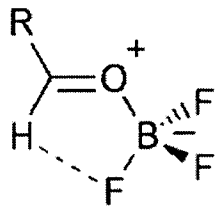
Formyl C-H···O Hydrogen Bonds

A Predictive Tool?



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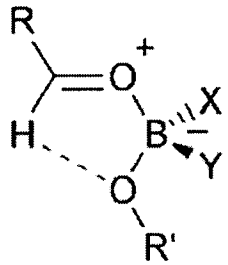

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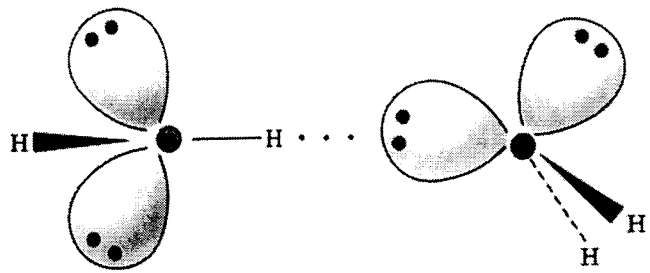
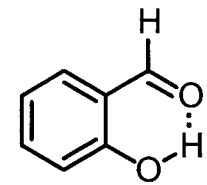
Justin Montgomery

September 17, 2002

Hydrogen Bonds





- hydrogen bond – "A strong dipole-dipole interaction (1-9 kcal mol^{-1}) that occurs between hydrogen atoms bonded to small strongly electronegative atoms (O, N, or F) and the nonbonding electron pairs on other such electronegative atoms."[1]

- "Hydrogen bonds are structurally characterized by an H···A distance that is at least 0.5 Å shorter than the calculated van der Waals distance between these atoms."[2]

- "Although many searches have been made for hydrogen bonding where A is carbon, only three types of C-H bonds have been found that are acidic enough to form weak hydrogen bonds. These are found in terminal alkynes (RC≡CH), chloroform and some other halogenated alkanes, and HCN."[3]

- "There is moderately abundant evidence that aldehydes undergo specific interactions with other groups (intramolecular) and other molecules (intermolecular). However, perhaps more than is the case with any other C-H containing groups, there has been considerable controversy over the interpretation of the available evidence as to whether the aldehyde group participates…in hydrogen bonds."[4]

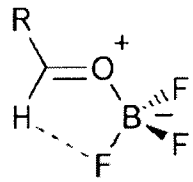
[1] T. W. G. Solomons, *Organic Chemistry*, 6th Ed, 1996.

[2] D. Voet, J. G. Voet, *Biochemistry*, 2nd Ed, 1995.

[3] M. B. Smith and J. March, *Advance Organic Chemistry*, 5th Ed, 2001.

[4] R. D. Green, *Hydrogen Bonding by C-H Groups*, Halsted Press, NY, 1974.

Evidence for Formyl CH···O H-Bonds



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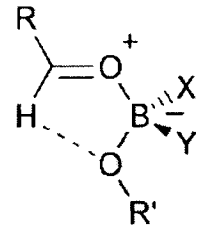

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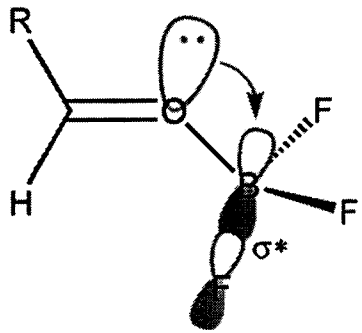
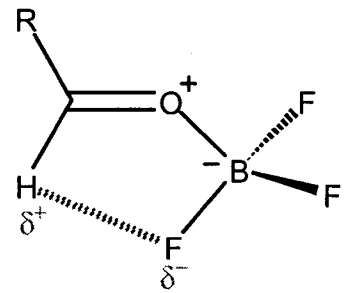




- A negative hyperconjugation (anomeric effect) is present when one B-F bond is antiperiplanar to the oxygen lone pair (eclipsed conformation)
- Maximum stabilization when dihedral angle of C-O-B-F = 0°

- Coordination of Lewis acid increases positive charge at the formyl hydrogen and increases electron density at the fluorine atoms attached to boron
- H···F bond distance of 2.35-2.36 Å is below the sum of the van der Waals radii of 2.67 Å (H = 1.20 Å, F = 1.47 Å)

Two competing interactions?

M. T. Reetz, M. Hüllmann, W. Massa, S. Berger, P. Rademacher, P. Heymanns, *J. Am. Chem. Soc.* **1986**, *108*, 2405.

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

B. W. Gung, M. A. Wolf, *J. Org. Chem.* **1992**, *57*, 1370.

X-Ray Evidence for Formyl CH H-Bonds

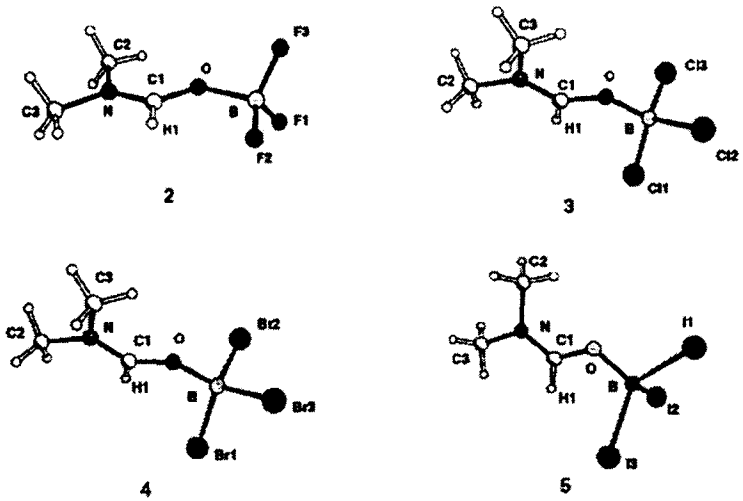
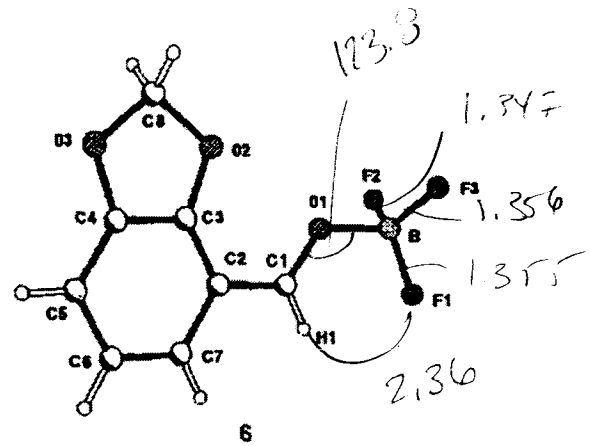


Figure 1. X-ray crystal structures of DMF•BX_3, X = F, Cl, Br, I (**2**, **3**, **4**, **5**).



Aldehyde BF_3 Complex

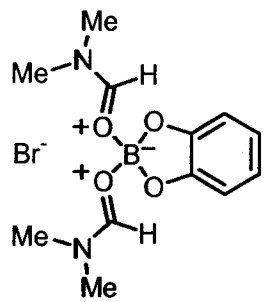
DMF·BF_3 (**2**)

- eclipsed-coplaner (6.5°) B-F/formyl arrangement (**3-5** are not)
- Formyl H···F distance = 2.35 Å (sum of radii = 2.67Å)

- HCBF dihedral angle = 10°
- H-F distance = 2.36 Å

E. J. Corey, J. J. Rohde, A. Fischer, M. D. Azimioara, *Tetrahedron Lett.* **1997**, *38*, 33.

X-Ray Evidence for Formyl CH H-Bonds (2)



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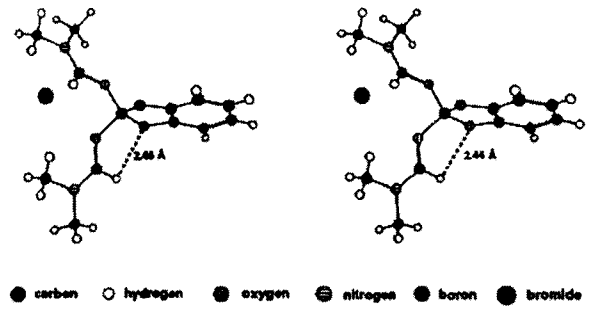
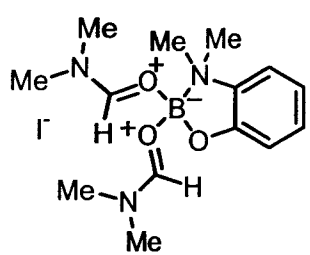


Figure 2. Stereopair representation of the DMF complex **7**.

