Literature Report 1

Diastereo- and Atroposelective Synthesis of Bridged Biaryls Bearing an Eight-Membered Lactone through an Organocatalytic Cascade

Reporter: Zi-Qi Hu
Checker: Zi-Biao Zhao
Date: 2019-12-09

Zhao, Y. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 17062.

CV of Prof. Zhao Yu

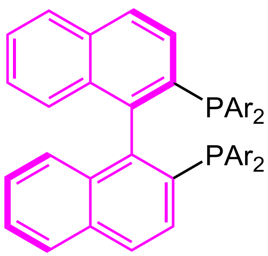
Education:

- **1998-2002** B.S., Peking University
- **2002-2008** Ph.D., Boston University
- **2008-2011** Postdoctoral associate, MIT
- **2011-2017** Assistant Professor, NUS
- **2017-Present** Associate Professor, NUS

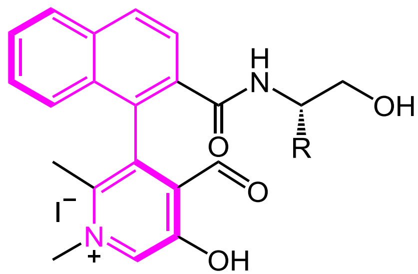
Research:

- Enantioselective Catalysis
- Organic and Organometallic Synthesis
- Mechanistic Studies

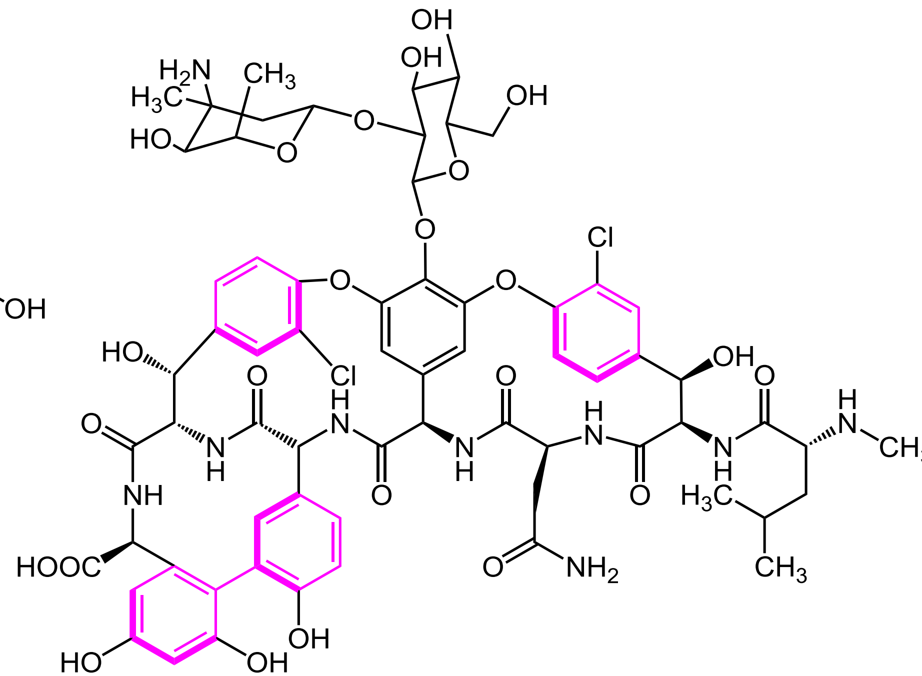
Introduction



BINAP

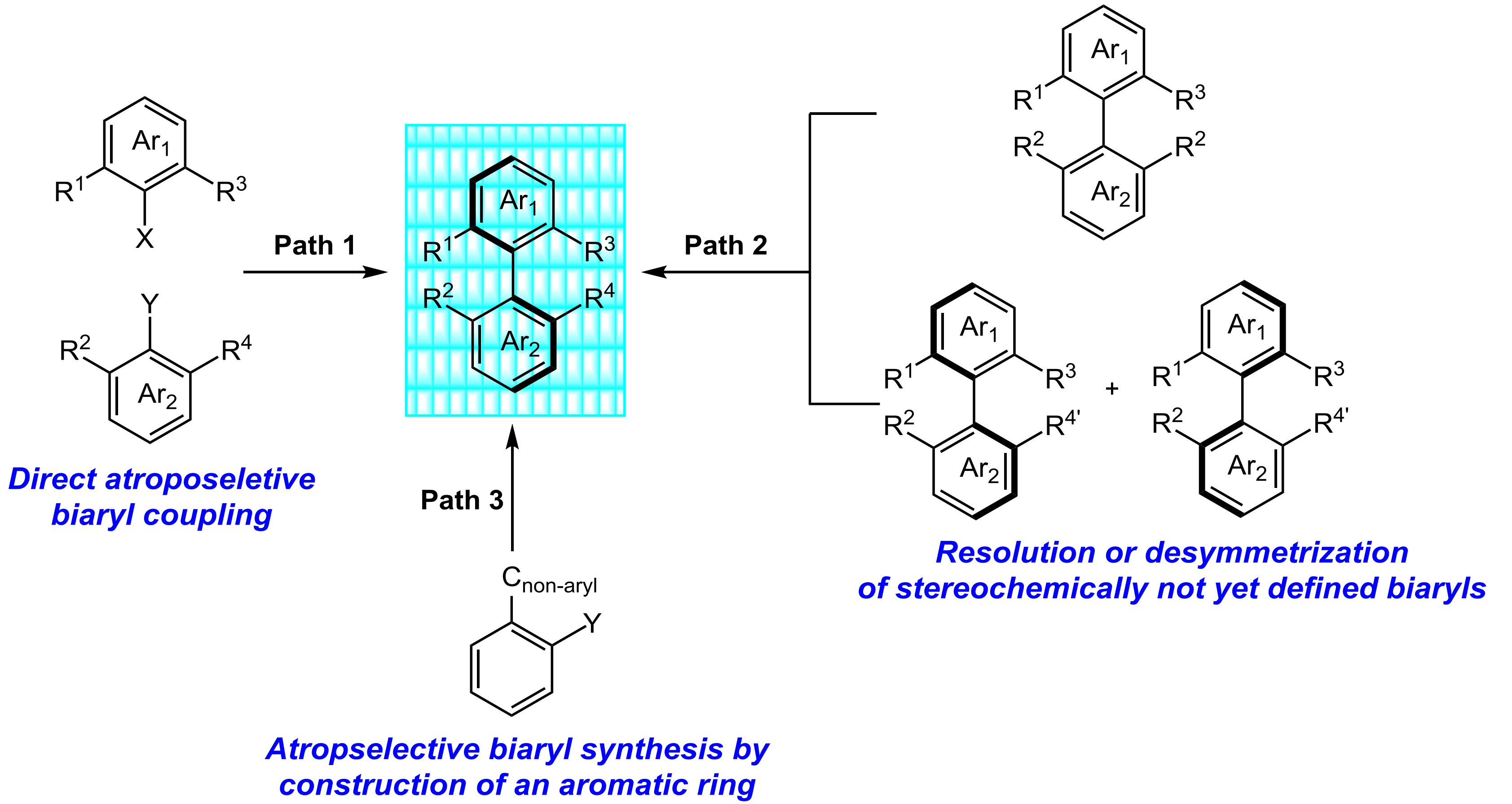


***N*-methylpyridoxal**



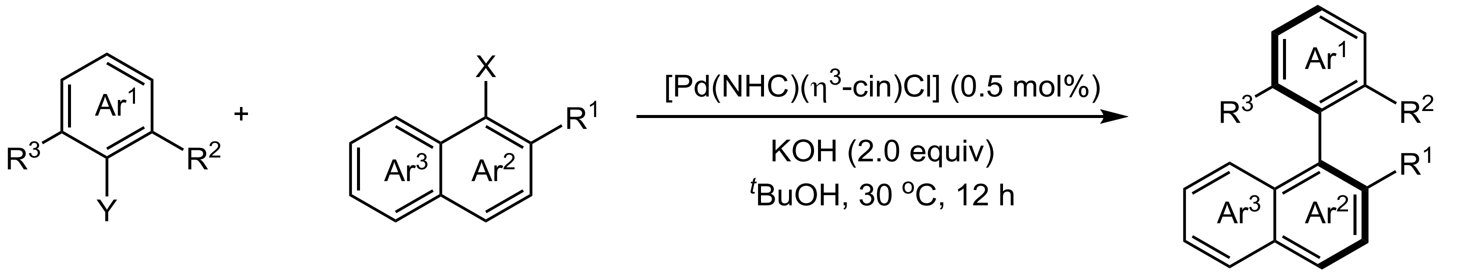
Vancomycin

Introduction



Bringmann, G. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2005**, *44*, 5384.

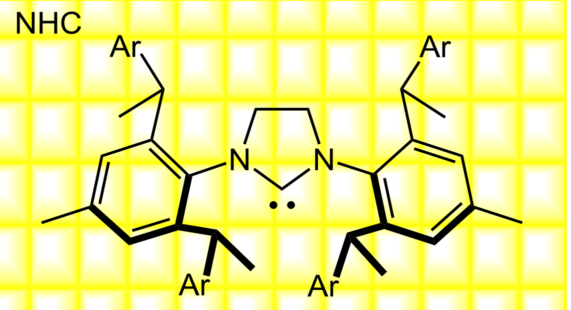
Direct Arylation Strategy



Y = $B(OH)_2$, Bneo
Bpin, or BF_3K

X = Br, Cl, or OTf

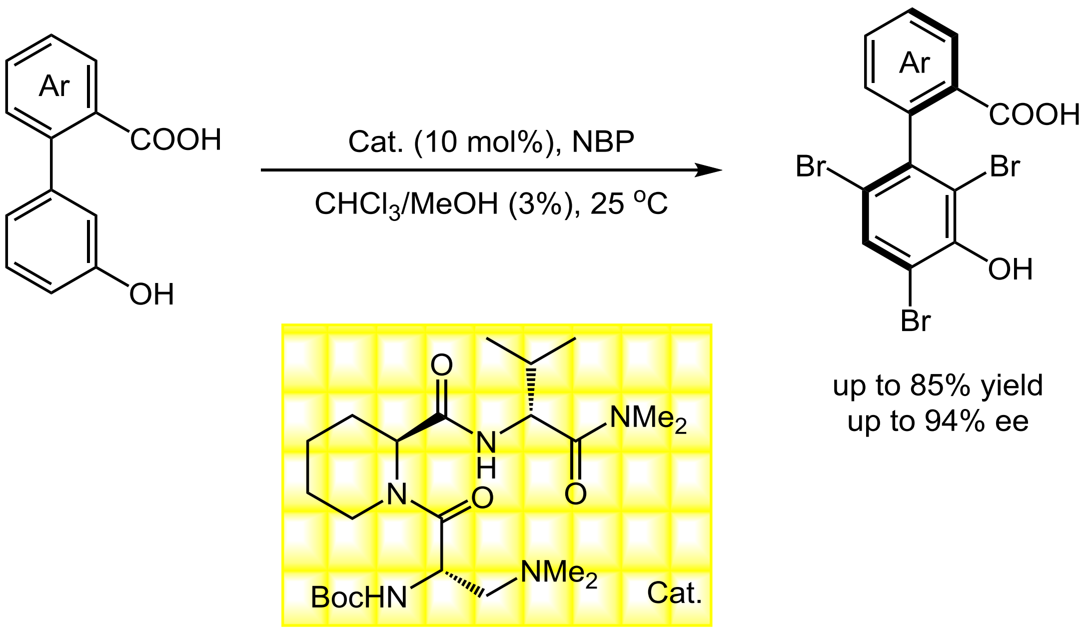
up to 99% yield
up to 99% ee



Ar = 3,5-^{t}Bu-C_6H_3

Shi, S.-L. *et al*. *J. Am. Chem. Soc*. **2019**, *141*, 14938.

