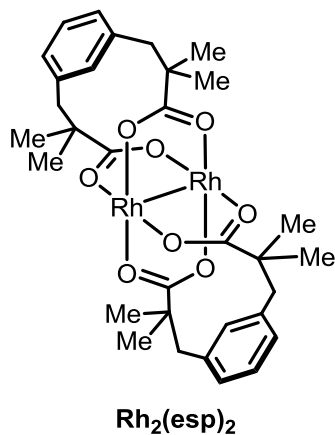


Rhodium-Catalyzed C-H Amination

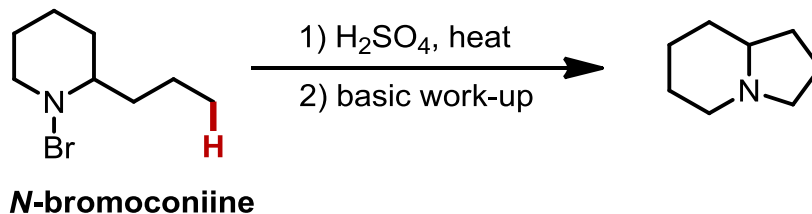


Zhongxing Huang
Dong Group Meeting
Oct. 17nd, 2012

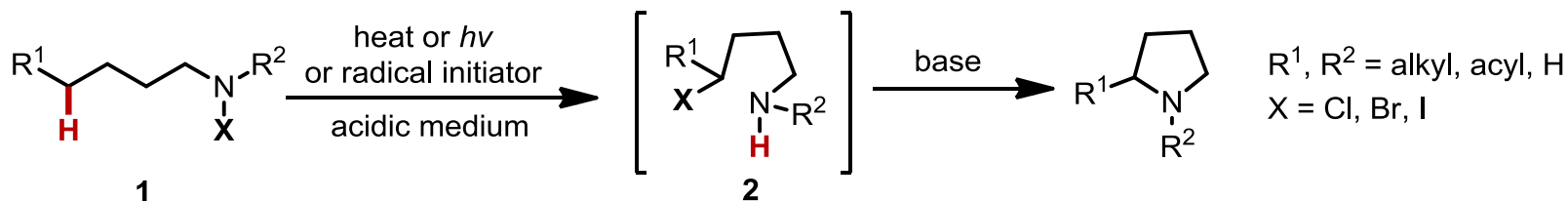
Early works on C-H amination

▪ Hofmann-Löffler-Freytag Reaction

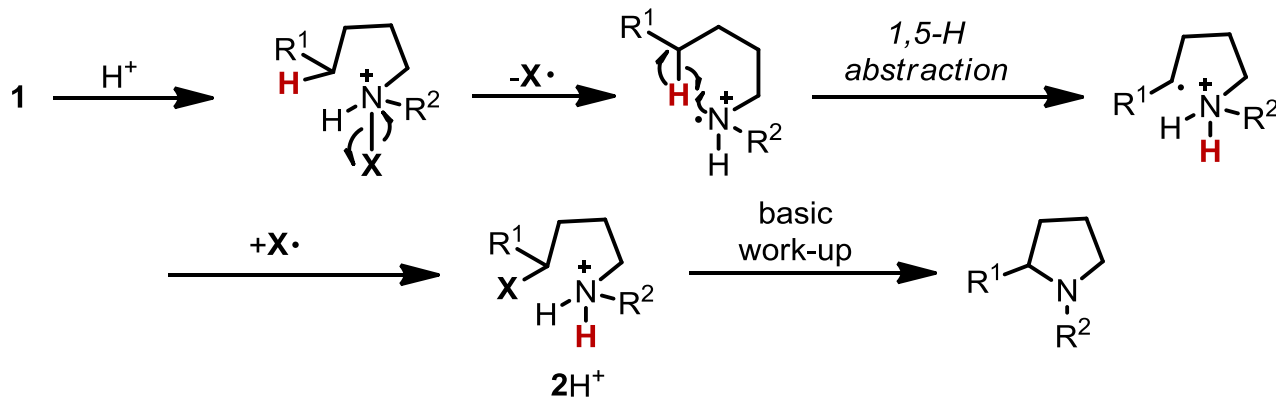
Hofmann, 1885



Löffler and Freytag, 1909



Radical mechanism



Hofmann, A. W. *Ber.* **1883**, *16*, 558

Hofmann, A. W. *Ber.* **1885**, *18*, 5

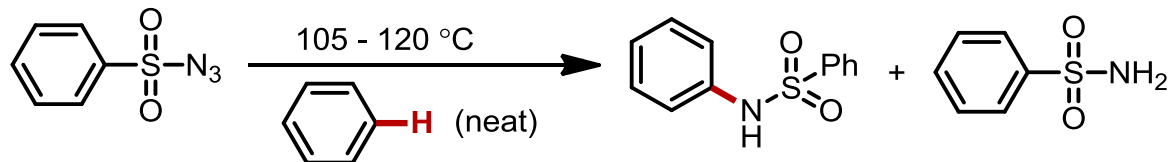
Hofmann, A. W. *Ber.* **1885**, *18*, 109

Löffler, K., Freytag, C. *Ber.* **1909**, *42*, 3427

Early works on C-H amination

- Decomposition of azide in aromatic solvents

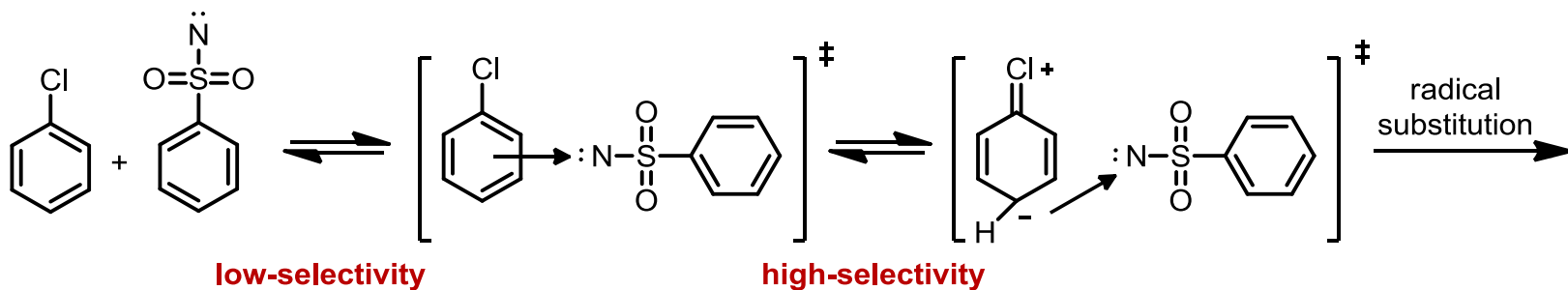
Curtius, 1930



Edmison, mechanistic studies, 1950s

Aromatic substrates	Rate factor				non-competitive yield
	X_H^k	X_{Ho}^k	X_{Hm}^k	X_{Hp}^k	
benzene	1.00	1.0	1.0	1.0	30.2%
toluene	1.00	1.8	0.03	2.3	55.3%
anisole	0.96	2.0	0.06	1.6	36.0%
phenol	0.80	1.2	0.05	2.3	N/A

- Electron-rich **arenes** are not preferred
- Electron-rich **sites** are preferred



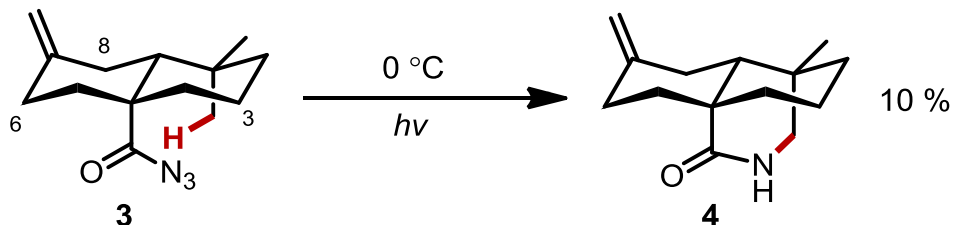
Curtius, T. J. *Praket. Chem.* **1930**, 125, 303

Heacock, J. F., Edmison, M. T. *J. Am. Chem. Soc.* **1960**, 82, 3460

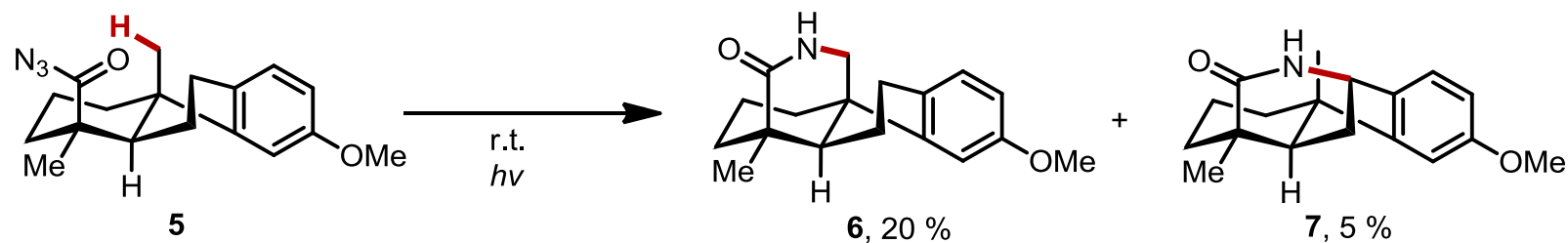
Early works on C-H amination

- Application in synthesis using azide as amination reagent

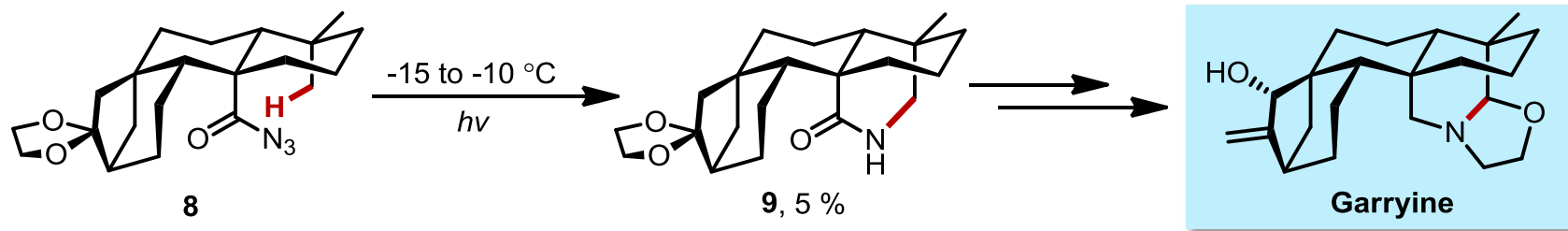
Meyer, 1962



Edwards, 1962



Masamune, 1963



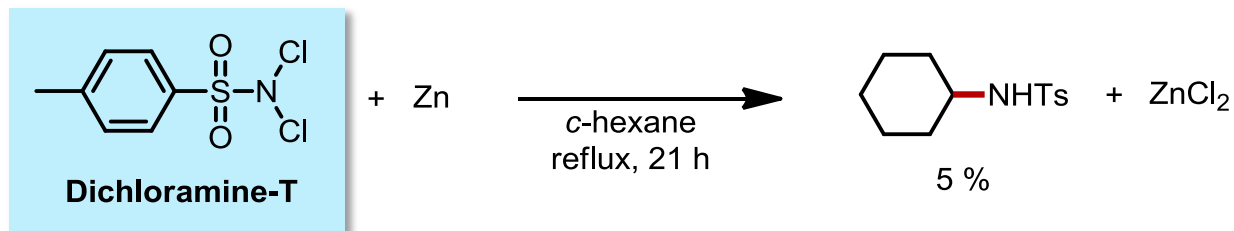
Apsimon, J.; Edwards, O. *Can. J. Chem.* **1962**, *40*, 896

Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 290

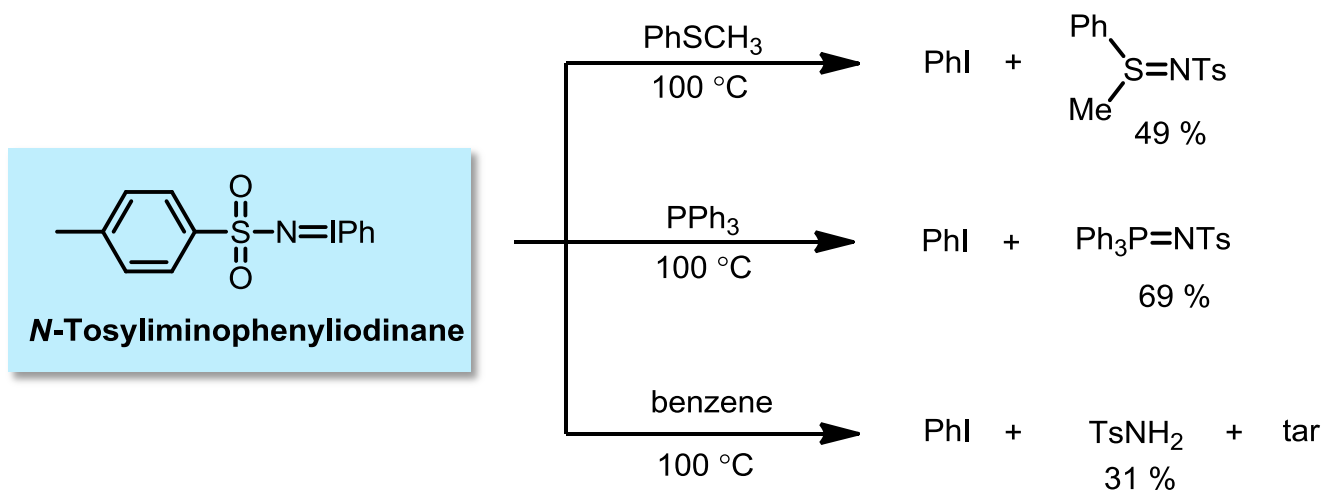
Development of New Amination Reagent

- Search of alternative nitrene precursors

Breslow, 1968



Abramovitch and Yamamoto, 1967-68



Breslow, R.; Sloan, M. *Tetrahedron Lett.* **1968**, 51, 5349

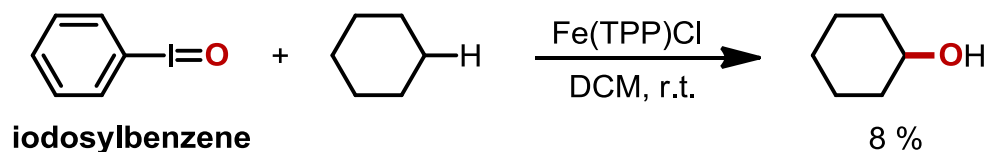
Abramovitch, R.; Bailey, T.; Takaya, T.; Uma, V. *J. Org. Chem.* **1974**, 39, 340

Yamada, Y.; Yamamoto, T.; Okawa, M. *Chem. Lett.* **1975**, 361

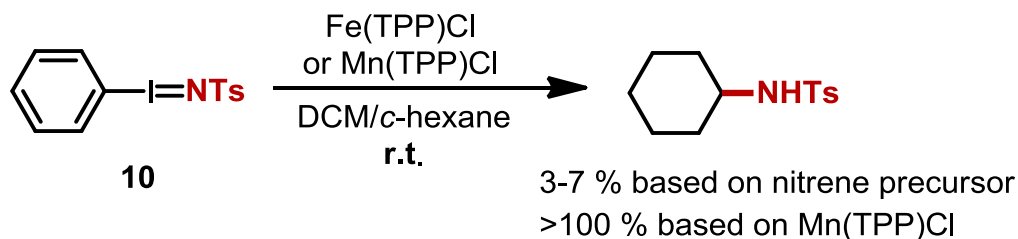
Development of Transition-Metal Catalyzed C-H Amination

- Challenges facing the traditional amination
 - Efficiency
 - Site-selectivity
- Again, transition-metal opens up a new area

