The Catalytic, Enantioselective Favorskii Reaction: In Situ Formation of Metal Alkynylides and Their Additions to Aldehydes

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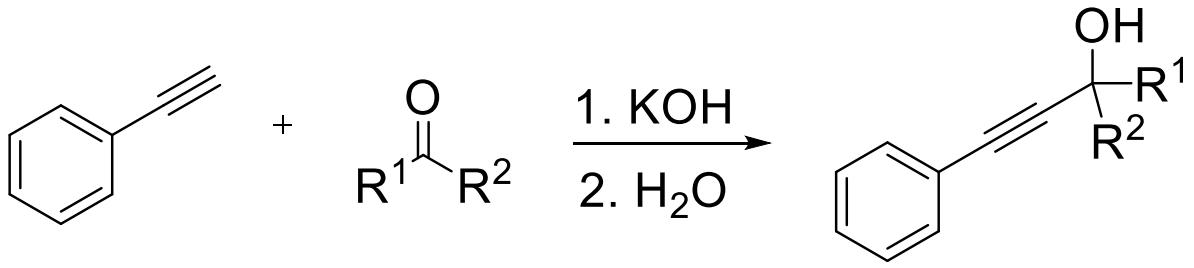
Denmark Laboratory Group Meeting

May 26, 2020

Overview

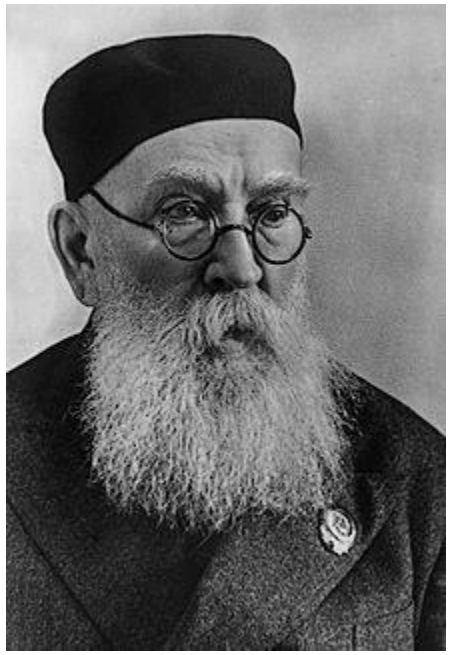
- Background
- Comparisons to Similar Methods
- Mechanism, Stereochemistry, and Scope
  - Zinc
  - Indium
  - Copper
  - Rhodium/Ruthenium
- Conclusions

The Classic Favorskii Reaction



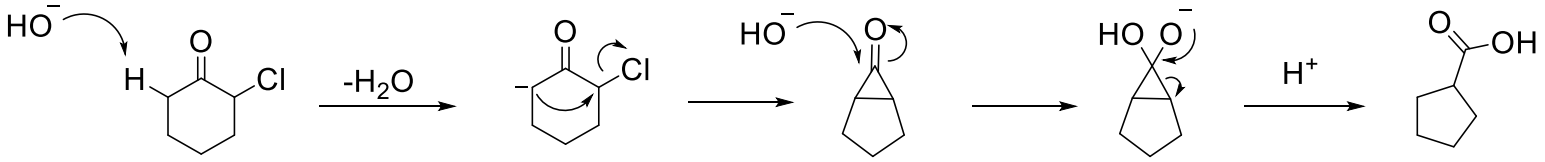
R^1= aryl, alkyl
R^2= alkyl, H

- Stoichiometric KOH
- Competitive formation of aldol condensation
- Other degradation byproducts



Alexei Favorskii

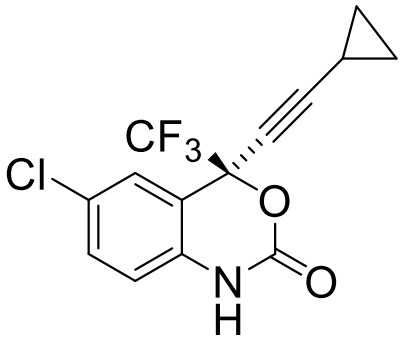
Not to be confused with the Favorskii Rearrangement:



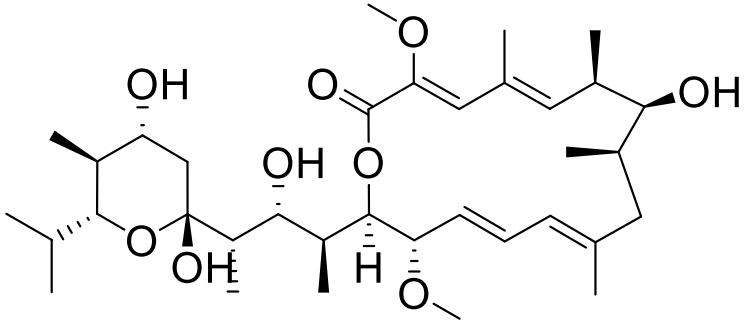
Favorsky, A. E. *Bull. Soc. Chim. Fr.* **1907**, *2*, 1087

Background

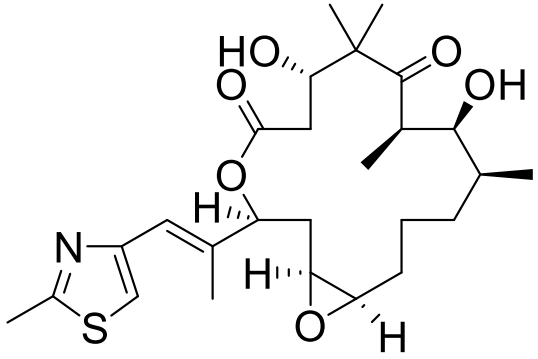
- C-C bond-forming reaction
- Resulting propargylic alcohol products are useful building blocks



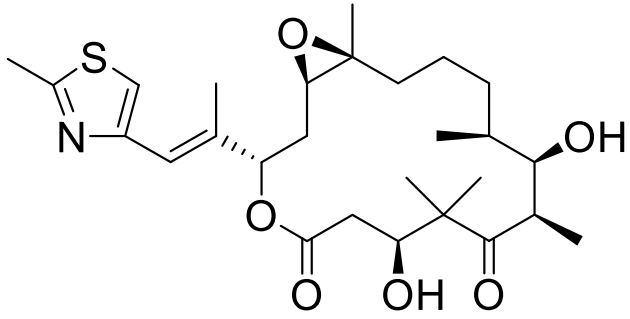
efavirenz



Bafilomycin A_1



Epothilone A

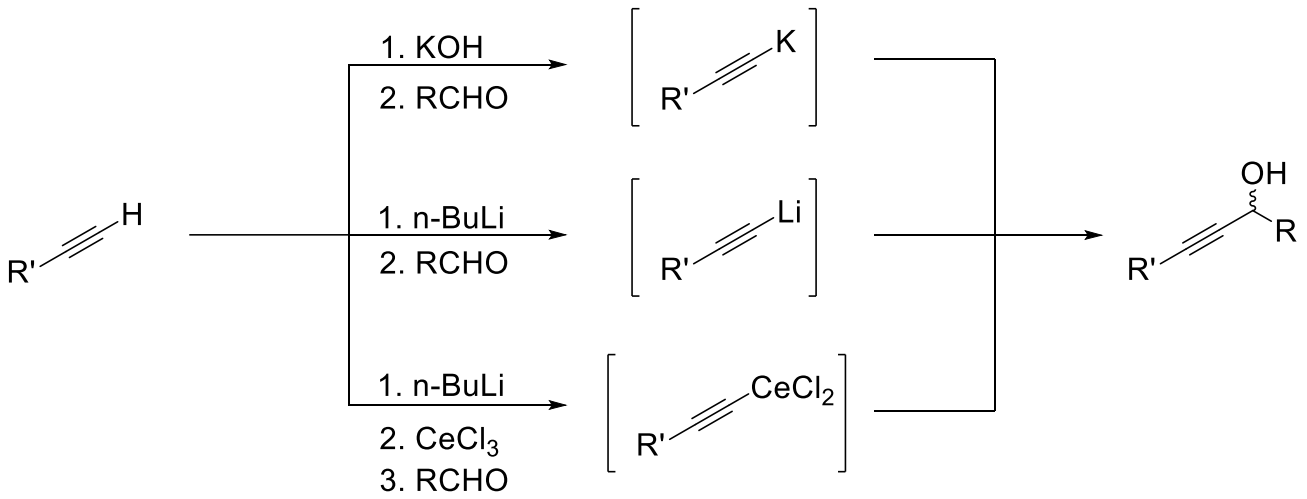


Epothilone B

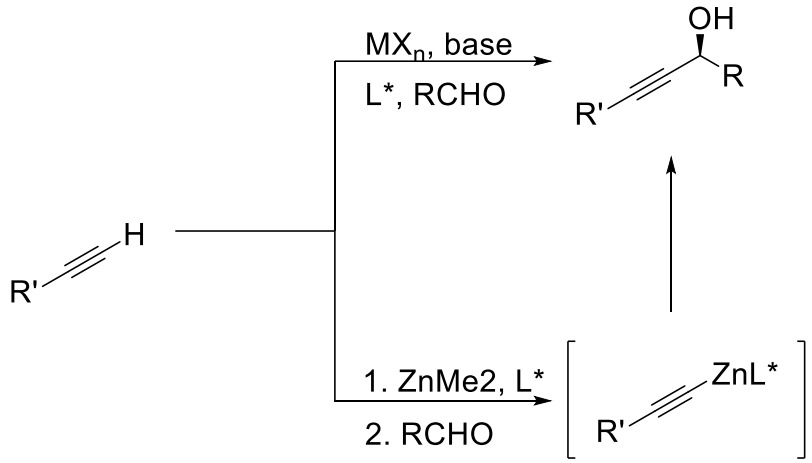
Carreira, E. M. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 2957.
Carreira, E. M. et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 578.
Carreira, E. M. et al. *J. Org. Chem.* **2001,** *66,* 6410.

Background

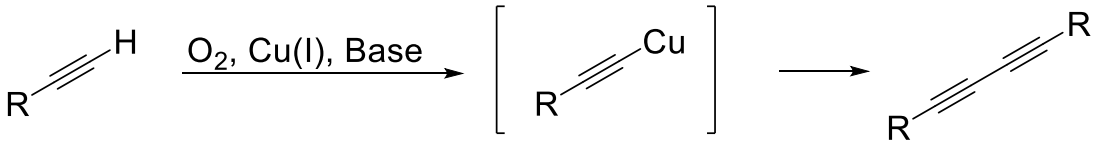
Traditional, non-enantioselective methods



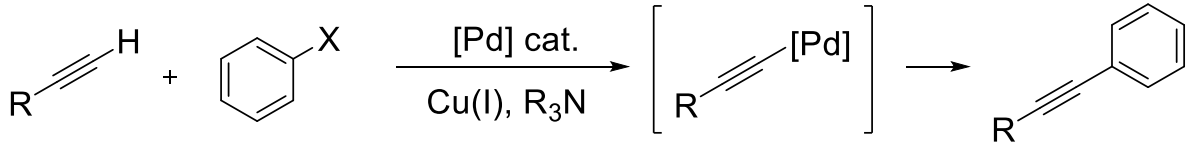
Enantioselective methods



Glaser-Hay



Sonogashira

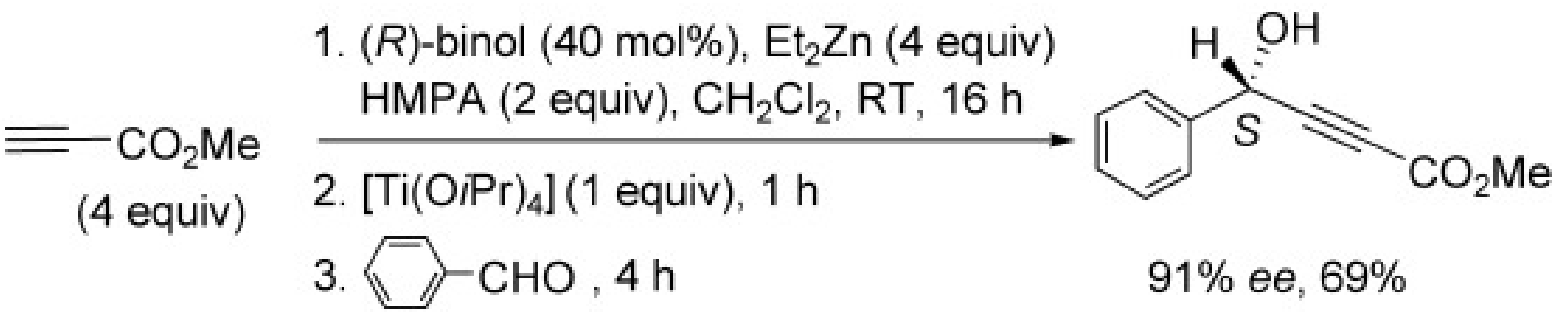


Phan, N. et al. *J. Org. Chem.* **1996**, *61*, 416.
Koert, U. et al. *Tetrahedron Lett.* **1997**, *38*, 3879.
Kobayashi, J. et al. *Tetrahedron* **1999**, *55*, 4583.
Hay, A. S. J. *Org. Chem.* **1962**, 27, 3320.
Sonogashira, K. et al. *Tetrahedron Lett.* **1975**, *16*, 4467.

Comparisons to Similar Methods

Dialkylzinc-Mediated Alkynylation of Aldehydes

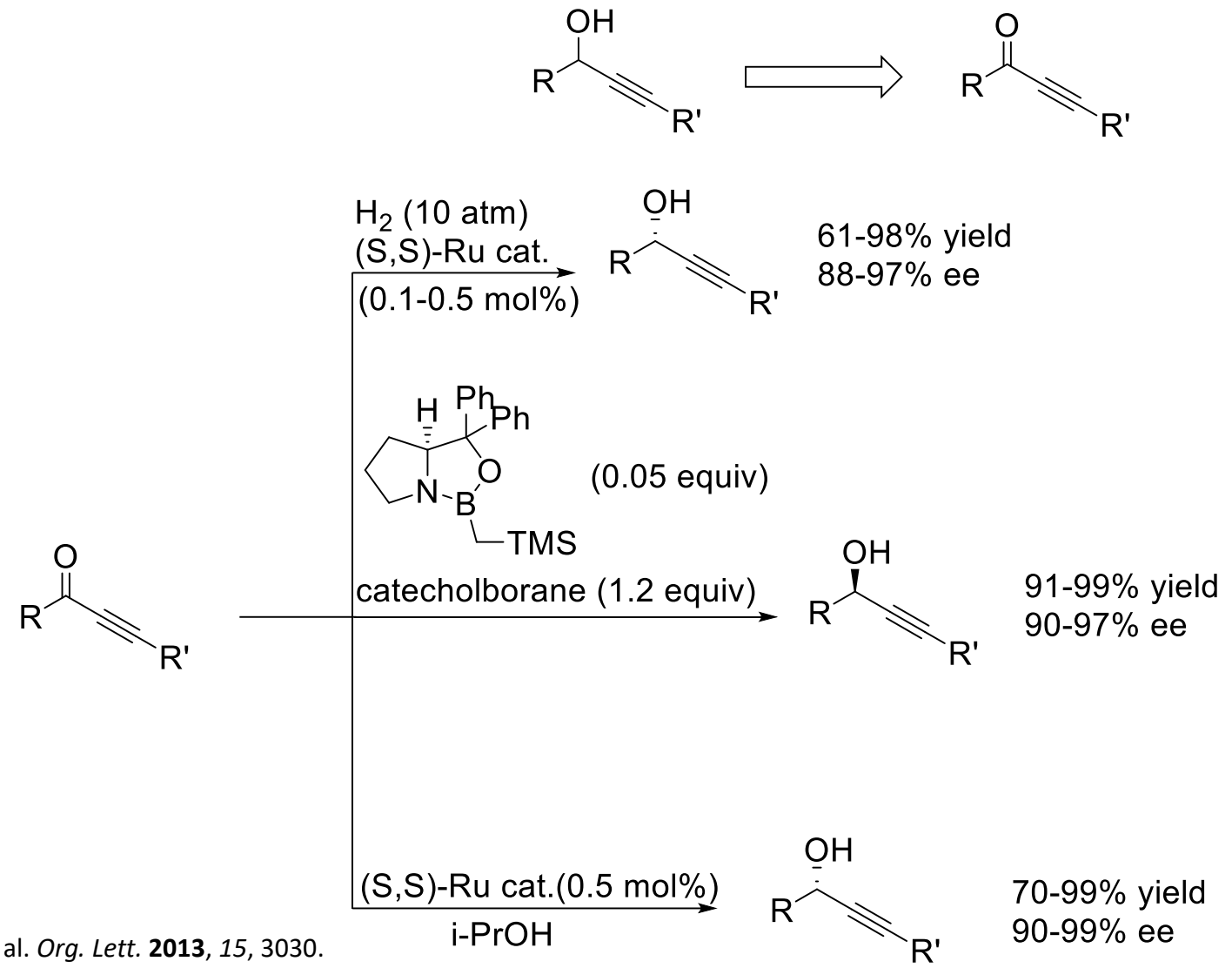
- Stoichiometric amounts of dialkylzinc reagents
- Robust and has similar broad scope to forming the metal alkynylide catalytically
- Can add alkyl propiolate nucleophiles
- Not atom economical
- Requires inert conditions

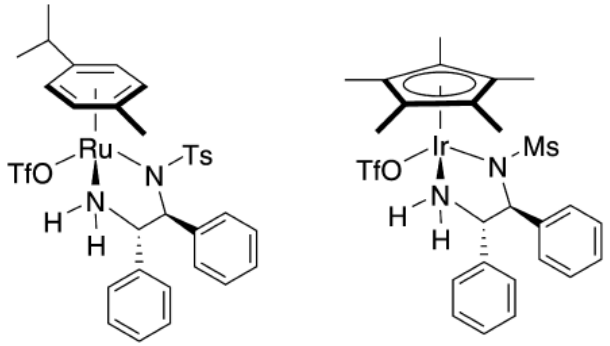


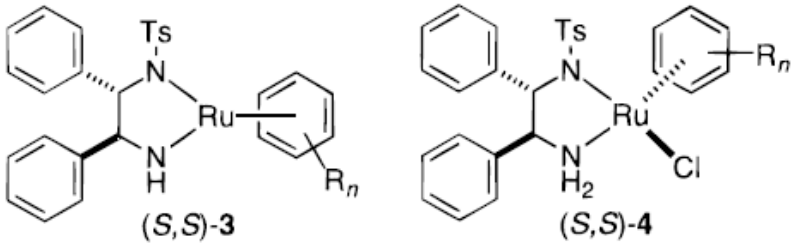
Pu, L. et al. *Angew. Chem., Int. Ed.* **2006**, *118*, 128.

