Frontiers in Chemical Synthesis II
Heterocyclic Chemistry

Seminar Program
May 17, BCH 5310
May 18, BCH 4119

	Speaker	Title
May 17, 2018, BCH 5310		
Session I: (Guillaume Pisella)		
13h30-14h30	Alexandre Leclair	*Synthesis of 5-membered azacycles by ring expansion of aziridine and azetidine*
14h30-15h30	Balasz Budai	*Oxidative O-cyclizations for the synthesis of oxacycles*
15h30-16h30	MingMing Wang	*Recent progress of oxaziridine chemistry*
May 18, 2018, BCH 4119		
Session II: (Balasz Budai)		
8h30-9h30	Guillaume Pisella	*Catalytic enantioselective hetero-Diels-Alder reactions of carbonyl and imines*
9h30-10h30	Mathias Mamboury	*Synthesis of heterocycles via (aza)-ortho-quinone methide intermediates*
10h30-11h30	Qui-Hien Nguyen	*Carbohydrate–N-heterocyclic carbene metal complexes: Applications in catalysis and medicinal chemistry*
Session III: (Mathias Mamboury)		
13h30-14h30	Benoit Audic	*Monoimino pyridine and derivatives as ligands for catalysis*
14h30-15h30	Sung Hwan Park	*Application and synthesis of imidazole, pyrazole and thiazole in medicinal chemistry*

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

ISIC - LSPN

Ring expansion of aziridines and azetidines for the synthesis of 5-membered azacycles

Frontiers in Organic Chemistry, EPFL

Alexandre Leclair, 1st year PhD Student

Laboratory of Synthesis and Natural Products, Prof. J. Zhu Group

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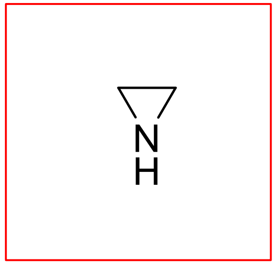
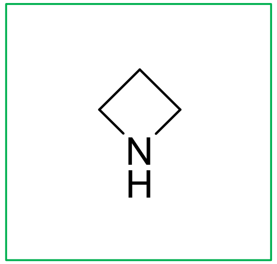
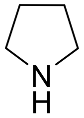
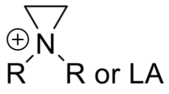
I. Introduction

Extensively studied ⇦   ⇨ Far less studied

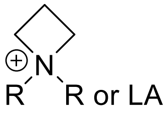
	Aziridine	Azetidine			
• Calculated ring strain: (kcal.mol^{-1})	27.3	25.2	In comparison:		27.4
• pKa (in water):	7.98	11.3	In comparison:		11.3

⇨ High ring strain energy / Basic: **Two key parameters for their reactivity**

Usually, activation through:



Aziridinium



Azetidinium

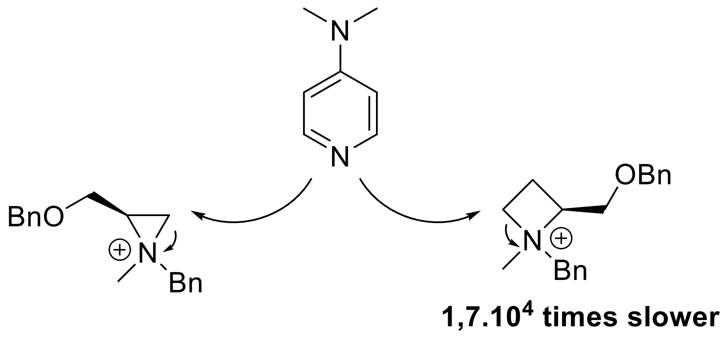
F. Couty, B. Drouillat, G. Evano, O. David, *Eur. J. Org. Chem.* **2013**, *11*, 2045-2056
J. D. Dill, A. Greenberg, J. F. Liebman, *J. Am. Chem. Soc.* **1979**, *101*, 6814-6826

I. Introduction

High ring strain energy / Basic: **BUT** not the only one

$\Delta E_{ring\ strain} = 2.1\ kcal.mol^{-1}$

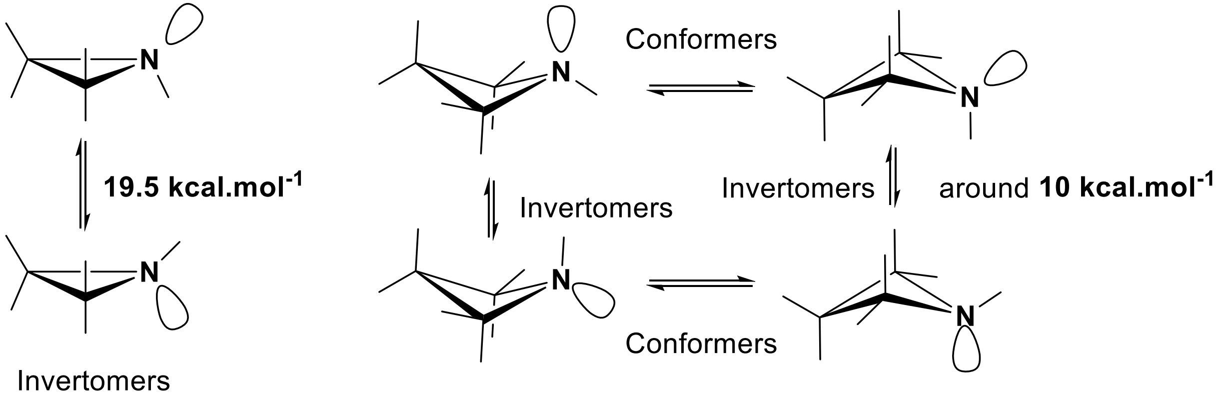
- Ring opening with DMAP:



From this rate difference:
→ $\Delta\Delta G^{\#} = 5.6\ kcal.mol^{-1}$

→ **Ring strain not the only important factor**

- Nitrogen inversion energy barrier:



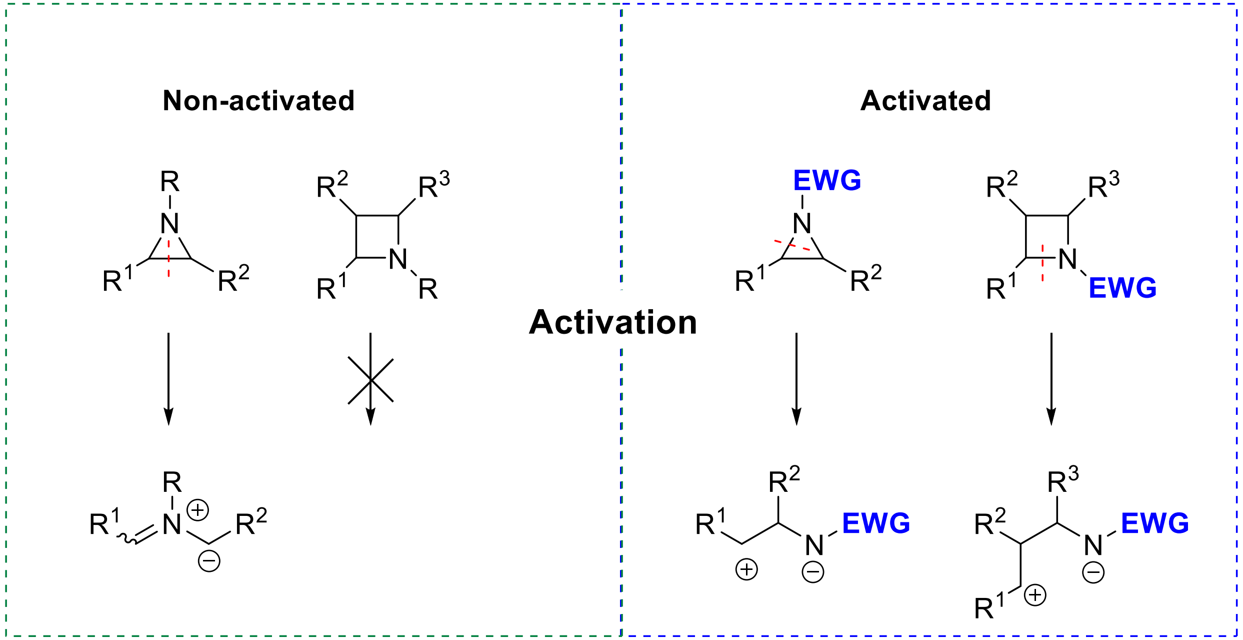
Invertomers
Often observable by NMR at rt

Not distinguishable in NMR at rt

N. De Rycke, O. David, F. Couty, *Org. Lett.* **2011**, *13*, 1836-1839

I. Introduction

Important to differentiate activated and non-activated substrates:



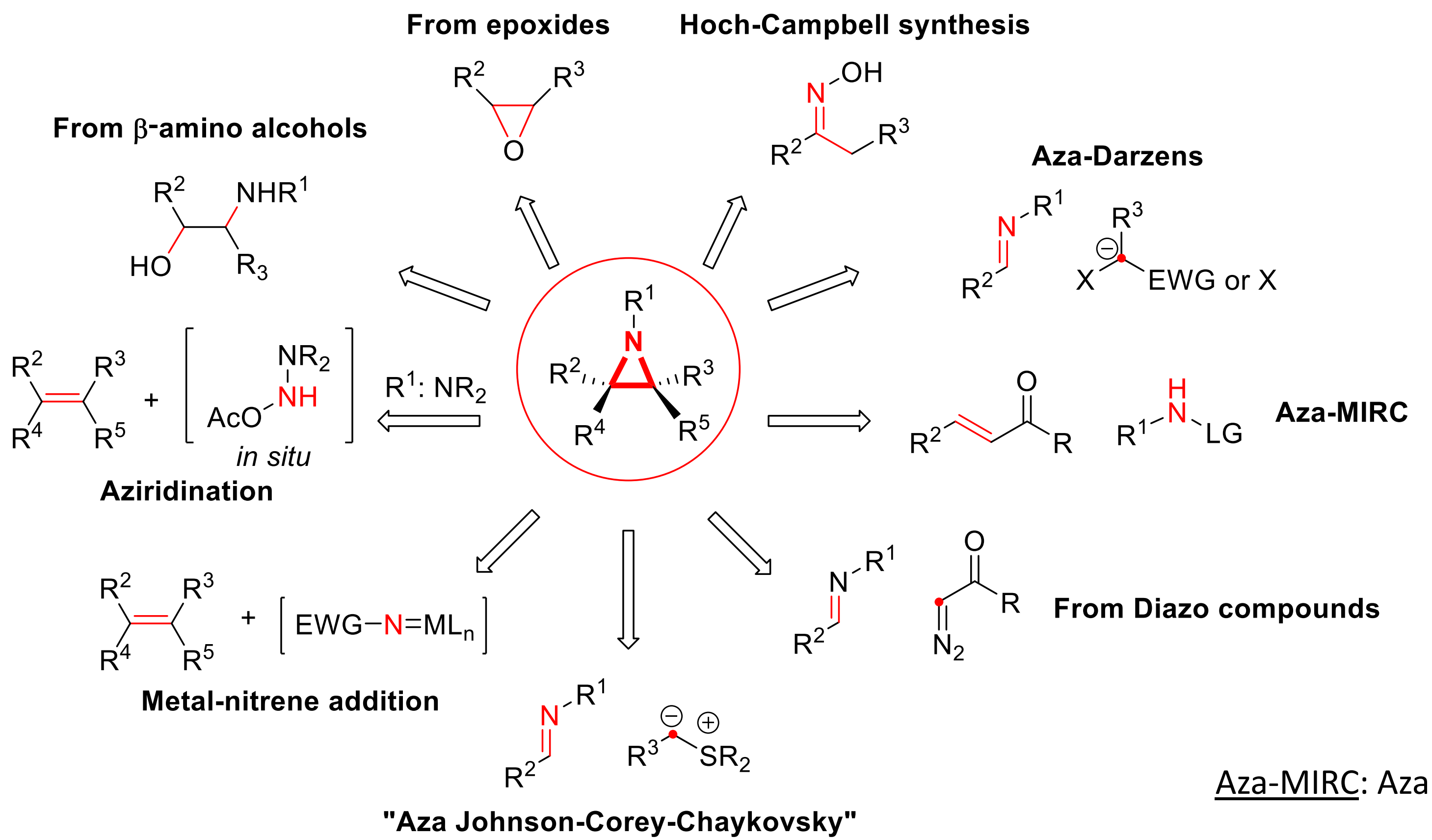
N rich in electron
Nucleophilic substrates

EWG on the nitrogen
Electrophilic substrates

Difference of reactivities

II. Synthesis of aziridine and azetidine

- Easy access to aziridines

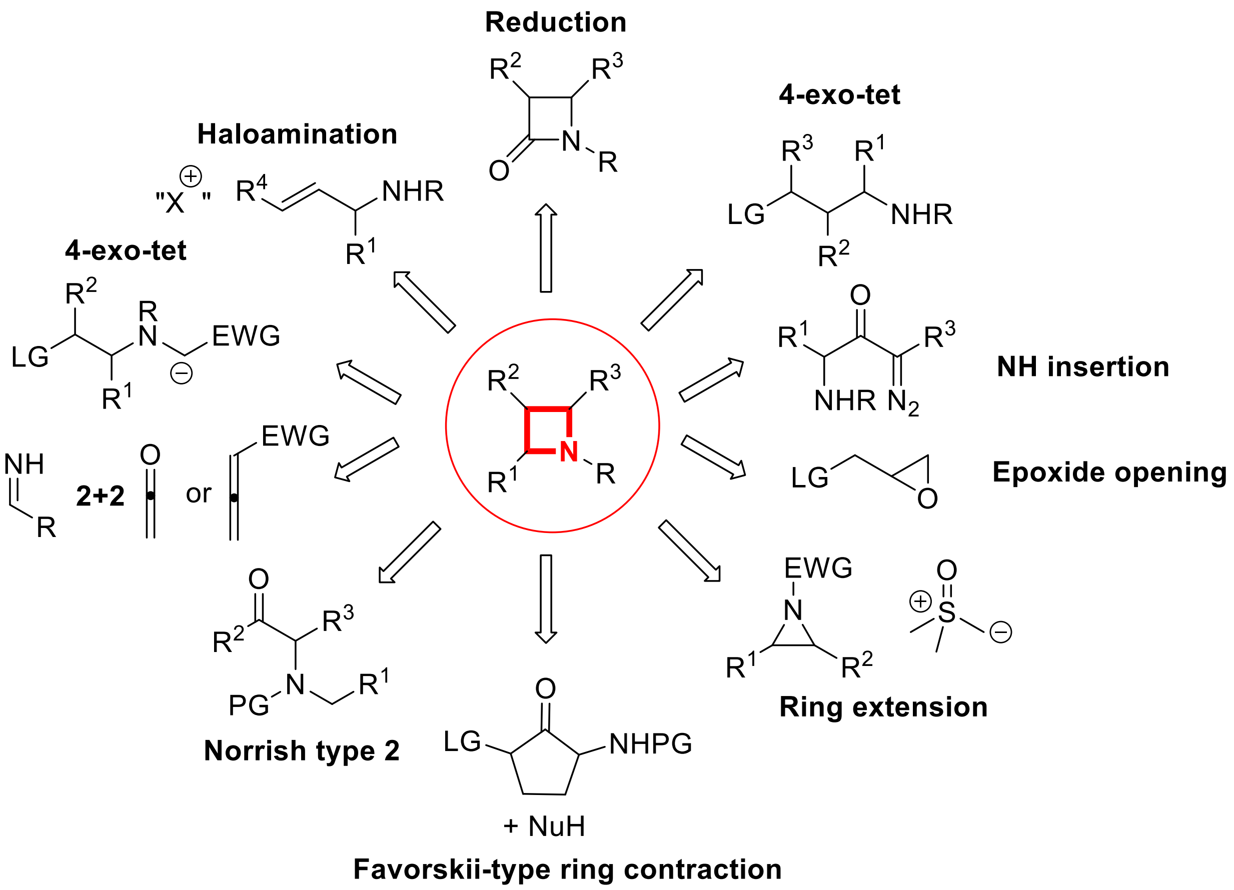


Aza-MIRC: Aza Michael Initiated Ring Closure

To learn more about stereoselective synthesis of aziridines:
L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881−7929

II. Synthesis of aziridine and azetidine

- Several methods for the synthesis of azetidine



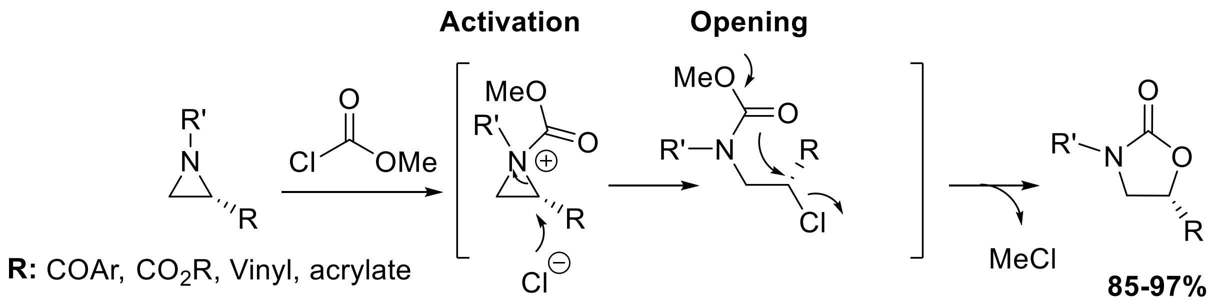
For a more intensive look to the synthesis of azetidine:
A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988-4035

III. Reactivity of non-activated aziridines and azetidines

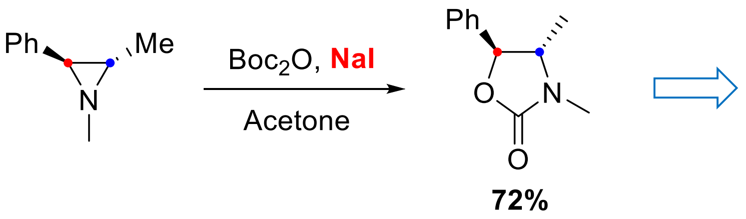
III. Reactivity of non-activated aziridines and azetidines

Ring expansion with "CX_2 inclusion":

- Double S_N2 inversion process



- Require an external nucleophile for other precursors:

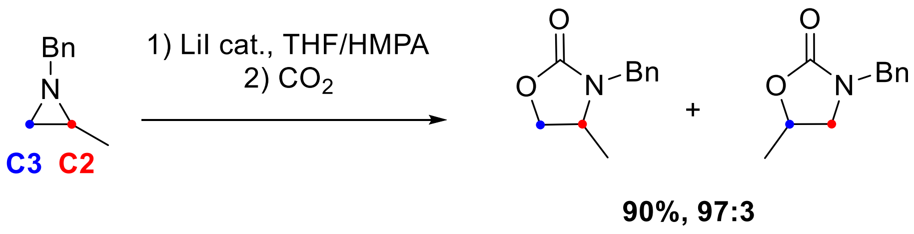


The released carbonate not sufficiently nucleophile
→ Halogen salt added to open the aziridinium

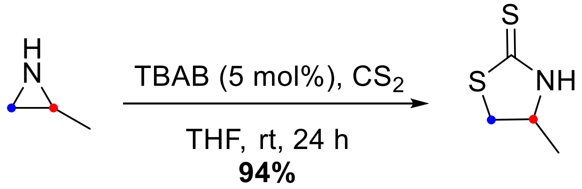
T. B. Sim, S. H. Kang, K. S. Lee, W. K. Lee, H. Yun, Y. Dong, H-J. Ha, *J. Org. Chem.* **2003**, *68*, 104-108
L. Testa, M. Akssira, E. Zaballos-Garcia, P. Arroyo, L. R. Domingo, J. Sepulveda-Arques, *Tetrahedron* **2003**, *59*, 677-683

Ring expansion with "CX_2 inclusion":

- Allow the trapping of $CO_{2\,(g)}$



- Other heteroatoms can be introduced: CS_2



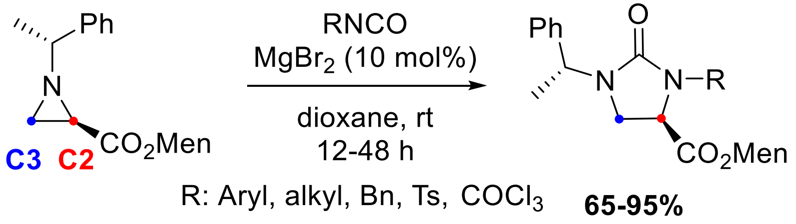
⇨ When only alkyl substituents: C3 opening → On the less hindered carbon

M. T. Hancock. A. R. Pinhas, *Tetrahedron Letters* **2003**, *44*, 5457-5460
A. Sudo, Y. Moriaka, E. Koizumi, F. Sanda, T. Endo, *Tetrahedron Letters* **2003**, *44*, 7889-7891

III. Reactivity of non-activated aziridines and azetidines

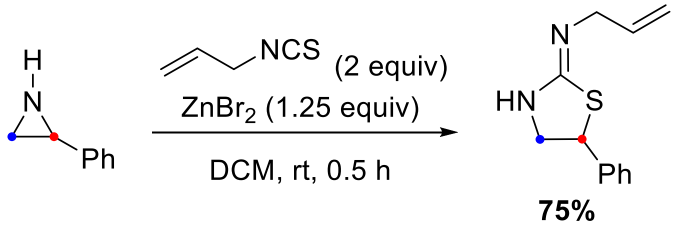
Ring expansion with “CX_2 inclusion”:

- Isocyanates upon activation can be used:



Men: Menthyl

- But also thioisocyanates



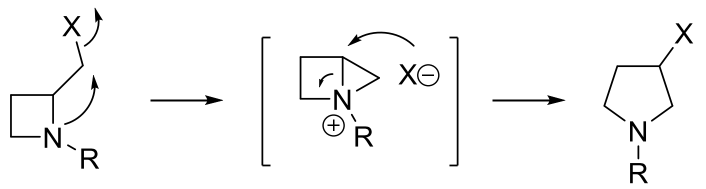
⇨ If Aryl or Ester substituted aziridine: C2 opening → On the most substituted carbon (Between Ph and CO_2R → opening at Ph position favored)

M. S. Kim, Y-W. Kim, H. S. Hahm, J. W. Jang, W. K. Lee, H-J. Ha, *Chem. Commun.* **2005**, *25*, 3062-3064
R. A. Craig, N. R. O’Connor, A. F. G. Goldberg, B. M. Stoltz, *Chem. Eur. J.* **2014**, *20*, 4806 – 4813
S. Stankovic, M. D’Hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, H-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643-665

III. Reactivity of non-activated aziridines and azetidines

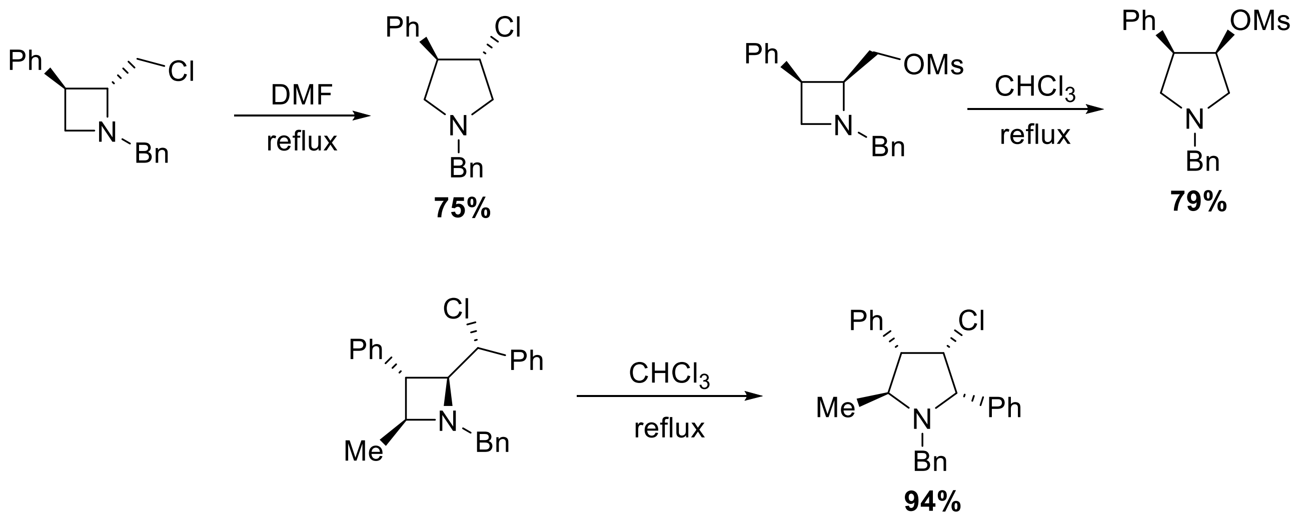
Ring expansion of 2-haloalkyl azetidines

- Proposed mechanism:



⇨ Calculations tend to favor this bicyclic intermediate in DMSO

Stereospecific:
→ Retention via double S_N2

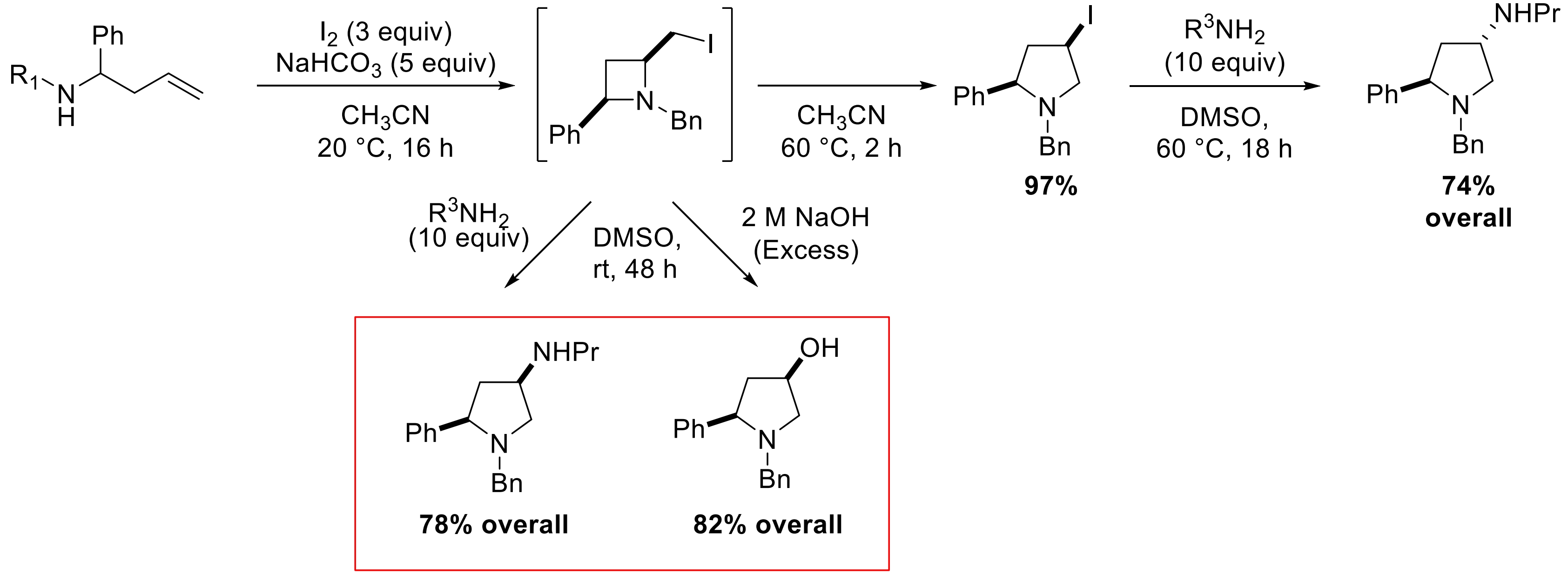


F. Couty, M. Kletskii, *J. Mol. Struct. THEOCHEM* **2009**, *908*, 26–30
F. Couty, F. Durrat, D. Prim, *Tetrahedron Letters* **2003**, *44*, 5209-5212

III. Reactivity of non-activated aziridines and azetidines

Ring expansion of 2-haloalkyl azetidines

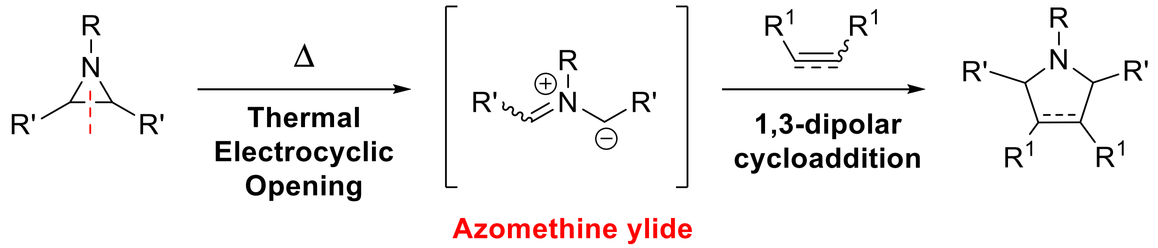
- Possible ring expansion of iodo-azetidine in presence of another nucleophiles

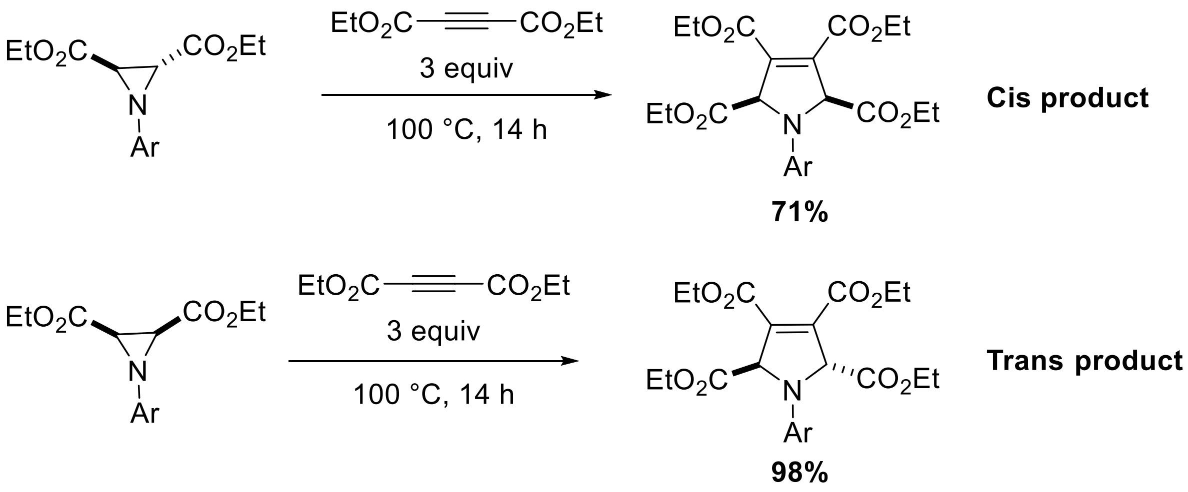


A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. Hama Salih, N. Spencer, L. Male, I. Magyary, W-P. Deng, F. Müller, J. S. Fossey, *Org. Biomol. Chem*. **2013**, *11*, 5083-5093

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides

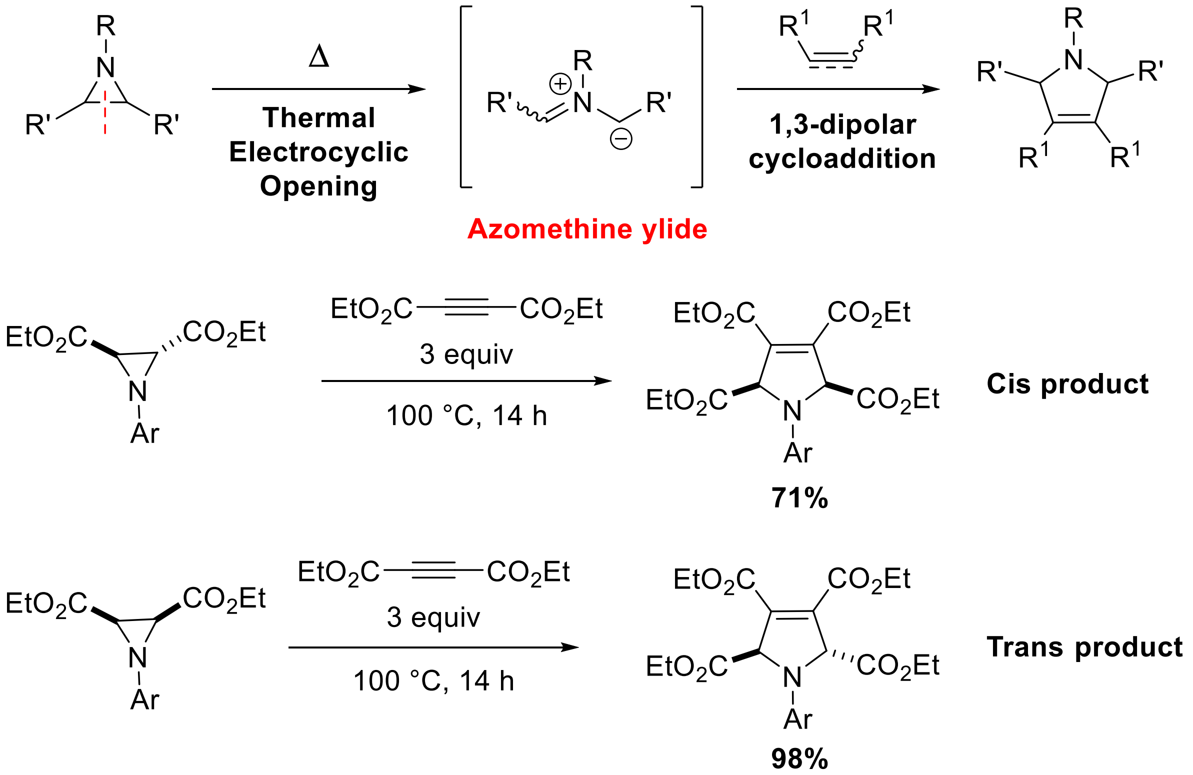




R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides



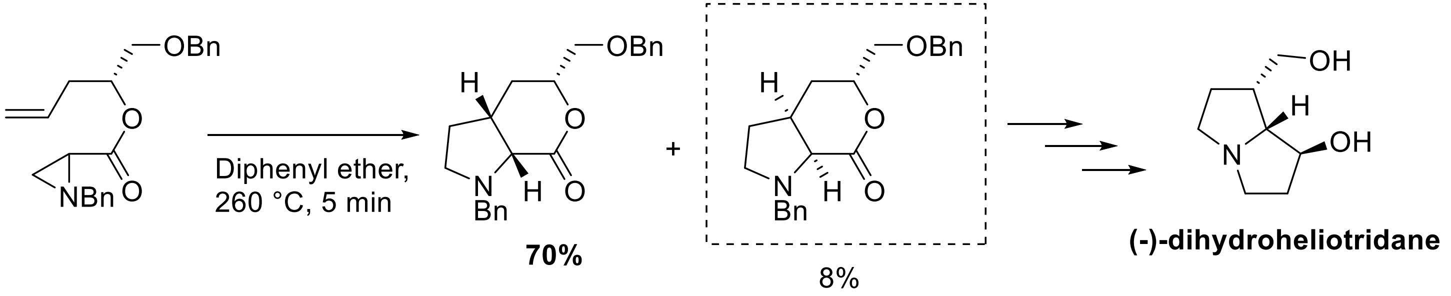
Question 1: How can you explain the stereoselectivity of these 2 examples?

R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

III. Reactivity of non-activated aziridines and azetidines

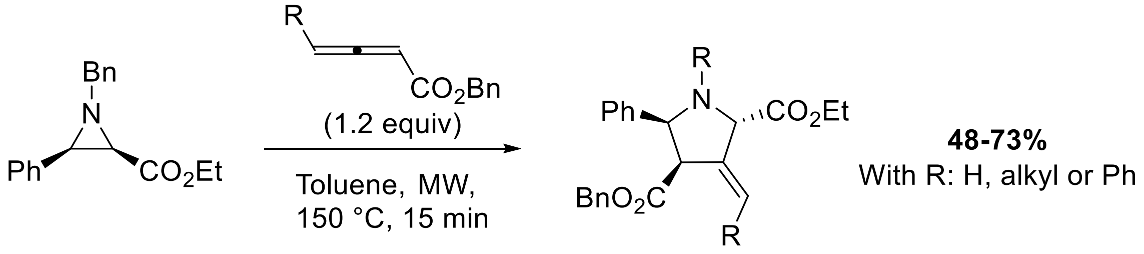
1,3-dipolar cycloadditions via azomethine ylides

- With non polarized alkenes

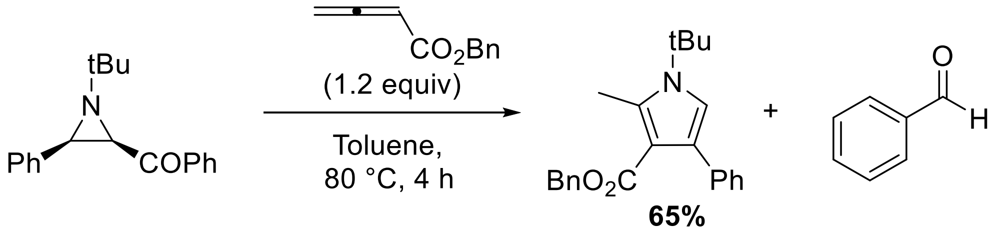


⇨ Intramolecular + require very high temperature

- With allenoates



- Interestingly if N protected with *t*Bu or Cy:

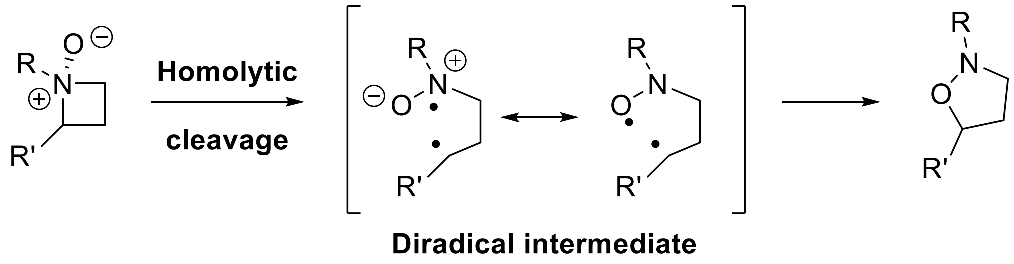


K. Hashimura, S. Tomita, K. Hiroya, K. Ogasawara, *J. Chem. Soc., Chem. Commun*. **1995**,*22*, 2291-2292
F. M. Ribeiro Laia, A. L. Cardoso, A. M. Beja, M. R. Silva, T. M.V.D. Pinho e Melo, *Tetrahedron* **2010**, *66*, 8815-8822

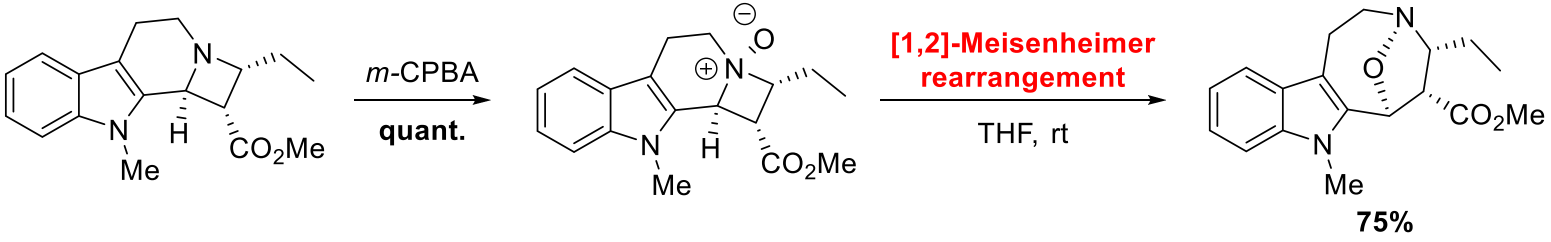
III. Reactivity of non-activated aziridines and azetidines

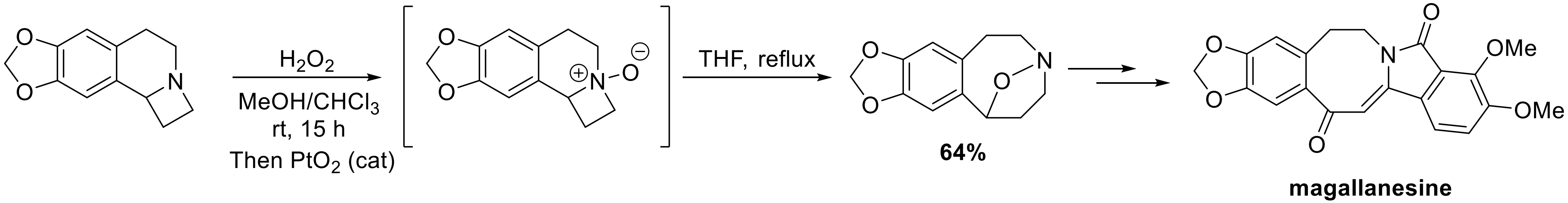
[1,2]-Meisenheimer rearrangement with N-oxide of azetidines

[1,2]-Meisenheimer rearrangement:



- Kurihara et al. 1993 and 1996:



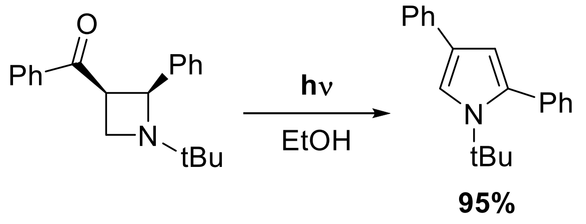


More details about mechanism: L. Menguy, B. Drouillat, J. Marrot, F. Couty, *Tetrahedron Letters* **2012**, *53*, 4697-4699
T. Kurihara, Y. Sakamoto, M. Takai, K. Ohuchi, S. Harusawa, R. Yoneda, *Chem. Pharm. Bull*. **1993**, *41*, 1221-1225
R. Yoneda, Y. Sakamoto, Y. Oketo, S. Harusawa, T. Kurihara, *Tetrahedron* **1996**, *46*, 14563-14576

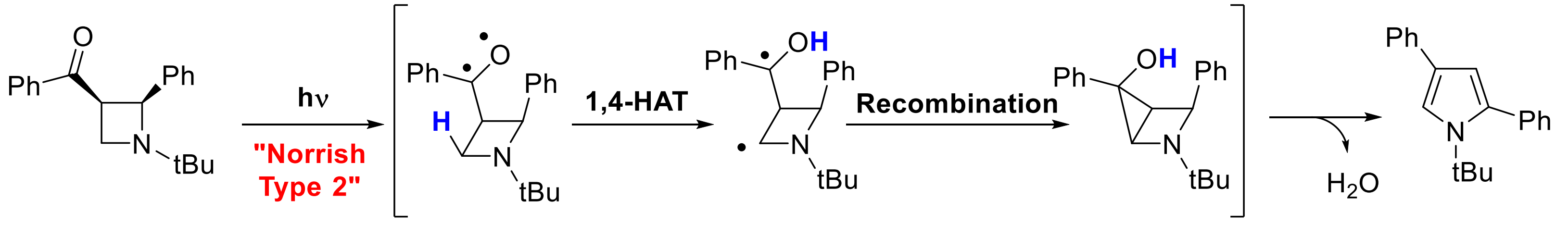
III. Reactivity of non-activated aziridines and azetidines

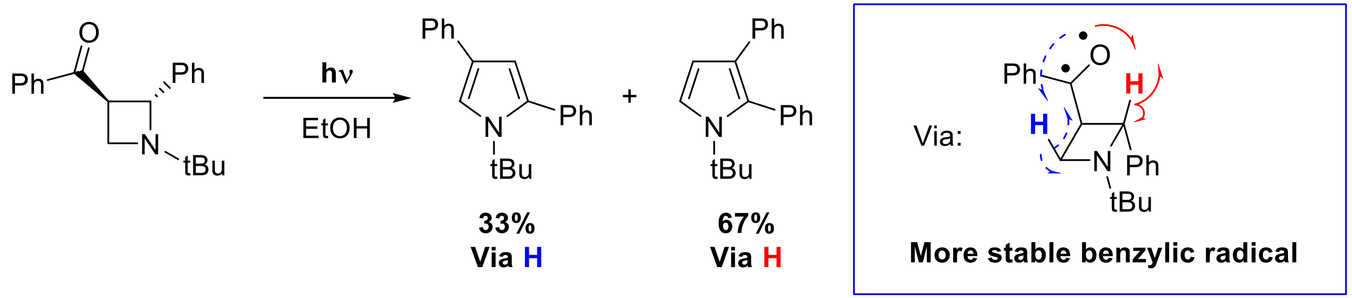
Photo-rearrangement of 3-benzoyl azetidine

- Padwa et al., 1967:



- Proposed mechanism:



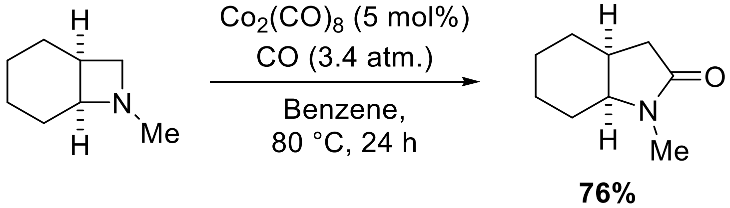


A. Padwa, R. Gruber, L. Hamilton, *J. Am. Chem. Soc.* **1967**, *89*, 3077-3078
A. Padwa, R. Gruber, *J. Am. Chem. Soc.* **1968**, *90*, 4456-4458

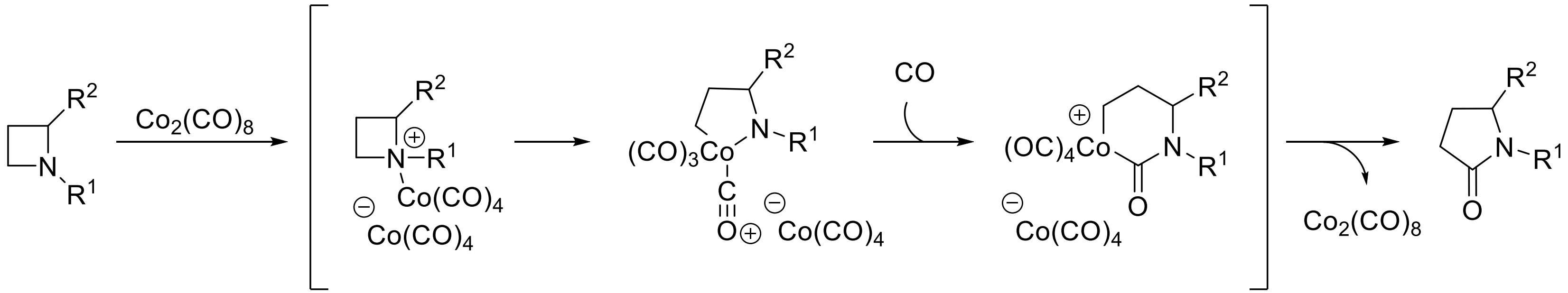
III. Reactivity of non-activated aziridines and azetidines

Cobalt-catalyzed carbonylation of azetidine

- Alper and Roberto, 1989

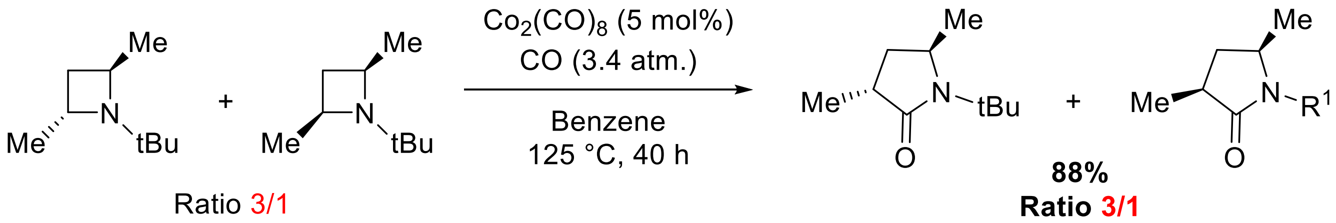


- Proposed mechanism:



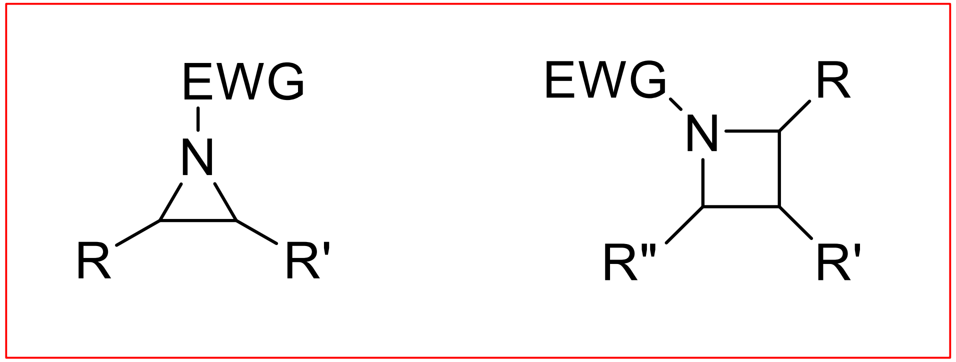
Insertion in the less substituted C-N bond

- Stereospecific process:



D. Roberto, H. Alper, *J. Am. Chem. Soc.* **1989**, *111*, 7539-7543

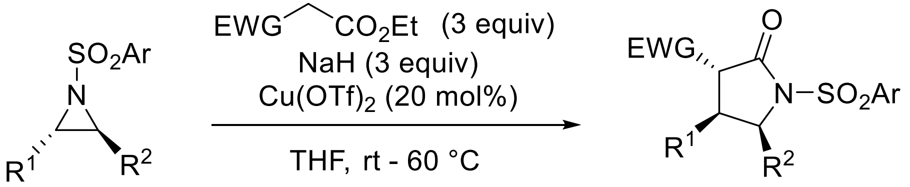
IV. Reactivity of activated aziridines and azetidines



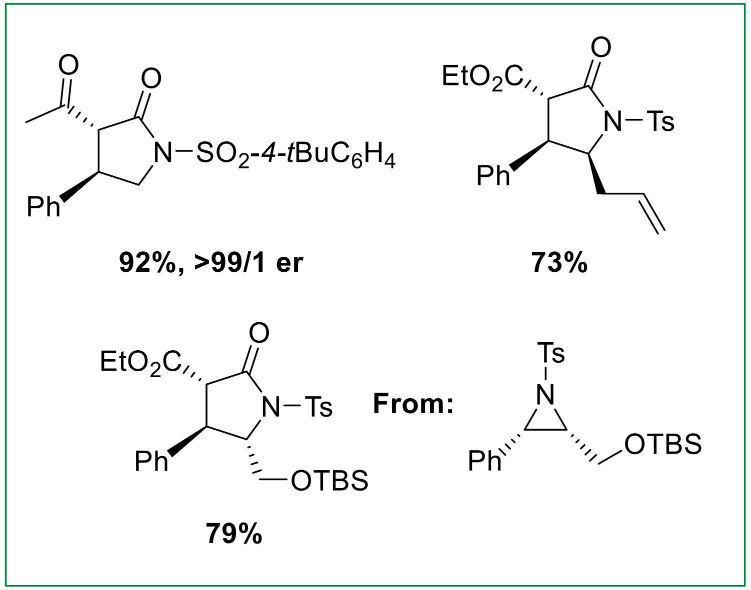
IV. Reactivity of activated aziridines and azetidines

- S_N2-type ring opening-cyclization:

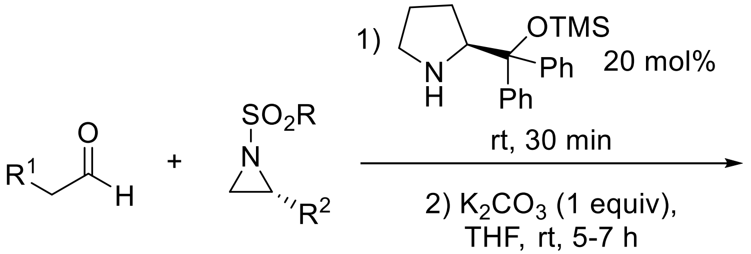
With enolates:



Only one diastereoisomer

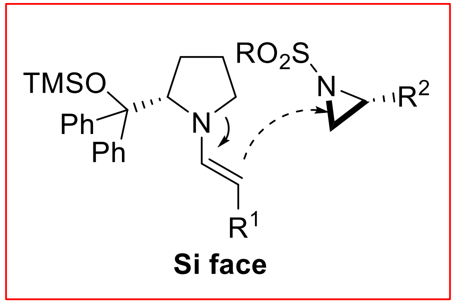


With enamine:



78-90%
Single diastereoisomer

Via:

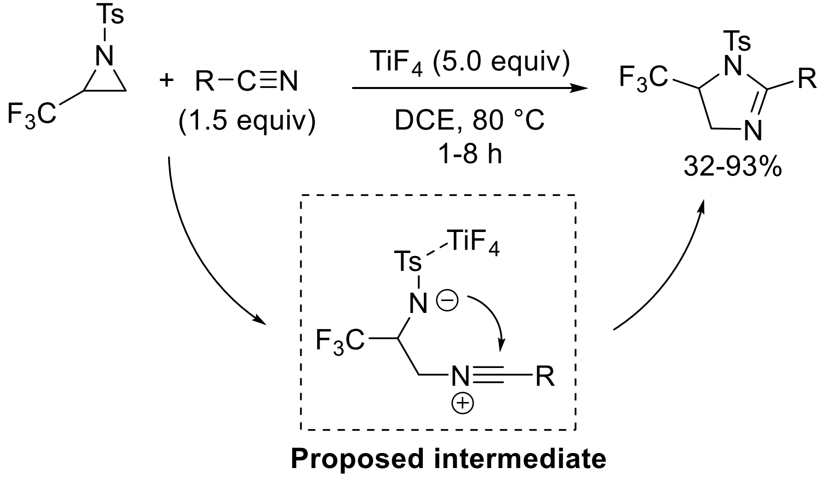


M. K. Ghorai, D. P. Tiwari, *J. Org. Chem*. **2010**, *75*, 6173–6181
A. Rai, D. S. Yadav, *Tetrahedron Letters* **2013**, *54*, 3127-3131

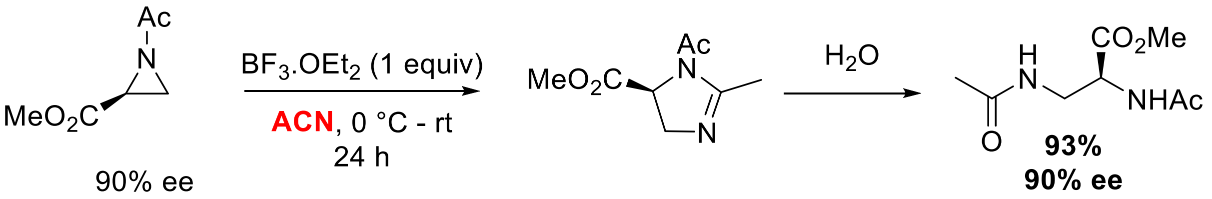
IV. Reactivity of activated aziridines and azetidines

- S_N2-type ring opening-cyclization:

Even with nitriles:



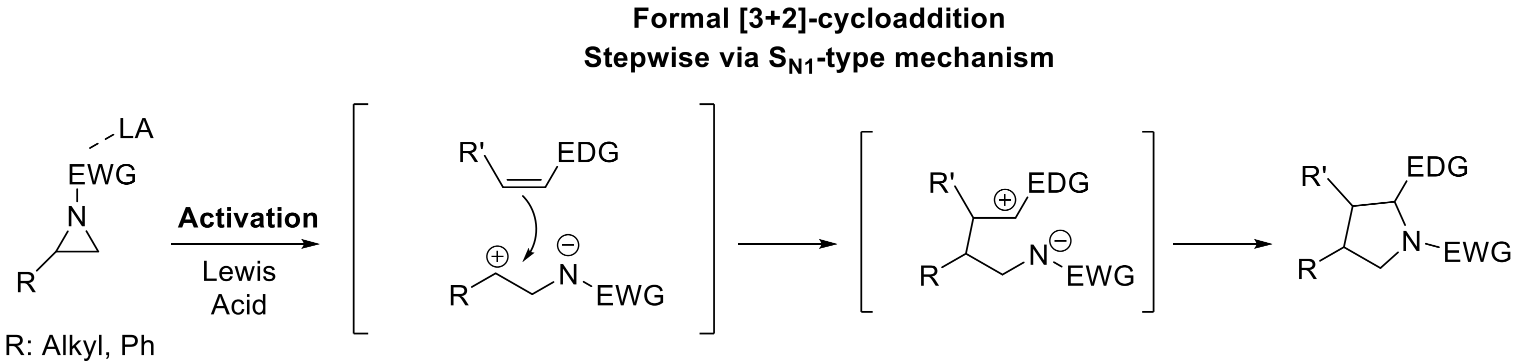
Retention of the stereochemistry:



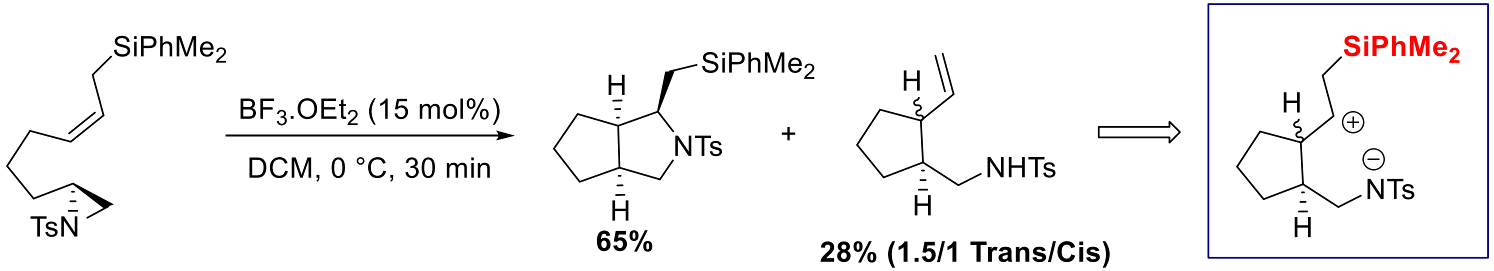
M. Yoshiki, R. Ishibashi, Y. Yamada, T. Hanamoto, *Org. Lett.* **2014**, *16*, 5509-5511
M. Bucciarelli, A. Forni, I. Moretti, F. Prati, G. Torre, *Tetrahedron: Asymmetry* **1995**, *6*, 2073-2080,

IV. Reactivity of activated aziridines and azetidines

- Formal [3+2] cycloaddition:



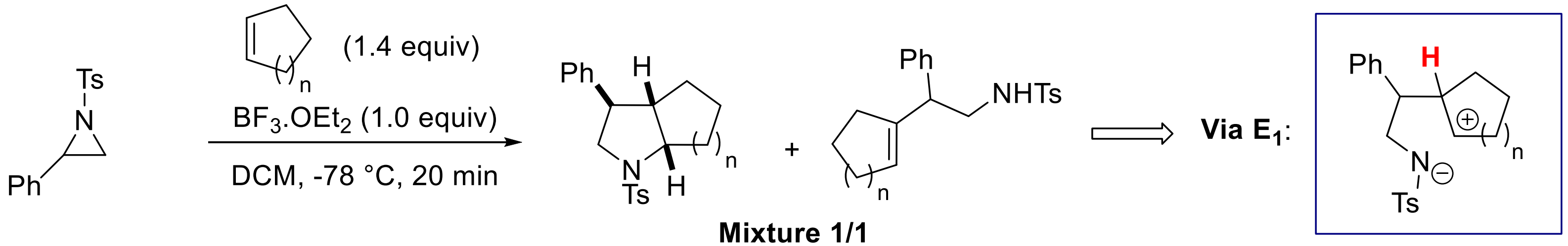
- Evidence: Presence of eliminated products



S.C. Bergmeier, S. L. Fundy, P. P. Seth, *Tetrahedron* **1999**, *55*, 8025-8038

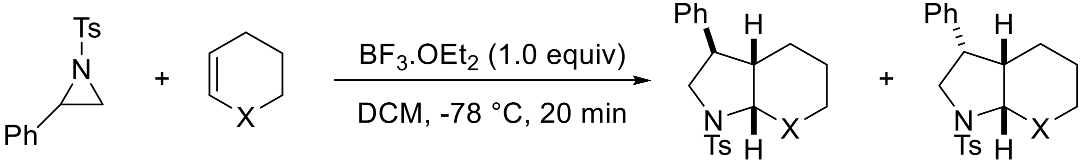
IV. Reactivity of activated aziridines and azetidines

- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

- With electron-enriched alkenes → no opened product BUT mixture exo/endo

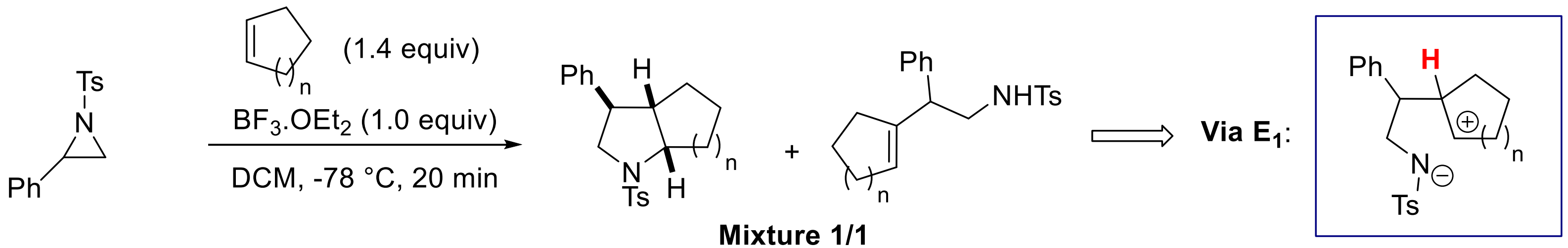


Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

IV. Reactivity of activated aziridines and azetidines

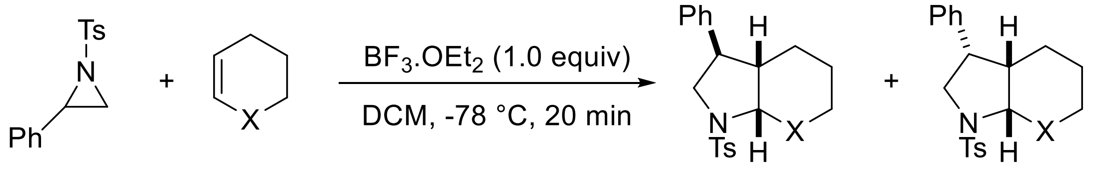
- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

Question 2: How can you explain this difference between these two examples ?

