Molecular Insights into Asymmetric Catalysis
– From Rationalization to Prediction

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Altering **Kinetic** Features (e.g., rate enhancement)

**Used in industry** for making various products (e.g., petroleum, fine chemicals), day-to-day life (e.g., automobile exhaust)

Academia: small scale reactions (typically ml, mg range) for **inventing new catalysts** and catalytic processes
Recent developments in computational chemistry have enabled high accuracy computations in understanding the mechanism of catalytic reactions.

Knowledge of turn-over-determining step of the catalytic cycle would help improve the catalytic efficiency.

Computational design of chiral catalyst can be of immense benefit for in silico screening of lead catalysts.
Properties of Enantiomers differ in Chiral medium

Biological properties of enantiomers are different, as the receptor sites are chiral

Thalidomide

- R against nausea
- S cause fetal damage

(+)-glucose is metabolized by animals but NOT (-) glucose!

Schematized Enantiomer Recognition in the Receptor Site of an Enzyme
When there is equal composition (1:1) of enantiomers in the mixture, the resulting solution is optically inactive.
Why Study Chiral Induction?

World drug market (several billion $): ~55% drugs are chiral

Depleting natural resources makes organic synthesis a major and viable alternative to generate chiral drugs

Produced using “Asymmetric Synthesis” [production of one enantiomer in excess of the other]
Multi-step reactions would involve various intermediates and interconnecting transition states.

Theoretical Methods can be effective employed to examine the electronic structure and energies of molecules.
Asymmetric Sulfoxidation

\[
\text{Ph} \quad \text{S} \quad \text{CH}_3 + \quad \text{H}_2\text{O}_2 \quad \text{Catalyst (2 mol%)}
\]

cyclohexane, rt

\[
\text{Ph} \quad \text{S}^+ \quad \text{CH}_3
\]

\[
\begin{aligned}
\text{Catalyst} & \quad \%\text{ee} \\
\text{I} & \quad 16 \\
\text{II} & \quad 56 \\
\text{III} & \quad 98 \\
\end{aligned}
\]

Importance: Omeprazole (Omez) is a chiral sulfur containing drug

Stereoselective Reactions – Energetics?

Stereoselectivity depends on the energy difference between diastereomeric transition states

\[ \Delta \Delta G^\ddagger = \Delta G^\ddagger_{Si} - \Delta G^\ddagger_{Re} \]
Stereocontrolling Transition State for oxygen transfer
Differential Stabilization in the Stereocontrolling TSs

III-re (0.0)
Number and extent of weak interactions are sufficiently large for high stereoselectivity

III-si (3.9)
M06-2X/6-31G**

Noncovalent Interactions – Energetics?

Noncovalent Interactions

- anion⋯π
- cation⋯π
- C–H⋯π
- lone pair⋯π
- C–H⋯X
- X–H⋯π
- H–bond

X = O, N, S, F, Cl

Current trends in Homogeneous Catalysis

Multicatalysis

Combination of transition metal catalysts with organo-catalysts

**α- Allylation: Cooperative Asymmetric Catalysis**

\[
\text{H}_2\text{O} + \text{PhOH} \xrightarrow{2 \text{ mol}\% \left[\text{Ir}(\text{COD})\text{Cl}_2\right]} \text{H}_2\text{O} + \text{PhOH} \\
\text{Me} \quad \text{Ph} \quad \text{Me} \quad \text{Ph}
\]

\[
\text{2 mol\% \left[\text{Ir}(\text{COD})\text{Cl}_2\right]} \quad 8 \text{ mol\% P1} \quad 10 \text{ mol\% C1} \\
\text{CCl}_3\text{COOH, DCE, 25°C, 24 h}
\]

\[
\text{Major} + \text{Minor}
\]

\[
\text{P1} = \text{phosphoramidite} \\
\text{C1} = \text{cinchona amine}
\]

