ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Recent Developments of Oxy-Michael Reaction and Applications in Natural Product Synthesis

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LSPN Seminar

22-10-2015

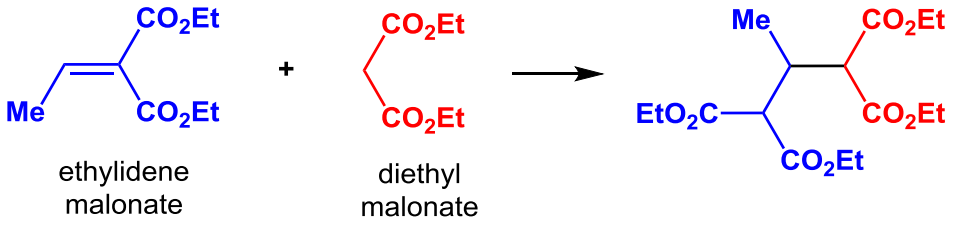
Outline

- *Introduction*
- *General Protocols*
- *Asymmetric Oxy-Michael Reaction*
- *Applications in Natural Product Synthesis*
- *Summary and Outlook*

Introduction

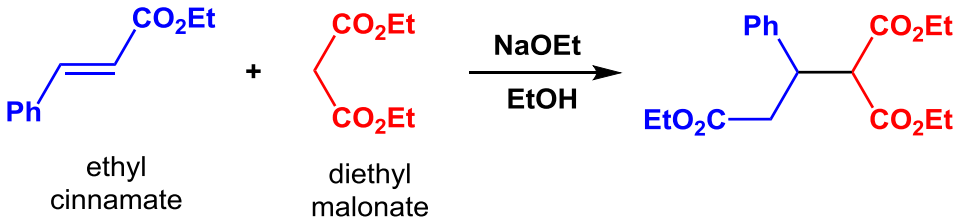
Michael Addition

- *The first example of carbon nucleophile adding to an electron-deficient double bond*



Komnenos, T. *Liebigs Ann. Chem.* **1883**, *218*, 145.

- *Michael systematically investigated the reaction of stabilized anions with α,β-unsaturated systems*

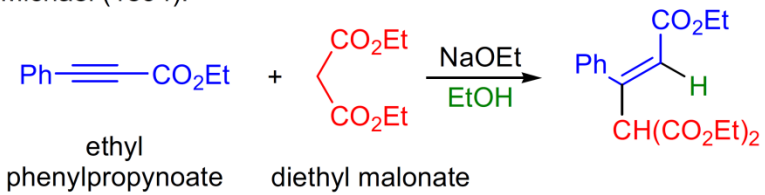


Michael, A. *J. Prakt. Chem./Chem.-Ztg.* **1887**, *35*, 349.

Introduction

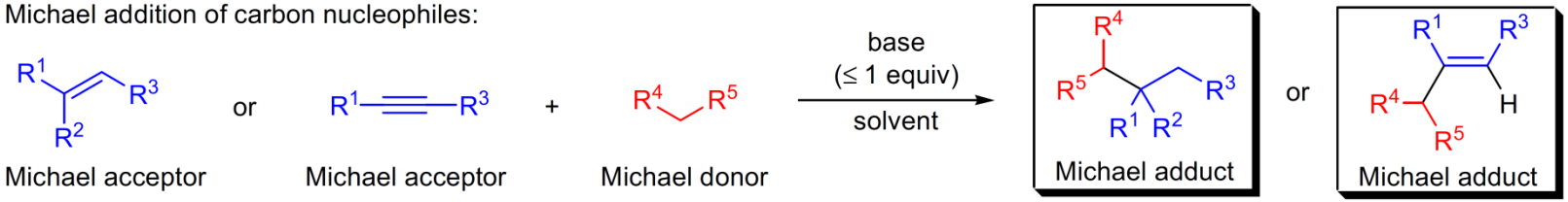
Michael Addition

Michael (1894):

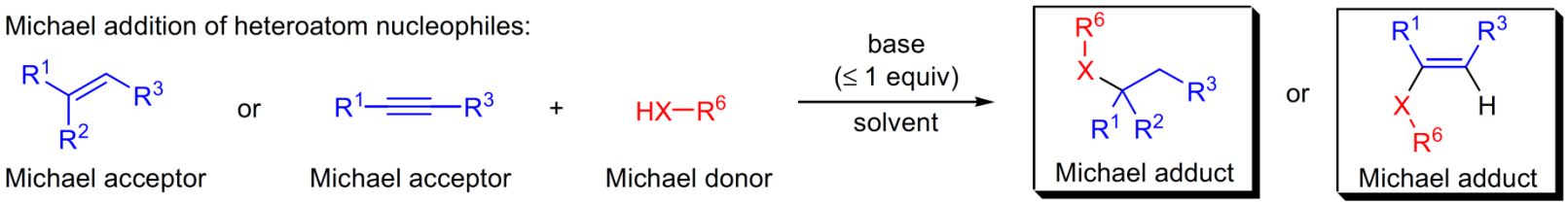


Michael, A. *J. Prakt. Chem./Chem.-Ztg.* **1894**, *49*, 20.

Michael addition of carbon nucleophiles:



Michael addition of heteroatom nucleophiles:

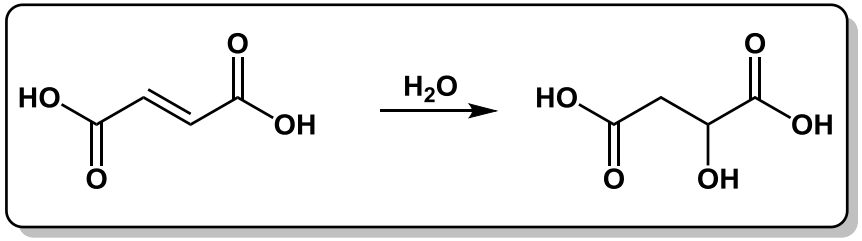


Currently, all reactions that involve the 1,4-addition (conjugate addition) of any nucleophile to activated π-systems are also referred to as the Michael addition.

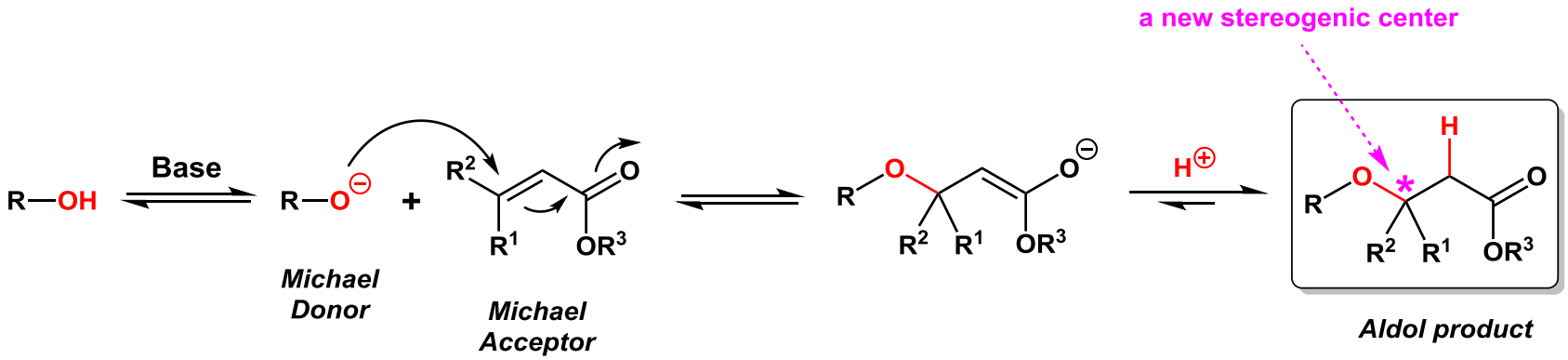
Introduction

Oxy-Michael reaction

- *The first oxy-Michael reaction was reported earlier than the carbon Michael reaction.*