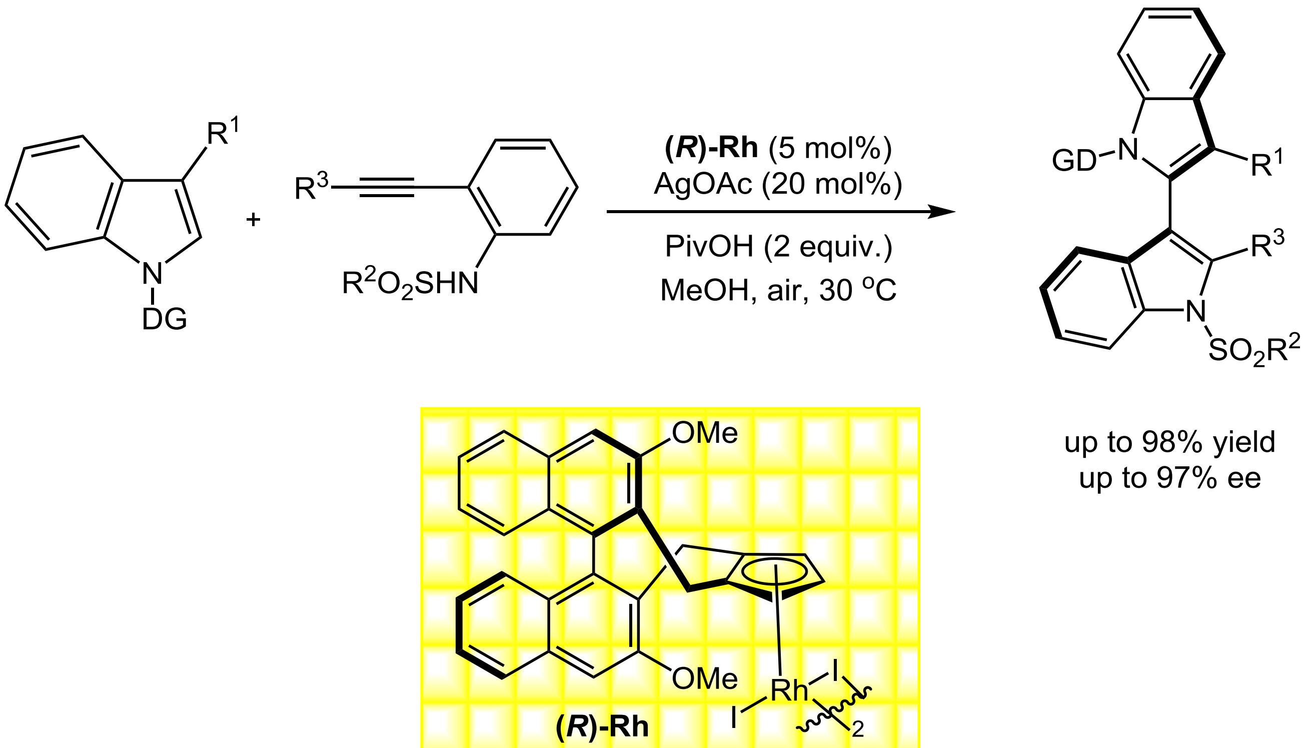
Dynamic Kinetic Resolution Strategy



up to 85% yield
up to 94% ee

Miller, S. J. *et al. Science* **2010**, *328*, 1251.

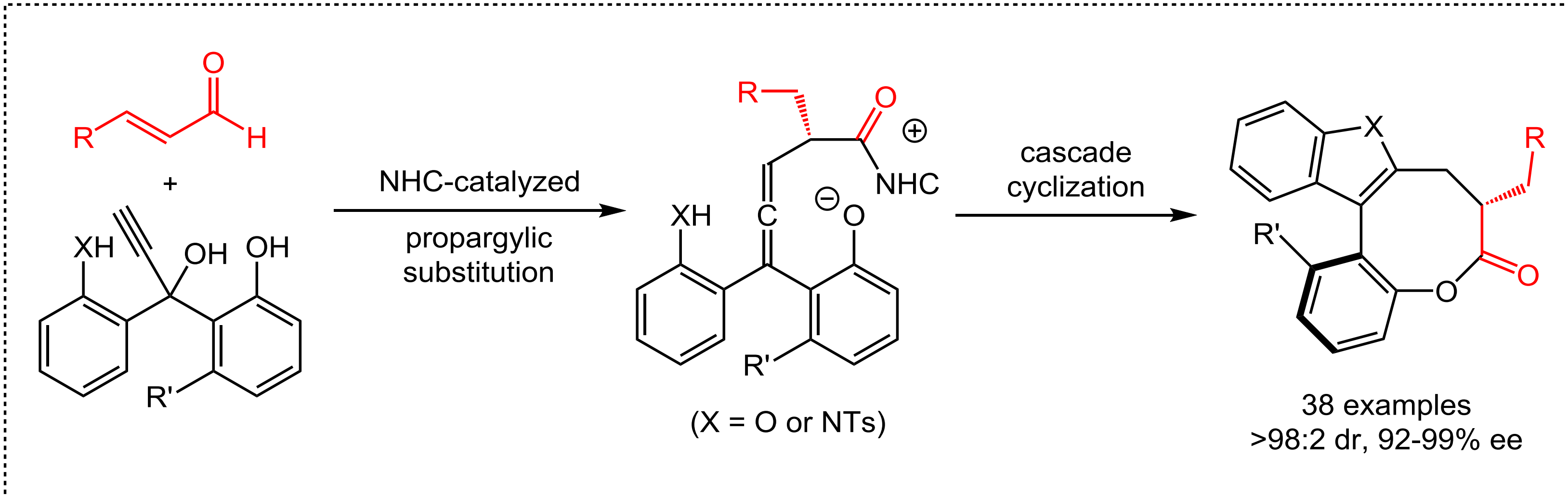
Construction of an Aromatic Ring



up to 98% yield
up to 97% ee

Li, X. *et al*. *J. Am. Chem*. Soc. **2019**, *141*, 9527.

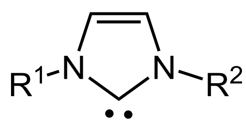
Construction of an Aromatic Ring

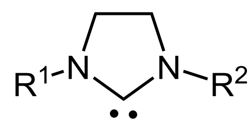


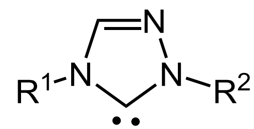
Zhao, Y. *et al*. *J. Am. Chem. Soc.* **2019**, *141*, 17062.

