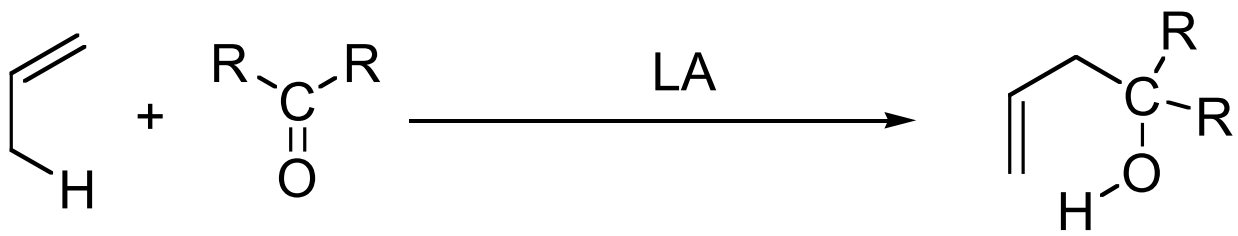
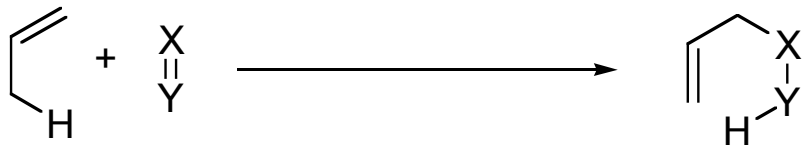
Lewis Acid Catalyzed Carbonyl-Ene Reaction



Michael Ober

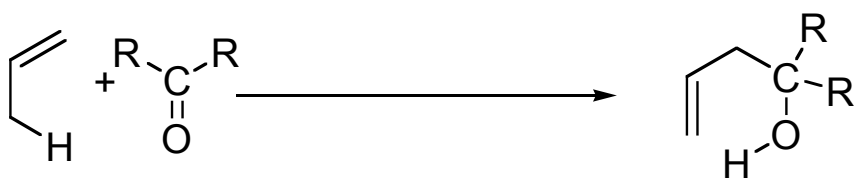
12/16/03

The Hetero-Ene Reaction



X=Y : C=C, C=O, C=N, C=S, O=O, N=N

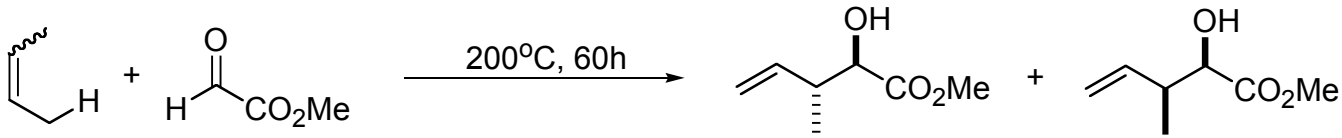
(1) All-carbon ene-reactions: takes place between an olefin bearing an allylic hydrogen atom (the carba-ene) and an activated alene or alkyne (the carba-enophile)



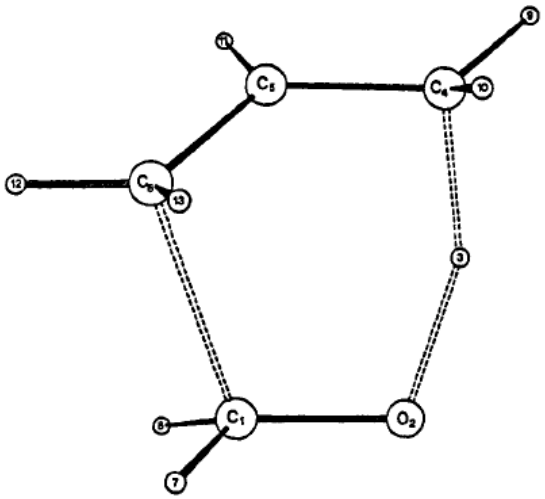
(2) The hetero-ene-reaction: describes a reaction between an ene or enophile, either of which contains at least one heteroatom

(a) Type I: reaction between all-carba-ene components with hetero-enophiles
(b) Type II: reaction between hetero-ene components and all carba-enophiles
(c) Type III: reaction between hetero-ene components and hetero-eneophiles

Thermal Carbonyl-Ene Reaction



cis-2-butene	7.4	:	1
trans-2-butene	0.6	:	1



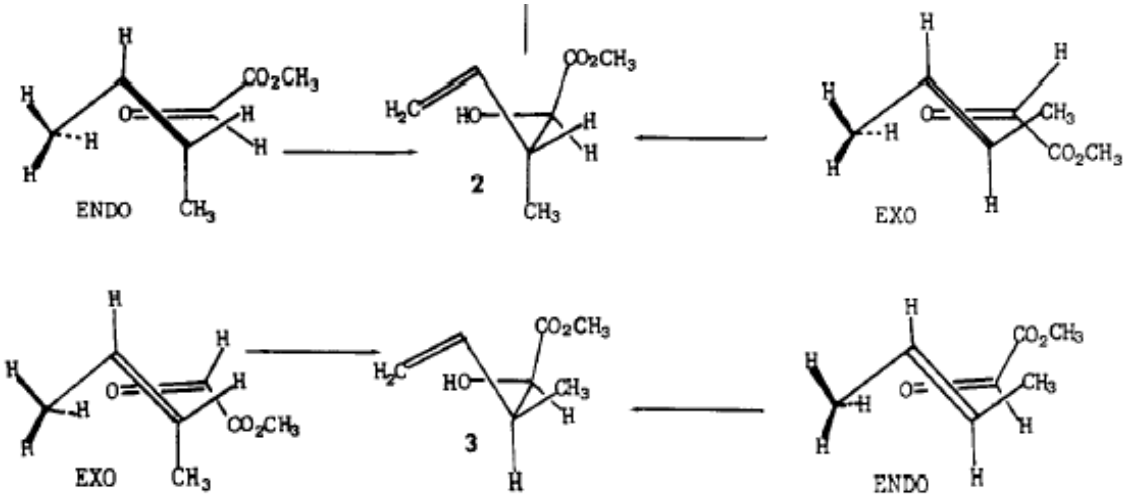
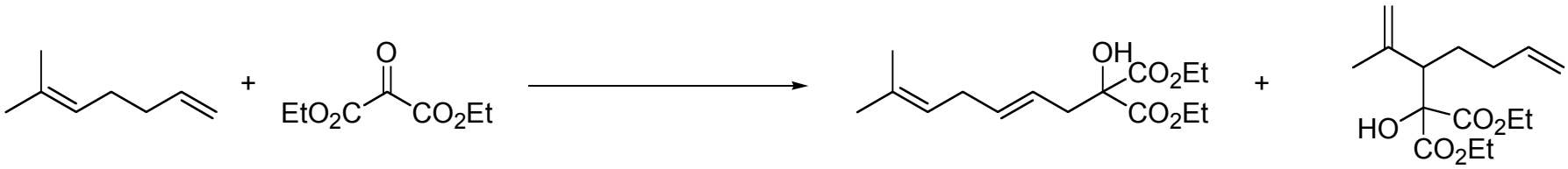


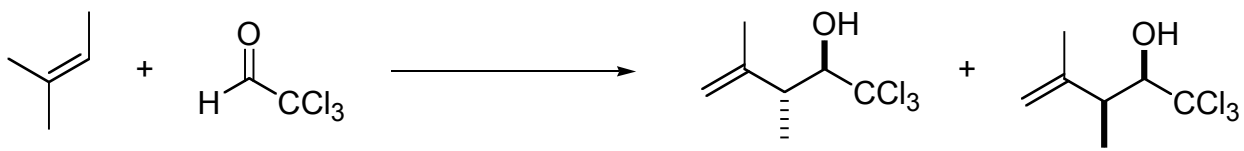
Figure 3. The STO-3G and 3-21G propene–formaldehyde ene reaction transition structures.

Houk, K.N. et al *J. Am. Chem. Soc.* **1987**, *109*, 6947.
Snider, B.B. et al *J. Org. Chem.* **1979**, *40*, 3567.

Thermal vs. LA Promoted Reactions



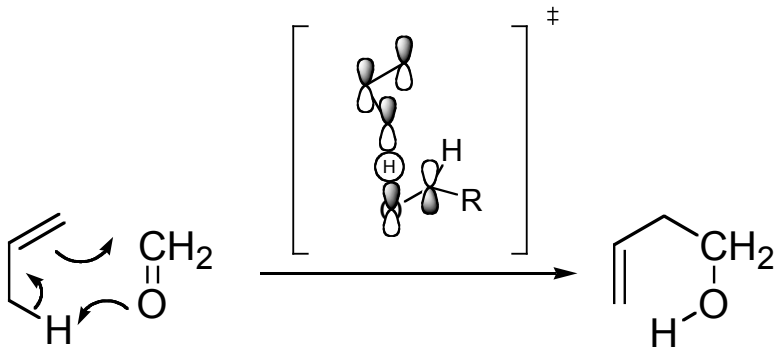
180°C, 48h	92	:	8	(75%)
$SnCl_4$ (0.2 eq) 0°C, 5 min	2.5	:	97.5	(40%)

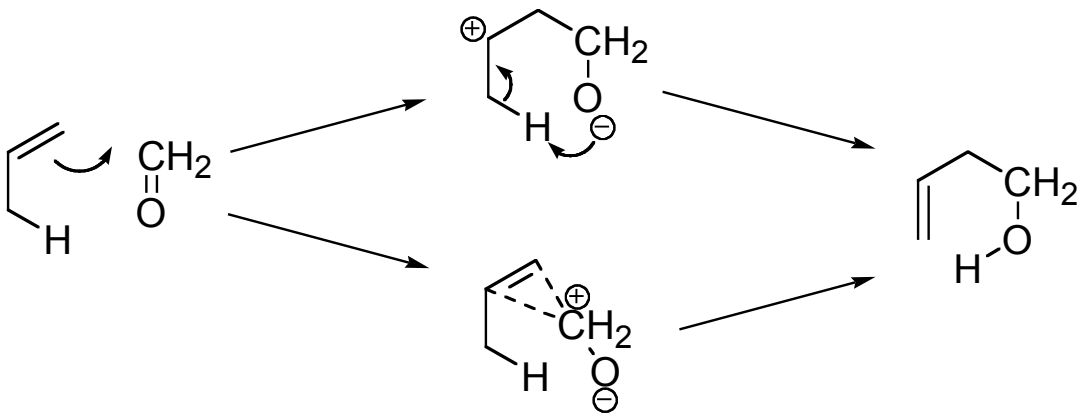


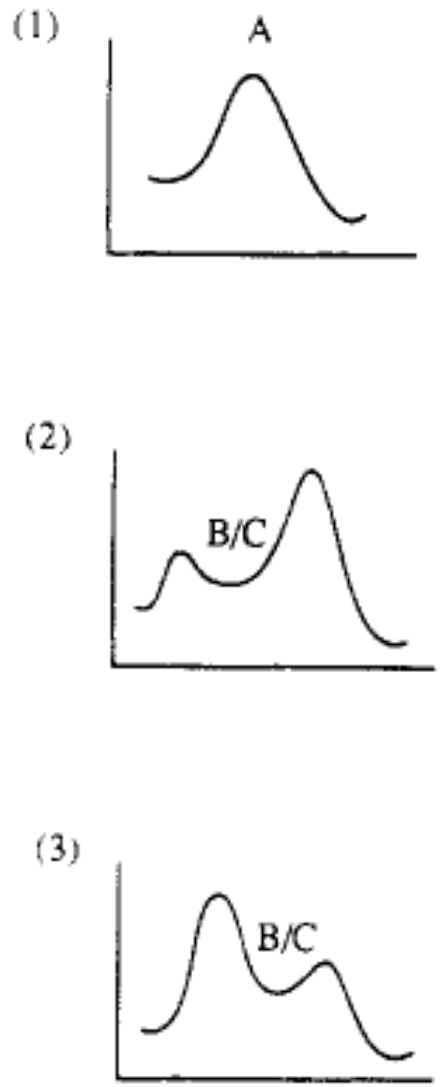
130°C	84	:	16
$AlCl_3$	15	:	85

Salomon, R.G. et al *J. Org. Chem.* **1984**, *49*, 2446.
Orfanopoulos, M. et al *J. Org. Chem. Soc.* **1981**, *46*, 2200.
Gill, G.B. et al *J. Chem. PT1* **1984**, 315.