- With electron-enriched alkenes → no opened product BUT mixture exo/endo

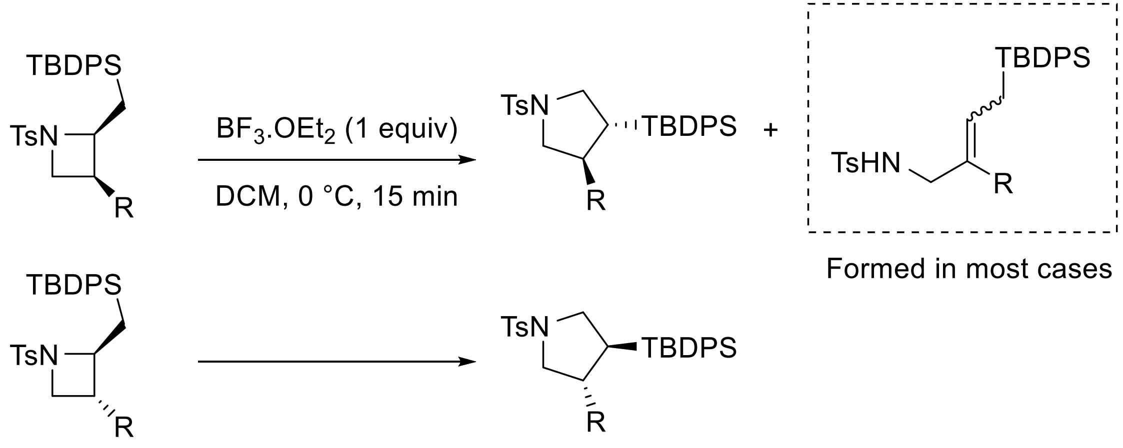


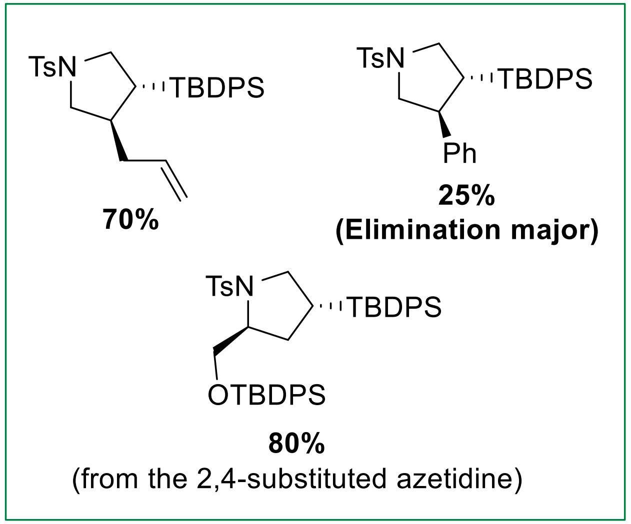
Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

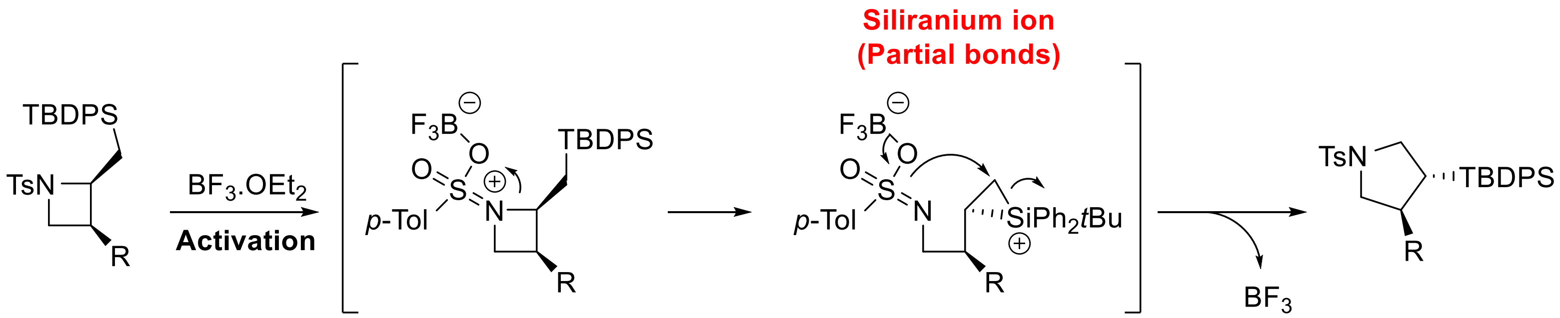
IV. Reactivity of activated aziridines and azetidines

- **Yadav et al., 2012**: Ring-expansion of 2-TBDPS methyl azetidine:





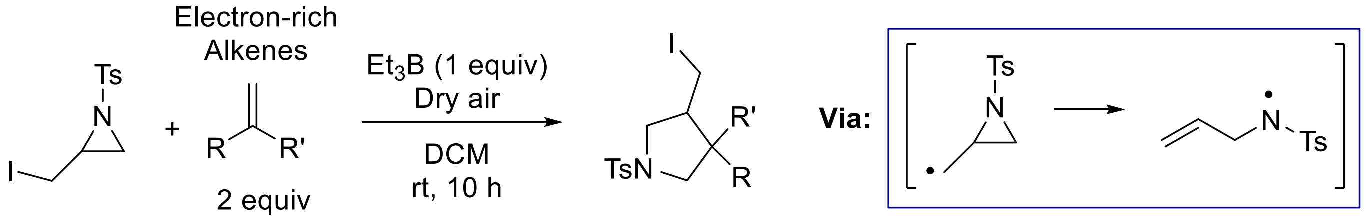
- Mechanism: Siliranium ion invariably trans to R substituent

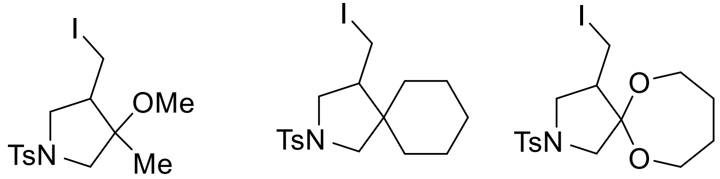


B. D. Narhe, V. Sriramurthy, V. K. Yadav, *Org. Biomol. Chem.* **2012**, *10*, 4390–4399

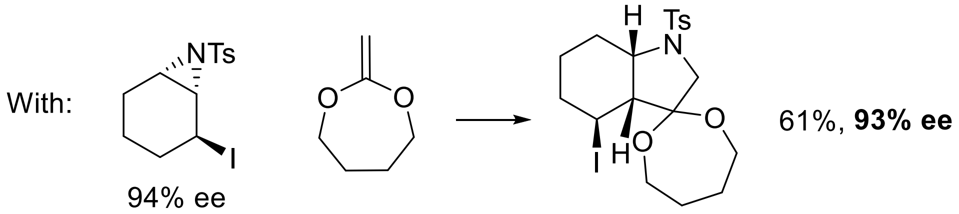
IV. Reactivity of activated aziridines and azetidines

- **Taguchi et al., 2003**: Radical [3+2] cycloaddition via Iodine Atom Transfer:





71%, 1/1.7 Cis/Trans **56%** **62%**

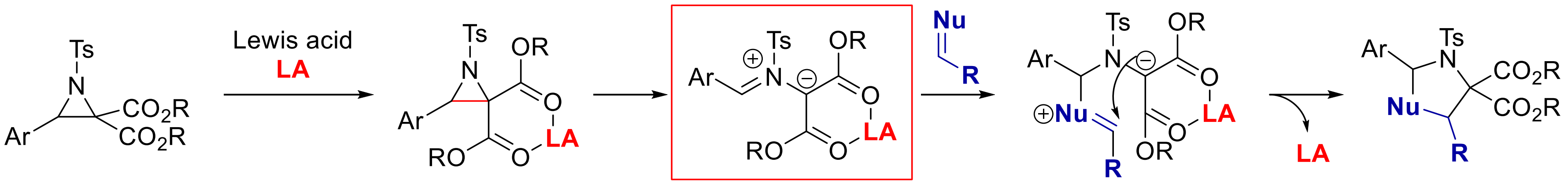


O. Kitagawa, S. Miyaji, Y. Yamada, H. Fujiwara, T. Taguchi, *J. Org. Chem.* **2003**, *68*, 3184-3189

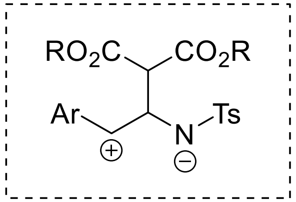
IV. Reactivity of activated aziridines and azetidines

- **Non-activated aziridine reactivity** using donor-acceptor activated aziridines

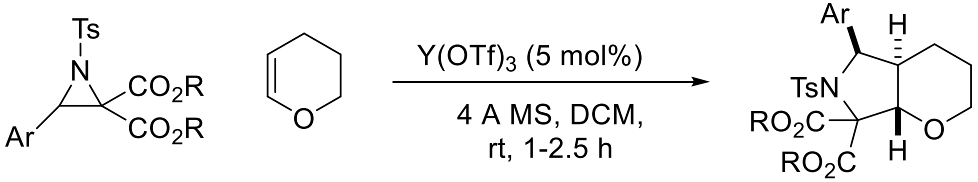
Electron-rich alkenes, imine, aldehyde, isocyanide



And not:

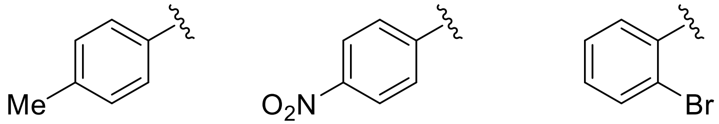


- Reaction with electron-rich alkene:



dr > 20/1 for cyclic olefins

Ar:

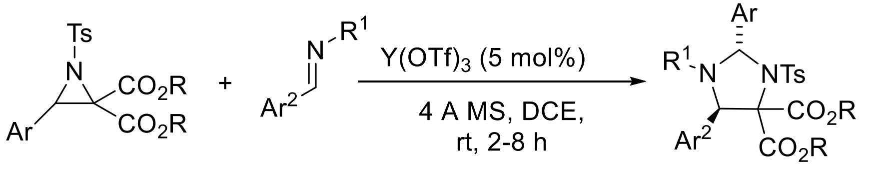


83% **74%** **68%**

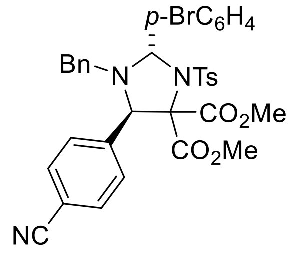
L. Li, X. Wu, J. Zhang, *Chem. Commun.* **2011**, *47*, 5049-5051

IV. Reactivity of activated aziridines and azetidines

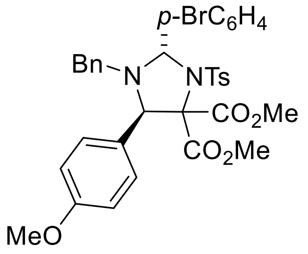
- Reaction with aromatic imine :



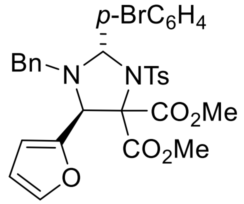
65-98%
dr trans/cis up to >50/1



65%, ratio trans/cis >50/1

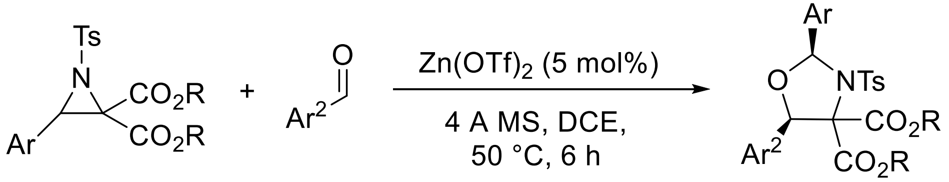


79%, ratio trans/cis: 3:1



98%, ratio trans/cis 1/1

- Reaction with aromatic aldehyde:

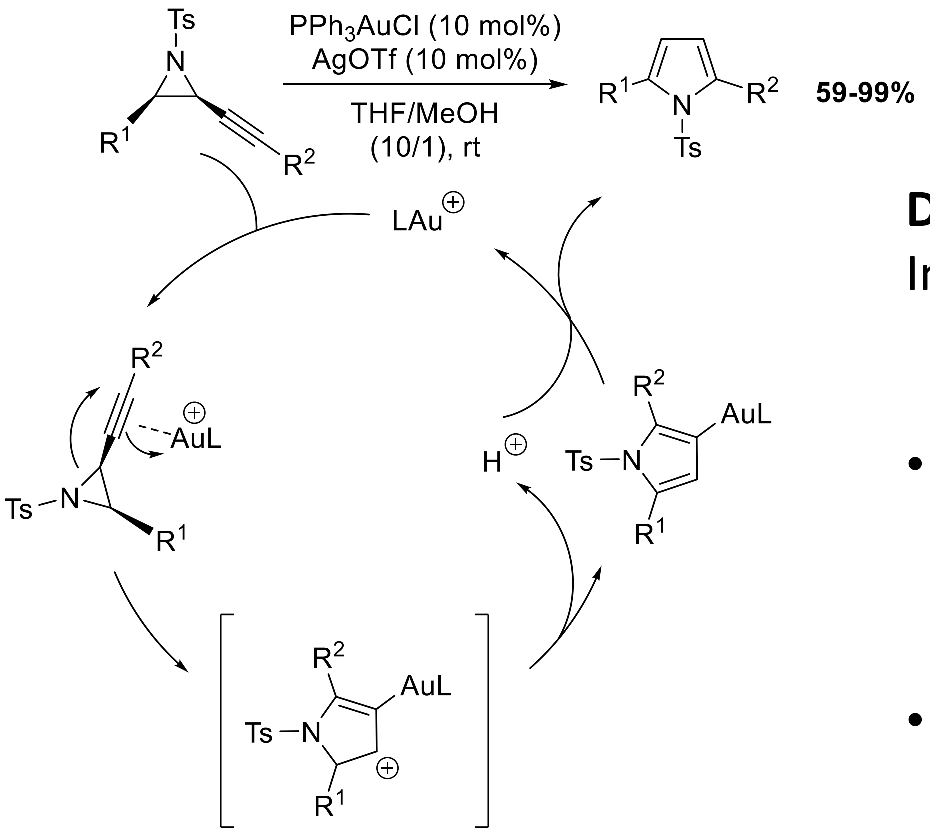


Both electron-rich and
poor aromatic aldehyde

52-97%
Most cases:
Only **cis** diastereoisomer

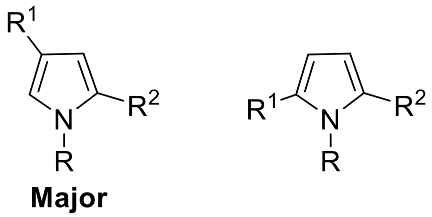
X. Wu, J. Zhang, *Synthesis* **2012**, *44*, 2147-2154
Z. Jiang, J. Wang, P. Lu, Y. Wang, *Tetrahedron* **2011**, *67*, 9609-9617

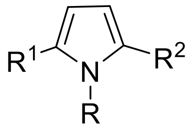
- **Chen and Davies groups, 2009**: Gold-catalyzed ring expansion:



Davies et al.:

In apolar solvents: Ag**X** play on the regioselectivity

- AgOTf in DCM → 

- AgOTs in DCM → Only prod. 

D-D. Chen, X-L. Hou, L-X. Dai, *Tetrahedron Letters* **2009**, *50*, 6944-694
P. W. Davies, N. Martin, *Org. Lett.* **2009**, *11*, 2293-2296

V. Conclusion

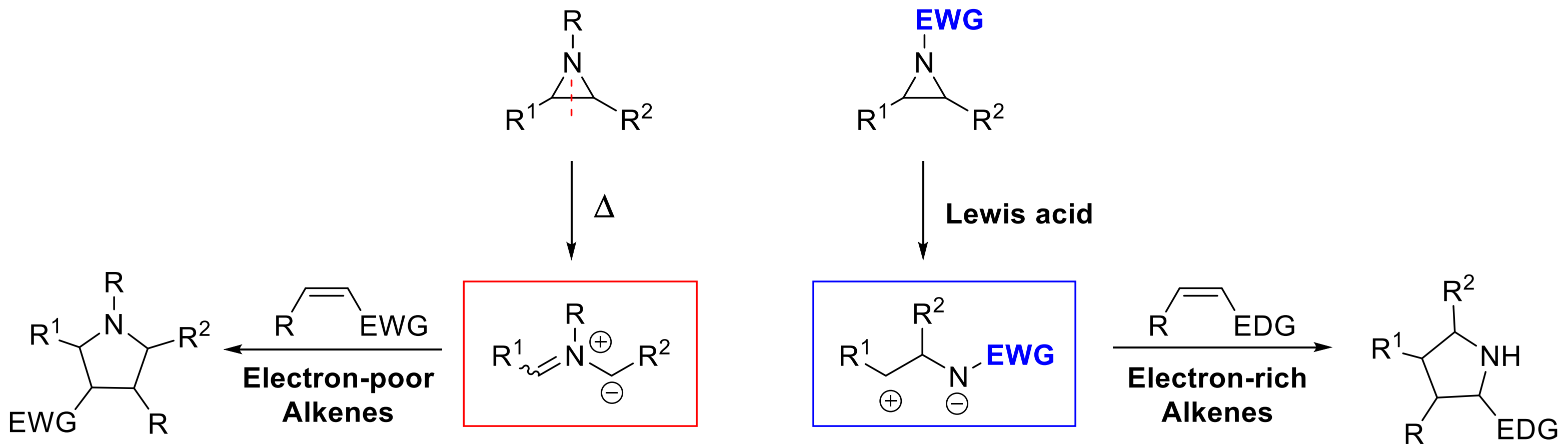
- Activated and non-activated aziridines/azetidines:

⇨ **Opposite reactivity**

↗ Non-activated: Act as a **nucleophile** then ring-expansion

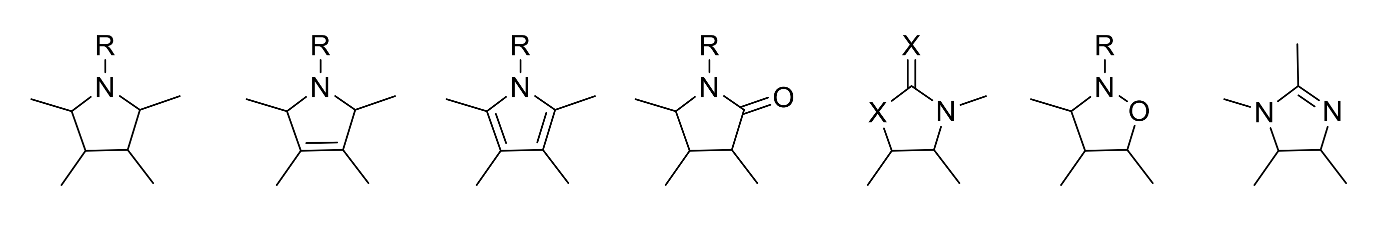
↘ Activated: Act as an **electrophile** then ring-expansion

- Upon activation, regioselectivity of the 1,3-dipole different:



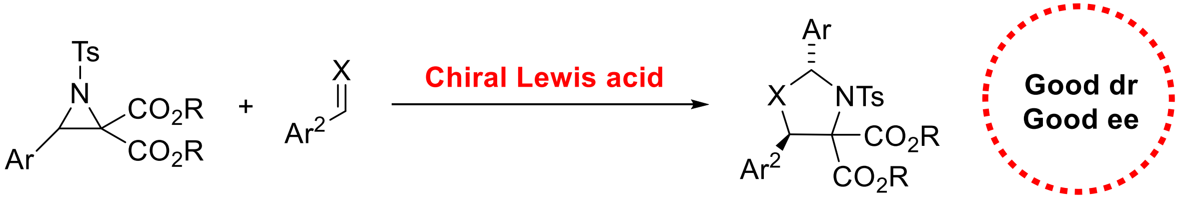
V. Conclusion

- Allow the synthesis of a diversity of 5-membered azacycles



- In many cases: good regio and stereoselectivity for the ring-expansions

- Still not much efficient enantioselective catalysis for the formal [3+2]

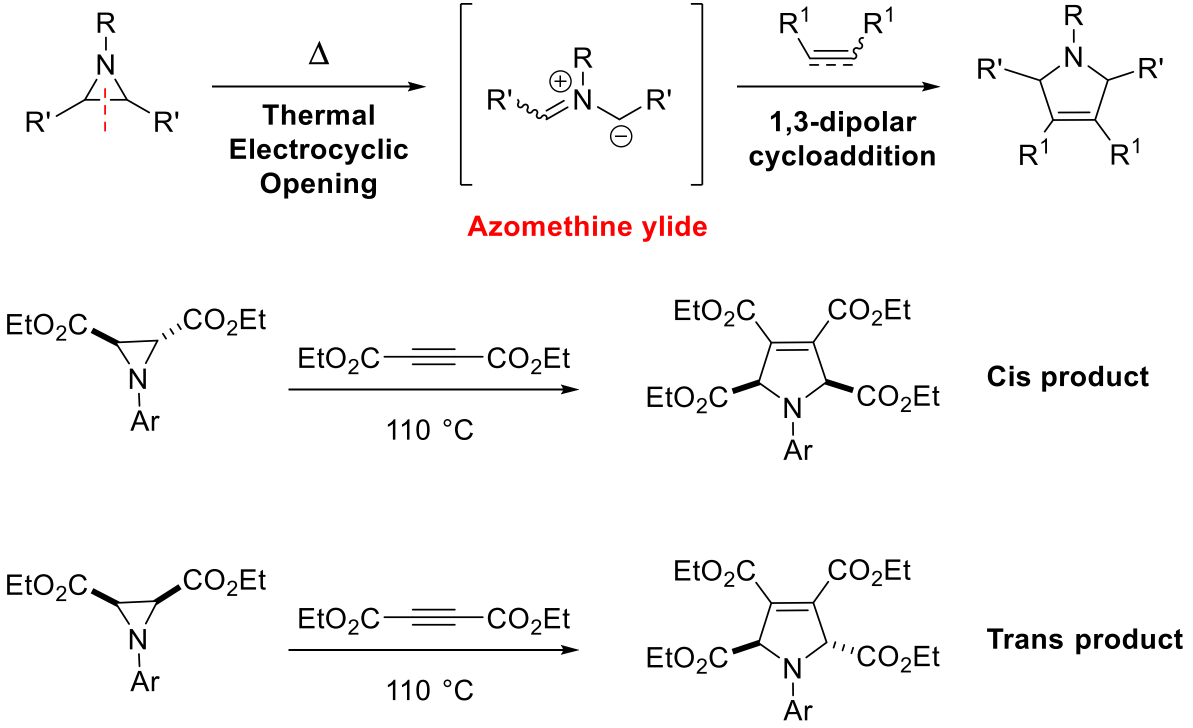


Thank you for your attention

Questions

III. Reactivity of non-activated aziridines and azetidines

Huisgen et al., 1967: 1,3-dipolar cycloadditions via azomethine ylides



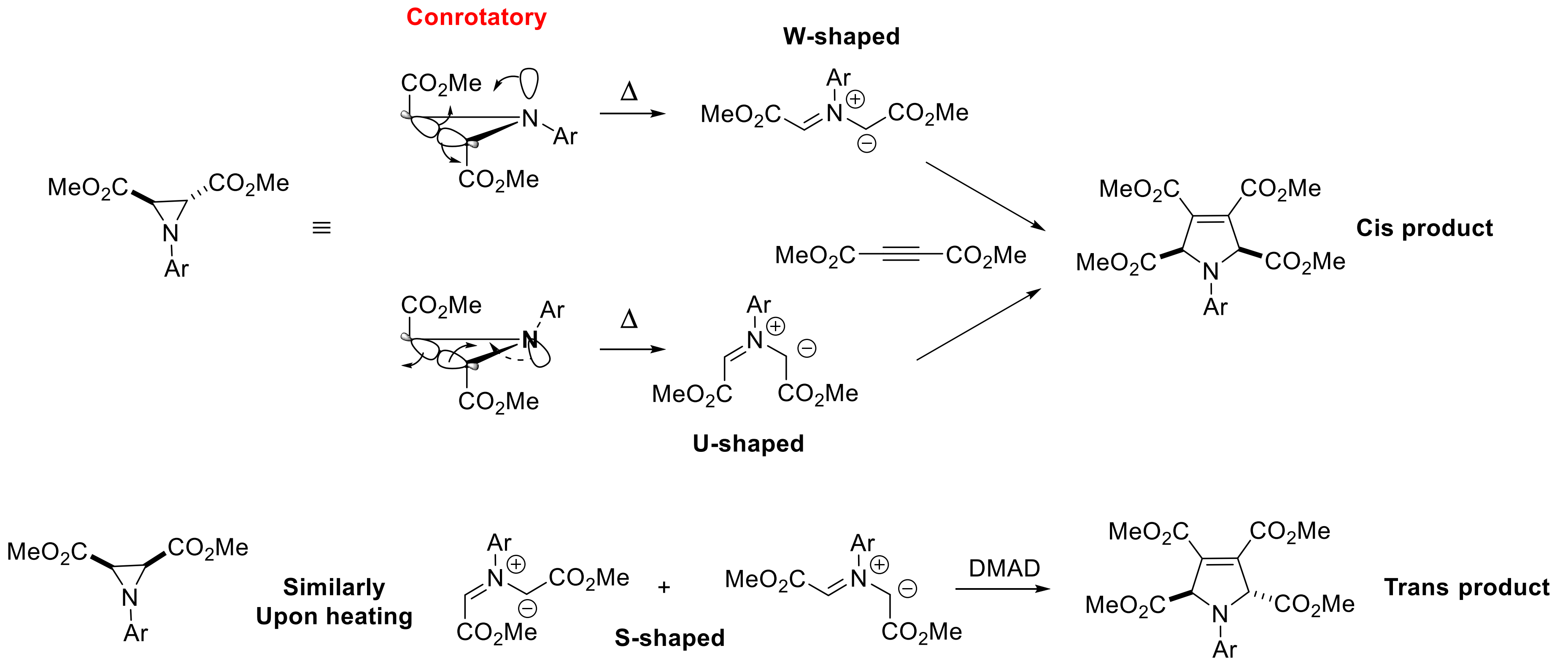
<u>Question 1</u>: How can you explain the stereoselectivity of these 2 examples?

R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

Questions

Question 1: How can you explain the relative stereoselectivity of these 2 examples?

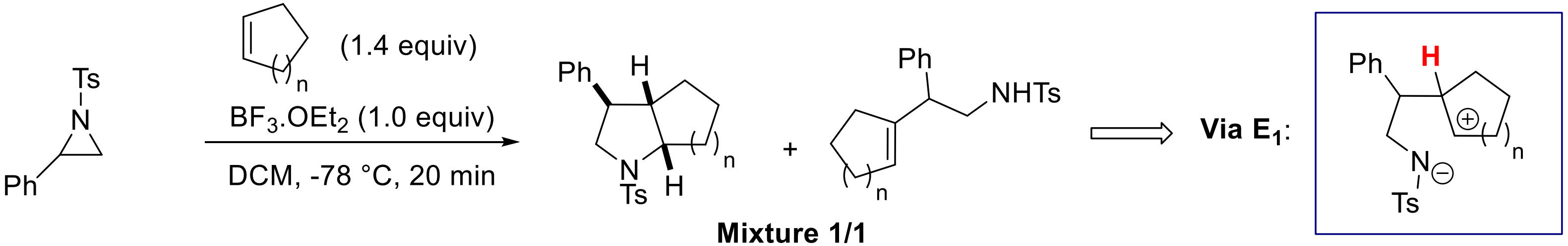
→ Using Woodward-Hoffmann rules: 4n electrocyclic opening in a thermal process: **Conrotatory**



R. Huisgen, W. Scheer, H. Huber *J. Am. Chem. Soc.* **1967**, 89, 1753-1755

IV. Reactivity of activated aziridines and azetidines

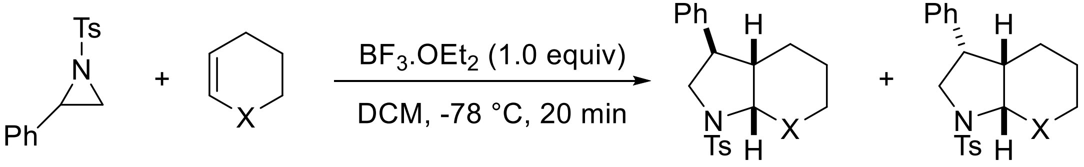
- Same observation without silylated moiety:



Mixture 1/1
For n=1, 45% overall
For n=2, 51% overall

<u>Question 2</u>: How can you explain this difference between these two examples ?

- With electron-enriched alkenes → no opened product BUT mixture exo/endo

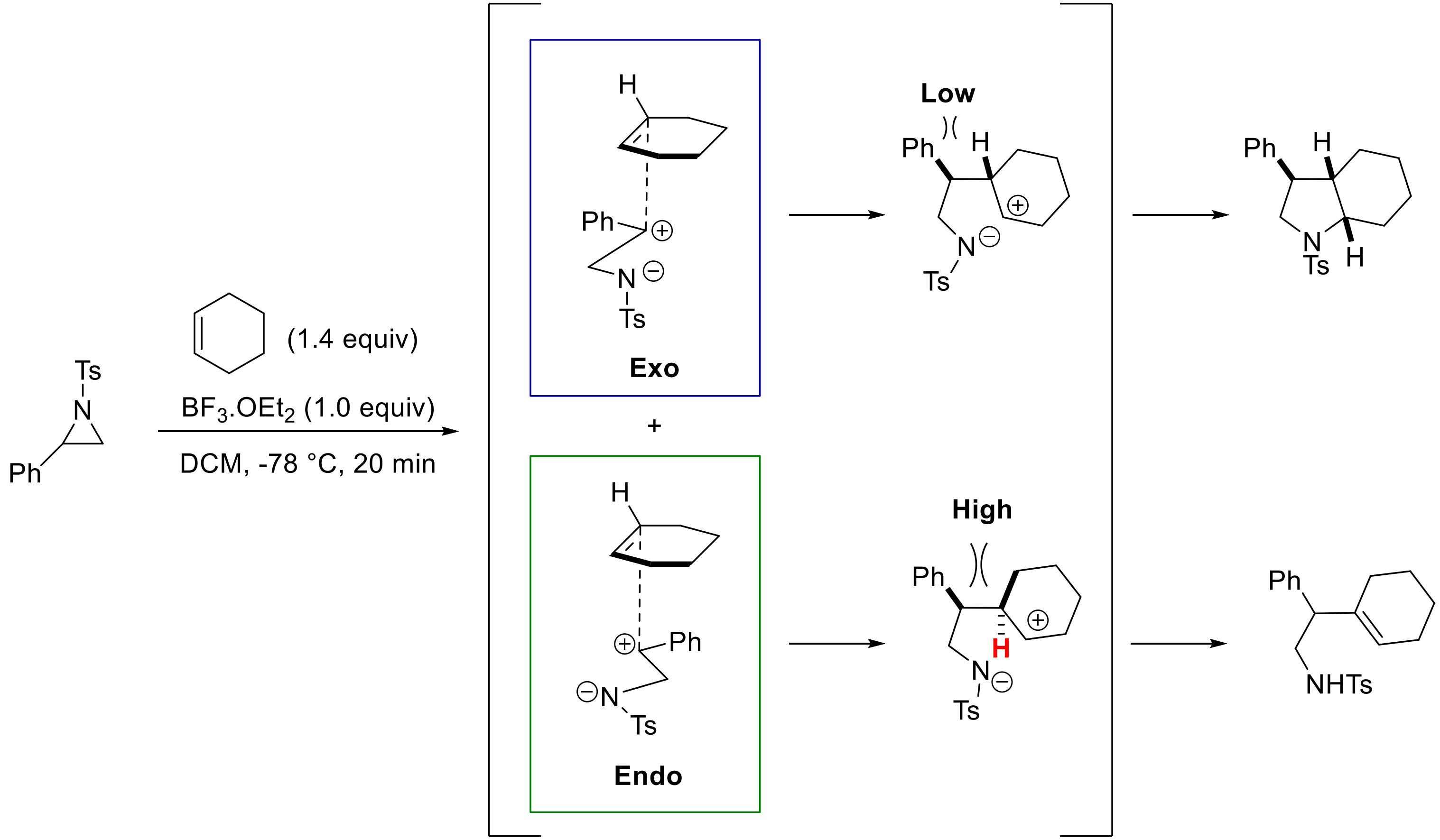


Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617
I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001** *42* 6087-6091

Questions

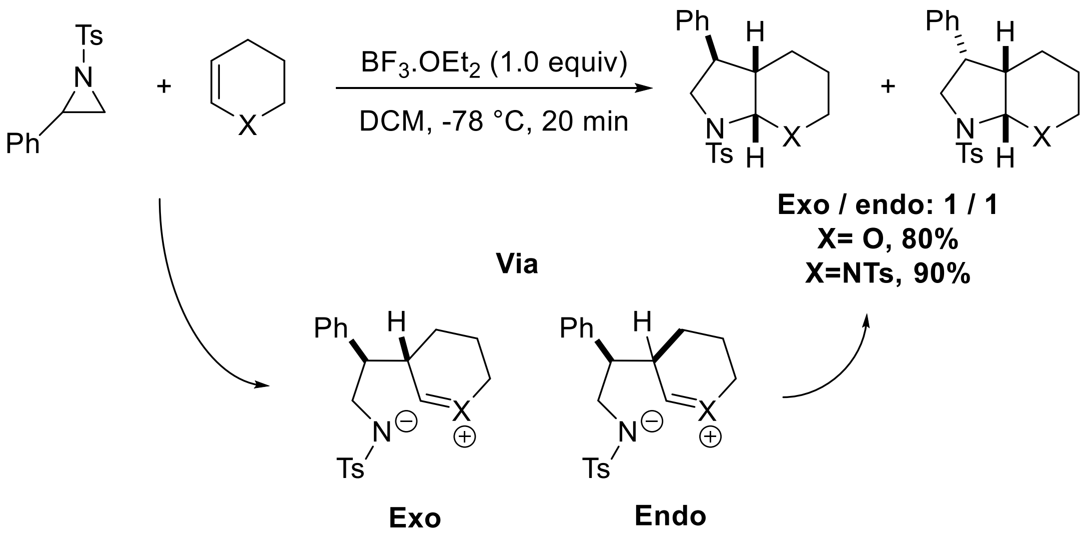
Question 2: How can you explain this difference between these two examples ?



I. Ungureanu, P. Klotz, A. Mann, *Angew. Chem. Int. Ed.* **2000**, *39*, 4615-4617

Questions

Question 2: How can you explain this difference between these two examples ?



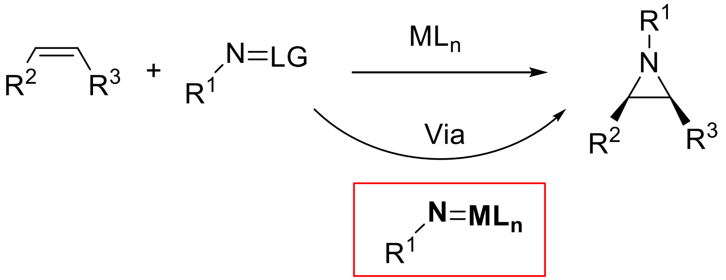
Exo / endo: 1 / 1
X= O, 80%
X=NTs, 90%

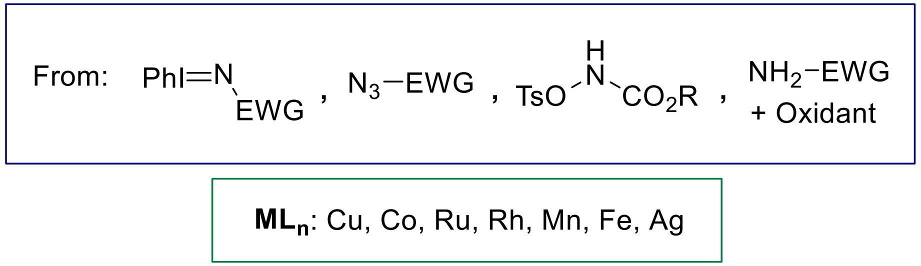
High stabilization due to the mesomeric effect of X
Both intermediates stable

I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Tetrahedron Letters* **2001,** *42,* 6087-6091

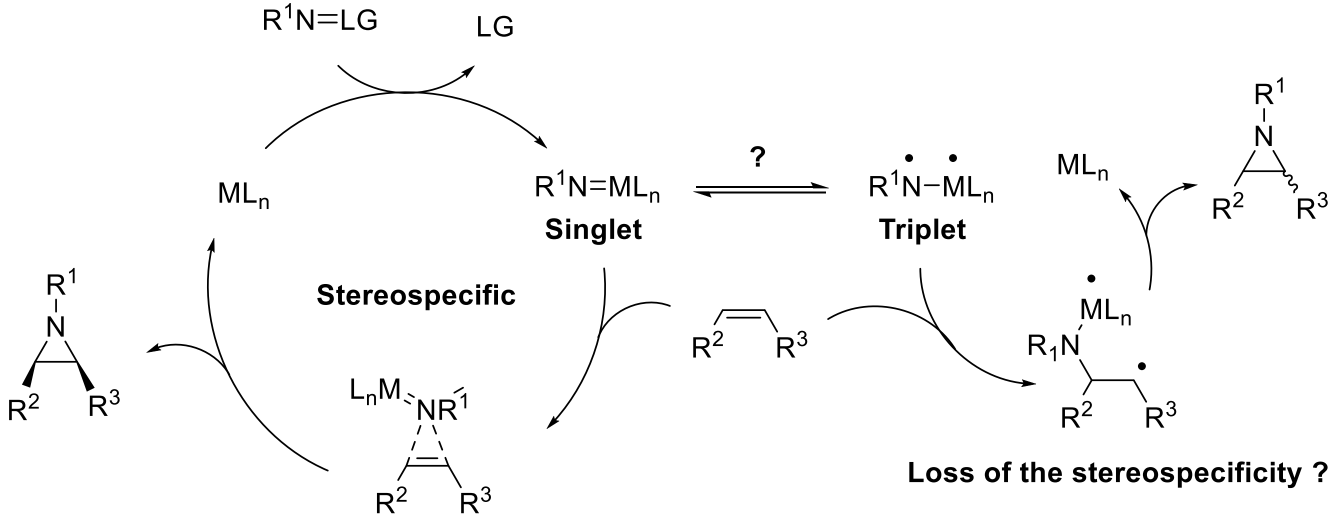
II. Synthesis of aziridine and azetidine

- Addition of Metal-nitrenes to olefins





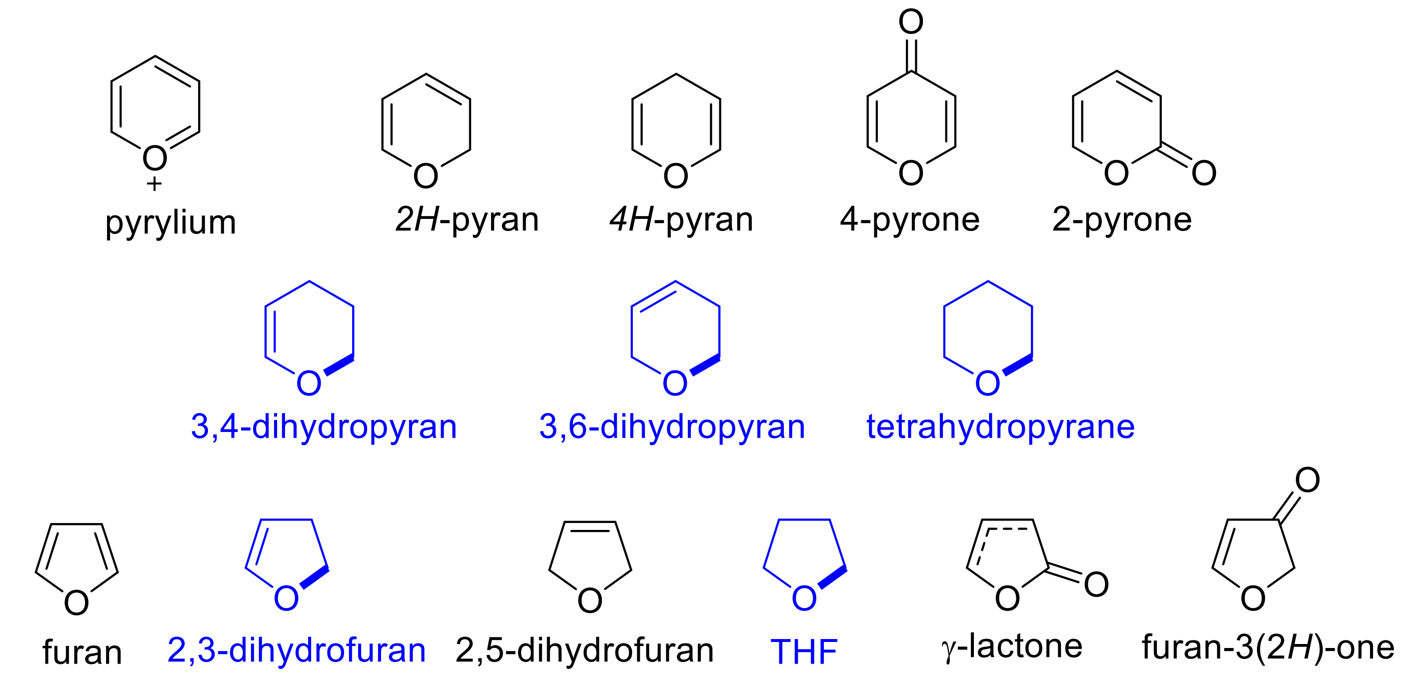
Two possible pathways:



*Oxidative **O**-cyclizations for **O**xacycles*

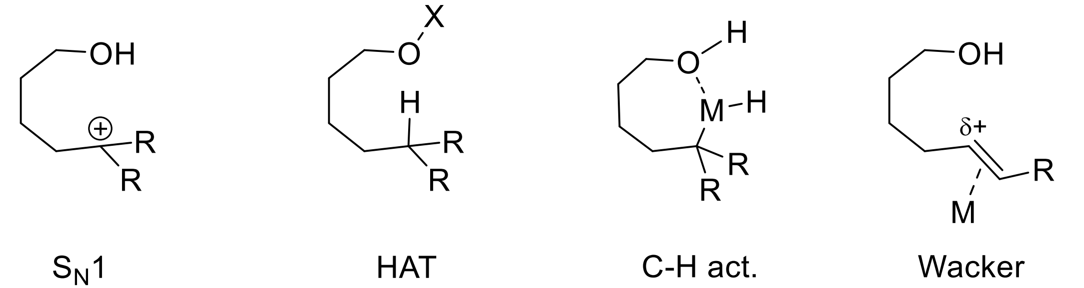
Focus on:

- Non-preactivated substrates
- 6-membered oxacycle construction
- One-pot reactions
- Most recent work in
    - Wacker-cyclization strategy
    - C-H activation strategy
    - HAT strategy



Briefly or Not Discussed:

- Oxidative cyclization of polyenes
- Oxidative lactonizations

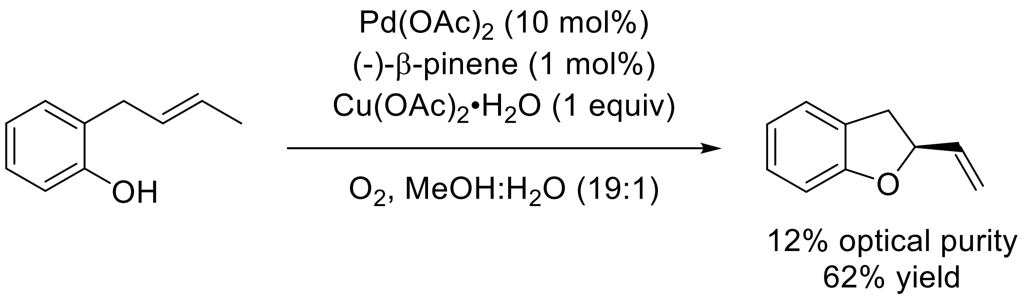


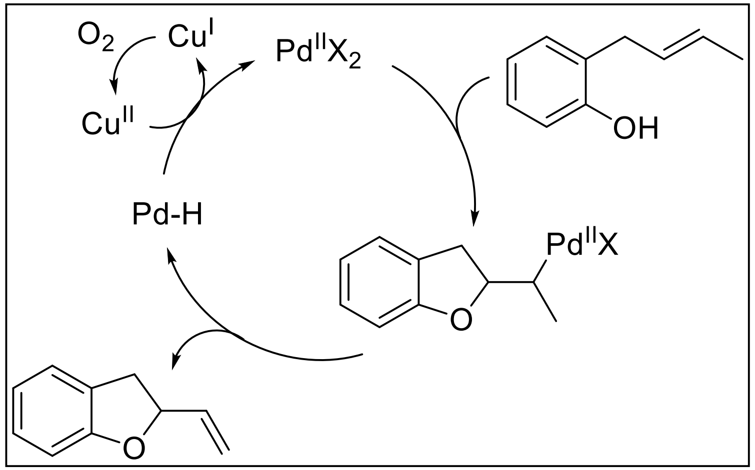
Key reviews

Piccialli, V. *Synthesis (Stuttg).* **2007**, No. 17, 2585–2607.
Rovis, T. *Angewandte Chemie - International Edition*. 2018, pp 62–101.
Nagib, D. A. *Synth.* **2018**, *50* (8), 1569–1586.
Liu, B.; Shi, B. F. *Tetrahedron Lett.* **2015**, *56* (1), 15–22.
Varela, J. A.; Saá, C. *Synth.* **2016**, *48* (20), 3470–3478.
Anilkumar, G. *Tetrahedron* **2016**, *72* (47), 7394–7407.
Čeković, Ž. *Tetrahedron* **2003**, *59* (41), 8073–8090.
Butt, N. A.; Zhang, W. In *Topics in Heterocyclic Chemistry*; 2013; Vol. 10, pp 77–107.
Santamaría, J.; Valdés, C. *Mod. Heterocycl. Chem.* **2011**, *3*, 1631–1682.

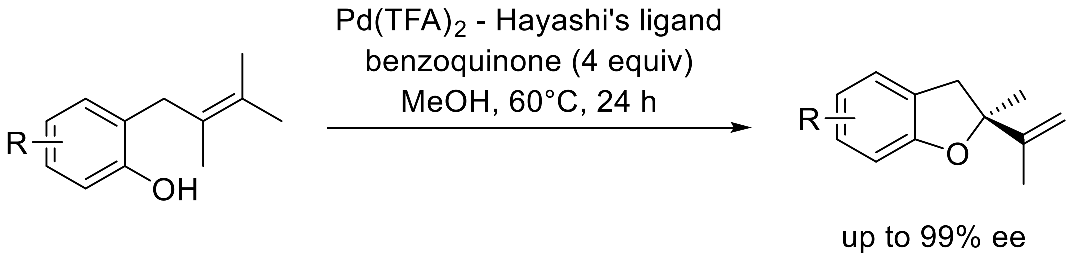
Wacker – cyclization, Seminal Works

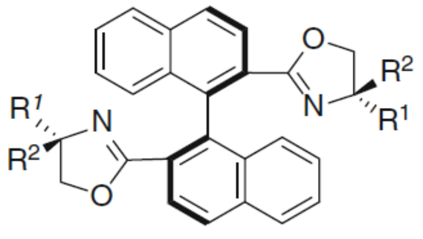
Hosokawa, 1978





Hayashi, 1997





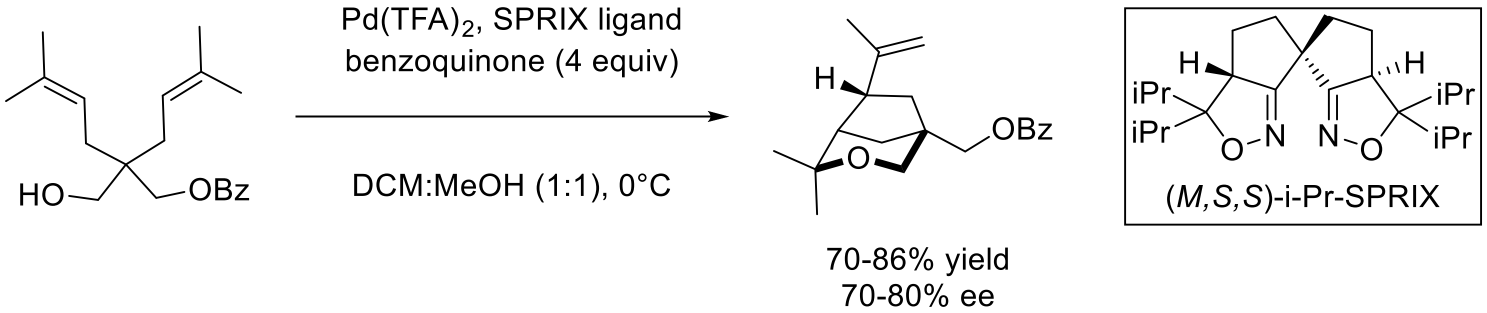
boxax 17

R^1 = Pr, R^2 = H
R^1 = H, R^2 = *i*-Pr
R^1 = Ph, R^2 = H
R^1 = CH_2Ph, R^2 = H

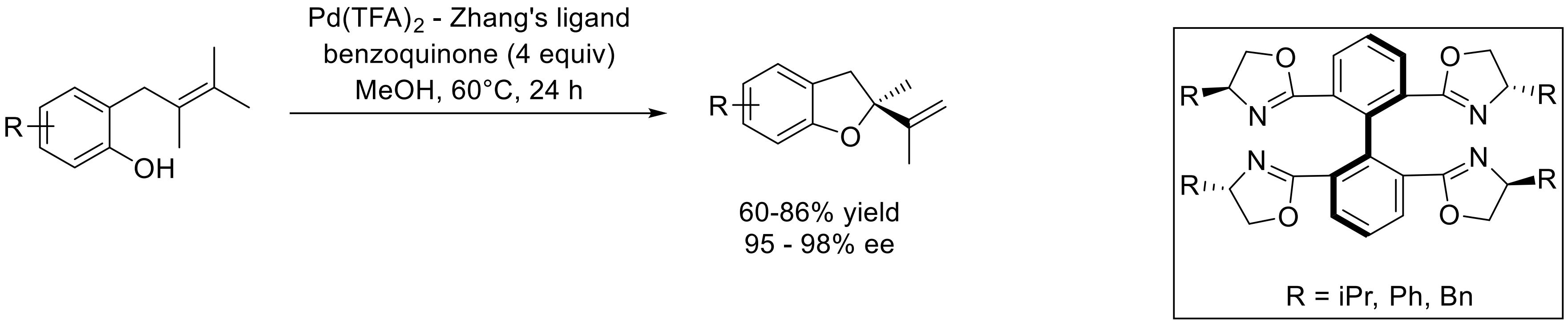
Hosokawa, T. *J. Chem. Soc., Chem. Commun.* **1978**, No. 16, 687–688.
Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119* (21), 5063–5064.

Developments in Enantioselective Wacker – type cyclization

Sasai, 2001



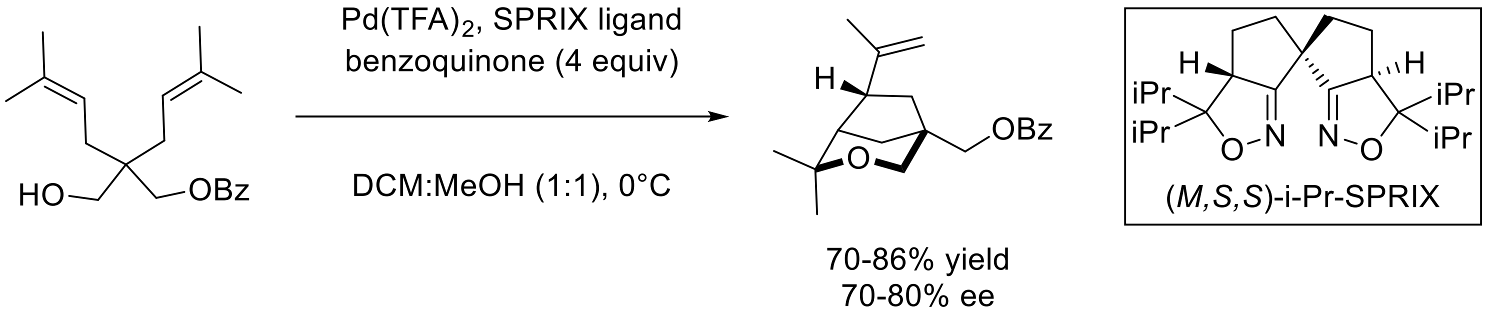
Zhang, 2007



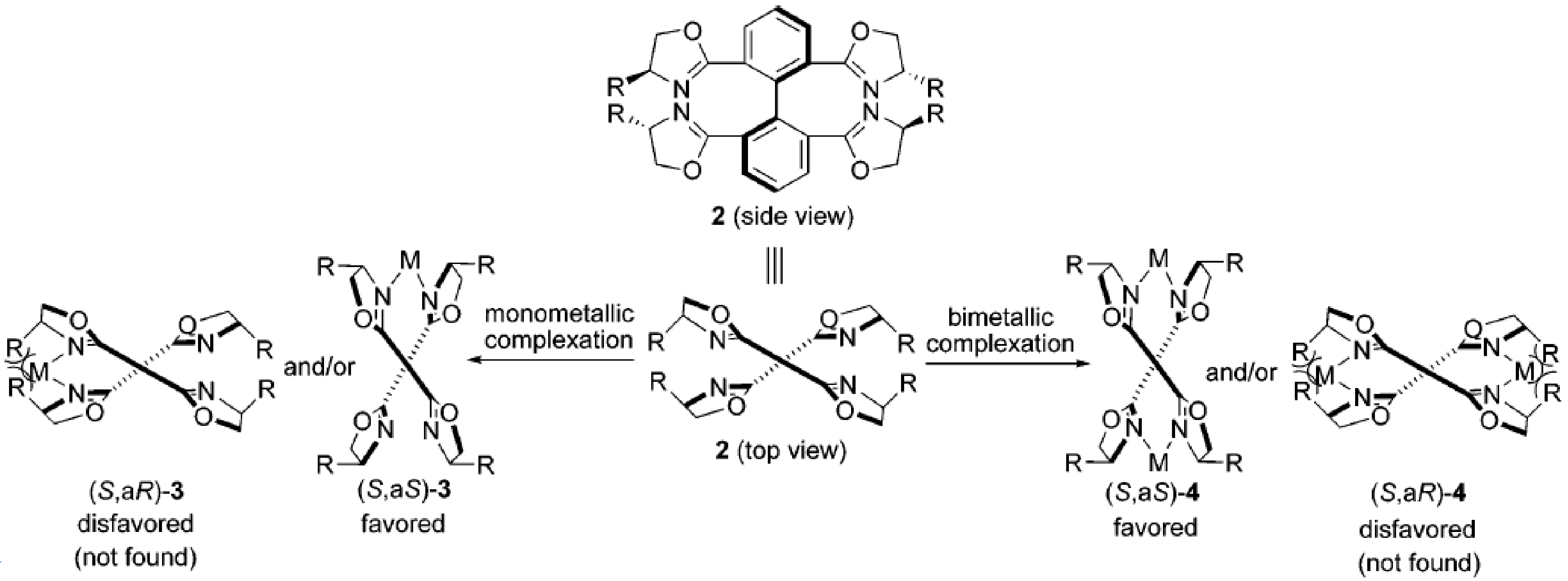
Hosokawa, T. *J. Chem. Soc., Chem. Commun.* **1978**, No. 16, 687–688.
Sasai, H. *J. Am. Chem. Soc.* **2001**, *123* (12), 2907–2908.
Zhang, W. *J. Org. Chem.* **2007**, *72* (24), 9208–9213.

Developments in Enantioselective Wacker – type cyclization

Sasai, 2001



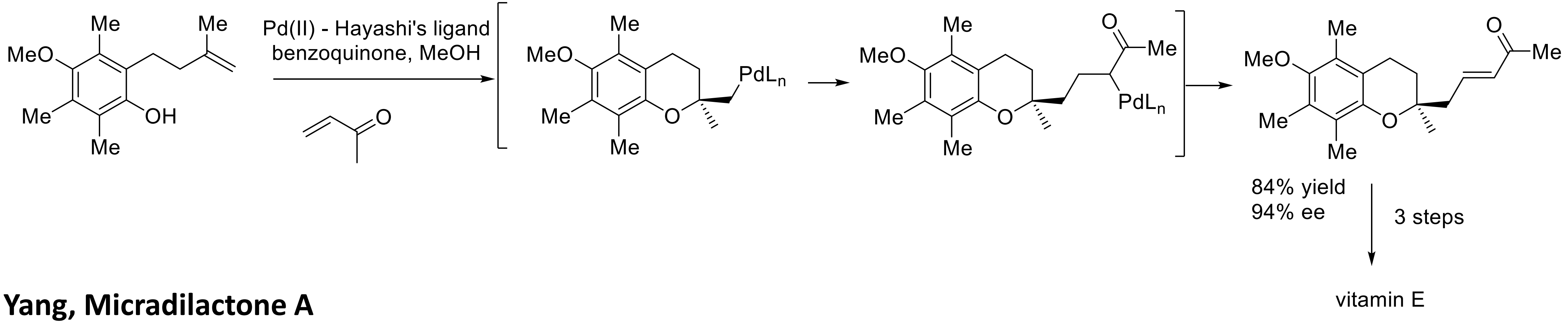
Zhang, 2007



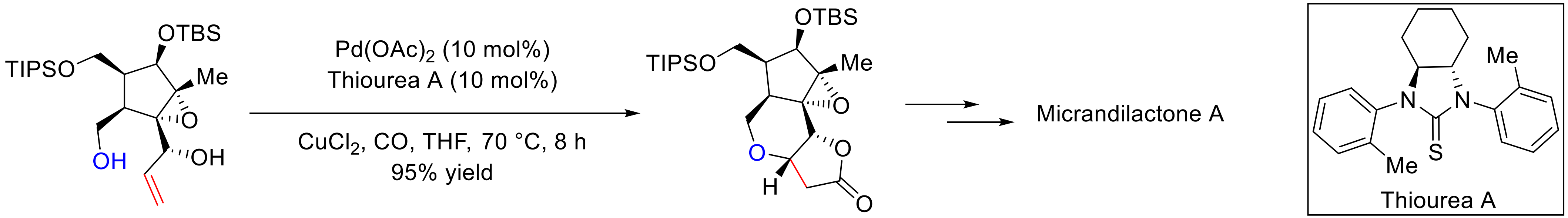
Hosokawa, T. *J. Chem. Soc., Chem. Commun.* **1978**, No. 16, 687–688.
Sasai, H. *J. Am. Chem. Soc.* **2001**, *123* (12), 2907–2908.
Zhang, W. *J. Org. Chem.* **2007**, *72* (24), 9208–9213.

Application in Total Synthesis

Tietze, Vitamin E

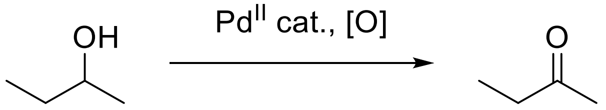


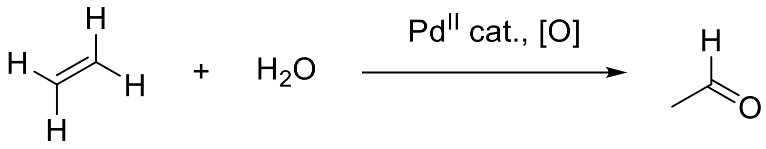
Yang, Micradilactone A

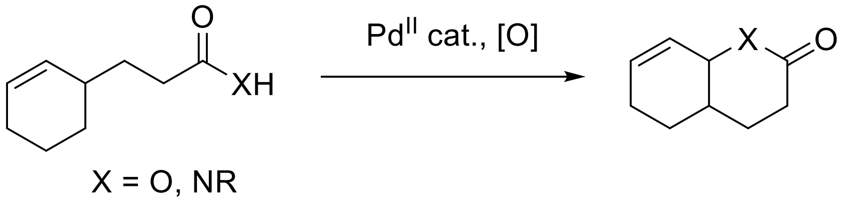


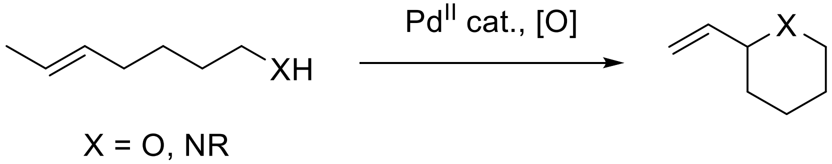
Tietze, L. F. *Angew. Chemie - Int. Ed.* **2004**, *44* (2), 257–259.
Yang, Z. *Org. Lett.* **2005**, *7* (5), 885–888.