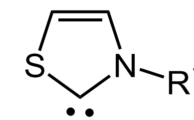
N-Heterocyclic Carbenes

General structures of *N*-heterocyclic carbens

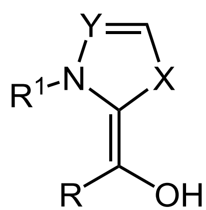

imidazolylidene

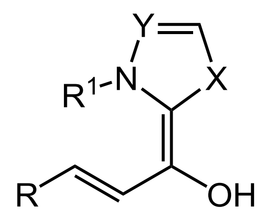

imidazolinylidene

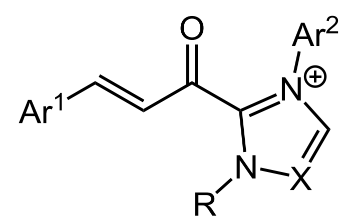

triazolylidene


thiozolylidene

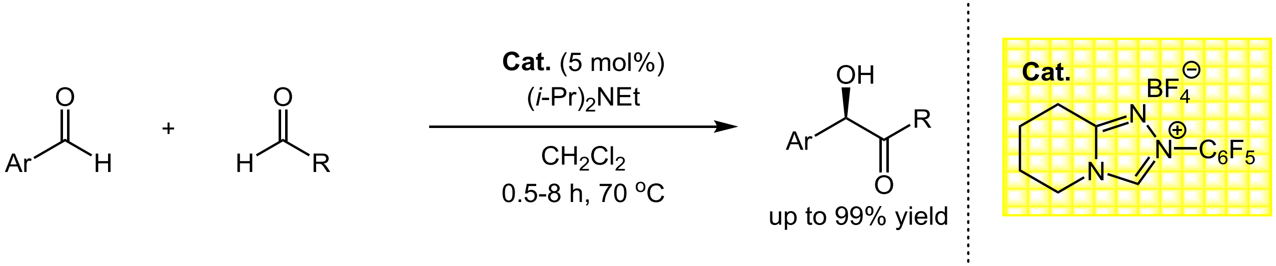
Common reaction intermediates

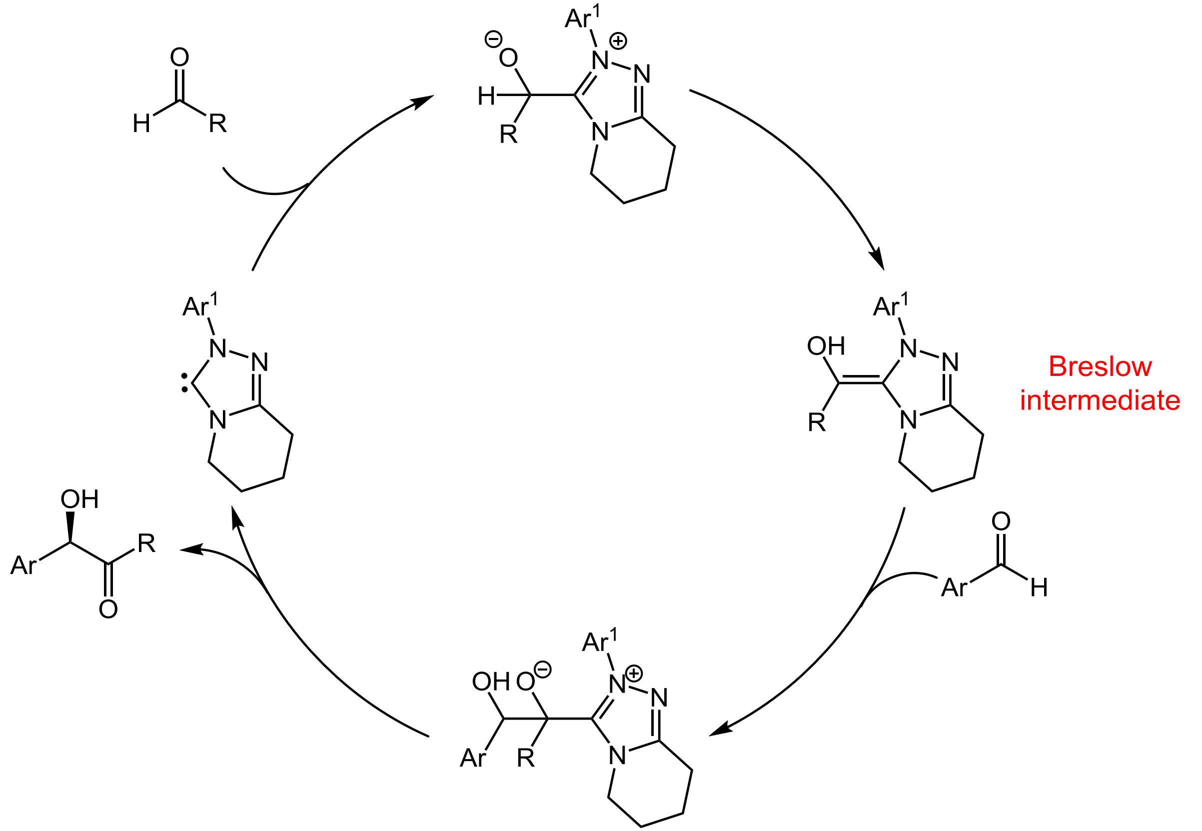

Breslow intermediates


extended
Breslow intermediates


α,β-unsaturated
acylazolium intermediates

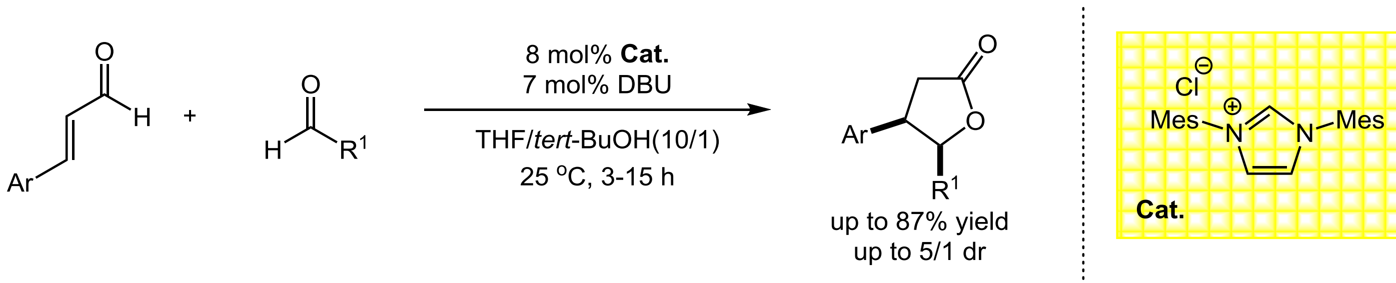
Breslow Intermediates

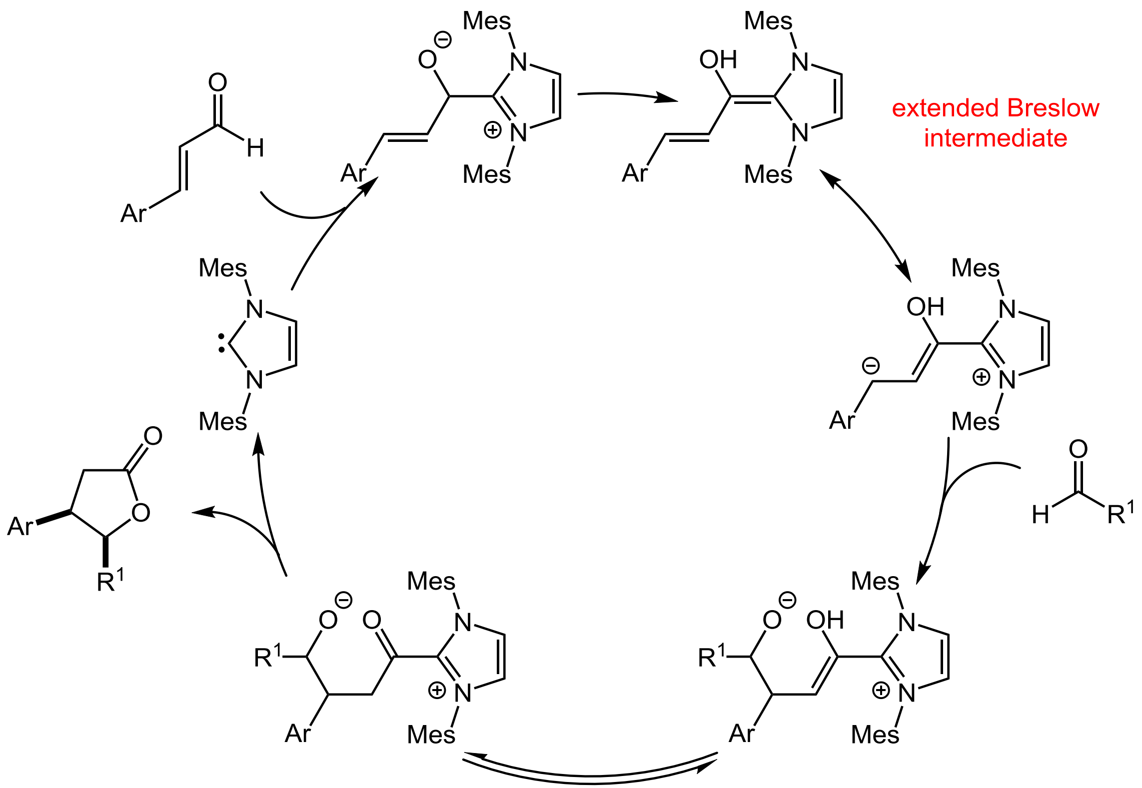




Gravel, M. *et al*. *J. Am. Chem. Soc*. **2004**, *136*, 7539.

