

Literature Report VII

Photoinduced Copper-Catalyzed Asymmetric C(sp³)-H Alkynylation of Cyclic Amines by Intramolecular 1,5-Hydrogen Atom Transfer

Reporter: Yu-Qing Bai

Checker: Zheng Liu

Date: 2022-10-12

Guo, Y.*; Qi, X.*; Zhang, G.* *et al.*
Angew. Chem. Int. Ed. **2022**, 61, e202208232.

CV of Prof. Guozhu Zhang



Research:

- Cheap transition metal-catalyzed asymmetric bonding of halogenated alkane radicals;
- Transition metal-catalyzed highly selective ring formation of cheap chemicals.

Background:

- ❑ **1996-2000** B.S., Nankai University
- ❑ **2000-2003** M.S., Nankai University
- ❑ **2006-2011** Ph.D., University of Nevada, Reno & University of California, UCSB
- ❑ **2011-2013** Postdoc., Harvard University
- ❑ **2013-2020** Professor, Shanghai Institute of Organic Chemistry
- ❑ **2020-Now** Professor, Central China Normal University

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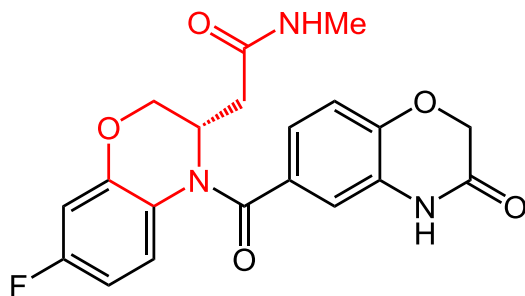
1 Introduction

2 Photoinduced Copper-Catalyzed Asymmetric C(sp³)-H Alkynylation

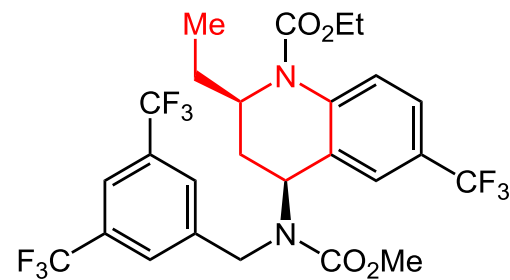
3 Summary

Introduction

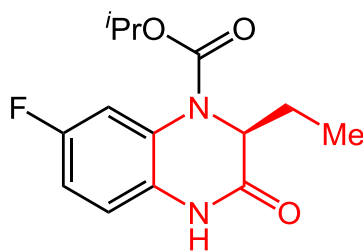
Bioactive Compounds Containing α -Chiral Cyclic Amines



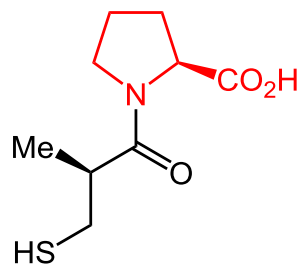
AZD-9977



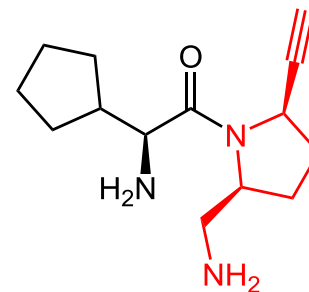
Torcetrapib



Opaviraline



Captopril

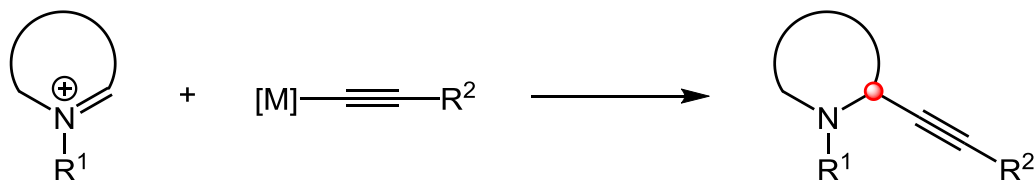


DPP4 activity

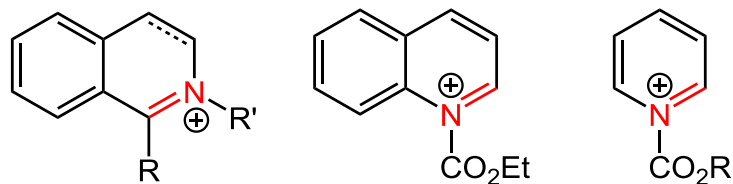
Njardarson, J. T. *et al. J. Med. Chem.* **2014**, *57*, 10257

Introduction

A. Nucleophilic Addition of Alkynylmetal Species to Cyclic Iminium Ions



B. Typical Cyclic Iminium Ions in Enantioselective Alkynylations

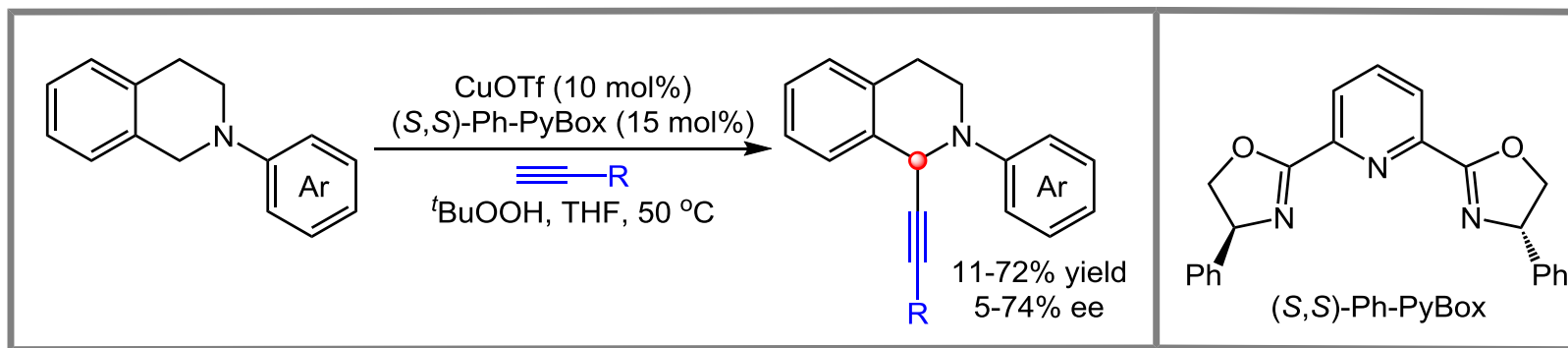


- ◆ stabilized iminium ions by resonance
- ◆ lack of acidic β-hydrogens, no E1 elimination

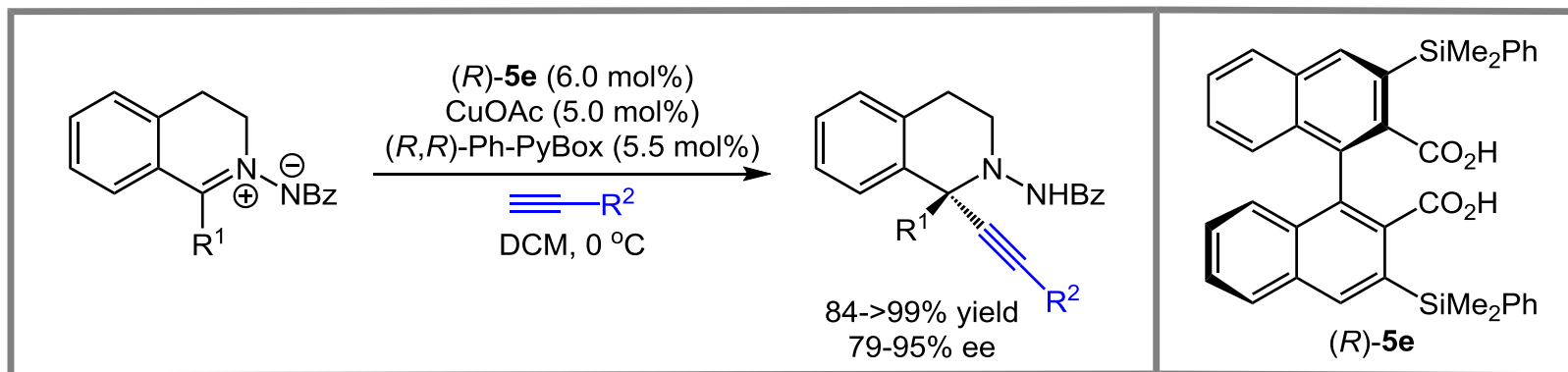
enantioselective
addition (few)

