# Literature Report 7

# Enantioselective Oxidative Cyclization/Mannich Addition Enabled by Gold(I)/Chiral Phosphoric Acid Cooperative Catalysis

**Reporter**: **Huan-Ping Xie**

**Checker**: **Hong-Qiang Shen**

**Date**: **2019/01/07**

Wei, H.; Bao, M.; Dong, K.; Qiu, L.; Wu, B.; Hu, W.; Xu, X. *Angew. Chem. Int. Ed.* **2018***, 57,* 17200*.*

# Contents

# Biography

Xinfang Xu

**Areas of interest:**

- **Research on synthetic methodology, metal carbene chemistry, chiral catalysis;**
- **Study on the synthesis of heterocyclic compounds and drugs and their intermediates.**

**Research experience:**

- **2014-至今** Professor, Soochow University.
- **2010-2014** Postdoctoral Fellow, University of Maryland, USA (Doyle, M. P.);
- **2005-2010** Ph. D., East China Normal University (Hu, W.);
- **2001-2005** B. S., East China Normal University;

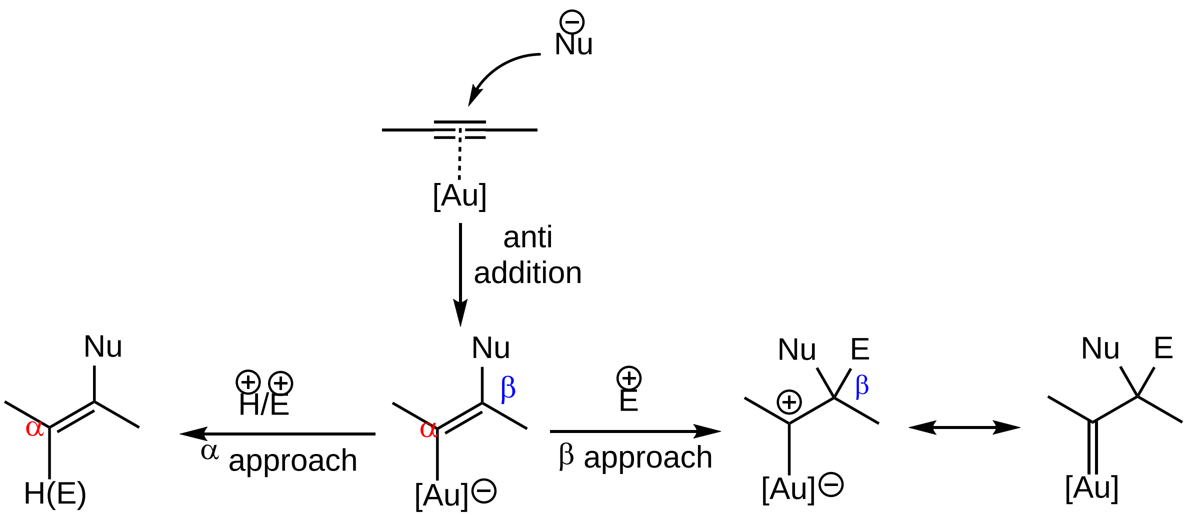
# Introduction

| |
|---|
| 79 |
| Au |
| $5d^{10}\ 6s^{1}$ |

- 原子半径：144 pm;
- 电负性: 2.54，电负性最强的金属;
- 常见的氧化态：+1，+3；其它氧化态：+2，+5;
- 化学性质不活泼, 可以被氯、氟、王水及氰化物侵蚀。

# Introduction

**Homogeneous gold catalysis activating C-C triple bond**

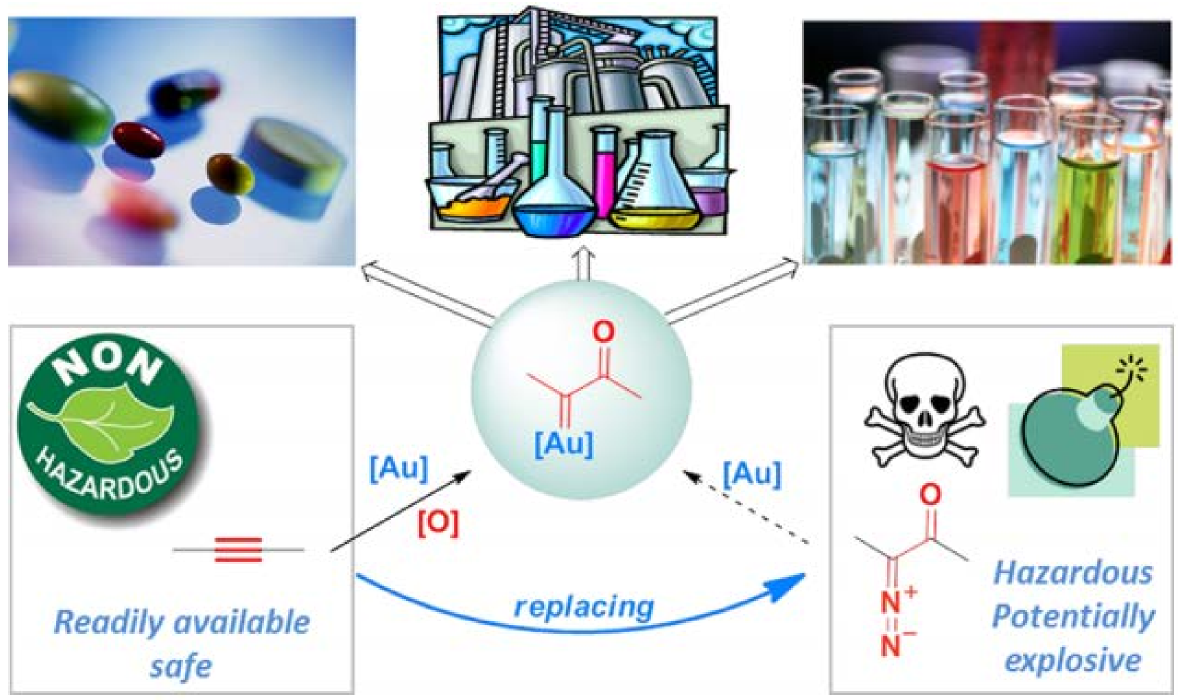


Au carbene intermediate

Shin, S. *et al. Acc. Chem. Res.* **2014**, *47*, 966.

# Introduction

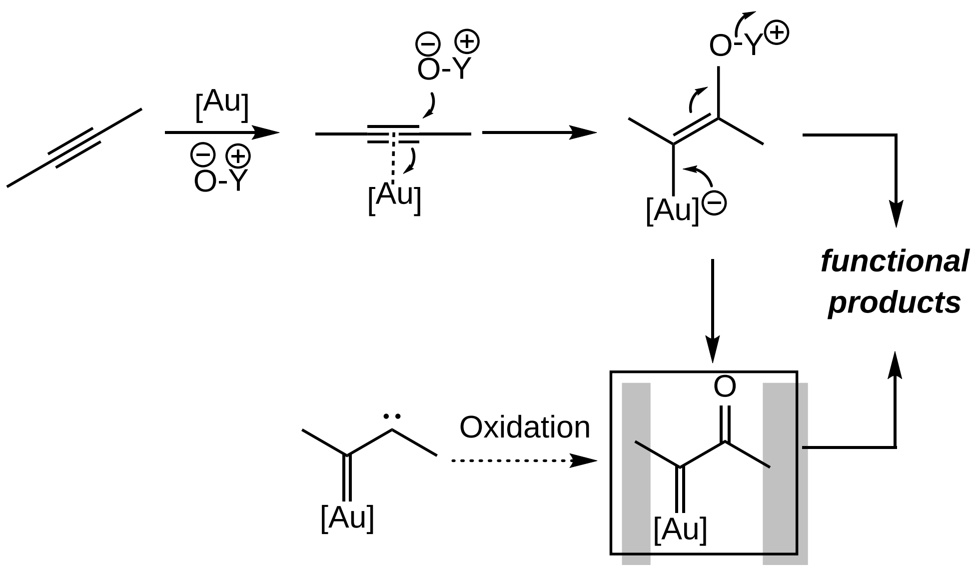
**α-Oxo gold carbenes**




Zhang, L. *et al. Acc. Chem. Res*. **2014**, *47*, 877.

