Streamlining Reaction Discovery and Development Through Kinetic Analysis

Professor Ryan D. Baxter
Outline: Direct Comparison of Initial Rates vs. Reaction Progression

- Order in [ynal], [silane], [Ni]
- 30 experiments

- Order in [substrate], [olefin], [Pd]
- Catalyst stability, product inhibition, relative binding constants
- 12 experiments
Nickel Catalyzed Reductive Couplings (Montgomery Group, –2010)

J. Am. Chem. Soc. 2004, 126, 3698
J. Am. Chem. Soc. 2007, 129, 9568
J. Am. Chem. Soc. 2008, 130, 9662

Org. Lett. 2006, 8, 4441
J. Am. Chem. Soc. 2008, 130, 8132

R¹ = alkyl, aryl
J. Am. Chem. Soc. 2006, 128, 14030
Angew. Chem. Int. Ed. 2010, 49, ASAP
R¹ = OMe
J. Am. Chem. Soc. 2009, 131, 17024

(+)–alopumiliotoxin-339B
J. Am. Chem. Soc. 2000, 122, 6950

(+)–testudinariol A


Distinguishing Between Mechanistic Possibilities

- Crossover experiment probes cleavage of Si–H/D bond
- Silane scrambling seems to be ligand-dependent
- Mechanism for silane?

\[ \text{O} = \text{O} \]

\[ \text{Et}_3\text{Si-D} + \text{Pr}_3\text{Si-H} \rightarrow 10\% \text{Ni(COD)}_2 \rightarrow \text{Ligand} \]

\[ \text{R}_3\text{SiO} \]

\[ x = \text{D}, > 98\% \]
\[ x = \text{H}, > 98\% \]

\[ \text{Et}_3\text{SiO} \]
\[ \text{Pr}_3\text{SiO} \]

\[ \text{Et}_3\text{SiO} \]
\[ \text{Pr}_3\text{SiO} \]

\[ J. \text{Am. Chem. Soc. 2004, 126, 3698} \]
In Situ Monitoring of Aldehyde/Alkyne Couplings

\[ \text{"Ynal"} \quad 1.0 \text{ equiv} \quad \text{Et}_3\text{SiH} \quad 2.0 \text{ equiv} \quad \text{Ni(COD)}_2 \quad 10\% \quad \text{PCy}_3 \quad \text{Et}_3\text{SiO} \quad \text{H} \quad \text{Ph} \]

THF (0.1 M) \quad -25 \degree C \quad 86\% \quad ~10\% \text{ crossover with PCy}_3

\[ \begin{align*}
\text{Et}_3\text{SiO} & \quad \text{X} & \quad \text{Ph} \\
\text{Pr}_3\text{SiO} & \quad \text{X} & \quad \text{Ph} \\
\text{X} &= \text{D}, \quad 90\% \quad & \quad \text{X} &= \text{D}, \quad 11\% \\
\text{X} &= \text{H}, \quad 10\% \quad & \quad \text{X} &= \text{H}, \quad 89\%
\end{align*} \]
In Situ Monitoring of Aldehyde/Alkyne Couplings

"Ynal"

1.0 equiv 2.0 equiv

\[ \text{Et}_3\text{Si-H} + 10\% \text{Ni(COD)}_2 + 20\% \text{PCy}_3 \rightarrow \text{Et}_3\text{SiO} \]

THF (0.1 M) -25 °C

1.0 equiv 2.0 equiv 86%

"Ynal" ~10% crossover with PCy3

\[ \text{X = D, 90\%} \quad \text{X = H, 10\%} \]

\[ \text{X = D, 11\%} \quad \text{X = H, 89\%} \]

\[ \text{O} \quad \text{Ph} \quad \text{Et}_3\text{Si-H} \quad \text{10\% Ni(COD)}_2 \quad \text{Et}_3\text{SiO} \quad \text{H} \quad \text{Ph} \]

\[ \text{86\%} \]

\[ \text{Pr}_3\text{SiO} \quad \text{X} \quad \text{Ph} \quad \text{X = D, 11\%} \quad \text{X = H, 89\%} \]

\[ \text{X = D, 90\%} \quad \text{X = H, 10\%} \]

\[ \text{O} \quad \text{Ph} \]

\[ \text{METTLER TOLEDO} \]

\[ y = 0.1836x \quad R = 0.9942 \]

\[ \text{Absorbance} \quad \text{[Substrate] (mol/L)} \]

\[ \text{AU} \quad \text{Wavenumber (cm}^{-1}) \]
Rate Dependence on Catalyst Concentration

