



Unlocking the Potential of Nickel Photoredox Catalysis for Enantioselective C(sp³)-H Functionalization

Lili Zhang

2024.10.25

Author Introduction



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厦门大学

Professional Experience

2019-present Professor of Chemistry, Xiamen University

2016-2019 Postdoctoral Fellow, California Institute of Technology

Advisor: Prof. Gregory C. Fu

Education

2012-2016 Ph.D. in Organic Chemistry, Philipps-Universität Marburg

Advisor: Prof. Eric Meggers

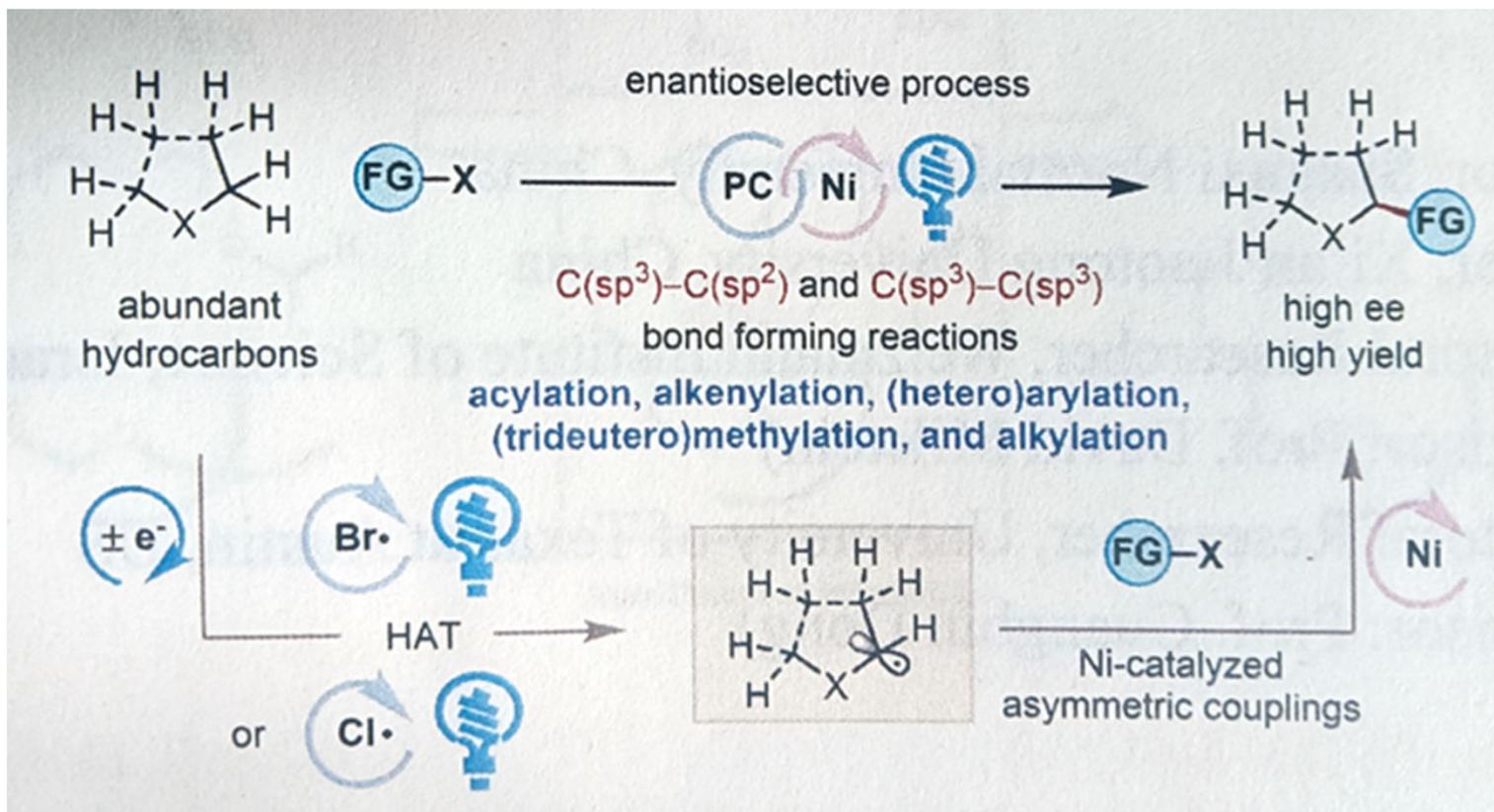
2005-2012 B.S. & M.S. in Chemistry, Xiamen University

Advisor: Prof. Pei-Qiang Huang

Research Topics:

光与过渡金属协同催化的不对称自由基C(sp³)-H官能团化。

目录



- $Br\cdot$ 介导的 $C(sp^3)-H$ 官能化
- $Cl\cdot$ 介导的 $C(sp^3)-H$ 官能化

1.1 Br•介导的C(sp³)-H官能化——酰基化

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Communication

Direct Enantioselective C(sp³)-H Acylation for the Synthesis of α -Amino Ketones

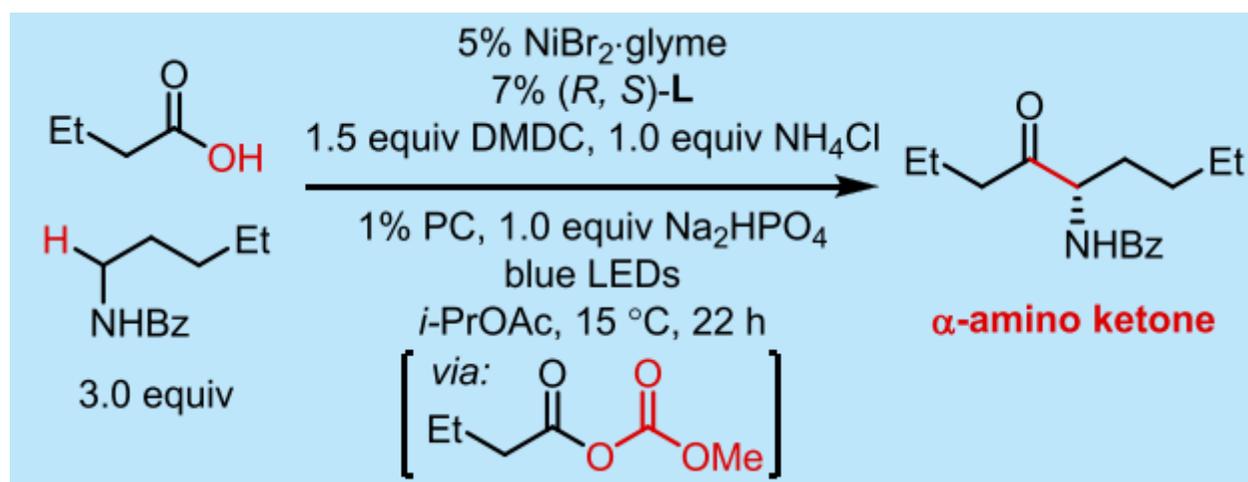
Xiaomin Shu,[†] Leitao Huan,[†] Qian Huang, and Haohua Huo*



Cite This: *J. Am. Chem. Soc.* 2020, 142, 19058–19064

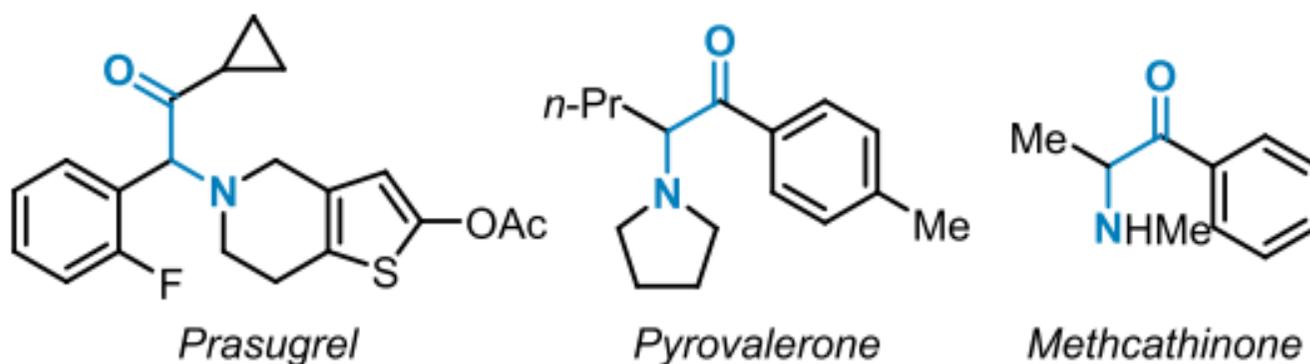


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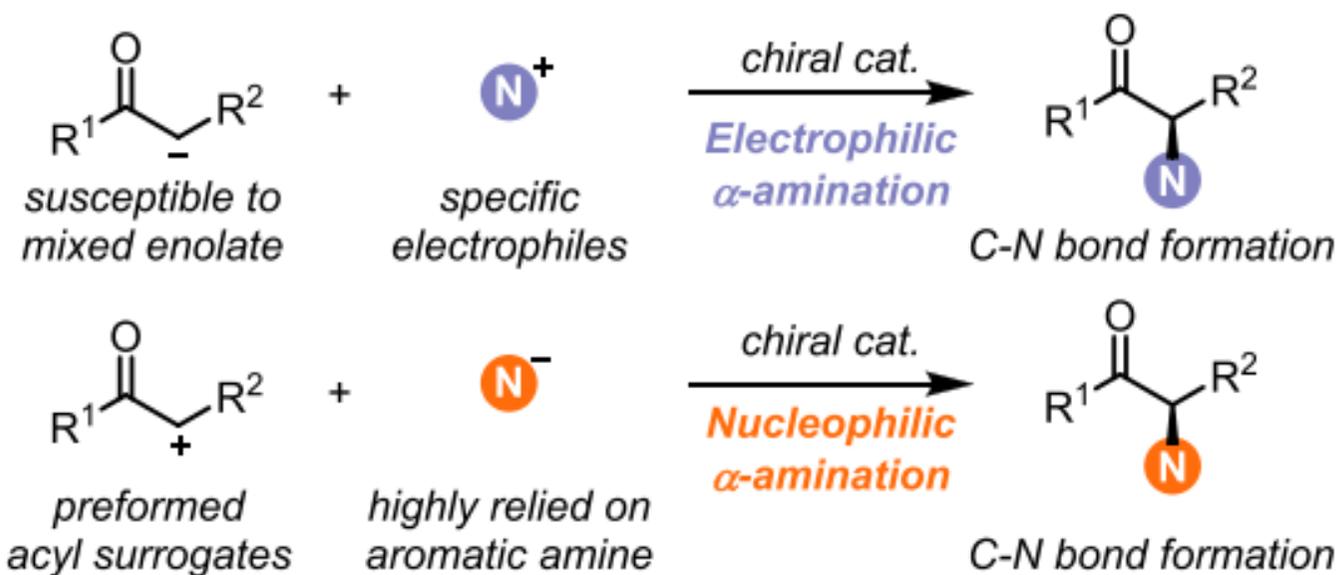


1.1 Br•介导的C(sp³)-H官能化——酰基化

a) Bioactive agents containing α -amino ketone motifs

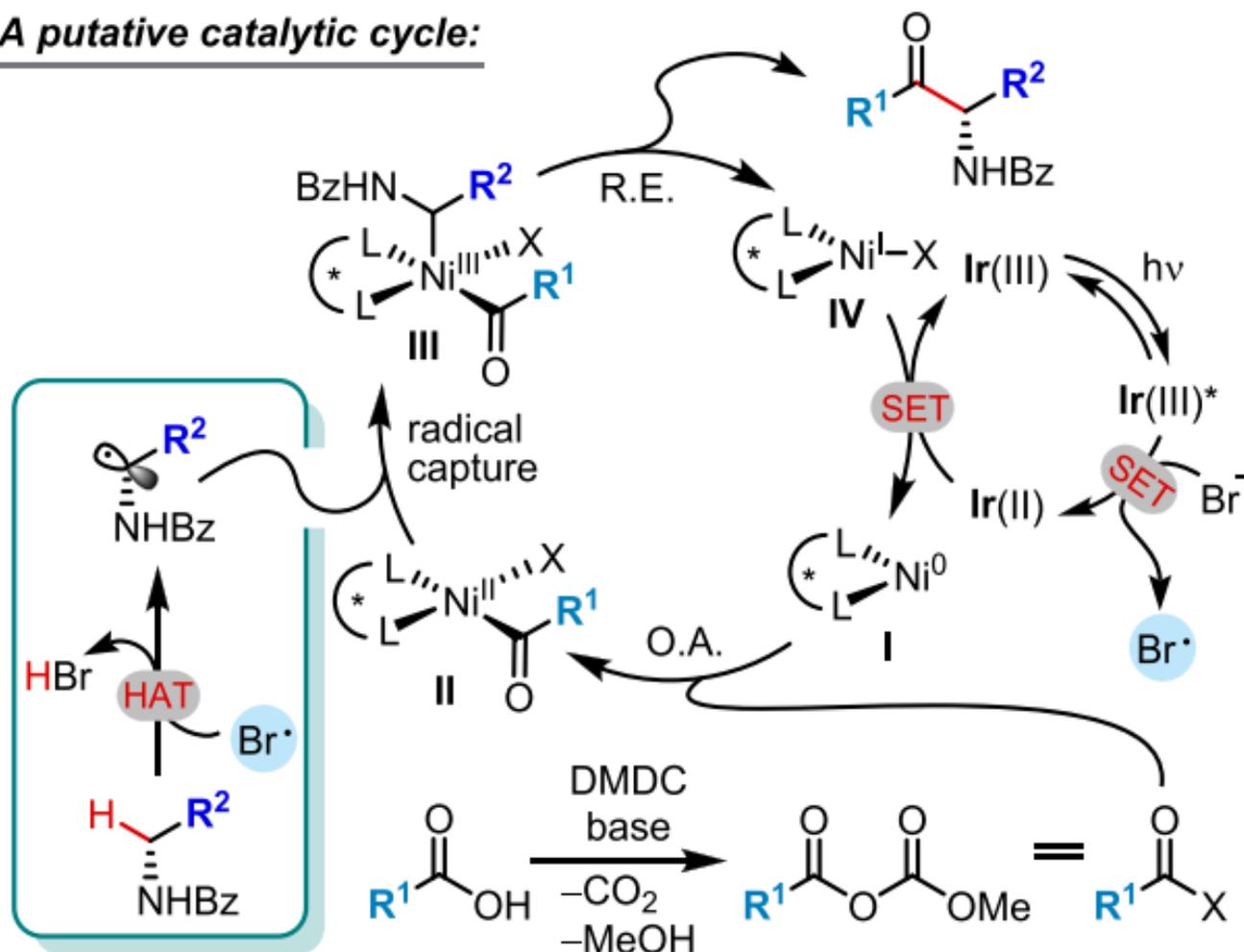


b) Classic strategies for asymmetric synthesis of α -amino ketones



1.1 Br•介导的C(sp³)-H官能化——酰基化

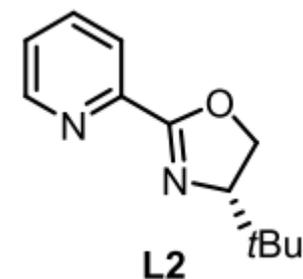
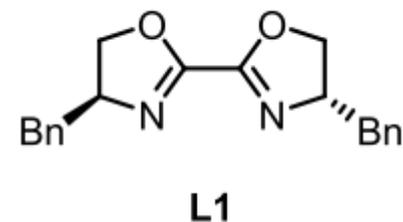
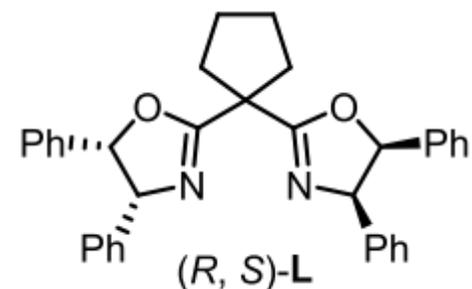
A putative catalytic cycle:



1.1 Br•介导的C(sp³)-H官能化——酰基化

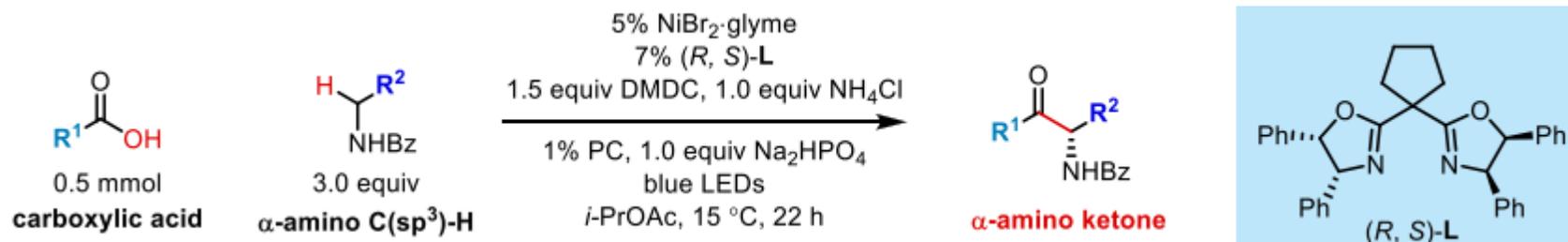


entry	variation from the "standard conditions"	yield (%) ^a	ee (%) ^b
1	none	90	92
2	no NiBr ₂ ·glyme	0	-
3	no (S, R)-L	0	-
4	no PC, or no light	0	-
5	no NH ₄ Cl	77	92
6	under air in a capped vial	77	92
7	25 °C, instead of 15 °C	89	91
8	Boc ₂ O, instead of DMDC	20	86
9	EA, instead of <i>i</i> -PrOAc	75	87
10	dioxane, instead of <i>i</i> -PrOAc	72	90
11	L1 , instead of (R, S)-L	89	-13
12	L2 , instead of (R, S)-L	79	-23

