

Enantioselective Reactions of Oxocarbenium Ions

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- Date: 01/19/2016

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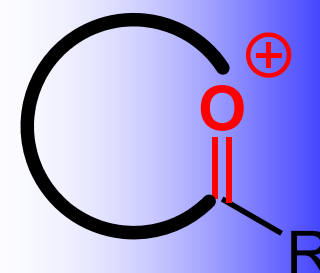
Asymmetric reduction reactions

Summary

Introduction

Oxocarbenium ions

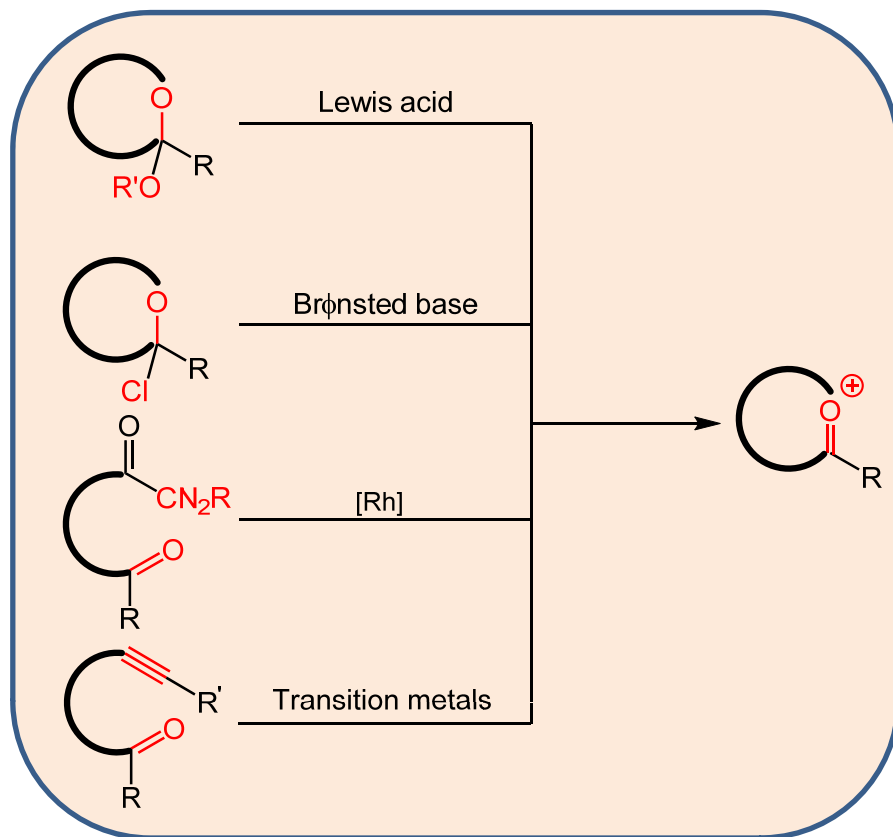
An oxocarbenium ion is a canonical form of a carbocation, **real or hypothetical**, which places a formal positive charge on an oxygen atom. They are common transition states for the hydrolysis of glycosidic bonds, and **are a commonly used strategy for chemical glycosylation**. These ions have since been proposed as transition states of a wide range of chemical transformations, and **have been utilized in the total synthesis of several natural products**.



From wikipedia

Introduction

Oxocarbenium ions: formation & challenge

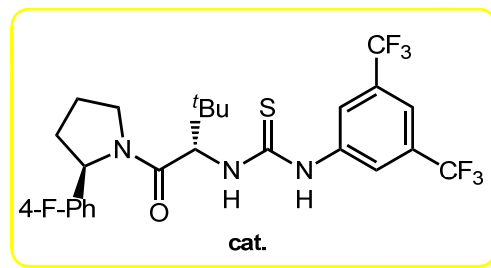
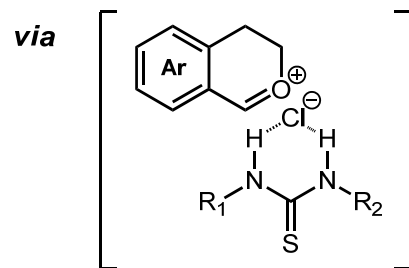
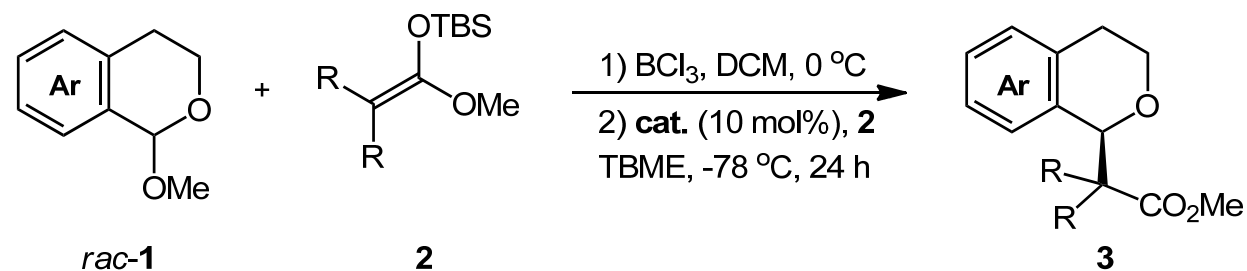


Challenges in asymmetric reactions

- ◆ Highly reactive intermediates
- ◆ Aromatic planar structure
- ◆ Lack of coordination sites

Asymmetric addition reactions

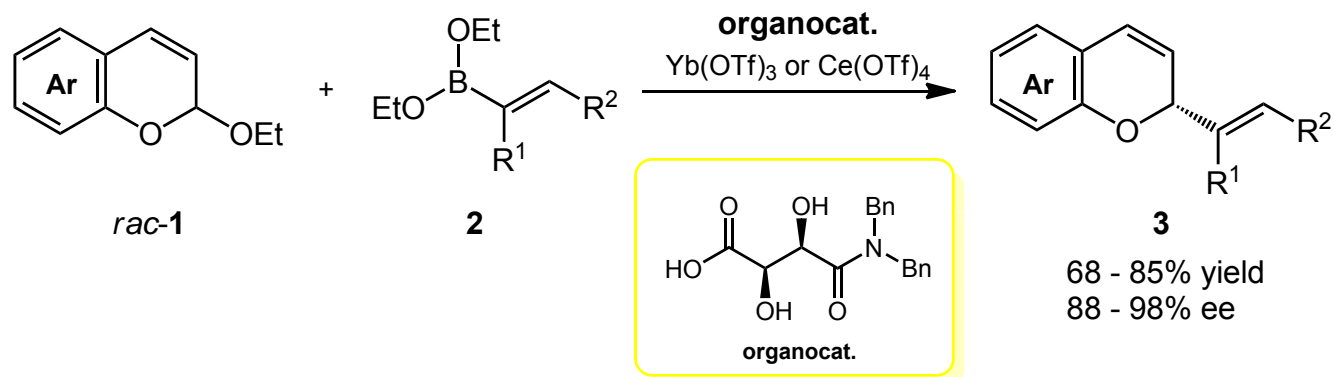
Thiourea-catalyzed addition of enolates



Jacobsen, E. N. *et al.* *J. Am. Chem. Soc.* **2008**, *130*, 7198.

