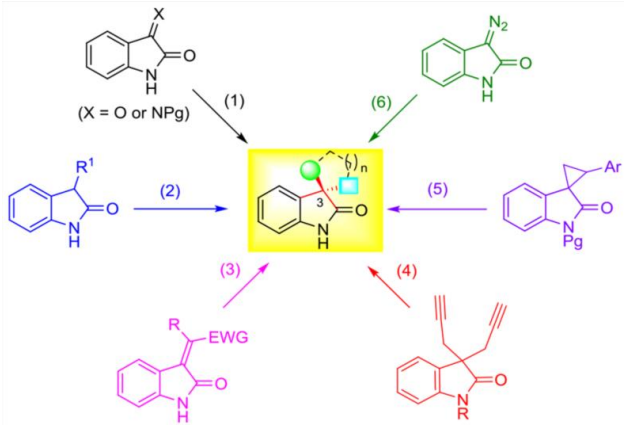
Development of Synthetic Methodologies via Catalytic Enantioselective Synthesis of 3,3-Disubstituted Oxindoles



Reporter: Fangfang Guo

Supervisor: *Prof.* Yong Huang

Date: 6/24/2019

Prof. Jian Zhou

Education

1993-1997, B.S. Sichuan Normal University

1999-2004, Ph.D. Shanghai Institute of Organic Chemistry (Advisor, Professor Yong Tang)

Academic Careers

2004.9-2005.8, Postdoctoral fellow, the University of Tokyo, Japan (Advisor: Professor Shu Kobayashi)

2005.10-2008.9, Postdoctoral fellow, Max-Planck-Institute für Kohlenforschung (Advisor: Professor Benjamin List)

2008.11-present, Professor, East China Normal University

Research interests

the efficient and economical construction of tetrasubstituted or quaternary carbon stereocenters.

Awards

2018, Youth Science and technology innovation leader

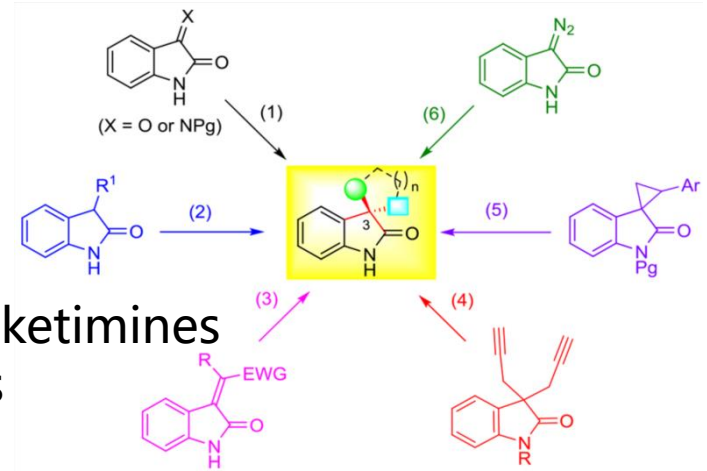
2017, National Natural Science Funds for Distinguished Young Scholar

2015, The CSJ Asian International Symposium Distinguished Lectureship Award (Awarded by Chemistry Society of Japan)

2014, Fellow of Royal Society of Chemistry)

2011 ,“Thieme Chemistry Journals Award”

Content



1. Introduction

2. Bifunctional catalysis

- ✓ Nucleophilic addition to isatin or isatin ketimines
- ✓ 3-substituted oxindoles as nucleophiles

3. Chiral Gold and mercury catalysis

- ✓ Functionalization of oxindole-derived alkenes
- ✓ Spirocyclopropyl oxindoles as donor−acceptor cyclopropanes

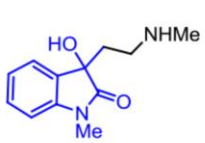
4. Others

Desymmetrization of oxindole-based diynes
Sequential tandem reaction

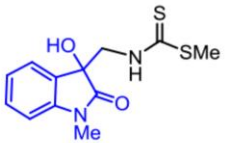
5. Conclusion

Introduction

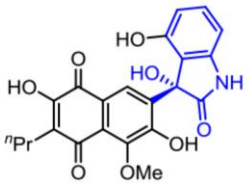
Natural Products



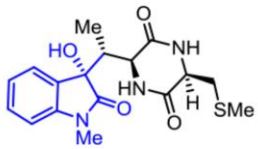
donaxaridine



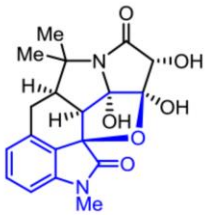
dioxibrassinine



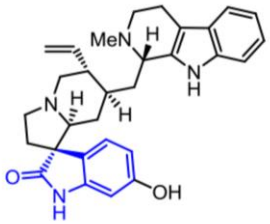
Coprisidin B



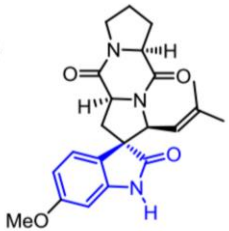
Maremycin A



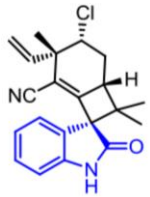
Aspergilline A



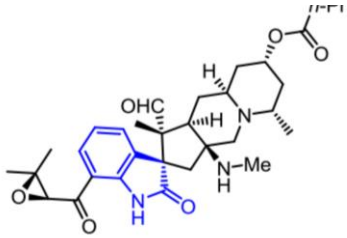
Strychnofoline



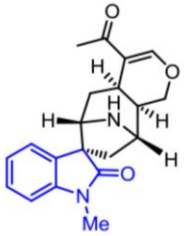
Spirotryprostatin A



Welwitindolinone A isonitrile

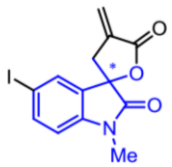


PF1270A

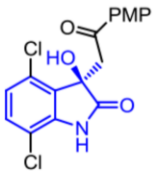


Alstonisine

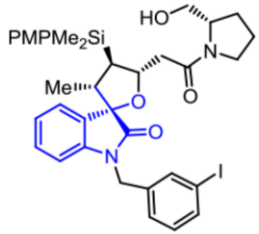
Drugs and bioactive compounds



Antibacterial

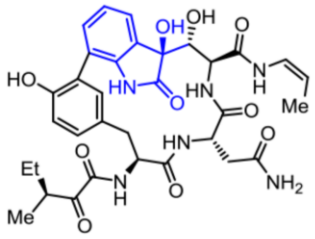


YK-4-279

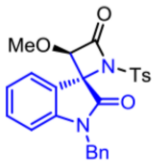


Growth inhibition (HepG2)

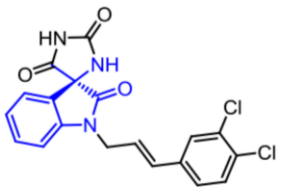
GHS-R EC_{50} = 3 nM
ent GHS-R EC_{50} = 210 nM



