Atropisomer Selective Oxidative Couplings

SED Group Meeting March 2nd
Definition of Atropisomerism

- A stereoisomer where the element of chirality is not located on a atom but instead on a molecular plane or axis.
- The isomerism is directly derived from “the potential energy barrier between 2 adjacent minima of the molecular entity as a function of the torsional angle.”

- The arbitrary definition is: an atropisomer exists when the half-life of the interconversion is greater than 1000 sec. (r.t.)

Energy of Activation in Atropisomerism:

- In dynamic NMR studies of biphenyl systems (1) a direct correlation between rotational energies around the central axis and the Van der Waals radii of the substituents is seen.

These observations have led to the accepted hypothesis that the governing force behind atropisomer's chirality lies primarily in steric manifestations.

Atrop-definitions:

1) The energy profile in unbridged biphenyls is composed of two parts:
   - A) The steric component of ortho and ortho/meta substituents that induce nonplanarity.
   - B) The opposing pi-electronic overlap

2) Half-life racemization factors:
   A) Tetra-ortho substituted are almost always resolvable, tri-ortho readily racemize when one substituent is small (otherwise slow), di-ortho are only resolvable if the substituents are large, mono-ortho not resolvable.
   B) Buttressing effect: meta positions enhance racemization by not allowing the ortho substituents to bend outwards.
   C) The size of the substituent (I>Br>>CH₃>Cl>NO₂>CO₂H>>OCH₃>F>H) relates to the rate of racemization.
Atrop-definitions Continued:

The two main accepted nomenclature for assigning atropisomers:

1) Cahn Ingold Prelog-

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

= \text{S}

2) Helical Nomenclature-

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

= \text{P (plus)}

\[
S = \text{Plus (P)} \\
R = \text{Minus (M)}
\]

For BINOL
Strategies: Intramolecular Coupling

- Chiral Auxiliary (Bridges):

  ![Chemical Reaction](image1)

  Inherent Chirality (Natural Bridge):

  ![Chemical Reaction](image2)


Failures of Intramolecular Strategy:

Evans’ synthesis of the A-B ring of the vancomycin aglycon set the incorrect atrop-diastereomer. Only after considerable functional manipulation as well as correctly setting the C-O-D ring could let thermodynamic equilibration take place:

Strategies: Intermolecular Coupling

• 1) Chiral Auxiliaries

\[
\text{MgBr}_\text{OMe} + \text{NOMe} \xrightarrow{\text{THF}} \text{OMe}_\text{R}^* \xrightarrow{71\%} \\
\]

2) Asymmetric Ni-Pd Coupling

\[
\text{MgBr} + \text{R}^1 \text{Br} + \text{R}^2 \xrightarrow{\text{NiBr}_2, \text{Catalyst}} \text{Et}_2\text{O}, \text{Toluene} \xrightarrow{-5 \degree C} \\
\text{R}^1 = \text{R}^2 = \text{Me}; 95 \% \text{ee} \]

3) Asymmetric Oxidative Coupling

\[
\text{Pb, V, Cu} \xrightarrow{\text{Chiral Source}} \\
\]

Aryllead(IV) Triacetate Coupling:

- Pinhey showed that Aryllead(IV) triacetates could couple to electron rich aryl groups in poor to moderate yields:

\[
\text{Ph} + \text{CF}_3\text{COOH} \rightarrow \text{Ph} + \text{CF}_3\text{COOH} \quad 10-88\% \text{ yield} \\
\text{4 - 30\%}
\]

Mechanistically, the reaction proved to be highly complex:

It was unknown whether it occurred via a radical mechanism.

Aryllead(IV) Triacetate Coupling:

Through Kinetic studies with several aryl coupling partners, a correlation between the rate of the reaction and increasing pi-donor ability was found.

Nonetheless, a consistent aryl-lead coupling was not possible, as the substrate scope was too limited and too varied.
Aryllead(IV) Triacetate - Phenol:

- Barton recognized the similarity of the lead triacetate work of Pinhey, and previous work of phenol-aryl couplings with bismuth species.

