New Au(I) Complexes for Homogeneous Enantioselective Catalysis

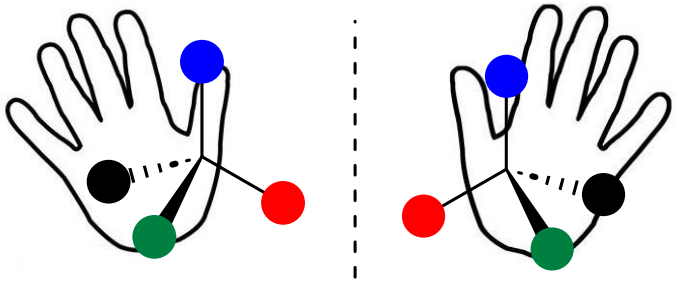
Xavier Guinchard

ICSN, Gif sur Yvette

Phosphorus Chemistry and Catalysis group

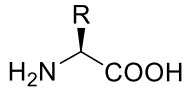
Chirality in nature

1) Organic molecules are chiral

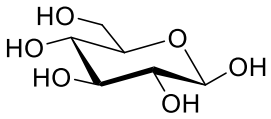


2 **enantiomers** are mirror images

2) Nature is asymmetric



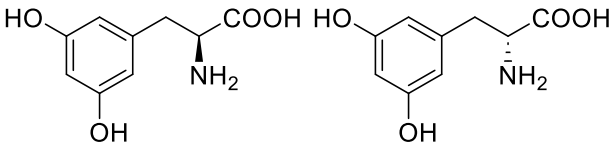
Aminoacids are all (*S*)-configured



Sugars are all *D*

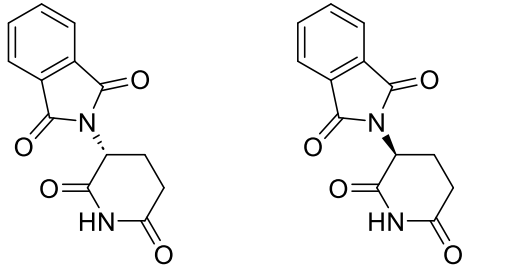
Proteins, nucleic acids are all chiral molecules

3) Configuration matters for bioactivity



(*S*)-dopamine vs (*R*)-dopamine

Médicament Parkinson — Poison

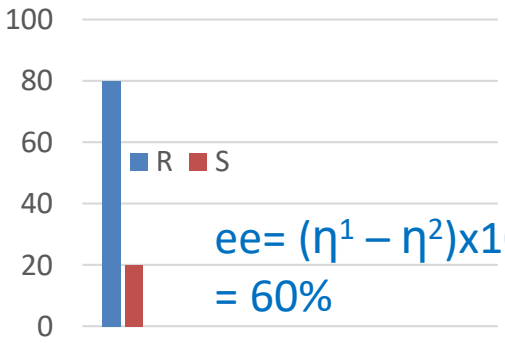


(*R*)-thalidomide vs (*S*)-thalidomide

Médicament sédatif — Tératogène

It is crucial to be able to access both enantiomers of a given molecule

4) Enantiomeric excess

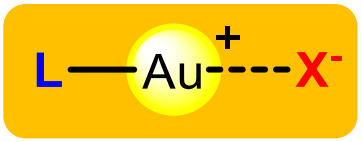


The highest the ee, the better!

Comptes Rendus Chimie, **2021**, *24*, 397

Au(I) catalysis

Structure



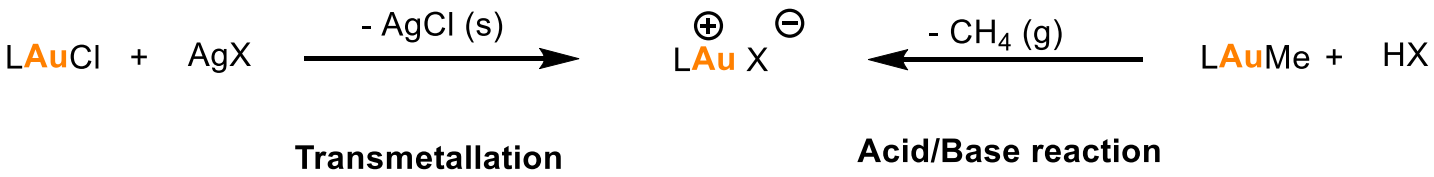
L : Phosphorus ligand or NHC

X : Weakly coordinating counterion

(Cl >>> BF_4, PF_6, SbF_6, NTf_2…)

➡ Complexes for homogenous catalysis!

Activation of the complexes

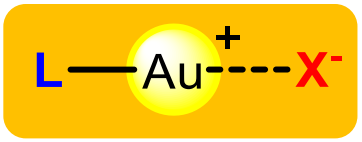


➡ It is necessary to activate the complex for catalytic purposes

For a review, see: Echavarren *et al*. Org. *Biomol. Chem.* **2015,** *13*, 7103

Au(I) catalysis

Structure



L : Phosphorus ligand or NHC

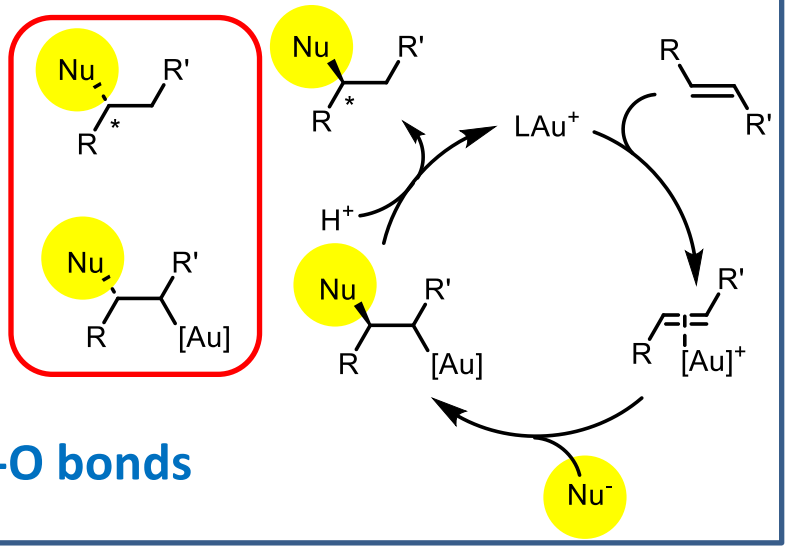
X : Weakly coordinating counterion
(Cl >>> BF_4, PF_6, SbF_6, NTf_2…)

➡ Complexes for homogenous catalysis!

Reactivity

Main property: Carbophilic Lewis acids
Main applications: To add nucleophiles to unsaturated bonds

How can we favor the formation of only one enantiomer?

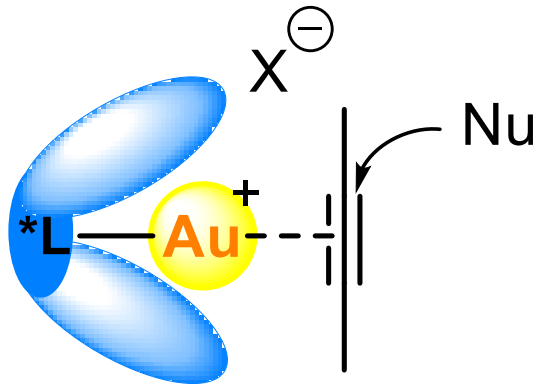


➡ **Creation of new C-C, C-N, C-O bonds**

For a review, see: Echavarren *et al*. Org. *Biomol. Chem.* **2015,** *13*, 7103

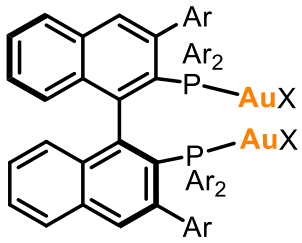
Strategies in enantioselective Au(I) catalysis

Chiral ligand-based approach

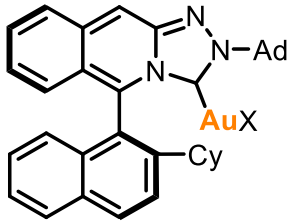


- **The chiral ligand creates an asymmetric environment**
- **The linearity of Au is a limitation**
- **Bulkyl ligands are required**

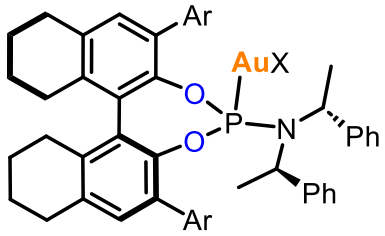
Representative chiral complexes



di-phosphine



NHC

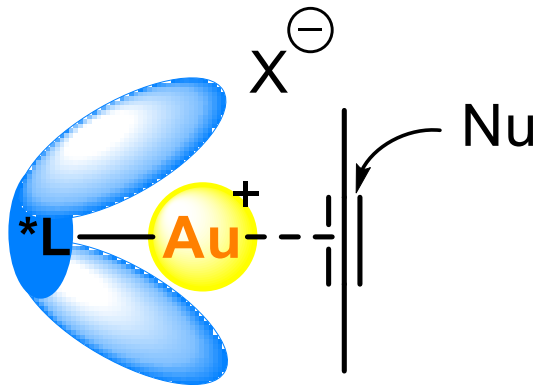


phosphoramidites

General reviews: Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567. b) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis*, **2011**, 1501. c) Patil, N. T. *et al. Isr. J. Chem.* **2023**, *63*, e202200039.

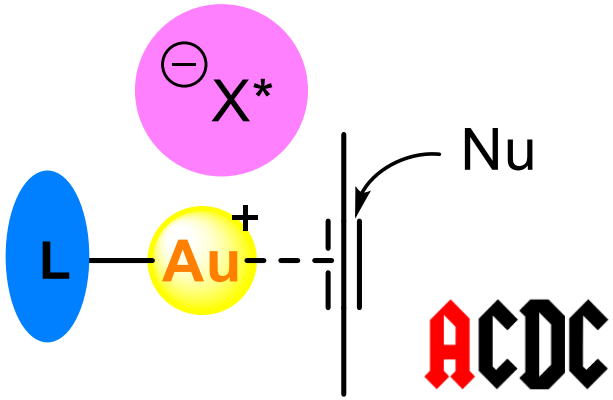
Strategies in enantioselective Au(I) catalysis

Chiral ligand-based approach



- **The chiral ligand creates an asymmetric environment**
- **The linearity of Au is a limitation**
- **Bulkyl ligands are required**

Chiral Counterion-based approach

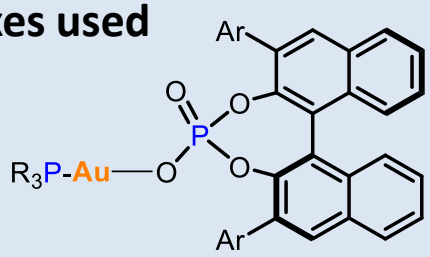


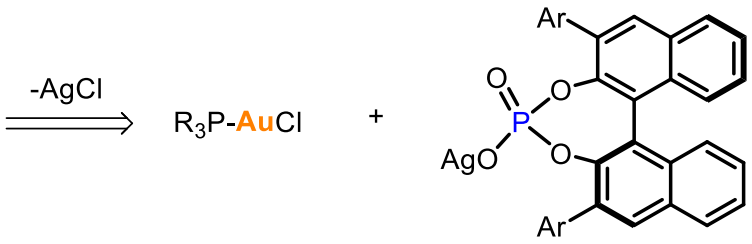
- **The chiral counterion is closer to the reacting center**
- **Asymmetric Counterion-Directed Catalysis strategy (List/Toste)**

General reviews: Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567. b) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis*, **2011**, 1501. c) Patil, N. T. *et al. Isr. J. Chem.* **2023**, *63*, e202200039.

