Combinatorial Approaches in Homogeneous Catalysis Development: Case Studies

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Combinatorial Mathematics

3 building blocks
A₁,₂,..,₁₀, B₁,₂,..,₁₀, C₁,₂,..,₁₀

2-step synthesis
A + B then + C

→ # of different compounds A-B-C ?
Combinatorial Chemistry

- a branch of applied chemistry concerned with the rapid synthesis and screening of large numbers of different but related chemical compounds generated from a mixture of known building blocks in order to recover new substances optimally suited for a specific function

For a historical review:
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Unique Aspects of Combinatorial Approach in Homogeneous Catalytic System

Necessity:
- Development of a new catalytic system.
- Optimization of a known catalyzed reaction for specific substrates.

Aspects:

Ligand library
- Rapid, modular, parallel synthesis

Reaction conditions

Reactivity, Selectivity
- High-throughput screening
Pyrrolidinemethanol Ligands via Solid State Synthesis

Ellman, JOC, 1995, 60, 7712
Combinatorial strategies may be useful for the development of asymmetric catalysts.
Peptide-derived Ligands

Potential opportunities for the establishment of a combinatorial catalyst library:

- Ease of Schiff base and peptide synthesis
- Readily available building blocks

Inoue, JACS, 1992, 114, 7969
Potential Catalytic System for Cyanide Opening of Epoxide

1

\[ \text{catalyst: Ti(OiPr)}_4 \quad 12\% \]
\[ \text{catalyst: Ti(OiPr)}_4 + 3 \quad 80\% \]

Hoveyda, ACIEE, 1996, 35, 1668
Peptidic Schiff Base Ligands

\[ \text{FMOC} = 9\text{-fluorenylmethyloxy carbonyl} \]

Hoveyda, ACIEE, 1996, 35, 1668
Optimization of Ligand via Position Screening

Hoveyda, ACIEE, 1996, 35, 1668
Optimized Ligands for Specific Substrates

Hoveyda, ACIEE, 1997, 36, 1704

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Product</th>
<th>ee [%][b]</th>
<th>Yield [%][c]</th>
<th>Conversion [%][d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (2b)</td>
<td>A</td>
<td>NC-OTMS</td>
<td>83 (63)</td>
<td>72</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>4a (4b)</td>
<td>10</td>
<td>NC-OTMS</td>
<td>87 (86)</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>5a (5b)</td>
<td>12</td>
<td>NC-OTMS</td>
<td>84 (69)</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>6a (6b)</td>
<td>8</td>
<td>NC-OTMS</td>
<td>78 (58)</td>
<td>69</td>
<td>81</td>
</tr>
</tbody>
</table>

[a] A=HO, B=HO, C=HO, D=HO

Hoveyda, ACIEE, 1997, 36, 1704
Unexpected Structure-Selectivity Relation

\[ \text{N-}^\beta\text{-trityl-L-asparagine} \]

Hoveyda, ACIEE, 1997, 36, 1704
Peptidic Ligands for Enantioselective Cyanide Addition to Imines

Hoveyda, JACS, 1999, 121, 4284
Hoveyda, JACS, 2000, 122, 2657
Mechanistic Insights from SAR Studies

Terminal amide participates in the stereo-determining step.

Scheme 33.7. Effect of the AA2 moiety on reactivity and

Hoveyda, JACS, 1999, 121, 4284
Hoveyda, JACS, 2000, 122, 2657
Proposed Model

Kelation control may be utilized to deliver other nucleophilic RM.
Zr Catalyzed Enantioselective Addition of Dialkylzinc to Imines

\[
\begin{align*}
38 & \quad \text{0.1 mol\% 40, 20 mol\% Zr(OiPr)_4\cdot HOiPr} \\
& \quad 5\text{ equiv Et}_2\text{Zn, 0 to 22 °C;} \\
& \quad 39 \\
& \quad 93\% \text{ ee, 82}\% \\
\end{align*}
\]

chiral ligand:

\[
\begin{align*}
30\text{ mol\% AgNO}_3 \\
7\text{ equiv } (\text{NH}_4)_2\text{S}_2\text{O}_8 \\
\text{MeCN / H}_2\text{O, 60 °C} \\
& \quad 40 \\
& \quad 93\% \text{ ee, 65}\% \\
\end{align*}
\]
Cu Catalyzed Enantioselective SN2’ of Allylic Phosphates

