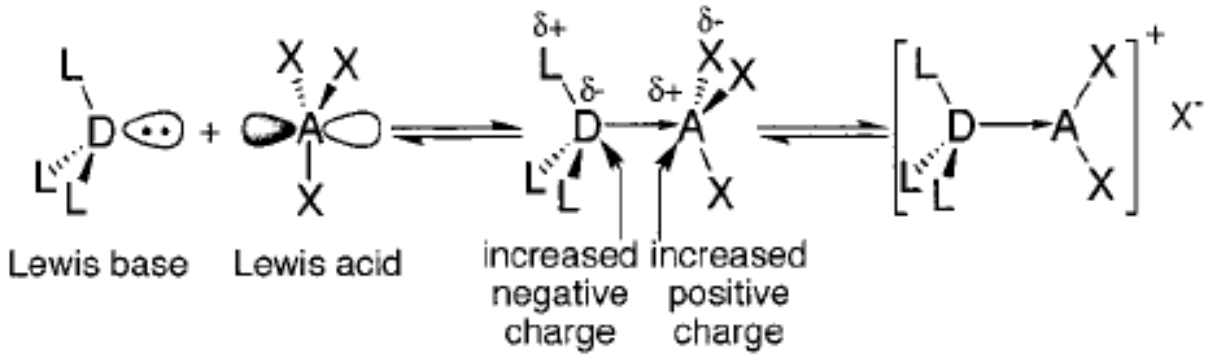
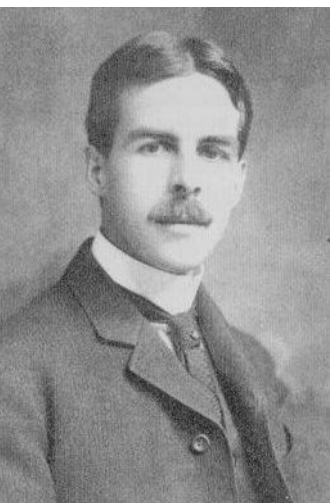
The Development of Lewis Base Catalyzed Aldol Reactions





Rob Matunas

Supergroup Meeting

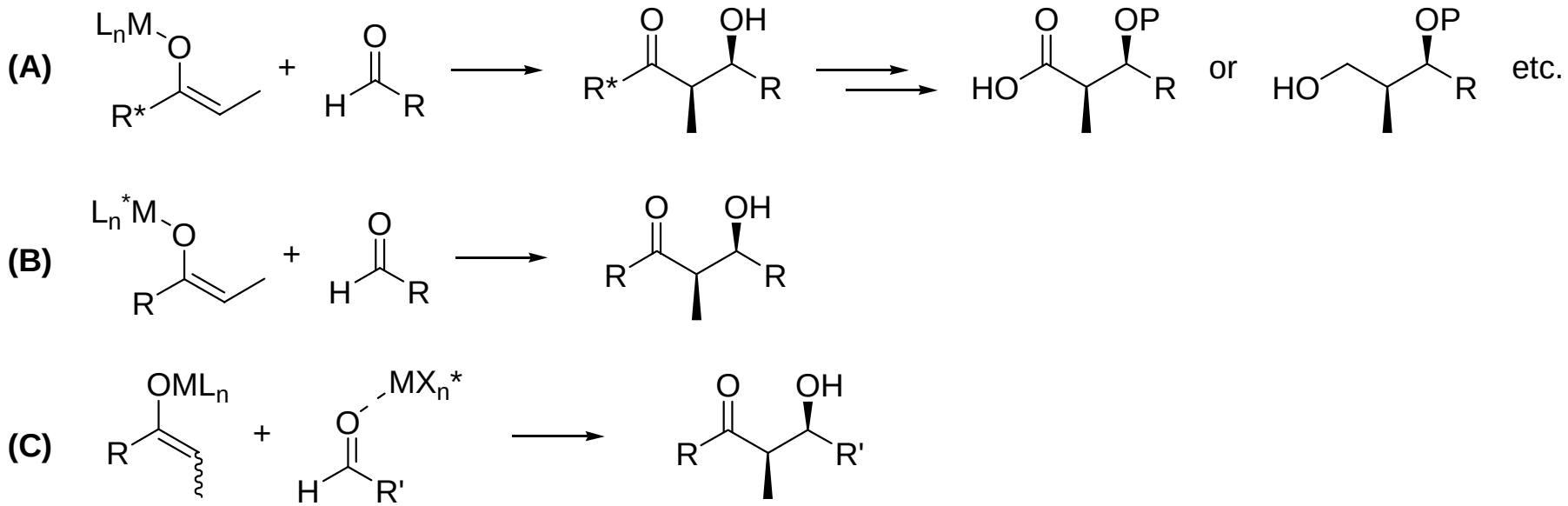
5/24/06

Introduction

Today's Menu:

1. Early investigations on Lewis base catalyzed aldol reactions (simple aldehydes)
2. Mechanistic Studies
3. Investigations on more complicated aldehyde systems
4. Crossed-aldol reactions of aldehydes
5. "Aldol" reactions with ketones
6. The emergence of a "2nd Generation" approach
7. Mechanistic Studies of the "2nd Generation" approach

Designing a New Aldol Reaction: Why and How?



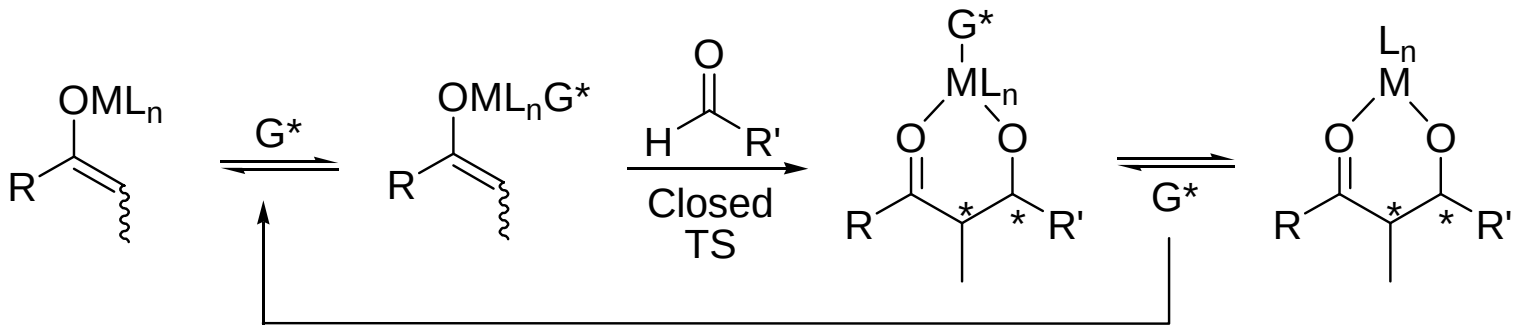
(A) Use a chiral auxiliary on the nucleophilic partner. This works well (closed TS, broad scope), but requires the removal of the auxiliary.

(B) Use a chiral metal/ligand complex to induce stereochemistry. This works well, but the metal/ligand complex is typically used in stoichiometric amounts.

(C) Use a chiral Lewis acid to activate the aldehyde. This works well, and can be catalytic, but proceeds through an open TS and is also less general.

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

Design Concept



Requirements:

(1) "M" must be capable of expanding its valence by two.

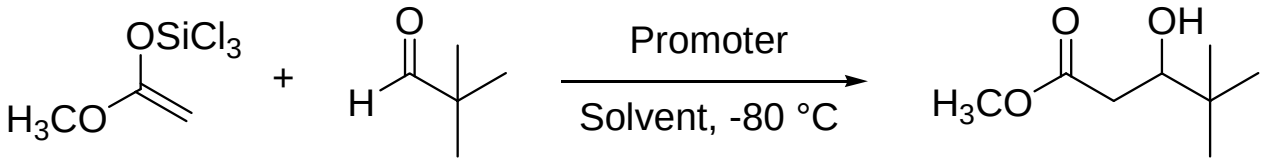
(2) The ML_n-enolate must not be sufficiently nucleophilic to undergo background addition without G*.

(3) G* must be a chiral Lewis base whose complexation to ML_n increases the nucleophilicity of the enolate and/or activates the aldehyde towards addition.

Suitable Candidate: "M" = Si!

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

First Examples

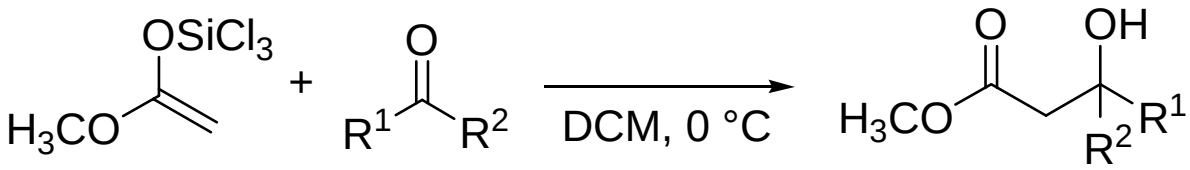


Solvent	Promoter	Conversion/time, %/min
Toluene-d_8	None	18/120
CD_2Cl_2	None	50/120
THF-d_8	None	69/120
CD_2Cl_2	HMPA	100/<3

Only pivaldehyde reacted slowly enough to allow reaction monitoring by NMR! (Other aldehydes were consumed spontaneously.) Most importantly, HMPA was found to be an exceptional Lewis-basic promoter.

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

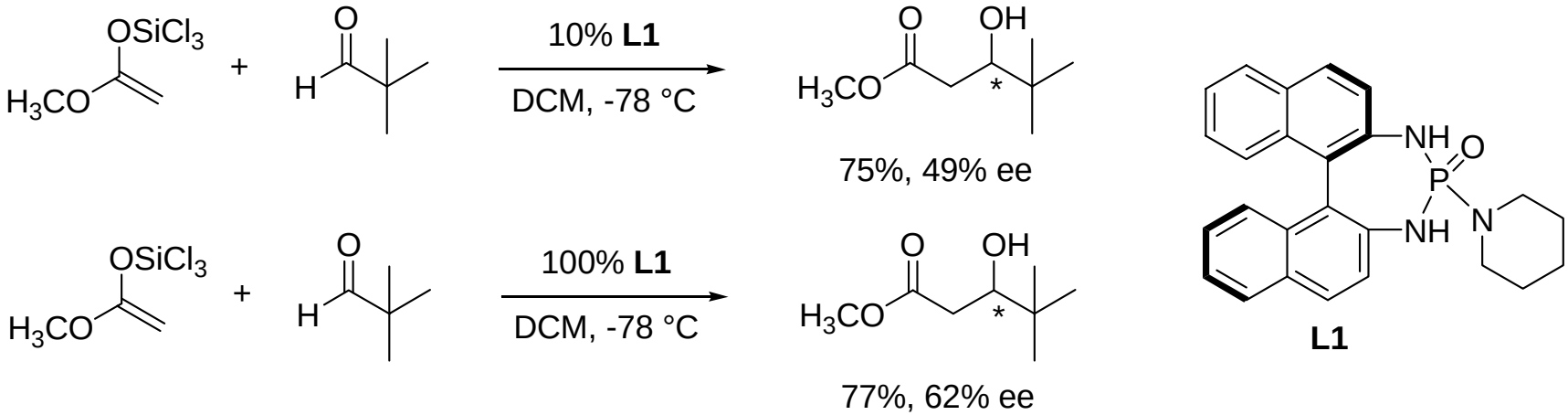
More Preliminary Examples



R^1	R^2	Yield, %
Ph	H	98
Bn	H	94
Cy	H	96
Ph	CH_3	97 (at 20 °C)

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

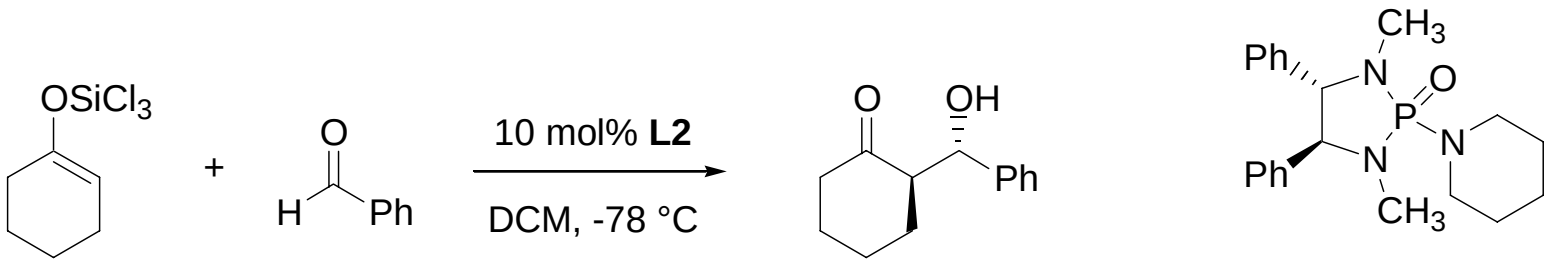
Induction of Chirality?



Unfortunately, the best chiral phosphoramide promoter **L1** failed to give high levels of ee – this was attributed to the all too-facile uncatalyzed background reaction.

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

A Promising Lead…



L2

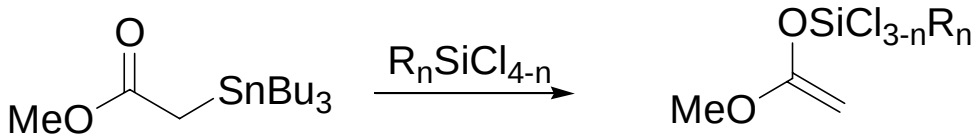
95%, *anti*:*syn* 65:1, 93% ee

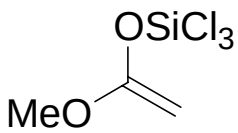
Off to a running start: good ee observed with a less reactive silyl enol ether. The initial explanation of the observed reactivity is: "a classic chairlike arrangement of reactive partners assembled around a hexacoordinate siliconate species."

J. Am. Chem. Soc. **1996**, *118*, 7404-7405.

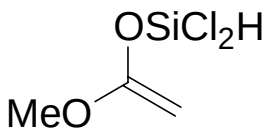
Back to the Ester-Derived Enolates: Attempts at Attenuating Reactivity

Trichlorosilyl ketene acetals were seen to be too reactive for asymmetric catalysis due to competitive background reactions. The logical thing to do would be to attenuate the reactivity of these species by changing the substituents on silicon (by removing Lewis-acidic chlorides).

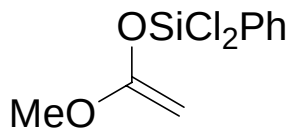




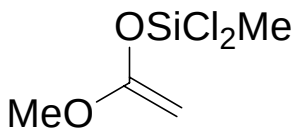
1a, 60-65%



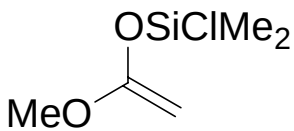
1b, 48%



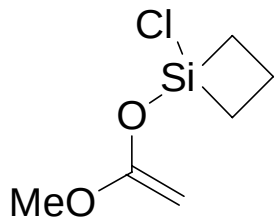
1c, 23%



1d, 57%



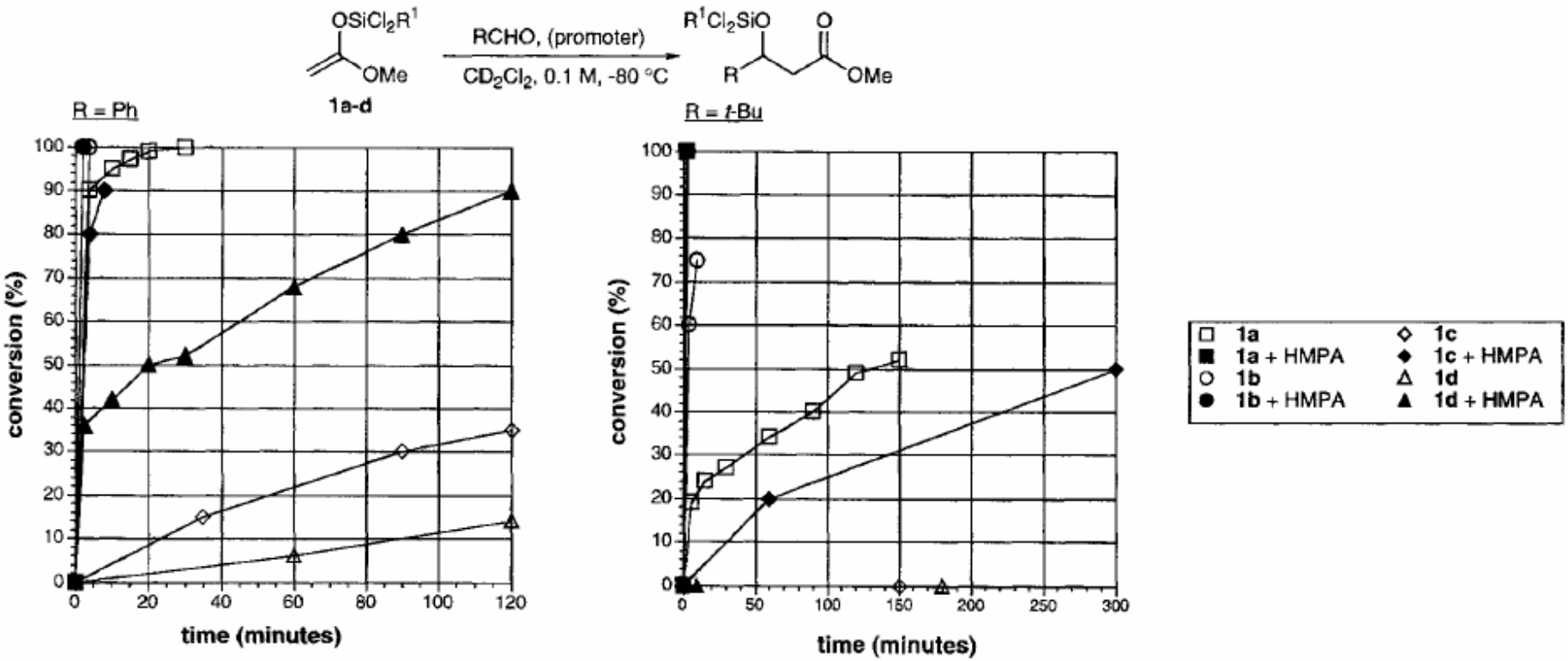
1e, 18%



1f, 19%

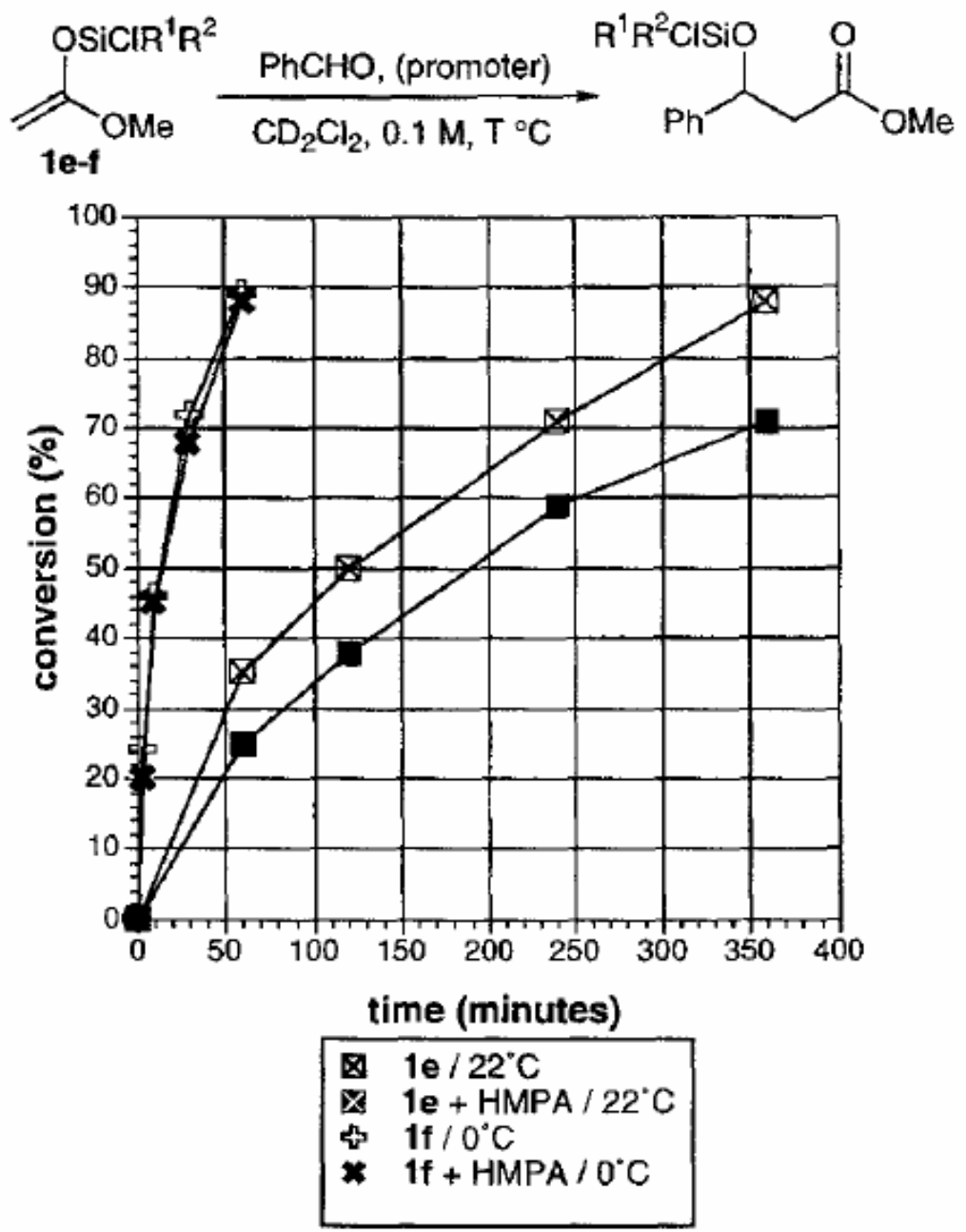
Synlett, **1997**, 1087-1089.

