Sukbok Chang

B.S.: Korea University, 1985
M.S.: KAIST (Korea Advanced Institute of Science and Technology), 1987, Prof. Sunggak Kim
Post Doctoral Fellow: Caltech, 1996-98, Prof. Robert Grubbs
Assistant Professor: Ewha Women’s University, 1998
Professor: KAIST, 2002

- Ph.D. work: epoxidation of cis-olefins

\[
\text{BOMO} + \text{Mn-salen} + \text{NaOCl} \rightarrow \text{high ee variable dr}
\]


\[
\text{Ph} = \text{Me}
\]

Postdoc work: novel applications of RCM

\[
\begin{align*}
\text{RCM} & \quad 80-90\% \\
\text{J. Org. Chem. 1998, 63, 864–866.}
\end{align*}
\]

\[
\begin{align*}
\text{Tet. Lett. 1997, 38, 4757–4760.}
\end{align*}
\]

Independent career: 206 Publications since 1999 over a broad range of subjects

- Heterogeneous catalysis
- Multicomponent couplings
- C–H alkylation/arylation
- C–H amination/amidation

\[
\begin{align*}
\end{align*}
\]

Plus many many others

Covered in this talk: group 9 C–H amination/amidation
Strategies to prepare aryl-amines

- Buchwald-Hartwig or Ullman coupling

Chang lab strategy: build in oxidation

- Applicable to aryl, alkyl, acyl azides

\[
\text{R}_1 \quad \text{NH} \quad \text{Ar} \quad \text{R}_2 \quad \text{N}_3 \quad [\text{Cp}^*\text{RhCl}_2]_2, \text{AgSbF}_6
\]

\[
\text{DCE, 85 ºC} \quad \rightarrow \quad \text{DG}
\]

\[
\text{R}_1 \quad \text{NHAr} \quad \text{R}_2
\]

50-97% yield


- Ir conditions tolerate diverse directing groups

\[
\text{R}_1 \quad \text{NH} \quad \text{Ar}
\]

\[
\text{O} \quad \text{Ar}
\]

45%


- Capable of aminating alkenyl substrates as well

\[
\text{R}_1 \quad \text{NH} \quad \text{Ar}
\]

\[
\text{O} \quad \text{Ar}
\]

60%

Ar=\text{p-(NO}_2\text{)-C}_6\text{H}_4

Other noteworthy applications:

Quinoline N-oxides

\[
\begin{align*}
\text{N}\text{O} & \quad \text{N}\text{O} \\
\text{DCE, AcOH, } 50 \degree \text{C} & \quad 89\%
\end{align*}
\]


Phosphine oxides (some dr with chiral auxiliaries on P)

\[
\begin{align*}
\text{Ph}_3\text{P} = \text{O} & \quad \text{Ph}_3\text{P} = \text{O} \\
\text{DCE, PivOH, } 85 \degree \text{C} & \quad 84\%
\end{align*}
\]


Phosphoramidates

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{DCE, } 60 \degree \text{C} & \quad 94\%
\end{align*}
\]

*Synthesis of medium-large rings (9-11) (up to 36-membered when dimerizing substrates)*


Selective amination of 1º C–H bonds, including in complex settings

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{DCE, } 60 \degree \text{C} & \quad 73\%
\end{align*}
\]

### The curious case of purine

1. **First C–H activation is directed by N1**
   - Reaction: \( \text{Ar} + \text{ArN}_3 \) (3 equiv.) + \([\text{Cp}^*\text{RhCl}_2]_2, \text{AgSbF}_6\) \( \rightarrow \) \( \text{ArNNHAr} \)
   - Condition: DCE, 85 °C
   - Yield: 65%

   - **X-ray**

2. **Two C–H aminations directed by different nitrogens?**
   - Reaction: \( \text{Ar} + \text{ArN}_3 \) (3 equiv.) + \([\text{Cp}^*\text{RhCl}_2]_2, \text{AgSbF}_6\) \( \rightarrow \) \( \text{ArHN}_1\text{NHAr} \)
   - Condition: DCE, 85 °C
   - Yield: 92%

   - **Rhodacycle is an intermediate**

3. **Hydrogen bonding restricts rotation supressing second C–H amination**
   - Reaction: \( \text{ArN}_3, \text{AgSbF}_6 \) \( \rightarrow \) \( \text{ArNNHAr} \)
   - Condition: DCE, 85 °C
   - Yield: 45%

   - **91% mono-amination with N1 and C7, N7 is not a competent director**

4. **Hydrogen bonding with N7 makes the other ortho position accessible**
   - Reaction: \( \text{ArN}_3 \) (3 equiv.) + \([\text{Cp}^*\text{RhCl}_2]_2, \text{AgSbF}_6\) \( \rightarrow \) \( \text{ArHN} \)
   - Condition: DCE, 85 °C
   - Yield: 91%

   - **First C–H activation is directed by N1**

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Key mechanistic experiments:

- [Cp*RhCl₂] (1.0 equiv.)
  