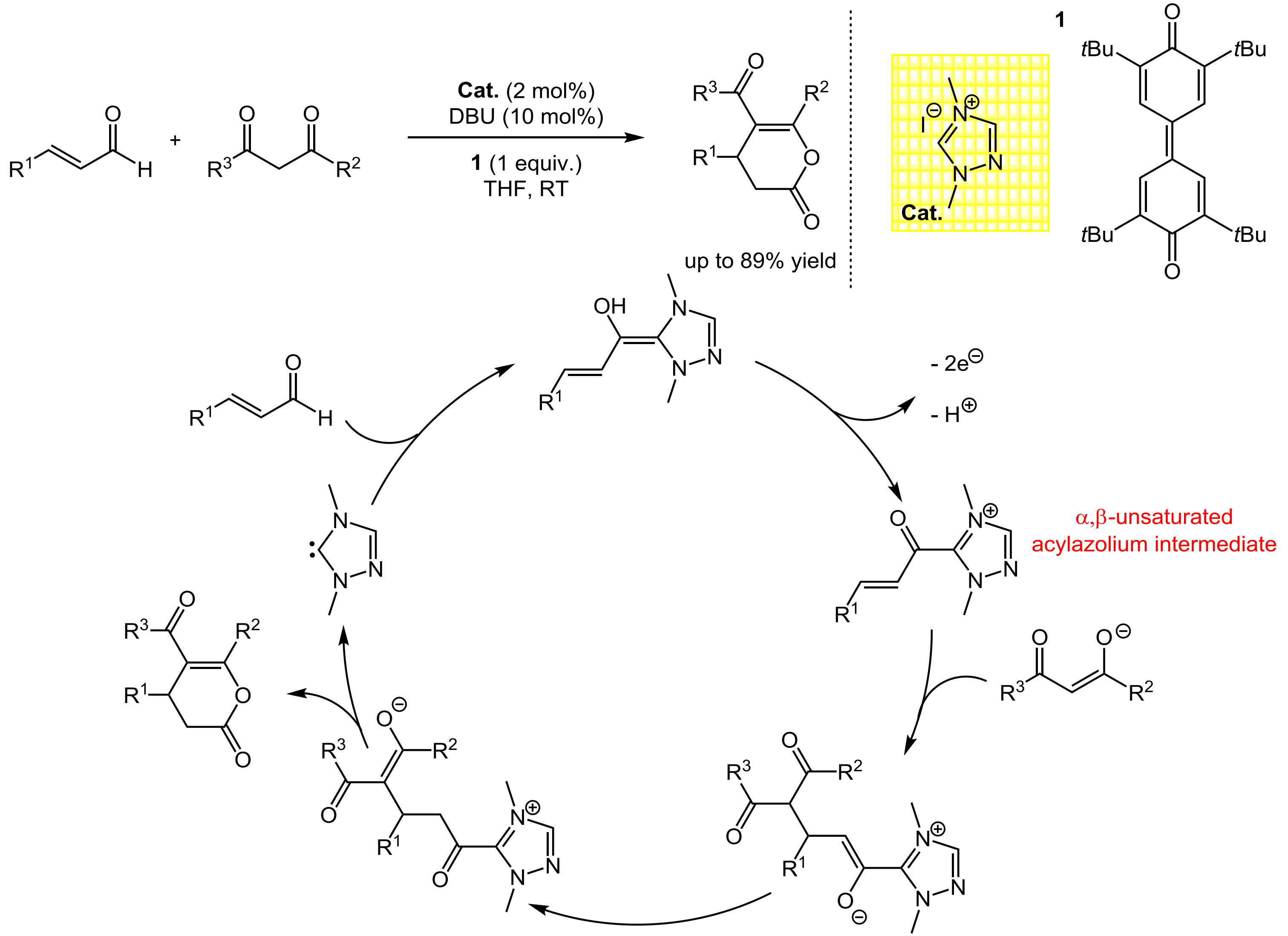
Extended Breslow Intermediates





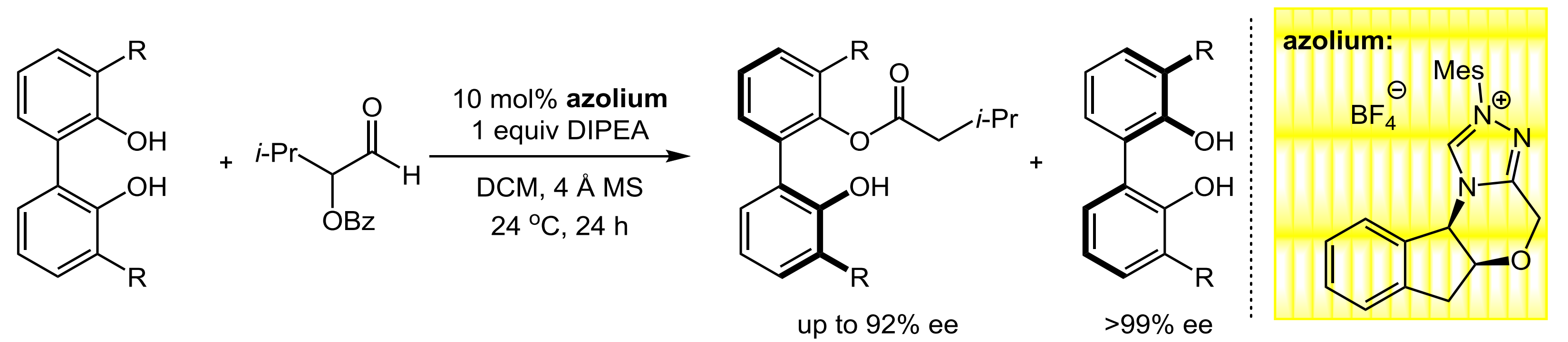
Bode, J. W. *et al*. *J. Am. Chem. Soc*. **2004**, *126*, 14370.

α,β-Unsaturated Acylazolium Intermediates

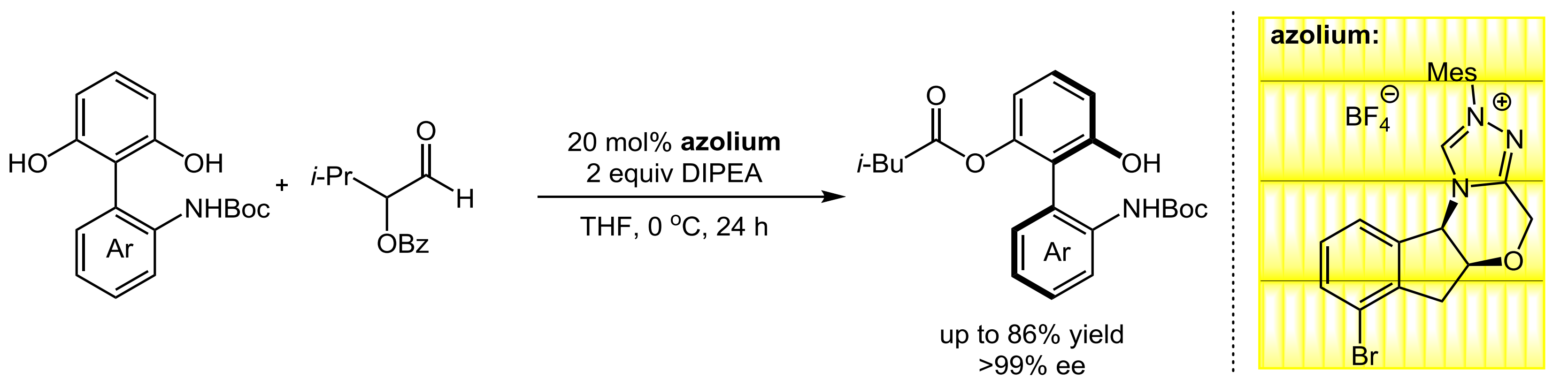


Studer, A. *et al*. *Angew. Chem. Int. Ed*. **2010**, *49*, 9266.

Previous Work

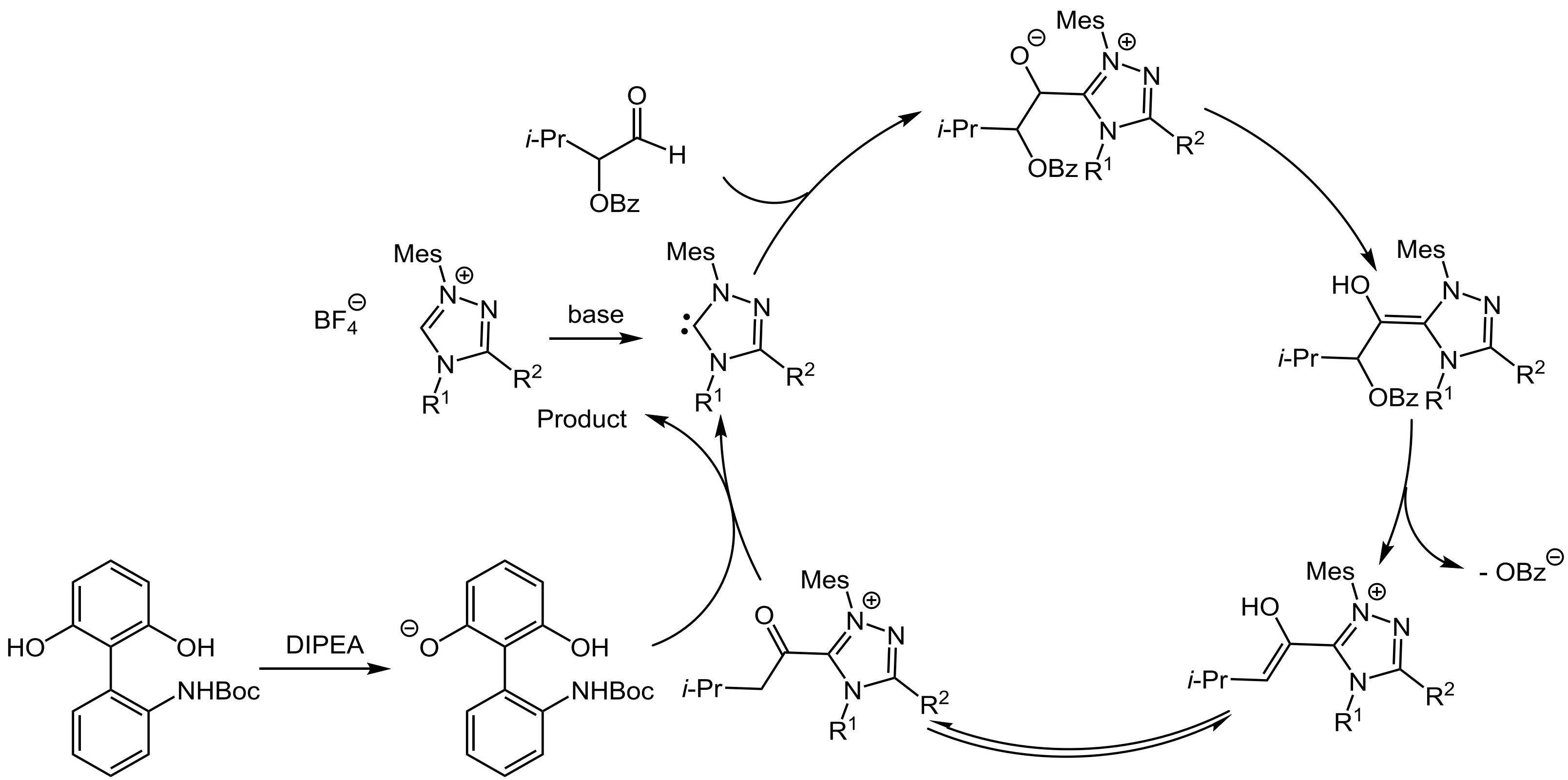


Zhao, Y. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041.



