

**Gold(I)-Catalyzed Highly Diastereo- and Enantioselective
Alkyne Oxidation/Cyclopropanation of 1,6-Enynes**

Reporter: Yue Ji

Checker: Zhang-Pei Chen

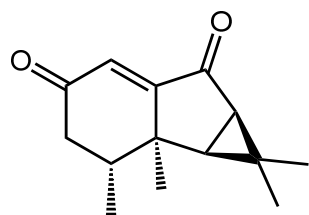
Date: 2015/01/20

Zhang, J. *et al.*
Angew. Chem. Int. Ed. **2014**, 53, 13751.

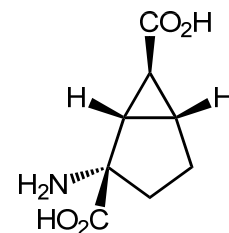
Content

- **Introduction**
- **Alkyne Oxidation/Cyclopropanation of 1,6-Enyne**
- **Cyclopropanation of Acceptor-Substituted Diazoacetates**
- **Summary**

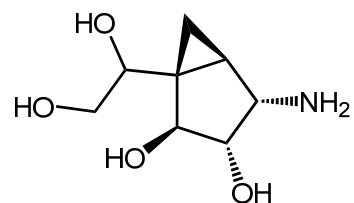
Introduction



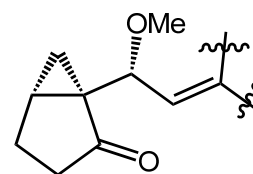
nardoaristolones **B**



LY314582
(anticonvulsant)



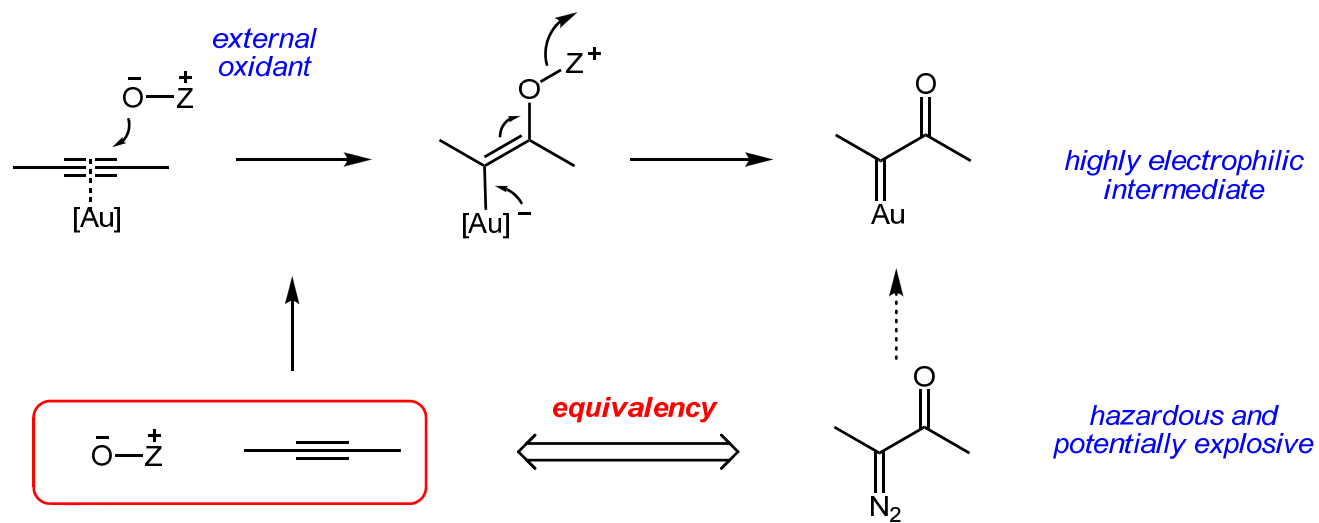
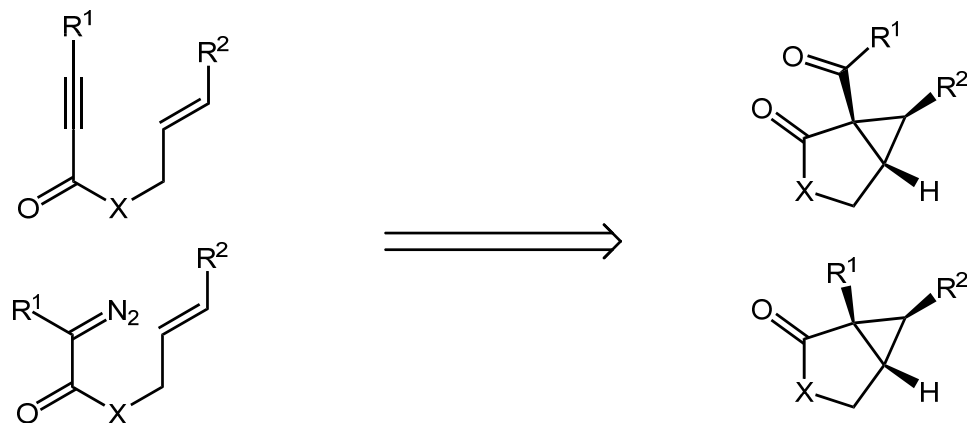
biological probe



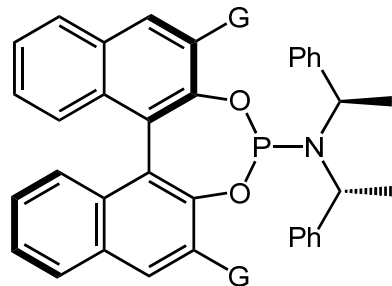
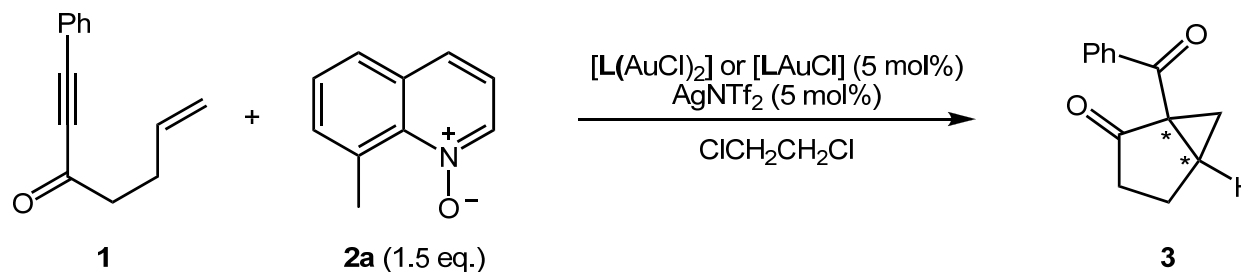
key fragment for
vitamin D analogues

