Catalytic enantioselective 1,4-additions

1 Key Concepts: Regioselectivity and Catalysis

1.1 Regioselectivity

1,2- vs 1,4-Addition: \(\alpha,\beta\)-unsaturated carbonyl compounds are \textit{ambident} electrophiles. The incoming nucleophiles can attack either the C=O or C=C bonds.

\[\text{R} = \begin{array}{c} \text{Cl} \\
\text{O} \\
\text{OMe} \\
\text{H}_2\text{N}
\end{array}\]

The regioselectivity is determined by a combination of the nature of \(R\), \(X\) and of the nucleophile:

- More reactive carbonyl
  - 1,2-addition only
  - Fleming, \textit{Molecular Orbitals and Organic Chemical Reactions}, 2010, p 188
- Less reactive carbonyl
  - 1,4-addition only

This selectivity can be described by the \textit{Klopman-Salem equation} and \textit{Hard-Soft Acid-Base} theory:

\[\Delta E = \frac{Q_{Nu}Q_{El}}{eR} + \frac{2(c_{Nu}c_{El})^2}{E_{HOMO(Na)} \pm E_{LUMO(El)}}\]

\begin{itemize}
  \item Coulombic (charge-charge) interactions
  \item Frontier Orbital (HOMO-LUMO) interactions
\end{itemize}

When Coulombic interactions predominate, \(Nu\)/\(El\) are called hard
When HOMO-LUMO interactions predominate, \(Nu\)/\(El\) are called soft

Klopman \textit{JACS}, 1968, 90, 223

\textit{HSAB} theory is a useful means of classifying the reactivity of nucleophiles + electrophiles, and serves as a good “rule-of-thumb”:

<table>
<thead>
<tr>
<th>Table 3. Classification of Bases</th>
<th>Table 4. Classification of Lewis Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard</td>
<td>Soft</td>
</tr>
<tr>
<td>H(_2)O, H(_2)S, H(_2)S(_2)(\text{O})</td>
<td>H(_2)O, H(_2)S, H(_2)S(_2)(\text{O})</td>
</tr>
<tr>
<td>(\text{CHCl}_3), (\text{CH}_2\text{Cl}_2), (\text{CH}_3\text{OH}), (\text{CH}_3\text{SH})</td>
<td>(\text{CHCl}_3), (\text{CH}_2\text{Cl}_2), (\text{CH}_3\text{OH}), (\text{CH}_3\text{SH})</td>
</tr>
<tr>
<td>(\text{NH}_3), (\text{NH}_2\text{CH}_3), (\text{NH}_2\text{CH}_2\text{CH}_3), (\text{NH}_2\text{NCH}_3)</td>
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<tr>
<td>(\text{H}_2\text{S})</td>
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<tr>
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<tr>
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<td>(\text{NH}_3, \text{NH}_2\text{CH}_3, \text{NH}_2\text{CH}_2\text{CH}_3, \text{NH}_2\text{NCH}_3)</td>
<td>(\text{NH}_3, \text{NH}_2\text{CH}_3, \text{NH}_2\text{CH}_2\text{CH}_3, \text{NH}_2\text{NCH}_3)</td>
</tr>
</tbody>
</table>

In general:
Hard \(Nu\) and \(El\) atoms are small, charged, and non-polarizable
Soft \(Nu\) and \(El\) atoms are large, unchanged and polarizable


Relevance to 1,4-conjugate addition: Properties of Acrolein

<table>
<thead>
<tr>
<th>Frontier Orbitals:</th>
<th>Charge Distribution:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{HOMO})</td>
<td>(\text{LUMO})</td>
</tr>
<tr>
<td>(\text{LUMO})</td>
<td>(\text{Charge})</td>
</tr>
<tr>
<td>(+23)</td>
<td>(-35)</td>
</tr>
<tr>
<td>(+46)</td>
<td>(+48)</td>
</tr>
</tbody>
</table>


These factors provide tremendous potential not only for the control of the regioselectivity, but also for the \textit{catalysis}.  

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Page 1
1.2 Common methods for achieving catalytic 1,4-conjugate additions
A catalyst is employed to control the regioselectivity (and ideally also the enantioselectivity) of the addition to only one of the reactive sites of an ambident molecule.

