Catalytic Reaction Profiling: Kinetics

Outline:

I. Introduction: Fundamentals of Catalytic Kinetics
   a. Michaelis-Menten Kinetics
II. Reaction Profiling
   a. Reaction Progress Kinetic Analysis
   b. Variable Time Normalization Analysis
III. Case studies
   a. Kinugasa Reaction
   b. Rational Ligand Design
   c. C-H Activation

Donna Blackmond

Topics not convered:
- Computer-Assisted Reaction Kinetics
- Classical Kinetic approaches.

Key references:

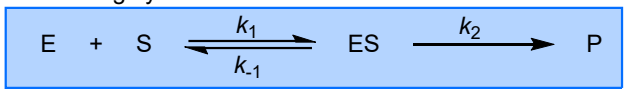
- Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711.
- Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302.
- Blackmond, D. G. *J. Am. Chem. Soc.* **2015**.
- Burés, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 16084.
- Blackmond, D. G. In *Trends in Process Chemistry*, **2008**, 455.

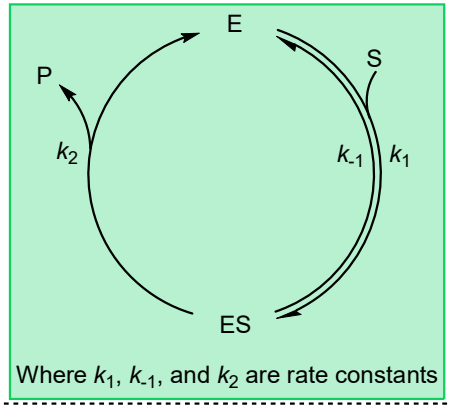
See also: Helfferich, F. *Kinetics of Homogenous Multistep Reactions,* **2001,** Vol. 38.

"[Classical kinetic methods] may evoke memories of dull undergraduate laboratory sessions, where the task of compiling tables of log values feels far removed indeed from the excitement of encountering a new organic transformation."
-Donna Blackmond

Michaelis-Menten Derivation:

Consider the following system:





Where k_1, k_{-1}, and k_2 are rate constants

A refresher on the derivation of the Michaelis-Menten Equation:

$$\frac{d[ES]}{dt} = k_1[S][E]$$ Rate of enzyme-substrate complex formation (1)

$$\frac{d[S]}{dt} = k_{-1}[ES]$$ Rate of degredation (2)

$$\frac{d[P]}{dt} = k_2[ES]$$ Rate of product formation (3)

- Assuming that (3) is rate limiting, a quantity for unmeasurable [ES] must be solved.
- Defining the concentration of availble enzyme as:

$$[E] = [E_t] - [ES] \quad (4)$$

- Where $[E_t]$ is the total concentration of enzyme
- Applying the Steady State Approximation: rate of formation = rate of degredation

$$k_1[S][E] = k_1[S]([E_t] - [ES]) = k_1[S][E_t] - k_1[S][ES] = k_2[ES] + k_{-1}[ES] \quad (5)$$

- Therefore:

$$[ES] = \frac{k_1[S][E_t]}{k_{-1} + k_2 + k_1[S]} = \frac{k_1[S][E_t]}{\frac{k_{-1} + k_2}{k_1} + [S]} \quad (6)$$

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Michaelis-Menten Kinetics Continued:

$$[ES] = \frac{k_1[S][E_t]}{k_{-1} + k_2 + k_1[S]} = \frac{k_1[S][E_t]}{\frac{k_{-1} + k_2}{k_1} + [S]} \quad (6)$$

- To further simplify (6), define V_{max} and K_m :

$$V_{Max} = k_2[E_t] \quad (7) \qquad K_M = \frac{k_{-1} + k_2}{k_1} \quad (8)$$

- V_{max} is the maximum rate allowed by the system
- K_m is the Michaelis constant, the [S] at which the system velocity is 50% of V_{max}.
  - This constant describes the binding affinity of [S] to [E].
- Substituting [ES] into (3):

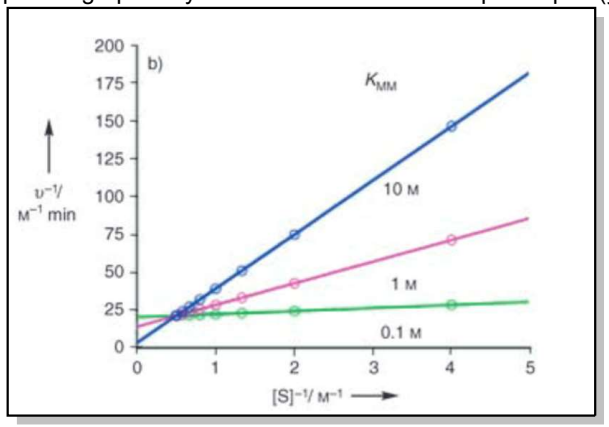
$$\frac{d[P]}{dt} = k_2[ES] = \frac{k_2[S][E_t]}{\frac{k_{-1} + k_2}{k_1} + [S]} = \frac{V_{Max}[S]}{K_M + [S]} \quad (3')$$

Graphical Methods

- K_m and V_{max} can be determined by modifying (3'):

$$\frac{d[P]}{dt} = \frac{V_{Max}[S]}{K_M + [S]} = \frac{K_M}{V_{Max}[S]} + \frac{1}{V_{Max}} \quad (10)$$

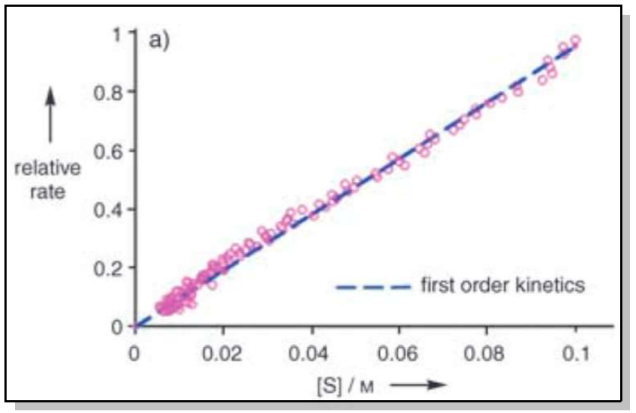
- This can be plotted graphically as a Lineweaver-Burk reciprocal plot (y=mx+b)



Reaction Progress Kinetic Analysis (RPKA)

- Reaction Progress Kinetic Analysis (RPKA) allows the rapid determination of reaction kinetics from catalytic systems, primarily through graphical rate equations.

The graph below shows an example of a graphical rate equation:



- RPKA requires *in situ* and accurate data measurement
- Ideally, this would be accomplished by isothermal reaction calorimetry (ITC)
- However, this can also be accomplished by *in situ* IR

	Differential (ITC)	Integral (IR)
Eq.	$\dot{q} = (\Delta H_{rxn} V) Rate$	$A = \varepsilon bc$
Parameter Measured:	Rate	Conversion
Data Processed:	Conversion	Rate

TA Instruments TAM IV

Metler Toledo's ReactIR

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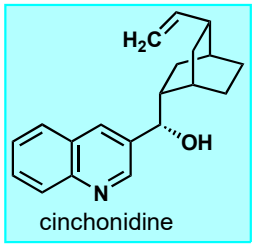
A Simple Example: Asymmetric Hydrogenation



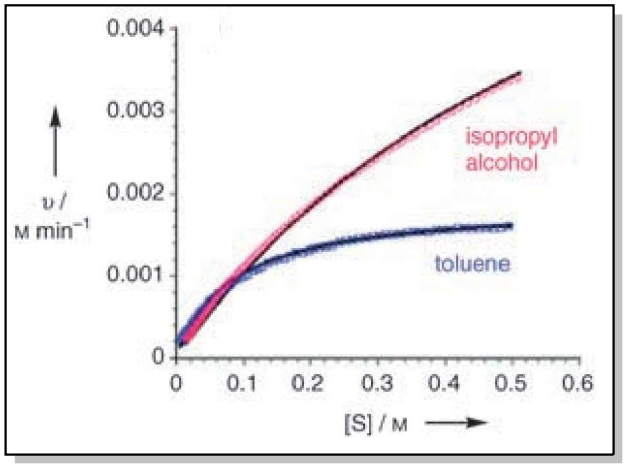
- RPKA can be used with Michalis-Menten kinetics to describe simple systems.
- The kinetics for the above constant pressure hydrogenation were measured

