
ACS Catalysis

- Newest ACS Journal
- Dedicated to heterogeneous, homogeneous, and bio-catalysis
- Will feature experimental and theoretical work
- Publishes Letters, Articles, Reviews, Perspectives, and Viewpoints

“The journal seeks to acquire content in the areas of new reactions and new approaches to synthesis involving known catalysts, discovery of or modification of new catalysts, novel mechanistic and investigatory studies on catalysis, practical enhancements of known processes, and conceptual advances.”

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Seemingly a consolidation of Mitsubishi Chemical Corporation and the fine chemicals division of Yoshitomi Pharmaceuticals

Specializes in Azidation, Asymmetric synthesis, Cyanation, Oxidation, Reduction, Resolution, Organometallic reaction, Cryogenic reactions (– 80 °C on 5000L scale, dedicated tank for \(n\)BuLi!!), bio-catalyzed asymmetric reduction

**C–H Activation Pros and Cons**

**Pros:**

- Direct functionalization
- Better atom economy
- Catalytic, no stoichiometric transition metals (sometimes)

**Cons:**

- Requires directing groups
- High catalyst loading
- Often requires stoichiometric oxidants
- Can over functionalize
Angiotensin II Receptor Blockers (ARBs)

- High blood pressure and congestive heart failure medication. 2005 US sales of Valsartan = $6.0 Billion
- Previous process routes towards ARBs require organometallics such as Grignards and boronic acids to generate the biphenyl triazole

Synthesis Plan and Catalyst Optimization

Retrosynthetic Analysis:

Catalyst Optimization:

<table>
<thead>
<tr>
<th>Ru Cat.</th>
<th>Ligand</th>
<th>PG</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[RuCl₂(Benzene)]₂, 10 mol %</td>
<td>PPh₃, 20 mol %</td>
<td>PMB</td>
<td>48</td>
</tr>
<tr>
<td>[RuCl₂(COD)]ₙ, 10 mol%</td>
<td>PPh₃, 20 mol %</td>
<td>PMB</td>
<td>63</td>
</tr>
<tr>
<td>RuCl₃·xH₂O, 1.3 mol%</td>
<td>PPh₃, 1.3 mol %</td>
<td>OMB</td>
<td>65</td>
</tr>
<tr>
<td>RuCl₃·xH₂O, 1.3 mol%</td>
<td>PPh₃, 2.34 mol %</td>
<td>OMB</td>
<td>81</td>
</tr>
</tbody>
</table>
Catalyst Optimization Part 2

Optimized Conditions:

- A literature report inspired these conditions; unstable catalysts are expected to provide higher rate acceleration (decreasing the activation energy by increasing the ground state energy)

- Triphenylphosphine is important; too little (0 mol%) or too much (4 mol %) results in poor conversion

- Large $N$–protecting groups also result in poor conversion

- Water plays a crucial role: anhydrous RuCl$_3$ nor anhydrous RuCl$_3$ and an equal amount of water resulted in good conversion

- Triphenylphosphine was the best (and cheapest!) phosphine ligand

- Order of addition matters, pre-forming the catalyst results in lower conversion

- This catalyst loading is the lowest reported so far for o-arylation!

Catalytic Cycle and Completion of Synthesis

Catalytic Cycle:

- The active catalyst most likely has one triphenylphosphine ligand, as 0.5 equiv. is needed to reduce Ru\textsuperscript{III} to Ru\textsuperscript{II}.

Completion of Synthesis:

- Oxidized egg shell Pd/C was crucial to the successful deprotection of the OMB group and benzyl ester (egg shell = Pd close to surface--50 to 1050 nm vs. thick shell--250 to 500 nm from surface).
Summary

- A novel C–H activation reaction has been developed specifically for the manufacture of a pharmaceutical
- The reaction uses low catalyst loadings and inexpensive reagents
- Higher activity of an unstable catalysts is invoked to explain enhanced reactivity
- Takes advantage of imbedded directing group in molecule
Prof. Zhi Li

- BSc Nanjing University (1982)
- MEng Chinese Academy of Forestry, Nanjing (1984)
- Ph. D. University of Vienna (1991)
- Associate Professor at National University of Singapore
- Research Interests: New Biocatalysts for enantioselective transformations, tandem biocatalysis, recyclable magnetic nanobiocatalysts for green oxidaitons
Enantiopure vicinal diols are important synthetic building blocks.