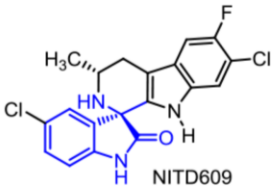
TMC-95A



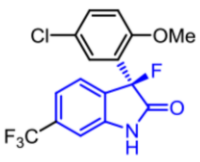
Poliovirus inhibitor



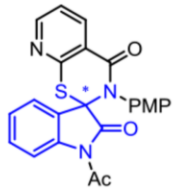
Spirohydantoin



NF54 IC_{50} = 9 nM
ent NF54 IC_{50} > 5000 nM

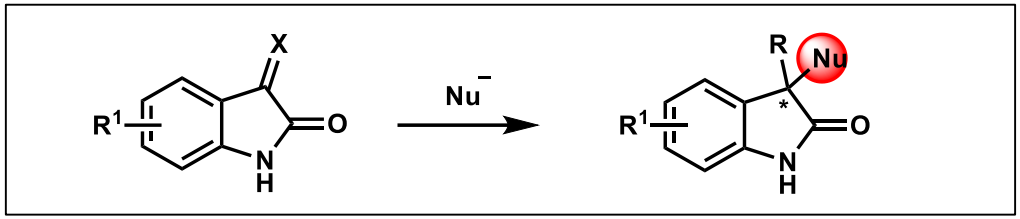


BMS-204352

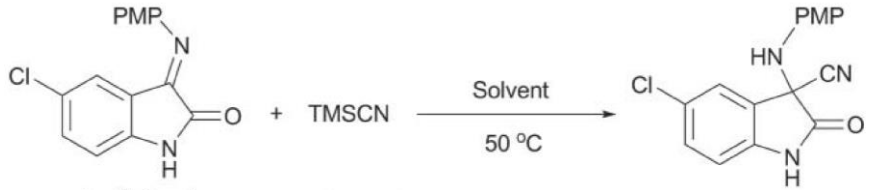


antiproliferative agent

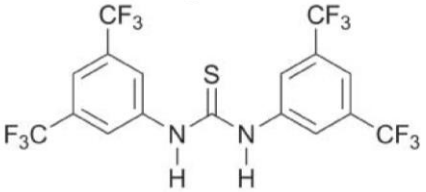
Bifunctional catalysis: Nucleophilic addition to isatin or isatin ketimines



The synthesis of 3-substituted-3-aminooxindoles *via* the Strecker reaction in catalyst-free strategy

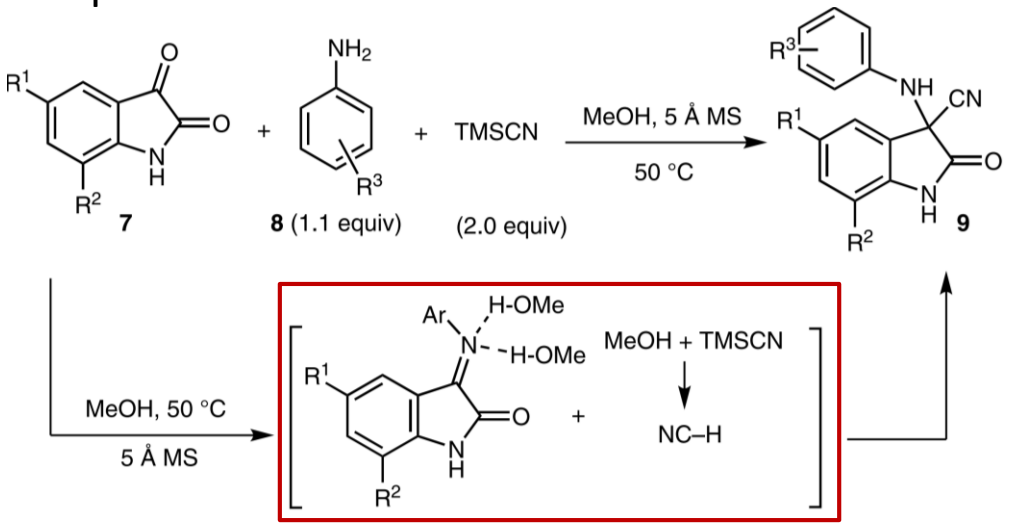


1a (1.0 eq) **2** (2.0 eq) **3**

Entry[a]	Solvent	Additive	Time/h	Yield[b] (%)
1	CH_2ClCH_2Cl	no	48	no
2	MeOH	no	15	84
3	EtOH	no	15	64
4	*i*-PrOH	no	15	52
5	CH_2ClCH_2Cl	MeOH (2.0 eq)	15	13
6	CH_2ClCH_2Cl	MeOH (4.0 eq)	15	15
7	CH_2ClCH_2Cl	MeOH (8.0 eq)	15	21
8	CH_2ClCH_2Cl	MeOH (12.0 eq)	15	64
9	CH_2ClCH_2Cl	MeOH (16.0 eq)	15	70
10	CH_2ClCH_2Cl	MeOH (20.0 eq)	15	79
11	CH_2ClCH_2Cl		15	36

4 (10 mol%)
MeOH (2.0 eq)

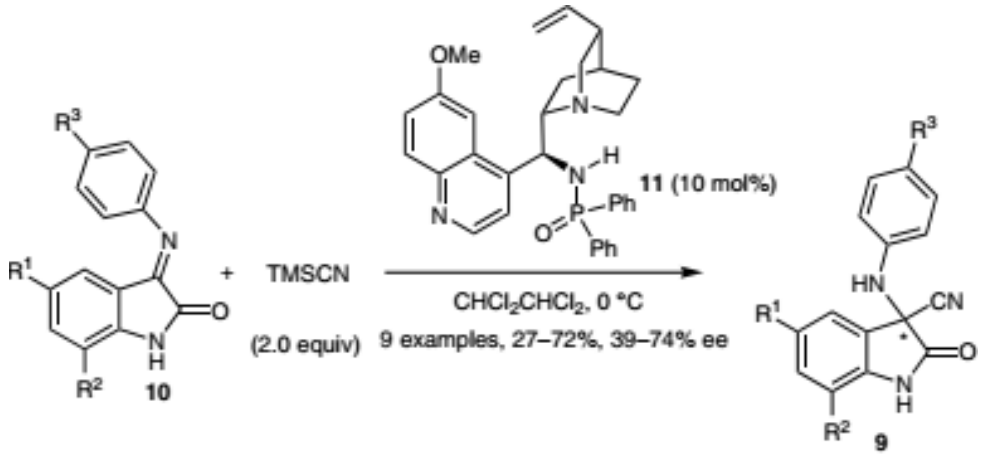
Proposed mechanism of the racemic reaction



Dule role:

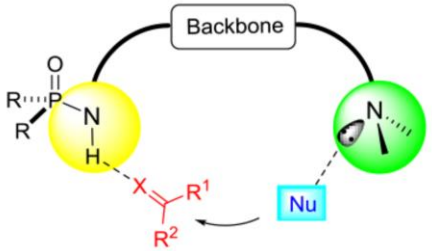
- ✓ Formation and activation of the corresponding isatin ketimines
- ✓ React with TMSCN to release hydrogen cyanide

The first catalytic asymmetric addition of nucleophiles to isatin ketimines.

