
Rhodium-Catalyzed Enantioselective Isomerization of Oxabicycles

Reporter: Jie Wang

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Yen, A.; Choo, K.-L.; Yazdi, S. K.; Franke, P. T.; Webster, R.; Franzoni, I.; Loh, C. C. J. Poblador-Bahamonde, A. I.; Lautens, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 6307.

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CV of Mark Lautens



Mark Lautens

Education:

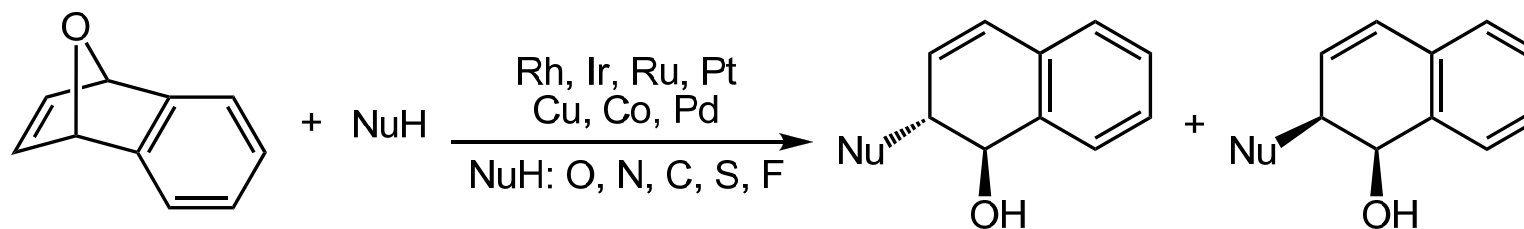
- ❑ B.S., University of Guelph (1981)
- ❑ Ph.D., University of Wisconsin-Madison
with Trost, B. M. (1981-1985)
- ❑ Postdoctoral Fellow., Harvard University
with Evans, D. A. (1985-1987)
- ❑ University of Toronto (1987-2017)

Research:

- Asymmetric catalysis with focus on rhodium, nickel
- Reactions of organosilicon and organotin compounds
- Fragmentation reactions

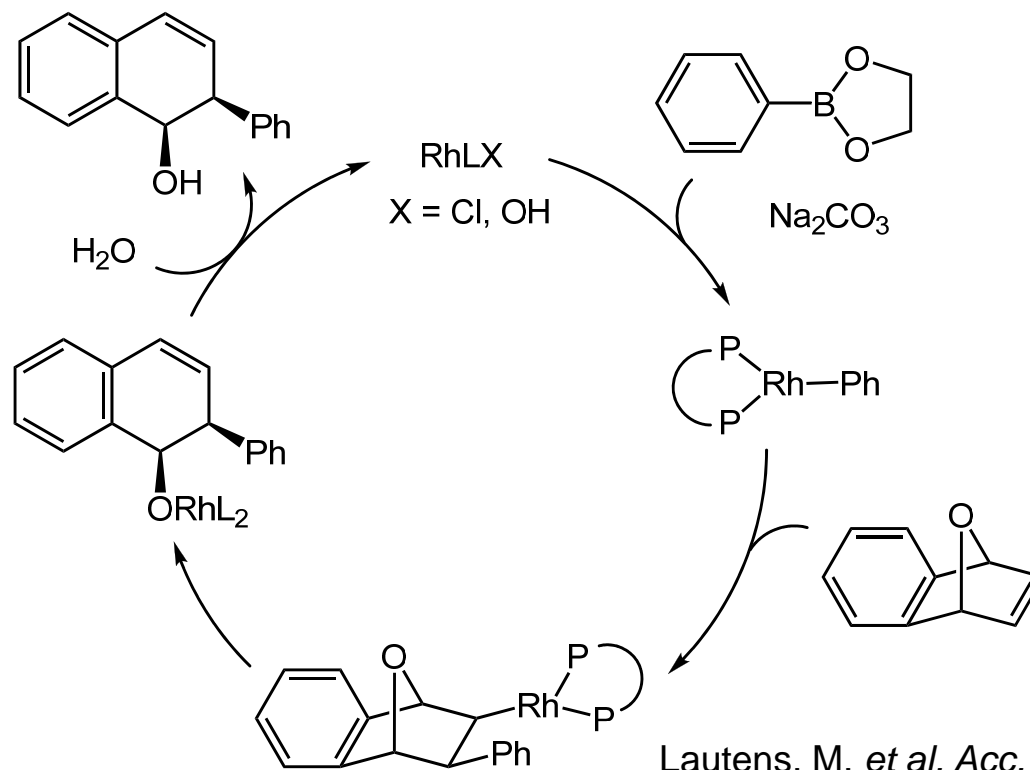
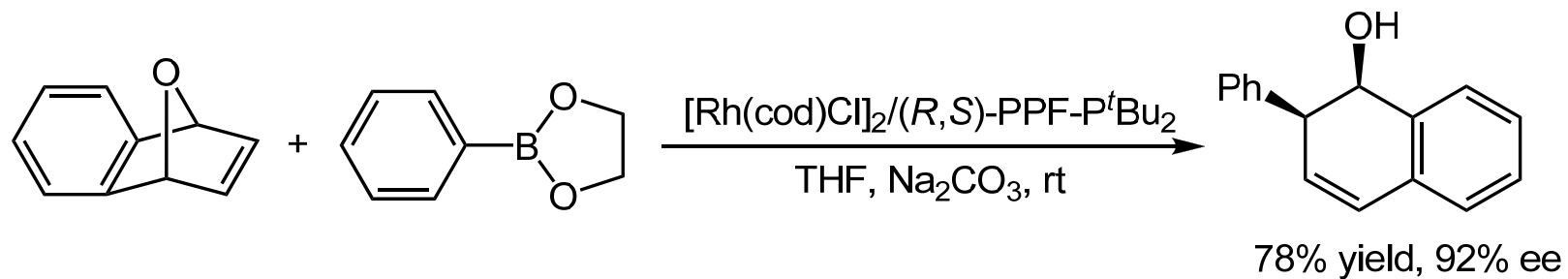
Introduction

Intermolecular asymmetric ring opening (ARO) reactions:

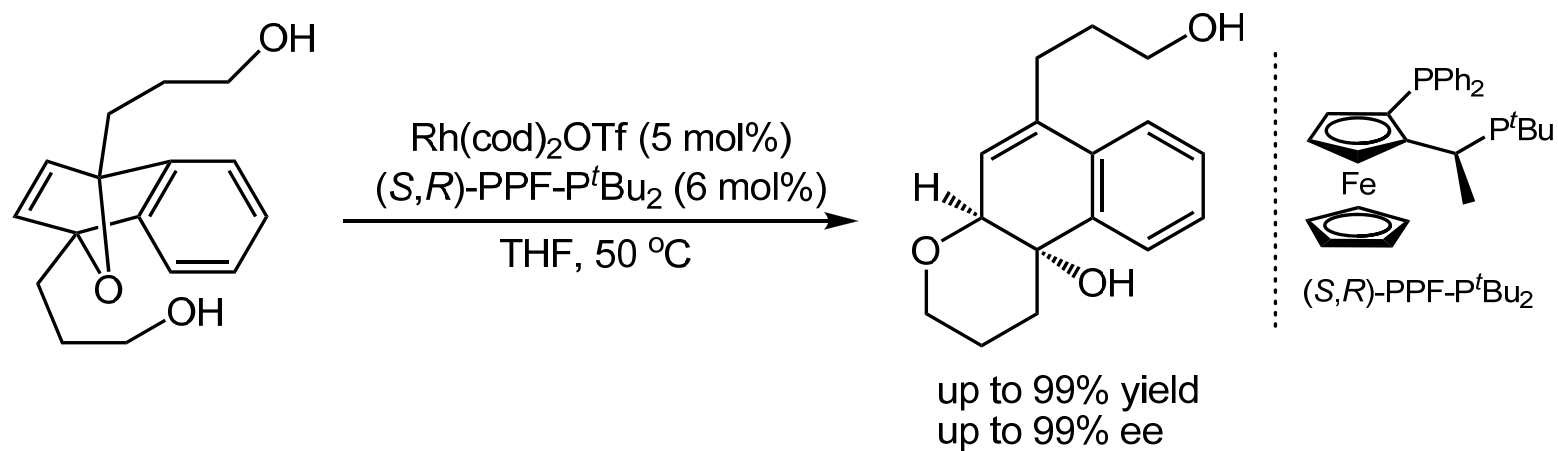


Lautens, M. *et al.* *Acc. Chem. Res.* **2003**, 36, 48.