Rate equation:

$$\frac{d[P]}{dt} = \frac{V_{Max}[S]}{K_M + [S]}$$

- k_2 is replaced by k',
a pseudo-first order constant

$$k' = k_2[H_2]$$

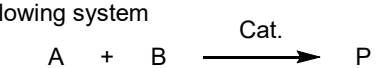


Key Findings:

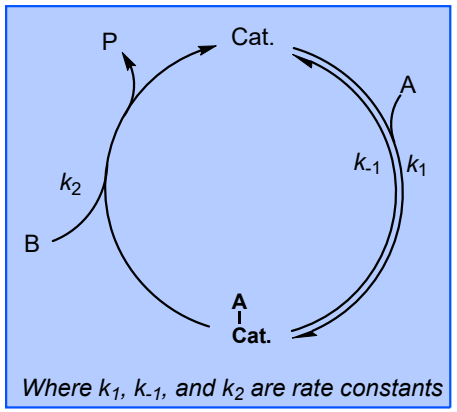
- This process required only two experiments. Classical experiments would require more
- The concavity can qualitatively describe the curve
  - i.e. the reaction has more-positive order kinetics in *i*PrOH than in PhMe.
- A Lineweave-Burk plot can be used to determine information about turnover number, and substrate-catalyst binding.
- Most systems catalytic systems do not follow as simple as a system as this

Two substrate catalytic Systems:

- Consider the following system



- One potential mechanism could be:



Where k_1, k_{-1}, and k_2 are rate constants

- Returning to the Michaelis-Mentan equation, the earlier rate equation can be adapted for two substrate systems:

$$v = \frac{v_{Max}[A]}{K_M + [A]} \quad (11)$$

$$v_{max} = k_2[B][Cat_t] \quad (12)$$

$$K_M = \frac{k_{-1} + k_2[B]}{k_1} \quad (13)$$

- The system is now dependent on two variables which complicates reaction kinetics from a classical perspective even further.
- Moreover, traditional methods would require flooding experiments, which are undesirable as they do not represent the system under synthetically meaninful conditions.
- RPKA can remedy this issue with a parameter defined as "excess."

$$['excess'] = [B]_0 - [A]_0 \quad (14)$$

- Where $[B]_0$ and $[A]_0$ are the initial concentrations of B and A.
- Considering the fact that [A] and [B] change over time, but that they are linked to reaction stoichiometry, [B] can be defined as:

$$[B] = ['excess'] + [A] \quad (15)$$

-(15) now eliminates the added variable that comes with a second substrate.

Catalytic Reaction Profiling: Kinetics

Bi-Substrate Catalytic Systems--Applying "Excess":

- Rewriting the Michaelis-Menten equation with two substrates:

$$v = \frac{k_1 k_2 [A][B][Cat_t]}{k_{-1} + k_1[A] + k_2[B]} \quad (16)$$

- Dividing (16) by k_{-1}:

$$v = \frac{a[A][B][Cat_t]}{1 + b[A] + c[B]} \qquad a = \frac{k_1 k_2}{k_{-1}}, b = \frac{k_1}{k_{-1}}, c = \frac{k_2}{k_{-1}} \quad (17)$$

- Substituting [B] from (15) into (17)

$$v = \frac{a'[Cat_t]([1]["excess"] + [1]^2)}{1 + b'[1]} \quad (18)$$

$$a' = \frac{k_1 k_2}{k_{-1} + k_2["excess"]}, b' = \frac{k_1 + k_2}{k_{-1} + k_2["excess"]}$$

- Equation (18) has eliminated the other variable, allowing rate to be easily measured, as only the concentration of one species must be known

Other Cases to Consider--Simplifying Equation (16):

- Equation 16 can be simplified by making assumptions about the pre-dominant active species in solution

Dominating Species	Dominant Term in Denominator	Observed rate eq.
Cat-A	b	$v = k_2[2][Cat_t]$
Cat	c	$v = k_1[1][Cat_t]$
None	neither	$v = \frac{\frac{k_1 k_2}{k_{-1}}[A][B][Cat_t]}{1 + \frac{k_1}{k_{-1}}[A] + \frac{k_2}{k_{-1}}[B]}$

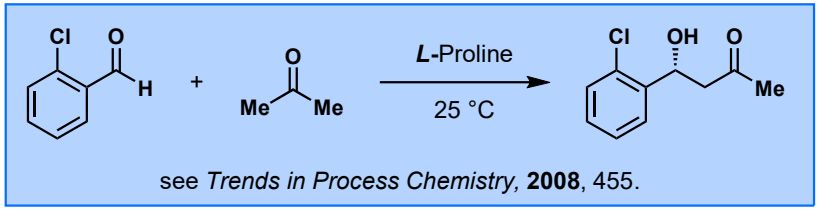
Same "Excess"--Probing Catalyst Stability

- Using the same "excess" but different initial concentrations, reactions can be carried-out as if they were starting from a different point in the reaction timeline
- This can be used to probe catalyst stability and product inhibition

Workflow:

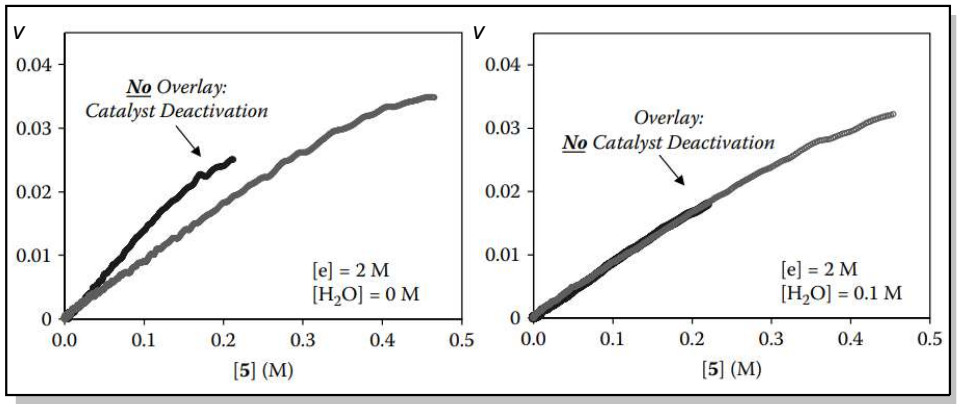
- Run a minimum of two experiments with the same "excess."
- Overlay the curves (rate vs concentration).
- If there is no overlay, product inhibition or catalyst deactiviation is present.
- To probe product inhibition, run an experiment with the same ["excess"] as one of the previous two and add a small amount of product.
- Overlay the curves.
- If the reaction overlays on the curve with the same initial concentration, product inhibition is responsible for the decrease in rate.

Example: Proline-Catalyzed Aldol Reaction:



see *Trends in Process Chemistry,* **2008**, 455.

- This reaction was noted to have possible catalyst deactivation via the formation of oxazolidinones.
- However, by addition of water, deactivation could be prevented.



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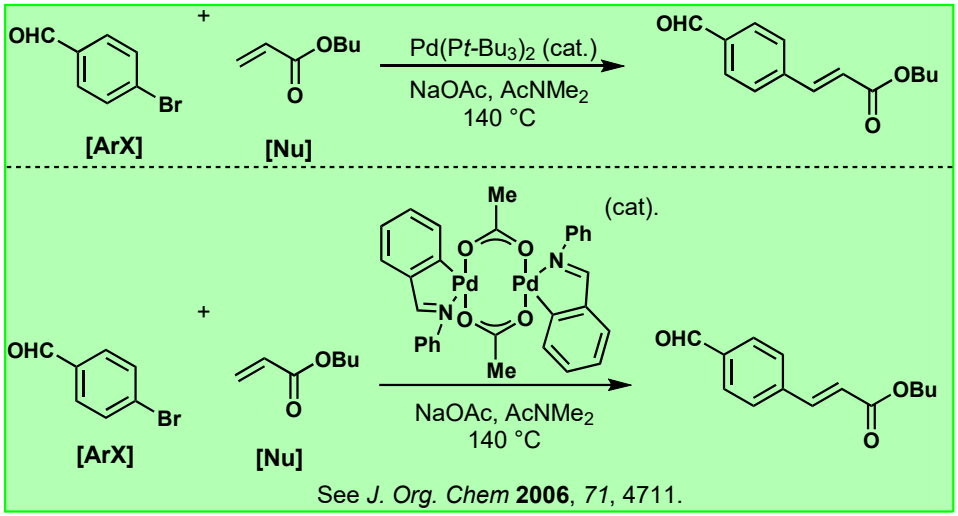
Different "Excess":