1.2.1 LUMO-Lowering Mediated by Lewis Acid
Classic Example: Diels-Alder reactions are strongly influenced by HOMO-LUMO interactions. Dramatic rate acceleration by AlCl₃ catalysis was observed 50 years ago:

```
+2.5 eV
```

LUMO coefficients correspond with increased reactivity of Cα.

```
-23.7 eV
```

HOMO

```
-14.5 eV
```

Yates *JACS* 1960, 82, 4436

The LUMO-lowering effect of Bronsted or Lewis acids has been calculated – again on acrolein as an example:

```
-6.5 eV
```

LUMO

```
+2.5 eV
```

-14.5 eV

LUMO

```
-14.5 eV
```

HOMO

```
-23.7 eV
```

Houk *JACS* 1973, 95, 4094

1.2.2 LUMO-Lowering by Catalytic Formation of Iminium Ions
A more recent discovery - analogy between Lewis acid-activated unsaturated aldehydes and unsaturated iminium ions

```
• Lewis acid complexation is LUMO-lowering
• C=O and C=C bonds become more electrophilic
• Iminium ions are positively charged
• Should be more electrophilic than parent aldehyde
```

MacMillan *JACS* 2000, 122, 4243

1.2.3 Catalytic Generation of Soft Nucleophiles by Transmetallation:
By addition of catalytic amounts of other metals, the regioselectivity of organometallic addition to unsaturated carbonyls can be altered. This was first observed in the case of Grignard reagents: without the addition of Cu salts the 1,2-addition products (and derivatives thereof) are formed exclusively. When Cu salts are present in catalytic amounts, the 1,4-addition product is favored.

Kharasch *JACS* 1941, 63, 2308
2 Catalytic, Enantioselective Conjugate Additions

2.1 LUMO lowering

2.1.1 Lewis acid activation

Important Considerations

Lewis acid binding to carbonyl oxygen is reversible and dynamic – for ligand and substrate design this must be taken into account. Therefore, ligands and substrates are equipped with extra coordination sites to control these aspects to limit the number of possible transition states in the enantiodetermining step. The number of coordination sites is determined by the metal ion.

2.1.1.1 \( \text{C}_2 \)-Symmetric Bis(Oxazoline) (“Box”)-Based Complexes:

Cu-Bis(Oxazoline) complexes are a versatile ligand/metal combinations for a large variety of reactions (including conjugate additions and cycloadditions). The best results are obtained with substrates bearing two coordination sites to the Cu atom (they can form stable 5- or 6-membered ring chelates with the chiral Cu complex).

Mukaiyama-Michael addition of silyl-ketene thioacetals proceed with very high selectivity; isolation of Cu-ligand-malonate complex showed distorted square-planar geometry; Cu-malonate in a boat conformation with shielded \( Re \) face:
Activated unsaturated carbonyls that form 5-membered ring chelates have also been developed. α-Ketoesters are highly electron-withdrawing and make particularly reactive electrophiles:

Evans *JACS* 1999, 121, 1994

Evans *JACS* 2001, 123, 4480

Jørgensen *ACIE* 2001, 40, 160
Other metal-ligand complexes based on oxazoline frameworks are known. For example, Mg\textsuperscript{2+}-catalyzed addition of hydrazines to imides provides pyrazolidinones:

\[
\text{PhN} = \text{N} - \text{R}_2 + \text{HN} - \text{NH}_2 \rightarrow \text{PhNH} - \text{NH} - \text{R}_2
\]

Sibi \textit{JACS} \textbf{2007}, \textit{129}, 4522

Higher oxidation state metals, for example Sc\textsuperscript{3+}, can be more Lewis acidic but require an extra coordinating group to occupy 3 of 6 open sites in the octahedral geometry (in contrast to the previously mentioned square-planar geometry): Pyridine-bis(oxazoline) ligands ("PyBox") are used:

\[
\begin{align*}
\text{N} & \text{N} \\
\text{O} & \text{O}
\end{align*}
\]

Evans \textit{JACS} \textbf{2007}, \textit{129}, 10029

This complex is an excellent catalyst for enantioselective Friedel-Crafts-type addition to unsaturated acylphosphonates - useful ester surrogates:

\[
\begin{align*}
\text{O} & \text{P} \\
\text{R} & \text{O}
\end{align*}
\]

Evans \textit{JACS} \textbf{2003}, \textit{125}, 10780

2.1.1.2 Other Classes of Catalysts for Electrophile Activation:

The first catalytic, enantioselective Mukaiyama-Michael reaction used a BINOL-Ti oxide complex to add to cyclic ketones:

\[
\begin{align*}
\text{O} & \text{Ti} = \text{O} \\
\text{OTMS} & \text{Ph}
\end{align*}
\]