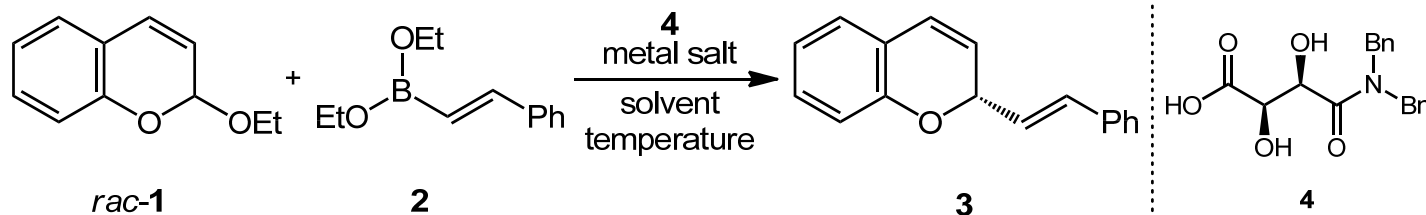
Asymmetric addition reactions

Chiral BA/LA -catalyzed addition of boronates



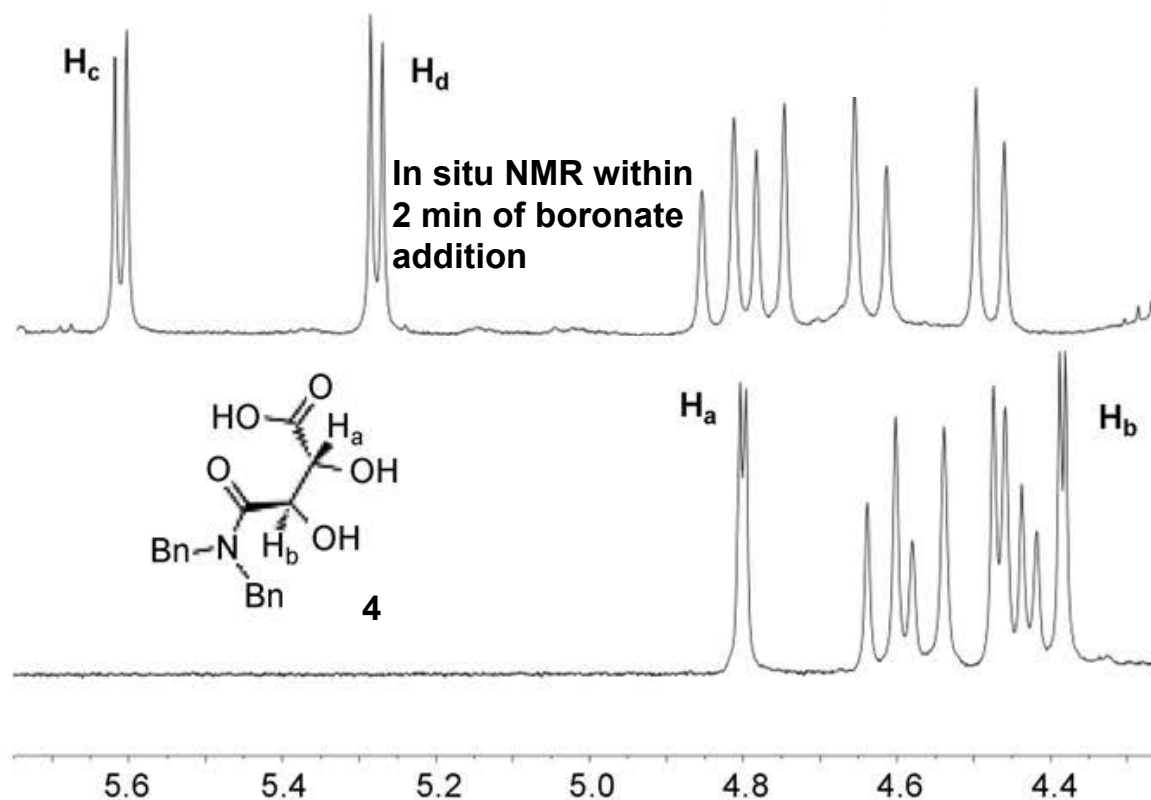
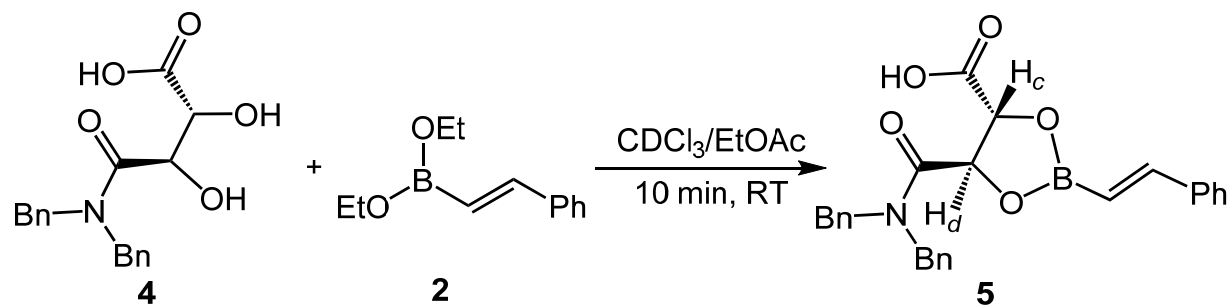
Schaus, S. E. *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 7096.

Optimization of reaction conditions

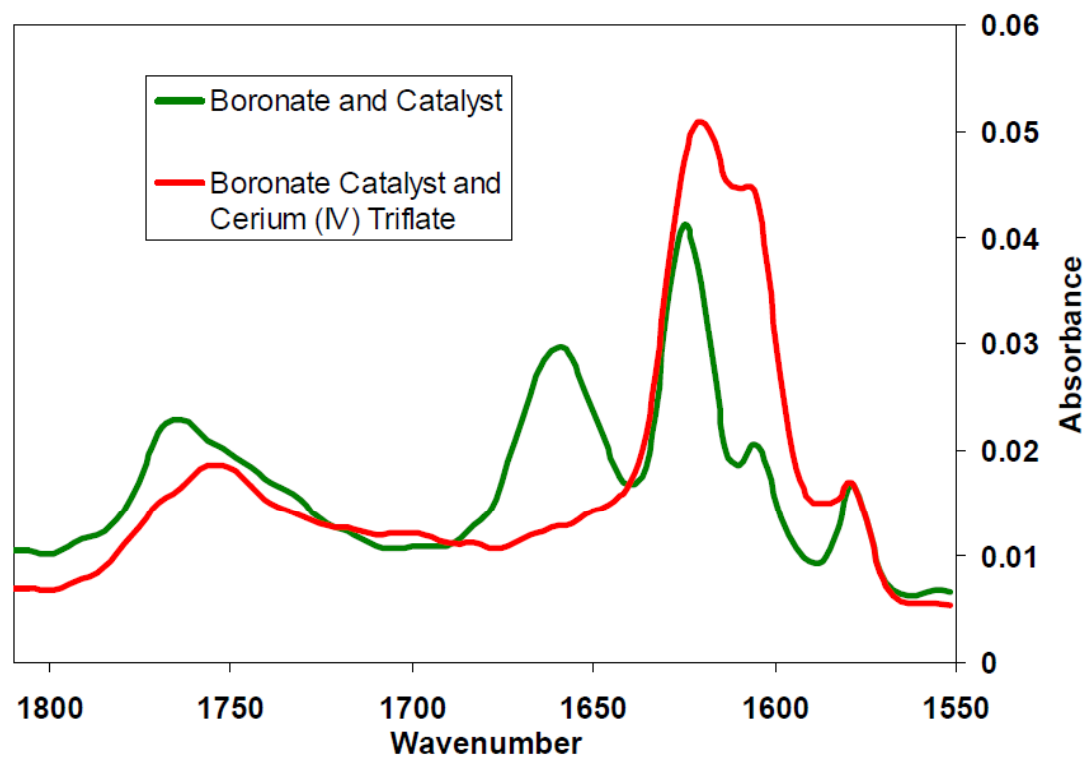
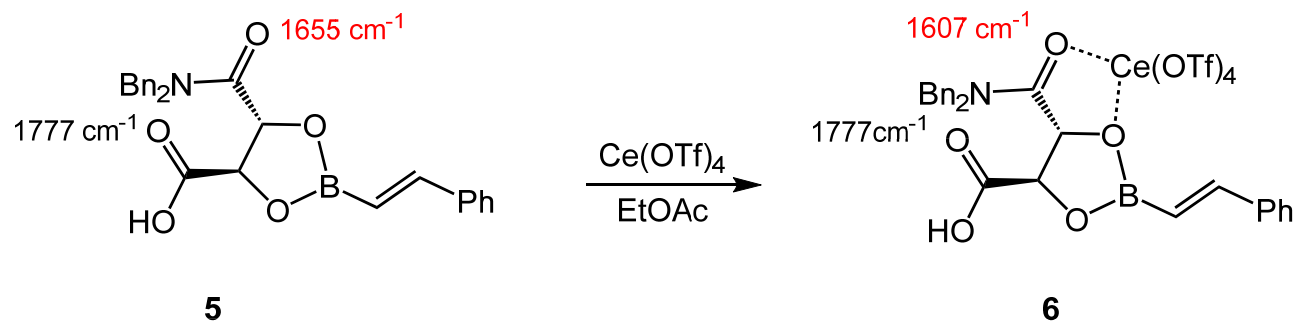