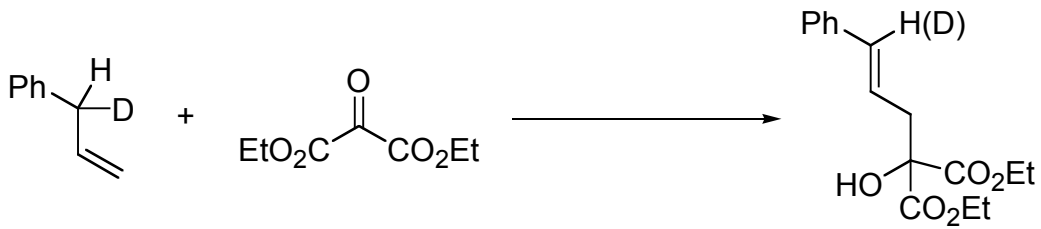
Mechanism of the Reaction



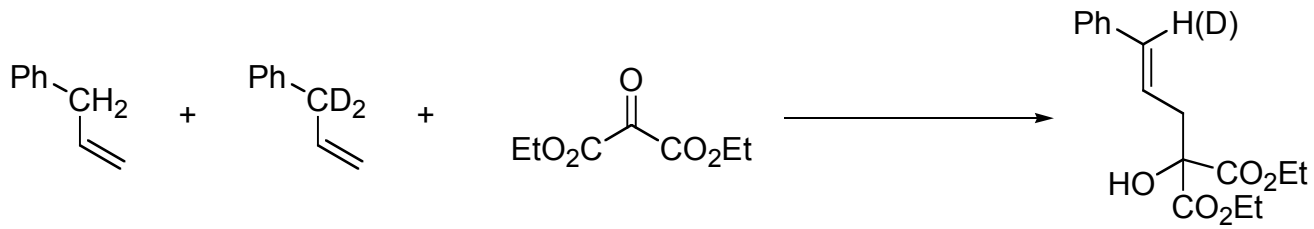




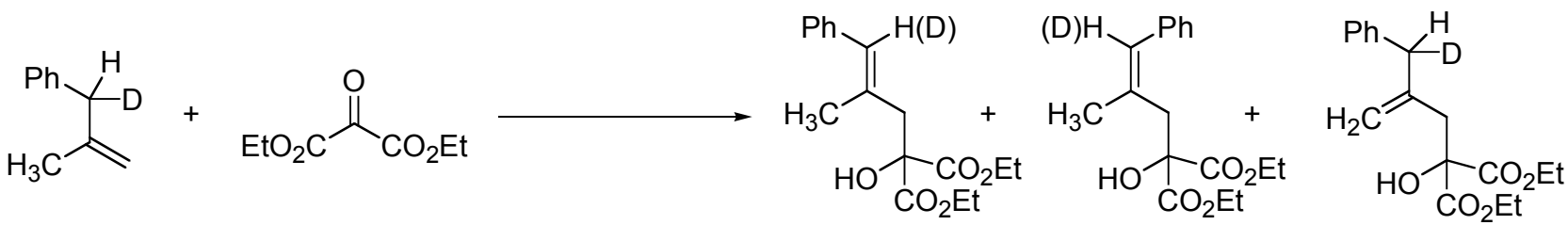
Mechanistic Insights : KIE



A k_H/k_D = 3.3
B k_H/k_D = 1.03



A k_H/k_D = 3.2
B k_H/k_D = 1.08



CONDITIONS
A : 130°C, 3days
B : $SnCl_4$, 3min, rt

A	55% (k_H/k_D = 3.14),	16% (k_H/k_D = 3.67),	29%
B	54% (k_H/k_D = 1.08),	trace,	46%

Orfanopoulos, M. et al *J. Org. Chem.* **1981**, *46*, 2200.

Thermal vs. LA Promoted Reactions

Conditions

A : 185 ^{o}C

B : $SnCl_4$ (0.1 equiv), 0°C

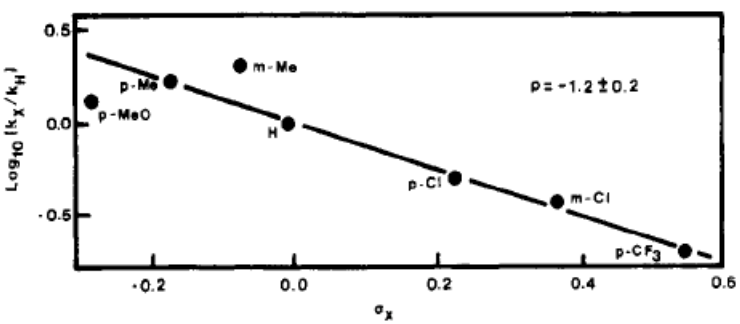


Figure 1. Substituent effects on thermal ene reactions of diethyl oxomalonate with 1-arylcyclopentenes.

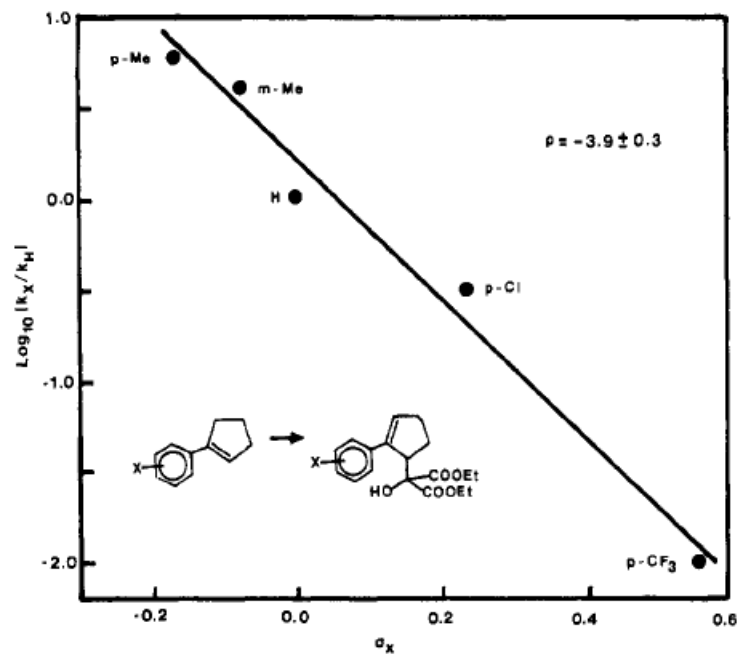
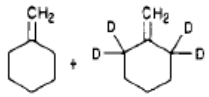
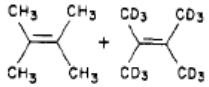
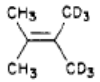
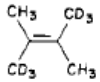
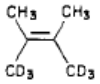


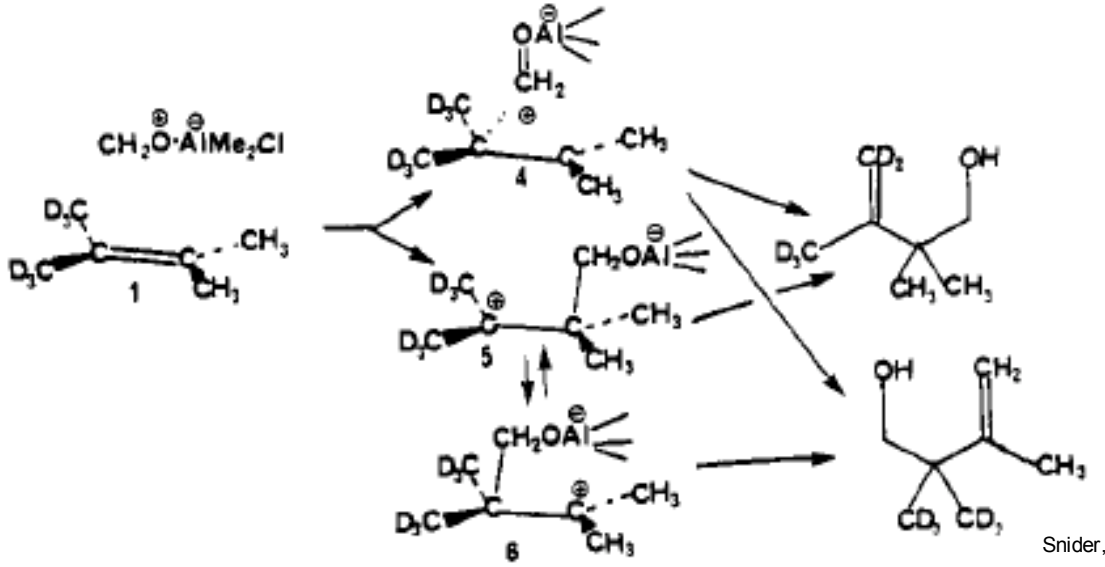
Figure 2. Substituent effects on $SnCl_4$-catalyzed ene reactions of diethyl oxomalonate with 1-arylcyclopentenes.

Salomon, R.G. et al *J. Org. Chem.* **1984**, *49*, 2446.