And the Results…

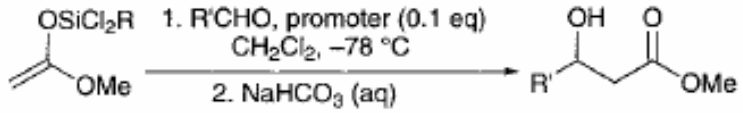


Apparent trend in rates: $R^1 = H > Cl > Ph > Me$

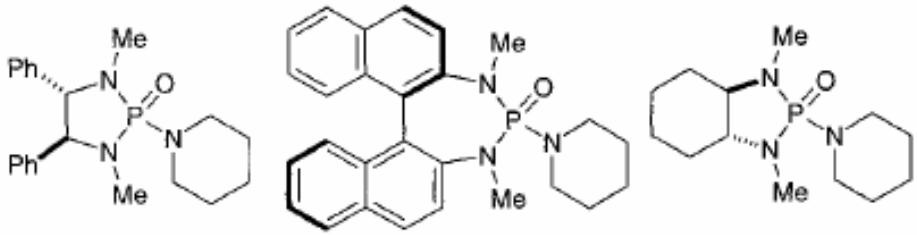
Synlett, **1997**, 1087-1089.



Synlett, **1997**, 1087-1089.



1a-d 70-90%



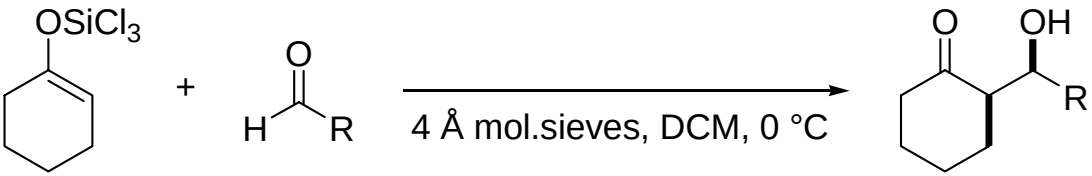
3 **4** **5**

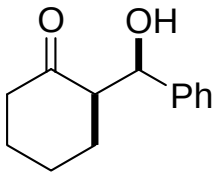
entry	promoter	aldehyde	ee, % (configuration)[b] 1a[c]	1b	1c	1d
1	**3**	PhCHO	33 (*S*)	4 (*R*)	23 (*R*)	26 (*S*)
2	**4**	PhCHO	23 (*S*)	< 2	< 2	27 (*R*)
3	**5**	PhCHO	20 (*R*)	6 (*R*)	12 (*S*)	< 2
4	**3**	*t*-BuCHO	40 (*S*)	46 (*R*)	12 (*S*)	4 (*S*)[d]
5	**4**	*t*-BuCHO	49 (*S*)	26 (*S*)	10 (*S*)	9 (*R*)[d]
6	**5**	*t*-BuCHO	26 (*R*)	25 (*R*)	ND	< 2[d]

[a] Yield of chromatographically homogeneous material. [b] Determined by chiral HPLC (Entries 1-3: Chiralcel® AD; 95:5 hexane:EtOH; 1 $mLmin^{-1}$; λ = 254 nm. Entries 4-6: Chiralcel® AD; 98:2 hexane:EtOH; 0.8 $mLmin^{-1}$; λ = 210 nm). [c] Ref 1. [d] 0°C

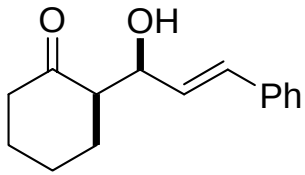
Synlett, **1997**, 1087-1089.

Where to Next?

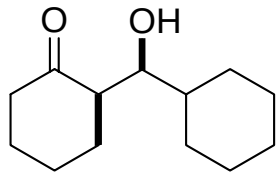




6 h, 92%,
syn:*anti* 49:1



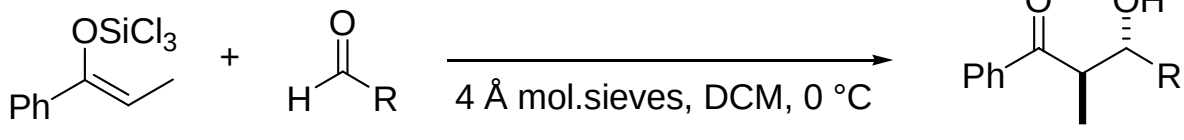
1 h, 83%,
syn:*anti* 49:1

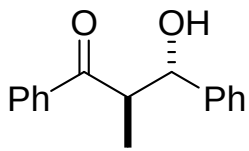


36 h, 92%,
syn:*anti* 1:1

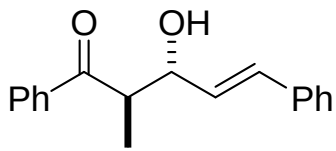
More *uncatalyzed* aldol reactions.

Notice the stereochemical outcome…*E* enolate → *syn* product, *Z* enolate → *anti* product.

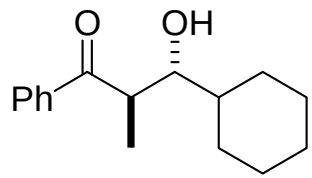




10 h, 97%,
syn:*anti* 1:2.3



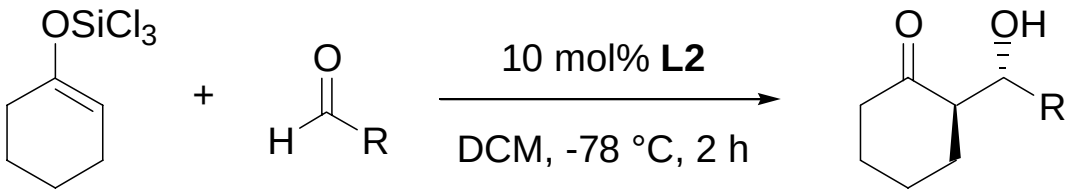
10 h, 95%,
syn:*anti* 1:1.9

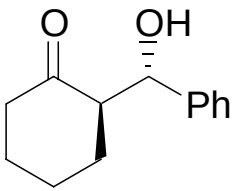


0%

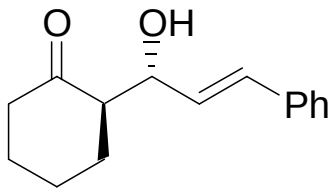
J. Am. Chem. Soc. **1997**, *119*, 2333-2334.

Now For More Chiral Examples



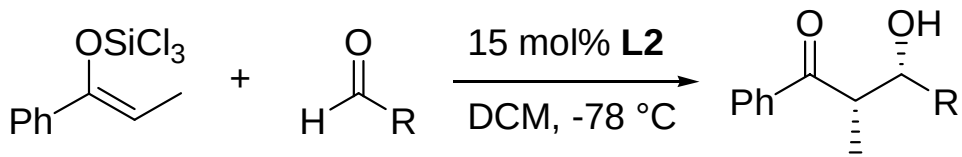


95%,
syn:*anti* 1:61,
93% ee

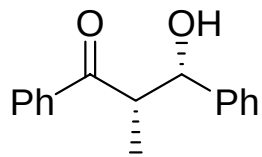


94%,
syn:*anti* <1:99,
88% ee

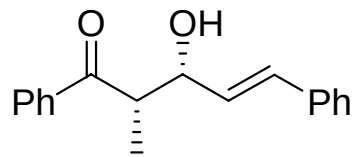
Aliphatic aldehydes don't work under these conditions…



…but good *syn*/*anti* ratios and ee's are observed. And the diastereoselectivity has reversed completely!



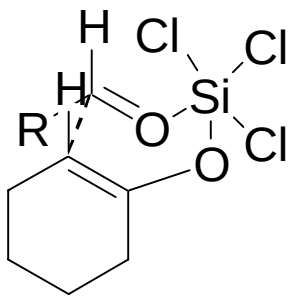
6 h, 95%,
syn:*anti* 18:1,
95% ee



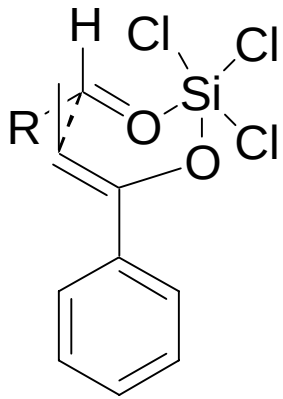
6 h, 97%,
syn:*anti* 9.4:1,
92% ee

J. Am. Chem. Soc. **1997**, *119*, 2333-2334.

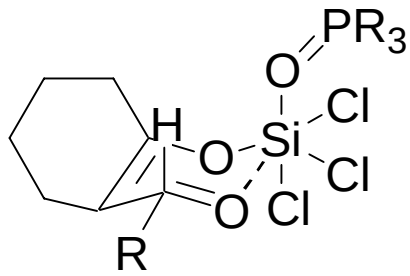
What's Going on Here?



I



II



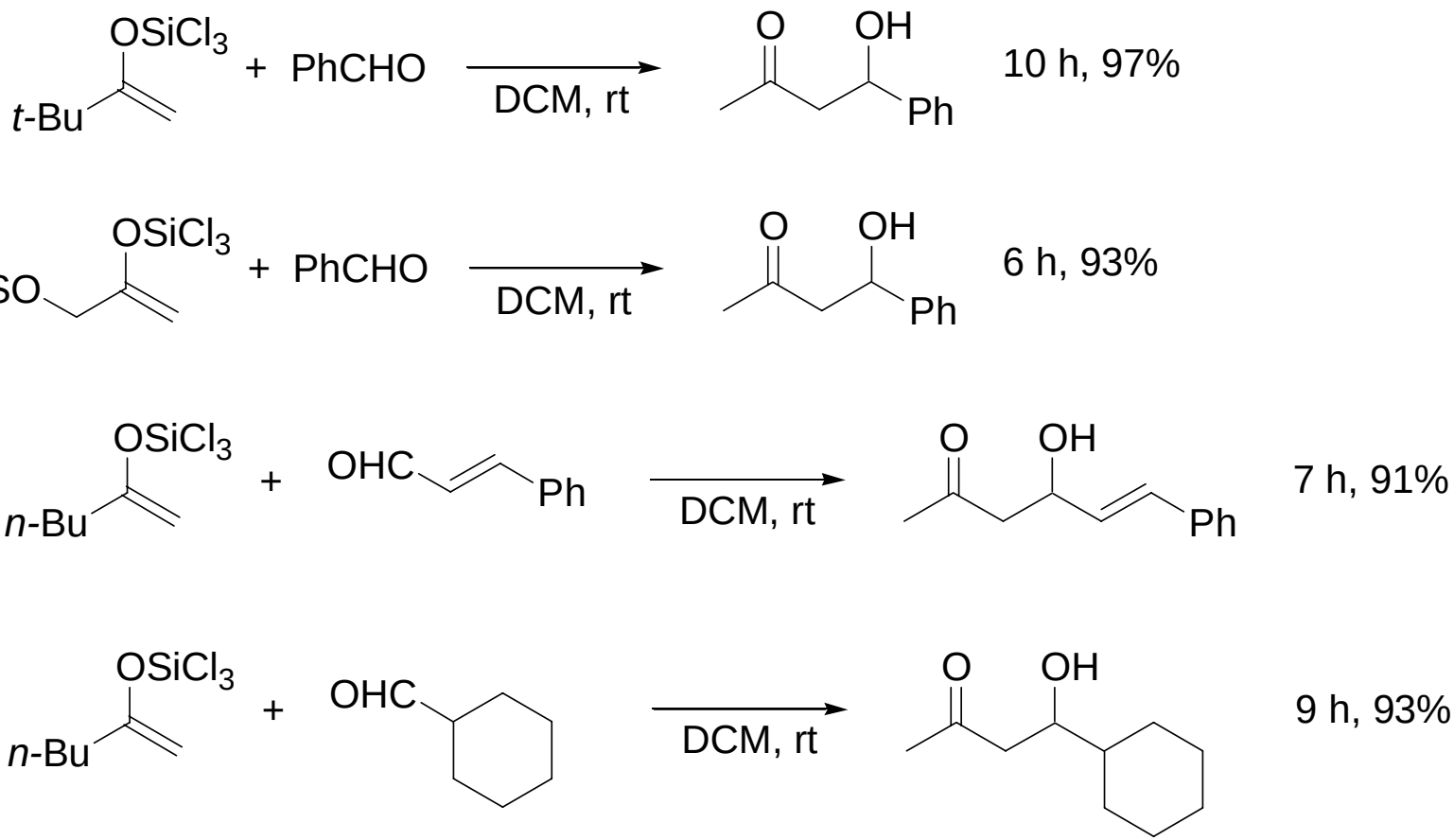
III

A preliminary explanation: In the absence of promoter, boat TS's **I** and **II** apply for *E* and *Z* enolates, respectively. In the presence of a promoter, a switch to chair TS **III** occurs.

J. Am. Chem. Soc. **1997**, *119*, 2333-2334.

What About Unsubstituted Enolates?

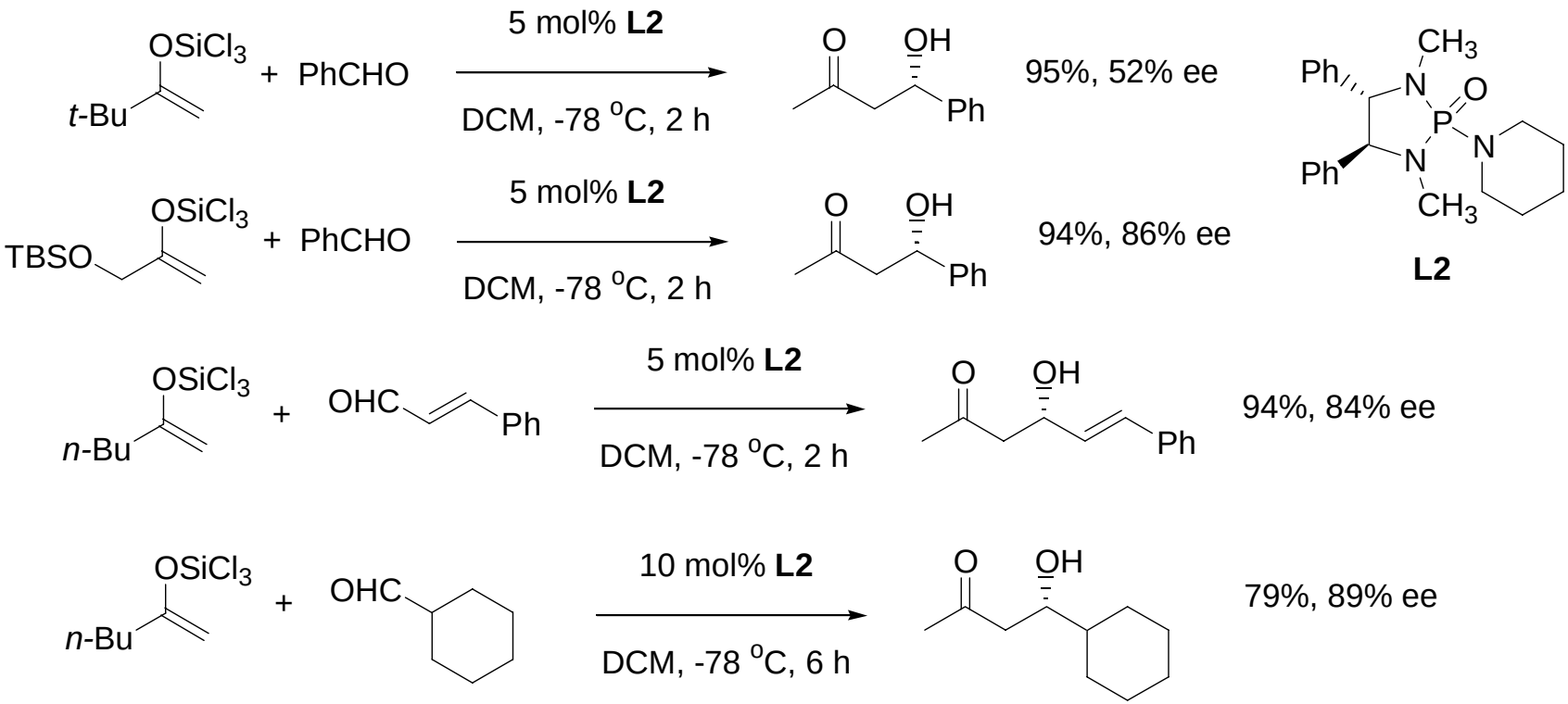
Generally excellent reactivity in *uncatalyzed* reactions:



J. Org. Chem. **1998**, *63*, 918-919.

More on Those Unsubstituted Enolates

With ligand **L2**, good yields and ee's are observed for most substrates.
Linear aliphatic aldehydes are again absent, however.

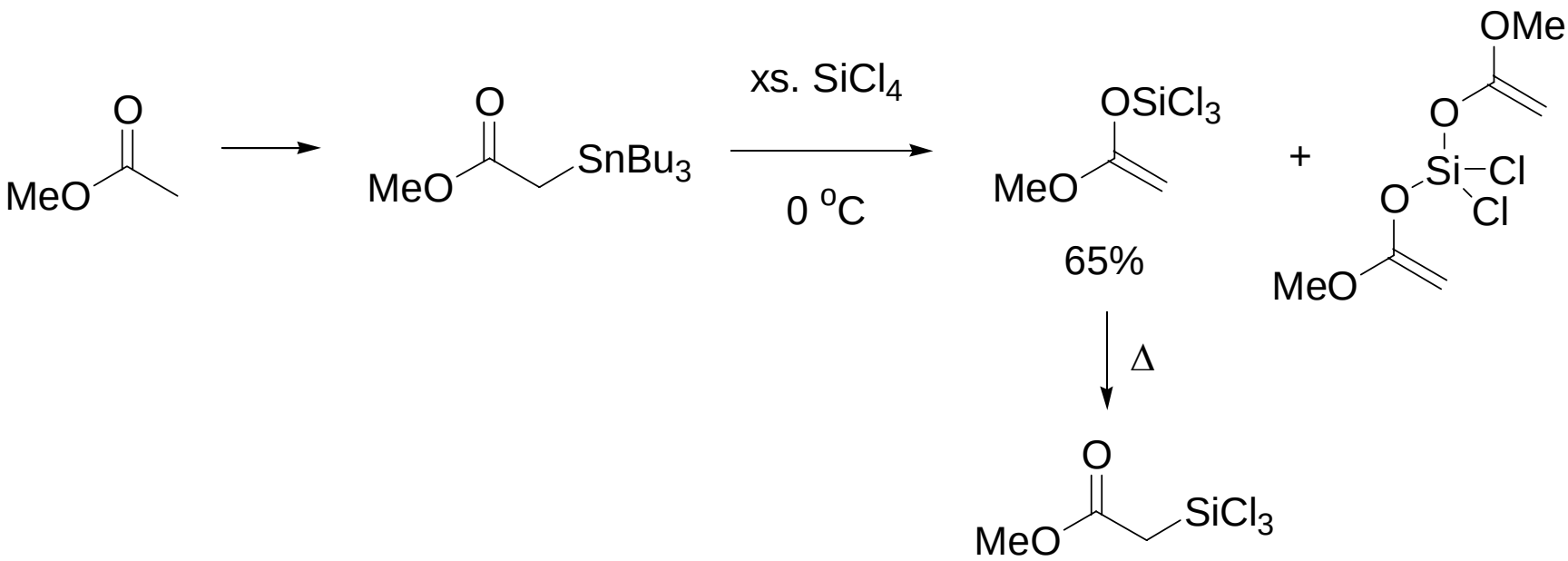


J. Org. Chem. **1998**, *63*, 918-919.

Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

The "Stannane Method" for esters:

Moderate yields; inconvenient experimental manipulations; excess $SiCl_4$ required to avoid "dimer" formation; careful, low-temperature distillation required for isolation (isomerization to *C*-silyl species can occur thermally)

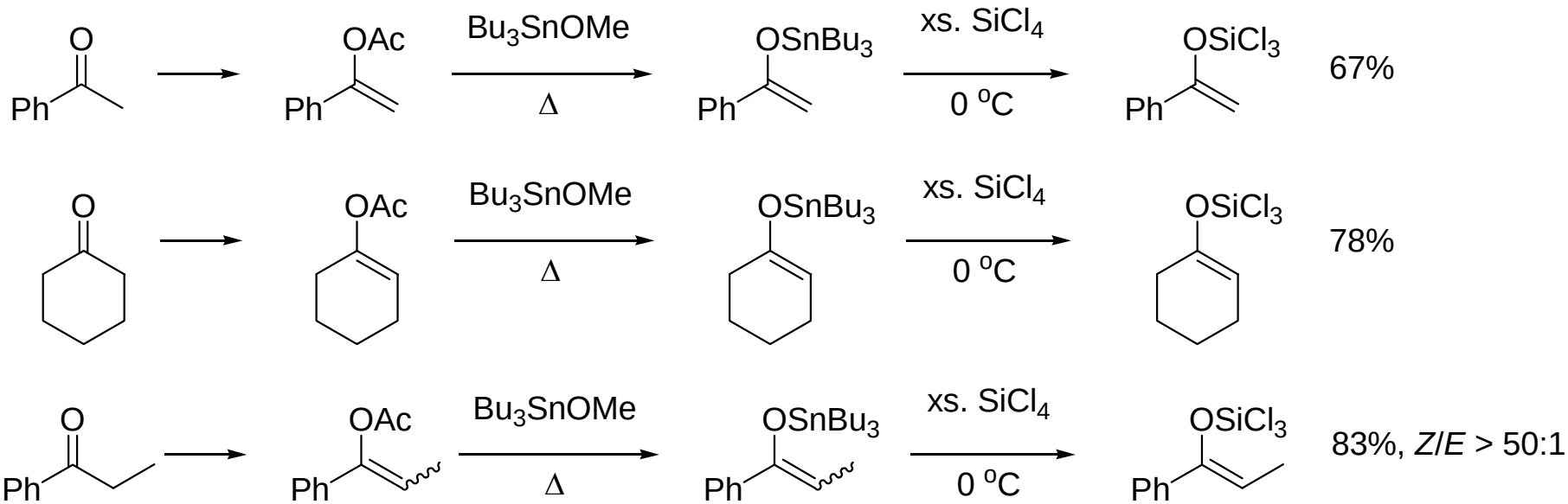


J. Org. Chem. **1998**, *63*, 9517-9523.

Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

The "Stannane Method" for ketones:

Requires formation of the desired enol acetate (regiochemically pure); moderate to good yields; products are thermally stable (unlike the esters), allowing for higher-temperature distillation

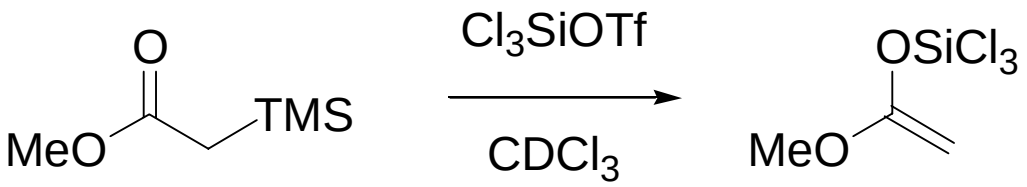


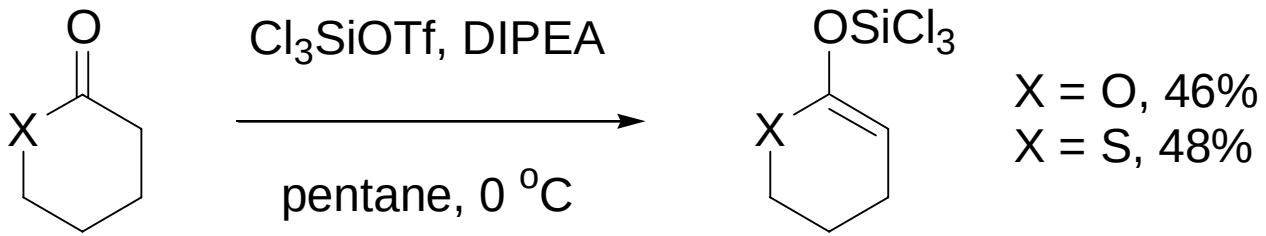
J. Org. Chem. **1998**, *63*, 9517-9523.

Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

Ester Enolates from Cl_3SiOTf:

Moderate yields for cyclic esters; acyclic esters react only slowly; pure products obtained after distillation





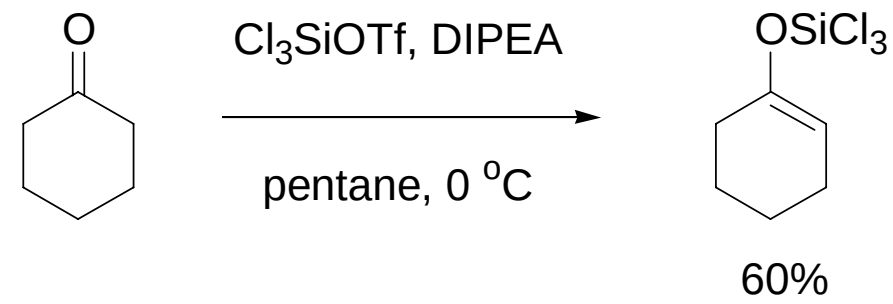
Why not try using $SiCl_4$ instead of $TfOSiCl_3$? No reaction is observed on treatment of an ester with $SiCl_4$ under "hard" or "soft" conditions!

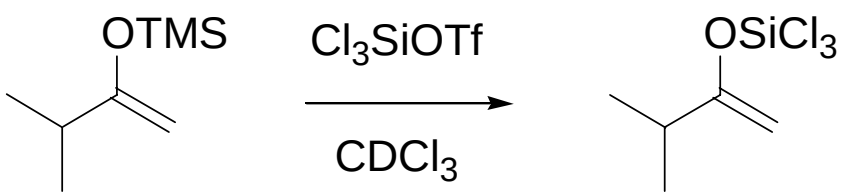
J. Org. Chem. **1998**, *63*, 9517-9523.

Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

Ketone Enolates from Cl_3SiOTf:

"…too capricious for general preparative purposes."

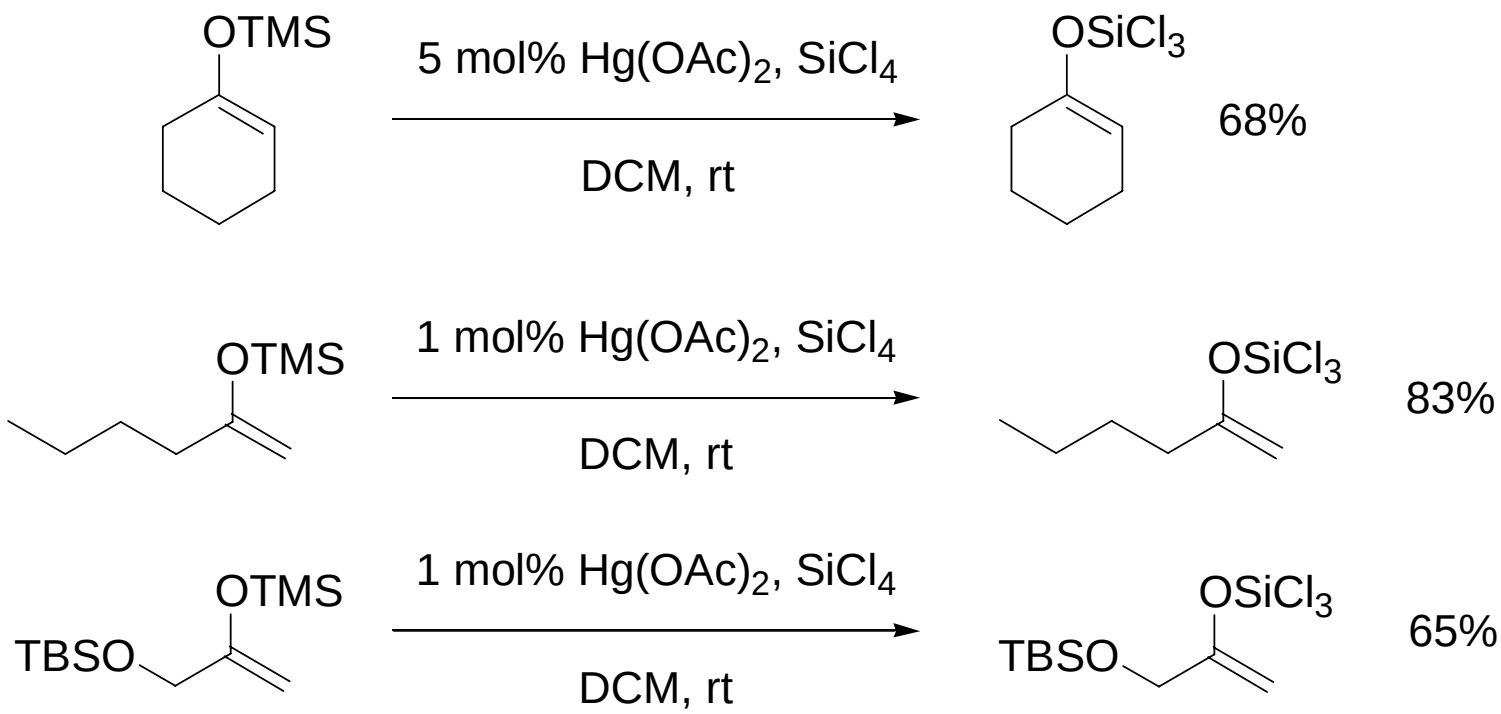




J. Org. Chem. **1998**, *63*, 9517-9523.

Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

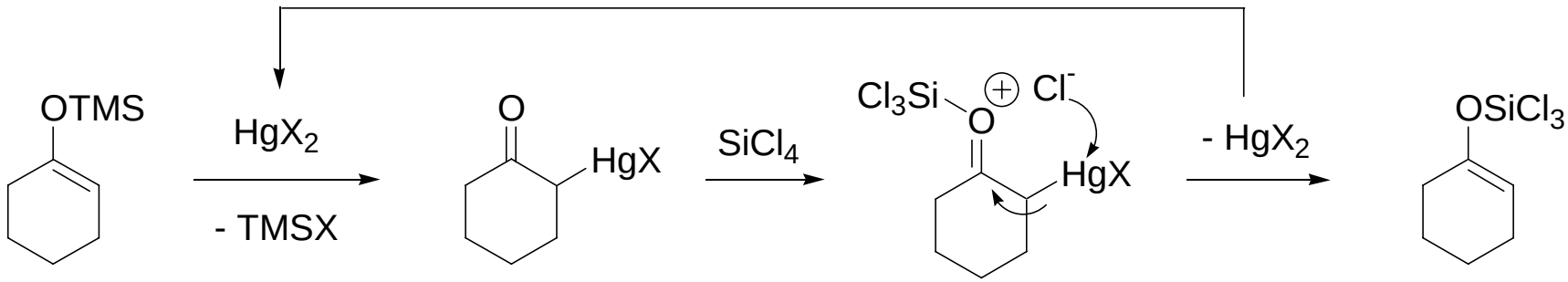
The Hg-catalyzed trans-silylation method for ketones:
Easily prepared starting materials; good yields and functional group tolerance; experimentally convenient; products useable directly without purification; minimal "dimer" formation



J. Org. Chem. **1998**, *63*, 9517-9523.

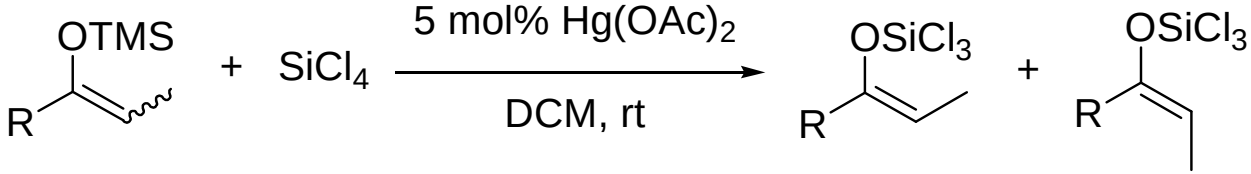
Before Going Further…Just How Do You Make These Trichlorosilyl Enolates?

Presumed mechanism of the Hg-catalyzed trans-silylation:



J. Org. Chem. **1998**, *63*, 9517-9523.

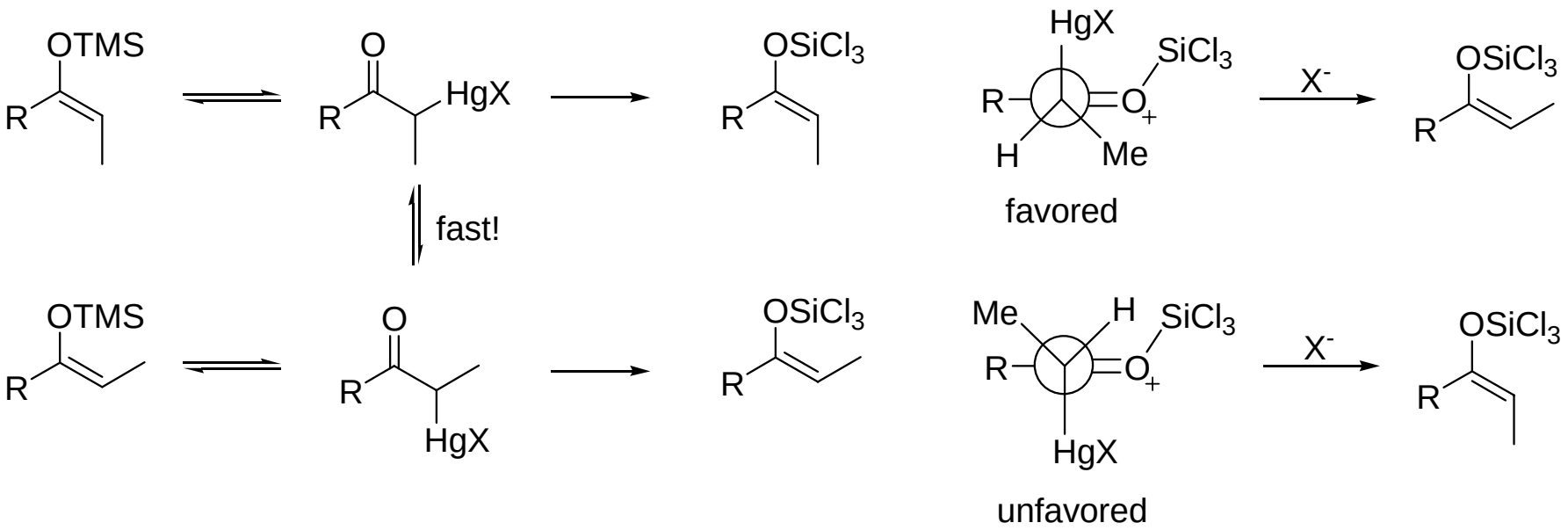
Problems with Some Enolate Types



R	yield, %	*E*/*Z*
Me	58	2/1
Et	72	2/1
i-Pr	65	8/1
t-Bu	55	>20/1
Ph	66	99/1

J. Org. Chem **2003**, *68*, 5045-5055.

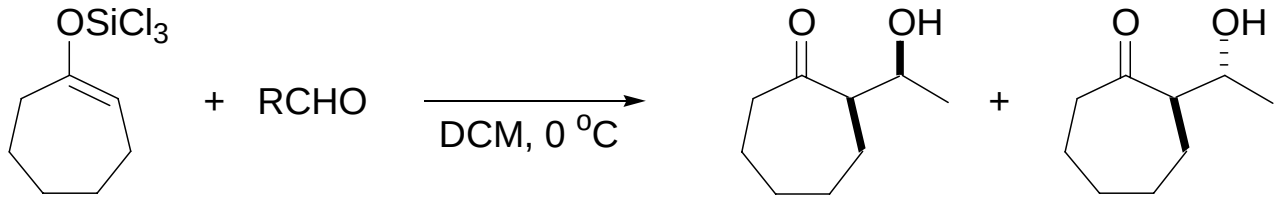
What's the Problem?



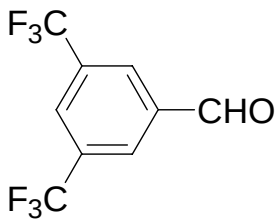
The geometry of the enol ether is controlled by the size of the R group!

J. Org. Chem **2003**, *68*, 5045-5055.

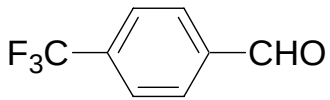
Dependence on Aldehyde Electronics



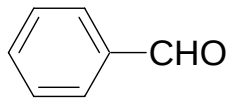
aldehyde	time, h	yield, %	*syn*:*anti*
a	11	90	19:1
b	9	92	28:1
c	10	96	26:1
d	8	96	>49:1
e	11	91	>49:1



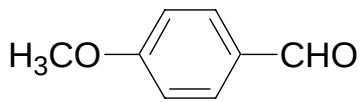
a



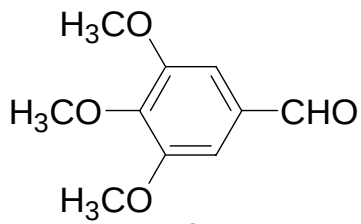
b



c



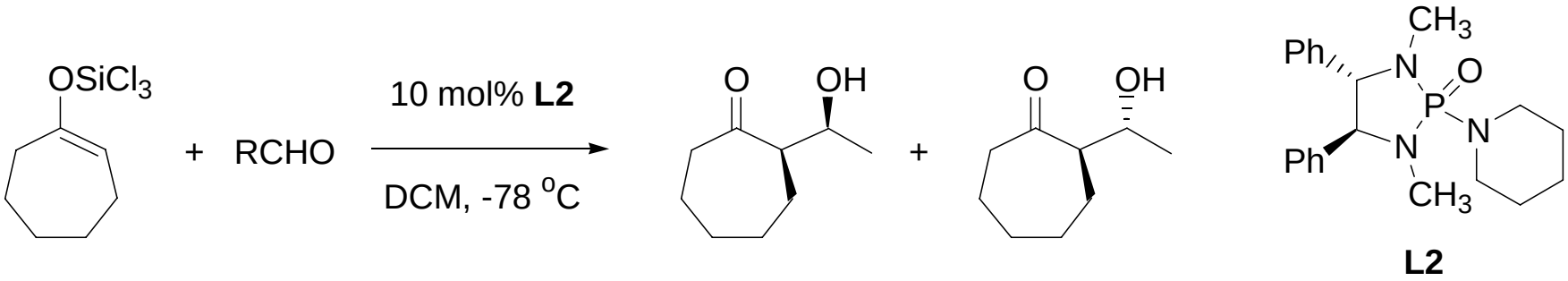
d



e

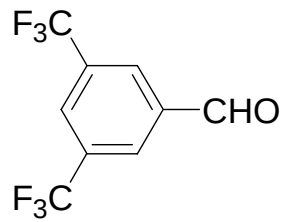
Tetrahedron, **1998**, *54*, 10389-10402.

Dependence on Aldehyde Electronics II

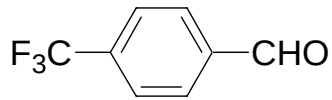


L2

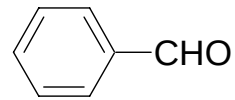
aldehyde	*syn:anti*	yield, % (ee)
a	1:17	91, (82)
b	1:15	96, (79)
c	1:29	97, (84)
d	1:35	97, (92)
e	1:20	94, (87)



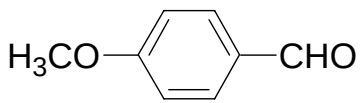
a



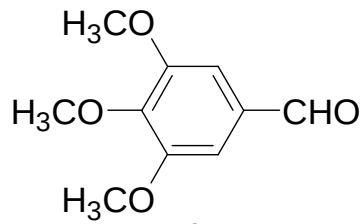
b



c



d



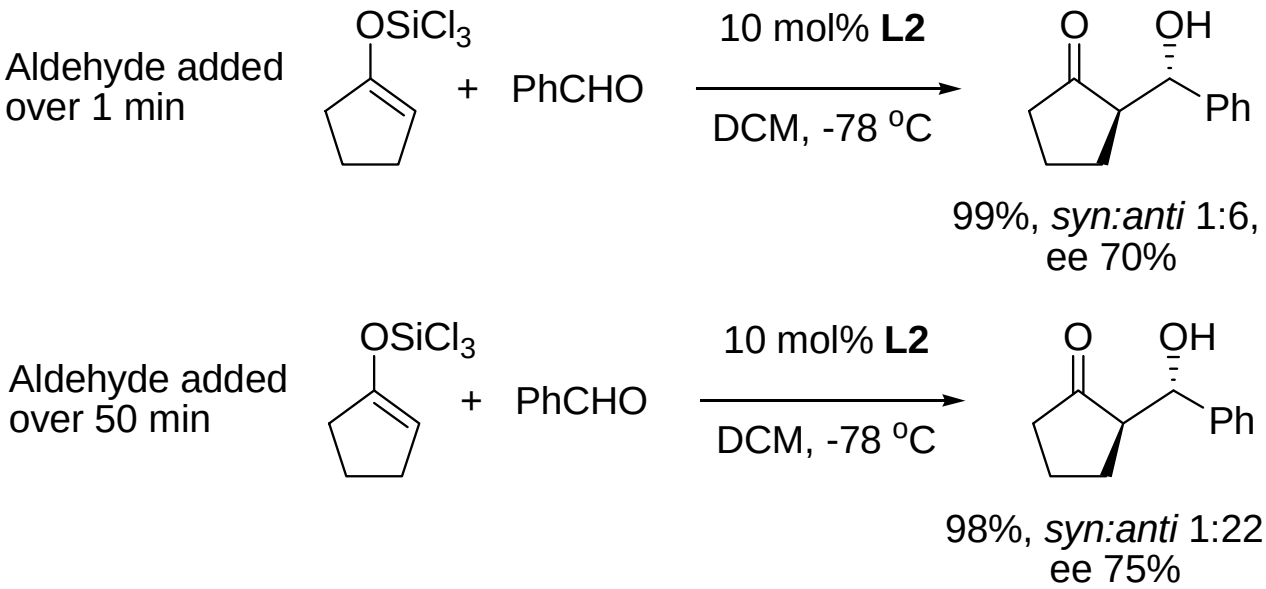
e

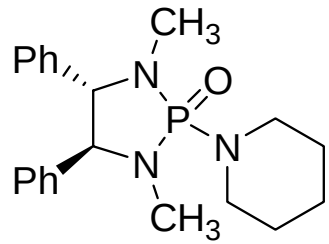
In both catalyzed and uncatalyzed reactions, electron-rich aldehydes give better *syn:anti* ratios.

Tetrahedron, **1998**, *54*, 10389-10402.

