

# Literature Report 2

## Iron-Catalyzed C(sp<sup>3</sup>)-C(sp<sup>3</sup>) Coupling to Construct Quaternary Carbon Centers

---

**Reporter: Yan-Xin Sun**

**Checker: Kai Xue**

**Date: 2024-03-25**

Zhang, Q.; Liu, X.-Y.; Zhang, Y.-D.; Huang, M.-Y.; Zhang, X.-Y.; **Zhu, S.-F.** *J. Am. Chem. Soc.* **2024**, *146*, 5051

# CV of Prof. Shou-Fei Zhu

---



## Background:

- **1996-2000** B.S., Nankai University
- **2000-2005** Ph.D., Nankai University
- **2005-2008** Lecturer, Nankai University
- **2008-2013** Associate Professor, Nankai University
- **2013-now** Professor, Nankai University

---

## Research:

- **Asymmetric Synthesis**
- **Homogeneous Catalysis**

# Contents

---

## 1 Introduction

---

## 2 C(sp<sup>3</sup>)-C(sp<sup>3</sup>) Coupling to Construct Quaternary Carbon Centers

---

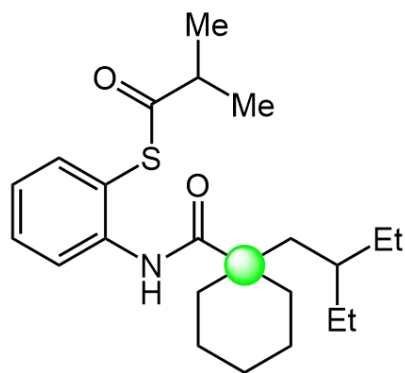
## 3 Summary

---

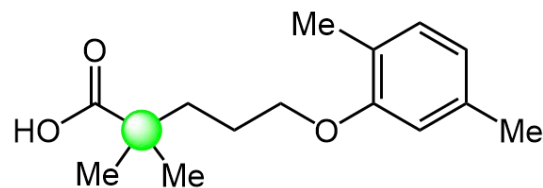
# Introduction

---

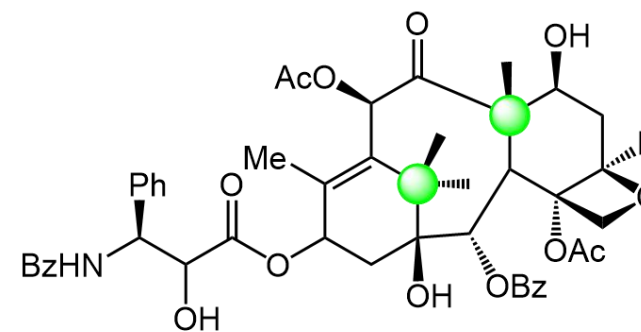
## Examples of the Bioactive Molecules Containing All-Carbon Quaternary Center



*delcetrapiib*



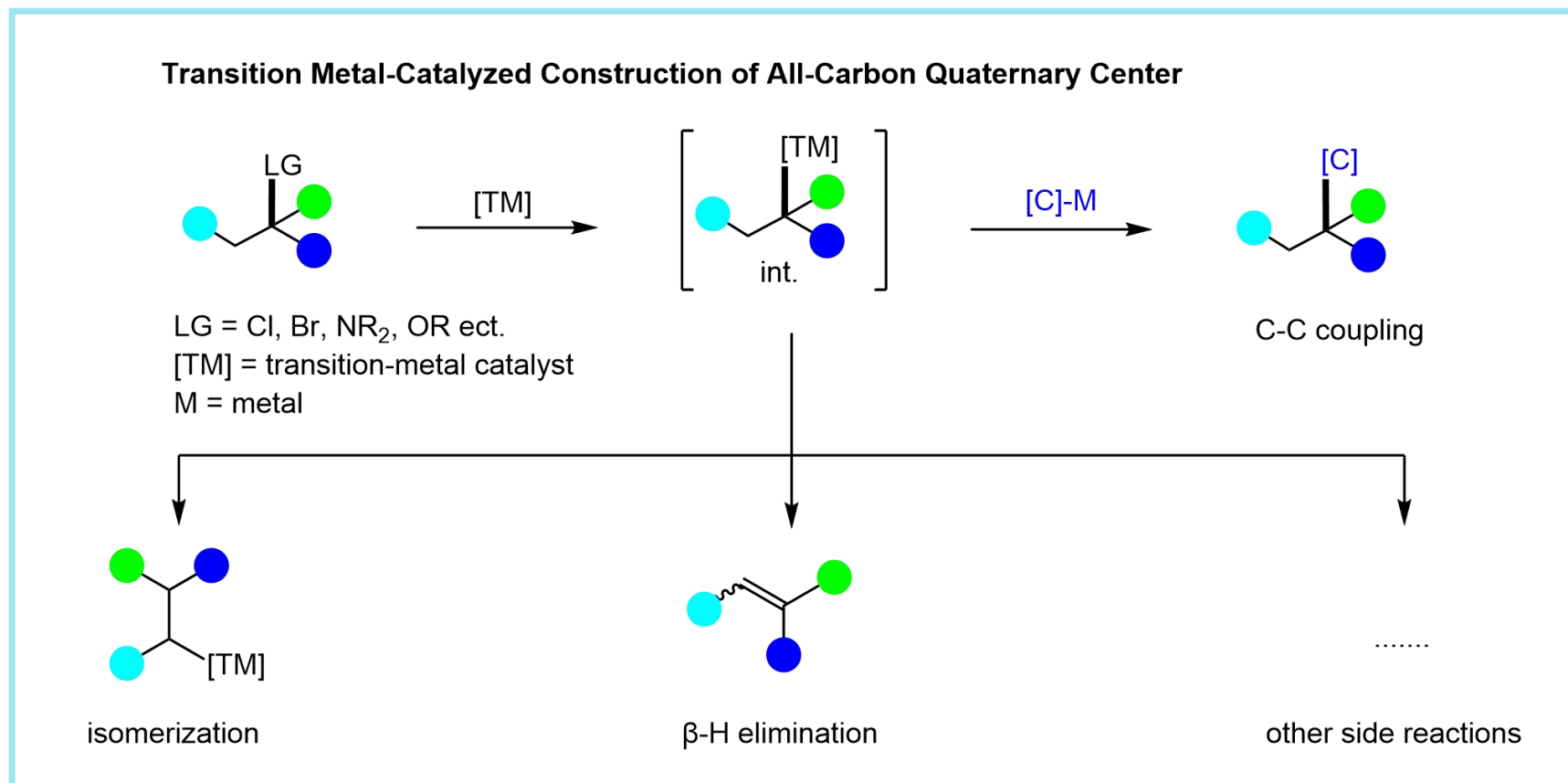
*gemfibrozil*



*paclitaxel*

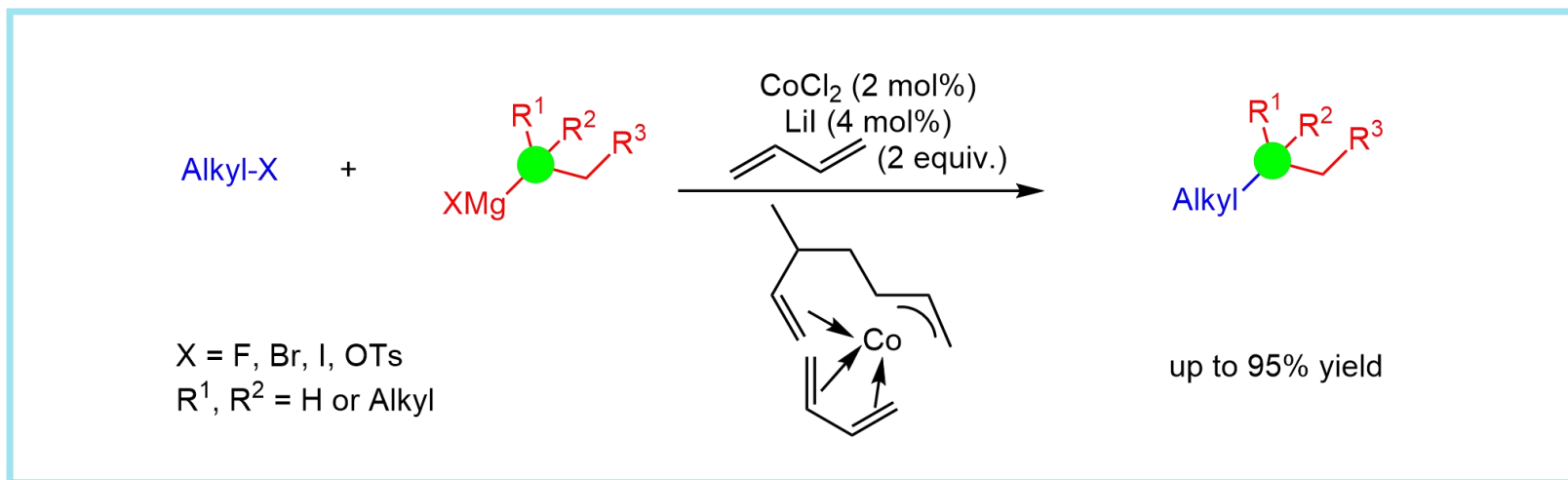
Ling, T.; Rivas, F.\* *Tetrahedron* **2016**, 72, 6729;  
Susse, L.; Stoltz, B. M.\* *Chem. Rev.* **2021**, 121, 4084;  
Xue, W.; Jia, X.; Wang, X.; Tao, X.; Yin, Z.; Gong, H.\* *Chem. Soc. Rev.* **2021**, 50, 4162