Chiral ligands:

\[
\begin{align*}
\text{ligand 68} & : & \text{ligand 69} \\
\end{align*}
\]

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

Chemical reactions:

\[
\begin{align*}
\text{72} & \quad \text{Me} & \quad \text{Me} & \quad \text{PO(OEt)}_2 \\
\text{TsO} & \quad \text{72} & \quad \text{Me} & \quad \text{Me} & \quad \text{PO(OEt)}_2 \\
\end{align*}
\]

10 mol % 68, 10 mol % CuCN
3 equiv Et₂Zn, THF, -78 °C

\[
\begin{align*}
\text{73} & \quad \text{Et} & \quad \text{Me} \\
\text{TsO} & \quad \text{73} & \quad \text{Et} & \quad \text{Me} \\
\end{align*}
\]

90% ee, 83%

\[
\begin{align*}
\text{74} & \quad \text{Me} & \quad \text{Me} & \quad \text{PO(OEt)}_2 \\
\text{F}_3\text{C} & \quad \text{74} & \quad \text{Me} & \quad \text{Me} & \quad \text{PO(OEt)}_2 \\
\end{align*}
\]

10 mol % 69, 10 mol % CuCN
3 equiv Et₂Zn, THF, -78 °C

\[
\begin{align*}
\text{75} & \quad \text{Et} & \quad \text{Me} \\
\text{F}_3\text{C} & \quad \text{75} & \quad \text{Et} & \quad \text{Me} \\
\end{align*}
\]

81% ee, 80%
Cu Catalyzed Enantioselective Conjugate Additions

chiral ligand: 

\[
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{NHBu}
\]

1.0 mol % \((\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6\)
2.4 mol % 55,
3 equiv \(\text{Bu}_2\text{Zn}, -30^\circ\text{C}\)

98% ee, 92%
Established MonoPhos Ligands in Catalytic Asymmetric Hydrogenation

Review:
Berg, Feringa, Minnaard
Synthesis of Phosphoamidite Ligands

Figure 2. Liquid handling robot in glove box. (Stock solutions on the left. In the middle, the oleophobic filter on a vacuum manifold. On the right the tray with vials in which ligands, metals and substrates are mixed.)
Table 1. Comparison of library ligands with purified ligands.

<table>
<thead>
<tr>
<th></th>
<th>Purified ligands</th>
<th>Library ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conv. [%]</td>
<td>ee [%]</td>
</tr>
<tr>
<td>Ib</td>
<td>8</td>
<td>46</td>
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<tr>
<td>Id</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>Ii</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>Im</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

Figure 4. Parallel synthesis and screening of monodentate phosphoramidites in asymmetric hydrogenation.
Mass Spec Screening

Advantages:

- High sensitivity.
- Minimal requirements on sample quality.
- Mild ionization method (electrospray) preserves structural information.
- Ideal for the detection of charged intermediates.
Pd Catalyzed Kinetic Resolution of Allylic Esters

A/B ratio directly reflects the selectivity of the catalyst.
How to differentiate A vs B with MassSpec?
- Pseudo racemates.
1a + 1b

1a: Ar = 4-methylphenyl
1b: Ar = 4-ethylphenyl

2 mol% [PdL₂] \[\text{M}^+\text{CEt(CO₂Et)}_2\]
\[\text{M}^+ = [\text{Na}([15] \text{crown-5})]^+]\]

\[\begin{align*}
\text{PdL}_2 & \quad \text{PdL}_2 \\
\text{A} & \quad \text{B}
\end{align*}\]

\[\begin{align*}
\text{L}_2 = & \quad \text{RO₂S} \\
& \quad \text{RO₂S}
\end{align*}\]

3: R = 2-naphthyl
Screening a Mixture of Catalysts

S factors calculated closely match with ESI-MS data (<10 % deviation).

Pfaltz, ACIEE, 2007, 43, 2498
Preparation and Screening of a Mixture of Quasi-diastereomeric Catalysts

Pfaltz, JACS, 2008, 130, 3234
Conclusion

• Combinatorial approach in the development of catalytic system is still developing, in terms of new types of ligands, libraries of ligands, and screening methods.
  - Facile synthesis of ligands is still the bottleneck.

• Ideally, combinatorial libraries of catalysts will resolve the dilemma of “high generality” and “high effectiveness”.
  - Screen for the optimum in a large toolkit for a specific transformation.