中國科學院大連化學物理研究所
DALIAN INSTITUTE OF CHEMICAL PHYSICS, CHINESE ACADEMY OF SCIENCES

Literature Report 4

Ligand-Controlled Nickel-Catalyzed Regiodivergent Cross-Electrophile Alkyl-Alkyl Couplings of Alkyl Halid

Reporter: Juan Wang
Checker: Qing-Xian Xie

2023-03-20

Zhao, W.-T.; Meng, H.; Lin, J.-N.; **Shu, W.**
Angew. Chem. Int. Ed. **2023,** *62*, e202215779

CV of Prof. Wei Shu (舒伟)

Research Interests:

- ☐ Medicinal Chemistry
- ☐ Asymmetric Catalysis
- ☐ Single Electron Catalysis

Background:

- ☐ **2001-2005** B.S., Nankai University
- ☐ **2005-2010** Ph.D., Shanghai Institute of Organic Chemistry (SIOC, CAS)
- ☐ **2010-2018** Postdoc., Massachusetts Institute of Technology
- ☐ **2010-2018** Postdoc., Princeton University, University of Zurich
- ☐ **2018-Now** Associate Professor to Professor, Southern University of Science and Technology (SUSTech)

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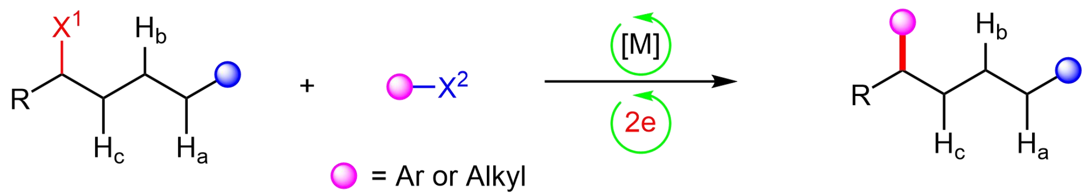
2 Ni-Catalyzed Regiodivergent Cross-Electrophile Couplings

3 Summary

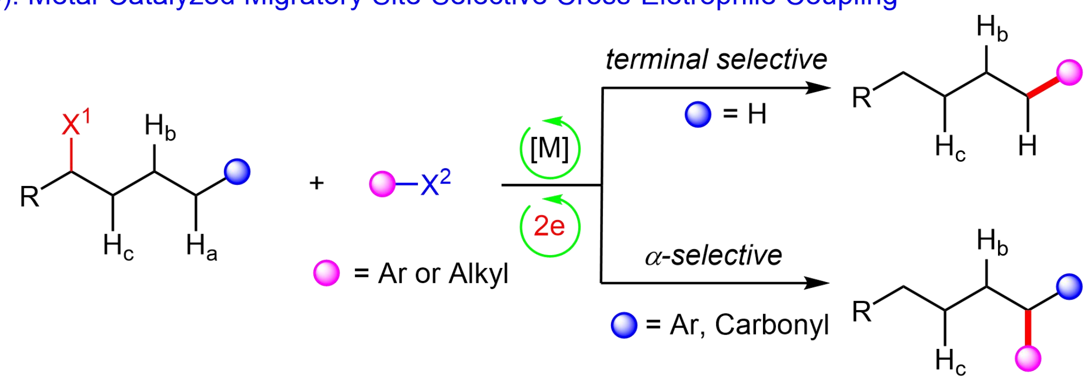
Introduction

Development of Regiodivergent Cross-Electrophile Couplings

a). Metal-Catalyzed Cross-Electrophile Coupling at *ipso*-Carbon

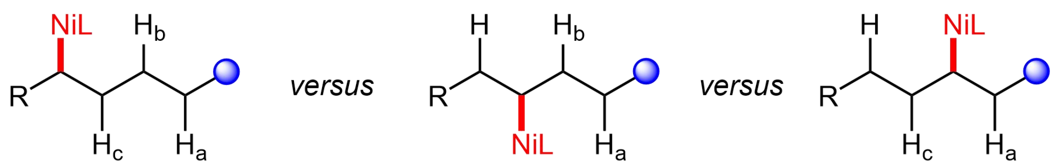


b). Metal-Catalyzed Migratory Site-Selective Cross-Eletrophile Coupling



♦ **Limited to Terminal- or α-Selectivity to Positioning Groups**

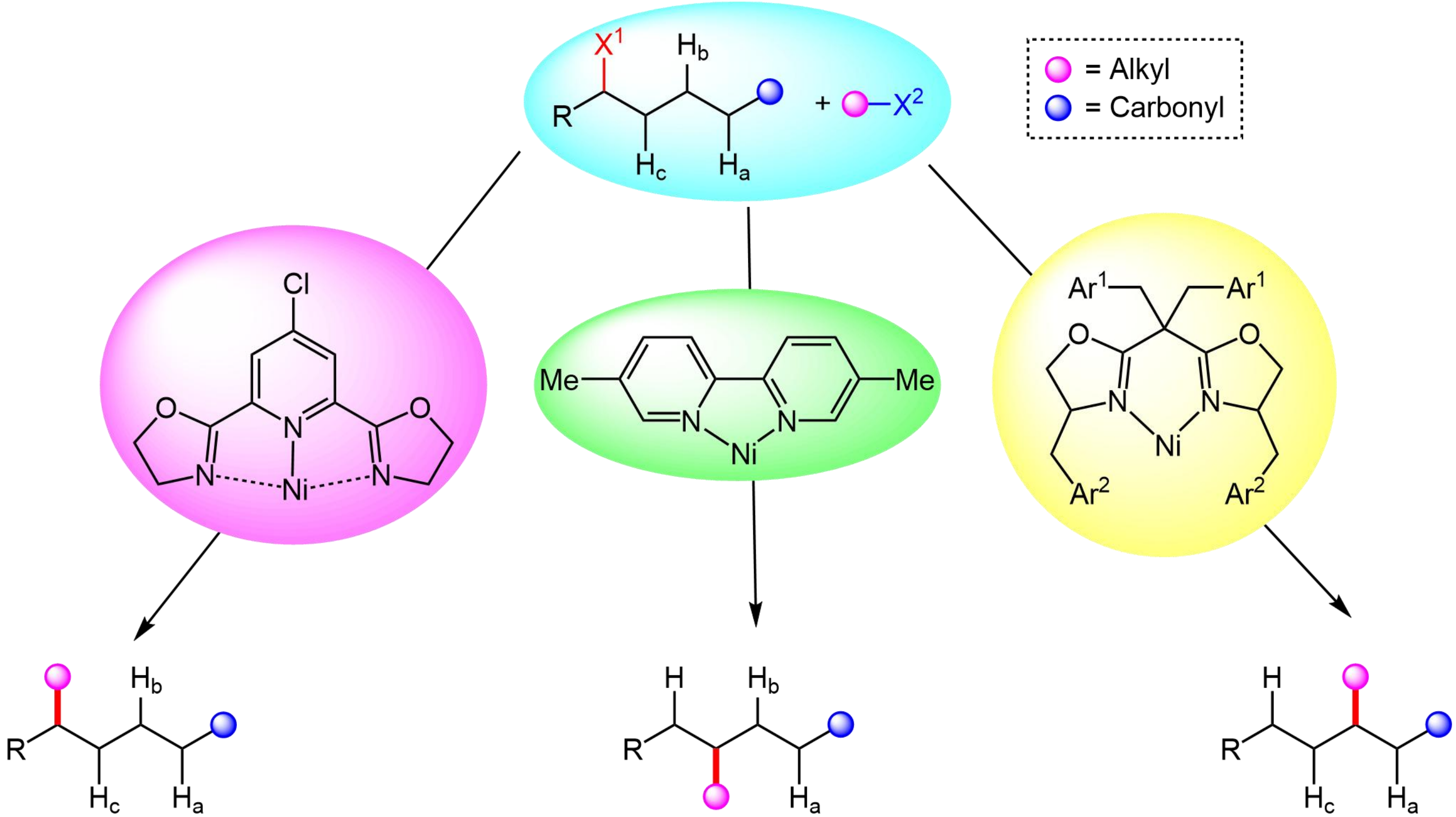
Challenge: Differentiate & Tune the Reactivity of Similar Intermediates



Introduction

Development of Regiodivergent Cross-Electrophile Couplings

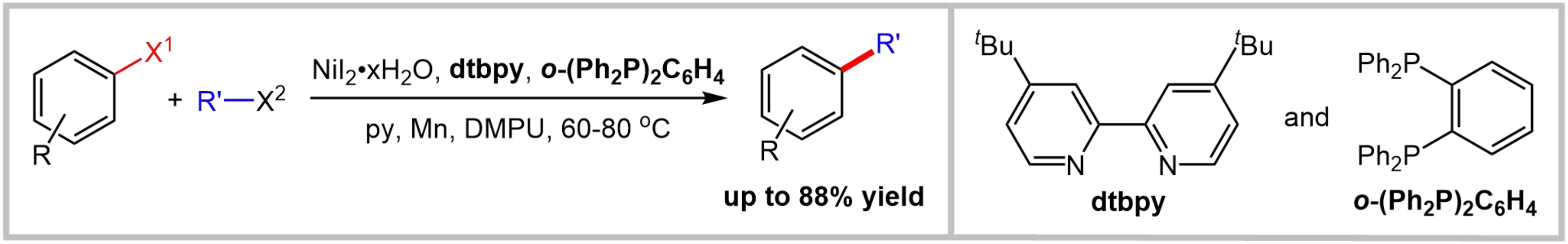
c). Ni-Catalyzed Regiodivergent Cross-Eletrophile Coupling (This work)