# Introduction



# Introduction

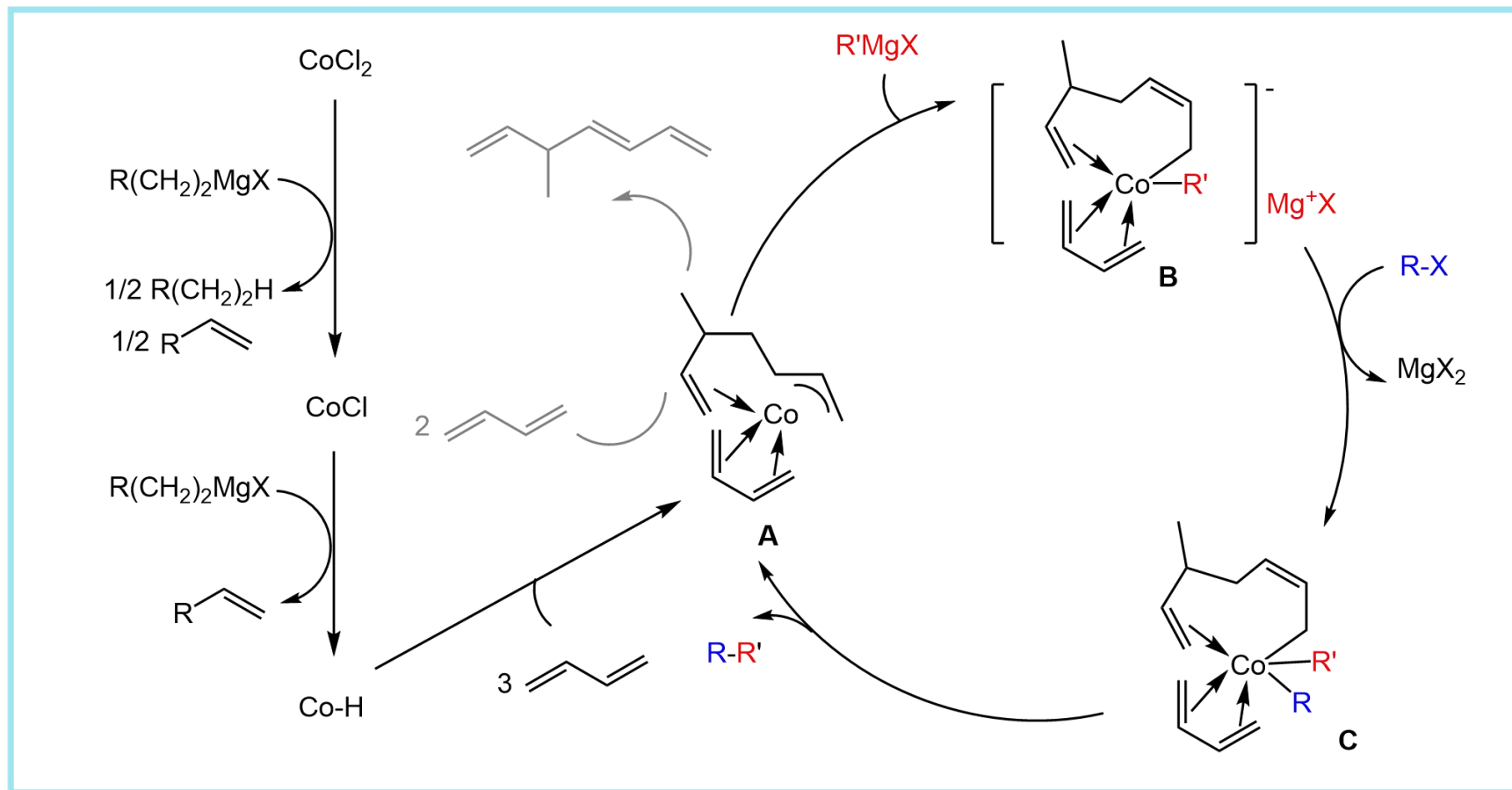
## 3° C(sp<sup>3</sup>)-1° C(sp<sup>3</sup>) Coupling



Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N.\* *J. Am. Chem. Soc.* **2013**, 135, 9604

# Introduction

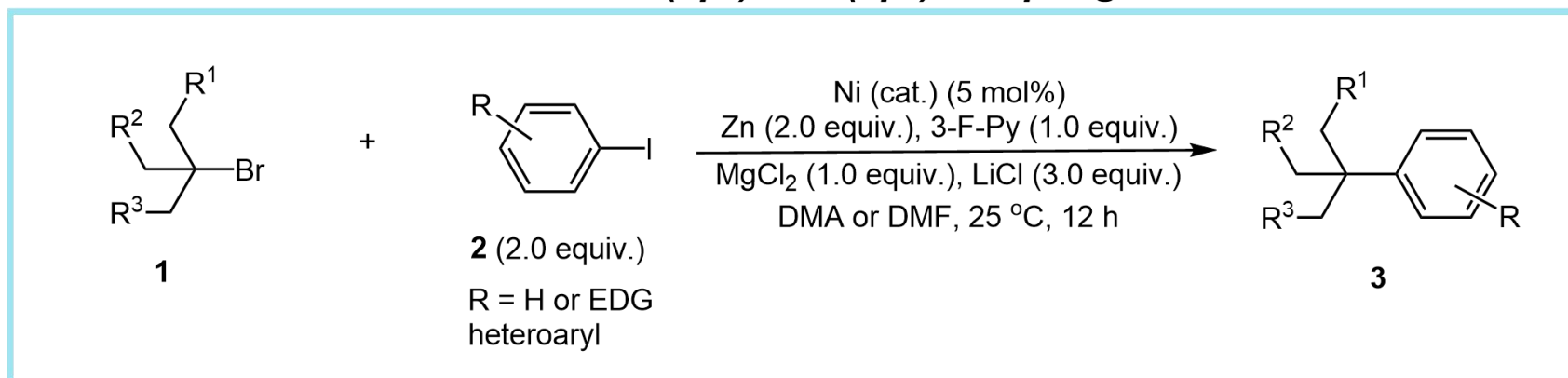
## 3° C(sp<sup>3</sup>)-1° C(sp<sup>3</sup>) Coupling



Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N.\* *J. Am. Chem. Soc.* **2013**, 135, 9604

# Introduction

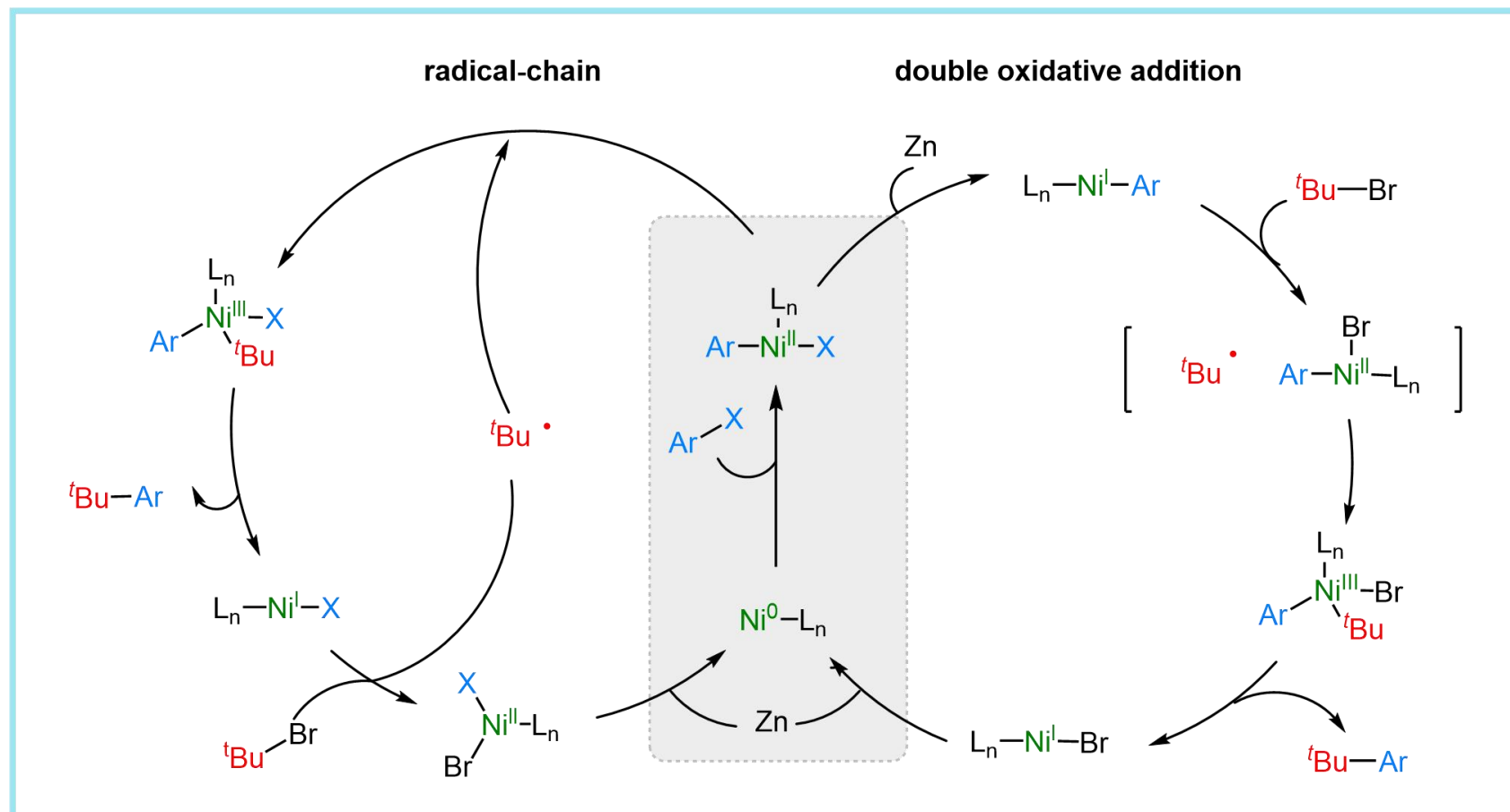
## 3° C(sp<sup>3</sup>)-1° C(sp<sup>2</sup>) Coupling



Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H.\* *J. Am. Chem. Soc.* **2018**, *140*, 14490



# Introduction

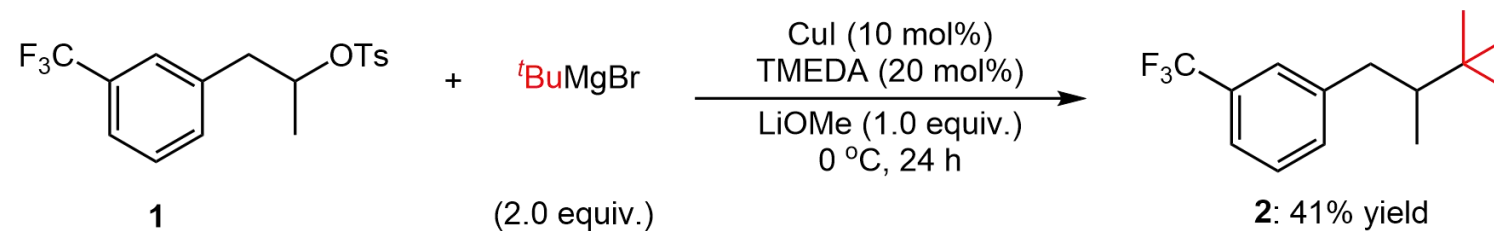


Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H.\* *J. Am. Chem. Soc.* **2018**, *140*, 14490

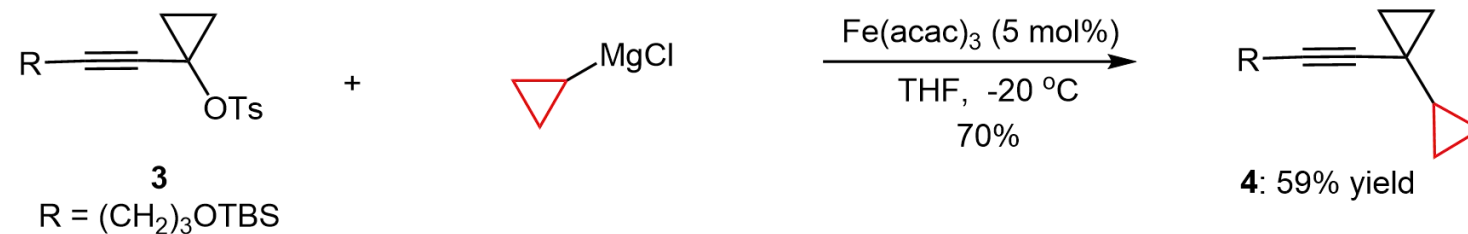
# Introduction

## The Coupling of 3° C(sp<sup>3</sup>) with 2° C(sp<sup>3</sup>)

Liu (2012):