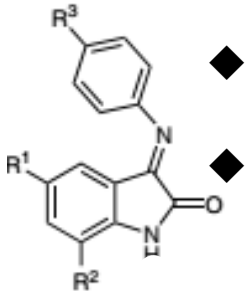


Org. Biomol. Chem. **2010**, *8*, 3847.

Bifunctional phosphoramide (phosphinamide) catalysts

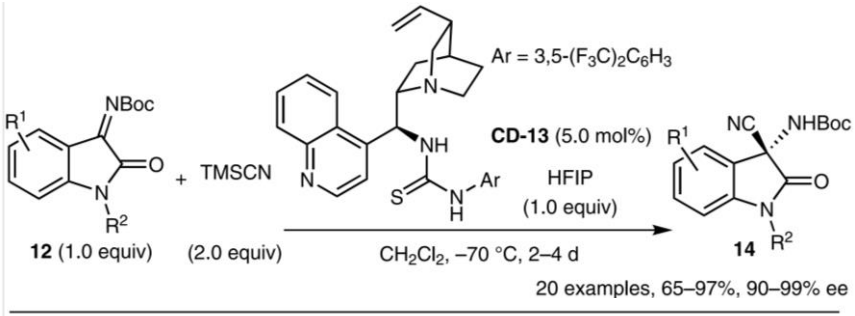


1) Readily accessed and modified
2) Tertiary amine as Brønsted base or Lewis base
3) Two amide substituents as shielding groups
4) Tunable pKa value of amide N-H bond
5) P=O bond as Lewis base

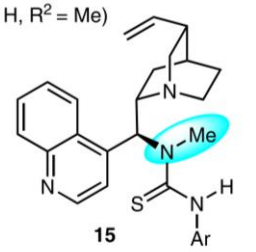


- Difficult to remove the N-aryl group
- low reactivity

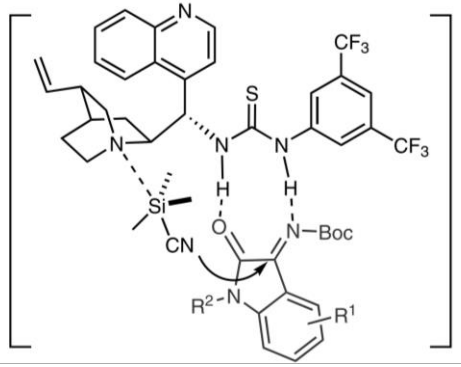
The Strecker reaction of N-Boc-substituted ketimines catalyzed by bifunctional cinchonidine derived tertiary amine–thiourea catalyst



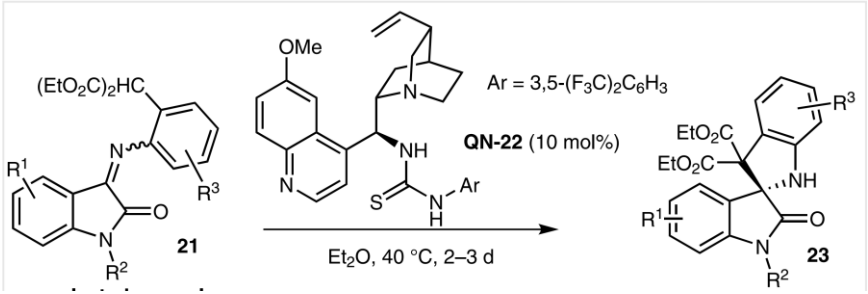
control experiments
(R^1 = H, R^2 = Me)

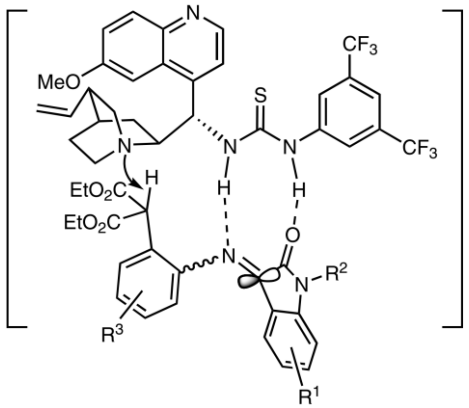


56%, 70% ee (using **15**)
vs
93%, 98% ee (using **CD-13**)



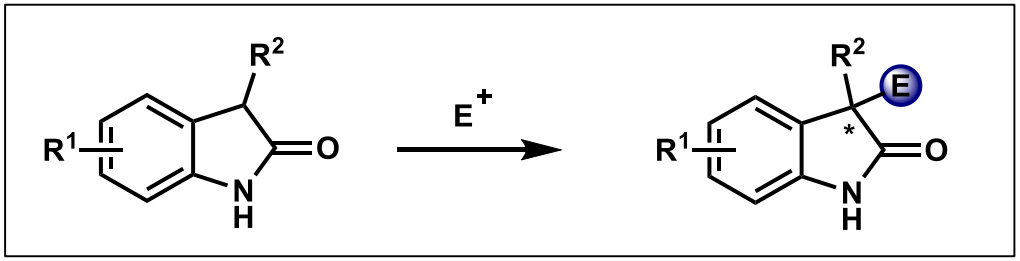
The first example of asymmetric 6π-electrocyclic reaction to construct a tetrasubstituted carbon center



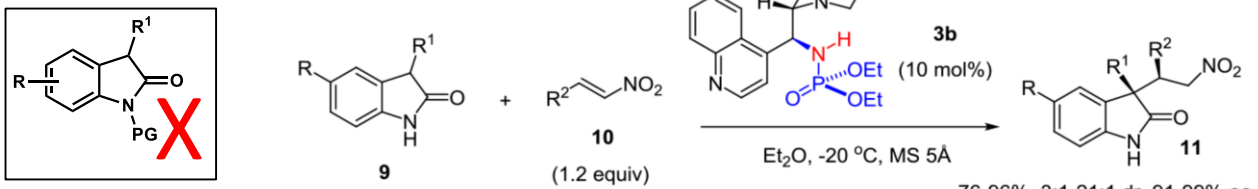


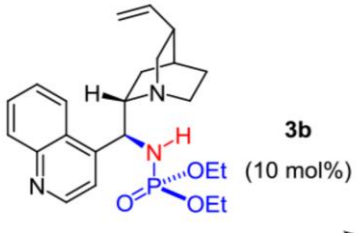
Chem. Commun. **2013**, 49, 4421.
Angew. Chem. Int. Ed. **2014**, *53*, 13740.

