Asymmetric Enamine Catalysis

The First Conceptualization of Asymmetric Enamine Catalysis:

\[
\begin{align*}
\text{O} & + \text{H}\text{C} & \xrightarrow{30 \text{ mol}\%} \text{O} \\
\text{H} & \text{N} & \text{C} & \text{O} & \text{2} & \text{H} & \text{3} & \text{0} & \text{m} & \text{o} & \text{l}\% \\
\text{D} & \text{M} & \text{S} & \text{O} & \text{N} & \text{O} & \text{2} & \text{H} & \text{O} & \text{6} & \text{8}\% & \text{7} & \text{5}\% \text{ ee} \\
\text{0} & \text{m} & \text{o} & \text{l}\% & \text{D} & \text{M} & \text{S} & \text{O} & \text{N} & \text{O} & \text{2} & \text{H} & \text{O} & \text{6} & \text{8}\% & \text{7} & \text{5}\% \text{ ee} \\
\end{align*}
\]


This concept has been successfully applied to:

Asymmetric Aldol Reactions
Asymmetric Michael Reactions
Asymmetric Mannich Reactions
Asymmetric α-Functionalization of Carbonyl Compounds
Asymmetric γ-Functionalization of Carbonyl Compounds


Despite the great advancements already made with regard to catalyst amounts (e.g., <1% loadings have already been occasionally realized!), very high turnover numbers might be considered yet another challenge.

--- Benjamin List
Enamine Catalysis with Low Catalyst Loadings – High Efficiency via Kinetic Studies

*XXXX*, xxx, 000

Hong Ren
10-31-09
Today’s Focus

How Did They Carry Out the Kinetic Study?

How Did the Results Guide Them to Further Decrease the Catalyst Loading?
Today’s Focus

How Did They Carry Out the Kinetic Study?

The Tool + The Model + Understanding of Chemical Kinetics

How Did the Results Guide Them to Further Decrease the Catalyst Loading?
The Tools for the Kinetic Study

*in-situ* FTIR

- Real time, *in situ*, quantitative analysis
- Easy to upgrade
- Wide temperature and pressure range
- Fully automated with integrated analysis
- Wide range of vessel sizes
- Wide wave number range

Single Reactor

MultiMaxIR™

https://admin.emea.acrobat.com/_a55714086/p55719895/
The Model for the Kinetic Study

No side products formed

No catalyst deactivation takes place

No additives are necessary

Chemical Kinetics

Kinetics – how fast does a reaction proceed?

*Reaction rate* is the change in the concentration of a reactant or a product with time (M/s).

Instantaneous rate = rate for specific instance in time

\[
\frac{\Delta[A]}{\Delta t} = \text{slope of tangent}
\]

Average Rate = \(-\frac{\Delta[A]}{\Delta t}\)  \[\Delta[A] = \text{change in concentration of A over time period } \Delta t\]

Instantaneous rate = rate for specific instance in time

Rate Law

The rate law expresses the relationship of the rate of a reaction to the rate constant and the concentrations of the reactants raised to some powers.

\[ aA + bB \rightarrow cC + dD \]

\[ \text{Rate} = k [A]^a[B]^b \]

reaction is \textit{a}th order in \( A \)
reaction is \textit{b}th order in \( B \)
reaction is \((a + b)\)th order overall

\[ \log (\text{rate}) = \log k + a \log [A] + b \log [B] \]

\[ \log (\text{rate}_0) = \log k + a \log [A_0] + b \log [B] \]

\[ y = a x + b \]

\[ a = \text{slope} = 0.98 \]

Reaction Order on Catalyst

Reaction progress was monitored by the N-O stretching vibration.

Product formation [4] vs. time at different catalyst loading (0.25 – 1.50 mol% = 1.1 – 6.6 mM) and log/log plot of initial rate vs. catalyst concentration [1]

A first order dependence of the reaction on catalyst

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000

0.3 order at lower concentration, zero order at higher concentration

Enamine Formation was not rate determining step. Attempts to detect the enamine were not successful.

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000
Reaction Order on Nitrostyrene

Wet conditions: (10 mol% H$_2$O)

Dry conditions:

The rate order of nitrostyrene depends on H$_2$O. It was observed that the addition of the H$_2$O slowed down the reaction.

Summary of the Kinetic Study

Rate Limiting Steps

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000
How to Further Decrease the Catalyst Loading

Reduction of the H$_2$O ------ Because H$_2$O slows down the reaction.

Increase the equivalent of nitrostyrene ------ Because it is involved in the rate limiting step.

```
entry | mol % | ratio 2:3 | cond  | time (h) | conv (%) | syn/anti | ee (%)  
----- | ----- | -------- | ----- | -------- | -------- | -------- | ------- 
  1   | 1     | 1.5:1    | std   | 16       | quant    | 98:2     | 97      
  2   | 1     | 1:1.5    | std   | 7        | >95      | 98:2     | 97      
  3   | 1     | 1:1.5    | dry   | 3        | >95      | 97:3     | 97      
  4   | 1     | 1:1.2    | dry   | 5        | >95      | 95:5     | 97      
  5   | 0.1   | 1:1.5    | dry   | 48       | ~90      | 94:6     | 97      
```

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000
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How to Further Decrease the Catalyst Loading

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How to Further Decrease the Catalyst Loading

Reduction of the $\text{H}_2\text{O}$ ------ Because $\text{H}_2\text{O}$ slows down the reaction.

Increase the equivalent of nitrostyrene ------ Because it is involved in the rate limiting step.

![Chemical reaction diagram]

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Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000
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\end{align*}
\]

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. J. Am. Chem. Soc. XXXX, xxx, 000
## Substrate Scope

![Chemical reaction diagram]

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<tr>
<th>entry</th>
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A Chemist does not always need to work on sophisticated chemistry to realize his dream.