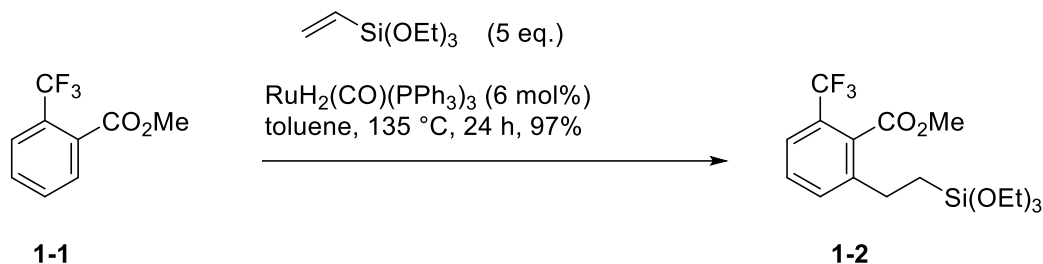


Problem Session (6)

2024.9.14. Shu Nakamura

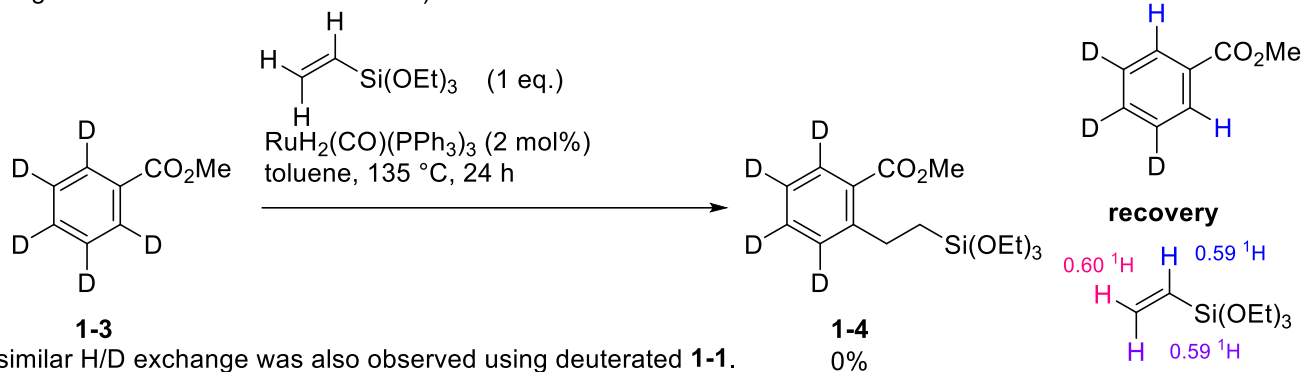
Please propose rational catalytic cycles consistent with the following observations in the boxes. Also, please indicate the rate-determining step (RDS; or turnover-limiting step) of each cycle.

1.



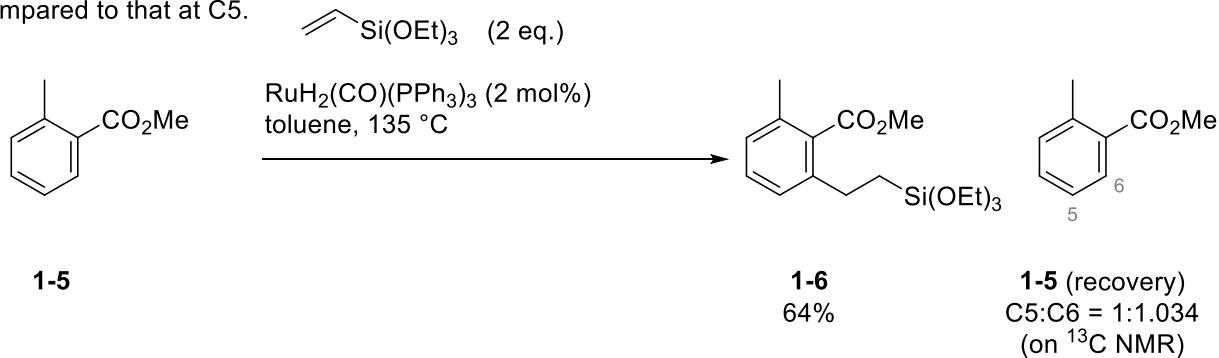
a) $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$ can also work in this reaction while $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ cannot.

b) Product **1-4** was not obtained. However, recovered materials contained both ^1H and D (^2H) (Integrations on ^1H NMR were shown).

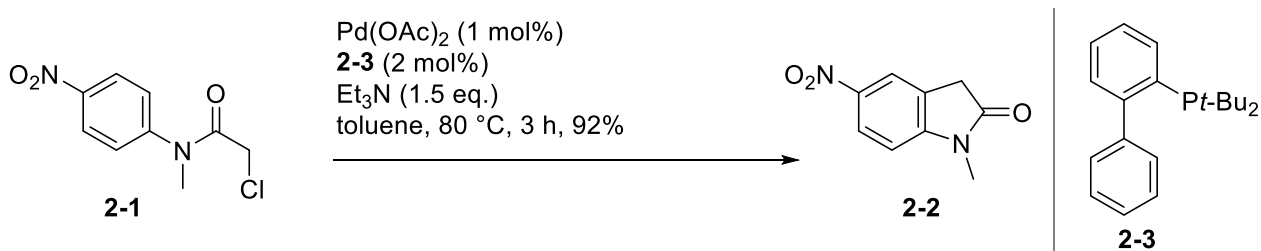


A similar H/D exchange was also observed using deuterated **1-1**.