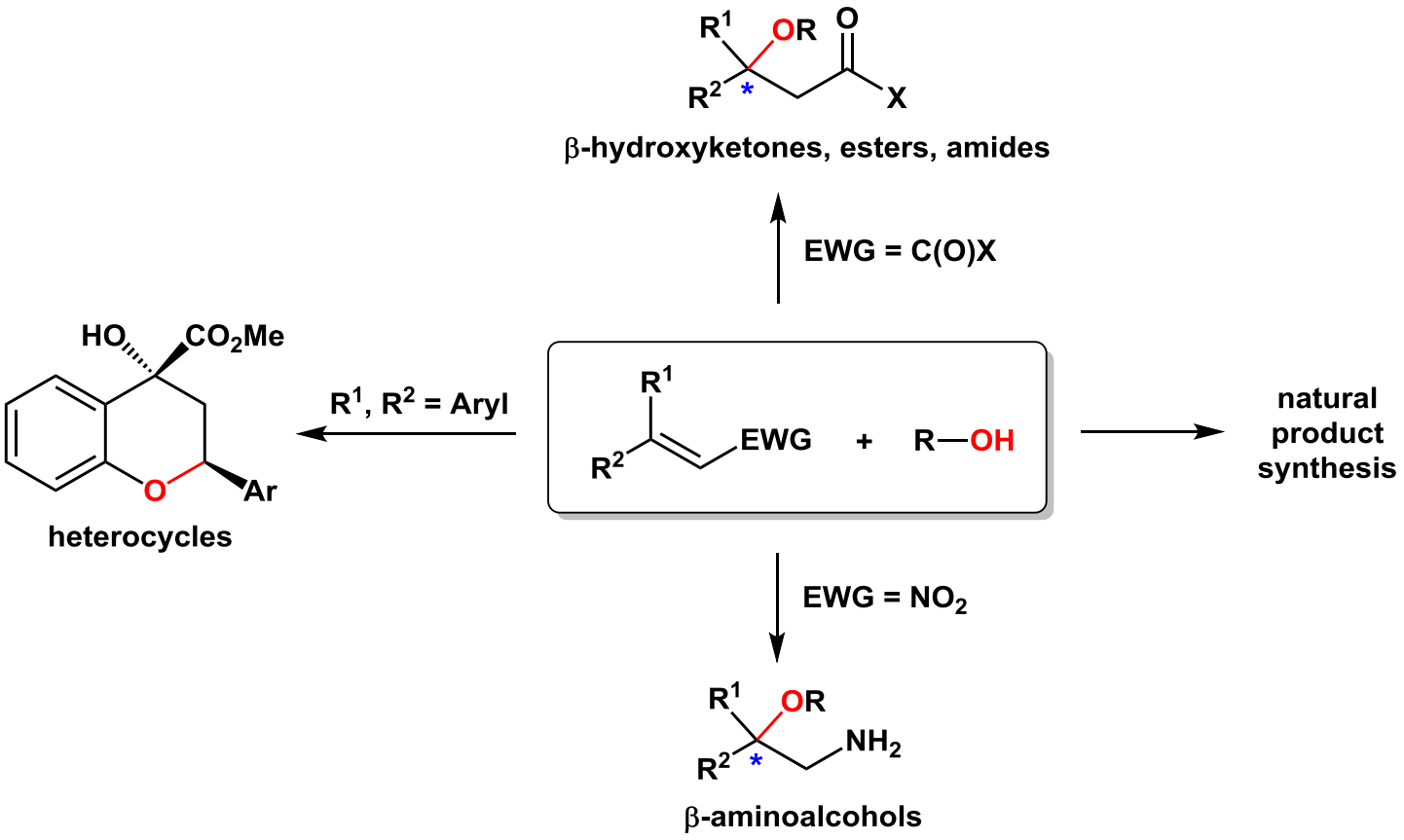


Loydl, F. *Justus Liebigs Ann. Chem.* **1878**, *192*, 80.



Introduction

Oxy-Michael reaction



Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218.

Outline

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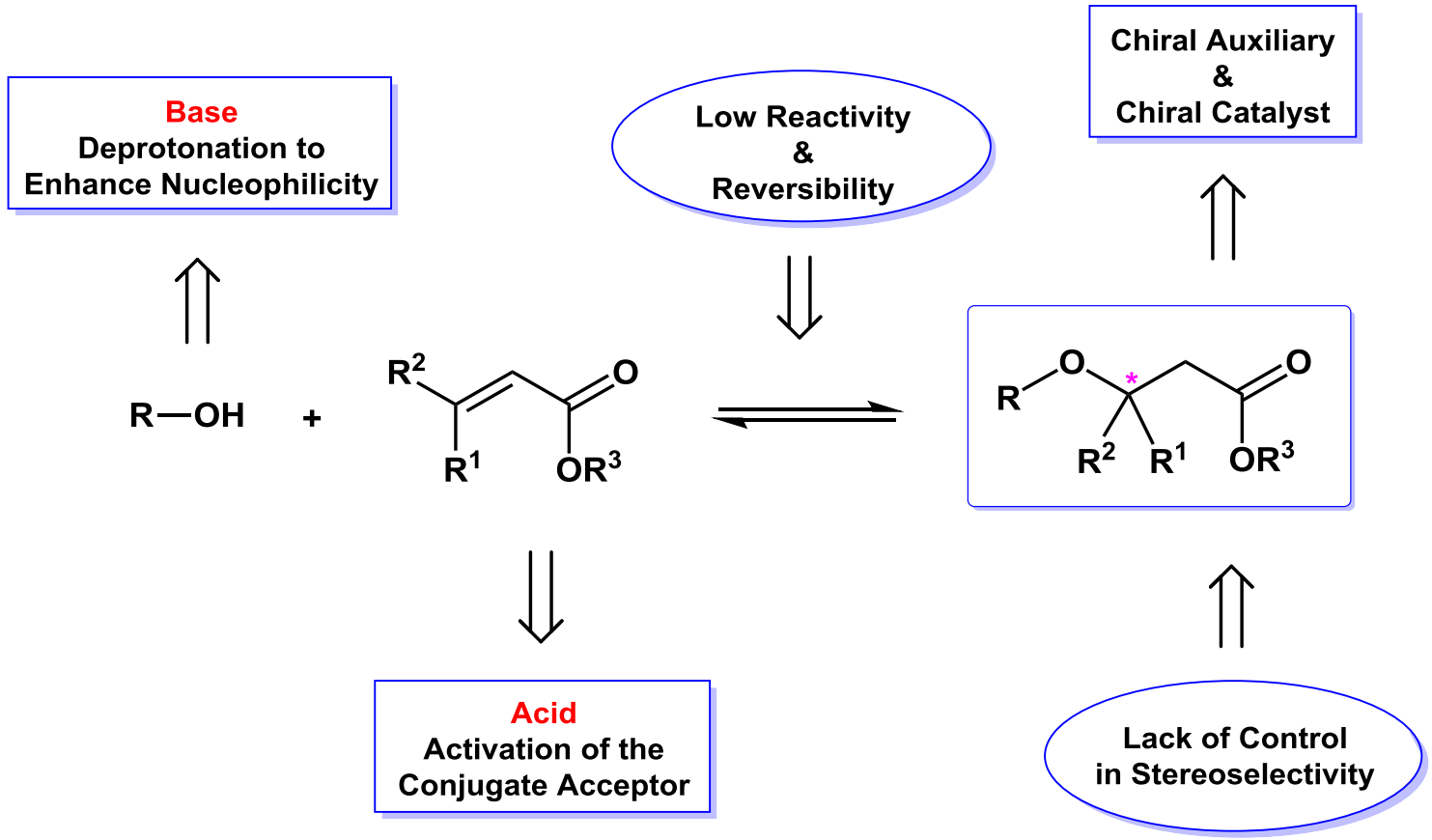
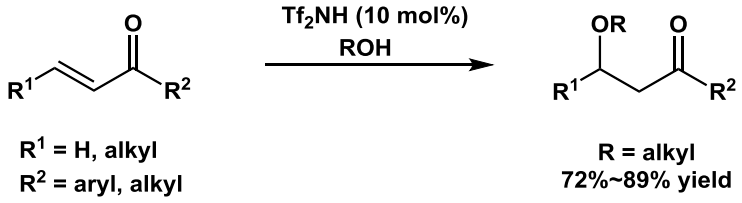
- *General Protocols*
- *Asymmetric Oxy-Michael Reaction*
- *Applications in Natural Product Synthesis*
- *Summary and Outlook*

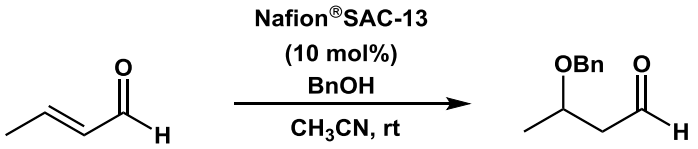
Ways of activation



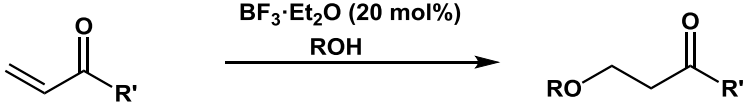
Acid as catalyst



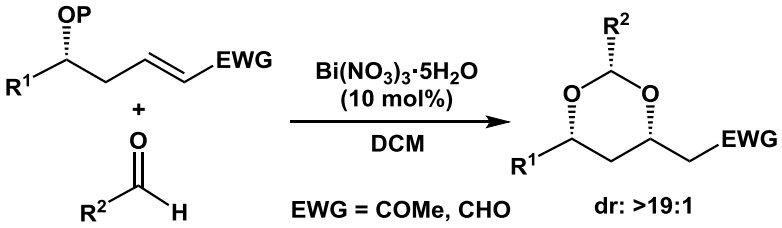
Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141.



Wabnitz , T. C.; Yu, J. Q.; Spencer, J. B. *Synlett*. **2003**, 1070.

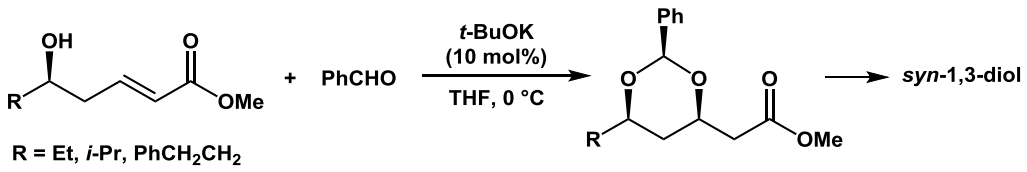


Bernal, P.; Tamariz, J. *Tetrahedron Lett.* **2006**, *47*, 2905.

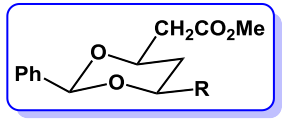


Evans, P. A.; Grisin, A.; Lawler, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 2856.