- One DMF has 14° dihedral angle with B-O bond
- 2.46 Å H-O distance (sum of radii = 2.72 Å)
- Weak H-bond or steric effects?
- Why not two H-bonds?



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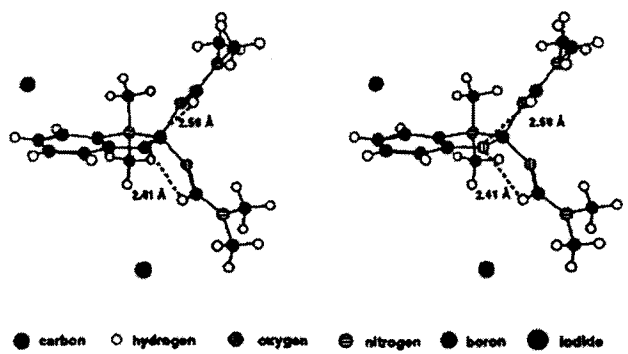


Figure 3. Stereopair representation of the DMF complex **8**.

1.460

- Two formyl H's within bond radii (2.41 Å, 2.59 Å)
- Weak H-bonds or steric effects?

E. J. Corey, J. J. Rohde, A. Fischer, M. D. Azimioara *Tetrahedron Lett.* **1997**, *38*, 33.

Calculating Relative Contribution of Anomeric Effect and H-Bonding

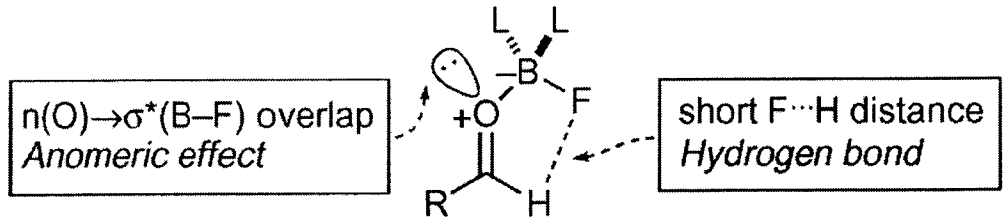


Fig. 1 Carbonyl H_2BF complexes: anomeric effect and hydrogen bond

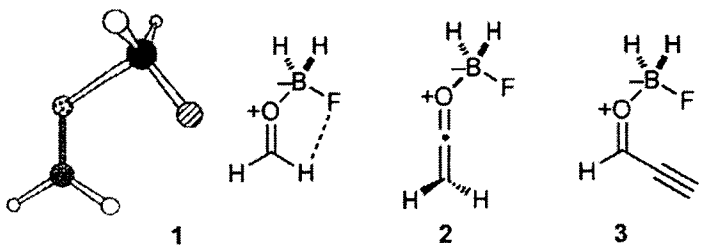


Fig. 2 Complexes with and without hydrogen bonds

Table 1 Results of calculations at the MP2/6-31G**//MP2/6-31G** level

Molecule	Barrier to rotation about O–B kJ mol^{-1}	H–F distance for lowest energy structure/Å	Strength of complexation/ kJ mol^{-1} [a]	C=O–B–F torsion angle for lowest energy structure (°)
1	15	2.20	48	0
2	1.4 [b]	—	15	0
3	6	—	34	0

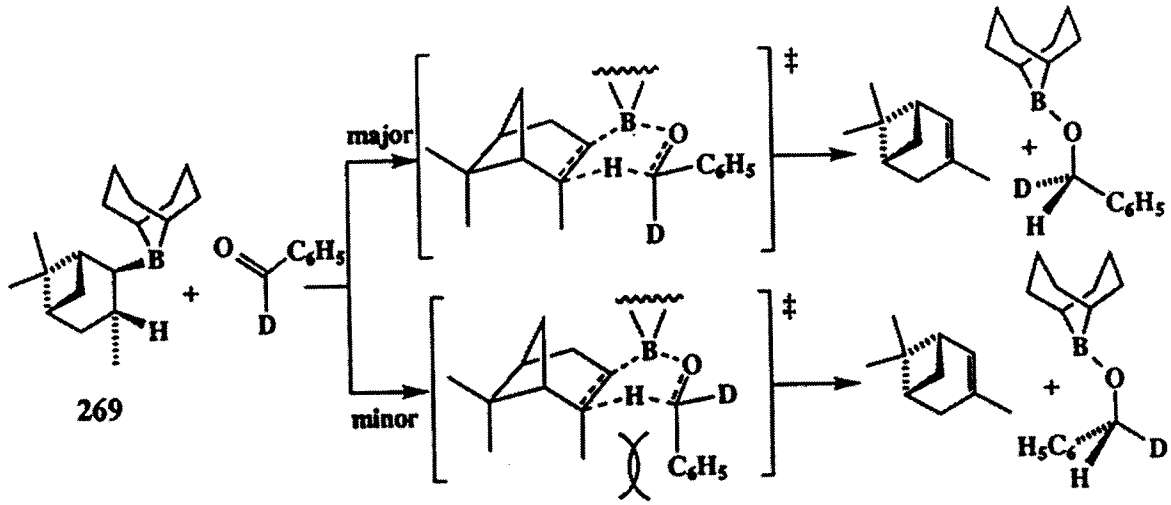
[a] No correction for BSSE or zero-point energy was made. [b] MP2/6-31G**//3-21G level.

"...if we accept the value of 6 kJ mol^{-1} for the anomeric effect, we are left with 9 kJ mol^{-1} (2.15 kcal mol^{-1}) to attribute to the hydrogen bonding interaction, for complex **1**. We may conclude, therefore, that both effects are important, but the hydrogen bonding interaction is probably larger."

M. D. Mackey, J. M. Goodman, *Chem. Commun.* **1997**, 2383.

Transition State Structure and Catalytic Enantioselective Synthesis

Understanding transition state structure and how it leads to enantioselection is essential to the application and extension of enantioselective reactions



Controlling Factors:

•Steric interactions

•Electronic requirements/interactions

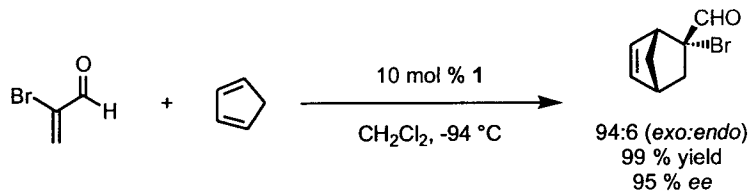
•Weak bonding/attractive forces (H-bonding)

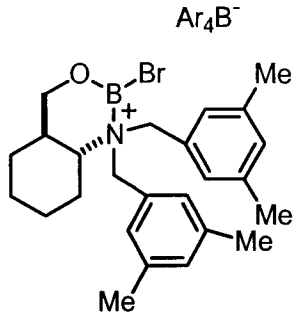
Understanding these factors allows for extension of current methodology as well as rational design of novel catalysts / ligands / reactions

E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994.

