The Development of Lewis Base Catalyzed Aldol Reactions

Rob Matunas
Supergroup Meeting
5/24/06
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.

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!

First Examples

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Promoter</th>
<th>Conversion/time, %/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene-$d_8$</td>
<td>None</td>
<td>18/120</td>
</tr>
<tr>
<td>CD$_2$Cl$_2$</td>
<td>None</td>
<td>50/120</td>
</tr>
<tr>
<td>THF-$d_8$</td>
<td>None</td>
<td>69/120</td>
</tr>
<tr>
<td>CD$_2$Cl$_2$</td>
<td>HMPA</td>
<td>100/&lt;3</td>
</tr>
</tbody>
</table>

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.

More Preliminary Examples

\[
\text{H}_3\text{CO} + \text{OsSiCl}_3 \xrightarrow{\text{DCM, } 0 \degree \text{C}} \text{H}_3\text{CO} + \text{O}_\text{H} + \text{R}^1\text{R}^2\text{R}^1
\]

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>94</td>
</tr>
<tr>
<td>Cy</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>Ph</td>
<td>CH\text{3}</td>
<td>97 (at 20 \degree \text{C})</td>
</tr>
</tbody>
</table>

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

A Promising Lead…

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.”

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).

\[ \text{MeO} \text{SnBu}_3 \xrightarrow{R_n\text{SiCl}} \text{MeO} \text{OSiCl}_{3-n}R_n \]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1a</td>
<td>60-65%</td>
</tr>
<tr>
<td>1b</td>
<td>1b</td>
<td>48%</td>
</tr>
<tr>
<td>1c</td>
<td>1c</td>
<td>23%</td>
</tr>
<tr>
<td>1d</td>
<td>1d</td>
<td>57%</td>
</tr>
<tr>
<td>1e</td>
<td>1e</td>
<td>18%</td>
</tr>
<tr>
<td>1f</td>
<td>1f</td>
<td>19%</td>
</tr>
</tbody>
</table>

*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.
\[
\text{OSiCl}_2R \xrightarrow{1. \text{R'CHO, promoter (0.1 eq)}} \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \xrightarrow{2. \text{NaHCO}_3 (aq)} \text{R'CHO}_2\text{Me} \quad \text{70-90%}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>promoter</th>
<th>aldehyde</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>PhCHO</td>
<td>33 (S)</td>
<td>4 (R)</td>
<td>23 (R)</td>
<td>26 (S)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>PhCHO</td>
<td>23 (S)</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>27 (R)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>PhCHO</td>
<td>20 (R)</td>
<td>6 (R)</td>
<td>12 (S)</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>
| 4     | 3        | t-BuCHO  | 40 (S) | 46 (R) | 12 (S) | 4 (S)
| 5     | 4        | t-BuCHO  | 49 (S) | 26 (S) | 10 (S) | 9 (R)
| 6     | 5        | t-BuCHO  | 26 (R) | 25 (R) | ND | < 2 |

\(^a\) Yield of chromatographically homogeneous material.

\(^b\) Determined by chiral HPLC (Entries 1-3: Chiralcel® AD; 95:5 hexane:EtOH; 1 mL/min\(^{-1}\); \(\lambda = 254\) nm. Entries 4-6: Chiralcel® AD; 98:2 hexane:EtOH; 0.8 mL/min\(^{-1}\); \(\lambda = 210\) nm). \(^c\) Ref 1. \(^d\) 0\(^\circ\)C
Where to Next?

OSiCl₃ + H₂C₃R → 4 Å mol.sieves, DCM, 0 °C →

More uncatalyzed aldol reactions.

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

Now For More Chiral Examples

\[
\begin{align*}
\text{OSiCl}_3 & \quad + \quad \text{HOCR} \\
\text{DCM, } -78 \, ^\circ C, \, 2 \, h & \quad \rightarrow \\
\text{PhOH} & \quad + \quad \text{PhOH}
\end{align*}
\]

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

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

10 mol\% L2

Aliphatic aldehydes don’t work under these conditions…

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

\[
\begin{align*}
\text{OSiCl}_3 & \quad + \quad \text{HOCR} \\
\text{DCM, } -78 \, ^\circ C & \quad \rightarrow \\
\text{PhOH} & \quad + \quad \text{PhOH}
\end{align*}
\]

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

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

\[J. \text{ Am. Chem. Soc. 1997, 119, 2333-2334.}\]
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.
What About Unsubstituted Enolates?

Generally excellent reactivity in *uncatalyzed* reactions:

\[ t-\text{BuOSiCl}_3 + \text{PhCHO} \xrightarrow{\text{DCM, rt}} \text{Ph} \text{CO}_{\text{Ph}} \quad 10 \text{~h}, \quad 97\% \]

\[ \text{TBSO} \text{OSiCl}_3 + \text{PhCHO} \xrightarrow{\text{DCM, rt}} \text{Ph} \text{CO}_{\text{Ph}} \quad 6 \text{~h}, \quad 93\% \]

\[ n-\text{BuOSiCl}_3 + \text{OHC} \text{CH} \text{Ph} \xrightarrow{\text{DCM, rt}} \text{Ph} \text{CO} \text{CH} \text{Ph} \quad 7 \text{~h}, \quad 91\% \]

\[ n-\text{BuOSiCl}_3 + \text{OHC} \text{Cyclohexane} \xrightarrow{\text{DCM, rt}} \text{OH} \text{OH} \text{Cyclohexane} \quad 9 \text{~h}, \quad 93\% \]