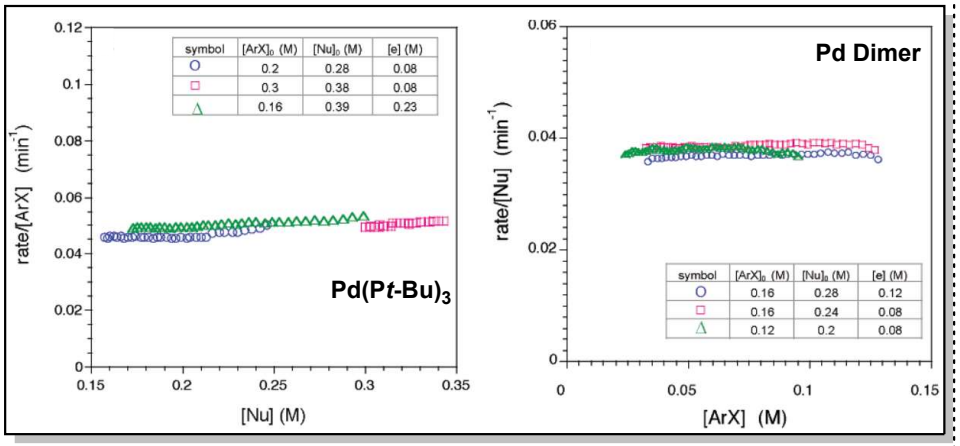
- To probe reaction order, reactions run at "different" excess can be conducted.
- This can be done a variety of ways, but usually, one substrate is held constant while the other is changed.

Ex. Heck Reaction



See *J. Org. Chem* **2006**, *71*, 4711.

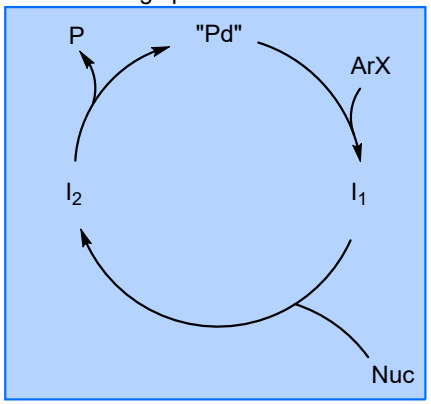
- The following plots were obtained



- Overlay suggests the reaction is independent of the x-axis
- The first Heck reaction first order in [ArX] near-zero order in [Nu]
- The second Heck reaction displays first order in [ArX], zero order in [Nu]

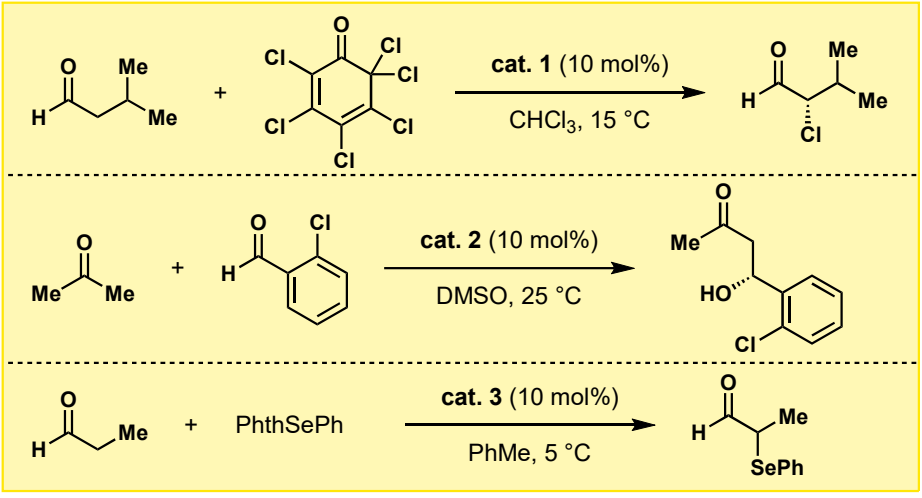
Exploring the Nature of the Catalytic Species:

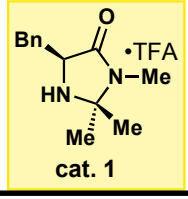
- RPKA can suggest plausible resting species.

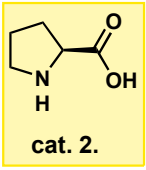


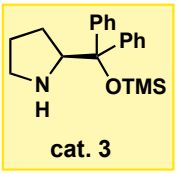
- In the previous example: the resting species for A is "Pd"; for B, I_1
- RPKA can also probe resting species without probing for order

Ex. Organo-catalyzed α–functionalization:



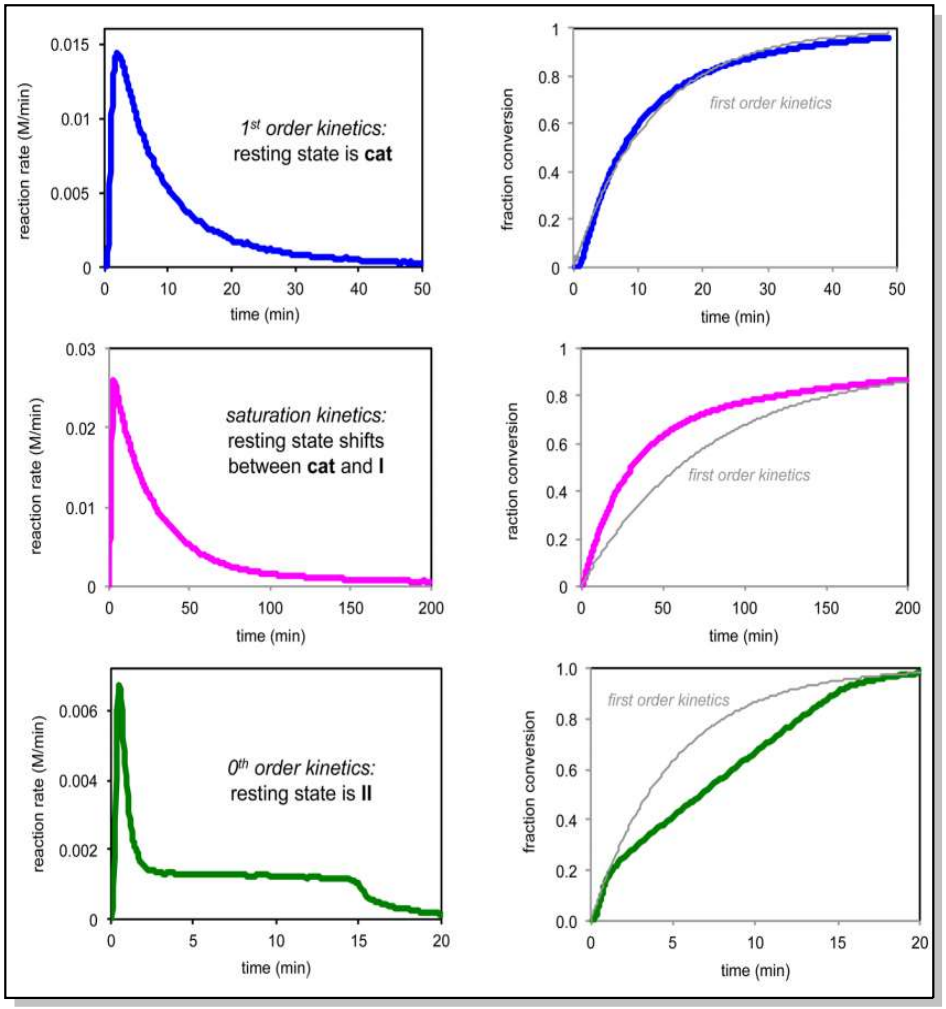






Catalytic Reaction Profiling: Kinetics

Catalyst Resting State Continued:



- Key take-home: By analyzing the global kinetic rate, useful information about the resting species can be obtained without analyzing any intermediates

Probing Catalyst Order:

- While RPKA can be used to probe catalyst order, a simpler method exists.
- Workflow:
  - Conduct a minimum of two experiments with different [cat.]
  - plot [Cat.]] vs t[cat]^n, where n is the proposed order of reaction
  - Solve for a system where all graphs overlay for a unique *n*.
  - This method does not require *in situ* techniques as rate is not being measured
- This method relies on the fact that [cat.] is not a thermodynamic driving force of the reaction; therefore, [cat.] is constant.