Mechanistic Insights : KIE Redux

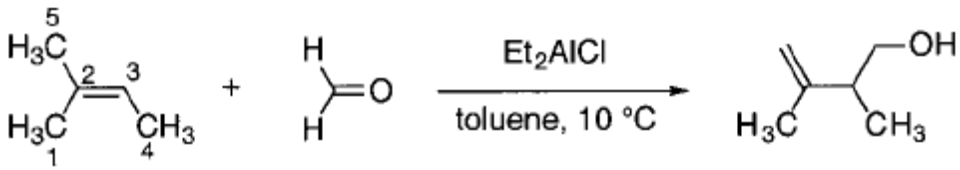
Table I. Kinetic Isotope Effects in Lewis Acid Catalyzed Ene Reactions

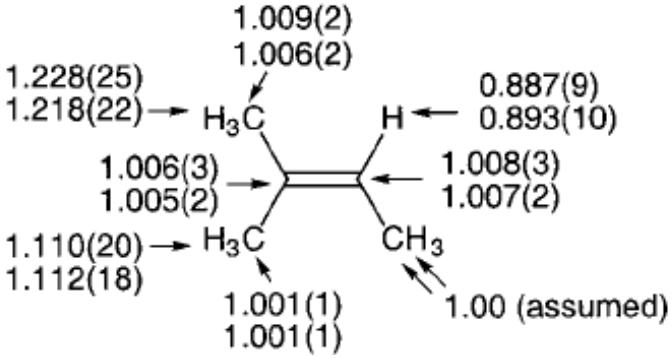
ene	enophile	Lewis acid	yield, %	k_H/k_D
intermolecular				
	CH_2O	Me_2AlCl	64	1.3 ± 0.15
	$HC{\equiv}CCO_2Me$	$EtAlCl_2$	60	1.2 ± 0.15
	$H_2C{=}CClCO_2Me$	$EtAlCl_2$	97	1.1 ± 0.15
	CH_2O	Me_2AlCl		1.4 ± 0.15
	$HC{\equiv}CCO_2Me$	$EtAlCl_2$	59	1.1 ± 0.15
intramolecular				
 1	CH_2O	Me_2AlCl	57	3.3 ± 0.15
	$HC{\equiv}CCO_2Me$	$EtAlCl_2$	78	2.5 ± 0.15
	$(EtO_2C)_2C{=}O$	$SnCl_4$	90	2.1 ± 0.15
	$CH_3CO\ SbCl_6 + NEt(i\text{-}Pr)_2$			1.9 ± 0.2
 2	CH_2O	Me_2AlCl	45	2.9 ± 0.15
	$HC{\equiv}CCO_2Me$	$EtAlCl_2$	56	1.8 ± 0.15
 3	CH_2O	Me_2AlCl	50	2.7 ± 0.15
	$HC{\equiv}CCO_2Me$	$EtAlCl_2$	56	1.6 ± 0.15
	$(EtO_2C)_2C{=}O$	$SnCl_4$	30	1.5 ± 0.15

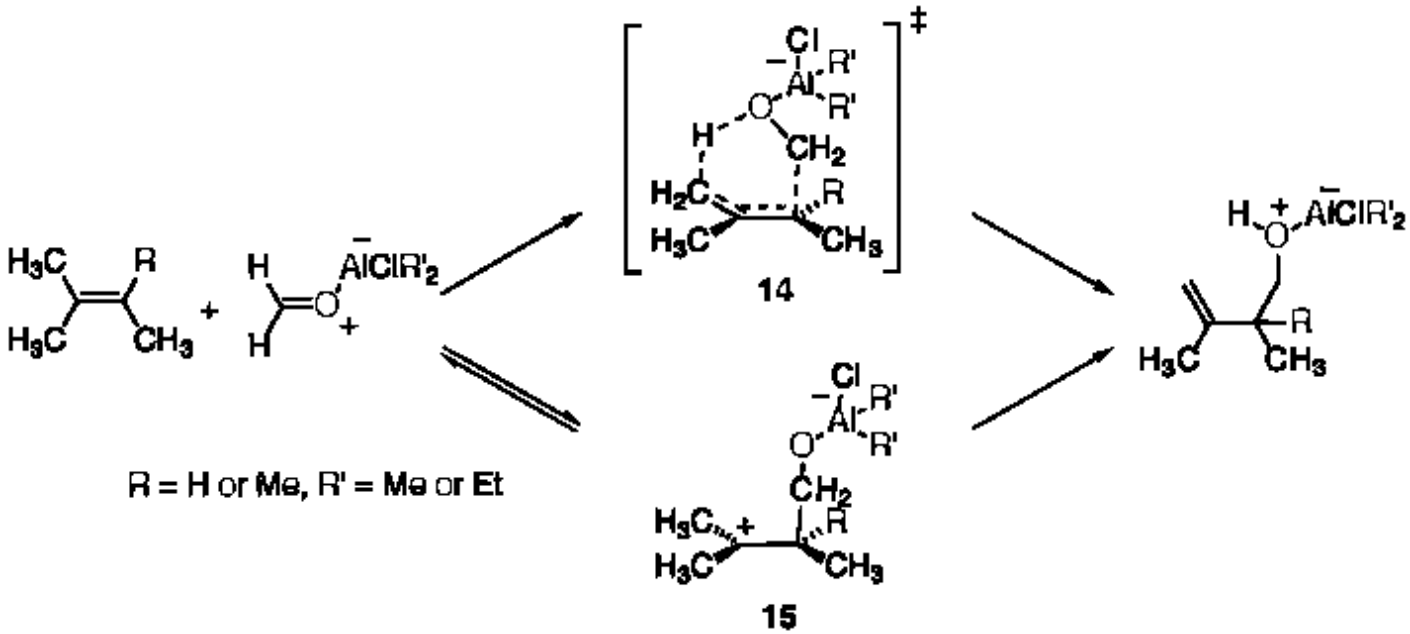


Snider, B.B. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

Mechanistic Insights : KIE Reloaded







Singleton, D.A. et al *J. Org. Chem.* **2000**, *65*, 895.

Mechanistic Insights : KIE Revolutions

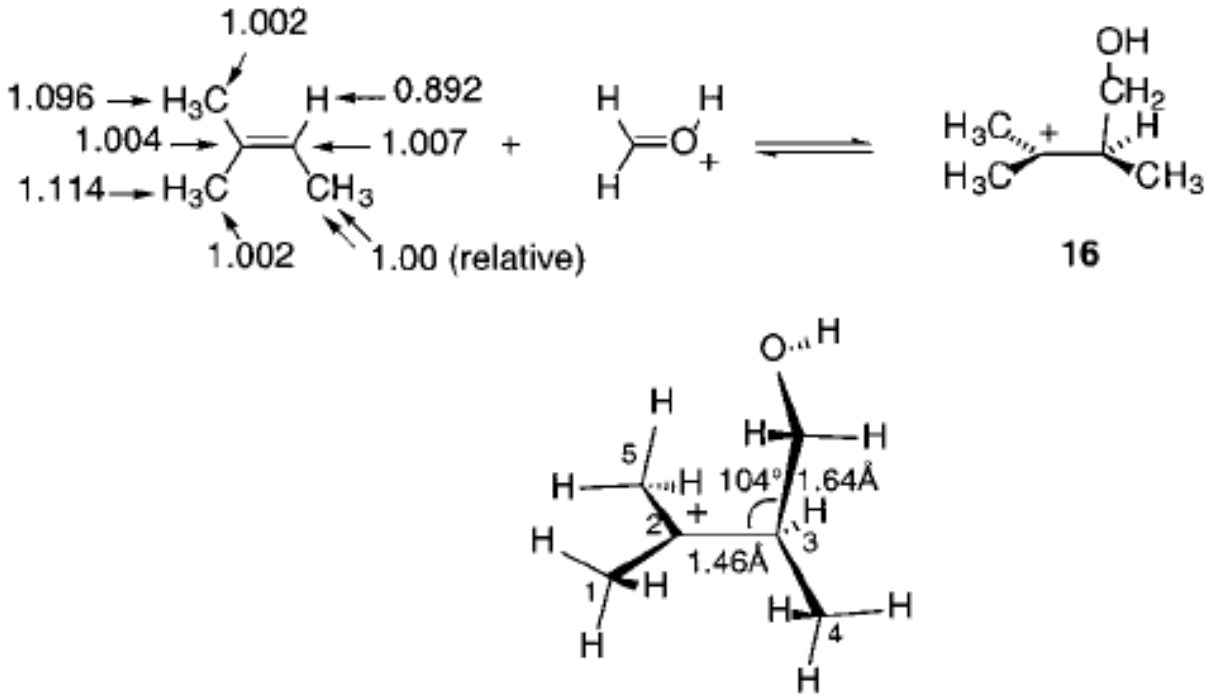
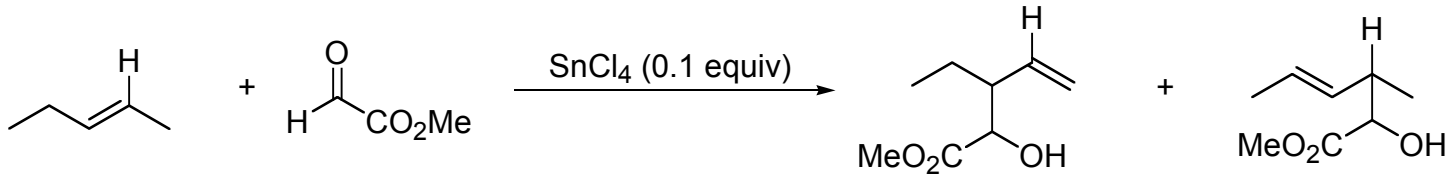


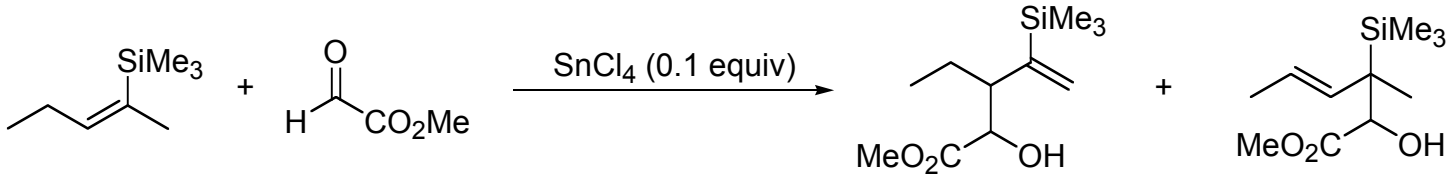
Figure 2. Predicted equilibrium isotope effects[23,17] (K_H/K_D or K^{12}_C/K^{13}_C, 25 °C) for the model reaction forming **16**, and calculated structure of **16**.

Singleton, D.A. et al *J. Org. Chem*. **2000**, *65*, 895.