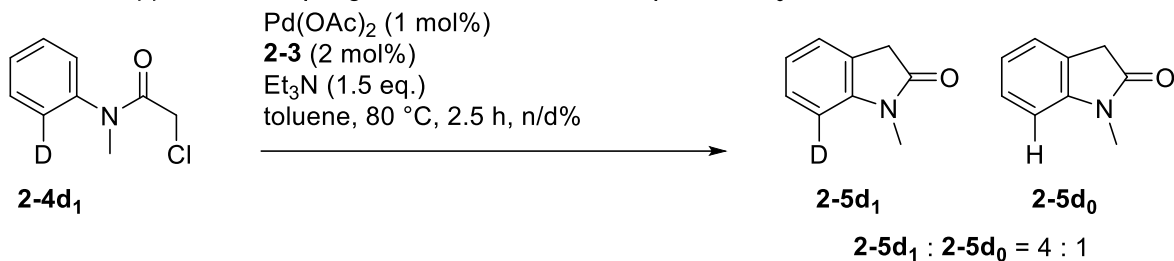
c) After the following experiment, the relative intensity of the ^{13}C isotope at C6 (of recovered **1-5**) was increased compared to that at C5.



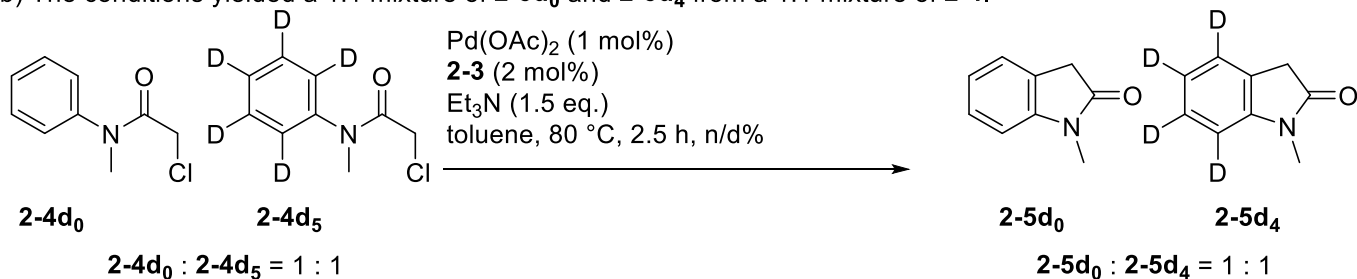
2.



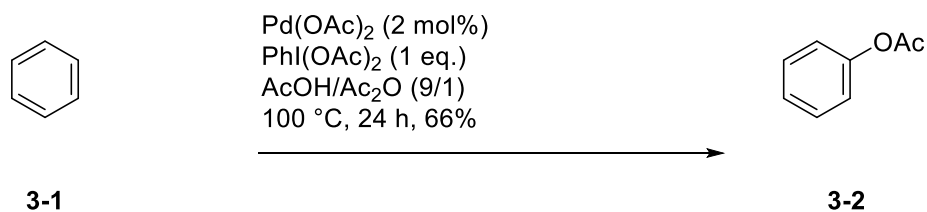
a) These conditions were applied to **2-4d₁** to give a 4:1 mixture of **2-5d₁** and **2-5d₀**.



b) The conditions yielded a 1:1 mixture of **2-5d₀** and **2-5d₄** from a 1:1 mixture of **2-4**.



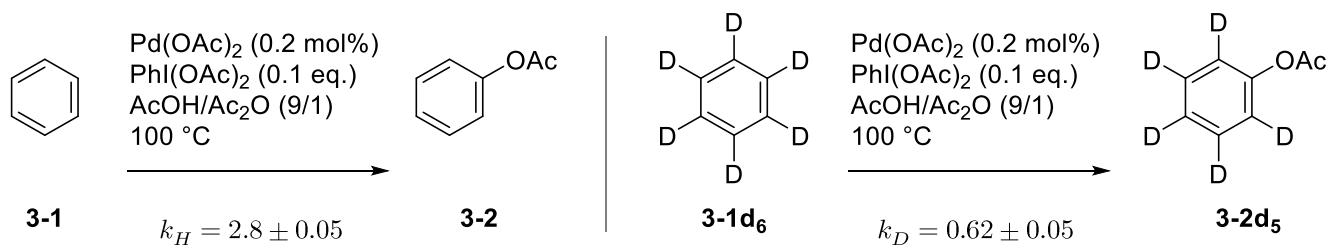
3.



a) The kinetic orders of Pd(OAc)₂, benzene, and PhI(OAc)₂ were estimated as below.