Introduction

Addition of Alkynylmetal to **Stabilized** Cyclic Iminium Ions



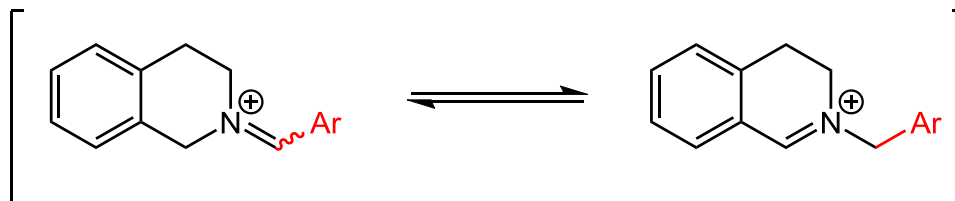
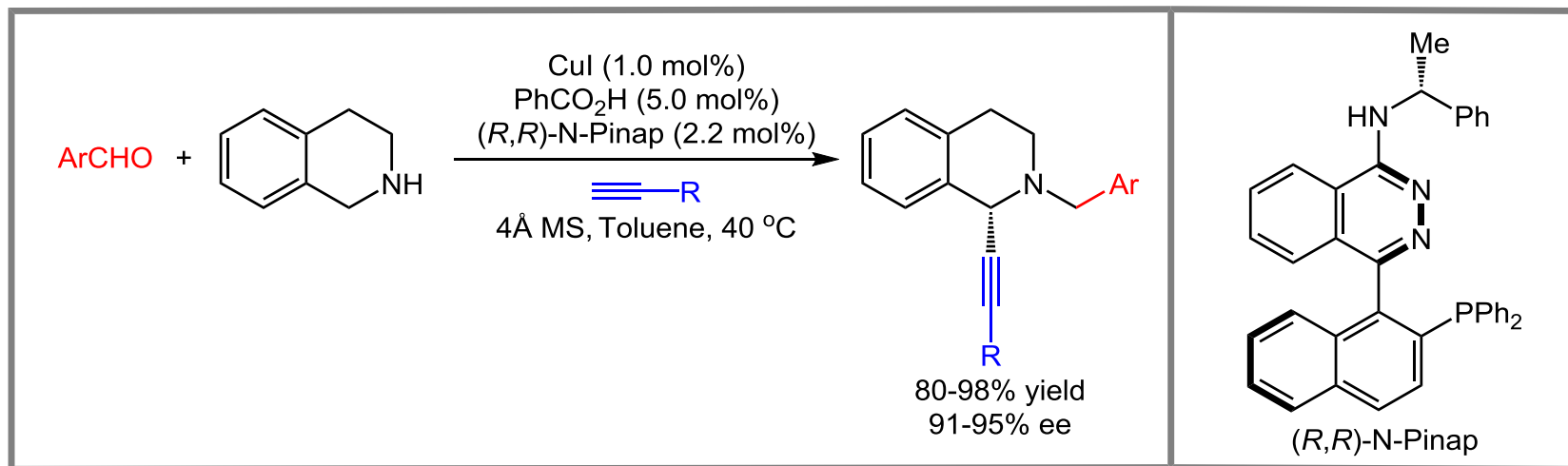
Li, C.-J. *et al. Org. Lett.* **2004**, 6, 4997



Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2011**, 50, 8952

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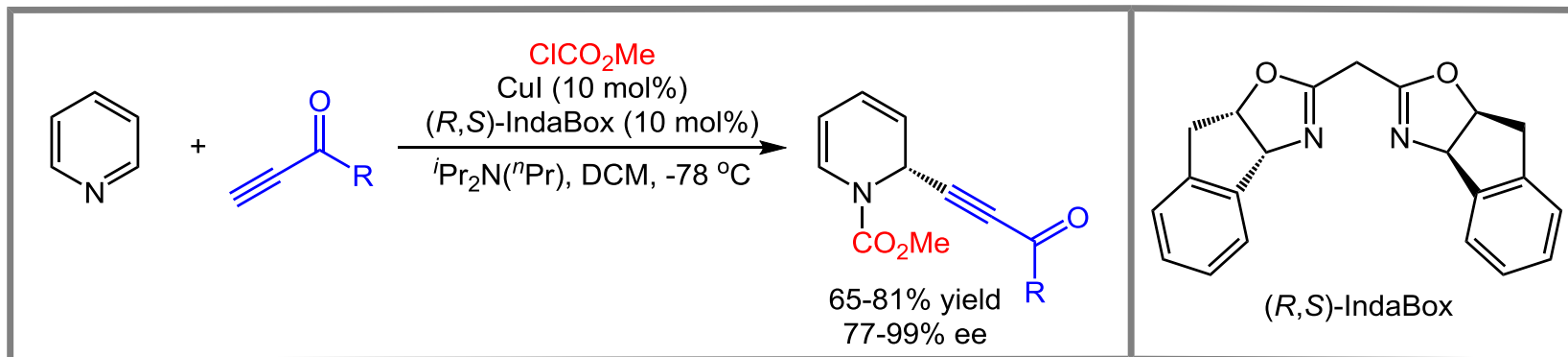
Addition of Alkynylmetal to **Stabilized** Cyclic Iminium Ions



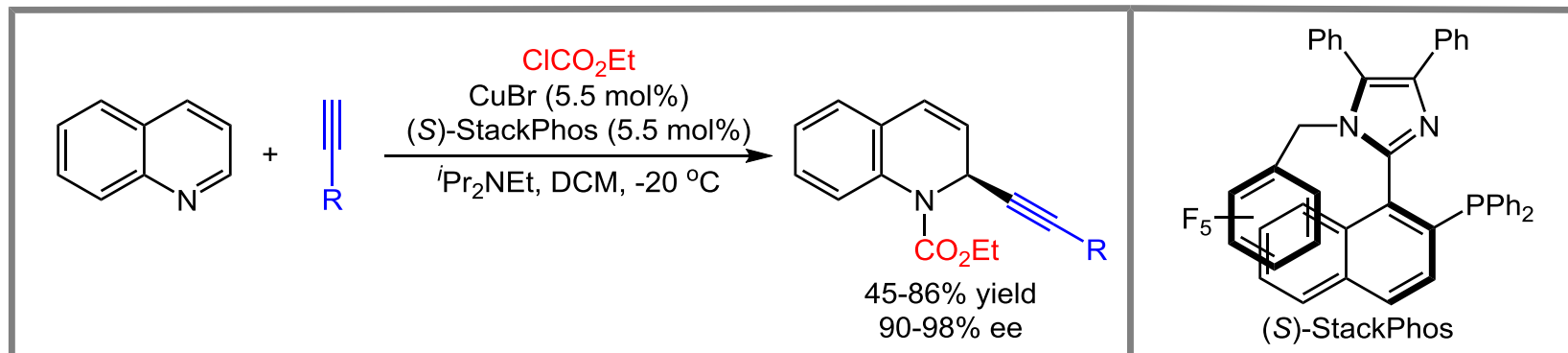
Ma, S. *et al.* *Angew. Chem. Int. Ed.* **2014**, 53, 277

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Addition of Alkynylmetal to **Stabilized** Cyclic Iminium Ions



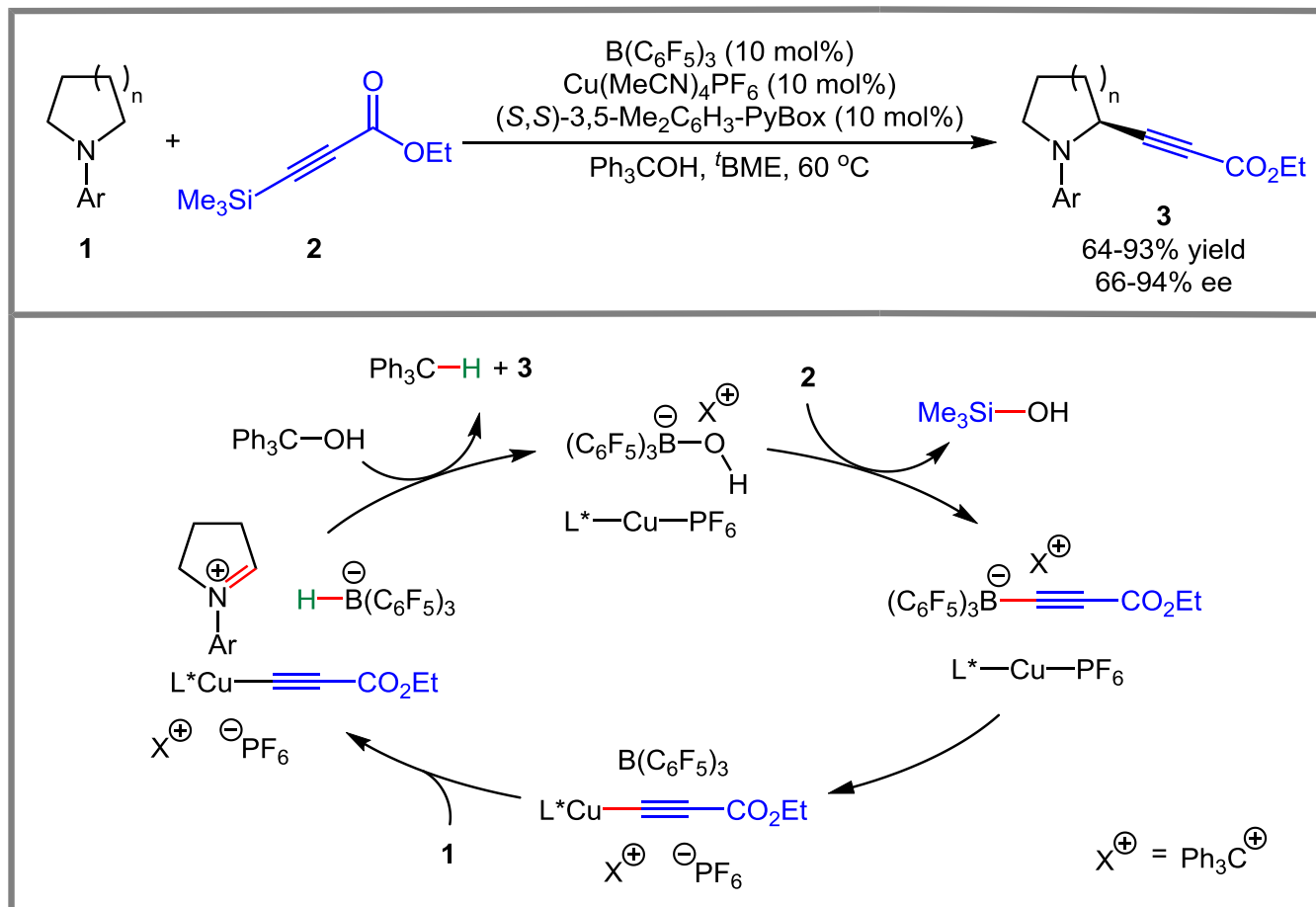
Ma, D. *et al. J. Am. Chem. Soc.* **2007**, 129, 9300



