Literature Report VI

Nickel-Catalyzed C–I-Selective C(sp^2)–C(sp^3) Cross-Electrophile Coupling of Bromo(iodo)arenes with Alkyl Bromides

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Checker: Yu-Qing Bai
Date: 2023-05-29

Ying, X.; Li, Y.; Li, L.; Li, C.
Angew. Chem. Int. Ed. **2023**, e202304177

CV of Dr. Chao Li

Dr. Chao Li

Education and Employment:

- **2004–2008** B.S., Qingdao University of Science and Technology
- **2008–2013** Ph.D., NIBS (Prof. Xiaoguang Lei)
- **2013–2014** Postdoc., NIBS (Prof. Xiaoguang Lei)
- **2014–2017** Postdoc., The Scripps Research Institute (Prof. Phil S. Baran)
- **2017–Now** Assistant Investigator, NIBS

Research Interest:

- Discovery of novel chemical reactions and their applications in the syntheses of natural products and bioactive molecules.

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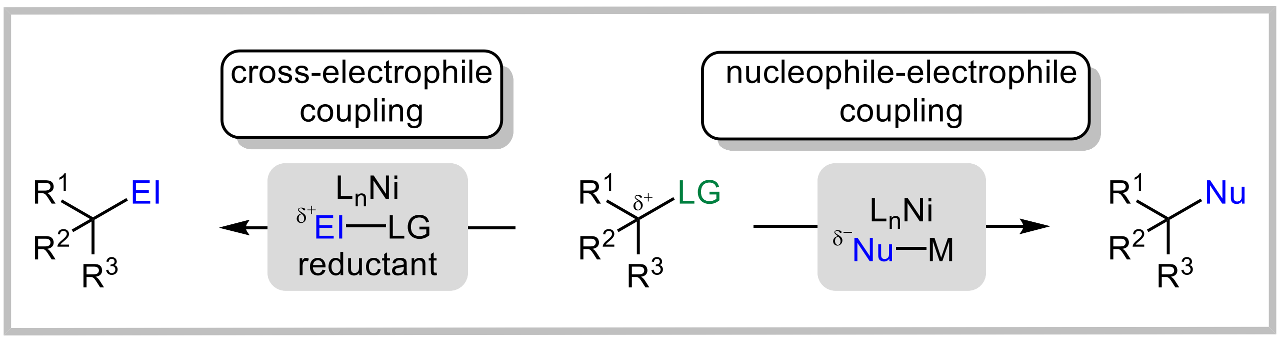
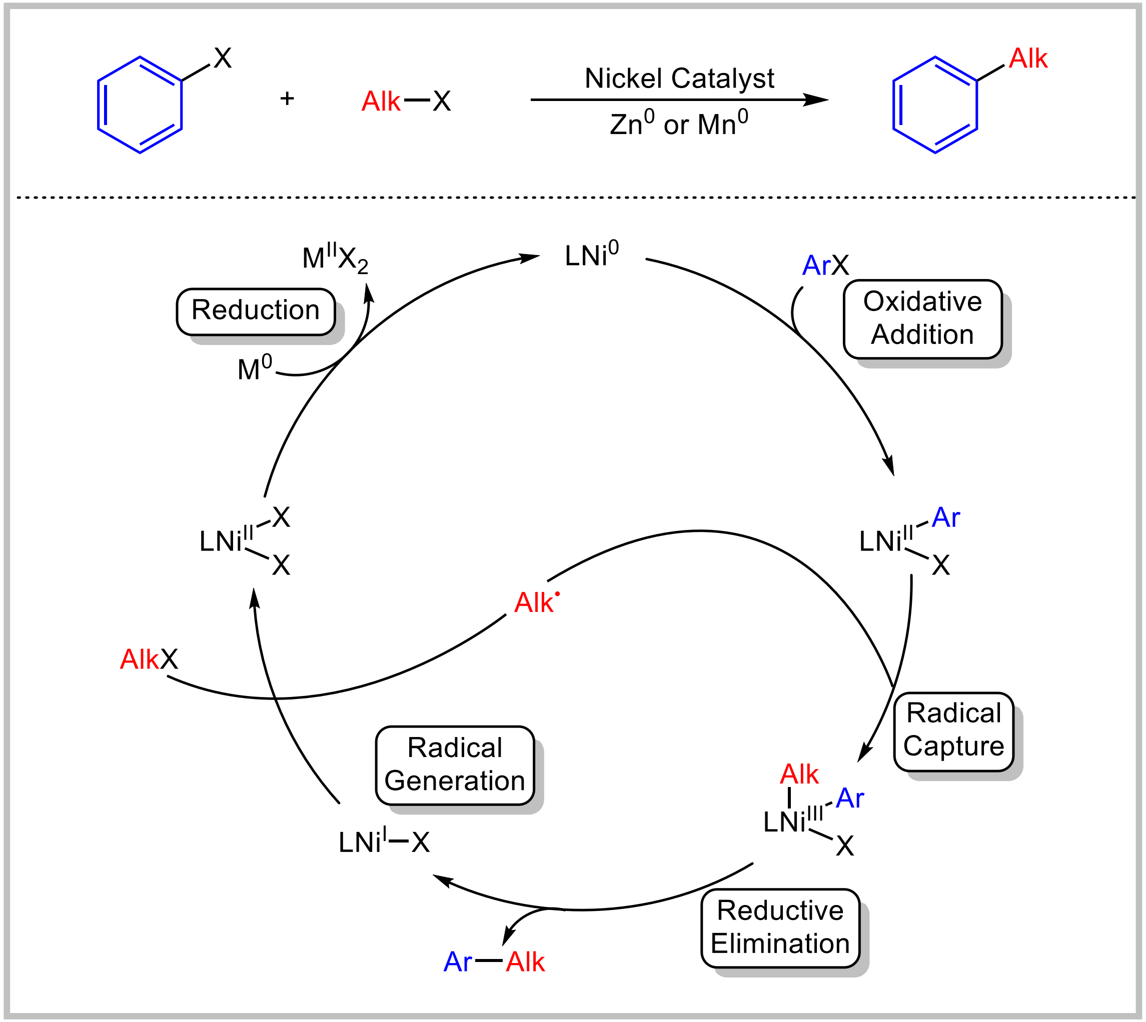


Xue, W.; Jia, X.; Gong, H. *et al*. *Chem. Soc. Rev.* **2021**, *50,* 4162

Introduction

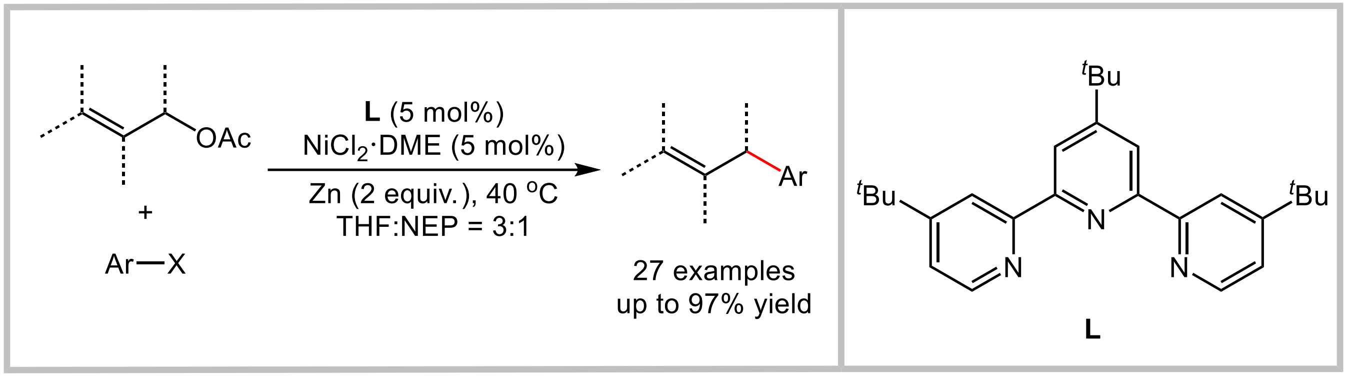
Conventional Cross-Electrophile Coupling



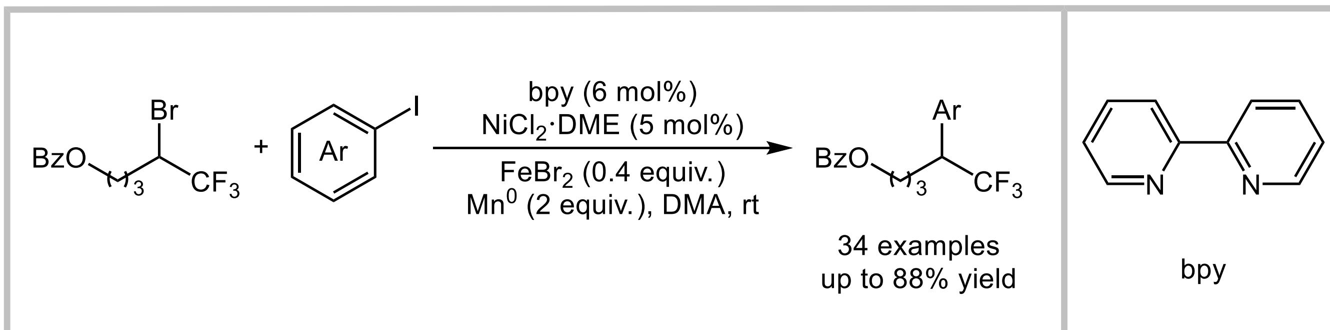
Xue, W.; Jia, X.; Gong, H. *et al*. *Chem. Soc. Rev.* **2021**, *50,* 4162

