Combinatorial Approaches to Chiral Catalyst Discovery

Florian Binder
I. Idea

Classical Approach

Diversity Approach

Combinatorial Approaches to Chiral Catalyst Discovery
II. Strategy: Two Tiered Development

1. Catalyst discovery
   Screen for reactivity
2. Optimization
   Screen for selectivity
1. Catalyst discovery

Reaction conditions? Catalyst?
1. Catalyst discovery

1.1 Parameters

Reaction conditions:
- Temperature
- Solvent
- Reaction time
- Mol % metal-ligand

Catalyst:
- Metal-salts
- Ligands
1. Catalyst discovery

1.1 Parameters

Catalyst
Metal-salts
Ligands
1. Catalyst discovery

1.2. Catalyst

Metal-salts (5)
- Al$(i$-PrO)$_3$
- Ba$(i$-PrO)$_2$
- Ti$(i$-PrO)$_4$
- Hf$(i$-PrO)$_4$
- Zr$(i$-PrO)$_4$

Ligands (10)

Combinatorial Approaches to Chiral Catalyst Discovery
1. Catalyst discovery

1.2. Catalyst

Ligands (10)

R=A...J
1. Catalyst discovery

1.2. Catalyst

Metal-salts (5)
- Al(i-PrO)₃
- Ba(i-PrO)₂
- Ti(i-PrO)₄
- Hf(i-PrO)₄
- Zr(i-PrO)₄

Ligands (10)

Combinatorial Approaches to Chiral Catalyst Discovery
**Metal-library (5)**

1. Al $^{3+}$  
   +10Ligands  
2. Ba $^{2+}$  
   +10Ligands  
3. Ti $^{4+}$  
   +10Ligands  
4. Hf $^{4+}$  
   +10Ligands  
5. Zr $^{4+}$  
   +10Ligands

**Ligand-library (10)**

1. Ligand A  
   +5metals  
2. Ligand B  
   +5metals  
3. Ligand C  
   +5metals  
   ⋮  
10. Ligand J  
   +5metals

**Background (5)**

1.1. Catalyst discovery
1.3. Indexed grid

---

*Combinatorial Approaches to Chiral Catalyst Discovery*
1. Catalyst discovery

1.3. Indexed grid

Information on the LAC of 20 reactions 50 individual metal-ligand complexes
1. Catalyst discovery

1.4. Results

Metal-Library

Ligand-Library

Combinatorial Approaches to Chiral Catalyst Discovery
1. Catalyst discovery

1.4. Results

Metal-Library \( \downarrow \) [Ti(OiPr)$_4$] \n
Ligand-Library

\[ \begin{align*}
\text{Ligand Structure} & \quad \text{resin} \\
\text{t-Bu} & \quad \text{OH} \\
\text{t-BuO} & \quad \text{resin}
\end{align*} \]
1. Catalyst discovery

1.5. Results

Combinatorial Approaches to Chiral Catalyst Discovery
2. Ligand optimization

Representational search strategy

Combinatorial Approaches to Chiral Catalyst Discovery
2. Ligand optimization

2.1 Positional scanning

Combinatorial Approaches to Chiral Catalyst Discovery
2. Ligand optimization

2.2 Results

3-fluorosalicylaldehyde

O-tert-butythreonine

Tert-leucine
2. Ligand optimization

2.2 Results

26 % ee

3 x 20 = 60 catalysts

89 % ee

(95:5 ratio)
IV. Restrictions

- Doubtable assumptions (additivity, cooperativity)
- Background effects
- Limited to immobilized ligands
- Screening of large libraries for chiral catalysts
V. Advantages

• Reduce number of synthetic steps, time, costs
• Wealth of data on reactivity and selectivity:
  ➢ Mechanistic parameters can be generated
  ➢ Facilitates the development of new catalysts
• Serendipity: unexpected catalytic effects may appear
Conclusion

• *Classical approaches*:  
  A priori decisions to determine which collection of catalysts needs to be prepared

• *Combinatorial approaches*:  
  Well-suited if little mechanistic data is available
References


• *High-Throughput Strategies for the Discovery of Catalysts*, Ken D. Shimizu, Marc L. Snapper, and Amir H. Hoveyda,

• *Combinatorial Chemistry Approach to Chiral Catalyst Engineering and Screening: Rational Design and Serendipity*, Kuiling Ding, Haifeng Du, Yu Yuan, and Jiang Long,
Thank you