Literature Report (9)

Enantioselective Vinylation of Activated Ketones and Imines

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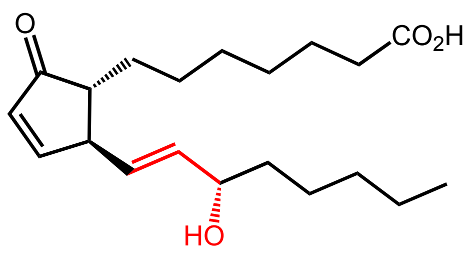
Checker: Guang-Shou Feng
Date: 2016/06/07

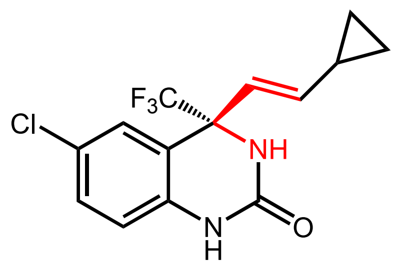
Content

- Introduction
- Organocatalytic Asymmetric Vinylation of Activated Imines
- Transition-Metal Catalyzed Enantioselective Vinylation of Activated Ketones and Imines
- Summary

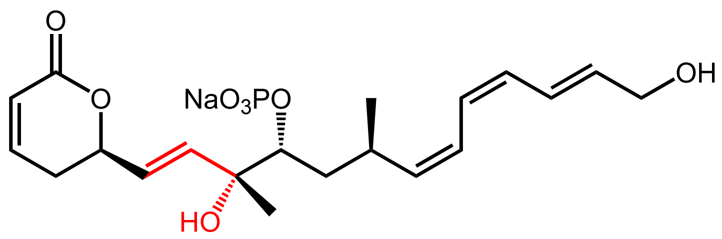
Introduction



Prostaglandin A_1 (anti-tumor)



DPC-083 (anti-HIV)



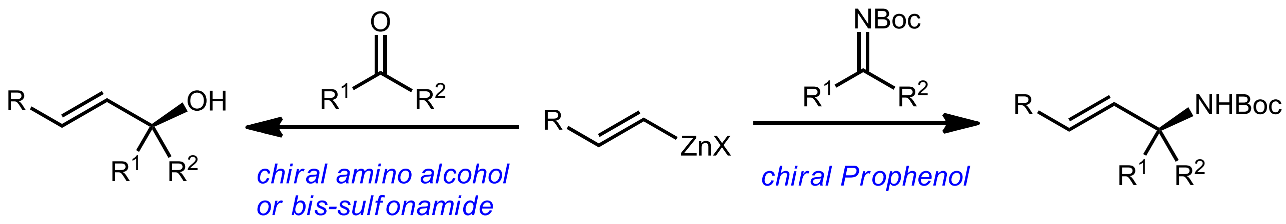
Fostriecin (anti-tumor)

Zhao, Y. *et al*. *J. Am. Chem. Soc*. **2016**, *138,* 6571.

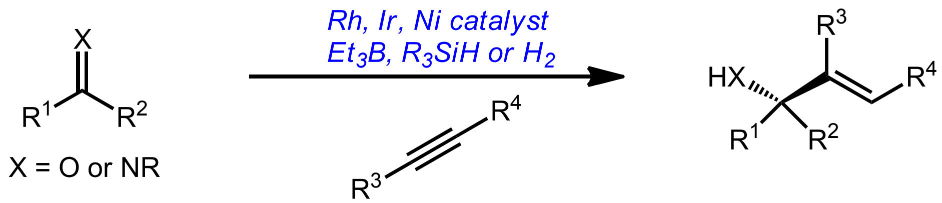
Introduction

➢ Strategies for Enantioselective Vinylation of Ketones and Imines

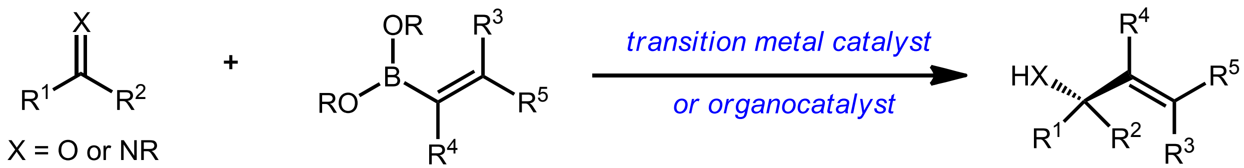
a) Enantioselective addition of vinyl zinc species



b) Reductive coupling of alkynes with ketones/imines



c) Enantioselective addition of vinyl borates to activated ketones and imines



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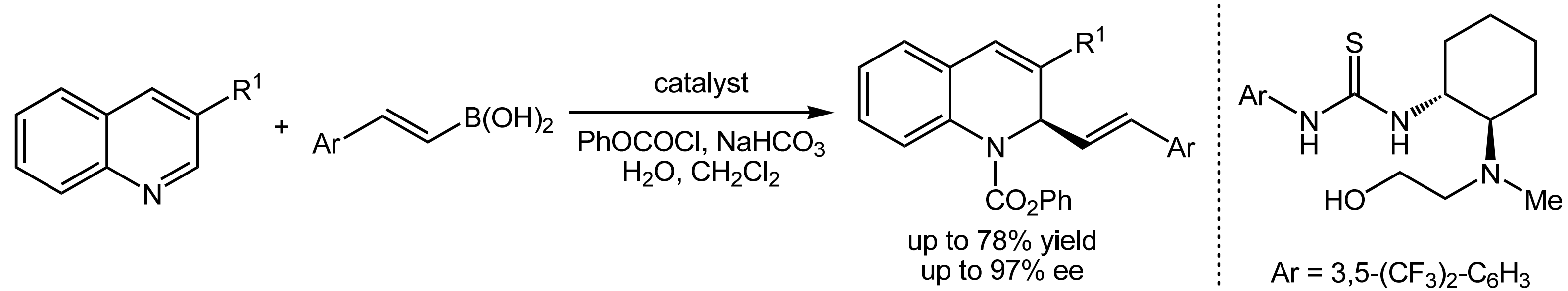
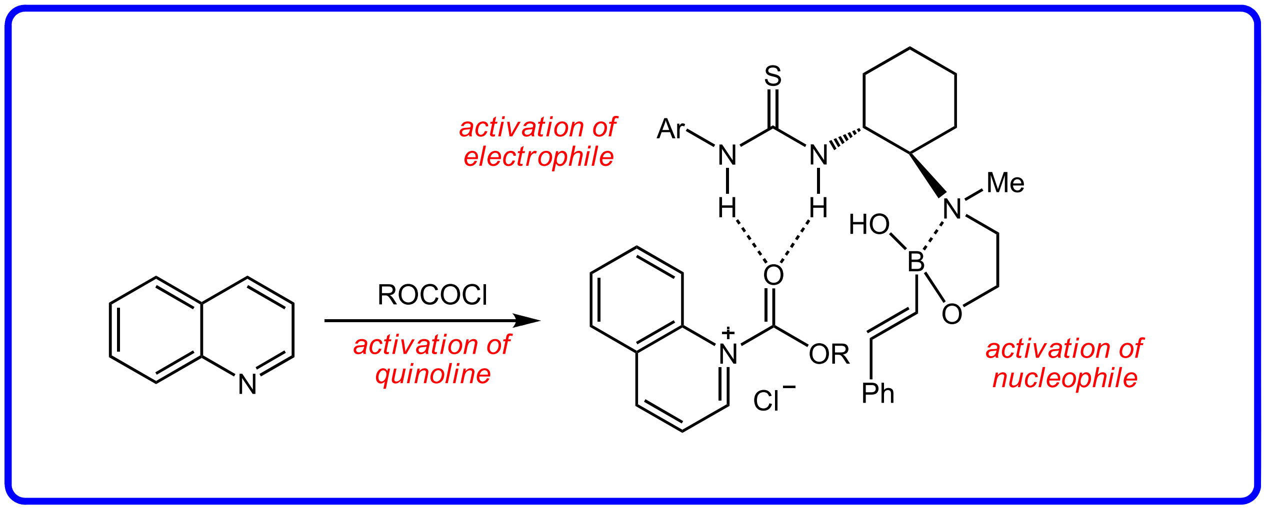
Organocatalytic Asymmetric Vinylation