Wacker - type cyclization





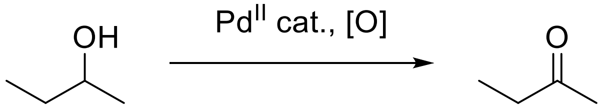


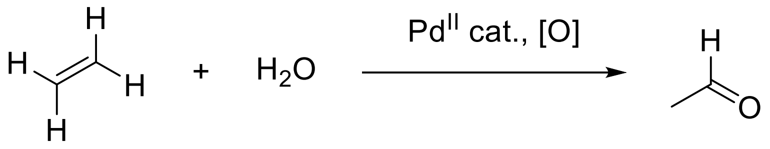


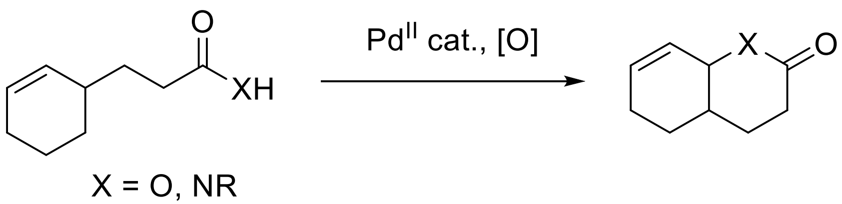
Oxidant: benzoquinone, Cu/ O_2, O_2 / DMSO

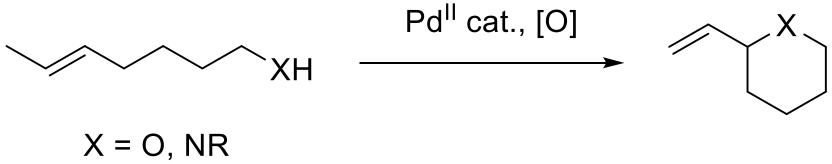
Solvent: DMSO or other polar, coordinating solvent

Wacker - type cyclization









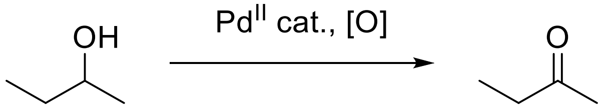
Oxidant: benzoquinone, Cu/ O_2, O_2 / DMSO

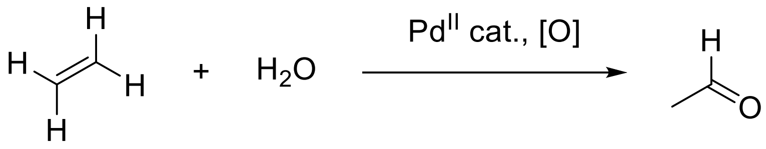
Stoichiometric oxidant needs to be removed

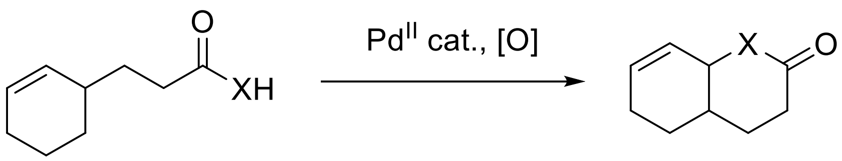
Copper competes with Pd for the ligand

Solvent: DMSO or other polar, coordinating solvent

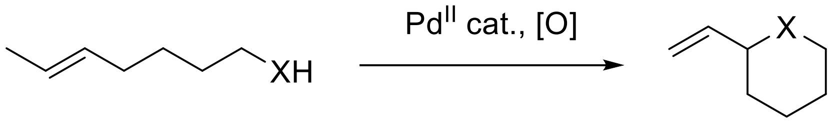
Wacker - type cyclization







X = O, NR



X = O, NR

Oxidant: benzoquinone, Cu/ O_2, O_2 / DMSO

Stoichiometric oxidant needs to be removed

Copper competes with Pd for the ligand

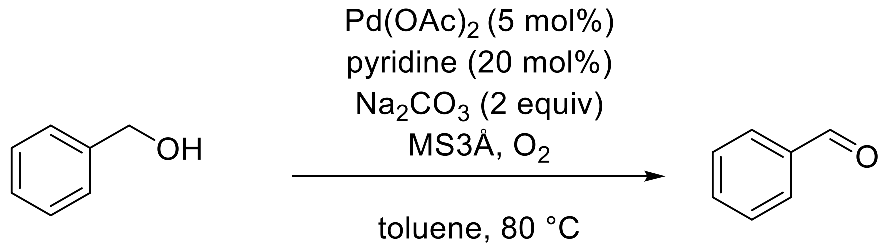
Solvent: DMSO or other polar, coordinating solvent

DMSO is strongly donating, coordinating solvent

Wacker - type cyclization, Stoltz, development

What is the role of molecular sieves?

Uemura - 1999

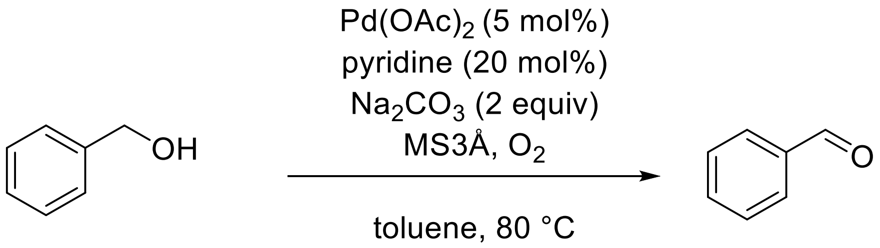


1. Non-coordinating solvent
2. O_2 as terminal oxidant
3. Accelerated by ligand

Wacker - *type cyclization, Stoltz, development*

What is the role of molecular sieves?

Uemura - 1999



1. Non-coordinating solvent
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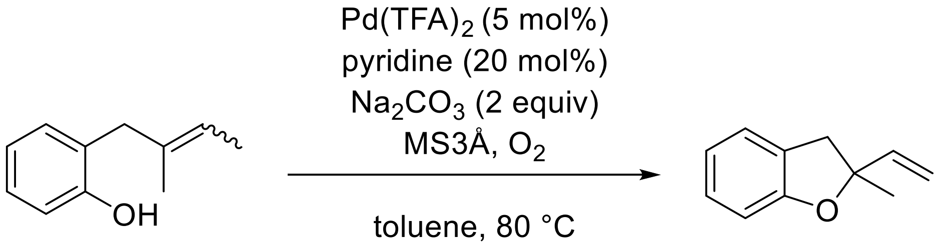
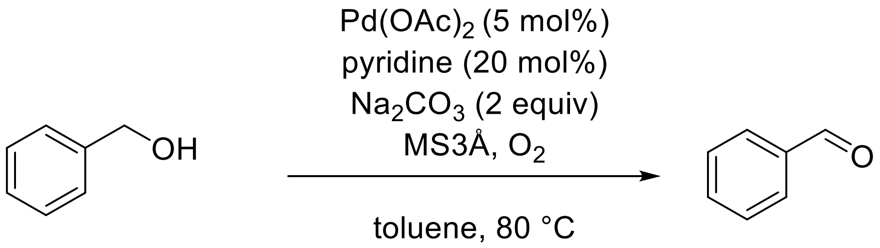
Stoltz - 2005



Wacker - type cyclization, Stoltz, development

What is the role of molecular sieves?

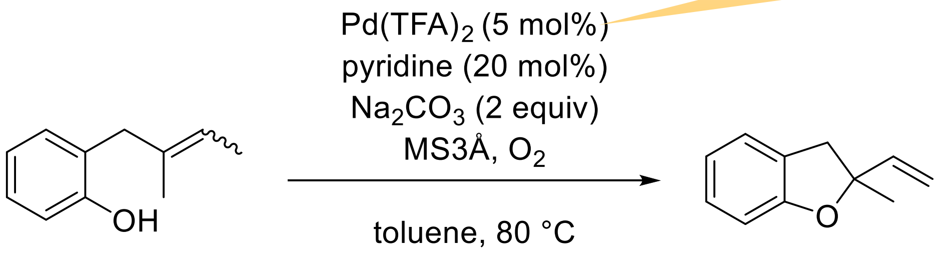
Uemura - 1999



1. Non-coordinating solvent
2. O2 as terminal oxidant
3. Accelerated by ligand

Stoltz - 2005

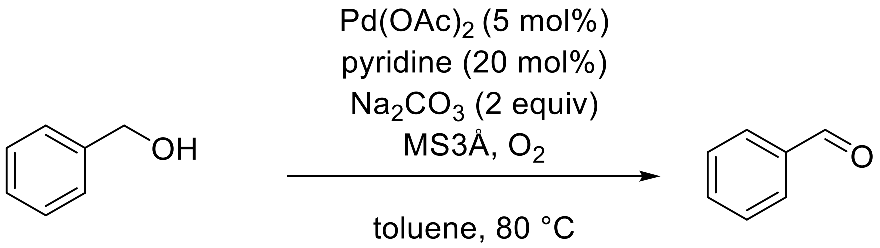
The more electrophilic the better



Wacker - type cyclization, Stoltz, development

What is the role of molecular sieves?

Uemura - 1999

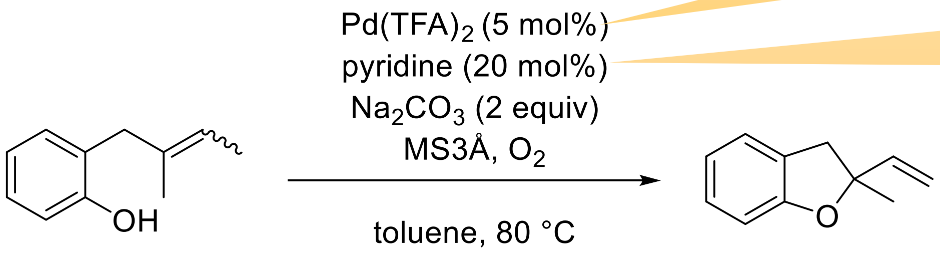


1. Non-coordinating solvent
2. O_2 as terminal oxidant
3. Accelerated by ligand

Stoltz - 2005

The more electrophilic the better

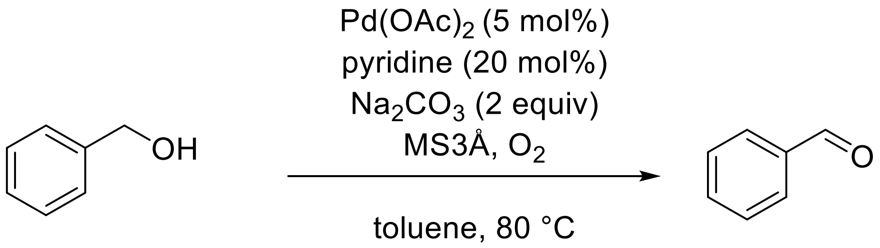
Monodentate pyridine- and nicotinate derivatives are the best



Wacker - type cyclization, Stoltz, development

What is the role of molecular sieves?

Uemura - 1999

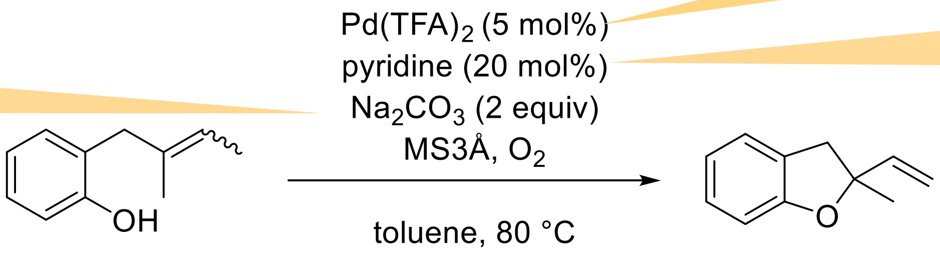


1. Non-coordinating solvent
2. O_2 as terminal oxidant
3. Accelerated by ligand

Stoltz - 2005

The more electrophilic the better

Increases the rate, renders catalyst less stable (Pd black)

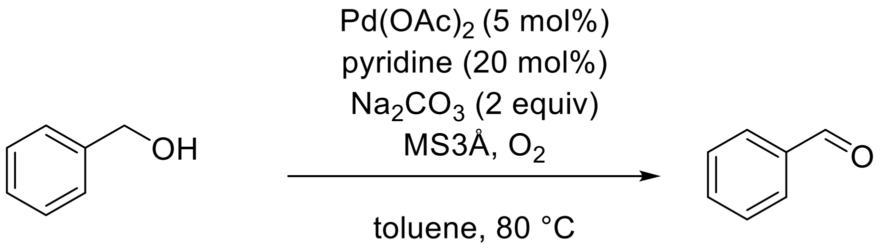


Monodentate pyridine- and nicotinate derivatives are the best

Wacker - *type cyclization, Stoltz, development*

What is the role of molecular sieves?

Uemura - 1999



1. Non-coordinating solvent
2. O_2 as terminal oxidant
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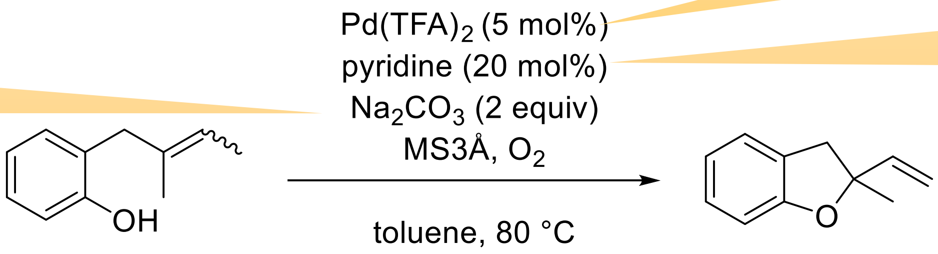


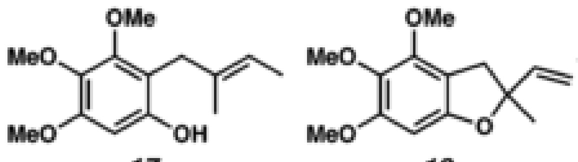
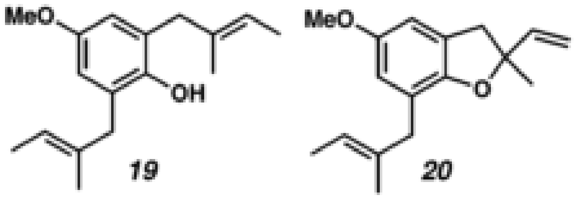
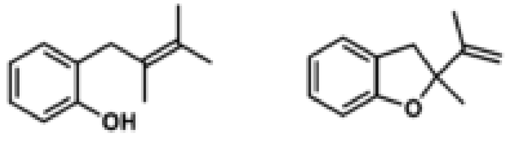
Highly selective to cyclization (vs alcohol oxidation) → substrate and Pd-source controlled.
Work-up = filtration through silica gel, often no need for purification

Uemura, S. *J. Org. Chem.* **1999**, *64* (18), 6750–6755.

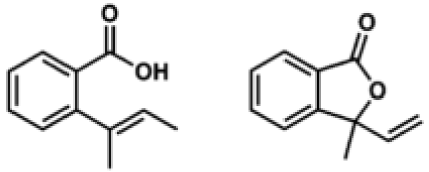
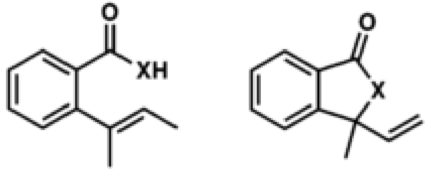
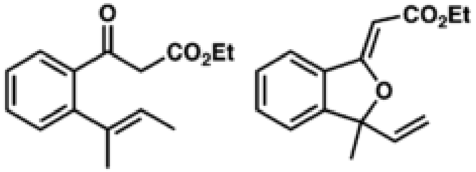
Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127* (50), 17778–17788.

Enantioselective Wacker - type cyclization

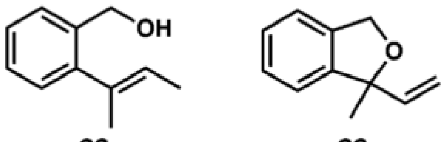
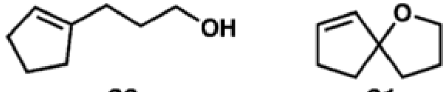
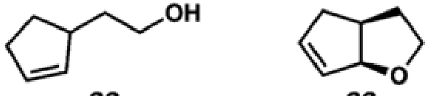
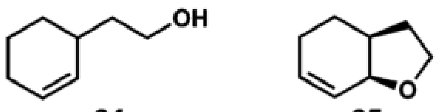
Phenols

entry	substrate	product	time	yield
9.	 17	18	10 min	86%
10.	 19	20	2 h	93%
11.	 21	22	25 min	80%
12.	 23	24	3 h	74%
13.[b]	 25	26	75 min	85%

Carboxylic acids

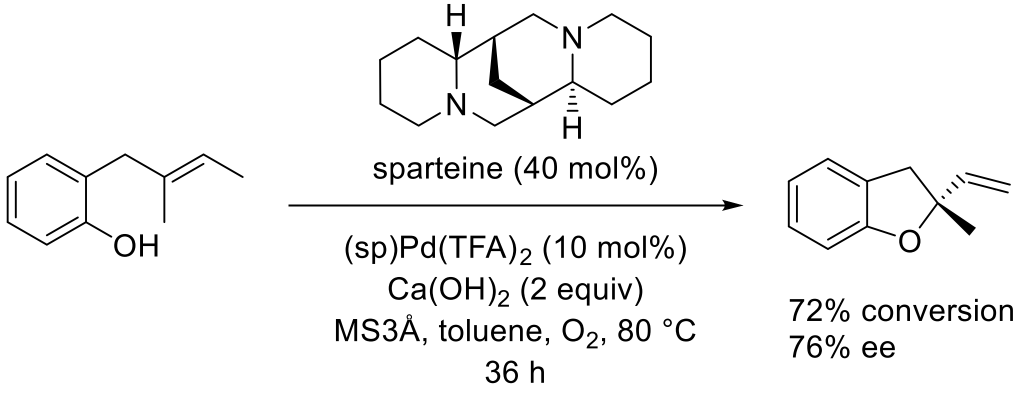
entry	substrate	product		time	yield
1.[b]	 36	37		8 h	90%
2.[b]	 38, 40	39, 41	X = NTs	8 h	88%
3.[b]			X = NOBn	4 h	82%
4.[b]	 42	43		48 h	63% [c,d]
5.	 44	45		48 h	62% [e]
6.	 46	47		2 h	77% [f]
7.	 48	49		12 h	86% [f,g]

Aliphatic alcohols

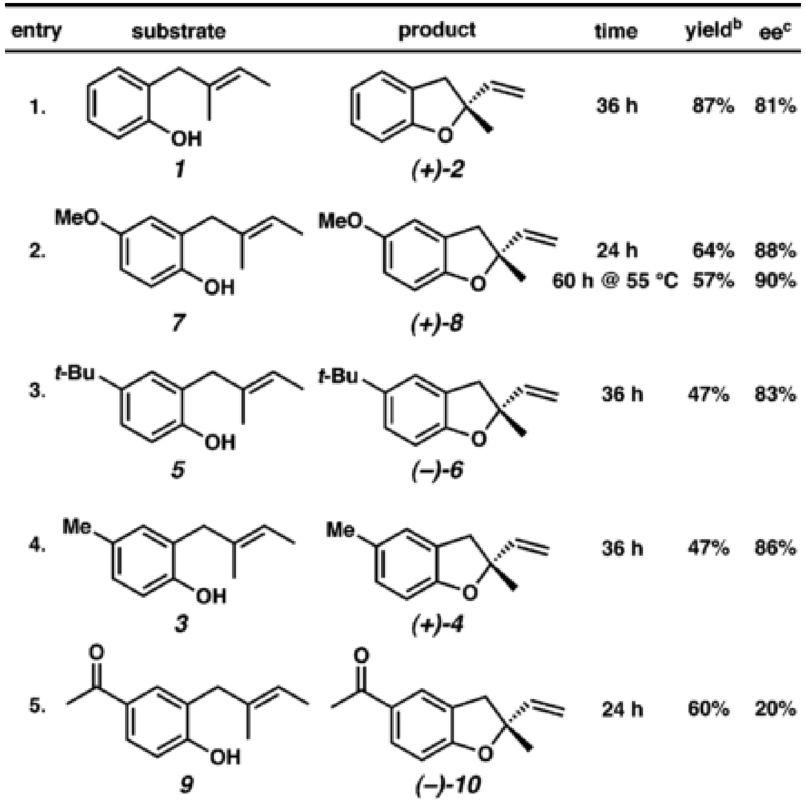
entry	substrate	product	time	yield
1.[b]	 28	29	3 h	87%
2.	 30	31	10 h	93%[c]
3.	 32	33	7.5 h	69%[d]
4.	 34	35	20 h	60%[e]

Enantioselective Wacker - type cyclization

Enantioselective Wacker conditions



Substrate Scope

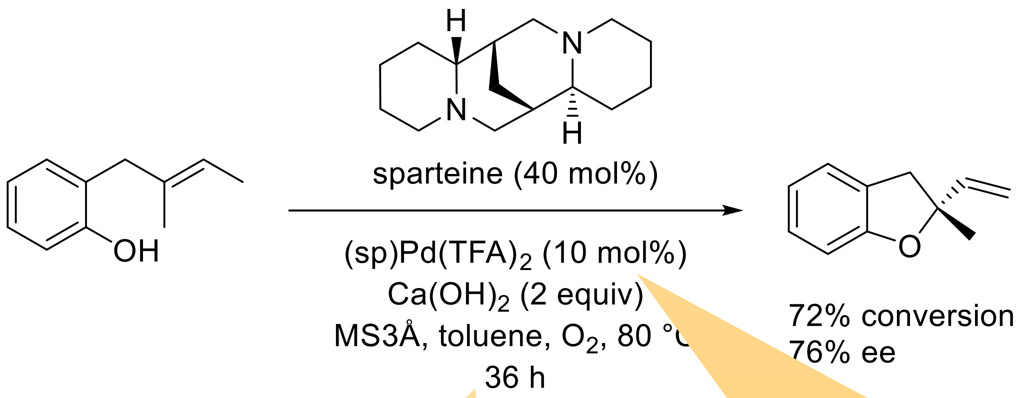


entry	substrate	product	time	yield[b]	ee[c]
1.	1	(+)-2	36 h	87%	81%
2.	7	(+)-8	24 h	64%	88%
			60 h @ 55 °C	57%	90%
3.	5	(−)-6	36 h	47%	83%
4.	3	(+)-4	36 h	47%	86%
5.	9	(−)-10	24 h	60%	20%

Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127* (50), 17778–17788.

Enantioselective Wacker - type cyclization

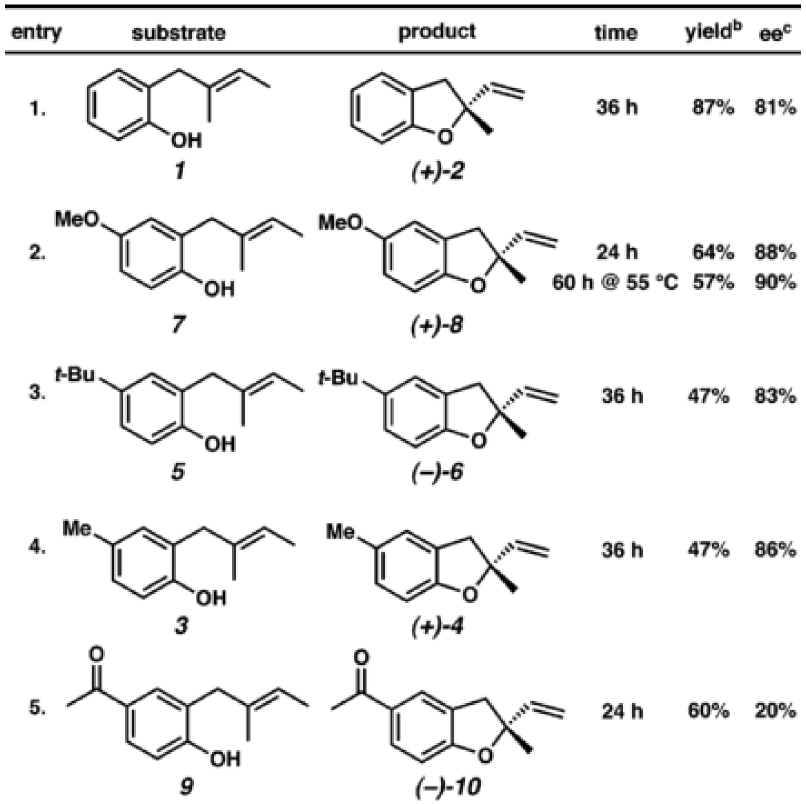
Enantioselective Wacker conditions



Rate drops when sparteine is added.

Conversion and ee varied a lot with different Pd sources.

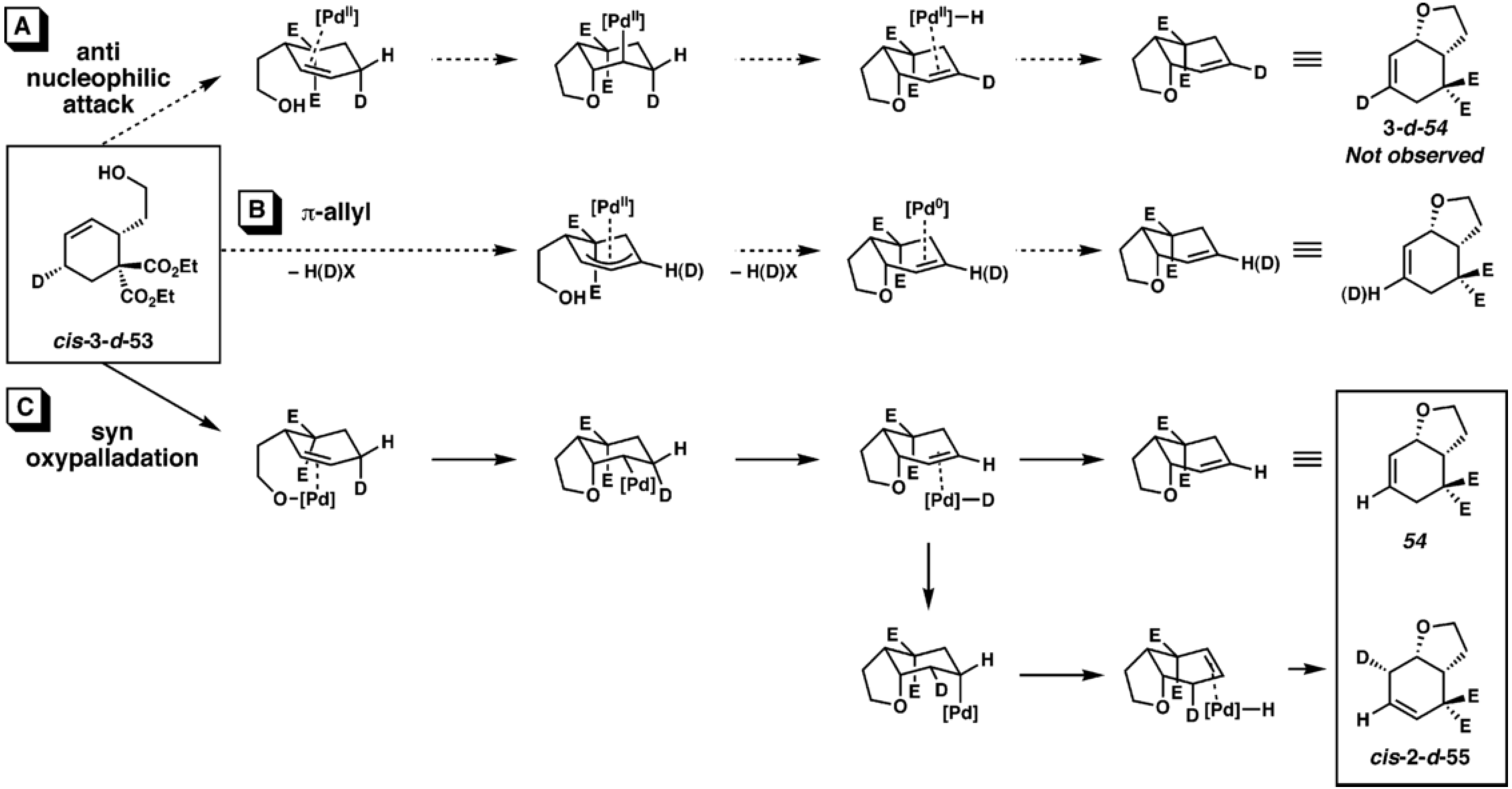
Substrate Scope



entry	substrate	product	time	yield[b]	ee[c]
1.	1	(+)-2	36 h	87%	81%
2.	7 (MeO)	(+)-8 (MeO)	24 h 60 h @ 55 °C	64% 57%	88% 90%
3.	5 (t-Bu)	(−)-6 (t-Bu)	36 h	47%	83%
4.	3 (Me)	(+)-4 (Me)	36 h	47%	86%
5.	9	(−)-10	24 h	60%	20%

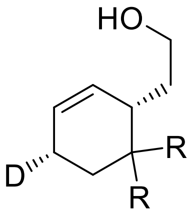
Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127* (50), 17778–17788.

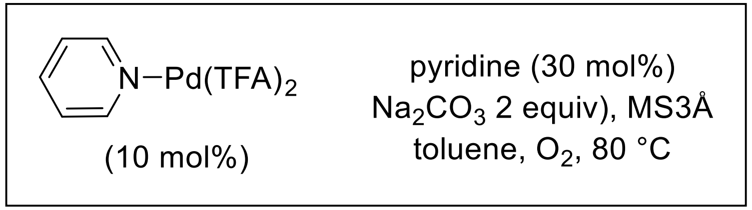
Enantioselective Wacker - type cyclization



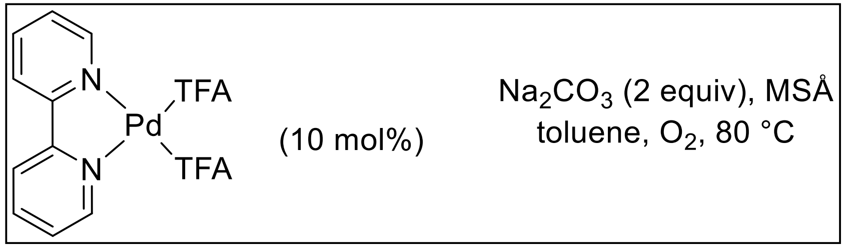
Enantioselective Wacker - type cyclization

Alcohol substrate



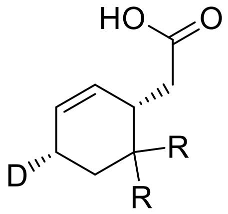


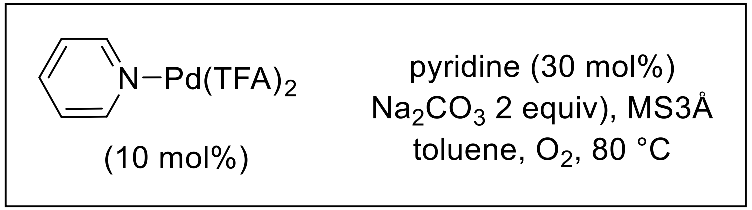
- **Syn-oxypalladation**
- Good yields
- Fast reaction



- **Syn-oxypalladation**
- Moderate yields
- Slow reaction
- Alcohol oxidation as side reaction

Carboxylic acid substrate





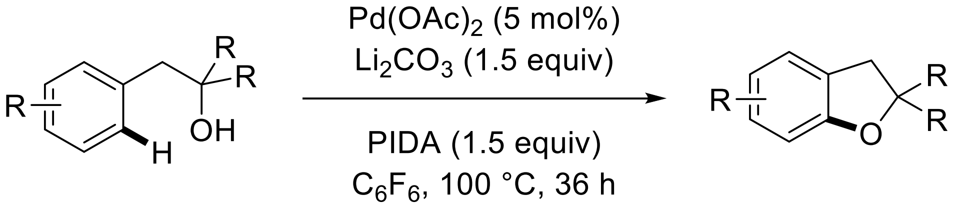
- **Anti-oxypalladation**
- Moderate yields
- Slow reaction

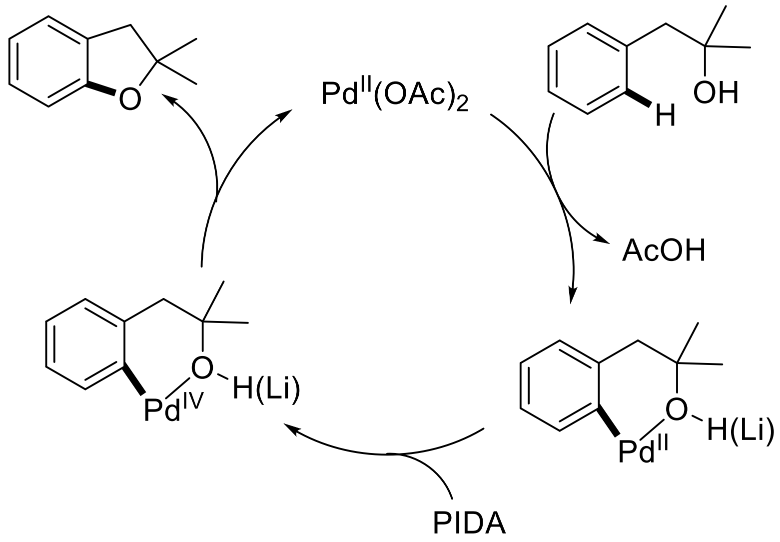
Summary

- Monodentate ligand > bidentate ligand
  - Monodentate ligand → better stabilizes TS
  - Monodentate ligand → difficult asymmetric-induction
- Both syn- and anti-oxypalladation are possible

C-H activation

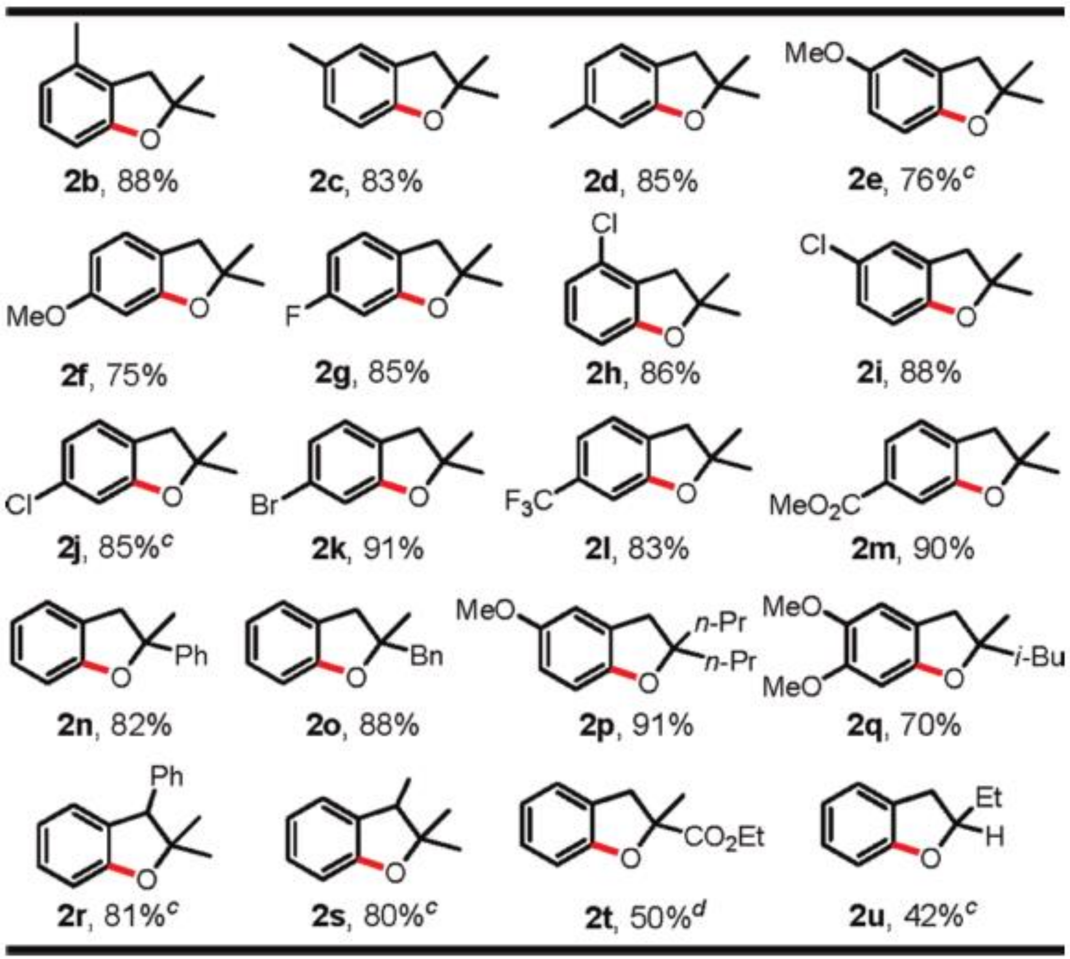
Yu, 2010 – seminal work





Yu, J. *J. Am. Chem. Soc.* **2010**, *132* (35), 12203–12205.
Yu, J. Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135* (18), 6774–6777.

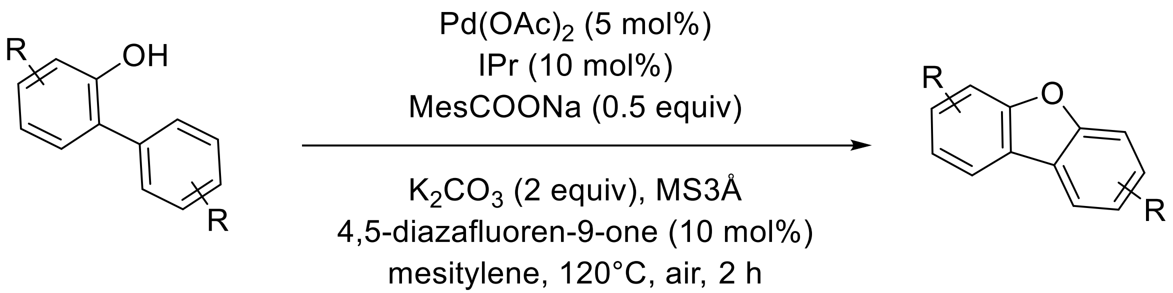
- Pd(II) / Pd (IV) cycle
- FGs are tolerated on aryl
- Harsh conditions limit the scope
- Orthogonal to Pd(0) coupling chemistry

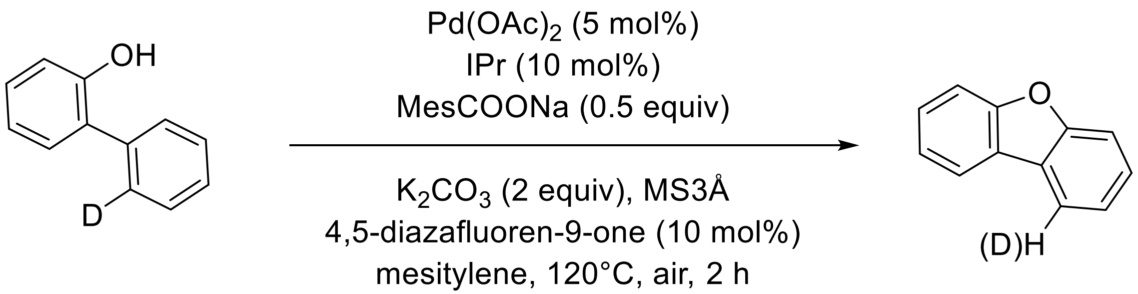


C-H activation

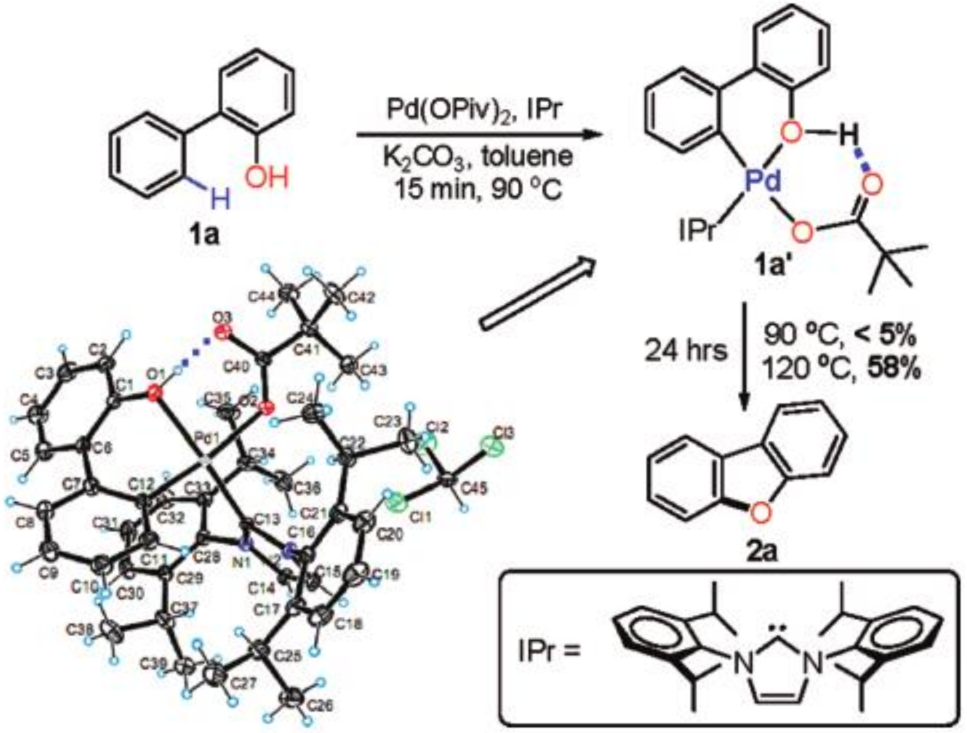
Liu, 2011

- Phenol directed
- Pd(0) / Pd(II)
- Air is the oxidant
- Milder conditions
- Pivalate additive acts as proton shuttle
- C-O red. elim. is turnover limiting





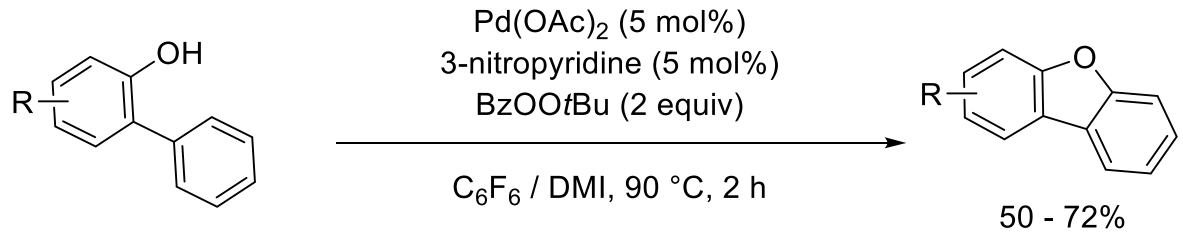
KIE = 1.0



Liu, L. *J. Am. Chem. Soc.* **2011**, *133* (24), 9250–9253.

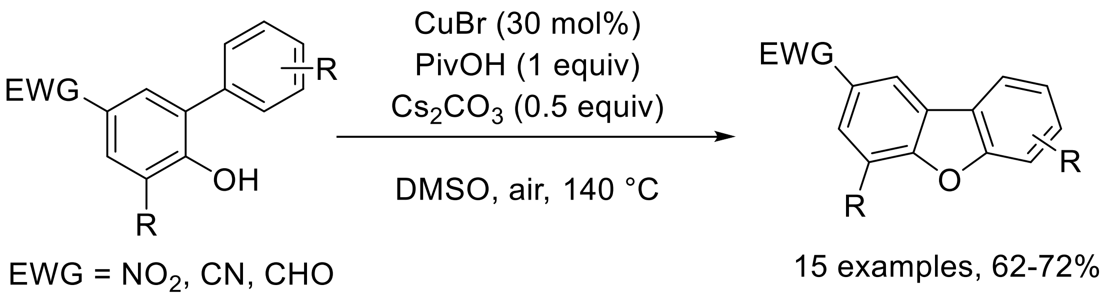
C-H activation

Yoshikai, 2011

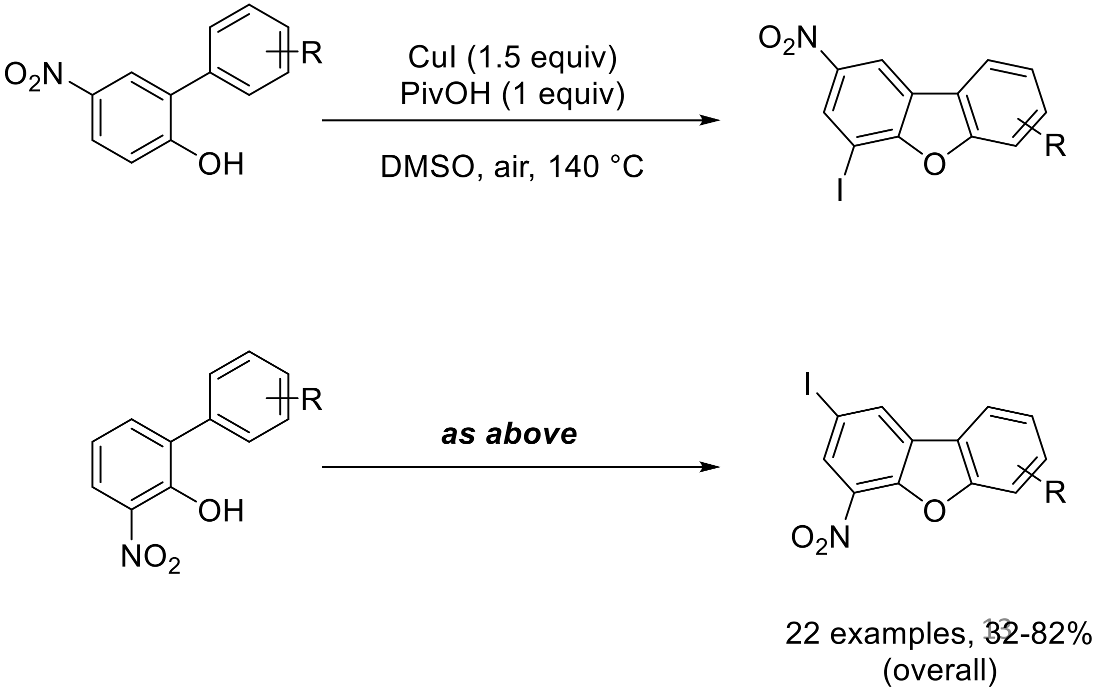


- Pd(II)/Pd(IV) cat. system
- C-H bond cleavage is rate limiting and irreversible

Zhu, 2011



Zhu, 2012

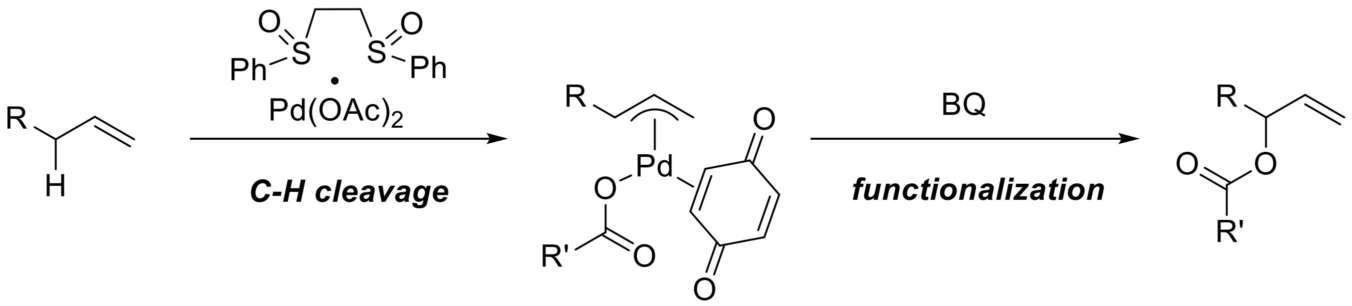


Yoshikai, N. *Org. Lett.* **2011**, *13* (20), 5504–5507.
Zhu, Q. *Org. Lett.* **2012**, *14* (20), 5362–5365.
Zhu, Q. *Org. Lett.* **2012**, *14* (4), 1078–1081.

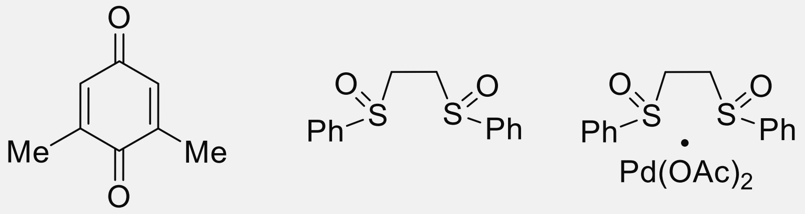
C-H activation, White, Serial Ligand Catalysis

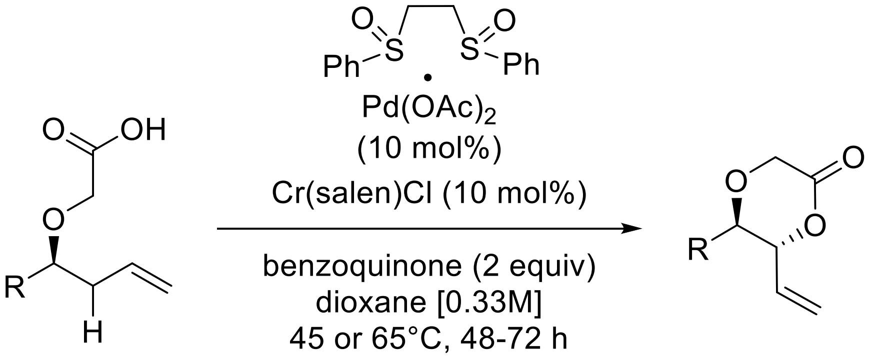
C-H oxidations include

- Amination
- Acetoxylation
- Alkoxylation
- Alkylation
- Macrolactonization



Mechanistic studies

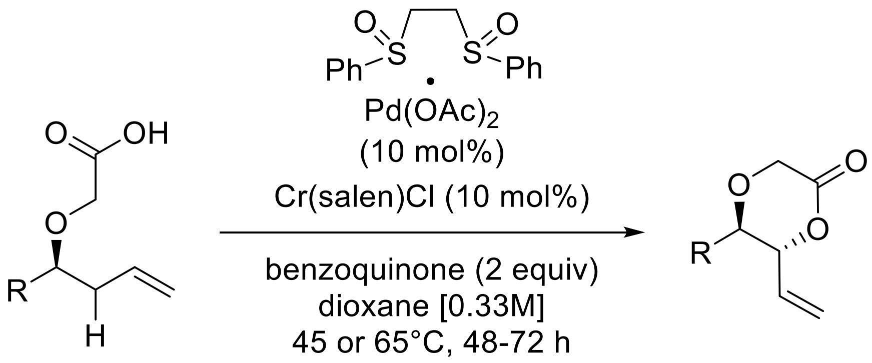


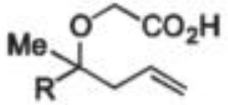
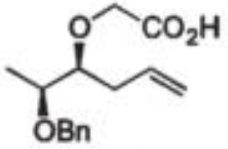
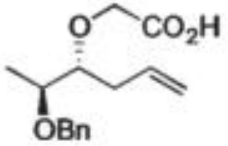


White, M. C. *J. Am. Chem. Soc.* **2005**, *127* (19), 6970–6971.
White, M. C. *J. Am. Chem. Soc.* **2011**, *133* (32), 12584–12589.
White, M. C. *Angew. Chemie Int. Ed.* **2008**, *47* (34), 6448–6451.
White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.
White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707.
White, M. C. *J. Am. Chem. Soc.* **2004**, *126* (5), 1346–1347.
White, M. C. *J. Am. Chem. Soc.* **2006**, *128* (28), 9032–9033.

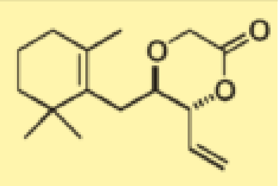
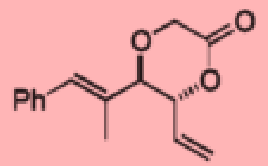
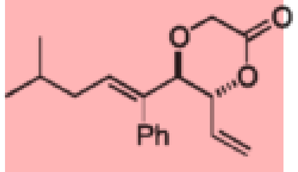
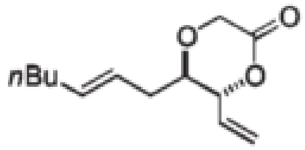
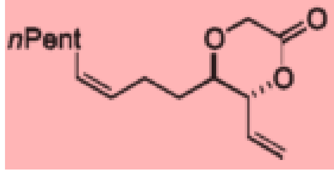
Selectivity and Scope

Comparison with SAP?



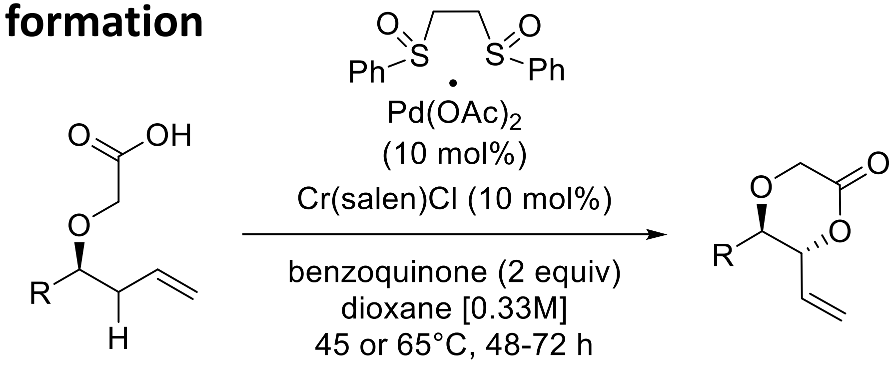
entry	R	product	isolated yield[a]	dr (anti:syn)[b]
1	*i*-Pr	(-)-**6a**	83 (80)[c]	9:1[d]
2	4-BrPh	**6b**	57	3:1
3	*n*-Pent	**6c**	82	2:1
4	*t*-Bu	**6d**	22	11:1
5		**6e** R=Ph	57	3:1
6		**6f** R=*n*-Bu	60	3:1
7		(-)-**6g**	62	8:1
8		(+)-**6h**	62	4:1

Demonstration of Chemo- and Regioselectivity

entry	product		isolated yield[a]	dr (anti:syn)[b]
1		**8a**	74	4:1
2		**8b**	77	6:1
3		**8c**	53	7:1
4		**8d**	72	3:1
5		**8e**	52	2:1

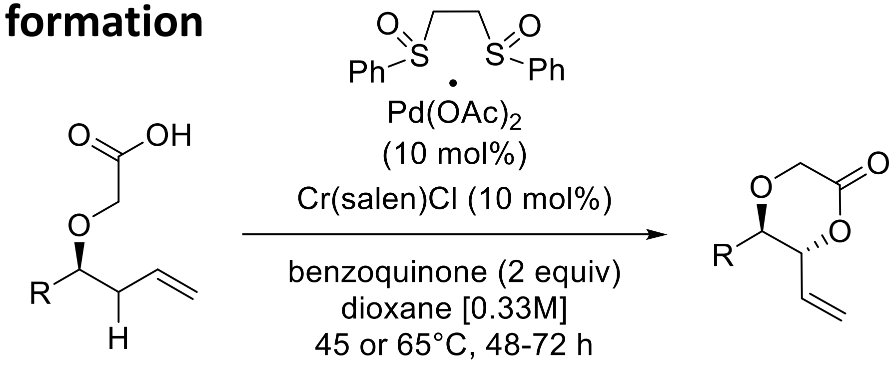
Extension of the Methodology, Substrate Scope

Lactone formation

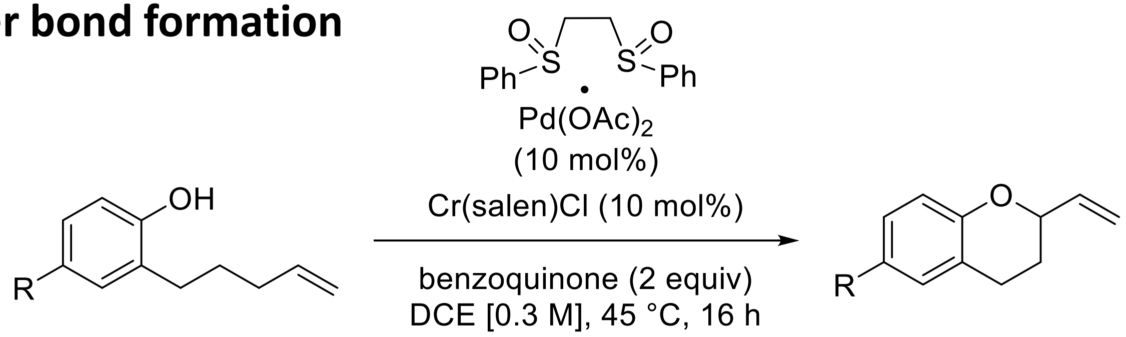


Extension of the Methodology, Substrate Scope

Lactone formation



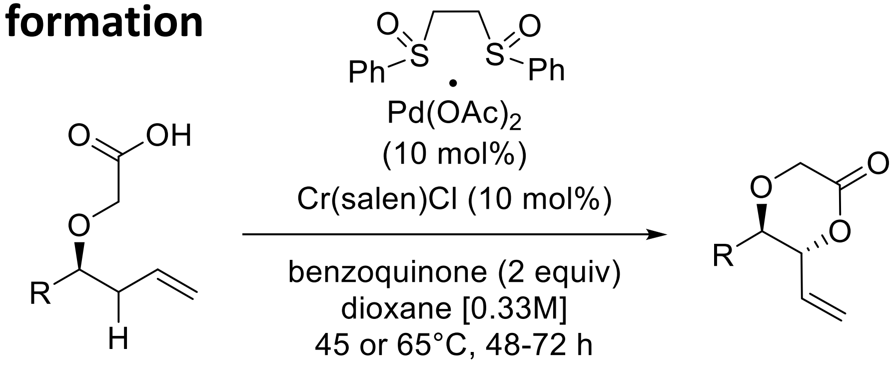
Ether bond formation



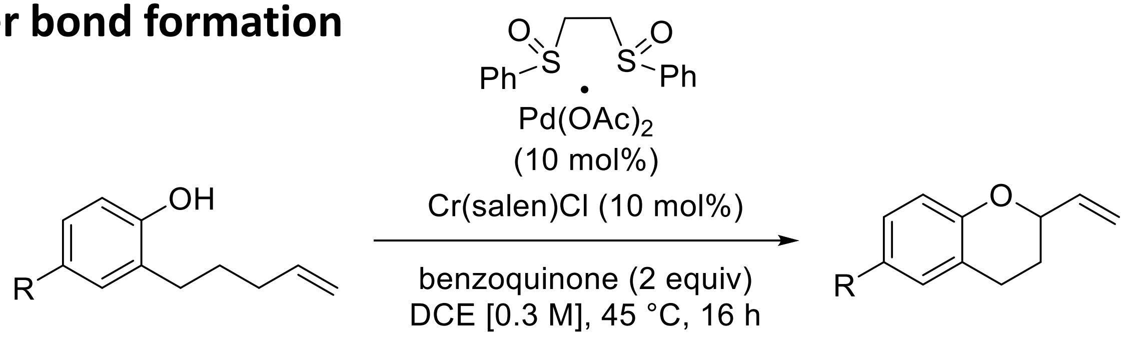
White, M. C. *J. Am. Chem. Soc.* **2014**, *136* (31), 10834–10837.

Extension of the Methodology, Substrate Scope

Lactone formation



Ether bond formation



White, M. C. *J. Am. Chem. Soc.* **2014**, *136* (31), 10834–10837.