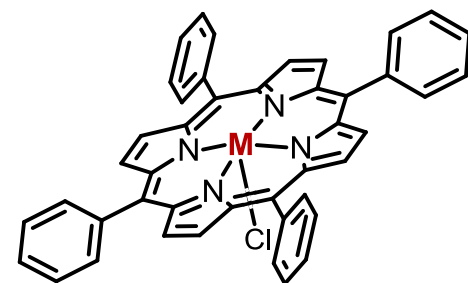
Groves, 1979



Breslow, 1982



- Low efficiency
- Important role of TM

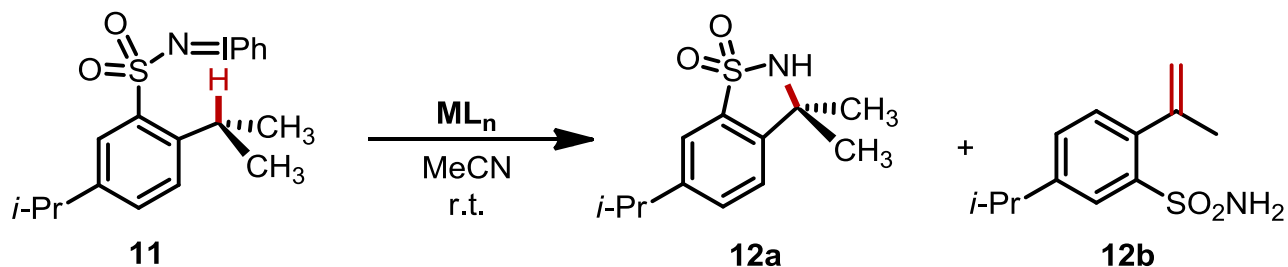


$M^{III}(\text{TPP})\text{Cl}$
TPP = tetraphenylporphyrin

Development of Transition-Metal Catalyzed C-H Amination

- Breslow's TM-catalyzed intramolecular amination

“The **additional valence** of nitrogen, relative to oxygen, permits **variations in structure** and makes it particularly clear how **intramolecular functionalization** could be performed”

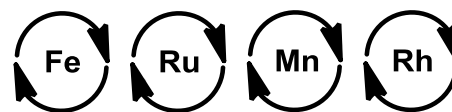


ML _n	Yield (%)	
	12a	12b
Mn ^{III} (TPP)Cl	16	4.5
Fe ^{III} (TPP)Cl	77	1.4
[Fe ^{III} (cyclam)Cl ₂]Cl	42	4.1
FeCl ₃	16	0.2
Rh₂(OAc)₄	86	0.2
–, in MeCN	1.4	0.3
–, in DCM	26	4.5

cyclam = 1,4,8,11-tetraazacyclotetradecane

- For TM-catalyzed C-H amination

- Milestone
- Opens up several fields

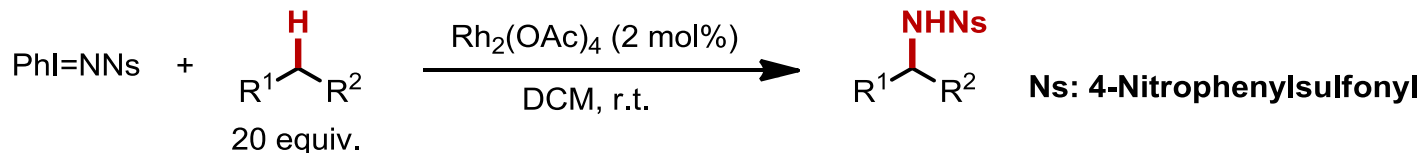


- For Rh-catalyzed C-H amination

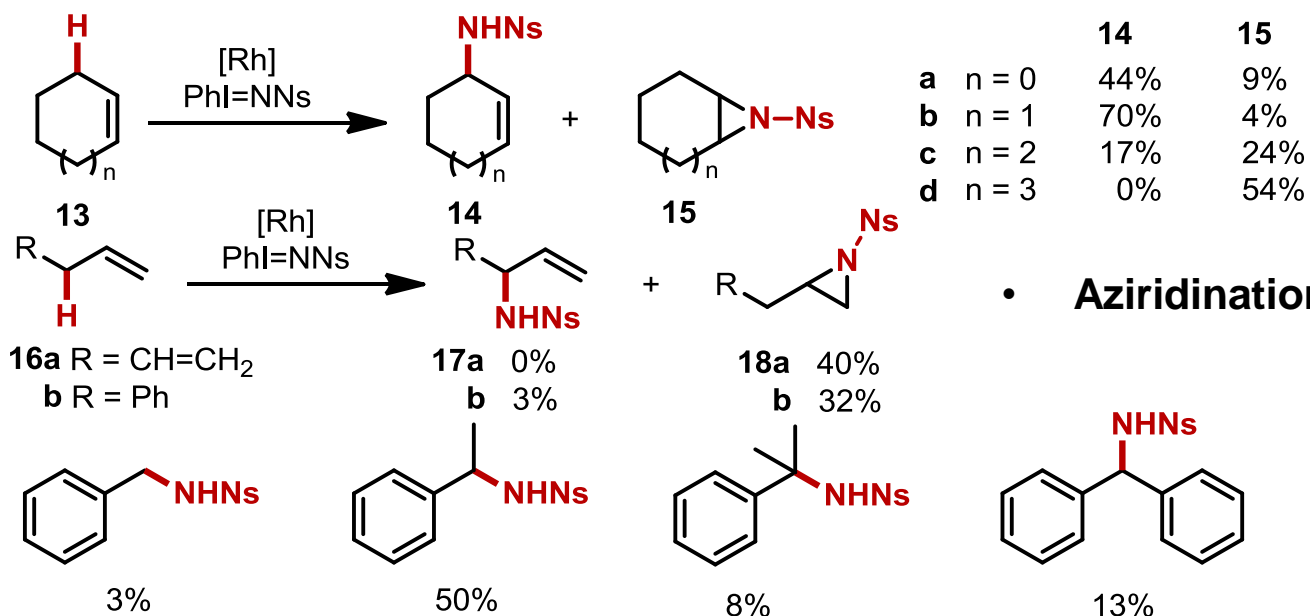
- Superior properties
- Most-studied and successful subfield later

Development of Rh-Catalyzed Aliphatic C-H Amination

- Müller's Rh-catalyzed intermolecular amination and mechanistic studies



- Representative examples



- Aziridination over insertion

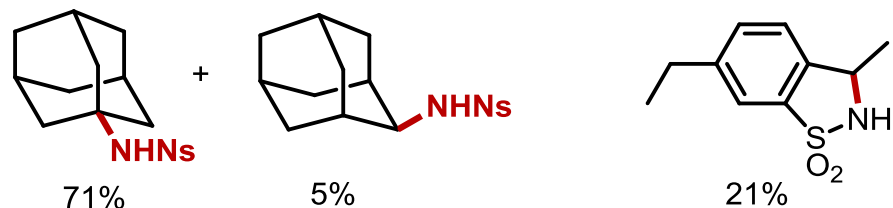
Müller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Nageli, I. *J. Phy. Org. Chem.* **1996**, 9, 341

Nageli, I.; Baud, C. Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta.* **1997**, 80, 1087

Müller, P.; Baud, C.; Naegeli, I. *J. Phy. Org. Chem.* **1998**, 11, 597

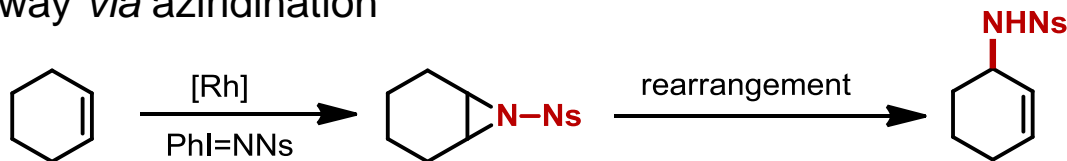
Development of Rh-Catalyzed Aliphatic C-H Amination

- Representative examples

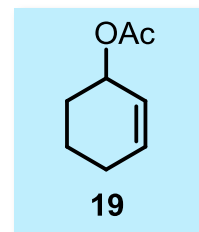
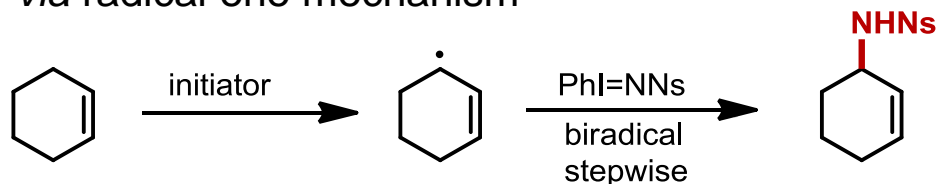


- Mechanistic studies

- Pathway *via* aziridination



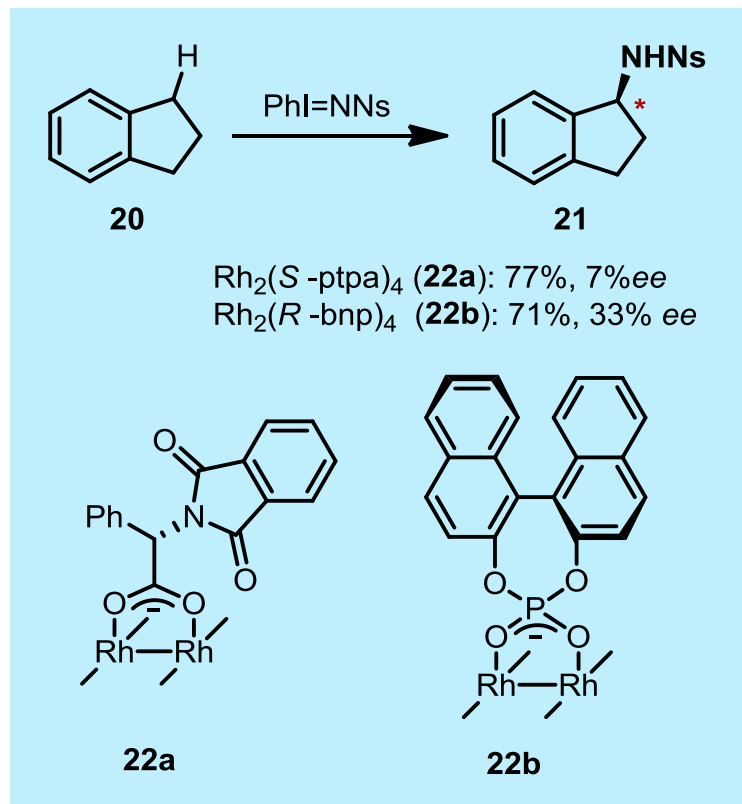
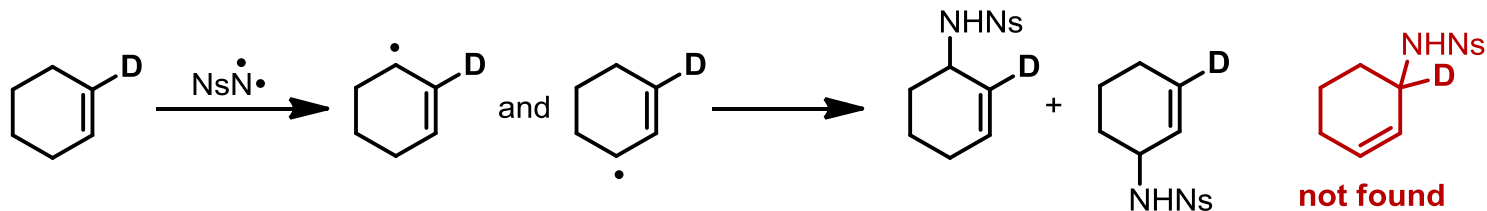
- Pathway *via* radical ene mechanism



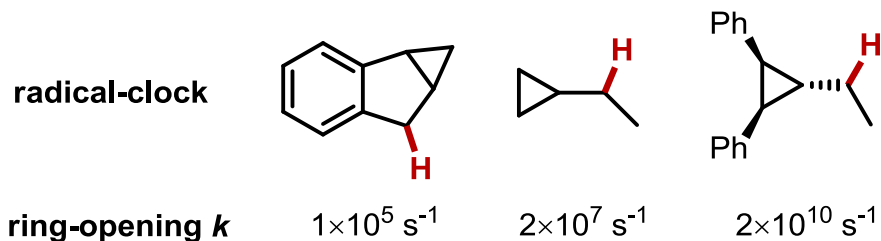
The reaction with **19** ruled out the first two pathways

Development of Rh-Catalyzed Aliphatic C-H Amination

- Mechanistic studies
 - Pathway via **H subtraction** and **radical recombination**



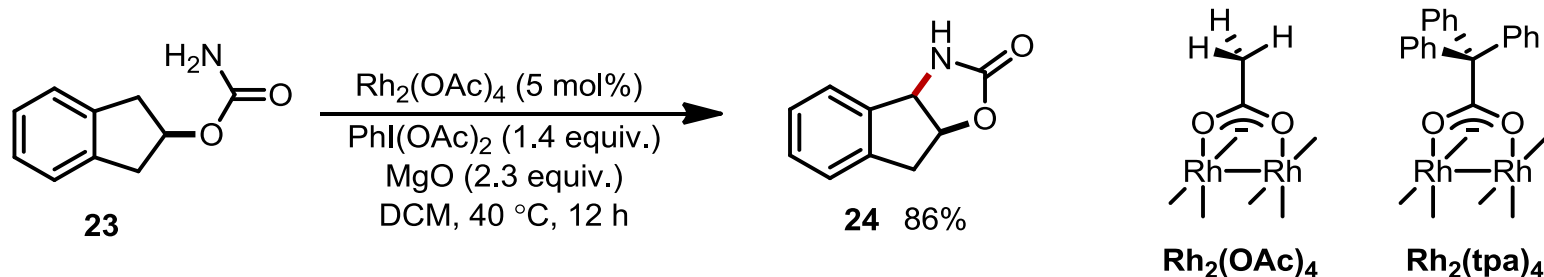
- No ring-opening product found



- Direct insertion of **metal-nitrene** is mostly likely
- No evidence for radical process (cannot be excluded neither)
- Restriction on substrate scope and selectivity

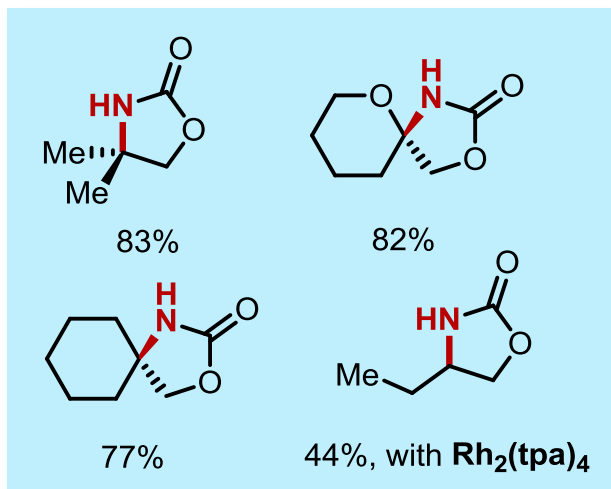
Development of Rh-Catalyzed Aliphatic C-H Amination

- Du Bois' intramolecular C-H amination-**Carbamate**



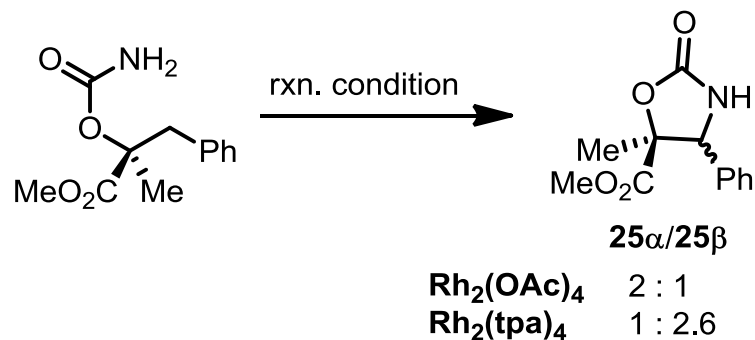
- Tuning of conditions increases the turnover of catalysts

- Higher **temperature**
- MgO** to neutralize AcOH
- More robust catalyst **$\text{Rh}_2(\text{tpa})_4$**



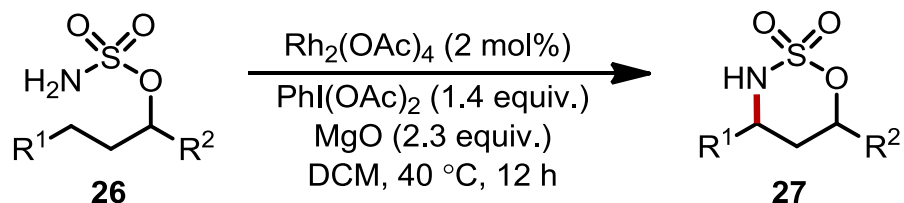
- Mechanistic aspects

- w/o catalyst, **23** doesn't react with $\text{PhI}(\text{OAc})_2$
- Rhodium-mediated insertion