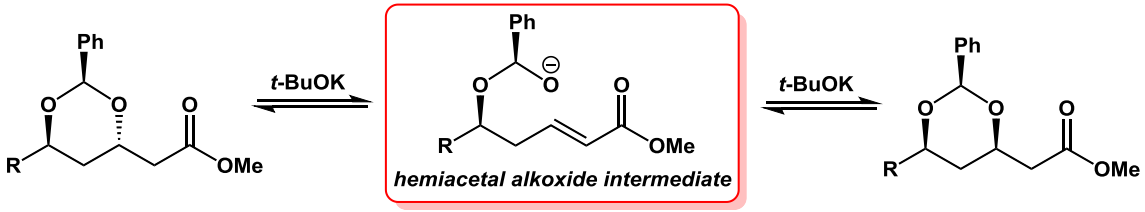
Base as catalyst

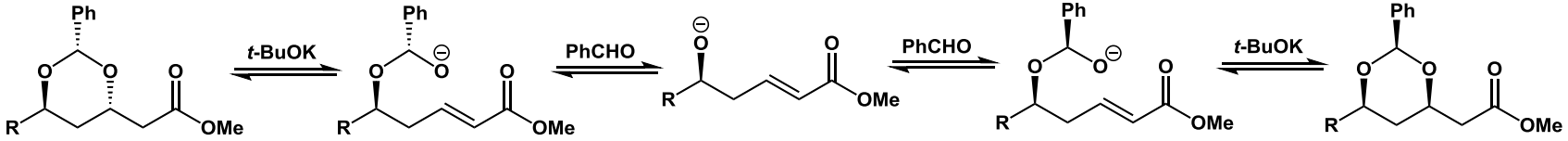


R = Et, *i*-Pr, $PhCH_2CH_2$

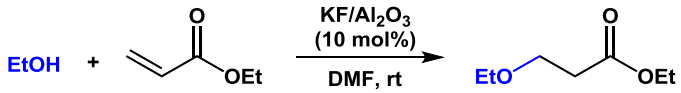


Thermodynamic control!

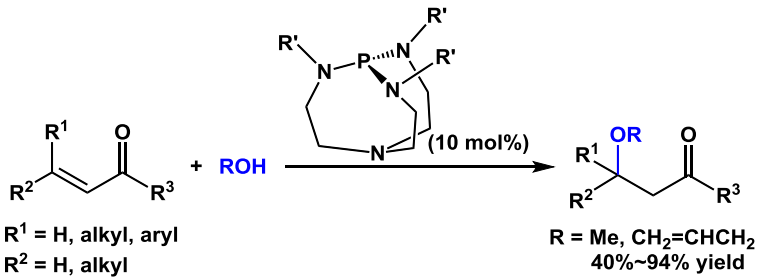




Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.



Kabashima, H.; Katou, T.; Hattori, H. *Appl. Catal. A: Gen.* **2001**, *214*, 121.
Yang, L.; Xu, L. W.; Xia, C. G. *Tetrahedron Lett.* **2005**, *46*, 3279.

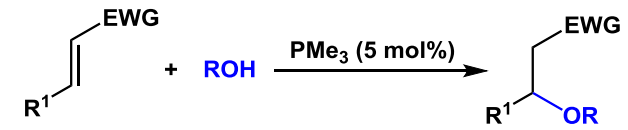


R^1 = H, alkyl, aryl
R^2 = H, alkyl
R^3 = alkyl

R = Me, CH_2=$CHCH_2$
40%~94% yield

Kisanga, P. B.; Verkade, J. G. *J. Org. Chem*. **2002**, *67*, 3555.

P-based catalyst

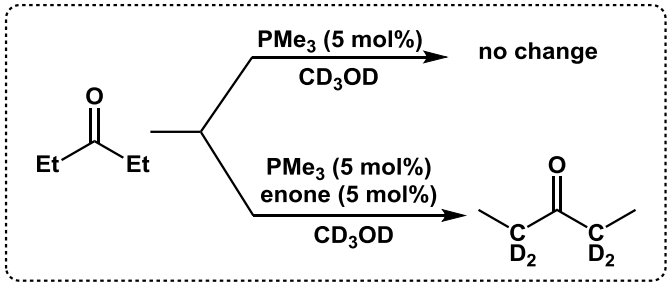


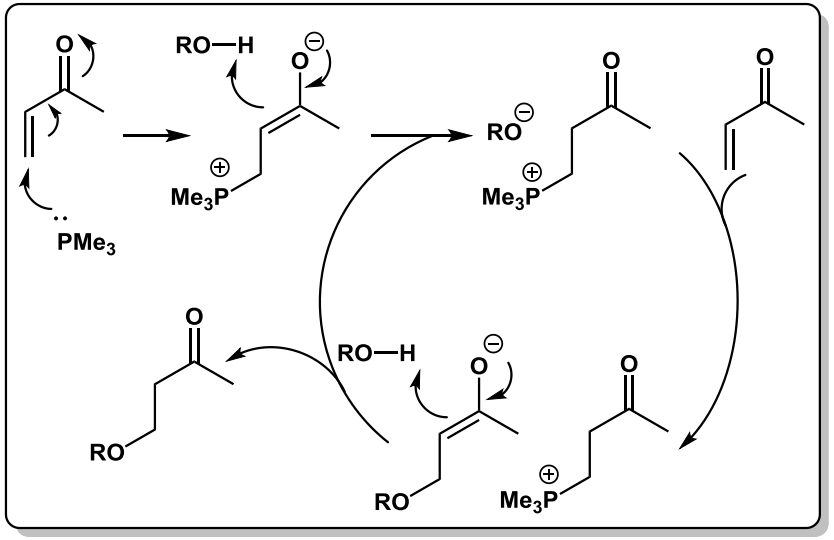
R^1 = H, Me, Ph
EWG = COMe, CO_2Me, CN

R = Me, *i*-Pr, Ph
59%~85% yield

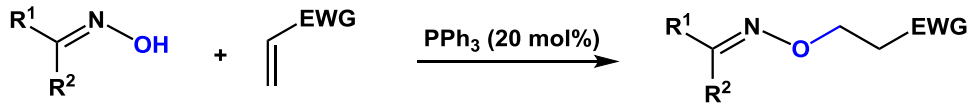
- Triethylamine does not work in this reaction.
- The phosphine probably does not merely act as a base.
- A strong base was generated during the reaction!

When deuterated protic solvent ROD was used, H/D exchange was observed at the α-position of α,β-unsaturated compound.





Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.



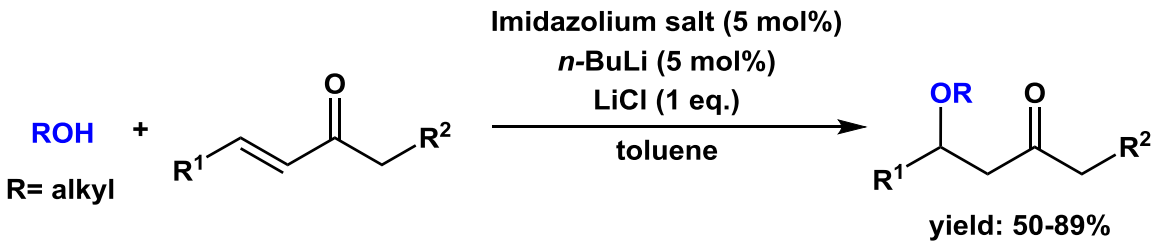
R^1 = alkyl, aryl
R^2 = H, aryl

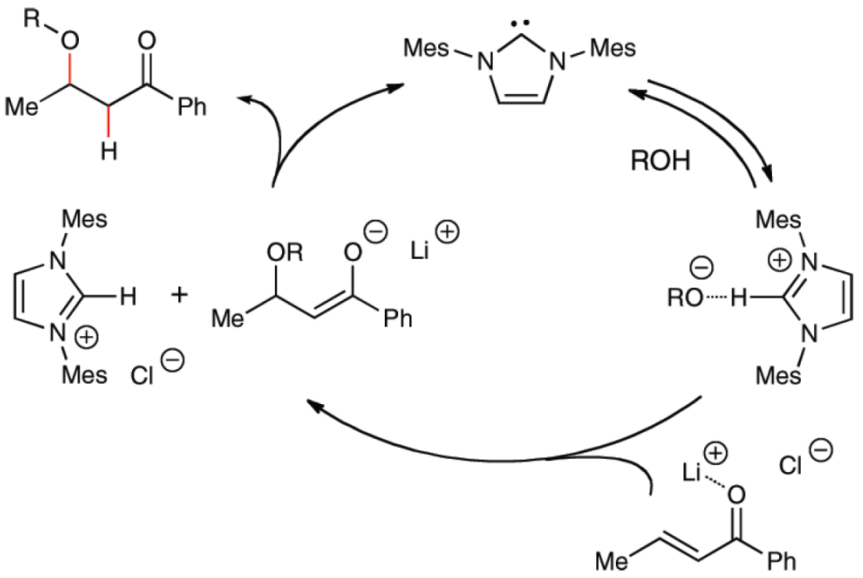
EWG = CN, CO_2Et, SO_2Ph

65%~90% yield

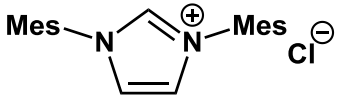
Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis* **2003**, 1018.