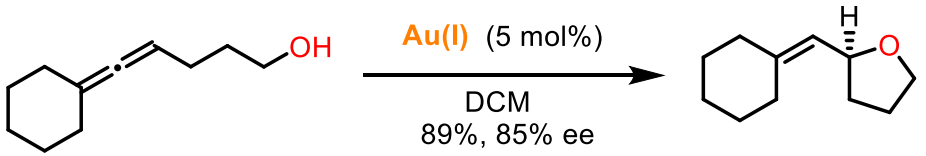
Chiral Au(I) phosphates

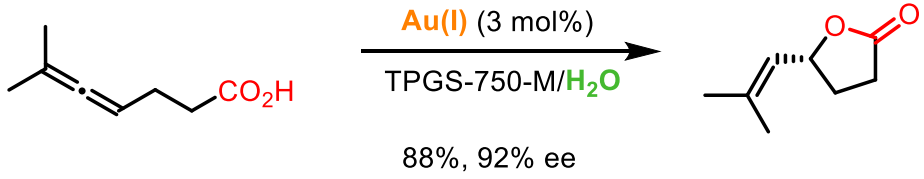
Chiral complexes used





Reactivity

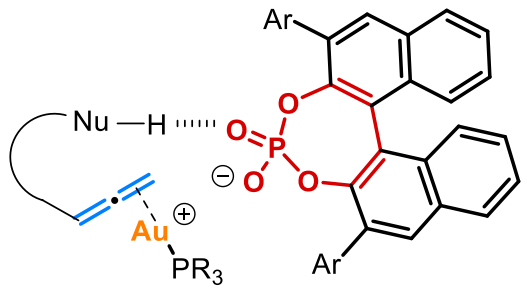




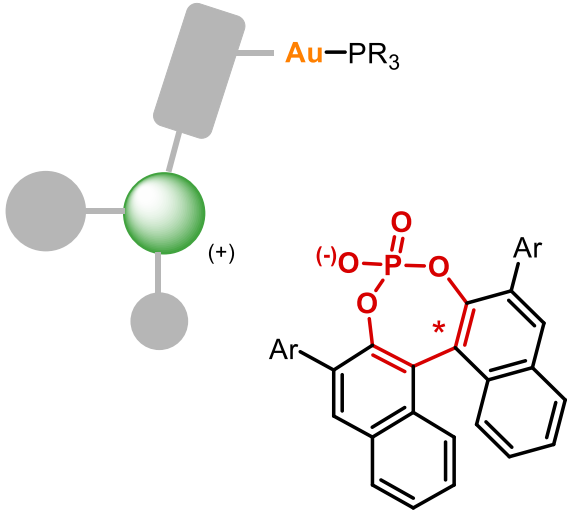
Hamilton, G.L., Kang, E.J. Mba, M. Toste, F.D. *Science* **2007**, *317*, 496.
S. Handa, D. J. Lippincott, D. H. Aue, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 10658.

Chiral Au(I) phosphates

Plausible scenario for intramolecular hydrofunctionnalizations

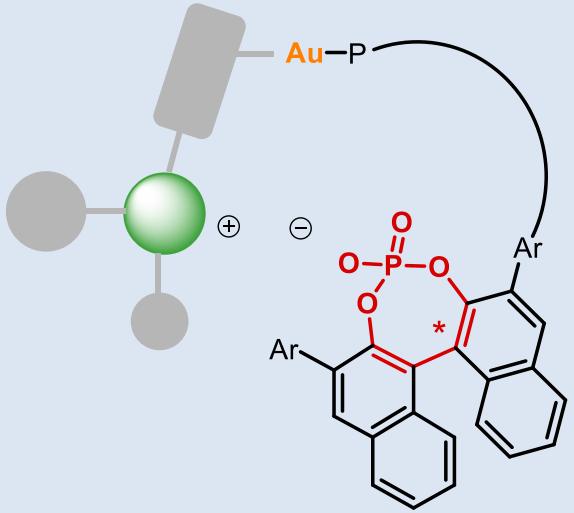


Other reactions involving ion pairs

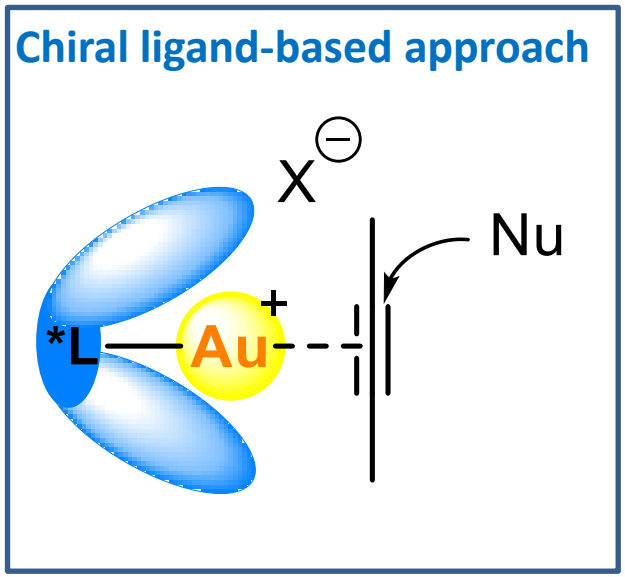


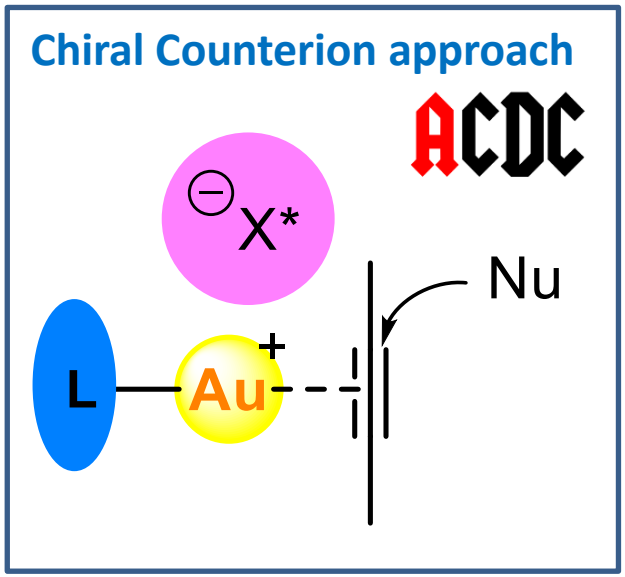
Tethered Counterion Directed Strategy (TCDC)

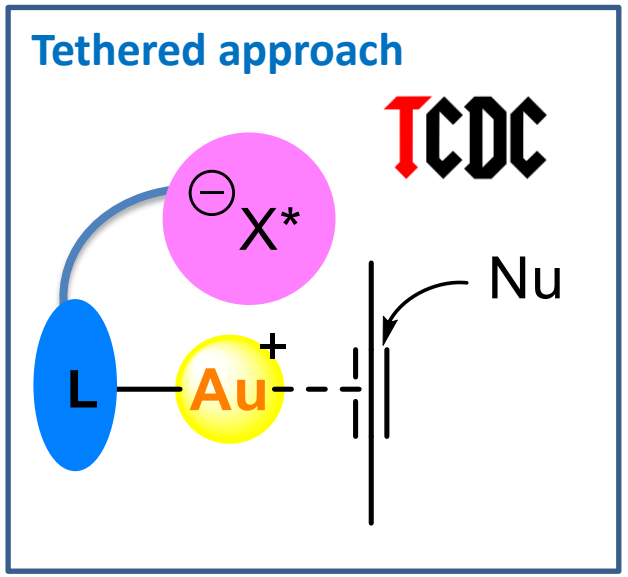
- Enhence rigidity
- Geometrical constraints
- Molecular organization



Strategies in enantioselective Au(I) catalysis







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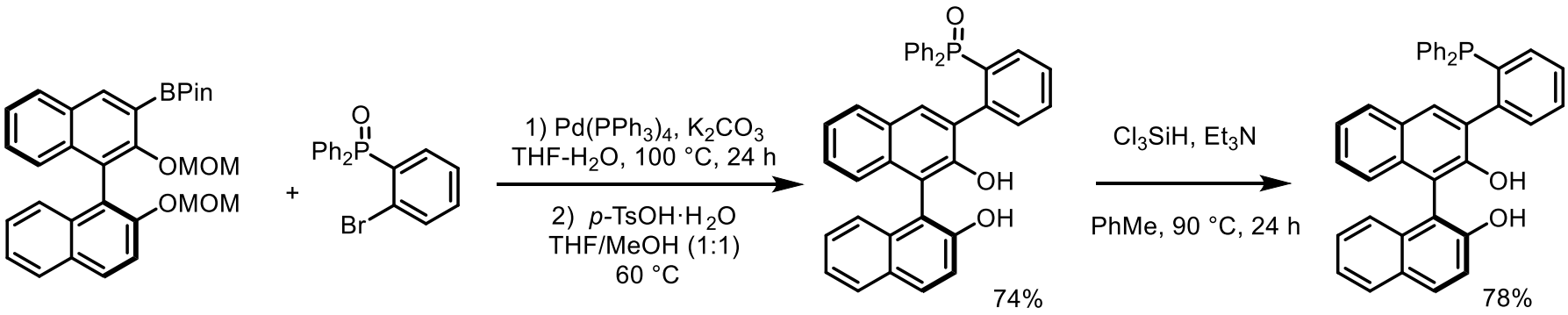
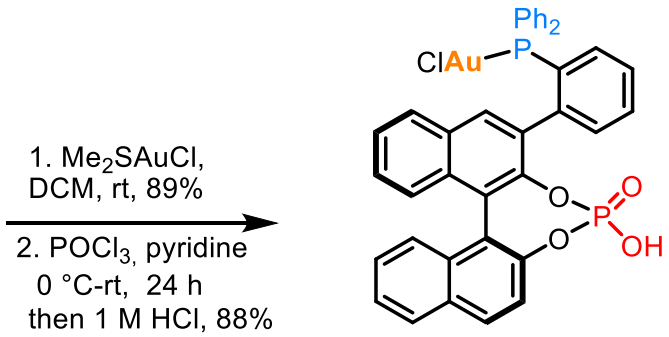
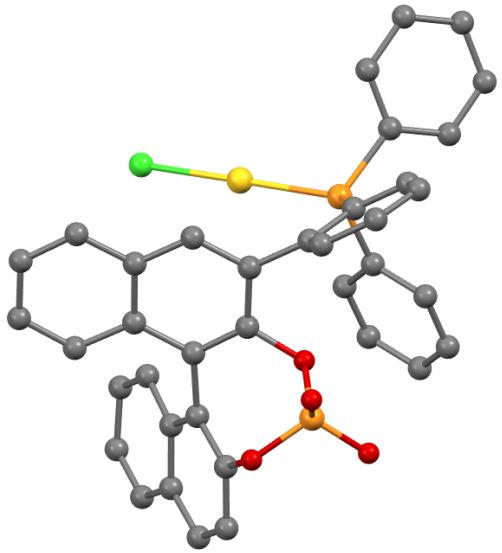
Synthesis of the chiral **Au(I)** precatalyst

