Chapter X: Imine Additions

X.1 Introduction

The available number of general, efficient asymmetric reactions involving nucleophilic additions to iminines pales when compared to the plethora and scope of methods for asymmetric additions to aldehydes. This disparity lies in part on the difference in reactivity between C=N and C=O. The azomethine carbon of imines undergoes nucleophilic addition less readily than aldehydes and competing deprotonation and enolization is a problem. This reactivity profile may not seem consistent compared to more electrophilic aldehydes, but the stability of the enamine tautomer (vs. the imine) alludes to the added stability. The tendency for enolization can be decreased with a simultaneous increase in the electrophilicity by functionalizing the nitrogen with electron withdrawing substituents such as acyl or tosylate groups. The drawback of an N-appendage approach, is that in most instances a subsequent step will be required to remove the modifier.

A difficulty associated with Lewis-acid catalysis of imine additions reactions is that the anionic amine that results following nucleophilic attack can sequester the Lewis acid catalyst and preclude reaction-turnover. Recently, Kobayashi and co-workers have identified scandium(III) triflate as being exceptional for its selective activation of ketones or imines in the presence of aldehydes.

An additional complicating factor in the development of asymmetric imine additions is the presence of a mixture of cis and trans stereoisomers. This feature complicates the development of effective reagent controlled process as a mixture of imine-Lewis acid complexes are generated. By contrast the complexes formed between aldehydes and Lewis acid complexes are well defined, with the complex that results from coordination of the Lewis acid cis to the formyl proton being the only observed structure.1

Despite the complications outlined, there have recently been a number of breakthroughs, especially as it pertains to catalytic asymmetric C=N additions. Although the formation and isolation of aldimes is readily achieved, their sensitivity to hydrolysis and oligomerization often makes their in situ preparation more desirable. As alternatives to imines, numerous approaches for the synthesis of amines by nucleophilic C=N additions employ synthetically equivalent functionality such as the more stable hydrazones. Although many of these recent developments are yet not sufficiently established, their promise for widespread use and their position as the state-of-the-art in imine additions warrants their discussion and classification as classics.

X.2 Reduction of Imines

One of the most well explored methods for the preparation of secondary chiral amines is the reduction of imines (reductive amination). Three of the most successful strategies for imine reduction include C=N hydroboration, hydrogenation, and hydrosilylation.

Hydroboration. The oxaborolidine X (CAB) complex pioneered by Corey has seen remarkable success in the catalytic reduction of ketones. Subsequent investigations by Cho have documented its use for catalytic reduction of imines in the presence of BH$_3$•THF providing optically active amines in up to 70% ee.2 Mukaiyama has examined the hydroboration of imino phosphinites with 1 mol%
of Co(II) complex \textbf{vii}. The stoichiometric reductant is generated in situ by allowing borane to react with an alcohol and has been formulated as \textbf{xx}. For a number of \(N\)-diphenylphosphinyl imines the corresponding amine products were isolated in up to 98\% ee.\(^3\)

\begin{center}
\begin{tikzpicture}
\node[draw,rounded corners] (A) at (0,0) {\includegraphics[width=0.5\textwidth]{example.png}};
\node[below=1cm of A] {then hydrolysis};
\node[below=1cm of A] {X 72\% yield 98\% ee};
\end{tikzpicture}
\end{center}

**Hydrogenation.** Impressive levels of asymmetric induction have been realized in the hydrogenation reaction of imines. Later improvements in substrate generality and enantioselectivity were founded on pioneering studies on homogenous catalytic hydrogenations of folic acids with a Rh(III)-DIOP system by Boyle,\(^4\) a Rh(I)-DIOP system for reducing aryl benzyl imines by Scorrano\(^5\) and a Ru(I)-DIOP complex for reducing oximes developed by Botteghi\(^6\). Improved selectivities in subsequent investigations were achieved for special substrate classes, such as \textbf{XXXX}, by employing bis-naphthyl ligands,\(^7\) such as \((S)\)-BINAP.