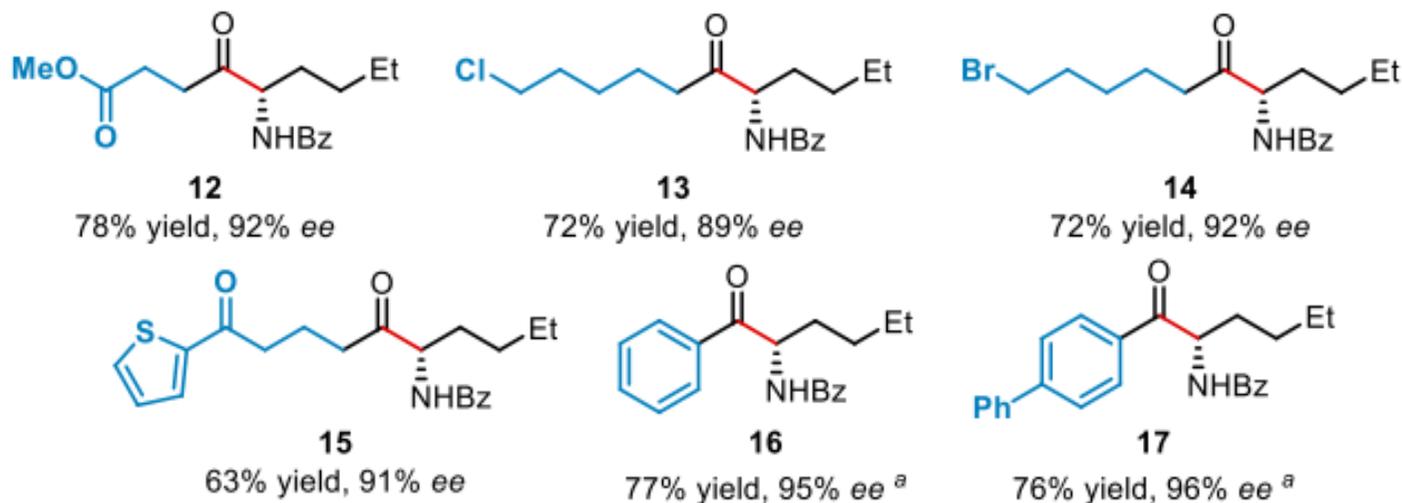


PC = Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. DMDC = Dimethyl dicarbonate.

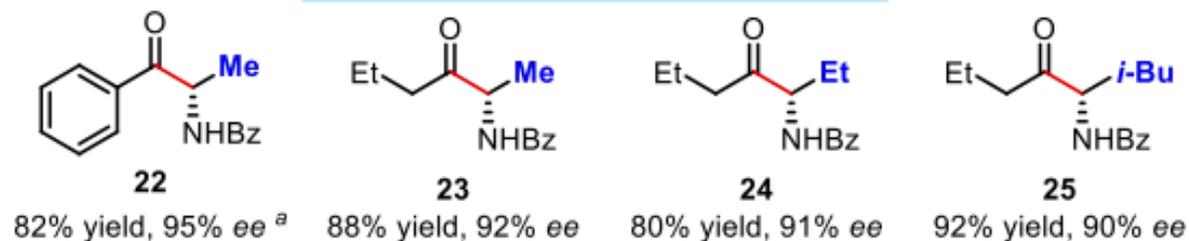
1.1 Br•介导的C(sp³)-H官能化——酰基化



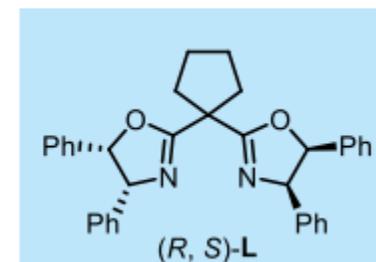
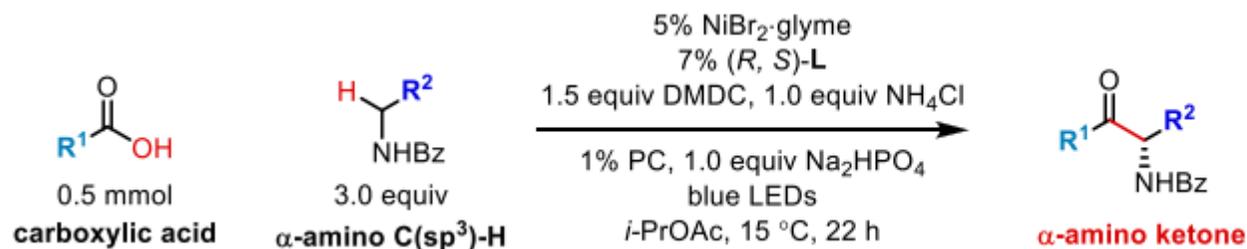
Scope of carboxylic acid



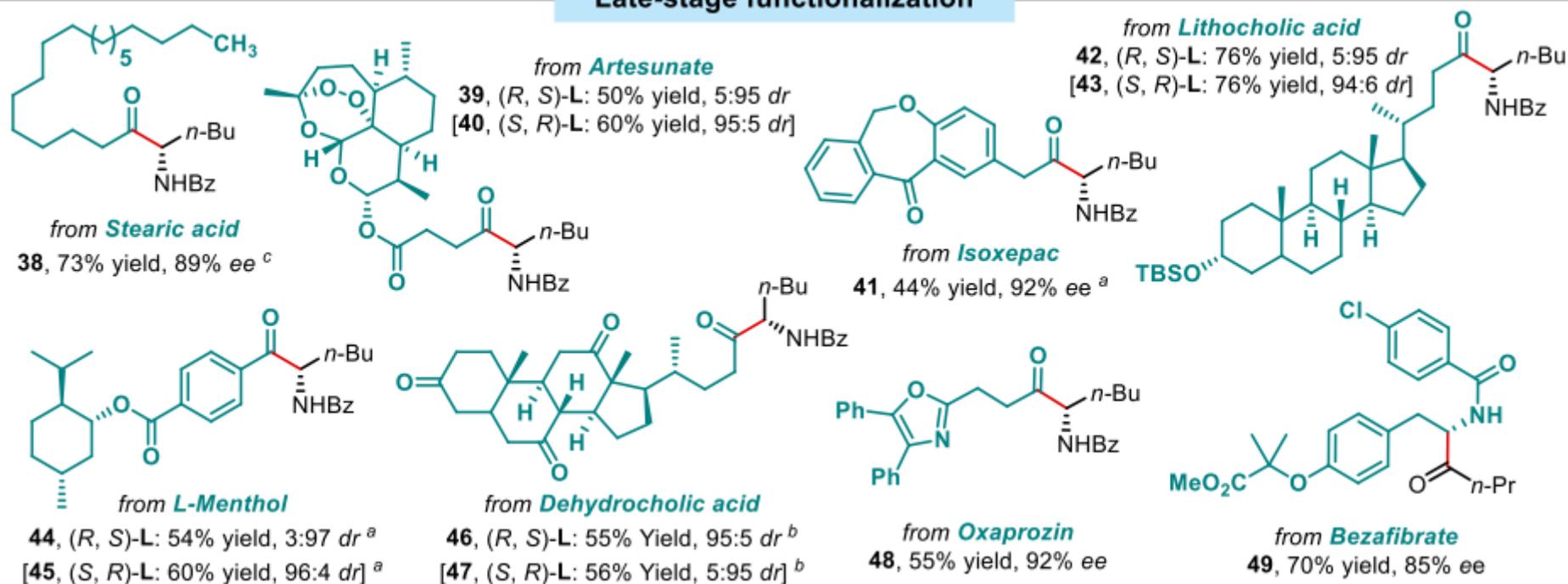
Scope of N-alkyl amide



1.1 Br•介导的C(sp³)-H官能化——酰基化

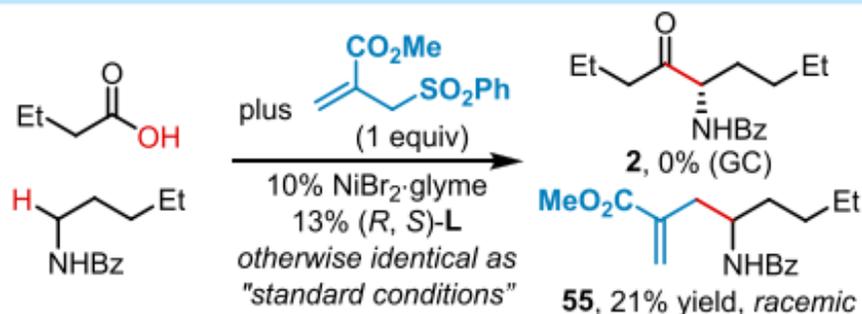


Late-stage functionalization

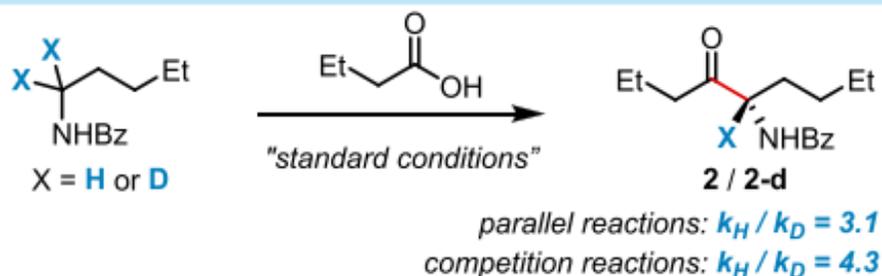


1.1 Br•介导的C(sp³)-H官能化——酰基化

a) α-Amino radical trapping experiment

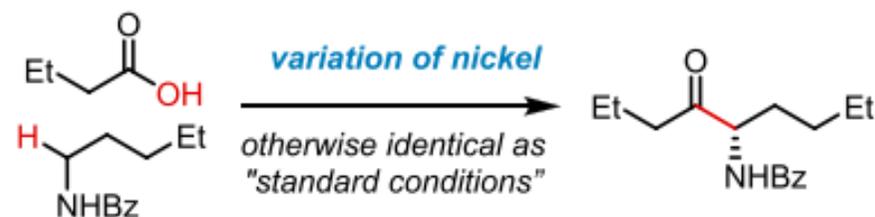


b) Kinetic isotope effect experiments



KIE值均大于2，为一级同位素效应，表明C-H裂解对速率决定步骤有重要贡献

c) Ni precatalyst control experiments



entry	conditions	yield (%) ^a	ee (%) ^b
1	$\text{NiBr}_2 \cdot \text{glyme}$ (stand. cond.)	90	92
2	$\text{Ni}(\text{cod})_2$	0	-
3	as entry 2, but plus 1.5 equiv NaBr	31	86
4	$\text{Ni}(\text{acac})_2$	8	nd
5	as entry 4, but plus 1.5 equiv NaBr	73	89

光氧化溴离子产生自由基：
 MacMillan, 2016, JACS
 Murakami, 2020, JACS
 Murakami, 2020, ACIE

1.2 Br•介导的C(sp³)-H官能化——酰基化



ARTICLE

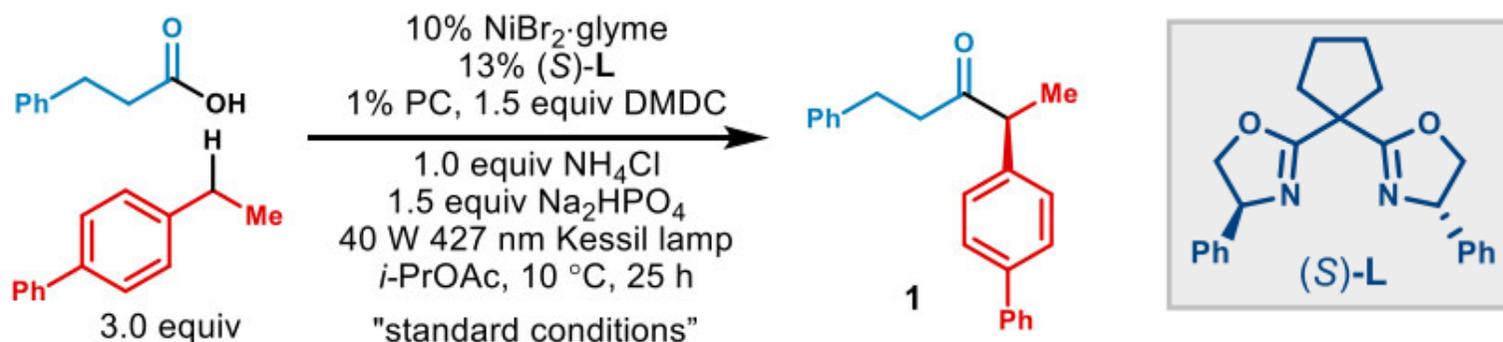


<https://doi.org/10.1038/s41467-021-23887-2>

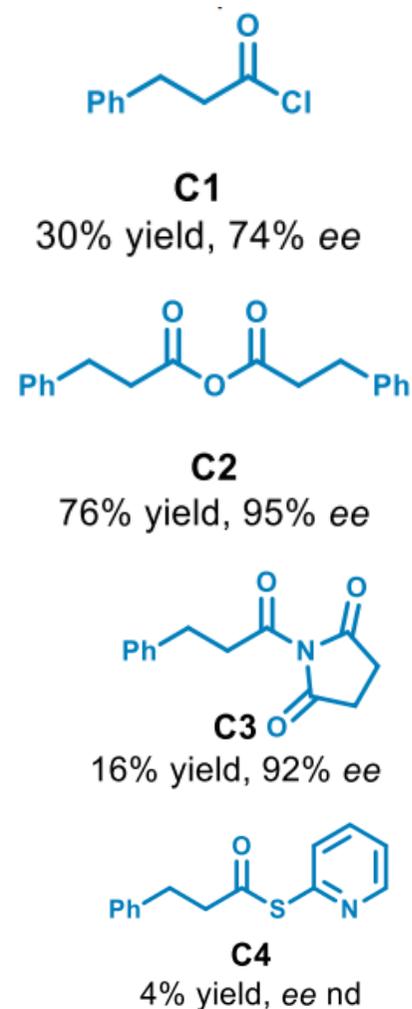
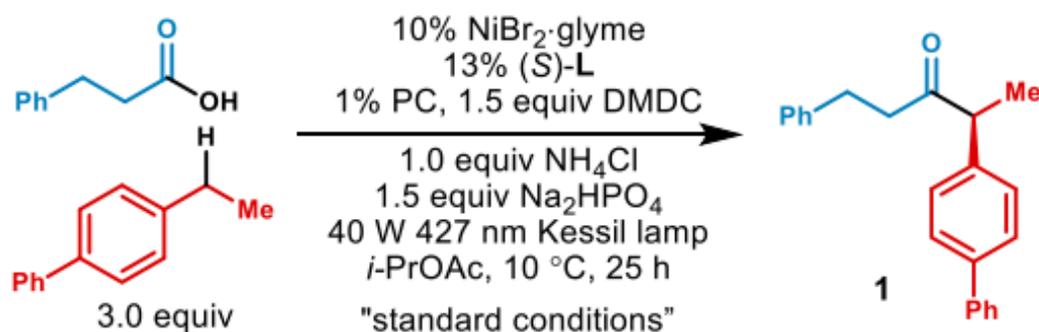
OPEN

