The Methodology for Mechanistic Study of Rate Determining Step

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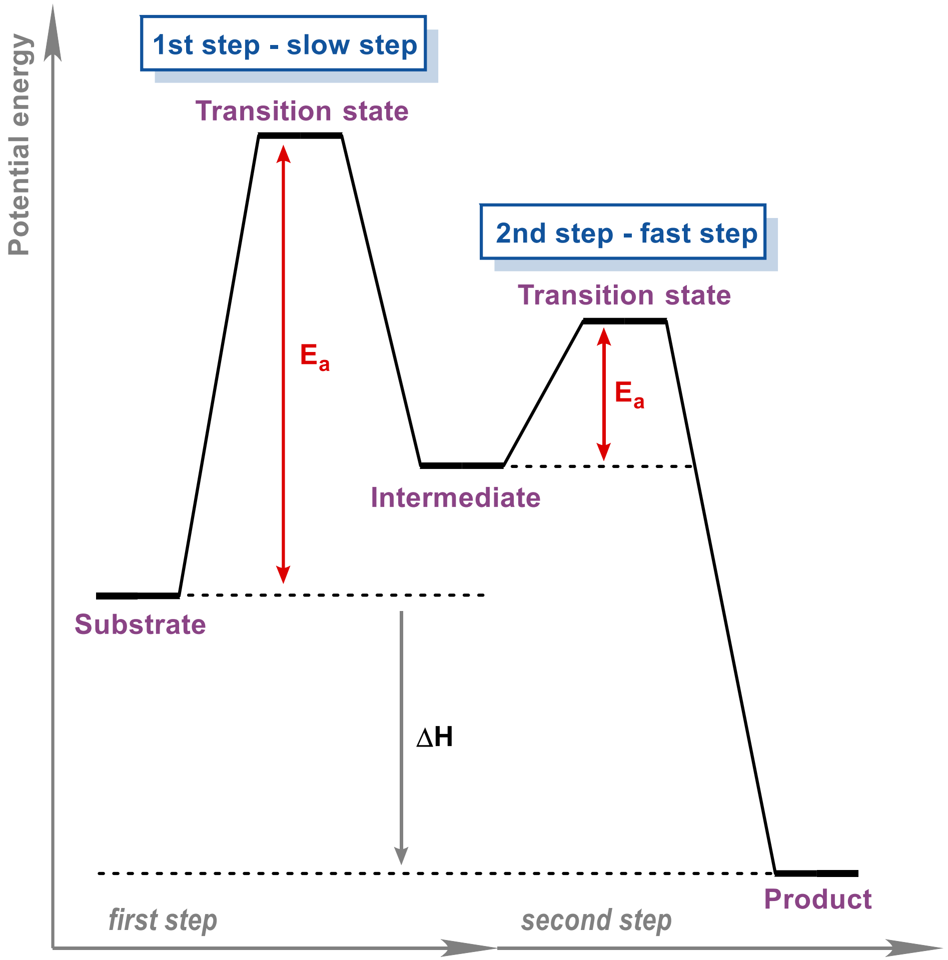
Supervisor: Prof. Jieping Zhu

04-04-2024

Contents

Introduction

Reactions can occur in *more than one step* and it is *the lowest step* that determines the rate of reaction.



The ***rate-determining step*** (RDS) is the slowest step of a chemical reaction that determines the speed (rate) at which the overall reaction proceeds.

The RDS is the step in a reaction mechanism that has the highest activation energy.

It was also called ***rate-limiting step*** or ***turnover-limiting step***.

Introduction

Example 1:

$$\mathbf{NO_2 + CO \rightarrow NO + CO_2}$$

If this reaction occurred in a single step, its reaction rate: $rate = k[NO_2]^1[CO]^1$

In fact, however, the observed reaction rate is **second-order** in NO_2 and **zero-order** in CO,

$\boldsymbol{rate = k[NO_2]^2[CO]^0 = k[NO_2]^2}$.

It includes two elementary steps:

$$NO_2 + NO_2 \rightarrow NO + NO_3 \ (\textit{slow step, rate-determining})$$

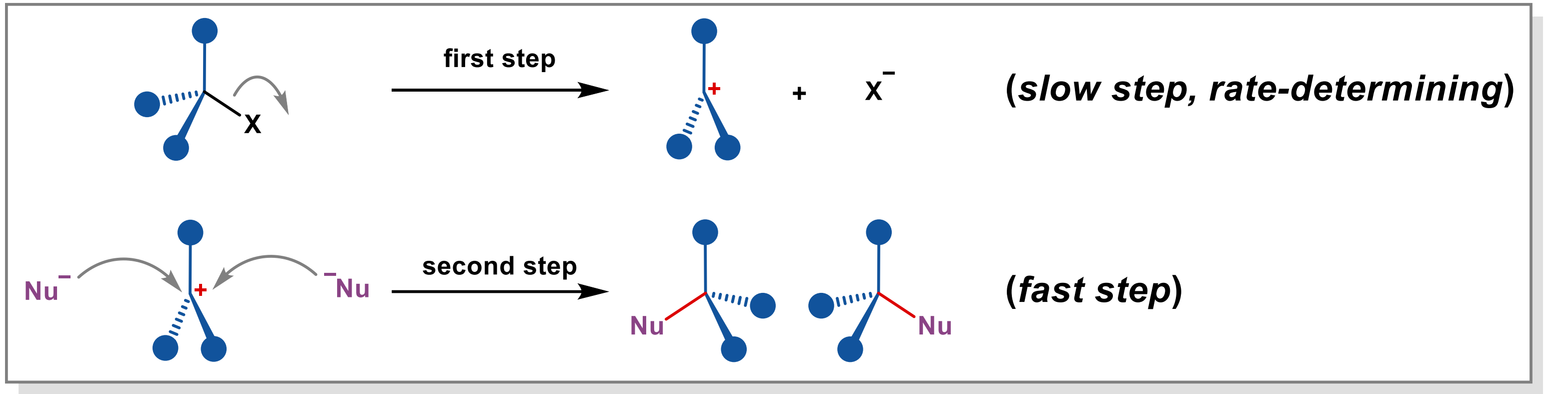
$$NO_3 + CO \rightarrow NO_2 + CO_2 \ (\textit{fast step})$$

Introduction

Example 2: Nucleophilic substitution reaction (simplification)

1. S_N1 reaction:

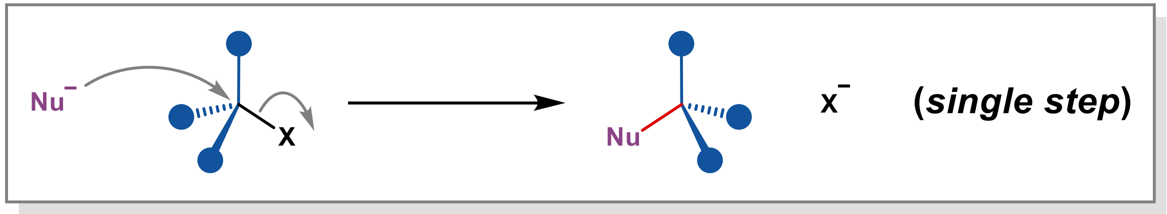
***rate* = *k*[R-X]^1**



This reaction is found to be first-order with ***rate* = *k*[R-X]**, which indicates that the first step is slow and determines the rate. The second step with nucleophilic reagent is much faster, so the overall rate is independent of the concentration of nucleophilic reagent .

2. S_N2 reaction:

***rate* = *k*[R-X]^1[Nu]^1**

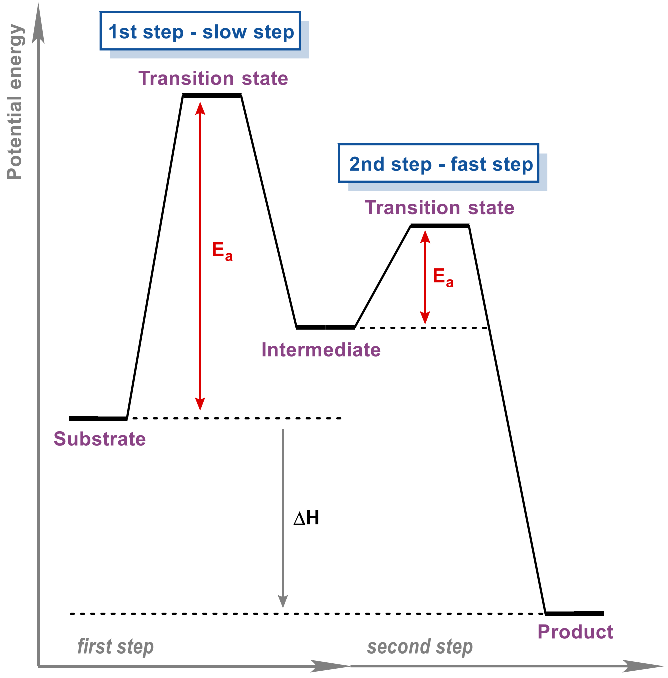


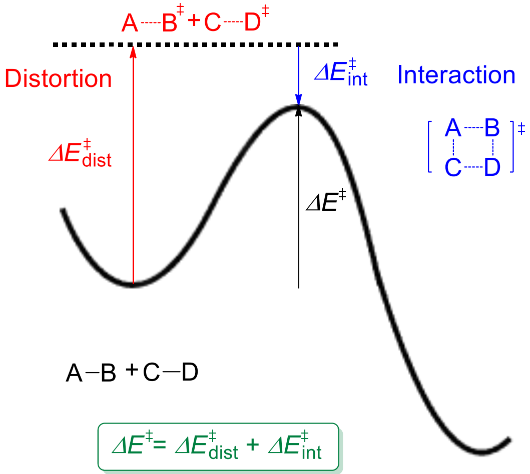
Introduction

How to find the rate-determining step?

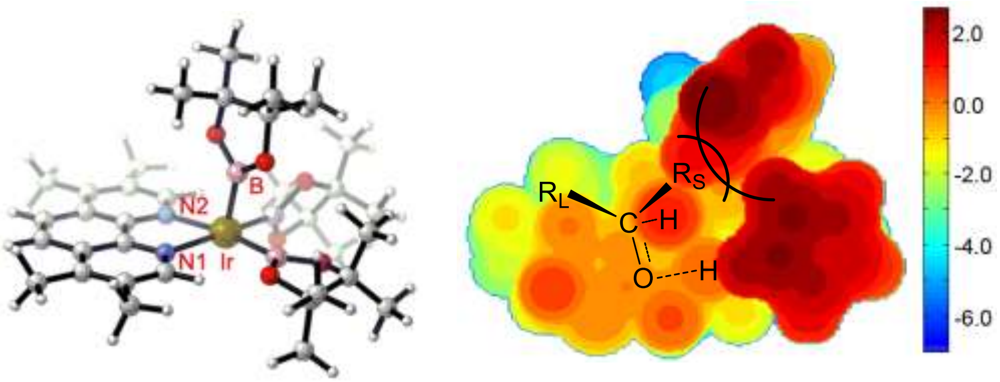
How to find the rate-determining step?

DFT calculation

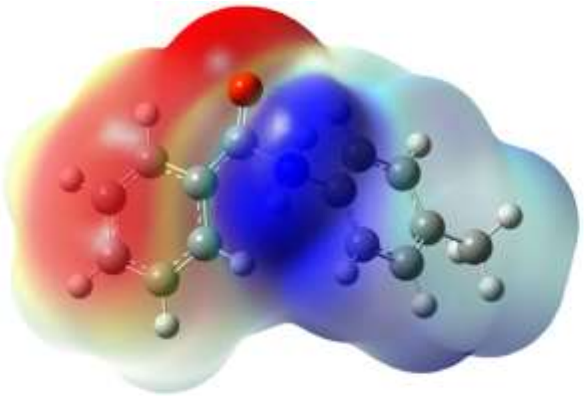




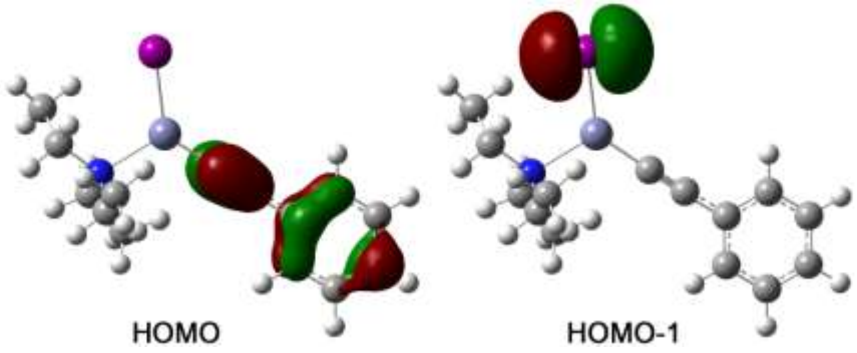
Energy information



Structural information



Charge distribution information



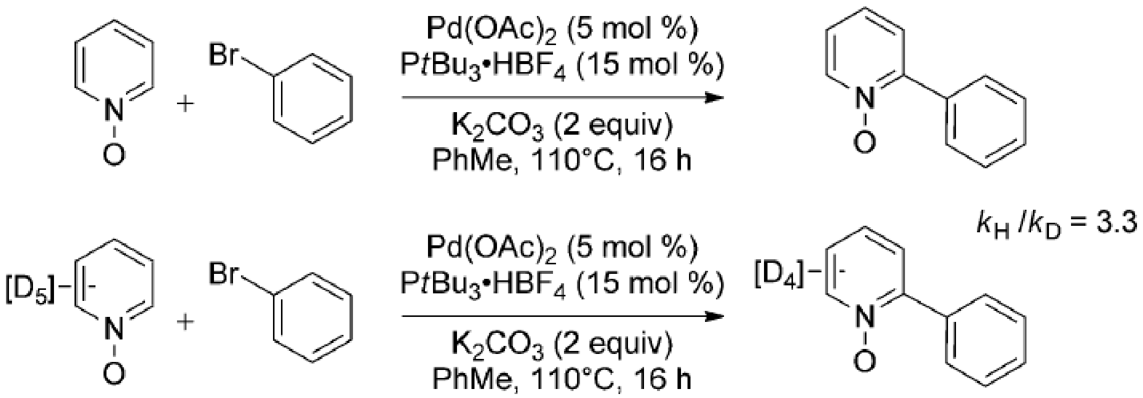
Orbital information

How to find the rate-determining step?

Kinetic Isotope Effect Experiment

H/D KIE experiment

It needs to synthesize the substrate and **deuterated substrate**.



Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-G.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180-8189.

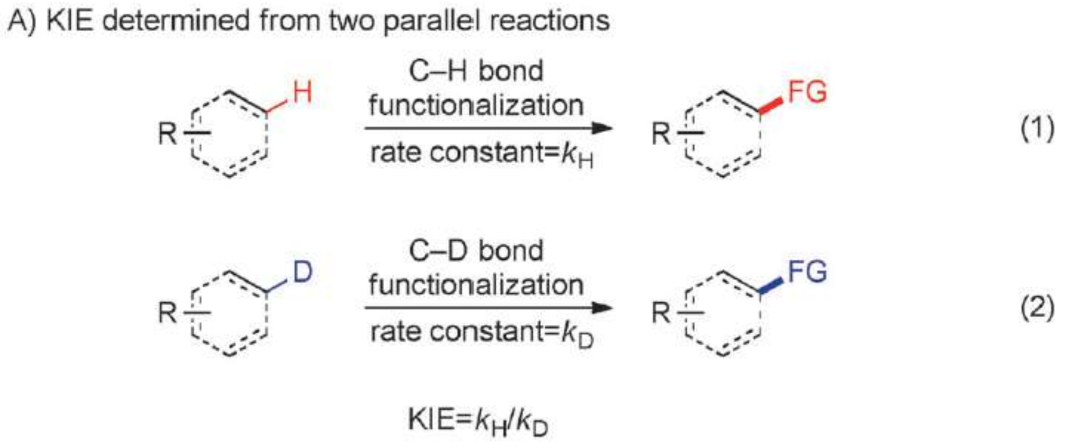
The C-H bond cleavage maybe the **rate-determining step** of a direct arylation reaction.

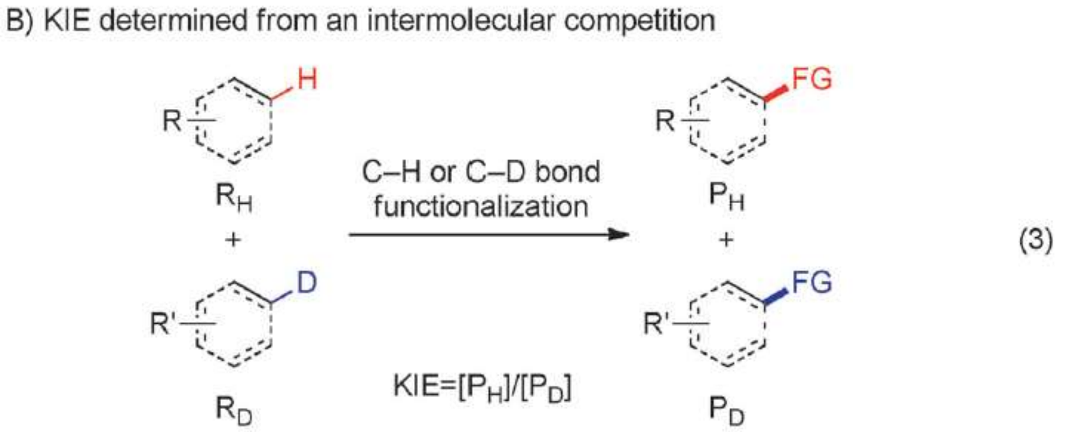
Generally speaking, **KIE = k_H/k_D > 2**; C-H bond cleavage maybe the **rate-determining step**.

