

# Literature Report 8

## Enantioselective Synthesis of Multisubstituted Allenes by Cooperative Cu/Pd-Catalyzed 1,4-Arylboration of 1,3-Enynes

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Reporter: Zhou-Hao Zhu

Checker: Yi-Xuan Ding

Date: 2020-06-16

Liao, Y.; Yin, X.; Wang, X.; Yu, W.; Fang, D.; Hu, L.; Wang, M.; Liao, J.\*  
*Angew. Chem. Int. Ed.* **2020**, *59*, 1176

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# CV of Prof. Jian Liao

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**Jian Liao**

## Background:

- 1990-1994 B.S., Shanghai Jiao Tong University
- 1996-2002 Ph.D., Chengdu Institute of Organic Chemistry
- 2002-2003 Assistant Researcher, Chengdu Institute of Organic Chemistry
- 2003-2006 Postdoctoral Associate, The Pennsylvania State University
- 2006-2010 Professor, Chengdu Institute of Organic Chemistry
- 2010-now Professor, Chengdu Institute of Biology

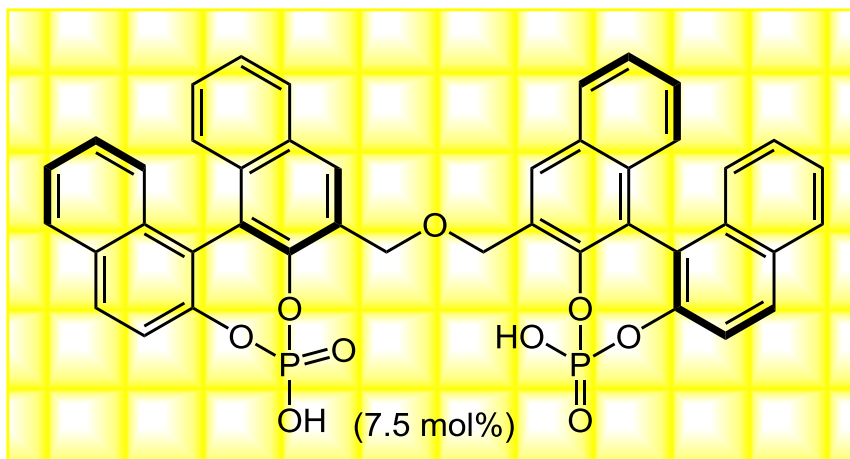
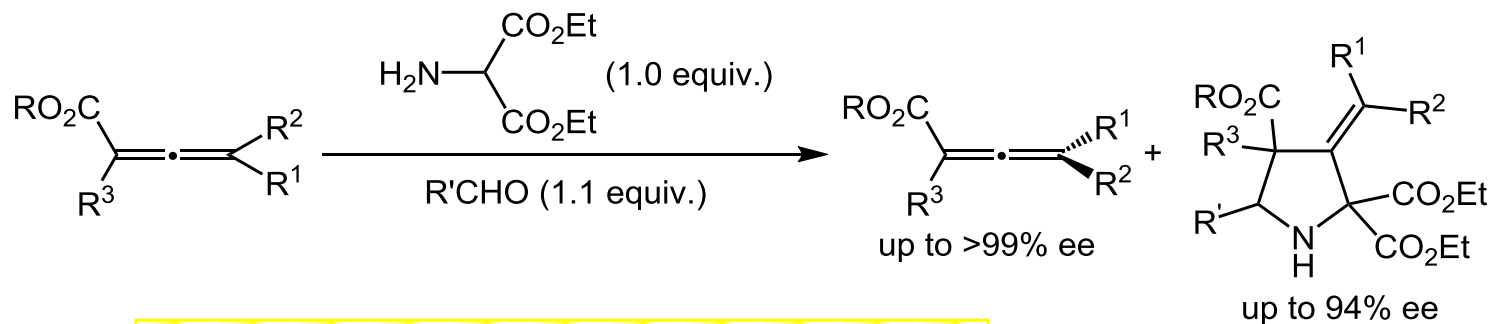
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## Research Interests:

- Design and synthesis of chiral ligands
- Synthesis of natural products
- Development of new catalytic asymmetric reactions

# Introduction

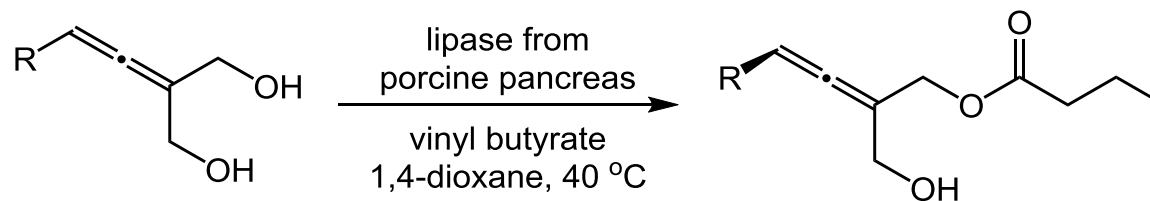
## Kinetic Resolution



Gong, L.-Z.\* *et al.* *Org. Lett.* **2010**, *12*, 4050

# Introduction

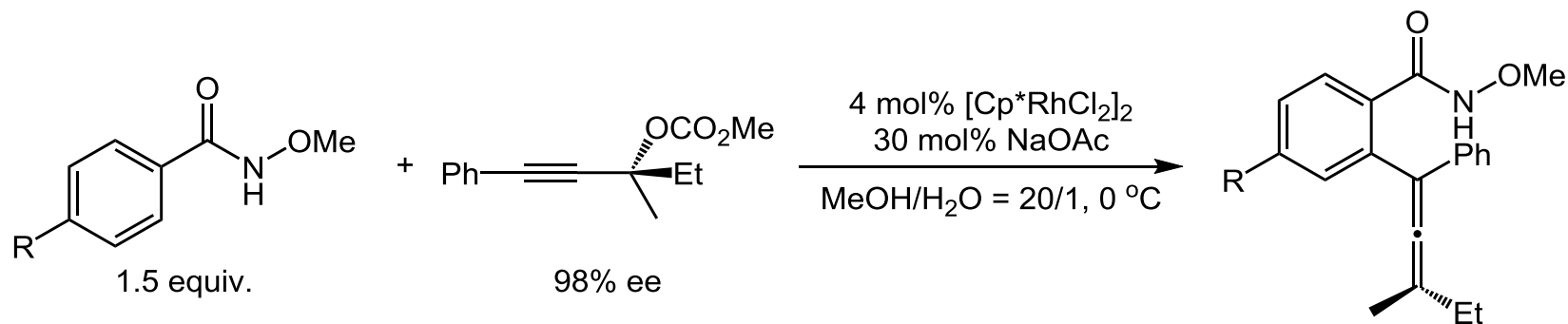
## Desymmetrization



up to 96% yield, 99% ee

Deska, J.\* *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 9731

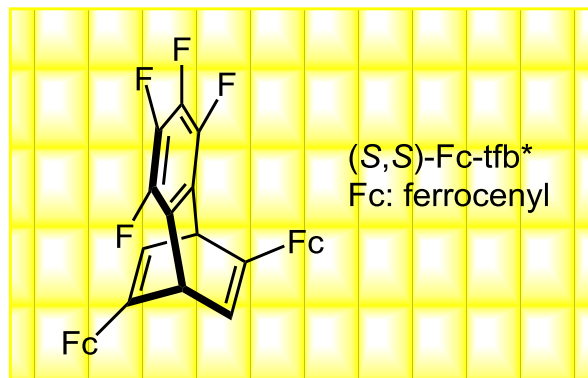
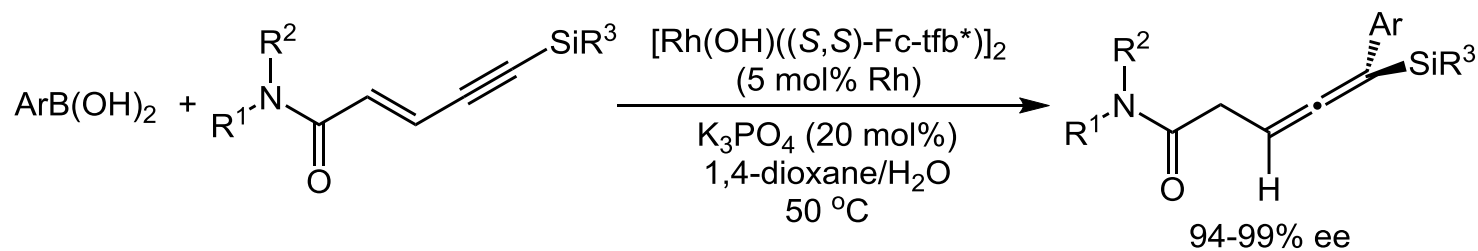
## Central-to-axial chirality transfer



98% ee  
up to 77% yield

Ma, S.\* *et al. Nat. Commun.* **2015**, *6*, 7946

# Introduction

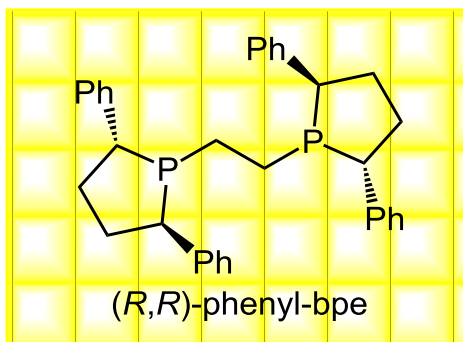
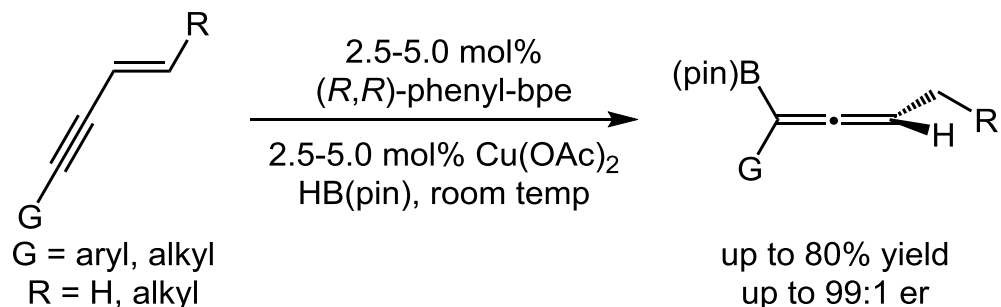


**1,3-Enynes** have been gradually considered ideal achiral precursors for the construction of highly valuable chiral allenes.