Aponick, A. *et al. Angew. Chem. Int. Ed.* **2015**, 54, 15202

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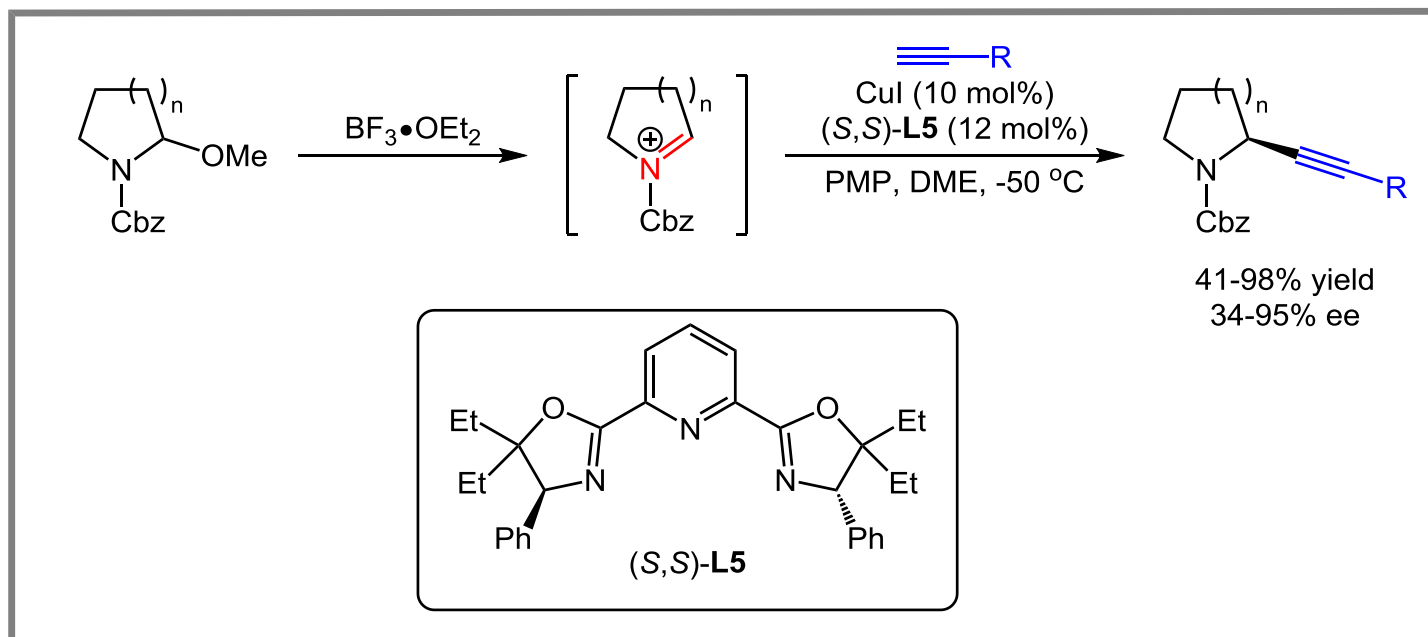
Addition of Alkynylmetal to **Unstabilized** Cyclic Iminium Ions