Introduction

Intramolecular Asymmetric Cyclopropanation

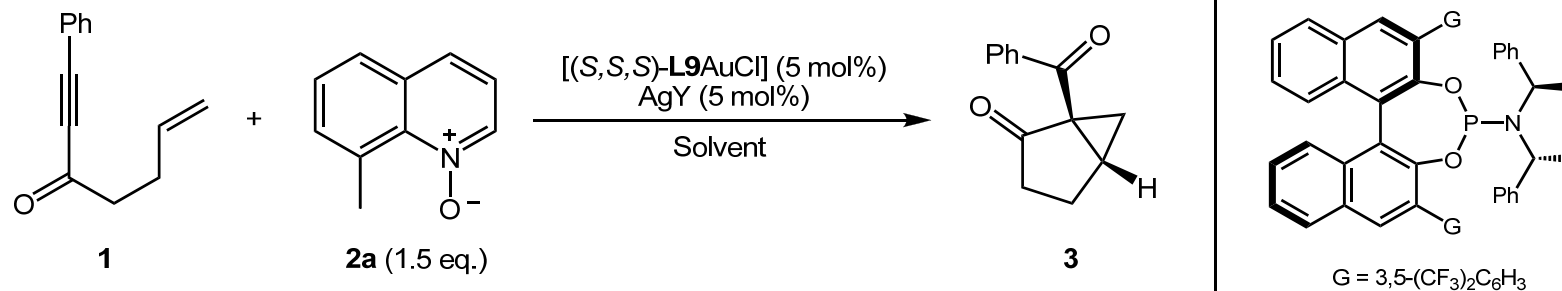


Asymmetric Alkyne Oxidation/Cyclopropannation of 1,6-Enyne



| Entry | G | t/h | Conv. (%) | e.r. |
|-------|---|-----|-----------|-------|
| 1 | H | 12 | >95 | 51:49 |
| 2 | 4-MeOC ₆ H ₄ | 5 | >95 | 57:43 |
| 3 | 3,5-Me ₂ C ₆ H ₃ | 10 | >95 | 68:32 |
| 4 | 3,5-tBu ₂ C ₆ H ₃ | 12 | >95 | 72:28 |
| 5 | 3,5-Ph ₂ C ₆ H ₃ | 12 | >95 | 75:25 |
| 6 | 3,5-(CF ₃) ₂ C ₆ H ₃ | 12 | >95 | 85:15 |
| 7 | 9-anthracenyl | 12 | >95 | 53:47 |
| 8 | SiPh ₃ | 24 | 85 | 63:37 |

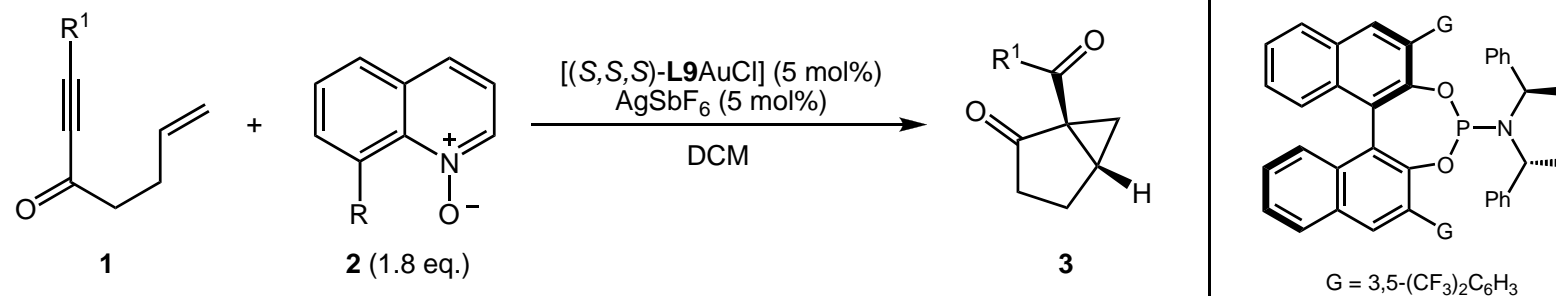
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



| Entry | AgY | Solvent | T/°C | t/h | Yield (%) | e.r. |
|----------------|--------------------|---------|------|-----|-------------|-------|
| 1 | AgNTf ₂ | DCE | 25 | 12 | >95 | 85:15 |
| 2 | AgNTf ₂ | DCM | 25 | 22 | 72 | 88:12 |
| 3 | AgNTf ₂ | THF | 25 | 12 | no reaction | -- |
| 4 | AgNTf ₂ | DMSO | 25 | 12 | no reaction | -- |
| 5 | AgSbF ₆ | DCM | 25 | 10 | >95 | 88:12 |
| 6 | AgClO ₄ | DCM | 25 | 48 | 52 | 88:12 |
| 7 | AgSbF ₆ | DCM | 0 | 23 | >95 | 89:11 |
| 8 | AgSbF ₆ | DCM | -15 | 96 | 83 | 92:8 |
| 9 ^a | AgSbF ₆ | DCM | -15 | 96 | 85 | 93:7 |

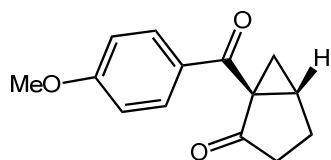
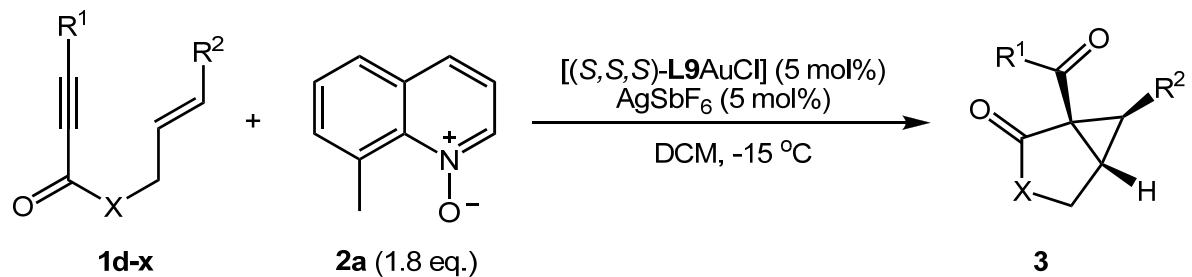
^a 4Å MS

Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne

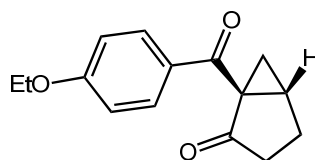


| Entry | R^1 , 1 | R | T/°C | t/h | Yield (%) | e.r. |
|-------|--|-------------|------|-----|-----------|-------|
| 1 | Ph, 1a | H | 25 | 70 | 30 | 90:10 |
| 2 | Ph, 1a | Me | 25 | 10 | 91 | 88:12 |
| 3 | Ph, 1a | <i>i</i> Pr | 25 | 18 | 90 | 84:16 |
| 4 | Ph, 1a | Me | 0 | 23 | 91 | 89:11 |
| 5 | Ph, 1a | Me | -15 | 96 | 85 | 93:7 |
| 6 | 4-FC ₆ H ₄ , 1b | Me | -15 | 96 | 55 | 91:9 |
| 7 | 4-MeC ₆ H ₄ , 1c | Me | -15 | 96 | 86 | 94:6 |
| 8 | 4-MeOC ₆ H ₄ , 1d | Me | -15 | 10 | 92 | 97:3 |

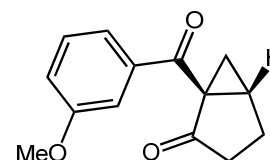
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



