Catalytic Enantioselective Alkyne Addition to Nitrones Enabled by Tunable Axially Chiral Imidazole-Based *P*,*N*-Ligands

Reporter: Bo Wu
Checker: Jian Chen
Date: 2024/05/13

Yin, S.; Weeks, K. N.; Aponick, A. *J. Am. Chem. Soc.* **2024**, *146*, 7185

Contents

CV of Prof. Aaron Aponick

Background:

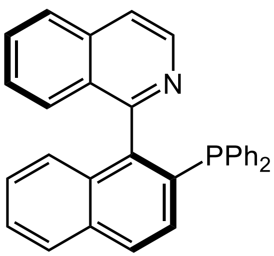
- **1994-1998** B.S., Lebanon Valley College
- **1998-2003** Ph.D., University of Michigan
- **2003-2006** Postdoc., Stanford University
- **2006-2013** Assistant Professor, University of Florida
- **2013-2020** Associate Professor, University of Florida
- **2020-present** Full Professor, University of Florida

Research Interests:

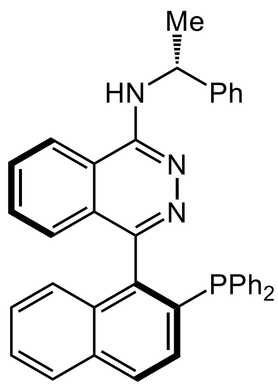
- ✓ The development of new small molecule catalysts that exhibit synthetically useful levels of selectivity in new chemical transformations.
- ✓ The development of efficient synthetic strategies for the preparation of bioactive natural products with interesting molecular architecture.

