Career in review: Sukbok Chang

Sukbok Chang

B.S.: Korea University, 1985

M.S.: KAIST (Korea Advanced Institute of Science and Technology), 1987, Prof. Sunggak Kim

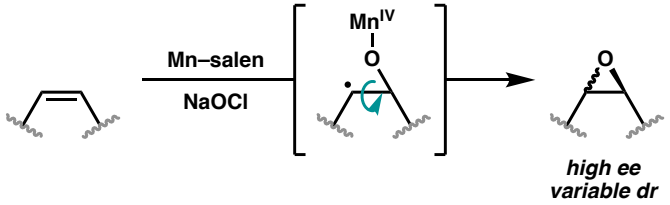
Ph.D.: Harvard, 1996, Prof. Eric Jacobsen

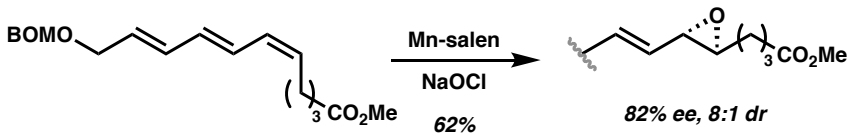
Post Doctoral Fellow: Caltech, 1996-98, Prof. Robert Grubbs

Assistant Professor: Ewha Women's University, 1998

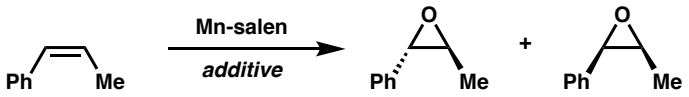
Professor: KAIST, 2002

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



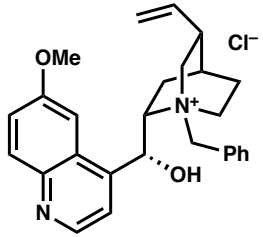


J. Org. Chem. **1993**, *58*, 6939–6941.



solvent	additive	*trans*:*cis*
DCM	none	29:71
PhCl	none	39:61
PhCl	R_4N^+	95:5

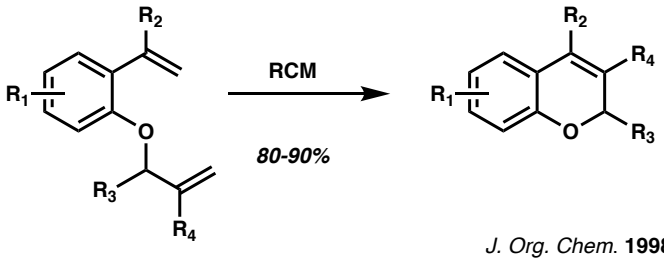
R_4N^+=



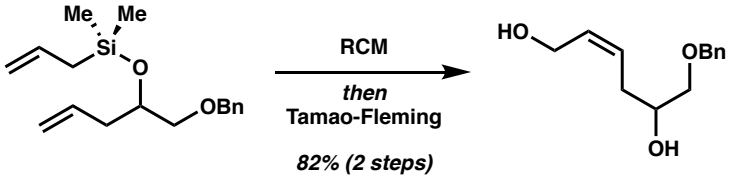
J. Am. Chem. Soc. **1994**, 116, 6937–6938.

Career in review: Sukbok Chang

- Postdoc work: novel applications of RCM



J. Org. Chem. **1998**, *63*, 864–866.

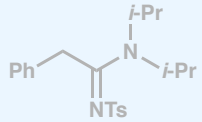


Tet. Lett. **1997**, *38*, 4757–4760.

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

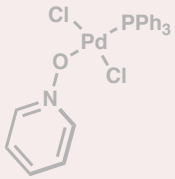
Heterogenious catalysis

J. Am. Chem. Soc. ***2003***, 127, 6844–6845.



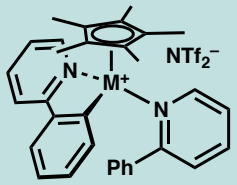
multicomponent couplings

J. Am. Chem. Soc. ***2005***, 127, 2038–2039.



C–H alkylation/ arylation

J. Am. Chem. Soc. ***2008***, 130, 9254–9256.



C–H amination/ amidation

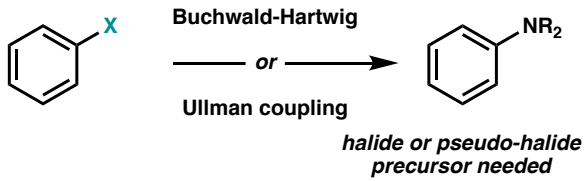
J. Am. Chem. Soc. **2012**, *134*, 9110–9114.

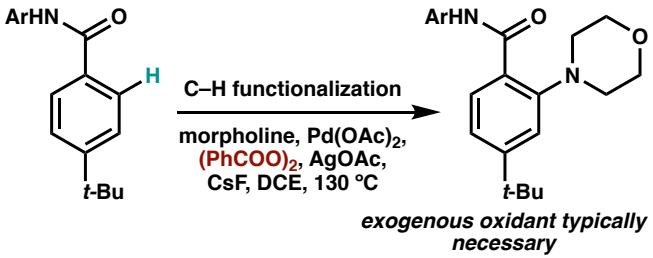
Plus many many others

Covered in this talk: group 9 C–H amination/amidation

Career in review: Sukbok Chang

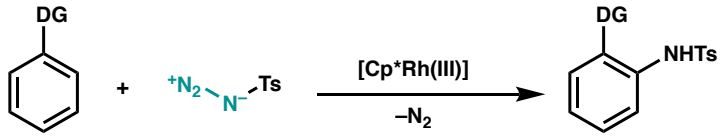
- Strategies to prepare aryl-amines

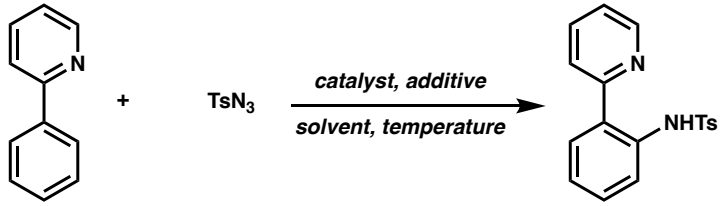




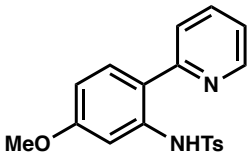
J. Am. Chem. Soc. **2011**, *133*, 7652–7655.

- Chang lab strategy: build in oxidation

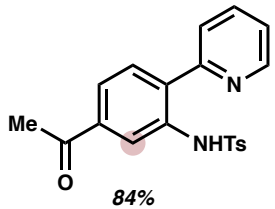




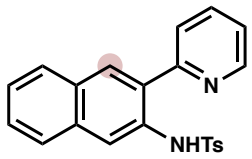
Cat.	Additive	Solvent	Temperature	Yield
$Rh_2(O_2CCF_3)_4$	none	toluene	110 °C	11%
$[RhCp^*Cl_2]_2$	none	toluene	110 °C	10%
$[RhCp^*Cl_2]_2$	$AgSbF_6$	toluene	110 °C	77%
$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	80 °C	96%
$[RhCp^*Cl_2]_2$	$AgBF_4$	DCE	80 °C	54%



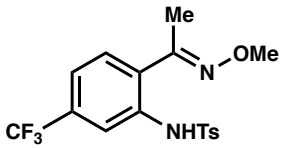
86%



84%



75%

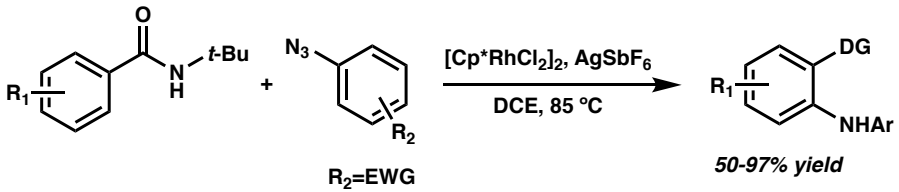


63%

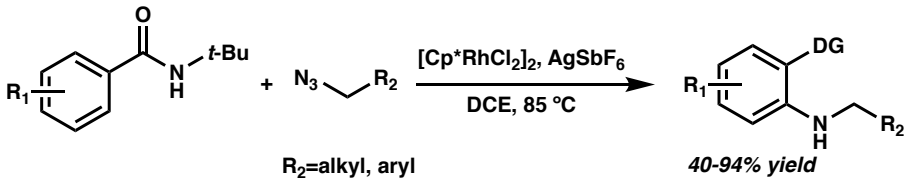
J. Am. Chem. Soc. **2012**, *134*, 9110–9114.