Scope

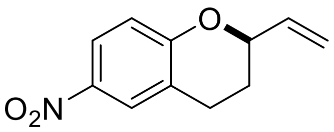
Chromans (20 ex., 57-88%)

Isochromans (4 ex., 65-76%)

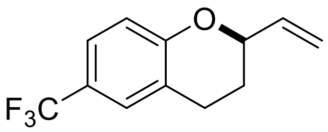
Pyrans (4 ex., 41-86%)

Substrate Scope – A Closer Look

Chromans



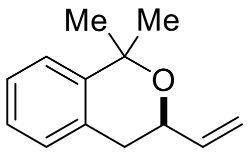
66%



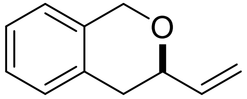
81%

poor reactivity under Pd(0) allylic
subst. conditions

Isochromans



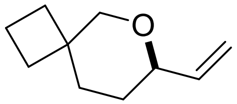
65%



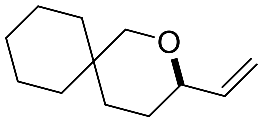
76%

no Thorpe-Ingold effect

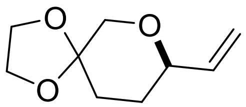
Tetrahydropyrans



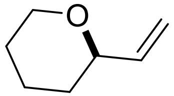
72%



76%



86%



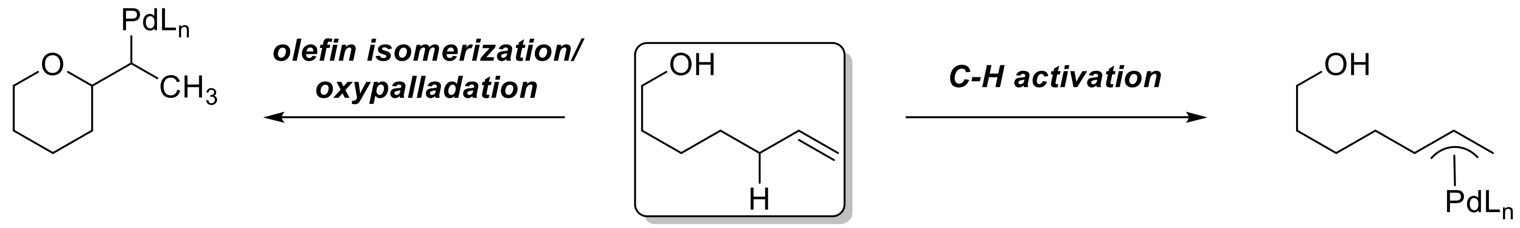
41% (79% brsm)

Thorpe-Ingold effect

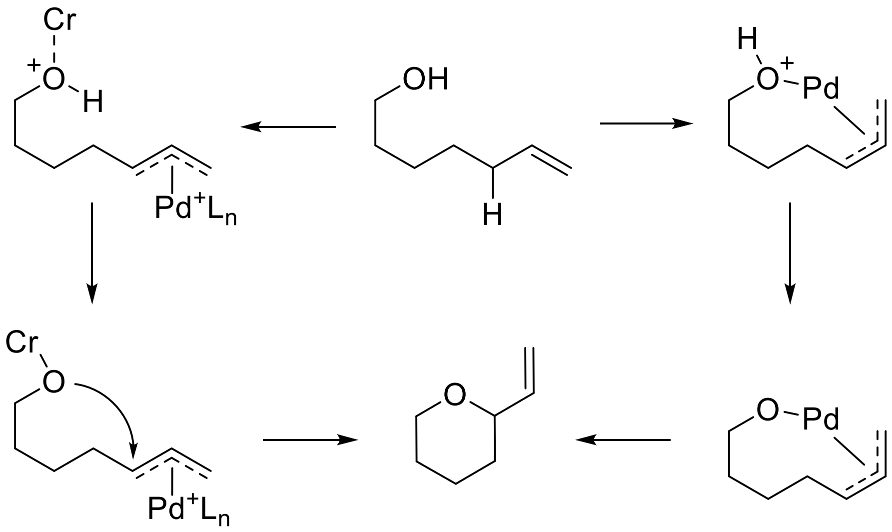
C-H activation, Mechanistic Studies

Pd(OAc)$_2$ • ligand (10 mol%)
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h

Isomerization / Oxypalladation pathway



Tsuji-Trost like reactivity

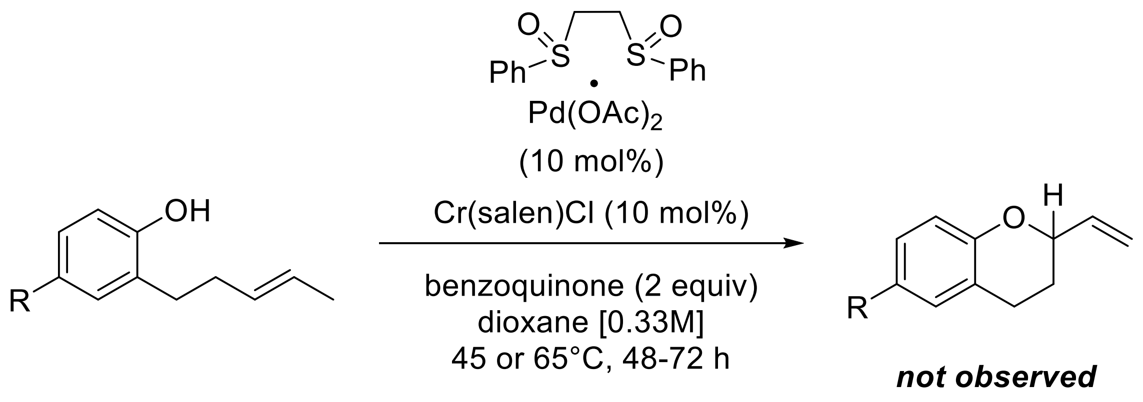


outer sphere mechanism

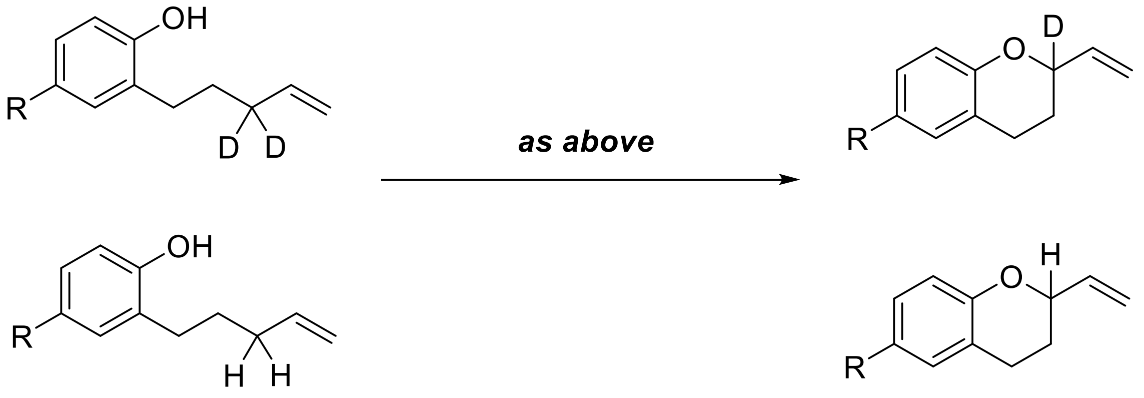
inner sphere mechanism

Isomerization/Oxypalladation vs C-H cleavage

Oxypalladation pathway



Deuterium labeling study



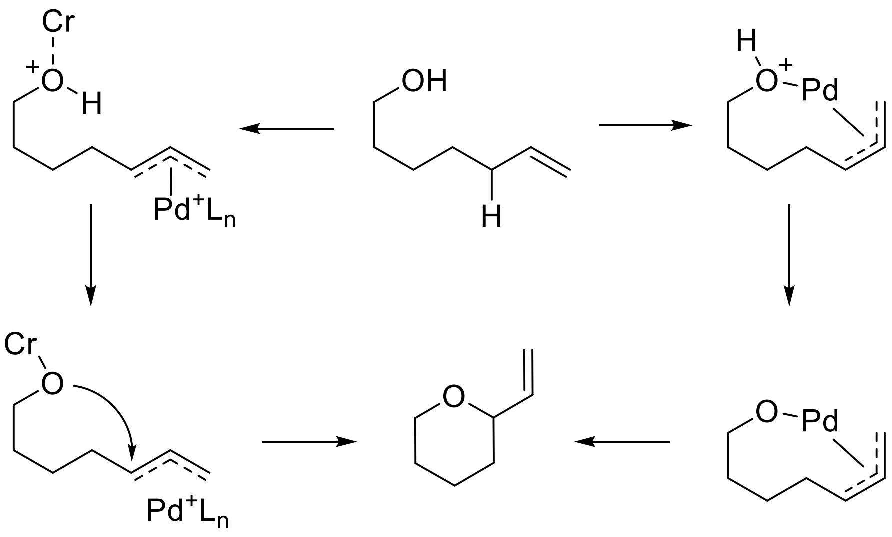
Entry	R	Rate (k(D)/k(H)
1	H	1.8
2	NO2	3.3
3	Ome	1.7

- C-H cleavage is not completely RD
- Deprotonation/functionalization is not completely RD
- KIE reflects multiple steps

Hartwig, J. F. *Angew. Chemie - Int. Ed.* **2012**, *51* (13), 3066–3072.

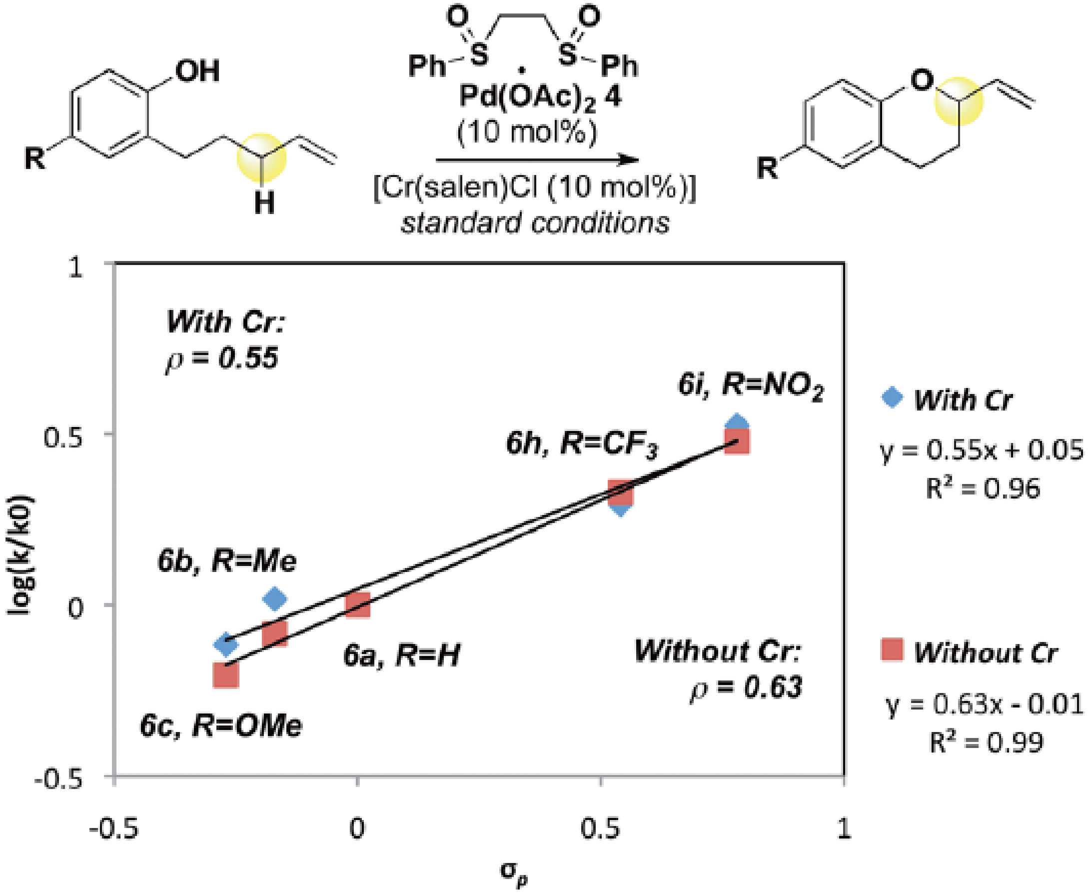
Outer Sphere vs Inner Sphere?

Role of Cr(salen)Cl



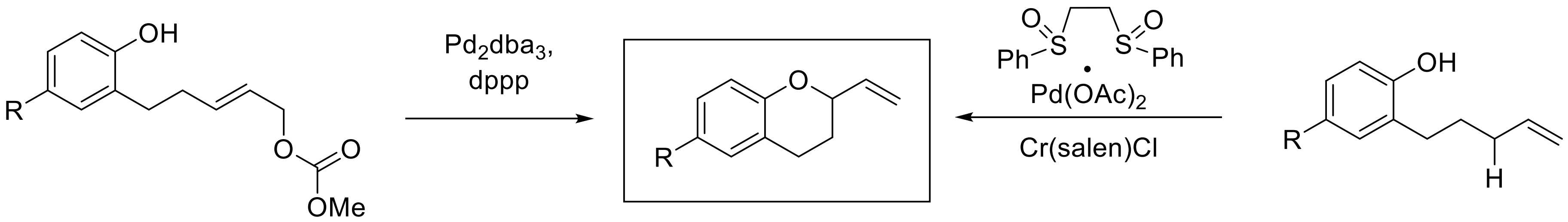
outer sphere mechanism

inner sphere mechanism



Outer Sphere vs Inner Sphere?

Tsuji-Trost like reactivity?

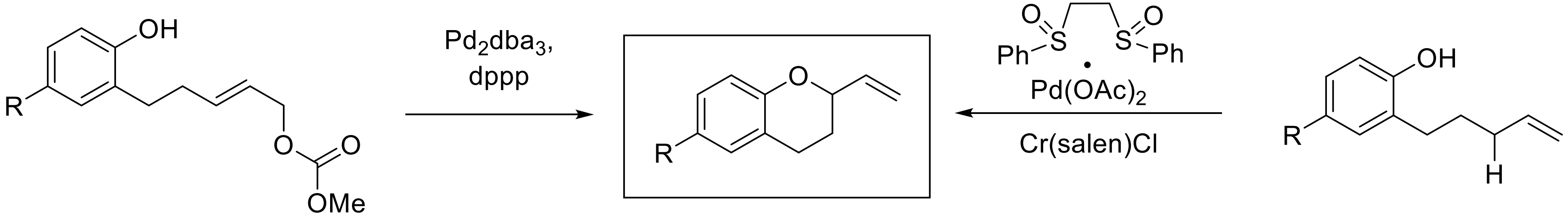


Entry	R	Rate (k(R)/k(H))	Yield
1	H	-	84%
2	NO2	0.03	7%
3	CF3	0.1	11%

Entry	R	Rate (k(R)/k(H))	Yield
1	H	-	79%
2	NO2	3.3	66%
3	CF3	2	81%

Outer Sphere vs Inner Sphere?

Tsuji-Trost like reactivity?



Entry	R	Rate (k(R)/k(H)	Yield
1	H	-	84%
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3	CF3	0.1	11%

Entry	R	Rate (k(R)/k(H)	Yield
1	H	-	79%
2	NO2	3.3	66%
3	CF3	2	81%

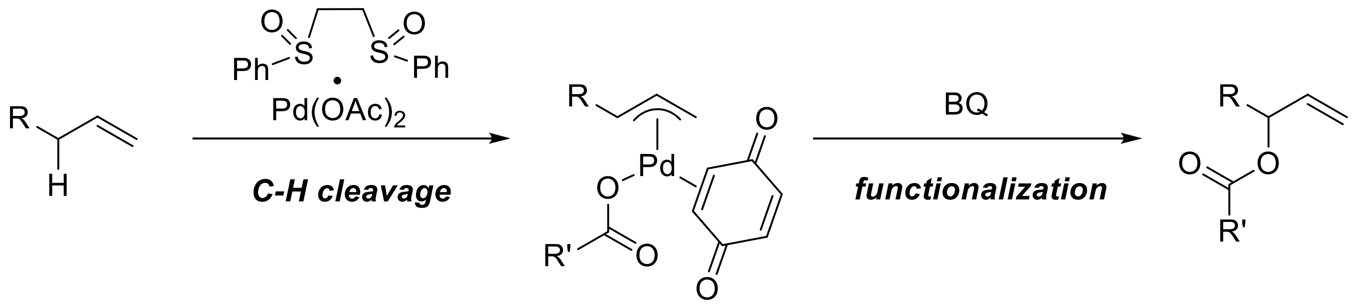
Author's conclusion:

- Outer sphere mechanism cannot be ruled out
- Dramatic change in reactivity → Inner sphere mechanism is likely
- Alternatively: different π-allylPd formation mechanism

Design of an Enantioselective Transformation

Challenges

Pd(OAc)$_2$ • ligand (10 mol%)
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h



White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

Design of an Enantioselective Transformation

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Pd(OAc)$_2$ • ligand (10 mol%)
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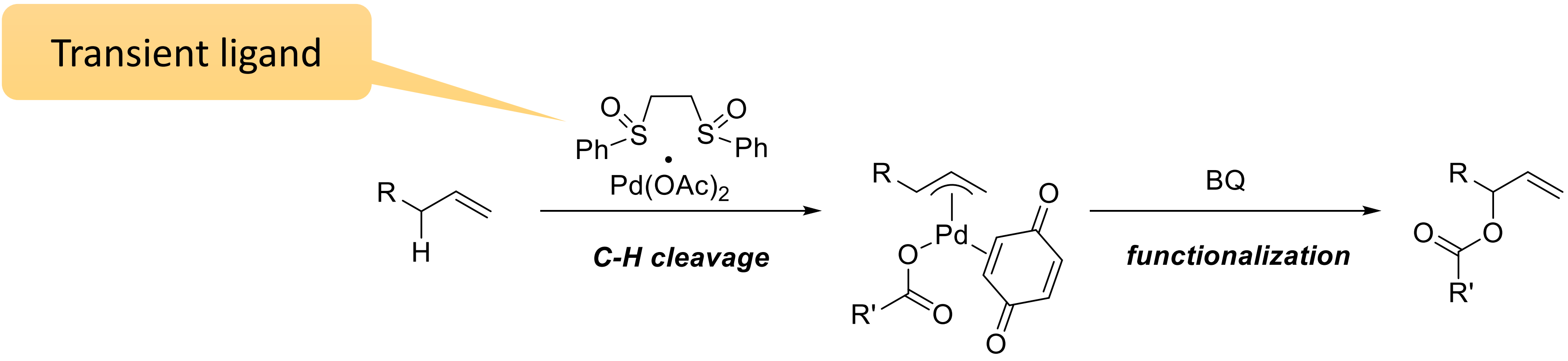
DCE [0.3 M], 45 °C, 16 h



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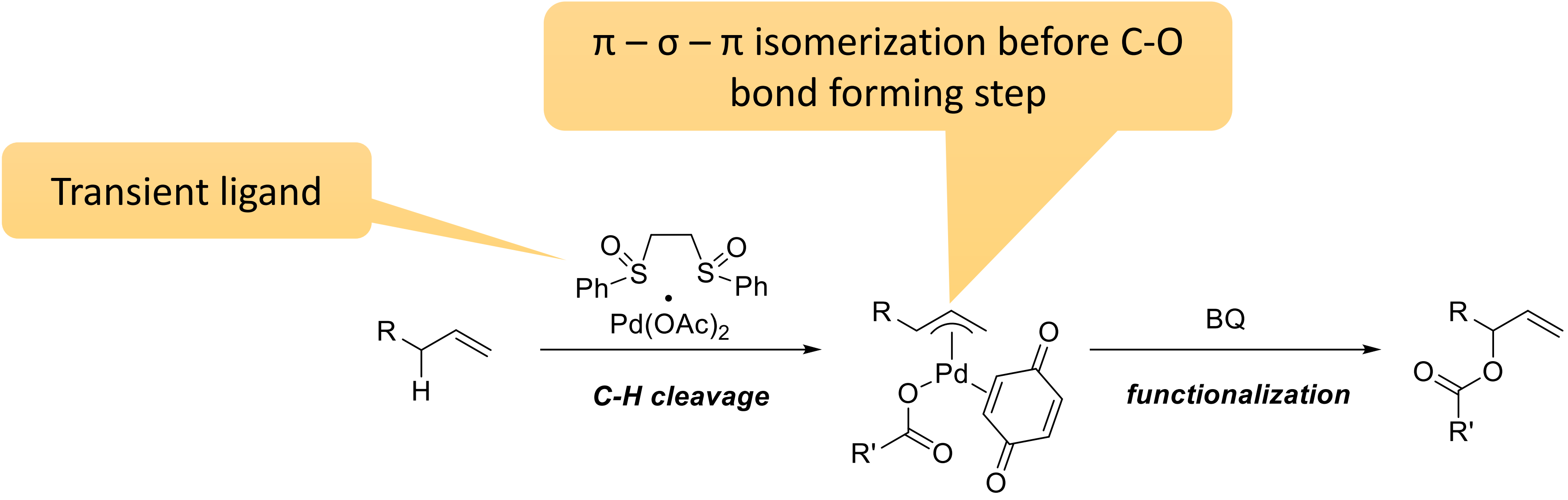
Design of an Enantioselective Transformation

Challenges



$Pd(OAc)_2$ • ligand (10 mol%)
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h

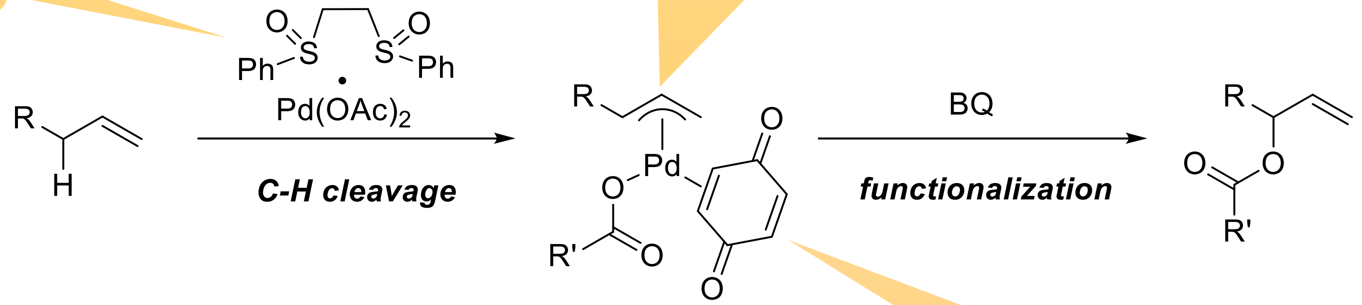
White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

Design of an Enantioselective Transformation

Challenges

π – σ – π isomerization before C-O bond forming step

Transient ligand

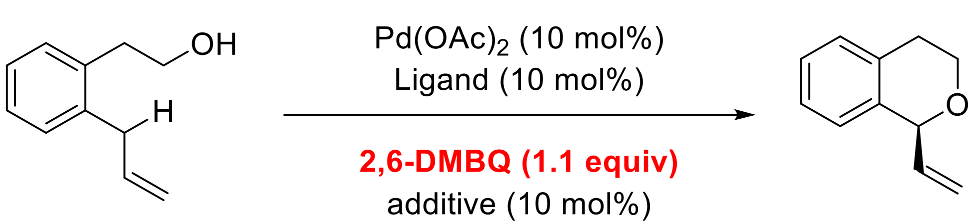


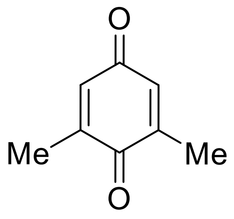
$Pd(OAc)_2$ • ligand (10 mol%)
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h

BQ can compete with other ligands, high cc.

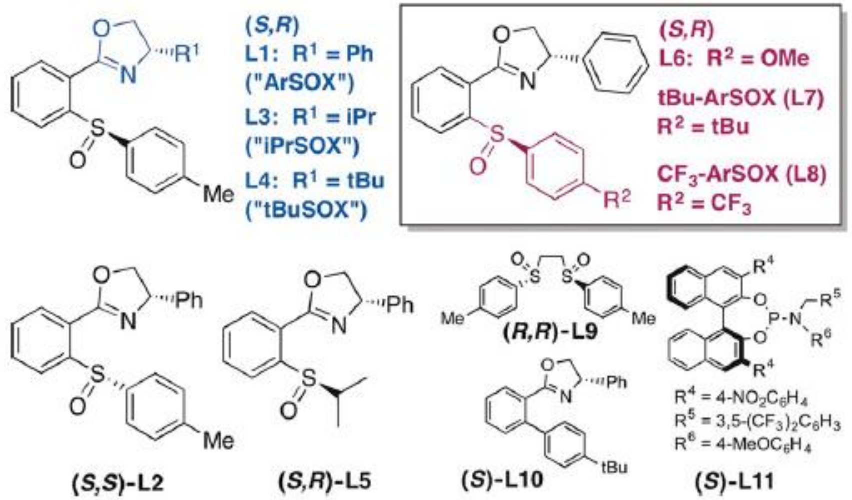
White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

Design of an Enantioselective Transformation





2,6-DMBQ



Entry	Ligand	Additive	Yield [%][a]	*ee* [%][a]
1	(*S*,*R*)-**L1**	none	8	83
2	(*S*,*R*)-**L1**	benzoic acid	13	84
3	(*S*,*R*)-**L1**	$(nBuO)_2PO_2H$	54	87
4	(*S*,*R*)-**L1**	$(PhO)_2PO_2H$	47	82
5	(*S*,*R*)-**L1**	Ph_2PO_2H	63	87
6	(*S*,*S*)-**L2**	Ph_2PO_2H	32	19
7	(*S*,*R*)-**L3**	Ph_2PO_2H	31	76
8	(*S*,*R*)-**L4**	Ph_2PO_2H	8	25
9	(*S*,*R*)-**L5**	Ph_2PO_2H	24	88
10	(*S*,*R*)-**L6**	Ph_2PO_2H	60	86
11	(*S*,*R*)-**tBu-ArSOX (L7)**	Ph_2PO_2H	70	92
12	(*S*,*R*)-**CF_3-ArSOX (L8)**	Ph_2PO_2H	49	93
13[b]	(*R*,*R*)-**L9**	Ph_2PO_2H	31	−6
14[b]	(*S*)-**L10**	Ph_2PO_2H	13	12
15[c]	(*S*)-**L11**	Ph_2PO_2H	< 5	n.d.
16[d]	(*S*,*R*)-**L7**	Ph_2PO_2H	59	77

Requirements:

- Non-coordinating oxidant
- Ligand effects C-H cleavage and C-O bond formation

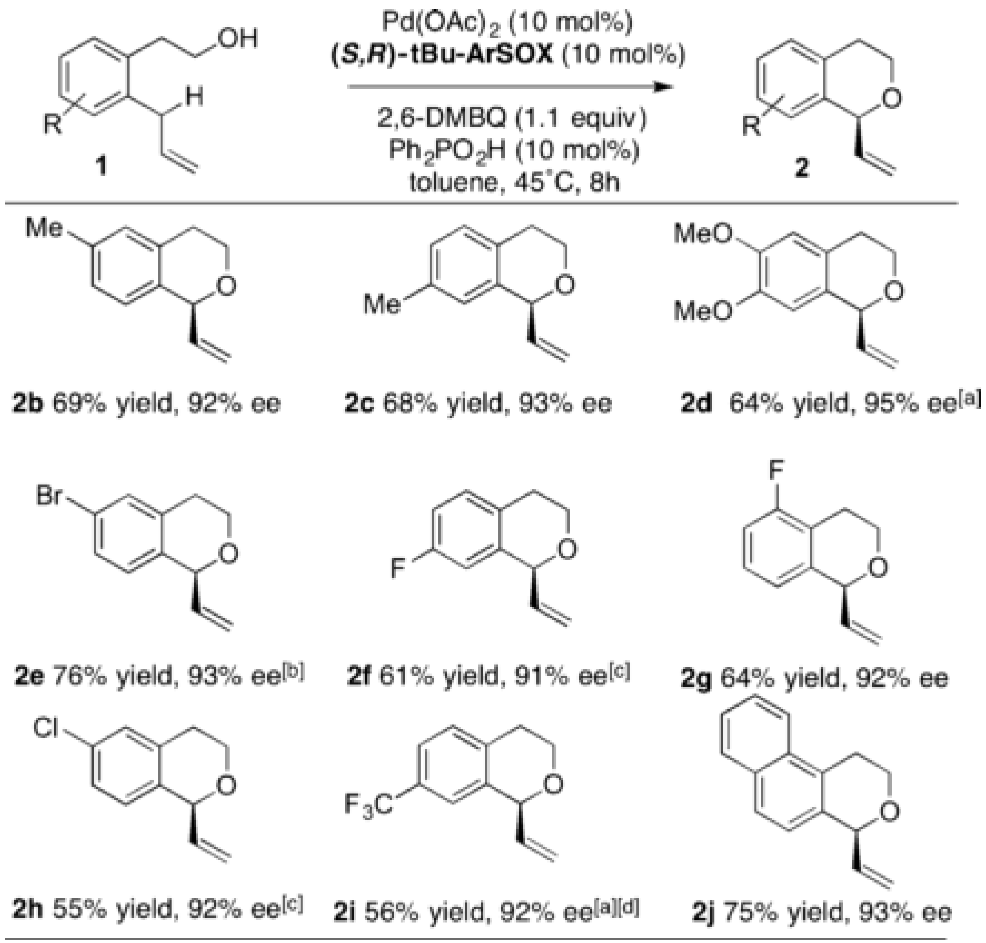
Idea:

- Mixed P,N-ligands → mixed S,N-ligands
- π – acidic / σ – donor oxazoline ~BQ

White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.

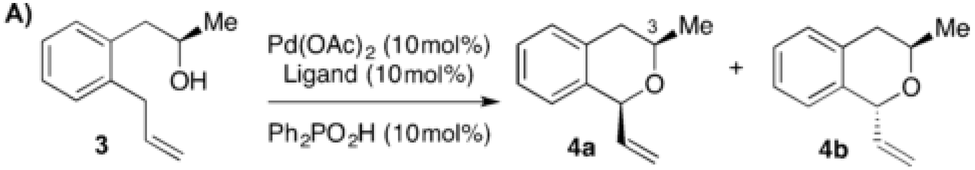
Scope and Catalyst Influence on Diastereoselective Cyclization

Scope



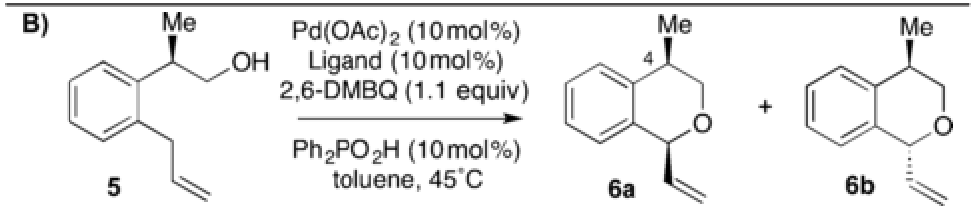
Catalyst Influence on Diastereoselective Cyclization

A)



Entry	Ligand	Yield [%][a]	d.r.[b] (4a/4b)
1	*meso*-1,2-bis(phenylsulfinyl)ethane (**L12**)	16	1.5:1
2	(*S*,*R*)-**tBu-ArSOX L7**	62	>20:1
3	(*R*,*S*)-**tBu-ArSOX L7**	49	1:2.8

B)



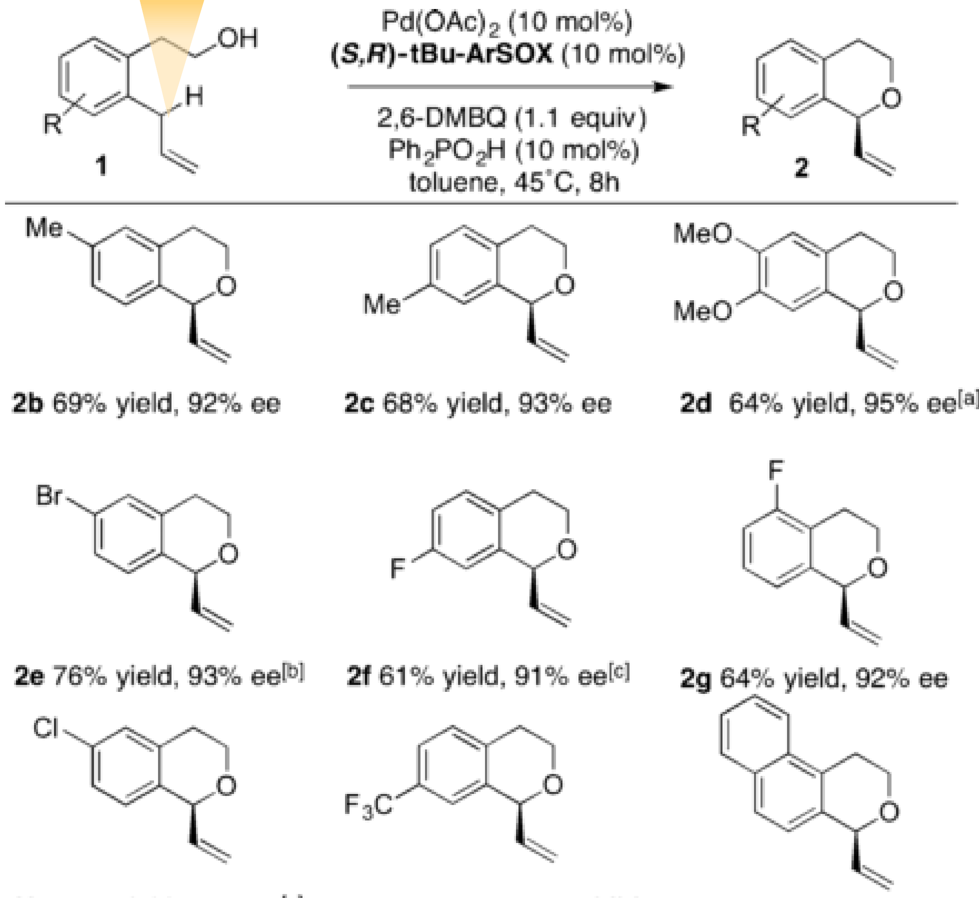
Entry	Ligand	Yield [%]	d.r. (6a/6b)
1	*meso*-1,2-bis(phenylsulfinyl)ethane (**L12**)	60	3.6:1
2	(*S*,*R*)-**tBu-ArSOX L7**	67	>20:1
3	(*R*,*S*)-**tBu-ArSOX L7**	68	1:1.4

[a] Yield is that of the isolated product, average of three runs.
[b] Determined by ^1H NMR analysis.

Scope and Catalyst Influence on Diastereoselective Cyclization

"2x activated" C-H

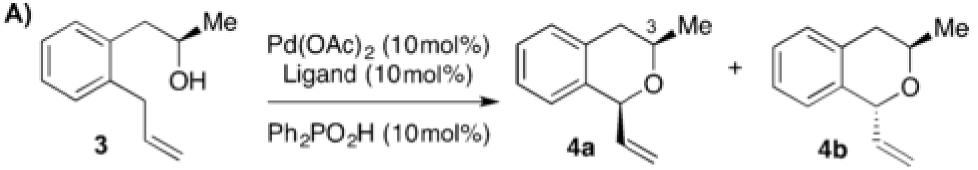
Scope



2b 69% yield, 92% ee
2c 68% yield, 93% ee
2d 64% yield, 95% ee[a]
2e 76% yield, 93% ee[b]
2f 61% yield, 91% ee[c]
2g 64% yield, 92% ee
2h 55% yield, 92% ee[c]
2i 56% yield, 92% ee[a][d]
2j 75% yield, 93% ee

Catalyst Influence on Diastereoselective Cyclization

A)



Entry	Ligand	Yield [%][a]	d.r.[b] (4a/4b)
1	*meso*-1,2-bis(phenylsulfinyl)ethane (**L12**)	16	1.5:1
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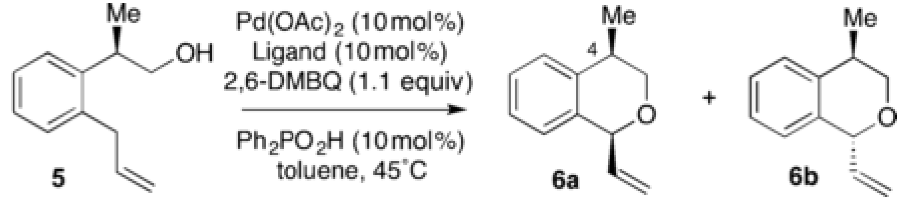
3	(*R*,*S*)-**tBu-ArSOX L7**	49	1:2.8

B)



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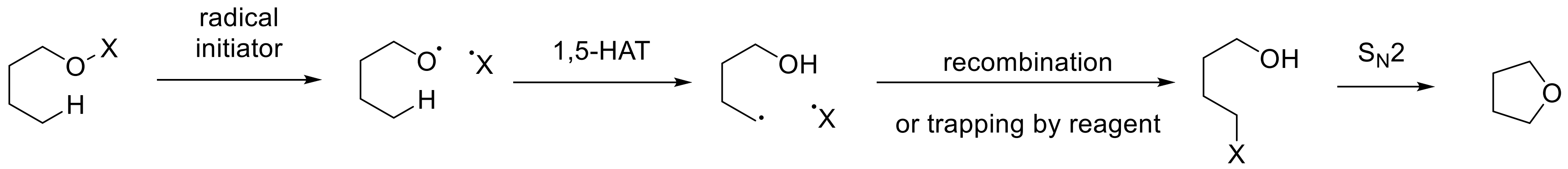
1	*meso*-1,2-bis(phenylsulfinyl)ethane (**L12**)	60	3.6:1
2	(*S*,*R*)-**tBu-ArSOX L7**	67	>20:1
3	(*R*,*S*)-**tBu-ArSOX L7**	68	1:1.4

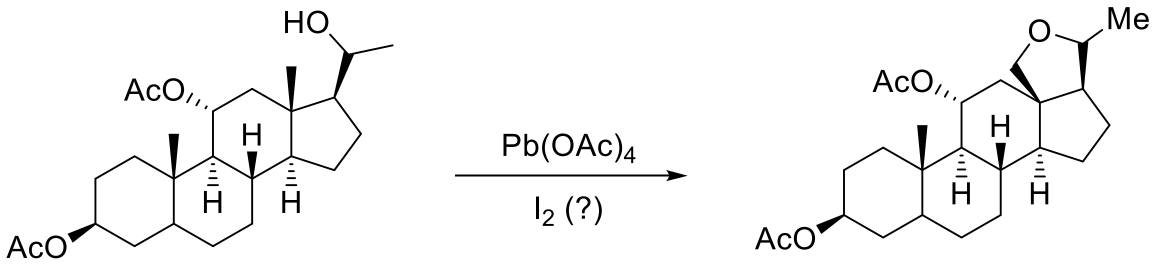
[a] Yield is that of the isolated product, average of three runs.
[b] Determined by ^{1}H NMR analysis.

Hydrogen Atom Transfer (HAT) based O-cyclizations

General mechanism

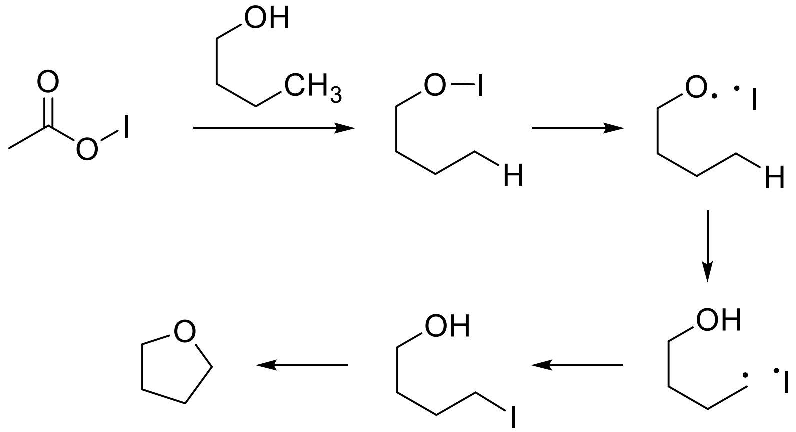


Kalvoda, 1962



First example of direct generation of an alkoxy radical

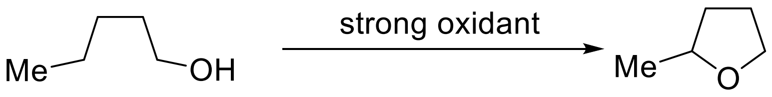
Proposed mechanism by Lusztyk



Kalvoda, J. A. *Helv. Chim. Acta* **1962**, *45* (4), 1317–1343.
Nagib, D. A. *Synth.* **2018**, *50* (8), 1569–1586.
Courtneidge, J. L.; Lusztyk, J.; Pagé, D. *Tetrahedron Lett.* **1994**, *35* (7), 1003–1006.

Hydrogen Atom Transfer (HAT) based O-cyclizations

<u>1964-1994</u> Cekovic, Mihailovic, Trahanovsky, Kalvoda, Williams, Danishefsky etc.



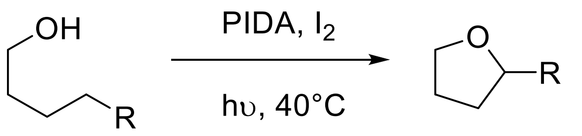
Reported conditions:

LTA, benzene
LTA, iodine, Cy
HgO, iodine, Cy
Ag_2O, Br_2, pentane
$Ph_2Se(OH)(OAc)$, iodine
$(NH_4)_2Ce(NO_3)_6$

- LTA / iodine dominates between 1962 – 1984
- Cerium and HgO are the alternatives
- Does not solve the problems with LTA

See details in the review of the reviews:
Čeković, Ž. *Tetrahedron* **2003**, *59* (41), 8073–8090.

Suárez, 1984 – seminal work



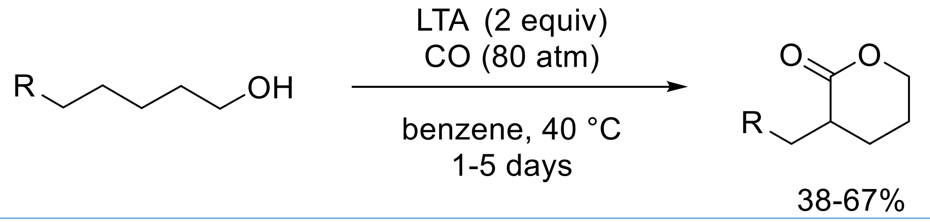
up to 90%

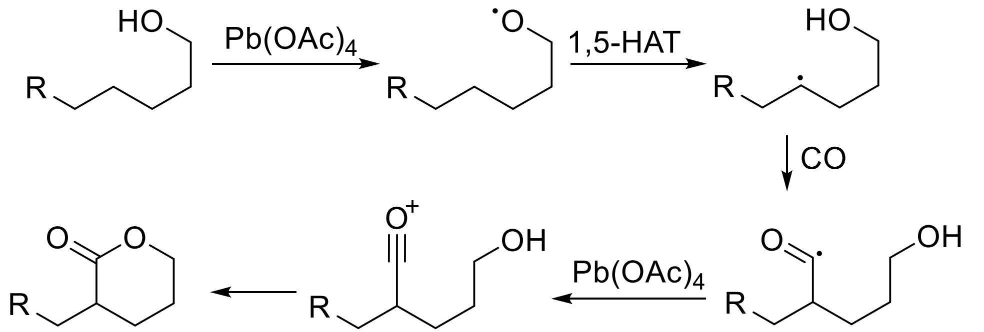
- Less toxic
- Milder condition
- Only 1 equiv PIDA and I_2 (large excess of LTA and I_2 is used)
- No complication by alpha-iodoether, and lactol formation
- Higher or comparable yields to LTA/iodine
- Often featured in total synthesis

Suárez, E. *Tetrahedron Lett.* **1984**, *25* (18), 1953–1956.
Čeković, Ž. *Tetrahedron* **2003**, *59* (41), 8073–8090.
Cekovic, Z. *J. Serb. Chem. Soc* **2005**, *70* (3), 287–318.

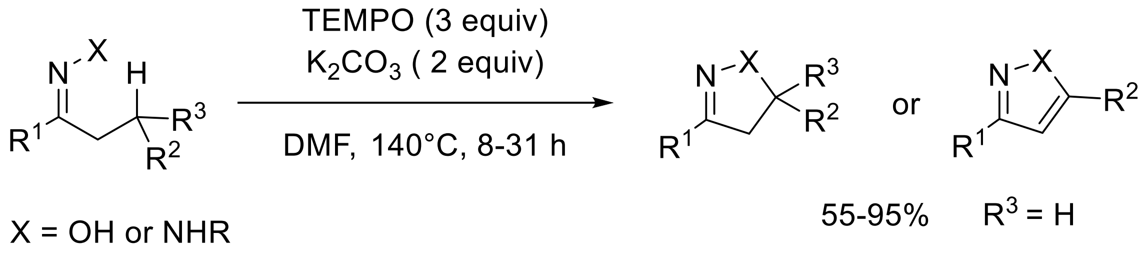
Hydrogen Atom Transfer (HAT) based O-cyclizations

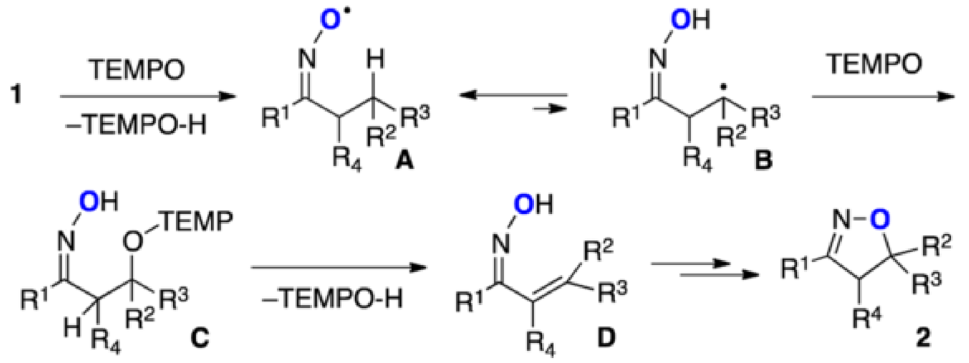
Ryu, 1998



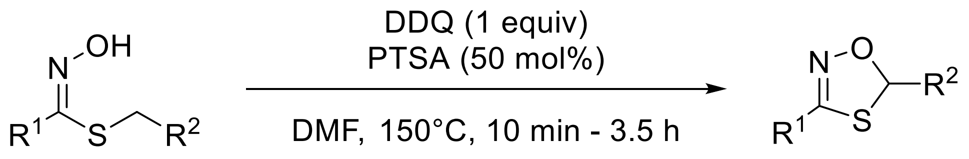


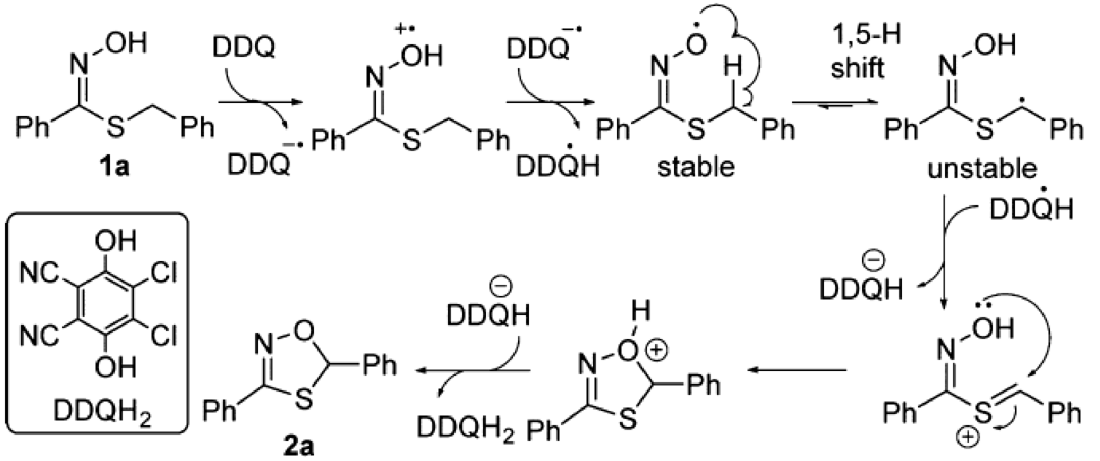
Chiba, 2013





Pierce, 2015





Ryu, I. *J. Am. Chem. Soc.* **1998**, *120* (34), 8692–8701.
Chiba, S. *Org. Lett.* **2013**, *15* (13), 3214–3217.
Pierce, J. G. *Org. Lett.* **2015**, *17* (18), 4542–4545.

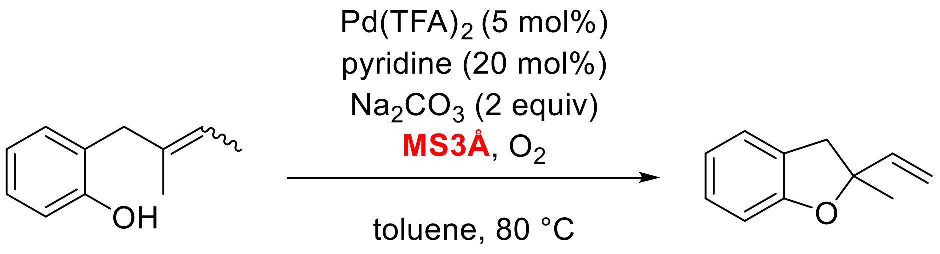
Wacker vs C-H activation vs HAT

	Wacker	*C-H activation*	*HAT*
Prefunctionalization	Double bond	C(sp2)-H allylic C-H	
Enantioselective			Not reported
5 membered ring		only (di)benzofuran	
6 membered ring		not many examples	Almost none
Scope	Many similar examples		
FG tolerance			
Mildness			
Future potential			Photoredox.

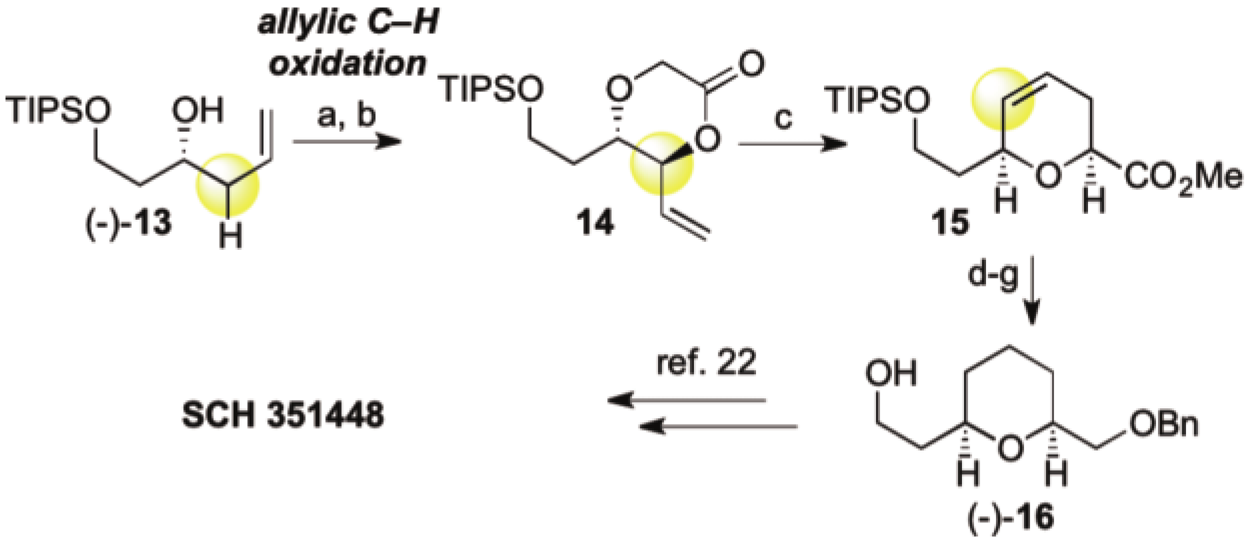
Thank you for your attention

QUESTIONS

1) What is the role of molecular sieves?

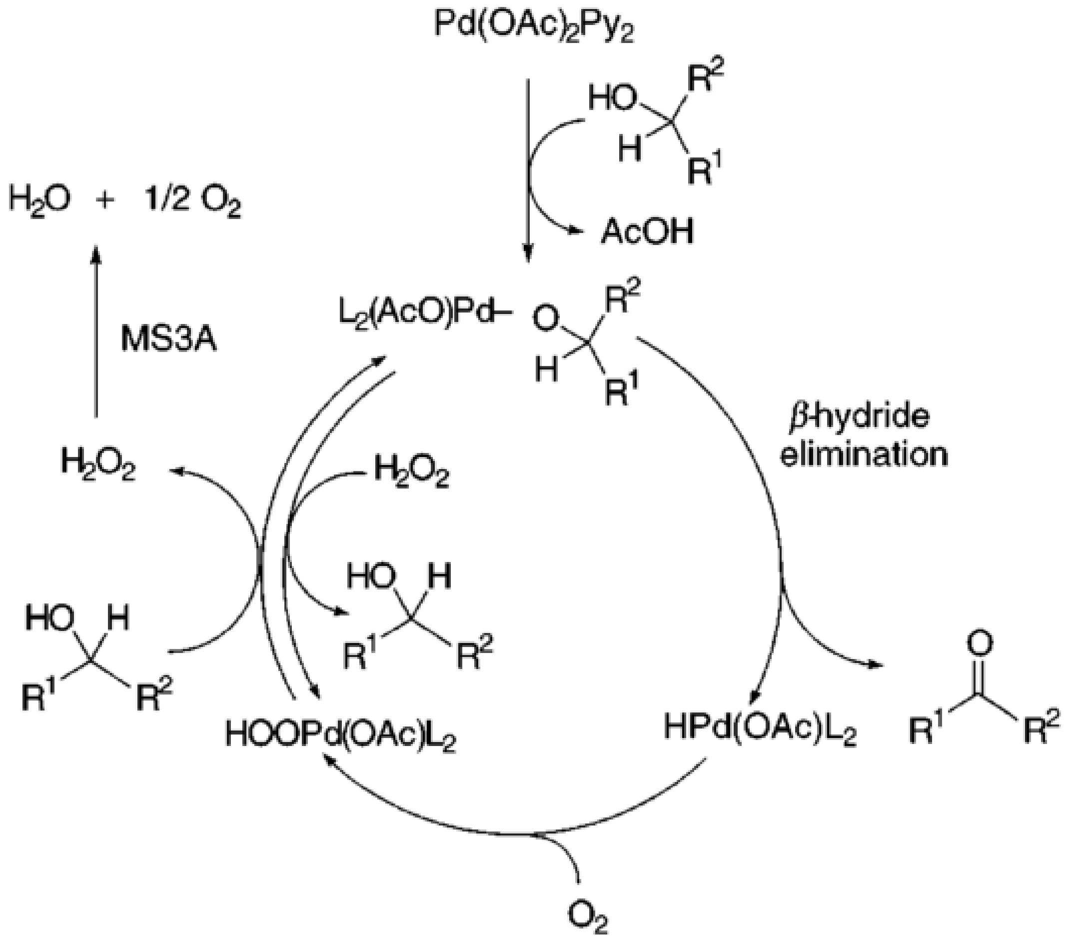


*2) Propose conditions for transformation **14** to **15**!*



Answers

Scheme 1. Plausible Reaction Pathway



Answers

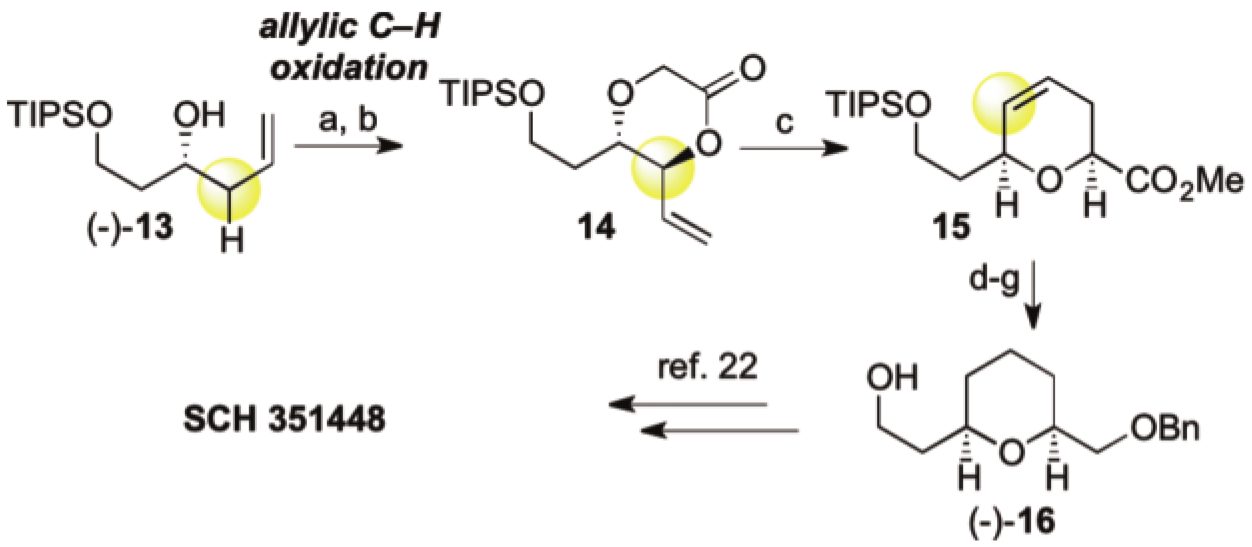
c) Reaktionen mit Bleitetracetat. – *3β,11α-Diacetoxy-18,20β-oxido-5α-pregnan (IV):* 100 g vorgetrocknetes Bleitetracetat und 30,0 g Calciumcarbonat wurden in 2,5 l Cyclohexan suspendiert und 15 Min. unter Rühren und Rückfluss gekocht. Nach anschliessender Zugabe von 21,0 g 3β,11α-Diacetoxy-20β-hydroxy-5α-pregnan (II) kochte man das Reaktionsgemisch weitere 19 Std. Die abgekühlte Lösung wurde filtriert, der Filterrückstand mit Methylenchlorid und Essigester gewaschen und die vereinigten Filtrate nacheinander mit 500 ml einer 5-proz. Kalium-

84

jodid- und mit 500 ml einer 10-proz. Natriumsulfit-Lösung und mit Wasser ausgeschüttelt. Die mit Natriumsulfat getrocknete Lösung lieferte nach Eindampfen im Wasserstrahlvakuum 23,8 g eines farblosen amorphen Produktes. Dieses wurde zwecks Auftrennung in 100 ml Petroläther gelöst und an 600 g neutralem Aluminiumoxid (Aktivität II) chromatographiert. Mit Benzol wurden neben komplexen Gemischen, bestehend aus oxydiertem bzw. acetyliertem Ausgangsmaterial, 4,73 g des rohen 3β,11α-Diacetoxy-18,20β-oxido-5α-pregnans (IV) eluiert. Nach dreimaligem Umlösen aus Äther-Petroläther schmolz das reine Präparat bei 143–143,5° und gab mit dem weiter oben beschriebenen etwas weniger reinen Äther keine Smp.-Erniedrigung. $[\alpha]_D^{26} = -22°$ ($c = 1{,}031$). Im IR.-Spektrum u. a. Banden bei 5,82 μ (Acetate); 8,05; 9,70; 10,38 und 11,68 μ.

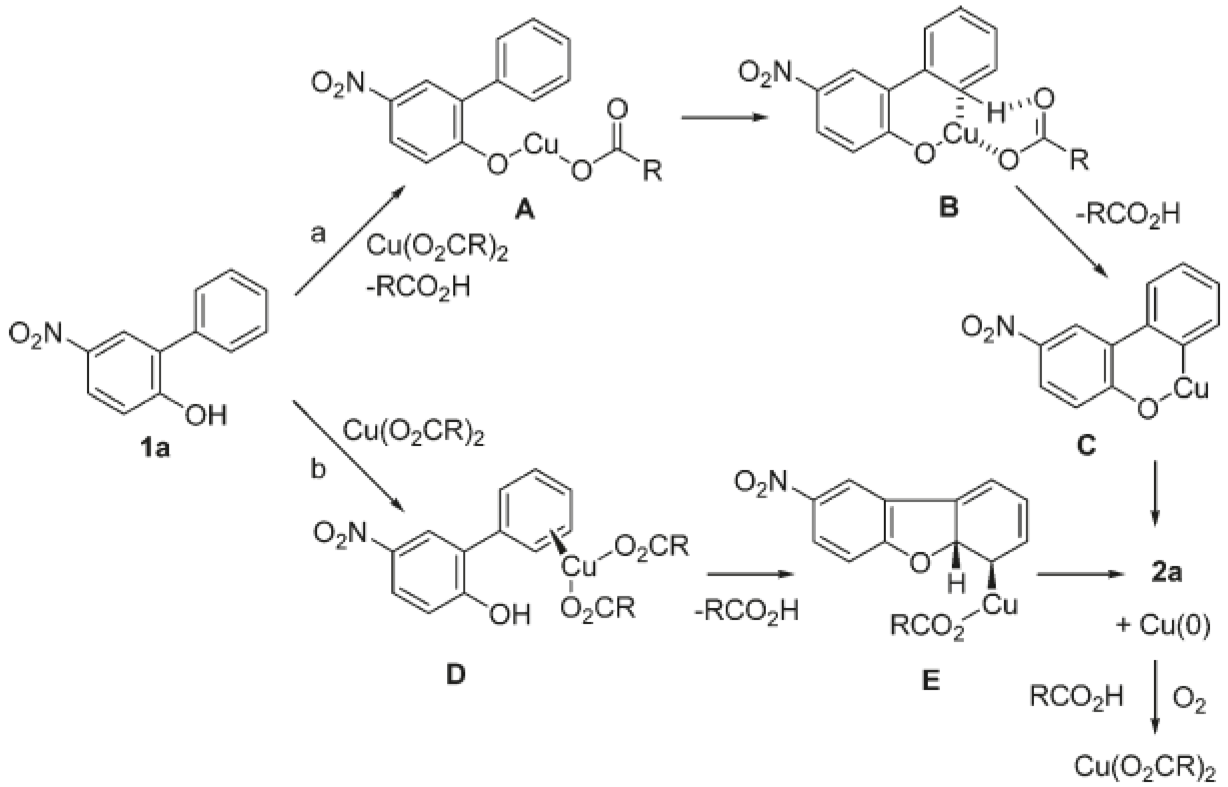
$C_{25}H_{38}O_5$ (418,55) Ber. C 71,74 H 9,15% Gef. C 71,72 H 8,97%

Answers



[a] Conditions: (a) NaH (3.0 equiv), BrAcOH (1.1 equiv), THF/DMF 0 °C to RT (70%); (b) 10% **1**, 10% Cr(salen)Cl, BQ (2.0 equiv), dioxane, 65 °C (83%, 3:1 crude dr, mixture of diastereomers taken forward); (c) (1) LiHMDS (2.0 equiv), 1:1 v/v TMSCl/Et_3N, THF, −78 °C then reflux in toluene, (2) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), DMF, RT (83%); (d) 10% wt of 5% Pd/C, H_2 (1 atm), EtOAc, RT (68% of >20:1 *syn*-diastereomer, 3:1 crude dr); (e) $LiAlH_4$ (2.0 equiv), THF, 0 °C; (f) BnBr (2.0 equiv), NaH (2.0 equiv), DMF, 0 °C to RT; (g) 3 M HCl, EtOH, RT (74%, 3 steps).

