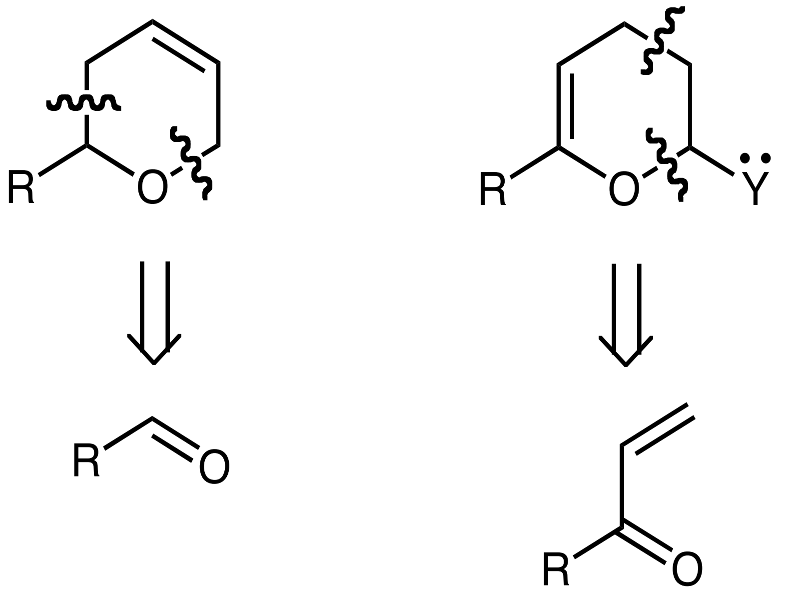
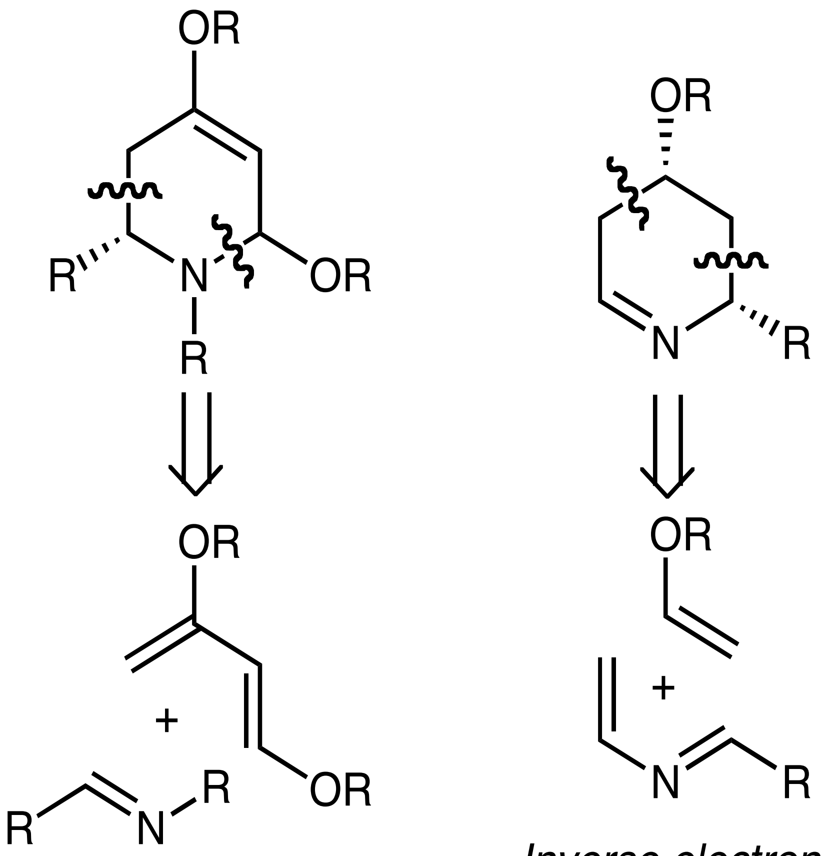
Hetero-Diels-Alder Reactions: General Strategies

Dihydropyrans



Inverse electron demand

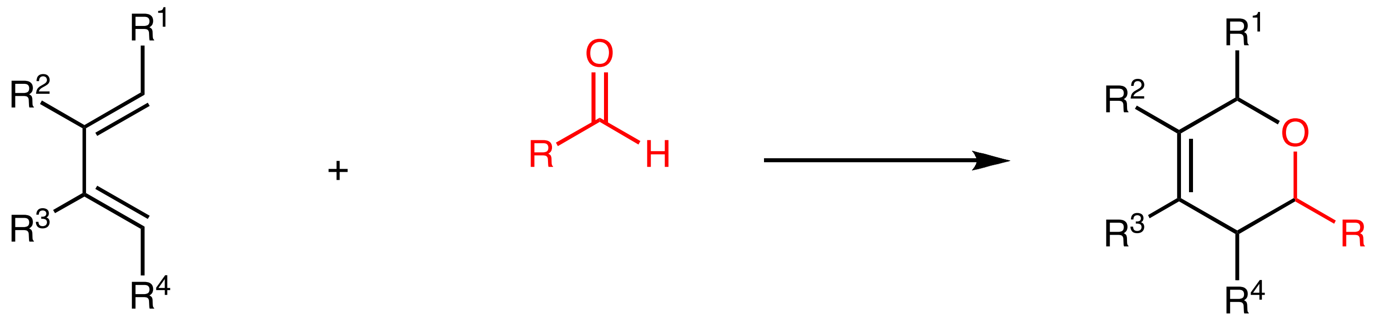
Piperidines



Inverse electron demand

➡ Chiral Lewis Acids; Chiral Bronsted Acids; Organocatalysts

Hetero-Diels-Alder: Introduction

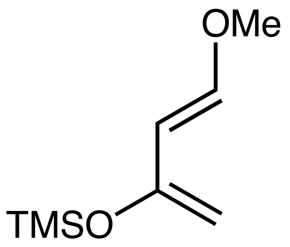


Diene
(Electron-rich)
Mostly with Danishefsky Diene

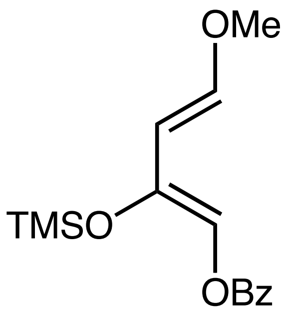
Dienophile
(Aldehyde)

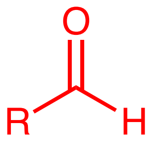
Dihydropyran

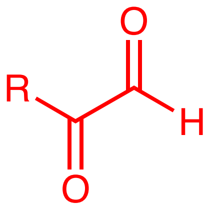
⇨ Avoid Allylic Hydrogen: Ene Reaction



Danishefsky's Diene

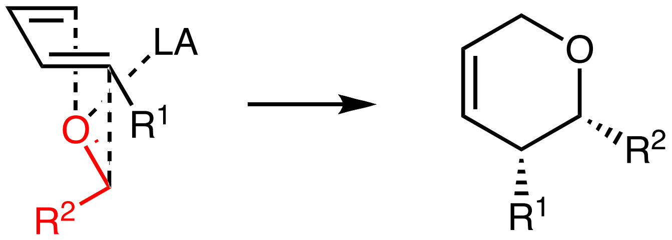




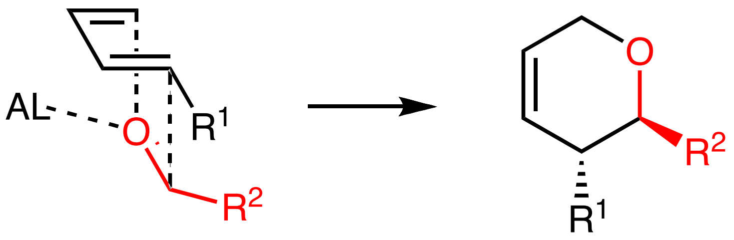


Activated
aldehydes

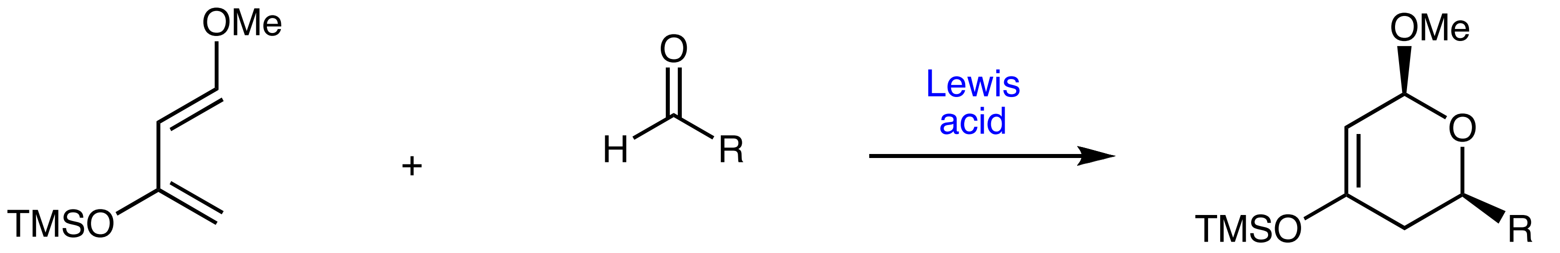
Hetero-Diels-Alder: Diastereoselectivity Issues



endo transition state

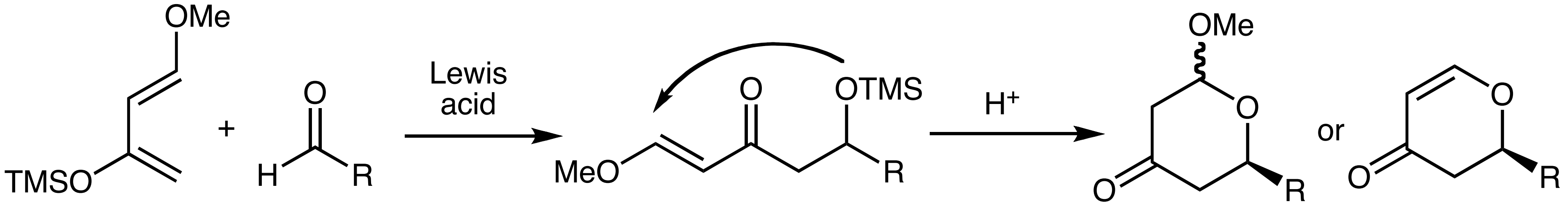


exo transition state



Lewis acids: $BF_3 \cdot OEt_2$, $MgBr_2$, $TiCl_4$, Ln^{3+}, etc.

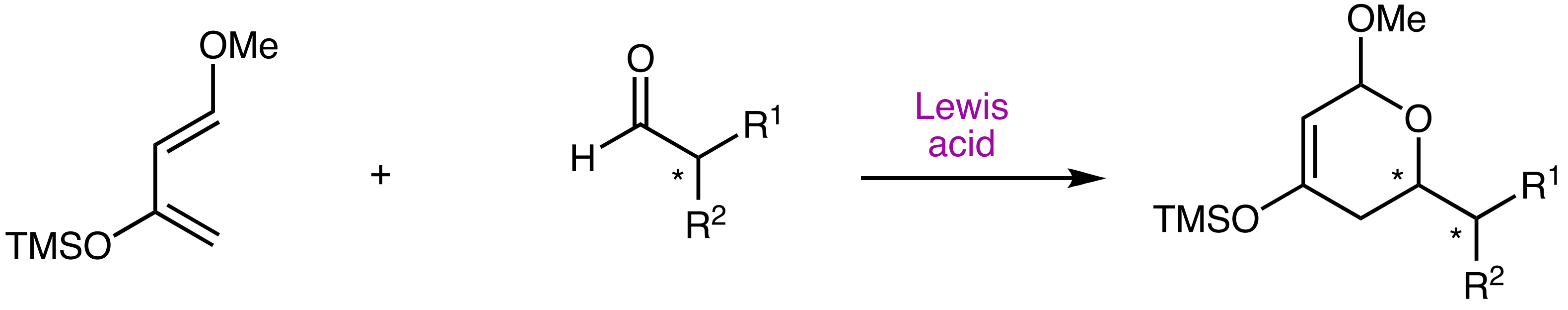
Alternative Pathway (Mukaiyama Aldol + cyclization):



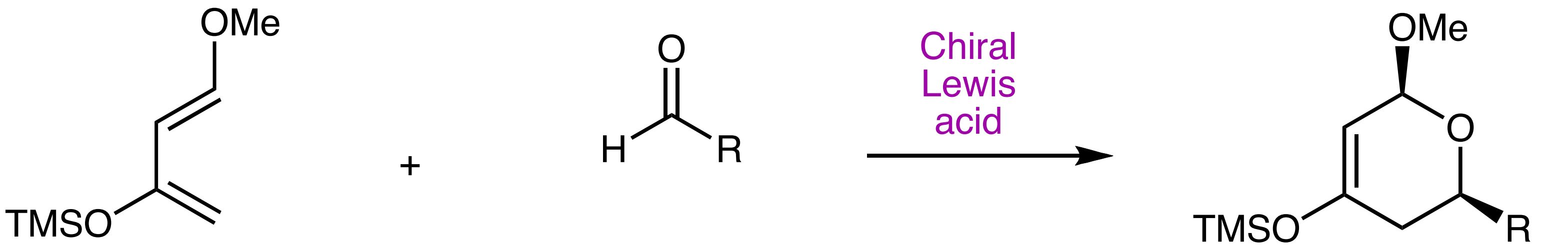
Reviews: (a) Danishefsky, S.J.; De Ninno, M.P. *Angew. Chem. Int. Ed.* **1987**, *26*, 15-23. (b) Waldmann, H. *Synthesis* **1994**, 535-551. (c) Jorgensen, K.A. *Angew. Chem. Int. Ed. Eng.* **2000**, *39*, 3558-3588.

Hetero-Diels-Alder: Relative Stereocontrol

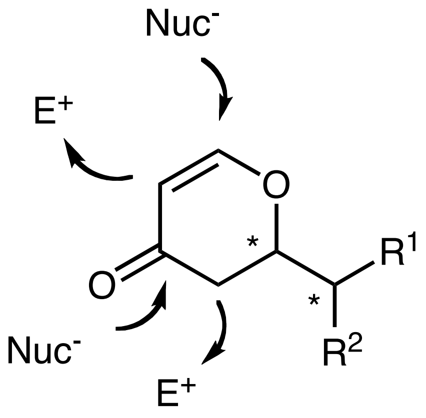
Relative stereocontrol



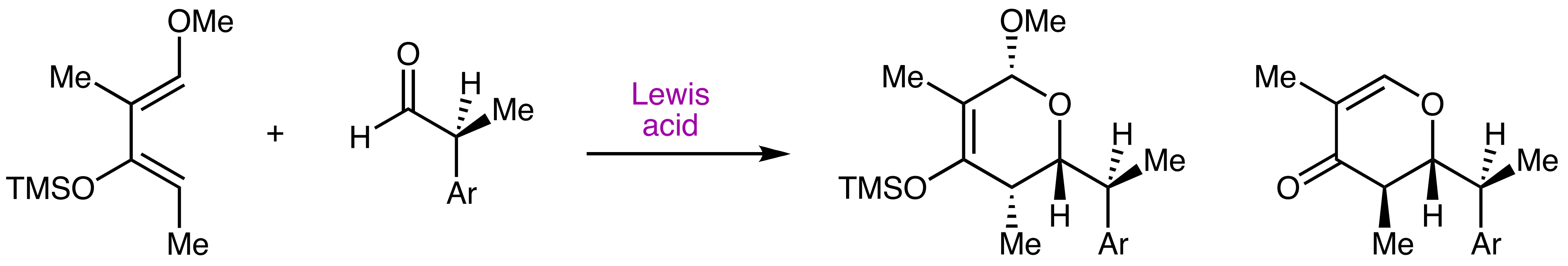
Absolute stereocontrol



⇨ Main Application: carbohydrate derivatives



Hetero-Diels-Alder: Relative Stereocontrol

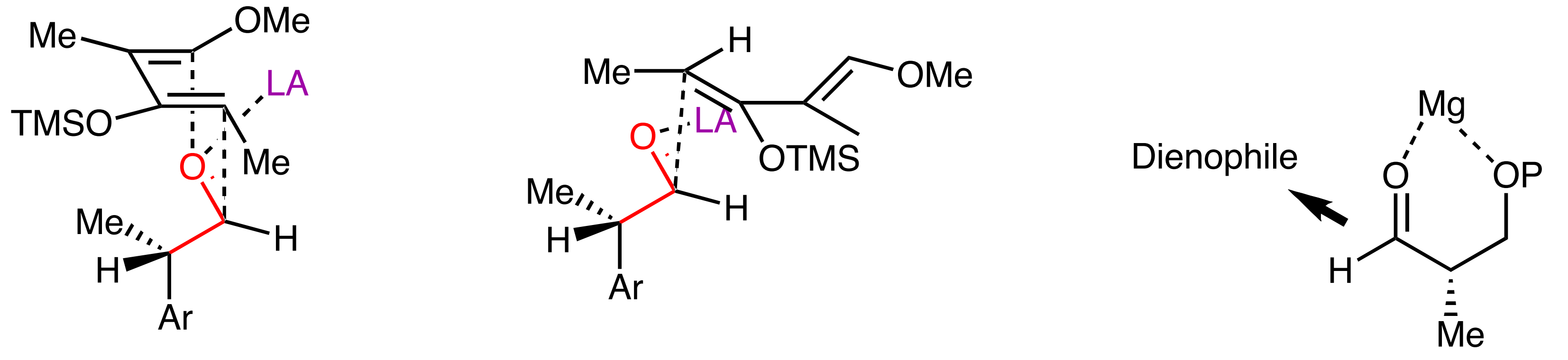


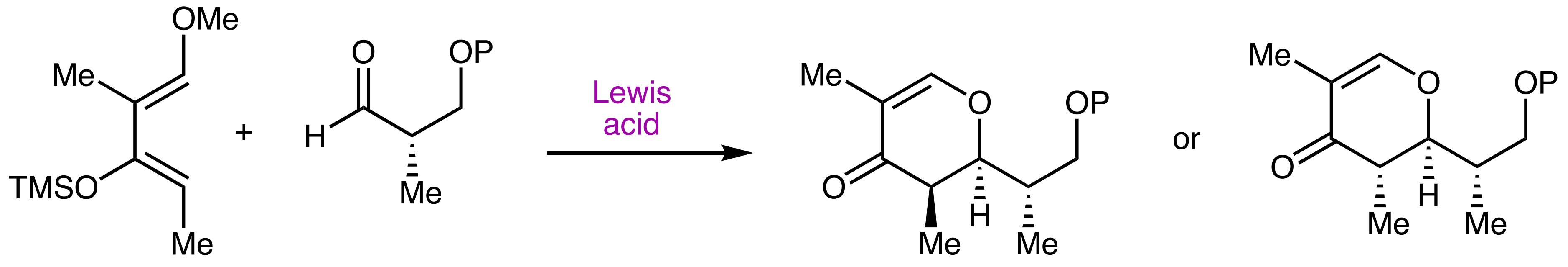
Eu(fod)$_3$

endo

BF$_3$•OEt$_2$

"aldol-like"





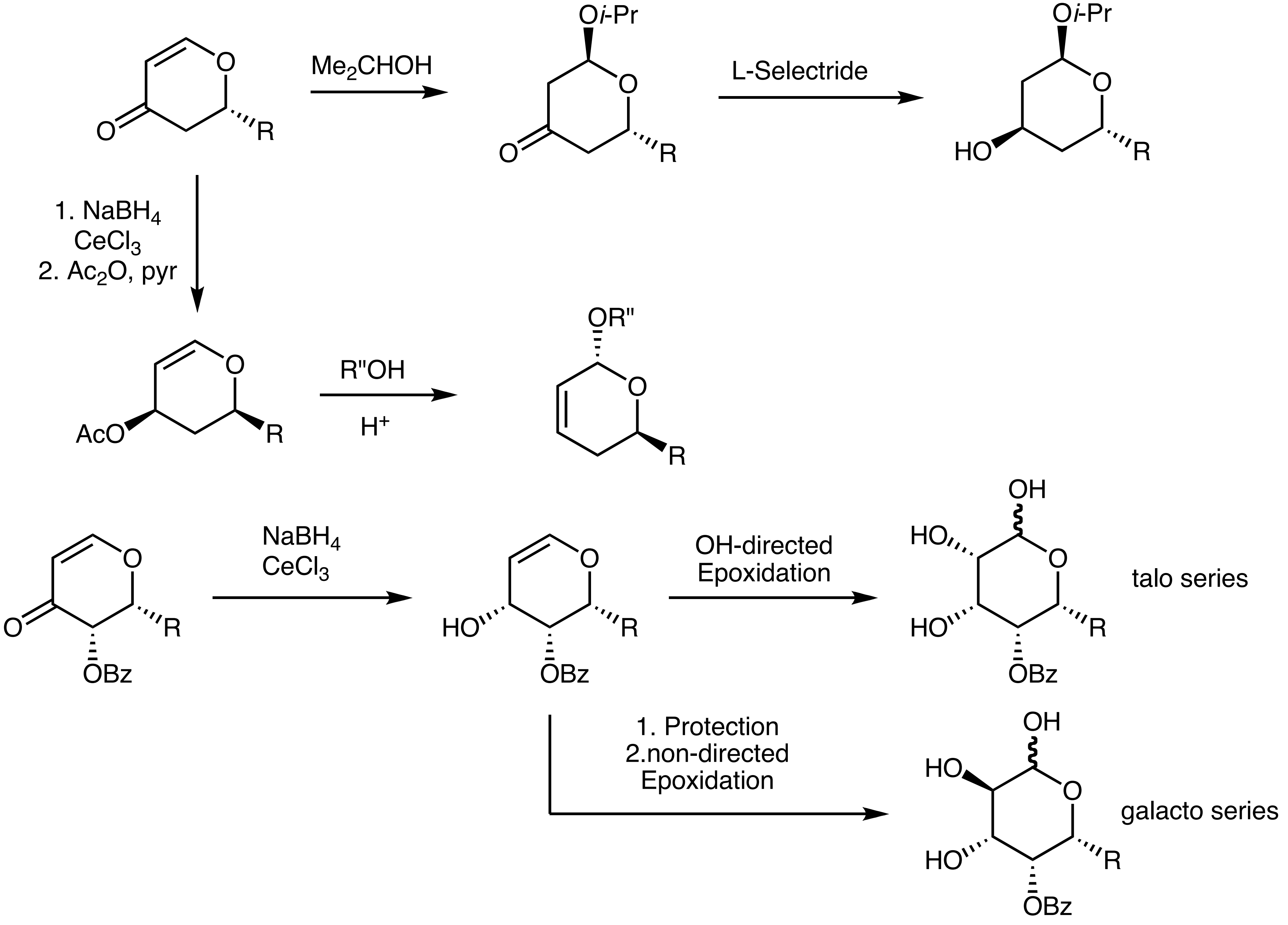
TiCl$_4$

"Aldol-like"

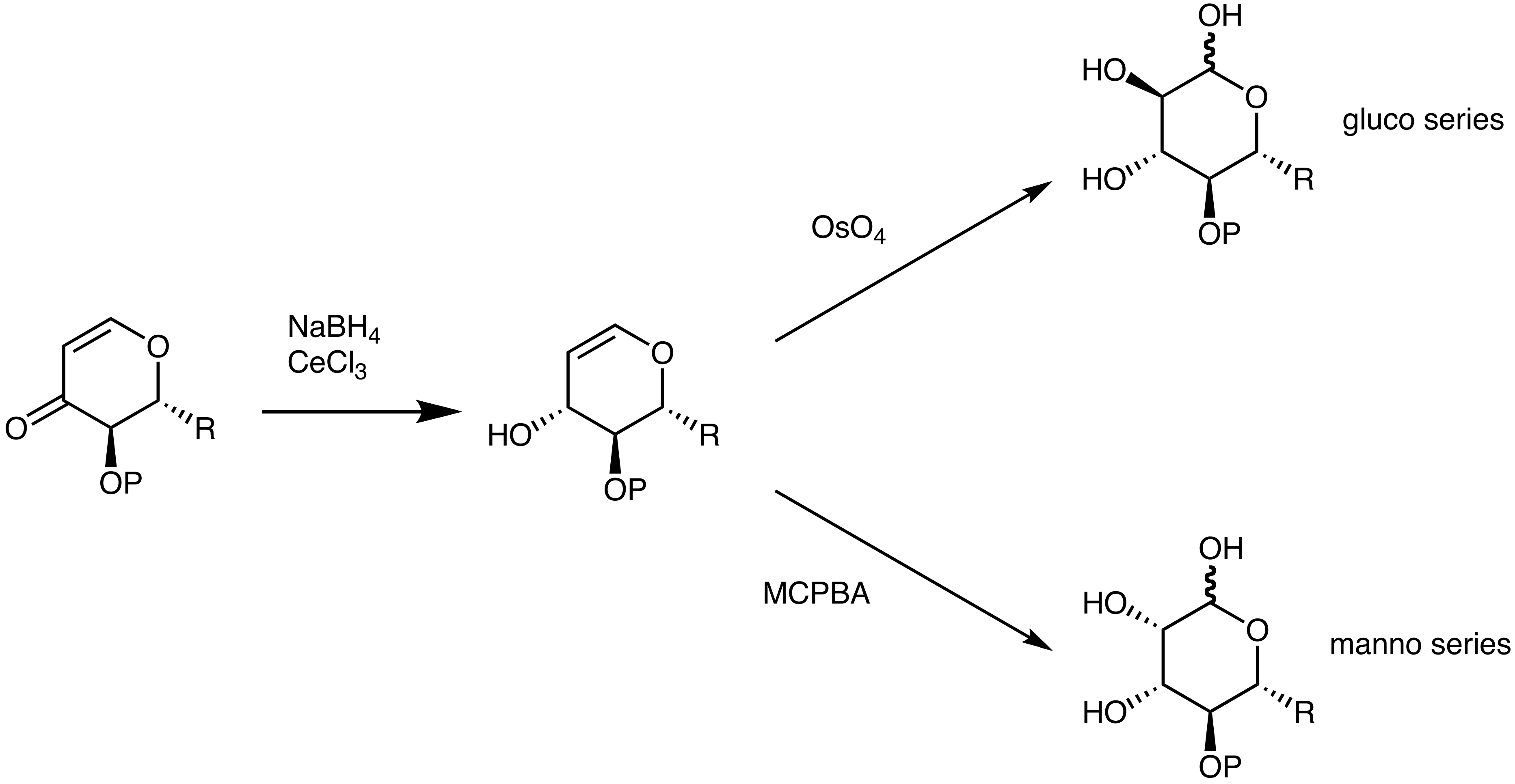
MgBr$_2$

exo (cycloaddition)

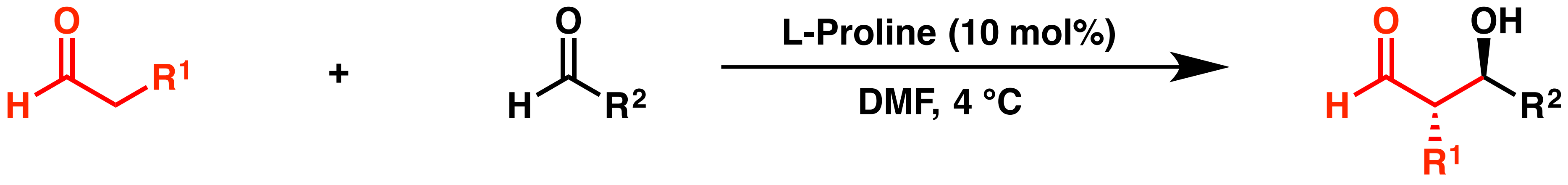
Functionalization of Dihydropyrone

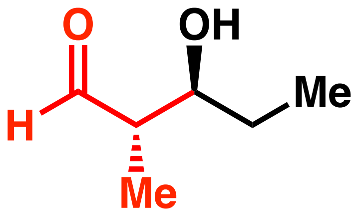


Functionalization of Dihydropyrone

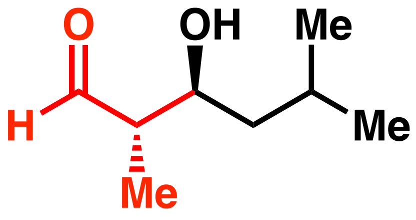


Direct Cross-Aldol Reaction of Aldehydes

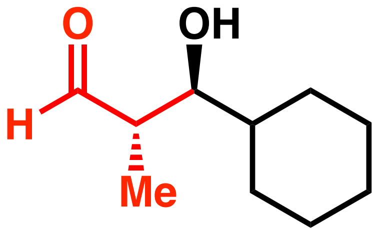




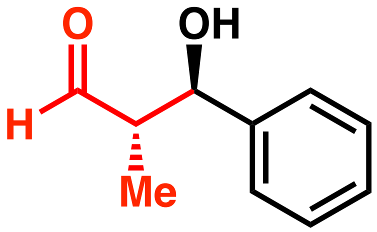
80%, 4:1, 99% ee



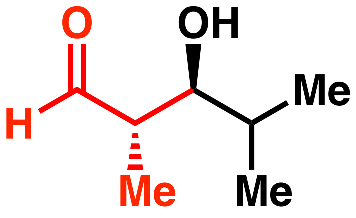
88%, 3:1, 97% ee



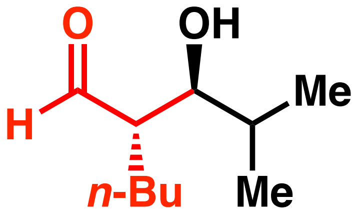
87%, 14:1, 97% ee



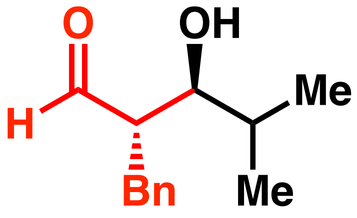
81%, 3:1, 99% ee



82%, 24:1, >99% ee



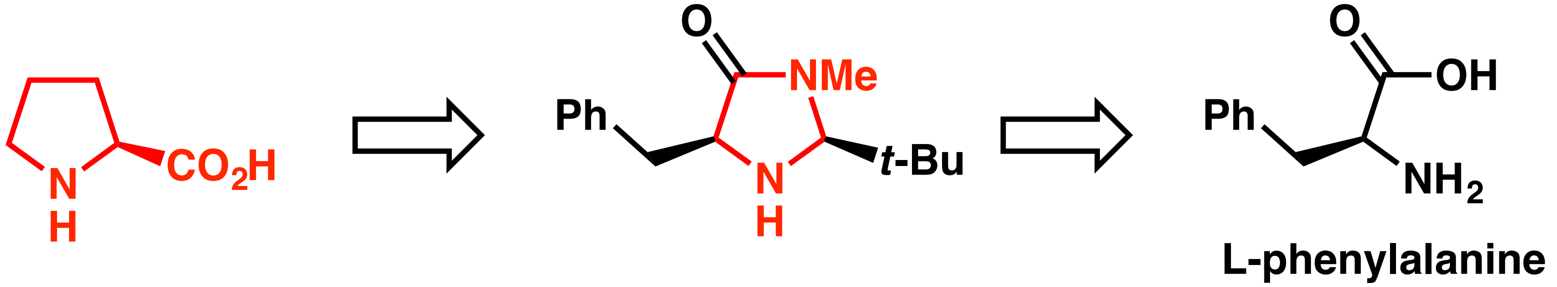
80%, 24:1, 98% ee

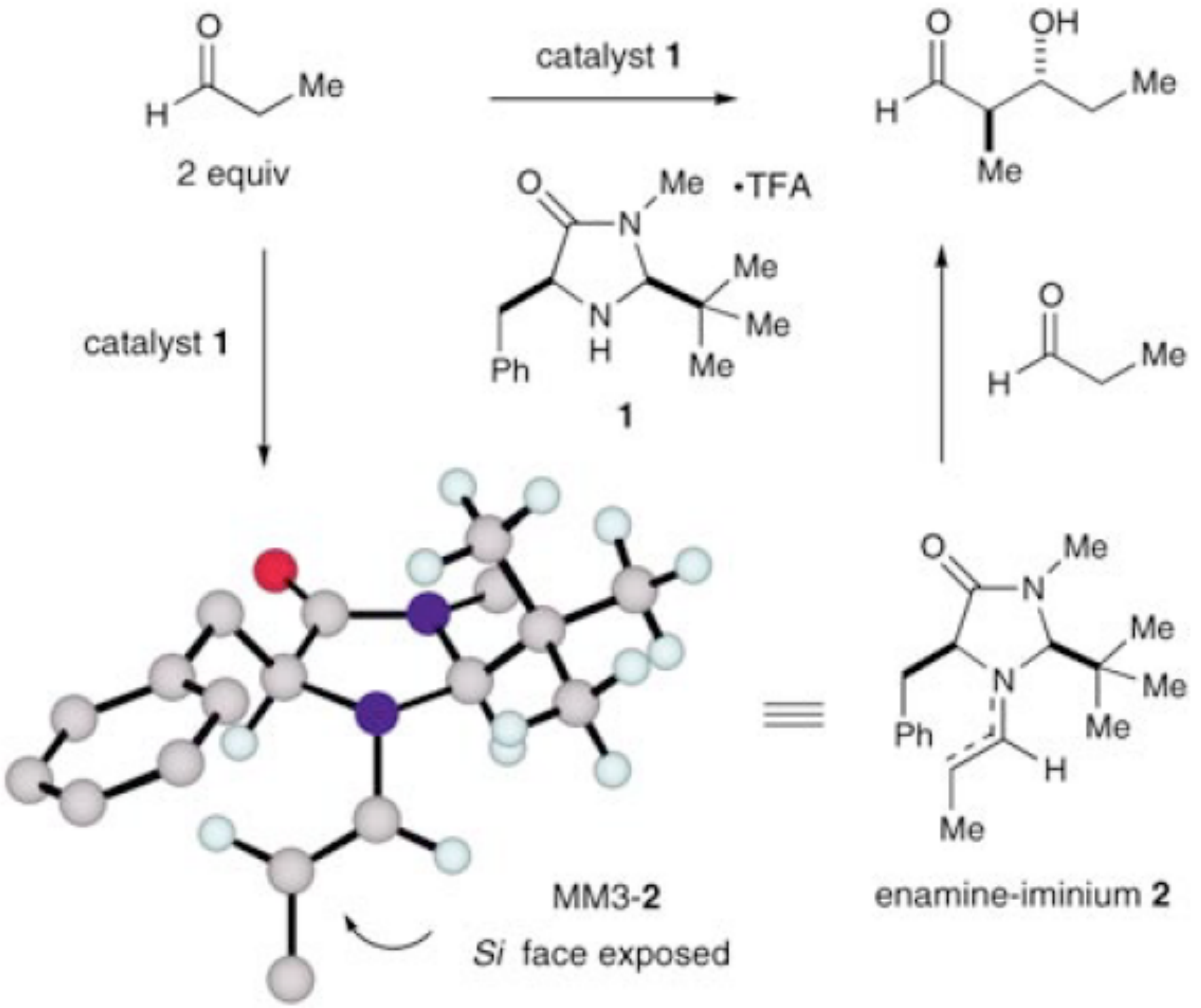


75%, 19:1, 91% ee

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

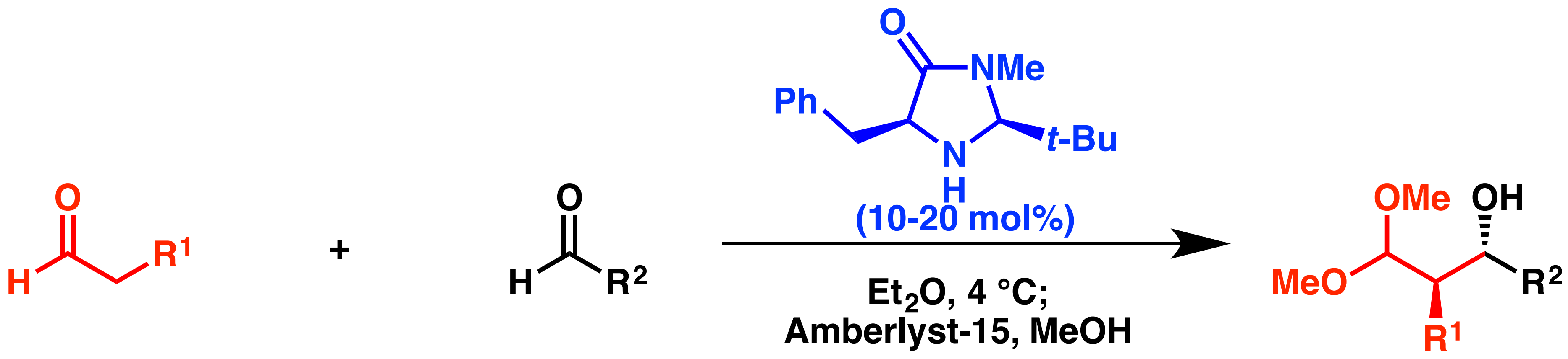
Direct Cross-Aldol Reaction of Aldehydes: 2nd Generation