In pioneering work, Pfaltz has documented high levels of asymmetric induction (85-95 \% ee) in the hydrogenation reaction of a variety of aryl imines with 0.1 mol \% of the COD iridium(I) complex formed with the chiral \(P,N\)-ligand \textbf{XX}.\(^8\) The ability to perform these reductions in environmentally friendly supercritical \(CO_2\) as solvent contributes to their growing importance.\(^9\)

Burk developed the first highly enantioselective catalyst for the reduction of a variety of \(N\)-acylhydrazones in the presence of 0.2 mol \% of a chiral Rh(I) complex.\(^{10}\) The catalyst generated upon mixing a Rh(I) triflate with Et-DuPHOS \textbf{XX} under 60 psi of \(H_2\) effects reduction with complete conversion to afford optically active amines in up to 99\% ee. Their mechanistic hypothesis was predicated on the importance of a donor group on the substrate capable of
binding to the metal. Indeed, optimal selectivities were observed for the reduction of enamides.\textsuperscript{11}

Additionally, an interesting result was obtained from their mechanistic investigations with deuterium. With 2-propanol as solvent the acylhydrazone \textsuperscript{XX} is in equilibrium with its enamine tautomer \textsuperscript{XX}. Performing the reduction in D\textsubscript{2} instead of H\textsubscript{2} should help reveal whether the reduction is occurring on the enamine or imine tautomers \textsuperscript{XX} \textsuperscript{XX} by detecting deuterium incorporation in the product. In the event, no deuterium incorporation was observed on the a-carbon, suggesting reduction is taking place at the imine tautomer \textsuperscript{XX} and not from the enamine \textsuperscript{XX}.

\textbf{Hydrosilylation}. To date, Buchwald has reported the best system for the asymmetric reduction of imines. The reaction works exceedingly well for many substrate classes, including aliphatic, aromatic and heteroaromatic imines, providing chiral amines in >98 \% ee. The active catalyst is proposed to be formed in situ from the difluoro titanium \textit{ansa}-metallocene complex \textsuperscript{X} following reduction with excess of the stoichiometric reductant phenyl silane.\textsuperscript{12,13} Buchwald has postulated the corresponding Ti(III) hydride as the active catalytically active species.

\textbf{X.3 Carbon-Carbon Bond Forming Reactions}

\textbf{Diastereoselective Additions}. Although diastereoselective nucleophilic additions to imines have been developed, the processes have not been as extensively studied as for corresponding C=O additions. The operative models for the diastereoselective additions invoke chelation and Felkin-Ahn arguments for explaining stereosecontrol. Although reaction rates are attenuated in THF, the addition of Grignard or alkyl lithiums to \textalpha-heterosubstituted imines proceeds well in diethyl ether, affording either the syn- or anti-adducts depending either on the reaction conditions or \textit{N}-imine functionality. Reetz reported a procedure for generating complementary diastereomers in the addition reactions of Grignards to \textalpha-amino imines \textsuperscript{X} and \textsuperscript{X}.\textsuperscript{14} By modifying both the Lewis acidity
of the counter ion and the imine protecting group, either syn- or anti-adducts can be selectively prepared.

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{NBr}_2 & \quad \xrightarrow{n\text{Bu-M}} & \quad \text{Me} & \quad \text{NBr}_2 & \quad \text{Me} & + & \quad \text{Me} & \quad \text{NBr}_2 & \quad \text{Me} \\
X, X = \text{SO}_2\text{Tol}, M = \text{MgCl} & \quad 1 : 9 & \quad \times & \quad 4.5 : 1 & \quad \times & \quad \times \\
X, X = \text{Bn}, M = \text{Li} & \quad \times & \quad \times & \quad \times & \quad \times & \quad \times
\end{align*}
\]

The lactaldimine X undergoes preferential syn addition with most Grignard reagents, consistent with the idea of a 5-membered ring chelate intermediate XX. The incoming nucleophile adds to the more accessible α-face of the imine resulting in primarily the syn product.