➢ **Chiral Thiourea Catalyst**

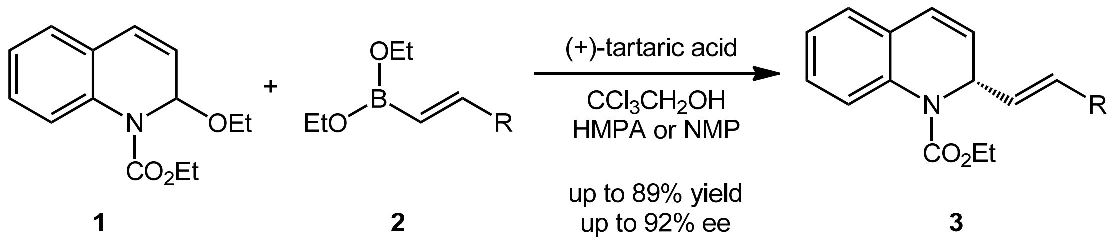


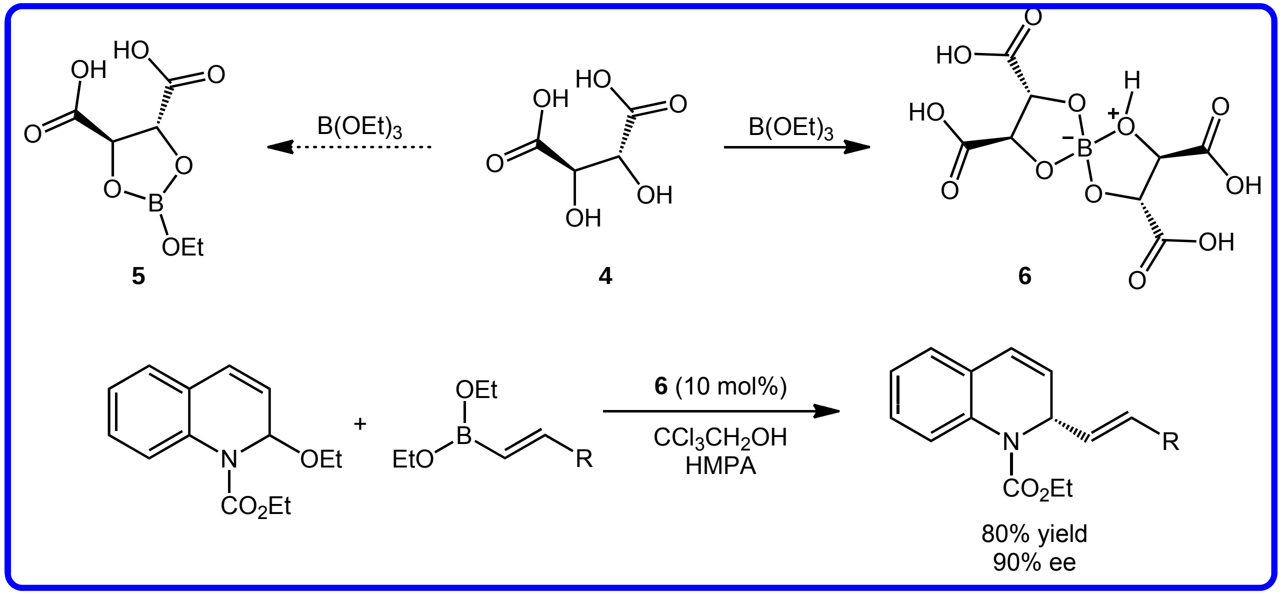


Takemoto, Y. *et al. J. Am. Chem. Soc.* **2007**, *129,* 6686.

Organocatalytic Asymmetric Vinylation

➢ **Chiral Tartaric Acid Catalyst**

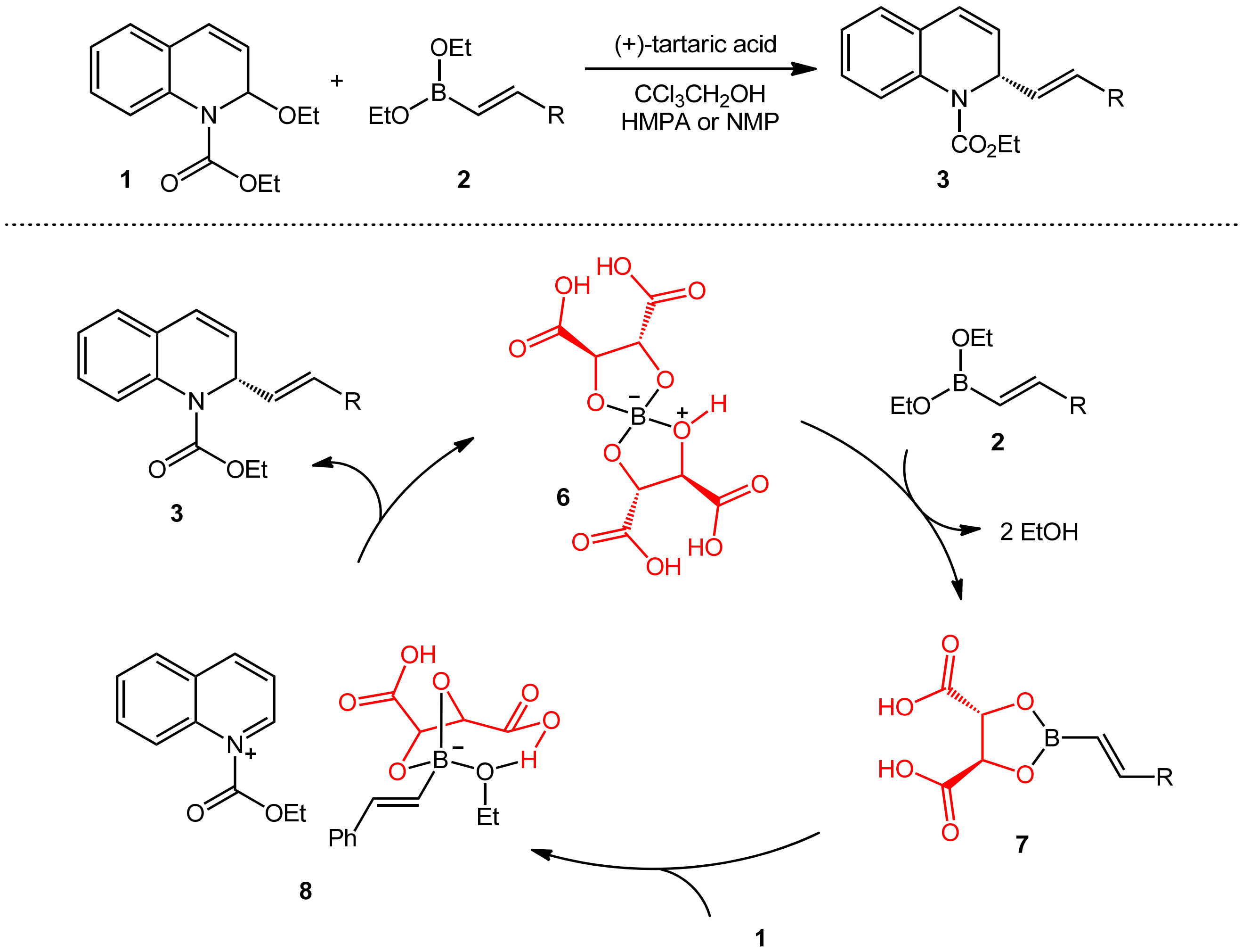




Schaus, S. E. *et al*. *Org. Lett.* **2011**, *13,* 6316.