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.

\[
\begin{align*}
\text{OSiCl}_3 + \text{PhCHO} & \xrightarrow{\text{5 mol\% L2}} \text{OSiCl}_3 + \text{PhCHO} \\
\text{OSiCl}_3 + \text{PhCHO} & \xrightarrow{\text{5 mol\% L2}} \text{OSiCl}_3 + \text{PhCHO} \\
\text{OSiCl}_3 + \text{PhCHO} & \xrightarrow{\text{10 mol\% L2}} \text{OSiCl}_3 + \text{PhCHO}
\end{align*}
\]

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

The “Stannane Method” for esters:
Moderate yields; inconvenient experimental manipulations; excess SiCl₄ required to avoid “dimer” formation; careful, low-temperature distillation required for isolation (isomerization to C-silyl species can occur thermally)

\[ \text{MeO} \overset{\text{xs. SiCl}_4}{\longrightarrow} \text{MeO} \overset{0 \degree C}{\longrightarrow} \text{MeO} \overset{\Delta}{\longrightarrow} \]

\[ \begin{align*}
\text{MeO} & + \text{O} \overset{\text{SiCl}_3}{} \\
\text{MeO} & \overset{\Delta}{} \\
\end{align*} \]

\[ \text{J. Org. Chem. 1998, 63, 9517-9523.} \]
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

\[
\text{Ph} \text{O} \xrightarrow{\text{Bu}_3\text{SnOMe}} \text{OAc} \xrightarrow{\Delta} \text{Ph} \overset{\text{Bu}_3\text{SnOMe}}{\xrightarrow{\Delta}} \text{OSnBu}_3 \xrightarrow{\text{xs. SiCl}_4} \text{OSiCl}_3
\]

\[
\text{Ph} \text{O} \xrightarrow{\text{Bu}_3\text{SnOMe}} \text{OAc} \xrightarrow{\Delta} \text{Ph} \overset{\text{Bu}_3\text{SnOMe}}{\xrightarrow{\Delta}} \text{OSnBu}_3 \xrightarrow{\text{xs. SiCl}_4} \text{OSiCl}_3 \quad 67\%
\]

\[
\text{O} \xrightarrow{\text{Bu}_3\text{SnOMe}} \text{OAc} \xrightarrow{\Delta} \text{OSnBu}_3 \xrightarrow{\text{xs. SiCl}_4} \text{OSiCl}_3 \quad 78\%
\]

\[
\text{Ph} \text{O} \xrightarrow{\text{Bu}_3\text{SnOMe}} \text{OAc} \xrightarrow{\Delta} \text{Ph} \overset{\text{Bu}_3\text{SnOMe}}{\xrightarrow{\Delta}} \text{OSnBu}_3 \xrightarrow{\text{xs. SiCl}_4} \text{OSiCl}_3 \quad 83\%, Z/E > 50:1
\]

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

**Ester Enolates from Cl₃SiOTf:**
Moderate yields for cyclic esters; acyclic esters react only slowly; pure products obtained after distillation

\[ \text{MeO} \quad \text{TMS} \quad \text{Cl}_3\text{SiOTf} \quad \text{MeO} \quad \text{OSiCl}_3 \]
\[ \text{CDCl}_3 \quad \text{Cl}_3\text{SiOTf, DIPEA} \quad \text{pentane, 0 °C} \quad \text{X} = \text{O, 46%} \quad \text{X} = \text{S, 48%} \]

Why not try using SiCl₄ instead of TfOSiCl₃? No reaction is observed on treatment of an ester with SiCl₄ under “hard” or “soft” conditions!

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

Ketone Enolates from $\text{Cl}_3\text{SiOTf}$:
“…too capricious for general preparative purposes.”

\[
\begin{align*}
\text{Ketone} & \xrightarrow{\text{Cl}_3\text{SiOTf, DIPEA, pentane, 0 } ^\circ\text{C}} \text{Enolate} \\
\text{OSiCl}_3 & \text{60\%}
\end{align*}
\]

\[
\begin{align*}
\text{OTMS} & \xrightarrow{\text{Cl}_3\text{SiOTf, CDCl}_3} \text{Enolate} \\
\text{OSiCl}_3 &
\end{align*}
\]

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

\[
\begin{align*}
\text{OTMS} & \quad 5 \text{ mol}\% \text{ Hg(OAc)}_2, \text{SiCl}_4 & \quad \text{OSiCl}_3 \\
& \quad \text{DCM, rt} & \quad \text{68\%} \\
\text{OTMS} & \quad 1 \text{ mol}\% \text{ Hg(OAc)}_2, \text{SiCl}_4 & \quad \text{OSiCl}_3 \\
& \quad \text{DCM, rt} & \quad \text{83\%} \\
\text{TBSO} & \quad 1 \text{ mol}\% \text{ Hg(OAc)}_2, \text{SiCl}_4 & \quad \text{OSiCl}_3 \\
& \quad \text{DCM, rt} & \quad \text{65\%}
\end{align*}
\]

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

Presumed mechanism of the Hg-catalyzed trans-silylation:

\[ \text{OTMS} \xrightarrow{\text{HgX}_2} \text{HgX} \xrightarrow{\text{SiCl}_4} \text{Cl}_3\text{Si}^+\text{Cl}^- \xrightarrow{-\text{HgX}_2} \text{OSiCl}_3 \]

Problems with Some Enolate Types

\[
\text{OTMS} + \text{SiCl}_4 \xrightarrow{5 \text{ mol\% } \text{Hg(OAc)}_2} \text{DCM, rt} \quad \text{OSiCl}_3 + \text{OSiCl}_3
\]

<table>
<thead>
<tr>
<th>R</th>
<th>yield, %</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>58</td>
<td>2/1</td>
</tr>
<tr>
<td>Et</td>
<td>72</td>
<td>2/1</td>
</tr>
<tr>
<td>i-Pr</td>
<td>65</td>
<td>8/1</td>
</tr>
<tr>
<td>t-Bu</td>
<td>55</td>
<td>&gt;20/1</td>
</tr>
<tr>
<td>Ph</td>
<td>66</td>
<td>99/1</td>
</tr>
</tbody>
</table>

What’s the Problem?