Hayashi, T.\* *et al. J. Am. Chem. Soc.* **2010**, *132*, 12865

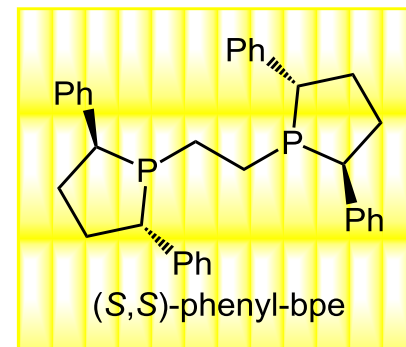
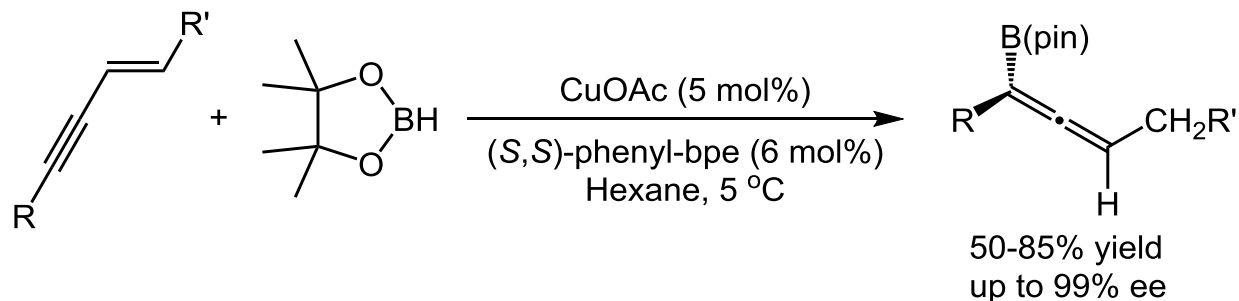
# Introduction

## Enantioselective **Cu-catalyzed** 1,4-hydrofunctionalization of 1,3-enynes

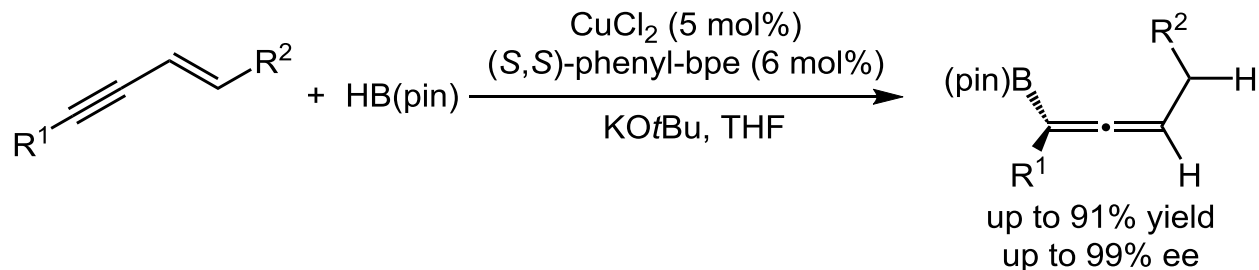


Hoveyda, A. H.\* *et al.* *J. Am. Chem. Soc.* **2018**, *140*, 2643

# Introduction



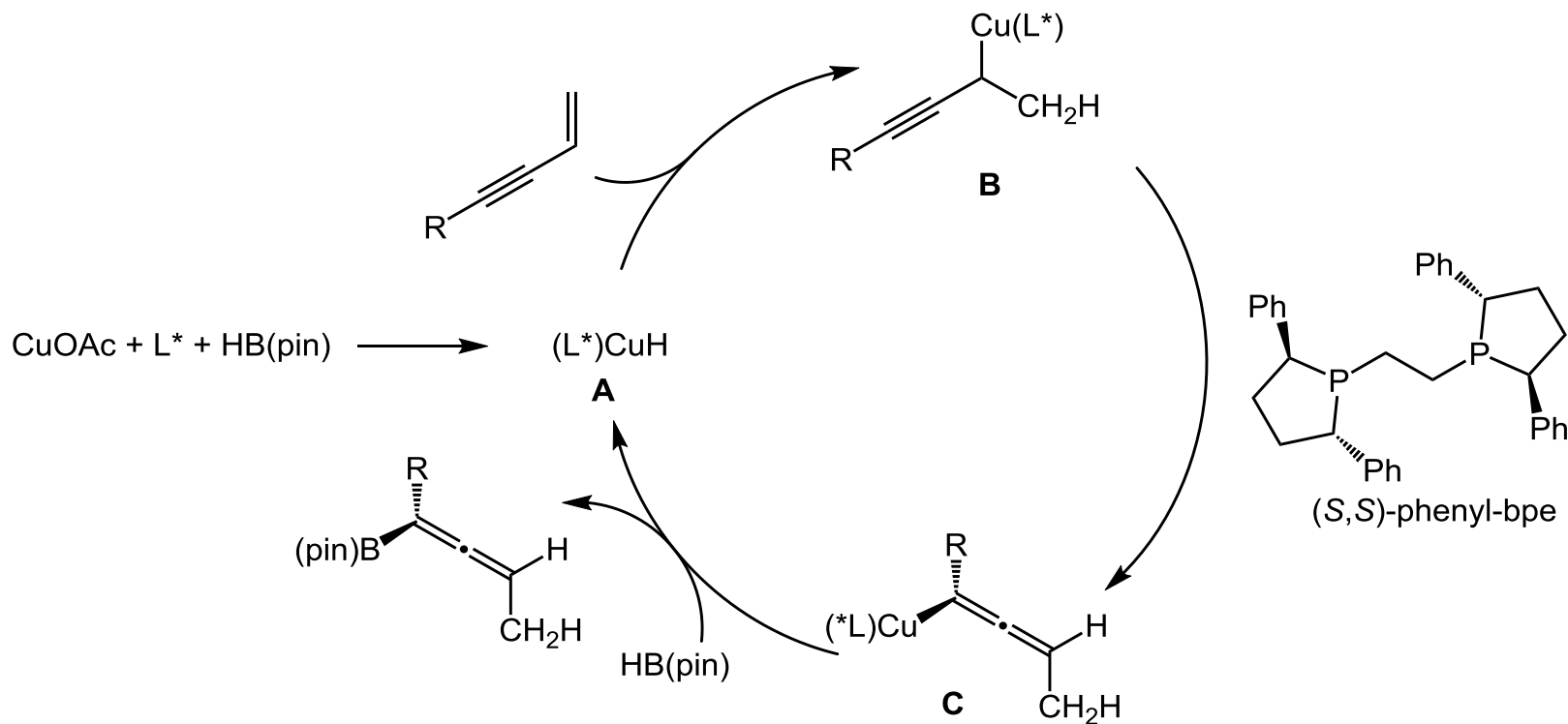
Ge, S.\* *et al. Org. Chem. Front.* **2018**, 5, 1284



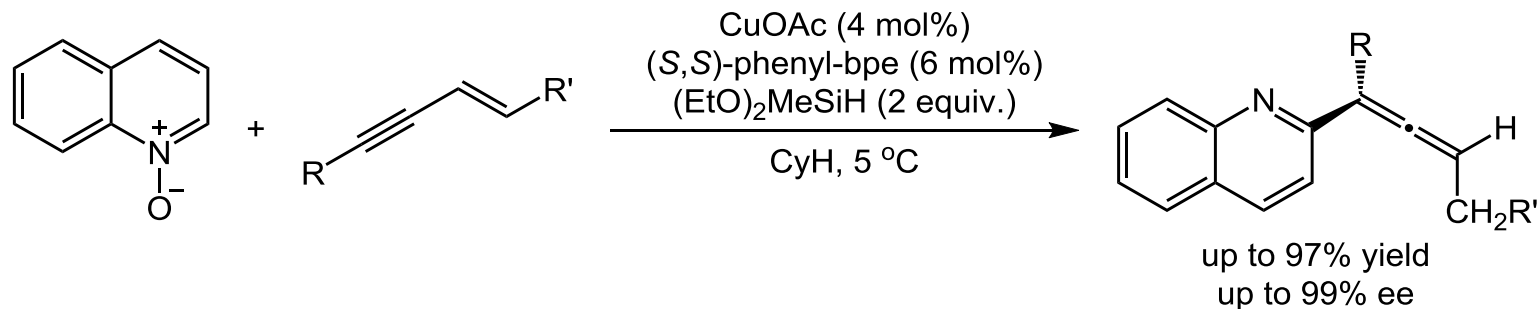
Engle, K. M.\* *et al. ACS Catal.* **2018**, 8, 3650