Zhenhao Zhang
Vitalii Smal





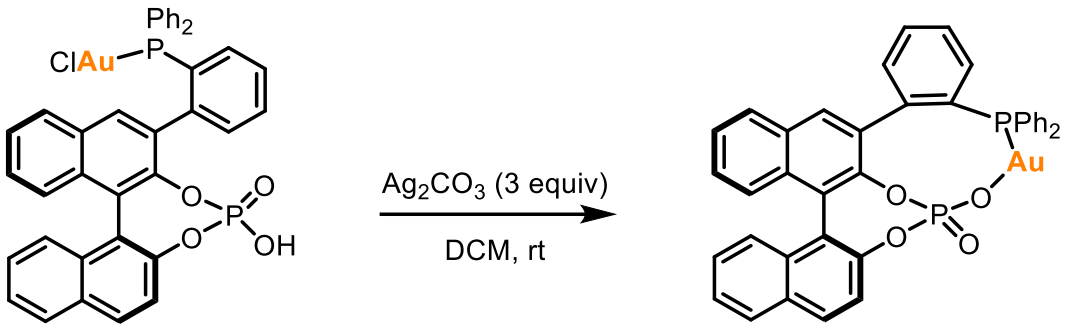
(CPA-Phos^{A})AuCl

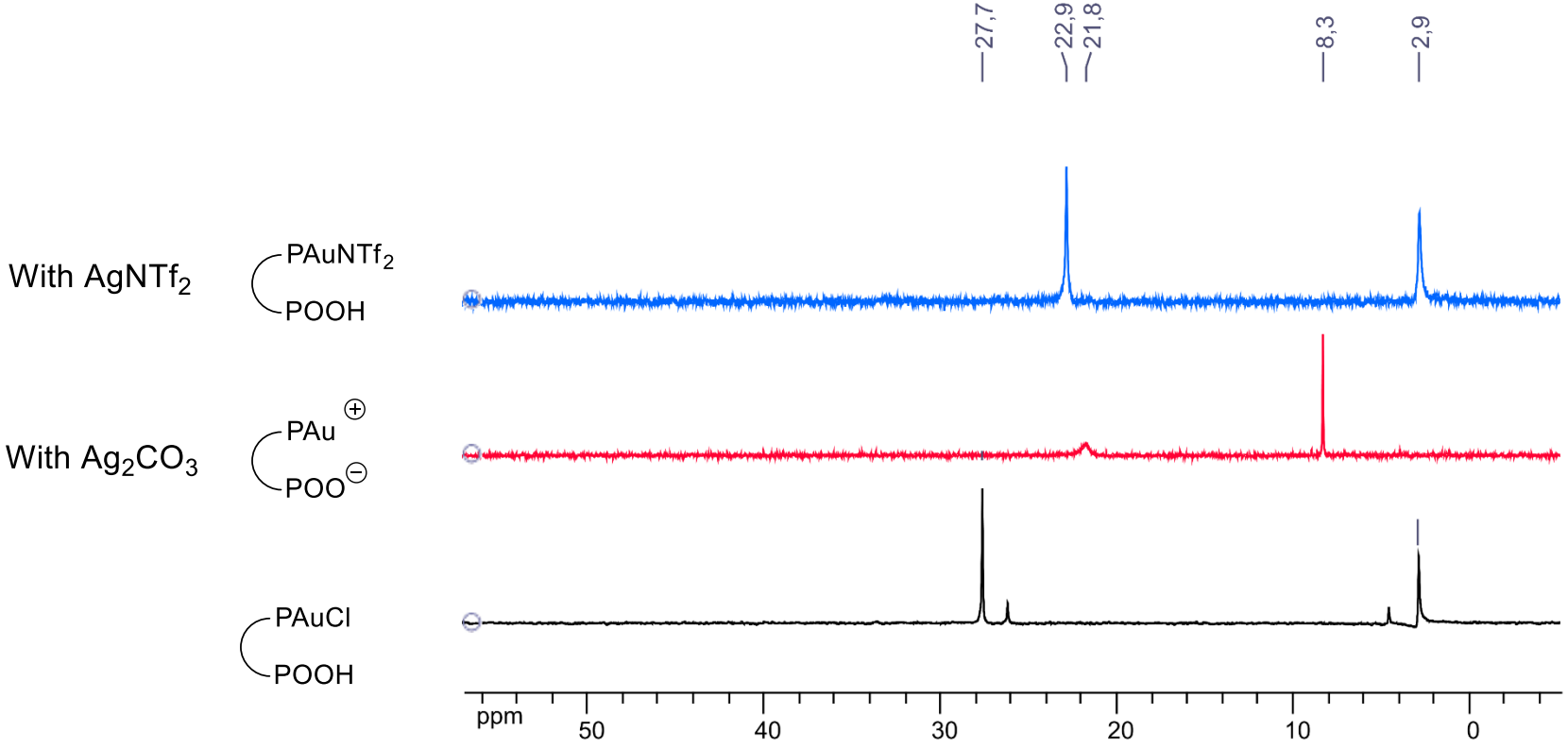


- Straightforward synthesis
- Scalable (3.5 g prepared)!

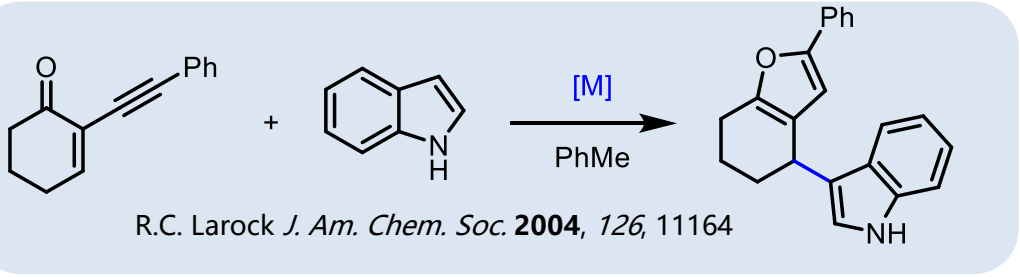
Silver-mediated activation of the chiral Au(I) catalyst

Zhenhao Zhang



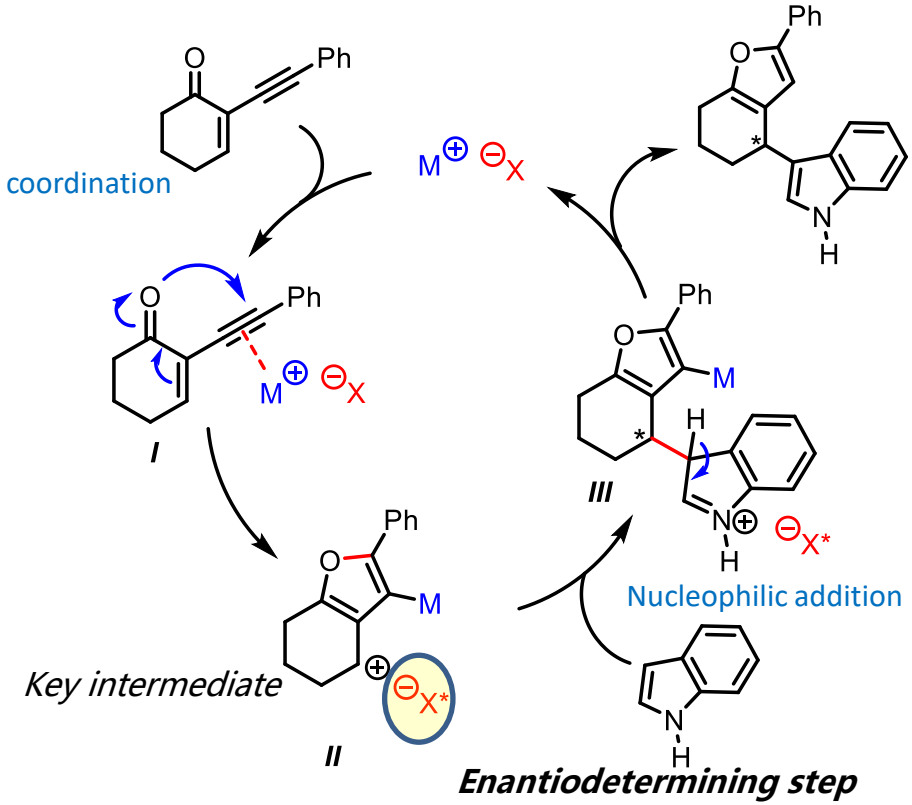


Tandem cycloisomerization/nucleophilic addition sequence

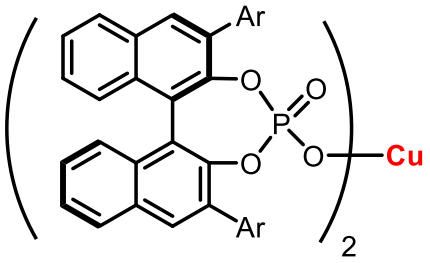


R.C. Larock *J. Am. Chem. Soc.* **2004**, *126*, 11164

Mechanism

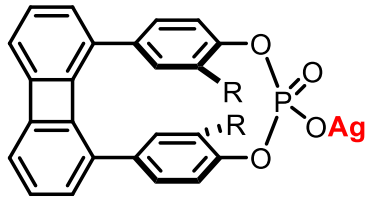


Previous enantioselective variants



92%, 91% ee

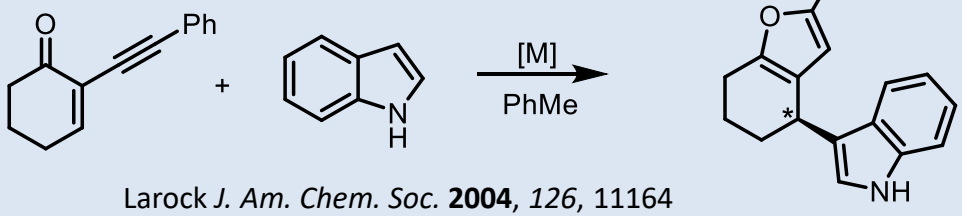
Toste *et al. J. Am. Chem. Soc.*, **2011**, *133*, 8486



83%, 86% ee

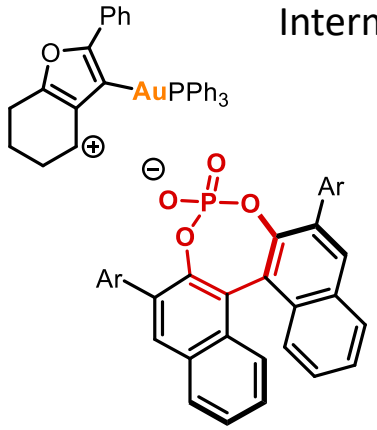
Betzer *et al. Adv. Synth. Catal.*, **2018**, *360*, 3356