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

Dependence on Aldehyde Electronics

\[
\text{OSiCl}_3 + \text{RCHO} \xrightarrow{\text{DCM, 0 }^\circ\text{C}} \text{alkene} + \text{aldehyde}
\]

<table>
<thead>
<tr>
<th>aldehyde</th>
<th>time, h</th>
<th>yield, %</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>11</td>
<td>90</td>
<td>19:1</td>
</tr>
<tr>
<td>b</td>
<td>9</td>
<td>92</td>
<td>28:1</td>
</tr>
<tr>
<td>c</td>
<td>10</td>
<td>96</td>
<td>26:1</td>
</tr>
<tr>
<td>d</td>
<td>8</td>
<td>96</td>
<td>&gt;49:1</td>
</tr>
<tr>
<td>e</td>
<td>11</td>
<td>91</td>
<td>&gt;49:1</td>
</tr>
</tbody>
</table>

**Dependence on Aldehyde Electronics II**

\[
\text{OSiCl}_3 + \text{RCHO} \xrightarrow{10 \text{ mol\% L2}} \text{DCM, -78 \degree C} \rightarrow \text{10 \% (ee)}
\]

<table>
<thead>
<tr>
<th>aldehyde</th>
<th>syn:anti</th>
<th>yield, % (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1:17</td>
<td>91, (82)</td>
</tr>
<tr>
<td>b</td>
<td>1:15</td>
<td>96, (79)</td>
</tr>
<tr>
<td>c</td>
<td>1:29</td>
<td>97, (84)</td>
</tr>
<tr>
<td>d</td>
<td>1:35</td>
<td>97, (92)</td>
</tr>
<tr>
<td>e</td>
<td>1:20</td>
<td>94, (87)</td>
</tr>
</tbody>
</table>

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

Dependence on Aldehyde Electronics III

This interesting trend was observed during optimization studies:

Aldehyde added over 1 min

\[
\text{OSiCl}_3 + \text{PhCHO} \xrightarrow{10 \text{ mol}\% \text{ L2}} \text{DCM, -78 }^\circ\text{C} \rightarrow \begin{array}{c}
\text{OH} \\
\text{Ph}
\end{array}
\]

99\%, syn:anti 1:6, ee 70%

Aldehyde added over 50 min

\[
\text{OSiCl}_3 + \text{PhCHO} \xrightarrow{10 \text{ mol}\% \text{ L2}} \text{DCM, -78 }^\circ\text{C} \rightarrow \begin{array}{c}
\text{OH} \\
\text{Ph}
\end{array}
\]

98\%, syn:anti 1:22, ee 75%

“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 silicate species.”

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?

\[
\begin{align*}
\text{OTMS} & \quad \text{1. Hg(OAc)}_2, \text{SiCl}_4 \\
\text{OR} & \quad \text{2. PhCHO, DCM, rt, 1 h} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>yield, %</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>82</td>
<td>1:1.2</td>
</tr>
<tr>
<td>Piv</td>
<td>71</td>
<td>1:2.4</td>
</tr>
<tr>
<td>Bn</td>
<td>75</td>
<td>1:3.4</td>
</tr>
</tbody>
</table>

Will Chiral Catalysts Help?

Will Chiral Catalysts Help?

A chiral phosphoramide catalyst is introduced for the enantioselective addition of enol ethers to aldehydes. The reaction is performed in DCM at -78 °C using 5 mol% of the catalyst. The results are summarized in the table below:

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Yield, %</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>(S,S)-L2</td>
<td>85</td>
<td>1.5:1</td>
</tr>
<tr>
<td>Piv</td>
<td>(S,S)-L2</td>
<td>78</td>
<td>3.4:1</td>
</tr>
<tr>
<td>Bn</td>
<td>(S,S)-L2</td>
<td>78</td>
<td>1:1.1</td>
</tr>
<tr>
<td>TBS</td>
<td>(R,R)-L2</td>
<td>85</td>
<td>73:1*</td>
</tr>
<tr>
<td>Piv</td>
<td>(R,R)-L2</td>
<td>78</td>
<td>20:1</td>
</tr>
<tr>
<td>Bn</td>
<td>(R,R)-L2</td>
<td>77</td>
<td>11:1</td>
</tr>
</tbody>
</table>

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

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

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.
What About Chiral Aldehydes? (I)

A slight preference for the \textit{anti} isomer is consistent, once again, with a boat transition state.

\[ \text{n-Bu}^{\text{OSiCl}_3} + \text{HOR} \xrightarrow{\text{DCM, rt}} \text{n-Bu}^{\text{RO}} \text{OH} \]

- \( R = \text{TBS}, 95\% \), \textit{syn:anti} 1:2.4
- \( R = \text{Bn}, 92\% \), \textit{syn:anti} 1:2.7

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.