M. M. Midland, A. Tramontano, S. A. Zderic, *J. Am. Chem.* Soc. **1977**, *99*, 5211.

Diels-Alder RXN: Cationic Oxazaborinane Catalysis

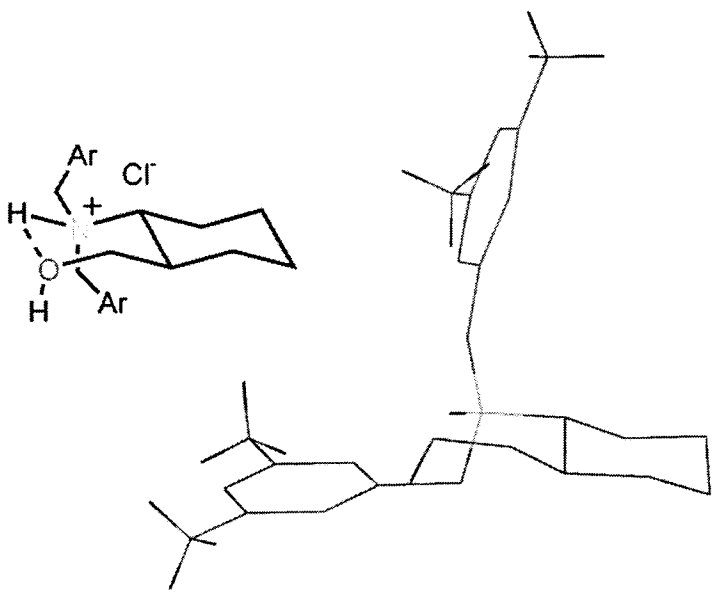




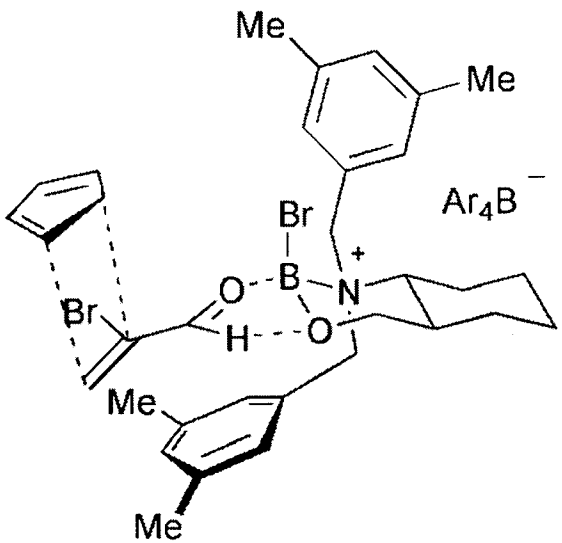
1

(Ar = C_6H_3-3,5-$(CF_3)_2$

X-Ray of Amine·HCl Salt



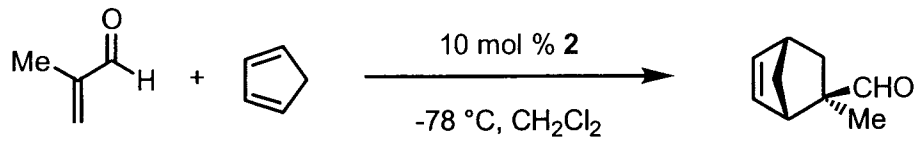
Proposed Transition State



Y. Hayashi, J. J. Rohde, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502.

E. J. Corey, J. J. Rohde, *Tetrahedron Lett.* **1997**, *38*, 37.

Diels-Alder RXN: Chiral Acyloxyborane (CAB) Catalysis



85% yield
96% *ee*
11/89 *endo/exo*

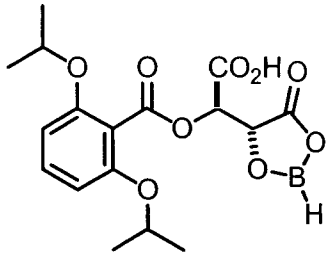


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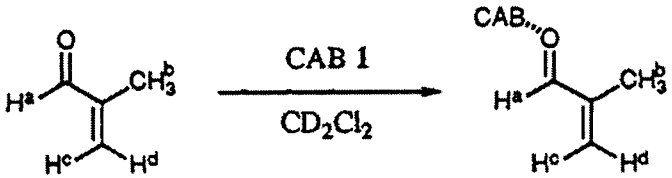
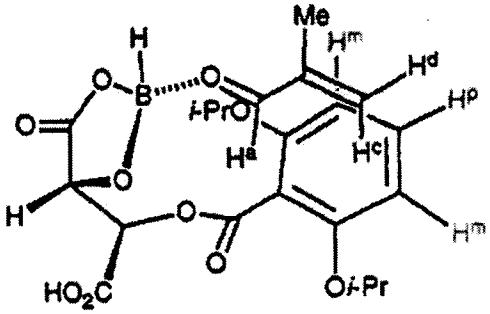
Table II. Summary of NOE Data for Methacrolein



complex	t (°C)	NOE (saturated/observed, %) H^a/H^b	H^a/H^c	H^a/H^d	H^c/H^a
methacrolein only	−95	0	6.3	0	18
methacrolein–1, R = H^b	−95	0	−10	0	6.3

[a] Calibrated probe temperature. [b] Complexed formed by addition of 0.72 equiv of the aldehyde to **1**.



methacrolein-1 (R = H)

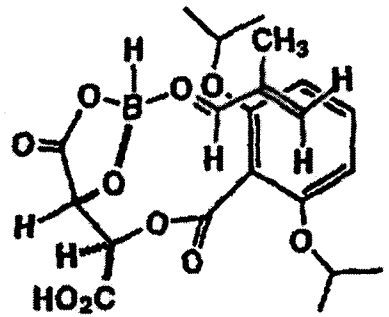
NOE (saturate/observe, %)			
$H^c/2H^m$	H^c/H^p	$H^d/2H^m$	H^d/H^p
-32	-12	-25	-29

the same condition with Table II

K. Furuta, S. Shimizu, Y. Miwa, H. Yamamoto, *J. Org. Chem.* **1989**, *54*, 1481.
K. Ishihara, Q. Gao, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 10412.

CAB Catalysis – H-Bonding

Experimentally obtained enantiomer



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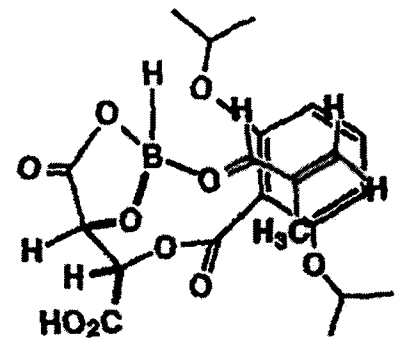

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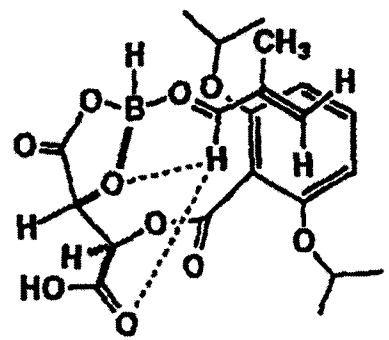

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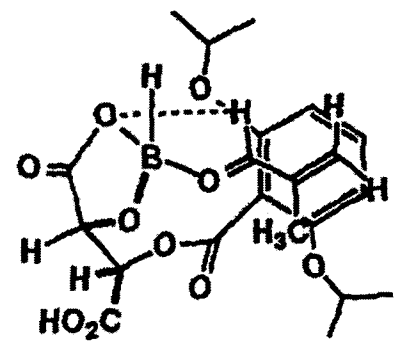


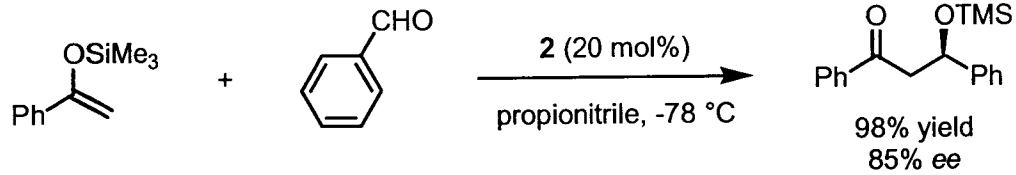
9

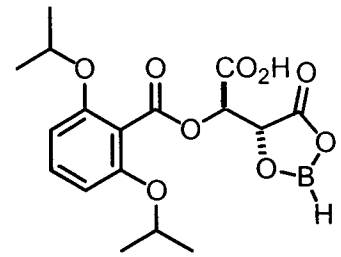
Wrong enantiomer

Transition structure **8** should be favored because it allows for *two* formyl H-bonds?!

E.J. Corey, J. J. Rohde, *Tetrahedron Lett.* **1997**, *38*, 37.

CAB Catalysis – Aldol Reaction





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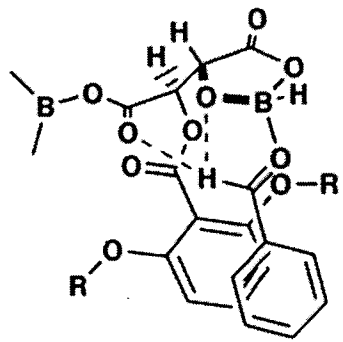
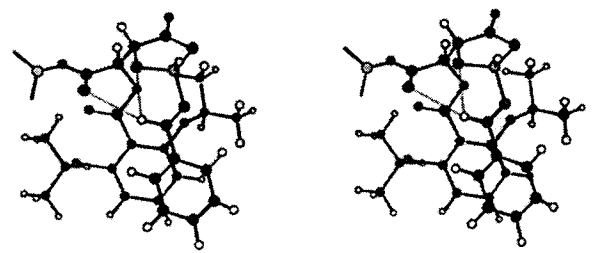
Corey's Transition Structure



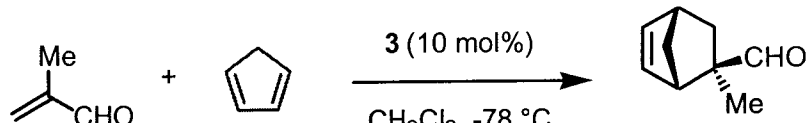


Bifurcated H-Bond leaves *re*-face of aldehyde exposed

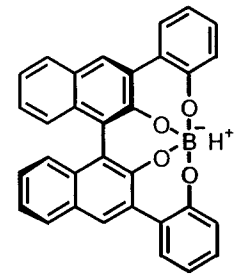
K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041.