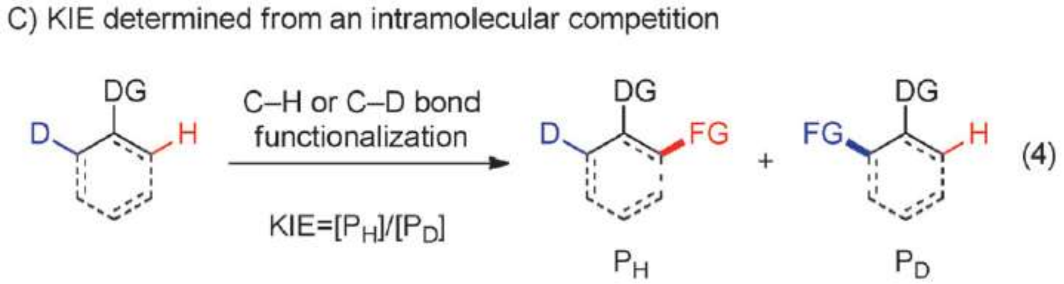
Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.
Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

H/D KIE experiment







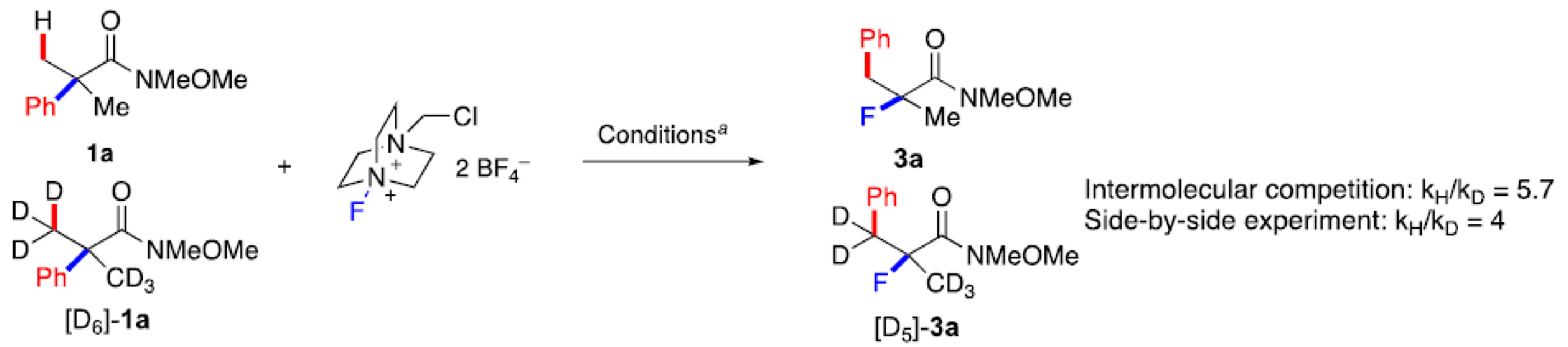
Method A is the **only one** that provides conclusive information on whether the C-H bond cleavage occurs during the **rate-determining step** of a reaction.

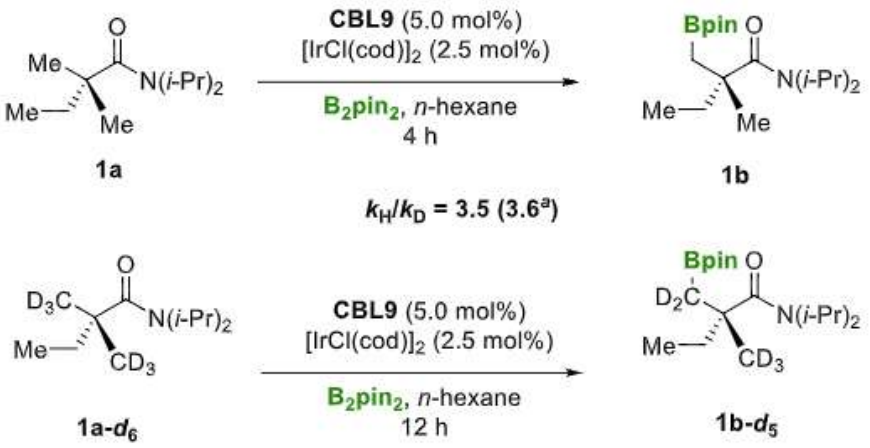
Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.

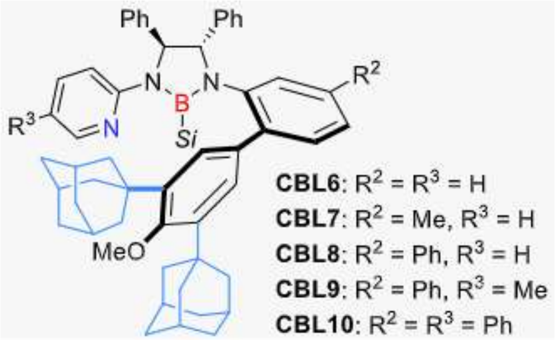
Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

H/D KIE experiment: many examples



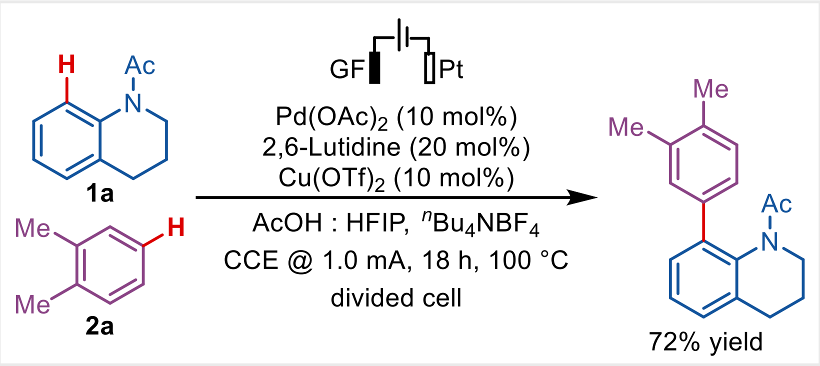




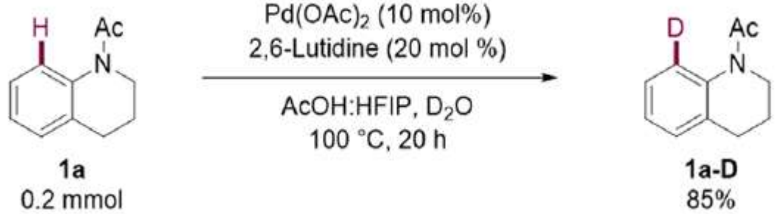
Yang, G.; Wu, H.; Gallarati, S.; Corminboeuf, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2022**, *144*, 14047−14052.
Yang, Y.; Chen, J.; Shi, Y.; Liu, P.; Feng, Y.; Peng, Q.; Xu, S. *J. Am. Chem. Soc.* **2024**, *146*, 1635-1643.

How to find the rate-determining step?

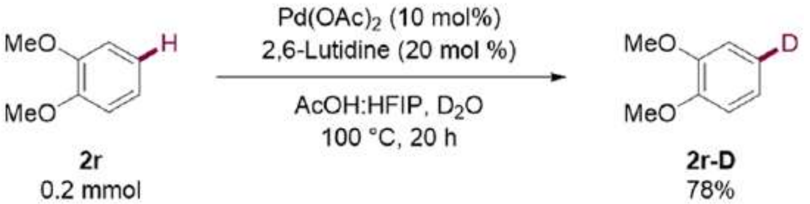
H/D KIE experiment: special examples



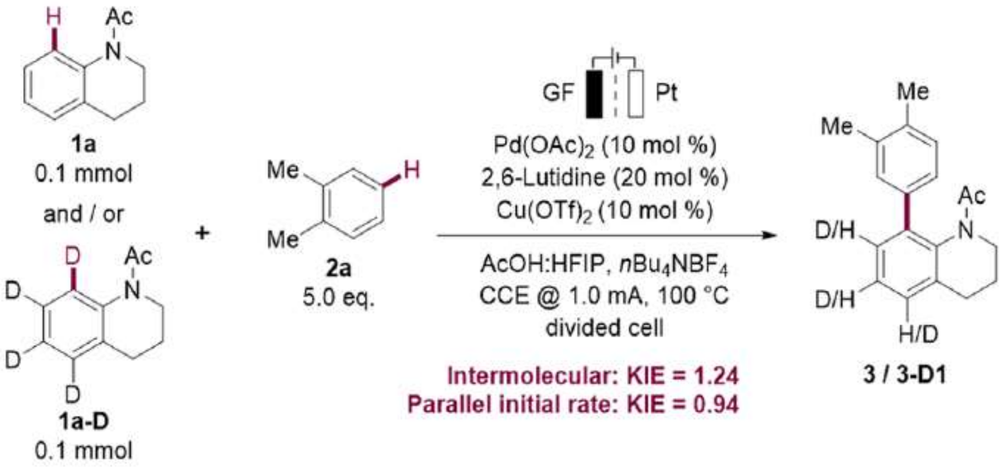
(a)



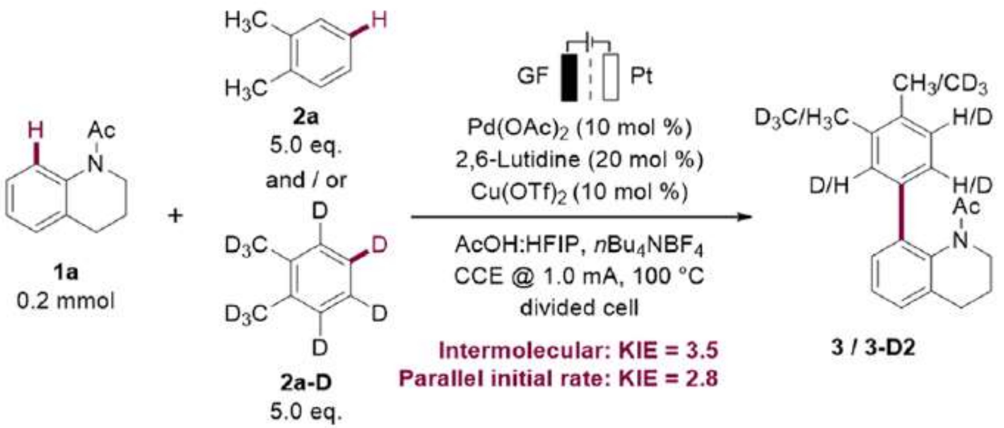
(b)



(c)



(d)

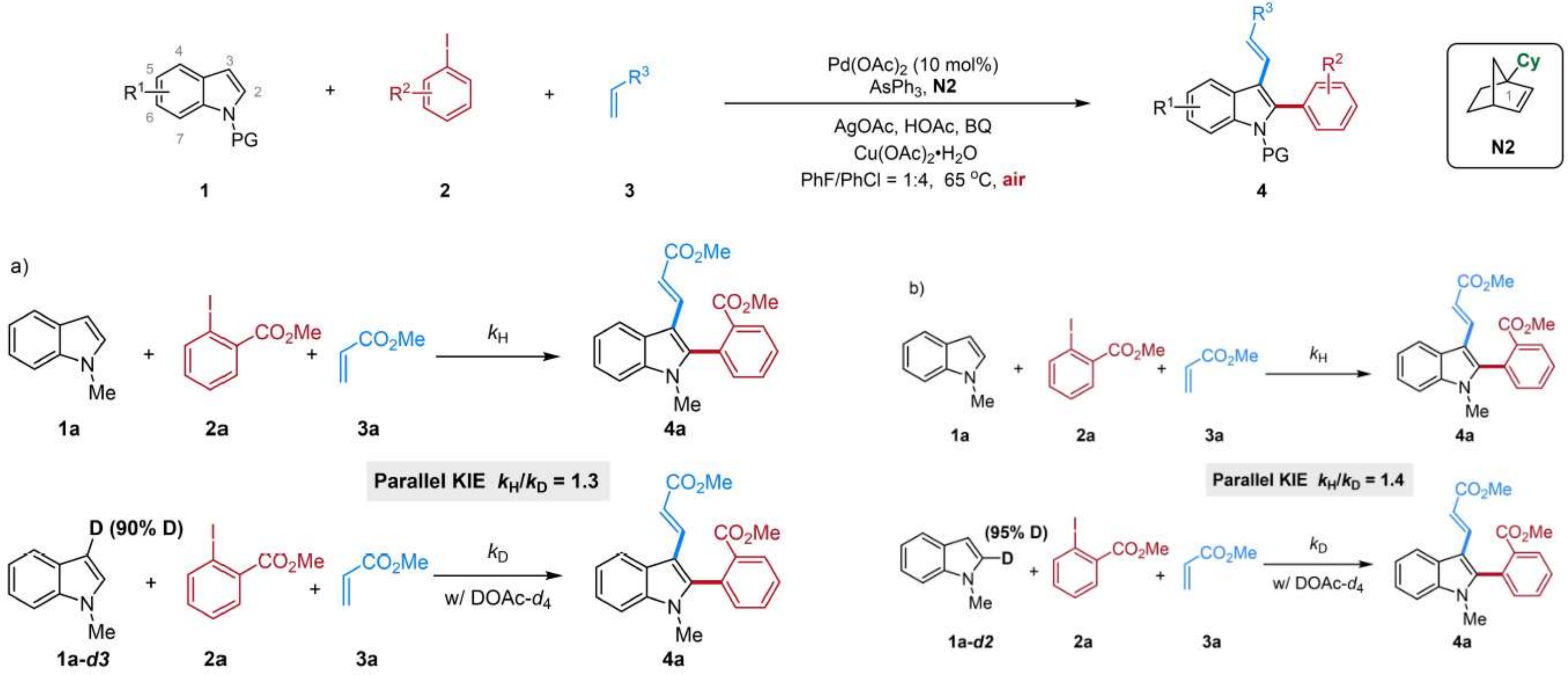


This step is rate-determining step?

Lin, Z.; Oliveira, J. C. A.; Scheremetjew, A.; Ackermann, L. *J. Am. Chem. Soc.* **2024**, *146*, 228-239.

How to find the rate-determining step?

H/D KIE experiment



How to determine the rate-determining step for the reaction that do not involve C-H bonds?

Liu, X.; Zhou, Y.; Qi, X.; Li, R.; Liu, P.; Dong, G. *Angew. Chem. Int. Ed.* **2023**, *62*, e202310697.

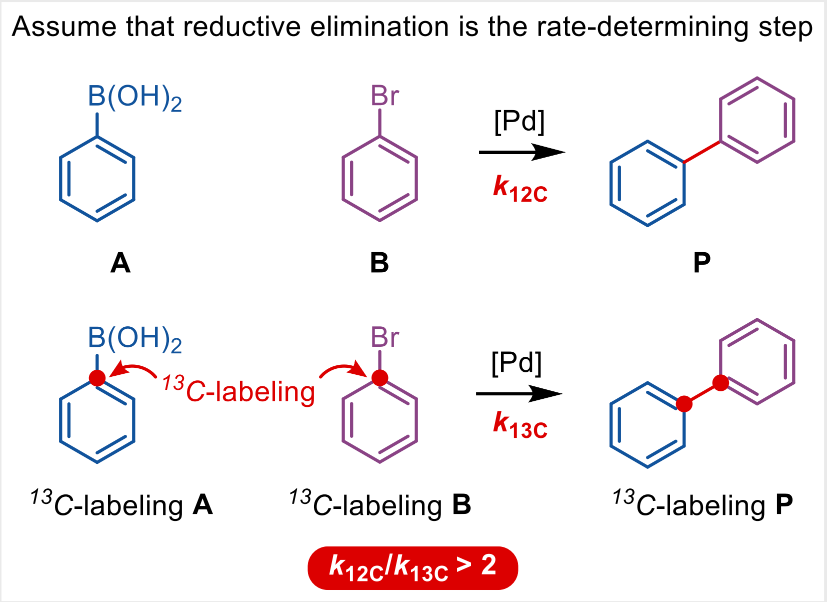
How to find the rate-determining step?

Kinetic Isotope Effect Experiment

^{13}C KIE experiment: KIE measured at natural-abundance

H/D KIE experiment need to synthesize the deuterated starting material;

However, it is difficult to synthesized ^{13}C labeled starting material.



Natural isotopes of atom:

Hydrogen: ^{1}H (99.9855%), ^{2}H (D, 0.0145%), ^{3}H (T, trace) **^{1}H NMR**

Fluorine: ^{19}F (100%), ^{18}F (trace) **^{19}F NMR**

Phosphorus: ^{31}P (100%), ^{32}P (trace), ^{33}P (trace) **^{31}P NMR**

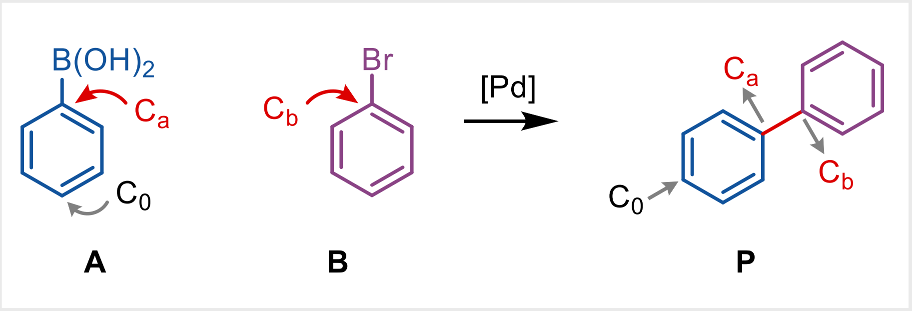
Carbon: ^{12}C (98.9%), ^{13}C (1.06%) **^{13}C NMR** ⇨ **Quantitative ^{13}C NMR**

Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

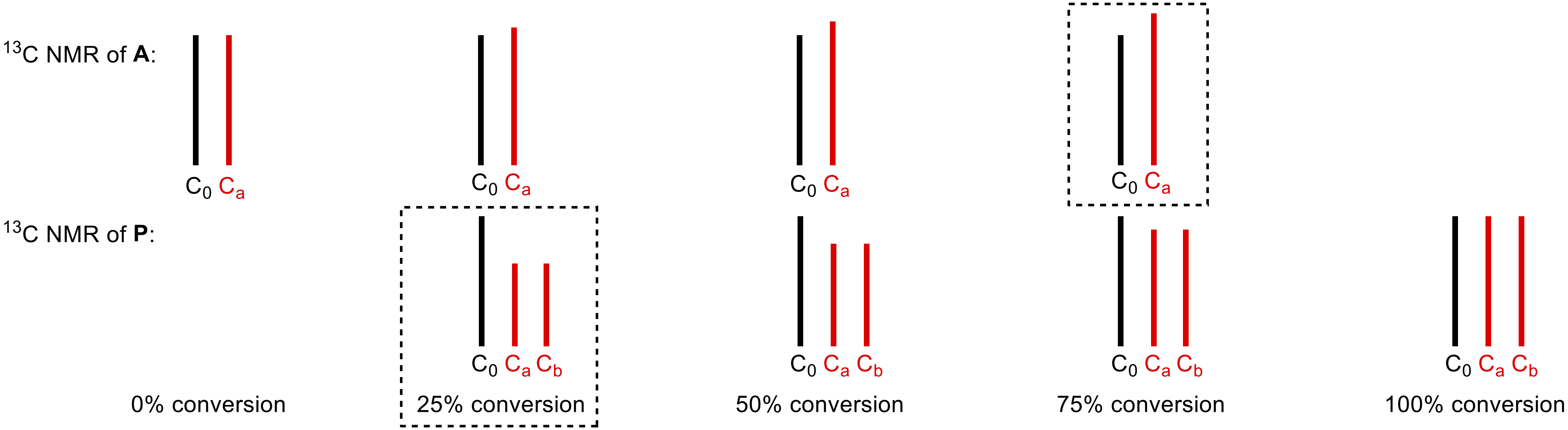
How to find the rate-determining step?