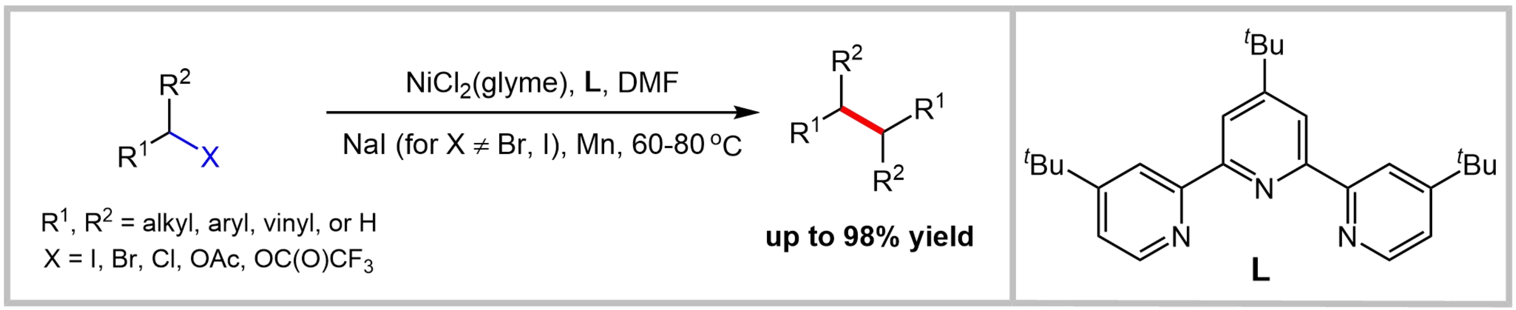


- ♦ Predictable Regioselectivities
- ♦ Regiodivergent Alkyl-Alkyl Coupling
- ♦ Access to Diverse Saturated Architectures
- ♦ Selective Migration on One Alkyl Bromides over Two Migratory Alkyl Bromides

Introduction

a) Metal-Catalyzed Cross-Electrophile Coupling at *ipso*-Carbon

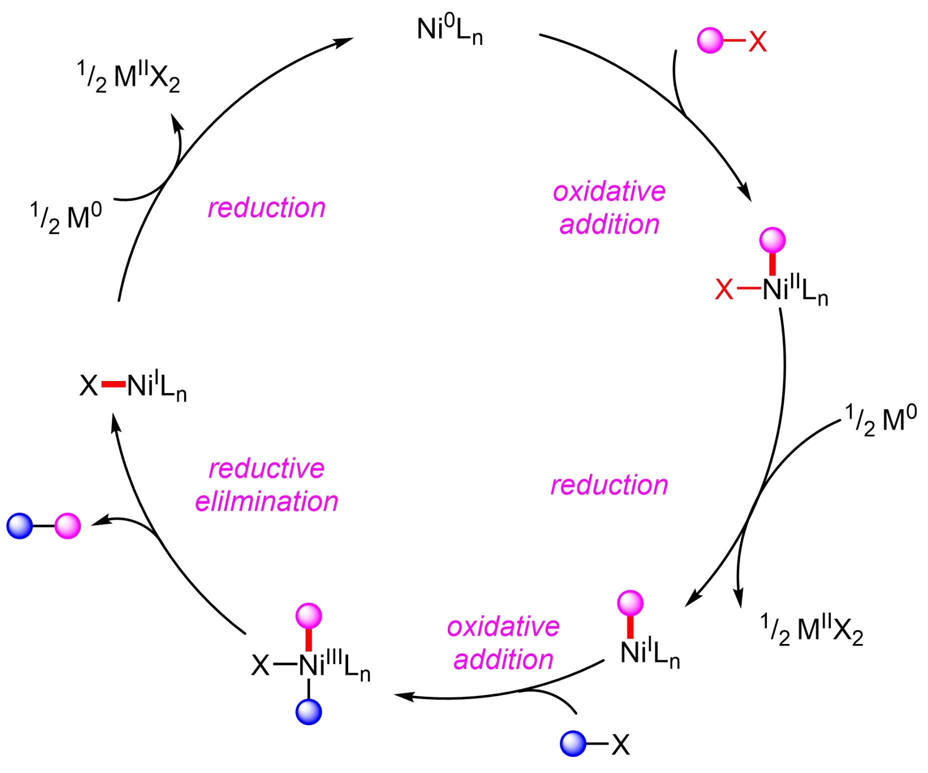




Everson, D. A.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920
Prinsell, M. R.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743

Introduction

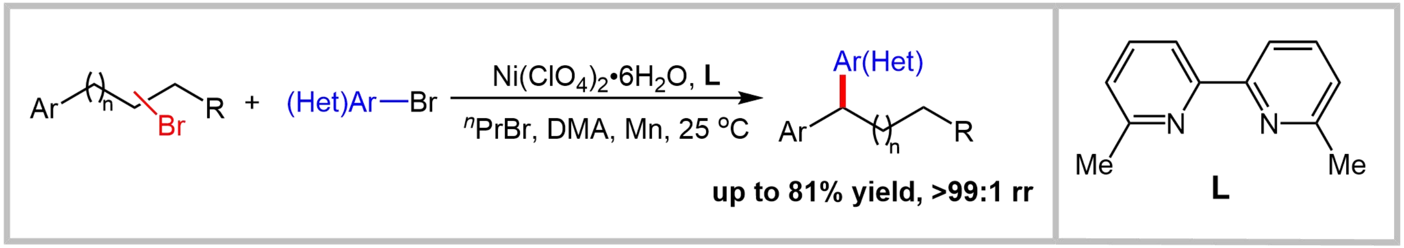
a) Metal-Catalyzed Cross-Electrophile Coupling at *ipso*-Carbon