# Introduction

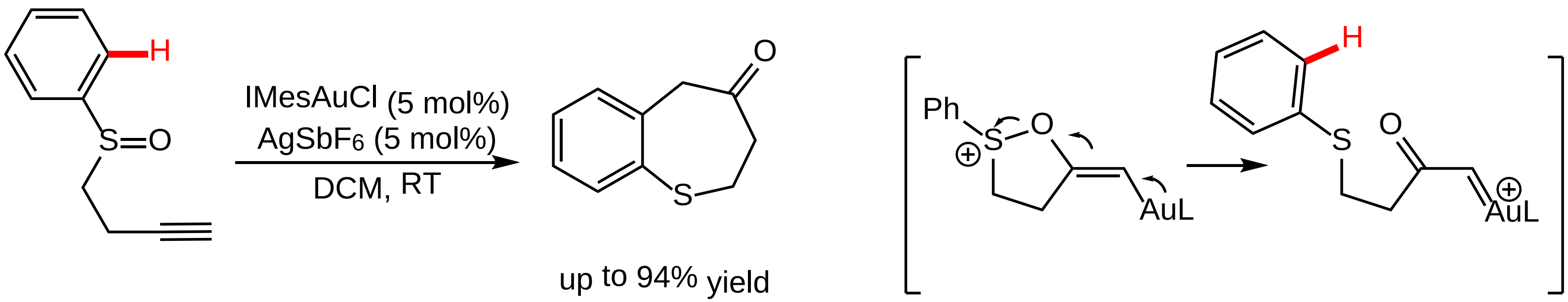
**Generation of α-oxo gold carbenes from alkynes**



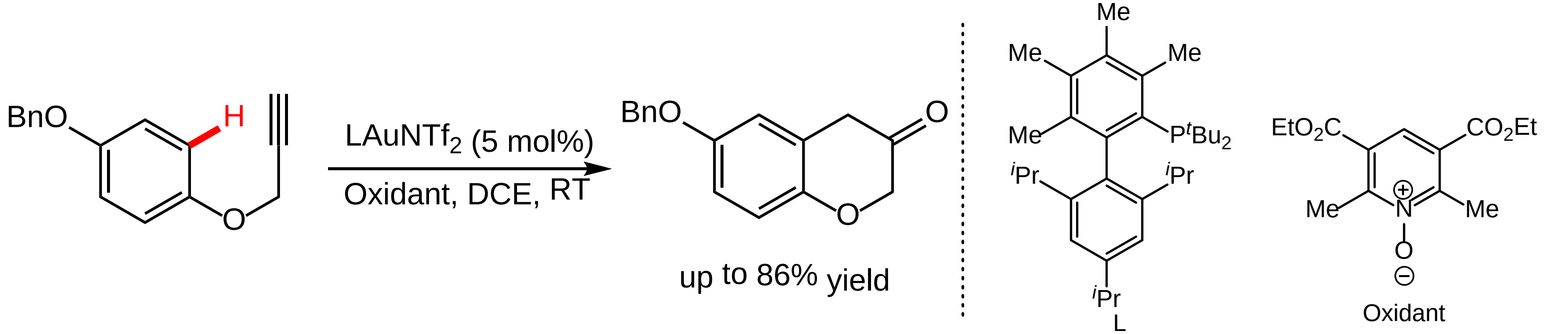

Oxidants: pyridine/quinolone N-oxides or sulfoxides

# Introduction

## $sp^2$ C-H Insertion:



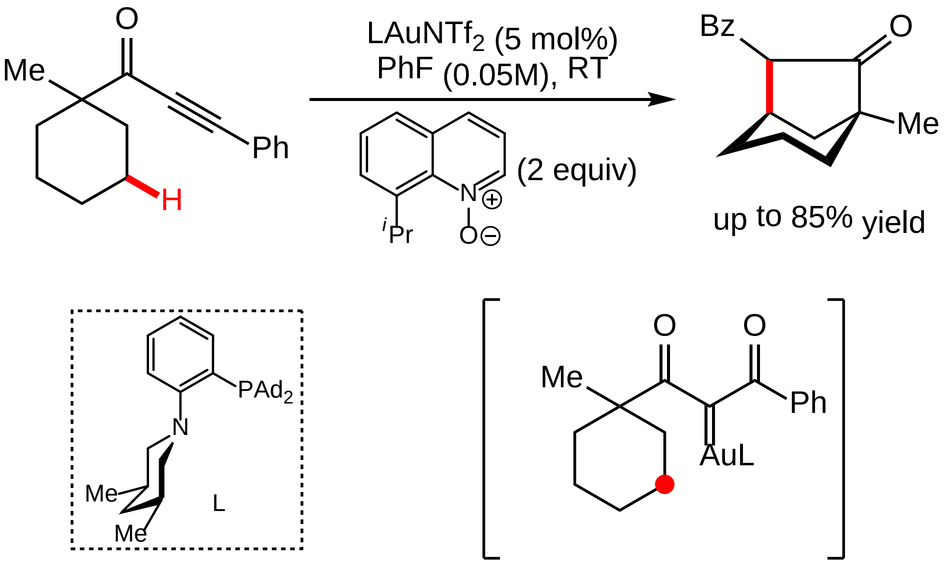

Toste, F. D. *et al. J. Am. Chem. Soc.* **2007**, *129*, 4160.




Zhang, L. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 1915.

# Introduction

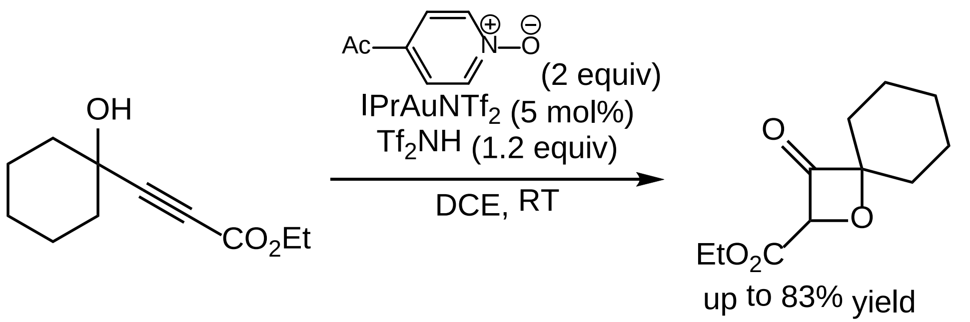
**sp$^3$ C-H Insertion:**




Zhang, L. *et al. J. Am. Chem. Soc.* **2015**, *137*, 5316.