^{13}C KIE experiment: KIE measured at natural-abundance

Assume that reductive elimination is the rate-determining step.



Quantitative ^{13}C NMR:



Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

^{13}C KIE experiment: KIE measured at natural-abundance

1. Quantitative ^{13}C NMR of starting material

$$\mathbf{KIE} = \frac{\ln(1-F)}{\ln\left[(1-F)\frac{R}{R_0}\right]}$$

F = conversion of starting material.

R = the peak ratio for the starting material at **high conversion**.

$\mathbf{R_0}$ = the peak ratio for the initial starting material.

2. Quantitative ^{13}C NMR of product

$$\mathbf{KIE} = \frac{\ln(1-F)}{\ln\left(1-F\frac{R}{R_0}\right)}$$

F = conversion of starting material.

R = the peak ratio for the product at **low conversion**.

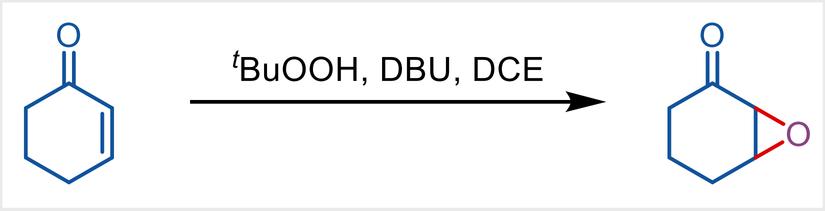
$\mathbf{R_0}$ = the peak ratio for the fully converted product.

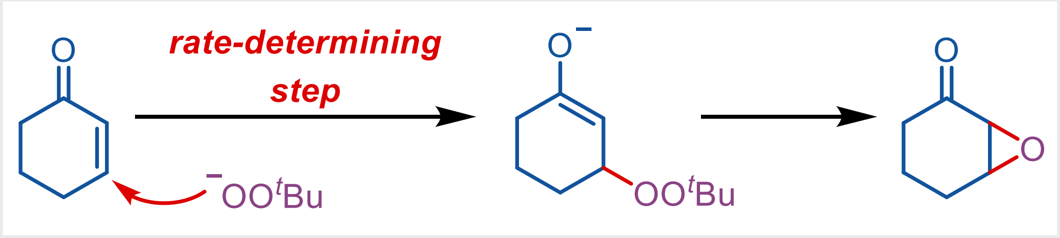
Classical $KIE_{12C/13C}$ values: $0.99 < KIE < 1.04$

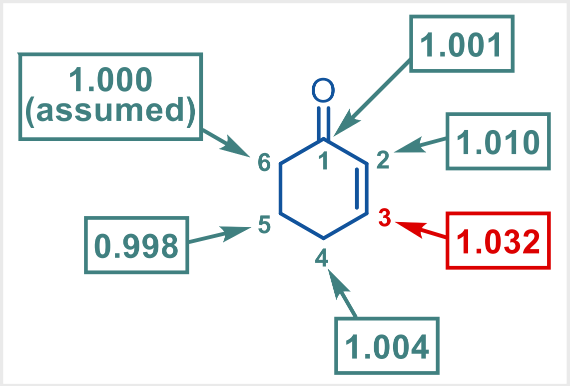
Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

^{13}C KIE experiment





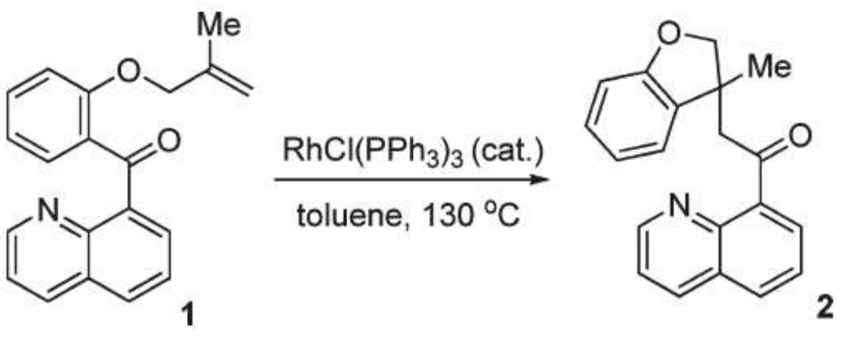


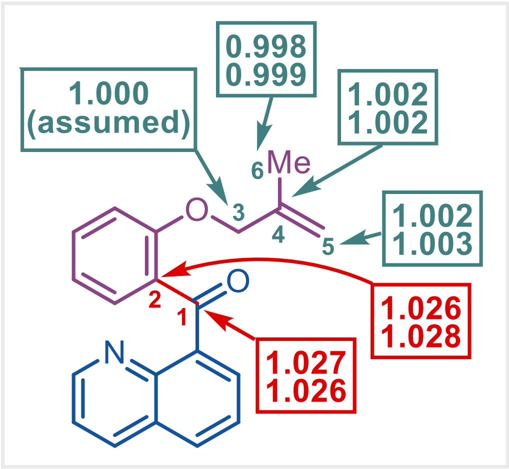
Strong KIE$_{12C/13C}$ at C3 and moderate one at **C2**.

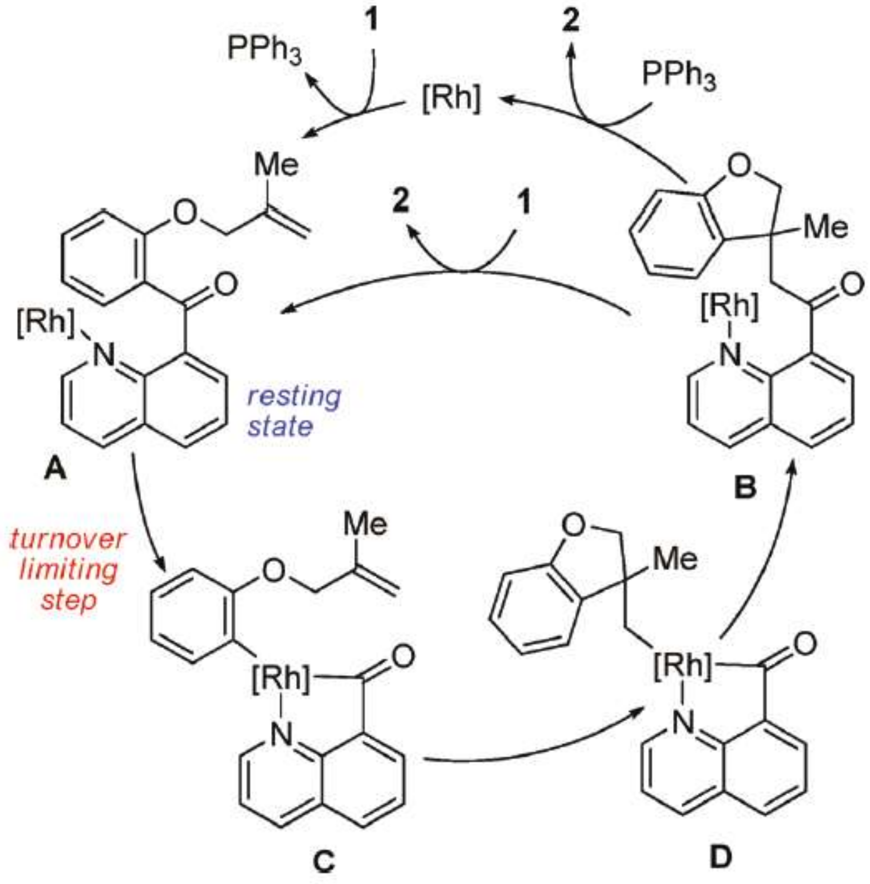
Christian, C. F.; Takeya, T.; Szymanski, M. S.; Singleton, D. A. *J. Org. Chem.* **2007**, *72*, 6183-6189.

How to find the rate-determining step?

^{13}C KIE experiment



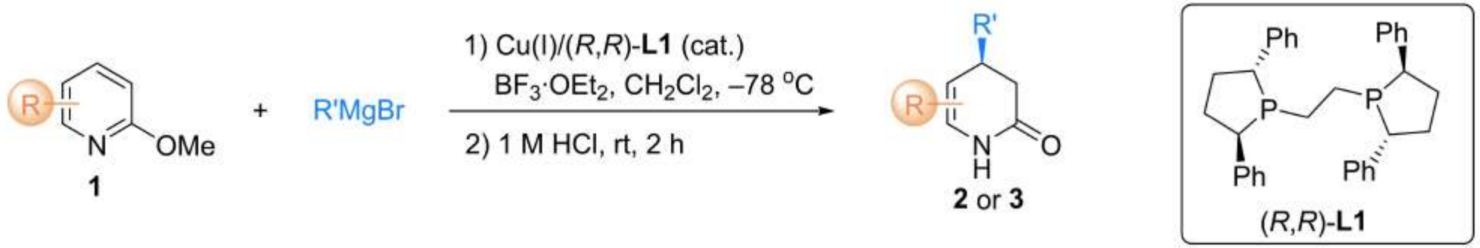


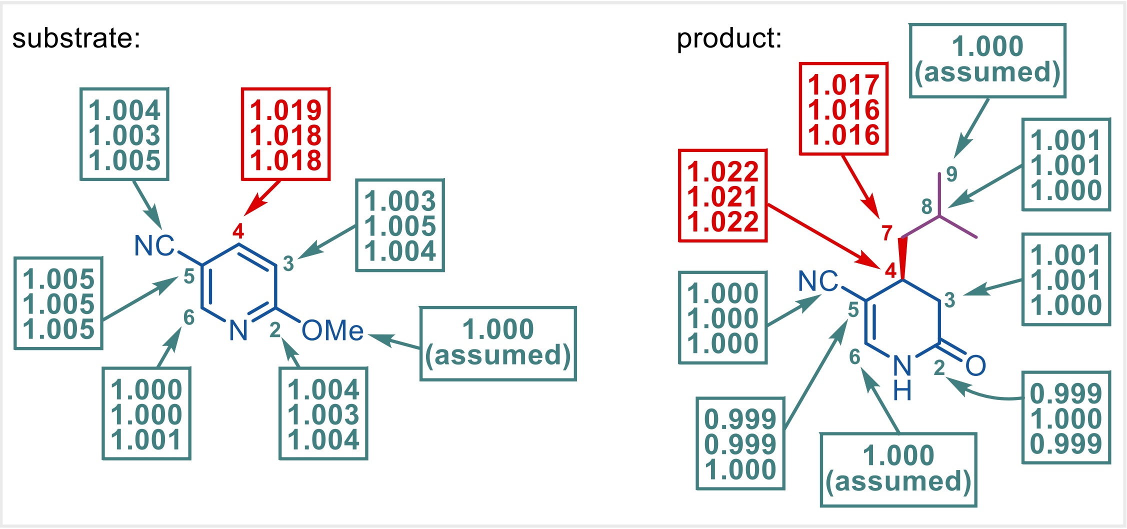


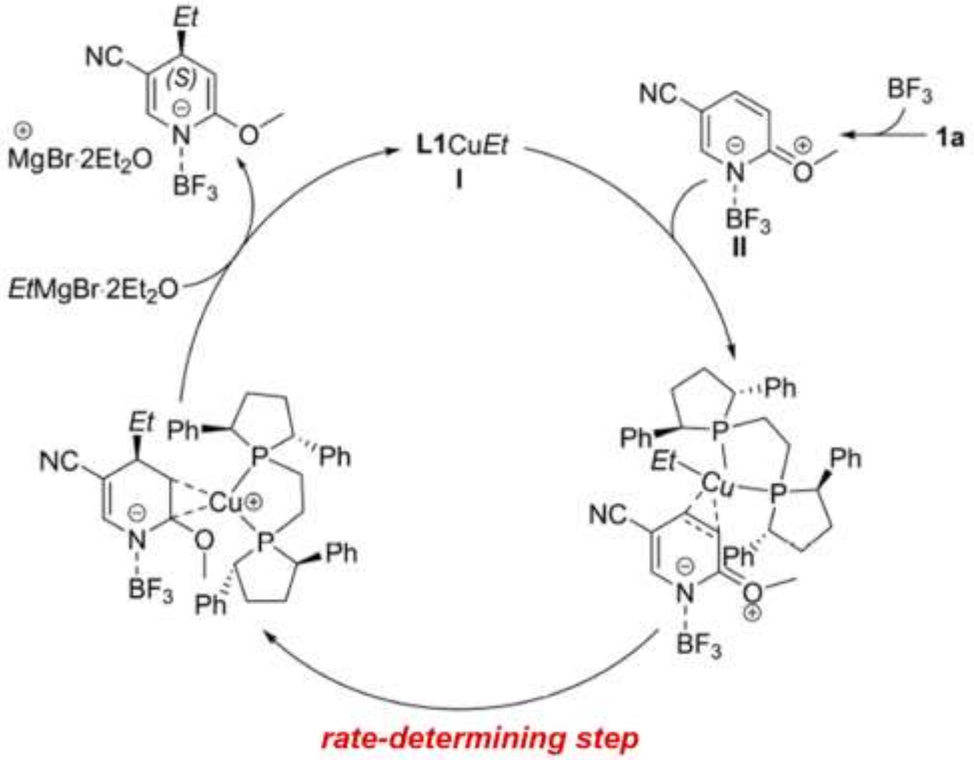
Rathbun C. M.; Johnson, J. B. *J. Am. Chem. Soc.* **2011**, *133*, 2031-2033.

How to find the rate-determining step?

^{13}C KIE experiment







Somprasong, S.; Reis, M. C.; Harutyunyan, S. R. *Angew. Chem. Int. Ed.* **2023**, *62*, e202217328.

How to find the rate-determining step?

Reaction Progress Kinetic Analysis (RPKA):

Reaction Progress Kinetic Analysis (RPKA) is a methodology that makes use of the voluminous data sets that are now readily obtained from continuous monitoring of the entire course of a reaction.

It can help to describe the driving forces of a reaction and may be used to help distinguish between different proposed mechanistic models.

The method: Reaction progress NMR; *In situ* FT-IR; *In situ* UV-vis; Reaction calorimetry.

Reaction at same "excess"

product inhibition or **catalyst deactivation**

Reaction at different "excess"

Reaction at different catalyst concentrations

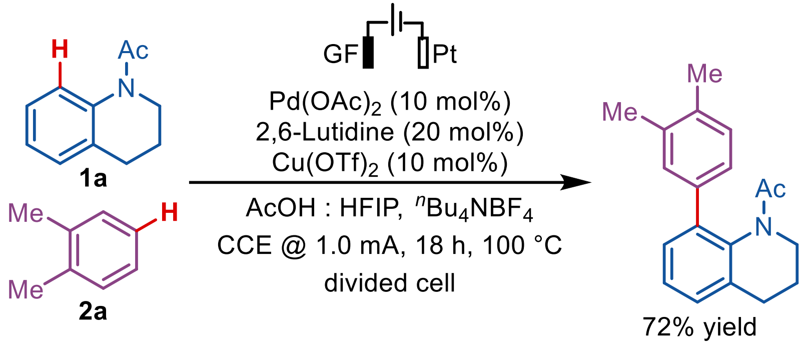
Determine the reaction order, include substrates and catalyst.

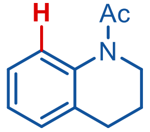
It is very useful to find the rate-determining step.

Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302-4320.

How to find the rate-determining step?