  X-ray

Rhodium bound Ts–amine is presumably also an intermediate in the reaction (corroborated by other groups working in the same space)

- Rhodacycle is an intermediate in the reaction

Azide-bound rhodium not observed but presumed to be an intermediate based on precedent by Shi with Ts–imines (more on this later)

- Two plausible mechanisms

Unable to detect either species spectroscopically but Rh⁵ TS is favored computationally by 20.3 kcal/mol

- Substrate C–H bond turns over catalyst rather than simple protonation

A good preliminary mechanistic picture, however, the nature of the nitrogen insertion proved difficult to experimentally validate and several idiosyncrasies were unexplained.
Some things didn’t quite add up

Despite every on cycle process being promoted at room temperature stoichiometrically, the catalytic process gave no reaction.

However:

In their initial mechanistic investigation, a product inhibitory effect was observed, presumably due to competitive binding on Rh.

Recall from our catalytic cycle:

Is it possible that dissociation/association kinetics of the substrate and azide are responsible for the temperature discrepancies?

Addition of substrate as a ligand on Rh inhibits the stoichiometric reaction.

A new nitrenoid precursor class that binds more strongly to Rh could solve this issue.

In their initial mechanistic investigation, a product inhibitory effect was observed, presumably due to competitive binding on Rh.

Dioxazoles as a convenient nitrene precursor

\[
\begin{align*}
\text{Dioxazoles} & \quad \text{light or heat} \quad \text{CO}_2 & \quad \text{Nitrone} \\
R \quad - \quad O \quad - \quad O \quad R & \quad \rightarrow & \quad R \quad - \quad O \quad : \quad R \\
R \quad - \quad O \quad - \quad S \quad O \quad R & \quad \rightarrow & \quad R \quad - \quad O \quad N \quad : \quad R
\end{align*}
\]

Easy to handle on scale (as compared to organic azides) and relatively simple to prepare

\[
\text{PhCONHOH} \quad \xrightarrow{\text{CDI, MeCN, c.a. quant.}} \quad \text{PhCON} = \text{NO}
\]


New nitrenoid source is able to promote stoichiometric conversion!

\[
\begin{align*}
\text{PhCONHOH} & \quad \xrightarrow{\text{catalyst, AgNTf}_2, \text{DCE, temp.}} \quad \text{PhCON} = \text{NPh} \\
\text{N-source} & \quad \text{Catalyst (mol\%)} & \quad \text{Temperature} & \quad \text{Yield} \\
\text{N}_2 & \quad \text{[Cp*RhCl}_2(5)} & \quad \text{RT} & \quad \text{trace} \\
\text{N}_2 & \quad \text{[Cp*RhCl}_2(5)} & \quad \text{100 °C} & \quad \text{74\%} \\
\text{PhSO}_2\text{N}_2 & \quad \text{[Cp*RhCl}_2(5)} & \quad \text{RT} & \quad \text{75\%} \\
\text{PhSO}_2\text{N}_2 & \quad \text{[Cp*RhCl}_2(5)} & \quad \text{40 °C} & \quad \text{80\%} \\
\text{PhN}_2 & \quad \text{[Cp*RhCl}_2(5)} & \quad \text{RT} & \quad \text{99\%} \\
\text{PhN}_2 & \quad \text{[Cp*RhCl}_2(1)} & \quad \text{40 °C} & \quad \text{99\%} \\
\text{PhN}_2 & \quad \text{[Cp*IrCl}_2(5)} & \quad \text{RT} & \quad \text{4\%}
\end{align*}
\]

\[\text{J. Am. Chem. Soc. 2015, 137, 4534–4542.}\]
The dioxazole not only binds more favorably, but also has a lower barrier to imido formation than azide ($\Delta \Delta G_{\text{calc}} = 7.8$ kcal/mol).

\[
\begin{align*}
&\text{(d$_5$)Ph}_N\text{PhN}_3 \\
&+ \text{OCON} \quad \text{OCON} \\
&\quad \text{(2 equiv)} \\
&\quad \text{(2 equiv)} \\
\end{align*}
\]

\[
\text{DCE then 5N HCl}
\]

The dioxazole not only binds more favorably, but also has a lower barrier to imido formation than azide ($\Delta \Delta G_{\text{calc}} = 7.8$ kcal/mol).