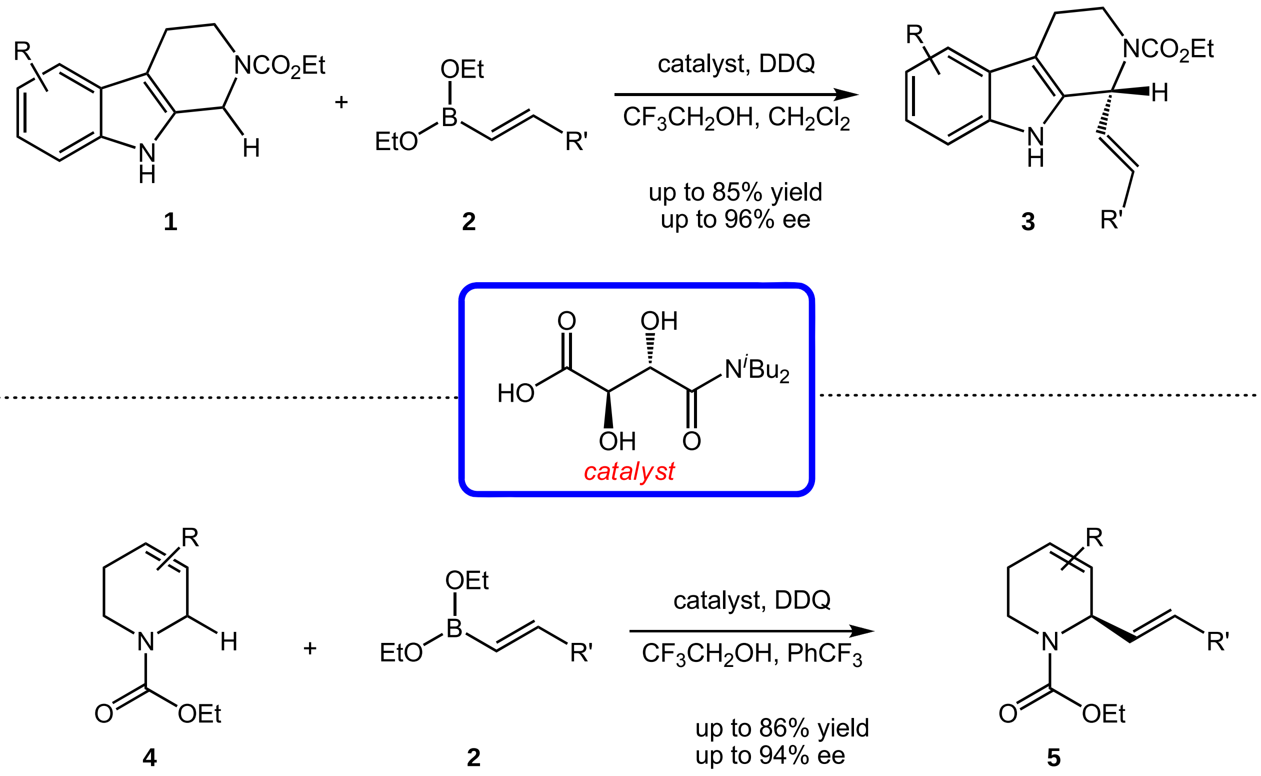
Organocatalytic Asymmetric Vinylation

➢ **Proposed Mechanism**



Organocatalytic Asymmetric Vinylation

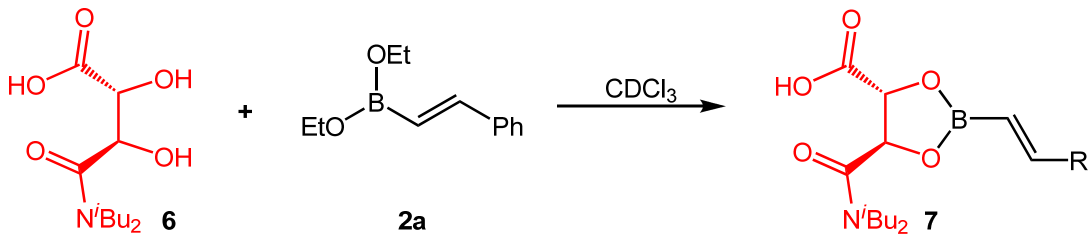
- **Chiral Tartaric Acid Derivatives**



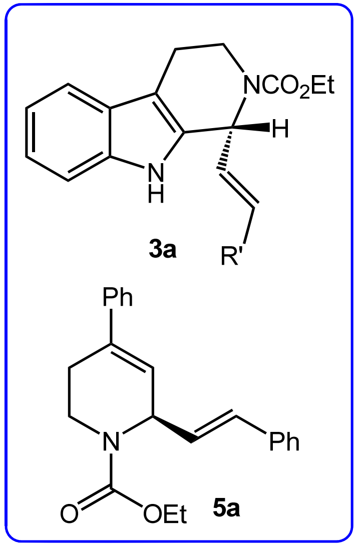
Liu, L. *et al. Angew. Chem. Int. Ed.* **2015**, *54,* 6012.

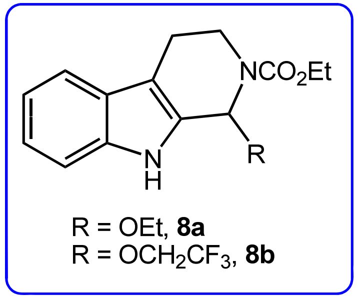
Organocatalytic Asymmetric Vinylation

➢ Control Experiments



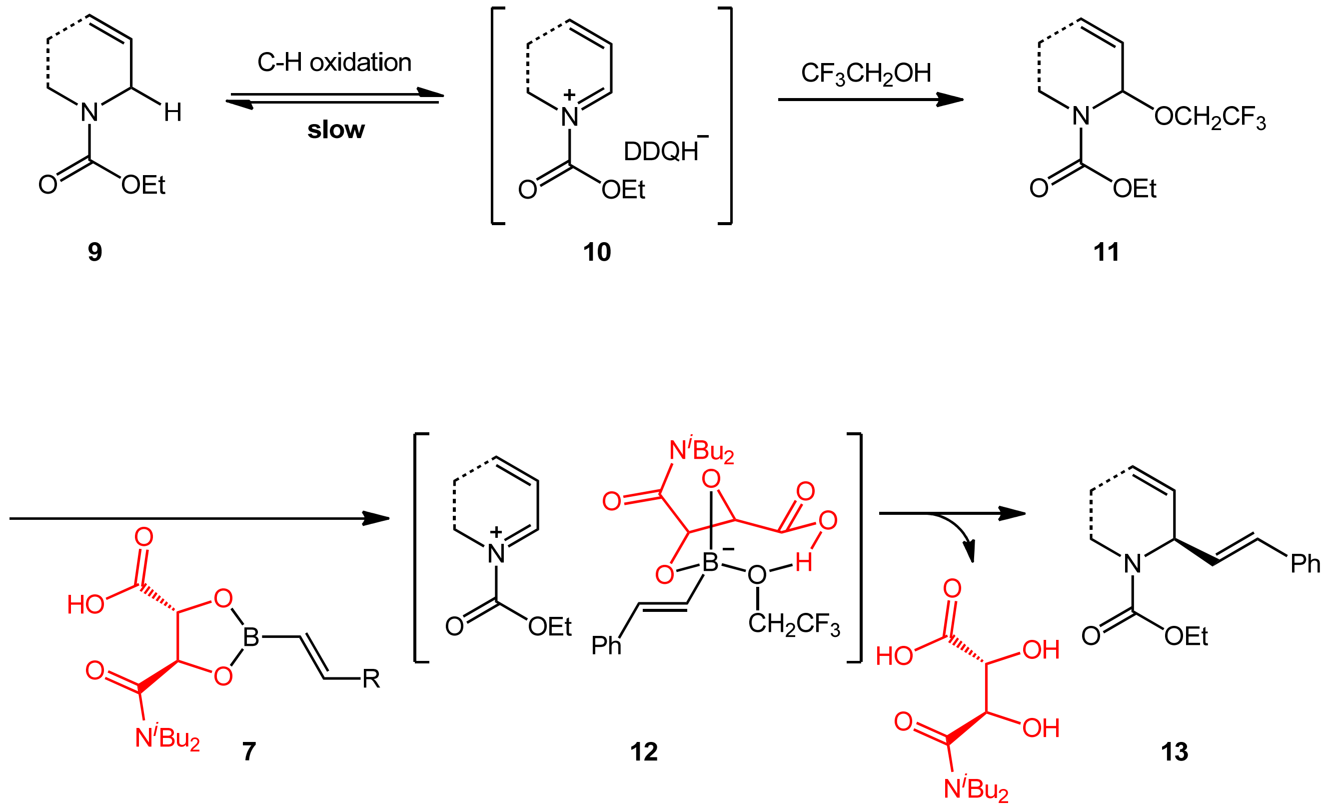
1a	+	**7**	DDQ, CF_3CH_2OH / CH_2Cl_2	**3a** 83%, 91% ee
4a	+	**7**	DDQ, CF_3CH_2OH / $PhCF_3$	**5a** 81%, 90% ee
8a	+	**2a**	without DDQ / CH_2Cl_2	**5a**
			CF_3CH_2OH	82%, 92% ee
			without CF_3CH_2OH	49%, 56% ee
8b	+	**2a**	without DDQ / $PhCF_3$	**5a**
			CF_3CH_2OH	83%, 94% ee
			without CF_3CH_2OH	60%, 78% ee