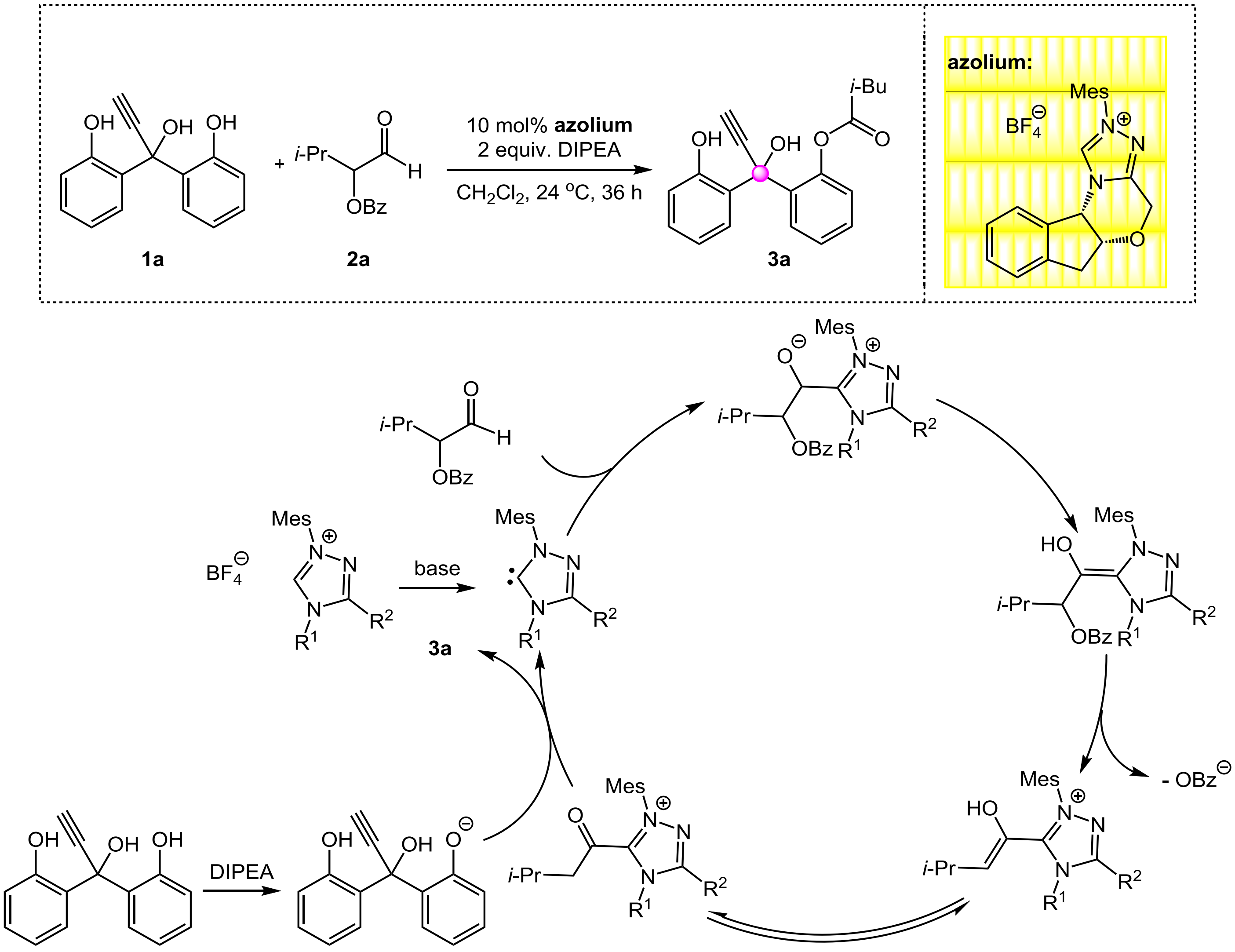
Zhao, Y. *et al*. *Org. Lett*. **2019**, *21*, 6169.

Proposed Mechanism

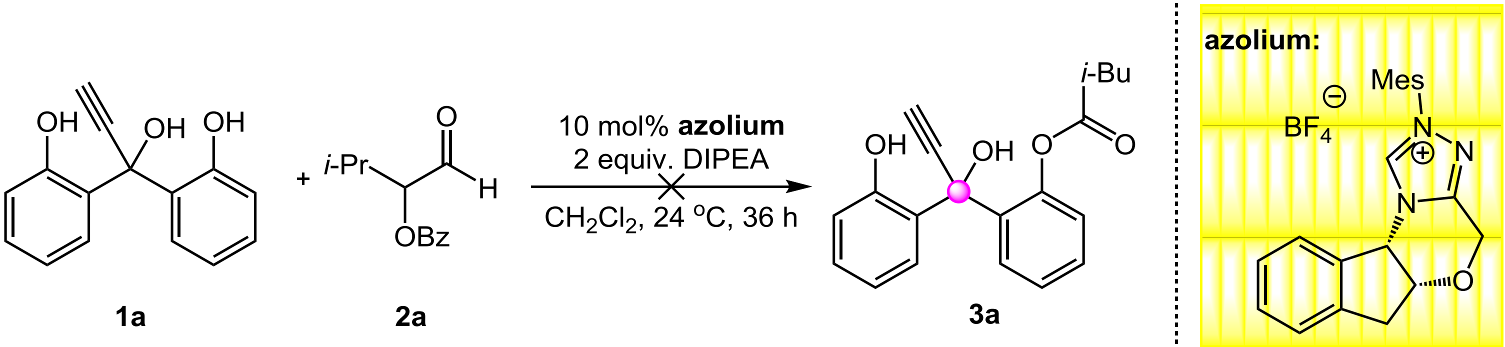


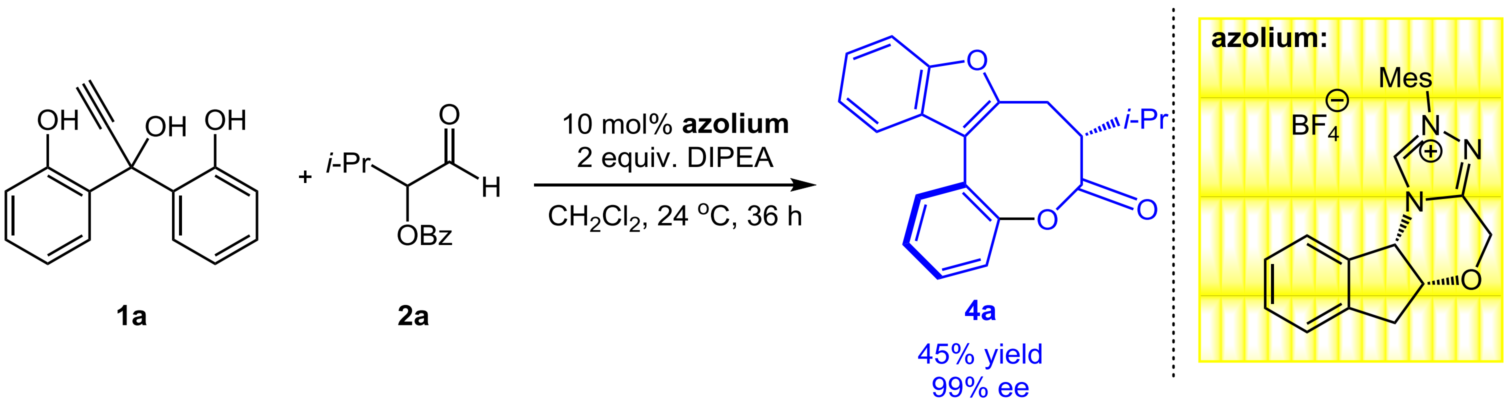
Zhao, Y. *et al*. *Org. Lett*. **2019**, *21*, 6169.

Reaction Assumption



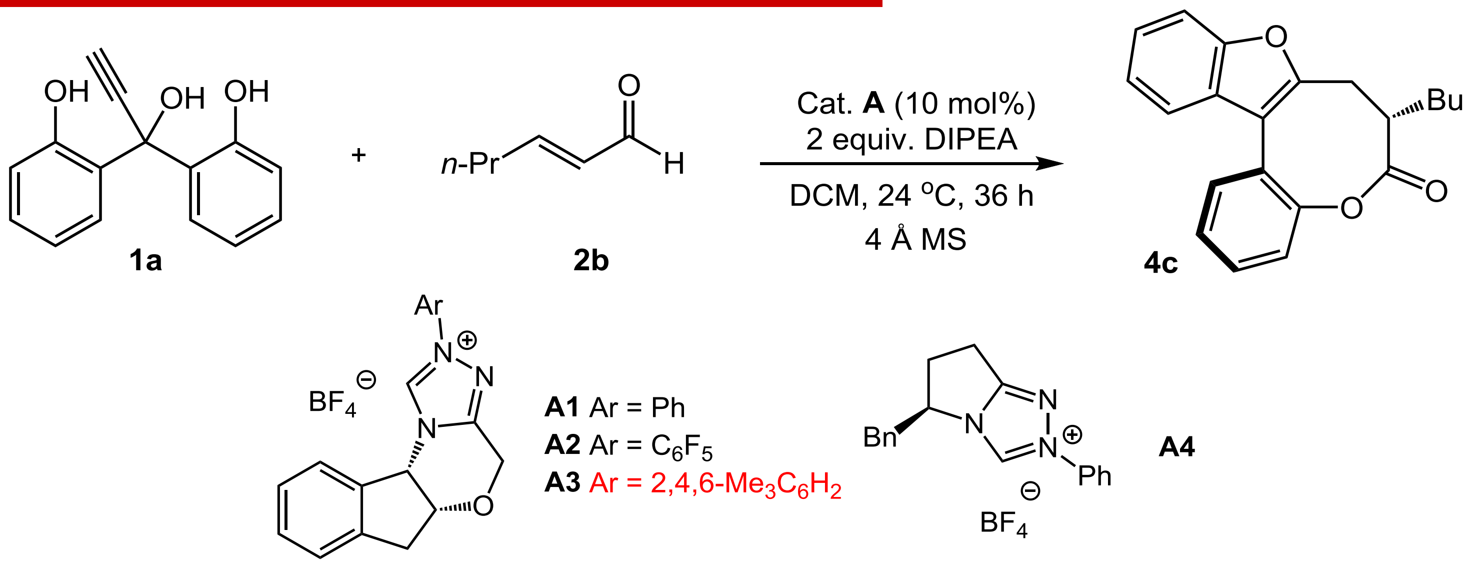
Reaction Assumption





Zhao, Y. *et al*. *J. Am. Chem. Soc.* **2019**, *141*, 17062.

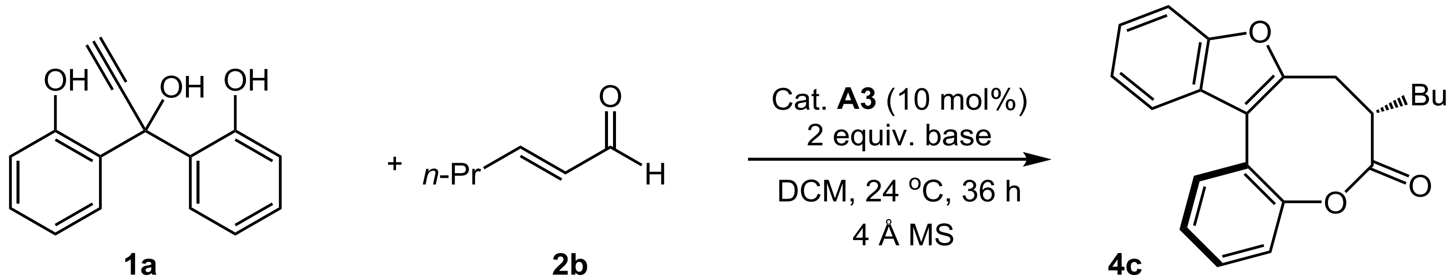
Optimization of Reaction Conditions



[a]Entry	**Cat.**	Yield (%)[b]	Ee (%)[c]
1	**A1**	76	90
2	**A2**	72	80
3	**A3**	85	99
4	**A4**	trace	n.d.