Optimization

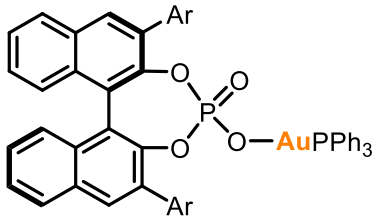


Larock *J. Am. Chem. Soc.* **2004**, *126*, 11164

Intermediate

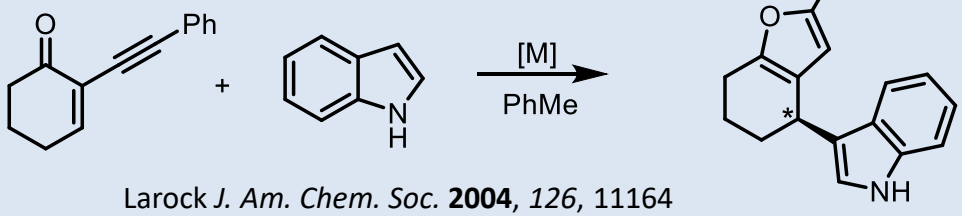


ACDC



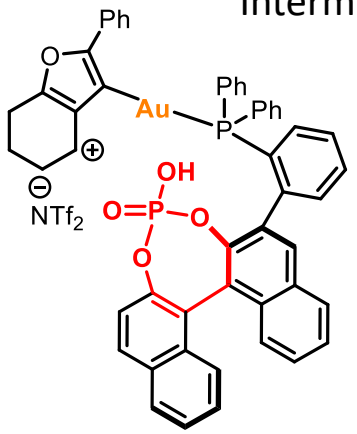
60%, 24% ee

Optimization

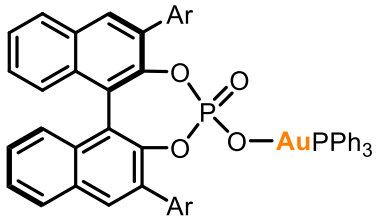


Larock *J. Am. Chem. Soc.* **2004**, *126*, 11164

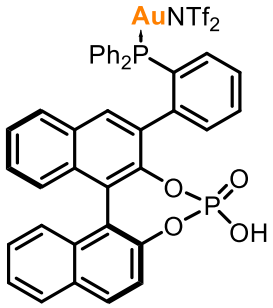
Intermediate



ACDC

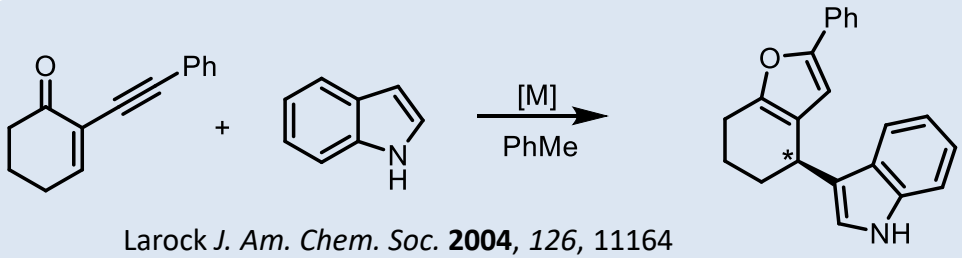


60%, 24% ee



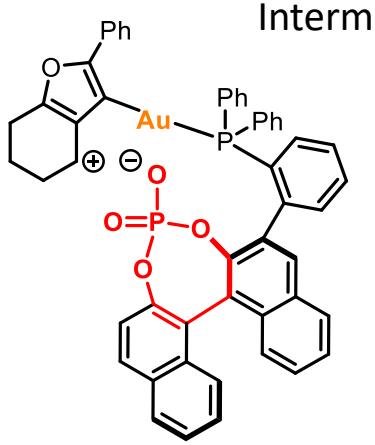
85%, 15% ee

Optimization

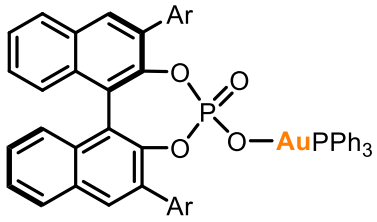


Larock *J. Am. Chem. Soc.* **2004**, *126*, 11164

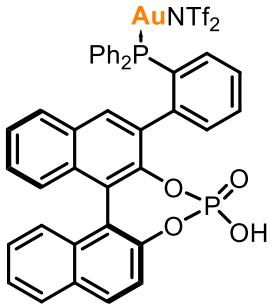
Intermediate



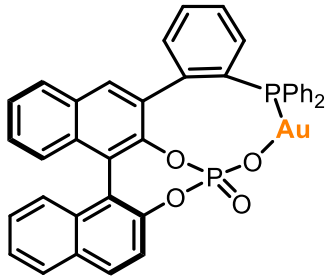
ACDC



60%, 24% ee



85%, 15% ee



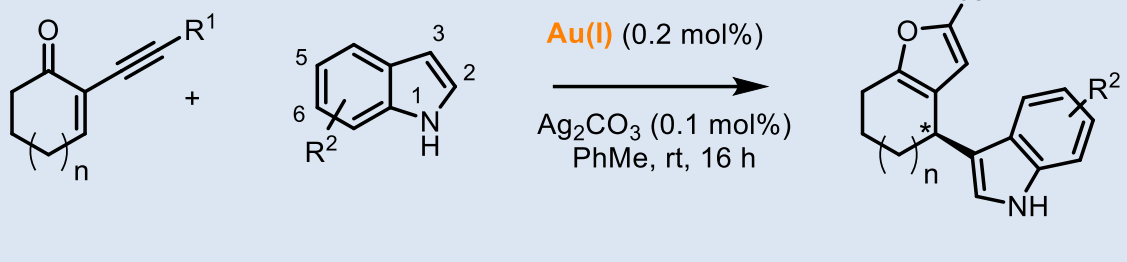
TCDC

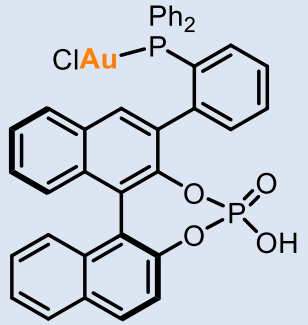
75%, 96% ee (0.2 mol%)

73%, 93% ee (0.1 mol%)

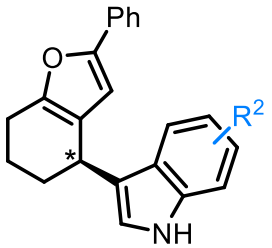
Scope of the reaction

Zhenhao Zhang

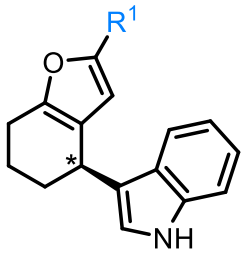




***C3*-alkylation**

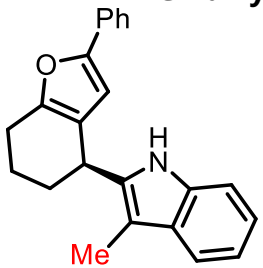


R^2= H, 75%, 96% ee
R^2= 5-OMe, 81%, 97% ee
R^2= 5-Br, 77%, 97% ee
R^2= 6-Me, 44%, 96% ee
R^2= 2-Me, 49%, 82% ee

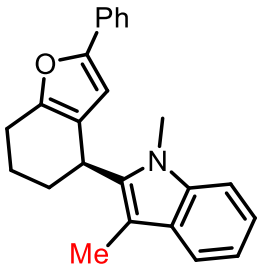


R^1= 4-$MeOC_6H_4$, 87%, 91% ee
R^1= 4-MeC_6H_4, 95%, 95% ee
R^1= 3-$MeOC_6H_4$, 77%, 84% ee
R^1= C_5H_{11}, 46%, 87% ee

***C2*-alkylation**

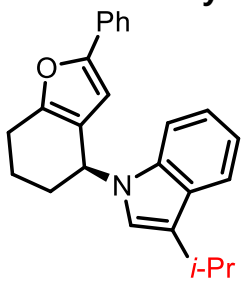


83%, 93% ee



91%, 95% ee

***N*-alkylation**

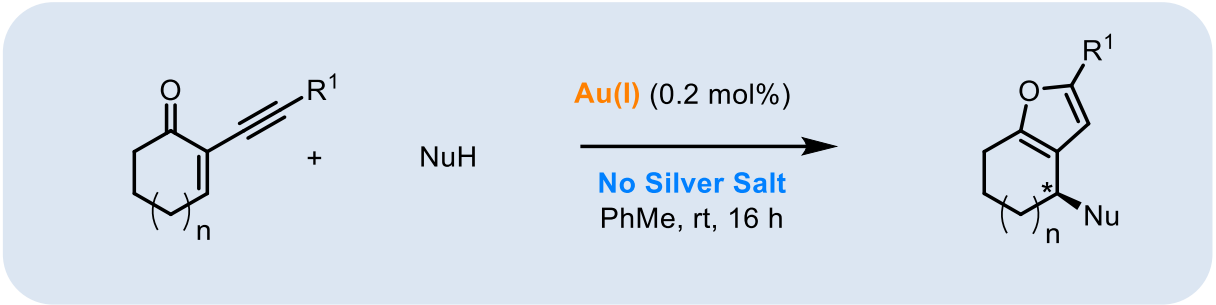


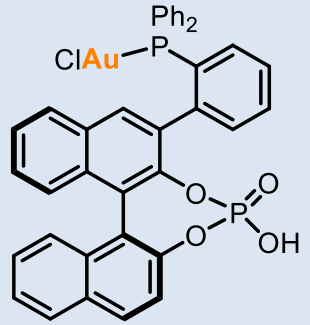
59%, 92% ee

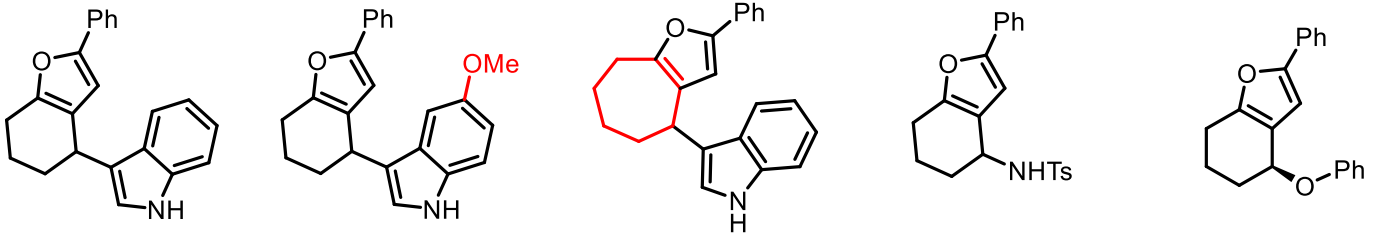
J. Am. Chem. Soc. **2020**, 142, 3797.

Scope of the reaction: silver-free protocol

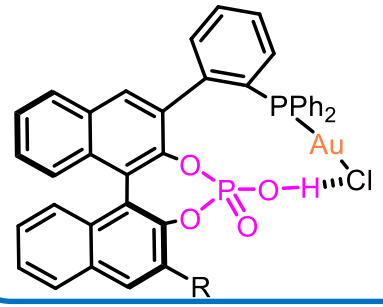
Zhenhao Zhang







No Ag_2CO_3	80%, **92% ee**	73%, **94% ee**	55%, **95% ee**	41%, **88% ee**	**Silver-free:** 93%, **90% ee**
With Ag_2CO_3	(75%, 96% ee)	(81%, 97% ee)	(41%, 94% ee)	(80%, 87% ee)	

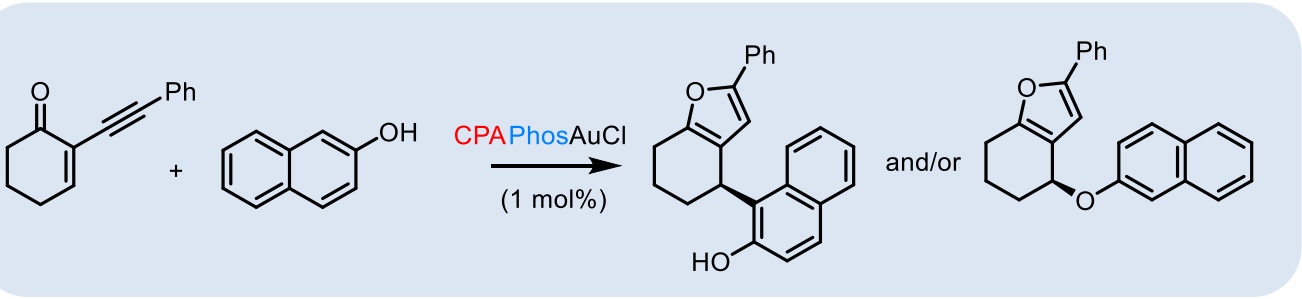


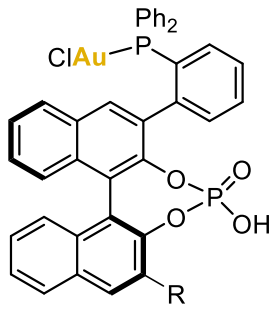
- The catalyst **self-activates** by hydrogen bonding
- **Silver-free approach** avoids any side reactions from the silver salt

Ag effects in Au(I) catalysis: *Shi et al. J. Am. Chem. Soc*. **2012**, *134*, 9012.
Ag-free Au(I) catalysis: Echavarren *et al. Bull. Chem. Soc. Jpn.* **2021**, *94*, 1099 and *Chem. Eur. J.* **2021**, *27*, 11989.