Career in review: Sukbok Chang

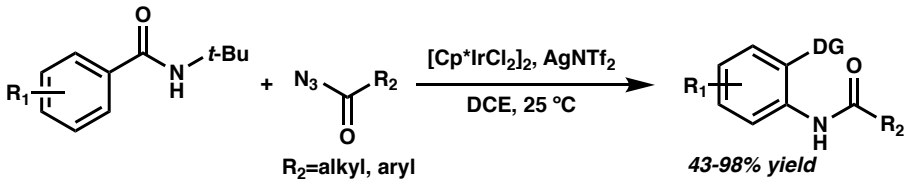
- Applicable to aryl, alkyl, acyl azides



Angew. Chem. Int. Ed. **2012**, *51*, 9904–9908.



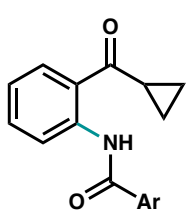
Angew. Chem. Int. Ed. **2013**, *52*, 8031–8036.

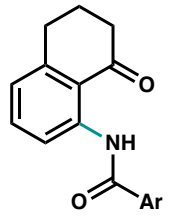


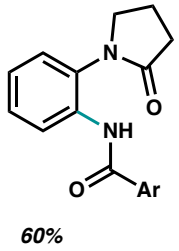
Lower temprature required to supress Curtius rearrangement

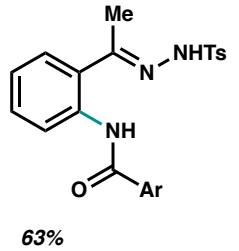
J. Am. Chem. Soc. **2013**, *135*, 12861–12868.

- Ir conditions tolerate diverse directing groups



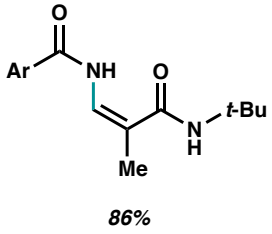


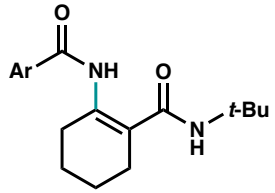




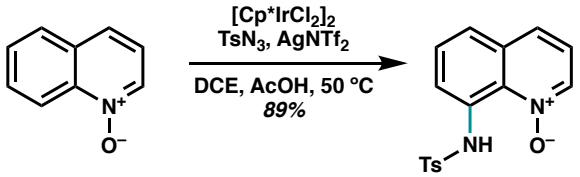
Ar=*p*-(NO_2)-C_6H_4

- Capable of aminating alkenyl substrates as well



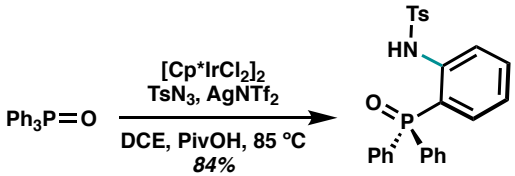


Other noteworthy applications:



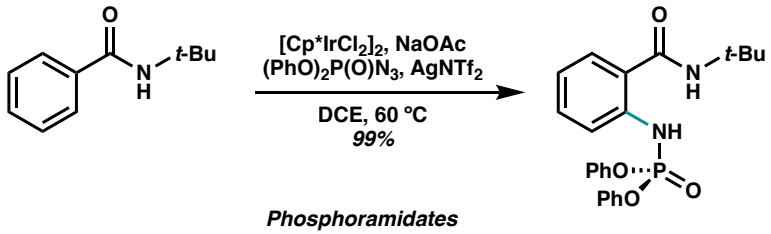
Quinoline N-oxides

J. Am. Chem. Soc. **2014**, *136*, 10770–10776.



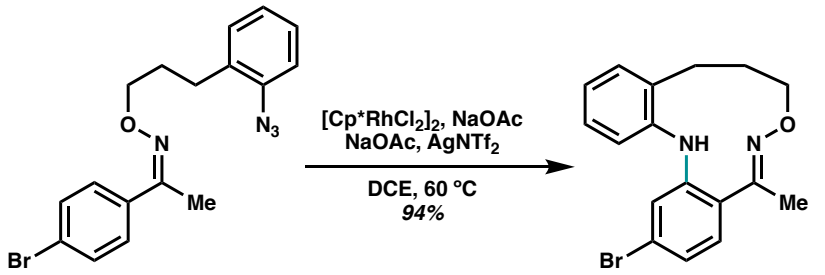
Phosphine oxides (some dr with chiral auxillaries on P)

Chem. Eur. J. **2014**, *20*, 12421–12425.



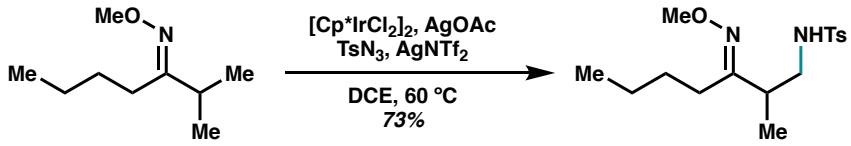
Phosphoramidates

Org. Lett. **2014**, *16*, 5466–5469.

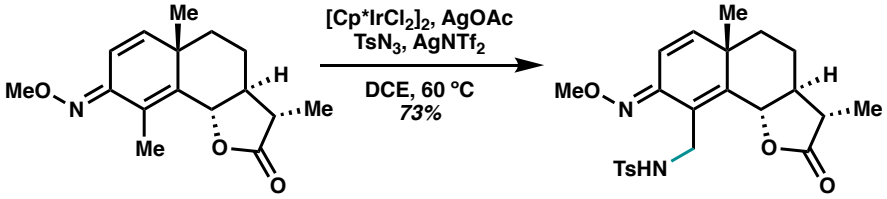


Synthesis of medium-large rings (9-11)
(up to 36-membered when dimerizing substrates)

Angew. Chem. Int. Ed. **2017**, *56*, 3344–3348.



Selective amination of 1° C–H bonds, inclusing in complex settings

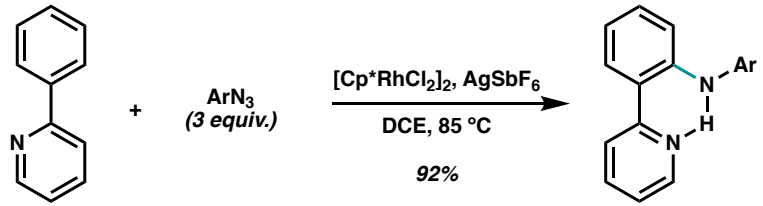


(–)-santonin derivative

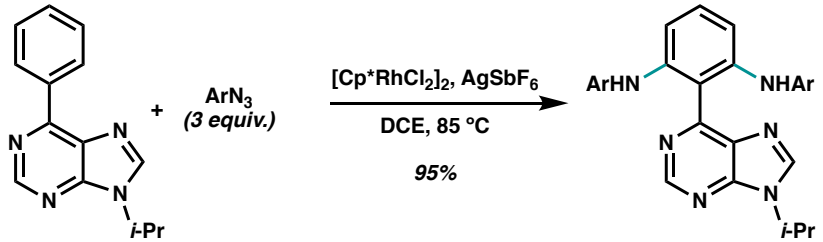
J. Am. Chem. Soc. **2014**, *136*, 4141–4144.