The reaction is represented as:

\[ n\text{-Bu}CH=CH\text{OSiCl}_3 + H\text{C}\text{O}\text{OTBS} \xrightarrow{10 \text{ mol\% cat.}} n\text{-Bu}CH\text{CH}CH\text{CH}\text{OH} \]

DCM, -78 °C

The yield and selectivity for different catalysts are given in the table:

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield, %</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMPA</td>
<td>41</td>
<td>1:1.3</td>
</tr>
<tr>
<td>(S,S)-L2</td>
<td>47</td>
<td>2.7:1</td>
</tr>
<tr>
<td>(R,R)-L2</td>
<td>50</td>
<td>1:15.6</td>
</tr>
</tbody>
</table>

\[ (S,S)-L2 \]

\[ J. \text{Am. Chem. Soc.} 2000, 122, 8837-8847. \]
So What’s Wrong With Aliphatic Aldehydes?

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

\[
\text{R}^2\text{OSiCl}_3 + \text{HCO}_\text{OTBS} \xrightarrow{10 \text{ mol}\% \text{ L2}} \text{n-BuO}_\text{OTBS} \xrightarrow{\text{DCM}, -78^\circ\text{C}} \text{n-Bu\text{CH}-\text{CH}_2\text{OH}}
\]

88%, 74% ee

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

\[
\text{R}^2\text{OSiCl}_3 + \text{HCO}_\text{R}^1\text{R}^1\xrightarrow{\text{R}_3\text{P}=\text{O}} \text{R}^2\text{O}_\text{SiCl}_3 + \text{H}_\text{R}_1\text{R}^1
\]

\[\text{J. Am. Chem. Soc. 2000, 122, 8837-8847.}\]
Onward to Mechanistic Studies
Mechanistic Studies Revise Earlier Models: I

\[
\text{OSiCl}_3 + \text{PhCHO} \xrightarrow{10 \text{ mol\% cat.}} \text{DCM, -78} \; ^\circ\text{C} \quad \text{catalyst} \quad \text{yield, } \% \quad \text{syn:anti}
\]

<table>
<thead>
<tr>
<th>catalyst</th>
<th>yield, %</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2</td>
<td>95</td>
<td>1:60</td>
</tr>
<tr>
<td>L3</td>
<td>94</td>
<td>97:1</td>
</tr>
<tr>
<td>L4</td>
<td>99</td>
<td>1:2.8</td>
</tr>
<tr>
<td>L5</td>
<td>93</td>
<td>27:1</td>
</tr>
<tr>
<td>L6</td>
<td>96</td>
<td>31:1</td>
</tr>
<tr>
<td>L7</td>
<td>95</td>
<td>40:1</td>
</tr>
</tbody>
</table>

Mechanistic Studies Revise Earlier Models: II

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

Mechanistic Studies Revise Earlier Models: III

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

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:

\[
\text{OSiCl}_3 + \text{PhCHO} \rightarrow \text{Product}
\]

\[
\text{DCM, -78 °C}
\]

<table>
<thead>
<tr>
<th>time, s</th>
<th>conversion, %</th>
<th>yield, %</th>
<th>ee, %</th>
</tr>
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<tr>
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<td>30</td>
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<td>53.7</td>
</tr>
<tr>
<td>480</td>
<td>100</td>
<td>95</td>
<td>53.3</td>
</tr>
</tbody>
</table>

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:

![The new model diagram](attachment:chemical_structure.png)

- **Cationic boat TS** (one phosphoramide)
- **Cationic chair TS** (two phosphoramides)

The “Grand Unified Mechanistic Scheme”

The Proof is in the Salt

Rate inhibition by Bu₄N⁺Cl⁻ (common salt effect) and acceleration by Bu₄N⁺OTf⁻ (increased ionic strength) support the mechanistic proposal of ionizing chloride from silicon.

The Glory of Rapid-Injection NMR

10 mol% cat.

DCM, -78 °C

\[
\begin{align*}
\text{OSiCl}_3 + \text{PhCHO} & \rightarrow \text{syn-3} + \text{anti-3} \\
\text{OSiCl}_3 + \text{t-BuCHO} & \rightarrow \text{8}
\end{align*}
\]

\[
\begin{align*}
cat. = 4, 95\%, \text{ anti: syn } 60:1 \\
cat. = 5, 94\%, \text{ anti: syn } 1/97
\end{align*}
\]

Most Importantly: 1\textsuperscript{st} order in 5, but 2\textsuperscript{nd} order in 4

\[
\begin{align*}
\end{align*}
\]
Now For Some More “Interesting” Substrates
Interestingly, diastereoselectivity with these $\alpha$-chiral $\beta$-alkoxy enolates can be controlled by the catalyst. Catalysis with an achiral phosphoramide shows a modest preference for the syn product.

\[
\begin{align*}
\text{TBSO} & \quad \text{OSiCl}_3 & \quad 10 \text{ mol\% L2, RCHO} & \quad \text{DCM, } -78 \, ^\circ\text{C} & \quad \text{TBSO} & \quad \text{O} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph}
\end{align*}
\]

**Synlett 2001**, 1024-1029.
Now Add More Complications

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

Yes, More TS Models

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.