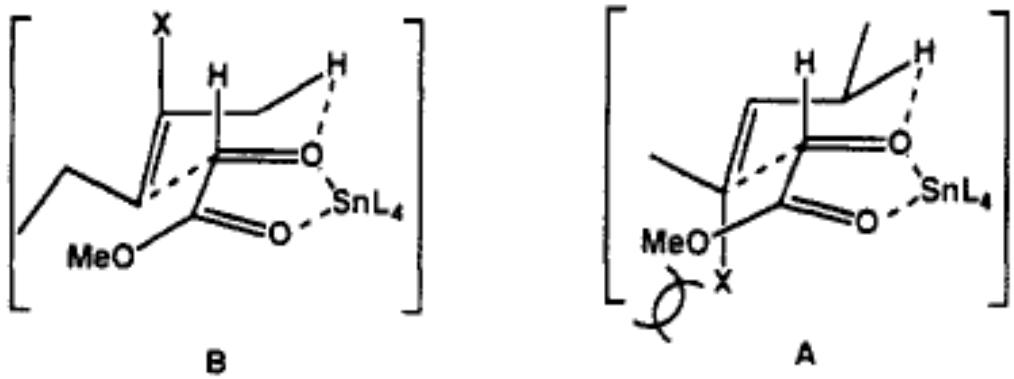
Regioselectivity of the Reaction



34 : 66

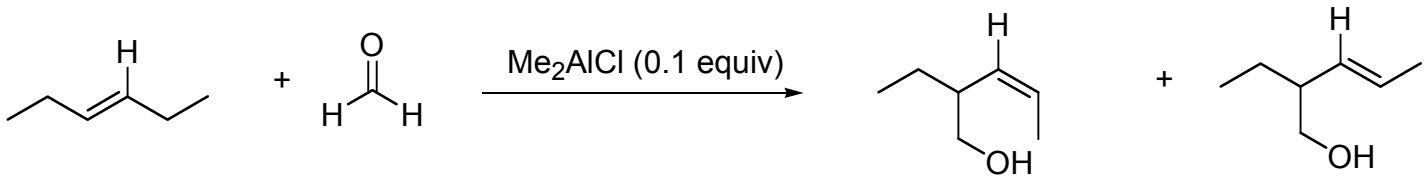


100 : 0

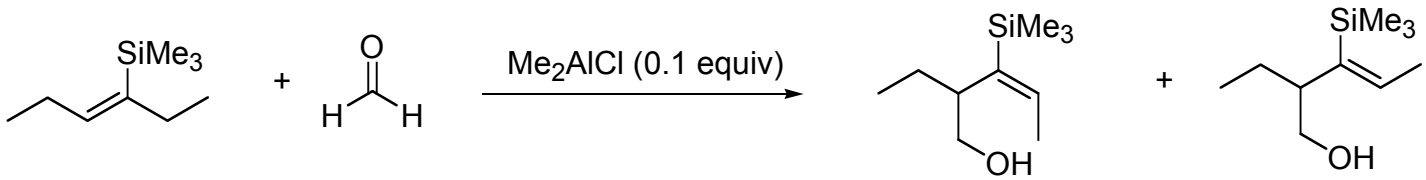


Mikami, K. et al *J. Am. Chem. Soc.* **1990**, *112*, 6737.
Mikami, K. et al *J. Org. Chem.* **1991**, *56*, 2952.

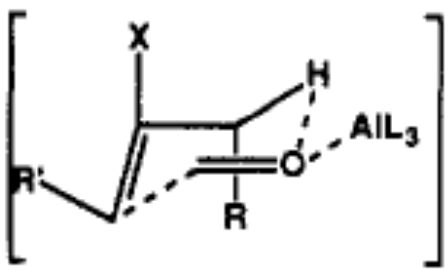
Stereoselectivity of the Reaction



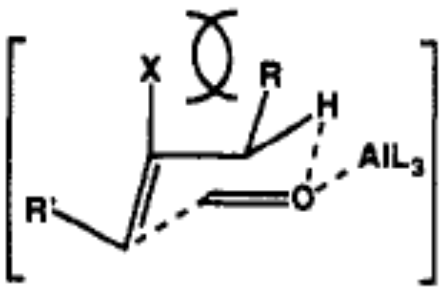
15 : 85



98 : 2



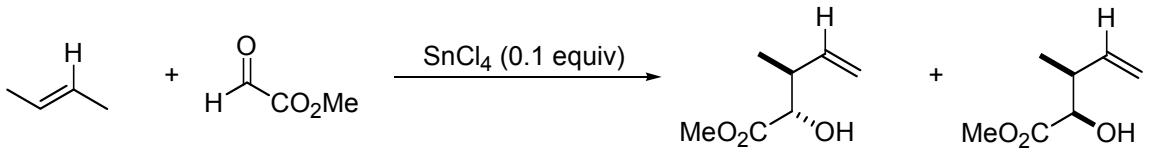
F



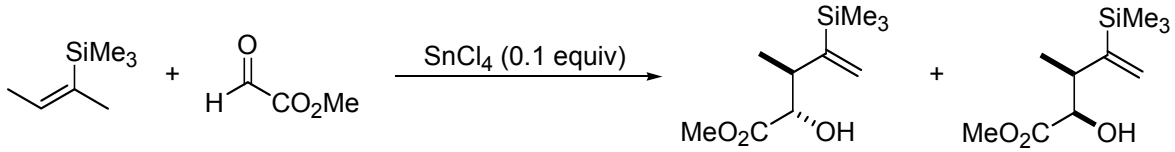
E

Mikami, K. et al *J. Org. Chem.* **1991**, *56*, 2952.
Mikami, K. et al *J. Am. Chem. Soc.* **1990**, *112*, 6737.

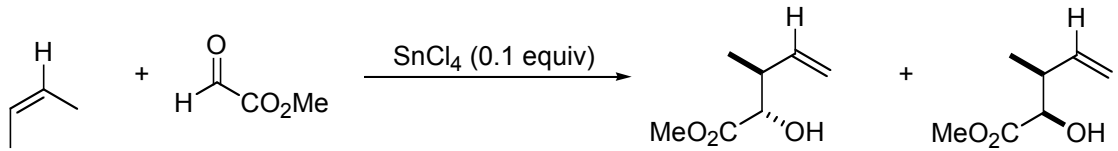
Diastereoselectivity of the Reaction



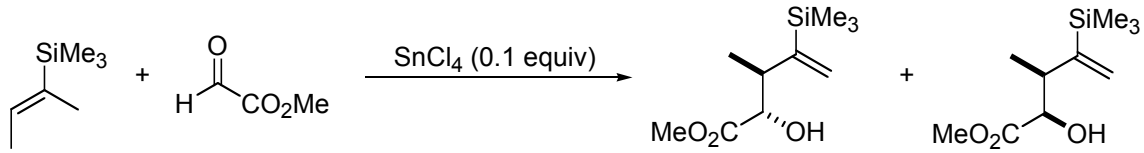
82 : 18



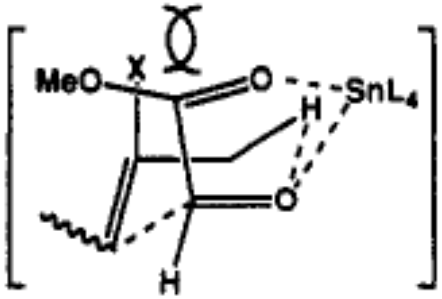
98 : 2



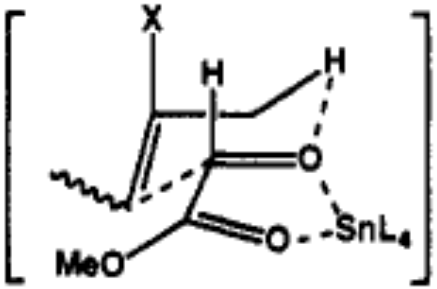
72 : 26



7 : 93



D



C

Mikami, K. et al *J. Am. Chem. Soc.* **1990**, *112*, 6737.

Diastereoselectivity of the Reaction

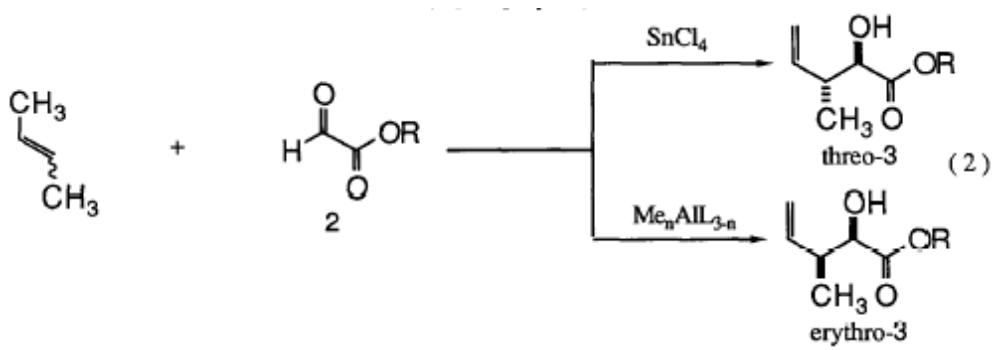
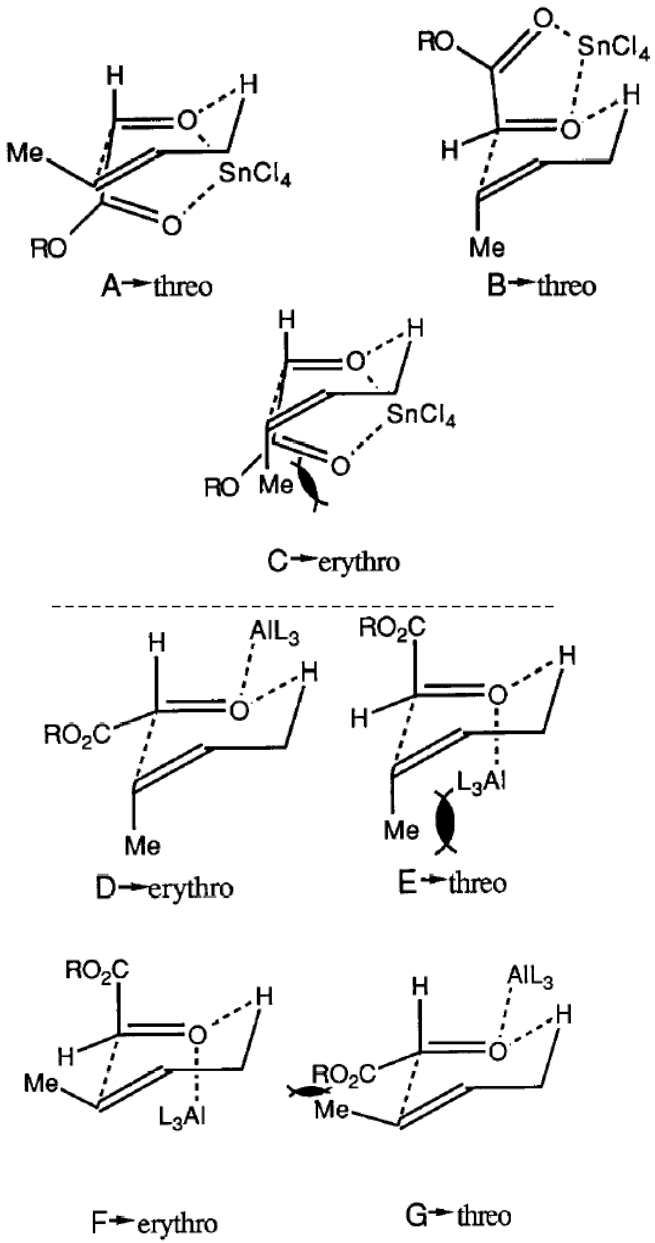


Table 1. Lewis Acid-Promoted Ene Reaction with Glyoxylates[a]

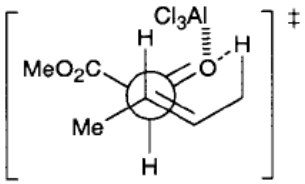
Run	Geometry of 2-butene	R in glyoxylate (2)	Lewis acid	%yield[b]	erythro : threo[c]
1	E	Me	$SnCl_4$	100	18 : 82
2	Z			100	28 : 72
3	E	i-Pr		100	8 : 92
4	Z			100	29 : 71
5	E	Me	Me_2AlCl	5	82 : 18
6			Me_2AlOTf	29	79 : 21
7			$MeAl(OTf)_2$	41	65 : 35
8	Z		Me_2AlCl	5	99 : 1
9			Me_2AlOTf	65	91 : 9
10		i-Pr	Me_2AlOTf	trace	
11			$MeAl(OTf)_2$	35	66 : 34
12			$MeAl(OTf)Cl$	44	81 : 19

[a] All reaction were carried out in CH_2Cl_2 at -78 °C by using a freshly distilled glyoxylate, 1 equiv. of Lewis acid and an excess (>3 equiv.) of 2-butene. [b] Isolated yield by column chromatography. [c] Determined by ^{1}Hnmr and GLC analyses as described in ref 5.