Career in review: Sukbok Chang

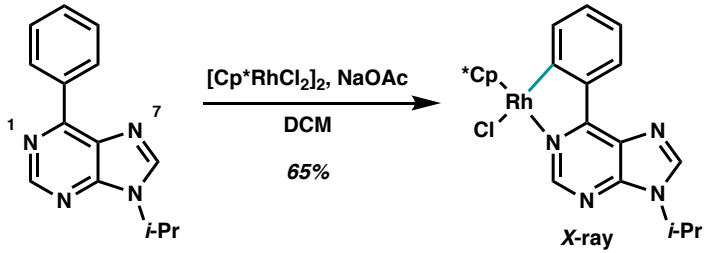
- The curious case of purine



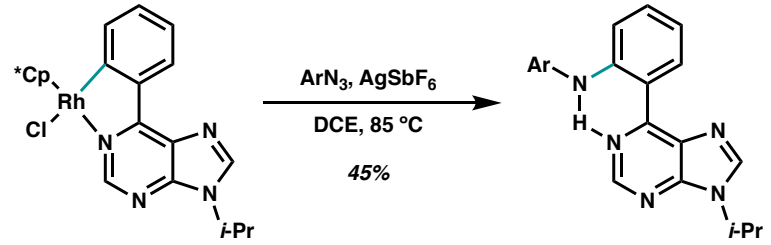
Hydrogen bonding restricts rotation supressing second C–H amination



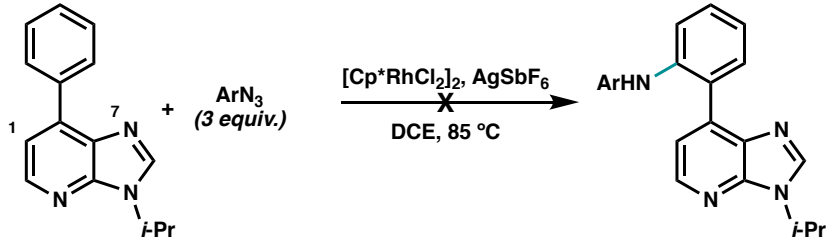
Two C–H aminations directed by different nitrogens?



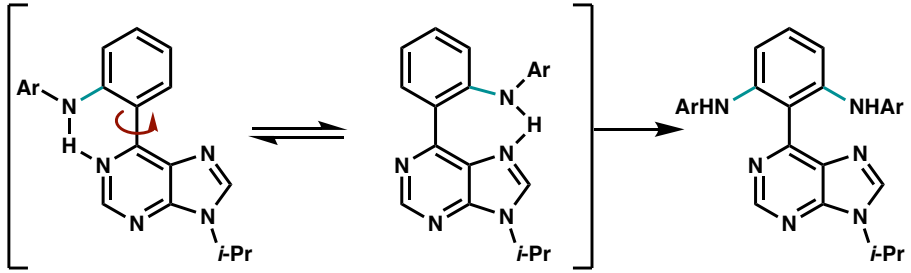
First C–H activation is directed by N1



Rhodacycle is an intermediate



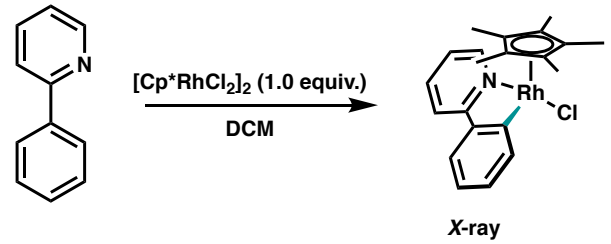
91% mono-amination with N1 and C7
N7 is not a competent director



Hydrogen bonding with N7 makes the other ortho position accessible
N1 mediates both aminations!

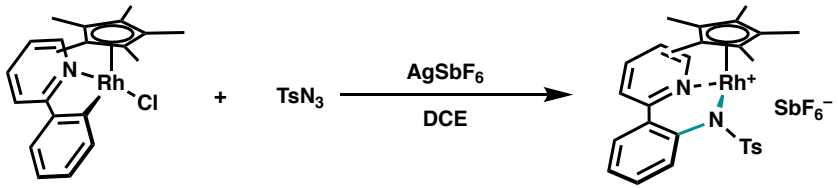
J. Am. Chem. Soc. **2014**, *136*, 1132–1140.

- Key mechanistic experiments:



X-ray

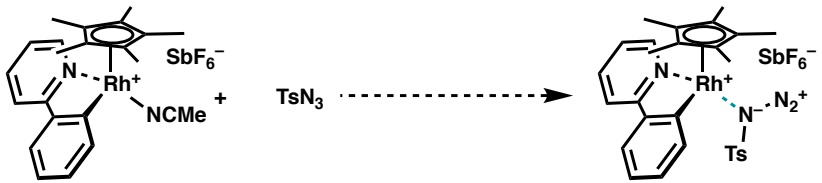
J. Am. Chem. Soc. **2012**, *134*, 9110–9114.



X-ray

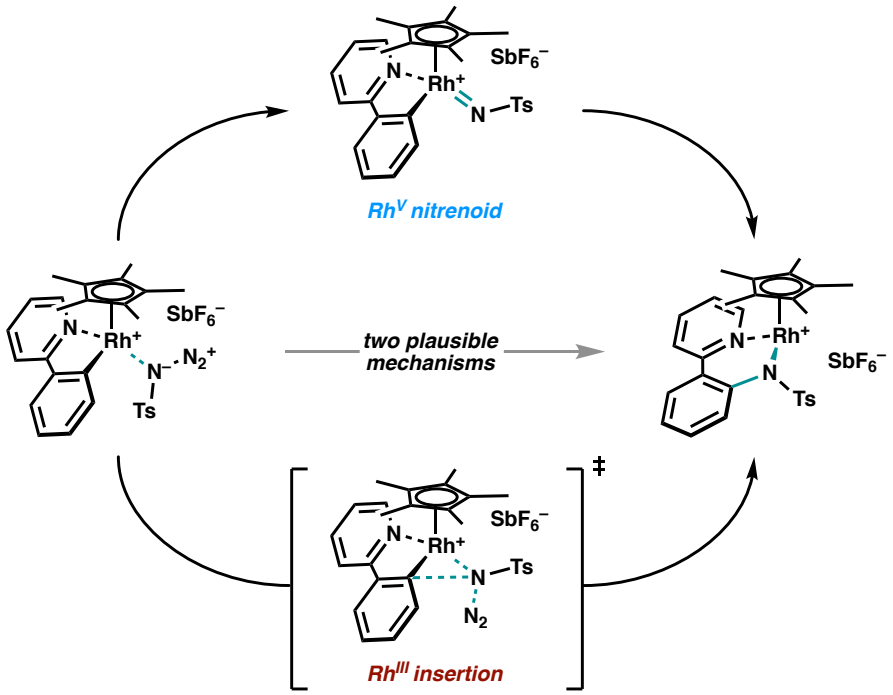
Rhodacycle is an intermediate in the reaction (corroborated by other groups working in the same space)

Rhodium bound Ts–amine is presumably also an intermediate in the reaction

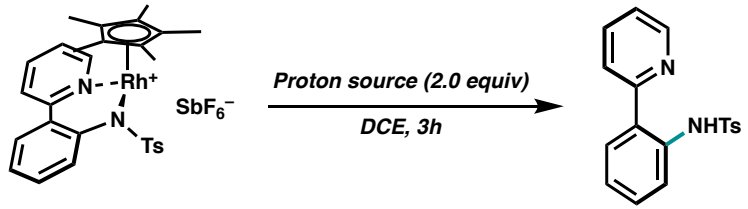


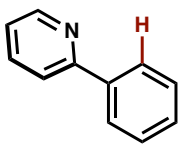
azide-bound rhodium not observed but presumed to be an intermediate based on precedent by Shi with Ts–imines (more on this later)