Formation Key Intermediates

**Nucleophilic** partner: Cinchona-Enamine

**Electrophilic** partner: Ir-π-allyl intermediate

TCA = CCl₃COOH, COD = cyclooctadiene

P = phosphoramidite, *= binaphthyl
Study of Intermediates (Triggered by?) Computational Results

\[ \text{[Ir(cod)Cl]}_2 + (R)-L \rightarrow (R,R,R)-2 \]

\[ \text{[Ir(cod)Cl]}_2 + (R)-L \rightarrow (R,R,S)-2 \]

Stereodivergence with two chiral catalysts

(2R,3R)

$\text{O} \quad \text{H} \quad \text{Me} \quad \text{Ph}$

$\text{H} \quad \text{Me} \quad \text{Ph}$

$\text{ee} > 99.0 \% (>99.0\%)$

$de > 99.2 \% (>90.5\%)$

$\text{O} \quad \text{H} \quad \text{Me} \quad \text{Ph}$

$\text{H} \quad \text{Me} \quad \text{Ph}$

$\text{ee} > 99.0 \% (>99.0\%)$

$de > 99.5 \% (=85.0\%)$

(2S,3R)

$\text{O} \quad \text{H} \quad \text{Me} \quad \text{Ph}$

$\text{H} \quad \text{Me} \quad \text{Ph}$

$\text{ee} > 99.0 \% (>99.0\%)$

$de > 99.5 \% (=90.5\%)$

SMD(DCE)/B3LYP-D3/6-311G**, def2-TZVP(Ir)/B3LYP-D3/6-31G**, Lanl2DZ(Ir)
Stereocontrolling Transition States: P1-C1

Interaction Wheel Model

P1-C1

re-si (0.0)  si-si (3.3)  si-re (7.6)

π···π  N···H

P1-C2

si-si (0.0)  re-si (3.6)  re-re (8.2)

C-H···π  lone pair (N)···π

P2-C1

re-re (0.0)  si-re (4.5)  si-si (12.3)

Cl···H  lone pair (Cl)···π

P2-C2

si-re (0.0)  re-re (2.1)  re-si (6.9)


Stereocontrol

Ir-(R)-phosphoramidite $\rightarrow$ endo-Ir-$\pi$-allyl $\rightarrow$ β-tertiary center (3R) $\rightarrow$ α-quaternary center (2R) $\rightarrow$ Cinchona-enamine

Stereochemistry at α and β centers are decided in two separate events in the formation of the reacting partners.
Diastereoselectivity is due to the two availability of the prochiral faces of the enamine.
Computational Chemistry

Rationalization
Gain insights on reactions, that are difficult to discern experimentally

Prediction
Catalyst design for asymmetric applications

-Prediction is very difficult, especially if it’s about the future!!!
-Niels Bohr
Dual Catalytic Enantioselective Heck-Matsuda Arylation

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

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\begin{align*}
\text{MeN} & \text{NMe} \\
\text{O} & \text{NMe} \\
\text{O} & \text{NMe} \\
\end{align*}
\]

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\end{align*}
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\end{align*}
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\text{O} & \text{NMe} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeN} & \text{NMe} \\
\text{O} & \text{NMe} \\
\text{O} & \text{NMe} \\
\end{align*}
\]
Catalytic Cycle

With no NaHCO₃
ΔG = 23.8 kcal/mol

Explicit NaHCO₃
ΔG = 14.3 kcal/mol

ΔΔG = 9.5 kcal/mol

Experimental yield
With no NaHCO₃ 07%
Explicit NaHCO₃ 90%

SMD(ε=3.44)/M06/def2-TZVP
Enantiocontrolling Migratory Insertion TSs

\[ a = 3.13 \, (0.723) \]
\[ b = 3.07 \, (0.824) \]
\[ c = 2.59 \, (0.742) \]
\[ d = 2.38 \, (1.160) \]
\[ e = 2.58 \, (0.967) \]
\[ f = 3.21 \, (0.508) \]
\[ g = 2.79 \, (0.589) \]

\[ \alpha \, (P3-N4-C5-C6) = 37^\circ \]
\[ \alpha' \, (P3-N7-C8-C9) = 0^\circ \]