O
Ph
Et₃Si-H⁺
X% Ni(COD)₂
Et₃SiO⁻
H
Ph₂X% PCy₃
THF (0.1 M)
-25 °C
1.0 equiv 2.0 equiv

"Ynal"

\[ \Delta \text{[Ynal]/\Delta time (M/s)} * 10^{-5} \]

\[ \text{[Ni(COD)₂] (mol/L)} \]

[0.00, 0.01, 0.02, 0.03]

[0, 4, 8, 12]

[J. Am. Chem. Soc. 2011, 133, 5728]
Rate Dependence on Substrate Concentration

O
Ph
Et
3
Si
-H

10% Ni(COD)₂
20% PCy₃
THF (0.1 M)
-25 °C

0.5–1.0 equiv 2.0 equiv

"Ynal"

[\text{Ynal}] (\text{mol/L})

\begin{align*}
\text{[Ynal] (mol/L)} & \quad 0.00 & 0.04 & 0.08 & 0.12 & 0.16 \\
\text{[Ynal] time (M/s) } * 10^{-5} & \quad 0 & 4 & 8 & 12 \\
\end{align*}
Rate Dependence on Silane Concentration

\[ \text{"Ynal" \ + \ Et}_3\text{Si-H} \rightarrow \text{Et}_3\text{SiO} - \text{Ph} \]

1.0 equiv \ 1.0–4.0 equiv

\[ 10\% \text{ Ni(COD)}_2 \]
\[ 20\% \text{ PCy}_3 \]
\[ \text{THF (0.1 M)} \]
\[ -25^\circ C \]

\[ \Delta [\text{Ynal}] / \Delta \text{time (M/s)} \times 10^{-5} \]

\[ [\text{Et}_3\text{SiH}] \text{ (mol/L)} \]

0.1 M Et\textsubscript{3}SiH
0.2 M Et\textsubscript{3}SiH
0.3 M Et\textsubscript{3}SiH
0.4 M Et\textsubscript{3}SiH

\[ [\text{Ynal}] \text{ (M)} \]

0.00
0.04
0.08
0.12

0 1000 2000 3000

J. Am. Chem. Soc. 2011, 133, 5728
Role of Silane in Reductive Coupling

Et₃Si-H + 10% - Ni(COD)₂ → Et₃SiO Ph

Et₃Si-D + THF (0.1M, 45 °C) → Et₃SiO Ph

(1.0 equiv) (3.0 equiv each)

H/D = 50:50
KIE = 1.00
(1.0 equiv)

No observable kinetic isotope effect

But what about crossover?!
A Tale of Two Catalytic Cycles

products without crossover

products with crossover

Et₃SiO LₙNi⁺⁺Ph

H

Ni(0)Lₙ

Et₃Si-H

Pr₃Si-H

products without crossover

Et₃SiO LₙNi⁺⁺Ph

H

Ni(0)Lₙ

Et₃Si-H

Pr₃Si-H

products with crossover

Summary of Nickel-Catalyzed Reductive Coupling

"Ynal"  
1.0 equiv  +  Et₃Si-H  
2.0 equiv  \[ \xrightarrow{10\% \text{Ni}(\text{COD})_2} \]  
20% PCy₃  \[ \xrightarrow{} \]  THF (0.1 M)  \[-25 \degree C\]  
Et₃SiO  \[ \xrightarrow{\text{86}\%} \]  86%  
X = D, 90%  
X = H, 10%  
X = D, 11%  
X = H, 89%  

- Order in [ynal], [silane], [Ni]  
- 30 experiments  
- 1/2 of a Ph.D...
Traditional Kinetic Analysis: Initial Rates

- A large excess of B ensures a small change in concentration during the first portion of the reaction (~10%)
- The majority of the acquired data is not factored into rate
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[A] (mol/L)

Initial Rates, \( \frac{[A]}{t} \)

note \([A]_0\) for a subsequent reaction
Traditional Kinetic Analysis: Initial Rates