Bandini and Umani-Ronchi were the first to demonstrate that one-point binding could also provide high enantioselectivity in the Friedel-Crafts alkylation. A chiral Salen ligand (Salen from salicylaldehyde and ethylenediamine) with bulky tert-butyl groups was employed, which creates a well-defined chiral geometry around the Al atom.
An improved version giving better selectivities using 3,3'-disubstituted-BINOL Zirconium complexes was described (Note: The bulky 3,3'-Br substituents on the BINOL are necessary for a high chiral induction):

\[
\text{OH} \quad \text{OH} \quad \text{Br} \quad \text{Br} \quad \text{Zr(OtBu)}_4^+ \quad (20 \text{ mol % each}) \quad \text{CH}_2\text{Cl}_2, \text{rt} \quad \text{N} \quad \text{H} \quad \text{R} \quad \text{Ar} \quad \text{O} \quad + \quad \text{O} \quad \text{Ar} \quad \text{R} \quad \text{N} \quad \text{H}
\]

Indoles: 54-91%, 72-97% ee
Pyrroles: 84-97%, 65-99% ee

In addition to Lewis acid catalysts, Brønsted acid catalysts also promote this type of reaction:

\[
\text{R} \quad \text{LUMO} \quad \text{lowered energy} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{O}_{\text{Me}} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Me}
\]

2.1.2 Iminium catalysis

- For these reactions to occur, \(\alpha,\beta\)-unsaturated aldehydes (sometimes ketones) are required for the formation of the iminium ions. This is in contrast with the metal-catalyzed reactions in Section 2.2 where unsaturated aldehydes are difficult substrates. Therefore, the nucleophile has to be unreactive with the aldehyde (or ketone) in the absence of a catalyst to prevent an unwanted background reaction. Electrophilicity of iminiums is greater than that of aldehydes - importantly, the groups, which provide the chiral environment, are also LUMO lowering, leading to enhanced reactivity.
Catalytic cycle: Formation of iminium, addition of nucleophiles, followed by protonation of enamine and hydrolysis - generates and requires molecule of water for catalyst turnover

Mayr *ACIE 2008, 47, 8723*

- Equilibrium between E/Z isomers leads to Curtin-Hammett control of product distribution - addition to E isomer faster than to Z


- Enantioselective Friedel-Crafts alkylation

MacMillan *JACS 2002, 123, 4370*

- Enantioselective Mukaiyama-Michael reactions employing 2-siloxyfurans as nucleophiles to furnish butenolide structures. Here, the nature of the catalyst governs the regioselectivity: Lewis acid-based
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Treatment of 2-siloxyfurans with a variety of $\alpha,\beta$-unsaturated aldehydes afforded syn-butenolide adducts with high diastereoselectivity and high enantioselectivity. Significantly, the use of different co-catalyst and solvent provided the opposite diastereomer with the same enantioselectivity.

This methodology was applied in the synthesis of spiculisporic acid and 5-epi-spiculisporic acid.

- Enantioselective Michael reactions of $\alpha,\beta$-unsaturated ketones:

- Conjugate reduction, formally, a $\text{H}^+$ is added in a 1,4-fashion to $\alpha,\beta$-unsaturated aldehydes. To render this process stereoselective, a $\beta,\beta'$-disubstituted aldehyde has to be used. In the following case, the Hantzsch ester (a dihydropyridine) is employed as the hydrogen source. It gets oxidized to a pyridine, thereby formally releasing an equivalent of $\text{H}_2$. (compare also with nature’s reducing agent NADH, which essentially works via the same principle)
Asymmetric counteranion directed catalysis (ACDC).
In this conjugate reduction of α,β-unsaturated aldehydes, the chiral 3,3'-BINOL derived phosphoric acid serves as the counterion to the iminium ion formed in situ. Electrostatic interactions keep the phosphate in close proximity to the electrophile, so that a face selection is induced. Important to note is that the bulky 3,3'-substituents on the BINOL are essential for asymmetric induction to occur.

α,β-unsaturated ketones: Neither ACDC catalysts nor chiral imidazolidinone catalysts gave good yields or enantioselectivities in the conjugate reduction of α,β-unsaturated ketones. A novel class of catalytic salts, in which both anion and cation are chiral was developed by List.