Introduction

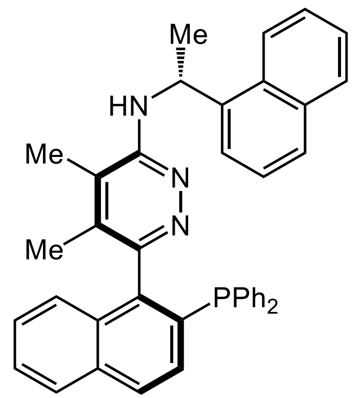
Atropisomeric *P*,*N*-Ligands



QUINAP

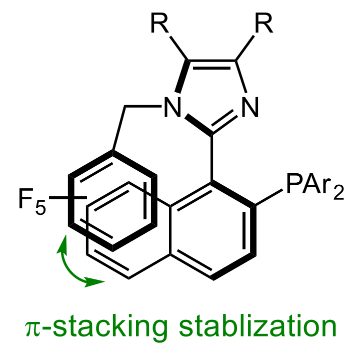


PINAP



Pyrinap

C_1, 6-Membered heteroaromatics

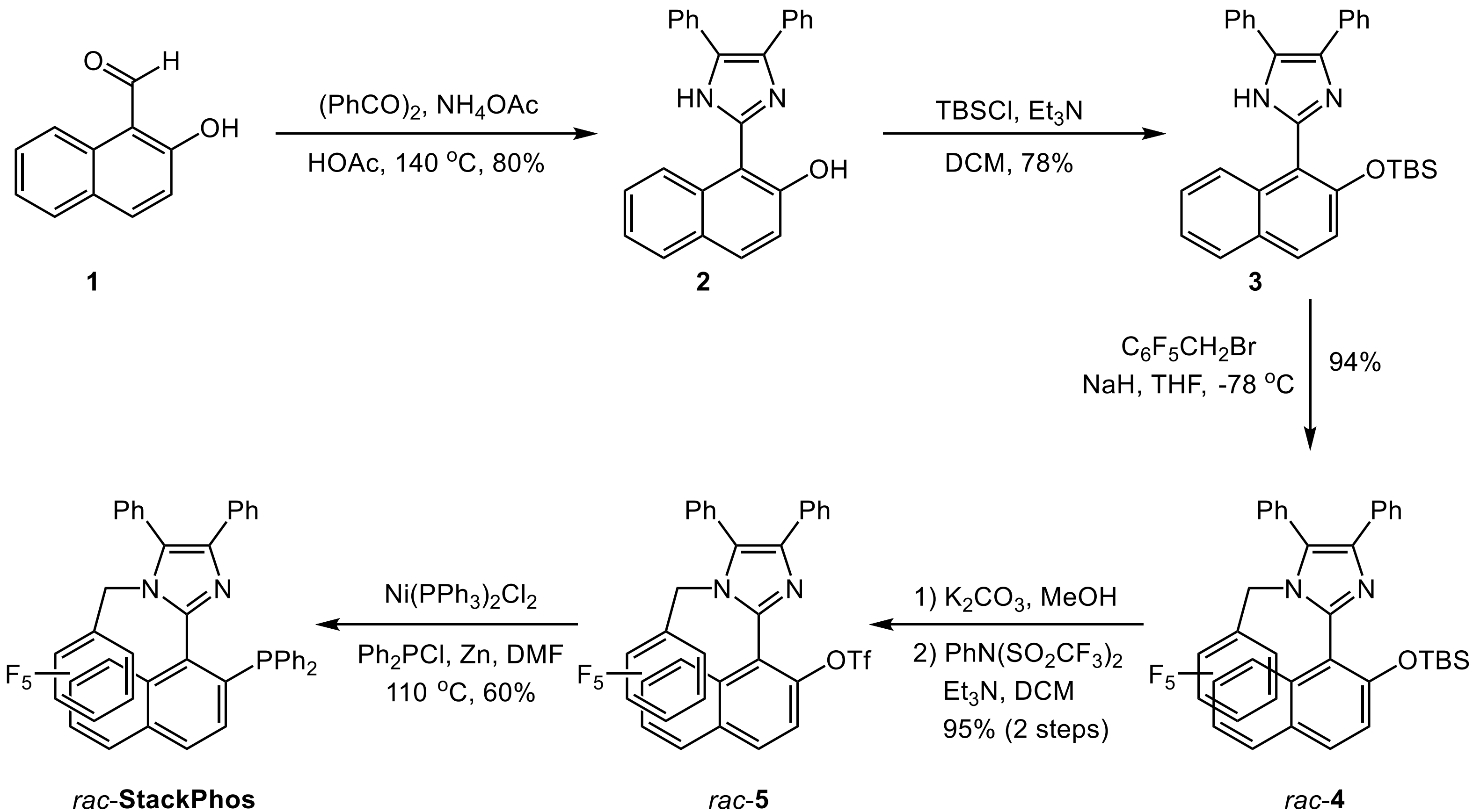


StackPhos

C_1, 5-Membered heteroaromatics

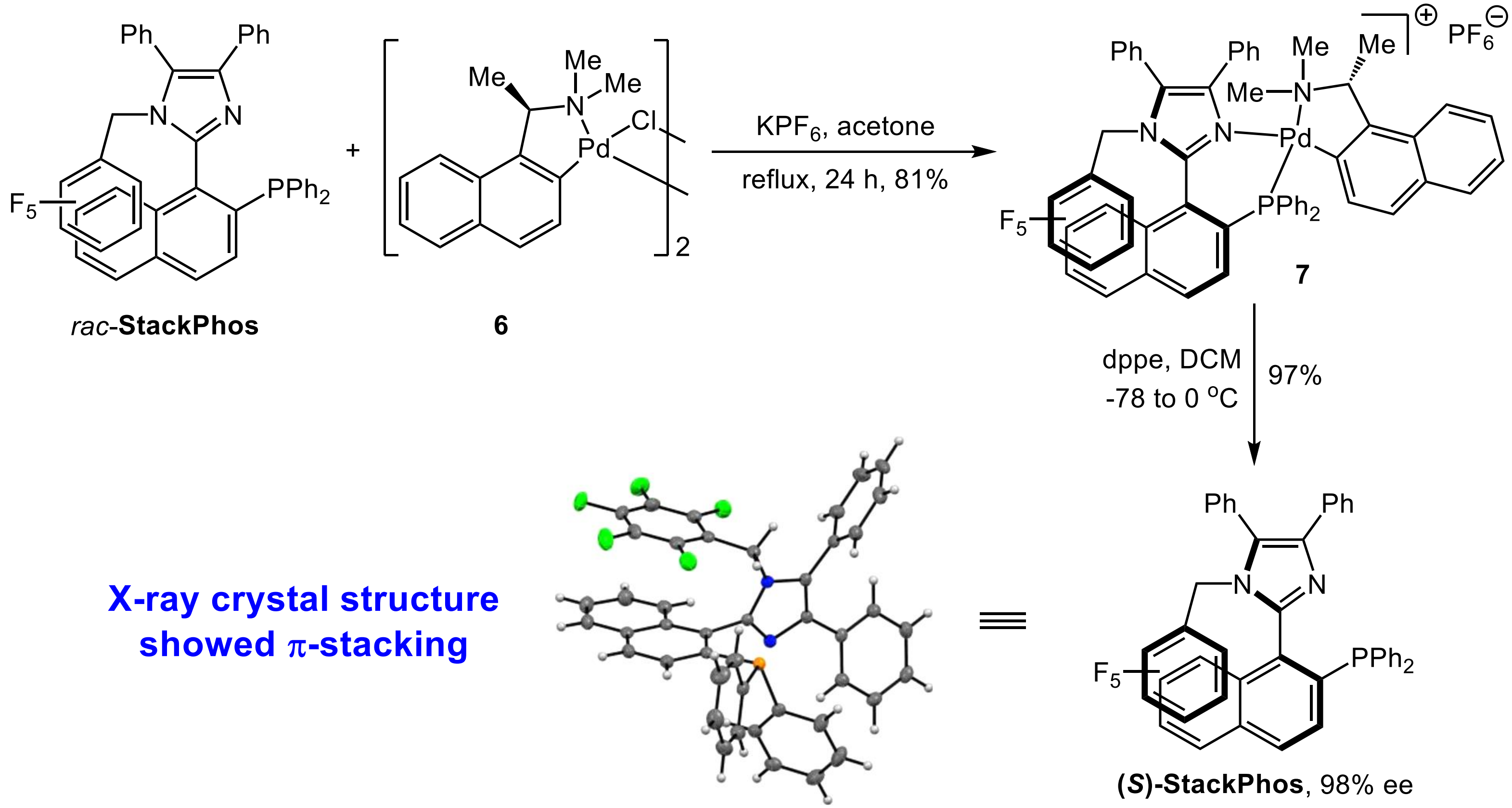
Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548

Synthesis of (*S*)-StackPhos



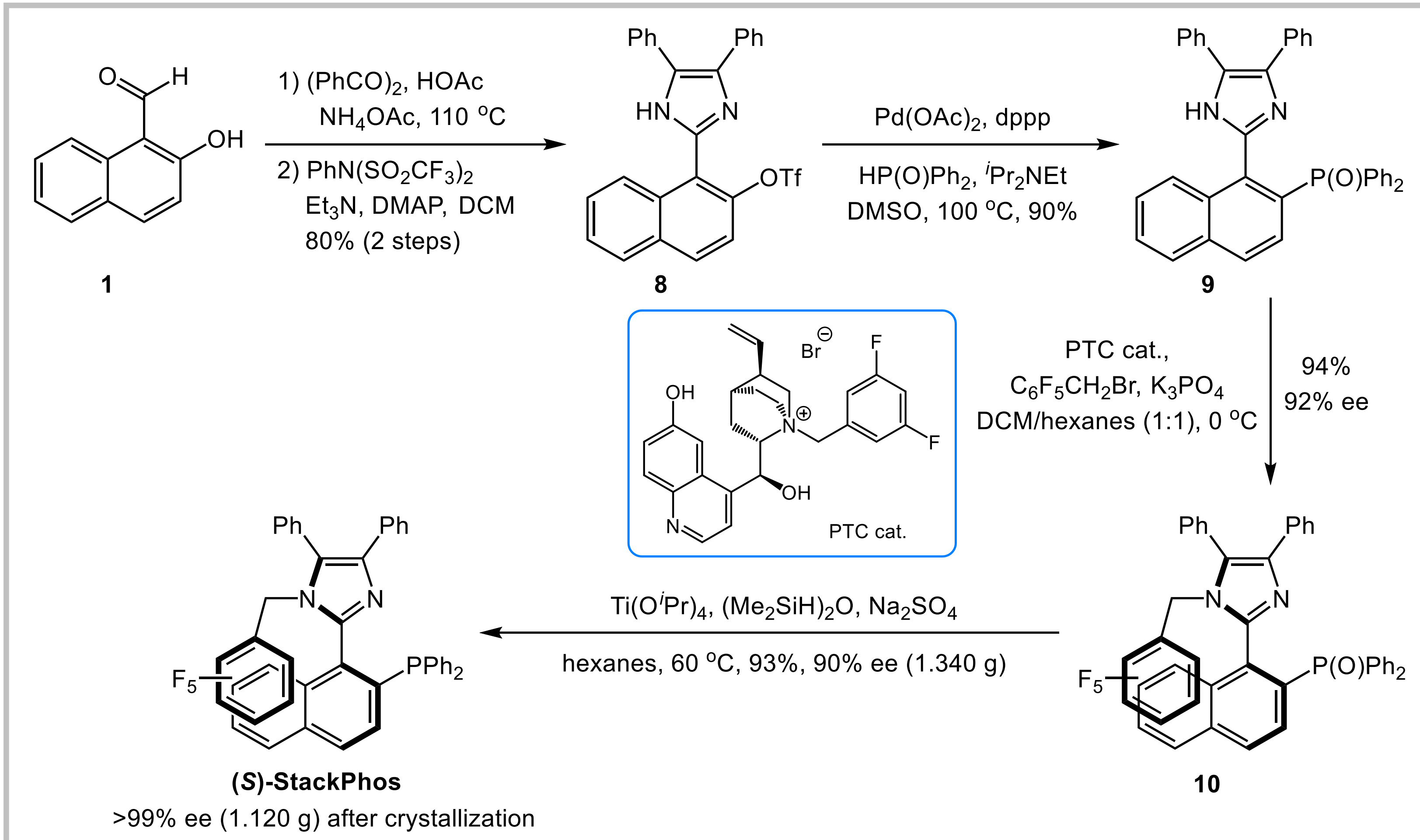
Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548

Synthesis of (*S*)-StackPhos



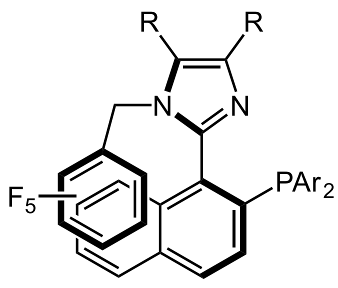
Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548

Catalytic Synthesis of (*S*)-StackPhos



Yin, S.; Liu, J.; Weeks, K. N.; Aponick, A. *J. Am. Chem. Soc.* **2023**, *145*, 28176