Asymmetric benzylic C(sp³)-H acylation via dual nickel and photoredox catalysis

Leitao Huan^{1,2}, Xiaomin Shu^{1,2}, Weisai Zu¹, De Zhong¹ & Haohua Huo¹✉



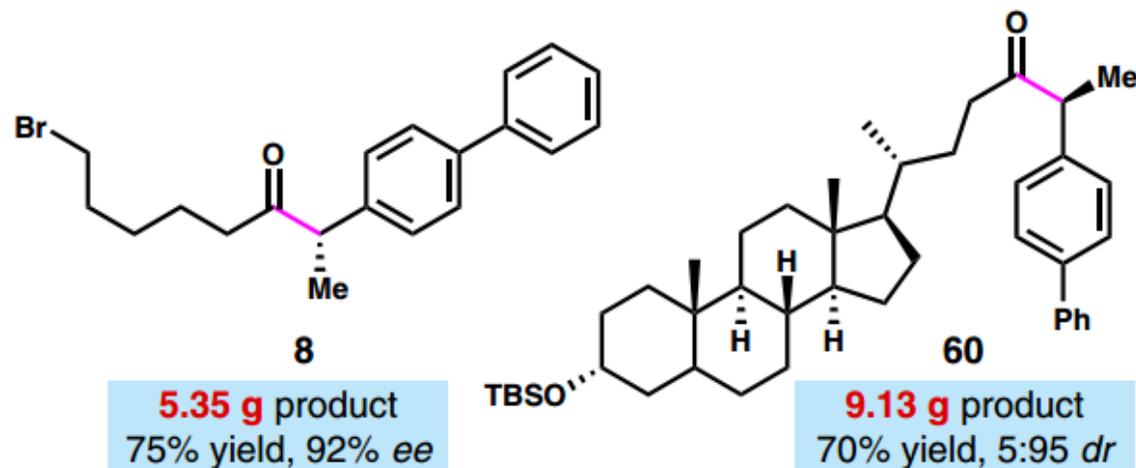
1.2 Br•介导的C(sp³)-H官能化——酰基化



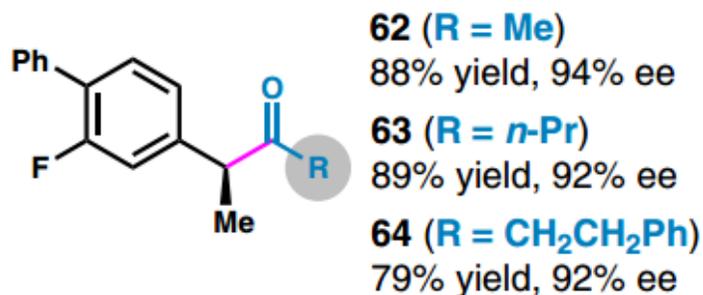
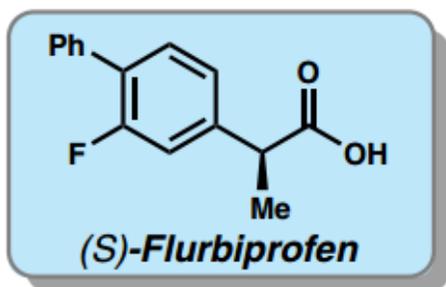
Entry	Variation from standard conditions	Yield (%)	ee (%)
1	None	85	94
2	25°C, instead of 10°C	83	90
3	Ni(acac) ₂ , instead of NiBr ₂ ·glyme	6	-
4	as entry 3, but plus 1.5 equiv NaBr	62	88
5	Boc ₂ O, instead of DMDC	14	93
6	DMBP, instead of PC	0	-
7	No NH ₄ Cl	54	93
8	No Ni, or no PC, or no light	0	-
9	C1-C4 , instead of (acid+DMDC + NH ₄ Cl)	as shown below	

1.2 Br•介导的C(sp³)-H官能化——酰基化

a. Gram-scale synthesis (20.0 mmol scale)



b. Parallel synthesis of drug analogues (>100 mg pdt in all cases)



1.2 Br•介导的C(sp³)-H官能化——酰基化

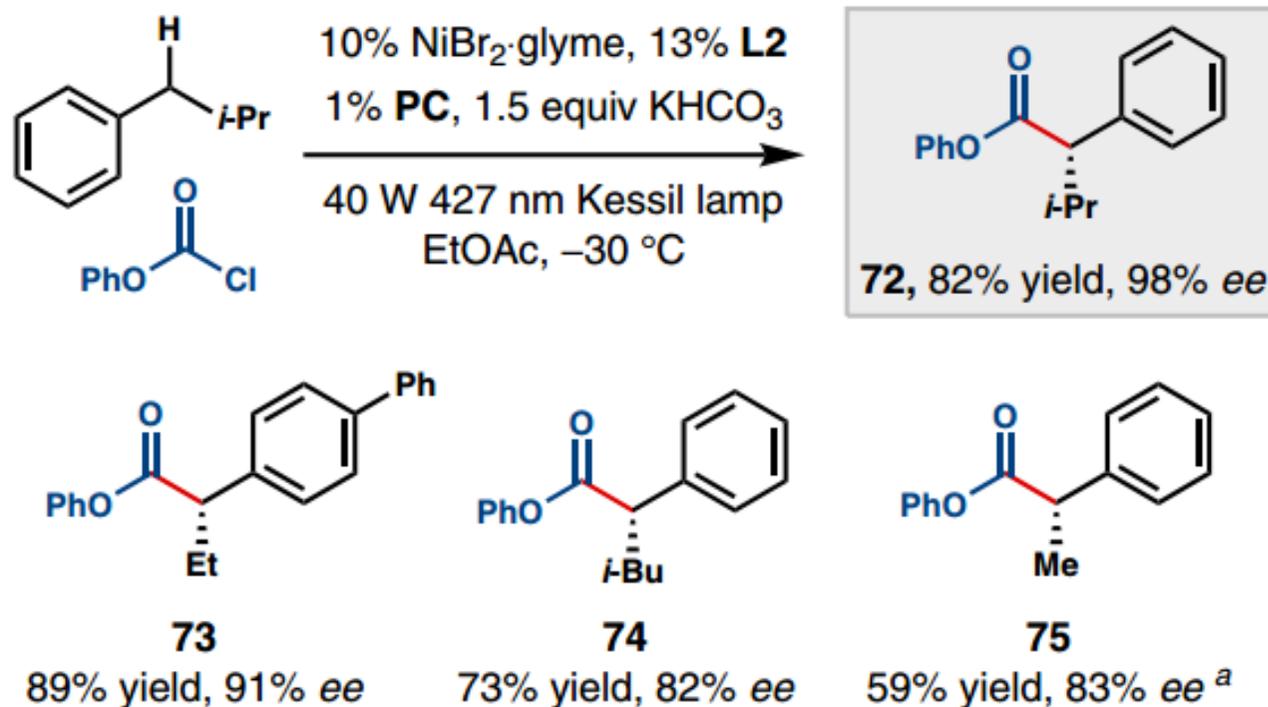


Fig. 6 Rational expansion for the synthesis of α -aryl esters. All data represent the average of two experiments. Unless otherwise noted, reactions were conducted on a 0.5 mmol scale under stated conditions. ^aIn place of the stated conditions, the reaction was conducted at -40°C with 5.0 equiv ethylbenzene.

1.3 Br•介导的C(sp³)-H官能化——烯基化

Stereodivergent Synthesis of Both *Z*- and *E*-Alkenes by Photoinduced, Ni-Catalyzed Enantioselective C(sp³)-H Alkenylation

Jitao Xu, Zhilong Li, Yumin Xu, Xiaomin Shu, and Haohua Huo*

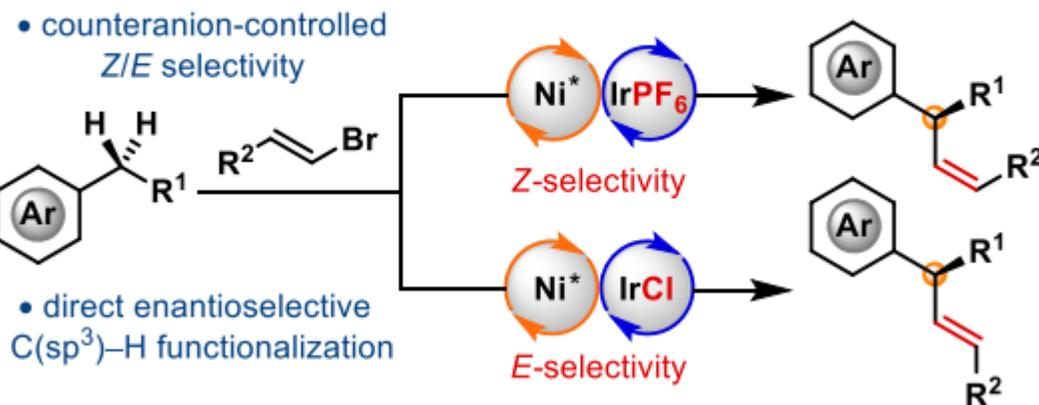


Cite This: *ACS Catal.* 2021, 11, 13567–13574

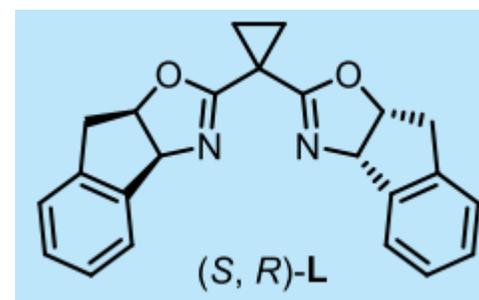
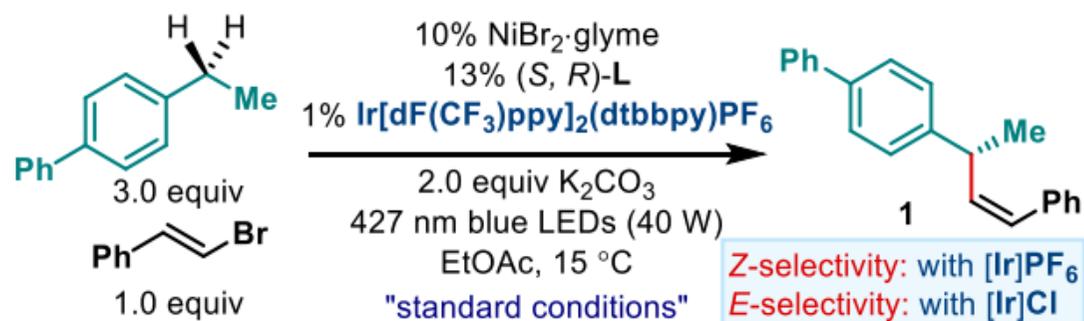


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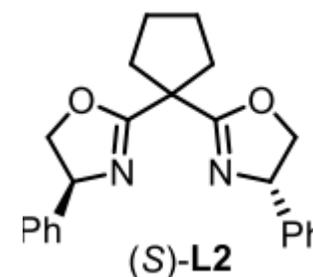
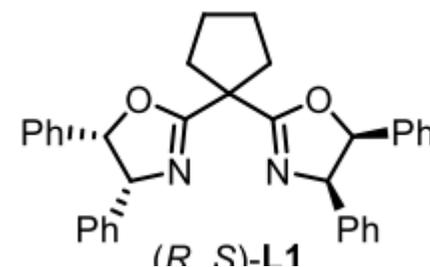
Switchable Stereodivergent C(sp³)-H Alkenylation



1.3 Br•介导的C(sp³)-H官能化——烯基化

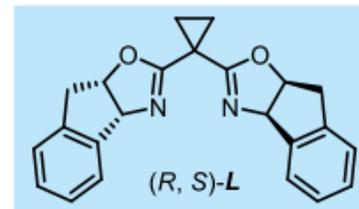
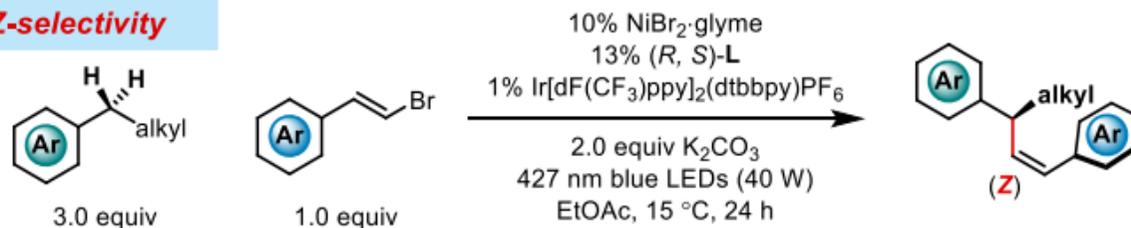


entry	variation from standard conditions	yield (%) ^a	Z/E ^a	ee (%) ^b
1	none	79	84:16	96
2	25 °C, instead of 15 °C	72	84:16	94
3	under air in a capped vial	69	84:16	96
4	1.0 equiv H ₂ O added	77	83:17	95
5	1.0 equiv of alkyl benzene	58	84:16	96
6	1% [Ir]Cl, instead of 1% [Ir]PF ₆	41	26:74	94
7	0.25% [Ir]Cl, dioxane as solvent	67	15:85	94
8	as entry 7, 25 °C, 1.5 eq K ₂ CO ₃	62	7:93	94
9	(R, S)-L1, instead of (S, R)-L	58	69:31	-19
10	(S)-L2, instead of (S, R)-L	47	60:40	58
11	No Ni, or no Ir, or no light	0	-	-

