Career of
Hisashi Yamamoto

Esther C. Y. Lee
Group Meeting
August 5, 2009

Hisashi Yamamoto

University of Chicago
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(773) 702-5059
yamamoto@uchicago.edu

EDUCATION

1967	Kyoto University, B. S. (Prof. H. Nozaki-advisor)
1971	Harvard University, Ph.D. (E. J. Corey-advsior)

PROFESSIONAL

2002-present	Professor, The University of Chicago-Arthur Holly Compton Distinguished Professor
1997-1999	Councilor of Nagoya University
1983-2002	Professor, Nagoya University
1980-1983	Associate Professor, Nagoya University
1977-1980	Associate Professor, University of Hawaii
1976-1977	Lecturer, Kyoto University
1972-1976	Instructor, Kyoto University
1971-1972	Toray Industries, Inc. (Prof. J. Tsuji-advisor)

PUBLICATIONS

483 original papers, 107 reviews (50 in Japanese)
148 invited lectures
advisory board for 21 journals

NOTABLE AWARDS

National Prize of Purple Metal (Japan)
Yamada Prize
Tetrahdron prize
Japan Academy Award
American Chemical Society Creativity Award

Hisashi Yamamoto

research interests

1972-1977 @ Kyoto University

Organoaluminum reagents for selective organic transformations

1977-1980 @ University of Hawaii

Regioselective carbonyl amination using DIBAL-H

1980-2002 @ Nagoya University (*Tetrahedron*, **2007**, *63*, 8377.)

Organoaluminum reagents for selective organic transformations

Development of designer Lewis acids

Bulky aluminum reagents for selective organic synthesis

Enantioselective synthesis using chiral Lewis acids

Development of designer Brønsted acids

2002-present @ The University of Chicago

Combined acid catalysis of Lewis and Brønsted acids

Asymmetric transformation of esterification, amidation, halogenation using designer acid catalysis

Optically active silver complexes for catalytic asymmetric reactions

Metal and non-metal catalysts for asymmetric oxidation

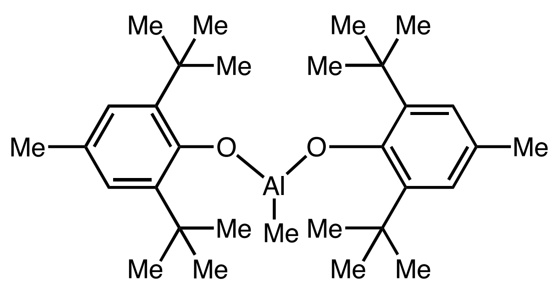
Super Silyl for one-flask reactions

Super Bronsted acid catalysis

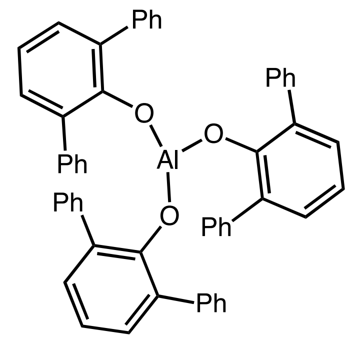
New metal catalysis using *cis*-β-configuration

Designer Lewis Acids

■ Bulky aluminum aryloxides



methyl**a**luminum bis (2,6-**d**i-*tert*-butyl-4-methylphenoxide)
(MAD)



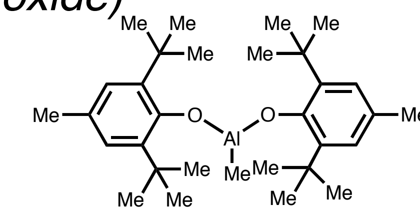
aluminum **t**ris (2,6-diphenyl**ph**enoxide)
(ATPH)

■ Properties

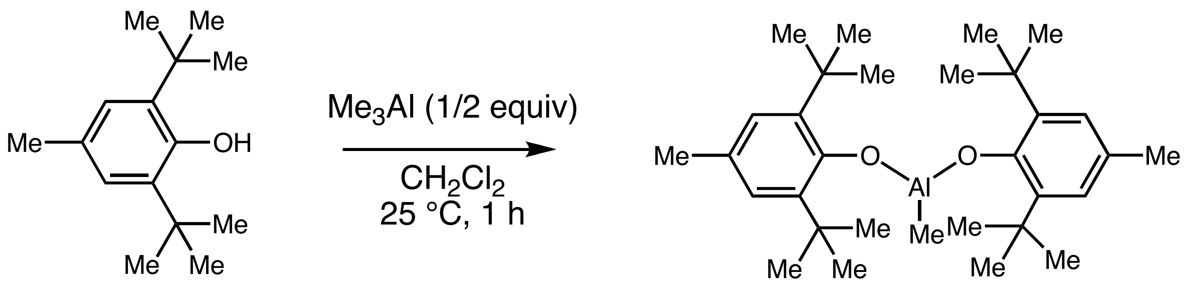
- Strong coordination to oxygen-containing substrates - similar to traditional LA
- Higher Lewis acidity and reactivity - monomeric in organic solvents
- *New* (greater) *selectivity* - molecular recognition
  stereoselective, regioselective, and chemoselective reactions
  -MAD or ATPH coordination to carbonyl increases NMR shifts: shielding

Yamamoto, H.; Maruoka, K. *Pure & Appl. Chem.* **1988**, *760*, 21.
Yamamoto, H.; Saito, S. *Pure & Appl. Chem.* **1999**, *71*, 239.

Methylaluminum bis (2,6-di-tert-butyl-4-methylphenoxide) (MAD)



■ Synthesis

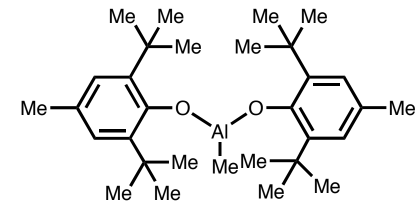


■ Synthetic utility

- Selective formation of equitorial alcohols
- Conjugate addition of organolitihium reagents to unsaturated carbonyl systems
- Discrimination between two different ethers, ketones, and esters

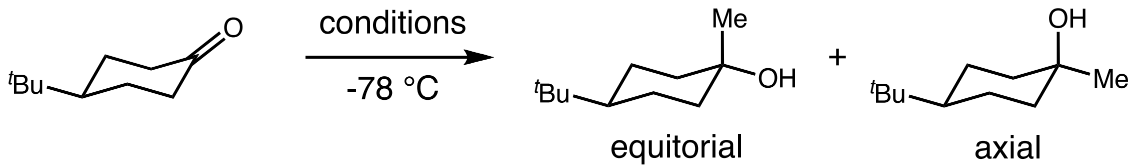
Yamamoto, H.; Maruoka, K. *Pure & Appl. Chem.* **1988**, *760*, 21.
Yamamoto, H.; Saito, S. *Pure & Appl. Chem.* **1999**, *71*, 239.

Methylaluminum bis (2,6-di-tert-butyl-4-methylphenoxide) (MAD)

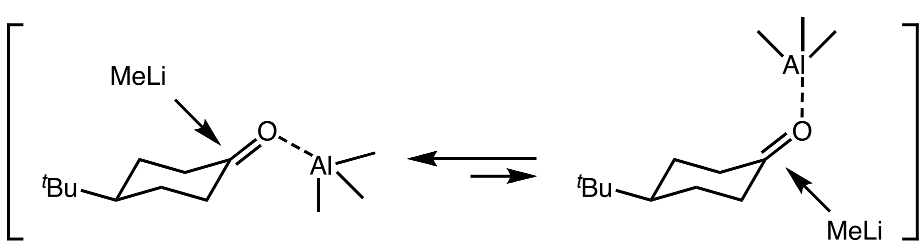


MAD

■ Selective ketone alkylation



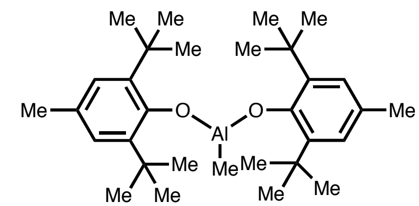
MeLi :	(21 : 79)
MAD/MeLi :	84%, (99 : 1)
EtMgBr:	95%, (48 : 52)
MAD/EtMgBr:	91% (100 : 0)



axial addition preferred

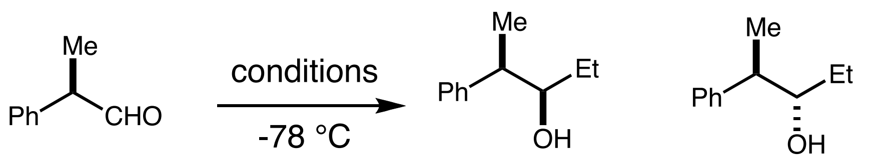
Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

Methylaluminum bis (2,6-di-tert-butyl-4-methylphenoxide) (MAD)



MAD

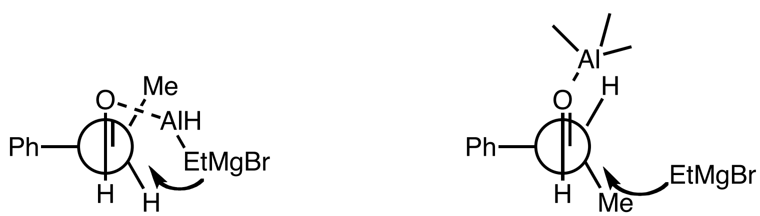
■ Selective aldehyde alkylation



Cram Anti-Cram

EtMgBr	78%, (84 : 16)
MAD/EtMgBr	90%, (25 : 75)

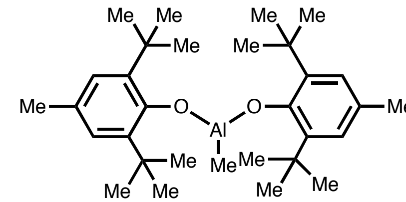
■ Anti-Cram selectivity in aldehyde alkylation



Cram Anti-Cram

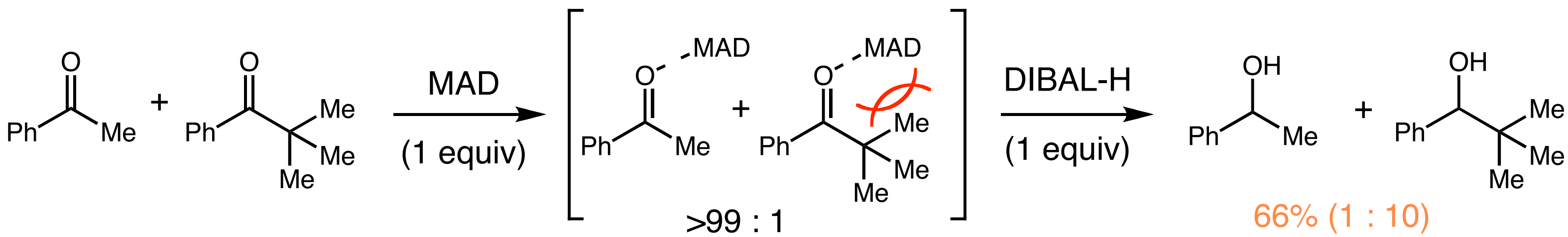
Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

Methylaluminum bis (2,6-di-tert-butyl-4-methylphenoxide) (MAD)



MAD

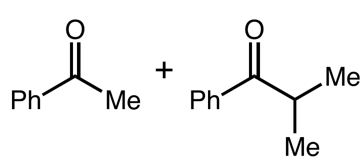
■ Selective for more hindered ketone



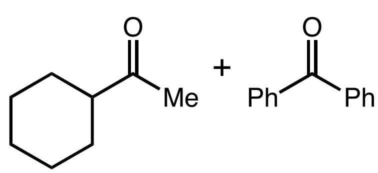
no MAD : 99% (2.6 : 1)

2 equiv MAD, 85% (1 : 16)

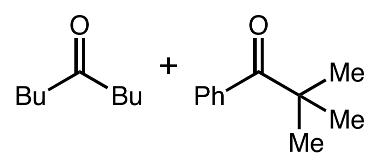
■ Examples



101% (1 : 6)



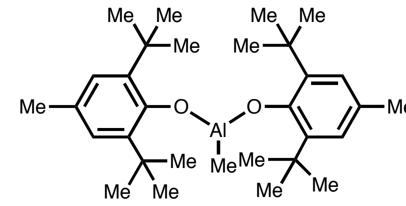
80% (1 : 15)



82% (1 : 8)

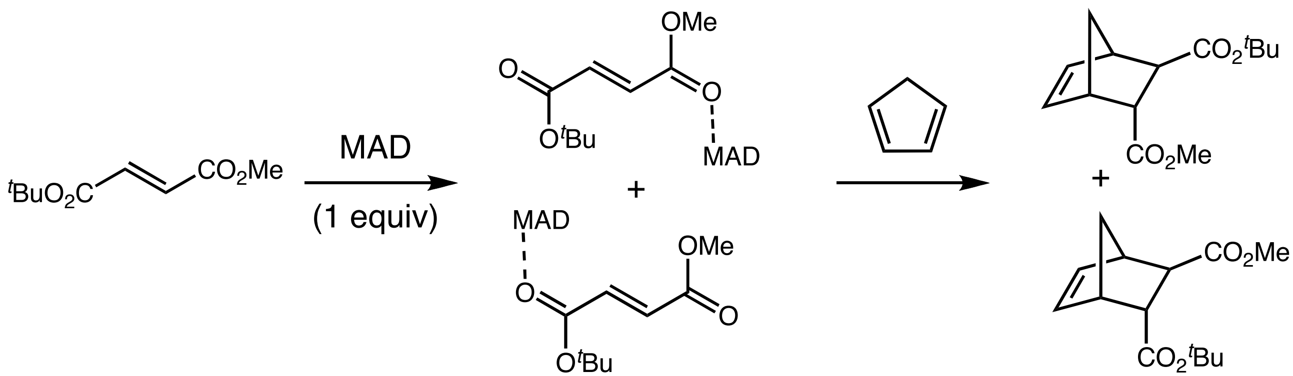
Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650.

Methylaluminum bis (2,6-di-tert-butyl-4-methylphenoxide) (MAD)



MAD

■ Discrimination between two different esters



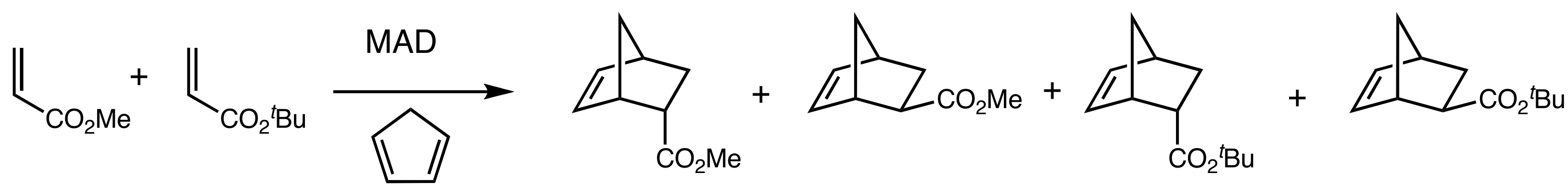
Et_2AlCl

>99 : 1

86 % 65 %

>99 : 1 46 : 54

■ Discrimination between two different esters: intermolecular

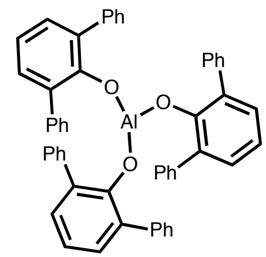


95% (94 : 3 : 3 : 0)

Et_2AlCl 72% (32 : 1 : 67 : 0)

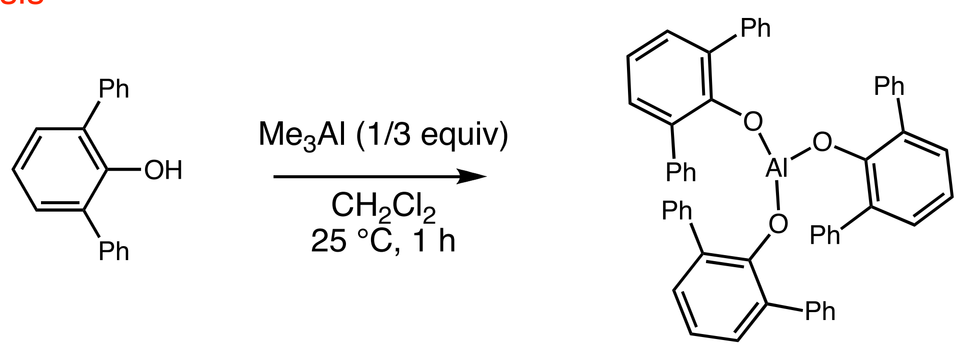
Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 1089.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



ATPH

■ Synthesis

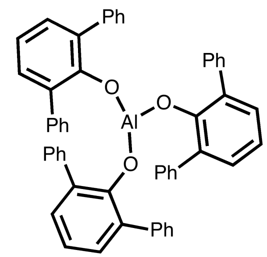


■ Synthetic utility

- Activates less-hindered aldehyde
- Conjugate addition to α,β-unsaturated carbonyl compounds
- *exo*-Selective Diels–Alder reaction
- Stereoselective and asymmetric Claisen rearrangement
- Selective alkylation at the α-carbon of unsymmetrical ketones
- Directed aldol ondensation
- Nucleophilic dearomatization functionalization