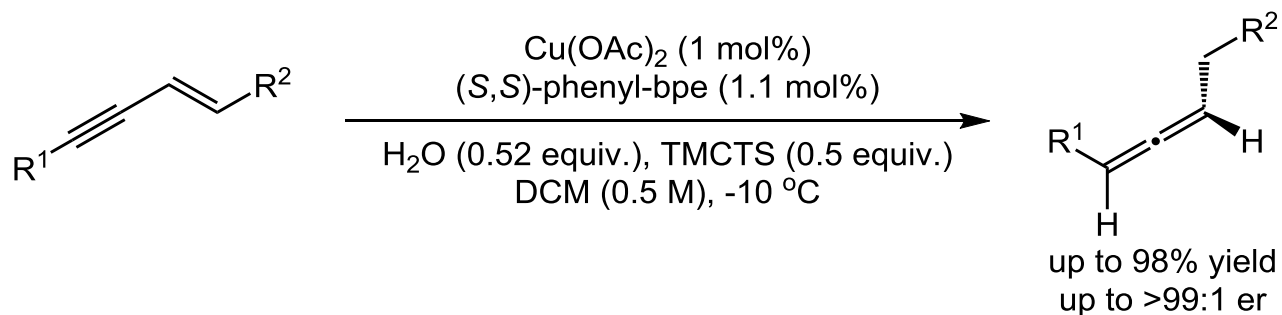
# Proposed Mechanism



# Introduction

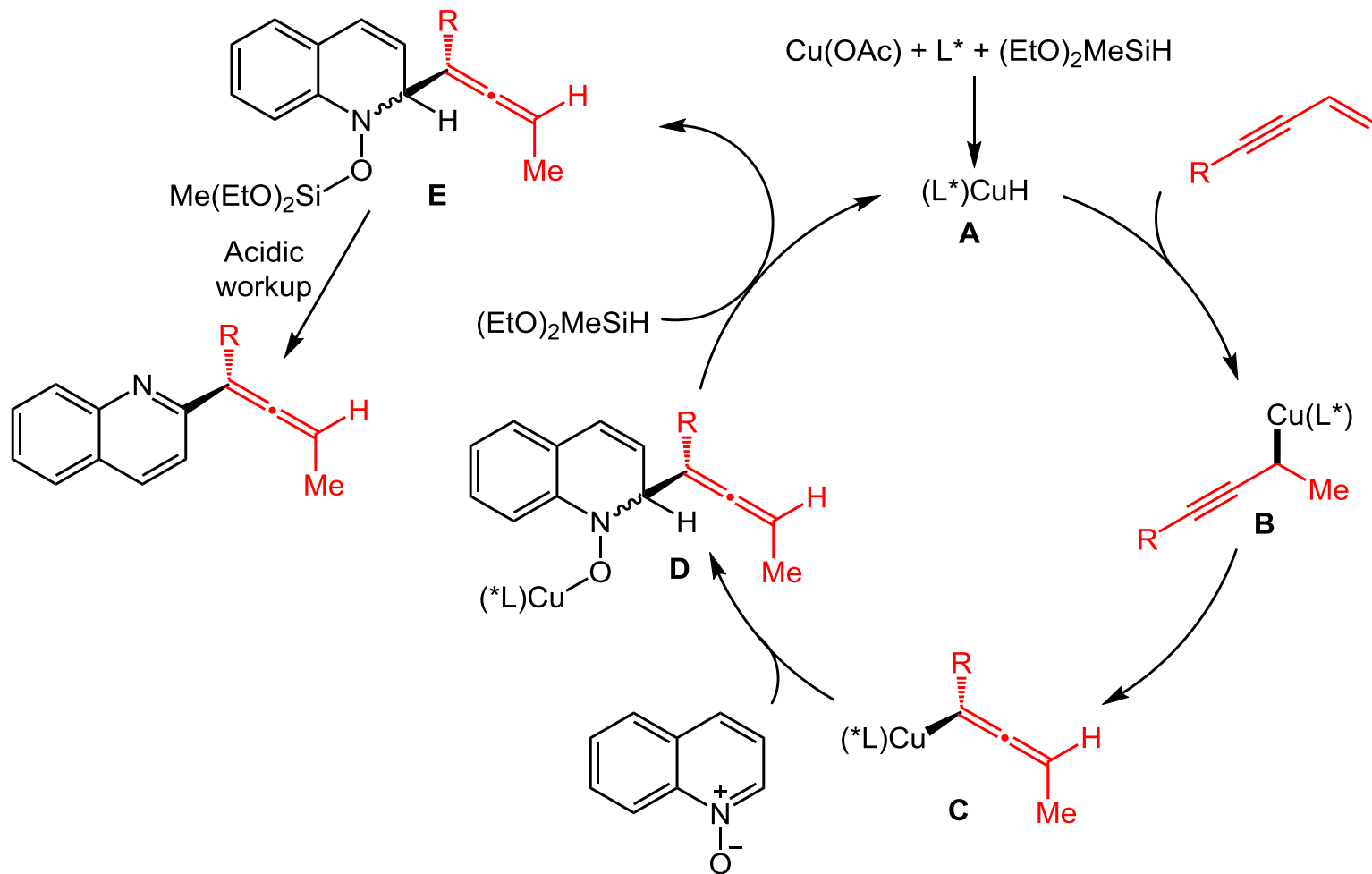


Ge, S.\* *et al. Commun. Chem.* **2018**, 1, 64

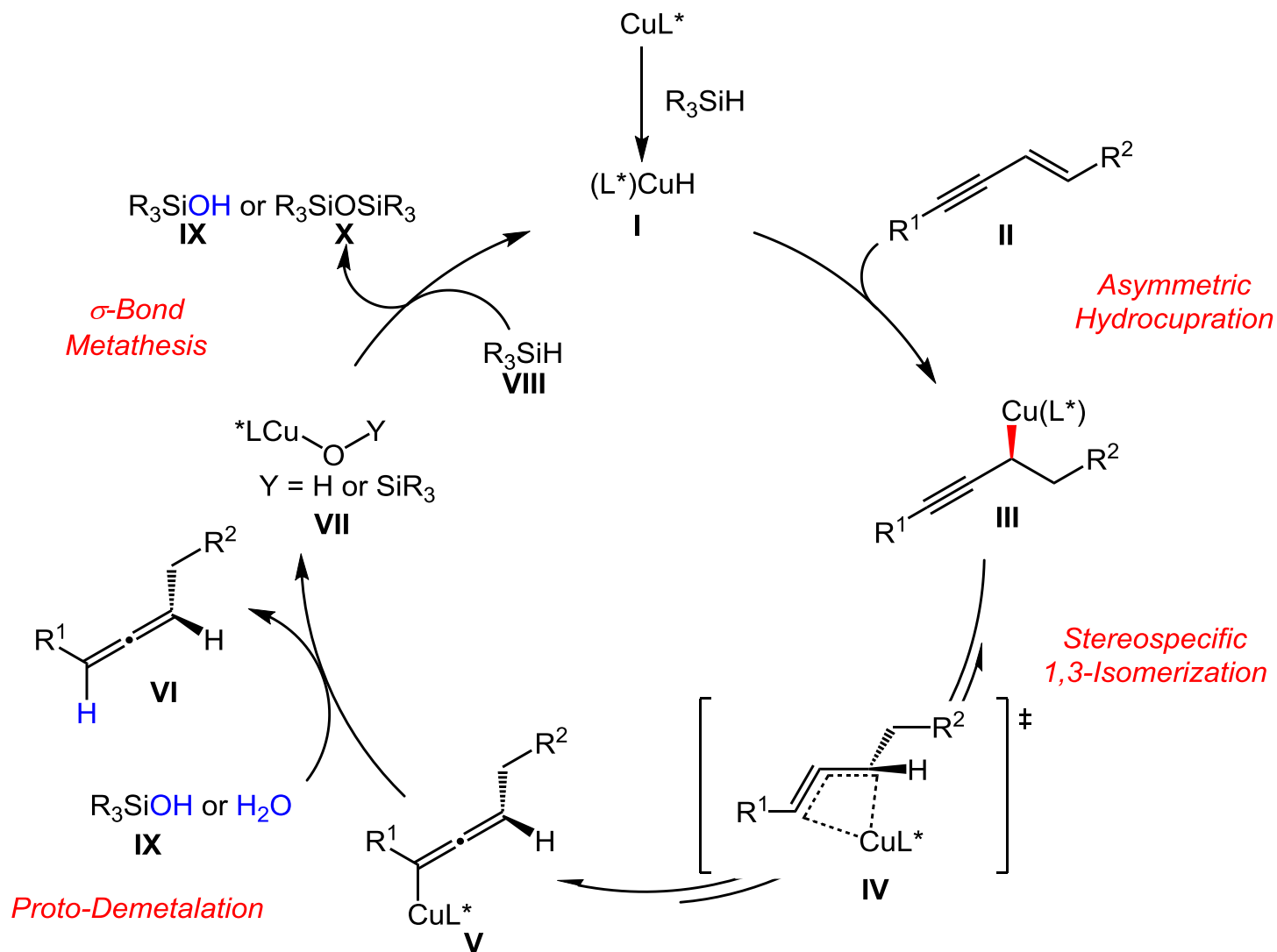


Buchwald, S. L.\* *et al. J. Am. Chem. Soc.* **2019**, 141, 13788

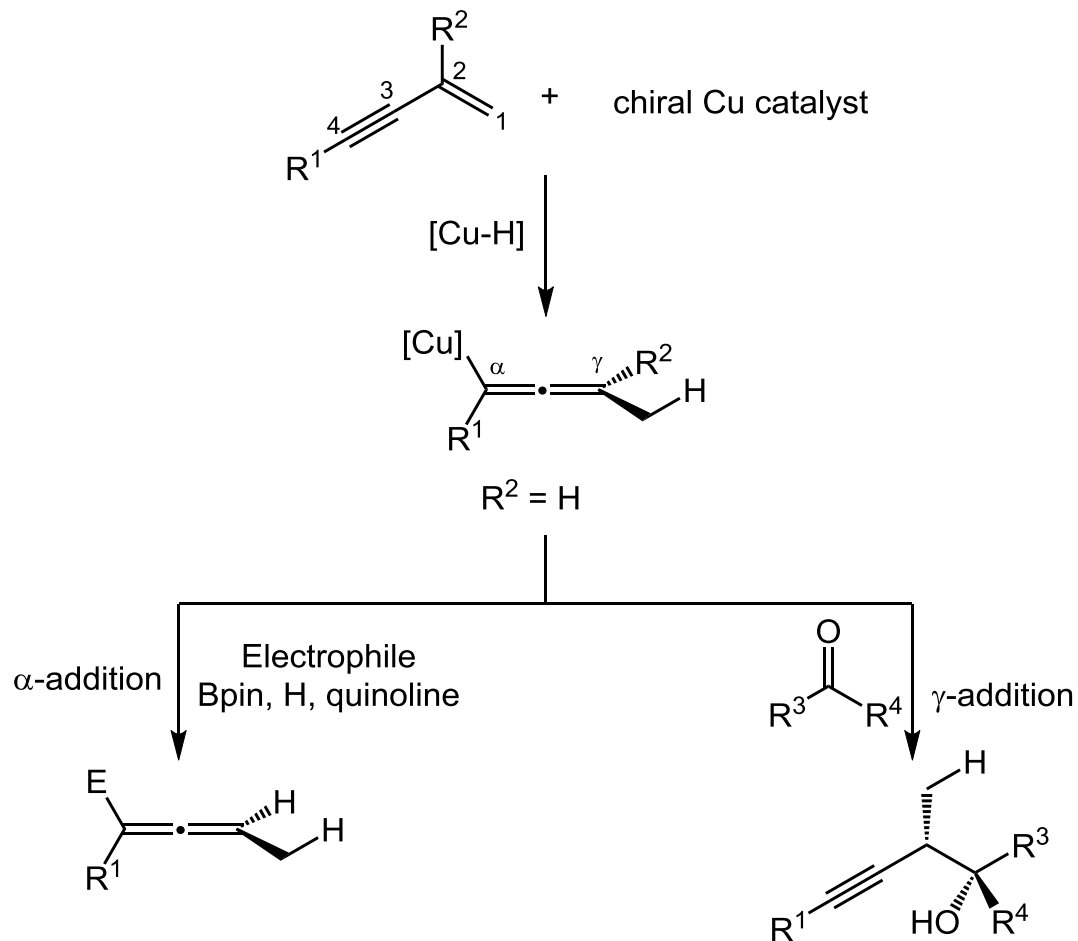