NHC-catalyst



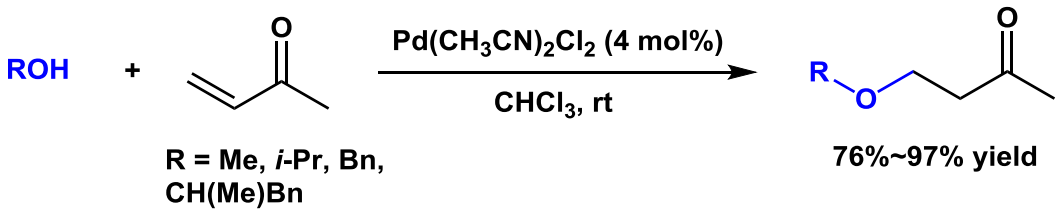


Imidazolium salt:

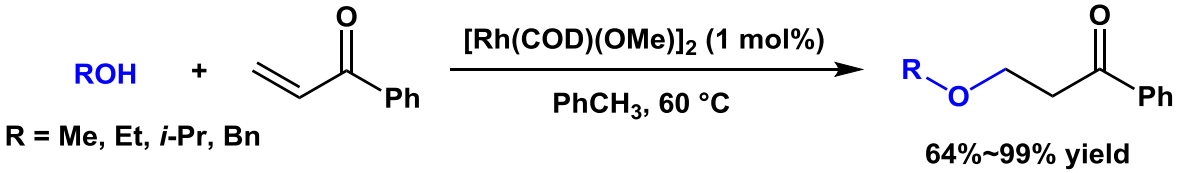


Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179.

Metal-catalyzed oxy-Michael



Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20, 4403.*



Farnworth, M. V.; Cross, M. J.; Louie, J. *Tetrahedron Lett.* **2004**, *45,* 7441.

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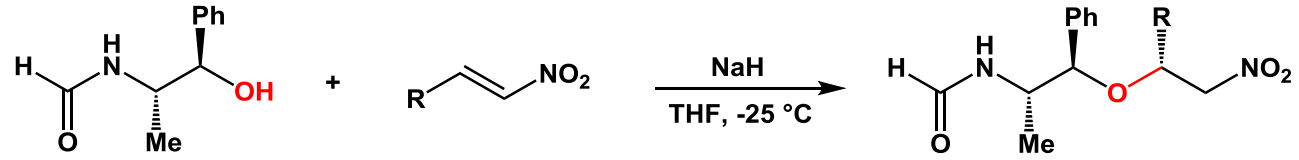
Chiral auxiliary

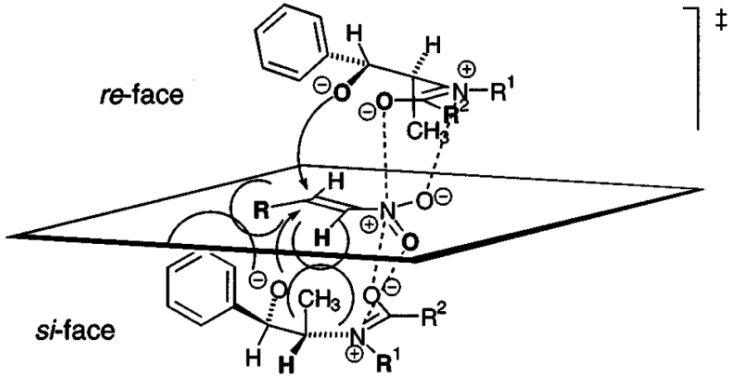


N-formylnorephedrine

vicinal amino alcohol

R	Yield/%	*de*/%
Me	60	94
Et	75	93
n-Pr	52	94
i-Pr	87	96
t-Bu	67	98
cyclohexyl	85	94
$(EtO)_2CH$	35	96
1-naphthyl-OCH_2	48	96
$PhCH{=}CH(CH_2)_2$	48	89
$PhCH{=}CHCH_2OCH_2$	65	96
Ph	23	71
ferrocenyl	26	94

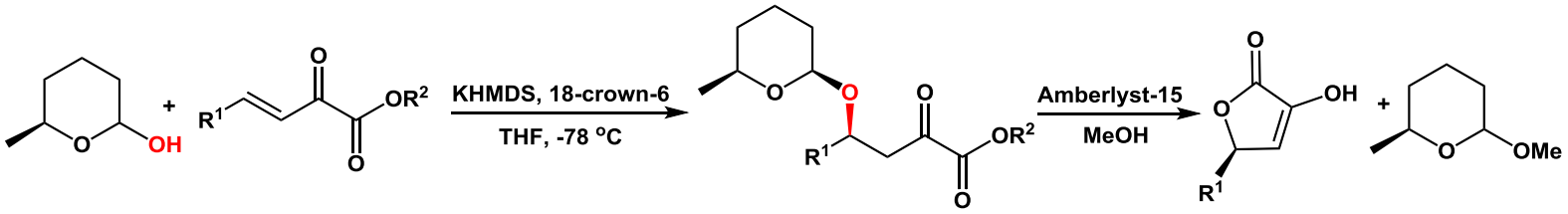
- **highly diastereoselective addition!**

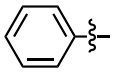
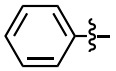
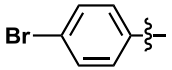
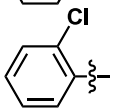


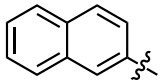
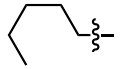
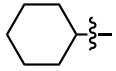
Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1771.

Chiral auxiliary

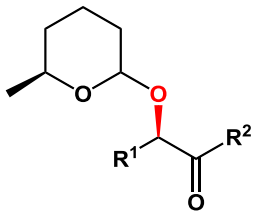
➢ ***enantiopure 6-methyl-δ-lactol as a chiral hydroxide equivalent***

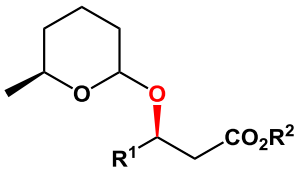


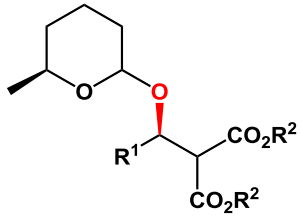
R^1	R^2	Yield/%	*de*/%
	Et	76	>95
	Me	68	>95
	Me	80	>95
	Me	73	>95

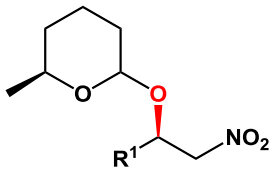
R^1	R^2	Yield/%	*de*/%
	Me	67	>95
Me	Et	60	>95
	Me	69	>95
	Me	77	>95
	Me	81	>95

Hydroxybutenolide products could be obtained via acid-mediated THP deprotection, lactonization, and enolization process.



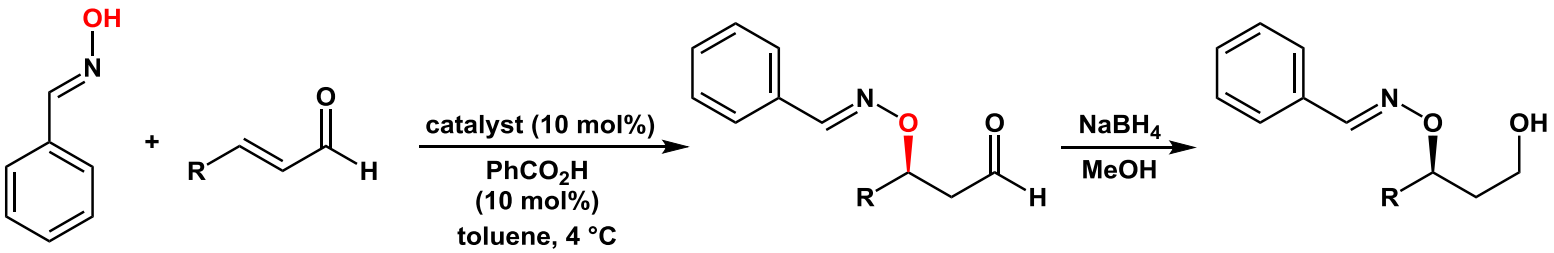






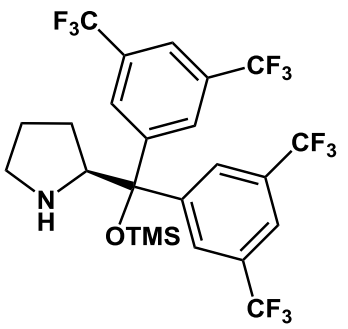
Buchanan, D. J.; Dixon, D. J.; Hernandez-Juan, F. A. *Org. Lett.* **2004**, *6*, 1357.
Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565.

Proline-type catalyst



R	time (h)	yield (%)	*ee* (%)
Et	1	72	95
Me	1	72	95
n-Pr	1	75	95
Bu	1	75	93
Hep	1	64	95
i-Pr	1.5	62	97
Hex-3-enyl	1	68	95
CO_2Et	8	60	98

catalyst:



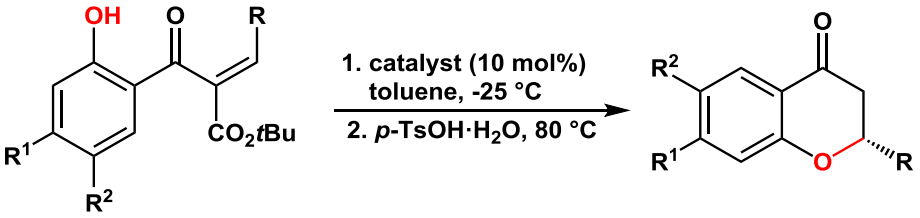
Bertelsen, S.; Diner, P.; Johansen, R. L.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536.

