

# Literature Report 3

## Enantioselective Nickel-Catalyzed C(sp<sup>3</sup>)-H Activation of Formamides

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**Reporter: Jian Chen**

**Checker: Wen-Jun Huang**

Wang, Y.-X.; Ye, M.\* *et al. Angew. Chem. Int. Ed.* **2022**, 61, e202209625

2022-11-16

# CV of Prof. Mengchun Ye

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## ***Background:***

- **1997-2001** B.S., Lanzhou University
- **2001-2006** Ph.D., SIOC (Prof. Yong Tang)
- **2006-2009** Post-Doc., UNC Chapel Hill
- **2009-2013** Post-Doc., The Scripps Research Institute
- **2014-Now** Professor, Nankai University



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## ***Research:***

- Organic synthesis, organometallic chemistry and chemical biology
- Ni-Al bimetallic catalyzed reactions

# Contents

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## 1 Introduction

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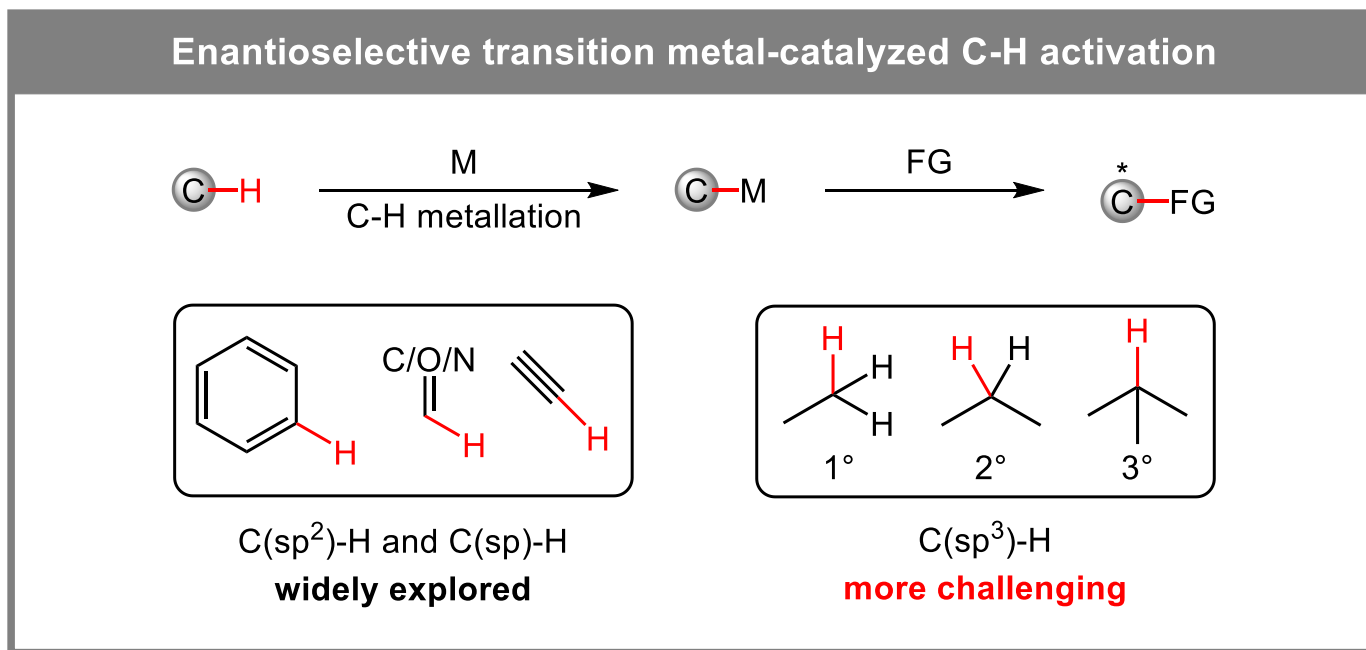
## 2 Enantioselective Ni-Catalyzed C(sp<sup>3</sup>)-H Activation

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## 3 Summary

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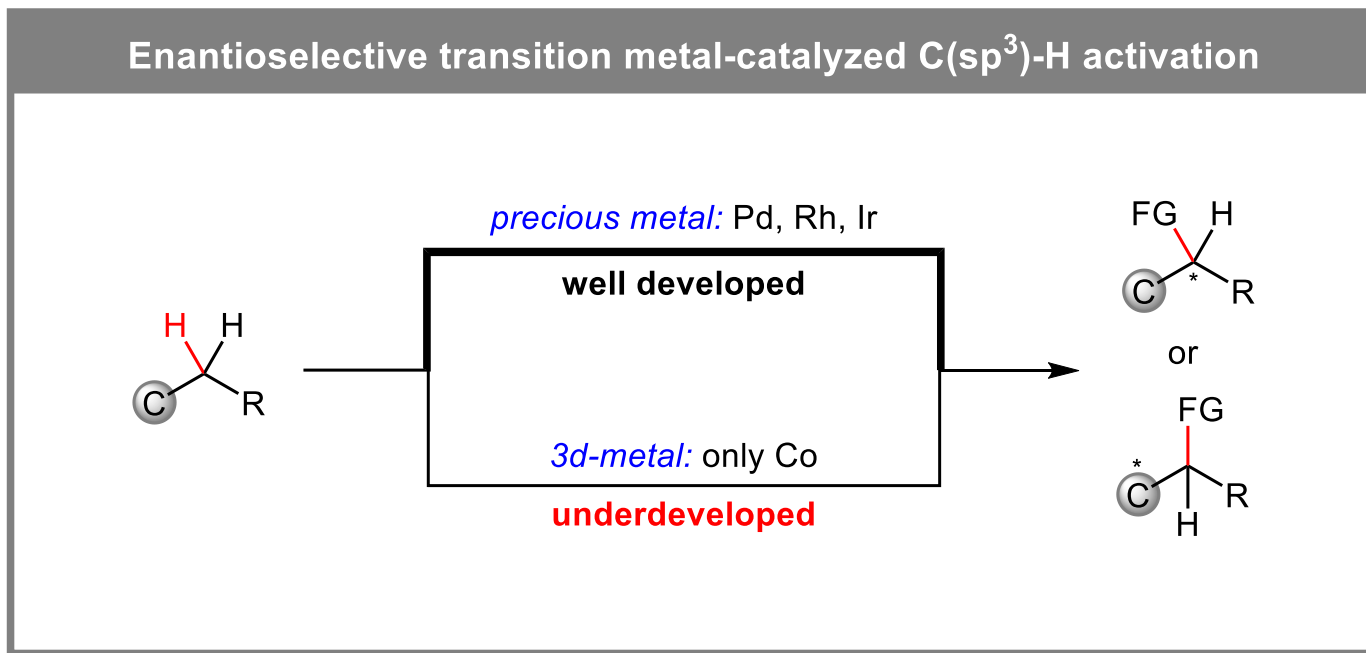
# Introduction



## Challenges

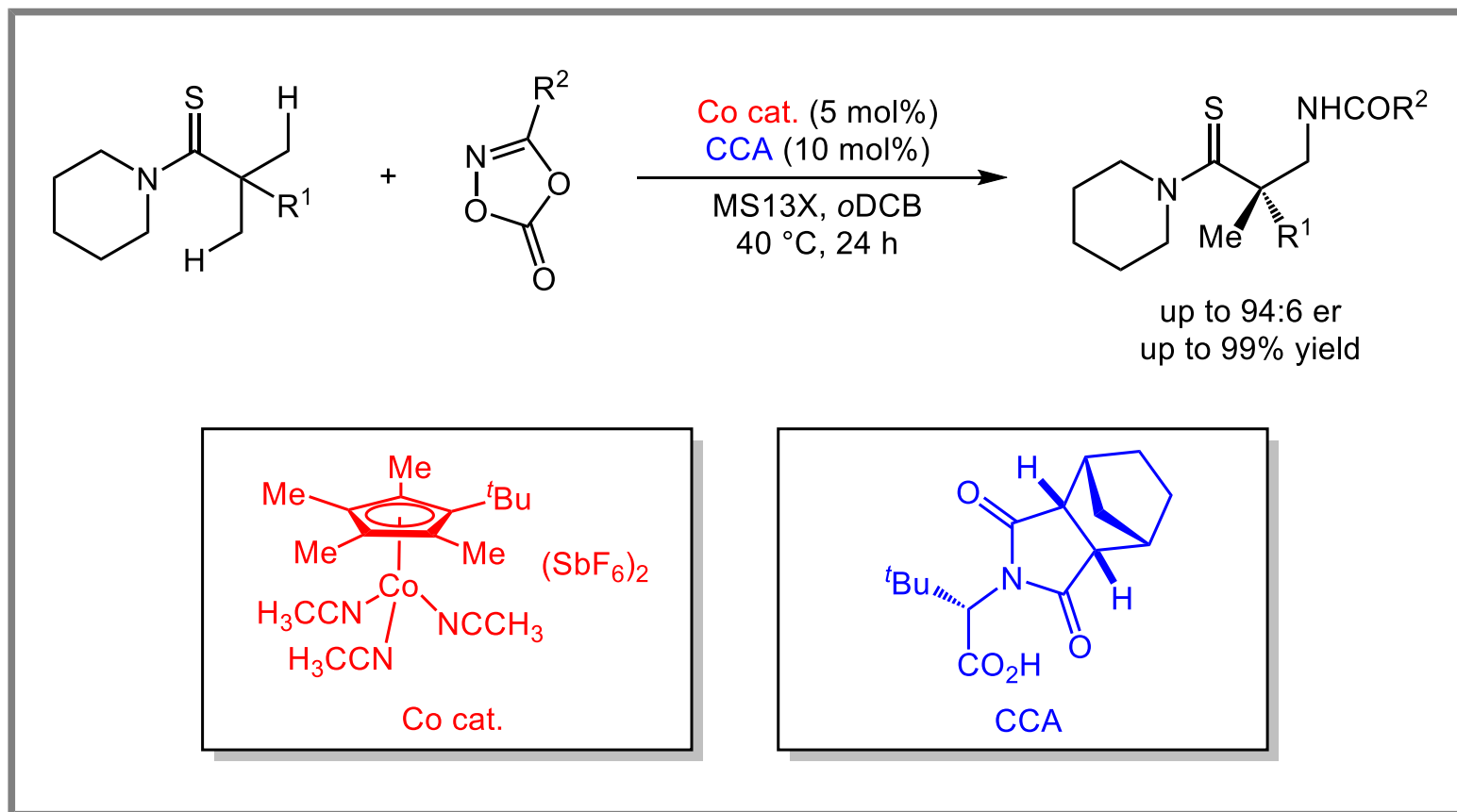
- ♥ Steric hindrance around C(sp<sup>3</sup>)-H bonds
- ♥ lack of  $\pi$ -orbitals to interact with metals