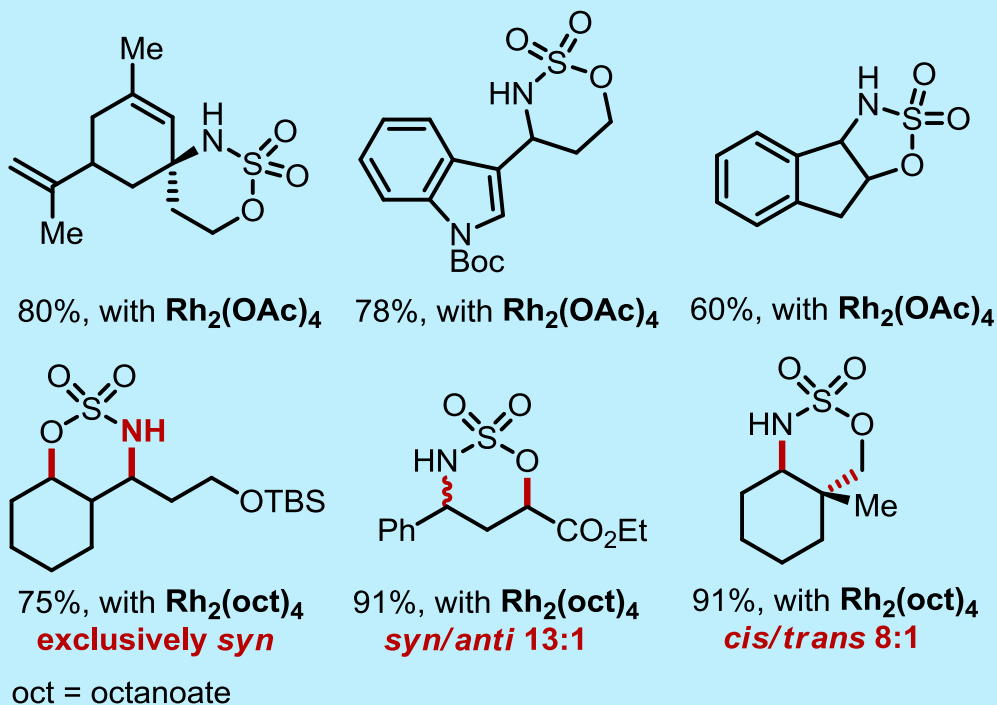


Development of Rhodium-Catalyzed C-H Amination

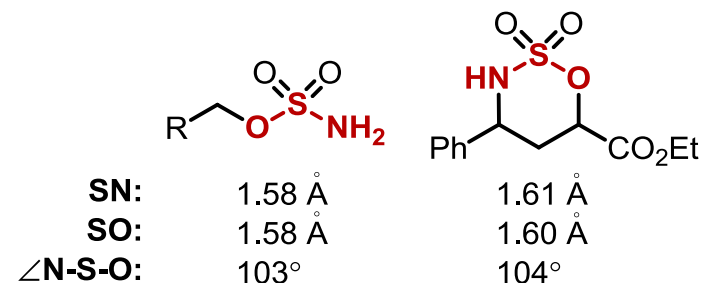
- Du Bois' intramolecular C-H amination-**Sulfamate**



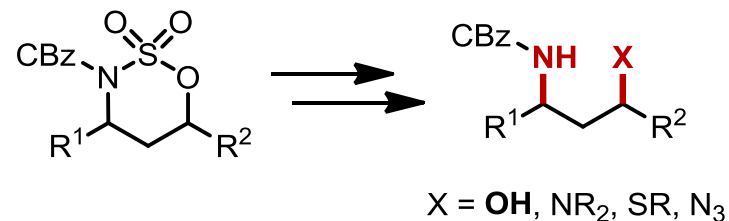
- Complementary to C-H amination of Carbamate



- Five vs six-membered ring

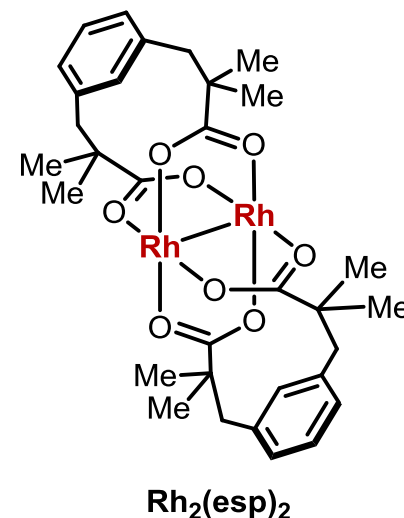
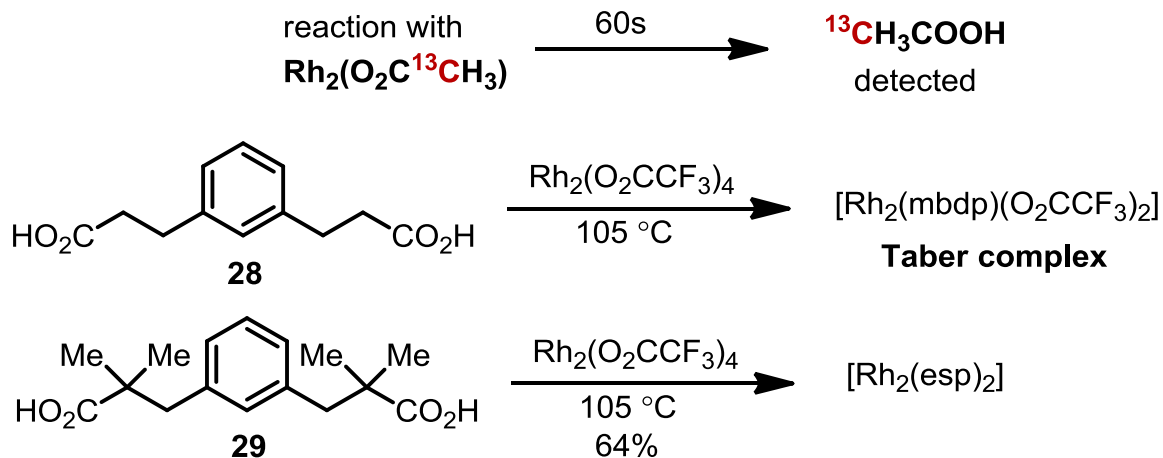


- Product as electrophile

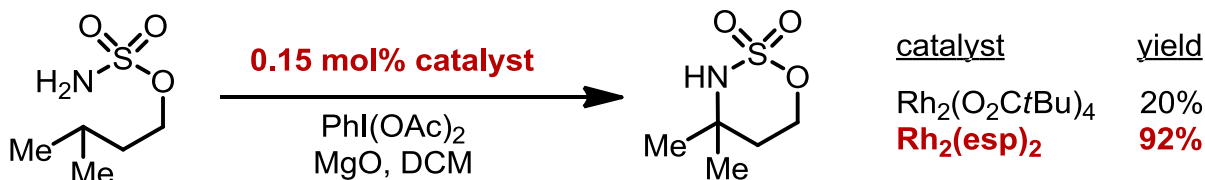


Development of Rh-Catalyzed Aliphatic C-H Amination

- Mechanistic study leads to a novel catalyst
 - Dinuclear Rh catalysts undergo structural changes in the reaction (**ligand exchange**)
 - **Carboxylate detachment** leads to catalyst **degradation**

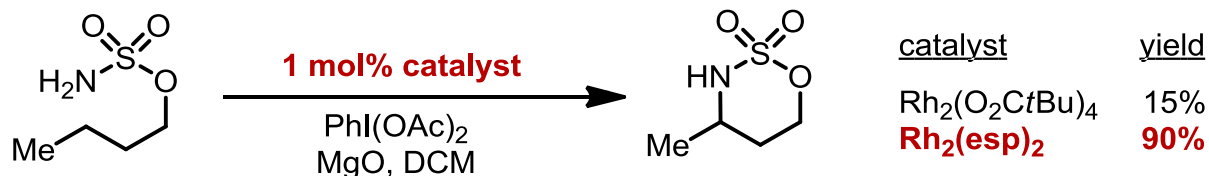


- Enhanced performances
 - Catalyst load

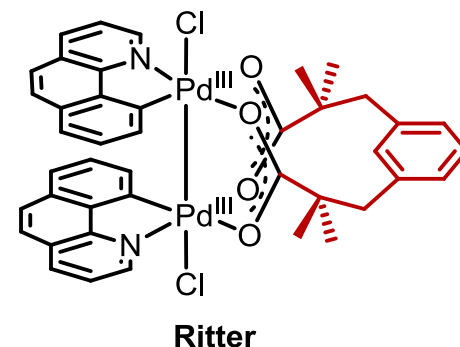
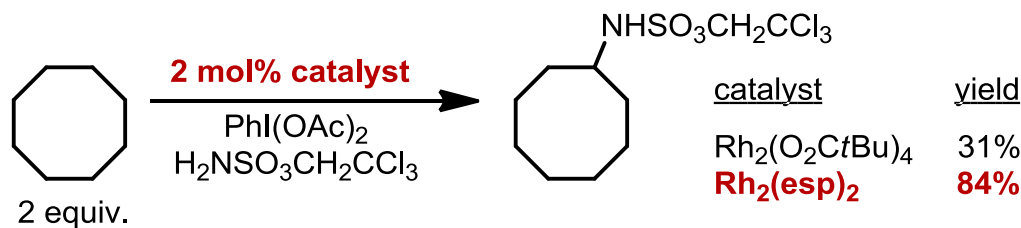
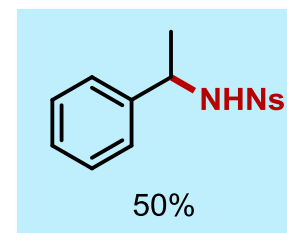
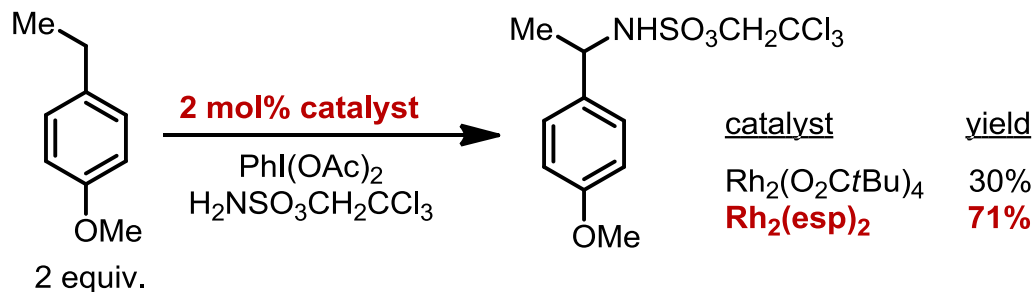


Development of Rh-Catalyzed Aliphatic C-H Amination

- Enhanced performances
 - Challenging substrate

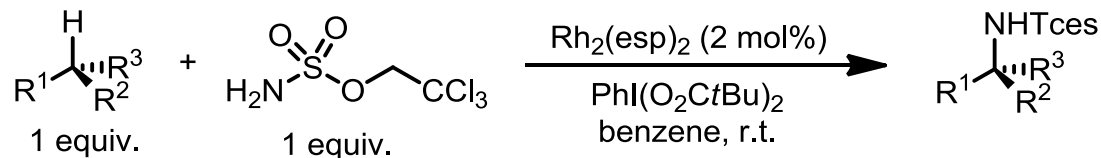


- Intermolecular amination

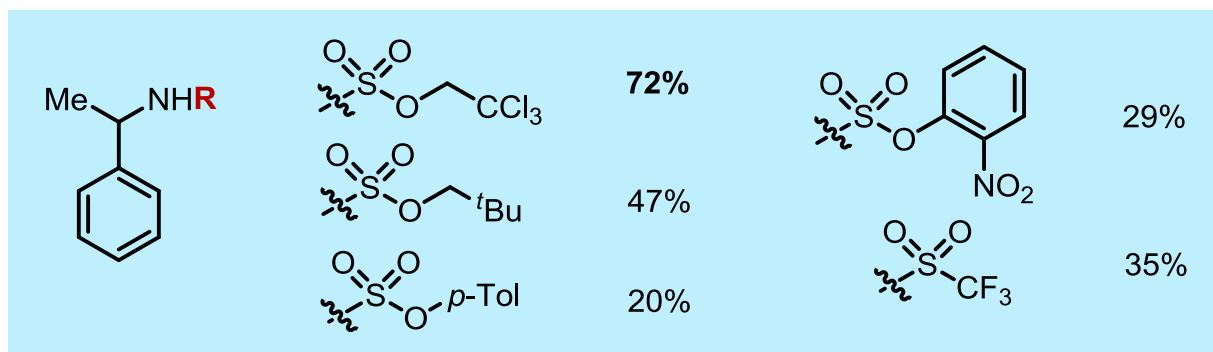


Development of Rh-Catalyzed Aliphatic C-H Amination

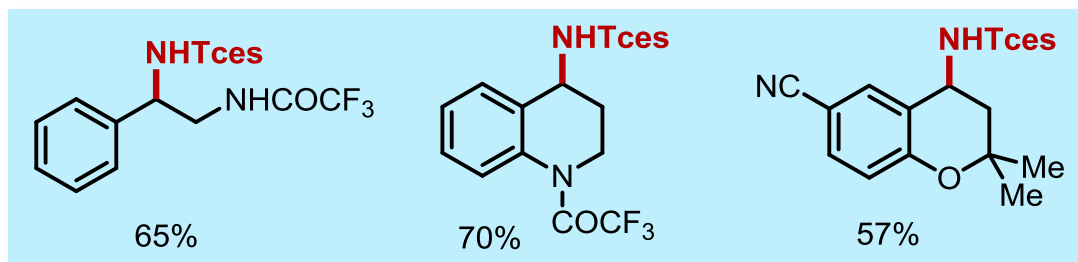
- Du Bois' intermolecular C-H amination-conditions



- Amide nitrogen source: superior and mystic property of **TcesNH₂**

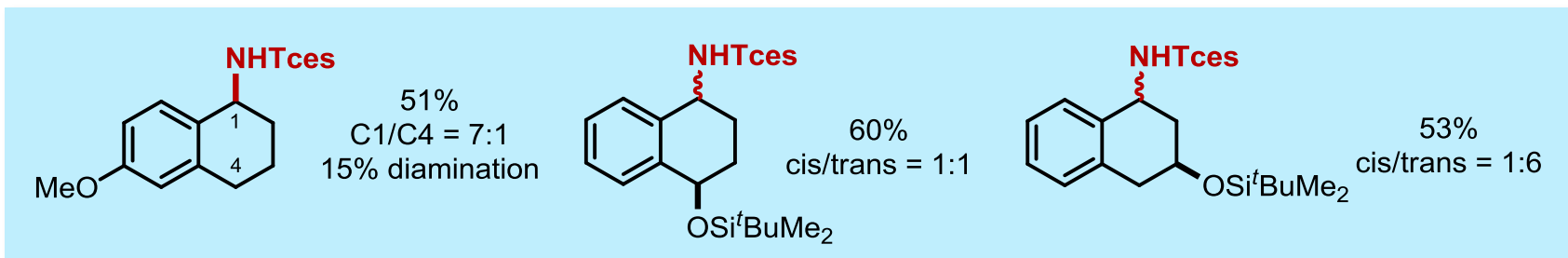


- Benzene as solvent (reaction **2.5 times** faster than in DCM)
 - Slow addition** of oxidant, PhI(O₂CtBu)₂ > PhI(OAc)₂
- Representative examples

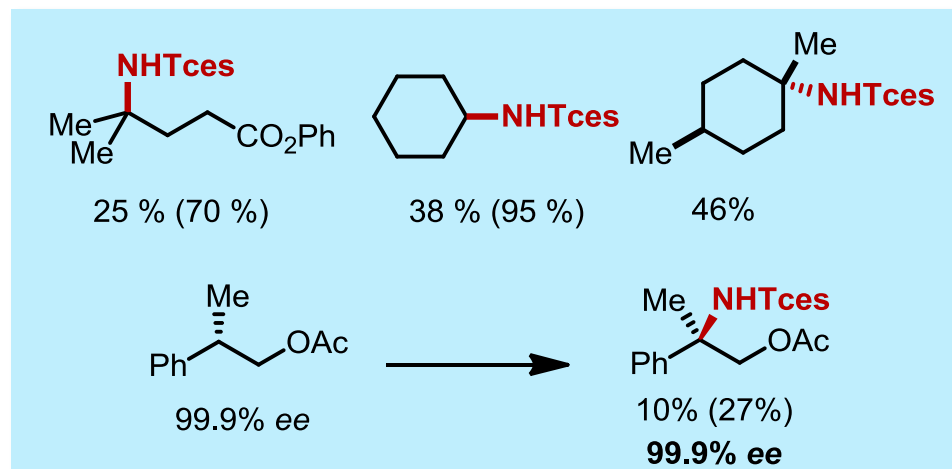


Development of Rh-Catalyzed Aliphatic C-H Amination

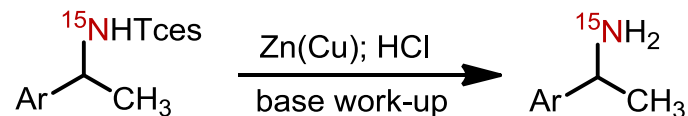
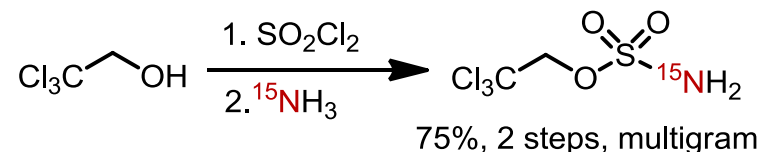
- More **sterically accessible** and/or more **electron-rich**