Mikami, K. et al *Tetrahedron Lett.* **1988**, 6305.

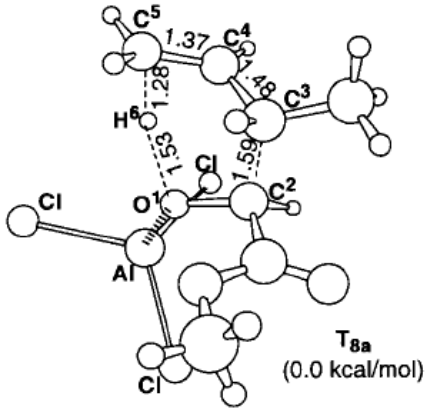
Diastereoselectivity of the Reaction



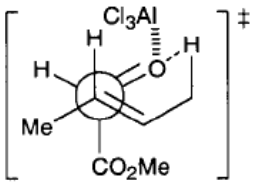
anti (minor)

Natural Charge

O^1: −1.02 C^4: +0.14
C^2: +0.09 C^5: −0.61
C^3: −0.33 H^6: +0.45



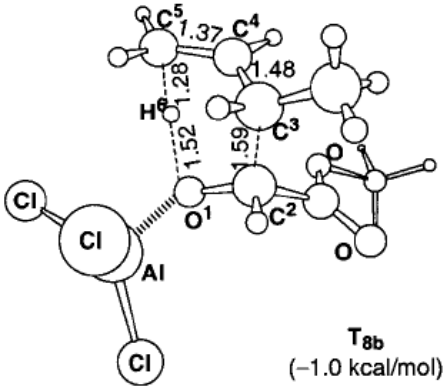
T_{8a}
(0.0 kcal/mol)



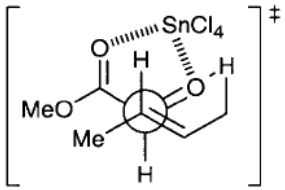
***syn* (major)**

Natural Charge

O^1: −1.01 C^4: +0.15
C^2: +0.09 C^5: −0.64
C^3: −0.34 H^6: +0.45



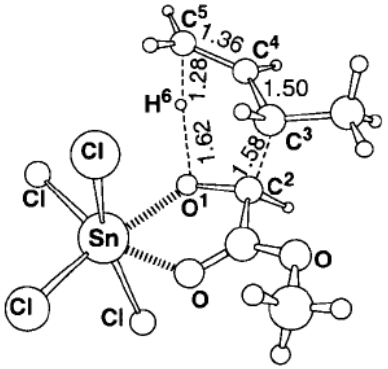
T_{8b}
(−1.0 kcal/mol)



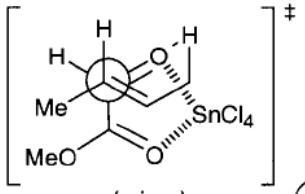
***anti* (major)**

Natural Charge

O^1: −1.01 C^4: +0.06
C^2: +0.08 C^5: −0.52
C^3: −0.32 H^6: +0.45



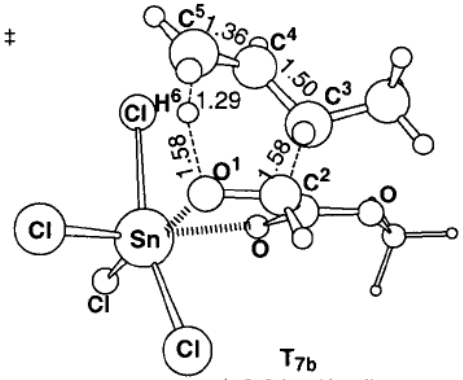
T_{7a}
(0.0 kcal/mol)



syn (minor)

Natural Charge

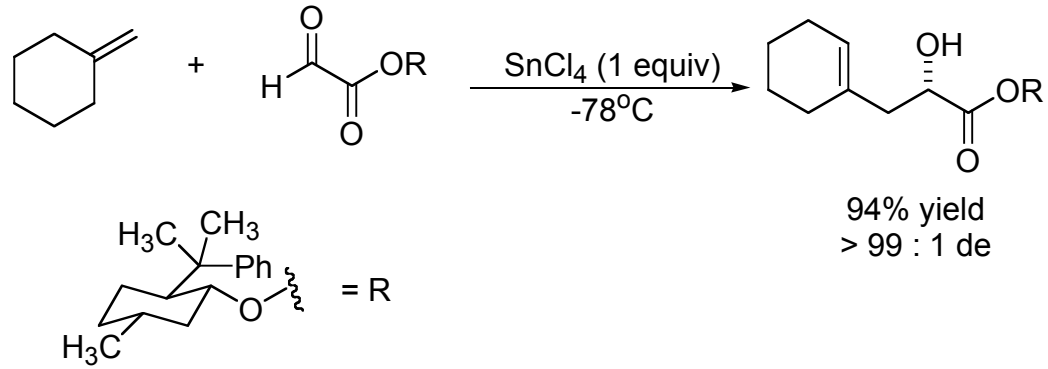
O^1: −1.00 C^4: +0.06
C^2: +0.07 C^5: −0.53
C^3: −0.31 H^6: +0.46



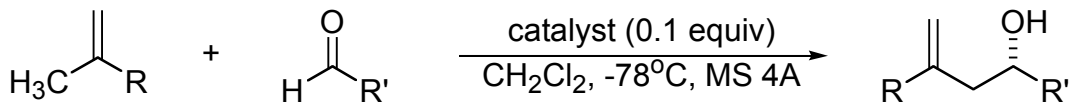
T_{7b}
(+2.8 kcal/mol)

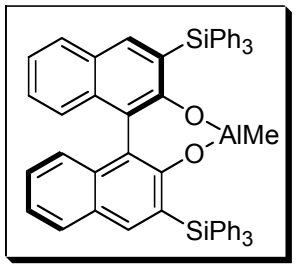
Mikami, K. et al *Helv. Chim. Acta* **2002**, *85*, 4264.

Asymmetric Catalysis: The Beginning



94% yield
> 99 : 1 de

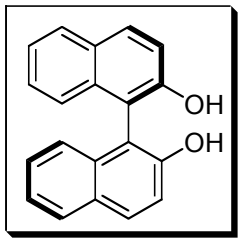




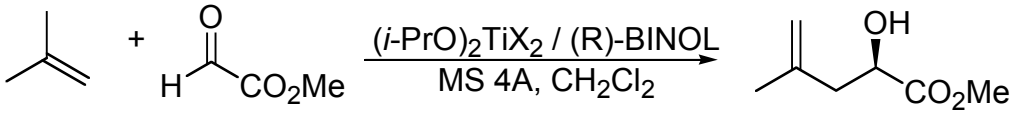
aldehyde	olefin	% yield	% *ee*
C_6F_6CHO	$CH_2=C(CH_3)_2$	56	84
	$CH_2=C(CH_2)_5$	43	86
	$CH_2=C(CH_2)_6$	48	80
	$CH_2=C(CHt_3)t\text{-}Bu$	43	92
	$CH_2=C(CHt_3)Ph$	85	71
Cl_3CCHO	$CH_2=C(CH_3)_2$	60	30
	$CH_2=C(CH_2)_6$	99	64
	$CH_2=C(CHt_3)Ph$	87	51

Whitsell, J.K. et al *Tetrahedron*, **1986**, *42*, 2993.
Yamamoto, H. et al *Tetrahedron Lett.* **1988**, *29*, 3967.

Asymmetric Catalysis: Titanium

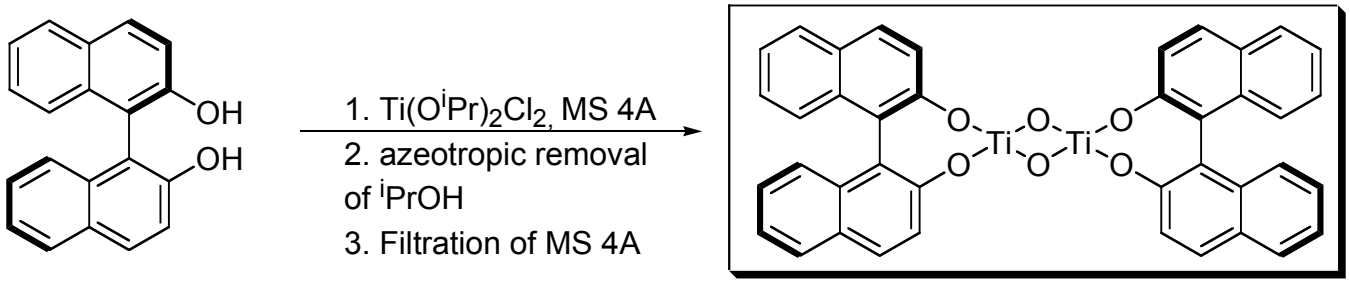


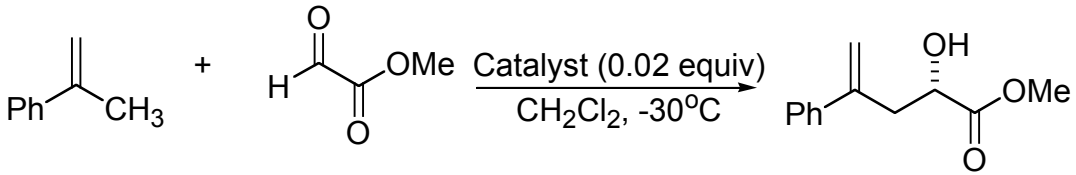
(R)-BINOL



X = Cl (10 mol%) 72% yield
95% ee
(1 mol%) 78% yield
93% ee

X = Br (10 mol%) 87% yield
94% ee

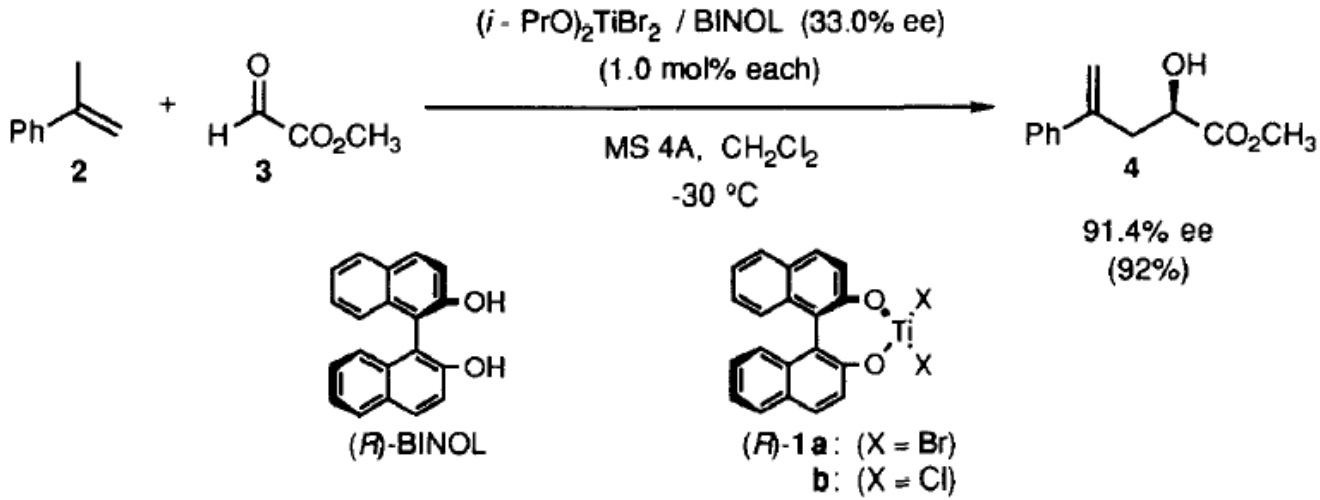




93% yield
98% ee

Mikami, K. et al *J. Am. Chem. Soc.* **1990**, *112*, 3949.
Mikami, K. et al *Chem. Comm.* **1994**, 833.