J. Am. Chem. Soc. **2014**, *136*, 2492–2502.
Chem. Sci. **2012**, 3, 1634-1639.

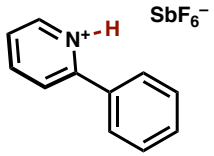


Unable to detect either species spectroscopically but Rh^{V} TS is favored computationally by 20.3 kcal/mol



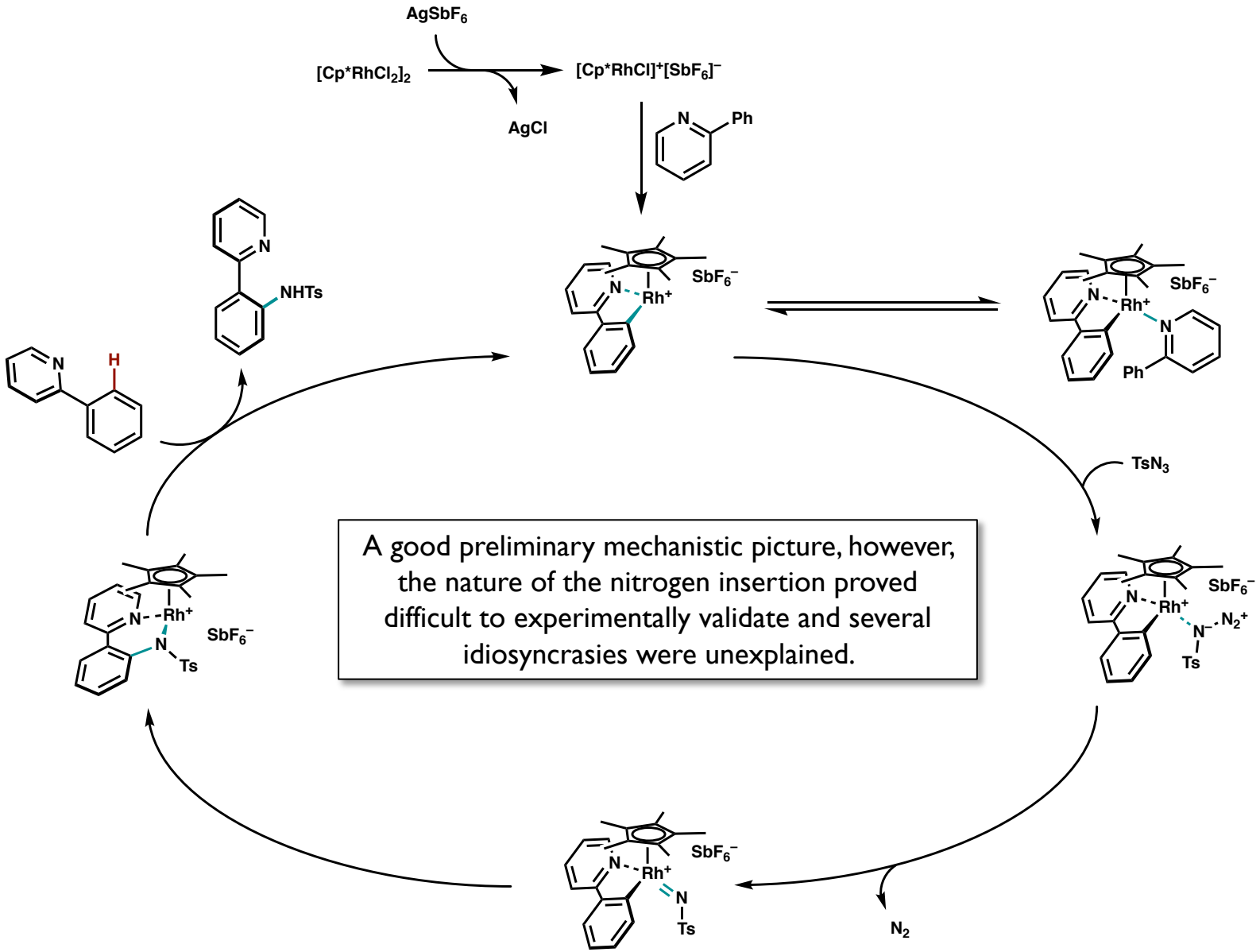


27%



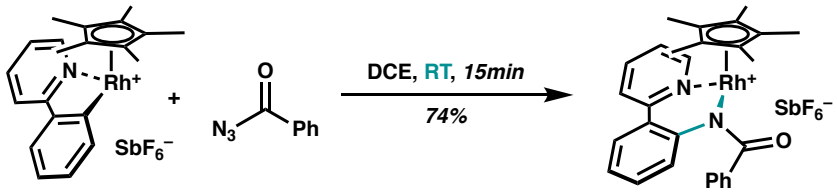
4%

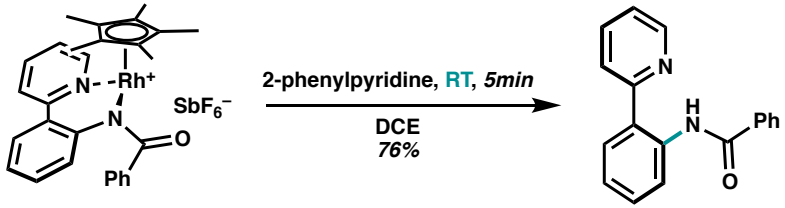
Substrate C–H bond turns over catalyst rather than simple protonation



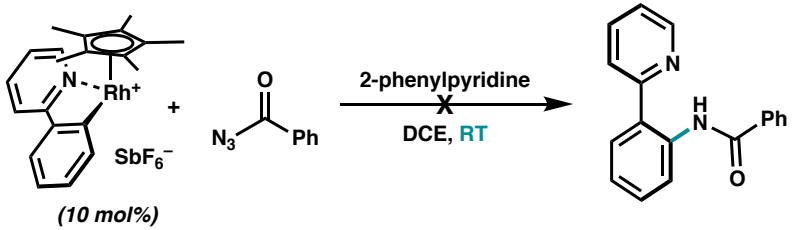
J. Am. Chem. Soc. **2014**, *136*, 2492–2502.

- Some things didn't quite add up





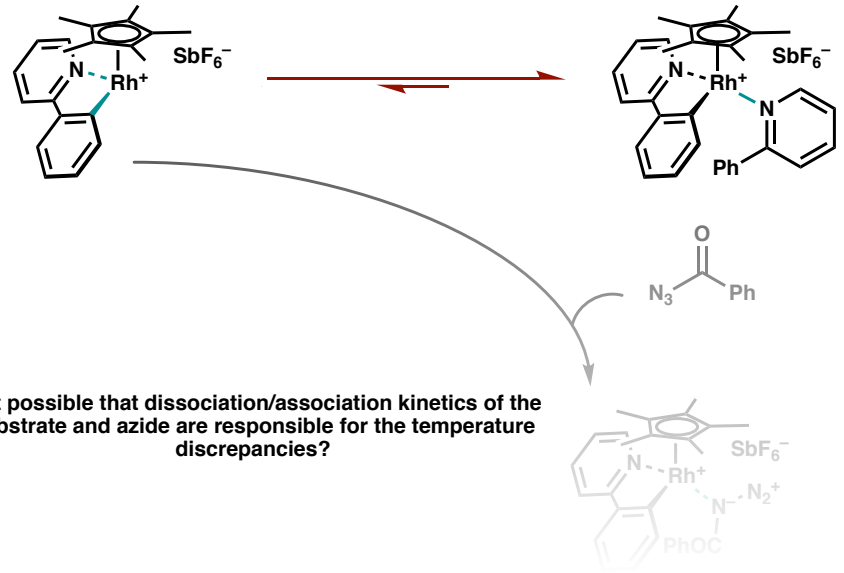
However:



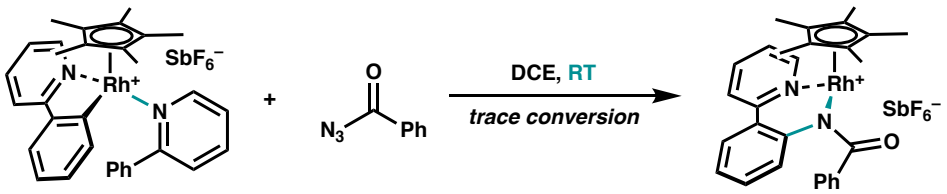
Despite every on cycle process being promoted at room temperature stoichiometrically, the catalytic process gave no reaction

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?