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Diels-Alder Reaction: BLA Catalysis

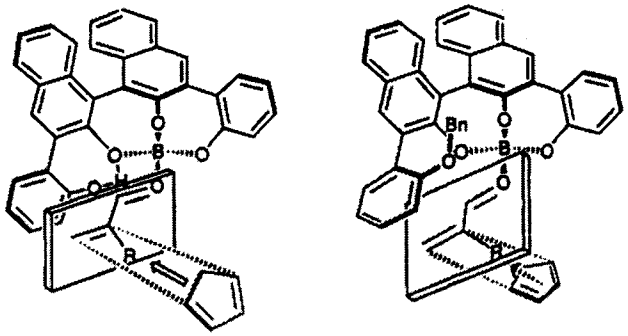


99 % yield
99 % *ee*
>99/1 *exo/endo*



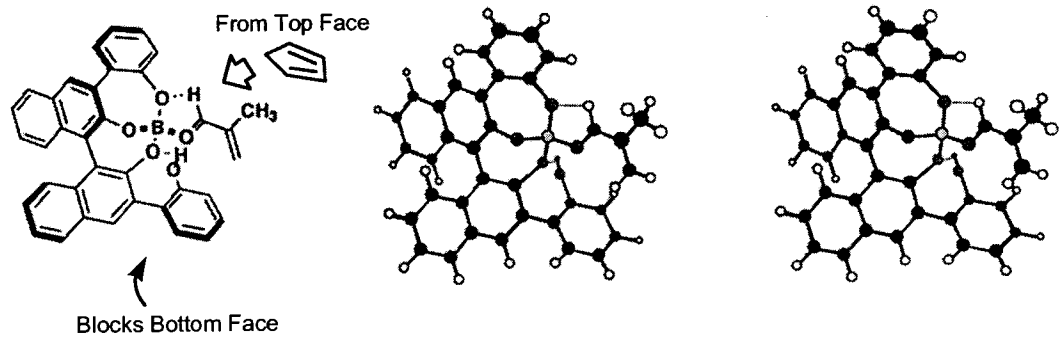
Brønsted Acid Assisted Chiral Lewis Acid (BLA) **3**

Yamamoto: s-*trans* proposal



Non-Helical Transition-State (A) *Helical* Transition-State (B)

Corey: s-*cis* proposal



- s-*trans* because it gives the right enantiomer for this proposal (doesn't give good reason to rule out s-*cis* but "steric compression factor" would favor s-*trans*)
- π-basic phenoxyl moiety and the π-acidic dienophile assume parallel orientation for donor-acceptor interaction (π-stacking)
- Triol (**B**) gives opposite enantioselectivity

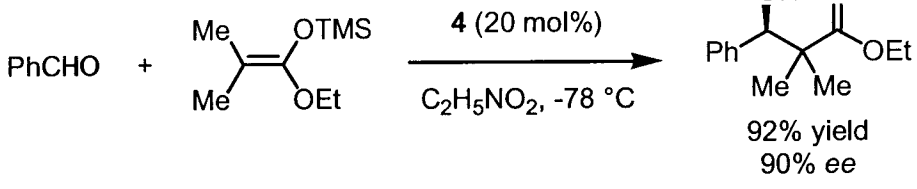
- Formyl H-bond organizes transition structure
- s-*cis* is favored due to "steric compression factor" involved with s-*trans* transition state
- No comments on change in enantioselectivity with **B** (though same argument can apply)

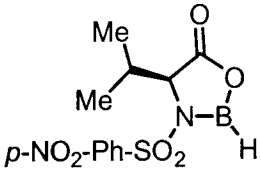
What's more important? – π-stacking or the formyl H-bond

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

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Aldol Reaction – Oxazaborolidine Catalysis





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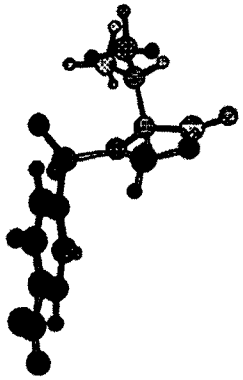
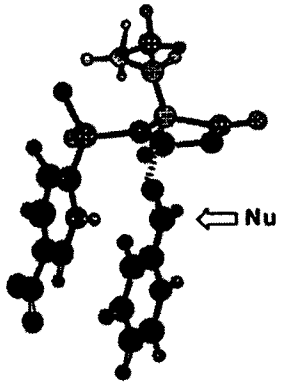


The Optimized Geometry of Chiral Borane Complex I Calculated by AM1 using MOPAC Version 6.0.



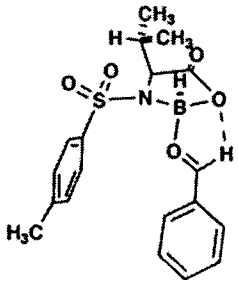
A Proposed Transition State.

Kiyooka Proposal

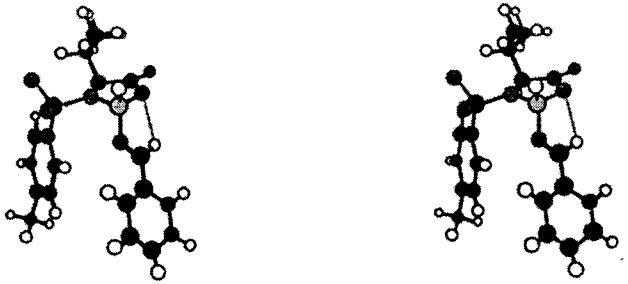
"preferential attack of the nucleophile might occur on the low side of the five membered ring…because the upper side is blocked by one of [the] methyl groups"

Corey Proposal

H-bonding between the formyl hydrogen and the oxazaborolidine oxygen organizes the transtion state leaving the *si* face of the aldehyde open for attack.



14



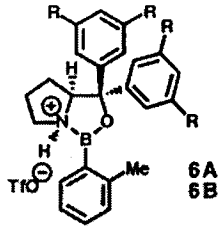
Stereopair representation of 14

S. Kiyooka, Y. Kaneko, K. Kume, *Tetrahedron Lett.* **1992**, *33*, 4927.

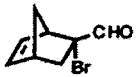
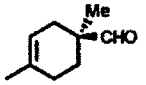
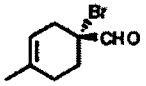
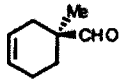
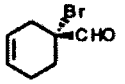
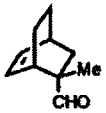
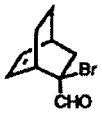
E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Diels-Alder RXN: Oxazaborolidine Catalysis

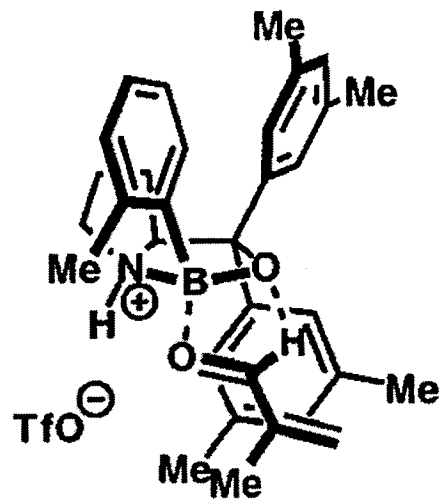
Table 2. Diels–Alder Reactions of 1,3-Dienes with 2-Methacrolein or 2-Bromoacrolein (CH_2Cl_2) Catalyzed by Chiral Lewis Acid **6A** or **6B**[3]



6A (R = H)
6B (R = Me)

Diene	Product	Cat.[a] (mol %)	Condt (°C, h)	% yield[b] (*exo*:*endo*)	%ee[c]
		A (6) B (6)	-95, 1 -95, 1	99 (91:9) 97 (91:9)	91 95
		A (6) B (6)	-95, 1 -95, 1	99 (91:9) 99 (91:9)	92 96
		B (6)	-78, 13	96	97
		A (6) B (6)	-95, 1 -95, 1	98 98	97 97
		B (20)	-78, 24	85	94
		A (6) B (6)	-95, 2 -95, 2	95 97	96 96
		A (20) B (20)	-78, 24 -78, 24	91 (5:95) 58 (6:94)	92 92
		A (6) B (6)	-95, 2 -95, 2	81 (6:94) 85 (7:93)	92 92

[a] Ratio of 1:TfOH = 1.2:1. [b] *Exo*:*endo* ratios were determined by ^1H NMR analysis. [c] Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^1H NMR analysis, or conversion to the benzoate and HPLC analysis.