Dependence on Aldehyde Electronics III

This interesting trend was observed during optimization studies:





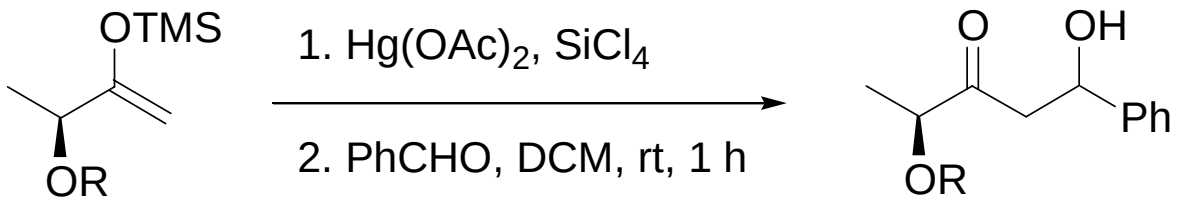
L2

"Since the enantiomeric ratio of the anti-diastereomer does not change with diastereomeric ratio, and as the syn-diastereomer is produced in much lower enantiomeric ratio in all cases we propose that *only the anti diastereomer arises from a hexacoordinate siliconate species.*"

Tetrahedron, **1998**, *54*, 10389-10402.

Investigations of 1,4-Stereoinduction

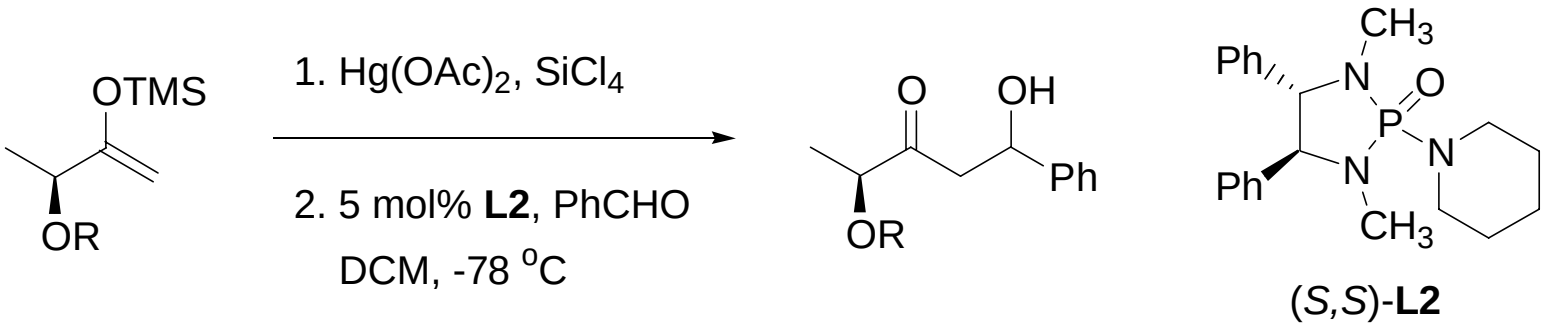
Since these reactions apparently proceed through tight, well-organized transition states (either boat or chair), can resident chirality be transferred from the nucleophile to the product as in other types of aldol reactions?



R	yield, %	*syn:anti*
TBS	82	1:1.2
Piv	71	1:2.4
Bn	75	1:3.4

J. Org. Chem. **1998**, *63*, 9524-9527.

Will Chiral Catalysts Help?



(*S*,*S*)-**L2**

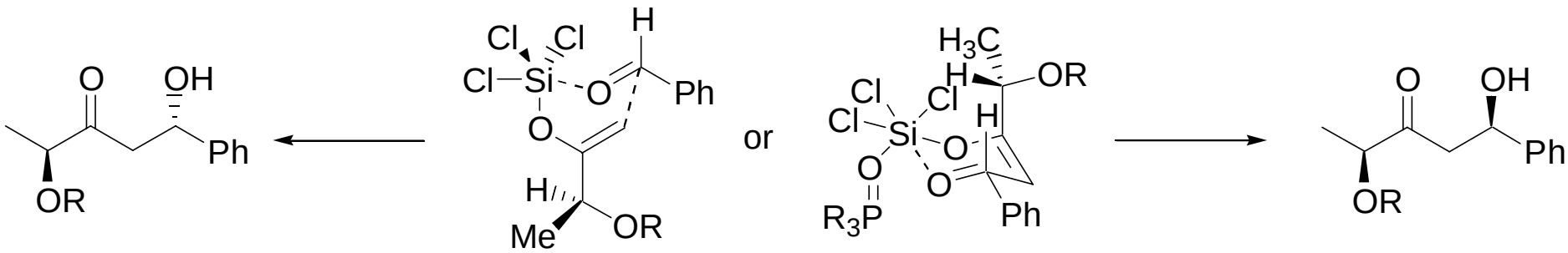
R	catalyst	yield, %	*syn:anti*
TBS	(*S*,*S*)-**L2**	85	1.5:1
Piv	(*S*,*S*)-**L2**	78	3.4:1
Bn	(*S*,*S*)-**L2**	78	1:1.1
TBS	(*R*,*R*)-**L2**	85	73:1*
Piv	(*R*,*R*)-**L2**	78	20:1
Bn	(*R*,*R*)-**L2**	77	11:1

* 95%, 70:1 *syn:anti* with purified enol ether

Chiral phosphoramide catalysis results in noticeably increased dr's in the matched cases.

J. Org. Chem. **1998**, *63*, 9524-9527.

Transition State Models for 1,4-Induction

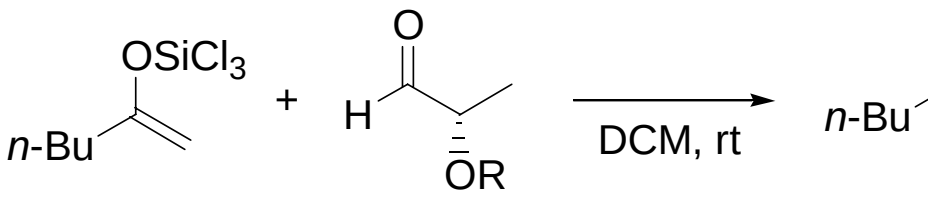


The stereochemical outcome can once again be rationalized by invoking a boat TS in the absence of promoter and the corresponding chair TS in the presence of the promoter.

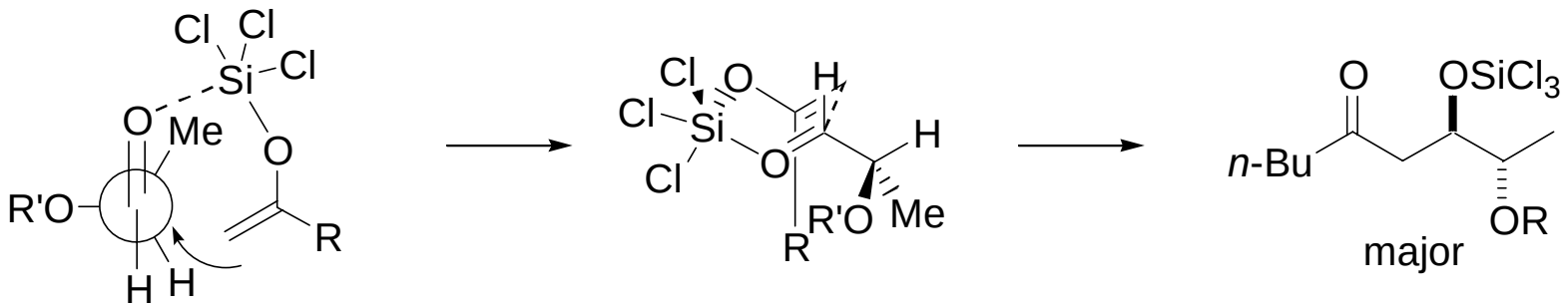
J. Org. Chem. **1998**, *63*, 9524-9527.

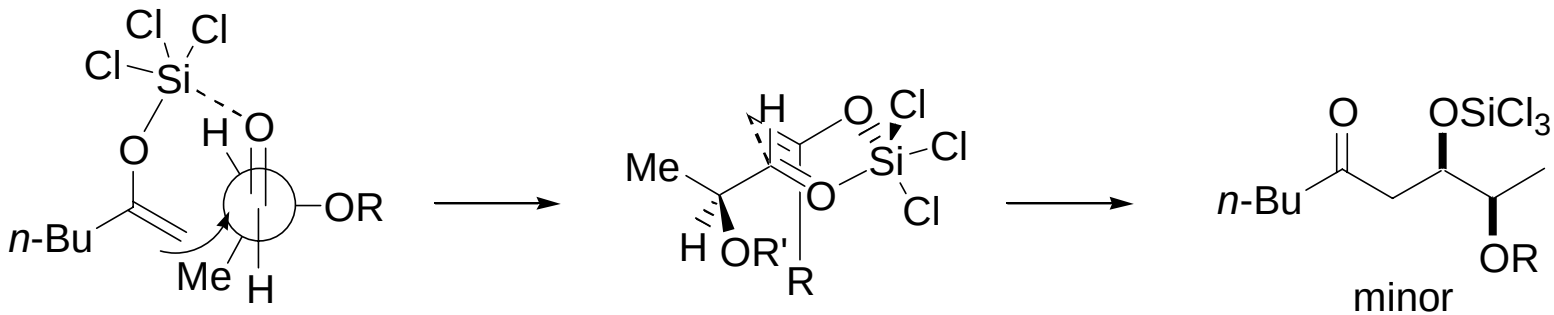
What About Chiral Aldehydes? (I)

A slight preference for the *anti* isomer is consistent, once again, with a boat transition state.



R = TBS, 95%, *syn:anti* 1:2.4
R = Bn, 92%, *syn:anti* 1:2.7

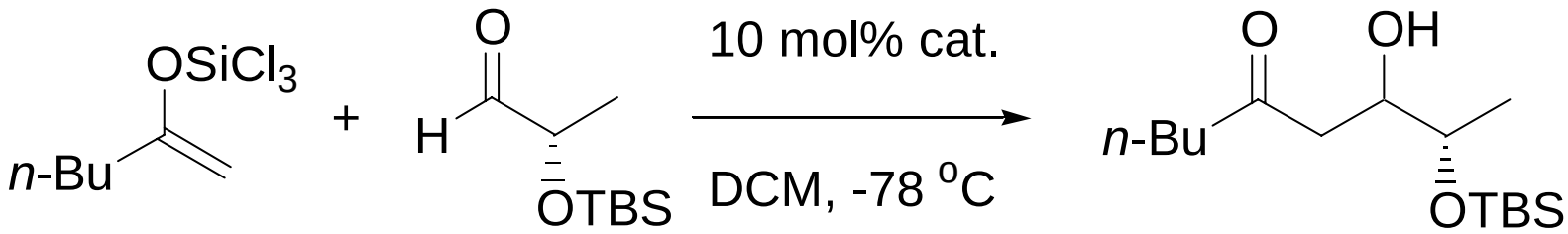




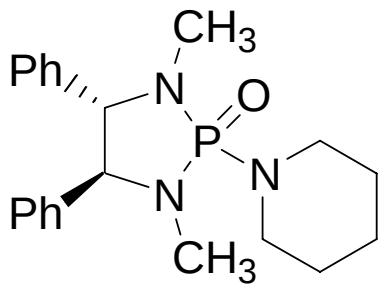
J. Am. Chem. Soc. **2000**, *122*, 8837-8847.

What About Chiral Aldehydes? (II)

The intrinsic bias of the substrate is stronger than the catalyst, i.e., dr's are good in the matched case but poor in the mismatched case.



catalyst	yield, %	*syn:anti*
HMPA	41	1:1.3
(*S,S*)-**L2**	47	2.7:1
(*R,R*)-**L2**	50	1:15.6

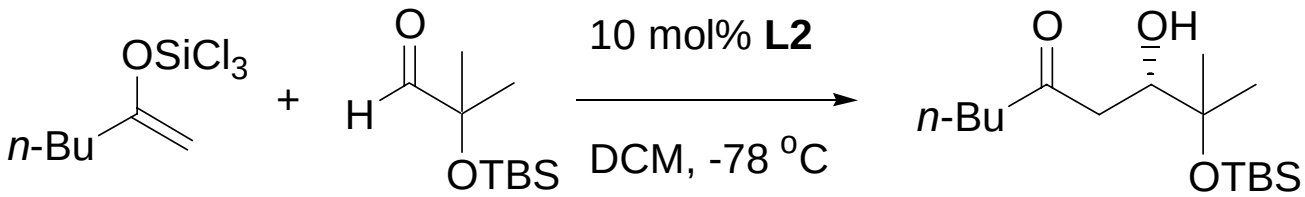


(*S,S*)-**L2**

J. Am. Chem. Soc. **2000**, *122*, 8837-8847.

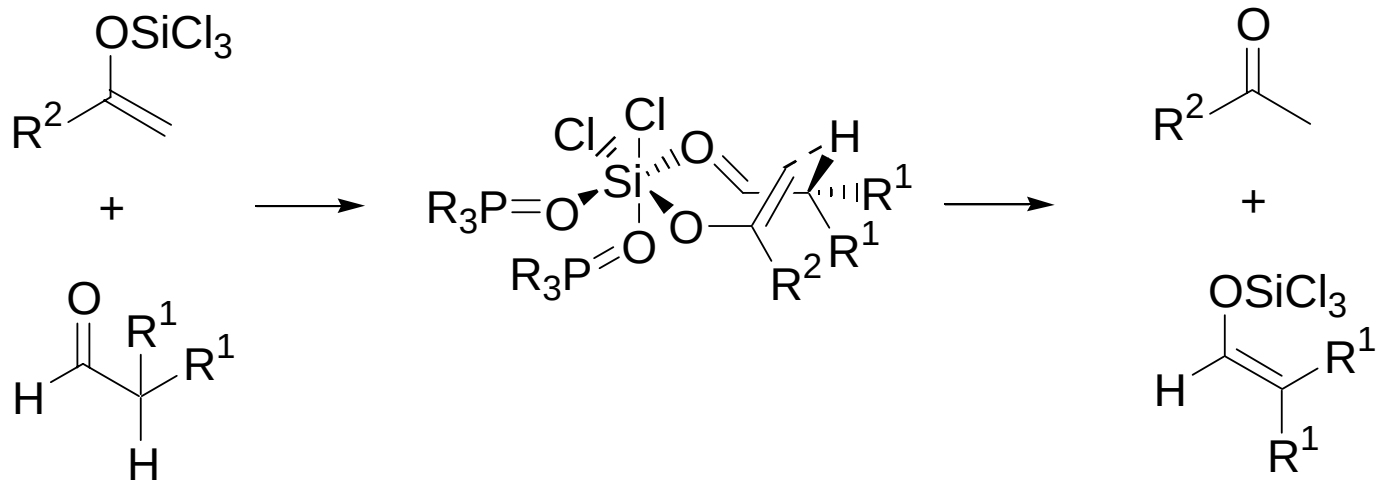
So What's Wrong With Aliphatic Aldehydes?

A control experiment implicated the possibility of enolization as the primary problem:



88%, 74% ee

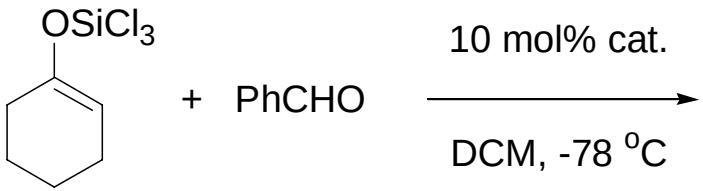
Enolization may also require dual activation, since stoichiometric enolization was ruled out by recovery of optically active aldehyde:

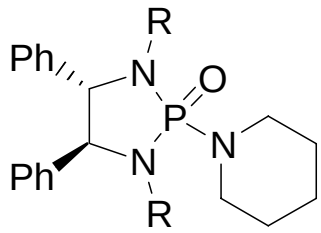


J. Am. Chem. Soc. **2000**, *122*, 8837-8847.

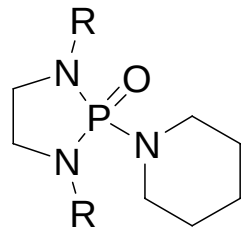
Onward to Mechanistic Studies

Mechanistic Studies Revise Earlier Models: I





L2, R = Me;
L3, R = Ph

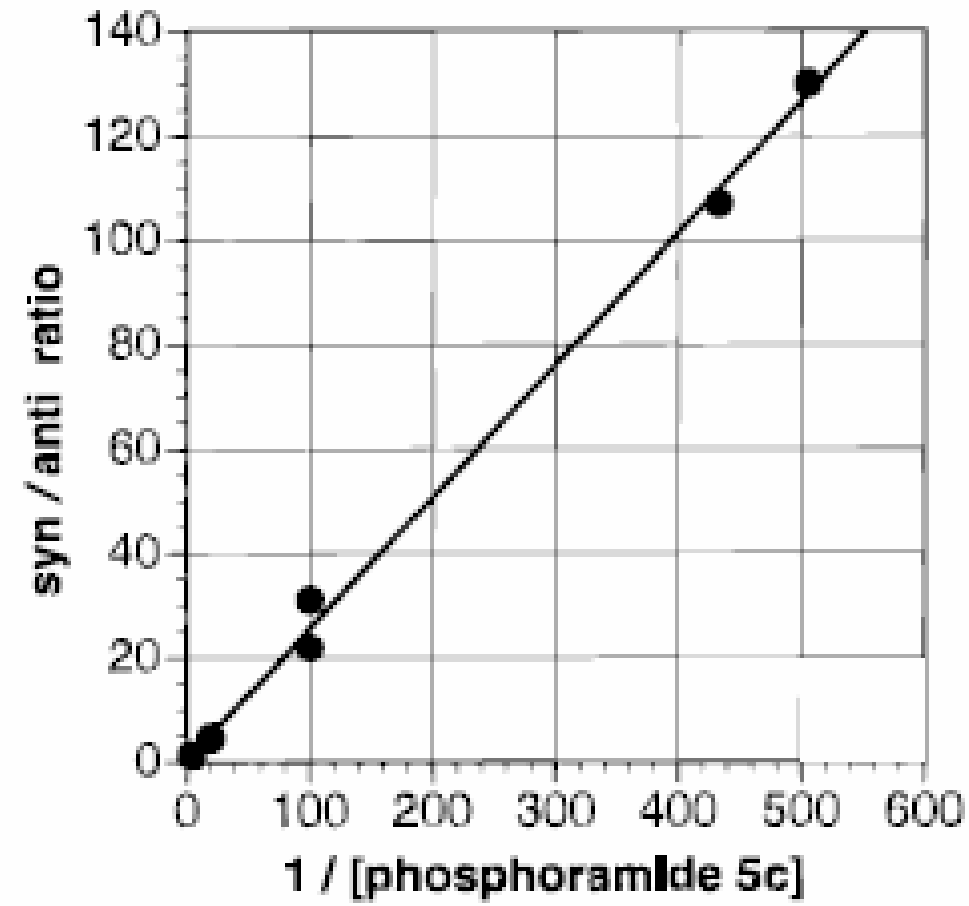


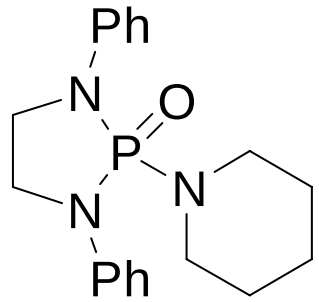
L4, R = Me;
L5, R = *i*-Pr;
L6, R = Ph;
L7, R = 1-naphthyl

catalyst	yield, %	*syn:anti*
L2	95	1:60
L3	94	97:1
L4	99	1:2.8
L5	93	27:1
L6	96	31:1
L7	95	40:1

J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

Mechanistic Studies Revise Earlier Models: II



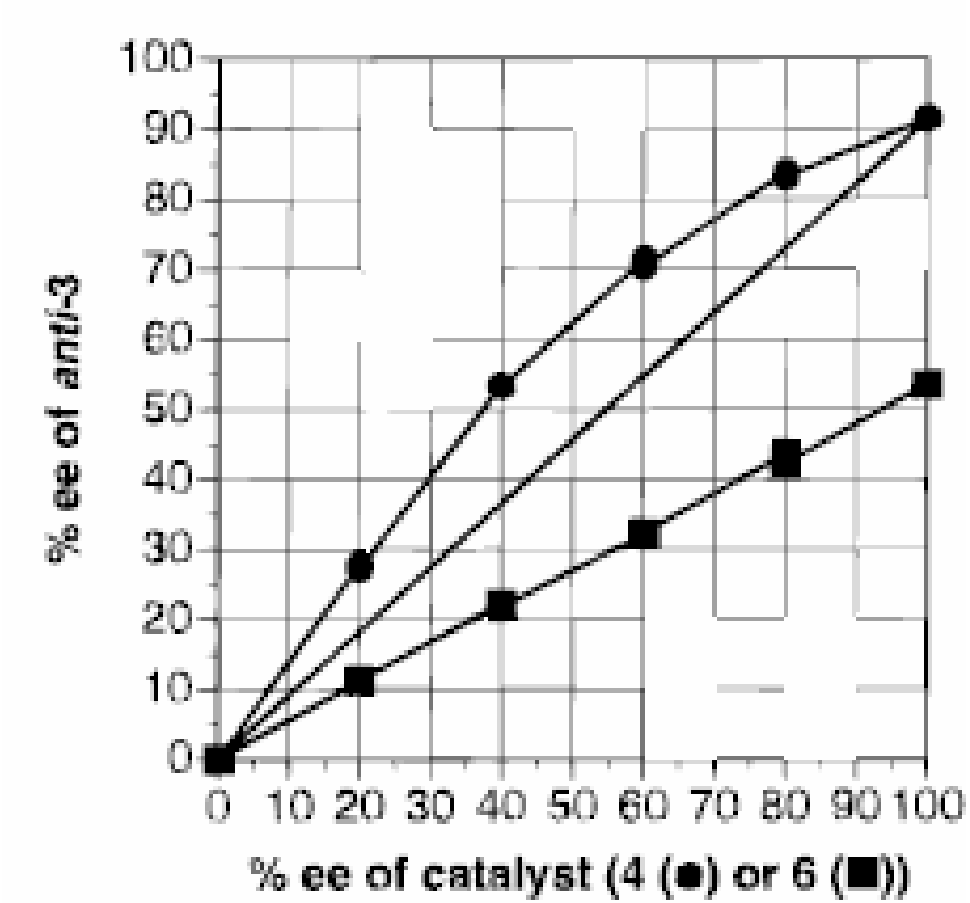


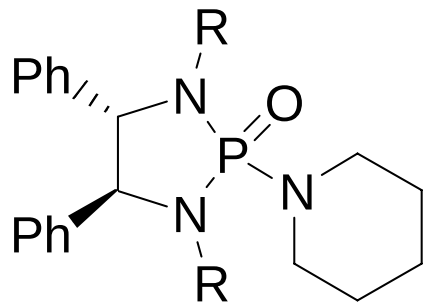
5c

Loading studies revealed that *syn:anti* selectivity decreased with increased loading of ligand.