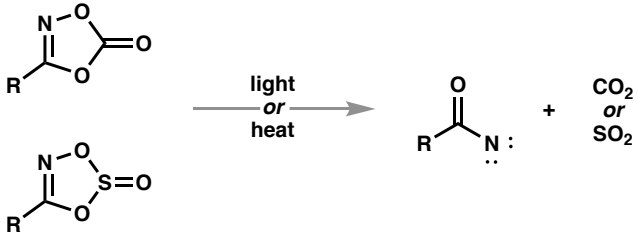
Addition of substrate as a ligand on Rh inhibits the stoichiometric reaction

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

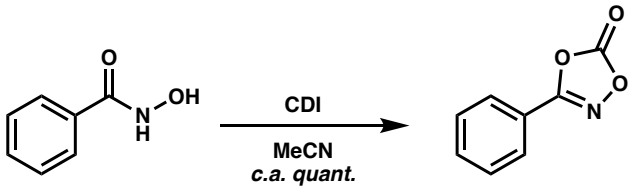
J. Am. Chem. Soc. **2015**, *137*, 4534–4542.

Career in review: Sukbok Chang

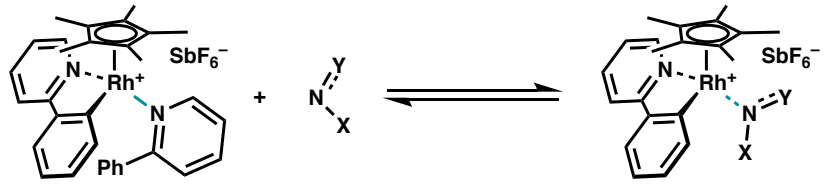
- Dioxazoles as a convenient nitrene precursor



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

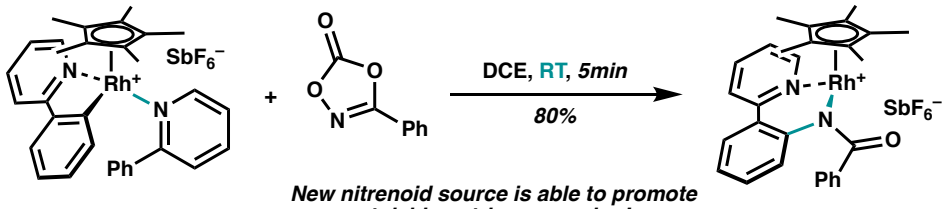


Org. Lett. **2009**, *11*, 5622–5625.

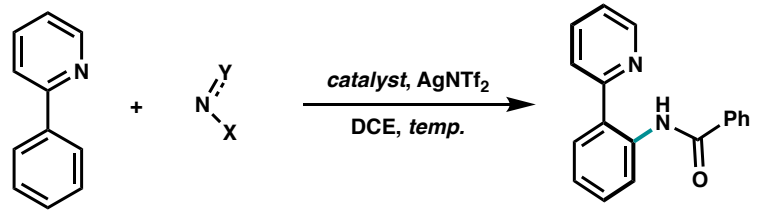


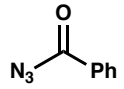
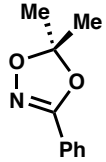
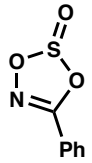
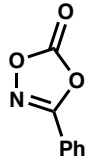
$K_{calcd}°$:	3.7×10^{-8}	1.4×10^{-4}	8.2×10^{-3}	8.1

J. Am. Chem. Soc. **2015**, *137*, 4534–4542.

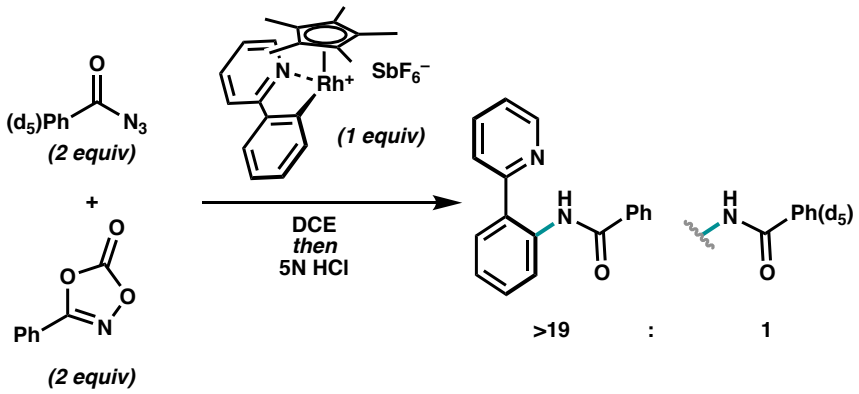


New nitrenoid source is able to promote stoichiometric conversion!

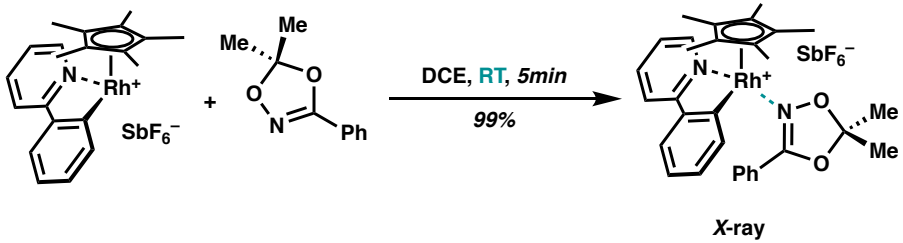


N-source	*Catalyst (mol%)*	*Temperature*	*Yield*
	$[Cp^*RhCl_2]_2$ (5)	RT	trace
	$[Cp^*RhCl_2]_2$ (5)	RT	trace
	$[Cp^*RhCl_2]_2$ (5)	100 °C	74%
	$[Cp^*RhCl_2]_2$ (5)	RT	75%
	$[Cp^*RhCl_2]_2$ (5)	40 °C	80%
	$[Cp^*RhCl_2]_2$ (5)	RT	99%
	$[Cp^*RhCl_2]_2$ (1)	40 °C	99%
	$[Cp^*IrCl_2]_2$ (5)	RT	4%

The dioxazole not only binds more favorably, but also has a lower barrier to imido formation than azide ($\Delta\Delta G^{\ddagger}_{calcd}$=7.8 kcal/mol)

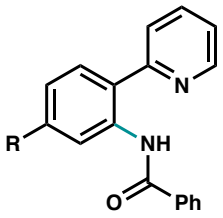


Competition experiment dioxazole in more competent even in the absence of a second substrate to displace

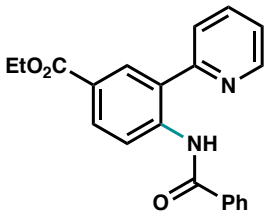


***X*-ray**

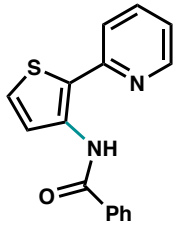
Crystal structure confirms presence of N-bound species. Moreover, upon heating this structure generates the nitrogen inserted rhodacycle