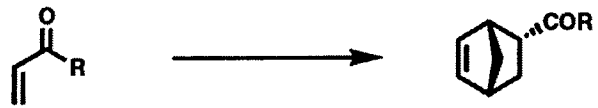
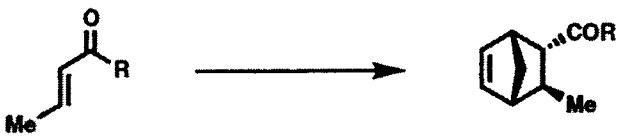
7

- π-π donor-acceptor interaction
- Formyl C-H···O hydrogen bond
- s-*trans* dienophile ?!

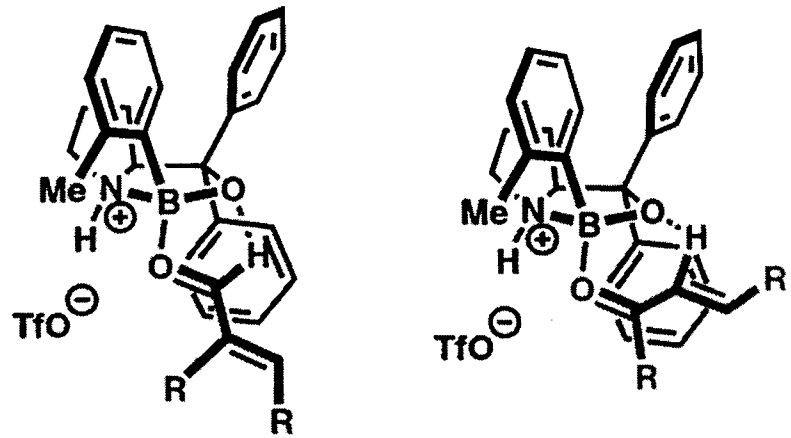
E.J. Corey, T. Shibata, T. W. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808.

Diels-Alder RXN: Vinylic CH···O H-Bonds?

Table 1. Diels–Alder Reactions of Cyclopentadiene with Representative Acyclic Dienophiles Catalyzed by Chiral Lewis Acid **1** or **2** in CH_2Cl_2

Dienophile R	Cat. (mol%)	Condt. (°C, h)	Product % yield[a] (*endo*:*exo*)[b]	%ee[c]
				
H	2 (6)	−95, 2	90 (92:8)	69[d]
Et	2 (20)	−20, 2	99 (94:6)	97
OH	1 (20)	−35, 1.5	99 (95:5)	98
OEt	1 (20)	−20, 16	94 (97:3)	98
OEt	2 (20)	−20, 16	96 (97:3)	>99
				
H	1 (20)	−95, 1.5	36 (84:16)	63[d]
Et	1 (20)	−20, 2	97 (69:31)	65
OEt	2 (13)	+4, 72	46 (91:9)	>98
OCH_2CF_3	1 (20)	−20, 16	93 (95:5)	>98

[a] Isolated yield. [b] Endo–exo ratios were determined by ^{1}H NMR or GC analysis or both. [c] Enantioselectivities were determined by ^{1}H NMR MTPA analysis or GC analysis. [d] Opposite enantiomer obtained.



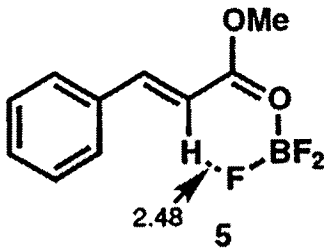
3 4

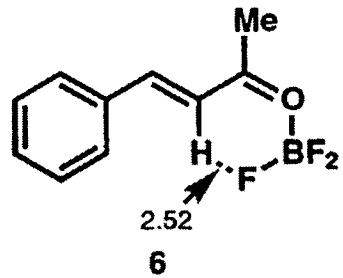
- Opposite enantiomer obtained when R≠H
- Vinylic CH···O H-bond proposed

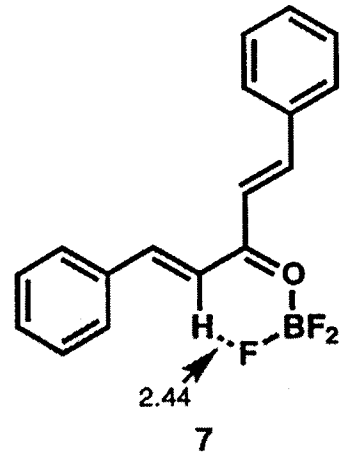
Can a vinyl hydrogen H-bond?

D. H. Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992.

Vinyl CH H-Bond Crystallographic Evidence



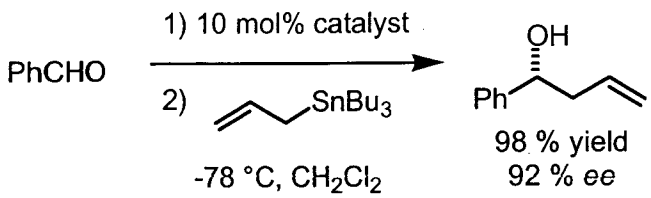




- Coordination of BF_3 *syn* to vinyl group in all cases
- H-F distances (Å) are within the sum of the van der Waals radii (2.67 Å)
- **Not eclipsed!** (not mentioned in paper)

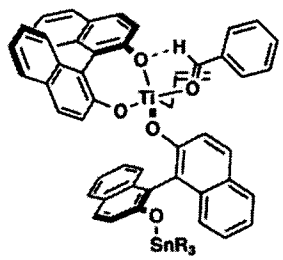
D. H. Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992.

Allylation: Ti(IV) Catalysis

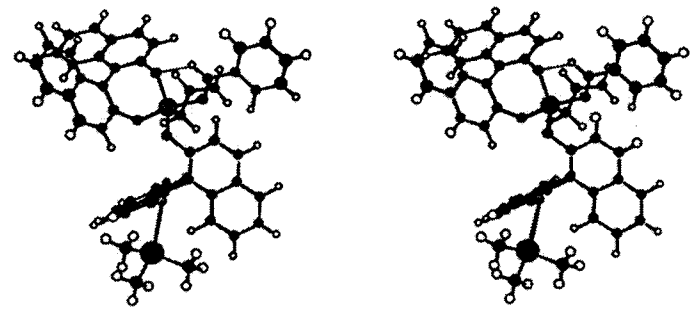


Catalyst: (*R*)-(+)-Binol is heated with Ti(O-*i*-Pr)$_4$ (2/1) in CH_2Cl_2 in the presence of trace CF_3SO_3H
Structure Unknown

Corey's Catalyst Complex Proposal



10

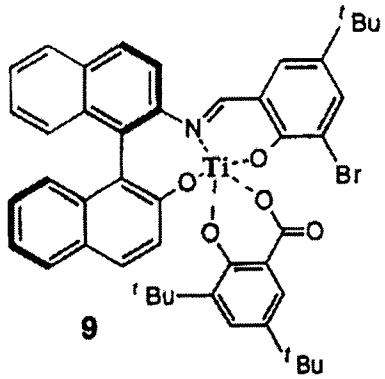


Stereopair representation of 10

- Allyltributyltin allylates Ti(IV) while the $SnBu_3$ group attaches to a BINOL oxygen causing dissociation from Ti
- Benzaldehyde coordinates to Ti forming a trigonal bipyramidal H-bonded structure **10**
  - minimizes non-bonded steric repulsion
  - allows formation of formyl H-bond
  - places allyl group in basal position and formyl oxygen in the apical position (ideal for allylation reaction)