# Proposed Mechanism



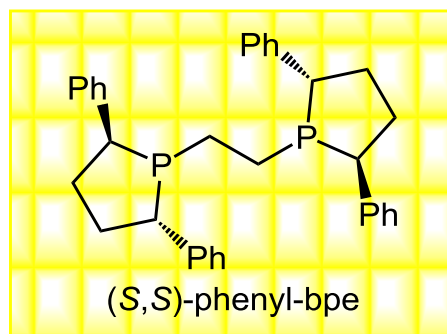
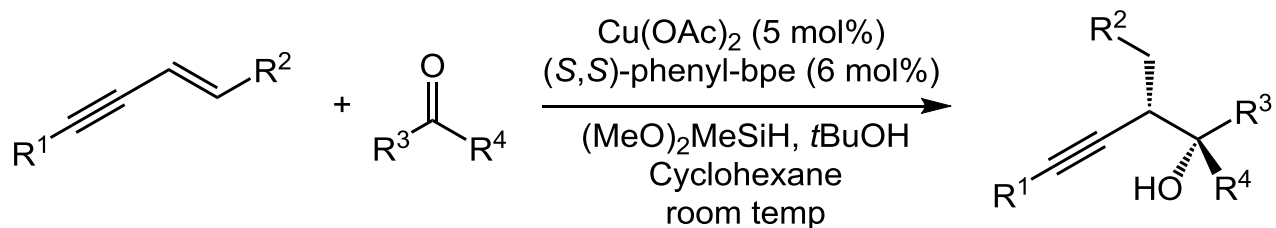
# Proposed Mechanism



# Introduction



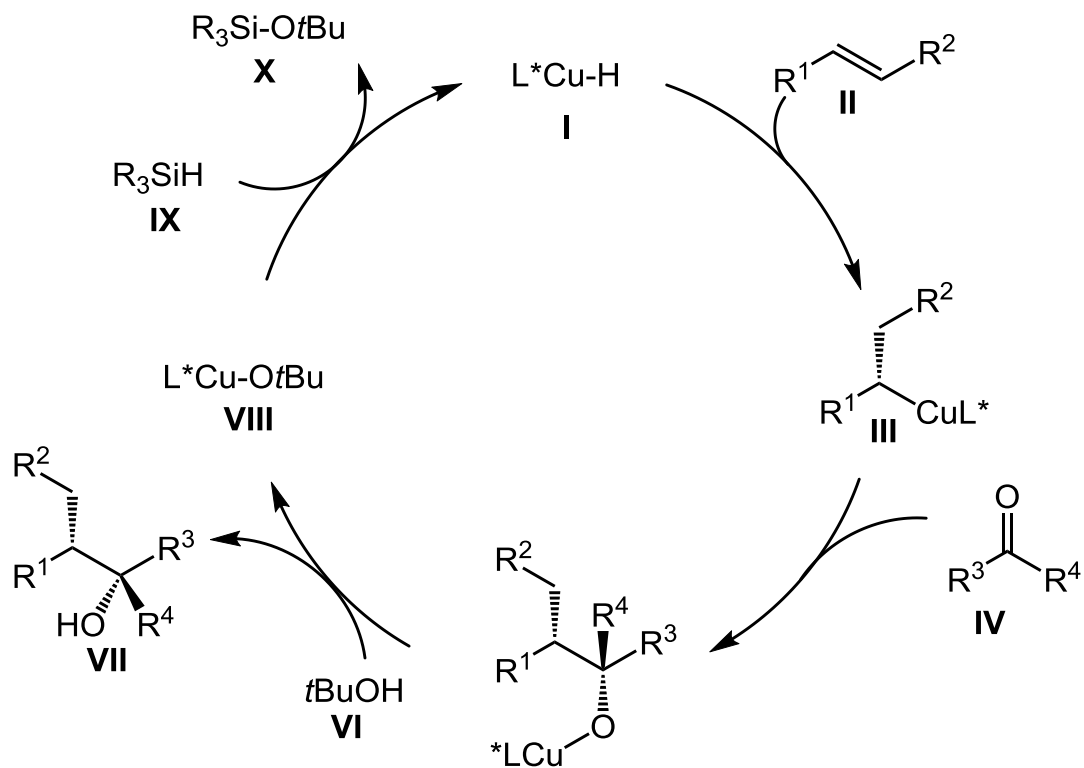
# Introduction



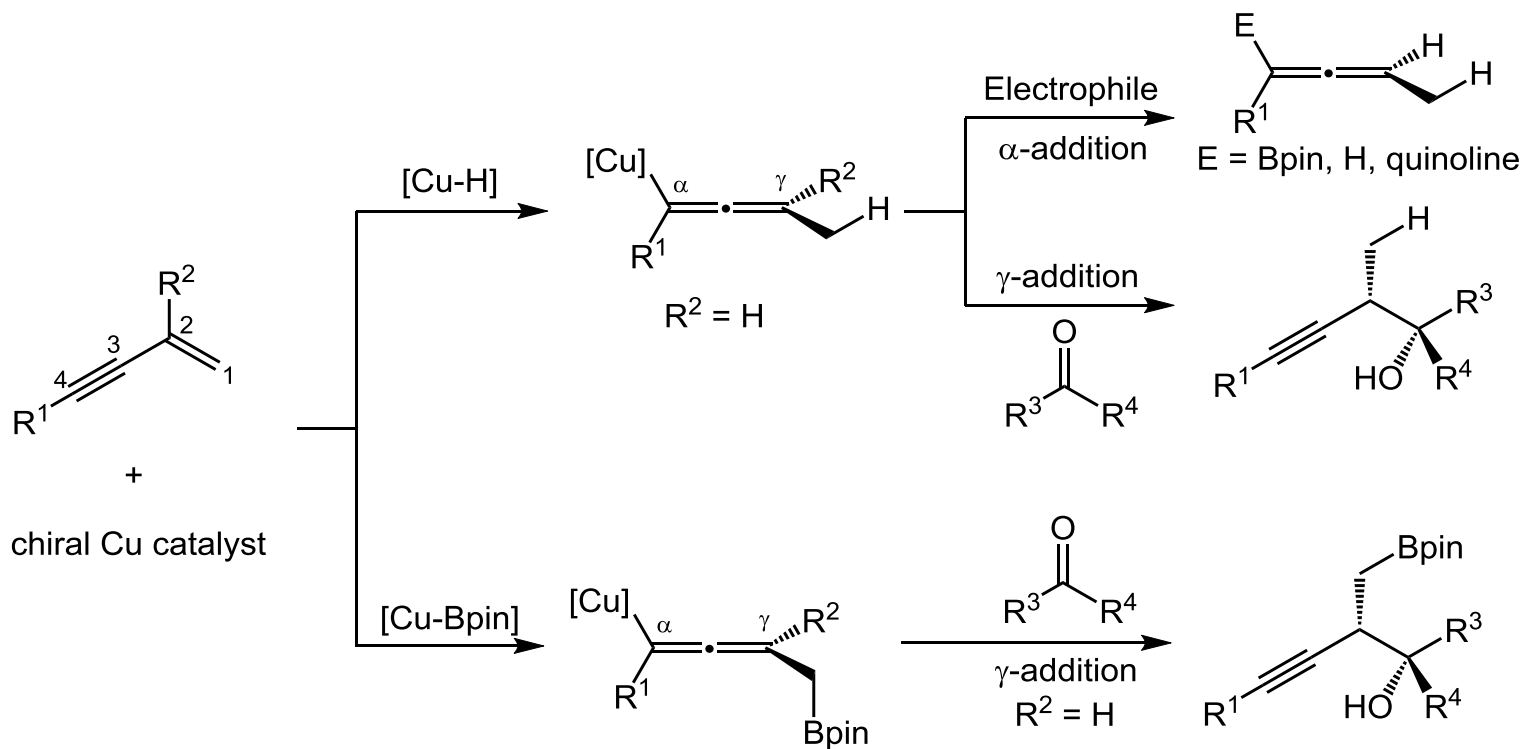
up to 95% yield  
up to > 99% ee  
up to > 10:1 dr