J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

Mechanistic Studies Revise Earlier Models: III





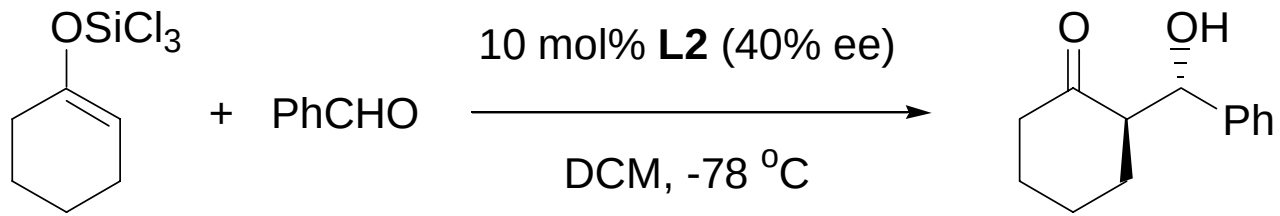
4, R = Me;
6, R = Ph

Positive nonlinear effect observed with sterically smaller catalyst **4**, but completely linear trend observed with bulky catalyst **6**!

J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

Mechanistic Studies Revise Earlier Models: IV

The lack of dependence of conversion on enantiomeric purity rules out the possibility of the product playing a role in the observed nonlinear effect:



time, s	conversion, %	yield, %	ee, %
10	55	52	53.2
30	63	61	53.7
480	100	95	53.3

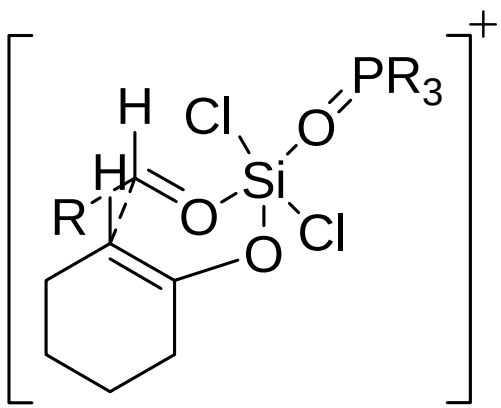
J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

Mechanistic Studies Revise Earlier Models: V (What does it all mean?)

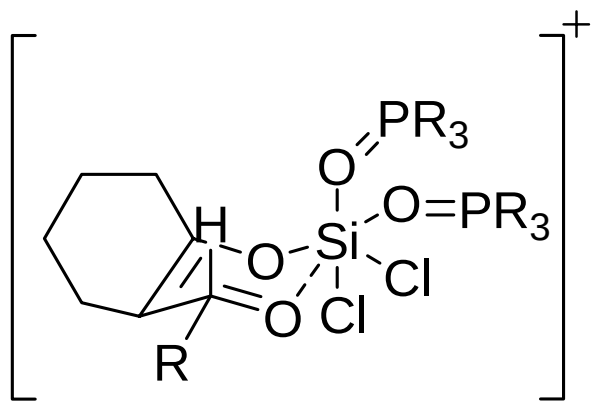
Problems with earlier model:

1. Hard to explain dramatic rate acceleration simply by change in coordination number and/or geometry about silicon
2. New evidence shows involvement of **two** molecules of phosphoramide in the major pathway

New Model:



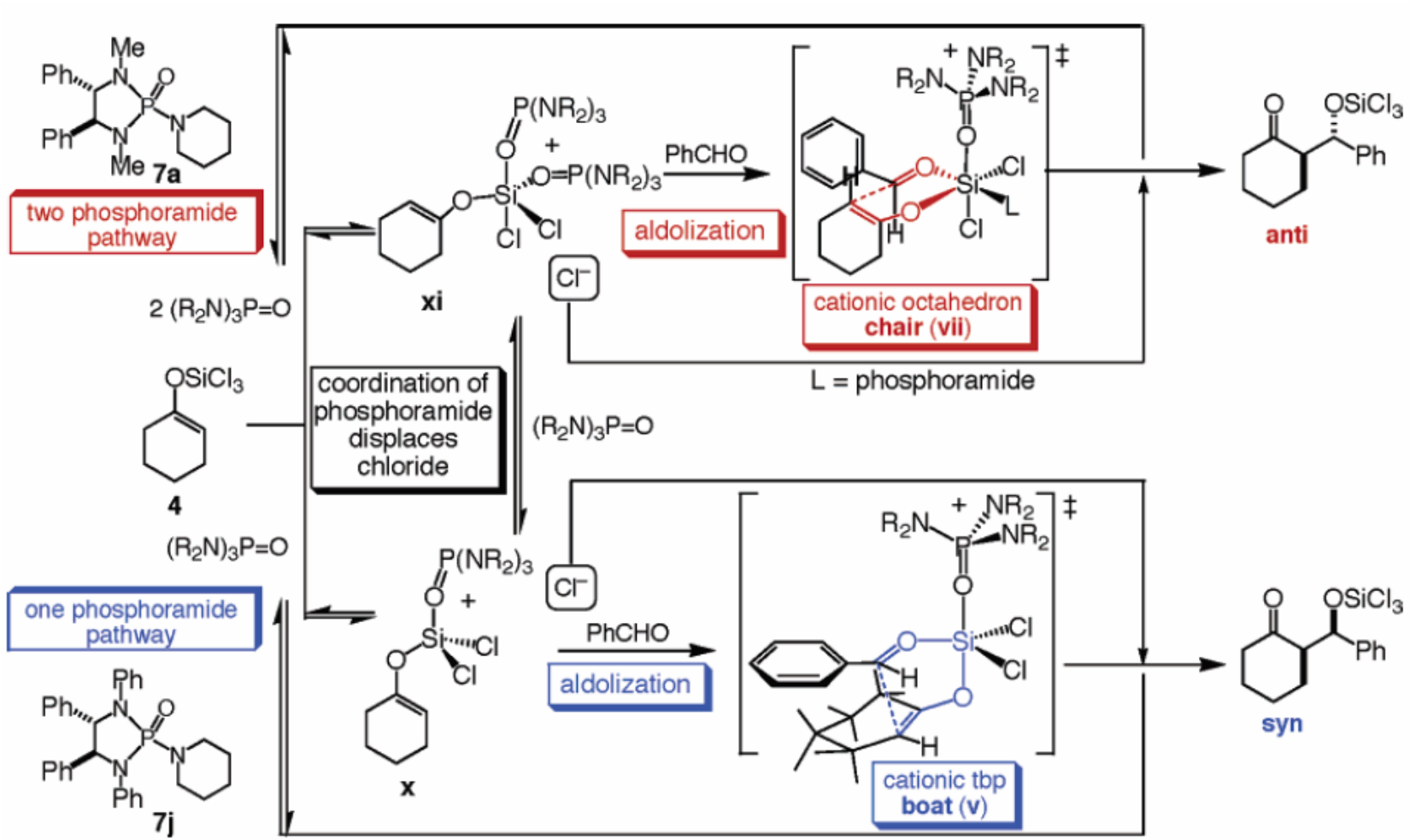
cationic boat TS
(one phosphoramide)



cationic chair TS
(two phosphoramides)

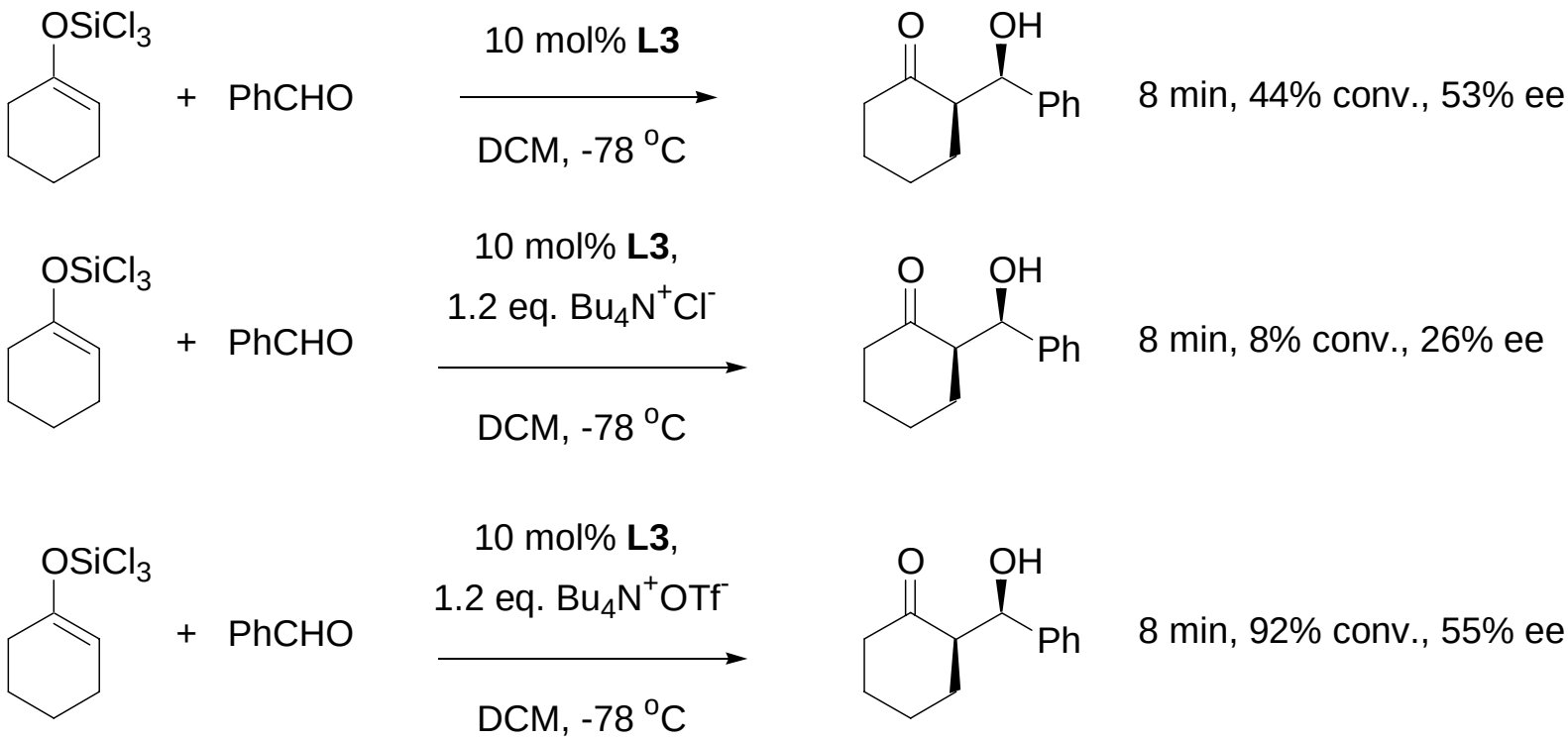
J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

The "Grand Unified Mechanistic Scheme"



J. Org. Chem. **2006**, *71*, 3904-3922.

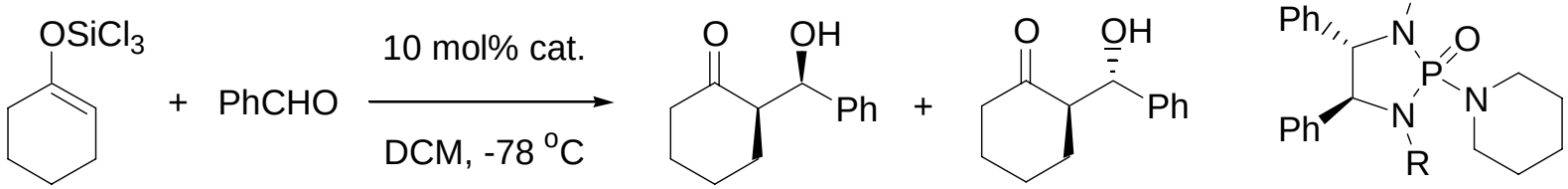
The Proof is in the Salt



Rate inhibition by $Bu_4N^+Cl^-$ (common salt effect) and acceleration by $Bu_4N^+OTf^-$ (increased ionic strength) support the mechanistic proposal of ionizing chloride from silicon.

J. Am. Chem. Soc. **1998**, *120*, 12990-12991.

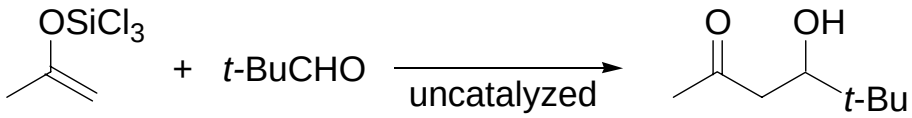
The Glory of Rapid-Injection NMR



1 **2** *syn*-**3** *anti*-**3**

4, R = Me;
5, R = Ph

cat. = **4**, 95%, *anti:syn* 60:1
cat. = **5**, 94%, *anti:syn* 1/97



6 **7** **8**

Most Importantly: 1st order in **5**, but 2nd order in **4**

Conditions	Method	Ea [kcal mol^{-1}]	A [M^{-1} s^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [cal mol^{-1} K^{-1}]	$\Delta G^{\neq}$ [kcal mol^{-1}]
Uncatalyzed 6 + 7	GC	6.4 ± 0.002	865 ± 7	5.8 ± 0.1	−56.7 ± 0.1	23.0 ± < 0.1
Uncatalyzed 6 + 7	*ReactIR*	6.5 ± 0.1	936 ± 117	5.9 ± 0.1	−55.4 ± 0.2	22.6 ± 0.2
Uncatalyzed **1** + **2**	*ReactIR*	3.0 ± 0.5	314 ± 258	2.4 ± 0.5	−58.2 ± 1.6	20.0 ± 1.0
1 + **2**, 5 mol-% **5**	*ReactIR*	0.9 ± 0.1	5.1 ± 1.7	0.3 ± 0.1	−67.1 ± 0.7	20.6 ± 0.2
1 + **2**, 5 mol-% **5**	RINMR	1.8	0.4	1.2	−63.3	20.4
1 + **2**, 10 mol-% **4**	RINMR	2.1 ± 0.5	224 ± 100	1.5 ± 0.5	−51.9 ± 1.0	17.3 ± 1.0

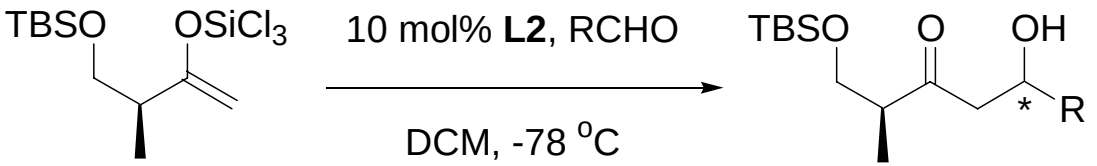
[a]) Activation parameters were calculated for $T = 303$ K.

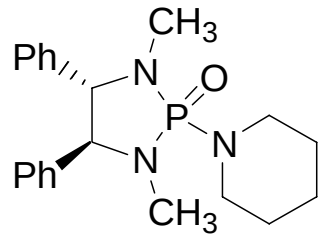
Helv. Chim. Acta, **2000**, *83*, 1846-1853.

Now For Some More “Interesting” Substrates

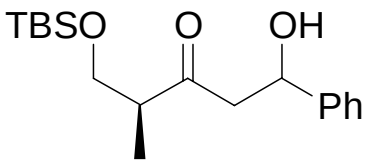
Additional Matters of Stereocontrol

Interestingly, diastereoselectivity with these α-chiral β-alkoxy enolates can be controlled by the catalyst. Catalysis with an achiral phosphoramide shows a modest preference for the *syn* product.

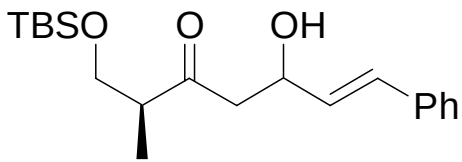




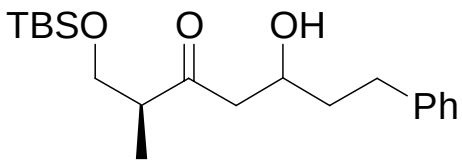
(*S,S*)-**L2**



(*R,R*)-**L2**, 80%, *syn:anti* 19.0:1
(*S,S*)-**L2**, 75%, *syn:anti* 1:7.33



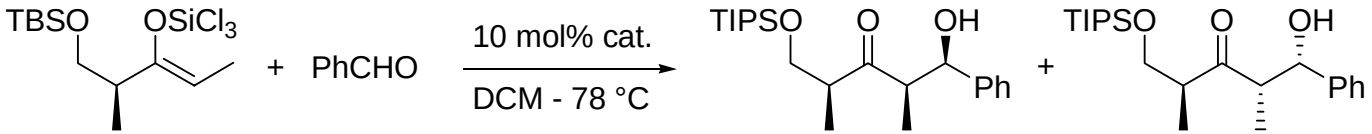
(*R,R*)-**L2**, 81%, *syn:anti* 8.00:1
(*S,S*)-**L2**, 82%, *syn:anti* 1:4.26



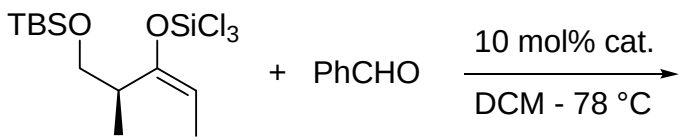
(*R,R*)-**L2**, 34%, *syn:anti* 10.1:1
(*S,S*)-**L2**, 22%, *syn:anti* 1:2.45

Synlett **2001**, 1024-1029.

Now Add More Complications

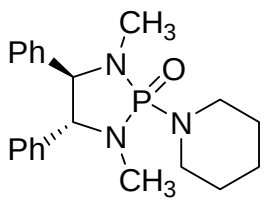


(*R,R*)-**L2**, 72%, rel dr 9:1, int dr 10:1
(*S,S*)-**L2**, 82%, rel dr 12:1, int dr 1:7



dr's *syn:anti*

(*R,R*)-**L2**, 72%, rel dr 1:4, int dr 6:1
(*S,S*)-**L2**, 72%, rel dr 1:2, int dr 2:1

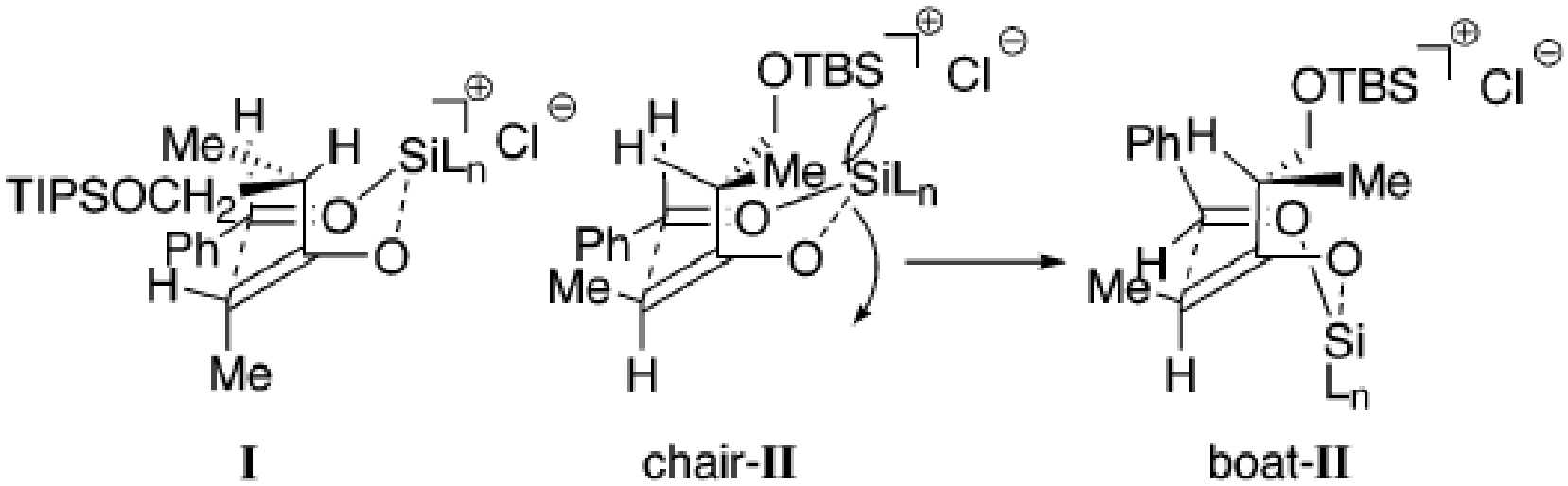


(*R,R*)-**L2**

With *Z* enol ethers, the catalyst has control over aldehyde facial selectivity, but this does not hold for the *E* enol ethers.

Org. Lett. **2002**, *4*, 3473-3476.