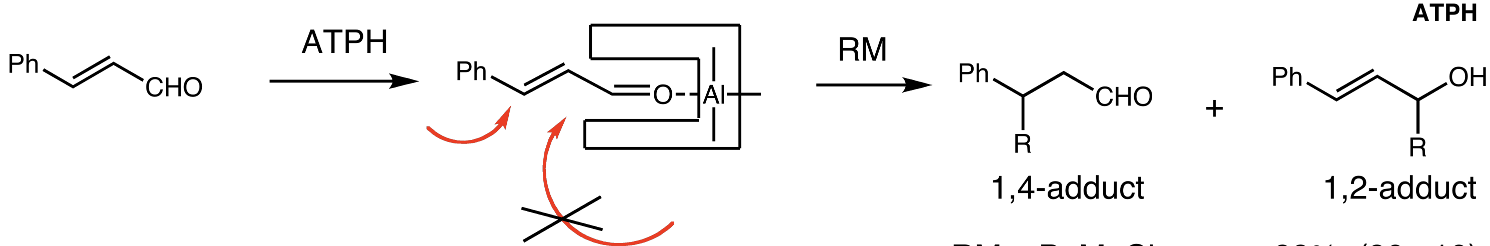
Yamamoto, H.; Maruoka, K. *Pure & Appl. Chem.* **1988**, *760*, 21.
Yamamoto, H.; Saito, S. *Pure & Appl. Chem.* **1999**, *71*, 239.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



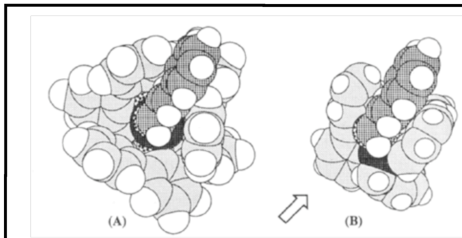
ATPH

Selective conjugate addition to α,β-unsaturated aldehyes



RM =	Yield, (1,4 : 1,2)
BuMgCl	99%, (90 : 10)
BuCaI	88%, (98 : 2)
BuSrI	60%, (95 : 5)
BuBaI	97%, (97 : 3)
PhCCLi	99%, (93 : 7)
$Me_3SiCCLi$	98%, (92 : 8)

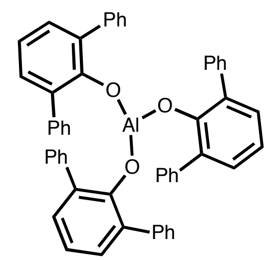
- Without ATPH, 1,2-adduct only
- Also compatible with lithium carbenoids and lithium enolates
- First Mukaiyama–Michael using silyl ketene acetals
- Three-component coupling leading to jasmonates[1]
- Chiral molecular recognition: asymmetric 1,4-addition[2]



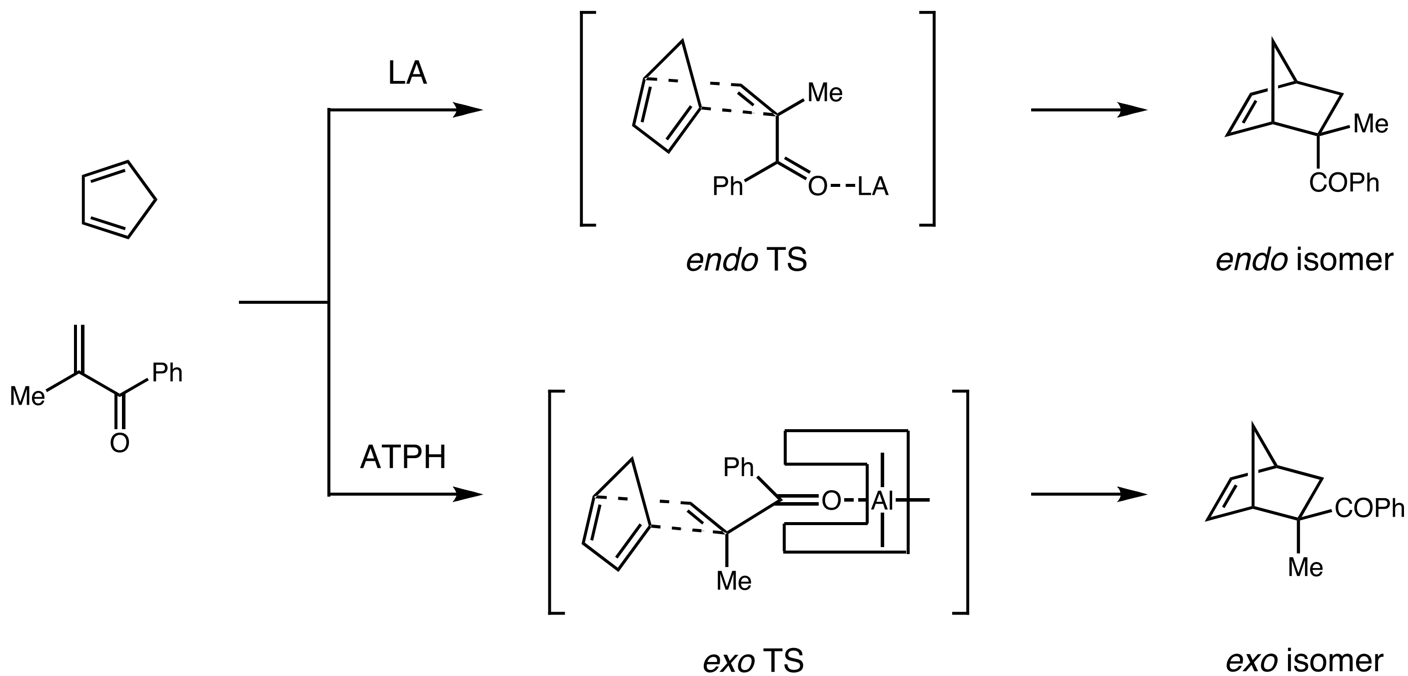
ATPH MAD
with cinnamaldehyde

Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.
[1]Saito, S.; Yamazaki, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3613.
[2]Ito, H.; Nagahara, T.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 994.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



■ *Exo*-Selective Diels–Alder Reaction: Molecular Recognition Approach

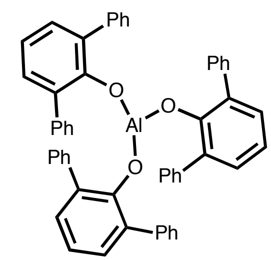


removes secondary orbital interactions

81%	Me_3Al
(4 : 96)	(37 : 63)

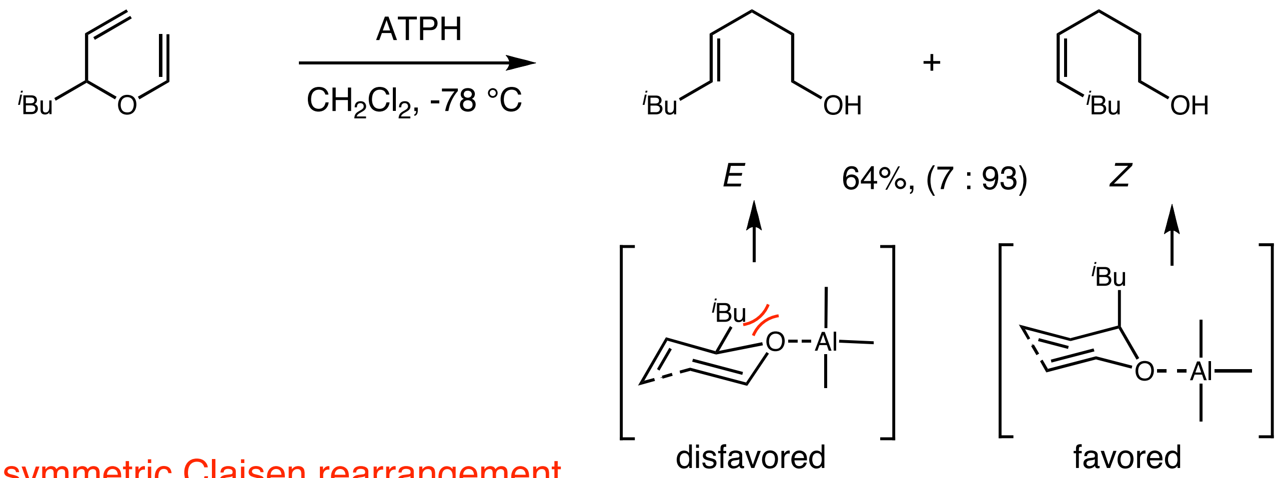
Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)

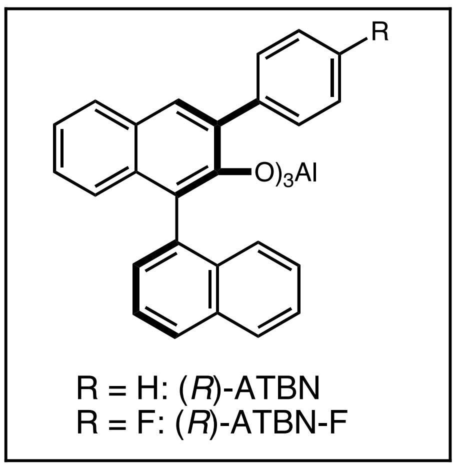


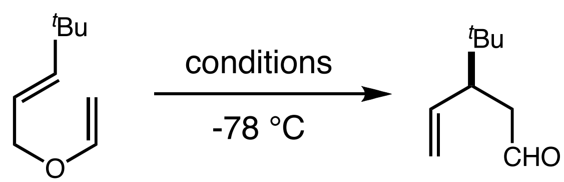
ATPH

■ Claisen rearrangement: (*Z*)-selective



■ Asymmetric Claisen rearrangement

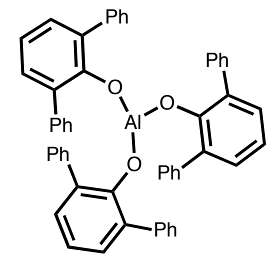




(*R*)-ATBN 63%, yield, 63% ee
(*R*)-ATBN-F 70% yield, 91% ee

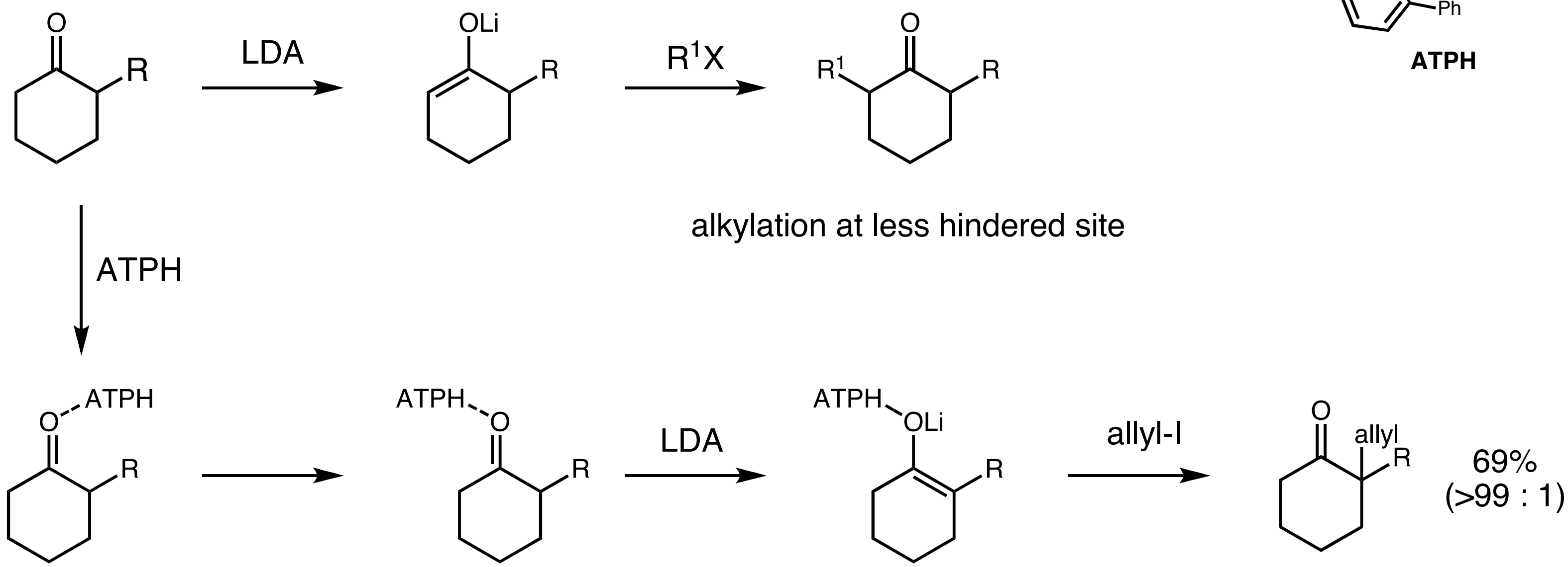
Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.
Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



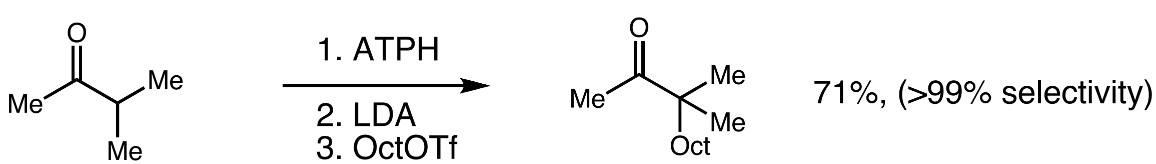
ATPH

■ Regioselective ketone alkylation: selective for the more hindered site



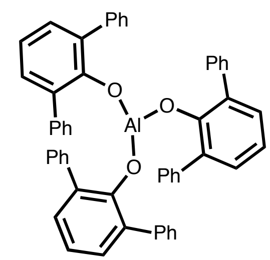
alkylation at more hindered site

■ Regioselective ketone alkylation: acyclic ketones



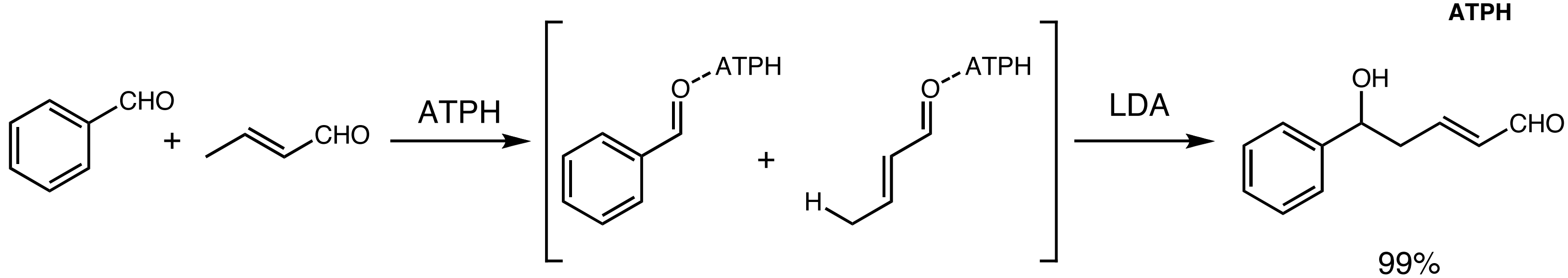
Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



ATPH

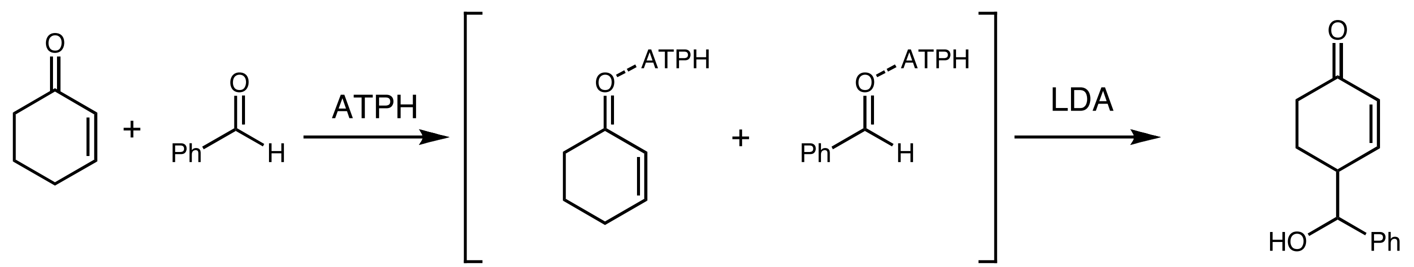
■ Directed aldol condensation: conjuated aldehydes with aldehydes



99%

- 1,2- and 2,2[1]-disubstitued conjugated aldehydes, extended conjugation allowed
- tertiary, aliphatic, and unsaturated aldehydes are compatible partners

■ Directed aldol condensation: conjuated ketones with aldehydes

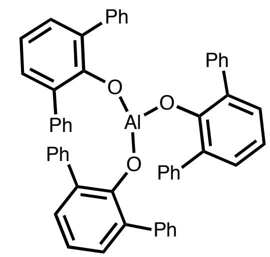


70% (4 : 1)

- 3-methyl substitued cyclohexenone and 4-methylacetophenone allowed
- tertiary, aliphatic, and unsaturated aldehydes are compatible partners

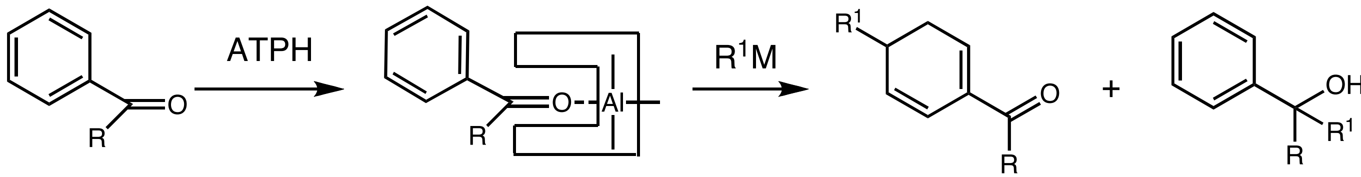
Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813.
[1]Saito, S.; Shiozawa, M.; Nagahara, T.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 7847.