Buchwald, S. L.\* *et al. Science* **2016**, 353, 144

# Proposed Mechanism

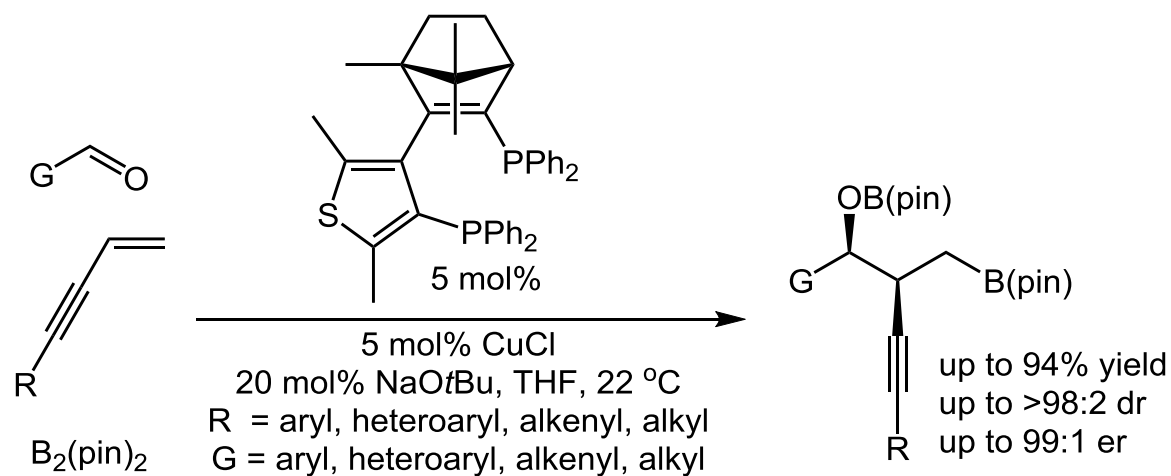


# Introduction



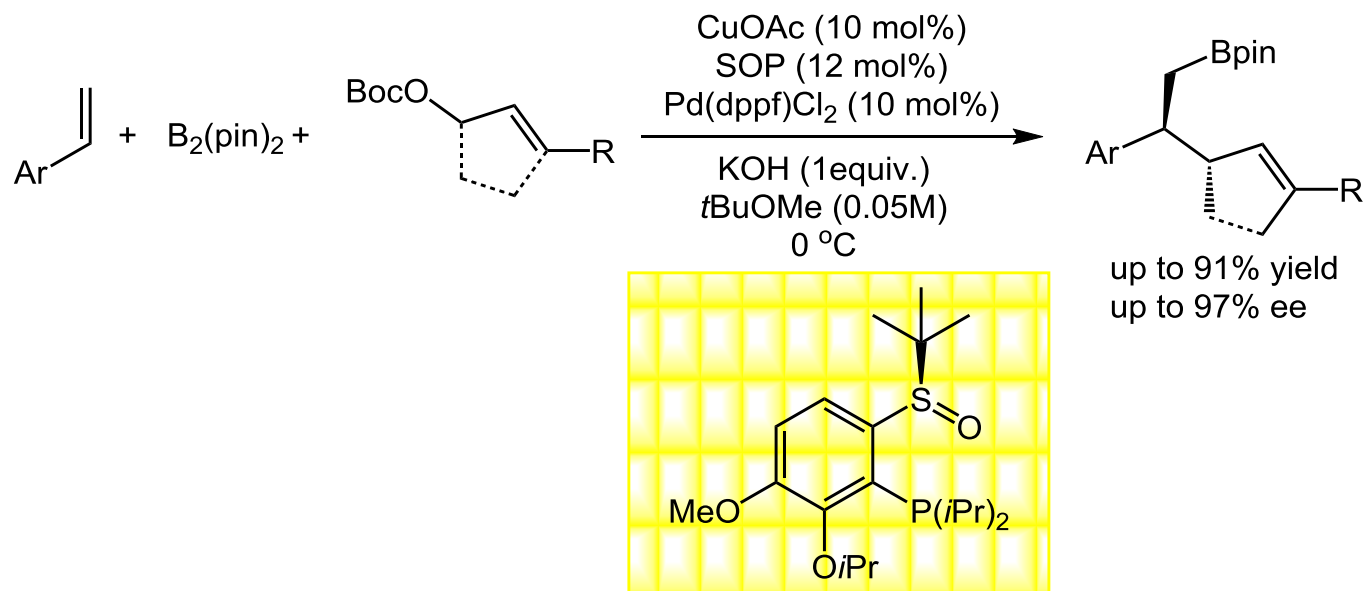


# Introduction



Hoveyda, A. H.\* *et al. J. Am. Chem. Soc.* **2014**, *136*, 11304

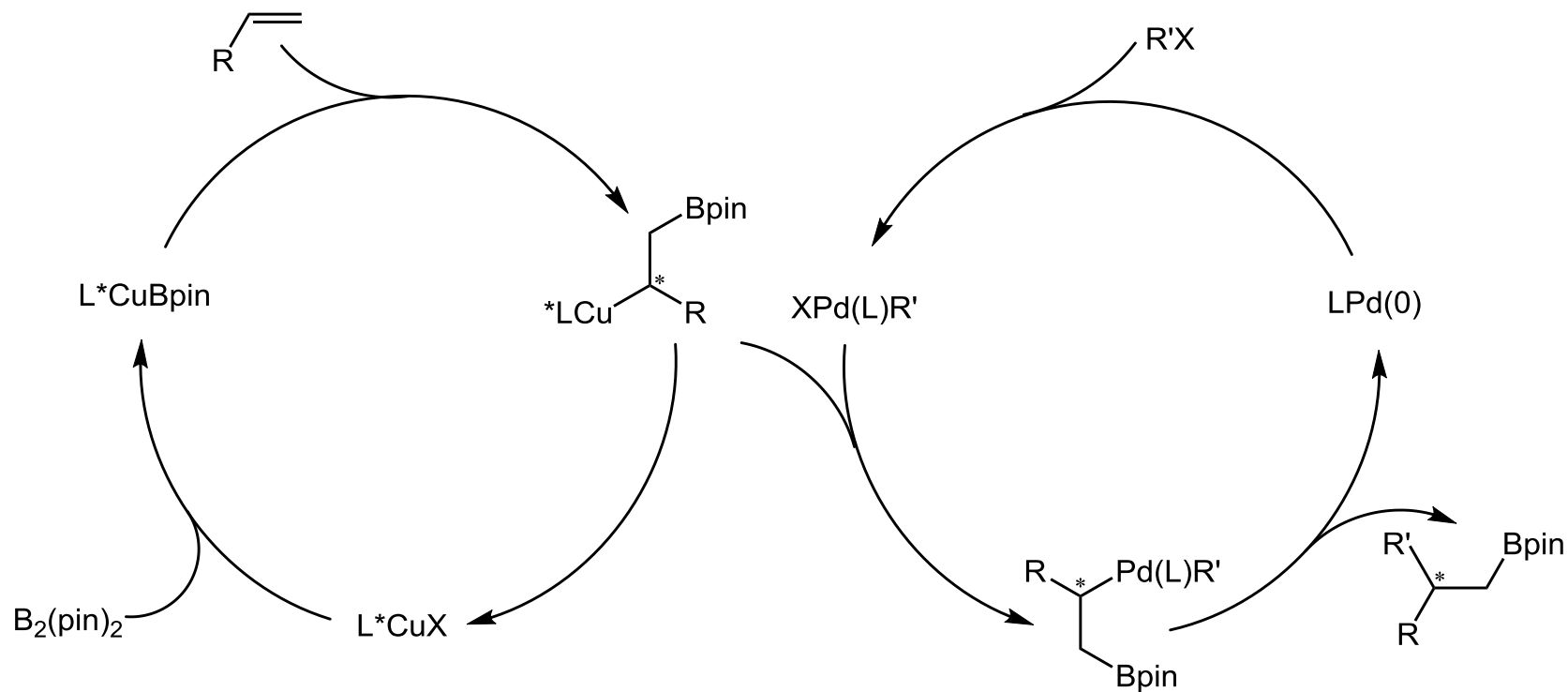
# Introduction



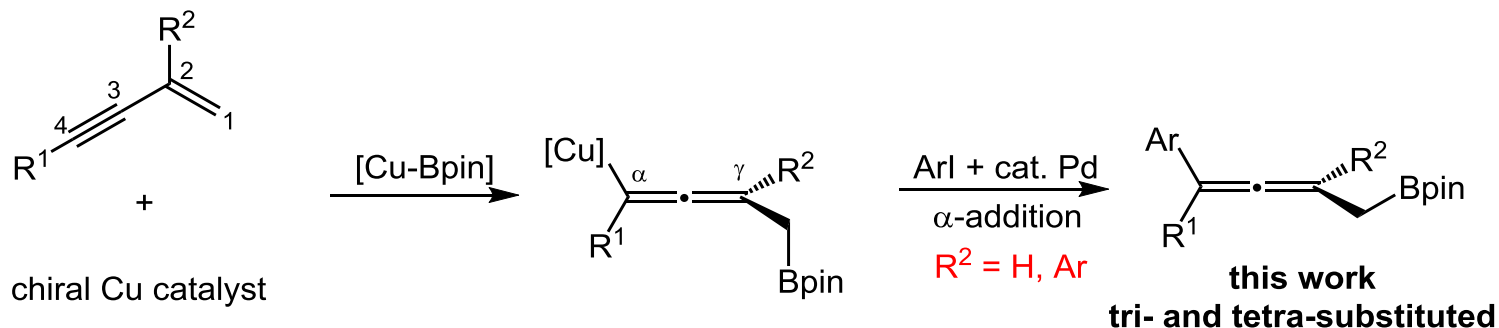
Liao, J.\* *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 13760