Silver-free addition of naphthols

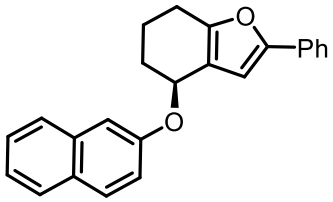
Yunliang Yu
Nazarii Sabat



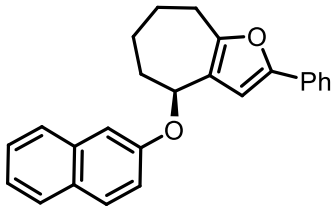


CPAPhos^{A}AuCl
CPAPhos^{B}AuCl

O-addition products

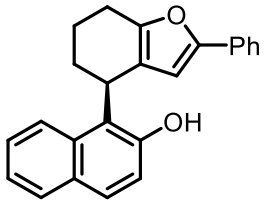


(*S*), 51%, 85% ee
(*R*), >90%, 85% ee (-)[a]

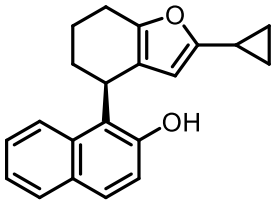


(-), 72%, 85% ee
(-), 53%, 69% ee

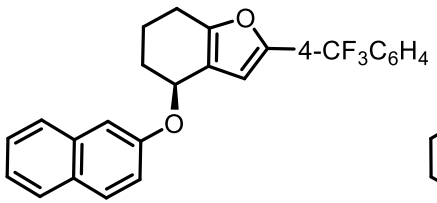
C-addition products



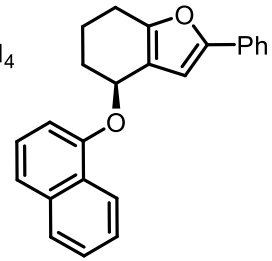
60%, 93% ee



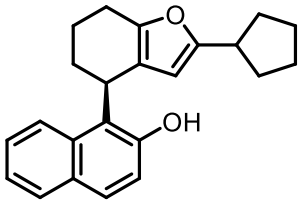
85%, 92% ee



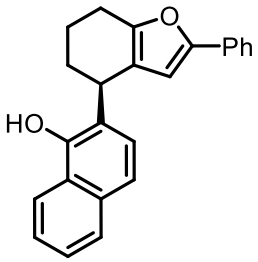
(-), 49%, 64% ee



(-), 36%, 88% ee
(+), 55%, 50% ee



68%, 99% ee

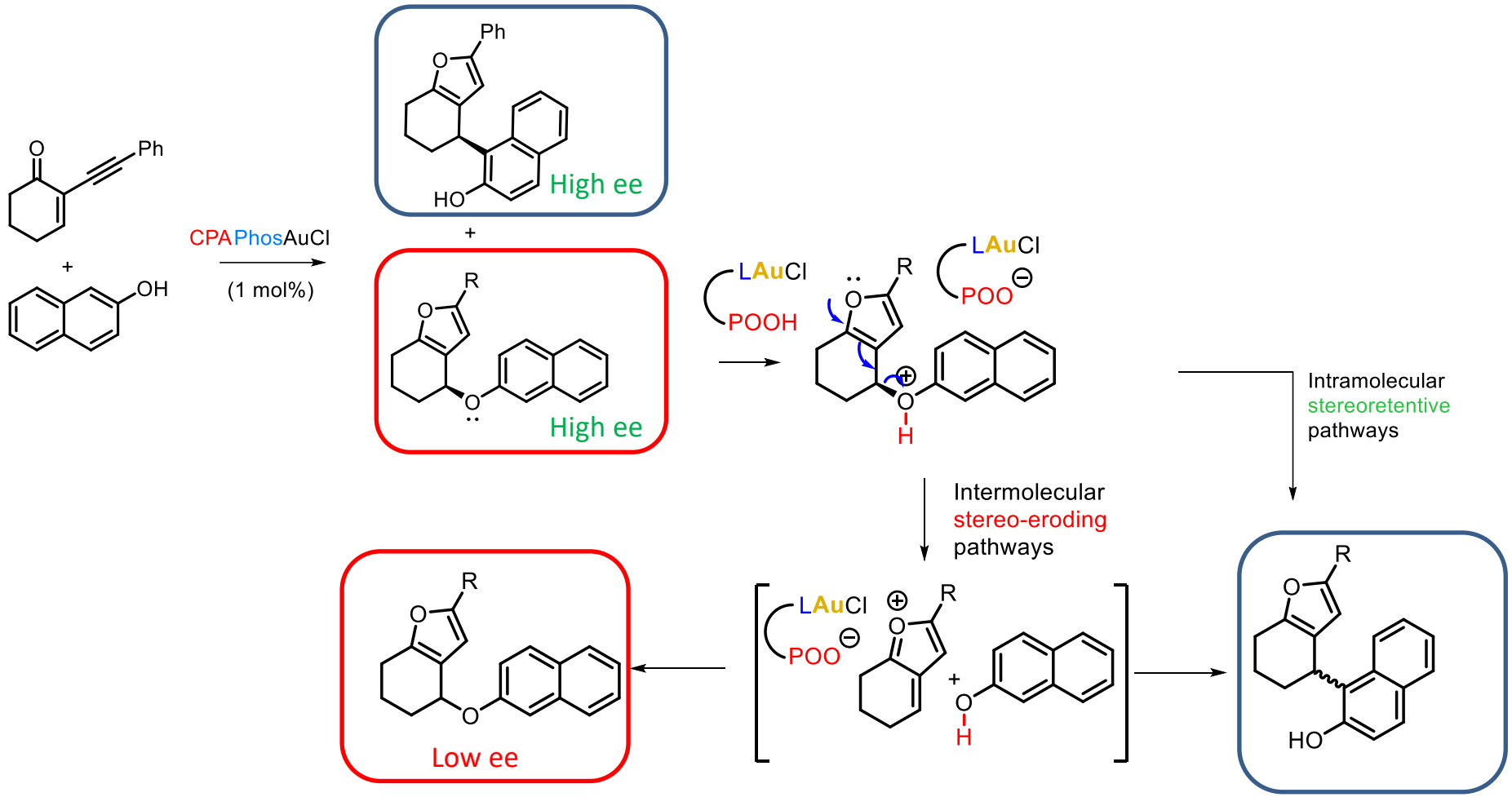


61%, 98% ee

(CPAPhos^{A})AuCl
(CPAPhos^{B})AuCl
(CPAPhos^{B})AuCl

Org. Chem. Front. **2023**, *10*, 2936

Mechanism of the stereo-eroding pathway

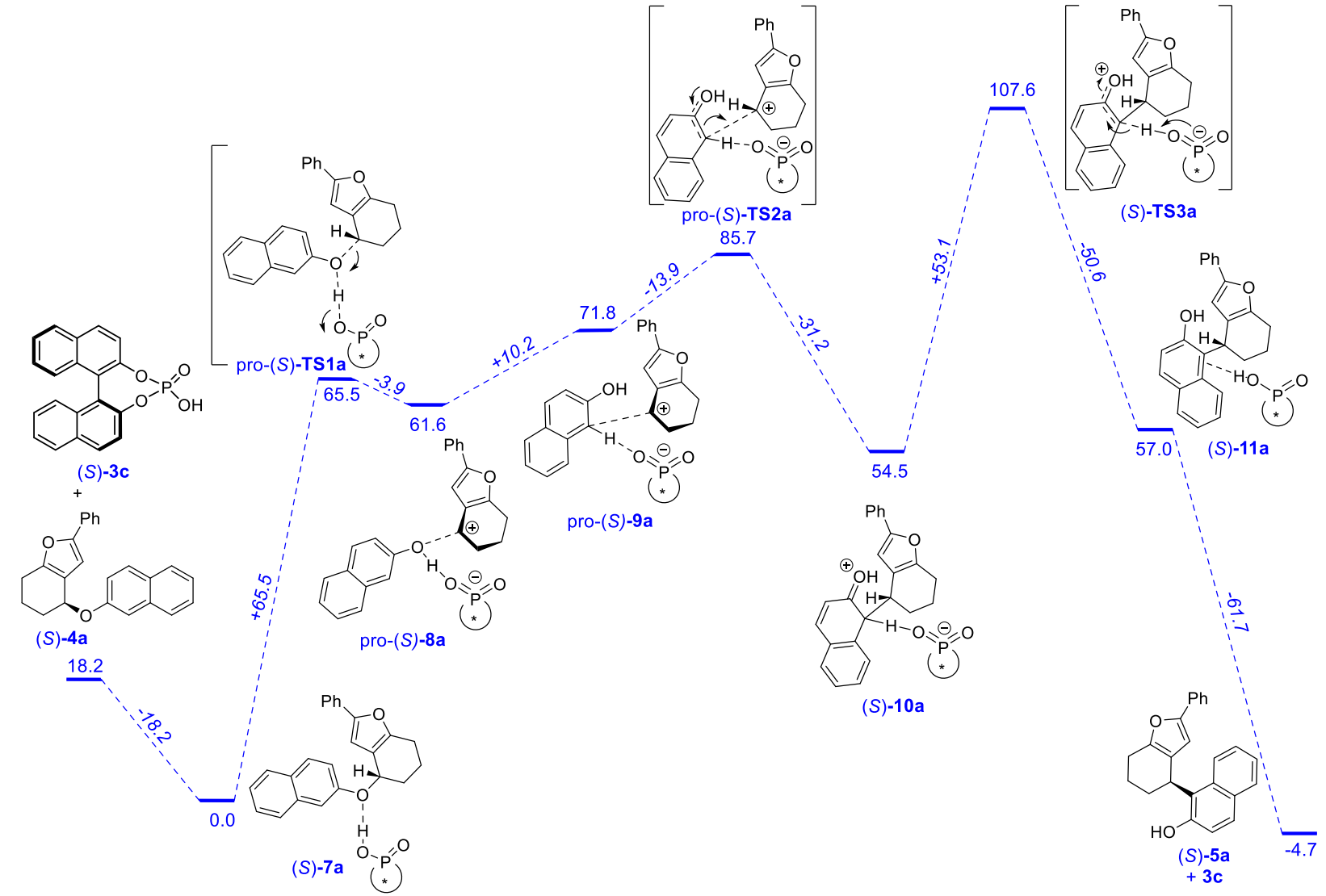


The final ees of both products depends in the end on the reaction time and the R group