Different "excess" experiments: Reaction order



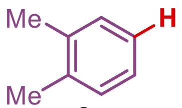


1a

KIE of **1a**:

Intermolecular: **KIE = 1.24**

Parallel initial rate: **KIE = 0.94**

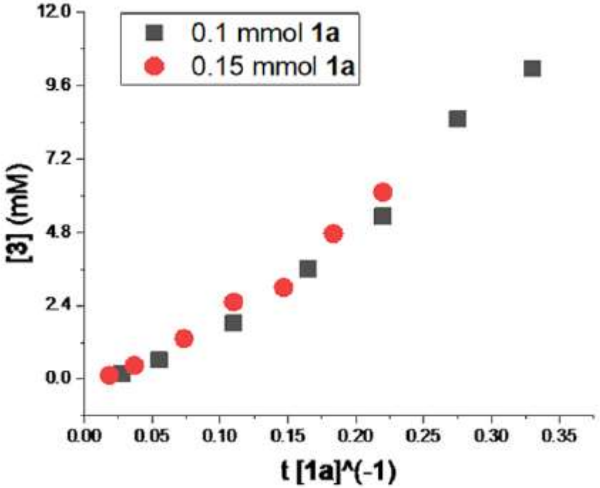


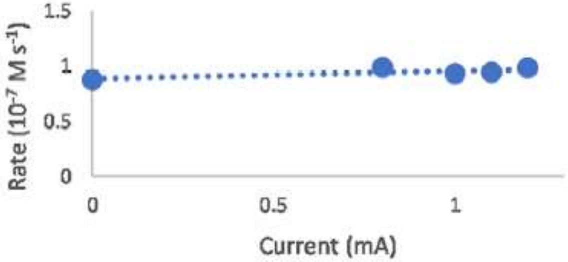
2a

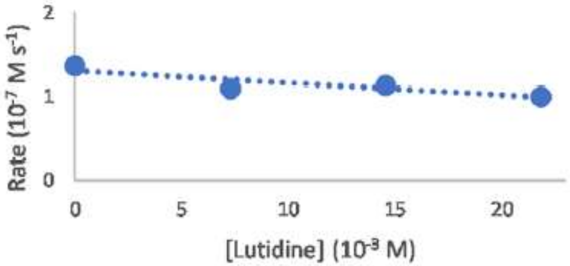
KIE of **2a**:

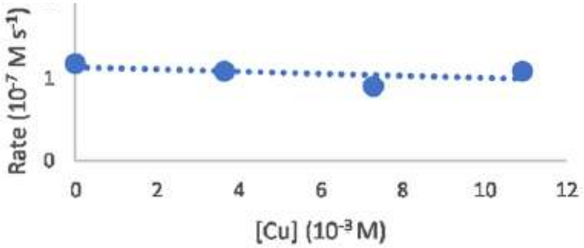
Intermolecular: **KIE = 3.5**

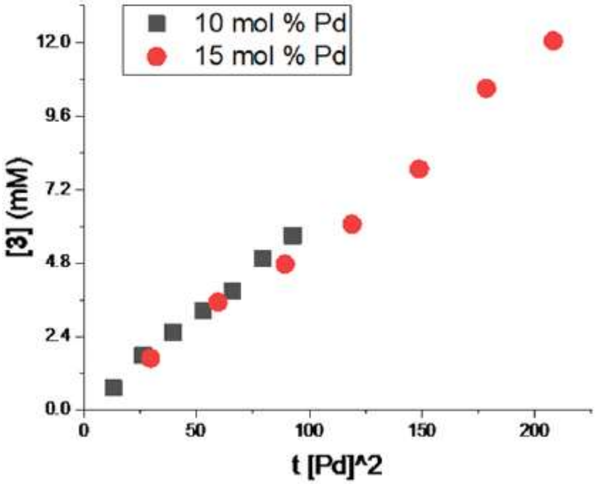
Parallel initial rate: **KIE = 2.8**

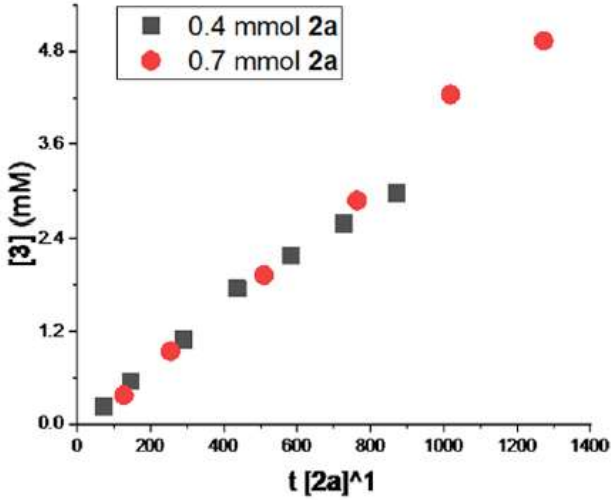












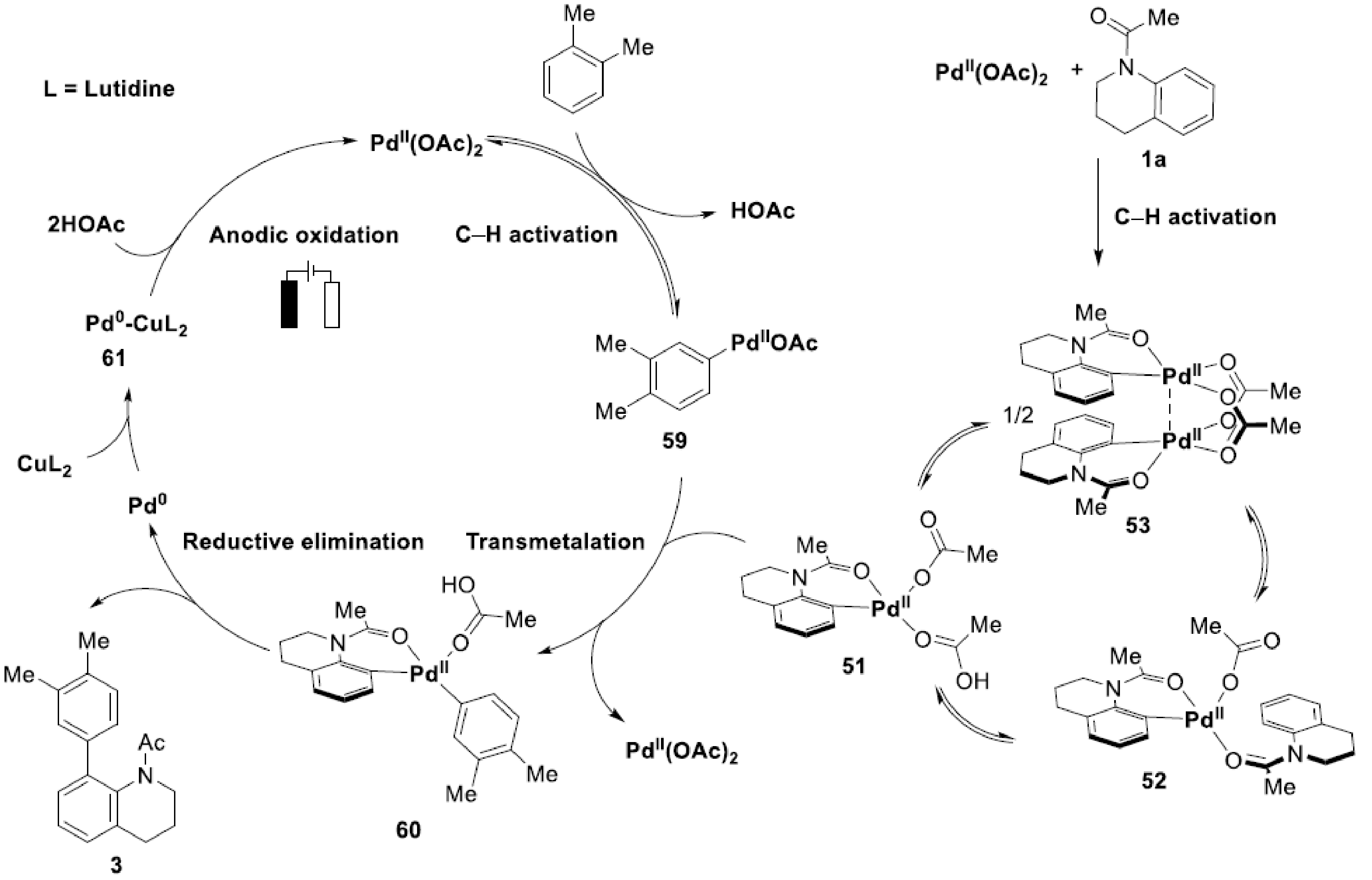
[1a]: inverse order
[2a]: first order
[Pd]: second order
[Cu]: zero order
Lutidine: zero order
Current: zero order

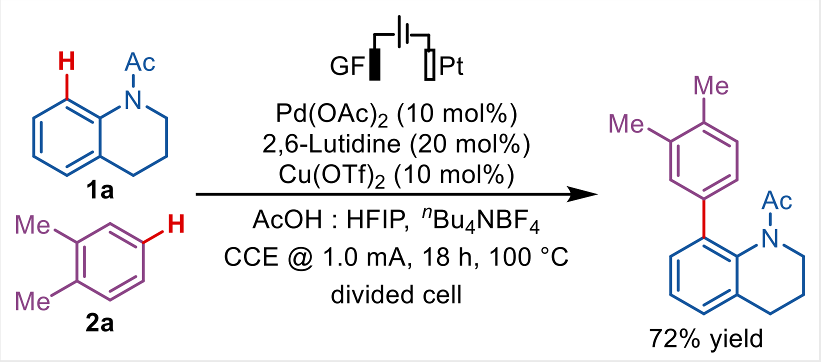
The rate-determining step is related to **two molecules of palladium** and **one molecule of 2a**, but the rate is **suppressed by 1a**.

Lin, Z.; Oliveira, J. C. A.; Scheremetjew, A.; Ackermann, L. *J. Am. Chem. Soc.* **2024**, *146*, 228-239.

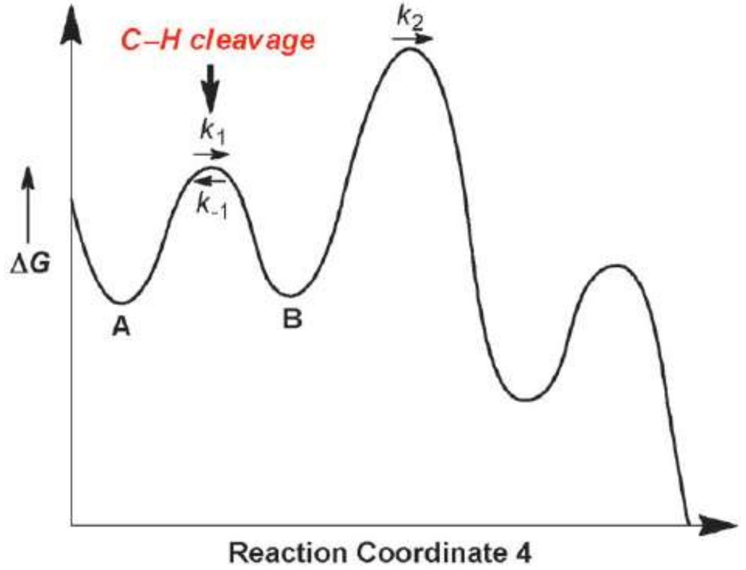
How to find the rate-determining step?

Different "excess" experiments: Reaction order





The C−H cleavages of **2a** occurring during the catalytic cycle but before the rate-determining step.



Detailed kinetic analysis for determining the rate-determining step is needed.

Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.
Lin, Z.; Oliveira, J. C. A.; Scheremetjew, A.; Ackermann, L. *J. Am. Chem. Soc.* **2024**, *146*, 228-239.

How to find the rate-determining step?

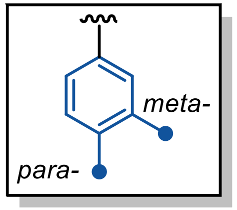
Hammett plots

Hammett equation describes a linear free-energy relationship relating reaction rates and equilibrium constants for many reactions involving benzoic acid derivatives with *meta*- and *para*-substituents to each other with just two parameters: a substituent constant and a reaction constant.

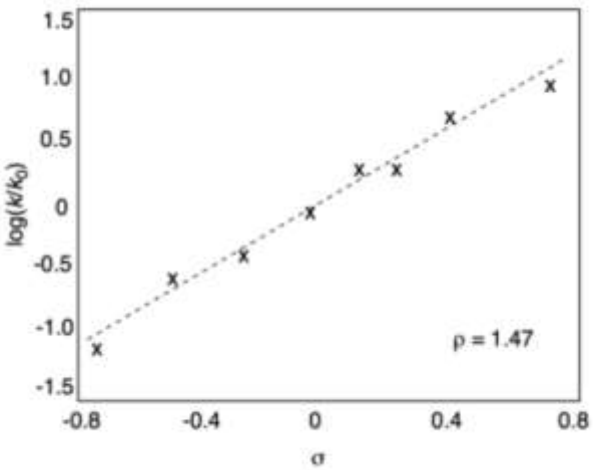
$$\log\frac{K}{K_0} = \sigma \cdot \rho$$

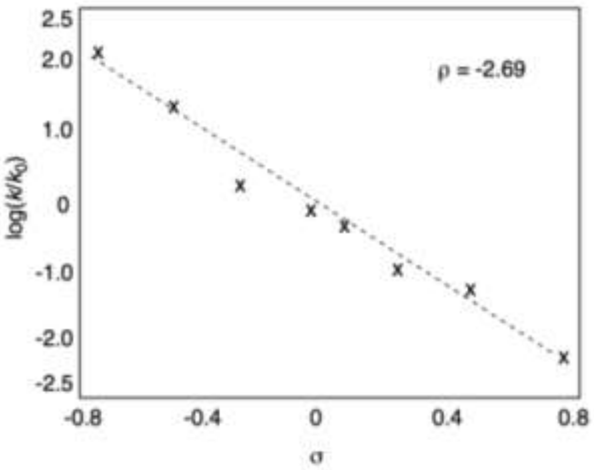
$$\boldsymbol{\log\frac{k}{k_0} = \sigma \cdot \rho}$$

σ = Substituent constant; ρ = Reaction rate constant;
k_0 is the reaction rate of the unsubstituted reactant, and k that of a substituted reactant.



Substituent	*para*- effect	*meta*- effect
Dimethylamino	−0.83	−0.211
Amino	−0.66	−0.161
Butylamino	−0.51	−0.34
Hydroxy	−0.37	+0.12
Methoxy	−0.268	+0.115
Ethoxy	−0.25	+0.015
Methyl	−0.170	−0.069
Trimethylsilyl	−0.07	−0.04
None	0.000	0.000
Fluoro	+0.062	+0.337
Chloro	+0.227	+0.373
Bromo	+0.232	+0.393
Iodo	+0.276	+0.353
Ethoxycarbonyl	+0.45	+0.37
Trifluoromethyl	+0.54	+0.43
Cyano	+0.66	+0.56
Nitro	+0.778	+0.710



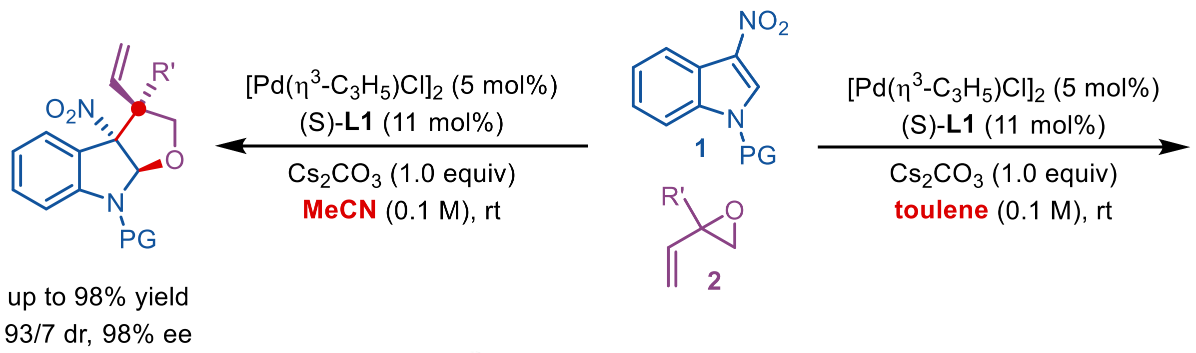


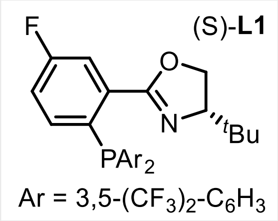
1. $\rho>0$, negative charge is built during the reaction (or positive charge is lost).
2. $\rho=0$, no sensitivity to substituents, and no charge is built or lost.
3. $\rho<0$, the reaction builds positive charge (or loses negative charge).

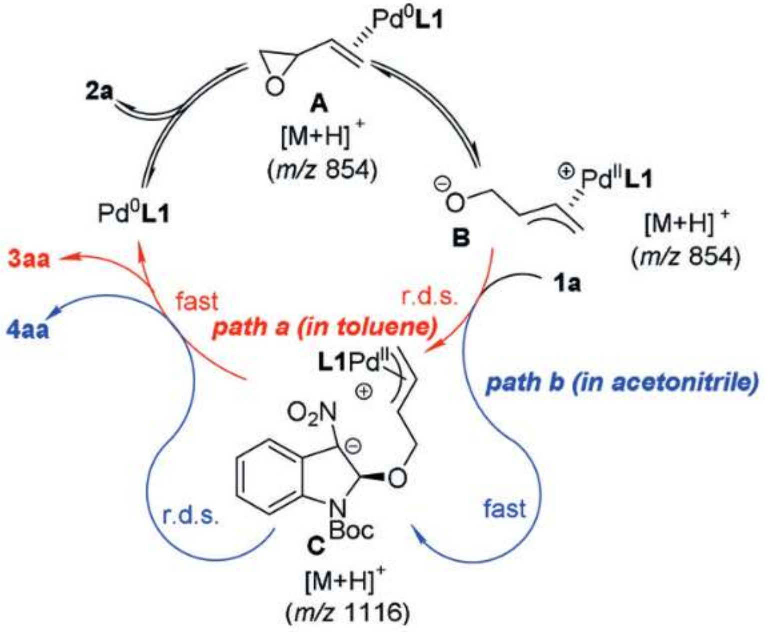
Hansch, C.; A. Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

How to find the rate-determining step?