Comparisons to Similar Methods

Asymmetric Reductions of Alkynyl Ketones

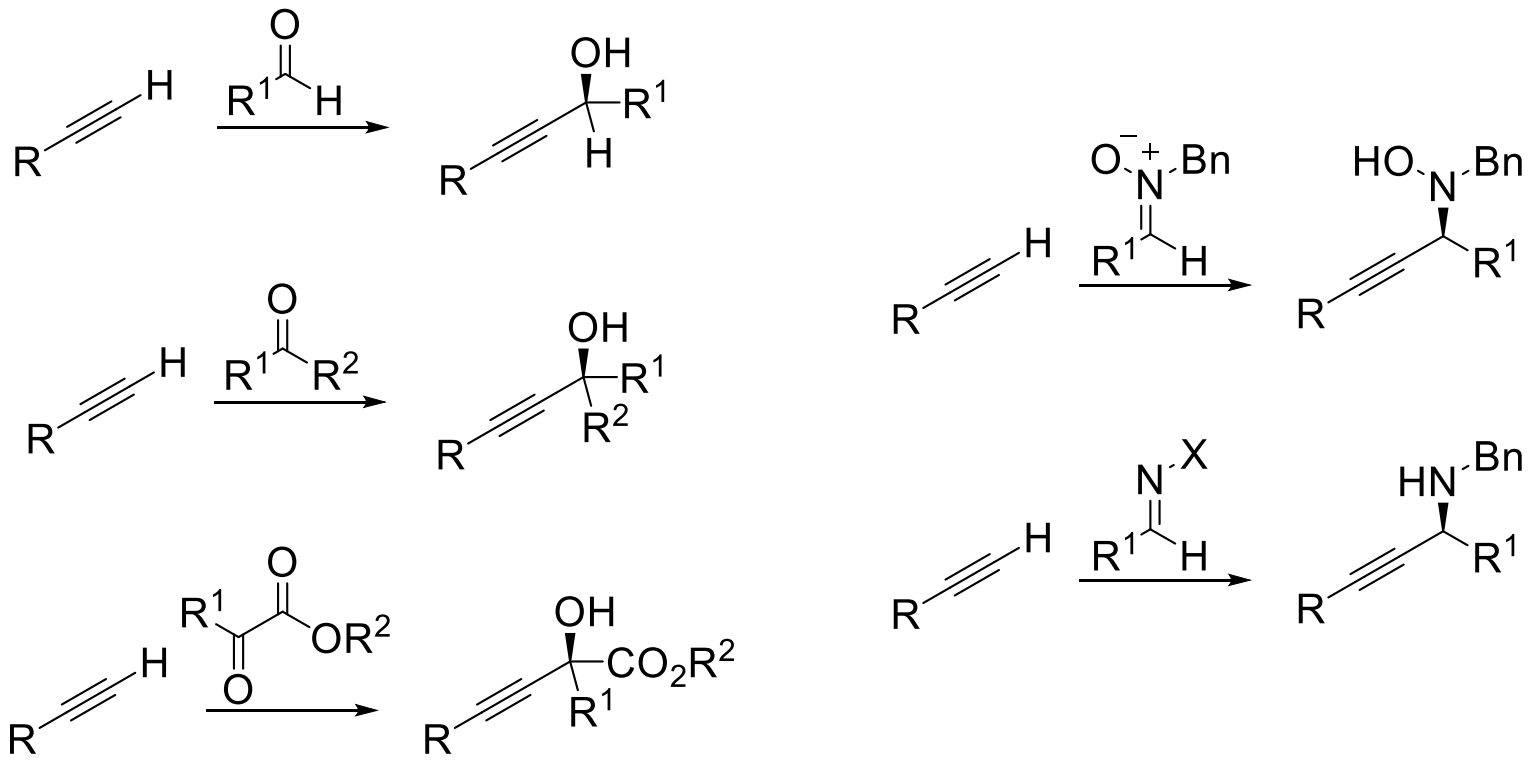






Ohkuma, T. et al. *Org. Lett.* **2013**, *15*, 3030.
Corey, E. J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 10938.
Noyori, R. et al. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

A Few C=Y Variants



Han, Z. et al. *Org. Lett.* **2004**, *6*, 4147.
Mashima, K. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6296.
Carreira, E. M. et al. *Acc. Chem. Res.* **2000**, *33*, 373.
Bolm, C. et al. *Chem. Commun.* **2006**, 4263.

Overview

- Background
- Comparisons to Similar Methods
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  - Zinc
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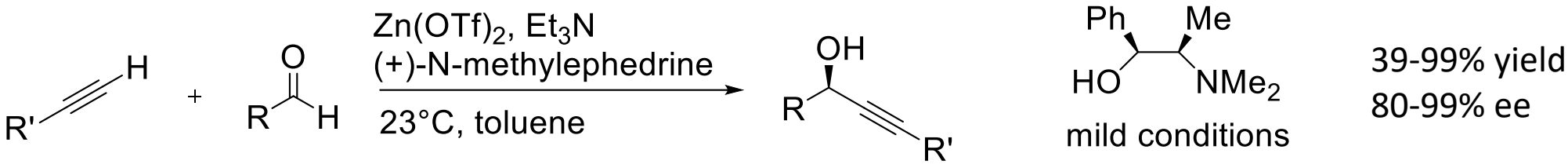
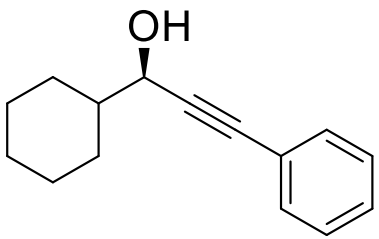
Zinc Salts

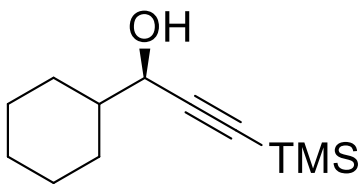


39-99% yield
80-99% ee

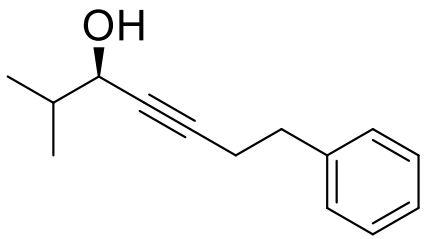
Carreira, E. M. et al. *J. Am. Chem. Soc.* **2000,** *122,* 1806.



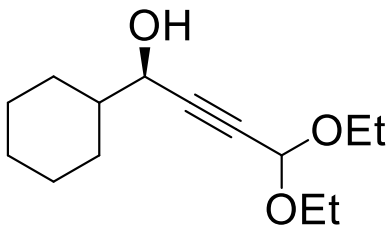
1h, 99% yield, 96% ee



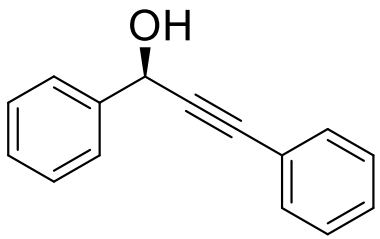
2h, 93% yield, 98% ee



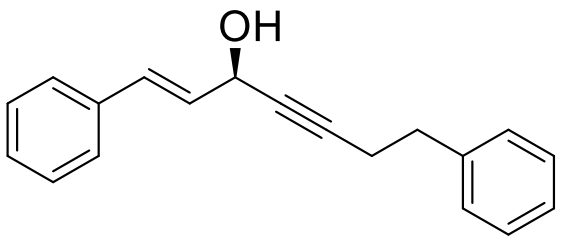
2h, 90% yield, 99% ee



8h, 90% yield, 98% ee

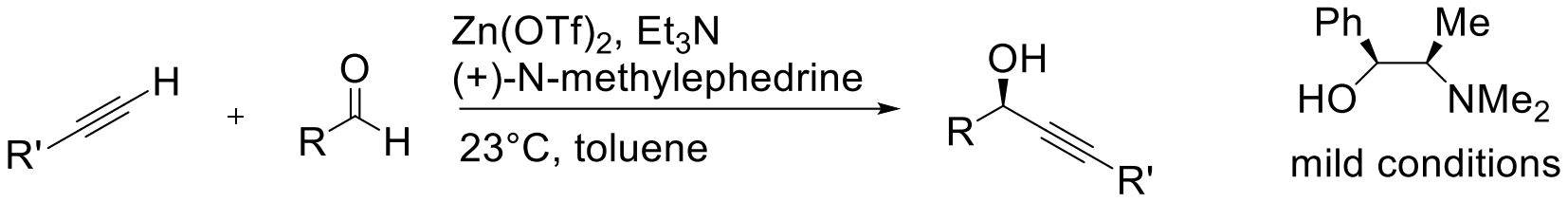


20h, 53% yield, 94% ee



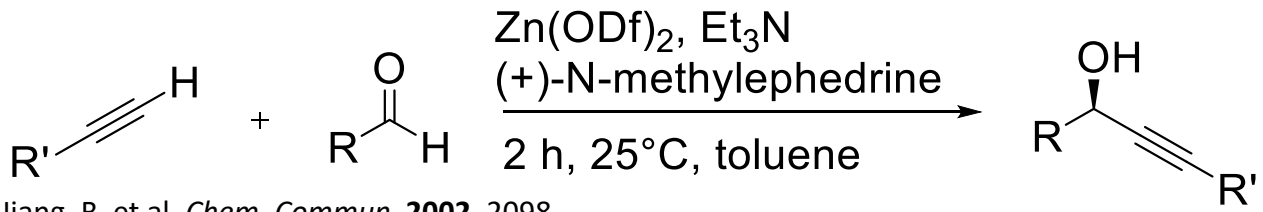
20h, 39% yield, 80% ee

Zinc Salts



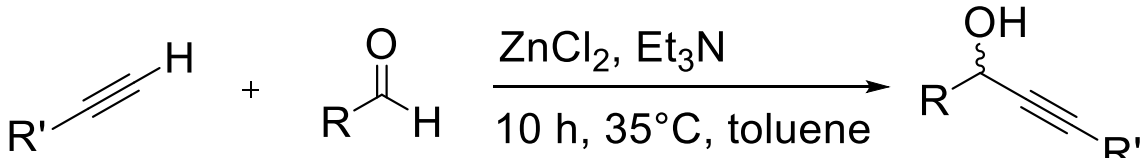
39-99% yield
80-99% ee

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2000,** *122,* 1806



51-99% yield
74-99% ee

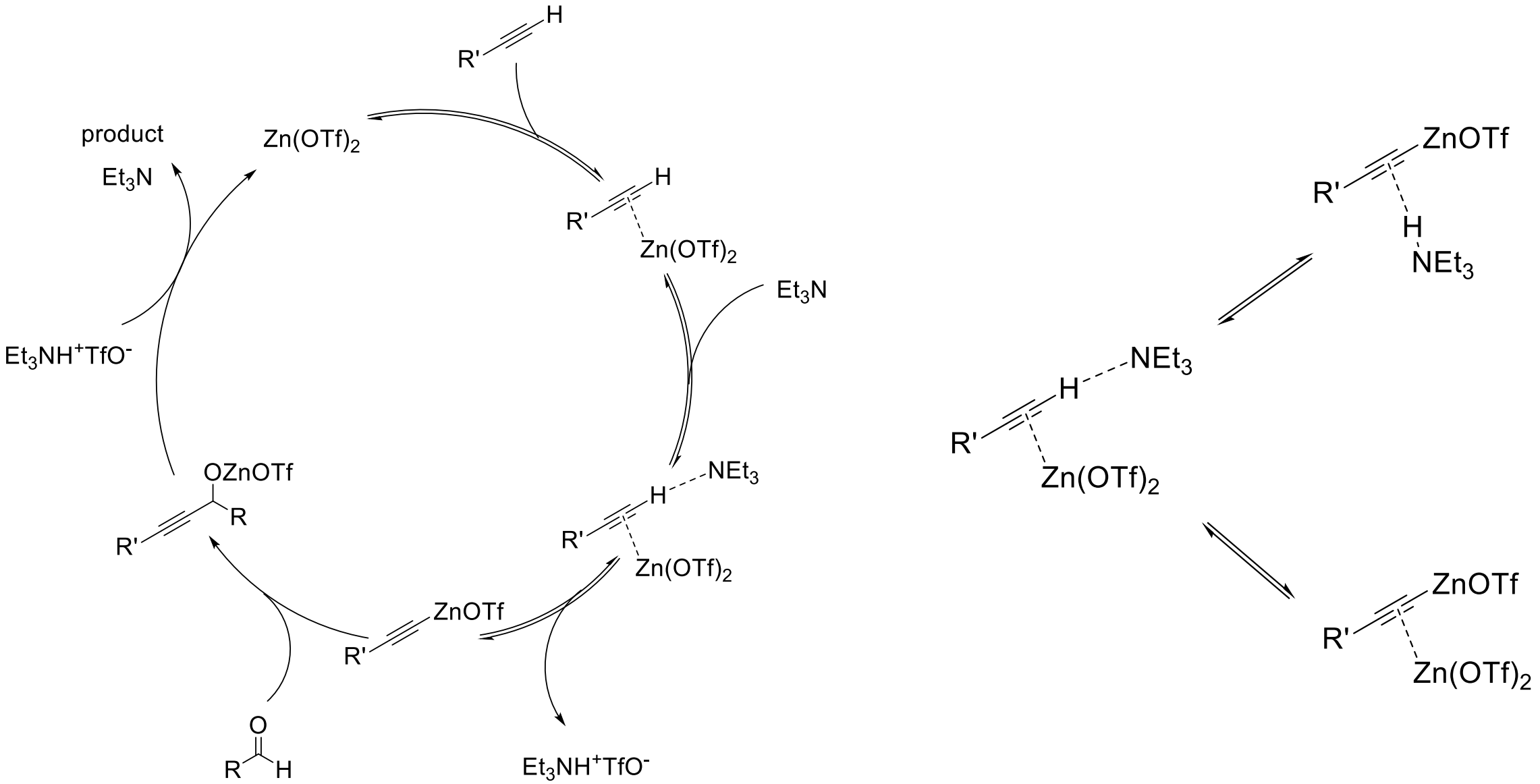
Jiang, B. et al. *Chem. Commun.* **2002**, 2098.