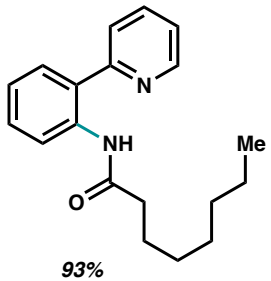
R= OMe, *92%*
CF_3, *90%*
CO_2Et, *98%*



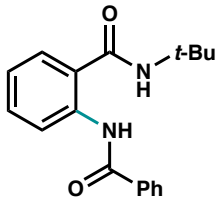
97%



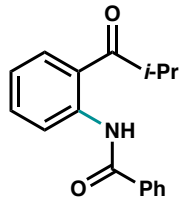
75%



93%



72% (80 °C)
vs 93% w/ Ir^{III}



N.R.
vs 48% w/ Ir^{III}

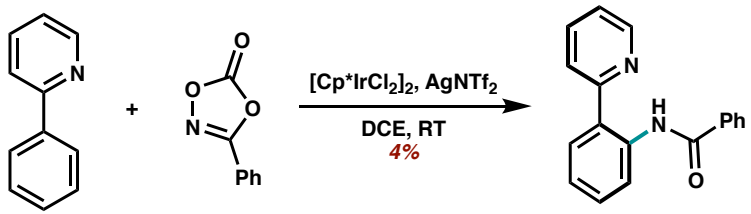
** Ir^{III} used p-NO_2Ph**

J. Am. Chem. Soc. **2015**, *137*, 4534–4542.
J. Am. Chem. Soc. **2013**, *135*, 12861–12868.

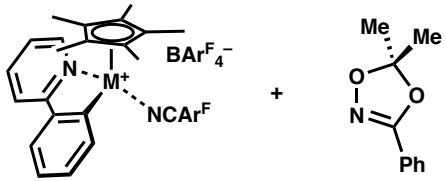
Career in review: Sukbok Chang

- Examining the details: Ir^{III} vs Rh^{III}

Recall:



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

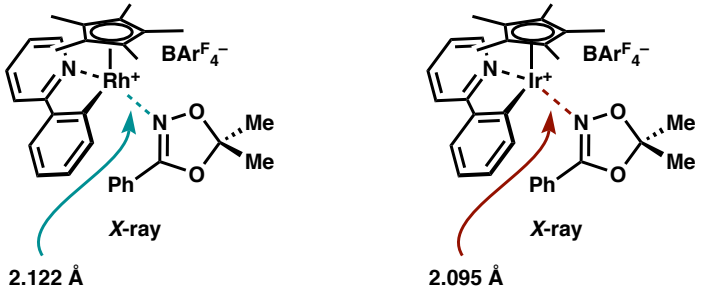


Rh reaction is notably faster than Ir with a nearly identical k_{obs} at –50 °C (Rh) vs –37 °C (Ir)

M = Rh, Ir

45 Rh

77 Ir

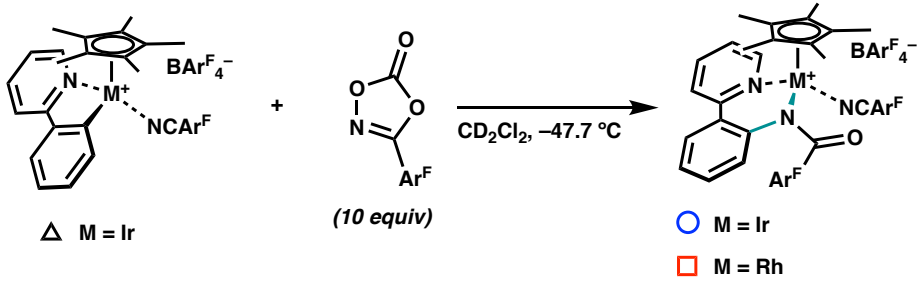


Relativistic contraction present in Ir makes the C–N bond shorter in the Ir complex than the Rh complex

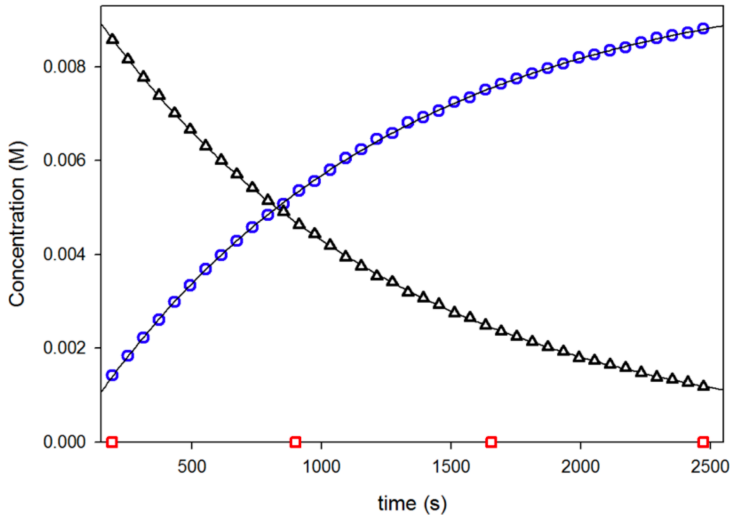
J. Am. Chem. Soc. **2016**, *138*, 14020–14029.

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.

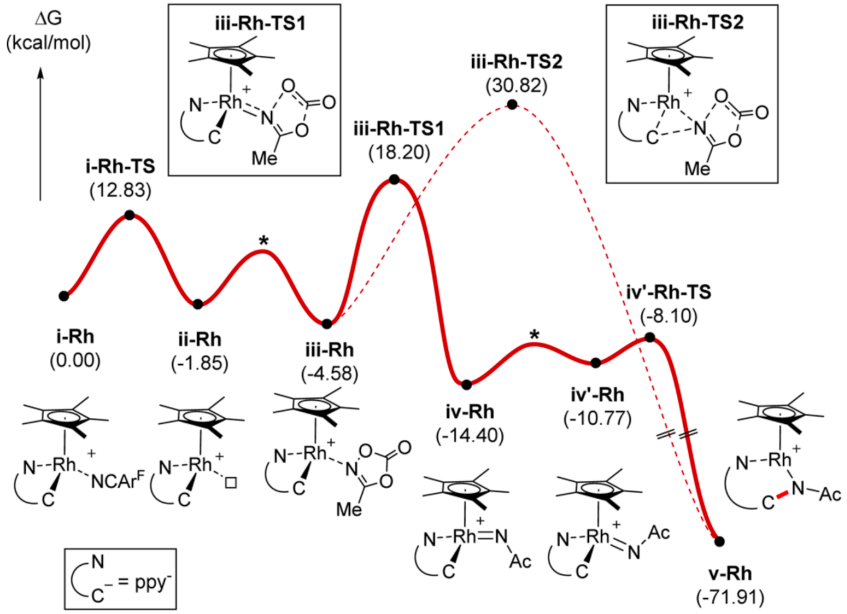
This explanis why Ir underperforms in some cases but does not rationalize why it is <u>better</u> in others.