Application of Chiral StackPhos

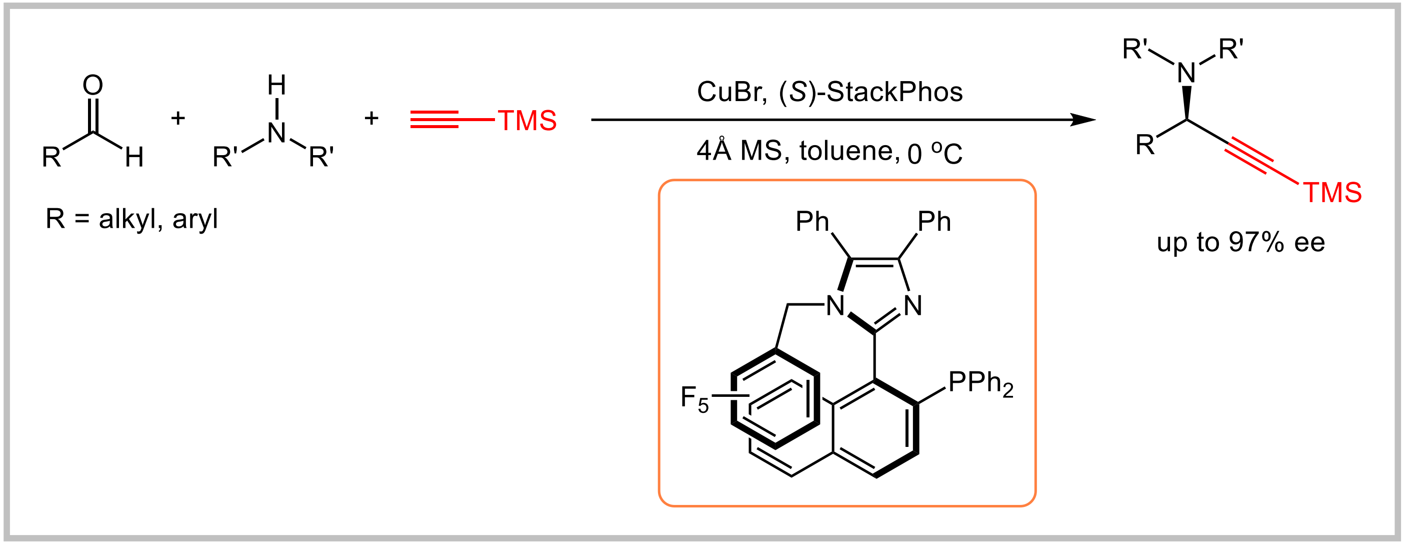


StackPhos

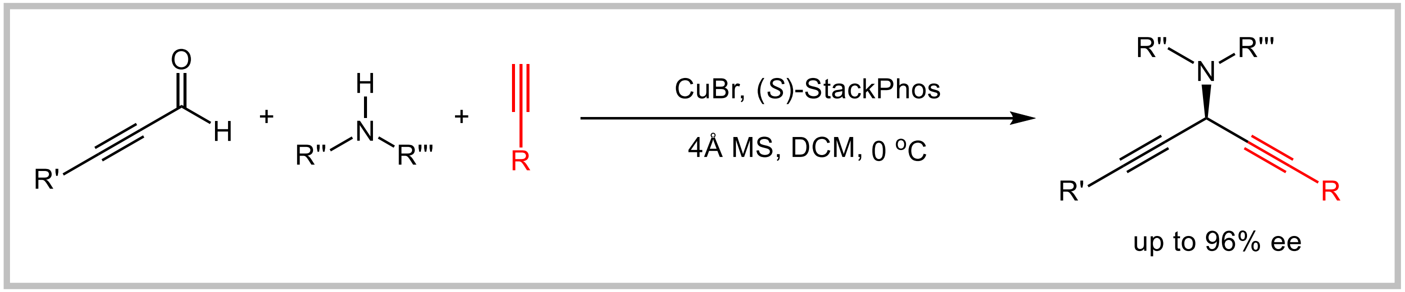
Application

Cu-Catalyzed Asymmetric Alkynylation
Alkynylation of Iminium Ions (C=N)
Alkynylation of *N*-Heteroarenes (C=N)
Alkynylation of Meldrum's Acids (C=C)
Alkynylation of Chromones (C=O)

Asymmetric Alkynylation of Iminium Ions

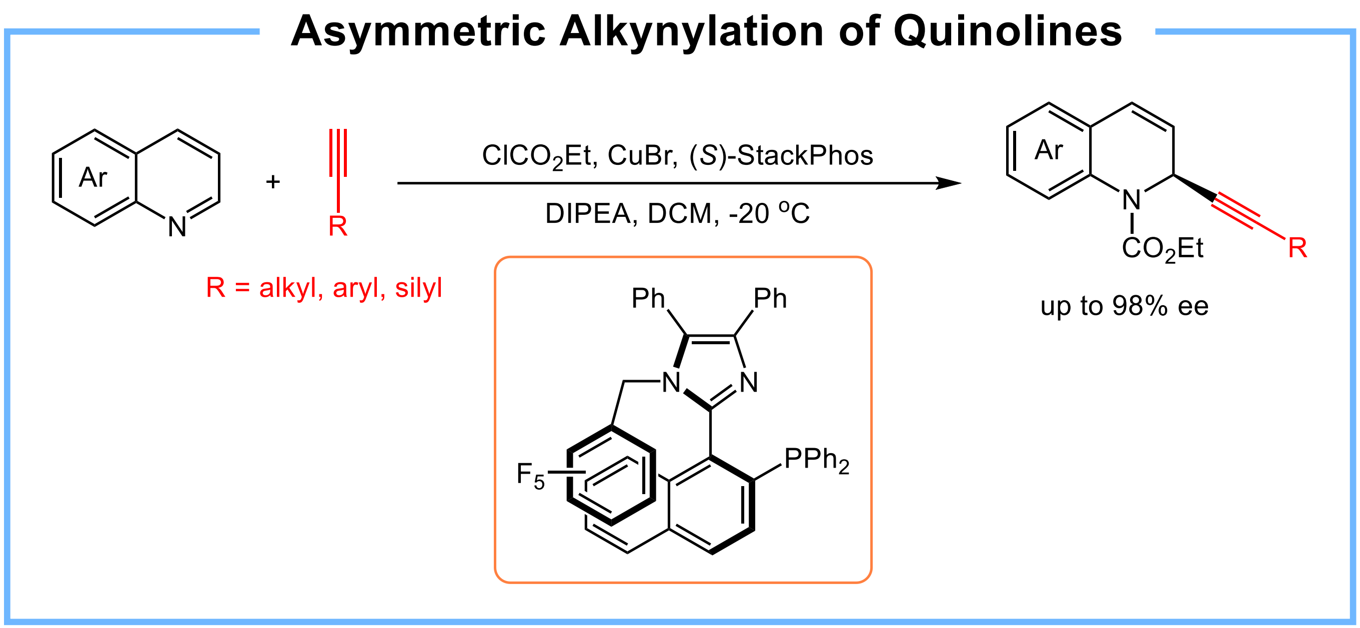


Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548



Paioti, P. H. S.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2016**, *138*, 2150

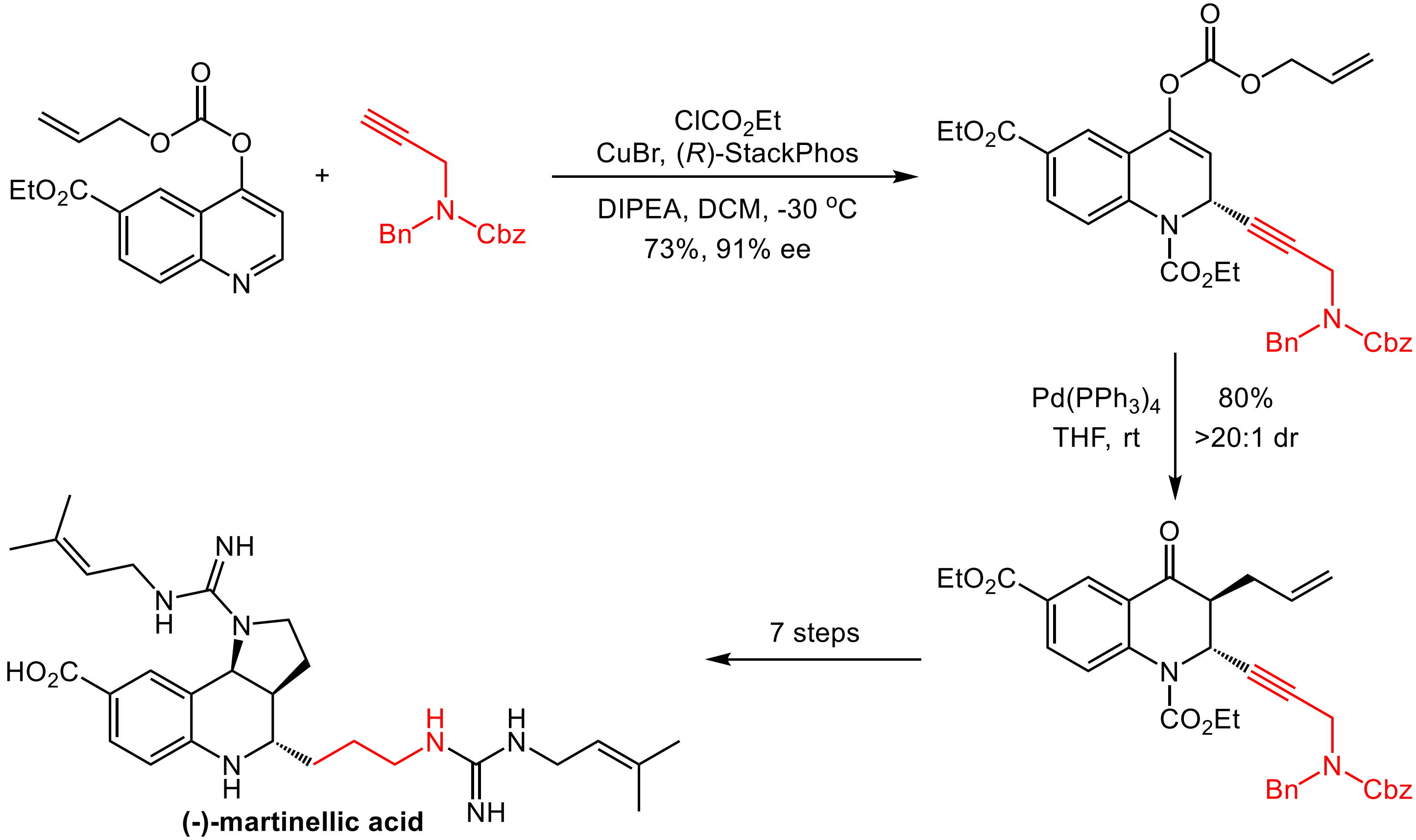
Asymmetric Alkynylation of *N*-Heteroarenes



Pappoppula, M.; Cardoso, F. S. P.; Aponick, A. *Angew. Chem. Int. Ed.* **2015**, *54,* 15202

Asymmetric Alkynylation of *N*-Heteroarenes

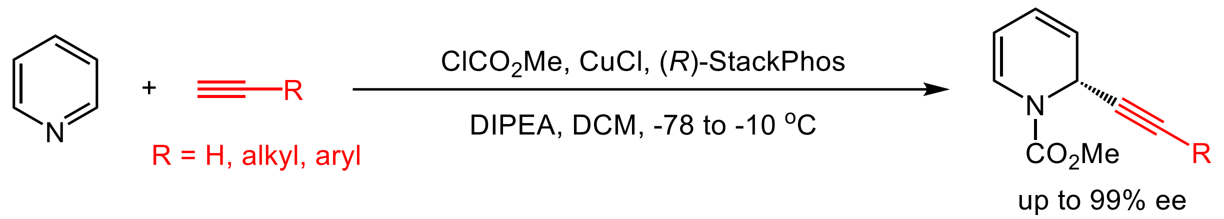
Total Synthesis of (-)-Martinellic Acid



Pappoppula, M.; Aponick, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 15827

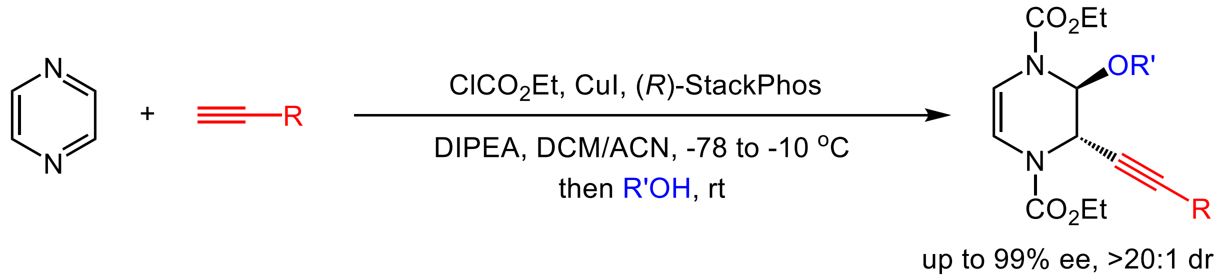
Asymmetric Alkynylation of *N*-Heteroarenes

Asymmetric Alkynylation of Pyridine



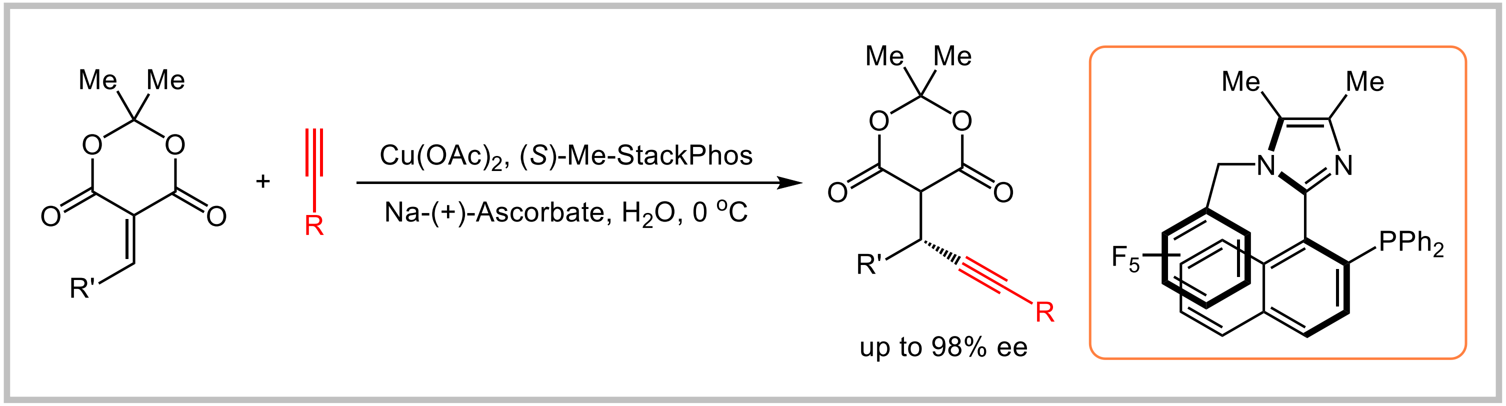
Pappoppula, M.; Aponick, A. *Angew. Chem. Int. Ed.* **2023**, *62,* e202312967

Asymmetric Alkynylation of Pyrazine



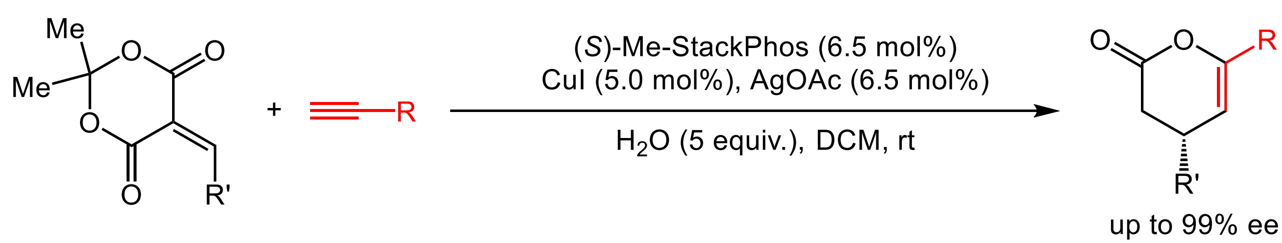
Ketelboeter, D. R.; Pappoppula, M.; Aponick, A. *J. Am. Chem. Soc.* **2024**, *146*, 11610

Asymmetric Alkynylation of Meldrum's Acids



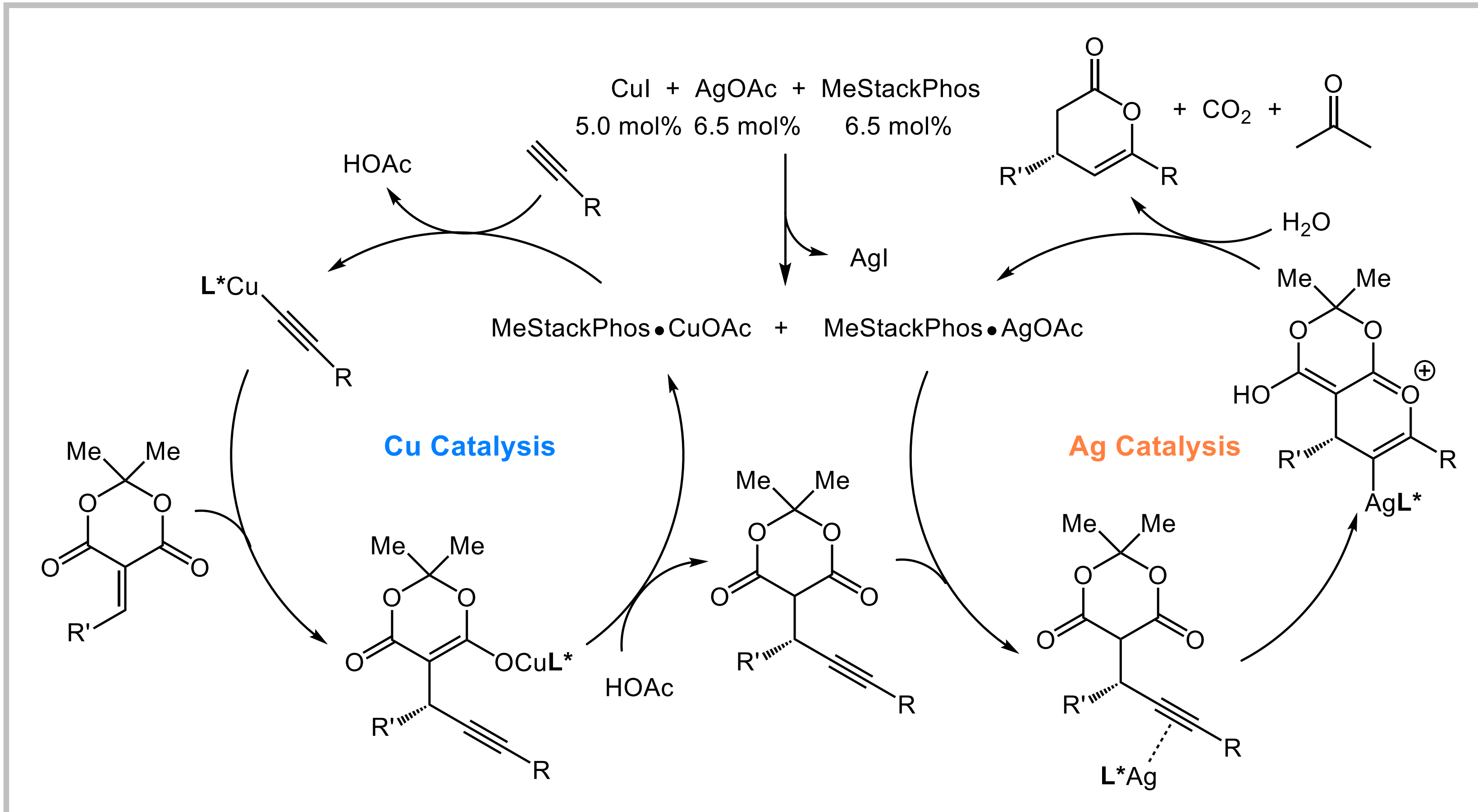
Mishra, S.; Liu, J.; Aponick, A. *J. Am. Chem. Soc.* **2017**, *139*, 3352

Asymmetric Orthogonal Tandem Reaction



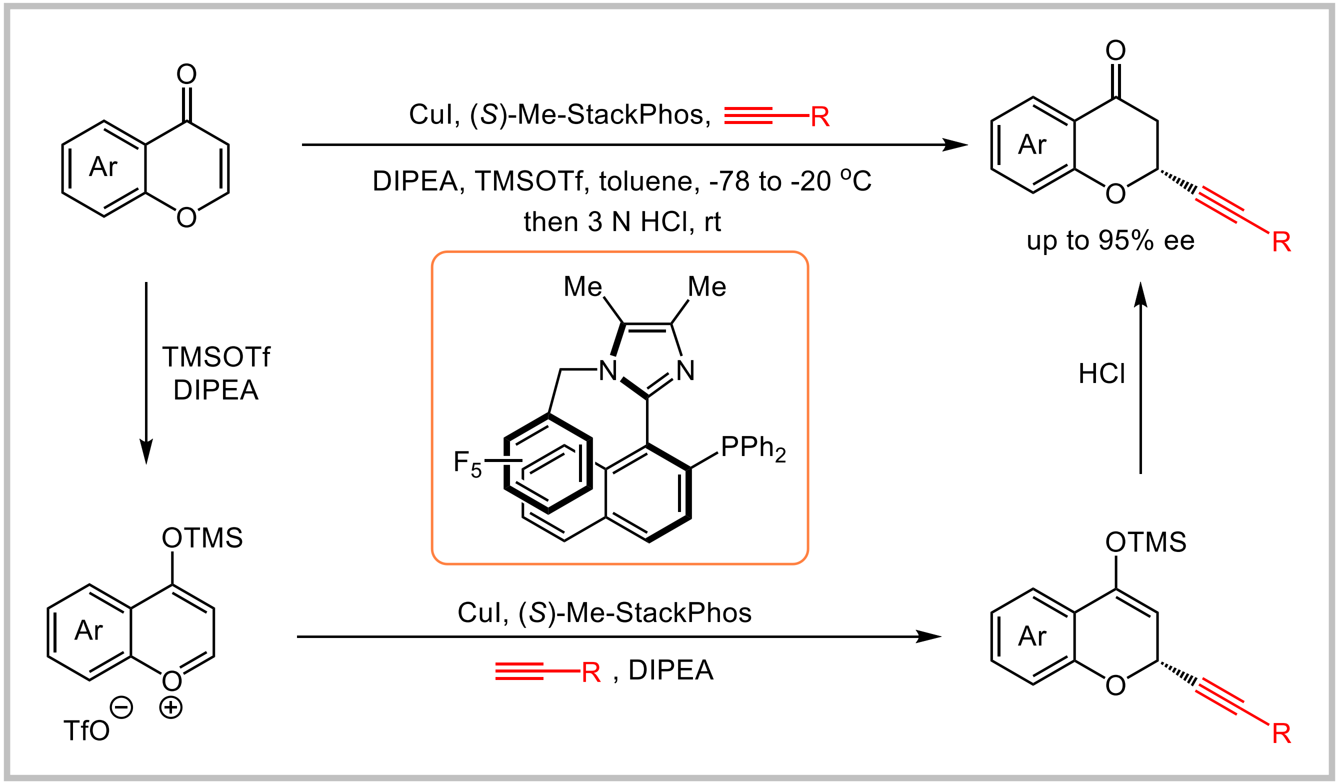
Mishra, S.; Aponick, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 9485

Asymmetric Alkynylation of Meldrum's Acids



Mishra, S.; Aponick, A. *Angew. Chem. Int. Ed.* **2019**, *58,* 9485

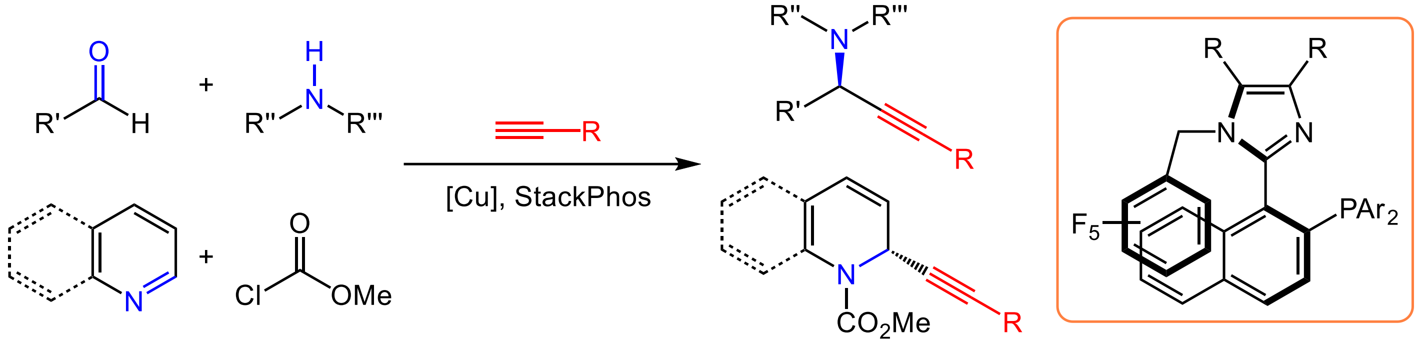
Asymmetric Alkynylation of Chromones



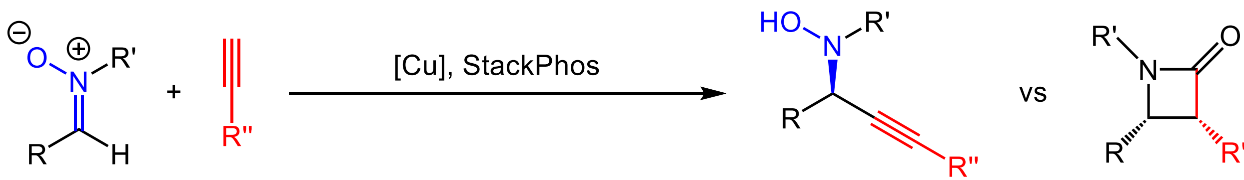
DeRatt, L. G.; Pappoppula, M.; Aponick, A. *Angew. Chem. Int. Ed.* **2019**, *58,* 8416

Asymmetric Alkynylation of Nitrones

Asymmetric Alkynylation of Iminium Ions and *N*-Heteroarenes



Asymmetric Alkynylation of Nitrones



Alkynylation Product
Desired

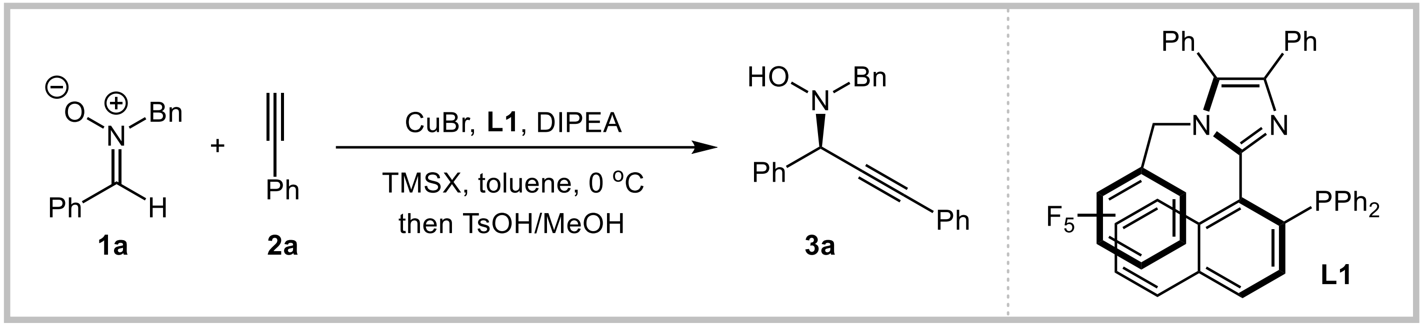
Kinugasa Product

Challenges

- ♠ **Competing Kinugasa reaction** ♠ **Low reactivity for Cu-acetylides addition**
- ♠ **Enantiocontrol for acyclic, unsymmetrical iminium-type intermediate**

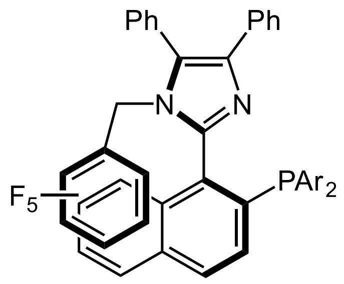
Yin, S.; Weeks, K. N.; Aponick, A. *J. Am. Chem. Soc.* **2024**, *146*, 7185

Optimization of Reaction Conditions

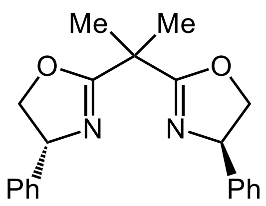


Entry	Activating Reagent	Yield (%)	Ee (%)
1	--	0	--
2	TMSOTf (1.3 equiv.)	95	55
3	TMSCl (1.3 equiv.)	31	80
4	TMSBr (1.3 equiv.)	94	81
5	**TMSBr (1.1 equiv.)**	**91**	**81**

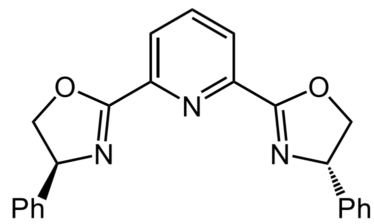
Optimization of Reaction Conditions



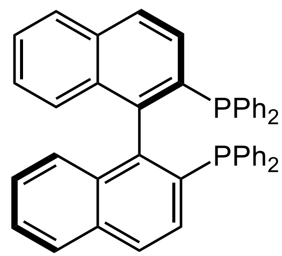
L1 Ar = C_6H_5, 91%, 81% ee
L2 Ar = 3,5-$Me_2C_6H_3$, 93%, 82% ee
L3 Ar = 4-$MeOC_6H_4$, 94%, 82% ee
L4 Ar = 4-$F_3CC_6H_4$, 92%, 75% ee
L5 Ar = 4-FC_6H_4, 91%, 88% ee
L6 Ar = 2-furyl, 92%, 89% ee
L6 Ar = 2-furyl, 92%, 93% ee (Tol./DCM 1:1, -40 ^{o}C)



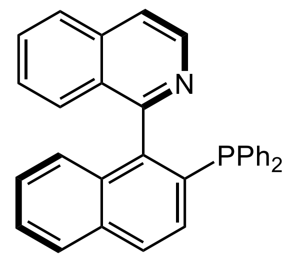
(*R*,*R*)-PhBOX
95%, 19% ee



(*S*,*S*)-PhPyBOX
45%, 25% ee



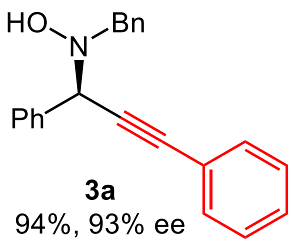
(*R*)-BINAP
39%, 4% ee



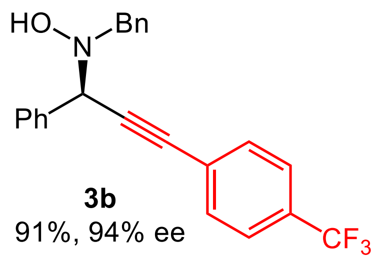
(*R*)-QUINAP
64%, 66% ee

Substrate Scope

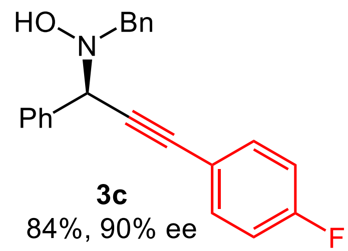
Scope of Alkynes



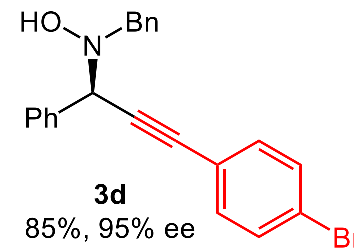
3a
94%, 93% ee



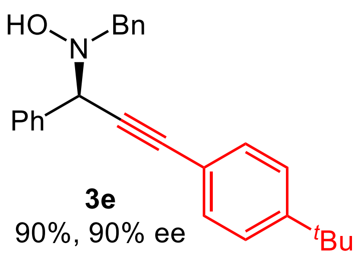
3b
91%, 94% ee



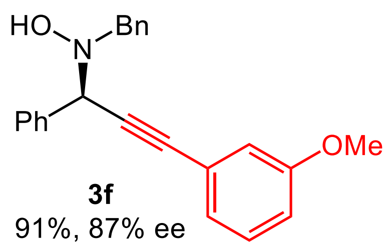
3c
84%, 90% ee



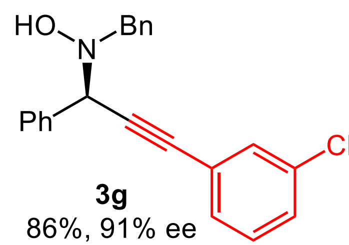
3d
85%, 95% ee



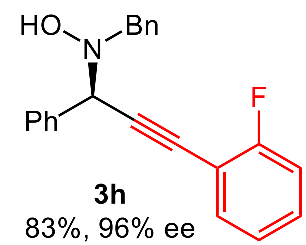
3e
90%, 90% ee



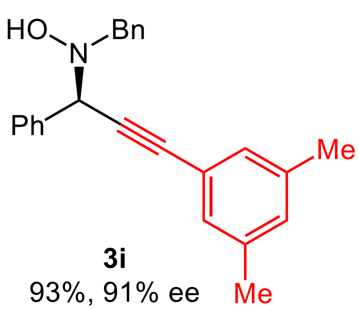
3f
91%, 87% ee



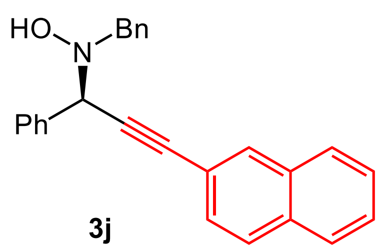
3g
86%, 91% ee



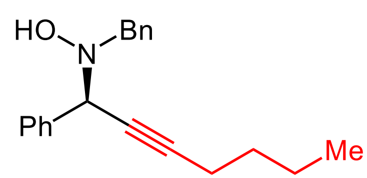
3h
83%, 96% ee



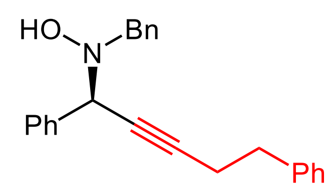
3i
93%, 91% ee



3j
96%, 92% ee



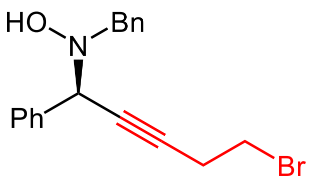
3k
92%, 91% ee



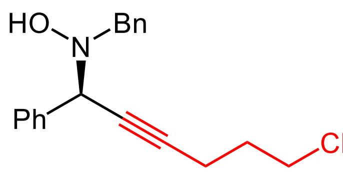
3l
87%, 91% ee

Substrate Scope

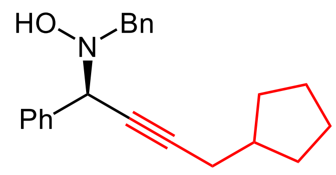
Scope of Alkynes



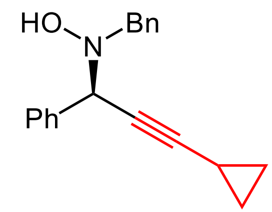
3m
86%, 94% ee



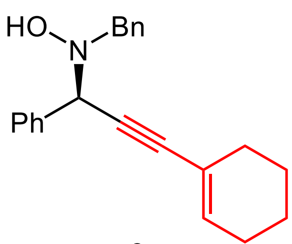
3n
87%, 93% ee



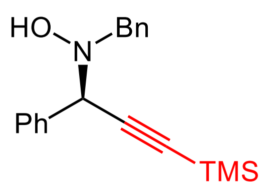
3o
88%, 91% ee



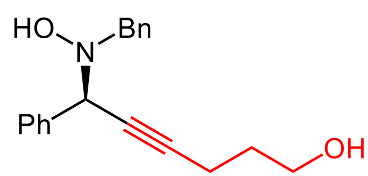
3p
81%, 90% ee



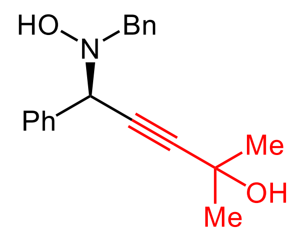
3q
85%, 92% ee



3r
94%, 92% ee



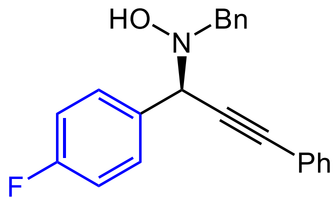
3s
84%, 87% ee



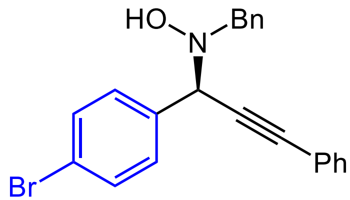
3t
80%, 82% ee

Substrate Scope

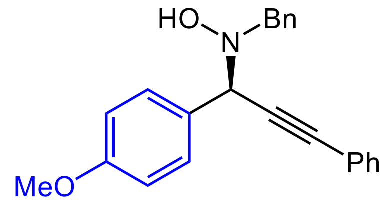
Scope of Nitrones



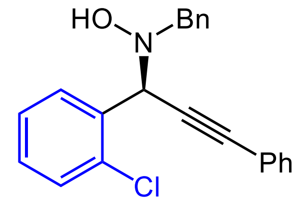
4a
92%, 92% ee



4b
93%, 94% ee

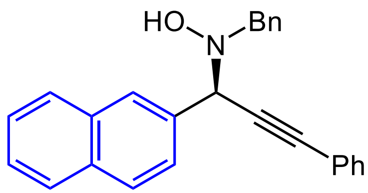


4c
96%, 92% ee

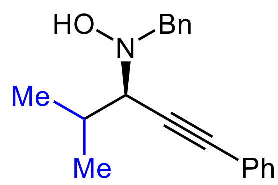


4d
90%, 96% ee

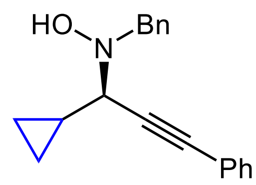
with (*S*)-StackPhos L1, TMSOTf



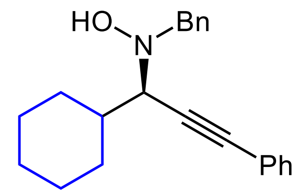
4e
86%, 95% ee



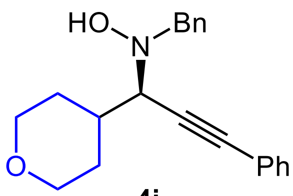
4f 86%, 97% ee
(71% ee with **L6**)