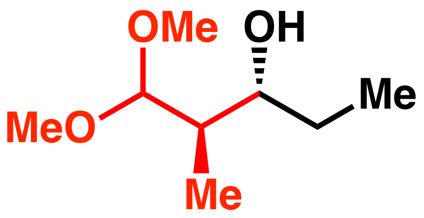




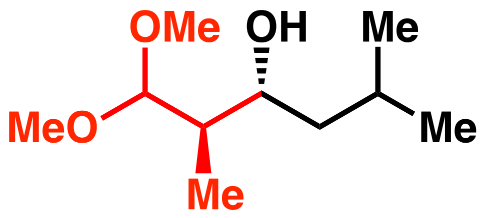
Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

Direct Cross-Aldol Reaction of Aldehydes: 2nd Generation

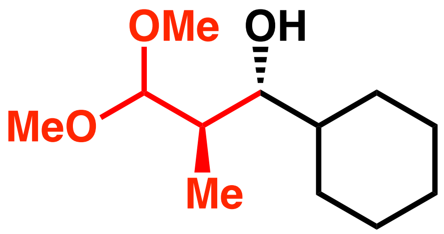




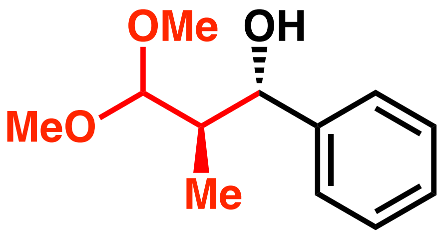
86%, 4:1, 94% ee



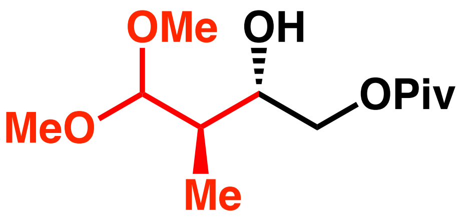
90%, 5:1, 95% ee



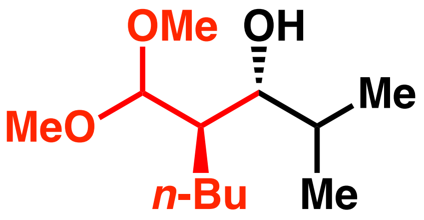
81%, 5:1, 97% ee



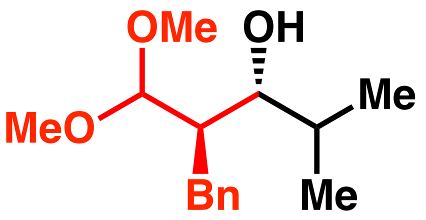
61%, 4:1, 93% ee



58%, 4:1, 90% ee



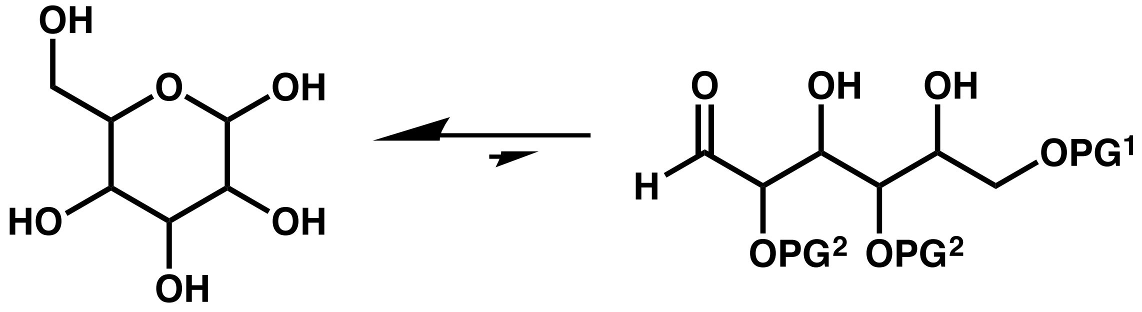
72%, 6:1, 94% ee



80%, 5:1, 91% ee

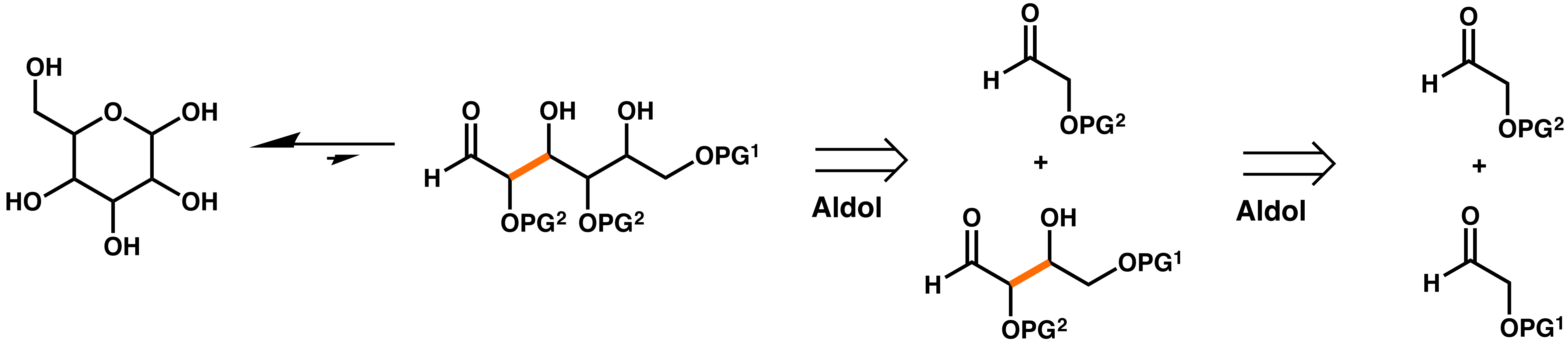
Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

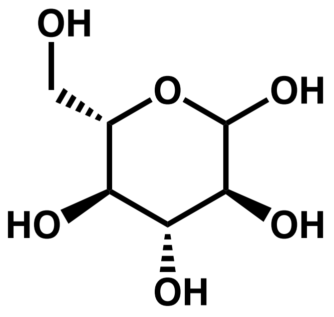
Carbohydrate Synthesis Using Organocatalysis/Mukaiyama Aldol



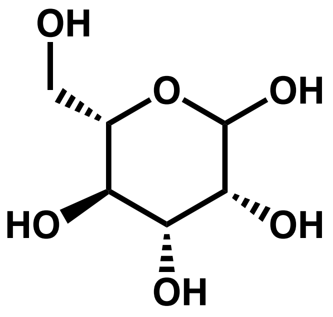
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

Carbohydrate Synthesis Using Organocatalysis/Mukaiyama Aldol

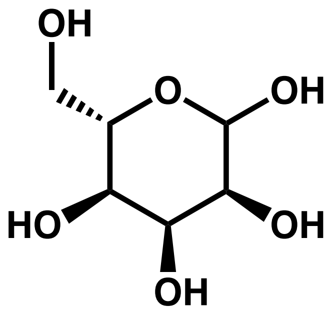




L-glucose



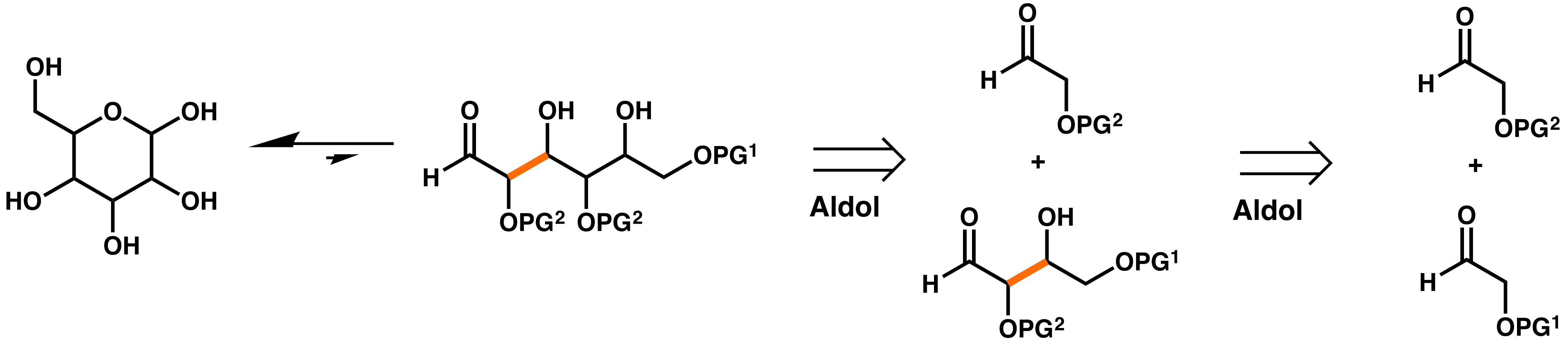
L-mannose

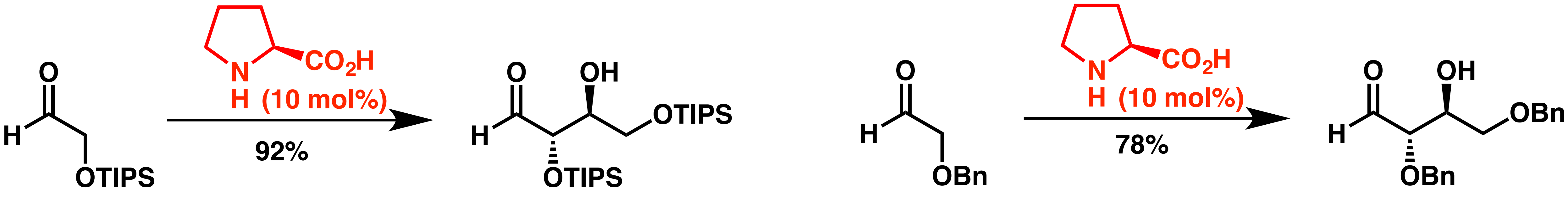


L-allose

Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

Carbohydrate Synthesis Using Organocatalysis/Mukaiyama Aldol



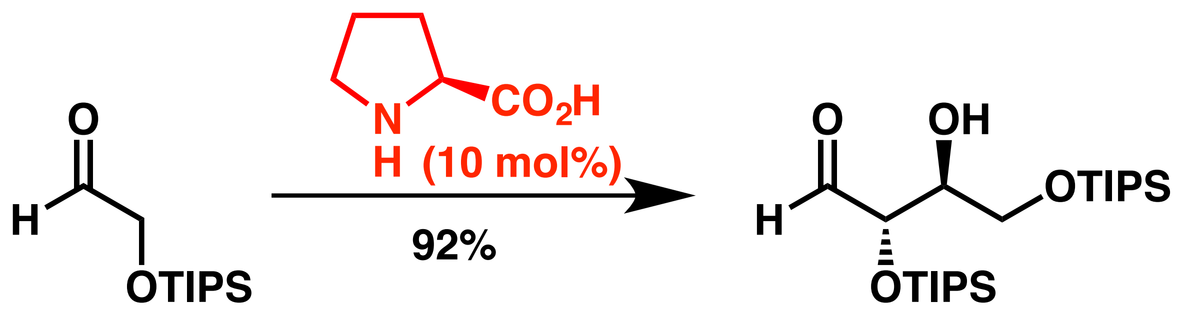


dr 4:1; 95% ee

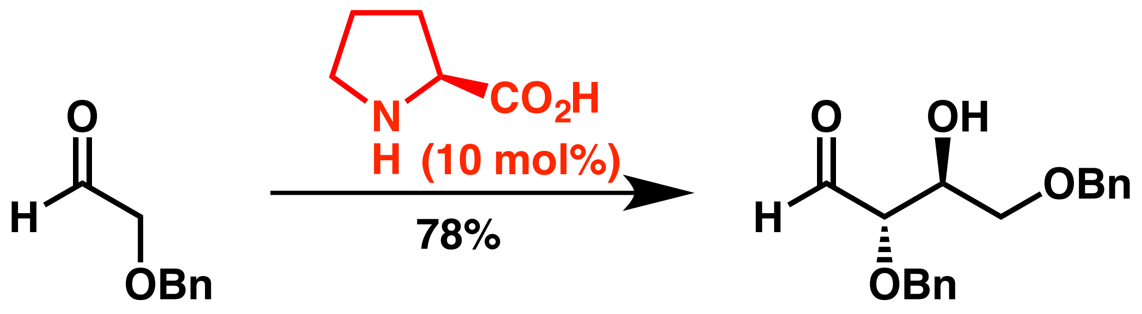
dr 4:1; 95% ee

Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

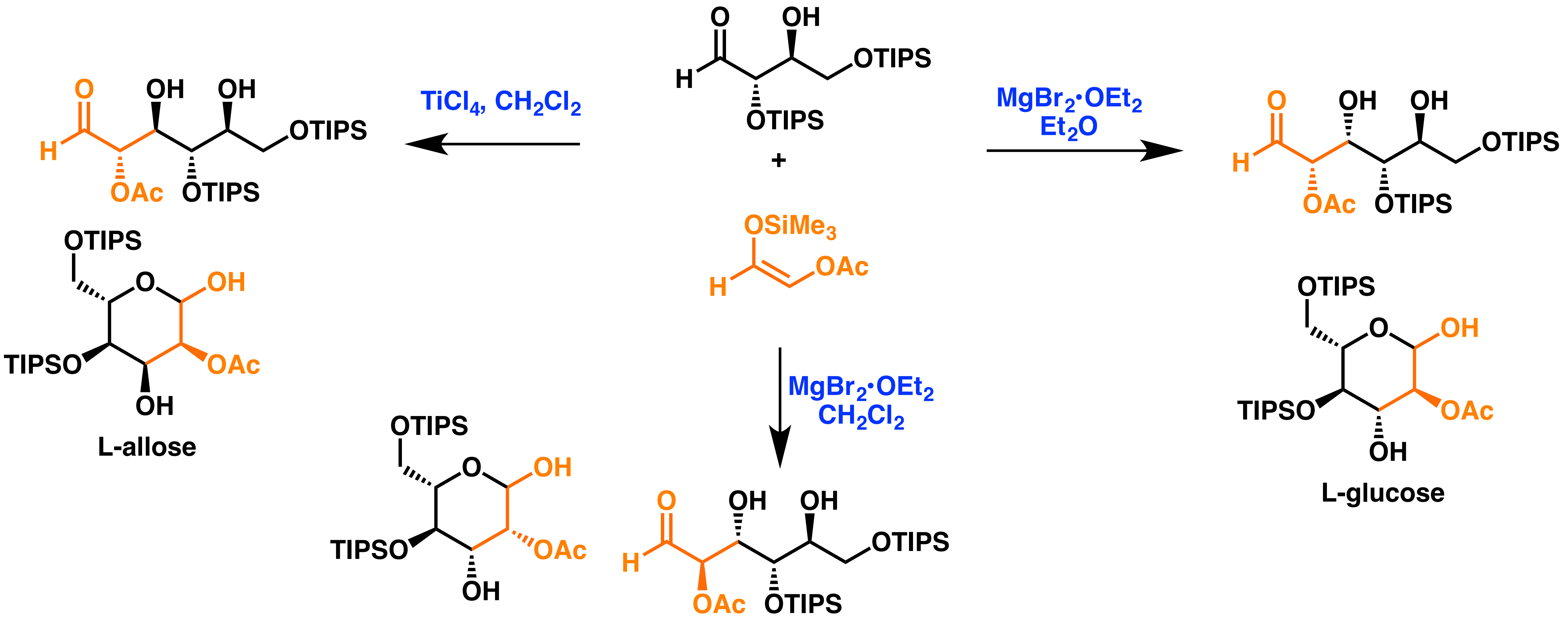
Carbohydrate Synthesis Using Organocatalysis/Mukaiyama Aldol



dr 4:1; 95% ee



dr 4:1; 95% ee



L-allose

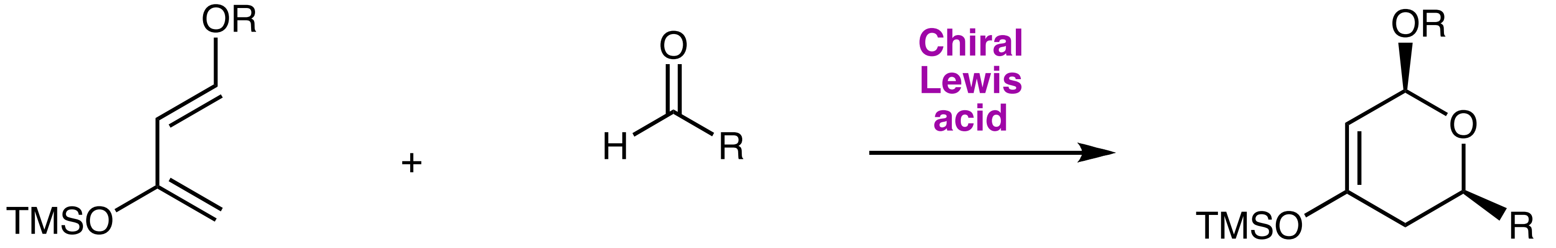
L-mannose

L-glucose

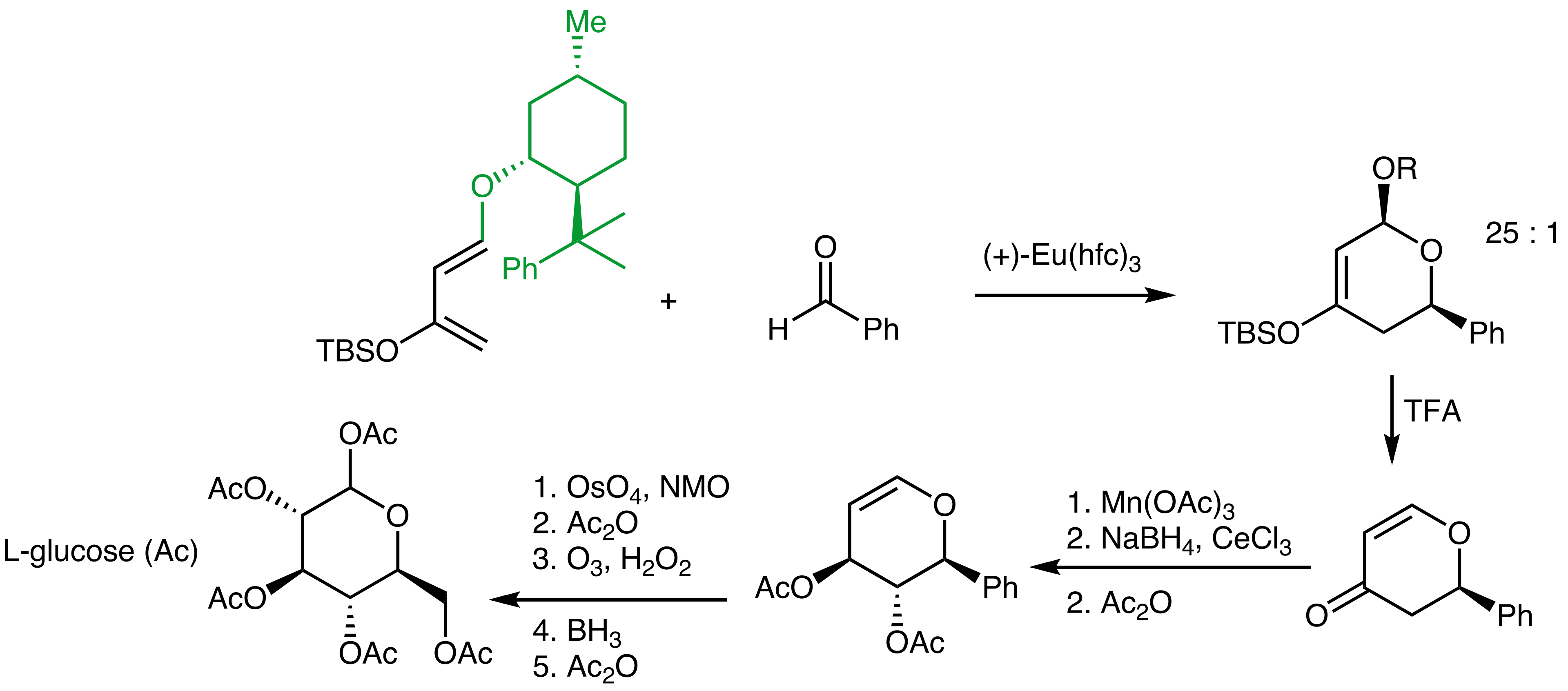
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.
Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752.

Chiral Catalysts for Hetero-Diels-Alder: Early Work

Absolute stereocontrol

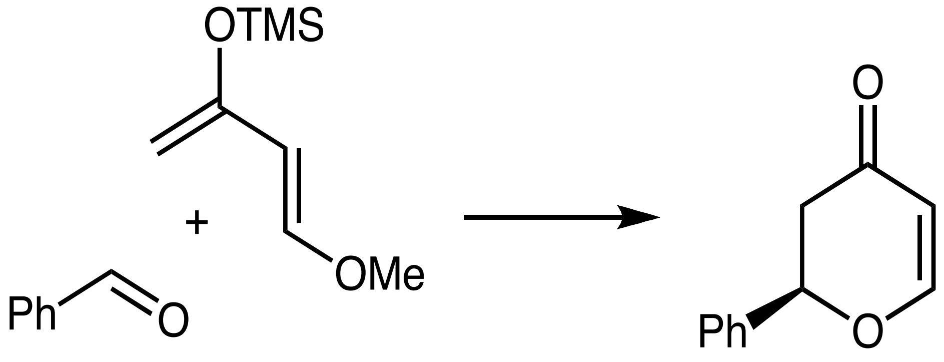


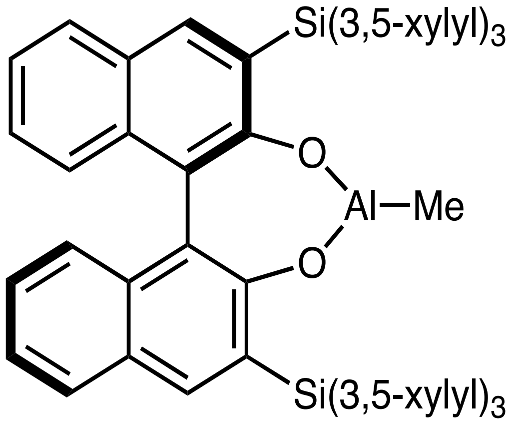
⇨ Early work involved chiral lanthanide catalysts but good enantioselectivities also require the presence of a chiral auxiliary (Danishefsky).



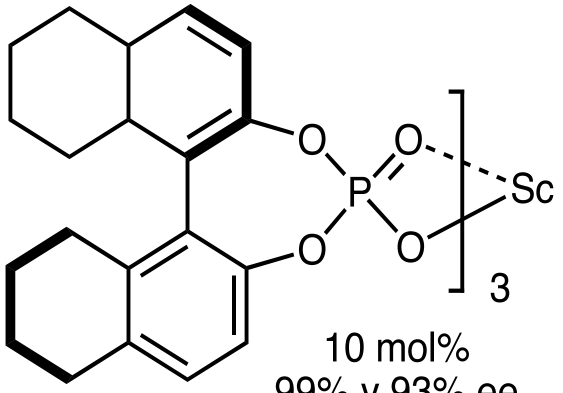
Hetero-Diels-Alder Reactions with Unactivated Aldehydes

Reaction between benzaldehyde and Danishefsky's diene:

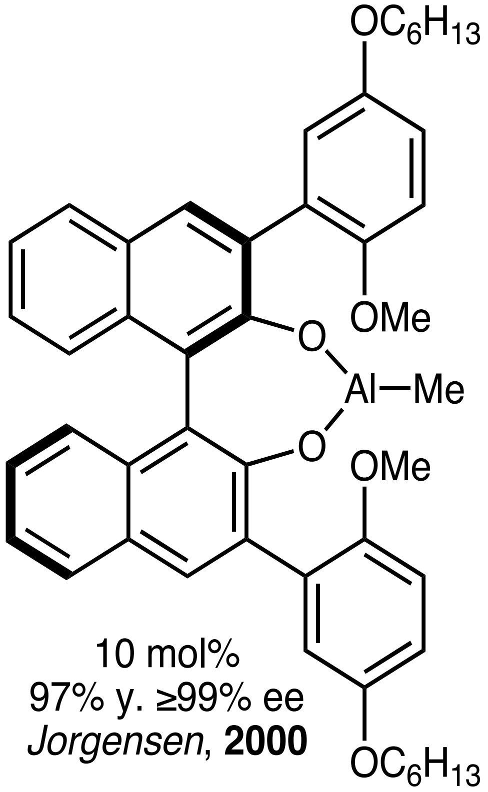




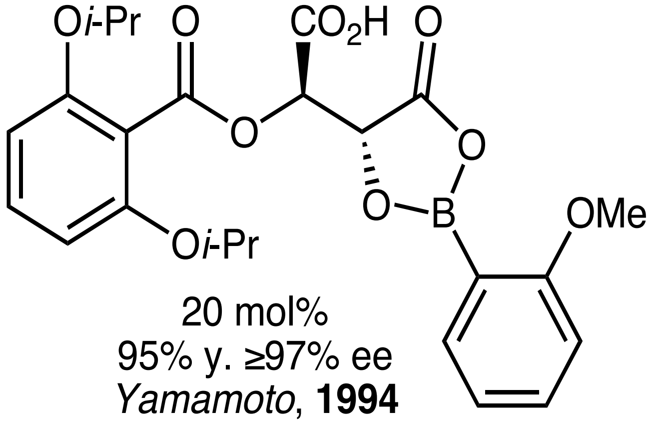
10 mol%
77% y. 85% ee
Yamamoto, **1988**
Better ee's with more substituted dienes



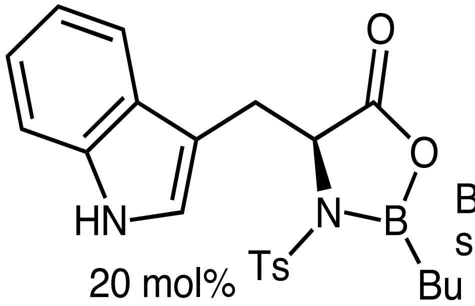
10 mol%
99% y.93% ee
Inanaga, **2003**



10 mol%
97% y. ≥99% ee
Jorgensen, **2000**



20 mol%
95% y. ≥97% ee
Yamamoto, **1994**



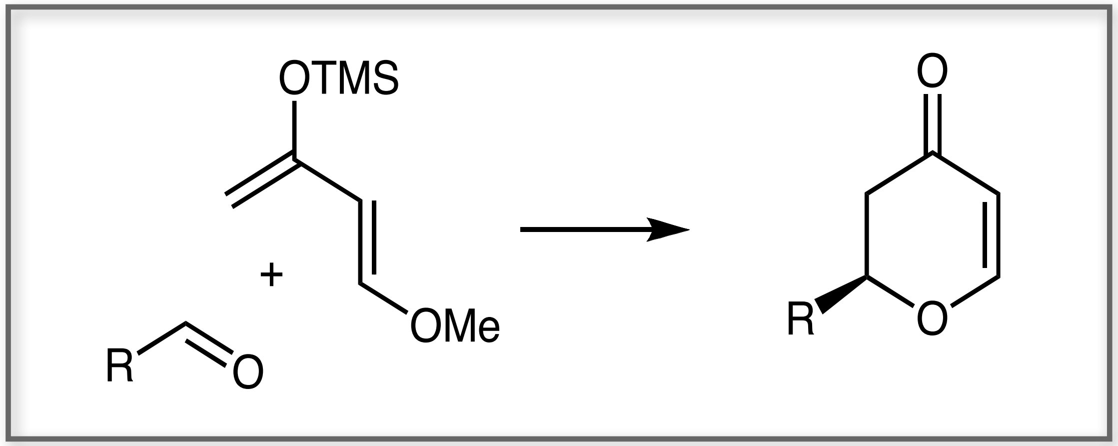
Better ee's with more substituted dienes

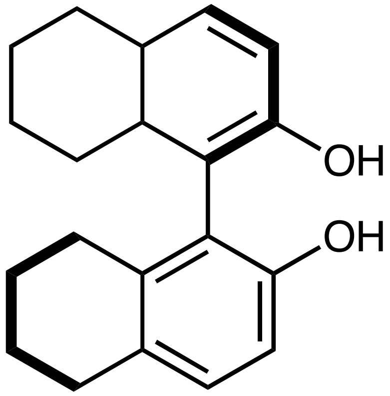
20 mol%
100% y. 82% ee
Corey, **1992**

All proceed via a Mukaiyama aldol pathway.

Hetero-Diels-Alder Reactions with Unactivated Aldehydes

Reaction between various aldehydes and Danishefsky's diene:





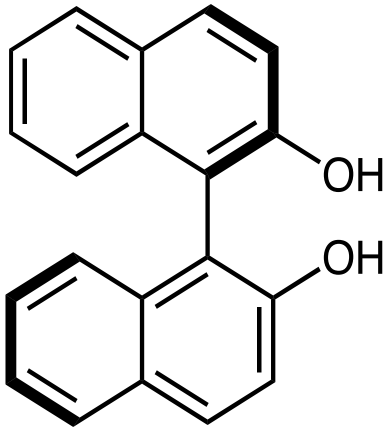
, $Ti(O\textit{i}\text{-}Pr)_4$ (20 mol%)

20 mol%

Feng, **2000**

Ph	92% y. 97% ee
2-ClPh	71% y. 90% ee
2-MeOPh	55% y. 90% ee
3-ClPh	81% y. 94% ee
3-MePh	81% y. 99% ee
3-MeOPh	51% y. 99% ee
4-CNPh	64% y. 95% ee
4-ClPh	67% y. 97% ee
4-FPh	54% y. 98% ee
4-MePh	60% y. 99% ee
2-furyl	**78% y. 96% ee**
2-pyridine	**55% y. 92% ee**
PhCH=CH	80% y. 98% ee
$CH_3(CH_2)_7$	57% y. 96% ee

Slightly lower yield with alkyl-substituted aldehydes



, $Ti(O\textit{i}\text{-}Pr)_4$ (10 mol%)

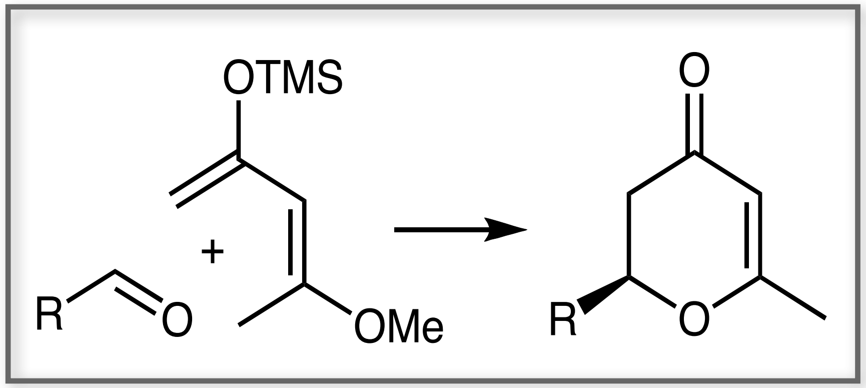
20 mol%

Keck, **1995**

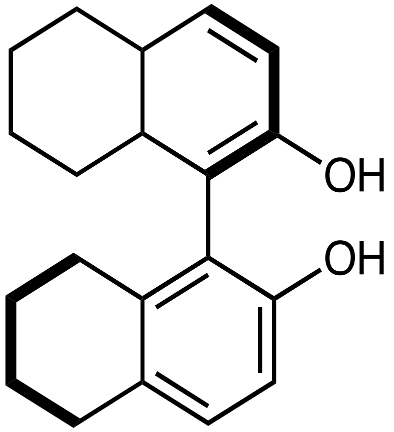
$TBSOCH_2CH_2$	55% y. 92% ee
$BnOCH_2$	60% y. 97% ee
2-furyl	61% y. 97% ee
$n\text{-}C_8H_{17}$	88% y. 97% ee
C_6H_{11}	69% y. 78% ee
$CH_3CH{=}CH$	50% y. 86% ee
Ph	40% y. 55% ee

Slightly lower yield with aryl-substituted aldehydes
Ligand:Ti ratio?

Hetero-Diels-Alder Reactions with Unactivated Aldehydes



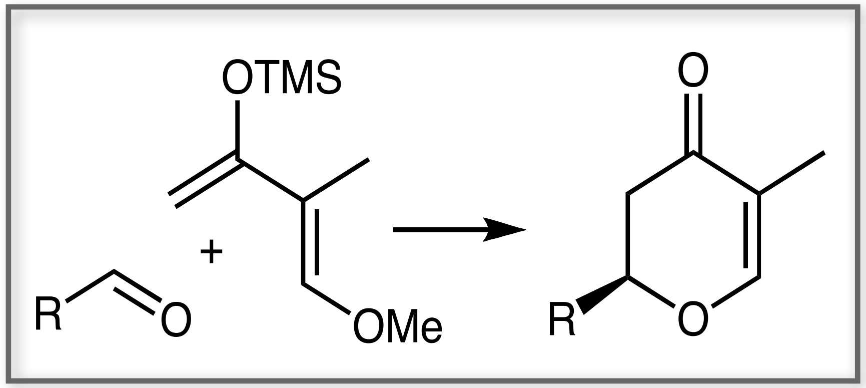
Ph	70% y. 99% ee
2-ClPh	90% y. 83% ee
2-MePh	66% y. 89% ee
3-ClPh	83% y. 98% ee
3-MePh	73% y. 99% ee
3-MeOPh	61% y. 98% ee
4-CNPh	86% y. 94% ee
4-BrPh	73% y. 93% ee
4-FPh	89% y. 94% ee
4-MePh	93% y. 99% ee
4-MeOPh	83% y. 99% ee
4-NO_2Ph	99% y. 99% ee
1-naphthyl	78% y. 99% ee
2-naphthyl	82% y. 97% ee
3,4-Cl_2Ph	77% y. 98% ee
3-pyridine	65% y. 98% ee
PhCH=CH	64% y. 92% ee
CH_3CH_2	88% y. 94% ee
$CH_3CH_2CH_2$	70% y. 92% ee
i-PrCH	84% y. 91% ee
$CH_3(CH_2)_3$	89% y. 91% ee
C_6H_{11}	61% y. 85% ee



20 mol%

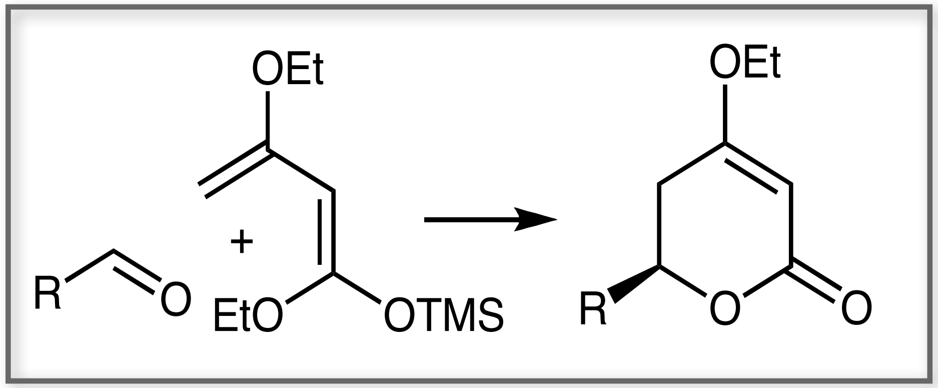
, Ti(O*i*-Pr)$_4$
(20 mol%)

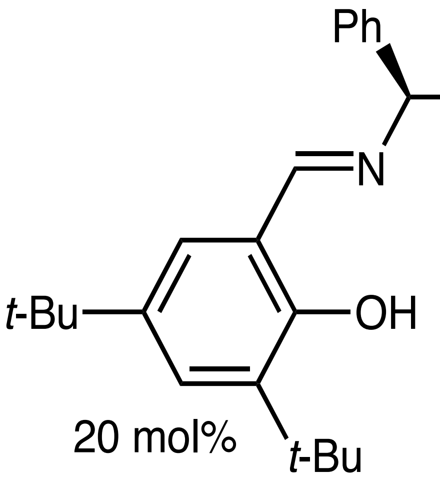
Feng, **2000**



Ph	86% y. 99% ee
2-ClPh	99% y. 90% ee
2-NO_2Ph	99% y. 91% ee
3-ClPh	82% y. 98% ee
3-NO_2Ph	85% y. 98% ee
3-MeOPh	99% y. 91% ee
4-CNPh	95% y. 92% ee
4-ClPh	66% y. 96% ee
4-FPh	73% y. 94% ee
4-MeOPh	84% y. 90% ee
4-NO_2Ph	80% y. 96% ee
1-naphthyl	40% y. 97% ee
2-naphthyl	69% y. 96% ee
3,4-Cl_2Ph	87% y. 99% ee
2,4-Cl_2Ph	70% y. 94% ee
2,6-Cl_2Ph	63% y. 83% ee
2-pyridine	99% y. 98% ee
3-pyridine	98% y. 96% ee
2-furyl	99% y. 97% ee
PhCH=CH	47% y. 85% ee
$CH_3(CH_2)_4$	41% y. 87% ee

Hetero-Diels-Alder Reactions with Unactivated Aldehydes



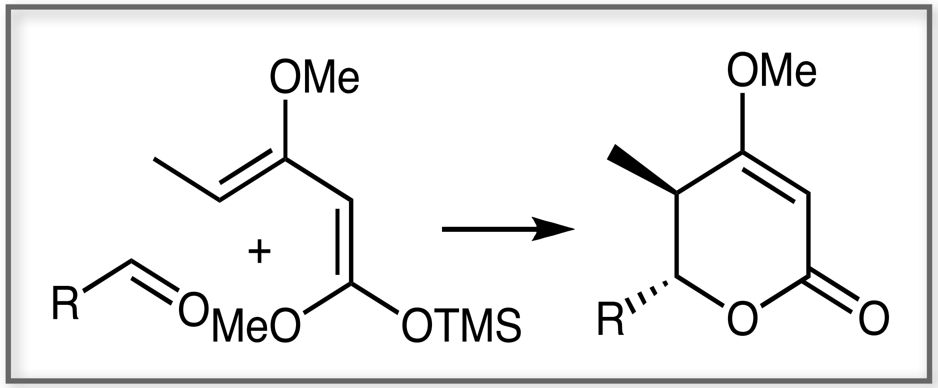


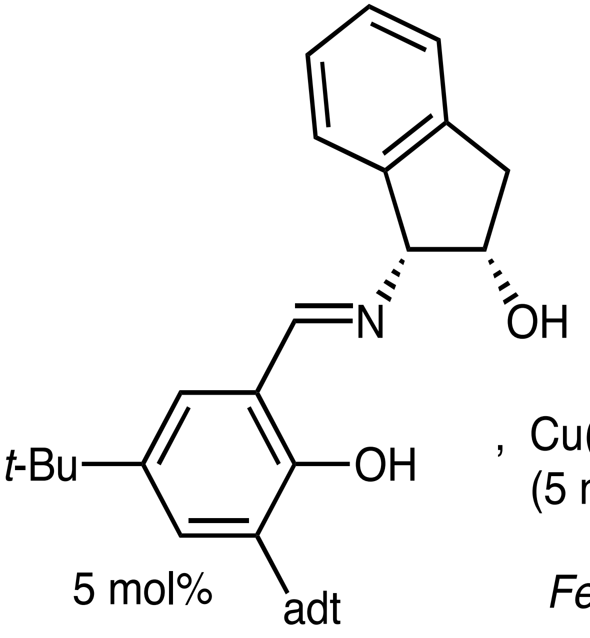
20 mol%

, Ti(O*i*-Pr)$_4$
(20 mol%)

Feng, **2004**

Ph	71% y. 93% ee
2-ClPh	70% y. 99% ee
3-MePh	53% y. 93% ee
3-ClPh	70% y. 90% ee
4-CNPh	61% y. 90% ee
4-ClPh	87% y. 97% ee
4-FPh	53% y. 93% ee
4-NO_2Ph	56% y. 91% ee
2-naphthyl	61% y. 96% ee
3,4-Cl_2Ph	54% y. 87% ee
2,4-Cl_2Ph	67% y. 95% ee





5 mol%

, Cu(OTf)$_2$
(5 mol%)

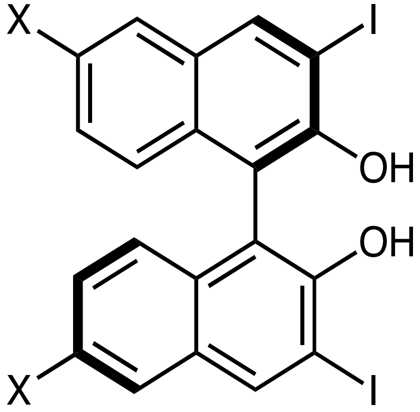
Feng, **2006**

Ph	70% y. 95:5, 98% ee
4-FPh	60% y. 97:3, 97% ee
4-ClPh	55% y. 95:5, 94% ee
4-BrPh	65% y. 94:6, 91% ee
3-NO_2Ph	53% y. 88:12, 90% ee
4-NO_2Ph	64% y. 89:11, 94% ee
2-naphthyl	63% y. 97:3, 97% ee

Limited scope; low yield and ee with aliphatic aldehydes.

