Asymmetric catalysis with chiral Lewis bases

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Abstract: The trichlorosilyl enolates of methyl ketones, ethyl ketones and cycloalkanones react readily with a variety of aldehydes in aldol addition reactions without external promoters at 0°C - rt. The aldol products are generated in excellent yield and with good to excellent diastereoselectivity (E to syn, Z to anti). In the presence of catalytic amounts (5-15 mol %) of chiral phosphoramidate promoters the aldol reactions of enoxytrichlorosilanes now proceed rapidly at -78°C and are extremely diastereoselective (E to anti, Z to syn, 61-99/1). The products are afforded with good to excellent enantioselectivity (anti: 82-97% ee, syn: 58-96% ee).

Catalytic, asymmetric aldol additions have come to the forefront of synthetic methodology due to both the synthetic utility of the products and the challenge of designing such a transformation.1 There are now a number of reports concerning the addition of silyl enol ethers or silyl ketene acetics to aldehydes using chiral Lewis acids that proceed with good-to-high enantioselectivity.2 Despite the advantages of chiral Lewis acid catalysis, an asymmetric catalytic aldol reaction with the generality and selectivity of the well known stoichiometric methods still remains to be developed. We envisioned the possibility of devising a new reaction that uses chiral Lewis base catalysis, that is, activation of the nucleophile, Scheme 1.3,4

Scheme 1

The challenges that face the development of nucleophilic catalysis of the aldol addition are outlined in Scheme 2. In this case the enoxymetal derivative is activated by pre-association with a chiral Lewis basic group. The ate complex must be more reactive than the free enolate for the ligand accelerated catalysis to be observed. Next, association of this still Lewis acidic ate complex with the Lewis basic carbonyl oxygen of the aldehyde produces a hyper-reactive complex in which the metal has expanded its valence by two. It is expected that this complex between enolate, aldehyde and the chiral Lewis basic group reacts through a closed type transition structure with a high degree of information transfer to produce the metal aldolate product. This represents a single turnover event and for catalysis to be observed, the complex must undergo the expulsion of the G* group with the formation of the chelated metal aldolate product.

Scheme 2

To formulate the criteria that are necessary to invent such a process we must consider the design elements that go into the enoxy metal and the G* group. For the metal, the MLn subunit must be able to expand its valence by two and balance nucleophilicity of enolate with electrophilicity to coordinate both the Lewis basic aldehyde and the chiral G* group. Such metals that would satisfy these criteria are those that can expand their valence such as silicon, tin, titanium, zirconium and aluminum. To impart sufficient Lewis acidity to the metal group, the ligands (L) should be strongly electron withdrawing such as halogen or carboxyl groups. The criteria necessary for the chiral Lewis basic G* group are that it must be able to activate the addition without cleaving OMLn linkage and provide an effective asymmetric environment with single point attachment. Candidates for the G* Lewis basic group would include phosphine oxides and derivatives such as phosphoramides, N-oxides, sulfoxides but not negatively charged alkoxides or amines and carboxylates. Thus, to reduce this concept to practice, we envisioned the use of a new class of aldol reagents, trichlorosilyl enolates, in conjunction with the Lewis basic phosphoramides. These agents can be seen as chiral analogs of HMPA the Lewis basicity of which is well documented.

A ready and efficient preparation of trichlorosilyl enol ethers was needed. A number of different approaches have been devised initially based on observations by Baukov who first described trichlorosilyl ketene acetics of esters. \(^5\) Trichlorosilyl enolates of ketones have been prepared beginning with enol acetates of the starting methyl ketones for example in this case pinacolone. The α-tri-butylstannyl ketone undergoes a metathesis with neat silicon tetrachloride at 0°C. Fractional distillation at reduced pressure afforded the O-bound trichlorosilyl enol ether, Scheme 3.