45-90% yield

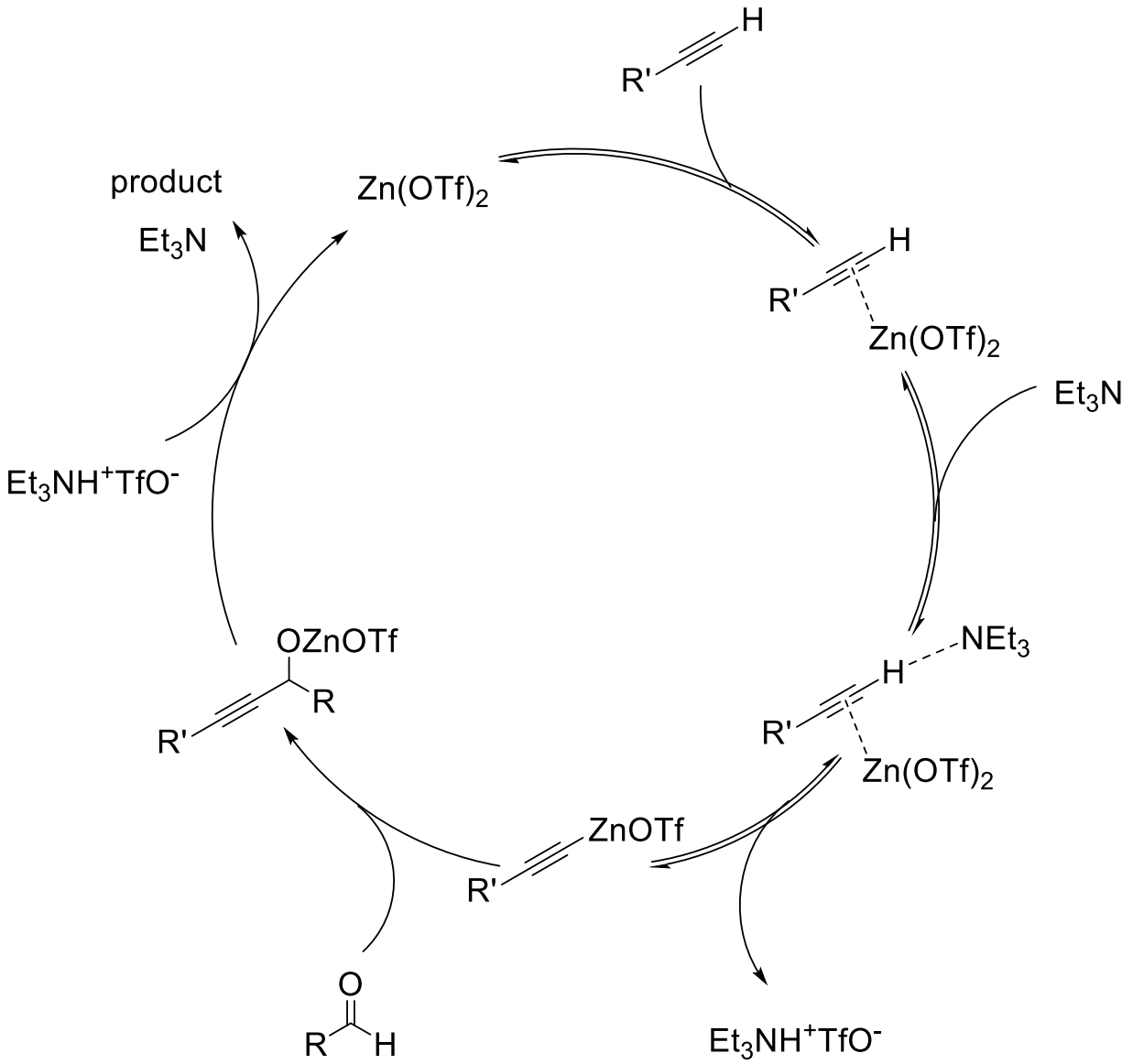
Jiang, B. et al. *Tetrahedron Lett.* **2002**, *43*, 8323.

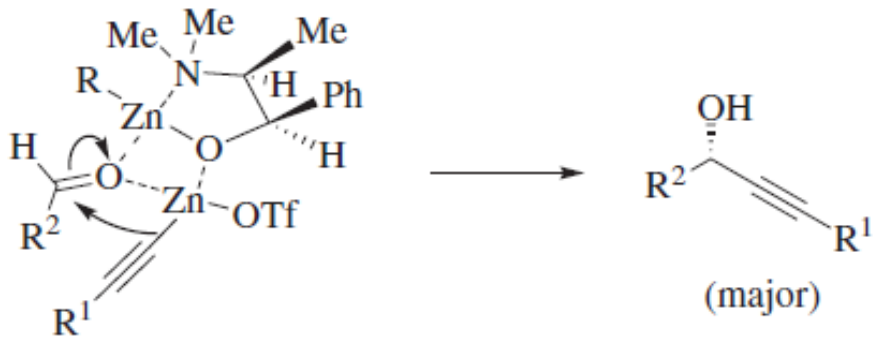
Mechanism, Stereochemistry, and Scope

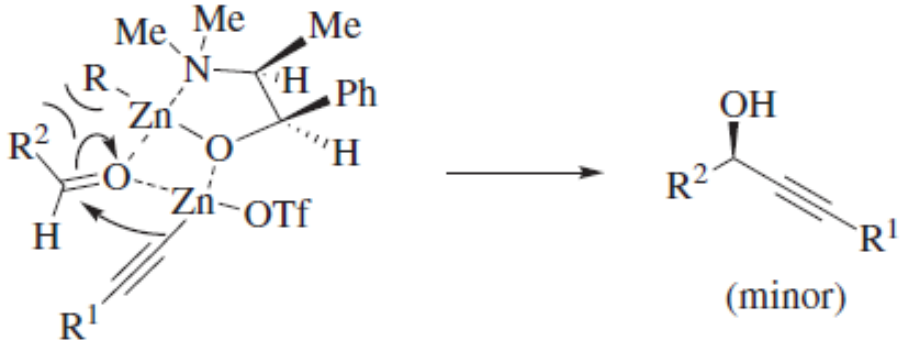


Carreira, E. M. et al. *Acc. Chem. Res.* **2000**, *33*, 373.
Noyori, R. et al. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

Mechanism, Stereochemistry, and Scope- Zinc



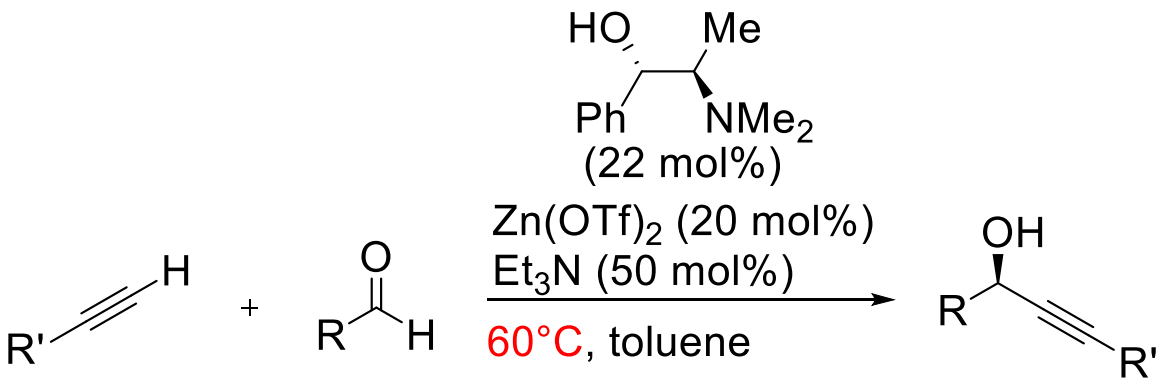


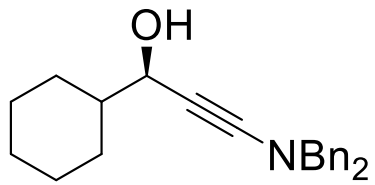


Carreira, E. M. et al. *Acc. Chem. Res.* **2000**, *33*, 373.
Noyori, R. et al. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

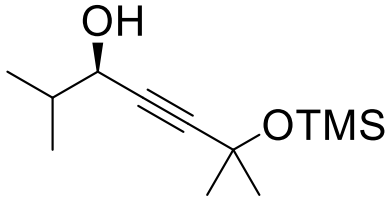
Mechanism, Stereochemistry, and Scope- Zinc

Alkyne Scope

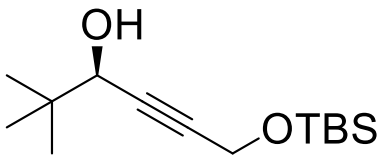




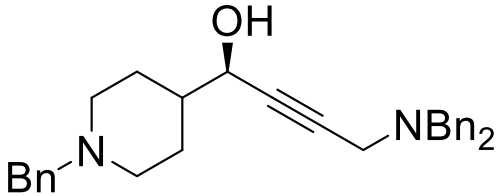
2h, 91% yield, 97% ee



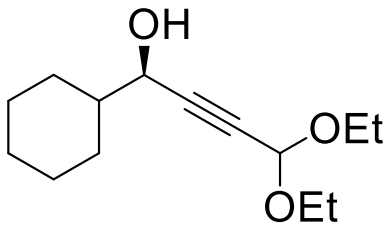
5h, 77% yield, 98% ee



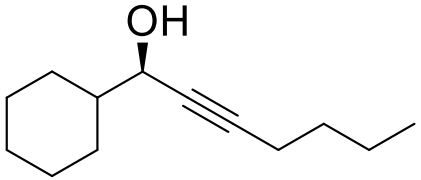
5h, 81% yield, 93% ee



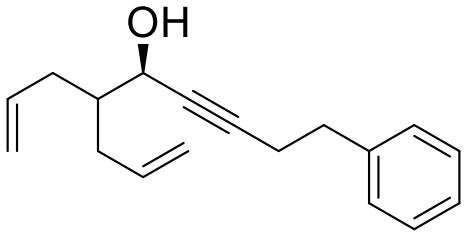
5h, 81% yield, 94% ee



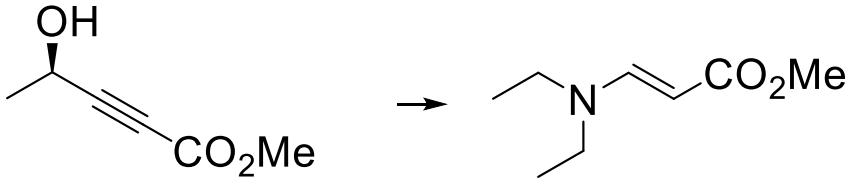
9h, 88% yield, 94% ee



6h, 81% yield, 93% ee



6h, 80% yield, 93% ee

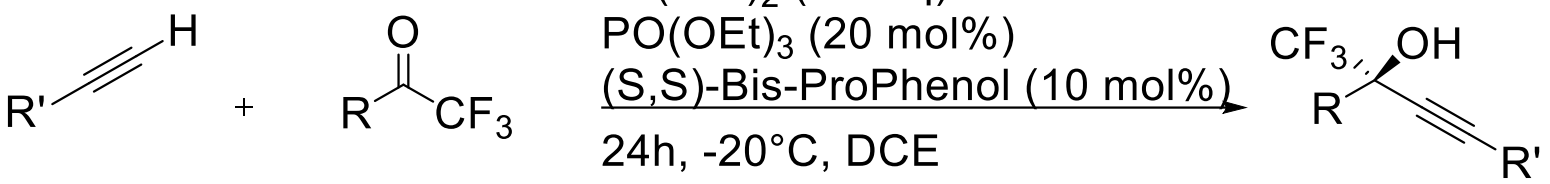


23°C, 30h, not detected

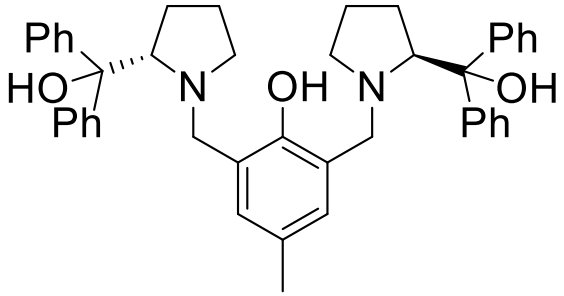
10-30%

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

Some Other Tolerated Substrates

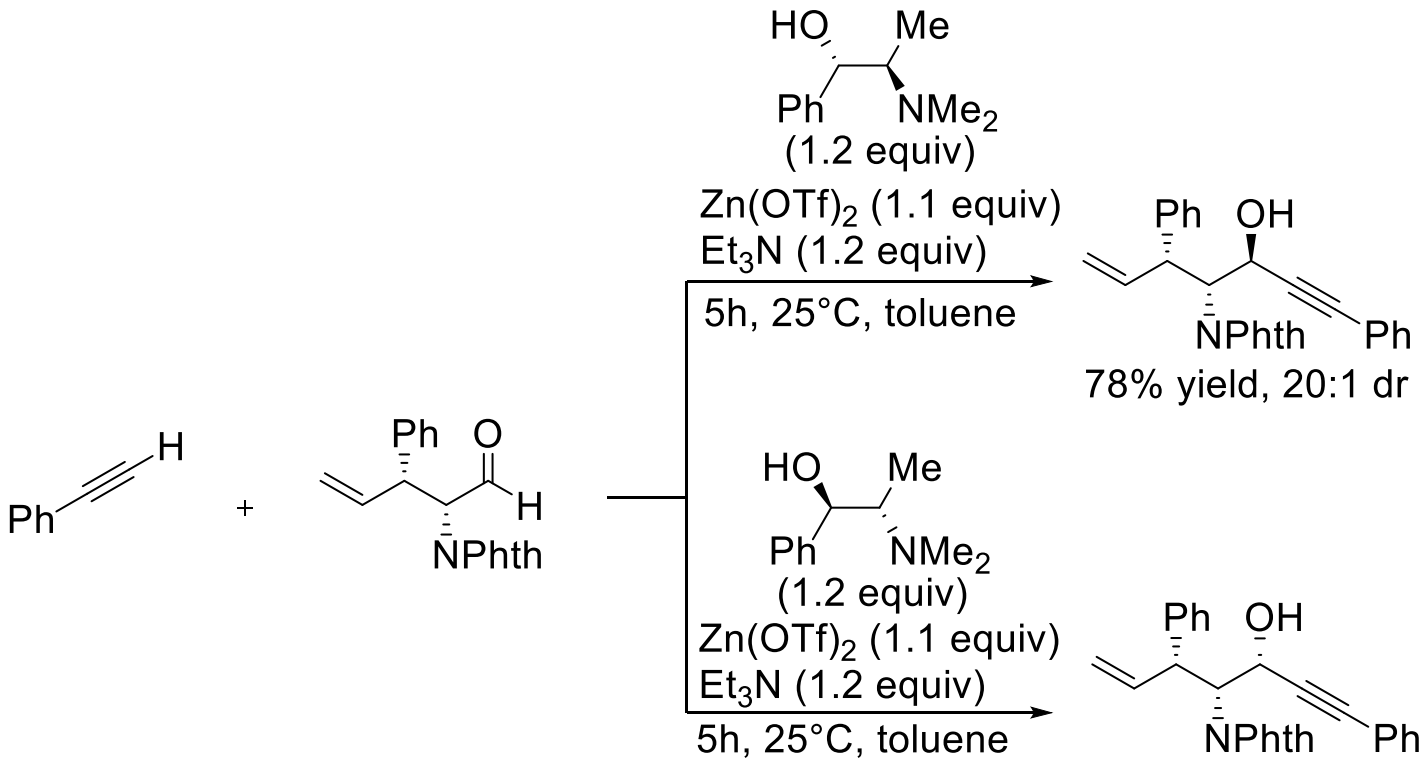


55-98% yield
65-94% ee



(S,S)-Bis-ProPhenol

Wolf, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2929.