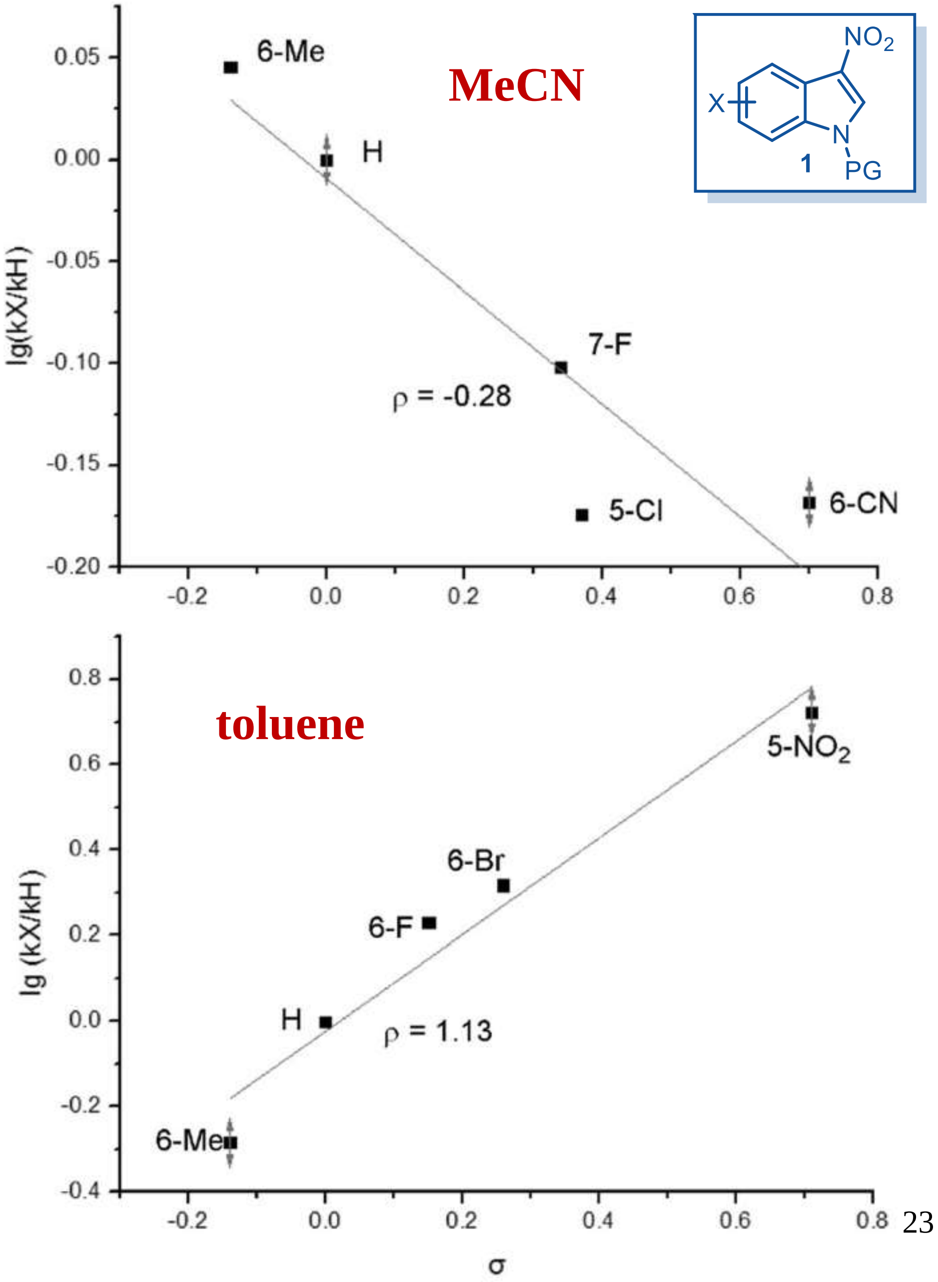
Hammett plots







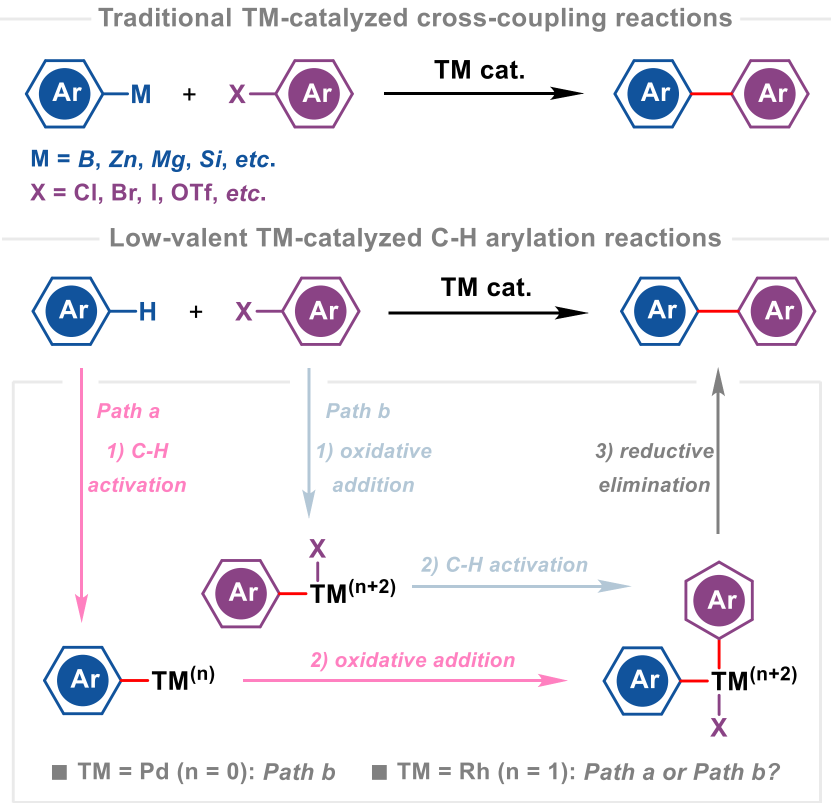
1. *ρ>0*, negative charge is built during the reaction (or positive charge is lost).
2. *ρ<0*, the reaction builds positive charge (or loses negative charge).

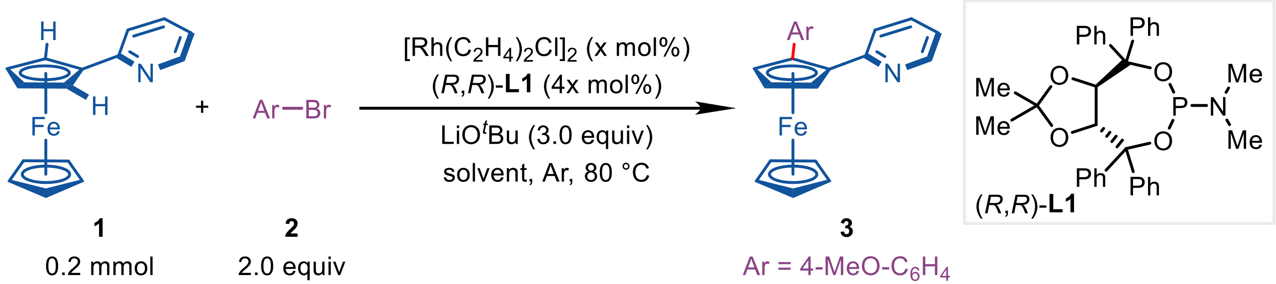


Cheng, Q.; Zhang, F.; Cai, Y.; Guo, Y.-L.; You, S.-L. *Angew. Chem. Int. Ed.* **2018**, *57*, 2134-2138.

The classic example

The classic example



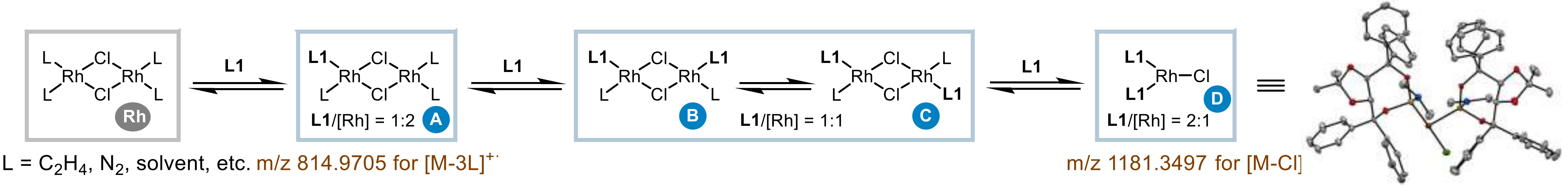


Condition	NMR yield	ee
x = 5, THF	80%	99%
x = 2.5, dioxane	92%	99%

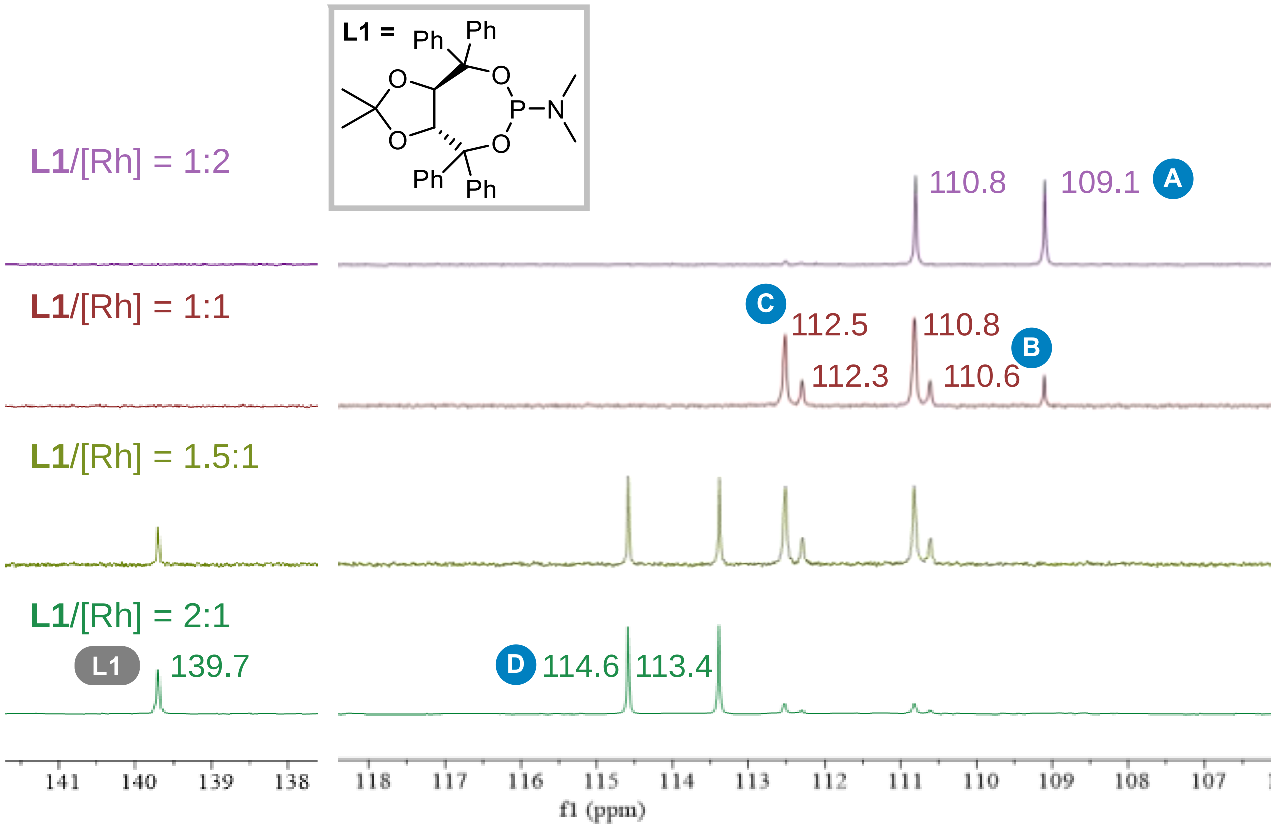
Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

Investigations on active catalytic species

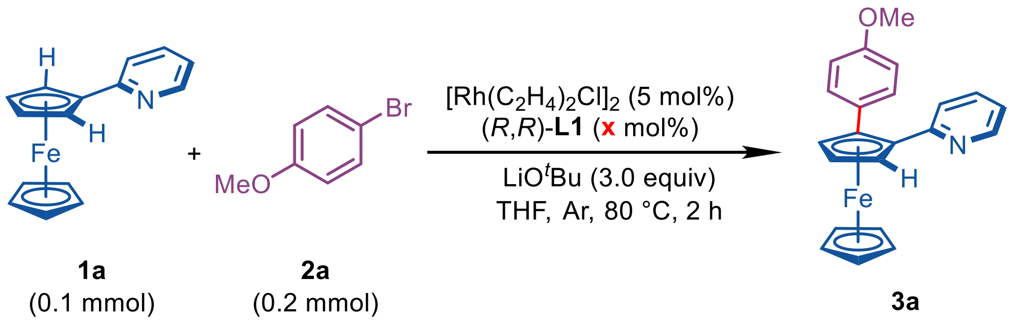
(a)



(b)



(c)



x	5	10	15	20	30
L1/[Rh]	1:2	1:1	1.5:1	2:1	3:1
NMR yield of **3a**	50%	76%	80%	80%	85%
ee of **3a**	97%	>99%	>99%	>99%	>99%

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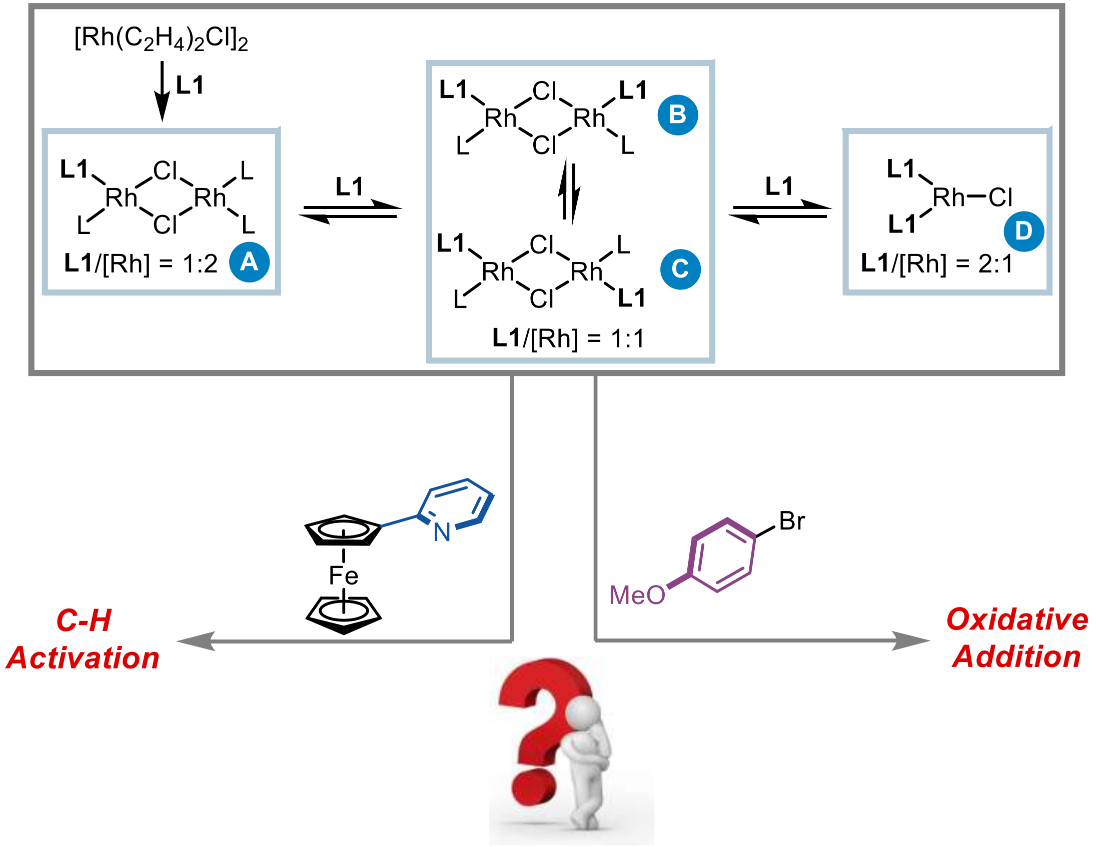
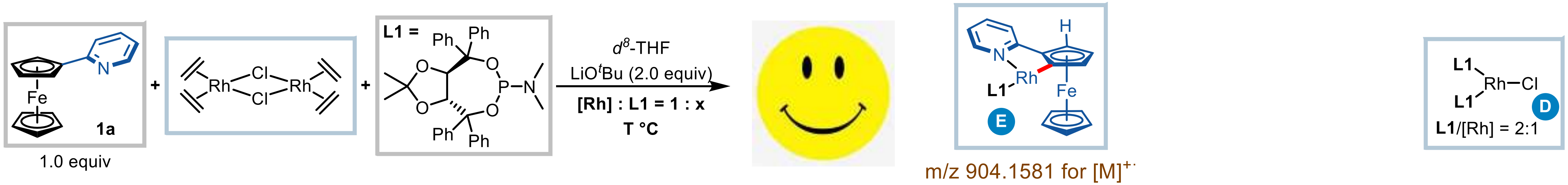
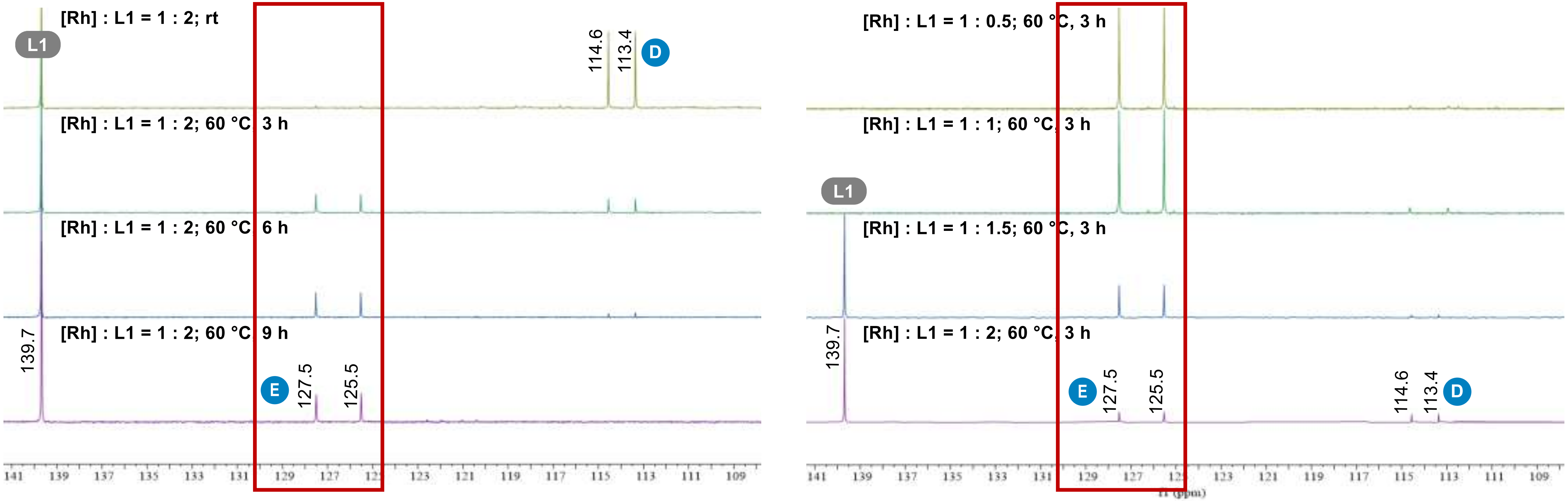
Investigations on the sequence of elementary steps



Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

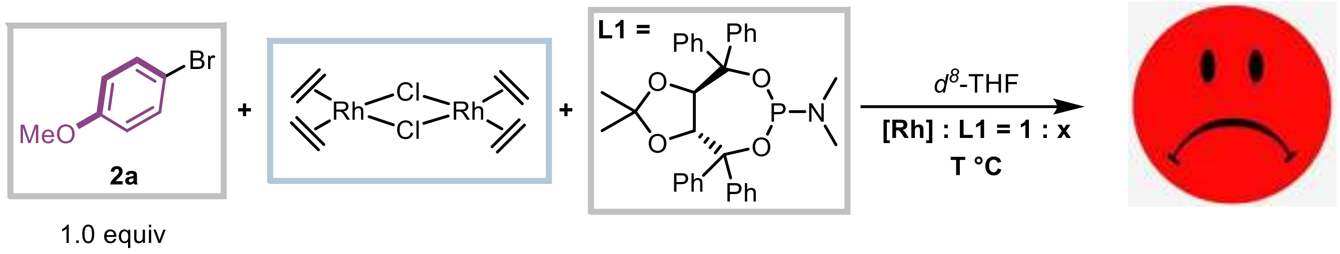
^{31}P NMR experiment: C-H activation

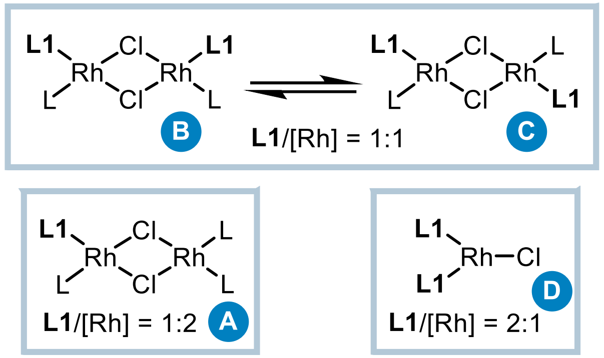


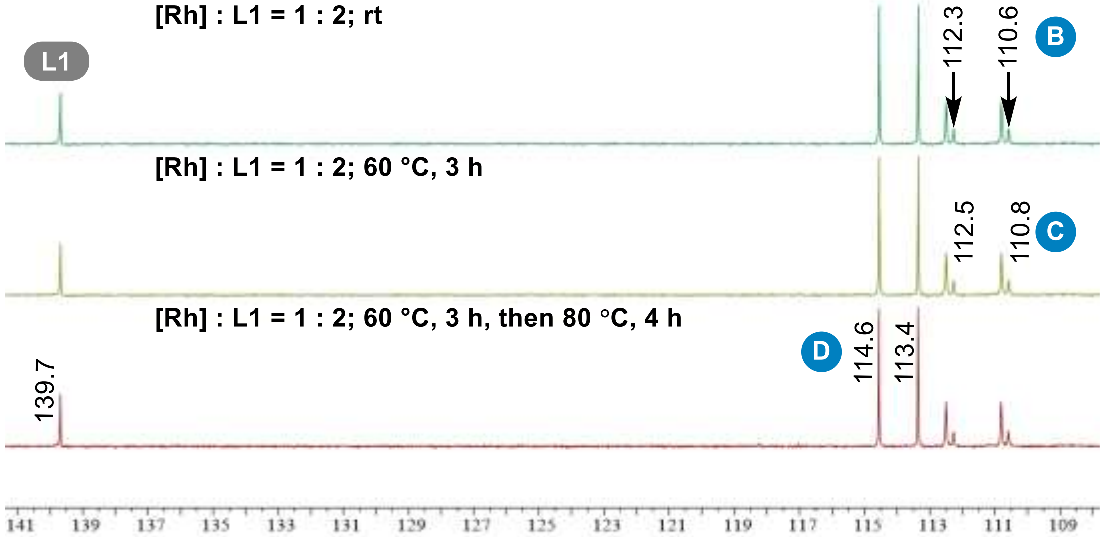


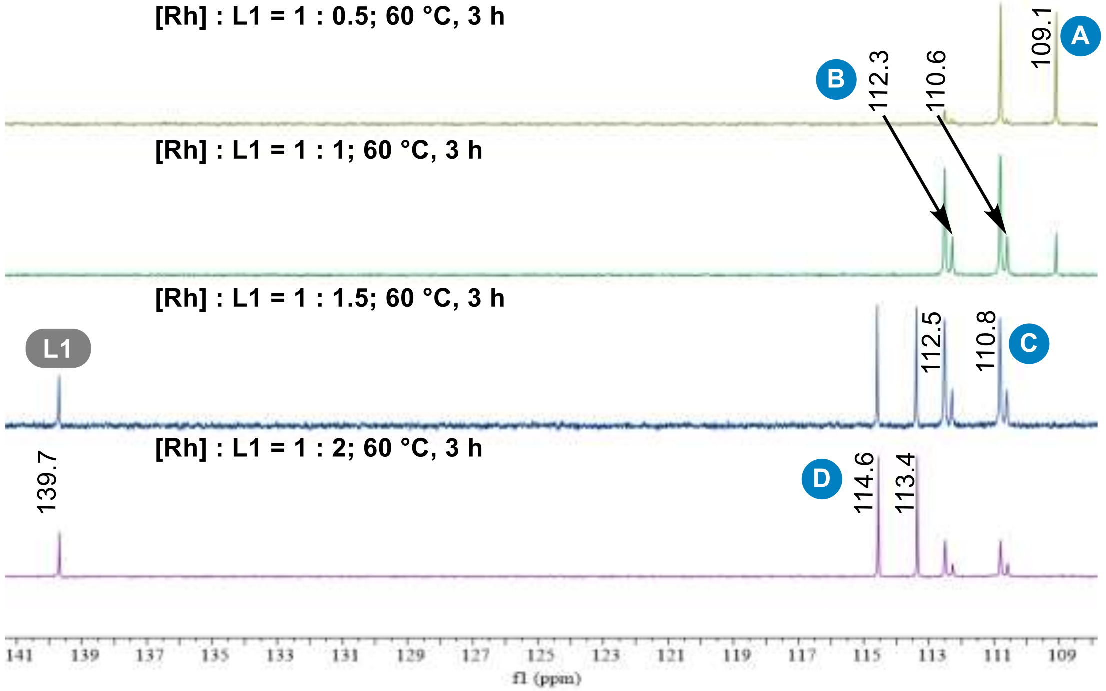
Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

^{31}P NMR experiment: oxidative addition



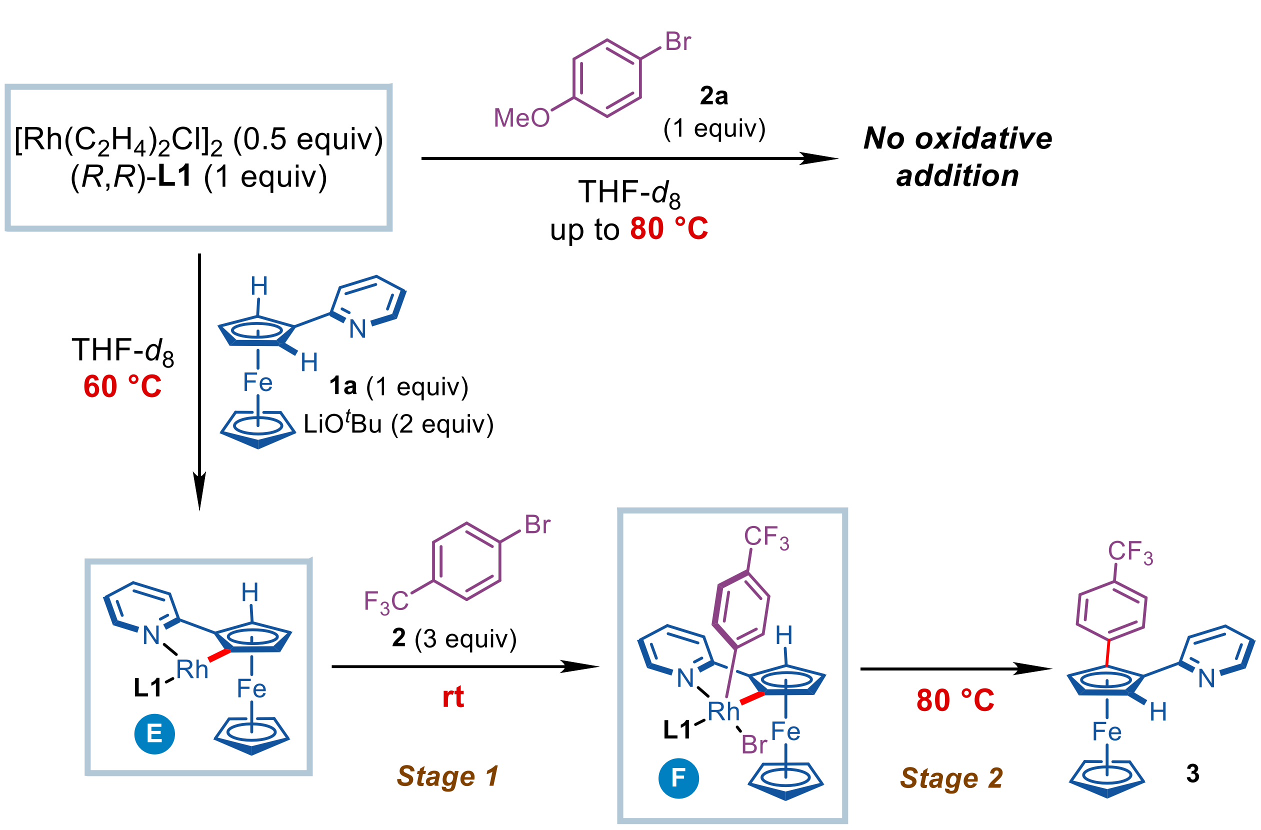


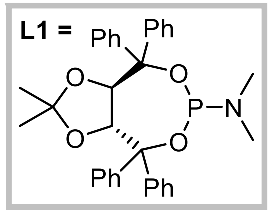


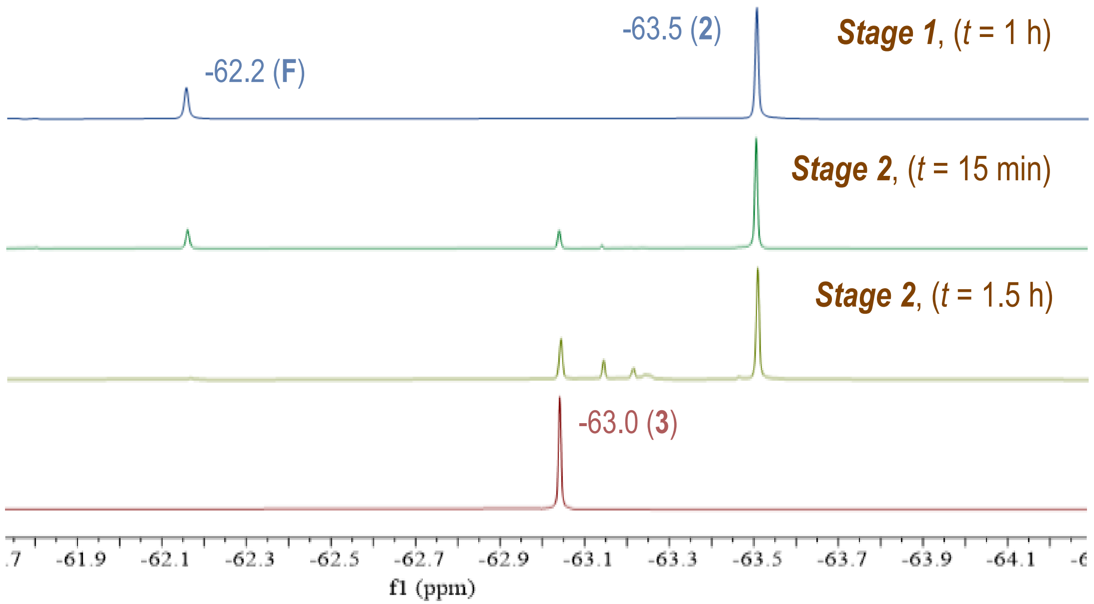


Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

^{19}F NMR experiment: oxidative addition & reductive elimination







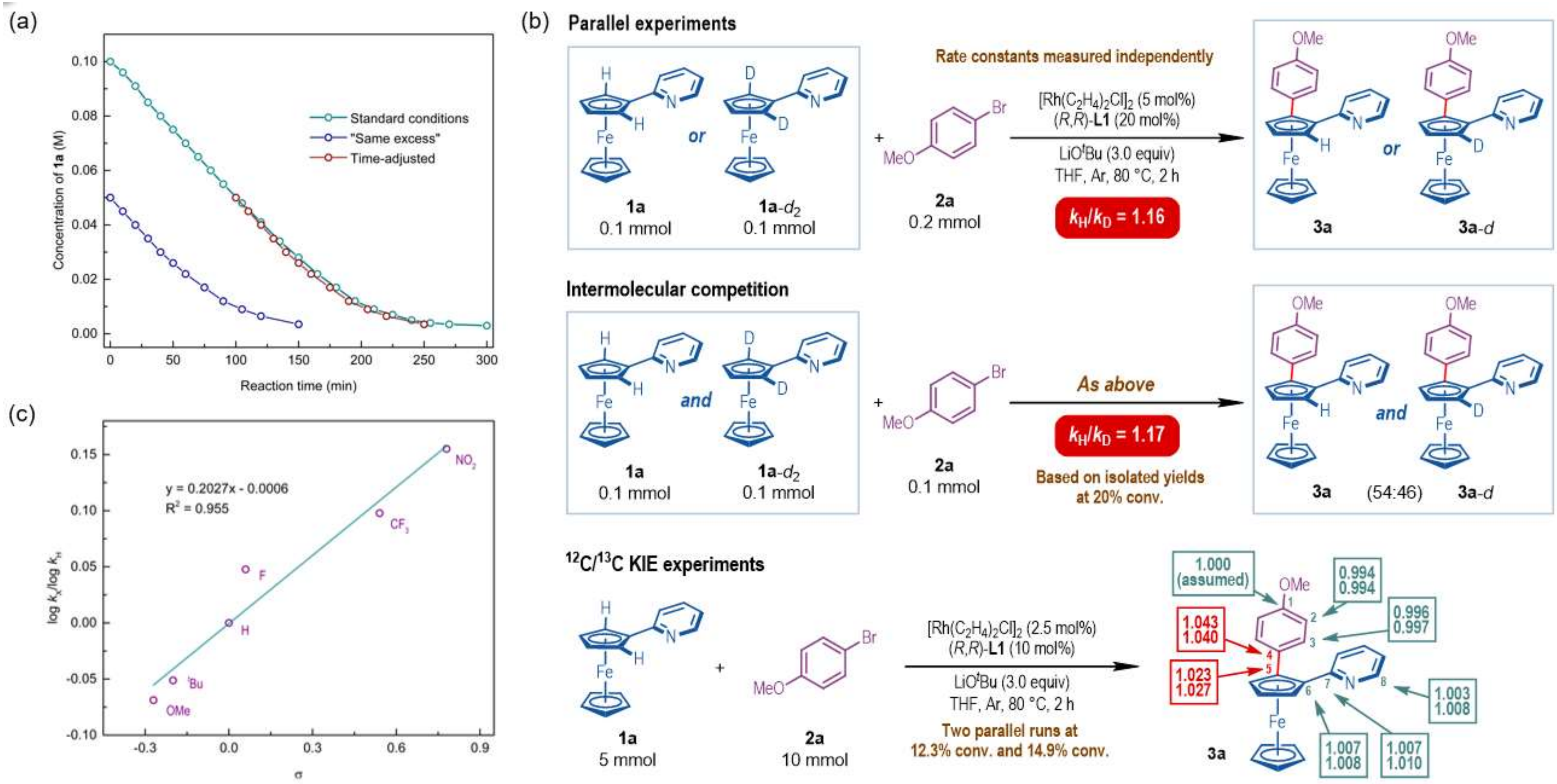
m/z 904.1581 for $[M]^{+\cdot}$

m/z 1049.1864 for $[M-Br]^{+}$

Rate-determining step?

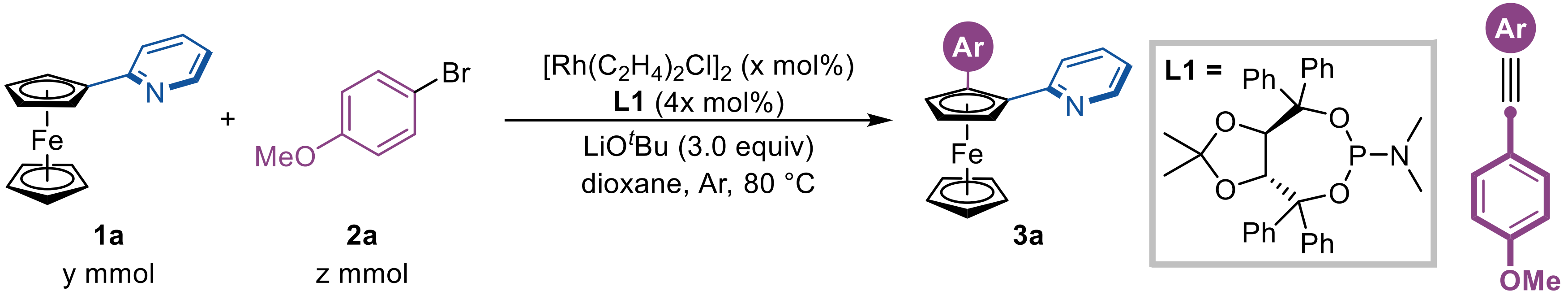
Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