Bifunctional catalysis: 3-substituted oxindoles as nuclephiles

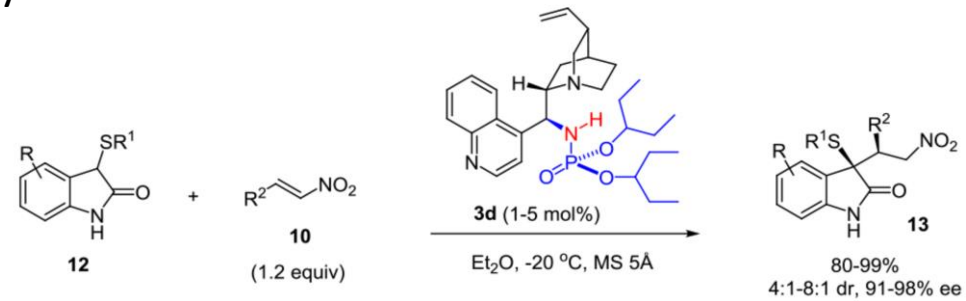


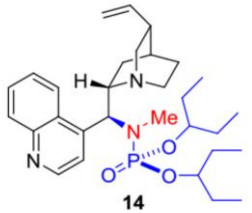
The asymmetric Michael addition of unprotected 3-substituted oxindoles to nitroolefins

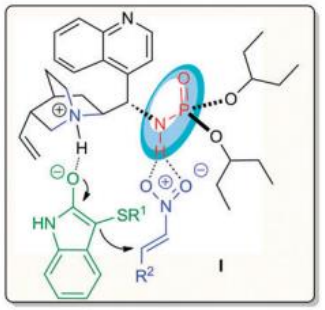




Highly enantioselective Michael addition of 3-alkylthio- and 3-arylthiooxindoles





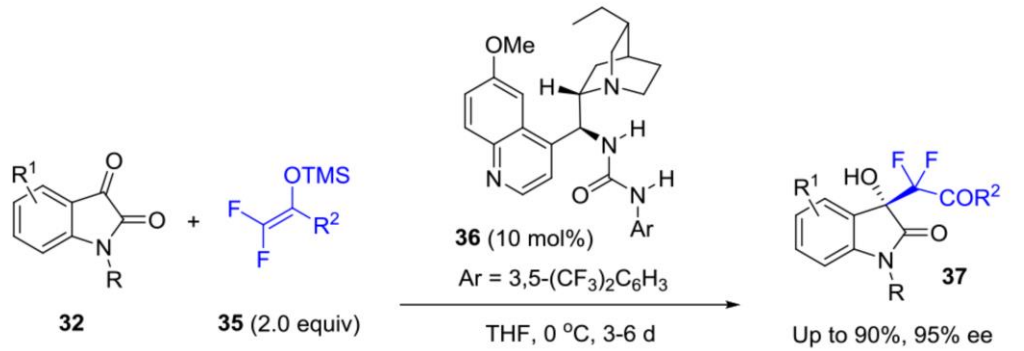


Varying the size of the alkoxy group of phosphoramide could effectively improve the enantiofacial control

Chem. Sci. **2011**, *2*, 2035.
Chem. Commun., **2014**, *50*, 15179.

Mukaiyama aldol reaction of isatins

Highly enantioselective quinine-derived urea-catalyzed Mukaiyama aldol reaction of isatins with difluoroenoxysilanes .

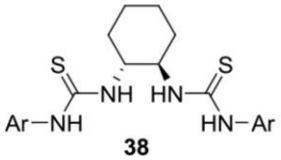


Control experiments (R = Me, R^1 = H, R^2 = Ph, CH_2Cl_2 as solvent):

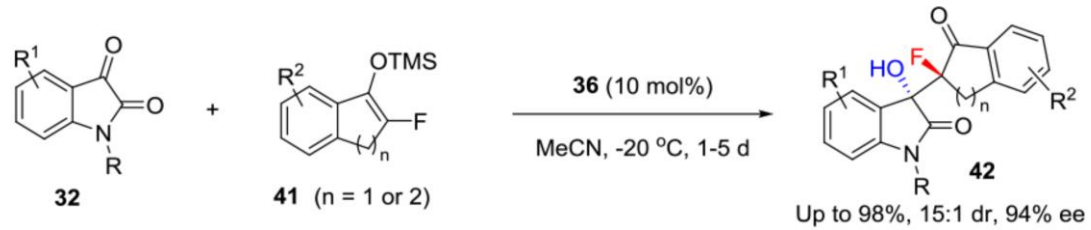
1) with **38** (10 mol%): 3 d, no reaction

2) with DMAP (10 mol%): 1 d, 95% yield

3) **38** (10 mol%) + DMAP (10 mol%): 3 d, 94% yield, 11% ee



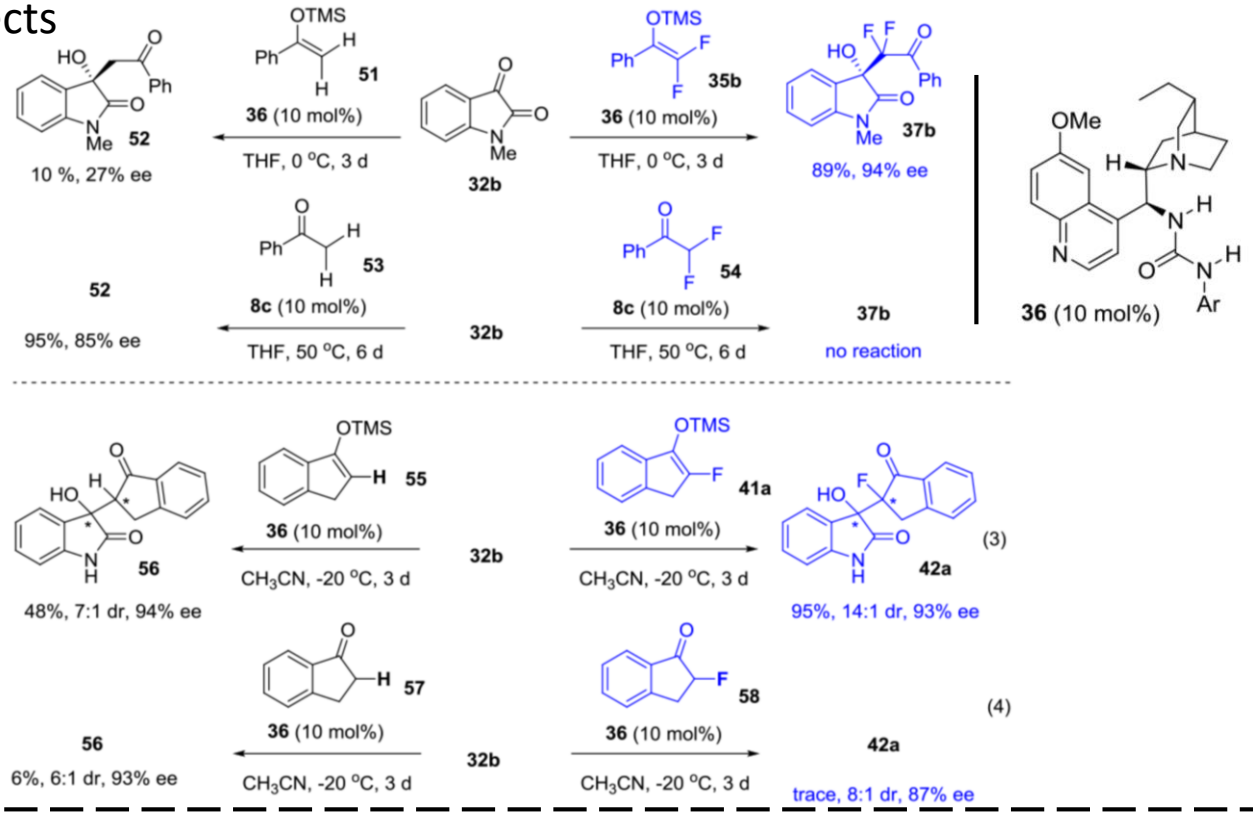
The Mukaiyama aldol reaction of isatins with monofluorinated silyl enol ethers