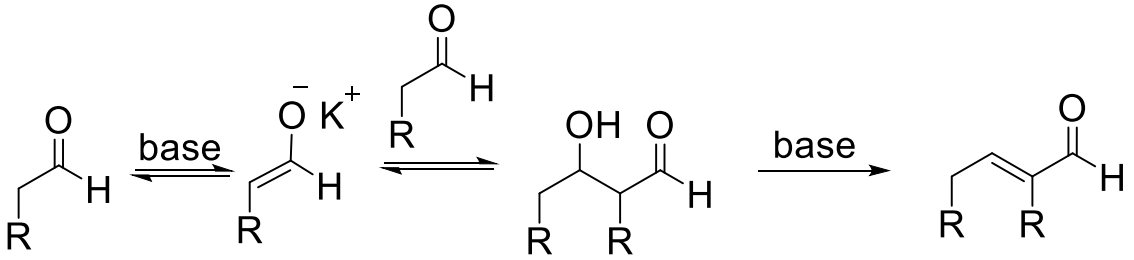


Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363.

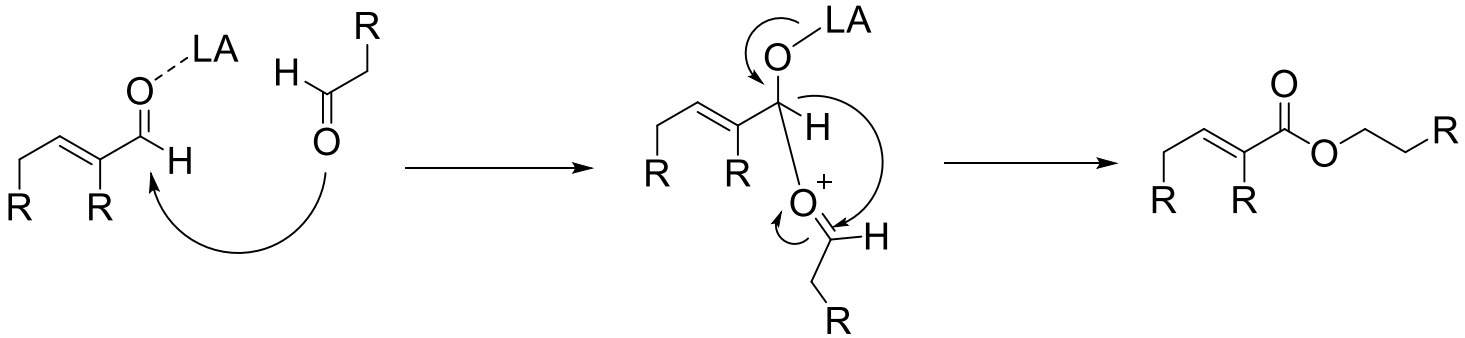
Mechanism, Stereochemistry, and Scope- Zinc

Side Reactions

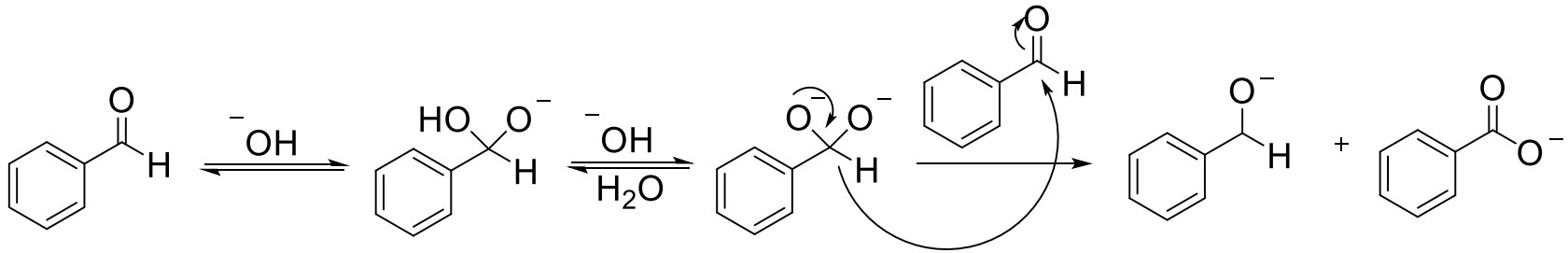
Self Aldol Condensation



Crossed Tishchenko Reaction



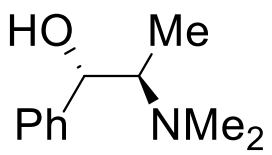
Cannizzaro Reaction



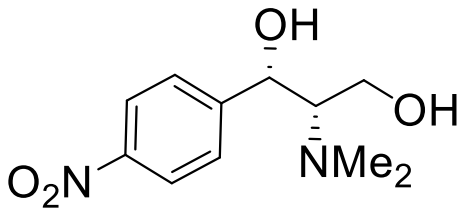
Carreira, E. M. Et al. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
Davis, B. G. et al. *Org. Lett.* **2006**, *8*, 207.

Mechanism, Stereochemistry, and Scope- Zinc

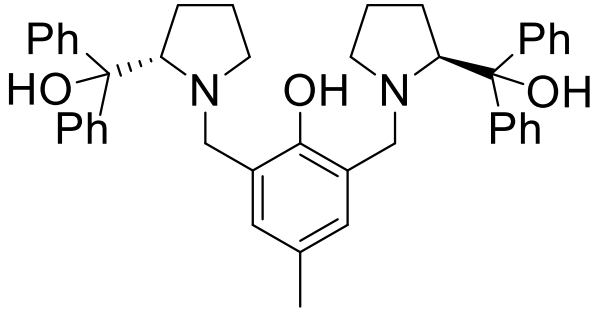
New Ligands



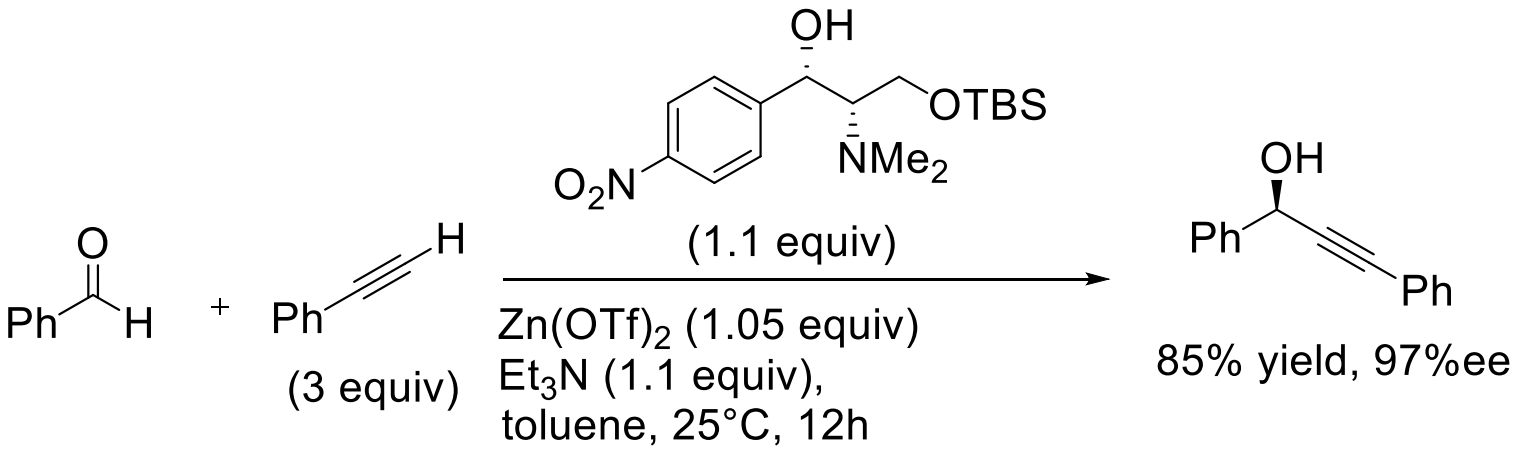
(+)-N-methylephedrine



(1S,2S)-2-amino-3-(p-nitrophenyl)propane-1,3-diol



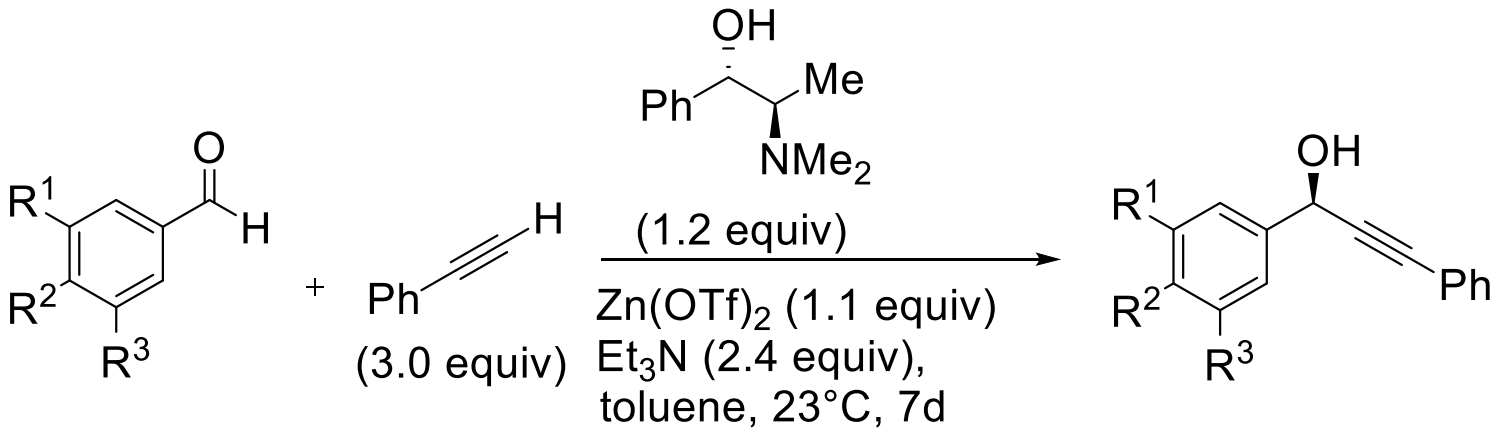
(S,S)-Bis-ProPhenol



Xiong, W. et al. *Chem. Commun.* **2002**, 1524.

Mechanism, Stereochemistry, and Scope- Zinc

Substitution?

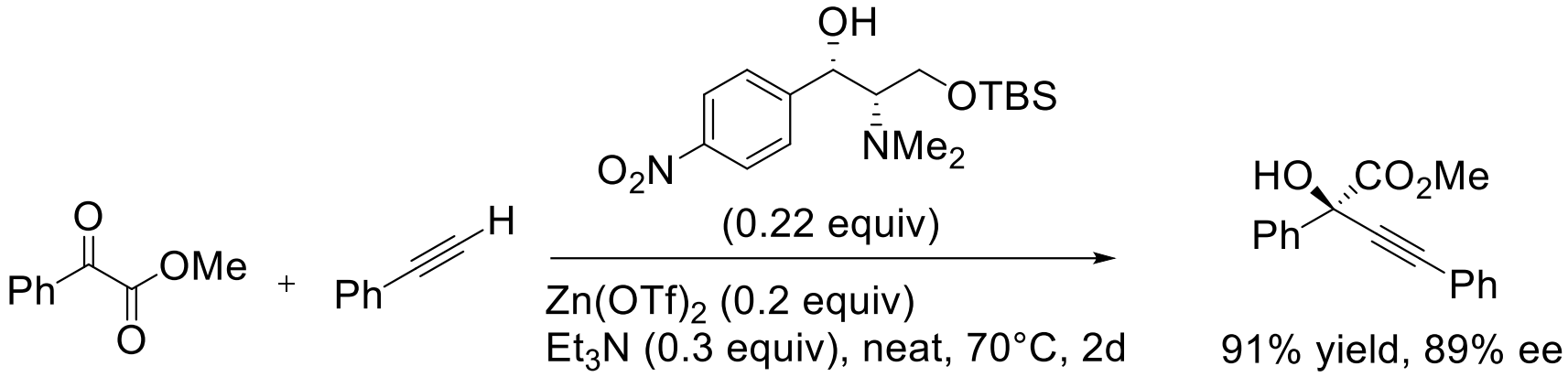


R^1	R^2	R^3	Yield (%)	er
H	H	H	80	90.5:9.5
H	F	H	60	91.5:8.5
F	H	H	98	92.5:7.5
F	H	F	90	99.5:0.5

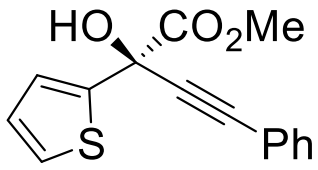
Muller, C. et al. *Synthesis* **2006**, 3099.
Singh, K. et al. *Synthesis* **2007**, 1491.

Mechanism, Stereochemistry, and Scope- Zinc

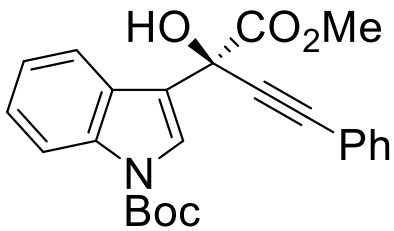
α-Keto Esters



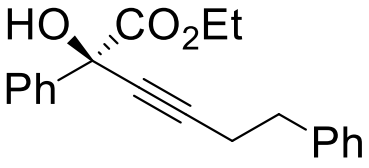
91% yield, 89% ee



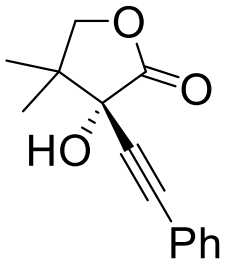
93% yield, 73% ee



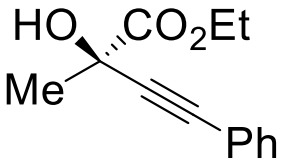
67% yield, 81% ee



88% yield, 94% ee



95% yield, 93.5% ee

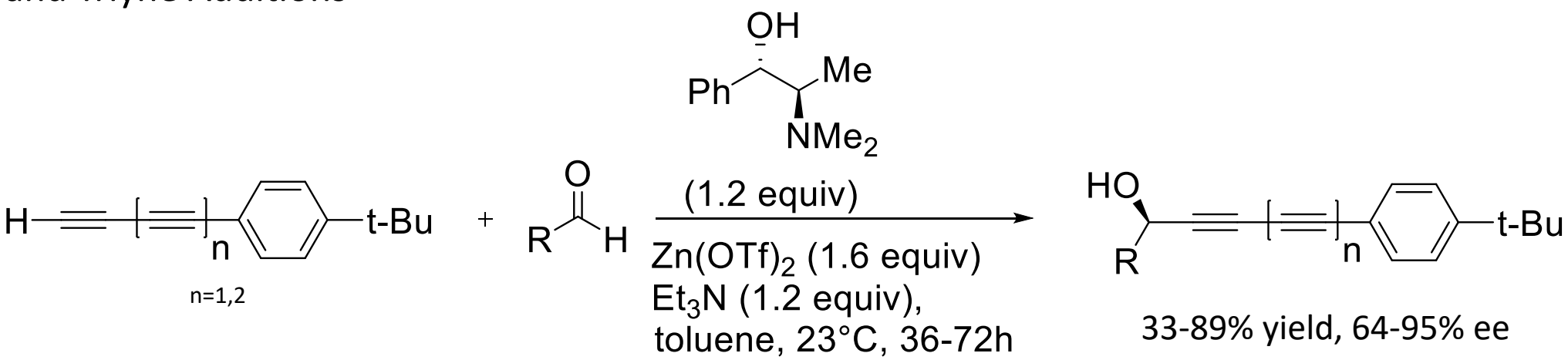


11% yield, 92% ee

Tang, X. *Org. Lett.* **2002**, *4*, 3451.