Aluminum tris(2,6-diphenylphenoxide) (ATPH)



ATPH

■ Conjugate addition of organolithiums to aromatic aldehydes and ketones

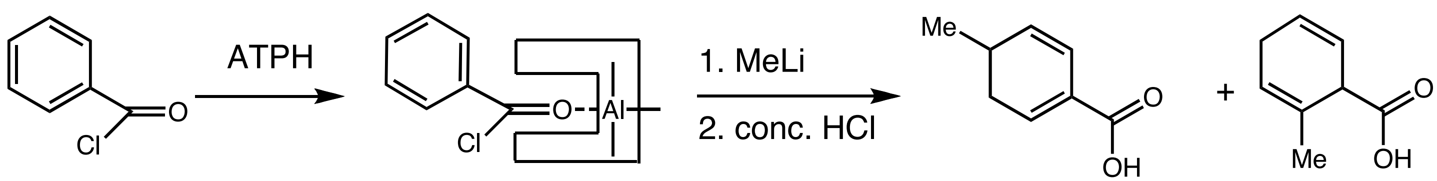


1,6-adduct 1,2-adduct

R = H, R^1M =	^{t}BuLi, no ATPH	92%, (0 : 100)
	^{t}BuLi	81%, (100 : 0)
	MeLi	99%, (1 : 99)
R = Me, R^1M =	^{t}BuLi	93%, (100 : 0)
	^{s}BuLi	80%, (100 : 0)
	^{n}BuLi	45%, (100 : 0)

Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091.

■ ATPH-ArCOCl complex for nucleophilic dearomatic functionalization



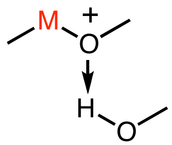
-ATPH-ArCOCl complex encapsulates carbonyl more effectively
-addition of Grignards possible

1,6-adduct 1,4-adduct
99%, (2.6 : 1)

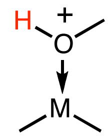
Saito, S.; Sone, T.; Murase, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10216.

Combined Acid Catalysis

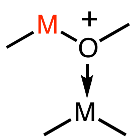
Brønsted acid assisted **L**ewis **a**cid catalyst
(BLA)



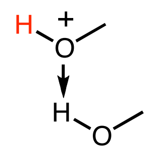
Lewis acid assisted **B**rønsted acid catalyst
(LBA)



Lewis acid assisted **L**ewis **a**cid catalyst
(LLA)



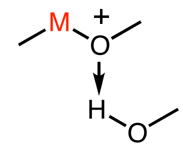
Brønsted acid assisted **B**rønsted **a**cid catalyst
(BBA)



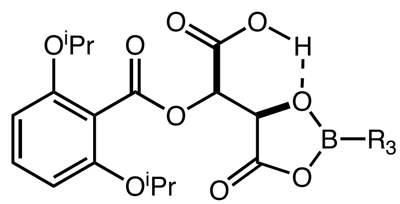
Enhances inherent reactivity
Allows for higher structured asymmetric environments

Yamamoto, H.; Futatsugi, K.; *Angew. Chem. Int. Ed.*, **2005**, *44*, 1924.

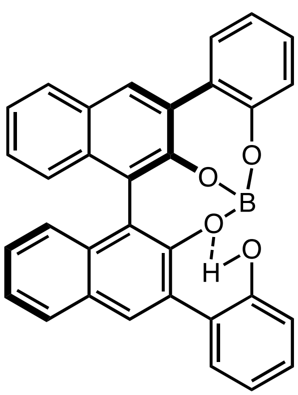
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)



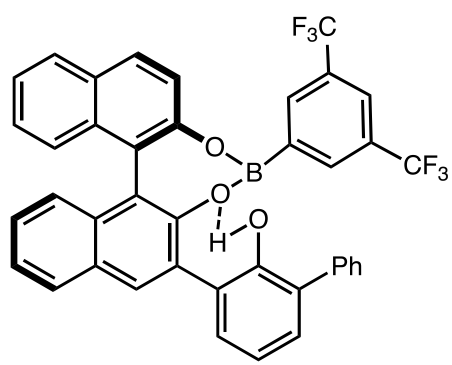
$HF \cdot BF_3$ $HCl \cdot AlCl_3$ $HSO_3 \cdot SbF_5$ $HF \cdot SbF_5$



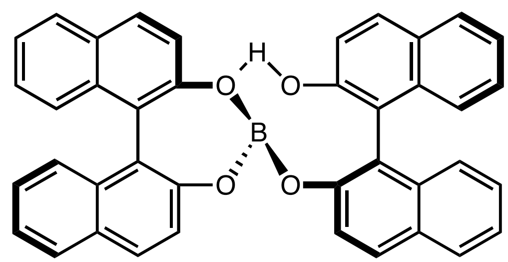
chiral (acyloxy) borane (CAB)



BLA (*R*)-1



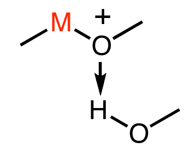
BLA (*R*)-2



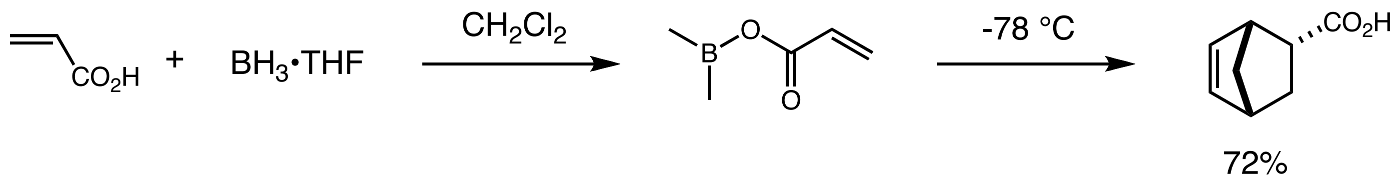
BLA (*R*)-3

Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

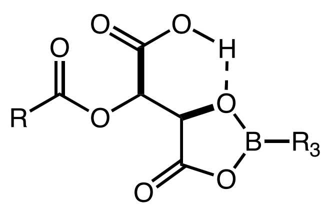
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)



Acyloxyborane: activating compound for carboxylic acids

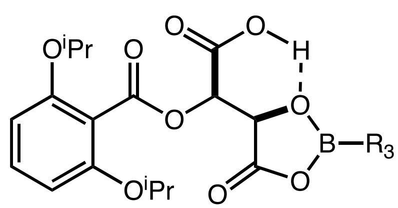


Chiral acyloxyborane: initial investigation



R = Me	66% yield, 34% ee
R = ^{t}Bu	68% yield, 51% ee
R = Ph	88% yield, 35% ee
R = 2,6-$(MeO)_2$Ph	93% yield, 78% ee

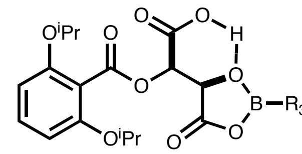
Chiral (acyloxy) borane (CAB)



- Catalytic asymmetric Diels–Alder reaction
- Catalytic asymmetric aldol reaction
- Catalytic asymmetric allylation of aldehydes

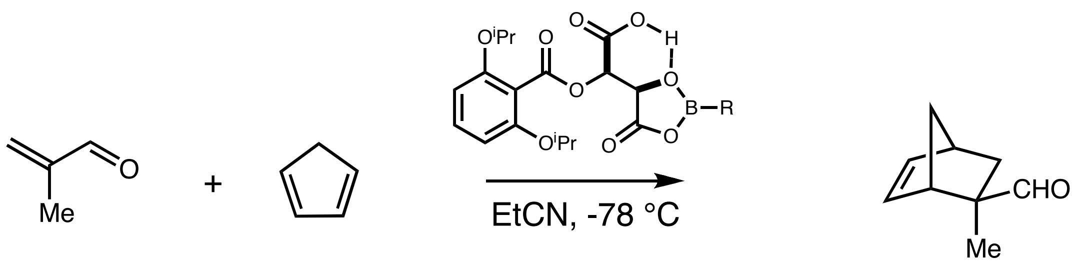
Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.

Brønsted Acid Assisted Lewis Acid Catalysts (BLA)

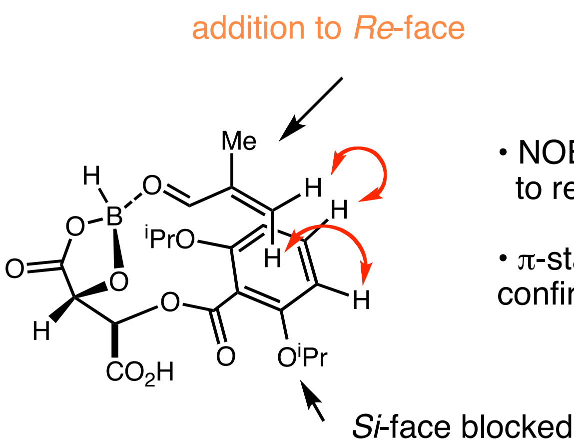


CAB

■ CAB-catalyzed asymmetric Diels–Alder reaction



R = H	87% ee
R = Ph	80% ee
R = PhOC$_6$H$_4$	93% ee



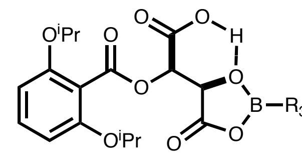
- NOE data confirms CAB enal complex to reside in the S-*trans* configuration

- π-stacking between the phenyl ring of CAB and the unsaturated aldeyde is confirmed by NOE data between the hydrogens on the aryl ring and enal

Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412.

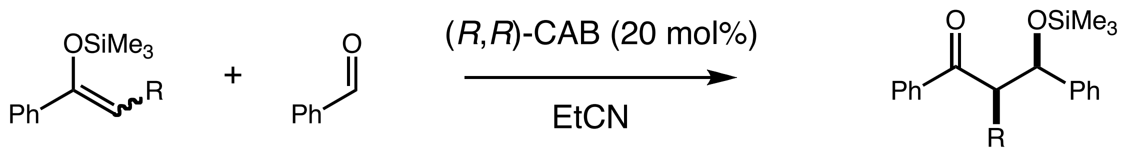
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)

chiral (acyloxy) borane (CAB)

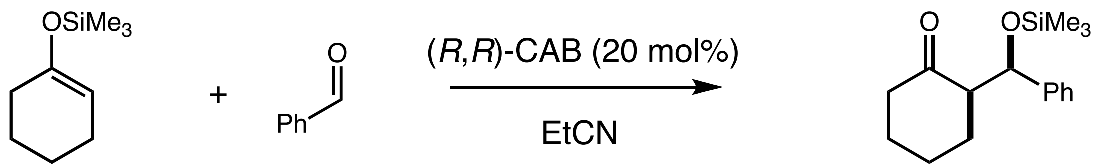


CAB

Catalytic asymmetric aldol reaction

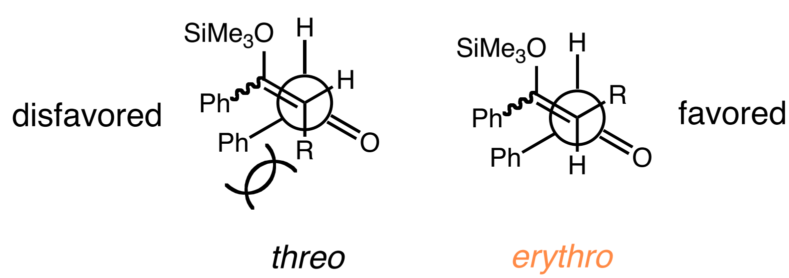


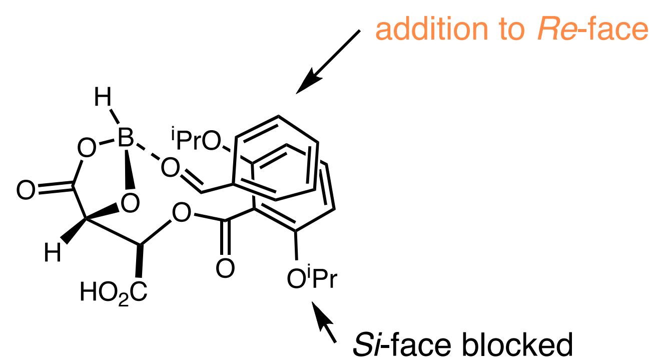
R = H 98% yield, 85% ee
R = Me 86% yield, 95% ee, (95 : 5) *erythro* : *threo*



57% yield, >95% ee, (>95 : 5) *erythro* : *threo*

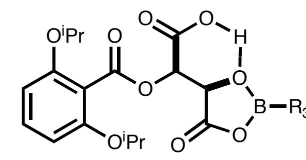
Erythro-selective





Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041.

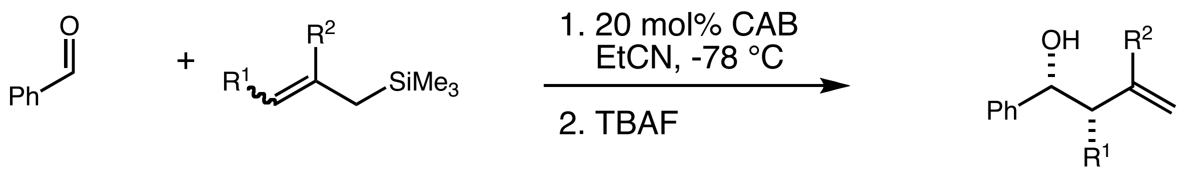
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)



CAB

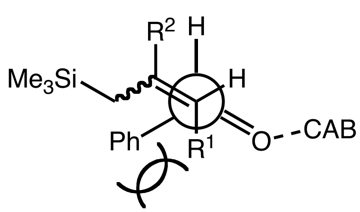
CAB-catalyzed asymmetric allylation of aldehydes

Sakurai-Hosomi allylation : homoallylic alcohols

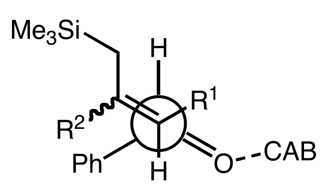


R^1,R^2 = H	46% yield, 55% ee
R^1 = H, R^2 = Me	68% yield, 82% ee
R^1,R^2 = Me	63% yield, 92% ee, (96 : 4) *erythro* : *threo*
R^1 = Me, R^2 = Et	74% yield, 96% ee, (97 : 3) *erythro* : *threo*

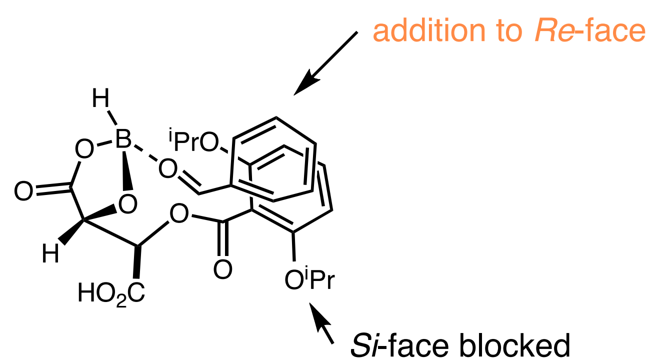
CAB-catalyzed asymmetric allylation of aldehydes



threo
disfavored



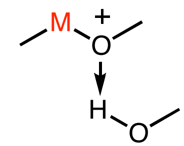
erythro
favored



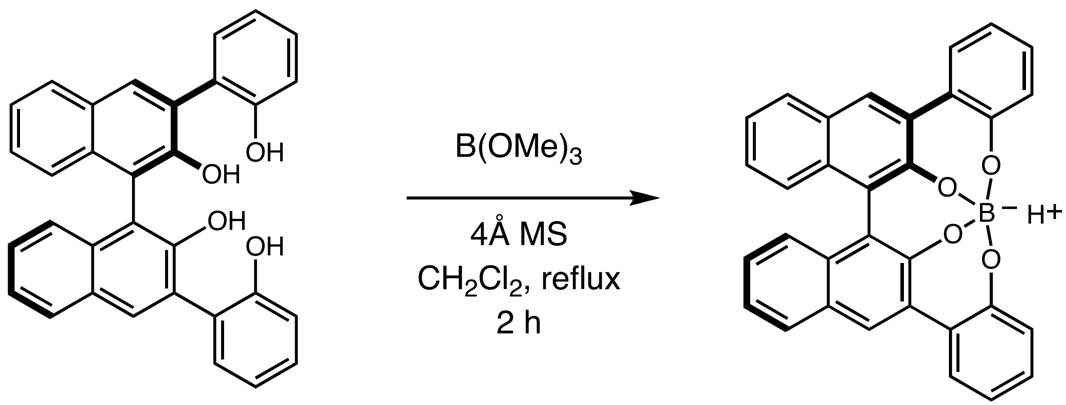
Ishihara, K.; Mouri, M.; Gao, Q.; Maruayma, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

Brønsted Acid Assisted Lewis Acid Catalysts (BLA)

boron binol derivative

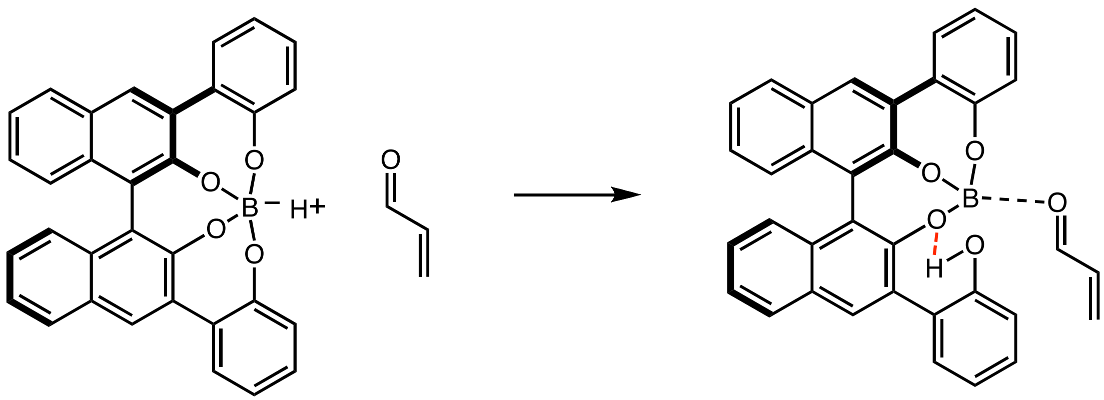


Synthesis of BLA catalyst



- asymmetric DA
- asymmetric aldol-type reaction with imines
- aza-DA

Properties



intramoleuclar H-bonding

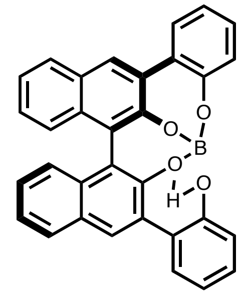
π-π donor-acceptor interaction

Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561.