Scheme 3

\[
\begin{align*}
\text{(CH}_3\text{)}_3\text{C=CH}_2 & \xrightarrow{\text{n-Bu}_3\text{SnOMe}} \text{(CH}_3\text{)}_3\text{C=CH}_2 \quad \text{SiCl}_3 (2 \text{ equiv}) / 0^\circ \text{C} \\
\quad & \rightarrow \text{(CH}_3\text{)}_3\text{C}=\text{CH}_2 \\
\text{1. distill (65 °C / 26 mm)}
\end{align*}
\]

A much more practical approach involves the metathesis of trimethylsilyl enol ethers easily prepared directly from ketones. One process involves metathesis with trichlorosilyl triflate to produce the trichlorosilyl enolate. An alternative and milder processes uses silicon tetrachloride itself in the presence of a catalytic amount of mercuric acetate, Scheme 4.\(^6\)

Scheme 4

\[
\begin{align*}
\text{(CH}_3\text{)}_3\text{C=CH}_2 & \xrightarrow{\text{SiCl}_4 (2.0 \text{ equiv}) / \text{Hg(OAc)}_2 (1 \text{ mol } \%)} \text{(CH}_3\text{)}_3\text{C}=\text{CH}_2 \\
\text{rt / 1-2 h}
\end{align*}
\]

The generality of the approach for the synthesis of trichlorosilyl enol ethers using the exchange of trimethylsilyl for trichlorosilyl with silicon tetrachloride in the presence of mercuric acetate is shown in Table 1. The enoxytrichlorosilanes of simple aliphatic methyl ketones as well cyclic ketones are formed in good yield and high efficiency.

**TABLE 1. Preparation of Enoxytrichlorosilanes from SiCl₄**

<table>
<thead>
<tr>
<th>ketones</th>
<th>enoltrimethylsilanes</th>
<th>yield (%)</th>
<th>enoxytrichlorosilanes</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=Me</td>
<td>OSiMe₃</td>
<td>92</td>
<td>R=SiCl₃</td>
<td>60</td>
</tr>
<tr>
<td>R=Pr</td>
<td>R=Me: 92</td>
<td></td>
<td>R=Pr: 83</td>
<td></td>
</tr>
<tr>
<td>R=Pr</td>
<td>R=Me: 90</td>
<td></td>
<td>R=Pr: 80</td>
<td></td>
</tr>
<tr>
<td>R=n-Bu</td>
<td>R=Me: 84</td>
<td></td>
<td>R=n-Bu: 81</td>
<td></td>
</tr>
<tr>
<td>R=n-Bu</td>
<td>R=Me: 76</td>
<td></td>
<td>R=n-Bu: 74</td>
<td></td>
</tr>
<tr>
<td>R=t-Bu</td>
<td>R=Me: 79</td>
<td></td>
<td>R=t-Bu: 65</td>
<td></td>
</tr>
<tr>
<td>R=TBSOCH₂</td>
<td>79</td>
<td></td>
<td>R=TBSOCH₂: 65</td>
<td></td>
</tr>
<tr>
<td>R=Ph</td>
<td>R=Me: 88</td>
<td></td>
<td>R=Ph: 69</td>
<td></td>
</tr>
</tbody>
</table>

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To survey the reactivity of these reagents, the trichlorosilyl enol ether of a variety of acyclic ketones were combined with aldehydes at room temperature in 0.5 M methylene chloride solution. In reactions with benzaldehyde as the acceptor a variety of substituted methyl ketones gave excellent yields between 91 and 96% of the aldol addition products. Furthermore, reaction of \( \alpha,\beta \)-unsaturated aldehydes with a number of different methyl ketone derivatives gave exclusively 1,2-addition with no trace of Michael addition being detected. Highly enolizable aldehydes such as phenylacetaldehyde undergo smooth aldol addition reaction with the pinacolone trichlorosilyl enolate. Aliphatic aldehydes, linear branched and highly substituted types all gave good yields in combination with methyl ketone enol ethers, Scheme 5.