Introduction

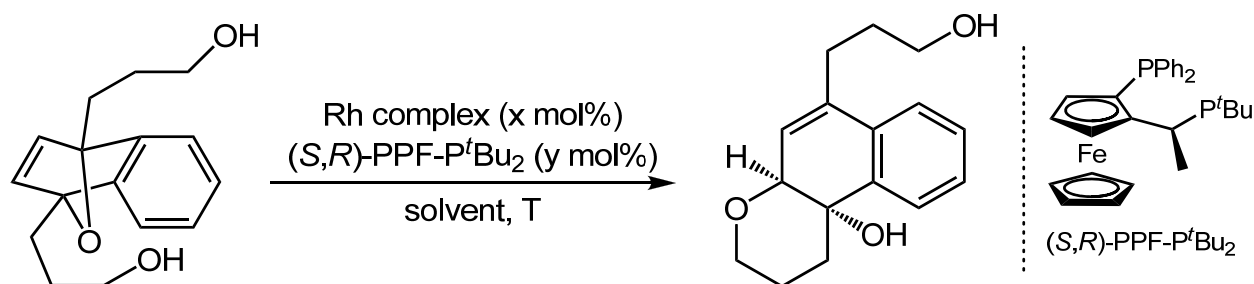


Intramolecular ARO



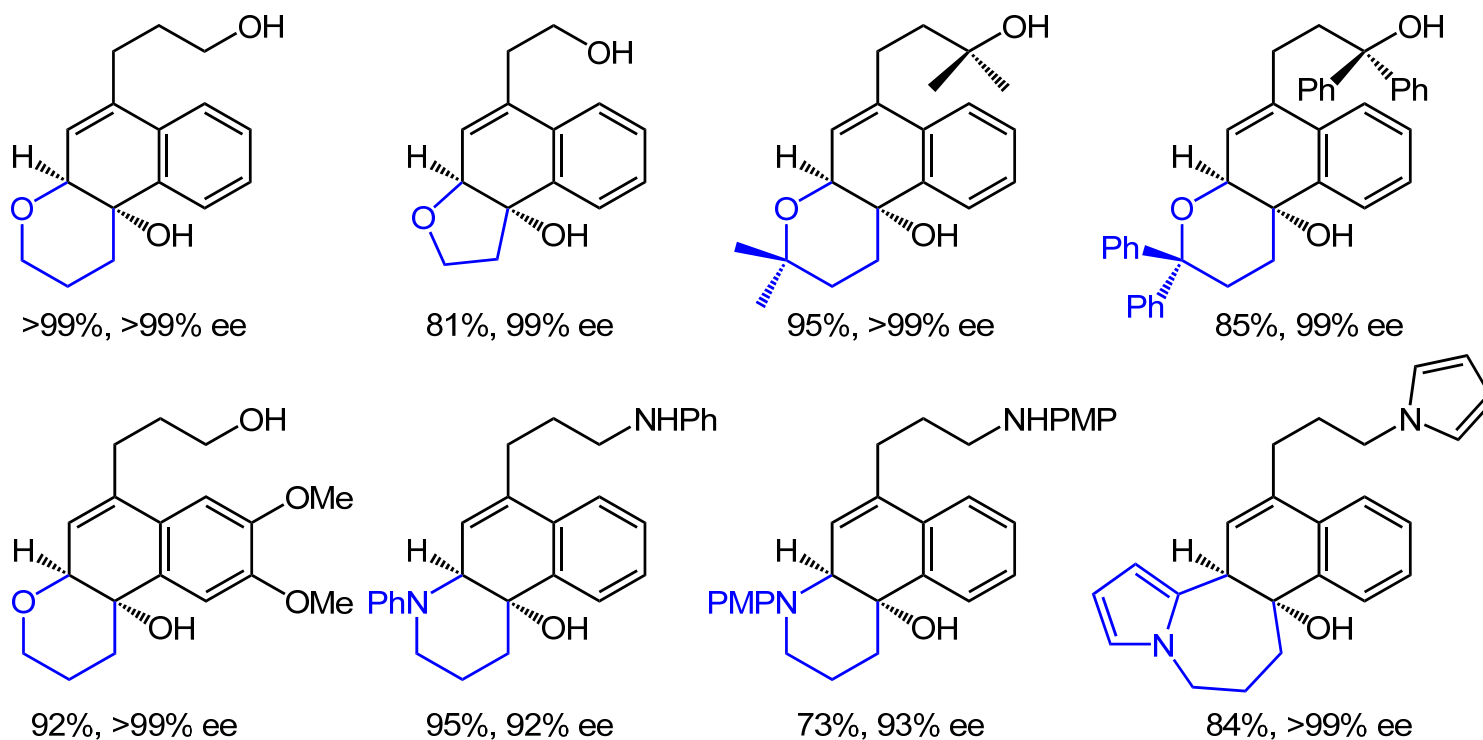
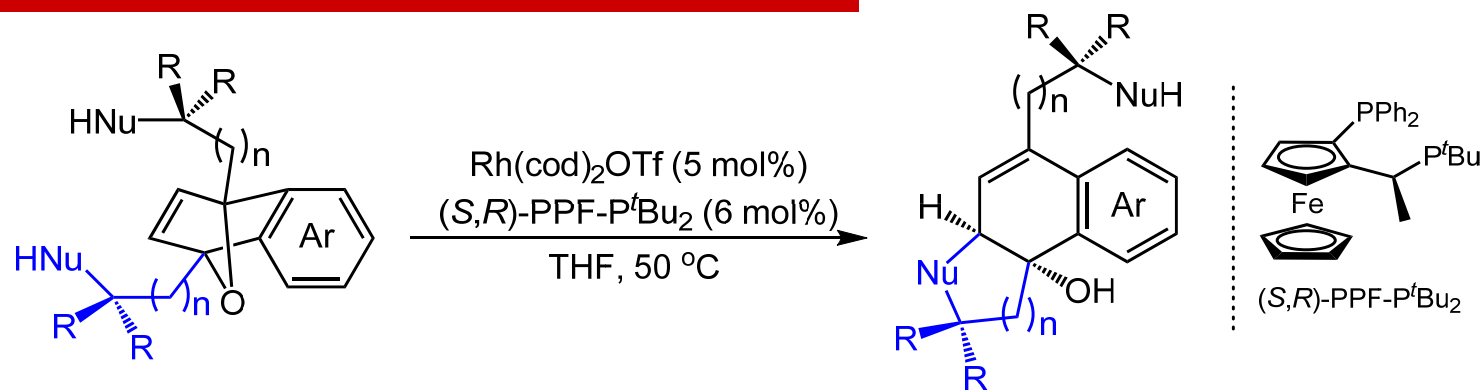
Lautens, M. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 10074.

