J. Am. Chem. Soc.* **1994**, 116, 3231
Campos, K. R.* et al. *J. Am. Chem. Soc.* **2006**, 128, 3538

Introduction

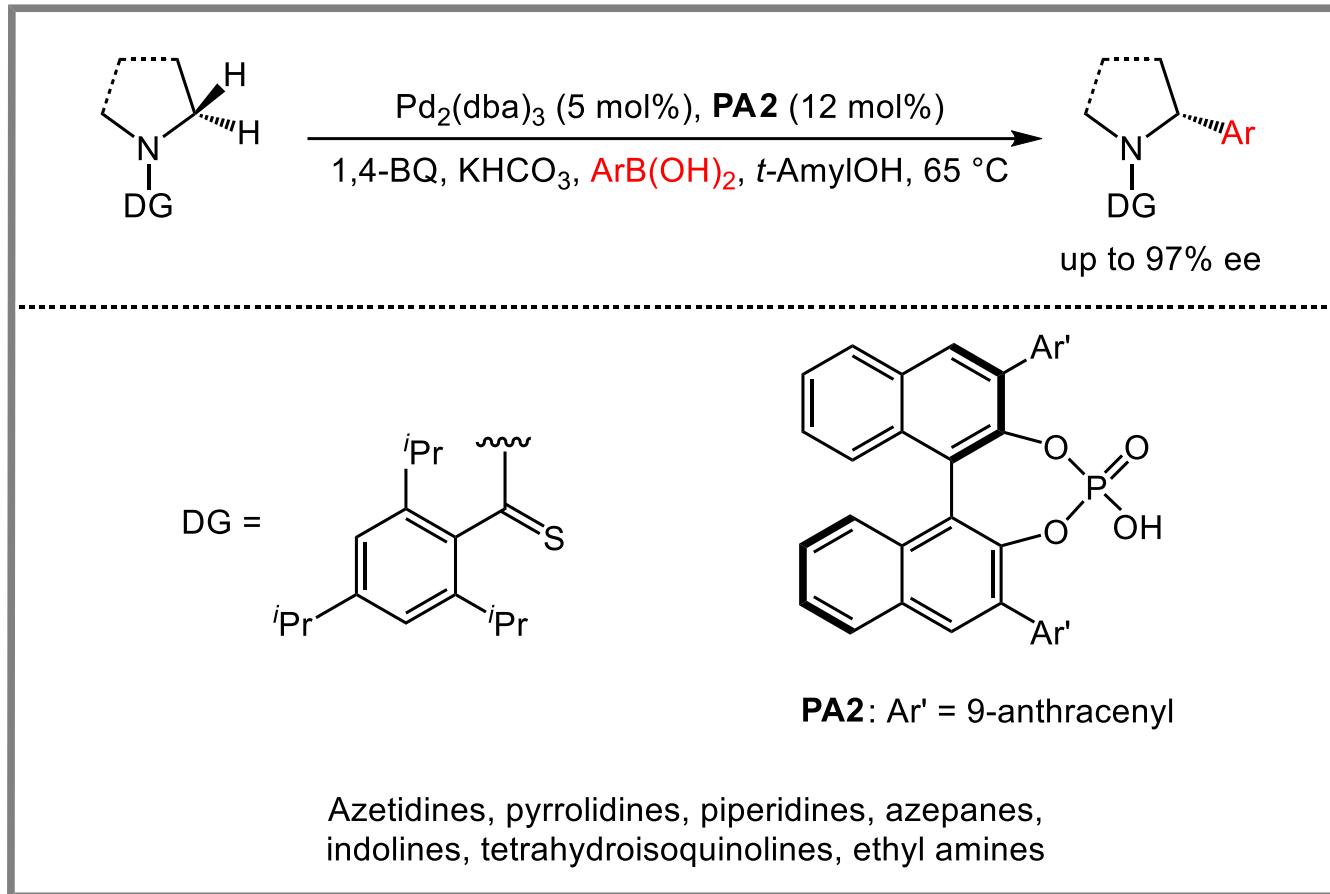
Ni-Catalyzed Enantioselective α -Alkylation of N-Heterocycles



Cordier, C. J.; Fu, G. C.* et al. *J. Am. Chem. Soc.* **2013**, *135*, 10946
Mu, X.; Fu, G. C.* et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 5821

Introduction

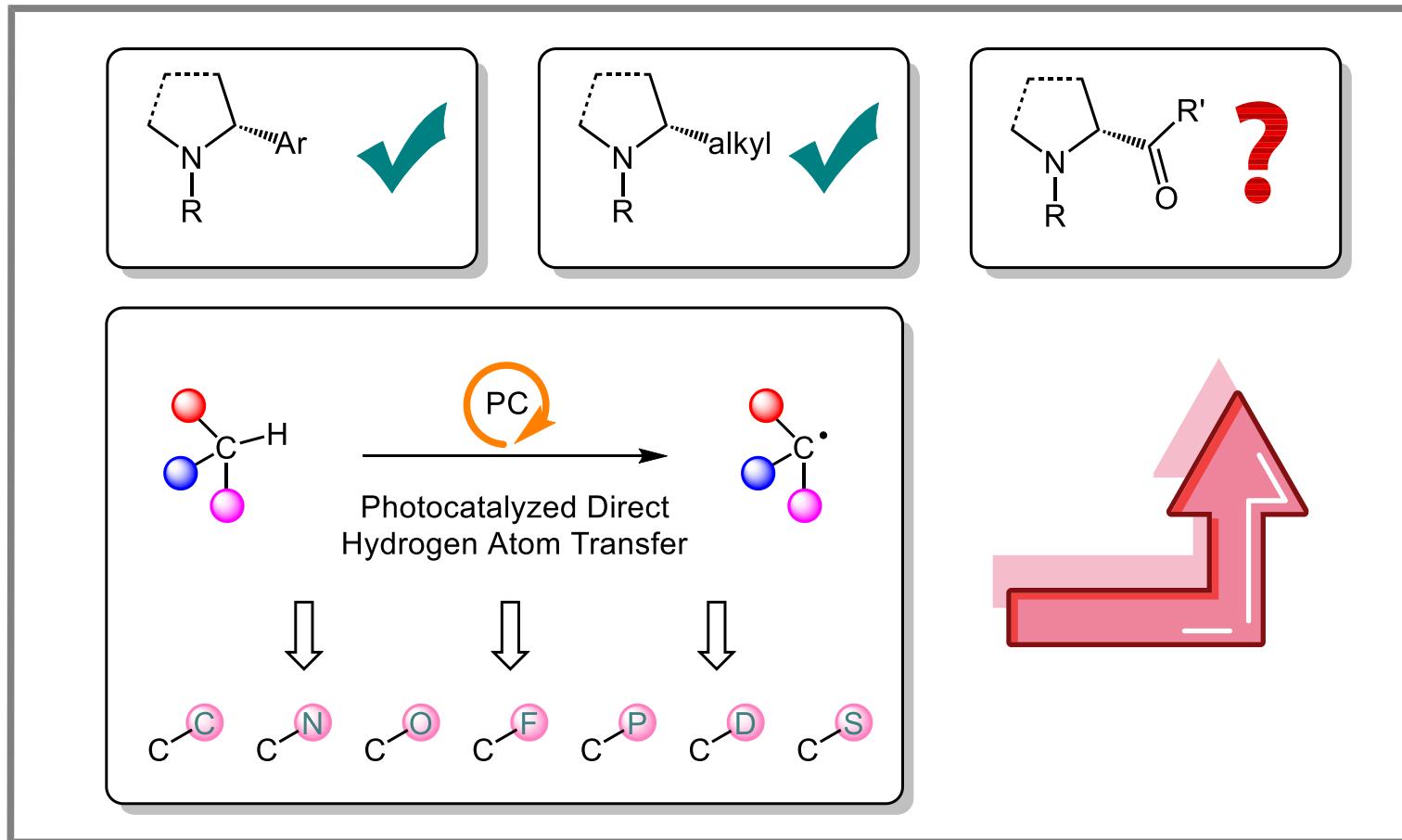
Pd-Catalyzed Enantioselective α -Arylation of N-Heterocycles



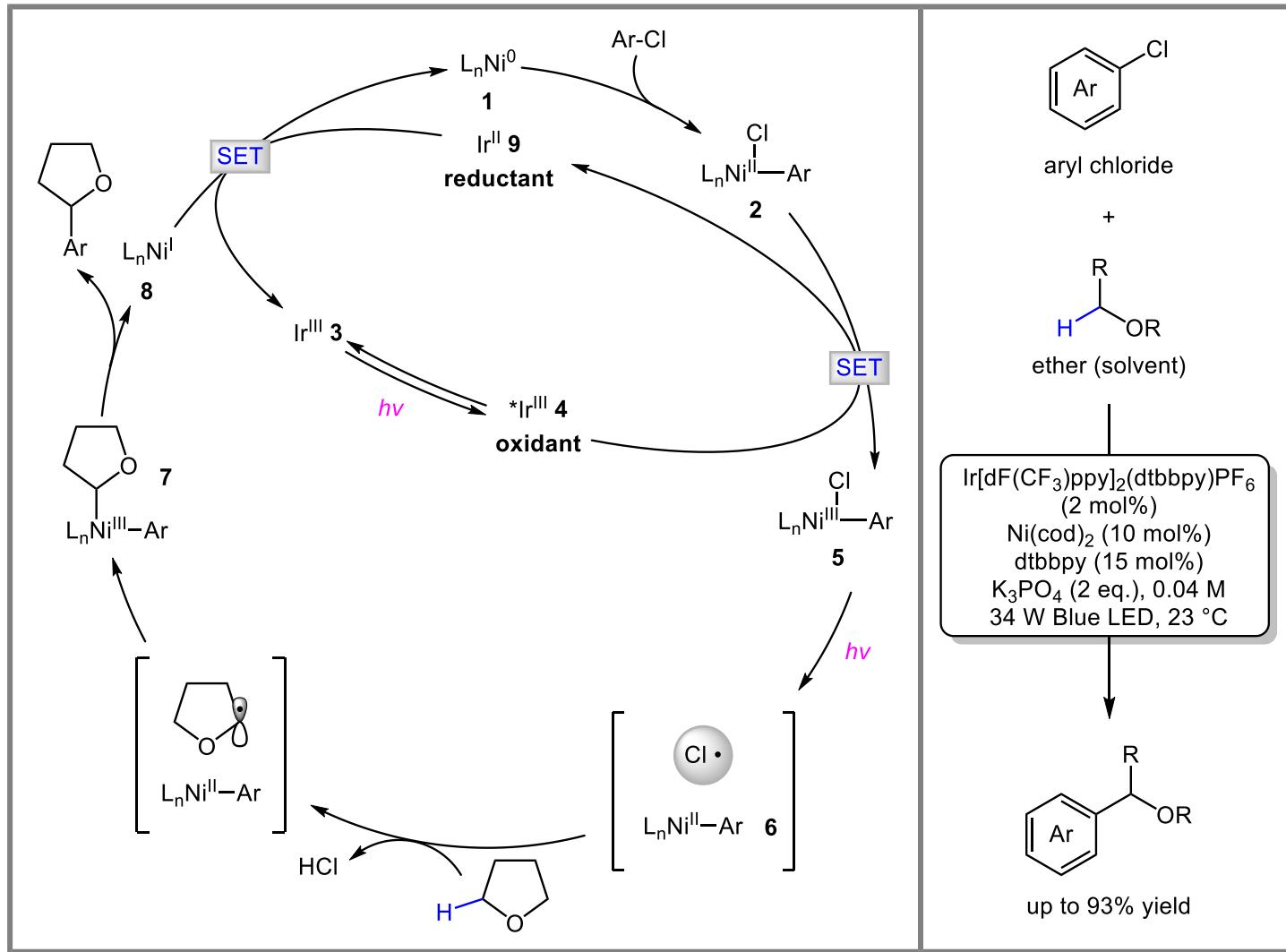
Jain, P.; Yu, J.-Q.* *et al.* *Nat. Chem.* **2017**, *9*, 140