- Comparatively poor performance at **non-benzylic** positions
- Yields increased when **more than 1 equiv.** of substrates are used (parentheses)

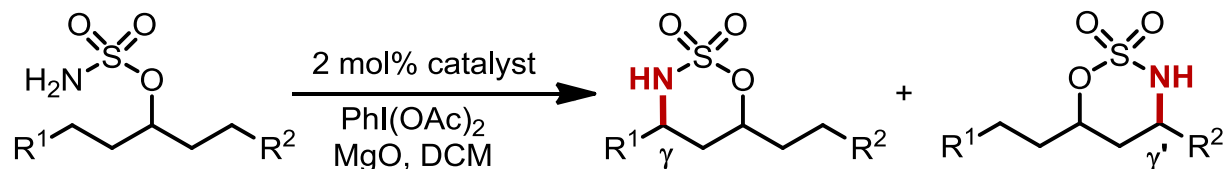


- Remove of Tces



Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

- Intramolecular amination
 - Reactivity trends

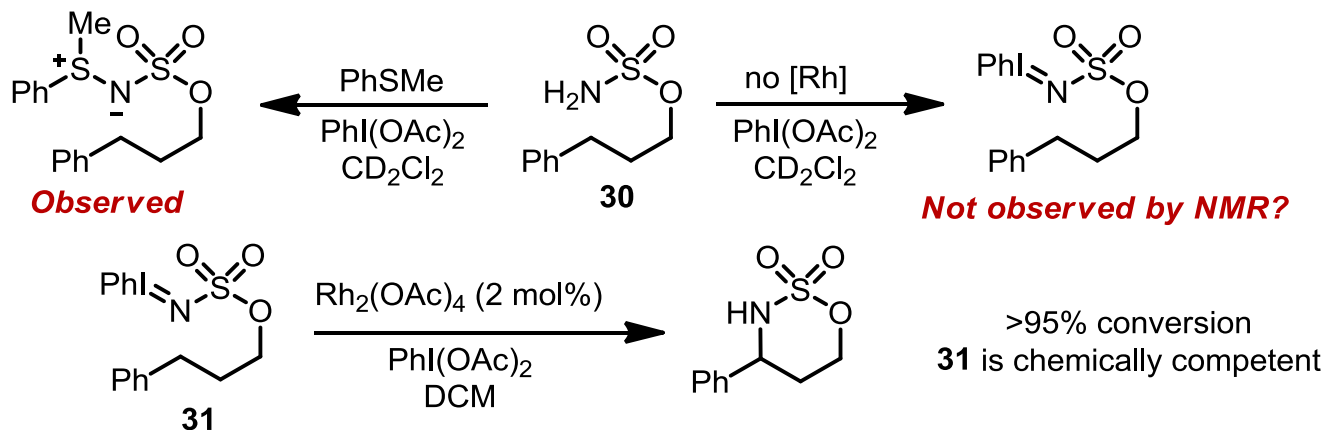


- $3^\circ > \text{etheral-benzylic} > 2^\circ \gg 1^\circ$
- Catalyst structure influences product selectivity
- Generally, aziridination over C-H insertion

Rh-mediated insertion

- Kinetic analysis

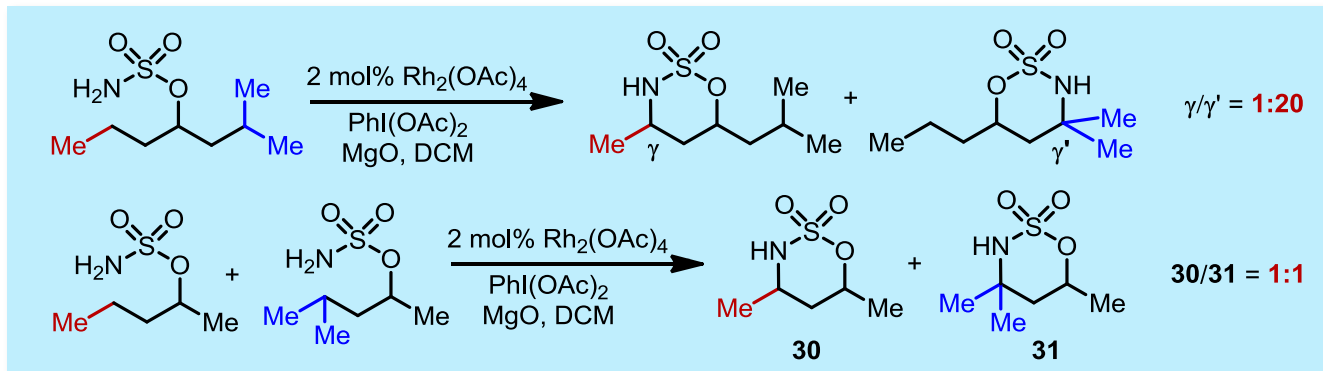
Question to answer



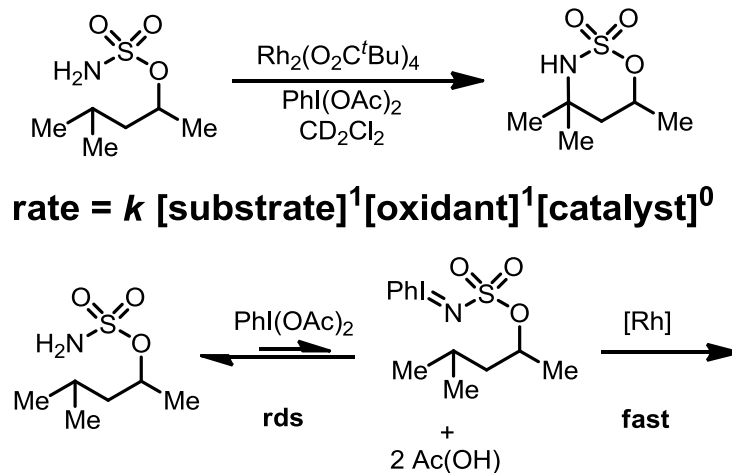
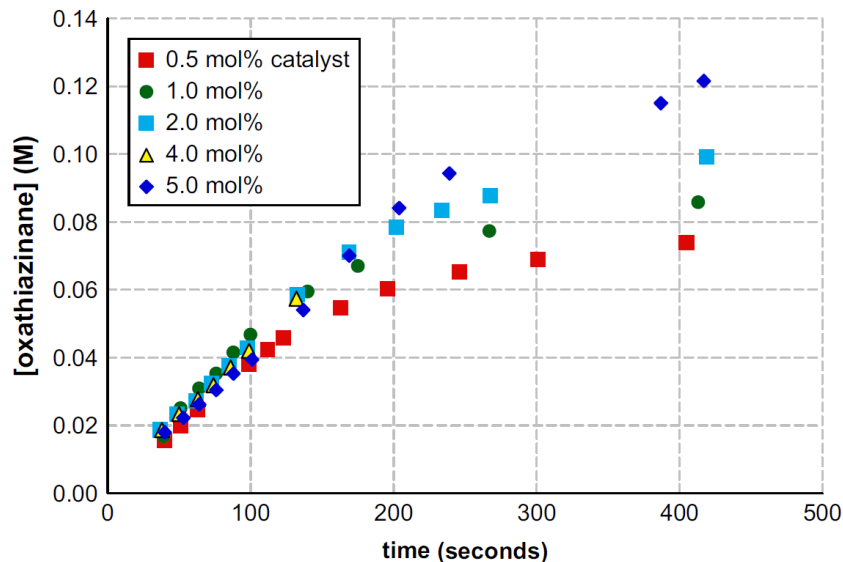
Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

- Intramolecular amination
 - Kinetic analysis

Rate-determining step is before the C-H insertion

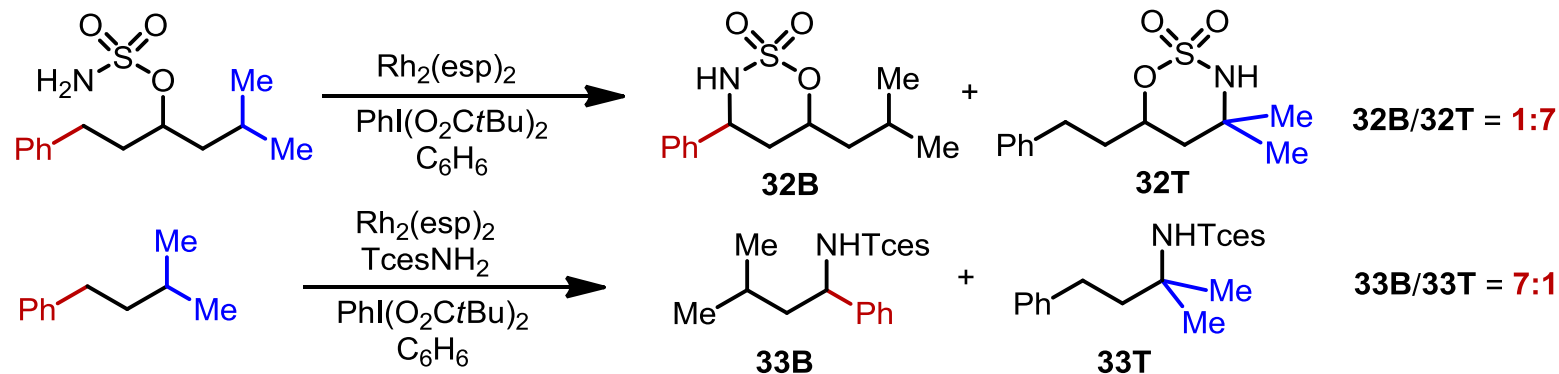


- Initial order



Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

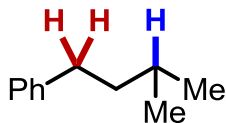
- Intermolecular amination



Different **oxidizing species** (mechanism) for inter- and intramolecular reaction?

Three Slides Omitted Here

NO, both are direct C-H insertion of Rh-nitrenes.

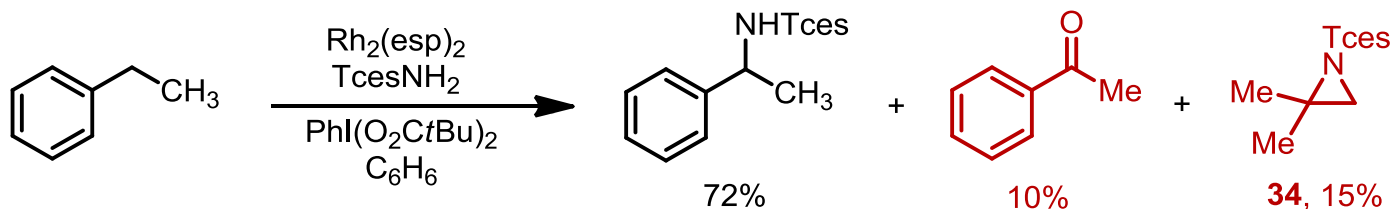


- Active oxidant trapped by substrate **vs decomposition**
- 2H at benzylic position **vs** 1H at tertiary position

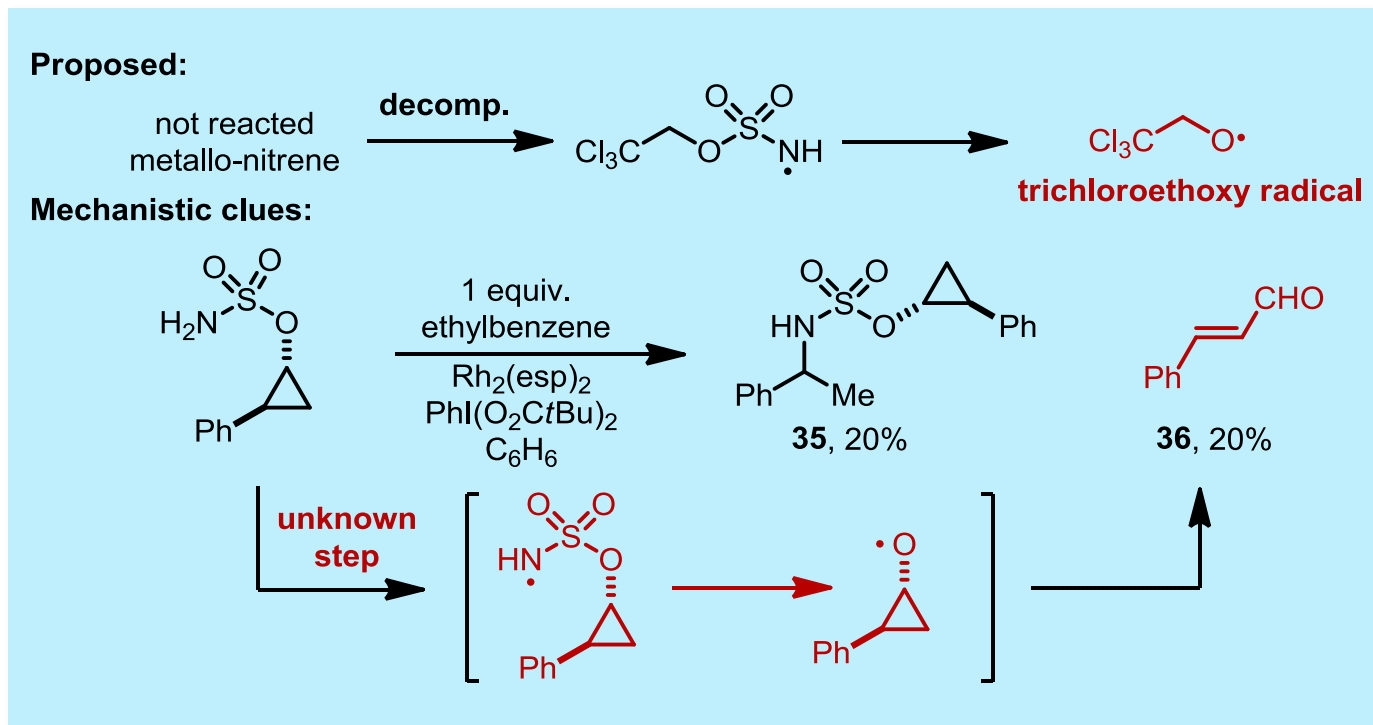
Question remained.

Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

- Insights from side-reaction

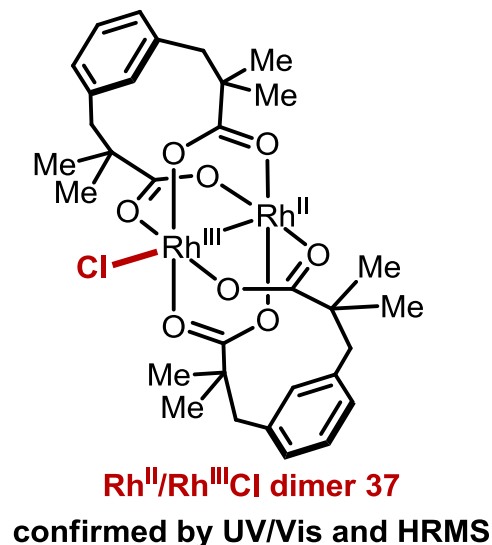
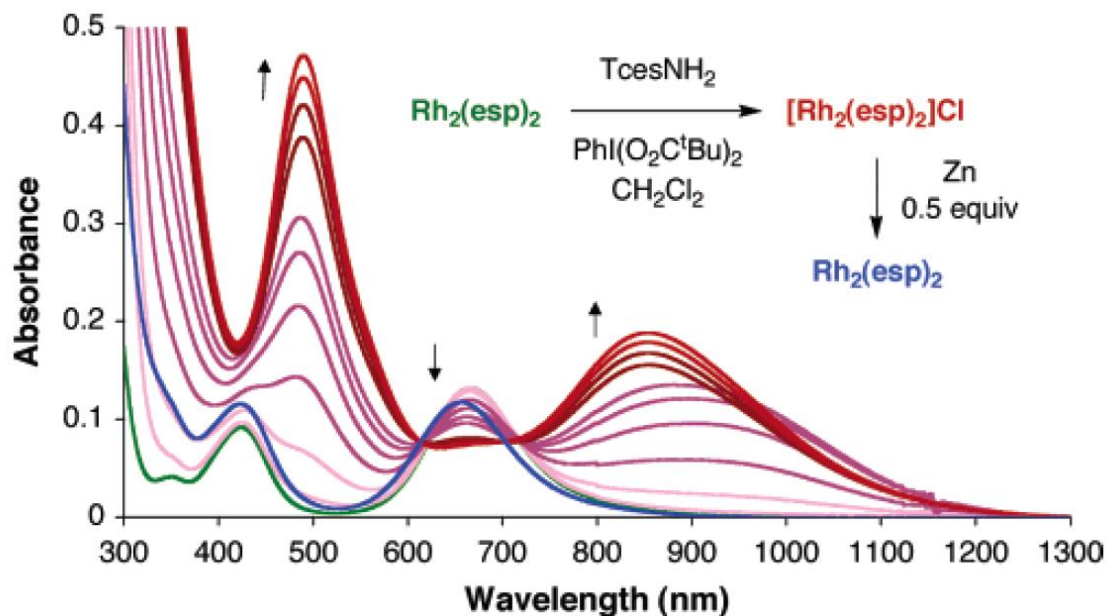


- Problems with **mass balance** of TcesNH₂
- No such byproducts in intramolecular reaction



Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

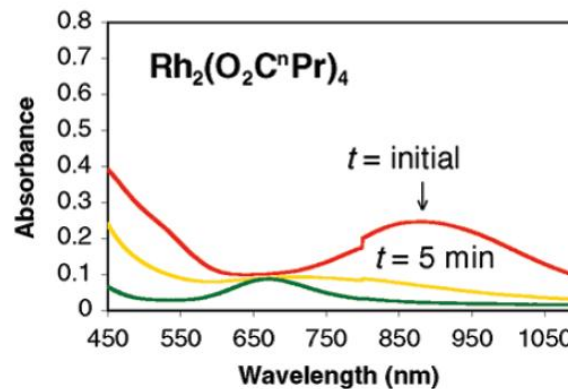
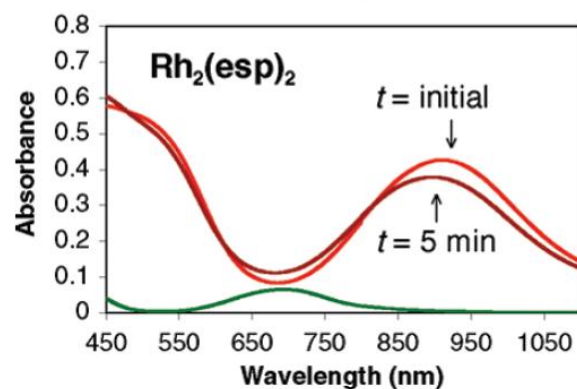
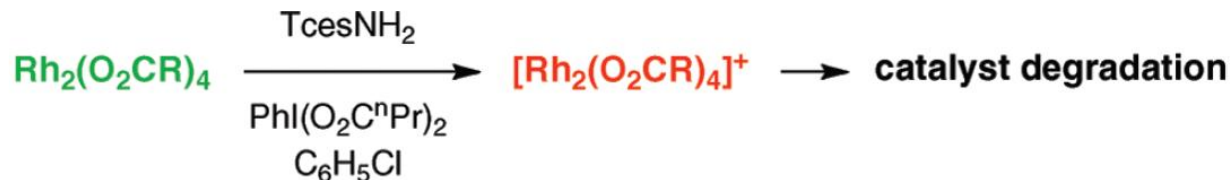
- Rh(II)/Rh(III) mixture dimer



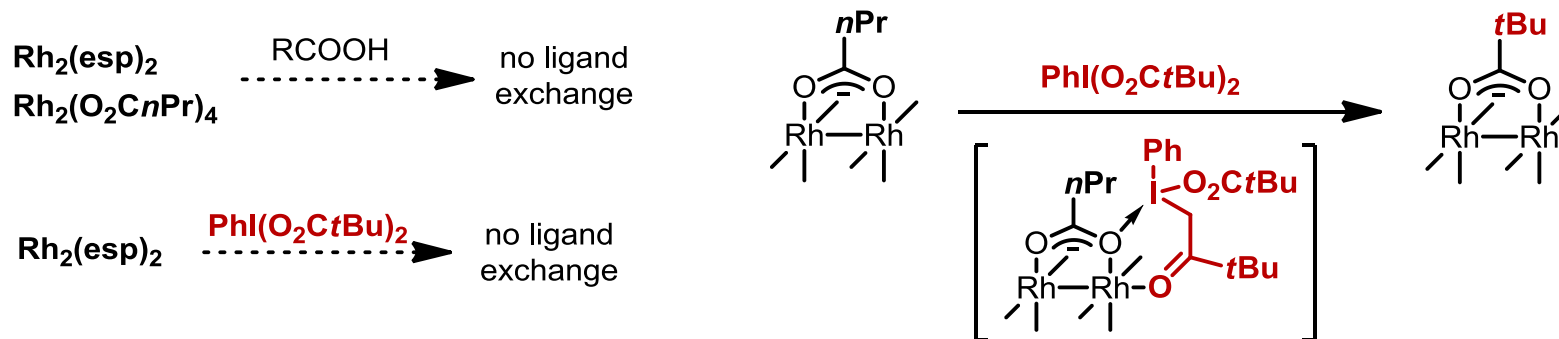
- **37** is stable at ambient temperature but **inactive** for C-H amination
- **Rh(II)/Rh(III) as the active catalyst**
 - Explained why benzene is better solvent than DCM (2.5 times faster reaction)
- OR
- **Rh(II)/Rh(II) as the active catalyst**
 - Which species reduce the Rh(II)/Rh(III) mixture dimer?
 - Is Rh(II)/Rh(III)'s stability related to catalyst TON?

Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

- Understanding the differential performance of $\text{Rh}_2(\text{esp})_2$
 - Kinetic stability of valence-mixture dimer of $\text{Rh}_2(\text{esp})_2$ and $\text{Rh}_2(\text{O}_2\text{C}^n\text{Pr})_4$

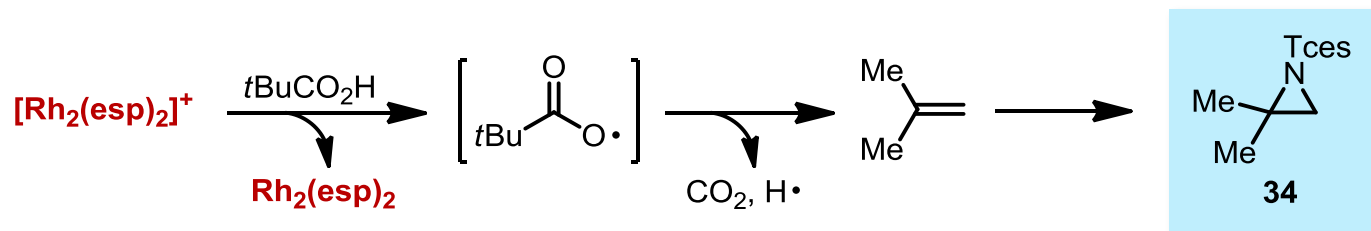


- Decomposition pathway

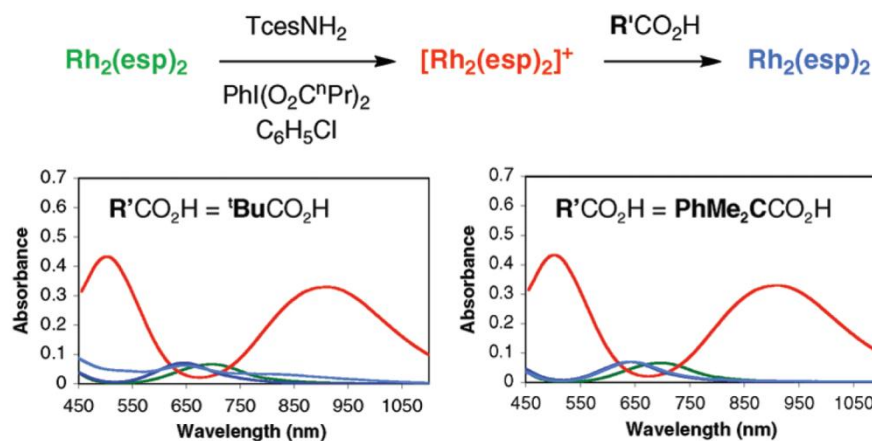
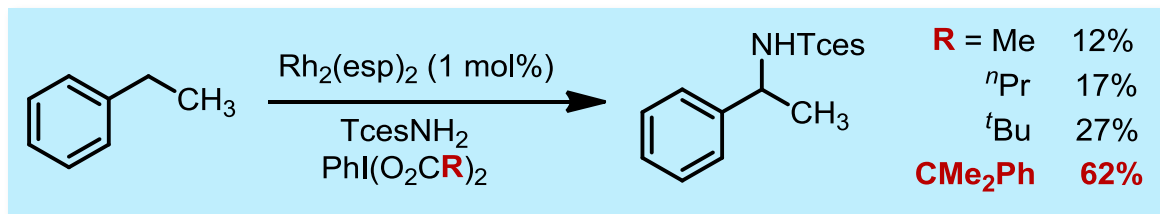


Mechanistic Study of Rh-Catalyzed Aliphatic C-H Amination

- Understanding the differential performance of $\text{Rh}_2(\text{esp})_2$



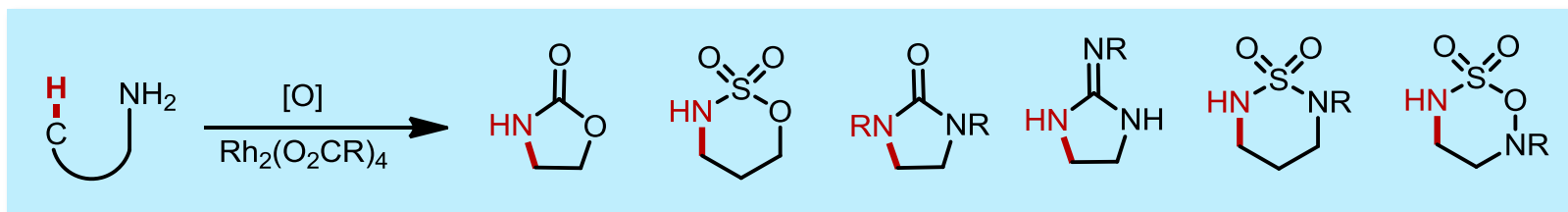
- Correlation between oxidation potential and stability of **carbon-radical**
- Reason why $\text{PhI}(\text{O}_2\text{C}^t\text{Bu})_2$ is a better oxidant than $\text{PhI}(\text{OAc})_2$



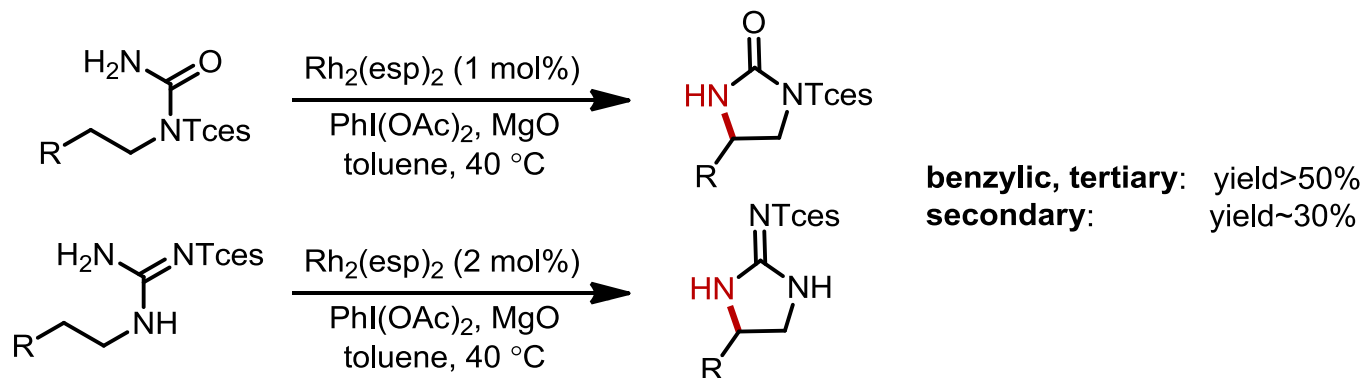
- New oxidant $\text{PhI}(\text{O}_2\text{CCMe}_2\text{Ph})_2$
- The active catalyst is $\text{Rh}_2(\text{esp})_2$
- Unclear aspects:
 - How does $[\text{Rh}_2(\text{esp})_2]^+$ form?
 - How does $[\text{Rh}_2(\text{O}_2\text{CR})_4]^+$ and Rh-nitrene decompose?

Application of Rh-Catalyzed Aliphatic C-H Amination

- Expanding substrate scope
- Exploring diastereoselectivity and enantioselectivity
- Uses of amination products
- Application in natural product synthesis

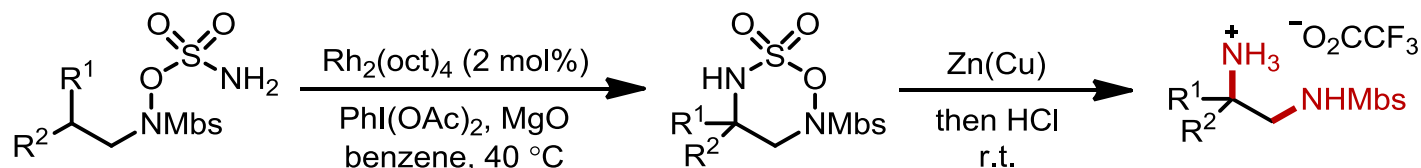


- Oxidative cyclization of urea and guanidine

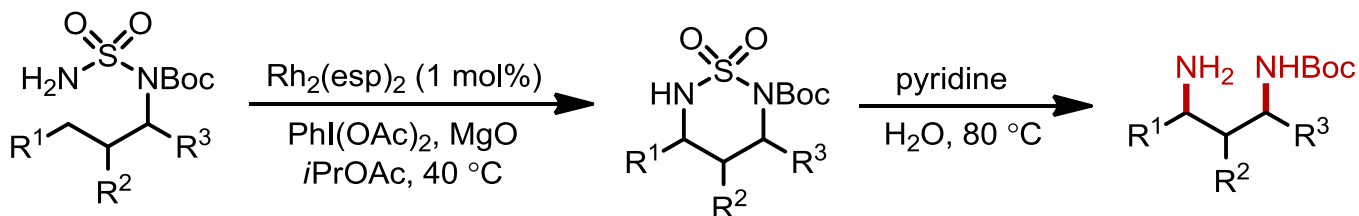


Substrate-scope exploration of Rh-Catalyzed Aliphatic C-H Amination

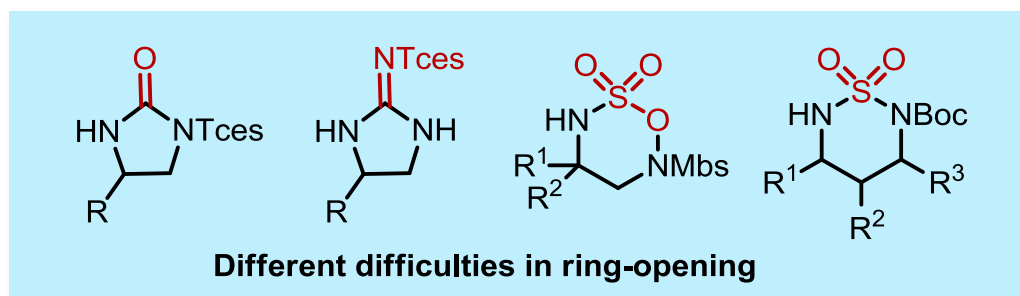
Preparation of 1,2-diamines



Preparation of 1,3-diamines



- More practical methods to prepare 1,2 or 1,3-diamine derivatives
- Mild conditions, good function-group tolerance