- A large excess of B ensures a small change in concentration during the first portion of the reaction (~10%)
- The majority of the acquired data is not factored into rate

\[ \text{Initial Rates, } \frac{[A]}{t} \]

\[ \text{note } [A]_0 \text{ for a subsequent reaction} \]
Reaction Progress Kinetic Analysis (RPKA)

- Reagents A and B are present in synthetic concentrations
- As A reacts with B, the concentration difference between them should remain unchanged
- EXCESS: $[A]_0 - [B]_0$

now we can compare data from experiments where both A and B are changing

synthetic conditions!
Reaction Progress Kinetic Analysis (RPKA)

Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions
Donna G. Blackmond

Keywords:
catalysis - in situ measurements - kinetics - reaction kinetics - reaction mechanisms

In memory of Keith J. Laidler (1916-2003)
C-H Activation of Arylacetic Acids

\[
\begin{align*}
\text{CO}_2\text{K} & \quad + \quad \text{CO}_2\text{n-Hex} \\
1 & \quad + \quad 2 \\
\text{CF}_3 & \quad \text{CO}_2\text{K} & \quad \text{CF}_3 & \quad \text{CO}_2\text{n-Hex} \\
\end{align*}
\]

\[
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
1 & \quad \text{CF}_3 & \quad \text{CO}_2\text{n-Hex} \\
\]

\[
\begin{align*}
Pd(II)-\text{cat.} & \quad \text{Ligand} \\
\text{t-AmylOH, 90°C} & \quad 1 \text{ atm O}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
1 & \quad \text{CF}_3 & \quad \text{CO}_2\text{n-Hex} \\
\end{align*}
\]

\[
\begin{align*}
[\text{Pd}^{	ext{II}}] & \quad [\text{Pd}^{	ext{II}}] \\
[\text{Pd}^{	ext{II}}] & \quad [\text{Pd}^{	ext{II}}] \\
[\text{Pd}^{	ext{II}}] & \quad [\text{Pd}^{	ext{II}}] \\
[\text{Pd}^{	ext{II}}] & \quad [\text{Pd}^{	ext{II}}] \\
\end{align*}
\]

\[
\begin{align*}
\text{Boc-Val-OH} & \quad \text{Ac-Val-OH} \\
\text{Boc-Ile-OH} & \quad \text{Ac-Ile-OH} \\
\text{~30-fold rate increase with amino acid ligands} \\
\end{align*}
\]
C-H Activation of Arylacetic Acids

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \quad 1 \\
\text{H} & \quad \text{CO}_2\text{n-Hex} \quad 2 \\
\text{Pd(II)-cat.} & \quad \text{Ligand} \\
\text{KHCO}_3 & \\
\text{t-AmylOH, 90°C} & \quad 1 \text{ atm } \text{O}_2 \\
\end{align*}
\]

ReactIR™ 45M fitted with a dicomp ATR probe

- absorbance data converted directly to concentration
- NMR calibration confirmed IR measurement of reaction progression

J. Am. Chem. Soc. 2012, 134, 4600
C-H Activation of Arylacetic Acids: Same Excess

\[
\text{CF}_{3}\text{CF}_{3} + \text{CO}_{2}\text{H} \quad \text{Pd(II)-cat. Ligand} \quad \text{KHCO}_{3} \\
\Longrightarrow \quad \text{CF}_{3}\text{CO}_{2}\text{K} + \text{CO}_{2}\text{n-Hex} \\
t-\text{AmylOH, 90°C} \quad 1\text{ atm O}_2
\]

"Same Excess" Protocol

<table>
<thead>
<tr>
<th>Reaction</th>
<th>([1]_0) (M)</th>
<th>([2]_0) (M)</th>
<th>Excess (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>0.222</td>
<td>0.278</td>
<td>0.056</td>
</tr>
<tr>
<td>b)</td>
<td>0.111</td>
<td>0.167</td>
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C-H Activation of Arylacetic Acids: Same Excess

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- The values of [1] and [2] will coincide when reaction a) is at 50% conversion and reaction b) is at 0% conversion
- Look for graphical overlay
C-H Activation of Arylacetic Acids: Same Excess

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J. Am. Chem. Soc. 2012, 134, 4600
C-H Activation of Arylacetic Acids: Same Excess, Product Added