Pd(OAc)₂: half order, benzene: first order, PhI(OAc)₂: zero order

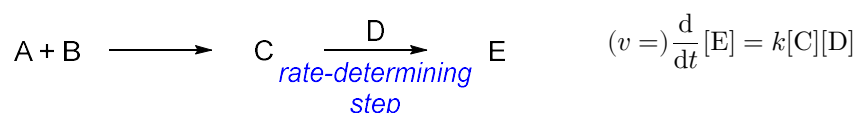
b) Rate constant (k_H , k_D) were estimated independently.



Problem Session (6)

2024.9.14. Shu Nakamura

Topic: Chemical kinetics



Usually, a reaction can be divided into several elementary reactions, among which the rate-determining step (RDS) is most important.

Kinetic Isotope Effect (KIE)

Zero-point energy (ZPE) of C-D bond is smaller than that of C-H bond.

→ More energy is required to activate C-D bond.

→ Cleavage of C-D bond is slower than that of C-H bond.

$$\begin{aligned} \text{ZPE}(\text{CD}) &= \frac{1}{2} h \nu_{\text{CD}} \\ &= \frac{1}{2} h \cdot \frac{1}{2\pi} \sqrt{\frac{k}{\mu_{\text{CD}}}} \\ &= \frac{1}{2} h \cdot \frac{1}{2\pi} \sqrt{\frac{\mu_{\text{CH}}}{\mu_{\text{CD}}}} \sqrt{\frac{k}{\mu_{\text{CH}}}} \\ &= \sqrt{\frac{\mu_{\text{CH}}}{\mu_{\text{CD}}}} \text{ZPE}(\text{CH}) \quad (\mu_{\text{CD}} > \mu_{\text{CH}}) \end{aligned}$$

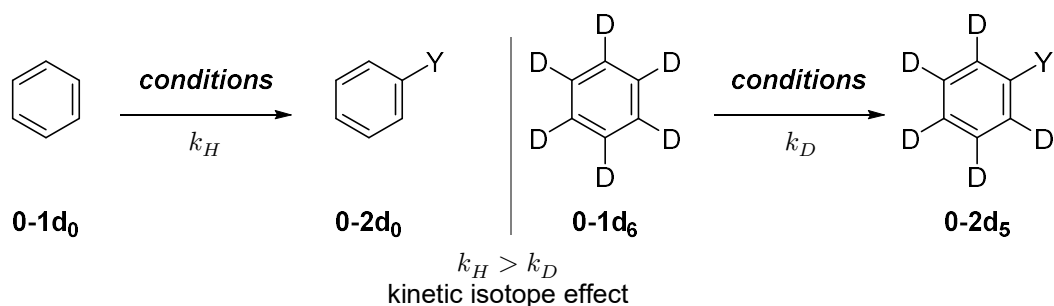
If RDS includes X-H bond dissociation, replacing H with D can slow down the overall reaction. (*kinetic isotope effect*)

→ Kinetic analysis with deuterated substrate can help to find RDS.

Isotope labeled experiment

There are three types of KIE experiments, and only type I can accurately observe KIE.¹⁾
(→ problem 2)

Type I: k_H and k_D are measured individually (problem 3).



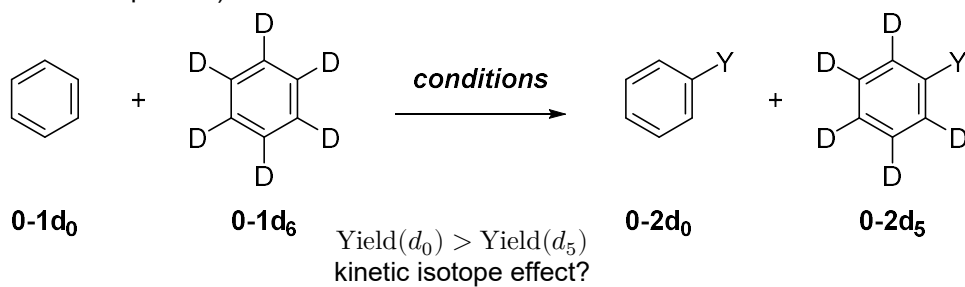
Typical magnitudes of KIE²⁾³⁾

$k_H/k_D \geq \sqrt{2}$: primary kinetic isotope effect (dissociation of C-D bond)

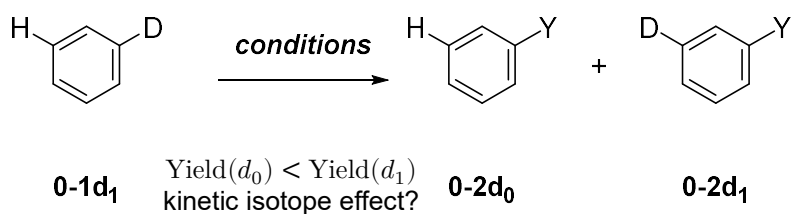
$1 < k_H/k_D < 1.2$: secondary KIE (change in hybridization (of the carbon bonding D) or C-D hyperconjugation)

$k_H/k_D < 1$: inverse KIE (rehybridization from sp^2 to sp^3)