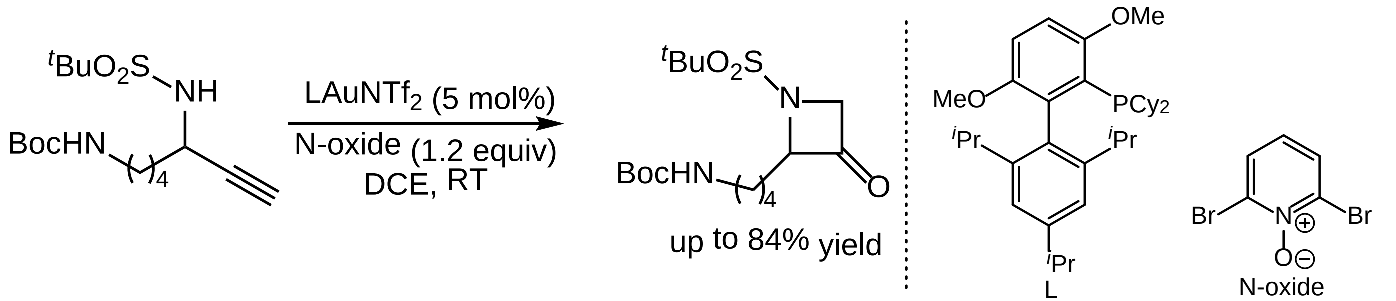
# Introduction

## O-H Insertion:




Zhang, L. *et al. J. Am. Chem. Soc.* **2010**, *132,* 8550.

## N-H Insertion:

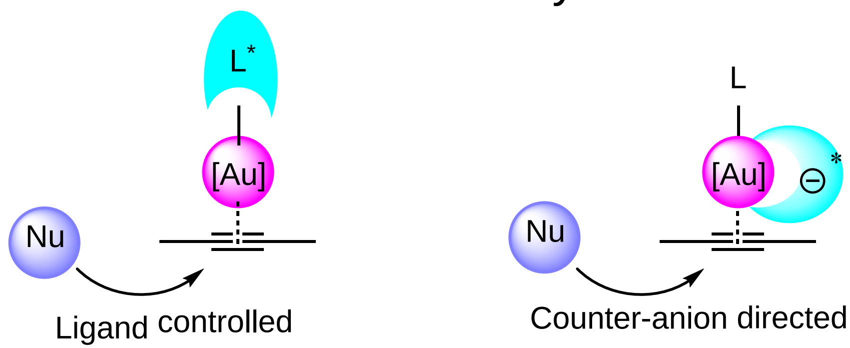



Zhang, L. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3236.

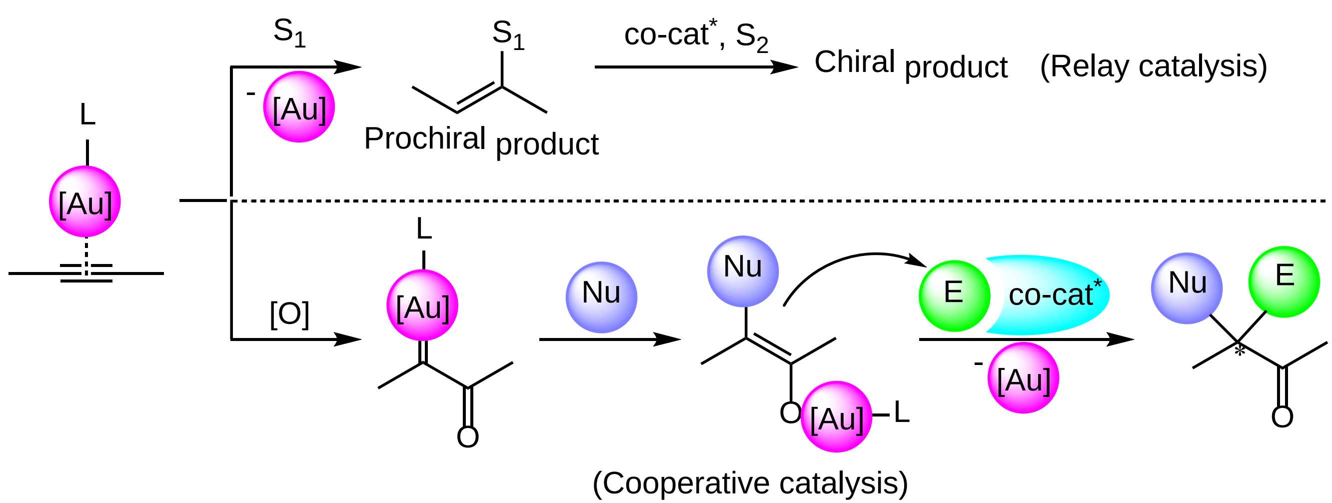
# Introduction

**Modes of asymmetric Au(I) catalysis:**

- Asymmetric induction with chiral Au catalyst:

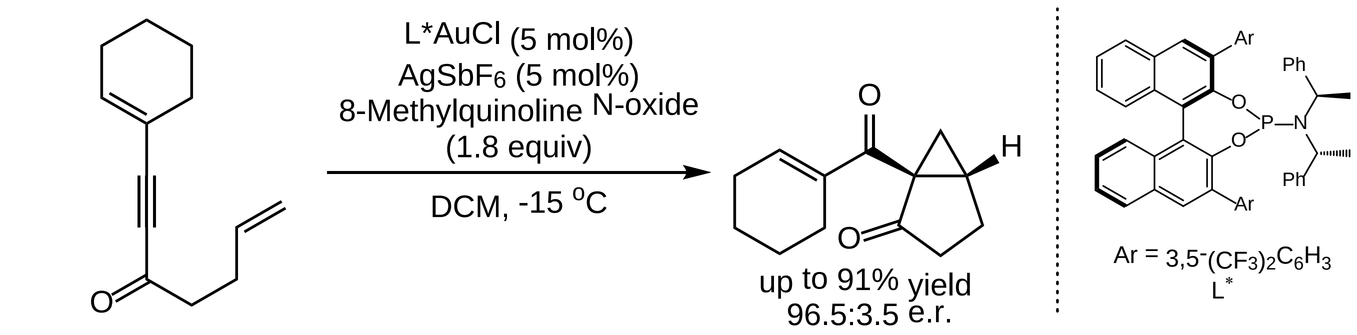



- Asymmetric induction with chiral co-catalyst:

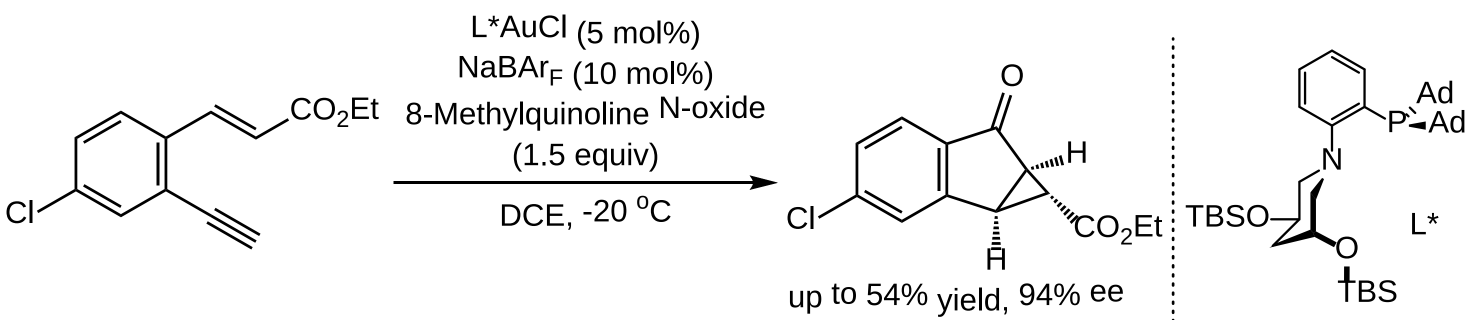


# Introduction

## Ligand controlled asymmetric induction



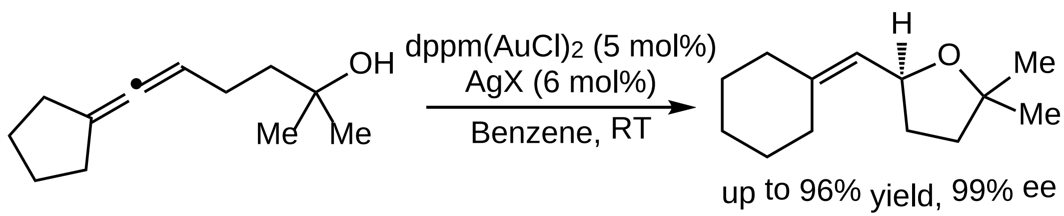

Zhang, J. *et al. Angew. Chem. Int. Ed.* **2014**, *53,* 13751.

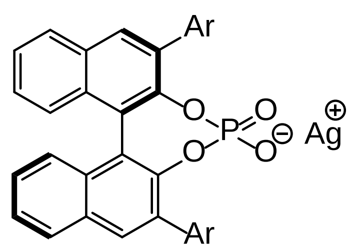



Zhang, L. *et al. Angew. Chem. Int. Ed.* **2015**, *54,* 1245.

# Introduction

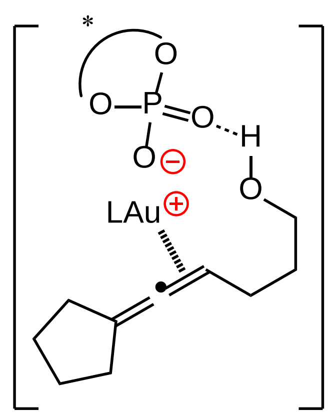
## Counter-anion directed asymmetric induction




Ar = 2,4,6-($^i$Pr)$_3$-$C_6H_2$

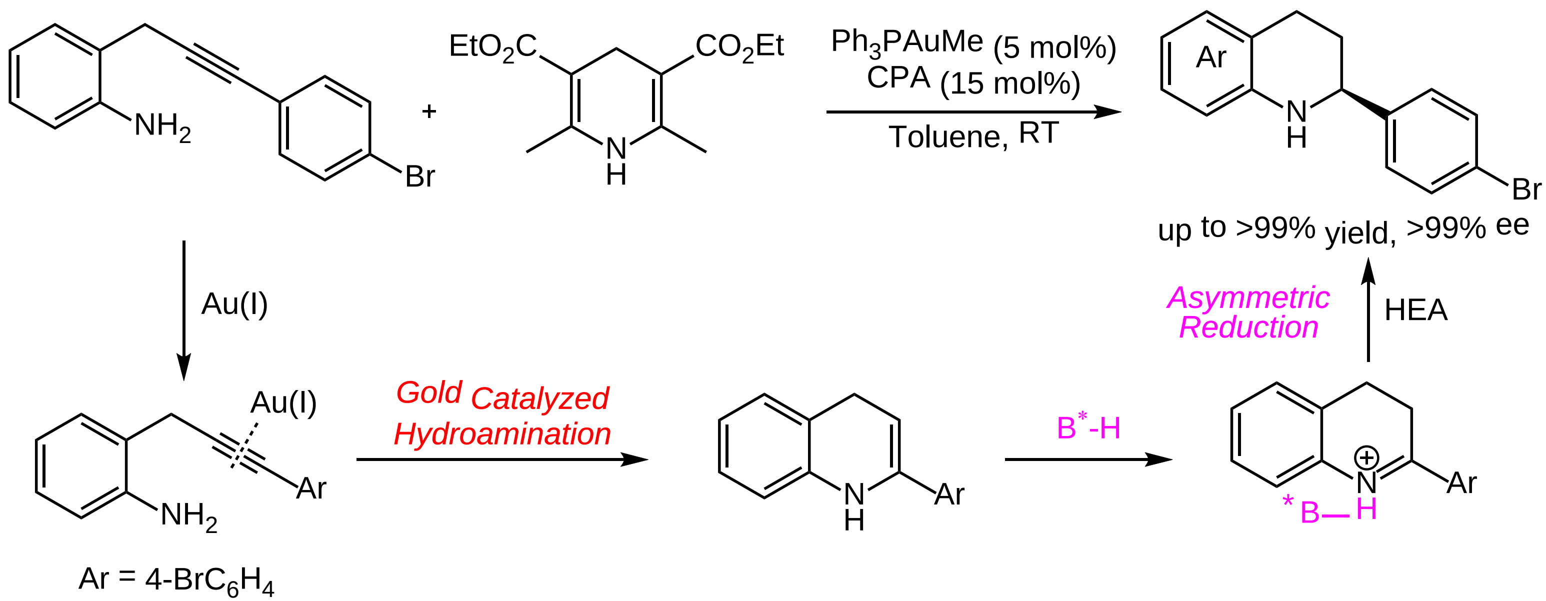
AgX




Toste, F. D. *et al. Science* **2007**, *317,* 496.