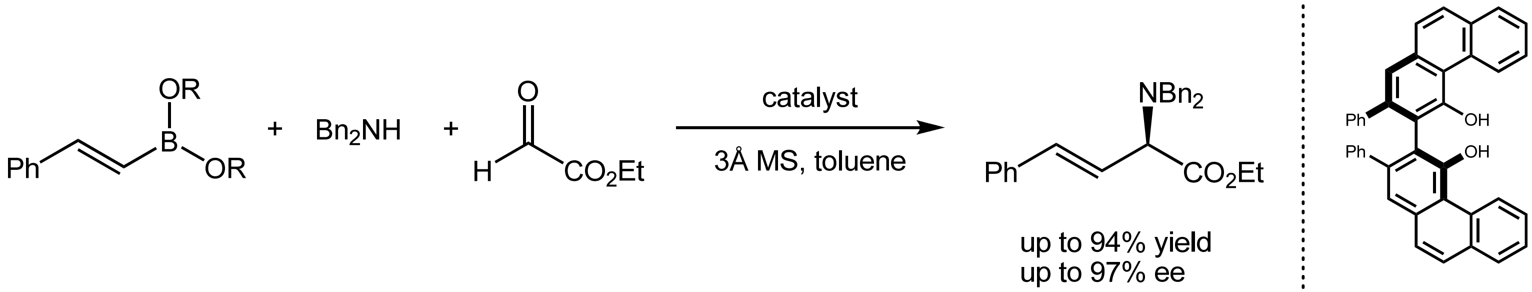
Organocatalytic Asymmetric Vinylation

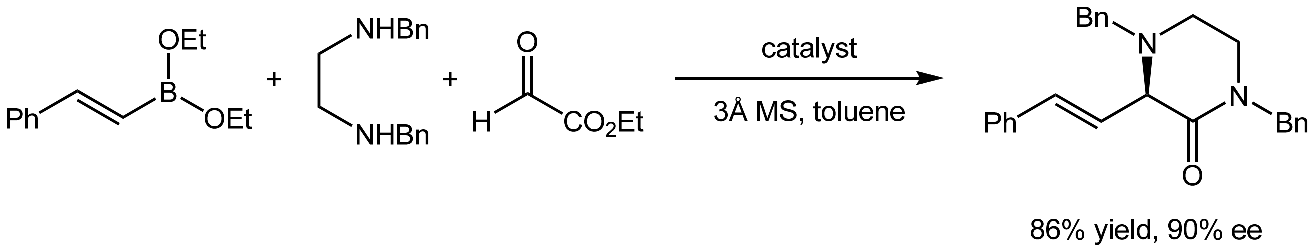
- **Proposed Mechanism**

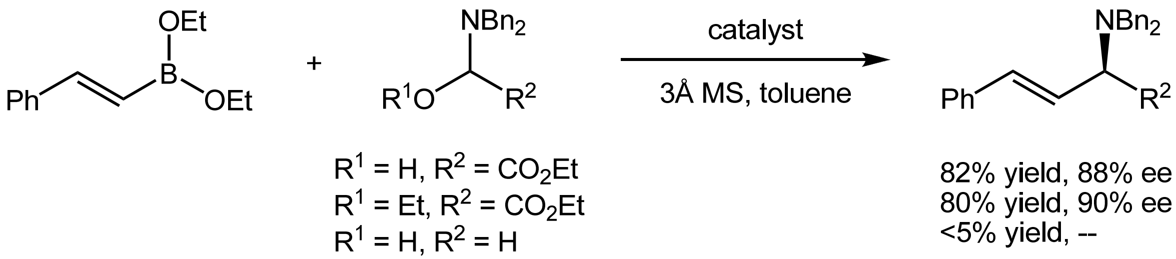


Organocatalytic Asymmetric Vinylation

➢ Chiral Biphenol Catalyst







Schaus, S. E. *et al. J. Am. Chem. Soc.* **2008**, *130,* 6922.

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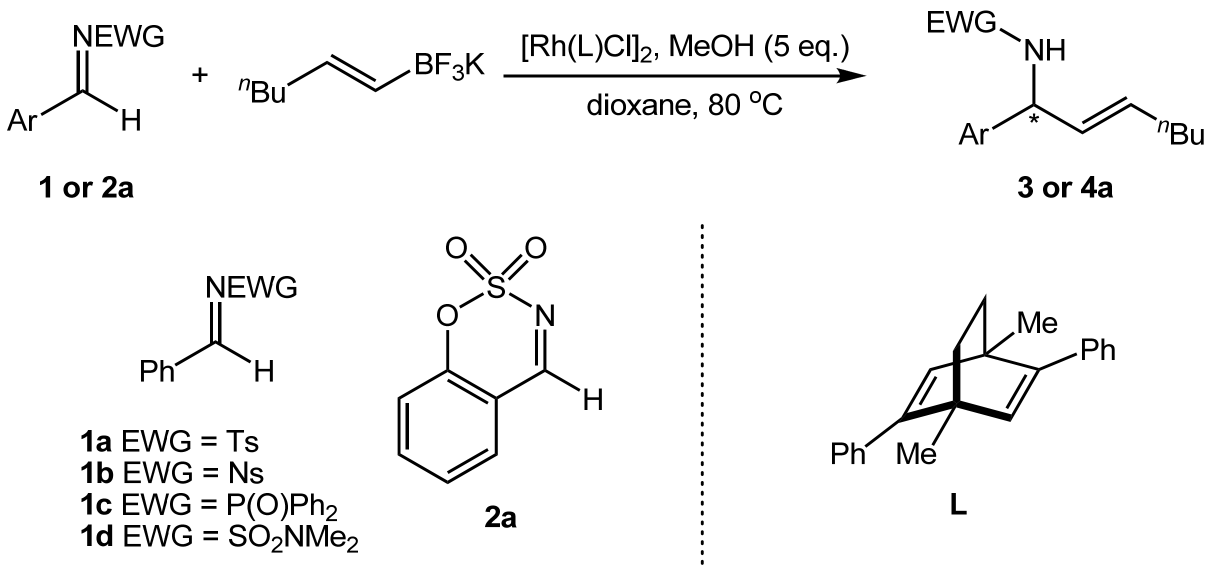
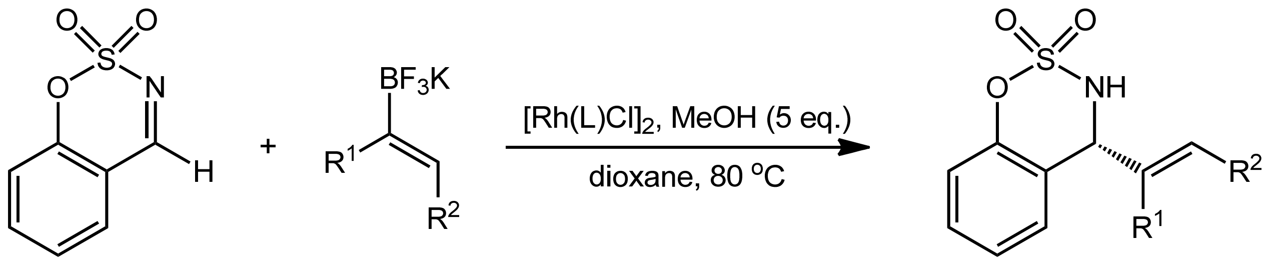
Rh-Catalyzed Enantioselective Vinylation



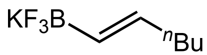
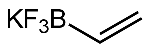
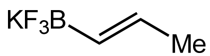
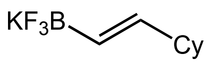
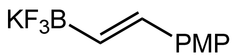
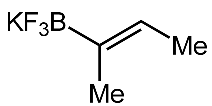
entry	imine	product	yield (%)	ee (%)
1	**1a**	**3a**	<5	--
2	**1b**	**3b**	80	7
3	**1c**	**3c**	<5	--
4	**1d**	**3d**	55	55
5	**2a**	**4a**	**>95**	**98**

Lam, H. W. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 6762.

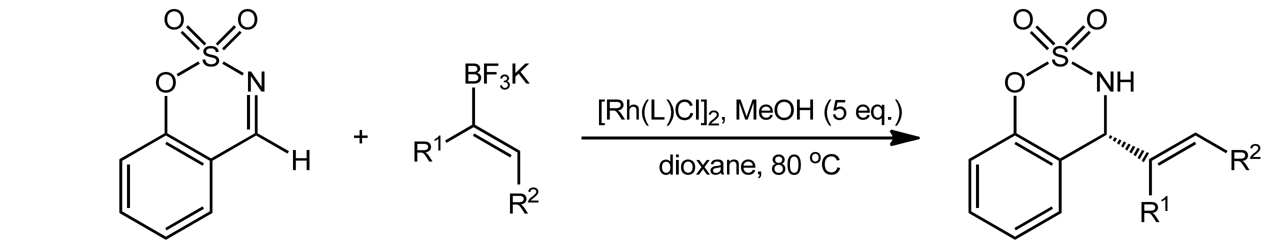
Rh-Catalyzed Enantioselective Vinylation