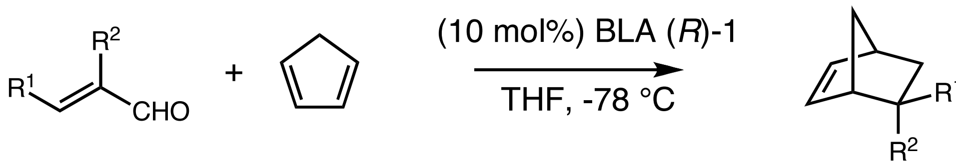
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)

boron binol derivative

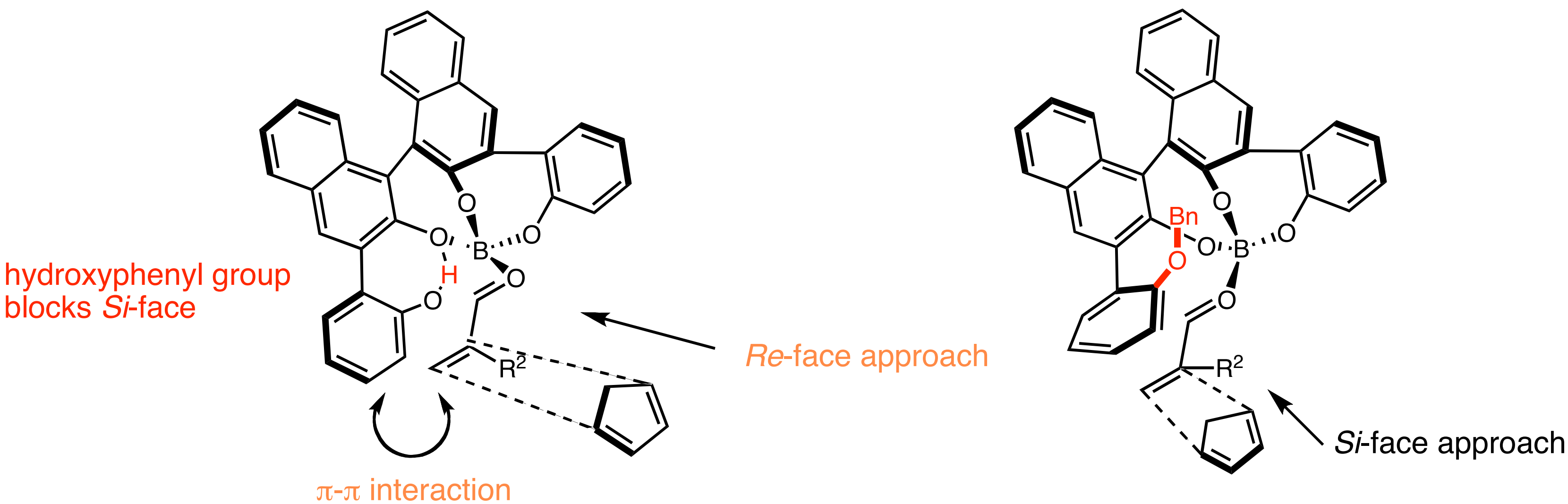


BLA (*R*)-1

■ BLA catalyst for asymmetric Diels–Alder reaction



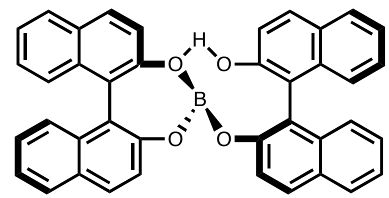
R^1 = H, R^2 = Br	>99% yield, 99% ee, (>99 : 1) *exo* : *endo*
R^1 = H, R^2 = Me	>99% yield, 99% ee, (>99 : 1) *exo* : *endo*
R^1 = Me, R^2 = Me	>99% yield, 98% ee, (>99 : 1) *exo* : *endo*
R^1 = R^2 = $-CH_2CH_2CH_2-$	>99% yield, 93% ee, (98 : 2) *exo* : *endo*



Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561.
Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.

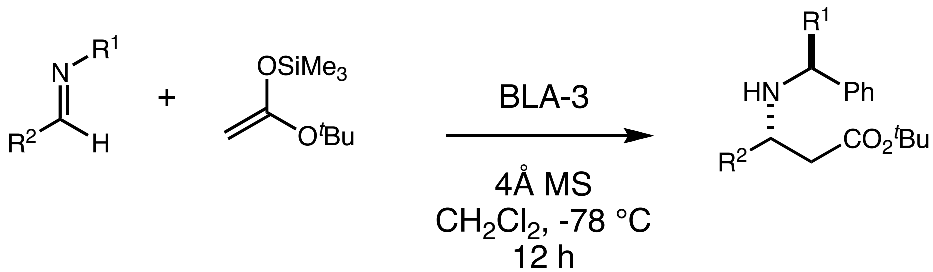
Brønsted Acid Assisted Lewis Acid Catalysts (BLA)

boron binol derivative

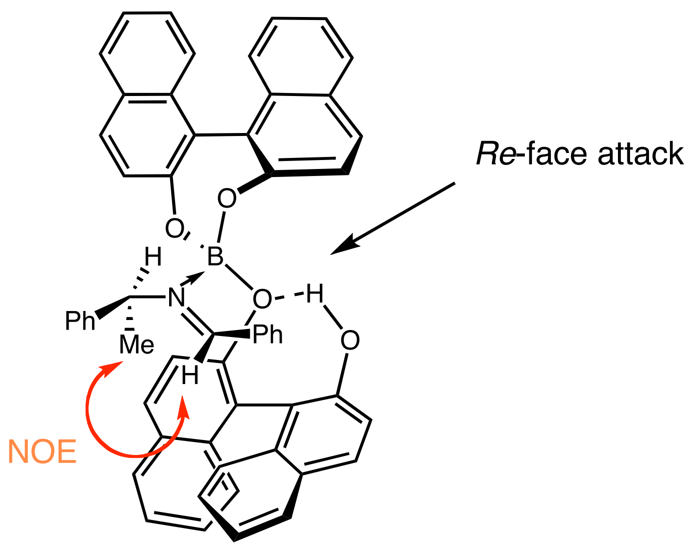


BLA-3

■ BLA promoter for asymmetric Aldol-type reaction



R^1 = Me, R^2 = Ph		63%, 94% de
Ph	Ph	58%, 96% de
Ph	*p*-MeC_6H_4	35%, 97% de
Ph	*p*-ClC_6H_4	45% 98% de

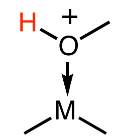


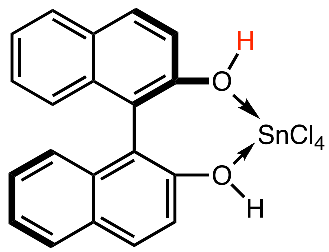
upon deprotection, β-aryl-β-amino acids

Ishihara, K.; Mayumi, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

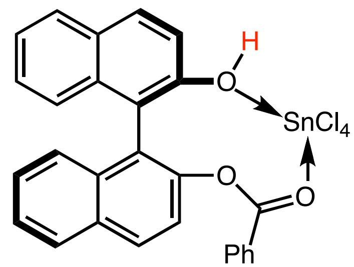
"unique proton"





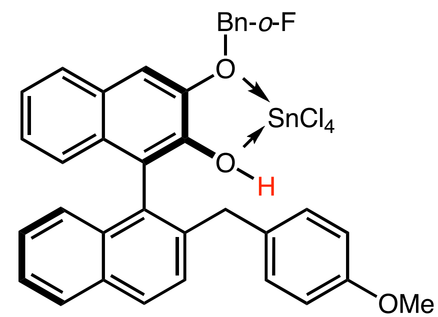
LBA (*R*)-1

Enantioselective protonations



LBA (*R*)-2

Artificial cyclase I



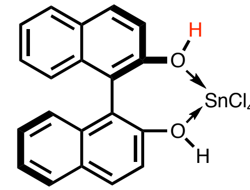
LBA (*R*)-3

Artificial cyclase II

Yamamoto, H.; Futatsugi, K.; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

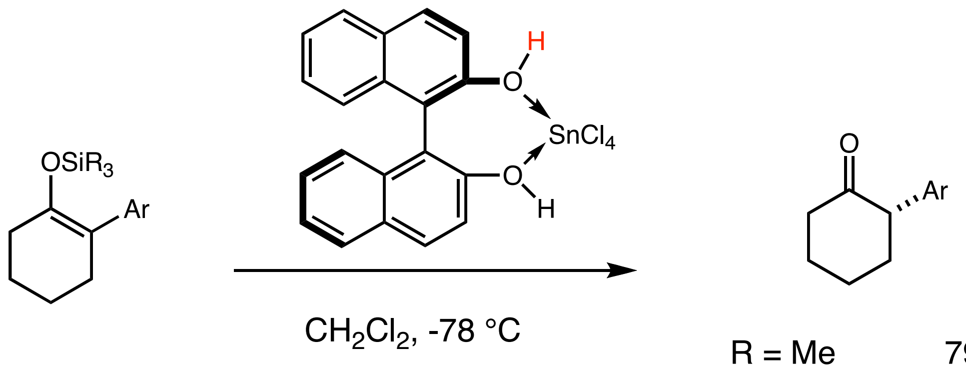
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"

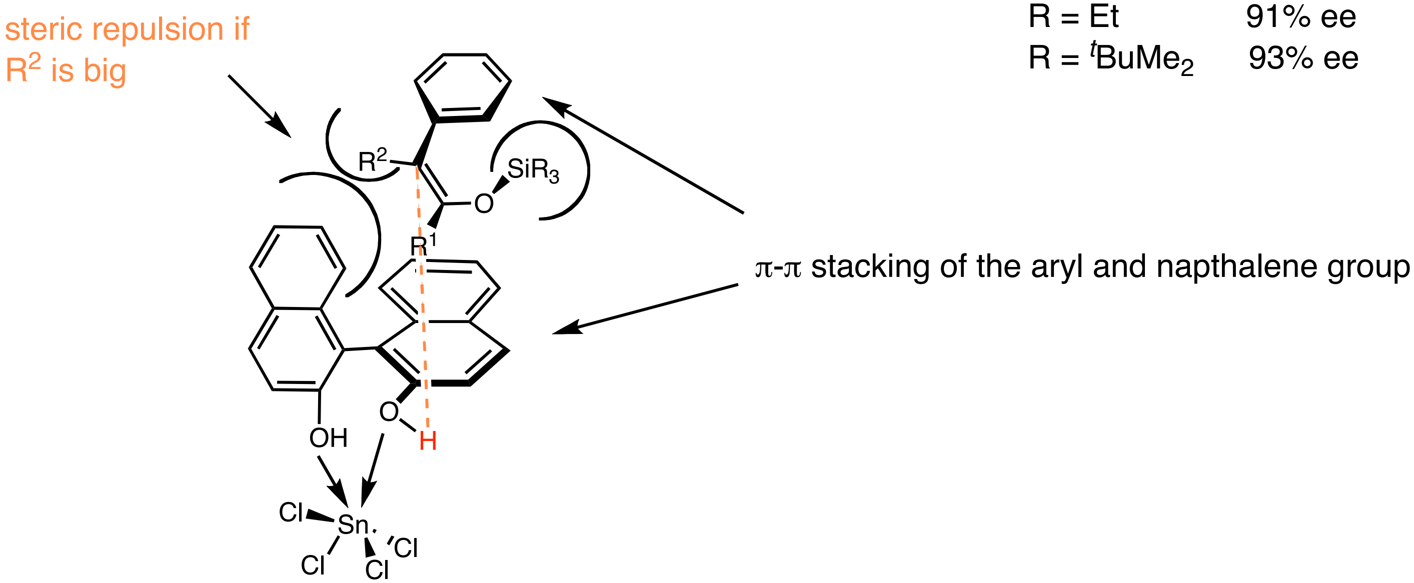


LBA (*R*)-1

■ LBA for enantioselective protonation of silyl enol ethers



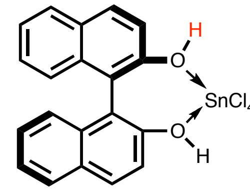
R = Me	79% ee
R = Et	91% ee
R = ^{t}BuMe$_2$	93% ee



Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

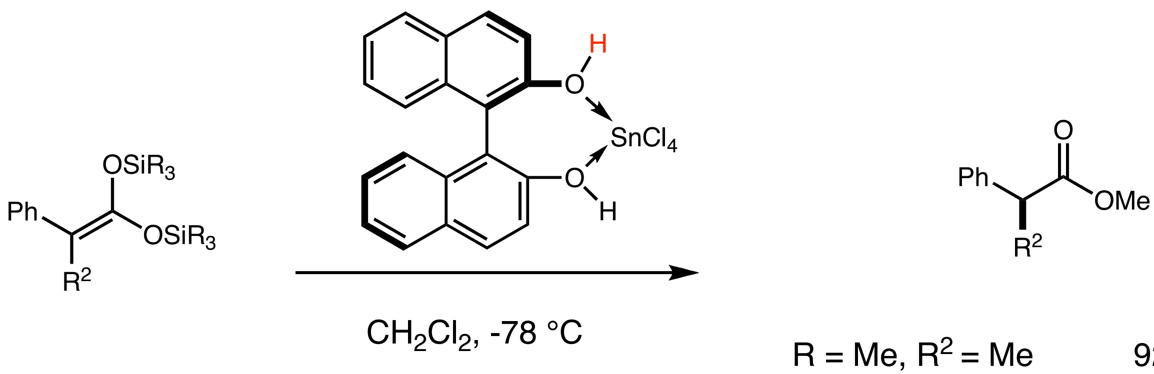
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"

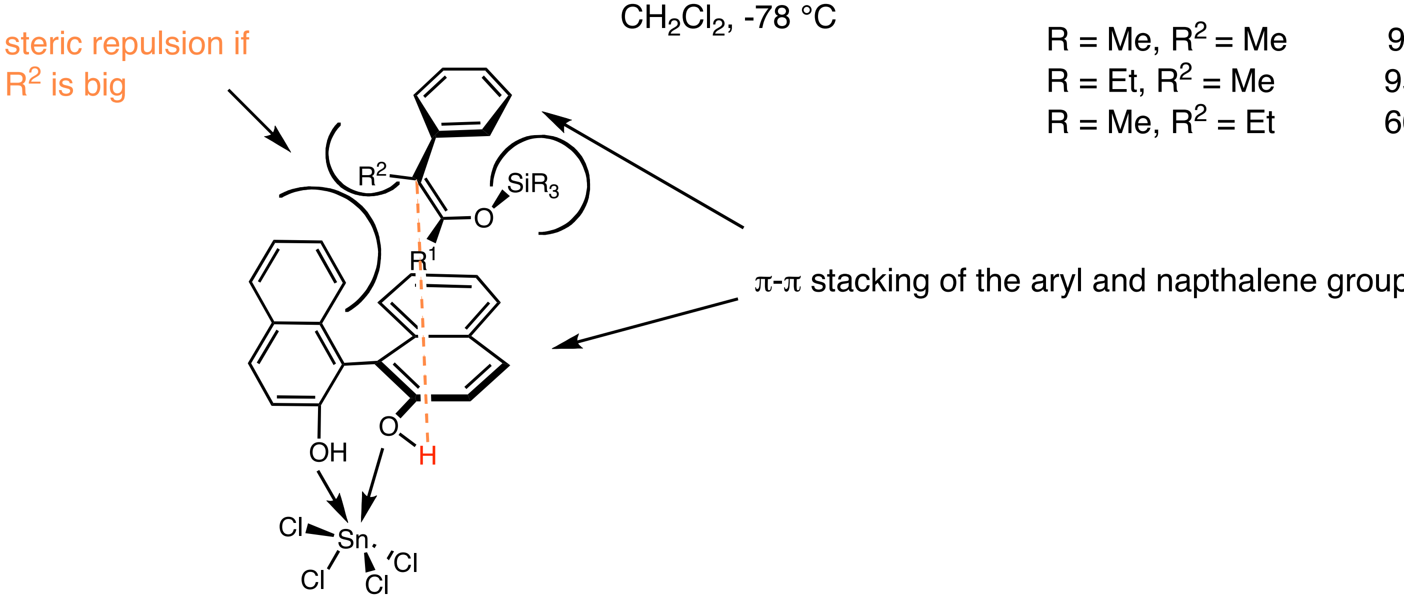


LBA (*R*)-1

■ LBA for enantioselective protonation of ketene bis(trialkylsilyl) acetals



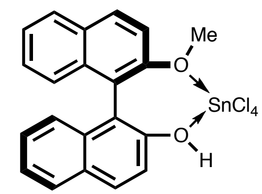
R = Me, R^2 = Me	92% ee
R = Et, R^2 = Me	95% ee
R = Me, R^2 = Et	60% ee



Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

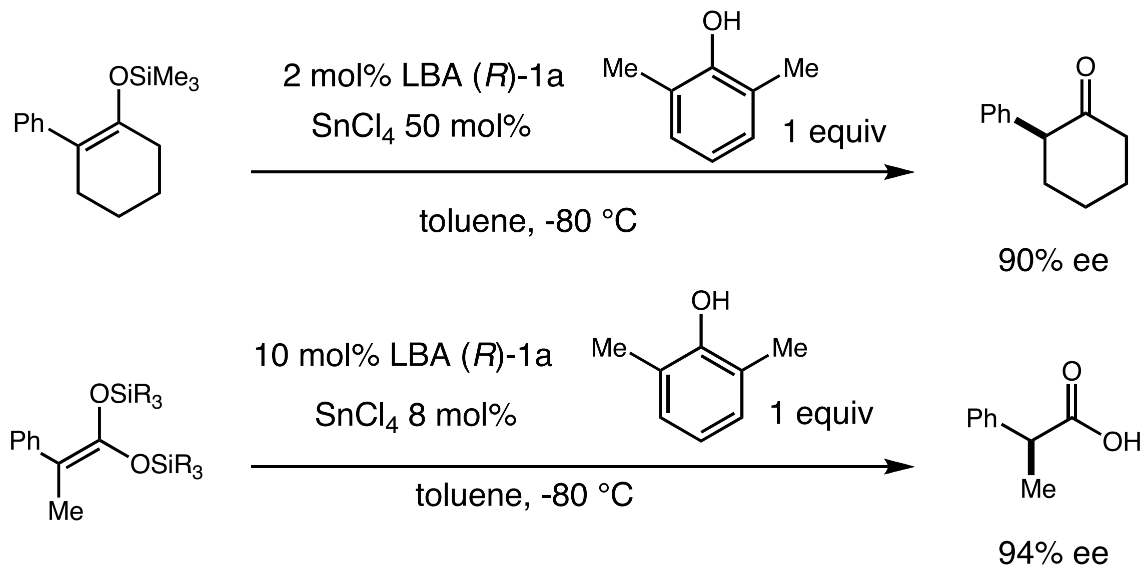
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"

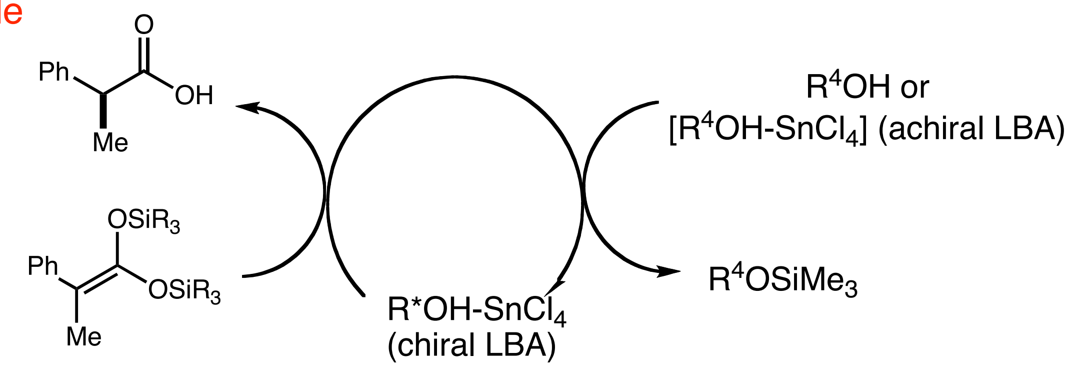


LBA (*R*)-1a

■ LBA for catalytic enantioselective protonation



■ Catalytic cycle

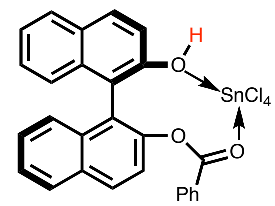


Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118,* 12854.

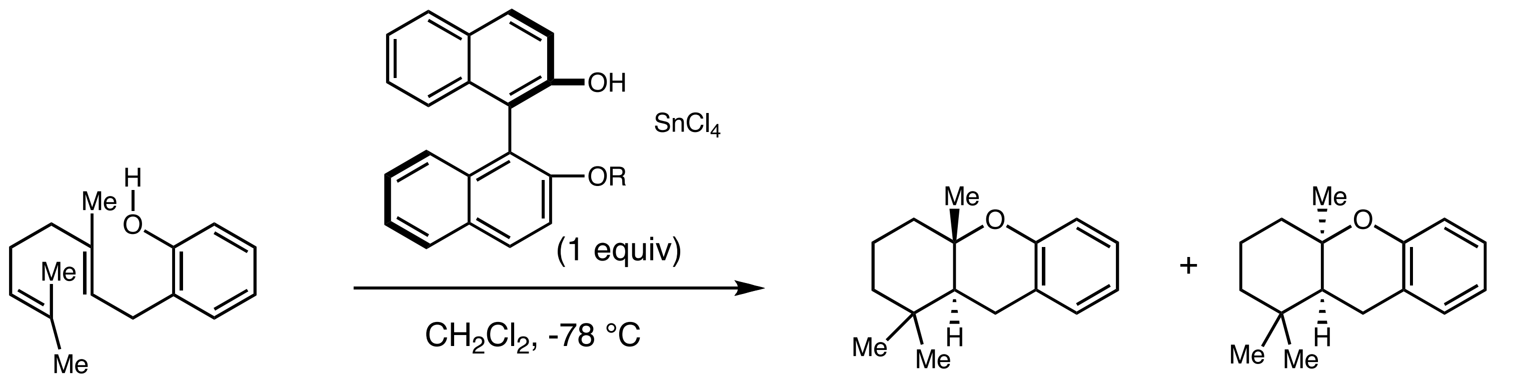
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"

■ LBA as artifical cyclases



LBA (*R*)-2



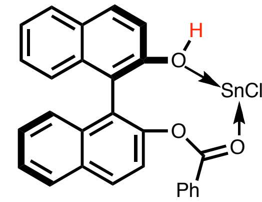
R = H	84% (36% ee), 16% (32% ee)
R = ^{i}Pr	>70%, (50% ee), >20% (34% ee)
R = COPh	95% (54% ee)

low enantioselectivity is attributed to coordination of phenol to catalyst

Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121,* 4906.

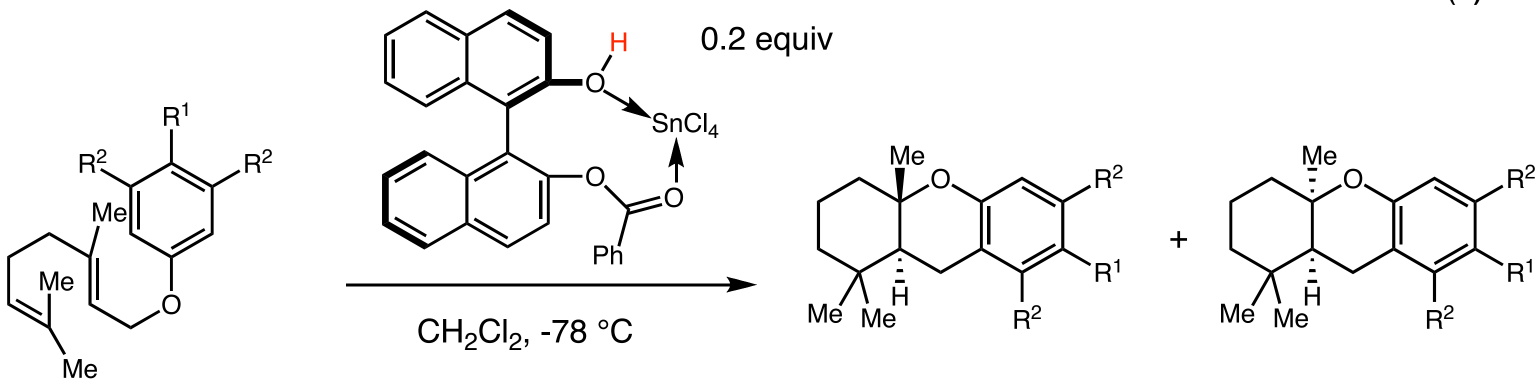
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"



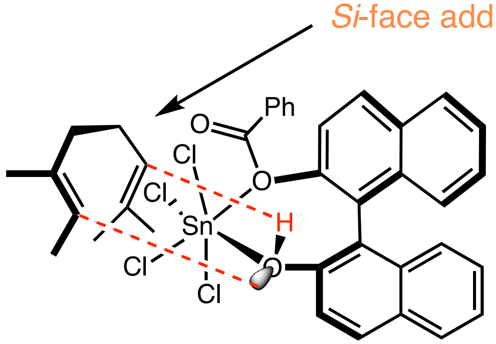
LBA (*R*)-2

■ LBA for enantioselective biomimetic cyclization of isoprenoids



R^1, R^2 = H	98% GCY, 77% ee, (98 : 2)
R^1 = F	72% GCY, 79% ee, (70 : 30)
R^1 = Cl	97% GCY, 82% ee, (97 : 3)
R^1 = Br	94% GCY, 90% ee, (95 : 5)
R^1 = Me	94% GCY, 67% ee, (97 : 3)
R^1 = OMe	92% GCY, 42% ee, (94 : 6)

Si-face addition

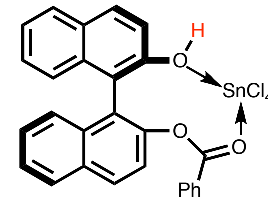


n-π* interaction between oxygen lone pair and LUMO of the olefin

Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121,* 4906.
Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122,* 8131.

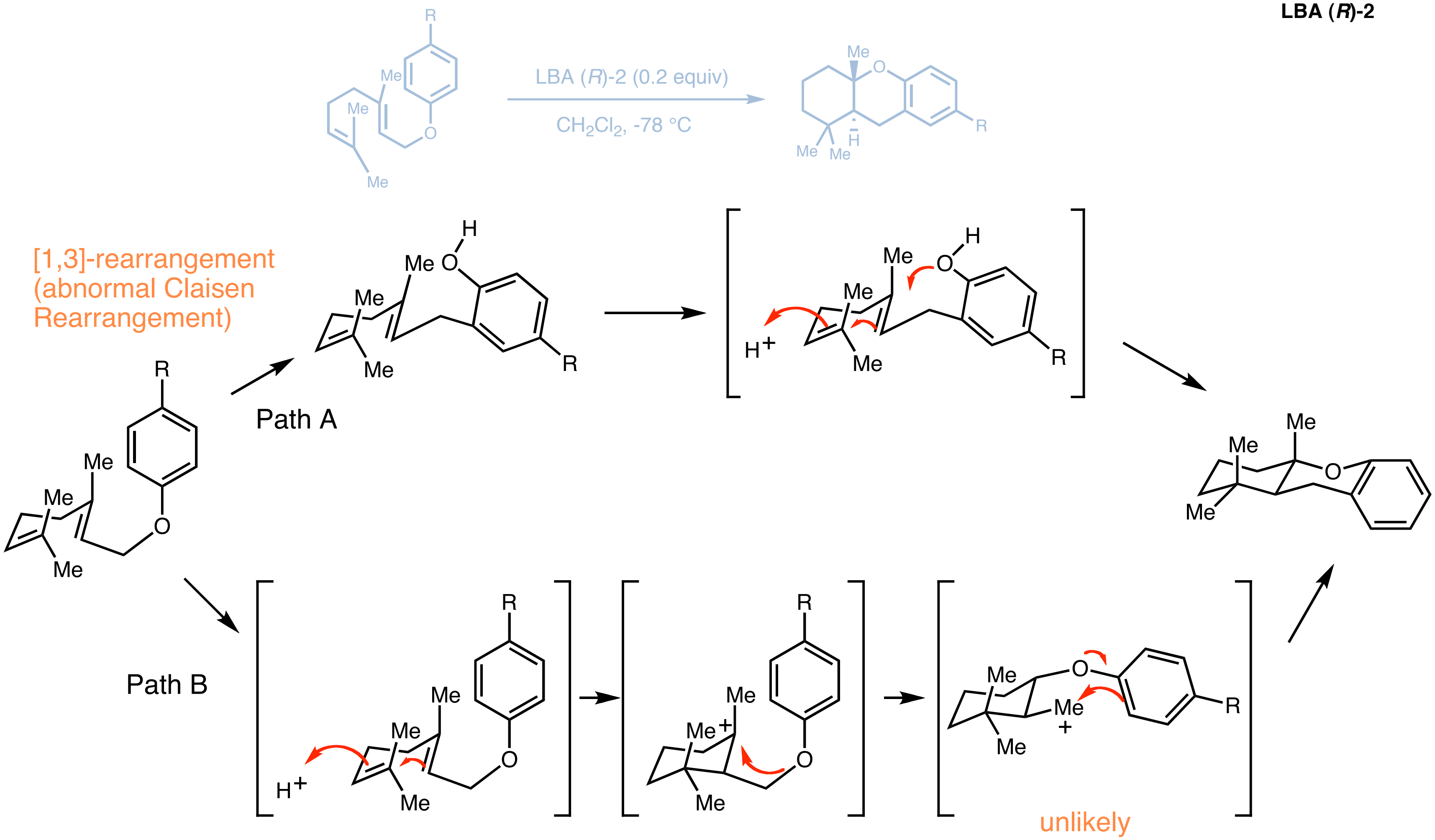
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"



LBA (*R*)-2

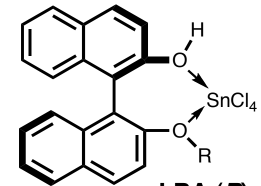
■ Mechanism of biomimetic cyclization of isoprenoids



Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122,* 8131.

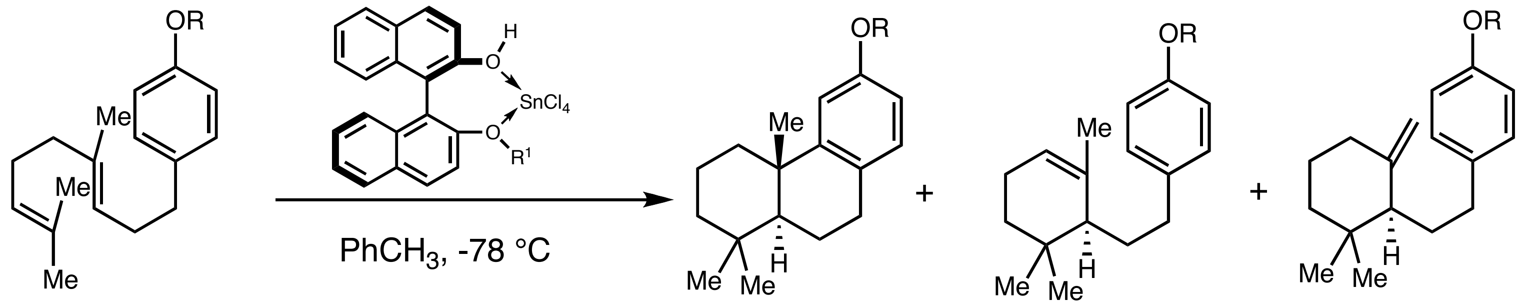
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"



LBA (*R*)-1

■ LBA for first enantioselective cyclization of homo(polyprenyl)arenes



A **B** **C**

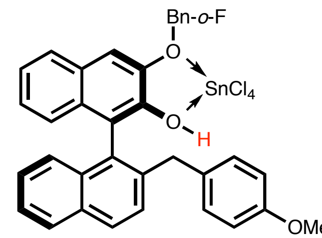
entry	cat (R^1)	substrate (R)	solvent/time (h)	% yield **A** (%ee)	% yield **B**	% yield **C**	SM
1	Me	H	CH_2Cl_2, 14	87 (38)	6	7	0
2	Me	H	$PhCH_3$, 14	28 (49)	40	32	0
3	Me	Me	$PhCH_3$, 19	10 (59)	36	36	18
4	Bn	Me	$PhCH_3$, 24	13 (61)	33	32	22
5	Me	$^tBuPh_2Si$	$PhCH_3$, 24	13 (72)	35	35	17
6	*o*-$FC_6H_4CH_2$	$^tBuPh_2Si$	$PhCH_3$, 48	9 (81)	44	47	0
7	$Ph_3SiCCCH_2$	$^tBuPh_2Si$	$PhCH_3$, 96	19 (80)	40	41	0

-subjecting **B** and **C** to achiral LBA lead to **A** , entry 3, 86% yield, 62% ee
-desilylating products from entry 6, 94% yield, 78% ee

Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123,* 1505.