Introduction

C(sp³)-H Functionalization Enabled by Hydrogen Atom Transfer Strategy

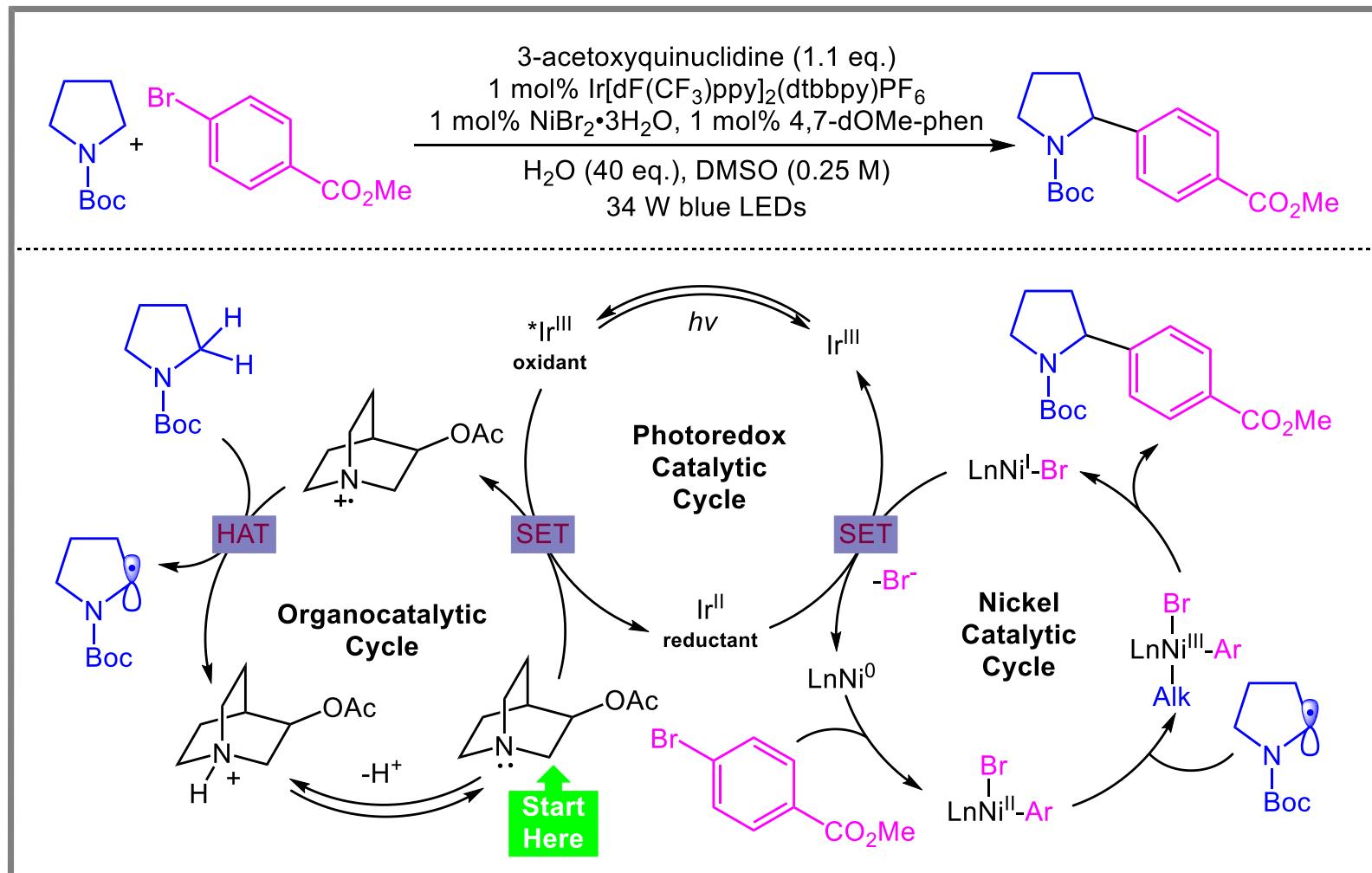


Introduction



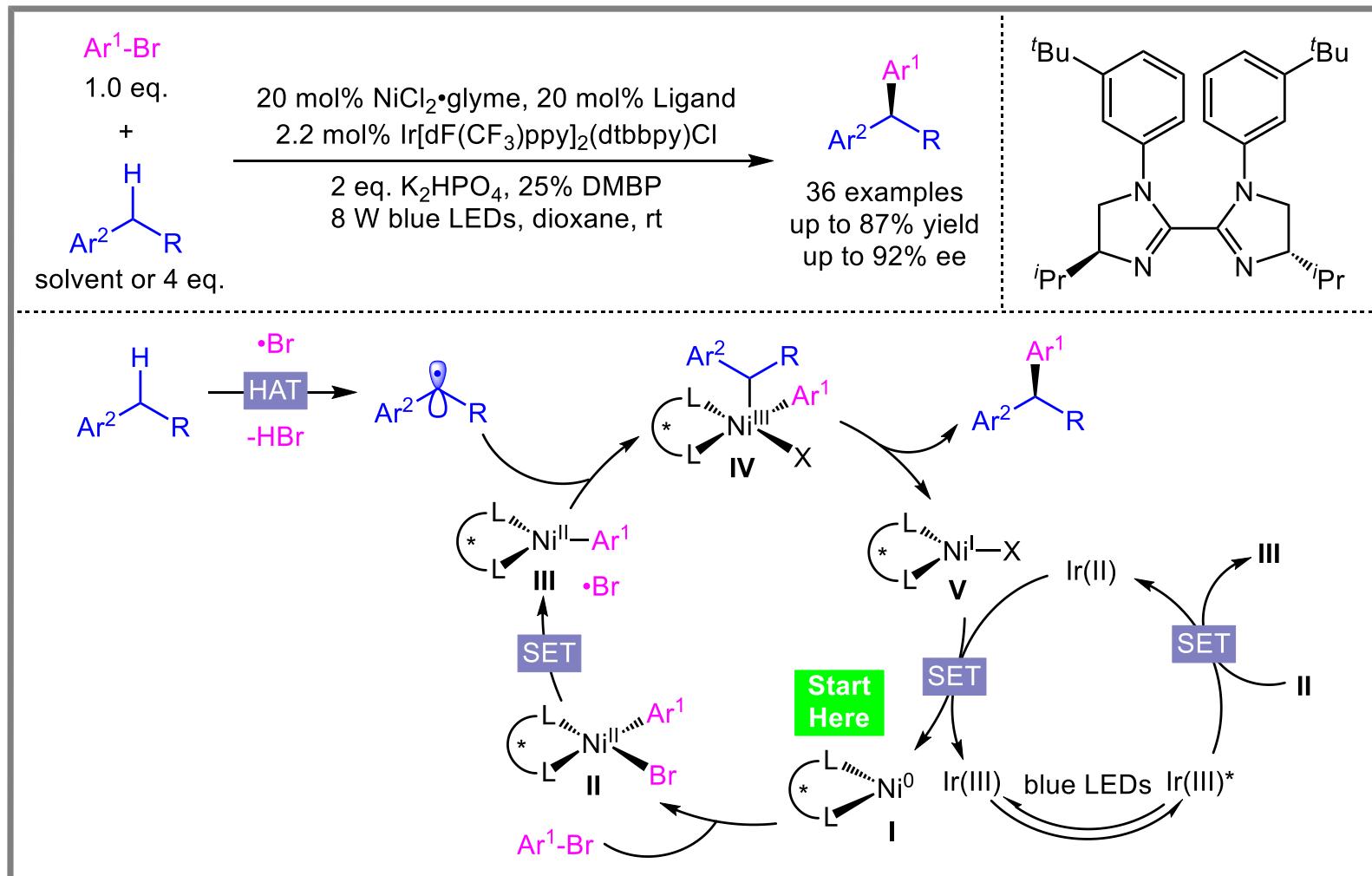
Shields, B. J.; Doyle, A. G.* *J. Am. Chem. Soc.* **2016**, 138, 12719