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<th>$[1]_0$ (M)</th>
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- Look for graphical overlay
C-H Activation of Arylacetic Acids: Same Excess, Product Added

```
\[
\begin{align*}
\text{CF}_3 \text{CO}_2\text{K} & + \text{CO}_2\text{n-Hex} \\
\text{CF}_3 \text{CO}_2\text{K} & \xrightarrow{\text{Pd(II)-cat. Ligand, KHCO}_3, \text{t-AmylOH, 90}^\circ\text{C}} \text{CF}_3 \text{CO}_2\text{n-Hex}
\end{align*}
\]
```

NEGATIVE-ORDER

**"Same Excess" Protocol**

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- The values of [1] and [2] will coincide when reaction a) is at 50% conversion and reaction b) is at 0% conversion

- Look for graphical overlay

**PRODUCT INHIBITION!**

C-H Activation of Arylacetic Acids: Different Excess

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
\text{H} & \quad \text{CO}_2\text{n-Hex} \\
\text{2} & \quad \text{Pd(II)-cat. Ligand} \\
\text{t-AmylOH, 90°C} & \quad \text{1 atm O}_2 \\
\rightarrow & \quad \text{CF}_3 \\
\text{CO}_2\text{K} & \quad \text{CO}_2\text{n-Hex} \\
\end{align*}
\]

NEGATIVE-ORDER

- DIFFERENT concentrations of

- SAME concentration of

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
\text{H} & \quad \text{CO}_2\text{n-Hex} \\
\end{align*}
\]

J. Am. Chem. Soc. 2012, 134, 4600
C-H Activation of Arylacetic Acids: Different Excess

\[
\text{CF}_3\text{C}_6\text{H}_4\text{CO}_2\text{K} + \text{CO}_2\text{C}_8\text{H}_{17} \xrightarrow{\text{Pd(II)-cat. Ligand, KHCO}_3, t-\text{AmylOH, 90}^\circ\text{C}, 1 \text{ atm O}_2} \text{CF}_3\text{C}_6\text{H}_4\text{CO}_2\text{K} + \text{CO}_2\text{C}_8\text{H}_{17}
\]

**ZERO-ORDER**

- **DIFFERENT** concentrations of \(\text{CO}_2\text{C}_8\text{H}_{17}\)
- **SAME** concentration of \(\text{CF}_3\text{C}_6\text{H}_4\text{CO}_2\text{K}\)

**NEGATIVE-ORDER**

\(\text{CF}_3\text{C}_6\text{H}_4\text{CO}_2\text{K}\)

**J. Am. Chem. Soc. 2012, 134, 4600**
C-H Activation of Arylacetic Acids: Different Excess

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
\text{H} & \quad \text{CO}_2\text{n-Hex} \\
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
\text{H} & \quad \text{CO}_2\text{n-Hex}
\end{align*}
\]

- SAME concentration of \#1
- DIFFERENT concentrations of \#2

\[\text{Pd(II)-cat. Ligand} \quad \text{KHCO}_3 \quad t-\text{AmylOH, 90}^\circ\text{C} \quad 1 \text{ atm O}_2\]

J. Am. Chem. Soc. 2012, 134, 4600
C-H Activation of Arylacetic Acids: Different Excess

\[
\begin{align*}
\text{CF}_3\text{CO}_2\text{K} \quad \text{1} \\
\text{H} \\
\text{CO}_2\text{K} \\
\text{2}
\end{align*}
\]

\[
\begin{align*}
P\text{d}(\text{II})-\text{cat.} \\
\text{Ligand} \\
\text{KHCO}_3 \\
t\text{-AmylOH, 90°C} \\
1 \text{ atm } \text{O}_2 \\
\text{NEGATIVE-ORDER}
\end{align*}
\]

- SAME concentration of \text{CO}_2\text{n-Hex}

- DIFFERENT concentrations of \text{CO}_2\text{n-Hex}

Lower rate at higher \text{CO}_2\text{n-Hex}
C-H Activation of Arylacetic Acids: Different Excess

\[
\begin{align*}
\text{CF}_3 & \quad \text{CO}_2\text{K} \\
\text{H} & \quad \text{CO}_2\text{n-Hex}
\end{align*}
\]

\[
\begin{align*}
\text{Pd(II)-cat.} & \quad \text{Ligand} \\
\text{KHCO}_3 & \quad \text{t-AmylOH, 90°C} \\
1 \text{ atm O}_2 & \quad \text{NEGATIVE-ORDER}
\end{align*}
\]