Using a two substrate system general rate law:

$$\frac{-d[A]}{dt} = f([A],[B],kinetic\ const.) * [cat.]_t^{\,n} \quad (18)$$

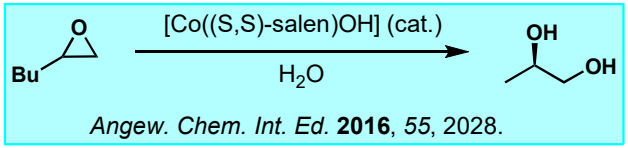
$$\int_{[A]_t}^{[A]_t} f^{-1}([A],[B],kinetic\ const.)d[A] = \int_0^t -[cat]_t^{\,n} dt \quad (19)$$

$$F^{-1}([A]_t,[A]_0,[B]_0,v_A,v_B,kinetic\ const.) = -t[cat]_t^{\,n} \quad (20)$$

$$[A]_t = G\left([A]_t,[A]_0,[B]_0,v_A,v_B,kinetic\ const.,t[cat]_t^{\,n}\right) \quad (21)$$

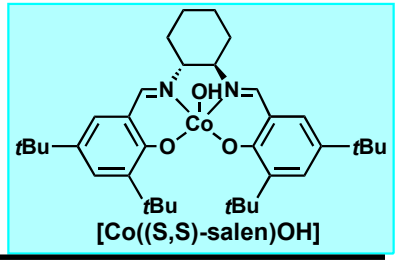
- This demonstates that $t[cat]_t^n$ is a paremeter of a function that describes $[A]_t$

Ex. Jacobsen HKR:



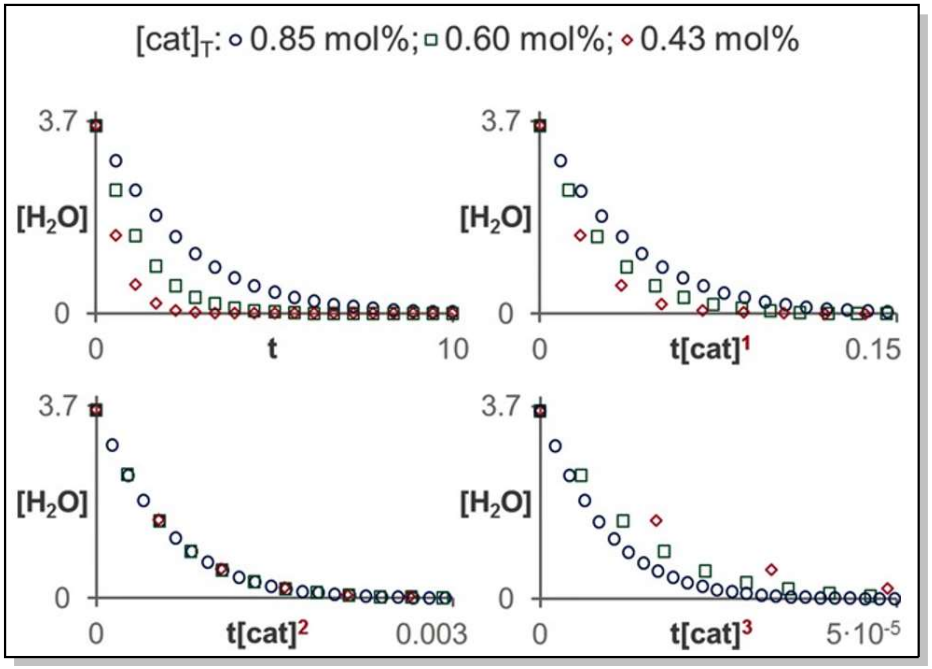
Angew. Chem. Int. Ed. **2016**, *55*, 2028.

- This reaction has been reported to be second order in catalyst.



Catalytic Reaction Profiling: Kinetics

Reaction Order Continued:



- This method is in agreement with 2nd order in catalyst, serving as validation.

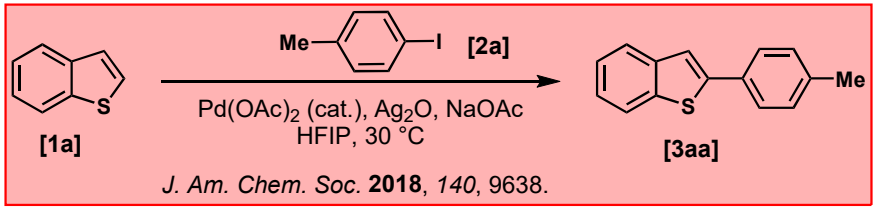
- **Variable Time Normalization Analysis (VTNA):**
  - In this method of order analysis, concentration profiles are the focus.
  - The time axis is replaced by the time integral of [A]^n, a normalization factor
  - Essentially, it normalizes the time between each data point via the avg. [A], removing any kinetic effect from the reaction.

$$-\frac{dA}{dt} = k[A]^{\alpha}[B]^{\beta} = -\frac{dA}{[B]^{\beta}dt} \quad (22)$$

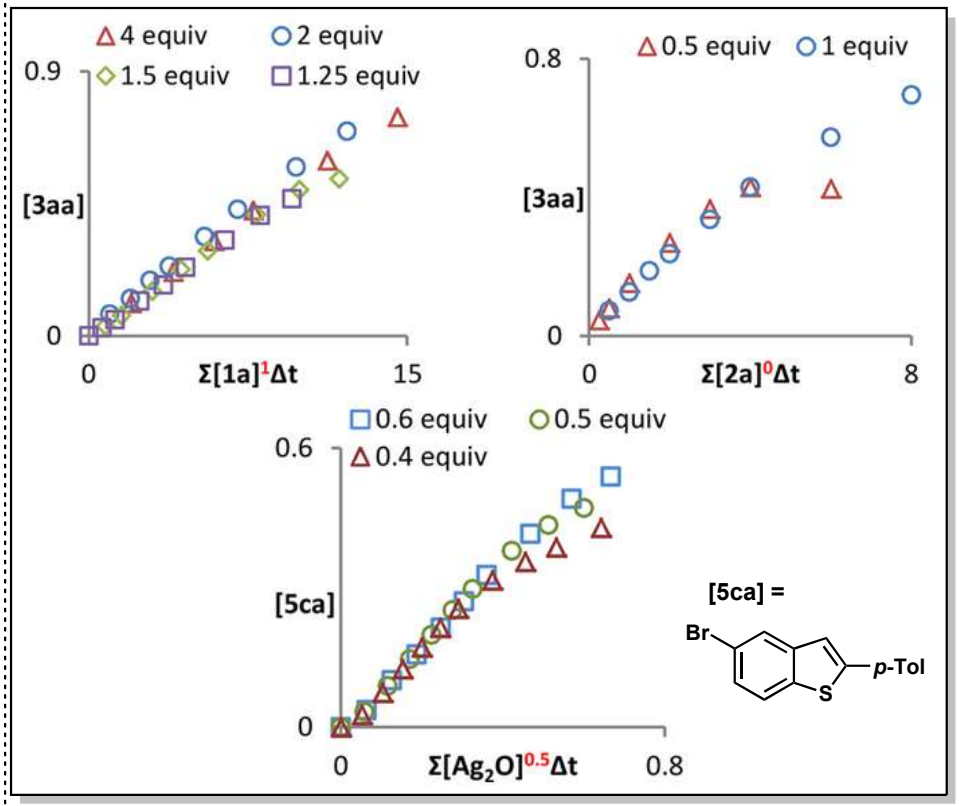
$$\int_0^{t_n} [B]^{\beta}dt \approx \sum_{i=1}^{n} \left(\frac{[B]_i + [B]_{i-1}}{2}\right)^{\beta} (t_i - t_{i-1}) \quad (23)$$

Variable Time Normalization Analysis (VTNA):

Ex. α-arylation of benzo[*b*]thiophenes:



J. Am. Chem. Soc. **2018**, *140*, 9638.

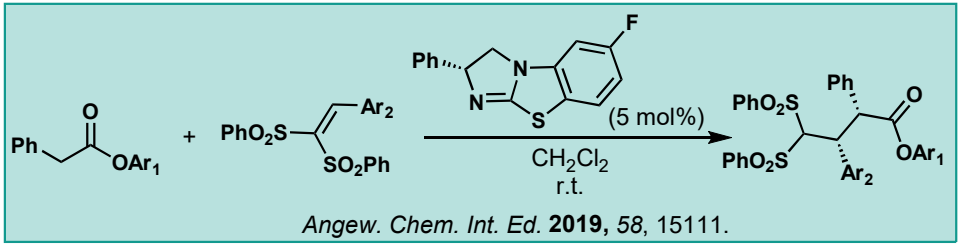


- This method was able to determine the all orders of reactants in a rapid fashion without significant difficulty.
- The major strength of this method is that it doesn't require ITC or *in situ* monitoring: only concentration profiles are required