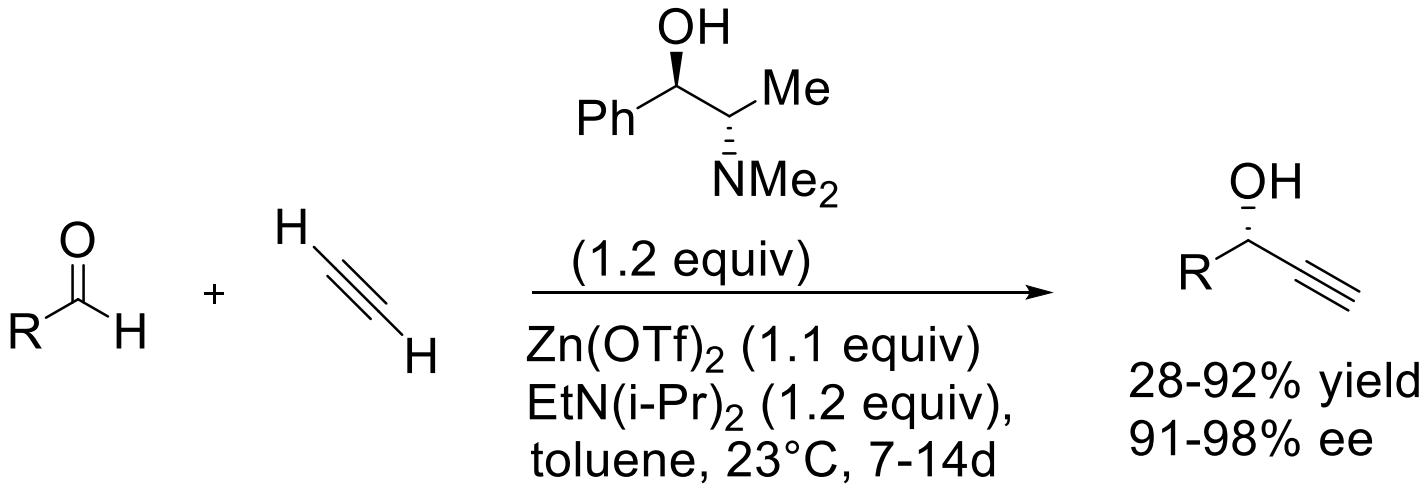
Mechanism, Stereochemistry, and Scope- Zinc

Di- and Triyne Additions



Tykwinski, R. R. et al. *J. Org. Chem.* **2011**, *76*, 6574.

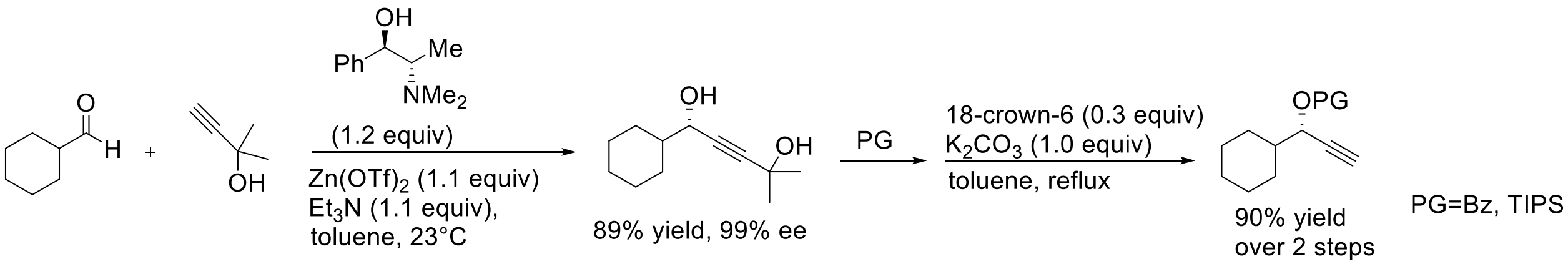
Addition of Ethyne to Aldehydes



Carreira, E. M. et al. *Org. Lett.* **2000**, *2*, 4233.

Mechanism, Stereochemistry, and Scope- Zinc

Addition of Ethyne to Aldehydes

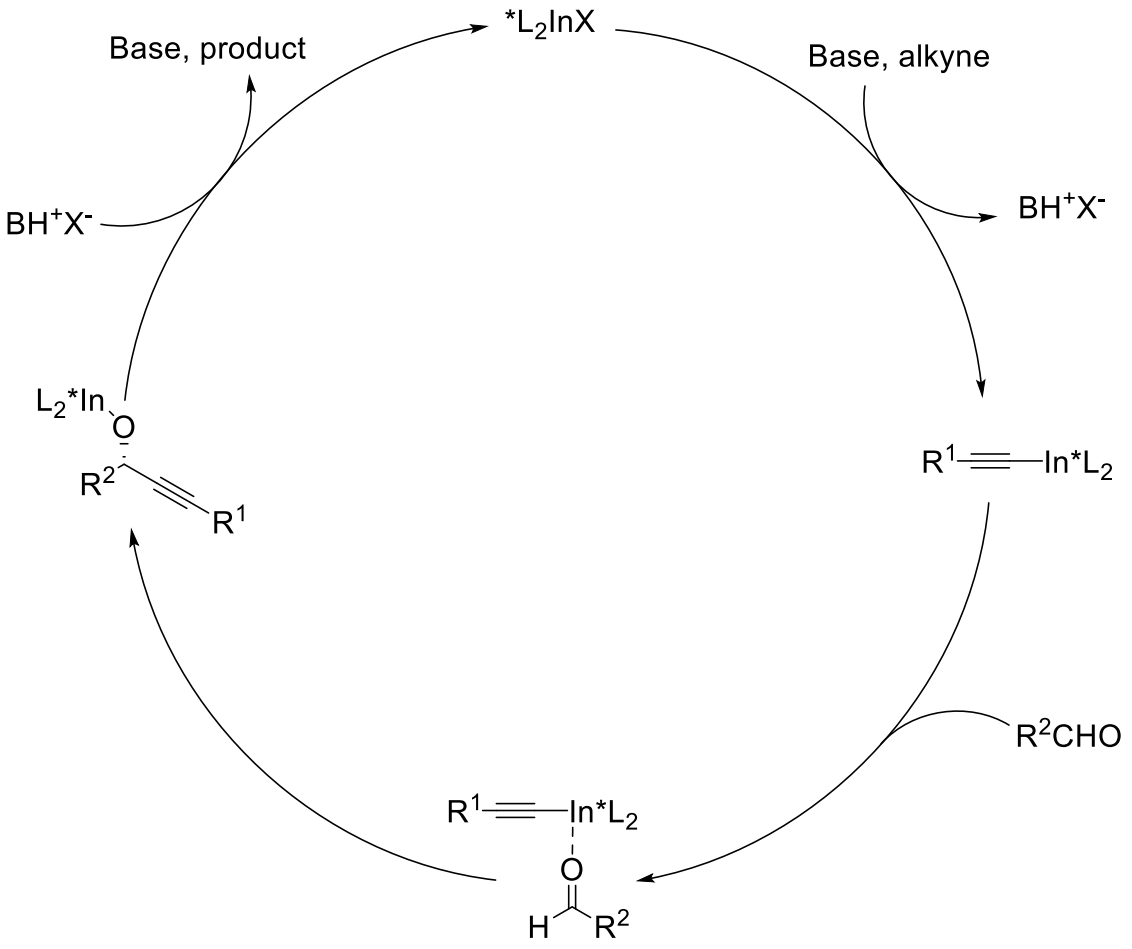


Carreira, E. M. et al. *Org. Lett.* **2000**, *2*, 4233.

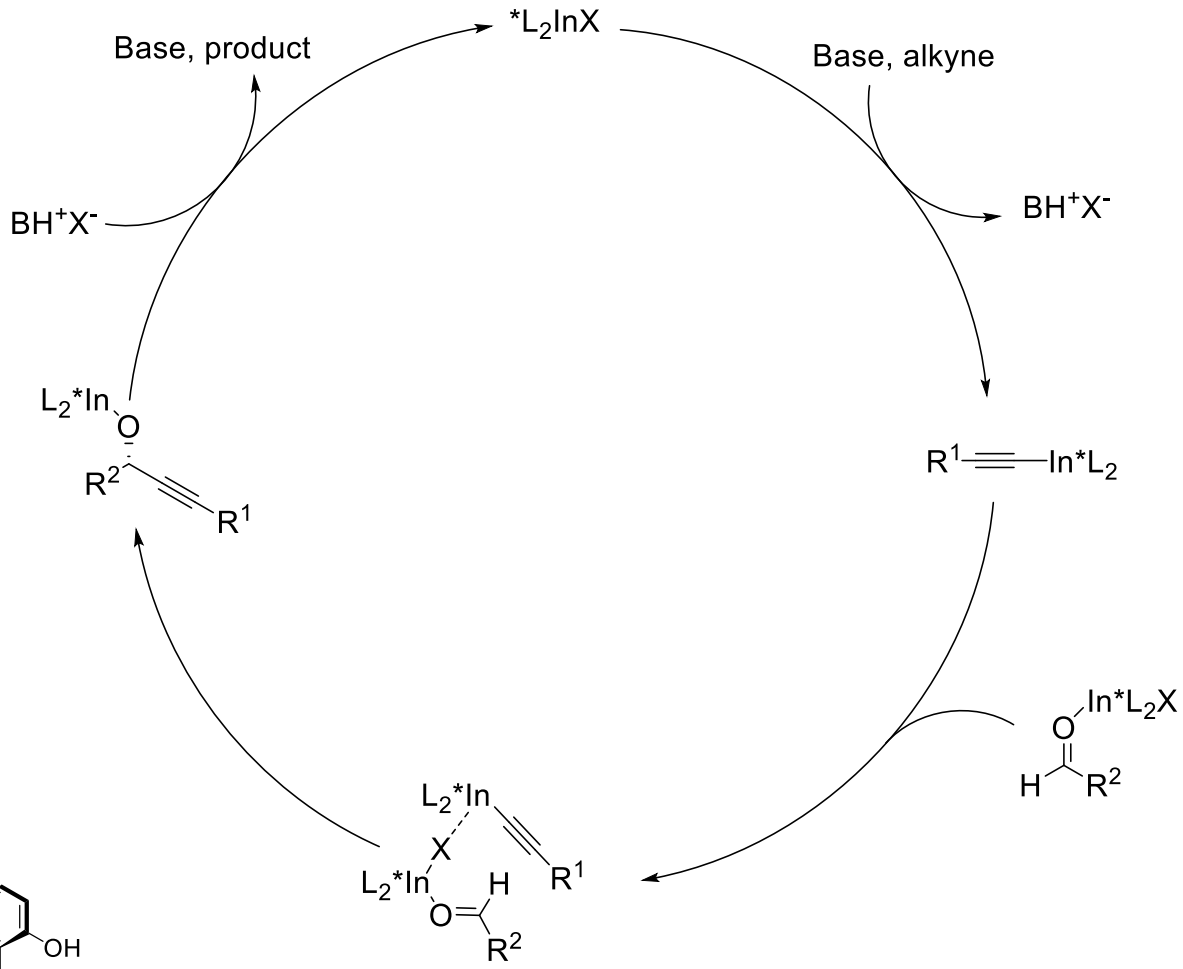
Mechanism, Stereochemistry, and Scope- Indium

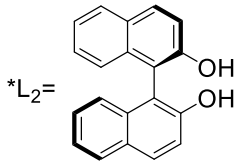
In(III) Salts Proposed Mechanisms

Monometallic Cycle



Bimetallic Cycle

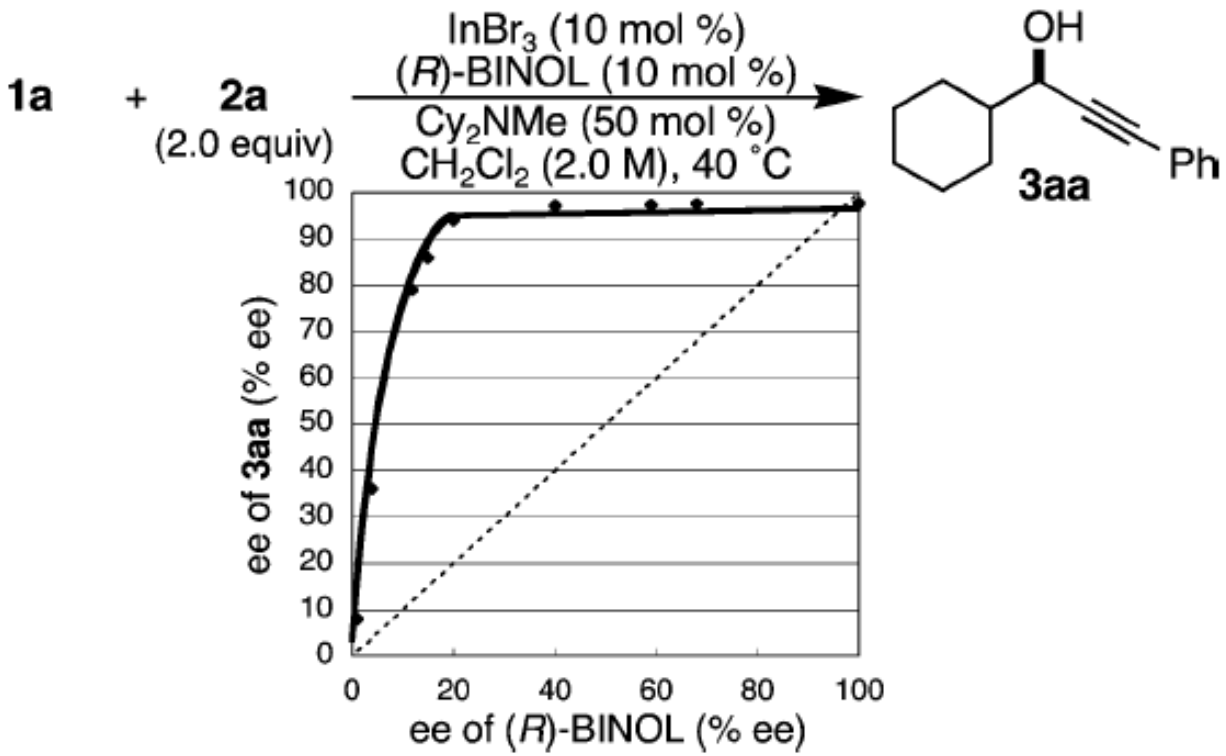




Shibasaki, M. et al. *Org. Lett.* **2005**, *7*, 1363.

Mechanism, Stereochemistry, and Scope- Indium

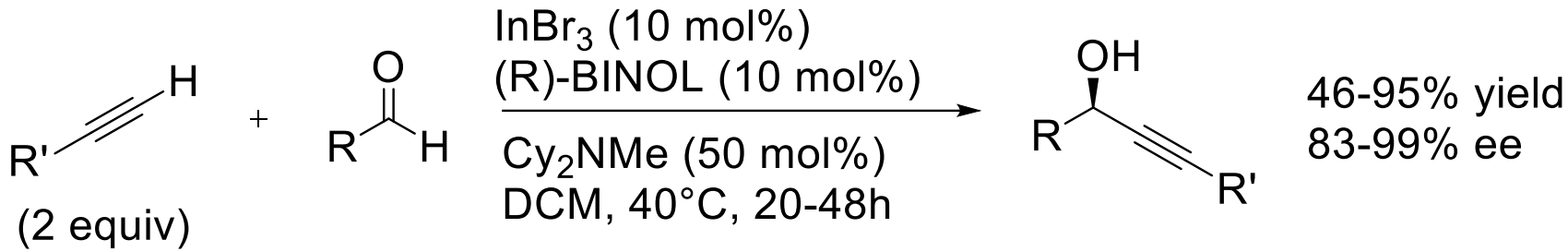
In(III) Salts Proposed Mechanisms



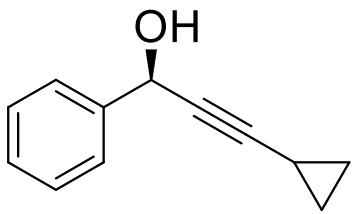
Shibasaki, M. et al. *Org. Lett.* **2005**, *7*, 1363.
Kagan, H.B. et al. *Angew. Chem. Int. Ed.* **1998**, 37, 2922.