Entry	4 (mol%)	Metal salt	Mol%	Solvent	T (°C)	Yield (%)	Ee (%)
1	30	--	--	EtOAc	20	44	66
2	30	--	--	Toluene	20	72	60
3	30	--	--	THF	20	< 5	ND
4	30	--	--	DCM	20	51	64
5	30	Zn(OTf) ₂	30	EtOAc	20	45	68
6	5	Zn(OTf) ₂	4.5	EtOAc	20	54	88
7	5	Sc(OTf) ₃	4.5	EtOAc	20	18	32
8	5	Ce(OTf) ₄	4.5	EtOAc	20	65	95
9	5	Ce(OTf) ₄	4.5	EtOAc	-20	75	95
10	5	Ce(OTf) ₄	4.5	EtOAc	-40	83	98
11	5	Yb(OTf) ₃	4.5	EtOAc	-40	87	97

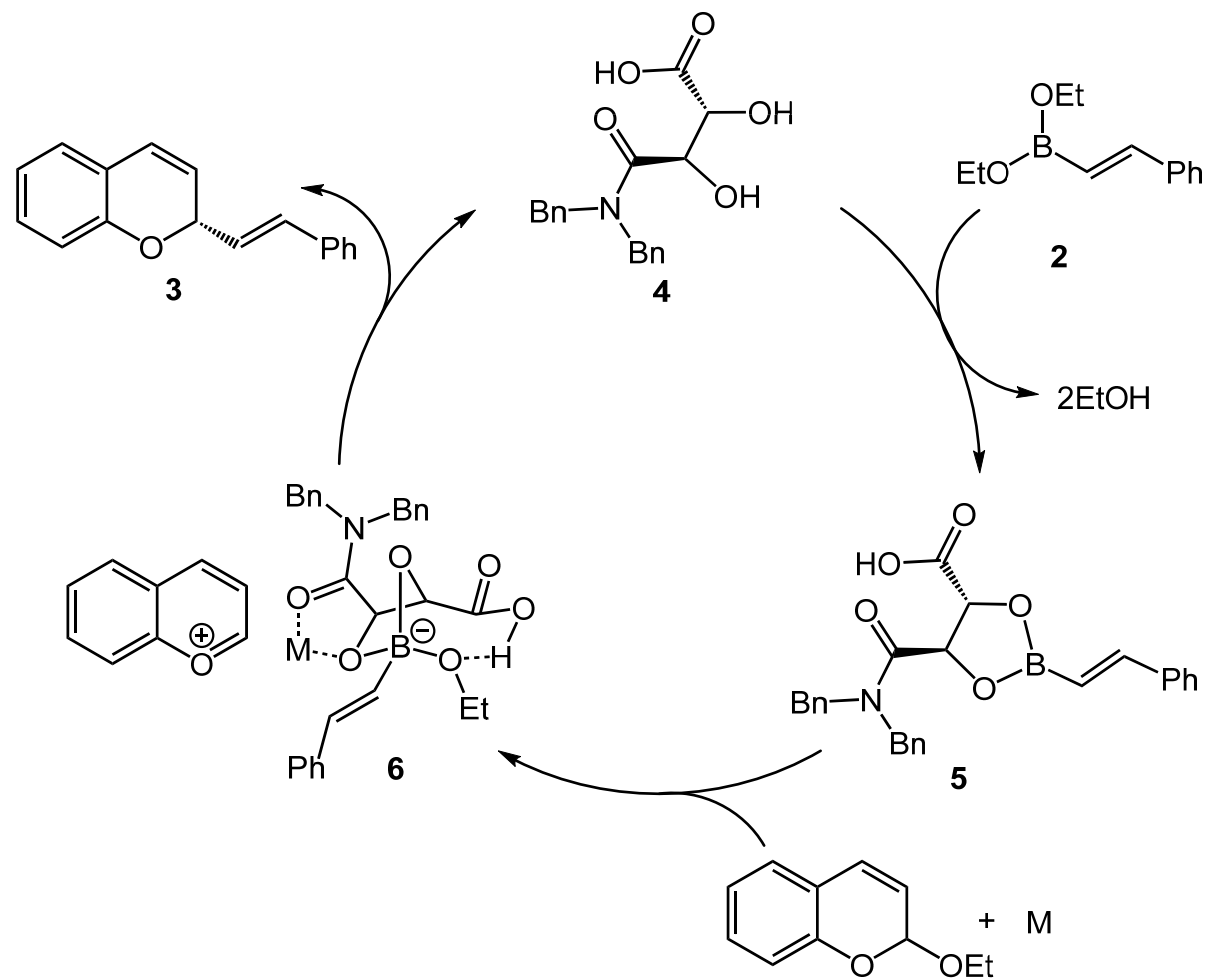
Exploration of reaction mechanism



Exploration of reaction mechanism



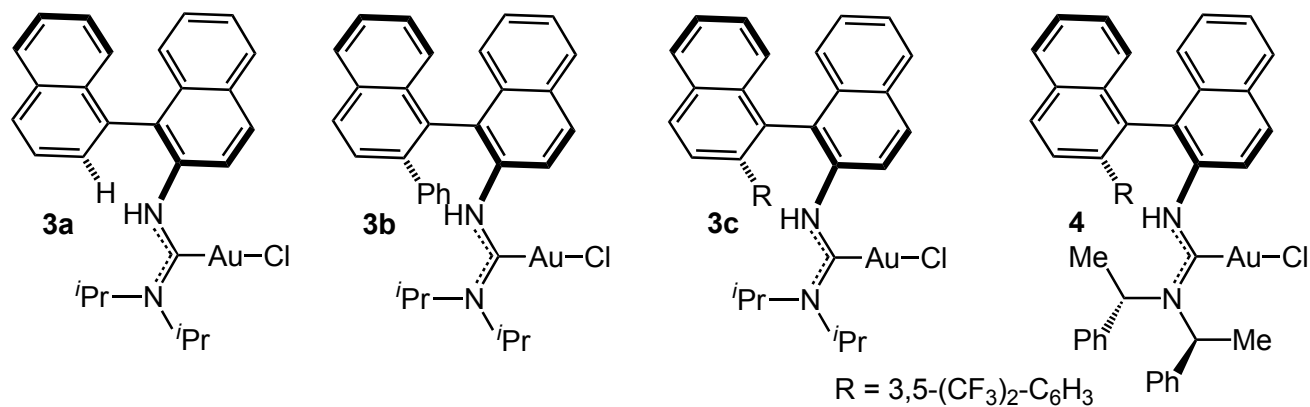
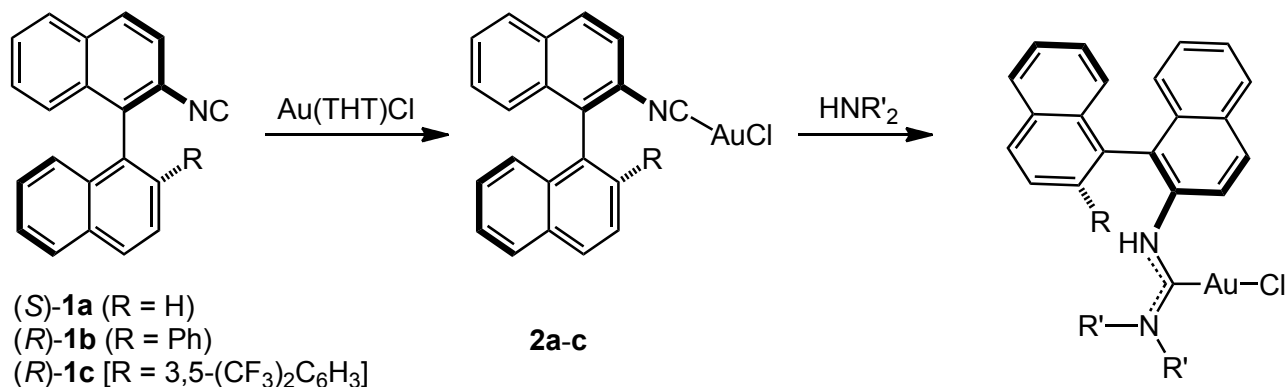
Proposed reaction mechanism