Yes, More TS Models

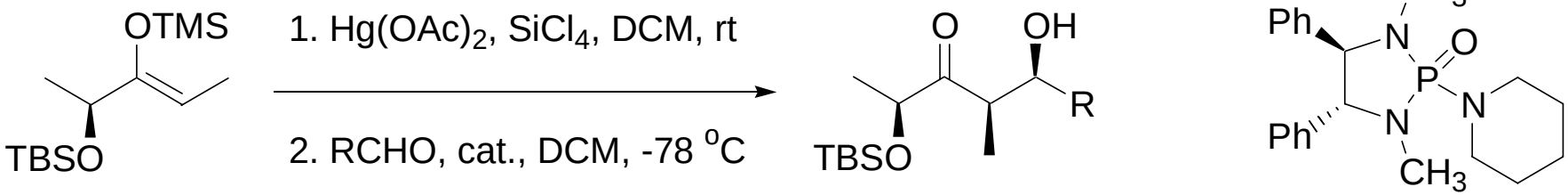


I chair-**II** boat-**II**

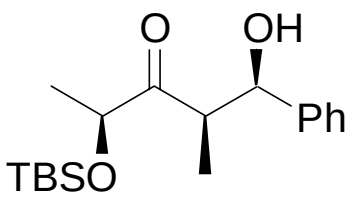
$A_{1,3}$ strain is avoided in "chair-II," but at the price of a steric clash with the ligands on silicon; thus "boat-II" becomes competitive and selectivity is eroded for the *E* enol ethers.

Org. Lett. **2002**, *4*, 3473-3476.

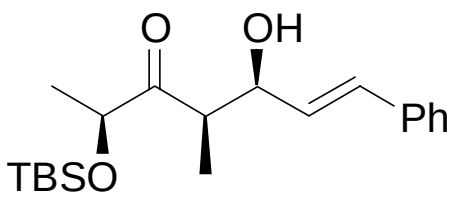
1,4-Induction With Substituted Trichlorosilyl Enolates



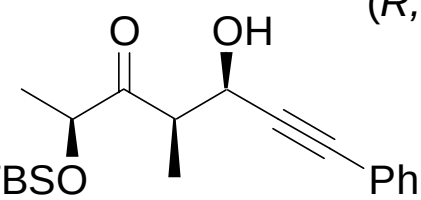
(*R,R*)-**L2**



(*R,R*)-**L2**, 88%, dr 95:5
HMPA, 87%, dr 94:2:2:2



(*R,R*)-**L2**, 81%, dr 93:5:2
HMPA, 79%, dr 91:6:3

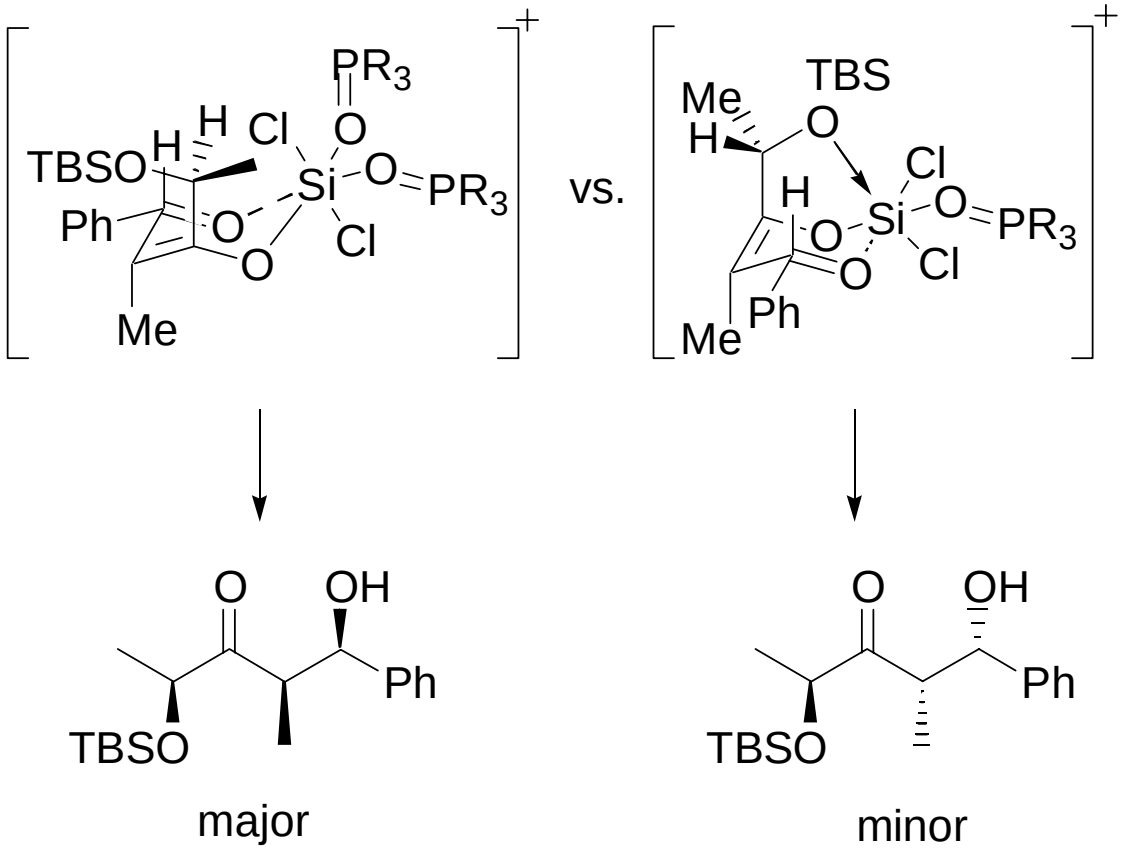


(*R,R*)-**L2**, 79%, dr 95:3:2
HMPA, 82%, dr 89:5:4:3

Here, HMPA performs about as well as the matched catalyst. Interestingly, *employing the* (S,S)-**L2** *catalyst gives essentially the same result!*

Org. Lett. **2001**, *3*, 2201-2204.

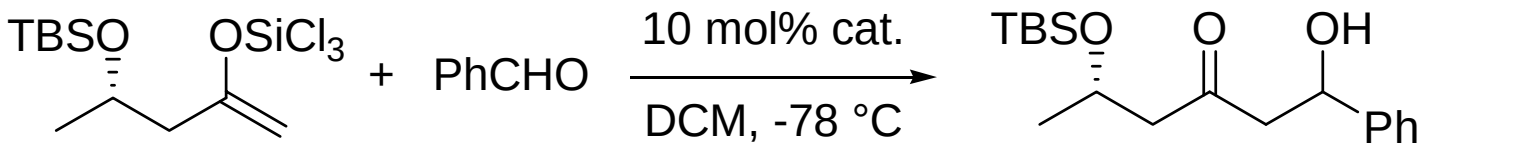
Even More Chairs…



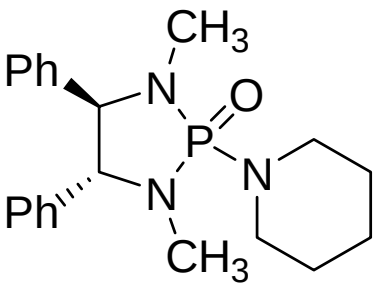
Org. Lett. **2001**, *3*, 2201-2204.

The Enigmatic 1,5-Induction

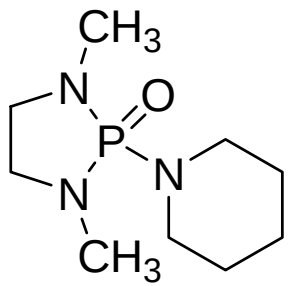
With a silyl protecting group, the inherent 1,5-induction is almost nonexistent, although catalyst control is similarly weak.



(*R,R*)-**L2**, 72%, *syn:anti* 1:2.5
(*S,S*)-**L2**, 72%, *syn:anti* 1.3:1
L4, 55%, *syn:anti* 1:1.4



(*R,R*)-**L2**

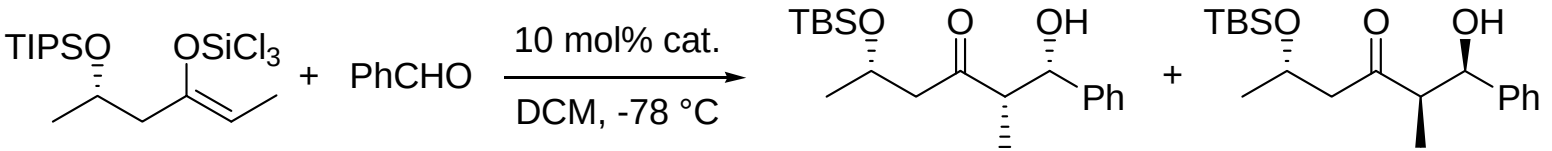


L4

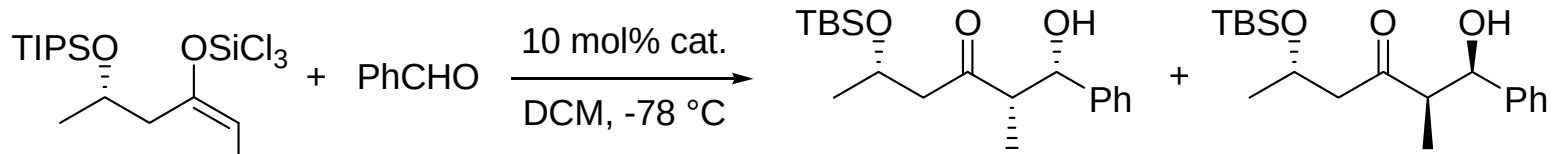
Would a PG change have made a difference here?

Org. Lett. **2002**, *4*, 3477-3480.

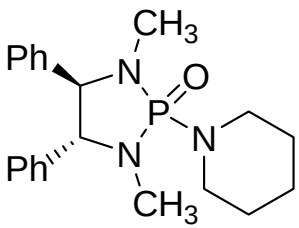
More Complicated 1,5-Induction



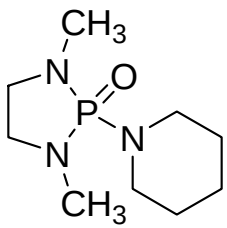
(*R,R*)-**L2**, 84%, rel dr 30:1, int dr 16:1
(*S,S*)-**L2**, 86%, rel dr 26:1, int dr 1:10
L4, 83%, rel dr 29:1, int dr 1.4:1



(*S,S*)-**L2**, 80%, rel dr 3:1, int dr 1:1



(*R,R*)-**L2**



L4

Once again, good catalyst control is seen for *Z* enol ethers, but not for the *E* enol ethers (more boats?).

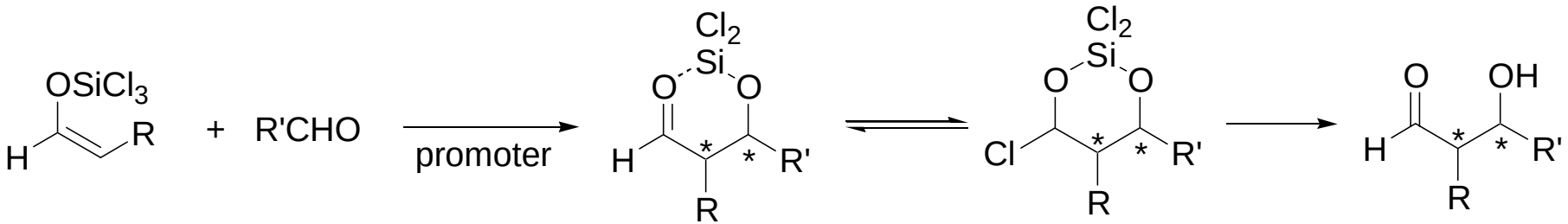
Org. Lett. **2002**, *4*, 3477-3480.

Crossed-Aldol Reactions of Aldehydes

Another Big Leap…Crossed-Aldol Reactions

Why would the Lewis base-catalyzed process be successful in this challenging area?

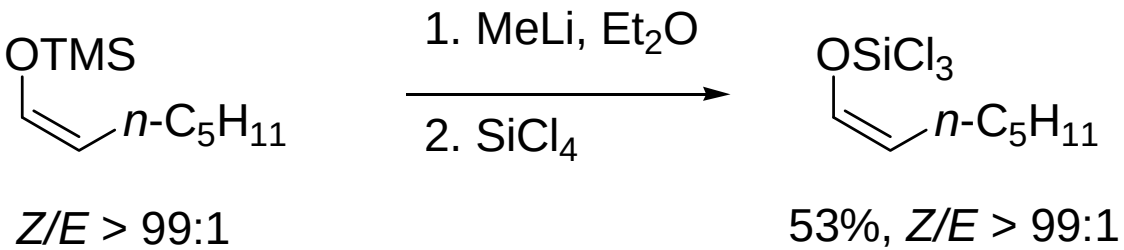
1. The product is "protected" from further reaction by coordination of the newly-formed aldehyde with the electron-deficient silicon.
2. The product may exist as the chlorohydrin, even better "protection" from further reaction.
3. The aldol addition can (presumably) be conducted at low temperature (as in previous studies), lowering the risk of other decomposition pathways.



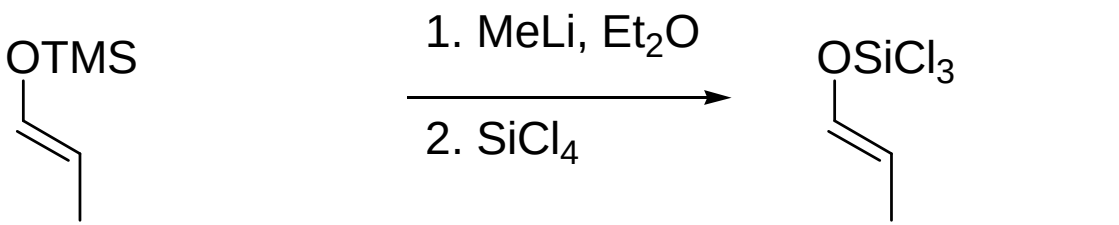
Angew. Chem. Int. Ed. **2001**, *40*, 4759-4762.

Preparation of the Trichlorosilyl Enol Ethers…Never a Trivial Task

All previously-developed methods of enolate generation failed for aldehyde substrates, so a new protocol was instated:



Z/E > 99:1 — 53%, *Z/E* > 99:1

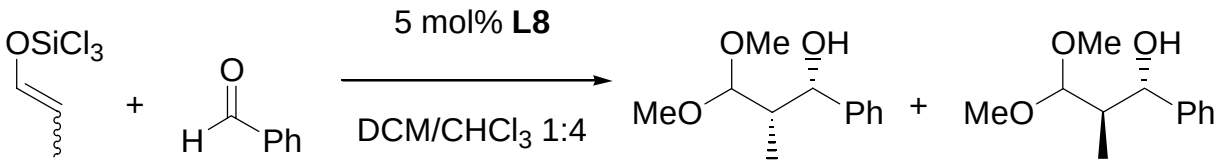


Z/E > 99:1 — 34%, *Z/E* > 99:1

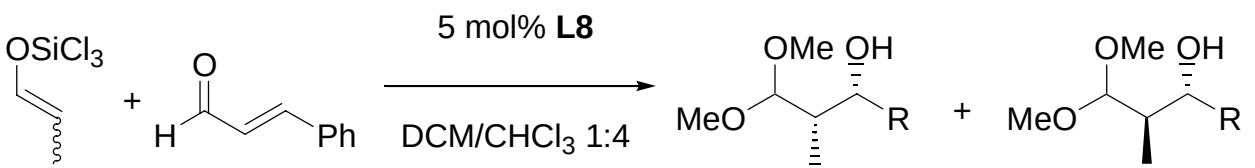
Angew. Chem. Int. Ed. **2001**, *40*, 4759-4762.

Debut of a Linked Catalyst

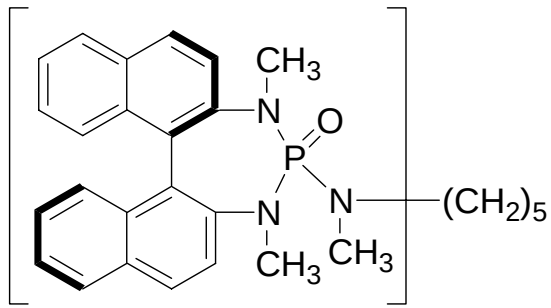
Based on the knowledge gained from earlier mechanistic work, a dimeric phosphoramide catalyst was found to be superior for enantioselection compared to previously-used monomeric catalysts.



Z enolate: 95%, *syn:anti* 98:2, 81% ee
E enolate: 97%, *syn:anti* 1:99, 59% ee



Z enolate: 86%, *syn:anti* 99:1, 42% ee
E enolate: 88%, *syn:anti* 1:99, 26% ee

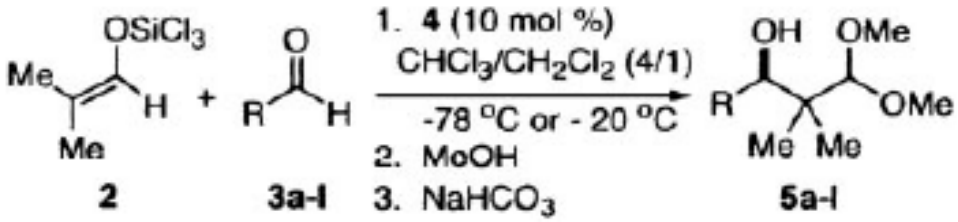


L8

Z enolate: 47%, *syn:anti* 95:5, 8% ee
E enolate: 79%, *syn:anti* 1:99, 66% ee

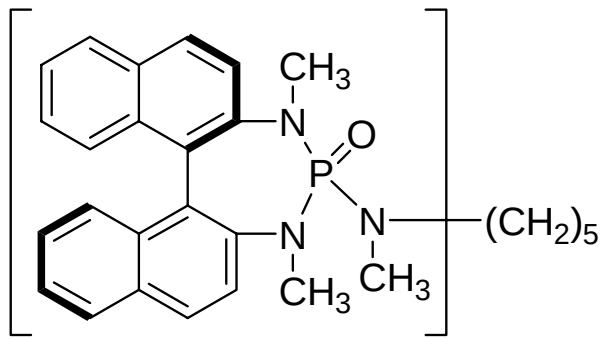
Angew. Chem. Int. Ed. **2001**, *40*, 4759-4762.

Additional Studies on Crossed-Aldol Reactions of Aldehydes



Entry	R	Product	Time, h	Yield,* %	er†
1	C_6H_4	5a	8	86	70.0/30.0
2	4-MeC_6H_4	5b	12	90	73.0/27.0
3	4-$MeOC_6H_4$	5c	20	92	75.5/24.5
4	3,4,5-$(MeO)_3C_6H_2$	5d	26	80	87.5/12.5
5	4-ClC_6H_4	5e	8	85	89.0/11.0
6	4-$CF_3C_6H_4$	5f	8	86	90.0/11.0
7	4-$NO_2C_6H_4$	5g	8	89	91.0/9.0
8	2-Naphthyl	5h	12	90	83.0/17.0
9	(*E*)-Cinnamyl	5i	12	90	67.5/32.5
10	Phenylpropargyl	5j	12	85	81.5/18.5
11	1-Propenyl	5k	15	82	56.0/42.0‡
12	*n*-Butyl	5l	30c	80	91.0/9.0‡

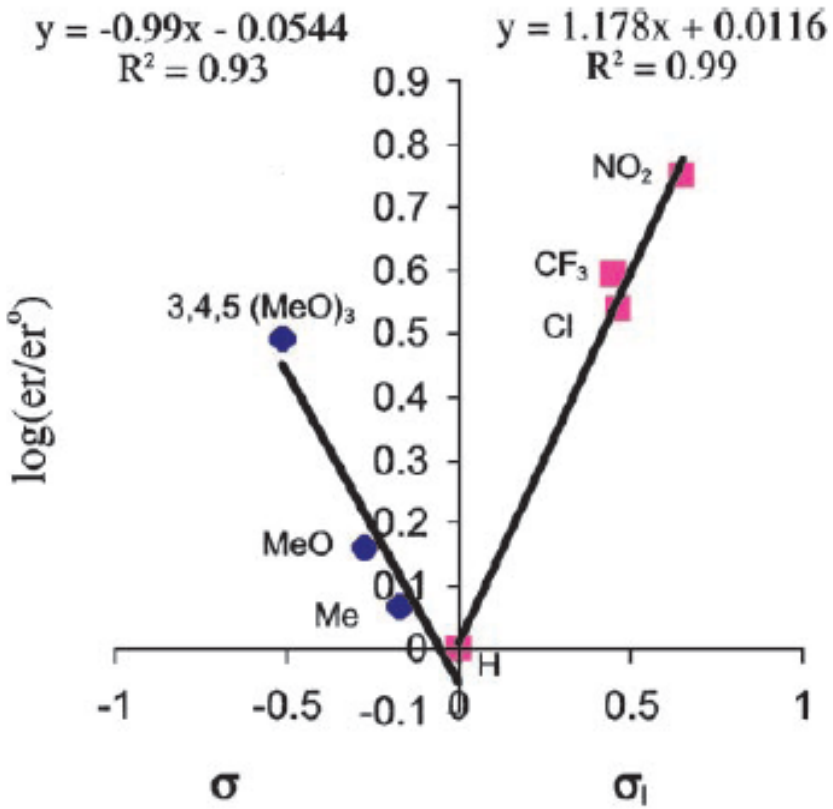
All reactions were run at −78°C except valeraldehyde at −20°C.
*Yield of analytically pure materials.
†Enantiomeric ratio determined by chiral stationary phase–supercritical fluid chromatography on Daicel Chiralpak, OD, AS, and AD columns.
‡Enantiomeric excesses were determined on the corresponding benzoate products.



4

Pro. Nat. Acad. Sci. U.S.A. **2004**, *101*, 5439-5444

…And More Interesting Trends



Increasing ee with either EDG's or EWG's suggests a change in RDS, stereochemistry-determining step, or in factors that influence selectivity.

Pro. Nat. Acad. Sci. U.S.A. **2004**, *101*, 5439-5444

$^{12}C/^{13}C$ KIE!

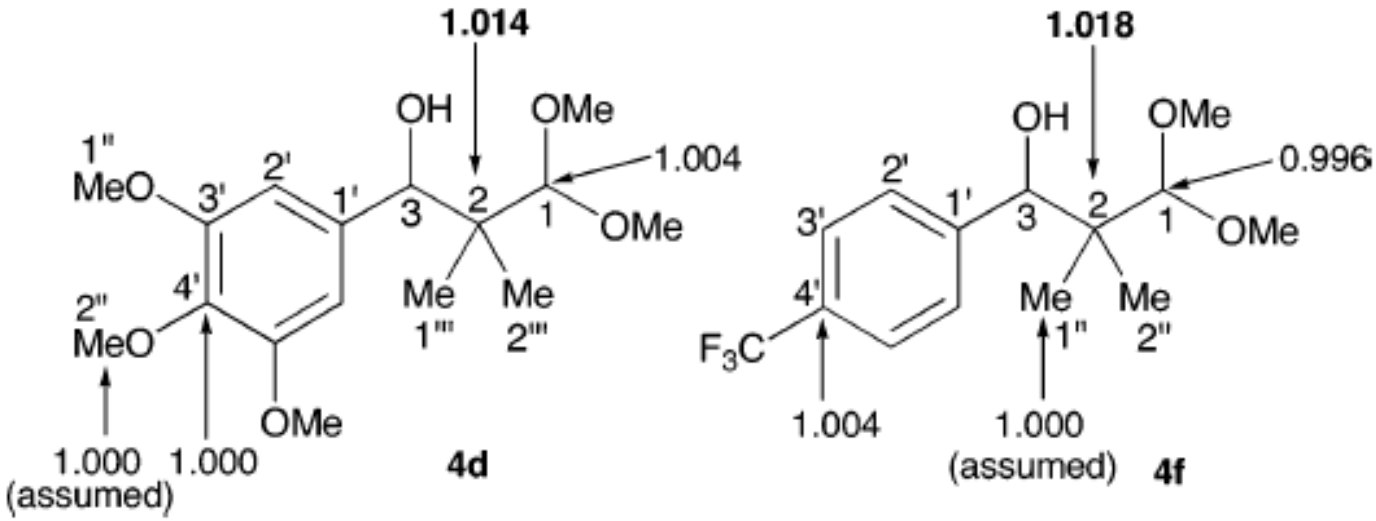
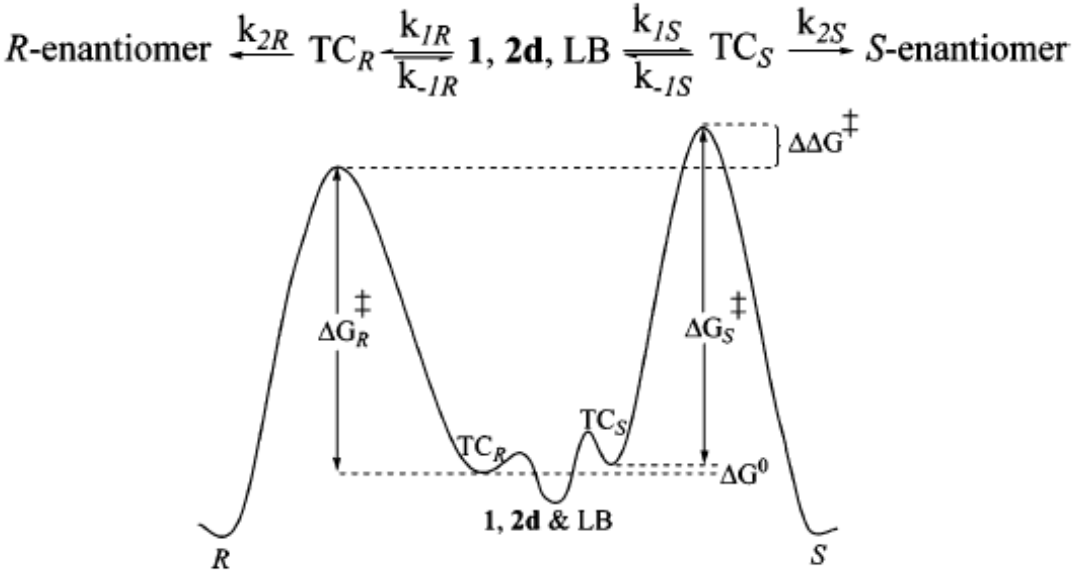


FIGURE 2. $^{12}C/^{13}C$ kinetic isotope effects at C(2).

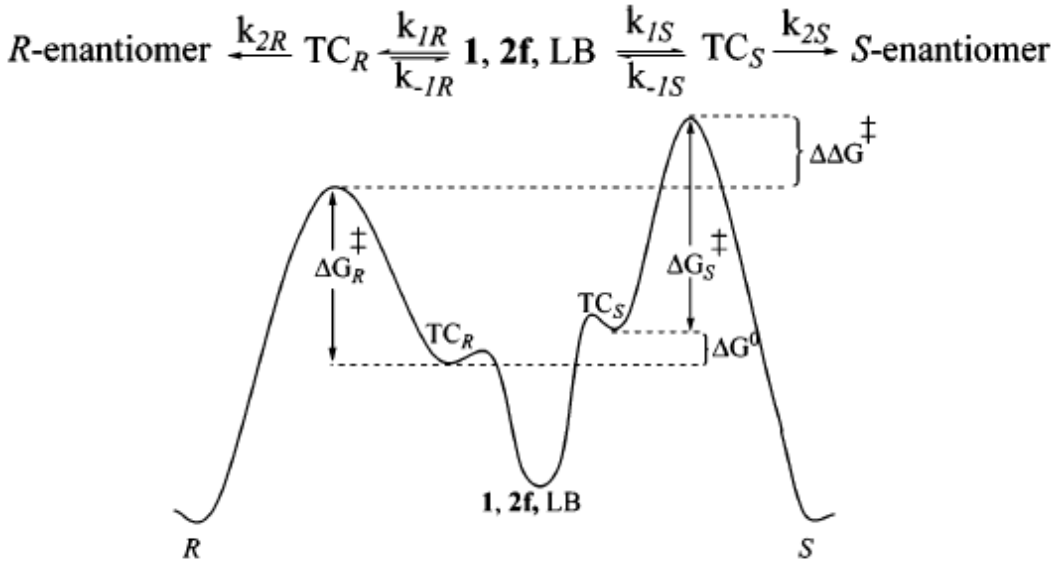
Looks like aldolization is the RDS, as suspected.

J. Org. Chem. **2005**, *70*, 10393-10399.

Some Energy Diagrams



2d: Electron-rich aldehyde
2f: Electron-poor aldehyde

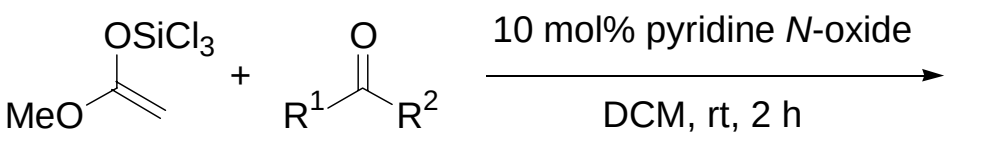


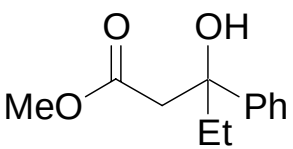
J. Org. Chem. **2005**, *70*, 10393-10399.

Reactions with Ketones!

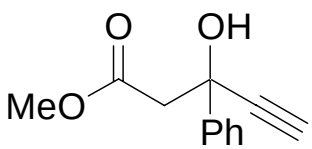
Ketones, Anyone?

Ketones are problematic substrates relative to aldehydes because of their attenuated reactivity and sterically more similar substituents. The solution: return to the "hyper-reactive" trichlorosilyl ketene acetals.

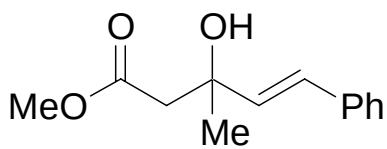




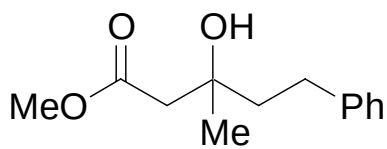
92%



72%



92%

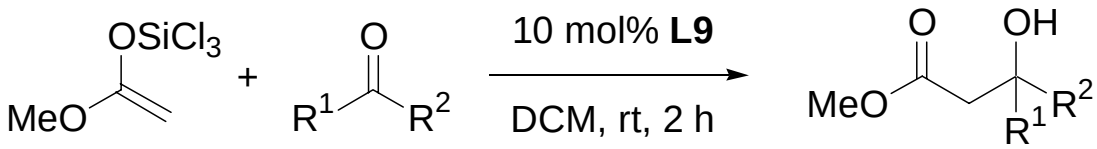


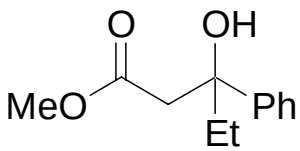
94%

Interestingly, although initial results demonstrated phosphoramides to be capable promoters for this transformation, *N*-oxides proved superior for enantioselectivity later on.

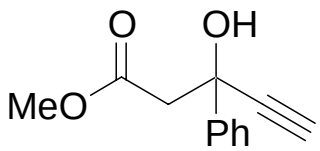
J. Am. Chem. Soc. **2002**, *124*, 4233-4235.

Enantioselective Additions to Ketones

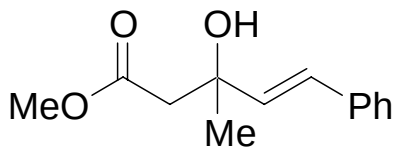




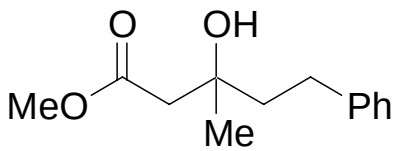
96%, 82% ee



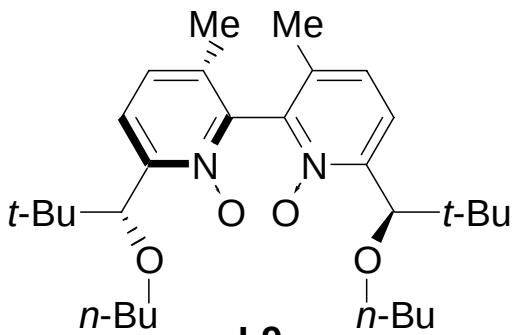
89%, 86% ee



87%, 11% ee



97%, 35% ee



L9

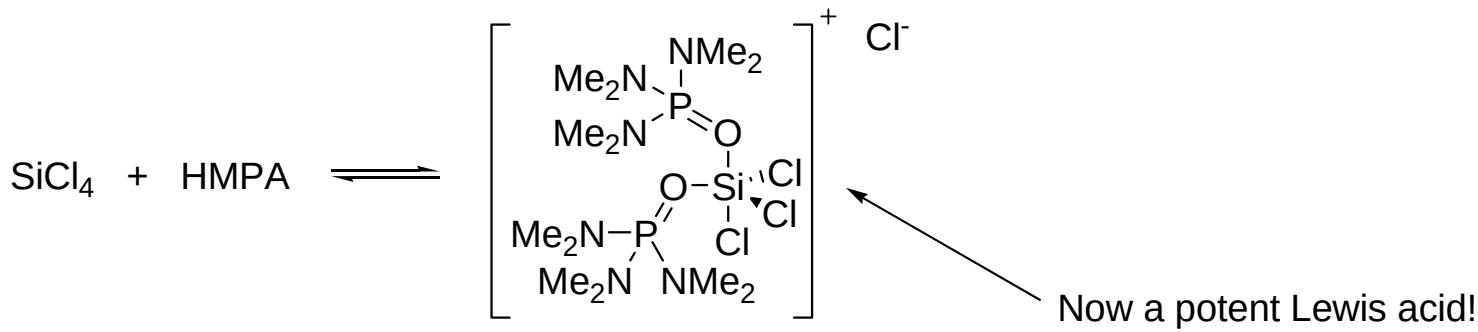
Highly substrate dependent!

J. Am. Chem. Soc. **2002**, *124*, 4233-4235.

The "2nd Generation" Approach

A New Concept

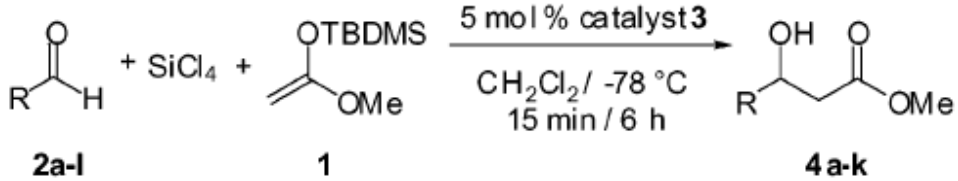
Why not *separate* the Lewis acidic component from the enol ether?

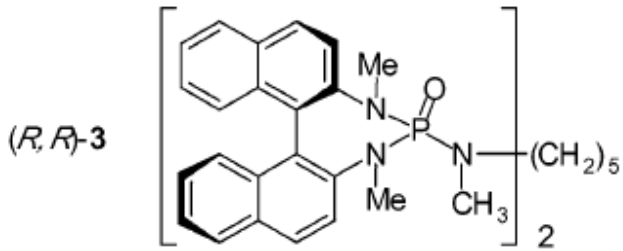


By generating this silicon-based Lewis acid *in situ*, "regular" silyl enol ethers can be used as nucleophiles, and undesirable background reactions will no longer occur (as with the previous trichlorosilyl enol ether methodology).

J. Am. Chem. Soc. **2002**, *124*, 13405-13407.

Less "Restrictive" Methodology I



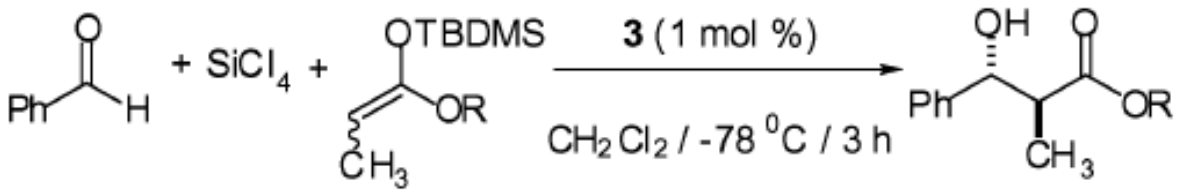


entry	R	product	yield, %[b]	er[c]
1	C_6H_5 (**2a**)	**4a**[d]	97[e]	96.5:3.5
2	1-naphthyl (**2b**)	**4b**	98	90:10
3	2-naphthyl (**2c**)	**4c**	98	97:3
4	4-$CH_3C_6H_4$ (**2d**)	**4d**	97	97:3
5	4-$CH_3OC_6H_4$ (**2e**)	**4e**	97	98.5:1.5
6	4-$CF_3C_6H_4$ (**2f**)	**4f**	97	95.5:4.5
7	(*E*)-PhCH=CH (**2g**)	**4g**	95[e]	97:3
8	(*E*)-PhCH=C(CH_3) (**2h**)	**4h**	98	72.5:27.5
9	2-furyl (**2i**)	**4i**	94[e]	93.5:6.5
10	cyclohexyl (**2j**)[f]	**4j**	86[e]	94:6
11	$PhCH_2CH_2$ (**2k**)[f]	**4k**	72[e]	90.5:9.5

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **1**, and 0.05 equiv of (*R,R*)-**3** at 0.2 M in CH_2Cl_2 at −78 °C for 15 min. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] *R* absolute configuration.[9] [e] Chromatographically homogeneous material. [f] Reaction time 6 h.

J. Am. Chem. Soc. **2002**, *124*, 13405-13407.

Less "Restrictive" Methodology II



2a **5a-d** **6a-d**

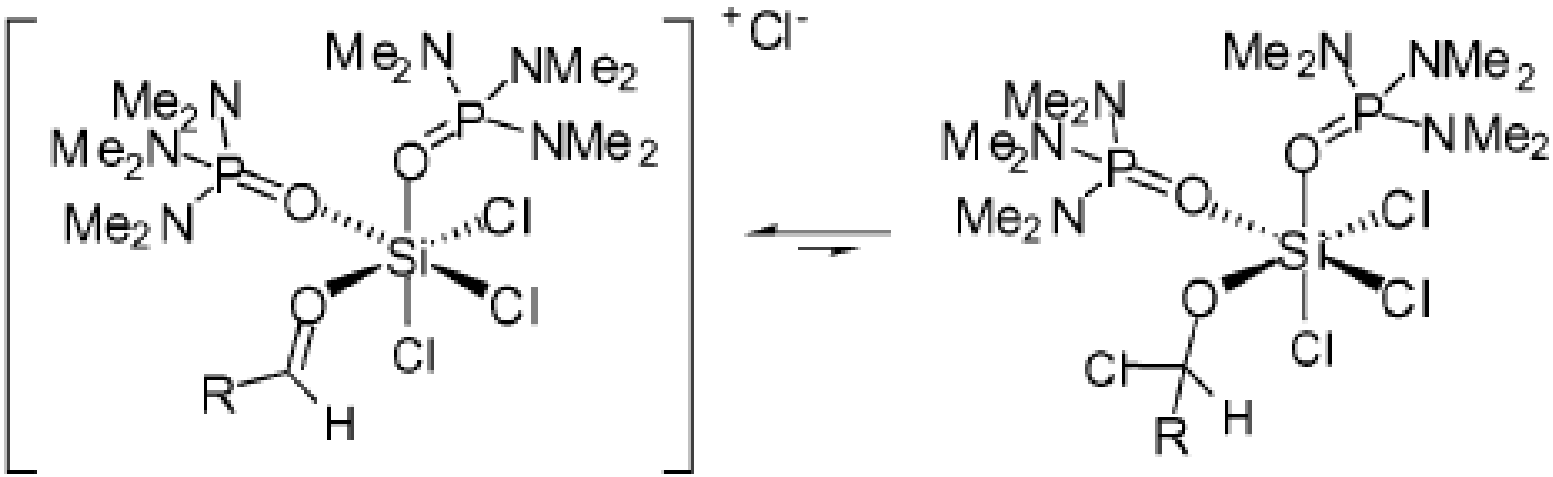
entry	R	*E*:*Z*[b]	product	yield, %[c]	er[d]	dr[b]
1	Me (**5a**)	82:18	**6a**	98	86:14	99:1
2	Et (**5b**)	95:5	**6b**[e]	78	88:12	98:2
3	Ph (**5c**)	94:6	**6c**	98	94:6	94:6
4	*t*-Bu (**5d**)	95:5	**6d**[e]	93[f]	>99:1	99:1
5	*t*-Bu (**5d**)	12:88	**6d**[e]	73	>99:1	99:1

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **5a**−**d**, and 0.01 equiv of (*R*,*R*)-**3** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [b] Determined by ^1H NMR analysis. [c] Chromatographically homogeneous material. [d] Determined by CSP-SFC. [e] *2S*,*3R* absolute configuration.[11] [f] Analytically pure material.

Both *E* and *Z* enol ethers give the *anti* product!! Evidence for an *open* transition state.

J. Am. Chem. Soc. **2002**, *124*, 13405-13407.

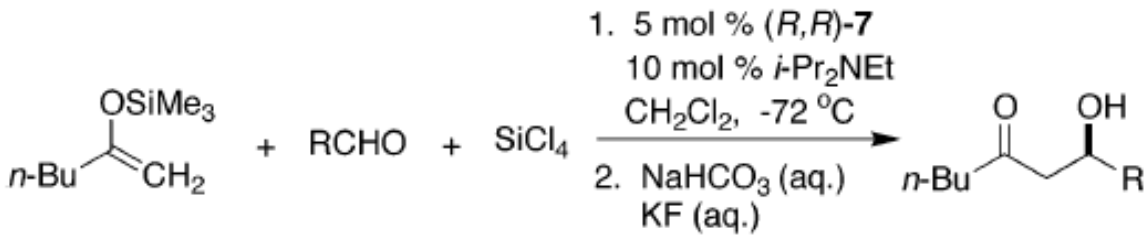
Explanation of Aliphatic Aldehydes' Recalcitrance



The equilibrium depicted above would be particularly troublesome for highly electrophilic aliphatic aldehydes, thus explaining their slow rate of addition.

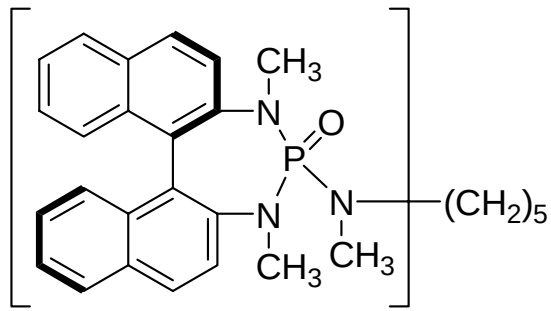
J. Am. Chem. Soc. **2002**, *124*, 13405-13407.

Methyl Ketone TMS Enol Ethers



entry	R	product	time, h	yield,[b] %	er[c]
1	(*E*)-PhCH=CH	(+)-**13**	4	97.5[e]	99.5/0.5
2	(*E*)-PhCH=C(CH$_3$)[d]	(+)-**14**	24	54$_e$	78.0/22.0
3	1-naphthyl	(+)-**15**	10	95[e]	96.0/4.0
4	2-naphthyl	(+)-**16**	4	92	99.5/0.5
5	4-CH$_3$OC$_6$H$_4$	(+)-**17**	4	97.5	99.5/0.5
6	4-CF$_3$C$_6$H$_4$	(+)-**18**	4	96	99.5/0.5
7	2-furyl	(+)-**19**	6	88	95.0/5.0
8	2-thiophenyl	(+)-**20**	8	79	99.0/10.0
9	PhCH$_2$CH$_2$		24	nr	nd

[a] All reactions employed 1.5 equiv of $SiCl_4$, 1.2 equiv of enolate, 10 mol % *i*-Pr$_2$NEt, and 5 mol % (*R*,*R*)-**1** at 0.5 M in CH_2Cl_2 at −72 °C for 3 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Reaction employed 10 mol % (*R*,*R*)-**1**. [e] Chromatographically homogeneous material.