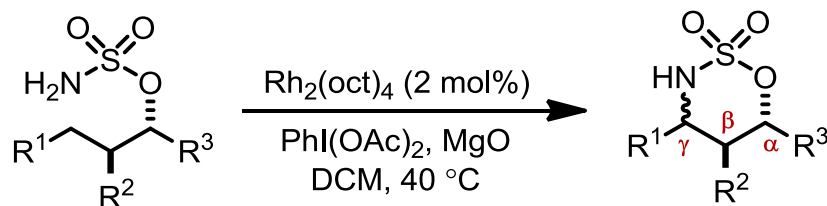


Olson, D.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248

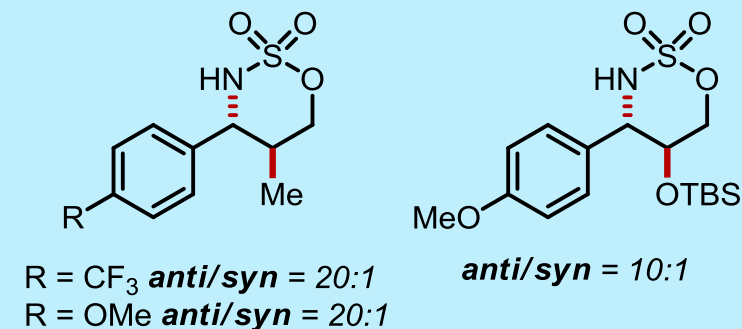
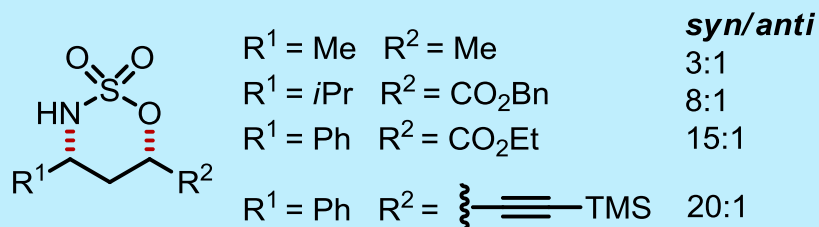
Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2777

Stereoselectivity of Rh-Catalyzed Aliphatic C-H Amination

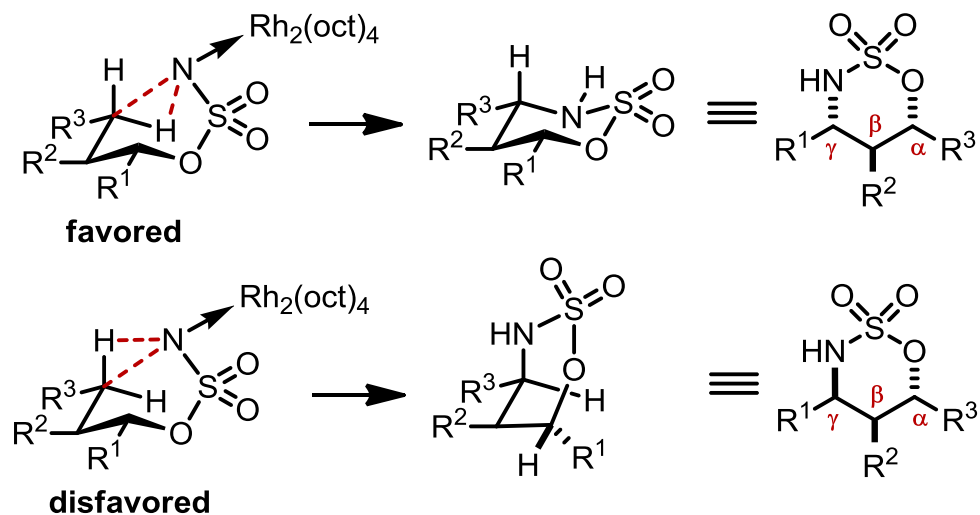
- Diastereoselective C-H amination



- Representative examples

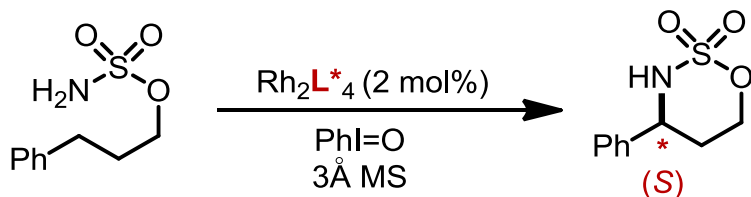


- Stereochemical model



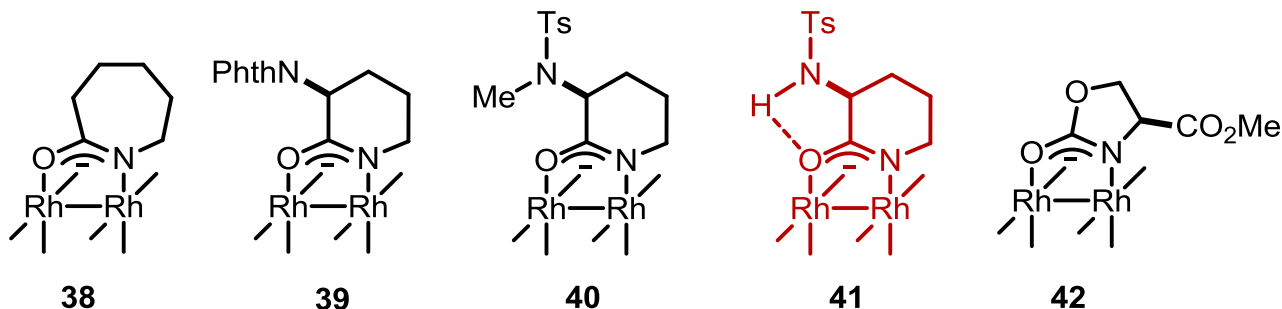
Stereoselectivity of Rh-Catalyzed Aliphatic C-H Amination

Enantioselective C-H amination

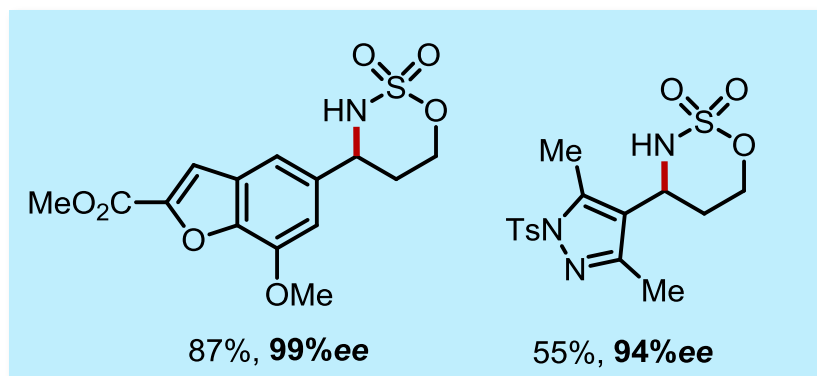


Rh_2L^*_4	E_{ox}	Yield(%)	%ee
38	11mV	<5	-
39	120mV	22	54
40	242mV	<5	nd
41	330mV	85	92
42	742mV	<10	nd

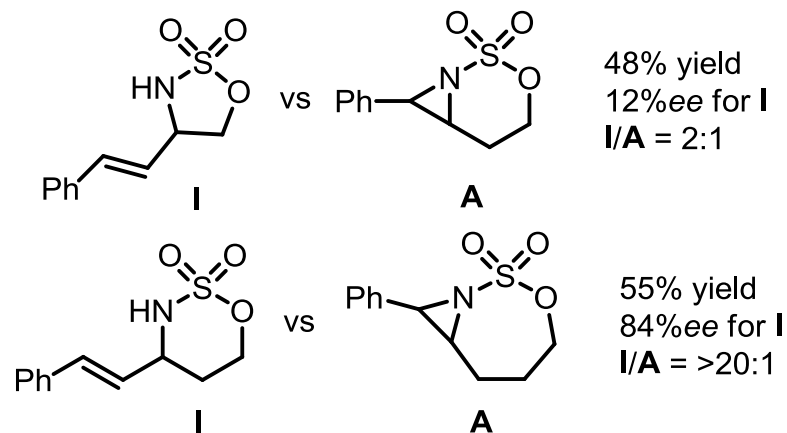
$\text{Rh}_2(\text{S-nap})_4$



Representative examples

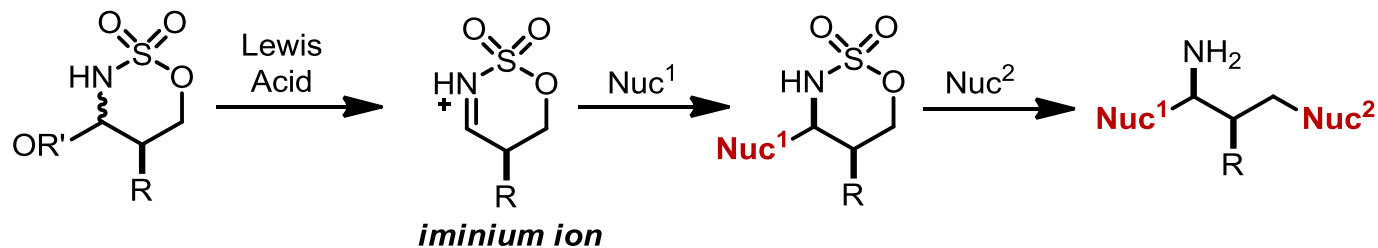


A special catalyst

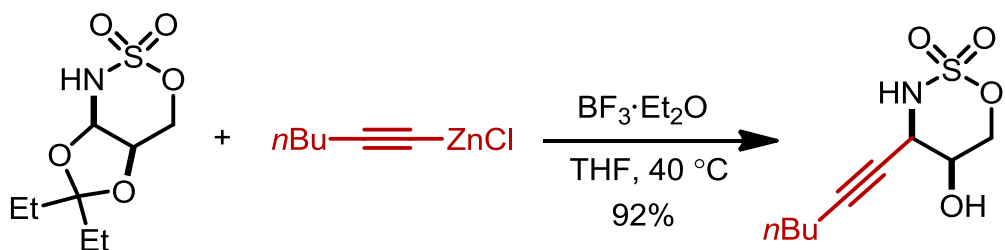


Uses of Rh-Catalyzed Aliphatic C-H Amination Products

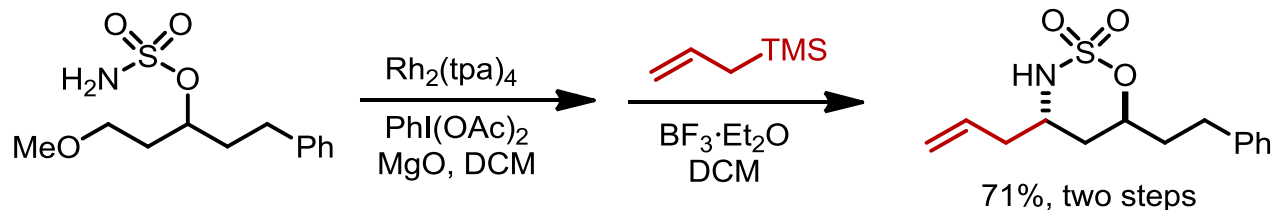
- As iminium ion equivalents



- Alkynylzinc reagent as nucleophile



- Allylsilane as nucleophile

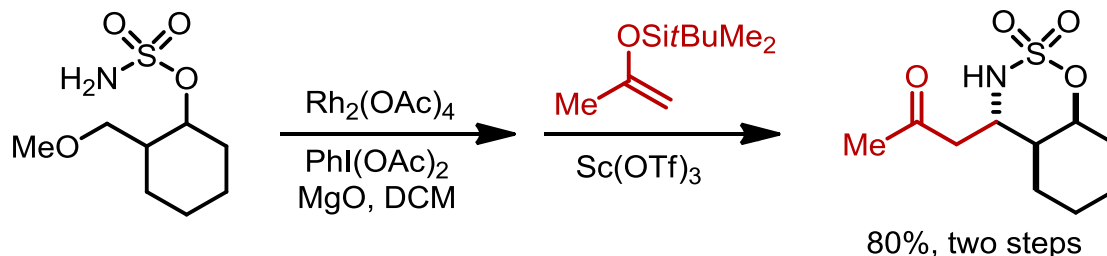


Fleming, J.; Fiori, K.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028

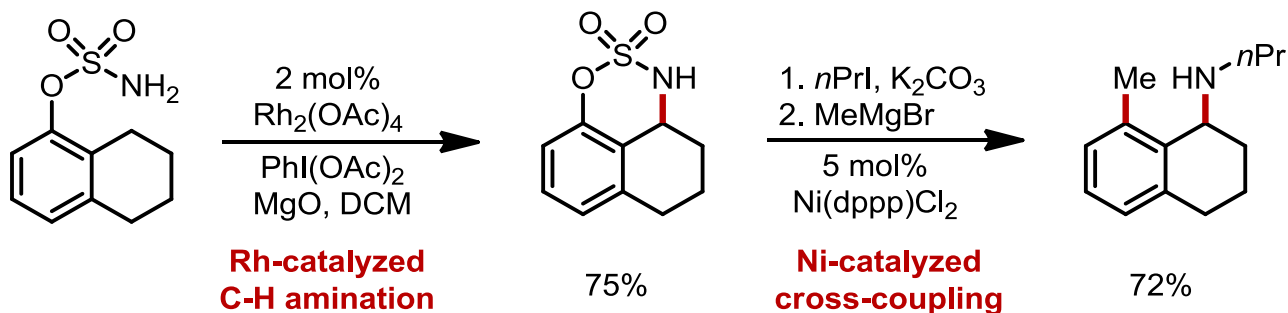
Williams, K.; Fleming, J.; Du Bois, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4349

Uses of Rh-Catalyzed Aliphatic C-H Amination Products

- As iminium ion equivalents
 - Silyl enol ether as nucleophile



- As coupling partners



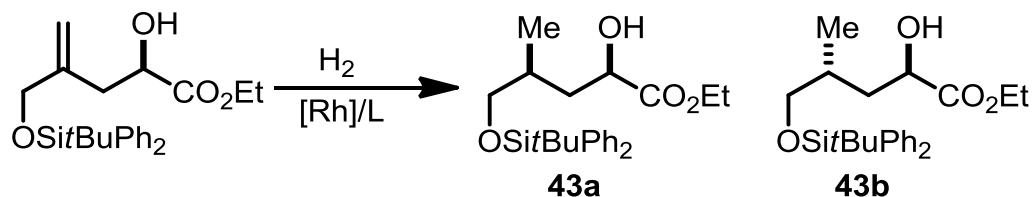
- No aryl C-H amination detected

Fiori, K.; Fleming, J.; Du Bois, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4349

Kim, M.; Mulcahy, J.; Espino, C.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073

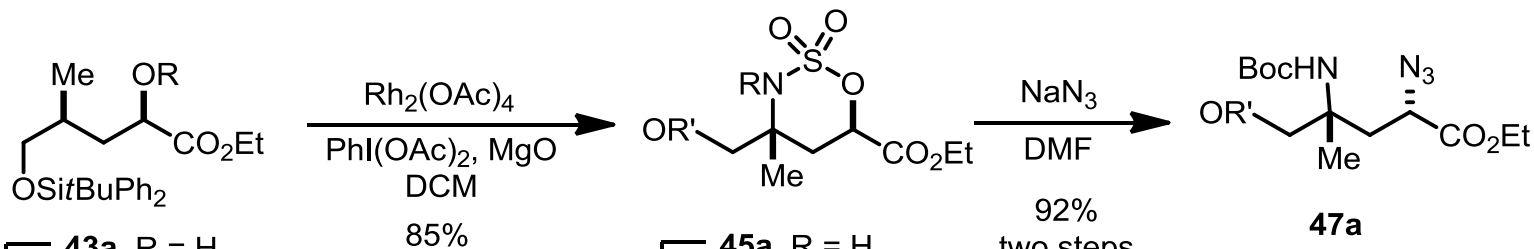
Application in Natural Product Synthesis

- First example in natural product synthesis
- Stereoselective synthesis of **Manzacidin A and C**
- Olefin hydrogenation gives both S.M.