# Introduction

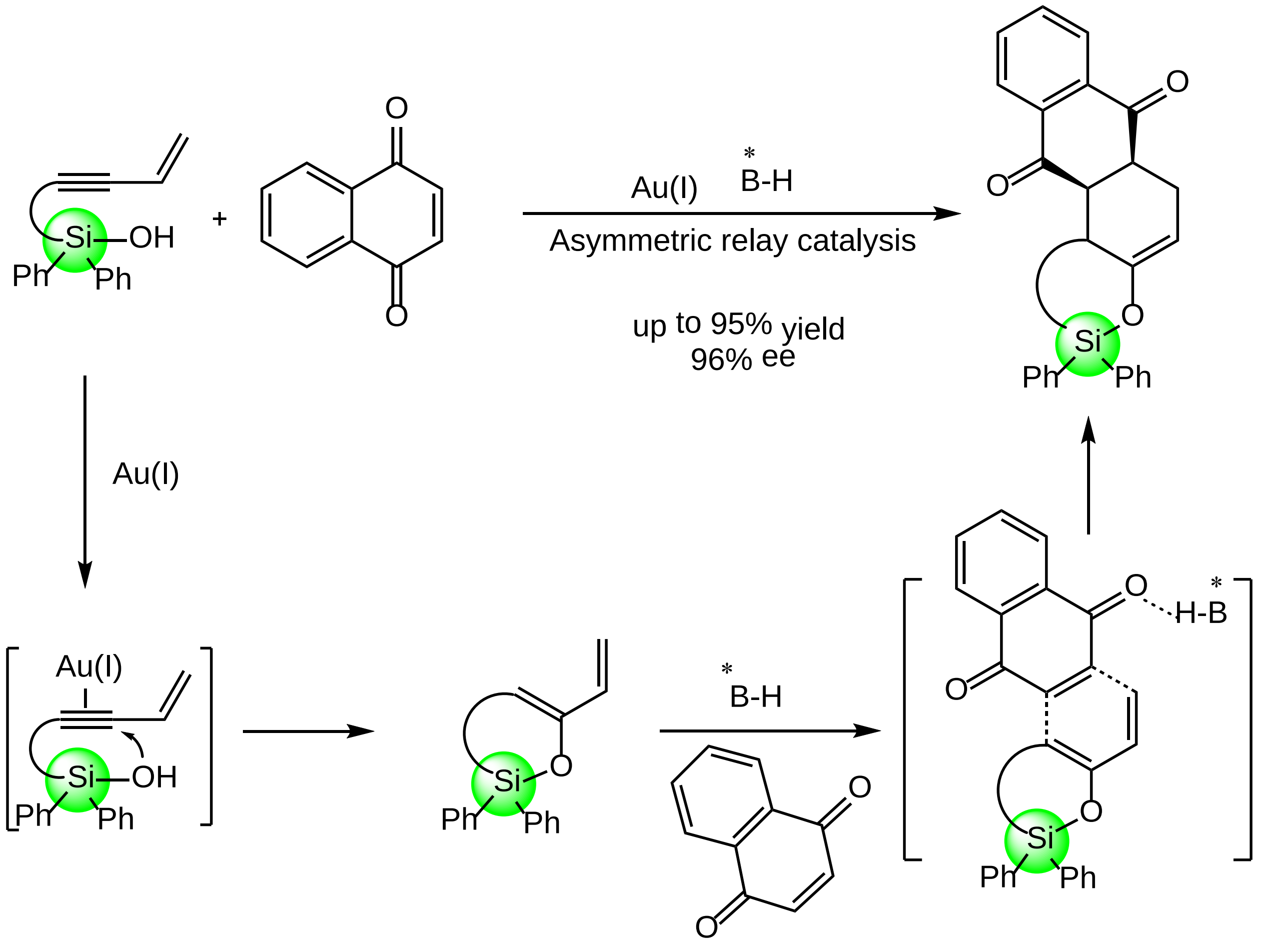
**Relay catalysis**




Gong, L.-Z. *et al. J. Am. Chem. Soc.* **2009**, *131*, 9182.