Hetero-Diels-Alder Reactions with Unactivated Aldehydes

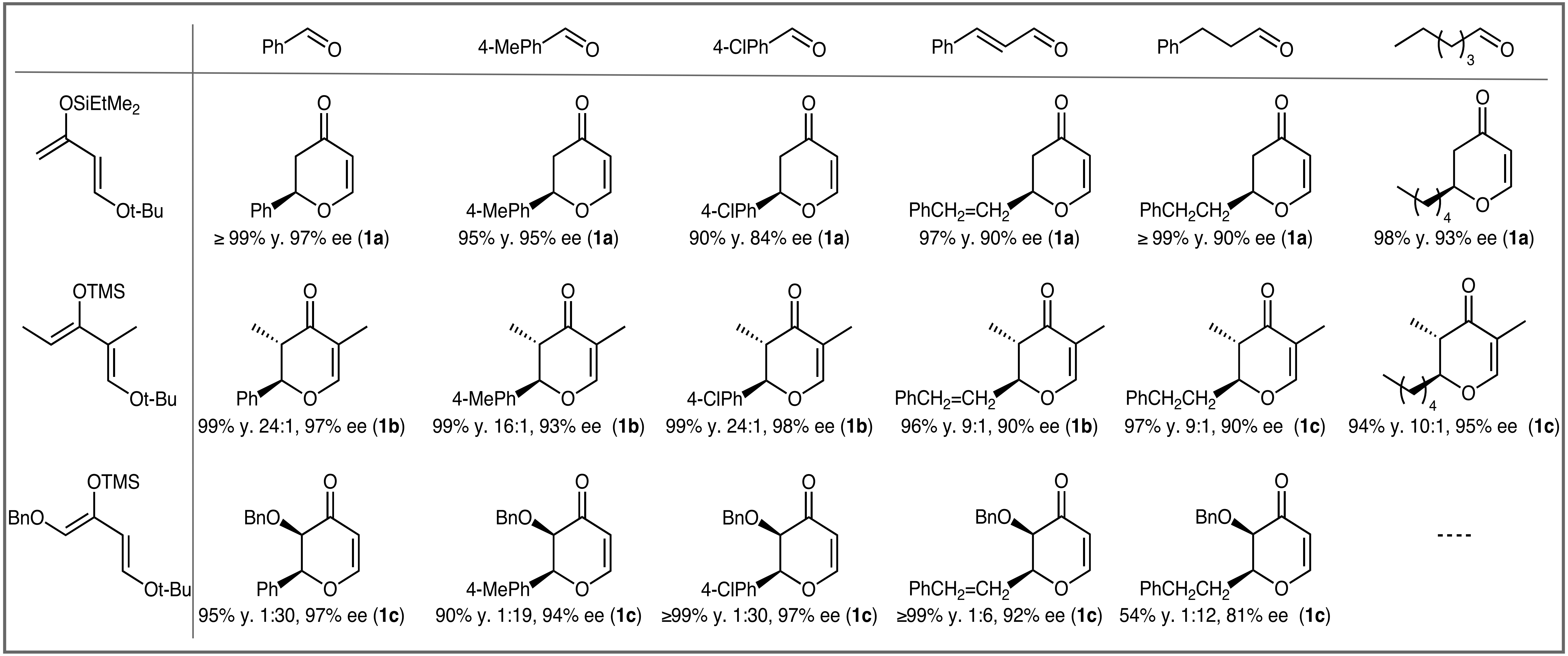
Kobayashi, **2003**



$Zr(Ot\text{-}Bu)_4$ (10 mol%)
Binol (12 mol%)
H_2O (20 mol%)
Toluene/*t*-BuOMe

(*R*)-**1a**, X = H
(*R*)-**1b**, X=C_2F_5
(*R*)-**1c**, X = I

Stepwise mechanism;
Anti aldol led to *trans-product*
Syn aldol led to *cis*-product



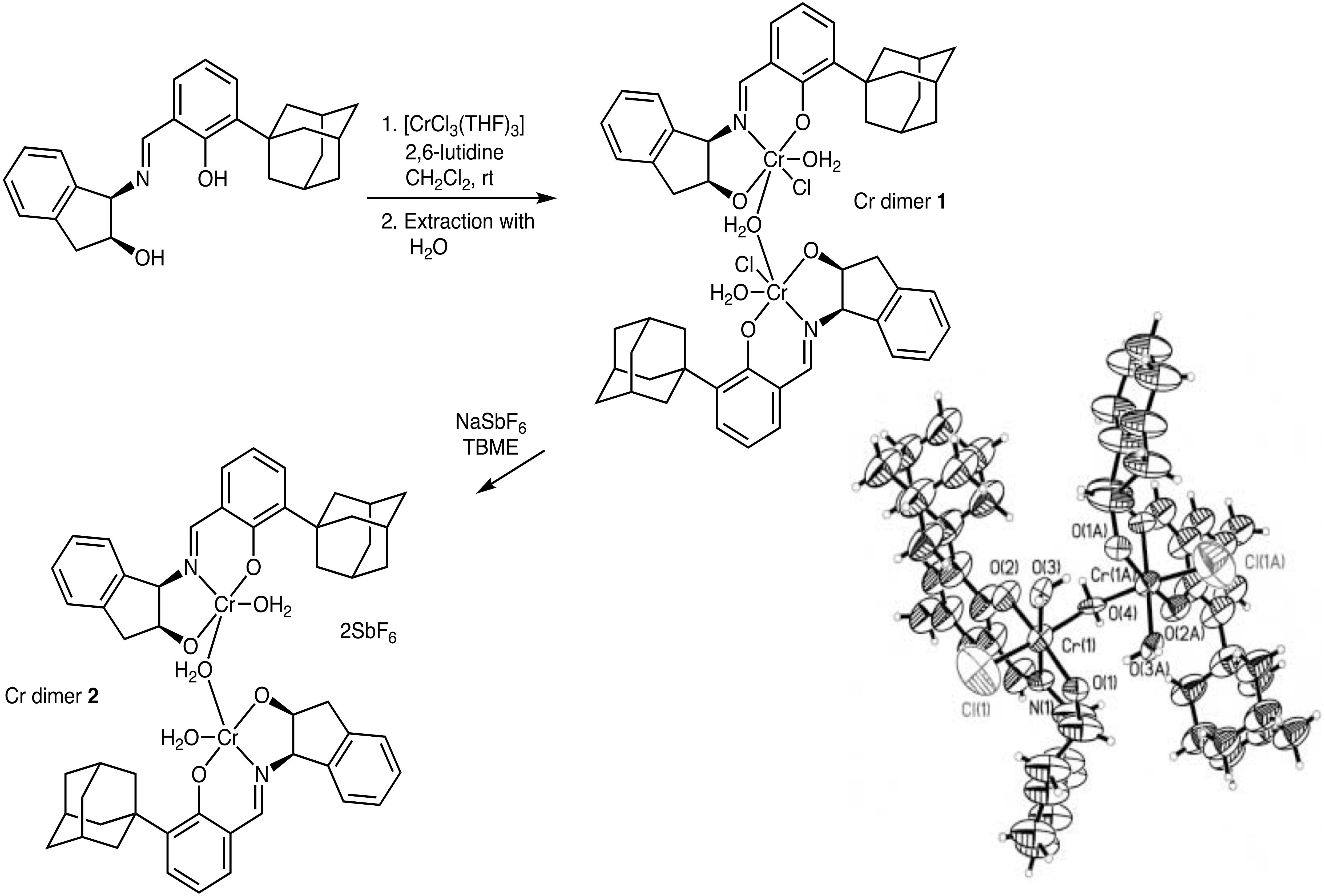
≥ 99% y. 97% ee (**1a**) | 95% y. 95% ee (**1a**) | 90% y. 84% ee (**1a**) | 97% y. 90% ee (**1a**) | ≥ 99% y. 90% ee (**1a**) | 98% y. 93% ee (**1a**)

99% y. 24:1, 97% ee (**1b**) | 99% y. 16:1, 93% ee (**1b**) | 99% y. 24:1, 98% ee (**1b**) | 96% y. 9:1, 90% ee (**1b**) | 97% y. 9:1, 90% ee (**1c**) | 94% y. 10:1, 95% ee (**1c**)

95% y. 1:30, 97% ee (**1c**) | 90% y. 1:19, 94% ee (**1c**) | ≥99% y. 1:30, 97% ee (**1c**) | ≥99% y. 1:6, 92% ee (**1c**) | 54% y. 1:12, 81% ee (**1c**)

Conclusion: High yields and high enantioselectivities with many catalysts but relative high catalyst loadings

Hetero-Diels-Alder Reactions with Unactivated Aldehydes



1. $[CrCl_3(THF)_3]$
2,6-lutidine
CH_2Cl_2, rt

2. Extraction with
H_2O

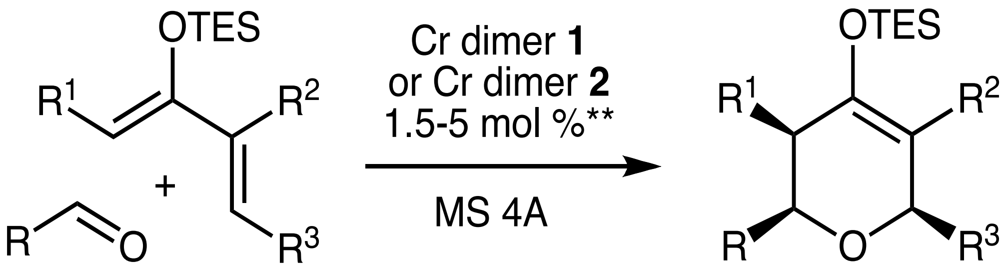
Cr dimer **1**

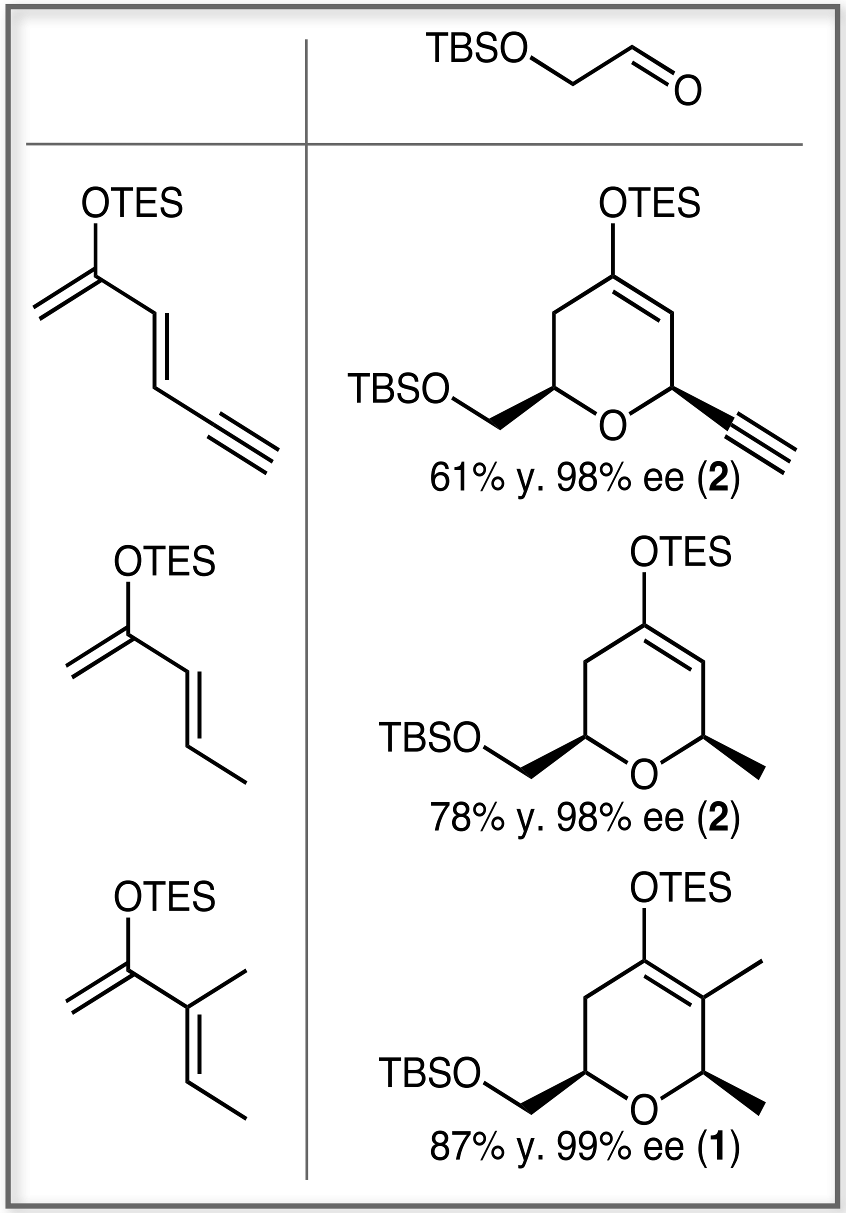
$NaSbF_6$
TBME

$2SbF_6$

Cr dimer **2**

Hetero-Diels-Alder Reactions with Unactivated Aldehydes



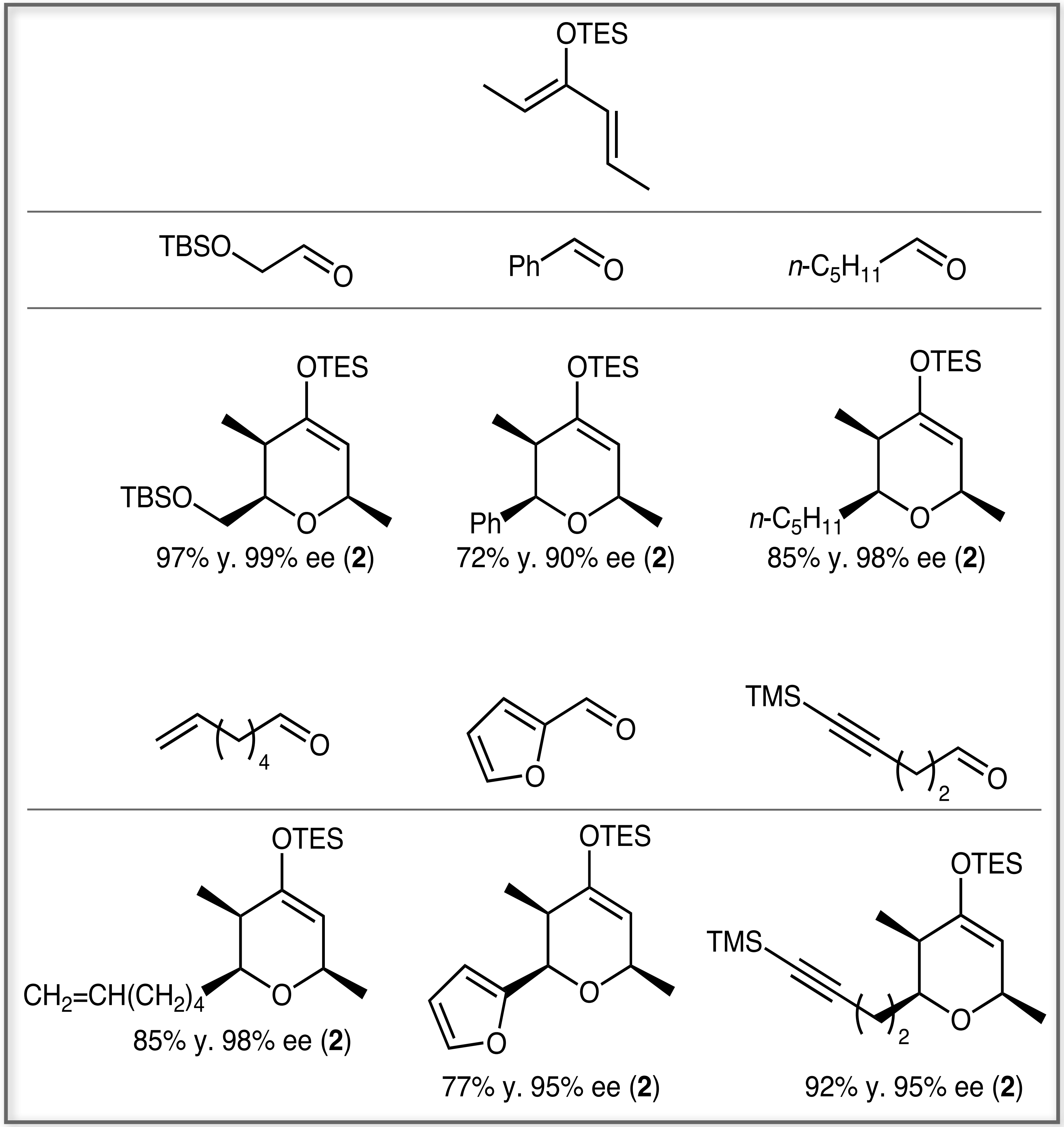


61% y. 98% ee (**2**)

78% y. 98% ee (**2**)

87% y. 99% ee (**1**)

**The catalyst loading is calculated based on the number of equivalents of chromium relative to the limiting aldehyde substrate.



97% y. 99% ee (**2**)

72% y. 90% ee (**2**)

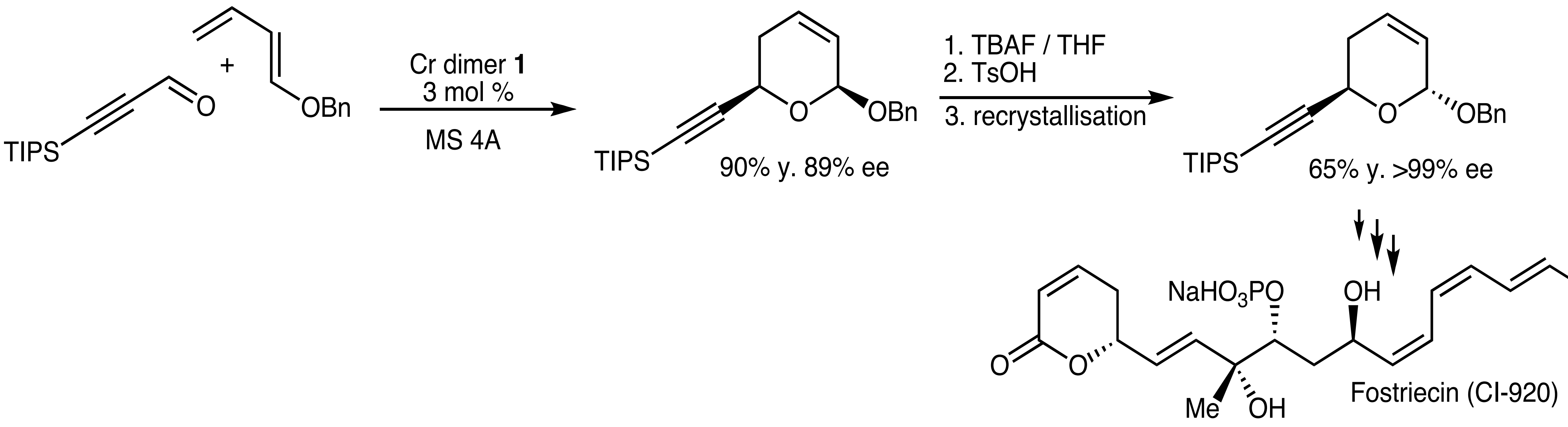
85% y. 98% ee (**2**)

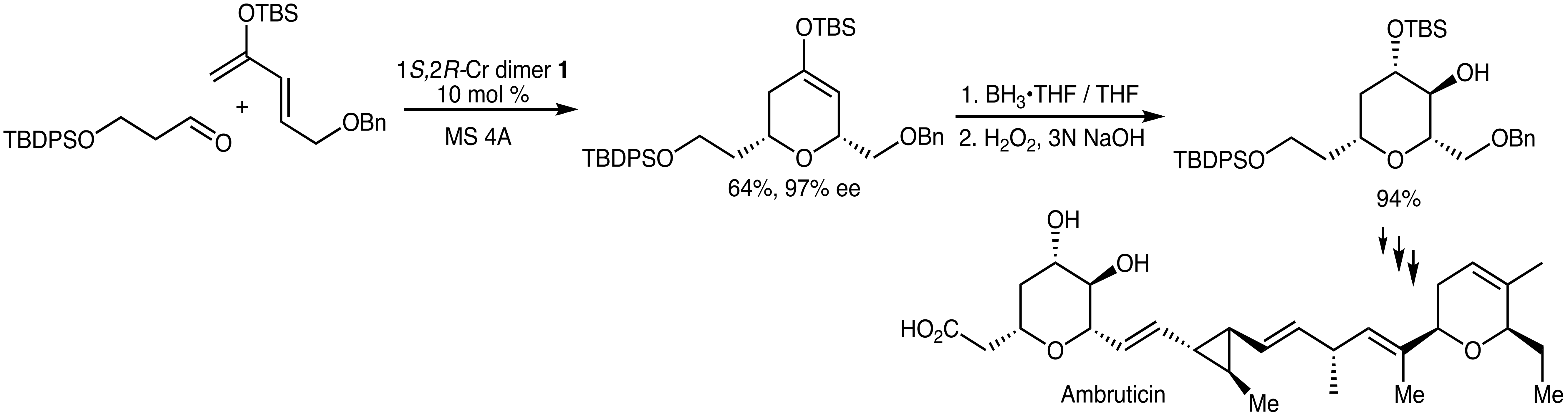
85% y. 98% ee (**2**)

77% y. 95% ee (**2**)

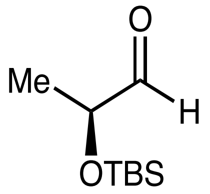
92% y. 95% ee (**2**)

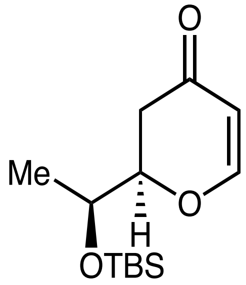
Hetero-Diels-Alder Reactions with Unactivated Aldehydes



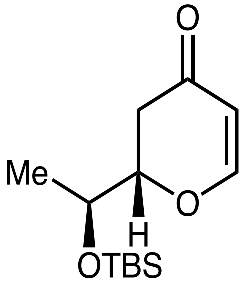


Hetero-Diels-Alder Reactions with Chiral Aldehydes

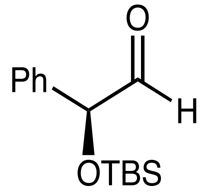


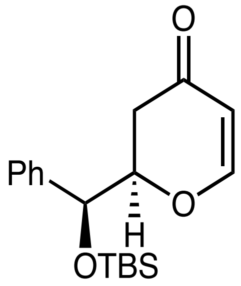


Achiral Cr, 81%, 1:2
(1*R*,2*S*)-**1**, 96%, 1:12, >99% ee

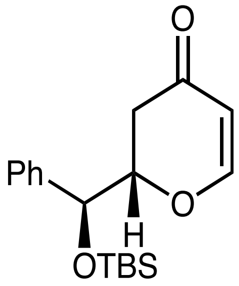


(1*S*,2*R*)-**1**, 97%, 15:1, >99% ee

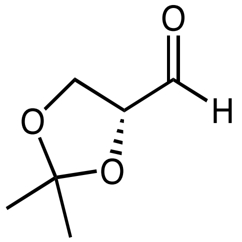


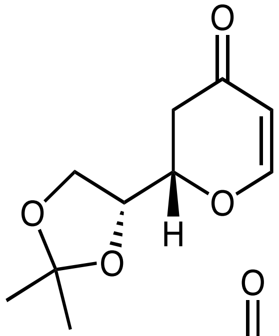


Achiral Cr,58%, 1:1.7
(1*R*,2*S*)-**1**, 58%, 1:3.6, 99% ee

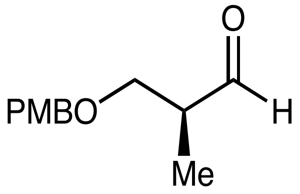


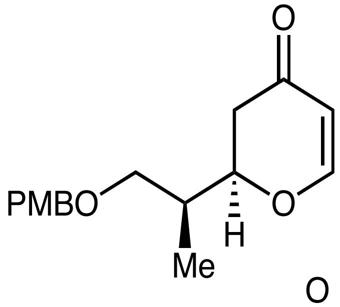
(1*S*,2*R*)-**1**, 44%, 2.6:1, 97% ee



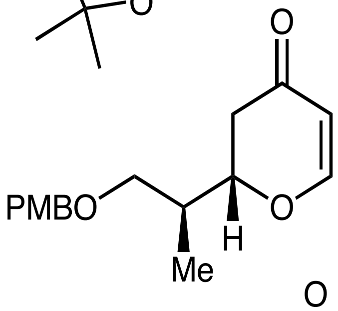


Achiral Cr, 68%, 4.5:1, >99% ee
(1*R*,2*S*)-**1**, 76%, 1.2:1, 98% ee
(1*S*,2*R*)-**1**, 97%, 33:1, 99% ee

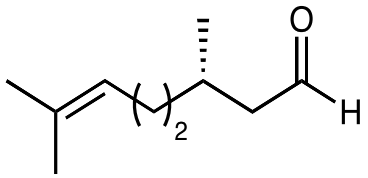


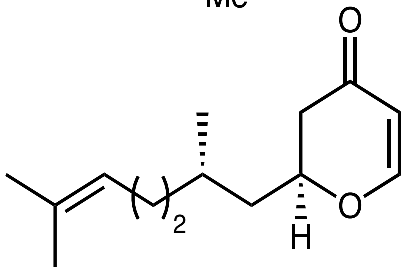


Achiral Cr, 50%, 1:1.1
(1*R*,2*S*)-**1**, 90%, 1:11, >99% ee

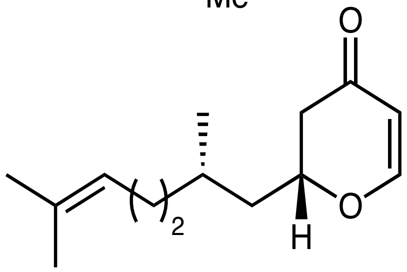


(1*S*,2*R*)-**1**, 86%, 9.3:1, 99% ee





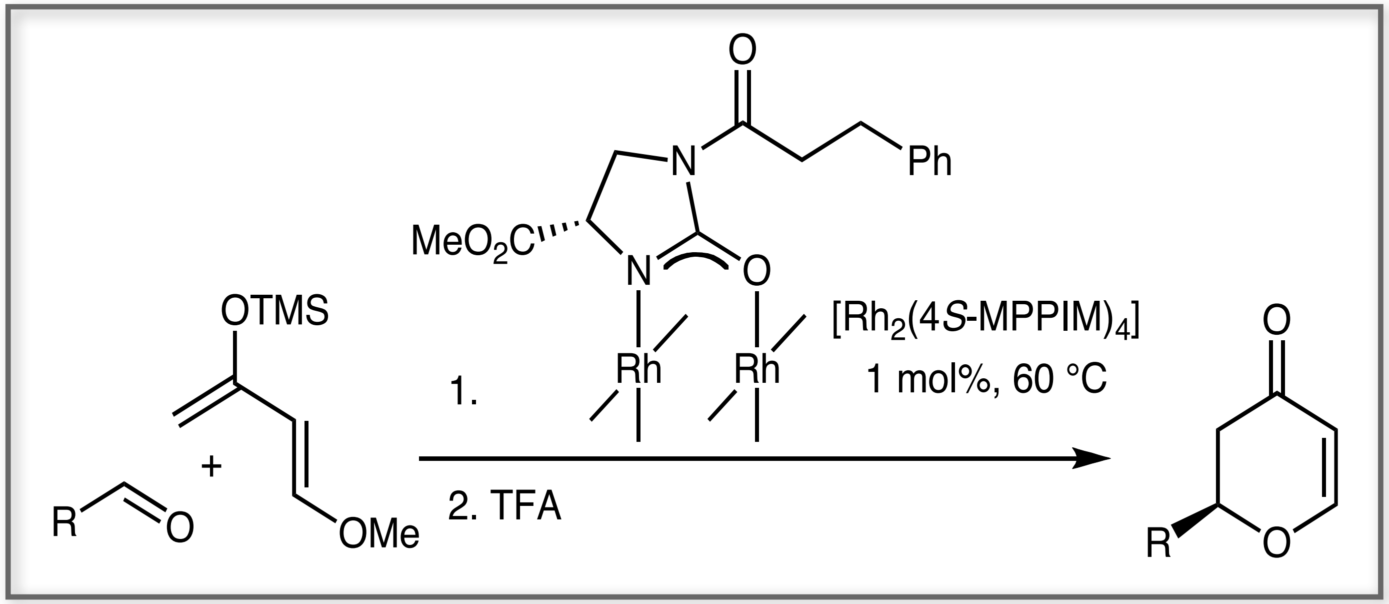
Achiral Cr, 85%, 1:1.3
(1*S*,2*R*)-**1**, 99%, 1:11



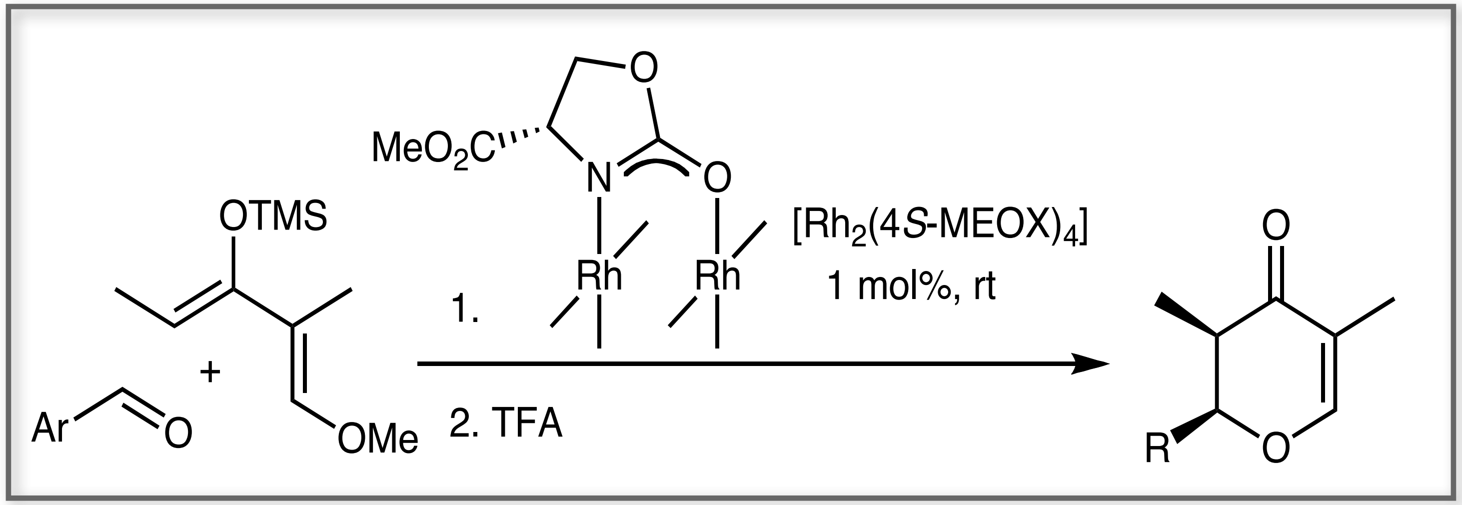
(1*R*,2*S*)-**1**, 98%, 16:1

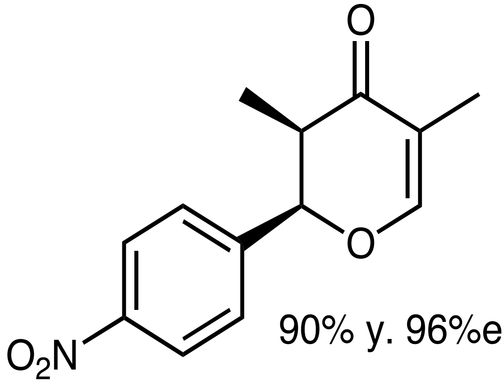
Hetero-Diels-Alder Reactions with Unactivated Aldehydes

Doyle (2001, 2004)

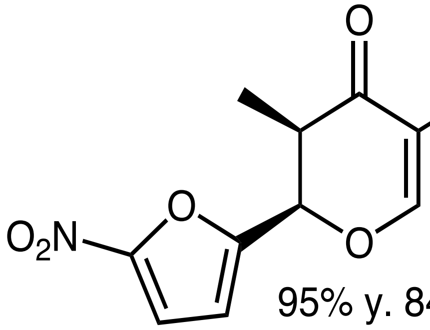


4-MeOPh	47% y. 93% ee
4-MePh	82% y. 90% ee
Ph	91% y. 93% ee
4-ClPh	90% y. 91% ee
4-CF_3Ph	88% y. 92% ee
4-FPh	82% y. 96% ee
4-NO_2Ph	95% y. 92% ee
2-NO_2Ph	87% y. 84% ee
3-NO_2Ph	66% y. 95% ee
2-naphthyl	90% y. 98% ee
2-furyl	88% y. 84% ee