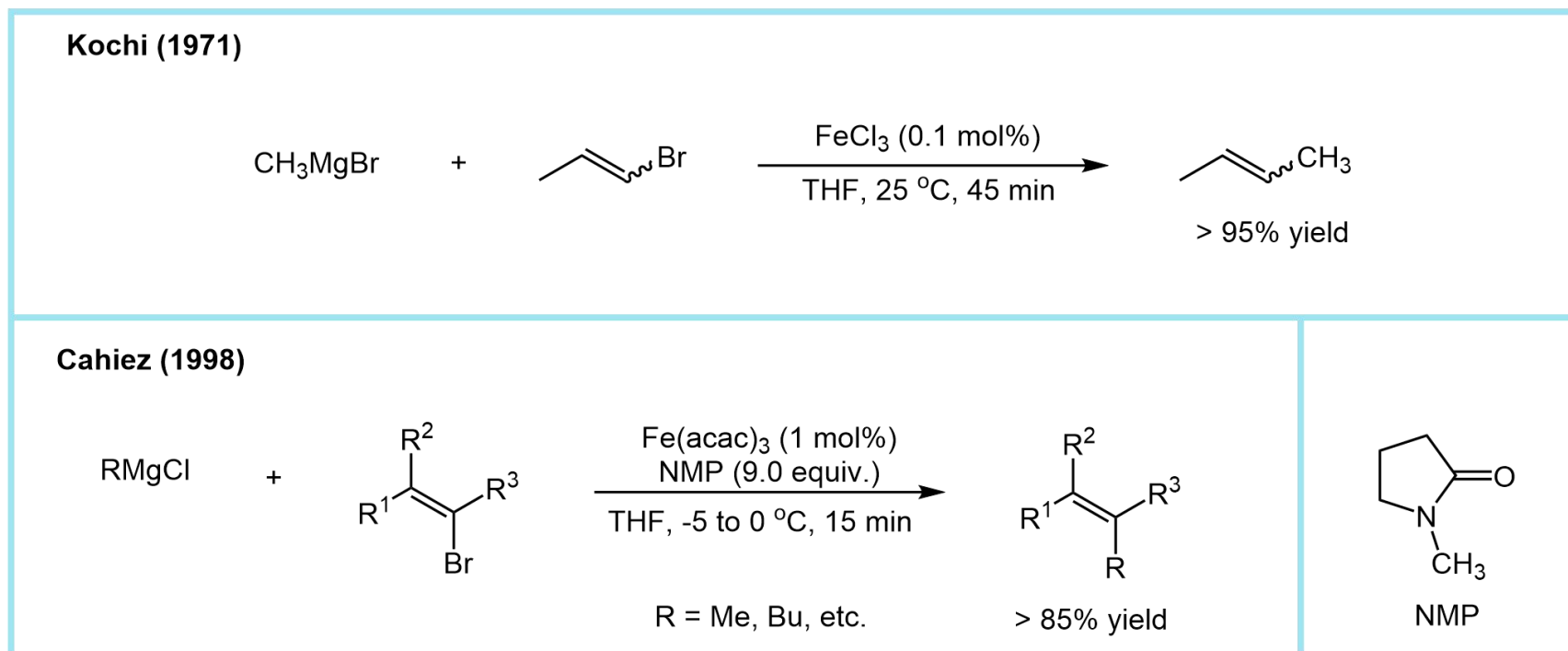
Furstner (2016):



Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L.\* *J. Am. Chem. Soc.* **2012**, *134*, 11124;  
Tindall, D. J.; Krause, H.; Furstner, A.\* *Adv. Synth. Catal.* **2016**, *358*, 2398

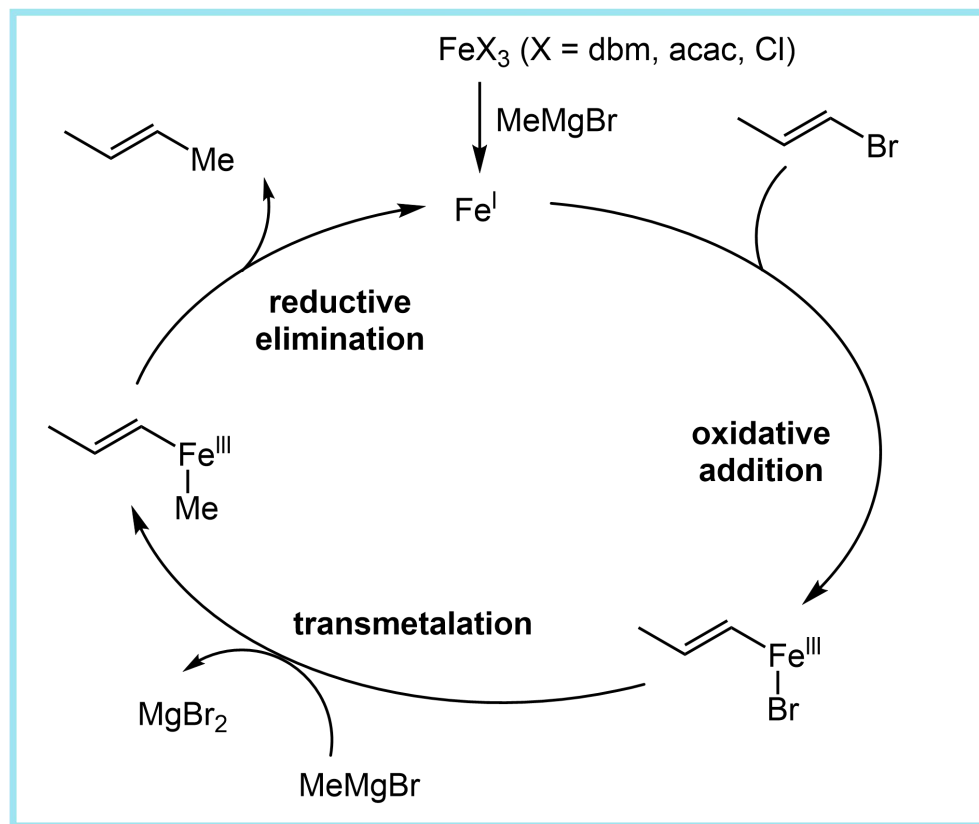
# Introduction

## Vinylation of Grignard Reagents



Tamura, M.; Kochi, J.\* *J. Organomet. Chem.* **1971**, 31, 289;  
Tamura, M.; Kochi, J. K.\* *J. Am. Chem. Soc.* **1971**, 93, 1487;  
Cahiez, G.; Avedissian, H.\* *Synthesis* **1998**, 1998, 1199

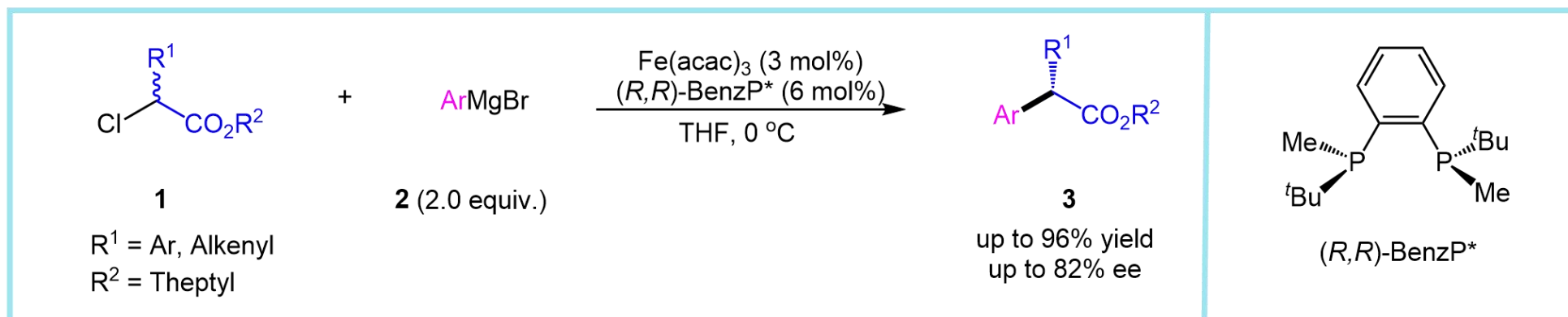
# Introduction



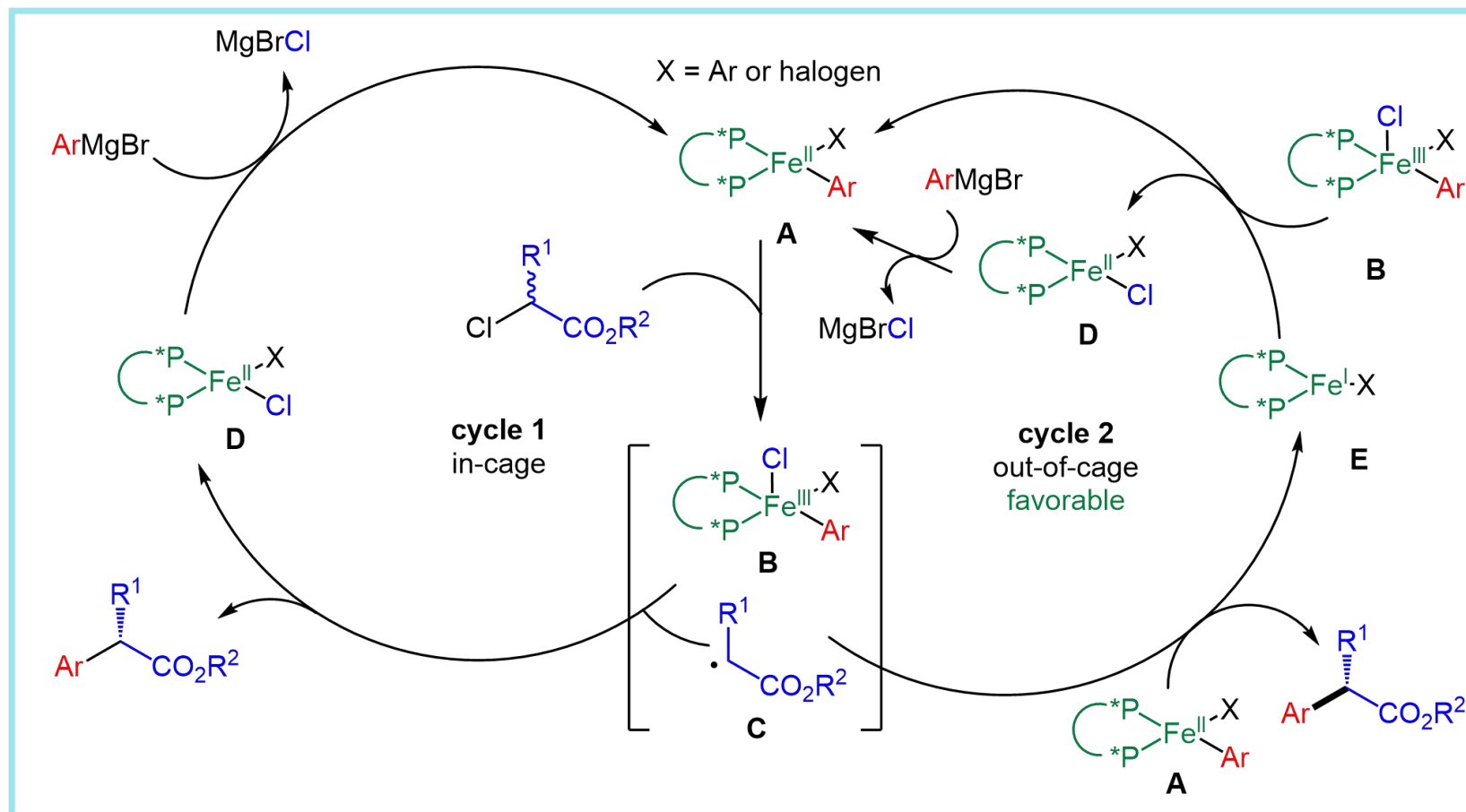
Smith, R. S.; Kochi, J. K.\* *J. Org. Chem.* **1976**, *41*, 502

