The Chemistry of Enamines
Structure, Reactivity, and Synthetic Applications

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Structure:
- Hyperconjugation
- Basicity

Reactivity:
- Alkylation
- Aldol
- Oxidation/Halogenation
- Ring Formation

Synthetic Applications:
- Heterocycles
- Total Synthesis

Useful references:
- Hickmott, P. W. Tetrahedron, 1984, 40, 2969

A Brief History of Enamines

- The term "enamine" was introduced in 1927 by Wittig to describe the nitrogen analog of "eneol"

- Enamine reactivity was reported as early as 1883 in the alkylation of aminocrotonic esters

\[
\begin{align*}
\text{Enamine} & \xrightarrow{\text{MeI}} \text{Enamine-\text{MeI}} \\
\text{Colise, J. Chem. Soc.} & : 1901, 1099-1109
\end{align*}
\]

- Stork's work on the alkylation of enamines brings this moiety to the forefront

\[
\begin{align*}
\text{Enamine} & \xrightarrow{\text{MeI, MeOH, } \Delta} \text{Enamine-\text{MeI}} \\
& \xrightarrow{\text{H}_2\text{O}} \text{Enamine-\text{MeH}} \\
& \text{70% yield}
\end{align*}
\]


- The Hajos-Parrish reaction sets the modern standard for quality in enamine catalysis

\[
\begin{align*}
\text{Enamine} & \xrightarrow{\text{3 mol % (L)-Proline, DMF}} \text{Enamine-\text{C}} \\
& \text{100% yield, 93% ee}
\end{align*}
\]

Physical Properties of Enamines

- Enamines display high nucleophilicity at their β-carbon due to hyperconjugation of the nitrogen lone pair

- Coplanarity of the lone pair and the alkene is necessary to achieve hyperconjugation

- The hyperconjugative interaction can be radically influenced by substituents on the alkene or on the nitrogen

- Steric interaction with amine reduces coplanarity, and therefore reactivity

- Electron-poor substituents attenuate reactivity

- Substituents that enforce orientation of lone pair (e.g., small carbocycle) are vital

- Aldehydes are more reactive than ketones, ketone ring size drastically impacts reactivity

NMR Spectroscopy of Enamines

- The chemical properties of an enamine are a function of the extent of hyperconjugation

- This effect can be accurately and easily correlated by 1H, 13C, and 15N NMR

- Substituents cis to the amine reduce planarity, and therefore electron density at the β-carbon
Hyperconjugation Through Bond Angles

- The nucleophilicity of the \( \beta \)-carbon can be predicted by bond angle measurements
- In theory, maximum delocalization is achieved when \( \theta \) is 0°

<table>
<thead>
<tr>
<th>( \theta )</th>
<th>“% pyramidality”</th>
<th>( \Delta H_f ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80°</td>
<td>57</td>
<td>20.2</td>
</tr>
<tr>
<td>0°</td>
<td>0</td>
<td>25.8</td>
</tr>
<tr>
<td>89°</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>23°</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>0°</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


- Rotational barriers for enamines tend to lie between 4-6 kcal/mol, but this is impacted by iminium character

The Value of a Lone Pair

- Conjugation with the nitrogen lone pair is known to be a good stabilizing force

\[
\Delta G = -2.3 \text{ kcal/mol}
\]

Wang, A.; Thargaraj, V. J. Org. Chem. 1980, 45, 3821

- Attempts to increase reactivity by heteroatom substitution at the nitrogen have not been successful

- Limitless spectroscopic and physical data for hundreds of enamines are readily available, allowing reasonably accurate predictions of reactivity for most situations
**Enamine Basicity - Am I Enammonium or Not?**

- The nitrogen of an enamine is not as basic as a saturated amine (depending on delocalization)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\text{PK}_a$</th>
<th>Compound</th>
<th>$\text{PK}_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Me}_2\text{NCH}_2\text{Ph}$</td>
<td>8.35</td>
<td>$\text{MeOC}_2\text{NCH}_2\text{Ph}$</td>
<td>10.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Me}_2\text{NCH}_2\text{Ph}$</td>
<td>7.85</td>
<td>$\text{MeOC}_2\text{NCH}_2\text{Ph}$</td>
<td>9.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{Me}_2\text{NCH}_2\text{Ph}$</td>
<td>10.66 (C-protonation)</td>
<td>$\text{MeOC}_2\text{NCH}_2\text{Ph}$</td>
<td></td>
</tr>
</tbody>
</table>


- Enammoniums are the kinetically favored product of protonation by hard acids

  \[
  \text{Me}_2\text{NCH}_2\text{Ph} + \text{HCl gas} \rightarrow \text{Me}_2\text{NCH}_2\text{Ph}^+ + \text{Cl}^- \text{ (crystalline, isolable)}
  \]

  Elguero, J.; Tamargo, G. TetraWxton Lett. 1995, 1112

- Iminium formation has been shown experimentally and computationally to be an intermolecular process

**Distribution of Protonated Enamines**

- The amount of enammonium in solution is highly dependent on reaction conditions

<table>
<thead>
<tr>
<th>% Protonation, -70°C</th>
<th>% Protonation, 23°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>at C</td>
<td>at N</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
</tr>
<tr>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
</tr>
</tbody>
</table>

  Enamines were treated with ethereal HCl, and then the salts treated with LiAPH$_4$ to measure evolved H$_2$.


- This divergent reactivity is comparable to that of other ambident nucleophiles (e.g., enols) in which hard-soft acid-base theory explains most observations
Enamine Methodology

- Stork's work on enamine alkylation generated the first major interest in the field.

> The alkylation of enamines with alkyl halides is a very good reaction and in many cases leads to a total disaster!

- Gilbert Stork

More Alkylation

- N-alkylation is a problem for enamines of aldehydes and certain ketones.

- This problem is avoided using bulkier amines.

- Alkylation with epoxides is also possible, but forcing conditions are required.
Asymmetric Alkylation

- Yamada discloses the first practical asymmetric alkylation procedure

\[
\begin{align*}
\end{align*}
\]

- Other alkylations are possible, but enantioselectivity is low

\[
\begin{align*}
\end{align*}
\]

- Use of a C$_2$-symmetrical amine overcomes this problem

\[
\begin{align*}
\end{align*}
\]

Metalloenamines

- Metalation of imines drastically increases reactivity of the resultant enamines

\[
\begin{align*}
\text{Stork, G., Doed, S. J. Am. Chem. Soc., 1963, 85, 2178}
\end{align*}
\]

- Various chiral imines are then used to little success until Meyers and Whitesell introduce chelation control

\[
\begin{align*}
\end{align*}
\]

\[
\begin{align*}
\end{align*}
\]
Dieter’s Hydrazones

- Enders introduces proline-based auxiliaries, RAMP and SAMP ([S]-1-Amino-2-methoxymethylpyrrolidine)

![Chemical structures and reactions](image1)

- This technology is then applied to acyclic ketones and aldehydes, albeit with mixed success

![Chemical structures and reactions](image2)

Palladium-Assisted Alkylation

- Enamines are alkylated by allyl acetates in the presence of palladium

![Chemical structures and reactions](image3)

- Asymmetric allylations are highly selective intramolecularly, but are less practical otherwise

![Chemical structures and reactions](image4)
**Unusual Methods for "Alkylating" Enamines**

- Efforts were made to enantioselectively protonate enamines to obtain enantiopure ketones

![Chemical structure]


- Iron-diene complexes can be activated towards attack by enamines

![Chemical structure]


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**Enamine Arylation**

- Highly electron-deficient aryl chlorides were reported to arylate enamines

![Chemical structure]


- More electron-rich aryl halogens only arylated the enamine nitrogen

- Aryl lead species have been shown to mildly arylate enamines

![Chemical structure]


- Sterically demanding ketones partition this process towards an undesired oxidation of the enamine
The Hajos-Parish Reaction

- Catalytic asymmetric enamine chemistry attained a high standard in the earliest studies

\[
\text{H}_{3}C-\text{CH}=\text{CH}-\text{CH}-(\text{L})-\text{Proline} \rightarrow \text{H}_{3}C-\text{O} \quad \text{3 mol %} \quad \text{DMF} \quad \text{100% yield} \quad \text{90% ee}
\]

Hajos, Z.; Parish, D. J. Org. Chem. 1974, 42, 1515

- Hajos proposes two mechanisms, and rules in favor of the second based on $^{18}$O studies

Mechanism A
Theoretically there will be $^{18}$O incorporation on proline turnover

Mechanism B
Theoretically there will be no $^{18}$O incorporation

Above experiment run in presence of 2% $^{2}$H$_{2}$ and in CH$_{3}$CN, proceeded 1 week
22% yield, 7.2% $^{18}$O enrichment

Control: product stirred in presence of proline, 2% $^{2}$H$_{2}$ in CH$_{3}$CN
33.1% $^{18}$O enrichment

List recently repeated this experiment with rigorously purified reagents and found >90% $^{18}$O enrichment

Proline-Catalyzed Aldol Mechanism

- Agami suggests that an enamine is operative, but observes a nonlinear effect

Presence of second amine would account for slight nonlinear effect as well as provide a more nucleophilic enamine


- Nonlinear effect later shown to be inaccurate, and theoretical calculations provide a plausible alternative

\[
\Delta H_{298} = 0.0 \text{ kcal/mol} \quad \Delta H_{298} = 1.0 \text{ kcal/mol} \quad \Delta H_{298} = 3.3 \text{ kcal/mol}
\]

DFT calculations B3LYP/6-31G*


- Houk rules against the possibility of a hydrogen-bonding interaction with the enamine nitrogen
Direct Aldol Applications

- Amine catalysts are now used in a wide variety of aldol and aldol-type reactions

\[
\begin{align*}
&\text{(L)-proline} \\
&30 \text{ mol}\% \\
&\text{R} = \text{Ar, i-Pr} \\
&68-97\% \text{ yield} \\
&60-96\% \text{ ee} \\
&\text{R} = \text{OR, i-Pr} \\
&42-92\% \text{ yield} \\
&86-99\% \text{ ee} \\
&4-9:1 \text{ anti:syn} \\
\end{align*}
\]


\[
\begin{align*}
&\text{(L)-proline} \\
&10-20 \text{ mol}\% \\
&\text{R} = \text{alkyl, OR, R} = \text{alkyl, OR, Ar} \\
&52-90\% \text{ yield} \\
&63-98\% \text{ ee} \\
&11:1 \text{ anti:syn} - 1:5 \text{ syn:anti} \\
&\text{then MeOH, H}^+ \\
\end{align*}
\]


Enamine Halogenation

- Enamines have been applied towards a range of other electrophiles, including halogen sources

\[
\begin{align*}
&\text{N}_2\text{F}_2 (g) \\
&\text{at } -78\,^\circ\text{C} \\
&53\% \text{ yield} \\
&Benjamin, J.; Mathey, F. Tetrahedron Lett. 1977, 9, 2797
\end{align*}
\]

\[
\begin{align*}
&\text{CO}_2\text{Et} \quad \text{Br}_2 \\
&\text{at } -15\,^\circ\text{C} \\
&48\% \text{ yield} \\
&37\% \text{ ee} \\
\end{align*}
\]

\[
\begin{align*}
&\text{Br}^+ \quad \text{Me}^+ \\
&\text{at } 5 \text{ mol}\% \\
&71-94\% \text{ yield} \\
&80-95\% \text{ ee} \\
\end{align*}
\]
**Enamine Oxidation**

- Enamines have also been functionalized by a variety of oxidants to access α-hydroxy carbonyls

  ![Chemical Structure]

  Augustine, R. J. Org. Chem. 1963, 28, 581

- Heavy metal acetates provide a direct, though procedurally undesirable method for oxidation

  ![Chemical Structure]

  Kuehne, M.; Giaidost, T. J. Org. Chem. 1968, 33, 3358

  Conti, F.; Rixton, B.; Solakoko, C. Tetrahedron 1973, 29, 3253

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**Nitrosobenzene As a Functionalizing Agent**

- Nitrosobenzene has proven a particularly effective oxidant for enantioselective catalysis

  ![Chemical Structure]


  Brown, S.; Beuzeh, M.; Sino, C.; McMillan, D. J. Am. Chem. Soc. 2003, 125, 10808

- Prior to the above results, nitrosobenzene had also been used for the amination of enamines

  ![Chemical Structure]


- Related studies of aminations and hydroxylations suggest acid activation may be responsible for chemoselectivity of nitrosobenzene oxidations

  ![Chemical Structure]
Other Enamine Aminations

- Dialkyl diazocarbonates have also been seen to effect amination of enamines

\[
\begin{align*}
\text{R} & \quad \text{EtO} & \quad \text{CON} & \quad \text{H} & \quad \text{HCO}_2\text{Et} \\
\text{R} & \quad \text{EtO} & \quad \text{CON} & \quad \text{H} & \quad \text{HCO}_2\text{Et} \\
\text{R} & \quad \text{EtO} & \quad \text{CON} & \quad \text{H} & \quad \text{HCO}_2\text{Et} \\
\end{align*}
\]


- Stable nitrenes can also furnish $\alpha$-amino ketones by way of an aziridination

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


Carbocycles From Enamines

- Most enamine-mediated three-membered ring formation is for ring expansion processes

\[
\begin{align*}
\text{N} & \quad \text{Ph} & \quad \text{Cl} \\
\text{N} & \quad \text{Ph} & \quad \text{Cl} \\
\text{N} & \quad \text{Ph} & \quad \text{Cl} \\
\end{align*}
\]


- Four-membered ring formation is limited to reaction with electrophilic alkenes and alkynes

\[
\begin{align*}
\text{N} & \quad \text{MeO}_2-\text{CO}_2\text{Me} \\
\text{N} & \quad \text{MeO}_2-\text{CO}_2\text{Me} \\
\text{N} & \quad \text{MeO}_2-\text{CO}_2\text{Me} \\
\end{align*}
\]


12
Five-Membered Ring Formation

- Tetracyanoethylene performs an unusual one-electron transfer process with enamines

- A different radical process allows cyclizations with aryl rings

- Reaction with \( \alpha, \alpha' \)-dibromo ketones in the presence of a reductant gives cyclopentenones

Six-Membered Ring Formation

- The most common method of six-membered ring formation from enamines is conjugate addition

- Both processes have been rendered enantioselective, although few catalytic methods exist

- A similar concept is being applied to an incredibly rapid synthesis of Littoralisone A
Other Ring Formations

- Examples of seven-membered ring formation from enamines are rare and limited

\[
\text{TsOH} + \text{AcO} \rightarrow \text{Ph(OAc)}_2 + \text{1:2 selectivity}
\]

- Far more common and well-studied are enamines in heterocyclic synthesis:
  
  **Thiophenes:**

  \[
  \text{R}^1\text{R}^2\text{H} + \text{R}^3\text{R}^4\text{H} \rightarrow \text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{H} \rightarrow \text{S}^\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{H} \rightarrow \text{S}^\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{H}
  \]

  **Pyroles:**

  \[
  \text{R}^1\text{R}^2\text{H} + \text{MeNHMe} \rightarrow \text{R}^1\text{R}^2\text{H} \rightarrow \text{R}^1\text{R}^2\text{H}
  \]

More Heterocycles

- Isoxazoles:

  \[
  \text{R}^1\text{R}^2\text{H} + \text{H}_2\text{NHO} \rightarrow \text{R}^1\text{R}^2\text{H} \rightarrow \text{R}^1\text{R}^2\text{H}
  \]

- Oxazoles:

  \[
  \text{R}^1\text{R}^2\text{H} + \text{ArCl} \rightarrow \text{R}^1\text{R}^2\text{H} \rightarrow \text{R}^1\text{R}^2\text{H}
  \]

- Pyridines:

  \[
  \text{R}^1\text{R}^2\text{H} + \text{NMe}_2 \rightarrow \text{R}^1\text{R}^2\text{H} \rightarrow \text{R}^1\text{R}^2\text{H}
  \]

- Substituted Hantzsch Esters:

  \[
  \text{R}^1\text{R}^2\text{H} + \text{CO}_2\text{Me} \rightarrow \text{R}^1\text{R}^2\text{H} \rightarrow \text{R}^1\text{R}^2\text{H}
  \]
**Enamines In Total Synthesis**

- Magnus uses an in situ generated amino diene in an elegant synthesis of aspidospermidine

![Chemical structures](image1)

33% yield

12% overall yield


- Proline methyl ester provides an effective platform for an enantioselective grignard addition

![Chemical structures](image2)

95% ee


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**Velleral, Pyrovellorolactone, and Ervatamine**

- An enamine-based [2+2] ring expansion provides fast access to a complex core

![Chemical structures](image3)

70% yield


- Here an enamine both aids reactivity and is an integral part of the molecule

![Chemical structures](image4)

**Leurosidine, Vinblastine, and Another Approach to Aspidospermidine**

- Different enamine oxidants provide access to diastereomeric natural products

- Enamine photocyclization furnishes a tricyclic building block towards aspidospermidine

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**Rosamicin Aglycone**

- Schlessinger uses a metalloc enamine to attain the requisite reactivity for a complex aldol coupling

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Conclusions

- Enamines are all around us!

- The literature contains physical and spectroscopic data for thousands of enamine-related compounds.

- Hundreds of different reactions have been tried using enamines, and many have been successful, but few are either asymmetric or catalytic.

- Enamines have been well studied mechanistically and provide a proven platform for rational design.