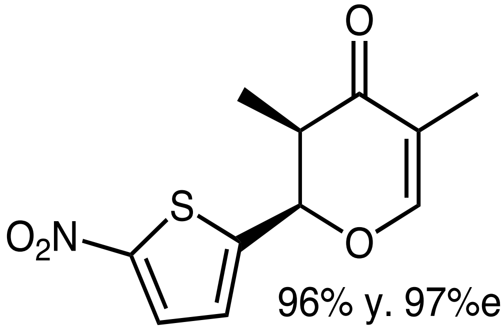




90% y. 96%ee



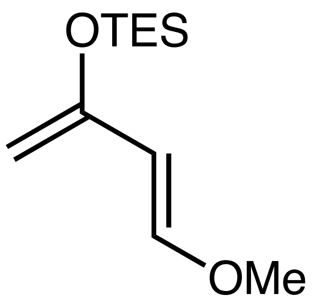
95% y. 84%ee

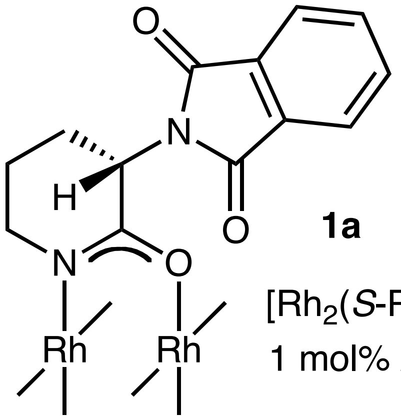


96% y. 97%ee

Hetero-Diels-Alder Reactions with Unactivated Aldehydes

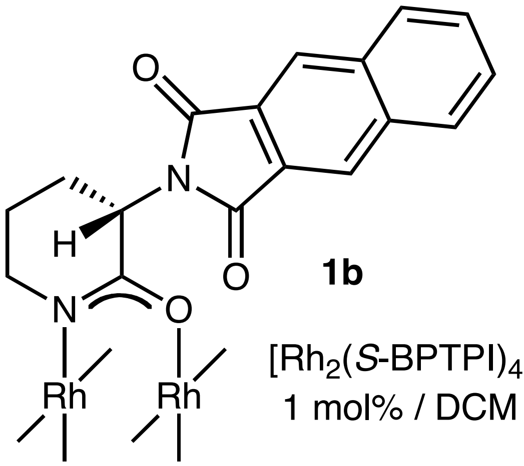
Hashimoto **2004**





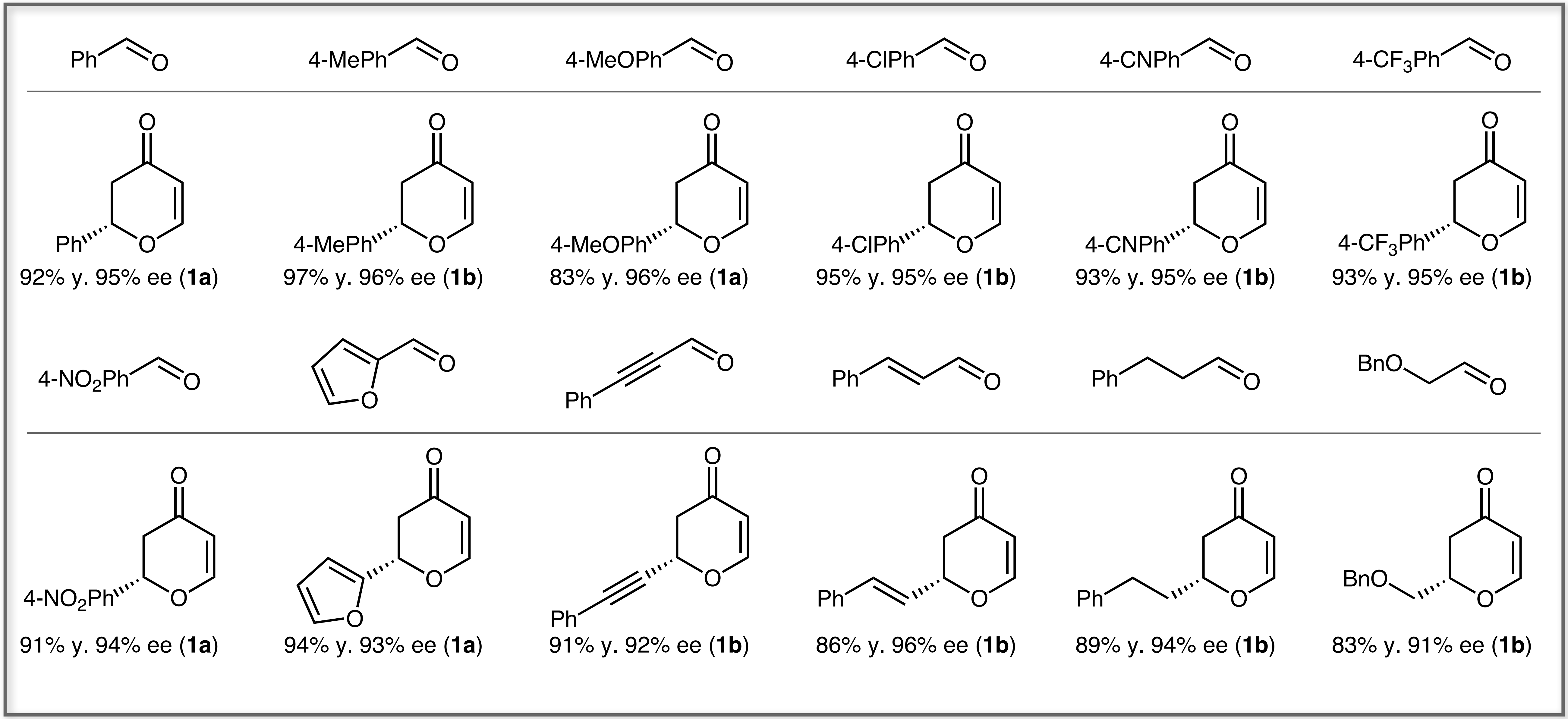
1a

[Rh_2(*S*-PTPI)$_4$]
1 mol% / DCM



1b

[Rh_2(*S*-BPTPI)$_4$]
1 mol% / DCM

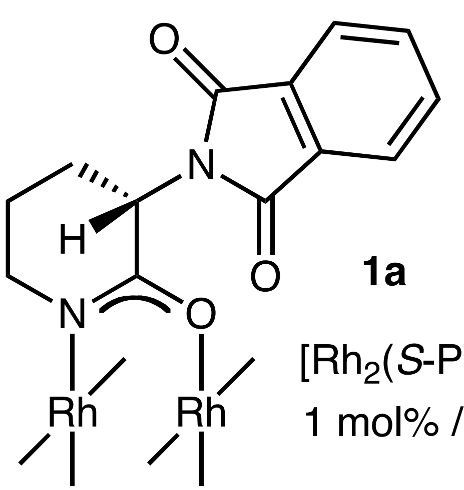


92% y. 95% ee (**1a**)
97% y. 96% ee (**1b**)
83% y. 96% ee (**1a**)
95% y. 95% ee (**1b**)
93% y. 95% ee (**1b**)
93% y. 95% ee (**1b**)

91% y. 94% ee (**1a**)
94% y. 93% ee (**1a**)
91% y. 92% ee (**1b**)
86% y. 96% ee (**1b**)
89% y. 94% ee (**1b**)
83% y. 91% ee (**1b**)

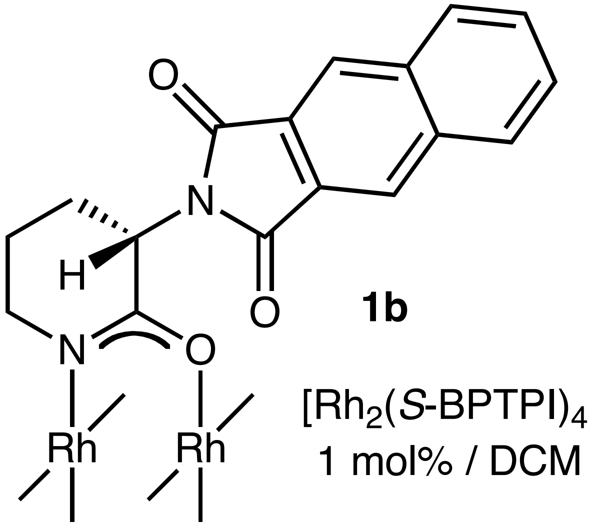
Hetero-Diels-Alder Reactions with Unactivated Aldehydes

Hashimoto (2004)



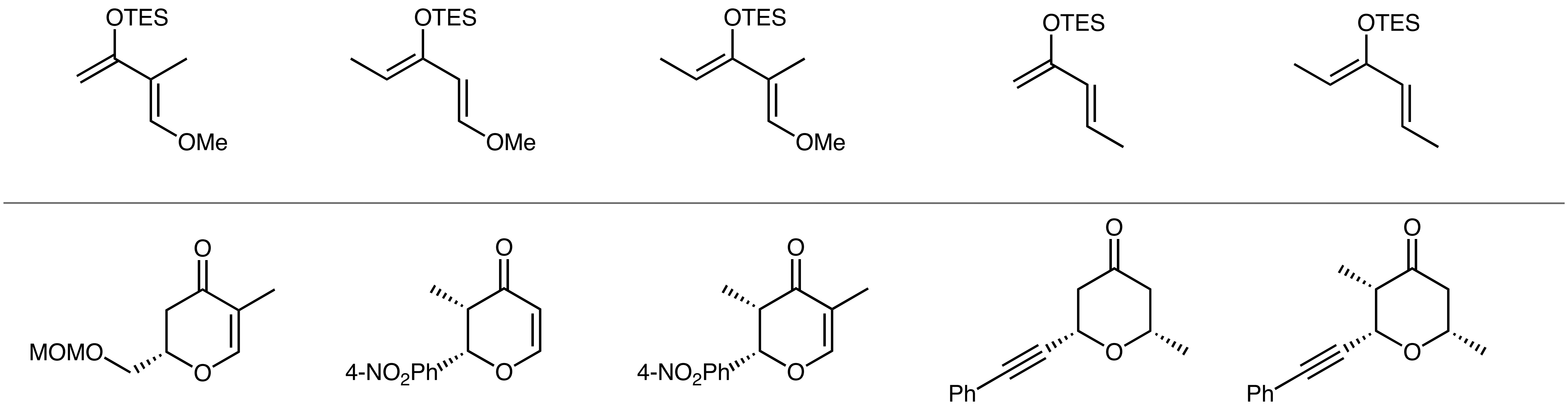
1a

[Rh_2(*S*-PTPI)$_4$]
1 mol% / DCM



1b

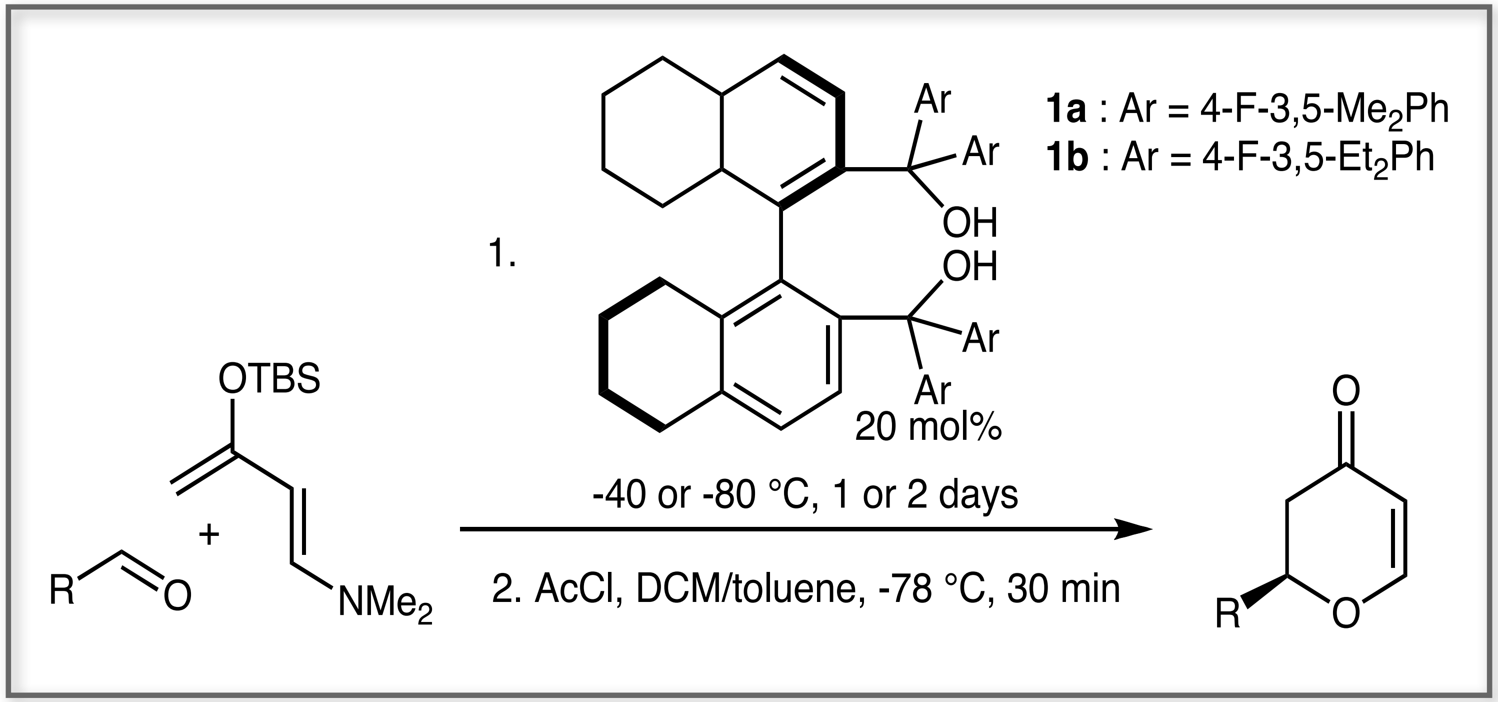
[Rh_2(*S*-BPTPI)$_4$]
1 mol% / DCM



86% y. 93% ee (**1b**)
97% y. 96% ee (**1b**)
92% y. 97% ee (**1b**)
87% y. 99% ee (**1b**)
81% y. 97% ee (**1b**)

Hetero-Diels-Alder Reactions with Unactivated Aldehydes

Rawal (2005)

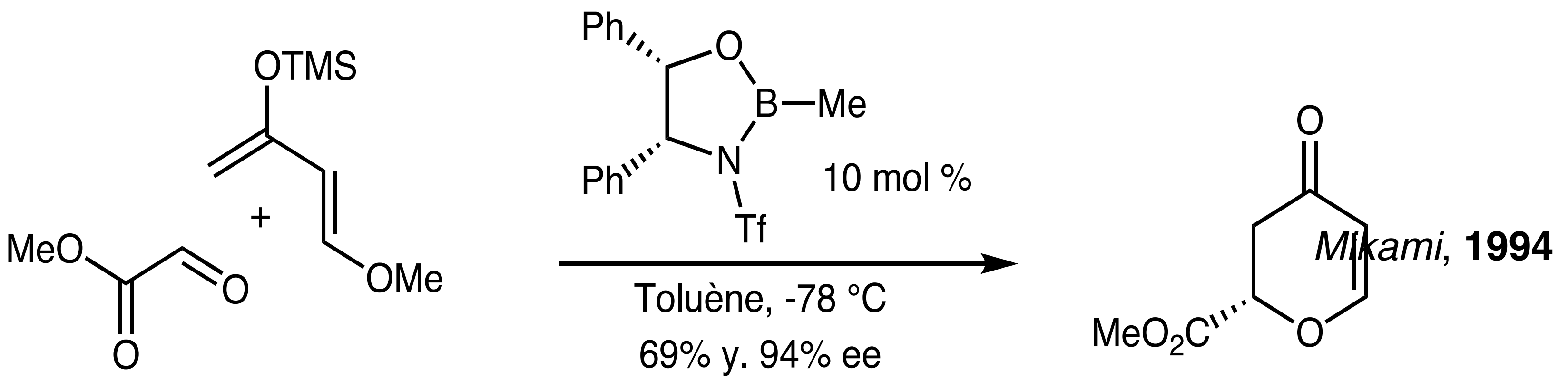


Me (**1b**)	75% y. 97% ee
n-propyl (**1a**)	76% y. 94% ee
$PhCH_2CH_2$ (**1a**)	95% y. 95% ee
$PhSCH_2CH_2$ (**1a**)	76% y. 94% ee
$Phth(CH_2)_3$ (**1a**)	67% y. 92% ee
1-propyny (**1a**)	42% y. 98% ee
i-butyl (**1a**)	79% y. 90% ee
c-hexyl (**1a**)	99% y. 84% ee

Ph (**1b**)	84% y. 98% ee
3-MeOPh (**1b**)	86% y. 98% ee
2-NO_2Ph (**1b**)	93% y. 98% ee
1-naphthyl (**1b**)	67% y. 97% ee
2-furyl (**1b**)	96% y. 99% ee

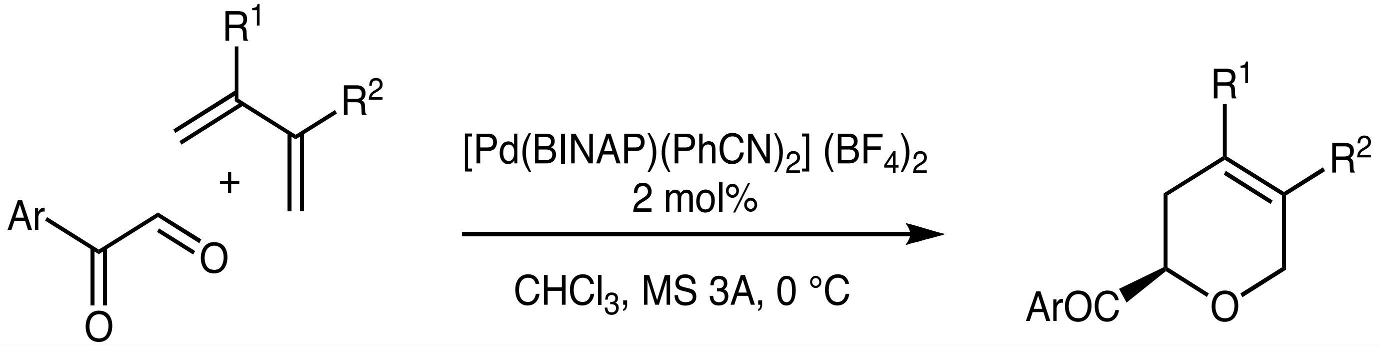
Hetero-Diels-Alder Reactions with Activated Aldehydes

Glyoxal Derivatives

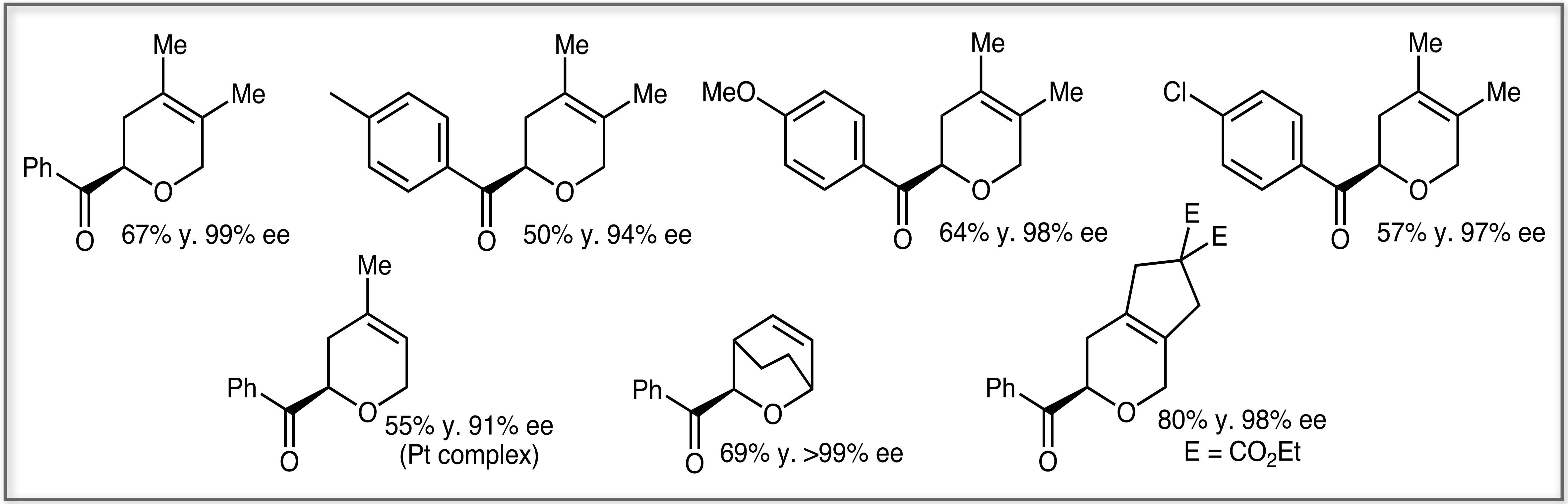


Mikami, **1994**

Ot atalytic systems led to lower ee and/or substantial amounts of the ene product (sometime the major product).[1]

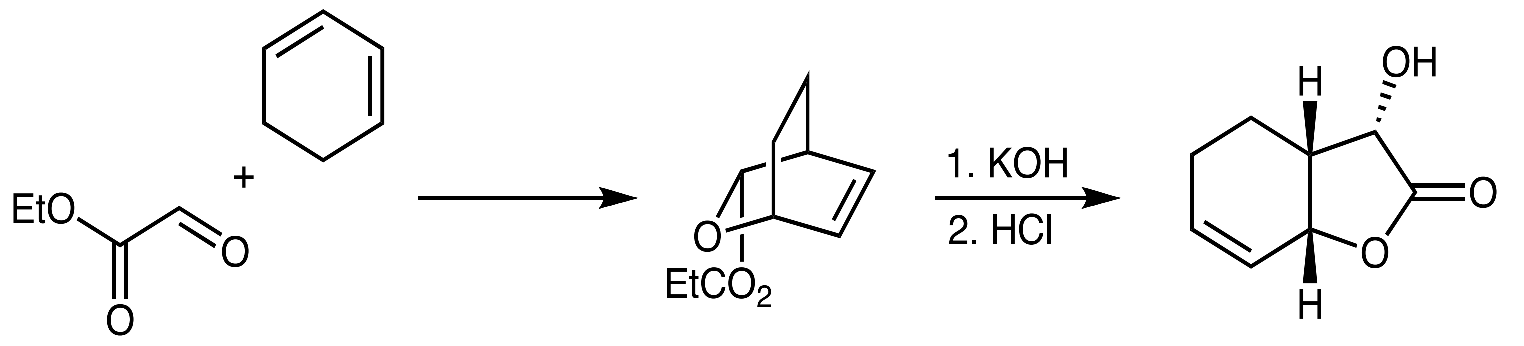


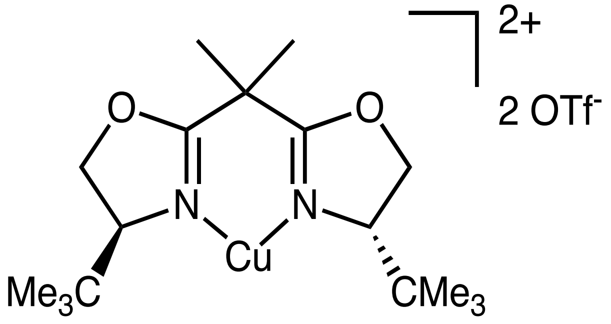
A chiral biscationic palladium (II) complex used as Lewis acid.
Oi, **1999.**



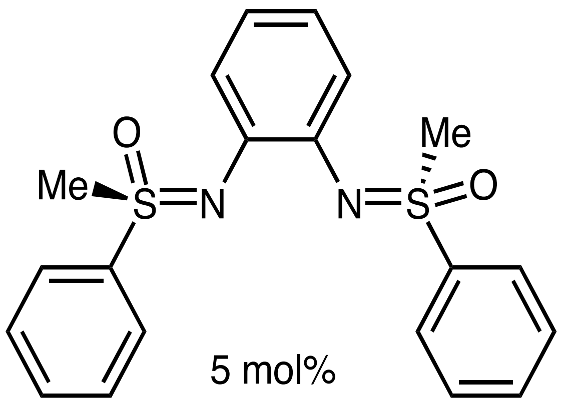
Hetero-Diels-Alder Reactions with Ethyl Glyoxylate

Reaction between ethyl glyoxylate and 1,3-cyclohexadiene:



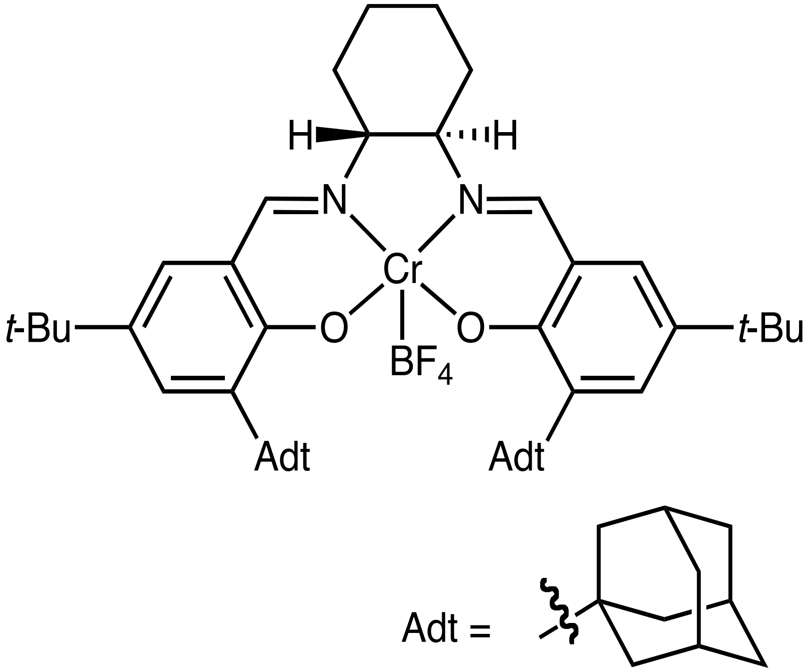


5 mol%
98% y. 97% ee, ≥98% endo
Jorgensen, **1997**

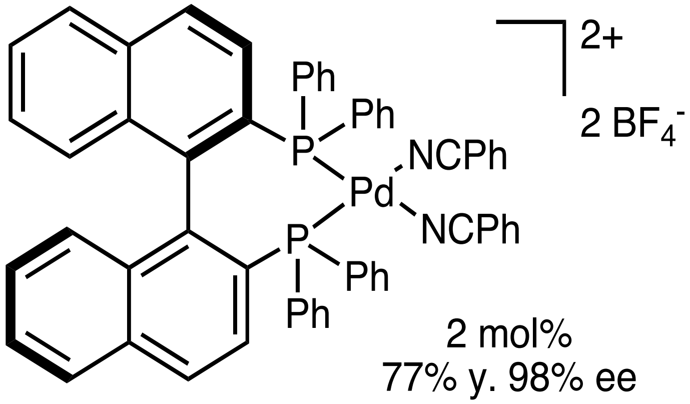


5 mol%

Cu(OTf)$_2$ (5 mol%)
81% y. 98% ee, 99% endo
Bolm, **2001**



2 mol%
69% y. 95% ee, 94% endo
Kwiatkowski, **2006**

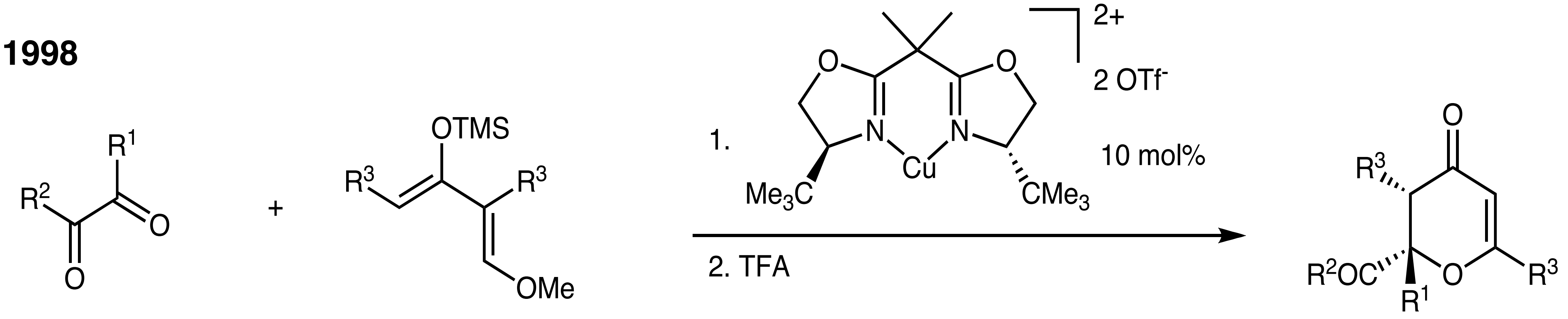


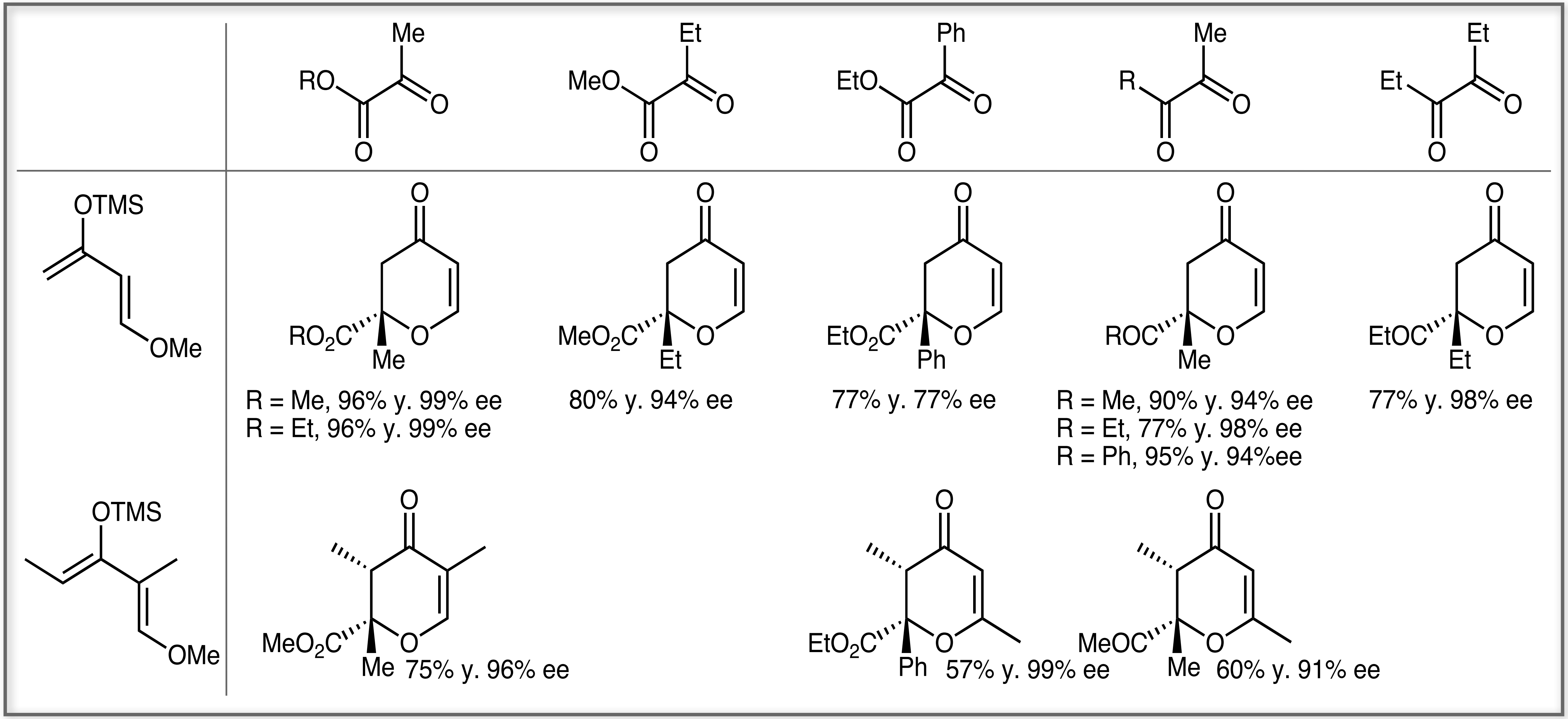
2 mol%
77% y. 98% ee
Oi, **1999**

➡ In all cases, freshly prepared ethyl glyoxylate is recommended. See: *Jorgensen*, **1997**.