Asymmetric Catalysis: Titanium NLE



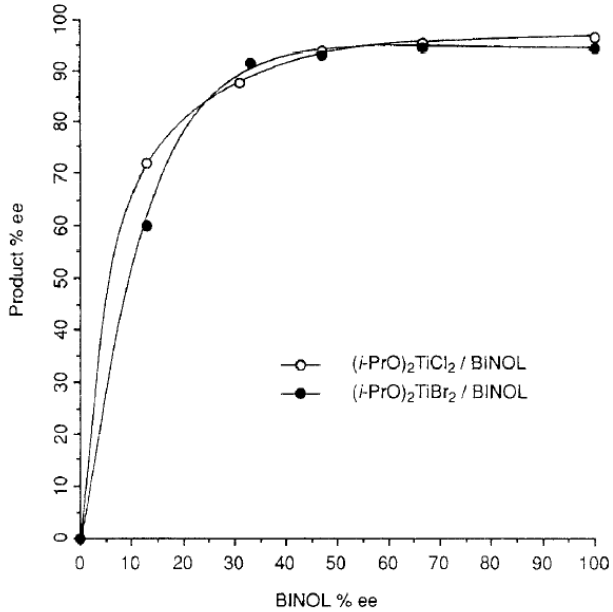
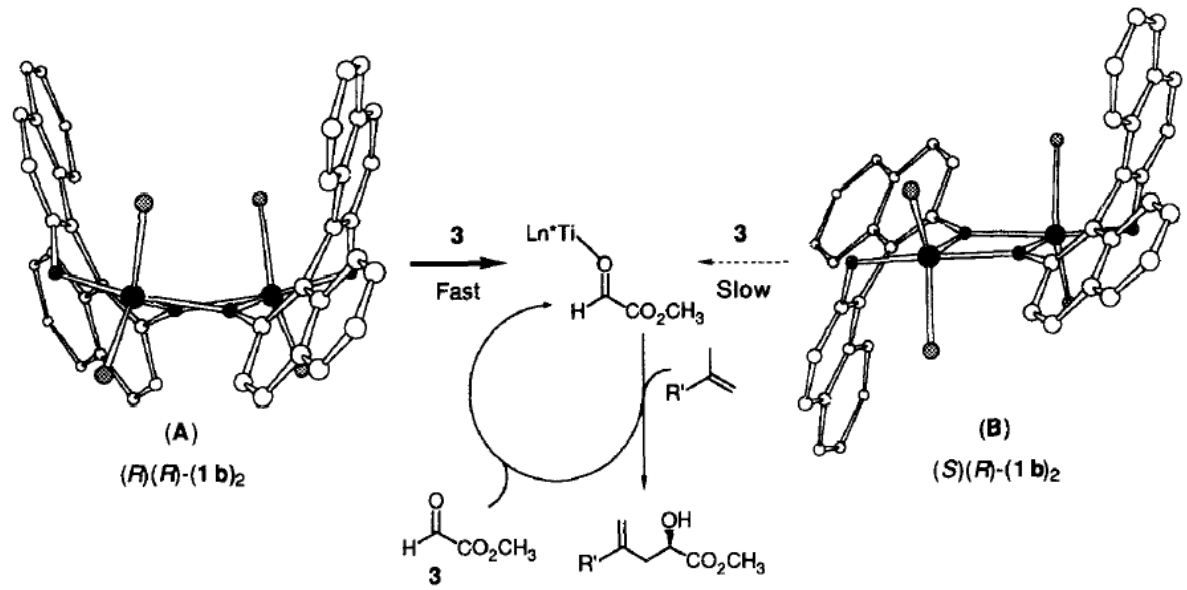
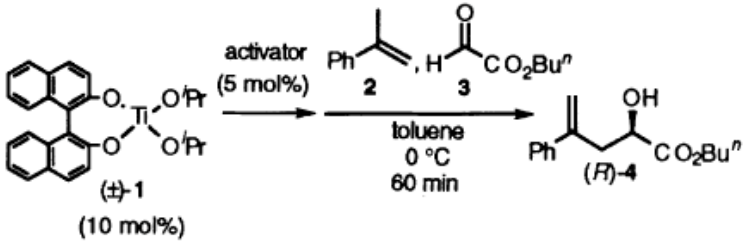


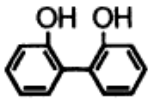
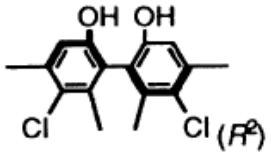
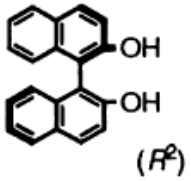
Fig. 2. (+)-NLE in asymmetric glyoxylate-ene reaction catalyzed by 1 (1.0 mol%).



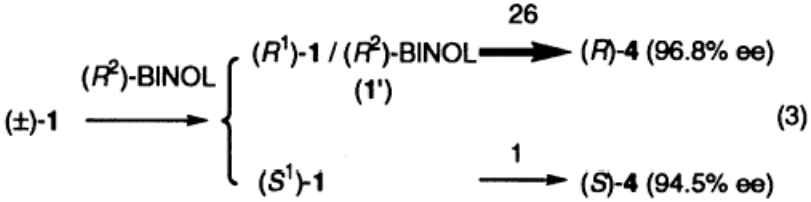
Mikami, K. et al *Tetrahedron* **1992**, *48*, 5671.

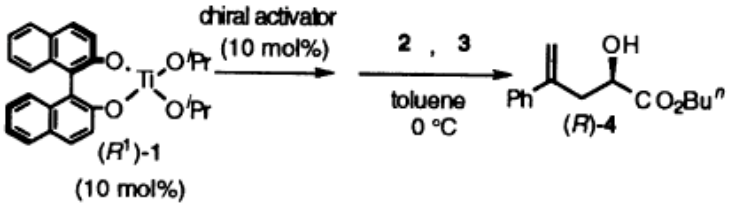
Asymmetric Catalysis: Titanium



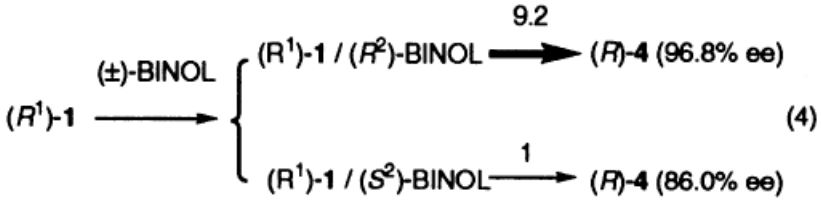
Run	Activator	Yield (%)	e.e. (%)
1	None	5.9	0
2		20	0
3		38	80.8
4		52	89.8
5*		35	80.0

Conditions as in the text, unless otherwise noted.
* The reaction was carried out with 2.5 mol% of (R^2)-BINOL.



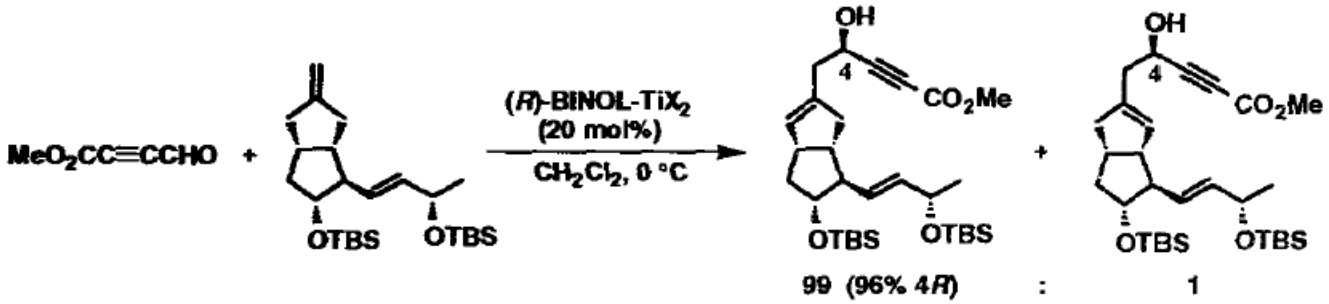


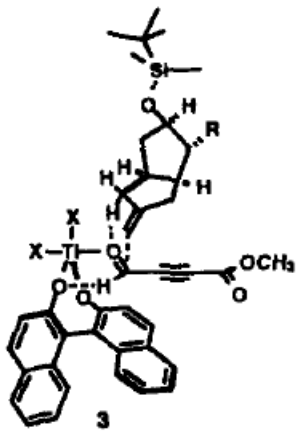
Run	Chiral activator	Time (min)	Yield (%)	e.e. (%)
1	None	60	19.8	94.5
2		1	1.8	94.5
3	(R^2)-5-Cl-BIPOL	60	66.0	97.2
4	(R^2)-BINOL	60	82.1	96.8
5		1	41.1	96.8
6		0.5	24.0	96.9
7	(S^2)-BINOL	60	48.0	86.0
8		0.5	2.6	86.0
9	(±^{2})-BINOL	60	69.2	95.7

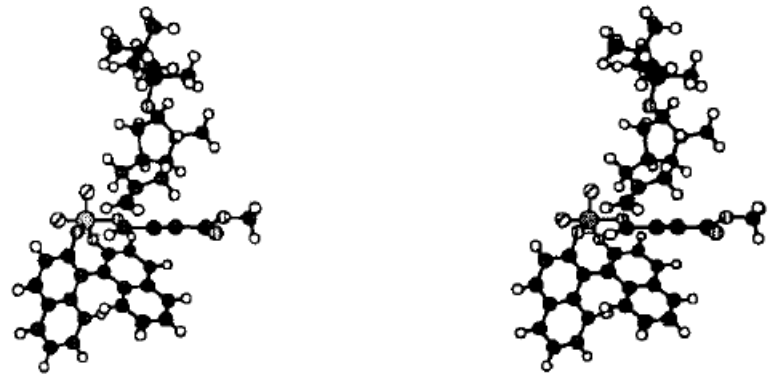


Mikami, K. et al *Angew. Chem. Int. Ed.* **1997**, *36*, 2768.
Chavarot, M. et al *Tetrahedron Asymm.* **1998**, *9*, 3889.