---

**Graph:**

- **X-axis:** [Pd] (mM)
- **Y-axis:** rate (mM/min)
- **Equation:** Boc-Val-OH

---

*J. Am. Chem. Soc. 2012, 134, 4600*
C-H Activation of Arylacetic Acids: Different Excess

\[
\begin{align*}
\text{CF}_3 & \text{CO}_2\text{K} \quad 1 \\
\text{H} & \quad \text{2} \\
\text{CF}_3 & \text{CO}_2\text{K} \quad \text{NEGATIVE-ORDER}
\end{align*}
\]

\[
\begin{align*}
\text{C-H Activation of Arylacetic Acids: Different Excess} \\
\text{Pd(II)-cat. FIRST-ORDER Ligand} \\
t-\text{AmylOH, 90°C, 1 atm O}_2 \\
\text{CO}_2\text{K} \quad \text{NEGATIVE-ORDER}
\end{align*}
\]

- Linear dependence of reaction rate on Pd concentration

FIRST-ORDER

\[\text{J. Am. Chem. Soc. 2012, 134, 4600}\]
Piecing Together the Mechanistic Puzzle: Driving Forces

- How do we incorporate this rate information into the previously proposed catalytic cycle?
Piecing Together the Mechanistic Puzzle: Driving Forces

Negative Order in Product

First-Order in Pd

Zero-Order in 1

N-H activation step

C-H activation step

J. Am. Chem. Soc. 2012, 134, 4600
Piecing Together the Mechanistic Puzzle: Off Cycle Catalyst Binding

\[
\begin{align*}
\text{2b} & \quad \text{AcO} \quad \text{Pd} \quad \text{HN} \quad \text{PG} \\
\text{3b} & \quad \text{AcO} \quad \text{Pd} \quad \text{HN} \quad \text{PG}
\end{align*}
\]

Negative Order in 2

Negative Order in Product

\[
\frac{K_{eq,2b}}{K_{eq,3b}} = \frac{[2]_b - [2]_a}{[3]_a - [3]_b} \approx 2
\]

product binding is stronger than substrate binding!

\[\text{(rate)}_a = \text{(rate)}_b\]
Piecing Together the Mechanistic Puzzle: Role of the Ligand

\[
Pd(OAc)_{2} + \text{Me}_{3}\text{C}O\text{H} \xrightarrow{\text{Fast Reaction}} \text{CF}_{3}\text{C}O\text{K} \xrightarrow{\text{Very Slow Reaction}} \text{Pd(OAc)}_{2} + \text{CO}_{2}\text{n-Hex}
\]
Piecing Together the Mechanistic Puzzle: Role of the Ligand

\[ \text{Pd(OAc)}_2 + \text{Me} - \text{Me} - \text{CO}_2\text{HN-Boc} \rightarrow \text{Fast Reaction} \]

- Identified by 2-dimensional NMR exchange spectroscopy (EXSY)
- Unfavorable geometry for C-H insertion

\[ \text{Pd(OAc)}_2 + \text{Me} - \text{Me} - \text{CO}_2\text{n-Hex} \rightarrow \text{Very Slow Reaction} \]
Summary of C-H Activation of Arylacetic Acids

- A complete description of rate-behavior was achieved through simple graphical analyses, without any special data treatment.
- A revised catalytic cycle was proposed based on kinetic data.

- 2-Dimensional NMR spectroscopy provided support for a less active catalyst species in the absence of amino-acid ligands.

J. Am. Chem. Soc. 2012, 134, 4600
Summary: Initial Rates vs. Reaction Progression

- Order in \([\text{ynal}], [\text{silane}], [\text{Ni}]\)
- 30 experiments

- Order in \([\text{substrate}], [\text{olefin}], [\text{Pd}]\)
- Catalyst stability, product inhibition, relative binding constants
- 12 experiments
Acknowledgements

Nickel Chemistry

M. Taylor Haynes, Ph. D.
Professor John Montgomery*

Palladium Chemistry

David Sale, Ph. D.
Keary M. Engle, Ph. D.
Professor Jin-Quan Yu
Professor Donna G. Blackmond*