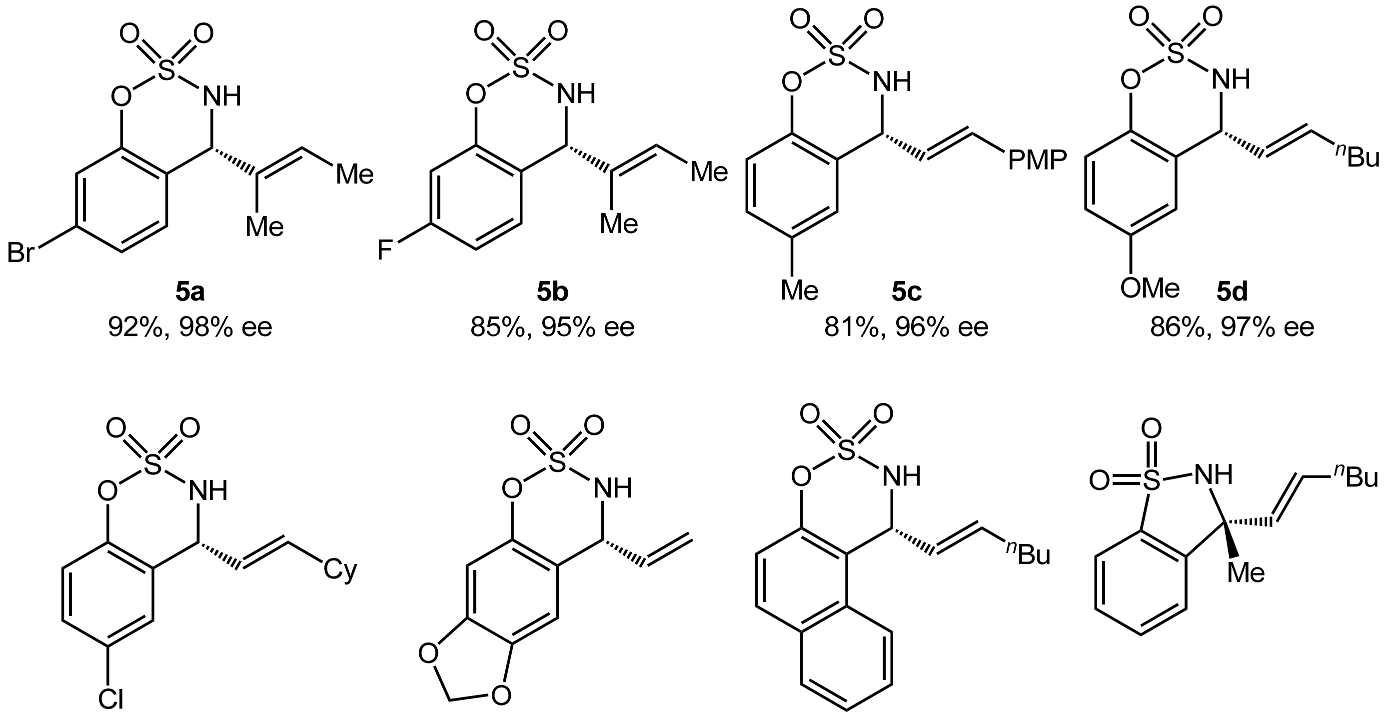
2a **4a-f**

entry	trifluoroborate	product	yield (%)	ee (%)
1		**4a**	90	98
2		**4b**	75	98
3		**4c**	79	97
4		**4d**	94	99
5		**4e**	88	95
6		4f	94	94