1,4-Induction With Substituted Trichlorosilyl Enolates

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

Even More Chairs…

The Enigmatic 1,5-Induction

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

\[
\text{TBSO} \quad \text{OSiCl}_3 \quad + \quad \text{PhCHO} \quad \xrightarrow{\text{10 mol\% cat.}} \quad \text{TBSO} \quad \text{O} \quad \text{OH} \quad \text{Ph}
\]

\[
\begin{align*}
\text{DCM, -78 °C} \\
(\text{R,R)-L2, 72\%, \text{syn:anti 1:2.5}} \\
(\text{S,S)-L2, 72\%, \text{syn:anti 1.3:1}} \\
\text{L4, 55\%, \text{syn:anti 1:1.4}}
\end{align*}
\]

Would a PG change have made a difference here?

More Complicated 1,5-Induction

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

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.

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:

\[ \text{OTMS} \quad \begin{array}{c} \text{n-C}_5\text{H}_{11} \\ \downarrow \\ \text{Z/E > 99:1} \end{array} \xrightarrow{1. \text{MeLi, Et}_2\text{O}} \quad \begin{array}{c} \text{OSiCl}_3 \\ \downarrow \\ \text{n-C}_5\text{H}_{11} \end{array} \xrightarrow{2. \text{SiCl}_4} \quad \text{Z/E > 99:1} \]

53%, Z/E > 99:1

\[ \text{OTMS} \quad \begin{array}{c} \downarrow \\ \text{Z/E > 99:1} \end{array} \xrightarrow{1. \text{MeLi, Et}_2\text{O}} \quad \begin{array}{c} \text{OSiCl}_3 \\ \downarrow \\ \end{array} \xrightarrow{2. \text{SiCl}_4} \quad \text{34%, Z/E > 99:1} \]

Debut of a Linked Catalyst

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

\[
\begin{align*}
\text{OSiCl}_3 + \text{HOC} & \quad \text{DCM/CHCl}_3 1:4 \\
\text{MeO} \quad \text{OMe} & \quad -78 \degree \mathrm{C}, 6 \text{ h} \\
\text{L8} & \\
\text{Z enolate: 95\%, syn:anti 98:2, 81\% ee} & \quad \text{E enolate: 97\%, syn:anti 1:99, 59\% ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{OSiCl}_3 + \text{HOC} & \quad \text{DCM/CHCl}_3 1:4 \\
\text{MeO} \quad \text{OMe} & \quad -78 \degree \mathrm{C}, 6 \text{ h} \\
\text{L8} & \\
\text{Z enolate: 86\%, syn:anti 99:1, 42\% ee} & \quad \text{E enolate: 88\%, syn:anti 1:99, 26\% ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{OSiCl}_3 + \text{HOC} & \quad \text{DCM/CHCl}_3 1:4 \\
\text{MeO} \quad \text{OMe} & \quad -25 \degree \mathrm{C}, 20 \text{ h} \\
\text{L8} & \\
\text{Z enolate: 47\%, syn:anti 95:5, 8\% ee} & \quad \text{E enolate: 79\%, syn:anti 1:99, 66\% ee} \\
\end{align*}
\]

Additional Studies on Crossed-Aldol Reactions of Aldehydes

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time, h</th>
<th>Yield, %</th>
<th>er †</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₄</td>
<td>5a</td>
<td>8</td>
<td>86</td>
<td>70.0/30.0</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄</td>
<td>5b</td>
<td>12</td>
<td>90</td>
<td>73.0/27.0</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC₆H₄</td>
<td>5c</td>
<td>20</td>
<td>92</td>
<td>75.5/24.5</td>
</tr>
<tr>
<td>4</td>
<td>3,4,5-(MeO)₃C₆H₂</td>
<td>5d</td>
<td>26</td>
<td>80</td>
<td>87.5/12.5</td>
</tr>
<tr>
<td>5</td>
<td>4-ClC₆H₄</td>
<td>5e</td>
<td>8</td>
<td>85</td>
<td>89.0/11.0</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃C₆H₄</td>
<td>5f</td>
<td>8</td>
<td>86</td>
<td>90.0/11.0</td>
</tr>
<tr>
<td>7</td>
<td>4-NO₂C₆H₄</td>
<td>5g</td>
<td>8</td>
<td>89</td>
<td>91.0/9.0</td>
</tr>
<tr>
<td>8</td>
<td>2-Naphthyl</td>
<td>5h</td>
<td>12</td>
<td>90</td>
<td>83.0/17.0</td>
</tr>
<tr>
<td>9</td>
<td>(E)-Cinnamyl</td>
<td>5i</td>
<td>12</td>
<td>90</td>
<td>67.5/32.5</td>
</tr>
<tr>
<td>10</td>
<td>Phenylpropargyl</td>
<td>5j</td>
<td>12</td>
<td>85</td>
<td>81.5/18.5</td>
</tr>
<tr>
<td>11</td>
<td>1-Propenyl</td>
<td>5k</td>
<td>15</td>
<td>82</td>
<td>56.0/42.0 †</td>
</tr>
<tr>
<td>12</td>
<td>n-Butyl</td>
<td>5l</td>
<td>30³</td>
<td>80</td>
<td>91.0/9.0</td>
</tr>
</tbody>
</table>

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.

…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.

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

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

Looks like aldolization is the RDS, as suspected.

Some Energy Diagrams

\[ R\text{-enantiomer} \xrightarrow{k_{2R}} TC_R \xrightarrow{k_{IR}} 1, 2d, \text{LB} \xrightarrow{k_{IS}} TC_S \xrightarrow{k_{2S}} S\text{-enantiomer} \]

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

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.