# Introduction

## Enantioselective Cross-Coupling Reactions of $\alpha$ -Chloroesters



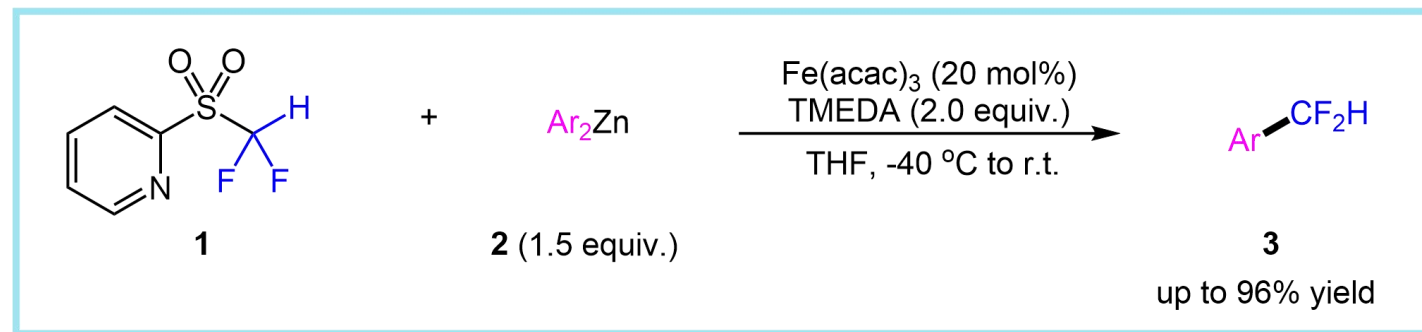
# Introduction



Jin, M.; Adak, L.; Nakamura, M.\* *J. Am. Chem. Soc.* **2015**, *137*, 7128

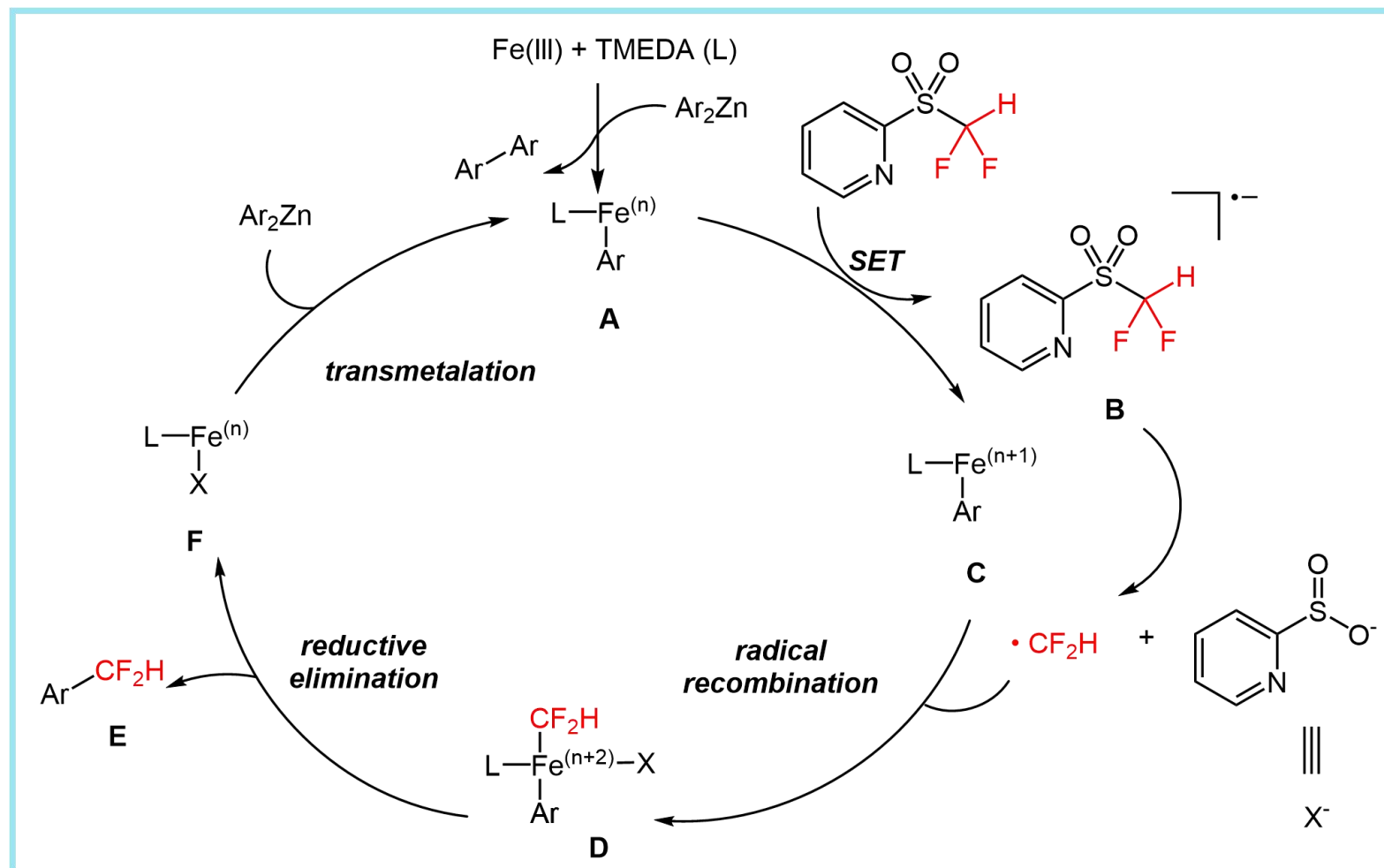
# Introduction

## Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone



Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J.\* *J. Am. Chem. Soc.* **2018**, *140*, 880

# Introduction



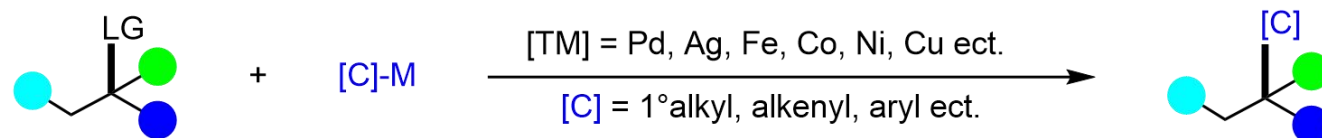
Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J.\* *J. Am. Chem. Soc.* **2018**, *140*, 880



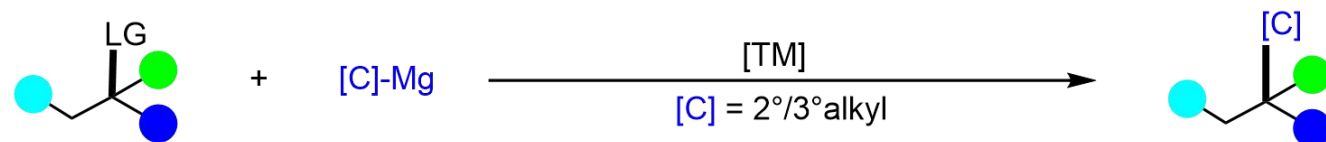
# Project Synopsis

## Transition Metal-Catalyzed Construction of All-Carbon Quaternary Center

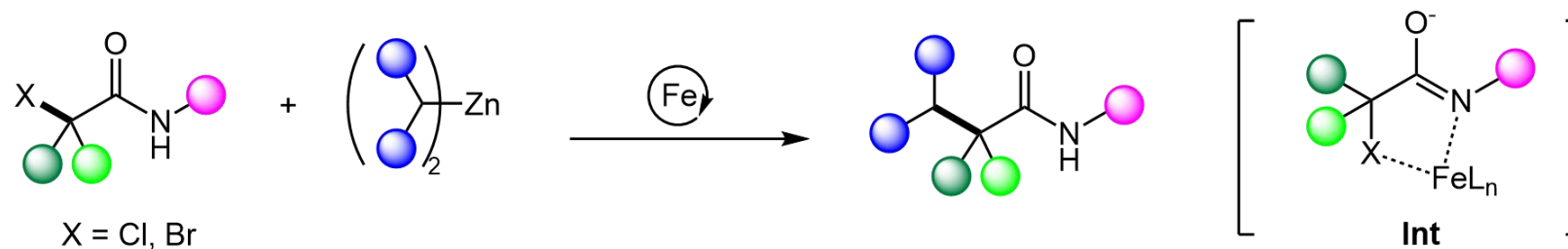
$3^\circ\text{C}(\text{sp}^3)$ - $1^\circ\text{C}(\text{sp}^3)/\text{C}(\text{sp}^2)$  coupling (a few successful examples):



$3^\circ\text{C}(\text{sp}^3)$ - $2^\circ/3^\circ\text{C}(\text{sp}^3)$  coupling (undeveloped):

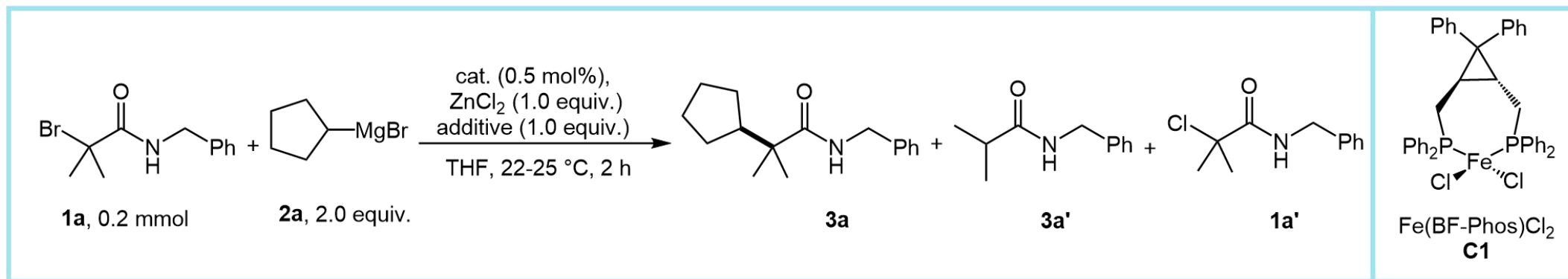


Fe-catalyzed  $3^\circ\text{C}(\text{sp}^3)$ - $2^\circ/3^\circ\text{C}(\text{sp}^3)$  coupling:



# Optimization of the Reaction Conditions

## Optimization of the Reaction Conditions



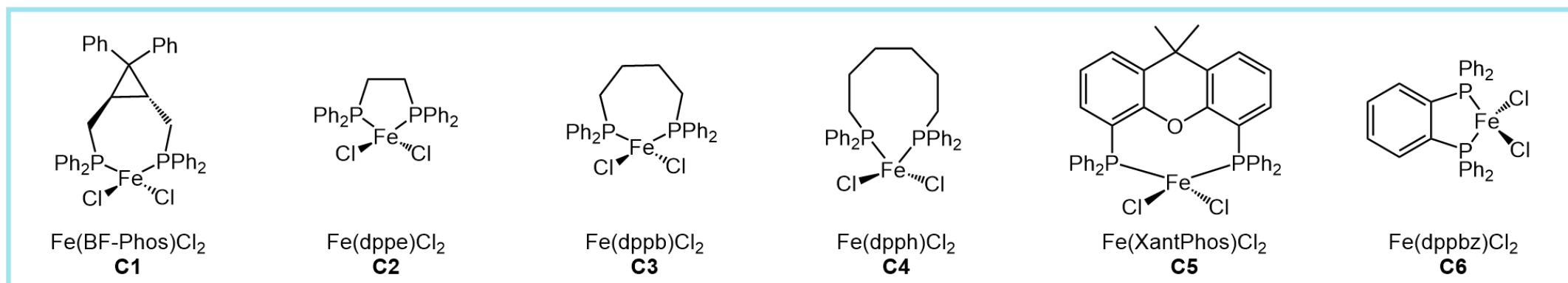
Entry <sup>a</sup>	Cat.	Additive	Conv. (%)	<b>3a</b> yield (%)	<b>3a'</b> yield (%)	<b>1a'</b> yield (%)
1	-	-	75	12	8	50
2 <sup>b</sup>	FeCl <sub>2</sub>	-	>98	49	44	0
3 <sup>c</sup>	<b>C1</b>	-	>98	78	19	0
4 <sup>c</sup>	<b>C1</b>	LiCl	>98	90	5	0
5	<b>C1</b>	LiCl	>98	90 (81)	4	0

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), [M] (0.5 mol%), ZnCl<sub>2</sub> (0.2 mmol, 1.0 equiv.), and additive (1.0 equiv.) in THF were stirred at 22–25 °C for 2 h. The yields were determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. The isolated yield was given in parentheses. <sup>b</sup>FeCl<sub>2</sub> (5 mol%). <sup>c</sup>Fe(BF-Phos)Cl<sub>2</sub> (1 mol%).

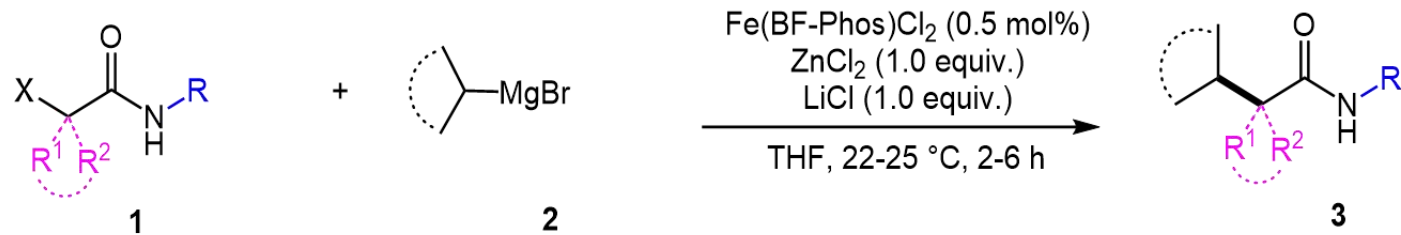
# Optimization of the Reaction Conditions

Entry <sup>a</sup>	Cat.	Additive	Conv. (%)	<b>3a</b> yield (%)	<b>3a'</b> yield (%)	<b>1a'</b> yield (%)
6	<b>C2</b>	LiCl	>98	77	19	2
7	<b>C3</b>	LiCl	>98	72	25	2
8	<b>C4</b>	LiCl	>98	76	21	2
9	<b>C5</b>	LiCl	>98	66	29	2
10	<b>C6</b>	LiCl	>98	70	25	2
11 <sup>d</sup>	[Co]	LiCl	>98	3	72	18
12 <sup>e</sup>	[Ni]	LiCl	96	4	69	13
13 <sup>f</sup>	[Cu]	LiCl	95	6	56	32

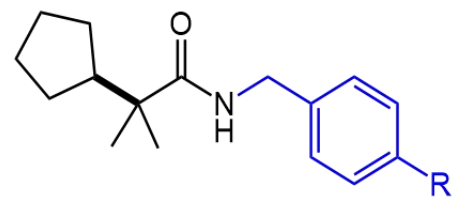
<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), [M] (0.5 mol%), ZnCl<sub>2</sub> (0.2 mmol, 1.0 equiv.), and additive (1.0 equiv.) in THF were stirred at 22–25 °C for 2 h. The yields were determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. The isolated yield was given in parentheses. <sup>b</sup>FeCl<sub>2</sub> (5 mol%). <sup>c</sup>Fe(BF-Phos)Cl<sub>2</sub> (1 mol%). <sup>d</sup>[Co] = Co(BF-Phos)Cl<sub>2</sub>. <sup>e</sup>[Ni] = Ni(BF-Phos)Cl<sub>2</sub>. <sup>f</sup>[Cu] = Cu(BF-Phos)Cl<sub>2</sub>.



# Substrate Scope



## Substrate Scope



**3a**, R = H, 81%

**3b**, R = Me, 64%

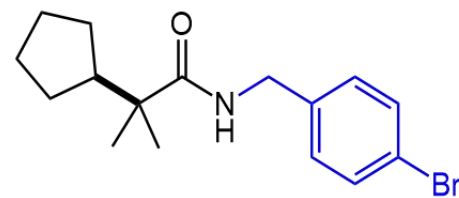
**3c**, R = <sup>t</sup>Bu, 72%

**3d**, R = OMe, 72%

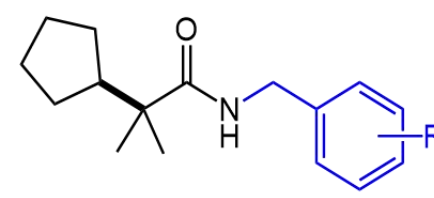
**3e**, R = OCF<sub>3</sub>, 74%

**3f**, R = Cl, 75%

**3g**, R = CF<sub>3</sub>, 63%



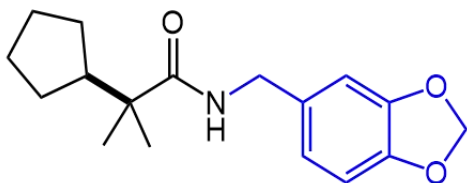
**3h**, 65%



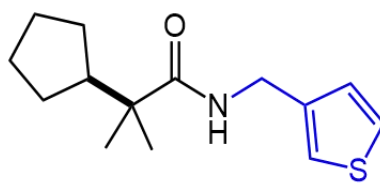
**3i**, R = 2-Me, 70%

**3j**, R = 3-Me, 69%

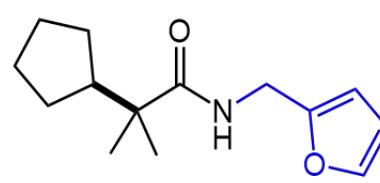
**3k**, R = 3-F, 79%



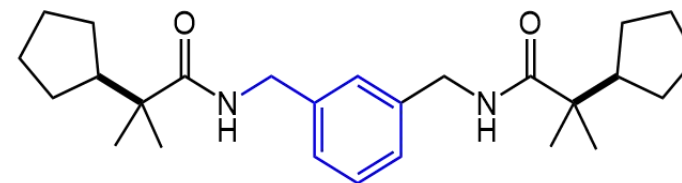
**3l**, 64%



**3m**, 66%



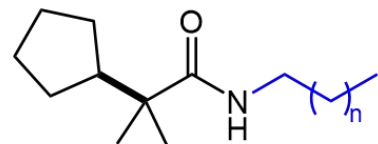
**3n**, 76%



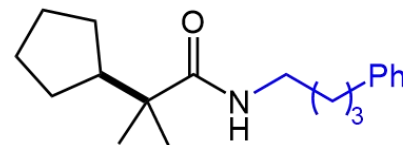
**3o**, 52%

# Substrate Scope

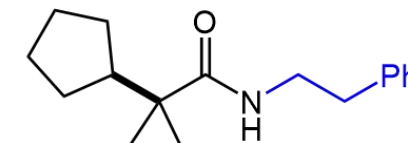
## Substrate Scope



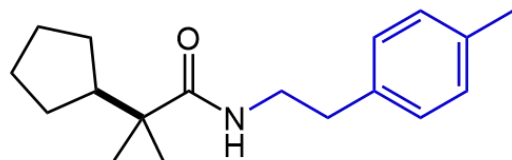
**3p**, n = 1, 66%  
**3q**, n = 2, 69%  
**3r**, n = 3, 72%  
**3s**, n = 4, 78%  
**3t**, n = 5, 72%  
**3u**, n = 6, 71%