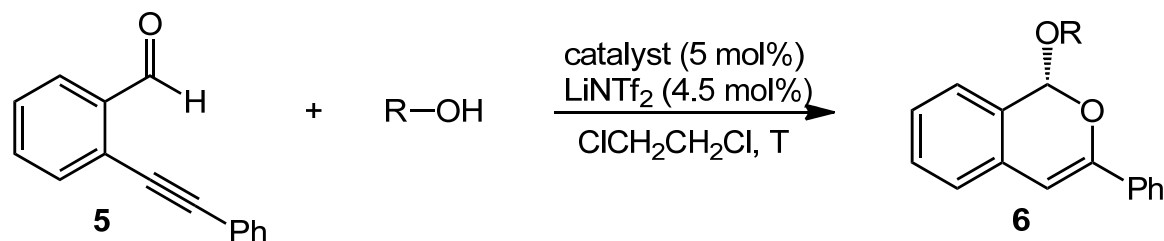
Asymmetric addition reactions

Au(I)-catalyzed tandem acetalization/cycloisomerization

Synthesis of Au(I) acyclic diaminocarbene catalyst



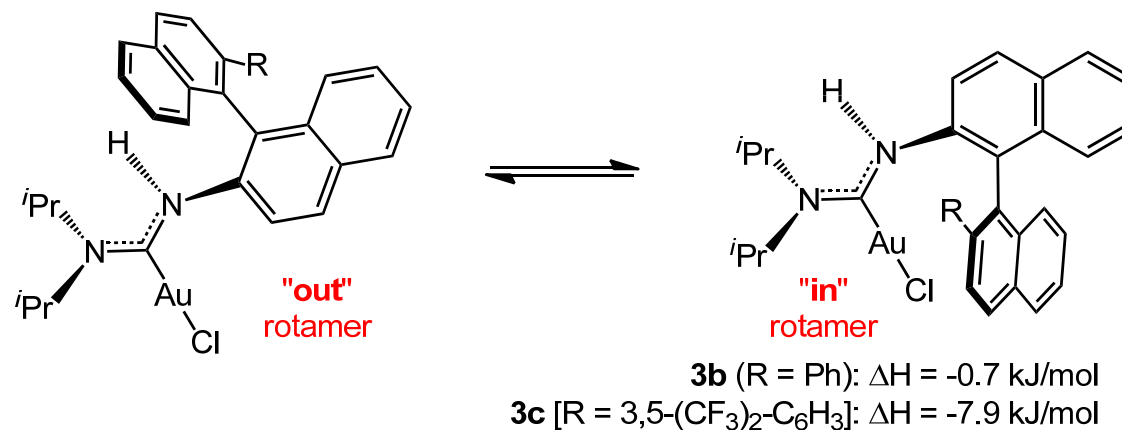
Catalytic alkynybenzaldehyde cyclization



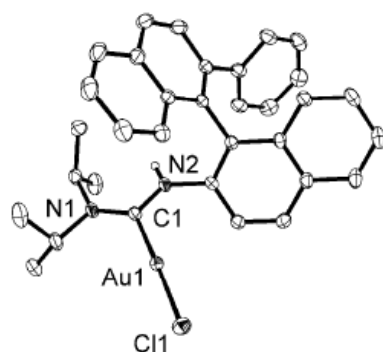
Entry	R	Catalyst	T (°C)	t (h)	Yield (%)	Ee (%)
1	<i>i</i> Pr	3a	25	37	12	8
2	<i>i</i> Pr	3b	25	36	28	61
3	<i>i</i> Pr	3c	25	12	68	84
4	^c Hex	3c	60	36	65	98
5	^t Bu	3c	60	36	66	96
6	benzyl	3c	60	28	68	98
7	ⁿ Oct	3c	60	36	87	99
8	ⁿ Bu	3c	60	36	12	ND
9	ⁿ Pr	3c	25	36	5	69
10	ⁿ Bu	4	60	36	59	92
11	ⁿ Pr	4	25	36	67	89
12	<i>i</i> Pr	4	25	18	70	> 99

Asymmetric addition reactions

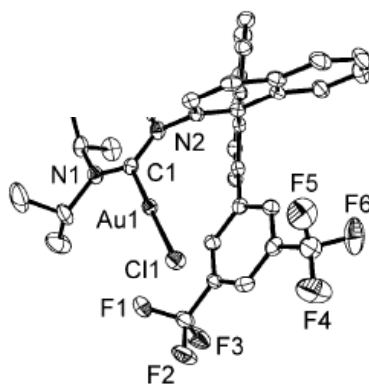
DFT-calculated relative energies of rotamers of 3b and 3c



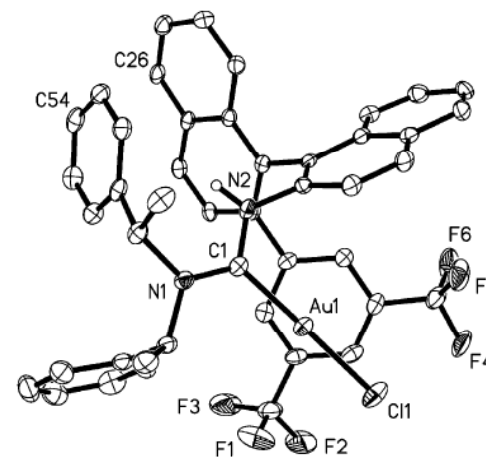
X-ray structure of 3b, 3c, 4



3b



3c

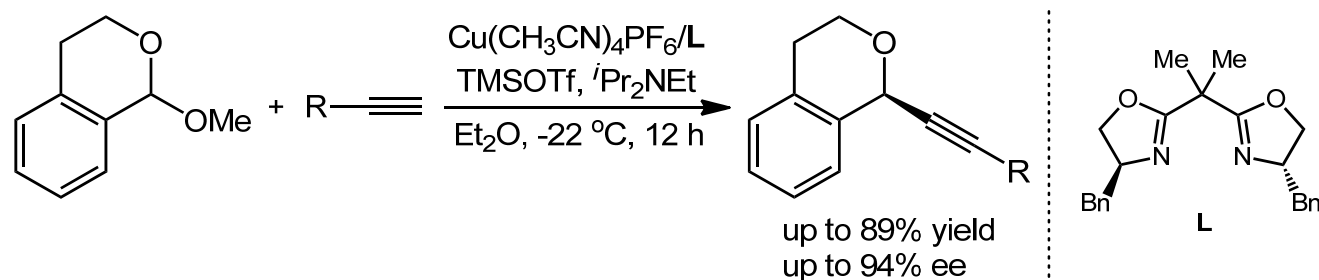


4

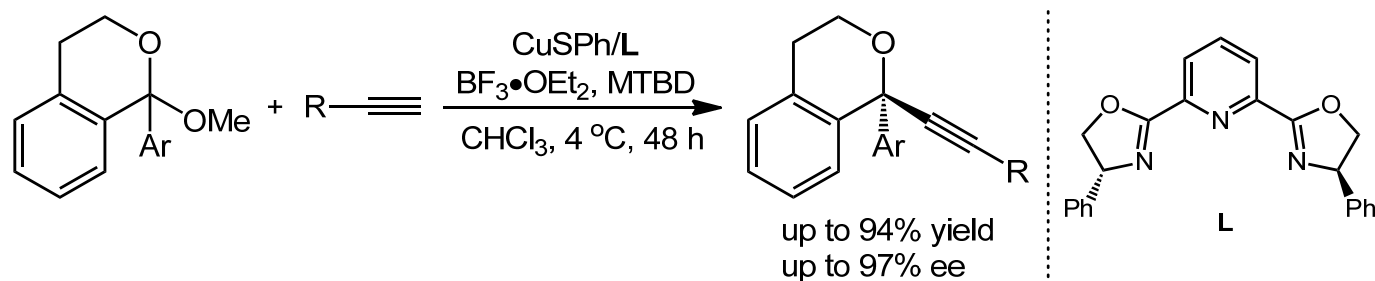
Typical cation- π interactions exist in 3c and 4

Asymmetric addition reactions

Copper-catalyzed alkylation of isochroman acetals



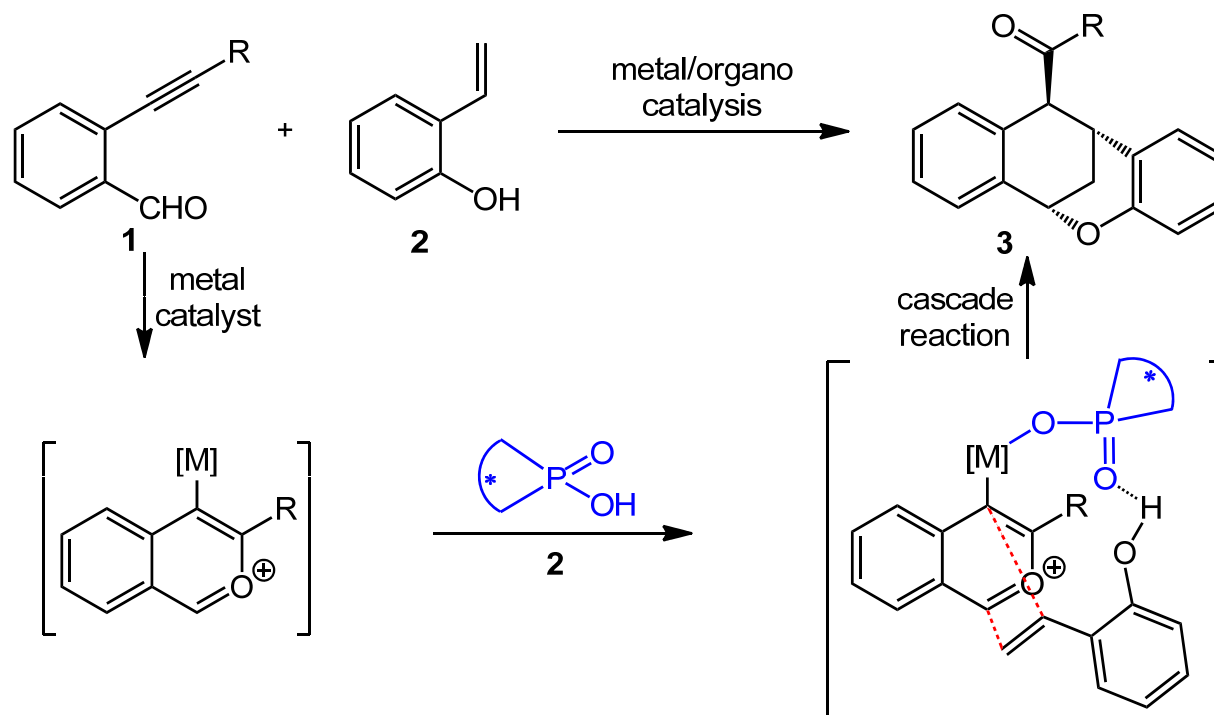
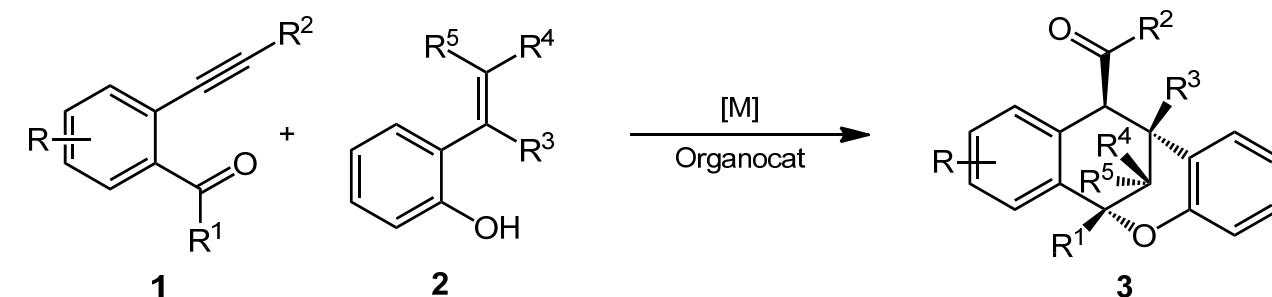
Watson, M. P. *et al.* *J. Am. Chem. Soc.* **2011**, *133*, 17142.



Watson, M. P. *et al.* *Angew. Chem. Int. Ed.* **2015**, *54*, 14154.

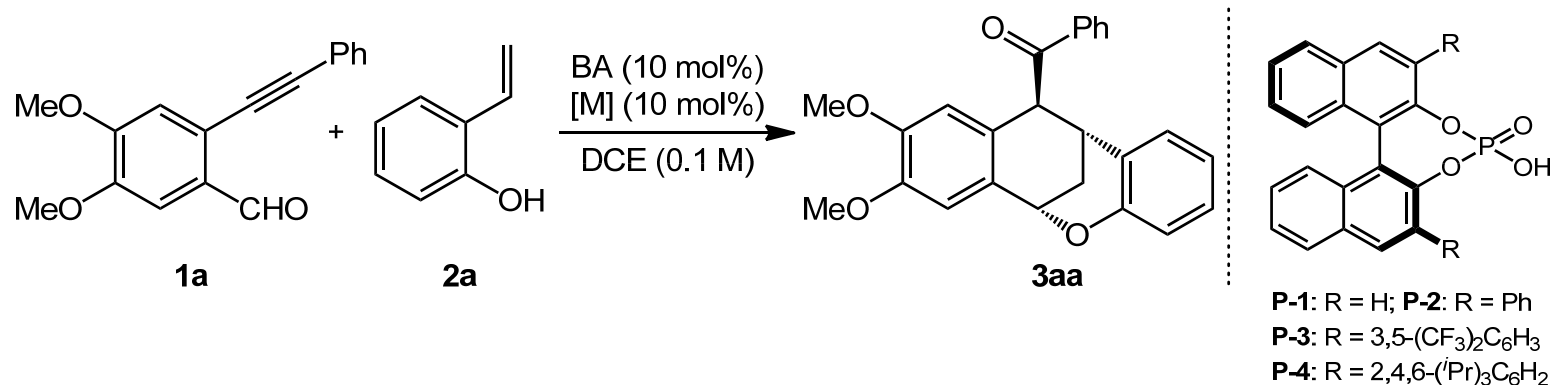
Asymmetric cycloaddition reactions

Pd(OAc)₂/(S)-Trip-catalyzed cascade annulation



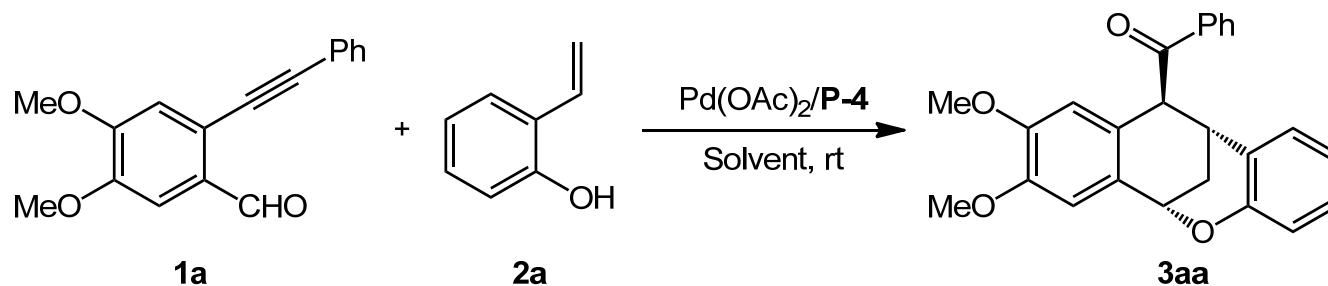
Yao, Z. -J. et al. *J. Am. Chem. Soc.* **2013**, 135, 11402.

Screening of binary catalyst combination



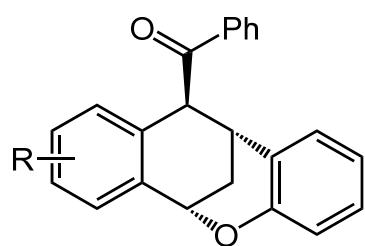
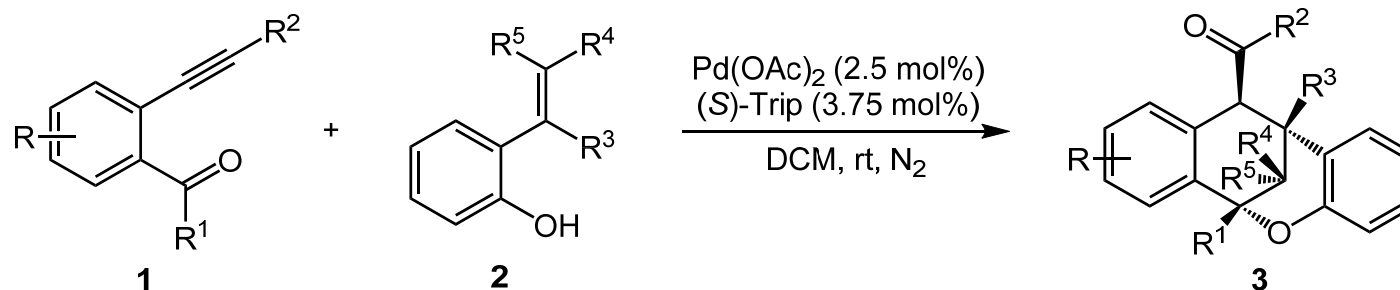
Entry	BA	[M]	T (°C)	Yield (%)	Ee (%)
1	P-1	--	reflux	88	10
2	P-1	AgOTf	rt	97	0
3	P-1	AuCl ₃	rt	63	0
4	P-1	PtCl ₂	rt	96	0
5	P-1	Cu(OTf) ₂	rt	20	20
6	P-1	Zn(OTf) ₂	rt	12	0
7	P-1	Pd(OAc) ₂	rt	96	26
8	P-2	Pd(OAc) ₂	rt	85	43
9	P-3	Pd(OAc) ₂	rt	73	15
10	P-4	Pd(OAc)₂	rt	75	79

Optimization of reaction conditions



Entry	$\text{Pd}(\text{OAc})_2$ (mol%)	P-4 (mol%)	Solvent	t (h)	Yield (%)	Ee (%)
1	10	10	DCE	4	75	79
2	10	10	THF	6	38	78
3	10	10	Toluene	4	68	79
4	10	10	MeCN	19	43	87
5	10	10	DCM	6	71	85
6	5	5	DCM	7	65	88
7	5	10	DCM	7	69	93
8	5	7.5	DCM	7	67	93
9	2.5	3.75	DCM	13	71	95
10	1	1.5	DCM	30	69	95