Type II: The conditions were applied to a mixture of starting material and deuterated one (problem 1, 2).
(intermolecular competition)



Type III: The experiment was performed using a deuterated substrate which had both reactive ^1H and D. (problem 2)
(intramolecular competition)

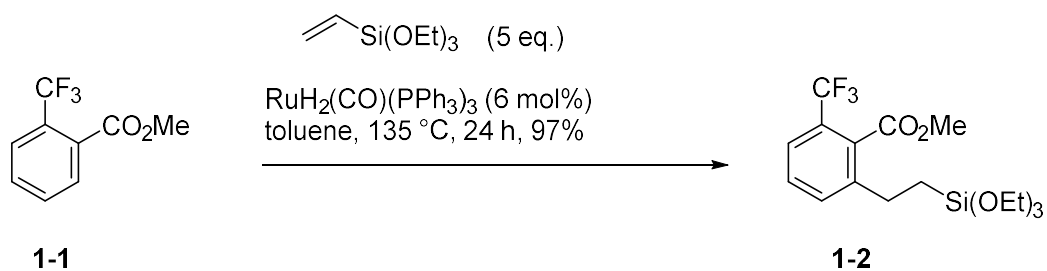


Note: **Oxidation numbers** are depicted in this answer.

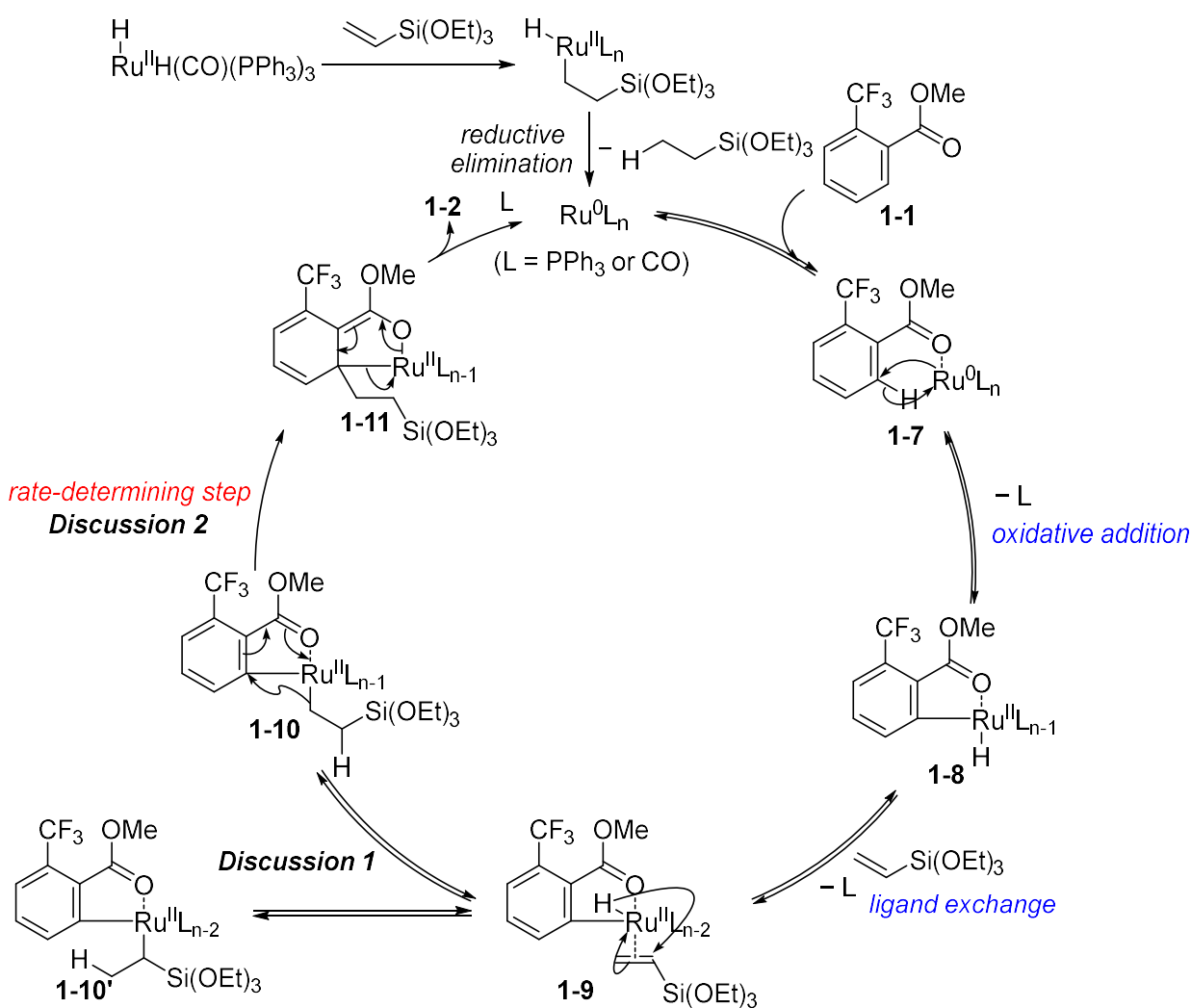
Sum of oxidation numbers or formal charges is preserved throughout the reaction (\leftarrow charge conservation)

Therefore, oxidation numbers and formal charges would be useful tools for thinking about the reaction mechanism.