# Introduction

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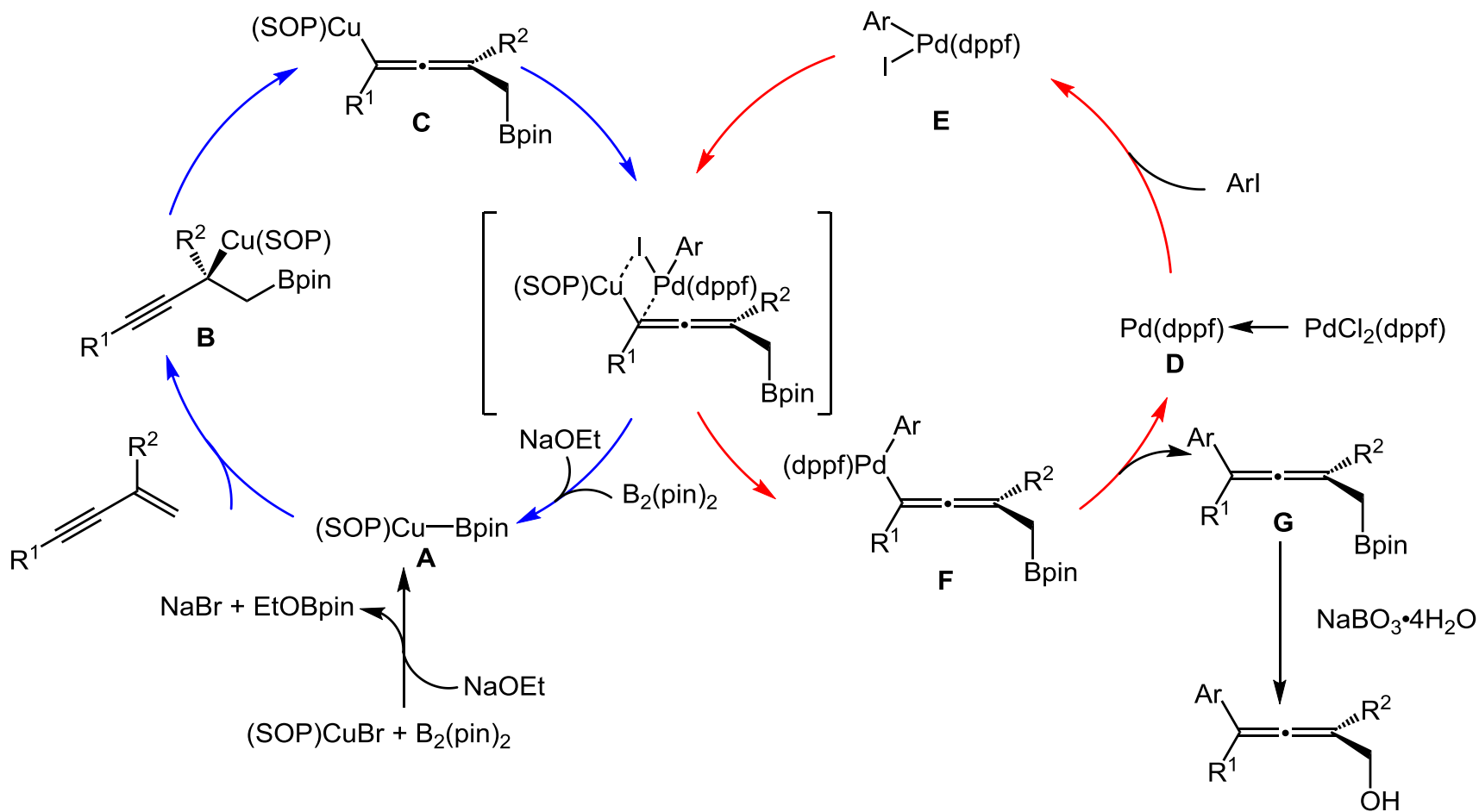


# Cooperative Cu/Pd-Catalyzed 1,4-Arylboration

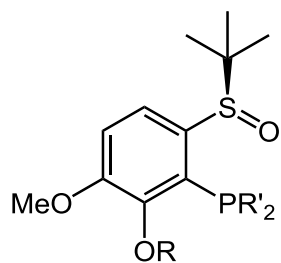
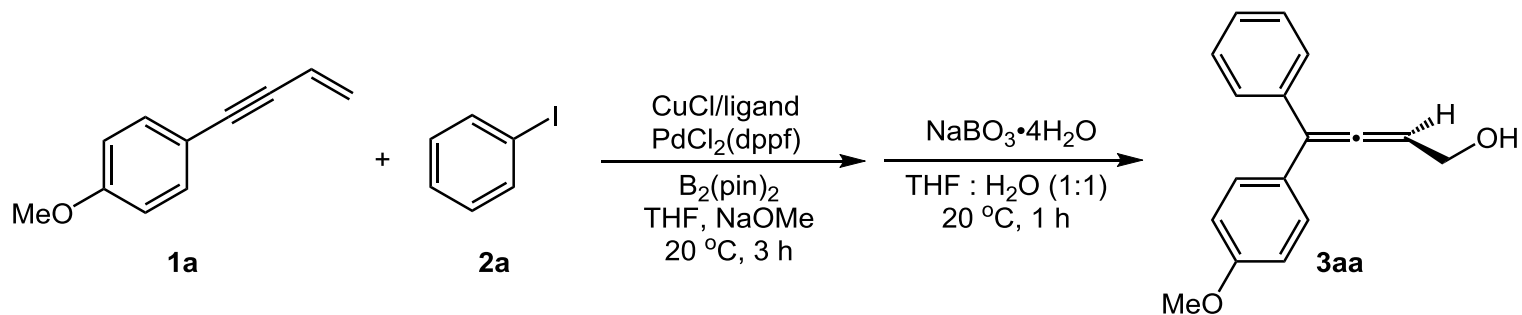


Liao, Y.; Yin, X.; Liao, J.\* *et al. Angew. Chem. Int. Ed.* **2020**, 59, 1176

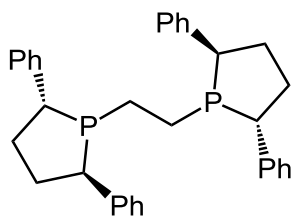
# Proposed Mechanism



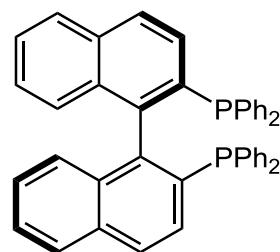
# Optimization of the Reaction Parameters



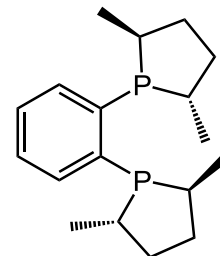
- R = Me, R' = *i*Pr (**L1**)  
R = Me, R' = Ph (**L2**)  
R = Cy, R' = *i*Pr (**L3**)  
R = Me, R' = Cp (**L4**)



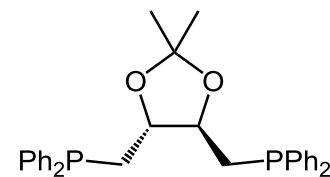
(*R,R*)-Ph-BPE (**L5**)



(*R*)-BINAP (**L6**)



(*S,S*)-MeDuphos (**L7**)



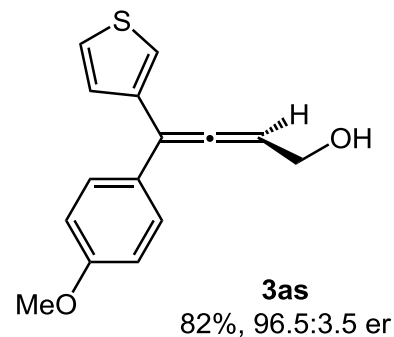
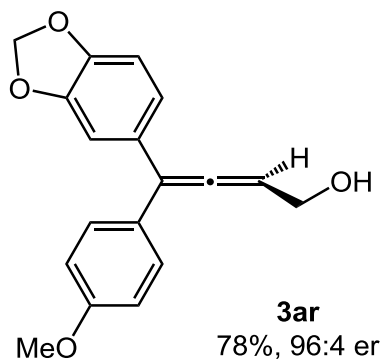
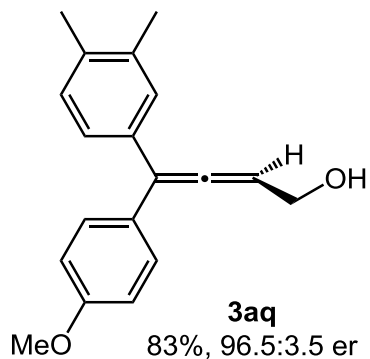
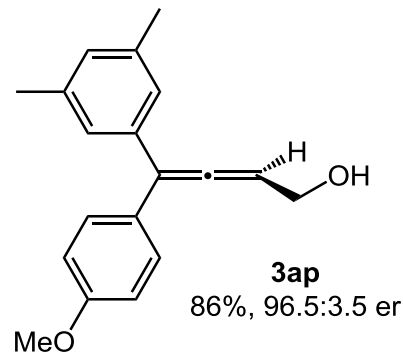
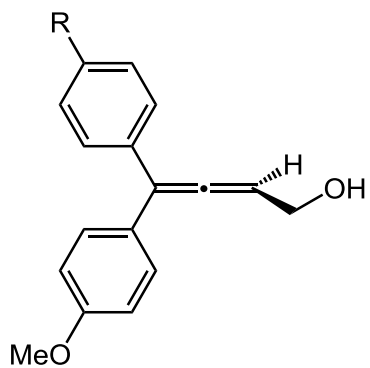
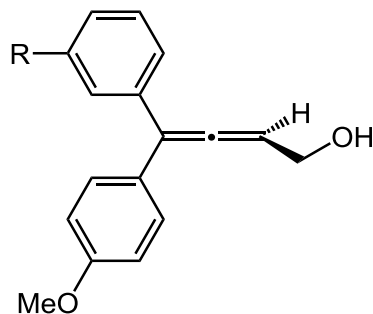
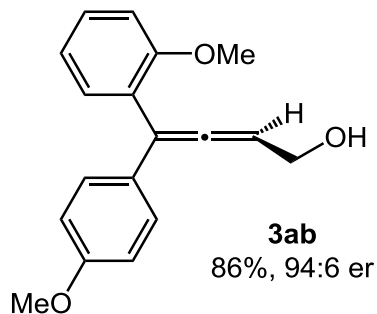
(*R,R*)-DIOP (**L8**)

# Optimization of the Reaction Parameters

entry <sup>a</sup>	PdCl <sub>2</sub> (dppf)	CuCl	Ligand	yield (%) <sup>b</sup>	er <sup>c</sup>
1	5	10	L1	90	78:22
2	10	10	L1	91	88:12
3	15	10	L1	86	91:9
4	20	10	L1	70	90:10
5	15	5	L1	86	93:7
6	15	2.5	L1	72	93:7
7 <sup>d</sup>	15	5	L1	88	93.5:6.5
8 <sup>d</sup>	15	5	L2	90	90:10
9 <sup>d</sup>	15	5	L3	89	93:7
10 <sup>d</sup>	15	5	L4	76	92:8
11 <sup>d</sup>	15	5	L5	65	55:45
12 <sup>d</sup>	15	5	L6	72	52:48
13 <sup>d</sup>	15	5	L7	80	54:46
14 <sup>d</sup>	15	5	L8	81	54:46
15 <sup>d,e</sup>	15	5	L1	90	94.5:5.5
16 <sup>d,e,f</sup>	15	5	L1	95	95.5:4.5
17 <sup>d,e,f,g</sup>	15	5	L1	94(88)	96:4

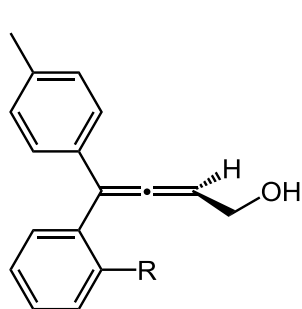
<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), B<sub>2</sub>(pin)<sub>2</sub> (0.4 mmol), PdCl<sub>2</sub>(dppf) (x mol%), CuCl (y mol%), and NaOMe (0.5 mmol) in THF (2.0 mL) at 20 °C for 3 h. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy with dimethyl terephthalate as an internal standard. Yield of the isolated product given within parentheses. <sup>c</sup>Determined by HPLC. <sup>d</sup>CuBr instead of CuCl. <sup>e</sup>10 mol% TFP was added as additive. <sup>f</sup>NaOEt instead of NaOMe. <sup>g</sup>Mixed solvents: 2.0 mL THF and 1.0 mL 2-MeTHF. THF= tetrahydrofuran.