Introduction



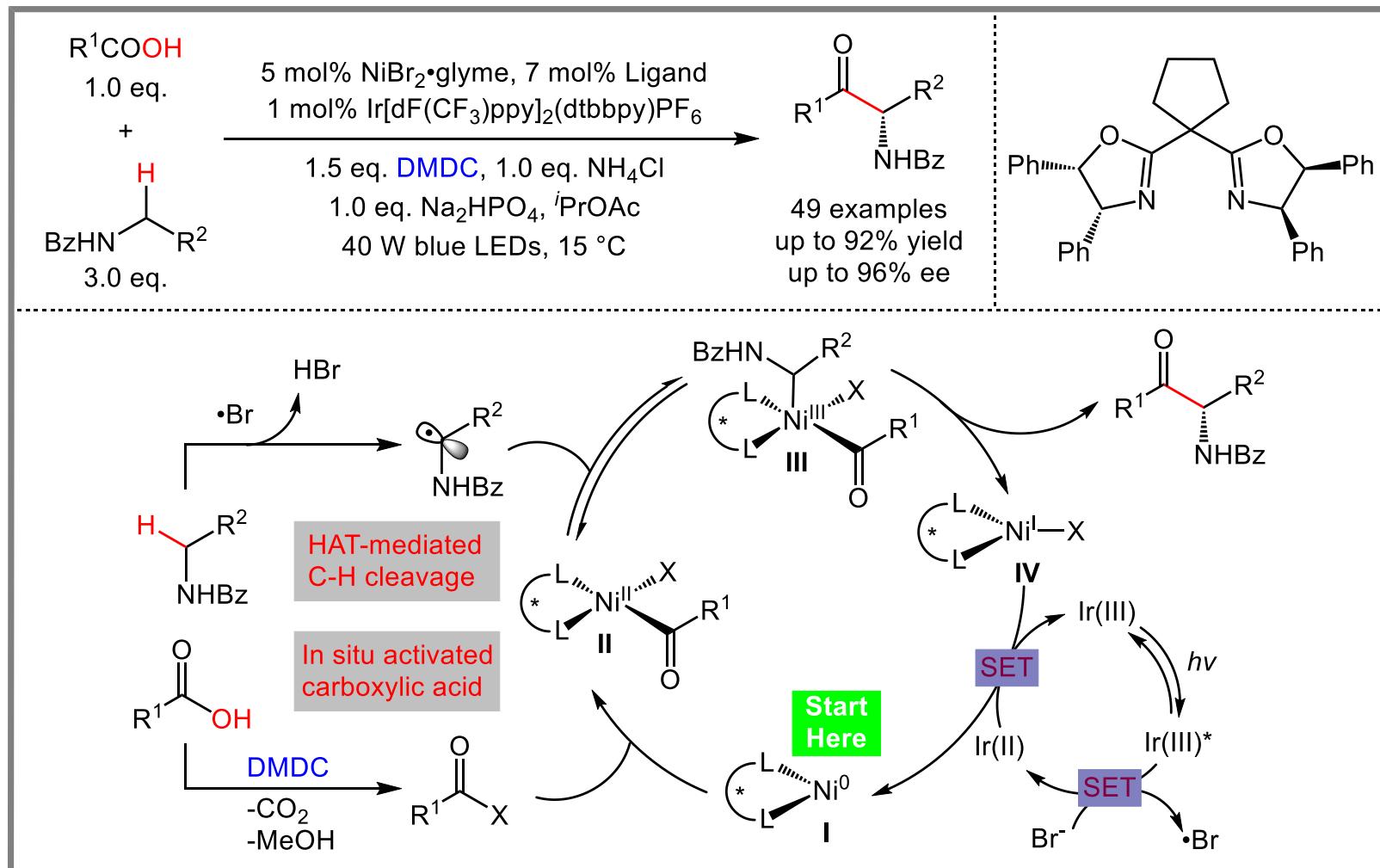
Shaw, M. H.; MacMillan, D. W. C.* *et al. Science* **2016**, 352, 1304

Introduction



Cheng, X.; Lu, Z.* et al. *Nat. Commun.* **2019**, *10*, 3549

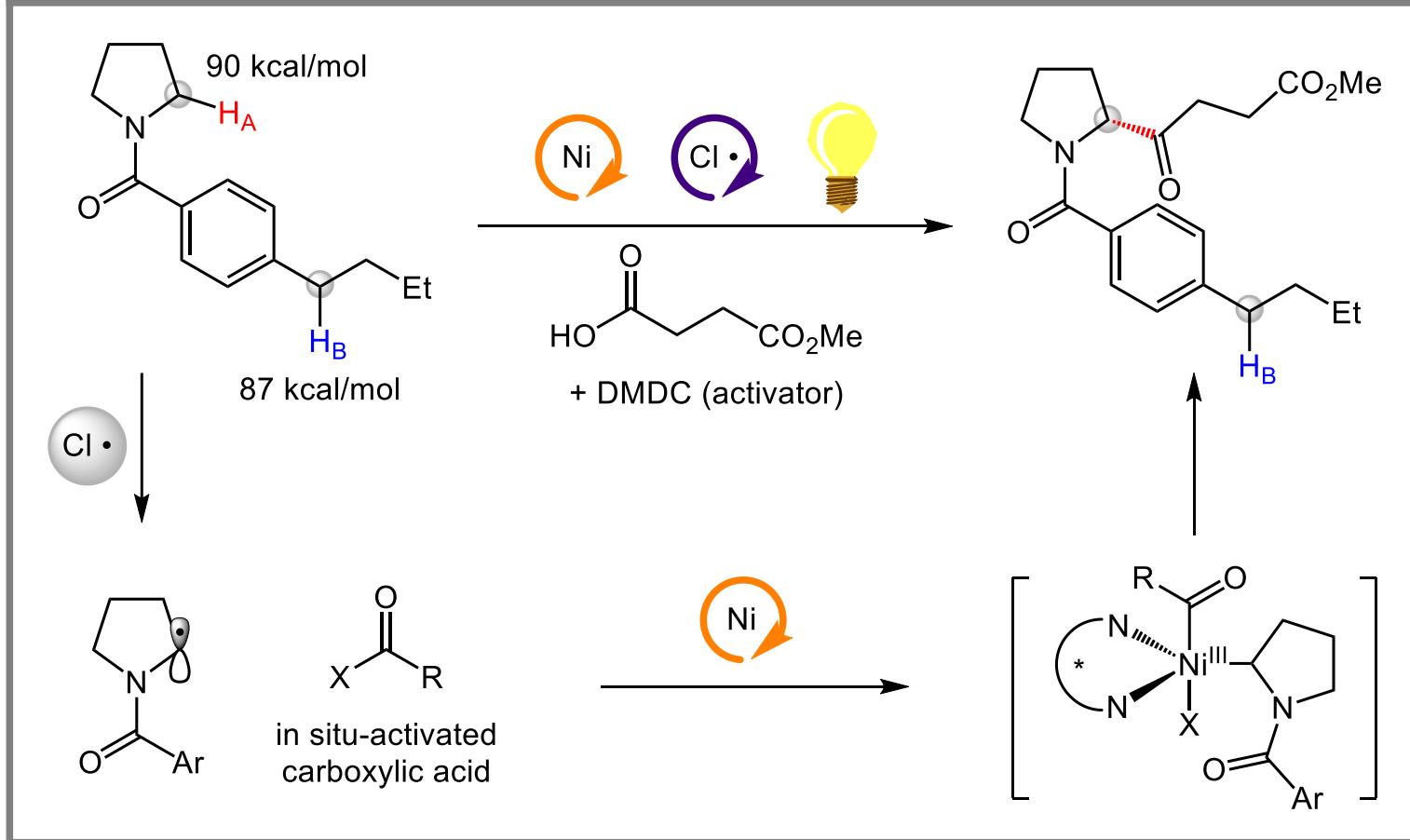
Introduction



Shu, X.; Huo, H.* et al. *J. Am. Chem. Soc.* **2020**, 142, 19058

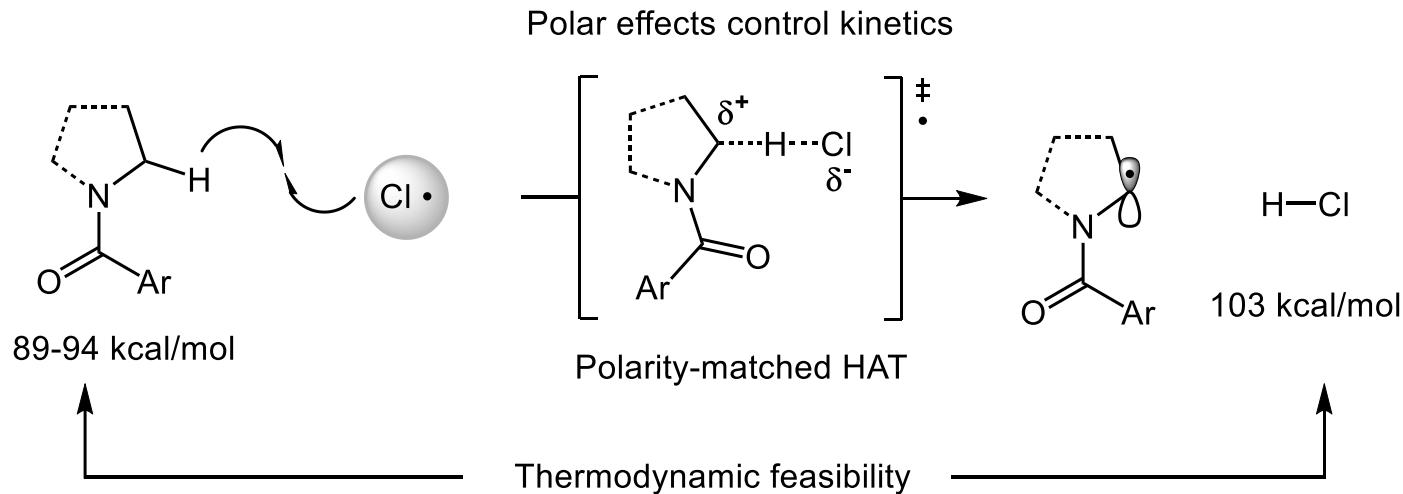
Project Synopsis

Site- and Enantioselective α -Acylation of Saturated Azacycles



Project Synopsis

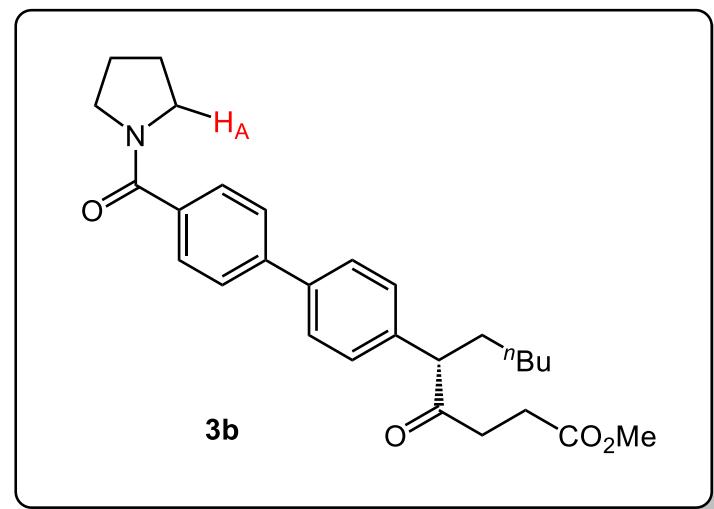
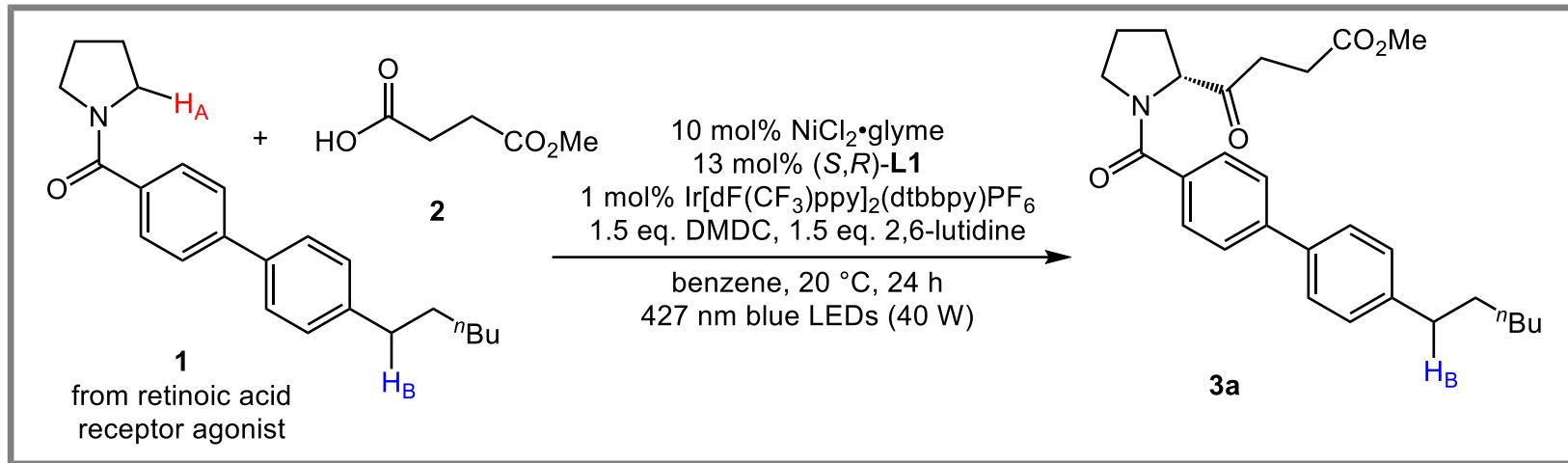
Site- and Enantioselective α -Acylation of Saturated Azacycles