Rh-Catalyzed Enantioselective Vinylation



2 → **5**



5a 92%, 98% ee

5b 85%, 95% ee

5c 81%, 96% ee

5d 86%, 97% ee

5e 86%, 97% ee

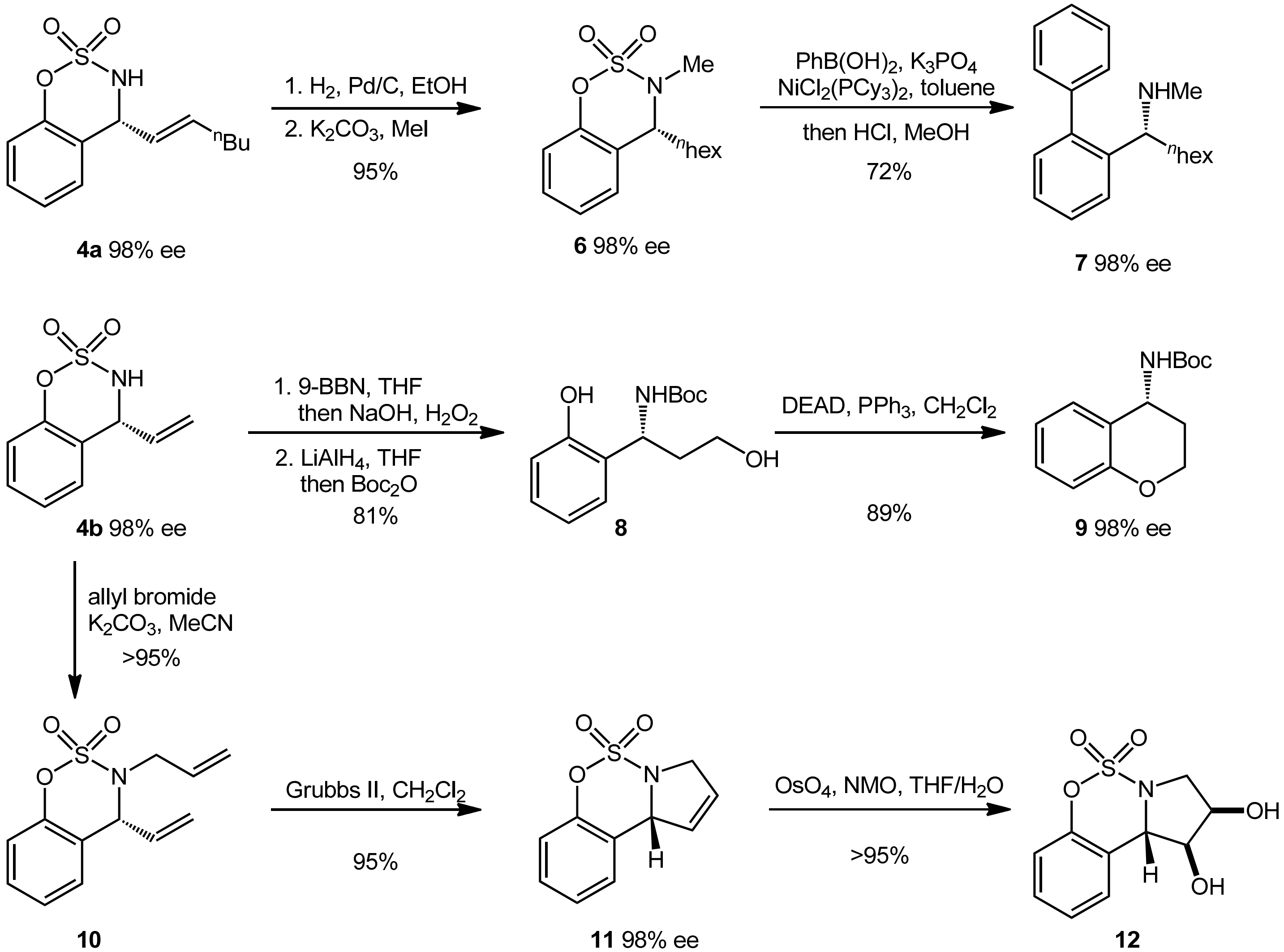
5f 50%, 97% ee

5g 55%, 96% ee

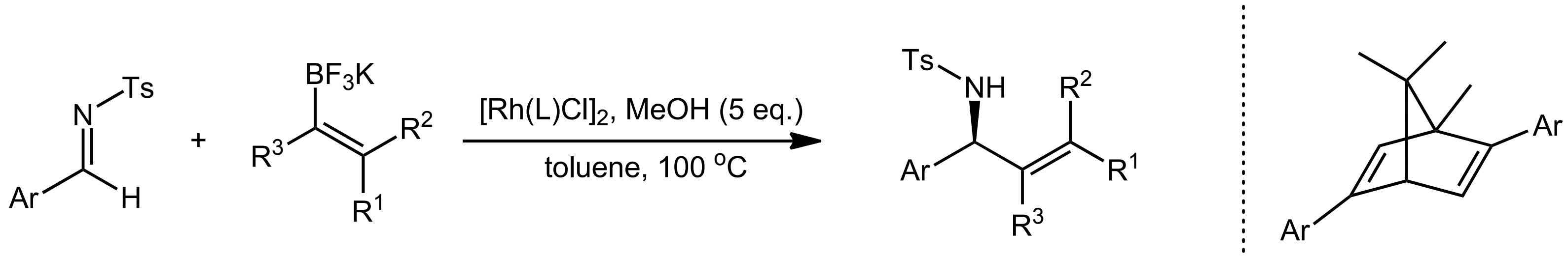
5h 68%, 90% ee

Rh-Catalyzed Enantioselective Vinylation

➢ **Transformations**

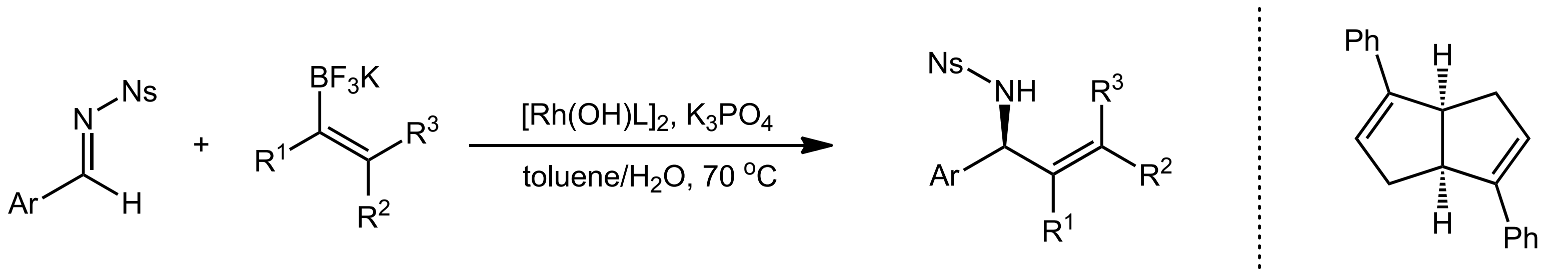


Rh-Catalyzed Enantioselective Vinylation



73-97% yield
72->99.5% ee

Ar = 4-$CF_3C_6H_4$

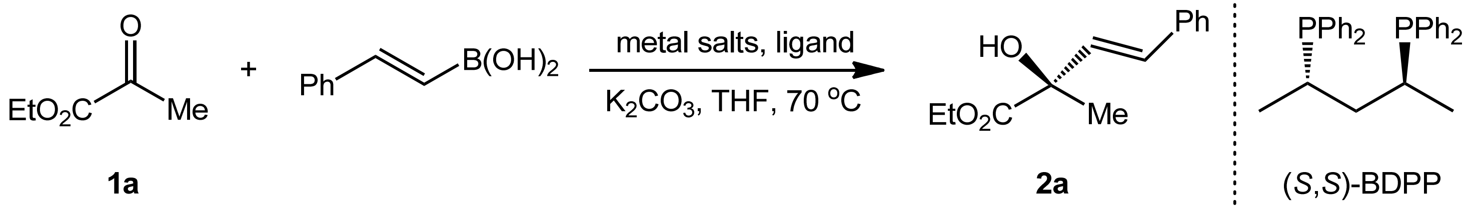


71-98% yield
97->99% ee

Wu, H.-L. *et al*. *Org. Lett.* **2014**, *16,* 632.
Lin, G.-Q. *et al*. *Org. Lett.* **2014**, *16,* 1016.

Co-Catalyzed Enantioselective Vinylation

➢ Enantioselective Vinylation of α-Ketoesters

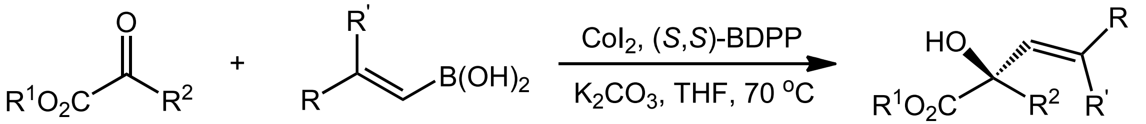


entry	metal	ligand	yield (%)	er
1	$FeBr_2$	DPPP	<2	--
2	$NiBr_2$	DPPP	<2	--
3	CuCl	DPPP	<2	--
4	$Co(OAc)_2$	DPPP	<2	--
5	CoI_2	DPPP	90	--
6	CoI_2	(*R*)-BINAP	<2	--
7	CoI_2	(*R*,*S*)-Josiphos	60	50:50
8	CoI_2	(*R*,*R*′,*S*,*S*′)-Duanphos	50	11:89
9	CoI_2	(*S*,*S*)-BDPP	60	96:4
10	$CoBr_2$	(*S*,*S*)-BDPP	54	94.5:5.5
11	$CoCl_2$	(*S*,*S*)-BDPP	30	93:7
12	CoF_2	(*S*,*S*)-BDPP	<2	--

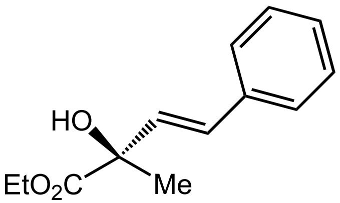
Zhao, Y. *et al. J. Am. Chem. Soc.* **2016**, *138*, 6571.

Co-Catalyzed Enantioselective Vinylation

- **Enantioselective Vinylation of α-Ketoesters**

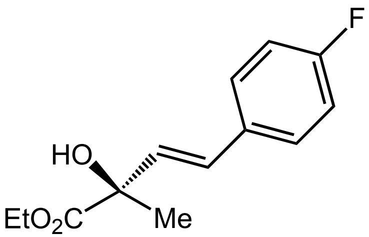


1 **2**



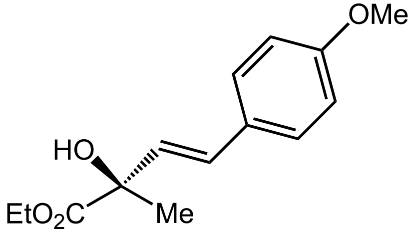
2a

60%, 96:4 er



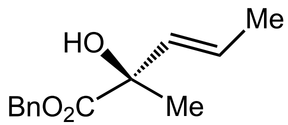
2b

60%, 95.5:4.5 er



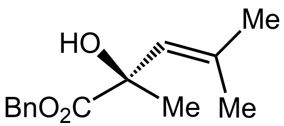
2c

75%, 95.5:4.5 er



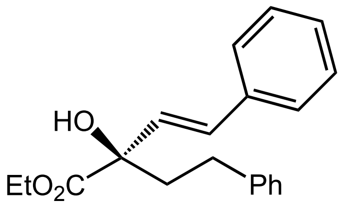
2d

74%, 94.5:5.5 er



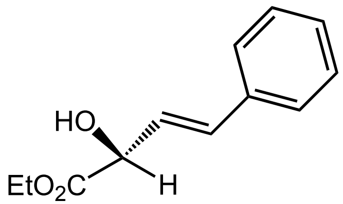
2e

30%, 98:2 er



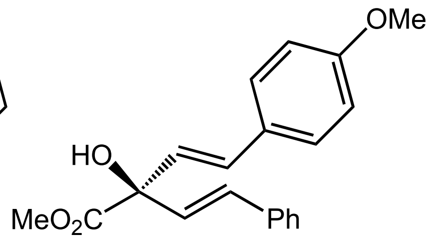
2f

50%, 95.5:4.5 er



2g

70%, 89:11 er

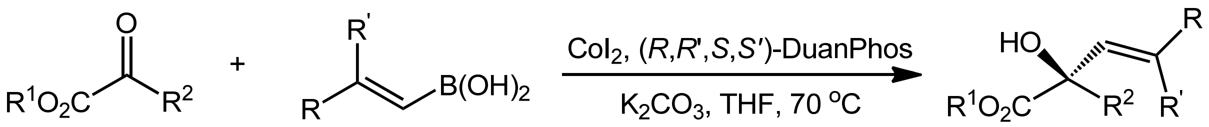


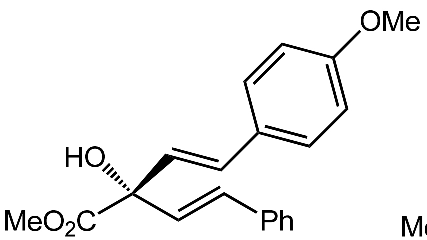
2h

67%, 92:8 er

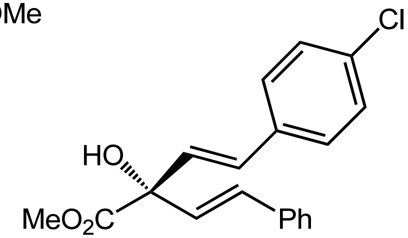
Co-Catalyzed Enantioselective Vinylation