# Scope with Respect to the Aryl Iodides

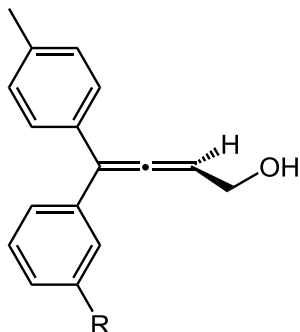




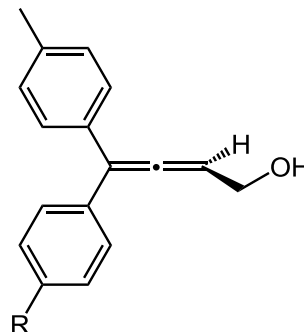
# Scope with Respect to the 1,3-Enynes



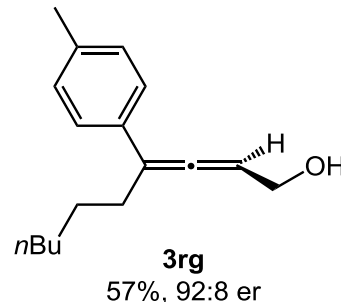
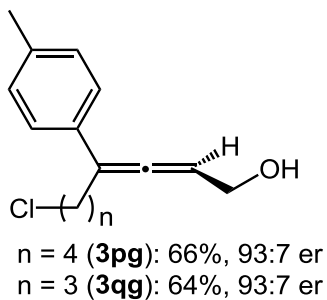
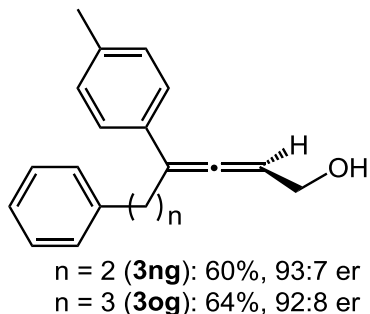
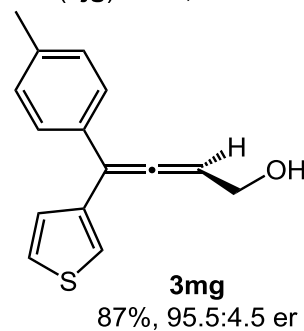
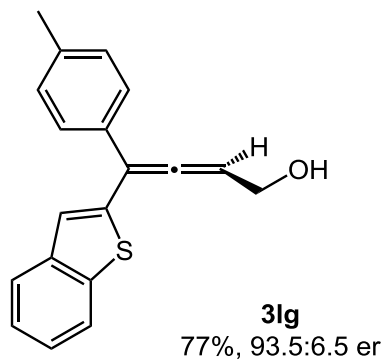
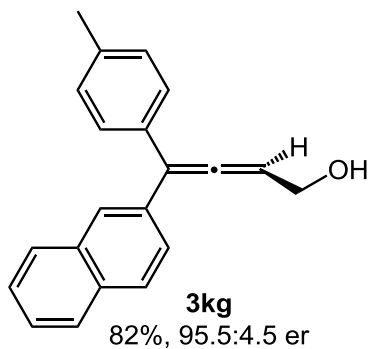
R = F (**3bg**): 80%, 94:6 er  
 R = OMe (**3cg**): 86%, 93:7 er



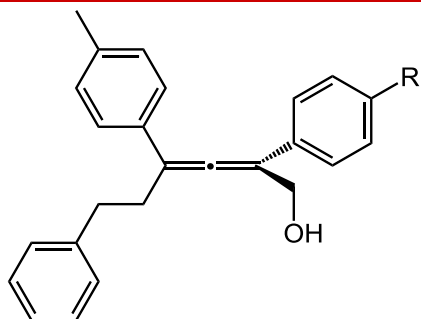
R = Me (**3dg**): 78%, 96.5:3.5 er  
 R = OMe (**3eg**): 84%, 95.5:4.5 er



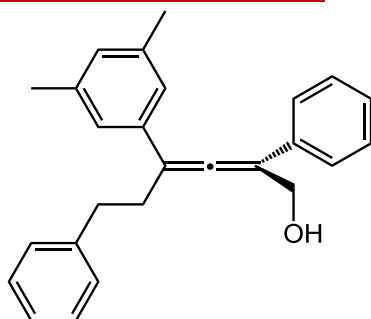
R = *t*Bu (**3fg**): 82%, 96:4 er  
 R = *n*Bu (**3gg**): 90%, 95.5:4.5 er  
 R = Et (**3hg**): 86%, 95.5:4.5 er  
 R = F (**3ig**): 78%, 93:7 er  
 R = Ph (**3jg**): 92%, 95:5 er



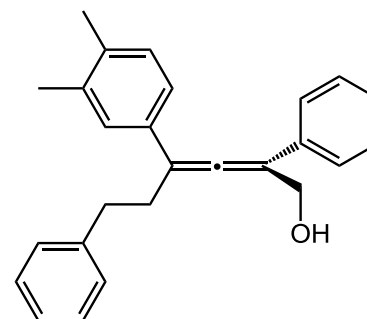
# Synthesis of Tetrasubstituted Allenes



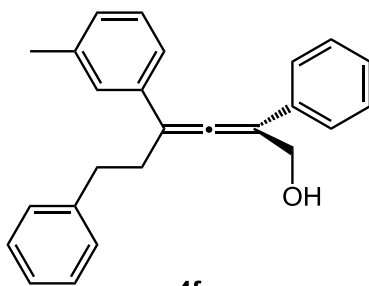
R = H (**4a**): 68%, 95:5 er  
R = Ph (**4b**): 61%, 93.5:6.5 er  
R = OMe (**4c**): 46%, 92.5:7.5 er



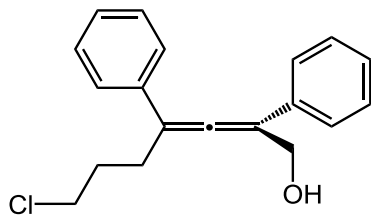
**4d**  
50%, 93.5:6.5 er



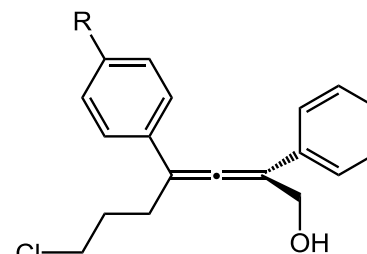
**4e**  
44%, 92.5:7.5 er



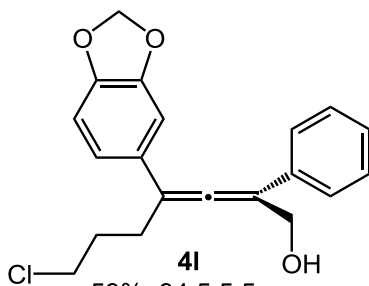
**4f**  
57%, 93:7 er



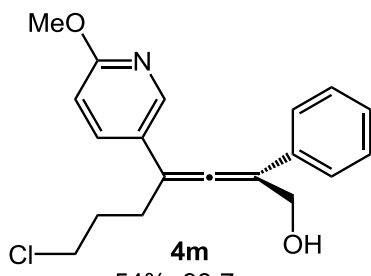
**4g**  
57%, 94.5:5.5 er



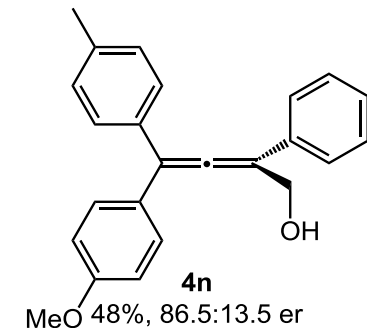
R = Me (**4h**): 58%, 95:5 er  
R = OEt (**4i**): 70%, 94.5:5.5 er  
R = Ph (**4j**): 46%, 94:6 er  
R = *t*Bu (**4k**): 66%, 95:5 er