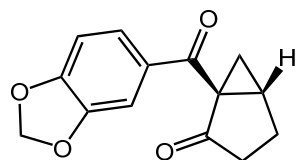
0.5 g, 81%, e.r. 96:4



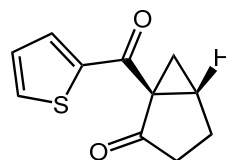
86%, e.r. 98:2



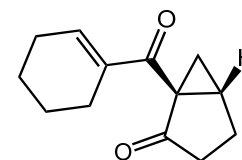
75%, e.r. 92:8



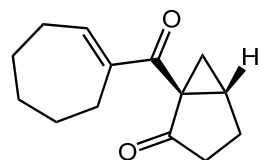
87%, e.r. 97:3



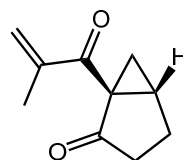
85%, e.r. 86:14



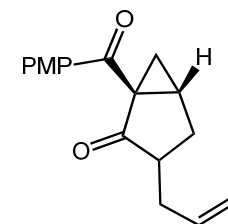
91%, e.r. 97:3



75%, e.r. 98:2

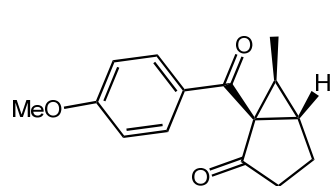
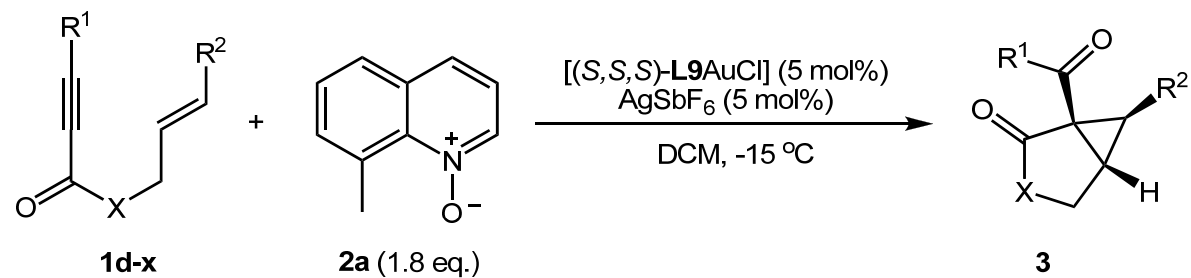


88%, e.r. 89:11

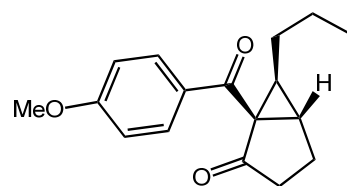


d.r. 15:1
84%, e.r. 89:11 (major)
e.r. 86:14 (minor)

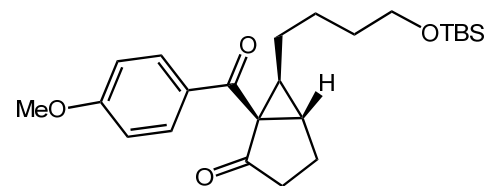
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