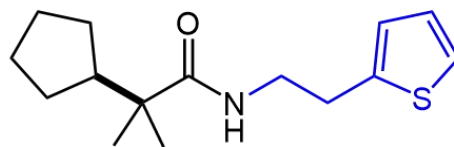
**3v**, 66%



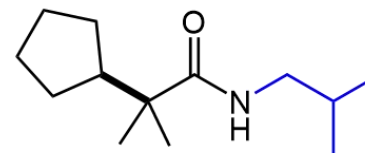
**3w**, 70%



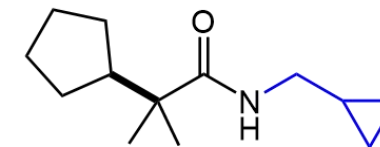
**3x**, 71%



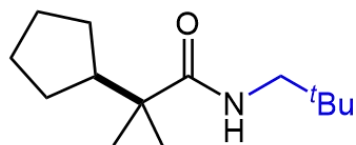
**3y**, 76%



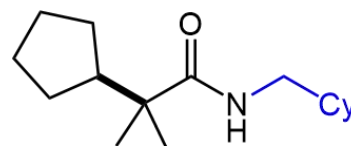
**3z**, 76%



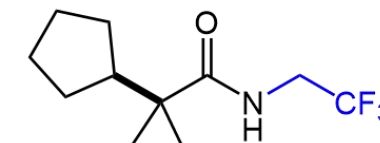
**3aa**, 71%



**3ba**, 65%



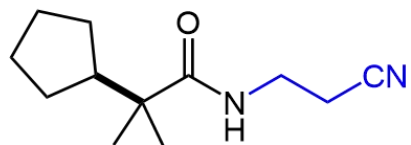
**3ca**, 66%



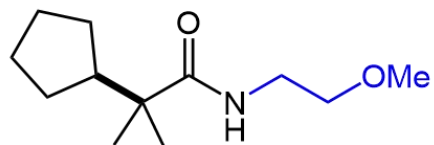
**3da**, 51%

# Substrate Scope

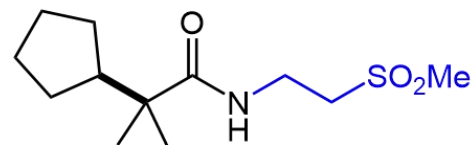
## Substrate Scope



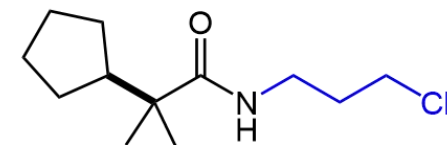
**3ea**, 70%



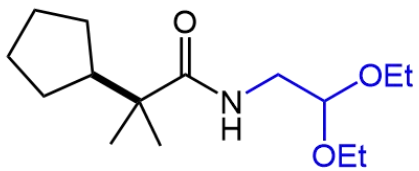
**3fa**, 42%



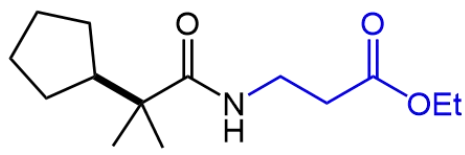
**3ga**, 53%



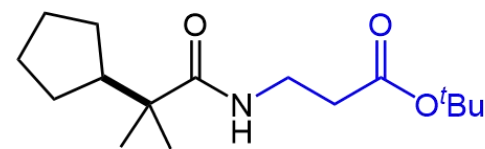
**3ha**, 71%



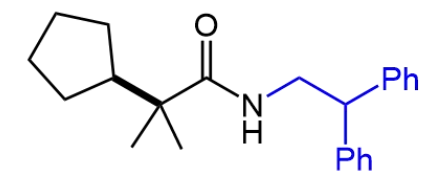
**3ia**, 46%



**3ja**, 53%



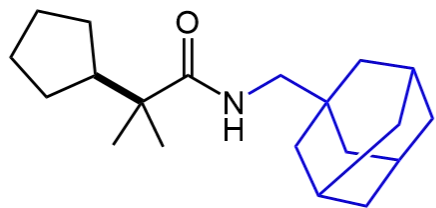
**3ka**, 68%



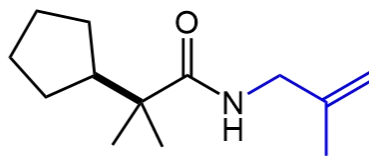
**3la**, 72%

# Substrate Scope

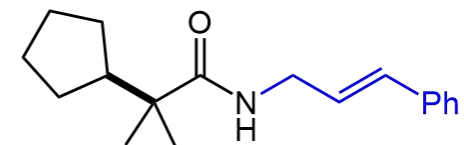
## Substrate Scope



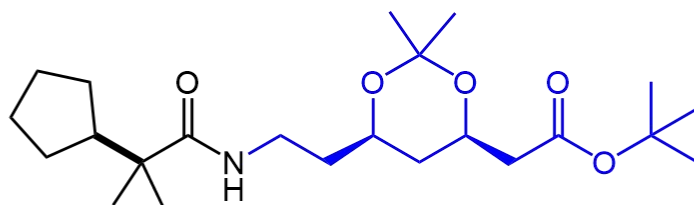
**3ma**, 69%



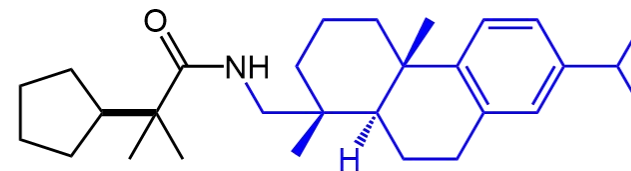
**3na**, 70%



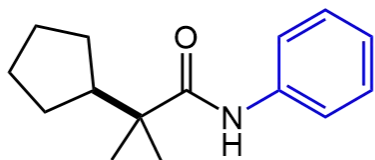
**3oa**, 72%



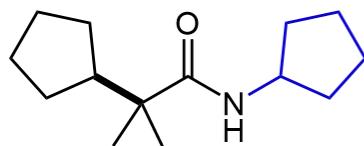
**3qa**, 50%



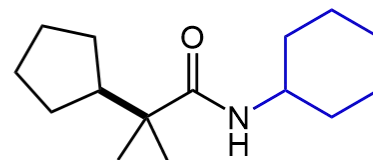
**3pa**, 56%



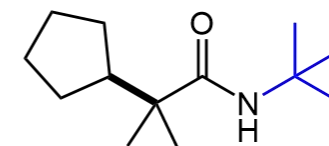
**3ra**, 45%



**3sa**, 29%



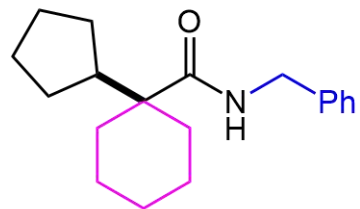
**3ta**, 28%



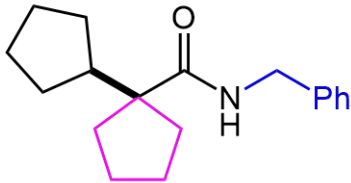
**3ua**, trace

# Substrate Scope

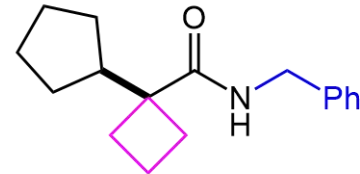
## Substrate Scope



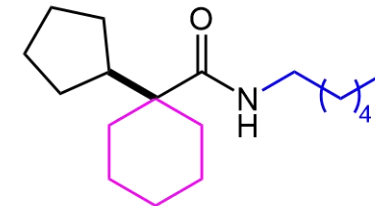
**3va**, 56%



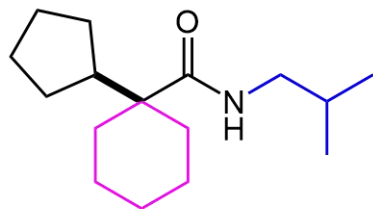
**3wa**, 43%



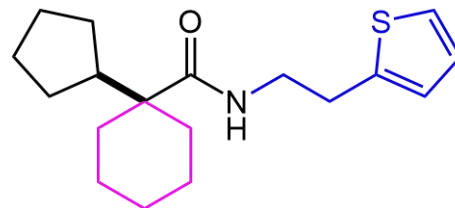
**3xa**, 21%



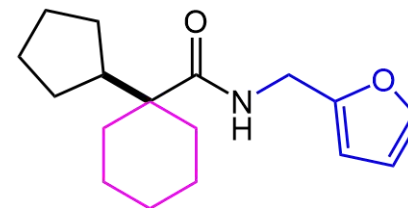
**3ya**, 61%



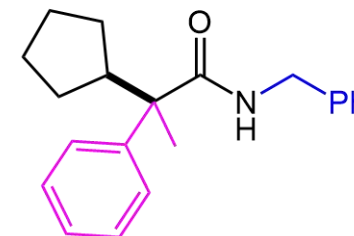
**3za**, 60%



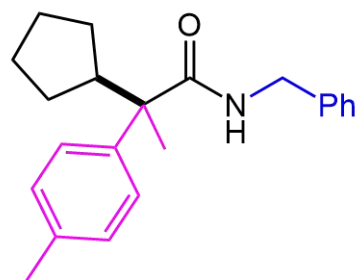
**3ab**, 72%



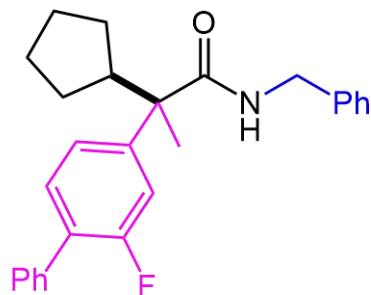
**3ac**, 58%



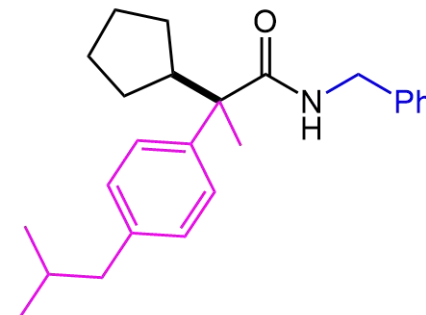
**3ad**, X = Cl, 70%



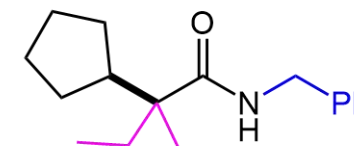
**3ae**, X = Cl, 62%



**3af**, X = Cl, 65%  
from flurbiprofen



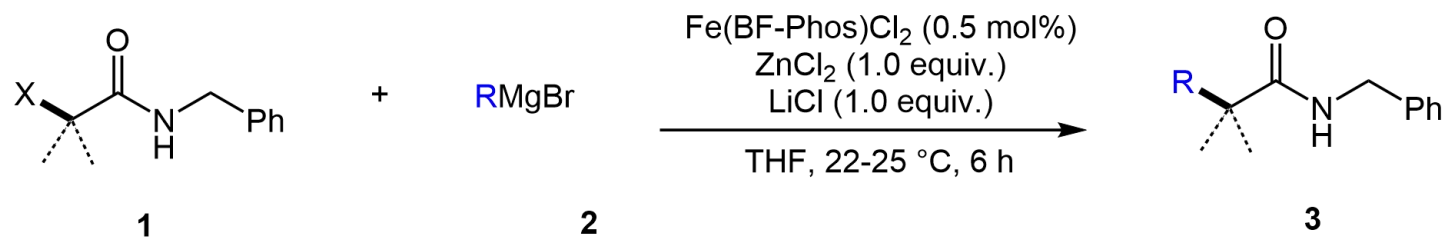
**3ag**, X = Cl, 52%  
from ibuprofen



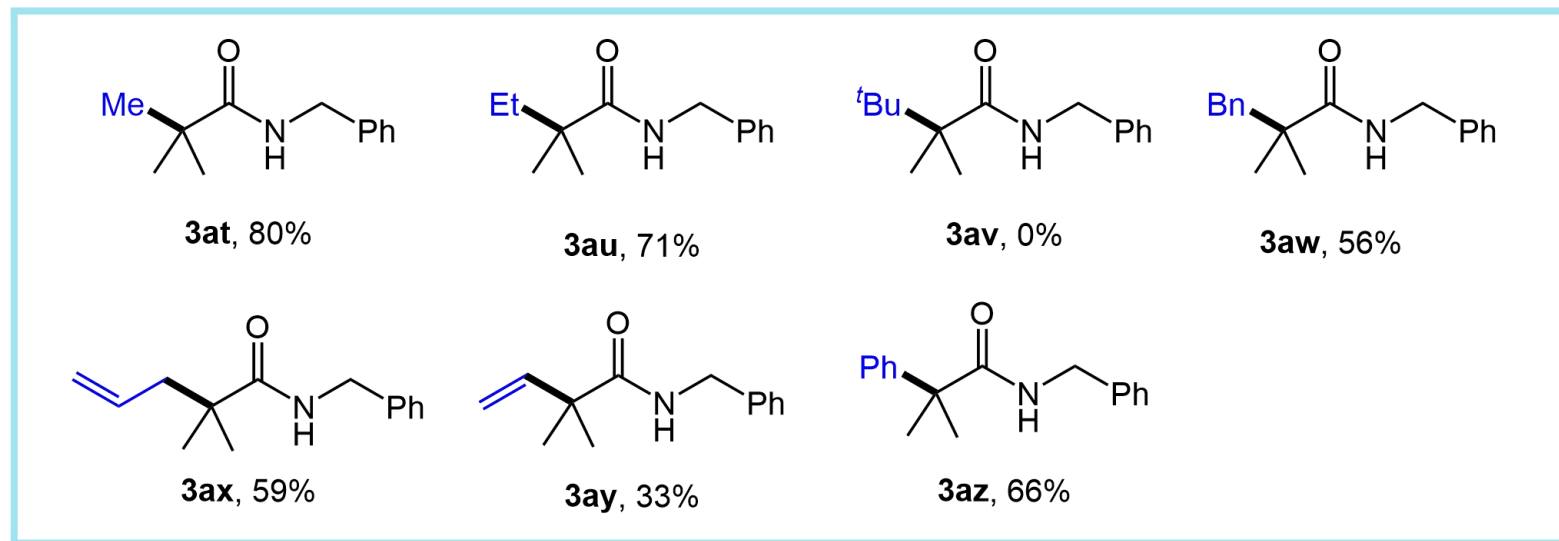
**3ah**, X = Cl, 45%



# Substrate Scope

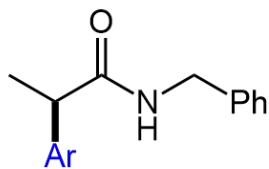


## Substrate Scope

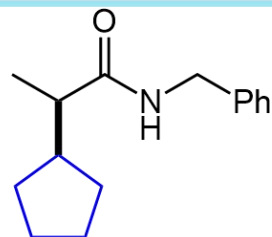


# Substrate Scope

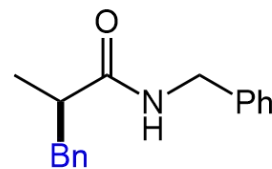
## Substrate Scope



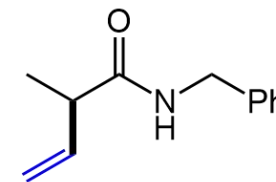
Ar = 4-OMeC<sub>6</sub>H<sub>4</sub>  
**3aaa**, 61%