Curiously, when the β-hydroxy aldimine is exposed to the same conditions the relative diastereoselectivity remains the same, suggesting that OBn group is a better chelate partner than OMgBr. However, in the presence of cerium(III) chloride additive, the selectivity is reversed, consistent with the 6-membered ring chelate XX and equatorial nucleophilic attack.\(^{15}\) For these substrates, the stereochemical divergence is attributed to the addition proceeding through either a five (no additive) or six (added CeCl\(_3\)) membered chelate assemblies, the reaction manifold for which is controlled by the reaction conditions. In is important to note that in these and other studies\(^ {16}\) the addition of allyl metal reagents tends to favor anti-adducts.

**Auxiliary-Based Additions:** In addition to serving as auxiliaries in asymmetric enolate alkylation reactions as described elsewhere in this text, the RAMP and SAMP hydrazones studied by Denmark\(^ {17}\) and Enders\(^ {18}\) are effective electrophiles for the diastereoselective addition of organocerium reagents. The process is characterized as being highly stereoselective (>97% diastereoselectivity), efficient (>70% yields), and possessing wide scope. Thus, the hydrazones derived from the chiral hydrazine and aliphatic, benzyl, and aromatic and α,β-unsaturated aldehydes may be utilized successfully as substrates in the asymmetric addition reaction. The range of suitable
nucleophiles is equally impressive and includes aromatic, vinylic, methyl, branched and tertiary aliphatic organometallic reagents.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{N} \\
& \quad \text{O} \quad \text{Me} \\
\downarrow & \\
\text{R'} & \quad \text{O} \quad \text{Me}
\end{align*}
\]

1) R’Li/CeCl₃  
2) ClCO₂Me

>97 % de  
>70 % yield

X.4. Asymmetric Catalytic Imine Addition reactions.

**Addition of Enolates.** In recent years, a number of exciting developments in the catalytic asymmetric addition of carbon nucleophiles to imines mediated by transition-metal complexes has appeared. Kobayashi has provided many of the ground-breaking contributions in this area. In this regard, Kobayashi has documented that a Zr(IV)•(BINOL)₂ complex catalyzes the asymmetric addition of silylketene acetals to imines. The enantioselectivity of the adducts was dramatically increased by employing imines derived from 2-aminophenol. It has been postulated that this unusual imine is important in two critical respects. The hydroxyl group provides a Basic site that may promote the formation of a chelate between imine and metal complex thereby minimizing conformational degrees of freedom available to the activated imine. In addition, it has been suggested that the phenol undergoes silylation, providing for efficient turnover in this silicon-atom transfer process. Although in its current stage of development the process is optimized for aromatic and heteroaromatic imines, the reaction provides adducts often in better than 90% ee with several silylketene acetals (Table). The reaction provides good selectivity not only with the parent acetate derived enoxysilane (Entry 1), but also isobutyrate and glycolate derived silyl ketene acetals (Entries 2 – 4). The geometry of the starting enoxy silane is directly correlated with the simple stereoselectivity in the products, allowing for the selective preparation of either syn or anti diastereomeric product.

\[
\begin{align*}
\text{HO} & \quad \text{H} \\
\downarrow & \\
\text{1-Nap} & \quad \text{Nu}
\end{align*}
\]

Table X. Kobayashi Additions to Imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product</th>
<th>syn : anti</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OSiMe₃</td>
<td>1-NapOEt</td>
<td>-</td>
<td>92</td>
</tr>
</tbody>
</table>
Two related processes describing the addition of silyl enolates and allylstannanes to glyoxate derived imines have recently been reported independently by Sodeoka and Lectka.\textsuperscript{19,20} Letcka has postulated that the substrate coordinates to the metal catalyst through a bidentate chelate. This key organizational feature likely leads to the remarkable observed selectivities (80-90% ee). The catalyst for enol silane addition is prepared by mixing a solution of 5 mol % of CuClO\textsubscript{4}•(MeCN)\textsubscript{4} with 5.5 mol % of (R)-Tol-BINAP for 30 minutes prior to introduction of the imino ester XX. The enol silane is then added by slow addition over one hour to a 0 °C solution of the prepared catalyst. The method displays excellent selectivities with a variety of enol silanes.