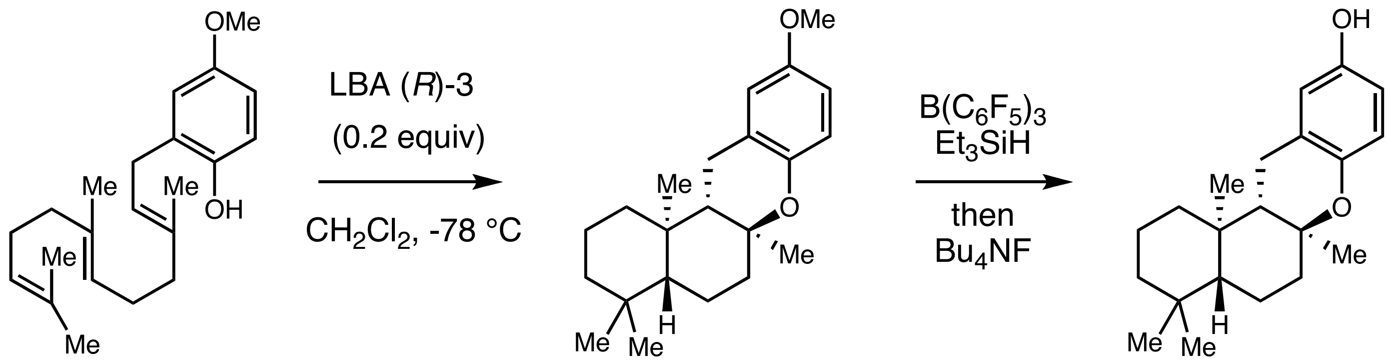
Lewis Acid Assisted Brønsted Acid Catalysts (LBA)

"unique proton"



LBA (*R*)-3

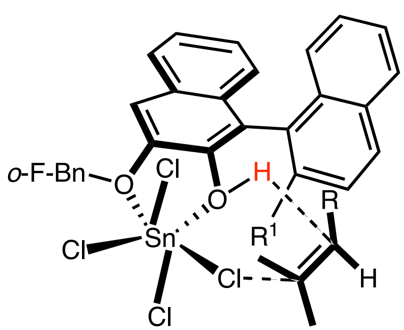
■ LBA for enantioselective total synthesis of (–)-chromazonarol



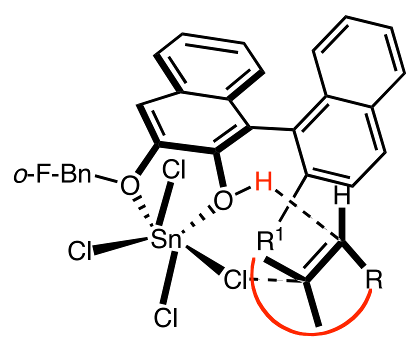
69% dr, 88% ee

83% dr, 91% ee

39% overall yield



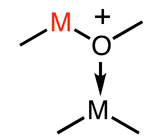
Re-face addition of alkene

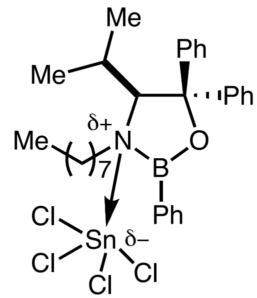


steric repulsion

Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126,* 11122.

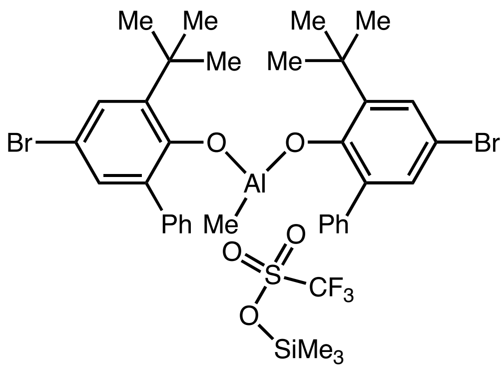
Lewis Acid Assisted Lewis Acid Catalysts (LLA)





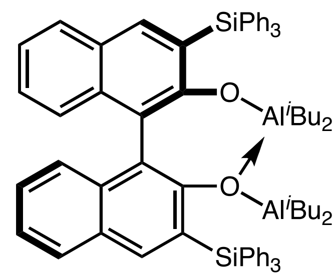
oxazaborolidine

enantioselective DA



MABR/Me$_3$SiOTf

Mukaiyama aldol reaction

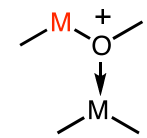


dialuminum binol complex

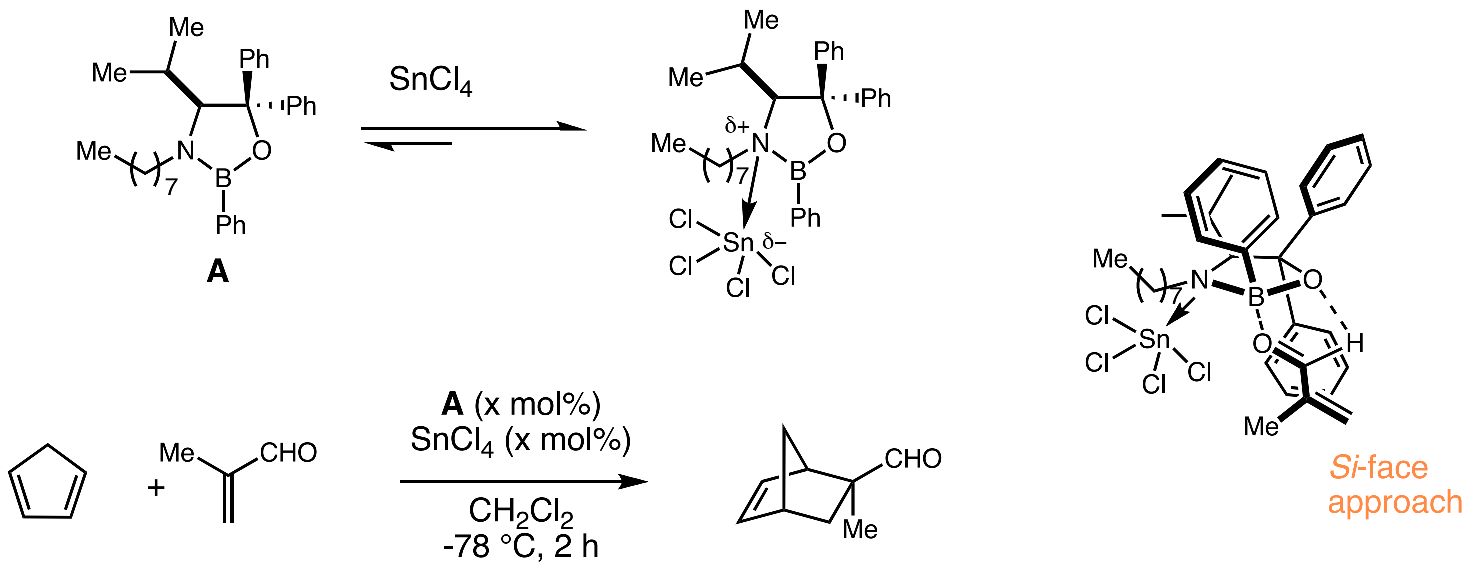
enantioselective DA

Yamamoto, H.; Futatsugi, K.; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

Lewis Acid Assisted Lewis Acid Catalysts (LLA)



■ Oxazaborolidine promoted enantioselective Diels–Alder reaction

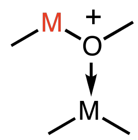


1 mol% **A**, 1 mol% $SnCl_4$ — 95%, (75 : 25) *exo* : *endo*, 84% ee (*exo*), 96% ee (*endo*)
2 mol% **A**, 0.5 mol% $SnCl_4$ — 86%, (75 : 25) *exo* : *endo*, 85% ee (*exo*), 96% ee (*endo*)

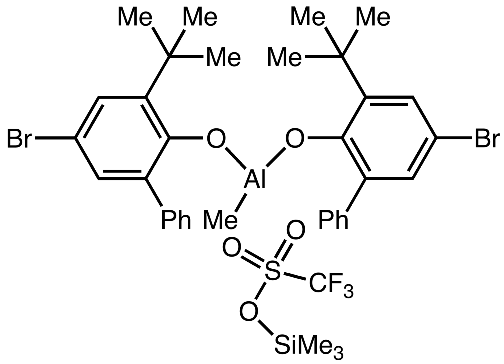
-since only small amounts of $SnCl_4$ is required to maintain high yield and ee,
excess $SnCl_4$ can coordinate H_2O (other deactivators for LA) to maintain reactivity and selectivity
therefore, ideal conditions are possible: non-purified LA, reagent-grade solvents, air

Futatsugi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1484.

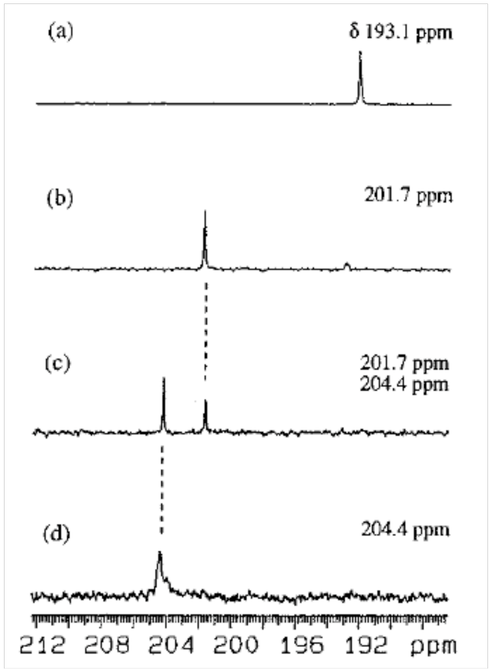
Lewis Acid Assisted Lewis Acid Catalysts (LLA)



■ LLA for the generation of naked silylium cation

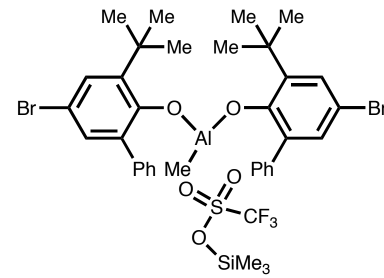


MABR/Me_3SiOTf



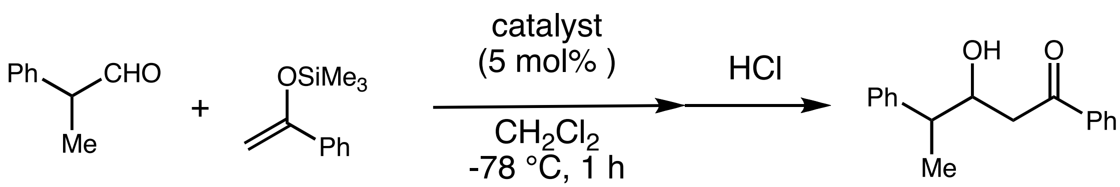
Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271.

Lewis Acid Assisted Lewis Acid Catalysts (LLA)



MABR/Me_3SiOTf

■ LLA for the enhancement of the Mukaiyama Aldol reaction

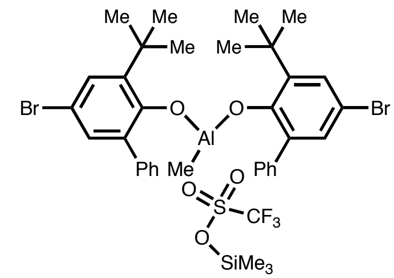


Entry	catalyst	% yield	*syn* : *anti*
1	$B(OTf)_3$	41	89 : 11
2	$Me_3SiOTf/B(OTf)_3$	43	90 : 10
3	Me_3SiOTf	15	75 : 25
4	Me_3SiOTf/MAD	62	91 : 1
5	Me_3SiOTf/MABR	76	89 : 11

unsubstituted and neopentyl aldehydes are compatible

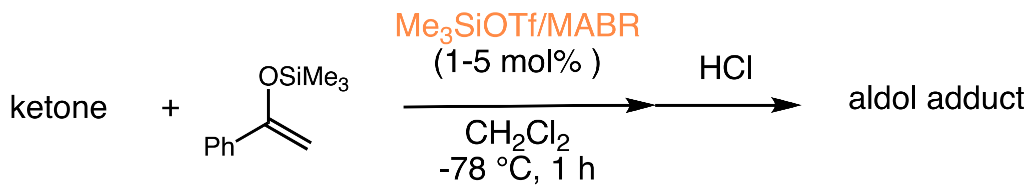
Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271.

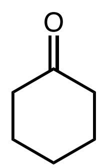
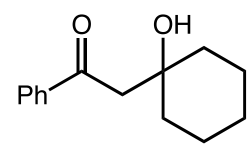
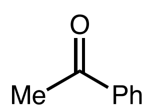
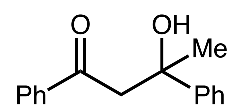
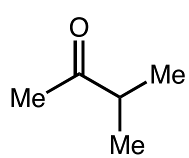
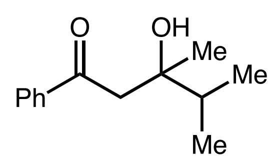
Lewis Acid Assisted Lewis Acid Catalysts (LLA)



MABR/Me_3SiOTf

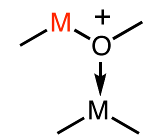
■ LLA enhancement of the Mukaiyama Aldol reaction: Substrate scope



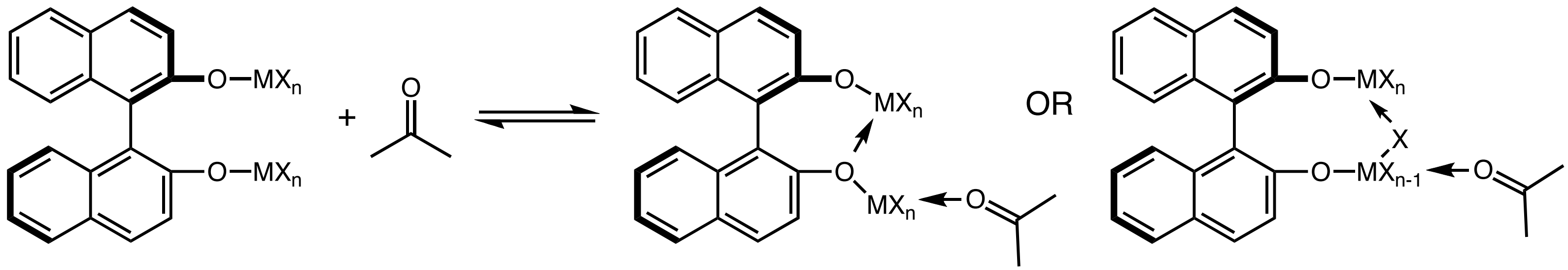
entry	ketone	aldol adduct	% yield
1			90
2			60
3			91

Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271.

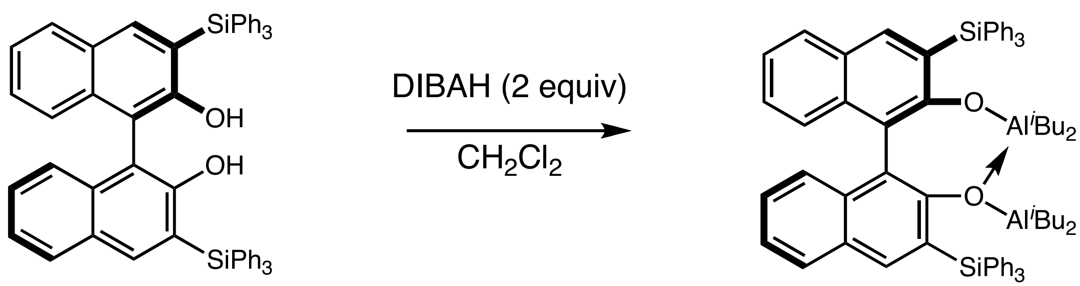
Lewis Acid Assisted Lewis Acid Catalysts (LLA)



■ Multinuclear chiral organoaluminum complexes: Binapthol derivatives

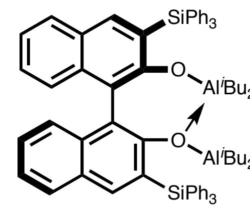


■ Synthesis of chiral dialuminum binol complex

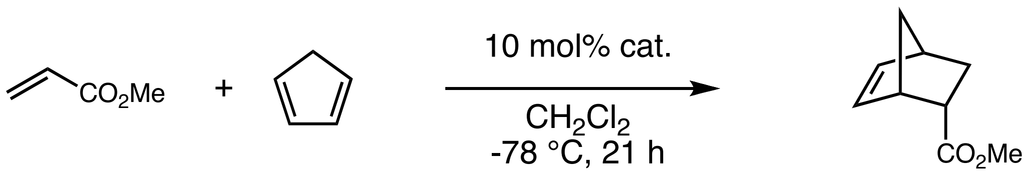


Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett,* **2001**, 394.