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

Enantioselective Additions to Ketones

\[
\text{MeO} - \text{OSiCl}_3 + \text{R}_1^1 \text{C} = \text{O} \text{R}_2 \xrightarrow{\text{DCM, rt, } 2 \text{ h}} 10 \text{ mol}\% \text{ L9} \rightarrow \text{MeO} - \text{C} = \text{O} \text{R}_1^1 \text{R}_2
\]

\[
\begin{align*}
\text{MeO} - \text{C} = \text{O} - \text{Et} - \text{Ph} & \quad \text{96\%, 82\% ee} \\
\text{MeO} - \text{C} = \text{O} - \text{Ph} & \quad \text{89\%, 86\% ee} \\
\text{MeO} - \text{C} = \text{O} - \text{Me} - \text{Ph} & \quad \text{87\%, 11\% ee} \\
\text{MeO} - \text{C} = \text{O} - \text{Me} - \text{Ph} & \quad \text{97\%, 35\% ee}
\end{align*}
\]

Highly substrate dependent!

The “2\textsuperscript{nd} Generation” Approach
A New Concept

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

\[
\text{SiCl}_4 + \text{HMPA} \rightarrow \quad \begin{array}{c}
\text{Me}_2\text{N}^+\text{P}=\text{O}^-
\\
\text{Me}_2\text{N}^+\text{NMe}_2^-
\\
\text{O-Si}^{+}\text{Cl}^-
\\
\text{Me}_2\text{N}^-\text{P}^+\text{Cl}^-
\\
\text{Me}_2\text{N}^-\text{NMe}_2^-
\end{array}
\]

Now a potent Lewis acid!

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).

Less “Restrictive” Methodology I

\[
\begin{align*}
R\text{H} & + \text{SiCl}_{4} + \text{O} + \text{OTBDMS} & \xrightarrow{5 \text{ mol}\% \text{ catalyst 3}} & \text{OH} \text{O}\text{Me} \\
\text{2a-l} & & & \text{4a-k}
\end{align*}
\]

\[
\begin{align*}
\text{1} & & \text{2}
\end{align*}
\]

\[
(R,R)-3
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, %</th>
<th>er²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅ (2a)</td>
<td>4aᵈ</td>
<td>97ᵉ</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td>2</td>
<td>1-naphthyl (2b)</td>
<td>4b</td>
<td>98</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl (2c)</td>
<td>4c</td>
<td>98</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>4-CH₃C₆H₄ (2d)</td>
<td>4d</td>
<td>97</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>4-CH₃OC₆H₄ (2e)</td>
<td>4e</td>
<td>97</td>
<td>98.5:1.5</td>
</tr>
<tr>
<td>6</td>
<td>4-CF₃C₆H₄ (2f)</td>
<td>4f</td>
<td>97</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>7</td>
<td>(E)-PhCH═CH (2g)</td>
<td>4g</td>
<td>95ᵉ</td>
<td>97:3</td>
</tr>
<tr>
<td>8</td>
<td>(E)-PhCH═C(CH₃) (2h)</td>
<td>4h</td>
<td>98</td>
<td>72.5:27.5</td>
</tr>
<tr>
<td>9</td>
<td>2-furyl (2i)</td>
<td>4i</td>
<td>94ᵉ</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>10</td>
<td>cyclohexyl (2j)⁷</td>
<td>4j</td>
<td>86ᵉ</td>
<td>94:6</td>
</tr>
<tr>
<td>11</td>
<td>PhCH₂CH₂ (2k)⁷</td>
<td>4k</td>
<td>72ᵉ</td>
<td>90.5:9.5</td>
</tr>
</tbody>
</table>

¹ All reactions employed 1.1 equiv of SiCl₄, 1.2 equiv of 1, and 0.05 equiv of (R,R)-3 at 0.2 M in CH₂Cl₂ at −78 °C for 15 min. ² Yield of analytically pure material. ³ Determined by CSP-SFC. ⁴ R absolute configuration. ⁵ Chromatographically homogeneous material. ⁶ Reaction time 6 h.

Less “Restrictive” Methodology II

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

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

Methyl Ketone TMS Enol Ethers

![Reaction Scheme]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>time, h</th>
<th>yield, %</th>
<th>er, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E)-PhCH=CH</td>
<td>(+)-13</td>
<td>4</td>
<td>97.5e</td>
<td>99.5/0.5</td>
</tr>
<tr>
<td>2</td>
<td>(E)-PhCH=C(CH3)d</td>
<td>(+)-14</td>
<td>24</td>
<td>54e</td>
<td>78.0/22.0</td>
</tr>
<tr>
<td>3</td>
<td>1-naphthyl</td>
<td>(+)-15</td>
<td>10</td>
<td>95e</td>
<td>96.0/4.0</td>
</tr>
<tr>
<td>4</td>
<td>2-naphthyl</td>
<td>(+)-16</td>
<td>4</td>
<td>92</td>
<td>99.5/0.5</td>
</tr>
<tr>
<td>5</td>
<td>4-CH3OC6H4</td>
<td>(+)-17</td>
<td>4</td>
<td>97.5</td>
<td>99.5/0.5</td>
</tr>
<tr>
<td>6</td>
<td>4-CF3C6H4</td>
<td>(+)-18</td>
<td>4</td>
<td>96</td>
<td>99.5/0.5</td>
</tr>
<tr>
<td>7</td>
<td>2-furyl</td>
<td>(+)-19</td>
<td>6</td>
<td>88</td>
<td>95.0/5.0</td>
</tr>
<tr>
<td>8</td>
<td>2-thiophenyl</td>
<td>(+)-20</td>
<td>8</td>
<td>79</td>
<td>99.0/10.0</td>
</tr>
<tr>
<td>9</td>
<td>PhCH2CH2</td>
<td></td>
<td>24</td>
<td>nr</td>
<td>nd</td>
</tr>
</tbody>
</table>

a All reactions employed 1.5 equiv of SiCl4, 1.2 equiv of enolate, 10 mol % i-Pr2NEt, and 5 mol % (R,R)-1 at 0.5 M in CH2Cl2 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.

