Transition Metal-Catalyzed Carbon-Carbon Bond Cleavage (C-C Activation)

Group Meeting
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- Fundamental considerations, C-H versus C-C activation
  - Orbital interactions
  - Evidence of M···C-C agostic interaction, C-C activation
  - Thermodynamics

- Stoichiometric reactions

- Catalytic reactions
  - Activation of strained molecules
    - Direct cleavage
    - Utilization of a carbonyl group
    - β-Alkyl elimination
  - Activation of unstrained molecules
    - β-Alkyl elimination, utilization of a π-allyl intermediate
    - Chelation assistance

- Conclusion
Orbital Interactions

Kinetic barriers of C-C activation due to:
1. High directionality of C-C σ bond
2. Substituents on both carbons (steric congestion)
3. Statistical abundance of C-H bonds

Murakami, M., Ito, Y. *Topics in Organometallic Chemistry* 1999, 97-129
Evidence of M···C-C Agostic Interaction

Supports for M···C-C Agostic Interaction, C-C Activation

Fluxional at RT

$^{1}H$ NMR
C11, C15, C21 and C25 are all equivalent at 298 K ($\delta(^1H) = 3.23$ppm, $\delta(^{13}C) = 25.5$ ppm)

5 signals (298 K) $\rightarrow$ 10 signals (200 K)
Thermodynamic Considerations

C-C bond
90 kcal/mol
M-C bond x2
40-60 kcal/mol

Microscopic reversibility

M-H bonds are generally stronger than M-C bonds by 15 – 25 kcal/mol even though Me-H and H-H have almost the same BDE.


Unlike in the gas phase, M-H bonds are generally stronger than M-C bonds in the solution.


Examples:

$(\eta^5\text{-}C_5\text{Me}_5)(\text{PMe}_3)_2\text{Ru}–\text{H}$ 167.4 kcal/mol

$(\eta^5\text{-}C_5\text{Me}_5)(\text{PMe}_3)_2\text{Ru}–\text{CH}_3$ 142.3 kcal/mol

CRC 88th Ed.
Strategies to facilitate C-C bond activation:
1. Employing strained starting materials

E(C-C) = 61 kcal/mol

Tipper (1955)
Chatt (1961)

Thermodynamic Considerations

Strategies to facilitate C-C bond activation (contd):
2. Use high energy metal complexes

Thermodynamic Considerations

Strategies to facilitate C-C bond activation (contd):

3. Extrusion of gas, aromatization

4. Formation of a stable metallacycle and chelation assistance

Five-membered metallacyclic complexes are relatively stable. Rh-C<sub>aryl</sub> and Ir-C<sub>aryl</sub> bonds are sometimes stronger than the corresponding M-H bonds.

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Direct Cleavage

\[
\begin{align*}
\text{entry} & \quad R & \quad \text{tot}^b \\
1 & \text{OSiMe}_3 & 0.98 \\
2 & \text{OH} & 0.25 \\
3 & \text{OAc} & 0.56 \\
\end{align*}
\]

\[
\begin{align*}
\text{entry} & \quad R & \quad \text{tot}^b \\
1 & \text{OSiMe}_3 & 1.78 & \text{no reaction} \\
2 & \text{OH} & \text{no reaction} & 0.28 \\
3 & \text{OAc} & \text{no reaction} & \text{no reaction} \\
\end{align*}
\]

\(^a\) 2.75 mM \((\text{PPh}_3)_3\text{RhCl}\) and 0.138 M substrate in anhydrous toluene.

\(^b\) Turnover frequency determined at 18 h.

Chirik, P. J., et. al. JACS 2003, 125, 886.
Direct Cleavage

1a (R = BnOCH₂)

CO, Rh(I) oxidative addition → CO insertion →

β-carbon elimination → reductive elimination → isomerization →

Ar = 4-MeC₆H₄

Zn AcOH rt (56%)

Ar Rh(I)–DPPP p-xylene 130 °C (82%)

Me₂Zn Ni(acac)₂ Et₂O, rt (75%)

(±)-β-cuparenone (14)

Utilization of a Carbonyl Group

Stoichiometric reactions showed that the insertion of Rh(I) into the α C-C bond is feasible.

Both reactions were carried out under argon.

Utilization of a Carbonyl Group

β-Alkyl Elimination (1)

β-Alkyl elimination is the reverse of insertion.

Oxidative Addition

**β-Alkyl Elimination (1)**

1. **1a (E)**
   - Reaction with 5 mol% Pd(0) and 7.5 mol% BINAP in THF, reflux, 9 h
   - Product: 2 86%, 3 8%

2. **1b (Z)**
   - Reaction with 5 mol% Pd(0) and 7.5 mol% BINAP in THF, reflux, 9 h
   - Product: 2 37%, 3 48%
   - Reaction in Et₂O, reflux, 72 h
   - Product: 2 83%, 3 8%

**Reaction Pathways**

- **1a**
  - $E$-IV
  - $E$-IV → V
  - V → 2

- **1b**
  - $Z$-IV
  - $Z$-IV → VI
  - VI → 3

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**Chemical Structures**

- **1a (E)**
- **1b (Z)**
- **2**
- **3**
β-Alkyl Elimination (1)

[Uemura, S. et. al. JACS, 2003, 125, 8862.]

79 % yield
78 % ee

93 % yield
73 % ee

93 % yield
91 % ee
**β-Alkyl Elimination (2)**

1. **Insertion** of Rh(I) cat into a C(O)-C bond
2. **β-Alkyl elimination**

C-C bond activation by

- 1. **Insertion** of Rh(I) cat into a C(O)-C bond
- 2. **β-Alkyl elimination**

Uemura, S. et al. JACS, 2003, 125, 8862.

β-Alkyl Elimination (3)

alkyne insertion

\[-\text{C-C-} + \equiv \xrightarrow{\text{transition metal}} \text{C=C}\]

\[
\begin{align*}
\text{1a} & \quad \text{Pr} \\
\text{Ph} & \quad \text{Me} \\
(0.20 \text{ mmol}) & \quad (0.30 \text{ mmol})
\end{align*}
\]

\[
\begin{align*}
\text{2a} & \quad \text{10 mol \% Ni(cod)\textsubscript{2}} \\
& \quad 20 \text{ mol \% P(c-Hex)\textsubscript{3}} \\
& \quad \text{toluene (1.0 mL)} \\
& \quad 100 \text{ °C, 3 h}
\end{align*}
\]

\[
\begin{align*}
\text{3a} & \quad 95\%
\end{align*}
\]

Other Strained Molecules for C-C Activation

\[ \text{Ru}_3(\text{CO})_{12}/\text{PEt}_3 \]

1,4-dioxane, CO 3 atm
150 °C, 20 h

11a

\[ n-\text{Bu} \]

12b

10 atm

\[ i-\text{PrO} \]

\[ \text{Ru}_3(\text{CO})_{12}/\text{PEt}_3 \]

1462.

Mechanism of the Pyranone Formation

\[ \text{Pyranone Formation} \]

\[ \text{[RuCl}_2\text{(CO)}_3]\text{]}_2 \text{ or [RhCl(CO)]}_2 \to \text{toluene, } 110\degree \text{C, } 12\text{ h} \]

\[ \begin{align*}
(\text{Z})-18 &\quad R &\quad (\text{E})-18 \\
18a: &\quad 79\% \quad (41/59) &\quad 18a: &\quad 86\% \quad (100/0)
\end{align*} \]

\[ \begin{align*}
\text{(Z)-2} &\quad (\text{M}) = \text{Ru} \\
(\text{E)-2} &\quad (\text{M}) = \text{Rh}
\end{align*} \]

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\[ \text{RuCl}_2(\text{PPh}_3)_3 \] 

\[ \text{CO} \text{ 10 atm, } \text{R-OAc} \] 

\[ 180^\circ \text{C, 15 h, } -\text{R}^3 \] 

\[ 5 \text{ mol\%} \]

**1a**: \( R^1=\text{Ph}, R^2=\text{Me}, R^3=\text{H} \)

**2a**: 91%

**1b**: \( R^1=R^2=\text{Ph}, R^3=\text{H} \)

**2b**: 87%

**1c**: \( R^1=R^2=\text{Bu}, R^3=\text{H} \)

**2c**: 71%

**1d**: \( R^1=\text{Ph}, R^2=\text{Me}, R^3=\text{Me} \)

β-Alkyl Elimination, Formation of a Pd-C(Sp²) Bond


\[
\begin{align*}
\text{bromide 1} & \quad \text{alcohol 2} & \quad \text{L} & \quad \text{time, h} & \quad \text{product, \%} \\
R^1, R^2 (\text{mmol}) & R^3 (\text{mmol}) & & & & \\
1a: H, H, (1.5) & 2g: H (0.5) & PPh_3 & 6 & 3e, 94 \\
1b: Me, H (0.6) & 2g: H (0.5) & PPh_3 & 4 & 3f, 90 (72) \\
1d: H, Me (1.5) & 2g: H (0.5) & PCy_3 & 8 & 3g, 94 (82) \\
e: H, \text{COOEt} (0.8) & 2g: H (0.5) & PPh_3 & 4 & 3h, 94 (91) \\
la: H, H (0.6) & 2h: OMe (0.5) & PPh_3 & 2.5 & 3l, 98 (82) \\
la: H, H (0.6) & 2h: OMe (0.5) & PPh_3 & 24^c & 3l, 92
\end{align*}
\]

\(^a\) [2]:[Ph(OAc)_2]:[L] = 0.5:0.025:0.1 (in mmol). \([1] = [\text{Cs}_2\text{CO}_3]\), in refluxing \(o\)-xylene. \(^b\) Determined by GC analysis. Value in parentheses is isolated yield. \(^c\) [Pd(OAc)_2]:[L] = 0.005:0.02.
β-Alkyl Elimination, Formation of a Pd-C(Sp) Bond

Sequential β-Alkyl Elimination, Conjugate Addition

$\ce{R^1\ce{C=CR^2} + \ce{C≡CR}} \xrightarrow{\text{Rh catalyst}} \ce{R\ce{C=CC≡CR}}$

$\ce{[Rh]C≡CR}$

$\ce{R^1\ce{C=C}R^2}$

$\ce{[Rh]C≡CR}$

$\ce{HO\ce{C=C}R}$

$\ce{[Rh]-OH}$

$-\text{H}_2\text{O}$

$\ce{[Rh]O\ce{C=C}R}$

$\ce{β-alkynyl elimination}$

$\ce{\text{conjugate addition}}$

$\ce{O\ce{C=C}R}$

$\ce{R^1\ce{C=C}R^2}$

$\ce{[Rh]C≡CR}$

$\ce{O\ce{C=C}R}$

$\ce{R^1\ce{C=C}R^2}$

$\ce{[Rh]C≡CR}$

Sequential β-Alkyl Elimination, Conjugate Addition

\[ \text{Ph} \text{C} = \text{C} + \text{Li} = \text{C} \text{SiMe}_2 \text{Bu} \rightarrow \text{Ph} \text{HO} \text{C} = \text{C} \text{SiMe}_2 \text{Bu} \]

\[ [\text{Rh(OH)(cod)}]_2 \]
(5 mol % Rh)

\[(R)-\text{binap} (6 \text{ mol} \%) \]
toluene, 60 °C, 3 h

\[ \text{Ph} \text{C} = \text{C} \rightarrow \text{Ph} \text{CH} = \text{CH} \text{SiMe}_2 \text{Bu} \]
\[ \text{Ph} \text{CH} = \text{CH} \text{SiMe}_2 \text{Bu} \]
\[ \text{TBAF, 90\%} \]
\[ \text{RhCl} \text{(PPh}_3)_3 \]
H\_2, 83\%

\[ \text{2a: 88\% yield} \]
\[ \text{94\% ee (S)} \]

\[ \text{2b: 91\%, 98\% ee (S)} \]

\[ \text{2c: 89\%, 91\% ee (S)} \]

\[ \text{2f: 88\%, 81\% ee (R)} \]

\[ \text{2g: 86\%, 71\% ee (S)} \]

**References:**

Chelation Assistance

\[(\text{PPh}_3)_3\text{RhCl} + \text{2-amino-3-picoline (57)}\]  
\[150^\circ C\]  
\[\text{trace} + \text{84\%}\]

Nickel-Catalyzed Arylcyanation of Alkynes

Conclusion

- Different strategies toward C-C single bond activation have emerged
- Mild reaction conditions need to be developed
- Substrate scopes are limited in many cases
- Only a few enantioselective reactions have been reported
- This technology is still at the exploration stage