Lewis Acid Assisted Lewis Acid Catalysts (LLA)



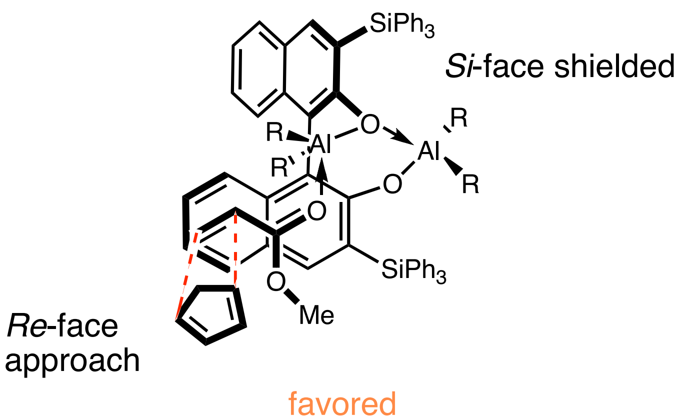
■ Enantioselective Diels–Alder reaction

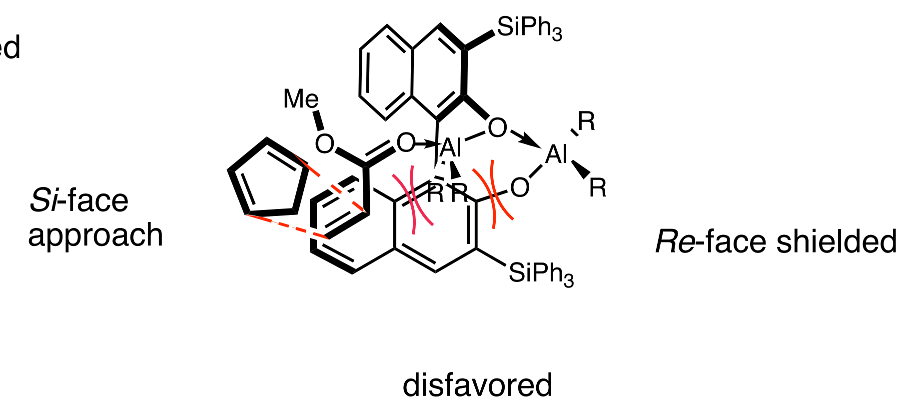


46%, 86% ee, 97 : 3 (*endo* : *exo*)
*99%, 80% ee, 97 : 3 (*endo* : *exo*)

* -78 to -40 °C, 42 h

■ Model for selectivity

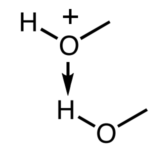


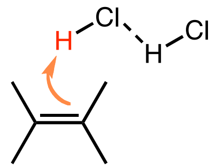


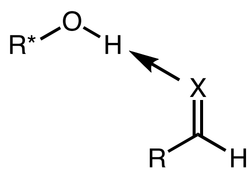
Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett*, **2001**, 394.

Brønsted Acid Assisted Brønsted Acid Catalysts (BBA)

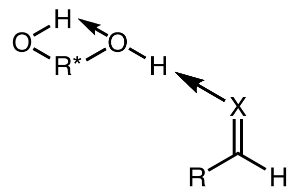
enzyme-like



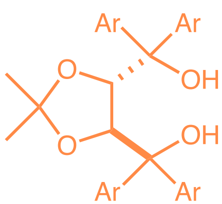




BA



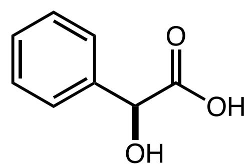
BBA



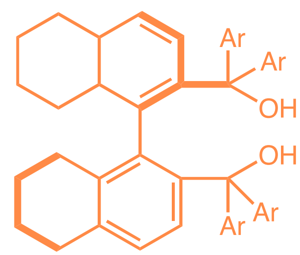
TADDOL

hetero Diels–Alder

enantioselective *N*-nitroso aldol



enantioselective *O*-nitroso aldol



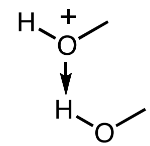
BAMOL

hetero Diels–Alder

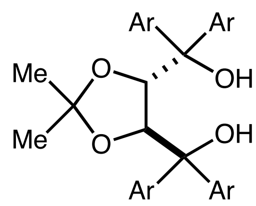
Yamamoto, H.; Futatsugi, K.; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

Brønsted Acid Assisted Brønsted Acid Catalysts (BBA)

enzyme-like

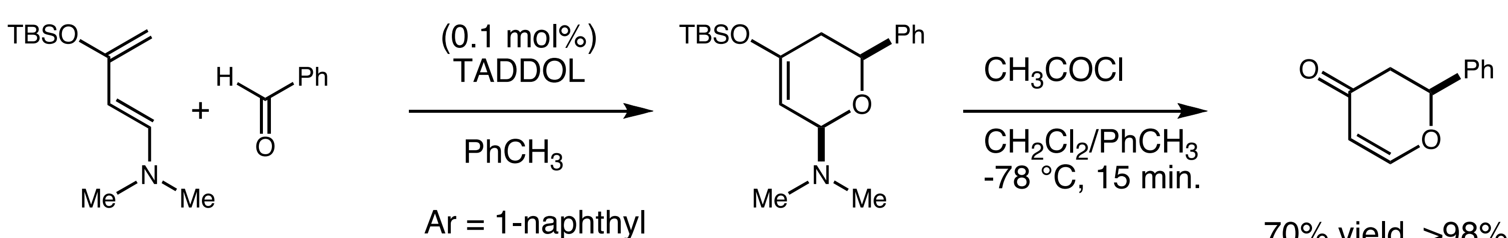


■ BBA: TADDOL



TADDOL

■ TADDOL for enantioselective hetero Diels–Alder reactions



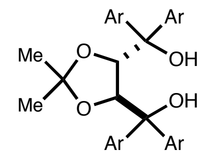
70% yield, >98% ee

various aromatic groups participate well
cyclohexyl lower ee

Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.
For a review on TADDOL, see Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

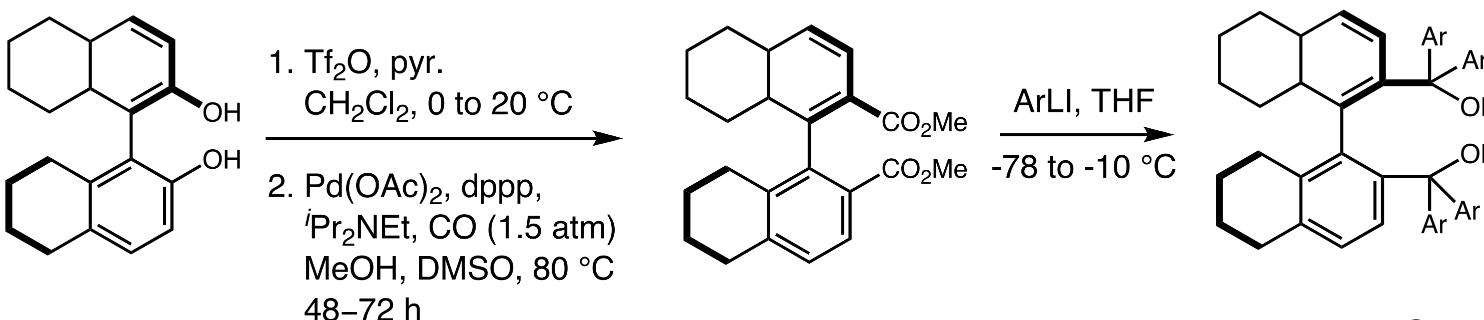
Brønsted Acid Assisted Brønsted Acid Catalysts (BBA)

enzyme-like



TADDOL

■ Synthesis of BAMOL

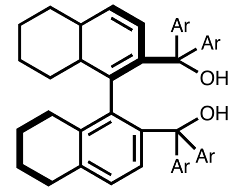


BAMOL

Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

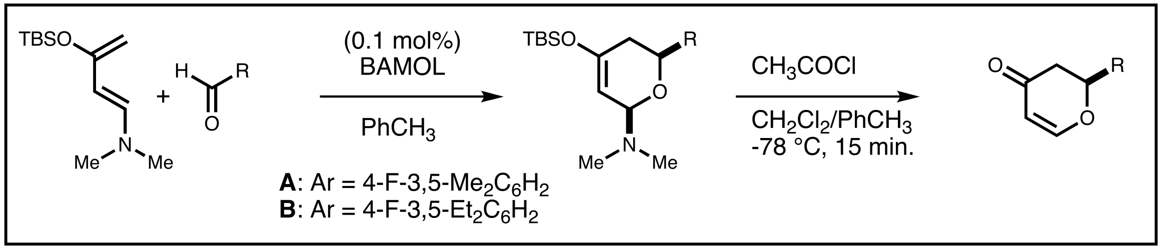
Brønsted Acid Assisted Brønsted Acid Catalysts (BBA)

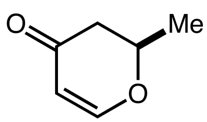
enzyme-like



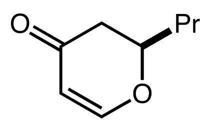
BAMOL

■ BAMOL for enantioselective hetero Diels–Alder reactions

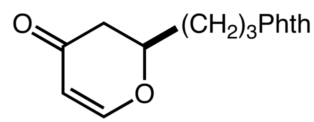




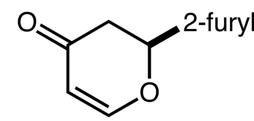
B: 75%, 97% ee



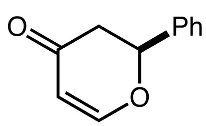
A: 76%, 94% ee



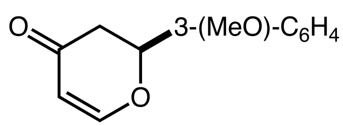
A: 67%, 92% ee



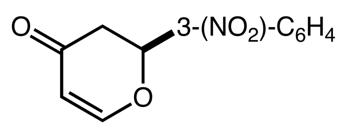
B: 96%, 99% ee
TADDOL: 67%, 92% ee



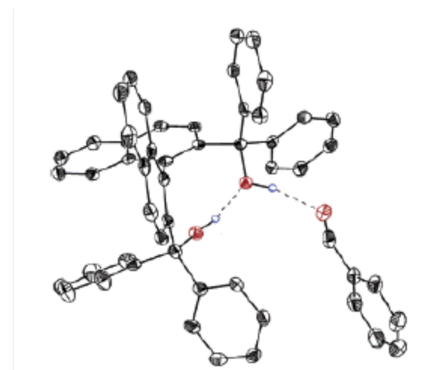
B: 84%, 98% ee
TADDOL: 70%, 98% ee



B: 86%, 98% ee
TADDOL: 68%, 94% ee



B: 93%, 98% ee



Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

Super Acids

strong

HOTf → $HNTf_2$

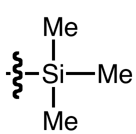
Super Brønsted acid

Mukaiyama aldol

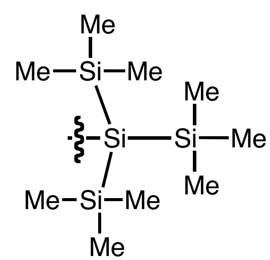
cascade Mukaiyama aldol

ketone Mukaiyama aldol

teriary carbinols



TMS

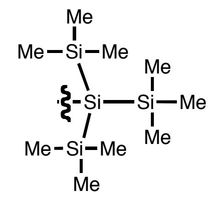


TTMSS

Super silyl

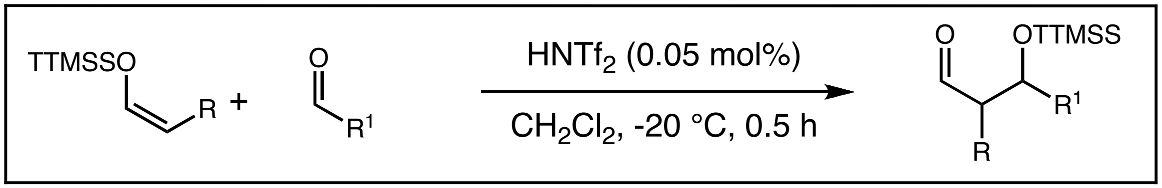
Boxer, M. B.; Albert, B. J.; Yamamoto, H. *Aldrichimica Acta* **2009**, *42*, 3.

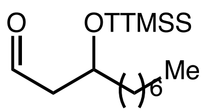
Super Silyl - TTMSS



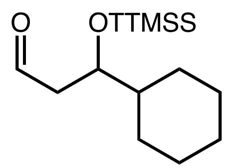
TTMSS
Super silyl

■ Mukaiyama Aldol reaction

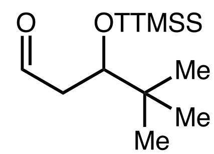




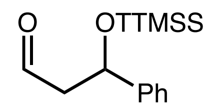
87% yield
w/ TBS, <10% yield



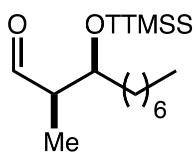
89% yield



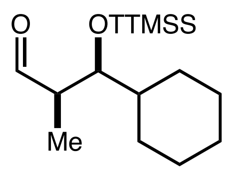
90% yield



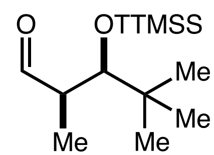
83% yield



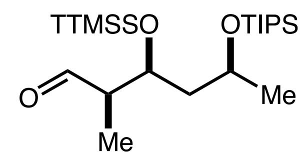
82% yield
80/20 *syn*/*anti*



72% yield
85/15 *syn*/*anti*



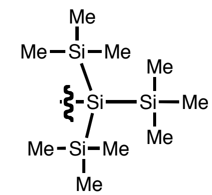
78% yield
95/5 *syn*/*anti*



88% yield
85/15 *syn*/*anti*

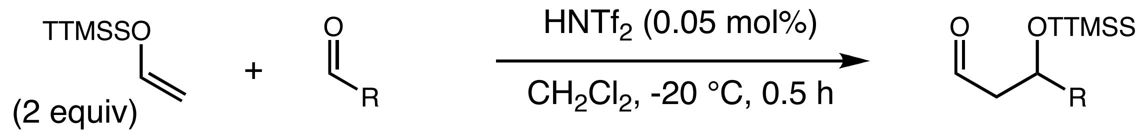
Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.

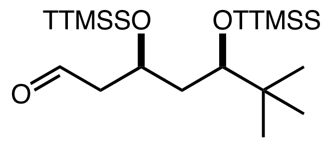
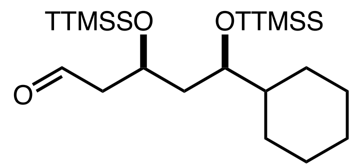
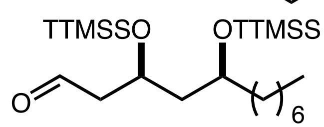
Super Silyl - TTMSS

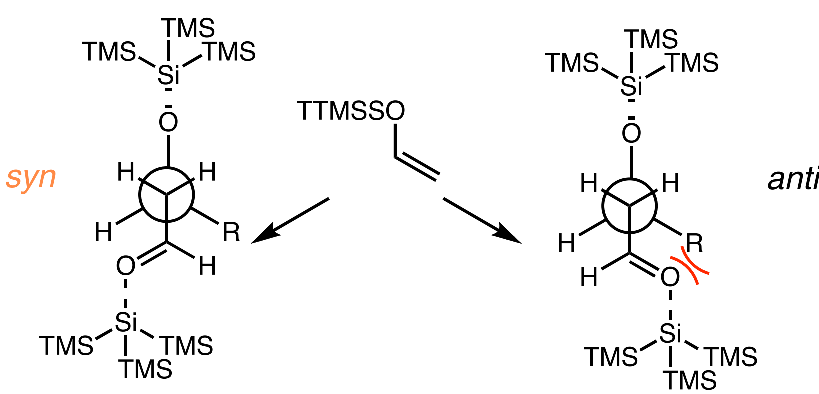


TTMSS
Super silyl

Cascade Mukaiyama aldol reaction

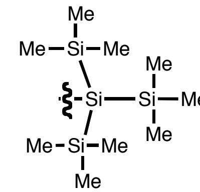


Entry	R	major product	% yield	*syn* : *anti*
1	^{t}Bu		75%	>99 : 1
2	*c*-hexyl		72%	95 : 5
3	$(CH_2)_6CH_3$		68%	90 : 10



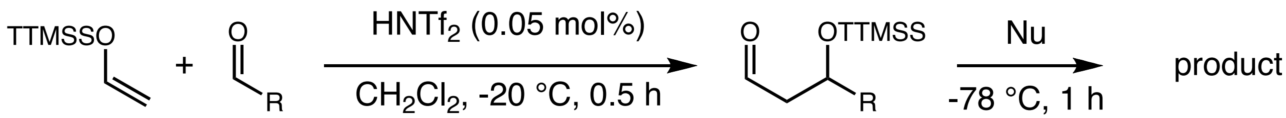
Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.