Reyes, E.; Talavera, G.; Vicario, J. L.; Bada, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701.

Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481.

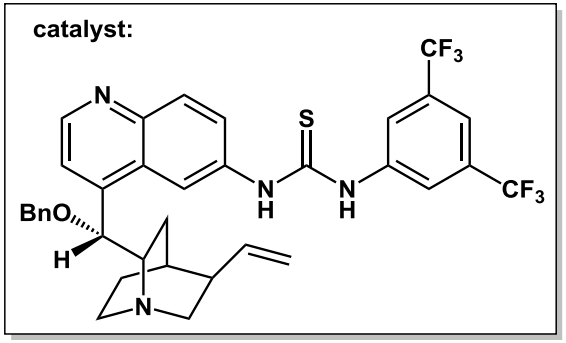
Primary amine catalyst: Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112.

Thiourea-type catalyst

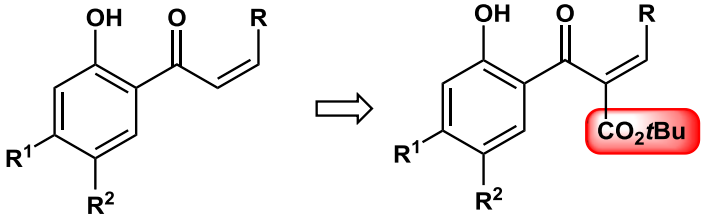


β-ketoester alkylidene

chiral flavanone



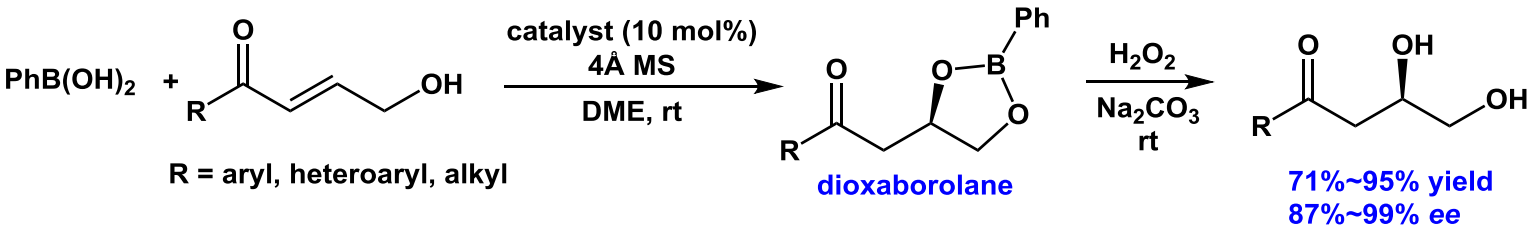
R	R^1	R^2	yield (%)	*ee* (%)
Ph	H	H	92	94
4-BrC_6H_4	H	H	65	92
2-naphthyl	H	H	89	91
4-MeC_6H_4	H	H	83	90
2-ClC_6H_4	H	H	67	88
4-$MeOC_6H_4$	H	H	94	91
Ph	OMe	H	71	89
Ph	Me	H	97	90

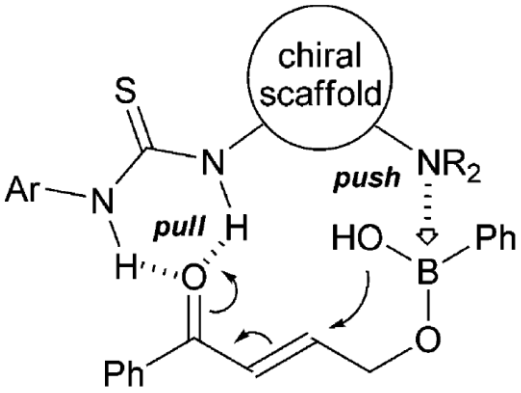


- *enhance the reactivity of conjugate acceptor*
- *potential interaction with catalyst*
- *removable under mild condition*

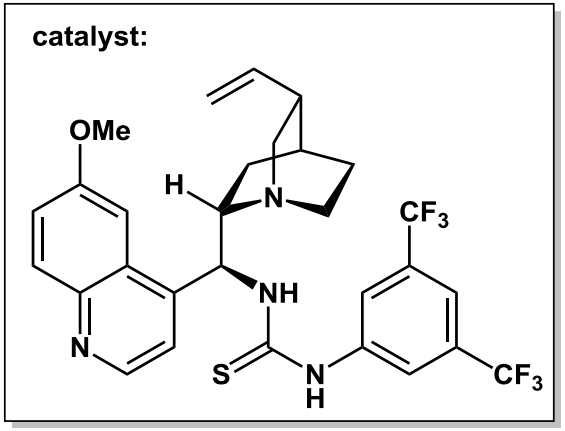
Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.

Cinchona-alkaloid-thiourea-based bifunctional catalyst





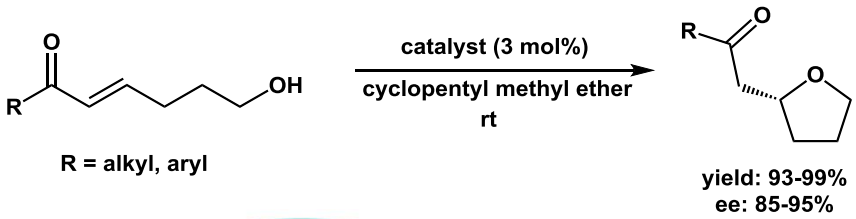
boronic acid hemiester

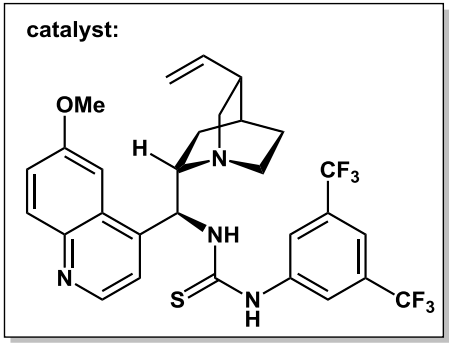


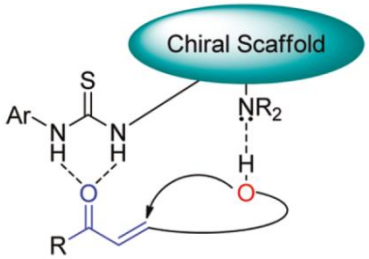
Li, D. R.; Murugan A.; Falck, J. R. *J. Am. Chem. Soc*. **2008**, *130*, 46.

Cinchona-alkaloid-thiourea-based bifunctional catalyst

- *ε-hydroxy-α,β-unsaturated ketones*



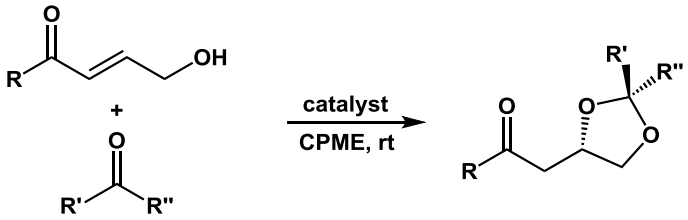




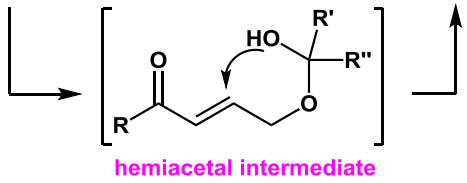
cycloetherification

Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711.

- *γ-hydroxy-α,β-unsaturated ketones*



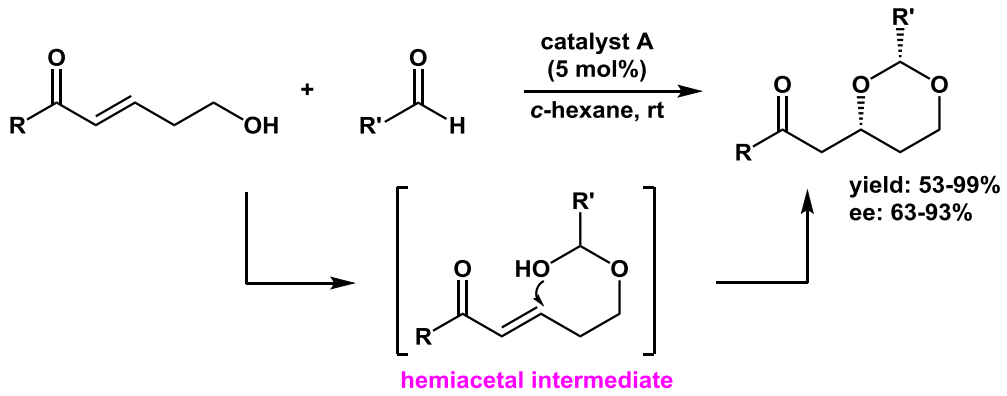
hemiacetalization/intramolecular oxy-Michael addition cascade