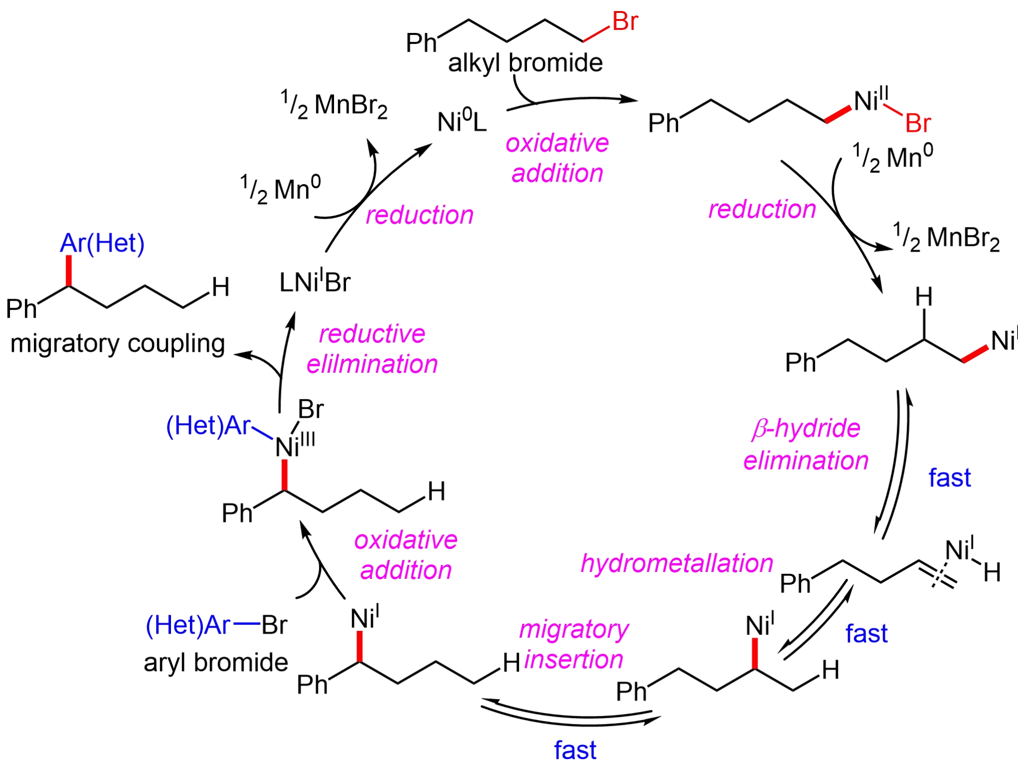


Everson, D. A.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920

Introduction

b) Metal-Catalyzed Migratory Site-Selective Cross-Electrophile Coupling





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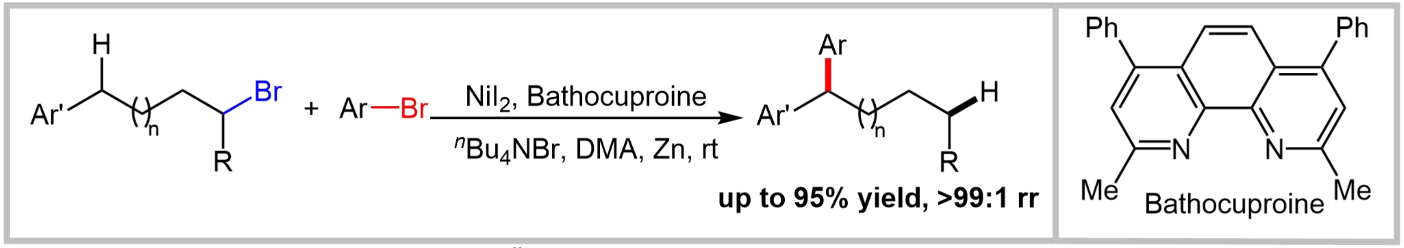
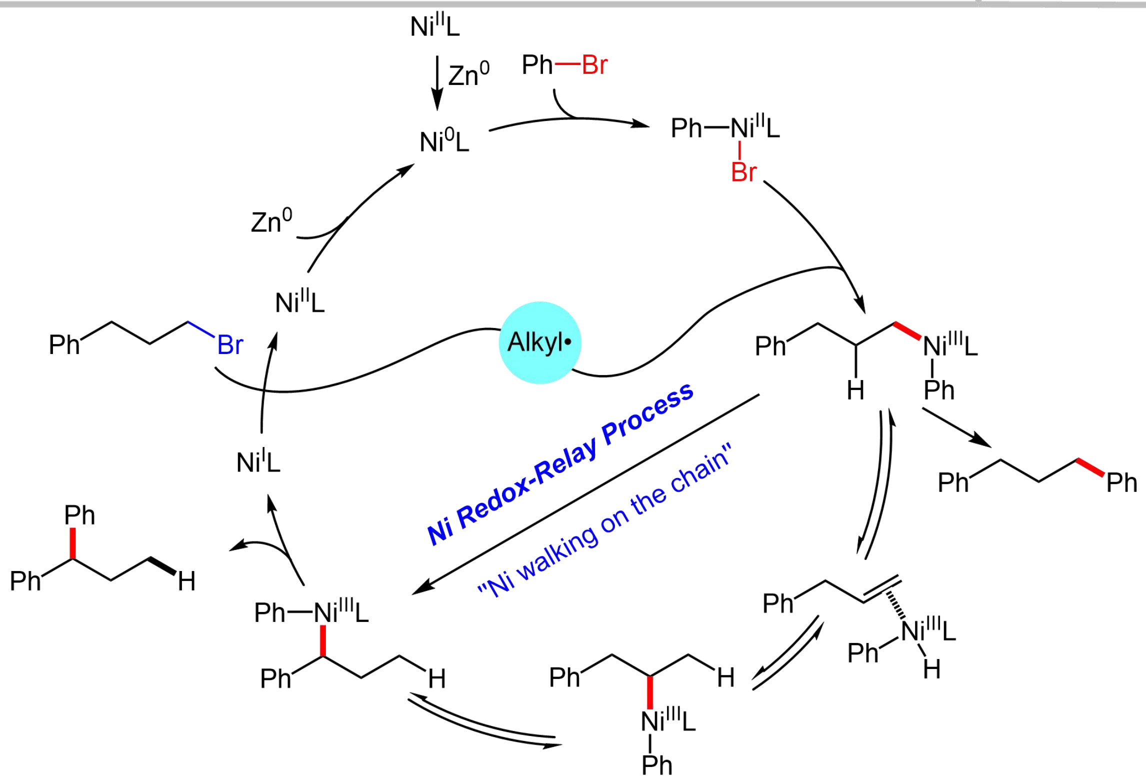
Introduction

b) Metal-Catalyzed Migratory Site-Selective Cross-Electrophile Coupling

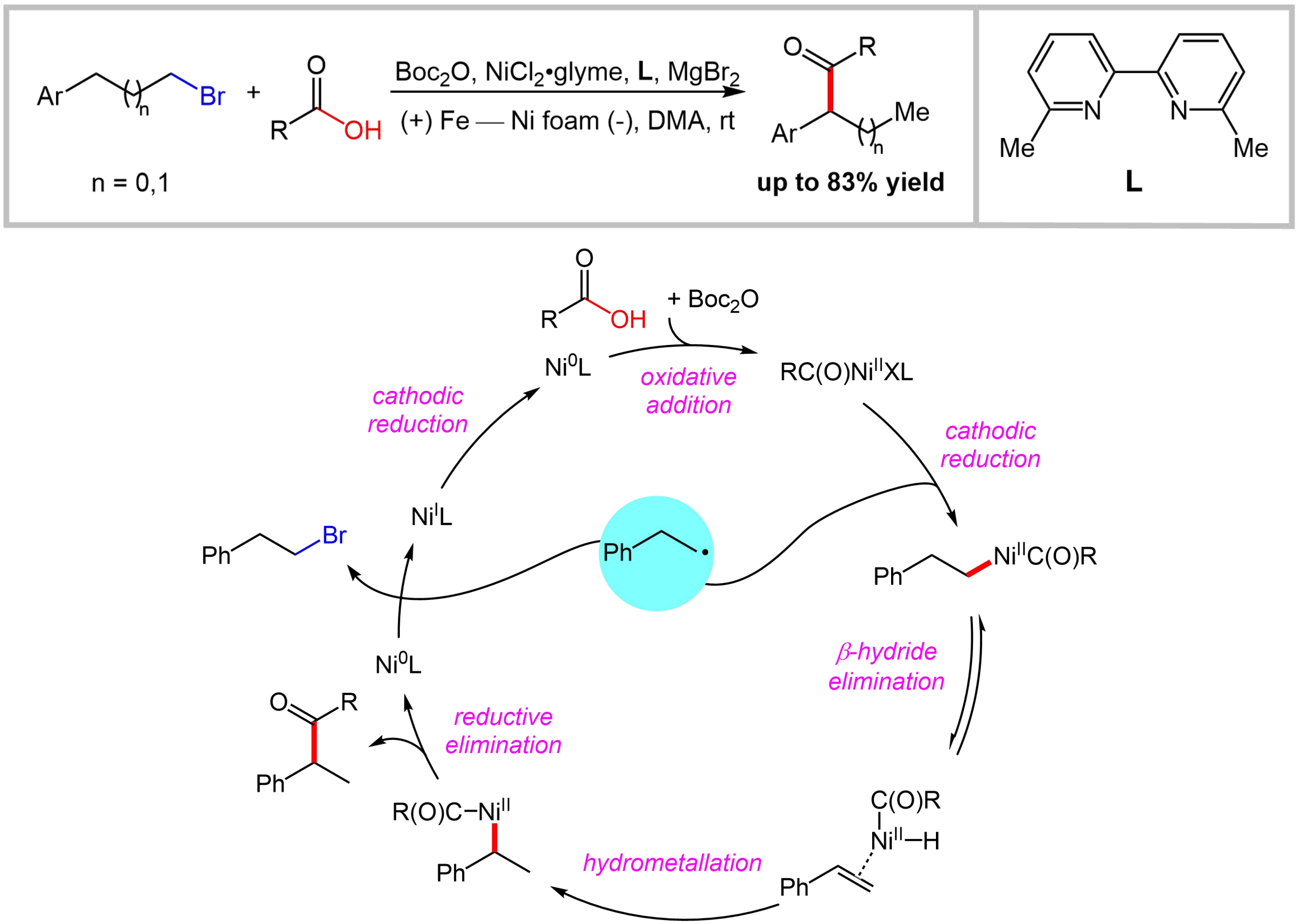




Peng, L.; Yin, G. *ACS Catal.* **2018**, *8*, 310

Introduction

b) Metal-Catalyzed Migratory Site-Selective Cross-Electrophile Coupling



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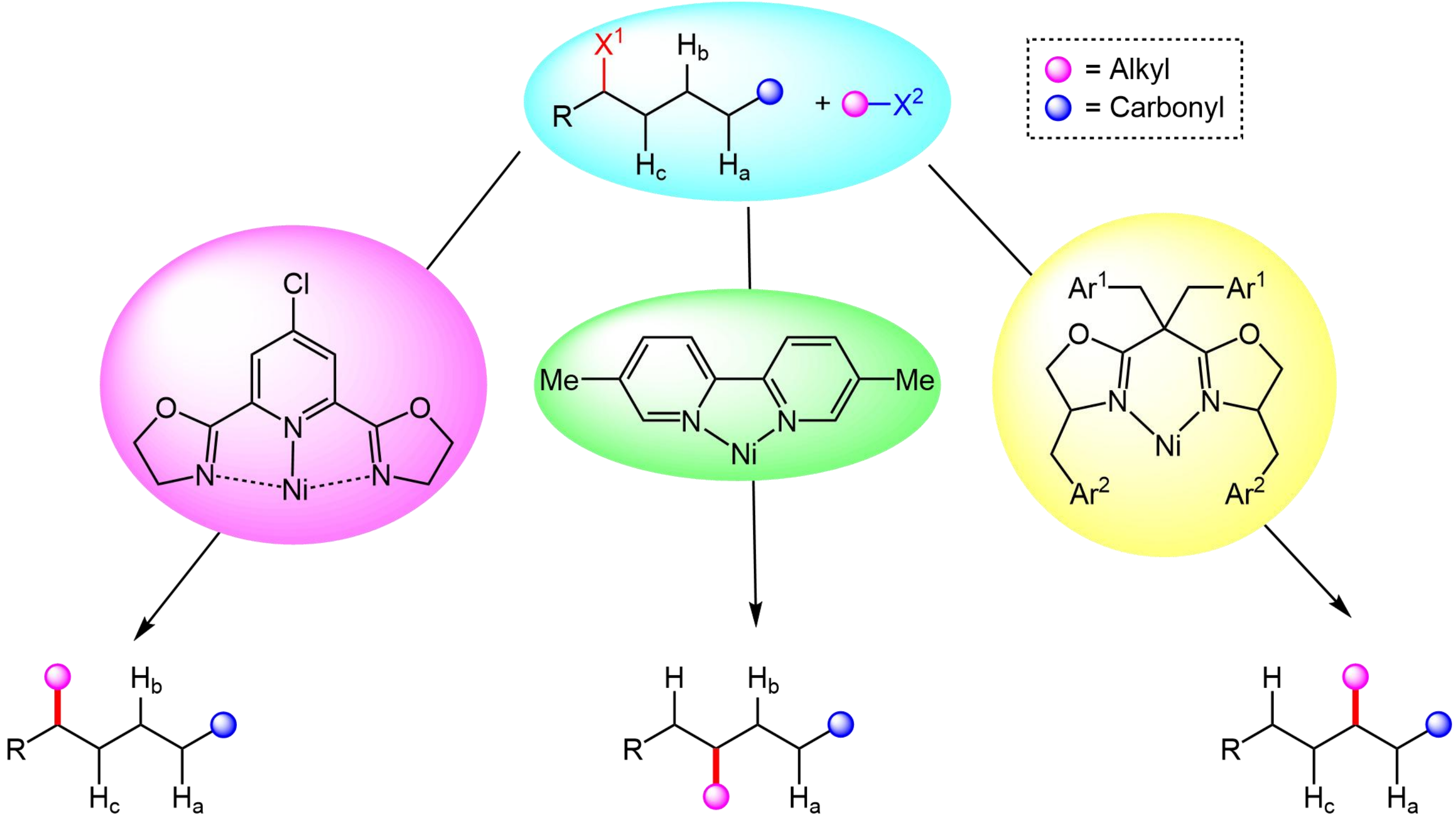
Introduction