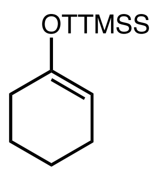
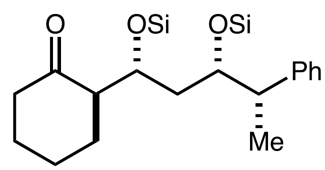
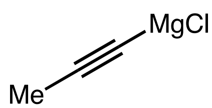
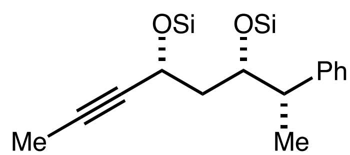
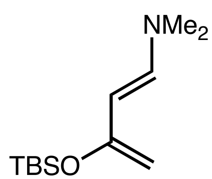
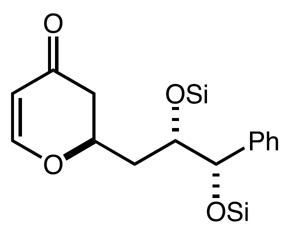
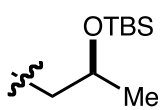
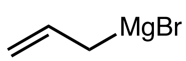
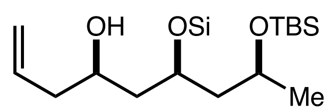
Super Silyl - TTMSS



TTMSS
Super silyl

■ Complex chiral architecture

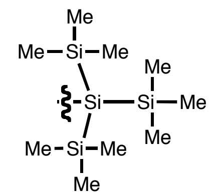


entry	R	nucleophile	major product	% yield	dr
1	CH(Me)Ph			80%	97/2<1/<1
2	CH(Me)Ph			79%	86/13/<1/<1
3	CH(Me)Ph			63%	95/4/<1/<1
4				85%	74/18/<5/<5

Si = TTMSS

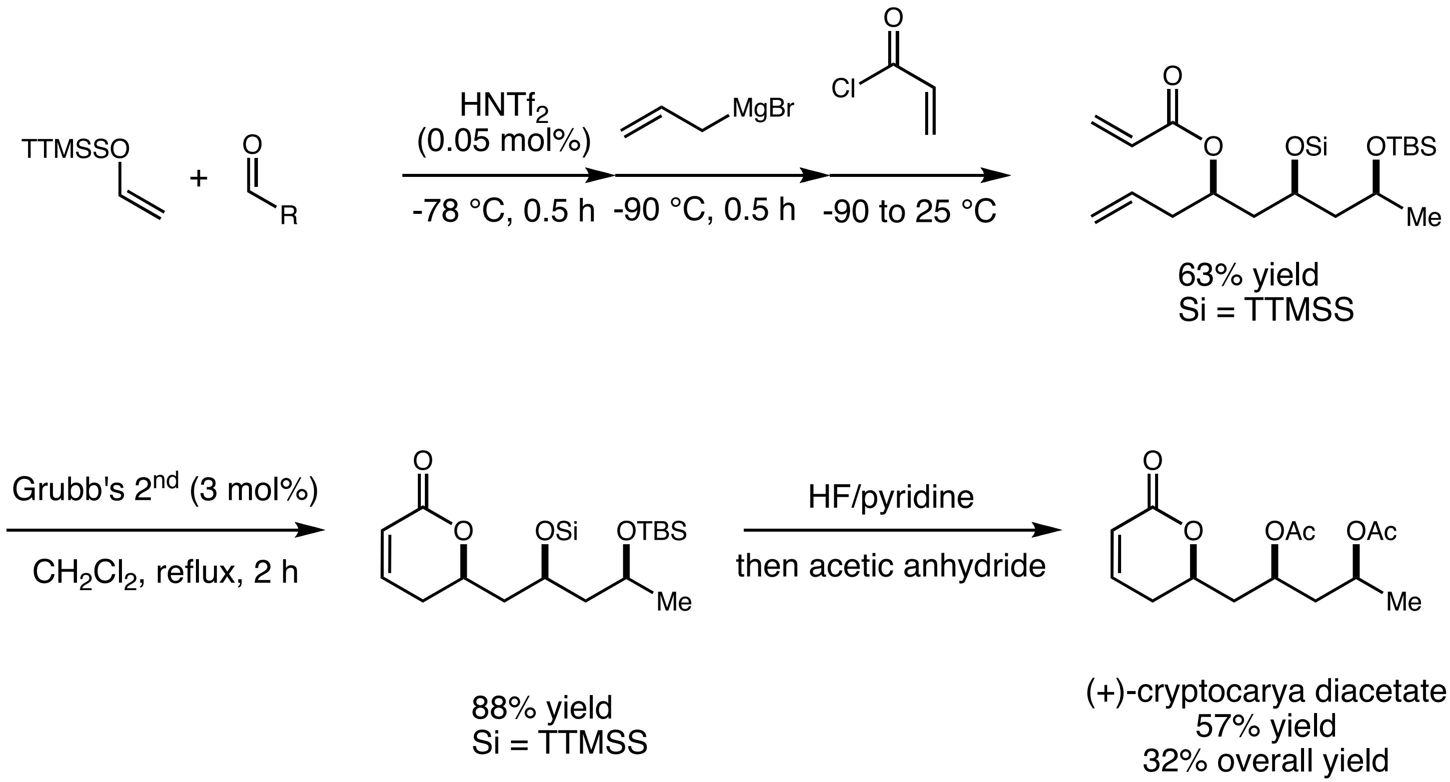
Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762.

Super Silyl - TTMSS



TTMSS
Super silyl

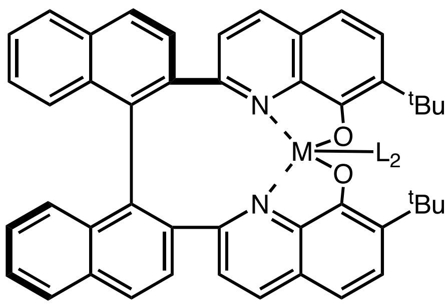
■ Three-step synthesis of (+)-cryptocarya diacetate



Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762.

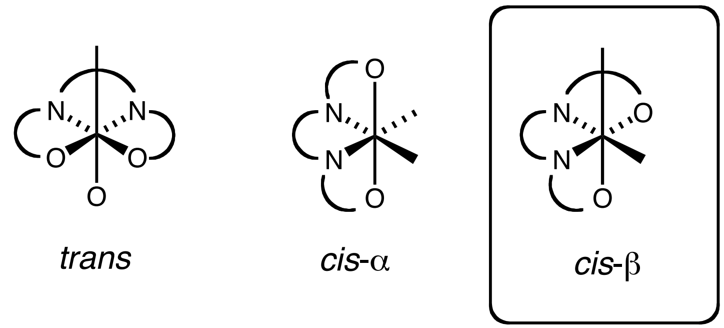
Tethered Bis(8-quinolinolato) Metal Complexes

■ Properties of tethered bis(8-quinolinolato) metal complexes

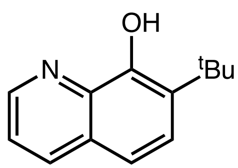


TBOxM

three possible geometric isomers



X-ray



8-hydroxyquinoline

versatile ligand for a myriad of metal ions
forms stable complexes with most metals

TBOxCrCl

Pinacol coupling
Nozaki-Hiyama allylation
allenylation reaction

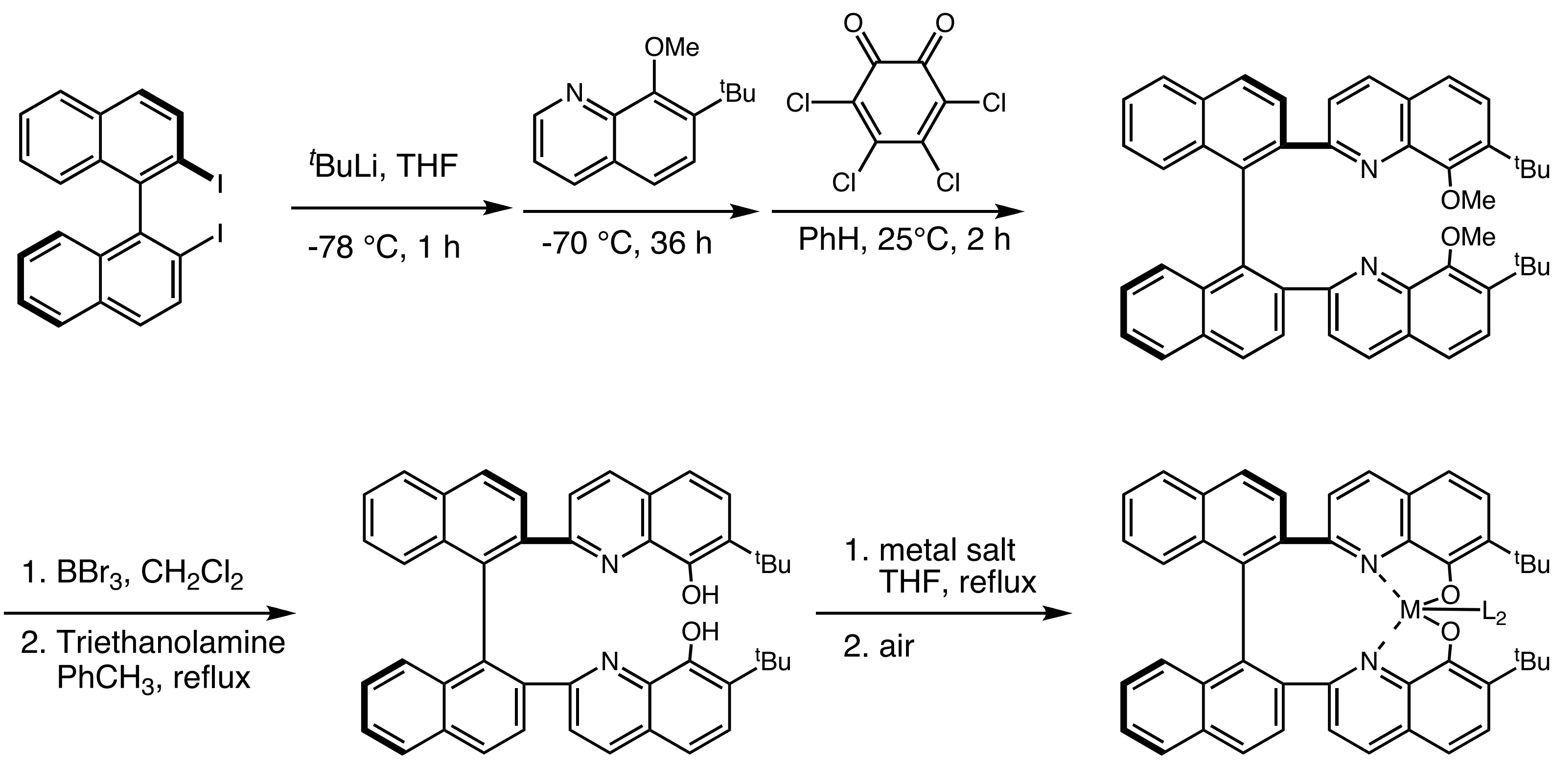
$TBOxAgSbF_6$

conjugate addition
indole Freidel–Crafts alkylation
Pudovik reaction

Takenaka, N.; Xia, G..; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198.
Yamamoto, H.; Xia, G. *Chem. Lett.* **2007**, *9*, 1082.

Tethered Bis(8-quinolinolato) Metal Complexes

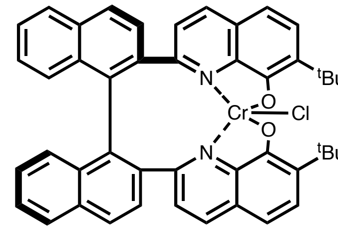
■ Synthesis of tethered bis(8-quinolinolato) metal complexes



TBOxH **TBOxM**

Takenaka, N.; Xia, G..; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198.

Tethered Bis(8-quinolinolato) Metal Complexes

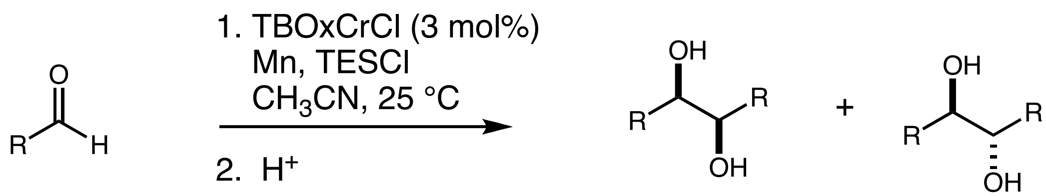


TBOxCrCl

■ Synthesis of TBOxCrCl

TBOxH + $CrCl_2$ —(THF, reflux / air oxidation)→ TBOxCrCl

■ Enantio- and diastereoselective Pinacol coupling with TBOxCrCl

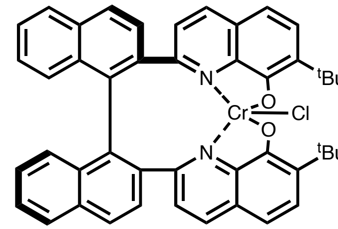


dl *meso*

R = Ph	94%, (98 : 2) *dl* : *meso*, 97% ee
o-MePh	93%, (98 : 2) *dl* : *meso*, 98% ee
p-MePh	93%, (97 : 3) *dl* : *meso*, 97% ee
m-MePh	92%, (98 : 2) *dl* : *meso*, 97% ee
p-BrPh	91%, (97 : 3) *dl* : *meso*, 98% ee
1-naph	92%, (96 : 4) *dl* : *meso*, 98% ee
c-hexyl	44%, (93 : 7) *dl* : *meso*, 84% ee

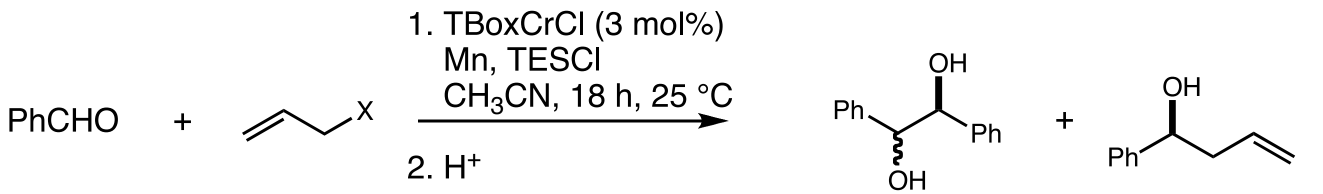
Takenaka, N.; Xia, G..; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198.

Tethered Bis(8-quinolinolato) Metal Complexes

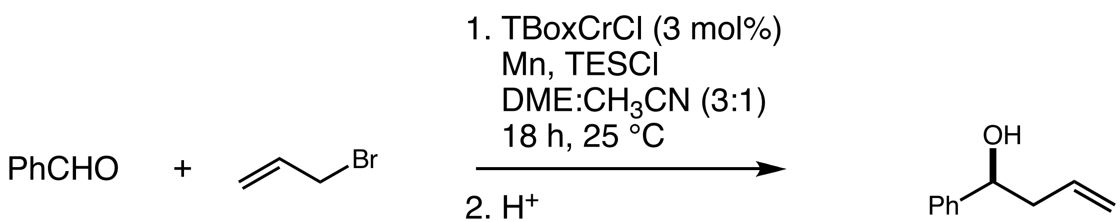


TBOxCrCl

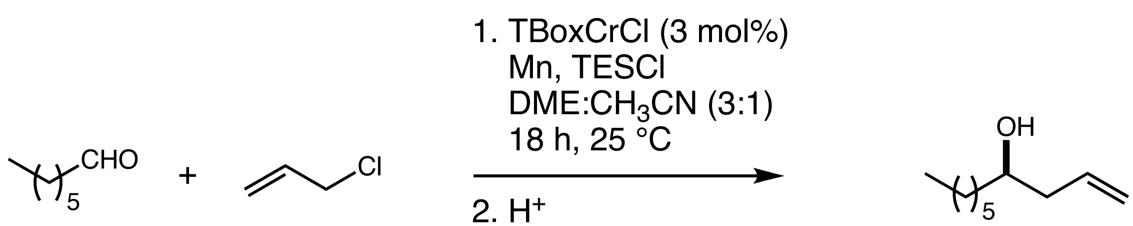
■ Enantioselective Nozaki-Hiyama allylation reaction with TBOxCrCl



EWG, EDG, heteroaromatics tolerable	X = Cl	75%	10%, 73% ee
	X = Br	<5%	82%, 74% ee



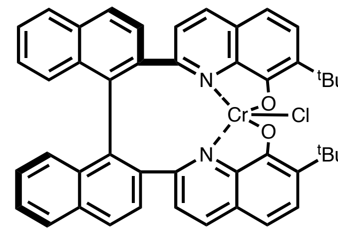
93%, 98% ee



76%, 98% ee

Xia, G..; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554.

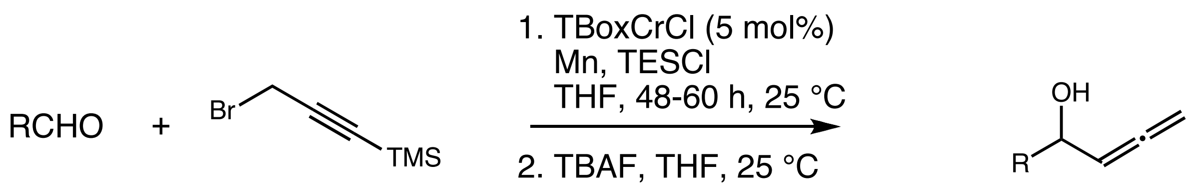
Tethered Bis(8-quinolinolato) Metal Complexes



TBOxCrCl

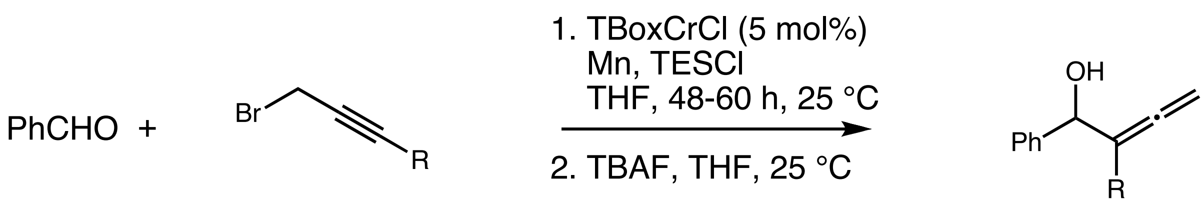
■ Enantioselective allenylation reaction with TBOxCrCl

■ Aldehyde scope



R = 4-(MeO)-C_6H_4	81%, 95%ee
4-Br-C_6H_4	57%, 92% ee
2-furyl	79%, 97% ee
c-hexyl	72%, 90% ee
$(CH_2)_7$	75%, 85% ee

■ Alkyne scope



R = Me	84%, 97% ee
Et	87%, 95% ee
Ph	58%, 88% ee

Xia, G..; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496.

"If a molecule used to be made in 20 steps,
but you can now make it in three then that changes the world."

-H. Yamamoto