### 2.2 Catalytic Generation of Soft anions

#### 2.2.1 Soft anions by transmetallation of hard anions

A wide variety of organometallic compounds can transfer their substituents (e.g. alkyl- or aryl ligands) to other catalytically active metals. Thereby, the reactivity of these substituents to be transferred can be altered.
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(see also section 1.2.3: Transmetallation of a ‘hard’ Grignard reagent RMgBr to ‘soft’ copper leads to a shift of 1,2-addition to 1,4-addition) Many different organometallic reagents are either commercially available or can be prepared readily, and therefore, the general approach to use them as alkyl- or aryl-donors for conjugate addition through transmetallation is attractive.

2.2.1.1 Copper-catalyzed addition of Grignard reagents
Some characteristics of Cu-catalyzed enantioselective 1,4-conjugate addition of Grignard reagents are:
- Grignard reagents have a relatively high reactivity. The competition of fast, uncatalyzed background 1,2-carbonyl addition and 1,4-addition.
- Unlike in iminium catalysis, α,β-unsaturated aldehydes cannot be employed because of their high reactivity. Ketones, esters and thioesters have to be employed.
+ Chiral copper complexes based on phosphine-, phosphoramidite- and NHC-ligands are well known and available
+ Many Grignard reagents are commercially available, and inexpensive

Good results with respect to yields and enantioselectivities are obtained with Cu/ferrocenyl-ligand complexes. Important to note is the fact that both cyclic and acyclic substrates give good stereoselectivities. This catalytic system works best for linear, unfunctionalized Grignard reagents. To introduce a chiral center with a methyl group (from MeMgBr), which is the most frequent pattern in natural products, one needs to use the more reactive thioesters instead of esters.

- Mechanism of the enantioselective 1,4 addition of α,β-unsaturated carbonyl compounds promoted by copper complexes of chiral ferrocenyl diphosphine. The reaction is believed to run via a Cu-π-complex followed by a formation of a Cu-σ-complex. The transfer of R to the α,β-unsaturated carbonyl compound was found to be the rate-determining step.


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Feringa  JACS 2006, 128, 9103
Results with ferrocenyl-based bisphosphine ligands:

**cyclic enones**

\[
\begin{align*}
\text{R} & \quad \% \text{yield} & \% \text{see} \\
\text{Me} & \quad 83 & 90 \\
n\text{Pr} & \quad 81 & 94 \\
n\text{Bu} & \quad 88 & 96 \\
n\text{Phent} & \quad 76 & 77
\end{align*}
\]

Feringa *PNAS 2004, 101, 5834*

**acyclic enones**

Feringa *JACS 2004, 126, 12784*

Thioesters employed in these reactions show a more “ketone-like” reactivity and can be easily used in follow-up reactions, e.g. in a direct transformation to aldehydes. The aldehydes can then be employed to construct another \(\alpha,\beta\)-unsaturated thioester via Horner-Wadsworth-Emmons reaction, which allows the conjugate addition to be carried out iteratively. Up to seven chiral methyl groups have been introduced using this method in the synthesis of phthioceranic acid.

Feringa *JACS 2005, 127, 9966*

- Similarly good results in terms of enantioselectivities can be obtained with BINAP-derived catalysts. This catalyst system requires higher temperatures than the ferrocenyl-derived one, but has a broader nucleophile scope. In contrast to the ferrocenyl-based system, one does not need to employ a thioester to achieve good enantioselectivities with MeMgBr.

Feringa *OL 2007, 9, 3013*

**2.2.1.2 Cu-Catalyzed Conjugate Addition of C-Zn and C-Al Nucleophiles + Application to All-Carbon Quaternary Centers**

A recent addition to enantioselective conjugate additions is the formation of very sterically hindered, quaternary carbon centers by asymmetric conjugate addition to \(\beta,\beta\)-disubstituted carbonyl compounds. As
Ange W. Che m. Int. Ed. 2007, 46, 1097–1100

These substrates are less reactive due to their steric hindrance, more reactive organometallic reagents are employed. One of the first examples used highly reactive trialkylaluminums as nucleophiles with a Cu/phosphoramidite catalyst:

Dialkylzinc nucleophiles are more functional group compatible than trialkylaluminums—additions to enones with β-ester groups proceed without acyl substitution and with complete regiochemistry for the more hindered site. A chiral NHC-Ag complex was employed as catalyst in this case.

Non-cyclic unsaturated carbonyls are less reactive than cycloalkenones, thus double activation of the alkene is common. Meldrum’s acid derivatives (2 electron withdrawing groups) have been employed as activated α,β-unsaturated carbonyl compounds for the addition of dialkylzinc reagents with a Cu/phosphoramidite complex as catalyst.