Org. Chem. Front. **2023**, *10*, 2936

Structural instability: conversion of O-add to C-add products

Coll. with G. Frison

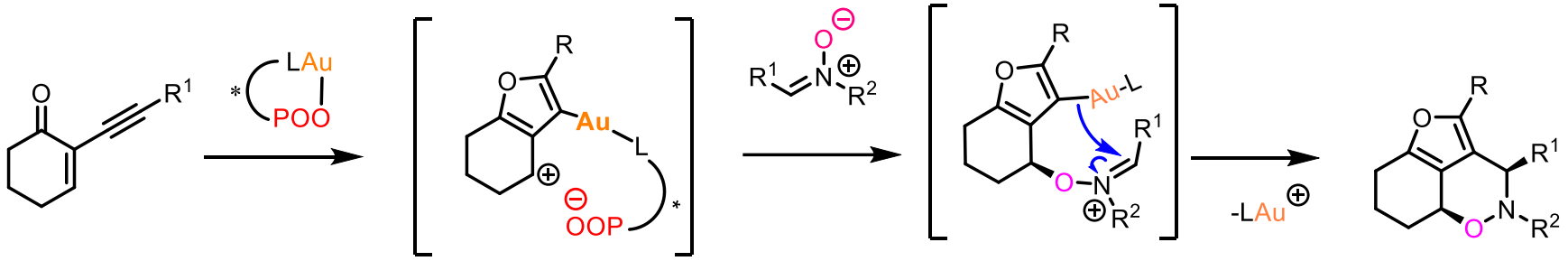


IEFPCM(DCM)-M06/Def2-TZVPP//IEFPCM(DCM)-M06/Def2-SVP level

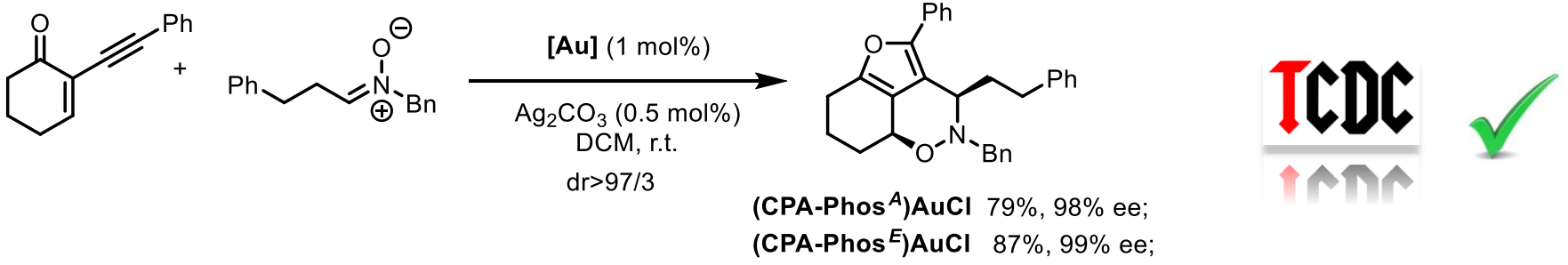
Tandem cycloisomerization/formal cycloaddition sequence

Zhenhao Zhang

Nucleophilic reactivity Electrophilic reactivity



From nitrone cycloadditions…

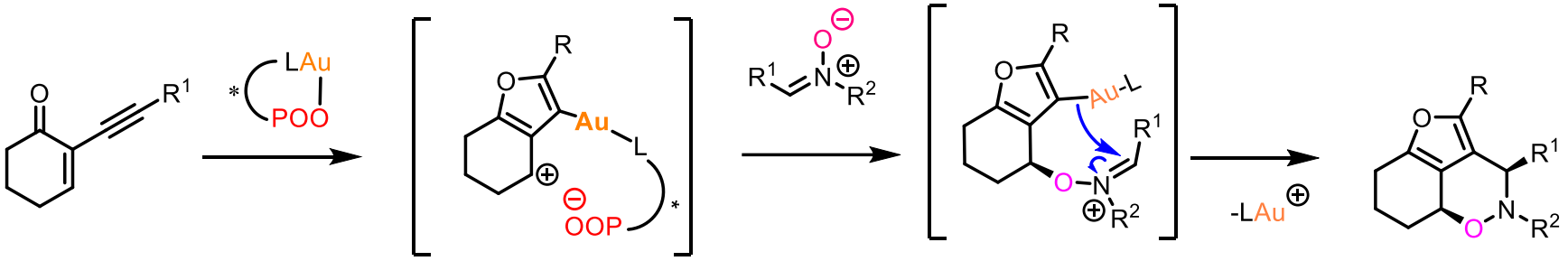


Previous results from the Zhang' group: a) Zhang, J. *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 5505; b) Zhang, J. *et al. Chem. Eur. J.* **2010**, *16*, 456; c) Zhang, J. *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 6669; d) Zhang, J. *et al. Chin. J. Chem.* **2018**, *36*, 519;

Tandem cycloisomerization/formal cycloaddition sequence

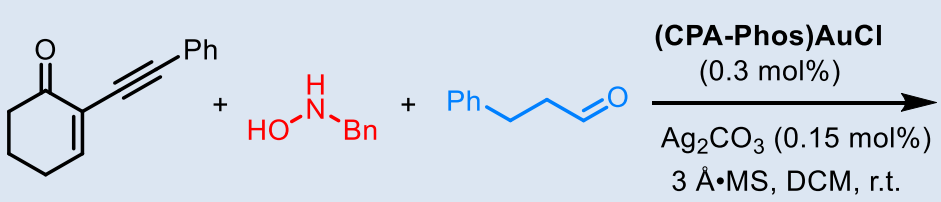
Zhenhao Zhang

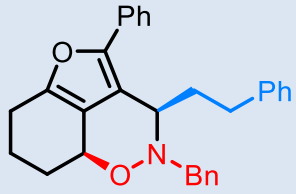
Nucleophilic reactivity Electrophilic reactivity



From nitrone cycloadditions…

… to a multicomponent version of the reaction!





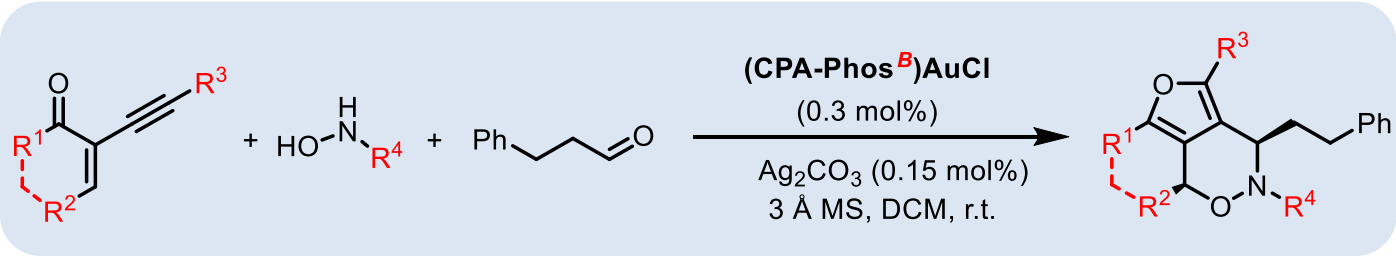
(CPA-Phos^{A})AuCl 31%, 89% ee
(CPA-Phos^{B})AuCl 96%, 99% ee

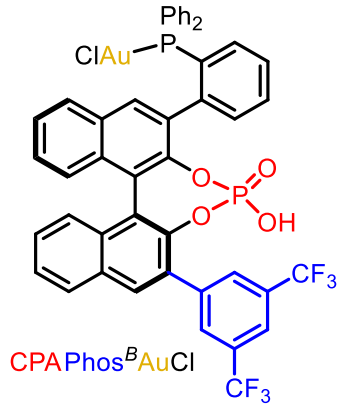
(CPA-Phos^{B})AuCl shows a higher performance

MCR version avoids the synthesis of the nitrone

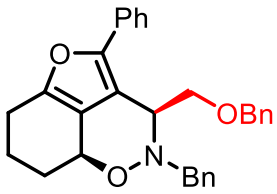
Scope of the multicomponent reaction

Zhenhao Zhang

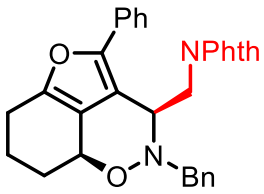




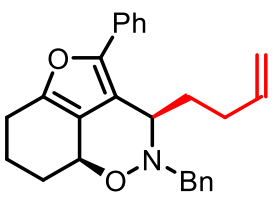
Aliphatic aldehydes



85%, 99% ee

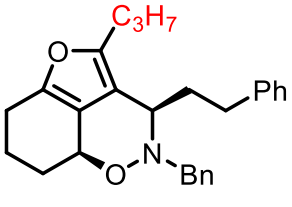


97%, 99% ee

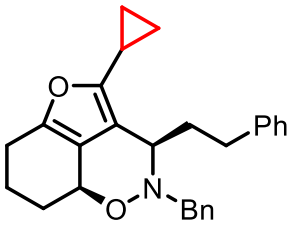


61%, 97% ee

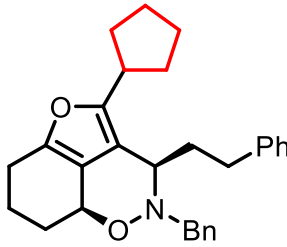
Alkyl R^3 substituent



44%, 89% ee

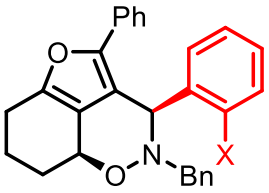


58%, 92% ee

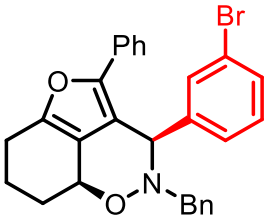


63%, 90% ee

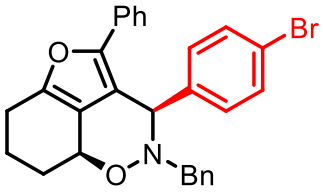
Aromatic aldehydes



X= Br, 48%, 99% ee
X= F, 70%, 97% ee

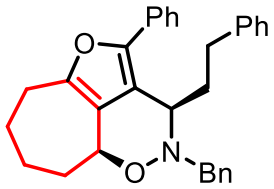


87%, 92% ee



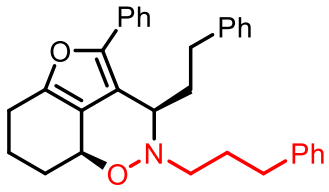
75%, 99% ee

7-membered ring



39%, 97% ee

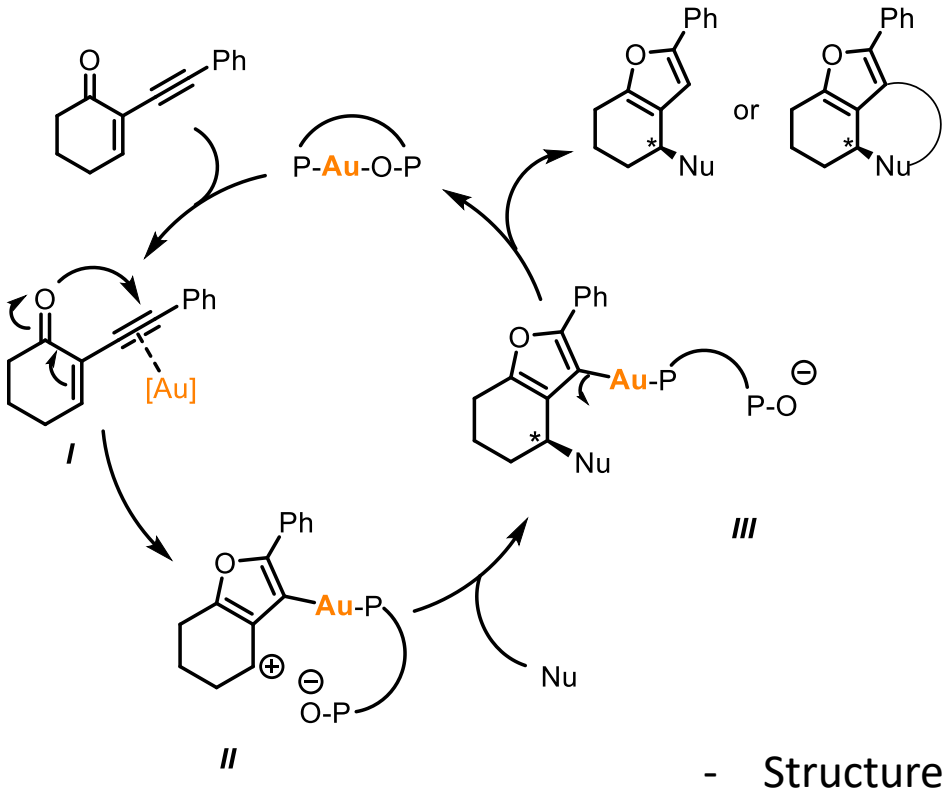
Other hydroxylamines



86%, 99% ee

ACS Catal. **2022**, *12*, 4046.