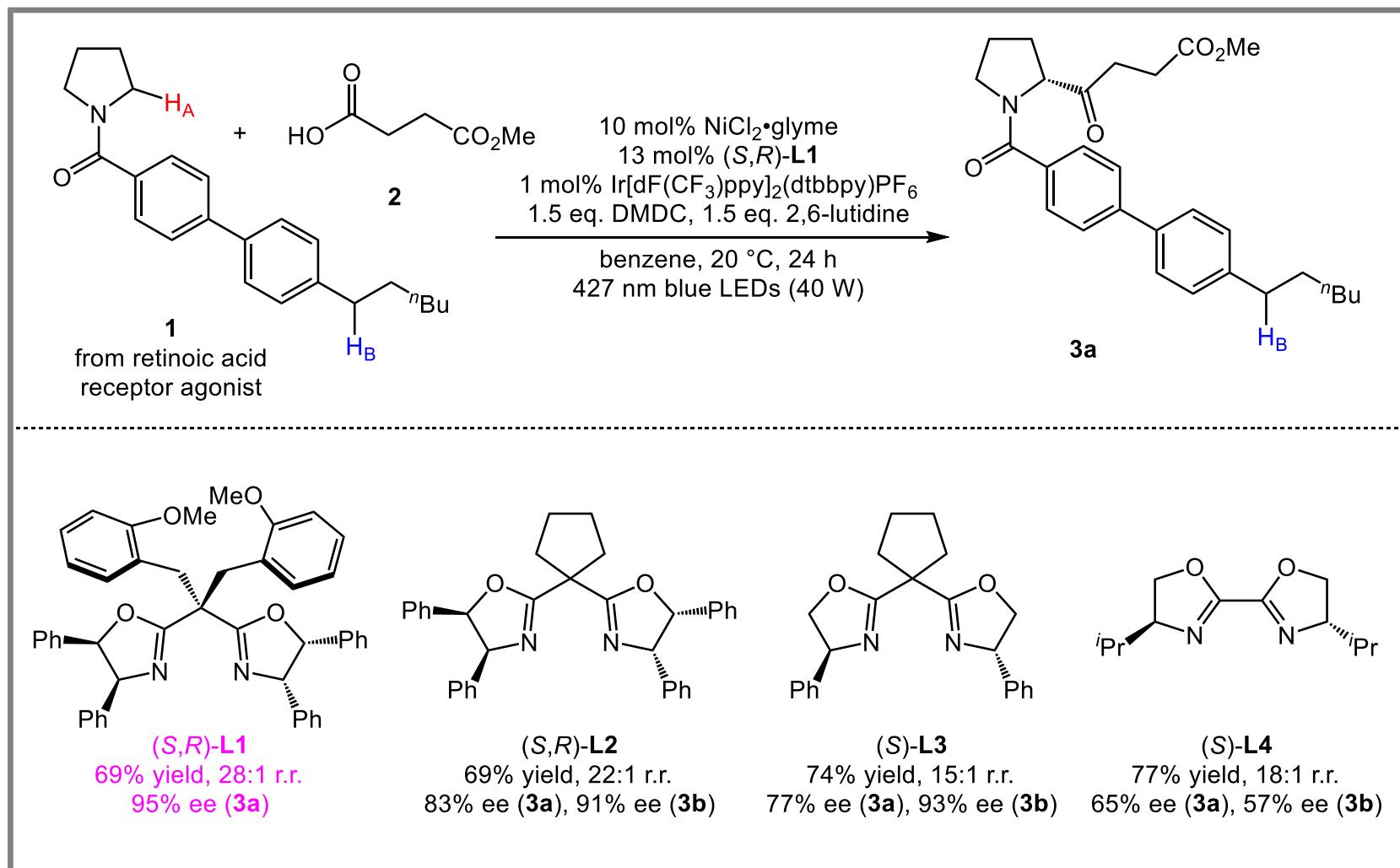
Challenges

- ❖ Control the site selectivity of HAT
- ❖ Control the enantioselectivity of the reaction
- ❖ Be amenable to late-stage diversifications
- ❖ No substrate preactivation steps required