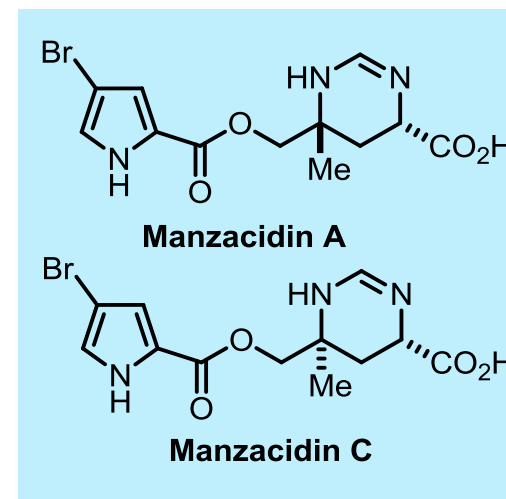
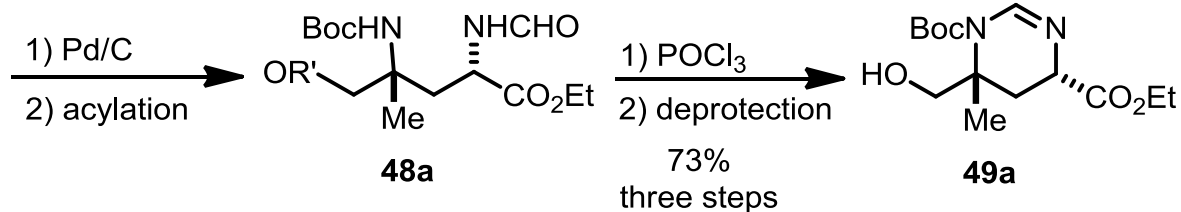
Rh(cod)₂OTf/(*R*)PhanePhos
43a/43b = 75:25

Rh(((*S,S*)-Et-DuPhos)(cod))OTf
44a/44b >5:95



43a, R = H
44a, R = SO₂NH₂

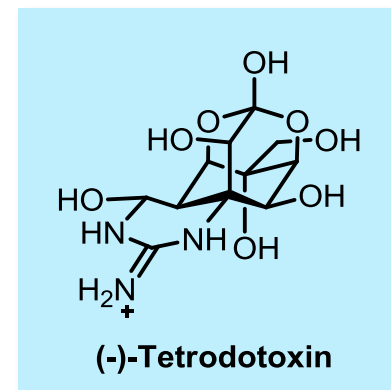
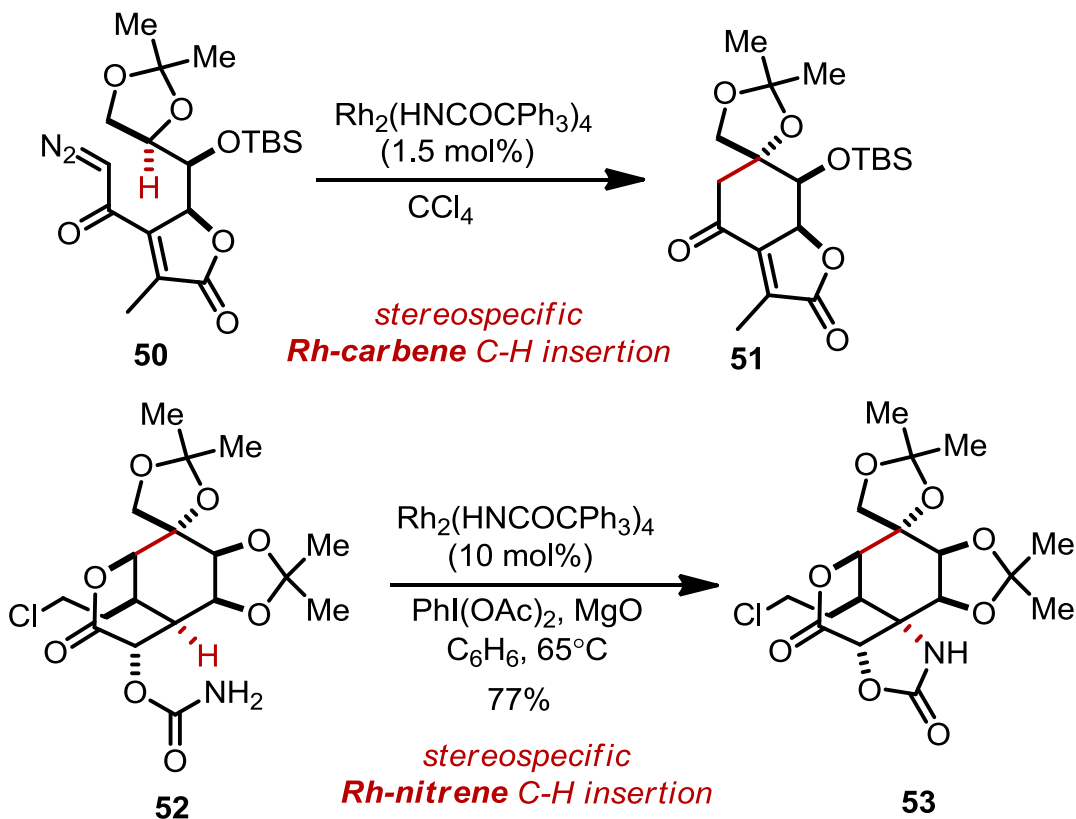
45a, R = H
46a, R = Boc



When, P.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950

Application in Natural Product Synthesis

- Stereoselective synthesis of (-)-Tetrodotoxin



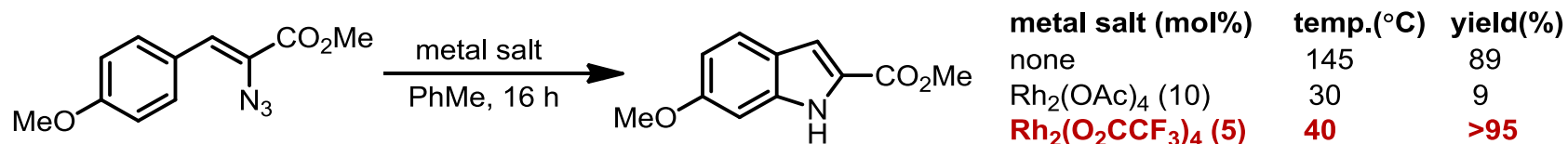
Summary of Rh-Catalyzed Aliphatic C-H Amination

- Development of a decade
 - From an **idea** to *in situ* generate the iminoiodinane
 - To a **platform** of C-H amination
- Mechanistic studies contribute significantly to the development
 - Better **catalyst** and better **oxidant** lead to higher **efficiency** and broader **scope**
 - Clarify the nature of catalysis
- Intramolecular C-H amination
 - $3^\circ > \text{ethereal}\sim\text{benzylic} > 2^\circ \gg 1^\circ$
 - No **aryl C-H activation**
 - **Aziridination** over C-H amination
- Intermolecular C-H amination
 - Only the efficiency of **benzylic C-H** activation is moderate

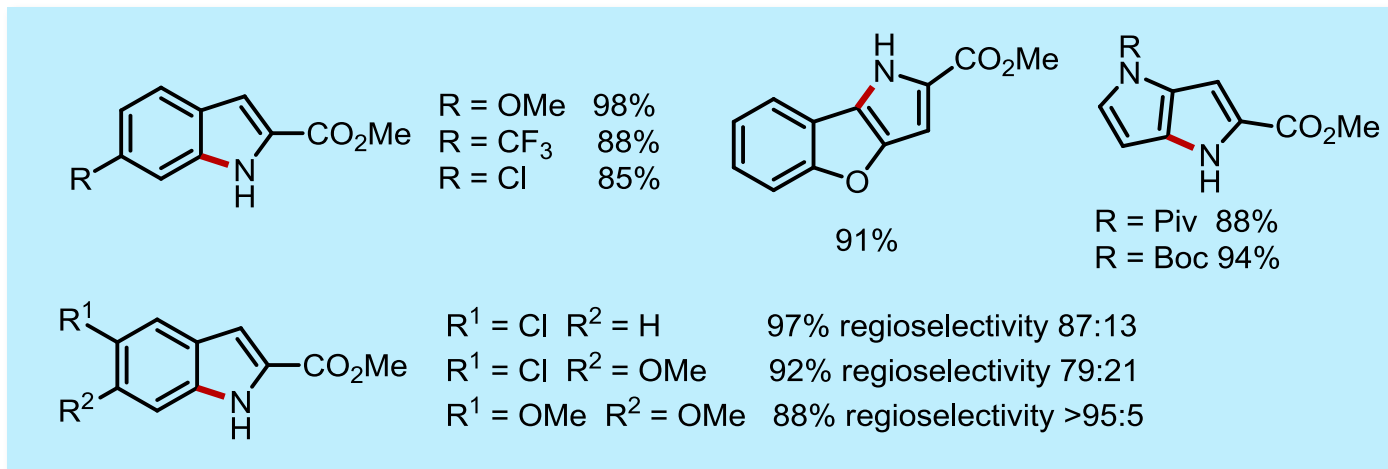
Too many Whys and Hows.

Novel Reactions with Classical Amination Reagent

- The revival of azide for the ***sp*² C-H amination**
 - Previously used as **aryl C-H activation** by decomposition
 - **Harsh condition and low selectivity**
- Driver's **Rh(II)-catalyzed** C-H amination

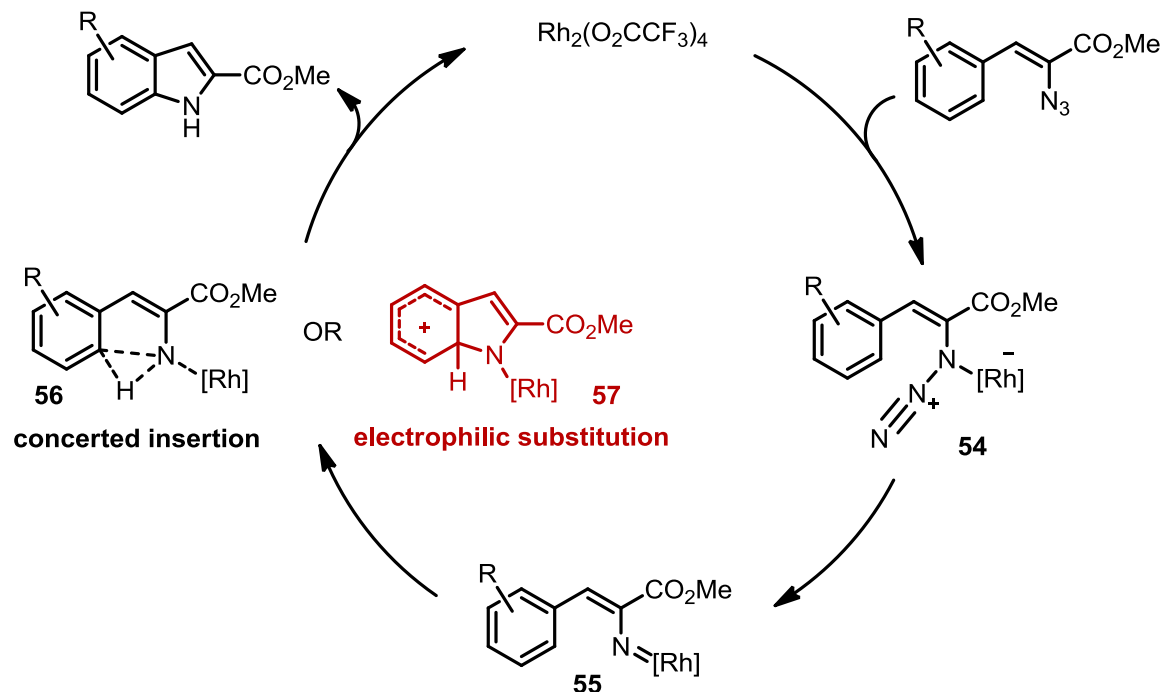


- Representative examples

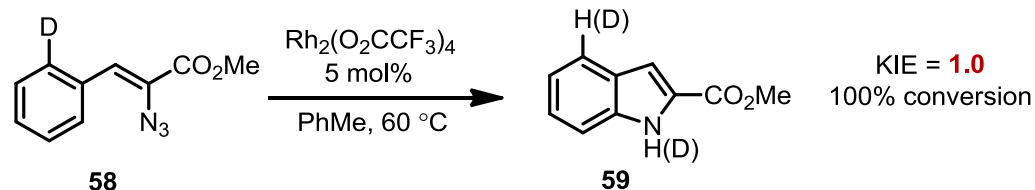


Novel Reactions with Classical Amination Reagent

- Driver's Rh(II)-catalyzed decomposition of azidoacrylates
 - First example of Rh-catalyzed *sp*² C-H amination
 - Novel reactivity might be related to **electron-deficient** Rh complex
- Proposed mechanism

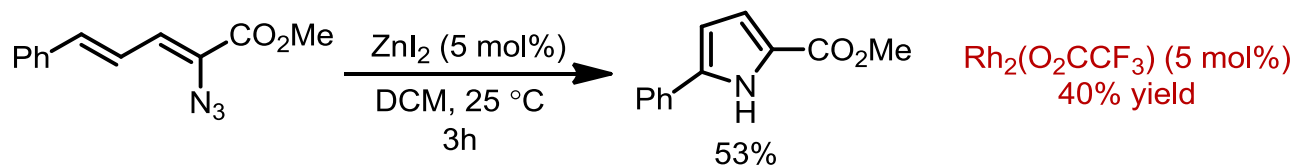


- Kinetic isotope effect

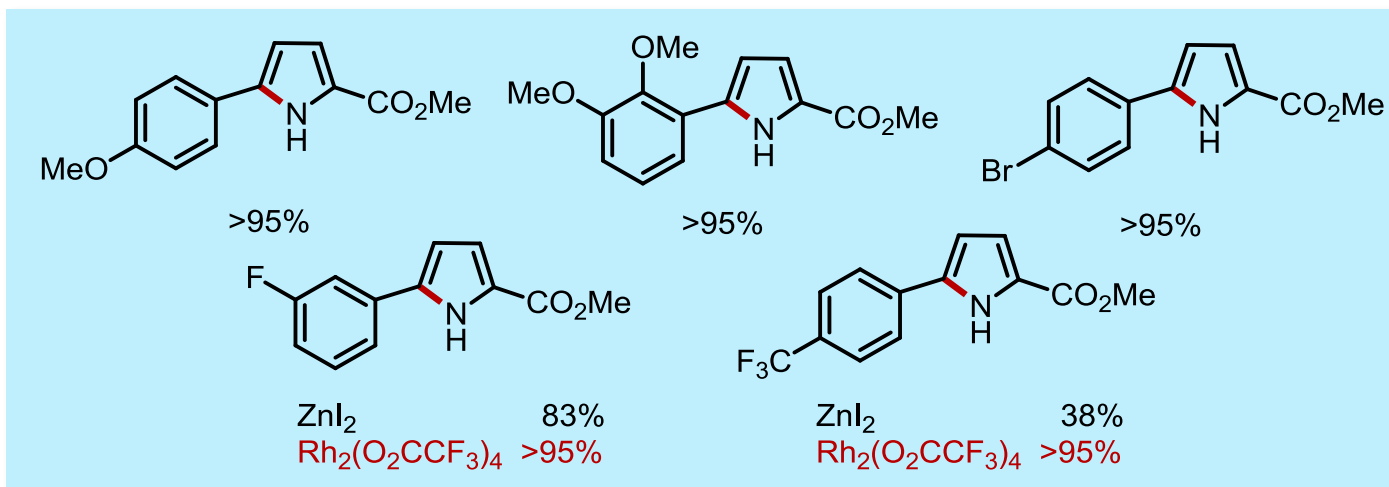


Novel Reactions with Classical Amination Reagent

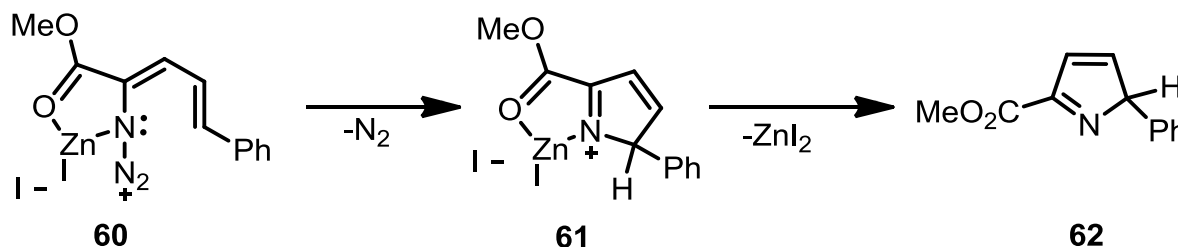
- Zinc can do the job too.