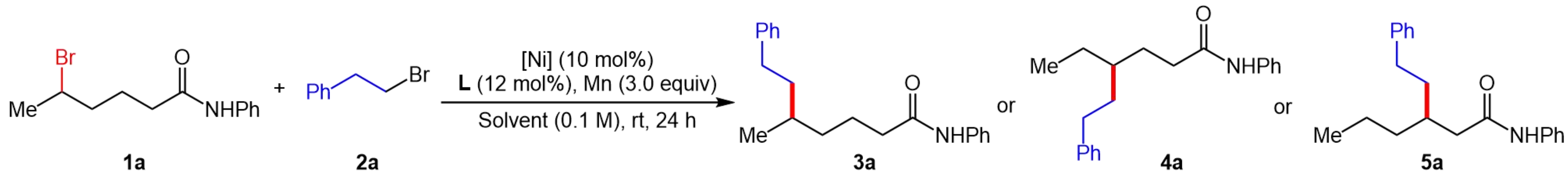
Development of Regiodivergent Cross-Electrophile Couplings

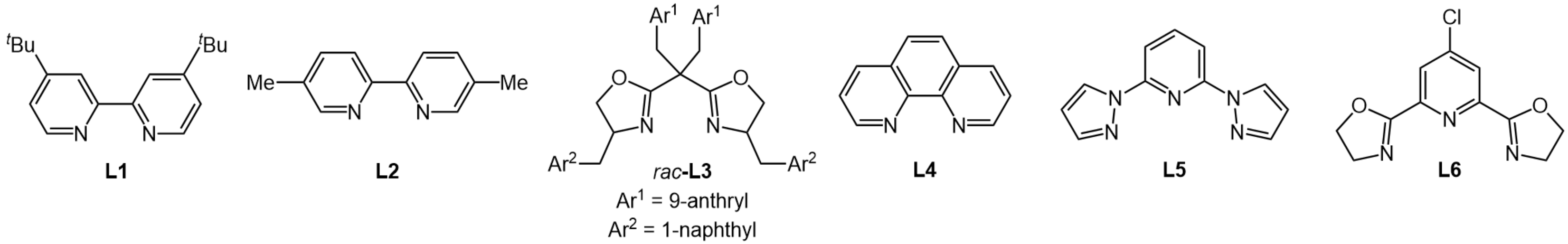
c). Ni-Catalyzed Regiodivergent Cross-Eletrophile Coupling (This work)



♦ Predictable Regioselectivities
♦ Regiodivergent Alkyl-Alkyl Coupling
♦ Access to Diverse Saturated Architectures
♦ Selective Migration on One Alkyl Bromides over Two Migratory Alkyl Bromides

Optimization of the Reaction Conditions

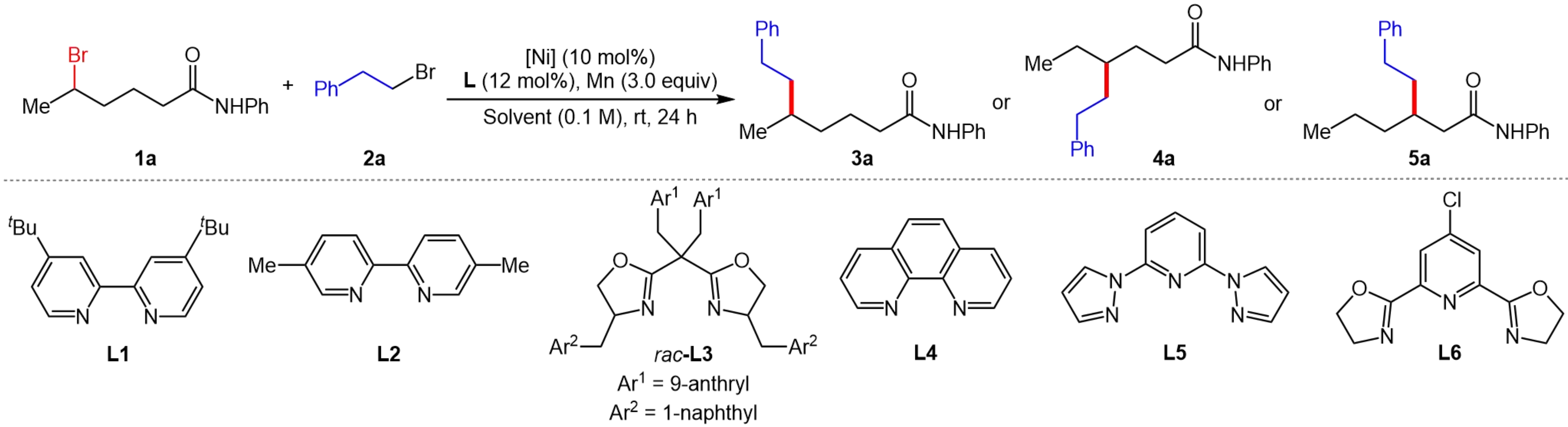




Entry	[Ni]	L	Solvent	Yield (**3a**)/r.r. (**3a**)	Yield (**4a**)/r.r. (**4a**)	Yield (**5a**)/r.r. (**5a**)
1	$NiCl_2·6H_2O$	**L1**	Acetone	11%/1:5	56%/5:1	n.d.
2	$NiCl_2·6H_2O$	**L1**	THF	9%/1:3	26%/3:1	n.d.
3	$NiCl_2·6H_2O$	**L1**	DMA	35%/3:1	11%/1:3	n.d.
4	$NiCl_2·6H_2O$	**L1**	MeOH	14%/1:5	63%/5:1	n.d.
5	$NiCl_2·6H_2O$	**L1**	MeOH/TFE (2/1)	5%/1:17	82%/10:1	3%/<1:20
6	$NiCl_2·6H_2O$	**L2**	MeOH/TFE (2/1)	n.d.	71%/>20:1	n.d.
7	$NiCl_2·6H_2O$	**L2**	MeOH/TFE (1/1)	n.d.	83%/>20:1	n.d.

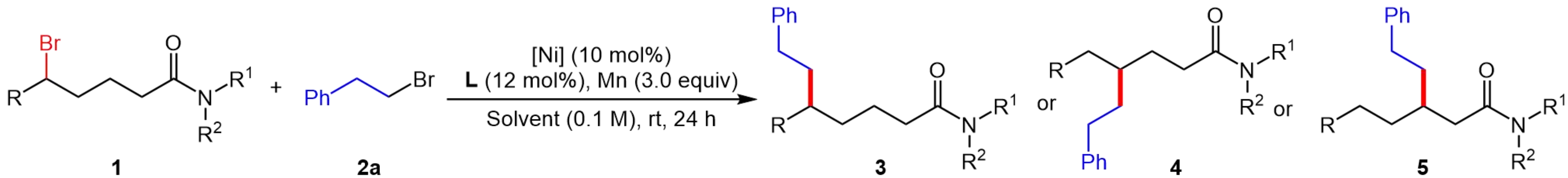
r.r. = Ratio of Regioisomers. r.r. refers to the ratio of the major regioisomer to all other regioisomers. Yield and r.r. were determined by GC analysis based on crude mixture of the reaction using *n*-dodecane as internal standard.

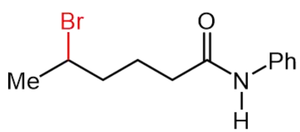
Optimization of the Reaction Conditions



Entry	[Ni]	L	Solvent	Yield (**3a**)/r.r. (**3a**)	Yield (**4a**)/r.r. (**4a**)	Yield (**5a**)/r.r. (**5a**)
8	$NiBr_2$·dme	**L3**	Acetone	n.d.	n.d.	93%/>20:1
9	$NiBr_2$·dme	**L3**	DMA	n.d.	n.d.	71%/>20:1
10	$NiBr_2$·dme	**L3**	THF	n.d.	n.d.	77%/>20:1
11	$NiBr_2$·dme	**L3**	MeOH	n.d.	n.d.	94%/>20:1
12	$NiBr_2$·dme	**L1**	NMP	38%/5:1	n.d.	7%/1:5
13	$NiBr_2$·dme	**L4**	NMP	28%/3:1	11%/1:3	n.d.
14	$NiBr_2$·dme	**L5**	NMP	66%/>20:1	n.d.	n.d.
15	$NiBr_2$·dme	**L5**	DMA	77%>20:1	n.d.	n.d.
16	$NiBr_2$·dme	**L6**	DMA	83%/>20:1	n.d.	n.d.

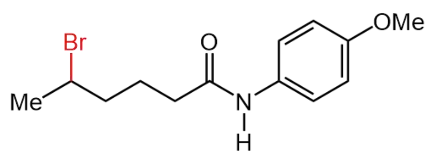
Scope For Migratory Alkyl Halides





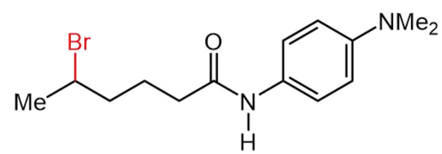
1a

3a[b]: 72% yield; >20:1 r.r.
4a[c]: 71% yield; 20:1 r.r.
5a[d]: 70% yield; >20:1 r.r.



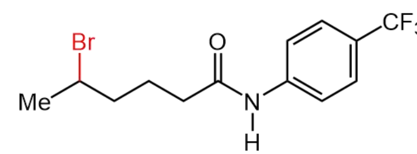
1b

3b[b]: 71% yield; >20:1 r.r.
4b[c]: 70% yield; >20:1 r.r.
5b[d]: 71% yield; >20:1 r.r.



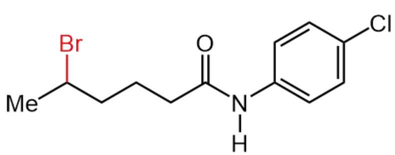
1c

3c[b]: 62% yield; >20:1 r.r.
4c[c]: 55% yield; >20:1 r.r.
5c[d]: 56% yield; >20:1 r.r.