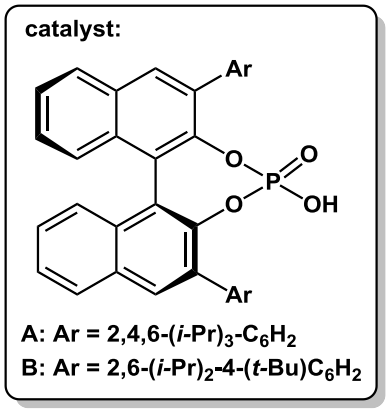


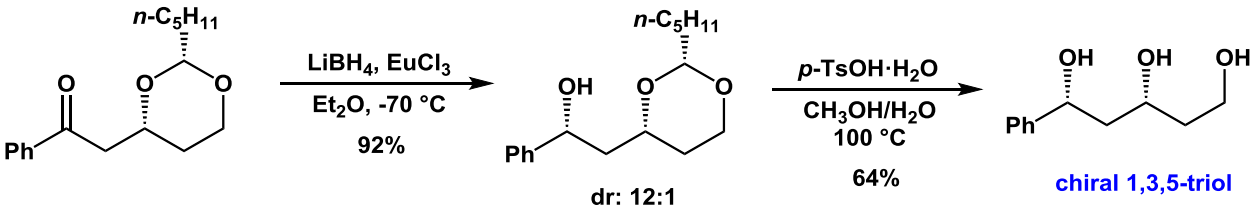
Ketone: Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620.
Aldehyde: Okamura, T.; Asano, K.; Matsubara, S. *Chem. Commun.* **2012**, *48*, 5076.
Formaldehyde: Yoneda, N.; Hotta, A.; Asano, K.; Matsubara, S. *Org. Lett.* **2014**, *16*, 6264.

Phosphoric acid catalyst

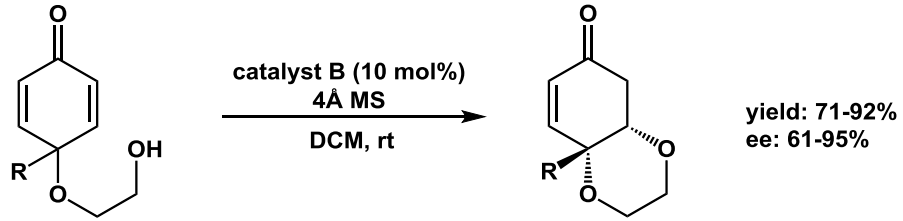
- *δ-hydroxy-α,β-unsaturated ketones*





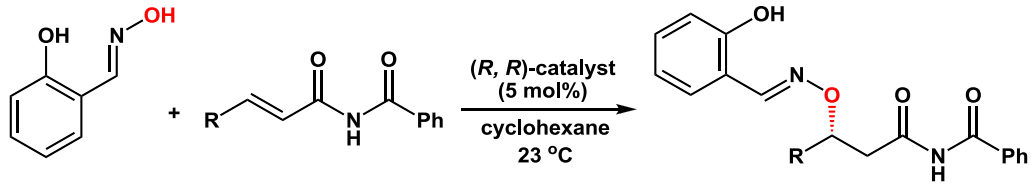


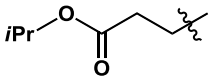
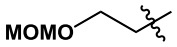
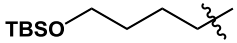
Matsumoto, A.; Asano, K.; Matsubara, S. *Chem. Commun.* **2015**, *51*, 11693.

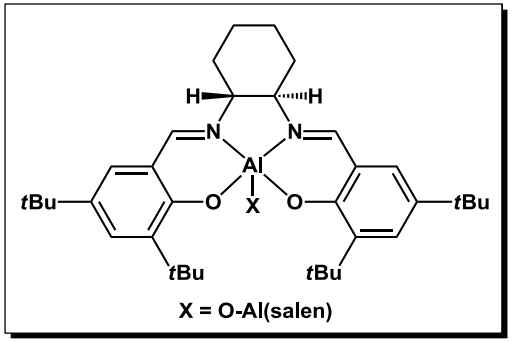


Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056.

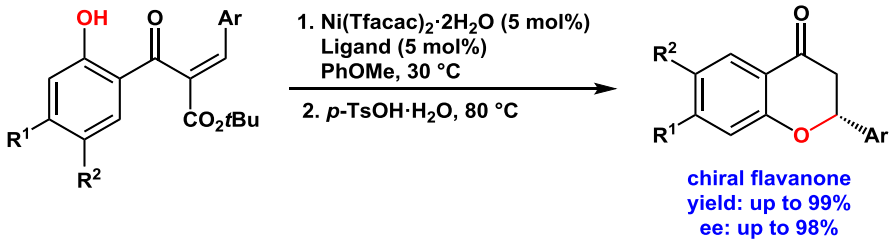
Organometallic catalysts

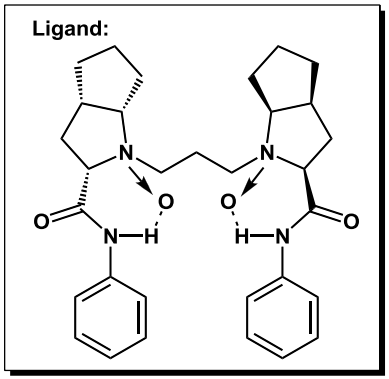


R	yield/%	*ee*/%
Me	90	97
Et	93	98
*i*Pr	81	98
	88	97
	88	97
	82	97



Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724.



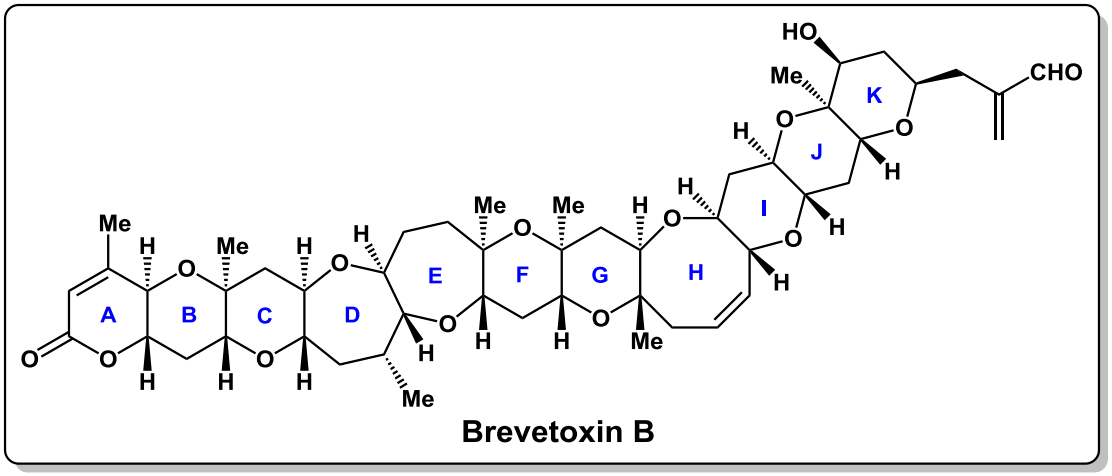


Wang, L.; Liu, X.; Dong, Z.; Fu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 8670.

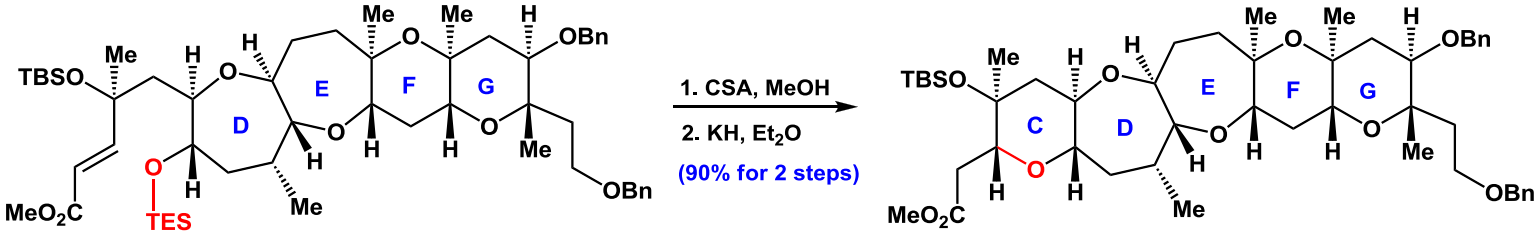
Outline

- *Introduction*
- *General Protocols*
- *Asymmetric Oxy-Michael Reaction*
- *Applications in Natural Product Synthesis*
- *Summary and Outlook*