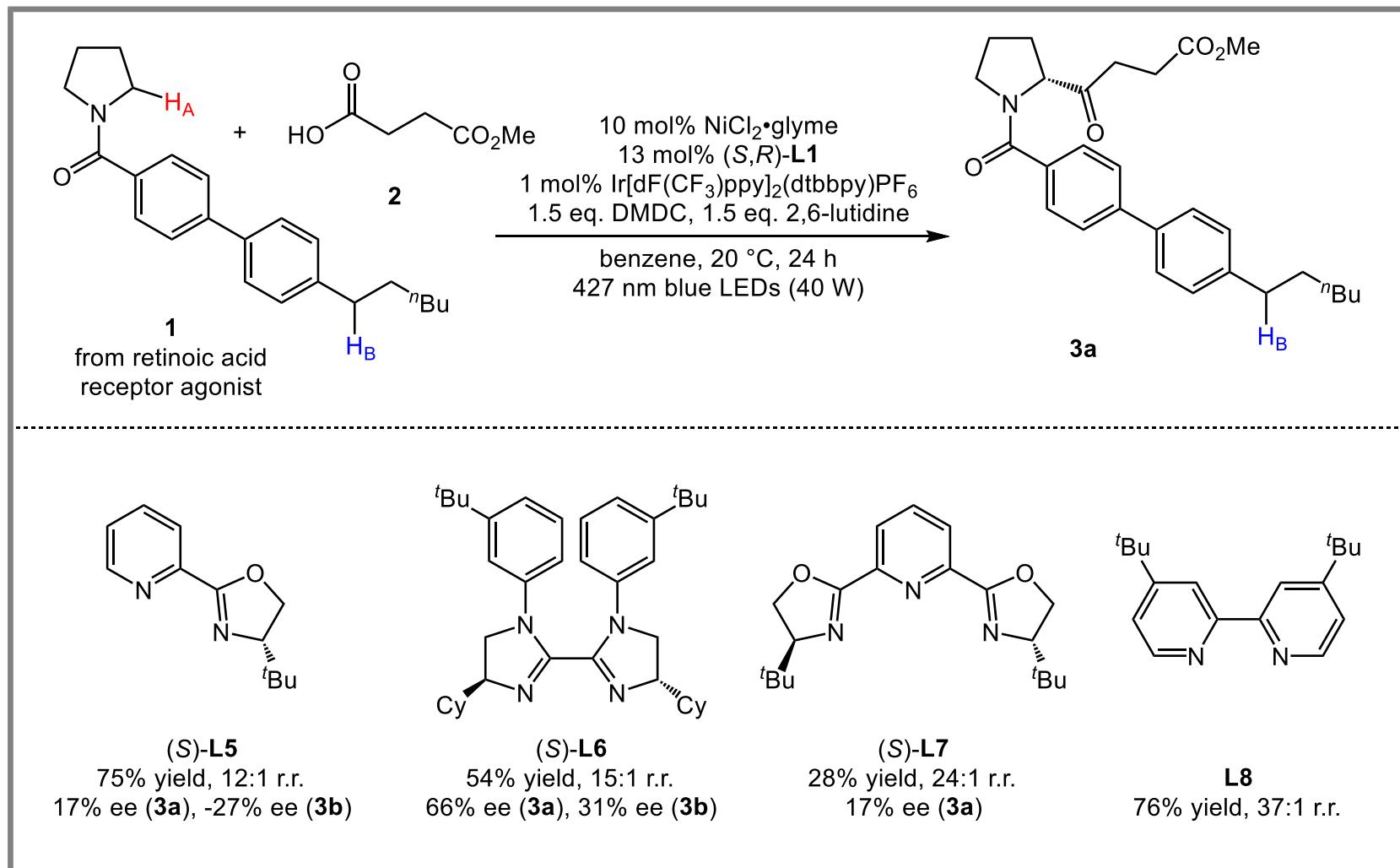
Optimization of Reaction Conditions



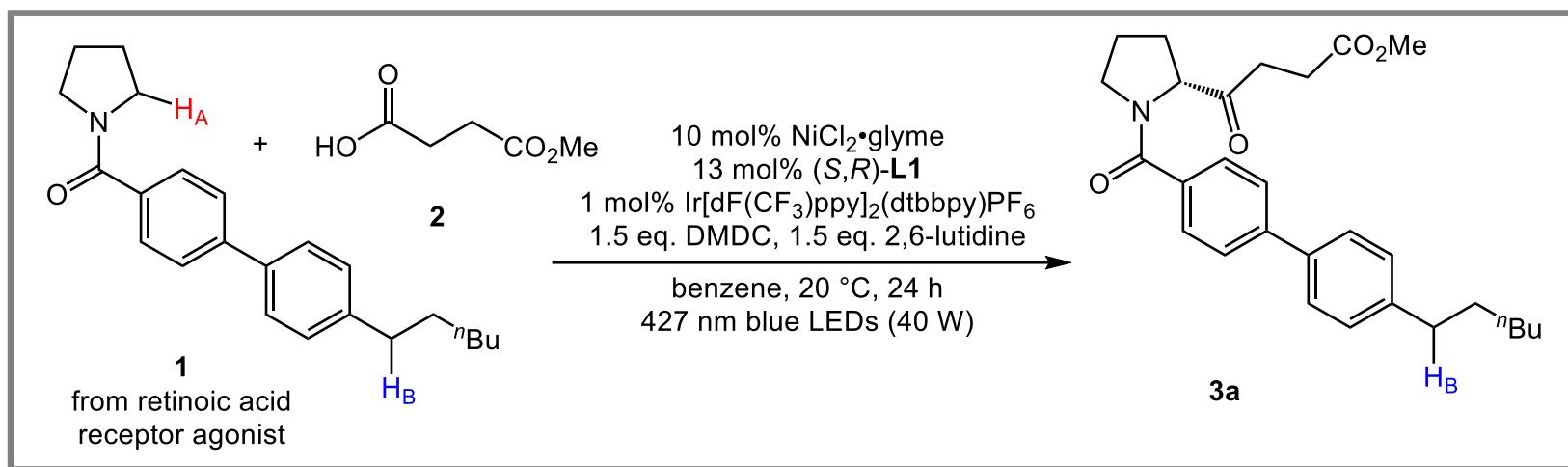
Optimization of Reaction Conditions



Optimization of Reaction Conditions



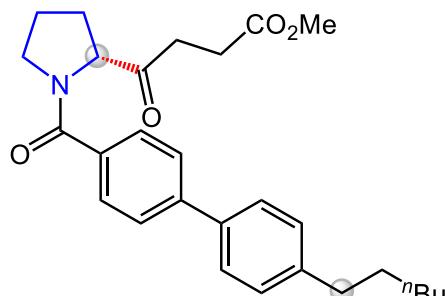
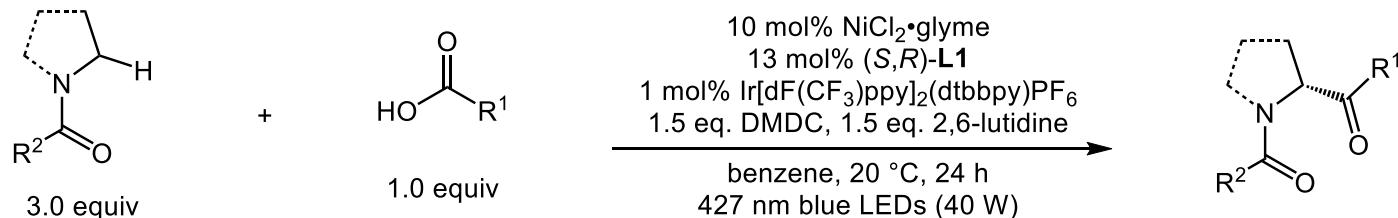
Optimization of Reaction Conditions



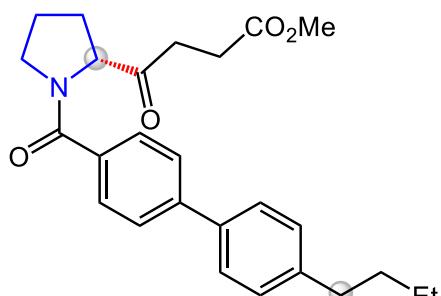
Entry	Variation from standard conditions	Yield (%)	r.r. (3a/3b)	ee (%) (3a/3b)
1	none	69	28:1	95/-
2	$\text{NiBr}_2 \cdot \text{glyme}$ instead of $\text{NiCl}_2 \cdot \text{glyme}$	19	1:1.7	92/73
3	NaHCO_3 instead of 2,6-lutidine	58	24:1	85/-
4	iPrOAc instead of benzene	71	20:1	89/-
5	1.5 eq. of NaBr added	39	2.8:1	95/74
6	1.0 eq. of H_2O added	69	39:1	93/-
7	under air in a capped 4-ml vial	70	27:1	95/-
8	No Ni, Ir, or light	0	-	-

Substrate Scope

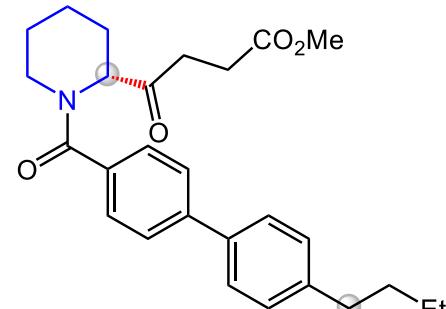
Intramolecular Selectivity



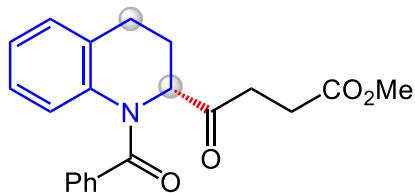
3a, 63% yield
95% ee, 28:1 r.r.



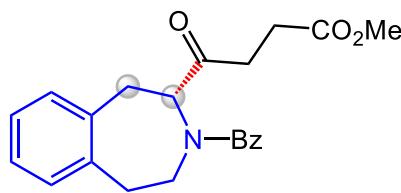
4, 68% yield
96% ee, > 20:1 r.r.



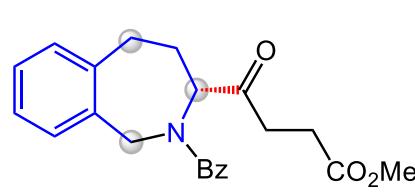
5, 60% yield
94% ee, > 20:1 r.r.



6, 85% yield
91% ee, > 20:1 r.r.



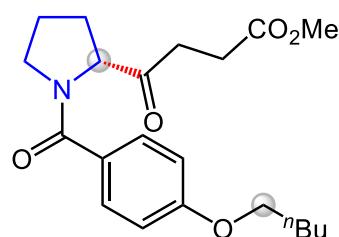
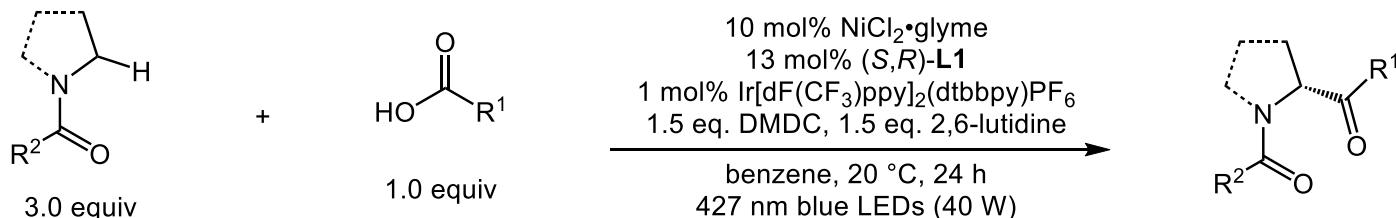
7, 46% yield
80% ee, > 20:1 r.r.



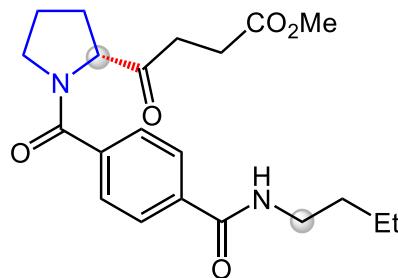
8, 44% yield
84% ee, 16:1 r.r.

Substrate Scope

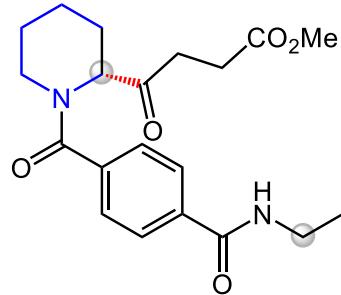
Intramolecular Selectivity



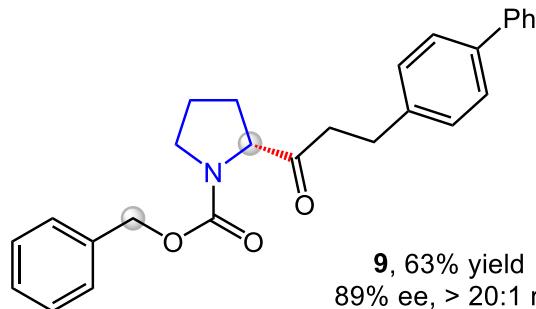
10, 65% yield
94% ee, 17:1 r.r.



11, 53% yield
89% ee, 15:1 r.r.



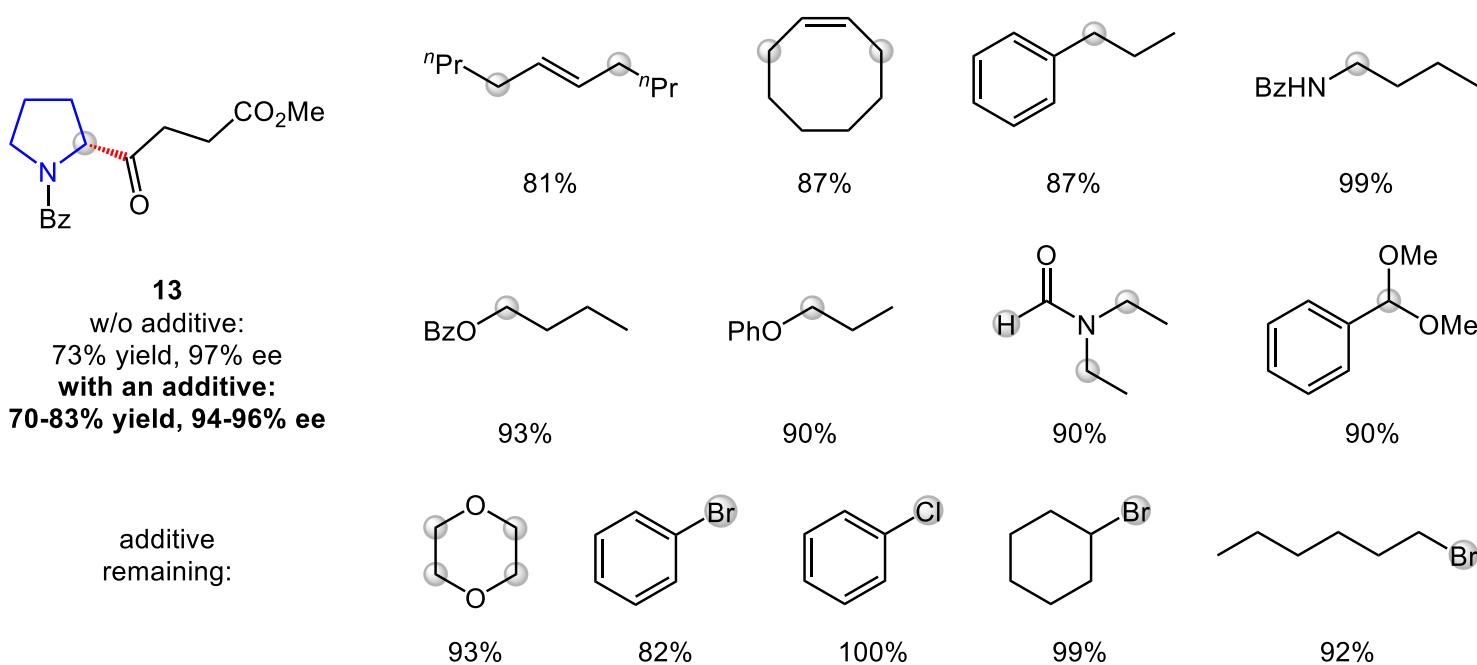
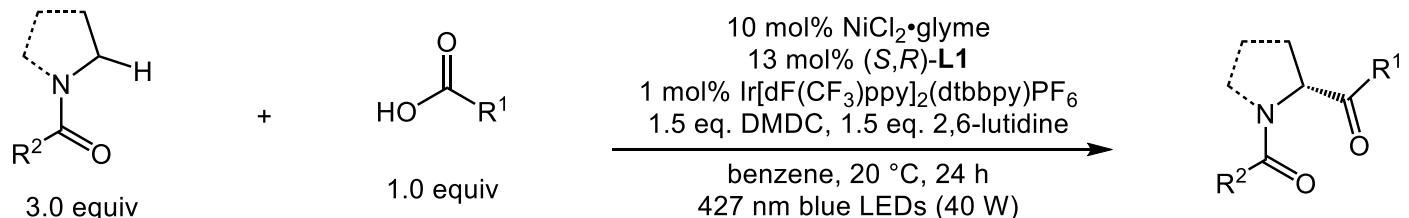
12, 51% yield
93% ee, 19:1 r.r.