Crossed Aldol Reactions of Aldehydes Revisited

Aliphatic aldehydes fail as usual.

\[
\begin{align*}
1a + 2a-i & \rightarrow 4a-i \\
1. & (R,R)-3 (15 \text{ mol } \%)
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, $^a$ %</th>
<th>er $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_4$</td>
<td>4a</td>
<td>80</td>
<td>97.1/2.9</td>
</tr>
<tr>
<td>2</td>
<td>2-naphthyl</td>
<td>4b</td>
<td>85</td>
<td>97.1/2.9</td>
</tr>
<tr>
<td>3</td>
<td>1-naphthyl</td>
<td>4c</td>
<td>78</td>
<td>92.2/7.8</td>
</tr>
<tr>
<td>4</td>
<td>4-CF$_3$C$_6$H$_4$</td>
<td>4d</td>
<td>84</td>
<td>98.1/7.8</td>
</tr>
<tr>
<td>5</td>
<td>4-ClC$_6$H$_4$</td>
<td>4e</td>
<td>81</td>
<td>97.9/2.1</td>
</tr>
<tr>
<td>6</td>
<td>cinnamyl</td>
<td>4f</td>
<td>60</td>
<td>98.2/1.8</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOC$_6$H$_4$</td>
<td>4g</td>
<td>30</td>
<td>91.2/8.8</td>
</tr>
<tr>
<td>8</td>
<td>$\alpha$-methylcinnamyl</td>
<td>4h</td>
<td>&lt;10</td>
<td>nd$^c$</td>
</tr>
<tr>
<td>9</td>
<td>n-butyl</td>
<td>4i</td>
<td>nr$^d$</td>
<td></td>
</tr>
</tbody>
</table>

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

Vinylogous Aldol Reactions

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

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>dienolate</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$R^4$</th>
<th>product</th>
<th>yield, %</th>
<th>$\gamma/\alpha$</th>
<th>$d_r$</th>
<th>$e_r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a$^d$</td>
<td>Ph (1a)</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>4aa</td>
<td>89$^e$</td>
<td>&gt;99:1</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3a$^d$</td>
<td>PhCH=CH (1b)</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>4ab</td>
<td>84$^e$</td>
<td>&gt;99:1</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3a$^d$</td>
<td>PhCH$_2$CH$_2$ (1c)</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>4ac</td>
<td>68$^e$</td>
<td>&gt;99:1</td>
<td>95:5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3b$^d$</td>
<td>Ph (1a)</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>4ba</td>
<td>93$^e$</td>
<td>&gt;99:1</td>
<td>99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3b$^d$</td>
<td>PhCH=CH (1b)</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>4bb</td>
<td>88</td>
<td>&gt;99:1</td>
<td>99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3b$^d$</td>
<td>PhCH$_2$CH$_2$ (1c)</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>4bc</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3c$^d$</td>
<td>Ph (1a)</td>
<td>Et</td>
<td>Me</td>
<td>H</td>
<td>4ca</td>
<td>91$^e$</td>
<td>&gt;99:1</td>
<td>96.4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3c$^d$</td>
<td>PhCH=CH (1b)</td>
<td>Et</td>
<td>H</td>
<td>Me</td>
<td>4cb</td>
<td>97$^h$</td>
<td>&gt;99:1</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3c$^d$</td>
<td>PhCH$_2$CH$_2$ (1c)</td>
<td>Et</td>
<td>H</td>
<td>Me</td>
<td>4cc</td>
<td>73</td>
<td>&gt;99:1</td>
<td>97.5:2.5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3d$^d$</td>
<td>Ph (1a)</td>
<td>t-Bu</td>
<td>H</td>
<td>H</td>
<td>4da</td>
<td>92$^i$</td>
<td>99:1</td>
<td>&gt;99:1</td>
<td>94.5:5.5</td>
</tr>
<tr>
<td>11</td>
<td>3d$^d$</td>
<td>PhCH=CH (1b)</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>4db</td>
<td>71</td>
<td>99:1</td>
<td>&gt;99:1</td>
<td>91:9</td>
</tr>
<tr>
<td>12</td>
<td>3d$^d$</td>
<td>PhCH$_2$CH$_2$ (1c)</td>
<td>t-Bu</td>
<td>H</td>
<td>Me</td>
<td>4dc</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Yields of analytically pure material. $^b$ Determined by $^1$H 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$_2$Cl$_2$ 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 t-Pr$_2$EtN at 0.2 M in CH$_2$Cl$_2$ at $-78$ °C for 24 h. $^g$ S absolute configuration. $^h$ E/Z, 97:3. $^i$ 4R,5R absolute configuration.