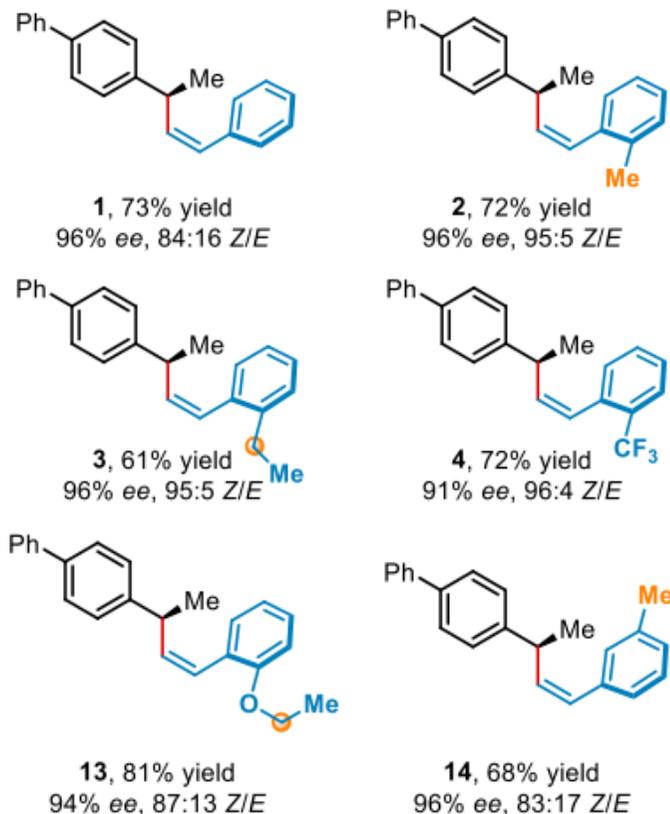


1.3 Br•介导的C(sp³)-H官能化——烯基化

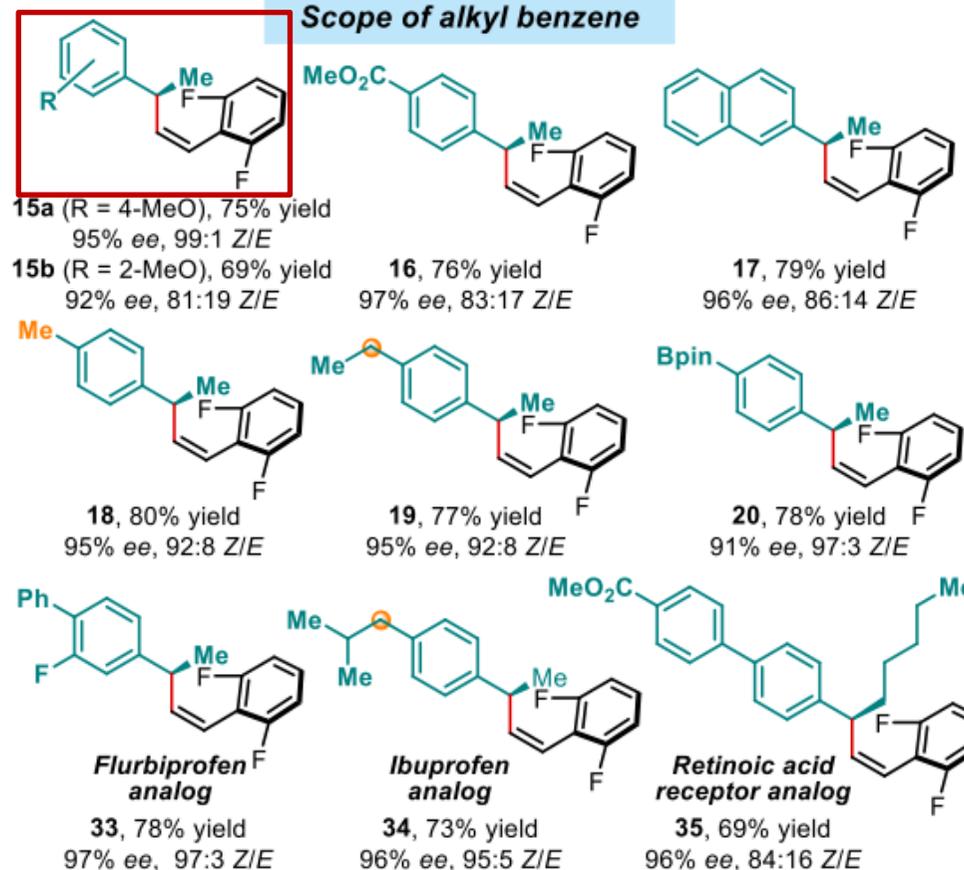
Z-selectivity



Scope of vinyl bromide



Scope of alkyl benzene



1.3 Br•介导的C(sp³)-H官能化——烯基化

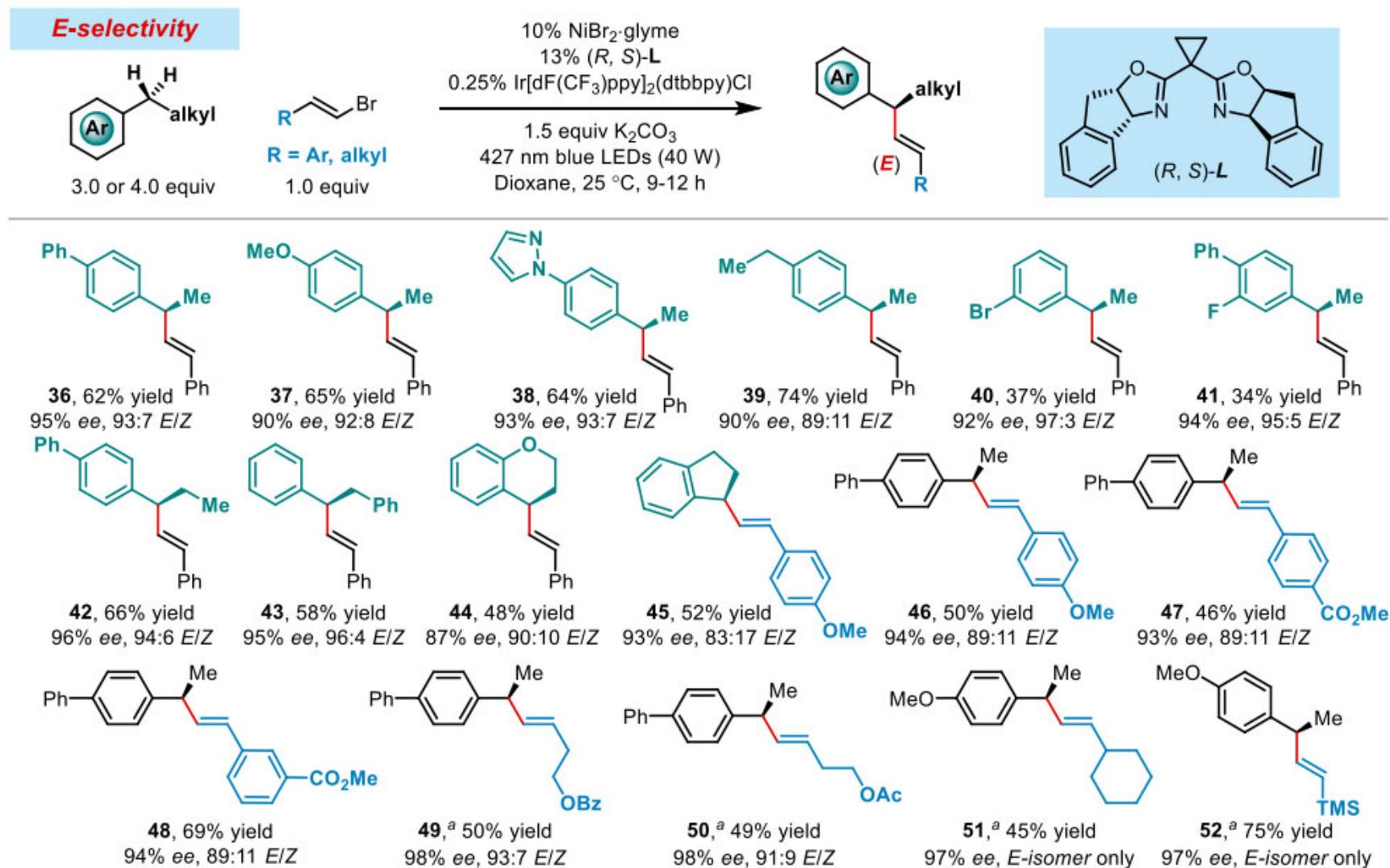
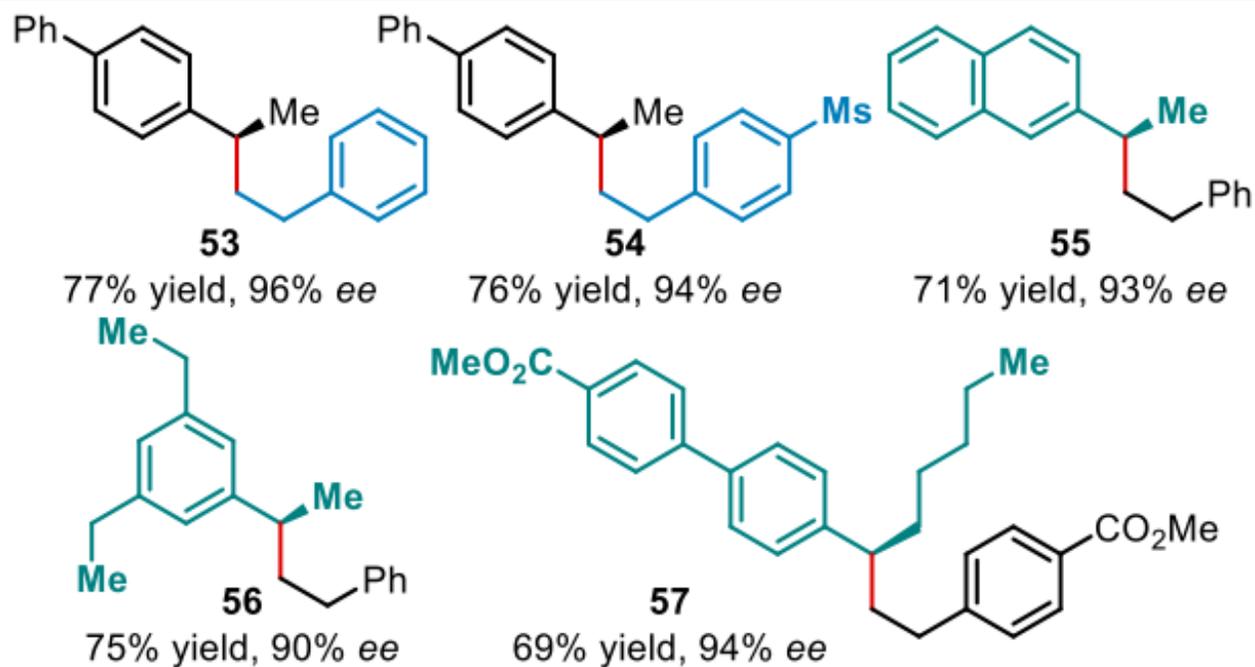


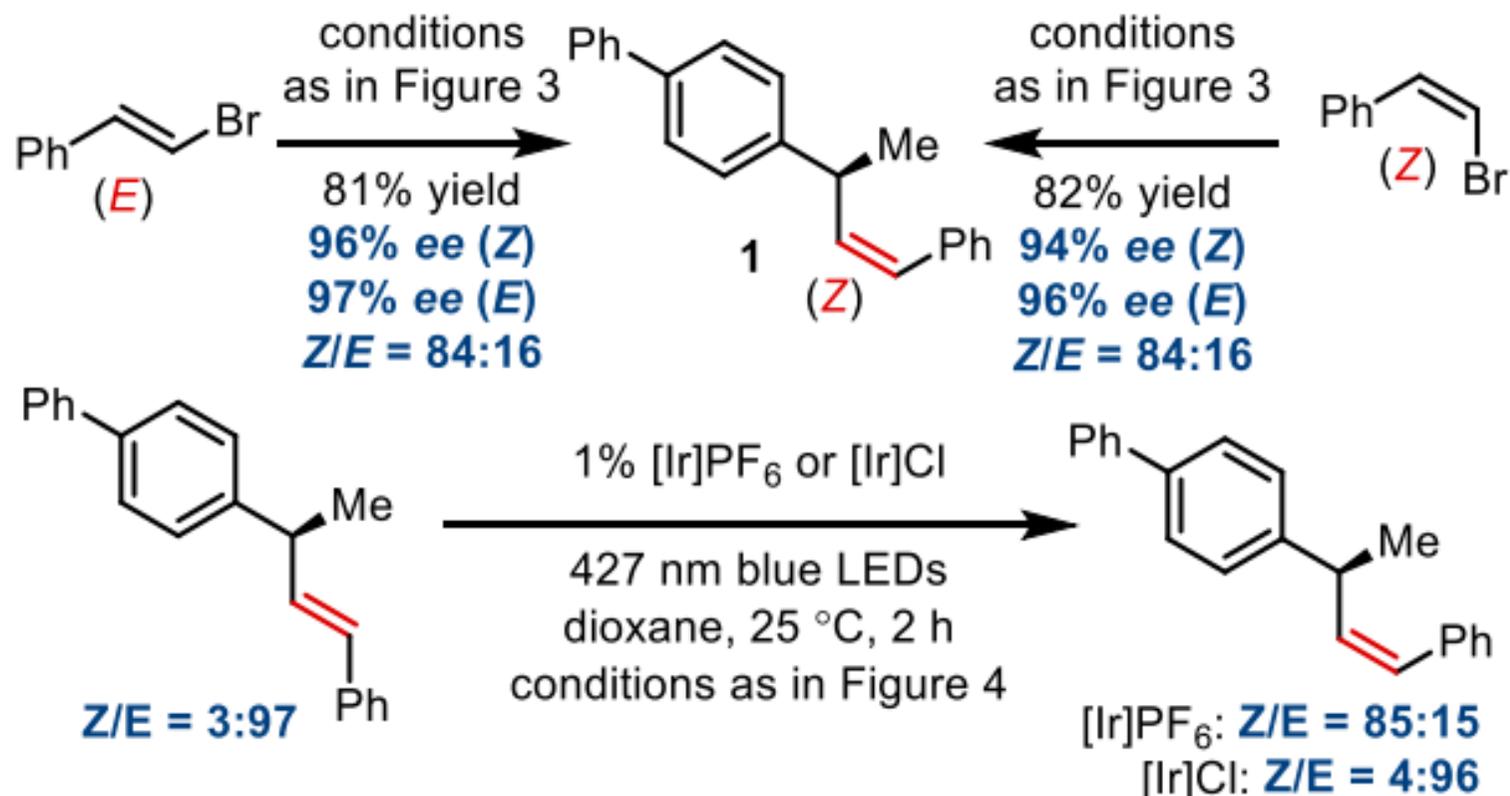
Figure 4. Enantio- and *E*-selective alkenylation of benzylic C(sp³)-H bonds with vinyl bromides. All data represent the average of two experiments run on a 0.2 mmol scale under standard conditions for the *E*-alkene synthesis (for **36**–**48**: 4.0 equiv of alkylarenes employed; for **49**–**52**: 3.0 equiv of alkylarenes employed). All yields are of purified products, and all *Z/E* values were determined through GC or ¹H NMR analysis of the crude products. ^aIn place of the standard conditions, 1% [Ir]PF₆, EA/dioxane (1:1), and –10 °C were used.

1.3 Br•介导的C(sp³)-H官能化——烯基化

B. A formal enantioselective benzylic C–H alkylation



1.3 Br•介导的C(sp³)-H官能化——烯基化



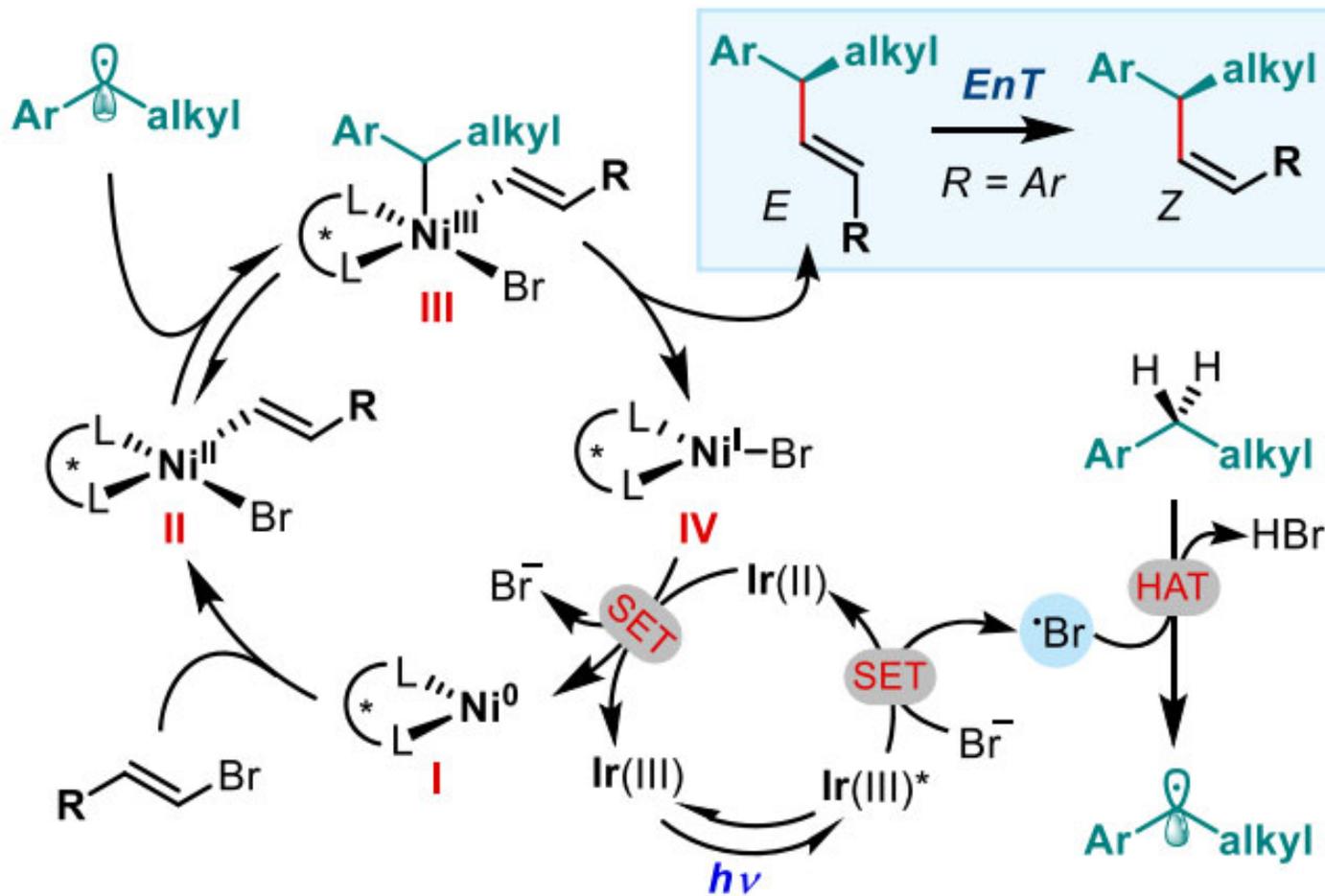
- Z/E选择性不是由底物的立体特异性决定的
- 光诱导的E→Z异构化过程的发生

[Ir]PF₆*: ET = 60.1 kcal/mol

E→Z: ET = ~ 55–60 kcal/mol

1.3 Br•介导的C(sp³)-H官能化——烯基化

Proposed mechanism



1.4 Br •介导的C(sp³)-H官能化——烷基化

nature catalysis

Article

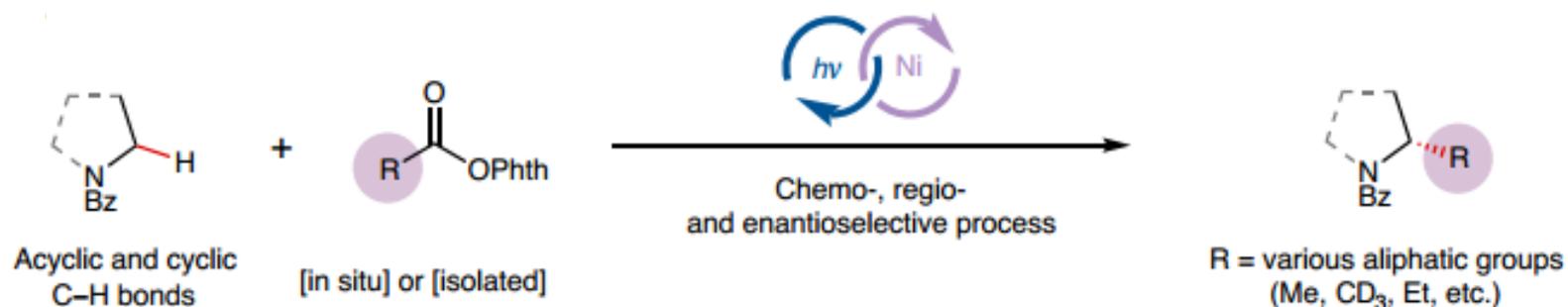
<https://doi.org/10.1038/s41929-024-01192-7>

Enantioselective alkylation of α -amino C(sp³)-H bonds via photoredox and nickel catalysis