Title


O2N
1a
OH
a
Cu(O2CR)2
-RCO2H
A
O
Cu
R
B
H
-RCO2H
C
b
Cu(O2CR)2
D
O2CR
E
RCO2
2a
+ Cu(0)
RCO2H
O2
Cu(O2CR)2

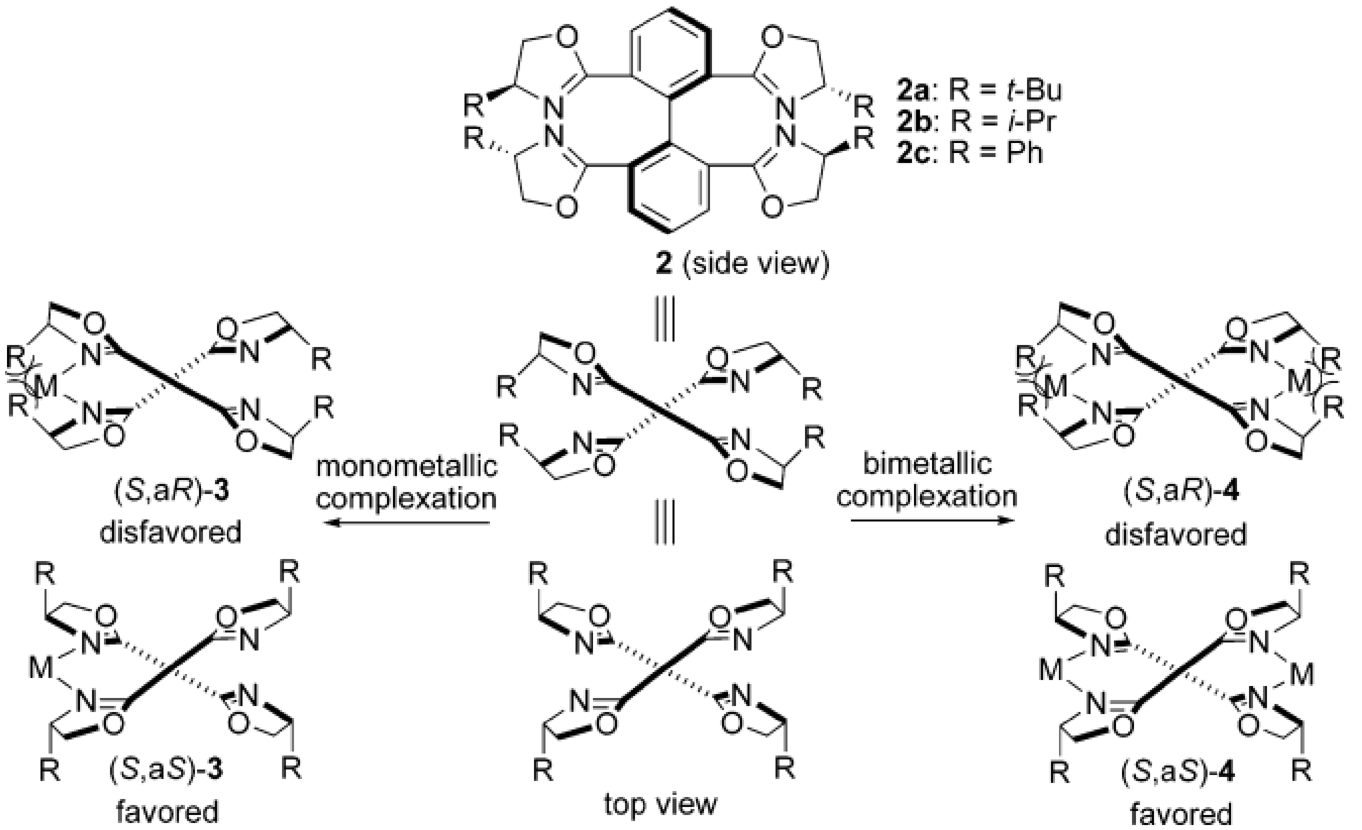
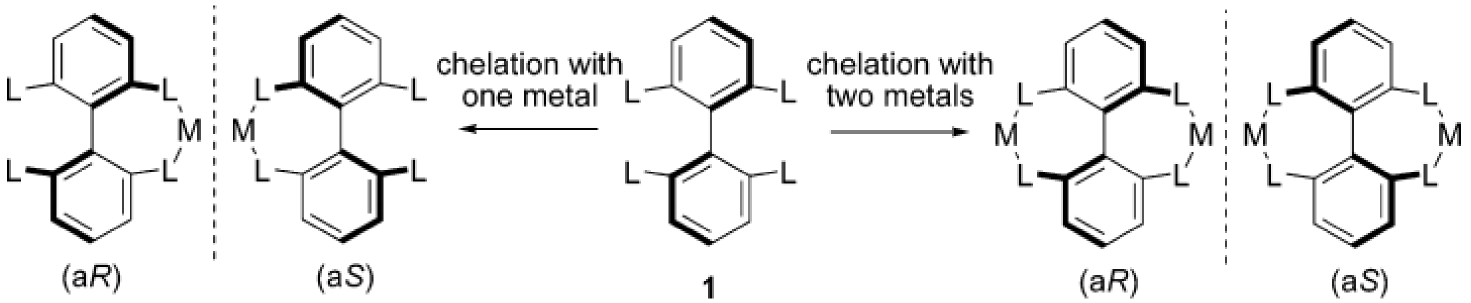
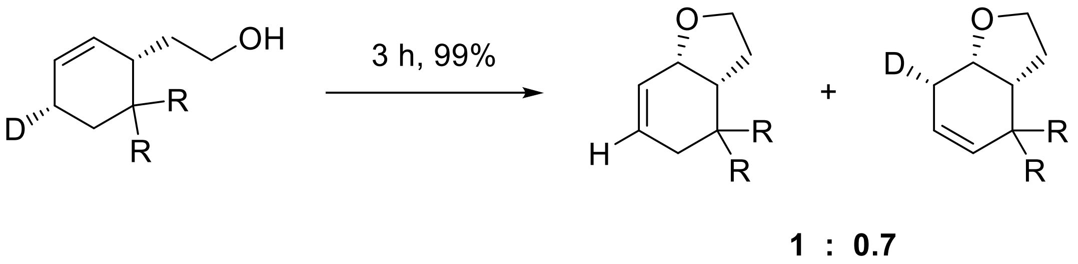


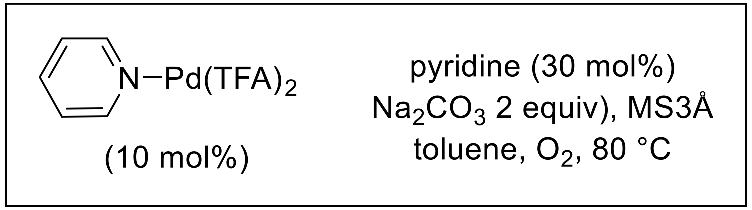
FIGURE 1. Model figures of diastereomeric monometallic and bimetallic complexes with tetraoxazoline ligands.

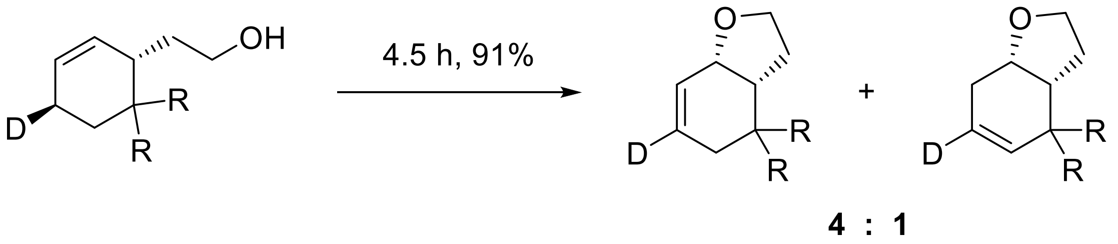
SCHEME 1. Chelation-Induced Axially Chiral Metal Complexes Formed by Destroying the Molecular Symmetry (L = Coordination Group)



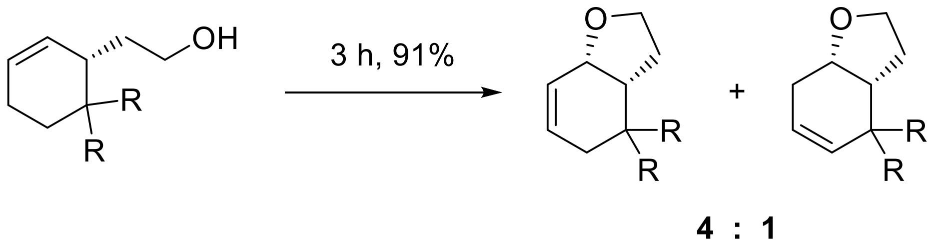
Enantioselective Wacker - type cyclization



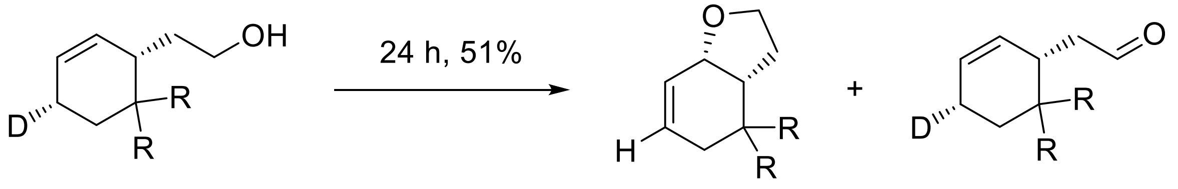




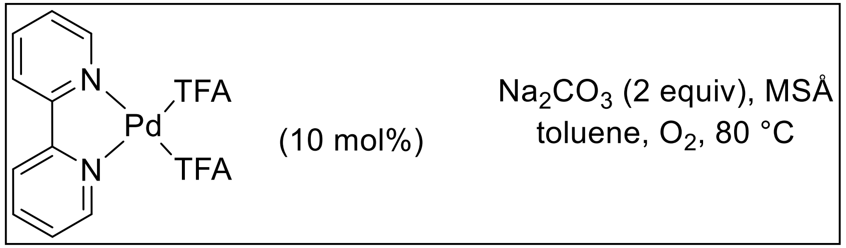
- Syn-oxypalladation
- Good yields
- Fast reaction
- Monodentate ligand

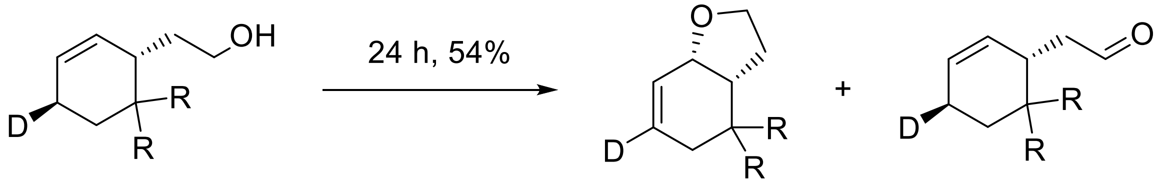


Enantioselective Wacker - type cyclization



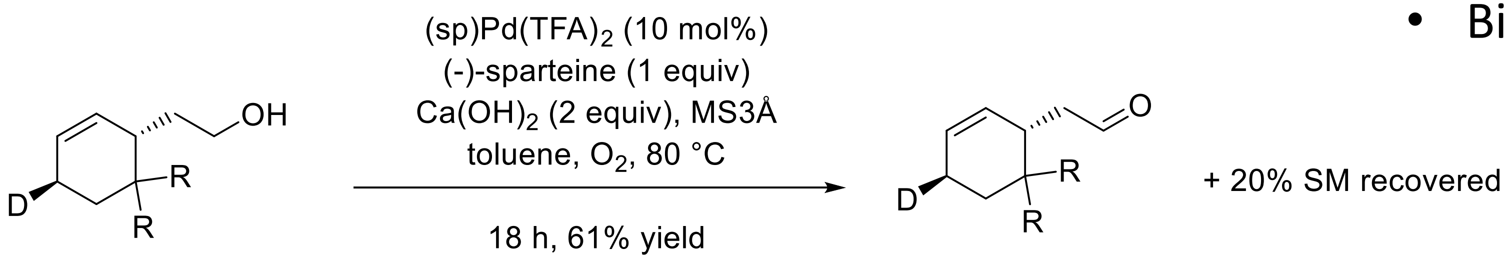
10 : 1



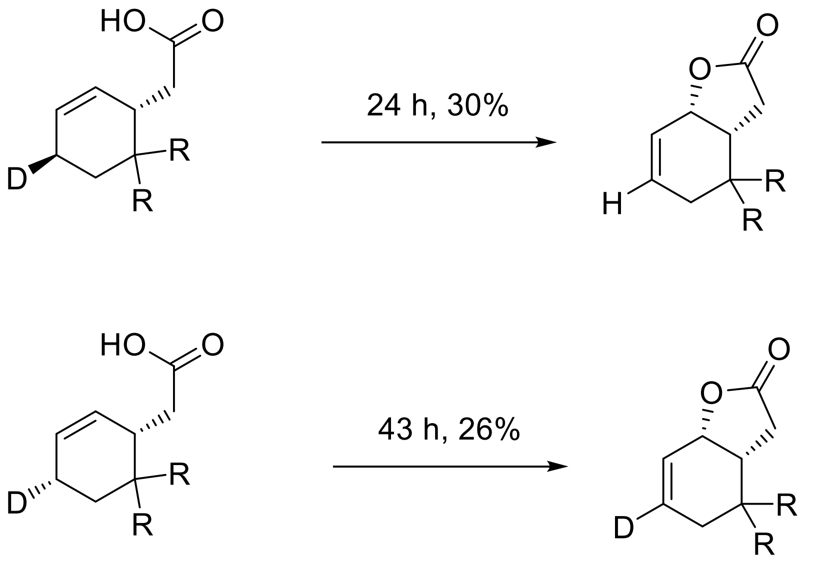


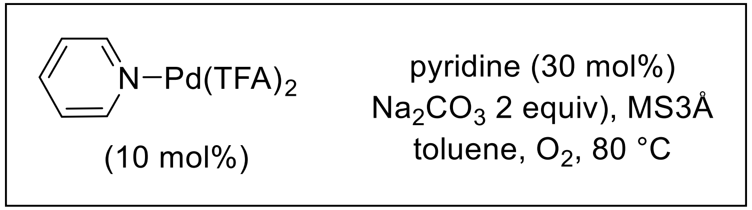
10 : 1

- Syn-oxypalladation
- Moderate yields
- Slow reaction
- Alcohol oxidation as side reaction
- Bidentate ligand



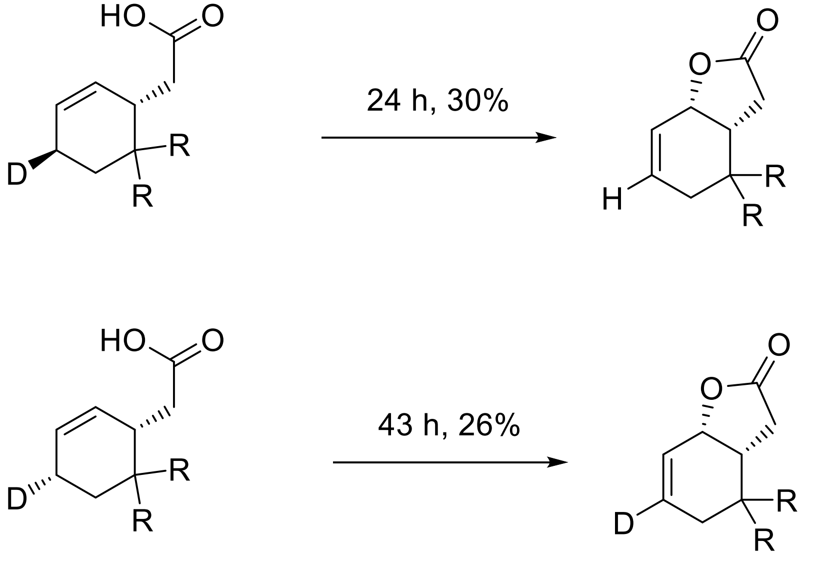
Enantioselective Wacker - type cyclization

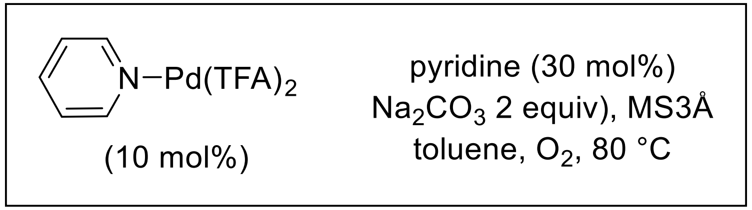




- Anti-oxypalladation
- Moderate yields
- Slow reaction
- Monodentate ligand

Enantioselective Wacker - type cyclization





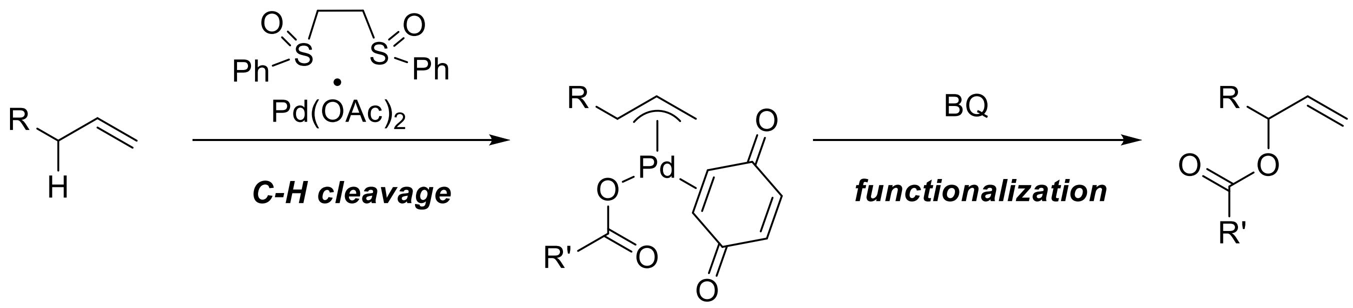
- Anti-oxypalladation
- Moderate yields
- Slow reaction
- Monodentate ligand

Summary

- Monodentate ligand > bidentate ligand
  - Monodentate ligand → better stabilizes TS
  - Monodentate ligand → difficult asymmetric-induction
- Both syn and anti oxypalladation are possible

Design of an Enantioselective Transformation

Challenges



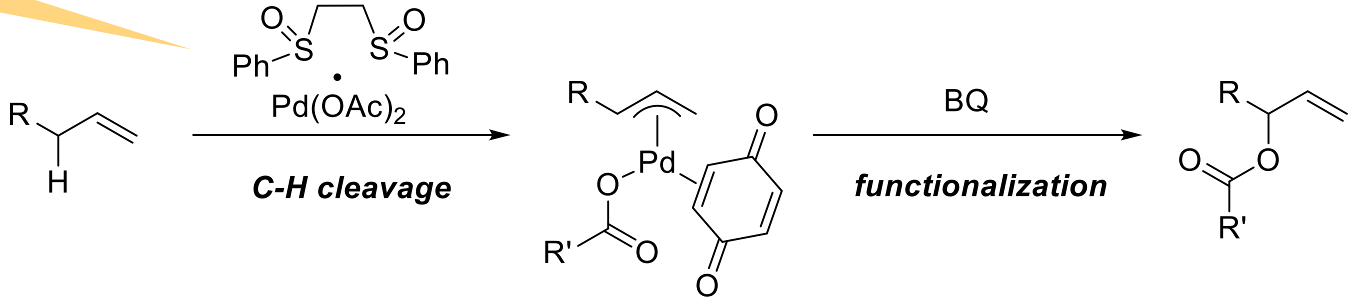
Pd(OAc)$_2$ • ligand (10 mol%)
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h

White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

Design of an Enantioselective Transformation

Challenges

Transient ligand



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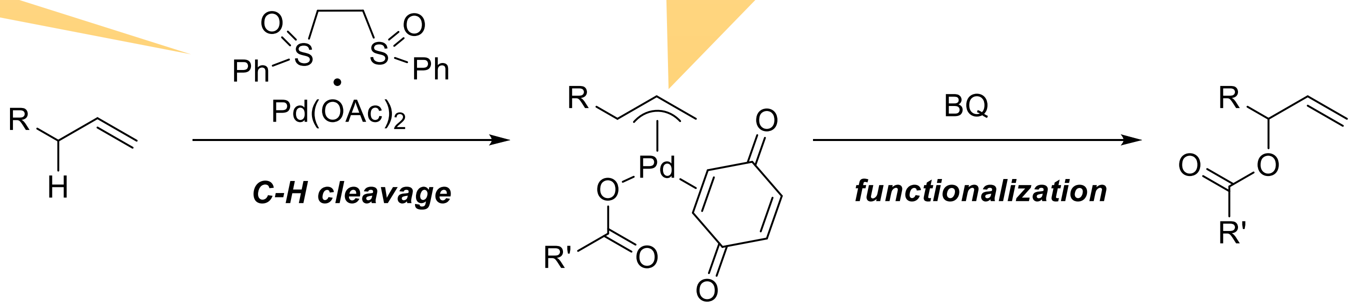
Design of an Enantioselective Transformation

Challenges

Transient ligand

$\pi - \sigma - \pi$ isomerization before C-O bond forming step



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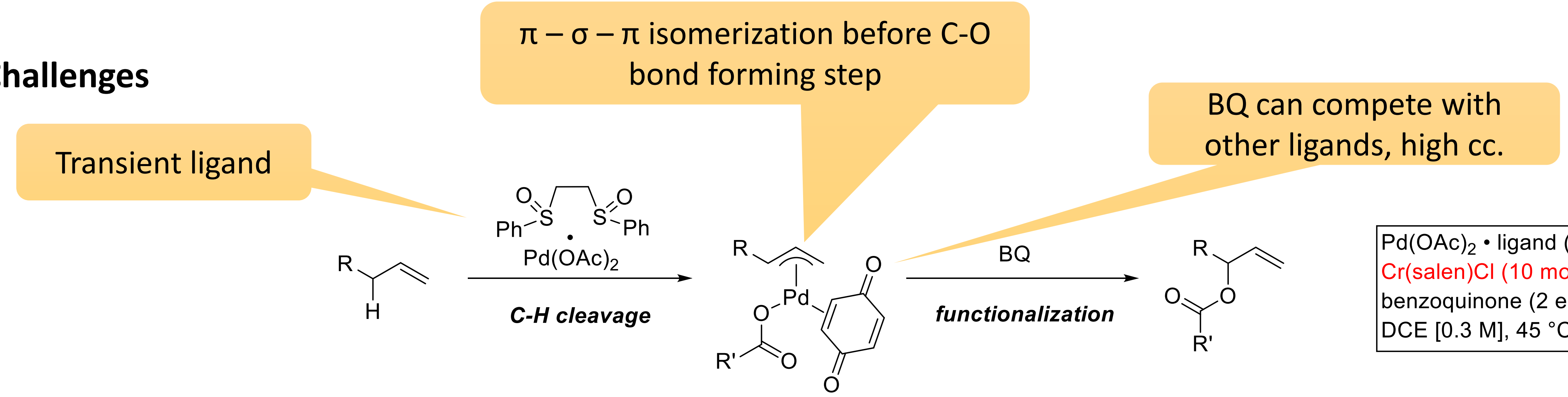
Design of an Enantioselective Transformation

Challenges



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White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

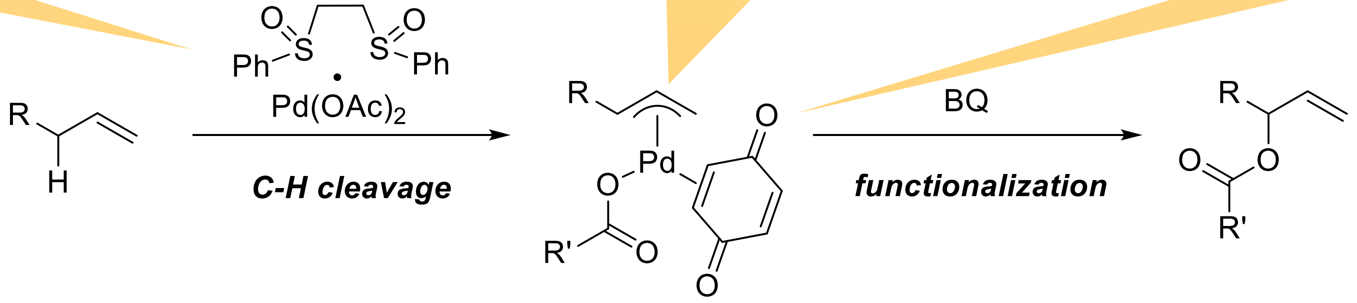
Design of an Enantioselective Transformation

Challenges

Transient ligand

π – σ – π isomerization before C-O bond forming step

BQ can compete with other ligands, high cc.



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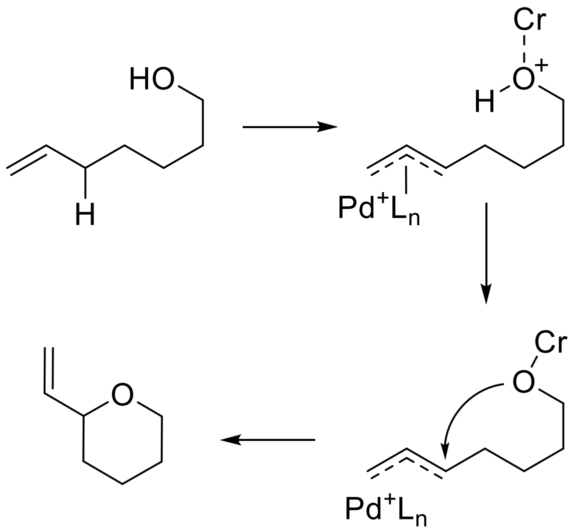
Cr(salen)Cl (10 mol%)
benzoquinone (2 equiv)
DCE [0.3 M], 45 °C, 16 h



outer sphere mechanism

White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.

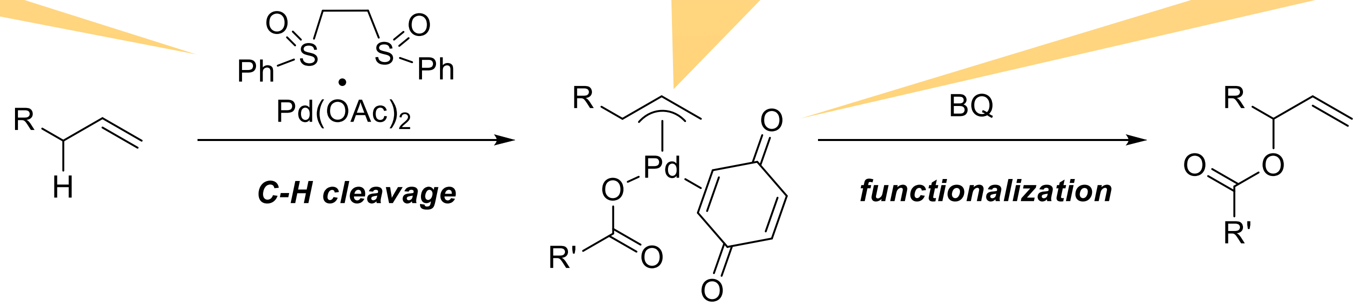
Design of an Enantioselective Transformation

Challenges

Transient ligand

π – σ – π isomerization before C-O bond forming step

BQ can compete with other ligands, high cc.



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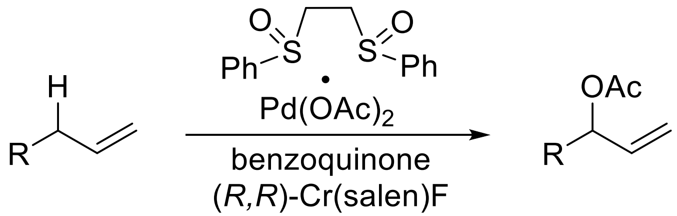
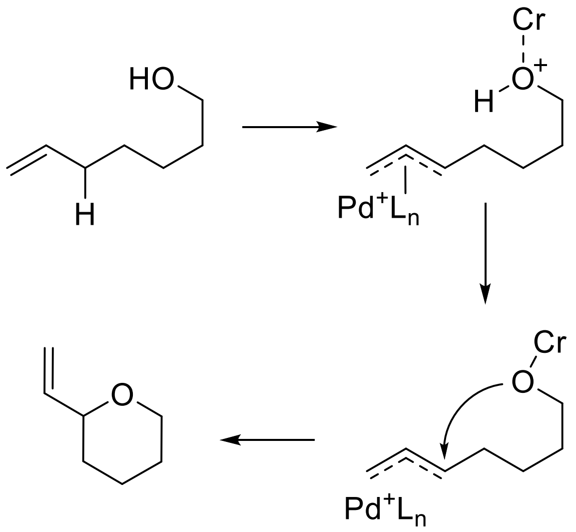


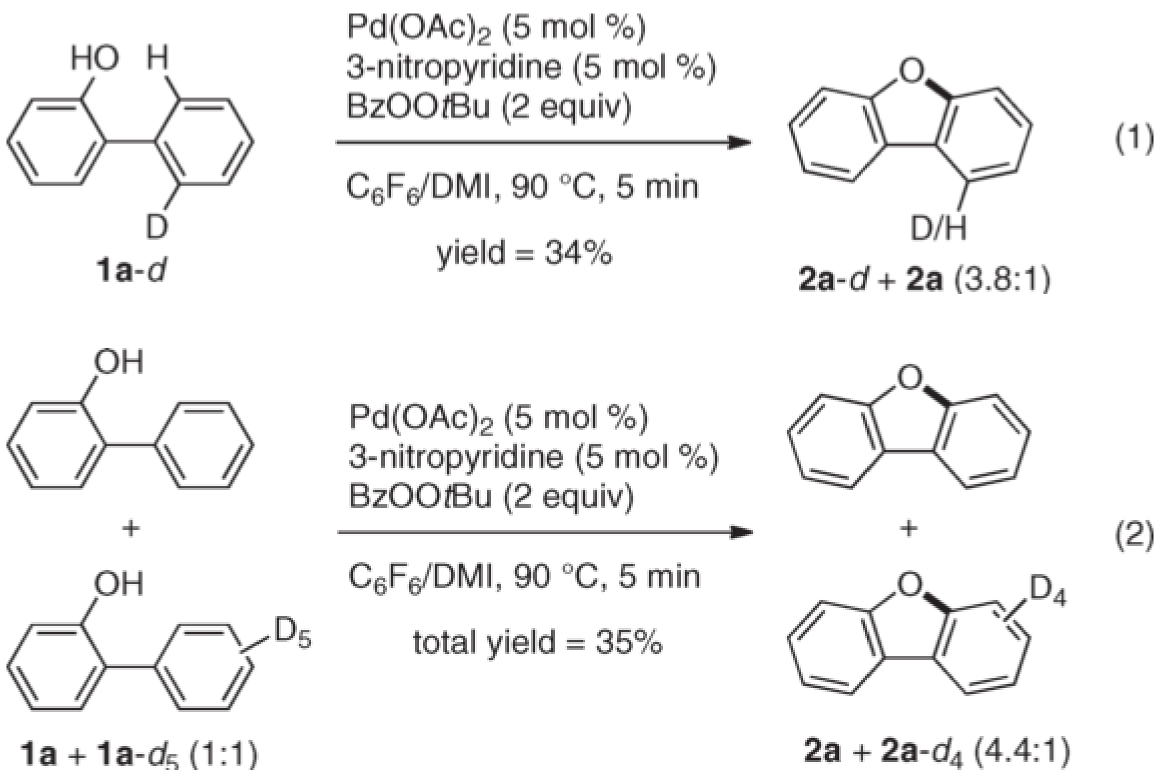
avg. 54% ee



→ Distant Cr* centre

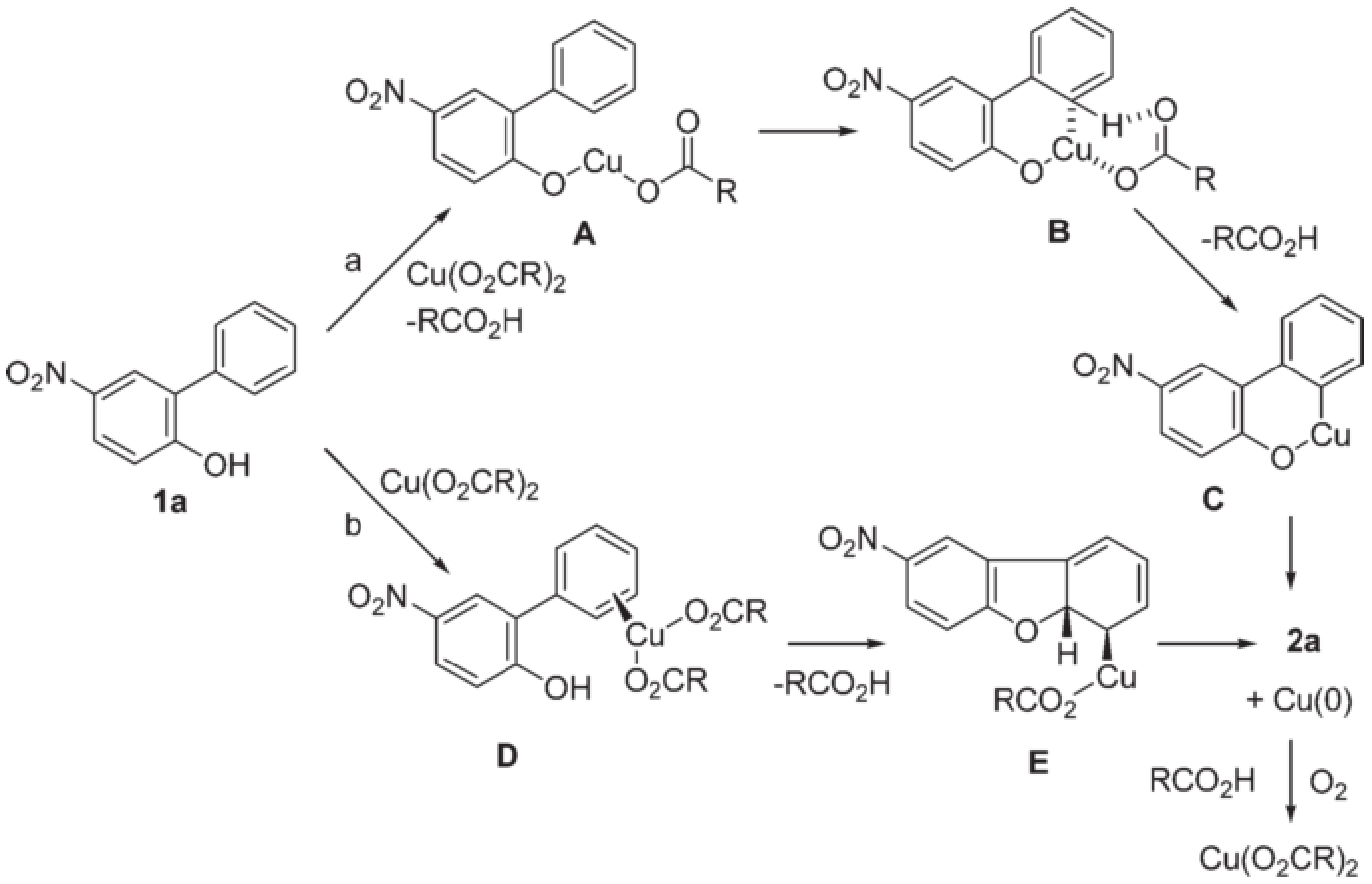
outer sphere mechanism

White, M. C. *Angew. Chemie - Int. Ed.* **2016**, *55* (33), 9571–9575.
White, M. C. *Angew. Chemie* **2008**, *120* (34), 6548–6551.


HO H
D
1a-d
Pd(OAc)2 (5 mol %)
3-nitropyridine (5 mol %)
BzOOtBu (2 equiv)
C6F6/DMI, 90 °C, 5 min
yield = 34%
O
D/H
2a-d + 2a (3.8:1)
(1)
OH
+
OH
D5
1a + 1a-d5 (1:1)
Pd(OAc)2 (5 mol %)
3-nitropyridine (5 mol %)
BzOOtBu (2 equiv)
C6F6/DMI, 90 °C, 5 min
total yield = 35%
O
+
O
D4
2a + 2a-d4 (4.4:1)
(2)

Zhang 2011

Scheme 4. Proposed Reaction Mechanism



Title

Title

Recent progress of Oxaziridine Chemistry

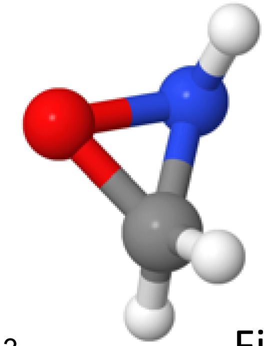
Frontier in Organic Chemistry
17.05.2018

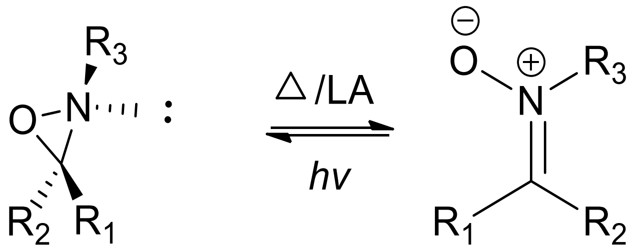
Mingming Wang

Laboratory of Catalysis and Organic Synthesis (LCSO)

Content

Introduction





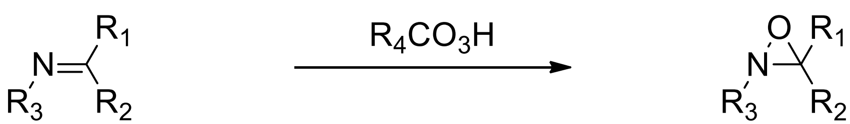
First discovered by Emmons in 1956

Strained three-member ring

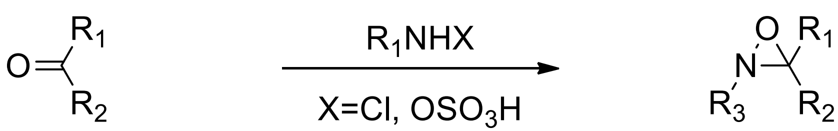
Weak N-O bond

Synthesis:

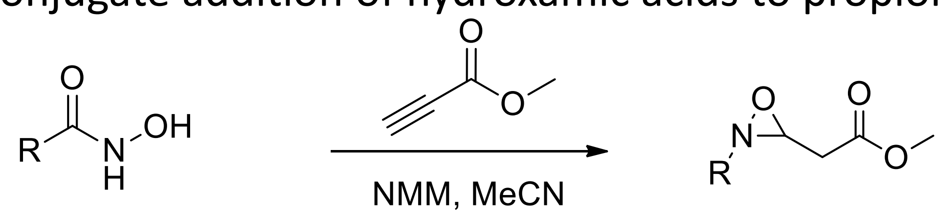
a) Oxidation of imines



b) Amination of carbonyls



C) Conjugate addition of hydroxamic acids to propiolates

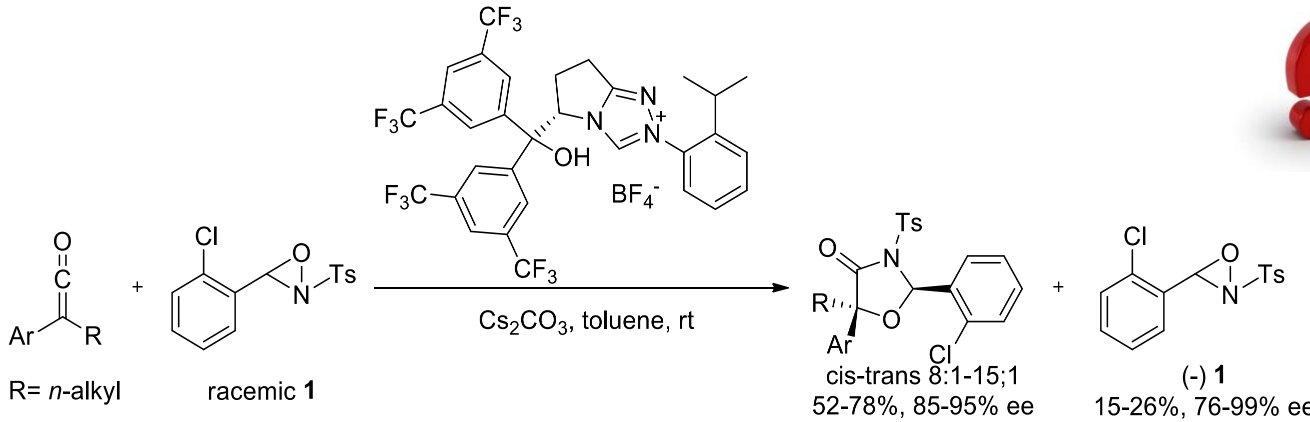


Emmons, W. D. *J. Am. Chem. Soc*. **1956**, *78*, 6208

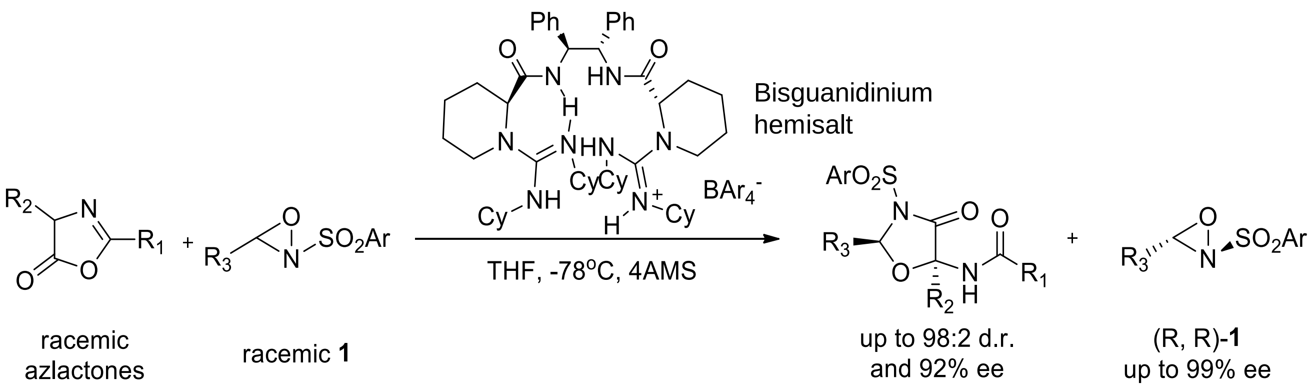
Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327

Zong, K.; Shin, S.: Ryu, E. K. *Tetrahedron Lett*. **1998**, *39*, 6227

Kinetic Resolution of Oxaziridines

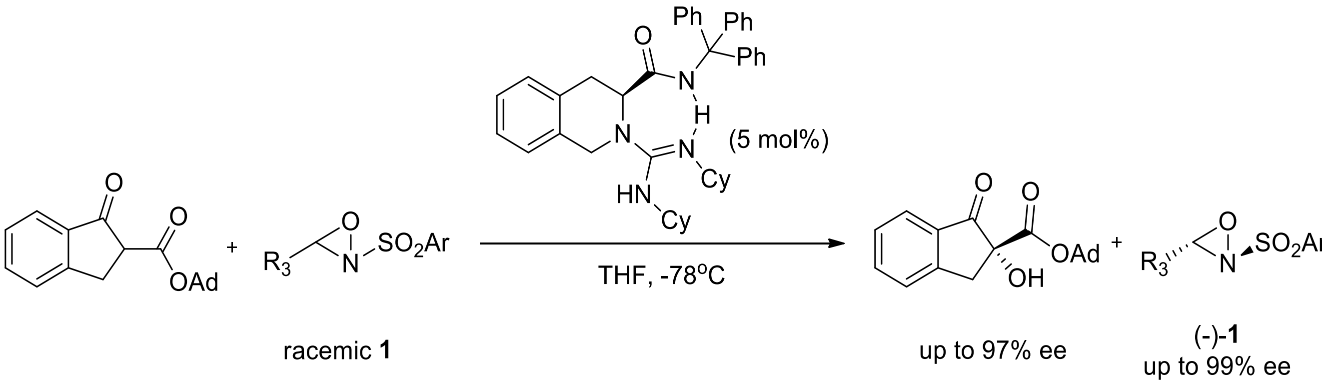


Shen, P.-L.; Chen, X.-Y.; Ye, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 8412



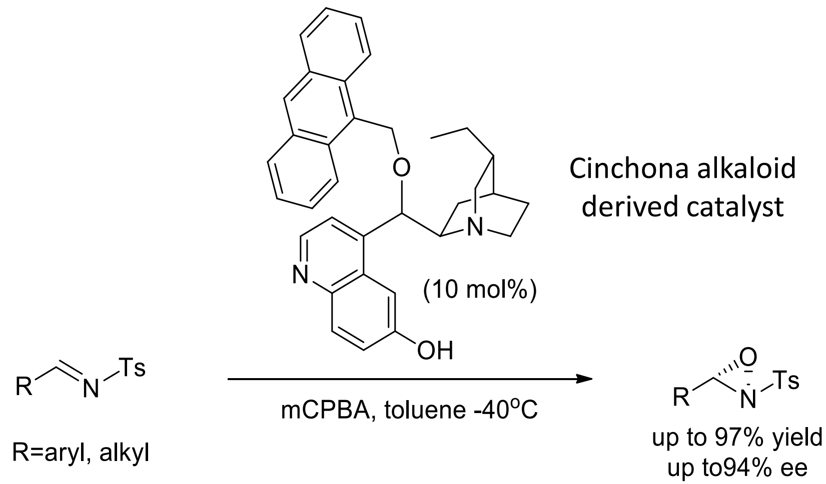
Dong, S.; Liu, X.; Zhu, Y.; He, P.; Lin, L.; Feng, X. *J. Am. Chem. Soc*. **2013**, *135*, 10026

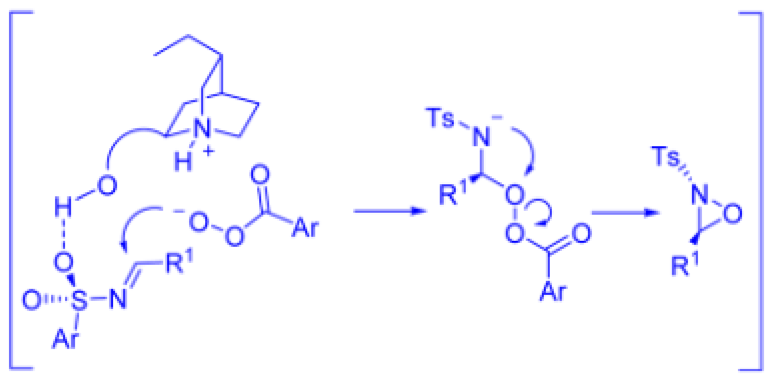
Kinetic Resolution of Oxaziridines



Lin, X.; Ruan, S.; Yao, Q.; Yin, C.; Lin, L.; Feng, X.; Liu, X. *Org. Lett*. **2016**, *18*, 3602

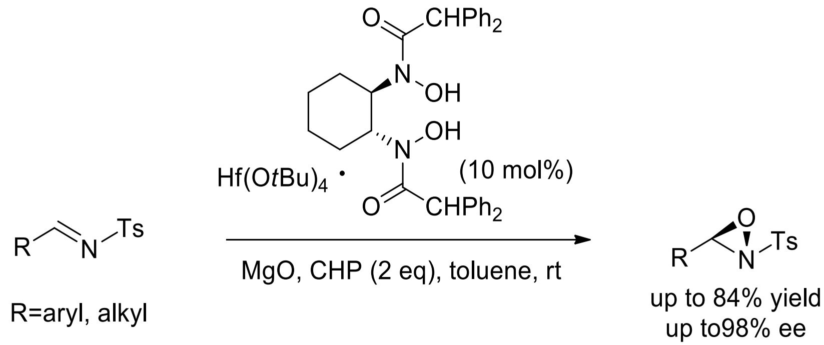
Enantioselective Oxaziridination





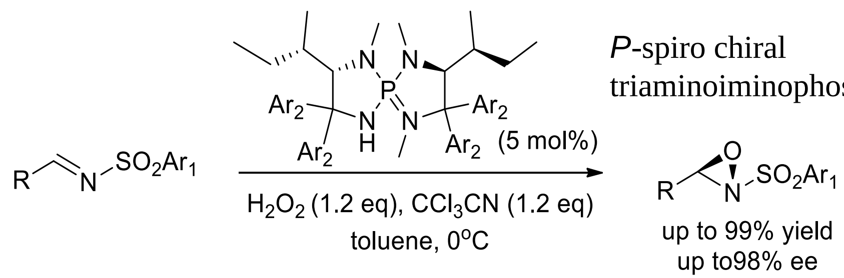
Lykke, L.; Rodriguez-Escrich, C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *133*, 14932

Enantioselective Oxaziridination



Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc*. **2012**, *134*, 5440

P-spiro chiral triaminoiminophosphorane

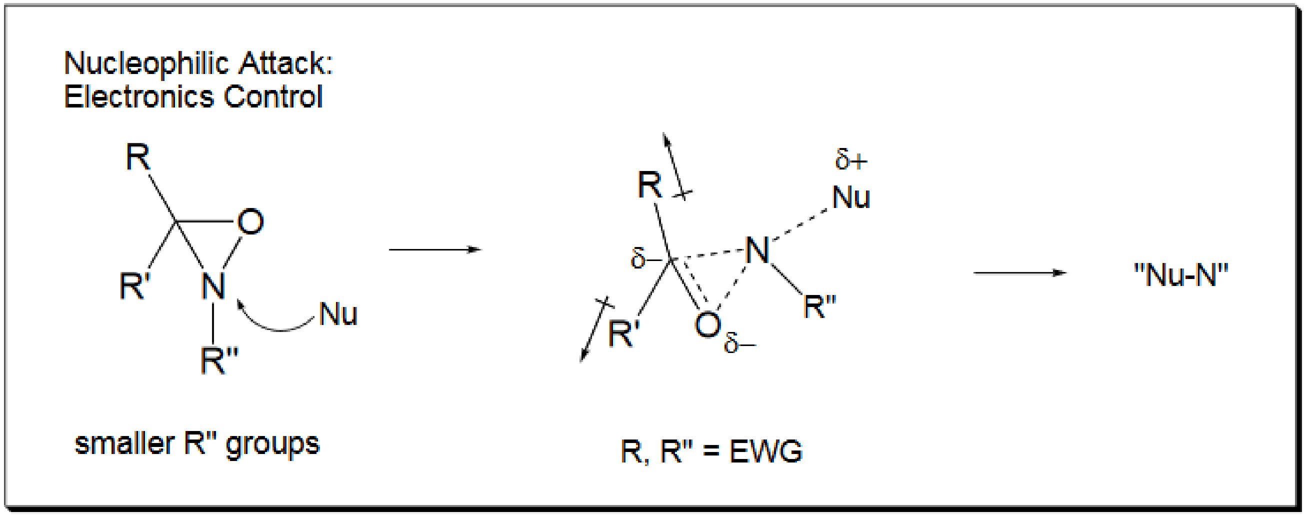


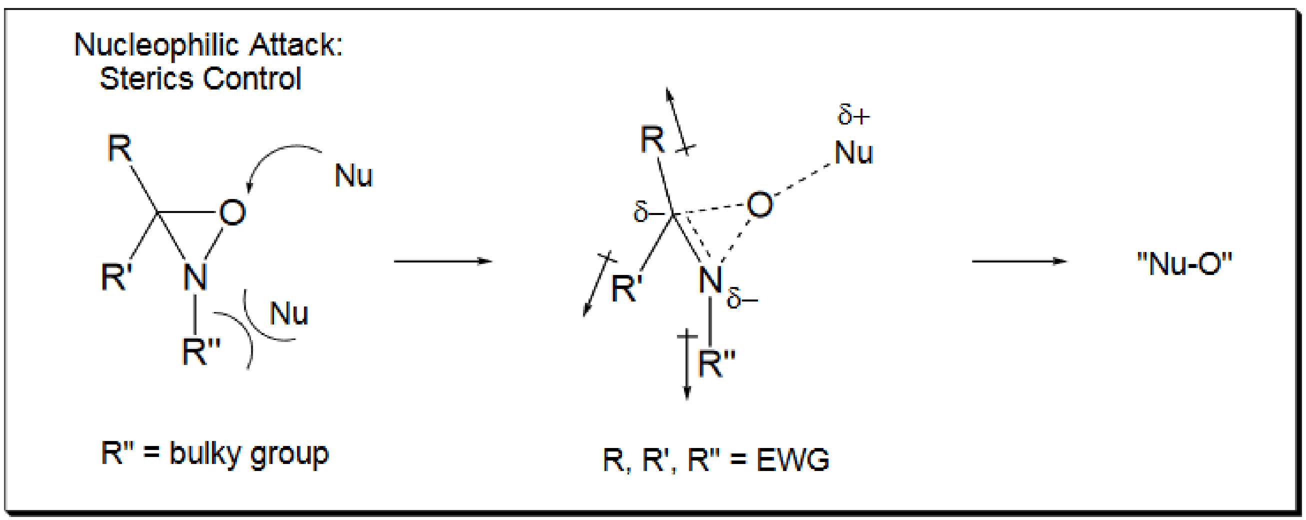
Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 8161

CCl_3CN
Requisite activator
How it plays the role?

Content

Heteroatom transfer reactions: O vs N Transfer



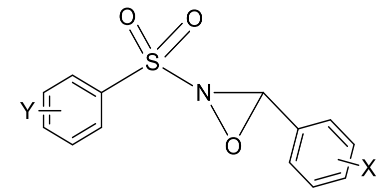


Vidal, J.; Damestoy, S.; Guy, L.; Hanachi, J.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**,*3*, 1691

O Transfer

1) Oxidation of Sulfides

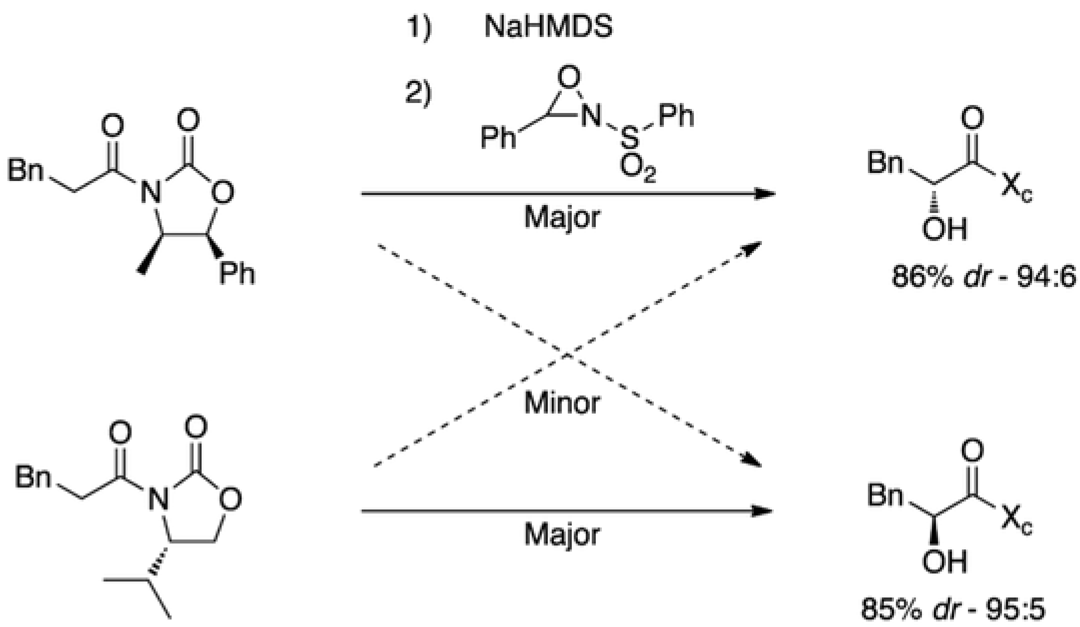
$$Ph_2S \xrightarrow[93\%]{\text{Davis Oxaziridine}} Ph_2SO$$



N-Sulfonyl Oxaziridines
(Davis Oxaziridines)

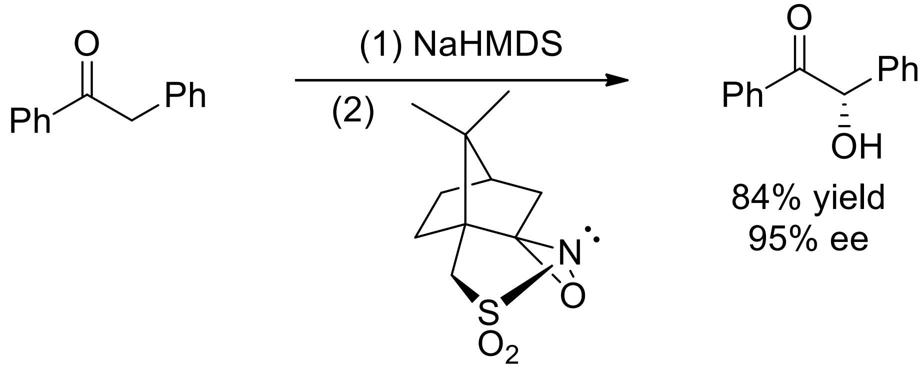
Davis, F. A.; Lal, S. G.; Durst, H. D. *J. Org. Chem*. **1988**, *53*, 5004

2) α-Hydroxylation of enolates

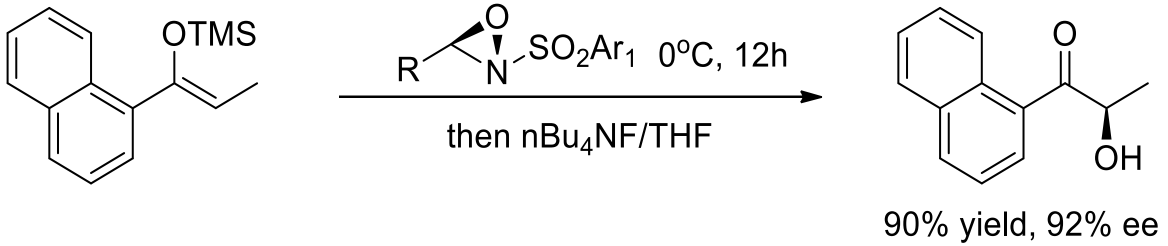


Evans, D. A.; Morrissay, M. M.; Dorow, R. L. *J. Am. Chem. Soc*. **1985**, *107*, 4346

O Transfer: α-Hydroxylation of enolates

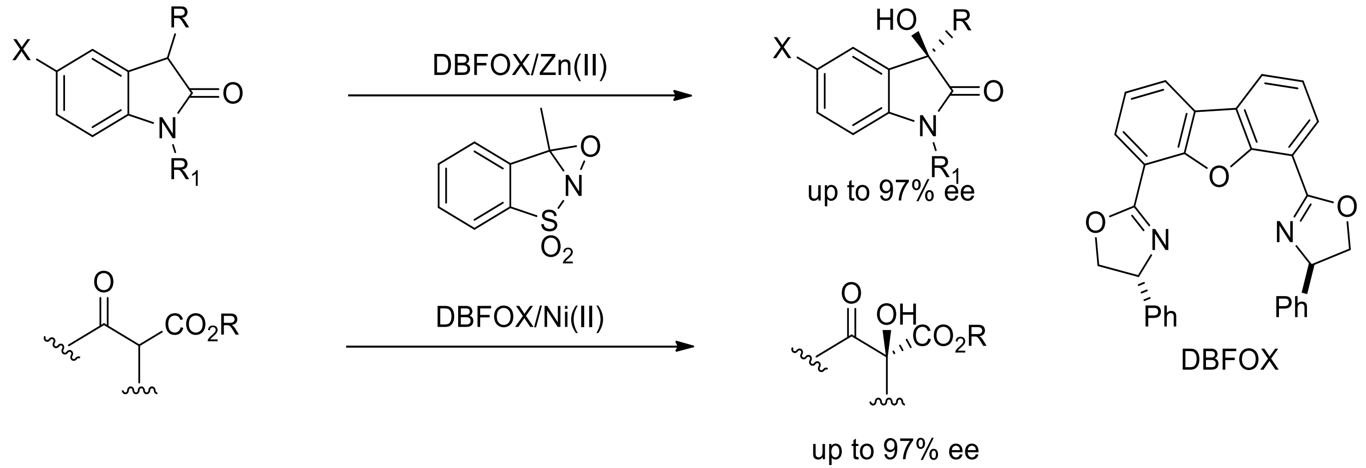


Towson, J. C.; Weismiller, M. C.; Lal, S. G.; Sheppard, A. C.; Davis, F. A. Org. Synth. **1990**, *69*, 158



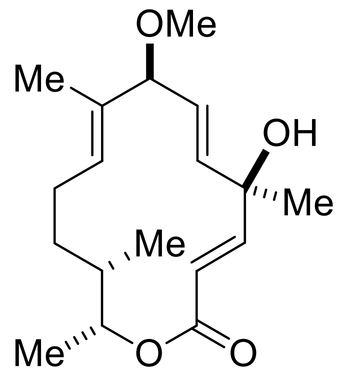
Tanaka, N.; Tsutsumi, R.; Uraguchi, D.; Ooi, T. *Chem. Commun.* **2017***, 53*, 6999

O Transfer: α-Hydroxylation of enolates

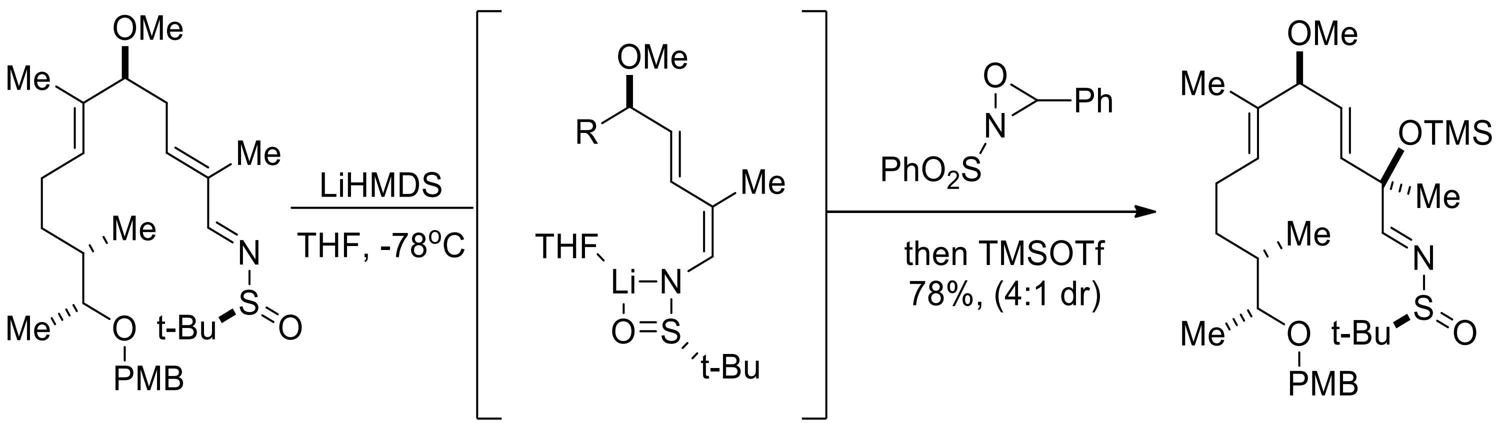


Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488

O Transfer: Applications in total synthesis

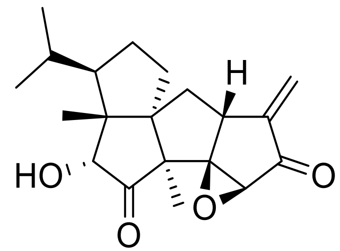


(-)-albocycline

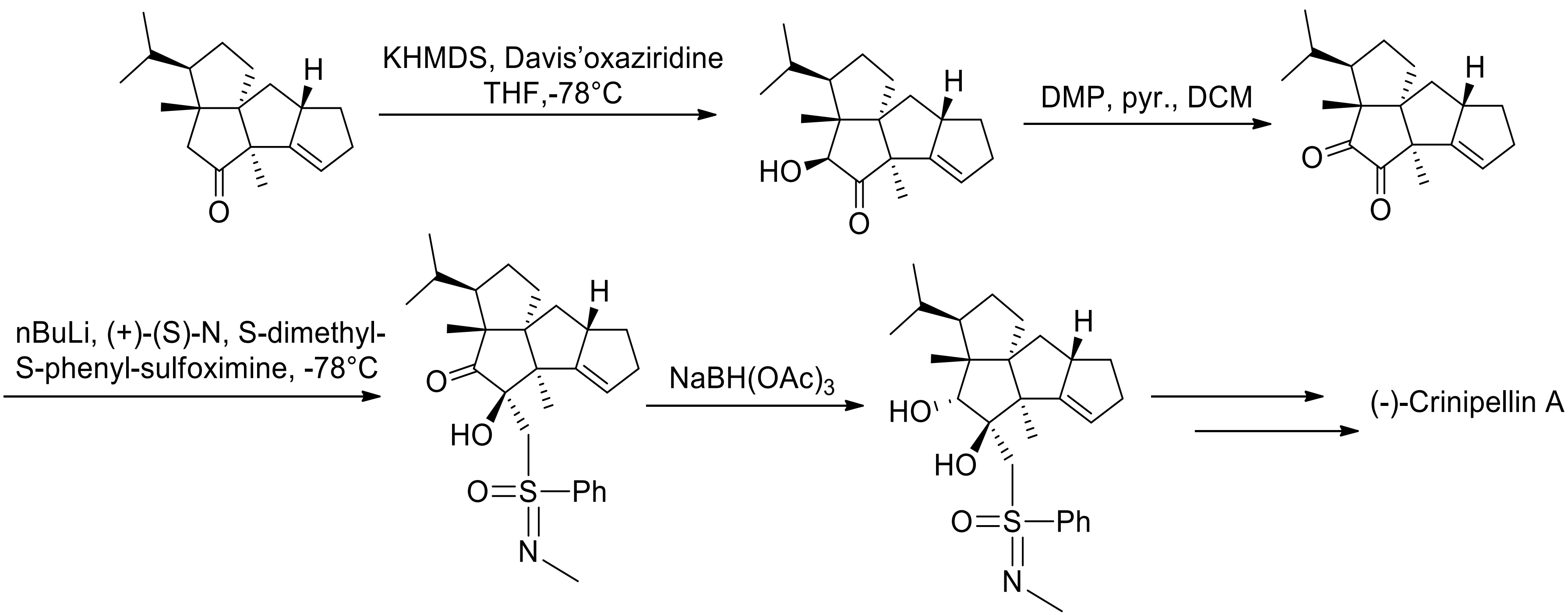


Chatare, V. K.; Andrade, R. B. *Angew. Chem. Int. Ed*. **2017**, *56*, 5909

O Transfer: Applications in total synthesis



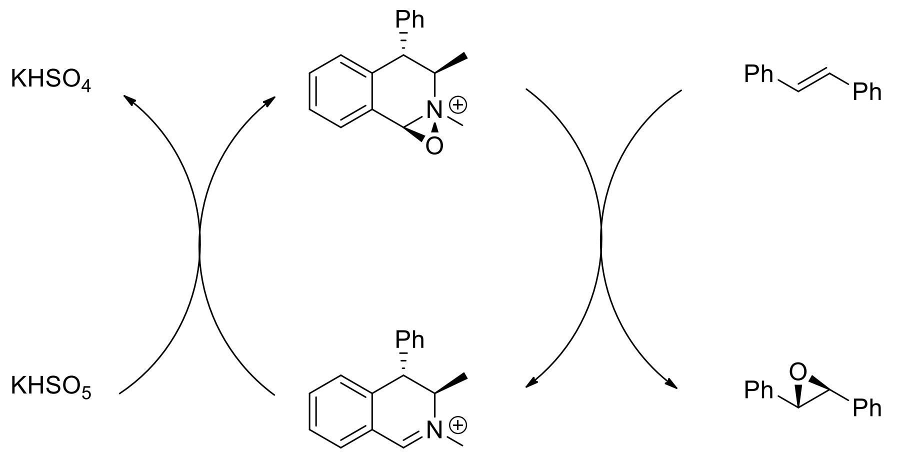
(-)-Crinipellin A



Kang, T.; Song, S. B.; Kim, W. Y.; Kim, B. G.; Lee, H. Y. *J. Am. Chem. Soc*. **2014**, *136*, 10274

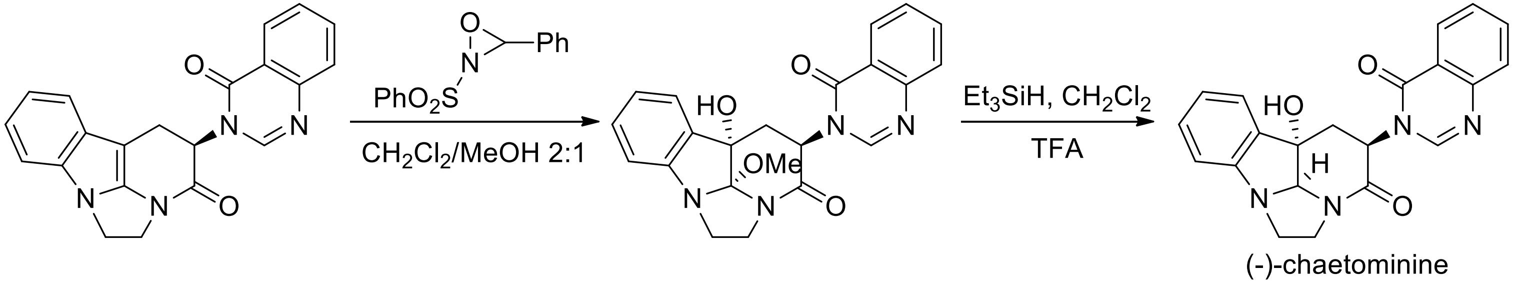
O Transfer: Epoxidation

Chiral Oxaziridinium Salt for asymmetric epoxidation of unfunctionalized alkenes



Luis, B.; Gilles, H.; Marie, L.; Xavier, L. *Tetrahedron Lett.* **1993**,*34*, 7271

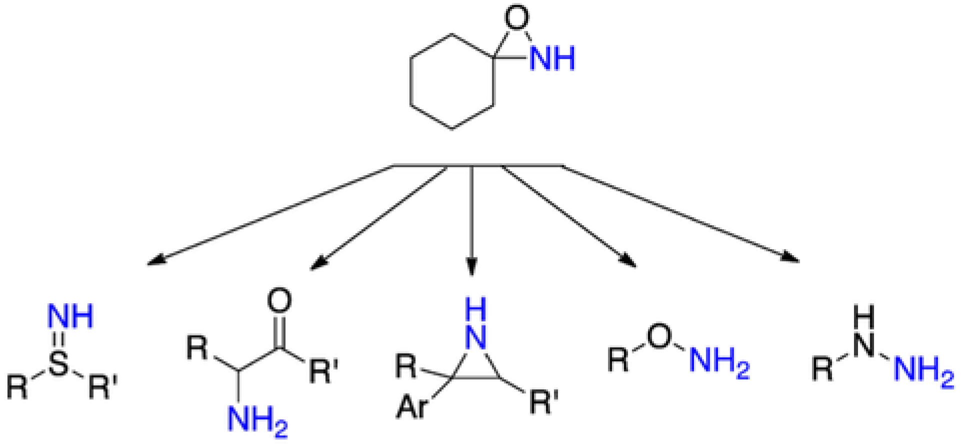
Epoxidation of alkenes



Malgesini, B.; Forte, B.; Borghi, D.; Quartier, F.; Gennari, C.; Papeo, G. *Chem. Eur. J.* **2009**,*15*, 7922

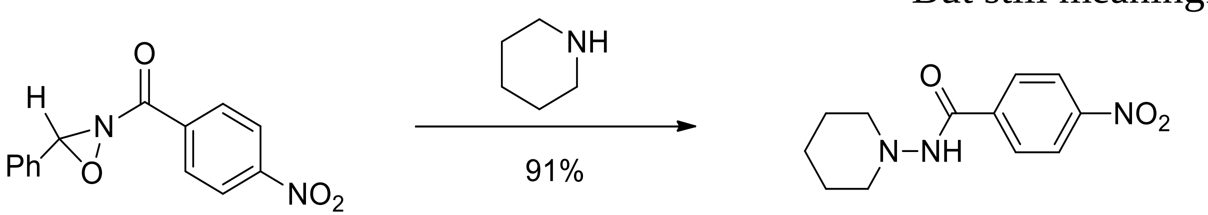
N Transfer

Amination of nucleophiles with *N*-unsubstituted oxaziridines



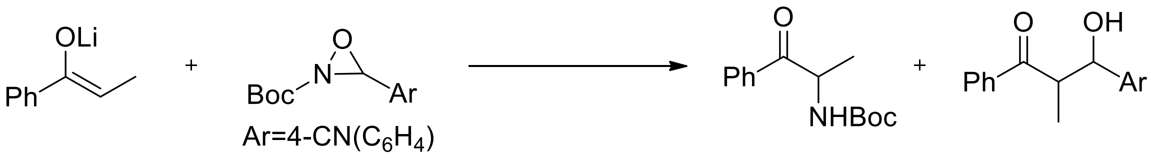
N-acylamidation with *N*-substituted oxaziridines

Rare
Challenging
But still meaningful!