Recently Hoveyda reported asymmetric conjugate additions of aryl- and alkylaluminum reagents to β,β-disubstituted acyclic enones.

2.2.1.3 Conjugate reduction
A Chiral copper-hydride catalyst is prepared in situ for the asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds. As in the case of the organocatalytic conjugate reduction (compare section 2.1.2), "H" is the nucleophile that is added in a 1,4-fashion. As stoichiometric reducing agents,
Silanes (compounds bearing a Si-H bond) are employed. PMHS is a side-product of silicone production, thus inexpensive and widely available.

2.2.1.4 Rh-Catalyzed Asymmetric Addition of Boronic Acids and their Derivatives

Hayashi and Miyaura described the Rh-catalyzed addition of aryl boronic acids to unsaturated ketones in 1998 - since that time this field has developed greatly. Even though boronic acids are not “organometallic” reagents in a strict sense, they do transmetallate. This stems from the fact that the C-B bond is polarized in a similar fashion like a C-Mg bond in a Grignard reagent. This enables the R group from a boronic acid to be transferred to a metal. Boronic acids are readily available and the reaction with Rh catalysts shows a high functional group tolerance as well as mild reaction conditions.

Buchwald *JACS* 2003, 125, 11253
Lipshutz *JACS* 2004, 126, 8352
Hayashi *JACS* 1998, 120, 5579
Mechanistic studies revealed the importance of water to help catalyst turnover and hydroxide to facilitate transmetallation and allow lower reaction temperatures:

An important discovery is that chiral dienes can be used as ligands rather than chiral phosphines - this leads to far more reactive catalysts. The reactions can be carried out at much lower reaction temperatures.

Diene ligands can provide exquisite chemo- and enantioselectivity - additions to unsaturated aldehydes proceed by 1,4-addition, not 1,2. This is in stark contrast to a Rh/phosphine catalyst, which furnishes the 1,2-addition product exclusively.
Other boron-based reagents can also be used. Most importantly, potassium trifluoroborate salts which are air and moisture stable and easy to prepare and handle:

\[
\text{Me}_3\text{OMe} + \text{RBF}_3\text{K} \rightarrow \text{Me}_3\text{O} + \text{RBF}_3
\]

The use of tetraarylborate salts allows synthesis of all-carbon quaternary centers. The coordination of \(\text{Ar}_3\text{B}\) to the carbonyl is proposed to assist activation of the electrophile to enable attack on the hindered \(\beta\)-position. One drawback of this methodology is that only one of four aryl groups can be transferred:

Boron nucleophiles can transmetallate with other soft metals beside rhodium. 1,4-Additions of aryl-boronic acids to \(\alpha,\beta\)-unsaturated aldehydes have been performed with a combination of Pd and amine catalysts.
### 2.2.1.5 Overview of some methods for conjugate additions

<table>
<thead>
<tr>
<th>$X$</th>
<th>$\text{Nu}$</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$= \text{CR}$</td>
<td>- allyl$\text{SiR}_3$ ($\text{Nu} = \text{allyl}$)</td>
<td>$\text{Cu}$</td>
<td>BOX</td>
<td>Lewis Acid catalyzed</td>
</tr>
<tr>
<td>$= \text{OR}$</td>
<td>- Silyl-thioketene acetalts</td>
<td>$\text{Cu}$</td>
<td>BOX</td>
<td>2-point binding of substrate to catalyst</td>
</tr>
<tr>
<td>$= \text{NR}$</td>
<td>- Aryls (Friedel-Crafts-type)</td>
<td>$\text{Cu}$</td>
<td>BOX</td>
<td></td>
</tr>
<tr>
<td>$= \text{CO}_2\text{R}$</td>
<td>- Carbamates</td>
<td>$\text{Cu}$</td>
<td>BOX</td>
<td></td>
</tr>
<tr>
<td>$= \text{P(O)(OMe)}_2$</td>
<td>- Aryls (Friedel-Crafts-type)</td>
<td>$\text{Si}$</td>
<td>PyBOX</td>
<td></td>
</tr>
<tr>
<td>$= \text{NR}$</td>
<td>- Hydrazines</td>
<td>$\text{Mg}$</td>
<td>BOX</td>
<td></td>
</tr>
<tr>
<td>$= \text{imidazoles}$</td>
<td>- Aryls (Friedel-Crafts-type)</td>
<td>$\text{Sc}$</td>
<td>BOX</td>
<td></td>
</tr>
<tr>
<td>$= \text{CR}$</td>
<td>- Silyl(thio) ketene acetalts</td>
<td>- Ti-BINOL</td>
<td>BINOL</td>
<td>One-point binding</td>
</tr>
<tr>
<td>$= \text{NR}$</td>
<td>- Hydrides: “H” (conjugate reduction)</td>
<td>- chiral BINOL-based phosphoric acids</td>
<td>Chiral counterions needed for ketones</td>
<td>“ACDC”</td>
</tr>
<tr>
<td>$= \text{H}$</td>
<td>- Aryls (Friedel-Crafts-type)</td>
<td>- Imidazolidinone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$= \text{CR}$</td>
<td>- Silyleneoethers (Mukaiyama-type)</td>
<td>- Al</td>
<td>Salen</td>
<td>One-point binding</td>
</tr>
<tr>
<td>$= \text{CR}$</td>
<td>- Aryls (Friedel-Crafts-type)</td>
<td>$\text{Zr}$</td>
<td>BINOL</td>
<td>One-point binding</td>
</tr>
</tbody>
</table>