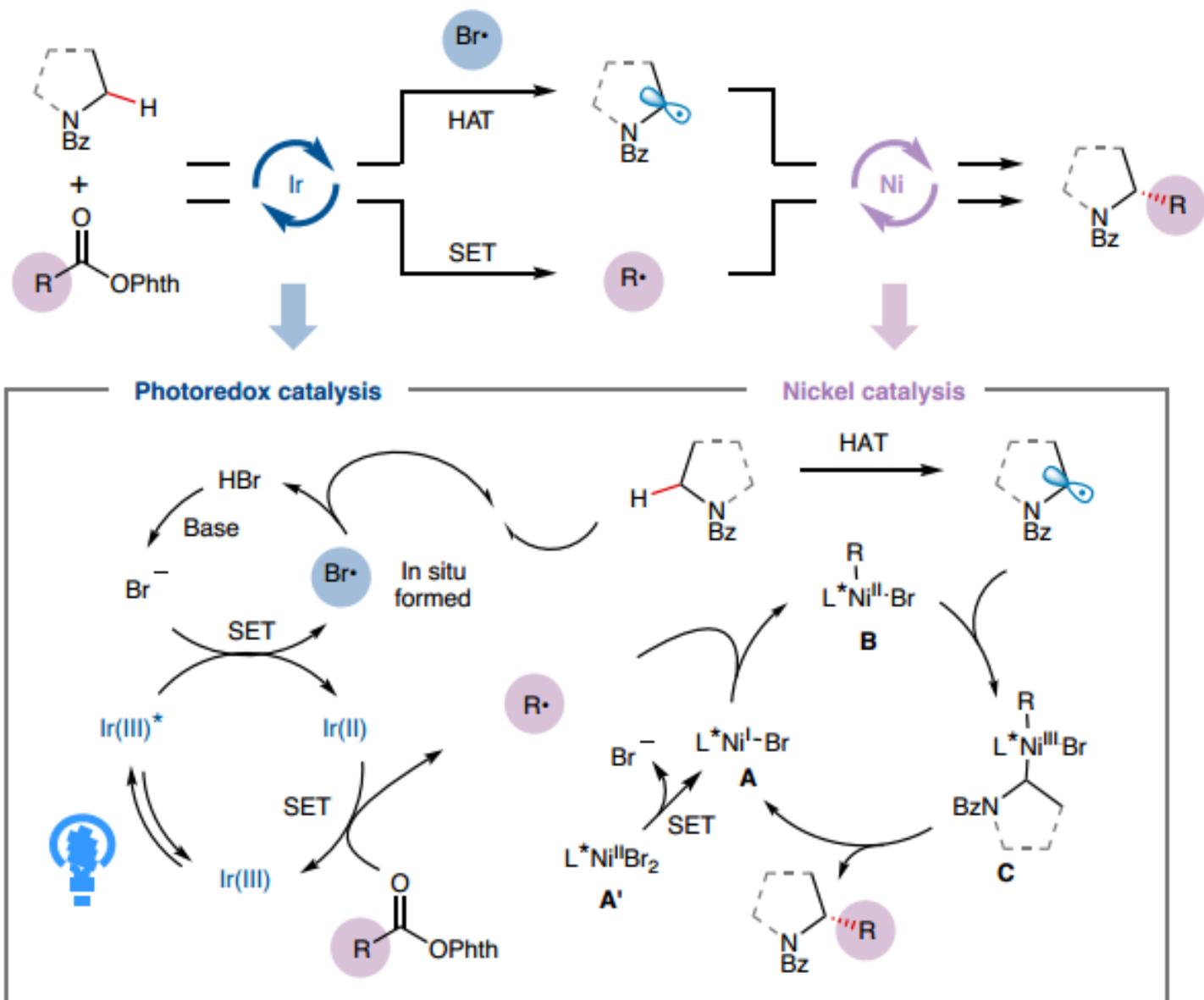
Received: 7 November 2023

Jian Li^{1,2}, Buqing Cheng^{1,2}, Xiaomin Shu¹, Zhen Xu¹, Chengyang Li¹ & Haohua Huo¹✉

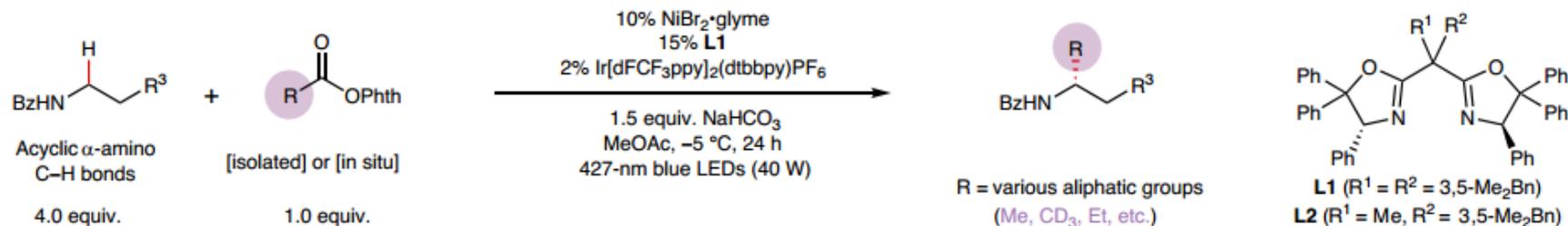
Accepted: 12 June 2024



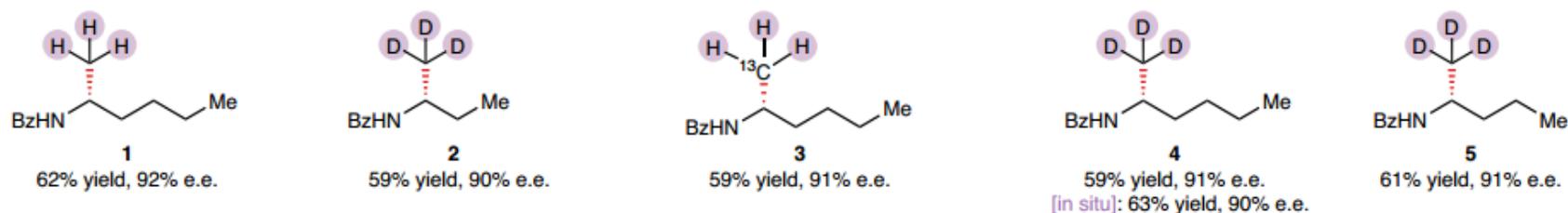
1.4 Br•介导的C(sp³)-H官能化——烷基化



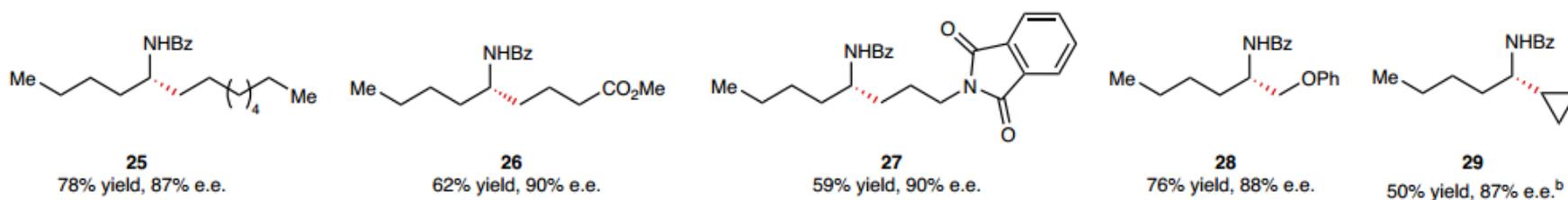
1.4 Br•介导的C(sp³)-H官能化——烷基化



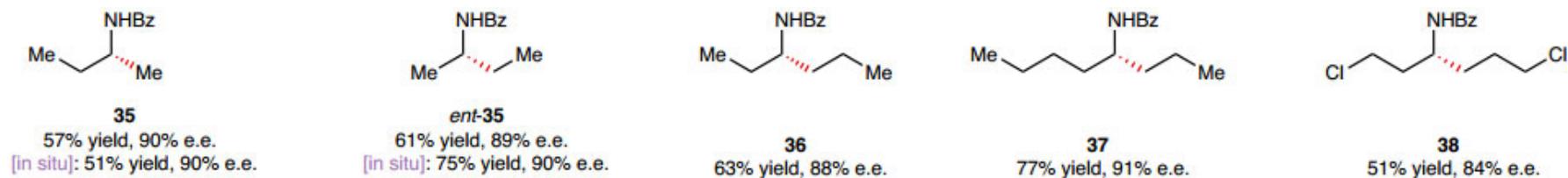
(Trideutero)methylation



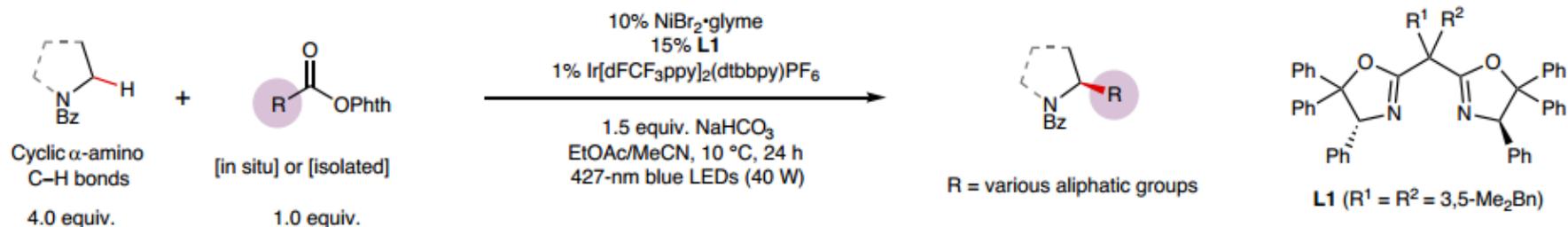
Other small aliphatic groups



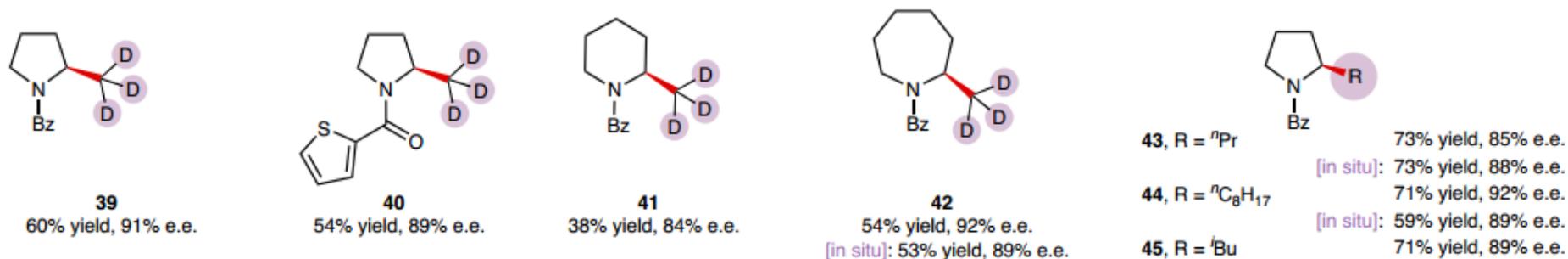
Dialkyl carbinamines with two minimally differentiated substituents



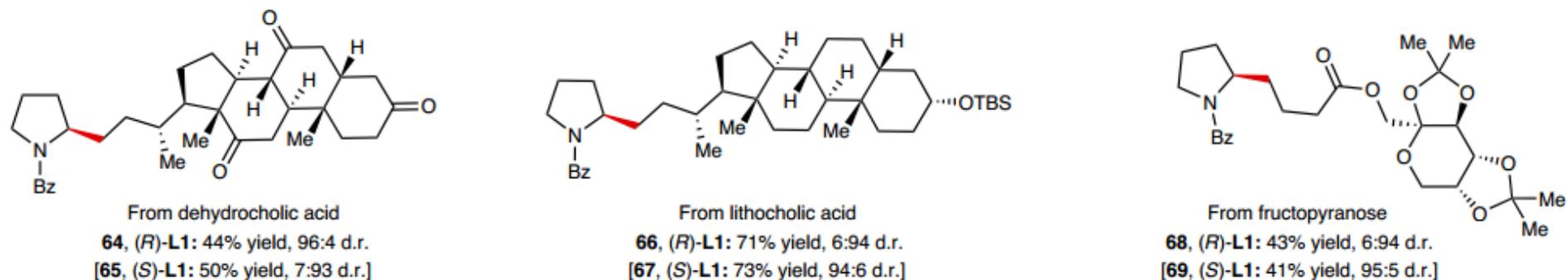
1.4 Br•介导的C(sp³)-H官能化——烷基化



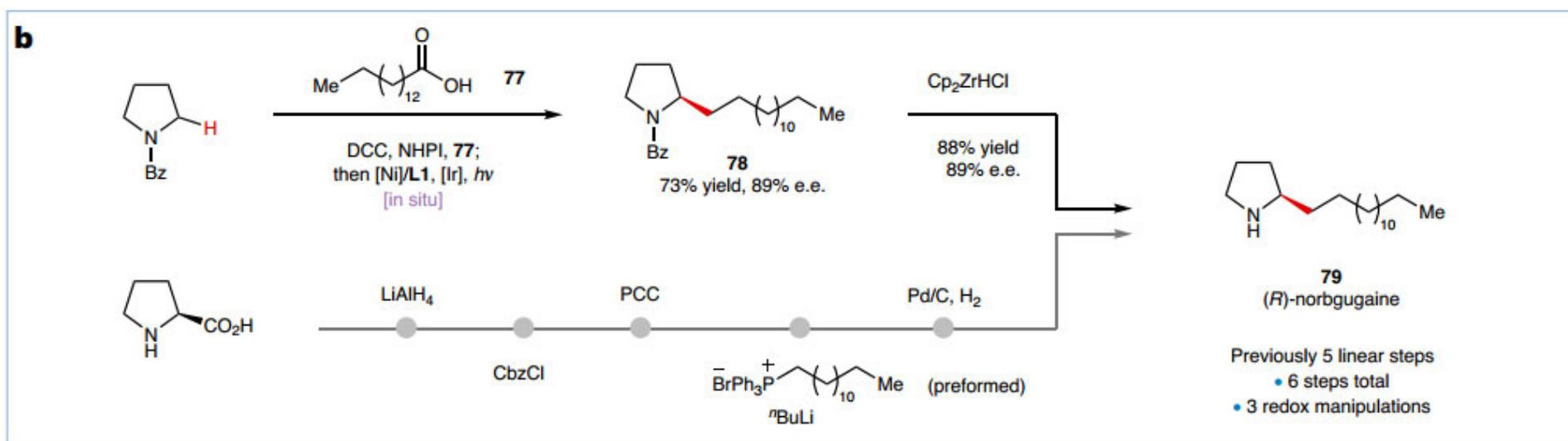
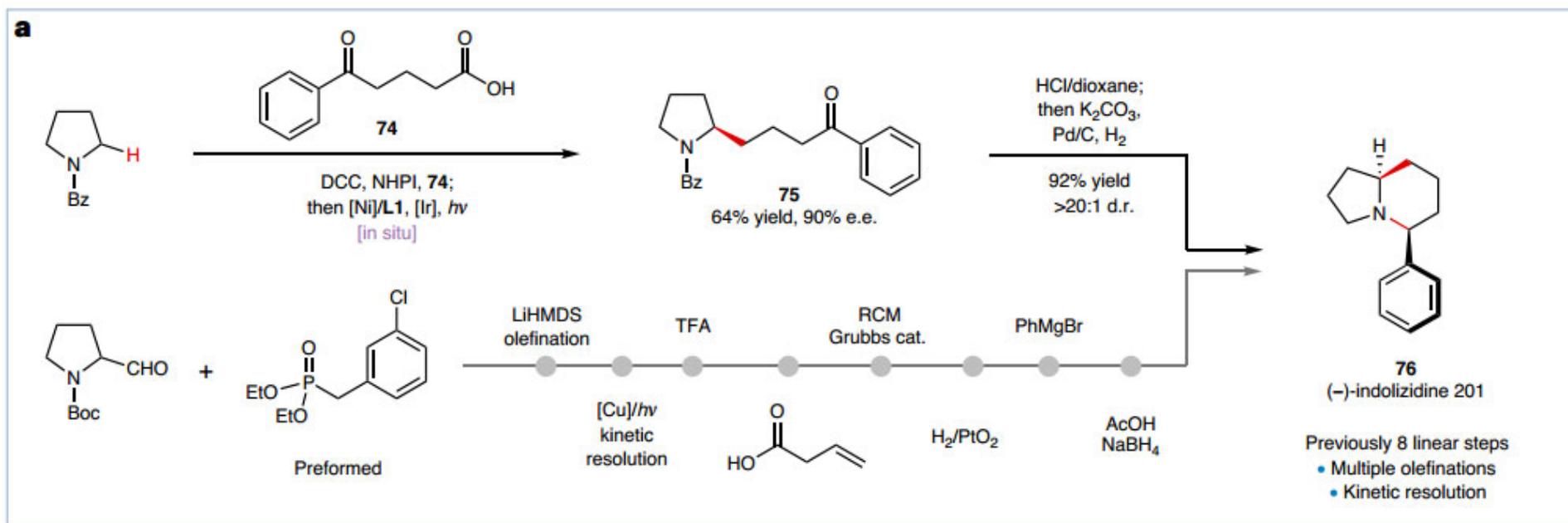
Deuteromethylation and alkylation