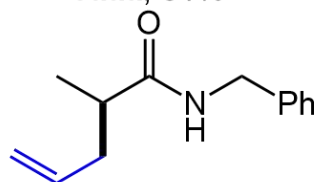
**3aab**, 26%



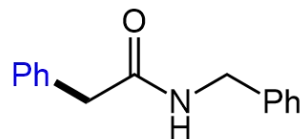
**3aac**, 29%



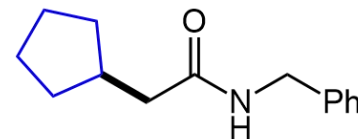
**3aad**, 33%



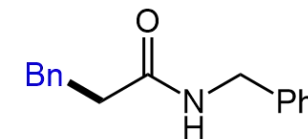
**3aae**, X = Cl, 26%



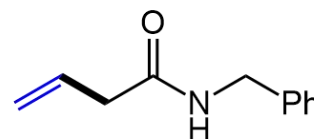
**3aaf**, 42%



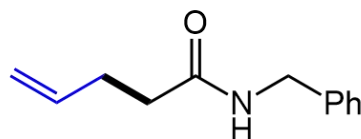
**3aag**, 69%  
**3aag**, X = Cl, 51%



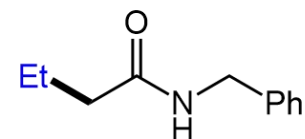
**3aah**, X = Cl, 25%



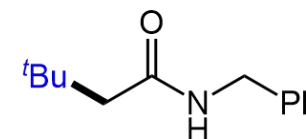
**3aai**, 31%



**3aaj**, X = Cl, 29%



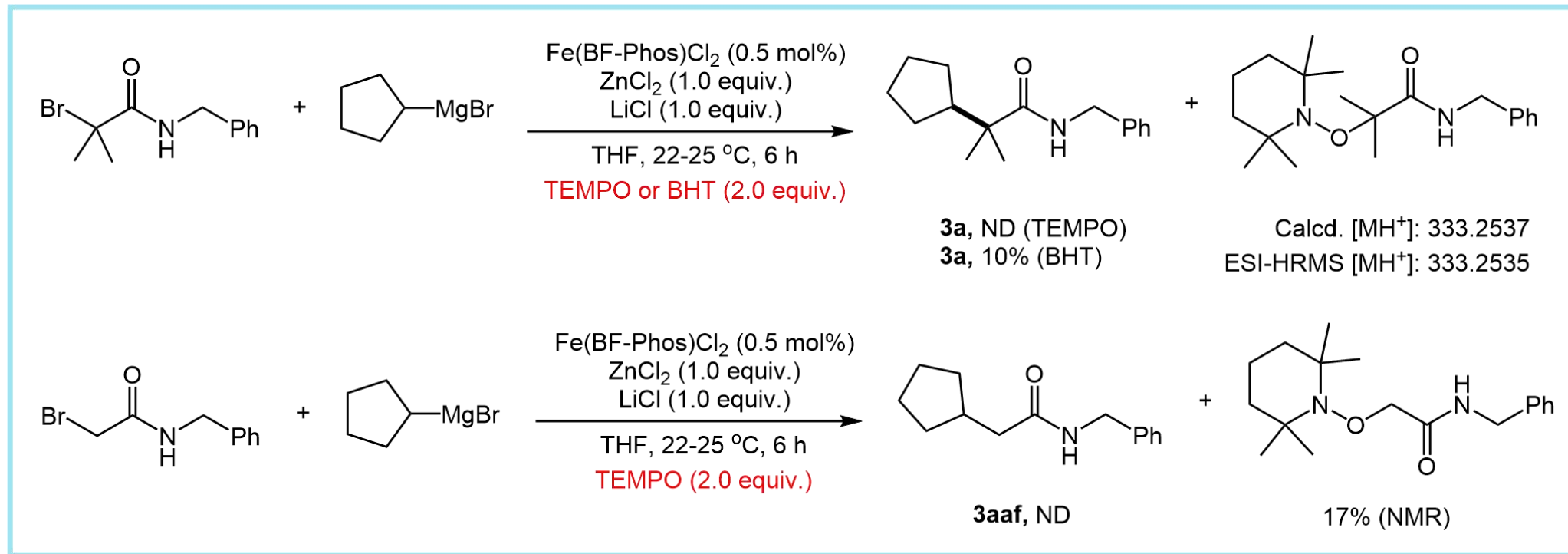
**3aak**, 55%



**3aal**, X = Cl, 43%

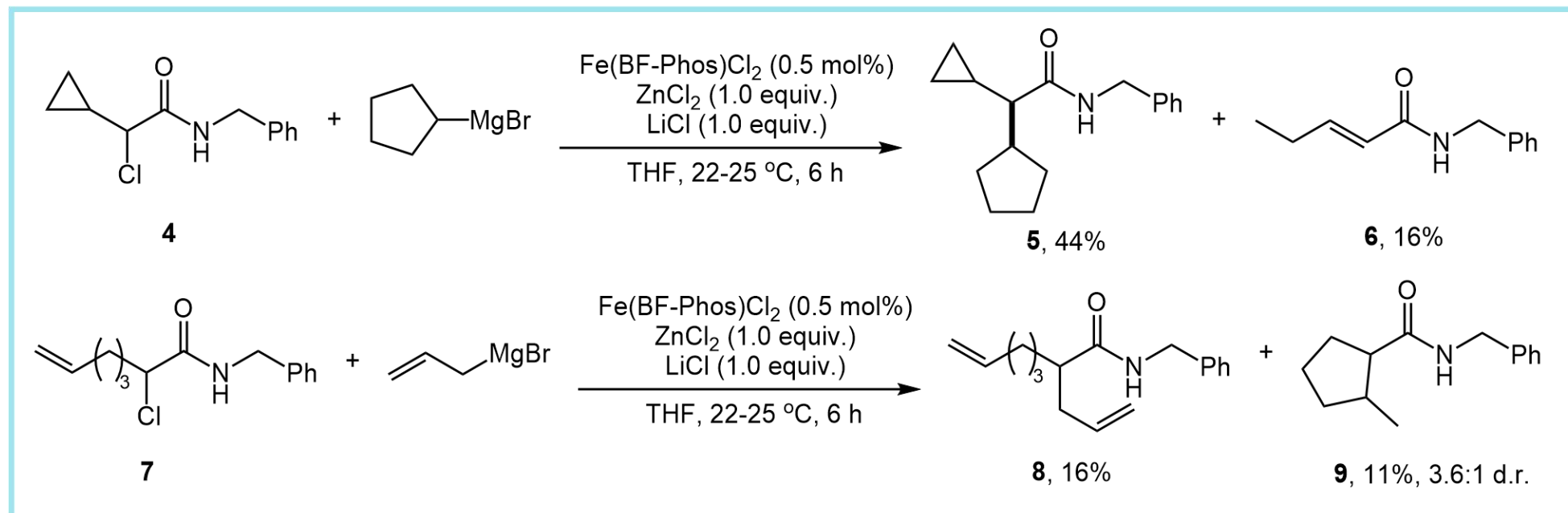
# Mechanistic Investigation

## Radical Trapping Experiments



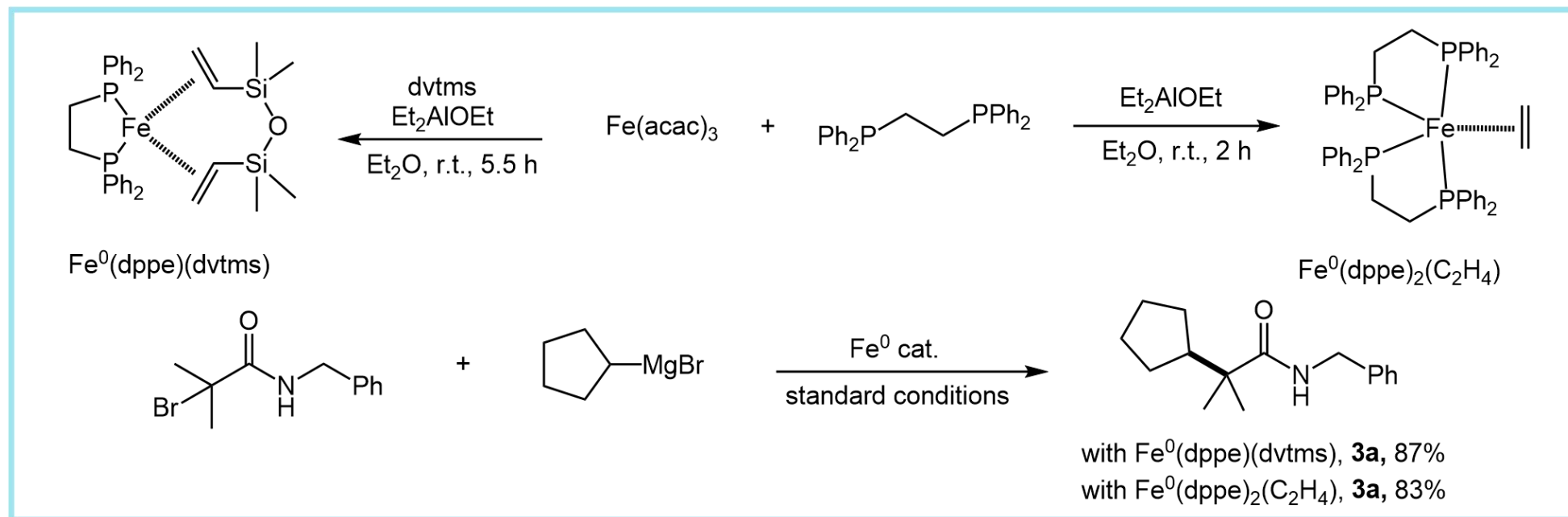
# Mechanistic Studies

## Radical Clock Experiments

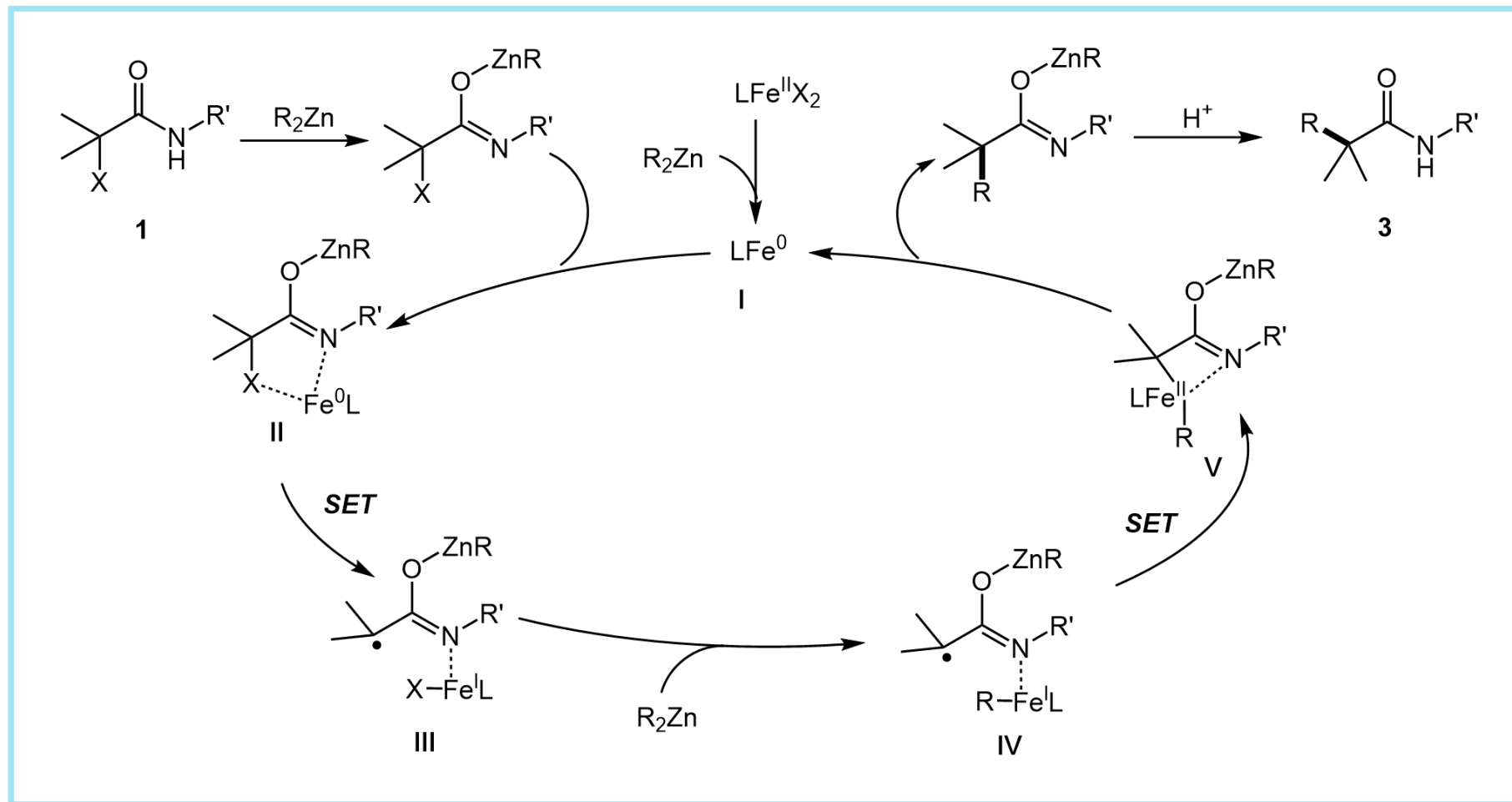


# Mechanistic Studies

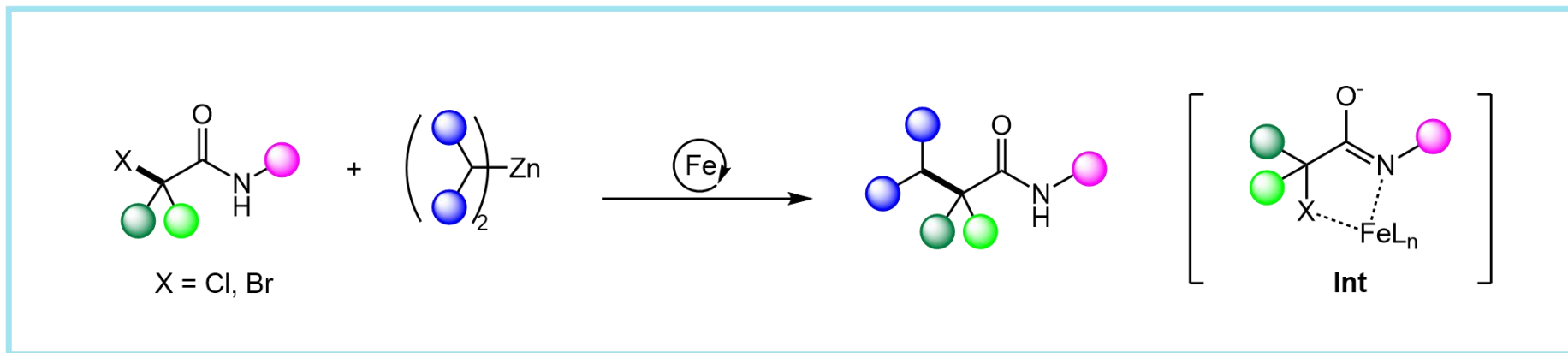
## Control Experiments with $Fe^0$ as the Catalysts



# Proposed Mechanism



# Summary



- Iron-catalyzed 3°C(sp<sup>3</sup>)-2°(sp<sup>3</sup>) coupling
- Efficient construction of all-carbon quaternary center
- Broad substrate scope and good functional group tolerance
- Directing group enabled C-C coupling strategy

# Strategy for Writing The First Paragraph

---

过去C-C键构建方法



引出本文工作

- ✓ The efficient construction of C–C bonds constitutes the quintessence of organic synthesis chemistry, with the unveiling of updated strategies for such bond construction significantly expanding the conceptual sphere of synthetic design and substantially elevating the liberty of synthetic exploration. As a result, the development of C–C bondforming methodologies has attracted considerable interest. Among these, transition-metal-catalyzed coupling reactions stand out as particularly potent, exemplified by the ubiquity of Suzuki and Negishi cross-couplings in the assembly of functional molecules relevant to pharmaceuticals and materials.....