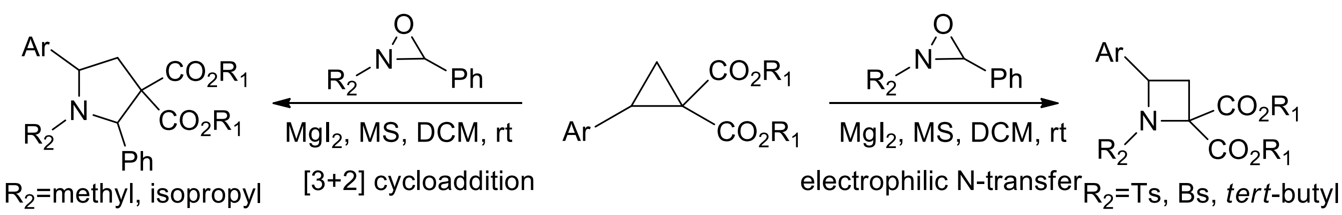


Andreae, S.; Schmitz, E. *Cheminform.* **1991**,*22*, 327

N Transfer: Applications

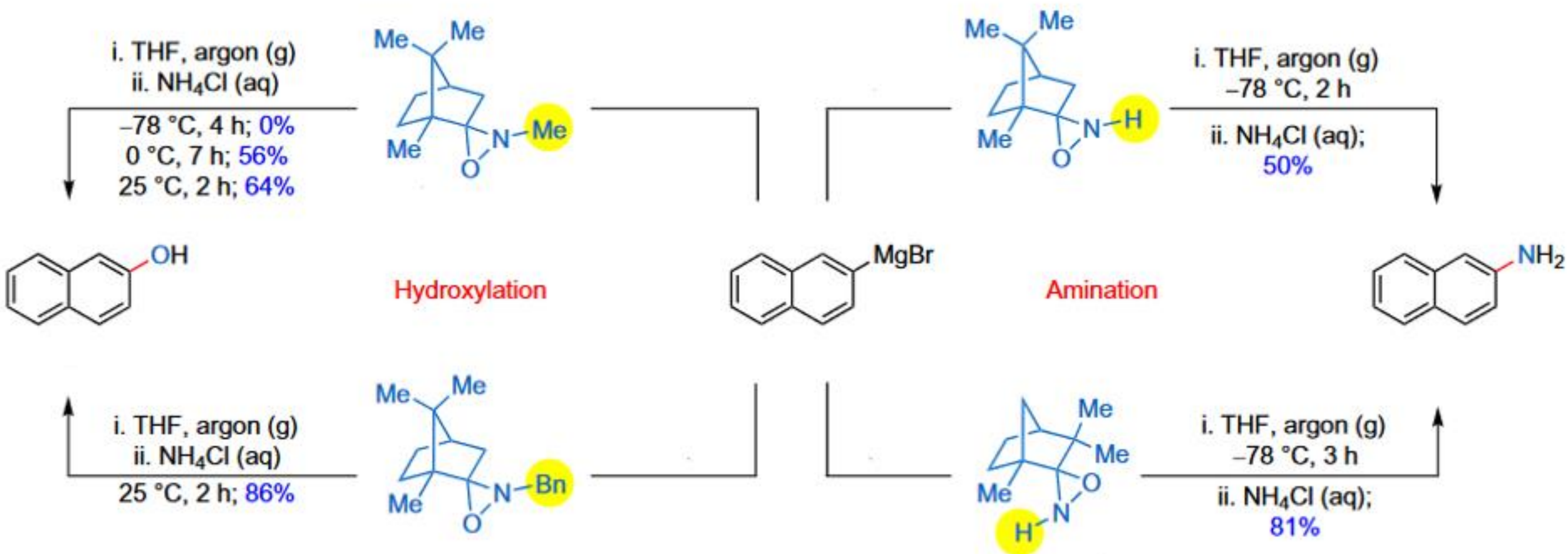


Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367



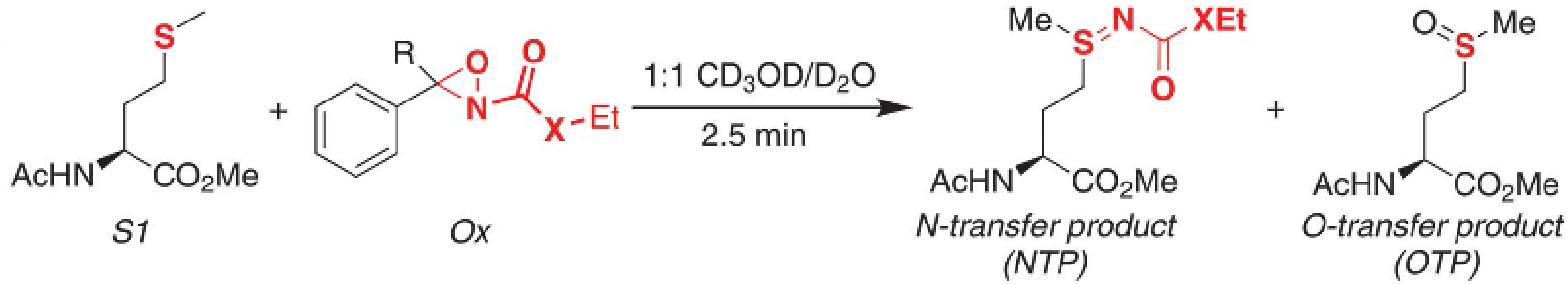
Ghosh, A.; Mandal, S.; Chattaraj, P. K.; Banerjee, P. *Org. Lett.* **2016**, *18*, 4940

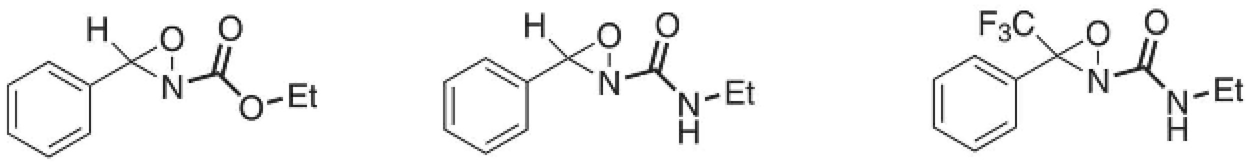
N Transfer: Applications



Gao, H.; Zhou, Z.; Kwon, D.-H.; Coombs, J.; Jones, S.; Behnke, N. E.; Ess, D. H.; Kürti, L. *Nat. Chem.* **2016**, *9*, 681

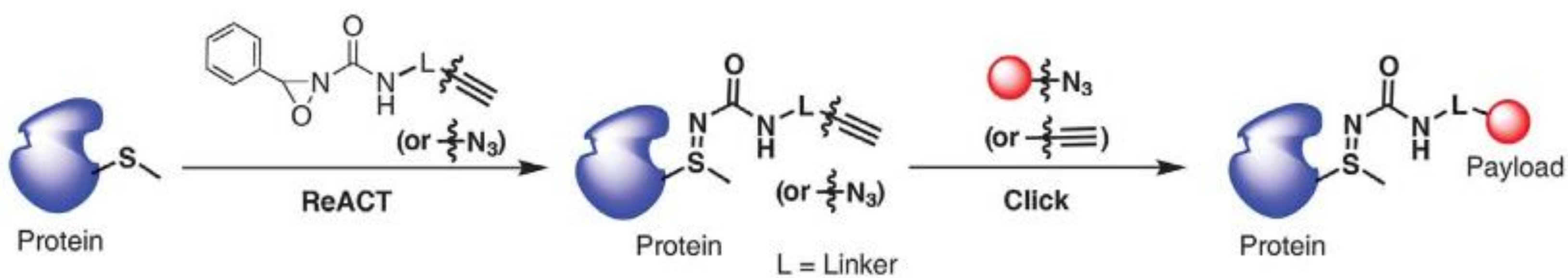
N Transfer: Applications





	Ox1	*Ox2*	*Ox3*
Conversion:	95%	93%	58%
Ratio (NTP/OTP):	5:1	12:1	2:1

(solvent: 100% CD_3OD, 60%, 6:1)
(solvent: 5% CD_3OD/D_2O, 95%, 18:1)



Lin, S.; Yang, X.; Jia, S.; Weeks, A. M.; Hornsby, M.; Lee, P. S.; Nichiporuk, R. V.; Iavarone, A. T.; Wells, J. A.; Tosta, F. D.; Chang, C. J. *Science.* **2017**, *355*, 597

Content

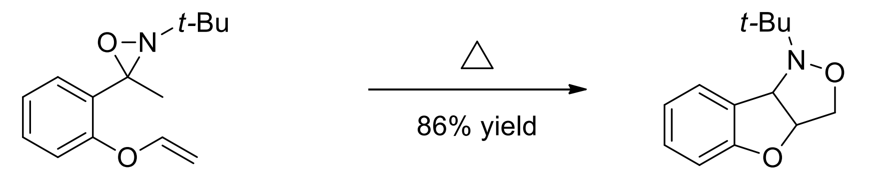
1. Introduction of Oxaziridines

2. Heteroatom transfer reactions: O vs N Transfer

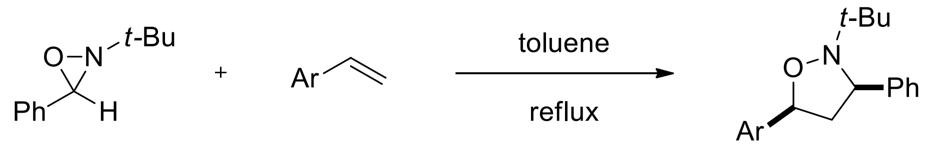
3. [3+2] cycloadditions: C-O vs N-O vs C-N bond cleavage

4. Conclusion

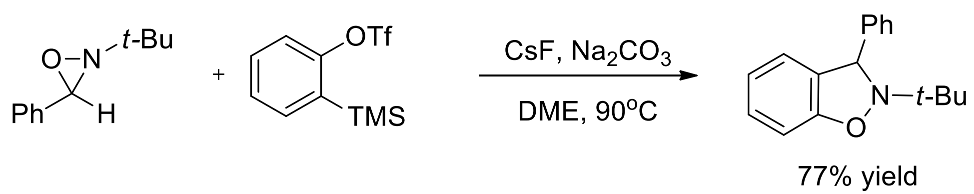
[3+2] cycloadditions



Padwa, A.; Koehler, K. F. *Heterocycles* **1986**, *24*, 611

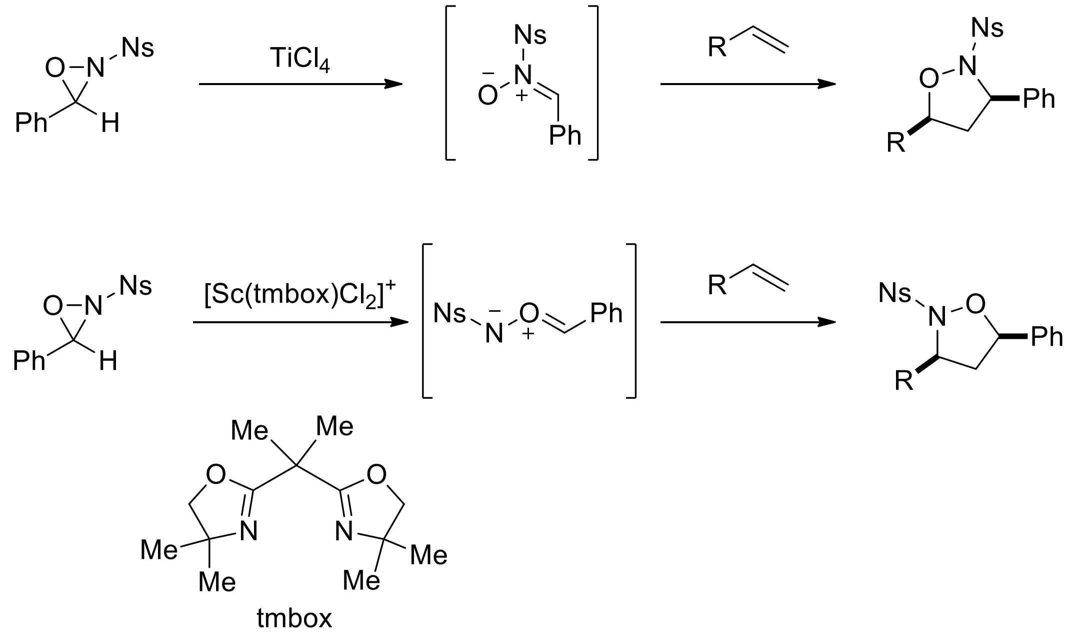


Fabio, M.; Ronzini, L.; Troisi, L. Tetrahedron 2007, 63, 12896



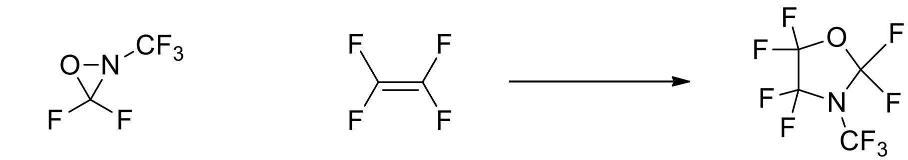
Kivrak, A.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 7381

[3+2] cycloadditions



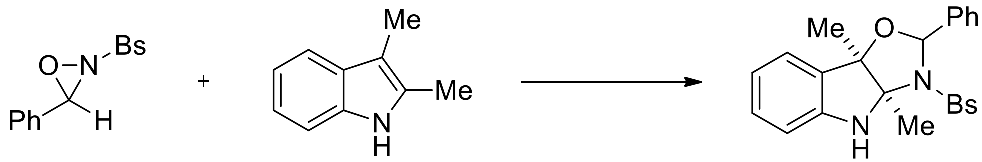
Partridge, K. M.; Anzovino, M. E.; Yoon, T. P. *J. Am. Chem. Soc*. **2008**, *130*, 2920
Partridge, K. M.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 930

[3+2] cycloadditions



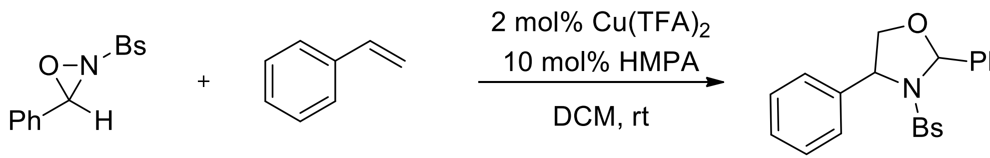
78% yield

Lam, W. Y.; DesMarteau, D. D. *J. Am. Chem. Soc.* **1982**, *104*, 4034



71% yield

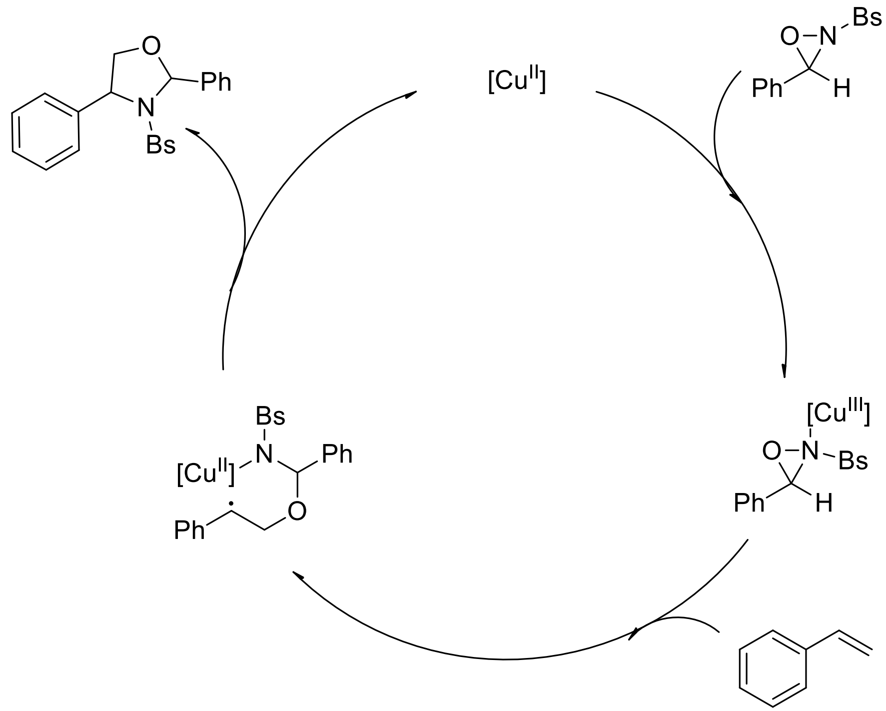
Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159



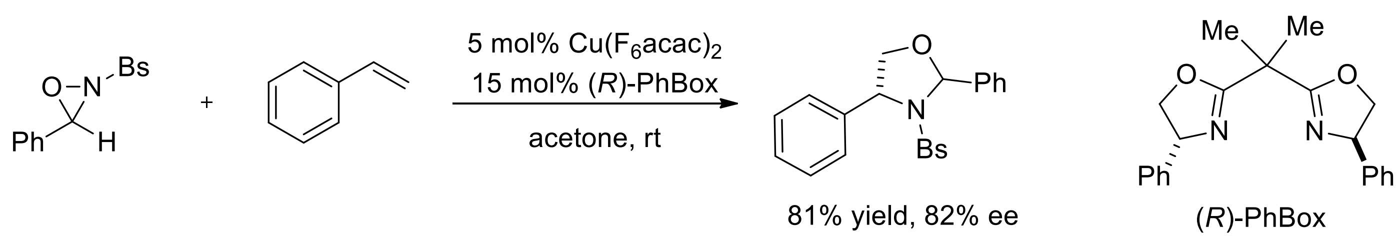
87% yield

Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866
Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610

[3+2] cycloadditions



Benkovics, T.; Du, J.; Guzei, I. A.; Yoon, T. P. *J. Org. Chem.* **2009**, *74*, 5545



Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, *65*, 5118

Content

1. Introduction of Oxaziridines

2. Heteroatom transfer reactions: O vs N Transfer

3. [3+2] cycloadditions: C-O vs N-O vs C-N bond cleavage

4. Conclusion

Conclusion

The chemistry of oxaziridines has developed in many diverse and unexpected directions over the past 6 decades

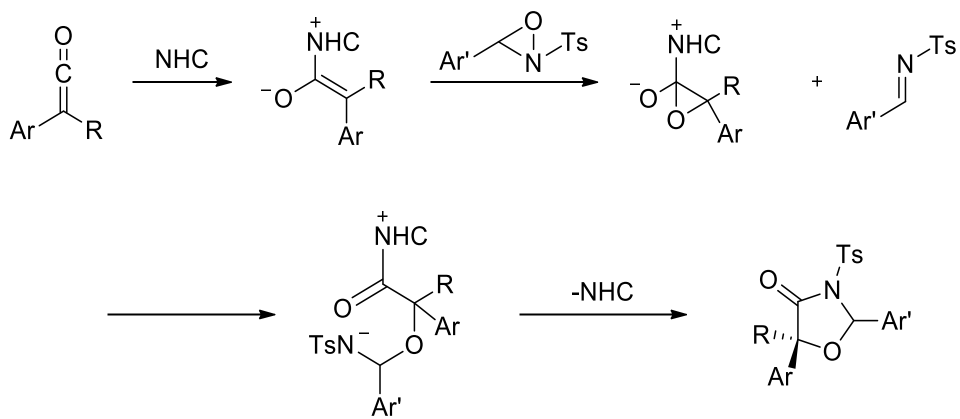
Heteroatom transfer: O vs N transfer (steric and electronic properties)
[3+2]cycloaddition reactions: C-O vs N-O vs C-N bond cleavage (Lewis acid catalysis)
skeletal rearrangement reactions

Synthetic potential in total synthesis

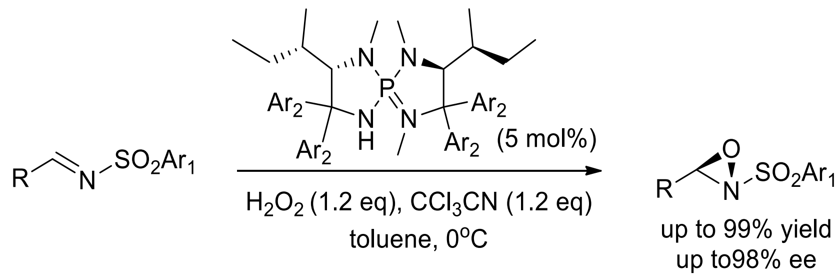
Thanks for your attention!

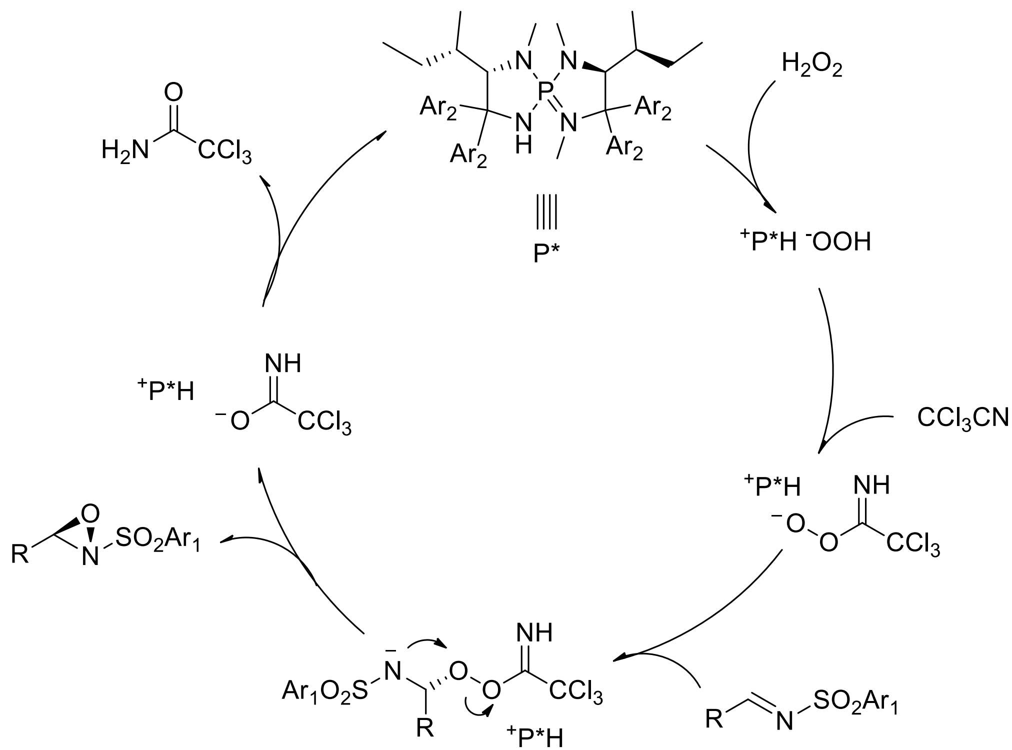
Question 1: Please propose a possible mechanism for the [3+2] cyclization

Proposed Mechanism:



Question 2: Please explain the role of CCl_3CN in this transformation





Frontier in Organic Chemistry – Heterocyclic Chemistry
18.05.2018

Catalytic Enantioselective Hetero-Diels-Alder reactions of Carbonyl and Imines

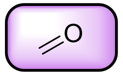
Guillaume Pisella

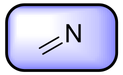
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Content

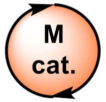
1. Introduction : Mechanistic Aspects of the Hetero Diels-Alder reaction (HDA)
2. Metal catalyzed enantioselective HDA
3. Organocatalyzed enantioselective HDA
4. Conclusion and Outlook
5. Questions

Oxo-DA (carbonyls) – Aza-DA (imines)





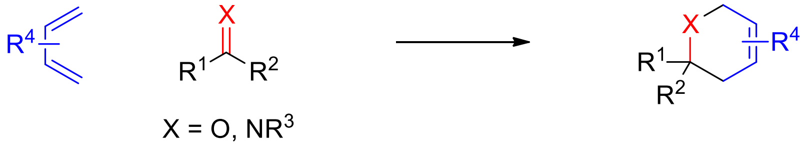
Metal cat. – Organo cat.



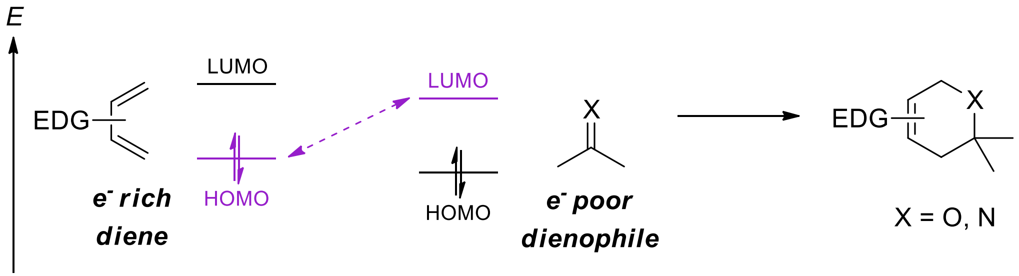
Normal Electron Demand (NED) – Inverse Electron Demand (IED)

1. Mechanistic Aspects of the Hetero Diels-Alder reaction (HDA)

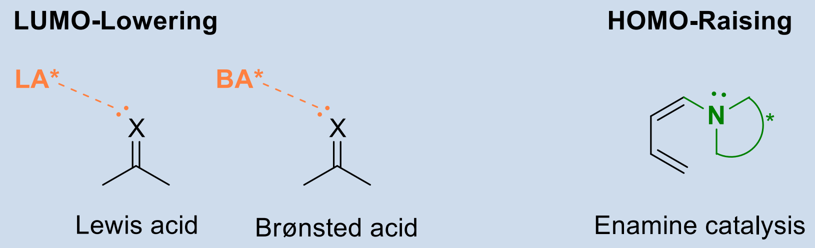
HDA = ***[4+2] cycloaddition*** in which the diene or the dienophile contains at least one ***heteroatom***.



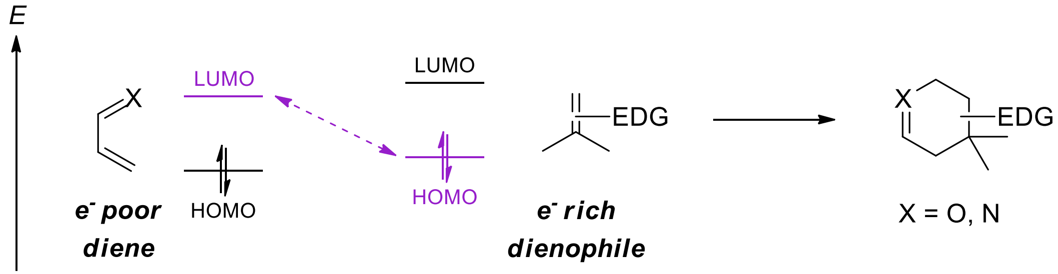
1. Normal electron demand HDA



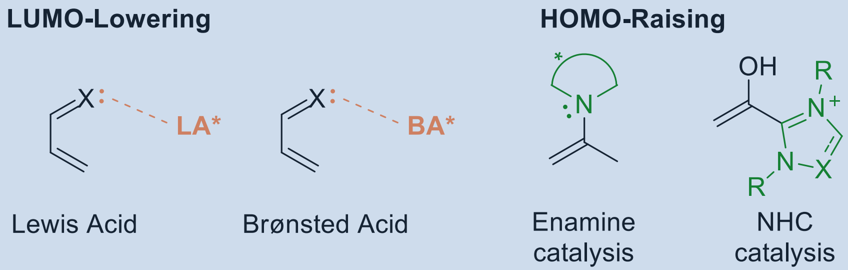
Activation modes:



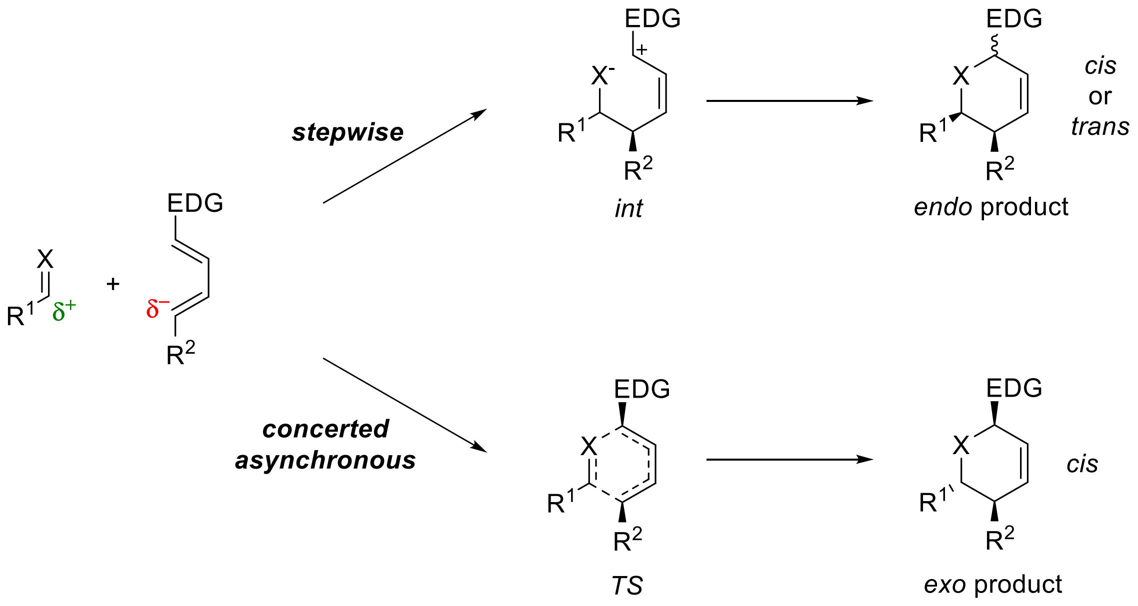
2. Inverse electron demand HDA

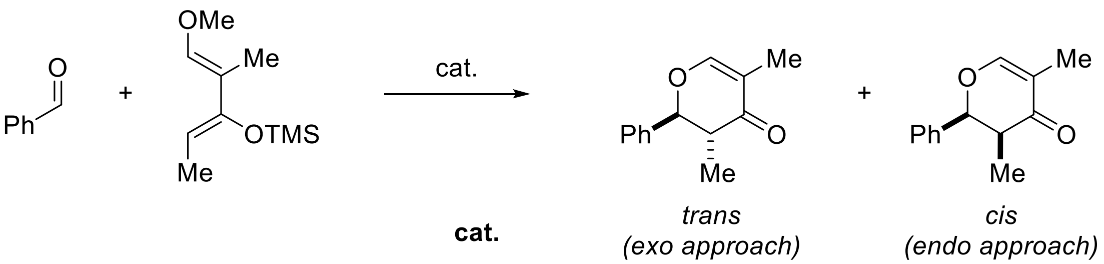


Activation modes:



3. Reaction pathway





cat.	trans (exo approach)	cis (endo approach)
BF_3	58	23
$ZnCl_2$	<2	78

The ***regiochemistry*** is rationalized by the favored ***electronics polar interactions***

The ***stereochemistry*** outcome depends of the favored **reaction pathway** and the **substrates geometry.**

And the **substrates approach**: *endo/exo*

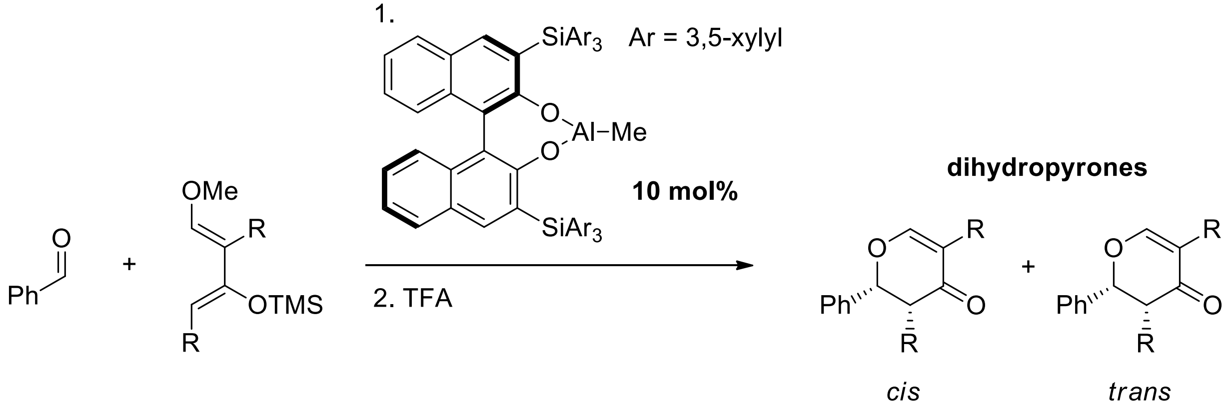
High influence of the catalyst !

S. J. Danishefsky, E. Larson, D. Ashkin, N. Kato, *J. Am. Chem. Soc.* **1985**, *107*, 1246.

Early examples of catalytic enantioselective HDA of carbonyl compounds

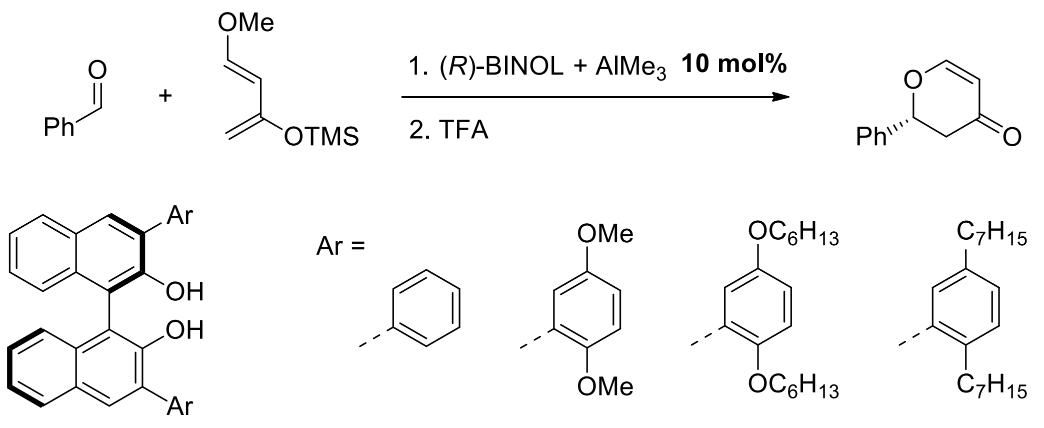
Yamamoto:

BINOL-Al^{III}

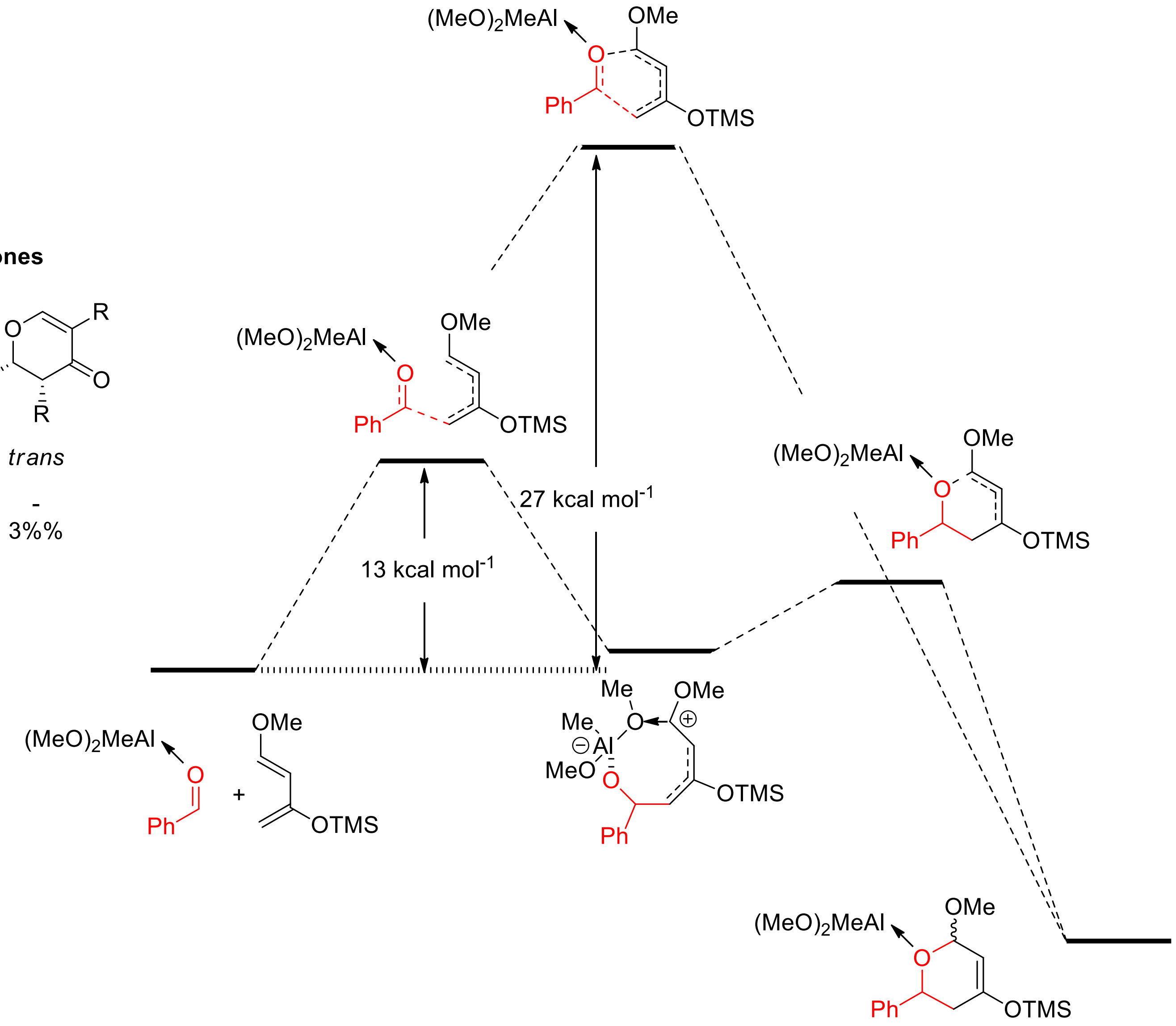


	cis	trans
R = H,	91%, 81%ee	-
R = Me,	90%, 975ee	3%%

Re-investigation by Jørgensen



29%, 63%ee 50%, 96%ee 97%, 99%ee 95%, 87%ee

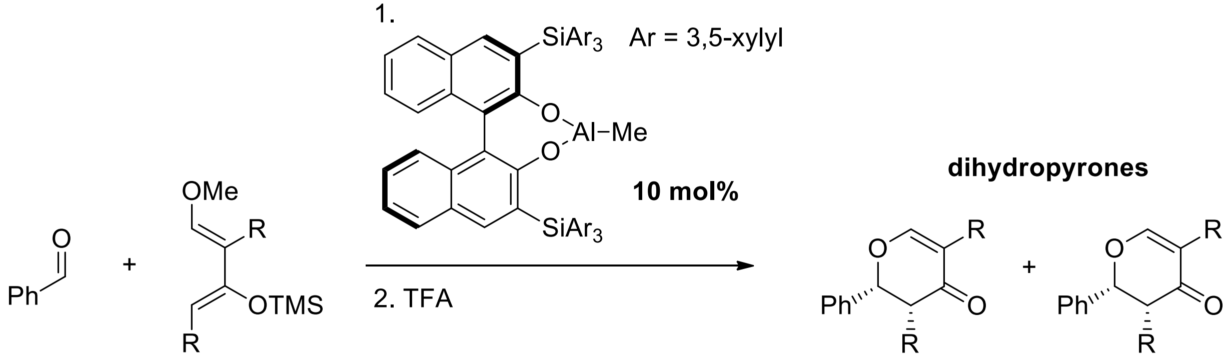


K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.
Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123.

Early examples of catalytic enantioselective HDA of carbonyl compounds

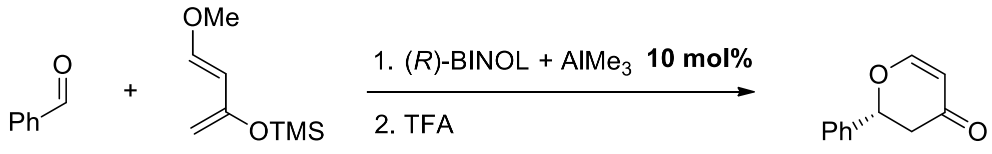
Yamamoto:

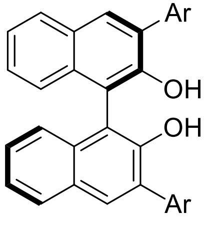
BINOL-Al^{III}



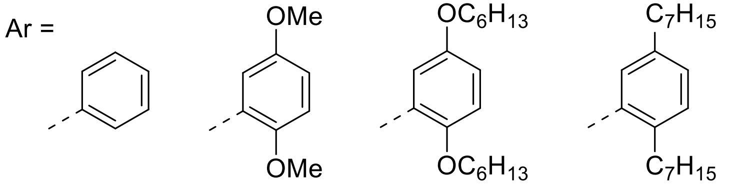
	cis	*trans*
R = H,	91%, 81%ee	-
R = Me,	90%, 975ee	3%%

Re-investigation by Jørgensen

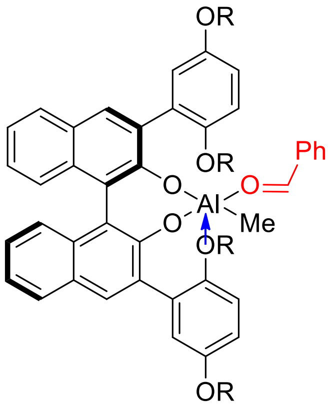




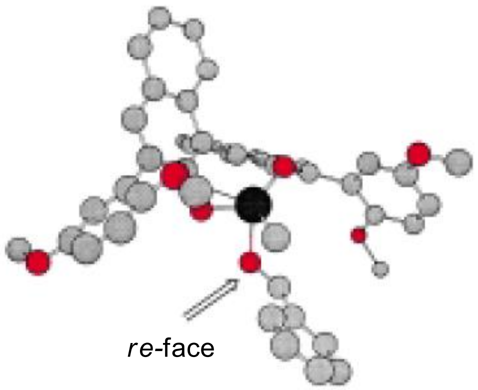
(*R*)-BINOL



29%, 63%ee 50%, 96%ee 97%, 99%ee 95%, 87%ee



model for selectivity

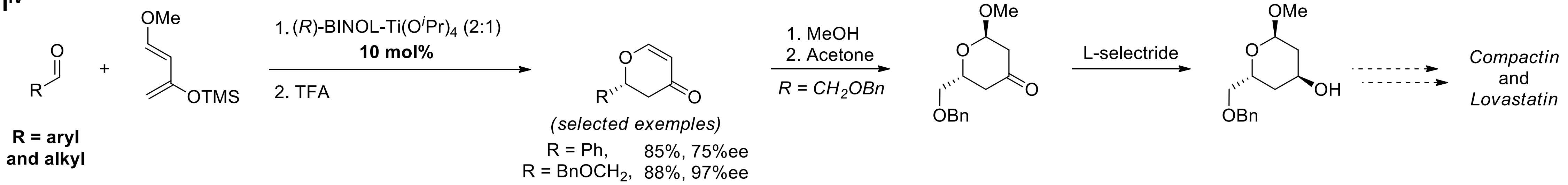


K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.
Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123.

Early examples of catalytic enantioselective HDA of carbonyl compounds

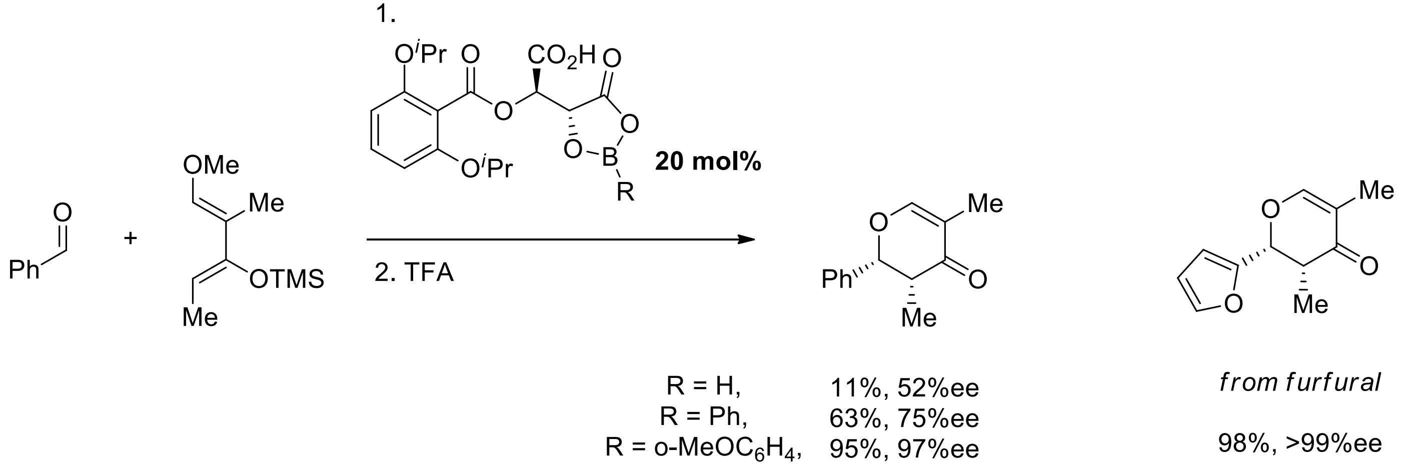
Keck:

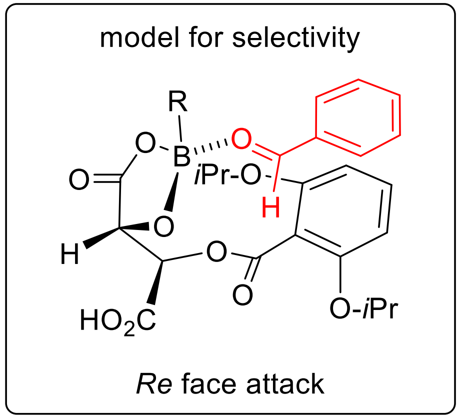
BINOL-Ti^{IV}



Yamamoto:

CAB Catalysts





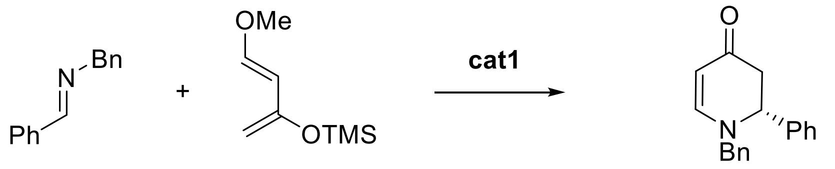
Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.

Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951.

Early examples of catalytic enantioselective HDA with imines

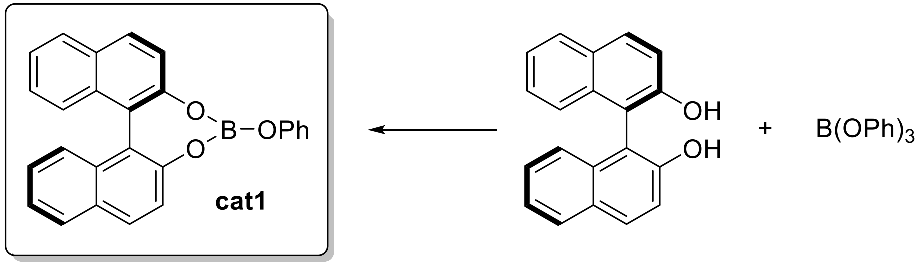
Yamamoto:

Chiral Boron

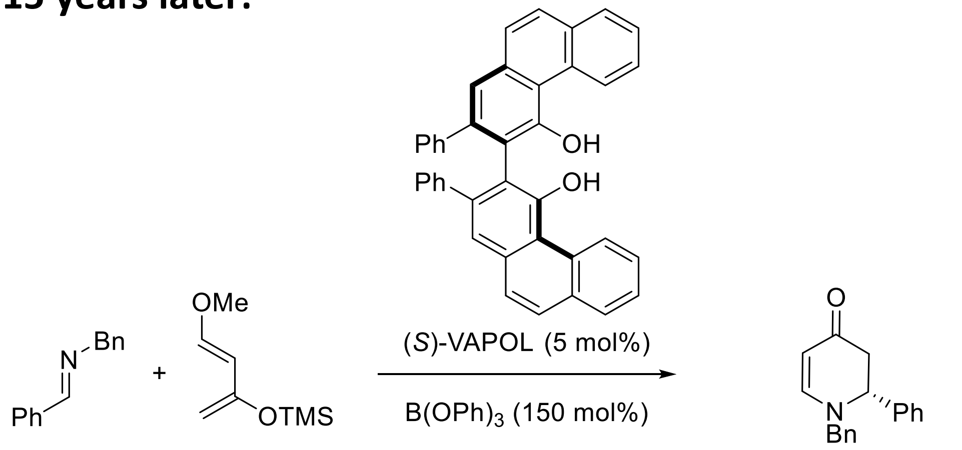


(5 mol%)
<5% yield
(stochiometric)
75% yield, 85% ee

Catalyst preparation:

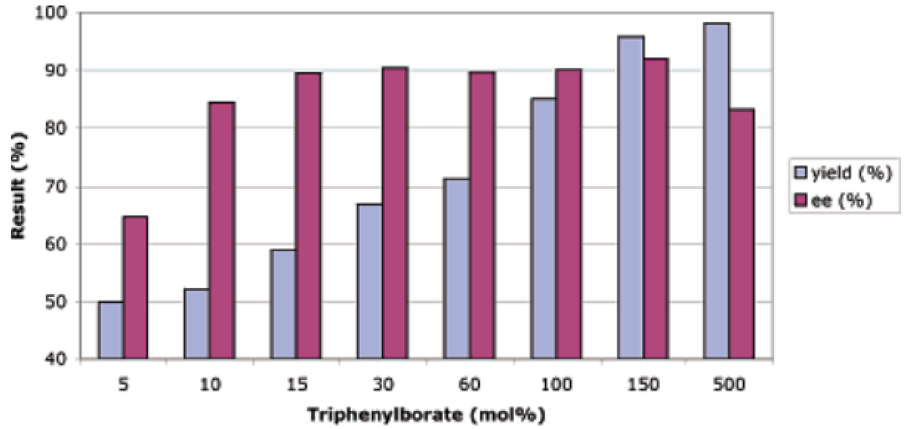


Wulff… 15 years later:



96% yield, 92% ee

Chart 1. Effect of Triphenylborate Loading with 5 mol % of VAPOL

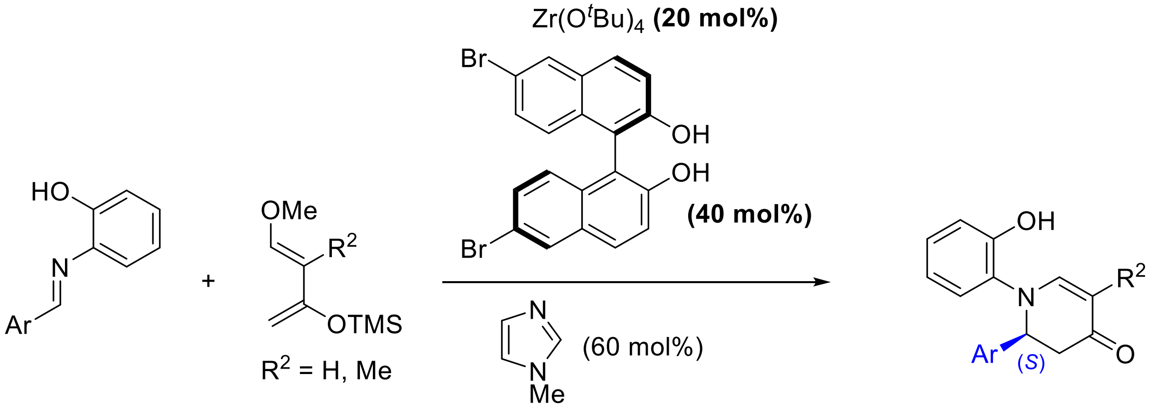


K. Hattori and H. Yamamoto, *J. Org. Chem*., **1992**, *57*, 3264; K. Hattori and H. Yamamoto, *Tetrahedron*, **1993**, *49*, 1749; K. Ishihara, M. Miyata, K.Hattori, T. Tada and H. Yamamoto, *J. Am. Chem. Soc*., **1994**, *116*, 10520.
C. A. Newman, J. C. Antilla, P. Chen, A. V. Predeus, L. Fielding, W. D. Wulff, *J. Am. Chem. Soc.* **2007**, *129*, 7216.

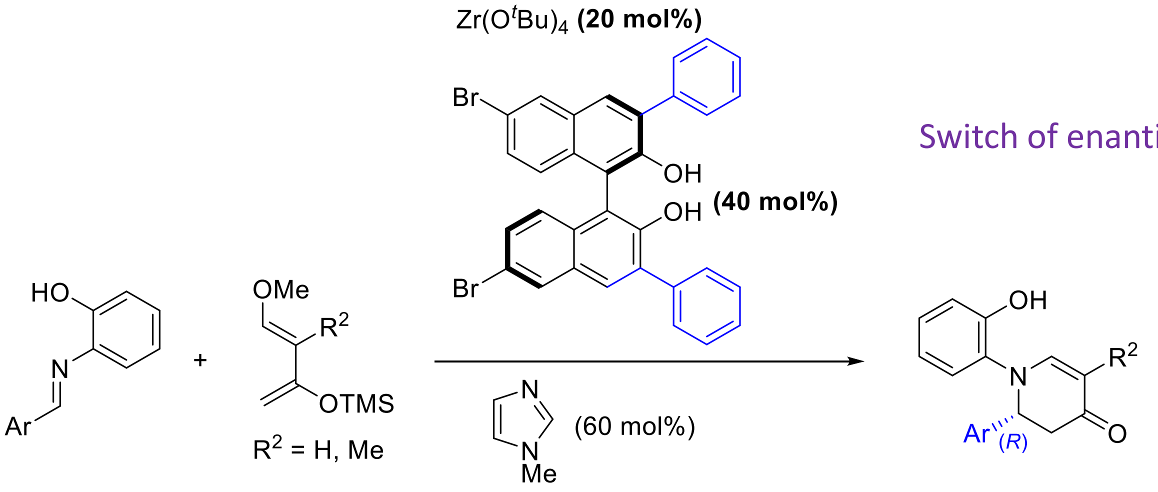
Early examples of catalytic enantioselective HDA with imines

Kobayahi:

BINOL-Zr^{II}

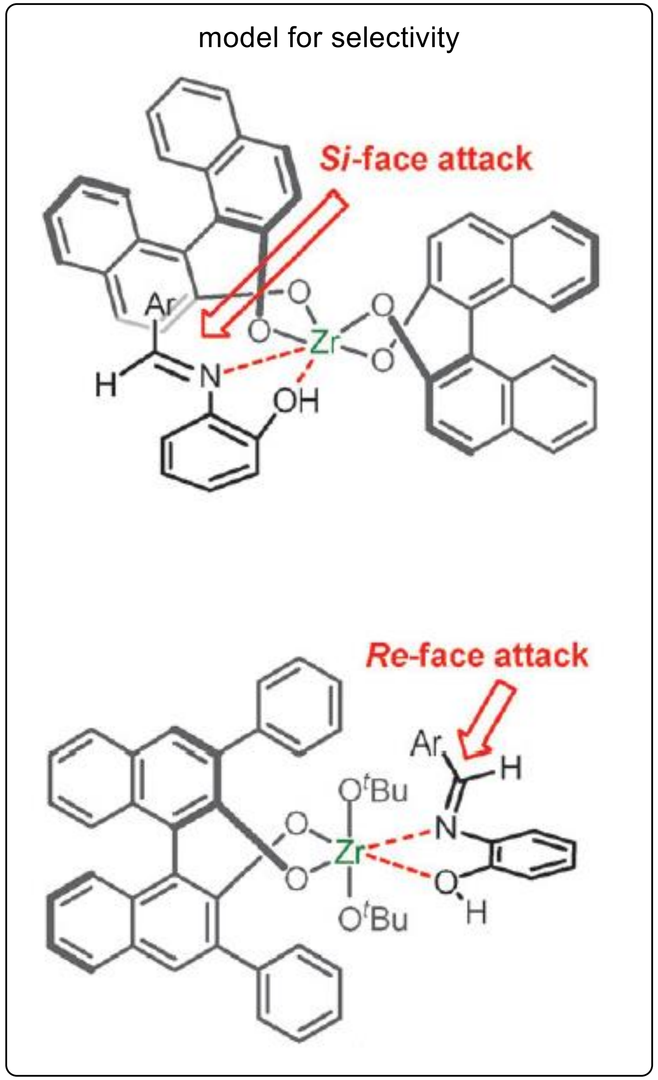


17 examples
47-98% yield
64-93%ee



Switch of enantioselectivity !