\[
\begin{align*}
&\text{Rh}^+\text{N}$SbF$_6^-$ \\
&\quad \text{(1 equiv)} \\
\end{align*}
\]

\[
\begin{align*}
&\text{Rh}^+\text{N}$SbF$_6^-$ \\
&\quad \text{(2 equiv)} \\
\end{align*}
\]

\[
\text{Rh}^+\text{N}$SbF$_6^-$ \\
\quad \text{(2 equiv)} \\
\]

\[
\text{DCE, RT, 5min}
\]

\[
\text{99%}
\]

\[
\text{93%}
\]

\[
\text{N.R. vs 48% w/ Ir$^{\text{III}}$}
\]

\[
\text{72% (80 ºC)}
\]

\[
\text{vs 93% w/ Ir$^{\text{III}}$}
\]

\[
\text{75%}
\]

\[
\text{97%}
\]

\[
R= \text{OMe, 92% CF}_3, 90% \text{ CO}_2\text{Et, 98%}
\]

\[
\text{X-ray}
\]

\[
\text{Crystal structure confirms presence of N-bound species. Moreover, upon heating this structure generates the nitrogen inserted rhodacycle}
\]

\[
J. Am. Chem. Soc. 2015, 137, 4534–4542. \\
\]
Examining the details: $\text{Ir}^{\text{III}}$ vs $\text{Rh}^{\text{III}}$

Recall:

$$\text{PhN} + \text{O}=\text{N}^\text{Ph} \xrightarrow{[\text{Cp}^*\text{IrCl}_2]_2, \text{AgNTf}_2} \text{DCE, RT, 4\%} \xrightarrow{} \text{PhN}=\text{O}$$

In some circumstances $\text{Ir}^{\text{III}}$ is superior (e.g. acyl azides) to $\text{Rh}^{\text{III}}$ but in others it underperforms, what gives?

Contraction of the Ir radius makes it a harder Lewis acid than Rh meaning that dative ligands are bound more tightly and have higher dissociation barriers.

This explains why Ir underperforms in some cases but does not rationalize why it is better in others.

$\text{Rh}$ reaction is notably faster than $\text{Ir}$ with a nearly identical $k_{\text{obs}}$ at $-50^\circ\text{C}$ (Rh) vs $-37^\circ\text{C}$ (Ir)

Kinetics paint a clear picture; while ligand exchange is faster for Rh, the imido formation and rearrangement are much faster for Ir.

Relativistic contraction present in Ir makes the C–N bond shorter in the Ir complex than the Rh complex

Extensive computation and Eyring analysis corroborate this conclusion.

For Rhodium, ligand exchange is facile but imido formation is challenging and is the turnover-limiting step.

For Iridium, imido formation is facile but ligand exchange is challenging and is the turnover-limiting step.

Observed $\Delta S^\ddagger = -14.6$ is consistent with a transition from Rh$^{III}$ to Rh$^{V}$ in the turnover limiting step.

Observed $\Delta S^\ddagger = 5.2$ is consistent with a dissociative process in the turnover limiting step.

First order with respect to dioxazole (Rh) vs zeroth order (Ir) also supports this conclusion.
A more detailed mechanistic picture:
What are the takeaways and what are the next steps?

Because Ir$^{III}$ catalyzed nitrenoid formation is so facile, the use of dioxazoles allows typically difficult to promote transformations to be run at low temperatures.

A case in point:

$\gamma$-lactam formation has long eluded the C–H activation community because the facile Curtius-type rearrangement of nitrenoid species typically outcompetes C–H insertion at synthetically relevant temperatures.

Computed energy profile shows that while rearrangement is higher in energy than C-sp$^2$ coupling, it is more favorable than C–H insertion.

Use of more electron donating ligand computationally destabilizes Curtius rearrangement TS.

Use of Het–Ir bond supresses C-sp$^2$ pathway

Use of a typical substrate gives sp$^2$ C–N bond formation

However, C–H insertion can be observed in engineered substrates!
Enantioselectivity achieved by two strategies in two (nearly) back to back publications

- **NH₃O**
  - 99%, >20:1dr
  
- **R=H**, 95%
  - **Br**, 94%
  - **NO₂**, 85%
  - **OMe**, 68%

**4 possible diastereomers**

Must diastereoselectively form the dioxazole complex as well as enantioselectively perform C–H insertion


* Concurrently published report of a very similar Ru based system

**Cat., NaBARF₄**

95%, 98%ee

- **O**
  - **Ir**
  - **Cl**
  - **Mes**
  - **Ts**
  - **HN**
  - **O**

Computation and solid state structure of amido (Ir–N) analogue suggest hydrogen bonding helps organize substrate.

Although all four diastereomers of the dioxazole adduct can form, only one is calculated to efficiently undergo decarboxylation


Career in review: Sukbok Chang

Second approach: exploit hydrophobic effect and noncovalent interactions to create a chiral pocket

New ligand class with chiral information further away from Ir center

X-ray structure of Cp*IrL7Cl

EPM of I


High levels of enantiocontrol in previously challenging contexts!

Conclusions:

- Careful mechanistic work can lead to big advances
- Look out for Cp*Co^{III} chemistry in the coming years!

“Be persistent and never give up”
– Sukbok Chang’s favorite saying