Mechanism, Stereochemistry, and Scope- Indium

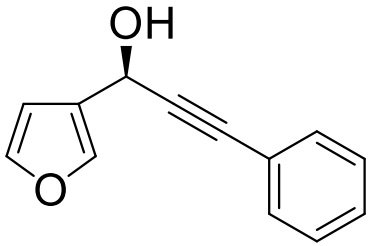
Noteworthy In(III) Salts Scope



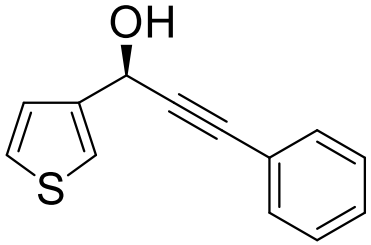
46-95% yield
83-99% ee



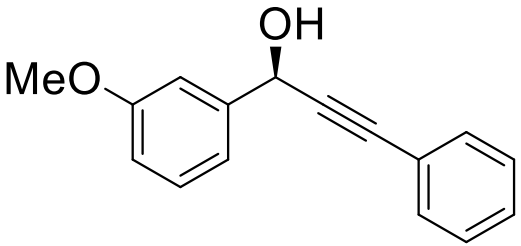
48h, 74% yield, 83% ee



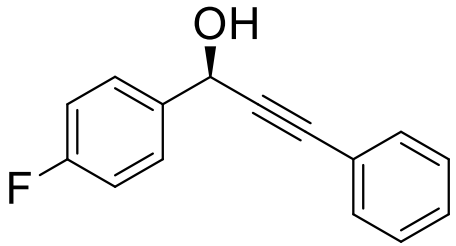
20h, 84% yield, 98% ee



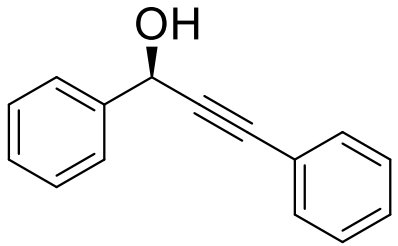
29h, 80% yield, 97% ee



48h, 77% yield, 97% ee



24h, 75% yield, 95% ee

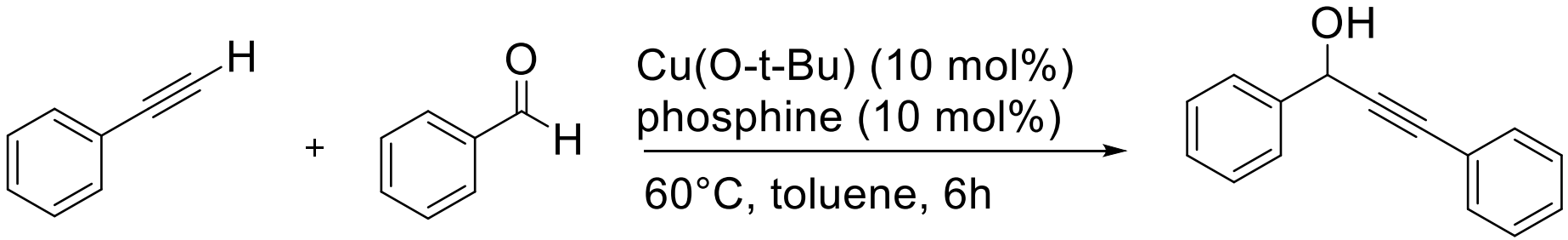


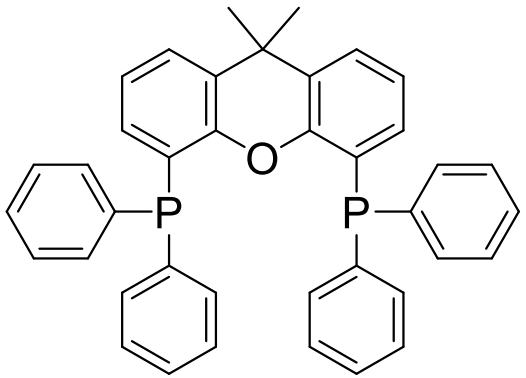
24h, 85% yield, 94% ee
run under air atmosphere

Shibasaki, M. et al. *J. Am. Chem. Soc.* **2005**, *127*, 13760.

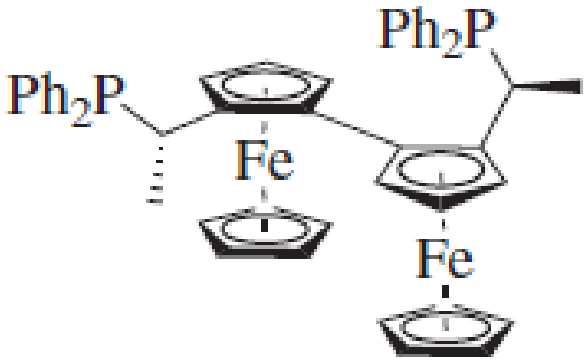
Mechanism, Stereochemistry, and Scope- Copper

Cu(I) Ligand Scope





Xantphos



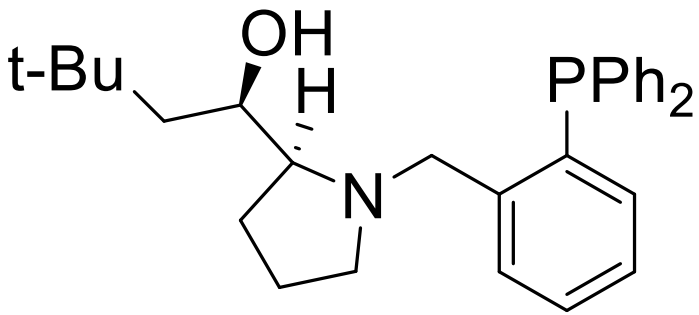
(S,S)-(R,R)-Ph-TRAP

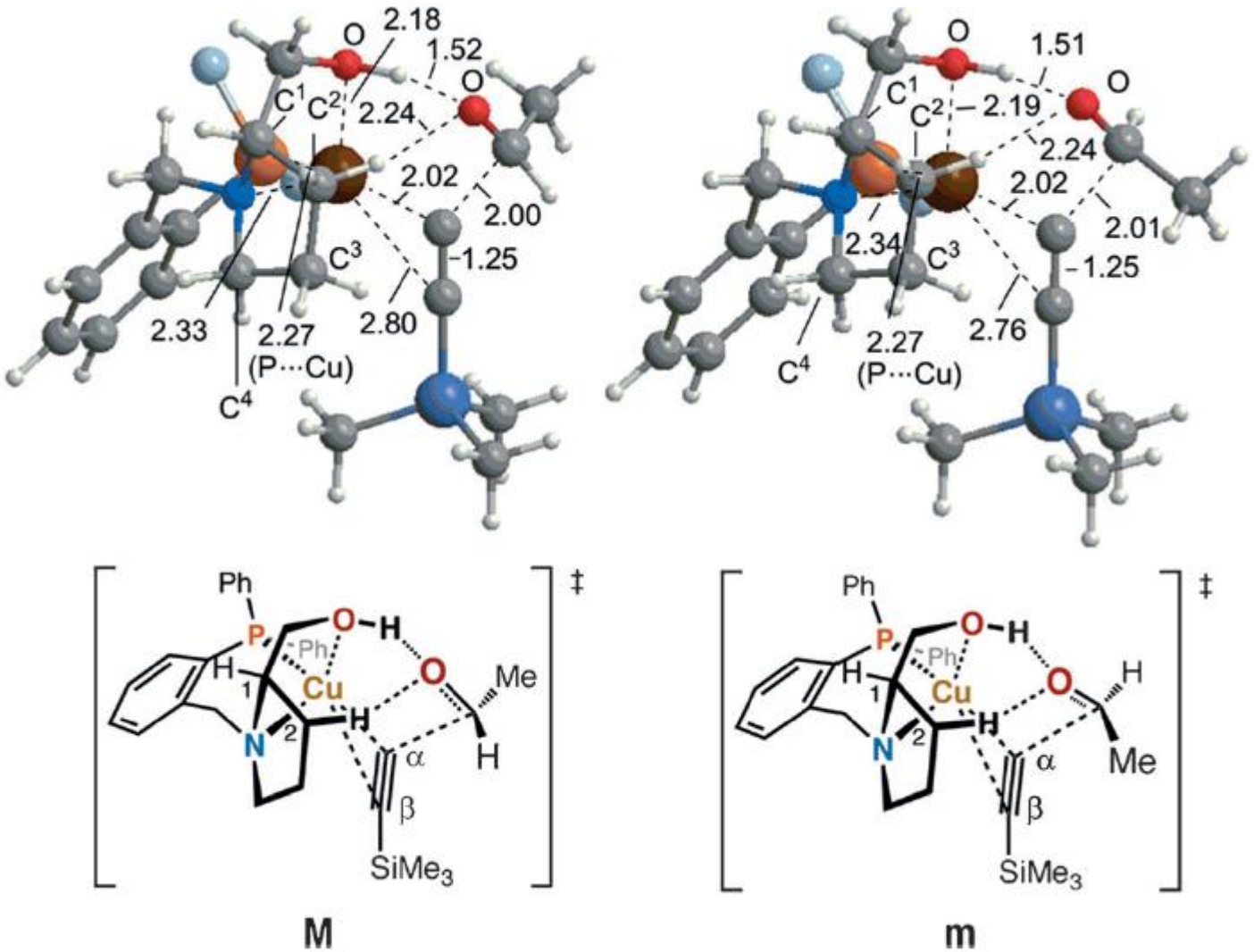
entry	phosphine	NMR yield[b] (%)
1	none	0
2[c]	PPh_3	0
3	dppe	0
4	dppp	0
5	dppb	0
6	dppf	0
7	DPEphos	trace
8	DBEphos	2
9	Xantphos	10
10	DTBM-Xantphos	20
11	(S,S)-$(R,R)_{Fe}$-Ph-TRAP	77 (27% ee, R)

Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901.

Mechanism, Stereochemistry, and Scope- Copper

Cu(I) Ligand Scope

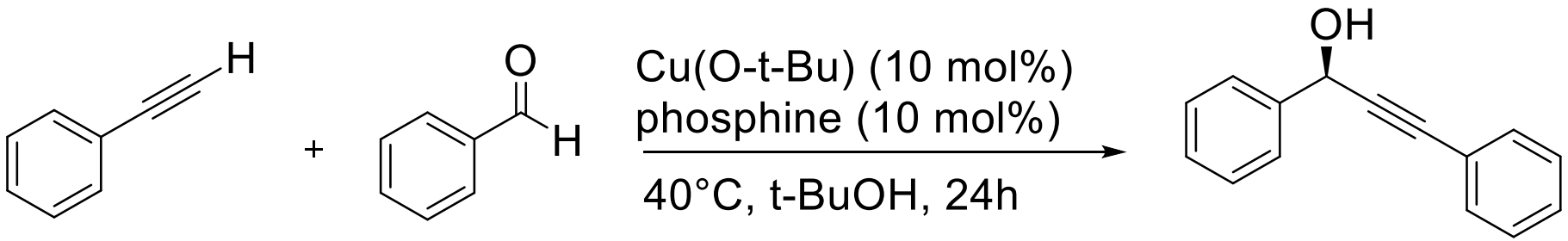


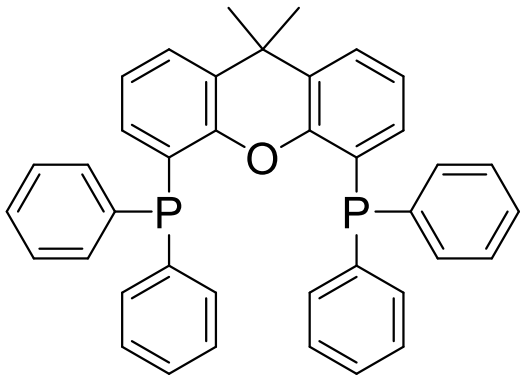


Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901.
Sawamura, M. et al. *Chem. Eur. J.* **2013**, *19*, 13547.

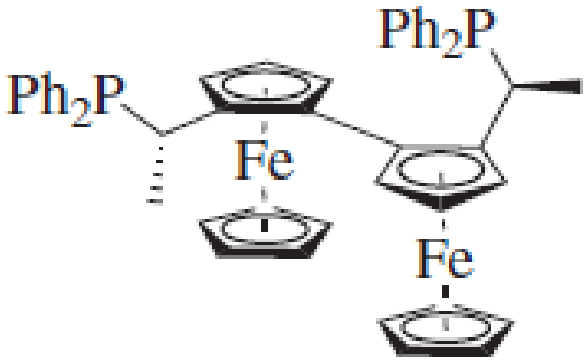
Mechanism, Stereochemistry, and Scope- Copper