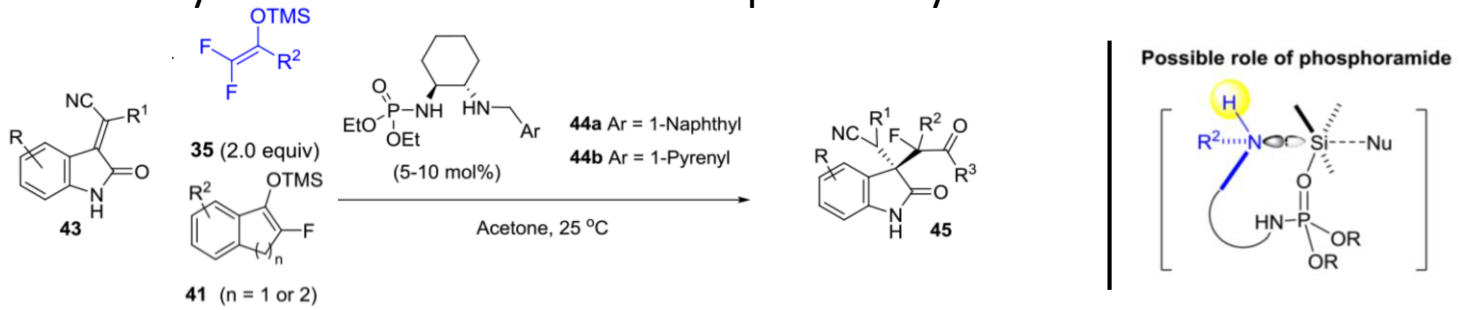
Chem. Commun. 2012, *48*, 1919.
Org. Chem. Front. 2014, *1*, 742.

Michael Addition of isatins

Fluorine Effects



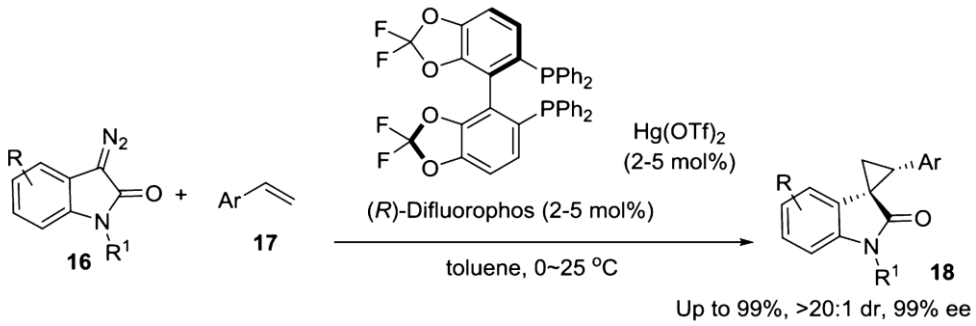
Michael addition catalyzed by chiral secondary amine phosphoramide using fluorinated silyl enol ethers: formation of quaternary carbon stereocenters

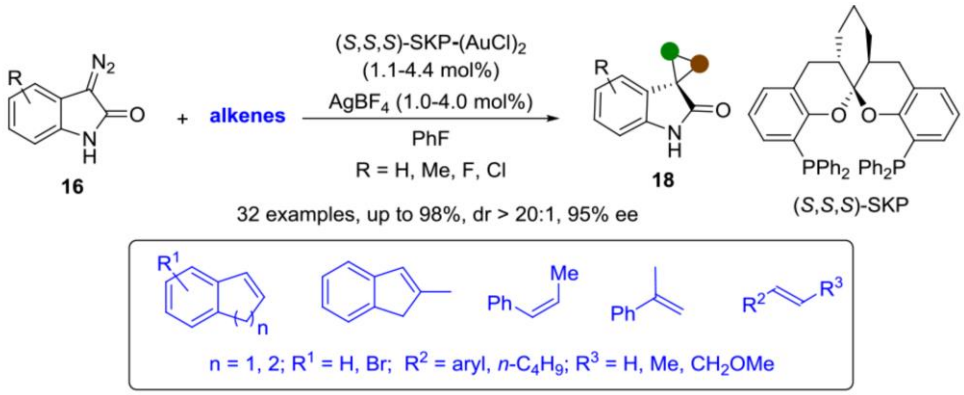


Angew. Chem., Int. Ed. **2015**, *54*, 7381.

Chiral Gold and mercury catalysis

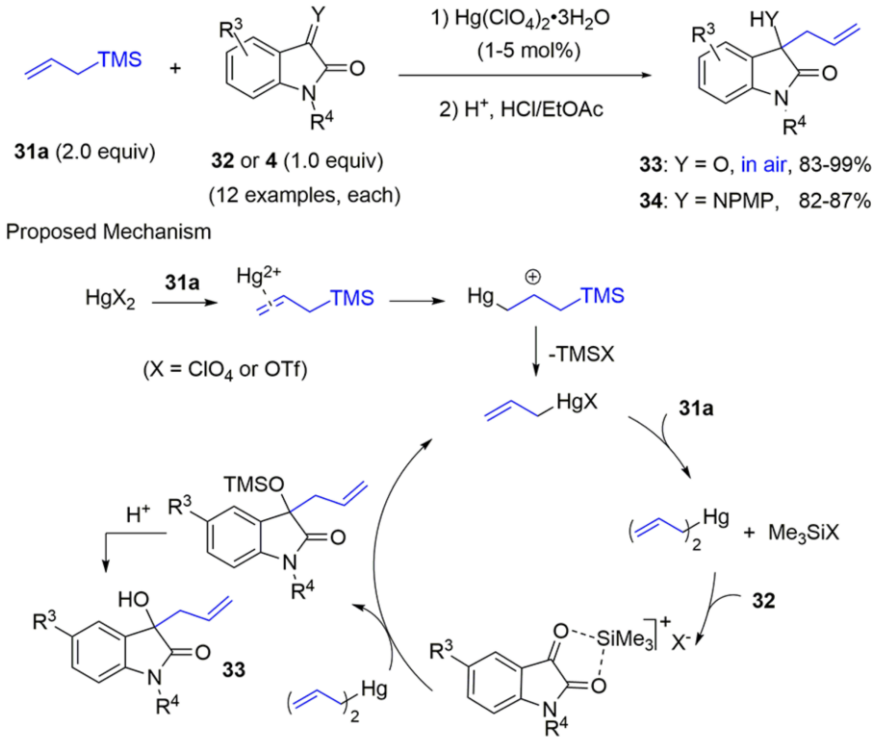
Hg(II)-Catalyzed Asymmetric Olefin Cyclopropanation functionalization of oxindole-derived alkenes