Importantly, after careful optimization it was found that pyridine greatly enhanced the reactivity of the coupling. Through extensive NMR studies a preliminary mech was proposed:

Aryl(IV) Lead Triacetate - Phenol:

• Further mechanistic work by Pinhey provided the following details:
  • 1) NMR studies showed the lead species in solution with 2 Lewis bases coordinating to it.
    Relative Rate: \[ \text{Relative Rate: } \begin{array}{c} \text{N} \text{N} \text{N} \text{N} \\
    \text{O} \\
    \text{H} \\
    \text{Pb(OAc)}_3 \\
    \end{array} > \begin{array}{c} \text{N} \text{N} \\
    \text{N} \\
    \text{P} \\
    \text{r} \text{0} \text{d} \text{c} \\
    \text{t} \\
    \text{0} \text{%} \\
    \end{array} > \begin{array}{c} \text{P} \\
    \text{r} \text{o} \\
    \text{d} \text{u} \\
    \text{t} \\
    \text{0} \text{%} \\
    \end{array} \]
  • 2) Using several trapping experiments, a radical mechanism possibility was removed.
  • 3) A preference for substitution at the ortho position, especially the more methylated site. This would seem to eliminate the possibility of an electrocyclic mechanism.
  • 4) Two possible intermediates were proposed (1-2). By synthesizing (3) and subjecting it to the conditions of the coupling reaction no rxn occurred.

Asymmetric Lead-Phenol Coupling:

- Yamamoto surveyed a number of chiral amines. Primary, secondary and most tertiary amines proved fruitless. The complex alkaloids strychnine, and brucine gave remarkable improvement.

After careful optimization it was found that both metallation of the phenol as well as removal of the acetic acid byproduct via molecular sieves enhanced the ee and yield:

Asymmetric Lead-Phenol Coupling:

- The proposed mechanism for the diastereo and enantioselectivity is seen below:

![Proposed binding pocket with the Brucine ligand.](image)

Asymmetric Lead-Phenol Coupling:

• The rational for the atrop-selectivity (major-R) is that the chiral axis provides the stereocontrol not the central chirality of the dienone.

• Semiemperical calculations (AM1) as Well as literature calc. show that tautomerism of a dienone to a phenol should be faster than rotational isomerism.

• It was unsure whether the diaryl coupling occurs through a kinetic resolution mech.
Vanadyl Phenolic Coupling:

- The observation of isolable phenoxyvanadium(V) compounds by Funk, prompted the initial studies of Scott:

Mechanistic work since has shown that this reaction proceeds via a one electron oxidation transfer (V(V) - V(IV)).

VO(acac)$_2$ Phenol/Naphthol Coupling

- Uang later showed that phenols and naphthols could be coupled using a catalytic amount of vanadyl acac and a co-oxidant:

\[
\text{R}^2\text{R}^1\text{R}^3 -> \text{VO(acac)$_2$ 10 mol%} \xrightarrow{\text{O}_2} \text{R}^2\text{R}^1\text{R}^3
\]

<table>
<thead>
<tr>
<th>Naphthol</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>t/h</th>
<th>Product$^b$</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>2a</td>
<td>92</td>
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<tr>
<td>1b</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>2b</td>
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</tr>
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<td>1c</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>9</td>
<td>2c</td>
<td>76</td>
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<tr>
<td>1d</td>
<td>H</td>
<td>H</td>
<td>CO$_2$Me</td>
<td>120</td>
<td>2d</td>
<td>35</td>
</tr>
</tbody>
</table>

$^a$ The reactions were run with 10 mol% VO(acac)$_2$ in CH$_2$Cl$_2$ at room temperature under 1 atm O$_2$. $^b$ Compounds 2a–d were identified according to data reported in ref. 5.

<table>
<thead>
<tr>
<th>Phenol</th>
<th>t/h</th>
<th>Product$^b$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>120</td>
<td>4a</td>
<td>66</td>
</tr>
<tr>
<td>3b</td>
<td>48</td>
<td>4b</td>
<td>62</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions were similar to those for 1a–d. $^b$ 4a, b were characterized according to data reported in ref. 11.

Asymmetric Vanadyl couplings:

- Initial survey of chiral templates for the oxovanadium species proved futile until tridentate Schiff bases derived from salicylaldehydes and alpha amino acids:

![Schiff base structure]

Asymmetric Vanadyl Coupling:

- Published later that month…The same catalyst, same substrate, different group, worse (ee).

\[
\text{O}_2, \text{RT} \quad \xrightarrow{\text{Additive 2 mol \%}} \quad \text{OH} \quad \text{OH}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>80</td>
<td>42</td>
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<tr>
<td>2</td>
<td>TFAA</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>HClO\textsubscript{4}</td>
<td>64</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>TMSCl</td>
<td>73</td>
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</tr>
<tr>
<td>5</td>
<td>TESCl</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>TBDPSCl</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>TMSBr</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>TMSCl + AgClO\textsubscript{4}</td>
<td>68</td>
<td>31</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by HPLC with Kromasil 100-5CHI-DMB column (iPrOH–hexane = 5:95, 1 mL min\textsuperscript{−}1).

Without the additives the reaction was tried in TfOH. This also gave moderate yield and poor (ee).

Whats going on here?

- Both catalysts are the same but supposedly operate on different mechanisms:
  Anson had previously reported that vanadium (IV) salen complexes undergoes disproportion to vanadium (III) and vanadium (V) in the presence of strong Lewis/Bronsted acids.

  $\text{VO(acac)}_2 \xrightarrow{\text{Lewis Acid}} [\text{V(acac)}_2]^{2+} \xrightarrow{\text{VO(acac)}_2} [(\text{acac})_2\text{VO(acac)}_2]^{2+}$

  A proposed mechanism for the mu-oxo divanadium (IV):

  Chen’s catalyst has a different mechanism as it catalyzes in a monomeric fashion:

  Chen gave no mechanistic rationale for his catalyst.

Asymmetric Vanadyl Coupling:

- Possible mechanisms:
  For Uang’s Dimer
  
  Pre-Catalysts for
  Chen and Uang
  (Tetragonal Pyr.)
Asymmetric Vanadyl Coupling:

- Through the condensation of chiral 3,3’-diformyl-2,2’-dihydroxy-1,1’-binaphthol with (S)-amino acids and vanadyl sulfate Gong was able to prepare a novel vanadyl catalyst.

The type (1) catalysts failed almost completely. Interestingly, much higher enantioselectivities were found for the type (2) catalysts. This would seem that the oxidative coupling is suited for double chirality.

Asymmetric Vanadyl Coupling:

- Possible Mechanistic Pathway:
Copper/Amine Coupling:

- The first example of copper-amine mediated biaryl coupling was demonstrated by Glaser (phenylacetylene to diphenylacetylene).
- Later Hay and Havinga independently showed the ability to couple naphtholic and phenolic compounds:

\[
\begin{align*}
\text{OH} & \quad \overset{\text{Cu (I) Salt Pyridine}}{\longrightarrow} \quad \overset{\text{O}_2}{\longrightarrow} \\
& \\
\text{OH} & \quad \overset{\text{Cu (I) Salt Pyridine}}{\longrightarrow} \quad \overset{\text{O}_2}{\longrightarrow} \quad \text{Dimers}
\end{align*}
\]

This was followed up many years later by Feringa and Wynberg in anaerobic cond:

\[
\begin{align*}
\text{OH} & \quad \overset{\text{Cu(II) Salt}}{\longrightarrow} \\
& \\
\text{OH} & \quad \overset{\text{N}_2}{\longrightarrow} \\
\text{N(Me)}_2 & \quad \overset{\text{N}_2}{\longrightarrow} \\
& \quad \overset{62\%}{\text{OH}}
\end{align*}
\]

Glaser. Ber. 1869, 2, 422.
Hay, A. J. Am. Chem. Soc. 1959, 81, 6335
Wynberg, H. Tett. Lett. 1977, 50, 4447
Copper/Amine Coupling:

- The first attempt at an asymmetric naphtholic dimerization was by Brussee:

\[
\begin{align*}
\text{HO-} \quad & \quad \text{Cu(II) Salt} \\
\text{HO-} \quad & \quad \text{Amine (chiral)} \\
\text{HO-} 
\end{align*}
\]

Up to 86% ee

A screen of available achiral amines as potential ligands showed a consistent 2-4 excess of amine to Cu(II). When a series of ethanolamines were tested a 2:1 ratio was found.

When the group moved to chiral amines: alpha-methyl-phenyl ethylamine (Amphetamine) the optical purity of the product could not be reproduced.

Copper/Amine Coupling:

- The irreproducibility was solved after careful temperature experiments:

  It was determined that the relationship between temperature and stereoselectivity ruled out that the reaction provided any stereocontrol. It was the recrystallization process that was highly temperature dependant.

  “2nd order Asymmetric Transformation”

This example was repeated several times in the literature:

Copper/Amine Coupling:

- The first successful, catalytic, enantioselective copper-amine complex for oxidative coupling of naphthols was completed by Nakajima:
  - The TMEDA ligand was examined first and provided excellent yields.
  - A chiral ligand / substrate survey provided the following:
    - Diamines derived from L-proline were similar enough in character to TMEDA to provide adequate yields and selectivity's.
    - The hydrate enhanced reactivity.
    - It is necessary for the ortho position to be substituted with an ester moiety.

\[
\text{Nakajima, M. Tett. Lett. 1995, 36, 9519.}
\]
\[
\text{Nakajima, M. JORG. 1999, 64, 2264.}
\]
Copper/Amine Coupling:

- The mechanistic postulate:
  1) Exchange of the hydroxyl group w/ Cu, followed by ester coordination
  2) Oxidative coupling affording a diketone w/ central chirality
  3) Transfer of central chirality to axial chirality through keto-enol isomerism
Copper/Amine Coupling:

- Through the condensation of (1R,2R) 1,2-diaminocyclohexane, with 2,6-diformylphenol in the presence of Cu(II) gave a structurally defined catalyst:

\[
\text{R} \quad \text{N}H \quad \text{N}H \quad \text{O} \quad \text{O} \\
\text{Cu(II)} \quad \text{Cu(II)} \quad \text{EtOH} \quad \text{EtOH}
\]

The C-H bonds from the stereogenic centers are Perpendicular to the N\textsubscript{4}O\textsubscript{2} plane. This catalyst is thus an alpha-beta-alpha-beta chiral compound,

Copper/Amine Coupling:

- The oxidative dimerization of naphthol was tested against all of the catalysts:

The best catalyst proved to be 3a:

- The polyaza cmpds proved to be more robust than the tetraimine analogs.
- Catalytic efficiency was insensitive to the bulk of the peripheral groups (compare 1a-c and 3a-c series).
- At higher temperatures the reaction yields improved but the enantioselectivity eroded slightly.

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<td>85</td>
<td>88</td>
<td>S</td>
</tr>
</tbody>
</table>

[a] The reaction was carried out at 0, 10 or 20 °C in the presence of 10 mol% of catalyst in CCl₄ solution. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC (Chiralpak AD) and the absolute configuration was assigned by comparison to literature.
Copper/Amine Coupling:

- Mechanistic rationale for the catalyst’s selectivity:
  1) A naphthol ligand exchanges with MeOH
  2) One electron transfer from substrate to Cu(II)
  3) The simultaneous process occurs on Cu-2
  4) Minimizing the steric interactions with the axial hydrogens on the cyclohexyl rings would produce the S product.
Summary:

Atropisomer selective oxidative coupling reactions are still in their infancy. Even the best examples provide only moderate enantiomeric excess and generally are substrate dependant. At this point in time the vanadyl based catalysts provide the highest yields/ee/in the shortest time, but there is considerable potential for the Glaser-Hay based catalyst system.

It is my speculation that atropisomer selective coupling (metal based) will be an avenue of focused research quite possibly in the near future.