9, 63% yield
89% ee, > 20:1 r.r.

Substrate Scope

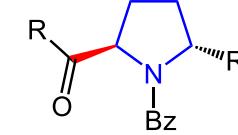
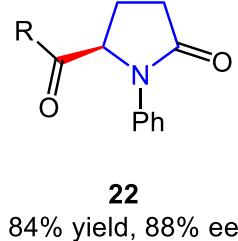
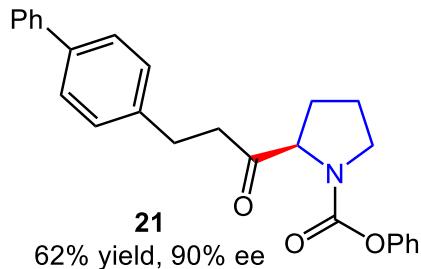
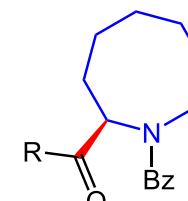
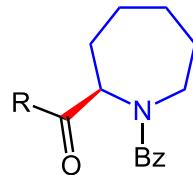
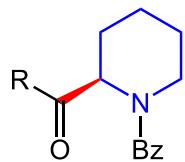
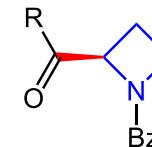
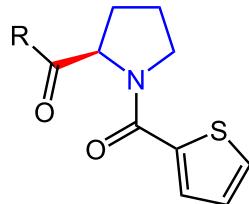
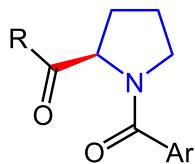
Intermolecular Selectivity



Substrate Scope

N-Heterocycle C-H Nucleophiles

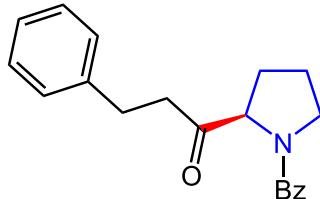
(R) = CH₂CH₂CO₂Me



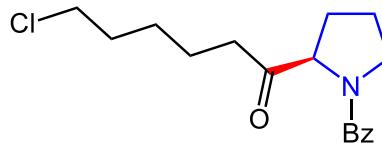
- 23, R' = Me 64% yield, > 99:1 dr
24, R' = Ph 65% yield, 99:1 dr
25, R' = CO₂Me 71% yield, 99:1 dr
26, R' = CH₂OTBDPS 55% yield, 99:1 dr

Substrate Scope

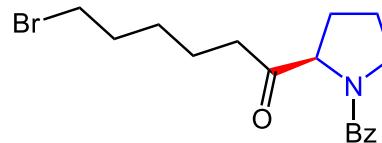
Alkyl and Aromatic Carboxylic Acids



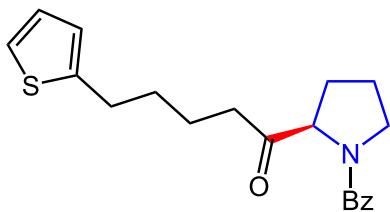
32
68% yield, 97% ee



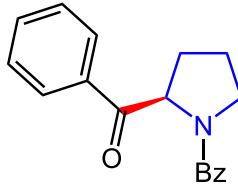
33
72% yield, 97% ee



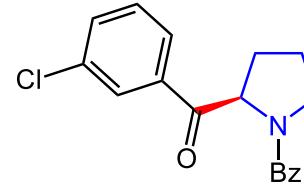
34
60% yield, 96% ee



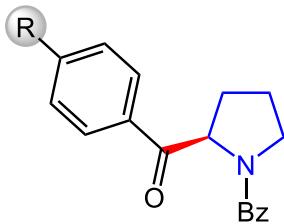
35
46% yield, 97% ee



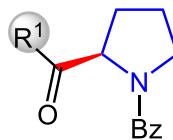
36
83% yield, 96% ee



41
68% yield, 97% ee



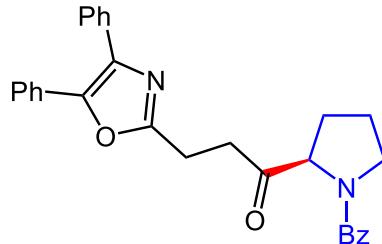
- 37**, R = Ac, 49% yield, 98% ee
38, R = F, 83% yield, 97% ee
39, R = Cl, 80% yield, 97% ee
39, R = OMe, 71% yield, 97% ee



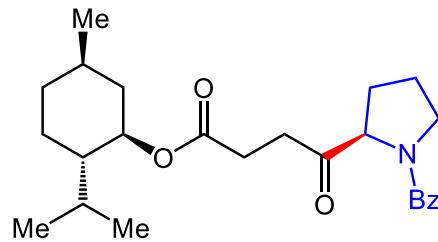
- 27**, R¹ = Me, 74% yield, 94% ee
28, R¹ = *n*Pr, 66% yield, 94% ee
29, R¹ = *i*Bu, 73% yield, 94% ee
30, R¹ = *i*Pr, 58% yield, 87% ee
31, R¹ = Cy, 65% yield, 83% ee

Substrate Scope

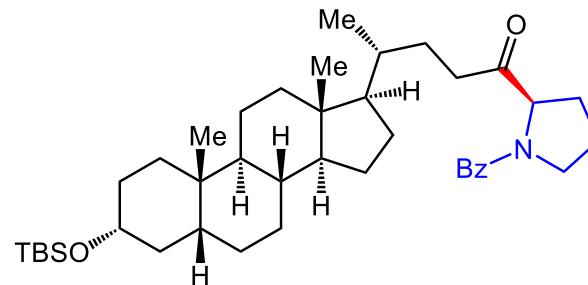
Drugs, Natural Products, and Biomolecules



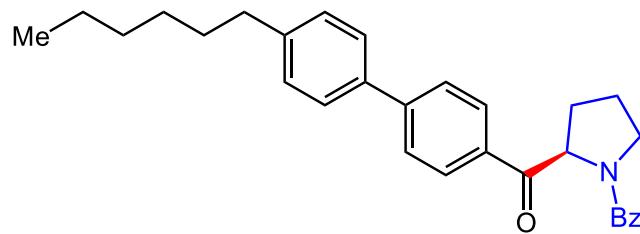
From **Oxaprozin**
42, 52% yield, 99% ee



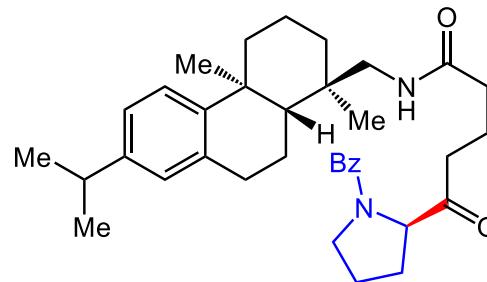
From **L-Menthol**
46, 71% yield, 98:2 dr