➢ Enantioselective Vinylation of α-Ketoesters

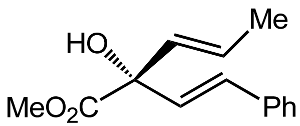




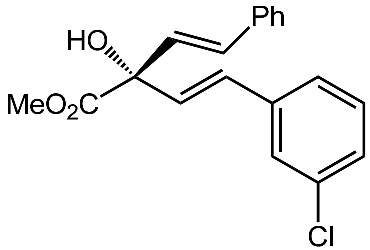
ent-**2h**
66%, 95.5:4.5 er



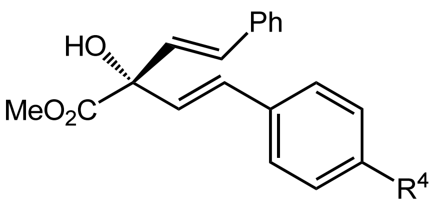
2i
48%, 96:4 er



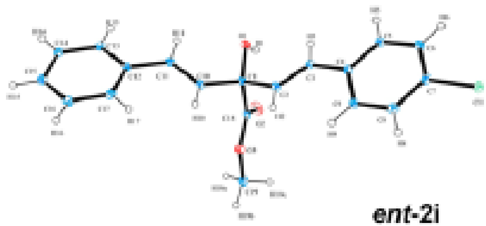
2j
60%, 95.5:4.5 er



2k
58%, 96.5:3.5 er



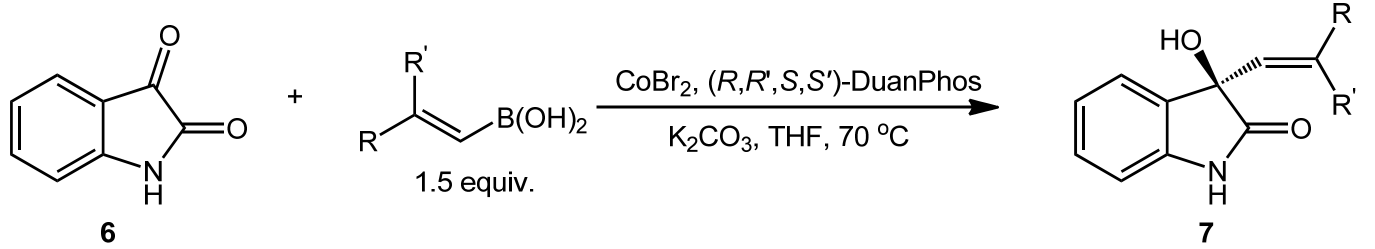
2l: R^4 = Me 55%, 96.5:3.5 er
2m: R^4 = CF_3 55%, 95.5:4.5 er
2n: R^4 = Br 60%, 95.5:4.5 er
2o: R^4 = F 62%, 97:3 er
2p: R^4 = CN 58%, 94:6 er
***ent*-2i**: R^4 = Cl 75%, 96.5:3.5 er

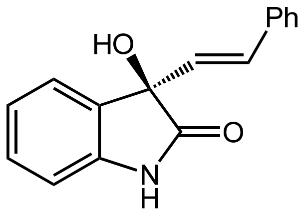


ent-**2i**

Co-Catalyzed Enantioselective Vinylation

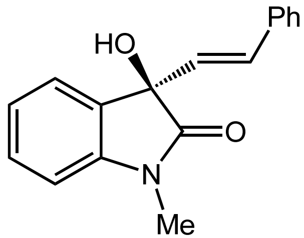
➢ Enantioselective Vinylation of Oxindoles





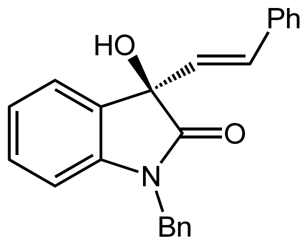
7a

80%, 96.5:3.5 er



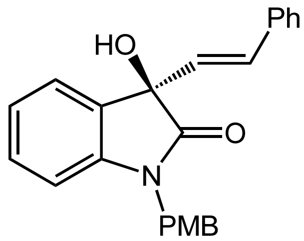
7b

90%, 95.5:4.5 er



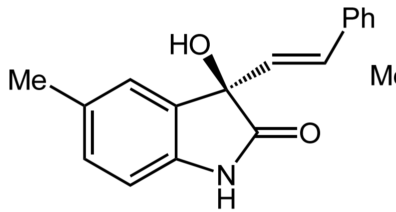
7c

80%, 93.5:6.5 er



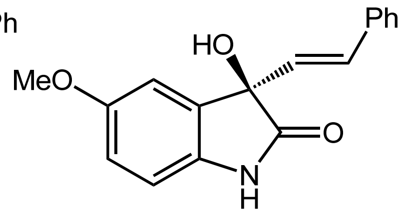
7d

70%, 93.5:6.5 er



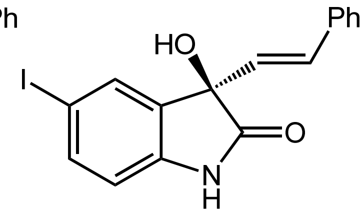
7e

50%, 96:4 er



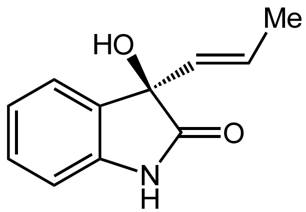
7f

73%, 96:4 er



7g

84%, 93.5:6.5 er

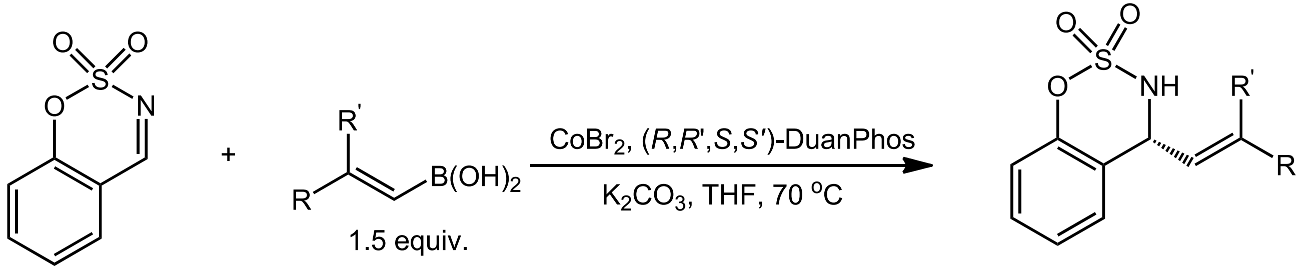


7a

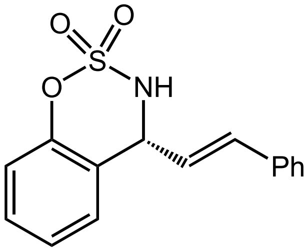
65%, 95:5 er

Co-Catalyzed Enantioselective Vinylation

➢ Enantioselective Vinylation of Imines

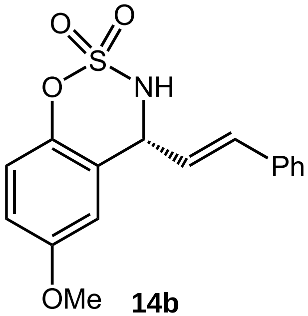


12 **14**



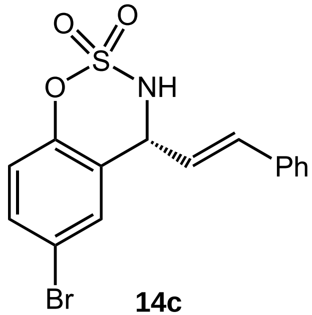
14a

75%, >99.5:0.5 er



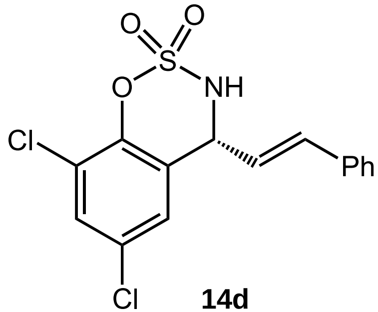
14b

73%, >99.5:0.5 er



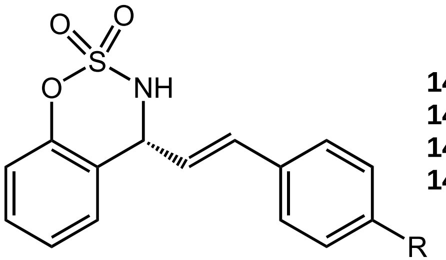
14c

52%, >99.5:0.5 er



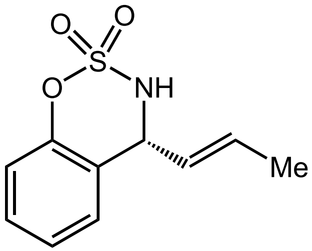
14d

69%, >99.5:0.5 er



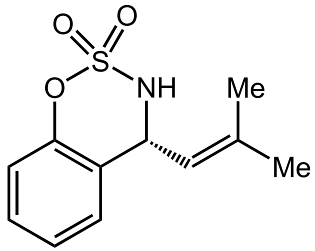
14

14e R = Me 80%, >99.5:0.5 er
14f R = MeO 85%, >99.5:0.5 er
14g R = Cl 77%, >99.5:0.5 er
14h R = F 58%, 99:1 er