Medicinally relevant molecules

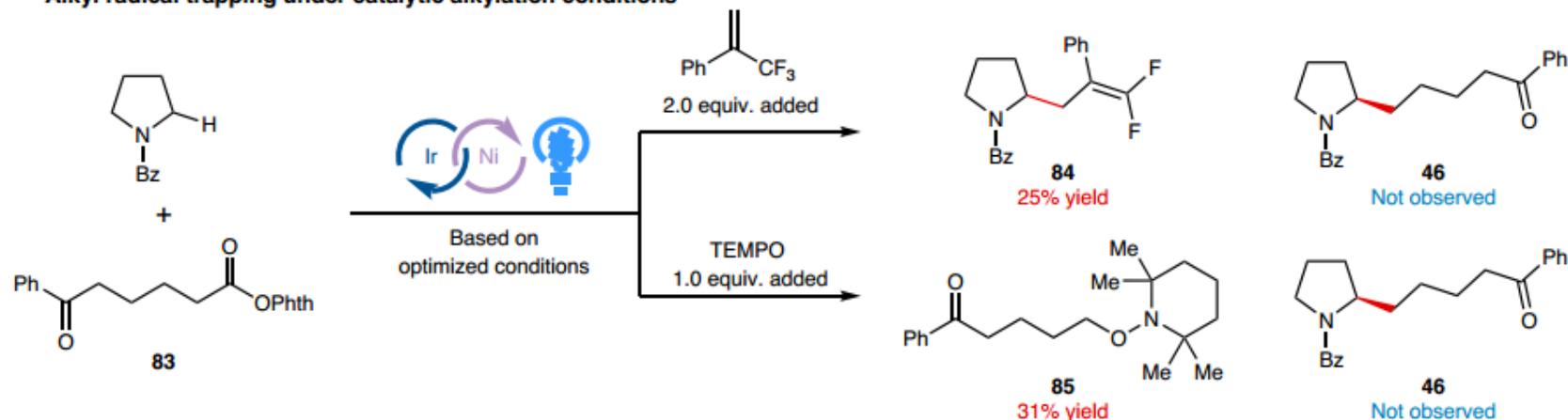


1.4 Br • 介导的C(sp³)-H官能化——烷基化

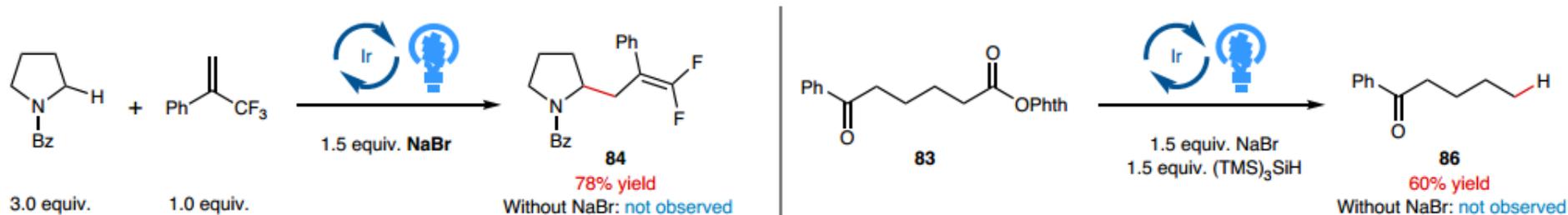


1.4 Br[•]介导的C(sp³)-H官能化——烷基化

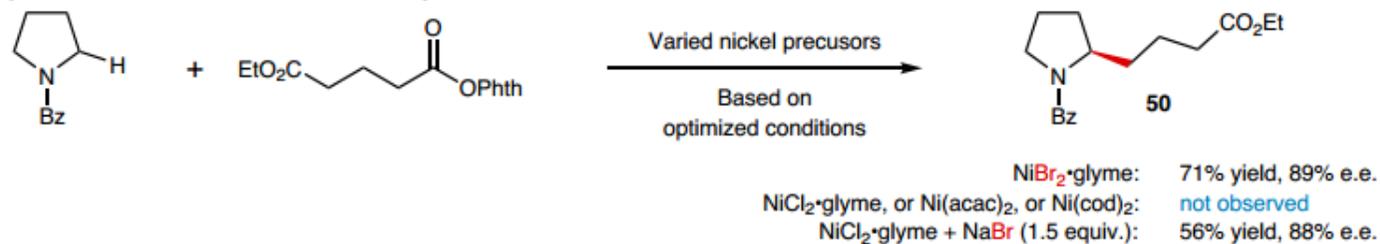
a Alkyl radical trapping under catalytic alkylation conditions



b Alkyl radical formation under Ni-free conditions using NaBr as halide sources

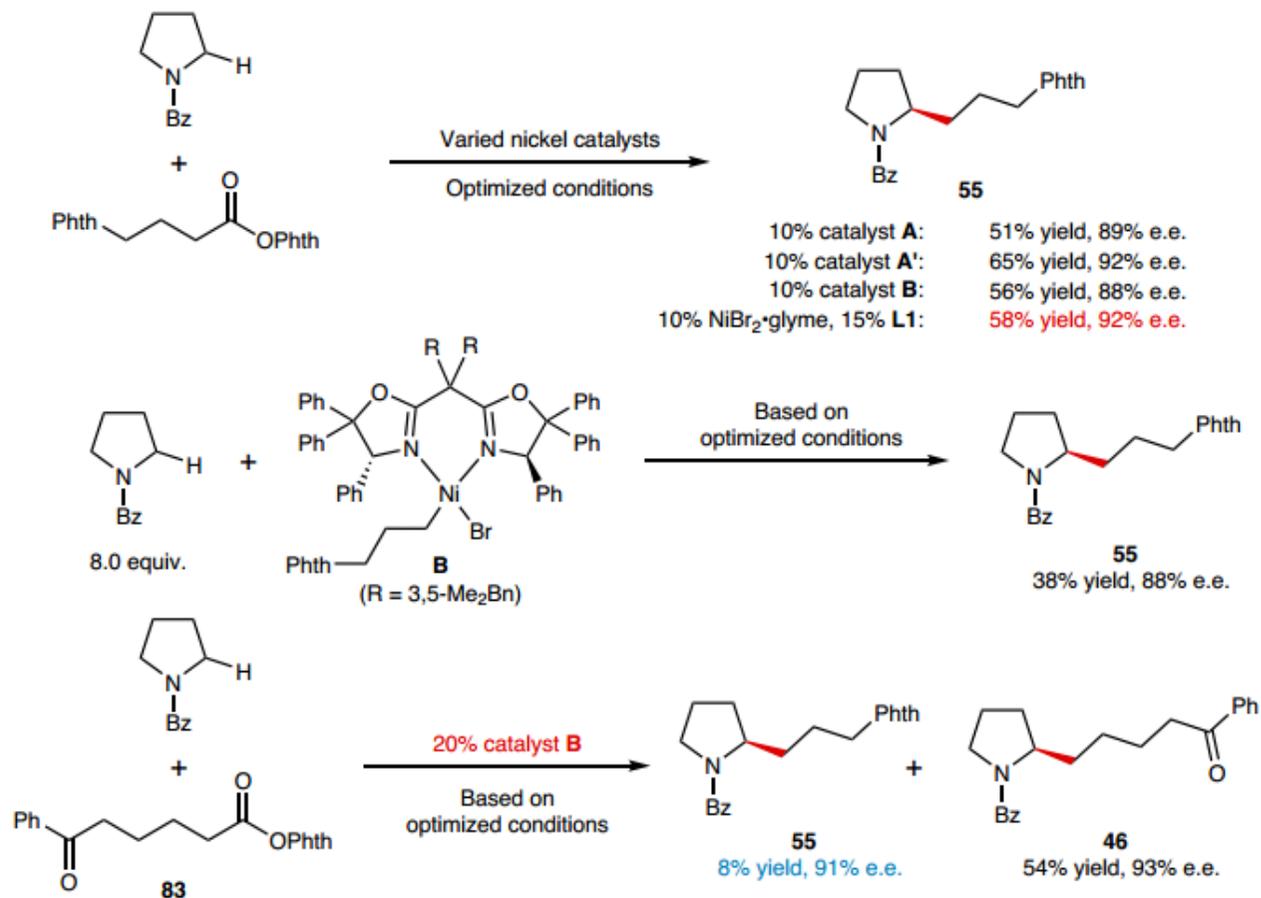
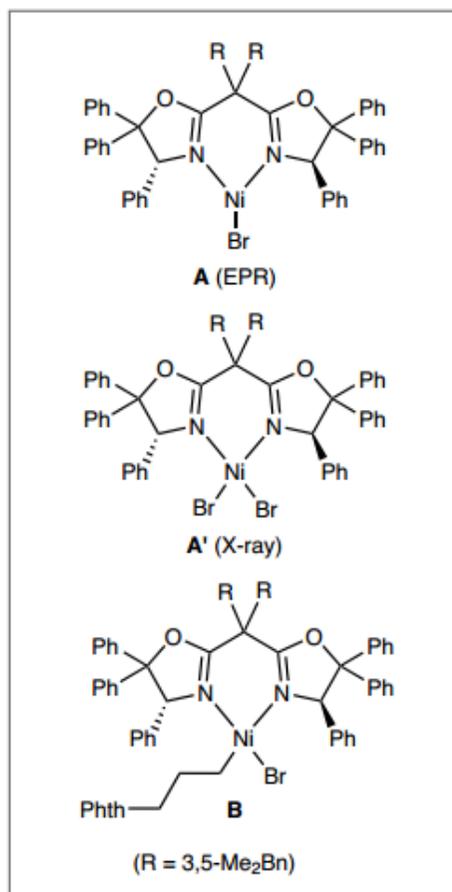


c The importance of bromide in the reaction performance



1.4 Br •介导的C(sp³)-H官能化——烷基化

d The reactivity of independently synthesized nickel complexes



2.1 Cl•介导的C(sp³)-H官能化——芳基化

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Article

Modular Access to Chiral α -(Hetero)aryl Amines via Ni/Photoredox-Catalyzed Enantioselective Cross-Coupling

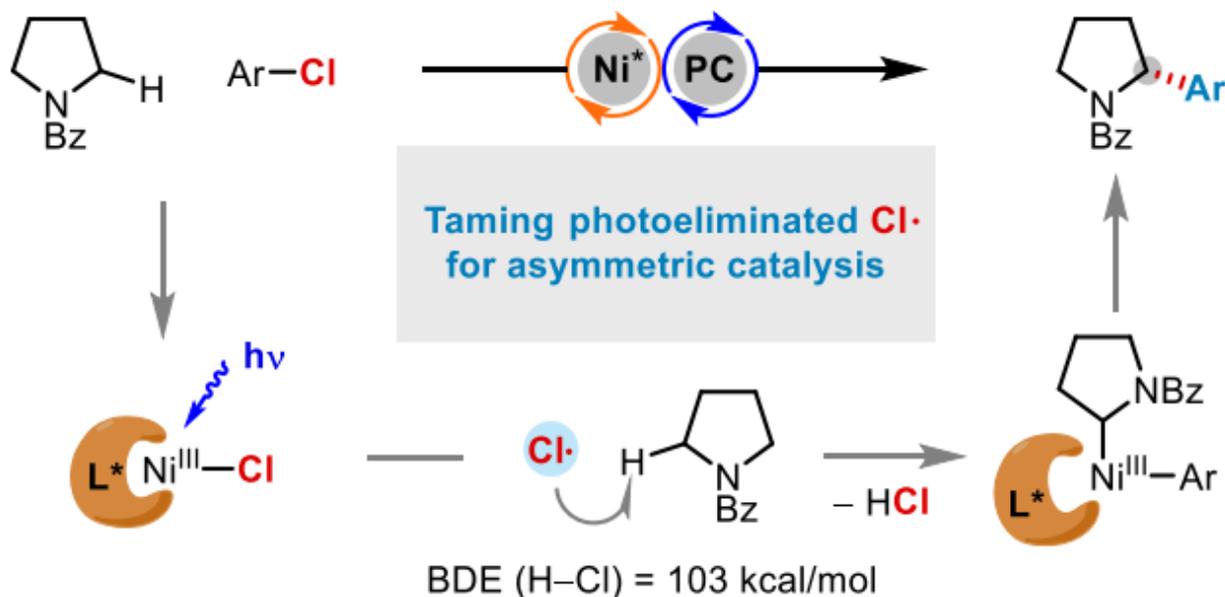
Xiaomin Shu,[†] De Zhong,[†] Yanmei Lin, Xiao Qin, and Haohua Huo*



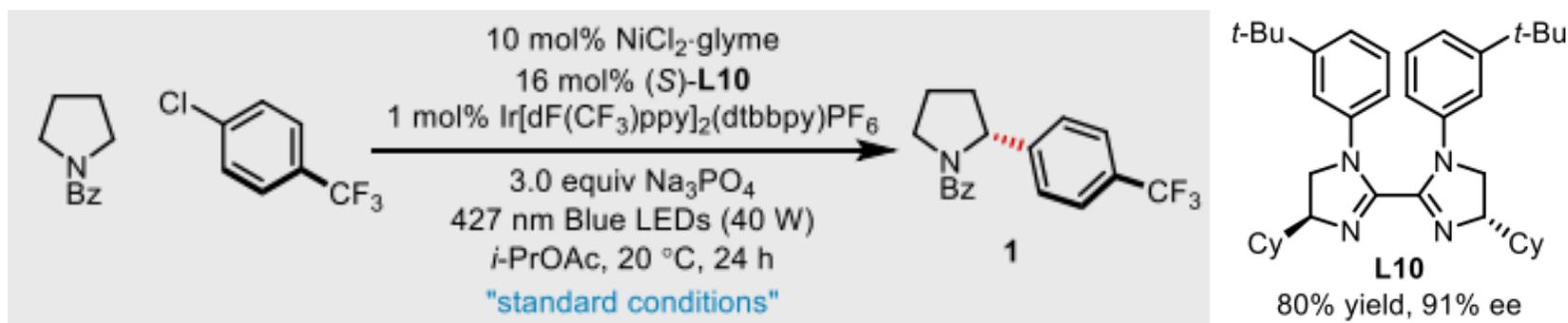
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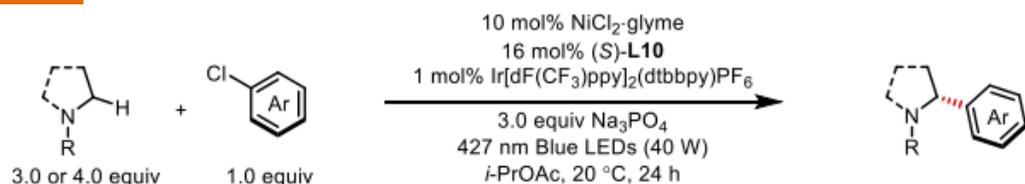


2.1 Cl•介导的C(sp³)-H官能化——芳基化



entry	variation from standard conditions	yield (%) ^b	ee (%) ^c
1	none	80	91
2	under air in a capped vial	68	89
3	5 mol % NiCl ₂ ·glyme, 8 mol % L10	79	86
4	EtOAc, instead of <i>i</i> -PrOAc	76	92
5	3 equiv of C–H nucleophile	70	90
6	K ₃ PO ₄ , instead of Na ₃ PO ₄	76	91
7	Na ₂ CO ₃ , instead of Na ₃ PO ₄	73	88
8	lutidine, instead of Na ₃ PO ₄	17	77
9	quinuclidine, instead of Na ₃ PO ₄	19	87
10	ArBr, instead of ArCl	75	80
11	no Ni, L10, Ir, base, or light	0	