Total synthesis of Brevetoxin B



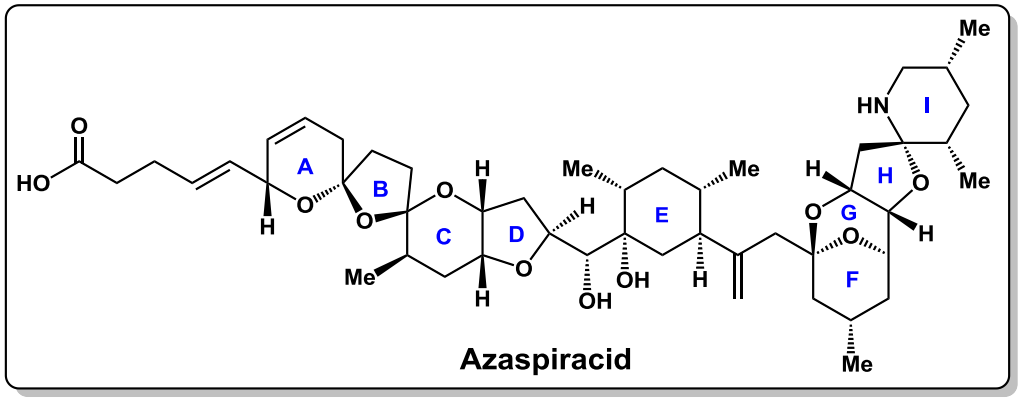
CDEFG Framework

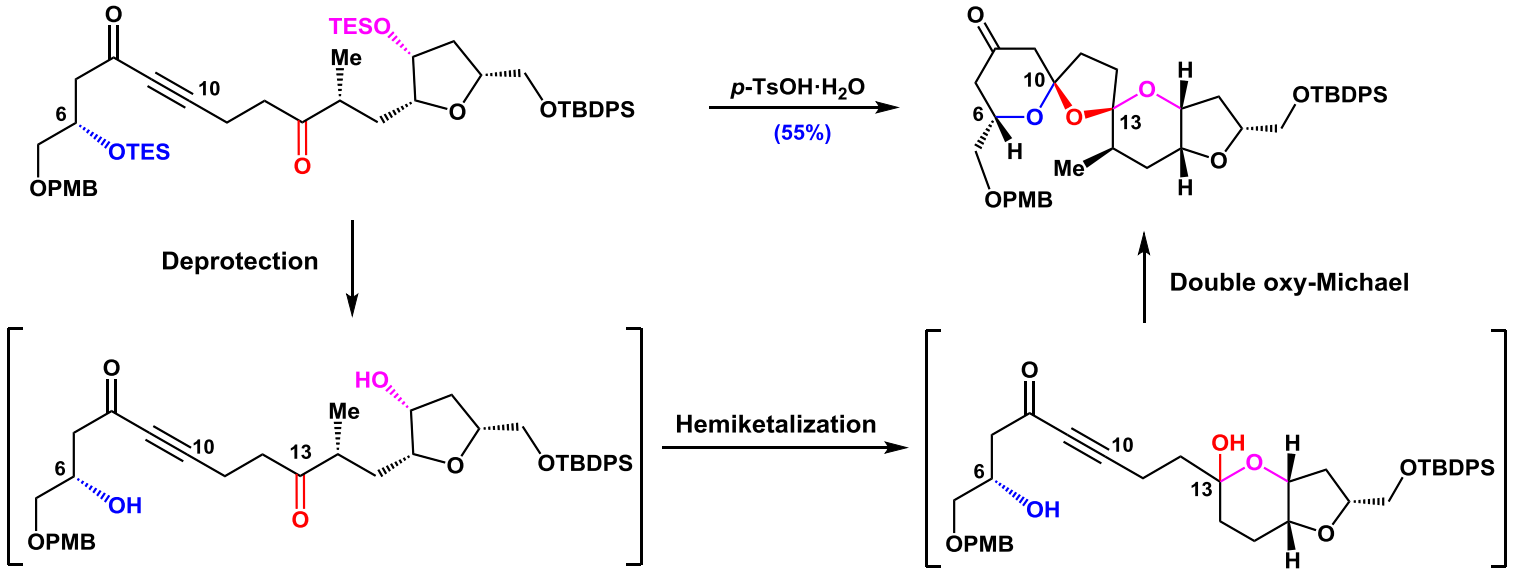


- The transformation is highly diastereoselective due to the reversibility of the oxy-Michael reaction and the resulting thermodynamically controlled ring closure.

Nicolaou, K. C.; Theodorakis, E. A.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171.

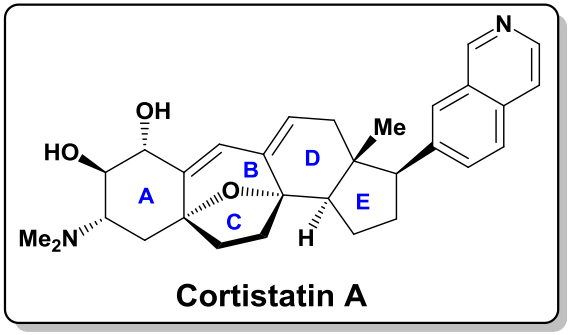
Total synthesis of Azaspiracid

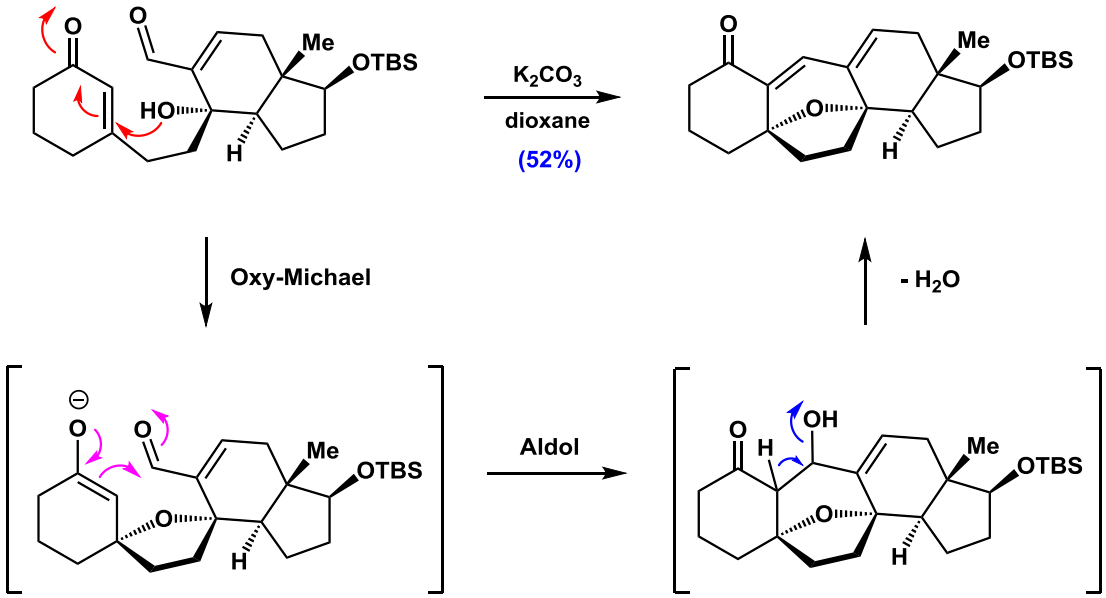




Geisler, L. K.; Nguyen S.; Forsyth, C. J. *Org. Lett*. **2004**, *6*, 4159.

Total synthesis of Cortistatin A

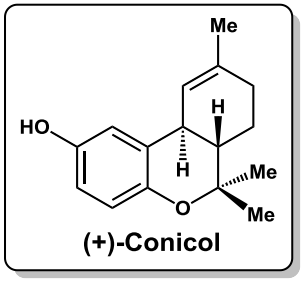


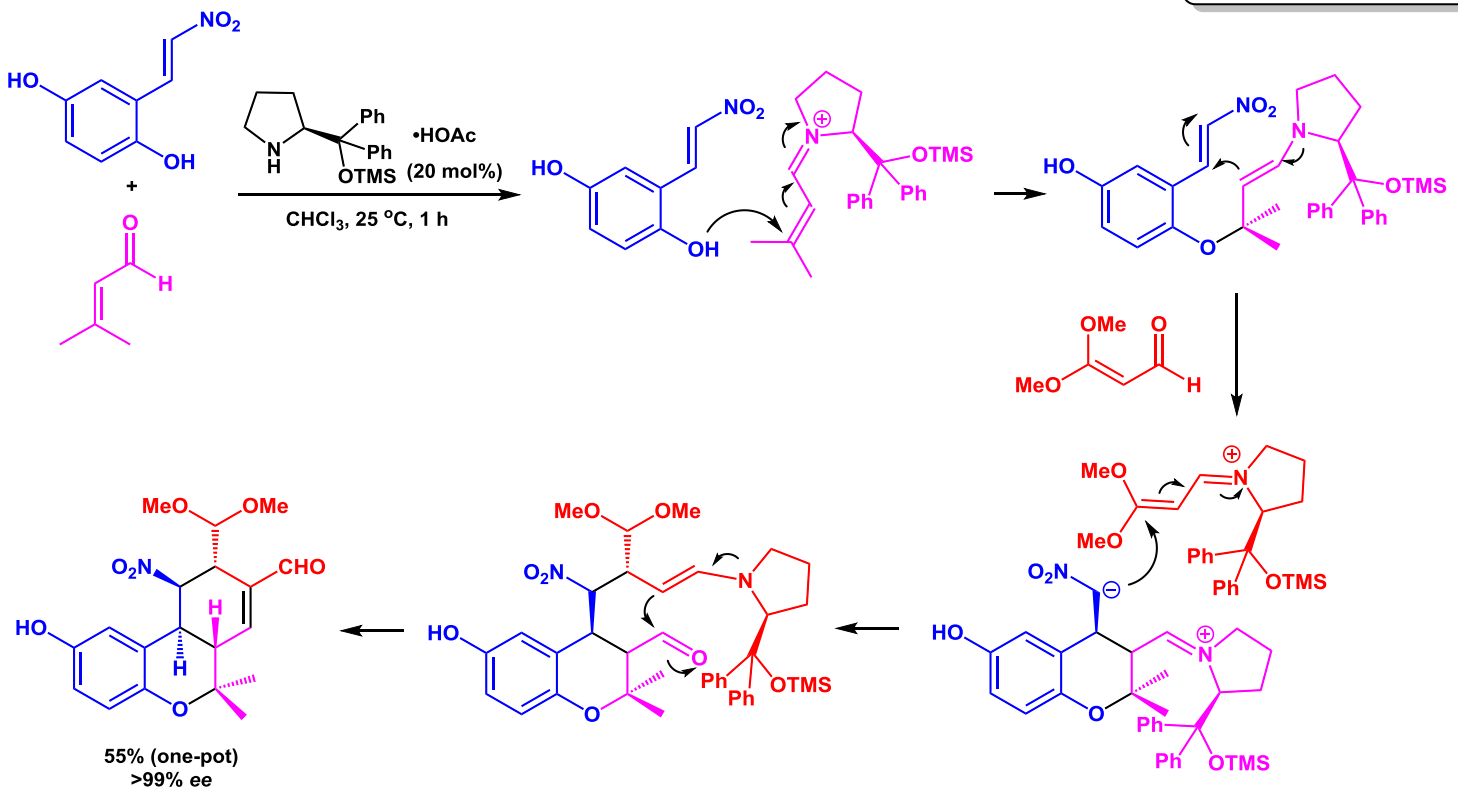


Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310.