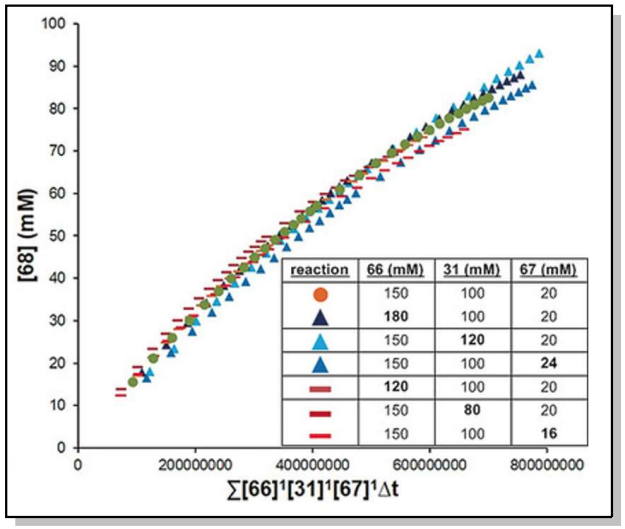
Catalytic Reaction Profiling: Kinetics

Variable Time Normalization Analysis (VTNA) Continued:

- One amazing application of this method is that all reactants can be normalized
- If the orders are correct, a y=x line will be obtained, with a slope of k_{obs}



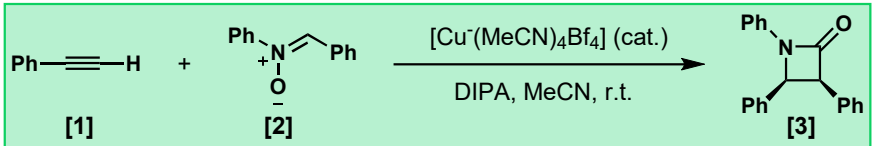
Angew. Chem. Int. Ed. **2019,** *58*, 15111.



- Where [66] is the ester, [31] is the catalyst, [67] is the olefin, and [68] is the product

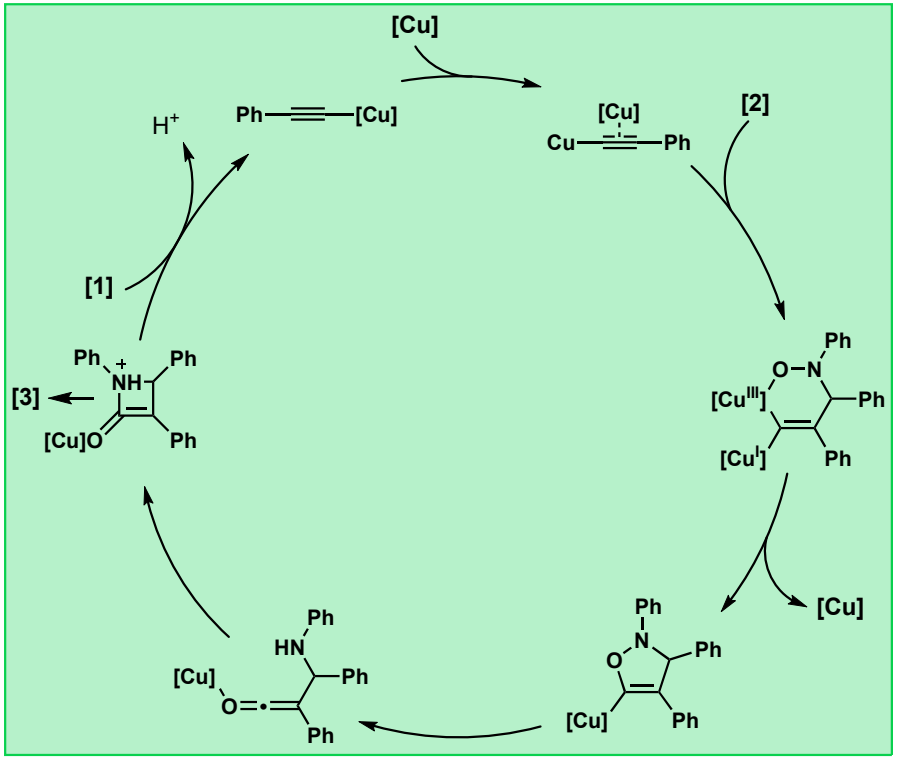
- In Summation:
  - RPKA and VTNA allow kinetic data to be obtained in a minimal amount of experiments
  - Depending on the scenario, both can obtain meaningful information about the overall reaction kinetics, the catalyst stability, and the catalytic resting state.

Case Studies: Evaluation of Kinugasa Reaction



See *J. Am. Chem. Soc.* **2018**, *140*, 9167.

- The following mechanism has been proposed (*J. Org. Chem.* **2015**, *80*, 2649.):

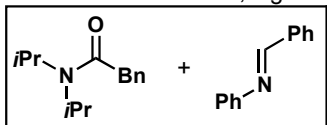


- Computational studies provide significant evidence for this mechanism
- No detailed kinetic analysis had been performed
- RPKA and VTNA used to determine global kinetics.
- Kinetics monitored by: HPLC-MS coupled to a robot

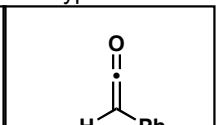
Catalytic Reaction Profiling: Kinetics

Kinugasa Reaction: Byproducts Detected:

-When run with DIPA, significant byproducts were obtained in 1:1 ratio:



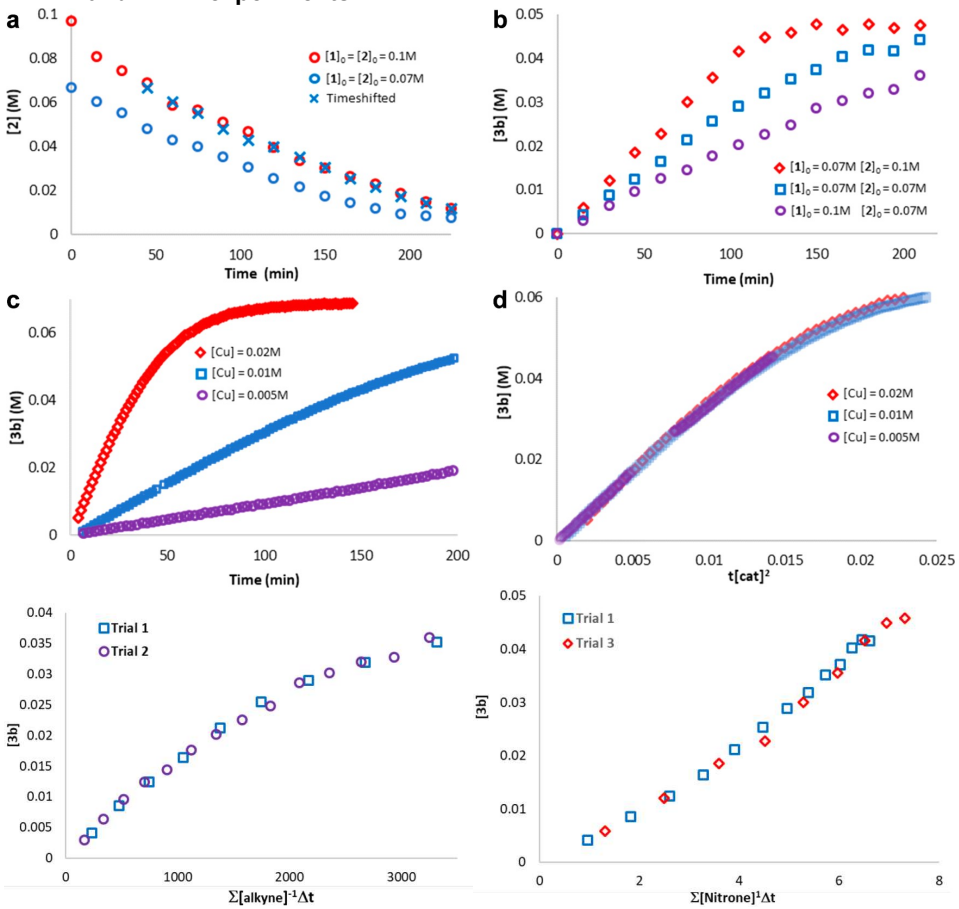
The amide was believed to come from a ketene