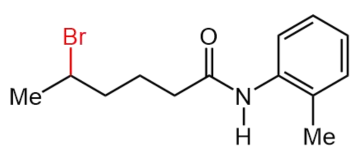
1d

3d[b]: 66% yield; >20:1 r.r.
4d[c]: 57% yield; 8:1 r.r.
5d[d]: 78% yield; >20:1 r.r.



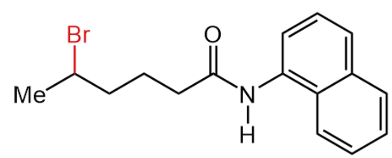
1e

3e[b]: 57% yield; >20:1 r.r.
4e[c]: 51% yield; 14:1 r.r.
5e[d]: 45% yield; >20:1 r.r.



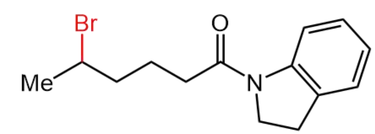
1f

3f[b]: 83% yield; >20:1 r.r.
4f[c]: 51% yield; >20:1 r.r.
5f[d]: 50% yield; >20:1 r.r.



1g

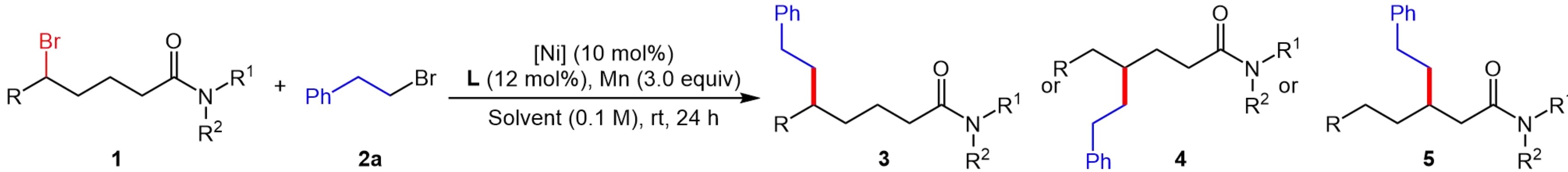
3g[b]: 66% yield; >20:1 r.r.
4g[c]: 50% yield; >20:1 r.r.
5g[d]: 52% yield; >20:1 r.r.

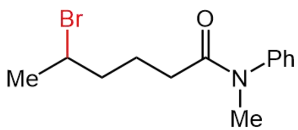


1h

3h[b]: 74% yield; >20:1 r.r.
4h[c,e]: 68% yield; 8:1 r.r.
5h[d]: 64% yield; >20:1 r.r.

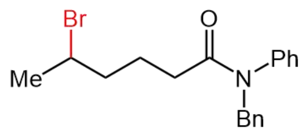
Scope For Migratory Alkyl Halides





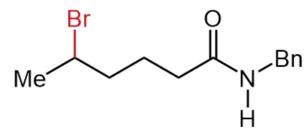
1i

3i[b]: 71% yield; >20:1 r.r.
4i[c]: 56% yield; 18:1 r.r.
5i[d]: 70% yield; 14:1 r.r.



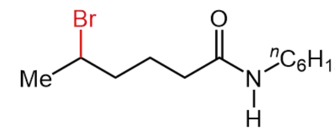
1j

3j[b]: 65% yield; >20:1 r.r.
4j[c]: 65% yield; 8:1 r.r.
5j[d]: 74% yield; >20:1 r.r.



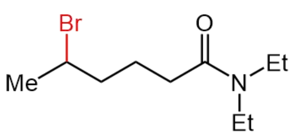
1k

3k[b]: 67% yield; >20:1 r.r.
4k[c]: 50% yield; 17:1 r.r.
5k[d]: 52% yield; >20:1 r.r.



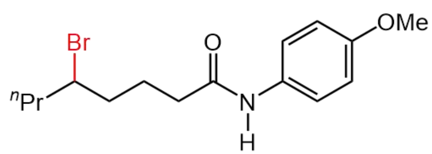
1l

3l[b]: 67% yield; >20:1 r.r.
4l[c]: 54% yield; 18:1 r.r.
5l[d]: 58% yield; >20:1 r.r.



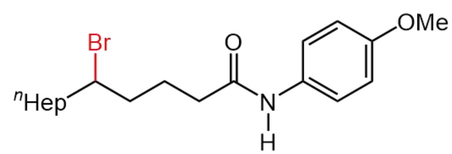
1m

3m[b]: 69% yield; >20:1 r.r.
4m[c]: 57% yield; 15:1 r.r.
5m[d]: 65% yield; >20:1 r.r.



1n

3n[b]: 69% yield; >20:1 r.r.
4n[c,f]: 66% yield; >20:1 r.r.
5n[d]: 61% yield; >20:1 r.r.

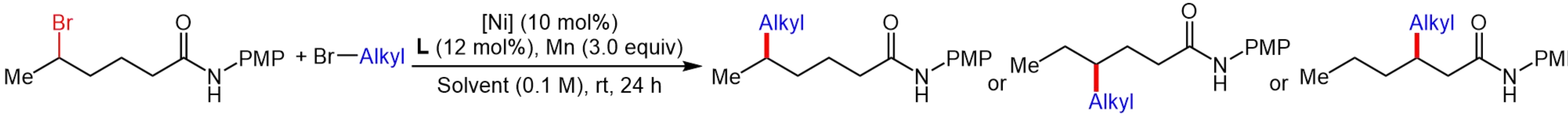


1o

3o[b]: 62% yield; >20:1 r.r.
4o[c,f]: 44% yield; >20:1 r.r.
5o[d]: 65% yield; >20:1 r.r.

Conditions A for 3[b]:
$NiBr_2$•dme/**L6** in DMA
Conditions B for 4[c]:
$NiCl_2$•$6H_2O$/**L2** in MeOH/TFE = 1/1
Conditions C for 5[d]:
$NiBr_2$•dme/**L3** in MeOH

Scope For Non-Migrated Alkyl Halides



1b **2** **3** **4** **5**

Br—Et

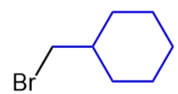
2b

3p[b]: 69% yield; >20:1 r.r.
4p[c]: 78% yield; 13:1 r.r. (X-ray)
5p[d,e]: 82% yield; >20:1 r.r. (X-ray)

Br—C_6H_{13}

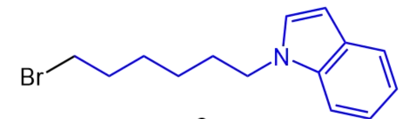
2c

3q[b]: 64% yield; >20:1 r.r.
4q[c,e]: 67% yield; >20:1 r.r.
5q[d,e]: 68% yield; 20:1 r.r.



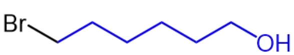
2d

3r[b]: 58% yield; >20:1 r.r.
4r[c]: 62% yield; 16:1 r.r.
5r[d]: 54% yield; >20:1 r.r.



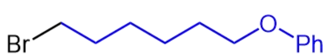
2e

3s[b]: 63% yield; >20:1 r.r.[g]
4s[c]: 60% yield; >20:1 r.r.[g]
5s[d,f]: 62% yield; >20:1 r.r.[g]



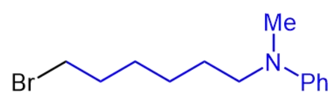
2f

3t[b]: 70% yield; >20:1 r.r.[g]
4t[c]: 56% yield; >20:1 r.r.[g]
5t[d,e]: 74% yield; >20:1 r.r.[g]



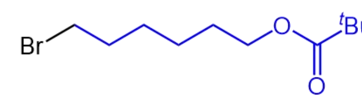
2g

3u[b]: 61% yield; >20:1 r.r.[g]
4u[c]: 65% yield; >20:1 r.r.[g]
5u[d,f]: 68% yield; >20:1 r.r.[g]



2h

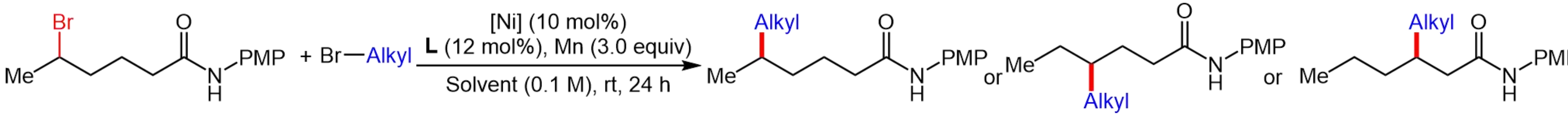
3v[b]: 66% yield; >20:1 r.r.[g]
4v[c]: 60% yield; >20:1 r.r.[g]
5v[d,f]: 56% yield; >20:1 r.r.[g]



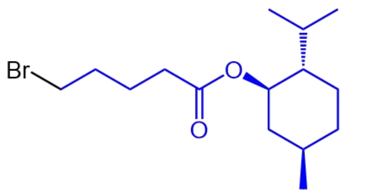
2i

3w[b]: 66% yield; >20:1 r.r.[g]
4w[c]: 69% yield; >20:1 r.r.[g]
5w[d,f]: 68% yield; >20:1 r.r.[g]

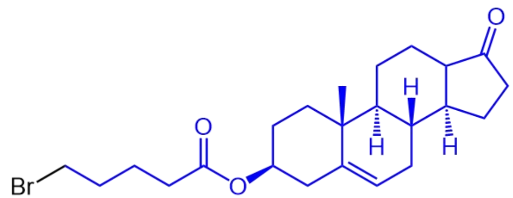
Scope For Non-Migrated Alkyl Halides



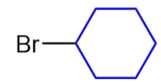
1b **2** **3** **4** **5**



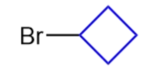
2j



2k



2l



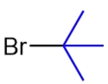
2m

3x[b]: 73% yield; >20:1 r.r.[g]; 1:1 d.r.[g]
4x[c]: 66% yield; >20:1 r.r.[g]; 1:1 d.r.[g]
5x[d,f]: 70% yield; >20:1 r.r.[g]; 5:1 d.r.[g]

3y[b]: 44% yield; >20:1 r.r.[g]
4y[c]: 54% yield; >20:1 r.r.[g]
5y[d,f]: 58% yield; 20:1 r.r.[g]

3z[b,e]: 54% yield; >20:1 r.r.
4z[c,e,h]: 50% yield; 3:1 r.r.
5z[d,e]: 35% yield; >20:1 r.r.