[a]Reaction were performed with **1a** (0.15 mmol,1.0 equiv.), **2b** (0.60 mmol,4.0 equiv.), Cat. **A** (10 mol%), DIPEA (0.30 mmol, 2.0 equiv) and 4 Å molecular sevie (100 mg) in DCM (2.0 mL) at 24 °C for 36 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. n.d. = not determined.

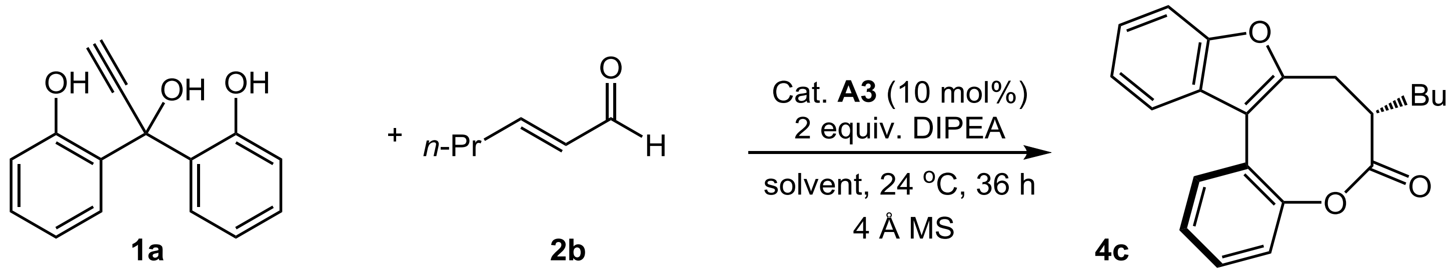
Optimization of Reaction Conditions



[a]Entry	Base	Yield (%)[b]	Ee (%)[c]
1	DIPEA	85	99
2	NaOAc	trace	n.d.
3	Cs_2CO_3	trace	n.d.

[a]Reaction were performed with **1a** (0.15 mmol,1.0 equiv.), **2b** (0.60 mmol,4.0 equiv.), cat. **A3** (10 mol%), base (0.30 mmol, 2.0 equiv) and 4 Å molecular sevie (100 mg) in DCM (2.0 mL) at 24 °C for 36 h. [b]Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. n.d. = not determined.

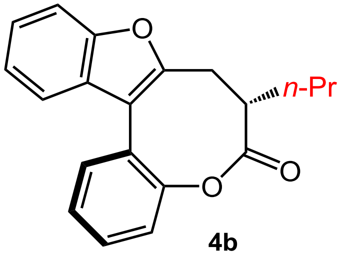
Optimization of Reaction Conditions



[a]Entry	Solvent	Yield (%)[b]	Ee (%)[c]
1	DCM	85	99
2	Toluene	70	97
3	$CHCl_3$	70	98
4	THF	65	98

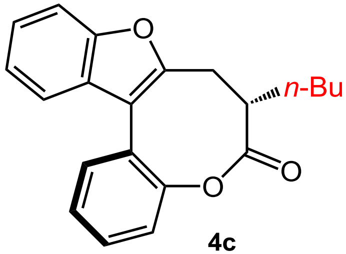
[a]Reaction were performed with **1a** (0.15 mmol,1.0 equiv.), **2b** (0.60 mmol,4.0 equiv.), Cat. **A3** (10 mol%), DIPEA (0.30 mmol, 2.0 equiv) and 4 Å molecular sevie (100 mg) in solvent (2.0 mL) at 24 °C for 36 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