Ketene precursor

- Switching to DBU lowered byproduct formation
- increased yield from 17% to 78%
- *trans* lactam obtained

RPKA and VTNA experiments:



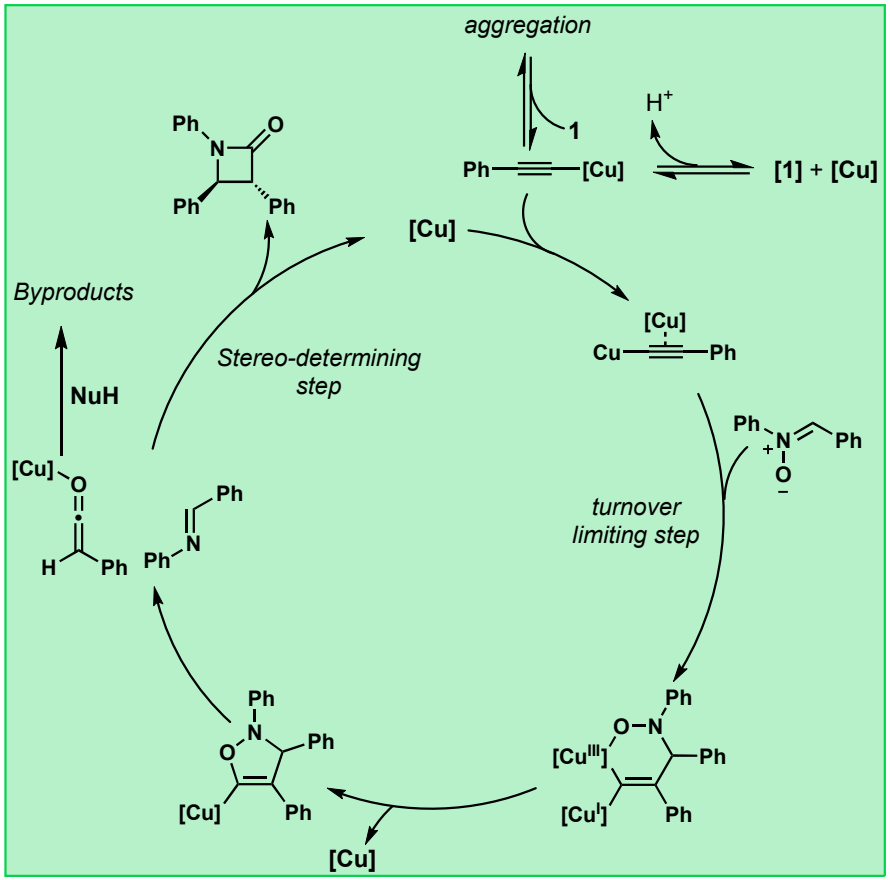
- Same excess experiments (A) show no catalyst decomposition or product inhibition
- Different excess experiments show positive order in [2], negative order [1]
- [Cu] confirmed to be positive, and VTNA suggests an order of 2
- VTNA further confirms order of -1 for [1] and order of 1 [2]

Case Studies: Evaluation of Kinugasa Reaction

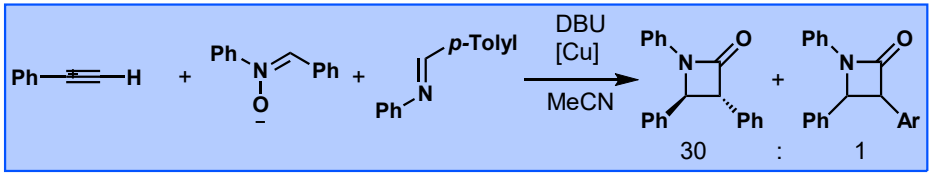
The rate law for this transformation is:

$$\frac{d[3]}{dt} = k_{obs}[1]^{-1}[2]^{1}[Cu]^{2} \quad (24)$$

- Moreover, deuterium labelling of nitrone revealed 2° KIE (0.95)



Evidence for formal [3+2]:



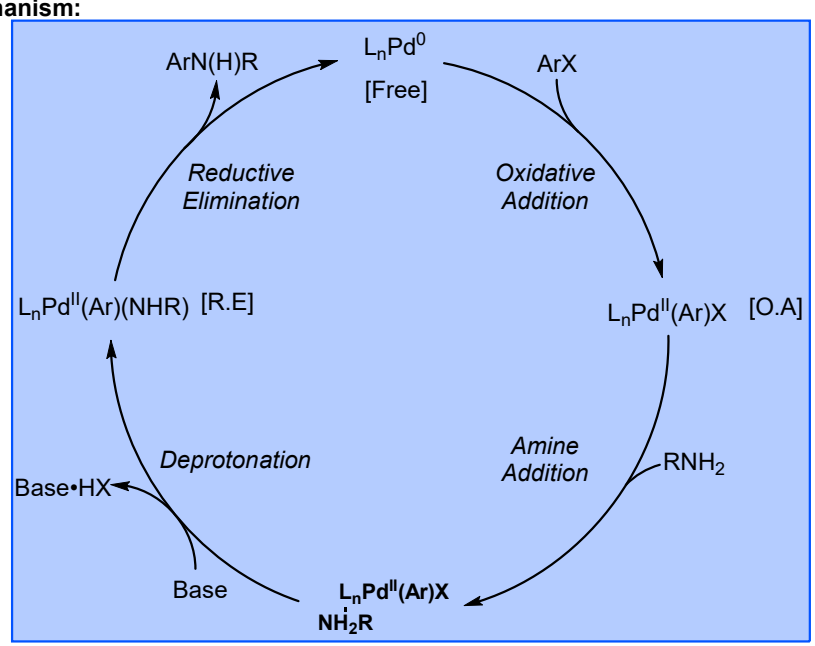
Catalytic Reaction Profiling: Kinetics

Improved Ligand Design *via* RPKA:

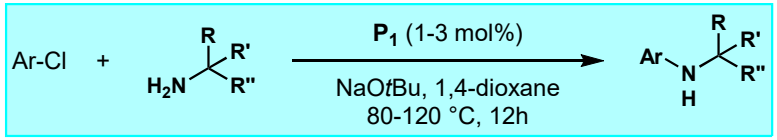
- Buchwald-Hartwig amination of sterically hindered 1° amines is challenging
- To overcome this, kinetic-guided rational design was implemented

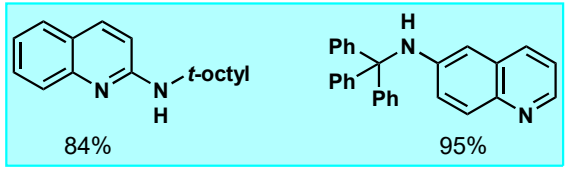
see *J. Am. Chem. Soc.* **2015,** *137*, 3085.

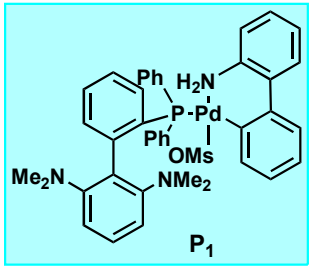
Mechanism:



Reaction of Interest:

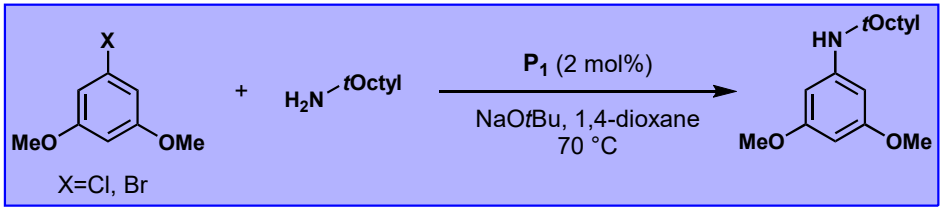


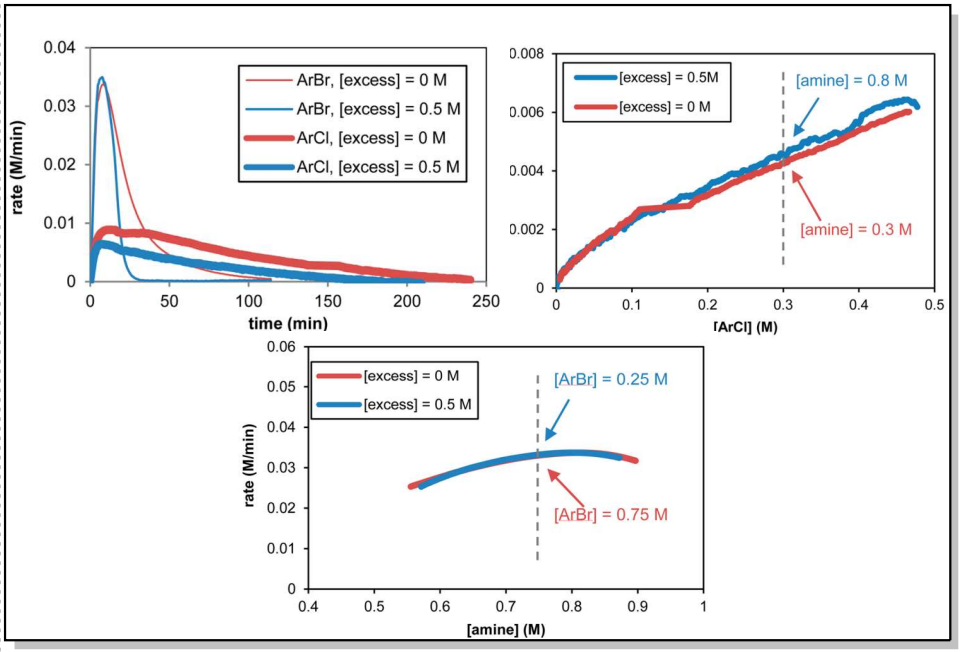




-A ligand screen revealed P_1 as the best pre-catalyst
- Temperatures and loading were still too high
- RPKA was used to explore the kinetics of the reaction with both ArBr and ArCl

RPKA--Round 1:



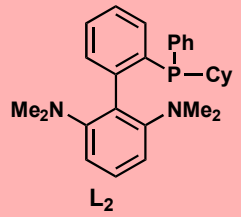


- For ArCl: positive order in [ArCl]; zero order in [Amine]
- For ArBr: zero order in both [ArBr] and [Amine]
  - Saturation kinetics for [excess] = 0M
- Conclusions: resting species for ArCl is [Free]
  resting species for ArBr is [R.E] at high [amine], [O.A.] at low [amine]
- Therefore, design a ligand with faster reductive elimination and oxidative addition

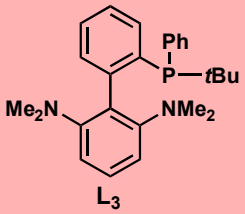
Catalytic Reaction Profiling: Kinetics

Ligand Design Continued:

Potential Candidates:

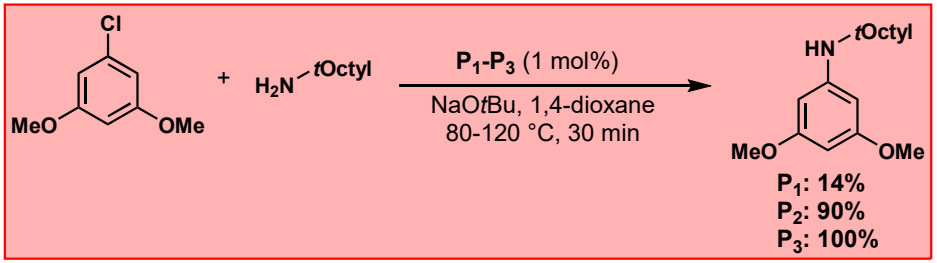


L_2



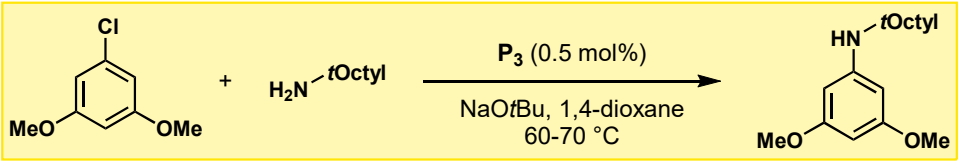
L_3

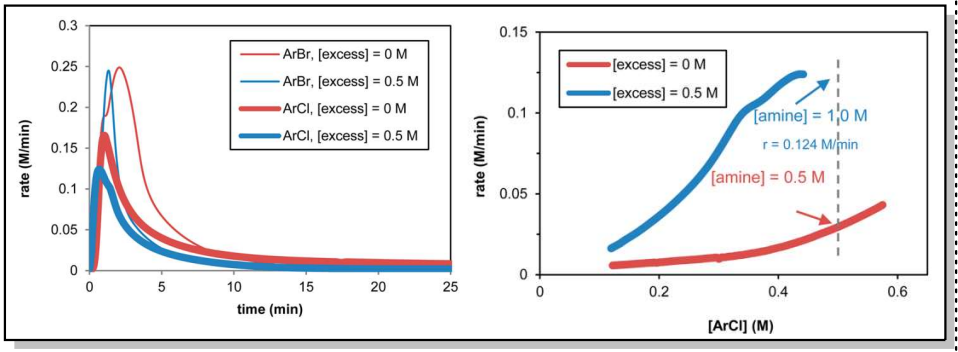
P_2, P_3 (L= L_2, L_3)



- With a better ligand, temperature was lowered to 60-70 °C, loading to .5mol%

RPKA--Round 2:





- Rate is a whole magnitude faster than previous system.
- [ArCl] is still positive order, but amine order is ambiguous
- [ArBr] system remains unchanged: [R.E] is still resting species

Ligand Design Continued:

Determining Amine order:

- Shape of the red curve is indicative of possible catalyst decactivation.
- This can be probed *via* quantitative reasoning of relative rates

$$\frac{r_{blue}}{r_{red}} = \frac{k^{obs}{}_{blue}[amine]^{x}{}_{blue}[ArX]^{y}{}_{blue}}{k^{obs}{}_{red}[amine]^{x}{}_{red}[ArX]^{y}{}_{red}} \quad (25)$$

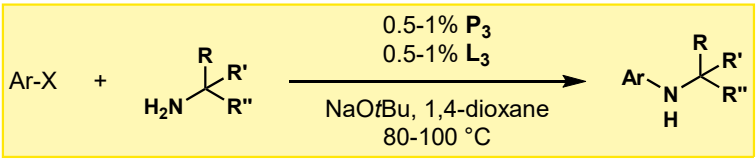
$$\frac{r_{blue}}{r_{red}} = \frac{0.124}{0.025} \approx 5 = \frac{k^{obs}{}_{blue}[amine]^{x}{}_{blue}}{k^{obs}{}_{red}[amine]^{x}{}_{red}} = \frac{k^{obs}{}_{blue}[1.0]^{x}{}_{blue}}{k^{obs}{}_{red}[0.5]^{x}{}_{red}} \quad (26)$$

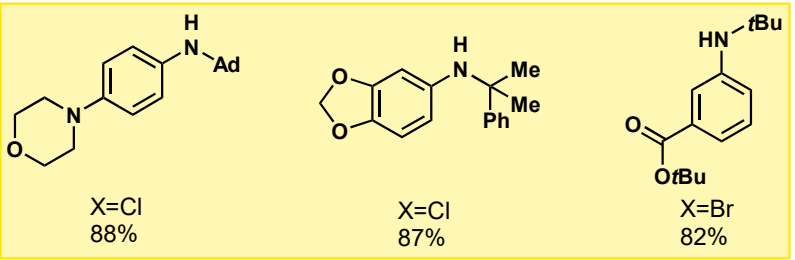
$$if\ k^{obs}{}_{blue} = k^{obs}{}_{red};\ x = 2.35 \quad (27)$$

$$if\ y = 0;\ k^{obs}{}_{blue} = 5k^{obs}{}_{red} \quad (28)$$

- A reaction order of two does not make sense with this system
- The x equation suggests if the order is 0, then the catalyst has been deactivated by a factor of 5. This explanation is more likely than the former.
- Catalyst deactivation is a major problem in the system. RPKA couldn't be used further.