Substrate scope



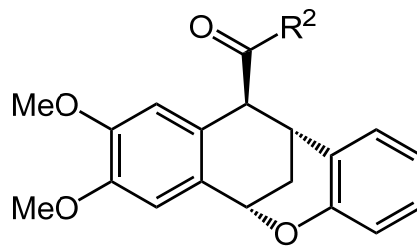
3aa, R = 4,5-diOMe, 71%, 95%ee

3ba, R = 4-OMe, 61%, 76%ee

3ca, R = 5-OMe, 66%, 75%ee

3da, R = H, 68%, 71%ee

3ea, R = 4,5-OCH₂O, 71%, 92%ee



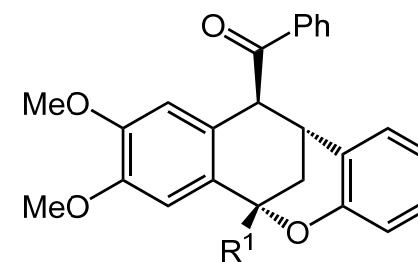
3fa, R² = 4-MeC₆H₄, 75%, >99.5%ee

3ga, R² = 4-OMeC₆H₄, 75%, >99.5%ee

3ha, R² = 4-BrC₆H₄, 80%, >99.5%ee

3ia, R² = 2-furfuryl, 37%, 86%ee

3ja, R² = ^cC₃H₅, 46%, 37%ee



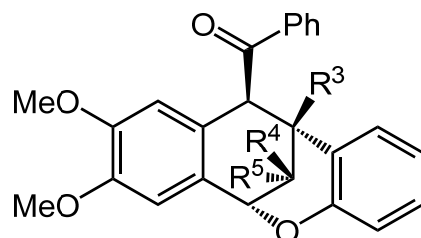
3ka, R¹ = Me, 80%, 93%ee

3la, R¹ = ⁱPr, 80%, 85%ee

3ma, R¹ = ^cHex, 86%, 93%ee

3na, R¹ = 4-MeC₆H₄, 78%, 83%ee

3oa, R¹ = 4-OMeC₆H₄, 87%, 85%ee



3ab, R⁴ = Me, R³ = R⁵ = H, 73%, 84%ee

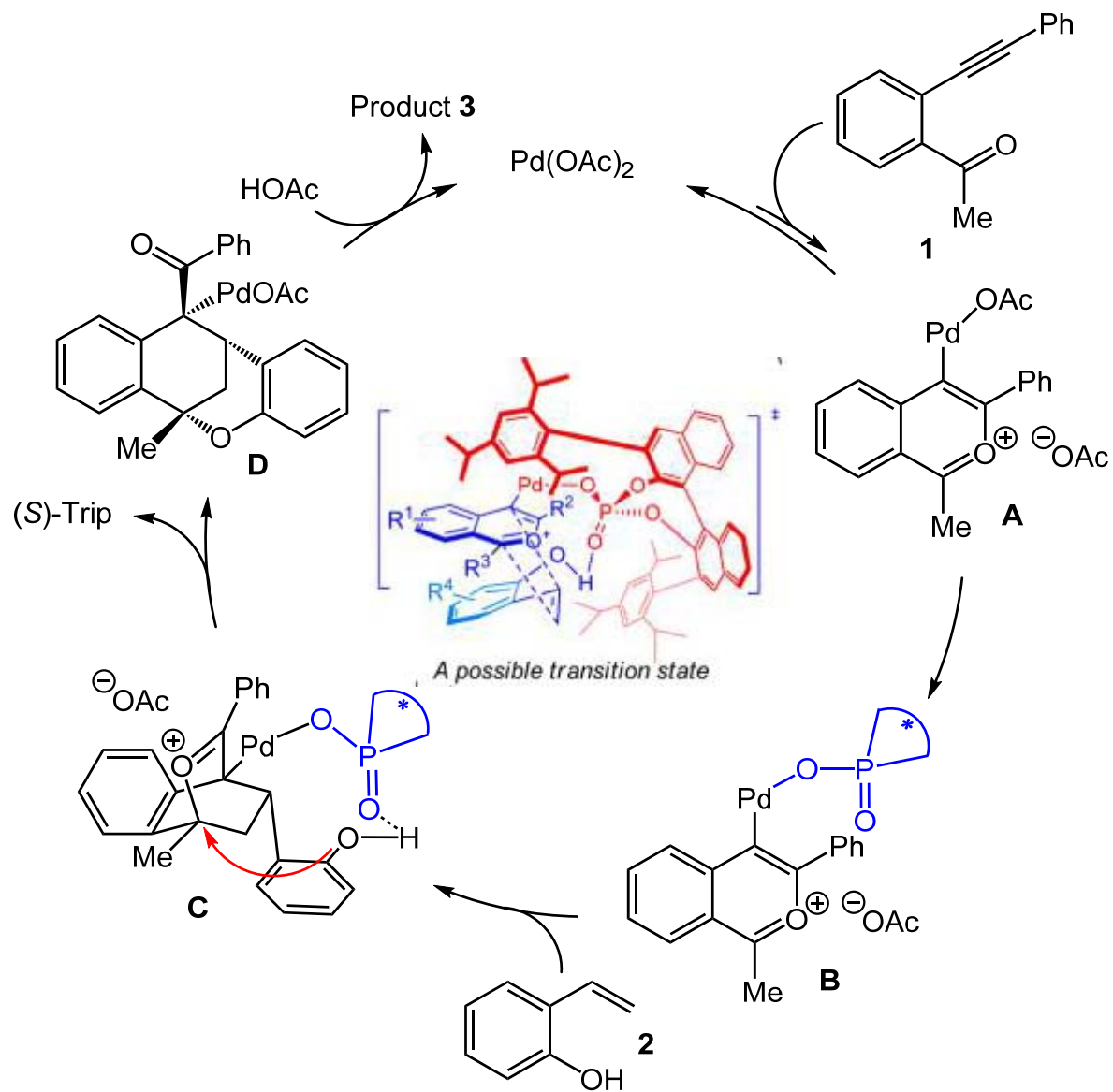
3ac, R⁴ = Et, R³ = R⁵ = H, 87%, 92%ee

3ad, R⁴ = ⁿBu, R³ = R⁵ = H, 90%, >99.5%ee

3ae, R³ = H, R⁴ = R⁵ = Me, 64%, 89%ee

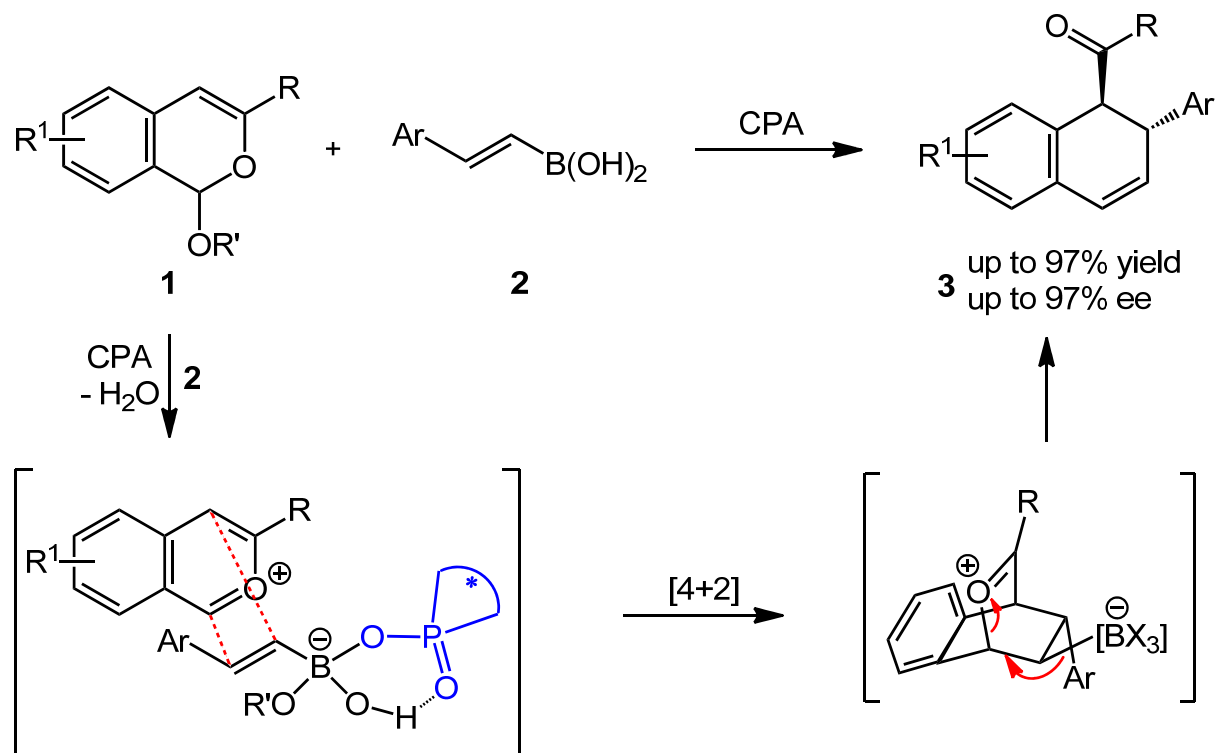
3af, R⁵ = H, R³ = R⁴ = Me, 48%, 33%ee

Proposed reaction mechanism



Asymmetric cycloaddition reactions

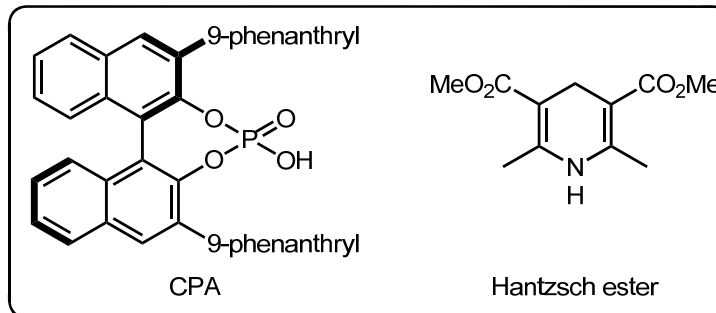
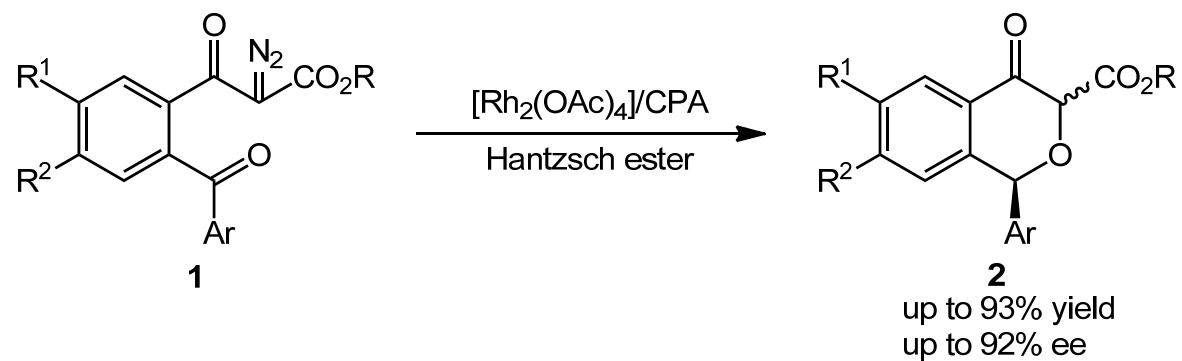
CPA-catalyzed cycloaddition with boronates



Sun, J. *et al.* *J. Am. Chem. Soc.* **2015**, 137, 560.