Hetero-Diels-Alder Reactions with α-Ketoesters

Jorgensen, **1998**





R = Me, 96% y. 99% ee
R = Et, 96% y. 99% ee

80% y. 94% ee

77% y. 77% ee

R = Me, 90% y. 94% ee
R = Et, 77% y. 98% ee
R = Ph, 95% y. 94%ee

77% y. 98% ee

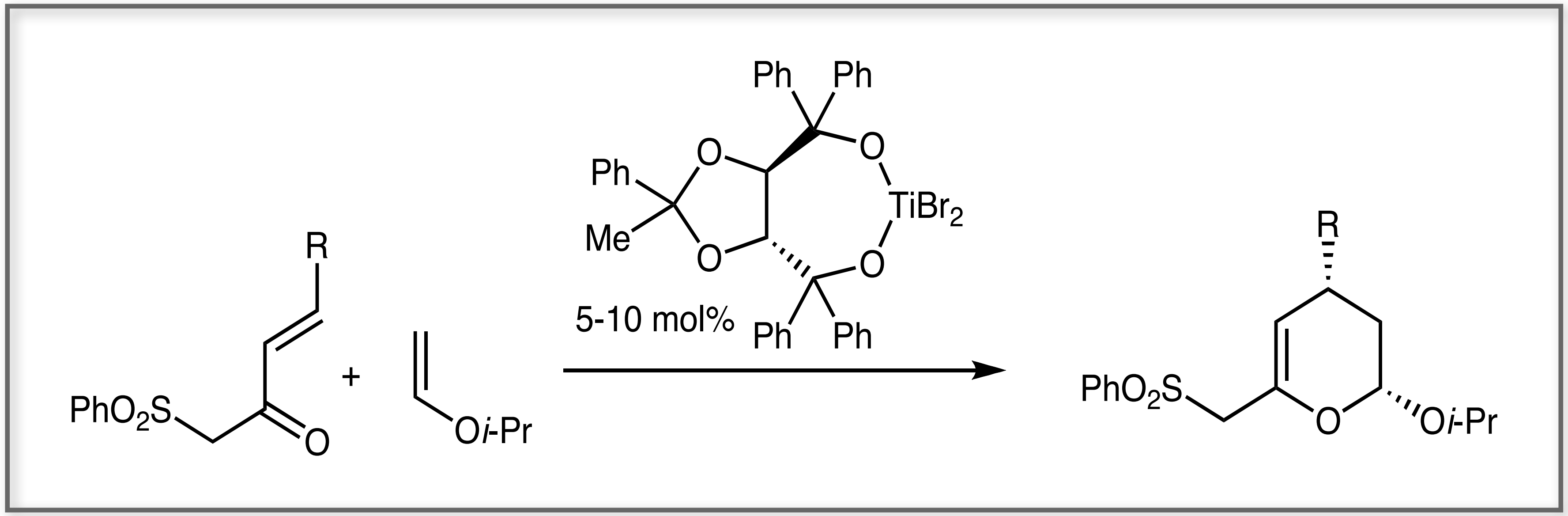
75% y. 96% ee

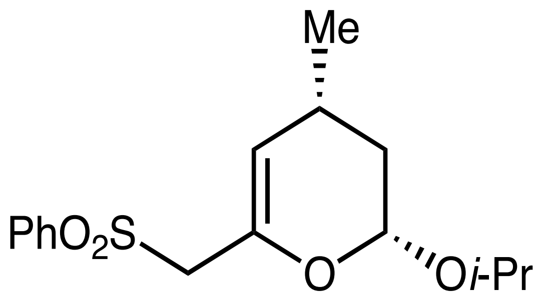
57% y. 99% ee

60% y. 91% ee

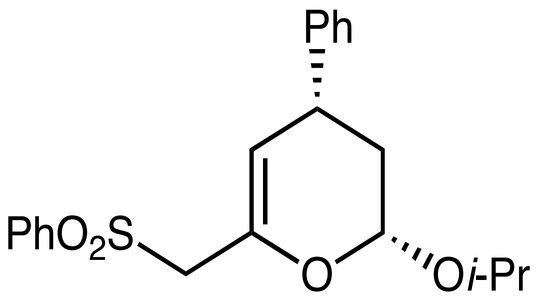
Inverse-Electron-Demand Hetero-Diels-Alder Reactions

Wada, **1994**

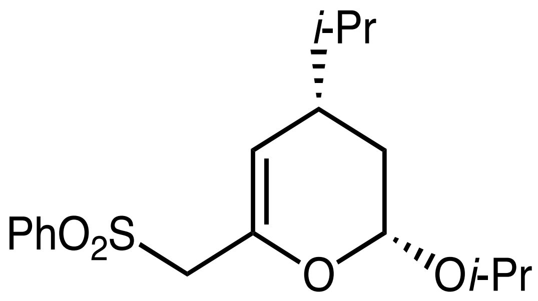




90% y. 95%ee

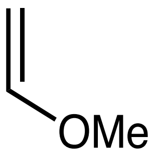


77% y. 97%ee

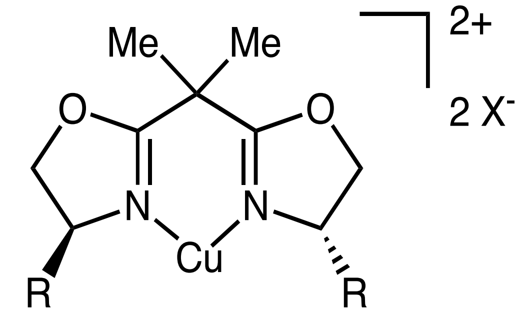


88% y. 86%ee

59% ee with

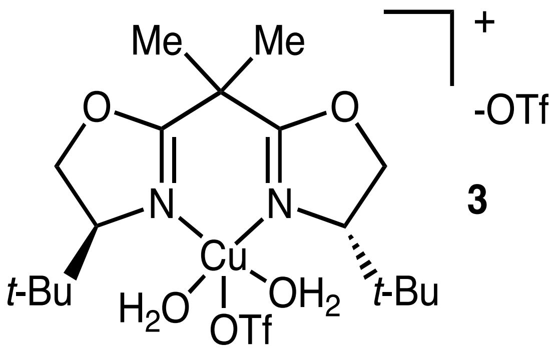


Inverse-Electron-Demand Hetero-Diels-Alder Reactions



1a, R = *t*-Bu, X = OTf
1b, R = *t*-Bu, X =SbF_6

2a, R = Ph, X = OTf
2b, R = Ph, X =SbF_6



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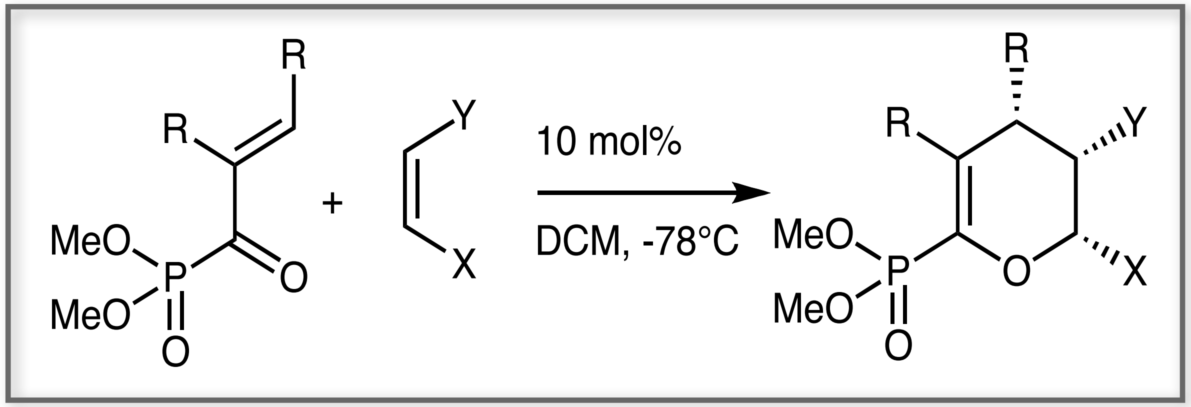
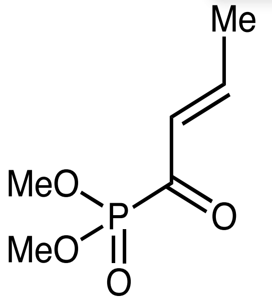
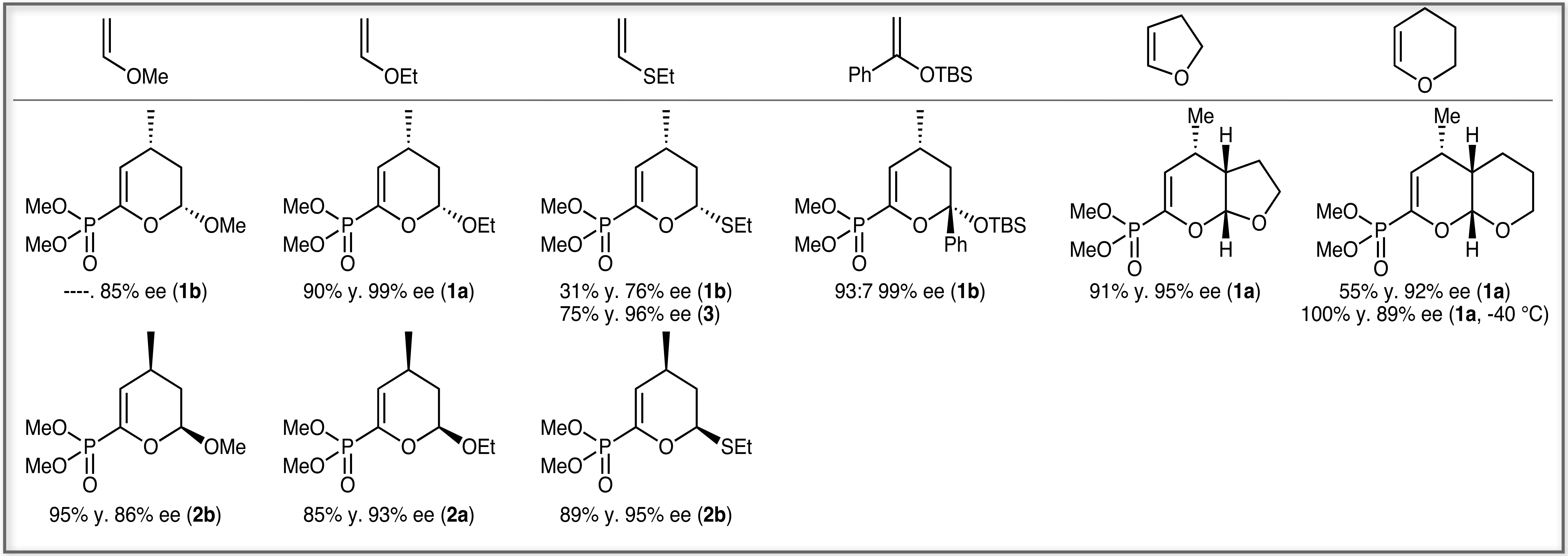






----. 85% ee (**1b**)

90% y. 99% ee (**1a**)

31% y. 76% ee (**1b**)
75% y. 96% ee (**3**)

93:7 99% ee (**1b**)

91% y. 95% ee (**1a**)

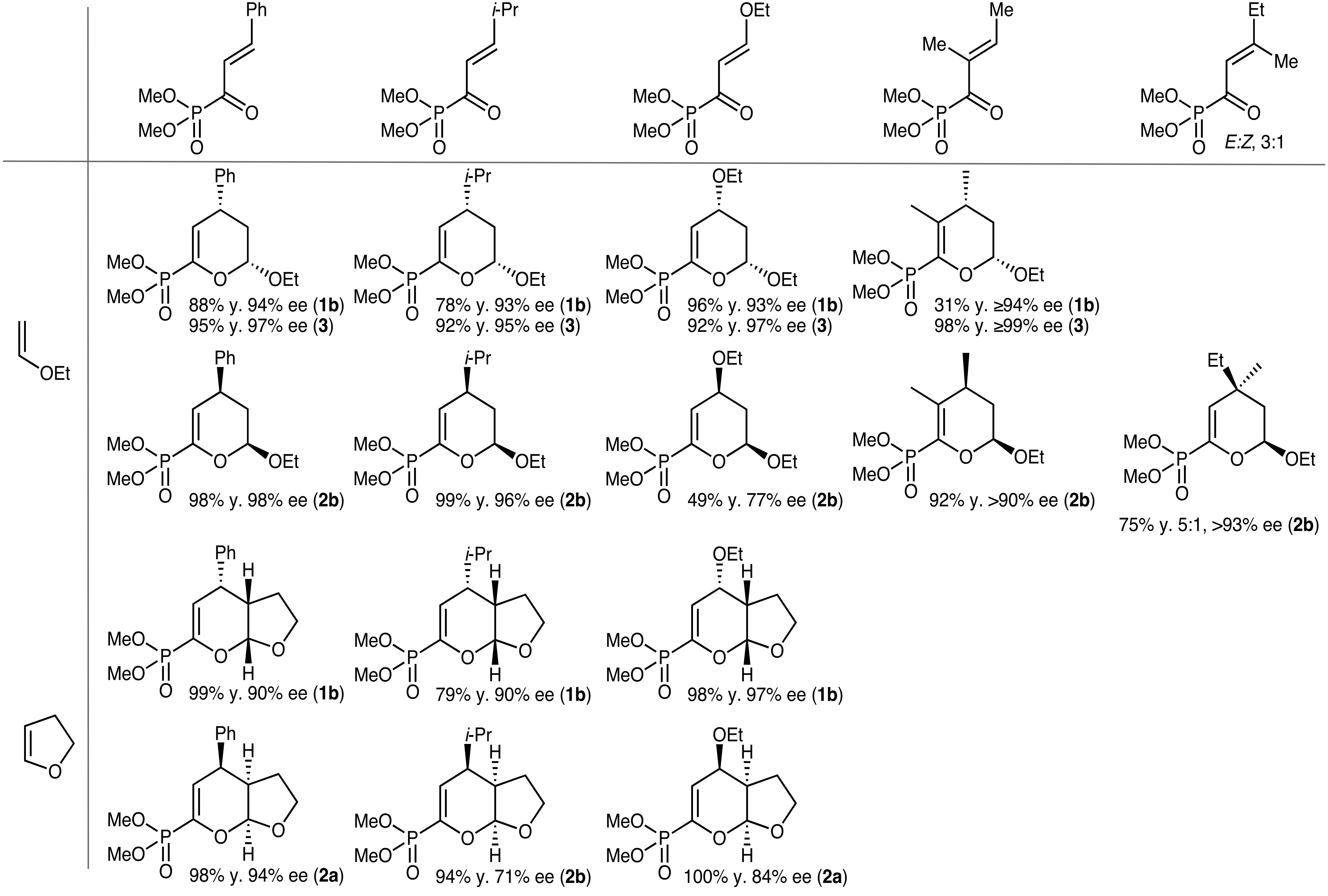
55% y. 92% ee (**1a**)
100% y. 89% ee (**1a**, -40 °C)

95% y. 86% ee (**2b**)

85% y. 93% ee (**2a**)

89% y. 95% ee (**2b**)

Inverse-Electron-Demand Hetero-Diels-Alder Reactions



88% y. 94% ee (**1b**)
95% y. 97% ee (**3**)

78% y. 93% ee (**1b**)
92% y. 95% ee (**3**)

96% y. 93% ee (**1b**)
92% y. 97% ee (**3**)

31% y. ≥94% ee (**1b**)
98% y. ≥99% ee (**3**)

98% y. 98% ee (**2b**)

99% y. 96% ee (**2b**)

49% y. 77% ee (**2b**)

92% y. >90% ee (**2b**)

75% y. 5:1, >93% ee (**2b**)

99% y. 90% ee (**1b**)

79% y. 90% ee (**1b**)

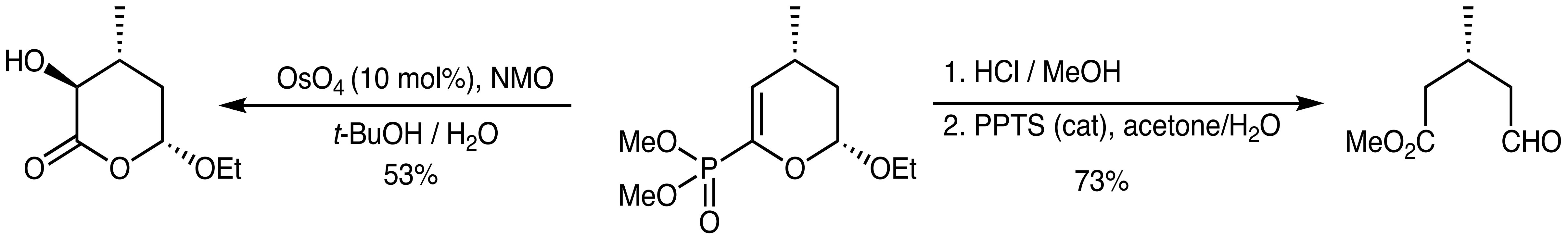
98% y. 97% ee (**1b**)

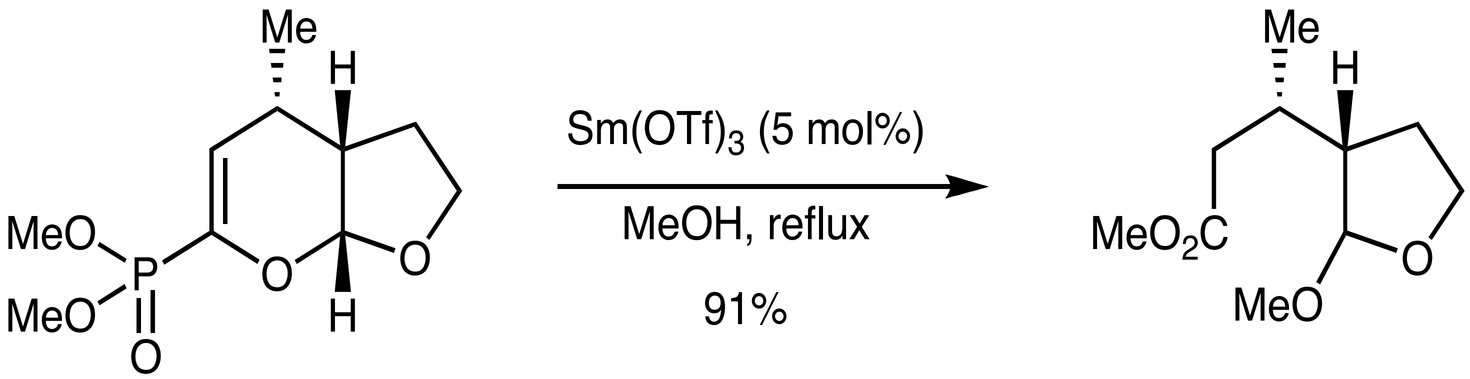
98% y. 94% ee (**2a**)

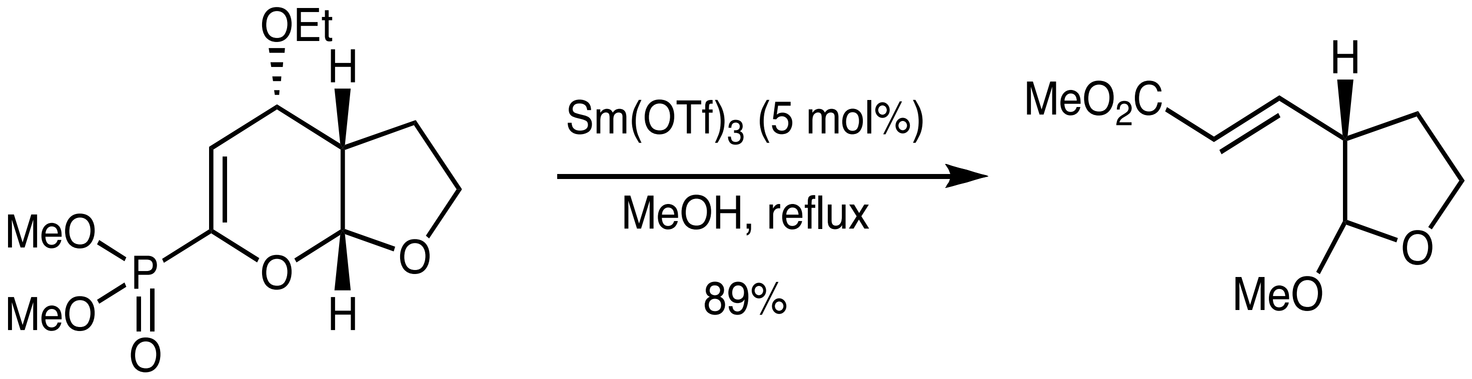
94% y. 71% ee (**2b**)

100% y. 84% ee (**2a**)

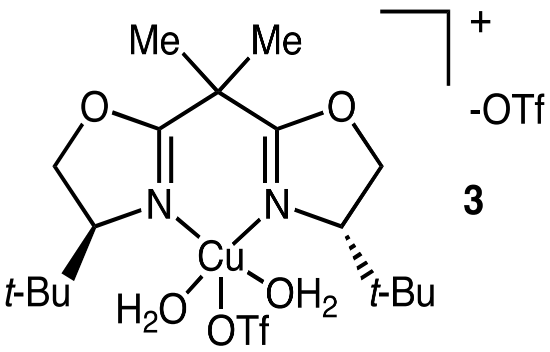
Inverse-Electron-Demand Hetero-Diels-Alder Reactions







Inverse-Electron-Demand Hetero-Diels-Alder Reactions



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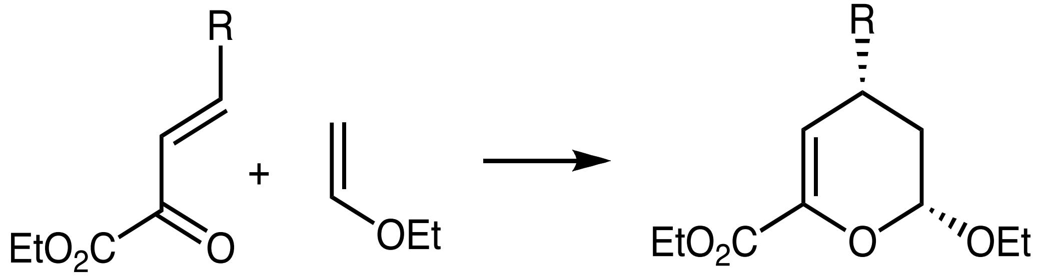
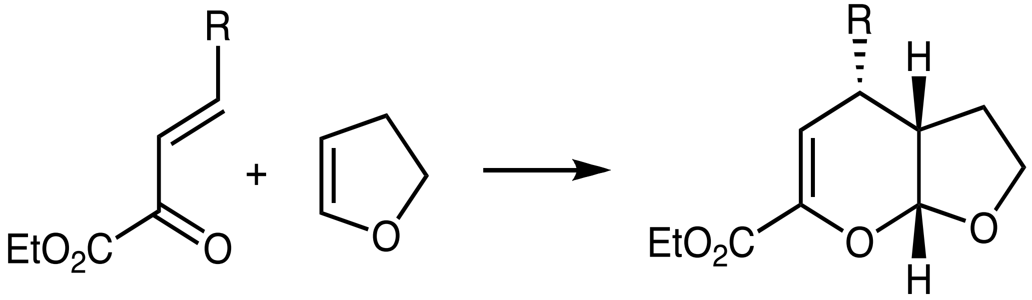
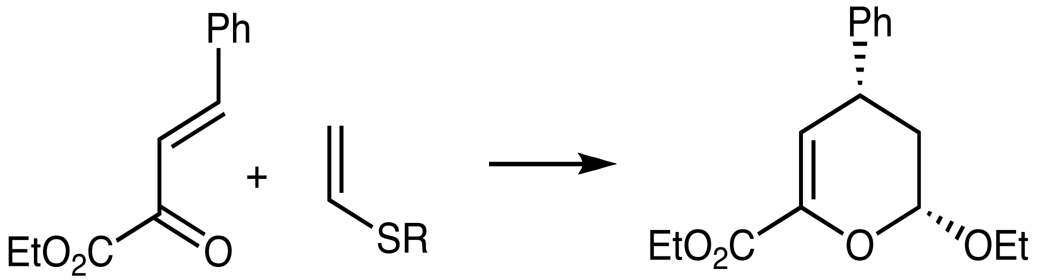


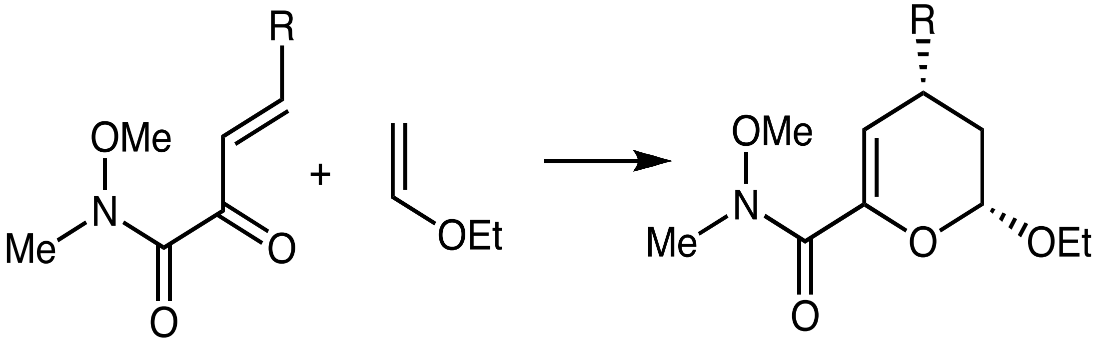
R = Me, 24:1, 87% y. 97% ee
R = Ph, >20:1, 93% y. 97% ee
R = *i*-Pr, 22:1, 95% y. 96% ee
R = OMe, 59:1, 90% y. 98% ee
R = OEt, 55:1, 98% y. 98% ee
R = SBn, >20:1, 97% y. 99% ee



R = Ph, 16:1, 96% y. 97% ee
R = *i*-Pr, 16:1, 94% y. 95% ee



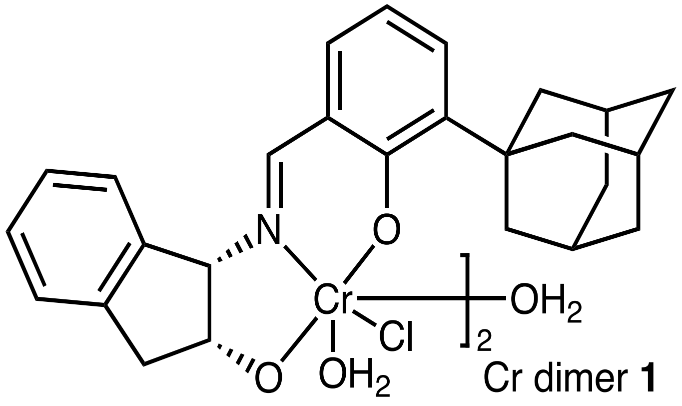
R = Et, >20:1, 94% y. 97% ee
R = Ph, >20:1, 91% y. 99% ee



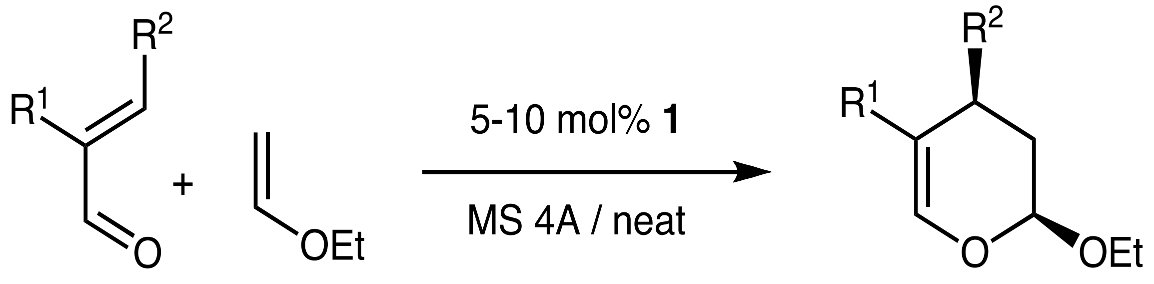
R = Me, 64:1, 99% y. 99% ee
R = OMe, 10:1, 94% y. 98% ee

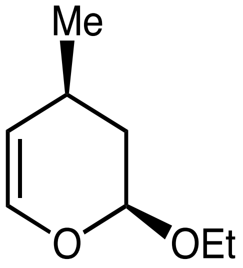
J. Am. Chem. Soc. **1998,** 120, 4895

Inverse-Electron-Demand Hetero-Diels-Alder Reactions

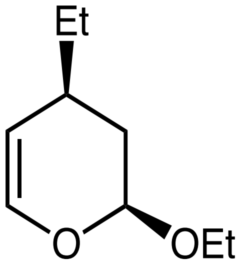


Cr dimer **1**

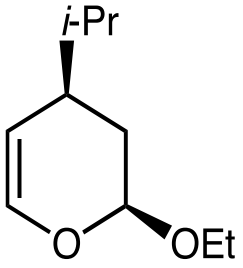




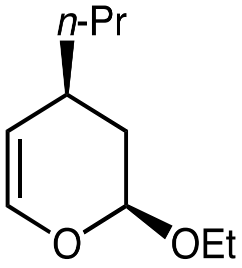
5 mol%, 75% y. 94% ee



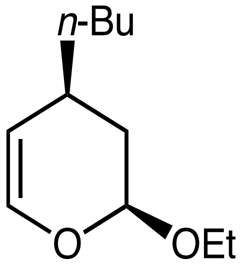
5 mol%, 75% y. 94% ee



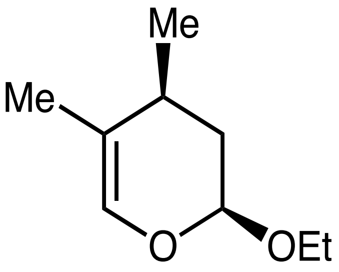
10 mol%, 72% y. 94% ee



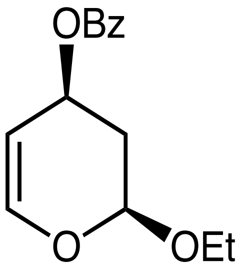
5 mol%, 73% y. 94% ee



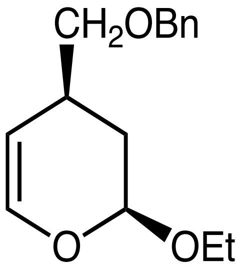
5 mol%, 70% y. 95% ee



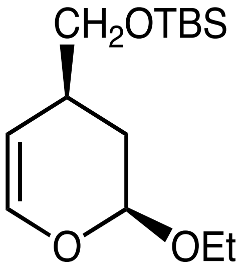
7 mol%, 75% y. 92% ee



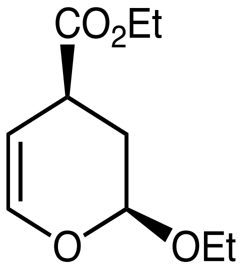
5 mol%, 80% y. 89% ee



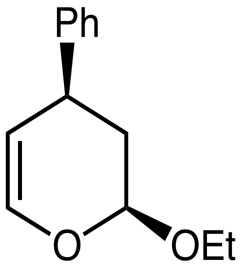
5 mol%, 90% y. 95% ee



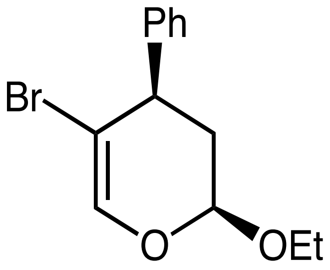
5 mol%, 95% y. 92% ee



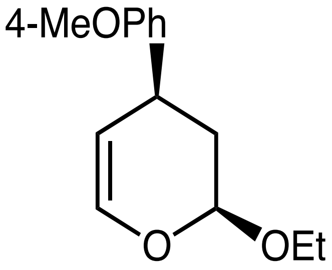
5 mol%, 90% y. 95% ee



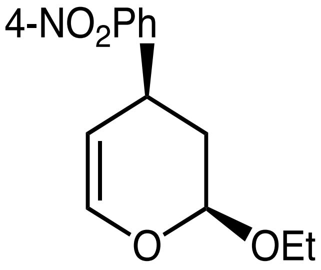
10 mol%, 75% y. 98% ee



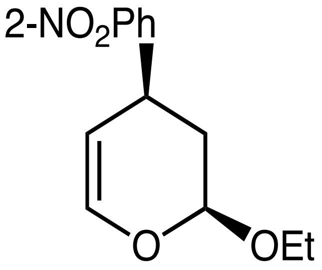
5 mol%, 75% y. 98% ee



10 mol%, 40% y. 98% ee



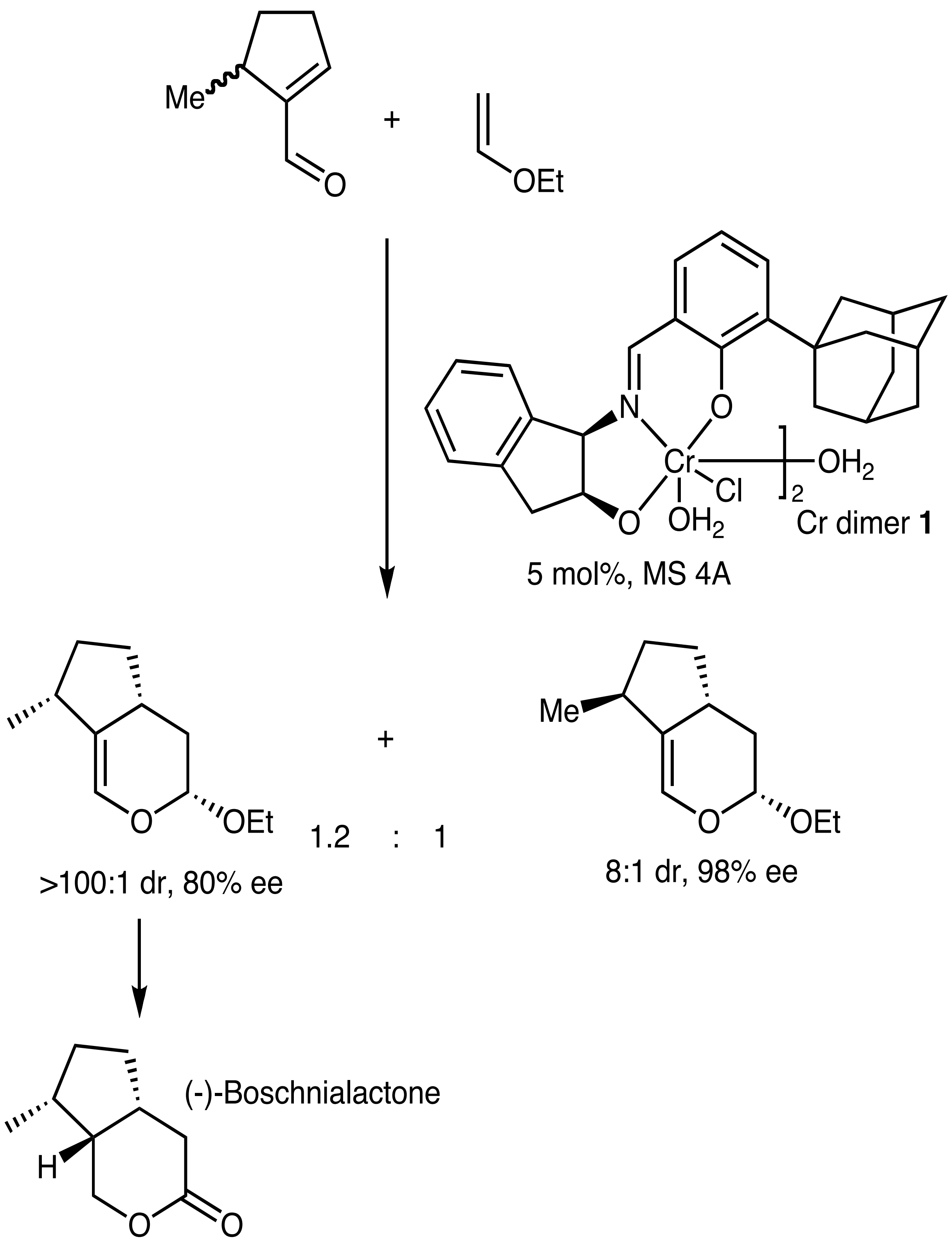
10 mol%, 90% y. 98% ee

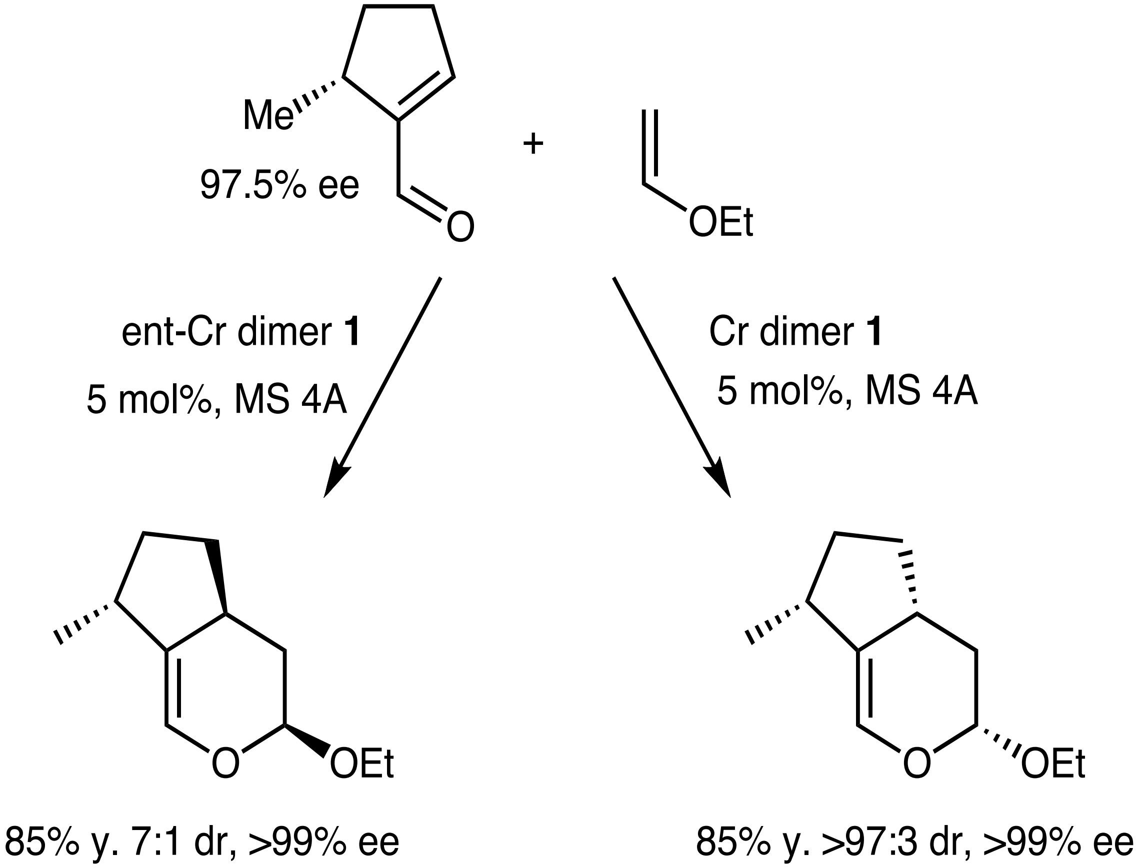


10 mol%, 80% y. 98% ee

Angew. Chem., Int. Edit. **2002,** 41, 3059

Inverse-Electron-Demand Hetero-Diels-Alder Reactions

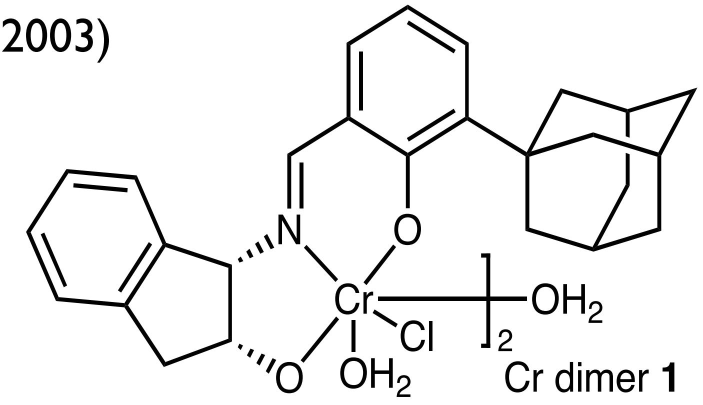




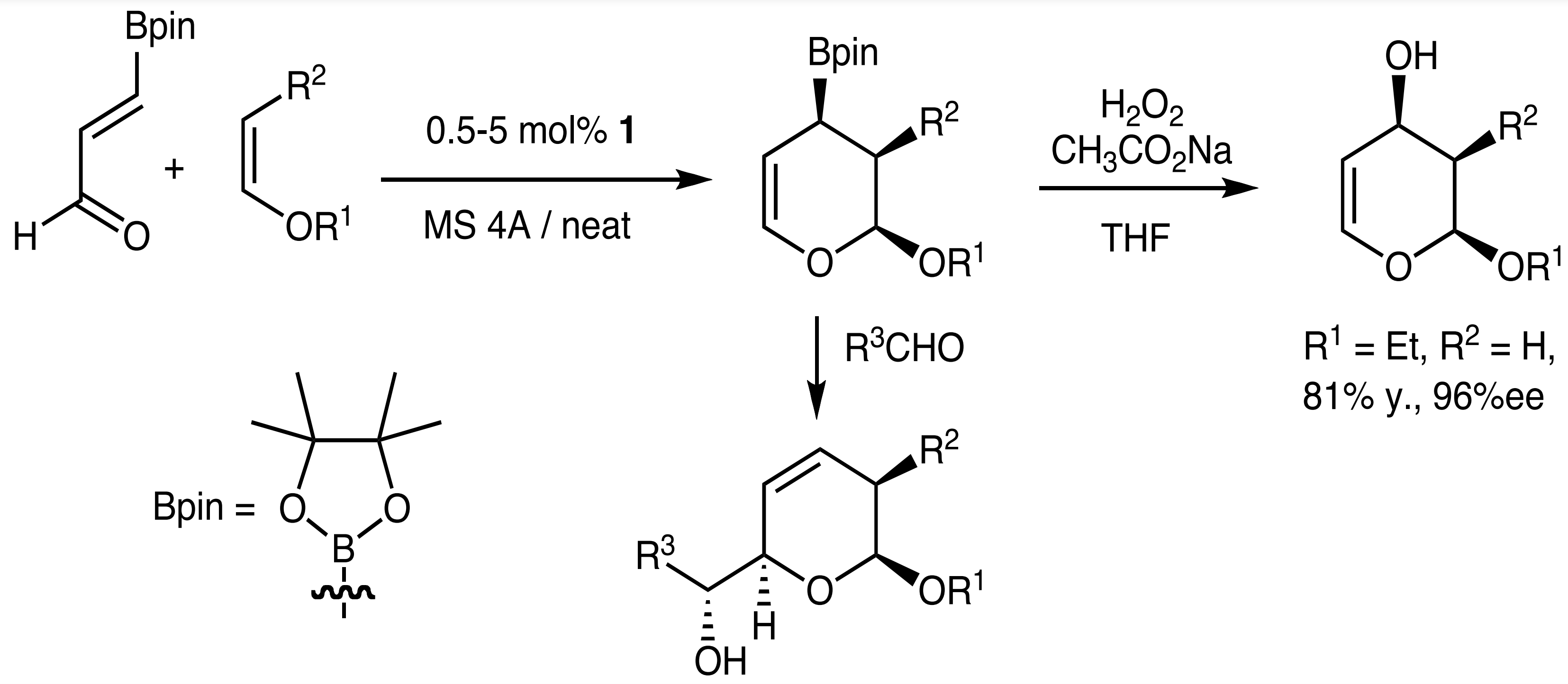
Org. Lett. **2003,** 5, 2563

Inverse-Electron-Demand Hetero-Diels-Alder Reactions

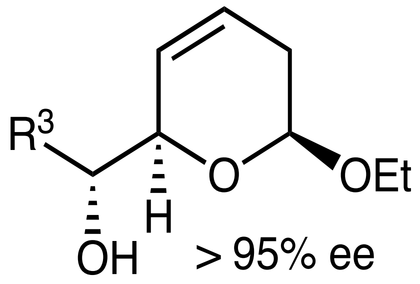
Hall (2003)



Cr dimer **1**

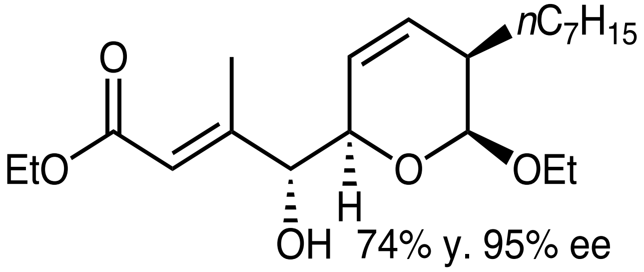


R^1 = Et, R^2 = H,
81% y., 96%ee

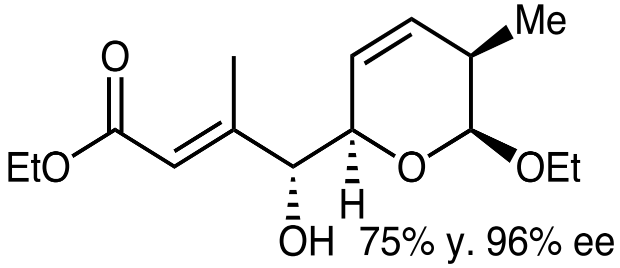


> 95% ee

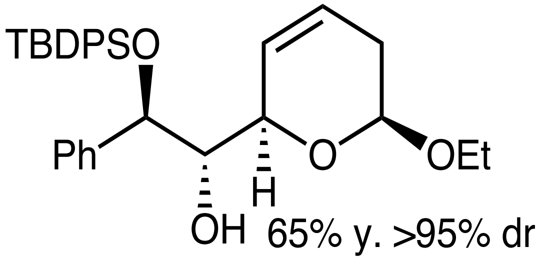
$PhCH_2$	82% y.	CH_2=CH	73% y.	Ph	82% y.
$PhCH_2CH_2$	74% y.	$CH_3(CH_2)_4CC$	86% y.	4-MeOPh	92% y.
i-butyl	81% y.	(*E*)-4-NO_2PhCH=CH	81% y.	4-NO_2Ph	81% y.
$TBSOCH_2$	82% y.	(*E*)-CH_3CH=C(CH_3)	76% y.	4-ClPh	77% y.
$C_{10}H_{21}$	89% y.	(*E*)-EtO_2CCH=CH(CH_3)	88% y.	4-FPh	75% y.
i-pr	78% y.				