Substrate Scope



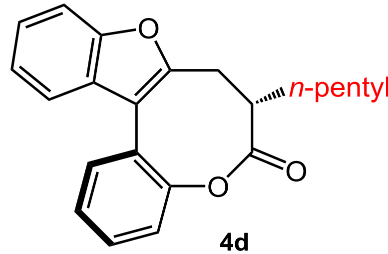
4b

60% yield, 99% ee



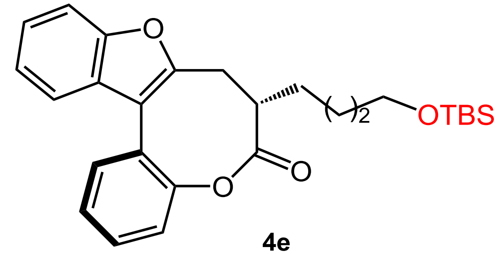
4c

85% yield, 99% ee



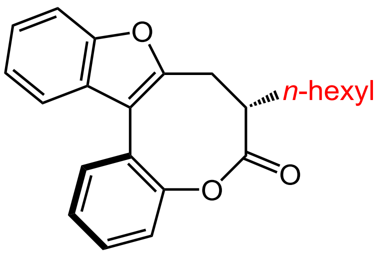
4d

84% yield, 99% ee



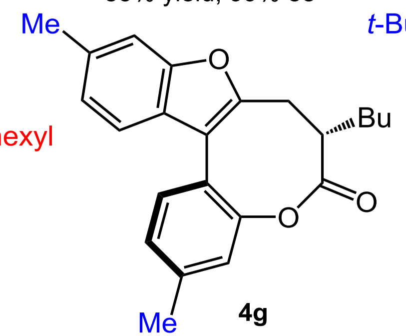
4e

56% yield, 99% ee



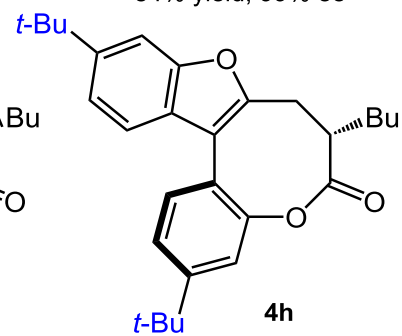
4f

50% yield, 99% ee



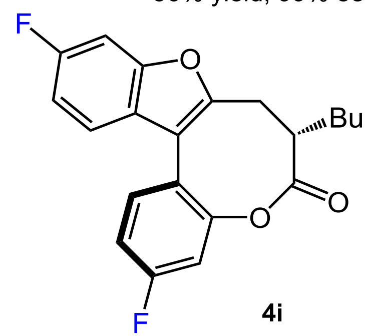
4g

70% yield, 99% ee



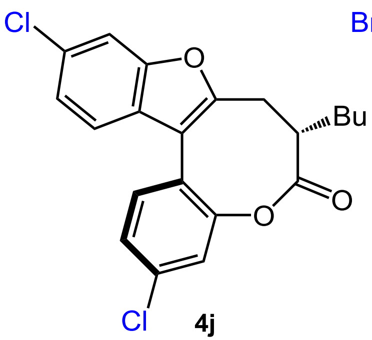
4h

75% yield, 99% ee



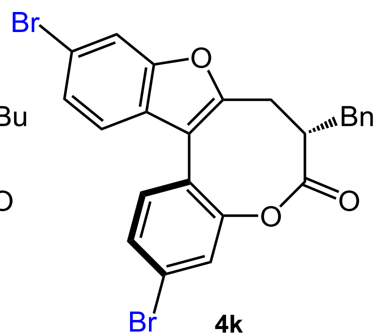
4i

56% yield, 97% ee



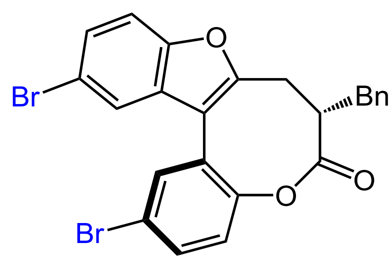
4j

55% yield, 97% ee



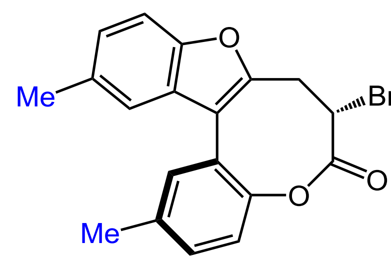
4k

51% yield, 97% ee



4l

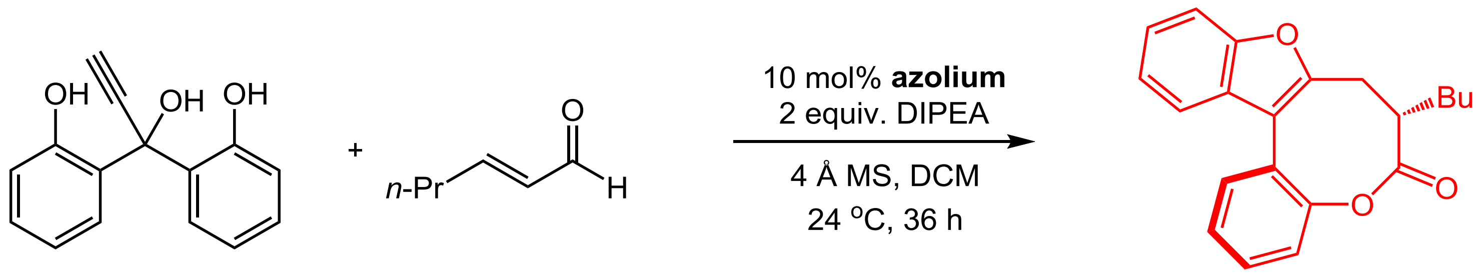
42% yield, 98% ee



4m

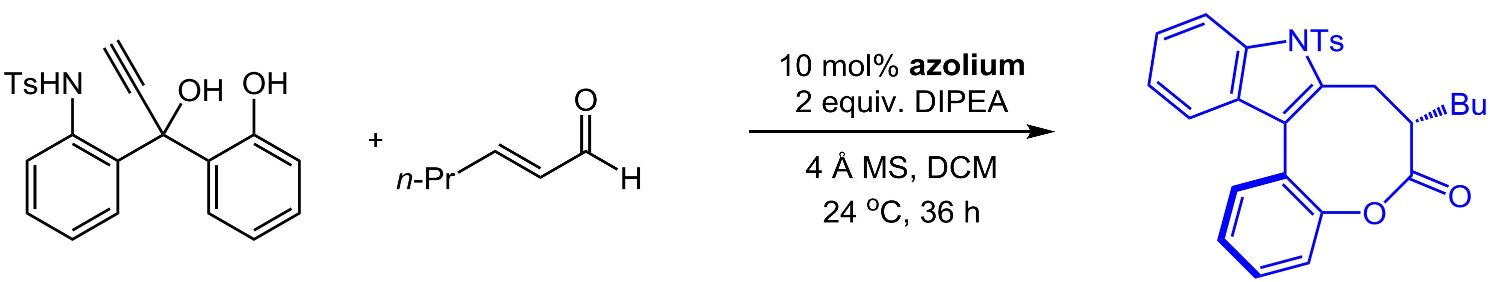
71% yield, 99% ee

Reaction Assumption



1a **2b** **4c**

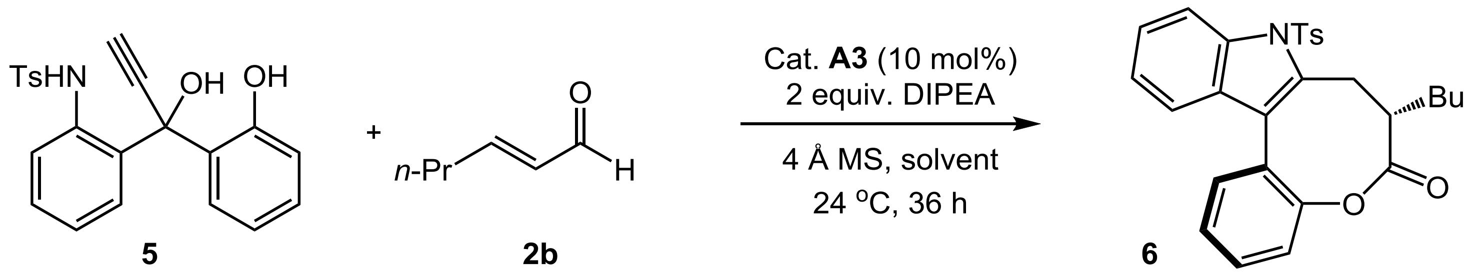
85% yield, 99% ee



5 **2b** **6**

20% yield, 97% ee

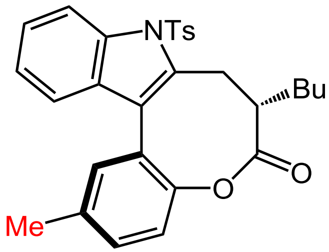
Optimization of Reaction Conditions



[a]Entry	Solvent	Yield (%)[b]	Ee (%)[c]
1	DCM	20	97
2	Toluene	17	96
3	THF	40	94
4	Dioxane	28	95
5	CH_3CN	trace	n.d.

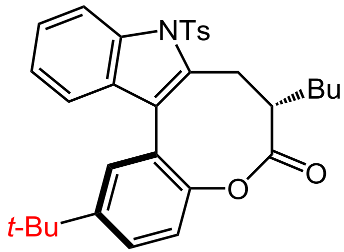
[a]Reaction were performed with **5** (0.15 mmol,1.0 equiv.), **2b** (0.60 mmol,4.0 equiv.), Cat. **A3** (10 mol%), DIPEA (0.30 mmol, 2.0 equiv) and 4 Å molecular sevie (100 mg) in solvent (2.0 mL) at 24 °C for 36 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. n.d. = not determined.