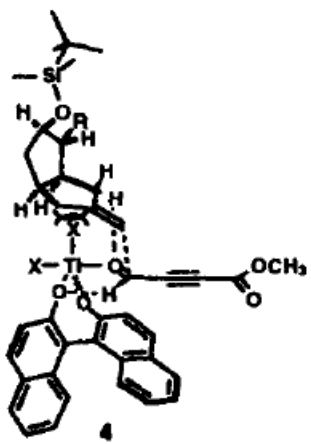
Asymmetric Catalysis: Titanium TS Model

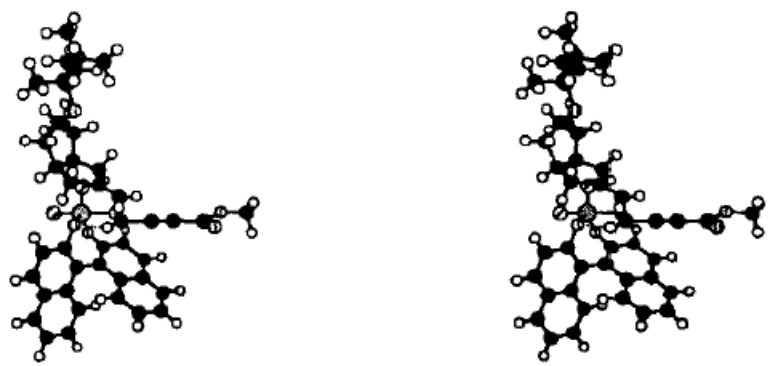






Stereopair representation of 3



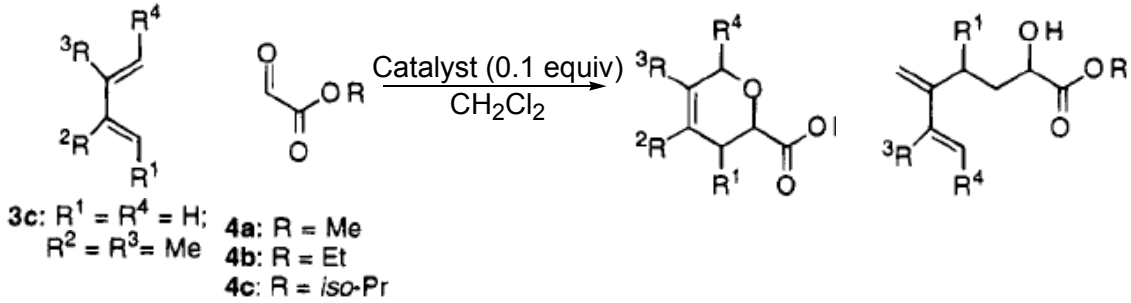


Stereopair representation of 4

● C ○ H ◍ O ◉ Ti ⊘ X ● Si

Corey, E.J. *Tetrahedron Lett.* **1997**, *38*, 6513.

Asymmetric Catalysis: Copper HDE vs ENE



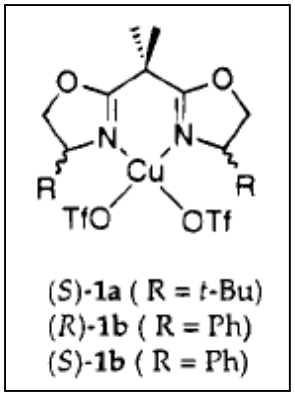
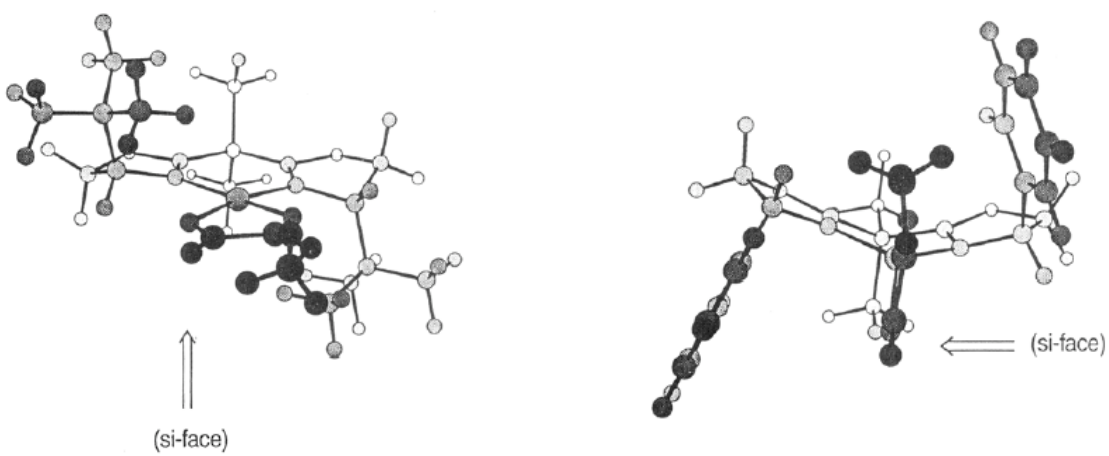


Table 2. Hetero Diels–Alder Reactions and Ene Reactions of 2,3-Dimethyl-1,3-butadiene (3c) and Different Alkyl Glyoxylates 4a–c Catalyzed by (*S*)-1a and (*R*)-1b

entry	catalyst	glyoxylate	Diels–Alder product: yield/%[a] (ee/%)[b] (confg)	ene product: yield/%[a] (ee)[b,c]	Diels–Alder product:ene product ratio
1	(*S*)-**1a**	**4a**	**5a**, 25 (90) (*S*)	**6d**, 39 (85)	1:1.6
2	–	**4b**	**5d**, 20 (85) (*S*)	**6c**, 36 (83)	1:1.8
3	–	**4c**	**5e**, 12 (77) (*S*)	**6d**, 12 (83)	1:1
4	(*R*)-**1b**	**4a**	**5c**, 36 (81) (*S*)	**6b**, 50 (85)	1:1.4
5	–	**4b**	**5d**, 31 (83) (*S*)	**6c**, 50 (88)	1:1.6
6	–	**4c**	**5c**, 31 (87) (*S*)	**6d**, 40 (90)	1:1.3



Jorgensen, K.A. *J. Org. Chem.* **1995**, *60*, 5757.

Asymmetric Catalysis: Copper

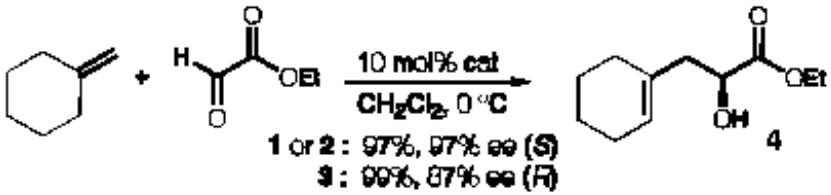
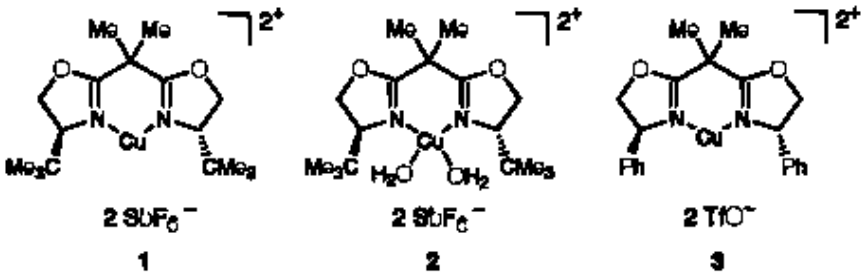
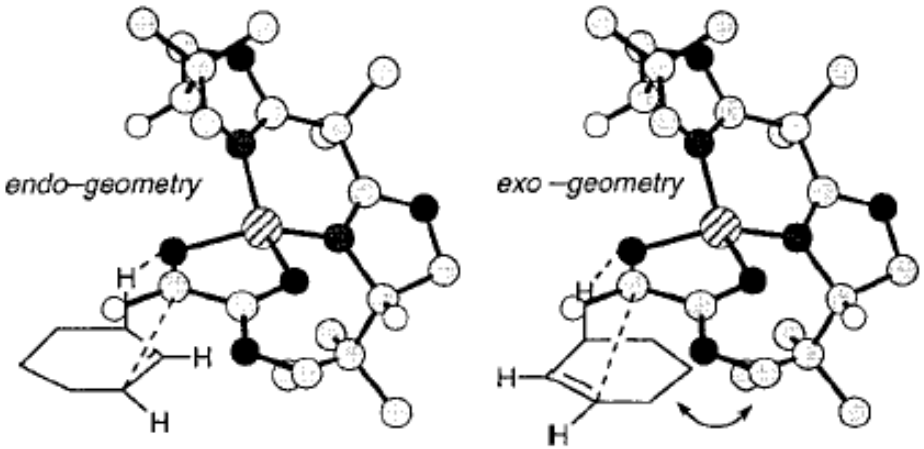


Table 1. Catalyzed Enantioselective Ene Reactions between Ethyl Glyoxylate and Representative Olefins

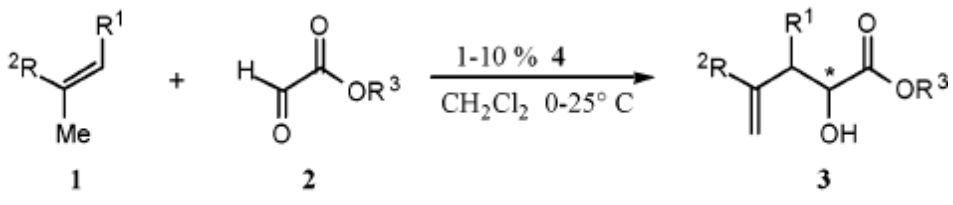
olefin	product[a]	cat (mol%)	T, °C	yield, %[b]	% ee[c]
	4	2 (1) 3 (10)	0	90 99	97 (*S*) 87 (*R*)
	5	2 (1) 3 (10)	0	83 92	96 (*S*) 92 (*R*)
	6	2 (1) 3 (10)	0	97 99	93 (*S*) 89 (*R*)
	7	2 (1) 3 (10)	0	95 97	96 (*S*) 76 (*R*)
	8	2 (1) 3 (10)	25	89[d] 81[e]	96 (*S*) 91 (*R*)
	11	1 (10) 3 (10)	0	95[g] 70[h]	98 (*S*) 94 (*R*)
	12	1 (10)	25	96[i]	98 (*S*)

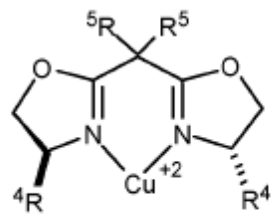




Evans, D.A. *J. Am. Chem. Soc.* **1998**, *120*, 5824.
Evans, D.A. et al *J. Am. Chem. Soc.* **2000**, *122*, 7936.