Evaluation Conditions

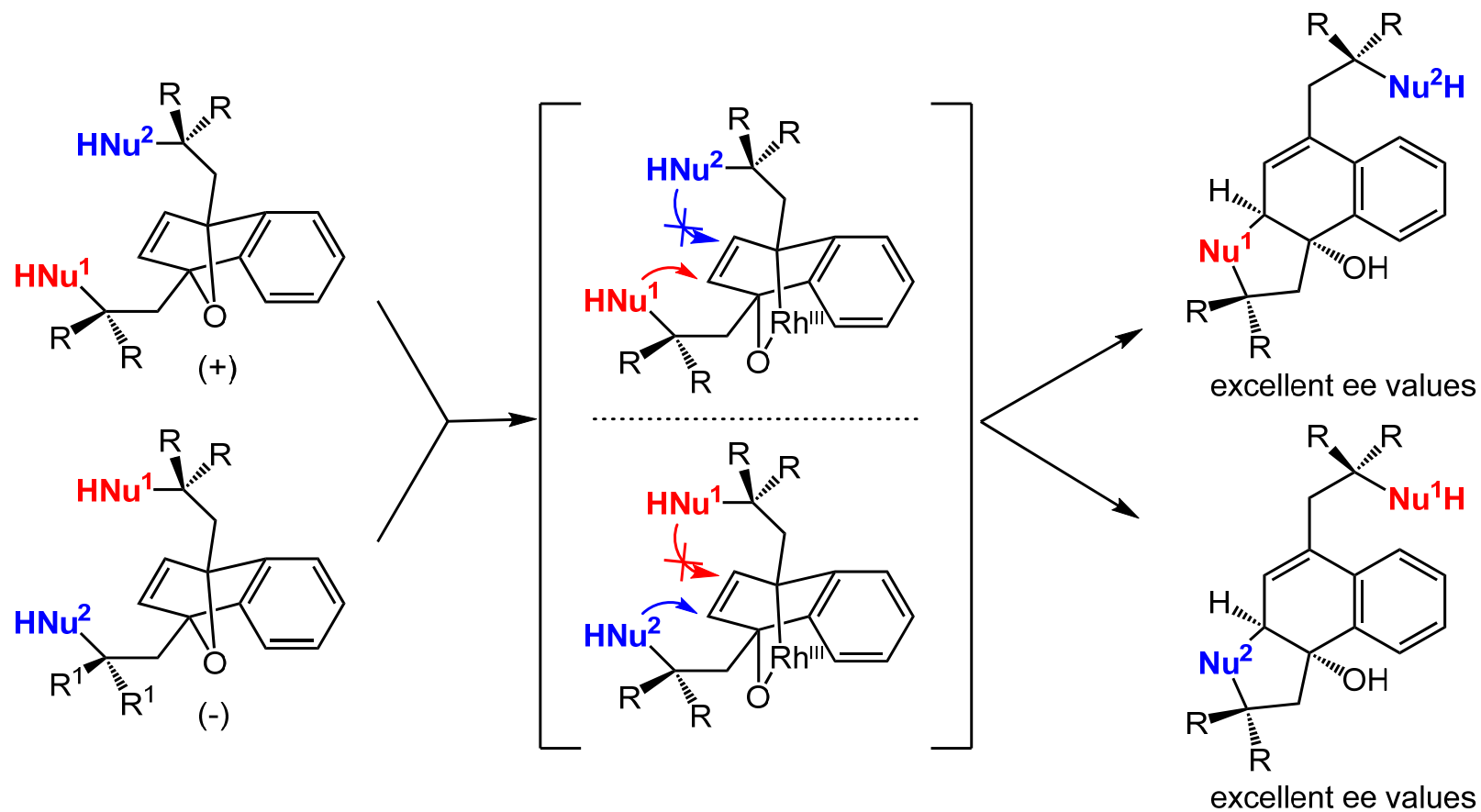


entry	[Rh]/L (x/y)	solvent	T (°C)	yield (%)	ee (%)
1	[Rh(cod)Cl] ₂ /L (4/8)	THF	80	22	ND
2	[Rh(cod)OH] ₂ /L (4/8)	THF	80	5	ND
3	Rh(cod) ₂ OTf/L (5/6)	THF	80	>99	98
4	[Rh(cod)Cl] ₂ /L (4/8) AgOTf, TBAI	THF	80	25	ND
5	Rh(cod) ₂ OTf/L (5/6)	DCE	80	76	98
6	Rh(cod) ₂ OTf/L (5/6)	Dioxane	80	>99	97
7	Rh(cod) ₂ OTf/L (5/6)	Toluene	80	>99	97
8	Rh(cod) ₂ OTf/L (5/6)	MeCN	80	-	Decomp.
9	Rh(cod)₂OTf/L (5/6)	THF	50	>99	>99

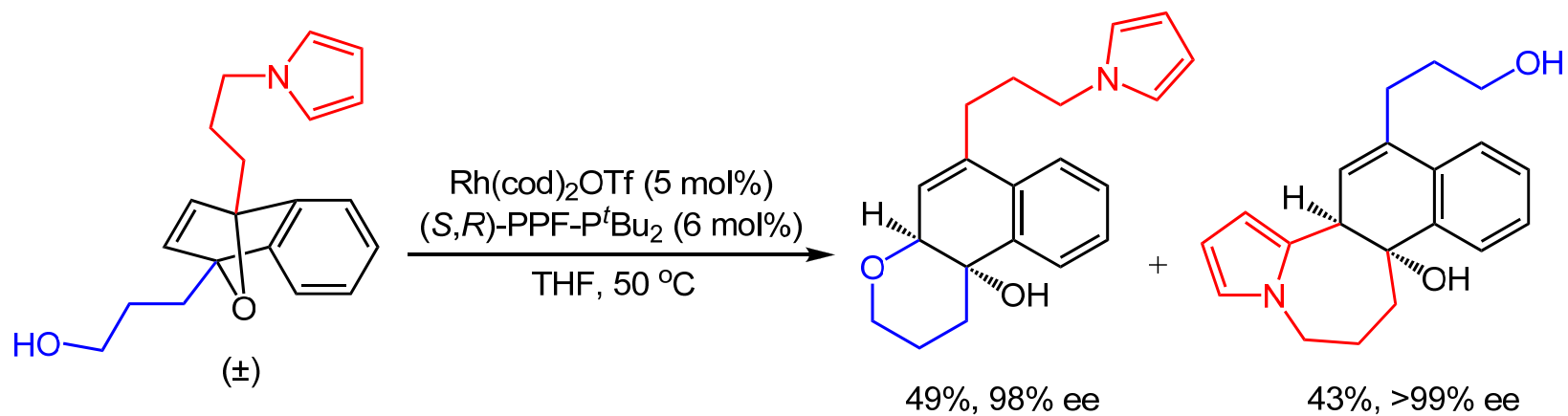
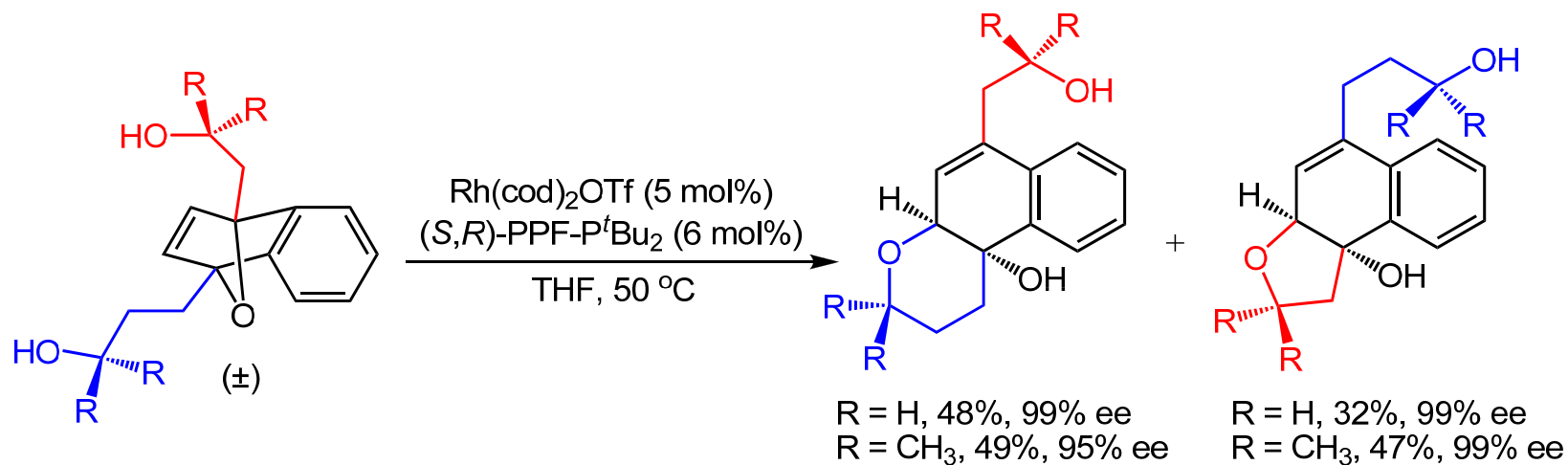
Substrate Scope