\textbf{Strecker.} As an important example of Lewis base catalyzed asymmetric reactions, Lipton reported a cyclic dipeptide for catalyzing the Strecker reaction with electron rich aromatic \textit{N}-benzylc imines.\textsuperscript{21} The guanidine terminated cyclic dipeptide serves well, and it is proposed that sufficient basicity (of the guanidine) is essential to facilitate proton transfer in the reaction of HCN with an aldime intermediate. In this regard, a structurally similar catalyst with a terminal
imidazole fails to catalyze the reaction. The cyclic dipeptide XX affords various N-benzhydryl α-amino nitriles with high enantioselectivity in typically >90% yield – provided the aromatic ring is sufficiently electron rich.

From the Jacobsen laboratories two quite different approaches towards catalyst design have resulted in effective methods for catalyzing the Strecker reaction. In the first approach, the chiral (Salen)Al(III) complex was employed as a Lewis acid catalyst.22 In the second approach, the Schiff base complex XX was obtained by optimization utilizing parallel synthesis.23 The catalyst provides good induction with aromatic imines, but more significantly, aliphatic substrates are also viable, providing products in >80% ee and near quantitative yields.

The bulk of the methods discussed in this chapter have involved additions to aldimines. However, another Schiff base catalyst developed in the Jacobsen laboratories provides excellent enantioselectivities in the addition of HCN to N-benzyl aryl methyl ketamines.24 High levels of asymmetric induction are maintained even with electron deficient aromatic substrates. Some of these products, such as XX (Br and NO2) are crystalline and their enantiomeric purity may be increased to >99.9% ee by recrystallization.
Another carbon-carbon bond forming reaction has been achieved by the asymmetric allylation of imines by allyl stannanes catalyzed by the bis-allyl palladium species $XX$. Enantioselectivities in the range of $\sim 80\%$ are achieved with a variety of $N$-benzyl aromatic imines. In strides toward more environmentally benign chemistry, the same workers found that the stannane could be replaced by a silane provided a fluoride additive was present. The enantioselectivities obtained with the silicon based reagent are comparable to those obtained with tin, and in some cases ($XXX$) even improved.

**Miscellaneous Reactions.** A unique shuttle mechanism leading to the formation of aziridines in up to $97\%$ ee from imines has been reported by Aggarwal. In the reaction, a solution of phenyl diazomethane $XX$ is added slowly to a solution of the imine (1 equivalent), sulfide $XX$ (20 mol %) and Rh$_2$(OAc)$_4$ (1 mol %) over three hours at room temperature. The resultant rhodium carbenoid is thought to react first with the chiral sulfide leading to a sulfonium ylide that subsequently combines with the imine giving aziridines in $55 - 70\%$ yield as a 3:1 ratio of trans:cis products.
Classics in Asymmetric Synthesis

\[
\begin{align*}
\text{苯} & + \begin{array}{c}
\text{Me} \\
\text{N} & \text{O}_2 \\
\text{SiMe}_3
\end{array} \\
\text{Me} & \xrightarrow{20 \text{ mol } \%} \\
\text{Me} & \xrightarrow{1 \text{ mol } \% \text{ Rh}_2(\text{OAc})_4} \\
\text{Me} & \xrightarrow{1 \text{ mol } \% \text{ Cu(acac)}_2}
\end{align*}
\]

References

   Pretot requires formatting my mac cant do.
11. Check these refs for relevance: Burk jacs, 1991, 113, 8518; jacs 1993, 115, 10125;
    jacs 1992, 114, 6266.