Asymmetric Catalysis: Copper





4a: R^4=Ph R^5=Me

4b: R^4=$C(CH_3)_3$ R^5=Me

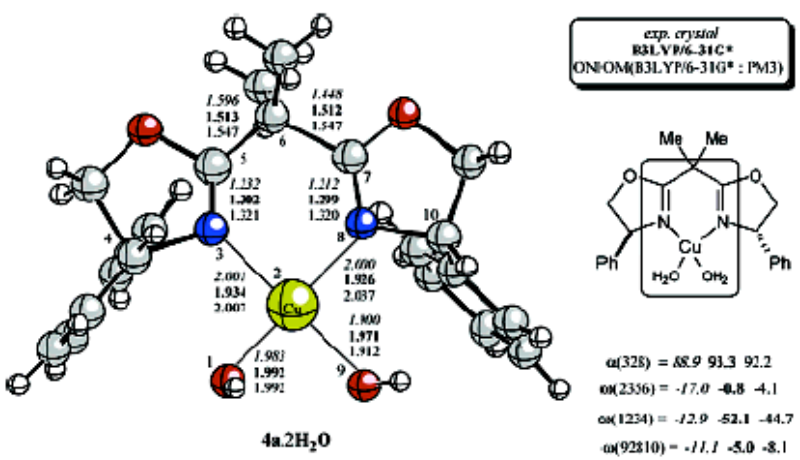


Figure 1. Main geometrical parameters for **4a·2H$_2$O**. Selected bond lengths (Å) and angles (deg). Atoms included in the high level region are within the box.

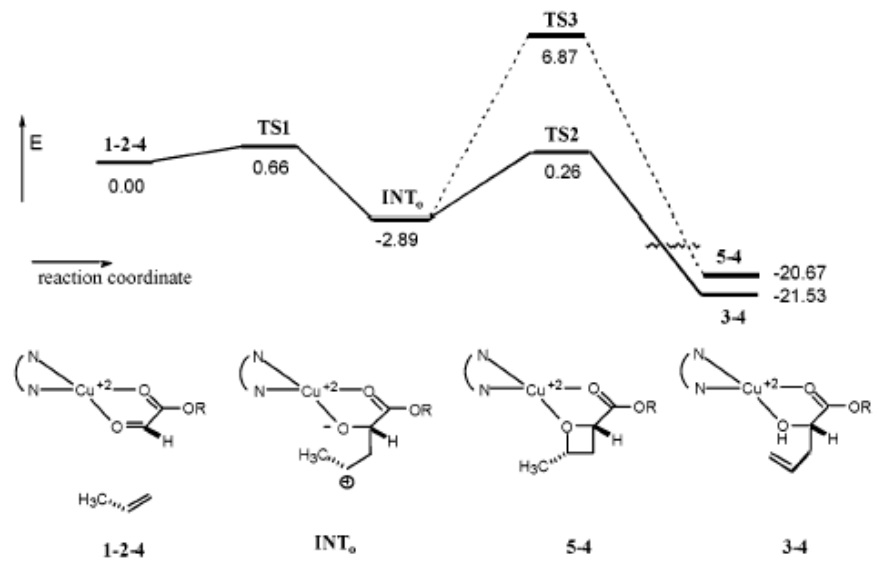
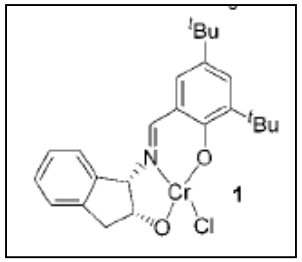


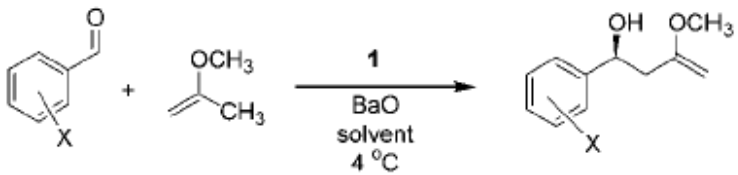
Figure 2. Relative free energies (in kcal/mol) on the pathway (**1** + **2** → **3**) catalyzed by **4** (solid lines) at the UB3LYP(PCM)/6-311G**//UB3LYP/6-31G* level. Only one enantiomer has been drawn (*exo* approach) for clarity. Alternative pathways are indicated by hashed lines.

Endo attack is slightly disfavored for R^4 = $C(CH_3)_3$

Hillier, I.H. *J. Am. Chem. Soc.* **2003**, *125*, 628.

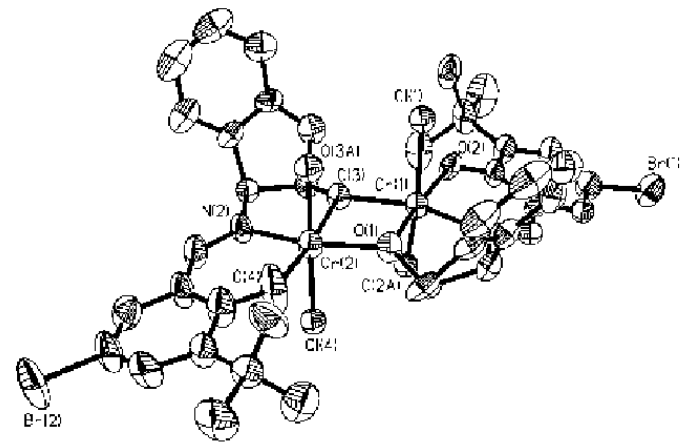
Asymmetric Catalysis: Chromium

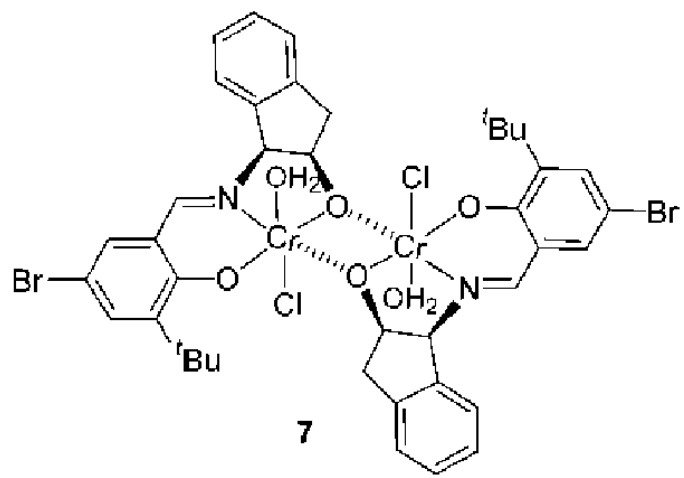




2a-r **3a-r**

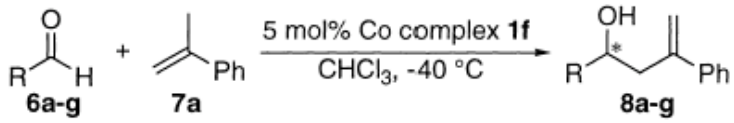
product	X	method[a]	ee (%)	yield (%)[e]	time (h)
3a	H	B	88[b]	82	40
3b	2-Br	A	96[b]	97	20
3c	3-Br	A	86[b]	94	36
3d	4-Br	B	87[b]	78	40
3e	2-CH_3	B	94[b]	41	40
3f	3-CH_3	B	90[b]	50	40
3g	4-CH_3	B	89[b]	26	40
3h	2-Cl	A	96[b]	98	20
3i	3-Cl	A	84[b]	97	36
3j	4-Cl	B	85[c]	78	40
3k	2-OCH_3	B	95[c]	75	40
3l	3-CN	A	86[d]	80	36
3m	4-CN	A	84[b]	92	40
3n	2-NO_2	A	96[b]	89	20
3o	3-NO_2	A	90[d]	85	36
3p	4-NO_2	A	70[d]	88	36
3q	2,4-Cl	A	92[b]	96	20
3r	2,6-Cl	A	86[b]	82	20



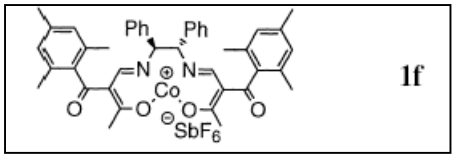


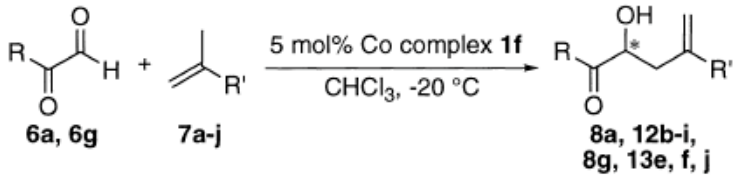
Jacobsen, E.N. et al *J. Am. Chem. Soc.* **2002**, *124*, 2882.

Asymmetric Catalysis: Cobalt

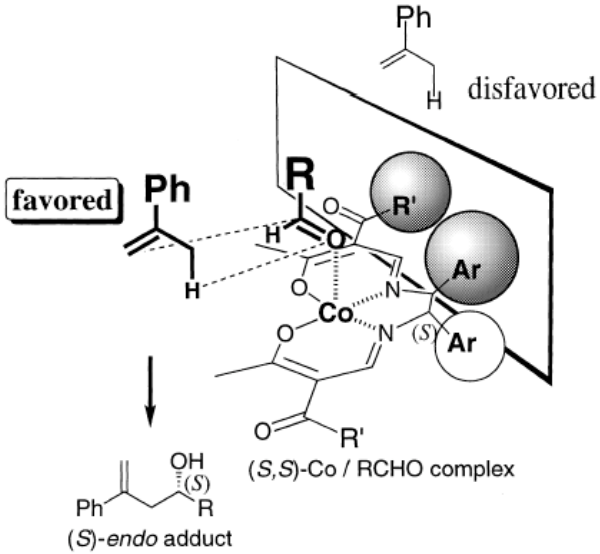


Entry[a)]	Glyoxal	Yield/%[b)]	Ee/%
1	X = H (**6a**)	95	94
2	X = NO_2 (**6b**)	80	92
3	X = F (**6c**)	81	92
4	X = Cl (**6d**)	89	92
5	X = Br (**6e**)	80	91
6	X = Me (**6f**)	45	91
7[c)]	**6g**	91	85





Entry[a)]	R	Alkene		Yield/%[b)]	Ee/%
1	Ph (**6a**)		X = F (**7b**)	92	88
2			X = H (**7a**)	93	93
3			X = Me (**7c**)	70	84
4			**7d**	87	92
5			**7e**	87	89
6			**7f**	81	91
7			**7g**	56	84
8			**7h**	75	94
9		OTBS	**7i**	60	94



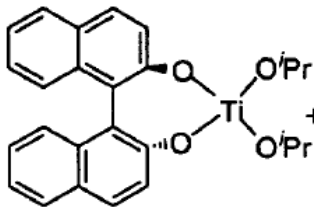
Yamada, T. et al *Bull. Chem. Soc. Jpn.* **2003**, *76*, 49.

Conclusions

-The LA catalyzed carbonyl-ene reaction is of great advantage over the thermal variant, allowing for a control point for modulation of the rate of reaction and product distribution.

-Key experiments have been successful at gaining insight into the mechanism of the LA catalyzed carbonyl-ene process, but relatively little work has been dedicated toward control of the regio- and stereo-selectivity of the reaction.

-The employment of chiral LAs has provided quite impressive results for asymmetric induction for the reaction for a number of simple substrates, but more work on complex systems is required.



(*S*)-**1a** (R = *t*-Bu)
(*R*)-**1b** (R = Ph)
(*S*)-**1b** (R = Ph)