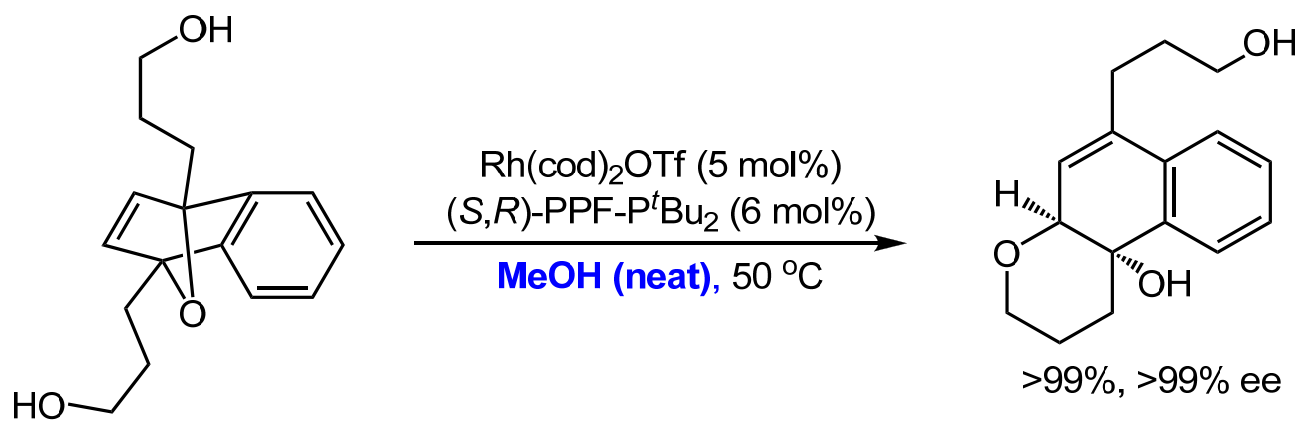
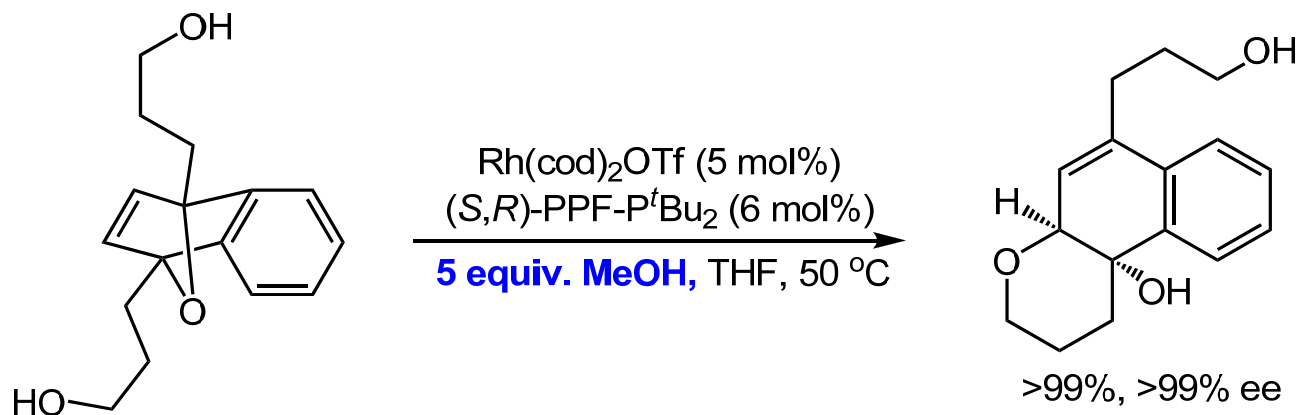
Mechanistic Basis of the PKR