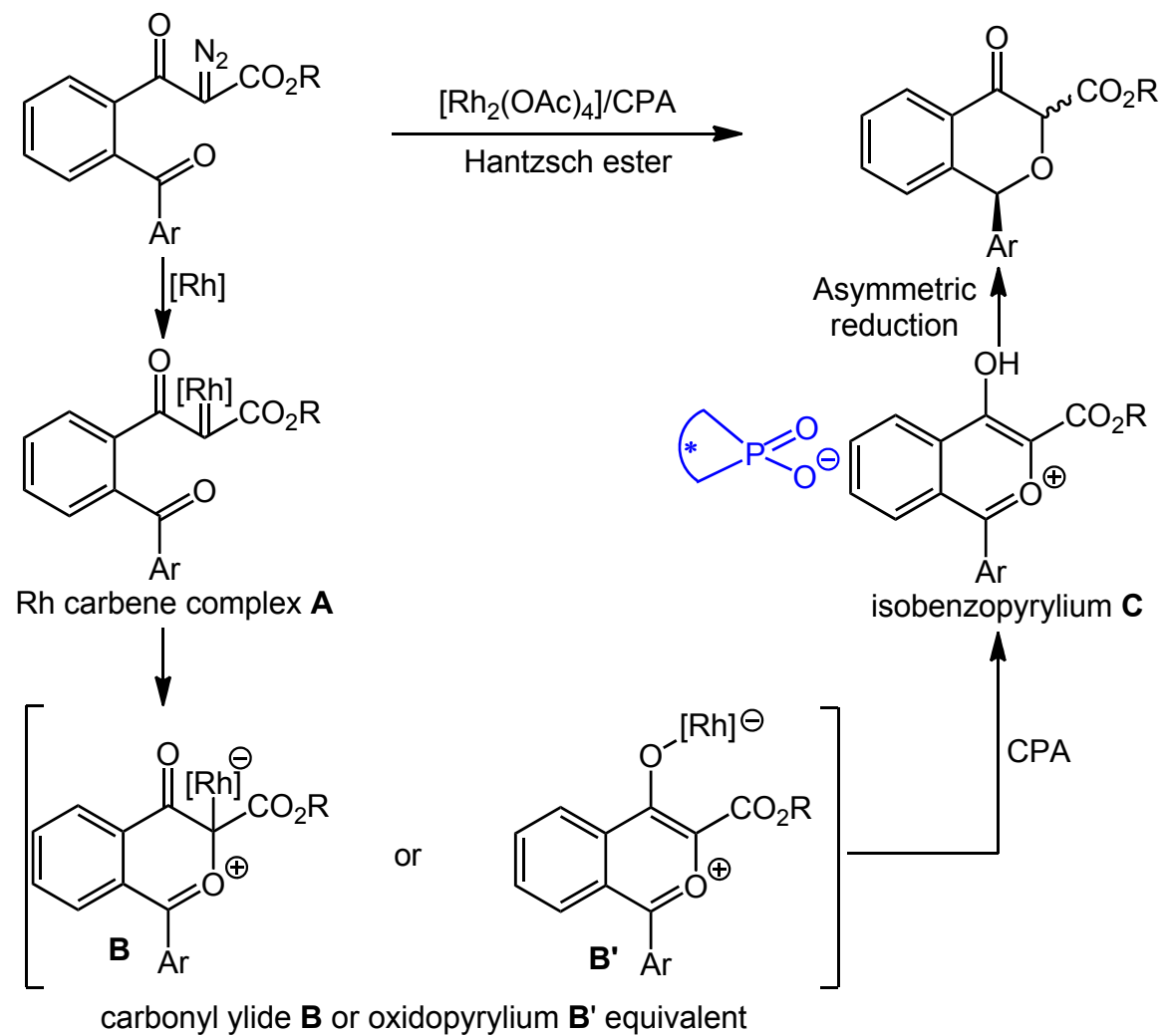
Asymmetric reduction reactions

Rh/CPA relay catalysis

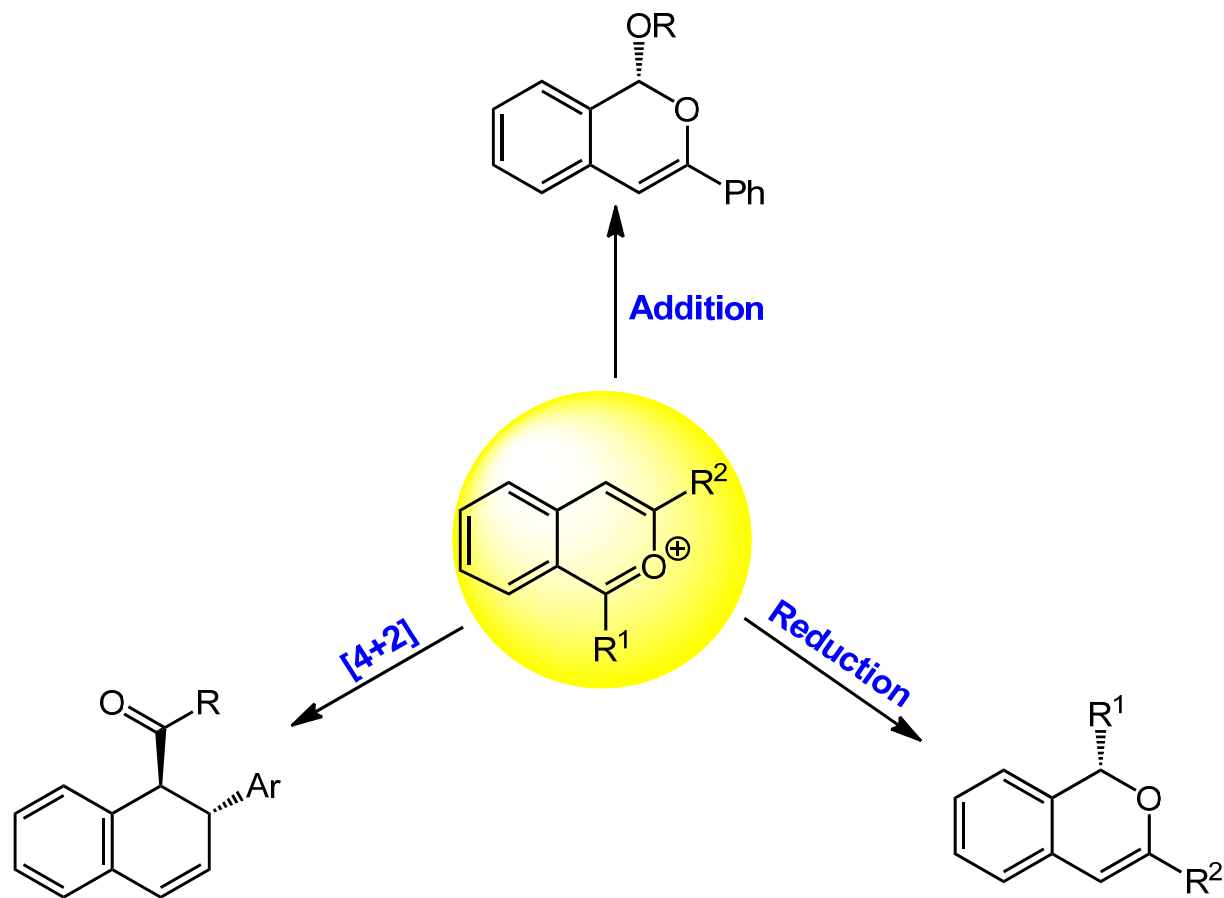


Terada, M. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 2093.

Proposed catalytic cycle



Summary



Boronates exhibit wide-ranging utility in synthesis. As carbon donors in cross-coupling reactions and metal-based nucleophiles in π addition reactions, their utility is characterized by their ease of preparation, stability towards isolation and storage, and predictable reactivity patterns to afford valuable products. In a seminal discovery, Petasis and coworkers demonstrated how boronates could be activated towards addition to iminiums. However, an elusive area of reactivity is the addition of vinyl and aryl boronates to carbonyl and oxonium compounds. While less reactive than imines and iminium compounds, carbonyl-based electrophiles would significantly expand the utility of boronates in synthesis. Coincident with our interest in new reaction methodology, we sought to expand the repertoire of nucleophilic boronate reactions to enantioselective addition to acetals.

In summary, we have developed a dual catalyst system for the enantioselective addition of boronates to oxoniums. The catalyst system is a tartaric acid derived Brønsted acid used in conjunction with a lanthanide triflate Lewis acid used in catalytic amounts to promote the enantioselective addition of alkenyl and aryl boronates to chromene acetals. The reaction was optimized for a range of chromene acetals possessing both electron-deficient and electron-rich substitution patterns. Mechanistic studies demonstrate an exchange process leading to a reactive dioxoborolane intermediate. Ongoing studies include further mechanistic investigations, expansion of the scope, and utility for the synthesis of natural products.