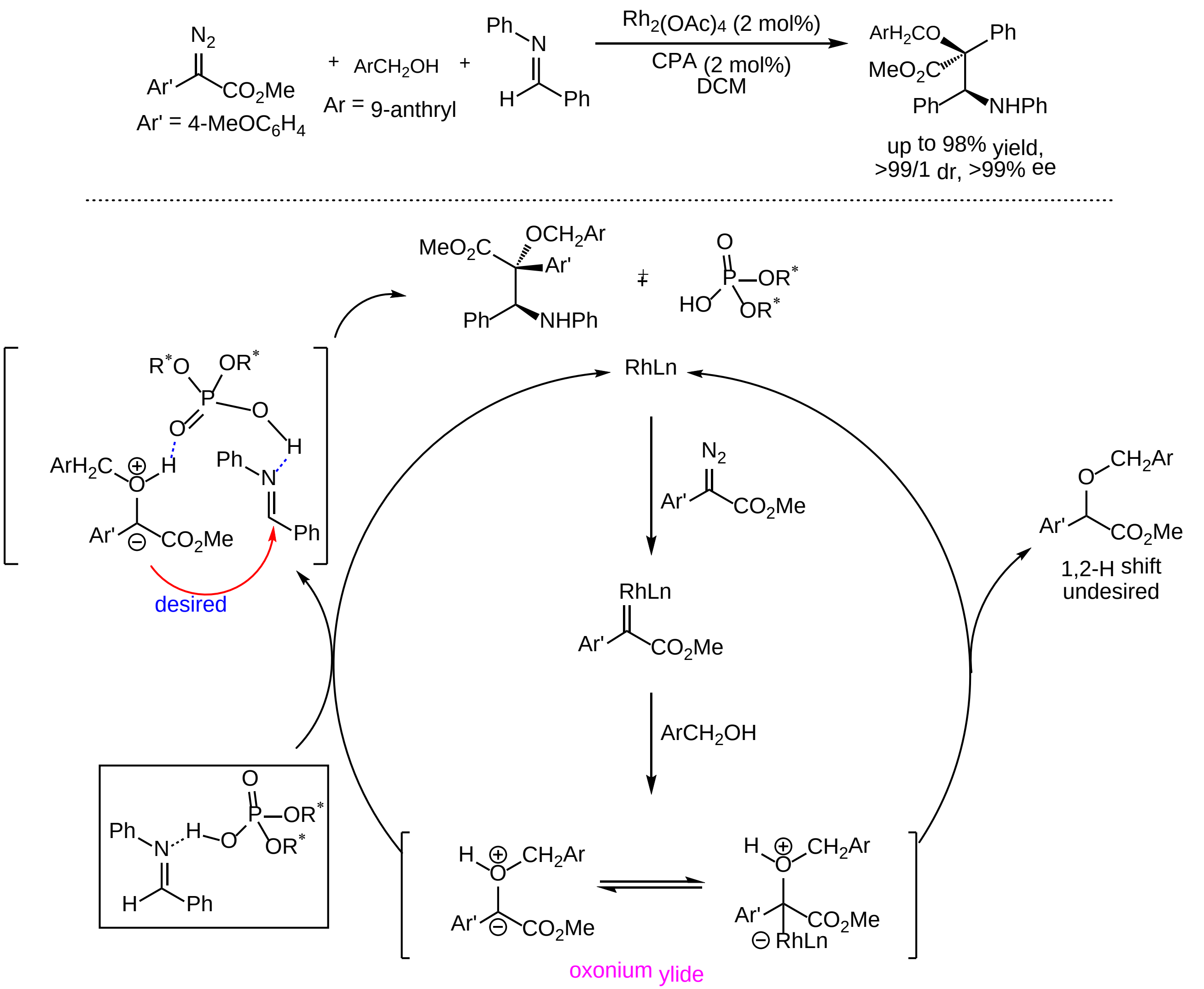
# Introduction

**Relay catalysis**



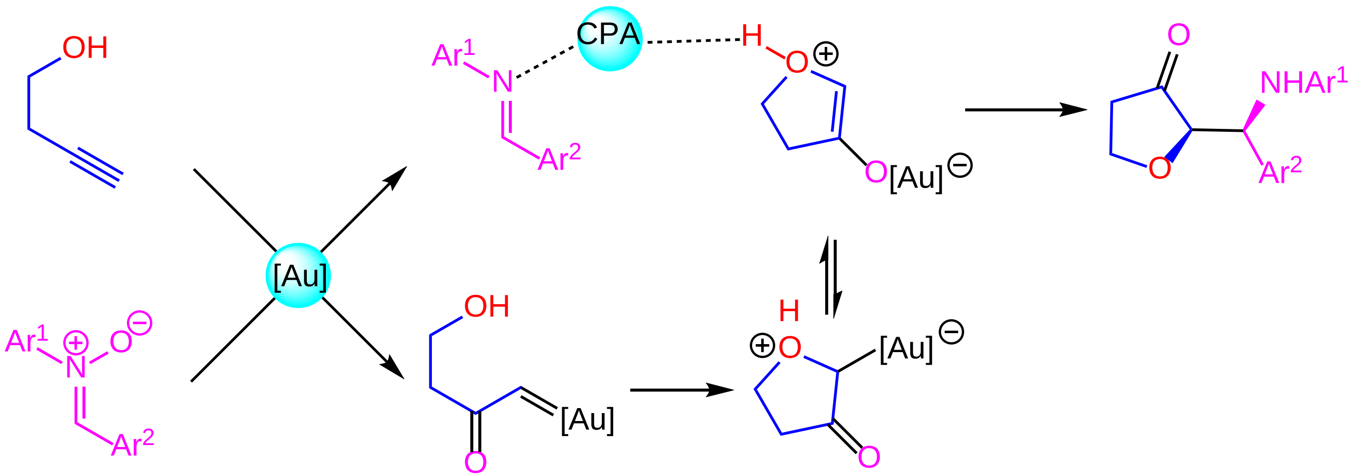

Gong, L.-Z. *et al. J. Am. Chem. Soc.* **2012**, *134*, 6532.

# Cooperative Catalysis-Rh(II)/CPA




Gong, L.-Z. *et al. J. Am. Chem. Soc.* **2008**, *130*, 7782.

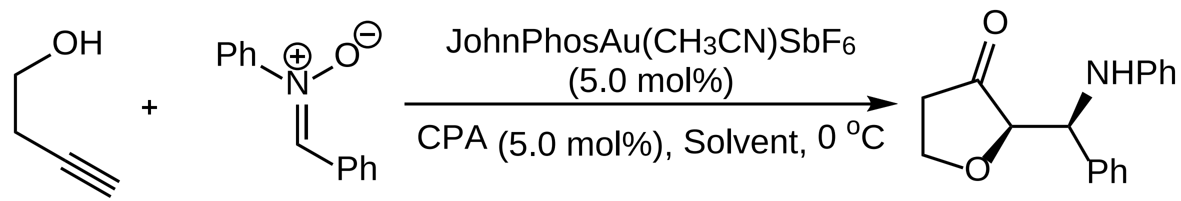
# Cooperative Catalysis-Au(I)/CPA




- Non-diazo carbene precursor
- Atom and step-economic method
- Au/organo cooperative catalysis
- Useful chiral dihydrofuran-3-one

Xu, X. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 17200.

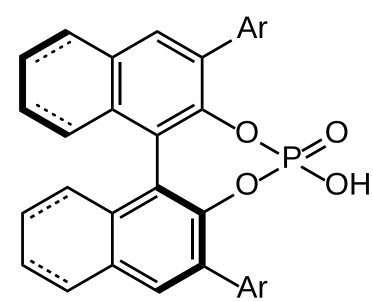
# Reaction Optimization




**1a** **2a** **3a**

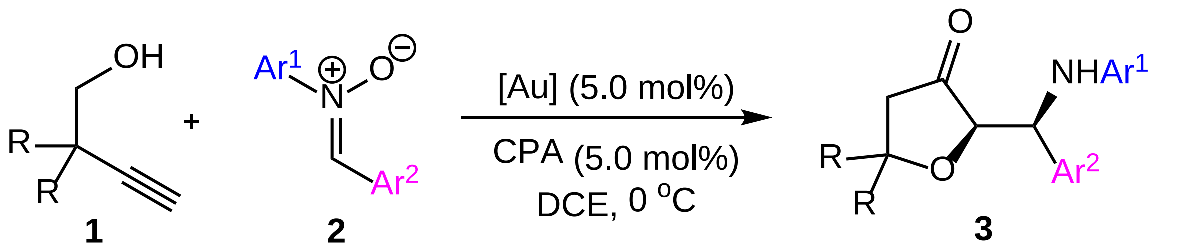
| Entry[a] | CPA | Solvent | Yield of **3a** (%)[b] | d.r.[c] | Ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **---** | DCE | 59 | 71:29 | 0 |
| 2 | **A1** | DCE | 61 | 92:8 | 51 |
| 3 | **A2** | DCE | 61 | >95:5 | 4 |
| 4 | **A3** | DCE | 63 | >95:5 | 82 |
| 5 | **A4** | DCE | 67 | >95:5 | 91 |
| 6 | **A5** | DCE | 63 | 91:9 | 87 |
| 7 | **A4** | DCM | 62 | >95:5 | 88 |
| 8 | **A4** | $CHCl_3$ | 43 | >95:5 | 74 |
| 9 | **A4** | $PhCF_3$ | 46 | 94:6 | 78 |
| 10 | **A4** | TBME | 25 | 89 :11 | 78 |

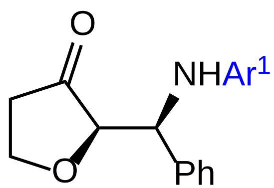
[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.20 mmol), JohnPhosAu($CH_3CN$)$SbF_6$ (5 mol%), CPA (5 mol%), solvent (2.0 mL). [b] Isolated yields. [c] Determined by NMR analysis. [d] Determined by HPLC.



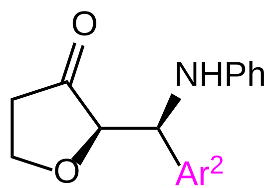

**A1:** Ar = Ph
**A2:** Ar = Si(Ph)$_3$
**A3:** Ar = 2,4,6-($^i$Pr)$_3$C$_6$H$_2$
H8-**A4:** Ar = 1-pyrenyl
H8-**A5:** Ar = 9-phenanthryl

# Substrate Scope

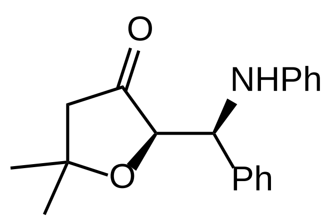


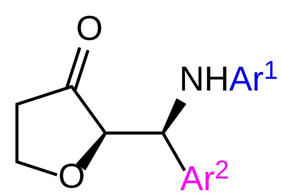

**3a:** $Ar^1$ = Ph, 67%, 91% ee
**3b:** $Ar^1$ = 4-Br$C_6H_4$, 62%, 94% ee
**3c:** $Ar^1$ = 4-Cl$C_6H_4$, 63%, 94% ee
**3d:** $Ar^1$ = 4-Me$C_6H_4$, 52%, 94% ee
**3e:** $Ar^1$ = 4-MeO$C_6H_4$, 51%, 90% ee
**3f:** $Ar^1$ = 4-$F_3CC_6H_4$, 83%, 93% ee
**3g:** $Ar^1$ = 4-NC$C_6H_4$, 71%, 90% ee
**3h:** $Ar^1$ = 3-Br$C_6H_4$, 66%, 90% ee




**3i:** $Ar^2$ = 4-F$C_6H_4$, 58%, 90% ee
**3j:** $Ar^2$ = 3-F$C_6H_4$, 65%, 92% ee
**3k:** $Ar^2$ = 2-$F_3CC_6H_4$, 56%, 93% ee
**3l:** $Ar^2$ = 3-$F_3CC_6H_4$, 69%, 90% ee
**3m:** $Ar^2$ = 2-Thienyl, 60%, 90% ee