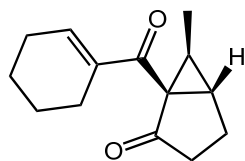
$t/c > 20:1$
71%, e.r. 95:5



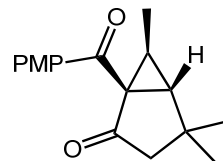
$t/c > 20:1$
67%, e.r. 96:4



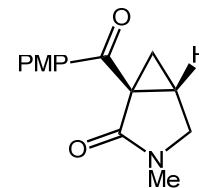
$t/c > 20:1$
56%, e.r. 96:4



$t/c > 20:1$
70%, e.r. 94:6



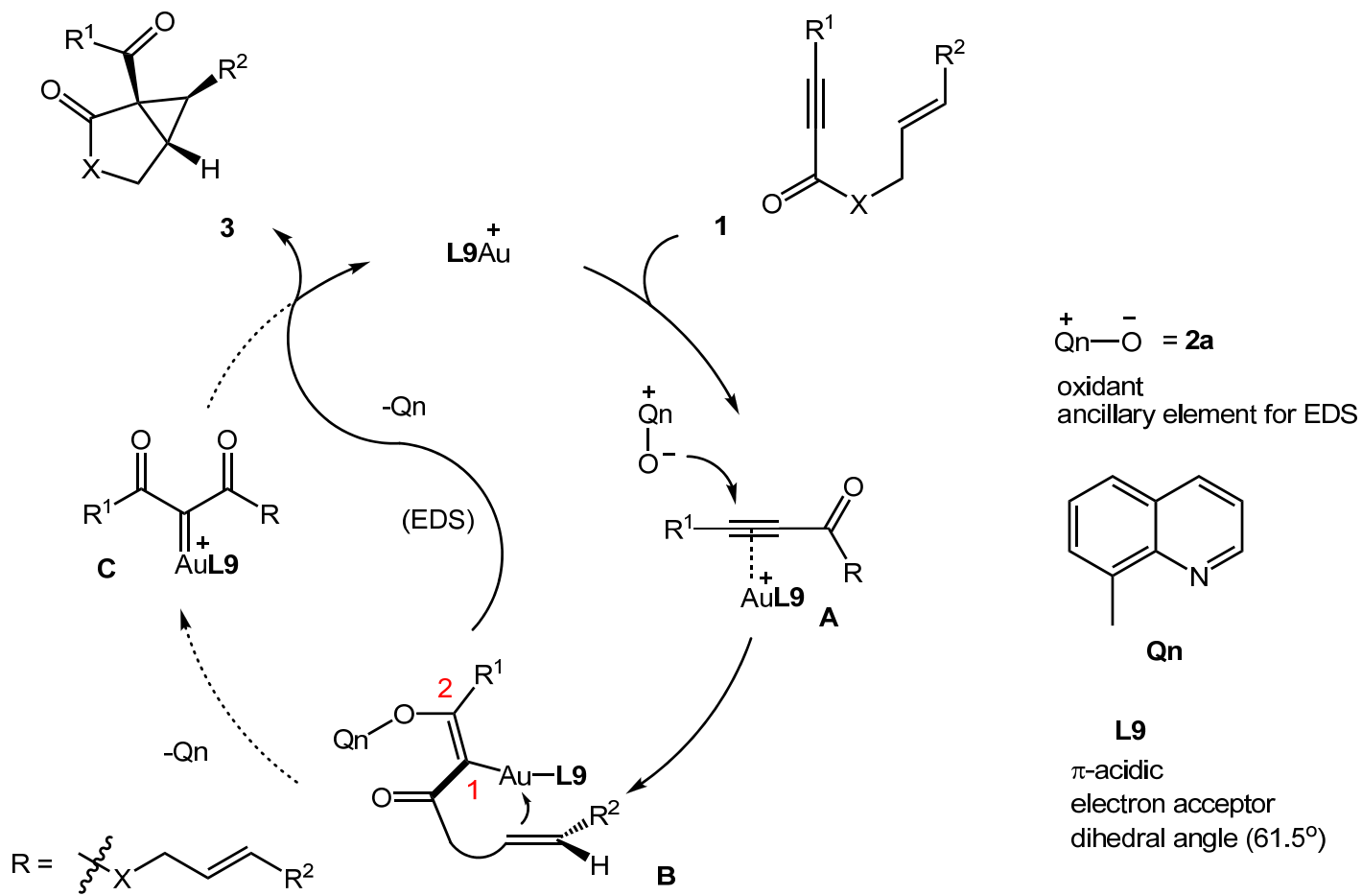
$t/c > 20:1$
89%, e.r. 91:9



80%, e.r. 92:8

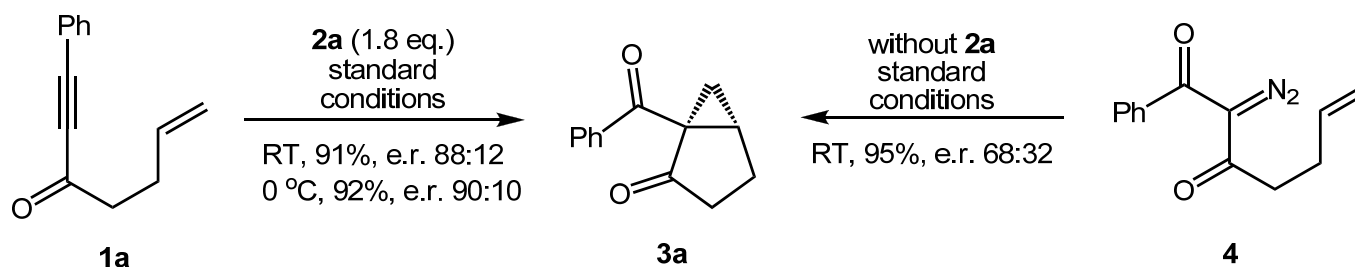
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne

ACP of Olefins: Mechanism

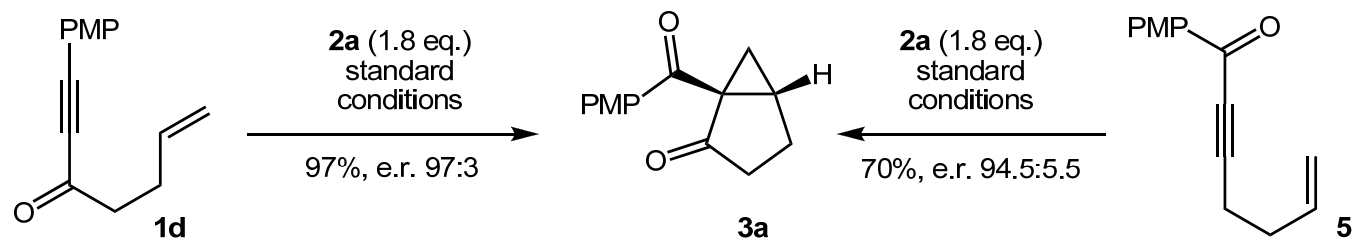


Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne

ACP of Olefins: Control Experiments

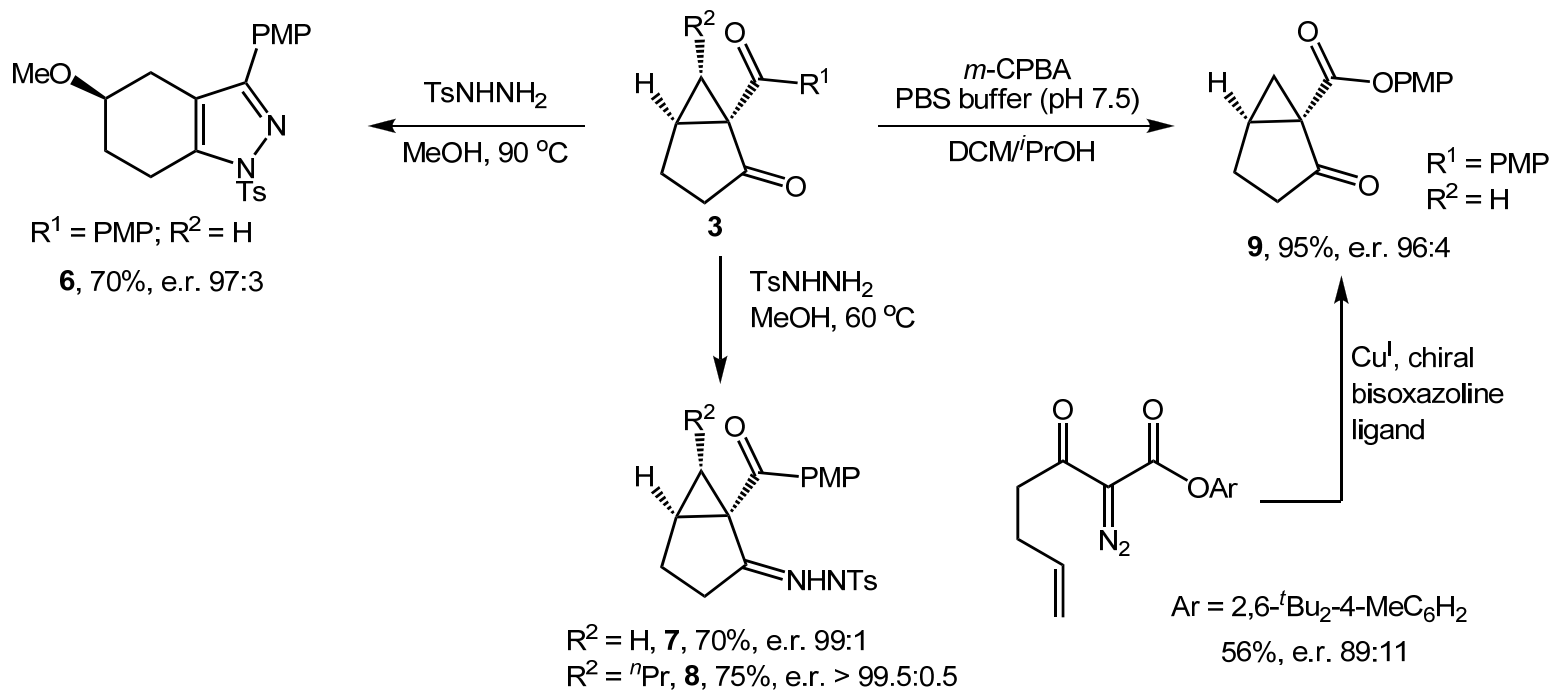


| | | |
|----|-------------------------|-----------------|
| a) | 0 °C | X |
| b) | Qn (0.5-1.0 eq.) | X |
| c) | Qn (5 mol%) | 81%, e.r. 69:31 |
| d) | 2a (0.5-1.0 eq.) | X |

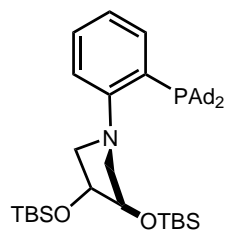
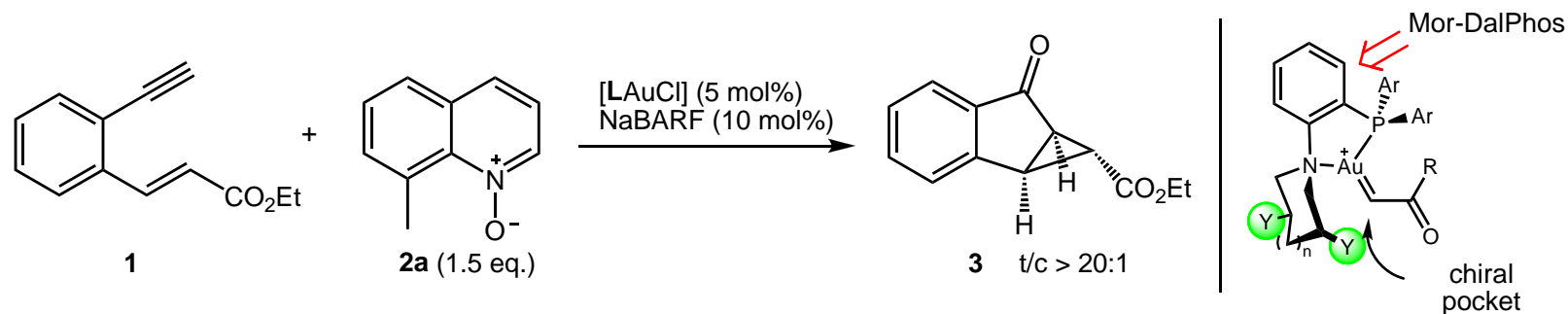


Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne

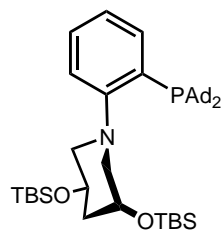
Transformation



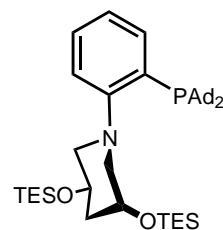
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



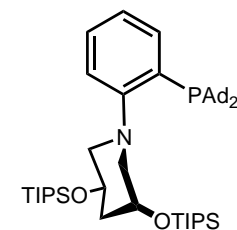
78%, 63% ee



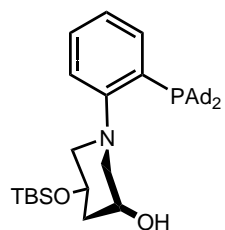
RT, 78%, 86% ee
0 °C, 70%, 90% ee
-20 °C, 68%, 94% ee



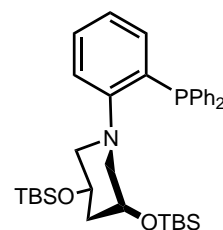
74%, 85% ee



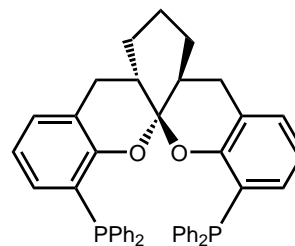
73%, 52% ee



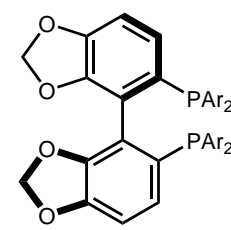
56%, 73% ee



78%, 3% ee



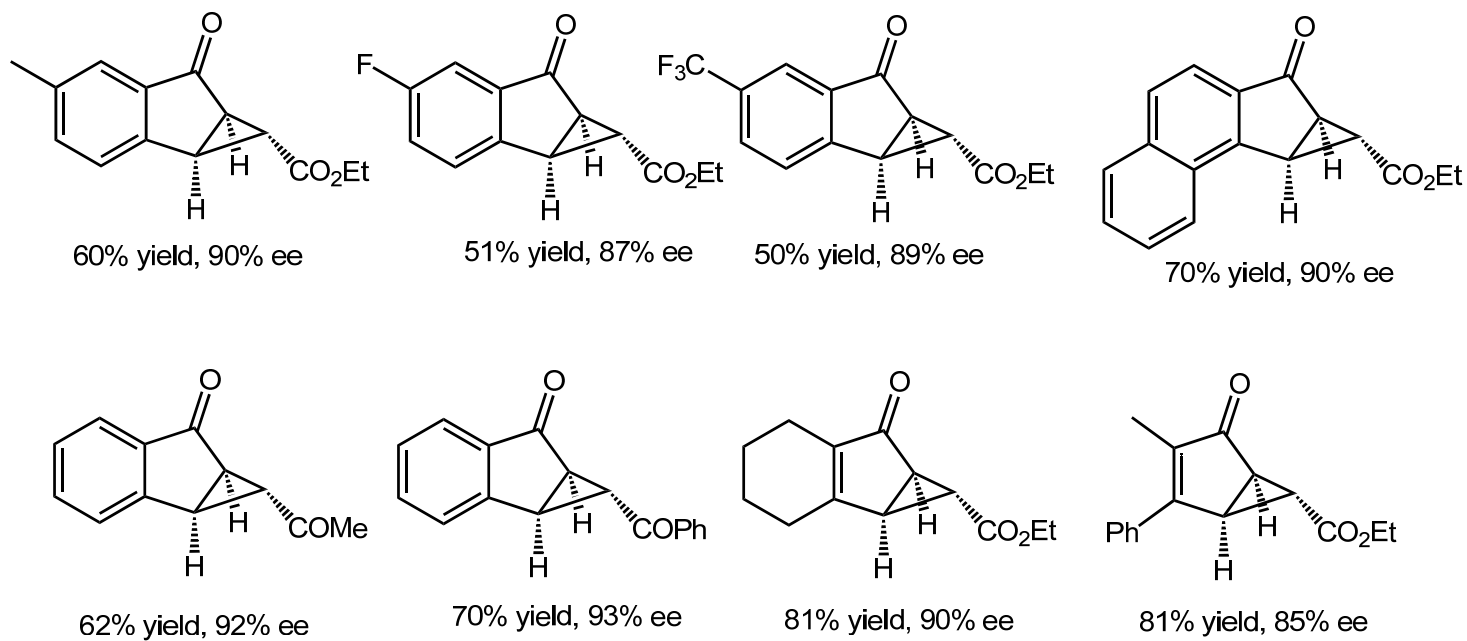
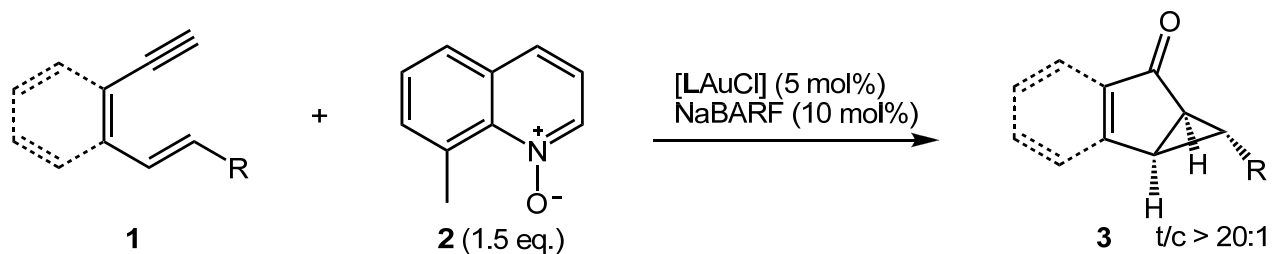
NR



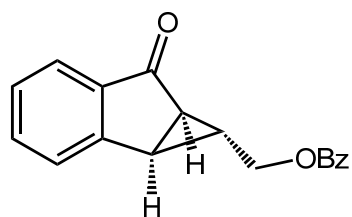
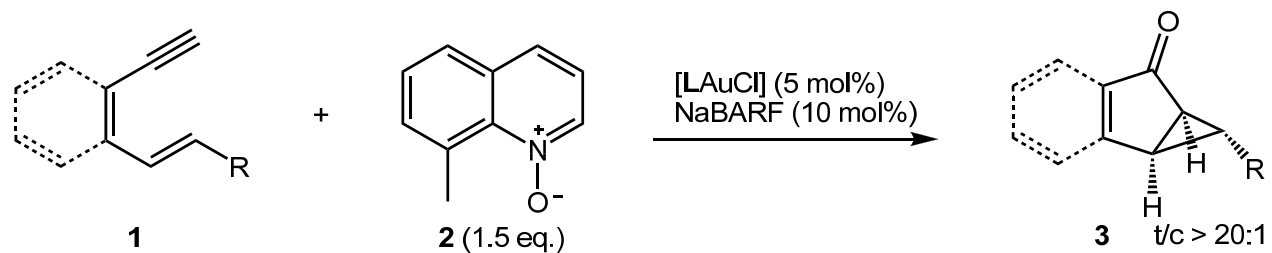
Mixture