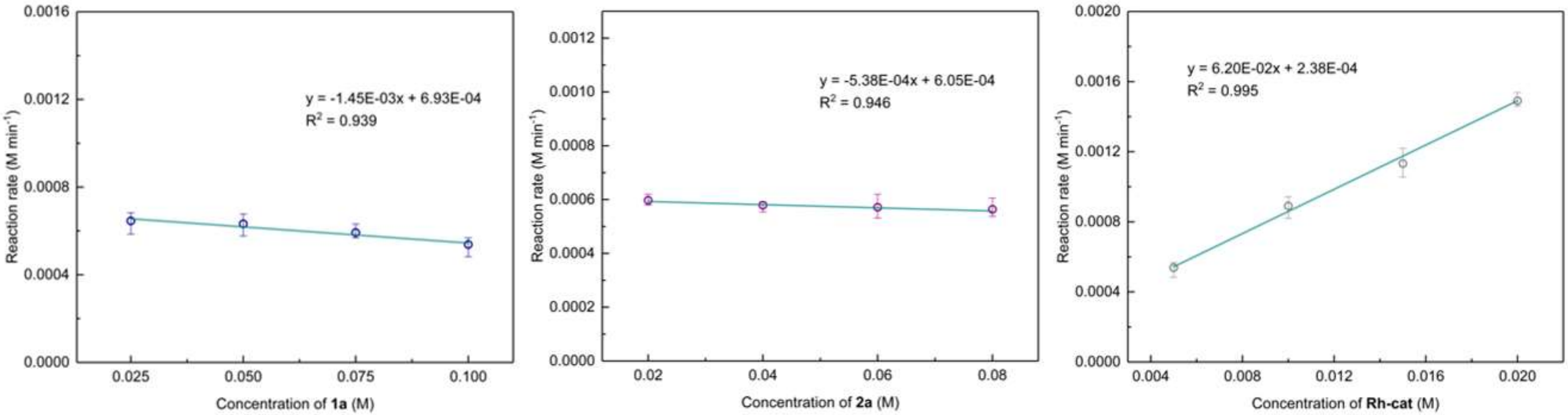
Kinetic studies



Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

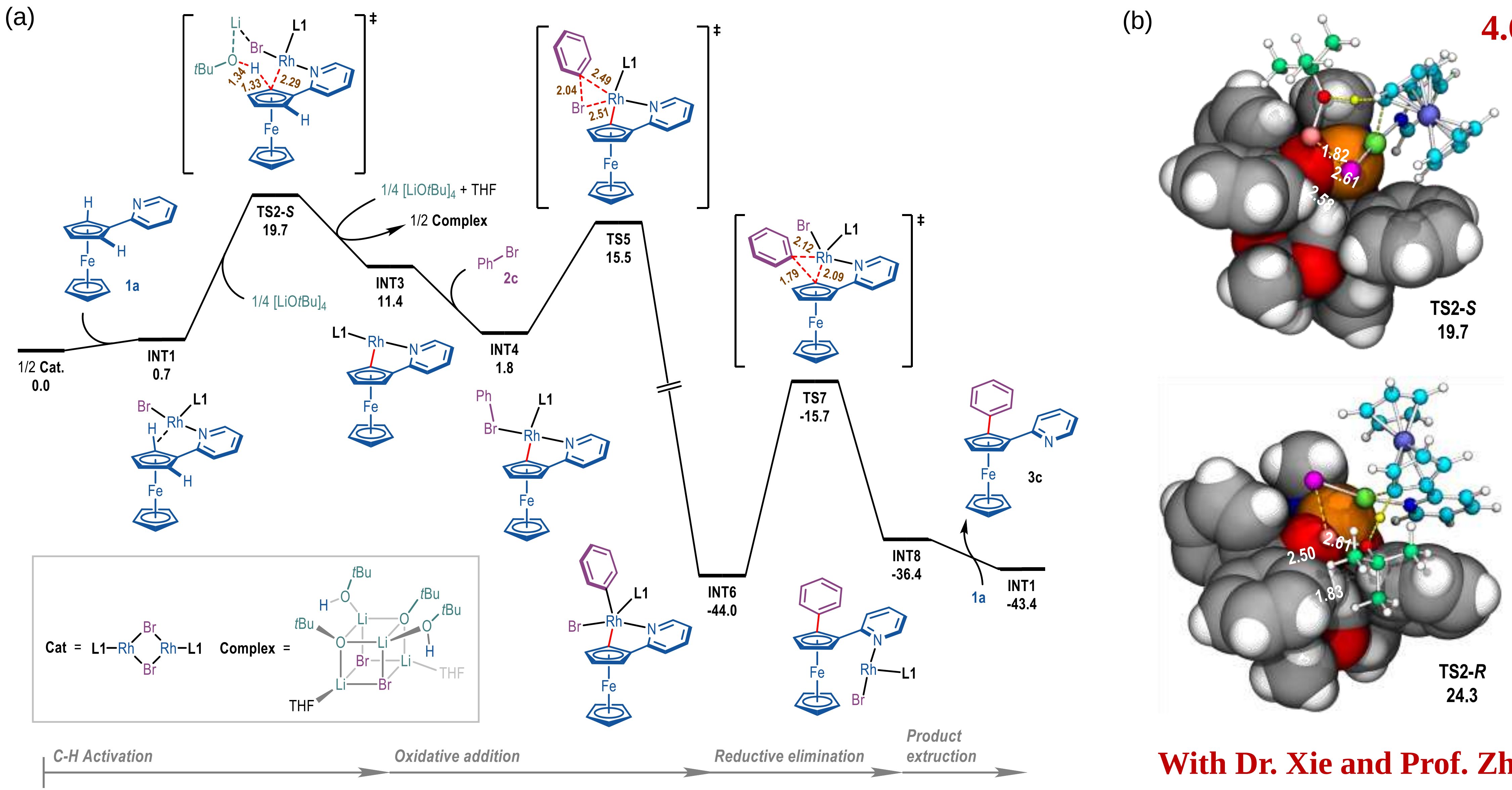
Kinetic studies





Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

DFT calculation

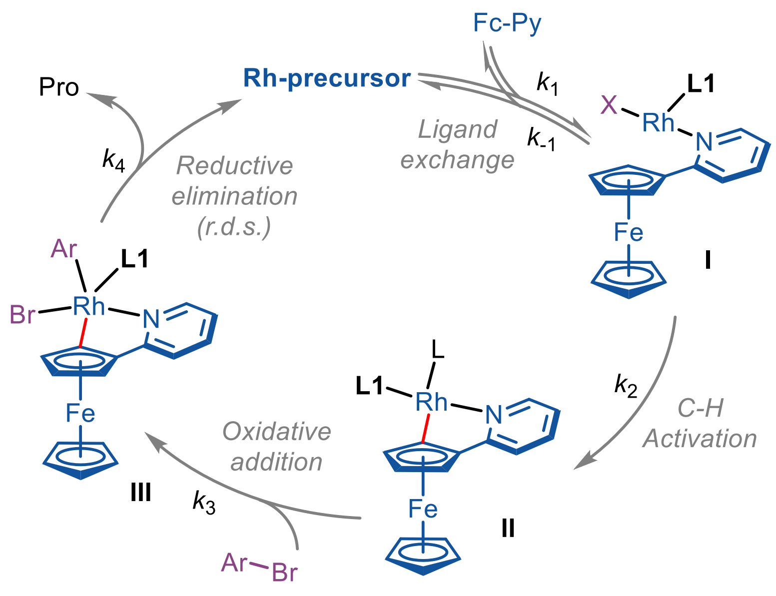


4.6 kcal/mol

With Dr. Xie and Prof. Zheng

Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

Derivation of the Rate Law



1. The rate of coordination of 2-pyridinylferrocenes with the Rh-precursors to form **I** is much faster than either the dissociation of **I** or the following C−H activation (k_1[Fc−Py] ≫ $k_{-1} + k_2$).

2. the rate of oxidative addition of **II** with aryl bromide is much faster than the C−H activation (k_3[Ar−Br] ≫ k_2).

Steady-state approximation for intermediates **I**, **II** and **III**:

k_1[Rh][Fc-Py] = ($k_{-1} + k_2$)[**I**]

k_2[**I**] = k_3[ArBr][**II**]

k_3[ArBr][**II**] = k_4[**III**]

Mass balance for all Rh species:

$$[\mathrm{Rh}]_{total} = [\mathrm{Rh}] + [\mathbf{I}] + [\mathbf{II}] + [\mathbf{III}]$$

$$= \frac{k_{-1}+k_2}{k_1[\mathrm{Fc-Py}]}[\mathbf{I}] + [\mathbf{I}] + \frac{k_2}{k_3[\mathrm{ArBr}]}[\mathbf{I}] + \frac{k_2}{k_4}[\mathbf{I}]$$

$$= \left(\frac{k_{-1}+k_2}{k_1[\mathrm{Fc-Py}]} + 1 + \frac{k_2}{k_3[\mathrm{ArBr}]} + \frac{k_2}{k_4}\right)[\mathbf{I}]$$

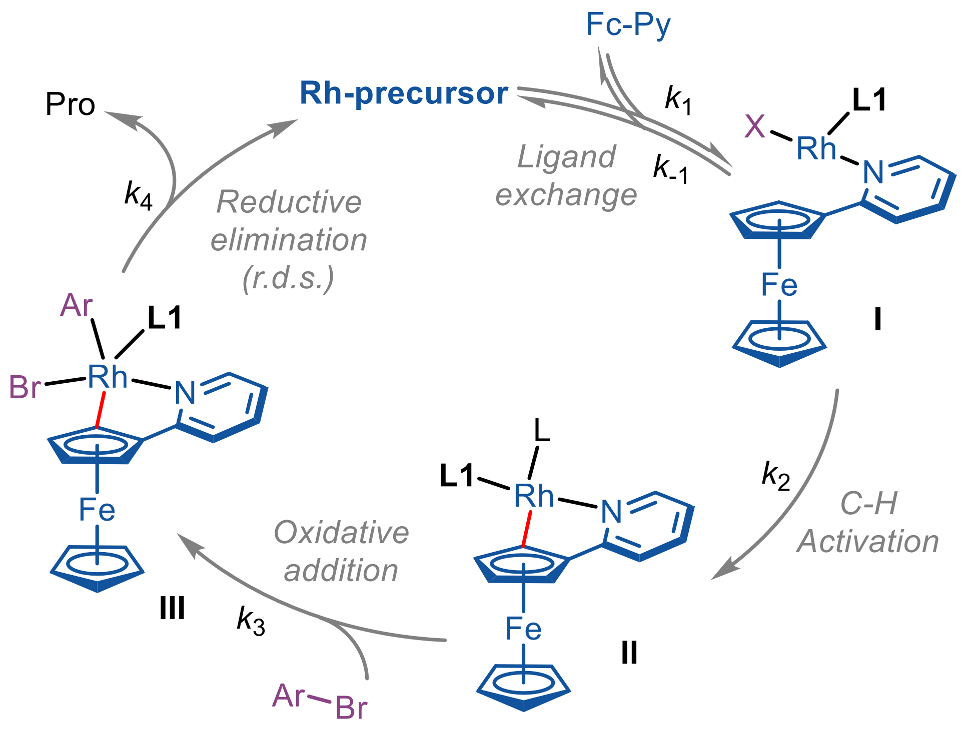
Final reaction rate equation:

$$\text{rate} = k_4[\mathbf{III}] = k_2[\mathbf{I}] = \frac{k_2[\mathrm{Rh}]_{total}}{\frac{k_{-1}+k_2}{k_1[\mathrm{Fc-Py}]} + 1 + \frac{k_2}{k_3[\mathrm{ArBr}]} + \frac{k_2}{k_4}} \approx \frac{k_2 k_4}{k_2 + k_4}[\mathrm{Rh}]_{total}$$

When k_1[Fc–Py] ≫ $k_{-1} + k_2$ and k_3[Ar–Br] ≫ k_2.

Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

Conclusion



The rate-determining step:

1. NMR experiments
2. DFT calculation
3. KIE experiments
4. Reaction Progress Kinetic Analysis (RPKA)
5. Hammett plots
6. Derivation of the Rate Law

The sequence of reaction:

1. NMR experiments
2. HRMS experiments

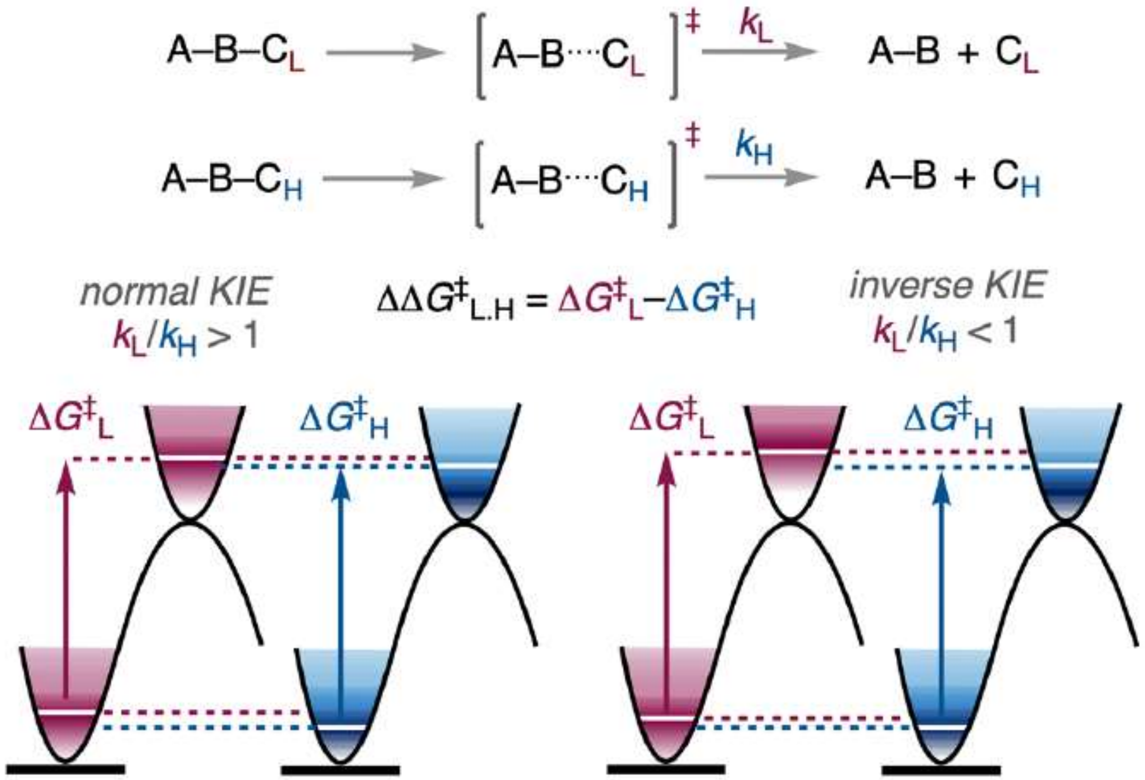
Liu, C.-X.; Xie, P.-P.; Zhao, F.; Wang, Q.; Feng, Z.; Wang, H.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2023**, *145*, 4765-4773.

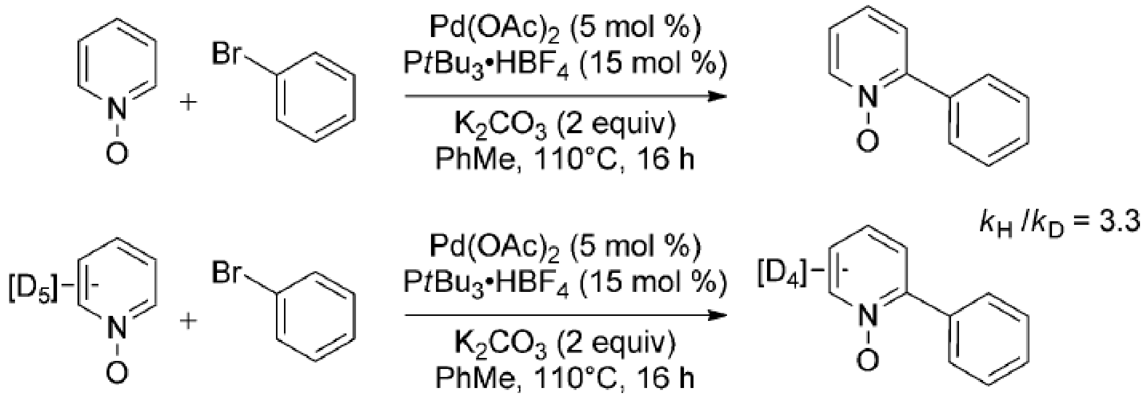
Thanks very much for your attention.

How to find the rate-determining step?

H/D KIE experiment

It needs to synthesize the substrate and **deuterated substrate**.





The C-H bond cleavage maybe the **rate-determining step** of a direct arylation reaction.

Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-G.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180-8189.

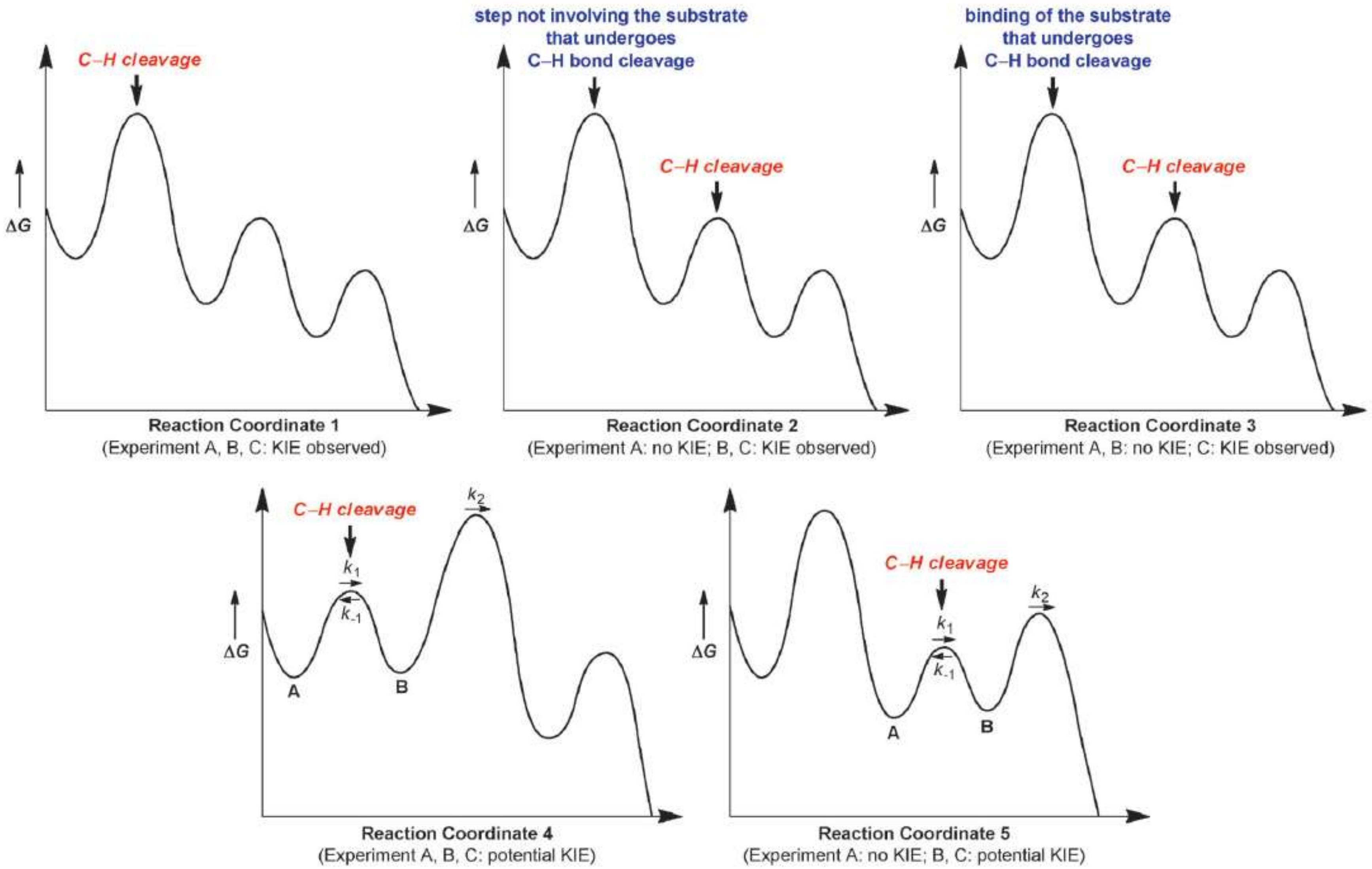
$\Delta G_L / \Delta G_H > 1$, so **normal KIE $k_L/k_H > 1$**

Generally speaking, **KIE = k_H/k_D > 2**; C-H bond cleavage maybe the **rate-determining step**.