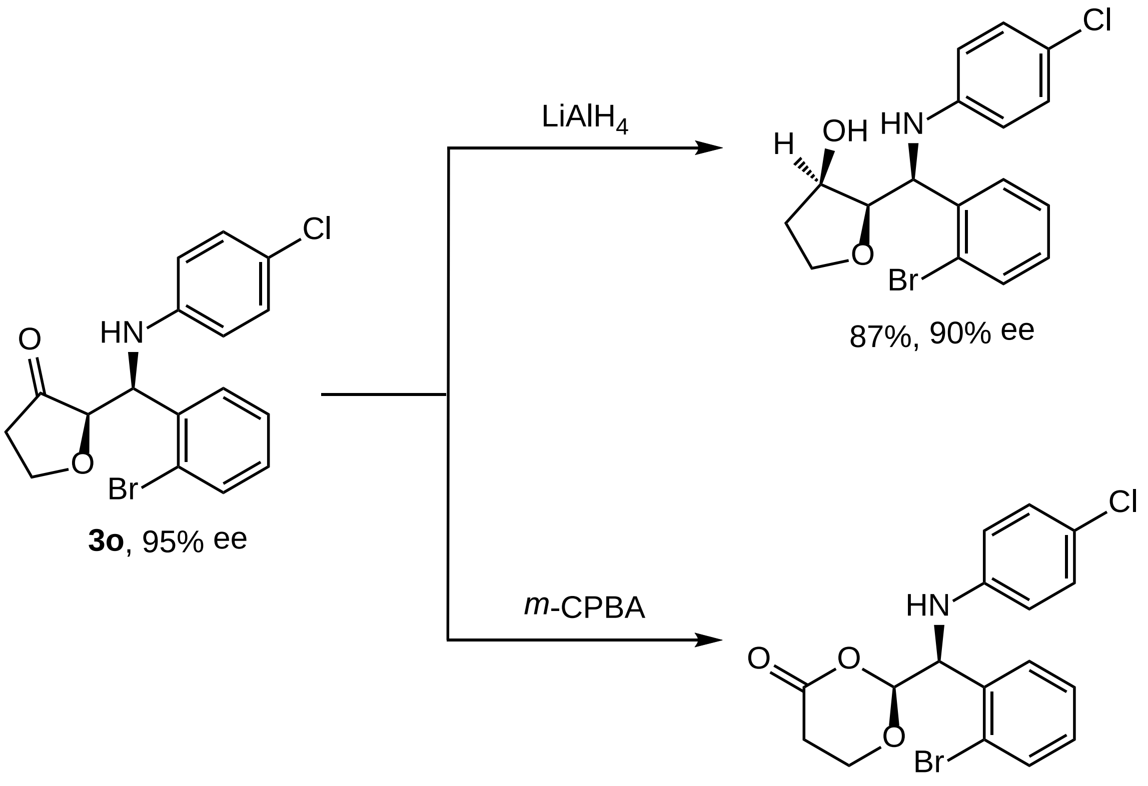

**3n:** 50%, 84% ee




$Ar^1$ = 4-Cl$C_6H_4$
$Ar^2$ = 2-Br$C_6H_4$

**3o:** 58%, 95% ee

# Synthetic Utility

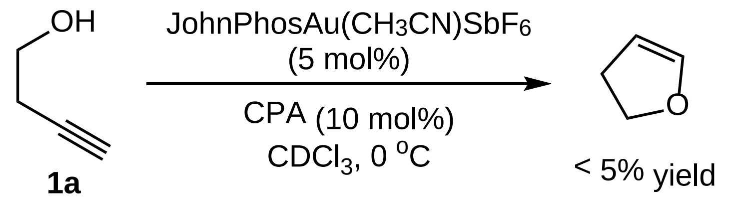


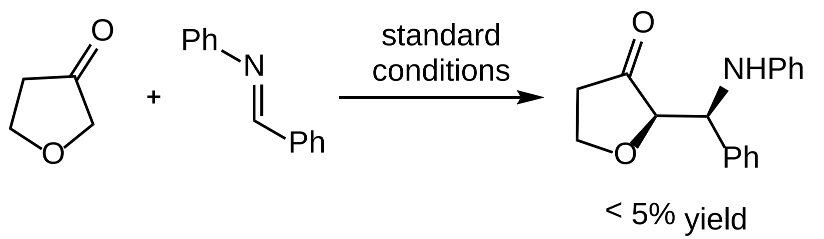

**3o**, 95% ee

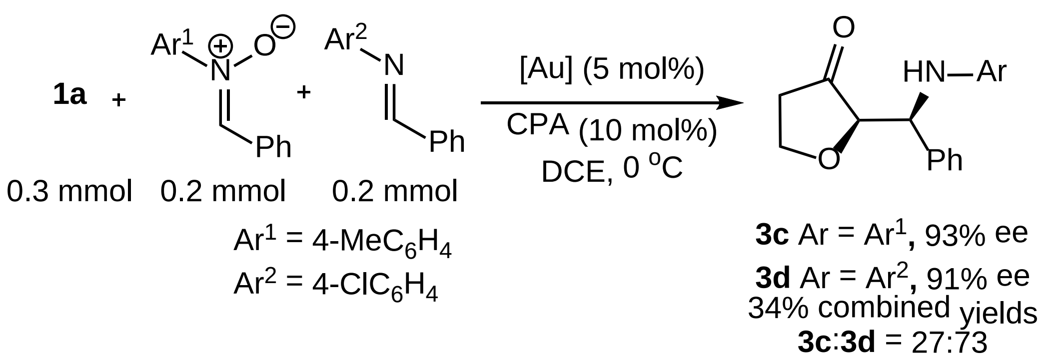
87%, 90% ee

51%, 93% ee
17% of **3o** recovered

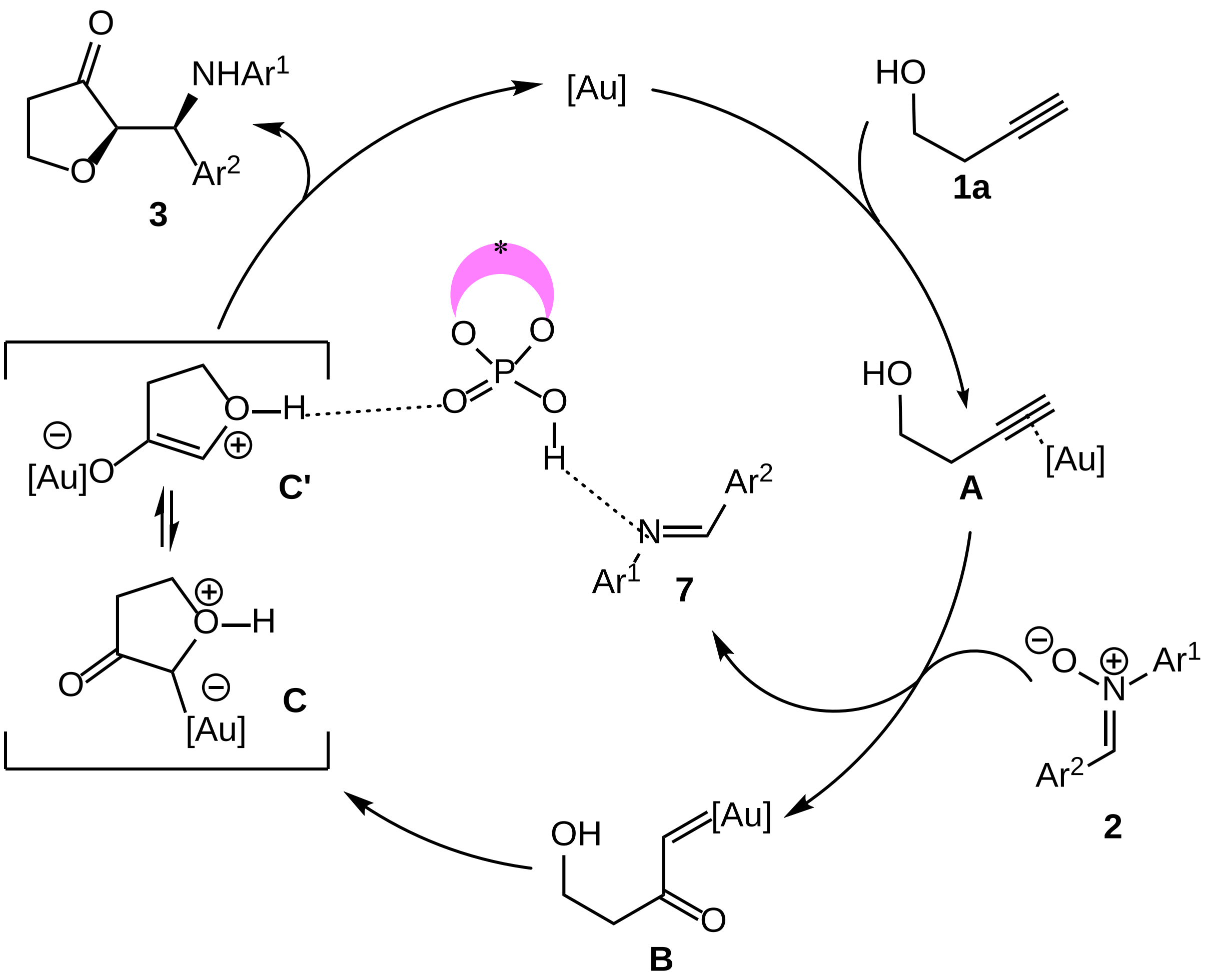
# Mechanistic Investigations



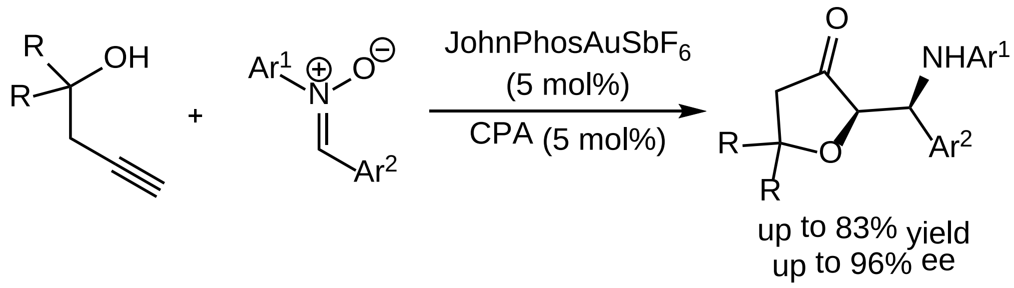



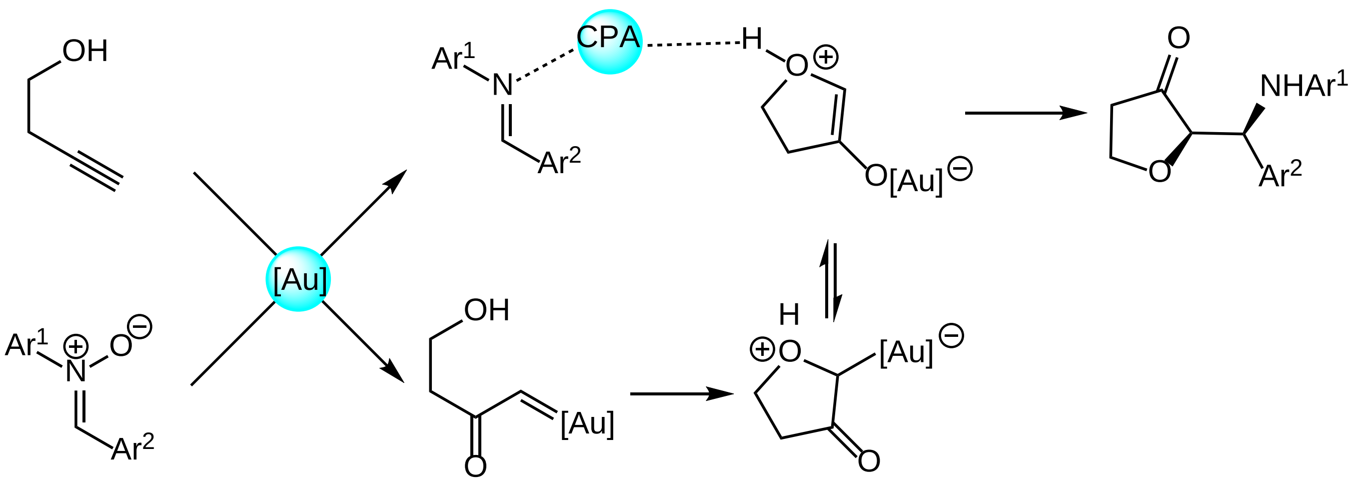



# Proposed Mechanism



# Summary




Xu. X. *et al. Angew. Chem. Int. Ed.* **2018**, *57,* 17200.

# The First Paragraph

Gold-catalyzed oxidative cyclization of alkynes allows construction of heterocyclic and carbocyclic frameworks. Preparation of α-oxo carbene from readily available and stable alkynes, rather than α-diazo carbonyl compounds, would be synthetically useful, and intermediates possessing gold carbene character have been postulated and verified experimentally. These intermediate α-oxo carbenes can undergo a variety of synthetically challenging yet highly useful transformations, such as $Csp^3$-H/$Csp^2$-H bond insertion, X-H insertion, cyclopropanation, ylide formation, and others.

# The First Paragraph

Over the last decade, remarkable advances have been made in the development of enantioselective gold catalysis, but major challenges remain. Despite these significant achievements in catalytic asymmetric reactions of alkynes, a limited number of approaches are available for efficient asymmetric induction in gold-catalyzed oxidation of alkynes via the a-oxo gold carbene route.

# The Last Paragraph

In summary, we report a gold(I)/CPA cooperatively catalyzed Mannich-type reaction of 3-butynol and nitrones to afford dihydrofuran-3-one derivatives in good yields with excellent diastereoselectivities and enantioselectivities. This novel pattern of alkyne transformation involves chemical bond cleavage, and a fragment modification and reassembly process provides an atom- and step-economic method with stable, inexpensive, and readily available materials. This work presents the first example of catalytic asymmetric trapping of a gold enolate in alkyne oxidations via an α-oxo gold carbene route and could inspire further discoveries in gold-catalyzed asymmetric alkyne transformations.

# Acknowledgement

**_Thanks for_**
**_your kind attention!_**