From **Lithocholic acid**
54, 48% yield, 96:4 dr

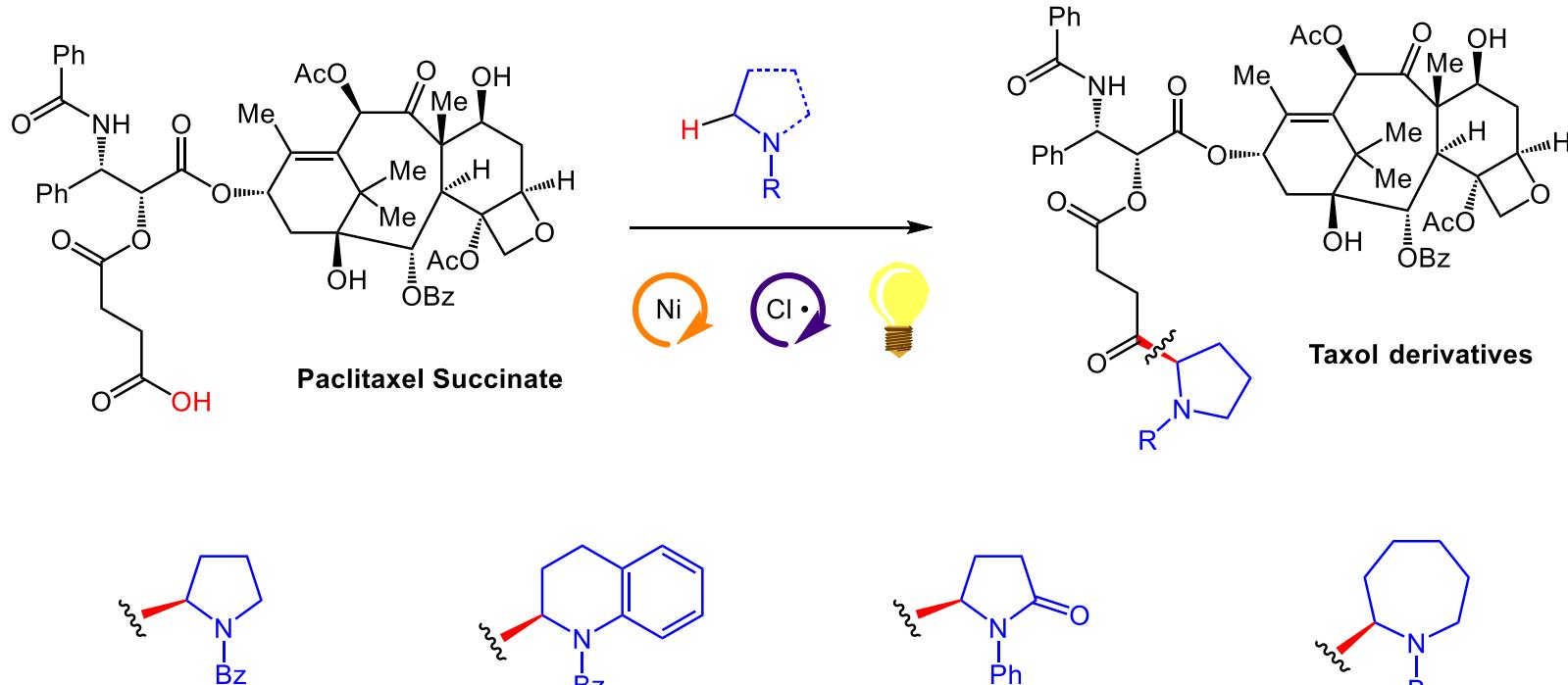


From **Retinoic acid receptor agonist**
60, 57% yield, 95% ee



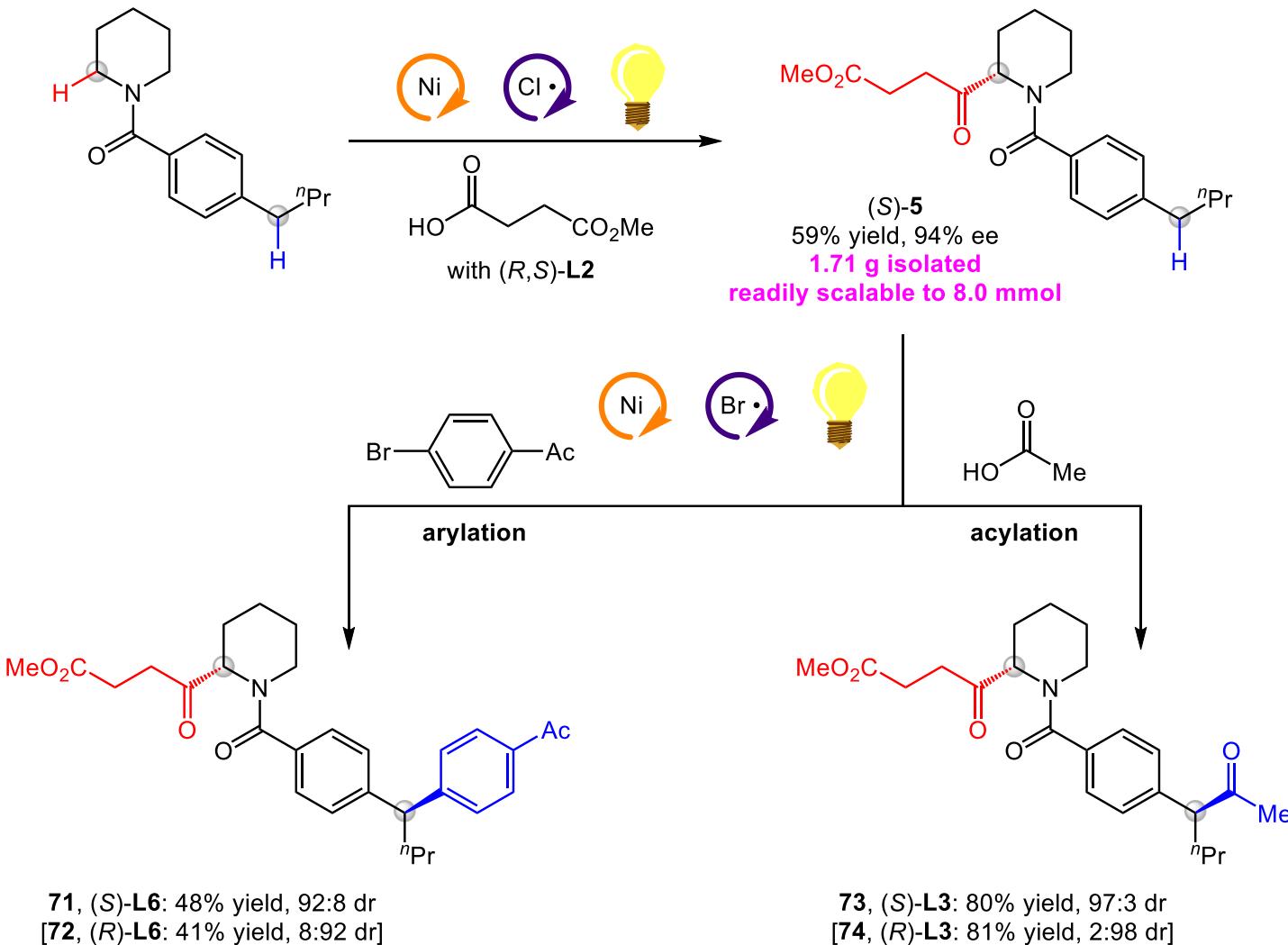
From **(+)-Dehydroabietylamine**
61, 36% yield, 99:1 dr

Substrate Scope

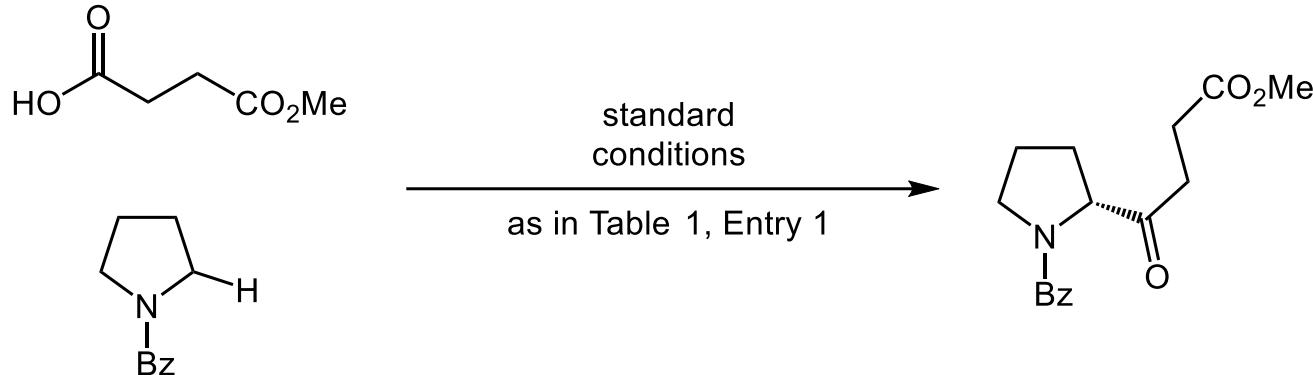


63, (*S,R*)-L: 60% yield, 98:2 dr 65, (*S,R*)-L: 85% yield, 98:2 dr 67, (*S,R*)-L: 60% yield, 95:5 dr 69, (*S,R*)-L: 34% yield, 95:5 dr
[64, (*R,S*)-L: 58% yield, 2:98 dr] [66, (*R,S*)-L: 84% yield, 2:98 dr] [68, (*R,S*)-L: 58% yield, 5:95 dr] [70, (*R,S*)-L: 32% yield, 7:93 dr]

Gram Scale & Iterative Coupling Sequence

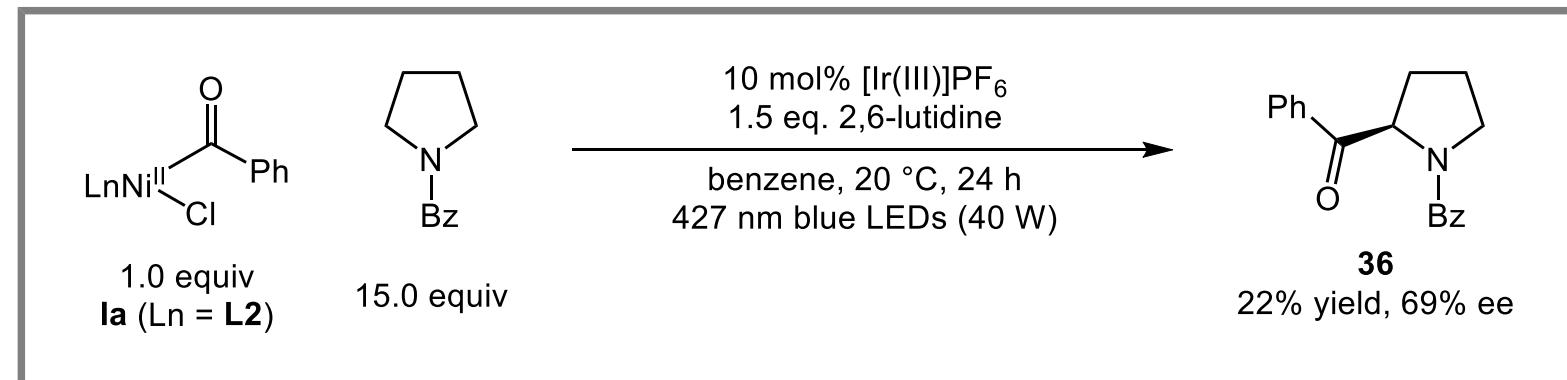
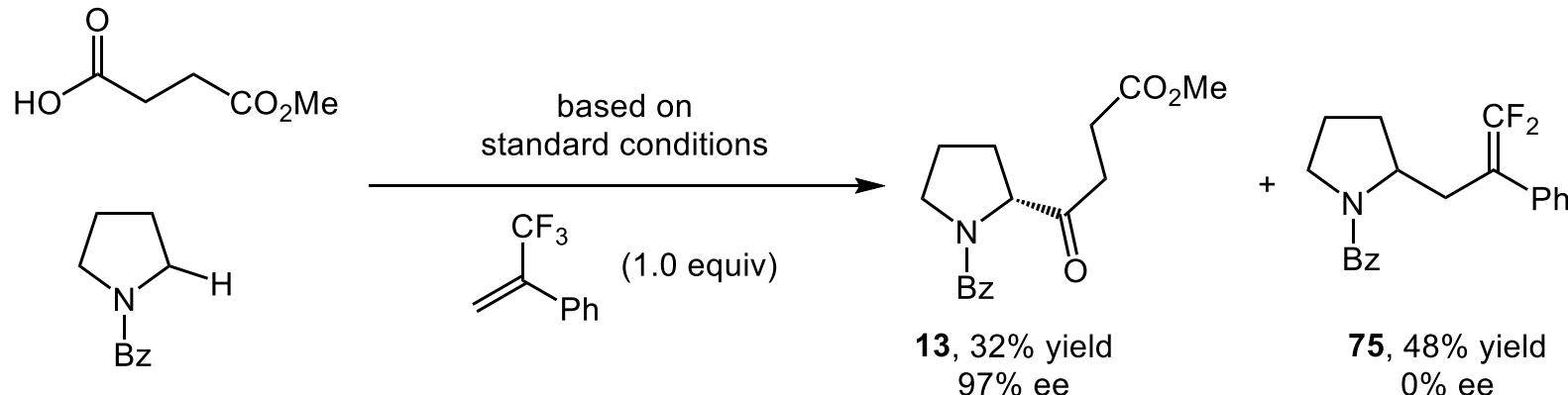