1.

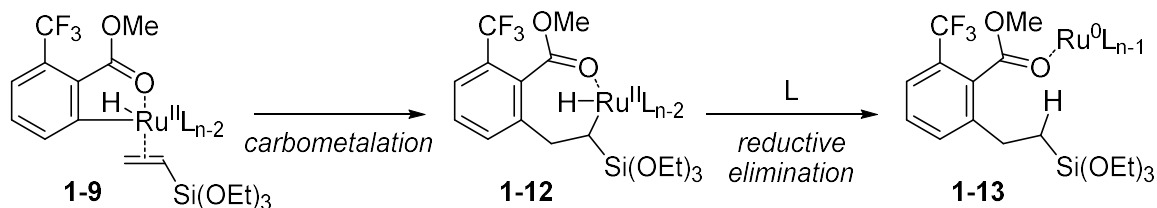
Kakiuchi, F.; Ohtaki, H.; Sonoda, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, *30*, 918.Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62.

- a) The active catalyst would be Ru^0 .
 b) C-H activation should be a reversible reaction.
 c) The rate-determining step involves C6 bond dissociation/construction.



Discussion 1: Construction of C-C bond

Another possible pathway



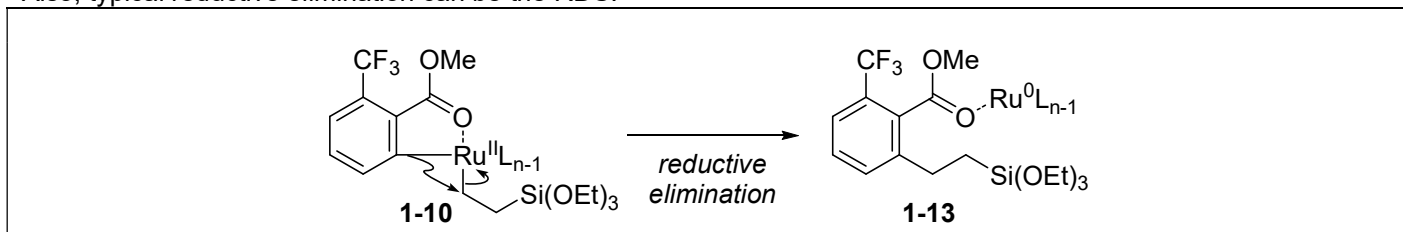
To explain the H/D exchange (b), reverse reaction from **1-13** to **1-9** should exist. However, that would conflict with the rate-determining step.

Discussion 2: Rate determining step

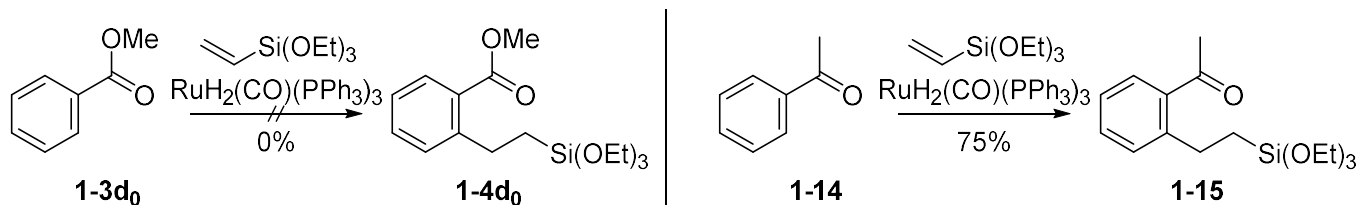
- b) The reverse reaction from **1-10** to **1-1** should exist.
- c) Kinetic isotope effect (of ^{13}C) was observed at C6.
(The reaction from C6 ^{13}C -isotoped substrate was slower.)

→RDS should be the reductive elimination.

Also, typical reductive elimination can be the RDS.