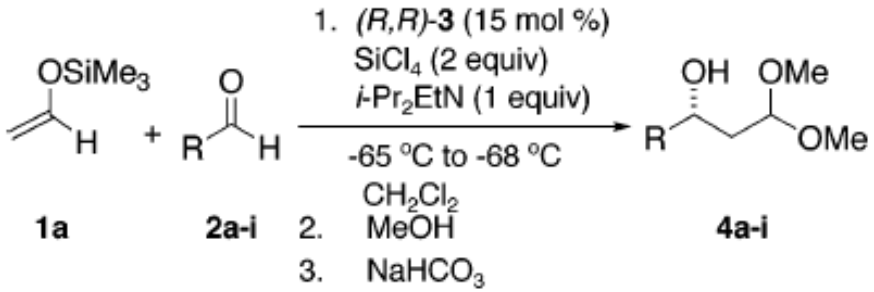


(*R*,*R*)-**7**

No aliphatics…

Org. Lett. **2003**, *5*, 2303-2306.

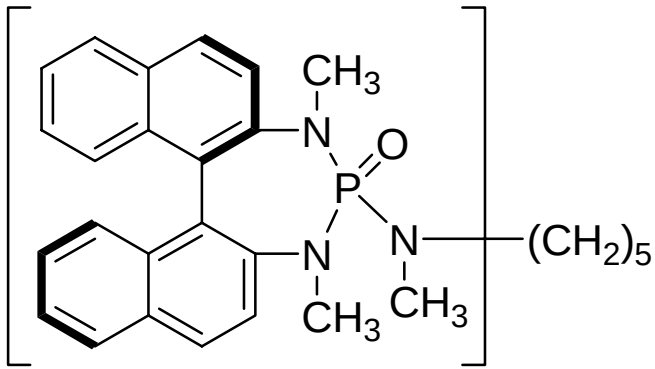
Crossed Aldol Reactions of Aldehydes Revisited



1a **2a-i** **4a-i**

entry	R	product	yield,[a] %	er[b]
1	C_6H_4	**4a**	80	97.1/2.9
2	2-naphthyl	**4b**	85	97.1/2.9
3	1-naphthyl	**4c**	78	92.2/7.8
4	4-$CF_3C_6H_4$	**4d**	84	98.1/1.9
5	4-ClC_6H_4	**4e**	81	97.9/2.1
6	cinnamyl	**4f**	60	98.2/1.8
7	4-$MeOC_6H_4$	**4g**	30	91.2/8.8
8	*α*-methylcinnamyl	**4h**	<10	nd[c]
9	*n*-butyl	**4i**	nr[d]	

[a] Yield of analytically pure materials. [b] er determined by CSP-SFC, Daicel Chiralpak, OD, AS, and AD columns. [c] Not determined. [d] No reaction.



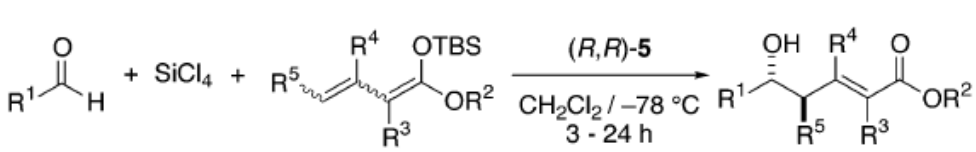
(*R,R*)-**3**

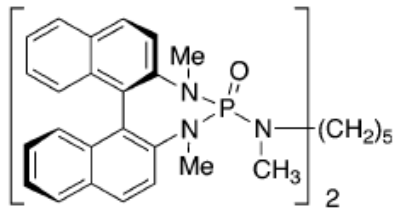
Aliphatic aldehydes fail as usual.

J. Org. Chem. **2005**, *70*, 10190-10193.

Vinylogous Aldol Reactions

The phosporamide catalyst is presumably bulky enough to force γ addition!





(*R*,*R*)-**5**

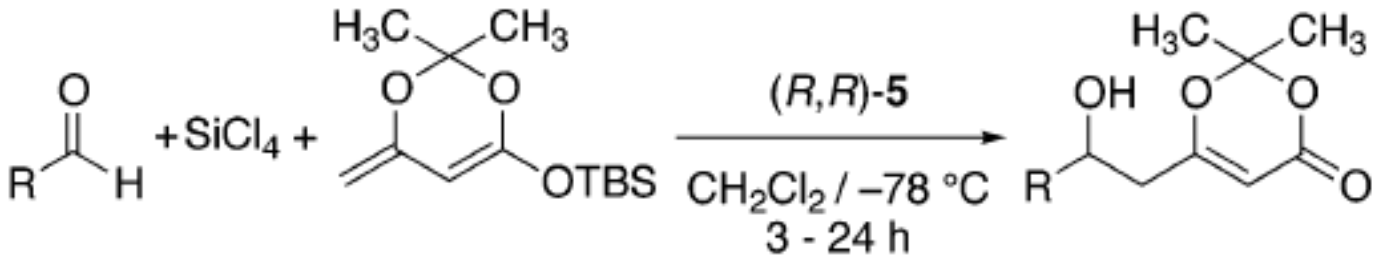
entry	dienolate	R^1	R^2	R^3	R^4	R^5	product	yield, %[a]	γ/α[b]	dr[b]	er[c]
1	**3a**[d]	Ph (**1a**)	Et	H	H	H	**4aa**	89[e]	>99:1		99:1
2	**3a**[d]	PhCH=CH (**1b**)	Et	H	H	H	**4ab**	84[e]	>99:1		98:2
3	**3a**[f]	$PhCH_2CH_2$ (**1c**)	Et	H	H	H	**4ac**	68[g]	>99:1		95:5
4	**3b**[d]	Ph (**1a**)	Me	Me	H	H	**4ba**	93[e]	>99:1		99.5:0.5
5	**3b**[d]	PhCH=CH (**1b**)	Me	Me	H	H	**4bb**	88	>99:1		99.5:0.5
6	**3b**[f]	$PhCH_2CH_2$ (**1c**)	Me	Me	H	H	**4bc**		ND		ND
7	**3c**[d]	Ph (**1a**)	Et	H	Me	H	**4ca**	91[e]	>99:1		96:4
8	**3c**[d]	PhCH=CH (**1b**)	Et	H	Me	H	**4cb**	97[h]	>99:1		94:6
9	**3c**[f]	$PhCH_2CH_2$ (**1c**)	Et	H	Me	H	**4cc**	73	>99:1		97.5:2.5
10	**3d**[d]	Ph (**1a**)	*t*-Bu	H	H	Me	**4da**	92[i]	99:1	>99:1	94.5:5.5
11	**3d**[d]	PhCH=CH (**1b**)	*t*-Bu	H	H	Me	**4db**	71	99:1	>99:1	91:9
12	**3d**[f]	$PhCH_2CH_2$ (**1c**)	*t*-Bu	H	H	Me	**4dc**		ND	ND	ND

[a] Yields of analytically pure material. [b] Determined by ^1H NMR analysis. [c] Determined by CSP-SFC. [d] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.01 equiv of (*R*,*R*)-**5** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [e] *R* absolute configuration. [f] Conditions as above with 0.05 equiv of (*R*,*R*)-**5**, 0.05 equiv of *i*-Pr_2EtN at 0.2 M in CH_2Cl_2 at −78 °C for 24 h. [g] *S* absolute configuration. [h] *E*/*Z*, 97:3. [i] 4*R*,5*R* absolute configuration.

Trouble with those aliphatics again

J. Am. Chem. Soc. **2003**, *125*, 7800-7801.

Vinylogous Aldol Reactions II



1a-c **2** **6** **7a-c**

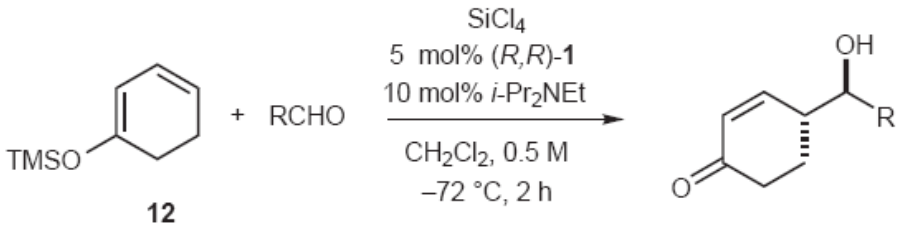
entry	R	product	yield, %[a]	γ/α[b]	er[c]
1	Ph (**1a**)[d]	**7a**	92[e]	>99:1	87:13
2	PhCH=CH (**1b**)[d]	**7b**	88[e]	>99:1	89:11
3	$PhCH_2CH_2$ (**1c**)[f]	**7c**	83[g]	>99:1	94.5:5.5

[a] Yields after chromatography. [b] Determined by ^1H NMR analysis. [c] Determined by CSP-SFC. [d] Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.01 equiv of (*R*,*R*)-**5** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [e] *R* absolute configuration. [f] Reactions employed 1.1 equiv of **2**, 1.2 equiv of dienolate, 0.05 equiv of (*R*,*R*)-**5**, 0.05 equiv of *i*-Pr_2EtN at 0.2 M in CH_2Cl_2 at −78 °C for 24 h. [g] *S* absolute configuration.

Aliphatics work quite well here!

J. Am. Chem. Soc. **2003**, *125*, 7800-7801.

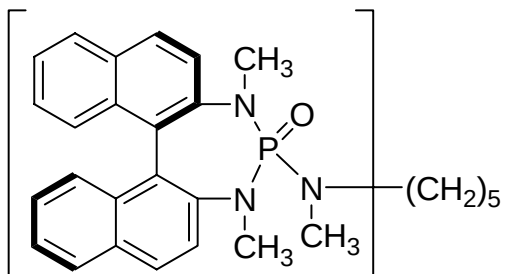
Vinylogous Aldol Reactions III



Entry	R^1	Product	Yield (%)[b]	γ/α[c]	dr (*anti*/*syn*)[d]	er *anti*[d]	er *syn*[d]
1	Ph	**13**	90[e]	>99:1	97.5:2.5	97.5:2.5	Nd
2[f]	1-Naphthyl	**14**	80[e]	>99:1	89.0:11.0	95.0:5.0	>99.5:0.5
3	(*E*)-PhCH=CH	**15**	74	>99:1	98.0:2.0	84.5:15.5	Nd
4	2-Furyl	**16**	94	>99:1	95.5:4.5	81.5:18.5	Nd
5	$PhCH_2CH_2$	**17**	0	Nd[g]	Nd	Nd	Nd

[a] Reactions employed 1.5 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.1 equiv of *i*-Pr_2NEt, 0.05 equiv of (*R*,*R*)-**1** at 0.5 M in CH_2Cl_2 at –72 °C for 2 h.
[b] Yields of analytically pure material.
[c] Determined by ^1H NMR analysis.
[d] Determined by CSP-SFC.
[e] Yield after chromatography.
[f] Conditions as above for 10 h.
[g] Nd: not determined.

Back to unreactive aliphatics



(*R*,*R*)-**1**

Synlett **2004**, 2411-2416.

Vinylogous Aldol Reactions IV

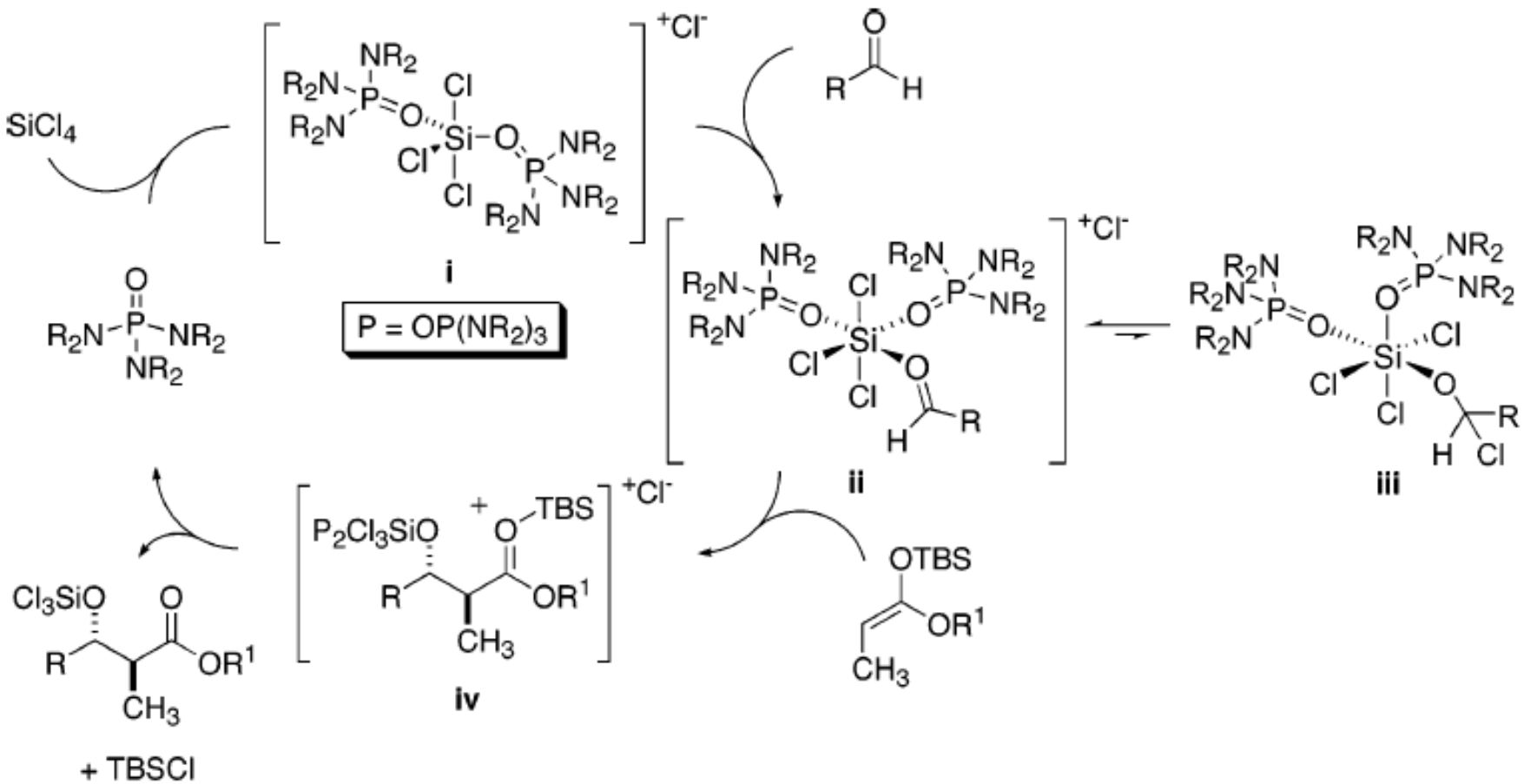
entry	R	product	yield, %[b]	γ: α[c]	er[d]
1[e]	$PhCH_2CH_2$	**12**	80[f]	>99:1	99.0:1.0
2[e]	$CH_3(CH_2)_4$	**13**	79[f]	>99:1	94.3:5.7
3[e]	$(CH_3)_2CHCH_2$	**14**	84[f]	>99:1	99.7:0.3
4[e]	cyclohexyl	**15**	63	>99:1	99.4:0.6
5	C_6H_5	**16**	95	>99:1	97.2:2.8
6	4-$CH_3OC_6H_4$	**17**	95	>99:1	99.0:1.0
7	4-$CF_3C_6H_4$	**18**	93	>99:1	95.4:4.6
8	2-furyl	**19**	94	>99:1	93.8:6.2
9[g]	(*E*)-PhCH=CH	**20**	94	>99:1	98.2:1.8
10	(*E*)-PhCH=C(CH_3)	**21**	91	>99:1	75.5:24.5

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **8**, 0.05 equiv of (*R,R*)-**3**, 0.1 equiv of *i*-Pr_2NEt at 0.1 M in CH_2Cl_2 at −72 °C. [b] Yield of analytically pure material. [c] Determined by ^1H NMR analysis. [d] Determined by CSP-SFC. [e] 0.05 equiv of TBAOTf was added. [f] Yield after chromatography. [g] Reaction employed 0.02 equiv of (*R,R*)-**3**.

Aliphatics work quite nicely!

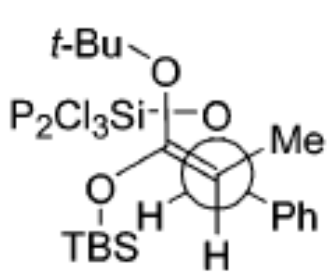
J. Am. Chem. Soc. **2006**, *128*, 1038-1039.

Some Final Explanations

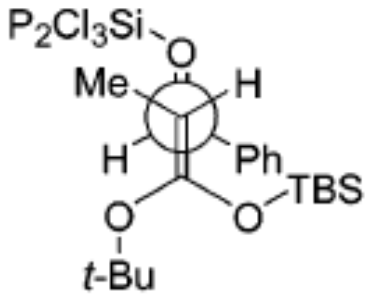


J. Am. Chem. Soc. **2005**, *127*, 3774-3789.

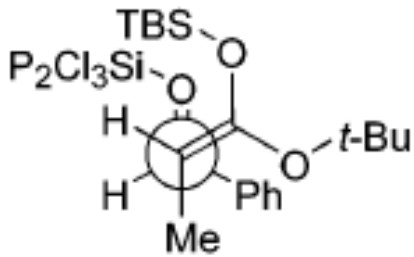
Origins of *Anti* Selectivity I



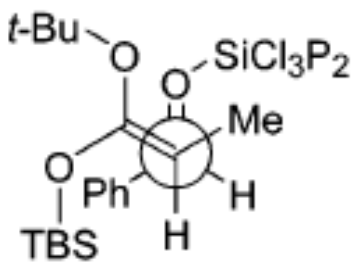
E-(-sc)$_{syn}$



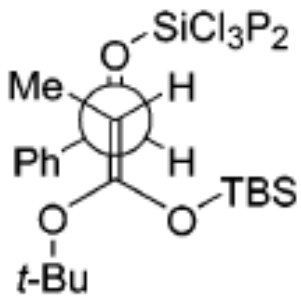
E-ap$_{syn}$



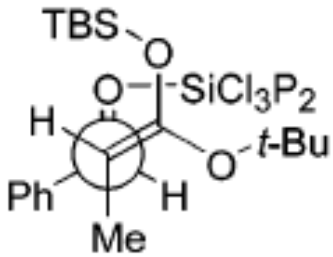
E-(+sc)$_{syn}$



E-(-sc)$_{anti}$



E-ap$_{anti}$

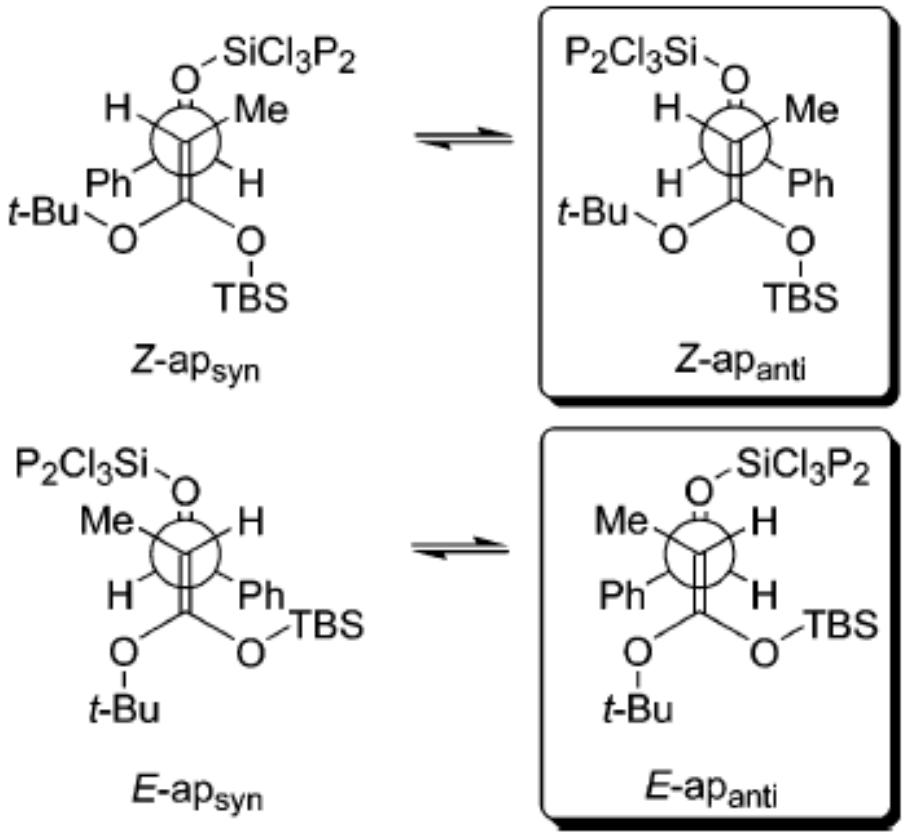


E-(+sc)$_{anti}$

Eliminate the synclinal structures on the basis of unfavorable dipole interactions!

J. Am. Chem. Soc. **2005**, *127*, 3774-3789.

Origins of *Anti* Selectivity II



The α-substituent is the culprit!

J. Am. Chem. Soc. **2005**, *127*, 3774-3789.

Conclusions

1. Trichlorosilyl enol ethers are highly reactive species that undergo aldol addition reactions in both promoted and unpromoted manifolds. High diastereo- and enantioselectivities can be obtained, but the method has some important limitations.
2. Trichlorosilyl enol ethers have also been shown to be viable nucleophiles in the challenging areas of the enantioselective crossed-aldol reaction of aldehydes and in enantioselective additions to ketones.
3. $SiCl_4$ can be used as a stoichiometric Lewis acid in the presence of a catalytic amount of a chiral Lewis base to effect the aldol additions of "typical" silyl enol ethers.