Scheme 5

\[
\begin{align*}
\text{OSiCl}_3 + \text{R'O} & \rightarrow \text{R'O} - \text{OH} \\
1. \text{CH}_2\text{C}_12 / \text{rt} / 0.5 \text{ M} & \\
2. \text{sat. NaHCO}_3 & \\
\end{align*}
\]

While these reagents are shown to be synthetically useful, the most important objective is to demonstrate asymmetric catalysis of the aldol addition. A number of structurally diverse chiral phosphoramides was surveyed for the reaction of trichlorosilyl enol ethers and benzaldehyde at \(-78^\circ\text{C}\) in 0.1 M methylene chloride solution. Remarkably, only a catalytic amount of the chiral phosphoramide was required. After an extensive survey, the best selectivities were obtained with the \(N,N\)-dimethylphospholidine derived from stilbenediamine in which the phosphorus bears a piperidino group.7 In this reaction the acetone aldol addition product is isolated in 93% yield and 85% enantiomeric excess.

With the stilbenediamine phosphoramide as catalyst at 5 mole % loading a variety of chlorosilyl enol ethers and aldehydes was surveyed to evaluate the generality of the reaction. The yields of analytically pure materials are shown underneath the aldol products and the enantiomeric excesses are in parenthesis, Scheme 6. The trend is clearly seen that the enantioselectivity is dependent upon the bulk of the spectator substituent of the ketone: the enantioselectivity increases with decreasing size of the spectator group such that the n-butyl methyl ketone and acetone aldol addition products proceed with the highest selectivities roughly in the middle 80% ee's.

Scheme 6

To further explore reaction generality we next examined the diastereoselectivity of reaction with configurationally defined enoxy chlorosilanes derived from cyclic ketones. The reaction of the configurationally defined trichlorosilyl enolate of cyclohexanone with aldehydes can give rise to two
diastereomers, syn and anti as clearly defined. These reactions take place readily in 0.5 M methylene chloride solution at 0°C to give high yields and remarkably high diastereoselectivities favoring the syn isomer. The diastereoselectivities are aldehyde dependent. For aromatic, olefinic and acetylenic aldehydes the syn diastereoselectivities are quite high, while aliphatic aldehydes of linear and branched type are less syn selective, Scheme 7.

Scheme 7

The predominance of the syn diastereomer is a remarkable result since the enolates are E-configured which implies a boat transition structure. The preference for a boat transition structure in this case is easily understood in terms of the pentacoordination which is expected from the association of the aldehyde with the enoxychlorosilane. The apical chlorine avoids severe non-bonded interactions with the aldehydic R group by proceeding through a boat transition structure.*

The ability of catalytic quantities of chiral phosphoramides to promote the addition of the cyclohexanone trichlorosilyl enolate with aldehydes was then assayed, Scheme 8. The diastereoselectivity of the addition was found to be remarkably sensitive to the structure of the phosphoramidate promoter. The results of the uncatalyzed reaction are reiterated to recall a 49/1 selectivity favoring the syn diastereomer. When the reactions are promoted by a catalytic amount of HMPA the syn selectivity drops to 3/1. Other phosphoramidate structures bring about a striking change in the diastereoselectivity to the point where with the N,N-dimethylstilbenediamine-derived phosphoramidate, the selectivity completely reverses now favoring the anti diastereomer to the extent of 49/1. Moreover, the enantiomeric excess of the anti diastereomer is 93%. Overall that product is obtained in 94% yield.

Scheme 8

The generality of this catalytic, asymmetric reaction was illustrated for a variety of different aldehyde types. It was found that aromatic and olefinic as well as acetylenic aldehydes all react with good diastereoselectivity in some cases exclusive anti selectivity and with respectable enantiomeric excess ranging from 82 - 97% ee. The yields in all cases of analytically pure materials are quite high.

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To illustrate that these reactions are indeed proceeding through highly-organized, closed type transition structures, it was important for us to demonstrate the response of the aldol addition reaction to a change in enolate geometry. Combining the trichlorosilyl enolate derived from propiophenone (which was demonstrated to be exclusively Z configured) with a variety of aldehydes at 0 °C in 0.5 M methylene chloride solution gave rise, in good yield, to the aldol addition products. In this case the anti diastereomers weakly predominated. It is not surprising that the anti-selectivity is not high considering again the preferred boat-like arrangement of the groups in the trigonal bipyramidal transition structures. In the boat, the apical chlorine atom now experiences non-bonded interactions with one of the substituents on the Z-enolate, in this case a methyl group. Thus, obtaining anti diastereomers from a Z-enoxysilane implies a boat transition state albeit with much lesser preference due to pseudoaxial interactions.