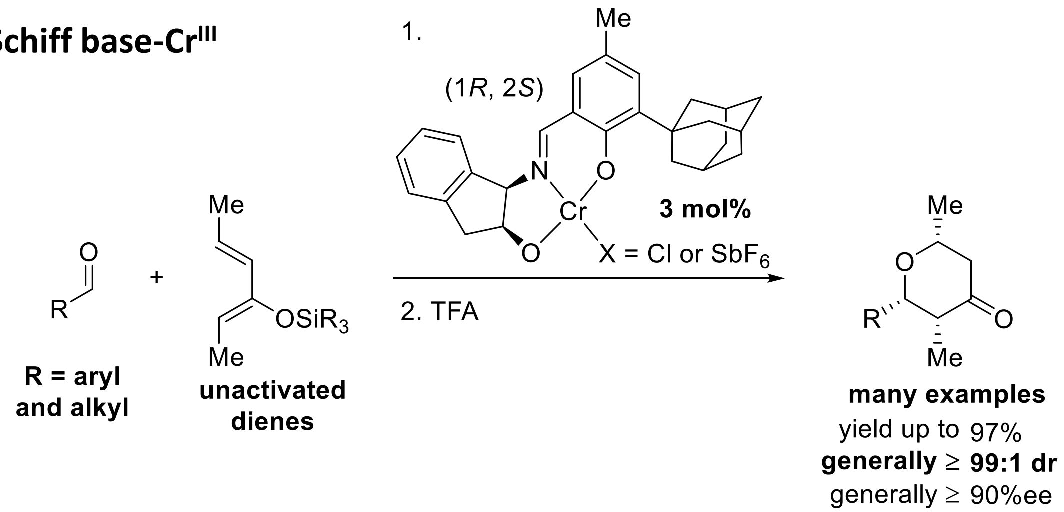
17 examples
64-99% yield
80-91%ee



S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem. Int. Ed.* **1998**, *37*, 979.
S. Kobayashi, K.-I. Kusakabe, S. Komiyama and H. Ishitani, *J. Org. Chem.*, **1999**, *64*, 4220–4221

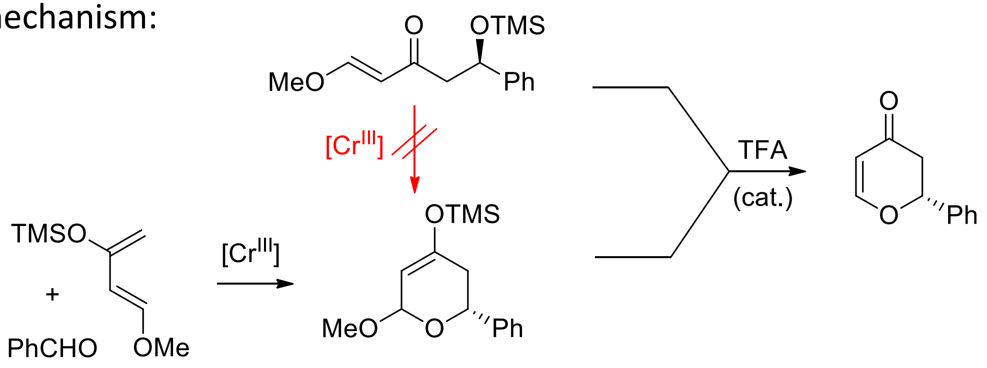
Jacobsen:

Schiff base-Cr^{III}

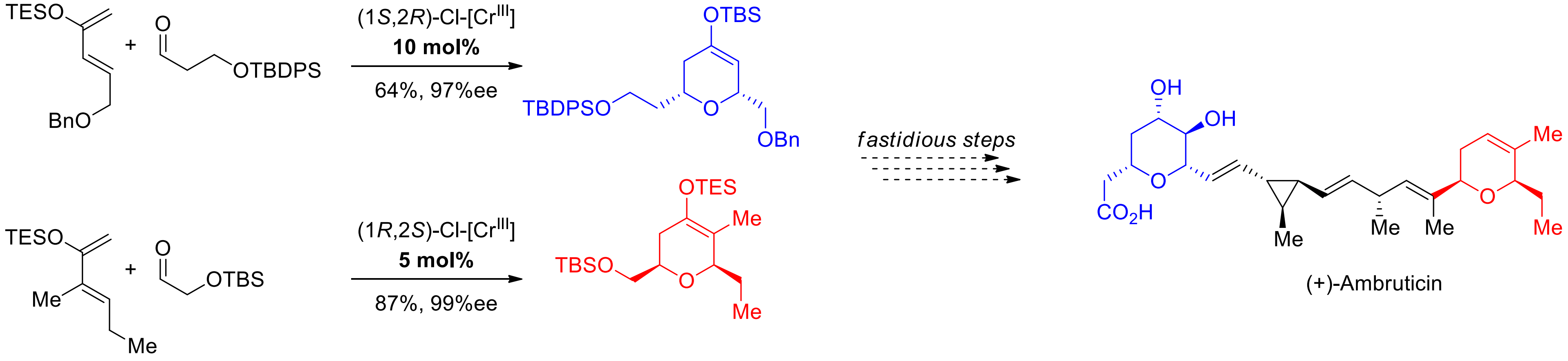


The most applied L.A. catalysts with **unactivated diene** !

Concerted mechanism:



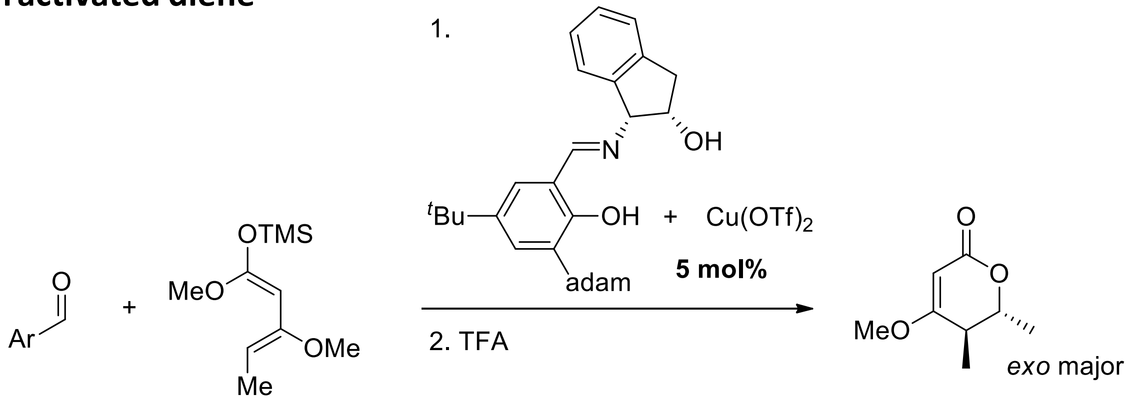
A “two birds with one stone” application



Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398.
For the seminal work and mechanistic studies see: Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. Total synthesis of (+)-Ambruticin : P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772.

Feng:

Schiff base-Cu^{II} with activated diene



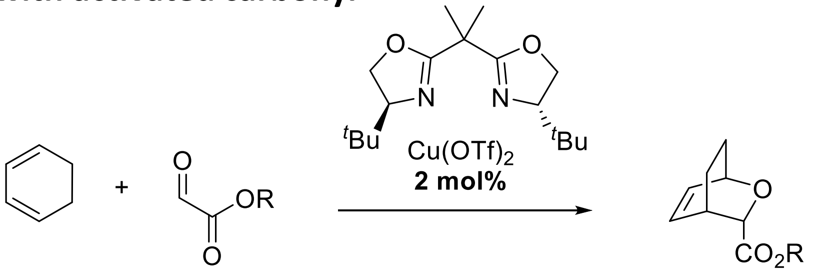
Brassard-type diene

yield = 40 - 70%
generally de ≥ 90%
generally ee ≥ 95%

Limitation !
Require activated dienes (e$^-$ rich)
or activated aldehydes (e$^-$ poor)

Jørgensen:

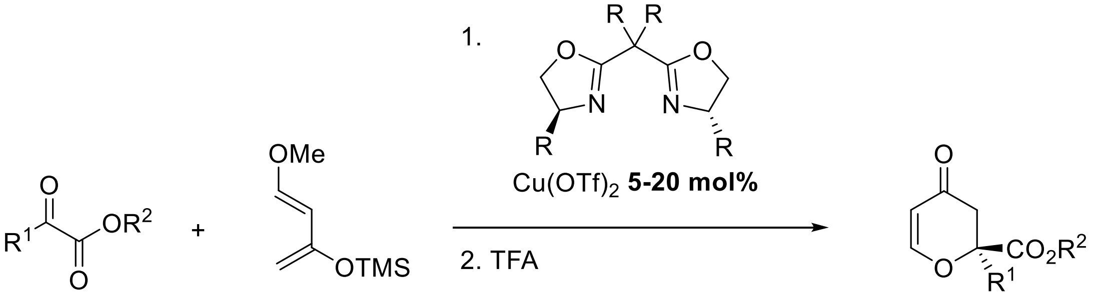
Box-Cu^{II} with activated carbonyl



oxo-ester

yield ≈ 60%
generally de ≈ 90%
generally ee = 95%

Ghosh and Shirai:



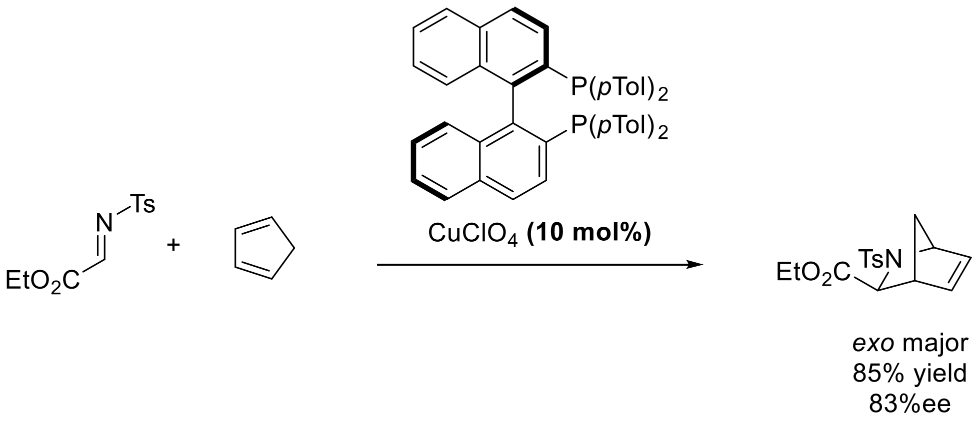
(selected exemples)

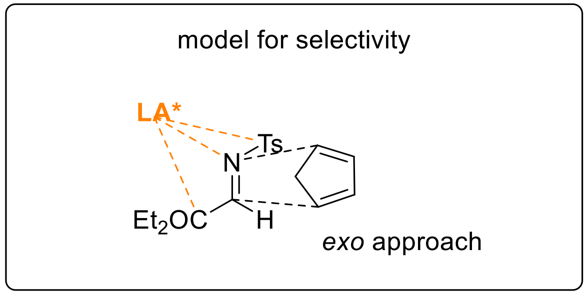
$R_1 = R_2$ = Me, 99%, 87%ee
R_1 = Me, R_2 = Et, 52%, 96%ee

Lin, L.; Fan, Q.; Qin, B.; Feng, X. *J. Org. Chem*. **2006**, *71*, 4141.
Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888. Ghosh, A. K.; Shirai, M. *Tetrahedron Lett*. **2001**, *42*, 6231.

Jørgensen:

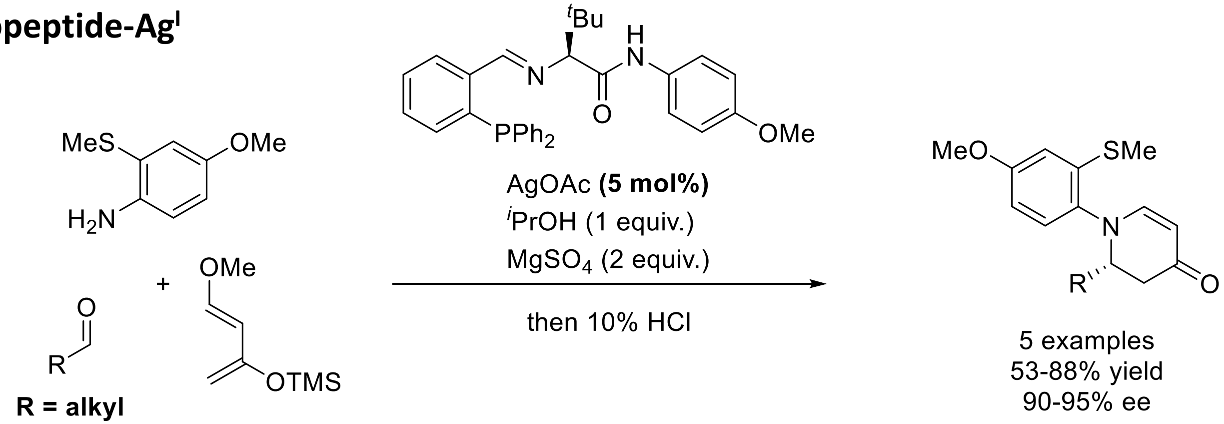
DiPhosphine-Cu^I





Hoveyda:

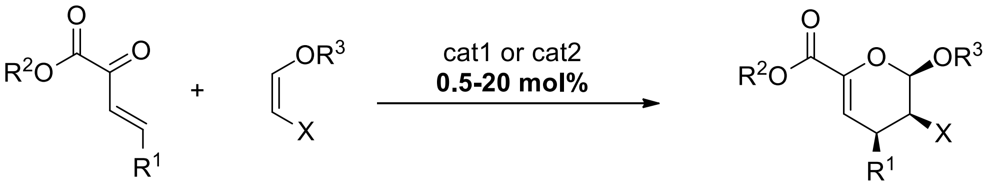
N,P-oligopeptide-Ag^I



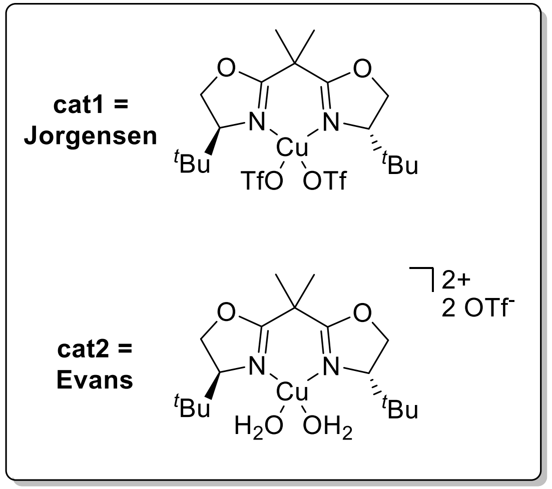
S. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.*, **2000**, *6*, 2435.
H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961.

Jørgensen and Evans:

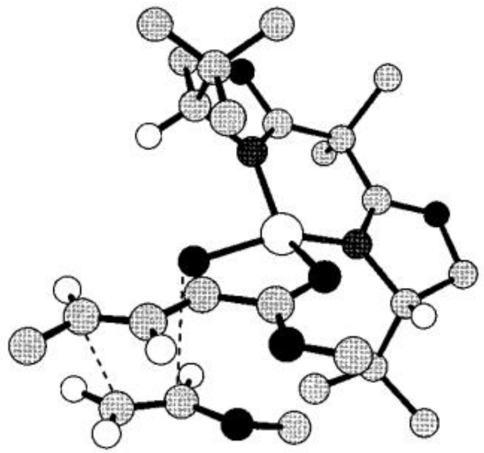
The Box-Cu^{II} revenge



generally very good yield, de and ee !!



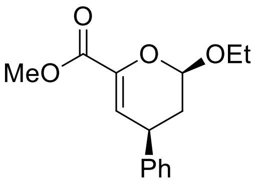
model for selectivity



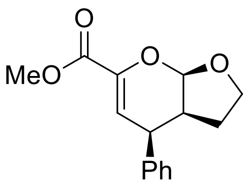
endo-E-syn approach

(selected exemples)

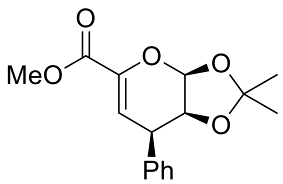
with cat1



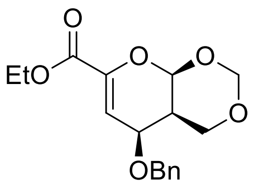
99%, 98de, 99%ee



96%, 100%de, 99%ee

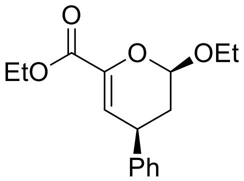


76%, 100%de, 99%ee

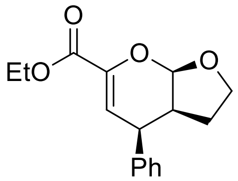


81%, 100%de, 91%ee

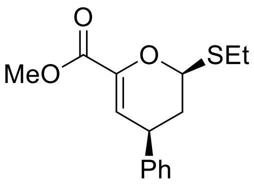
with cat2



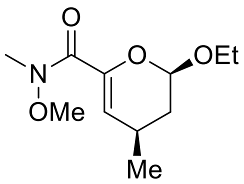
93%, 90de, 97%ee



96%, 100%de, 97%ee

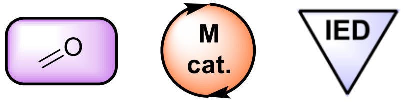


94%, 90%de, 97%ee



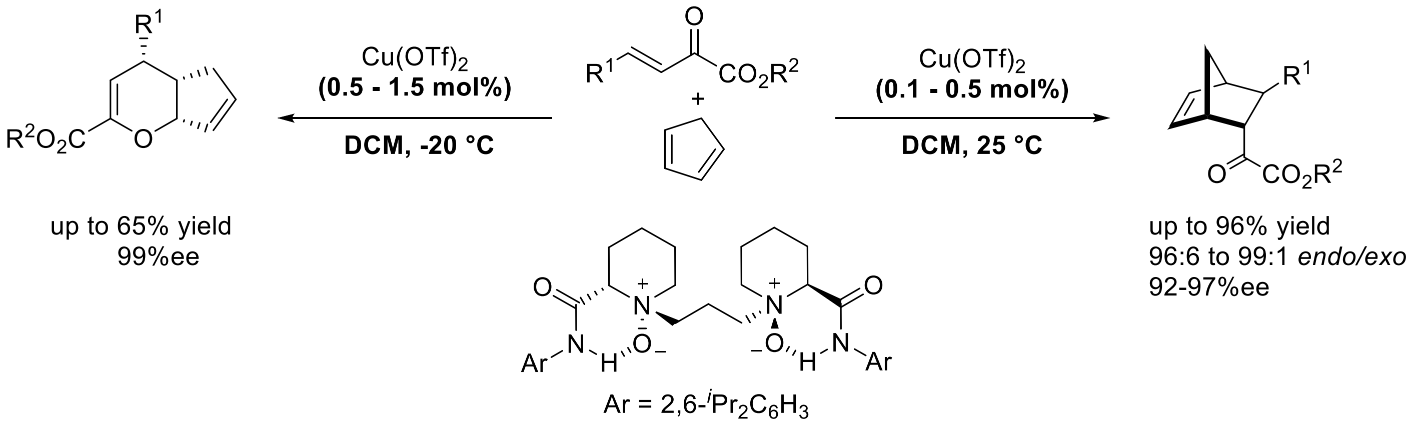
99%, 100%de, 99%ee

Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jorgensen, K.A. *J. Org. Chem*. **2000**, *65*, 4487.
Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc*. **2000**, *122*, 1635.

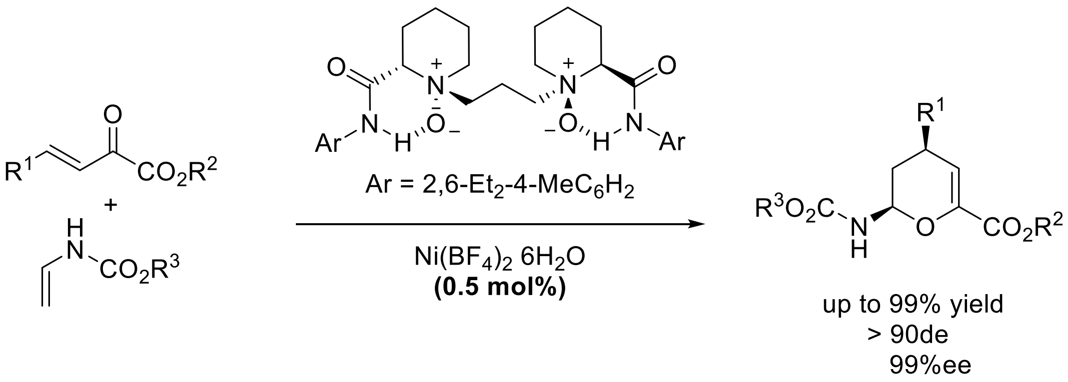


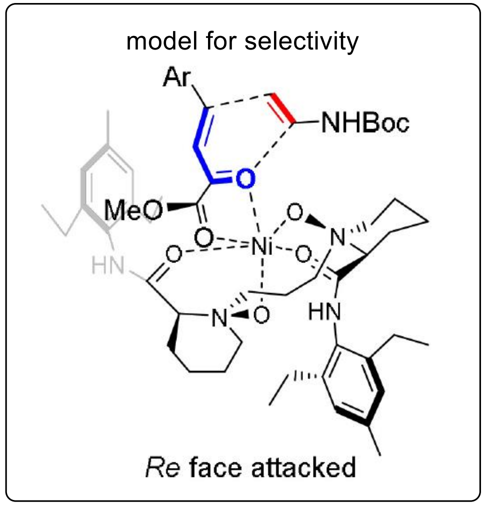
Feng:

N,N'-Dioxide-Cu^{II}



N,N'-Dioxide-Ni^{II}



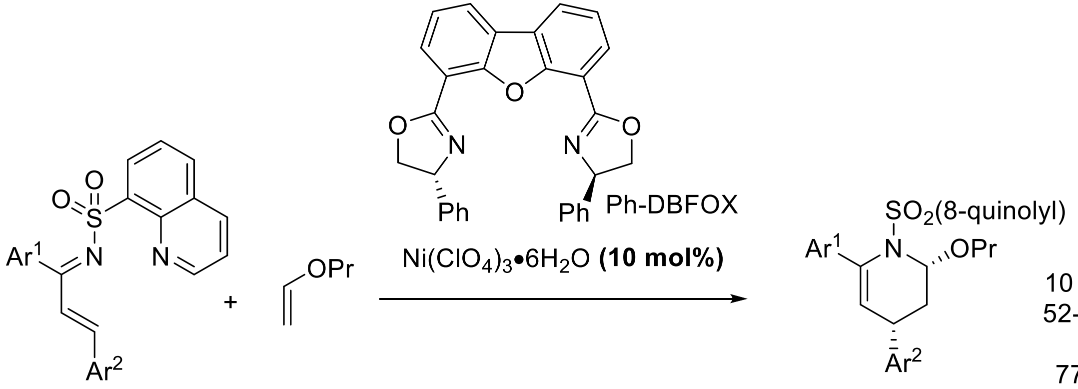


Y. Zhu, X. H. Chen, M. S. Xie, S. X. Dong, Z. Qiao, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 11963.
Y. H. Zhou, Y. Zhu, L. L. Lin, Y. L. Zhang, J. F. Zheng, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2014**, *20*, 16753.

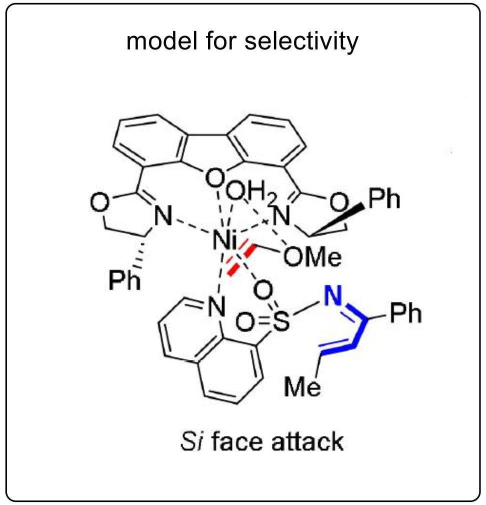
Inverse Electron Demand HDA with imines

Carretero:

Ni^{II}

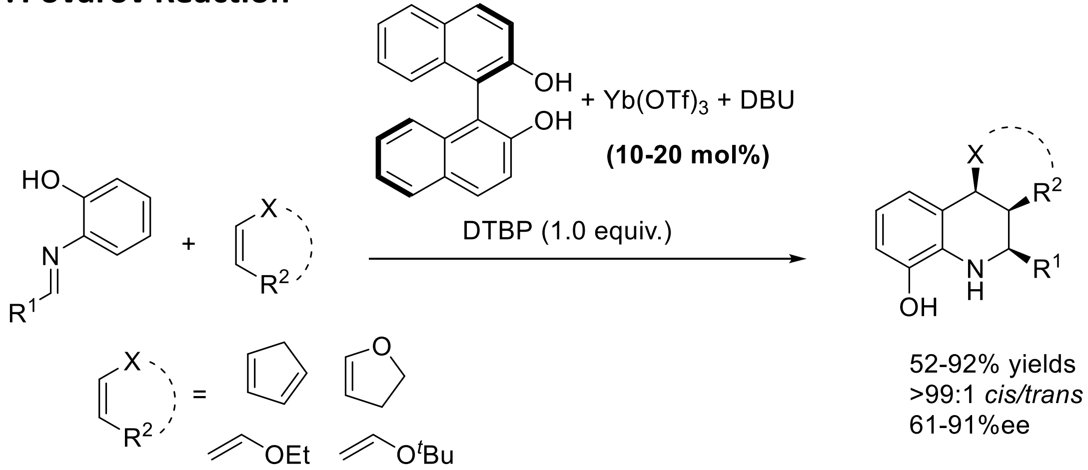


10 examples
52-75% yield
95% dr
77-92% ee

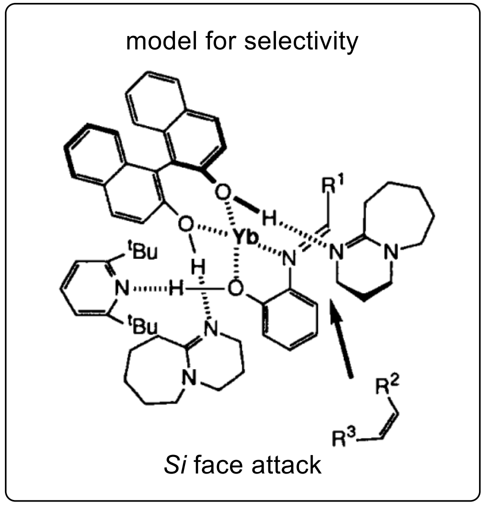


Kobayashi:

BINOL-Yb^{III} : Povarov Reaction



52-92% yields
>99:1 *cis/trans*
61-91%ee

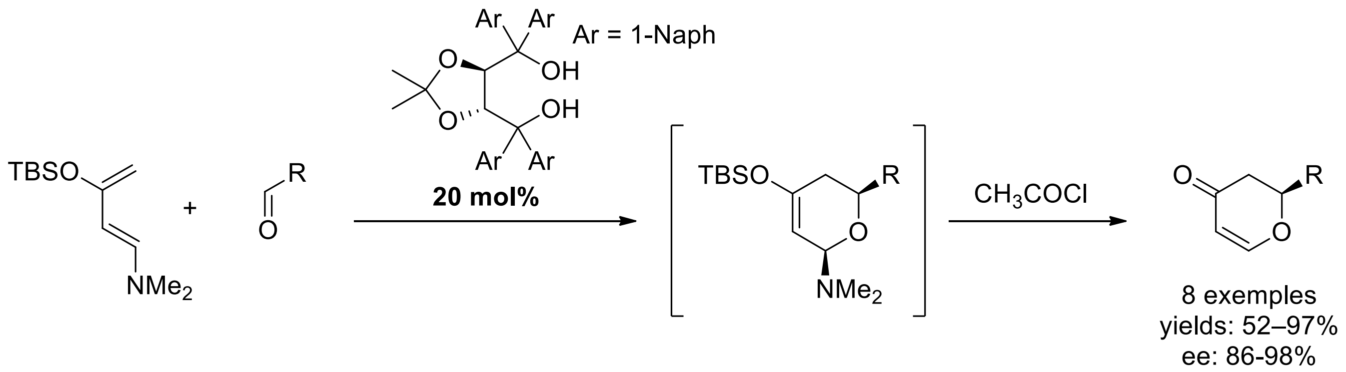


J. Esquivias, R. Gomez Arrayas, J. C. Carretero, *J. Am. Chem. Soc.*, **2007**, *129*, 1480.
H. Ishitani, S. Kobayashi, *Tetrahedron Lett*. **1996**, *37*, 7357.

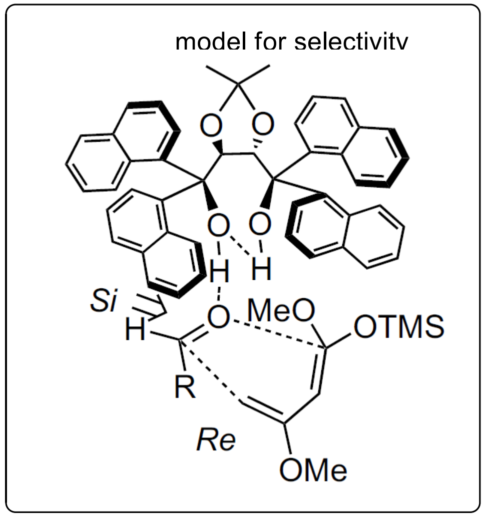
HDA of carbonyl compounds with chiral organocatalysts

Rawal:

Chiral alcohol catalysis

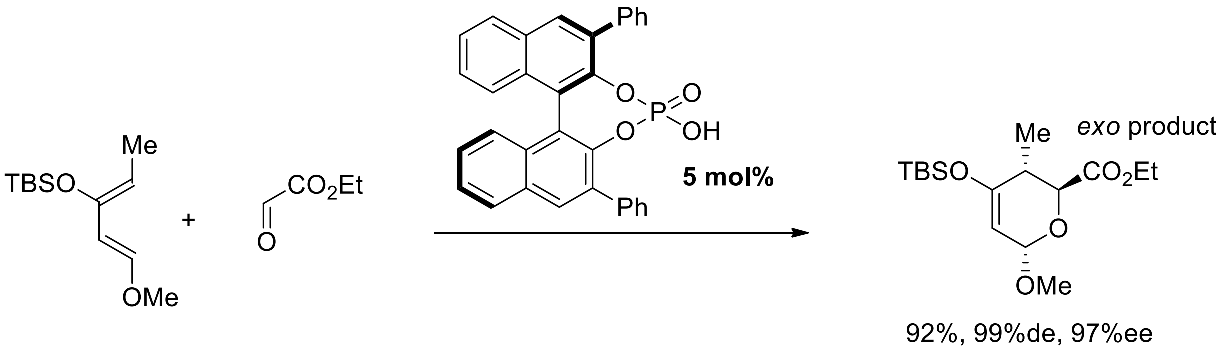


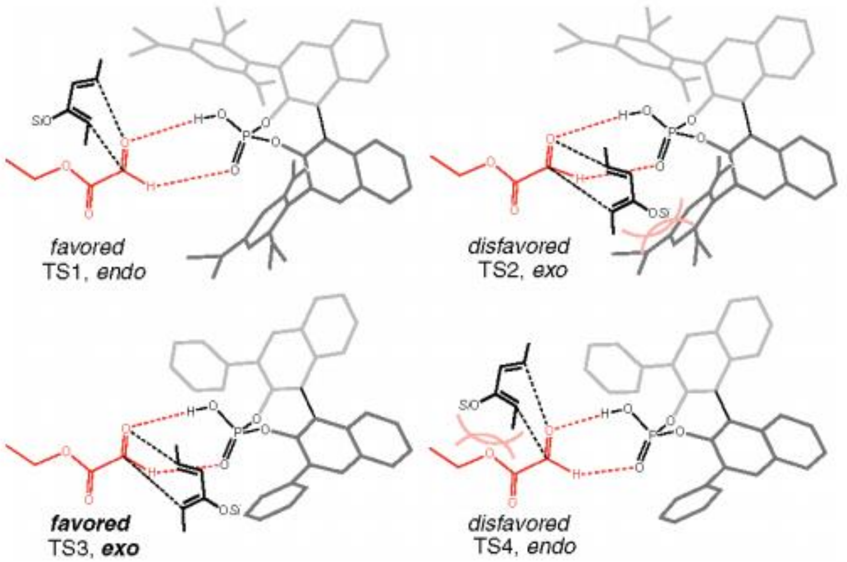
Ding:



Terada:

Chiral phosphoric acid



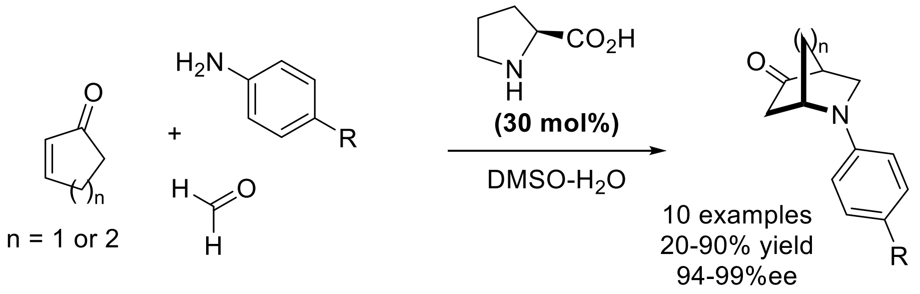


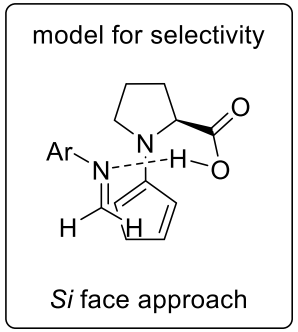
Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146. Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem*. **2006**, *71*, 2862.
N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* **2009**, *131*, 12882.

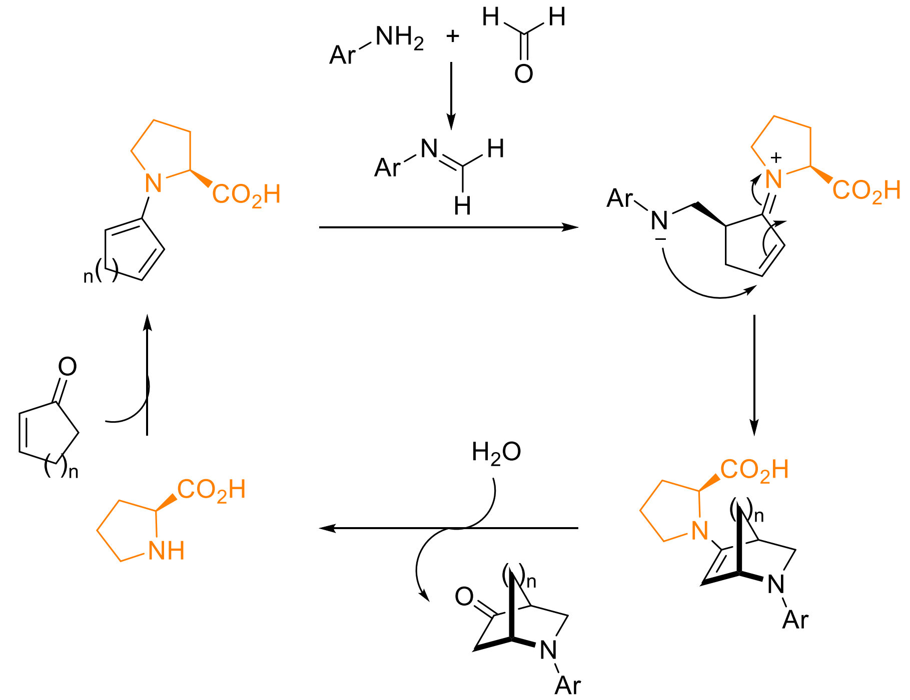
HDA of imines with chiral organocatalysts

Córdova:

Proline organocatalysis

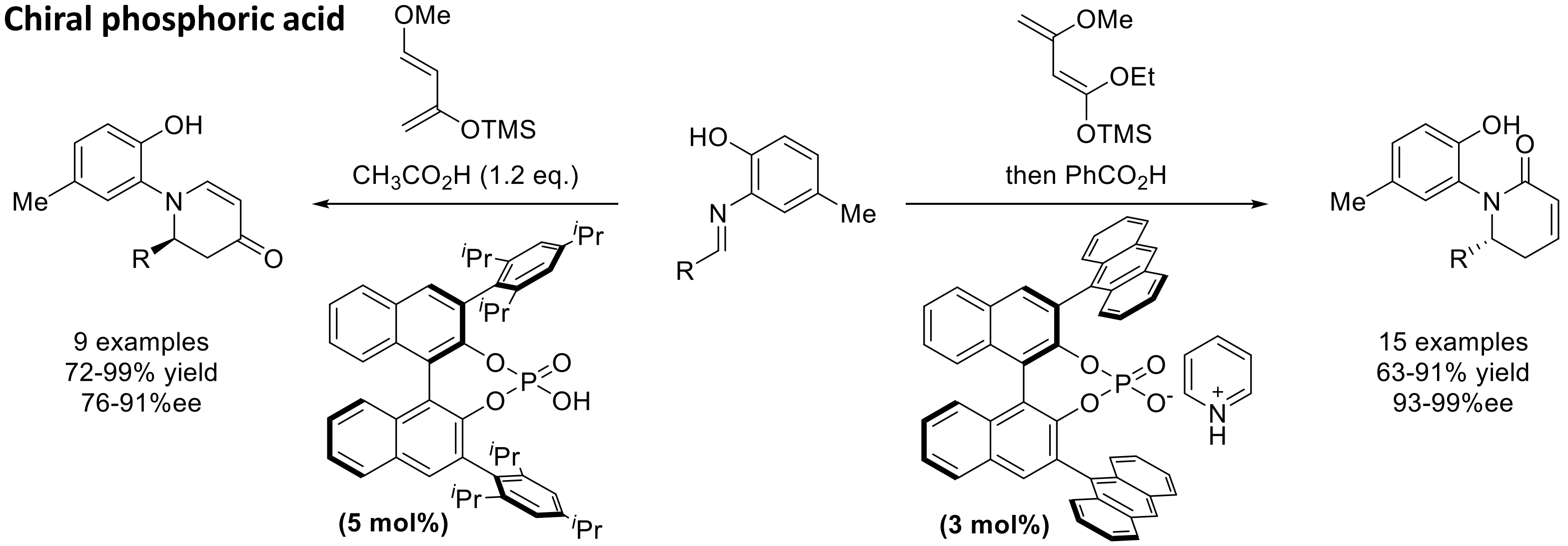


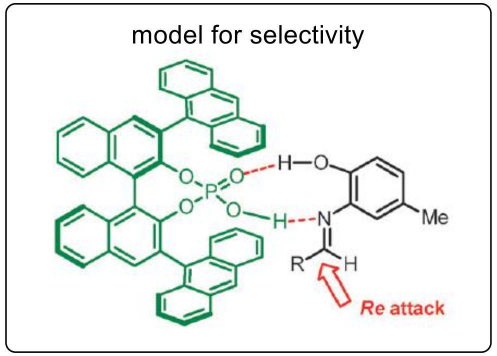




Akiyama:

Chiral phosphoric acid



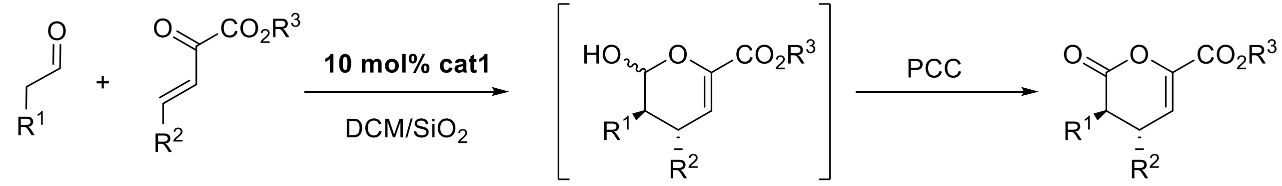


H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 4877.
T. Akiyama, Y. Tamura, J. Itoh and K. Fuchibe, *Synlett*, **2006**, 141. J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, **2006**, *45*, 4796.

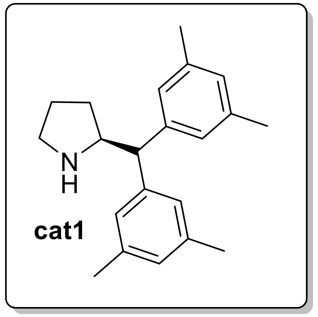
Inverse Electron Demand HDA of carbonyl compounds with organocatalysts

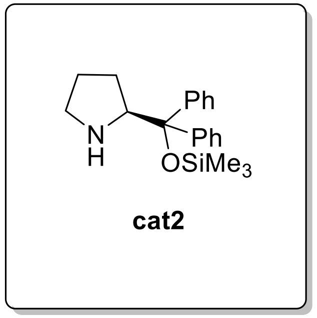
Jørgensen:

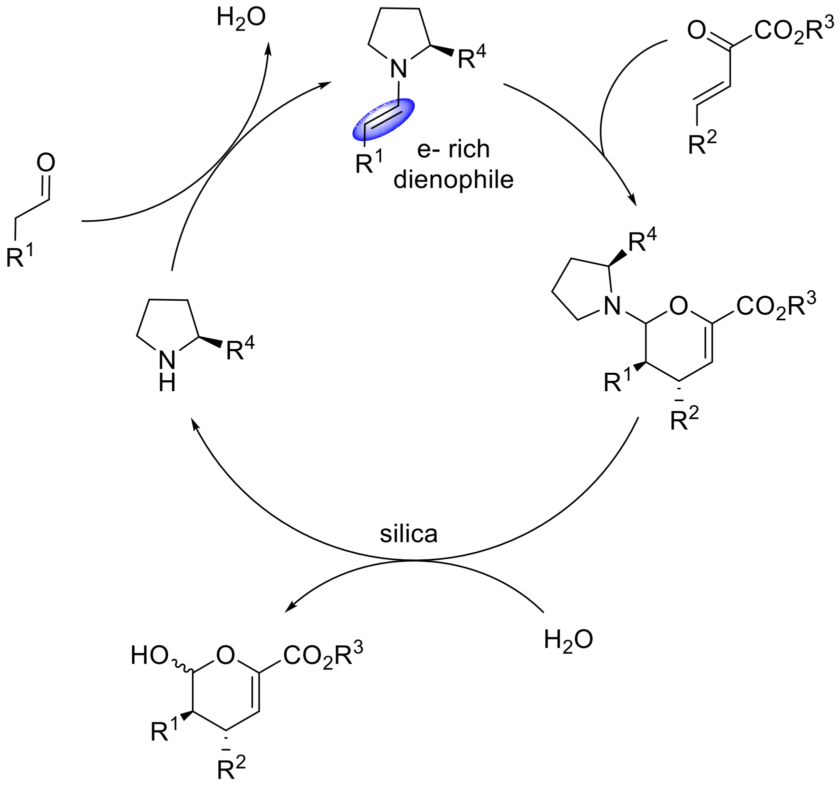
Enamine catalysis



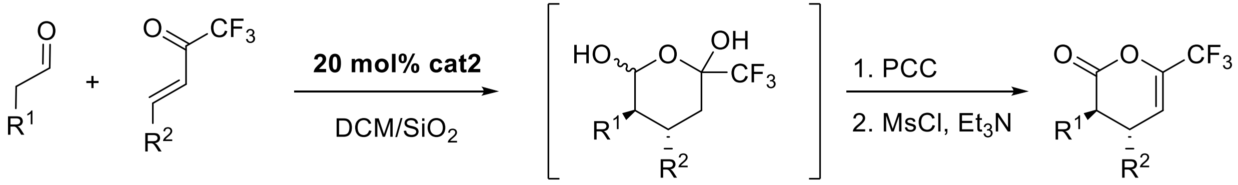
9 examples
80-94% yield
62-93%ee







Liu:



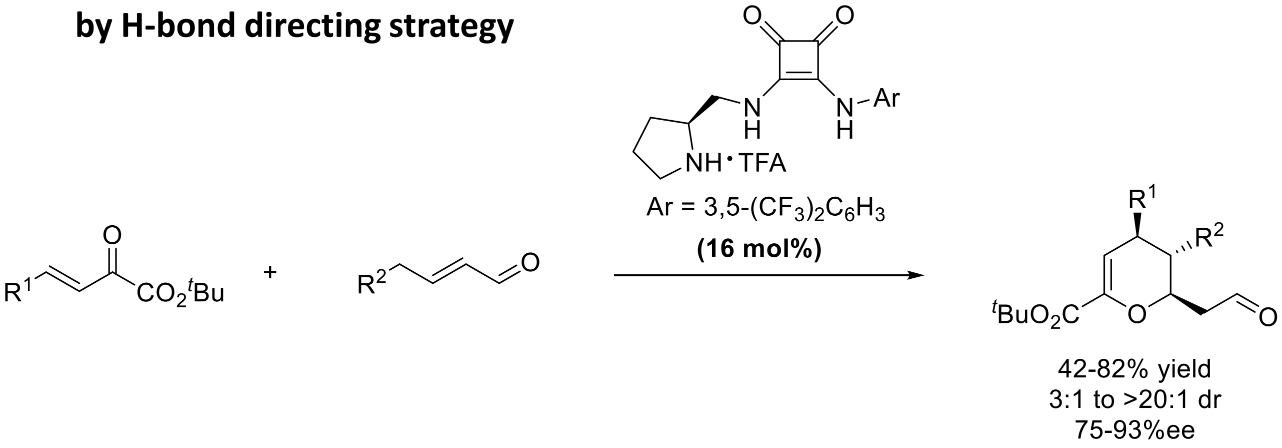
10 examples
46-97% yield
50-76%ee

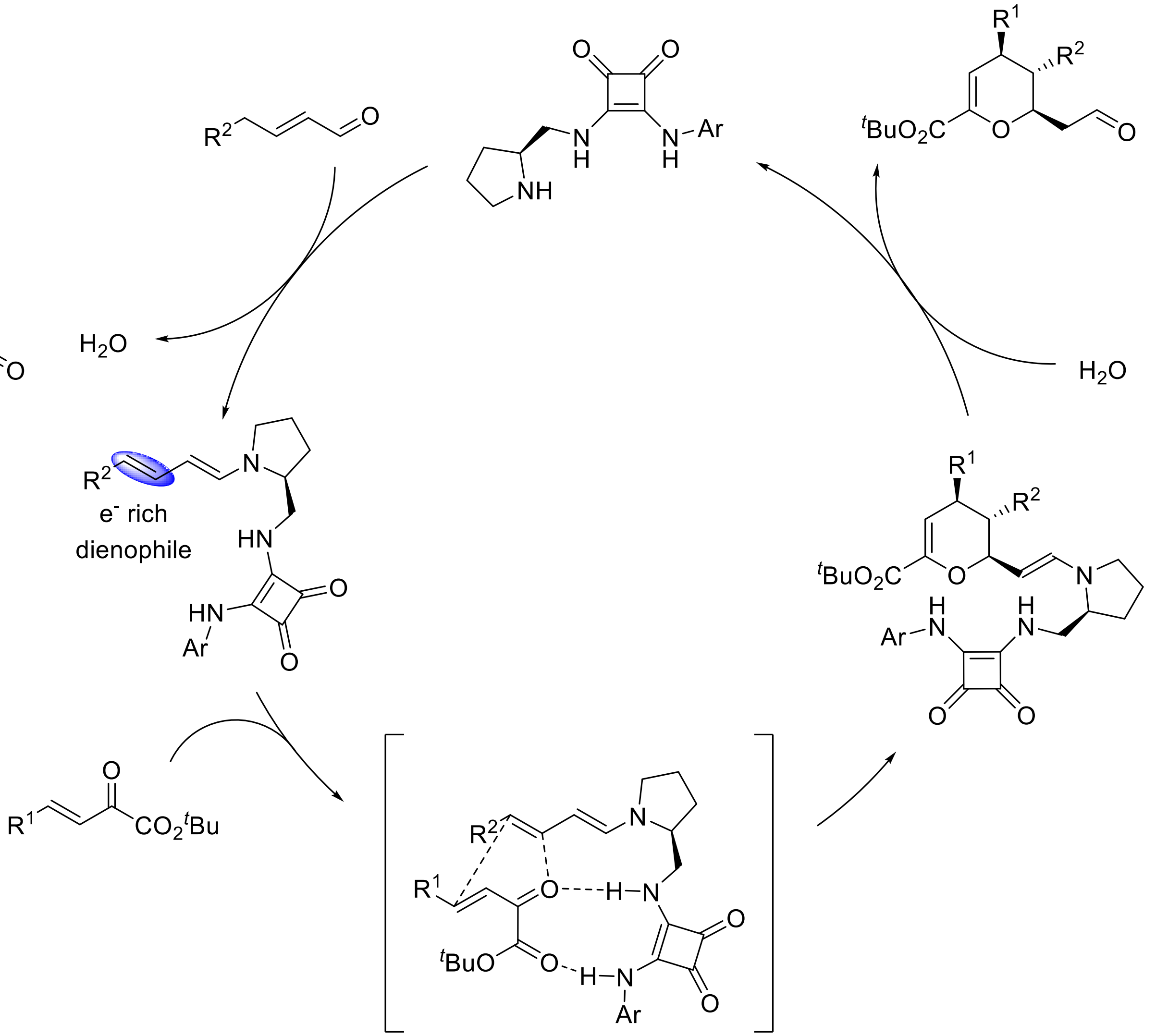
K. Juhl, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.
Zhao, Y.; Wang, X.-J.; Liu, J.-T. *Synlett* , **2008**, 1017.

Inverse Electron Demand HDA of carbonyl compounds with organocatalysts

Jørgensen:

Dienamine catalysis assisted by H-bond directing strategy

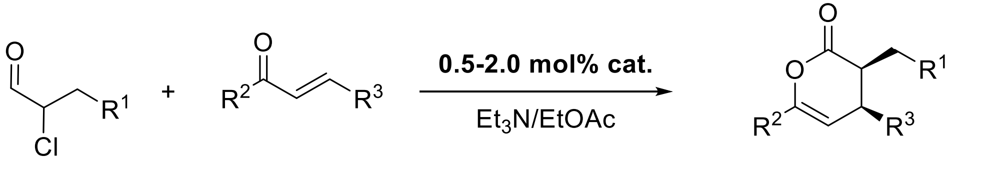




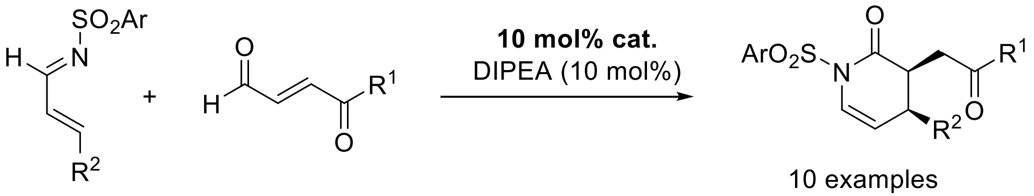
Ł. Albrecht, G. Dickmeiss, C. F. Weise, C. Rodrıguez-Escrich, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2012**, *51*, 13109.

Bode:

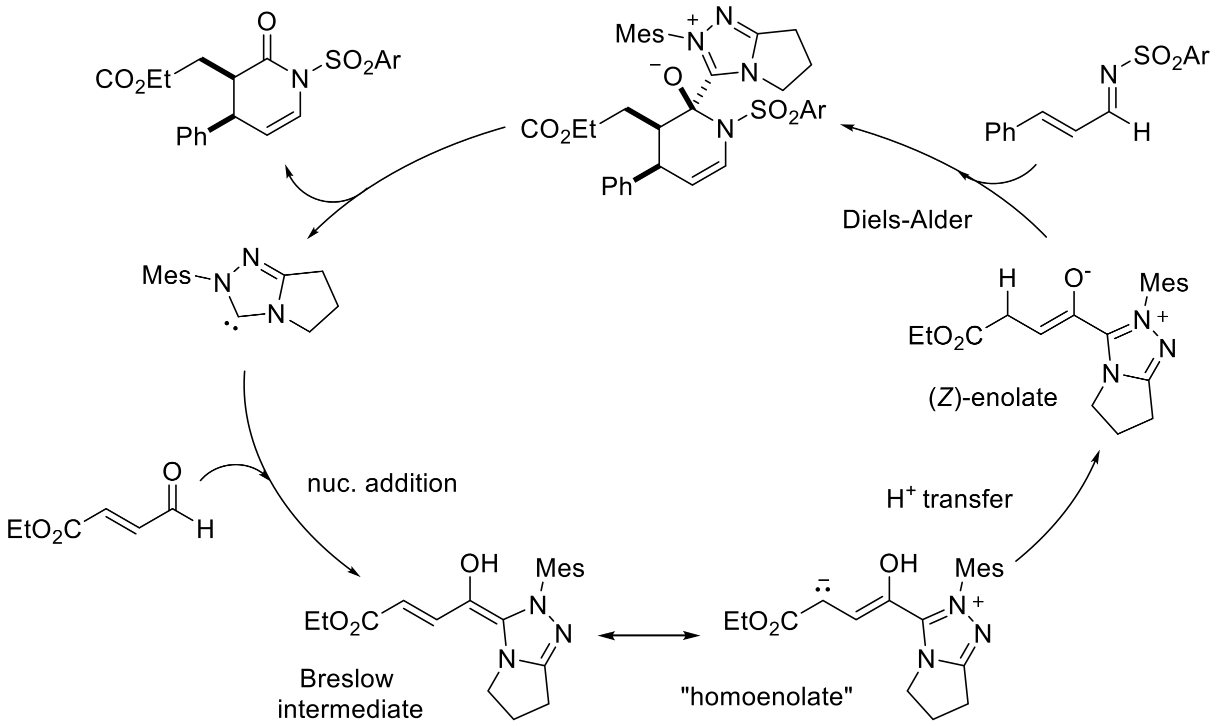
NHC catalysis

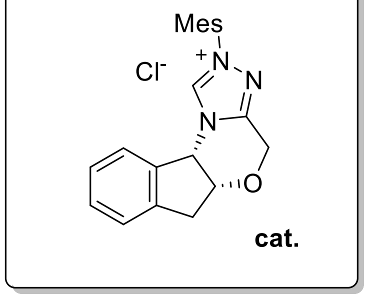


9 examples
62-93% yield
80-94%ee

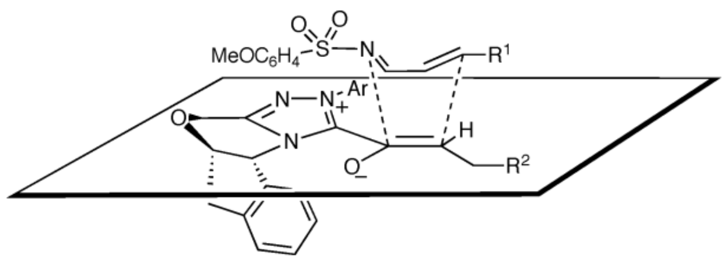


10 examples
51-90% yield
> 50:1 dr
97-99ee





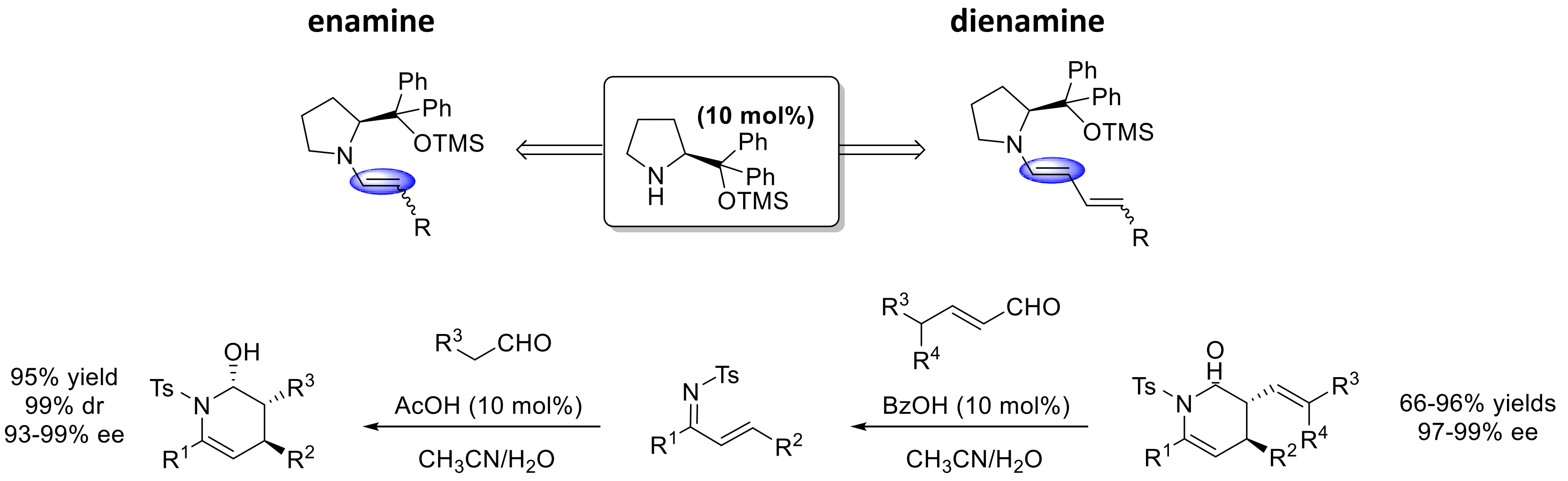
model for selectivity



M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088.
M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.

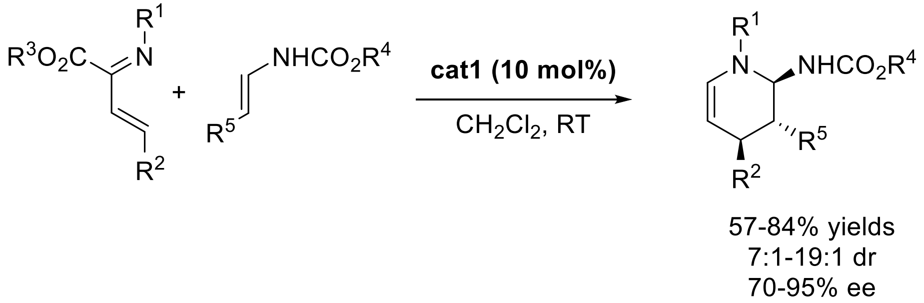
Chen:

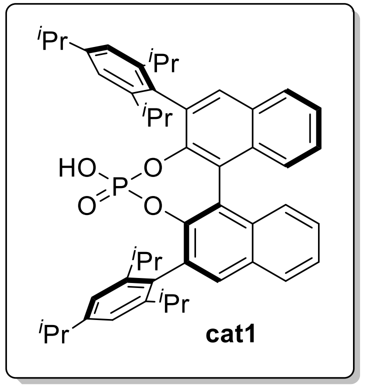
Prolinol catalyst

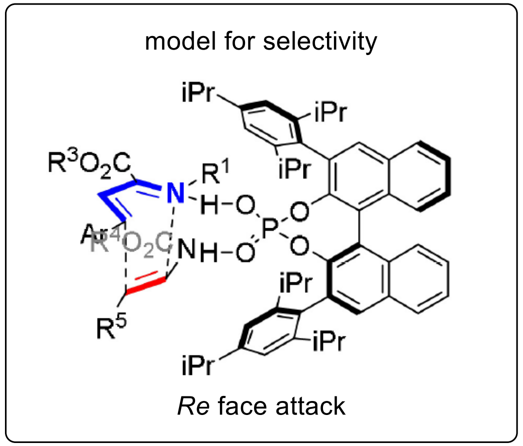


Masson:

Bifunctional chiral phosphoric acid







B. Han, J.-L. Li, C. Ma, S.-J. Zhang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2008**, *47*, 9971. B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474.
L. He, G. Laurent, P. Retailleau, B. Folleas, J.-L. Brayer, G. Masson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11088.

Conclusion and Outlook

- Highly efficient and selective reactions to construct 6-membered *N*- and *O*-heterocycles

- Stimulating field to develop new catalytic methodologies: Metal and Organo-catalysis.