Cu(I) Ligand Scope

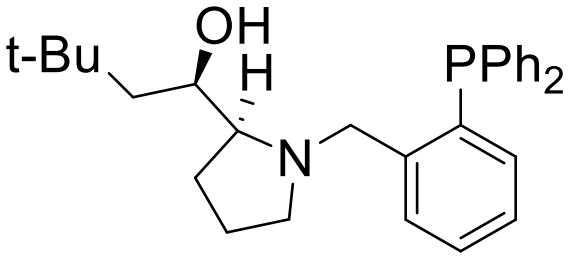




Xantphos



(S,S)-(R,R)-Ph-TRAP

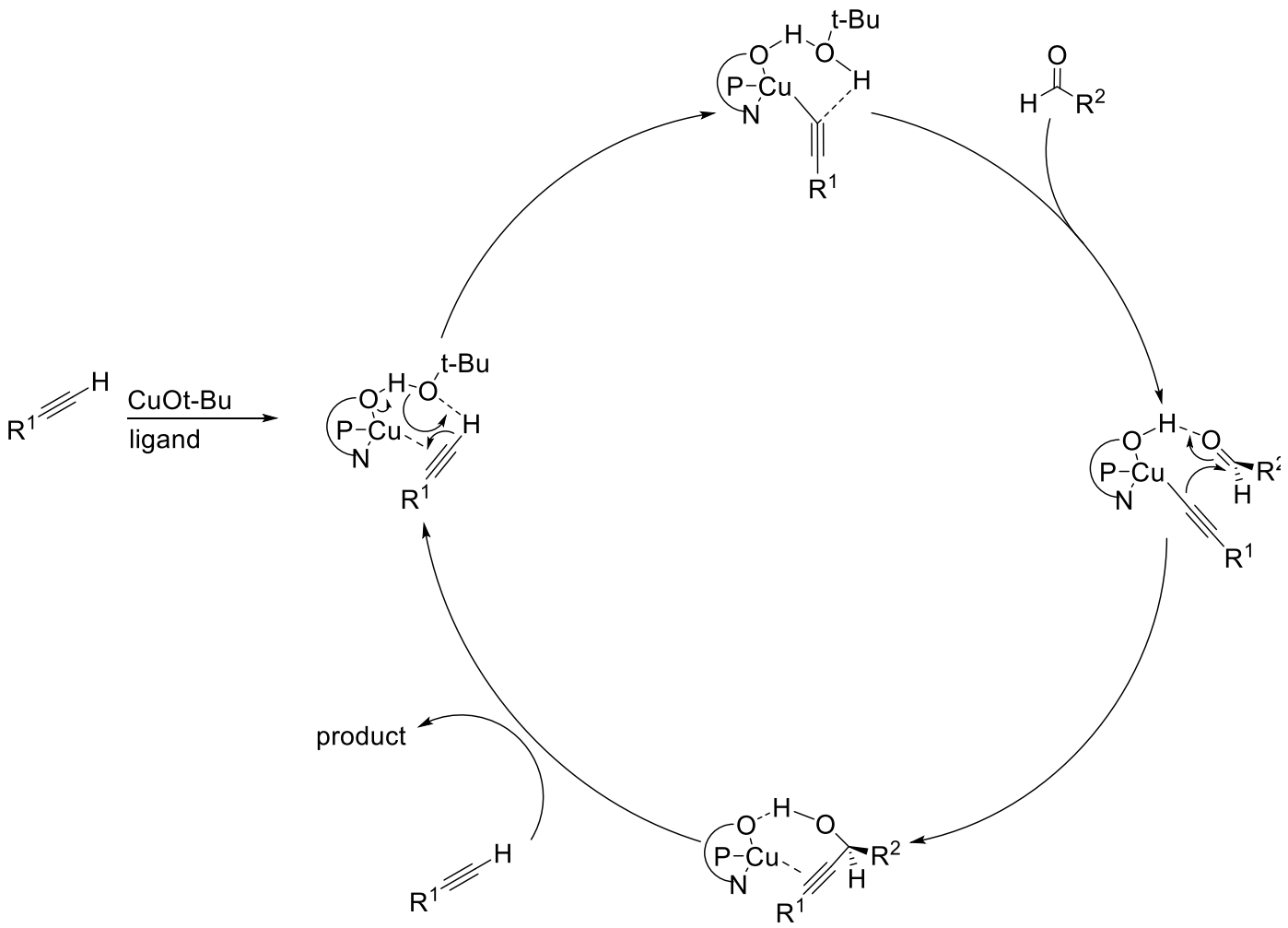


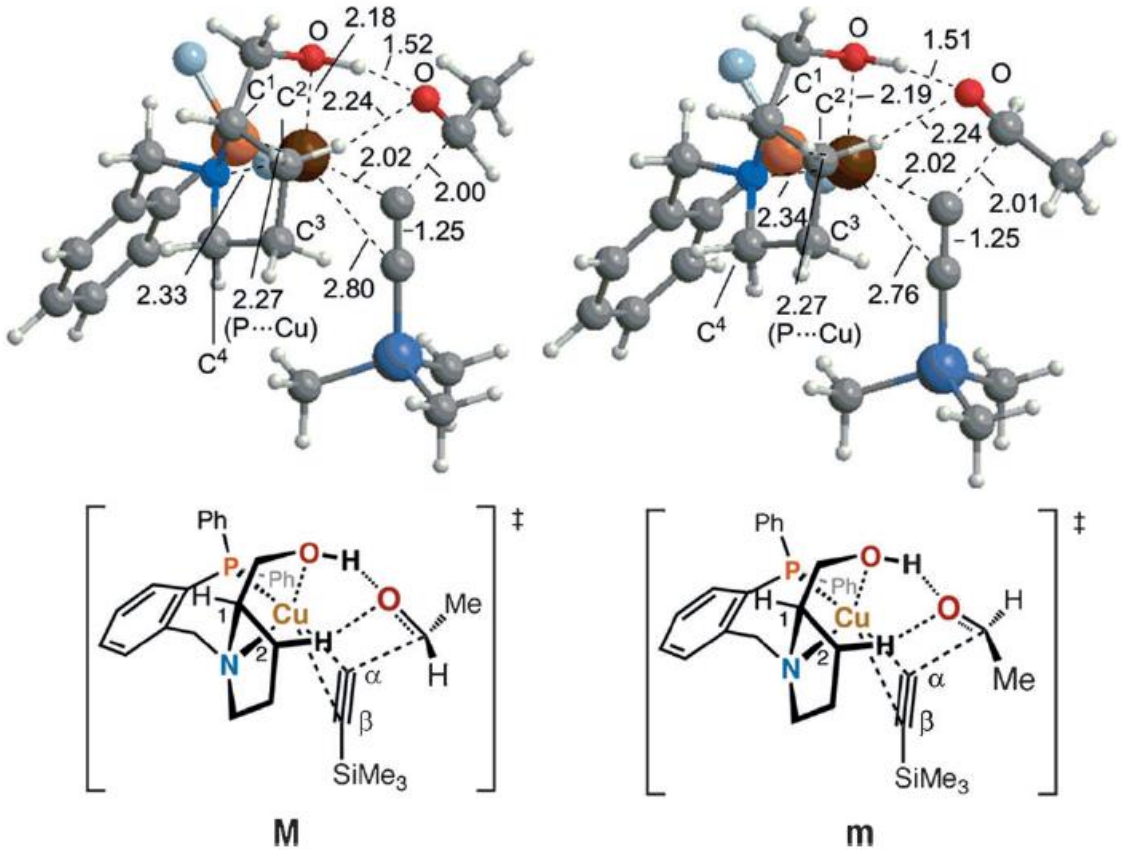
Prolinol-based hydroxyamino phosphates

Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901.
Sawamura, M. et al. *Chem. Eur. J.* **2013**, *19*, 13547.

Mechanism, Stereochemistry, and Scope- Copper

Cu(I) Catalytic Cycle

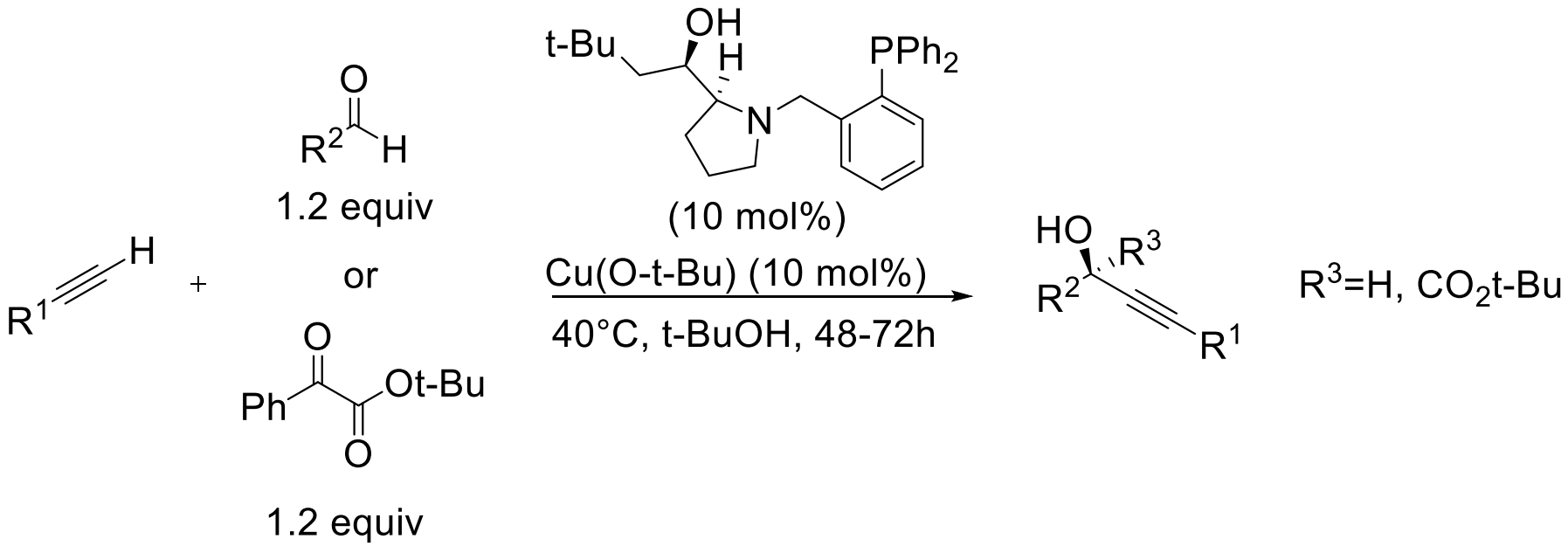


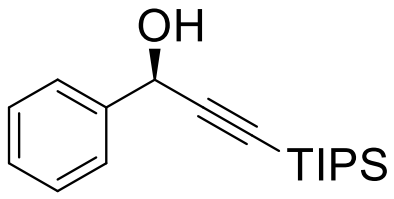


Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901.
Sawamura, M. et al. *Chem. Eur. J.* **2013**, *19*, 13547.

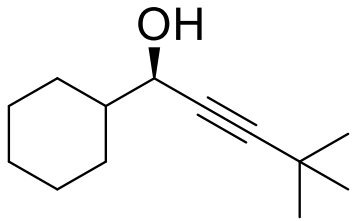
Mechanism, Stereochemistry, and Scope- Copper

Cu(I) Scope

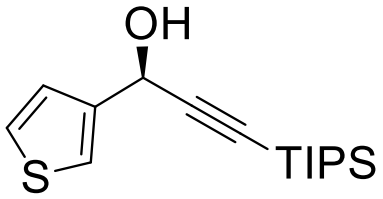




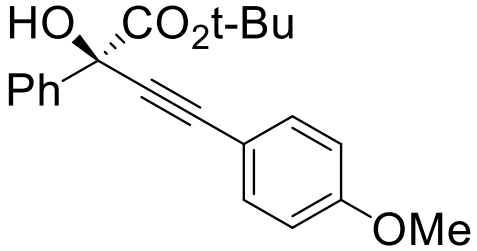
71% yield, 78% ee



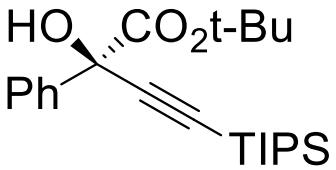
97% yield, 86% ee



73% yield, 90% ee



97% yield, 93% ee

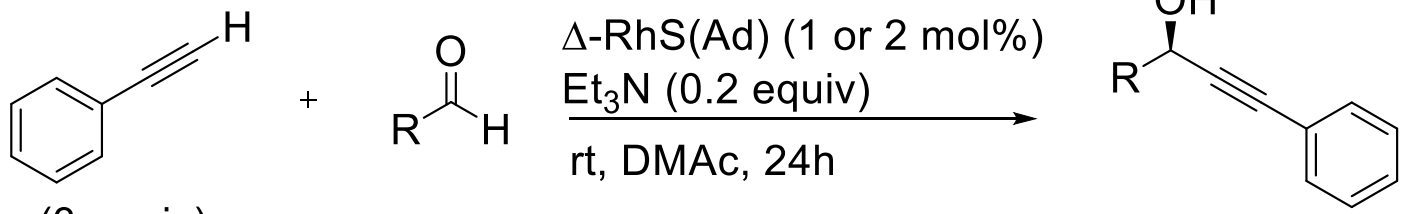


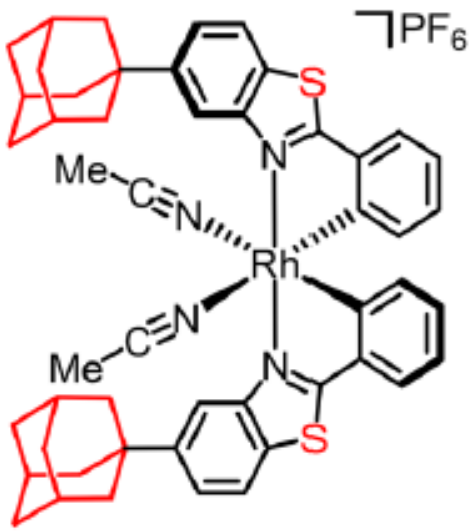
not detected

Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901.
Sawamura, M. et al. *Chem. Eur. J.* **2013**, *19*, 13547.

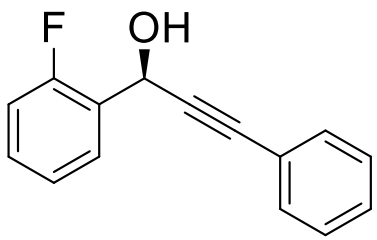
Mechanism, Stereochemistry, and Scope- Rhodium/Ruthenium

Rhodium/Ruthenium

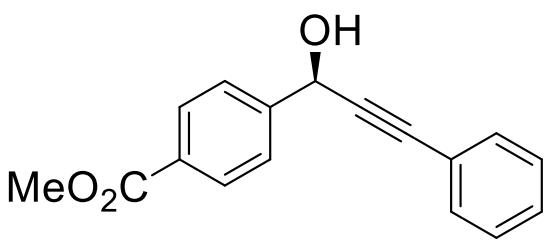




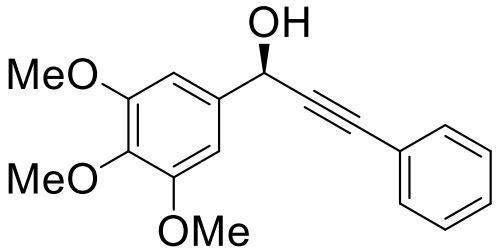
Δ-RhS(Ad)



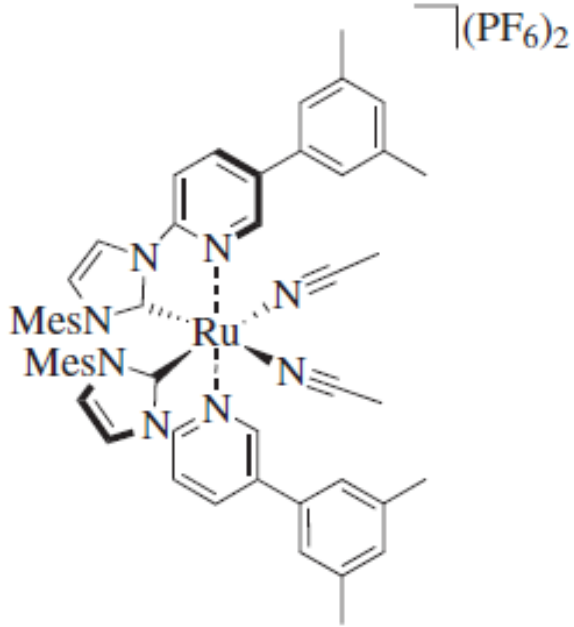
84% yield, 88% ee

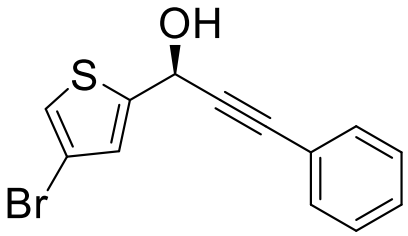


82% yield, 90% ee

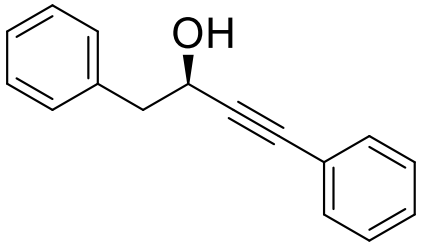


91% yield, 98% ee

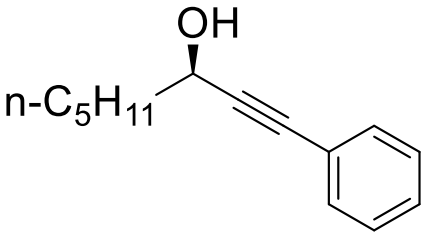




82% yield, 85% ee



92% yield, 26% ee

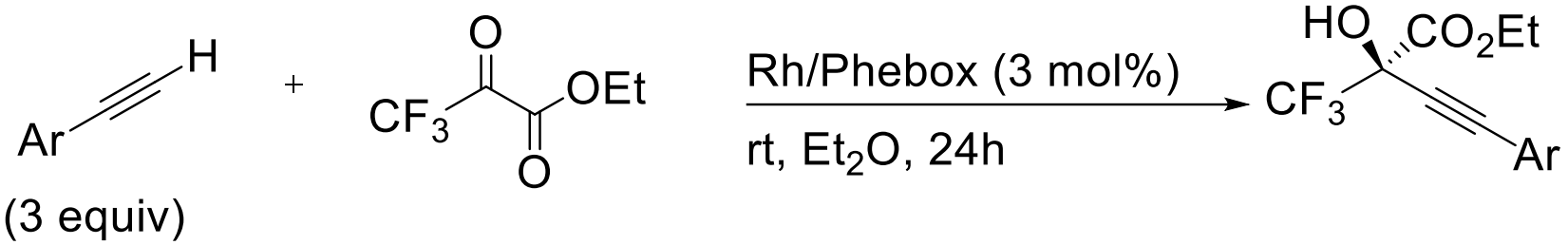


93% yield, 4% ee

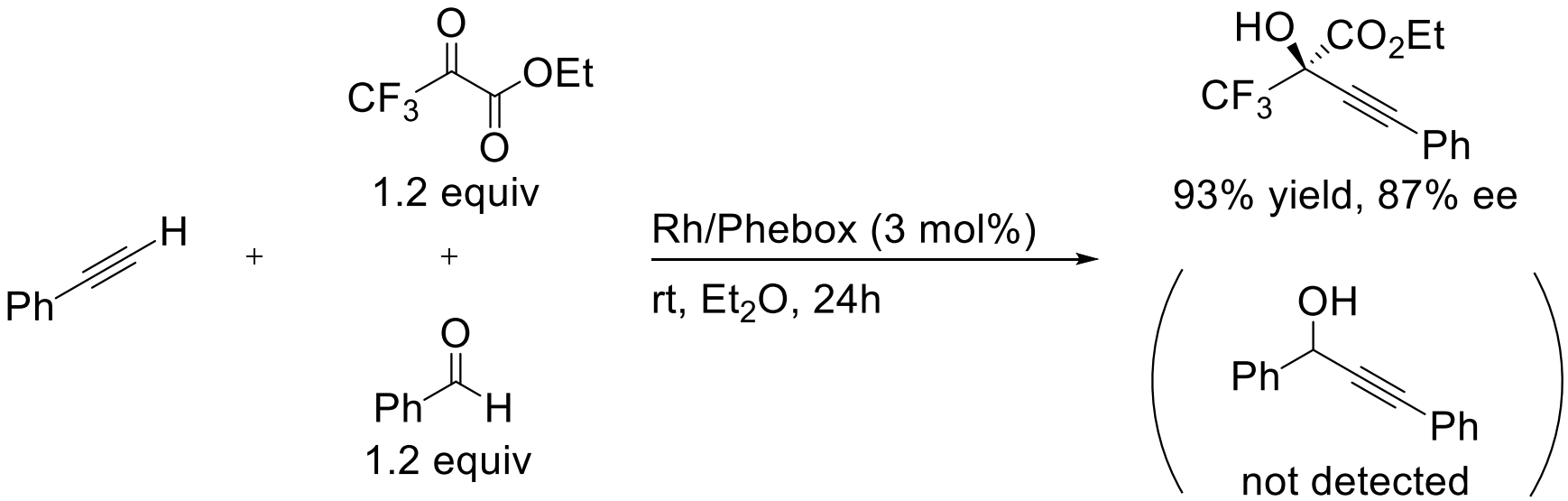
Meggers, E. et al. *J. Org. Chem.* **2017**, *82*, 8995.