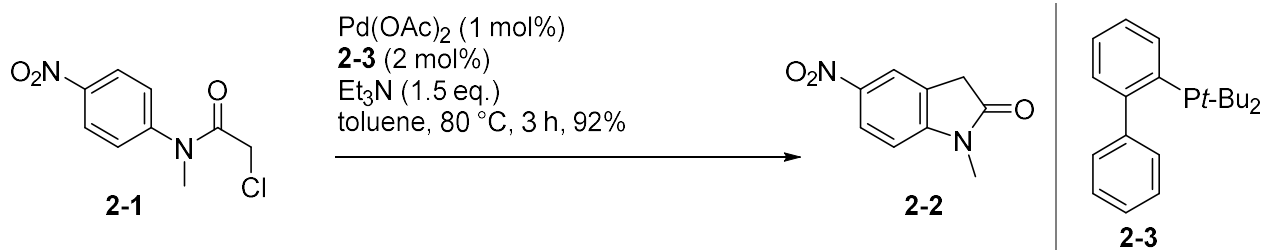
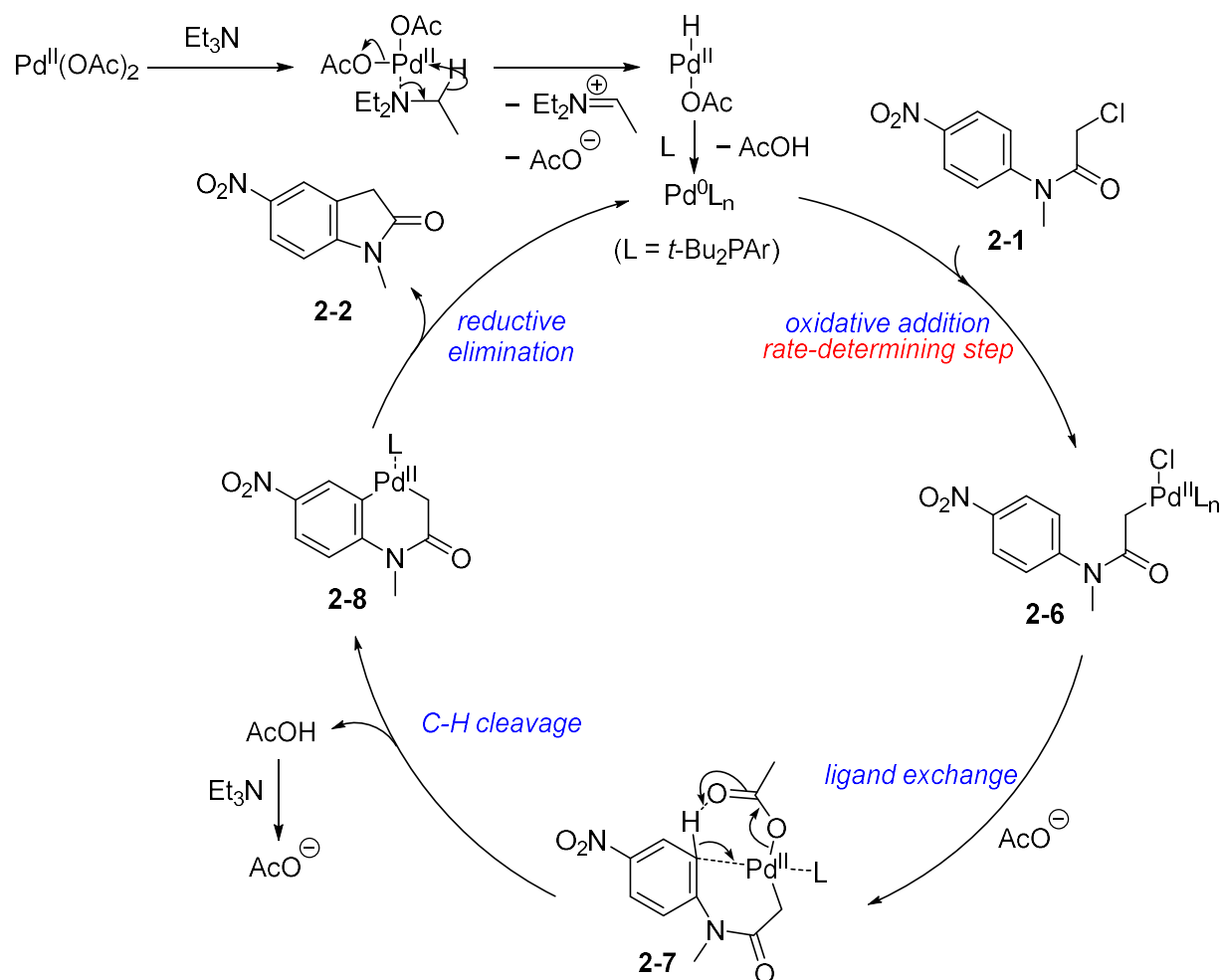


This type of elimination is known to be accelerated by electron donating group⁴), which conflicts with the observation (b).



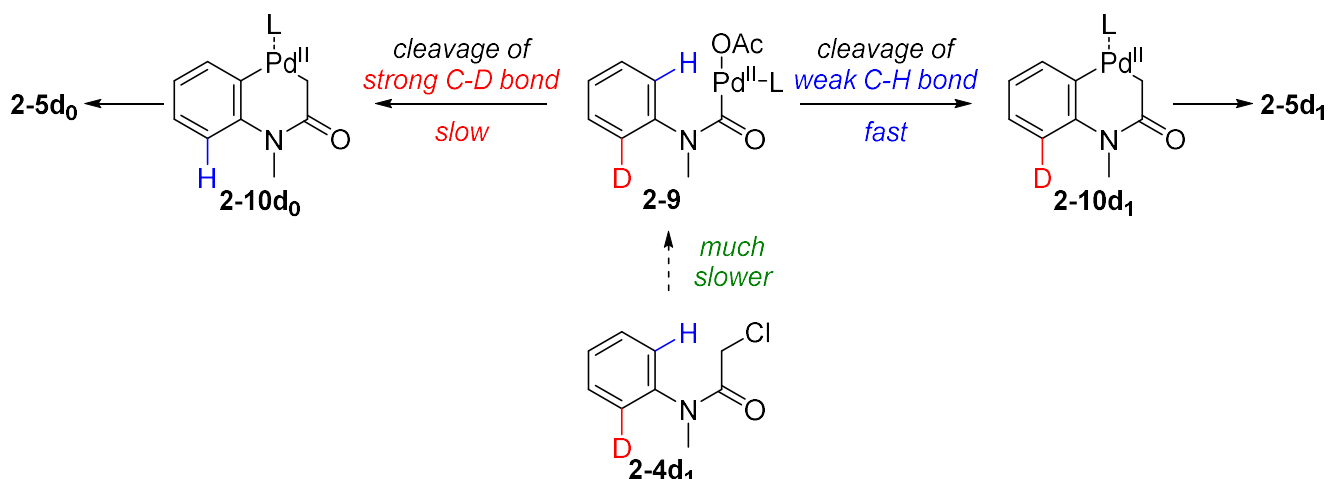
Considering these observations, nucleophilic C-C bond formation was proposed this time.

2.

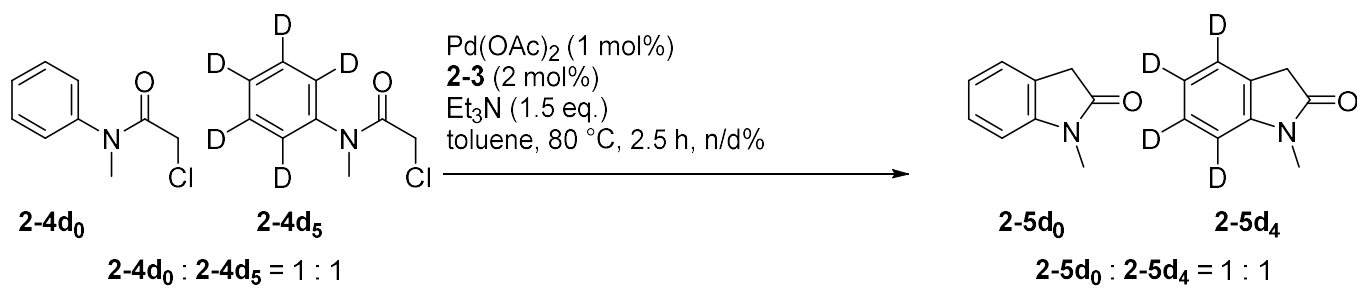
Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

Discussion: Kinetic Isotope Effect (KIE)

The bond strength of C-D and C-H bonds is different, so the weaker C-H bond of **2-9** can be selectively cleaved (a). However, that result does not exclude that much slower step (RDS) exist *before* the C-H cleavage.

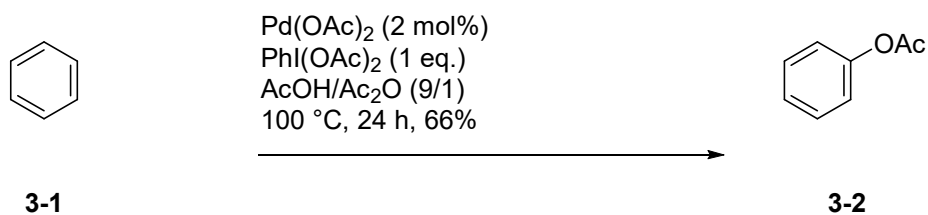


Actually, the overall rate was same for **2-4_{d0}** and deuterated **2-4_{d5}**, indicating that the C-H cleavage was not the rate-determining step.