Introduction

Nickel-Catalyzed Cross-Electrophile Coupling



Anka-Lufford, L. L.; Prinsell, M. R.; Weix, D. J. *J. Org. Chem.* **2012**, *77*, 9989



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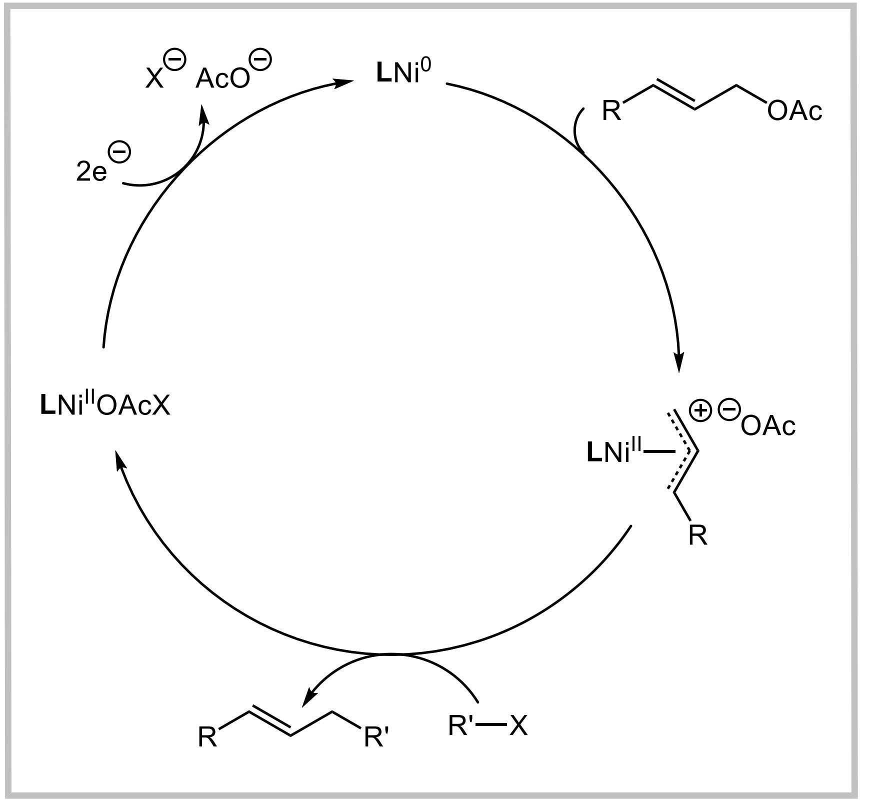
Introduction

Nickel-Catalyzed Cross-Electrophile Coupling



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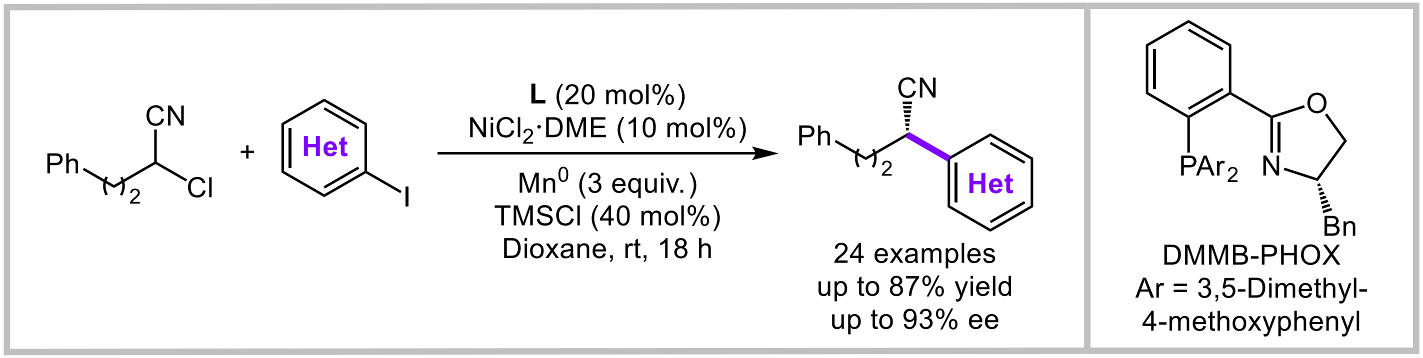
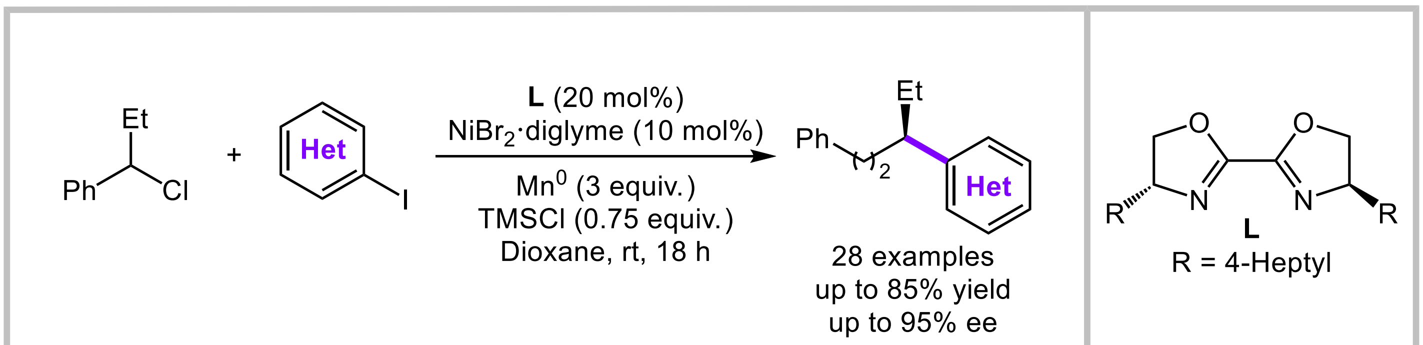
Nickel-Catalyzed Asymmetric Reductive Cross-Coupling



Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*,10480



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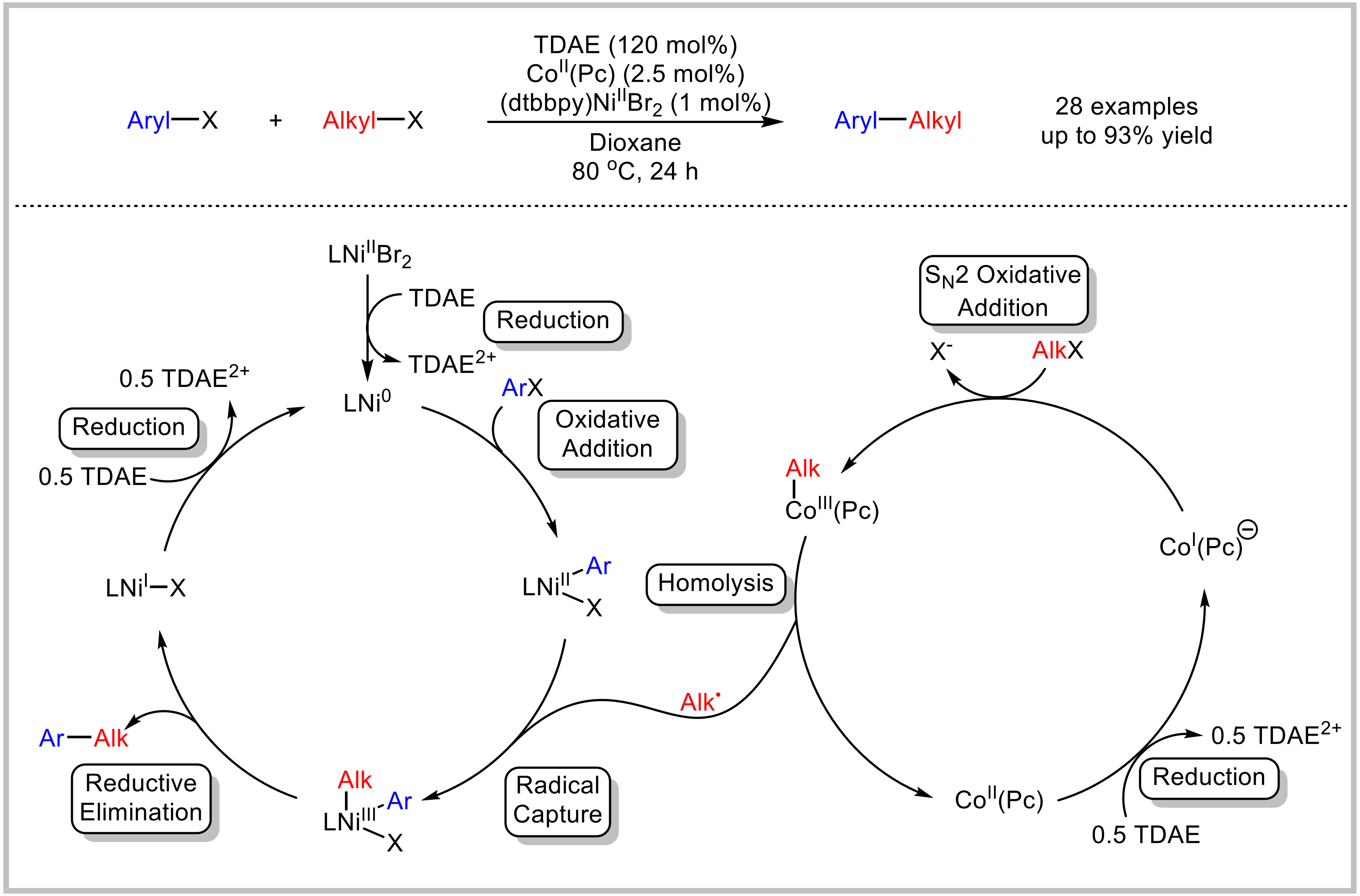
Dual-Catalyzed Cross-Electrophile Coupling