R = DTBM-SegPhos

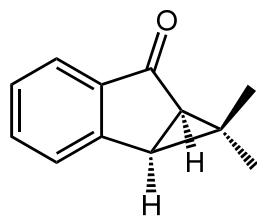
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



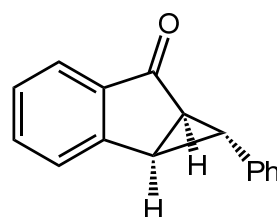
Asymmetric Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



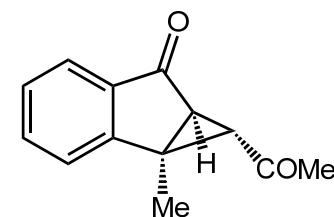
90% yield, 88% ee



90% yield, 63% ee

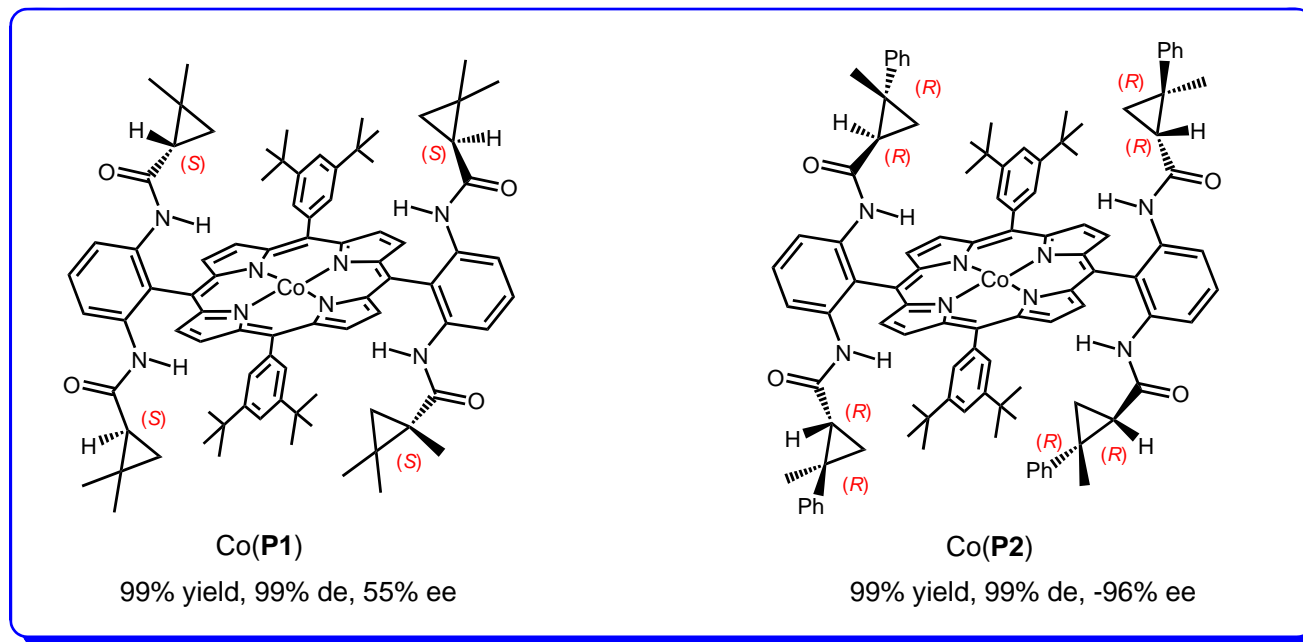
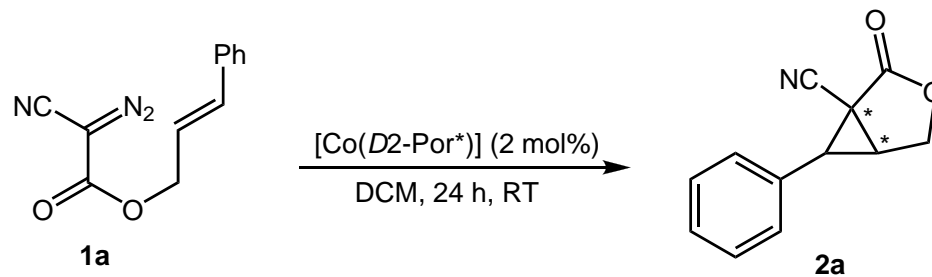


88% yield, 87% ee

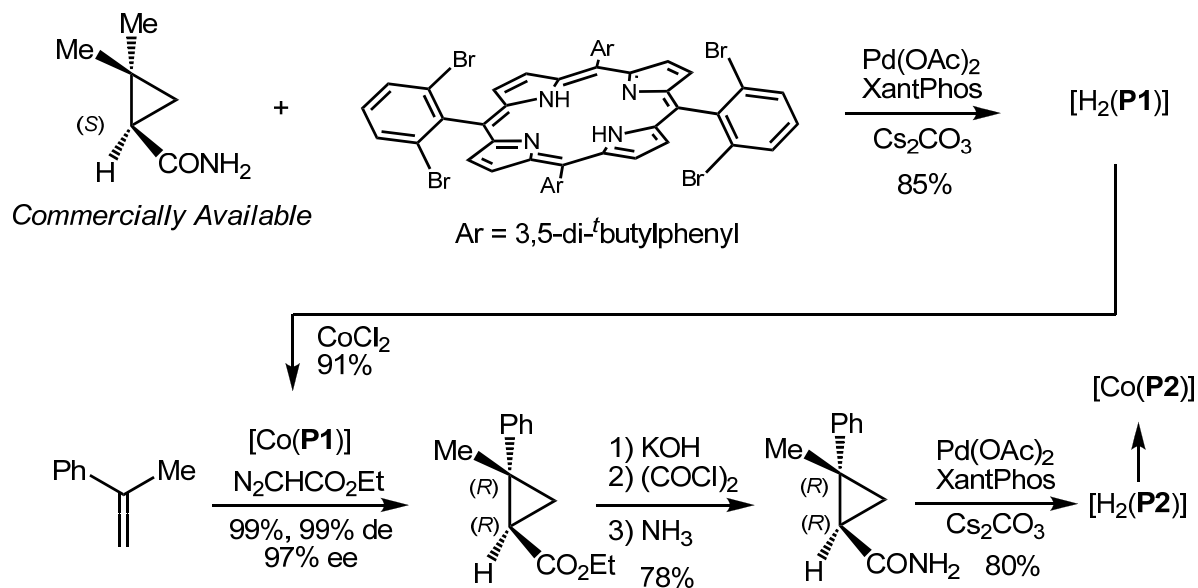
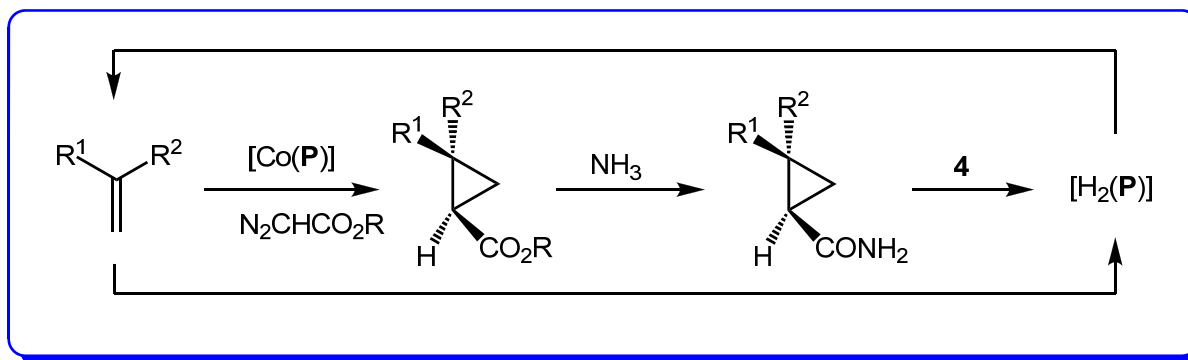