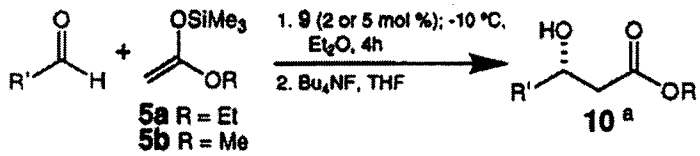
G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467.
G. E. Keck, D. Krishnamurthy, M. C. Grier, *J. Org. Chem.* **1993**, *58*, 6543.
E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Aldol: Ti(IV) Catalysis



9

Table 1. Catalytic Asymmetric Aldol Additions of Alkyl Aceate Ketene Acetal[b,c]



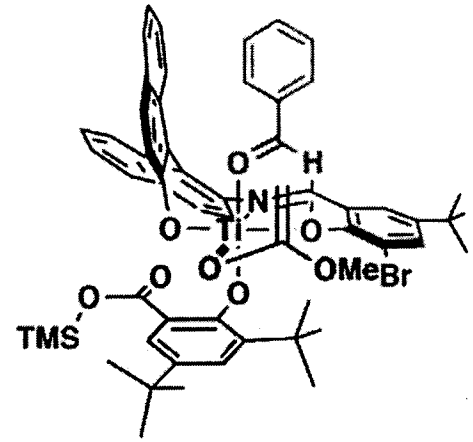
5a R = Et
5b R = Me

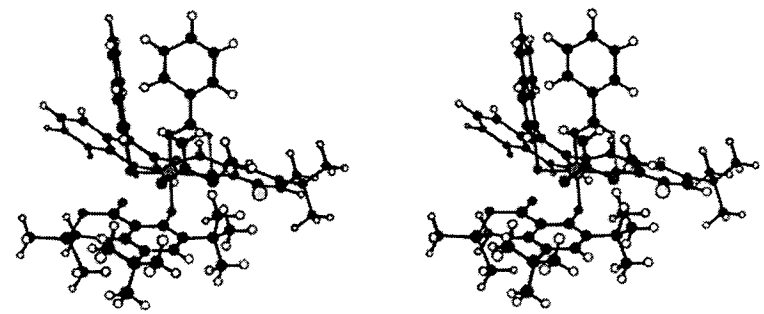
10 [a]

Entry	Aldehyde	ee: R = Et [d]	ee: R = Me [e]
1	Me, CHO	92%	97%
2	Me, CHO	88%	95%
3	Ph, CHO	93%	97%
4	Ph, CHO	89%	94%
5	$C_6H_{11}CHO$	94%	95%
6	PhCHO	93%	96%

[a] Absolute configuration was determined by reduction to the known 1,3-diols.[1h] [b] Yields for two steps (addition and desilylation) range from 72 to 98%. [c] For each entry, the *ee* was determined by preparation of the derived (*S*)-MTPA ester and analysis by ^{1}H NMR spectroscopy. [d] 5 mol % catalyst used. [e] 2 mol % catalyst used.

Corey's Proposal





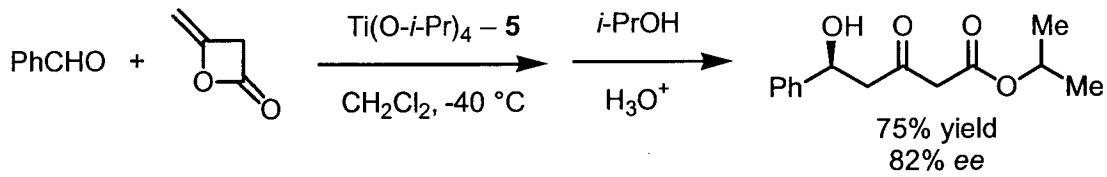
Stereopair representation of 11

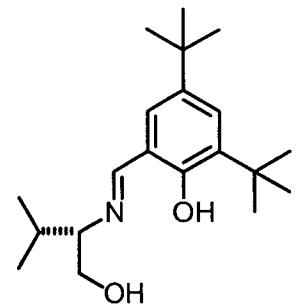
- aldehyde and enolate ligands must be *cis* in order to react
- 2 possibilities – only one allows for formyl H-bond while minimizing steric repulsion with the di-*tert*-butyl phenoxide ligand
- this one leads to the experimentally observed enantiomer

E. M. Carreira, R. A. Singer, W. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 8837.

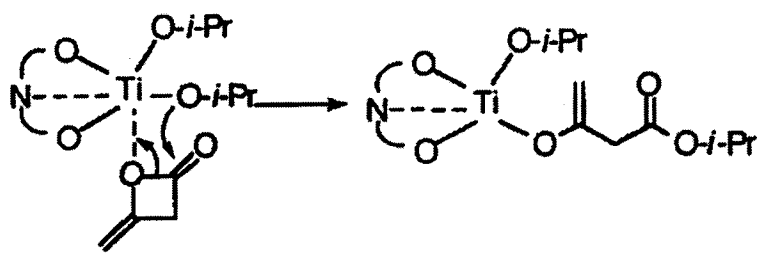
E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Diketene Aldol Reaction: Ti(IV) Promotion





5



Scheme 1. Generation of titanium enolate

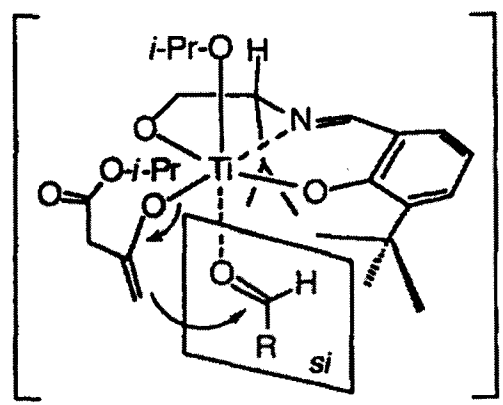
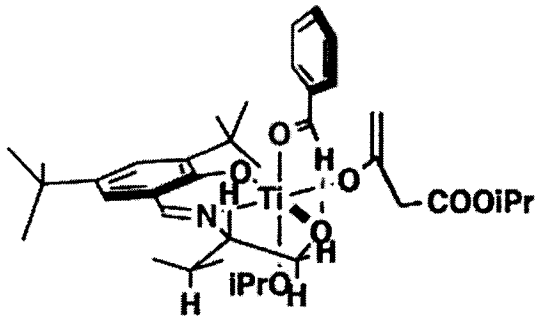


Figure 1

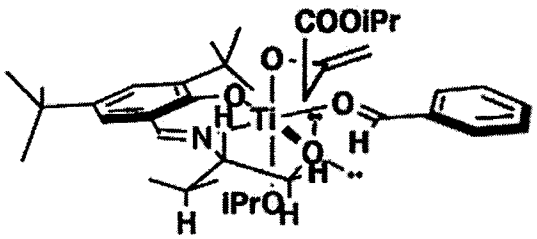
Proposed transition state
based on observed product

M. Hayashi, T. Inoue, Y. Miyamoto, N. Oguni, *Tetrahedron* **1994**, *50*, 4385.

Diketene Aldol Reaction: Ti(IV) Catalysis (2)

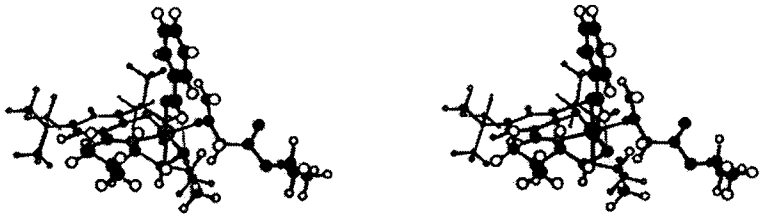


16
Favored

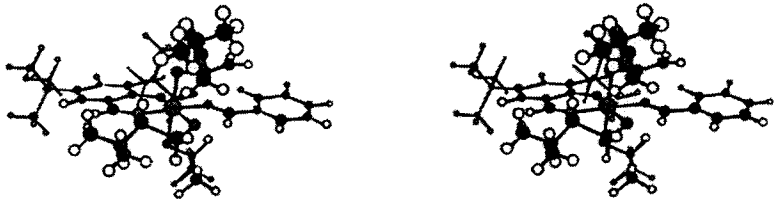


17
Disfavored

Corey



Stereopair representation of 16



Stereopair representation of 17

Oguni

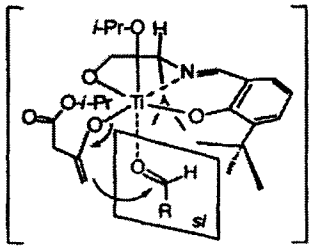
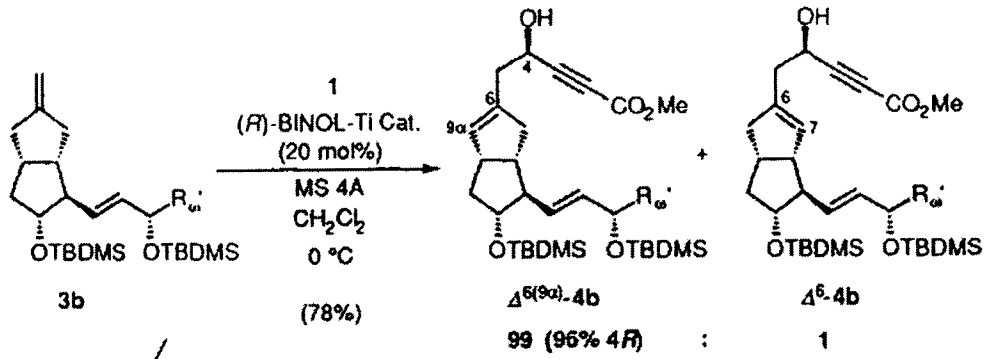


