Stereochemistry of Cyclopropane Formation Involving Group IV Organometallic Complexes

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J. AM. CHEM. SOC. 2004, 126, 1699–1704
Background

- Isolation of the novel natural compounds bearing cyclopropane rings accelerated the progress of cyclopropane chemistry

\[ \text{FR-90848 (1)} \]

*J. Antibiotic. 1990, 43, 748*

\[ \text{U-106305 (2)} \]

*J. Am. Chem. Soc. 1995, 117, 10629-10634*
Background

- 4 basic ways to install a cyclopropane ring.

\[ \text{ EWG } \xrightarrow{\text{RCH-LG}} \xrightarrow{\text{EWG-LG}} \xrightarrow{\text{R}} \]

\[ \text{ EWG } \xrightarrow{\text{RCH}} \xrightarrow{\text{LG}} \xrightarrow{\text{EWG}} \xrightarrow{\text{R}} \]

\[ \text{ EWG } \xrightarrow{\text{HCH}_2} \xrightarrow{\text{EWG-LG}} \xrightarrow{\text{R}} \]

\[ \text{ EWG } \xrightarrow{\text{MCH}_2X'} \xrightarrow{\text{R}} \]

Background

- Representative ways to prepare cyclopropanol

Scheme 1

\[
\begin{align*}
\text{Ph} & \text{O} \xrightarrow{\text{LDA}} \left[ \begin{array}{c}
\text{Ph} \\
\text{Li} \\
\text{O}
\end{array} \right] \\
& \xrightarrow{1. \text{CH}_2\text{Br}_2\text{Sm} \quad 2. \text{H}_2\text{O}^+} \text{Ph} \\
& \xrightarrow{66\%} \text{Ph}
\end{align*}
\]

Scheme 2\(^a\)

\[
\begin{align*}
\text{Ph} & \text{O} \xrightarrow{\text{CH}_2\text{Br}_2\text{Sm}} \left[ \begin{array}{c}
\text{Ph} \\
\text{I}_n\text{Sm} \\
\text{O}
\end{array} \right] \\
& \xrightarrow{\text{CH}_2\text{Br}_2\text{Sm}} \left[ \begin{array}{c}
\text{Ph} \\
\text{I}_n\text{Sm} \\
\text{O}
\end{array} \right] \\
& \xrightarrow{\text{H}_2\text{O}^+} \text{Ph} \\
& \xrightarrow{88\%} \text{Ph}
\end{align*}
\]

\(^a n = 1 \text{ or } 2.\)

Scheme 5

\[
\begin{align*}
\text{Ph} & \text{CO} \xrightarrow{1. \text{CH}_2\text{Br}_2\text{Sm} \quad 2. \text{H}_2\text{O}} \left[ \begin{array}{c}
\text{Ph} \\
\text{CH}_2
\end{array} \right] \\
& \xrightarrow{71\%} \text{Ph}
\end{align*}
\]
Background

- Representative ways to prepare cyclopropanol (continued)

**Scheme 6**

\[
\text{Sml}_2 \text{, r.l., 1min} \\
\begin{align*}
\text{11} & \rightarrow \\
\text{13} & \rightarrow \\
\text{Sml}_2 & \rightarrow \\
\text{12} & \rightarrow \\
\end{align*}
\]

**Scheme 7**

1. 3 EtMgBr
2. Ti(Oi-Pr)\(_4\), -78 to 0 °C
3. H\(_2\)O

\[
\text{H}_4\text{C}_5\text{O}_\text{Me} \rightarrow \text{H}_4\text{C}_5\text{OH} \quad 93\%
\]

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Background

- Kulinkovich reaction
Background

- Cyclopropylamine
Background

- A one-pot cyclopropane synthesis from allylic ethers

\[ \text{OR} \quad \text{Cp}_2\text{Zr}I(1)\text{Cl} (1.0 \text{ eq.}) \quad \text{Cl}_2\text{C}_2\text{H}_5, \text{rt} \quad \text{BF}_3\cdot\text{OEt}_2 (1.1 \text{ eq.}) \quad 0^\circ \text{C to rt, 1h} \quad \text{OR} \]

- Proposed mechanism

\[ \text{OR} \quad 1. \text{Cp}_2\text{Zr(H)}\text{Cl} \quad 	ext{Cl}_2\text{C}_2\text{H}_5 \quad L.A. \quad \text{ClCp}_2\text{Zr} \quad \text{OR} \quad 2. \text{L.A.} \quad \text{Scheme 2} \quad \text{R}^1 \quad \text{R}^2 \]

*Chem. Commun.* **2002**, *1308-1309*
Cyclopropane

• But is it a reasonable mechanism?

\[ \Theta \]

2 bonds + 2 coordinations

• And another mechanism is possible.

W-shaped mechanism

• Which one is correct? And how can it be found?
Cyclopropane

- The answer was found by installing stereocenter!

R: retention  I: inversion of stereochemistry
Cyclopropane

- Preparation of intermediate 2

\[ \text{Cp}_2\text{Zr(D)Cl} \]

\[ \begin{align*}
\text{Cp}_2\text{ZrCl}_{\text{HD}} & \quad \text{OMe} \\
\text{HPh} & \\
\text{Cp}_2\text{ZrCl}_{\text{DH}} & \quad \text{OMe} \\
\text{DH} & \quad \text{HPh}
\end{align*} \]

\[ \begin{align*}
\text{2a} & \\
\text{2b}
\end{align*} \]
Cyclopropane

- Reaction with Lewis acid

\[ \text{BF}_3 \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \quad \text{H} \quad \text{D} \quad \text{BF}_3 \\
\text{H} \quad \text{D} \quad \text{H} \quad \text{Ph}
\end{array}
\end{array} \Rightarrow \begin{array}{c}
\begin{array}{c}
\text{D} \quad \text{D} \quad \text{H} \quad \text{Ph}
\end{array}
\end{array} \]

\[ \text{BF}_3 \quad \begin{array}{c}
\begin{array}{c}
\text{Cl} \quad \text{D} \quad \text{H} \quad \text{BF}_3 \\
\text{D} \quad \text{H} \quad \text{H} \quad \text{Ph}
\end{array}
\end{array} \Rightarrow \begin{array}{c}
\begin{array}{c}
\text{D} \quad \text{Ph}
\end{array}
\end{array} \]

Only \emph{cis}!

No \emph{trans} isomer was found!

\[ 3a : 3b = 5 : 1 \]
Cyclopropane

- Assignment of stereochemistry

![Chemical Structures]

Conclusion: W-shaped mechanism was right!
Cyclopropanol

- In the case of cyclopropanol

Before we start.....

Revisit to the mechanism of Kulinkovich reaction

If the olefin is not a simple ethene.....
Cyclopropanol

- Modified Kulinkovich reaction

Olefin exchange step:

Which path way is correct?
Cyclopropanol

- If the pathway 2 is correct, when a deutrated Grignard rgt was used, deutrated cyclopropane is expected to be formed

But in real, deutrated cyclopropane was not found

**Conclusion: the olefin exchange step follows pathway 1 exclusively.**

*Tet. Lett. 1999, 40, 5935-5938*
Cyclopropanol

- Regioselectivity and stereoselectivity issue of Kulinkovich reaction

Why $E$?

Why not
Cyclopropanol

- It was because of the steric hindrance

\[ \text{R} \text{O} \text{OMe} \xrightarrow{\text{R'} \text{MgBr}} \text{H} \xrightarrow{\text{Ti(OR)}_4} \text{R'} \text{H} \xrightarrow{\text{MeC}} \text{R'} \text{H} \xrightarrow{\text{TiOR}} \text{R'} \text{H} \xrightarrow{\text{MeO}} \text{TiOR} \]

To avoid steric hindrance

\[ \text{(RO)}_2 \text{Ti} \text{O} \text{OMe} \quad \text{(RO)}_2 \text{Ti} \text{O} \text{OMe} \]

Favored

Disfavored

OK… But what is the exact transition state?

Cyclopropanol

- Introduction of deuterium in the olefin

The result was:

Exclusively

Confirmed by NOE
Cyclopropanol

- W-shaped mechanism does not work in this case.

Reaction proceeds through front attack of titanium-carbon bond. Titanium-oxygen coordination plays an important role.
Cyclopropanylamine

- In the case of cyclopropylamine

Would W-shaped mechanism work?
Cyclopropanylamine

- Possible mechanisms:

\[ \text{I} \quad \text{J} \]

\[ \text{K} \quad 6a \]

\[ \text{K} \quad 6b \]
Cyclopropanylamine

- The result.

\[ \text{Ti(O-iPr)}_4 \rightarrow (i-PrO)_2\text{TiCH}_3 \rightarrow (i-PrO)_2\text{Ti-} \]

\[ \text{DMF} \rightarrow \text{Ph} \]

\[ \delta 1.84 \]

\[ \delta 1.98 \]

\[ \delta 1.04, \text{dd, } J = 9.0, 6.9 \text{ Hz} \]

\[ 6b \]

\[ 12\% \]

\[ \delta 1.08, \text{dd, } J = 9.6, 4.5 \text{ Hz} \]

\[ \delta 1.98 \]

\[ 6a \]

\[ 36\% \]

\[ 4.6\% \text{ nOe} \]

\[ 0.5\% \text{ nOe} \]

W-shaped mechanism works!
Conclusion

• The mechanisms of cyclopropane formation steps were confirmed to be:

  ➢ W-shaped mechanism for cyclopropane formation from allylic ethers, Cp2Zr(H)Cl, and Lewis acid and for cyclopropylamine formation.

  ➢ W-shaped mechanism does not work for Kulinkovich reaction presumably because of titanium-oxygen coordination.

through a very simple way (only introducing deuterium)!