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### 2.2.2 Generation of soft anions by deprotonation

#### 2.2.2.1 Deprotonation of terminal alkynes

Terminal alkynes are relatively acidic ($\text{pK}_a \approx 23$ in $\text{H}_2\text{O}$) and are easily deprotonated by weak bases in the presence of $\pi$-acidic Lewis acids such as Cu. However, alkynes often act as “dummy ligands” as they are poor nucleophiles; in the first catalytic, asymmetric alkyne addition, highly reactive electrophiles were used to overcome this poor reactivity:
Alkyne 1,4-addition to less electrophilic substrates can be carried out at elevated temperatures. Unfortunately alkyne dimerization is a common side reaction, which can be avoided using very bulky and electron-rich phosphine ligands.

Carreira *JACS* 2005, *127*, 9682

2.2.2.2 Deprotonation of nitroalkanes and malonates

Nitroalkanes (pKa ~ 10 in H₂O) are readily deprotonated by weak bases - use of a bulky chiral cation gives high enantiom- and diastereoselectivity in conjugate additions. Note that the chiral catalyst has to carry bulky 3,3'-substituents in order to achieve high ee's. Malonates (pKa ~ 13 in H₂O) are the classic Michael donors.

Hayashi *JACS* 2008, *130*, 1576

Maruoka *OL* 2005, *7*, 5143
2.3 Dual Activation of Nucleophiles and Electrophiles

2.3.1 3,3'-Disubstituted BINOL Catalysts in Conjugate Additions of Boronic Acids

Extensive computational studies by Goodman suggest that BINOL-derived boronates are more Lewis acidic than the parent boronates as the twisted orientation limits B-O interactions. Subsequently, this adduct with the ketone has a lower lying LUMO and a higher energy HOMO than the adduct of the parent boronate. Therefore, this is an example of a ligand-accelerated reaction.

This concept has been shown to be practical in synthetic applications:

Chong has demonstrated that BINOLs catalyzed the addition of alkynylboronates to unsaturated ketones. The proposed catalytic cycle is based on ligand exchange around the boron atom.

Similarly high enantioselectivities were observed for attack of alkenylboronates- a six-membered ring transition state was proposed to explain the sense of addition: (diagrams of favored and disfavored conformations are shown)
2.3.2 Al-Salen Catalyzed Conjugate Additions to Unsaturated Imides

Jacobsen has made extensive use of salen ligands for enantioselective conjugate reactions - in the initial report on addition of hydrazoic acid (pKa 4.72 in H2O), high ee was obtained for addition to β-alkyl-substituted imides. This was proposed to occur through a one-point binding, Lewis acid activation:

In the conjugate addition of cyanide to imides, high enantioselectivity was obtained for β-alkyl substrates but β-aryl ones showed no reactivity. An important observation was a 2nd order rate dependence on catalyst concentration, evidence for a bimetallic catalytically active species.

Therefore, a new ligand was designed which contains two Al-salen groups tethered together - dramatic rate acceleration and higher ee’s were observed. Importantly, previously unreactive electrophiles could be used.

Formation of Salen-CN as more reactive nucleophile, and Salen-Imide as more reactive electrophile

Jacobsen *JACS 1999, 121, 8959*

Jacobsen *JACS 2003, 125, 4442*

Jacobsen *ACIE 2008, 47, 1762*