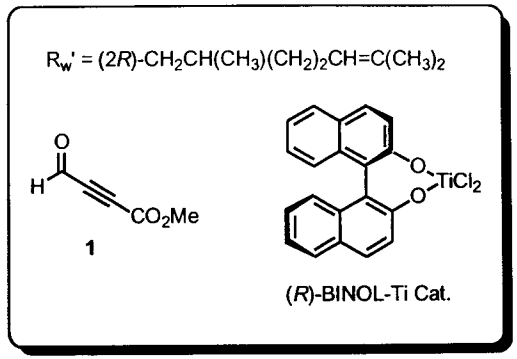
Figure 1

- 3 donor groups planar with puckered 5-membered ring placing *i*-Pr group pseudoequatorial
- Axial coordination of aldehyde with formyl H-bond
- *Cis* coordination of the enolate to allow carbonyl addition via a 6-membered TS‡
- *Si*-face attack of enolate gives observed product
- Disfavored TS ‡ **17** does not allow for formyl H-bonding due to poor positioning of lone pairs on oxygen

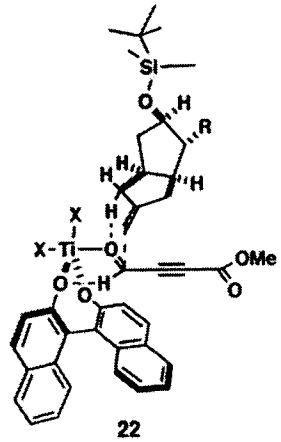
E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

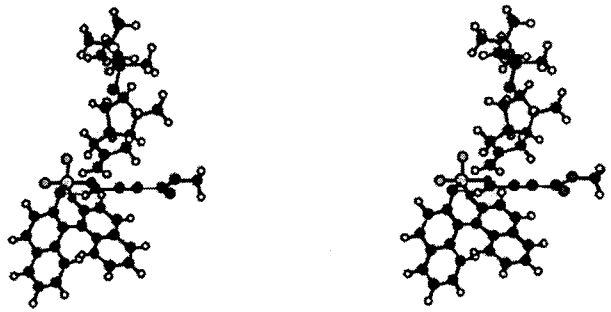
Ene Reaction: Ti(IV) Catalysis





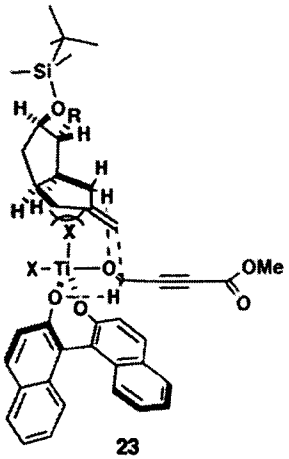
Favored

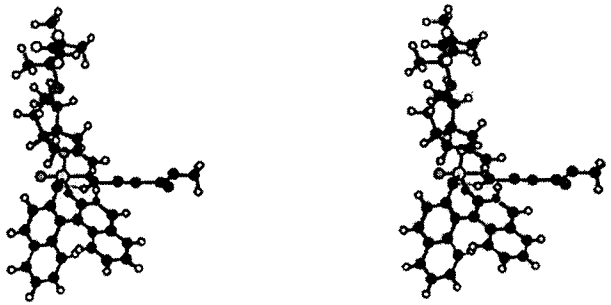




Stereopair representation of 22

Disfavored





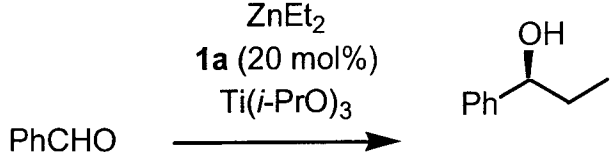
Stereopair representation of 23

- Aldehyde activated by binding to Ti giving pentacoordinate Ti structure
- Trigonal bipyramidal geometry results with aldehyde and one chlorine apical [two most electronegative (weakest) ligands]
- Formyl H-bond with less sterically hindered binapthol oxygen exposes *re* face of aldehyde
- Major product forms through **22** where convex face of alkene reacts and chlorine/ring steric interactions (**23**) are minimized

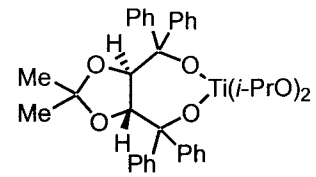
K. Mikami, A. Yoshida, Y. Matsumoto, *Tetrahedron Lett.* **1996**, *37*, 8515.

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

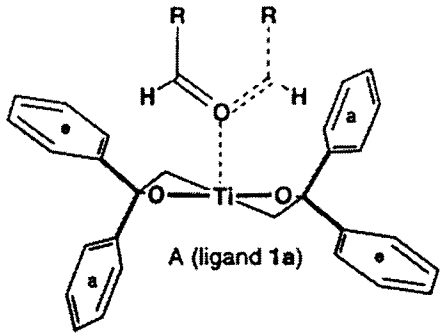
Diethyl Zinc Addition: TADDOL Catalysis



99% yield
99:1 *er*

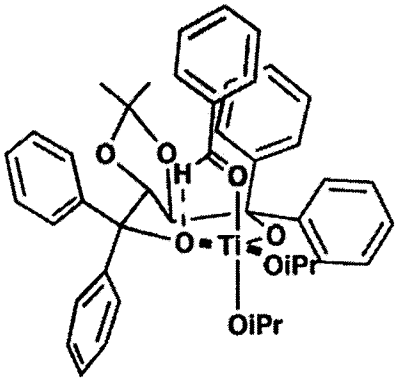


TADDOLate **1a**

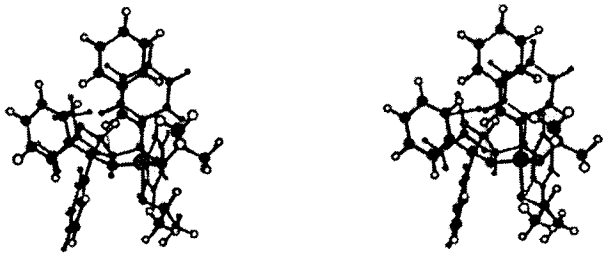


A (ligand **1a**)

TADDOL (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol)



15



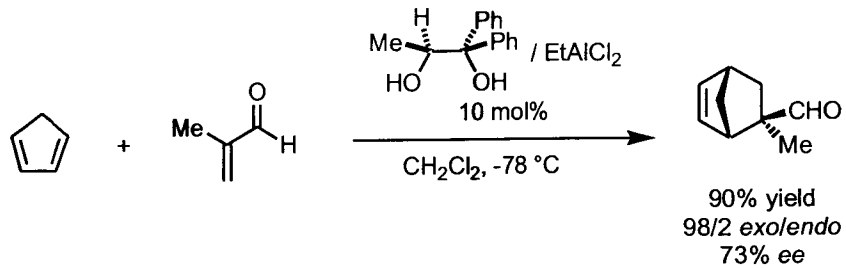
Stereopair representation of 15

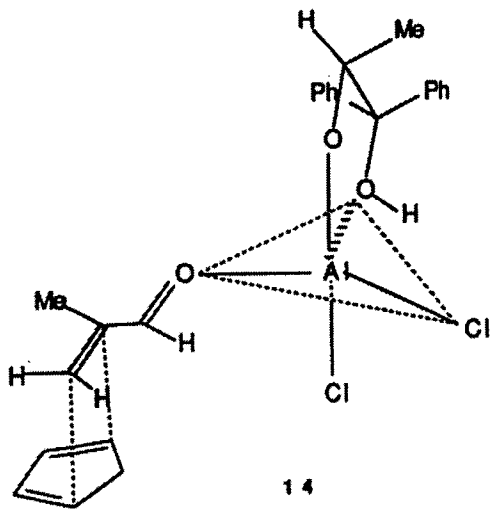
- Pentacoordinate Ti – trigonal bipyramidal – TADDOL in basil positions to minimize strain and allow access to Ti by aldehyde
- Apical binding of aldehyde (weakest ligand) and formyl H-bond
- H-bond position determined by avoidance of interaction with axial phenyl group
- *si*-face open for attack of nucleophile