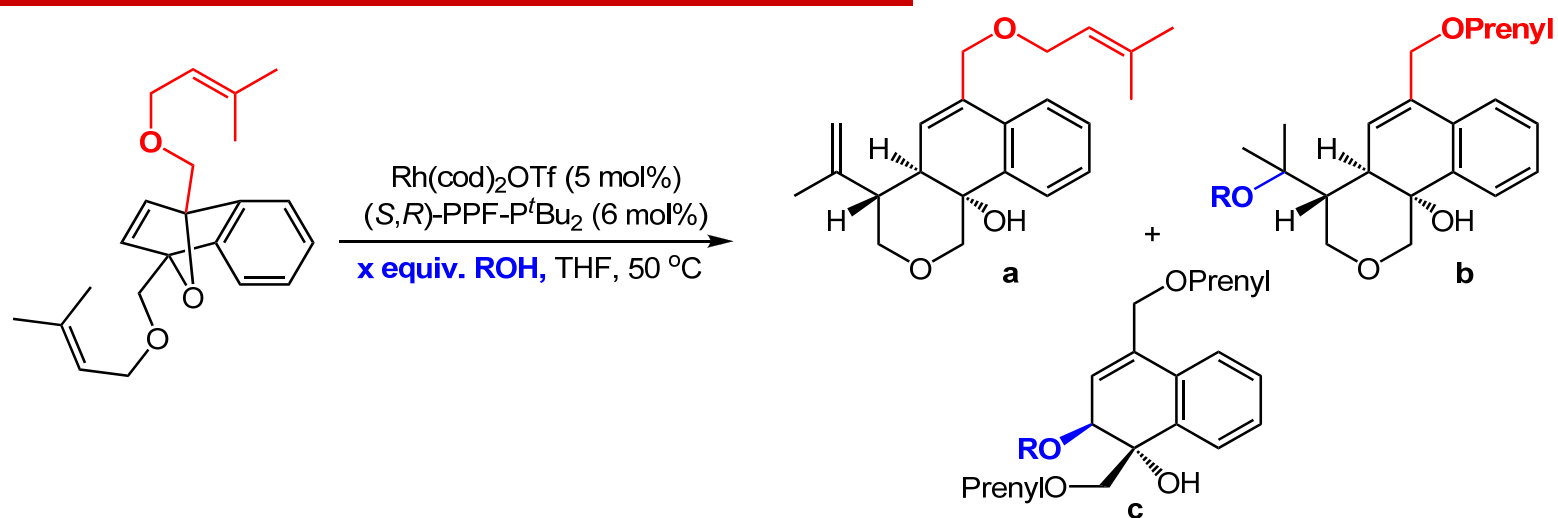
Substrate Scope of PKR



Control Experiments

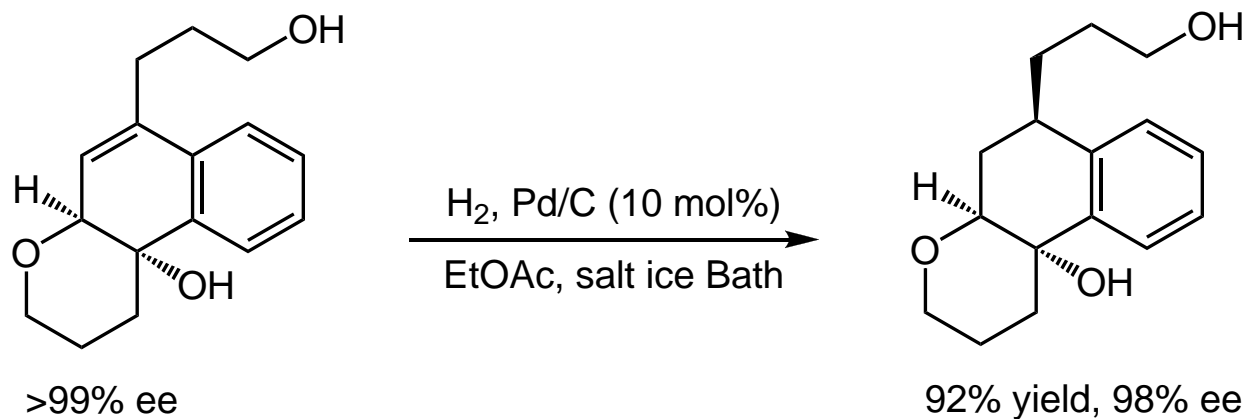


Perturbation Experiments with ROH

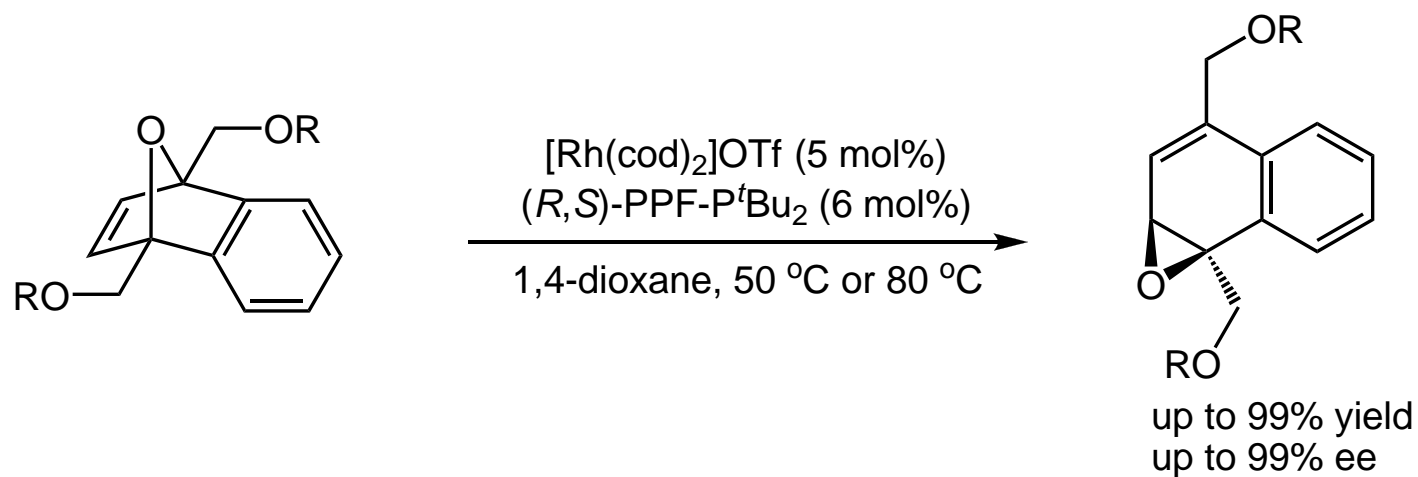


entry	ROH (equiv.)	a yield (ee)	b yield (ee)	c yield (ee)
1	NO ROH	97 (>99)	-	-
2	MeOH (5)	45 (>99)	40 (>99)	Traces
3	MeOH (20)	29 (>99)	54 (>99)	14 (97)
4	MeOH (50)	15 (>99)	59 (>99)	24 (99)
5	MeOH (100)	9 (>99)	54 (>99)	33 (97)
6	MeOH (neat)	-	39 (>99)	50 (97)
7	t BuOH	80 (>99)	19 (>99)	-

Diastereoselective Hydrogenation

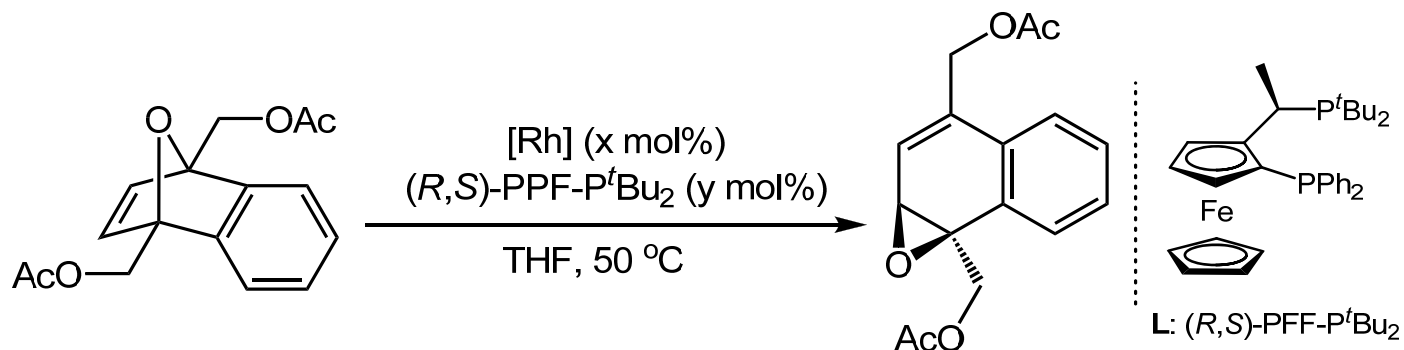


Isomerization of Oxabicycles



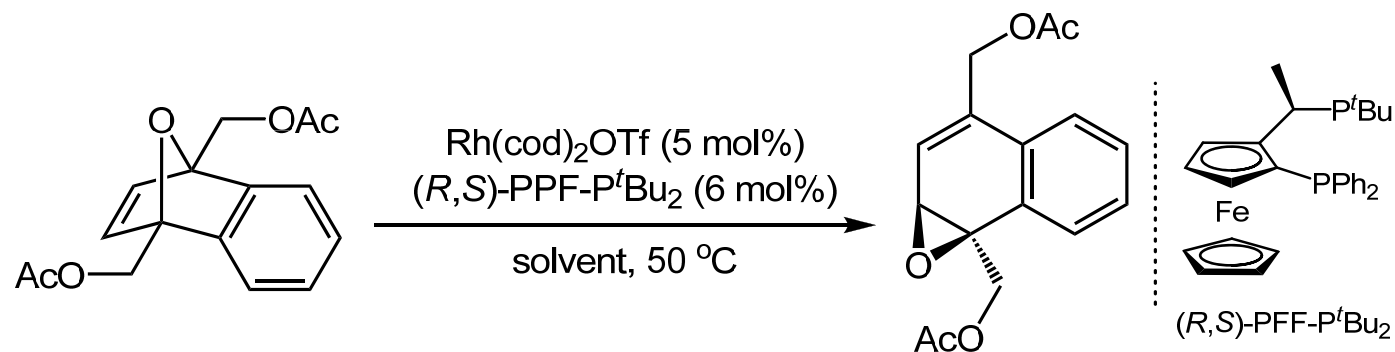
Lautens, M. *et al.* *Angew. Chem. Int. Ed.* **2017**, 56, 6307.

Evaluation of the Catalysts



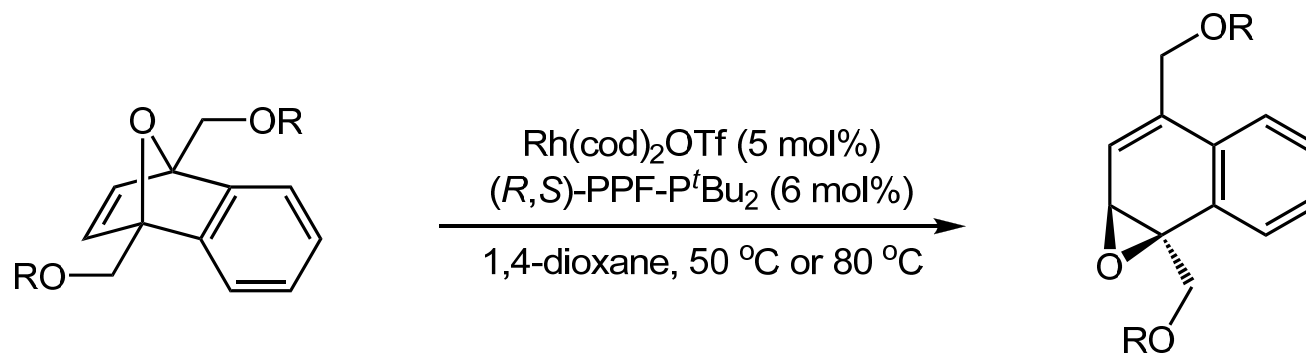
entry	[Rh]/L (x/y)	yield (%)	ee (%)
1	Rh(cod)₂OTf/L (5/6)	88	96
2	[Rh(cod)Cl] ₂ /L (2.5/6)	NR	ND
3	[Rh(cod)OH] ₂ /L (2.5/6)	NR	ND
4	Rh(cod) ₂ OTf/L (2/3)	<1	ND
5	Rh(cod) ₂ OTf/L (3/4)	43	ND

Evaluation of the Solvents



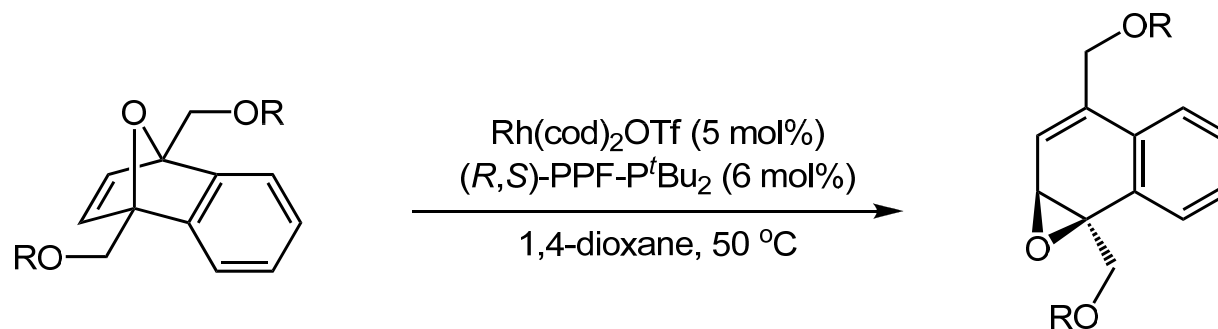
entry	solvent	yield (%)	ee (%)
1	THF	88	96
2	1,4-dioxane	98	97
3	MeCN	NR	ND
4	DCE	83	95
5	PhMe	NR	ND
6	DCM	94	95
7	DMAc	<1	ND

Substrate Scope



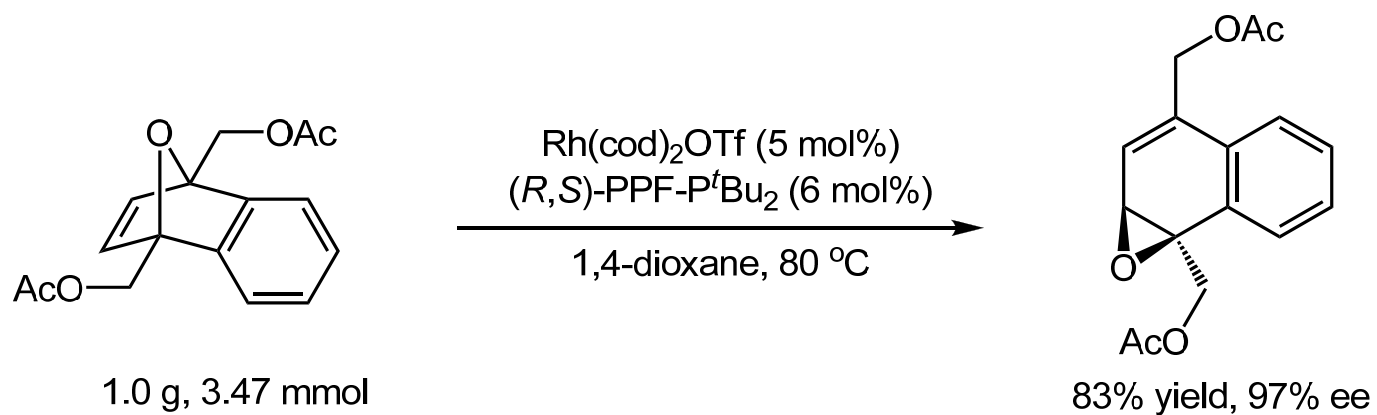
entry	R	yield (%)	ee (%)
1	CH ₃ CO	88	96
2	^t BuOCO	99	96
3	C ₆ H ₅ CO	60	99
4	4-MeOC ₆ H ₄ CO	92	>99
5	4-BrC ₆ H ₄ CO	56	>99
6	4-MeSC ₆ H ₄ CO	66	99
7	2-ThienylCO	79	99
8	C ₆ H ₅ NHCO	56	96

Substrate Scope

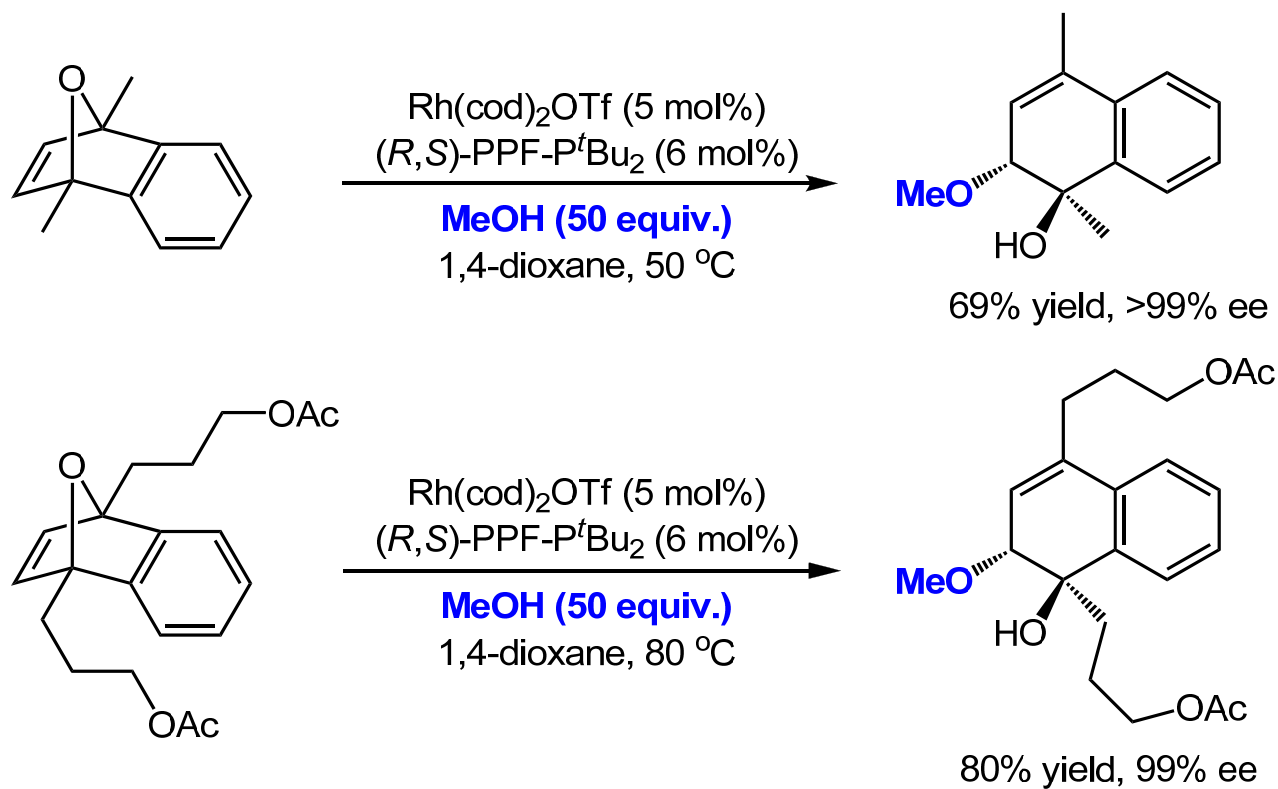


entry	R	yield (%)	ee (%)
1	C ₆ H ₅ CH ₂	87	97
2	4-BrC ₆ H ₄ CH ₂	64	97
3	4-CF ₃ C ₆ H ₄ CH ₂	85	97
4	4-(MeCOO)C ₆ H ₄ CH ₂	62	98
5	4-MeSC ₆ H ₄ CH ₂	93	95
6	4-MeOC ₆ H ₄ CH ₂	73	95