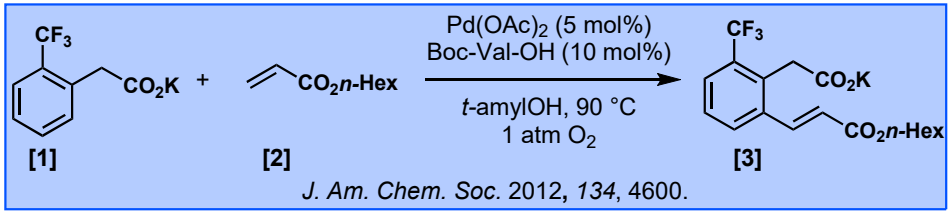
Reaction Scope:





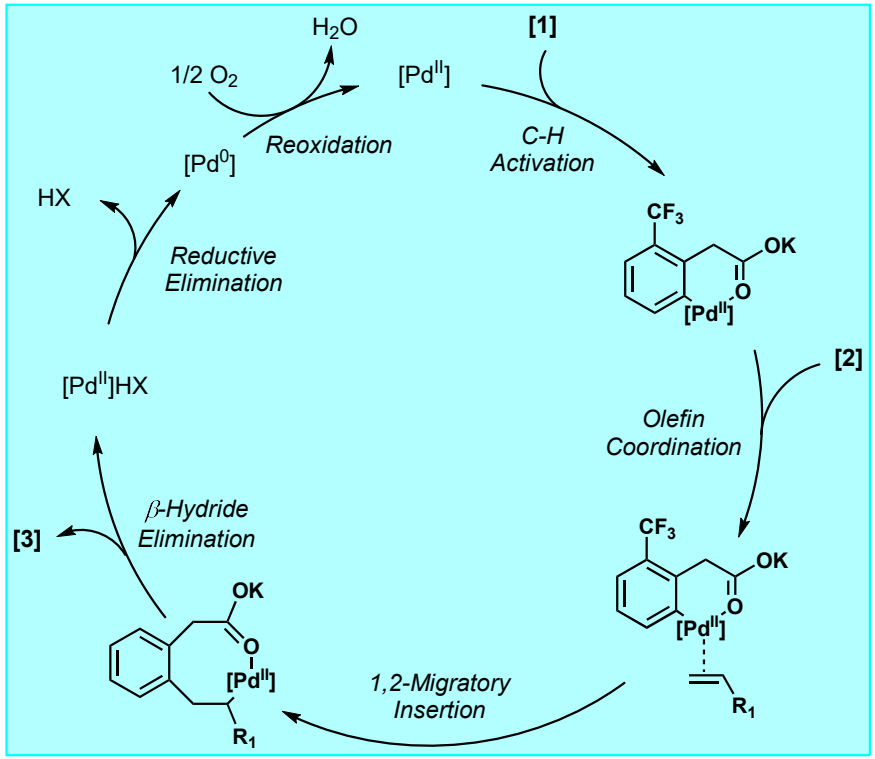
Catalytic Reaction Profiling: Kinetics

C-H Activation:



J. Am. Chem. Soc. 2012, *134*, 4600.

Proposed Mechanism:

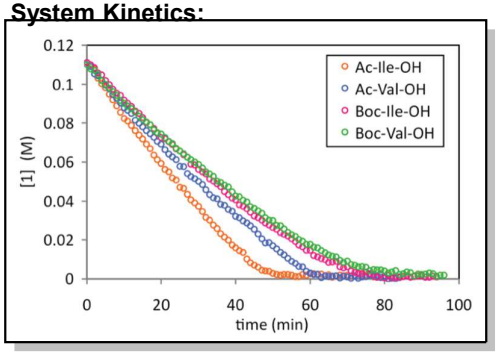


- This system however does not explain why there is a rate increase of a factor of 10 with the mono-protected amino acid ligands
- Kinetic data has not also validated this mechanism

RPKA: Same and Different "Excess":

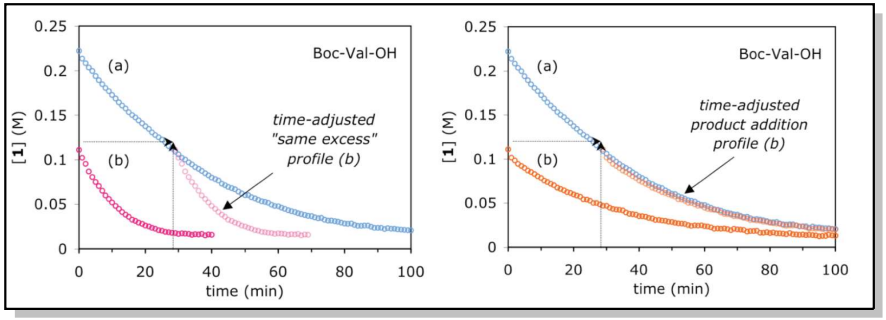
- Initial rate analysis determined that [Pd] is first order O_2 is zero order

System Kinetics:



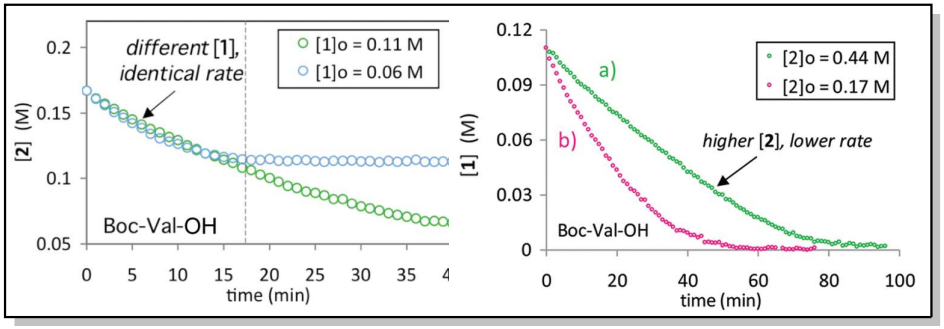
- Overall reaction kinetics appear to be near 0 order

Same "Excess":



- The left graph does not overlay: product inhibition or catalyst deactivation affect rate
- The right graph spikes reaction (b) with product. Overlay suggests product inhibition

Different "Excess":

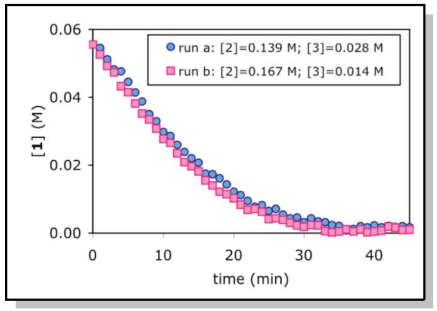


- Reaction is zero order in [1], negative order in [2].

Catalytic Reaction Profiling: Kinetics

Determining an Empirical Order for [3]

- By varying [2] and [3], an order for [3] can be determined



- Because of the overlay, the rate of run a and b are the same. Therefore:

$$rate_a = rate_b = (k'[2]^y[3]^z)_a = (k'[2]^y[3]^z)_b \quad (29)$$

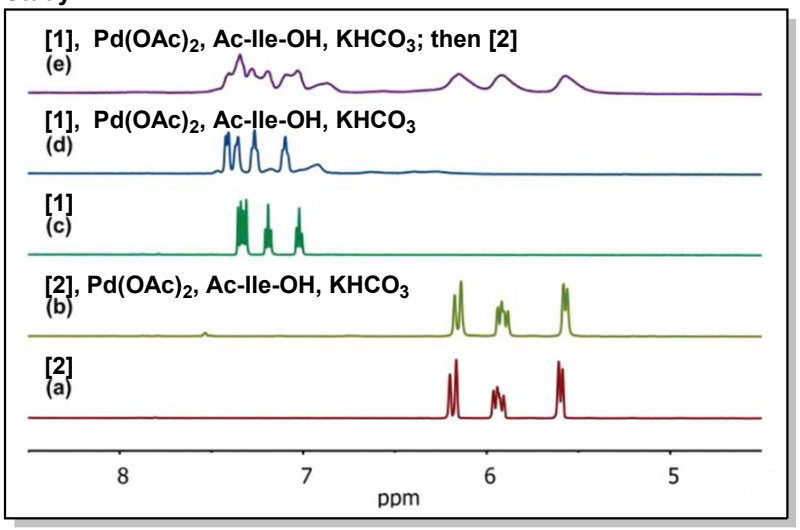
- Where k' is a pseudo order constant
- Plugging in known values leads to z = -0.13
- WIth this data, a power-rate-law can be developed:

$$rate = k'[2]^{-0.5}[3]^{-0.13}[Pd]_{total} \quad (30)$$

Probing the Nature of the Ligand:

- EXSY correlation with $Pd(OAc)_2$ and [1] indicate a 1:1 ratio of two acetate species
  - Addition of [2] to this complex does not lead to product

NMR Study:



Modified Mechanism--Kinetically Relevant Steps: