



**SELECTIVE CATALYTIC C-H ALKYLATION OF ALKENES  
WITH ALCOHOLS**

**SCIENCE 2011, 333(6049), 1613-1616**

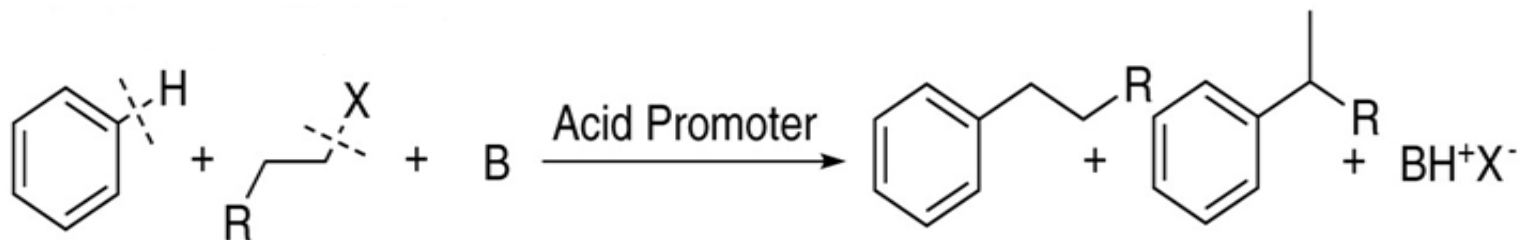
**DONG-HWAN LEE, KI HYEOK KWON, AND CHAE S. YI**

# Applications of Selective Catalytic Alkylation

- Petrochemical processing
- Synthesis of pharmaceutical products
- Production of desired compounds from available and environmentally benign feedstock



# Friedel-Crafts Alkylation



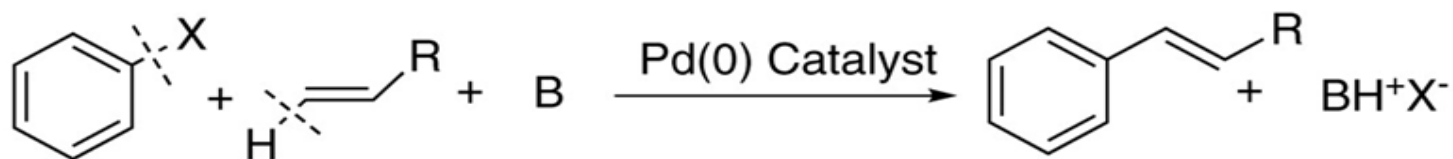
B = organic or inorganic base; R = alkyl, aryl; X = Cl, Br, I, OTf

- ⊙ Used in industrial-scale alkylation processes

Drawback:

- ⊙ Requires stoichiometric amounts of Lewis acid promoters and base to neutralize acid by-products

# Mizoroki-Heck Coupling Reaction



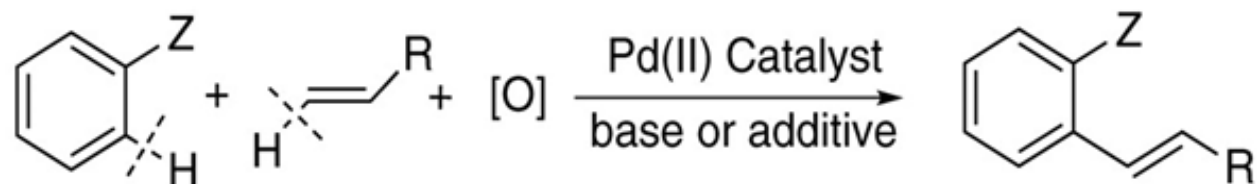
B = organic or inorganic base; R = aryl, carbonyl group; X = Cl, Br, I, OTf

- ⊙ Used for direct alkenylation of arenes

Drawbacks:

- ⊙ Requires stoichiometric base
- ⊙ Limited to activated olefins reagents

# Chelate-Assisted Arene C-H Alkyenylation



Z = oxygen or nitrogen chelate directing group; R = alkyl, aryl, carbonyl group  
[O] = O<sub>2</sub>, H<sub>2</sub>O<sub>2</sub> or metal oxidant

- ⊙ C-H bond activation reactions for direct couplings of arenes and alkenes

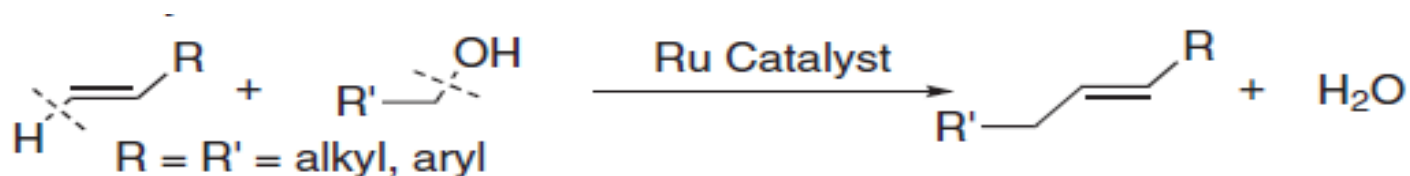
Drawbacks:

- ⊙ Limited substrate scope
- ⊙ Requires chelate-directing group, stoichiometric oxidants and additives

# To Alcohol!



# Why Alcohols as Alkylating Reagents?



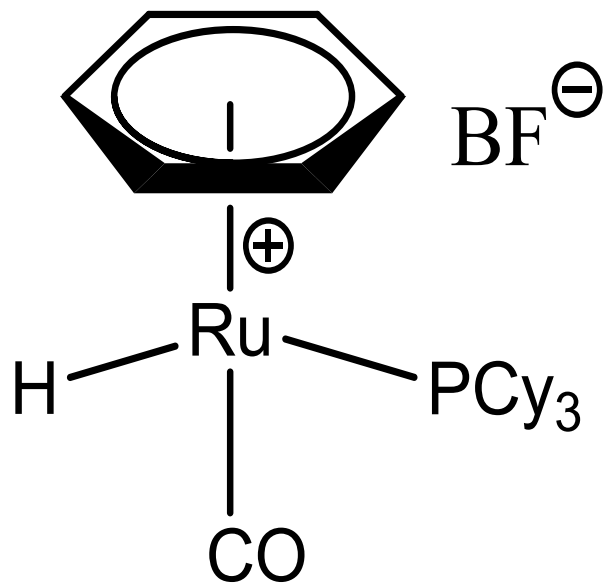
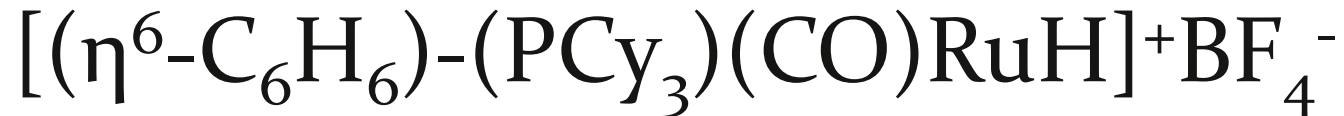
- ⊙ Economical (aka: CHEAP)
- ⊙ Water only by-product (aka: GREEN)

Drawback:

- ⊙ Tendency to undergo alkoxylation and dehydrogenation instead of C-O bond cleavage step



# Cationic Ruthenium Hydride Complex:

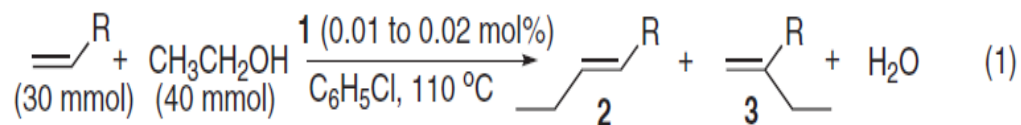


Oxidation State: Ru<sup>2+</sup>  
Total e<sup>-</sup> count: 18e<sup>-</sup>

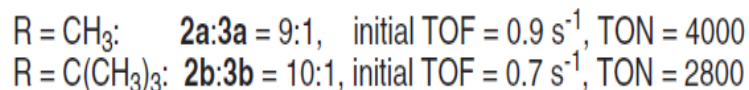
ivory- colored solid

# Initial Experiments with Catalyst

- Test feasibility of alcohols as alkylating agents using catalyst



**Equation 1.**



**Figure 1.** Fischer-Porter pressure bottle



# Other Catalysts Tested

**Table S1.** Catalyst survey for the alkylation of indene with 4-methoxybenzyl alcohol.<sup>†</sup>

| entry | Catalyst   | additive                           | time (h) | yield (%) |
|-------|--|------------------------------------|----------|-----------|
| 1     | [(C <sub>6</sub> H <sub>6</sub> )(PCy <sub>3</sub> )(CO)RuH]BF <sub>4</sub> (1)  |                                    | 2        | 96        |
| 2     | HBF <sub>4</sub> ·OEt <sub>2</sub>   |                                    | 2        | 0         |
| 3     | [RuH(CO)(PCy <sub>3</sub> ) <sub>4</sub> (O)(OH) <sub>2</sub>  |                                    | 2        | 2         |
| 4     | [RuH(CO)(PCy <sub>3</sub> ) <sub>4</sub> (O)(OH) <sub>2</sub>  | HBF <sub>4</sub> ·OEt <sub>2</sub> | 2        | 72        |
| 5     | RuCl <sub>3</sub> ·3H <sub>2</sub> O   | HBF <sub>4</sub> ·OEt <sub>2</sub> | 2        | 0         |
| 6     | RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>   |                                    | 2        | 0         |
| 7     | RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub>   | HBF <sub>4</sub> ·OEt <sub>2</sub> | 2        | trace     |
| 8     | RuH <sub>2</sub> (CO)(PPh <sub>3</sub> ) <sub>3</sub>  |                                    | 2        | 0         |
| 9     | RuH <sub>2</sub> (CO)(PPh <sub>3</sub> ) <sub>3</sub>  | HBF <sub>4</sub> ·OEt <sub>2</sub> | 2        | trace     |
| 10    | [RuCl <sub>2</sub> (COD)] <sub>x</sub>   | HBF <sub>4</sub> ·OEt <sub>2</sub> | 2        | 0         |
| 11    | [RuH(CO)(PCy <sub>3</sub> ) <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub> ] <sup>+</sup> BF <sub>4</sub> <sup>-</sup> |                                    | 2        | <5        |
| 12    | [( <i>p</i> -cymene)RuCl <sub>2</sub> ] <sub>2</sub>   |                                    | 2        | 0         |
| 13    | Ru <sub>3</sub> (CO) <sub>12</sub>   | NH <sub>4</sub> PF <sub>6</sub>    | 2        | 0         |
| 14    | CF <sub>3</sub> SO <sub>3</sub> H  |                                    | 2        | trace     |
| 15    | BF <sub>3</sub> ·OEt <sub>2</sub>  |                                    | 2        | 0         |
| 16    | Cy <sub>3</sub> PH <sup>+</sup> BF <sub>4</sub> <sup>-</sup>   |                                    | 2        | trace     |
| 17    | AlCl <sub>3</sub>  |                                    | 2        | trace     |
| 18    | FeCl <sub>3</sub> ·H <sub>2</sub> O  |                                    | 2        | 0         |
| 19    | Eu(OTf) <sub>3</sub>   |                                    | 2        | <5        |



<sup>†</sup> Reaction conditions: indene (1.0 mmol), 4-methoxybenzyl alcohol (1.1 mmol), catalyst (1.0 mol %), additive (1.0 equivalent to Ru), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), 75 °C. The product yield was determined by GC and GC-MS.

# Primary Alcohols with Cyclic Alkenes

| Entry | Alkene  | Alcohol   | Product(s)  | Temp (°C) | Time (h) | Yield (%) |
|-------|---|---|---|-----------|----------|-----------|
|       |  |   |  |           |          |           |
| 1     |   | ethanol   | 4a (n = 2, R = Et)  | 90        | 6        | 88*       |
| 2     |   | 1-hexanol   | 4b (n = 2, R = n-Hexyl)   | 90        | 6        | 79        |
| 3     |   | ArCH <sub>2</sub> OH  | 4c (n = 2, R = CH <sub>2</sub> Ar)  | 75        | 4        | 90        |
| 4     |   | (±)-ArCH(CH <sub>3</sub> )OH  | (±)-4d (n = 2, R = CH(CH <sub>3</sub> )Ar)  | 75        | 5        | 91        |
| 5     |   | p-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH | 4e (n = 1, R = CH <sub>2</sub> -p-Tol)  | 75        | 4        | 92        |
| 6     |   | ArCH <sub>2</sub> OH  | 4f (n = 3, R = CH <sub>2</sub> Ar)  | 75        | 4        | 84        |
| 7     |   | ArCH <sub>2</sub> OH  | 4g (n = 4, R = CH <sub>2</sub> Ar)  | 75        | 4        | 87        |

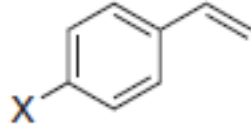
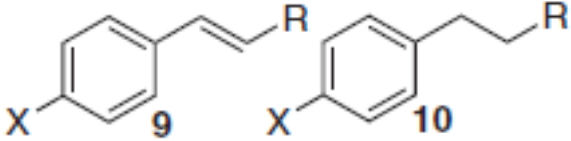
- Only linear alkylation products were formed
- Secondary aliphatic alcohols were found to be “sluggish,” resulting in lower yields

# Primary and Secondary Alcohols with Indene

| Entry | Alkene  | Alcohol   | Product(s)  | Temp (°C) | Time (h) | Yield (%) |
|-------|---|---|---|-----------|----------|-----------|
|       |  |   |      |           |          |           |
| 8     |   | ethanol   | 5a (R = Et)   | 90        | 5        | 84        |
| 9     |   | 1-hexanol   | 5b (R = <i>n</i> -Hexyl)  | 90        | 5        | 71        |
| 10    |   | 2-ethyl-1-hexanol   | 5c (R = CH <sub>2</sub> CH(CH <sub>3</sub> )C <sub>4</sub> H <sub>9</sub> )           | 90        | 5        | 57        |
| 11    |   | ( <i>R</i> )-PhCH(CH <sub>3</sub> )OH   | (±)-5d (R = CH(CH <sub>3</sub> )Ph)   | 75        | 3        | 86        |
| 12    |   | (±)-ArCH(CH <sub>3</sub> )OH  | (±)-5e (R = CH(CH <sub>3</sub> )Ar)   | 75        | 3        | 97        |
| 13    |   | ArCH <sub>2</sub> OH  | 5f (R = CH <sub>2</sub> Ar)   | 75        | 2        | 95        |
| 14    |   | <i>p</i> -CO <sub>2</sub> Me-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH | 5g (R = CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -CO <sub>2</sub> Me) | 75        | 3        | 91        |




- Regioselective 2-alkylation products formed

# Styrene Derivatives

| Entry | Alkene  | Alcohol              | Product(s)   | Temp (°C) | Time (h) | Yield (%) |
|-------|---|----------------------|--|-----------|----------|-----------|
|       |  |                      |  |           |          |           |
| 22    |   | 1-hexanol            | <b>9a:10a</b> = 8:1 (X = CH <sub>3</sub> , R = <i>n</i> -Hexyl)                    | 110       | 5        | 84        |
| 23    |   | ArCH <sub>2</sub> OH | <b>9b:10b</b> = 10:1 (X = CH <sub>3</sub> , R = CH <sub>2</sub> Ar)                | 90        | 5        | 91        |
| 24    |   | 1-hexanol            | <b>9c:10c</b> = 6:1 (X = Cl, R = <i>n</i> -Hexyl)                                  | 110       | 8        | 78        |
| 25    |   | ArCH <sub>2</sub> OH | <b>9d:10d</b> = 9:1 (X = Cl, R = CH <sub>2</sub> Ar)                               | 90        | 6        | 83        |

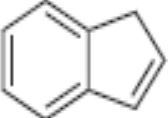
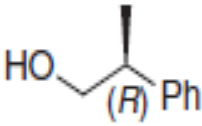
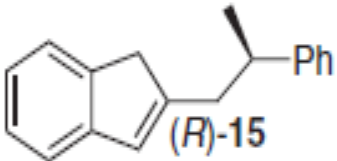
- Formed trans-alkylation products (>98% trans)
- Small amounts of hydrogenation products

# Intramolecular Alkylation

| Entry | Alkene  | Alcohol   | Product(s)   | Temp (°C) | Time (h) | Yield (%) |
|-------|---|---|--|-----------|----------|-----------|
| 28    |  |  | <br>14 | 110       | 8        | 71        |

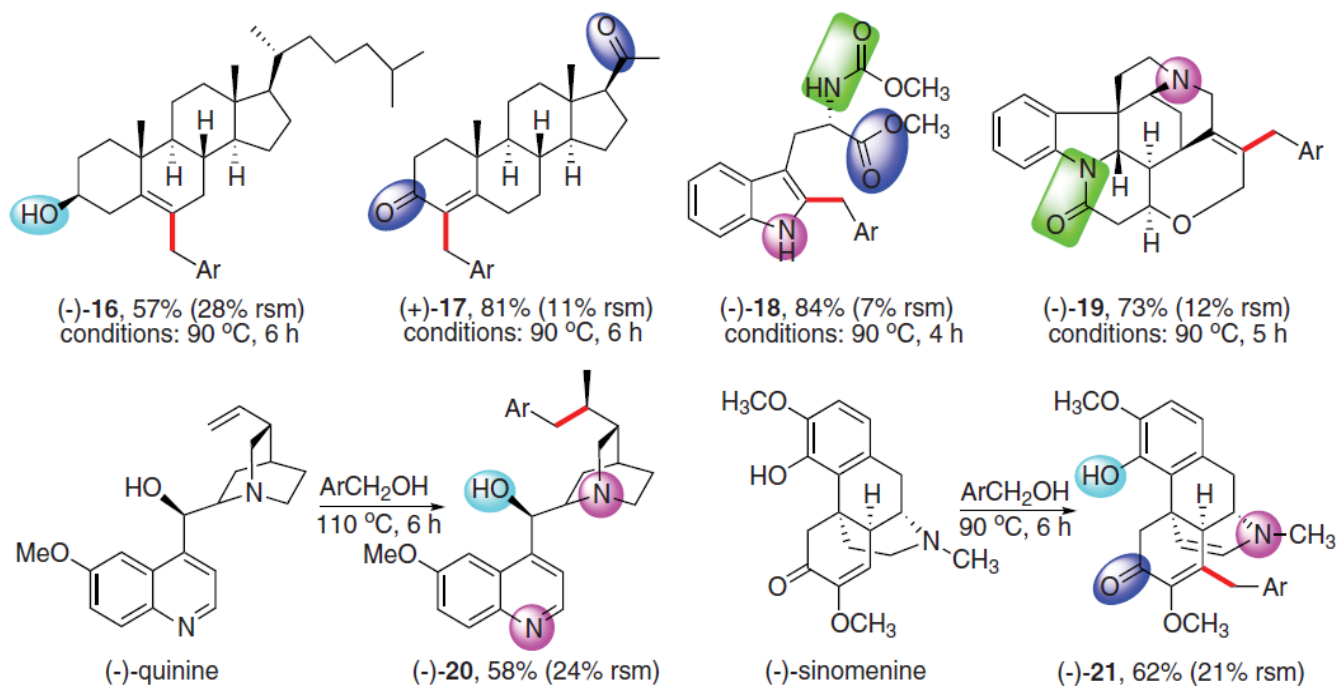
- Only formed p-cymene

# Indene

| Entry | Alkene  | Alcohol   | Product(s)   | Temp (°C) | Time (h) | Yield (%) |
|-------|---|---|--|-----------|----------|-----------|
| 29    |  |  |  | 90        | 3        | 87        |

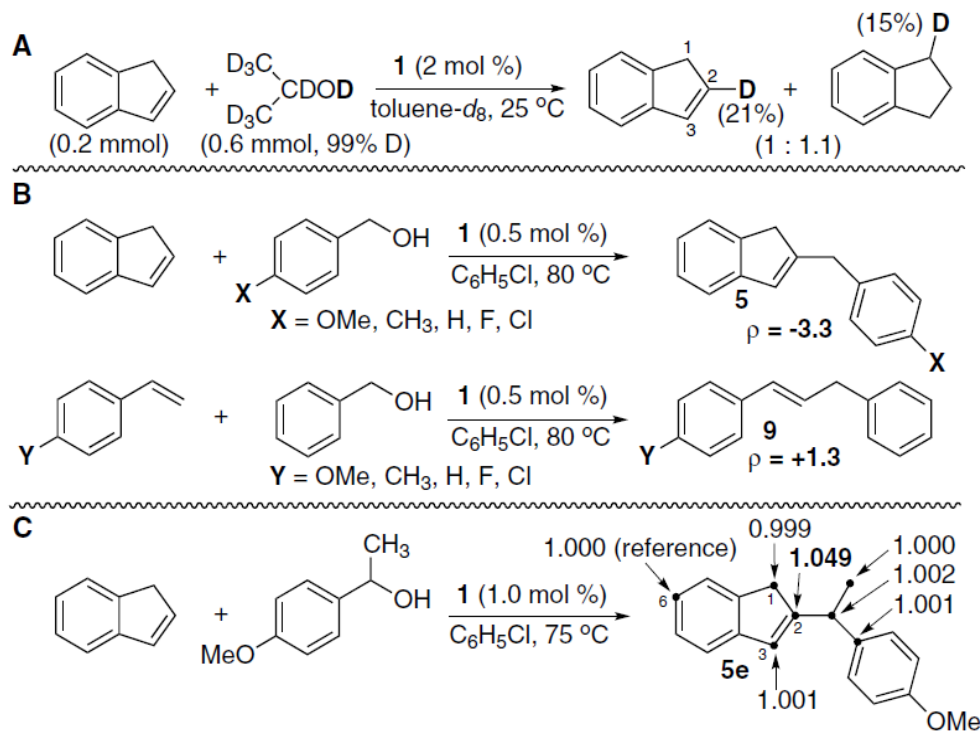
- ⊙ Formed optically PURE product
- ⊙ No racemization or branched alkylation products

# Alkylation of Biologically Active Alkene Substrates



**Fig. 2.** Alkylation of bioactive alkene compounds with 4-methoxybenzyl alcohol in C<sub>6</sub>H<sub>5</sub>Cl. rsm, recovered starting material; Ar, C<sub>6</sub>H<sub>4</sub>-*p*-OMe; Me, methyl.

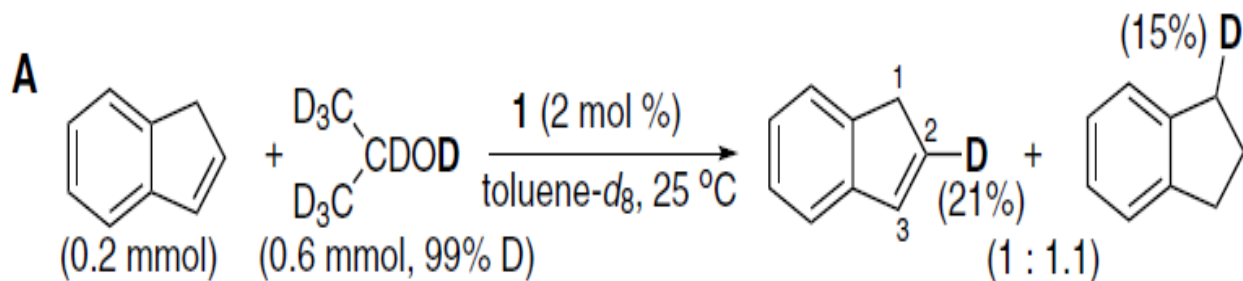
# Mechanistic Studies



**Fig. 3.** (A) Hydrogen-deuterium exchange experiment from the treatment of indene with 2-propanol- $d_8$  in toluene- $d_8$  at 25°C. (B) Hammett studies of the alkylations of indene with  $p\text{-X-C}_6\text{H}_4\text{CH}_2\text{OH}$  (X = OCH<sub>3</sub>, CH<sub>3</sub>, H, F, Cl) and  $p\text{-Y-C}_6\text{H}_4\text{CH}=\text{CH}_2$  (Y = OCH<sub>3</sub>, CH<sub>3</sub>, H, F, Cl) with benzyl alcohol. (C) Carbon isotope effect measurement for the alkylation of indene with 1-(4-methoxyphenyl)ethanol by using Singleton's method. The  $^{13}\text{C}$  isotope ratio of **5e** at 95% conversion was compared with the product isolated at 11 to 18% conversion (average of three runs).

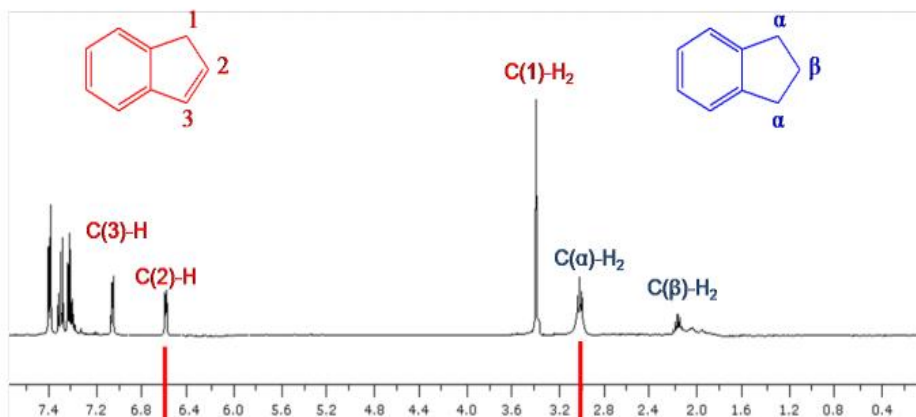
# Hydrogen-Deuterium Exchange

- In order to gain insight into the mechanism of this process, hydrogen-deuterium exchange was used



# $^1\text{H}$ and $^2\text{H}$ NMR Studies

$^1\text{H}$  NMR



$^2\text{H}$  NMR

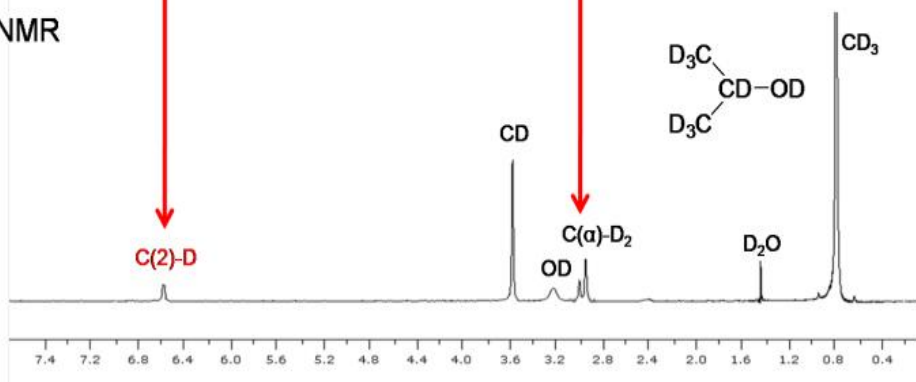
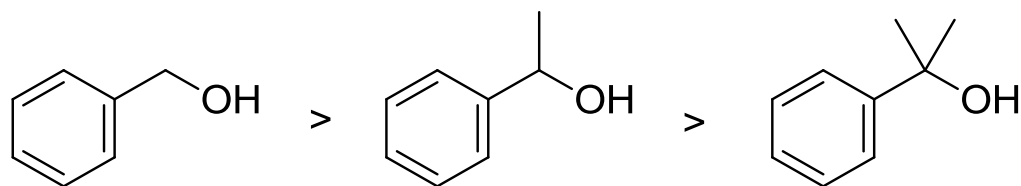


Figure S2.  $^1\text{H}$  and  $^2\text{H}$  NMR spectra of the reaction mixture of indene with 2-propanol-*d*<sub>8</sub> at 25 °C.

$3^\circ > 2^\circ > 1^\circ$ ?

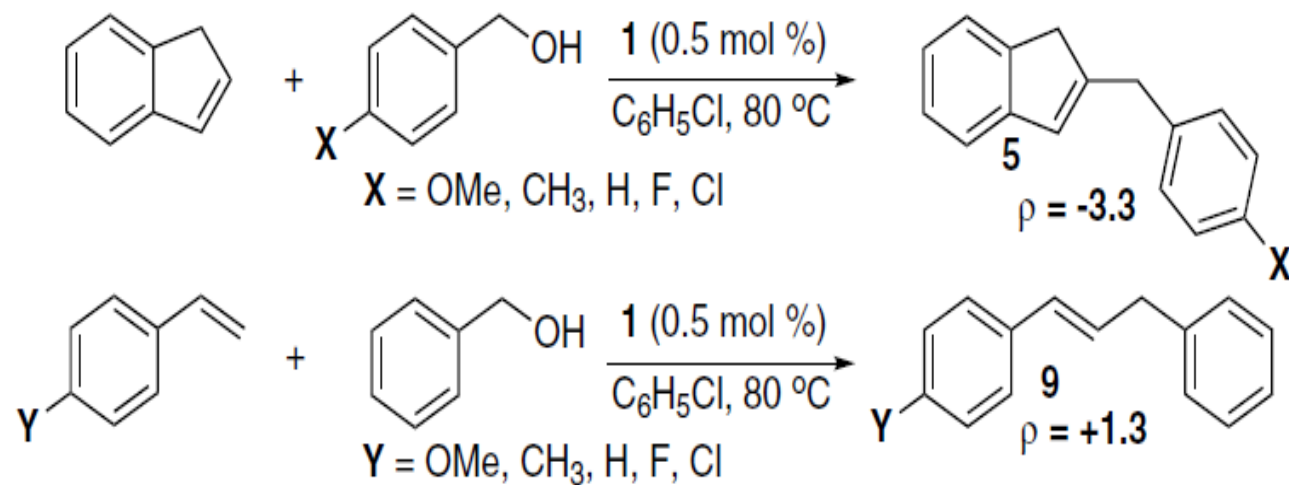
- ⊙ In contrast to the trend seen in Friedel-Crafts-type electrophilic alkylation reactions, reaction rates are generally fastest with primary alcohols



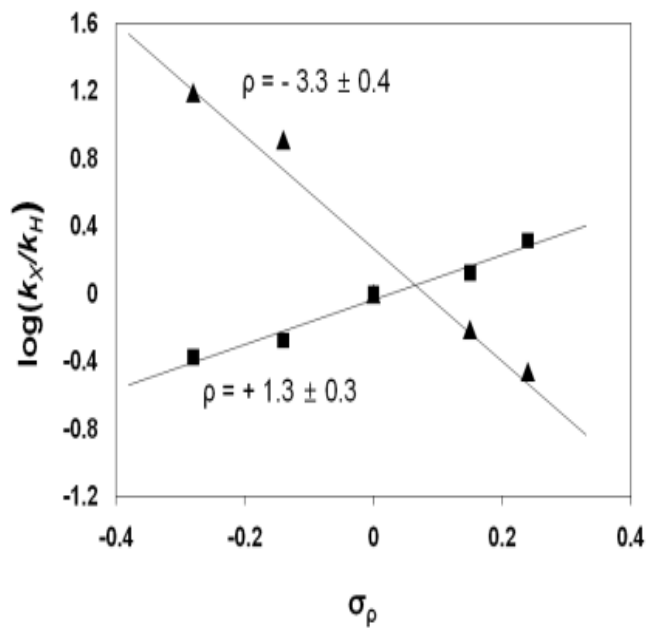
- ⊙ Perhaps preferred due to steric hindrance in subsequent steps

# Hammett Studies of Electronics

B

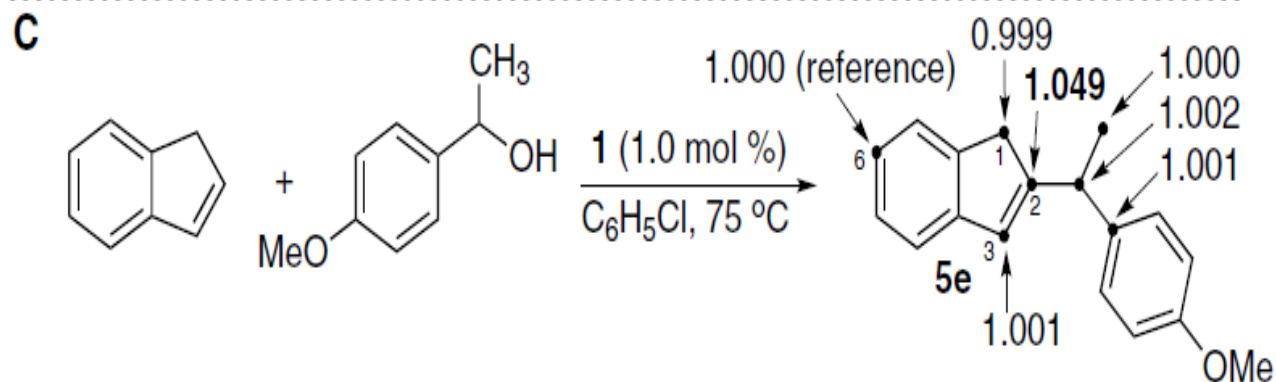


# Hammett Plots



**Figure S3.** Hammett plot of the alkylation of indene with  $p$ -X-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OH (X = OCH<sub>3</sub>, CH<sub>3</sub>, H, F, Cl) (▲), and  $p$ -Y-C<sub>6</sub>H<sub>4</sub>CH=CH<sub>2</sub> (Y = OCH<sub>3</sub>, CH<sub>3</sub>, H, F, Cl) with PhCH<sub>2</sub>OH (■).

# Kinetic Isotope Effect



- Singleton NMR Technique

**Table S3. Carbon isotope ratio of 5e.**

| carbon no. | recovered<br>(95% conv.) | recovered<br>(11% conv.) | 95%/11%      | change (%)  |
|------------|--------------------------|--------------------------|--------------|-------------|
| 1          | 0.997                    | 0.999                    | 0.998        | -0.20       |
| 2          | <b>1.133</b>             | <b>1.061</b>             | <b>1.068</b> | <b>6.80</b> |
| 3          | 1.051                    | 1.049                    | 1.002        | 0.20        |
| 4          | 0.992                    | 0.995                    | 0.997        | -0.30       |
| 5          | 1.054                    | 1.060                    | 0.994        | -0.60       |
| 6 (ref)    | 1.000                    | 1.000                    | 1.000        | 0.00        |
| 7          | 1.020                    | 1.016                    | 1.004        | 0.40        |
| 8          | 1.055                    | 1.054                    | 1.001        | 0.10        |
| 9          | 1.071                    | 1.073                    | 0.998        | -0.20       |
| 10         | 2.232                    | 2.229                    | 1.001        | 0.10        |

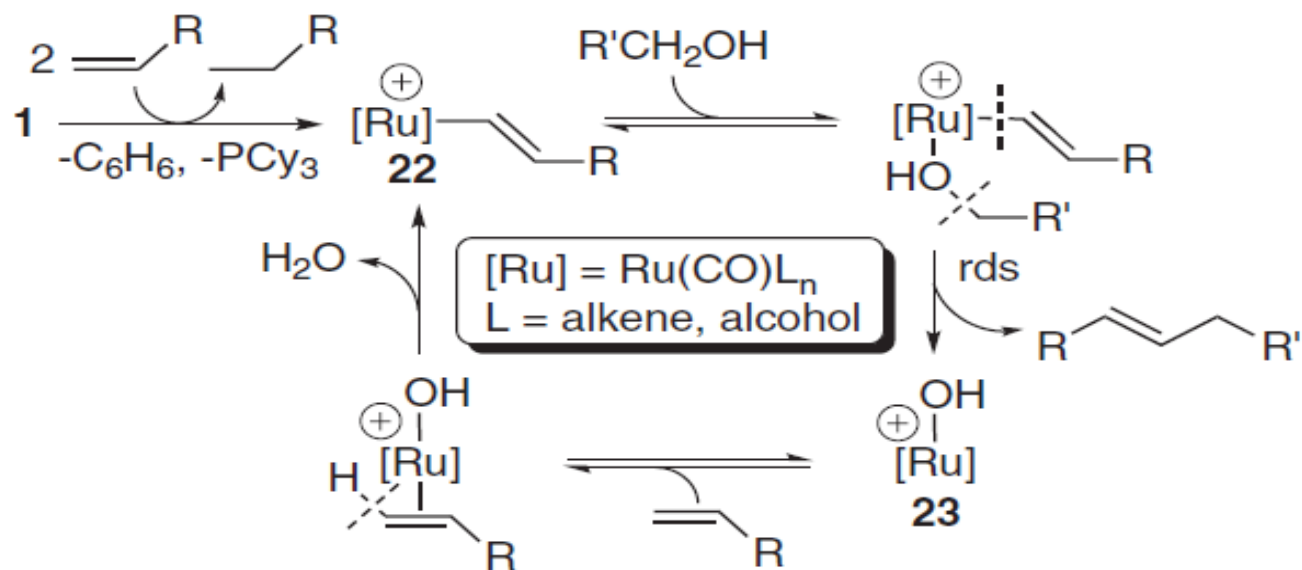
| carbon no. | recovered<br>(95% conv.) | recovered<br>(15% conv.) | 95%/15%      | change (%)  |
|------------|--------------------------|--------------------------|--------------|-------------|
| 1          | 0.997                    | 0.995                    | 1.002        | 0.20        |
| 2          | <b>1.133</b>             | <b>1.086</b>             | <b>1.043</b> | <b>4.30</b> |
| 3          | 1.051                    | 1.052                    | 0.999        | -0.10       |
| 4          | 0.992                    | 0.994                    | 0.998        | -0.20       |
| 5          | 1.054                    | 1.055                    | 0.999        | -0.10       |
| 6 (ref)    | 1.000                    | 1.000                    | 1.000        | 0.00        |
| 7          | 1.020                    | 1.020                    | 1.000        | 0.00        |
| 8          | 1.055                    | 1.055                    | 1.000        | 0.00        |
| 9          | 1.071                    | 1.069                    | 1.002        | 0.20        |
| 10         | 2.232                    | 2.230                    | 1.001        | 0.10        |

| carbon no. | recovered<br>(95% conv.) | recovered<br>(18% conv.) | 95%/18%      | change (%)  |
|------------|--------------------------|--------------------------|--------------|-------------|
| 1          | 0.997                    | 0.999                    | 0.998        | -0.20       |
| 2          | <b>1.133</b>             | <b>1.094</b>             | <b>1.036</b> | <b>3.60</b> |
| 3          | 1.051                    | 1.051                    | 1.000        | 0.00        |
| 4          | 0.992                    | 0.991                    | 1.001        | 0.10        |
| 5          | 1.054                    | 1.056                    | 0.998        | -0.20       |
| 6 (ref)    | 1.000                    | 1.000                    | 1.000        | 0.00        |
| 7          | 1.020                    | 1.018                    | 1.002        | 0.20        |
| 8          | 1.055                    | 1.055                    | 1.000        | 0.00        |
| 9          | 1.071                    | 1.068                    | 1.003        | 0.30        |
| 10         | 2.232                    | 2.229                    | 1.001        | 0.10        |

# Summary from Mechanistic Studies

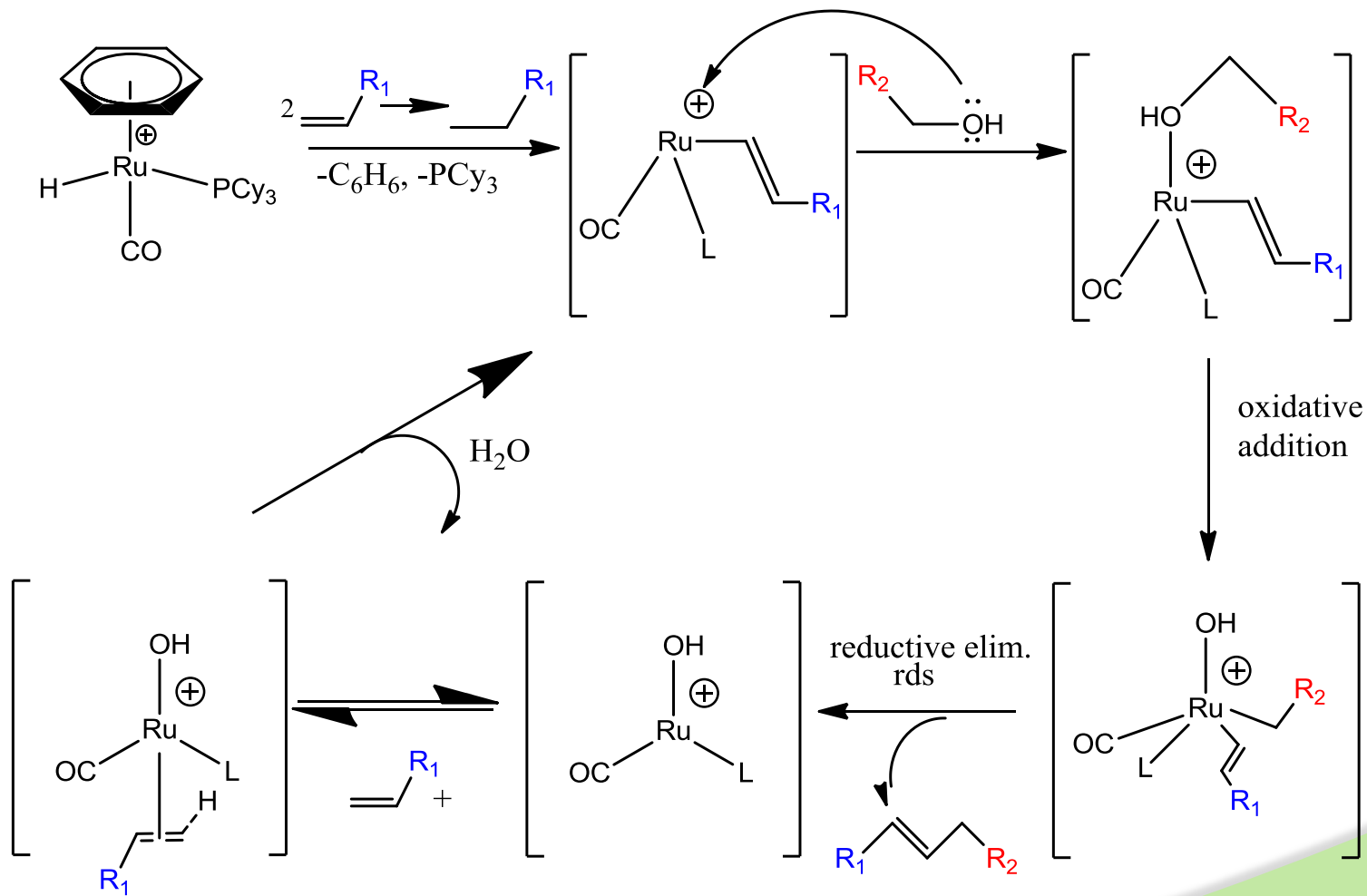
- ⊙ Hydrogen-deuterium exchange:
  - suggests facile vinyl C-H activation step
- ⊙ Hammett studies:
  - positively charged transition state likely
- ⊙  $^{12}\text{C}/^{13}\text{C}$  isotope effects:
  - C-C bond formation is rate limiting step

# Proposed Mechanism

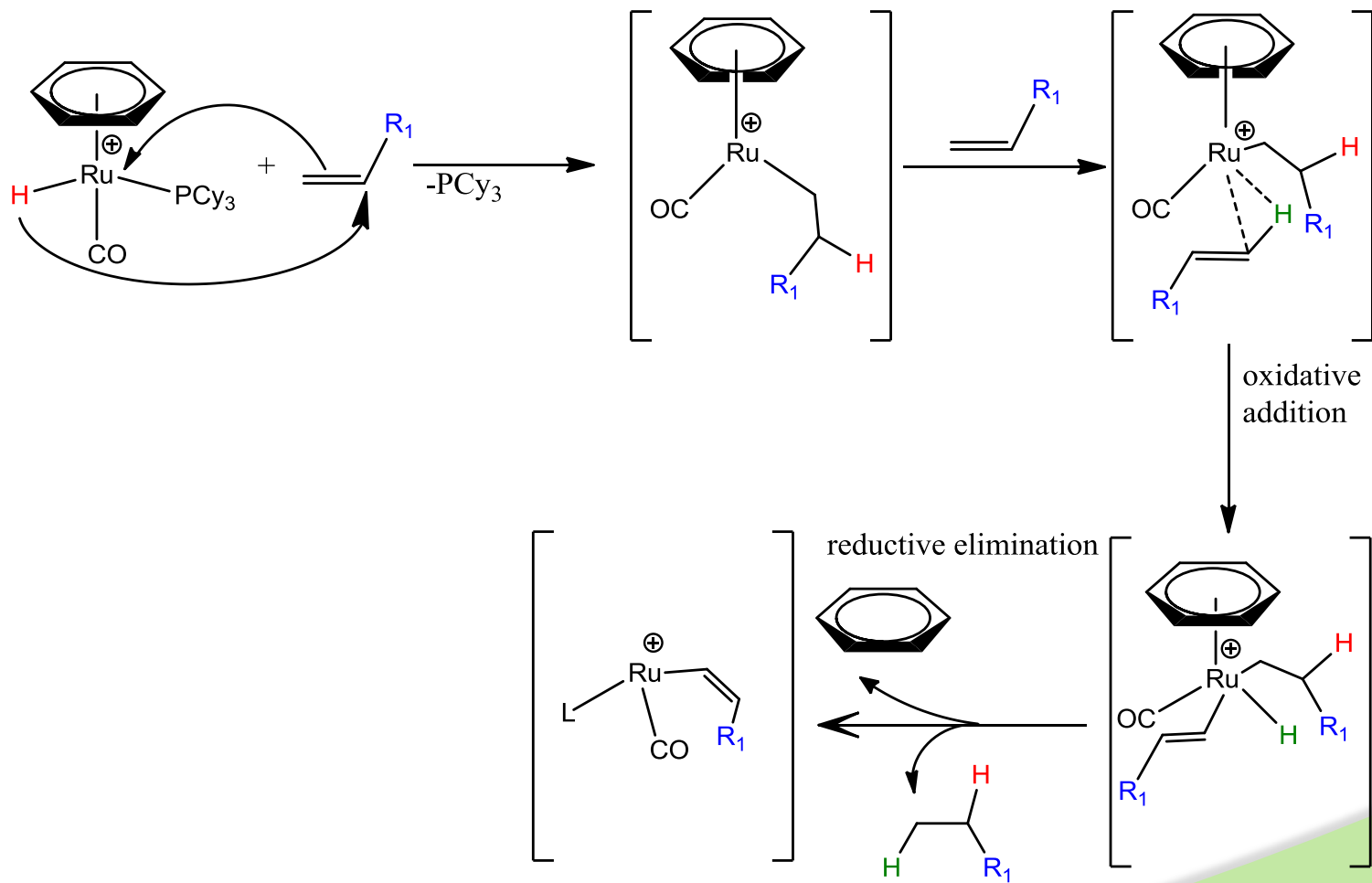




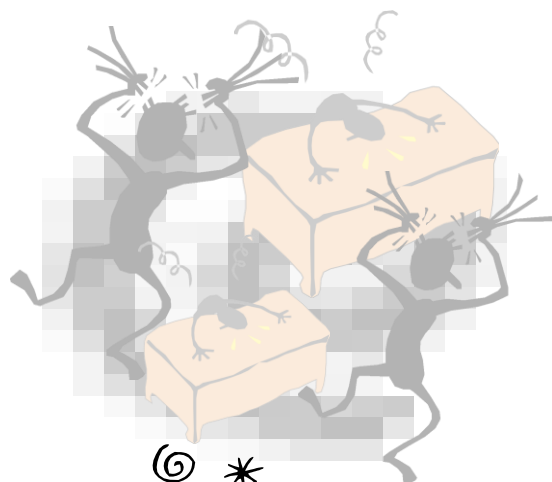
# Mechanism of Alkylation of Alkene with Alcohols



# Mechanism for C-H Bond Activation



Somewhere in Milwaukee on a fine Saturday evening...



At BMC's Chemistry student lounge....

Dear Ms. Lee:

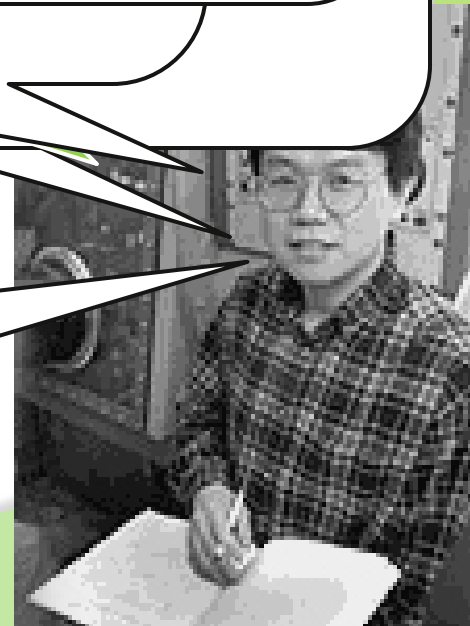
Thank you for having interest in our paper. We do not understand the reaction mechanism completely, but I will try to answer your questions as indicated by

There  
from R  
recomm  
the vi  
the Ru

You  
act  
spe

4) In addition, in your studies, your paper mentions that tertiary alcohols are least favored in this reaction. We were unsure but speculated that this might be due to steric hindrances that may arise when the alcohol is coordinated to the ruthenium catalyst.

That is a reasonable explanation.



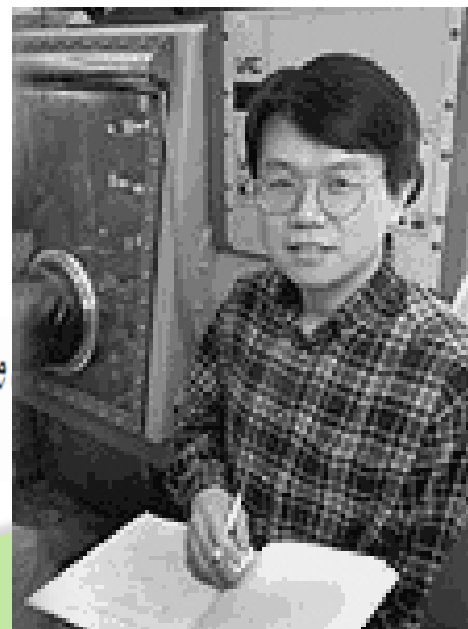
1) We are assuming that this alkene or alcohol is an L-type and not a  $\pi$ -allyl catalyst that was stated in the paper to represent an alkene or alcohol.

Dear Ms. Lee, as I said in the previous message, we do not have much evidence to support (or eliminate) these hypothesis. Drawing a plausible mech is one thing, but to prove/disapprove is a much more challenging task. It often takes years of effort to do that and we just don't have any supporting evidence at this time. For your purpose, you may propose any of these possible mech.

Best, Chae Yi

2) If the ligand on the Ru catalyst is an alcohol, have these alcohols instead participated in the reaction where the alkyl group being generated in the

3) If the ligand on the Ru catalyst is an alcohol, have these alcohols instead participated in the reaction where the alkyl group being generated in the on the Ru catalyst instead of the alcohol added to the reaction?



ligand

# Conclusions

- ⦿ Successfully used cationic ruthenium hydride complex catalyze alkylation of diverse substrate
- ⦿ High degree of regio- and chemoselectivity
- ⦿ Generates no wasteful by-products
- ⦿ Reactions also proven successful with non-chlorinated solvents like toluene and tetrahydrofuran
- ⦿ Advance green chemistry (with the potential for applications in industry)!

# References

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