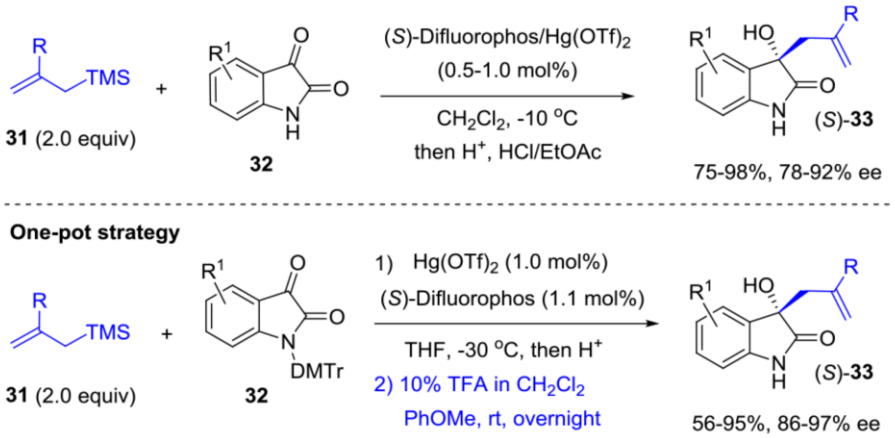


Tetrahedron Lett. **2008**, *49*, 6781.
Org. Lett. **2013**, *15*, 42.
J. Am. Chem. Soc. **2013**, 135, 8197.

Hg(II)-Catalyzed asymmetric allylation of isatins or isatin ketemines

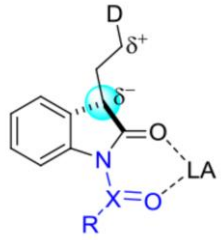


The allylation of unprotected isatins with allyltrimethylsilane by Hg(II)



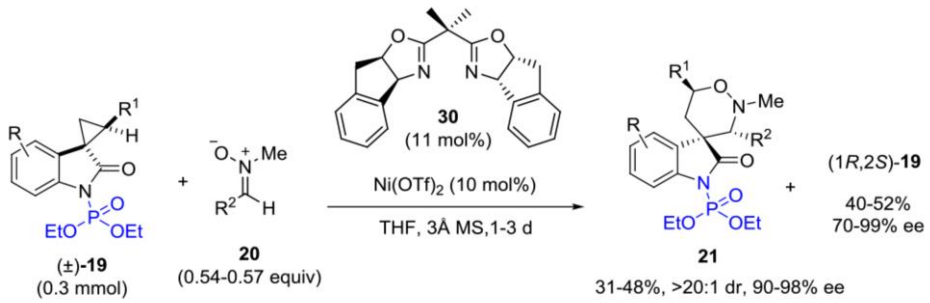
Org. Biomol. Chem. **2016**, *14*, 5500.

Activation of spirocyclopropyl oxindoles

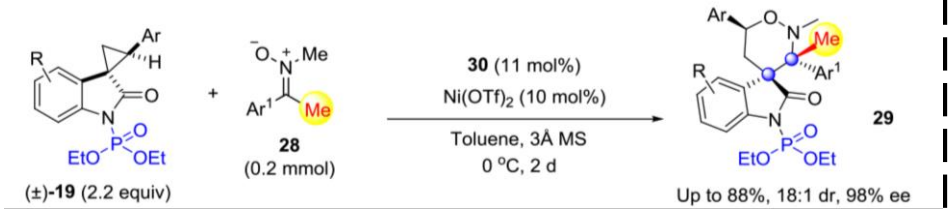


1) Stabilize the negative charge developed at C3
2) Enable chelation control for enantiofacial control
3) Easily installed and removed

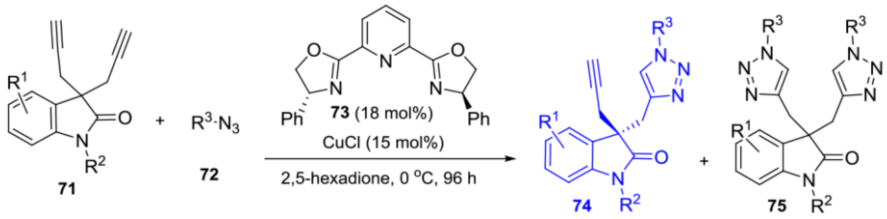
Highly stereoselective [3 + 3] cycloaddition with nitrone



The first example based on unactivated ketonitrones



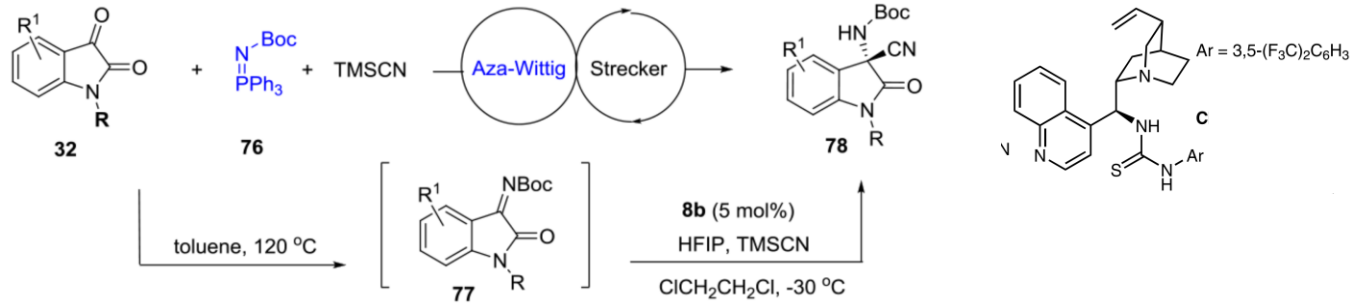
Others: the first highly enantioselective desymmetric Cu-catalyzed alkyne-azide cycloaddition of oxindole-based 1,6-heptadiynes



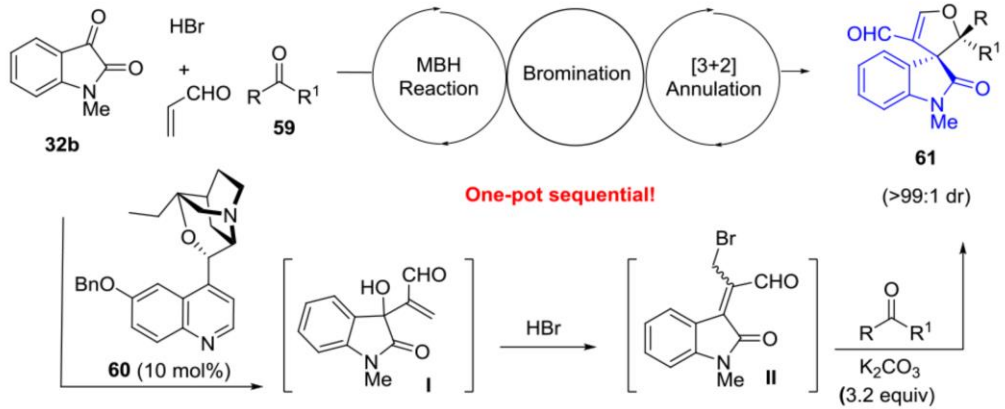
Angew. Chem., Int. Ed. **1999**, *38,* 3186. *Nat. Commun*. **2017**, *8*, 1619.
Angew. Chem., Int. Ed. **2015**, *54*,11205. *Nat. Commun*. **2017**, *8*, 1619.
J. Am. Chem. Soc. **2013**, *135*, 10994.