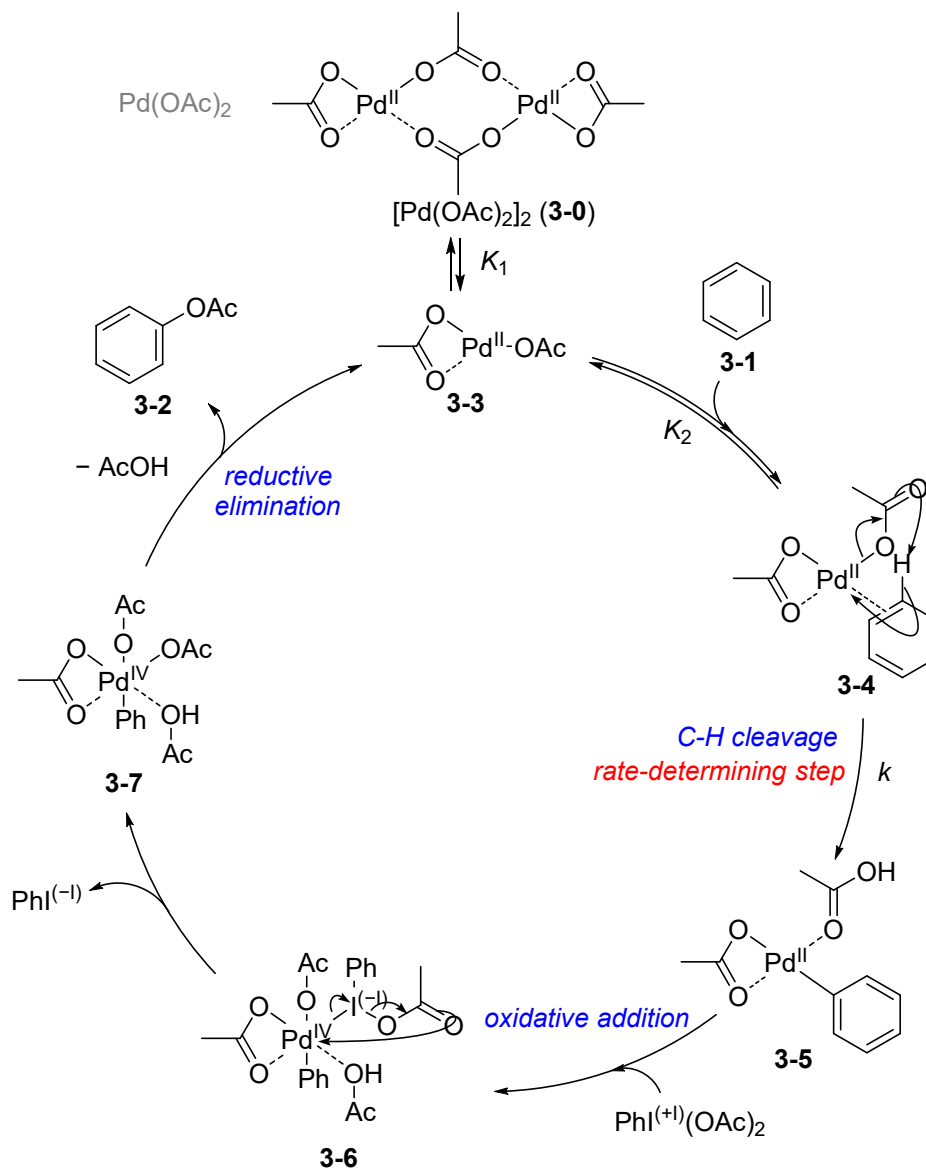


To correctly observe KIE, the reaction rates k_H, k_D should be estimated independently.
(Type II can show wrong effect if actual RDS is a step *without* deuterated substrate before C-H cleavage.¹⁾)

3.

Cook, A. K.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3109.

- a) A dimeric resting state of [Pd] would exist.
 RDS should involve benzene, but not PhI(OAc)_2 .
- b) RDS should involve C-H cleavage.



$$\begin{aligned}
 \frac{d}{dt}[\mathbf{3-2}] &= k[\mathbf{3-4}] \\
 &= kK_2[\mathbf{3-3}][\text{benzene}] \\
 &= kK_2\sqrt{K_1}[\mathbf{3-0}]^{1/2}[\text{benzene}] \quad \left(\because K_1 = \frac{[\mathbf{3-3}]^2}{[\mathbf{3-0}]} \right)
 \end{aligned}$$

Discussion 1: Aggregation

When $\text{Pd}(\text{OCOFCF}_3)_2$, which was known to exist as a monomer in organic solvents, was used instead of palladium diacetate, the acetoxylation was **first order** in $[\text{Pd}]$.

→Equilibrium with a dimeric form would account for the half-order dependence.

Discussion 2: C-H activation

KIE was observed. ($k_H/k_D = 4.5$)

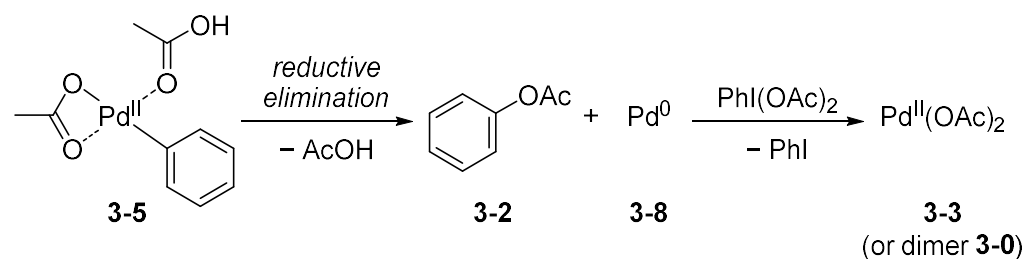
→RDS should be C-H cleavage.

This reaction is zero order in $\text{PhI}(\text{OAc})_2$.

→The step involving $\text{PhI}(\text{OAc})_2$ should be after RDS.

Therefore, C-H activation should take place from **3-4**.

Also, reductive elimination from **3-5** (O/II-cycle) can be drawn.



If this cycle proceeded, PhOCOFCF_3 would be produced instead of **3-2** and $\text{Pd}(\text{OCOFCF}_3)_2$ would become the same Pd species **3-3** in the 2nd cycle. Therefore, oxidation of **3-5** would be the actual path.

References:

- 1) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.
- 2) Gómez-Gallego, M.; Sirra, M. A. *Chem. Rev.* **2011**, *111*, 4857.
- 3) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401.
- 4) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857.