Mechanism Study

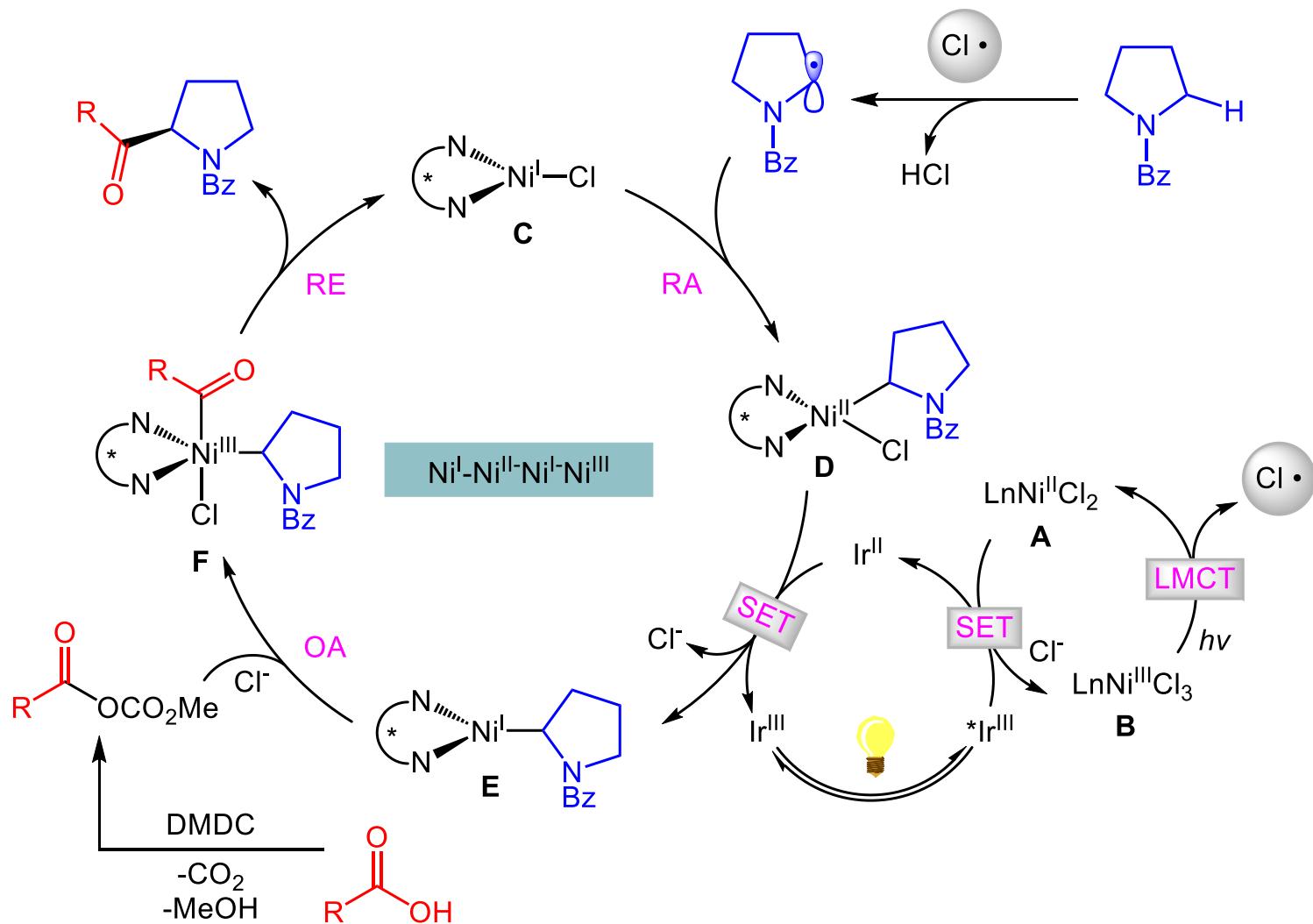


Entry	Variation	Results
1	NiCl ₂ •glyme (none)	73% yield, 97% ee
2	NiBr ₂ •glyme	8% yield, 98% ee
3	Ni(COD) ₂	2% yield, ee: ND
4	Ni(COD) ₂ , 1.5 equiv of LiCl added	6% yield, ee: ND
5	Ni(acac) ₂	28% yield, 89% ee
6	Ni(acac) ₂ , 1.5 equiv of LiCl added	64% yield, 95% ee

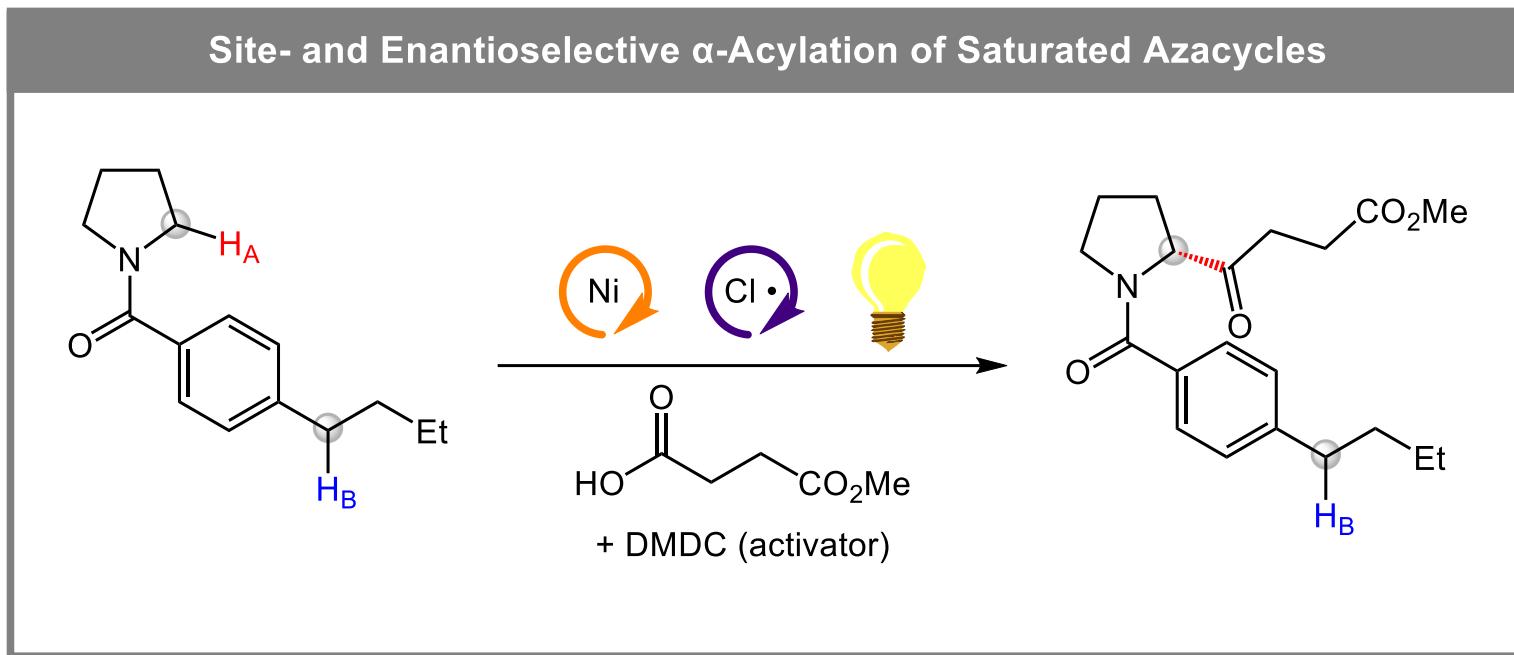
Mechanism Study



Proposed Mechanism



Summary



- 开发了一种具有高对映选择性的饱和氮杂环的 α 位酰基化反应；
- 采用氯原子介导的氢原子转移策略，对氮 α 位C-H键具有高选择性；
- 具有很广阔的底物适用范围，产物易于大规模合成、便于衍生化。

Writing Strategies

□ The First Paragraph

The Importance of Chiral α -Functionalized Azacycles



Chiral α -functionalized azacycles are commonly found in pharmaceutical drugs, natural products, and catalysts for asymmetric synthesis.

Prior Art for Enantioselective α -Functionalization of Saturated Azacycles



A particularly attractive approach to access enantioenriched α -functionalized azacycles is metal-catalyzed α -functionalization of readily available *N*-heterocycles.....

The Necessity of This Work

Although there have been a limited number of examples for..... A general strategy for the direct enantioselective α -acylation of common saturated azacycles has yet to be developed.

Writing Strategies

□ The Last Paragraph

Summary of This Work



In summary, we have developed a highly site- and enantioselective α -acylation of saturated N-heterocycles.

Elucidate the Highlights



This general and modular approach exploits the HAT reactivity of photoeliminated chlorine radicals to selectively functionalize cyclic α -amino $C(sp^3)$ -H bonds in the presence of benzylic, allylic, acyclic.....

The Prospects of This Work

We anticipate that this new chlorine-radical-mediated HAT strategy will serve as a general and practical platform for direct enantioselective α -functionalization of saturated azacycles.

Representative Examples

- The mild and scalable protocol requires no organometallic reagents, displays excellent chemo-, site- and enantioselectivity, and **is amenable to** (有…的义务，经得起…的检验) late-stage diversification.
- Finally, control experiments revealed that the nickel catalyst, photocatalyst, and visible light are **indispensable** (不可或缺的；必不可少的) for the acylation product formation.
- Although carboxylic acids are **arguably** (可论证地；按理) the most operationally convenient and commercially abundant acyl **surrogates** (代表；代用品), moisture sensitive.....

Acknowledgement

Thanks for Your Attention