Wasa, M. *et al.* *J. Am. Chem. Soc.* **2020**, *142*, 16493

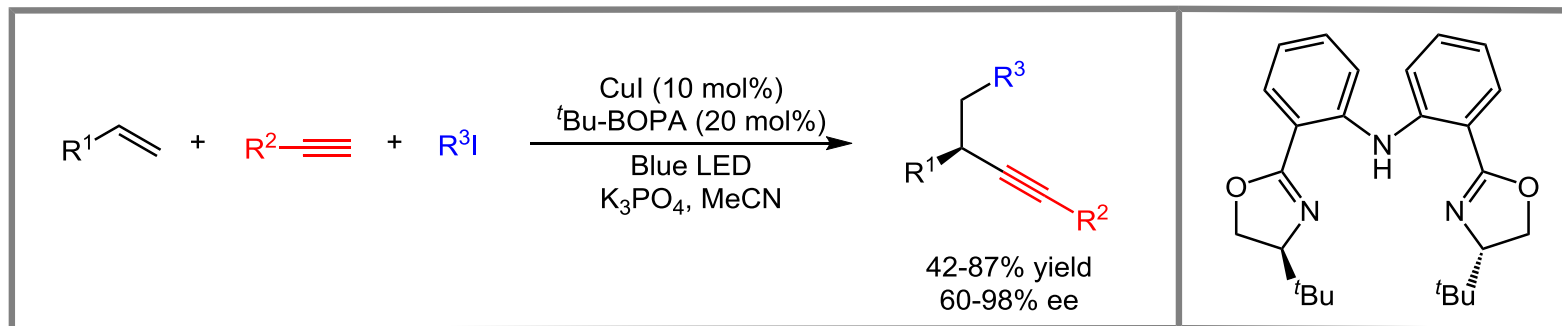
Introduction

Addition of Alkynylmetal to **Unstabilized** Cyclic Iminium Ions



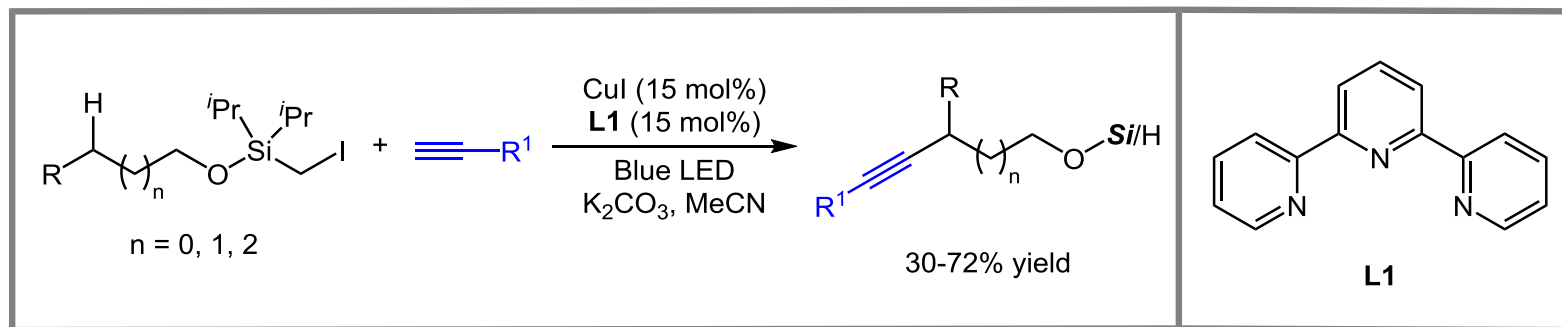
Introduction

Photoinduced Copper-Catalyzed Asymmetric Coupling Strategy



Zhang, G. *et al. Org. Lett.* **2020**, *22*, 1490

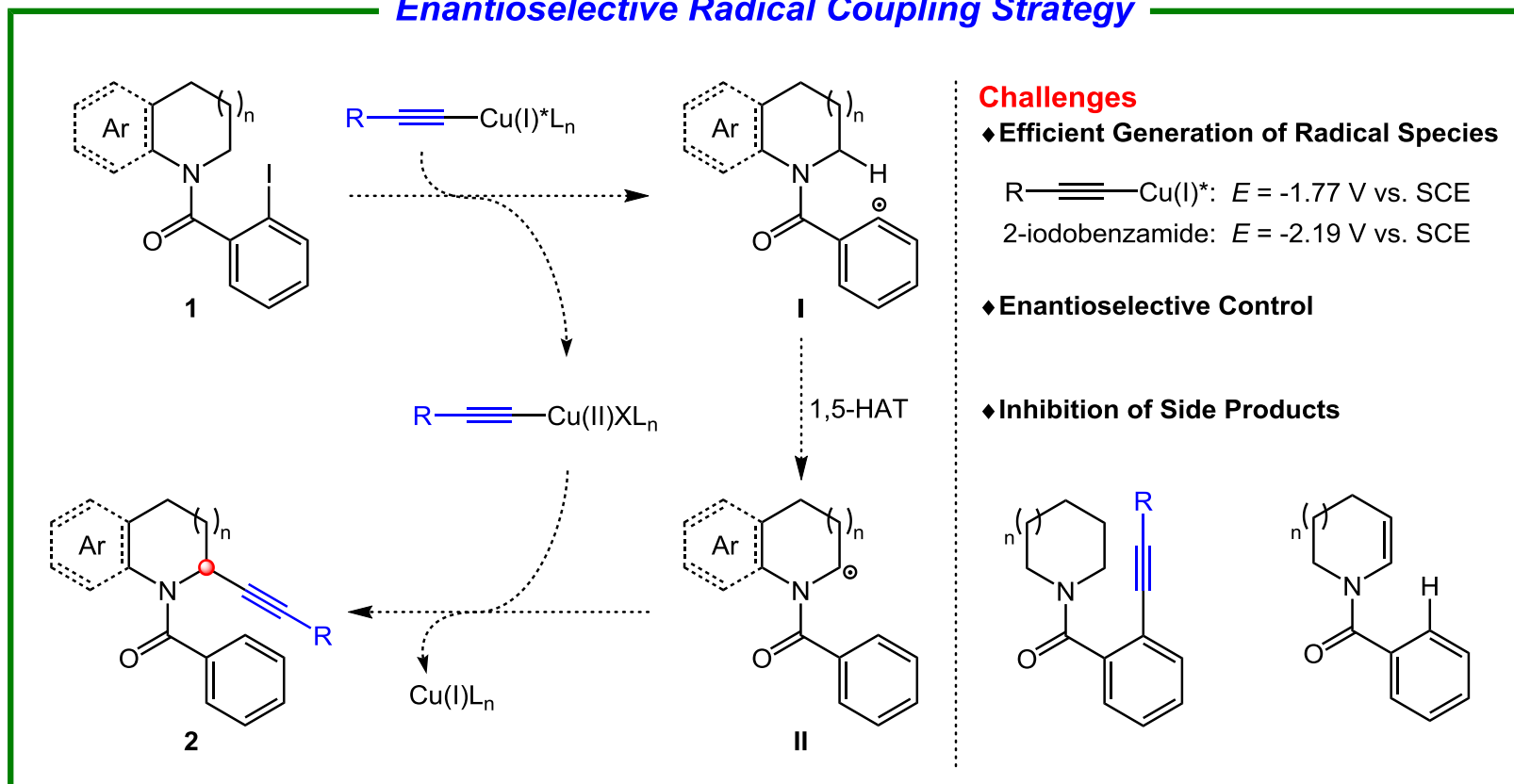
Photoinduced Copper-Catalyzed Alkynylation of Remote C-H Bonds



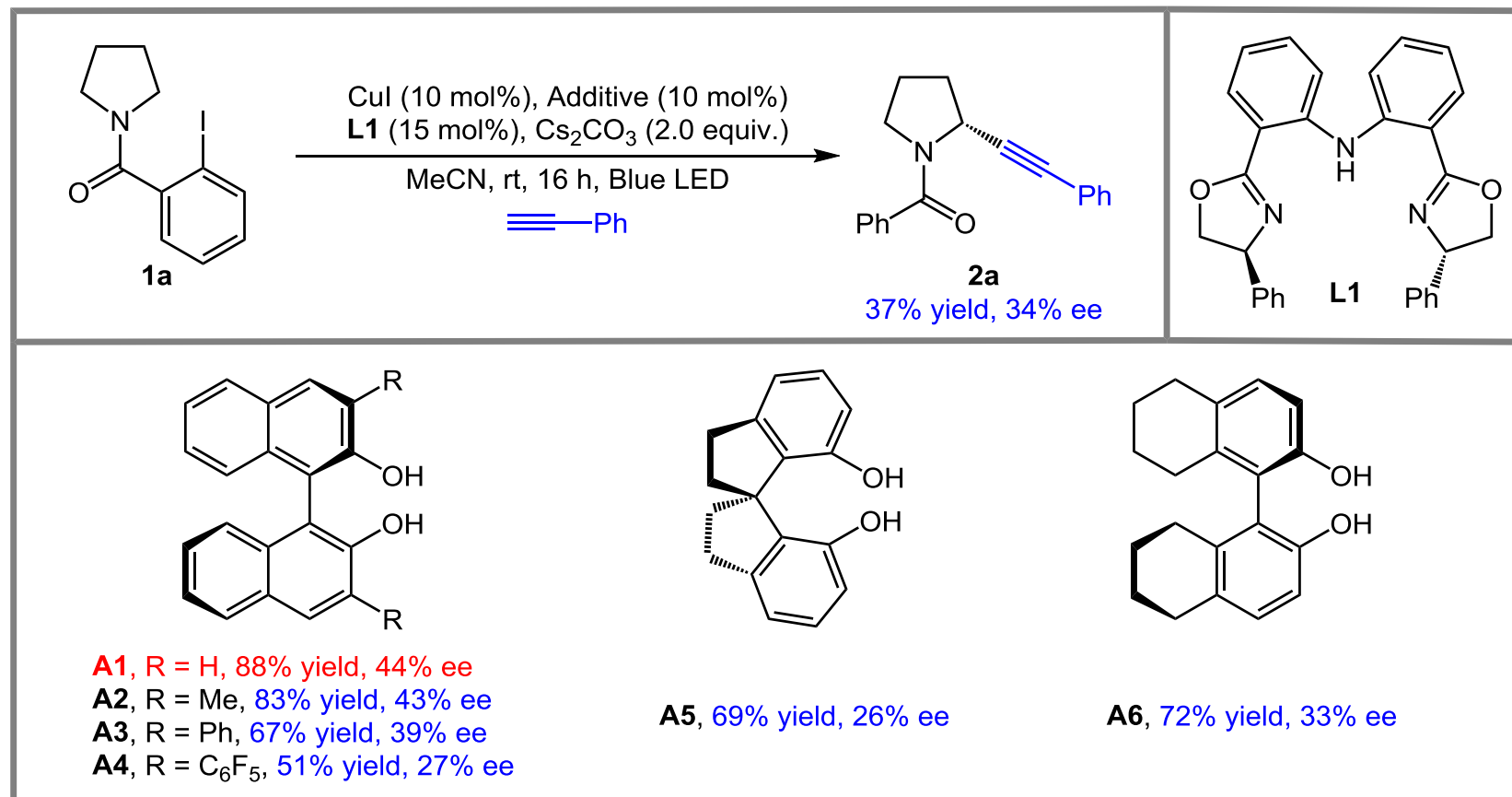
Zhang, G. *et al. Chem. Sci.* **2021**, *12*, 4836

Project Synopsis

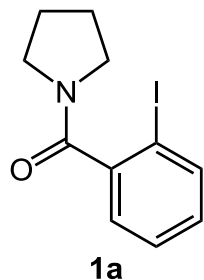
Enantioselective Radical Coupling Strategy



Optimization of Reaction Conditions

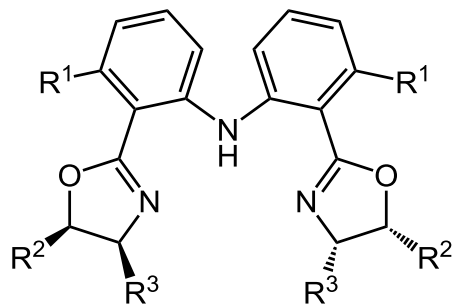
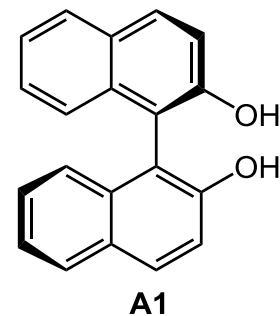
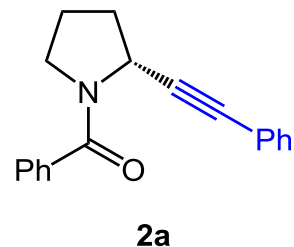


Optimization of Reaction Conditions



CuI (10 mol%), **A1** (10 mol%)
Ligand (15 mol%), Cs₂CO₃ (2.0 equiv.)