Substrate Scope



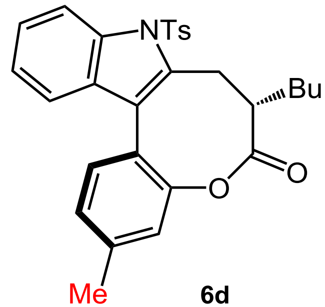
6b

60% yield, 97% ee



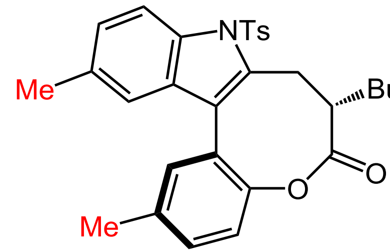
6c

68% yield, 97% ee



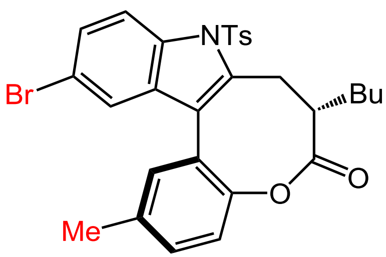
6d

60% yield, 95% ee



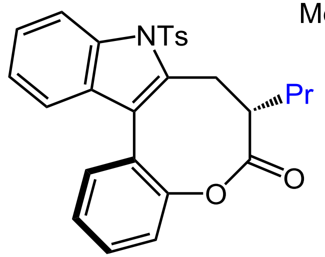
6e

62% yield, 97% ee



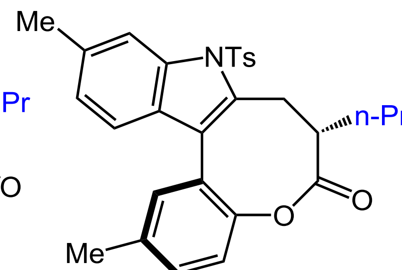
6f

40% yield, 94% ee



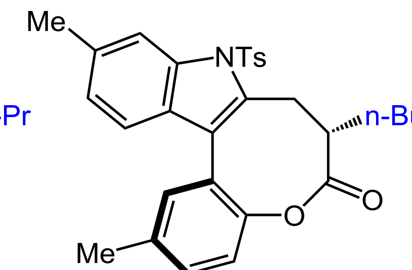
6g

56% yield, 92% ee



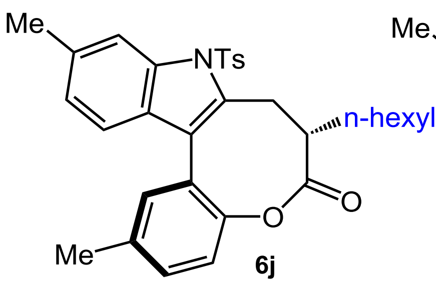
6h

58% yield, 99% ee



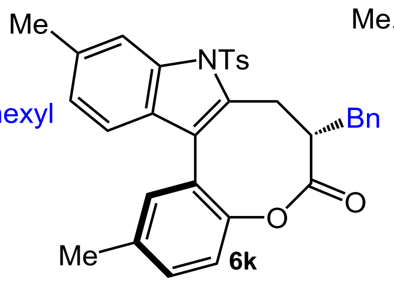
6i

70% yield, 98% ee



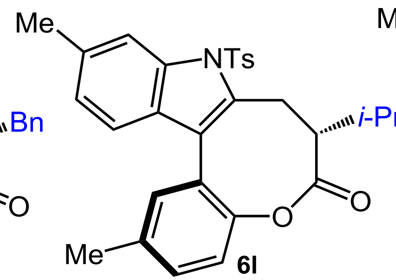
6j

40% yield, 99% ee



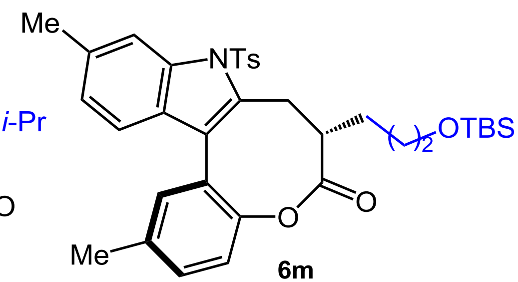
6k

25% yield,98% ee



6l

40% yield, 99% ee

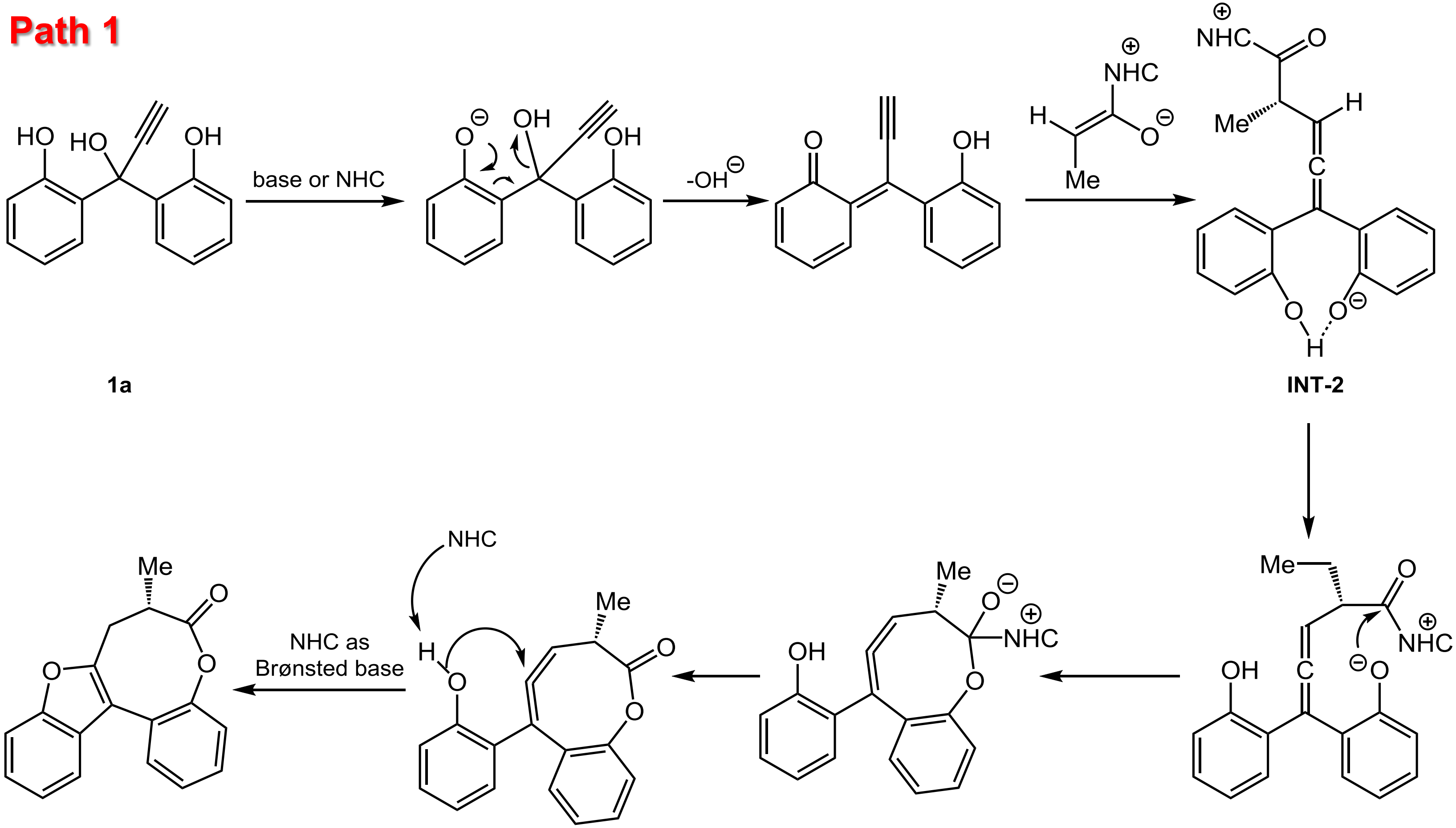


6m

45% yield, 98% ee

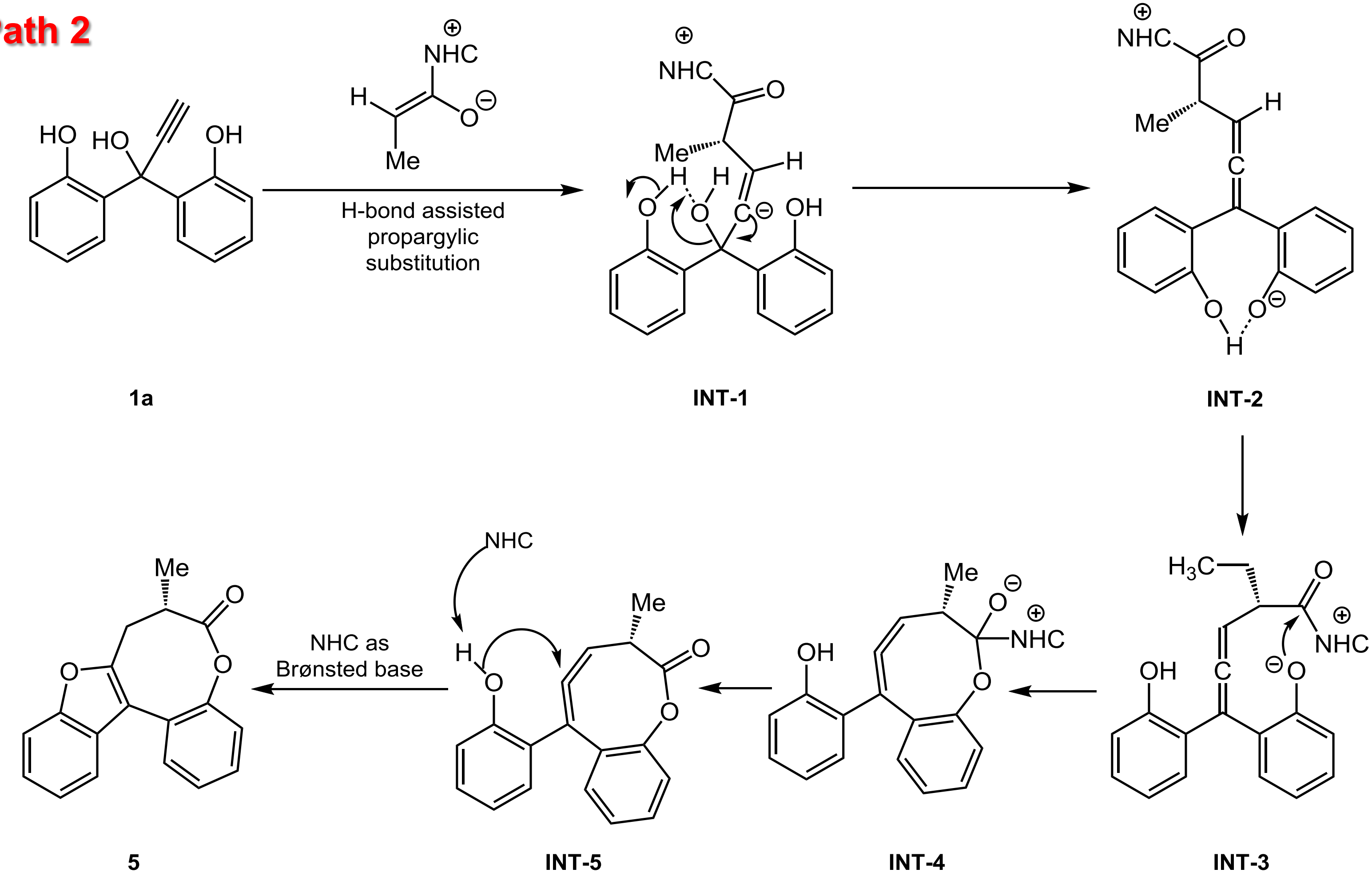
Proposed Mechanism

Path 1

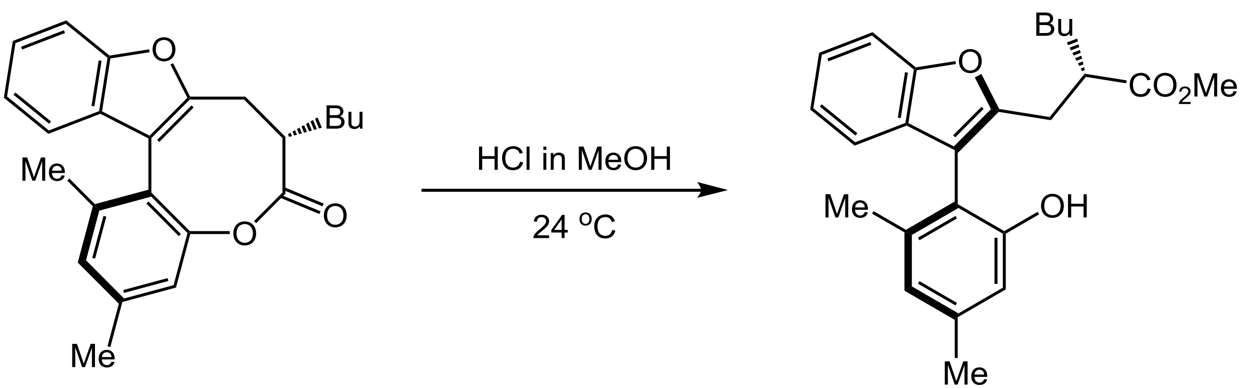


Proposed Mechanism

Path 2



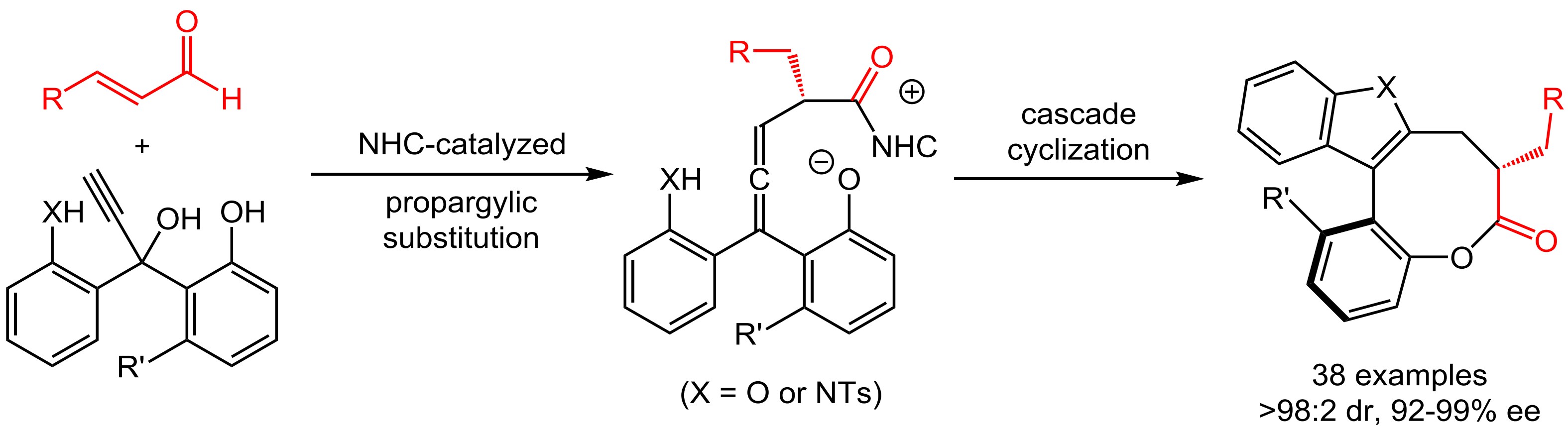
Product Transformation



91% ee

98% yield
91% ee

Summary



- NHC-catalyzed propargylic substitution & cyclization;
- Bridged biaryls with an eight-membered lactons;
- Excellent control of both axial & central chirality.

Zhao, Y. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 17062.

The First Paragraph

Writing thought

Significant role of axial chiral biaryl compounds

↓

Limitations of traditional axial chiral biaryl compounds

↓

Proposing author's methods and advantages by comparing past methods

The First Paragraph

The significance of axially chiral biaryls has been widely recognized in catalysis and drug delivery, due to their exceptionally compact architectures and promising pharmacological profiles. An important subclass is bridged biaryls, which bear an additional linkage between the two arens and often with stereocenters. These structures are of high natural abundance, as exemplified by the anti-leukemic lignan (-)-steganacin and the tubin inhibitor (-)-rhazinilam. Notably, these compounds are structurally related to helicenes, a significant class of helically chiral, *ortho*-condensed polycyclic compounds.

The Last Paragraph

Writing thought

Summarize the work

↓

Propose the advantages of this method

↓

The next plan of the team and potential challenge

The Last Paragraph

In summary, we have developed a catalytic, diastereo- and atropoenantioselective synthesis of bridged biaryls from readily available starting materials. This NHC-catalyzed transformation proceeds through a propargylic substitution-two-directional cyclization cascade and delivers the products with uniformly excellent control of axial and central chirality. The development of new catalytic procedures to access other challenging structures bearing different types of chirality is currently under investigation.

Representative Examples

Due to their significant utility, extensive efforts were devoted to the atropoenantioselective synthesis of axially chiral biaryls.

Previous investigation in our laboratory has led to the development of NHC-catalyzed enantioselective acylative kinetic resolution of alcohols/phenols as well as desymmetrization of meso-bisphenols.

In addition to desymmetrization of symmetrical triols, we were curious whether a chemoselective cascade cyclization could be achieved for unsymmetrical racemic triols as well.

To the best of our knowledge, the direct catalytic synthesis of bridged biaryls with simultaneous control of axial and central chirality remains elusive in the literature.

Acknowledgement

Thanks
for your attention