# Introduction



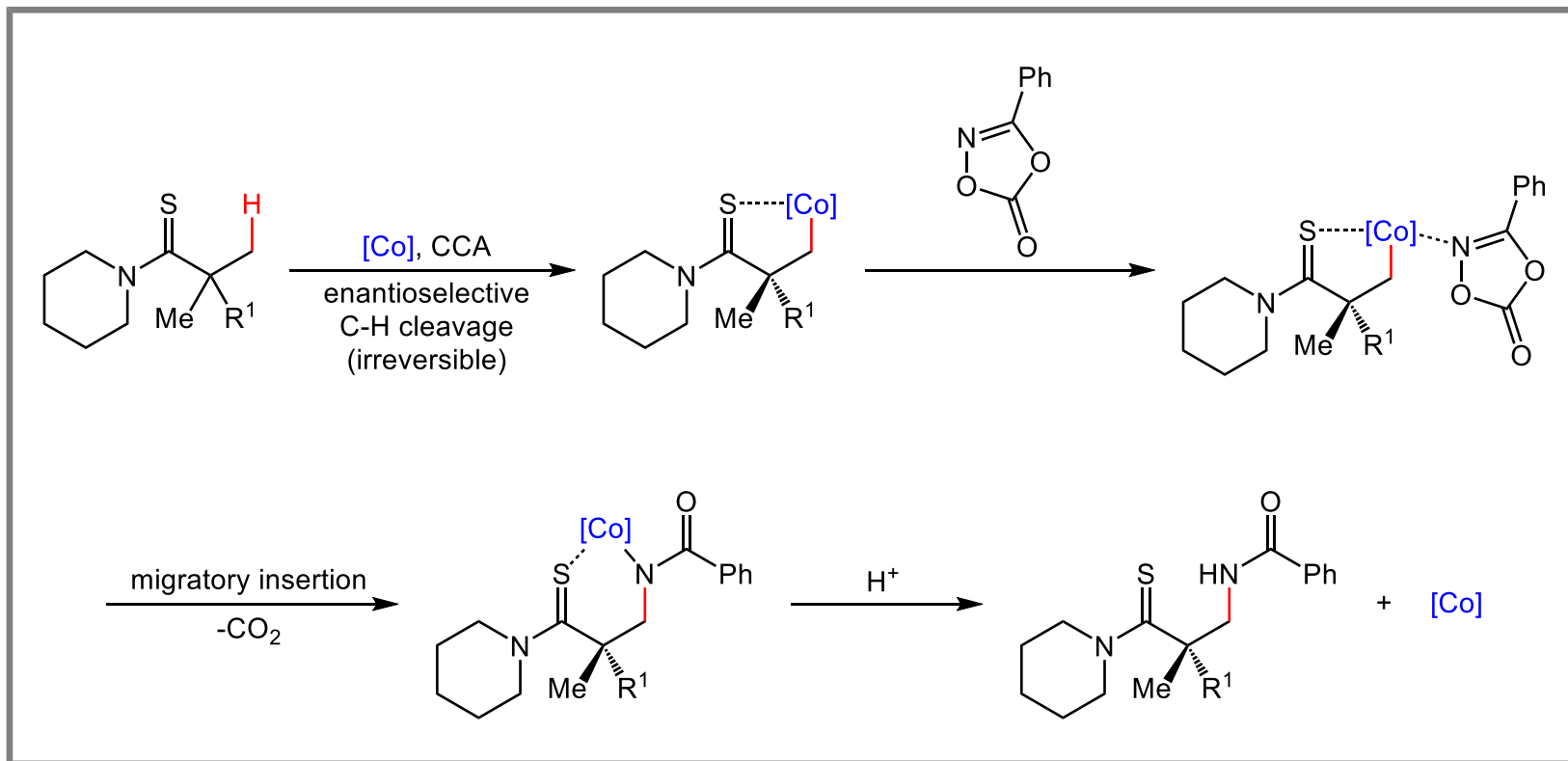
- ♥ Precious metals such as Pd, Rh and Ir have been capable of catalyzing a broad range of enantioselective C(sp<sup>3</sup>)-H bond activation reactions.
- ♥ Same strategies are in general ineffective to most 3d-transition metals that are very sensitive to the structure of substrates and ligand.

# Co-Catalyzed Asymmetric C(sp<sup>3</sup>)-H Activation



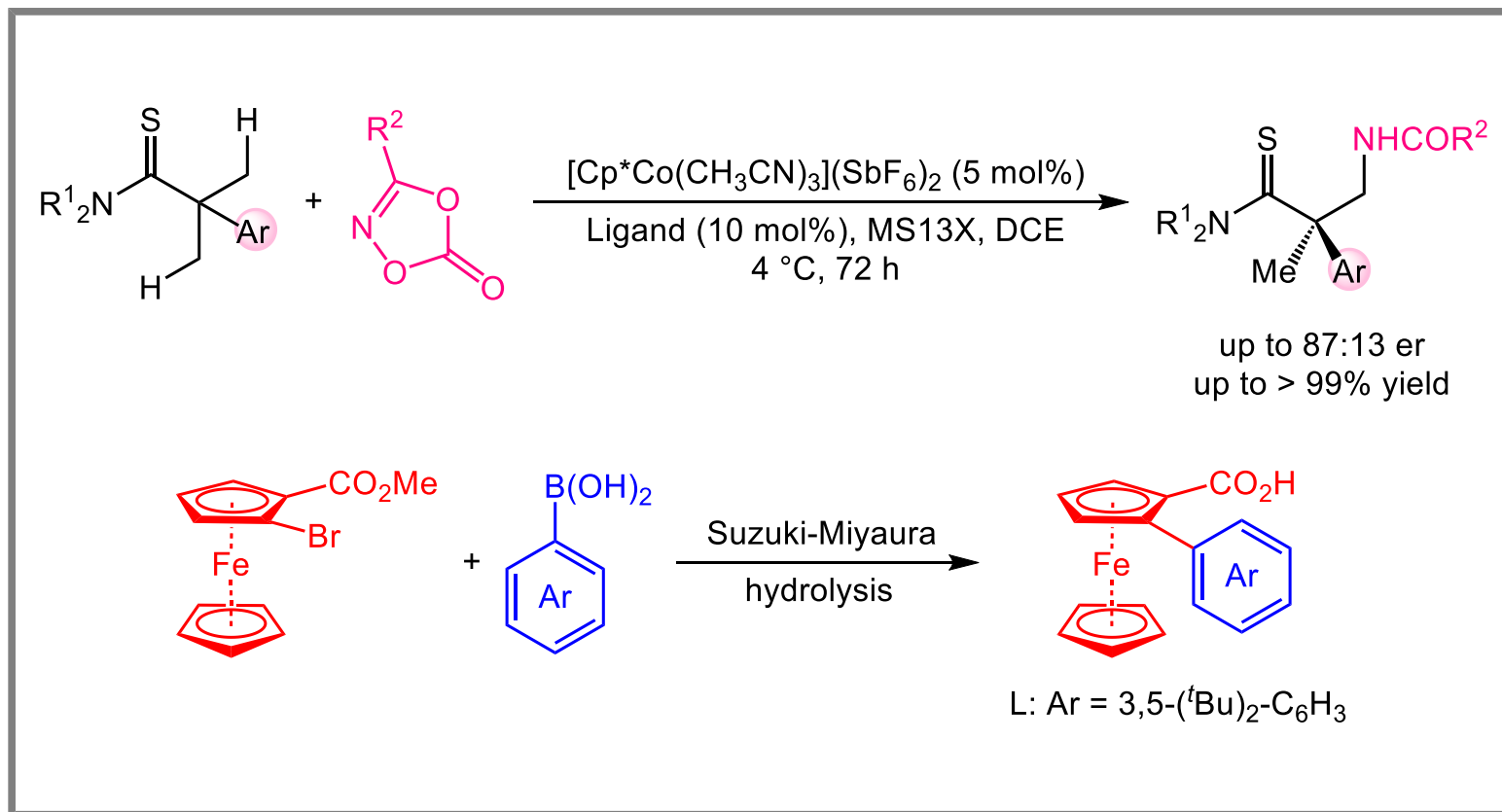
Fukagawa, S.; Matsunaga, S.\* *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 1153

# Co-Catalyzed Asymmetric C(sp<sup>3</sup>)-H Activation



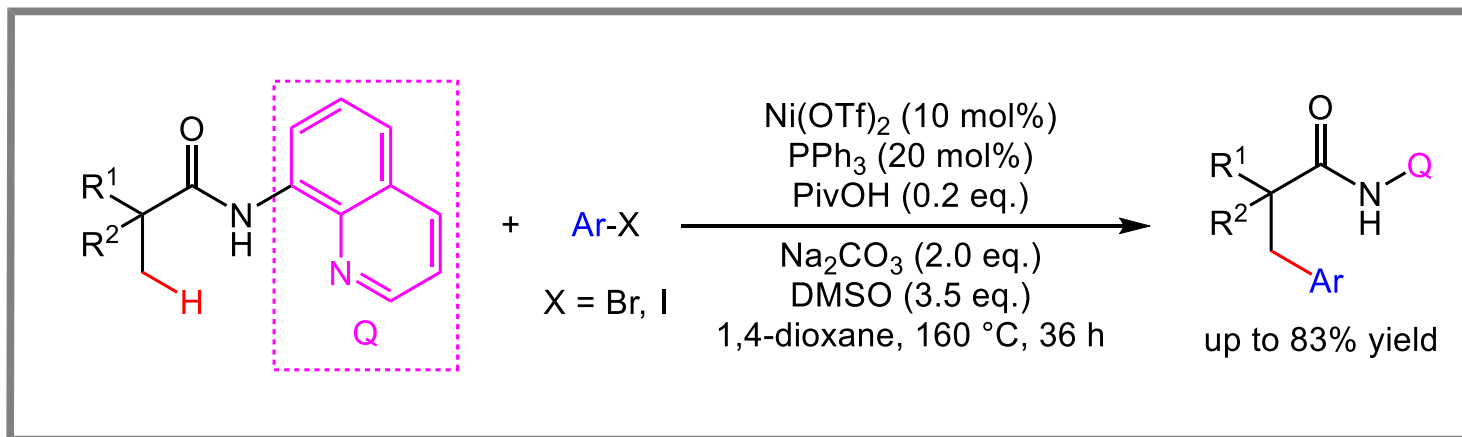
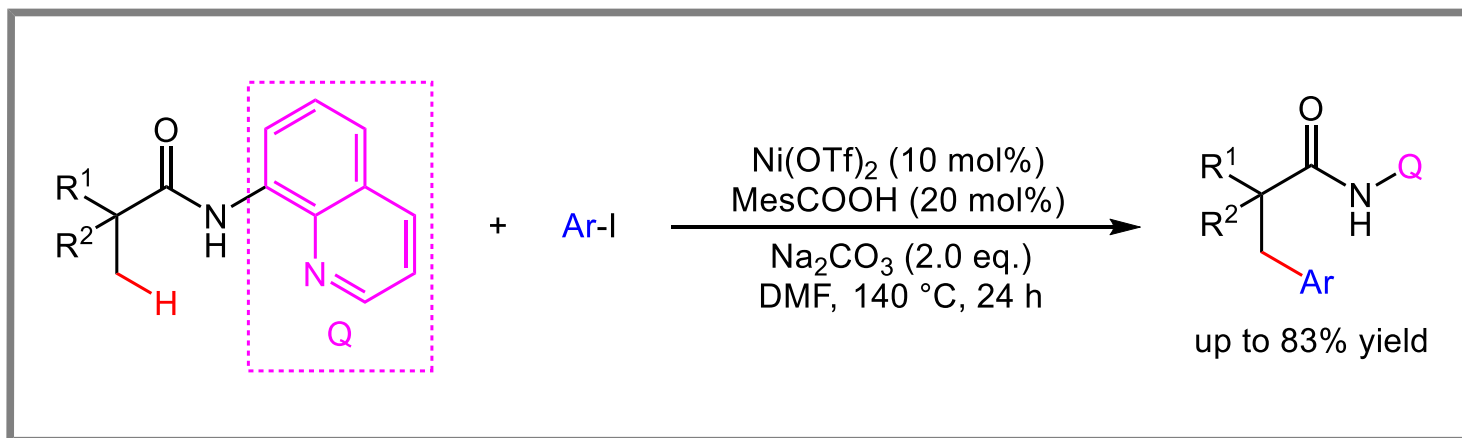
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# Co-Catalyzed Asymmetric C(sp<sup>3</sup>)-H Activation



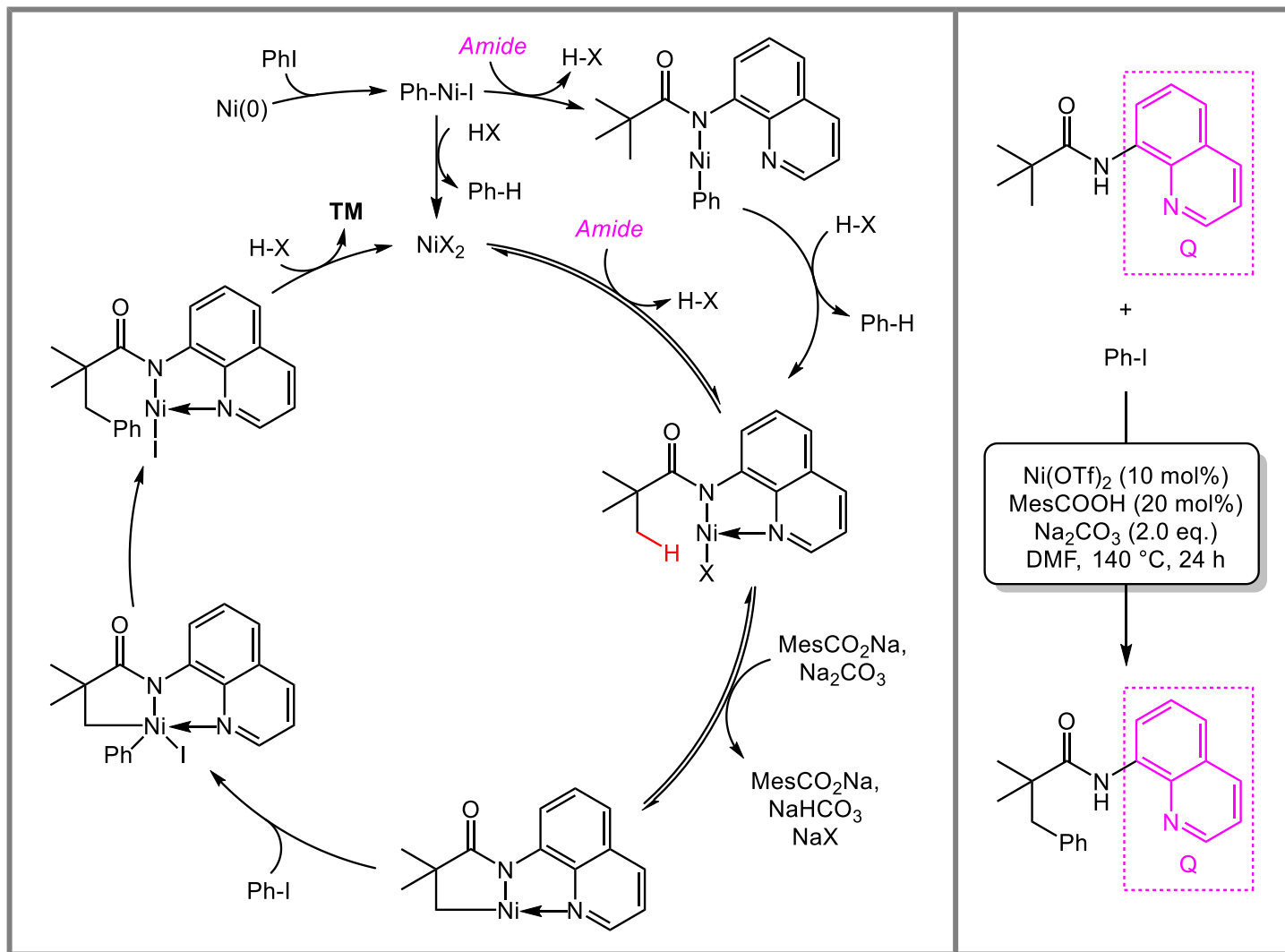


# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



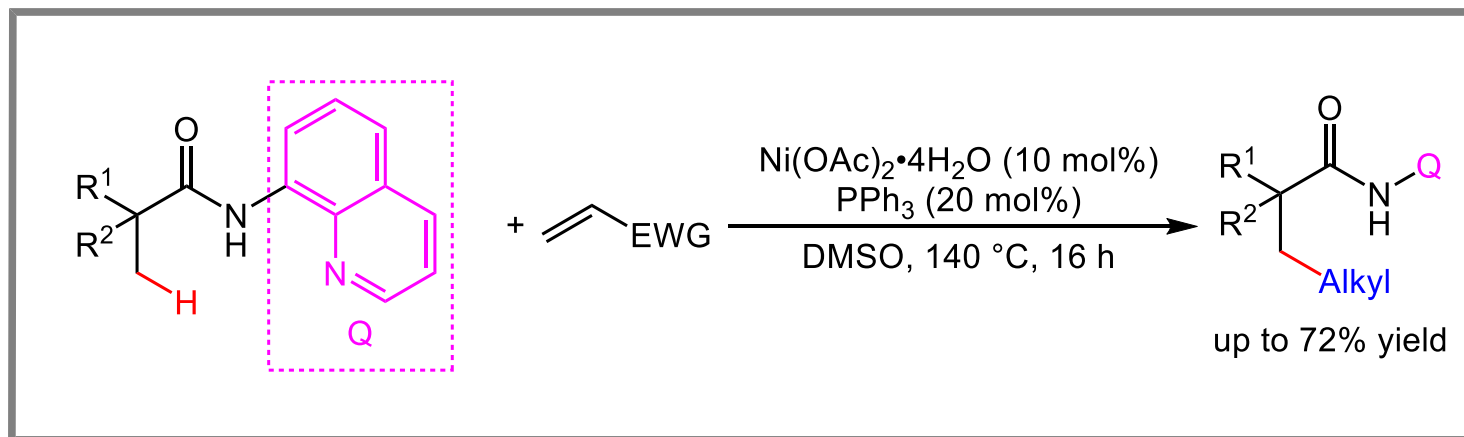
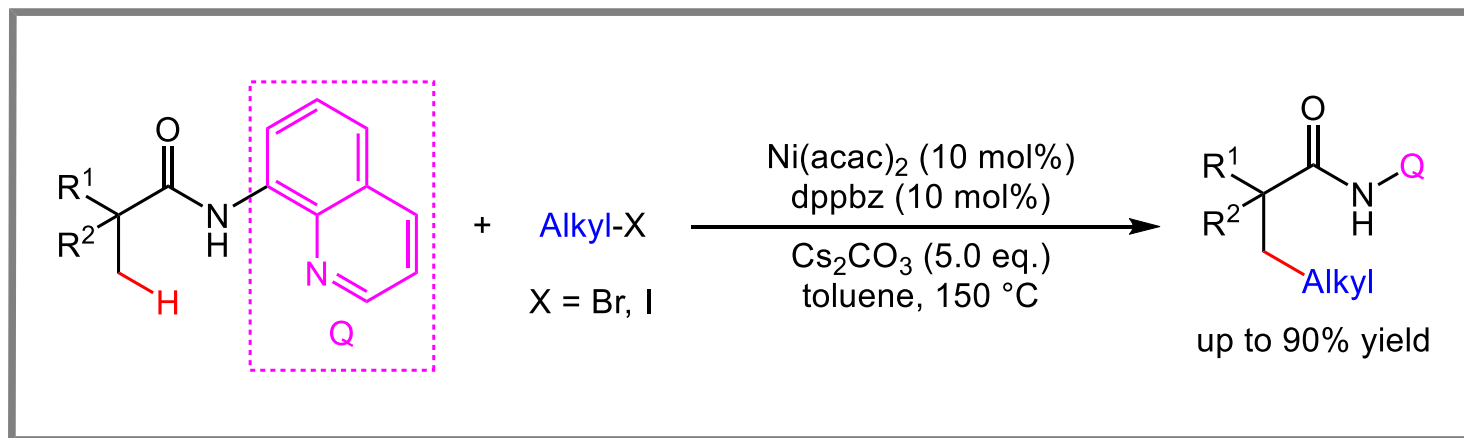
Aihara, Y.; Chatani, N.\* *et al. J. Am. Chem. Soc.* **2014**, *136*, 898  
Li, M.; You, J.\* *et al. Chem. Commun.*, **2014**, *50*, 3944

# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



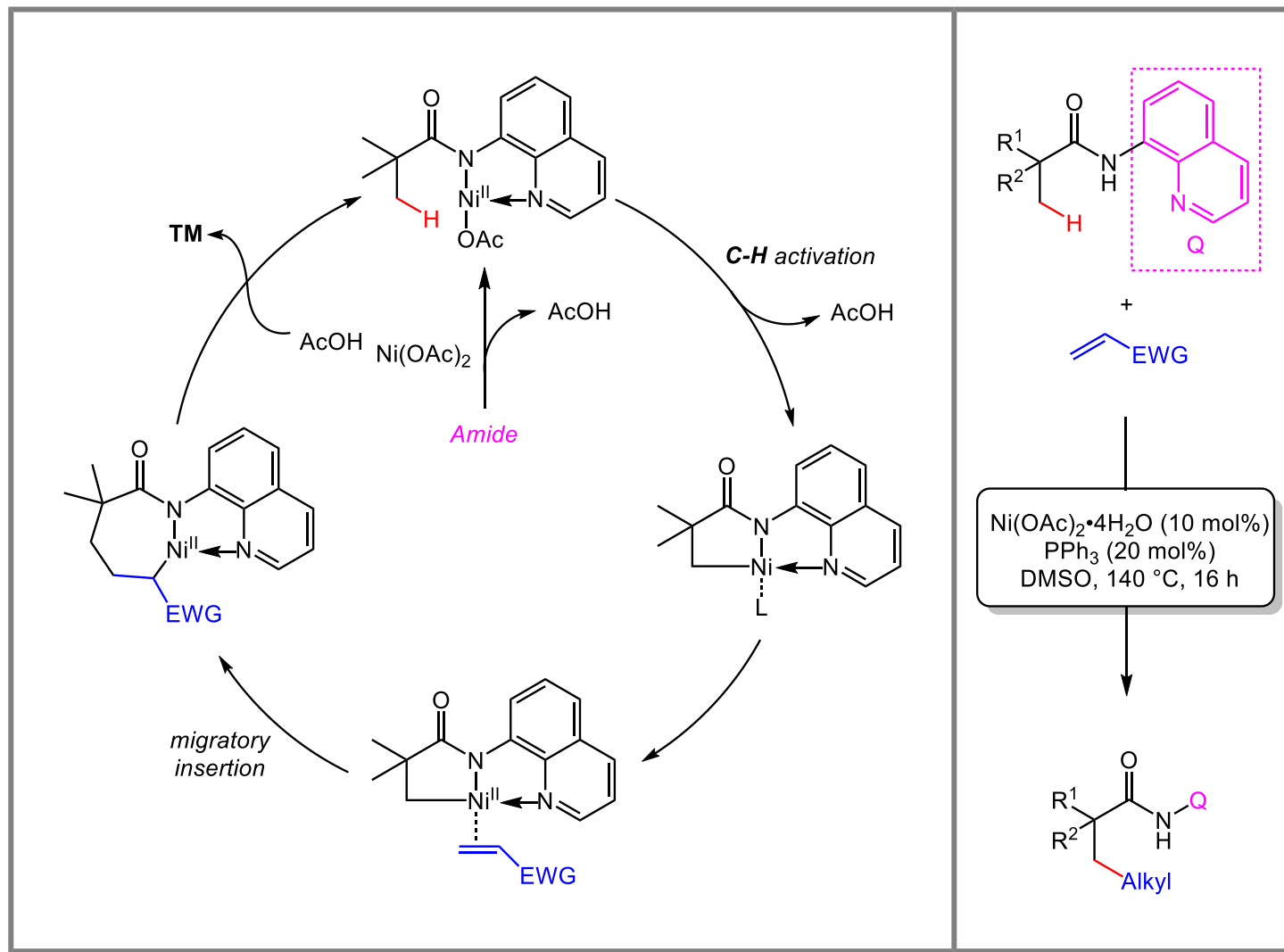
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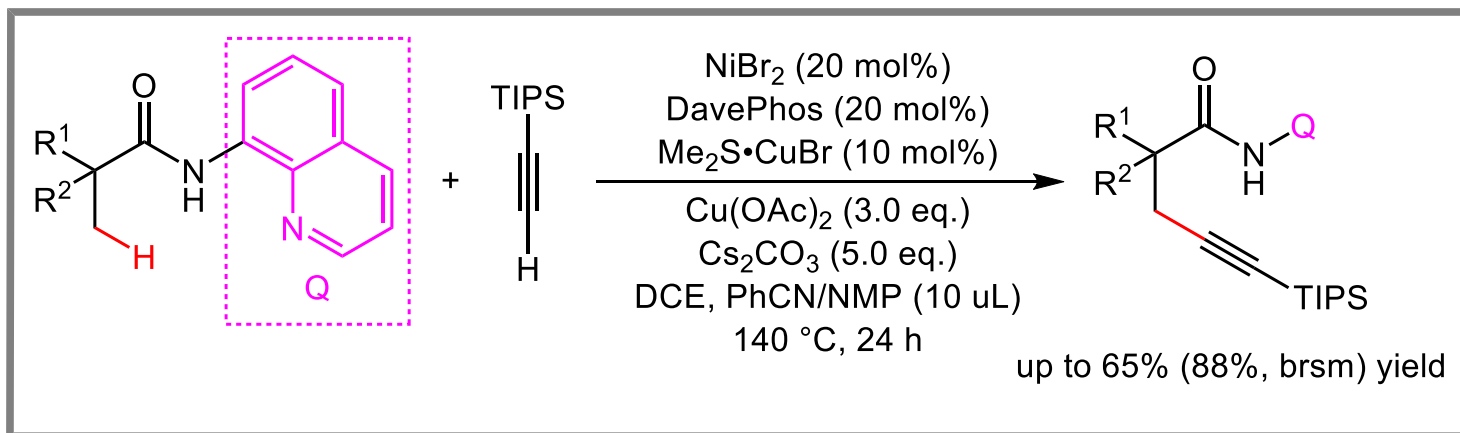
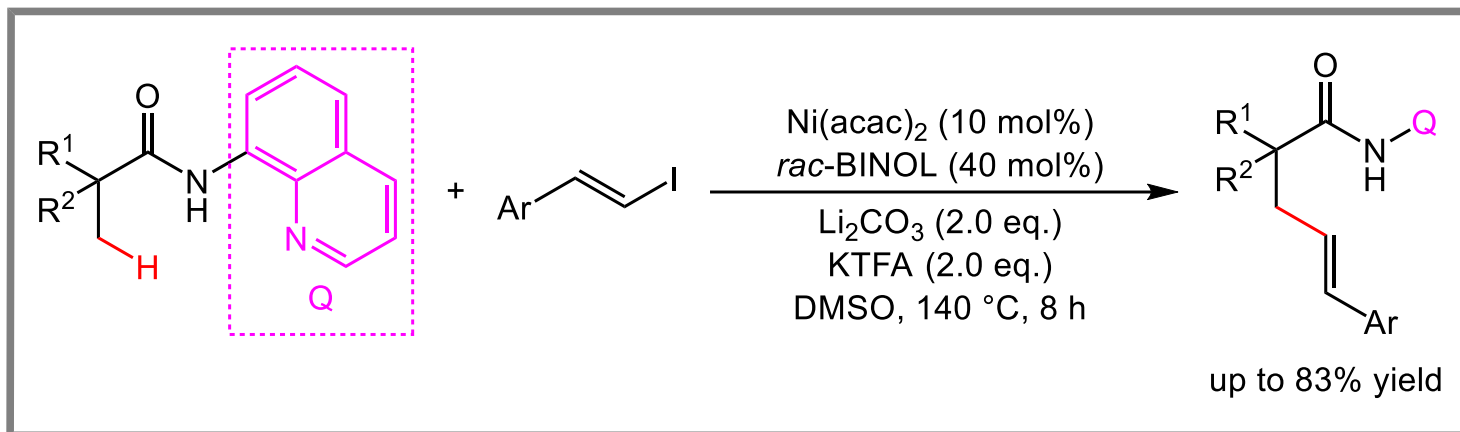
Wu, X.; Ge, H.\* *et al.* *J. Am. Chem. Soc.* **2014**, *136*, 1789  
Maity, S.; Maiti, D.\* *et al.* *Chem. Eur. J.* **2015**, *21*, 11320

# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



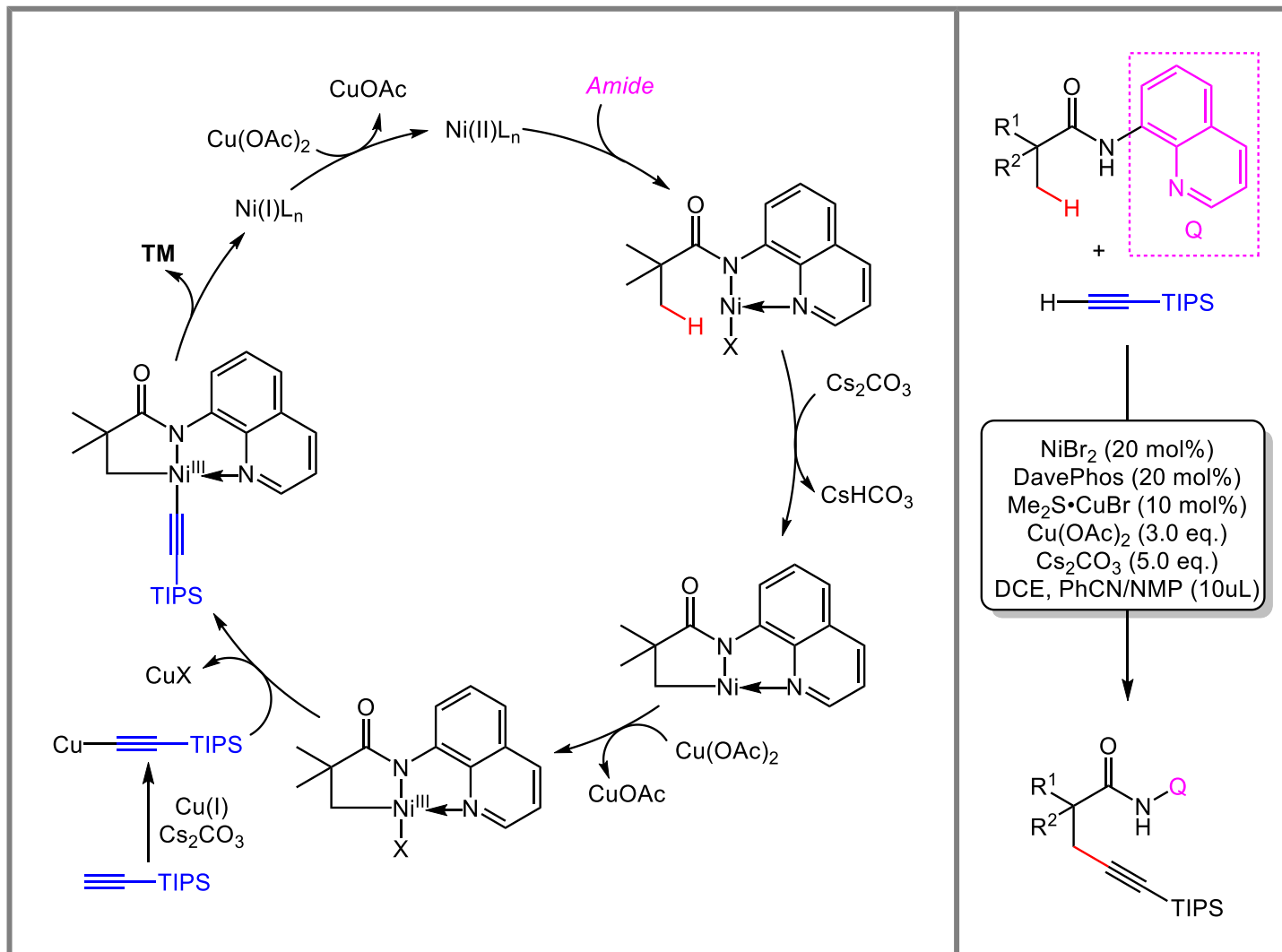
Maiti, S.; Maiti, D.\* *et al. Chem. Eur. J.* **2015**, *21*, 11320

# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



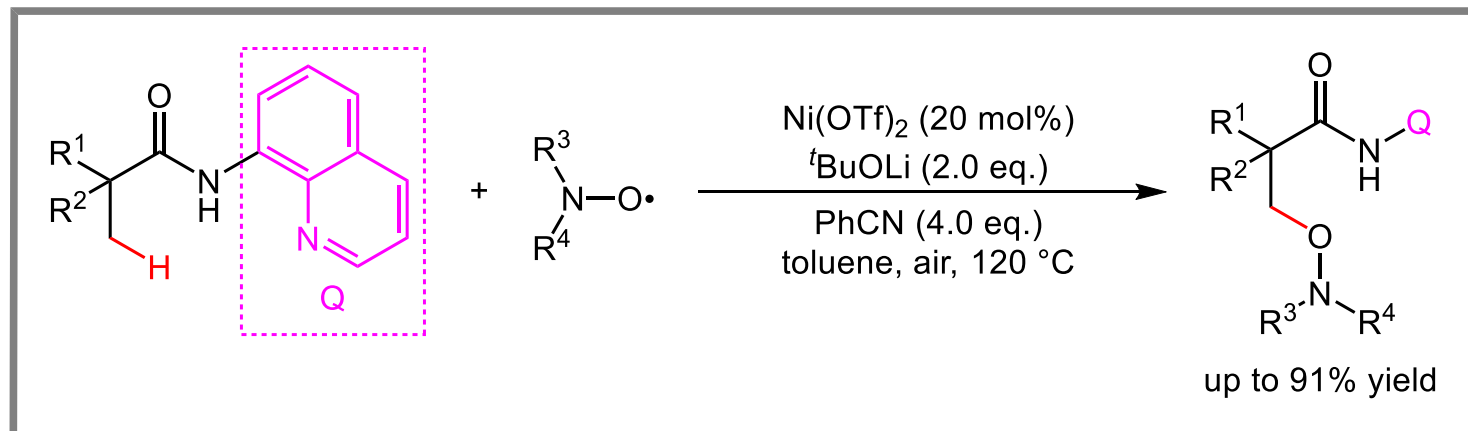
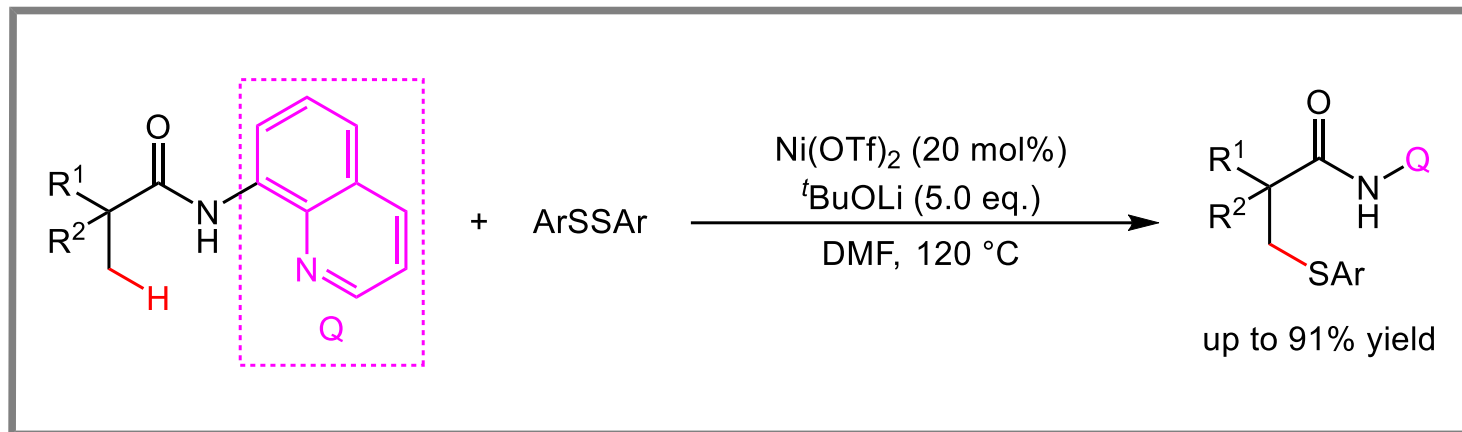
Liu, Y.-J.; Shi, B.-F.\* *et al. Chem. Commun.*, **2015**, 51, 7899  
Luo, F.-X.; Shi, Z.-J.\* *et al. Organometallics* **2017**, 36, 18

# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



Luo, F.-X.; Shi, Z.-J.\* *et al. Organometallics* **2017**, *36*, 18

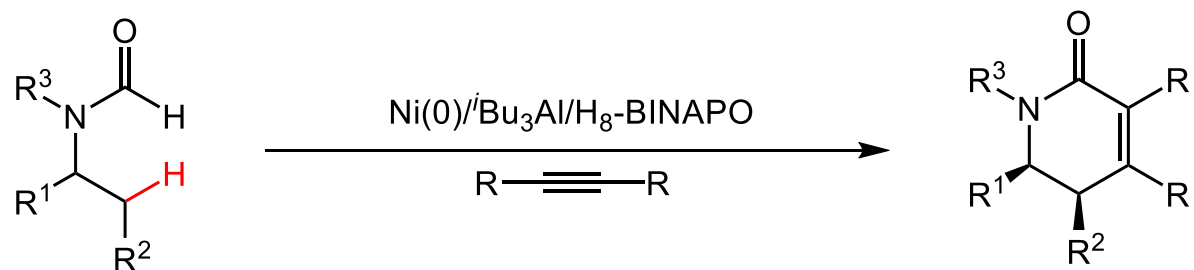
# Ni-Catalyzed C(sp<sup>3</sup>)-H Activation



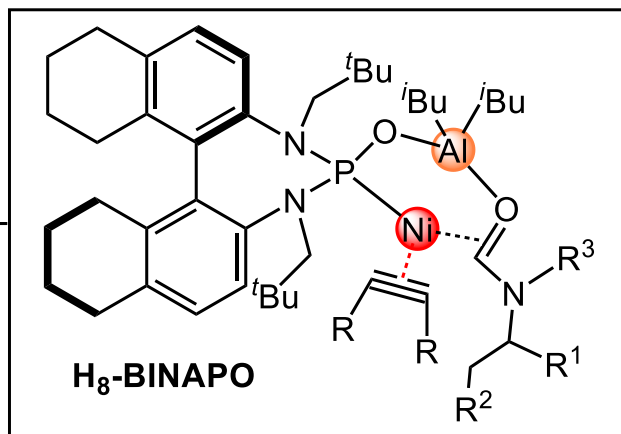
Ye, X.; Shi, X.\* *et al. Chem. Commun.*, **2015**, 51, 7863  
Wang, C.; You, J.\* *et al. Org. Lett.* **2017**, 19, 1690

# Project Synopsis

First example on enantioselective Ni-catalyzed C(sp<sup>3</sup>)-H activation

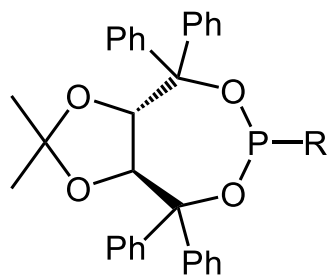
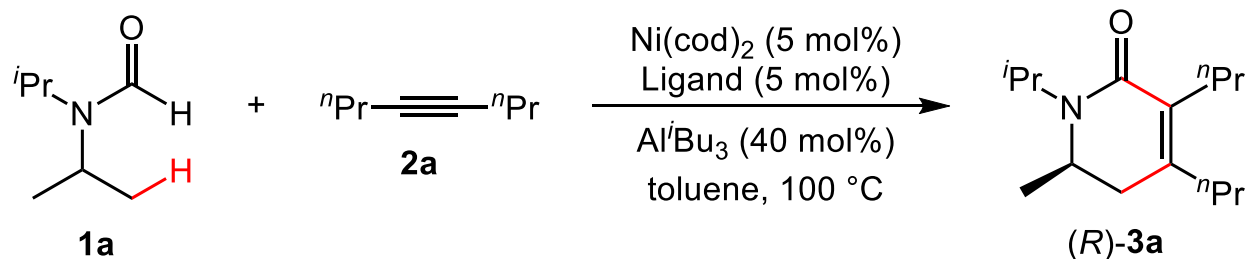


40-95% yield  
70-95% ee

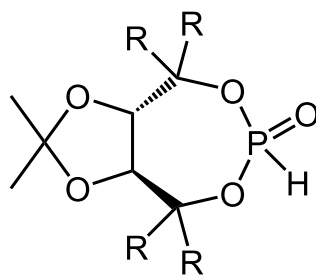




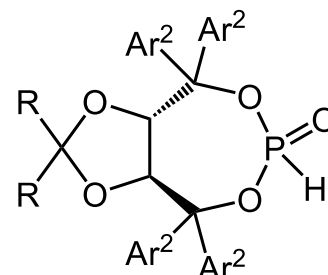
# Optimization of Reaction Conditions



*mono-Phos*



TADOPO



TADOPO

**L**<sub>1</sub>, R = OPh: 0

**L**<sub>2</sub>, R = NMe<sub>2</sub>: 40%, 40% ee

**L**<sub>3</sub>, R = Pip: 30%, 32% ee

**L**<sub>4</sub>, R = Ph: 90%, 44% ee

**L**<sub>5</sub>, R = Ar<sup>1</sup>: 97%, 48% ee

**L**<sub>6</sub>, R = Ar<sup>2</sup>: 98%, 67% ee

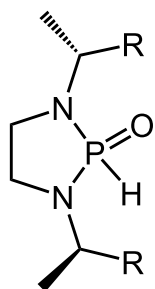
**L**<sub>7</sub>, R = Ph: 96%, 57% ee

**L**<sub>8</sub>, R = Cy: 94%, 68% ee

**L**<sub>9</sub>, R = <sup>i</sup>Pr: 98%, 65% ee

Ar<sup>1</sup> = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, Ar<sup>2</sup> = 2-MeC<sub>6</sub>H<sub>4</sub>

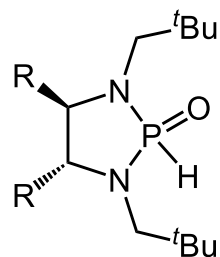
# Optimization of Reaction Conditions



DAPO

L<sub>10</sub>, R = Ph: 74%, 6% ee

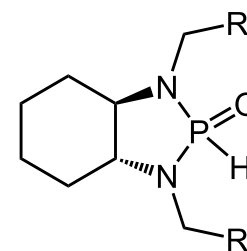
L<sub>11</sub>, R = 1-Np: 74%, 6% ee



DAPO

L<sub>12</sub>, R = Ph: 73%, 51% ee

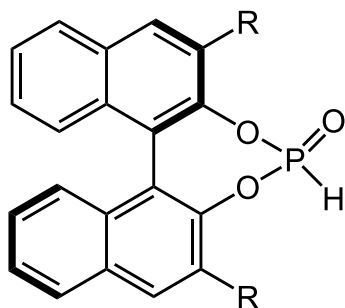
L<sub>13</sub>, R = 1-Np: 72%, 60% ee



DAPO

L<sub>14</sub>, R = Ph: 82%, 5% ee

L<sub>15</sub>, R = *t*Bu: 90%, 7% ee

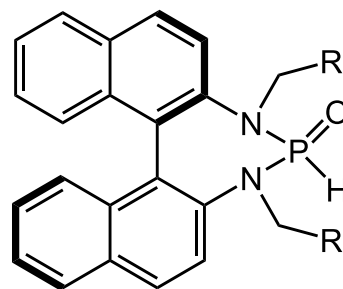


BINOPO

L<sub>16</sub>, R = H: 20%, 40% ee

L<sub>17</sub>, R = Et: 24%, 67% ee

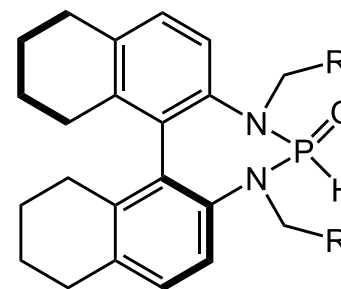
L<sub>18</sub>, R = TMS: 68%, 0% ee



BINAPO

L<sub>19</sub>, R = Ph: 72%, 23% ee

L<sub>20</sub>, R = *t*Bu: 86%, 46% ee

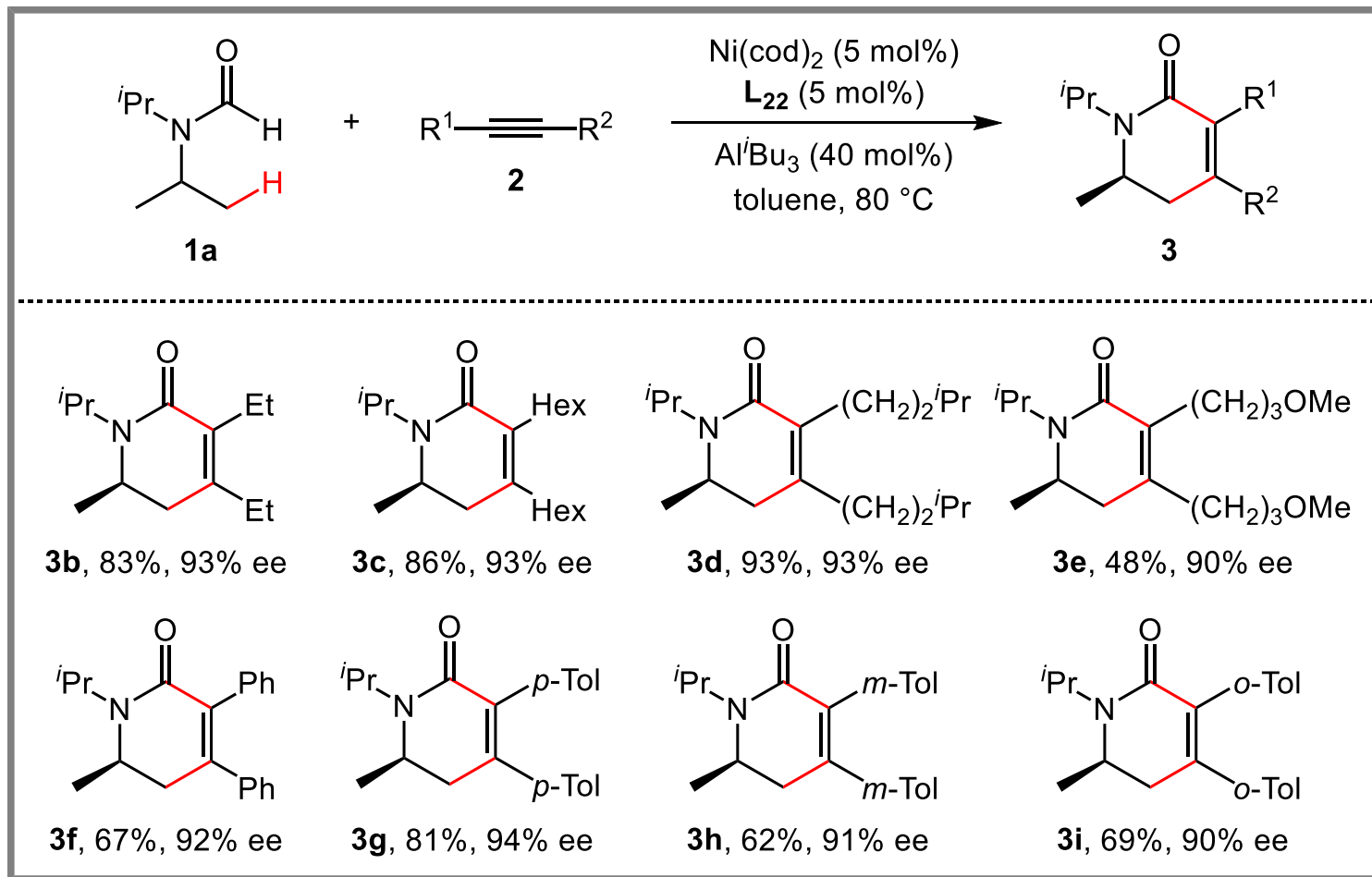


H<sub>8</sub>-BINAPO

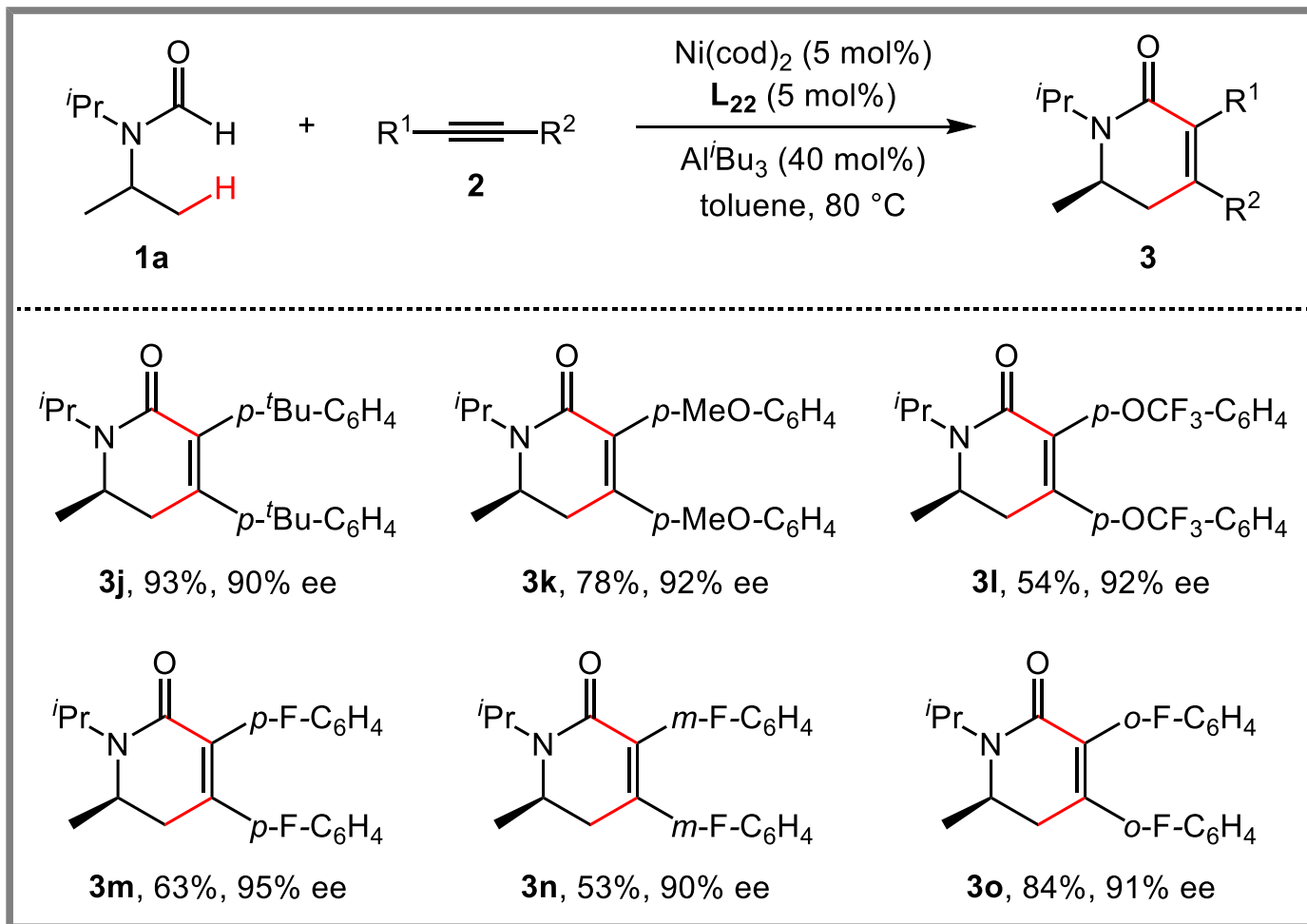
L<sub>21</sub>, R = Ph: 76%, 59% ee

L<sub>22</sub>, R = *t*Bu: 92%, 90% ee

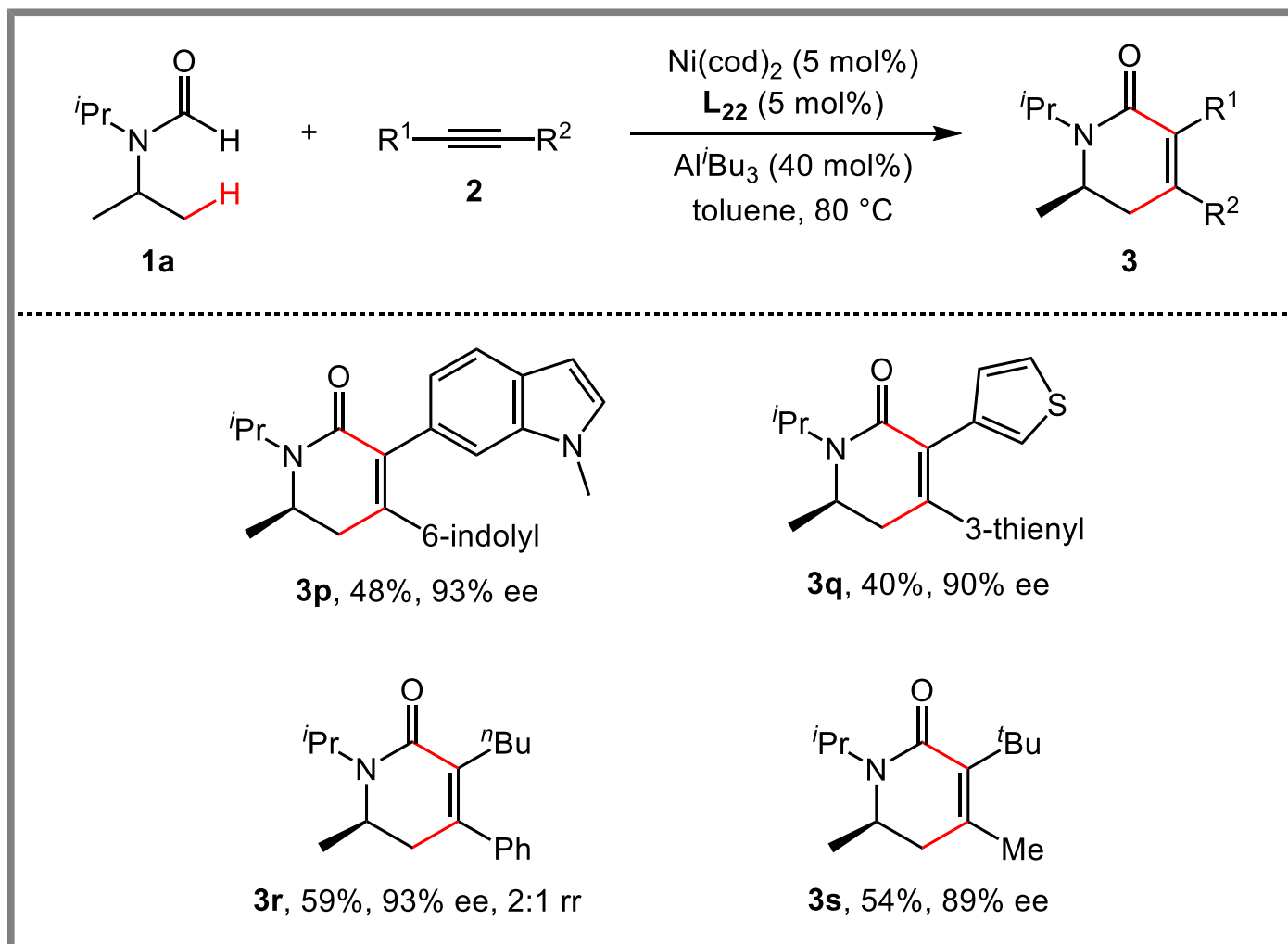
# Substrate Scope



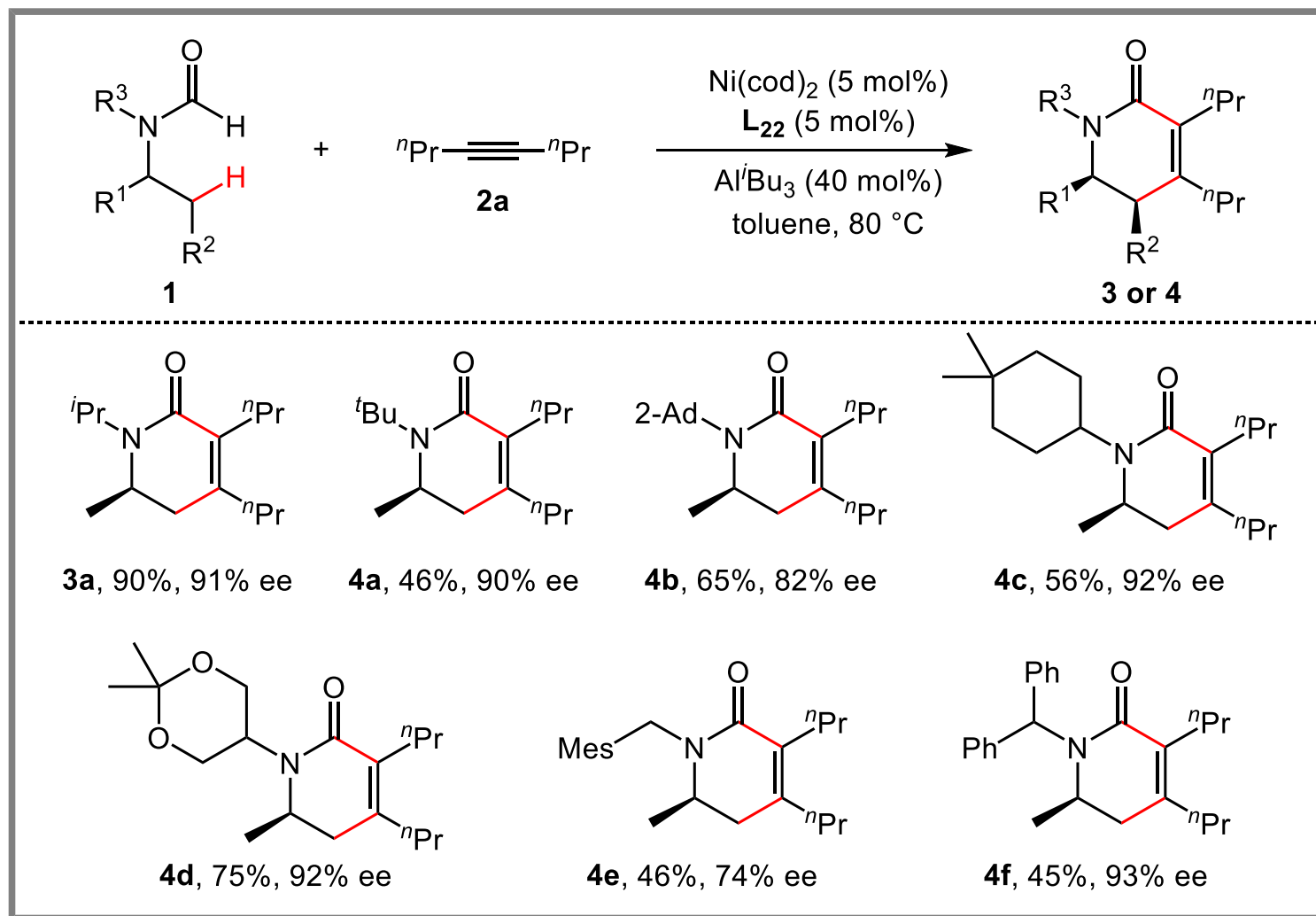
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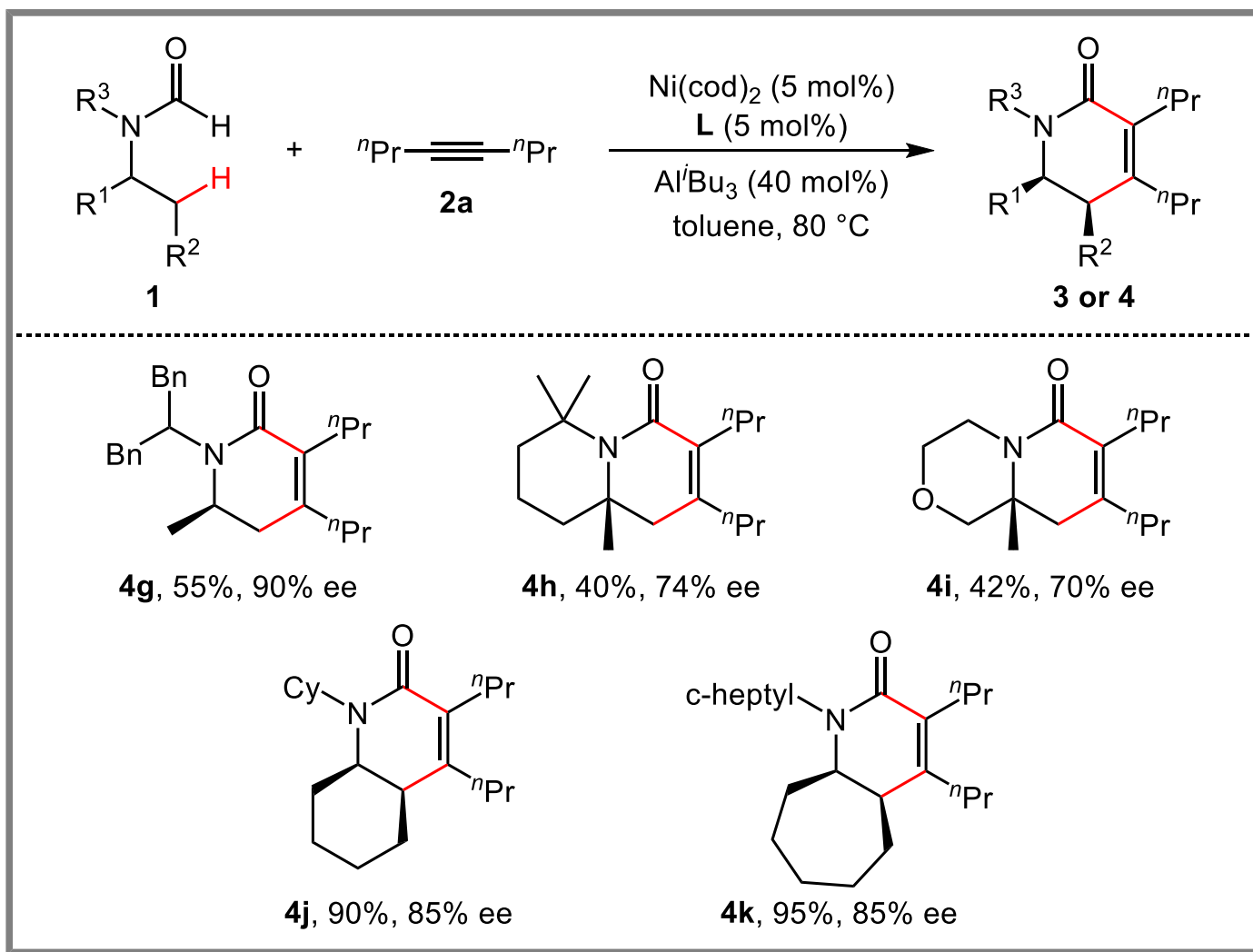
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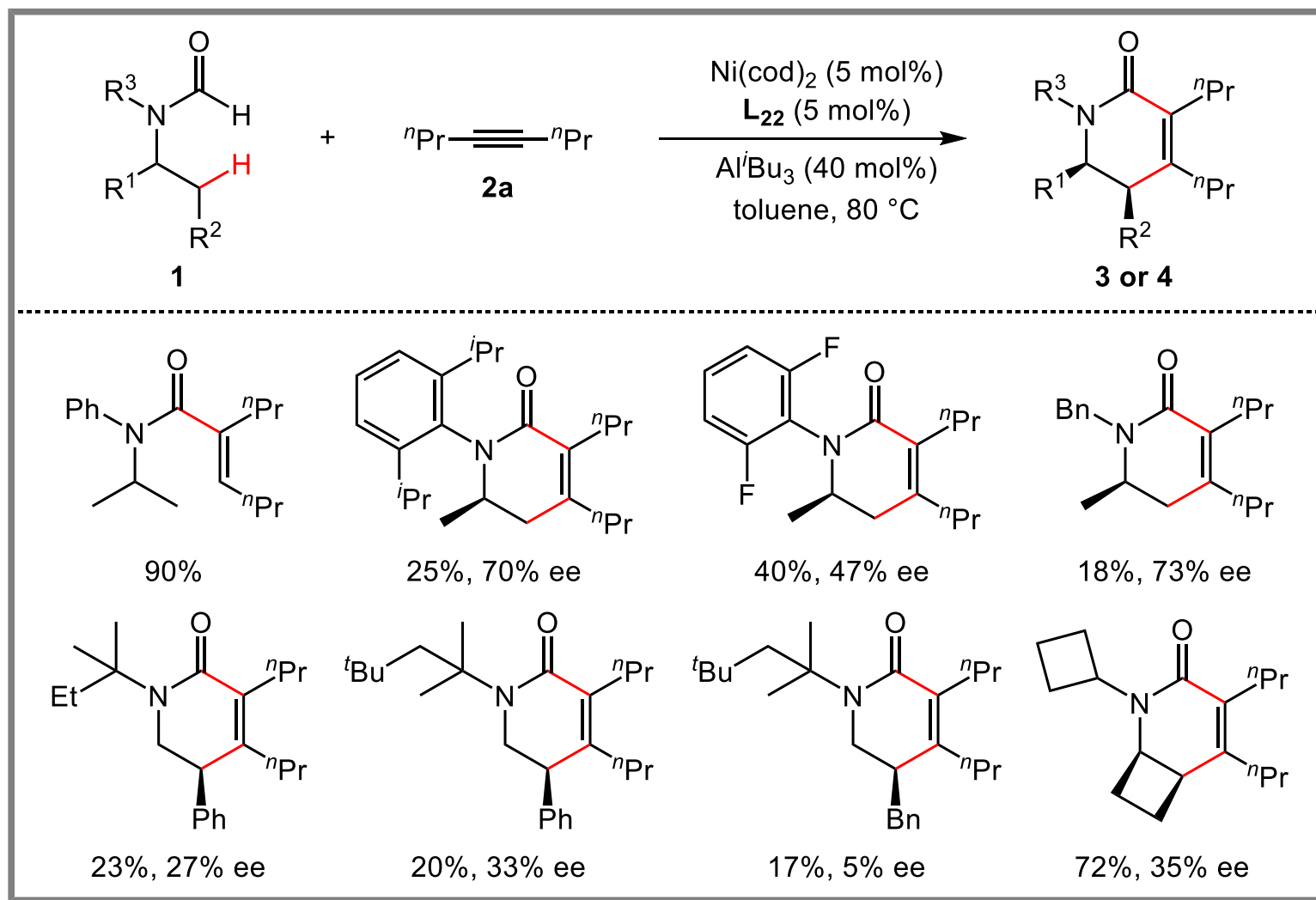
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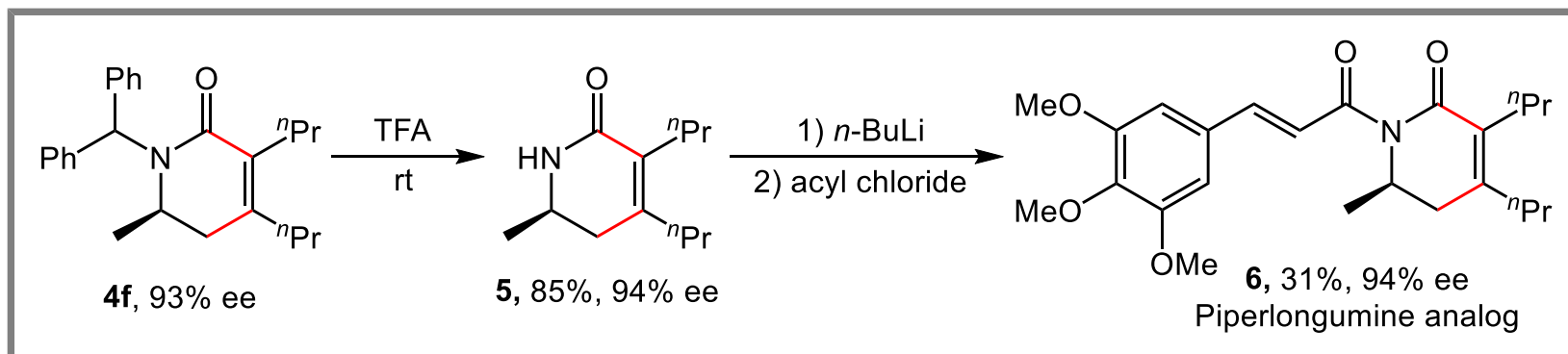


# Substrate Scope



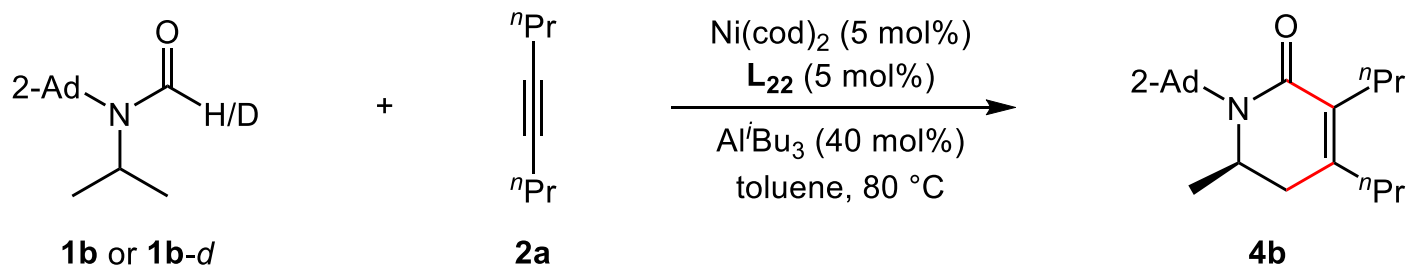


# Transformations of Products



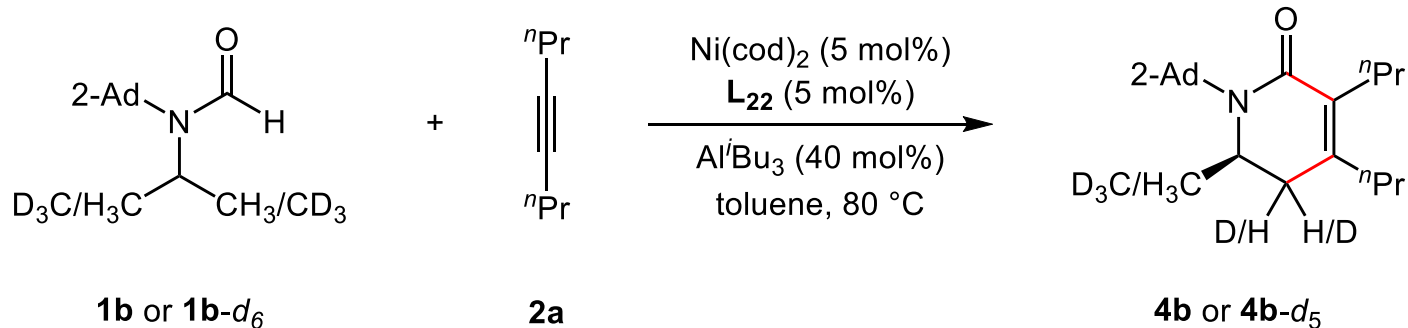
# Deuterium-labeling experiments

Kinetic isotope effect of formyl H



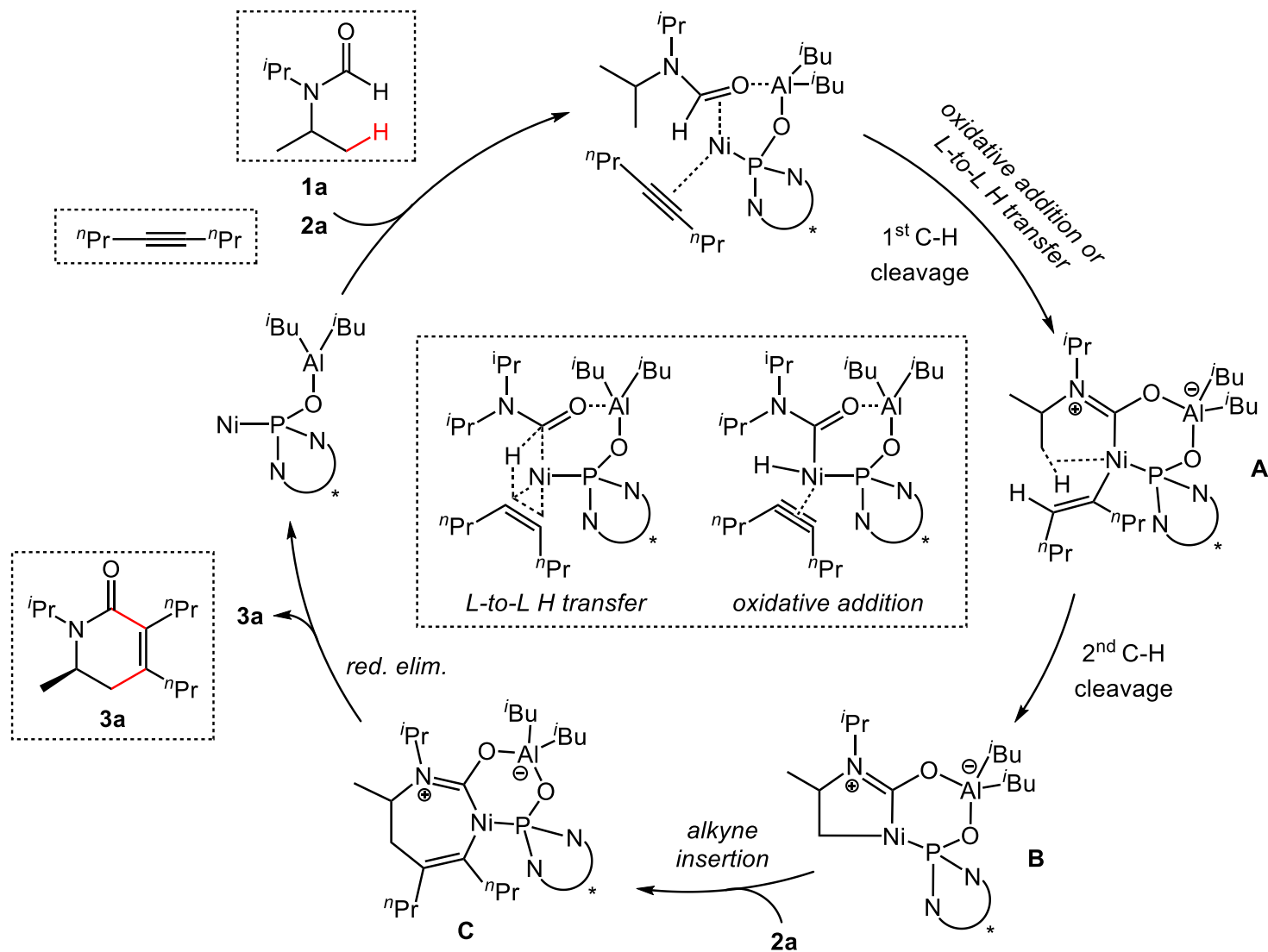
parallel experiments:  $k_{\text{H}}/k_{\text{D}} = 1.14$

Kinetic isotope effect of methyl H



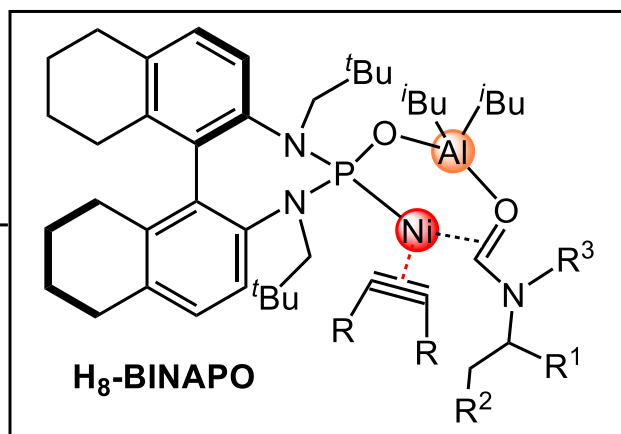
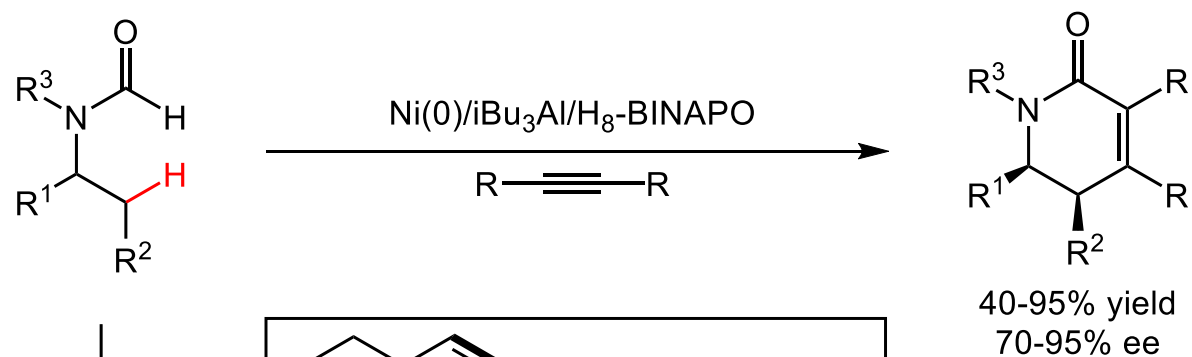
parallel experiments:  $k_{\text{H}}/k_{\text{D}} = 2.13$

# Proposed Mechanism



# Summary

First example on enantioselective Ni-catalyzed C(sp<sup>3</sup>)-H activation



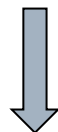
使用新型配体以较高的收率和对映选择性首次实现了镍催化的 sp<sup>3</sup>碳氢键活化，具有良好的底物适用范围和反应实用性。

# The First Paragraph

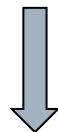
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## Writing Thought

碳氢键活化反应的重要性



碳氢键活化反应的发展现状



镍催化的碳氢键活化及本文的工作

# The First Paragraph

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Enantioselective transition metal-catalyzed C-H activation via C-H metallation represents one of the most convenient and economical routes to chiral molecules that exist in a large number of natural products and bioactive compounds such as pharmaceuticals and agrochemicals.

Extensively explored C-H bonds in these reactions are C(sp<sup>2</sup>)-H or C(sp)-H bonds of arenes, alkenes, aldehydes, imines, formamides or alkynes. In contrast, unreactive C(sp<sup>3</sup>)-H bonds such as primary, secondary and tertiary C(sp<sup>3</sup>)-H bonds are quite resistant to enantioselective activation by chiral metal complexes, because of steric hindrance around C(sp<sup>3</sup>)-H bonds and the lack of  $\pi$ -orbitals to interact with metals.

# The First Paragraph

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In the last two decades, relying on well-designed chiral ligands or chiral anions, precious metals such as Pd, Rh and Ir have been capable of catalyzing a broad range of enantioselective C(sp<sup>3</sup>)-H bond activation reactions, providing good yields and high ee. However, same strategies are in general ineffective to most 3d-transition metals that are very sensitive to the structure of substrates and ligands. So far, only one successful example has been reported by Matsunaga, Yoshino and co-workers, who used achiral Co<sup>III</sup> with an amino acid derivative as a chiral anion to facilitate an enantioselective amidation of primary C(sp<sup>3</sup>)-H bonds of thioamides. Given appealing advantages of 3d metals, including high earth abundance, low cost and low bio-toxicity, the development of 3d metal catalyzed enantioselective C(sp<sup>3</sup>)-H bond activation reactions are in high demand.

# The First Paragraph

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Till now, although great progress has been achieved for Ni-catalyzed C-H bond activation and even enantioselective Ni-catalyzed C(sp<sup>2</sup>)-H bond activation, enantioselective Ni-catalyzed aliphatic C(sp<sup>3</sup>)-H bond activation still remains an elusive challenge. Herein, we used a new type of H8-bi(2-naphthylamine)-derived chiral phosphine oxide (H8-BINAPO) to enable an enantioselective Ni-catalyzed C(sp<sup>3</sup>)-H activation of formamides for the first time, providing a series of nitrogen-containing heterocycles in 40–95% yield and 70–95% ee. The H8-BINAPO-ligated Ni-Al bimetallic catalyst may play a critical role in enabling the formyl C(sp<sup>2</sup>)-H bond activation, and accelerating subsequent aliphatic C(sp<sup>3</sup>)-H activation by orienting nickel.

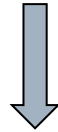


# The Last Paragraph

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## Writing Thought

对本文工作的总结



对新配体的应用进行展望

# The Last Paragraph

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In summary, we have developed the first example on enantioselective Ni-catalyzed aliphatic C(sp<sup>3</sup>)-H bond activation of formamides, providing a series of chiral N-containing heterocycles in 40–95% yield and 70–95% ee. Various dialkyl, diaryl and alkylaryl alkynes, together with primary and secondary C(sp<sup>3</sup>)-H bonds were well compatible. The newly-developed H8-BINAPO ligand could be applied in a wider range of enantioselective C-H activation reactions in future.

# Representative Examples

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- Till now, although **great progress has been achieved for** Ni-catalyzed C-H bond activation **and even** enantioselective Ni-catalyzed C(sp<sup>2</sup>)-H bond activation, enantioselective Ni-catalyzed aliphatic C(sp<sup>3</sup>)-H bond activation **still remains** an elusive challenge.

某项工作，甚至更困难一项工作已经取得了巨大进展，但本文的工作依然是一个重大的挑战（强调本文工作的难度）

- **To gain more insights into the mechanism**, we conducted deuterium-labeling experiments to determine kinetic isotope effect of the activation of two C-H bonds of substrate **1b**.

为了更深入的了解反应的机理

- **Given appealing advantages of 3d metals**, including high earth abundance, low cost and low bio-toxicity, the development of 3d metal catalyzed enantioselective C(sp<sup>3</sup>)-H bond activation reactions are in high demand.

考虑到.....的吸引力

# Acknowledgement

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*Thanks for Your Attention*