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

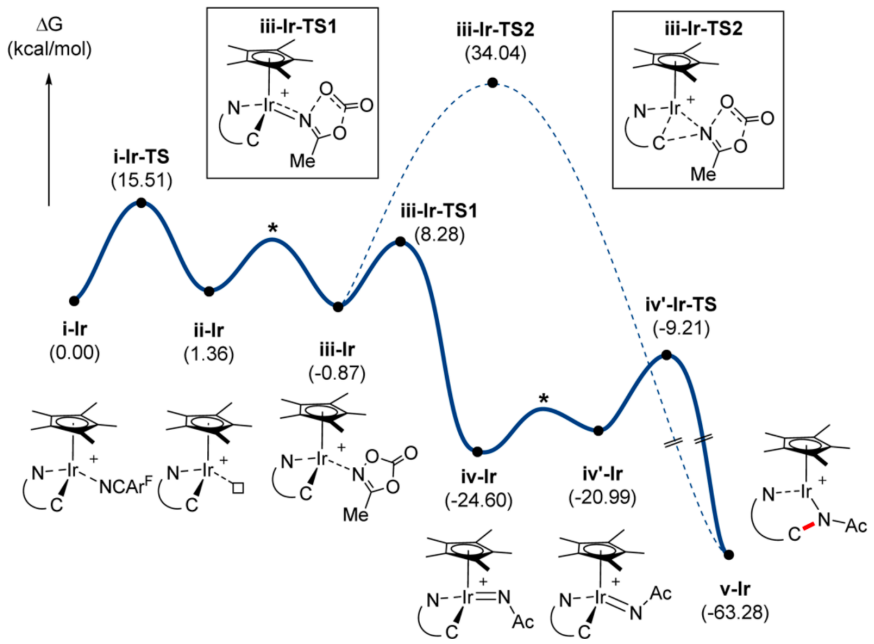


- Extensive computation and Eyring analysis corroborate this conclusion



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

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



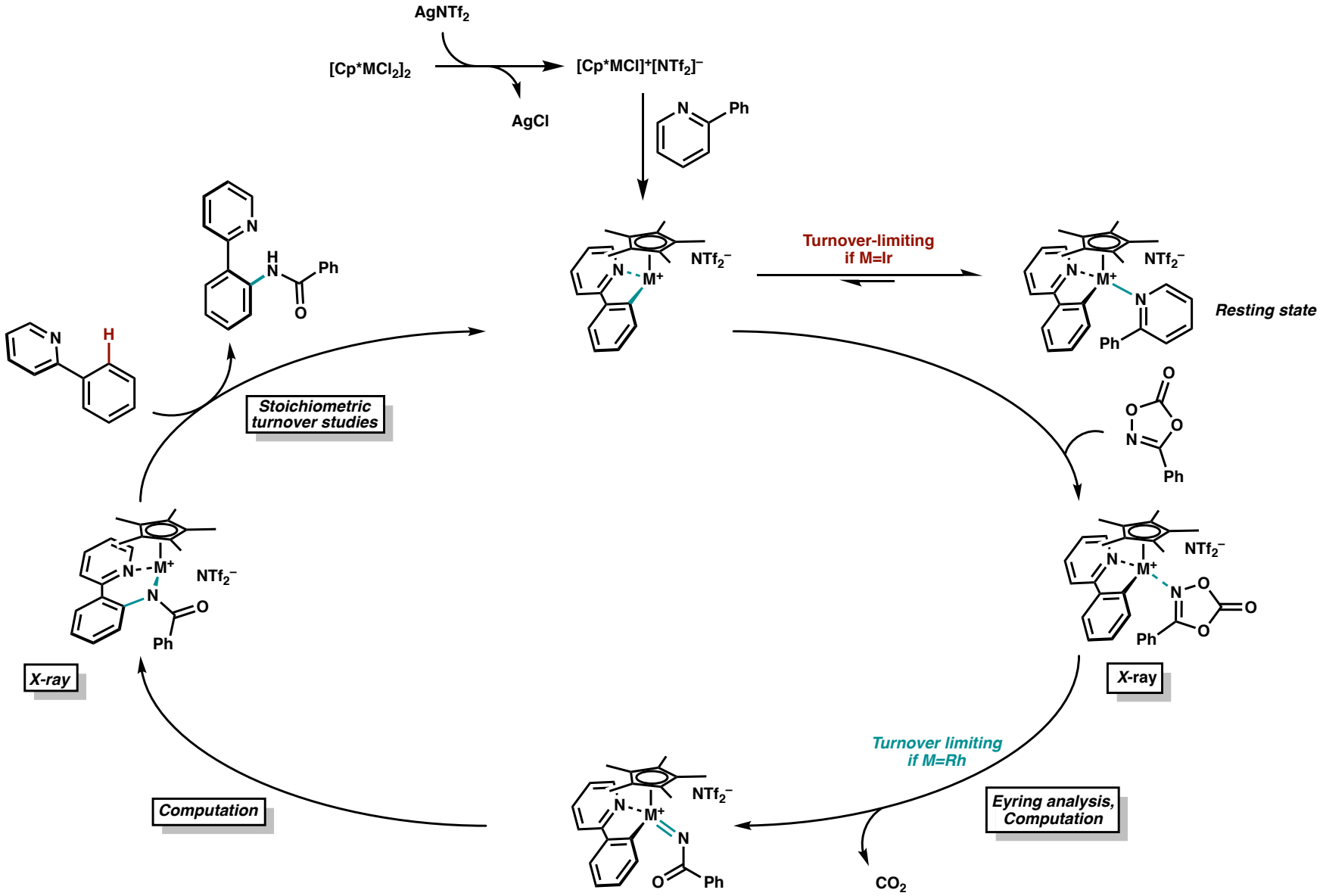
For Iridium, imido formation is facile but ligand exchange is challenging and is the turnover-limiting step.

Observed $\Delta S^{\ddagger}$=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.

Career in review: Sukbok Chang

- A more detailed mechanistic picture:

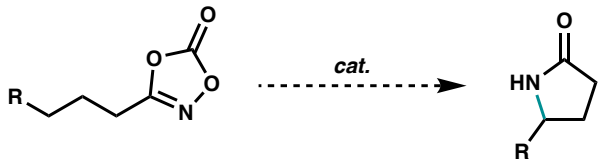


Career in review: Sukbok Chang

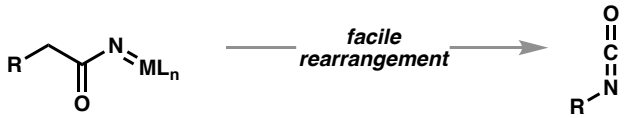
- What are the takeaways and what are the next steps?

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.

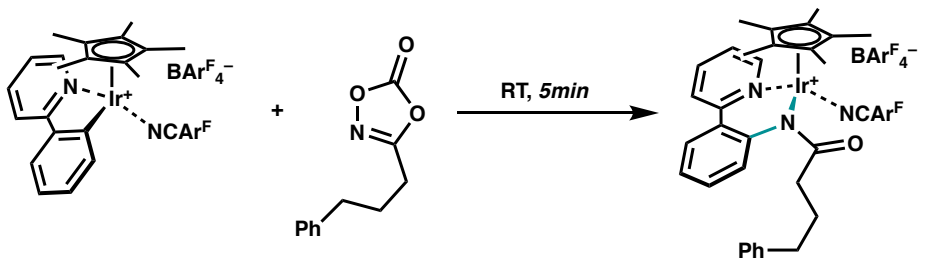
A case in point:



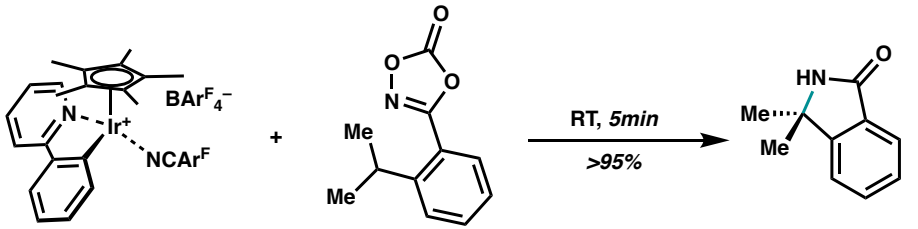
γ–lactam formation has long eluded the C–H activation community because the facile Curtius-type rearrangement of nitrenoid species typically outcompetes C–H insertion at synthetically relevant temperatures



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

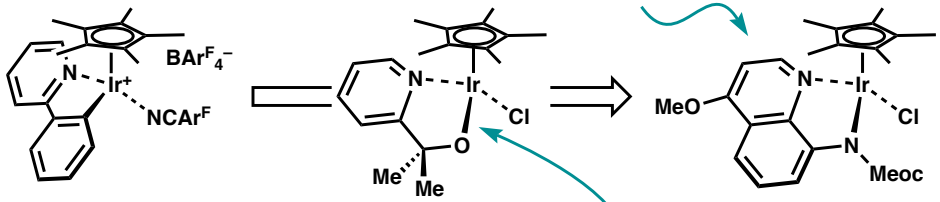


Use of a typical substrate gives sp^2 C–N bond formation



However, C–H insertion can be observed in engineered substrates!