D. Seebach et al., *Helv. Chem. Acta* **1994**, *77*, 2071.

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Diels-Alder: Aluminum Catalysis





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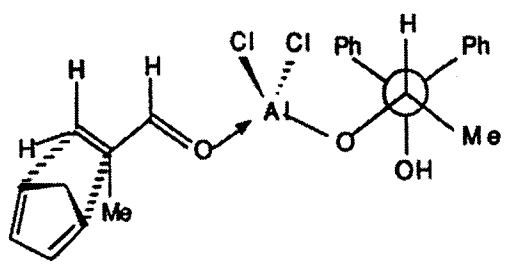
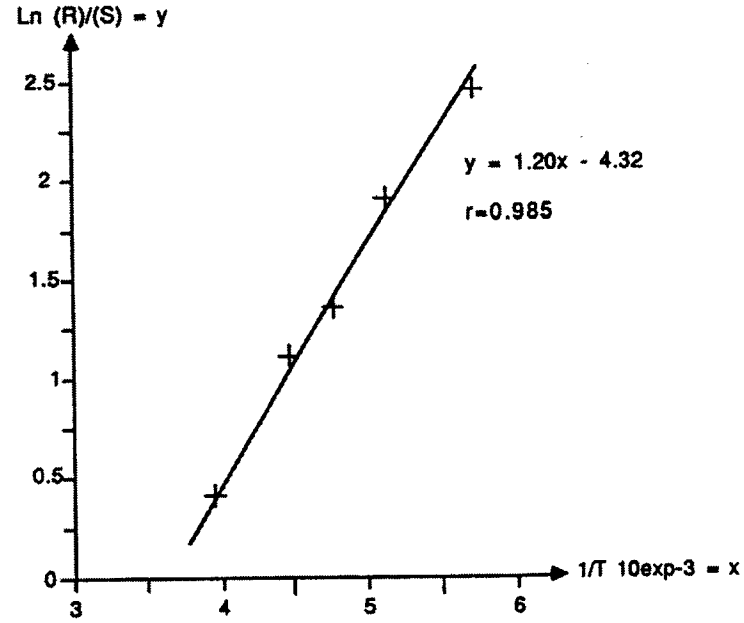


15

3/ Influence of temperature:

Comparative experiments were performed between -20°C and -100°C with the standard system (catalyst ratio = 0.1). There is an important increase in the optical yield when decreasing the temperature. At the lowest temperature (-)-2a was prepared with 86% ee. The plot Ln[R]/[S] versus 1/T (T absolute temperature) gives a straight line (Figure 2) with an excellent correlation coefficient (r=0.985). From the equation of the line , and using the relation $Ln[R]/[S] = -\Delta H/RT + \Delta S/R$ it is possible to calculate $\Delta H = -2.46$ kcal mol^{-1} and $\Delta S = -8.9$ eu.

At -78°C the observed enantioselectivity arises from an enthalpic control since $\Delta G = -0.74$ kcal mol^{-1}, $\Delta H = -2.46$ kcal mol^{-1} and $-T\Delta S = +1.73$ kcal mol^{-1}. A more negative entropy characterises the preferred transition state and opposes to the enantioselectivity of the reaction. Lowering of temperature significantly decreases the $-T\Delta S$ term. Calculations indicate that 99% ee should be attained for T = 123 K (-150°C).



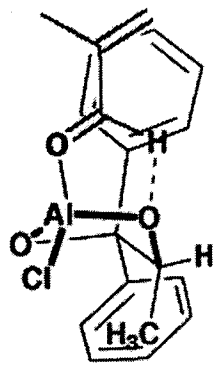
Influence of temperature on the asymmetric Diels-Alder reaction giving (-)-2a in CH_2Cl_2 at -78°C (0.1 mol equiv catalyst prepared from $EtAlCl_2$ and (S)-5a (1:1). Details are in experimental section.

Figure 2

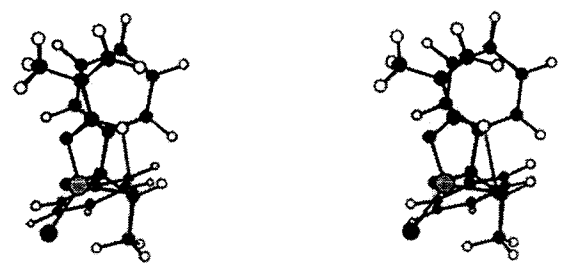
F. Rebiere, O. Riant, H. B. Kagan, *Tetrahedron Asymmetry* **1990**, *1*, 199.

Diels-Alder: Aluminum Catalysis (2)

Corey's Proposal



18

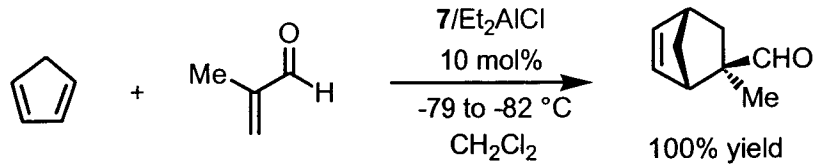


Stereopair representation of 18

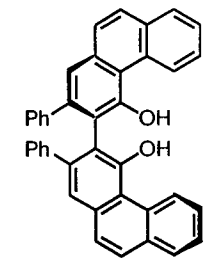
- One chlorine has disassociated from the complex
- Tetracoordinate alumninum w/ five-membered ligand ring fixed through steric repulsion
- Coordination of aldehyde with H-bond to more sterically accessible oxygen and π-stacking with phenyl ring
- s-*trans* aldehyde to minimize steric compression during the reaction
- Highly ordered (temperature effect) and gives experimentally observed enantiomer

E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

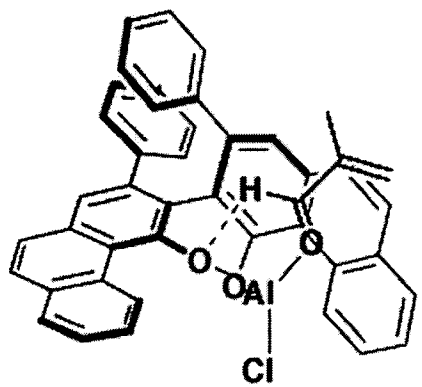
Diels-Alder: VAPOL Catalysis



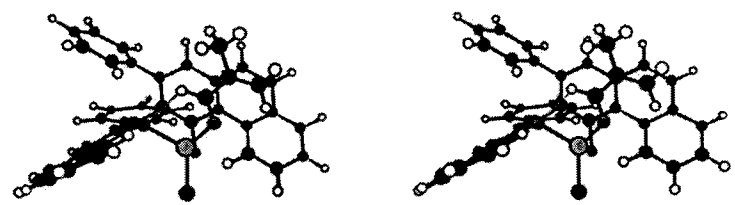
100% yield
98/2 *exo/endo*
97.8% *ee*



vaulted biphenanthrol (VAPOL)
7



19



Stereopair representation of 19

- **19** shows only TS‡ where a favorable formyl C-H hydrogen can form
- Cyclopentadiene adds to the accessible *si* face leading to the observed enantiomer
- Dienophile in s-*cis* conformation to minimize steric compression upon reaction

J. Bao, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 3814.
E. J. Corey, T. W. Lee, *Chem. Commun.* **2001**, 1321.

Conclusions

- The formyl C-H···O(F) hydrogen bond provides a mechanistic rationale for many catalytic enantioselective transformations that are difficult to understand without this structure controlling concept
  - Diels-Alder
  - Aldol
  - Allyation
  - Ene
  - Alkylation
- Quite a few issues remain with the proposed transition states
- The concept needs to be proven through rational design of new catalysts
- More computational studies should be performed to quantify these interactions