14i

65%, >99.5:0.5 er

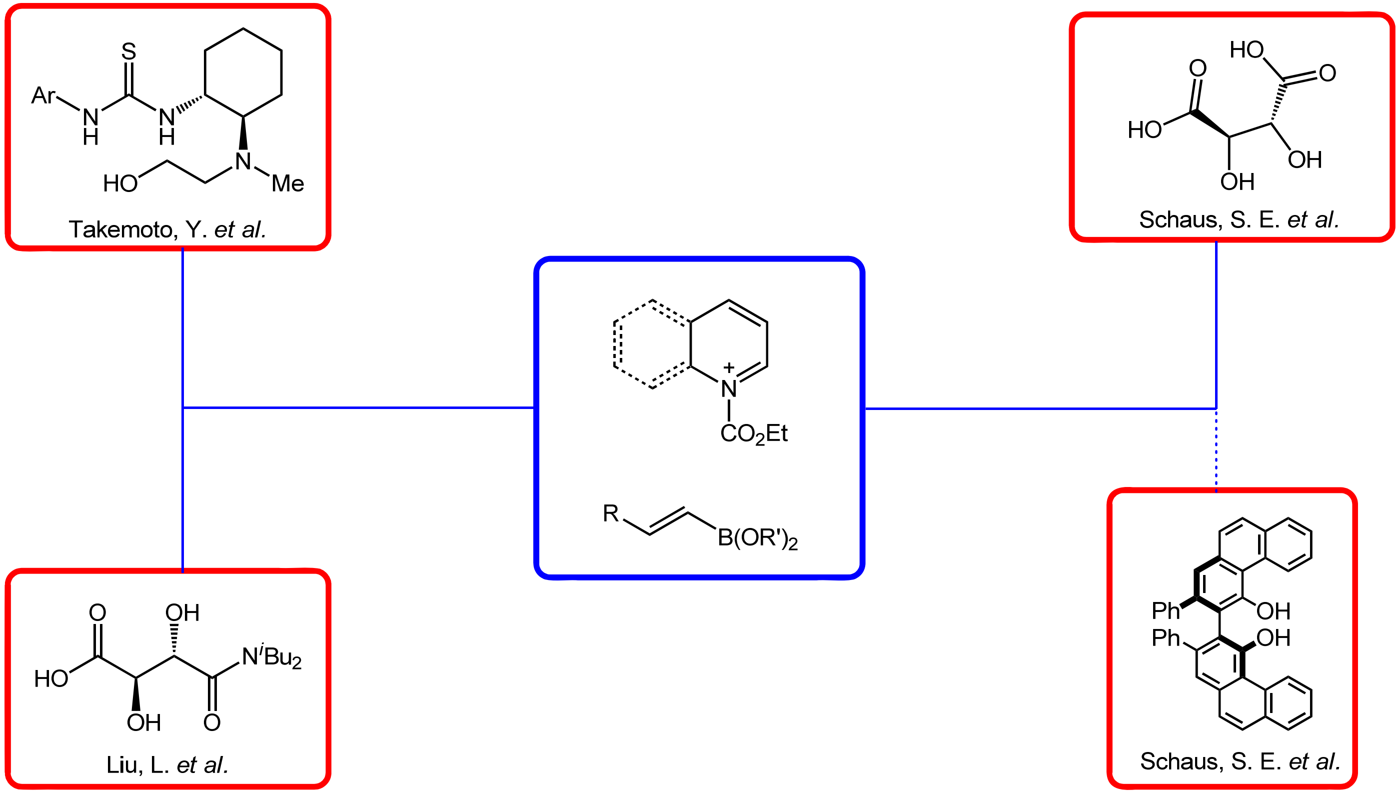


14j

70%, >99.5:0.5 er

Summary

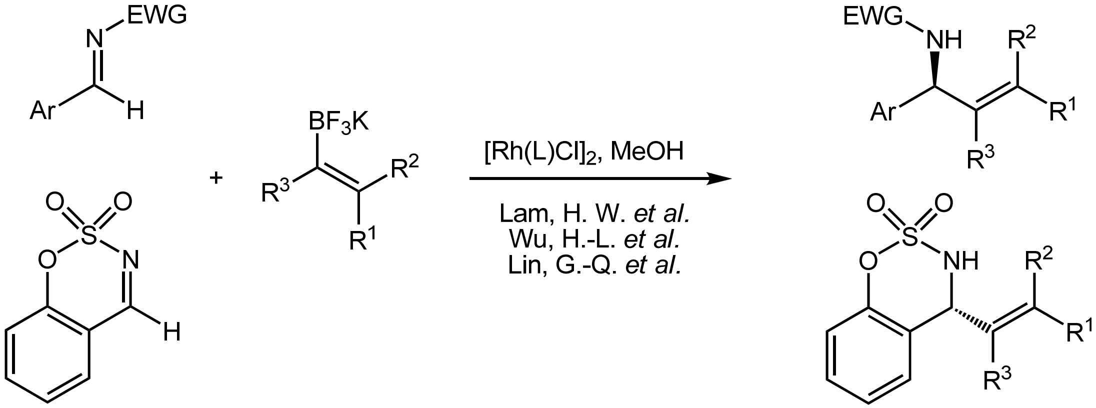
1. Organocatalytic Asymmetric Vinylation of Activated Imines



Summary

2. Transition-Metal Catalyzed Enantioselective Vinylation of Activated Ketones and Imines

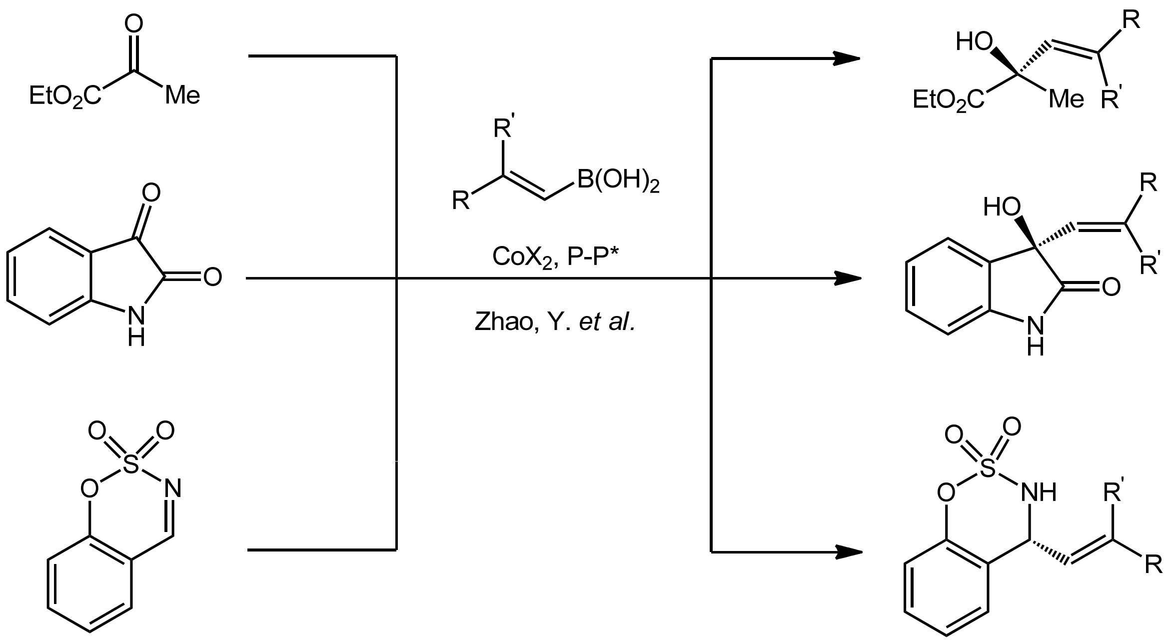
➢ **Rh-Catalyzed Enantioselective Vinylation**



Summary

2. Transition-Metal Catalyzed Enantioselective Vinylation of Activated Ketones and Imines

- **Co-Catalyzed Enantioselective Vinylation**



Allylic alcohols and amines are among the most abundant and significant structural motifs in organic synthesis. They are present in numerous biologically active molecules and drugs; they can also undergo various selective transformations with high fidelity to afford a range of stereodefined compounds of value in chemistry and medicine. Consequently, the construction of allylic alcohols and amines in a stereoselective fashion has been a focal point in methodology development for decades. Traditional approaches that have proven to be highly successful include kinetic resolution of allylic alcohols by the Sharpless asymmetric epoxidation, enantioselective reduction of enones, as well as vinylation of carbonyls and imines. Other approaches such as metal-catalyzed rearrangement of allylic imidates, allylic oxidation or amination, amination of allenes, and organocatalytic tandem reactions have also been documented in recent years.

We have demonstrated, for the first time, a cobalt-catalyzed enantioselective vinylation of α-ketoesters, isatins, and imines, which greatly expands the scope of cobalt catalysis in asymmetric synthesis. This transformation utilizes a convenient procedure using commercially available catalysts and reagents and delivers tertiary allylic alcohols and cyclic allylic amines in excellent enantioselectivity. The high efficiency, selectivity, and operational simplicity of this transformation, coupled with the wide range of electrophiles, are expected to render this method a valuable tool in asymmetric synthesis.