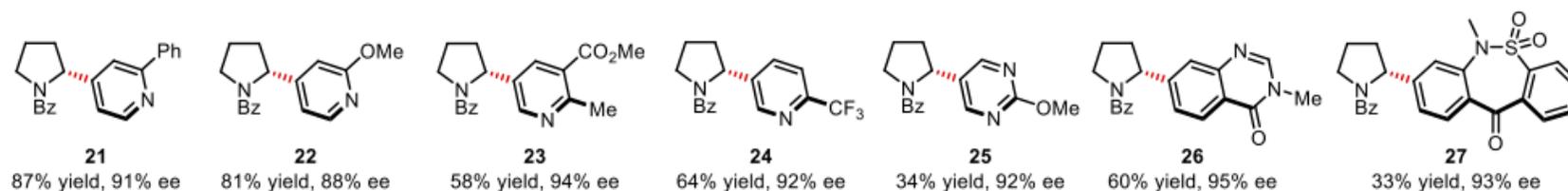
2.1 Cl•介导的C(sp³)-H官能化——芳基化



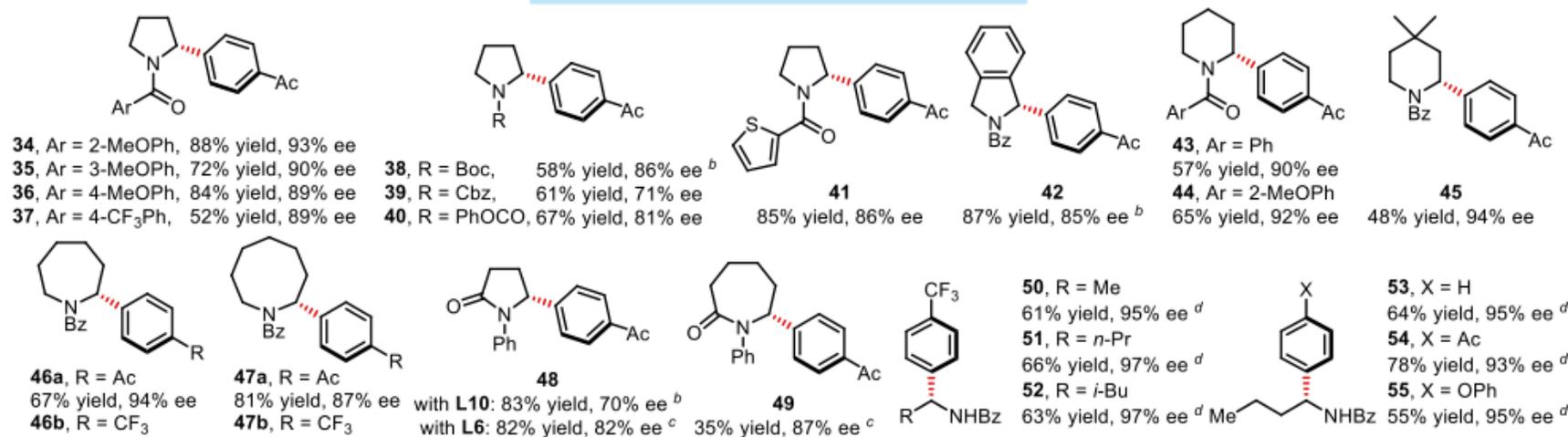
aryl chlorides



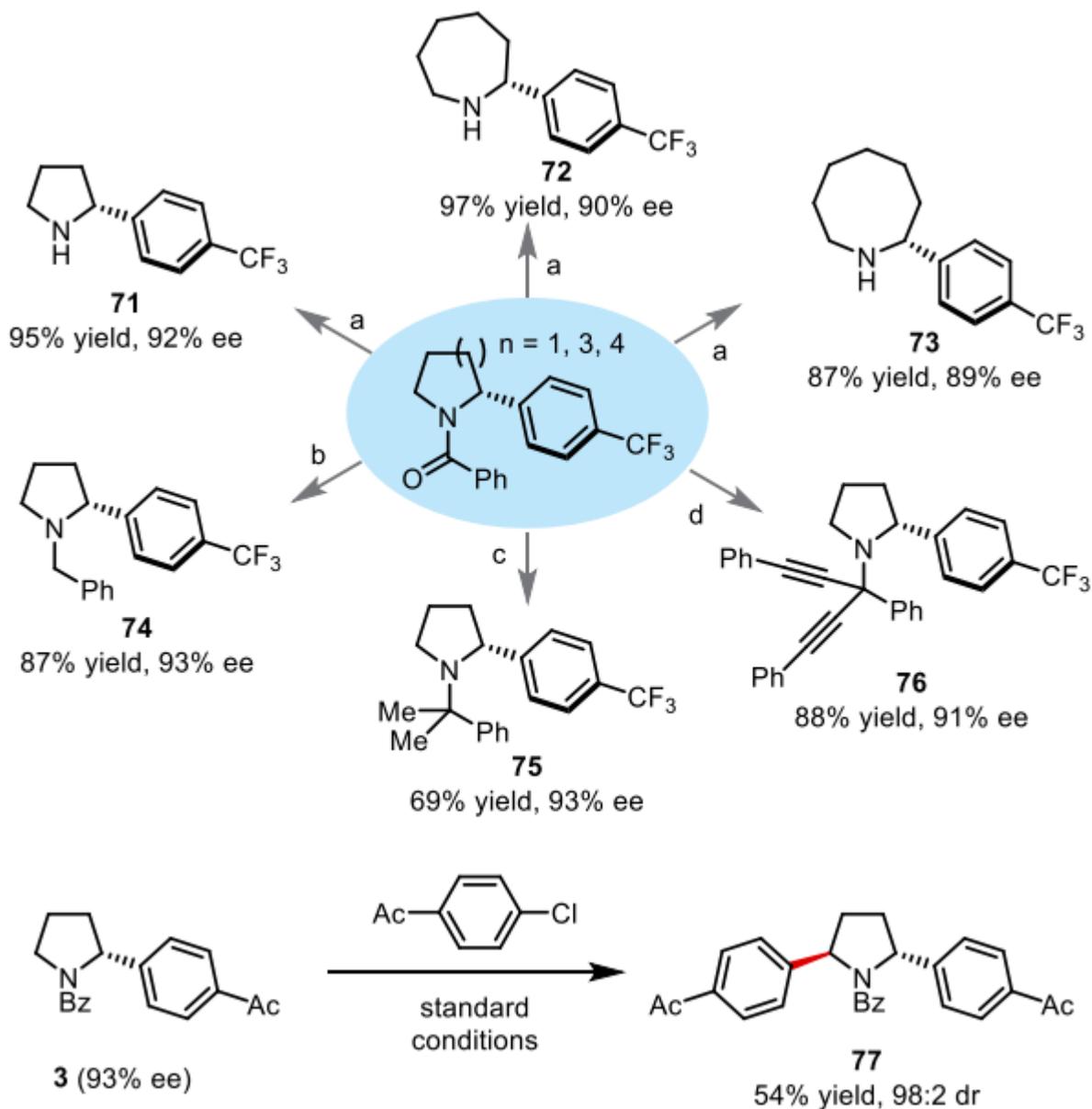
heteroaryl chlorides



cyclic and acyclic C-H nucleophiles



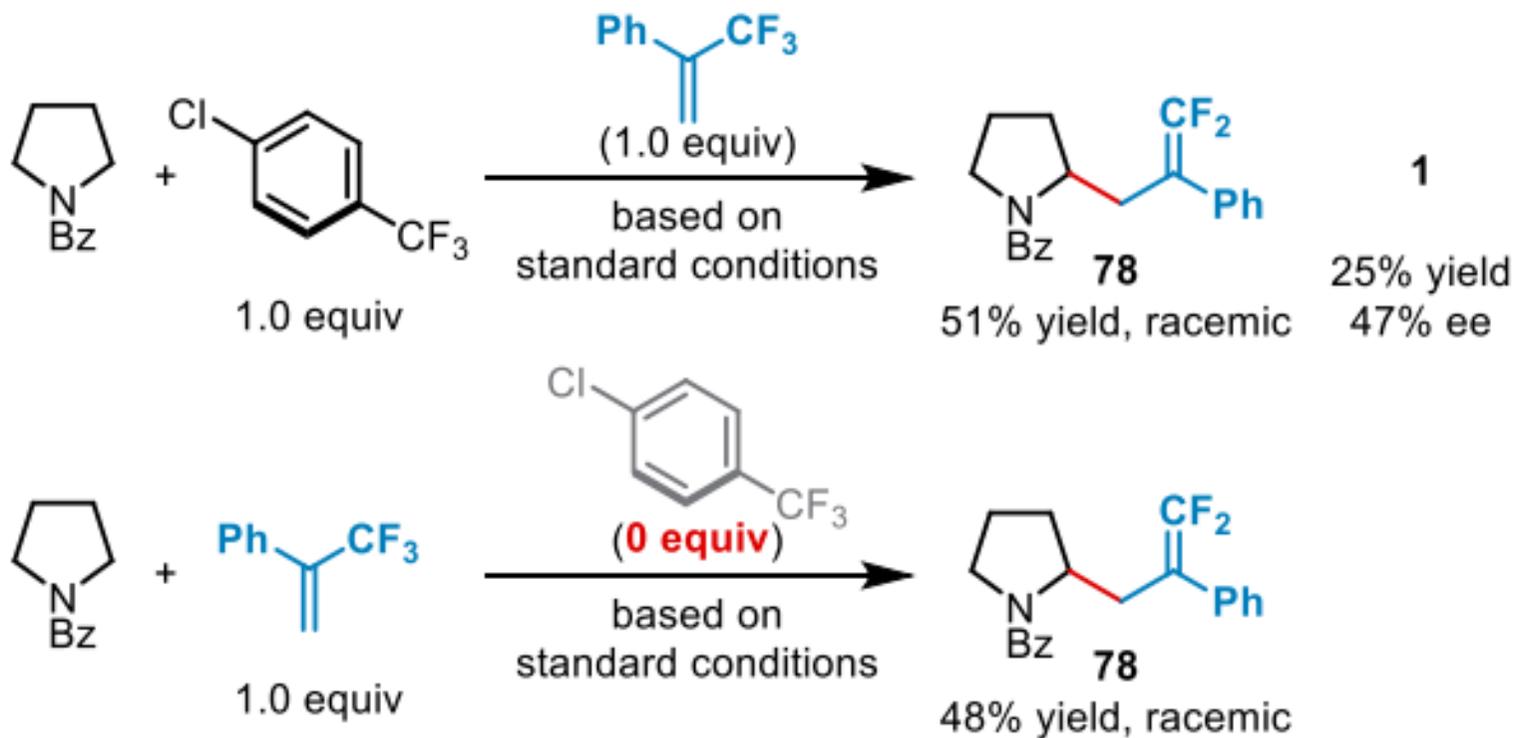
2.1 Cl•介导的C(sp³)-H官能化——芳基化



(a) Cp₂ZrHCl, THF; (b) BH₃·SMe₂, THF, reflux; (c) Tf₂O, TTBP, CH₃MgBr, DCM, -78 to 40 ° C; (d) Tf₂O, DTBMP, lithium phenylacetylide, DCM, -78 ° C.

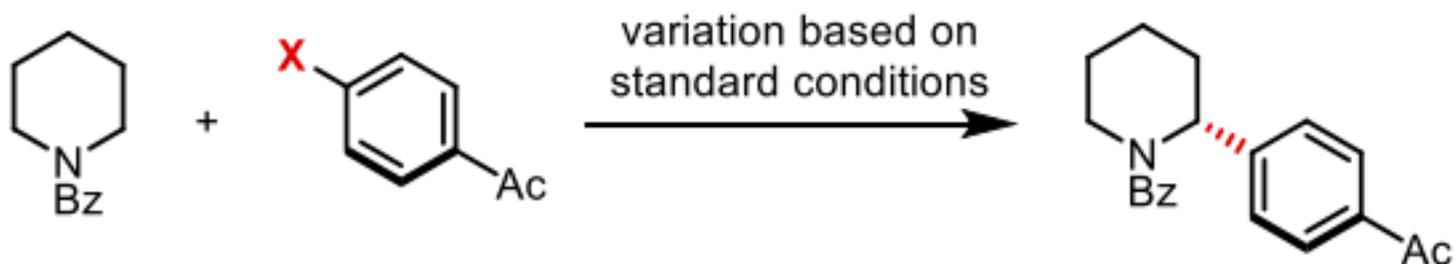
2.1 Cl•介导的C(sp³)-H官能化——芳基化

A. The evidence for the intermediacy of α -amino radicals



2.1 Cl•介导的C(sp³)-H官能化——芳基化

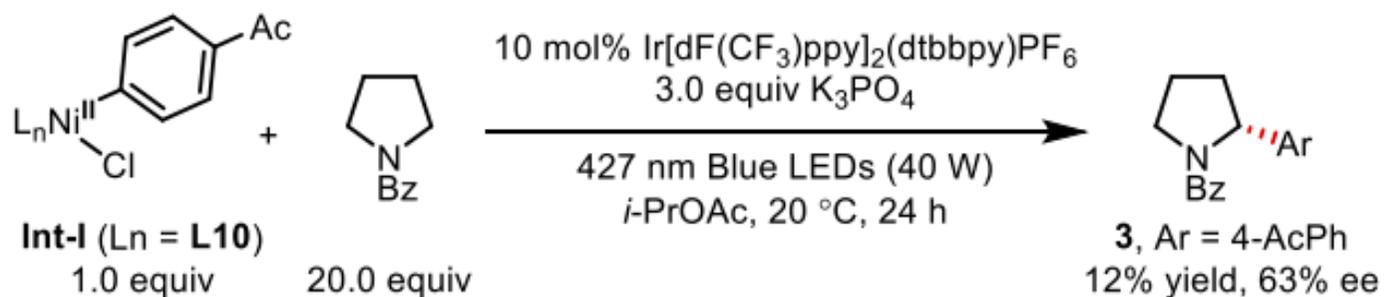
B. The importance of chloride in the reaction



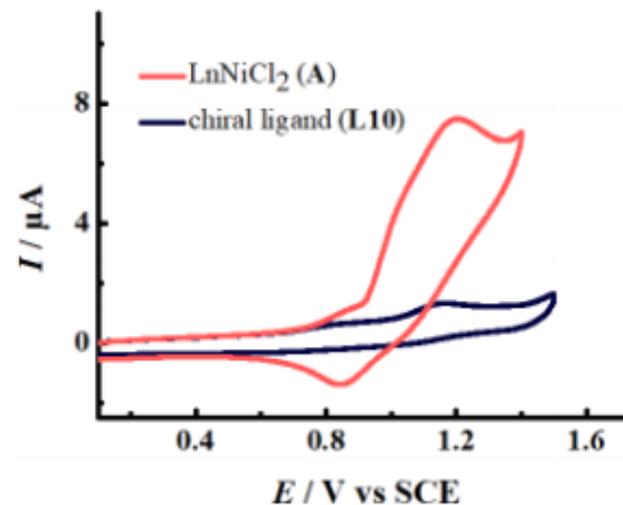
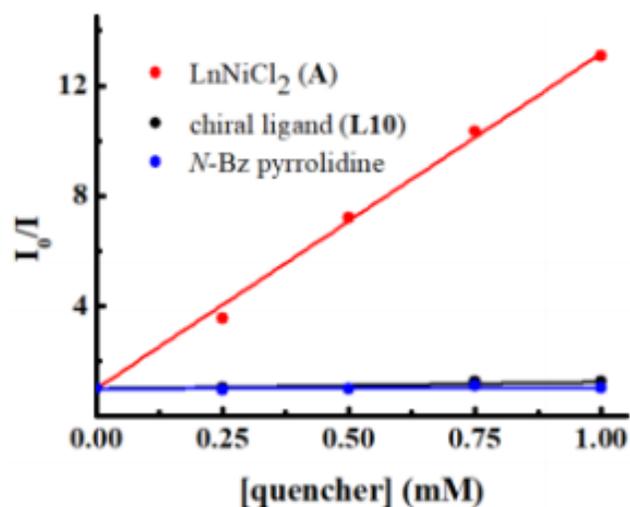
entry	Ni source	Ar-X	results
1	Ni(acac) ₂	Ar- Cl	0% yield
2	Ni(COD) ₂	Ar- Cl	25% yield, 82% ee
3	NiBr ₂ ·glyme	Ar- Cl	23% yield, 80% ee
4	NiBr ₂ ·glyme	Ar-Br	13% yield, 75% ee
5	Ni Cl ₂ ·glyme	Ar- Cl	57% yield, 90% ee

2.1 Cl•介导的C(sp³)-H官能化——芳基化

C. Stoichiometric experiment with pregenerated Ni(II) aryl chloride complex

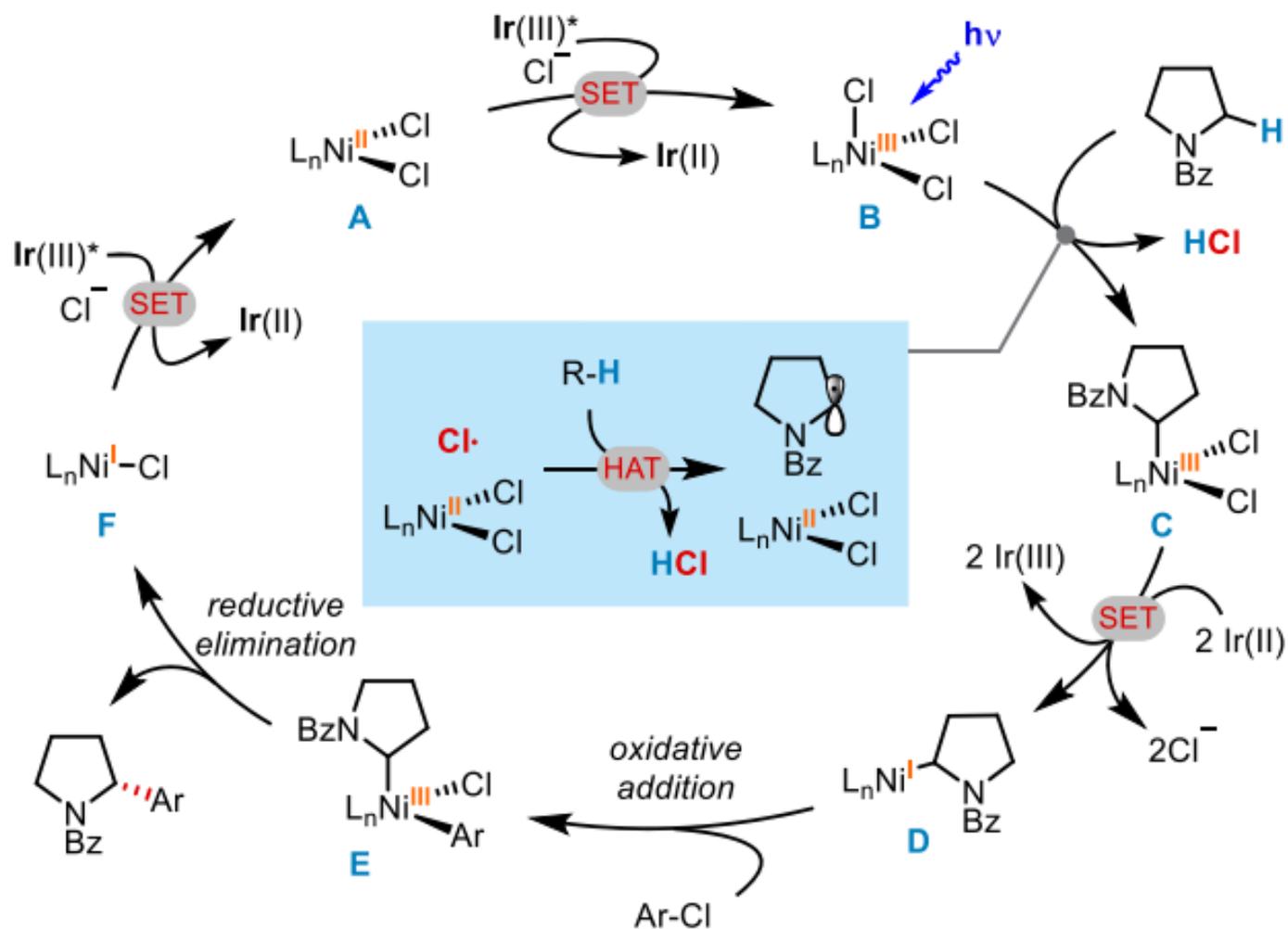


D. Luminescence quenching experiments and cyclic voltammogram studies



2.1 Cl•介导的C(sp³)-H官能化——芳基化

E. Proposed mechanism



2.2 Cl•介导的C(sp³)-H官能化——酰基化

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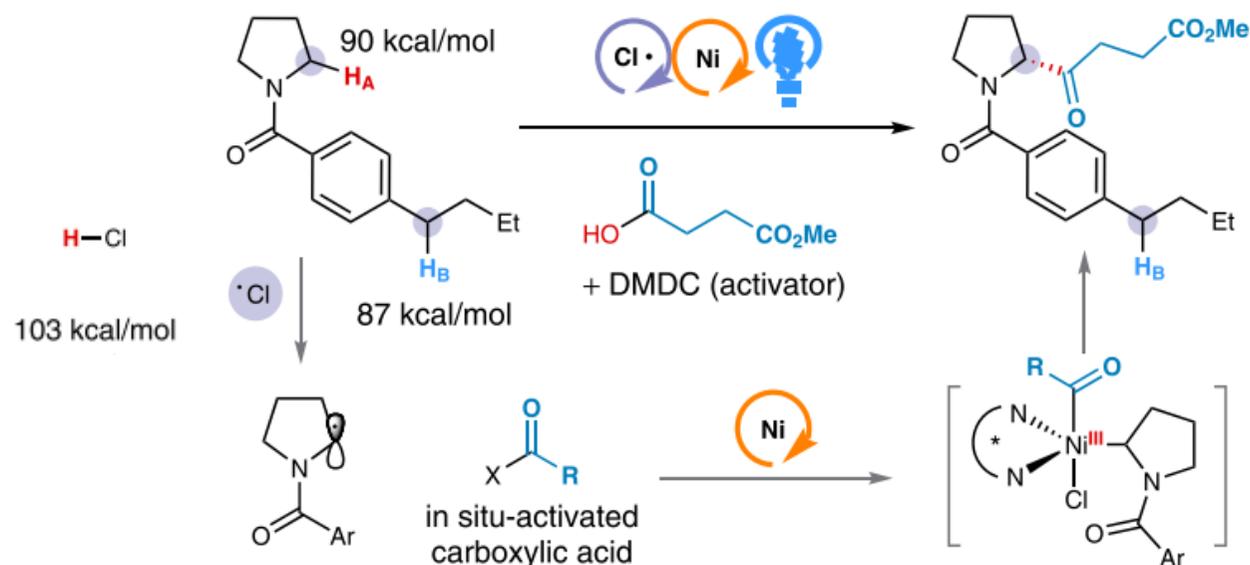
<https://doi.org/10.1038/s41467-023-35800-0>

Site- and enantioselective cross-coupling of saturated *N*-heterocycles with carboxylic acids by cooperative Ni/photoredox catalysis

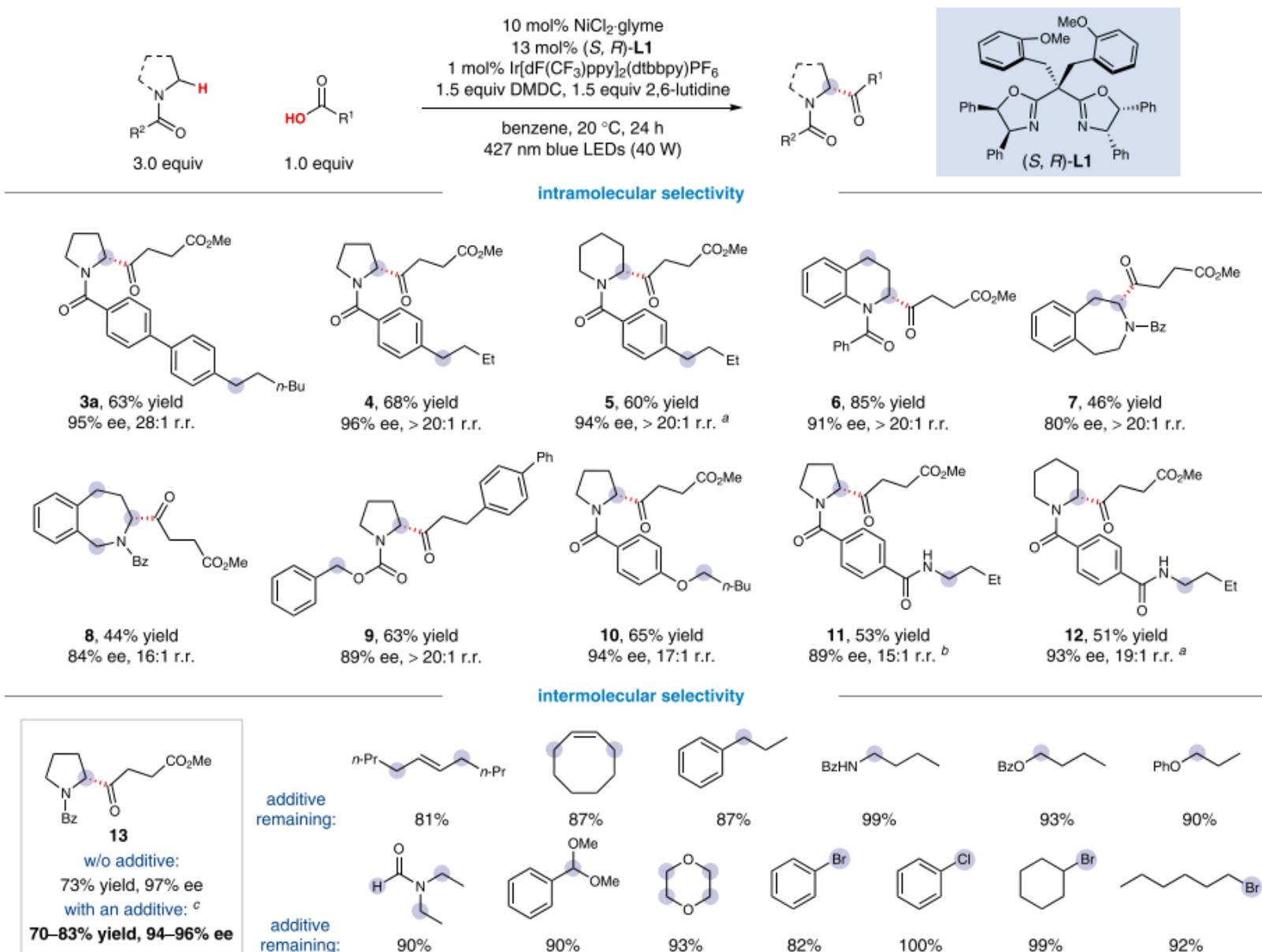
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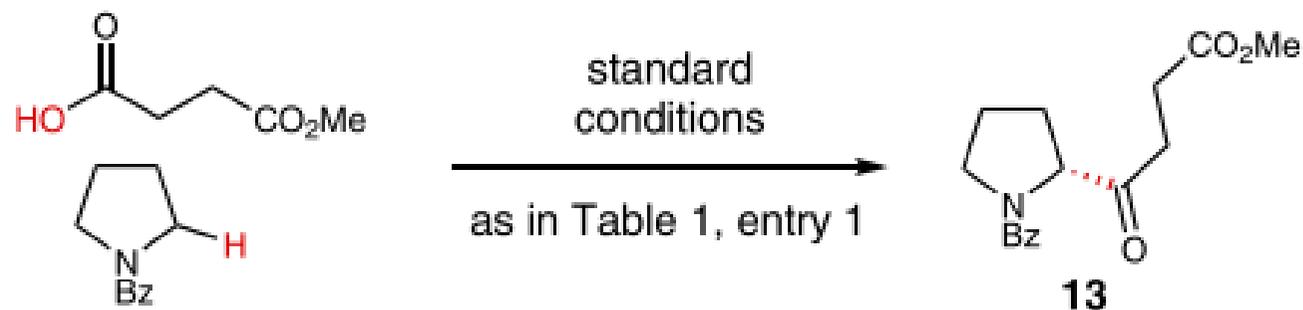


2.2 Cl•介导的C(sp³)-H官能化——酰基化



2.2 Cl•介导的C(sp³)-H官能化——酰基化

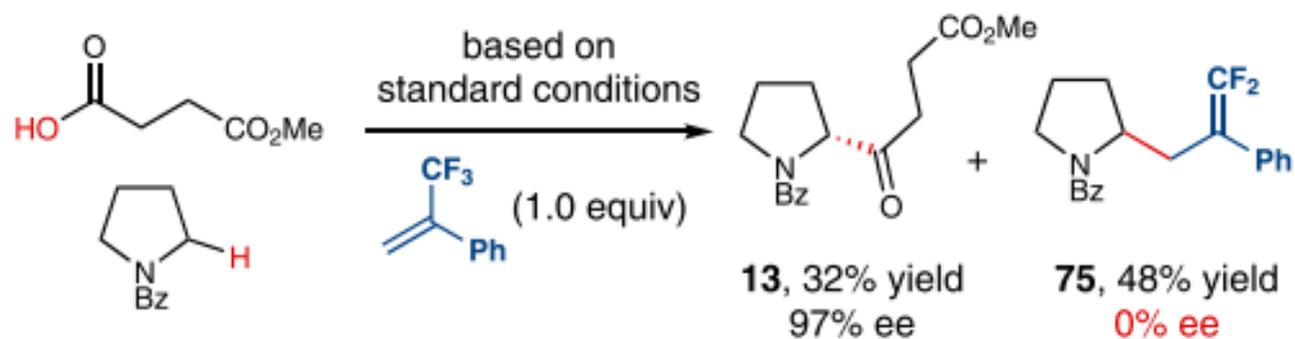
a. The importance of chloride for the reactions



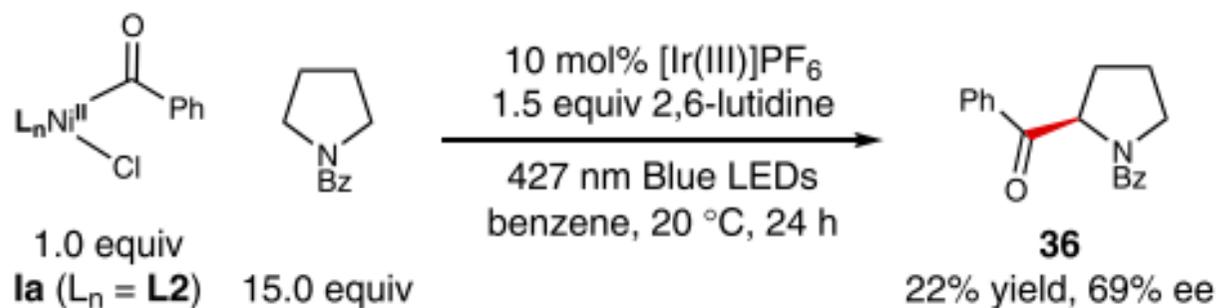
entry	variation	results
1	NiCl ₂ ·glyme (none)	73% yield, 97% ee
2	NiBr ₂ ·glyme	8% yield, 98% ee
3	Ni(COD) ₂	2% yield, ee: ND
4	Ni(COD) ₂ , 1.5 equiv of LiCl added	6% yield, ee: ND
5	Ni(acac) ₂	28% yield, 89% ee
6	Ni(acac) ₂ , 1.5 equiv of LiCl added	64% yield, 95% ee

2.2 Cl•介导的C(sp³)-H官能化——酰基化

b. The intermediacy of α -amino radicals

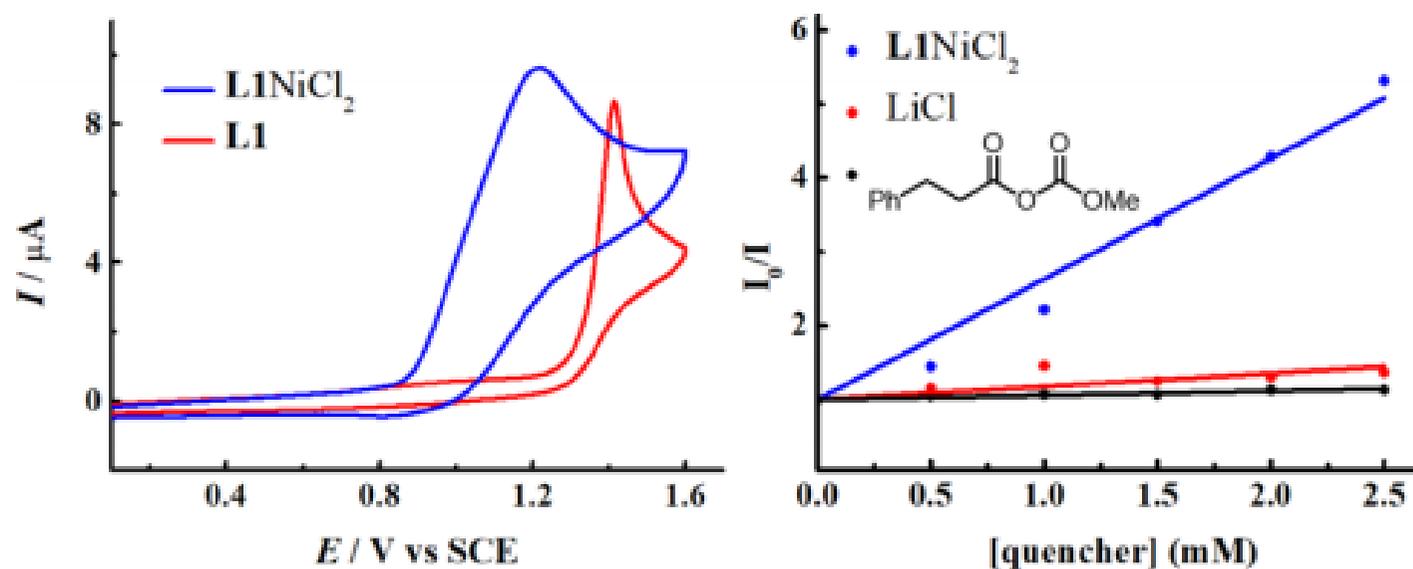


c. Stoichiometric experiments with pregenerated Ni(II) acyl chloride species



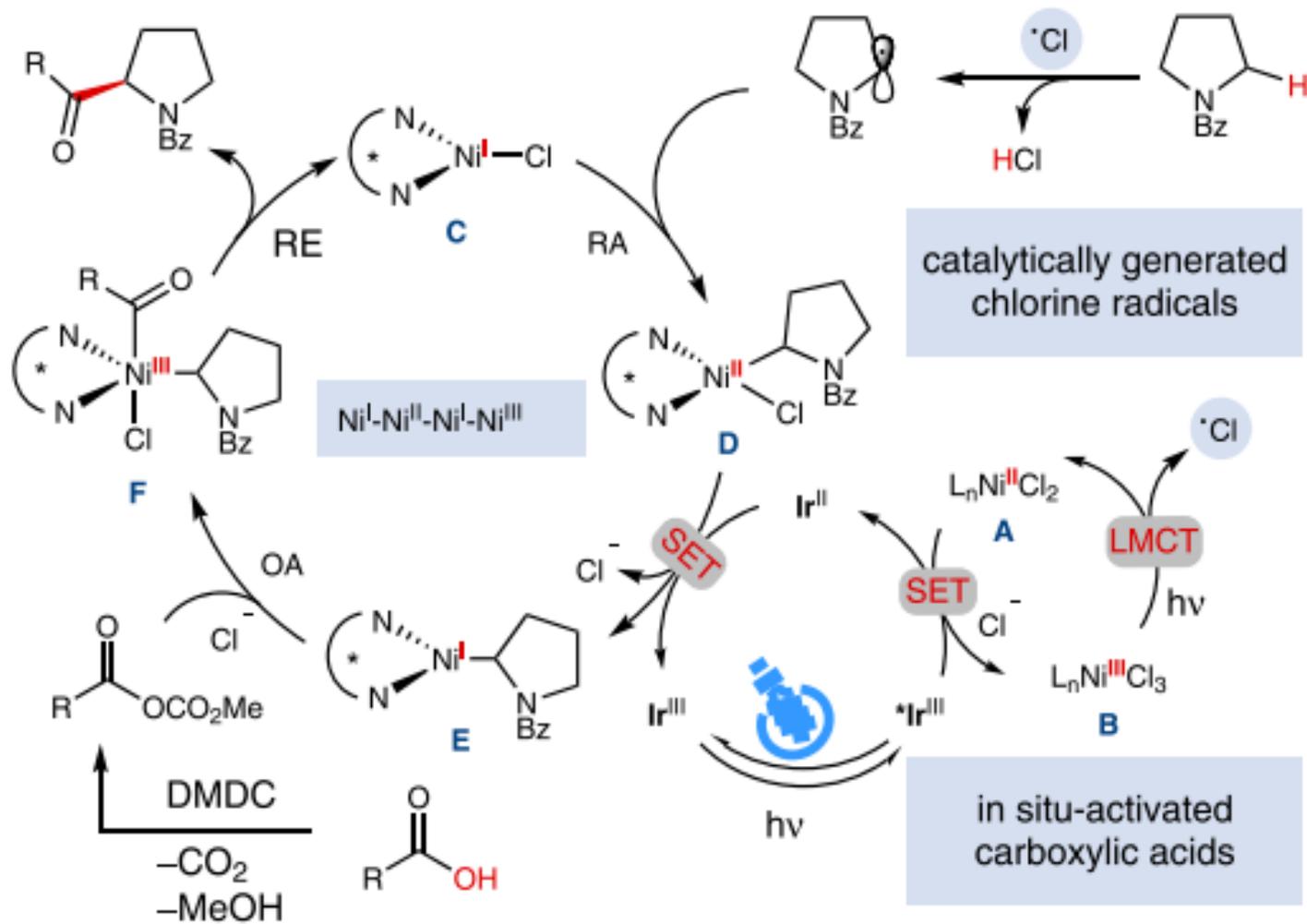
2.2 Cl•介导的C(sp³)-H官能化——酰基化

d. Cyclic voltammogram studies and luminescence quenching experiments



E: $E_{p/2ox} = +1.02 \text{ V vs SCE}$ in CH_3CN
 $E_{1/2}[\text{Ir}(\text{III}^*/\text{II})] = +1.21 \text{ V vs SCE}$ in CH_3CN

2.2 Cl•介导的C(sp³)-H官能化——酰基化



Thanks!