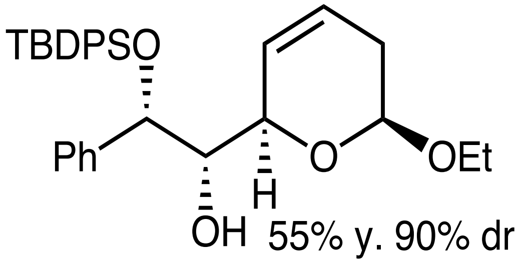
74% y. 95% ee



75% y. 96% ee



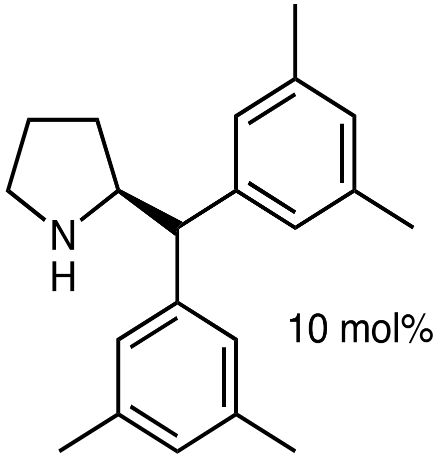
65% y. >95% dr

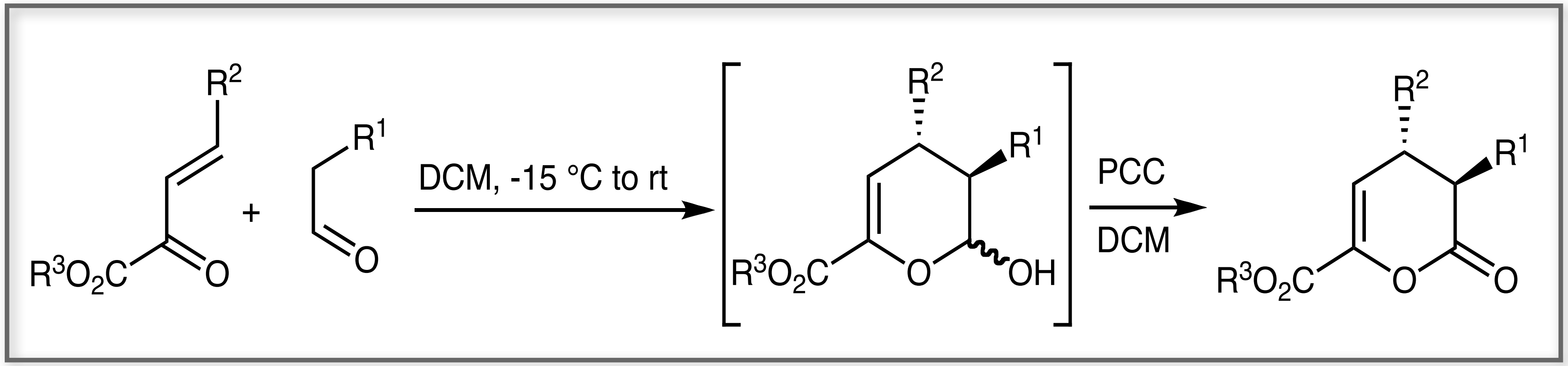


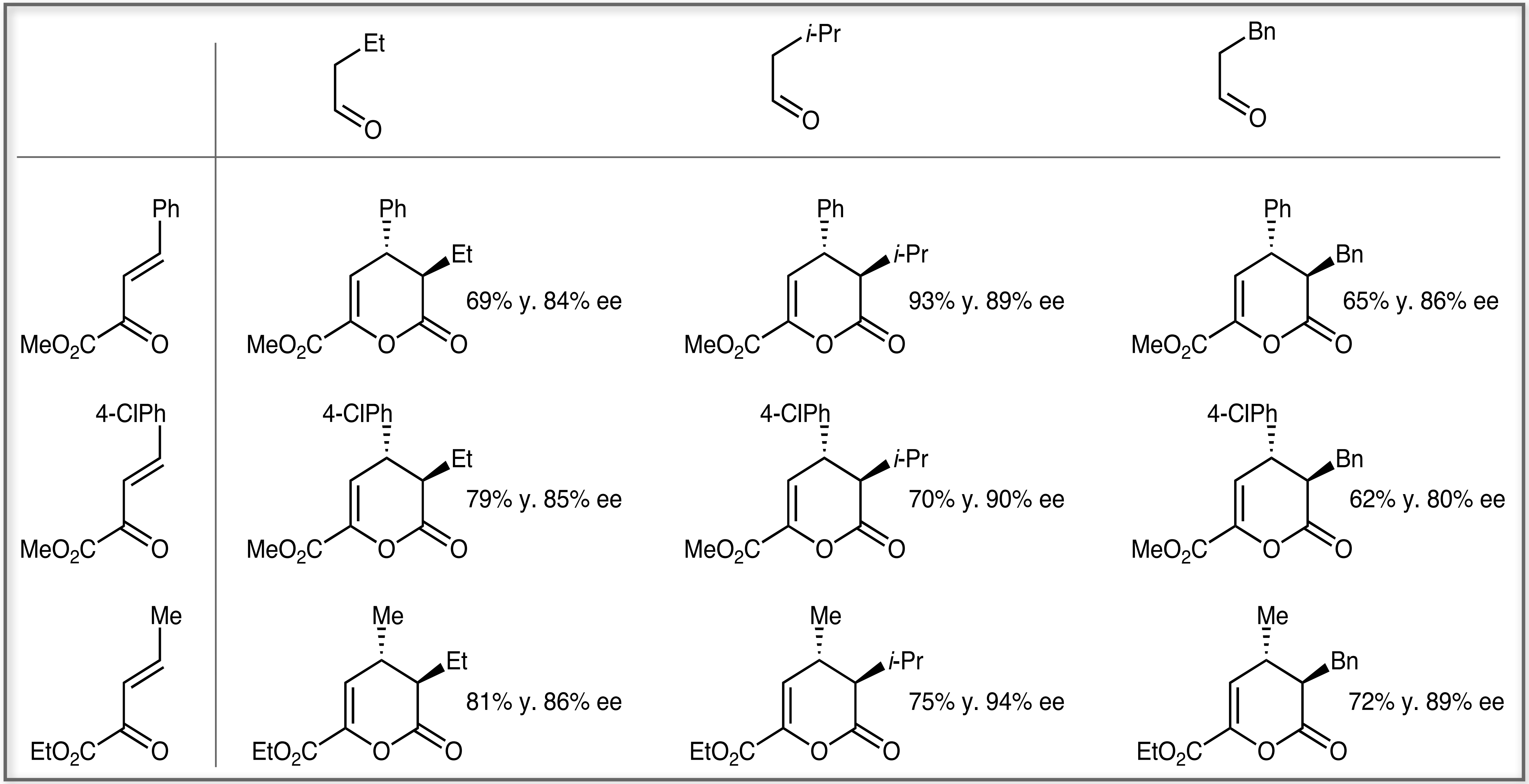
55% y. 90% dr

J. Am. Chem. Soc. **2003**, 125, 9308

Inverse-Electron-Demand Hetero-Diels-Alder



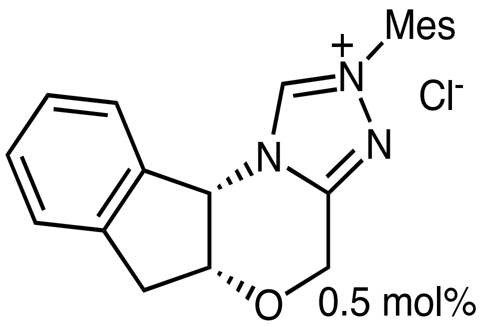


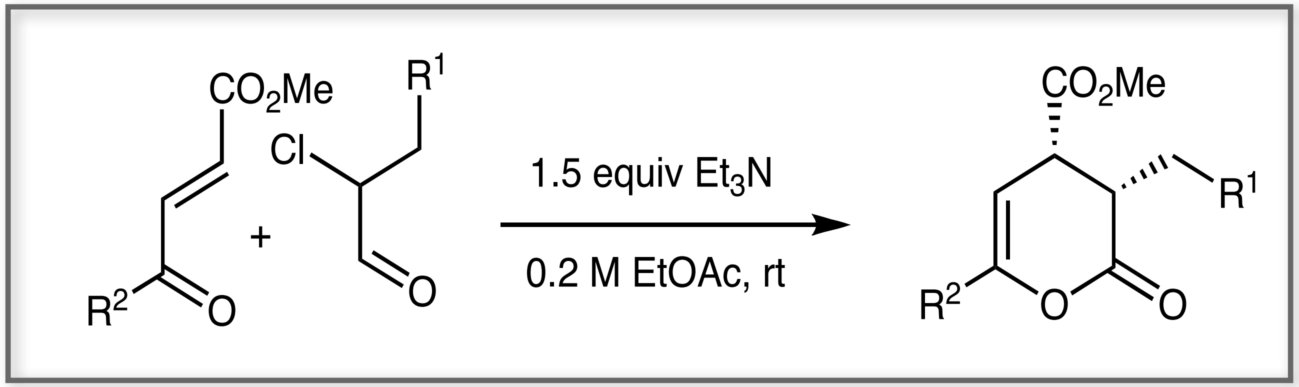


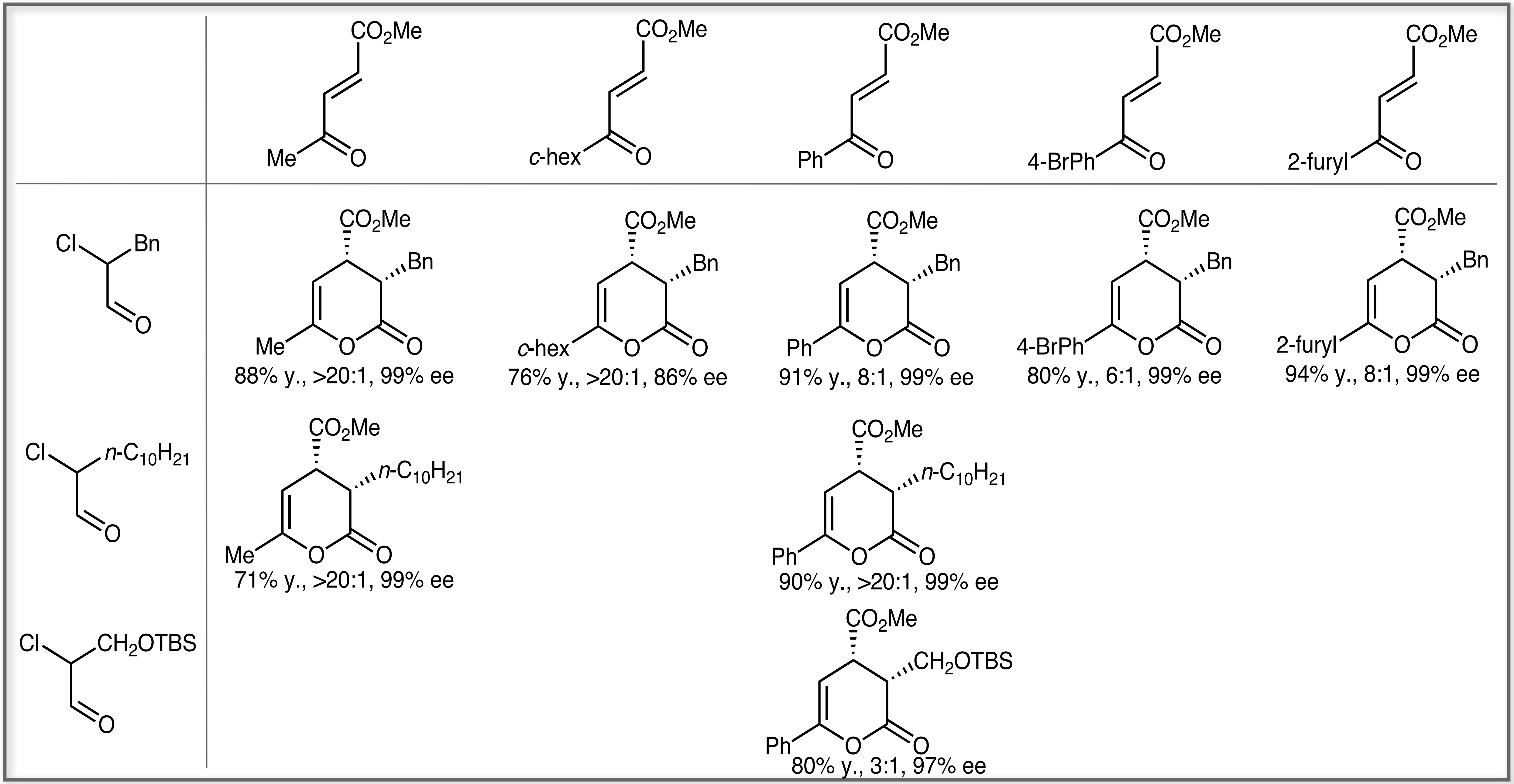
Angew. Chem., Int. Edit. **2003**, 42, 1498

Inverse-Electron-Demand Hetero-Diels-Alder

Bode (2006)



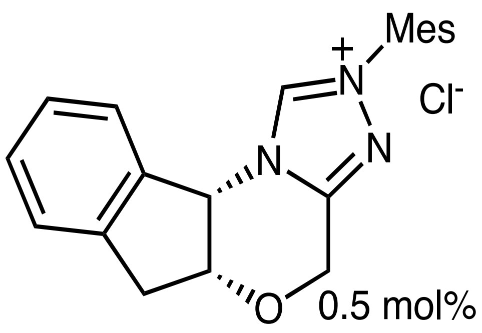




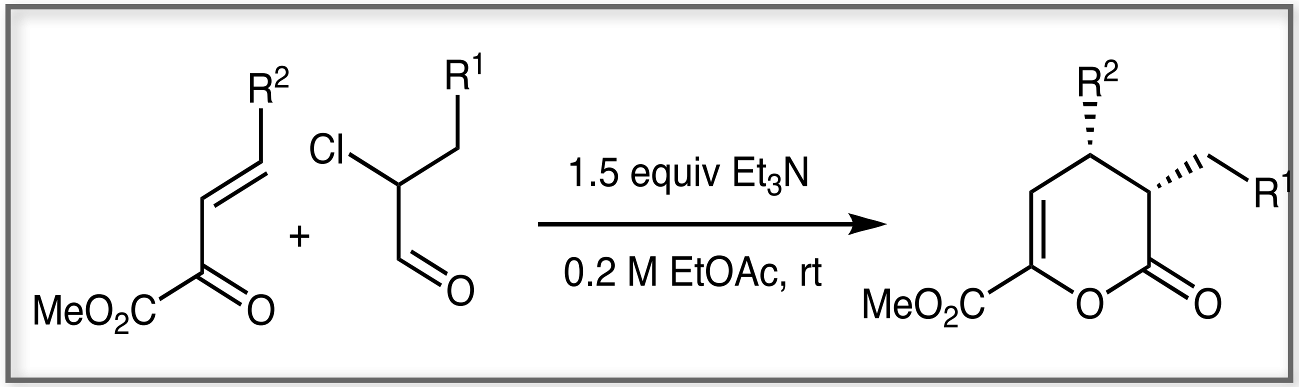
	Me	c-hex	Ph	4-BrPh	2-furyl
Bn	88% y., >20:1, 99% ee	76% y., >20:1, 86% ee	91% y., 8:1, 99% ee	80% y., 6:1, 99% ee	94% y., 8:1, 99% ee
n-$C_{10}H_{21}$	71% y., >20:1, 99% ee		90% y., >20:1, 99% ee		
CH_2OTBS			80% y., 3:1, 97% ee		

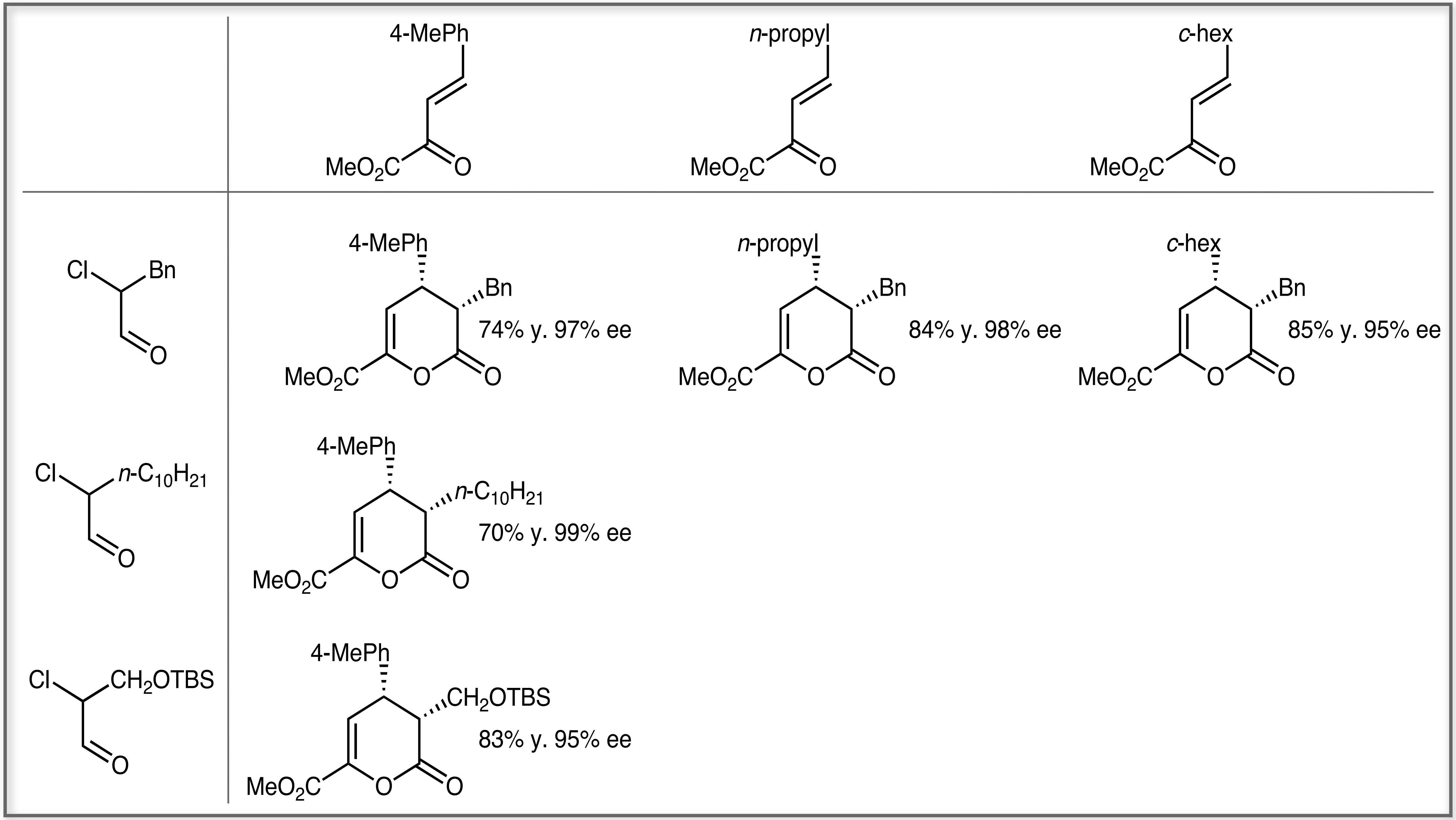
J. Am. Chem. Soc. **2006**, 128, 15088

Inverse-Electron-Demand Hetero-Diels-Alder



0.5 mol%





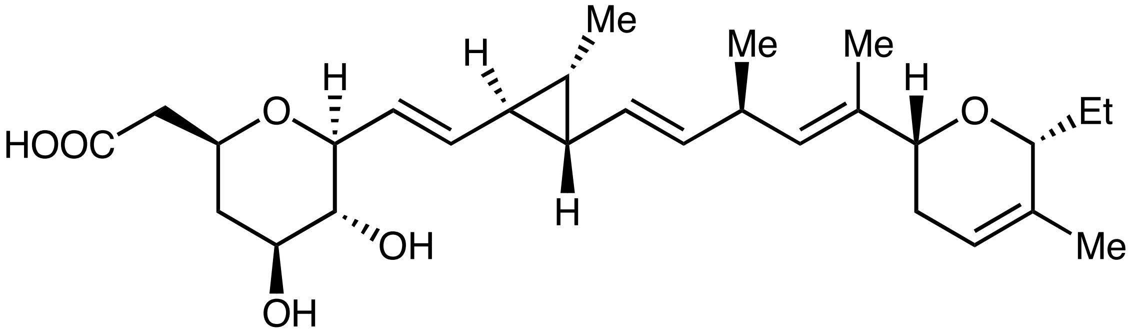
J. Am. Chem. Soc. **2006,** 128, 15088

Total Synthesis of Ambruticin S

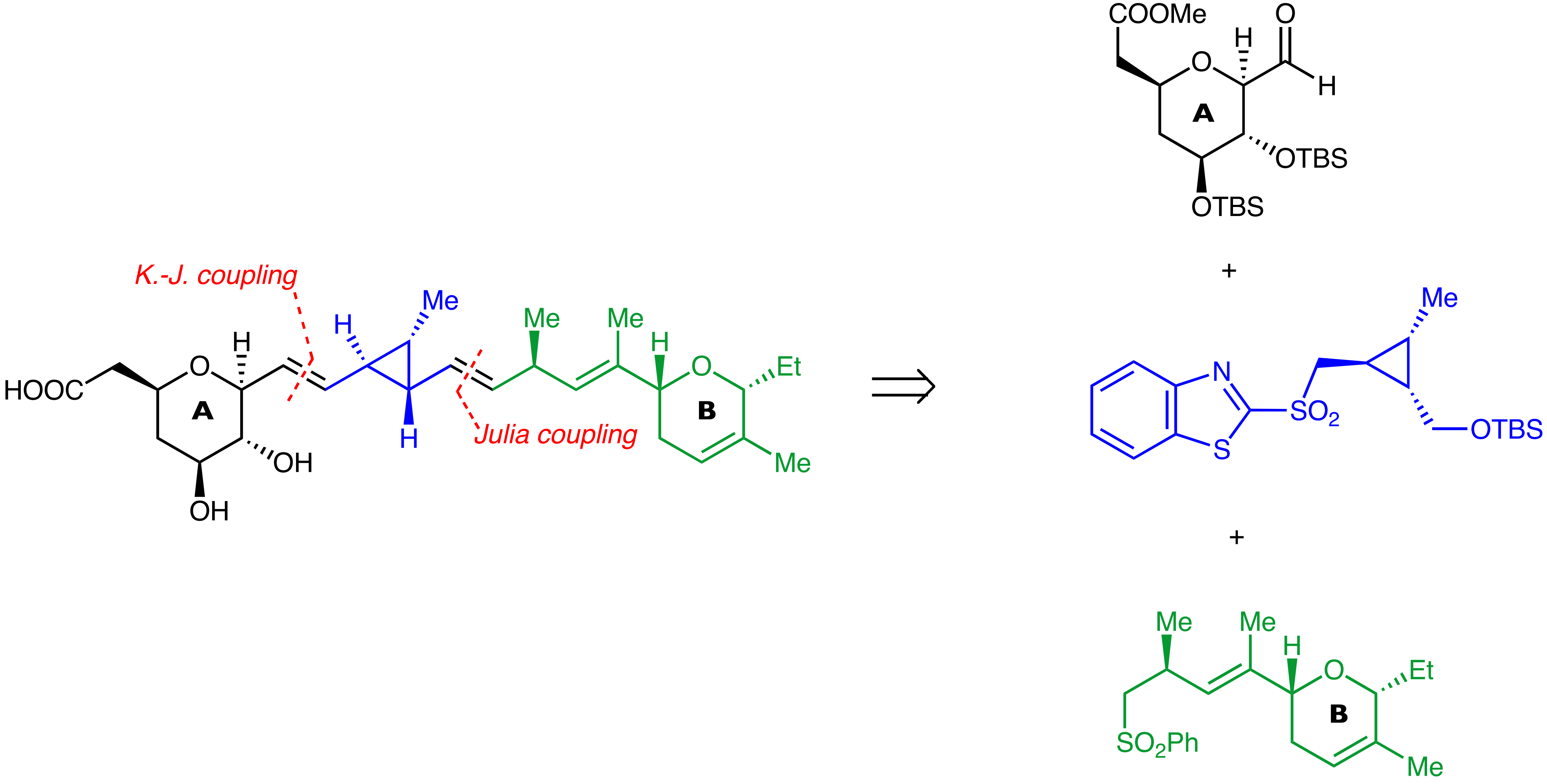
Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin Jr., D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432-12433.

Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772-10773.

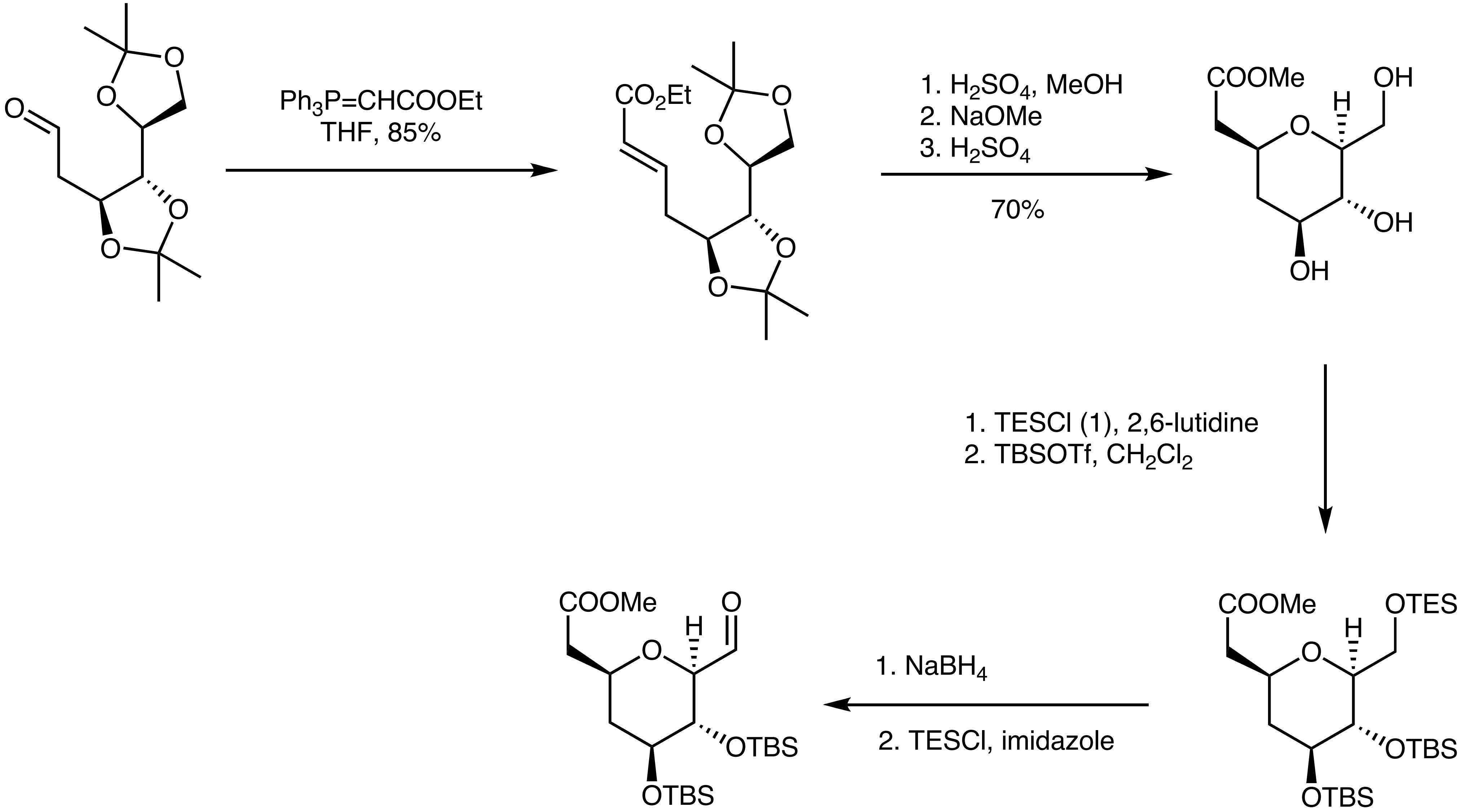
(antifungal agent)