H: heavy (D)
L: light (H)

Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.
Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

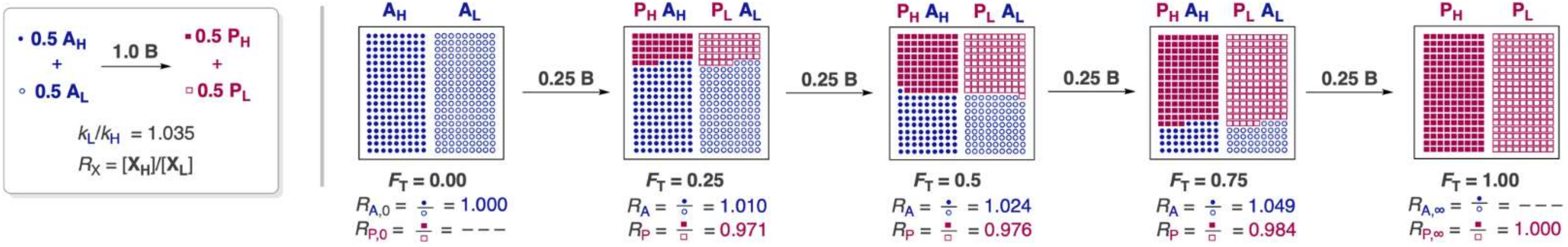


Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.

How to find the rate-determining step?

^{13}C KIE experiment: KIE measured at natural-abundance

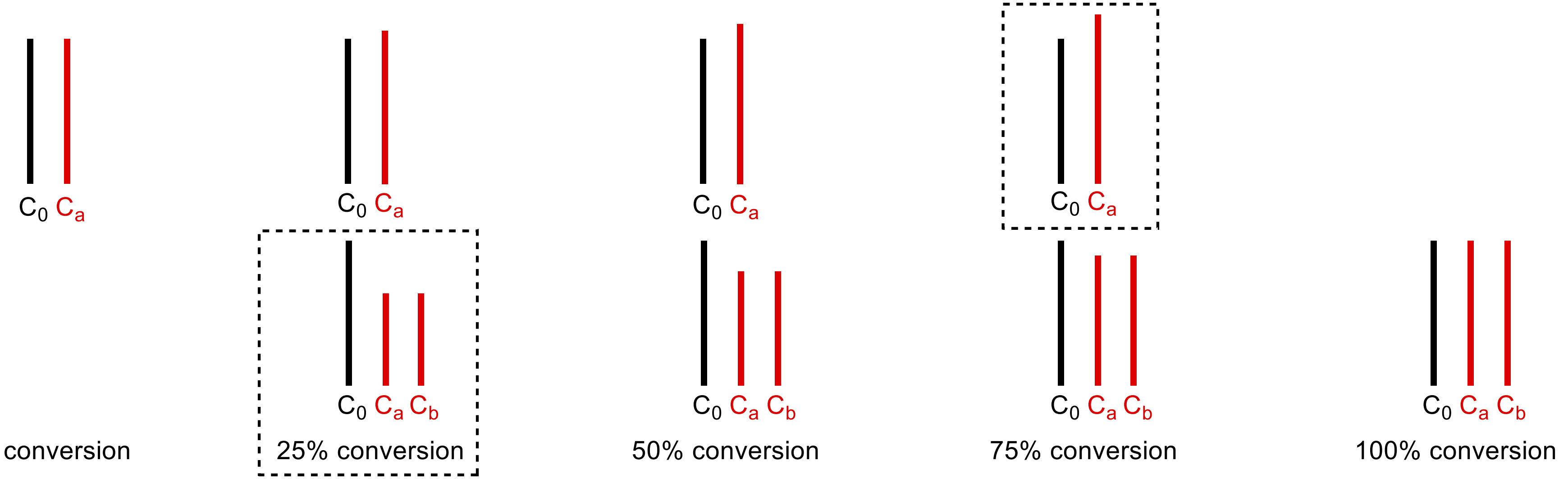
H: heavy; L: light



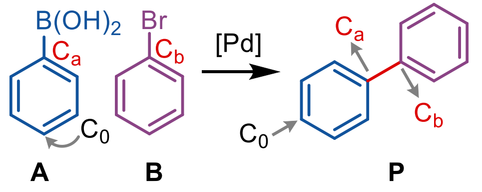
Quantitative ^{13}C NMR:

^{13}C NMR of **A**:

^{13}C NMR of **P**:



For example:



Assume that reductive elimination is the rate-determining step.

Dale, H. J. A.; Leach, A. G.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2021**, *143*, 21079-21099.

How to find the rate-determining step?

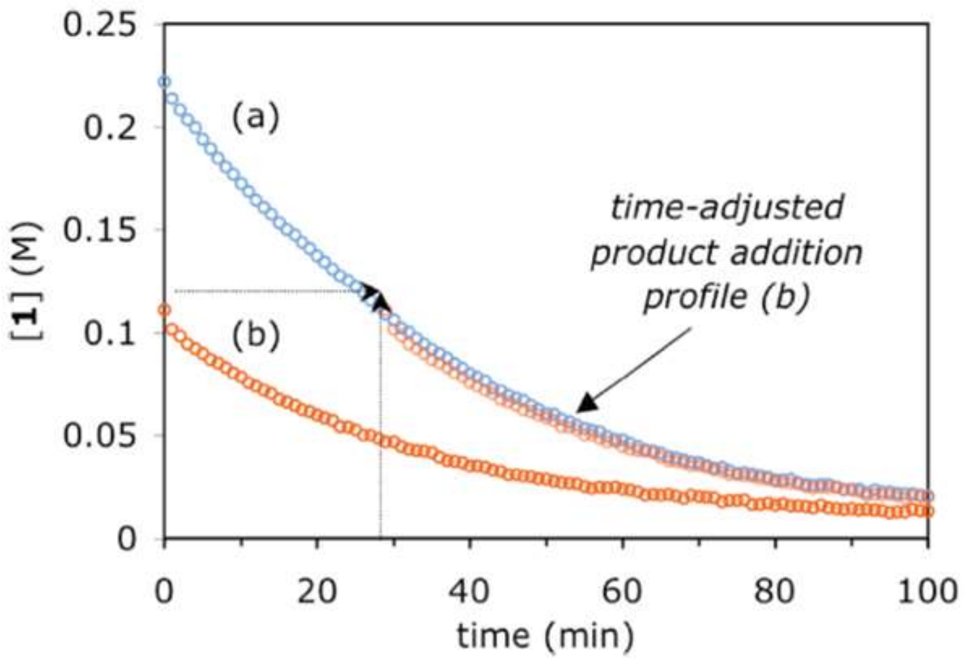
Same "excess" experiments

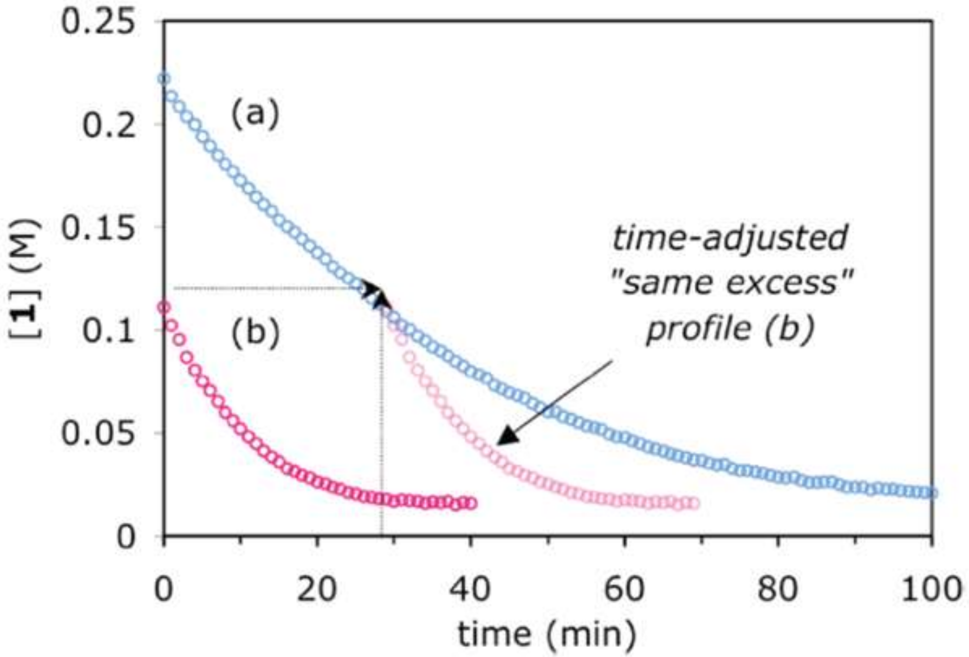
1 + **2** (2.0 equiv) → **3**

(a) $[1]_0$ = 0.22 M, $[2]_0$ = 0.44 M; **$[2]_0$ - $[1]_0$ = 0.22 M**

(b) $[1]_0$ = 0.11 M, $[2]_0$ = 0.33 M; **$[2]_0$ - $[1]_0$ = 0.22 M**

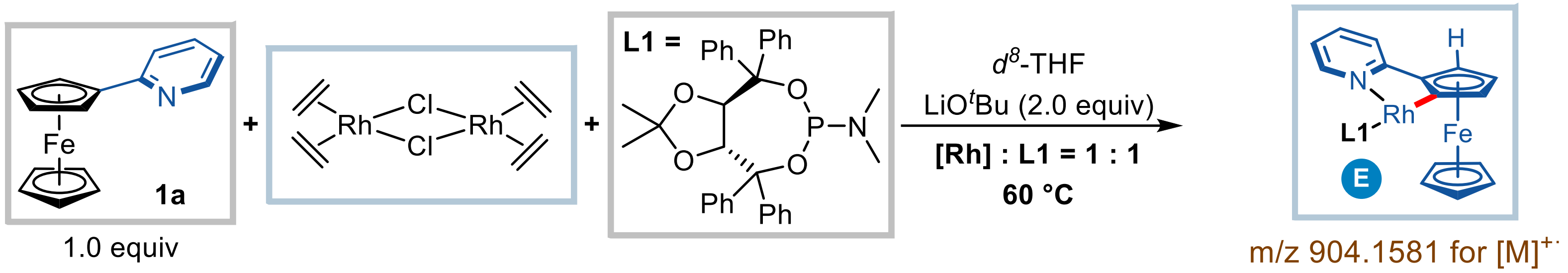
The "same excess" protocol: runs (a) and (b) have different initial concentration of substrates **1** and **2**, with the difference between the two (defined as the excess = $[\mathbf{2}]_0 - [\mathbf{1}]_0$) held the same.

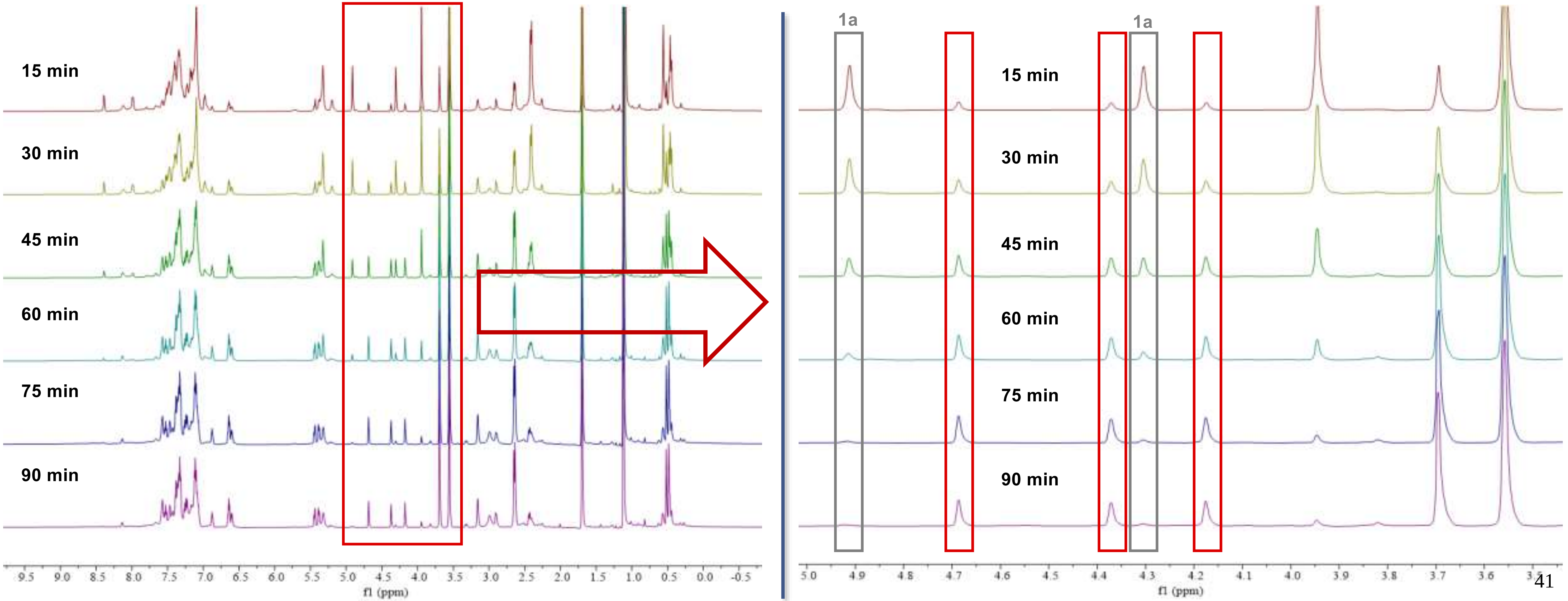




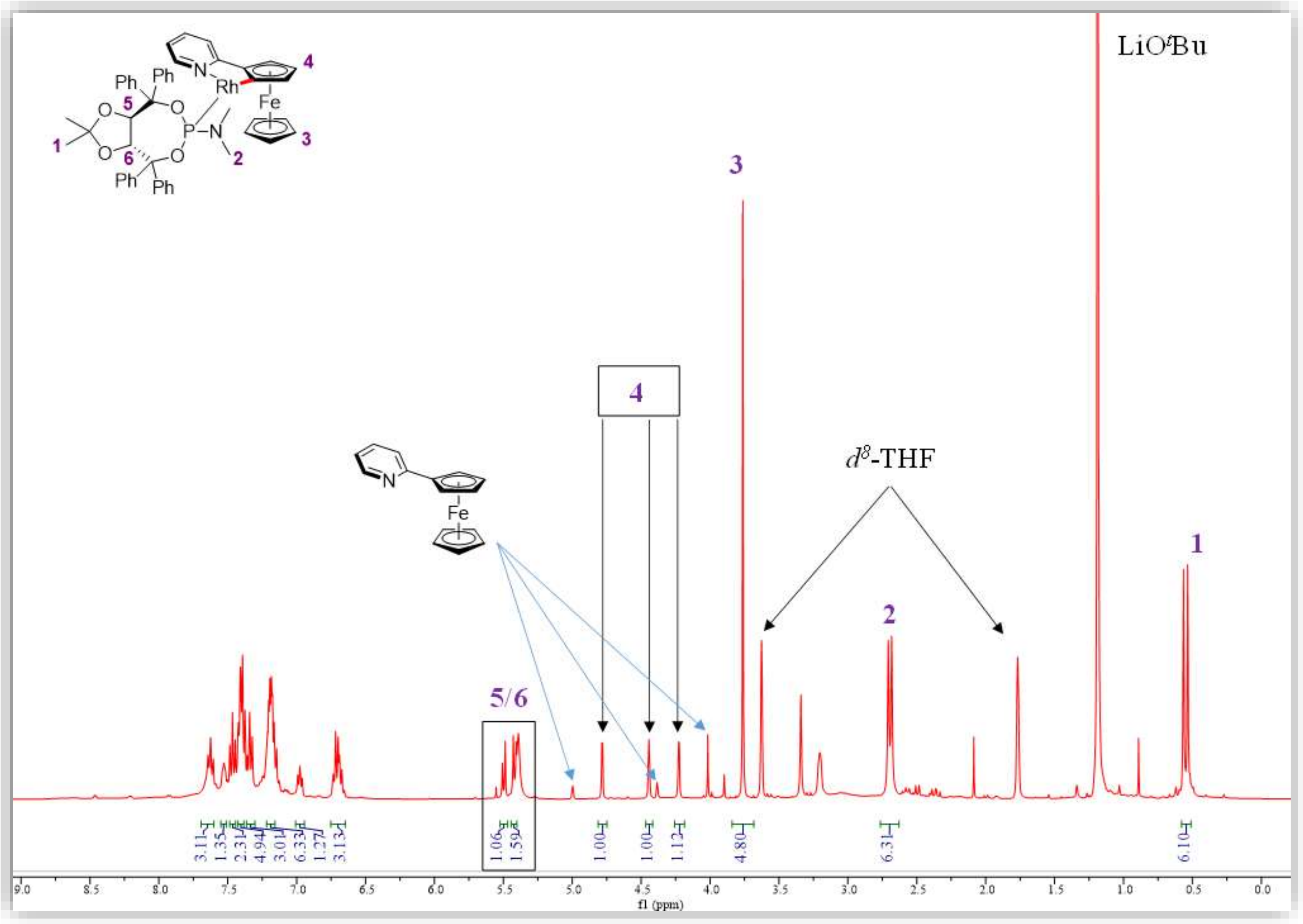
This possibility becomes useful to probe reactions for complexities such as **product inhibition** or **catalyst deactivation**.

^{1}H NMR experiment: C-H activation





^{1}H NMR experiment: C-H activation



How to find the rate-determining step?

Steady-state approximation

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

1. The overall rate of product formation: $v = k_2 [ES]$

2. Rate of formation of [ES]: $v_f = k_1[E][S]$

3. Rate of decomposition of [ES]:

$$v_d = k_{-1}[ES] + k_2 [ES]$$

4. Rate of ES formation = Rate of ES decomposition (steady state)

5. So: $k_1[E][S] = k_{-1}[ES] + k_2 [ES]$