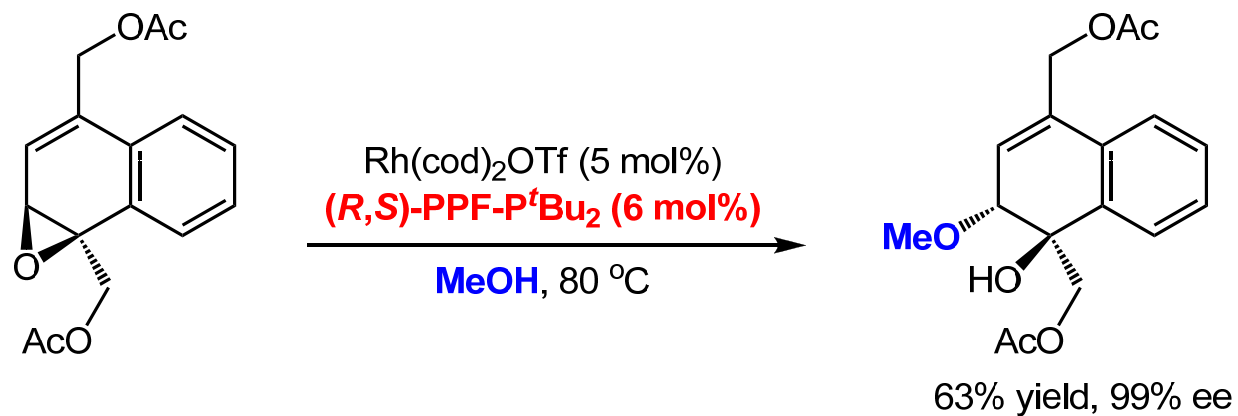
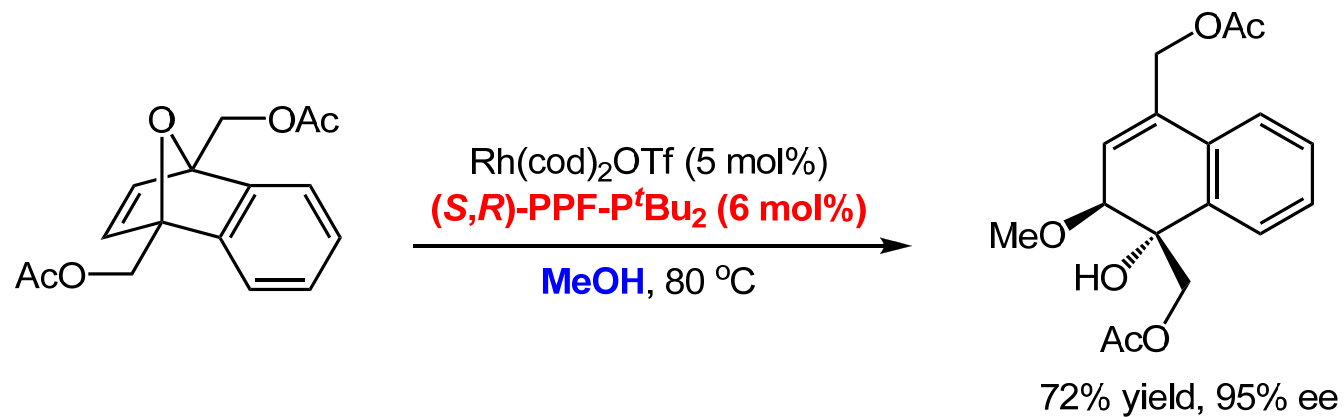
Gram-Scale Synthesis