Metal–catalyzed approaches: Sharpless asymmetric dihydroxylation, asymmetric hydrogenation of hydroxy ketones, enantioselective hydrolysis of epoxides.

Enzymatic catalysis has not been effective; dihydroxylation of styrene with dioxygenase, reduction of hydroxy ketones with baker’s yeast, lipase catalyzed resolutions, and epoxide hydrolase–catalyzed hydrolysis of racemic epoxides all give poor yield and/or ee.

The authors wondered if an oxidative kinetic resolution with whole cells would be possible.
Cell Screening and Reaction Mechanism

• Authors screened 70 microorganisms that can grow on \( n \)-octane for oxidative resolution

• Strains degrading \( n \)-octane often contain oxygenase and other oxidative enzymes

• HXN-200 (which contains monooxygenase and epoxide hydrolase activity) performed the reaction

\[
\begin{align*}
\text{Sphinogomonas sp. HXN–200} & \quad \text{Tris buffer, 25 °C} \\
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2 \\
\text{H}
\end{align*}
\]

Proposed Reaction Mechanism:

\[
\begin{align*}
\text{(R)-1} & \quad \text{(S)-1} \\
\text{Fast} & \quad \text{Fast} \\
\text{Cell of HXN-200} & \quad \text{Slow}
\end{align*}
\]

Time Course Oxidative Resolution

• Only 1, 5 and 6 were detected by LC–MS

\[
\begin{align*}
\text{Conc. of (R)-1} & \quad \text{Conc. of (S)-1} \\
\text{Conc. of 5} & \quad \text{Conc. of 6}
\end{align*}
\]
Optimization and Substrate Scope

\[
\begin{align*}
\text{Sphinogomonas sp. HXN–200} & \quad \text{Tris buffer, 25 °C} \\
\text{R} & \quad \text{OH} \\
\text{R} & \quad \text{CO}_2 \text{H} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>conc. (mM)</th>
<th>cells (g/L)</th>
<th>activity (U/g cdw)</th>
<th>time (h)</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.8</td>
<td>10</td>
<td>4.2</td>
<td>3</td>
<td>26</td>
<td>99.9</td>
</tr>
<tr>
<td>1</td>
<td>10.8</td>
<td>10</td>
<td>3.5</td>
<td>6</td>
<td>26</td>
<td>99.6</td>
</tr>
<tr>
<td>1</td>
<td>19.4</td>
<td>10</td>
<td>2.5</td>
<td>15</td>
<td>32</td>
<td>99.2</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>7.9</td>
<td>1.4</td>
<td>18</td>
<td>48</td>
<td>98.4</td>
</tr>
<tr>
<td>3</td>
<td>7.9</td>
<td>14</td>
<td>3.4</td>
<td>4</td>
<td>45</td>
<td>99.6</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>17</td>
<td>0.5</td>
<td>21</td>
<td>36</td>
<td>98.7</td>
</tr>
</tbody>
</table>

- Substituents at the para position increased activity of HXN–200, but there was no discriminating between groups
Optimization and Substrate Scope

• Substrates 2–4 give the R enantiomer diol, time course plots show the S enantiomer reacts much faster

\[
\begin{align*}
\text{Sphinogomonas sp. HXN–200} & \quad \text{Tris buffer, 25 °C} \\
R\text{-OH} + R\text{-OH} & \quad \rightarrow \quad R\text{-OH} + R\text{-CO}_2\text{H}
\end{align*}
\]

\[
R = \begin{cases} 
1 & \text{Cl} \\
2 & \text{Me} \\
3 & \text{X} \\
4 & \text{X}
\end{cases}
\]

• This novel process gives the best results so far for bio-resolution of 1,2 diols
Summary

• Oxidative kinetic resolution gives access to useful 1,2 diols

• Screening of whole cells instead of enzymes led to the discovery HXN–200 preforms the reaction well

• Higher concentrations increase yield but slightly decrease ee

• Using whole cells is much cheaper than using enzymes, and cell systems could be engineered to possess multiple oxidative enzymes for more efficient transformations

The Heat are going up in flames!!!