Sequential tandem reaction

The one-pot Strecker reaction of ketimines formed in situ from achiral ketones: tandem aza-Wittig/ Strecker reaction of isatins



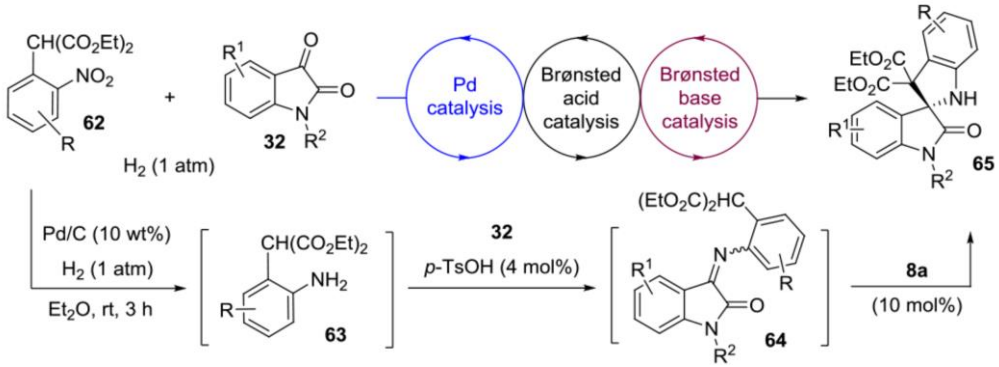
Novel MBH/bromination/annulation sequence consisting of three intermolecular reactions



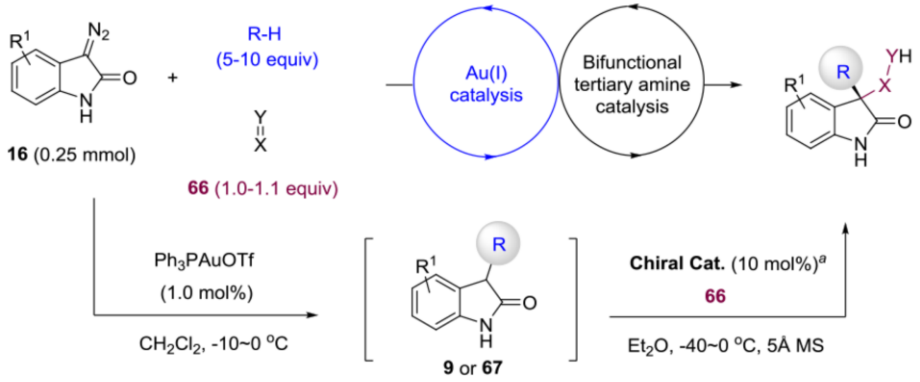
Chem. Commun. **2013**, *49*, 4421.
J. Am. Chem. Soc. **2010**, *132*, 15176.
Angew. Chem. Int. Ed. **2013**, *52*, 13735.

Sequential tandem reaction

Novel Pd/Brønsted acid/Brønsted base sequential catalysis



Sequential Au(I)/chiral tertiary amine catalysis

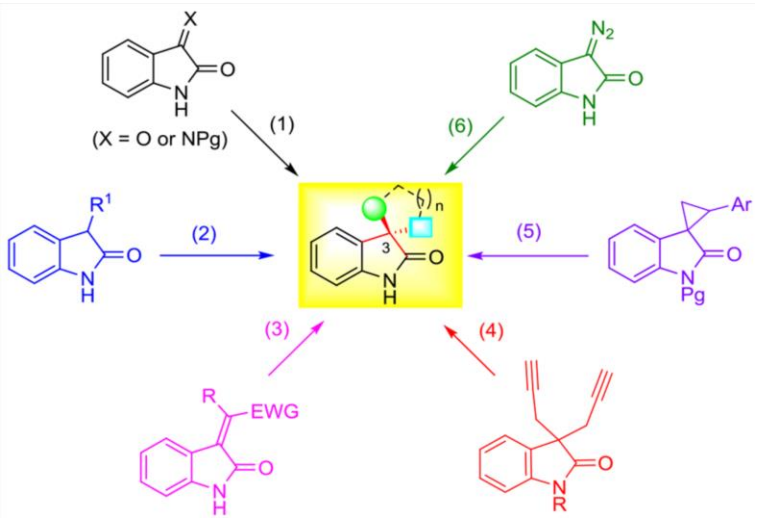


Angew. Chem., Int. Ed. **2014**, *53*,13740.
Chem. Commun. **2016**, *52*, 2537.

Conclusion

1. Developed a variety of **effi**cient protocols based on six approaches classi**fi**ed by the oxindole synthons involved, allowing facile access to oxindole derivatives with broad structural diversity.

- Nucleophilic addition to isatin ketimines
- 3-substituted oxindoles as nucleophiles
- Functionalization of oxindole-derived alkenes
- Desymmetrization of oxindole-based diynes
- Spirocyclopropyl oxindoles as donor–acceptor cyclopropanes
- Sequential tandem reaction