Trouble with those aliphatics again

Vinylogous Aldol Reactions II

Aliphatics work quite well here!

\[
\begin{align*}
\text{entry} & \quad R & \quad \text{product} & \quad \text{yield, \%}^a & \quad \gamma/\alpha^b & \quad \text{er}^c \\
1 & \text{Ph (1a)}^d & 7a & 92^e & > 99:1 & 87:13 \\
2 & \text{PhCH=CH (1b)}^d & 7b & 88^e & > 99:1 & 89:11 \\
3 & \text{PhCH}_2\text{CH}_2 (1c)^f & 7c & 83^g & > 99:1 & 94.5:5.5 \\
\end{align*}
\]

\(^a\) Yields after chromatography. \(^b\) Determined by \(^1\)H 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\(_2\)Cl\(_2\) at \(-78^\circ\)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\(_2\)EtN at 0.2 M in CH\(_2\)Cl\(_2\) at \(-78^\circ\)C for 24 h. \(^g\) S absolute configuration.

## Vinylogous Aldol Reactions III

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>γ/α&lt;sup&gt;c&lt;/sup&gt;</th>
<th>dr (anti/syn)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>er anti&lt;sup&gt;d&lt;/sup&gt;</th>
<th>er syn&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>13</td>
<td>90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;99:1</td>
<td>97.5:2.5</td>
<td>97.5:2.5</td>
<td>Nd</td>
</tr>
<tr>
<td>2&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1-Naphthyl</td>
<td>14</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;99:1</td>
<td>89.0:11.0</td>
<td>95.0:5.0</td>
<td>&gt;99.5:0.5</td>
</tr>
<tr>
<td>3</td>
<td>(E)-PhCH=CH</td>
<td>15</td>
<td>74</td>
<td>&gt;99:1</td>
<td>98.0:2.0</td>
<td>84.5:15.5</td>
<td>Nd</td>
</tr>
<tr>
<td>4</td>
<td>2-Furyl</td>
<td>16</td>
<td>94</td>
<td>&gt;99:1</td>
<td>95.5:4.5</td>
<td>81.5:18.5</td>
<td>Nd</td>
</tr>
<tr>
<td>5</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>17</td>
<td>0</td>
<td>Nd&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Nd</td>
<td>Nd</td>
<td>Nd</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions employed 1.5 equiv of SiCl<sub>4</sub>, 1.2 equiv of dienolate, 0.1 equiv of i-Pr<sub>2</sub>NEt, 0.05 equiv of (R,R)-1 at 0.5 M in CH<sub>2</sub>Cl<sub>2</sub> at −72 °C for 2 h.

<sup>b</sup> Yields of analytically pure material.

<sup>c</sup> Determined by <sup>1</sup>H NMR analysis.

<sup>d</sup> Determined by CSP-SFC.

<sup>e</sup> Yield after chromatography.

<sup>f</sup> Conditions as above for 10 h.

<sup>g</sup> Nd: not determined.

---

**Synlett 2004, 2411-2416.**
Vinylogous Aldol Reactions IV

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>γ: α&lt;sup&gt;c&lt;/sup&gt;</th>
<th>er&lt;sup&gt;d&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>PhCH₂CH₂</td>
<td>12</td>
<td>80&lt;sup&gt;f&lt;/sup&gt;</td>
<td>&gt;99:1</td>
<td>99.0:1.0</td>
</tr>
<tr>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>CH₃(CH₂)₄</td>
<td>13</td>
<td>79&lt;sup&gt;f&lt;/sup&gt;</td>
<td>&gt;99:1</td>
<td>94.3:5.7</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(CH₃)₂CHCH₂</td>
<td>14</td>
<td>84&lt;sup&gt;f&lt;/sup&gt;</td>
<td>&gt;99:1</td>
<td>99.7:0.3</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>cyclohexyl</td>
<td>15</td>
<td>63</td>
<td>&gt;99:1</td>
<td>99.4:0.6</td>
</tr>
<tr>
<td>5</td>
<td>C₆H₅</td>
<td>16</td>
<td>95</td>
<td>&gt;99:1</td>
<td>97.2:2.8</td>
</tr>
<tr>
<td>6</td>
<td>4-CH₃OC₆H₄</td>
<td>17</td>
<td>95</td>
<td>&gt;99:1</td>
<td>99.0:1.0</td>
</tr>
<tr>
<td>7</td>
<td>4-CF₃C₆H₄</td>
<td>18</td>
<td>93</td>
<td>&gt;99:1</td>
<td>95.4:4.6</td>
</tr>
<tr>
<td>8</td>
<td>2-furyl</td>
<td>19</td>
<td>94</td>
<td>&gt;99:1</td>
<td>93.8:6.2</td>
</tr>
<tr>
<td>9&lt;sup&gt;g&lt;/sup&gt;</td>
<td>(E)-PhCH=CH</td>
<td>20</td>
<td>94</td>
<td>&gt;99:1</td>
<td>98.2:1.8</td>
</tr>
<tr>
<td>10</td>
<td>(E)-PhCH=C(CH₃)</td>
<td>21</td>
<td>91</td>
<td>&gt;99:1</td>
<td>75.5:24.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions employed 1.1 equiv of SiCl₄, 1.2 equiv of 8, 0.05 equiv of (R,R)-3, 0.1 equiv of i-Pr₂NEt at 0.1 M in CH₂Cl₂ at −72 °C. <sup>b</sup> Yield of analytically pure material. <sup>c</sup> Determined by ¹H NMR analysis. <sup>d</sup> Determined by CSP-SFC. <sup>e</sup> 0.05 equiv of TBAOTf was added. <sup>f</sup> Yield after chromatography. <sup>g</sup> Reaction employed 0.02 equiv of (R,R)-3.

Some Final Explanations

Origins of *Anti* Selectivity I

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

Origins of *Anti* Selectivity II

The $\alpha$-substituent is the culprit!

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. SiCl₄ 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.