MeCN, rt, 16 h, Blue LED



L1, R¹ = R² = H, R³ = Ph

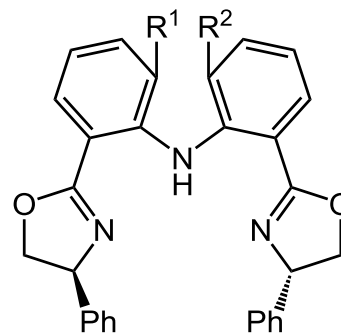
88% yield, 44% ee

L2, R¹ = H, R² = R³ = Ph

50% yield, 7% ee

L3, R¹ = F, R² = H, R³ = Ph

85% yield, 42% ee



L4, R¹ = Cl, R² = H

82% yield, 55% ee

L5, R¹ = R² = Cl

81% yield, 93% ee

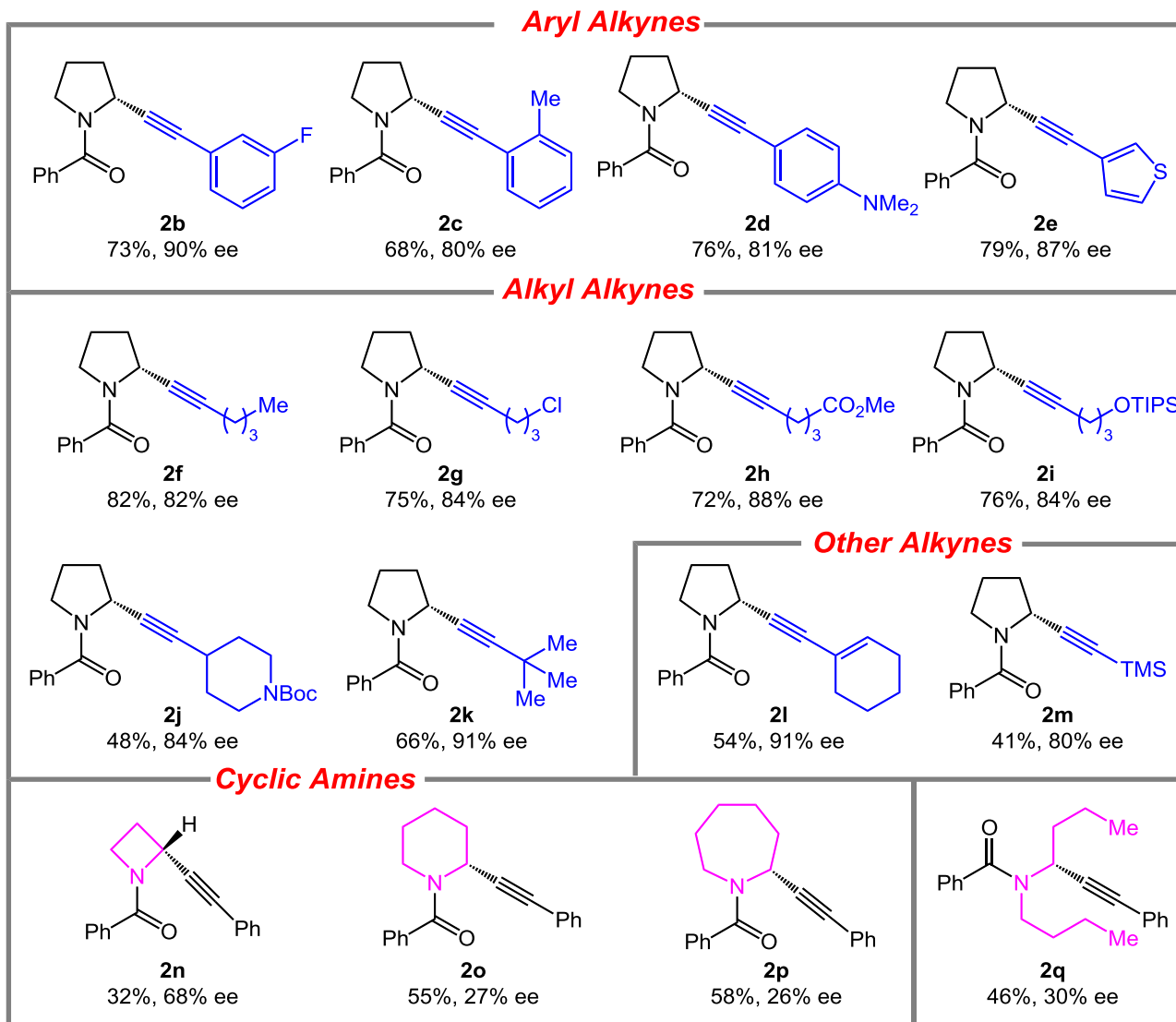
L6, R¹ = R² = F

84% yield, 80% ee

L7, R¹ = R² = Br

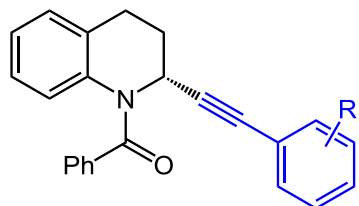
27% yield, 20% ee

Substrate Scope

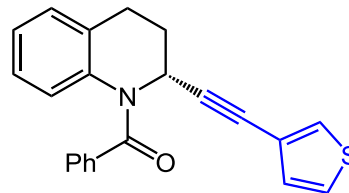


Substrate Scope

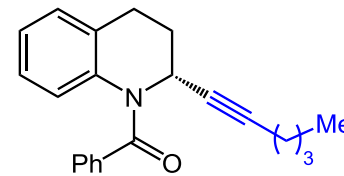
Alkynes



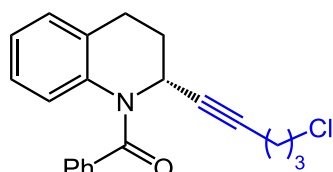
4a, R = H, 62%, 90% ee
4b, R = 2-Me, 53%, 84% ee
4c, R = 2-OMe, 50%, 82% ee
4d, R = 3-OMe, 59%, 88% ee
4e, R = 4-OMe, 61%, 87% ee
4f, R = 4-NMe₂, 48%, 88% ee



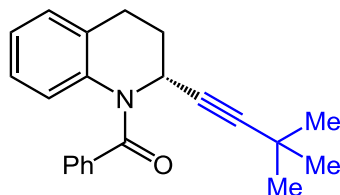
4g
55%, 86% ee



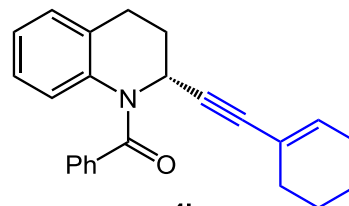
4h
64%, 84% ee



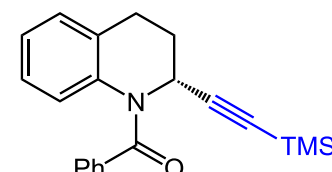
4i
57%, 80% ee



4j
42%, 81% ee

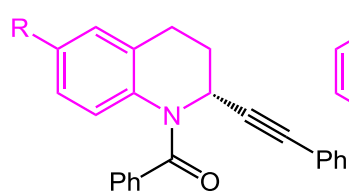


4k
56%, 88% ee

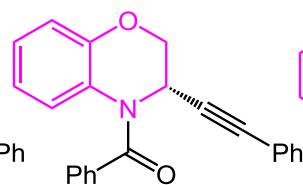


4l
45%, 84% ee

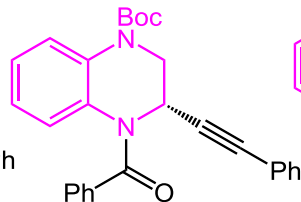
Benzo-fused Cyclic Amines



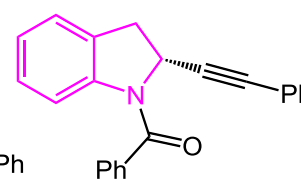
4m, R = F, 59%, 85% ee
4n, R = Br, 48%, 85% ee
4o, R = OMe, 53%, 82% ee