2. These new catalysts, activation models, and methodologies can be utilized by synthetic chemist.

Acknowledgement

Prof. Yong Huang

Dr. Chen

All members in E201

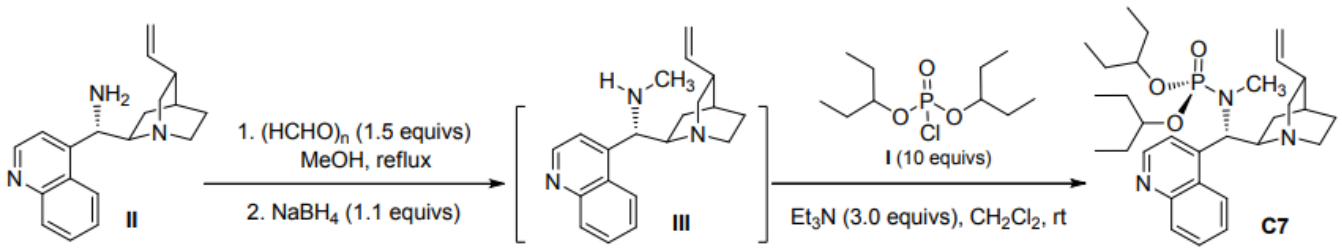
All of you here

Backup

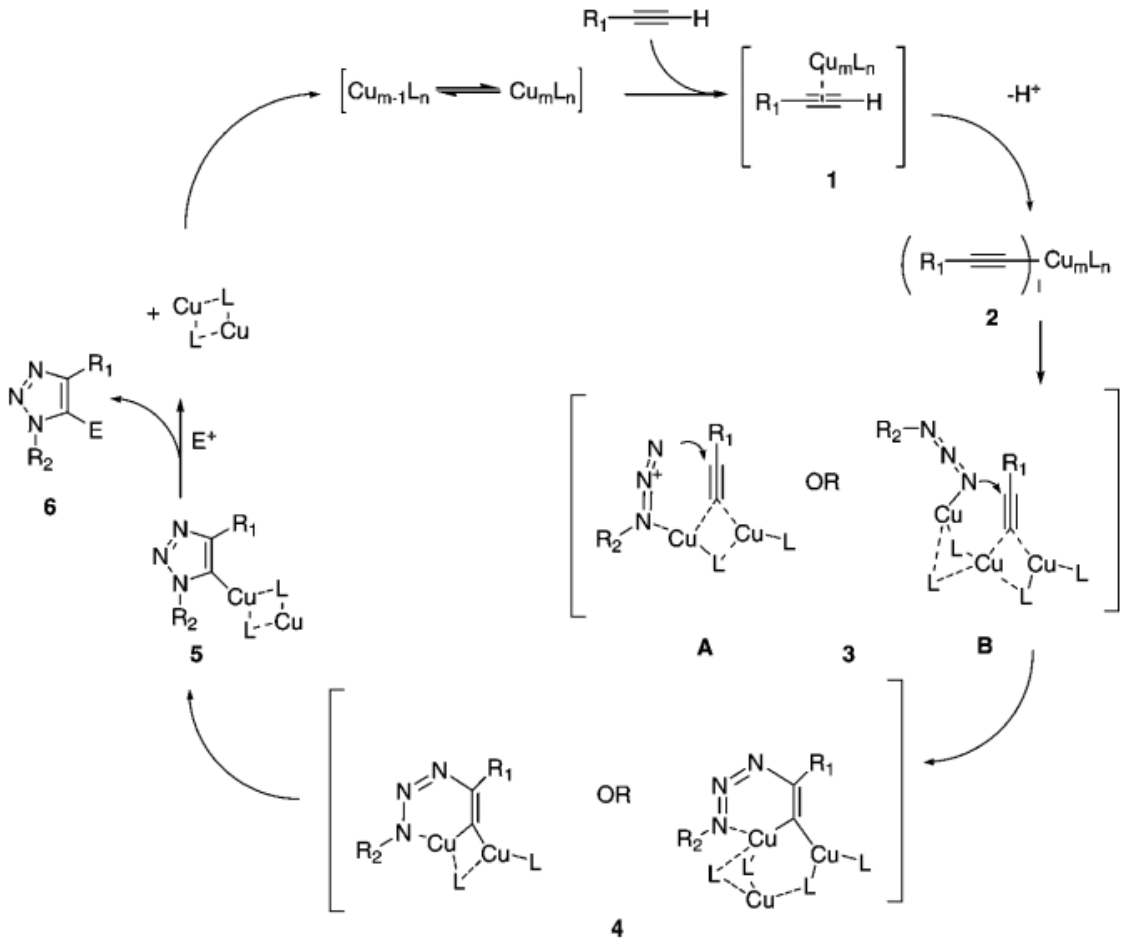
Control experiment

Control experiments:

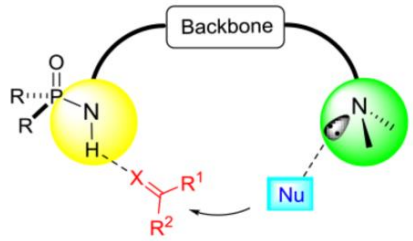
1) no $Ph_3PAuOTf$: 3 d, 82%, 6:1 dr, 97% ee
2) $Ph_3PAuOTf$ (1.0 mol%): 3 d, 80%, 6:1 dr, 97% ee
3) $Ph_3PAuOTf$ (2.0 mol%): 4 d, 82%, 5:1 dr, 72% ee
4) $Ph_3PAuOTf$ (5 mol%): 4 d, 73%, 4:1 dr, 69% ee
5) $Ph_3PAuOTf$ (10 mol%): 4 d, 38%, 2:1 dr, 33% ee



Scheme 1. Outline of Plausible Mechanisms for the Cu(1) Catalyzed Reaction between Organic Azides and Terminal Alkynes[a]



Bifunctional phosphoramide (phosphinamide) catalysts



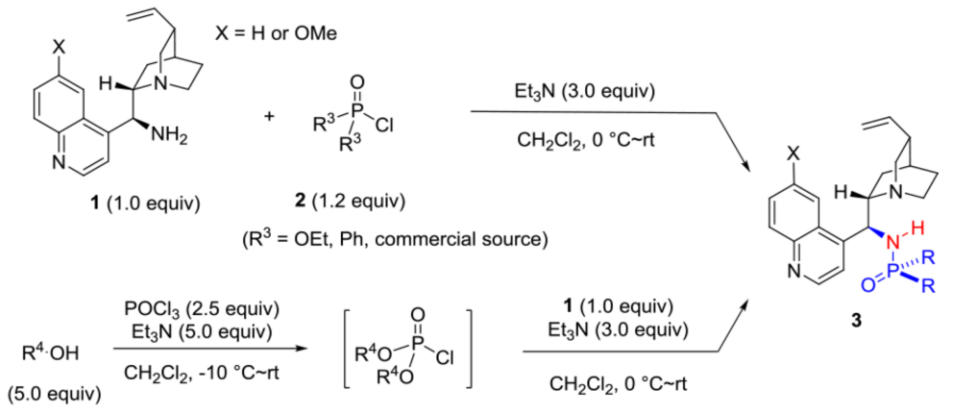
1) Readily accessed and modified

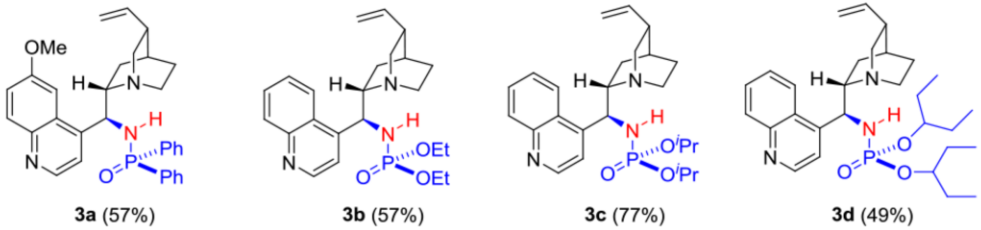
2) Tertiary amine as Brønsted base or Lewis base

3) Two amide substituents as shielding groups

4) Tunable pKa value of amide N-H bond

5) P=O bond as Lewis base





3a (57%) **3b** (57%) **3c** (77%) **3d** (49%)