- ✓ To date, only a few successful couplings involving tertiary C(sp<sup>3</sup>) with C(sp<sup>2</sup>) and primary C(sp<sup>3</sup>) have been reported. Moreover, the coupling of tertiary C(sp<sup>3</sup>) with secondary C(sp<sup>3</sup>) has been rarely recorded with two special examples, and both used Grignard reagents as nucleophiles. Addressing this challenge is not only a key fundamental issue for synthetic chemistry but also provides a foundation toward a paradigm shift in the synthetic approach to the construction of quaternary carbons.



# Strategy for Writing The Last Paragraph

---

总结工作



强调亮点

- ✓ In conclusion, we have successfully realized the coupling of tertiary, secondary, and primary alkyl halides with organozinc reagents catalyzed by cost-effective iron complexes.
- ✓ Notably, this work represents remarkable achievement in coupling tertiary C(sp<sup>3</sup>) with secondary C(sp<sup>3</sup>) centers, overcoming the substantial steric hindrances that have historically impeded transition-metal-catalyzed couplings and suppressing side reactions like elimination and isomerization. Our preliminary mechanistic studies suggest the involvement of alkyl radicals in the reaction pathway, with the amide bond potentially acting as a directing group, and Fe<sup>0</sup> initiated the process. This breakthrough marks a pivotal advancement for the efficient construction of all-carbon quaternary carbon centers. The detail mechanistic studies are underway in our laboratory.

# Representative Examples

---

- Among these, transition-metal-catalyzed coupling reactions stand out as particularly potent, exemplified by the **ubiquity** of Suzuki and Negishi cross-couplings in the assembly of functional molecules relevant to pharmaceuticals and materials. (**ubiquity**, n. 到处存在, 普遍存在)
- This protocol marks the **inaugural** instance of efficient catalytic coupling between tertiary C(sp<sup>3</sup>) and secondary C(sp<sup>3</sup>) using organo zinc reagents. (**inaugural**, adj. 就职的, 就任的; 创始的, 最早的)
- In conclusion, we have successfully realized the coupling of tertiary alkyl halides with organozinc reagents catalyzed by **cost-effective** iron complexes. (**cost-effective**, adj. 划算的; 成本效益好的)

# Acknowledgement

---

*Thanks for your attention*