**4l**  
59%, 94.5:5.5 er

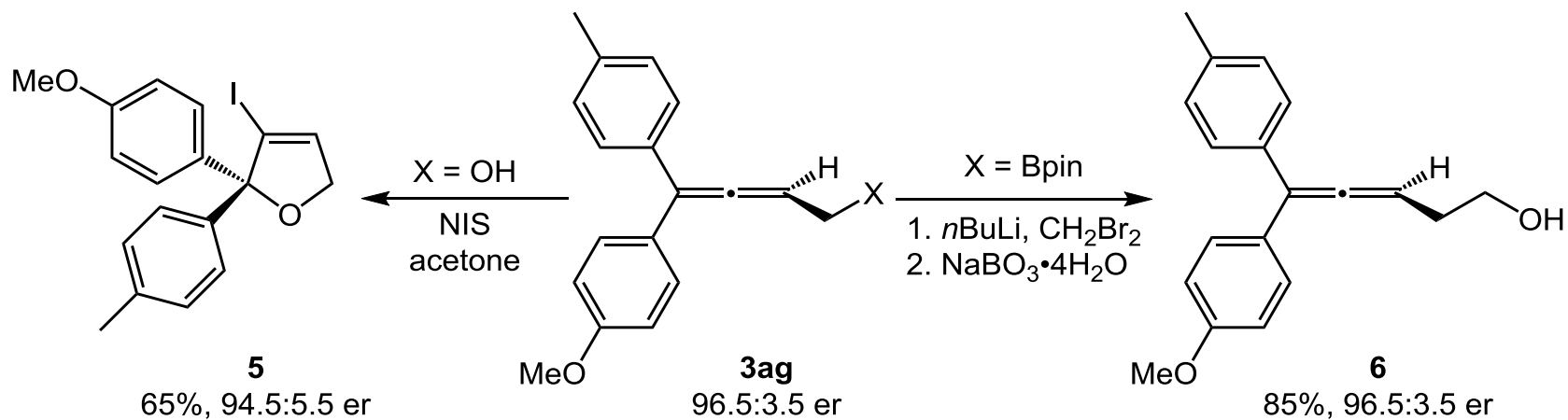


**4m**  
54%, 93:7 er

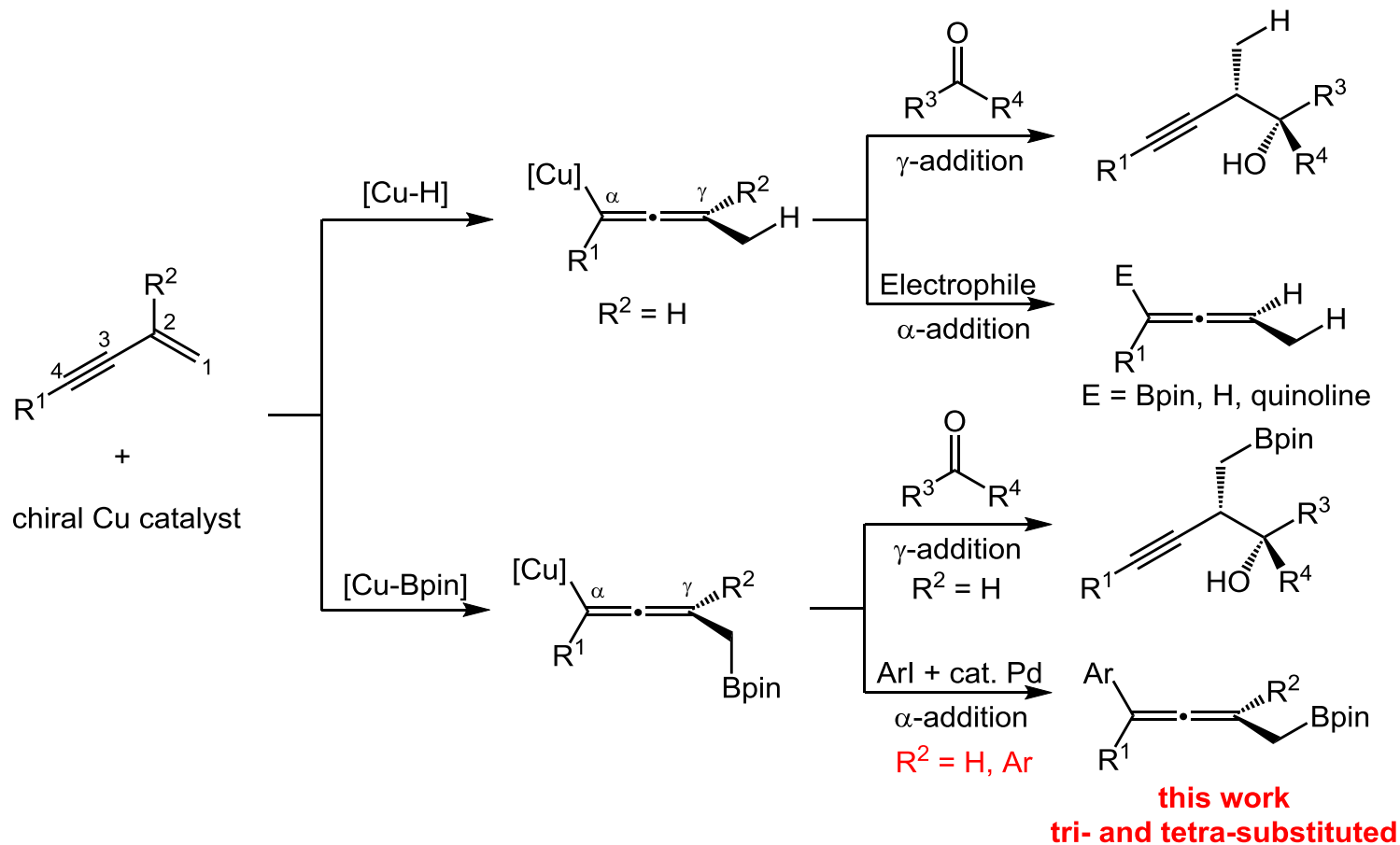


**4n**  
48%, 86.5:13.5 er

# Transformations of Products

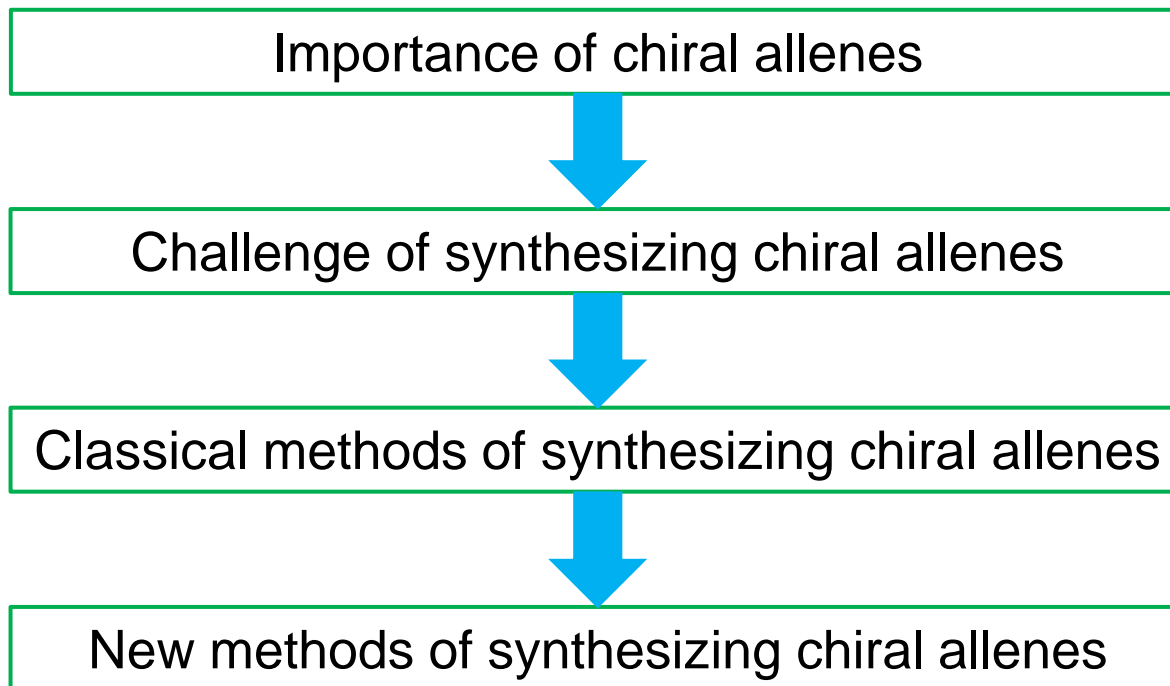


# Summary



# Writing Strategy

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# The First Paragraph

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Given their unique structural characteristics (cumulated diene and axial chirality), related biological activities, and physical and chemical properties, chiral allene scaffolds are not only widely present in natural products, pharmaceuticals, and materials, but also frequently employed as an important class of synthetic intermediates in various organic transformations. Allene chemistry has stimulated the interest of organic and medicinal chemists for decades. However, general and efficient enantioselective synthetic method to access axially chiral allenes from prochiral precursors is a longstanding challenge. Many classical methods predominantly rely on central-to-axial chirality transfer or resolution of racemic allenes. Until recently, increasing attention has focused on developing catalytic asymmetric approaches for the synthesis of chiral allenes.

# Writing Strategy

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Summary of this work



Explanation of the  
mechanism by theoretical  
calculations

## The Last Paragraph

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In summary, we have developed an efficient approach for the synthesis of multisubstituted chiral allenes with excellent enantioselectivities by cooperative Cu/Pd-catalyzed 1,4-arylboration of 1,3-enynes. By employing this protocol, the prochiral aryl-, alkyl-, and 2-substituted 1,3-enynes were smoothly converted into the corresponding tri- and tetrasubstituted allenes. Theoretical calculations disclosed that the transmetallation of allenylcopper species was the rate-limiting step, which had a much lower energy barrier than both racemization steps, to realize a highly stereospecific 1,4-arylboration of 1,3-enynes.



## Representative Examples

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**Shortly thereafter** (此后不久 soon afterwards), the groups of Ge and Engle independently disclosed the same **protocols** (协议, 规则: 方法).

Similarly, the addition of chiral Cu-Bpin species to 1,3-enynes also enables the generation of chiral allenylcopper intermediates, **which** were readily captured by aldehydes and ketones to afford the corresponding propargylic products with excellent selectivities.

关系代词**which**在非限制性定语从句中所指代和修饰的可以是主句中的名词、形容词、短语、其他从句或整个主句，在从句中作主语、动词宾语、介词宾语或表语。

The **challenge** of this strategy is **to maintain** the highly stereospecific metal-to-metal transfer.

表示“做某事的挑战”“挑战做某事”，习惯上要接不定式。

也可以改为: This strategy faces the **challenge of maintaining** the highly stereospecific metal-to-metal transfer.

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***Thanks  
for your attention***