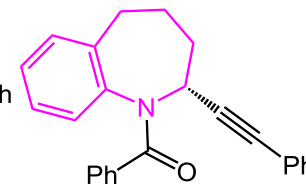
4p, 56%, 84% ee



4q, 37%, 84% ee



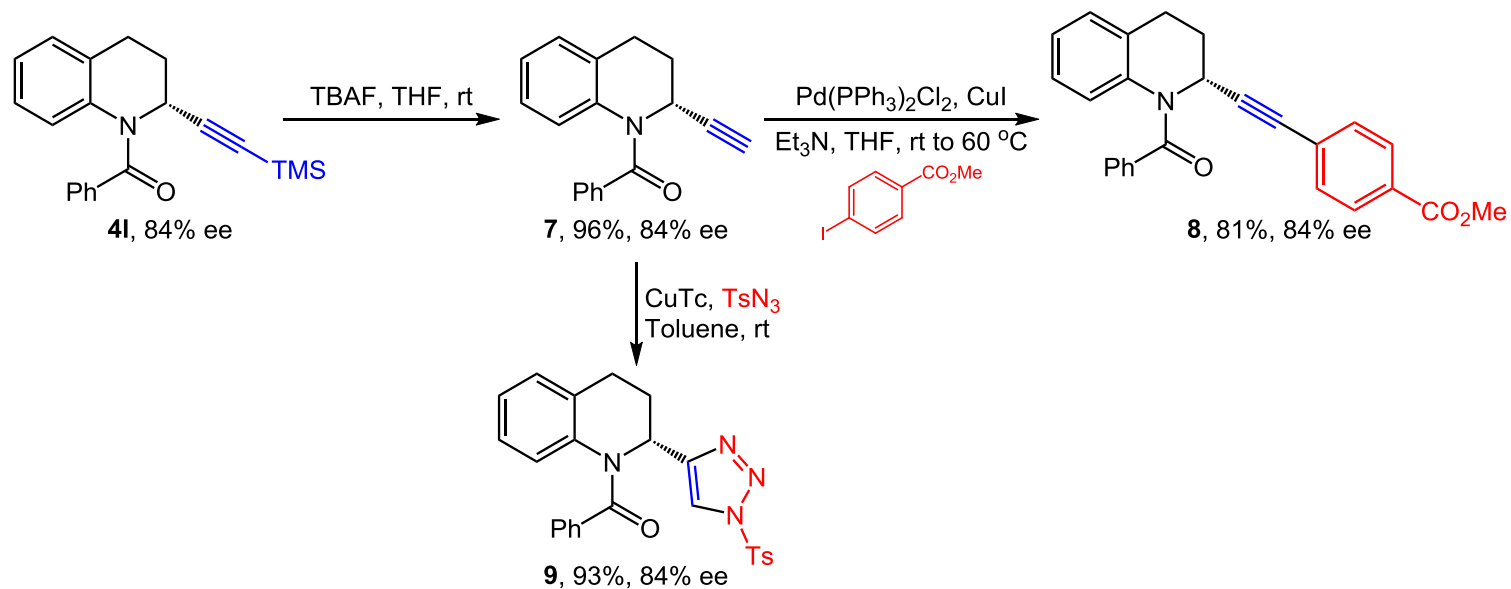
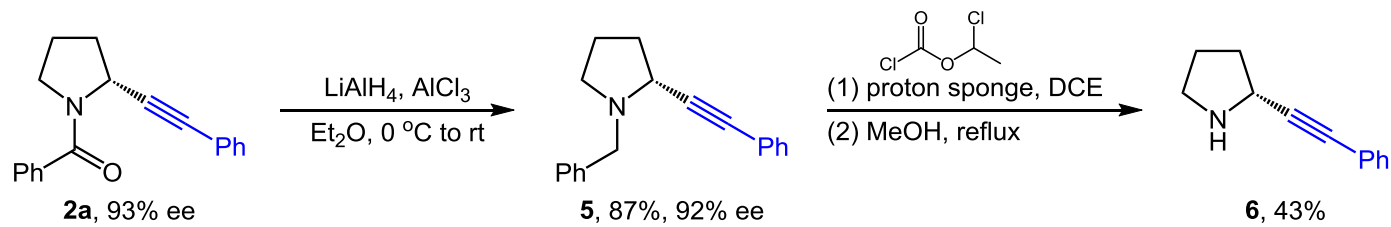
4r, 50%, 75% ee^b



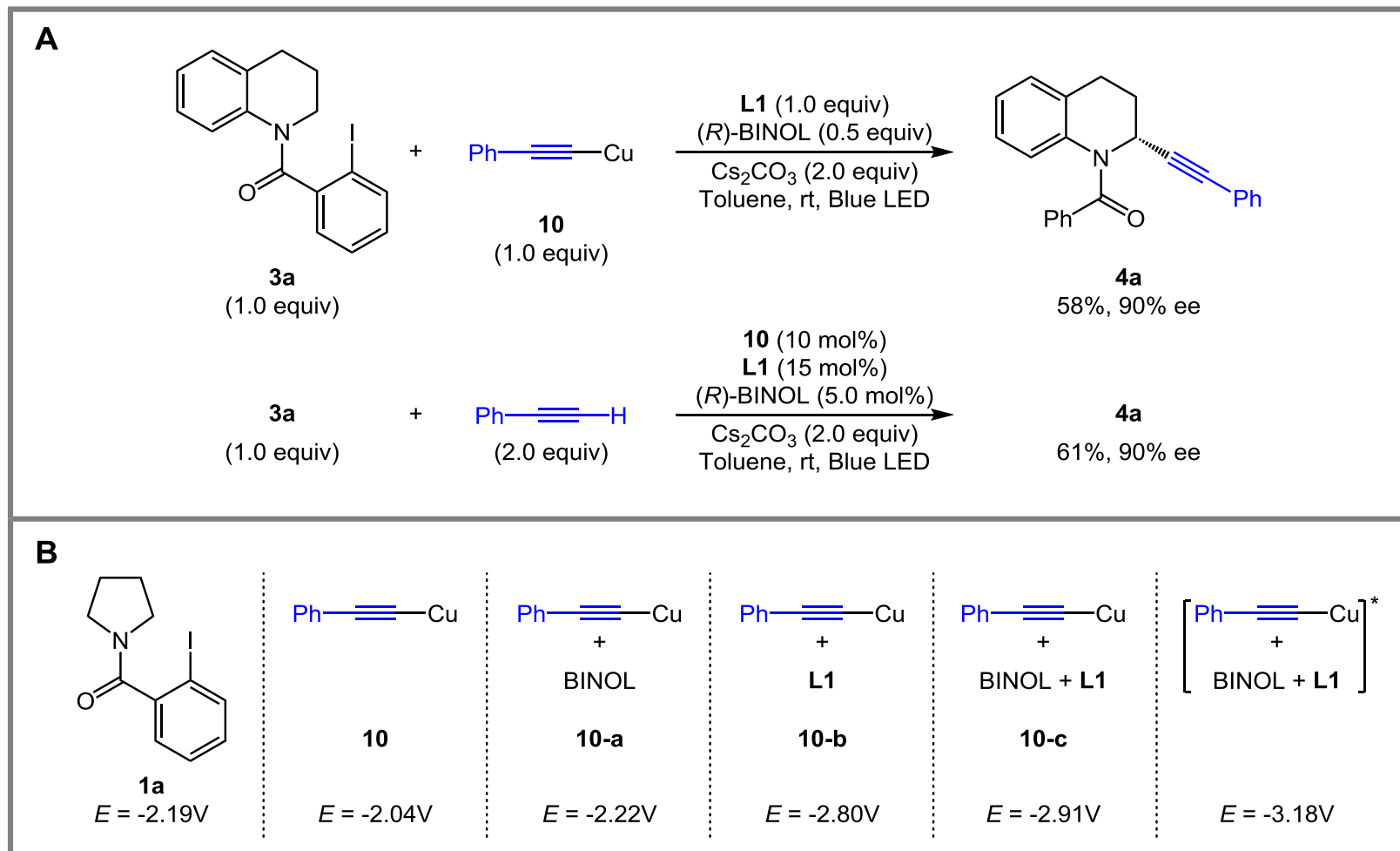
4s, 54%, 81% ee

Reaction conditions: **3** (0.1 mmol), alkyne (0.2 mmol), Cul (10 mol%), **A1** (5.0 mol%), **L1** (15 mol%), Cs₂CO₃ (0.2 mmol) in toluene (0.1 M) at rt under Blue LED for 48 h. [b] Use **L5** as Ligand.

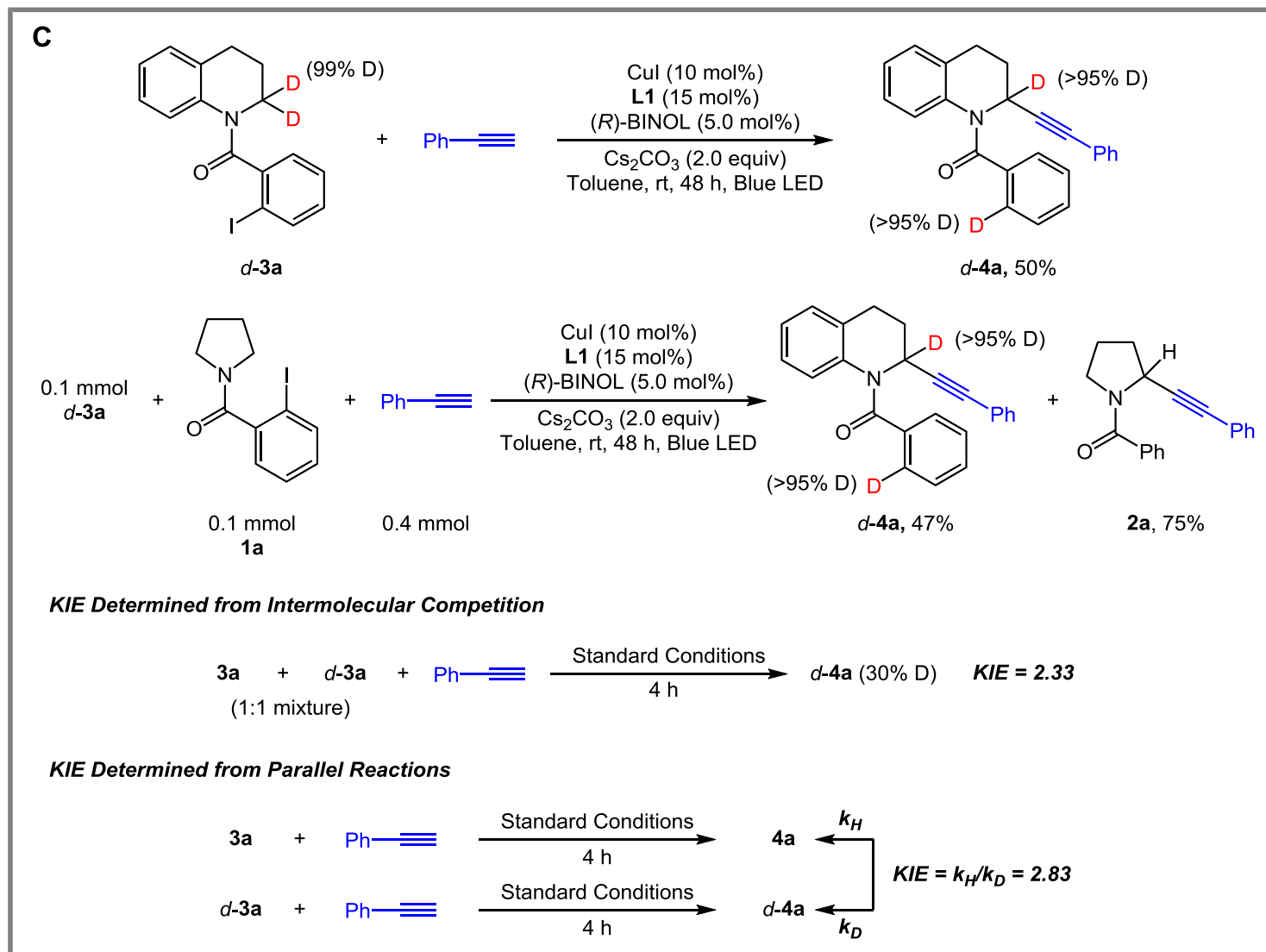
Synthetic Applications



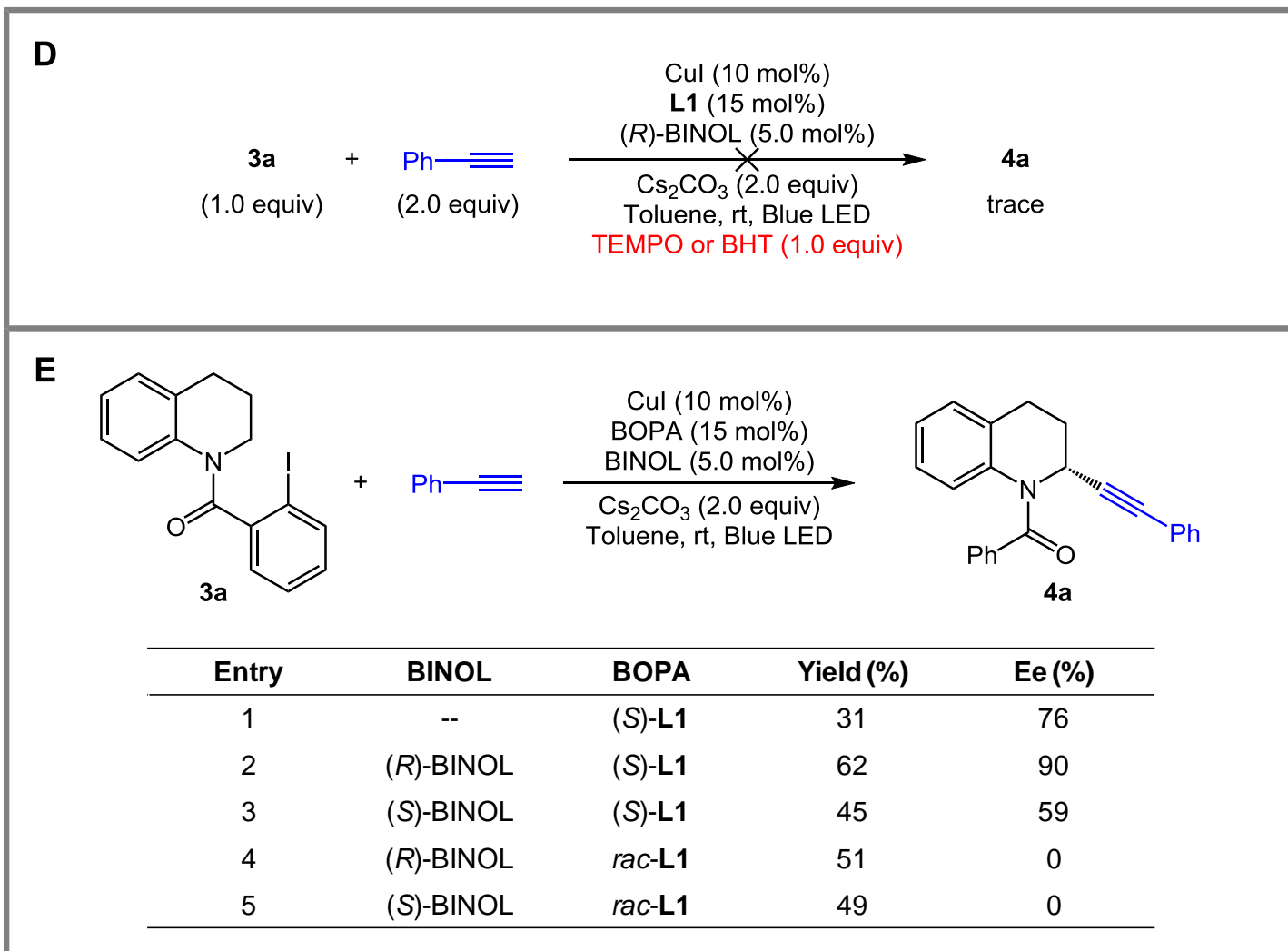
Mechanistic Investigation



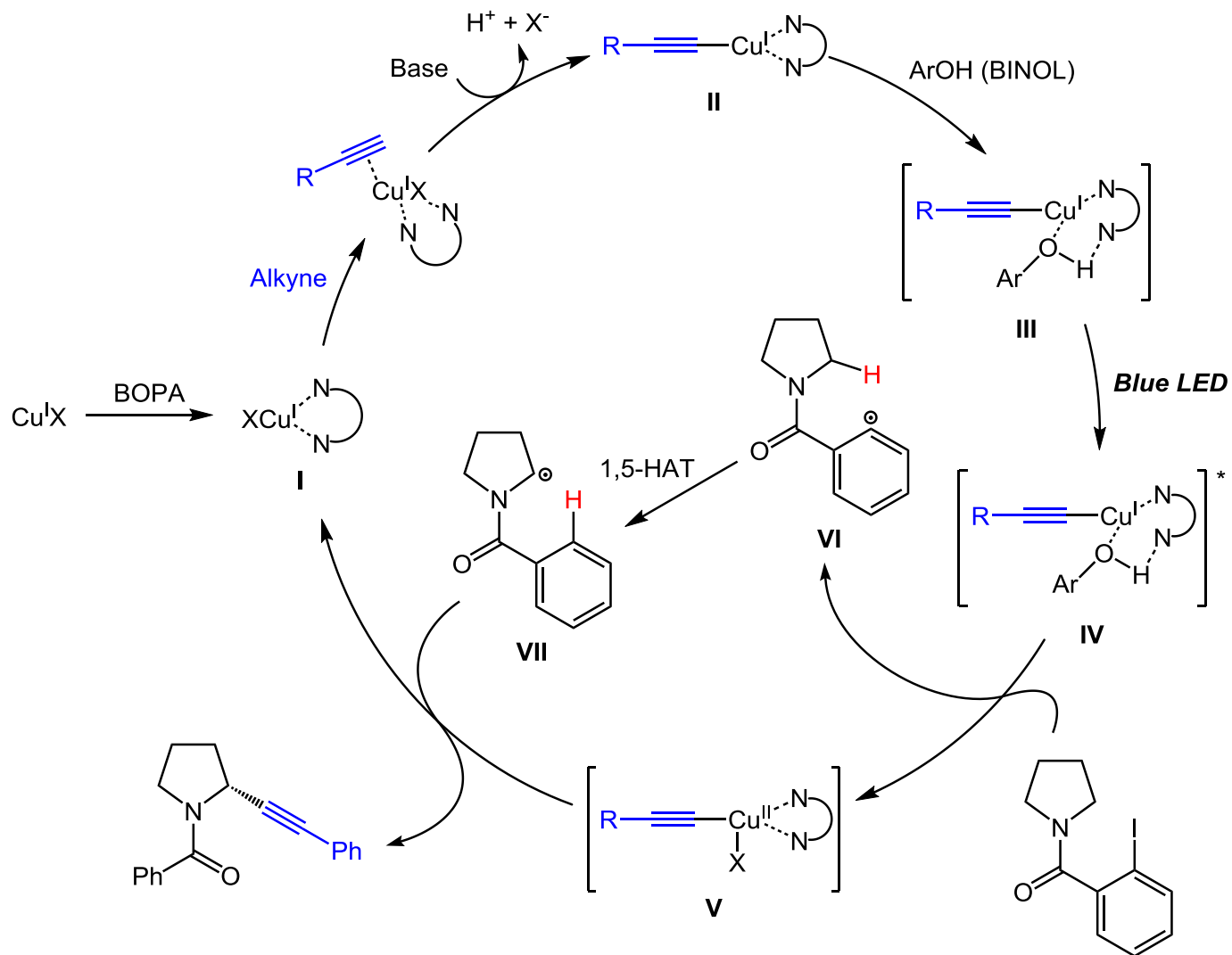
Mechanistic Investigation



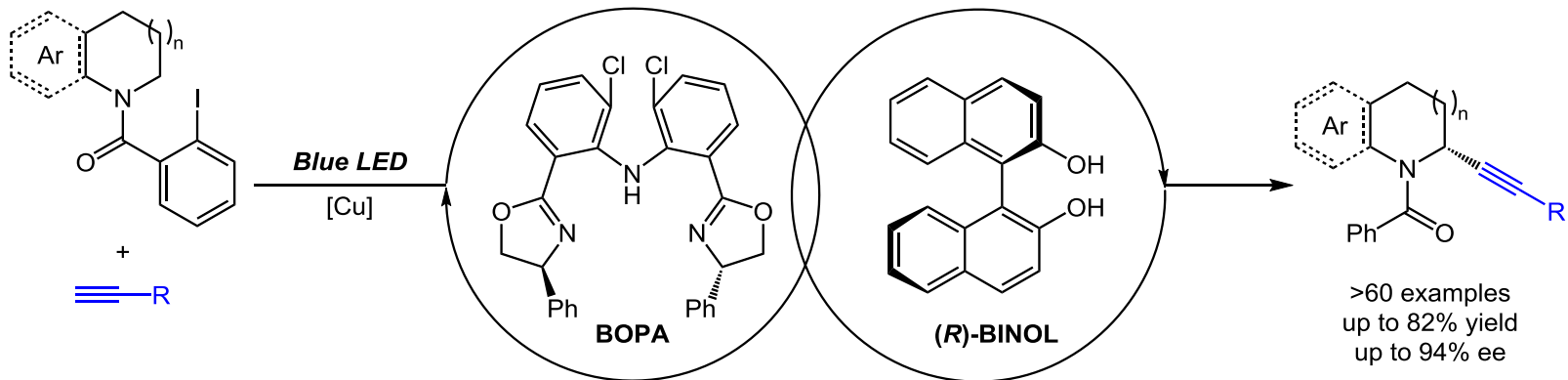
Mechanistic Investigation



Proposed Mechanism



Summary



- ◆ The BOPA-coordinated copper acetylide complex served the dual role as a photoredox and coupling catalyst;
- ◆ BINOL improved the generation efficiency of the initial phenyl radical and facilitated the stereoselective control.

The First Paragraph

Writing strategy

**The importance of α -functionalized
chiral cyclic amines**



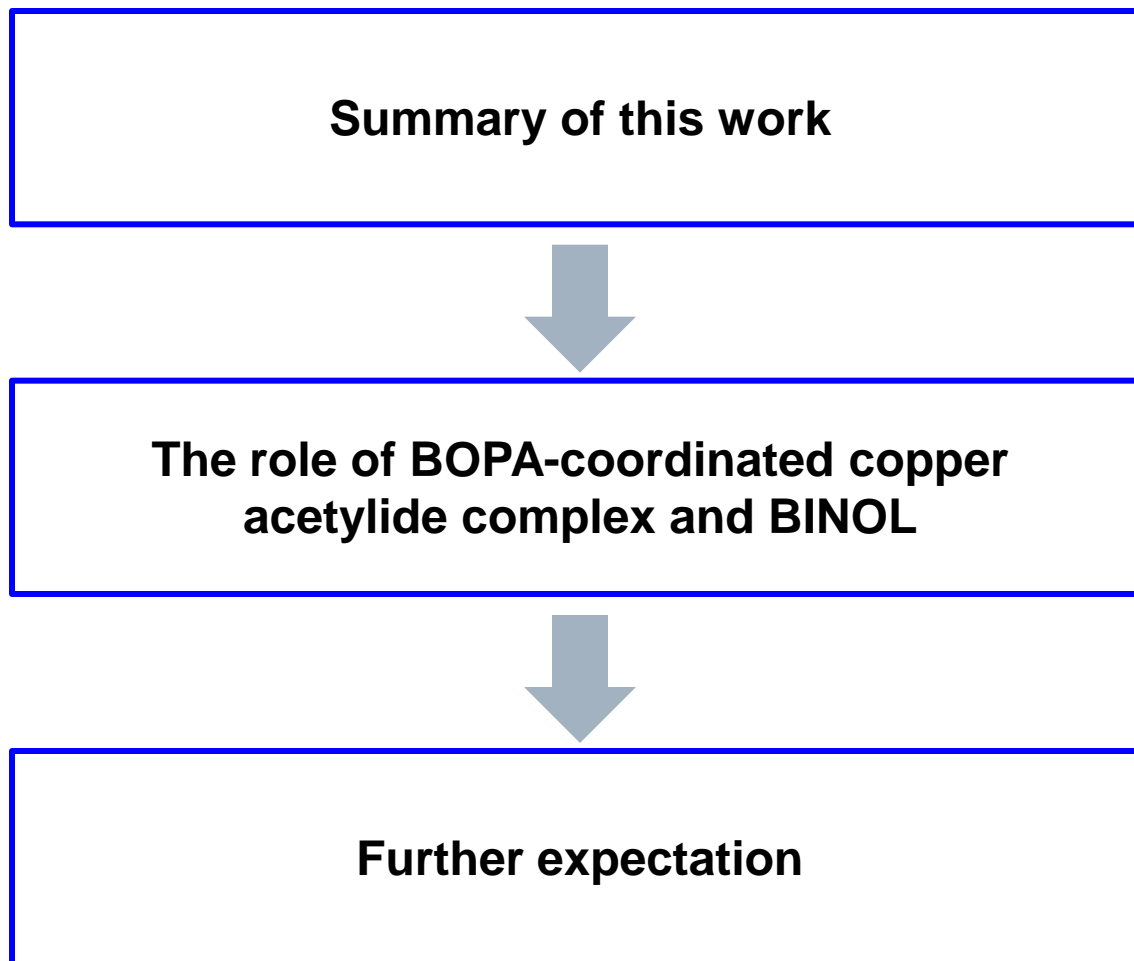
**The development of methods for
the α -functionalization of these nitrogen-
containing heterocyclic**

The First Paragraph

Partially or fully saturated α -functionalized chiral cyclic amines, particularly tetrahydroquinolines and pyrrolidines are significant and ubiquitous motifs in a broad range of natural products, pharmaceuticals, and bioactive molecules. In addition, proline and its derivatives are widely used as key intermediates or catalysts in synthetic chemistry and asymmetric catalysis. Therefore, the development of efficient and highly stereocontrolled methods for the α -functionalization of these nitrogen-containing heterocyclic systems are of great importance, particularly attractive approach entails the direct functionalization of an α -amino C(sp³)-H bond.

The Last Paragraph

Writing strategy



The Last Paragraph

In conclusion, with the cooperative effects of BINOL and the new 2-chlorine substituted BOPA ligand, the longstanding challenge of the enantioselective α -C(sp³)-H alkylation of unactivated cyclic amines was addressed using novel photoinduced copper catalysis via the intramolecular 1,5-HAT of readily available 2-iodobenzamide. A broad range of bio-relevant cyclic amines including pyrrolidines and benzocyclic amines were found to be suitable substrates for this reaction.

The Last Paragraph

The mechanism studies revealed that the BOPA-coordinated copper acetylide complex served as a basic photosensitizer and coupling catalyst, and BINOL sufficiently improved the generation efficiency of the initial phenyl radical and facilitated the stereoselective control in the asymmetric C-C bond formation step. Efforts to elucidate the reaction mechanism similar to the exact role of BINOL will be made in the future, and this novel strategy may be used to solve other challenging problems in asymmetric catalysis.

Representative Examples

More recently, we **advanced** an approach for the visible-light promoted, copper-catalyzed remote alkynylation. (发展)

We selected phenylacetylene and readily available 1-aryl-pyrrolidine 1a as model substrates for optimization, **drawing lessons from** our previous success. (借鉴; 从…中吸取教训)

After identifying the optimal ligand, we **assessed** the other elements in this coupling reactions. (评估; 考察)

***Thanks
for your attention***