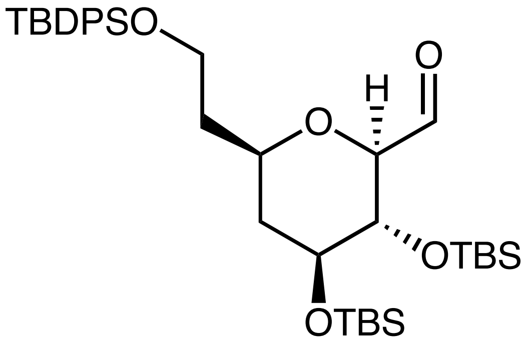
Retrosynthetic Analysis of Ambruticin

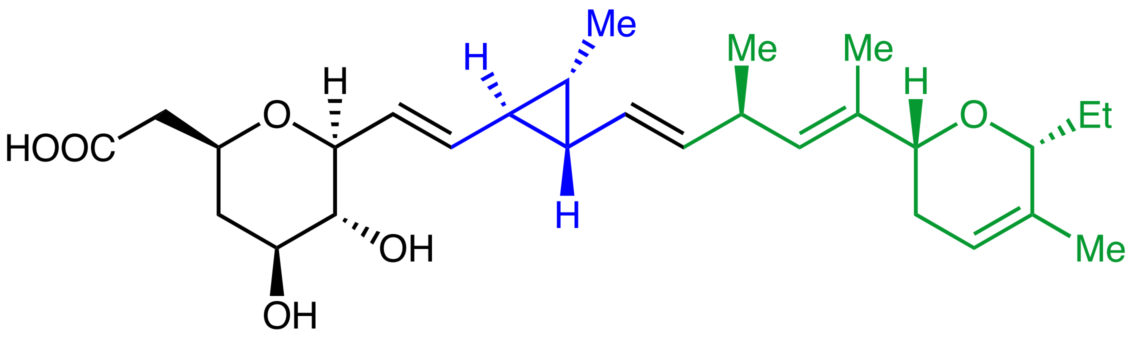


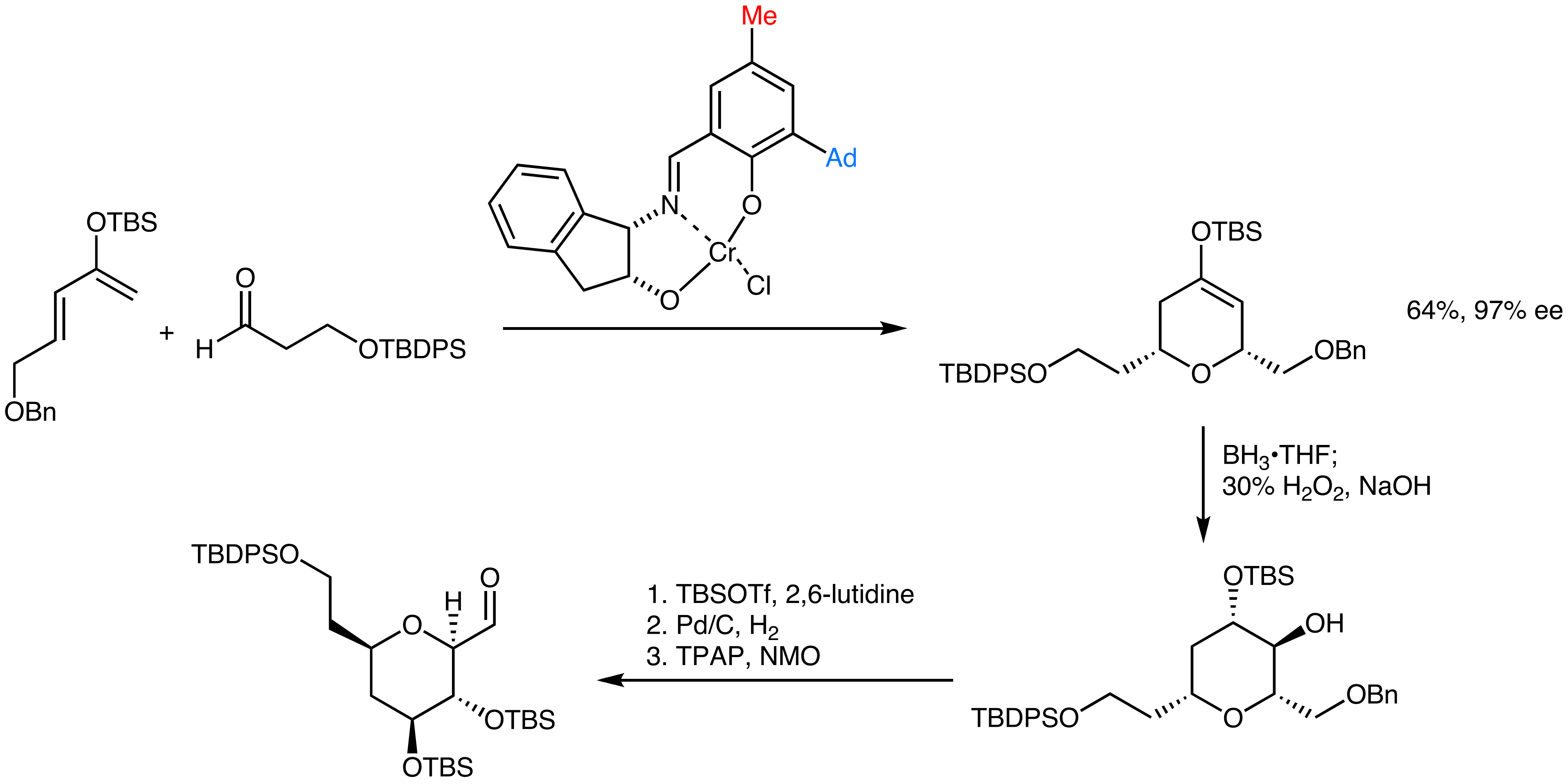
Martin Synthesis of the A Ring



Jacobsen's Synthesis of the A Ring





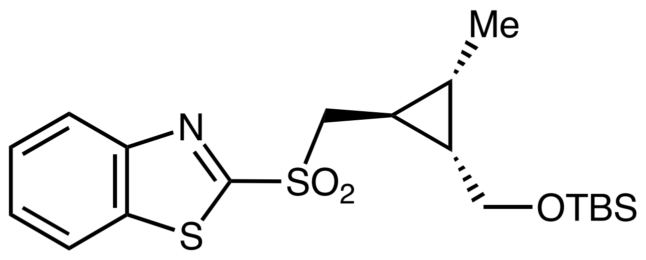


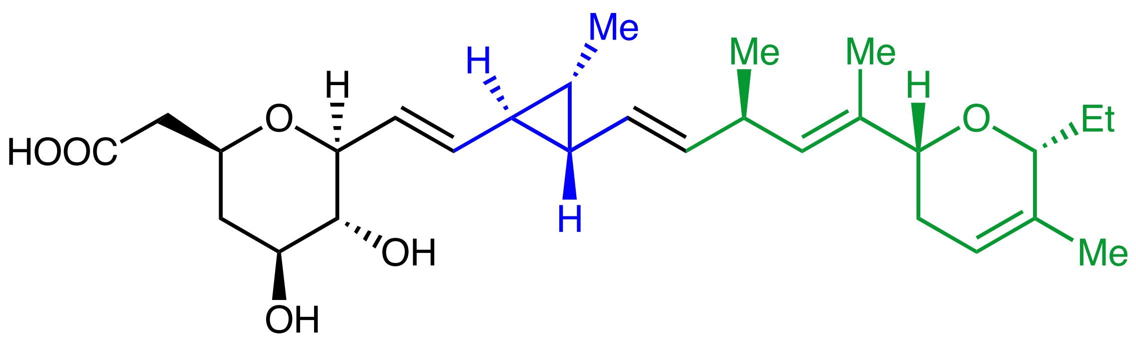
64%, 97% ee

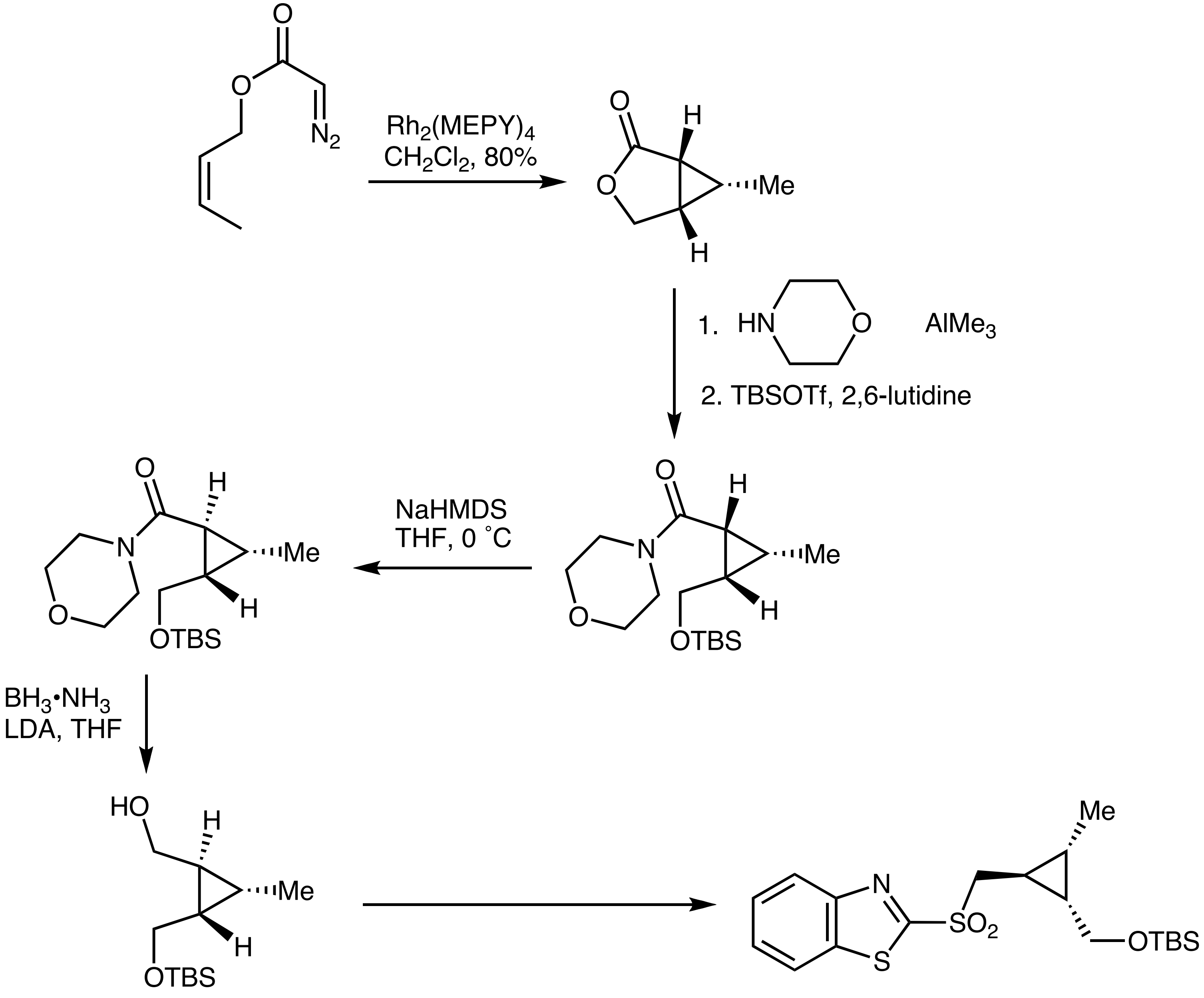
BH_3•THF;
30% H_2O_2, NaOH

1. TBSOTf, 2,6-lutidine
2. Pd/C, H_2
3. TPAP, NMO

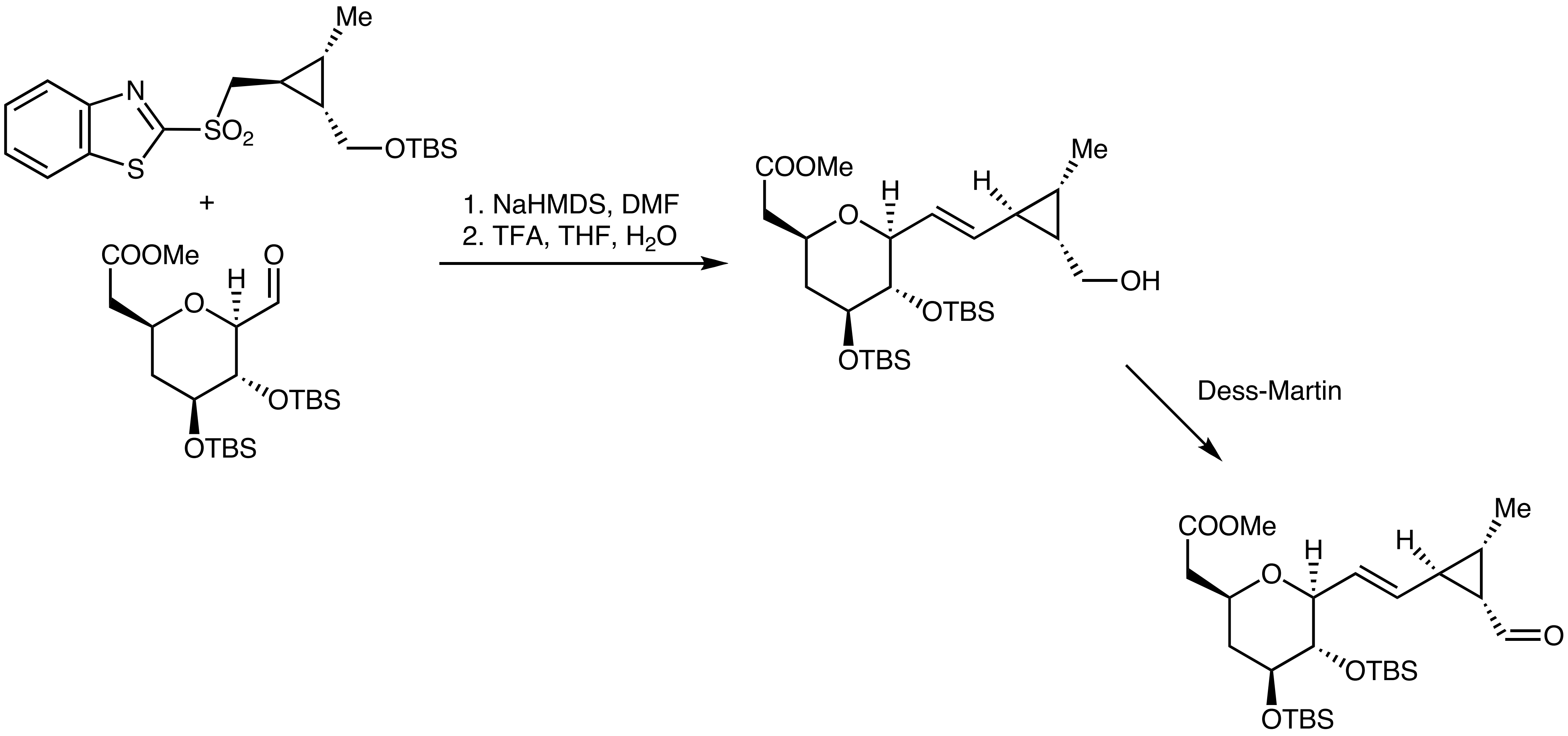
Martin's Synthesis of the Cyclopropane Unit

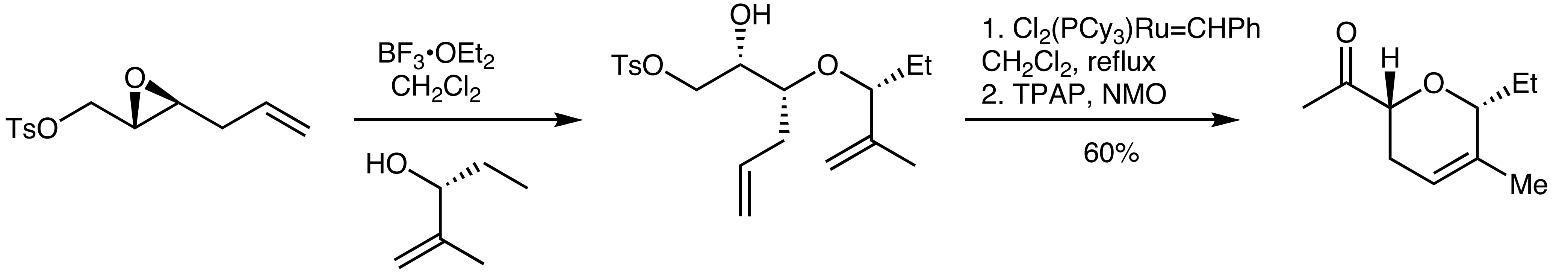




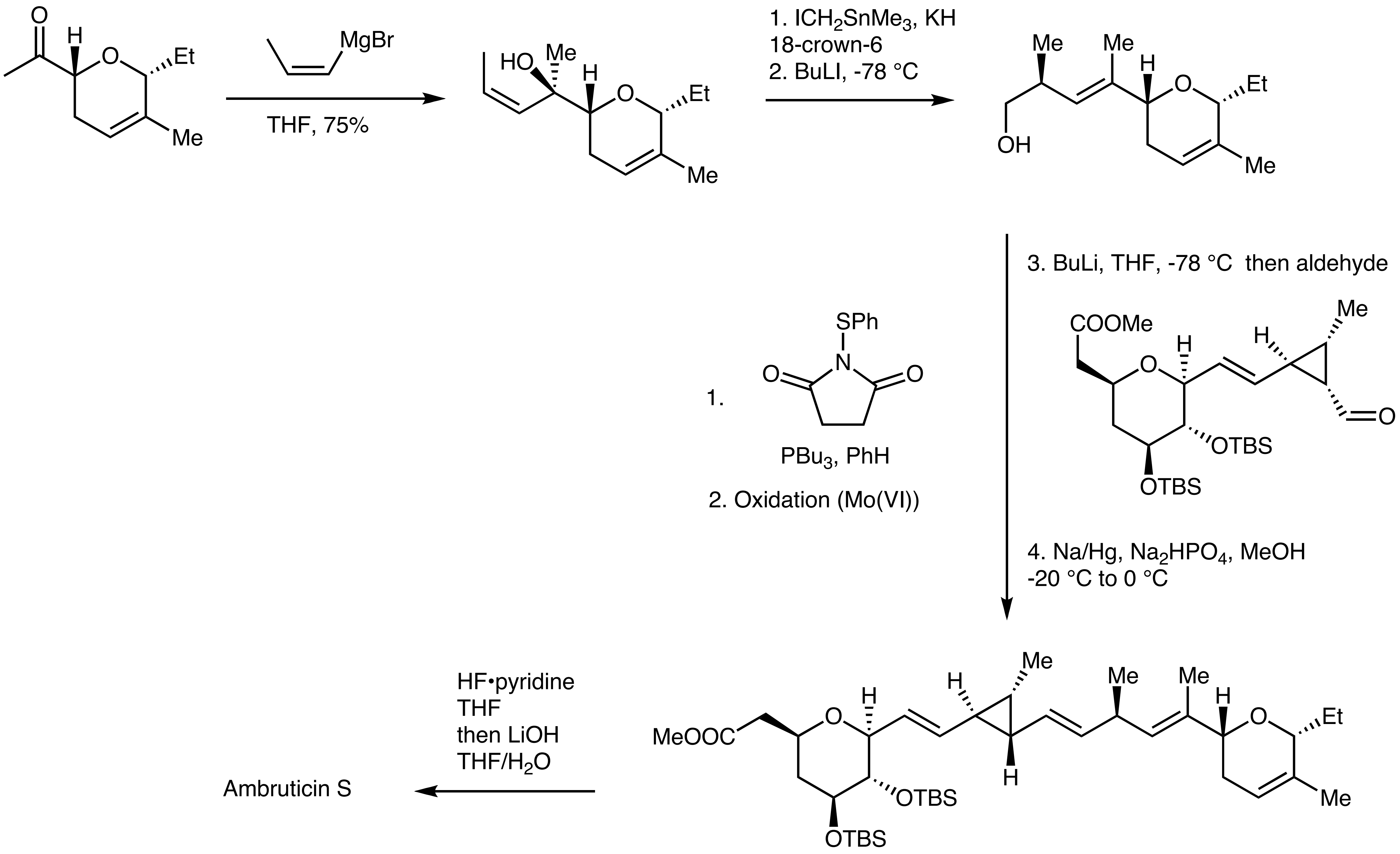


Martin’s Final Assembly of Ambruticin S





Martin's Final Assembly of Ambruticin S



THF, 75%

1. ICH_2SnMe_3, KH
18-crown-6
2. BuLI, -78 °C

3. BuLi, THF, -78 °C then aldehyde

1. PBu$_3$, PhH

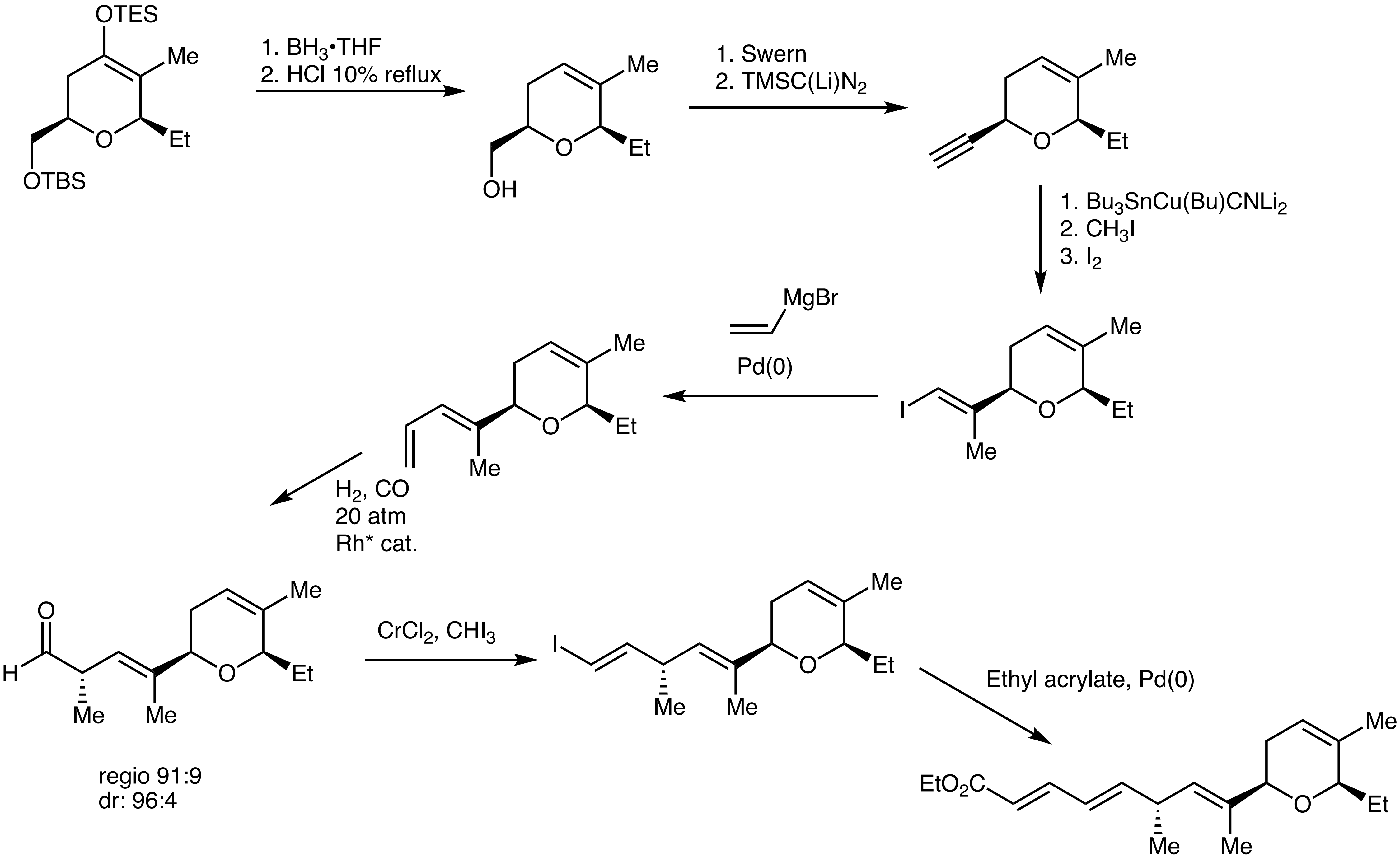
2. Oxidation (Mo(VI))

4. Na/Hg, Na_2HPO_4, MeOH
-20 °C to 0 °C

HF•pyridine
THF
then LiOH
THF/H_2O

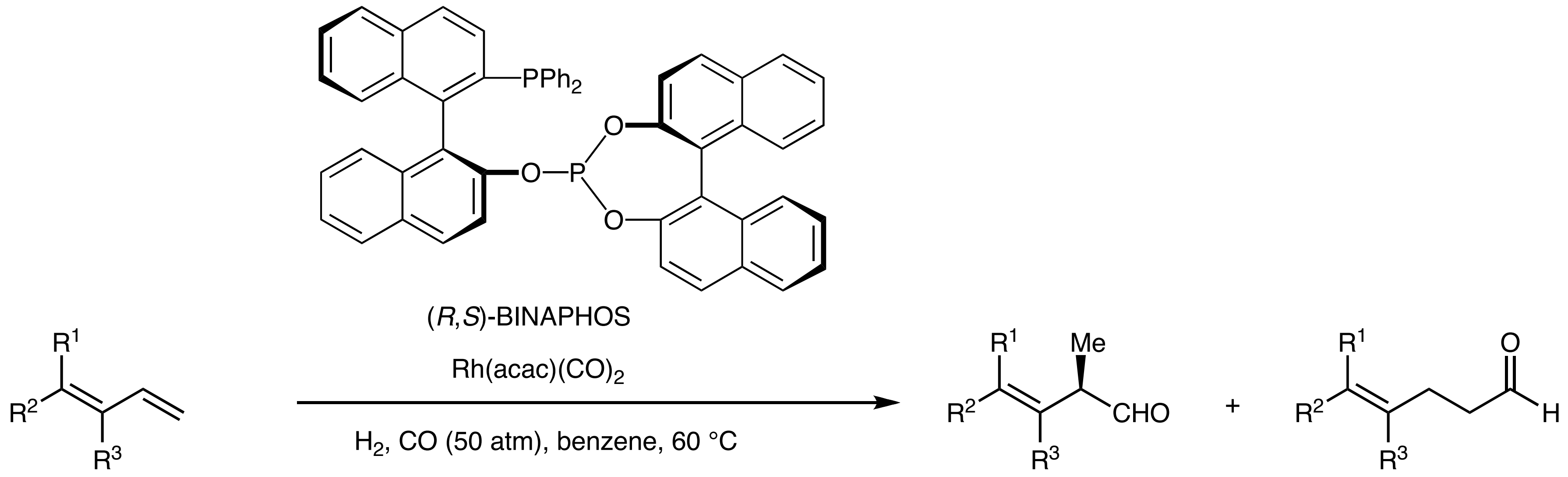
Ambruticin S

Jacobsen's Synthesis of Ambruticin S

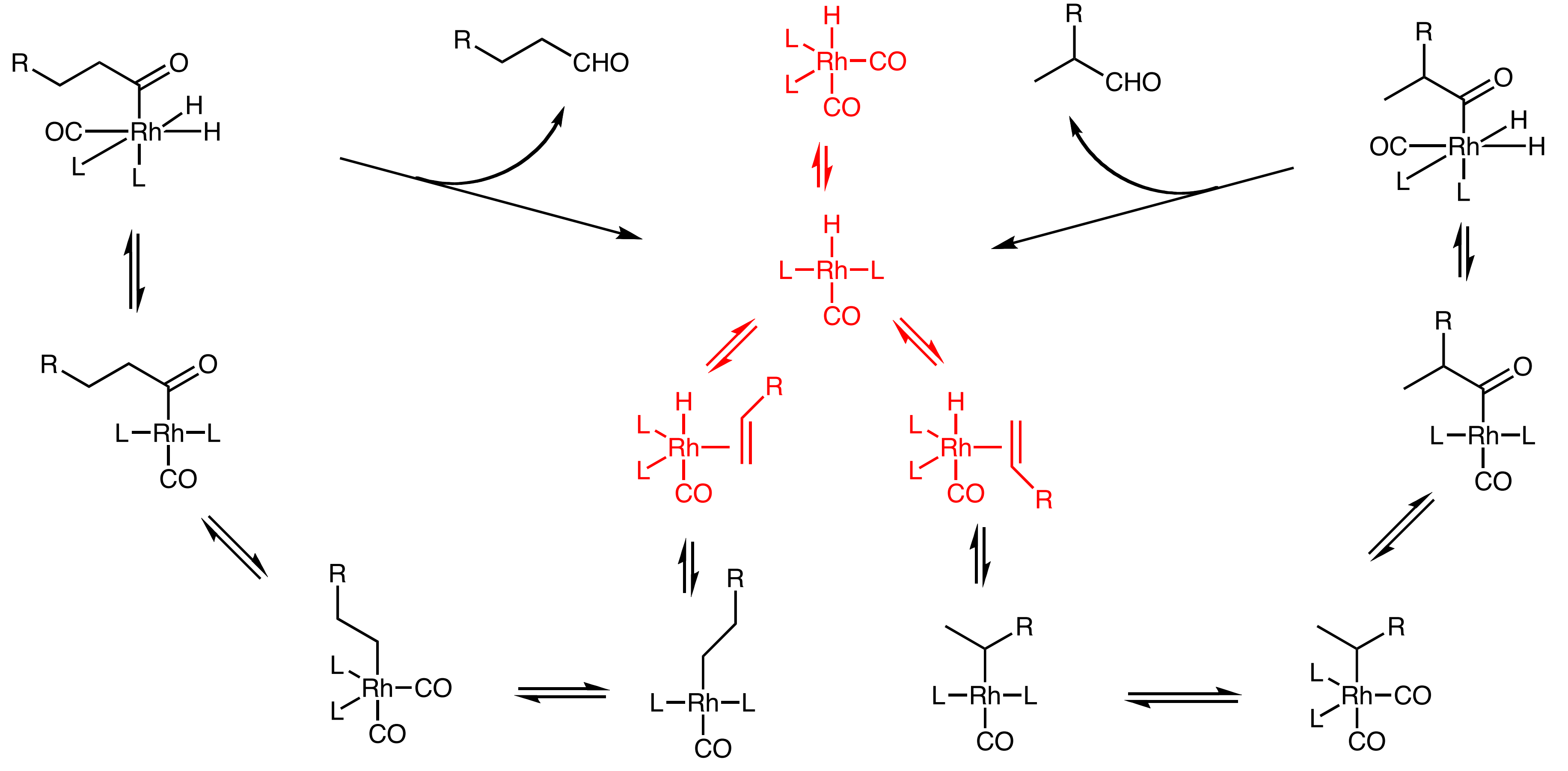


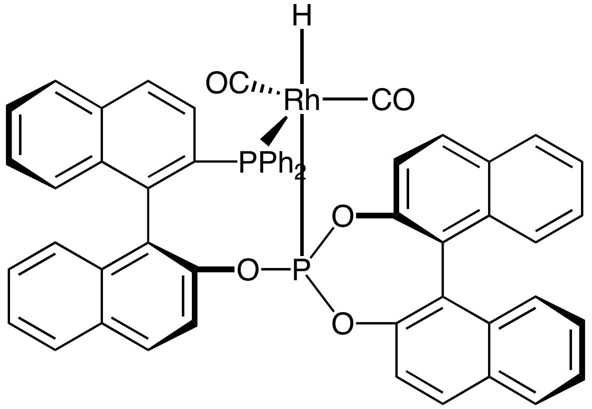
regio 91:9
dr: 96:4

Asymmetric Hydroformylation



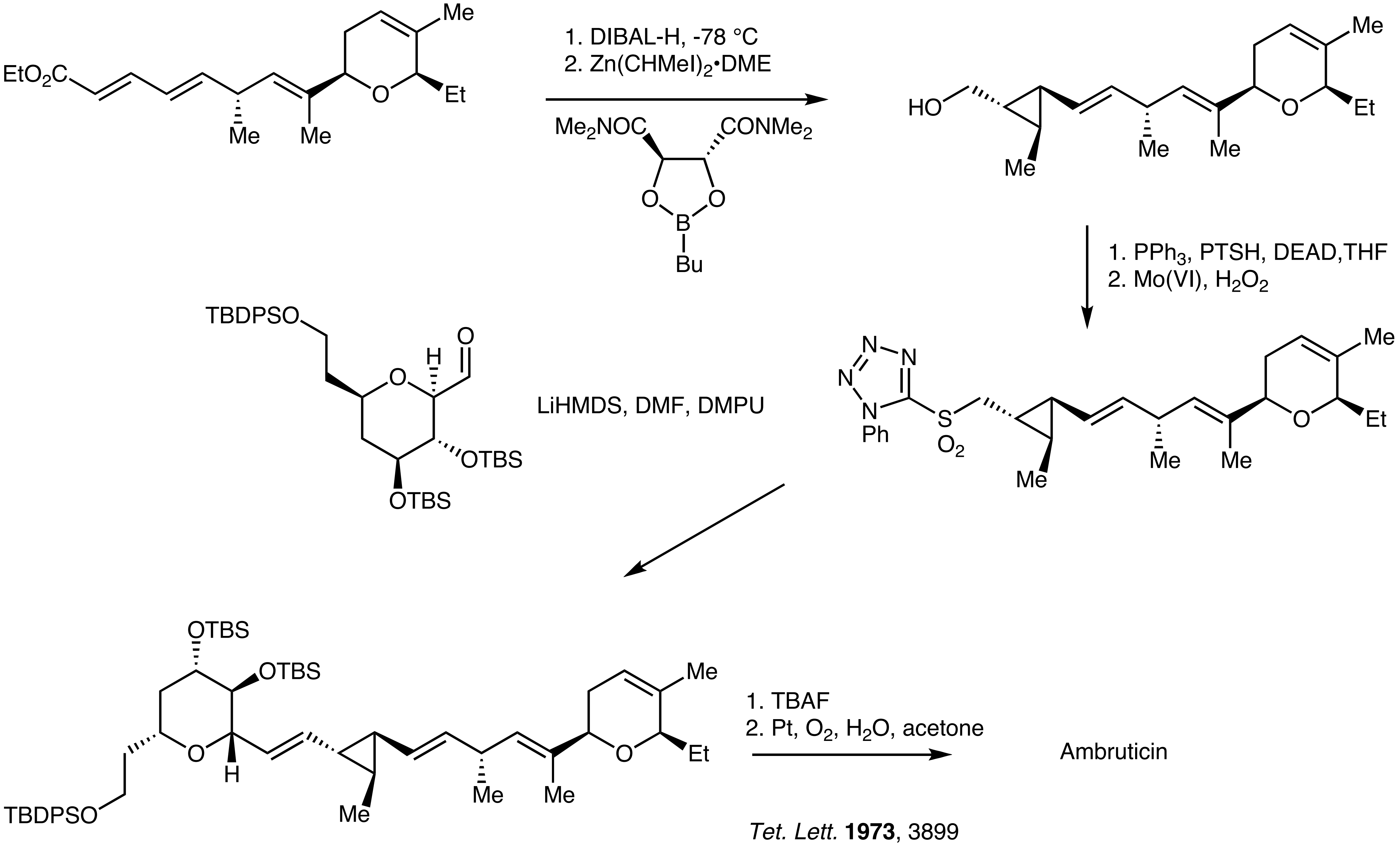
$R^1 = H, R^2,R^3 = \text{-}(CH_2)_4\text{-}$	96% ee	87 : 13
$R^1 = Me, R^2 = Me, R^3 = H$	72% ee	78 : 22
$R^1 = H, R^2 = Ph, R^3 = H$	81% ee	95 : 5