- Representative examples

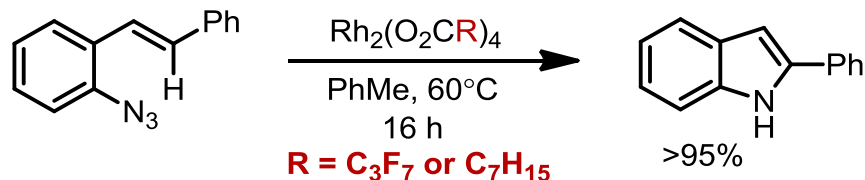


- Lewis-acid-catalyzed mechanism

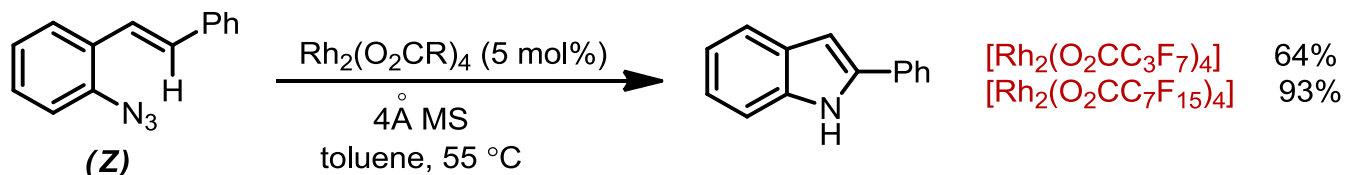


Novel Reactions with Classical Amination Reagent

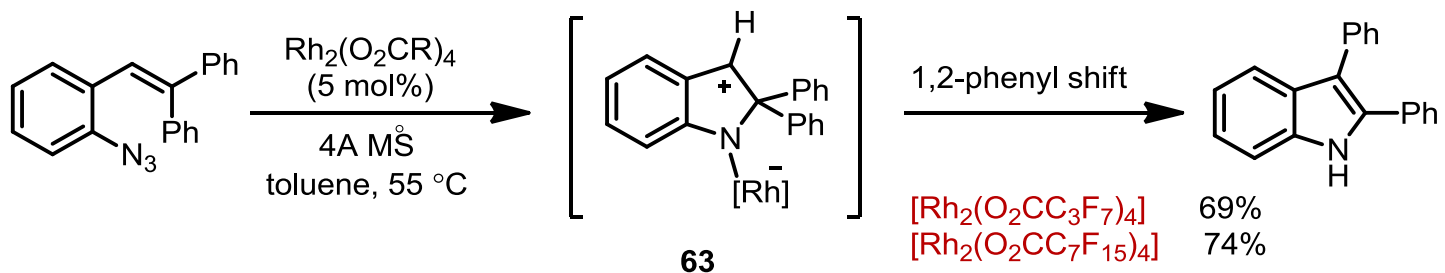
- Complimentary indole synthesis from aryl azide



- Two supportive reactions for electrophilic substitution



- C-N bond formation is **before** C-H bond cleavage

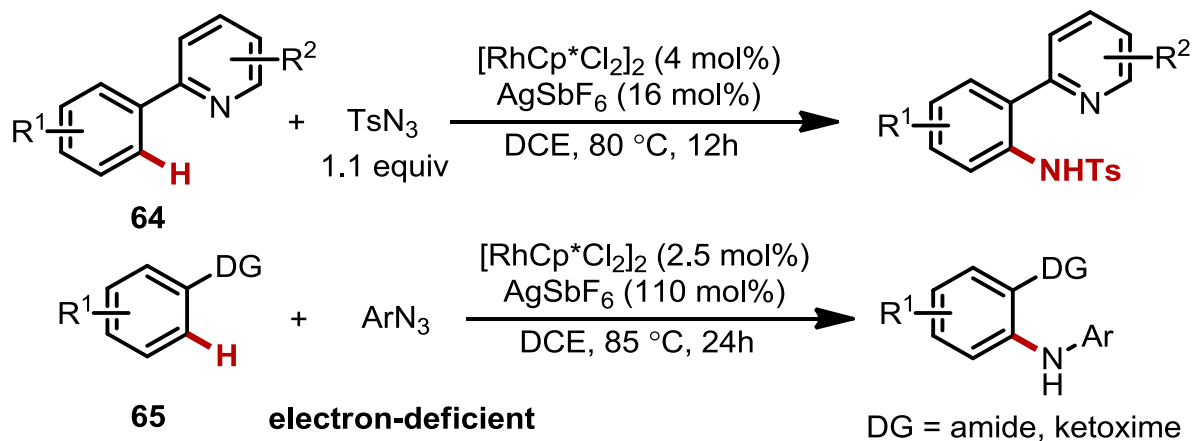


- Not conclusive, but proved such electrophilic substitution is feasible

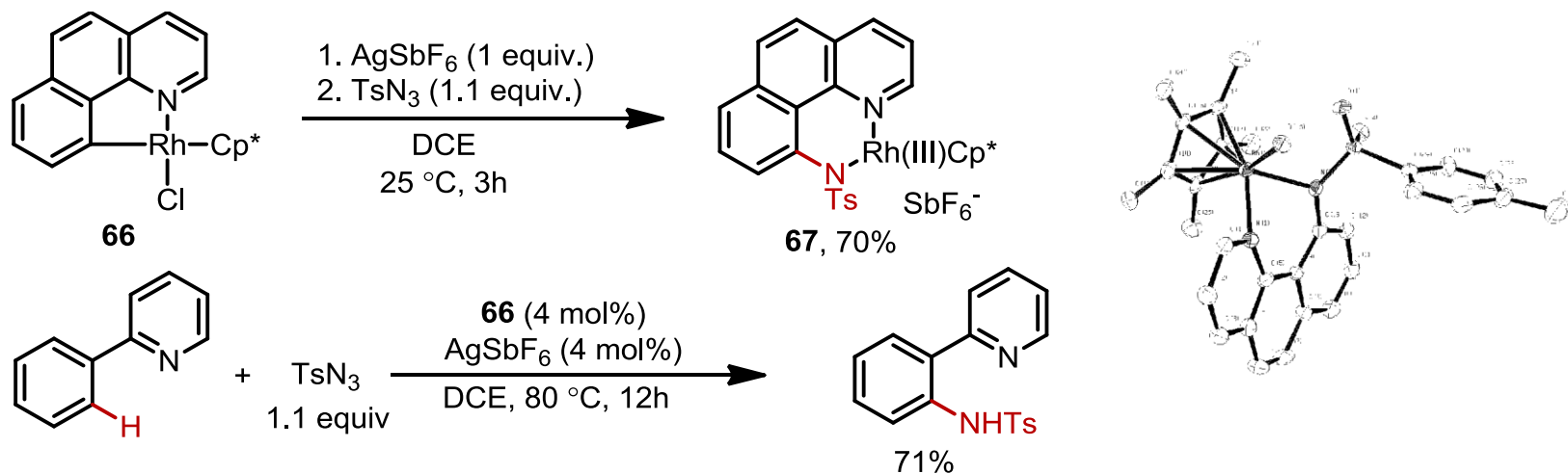
Shen, M.; Leslie, B.; Driver, T. G. *Angew. Chem. Int. Ed.* **2008**, 47, 5056

Novel Reactions with Classical Amination Reagent

- Chang's **Rh(III)-catalyzed** C-H amination



- Mec Jaeyune Ryu, Kwangmin Shin, Sae Hume Park, Ji Young Kim, and Sukbok Chang*

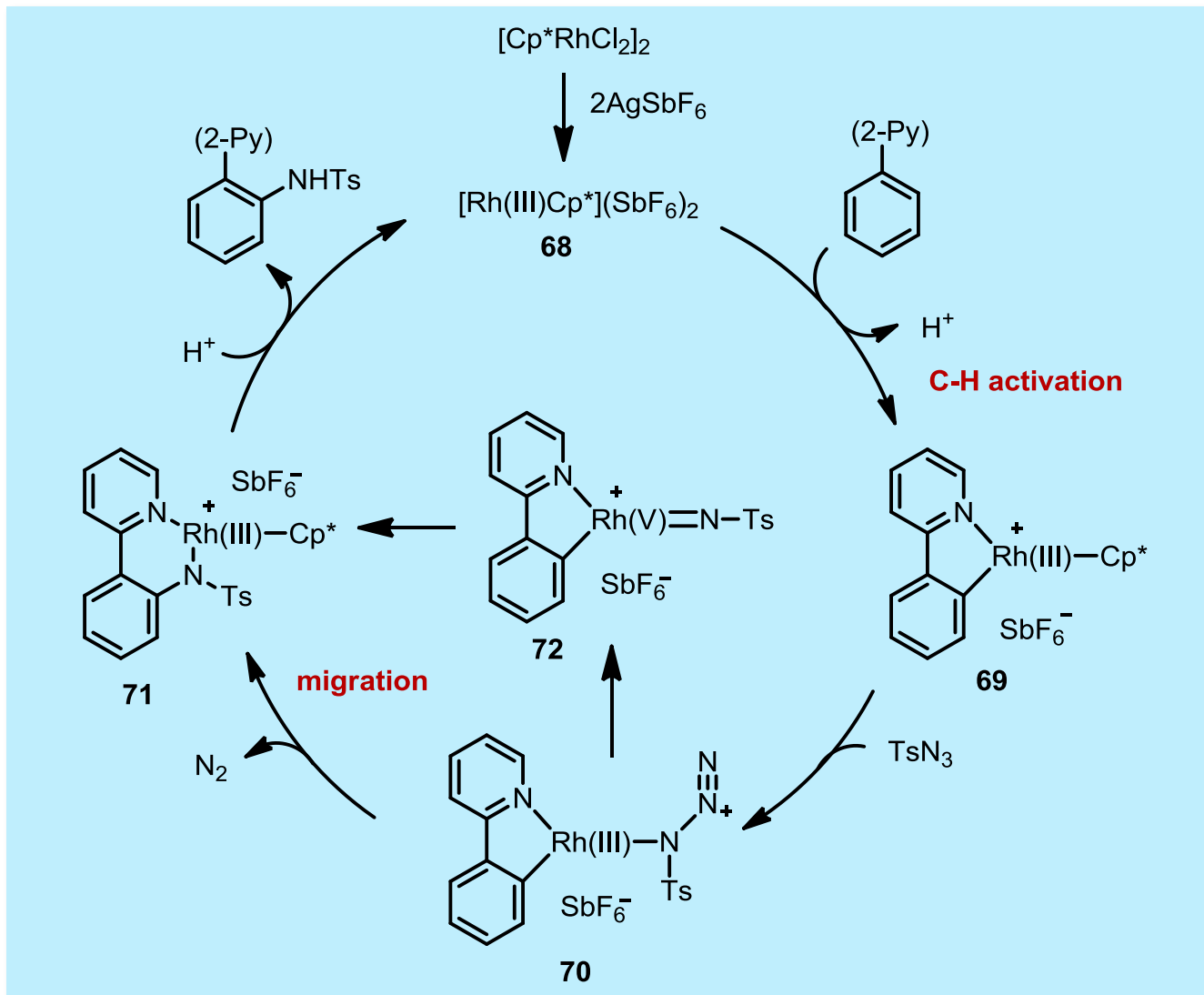


Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H. Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110

Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 9904

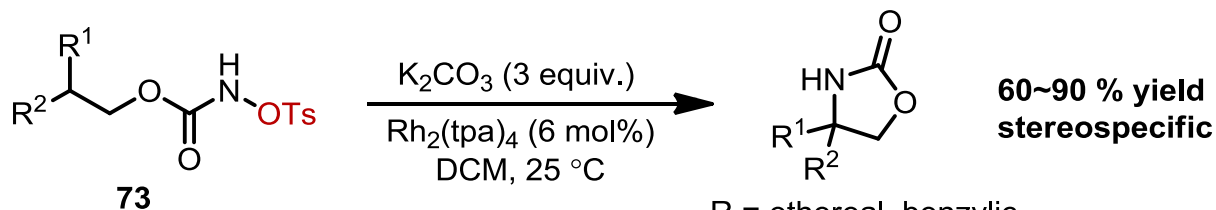
Novel Reactions with Classical Amination Reagent

- Proposed mechanism



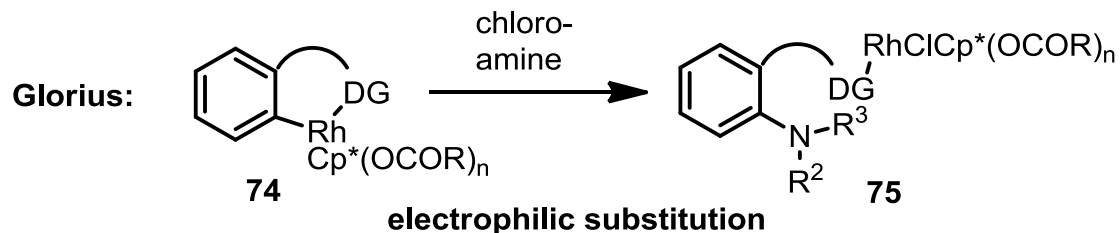
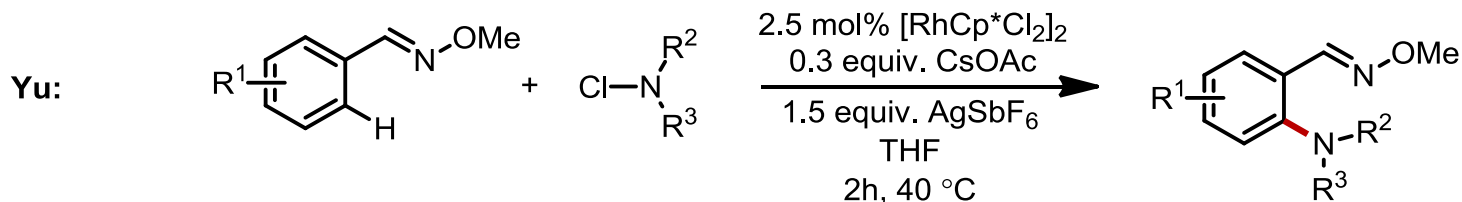
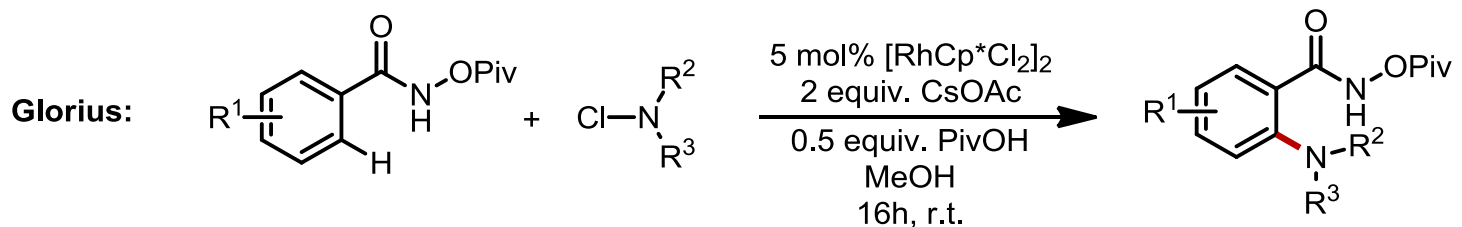
Miscellaneous

- *N*-Tosylloxycarbamate as metal nitrene source



R = ethereal, benzylic, tertiary, secondary

- *N*-Chloroamine as metal nitrene source



Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656

Ng, K-H.; Zhou, Z.; Yu, W-Y. *Org. Lett.* **2012**, *14*, 272

Summary

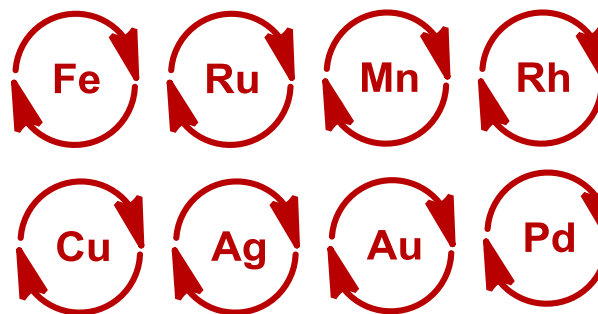
▪ Diversity of catalysts and nitrogen sources

- Rh(II) with iminoiodinane: aliphatic amination
- Rh(II) with azide: intramolecular aryl amination
- Rh(III) with azide and chloroamine: directed aryl amination

▪ This is only Rhodium!

ML _n	Yield (%)	
	12a	12b
Mn ^{III} (TPP)Cl	16	4.5
Fe ^{III} (TPP)Cl	77	1.4
[Fe ^{III} (cyclam)Cl ₂]Cl	42	4.1
FeCl ₃	16	0.2
Rh₂(OAc)₄	86	0.2
–, in MeCN	1.4	0.3
–, in DCM	26	4.5

cyclam = 1,4,8,11-tetraazacyclotetradecane



- Diverse mechanism
- Diverse selectivity
- Diverse scope

Welcome to transition-metal-catalyzed amination!