Total synthesis of (+)-Conicol

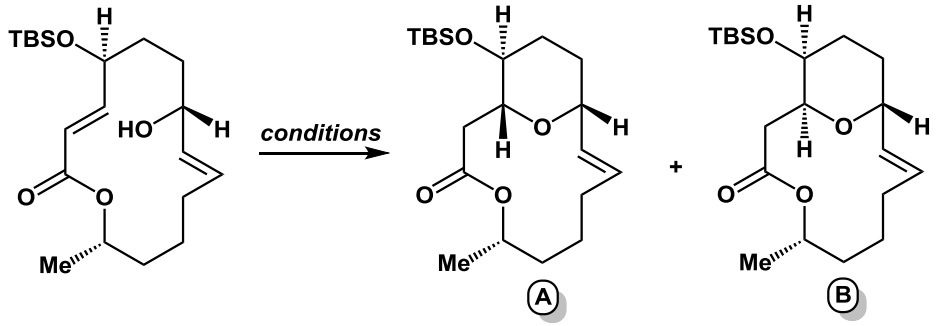
- *domino oxy-Michael-Michael-Michael-Aldol condensation*
- *construction of four new bonds and five stereocenters in one single step*

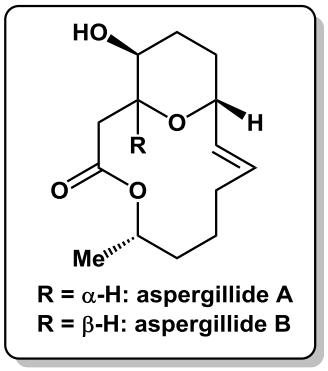




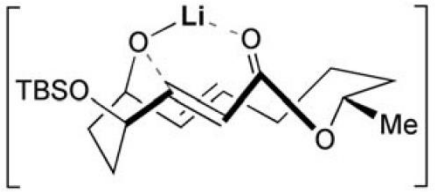
Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776.

Total synthesis of Aspergillide A and B



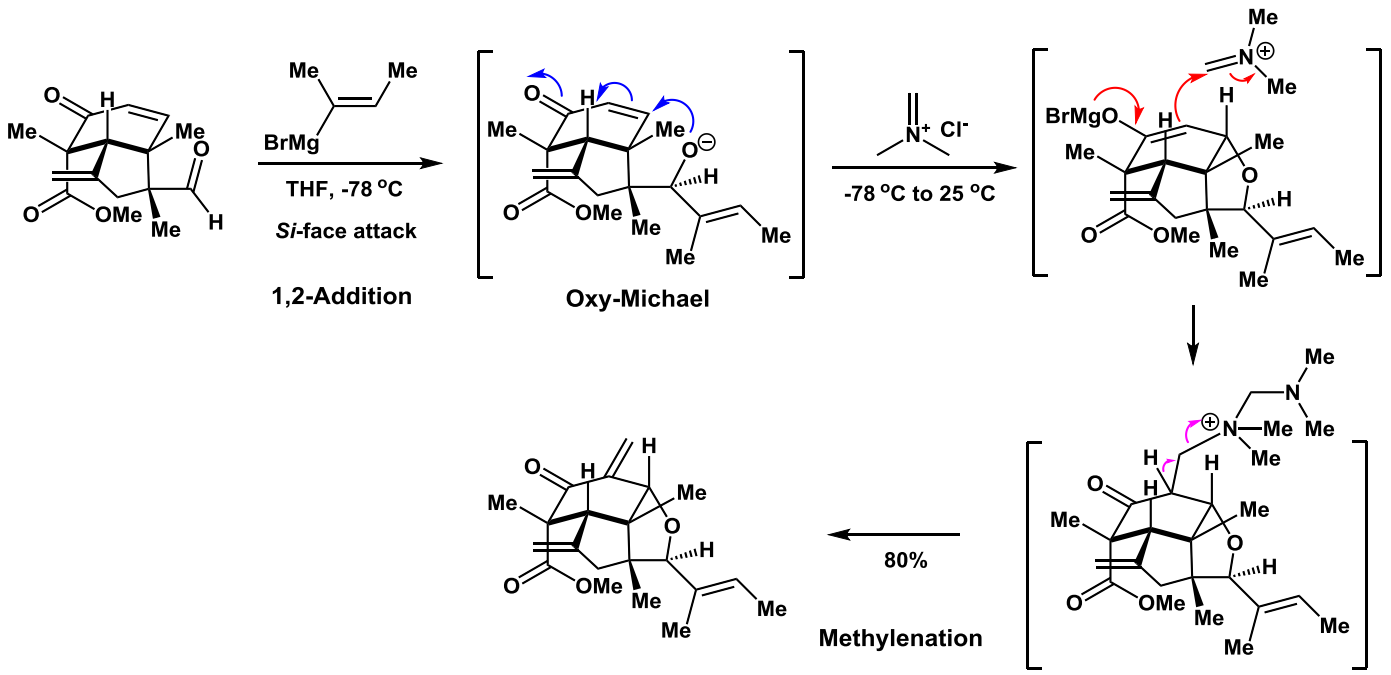


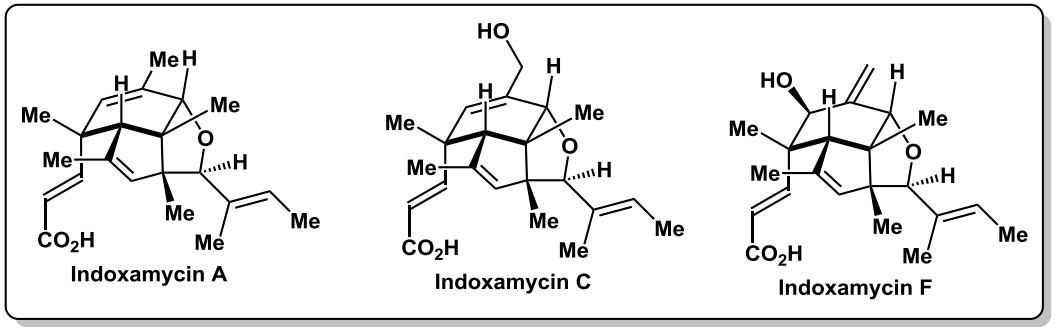
Entry	Reaction conditions	Yield [%]	A/B
1	DBU (10 equiv), CH_3CN, reflux, 10 h	50	1:6
2	DBU (10 equiv), LiCl (10 equiv) CH_3CN, reflux, 2 h	quant.	7:1
3	DBU (10 equiv), LiCl (10 equiv), CH_3CN, RT, 1.5 h	quant.	1:0
4	KH (1.1 equiv), THF, 0 °C, 0.5 h	90	1.6:1
5	KH (1.1 equiv), THF, 0 °C, 2 h	91	0:1
6	KH (1.1 equiv), [18]crown-6 (5 equiv), THF, 0 °C, 0.5 h	96	0:1



Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2618.

Total synthesis of Indoxamycin





He, C.; Zhu, C.; Dai, Z.; Tseng, C. C.; Ding, H. *Angew. Chem., Int. Ed.* **2012**, *52*, 13256.

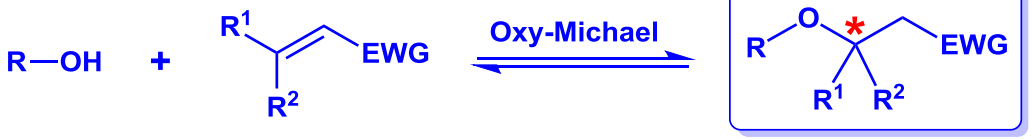
Outline

- *Introduction*
- *General Protocols*
- *Asymmetric Oxy-Michael Reaction*
- *Applications in Natural Product Synthesis*
- *Summary and Outlook*

Summary and outlook

Intermolecular & Intramolecular

Asymmetric: chiral auxiliaries & chiral catalysts



Low Reactivity & Reversibility

Domino Reactions

Natural Product Synthesis

- *General reaction protocols to realize intermolecular oxy-Michael reactions*
- *Expansion of the scope of substrates*
- *Efficient catalysts for asymmetric oxy-Michael reactions*


Thank You!