3aa[b]: 51% yield; >20:1 r.r.
4aa[c,e]: 58% yield; 7:1 r.r.
5aa[d,e,f]: 54% yield; >20:1 r.r.

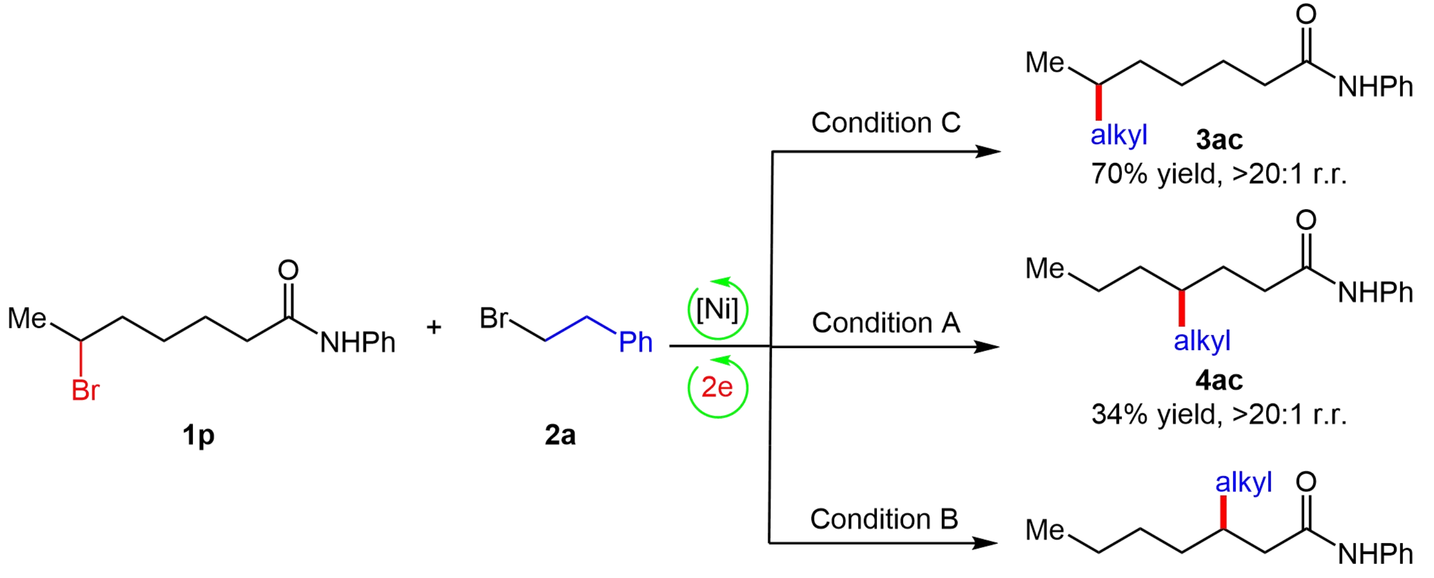


2n

3ab[b]: n.d.
4ab[c]: n.d.
5ab[d,e]: n.d.

Conditions C for 3[b]:
$NiBr_2$•dme/**L6** in DMA
Conditions A for 4[c]:
$NiCl_2$•$6H_2O$/**L2** in MeOH/TFE = 1/1
Conditions B for 5[d]:
$NiBr_2$•dme/**L3** in MeOH

Regiodivergent Alkyl-Alkyl Coupling



1p

2a

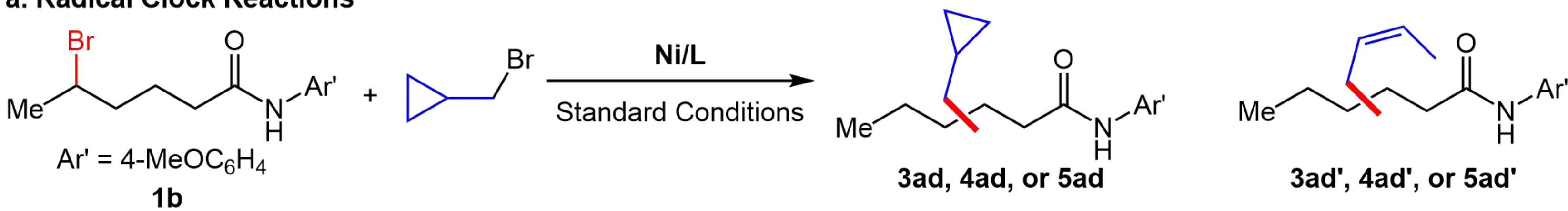
3ac
70% yield, >20:1 r.r.

4ac
34% yield, >20:1 r.r.

5ac
60% yield, >20:1 r.r.

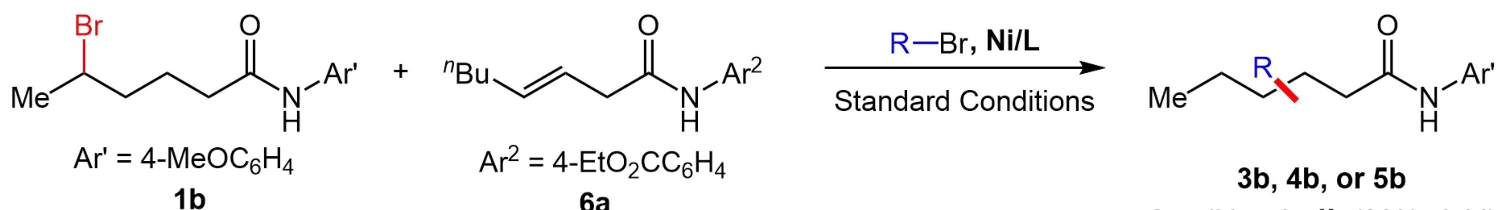
Mechanistic Investigation

a. Radical Clock Reactions



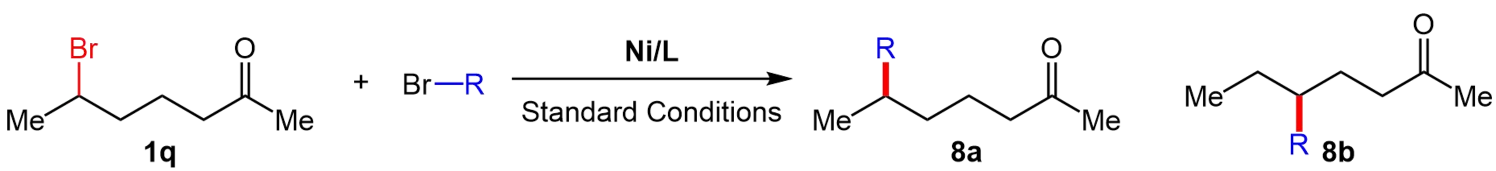
Condition A: γ-alkylation (**4ad'**), 43% conversion, <5% yield
Condition B: β-alkylation (**5ad'**), 55% conversion, 24% yield
Condition C: δ-alkylation (**3ad'**), 63% conversion, 33% yield

b. Intermolecular Cross-Over Reactions

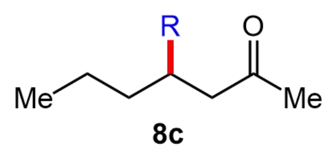


Condition A: **4b** (28% yield)
Condition B: **5b** (45% yield)
Condition C: **3b** (9% yield)

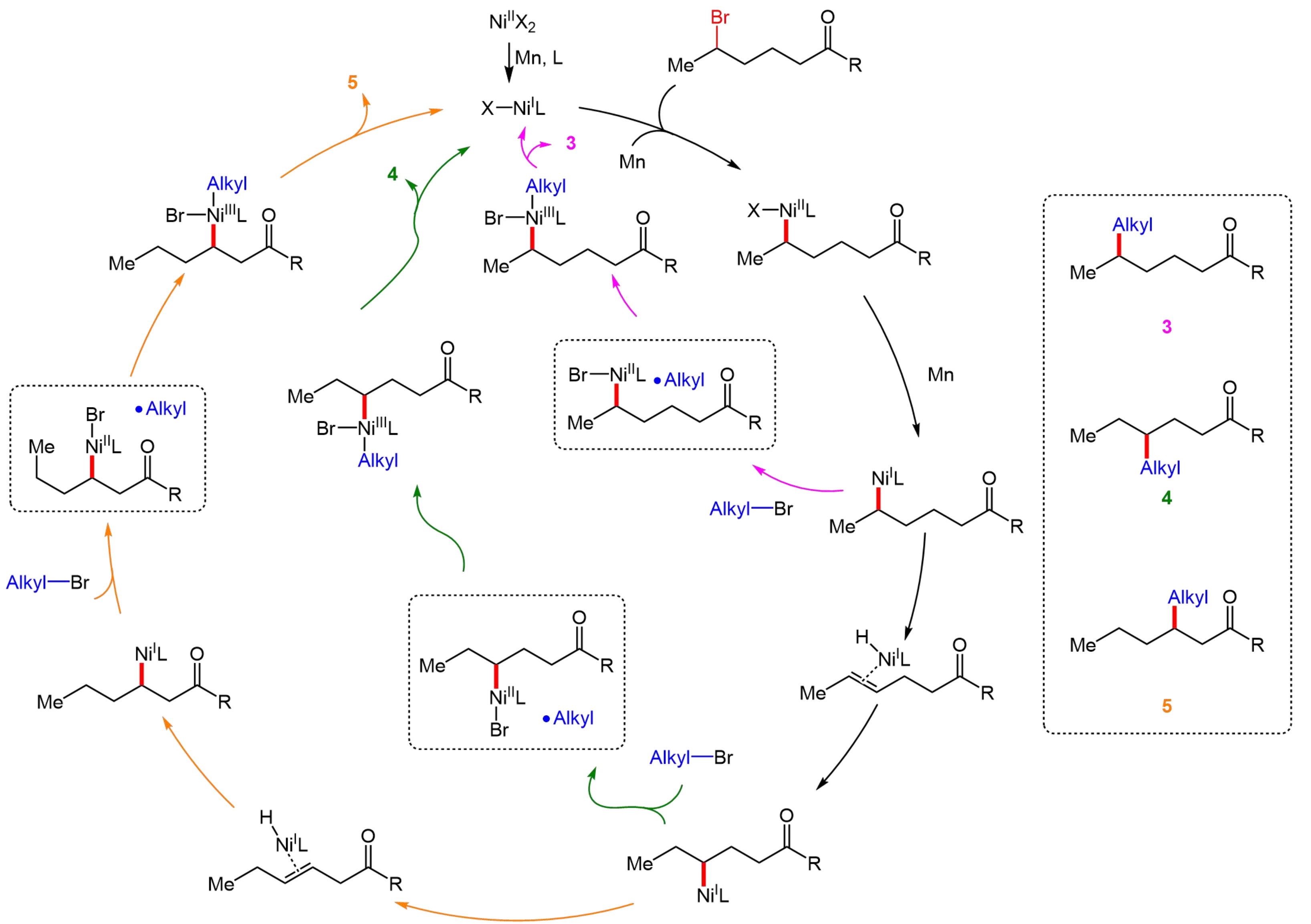
c. Ni-Catalyzed Regiodivergent Reductive Alkyl-Alkyl Couplings with δ-Bromoketone



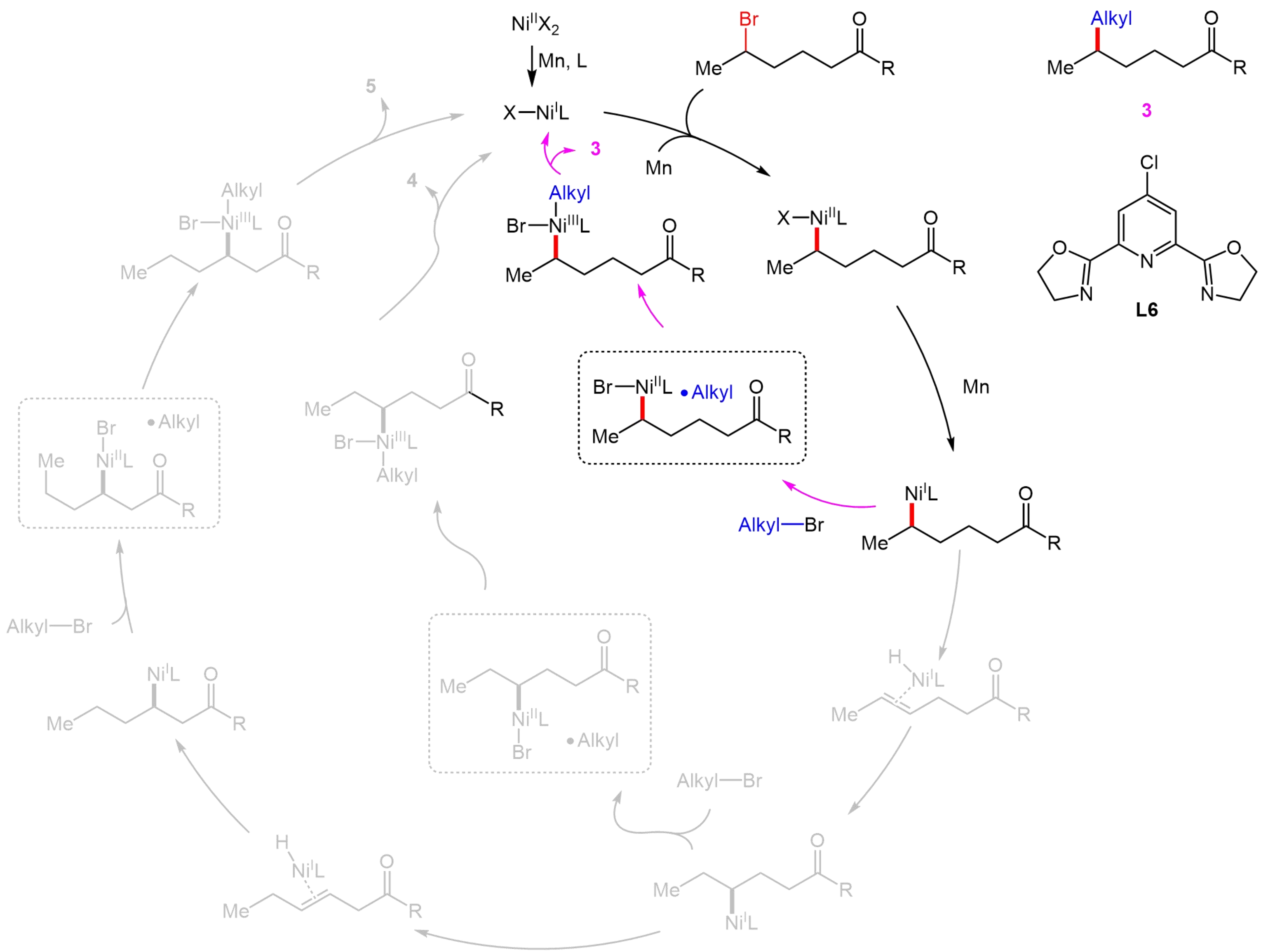
Condition A (R = $PhO(CH_2)_6$): **8b** (55% yield, 4:1 r.r.)
Condition B (R = PhEt): **8c** (62% yield, >20:1 r.r.)
Condition C (R = PhEt): **8a** (56% yield, >20:1 r.r.)



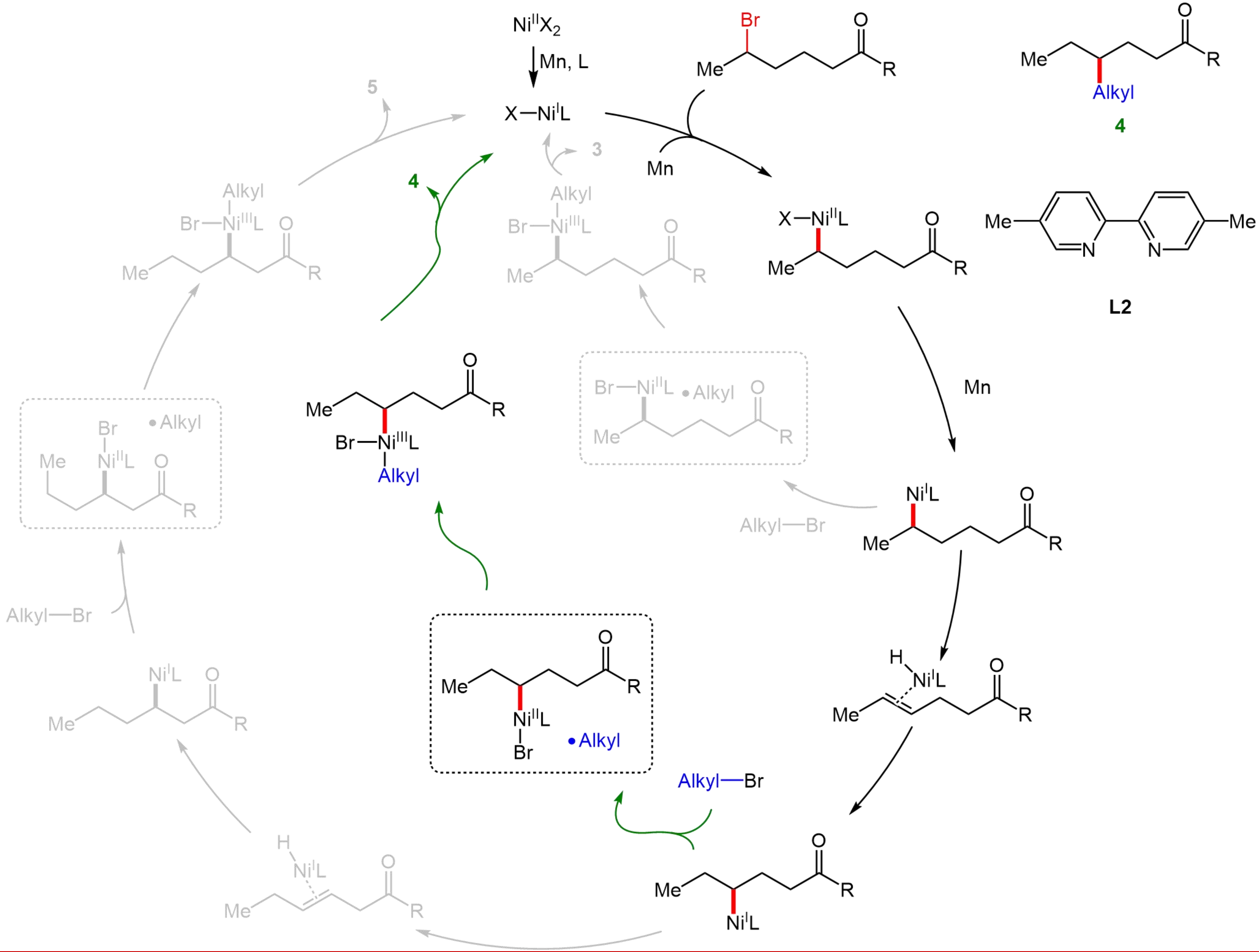
Proposed Mechanism



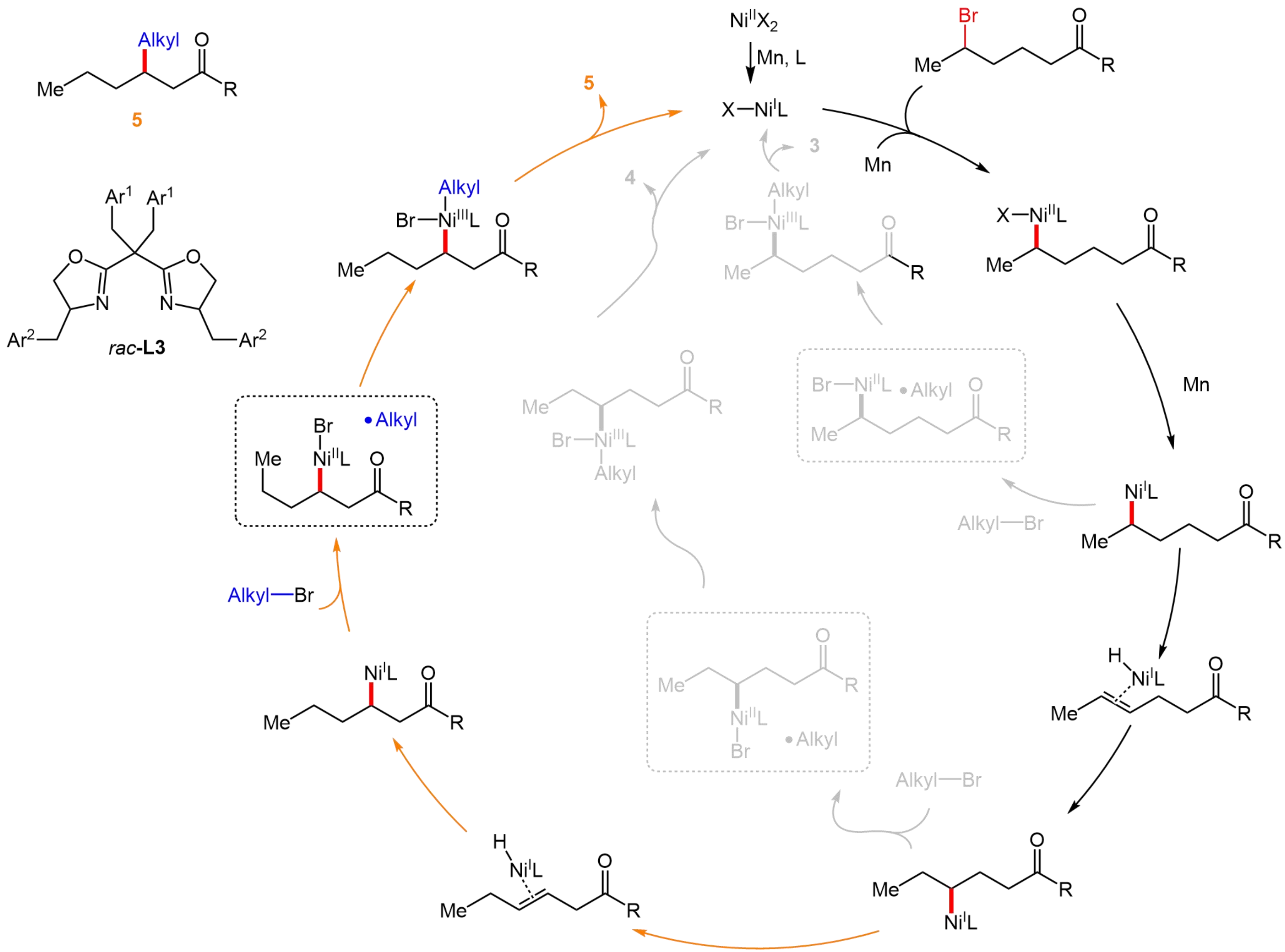
Proposed Mechanism



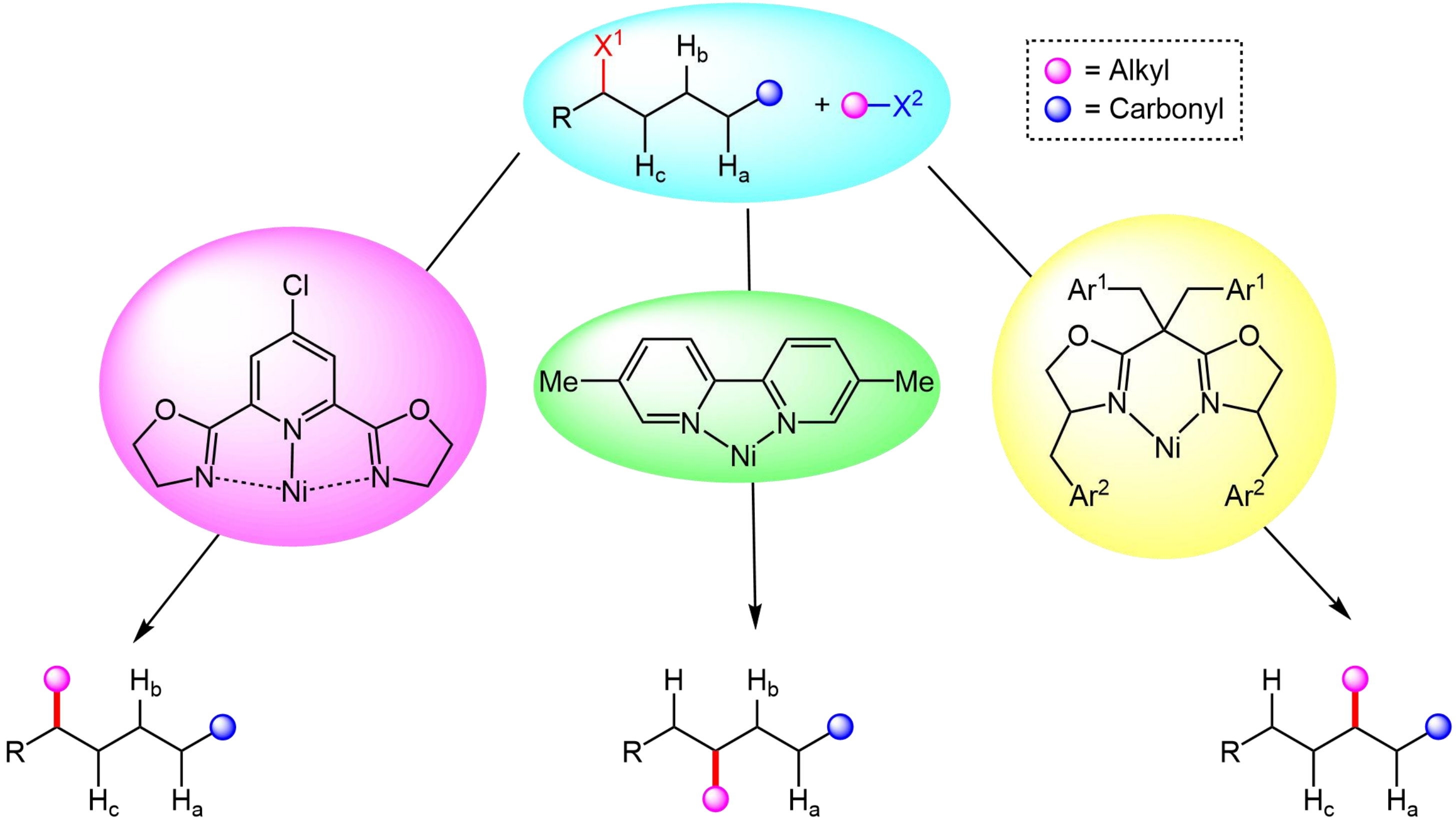
Proposed Mechanism



Proposed Mechanism



Summary



- Predictable Regioselectivities
- Regiodivergent Alkyl-Alkyl Coupling
- Access to Diverse Saturated Architectures
- Selective Migration on One Alkyl Bromides over Two Migratory Alkyl Bromides

The First Paragraph

Writing Strategies

The Importance of Metal-Catalyzed C-C Cross-Coupling

↓

The Progress and Challenge of Metal-Catalyzed C-C Cross-Coupling

↓

The Introduction of This Work

1. Metal-catalyzed carbon-carbon cross-coupling reactions have evolved into one of the major technologies for C-C bond-forming event. (重要性)

2. Over the past decades, reductive cross-coupling between two carbon electrophiles has become an attractive alternative for C-C bond-forming… However, control site-selectivity over similar secondary alkyl-Ni intermediates along the alkyl chain to realize divergent regioselectivity remains a formidable challenge. (进展及挑战)

3. Herein, we reported a ligand-controlled regiodivergent cross-electrophile coupling at specific sites… (介绍本文工作)

The Last Paragraph

Writing Strategies

The Summary of This Work

↓

The Features of This Work

1. In summary, a ligand-controlled Ni-catalyzed regiodivergent cross-electrophile couplings with two distinct alkyl bromides in a predictable manner have been developed. Diverse site-selectivities have been realized using alkyl bromides by judicious choice of ligand and conditions to tune the migration of alkyl nickel species and alkyl-alkyl coupling. (**总结**)

2. The reaction features exclusive control the migration over non-migration between two migratory alkyl bormides as well as reativity differentiation between several similar alkyl-Ni species to afford *β*-, *γ*-, *δ*-alkylated amides from identical starting materials, offering a straightforward and unified means to building diverse saturated architectures from easily available and cost-effective alkyl halides. (**介绍亮点**)

Representative Examples

1. The reaction undergoes site-selective isomerization on one alkyl bromides in a controlled manner, providing switchable access to diverse alkylated structures at different sites of alkyl bromides. T. (用一种可以控制的方式；提供可转化的通向/得到……)

2. This reaction offers a catalytic platform to diverse saturated architectures by alkyl-alkyl bond-formation from identical starting materials. (提供了一个催化方式……)

3. The reaction features exclusive control the migration over non-migration… offering a straightforward and unified means to building diverse saturated architectures from easily available and cost-effective alkyl halides. (提供一个直接和统一的手段……)

Acknowledgement

Thanks for your attention!