78% yield, 11% ee

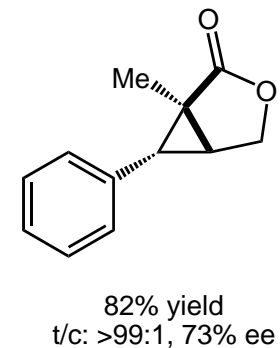
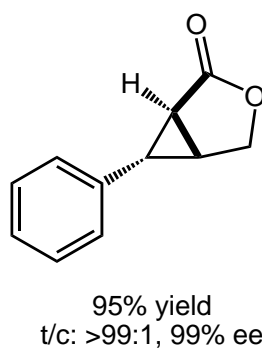
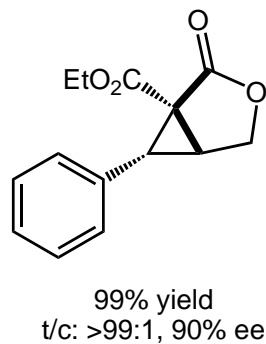
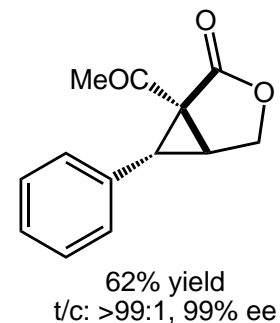
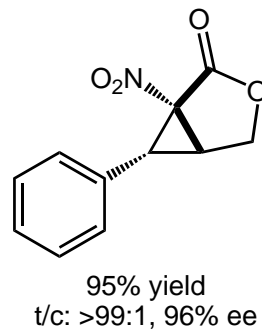
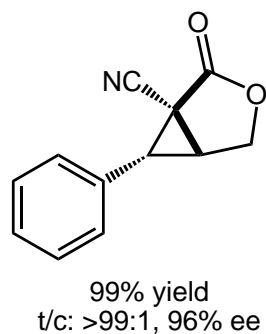
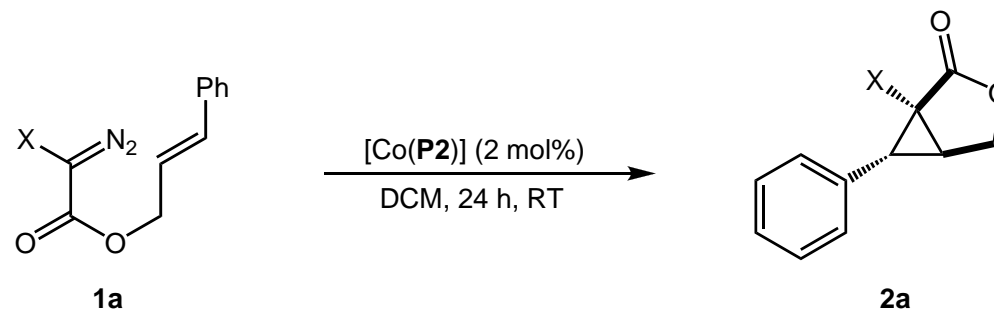
Cyclopropanation of Acceptor-Substituted Diazoacetates



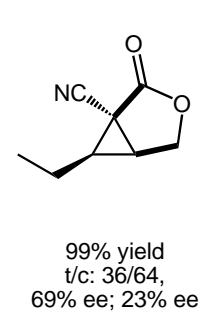
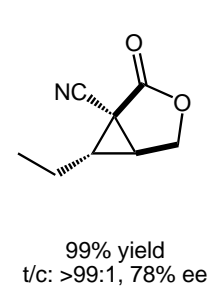
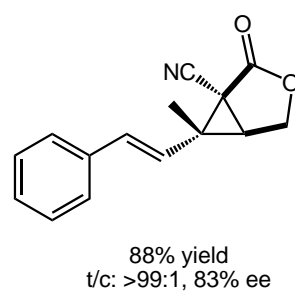
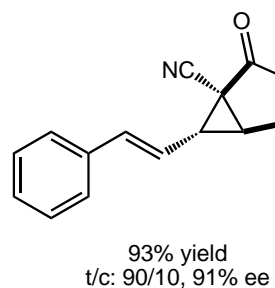
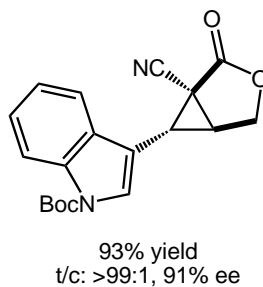
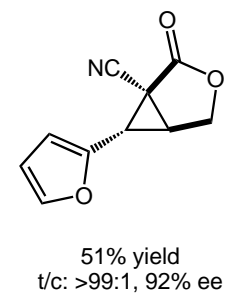
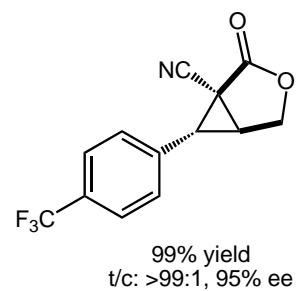
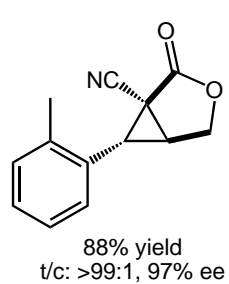
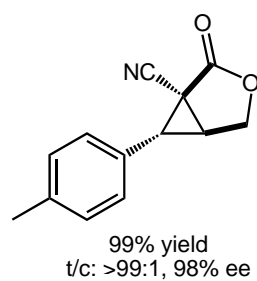
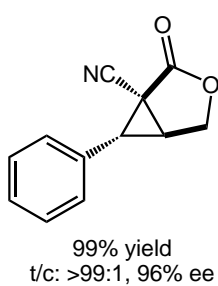
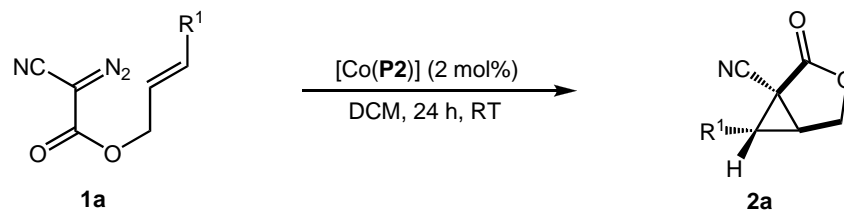
Cyclopropanation of Acceptor-Substituted Diazoacetates