Nevertheless, the reactions promoted by the N,N-dimethylstilbenediamine-derived phosphoramide proceeded rapidly at -78 °C to afford the aldol products with good syn-diastereoselectivity and in many cases with excellent enantiomeric excess, Scheme 9. A variety of aromatic and olefinic aldehydes reacted with syn-diastereoselectivity, and the syn-diastereomer was highly enantiomerically enriched.

### Scheme 9

<table>
<thead>
<tr>
<th>chiral promoter</th>
<th>syn / anti</th>
<th>syn ee (%)</th>
<th>anti ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>1 / 2</td>
<td>-</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>N,N-dimethylstilbenediamine-derived phosphoramide</td>
<td>1 / 2.7</td>
<td>15</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>N,N-dimethylstilbenediamine-derived phosphoramide</td>
<td>11.5 / 1</td>
<td>94</td>
<td>11</td>
<td>77</td>
</tr>
</tbody>
</table>

Thus, it has been clearly shown that catalytic quantities of chiral phosphoramides are capable of effectively promoting the aldol addition reactions of trichlorosilyl enolates derived from methyl ketones as well as E- and Z-configured substituted enolates of ketones.

While the synthetic utility of trichlorosilyl enolates is now documented, the origin of their remarkable reactivity is not clearly understood. The most important feature of this new reaction is the susceptibility of the trichlorosilyl enolates to catalysis by trace amounts of the phosphoramide. The most important effects attributable to the chiral promoter are summarized in Scheme 10.

### Scheme 10

<table>
<thead>
<tr>
<th>Rate of Reaction</th>
<th>R=Me 0.0 equiv 8 min/-78°C</th>
<th>2% yield (96% recovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastereoselectivity</td>
<td>R=Me 0.1 equiv 8 min/-78°C</td>
<td>99% yield</td>
</tr>
<tr>
<td></td>
<td>anti</td>
<td>syn</td>
</tr>
<tr>
<td></td>
<td>0.0 equiv</td>
<td>2 h/0°C</td>
</tr>
<tr>
<td></td>
<td>0.1 equiv</td>
<td>8 min/-78°C</td>
</tr>
<tr>
<td></td>
<td>0.1 equiv</td>
<td>3 h/-78°C</td>
</tr>
<tr>
<td>Enantioselectivity</td>
<td>R=Me 0.1 equiv 8 min/-78°C</td>
<td>92% ee</td>
</tr>
<tr>
<td></td>
<td>R=Ph 0.1 equiv 3 h/-78°C</td>
<td>51% ee</td>
</tr>
</tbody>
</table>
To understand the origin of phosphoramide catalysis, it is first necessary to consider the origin of activation of the chlorosilyl enolates in their reactions with aldehydes alone. The nature of this process is similar to the behavior of boron enolates in their reactions with aldehydes. Both boron enolates and trichlorosilyl enolates are non-nucleophilic species. The boron enolate bears an empty orbital which withdraws electron density from the enolate. Complexation with the Lewis basic oxygen of an aldehyde now generates a boron ate complex which is doubly activated. The enolate is nucleophilically activated as a result of B-O weakening and interruption of the oxygen lone pair backbonding. The aldehyde is electrophilically activated by polarization of the carbonyl oxygen. Through this ate complex the dual nucleophilic and electrophilic activation leads to rapid reaction rates and high diastereoselectivities characteristic of the chair-like arrangement of groups; namely Z-enolate to syn-aldol product and E-enolate to anti-aldol product, Scheme 11.

Scheme 11

Trichlorosilyl enolates are also non-nucleophilic. Upon complexation of the Lewis basic oxygen of an aldehyde, the resulting trigonal bipyramidal ate complexes enjoy a similar dual activation. Electrophilic activation of the aldehyde occurs by polarization of electron density towards the silicon and nucleophilic activation of the enolate occurs by formation of the negatively charged ate complex. Reactions of these species also illustrate the characteristics of closed transition structures proceeding through boat like arrangements in the correlation of E-enolate to syn aldol product and Z-enolate to anti aldol product. Aldehyde coordination of these species activates both nucleophilic and electrophilic components and reaction takes place only in the coordination sphere of the boron or silicon.