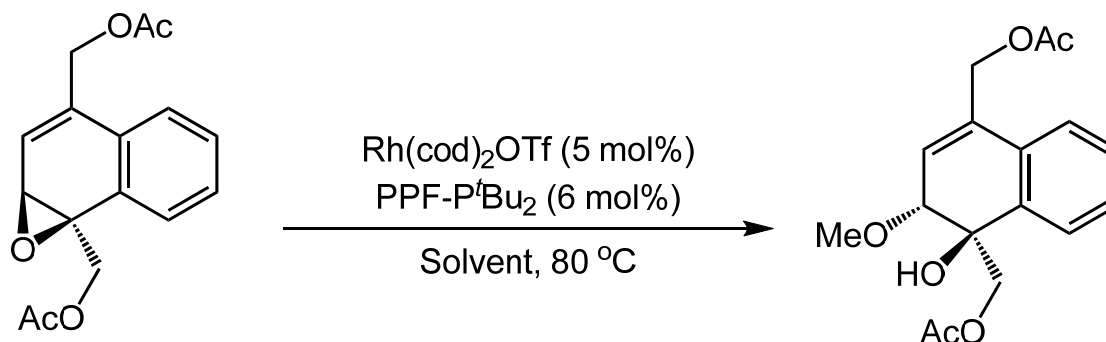
Enantioselective Methanolysis



Epoxides in ARO

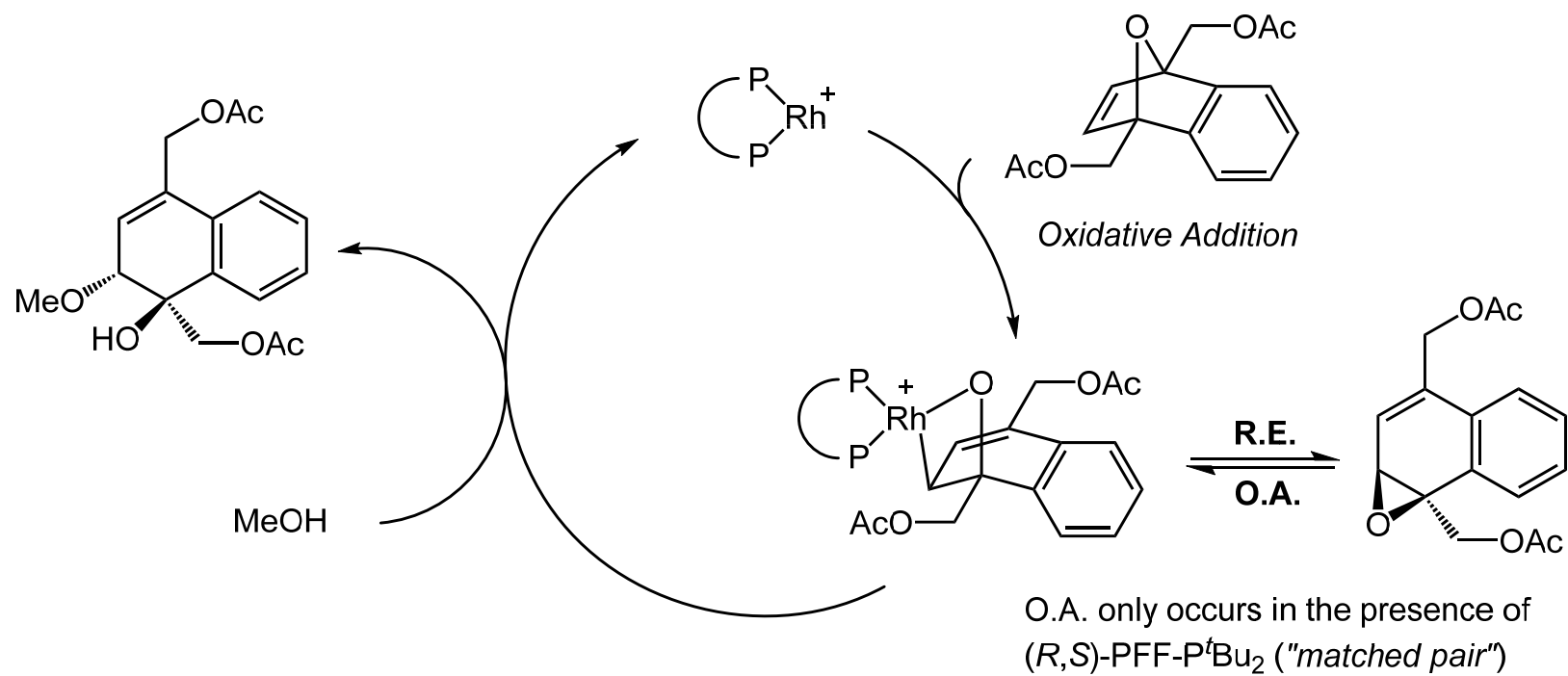


Participation of the Rhodium Catalyst

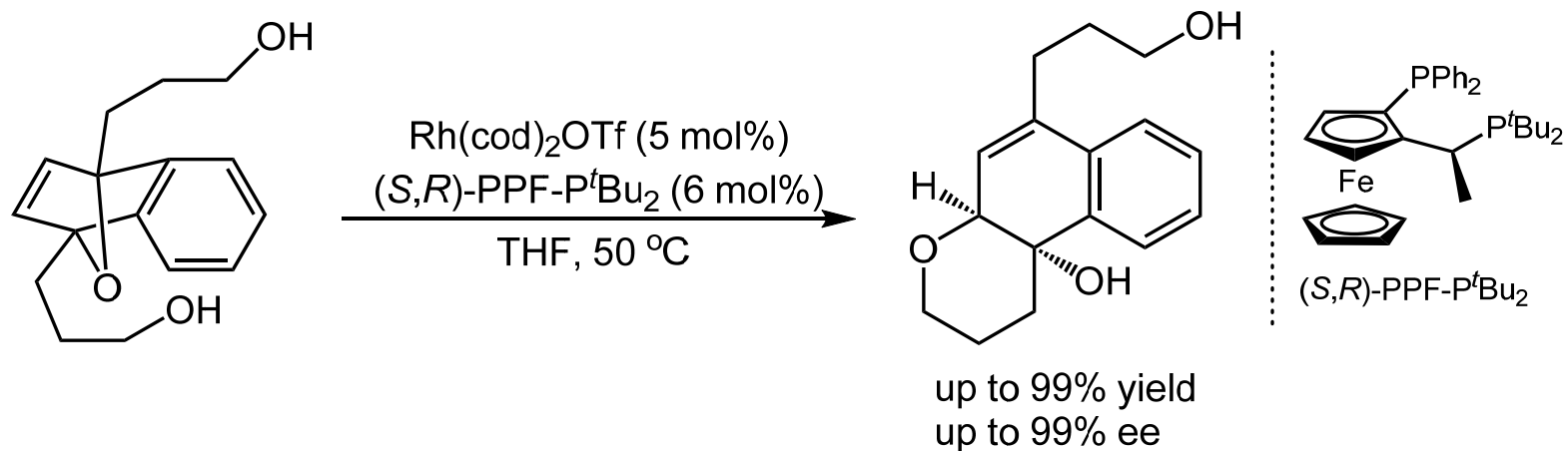


entry	[Rh]	PPF-P ^t Bu ₂	solvent	result
1	Yes	(<i>R,S</i>)	MeOH	63%
2	No	No	MeOH	NR
3	Yes	No	MeOH	decomposition
4	Yes	(<i>S,R</i>)	1,4-dioxane (50 eq. MeOH)	NR
5	Yes	(<i>S,R</i>)	MeOH	26% recovery
6	Yes	(<i>R,S</i>)	1,4-dioxane	80% recovery

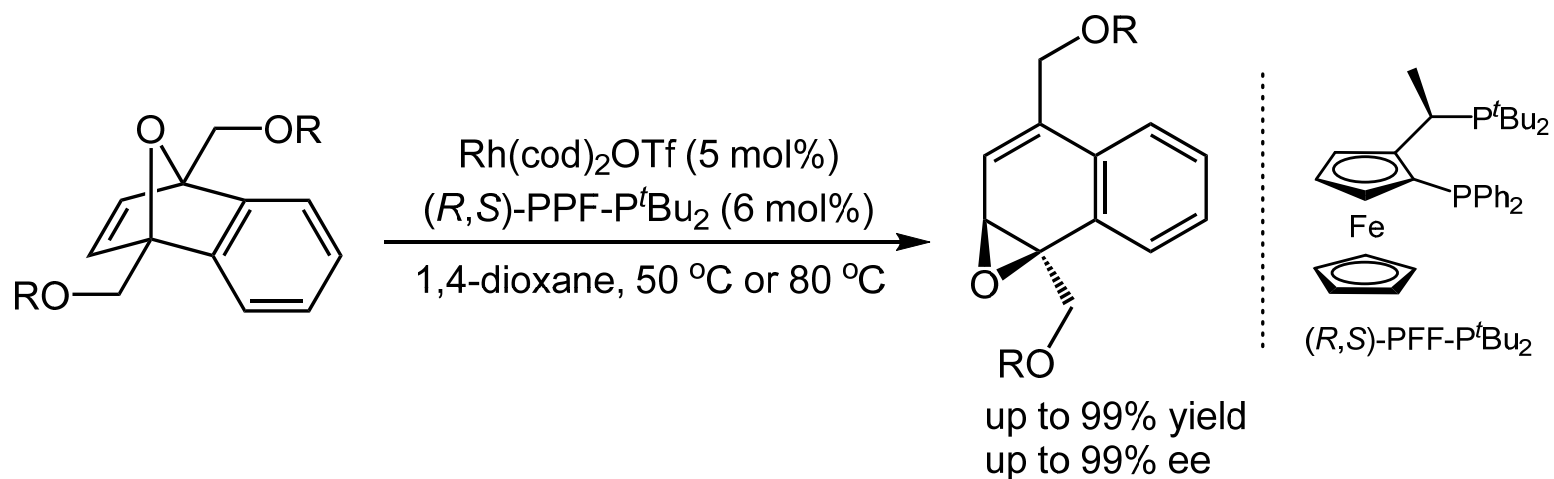
Proposed Mechanism



Summary



Lautens, M. *et al.* *Angew. Chem. Int. Ed.* **2016**, 55, 10074.



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The first paragraph

The rhodium-catalyzed asymmetric ring-opening (ARO) reaction of oxabicyclic alkenes offers a facile entry into chiral hydronaphthalene frameworks that are ubiquitous motifs found in a wide variety of biologically active natural products. For this reason, the development of the ARO reaction represents an area of increasing interest by various research groups, with many new methodologies emerging over the past two decades since we first disclosed this transformation.

The last paragraph

In summary, we have demonstrated the first rhodium catalyzed enantioselective isomerization of meso-oxabenzonorbornadienes to 1,2-naphthalene oxides. **This methodology delivers potentially useful building blocks in moderate to excellent yields with consistently impressive enantioselectivities.** Efforts to access enantioenriched products from the stereospecific ring-opening reactions of this class of compounds are underway in our laboratories.