Cyclopropanation of Acceptor-Substituted Diazoacetates

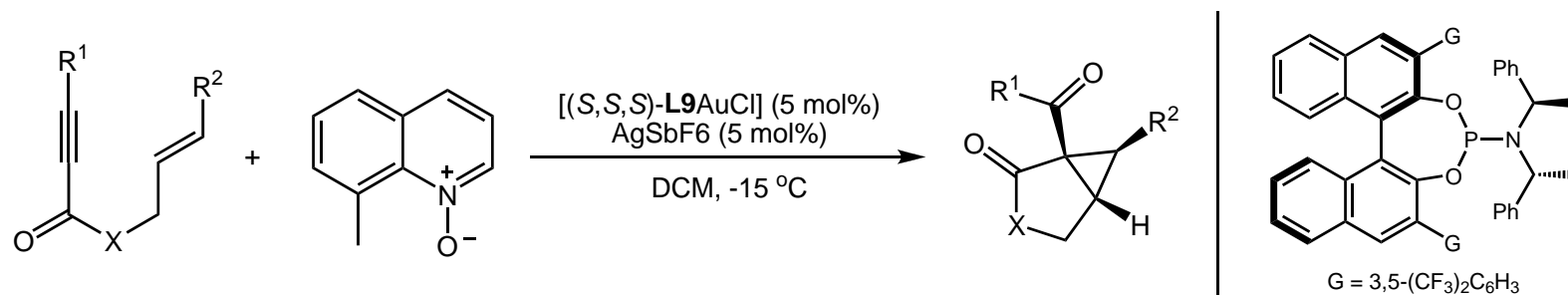


Cyclopropanation of Acceptor-Substituted Diazoacetates

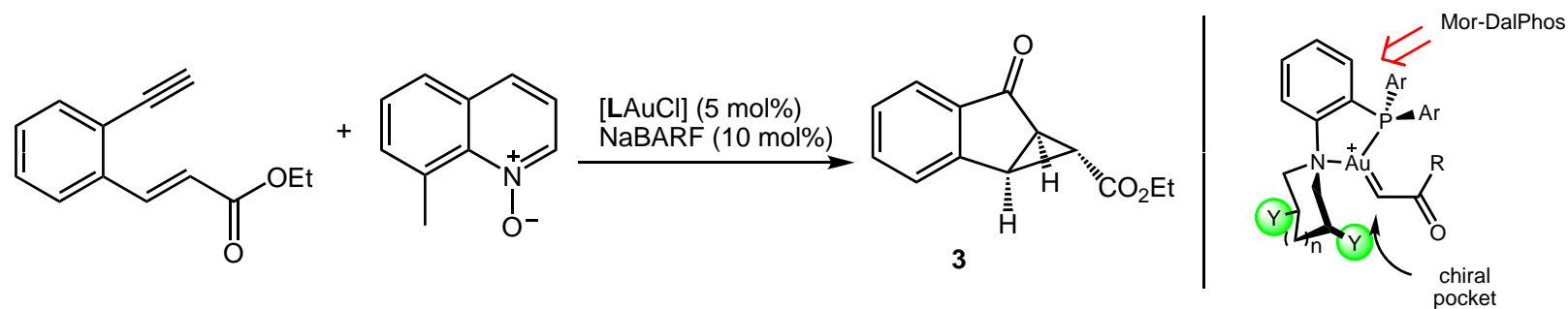


Summary

1. Alkyne Oxidation/Cyclopropanation of 1,6-Enyne



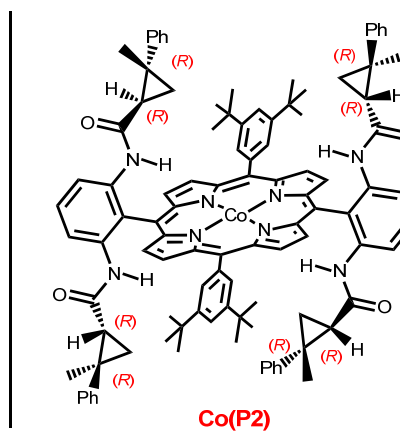
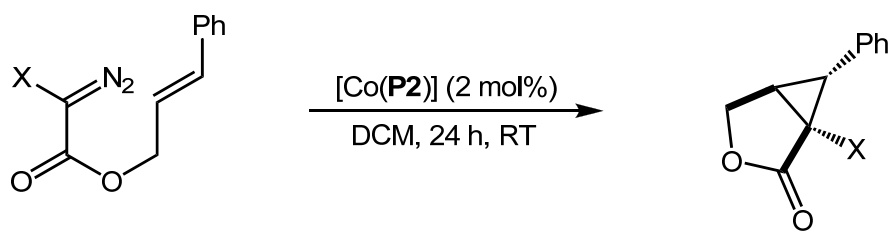
Zhang, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 13751.



Zhang, L. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 1245.

Summary

2. Intramolecular Cyclopropanation of Acceptor-Substituted Diazoacetates



Zhang, X. P. *et al.* *J. Am. Chem. Soc.* **2011**, *133*, 15292.

Asymmetric cyclopropanation (ACP) of olefins with metallo-carbenes serves as a bedrock for synthetic chemistry. In this context, the intramolecular ACP reaction of linear unsaturated diazo precursors for the stereoselective construction of [n.1.0]bicyclic ring systems has recently attracted renewed attention owing to its fundamental scientific interest and daunting challenge. Over the years, remarkable progress has been described in the formation of optically active 3-oxa- and 3-azabicyclo[3.1.0]hexane derivatives.

More recently, P. Zhang and co-workers successfully developed an intramolecular ACP reaction leading to 3-oxabicyclo[3.1.0]hexanes with diverse substituents by the application of chiral cobalt(II)–porphyrin complexes as metalloradical catalysts. In contrast, highly catalytic ACP reactions with metal carbenoids for the synthesis of bicyclo[3.1.0]hexanes, in particular those containing a challenging all-carbon quaternary stereocenter, remain comparatively rare, although such enantiomerically enriched skeletons are tremendously important because of their wide occurrence in bioactive natural products, pharmaceuticals, and conformationally restricted biological probes as well as their versatility in organic synthesis as chiral building blocks. Thus, a new and complementary approach that enables fast access to such architectures with multifunctionalized stereocenters is still in great demand.

In summary, we have demonstrated a highly efficient and selective synthesis of enantiomerically enriched bicyclo[3.1.0]hexan-2-ones through gold(I)-catalyzed asymmetric alkyne oxidation/cyclopropanation. With the readily available chiral phosphoramidite ligand **L9**, a variety of bicyclo[3.1.0]hexane derivatives containing three contiguous stereocenters with multiple functionalities were obtained with up to e.r. 98:2 under mild conditions. Moreover, the efficiency of ynones as safe surrogates of acceptor/acceptor diazo reagents was recognized. Mechanistic studies suggest that the β -gold vinyloxyquinolinium species contributes to the enantioselectivity of the cyclopropanation. This demonstration of gold(I)-catalyzed alkyne oxidation for asymmetric intramolecular cyclopropanation may open the door for the discovery of other reactions for the enantioselective functionalization of alkynes by oxidation with pyridine/quinoline *N*-oxides.