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



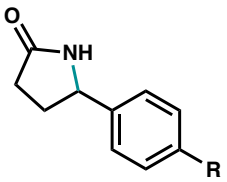
$C\text{-}sp^2$ only

~1:1 (desired:NCO)

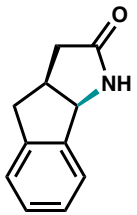
97:3 (!)

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

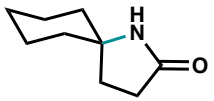
Career in review: Sukbok Chang



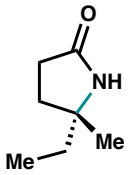
R=H, *95%*
Br, *94%*
NO_2, *85%*
OMe, *68%*



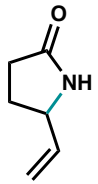
99%, >20:1dr



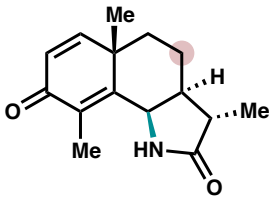
75%



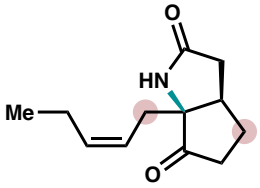
83%, 99% es



63%
(no aziridination)



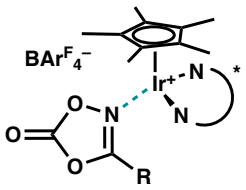
43%
(–)-santonin derivative

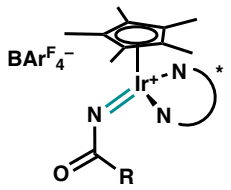


70%
(±)-jasmonic acid derivative

Science **2018**, *359*, 1016–1021.

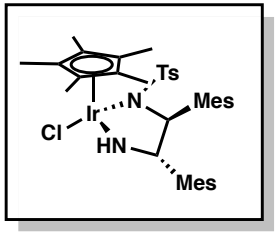
Enantioselectivity achieved by two strategies in two (nearly) back to back publications

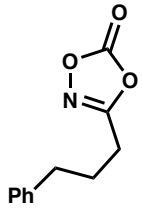




4 possible diastereomers

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

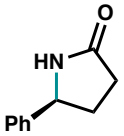


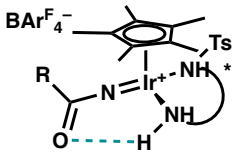


Cat., $NaBAr^F_4$

TCE

95%, 98%ee





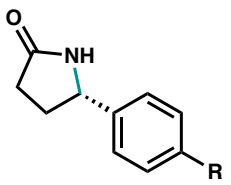
Computation and solid state structure of amido (Ir–N) analogue suggest hydrogen bonding helps organize substrate.

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

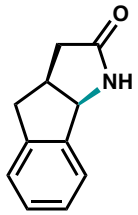
* Concurrently published report of a very similar Ru based system

Nat. Cat. **2019**, *2*, 219–227.
J. Am. Chem. Soc. **2019**, *141*, 3849–3853.*

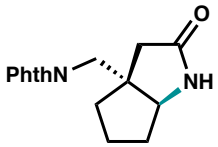
Career in review: Sukbok Chang



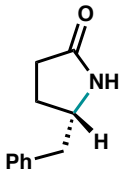
R=H, *96%, 98% ee*
Br, *98%, 96% ee*
NO_2, *51%, 82% ee*
Me, *80%, 94% ee*



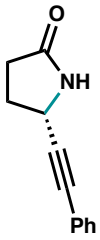
98%, >20:1dr, 94% ee



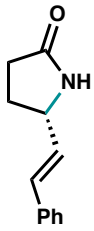
88%, 92% ee



86%, 92% ee



67%, 72% ee



40%, 74% ee

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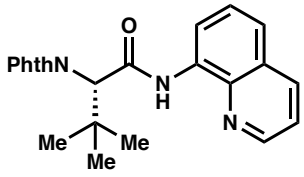
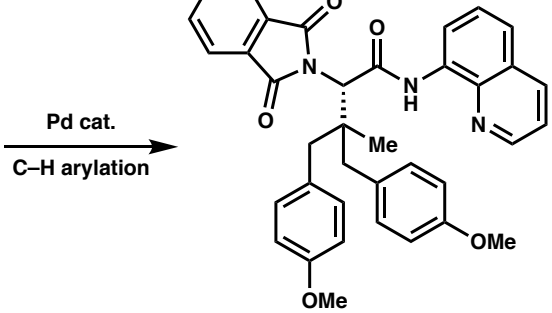
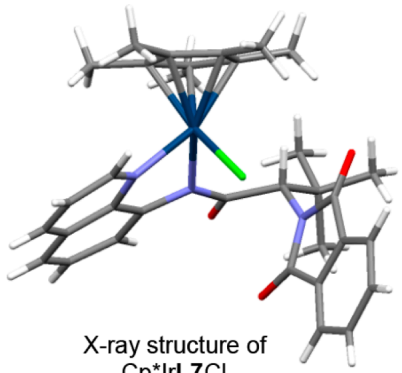
Second approach: exploit hydrophobic effect and noncovalent interactions to create a chiral pocket



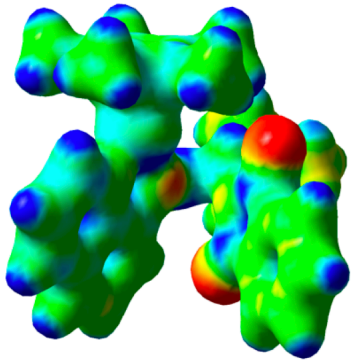
L7



New ligand class with chiral information further away from Ir center



X-ray structure of Cp*Ir**L7**Cl



EPM of **I**

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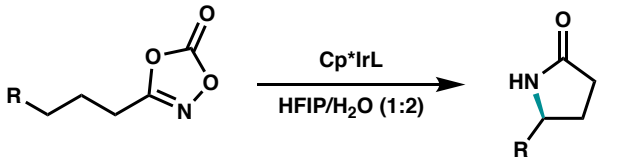
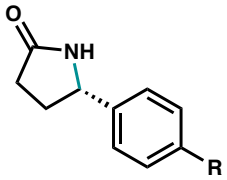
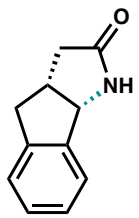
Career in review: Sukbok Chang

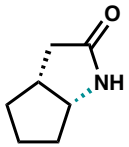




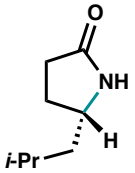
R=H, *98%, 98% ee*
Br, *84%, 99% ee*
NO_2, *68%, 92% ee (82% ee)*
Me, *95%, 99% ee*



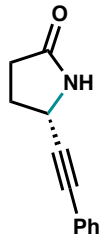
98%, >20:1dr, 94% ee



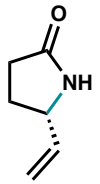
88%, 92% ee



70%, 99% ee



89%, 99% ee (72% ee)



90%, 99% ee

High levels of enantiocontrol in previously challenging contexts!

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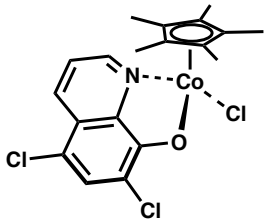
- Conclusions:
  - Careful mechanistic work can lead to big advances
  - Look out for Cp^*Co^{III} chemistry in the coming years!



27 Co
45 Rh
77 Ir

J. Am. Chem. Soc. **2020**, *XXX*, XXXX–XXXX.

"Be persistant and never give up"
– Sukbok Chang's favorite saying

Angew. Chem. Int. Ed. **2013**, *52*, 3804.