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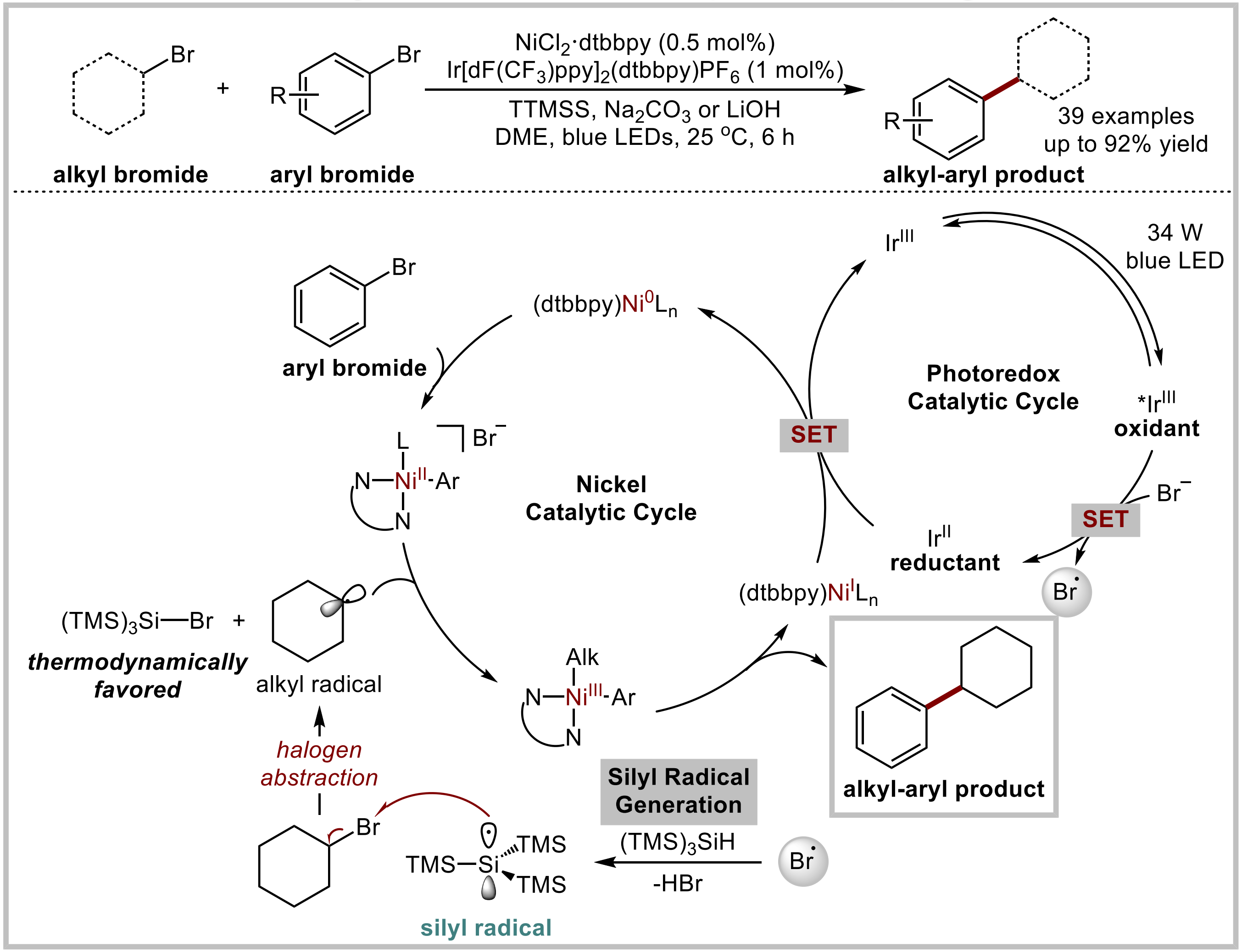
Introduction

Metallaphotoredox-Catalyzed Cross-Electrophile Coupling



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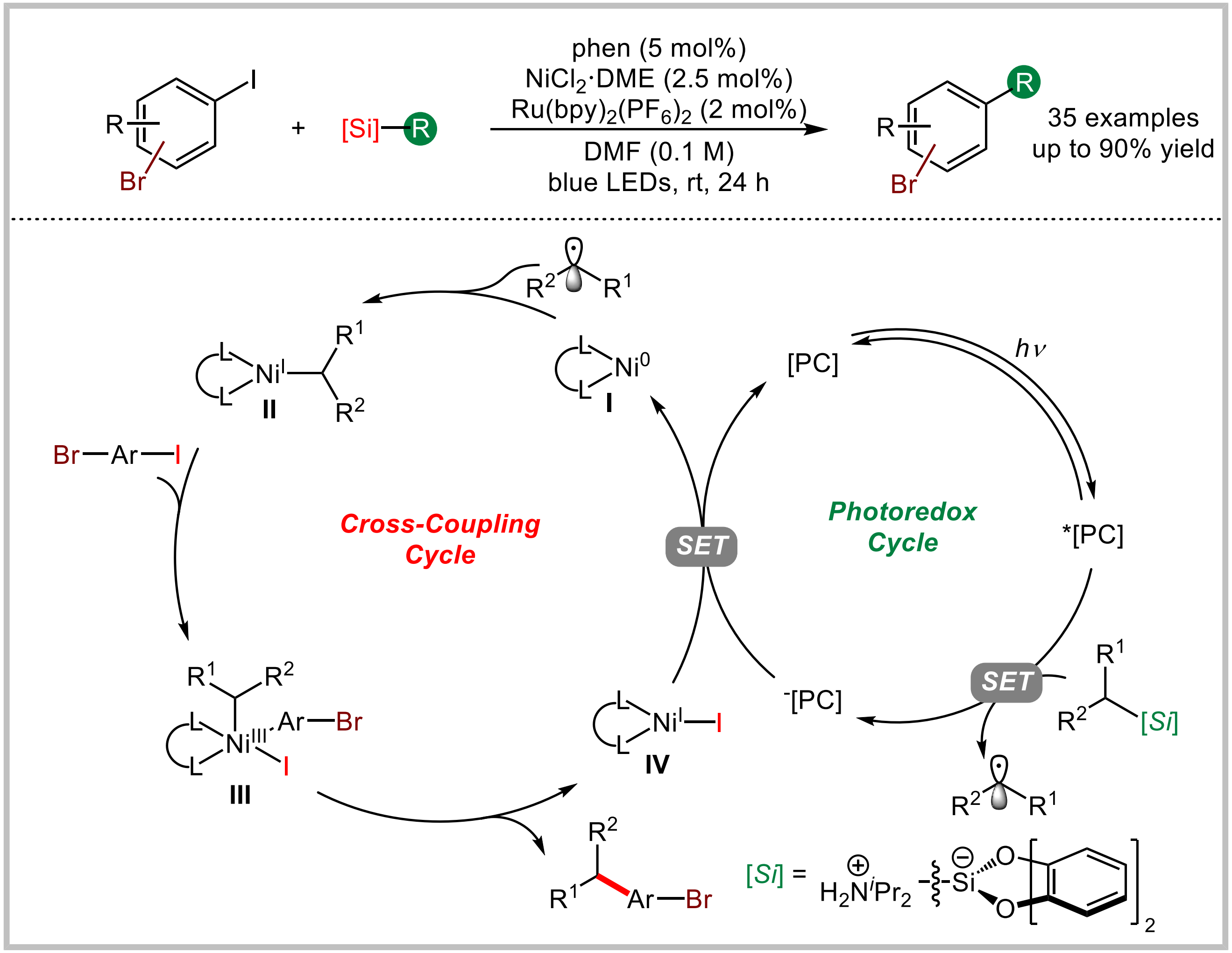
Introduction

Metallaphotoredox-Catalyzed Cross-Electrophile Coupling



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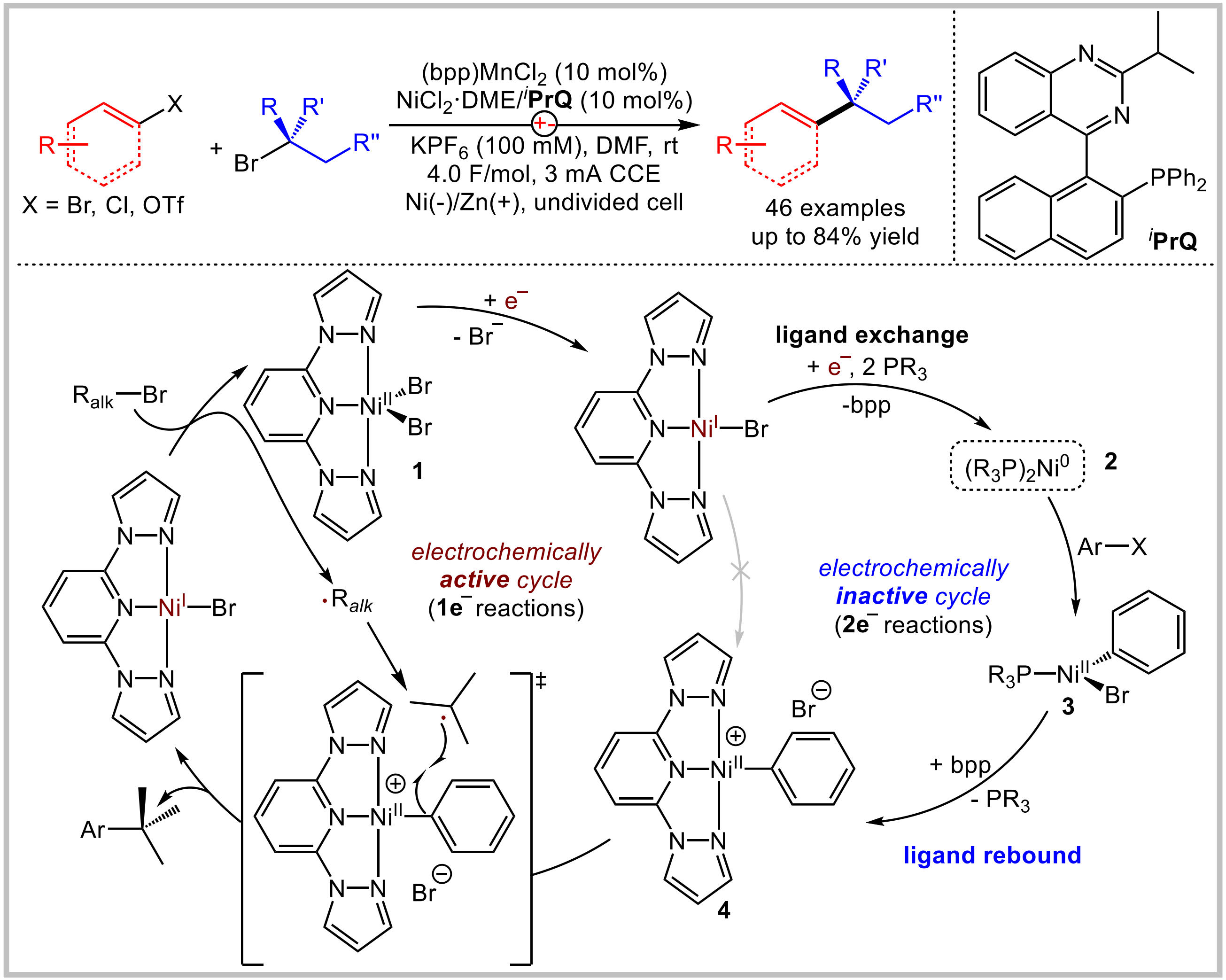
Electrochemical Nickel-Catalyzed Cross-Electrophile Coupling



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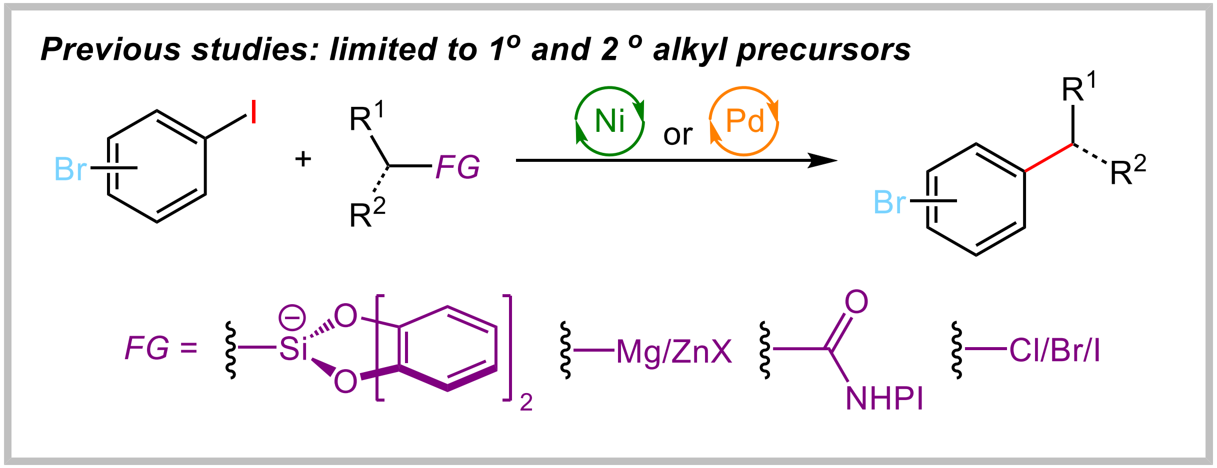
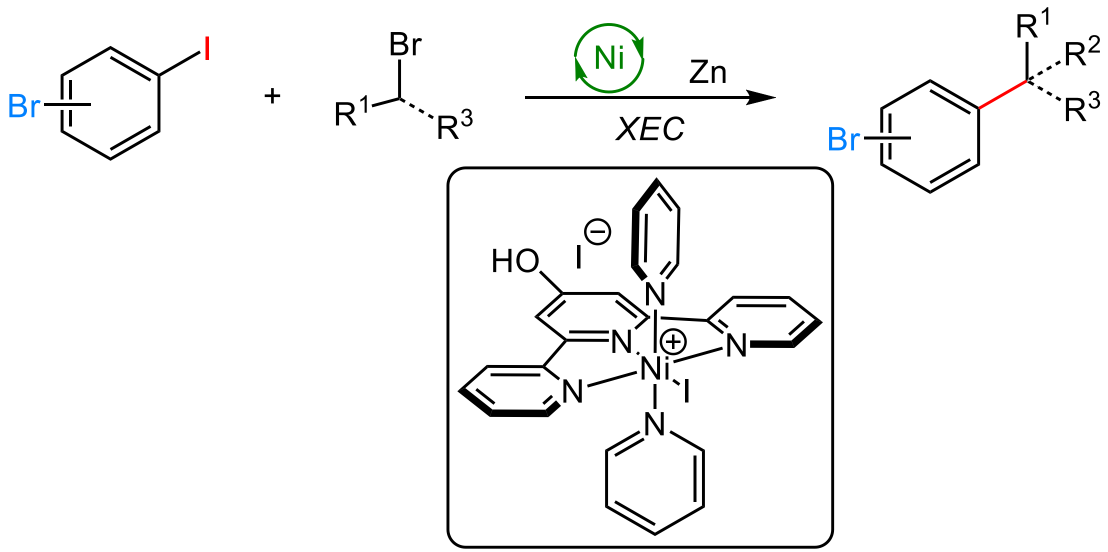


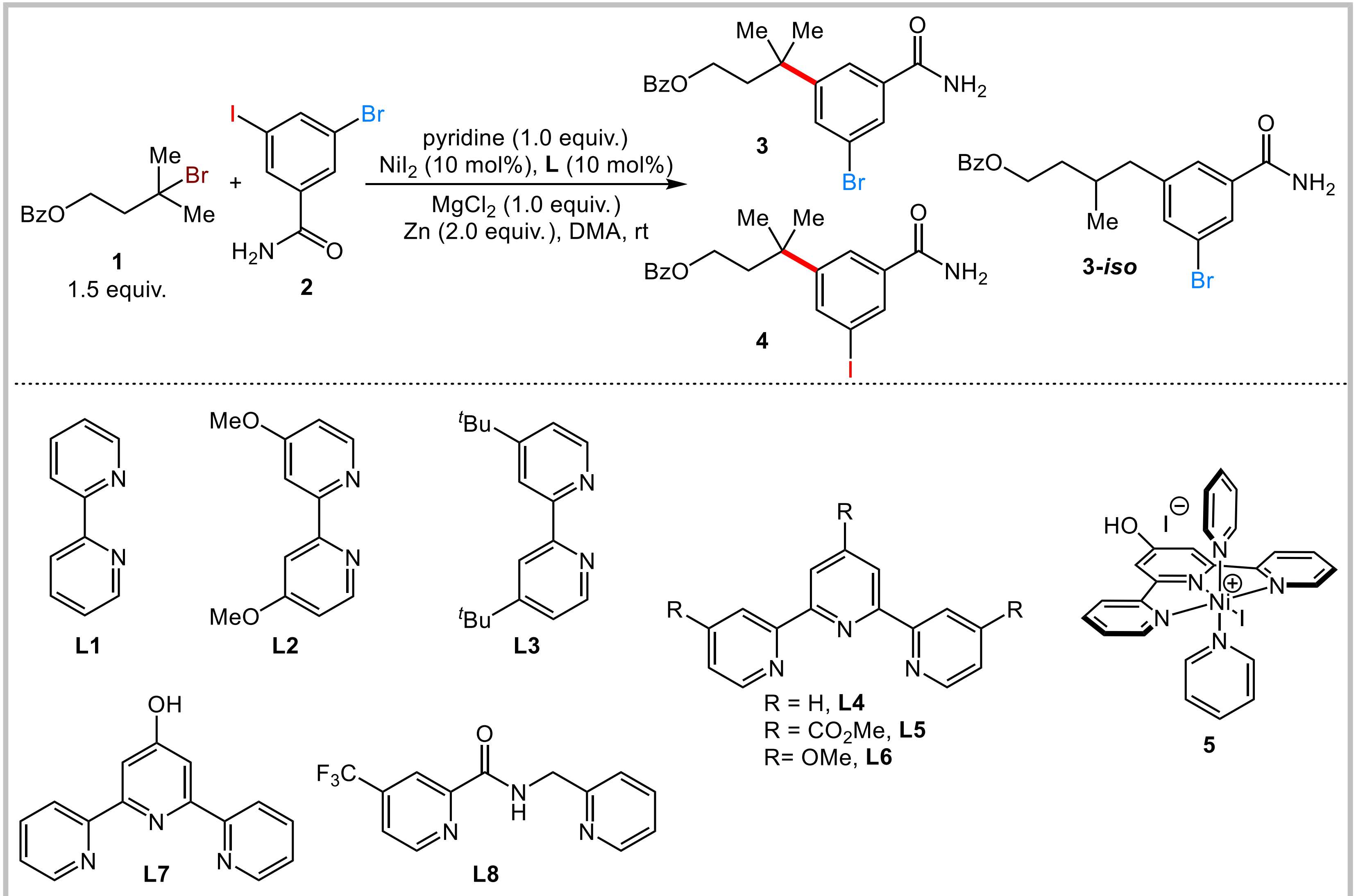
Introduction

Nickel-Catalyzed Cross-Electrophile Coupling

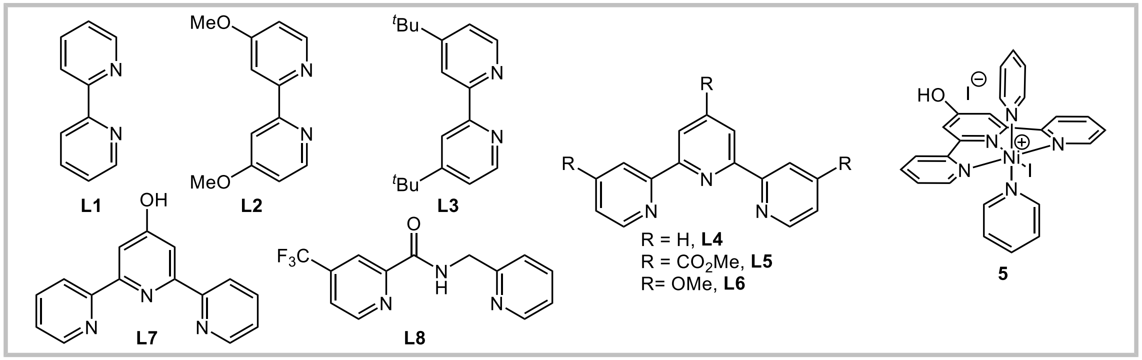
This work: 3º, 2º and 1 º alkyl bromides are viable coupling partners



Optimization of the Reaction Conditions



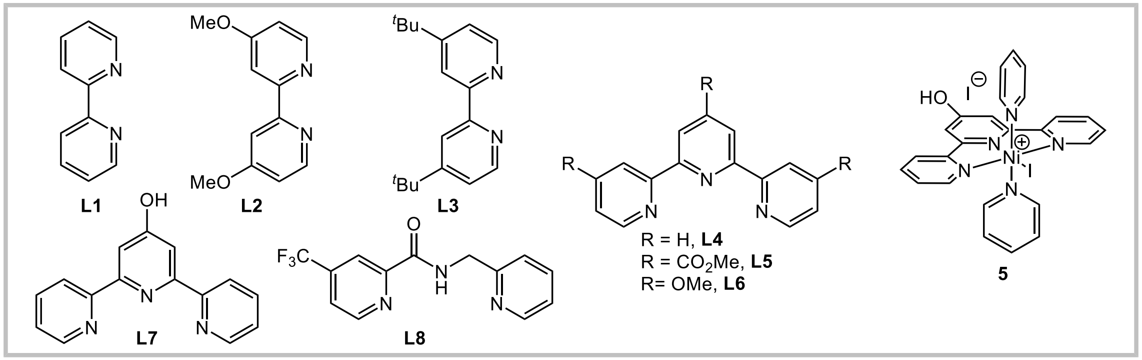
Optimization of the Reaction Conditions



Entry[a]	Conditions	**3**/**4**/**3**-*iso*[b]	Yield (%) of **3**[b]
1	**L1**	/	< 5
2	**L2**	/	< 5
3	**L3**	100/5/28	10
4	**L4**	100/10/4	35
5	**L5**	100/17/1	17
6	**L6**	100/10/4	46
7	**L7**	100/7/4	56
8	**L8**	100/1/4	14
9	**5** (10 mol%) instead of NiI_2/**L**	100/6/4	52

[a] The reactions were conducted at a 0.15 mmol scale of **2** at a 0.06 M concentration for 12 h. [b] Yields and the ratio of **3**, **3-*iso***, and **4** were determined by LC/MS with external calibration.

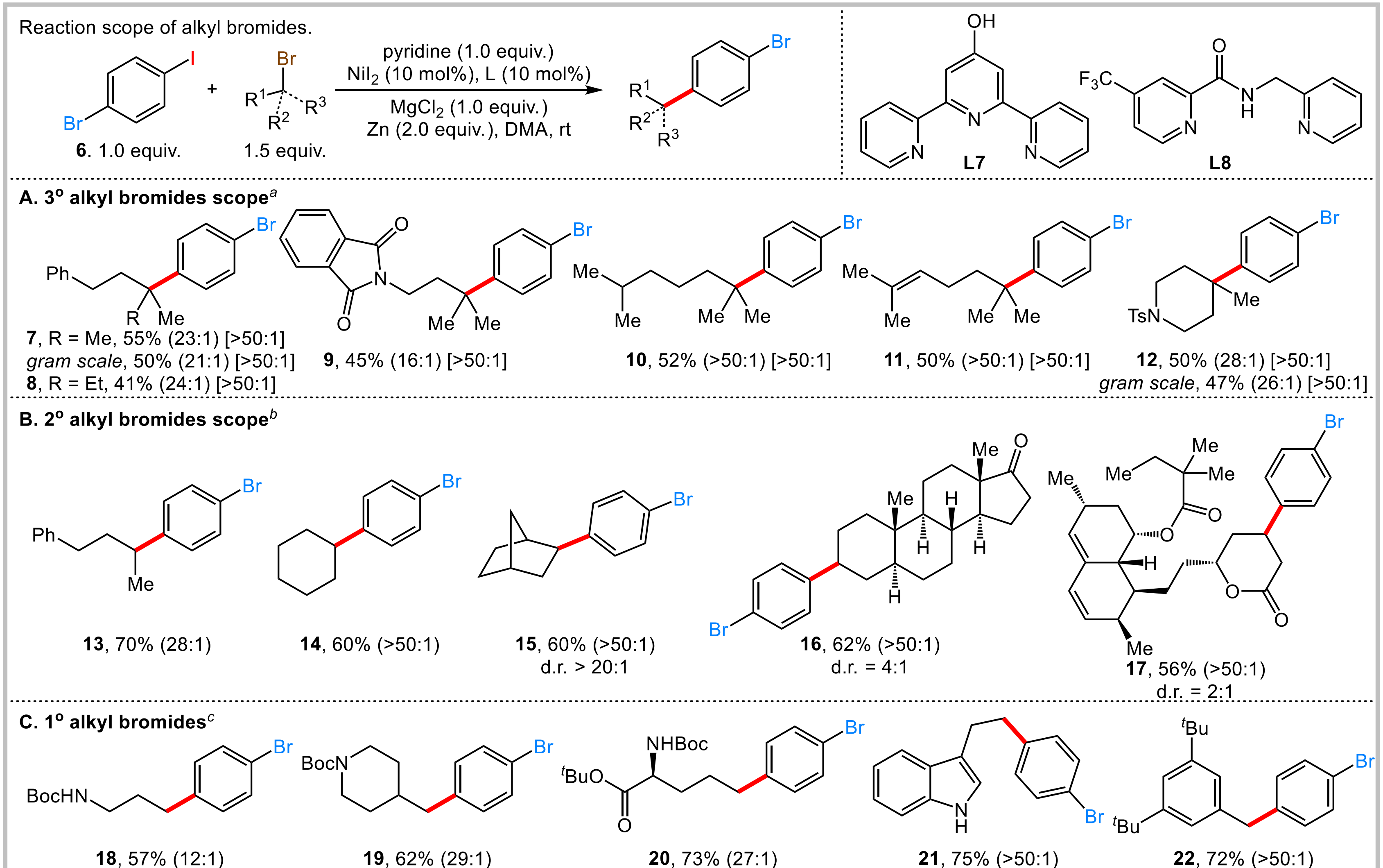
Optimization of the Reaction Conditions



Entry[a]	Conditions	**3**/**4**/**3**-*iso*[b]	Yield (%) of **3**[b]
10	w/o **L**	100/20/5	20
11[c]	Ni(TMHD)$_2$ instead of NiI_2	/	< 5
12[c]	Ni(acac)$_2$ instead of NiI_2	/	< 5
13[c]	LiCl instead of $MgCl_2$	100/10/3	52
14[c]	w/o $MgCl_2$	/	< 5
15[c]	w/o pyridine	100/1/1	17
16[c]	3-F pyridine instead of pyridine	100/7/6	44
17[c]	DMAP instead of pyridine	100/20/5	24
18[c]	Mn instead of Zn	100/10/6	19

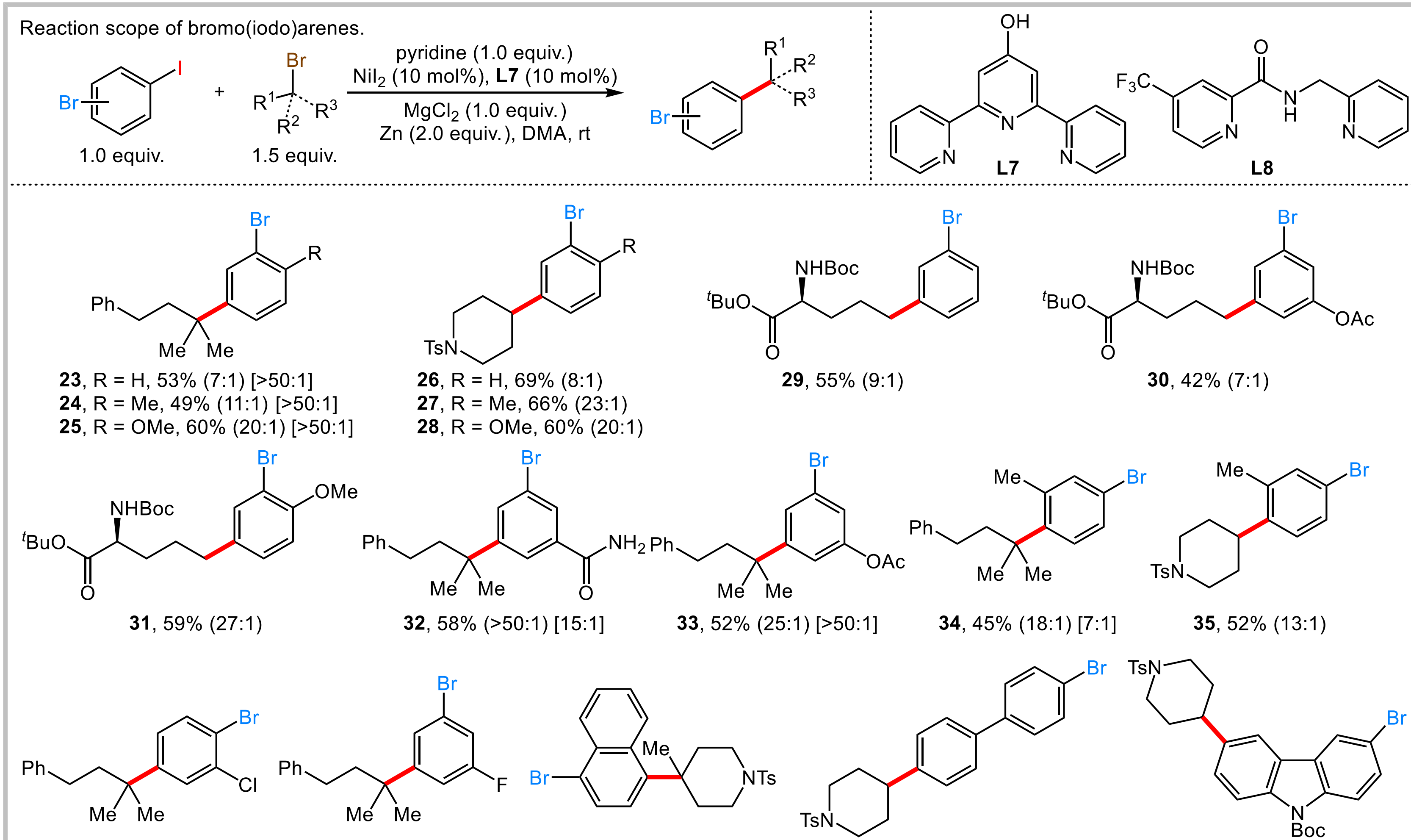
[a] The reactions were conducted at a 0.15 mmol scale of **2** at a 0.06 M concentration for 12 h. [b] Yields and the ratio of **3**, **3-*iso***, and **4** were determined by LC/MS with external calibration. [c] **L7** was used as the ligand.

Substrate Scope



[a] 3 equiv. of LiCl was used instead of $MgCl_2$. [b] 1.0 equiv. of alkyl bromides was used. [c] **L8** (10 mol%) was used instead of **L7**.

Substrate Scope



23, R = H, 53% (7:1) [>50:1]
24, R = Me, 49% (11:1) [>50:1]
25, R = OMe, 60% (20:1) [>50:1]

26, R = H, 69% (8:1)
27, R = Me, 66% (23:1)
28, R = OMe, 60% (20:1)

29, 55% (9:1)

30, 42% (7:1)

31, 59% (27:1)

32, 58% (>50:1) [15:1]

33, 52% (25:1) [>50:1]

34, 45% (18:1) [7:1]

35, 52% (13:1)

36, 40% (>50:1) [>50:1]

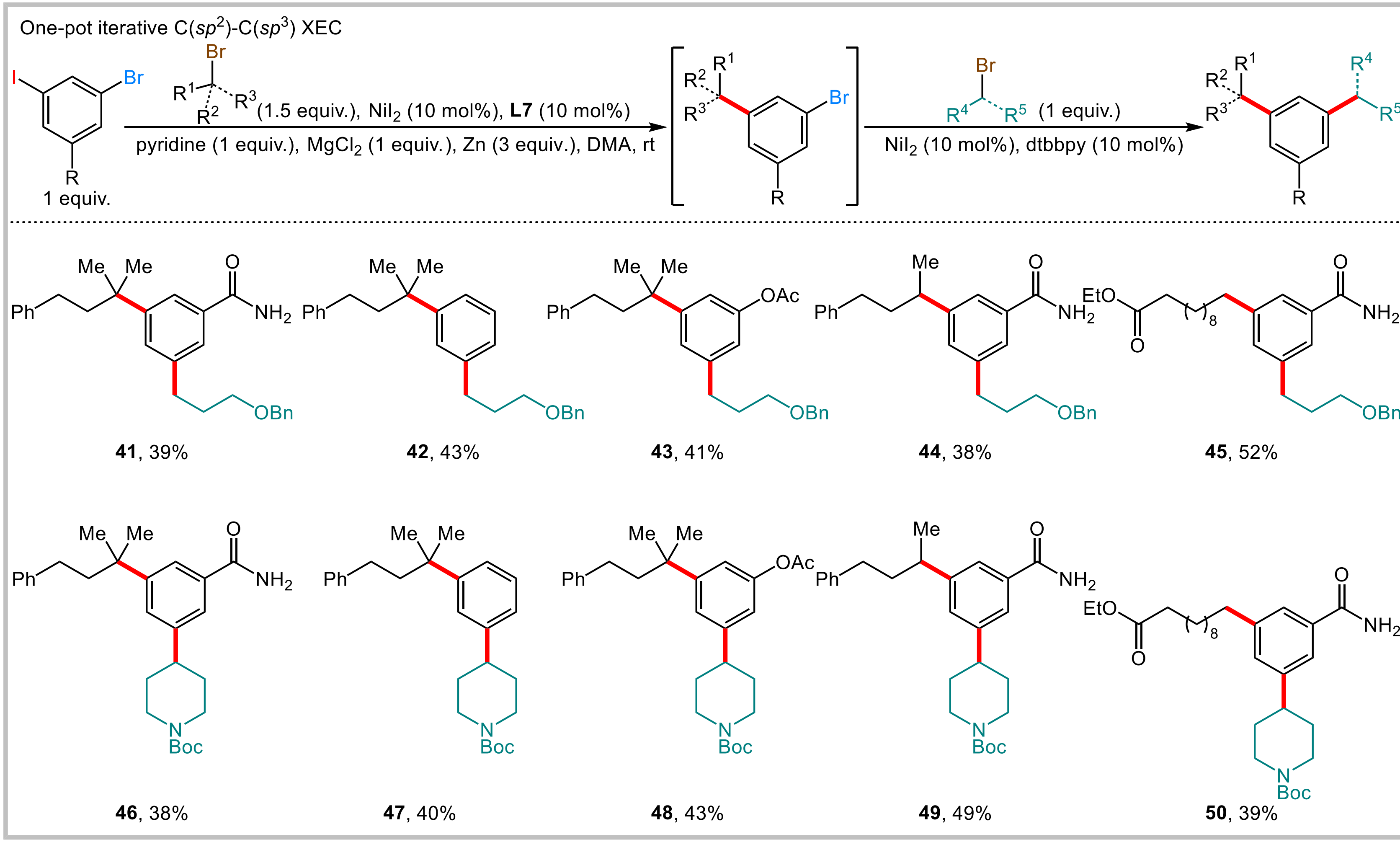
37, 41% (25:1) [>50:1]

38, 48% (>50:1) [>50:1]

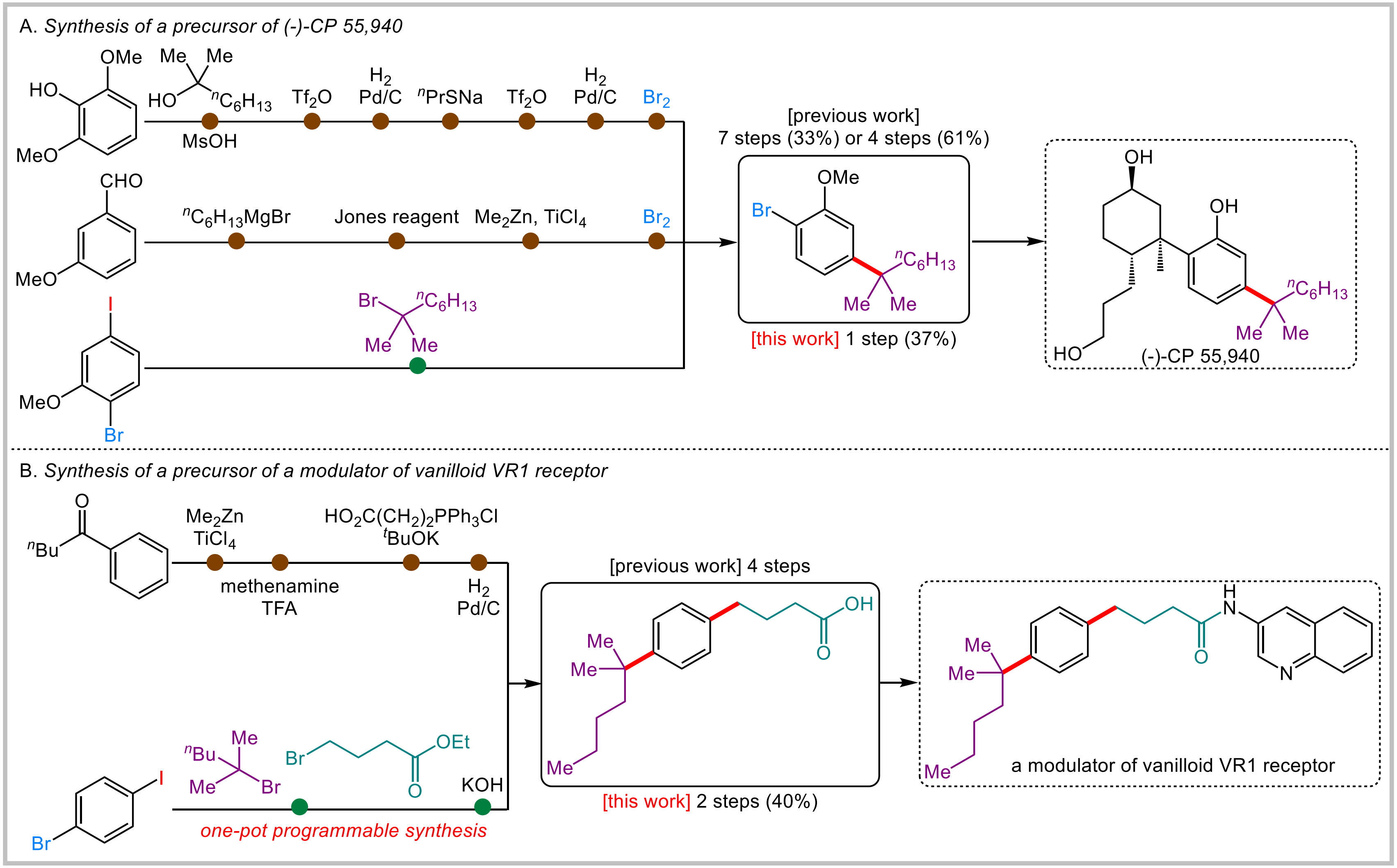
39, 57% (>50:1)

40, 49% (27:1)

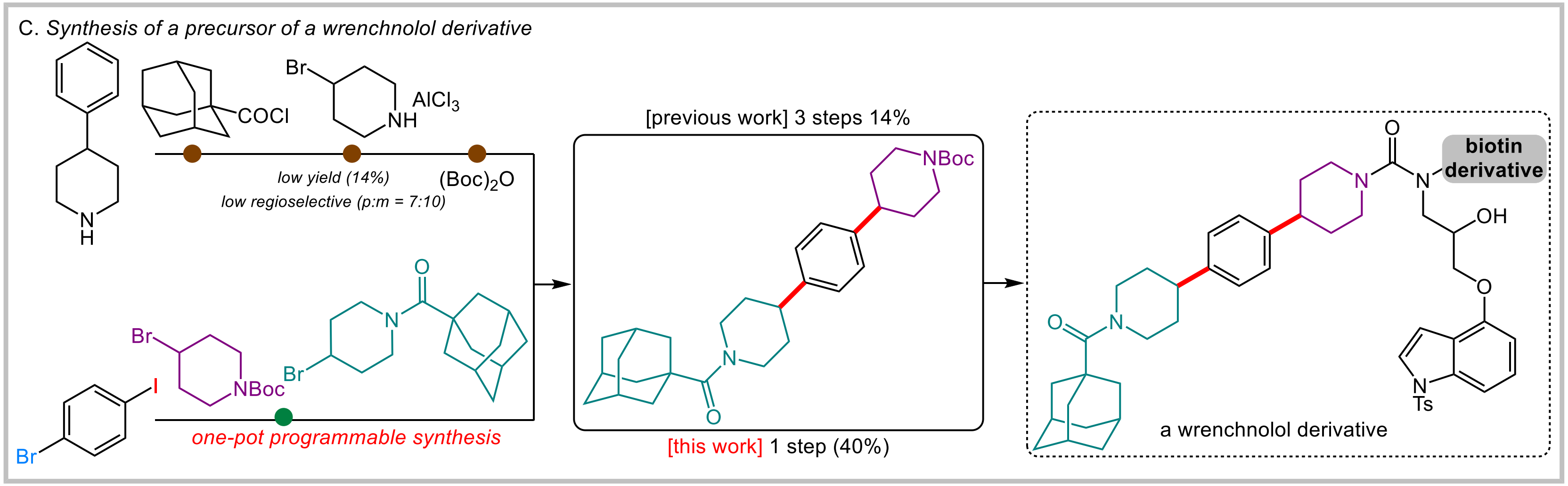
Substrate Scope



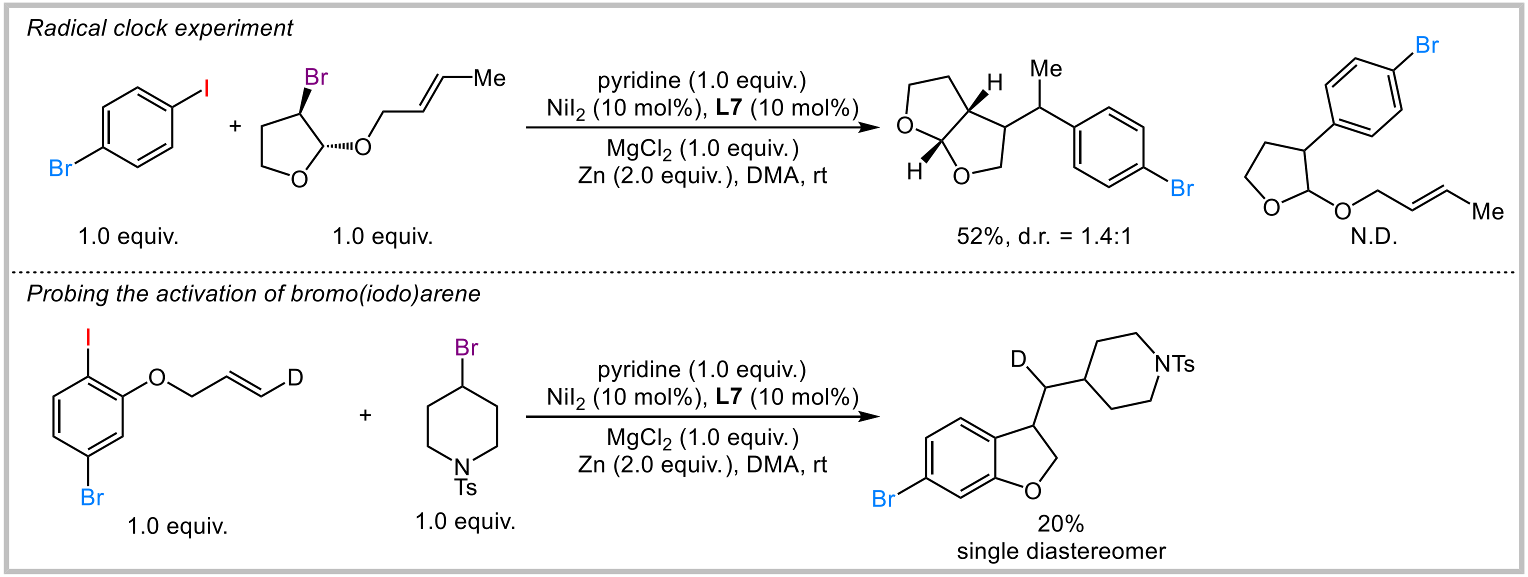
Synthetic Utility



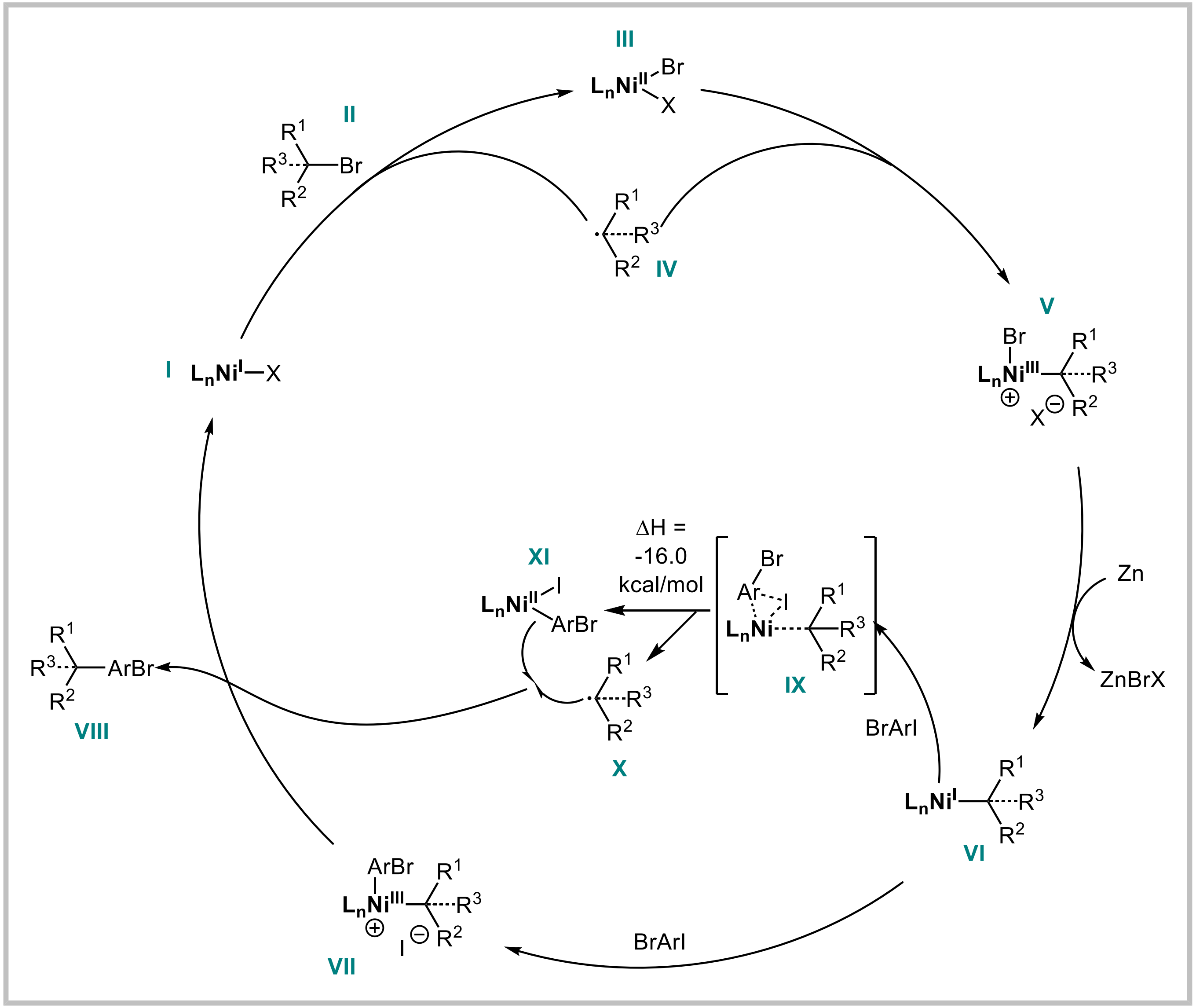
Synthetic Utility



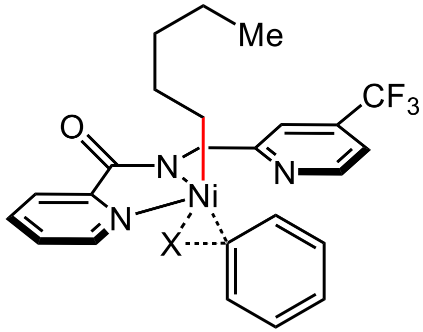
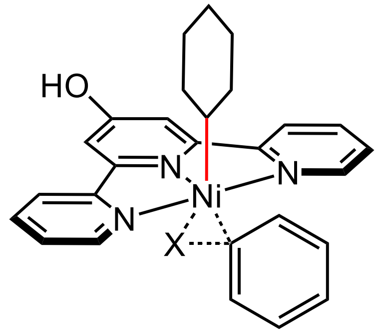
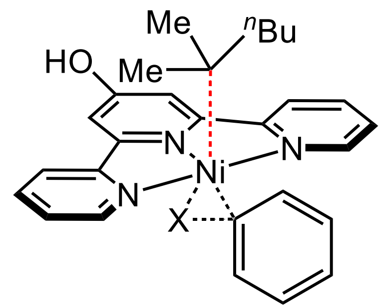
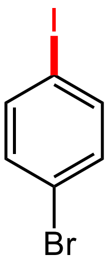
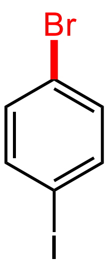
Control Experiments



Proposed Mechanism

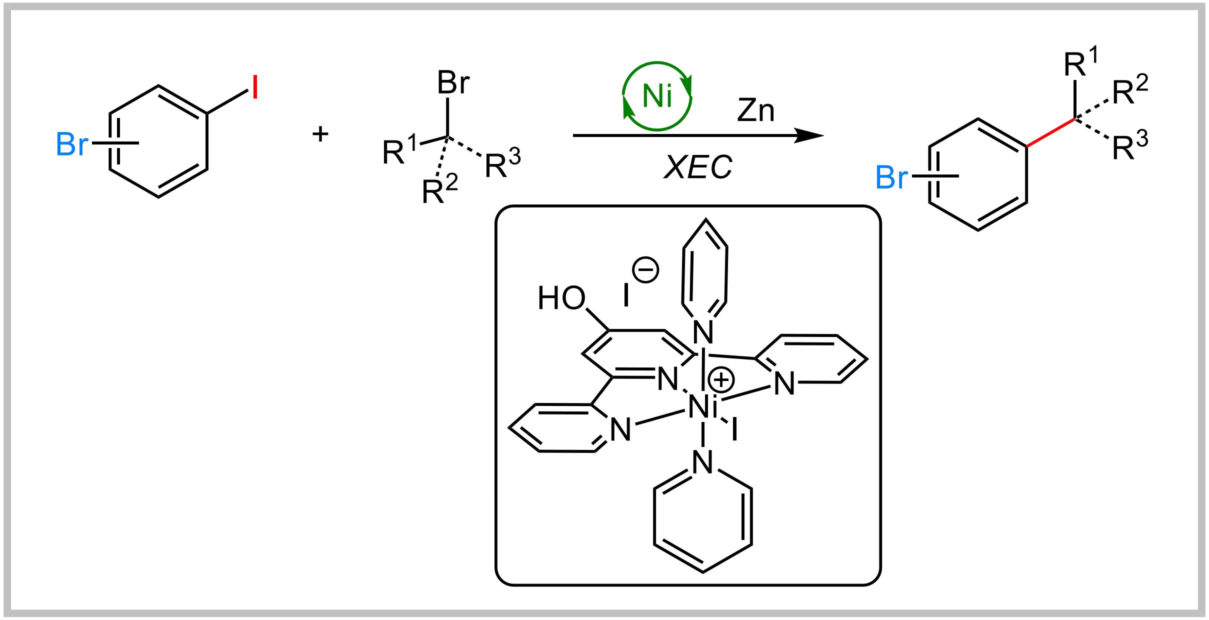


Calculated Energy Changes

	 VII-TS1	 VII-TS2	 IX
	$\Delta H^{\ddagger}$ = 10.3 kcal/mol	$\Delta H^{\ddagger}$ = 9.2 kcal/mol	$\Delta H^{\ddagger}$ = 17.2 kcal/mol
	$\Delta H^{\ddagger}$ = 15.4 kcal/mol	$\Delta H^{\ddagger}$ = 14.4 kcal/mol	$\Delta H^{\ddagger}$ = 18.5 kcal/mol

Summary

Nickel-Catalyzed Cross-Electrophile Coupling



- 3º, 2º, and 1º alkyl bromides;
- High C(sp²)-I Selectivity;
- Broad substrate scope;
- Excellent functional group tolerance.

Writing Strategy

介绍sp³杂化碳在药物分子中的重要性

↓

指出交叉偶联反应对引入sp³杂化碳的意义

↓

指出交叉偶联反应目前的挑战

- Lead compounds with greater molecular complexity and 3-dimensionality—which can be assessed based on the relative abundance of C(sp^3) groups—tend to have higher clinical success rates, owing to their increased binding specificity with target proteins. Accordingly, developing general and practical methods that can unbiasedly introduce various sp^3-hybridized carbons to flat aromatic rings can enrich modern drug discovery programs.

- Transition-metal catalyzed cross-couplings are among the most powerful strategies in forging C(sp^2)−C(sp^3) bonds, and broadly available aryl bromides and iodides are two of the most reactive and useful aryl sources in these cross-coupling reactions.

- However, the presence of bromo and iodo substitutions on the same arene raises the challenge of haloselectivity (differentiating C−I from C−Br bonds). If the reactivities of iodo and bromo groups on the same aromatic ring can be readily distinguished, then these two reactive halides can be used in an iterative and programable manner to increase the molecular complexity and expand the 3-dimensionality of flat aromatic rings.

Writing Strategy

总结本文工作

↓

强调方法优势

↓

展望未来发展

- In summary, we have developed a highly practical $C(sp^2)-I$ selective XEC of bromo(iodo)arenes with diverse 1°, 2°, and 3° alkyl bromides under mild conditions.

- Beyond the exceptional substrate generality, the wide functional group compatibility, and the excellent $C(sp^2)-I$ selectivity, this XEC is attractive in that it provide an efficient method to construct aryl bromide-flanked quaternary carbons. When viewed alongside the diverse crosscoupling reactions available with aryl bromides, this $C(sp^2)-I$ selective XEC opens access to a broad array of alkyl-substituted arenes covering a large chemical space.

- We anticipate that this $C(sp^2)-I$ selective XEC is likely to find wide applications, including beyond medicinal chemistry, on account of its ease-of-use and the ready availability of its essential building blocks: bromo(iodo)arenes and alkyl bromides. Further development and practical application of this reaction, as well as detailed mechanistic studies, are currently underway in our laboratory

Representative Examples

- Additionally, we **showcase the practical utility of** this C(sp^2)−I selective XEC **in**··· （展现··· 的实用性）

- **Mechanistically**, we found that ··· （从机理的角度）

- **When viewed alongside** the diverse crosscoupling reactions available with aryl bromides, ··· （从客观角度观察）

Thanks
for your attention !