**TS-si_{C1}**

\[ \text{C-H} \cdots \text{O, C-H} \cdots \pi, \text{lp} \cdots \pi, \text{O-H} \cdots \pi \text{ and C-F} \cdots \pi \]

**TS-re_{C1}**

\[ \text{calc. } \%\text{ee} = 37 \]
\[ \text{exp. } \%\text{ee} = 34 \]

\[ \text{M1(mix)} = \text{SMD}_{(\varepsilon=3.44)}/\text{M06/def2-TZVP}, \; \text{M2(tol)} = \text{SMD}_{(toluene)}/\text{M06/def2-TZVP} \]
Effect of N-aryl Substituents on the Enantioselectivity

Enantiocontrolling Migratory Insertion TSs using C3 catalyst

C–H···O, C–H···π, lp···π, and C–F···π

TS-\(si_{C3}\)

TS-\(re_{C3}\)

\[\begin{align*}
c &= 2.56 (0.789) \\
d &= 2.37 (1.207) \\
k &= 2.57 (0.791) \\
l &= 2.72 (0.702) \\
m &= 2.49 (0.904) \\
n &= 2.72 (0.680) \\
o &= 2.49 (0.968) \\
e &= 2.74 (0.753) \\
f &= 3.13 (0.584) \\
\end{align*}\]

\[\begin{align*}
\alpha &= 37^\circ \\
\alpha' &= -1^\circ \\
M1 &= [0.0] \\
M2 &= [0.0] \\
\end{align*}\]

\[\begin{align*}
h &= 2.72 (1.014) \\
p &= 2.96 (0.511) \\
q &= 2.82 (0.619) \\
r &= 2.31 (1.881) \\
s &= 2.54 (0.698) \\
\end{align*}\]

\[\begin{align*}
\alpha &= 51^\circ \\
\alpha' &= -41^\circ \\
\end{align*}\]

calc. \(\% ee = 88\)

exp. \(\% ee = 84\)

\[\begin{align*}
M1_{(mix)} &= \text{SMD}_{(\varepsilon = 3.44)}/\text{M06/def2-TZVP} \\
M2_{(tol)} &= \text{SMD}_{(toluene)}/\text{M06/def2-TZVP} \\
\end{align*}\]
## Experimental Validation of the Predicted Enantioselectivities


<table>
<thead>
<tr>
<th>entry</th>
<th>cycloalkene</th>
<th>aryl diazonium salt</th>
<th>BDPA</th>
<th>base</th>
<th>solvent</th>
<th>conv. (%)</th>
<th>ee (exp.)</th>
<th>ee (comp.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A1</td>
<td>D1</td>
<td>C1</td>
<td>none</td>
<td>toluene/MTBE (1/1)</td>
<td>07</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>A1</td>
<td>D1</td>
<td>C1</td>
<td>b1</td>
<td>&quot;</td>
<td>90</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>A1</td>
<td>D1</td>
<td>C4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>73</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>A1</td>
<td>D1</td>
<td>C2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>71</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>A1</td>
<td>D1</td>
<td>C3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>83</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>A2</td>
<td>D2</td>
<td>C1</td>
<td>b2</td>
<td>toluene</td>
<td>92(^a)</td>
<td>09</td>
<td>02</td>
</tr>
<tr>
<td>7</td>
<td>A2</td>
<td>D2</td>
<td>C2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>74(^a)</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>A2</td>
<td>D2</td>
<td>C3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>63</td>
<td>22</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^a\)isolated yields. **b1** = Na\(_2\)CO\(_3\) and **b2** = Na\(_2\)HPO\(_4\)
Asymmetric Induction

• Differential weak interactions holds the key

Inspired by Experiments, Inspiring more experiments
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