Horiuchi Chem. Comm. 1996, 155
Nozaki Tetrahedron 1997, 7795

Jacobsen's Completion of the Synthesis



1. DIBAL-H, -78 °C
2. $Zn(CHMeI)_2$•DME

Me_2NOC / $CONMe_2$ dioxaborolane, B–Bu

1. PPh_3, PTSH, DEAD,THF
2. Mo(VI), H_2O_2

LiHMDS, DMF, DMPU

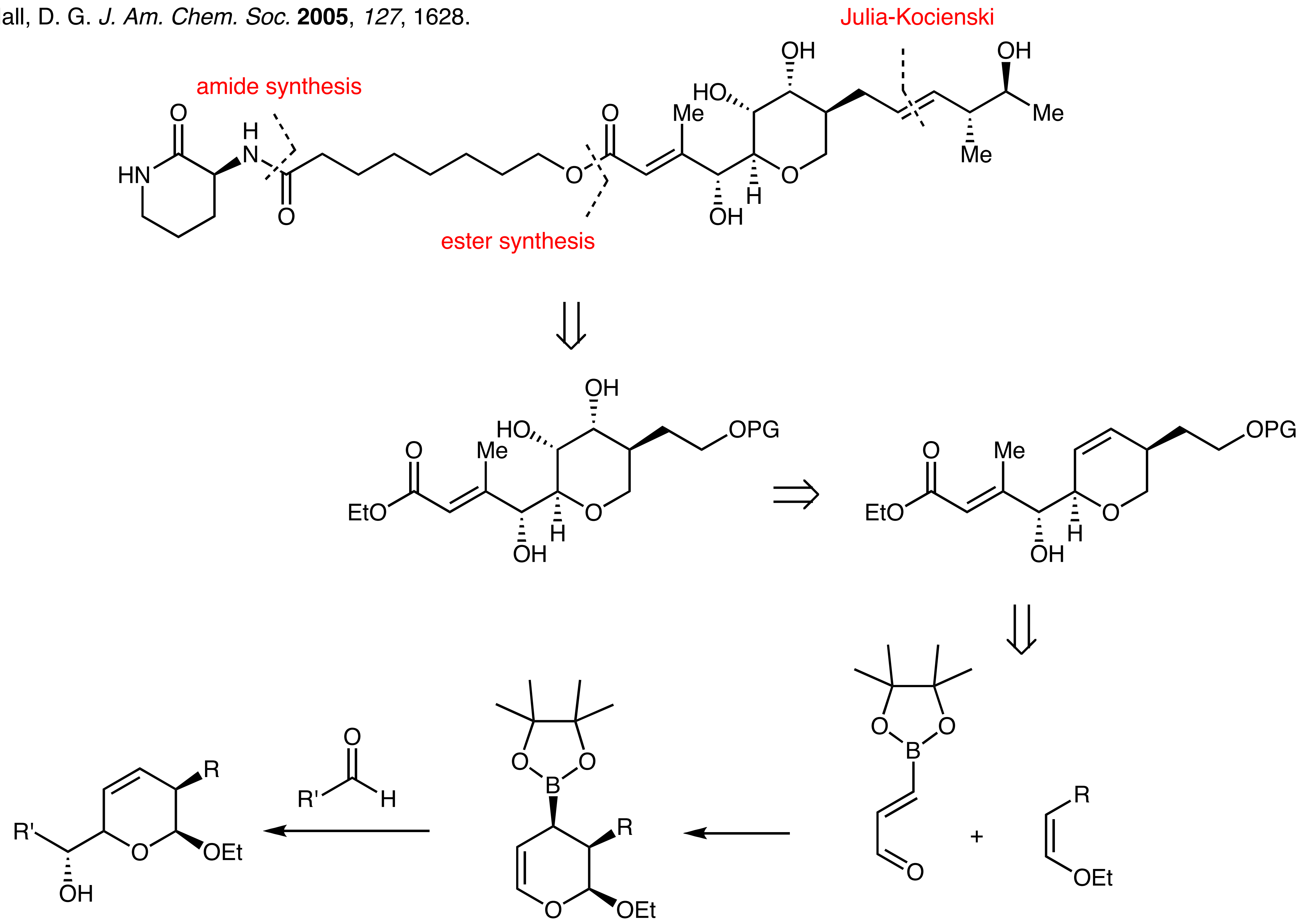
1. TBAF
2. Pt, O_2, H_2O, acetone

Ambruticin

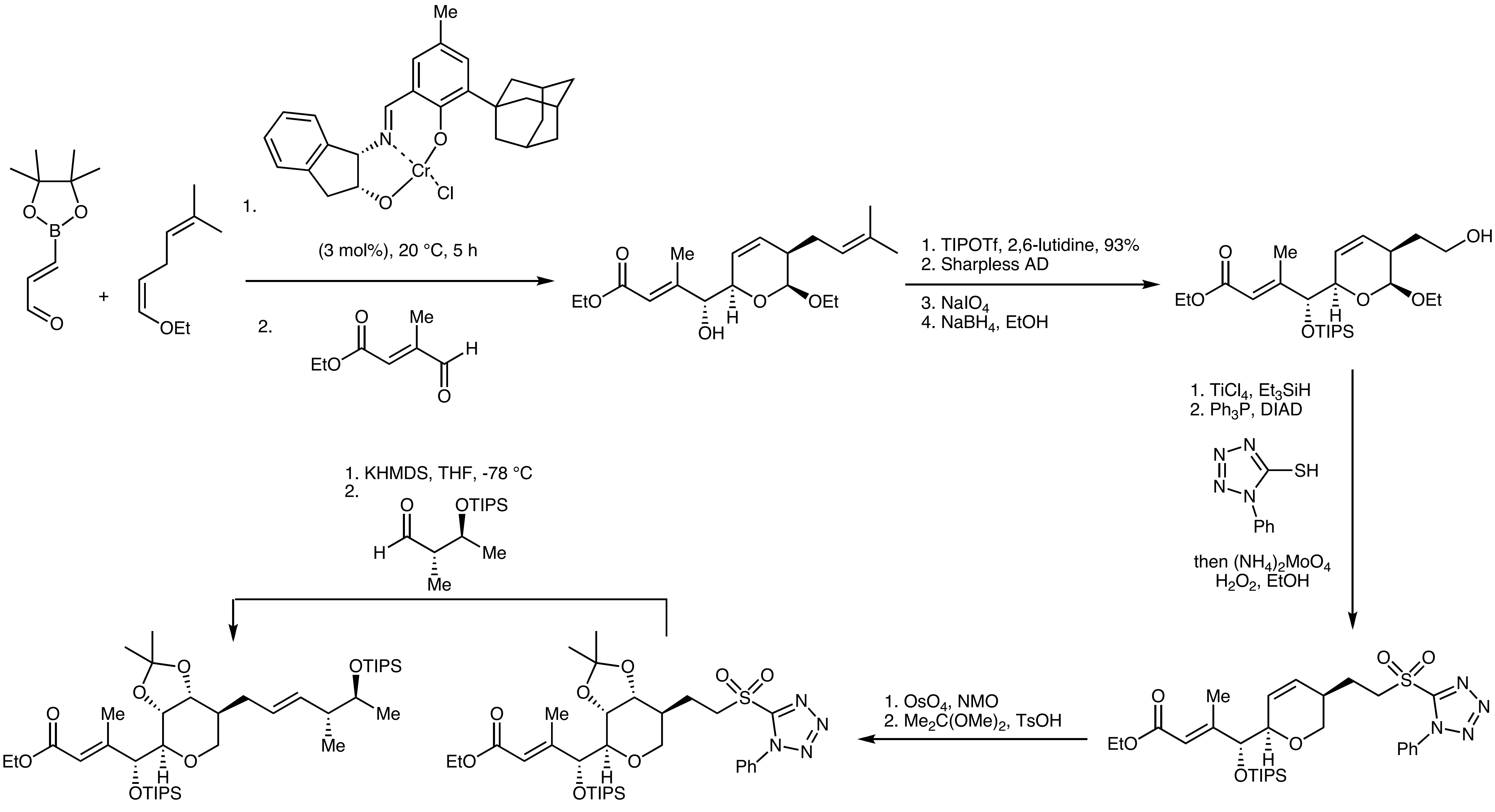
Tet. Lett. **1973**, 3899

Synthesis of Pseudomonic Acid A

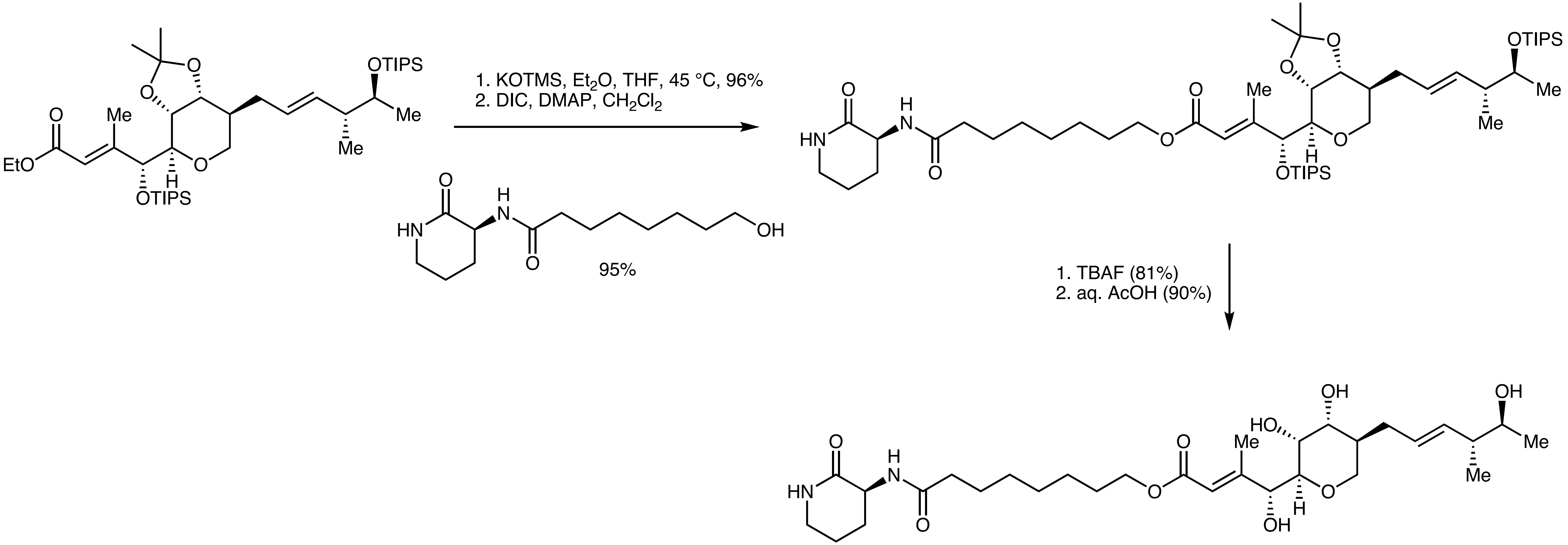
Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628.



Synthesis of Pseudomonic Acid A



Synthesis of Pseudomonic Acid A

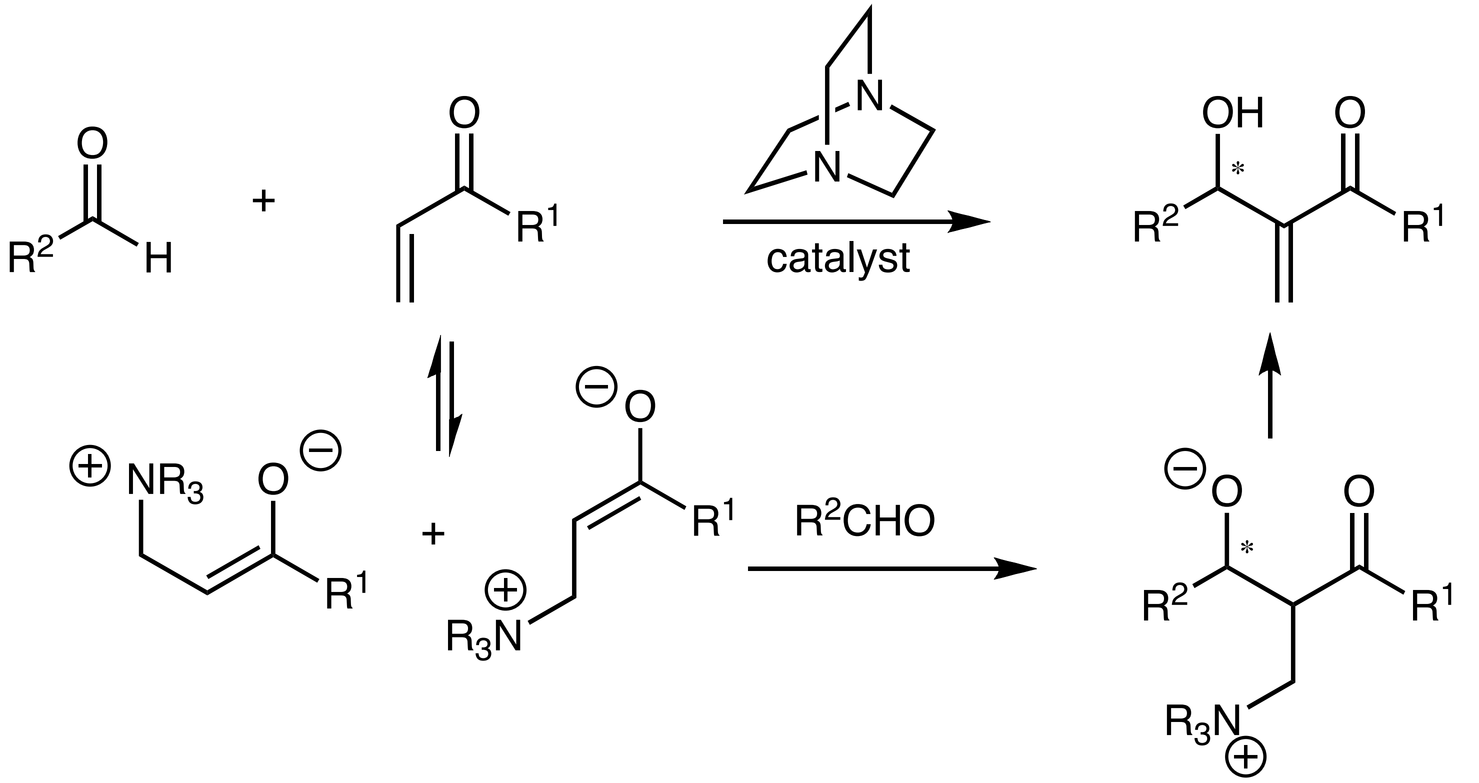


1. KOTMS, Et_2O, THF, 45 °C, 96%
2. DIC, DMAP, CH_2Cl_2

95%

1. TBAF (81%)
2. aq. AcOH (90%)

Morita-Baylis-Hillman Reaction



- Aziridines
- epoxides
- triols
- anti-aldol product (H_2)

Problem

Low rate
Low conversion/yield
Highly substrate dependant

Improvements

High pressure and microwave

N.S. Isaacs. *J.Chem.Res.(S)***1988,** 330-331
S.V. Bhat, *Synlett.* **1994,** 444

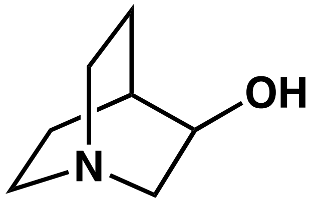
Low temperature

J. W. Leahy, *J. Org. Chem.* **1997,** *62,* 1521-1522

Base modification (quinuclidinol, DBU, DABCO)

S. E. Drewes, *Synth. Commun.* **1988,** *18,* 1565-1568

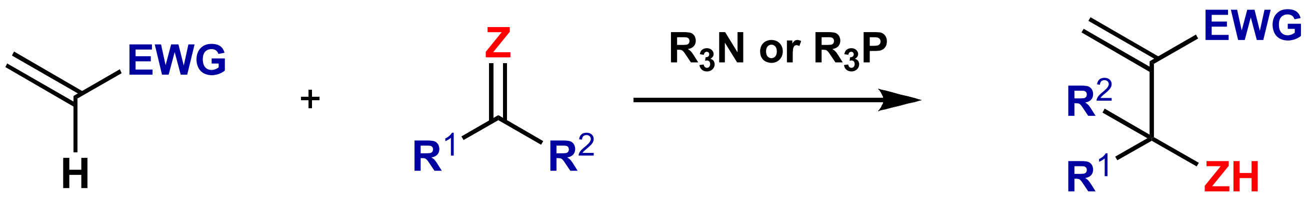
V. K. Aggarwal,*Chem. Commun.* **1999,** *62,* 2311-2312



Addition of Lewis acids

V. K. Aggarwal, *J. Org. Chem.* **1998,** *63,* 7183-7189

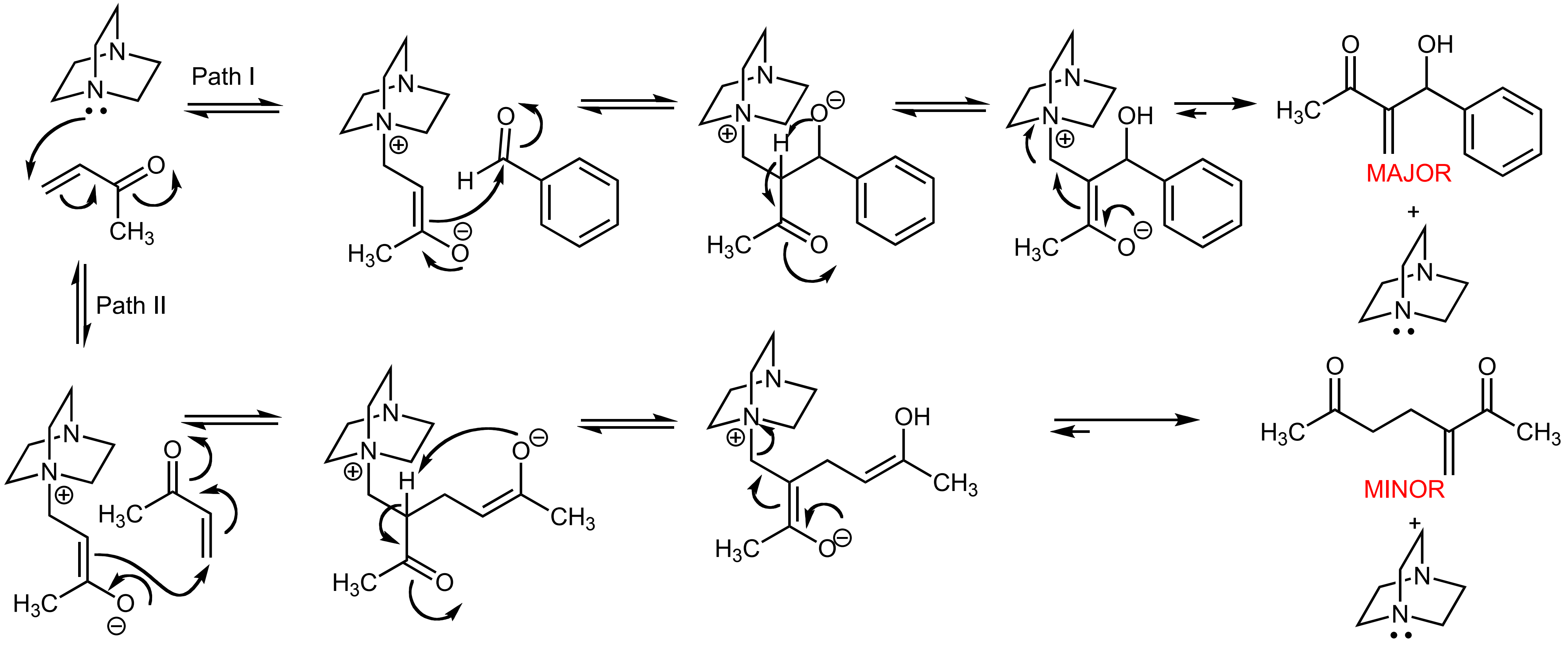
Morita-Baylis-Hillman Reaction



EWG = $CONH_2$, $CONR_2$, COOR, *etc.*

Z = O, NTs, NCO_2R, NSO_2Ar

R^1, R^2 = Alkyl, Aryl, H

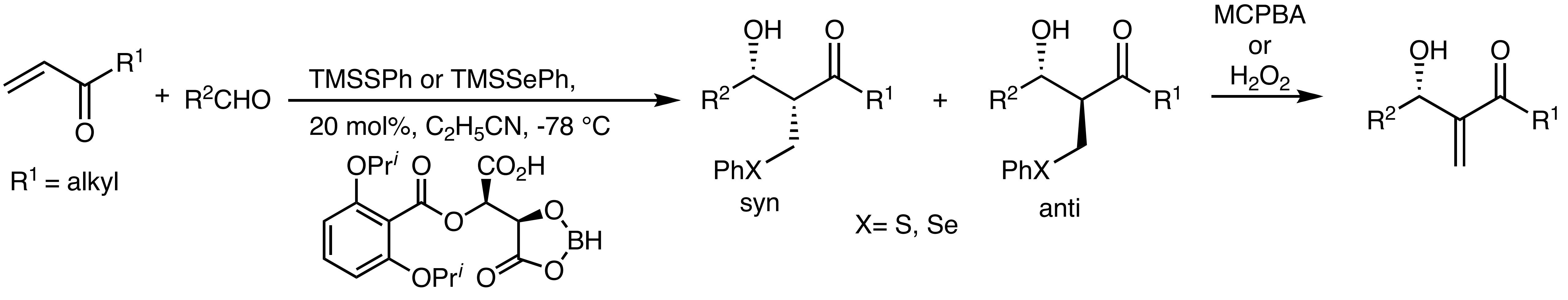


- Chiral tertiary amine catalysts (Hatakeyama)
- Chiral tertiary phosphine catalysts (only effective in aza-MBH)
- Lewis acid catalysts
- Bronsted Acid catalysts (thioureas, binol, proline, ammonium salts

Morita-Baylis-Hillman: Background

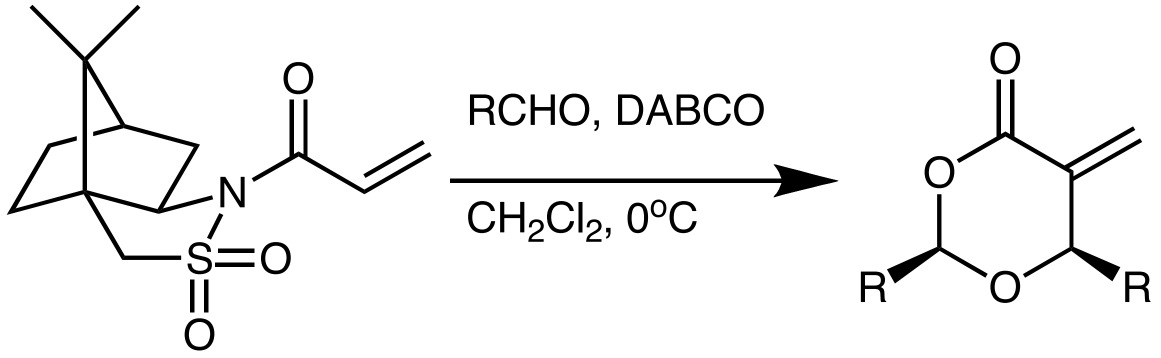
Stepwise Baylis-Hillman

A. G. M. Barrett and Akio Kamimura. *J. Chem. Soc., Chem. Commun.* **1995**, 1755-1756



Chiral Auxiliary-based Baylis-Hillman

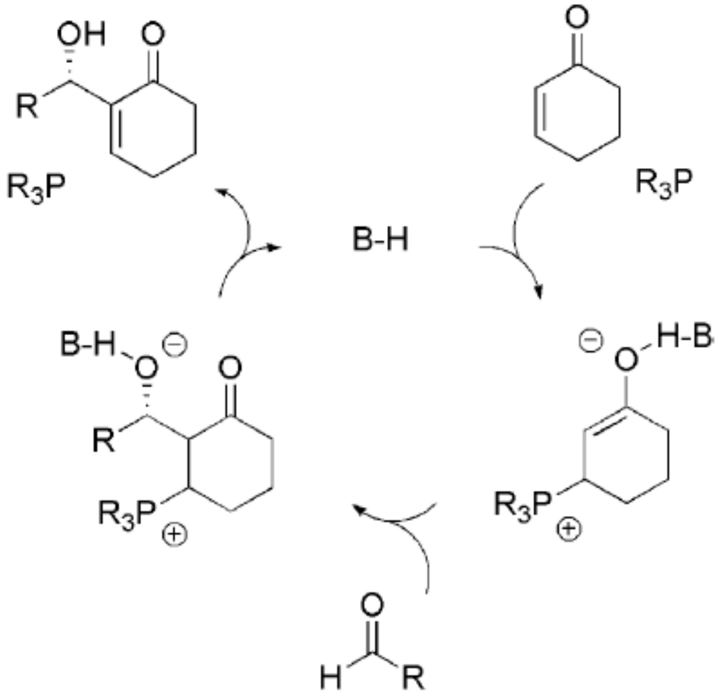
J. W. Leahy. *J. Am. Chem. Soc.* **1997,** *119,* 4317-4318



R	Yield (%)	ee (%)
CH_3	85	>99
CH_3CH_2	98	>99
$CH_3CH_2CH_2$	70	>99
$(CH_3)_2CH$	33	>99
$PhCH_2CH_2$	68	>99
$AcOCH_2$	68	>99
$(CH_3)_2CHCH_2$	67	>99
Bn	0	-

Asymmetric Morita-Baylis-Hillman Reaction

Scheme 1. Proposed Catalytic Cycle for the Brønsted-Acid-Catalyzed Morita−Baylis−Hillman Reaction



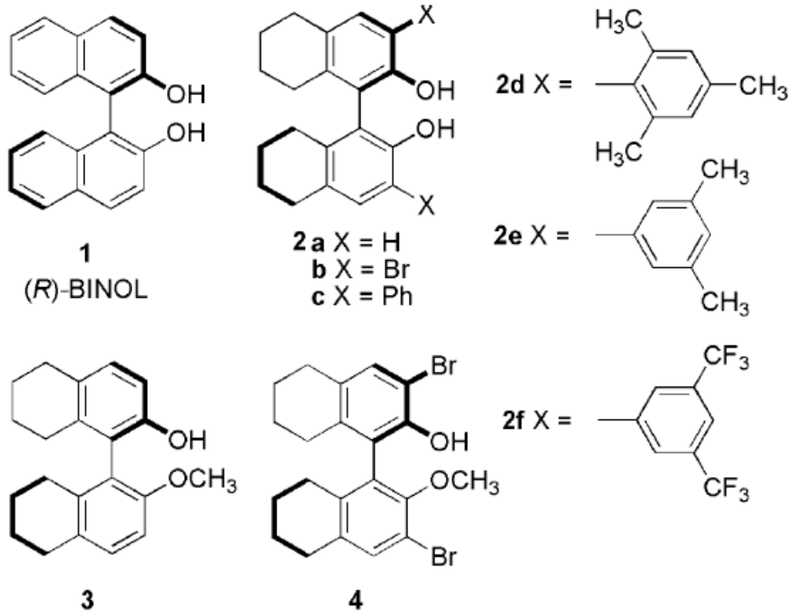
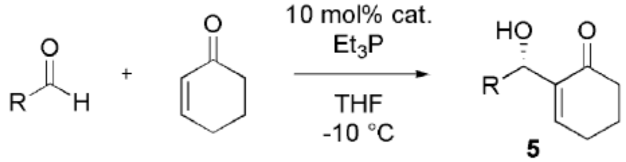
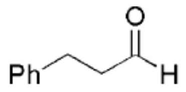
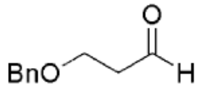
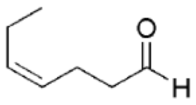
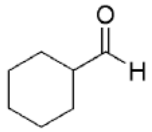
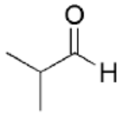
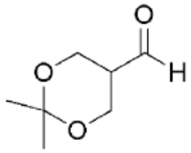
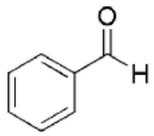
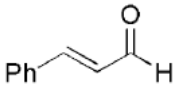


Figure 1. Binaphthol-derived Brønsted acids.



5

entry	aldehyde	catalyst	yield (%)[b]	% ee[c]
a		**2f**	**5a** (88)	90
b		**2f**[d]	**5b** (74)	82
c		**2e**	**5c** (72)	96
d		**2e**	**5d** (71)	96
e		**2e**	**5e** (82)	95
f		**2e**[d]	**5f** (70)	92
g		**2f**	**5g** (40)	67
h		**2e**	**5h** (39)	81

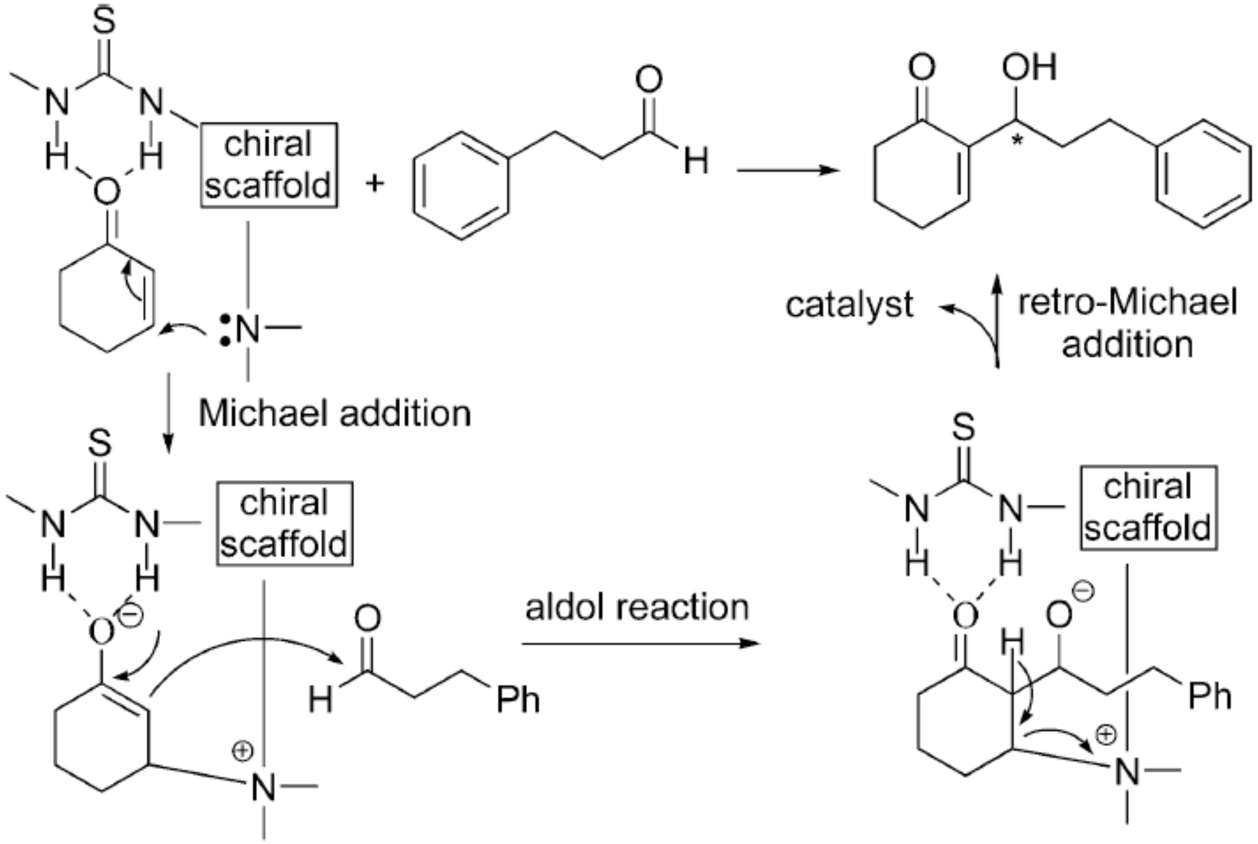
[a] Reactions were run with 1 mmol of aldehyde, 2 mmol of cyclohexenone, 2 mmol of PEt_3, and 10 mol % catalyst in THF (1 M) at −10 °C for 48 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 20 mol % catalyst.

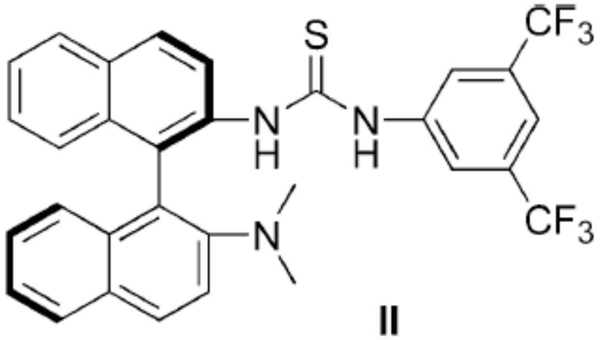
J. Am. Chem. Soc. **2003,** 125, (40), 12094

Angew. Chem. Int. Ed. **2006,** 45, (30), 4929

Asymmetric Morita-Baylis-Hillman Reaction

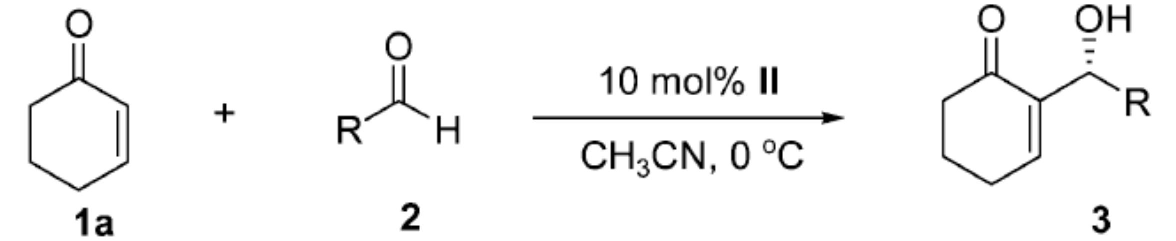
Scheme 1. Proposed Catalytic Cycle for Amine-Thiourea-Promoted MBH Reaction

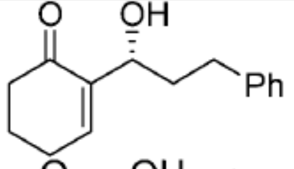
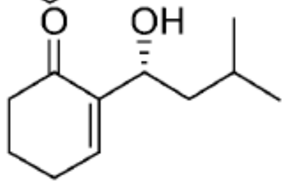
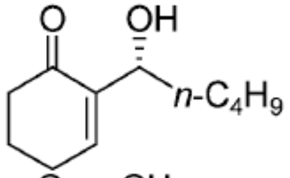
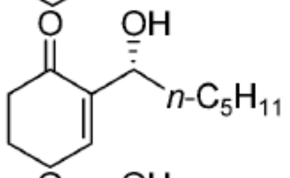
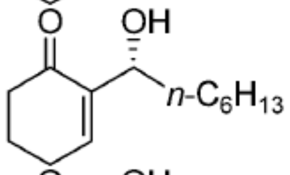
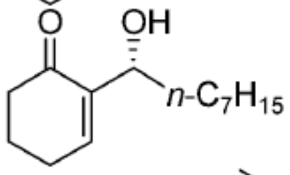
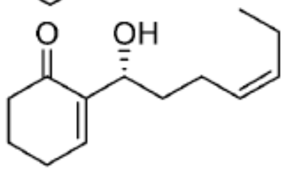




II

Table 2. Catalyst **II**-Catalyzed MBH Reactions of 2-Cyclohexen-1-one **1a** with Aldehydes **2**[a]

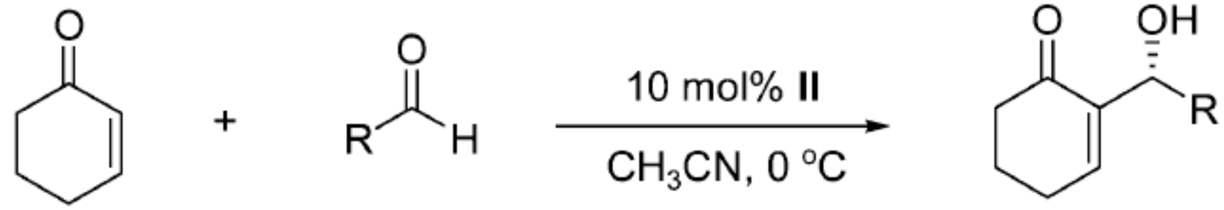


entry	product	t (h)	yield (%)[b]	ee (%)[c]
1		48	80	83
2		72	72	80
3		48	84	81
4		60	75	81
5		72	71	80
6		72	74	82
7		72	82	81

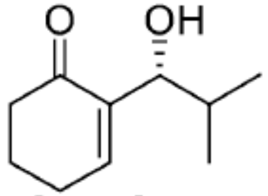
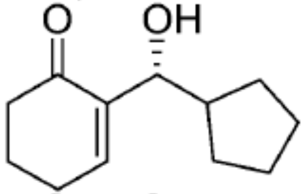
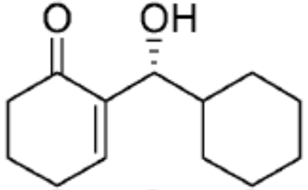
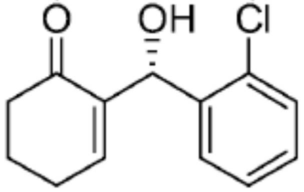
Org. Lett. **2005,** 7, (19), 4293

Asymmetric Morita-Baylis-Hillman Reaction

Table 2. Catalyst **II**-Catalyzed MBH Reactions of 2-Cyclohexen-1-one **1a** with Aldehydes **2**[a]



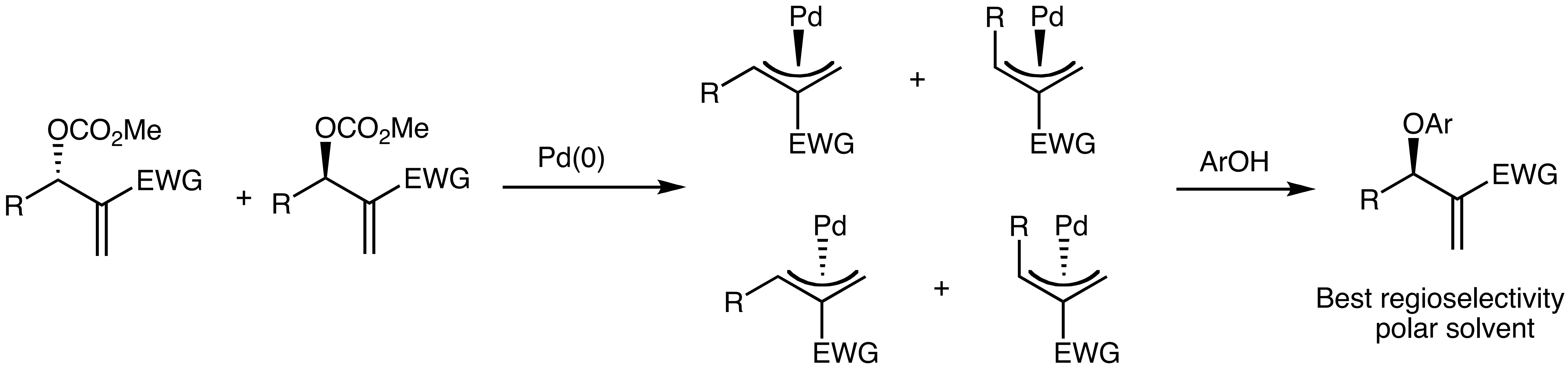
1a **2** **3**

entry	product	t (h)	yield (%)[b]	ee (%)[c]
8		72	63	94
9		96	71	90
10		120	67	92
11		108	55	60

[a] See footnote in Table 1. [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or Chiralcel OD-H).

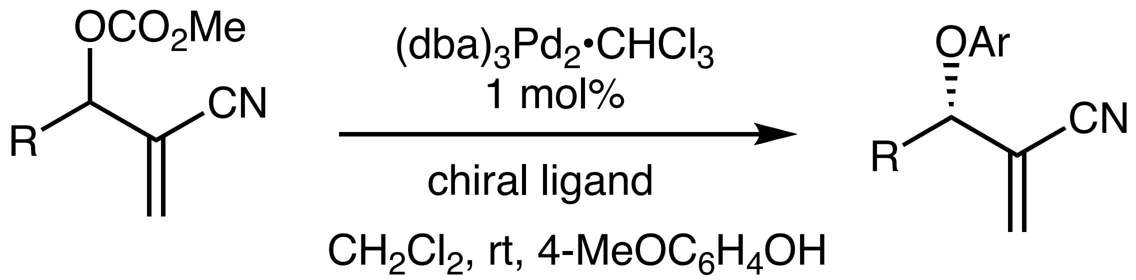
Deracemization of Baylis-Hillman Adducts

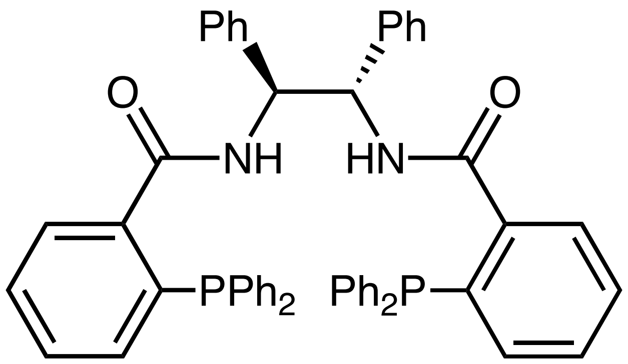
Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534-3535.



Best regioselectivity in polar solvent

Ligand optimization





R = alkyl or aryl   Yield: 52-77% ee: 85-98% (most are >95% ee)

⇨ Other phenols can be used

⇨ p-MeOC$_6$H$_4$ group can be cleaved with CAN in 87-94% yield without epimerization.