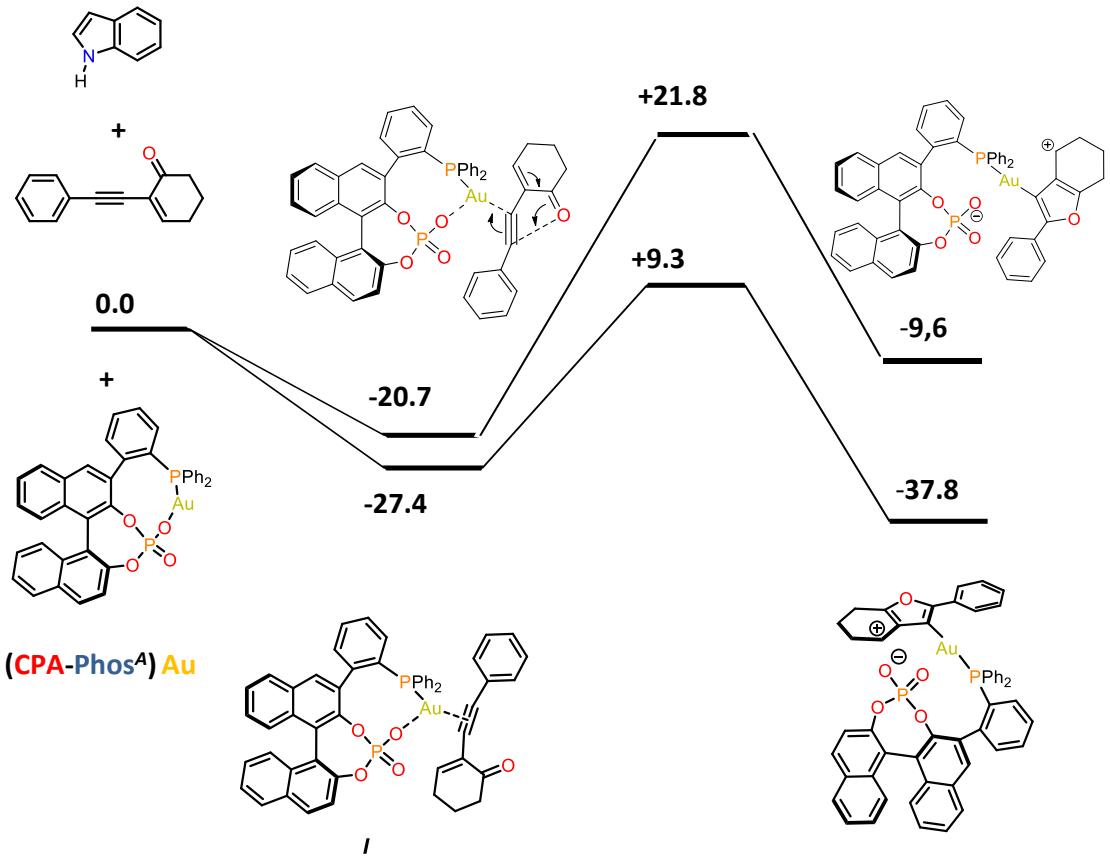
Mechanisms and DFT Calculations

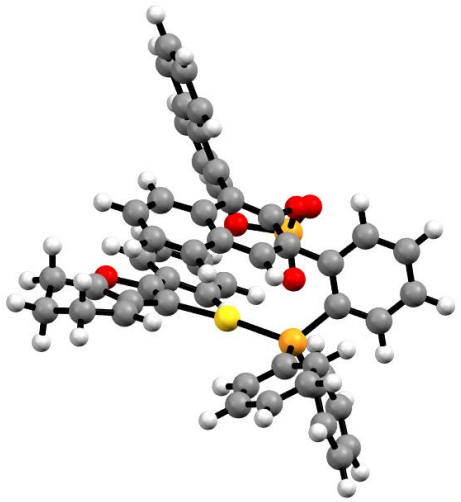


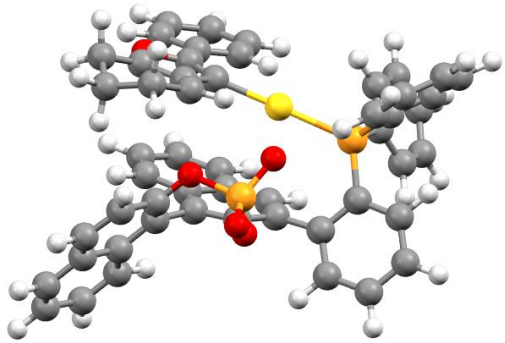
- Structure of the actual catalysts
- Stereoselectivity

DFT Calculations: enantioselectivity

Coll. with G. Frison



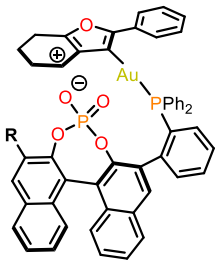




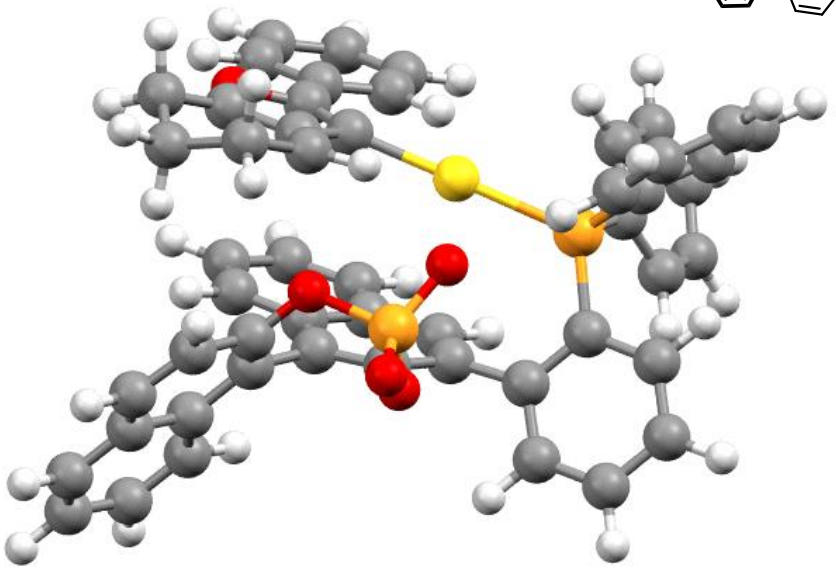
DFT calculations: Carbocation intermediates

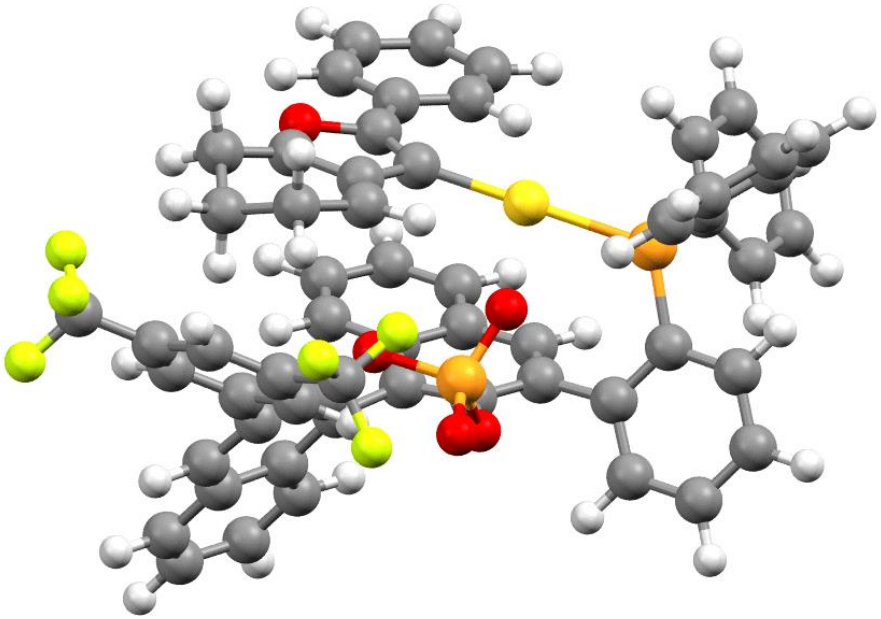
Coll. with G. Frison

With (CPA-Phos^{A})AuCl



With (CPA-Phos^{B})AuCl

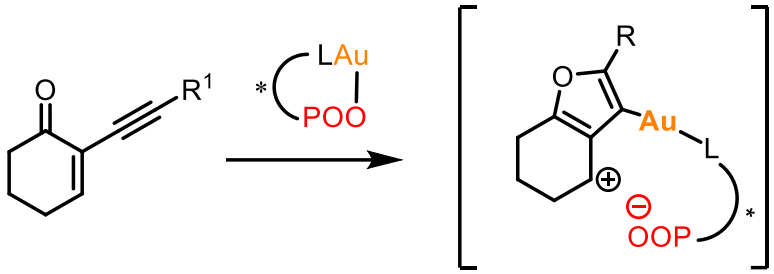




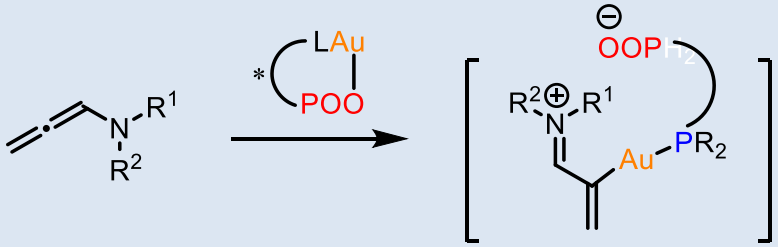
IEFPCM(DCM)-M06/def2-TZVPP

- Both intermediates display similar geometries
- The fluorinated aryl group has litle impact on the enantioselectivity
- The presence of a hydrogen bond may result in a better charge separation

New modes of activation for TCDC strategy



Activation of 2-alkynyl ketones

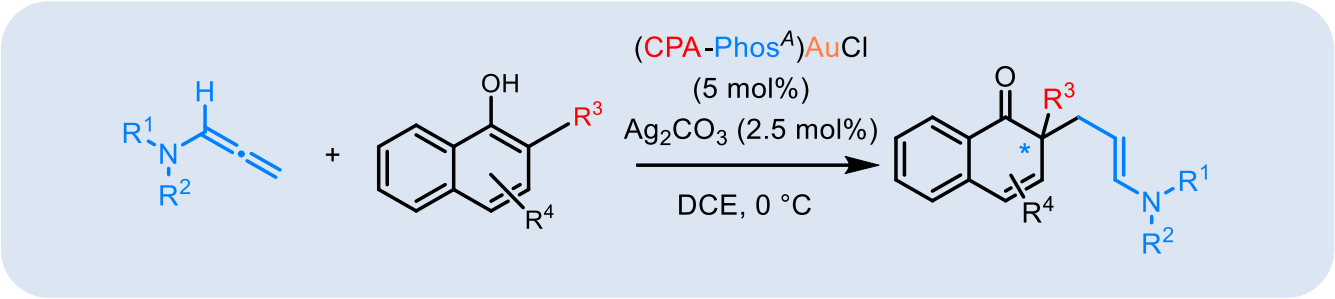


Activation of allenamides

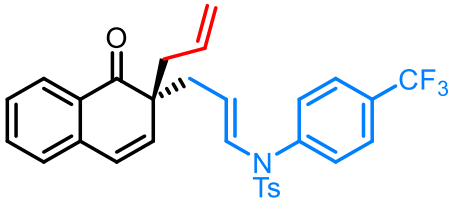
Chem. Commun. **2021**, *57*, 10779.

Dearomatization of naphthols with allenamides

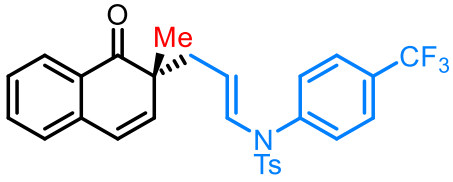
Yunliang Yu



Representative examples

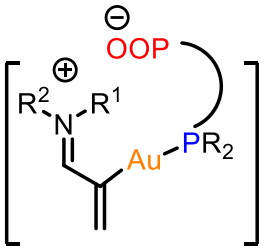


68%, 88% ee



70%, 81% ee

Intermediate



- Dearomatisation of naphthols with allenamides
- Applies to both 1- and 2-naphthols

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Mechanistic hypothesis

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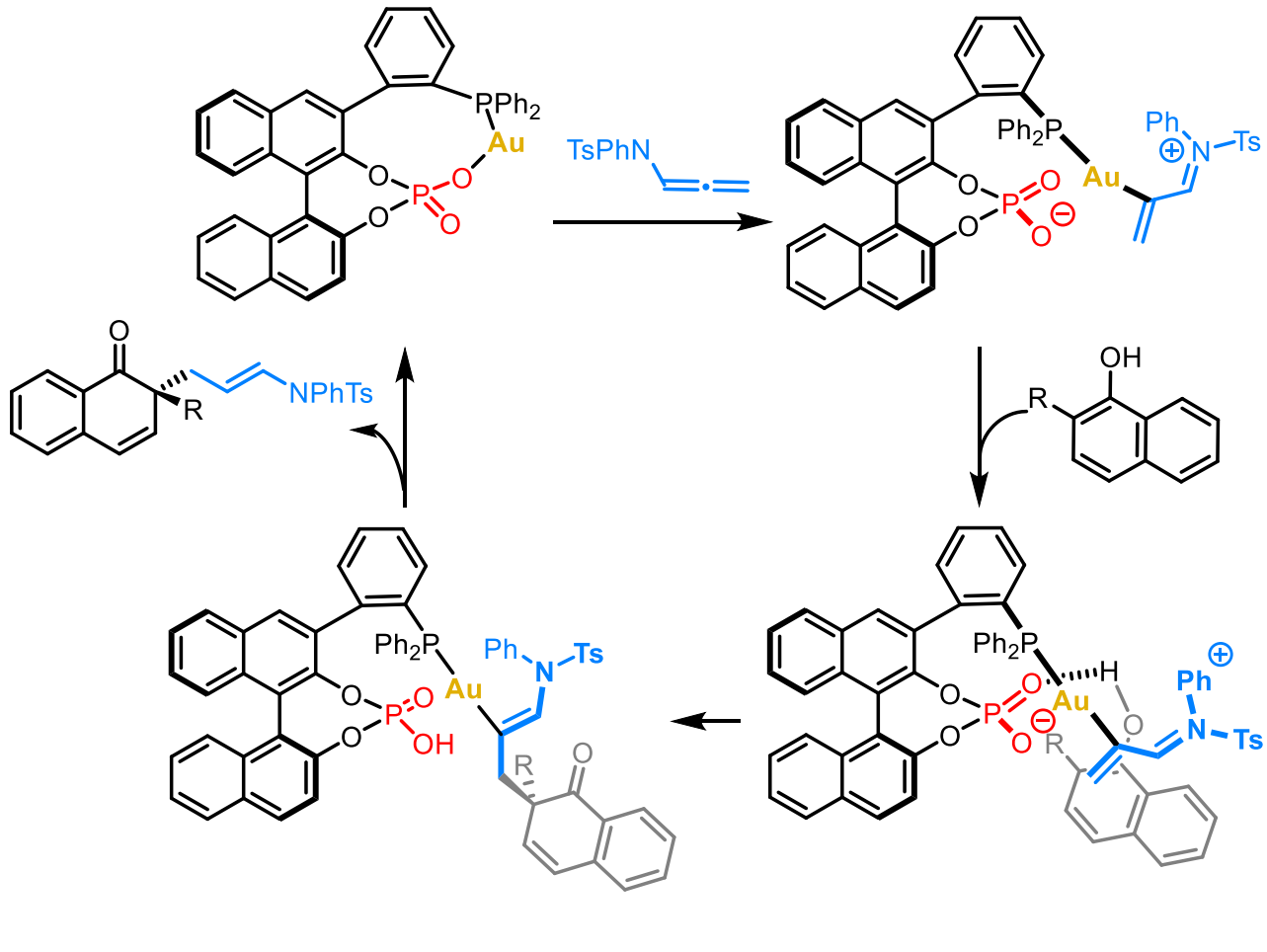

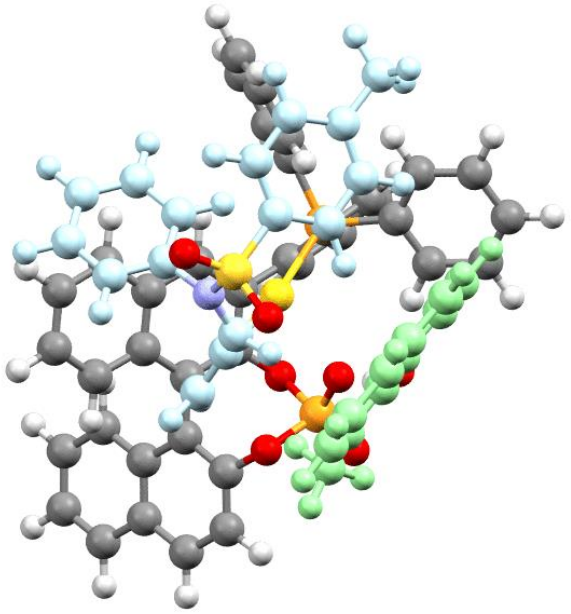

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DFT calculations

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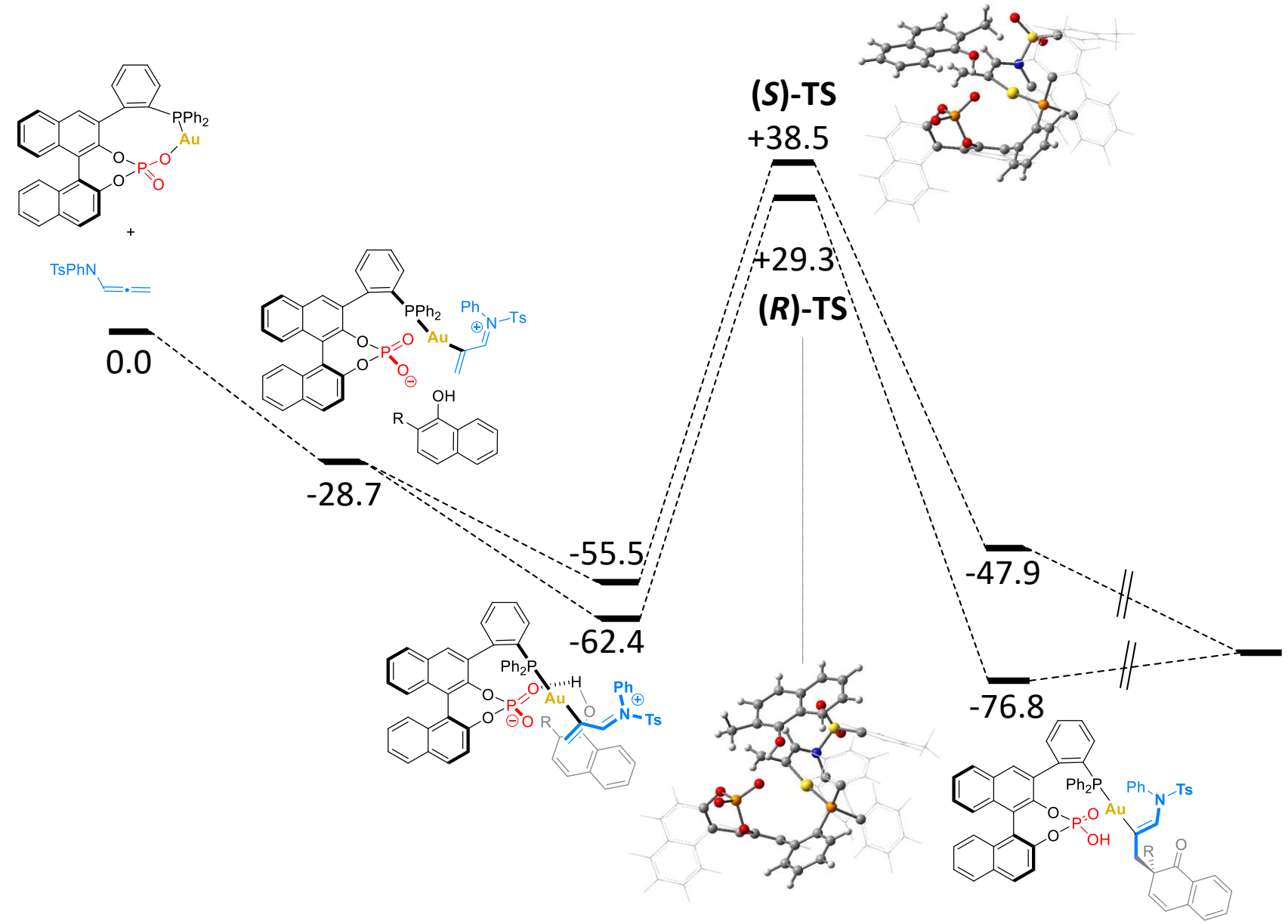
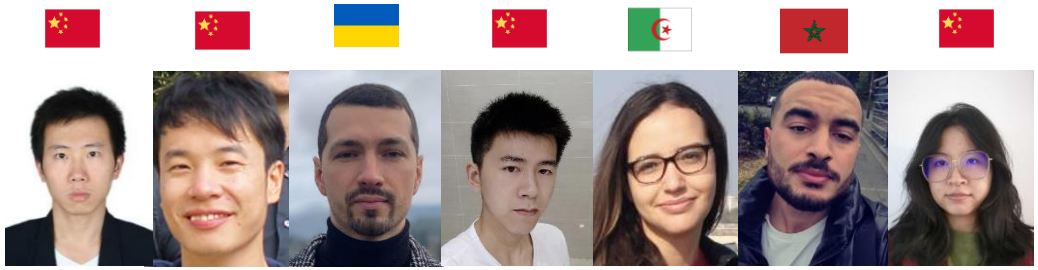


Acknowledgements



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