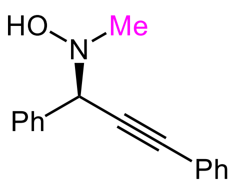
4g
87%, 91% ee



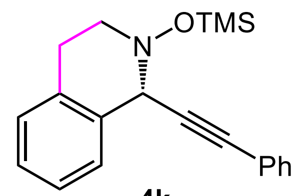
4h
90%, 95% ee



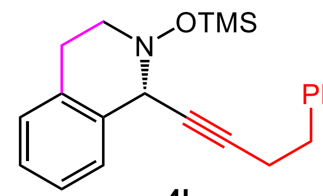
4i
90%, 93% ee



4j
85%, 91% ee

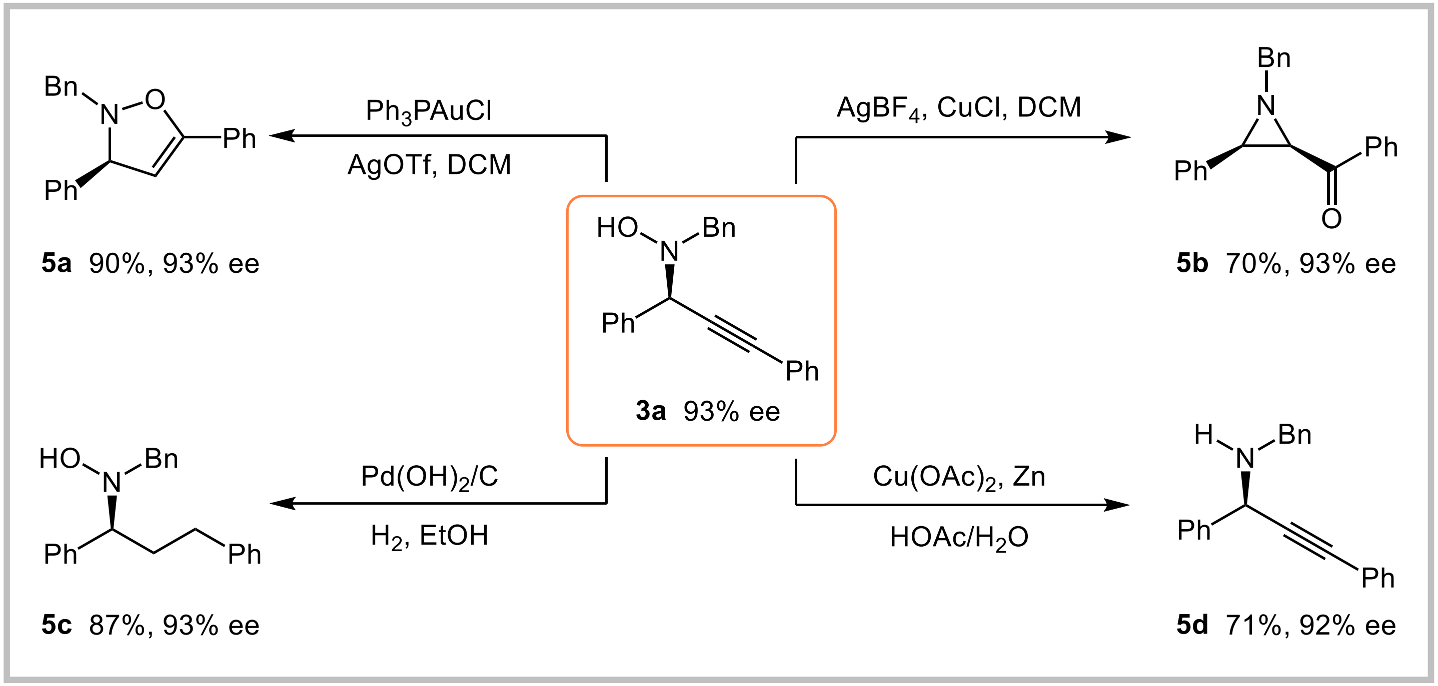


4k
75%, 95% ee



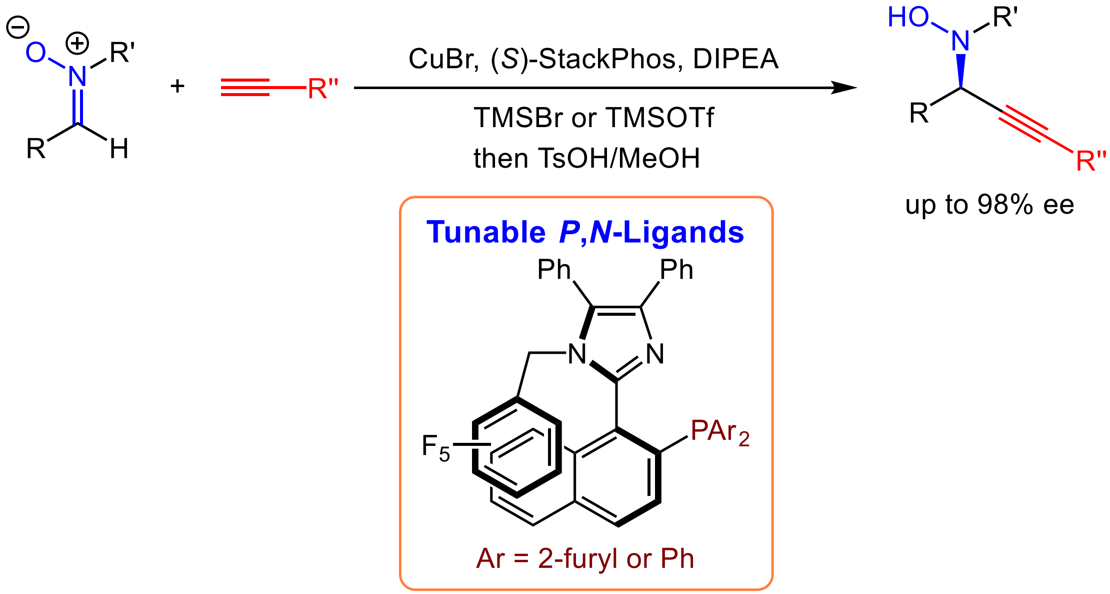
4l
72%, 98% ee

Transformations



Summary

Asymmetric Alkynylation of Nitrones



The First Paragraph

Writing Strategy

The importance of the development of new chiral ligands and catalysts in the synthesis of enantioenriched molecules

↓

The importance of metal-catalyzed enantioselective alkyne addition to C=O and C=N electrophiles

The First Paragraph

Advances in enantioselective catalysis, fueled by the design of new chiral ligands and catalysts, have revolutionized the synthesis of enantioenriched molecules. In metal-catalyzed enantioselective alkyne addition to C=O and C=N electrophiles, the use of specific metal-based catalysts such as copper or zinc obviate the need for strong bases or stoichiometric amounts of preformed metal acetylides. This strategy enables the direct addition of abundant, commercially available terminal alkynes. A variety of chiral ligands or chiral cocatalysts have been applied in these enantioselective C−C bond forming reactions, providing chiral propargylic alcohols and amines efficiently.

The Last Paragraph

Writing Strategy

Summary of this work

↓

Outlook of this work

The Last Paragraph

In conclusion, we have developed a Cu-catalyzed enantioselective alkyne addition to nitrones that addresses the challenges faced in Zn- or In-catalyzed processes. By tuning the substituents on the phosphorus of the axially chiral imidazole-based *P*,*N*-ligands, a highly enantioselective reaction across a broad scope of alkynes and nitrones was achieved. This method enables the streamlined synthesis of chiral propargyl *N*-hydroxylamines by enantioselective C-C bond formation and offers a new way to produce optically active nitrogen-containing compounds. Further applications of these ligands will be reported in due course.

Representative Examples

Advances in enantioselective catalysis, fueled by the design of new chiral ligands and catalysts, have revolutionized the synthesis of enantioenriched molecules. (阐述配体或催化剂的重要性)

In contrast, nitrones are versatile intermediates used in the synthesis of biologically important nitrogen-containing compounds, but the corresponding reaction is quite difficult *vide infra*. (见下文，阐述原因)

With the seminal work on $Zn(OTf)_2$-catalyzed alkyne addition to nitrone, Carreira later utilized a mannose-derived chiral auxiliary on nitrones with substoichiometric $Zn(OTf)_2$ or stoichiometric $ZnCl_2$ for selective alkyne addition. (阐述别人工作)

Acknowledgement

Thanks
for your attention