This analysis is relatively straightforward and finds good analogies in other areas of chemistry. However to understand the origin of the remarkable catalysis due to the chiral phosphoramides, we must understand the changes in bonding that take place around the coordination sphere of silicon as the Lewis bases coordinate, Scheme 12. One of the most powerful and universal indices of bonding changes around a central atom is the re-distribution of s-character in the bonds connected to a central atom.

Scheme 12

An interesting insight is revealed if one considers the redistribution of s-character upon bonding the fifth and sixth ligands to the trichlorosilyl enolate reagents. In the tetracoordinate enoxytrichlorosilanes the silicon is formally sp³ hybridized. Coordination of the Lewis basic oxygen of the aldehyde results in a trigonal bipyramidal complex in which the electronegative positively charged oxygen of the aldehyde presumably takes up an apical position. If we analyze the redistribution of s-character in a trigonal
bipyramid we note that the apical bond to the aldehyde is devoid of s-character being composed of a dp-type hybrid. Furthermore, the equatorial or basal bond to the enolate oxygen is now sp² hybridized.

It is interesting to consider the consequences of s-character redistribution upon coordination of the sixth Lewis basic ligand which activates the aldol addition over the background unpromoted reaction. Upon coordination of another Lewis basic group to form an octahedral hexacoordinate silicon ate complex, the apical bond to the aldehyde changes from a dp to a d²sp³ hybrid (assuming equal s-character distribution along the directions of the six equivalent bonds in the octahedron). This constitutes an increase s-character from dp to d²sp³, i.e. from 0 to 16% s-character in the change from a trigonal bipyramid to an octahedron. Thus, the bond strength to the aldehyde increases thereby increasing the polarization and activation of the aldehyde towards nucleophilic attack. Upon coordination of a sixth Lewis basic ligand the change in s-character of the basal enolate bond (formerly sp² that is 33% s-character) changes again to a d²sp³ hybrid now 16% s-character. Thus, the bond from the silicon to the enolate decreases in s-character upon changing from a trigonal bipyramid to an octahedron. Consequently the bond strength decreases, thus increasing the activation of the enolate by polarizing electron density away from the silicon towards the nucleophilic end of the enolate.

Interestingly, the overall consequence of the coordination of the sixth ligand is that it generates a highly reactive species which experiences a simultaneous activation of both reacting partners in the coordination sphere of the silicon. This process constitutes a unique kind of simultaneous activation both of electrophilic and nucleophilic nature by a redistribution of the bonding character to the two participating species.

In summary, the key features that have been highlighted in this lecture are that: (1) trichlorosilyl enolates of ketones are easily prepared from trimethylsilyl enol ethers or stannyli ketones, (2) trichlorosilyl enolates of ketones react rapidly at room temperature with aldehydes, (3) the uncatalyzed aldol reactions of enoxychlorosilanes provide syn products from E-enolates and thus proceed via boat-like transition structures, (4) the reactions of trichlorosilyl enolates of ketones are susceptible to nucleophilic catalysis with chiral phosphoramides in high de and excellent ee, (5) the reactions appear to proceed via closed transition structures, with a phosphoramide in a hexacoordinate silicon species.

We believe that this aldol addition represents a new, emerging class of reactions characterized by the ability to simultaneously employ Lewis acid and Lewis base activation. These reactions proceed around a defined organizational center and include ligands that can craft an effective asymmetric environment for the reaction. Finally, the invention of new catalytic systems and the design of effective catalytic agents constitutes an important challenge for the future and involves the interplay of physical-organic, structural, computational and synthetic chemistry.

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REFERENCES


We have previously demonstrated that the E-enolate to syn adduct correlation is characteristic of uncatalyzed aldol reactions of enoxysilacyclobutanes. The putative pentacoordinate siliconate transition structures were shown computationally to prefer boat-like arrangements in this array.