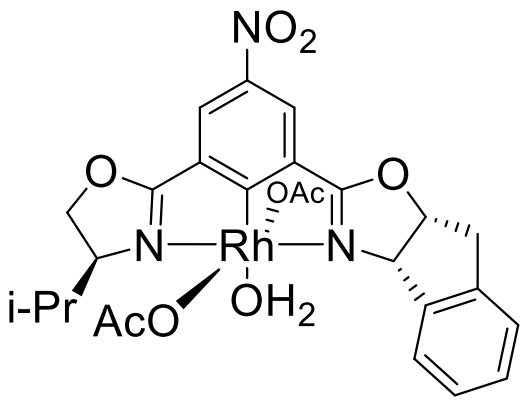
Mechanism, Stereochemistry, and Scope- Rhodium/Ruthenium

Rhodium/Ruthenium



88-99% yield
90-95% ee





Rh/Phebox complex

Nishiyama, H. et al. *Chem.Eur. J.* **2016**, *22*, 16801.
Mashima, K. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6296.
Nishiyama, H. et al. *Org. Lett.* **2010**, *12*, 3860.

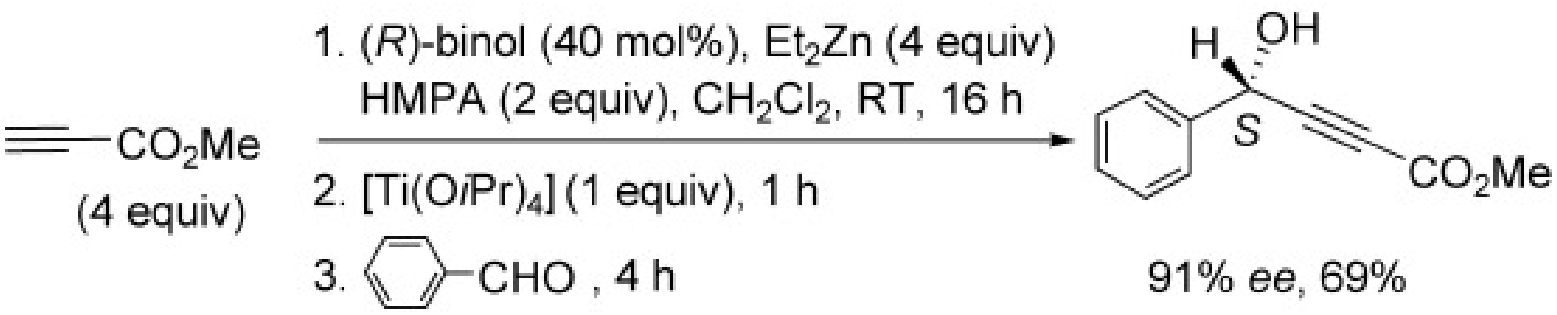
Overview

- Background
- **Comparisons to Similar Methods**
- Mechanism, Stereochemistry, and Scope
  - Zinc
  - Indium
  - Copper
  - Rhodium/Ruthenium
- Conclusions

Comparisons to Similar Methods

Dialkylzinc-Mediated Alkynylation of Aldehydes

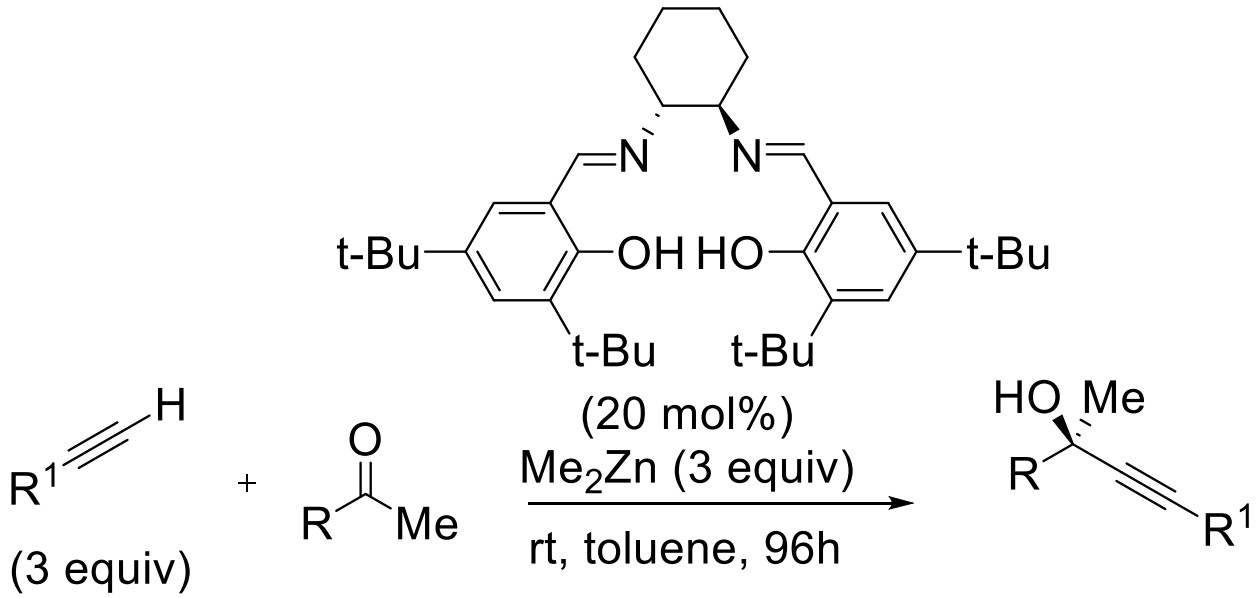
- Stoichiometric amounts of dialkylzinc reagents
- Robust and has similar broad scope to forming the metal alkynylide catalytically
- Can add alkyl propiolate nucleophiles
- Not atom economical
- Requires inert conditions



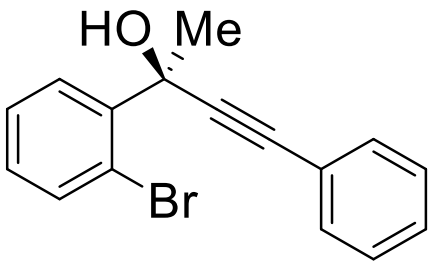
Pu, L. et al. *Angew. Chem., Int. Ed.* **2006**, *118*, 128.

Comparisons to Similar Methods

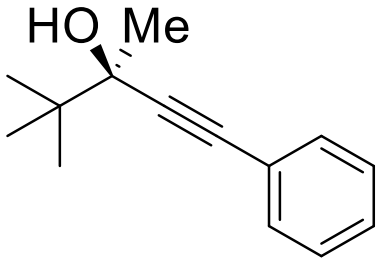
Dialkylzinc-Mediated Alkynylation of Carbonyls



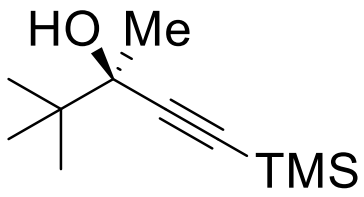
40-89% yield
32-81% ee



50% yield, 70% ee



89% yield, 80% ee

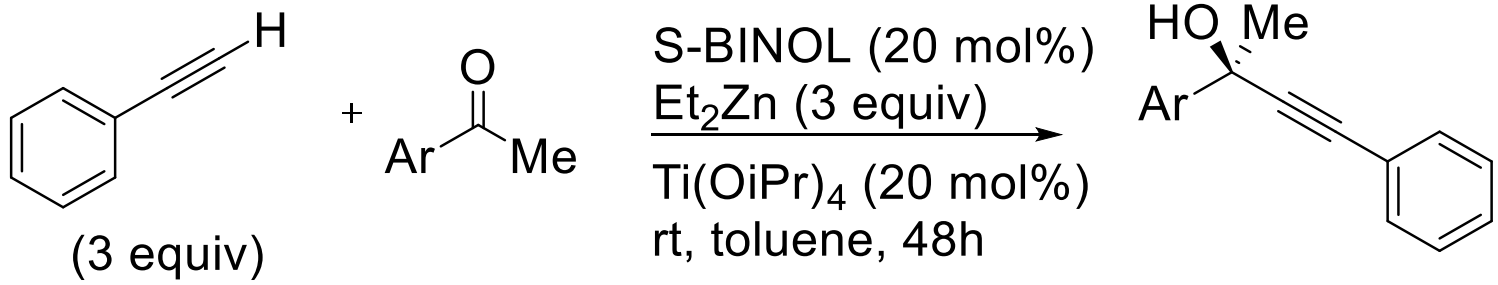


40% yield, 81% ee

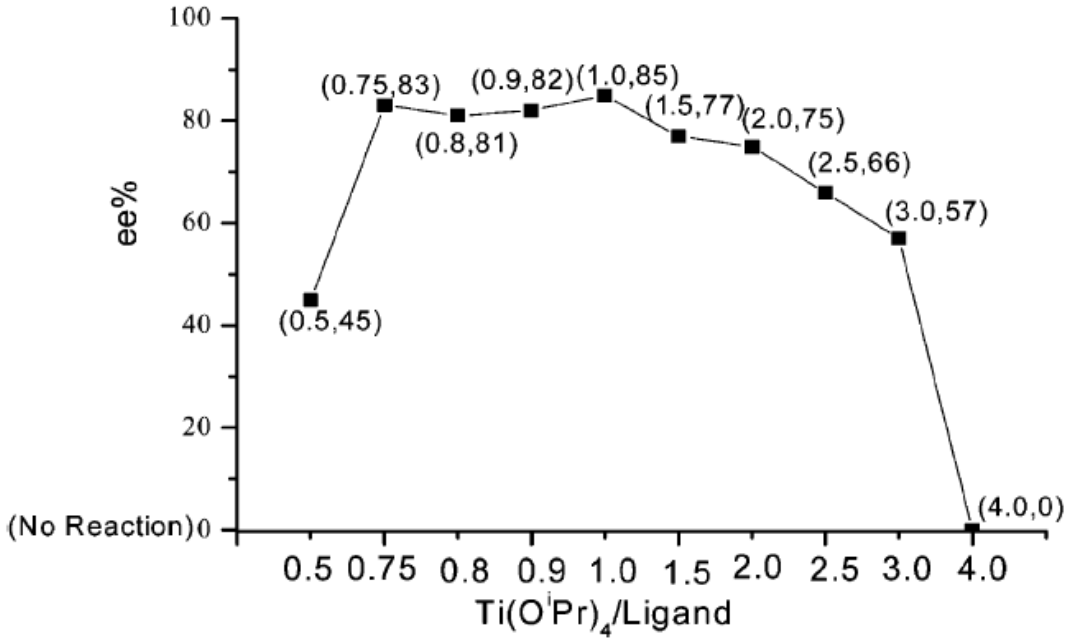
Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895.

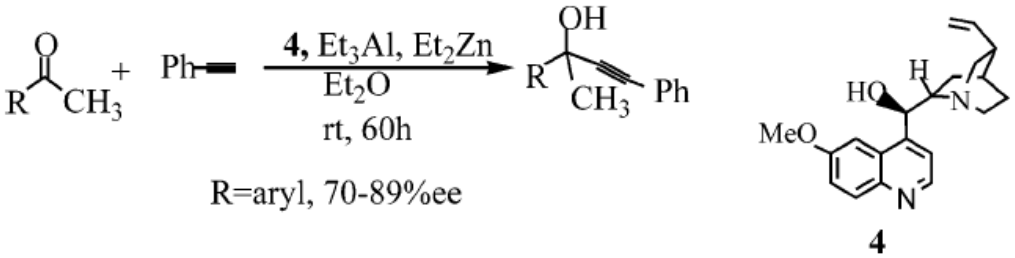
Comparisons to Similar Methods

Dialkylzinc-Mediated Alkynylation of Carbonyls



substrate	isolated yield (%)	ee (%)
acetophenone	67	85
3′-methoxyacetophenone	81	92
3′-methylacetophenone	66	90
4′-methylacetophenone	64	87
4′-chloroacetophenone	73	89
3′-bromoacetophenone	68	86
2′-naphthacetophenone	72	85
1′-naphthacetophenone	71	91
2′-fluoroacetophenone	80	66
4-methyl-2-pentanone	91	63
benzalacetone	88	73

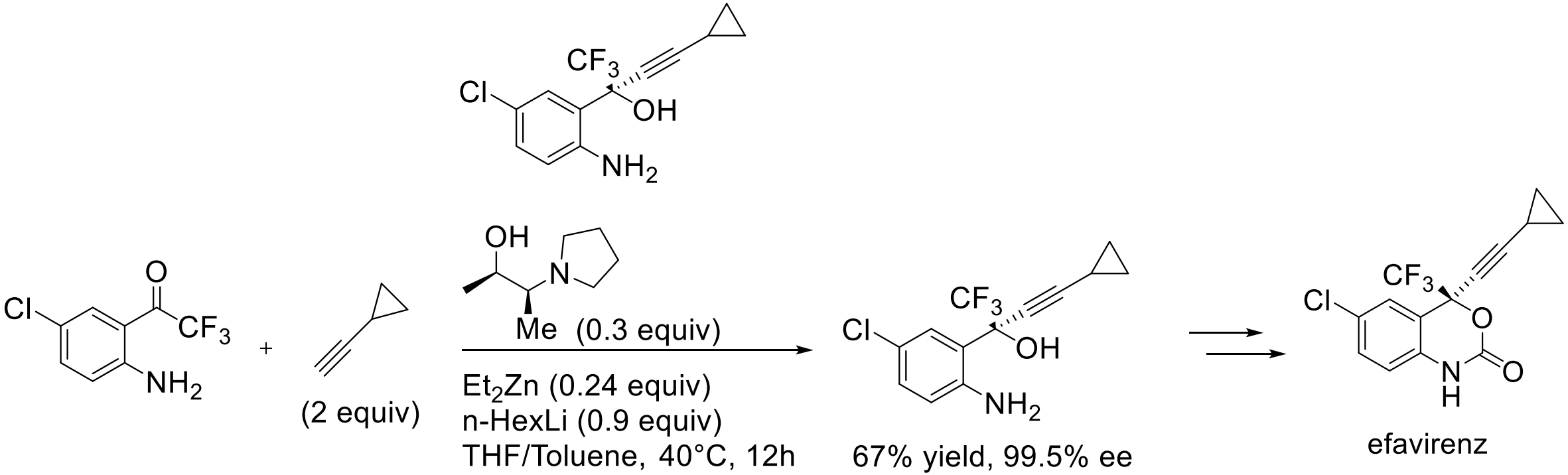




Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895.
Gong, M.-Z. et al. *J. Org. Chem.* **2005**, *70*, 1084.

Comparisons to Similar Methods

Dialkylzinc-Mediated Alkynylation of Carbonyls



Pu, L. et al. *Angew. Chem., Int. Ed.* **2006**, *118*, 128.
Carreira, E. M. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 2957.

Overview

- Background
- Comparisons to Similar Methods
- Mechanism, Stereochemistry, and Scope
  - Zinc
  - Indium
  - Copper
  - Rhodium/Ruthenium
- **Conclusions**

Conclusions

Quick Summary of Metal Salts

- Zn-
  - Most widely studied
  - Broadest Scope- aldehydes, a-keto esters (not enolizable)
  - has some issues with some aromatics
  - Not always catalytic
- In-
  - works well with heteroaromatics, aromatics, catalytically
  - Not terribly susceptible to air and moisture
  - more expensive
  - Doesn't work with silyl ethers or esters on the alkyne
- Cu-
  - tested due to demand of environmentally friendly processes, try to avoid stoichiometric reagents.
  - Ligands must be synthesized
  - does aromatic, heteroaromatic, a-sub aliphatic aldehydes well.
  - Base not needed
  - Otherwise generally lower yields and ee's compared to the other metal salt systems
- Rh/Ru-
  - Rather recent
  - must use aromatic aldehydes or ee's suffer
  - low cat, ligand loading

Conclusions

Future Directions

- Optimization to make the enantioselective Favorskii reaction catalytic for different additions
  - Temperature
- Conditions for aromatic and heteroaromatic aldehydes
- Effects of substituents on aryl groups
- Wider carbonyl substrate scopes
  - Aliphatic Ketones
- Optimization of diyne and triyne additions to catalytic levels,
- Optimizing other metal systems