- New hetero-diene and –dienophile need to be expanded (unactivated dienes, S containing components…)

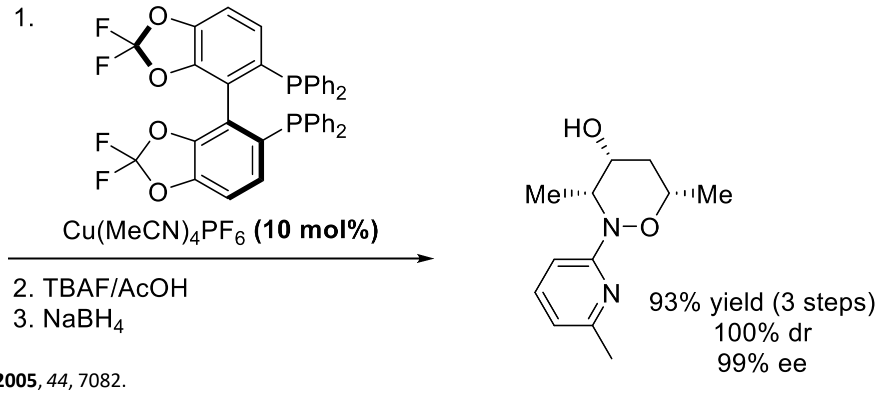
Questions

- You, first…

- You, first…

- Please, explain why Schiff base-Cr^{III} Lewis acid (Jacobsen's catalyst) is a very powerful catalyst for asymmetric HDA?

- Propose starting materials for this reaction sequence? Could you propose a model supporting the absolute stereochemistry?



Y. Yamamoto, H. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 7082.

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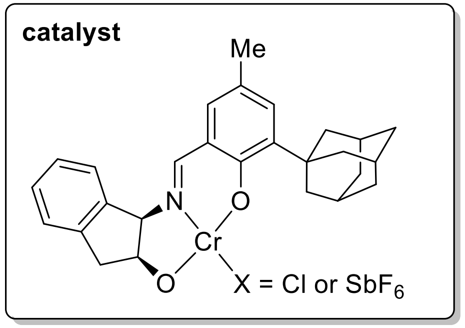

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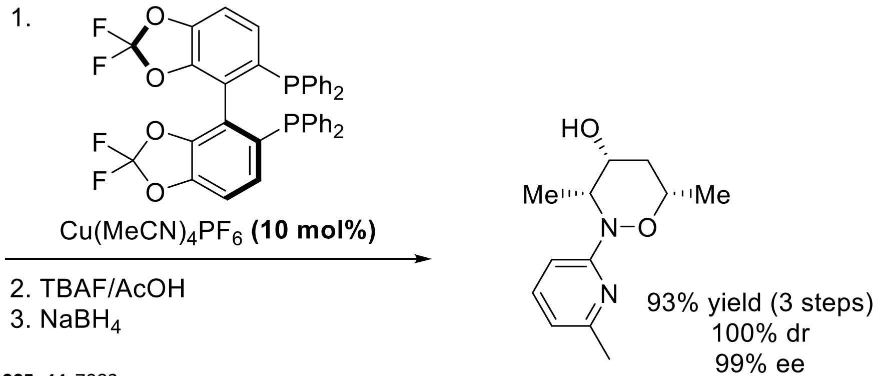

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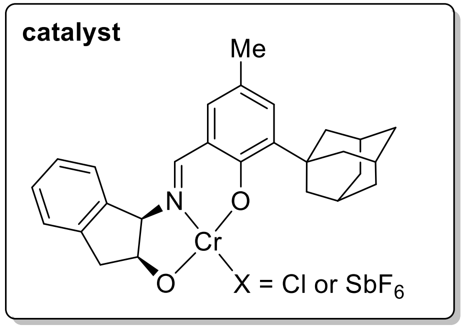

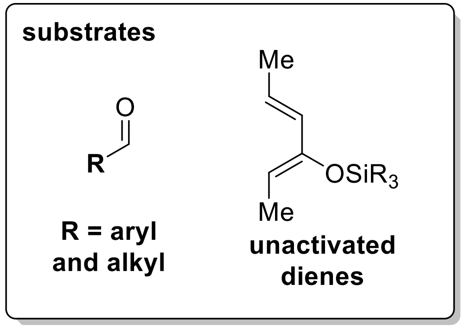

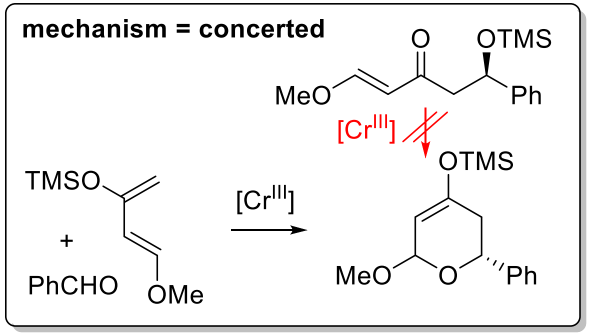

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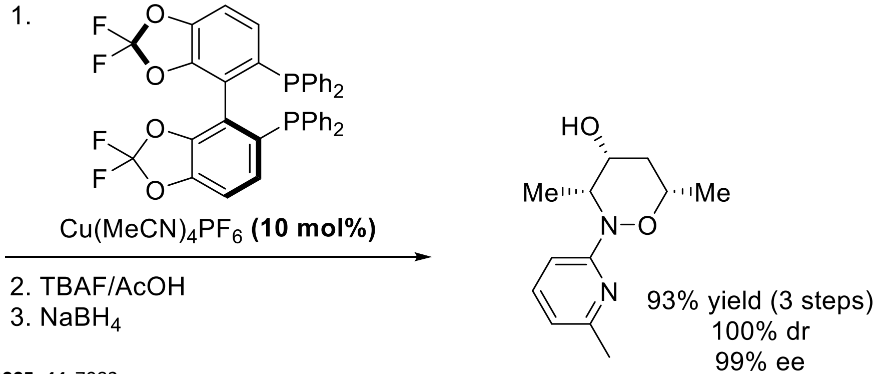

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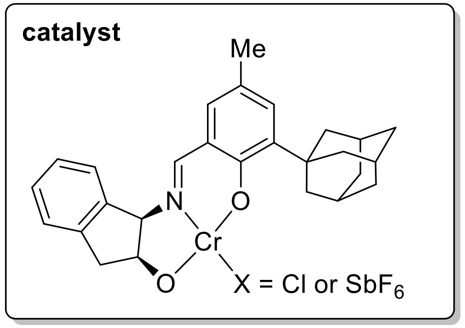

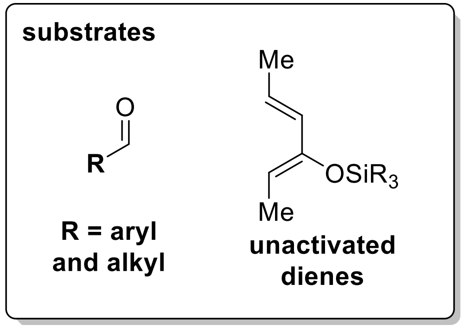

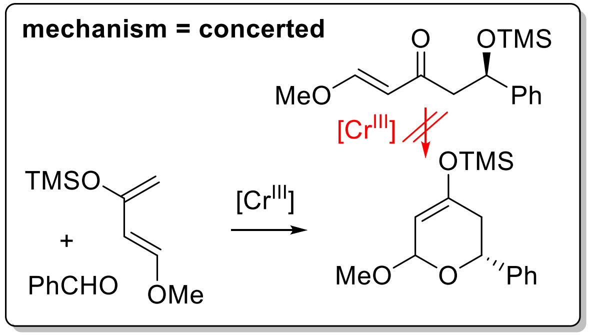

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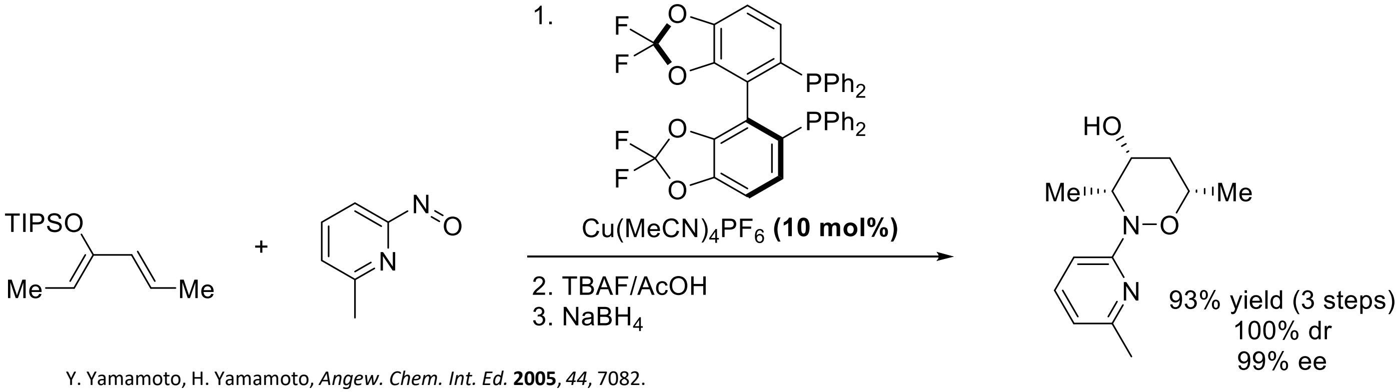

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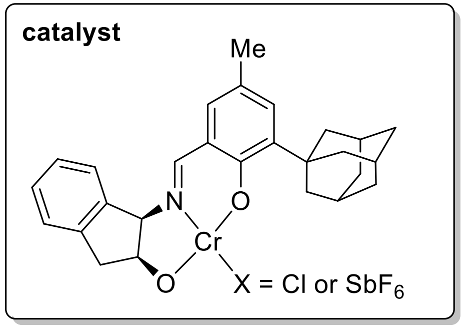

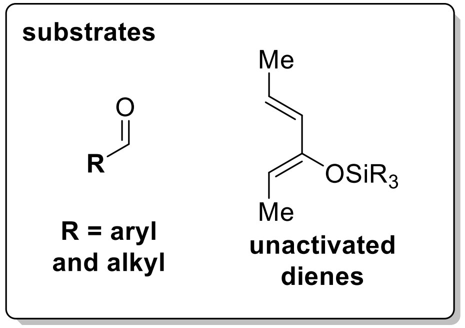

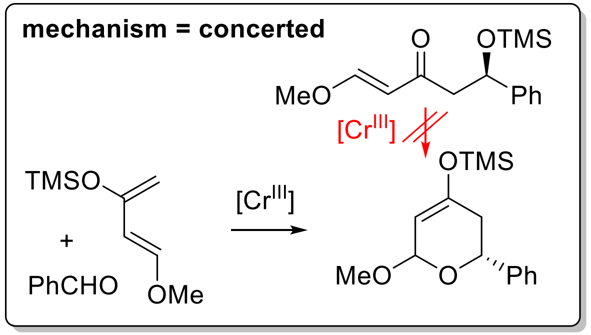

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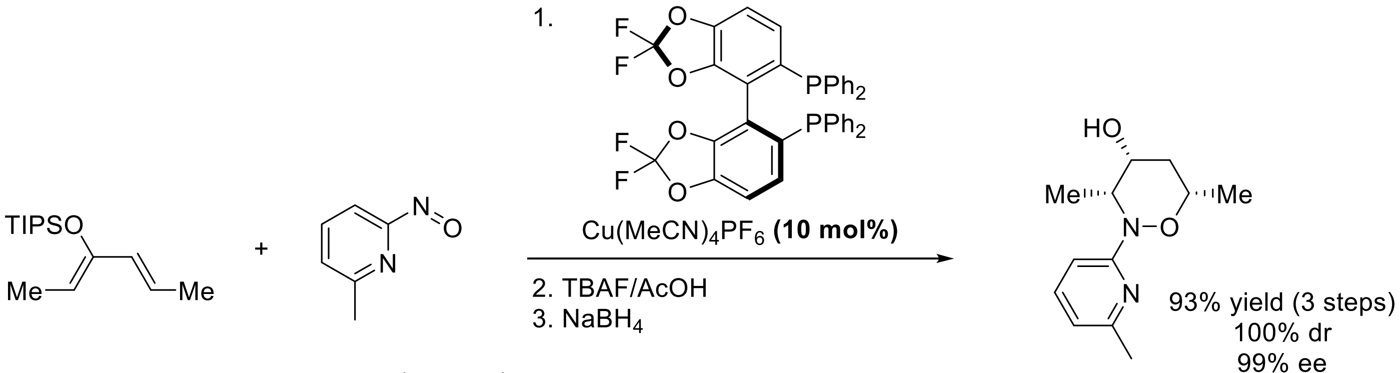

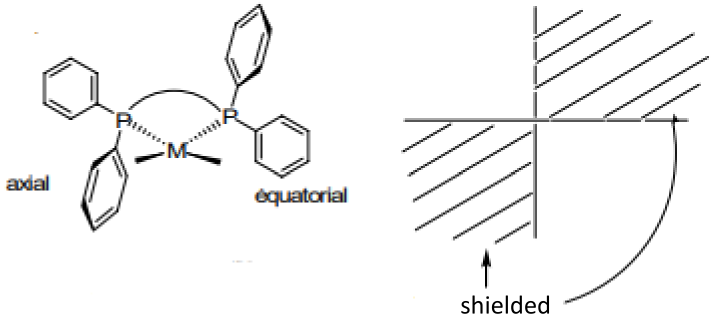

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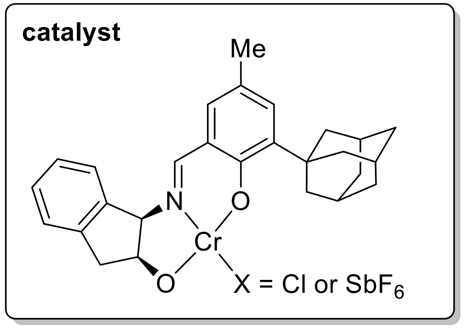

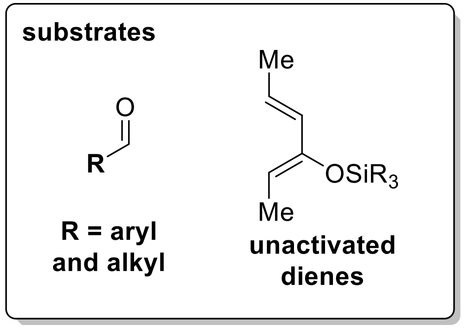

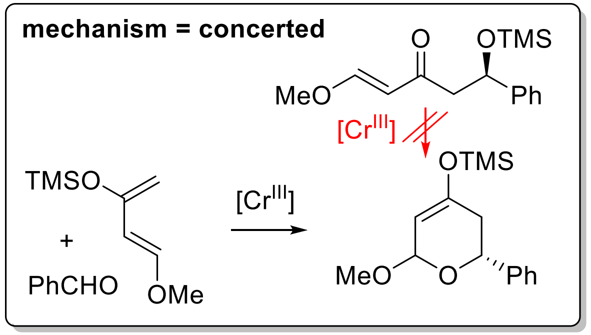

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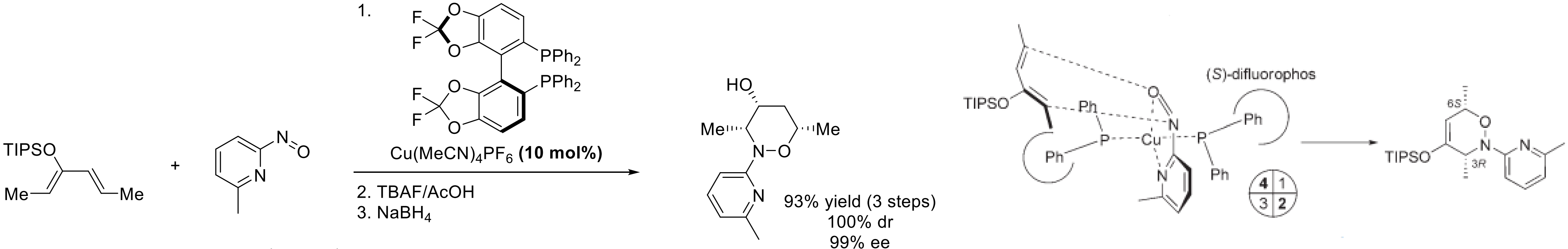
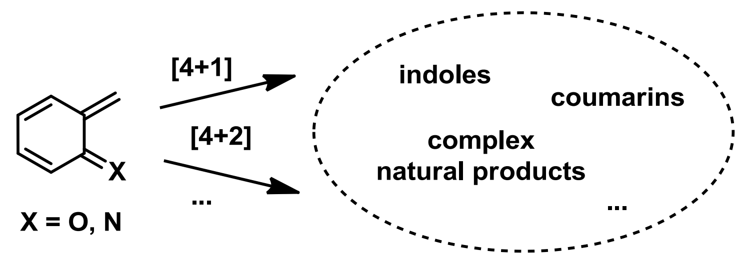


Y. Yamamoto, H. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 7082.

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

EPFL - ISIC

Synthesis of Heterocycles *via* (aza)-ortho-quinone Methide Intermediates



Seminar : Frontiers in Chemical Synthesis II
Heterocyclic Chemistry

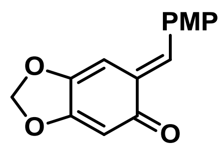
Mathias Mamboury (LSPN)

May 18, 2018

Table of contents

Generation of ortho-quinone methides (oQM) :

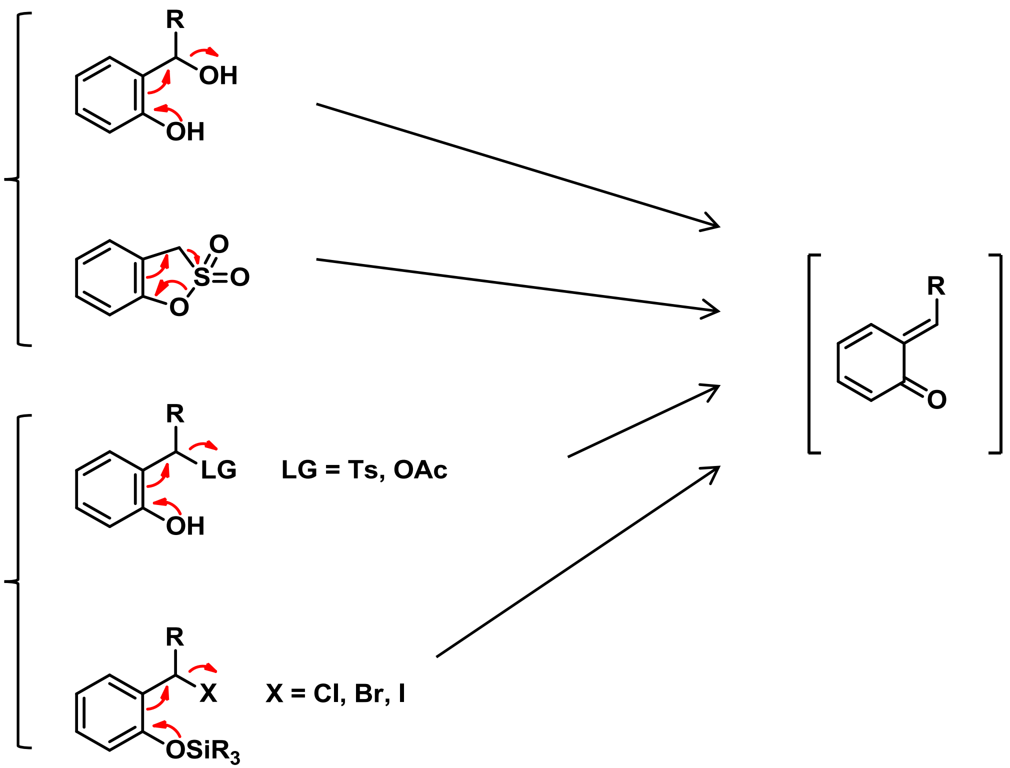
Stable ortho-quinone methide :



PMP = para-methoxy phenyl

«Harsh» activation (strong acid, thermal)

Mild activation (weak acid/base or fluoride)



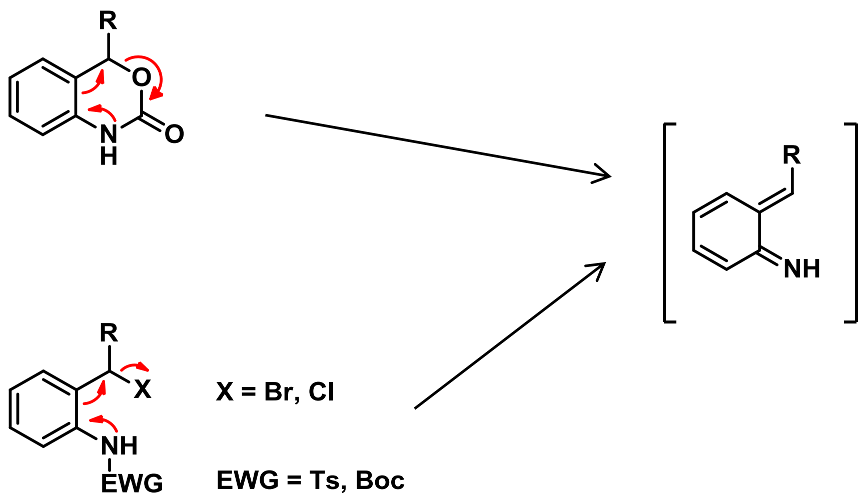
ortho-quinone methide

oQM

Generation of aza-ortho-quinone methides (aoQM) :

«Harsh» activation :
(thermal)

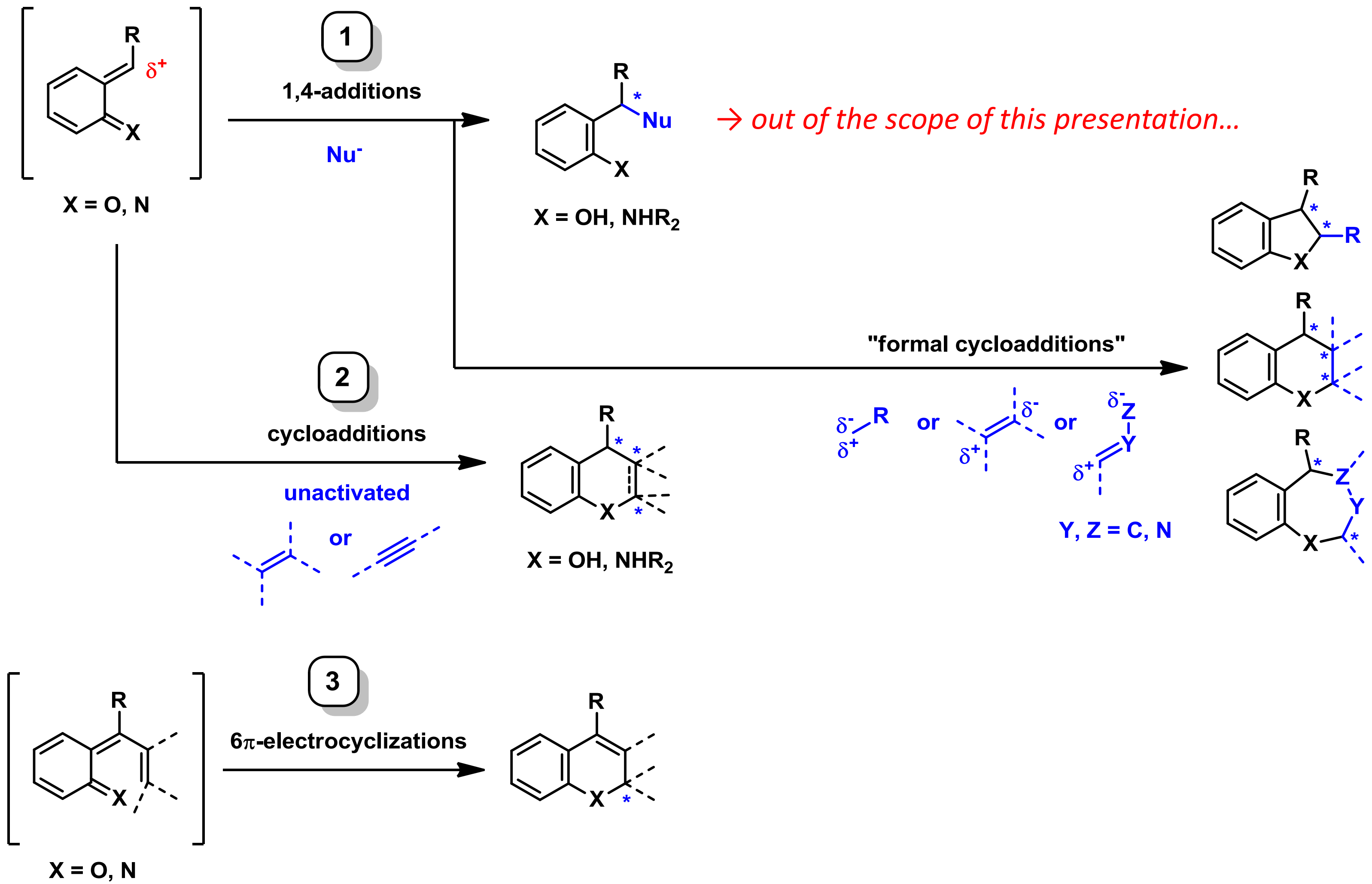
Mild activation :
(weak base)



aza-ortho-quinone methide

aoQM

Reactivity profile of (aza)-ortho-quinone methides :



Choice of this topic :

- Renewed interest for (a)oQMs although they are known for decades as they are involved the biosynthesis of natural products.

- «Simple» reactivity profile but versatile chemistry :
    - Organocatalysis
    - Umpolung reactions
    - Cascade reactions

- Relevant applications :
    - Heterocycles (medicinal chemistry, etc.)
    - Total synthesis

Scope of this presentation :

- Classification based on the structure of the products, not the mechanism
- Highlight on the most advanced examples of each category
- Examples of applications in total synthesis (not exhaustive)

Reviews after 2010

Ortho-Quinone Methides in Natural Product Synthesis.
Bray, C. D. *et al. Chemistry – A European Journal* **2012**, *18* (30), 9160–9173.

Ortho-Quinone Methide (o-QM): A Highly Reactive, Ephemeral and Versatile Intermediate in Organic Synthesis.
Chowdhury, S. *et al. RSC Adv.* **2014**, *4* (99), 55924–55959.

The Domestication of Ortho-Quinone Methides.
Pettus, T. R. R. *et al. Acc. Chem. Res.* **2014**, *47* (12), 3655–3664.

The Emergence of Quinone Methides in Asymmetric Organocatalysis.
Bernardi, L. *et al. Molecules* **2015**, *20* (7), 11733–11764.

Recent Advances in Catalytic Asymmetric Reactions of O-Quinone Methides.
Sun, J. *et al. Synthesis* **2015**, *47* (23), 3629–3644.

Emerging Roles of in Situ Generated Quinone Methides in Metal-Free Catalysis.
Scheidt, K. A. *et al. J. Org. Chem.* **2016**, *81* (21), 10145–10153.

Asymmetric catalytic reactions

1) **Introduction**

2) **[4+1] Cycloadditions**

Dihydrobenzofurans → **oQM (X=O)**

Indoles and indolines → **aoQM (X=N)**

3) **[4+2] Cycloadditions**

Chromenes, chromanes, dihydrocoumarins → **oQM (X=O)**

N-containing 6-membered heterocycles → **aoQM (X=N)**

4) **[4+3] Cycloadditions**

Benzoxepin derivatives → **oQM (X=O)**

Benzazepin derivatives → **aoQM (X=N)**

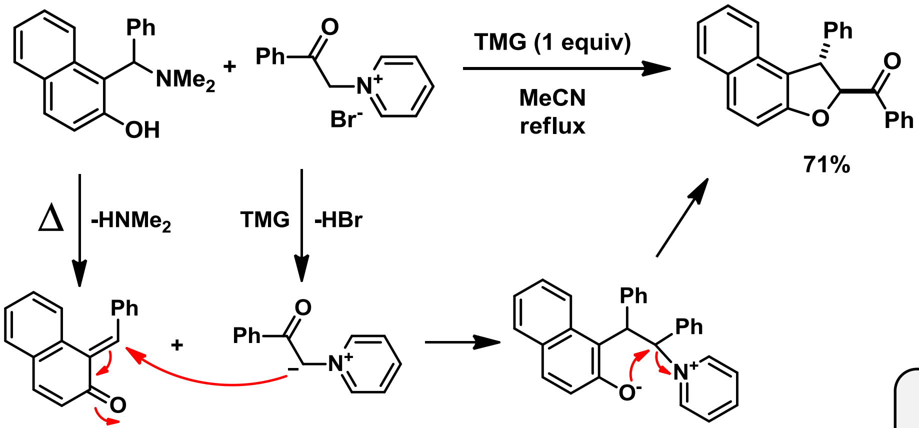
5) **[4+4] Cycloaddition**

6) **Applications in Total Synthesis**

7) **Conclusion & Questions**

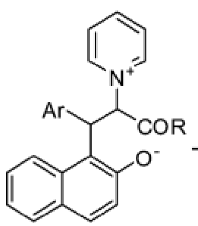
Most cases : *formal* cycloadditions !

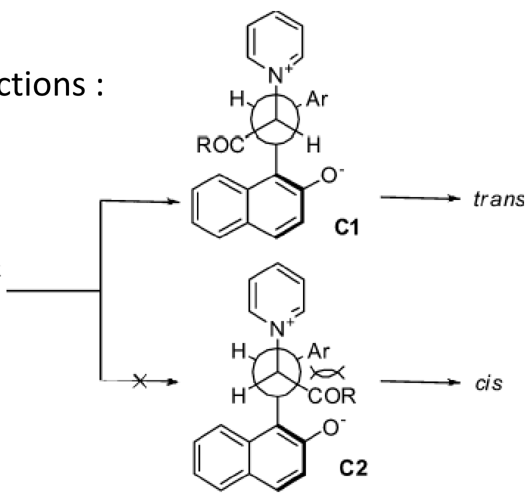
Synthesis of dihydrobenzofurans

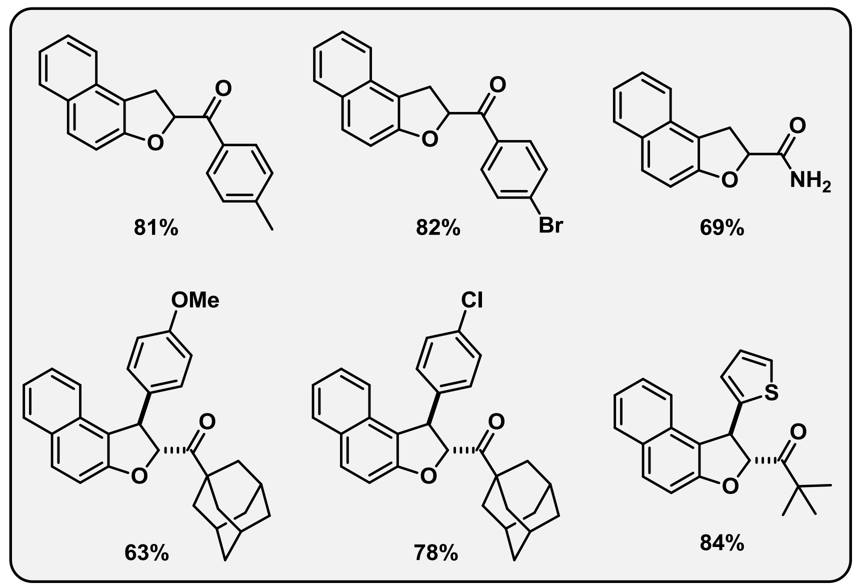


- *also works without base*
- *no reaction at lower temperatures*

Newman projections :

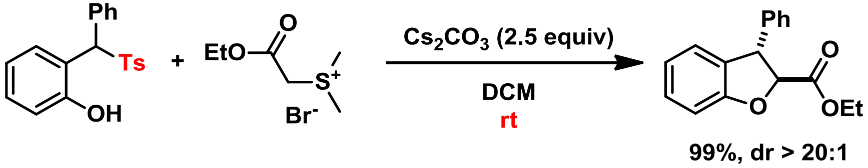




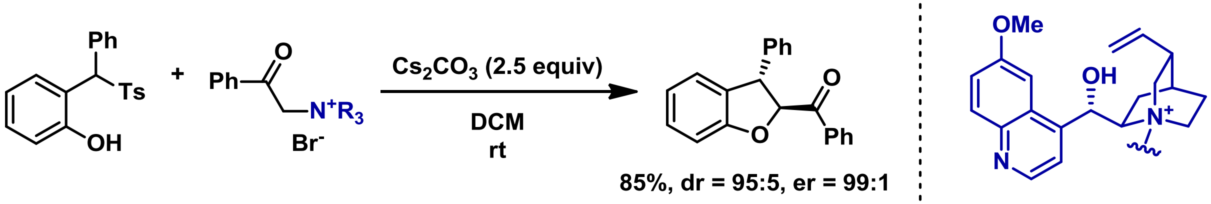


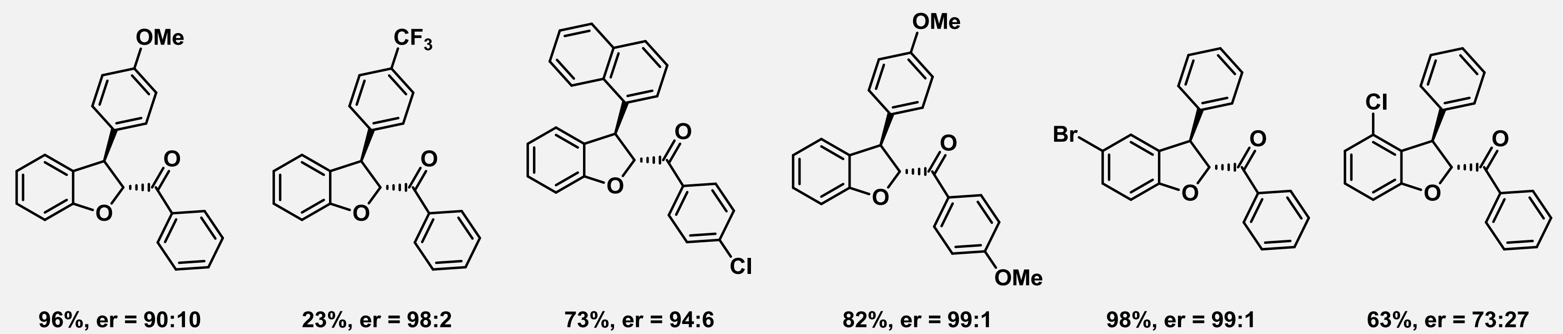
Osyanin *et al. J. Org. Chem.* **2013**, *78* (11), 5505–5520.

Synthesis of dihydrobenzofurans



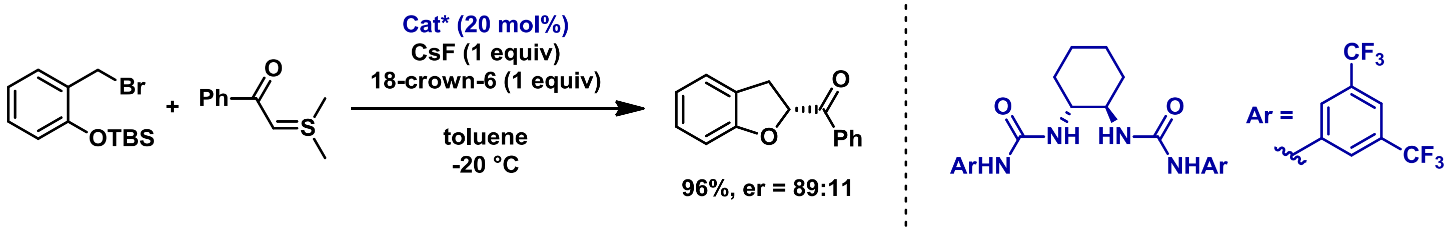
Mild generation of the oQM !



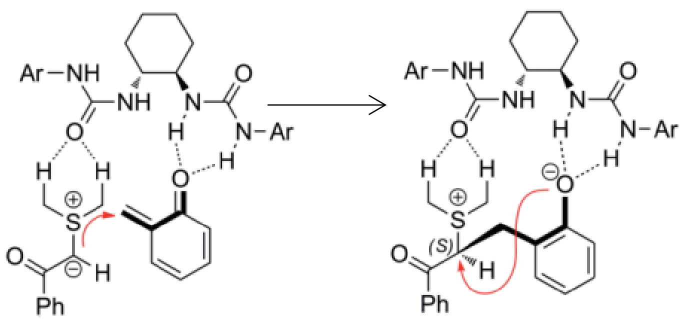


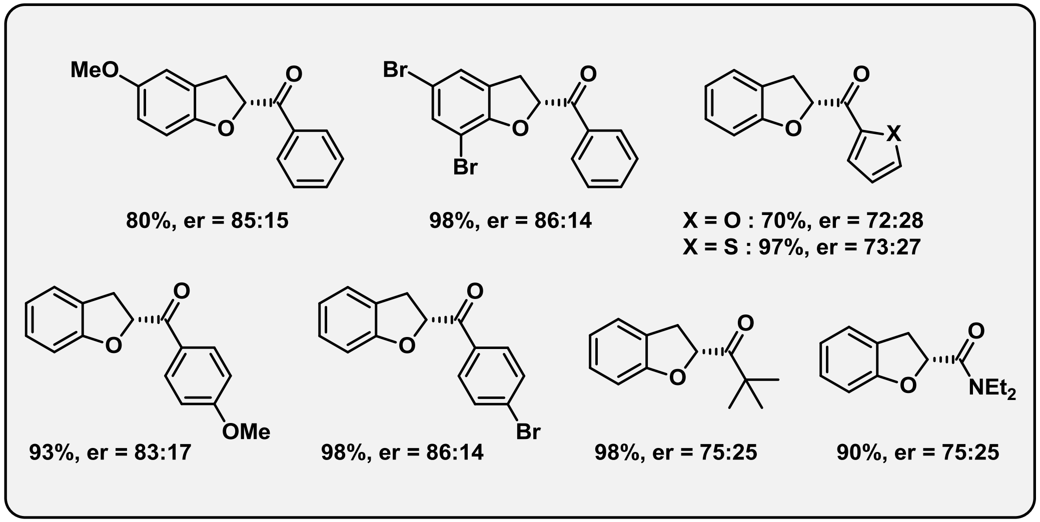
Zhou, Y.-G. *al. Chem. Commun.* **2013**, *49* (16), 1660–1662.
Waser, M. *al. Chem. Eur. J.* **2017**, *23* (21), 5137–5142.

Synthesis of dihydrobenzofurans



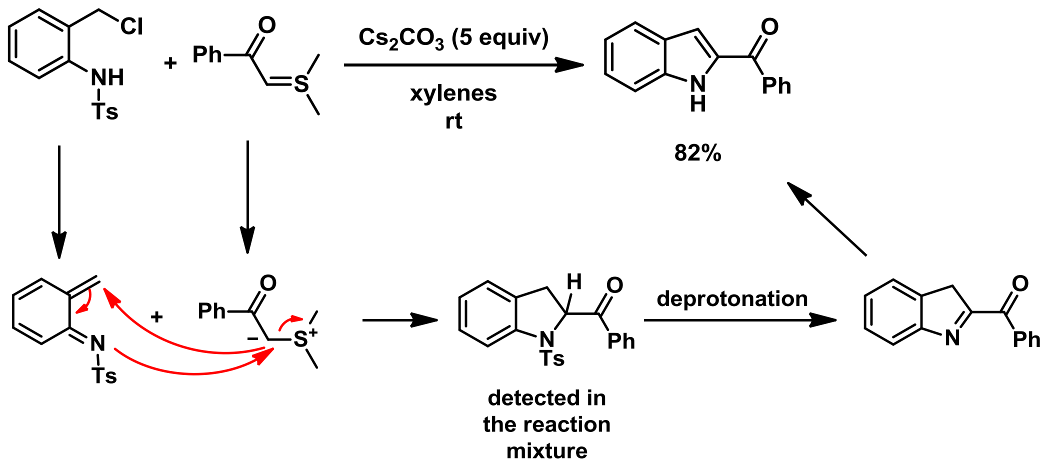
Proposed transition state :

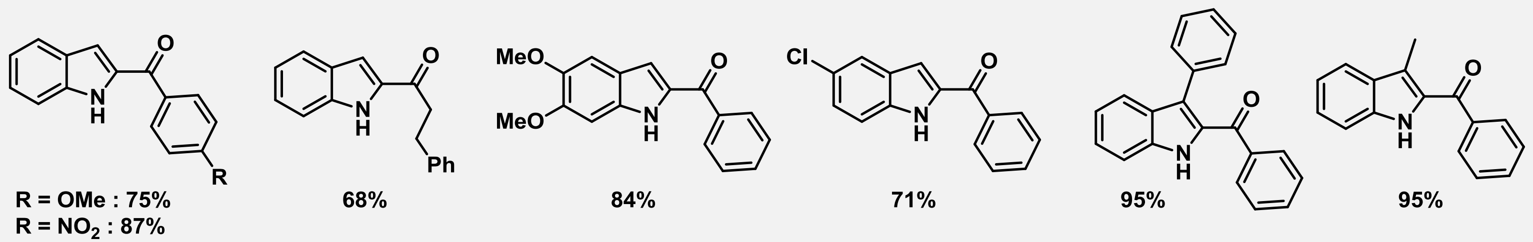




Xiao, W.-J. *et al. Eur. J. Org. Chem.* **2017**, *2017* (2), 233–236. ***VIP Paper!***

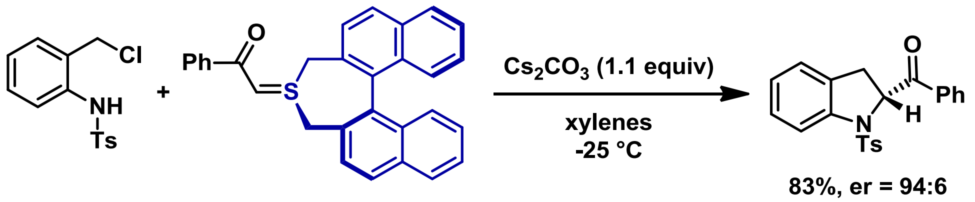
Synthesis of indoles



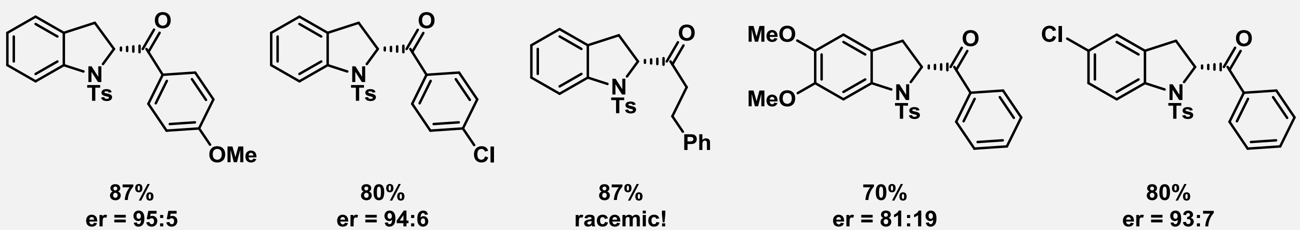


Xiao, W.-J. *et al. Angew. Chem. Int. Ed.* **2012**, *51* (36), 9137–9140.

Synthesis of indolines

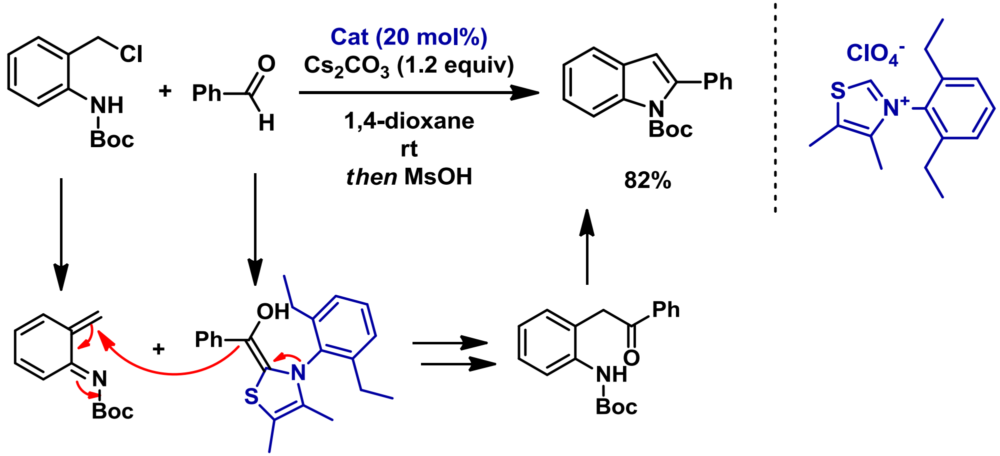


No deprotonation to form indoles !

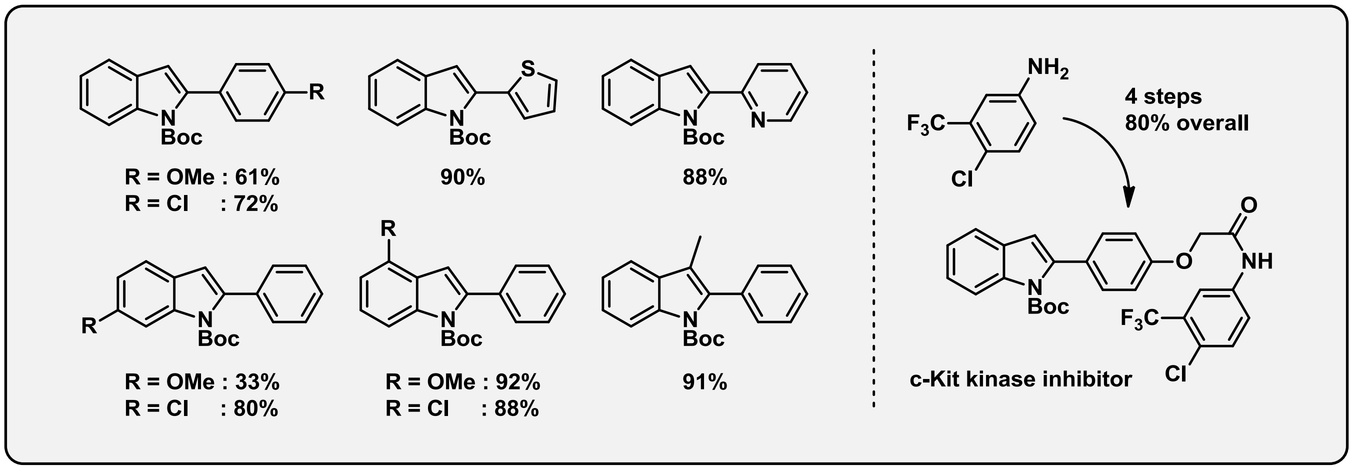


Xiao, W.-J. *et al.* Chem. Eur. J. **2013**, *19* (26), 8401–8404.

Synthesis of indoles



Simple starting materials !



Scheidt, K. A. *et al. Angew. Chem. Int. Ed.* **2014**, *53* (36), 9603–9607.
Scheidt, K. A. *et al. Chem. Commun.* **2016**, *52* (59), 9283–9286. (extension to azaindoles)

1) **Introduction**

2) **[4+1] Cycloadditions**

Dihydrobenzofurans

Indoles and indolines

3) **[4+2] Cycloadditions**

Chromenes, chromanes, dihydrocoumarins

N-containing 6-membered heterocycles

4) **[4+3] Cycloadditions**

Benzoxepin derivatives

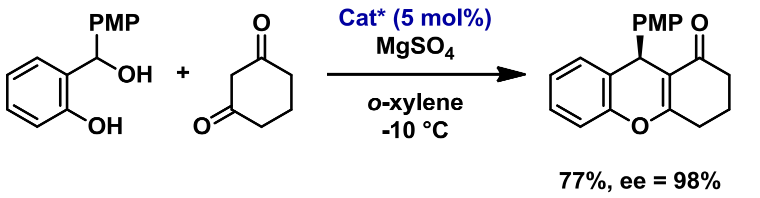
Benzazepin derivatives

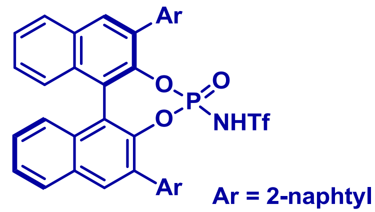
5) **[4+4] Cycloaddition**

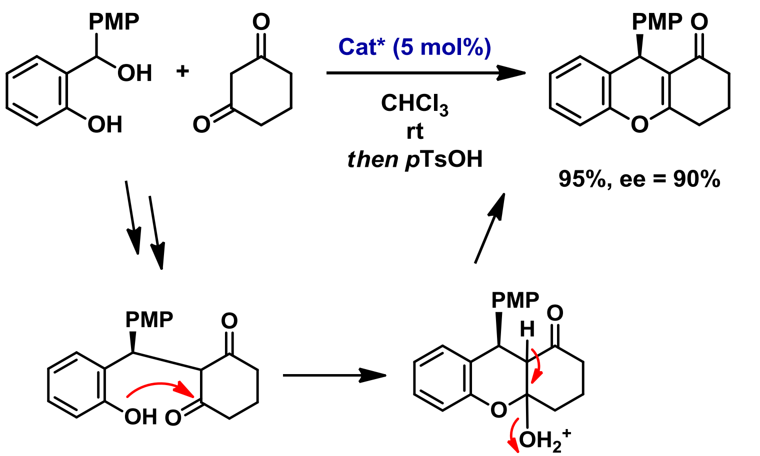
6) **Applications in Total Synthesis**

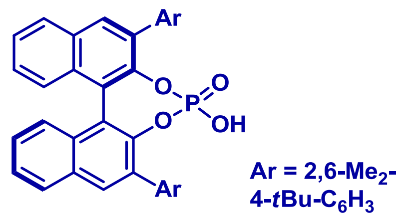
7) **Conclusion & Questions**

Synthesis of chromenes



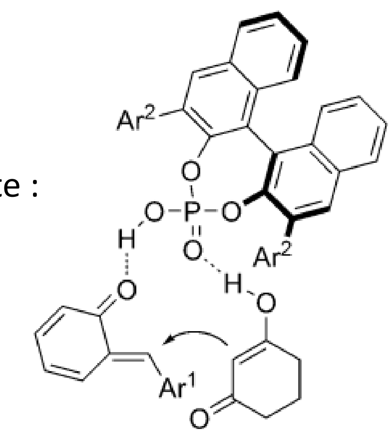






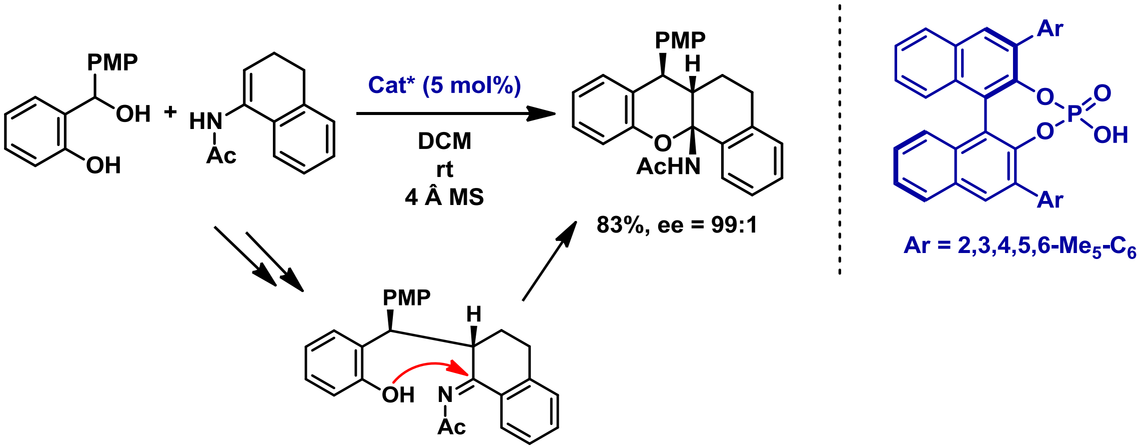
- *better yields*
- *broader scope (PMP not necessary)*

Proposed transition state :

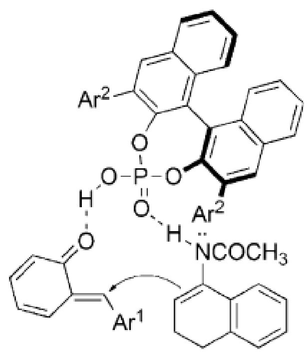


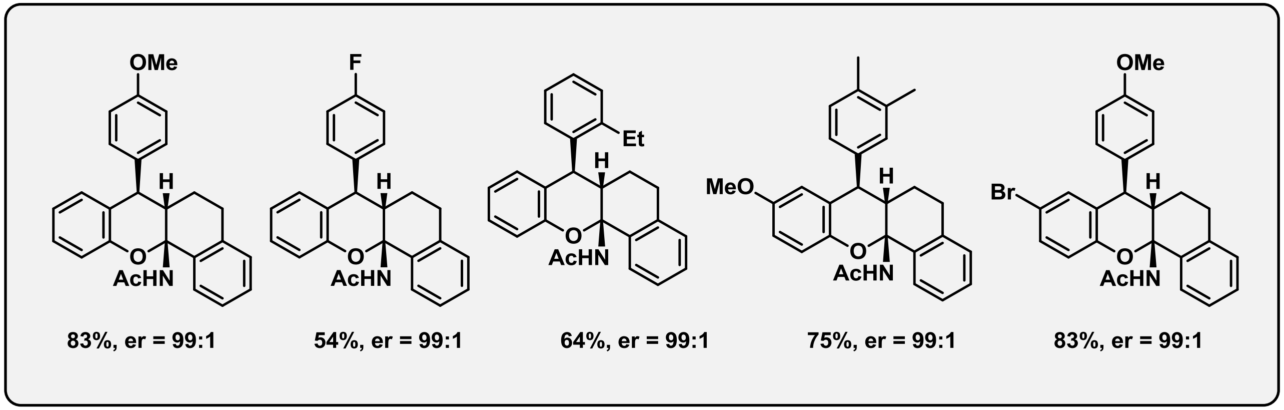
Rueping, M. *et al. Angew. Chem. Int. Ed.* **2014**, *53* (48), 13258–13263.
Schneider, C. *et al. Angew. Chem. Int. Ed.* **2014**, *53* (30), 7923–7927.
Shi, F. *et al. Synthesis* **2017**, *49* (09), 2035–2044. (reaction with enaminone)

Synthesis of chromanes



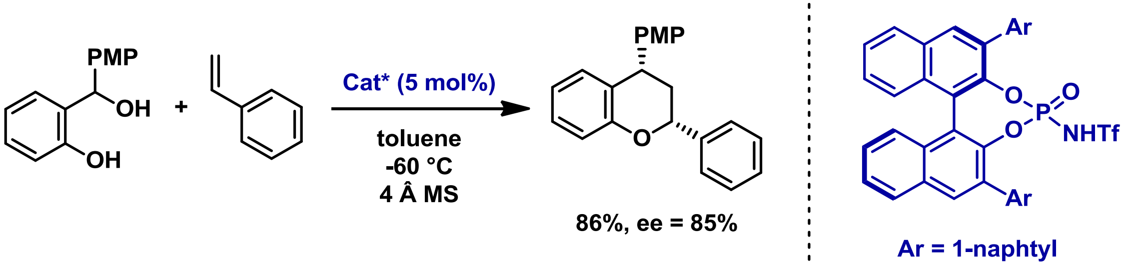
Proposed transition state :





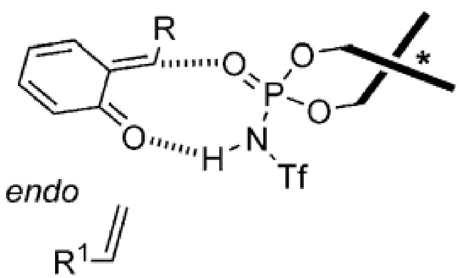
Schneider, C. *et al. Chem. Eur. J.* **2015**, *21* (6), 2348–2352.

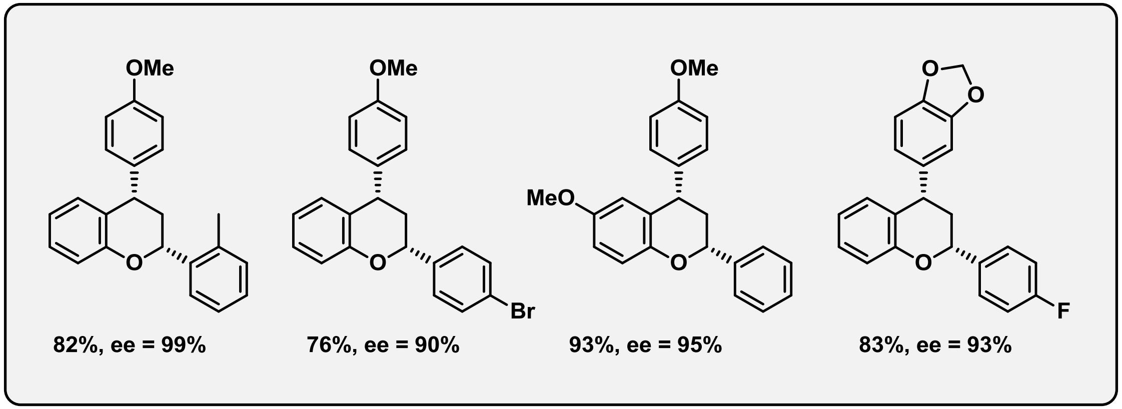
Synthesis of chromanes



Reaction with unactivated alkene !

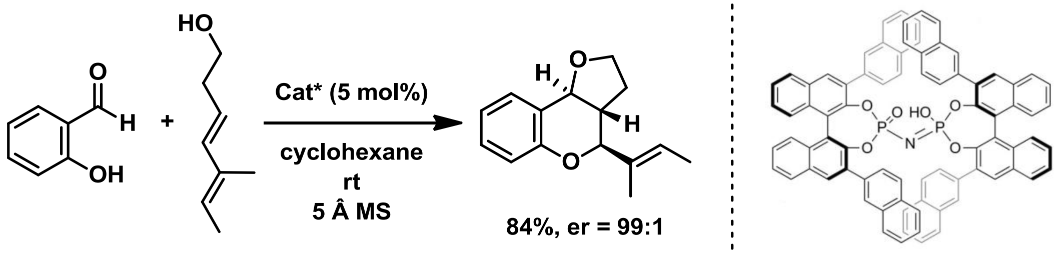
Proposed transition state :

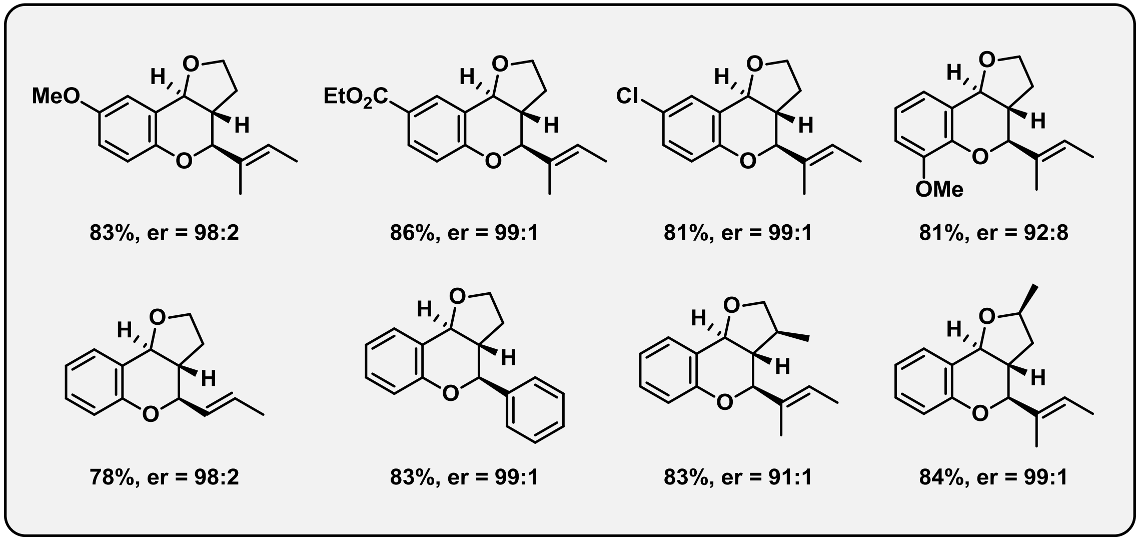




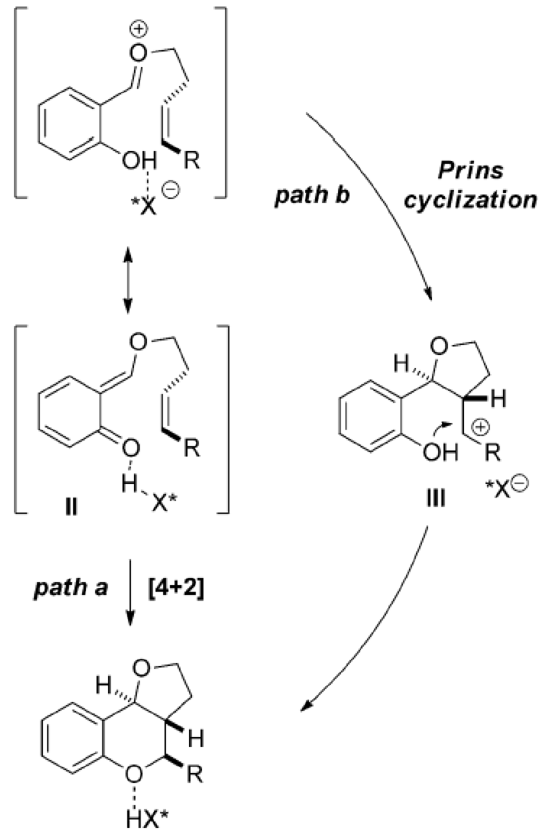
Rueping, M. *et al. Angew. Chem. Int. Ed.* **2015**, *54* (19), 5762–5765.
Shi, F. *et al. Angew. Chem. Int. Ed.* **2015**, *54* (18), 5460–5464. (similar)

Synthesis of chromanes





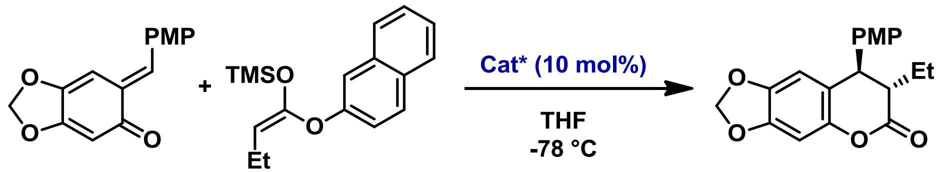
Proposed mechanisms :



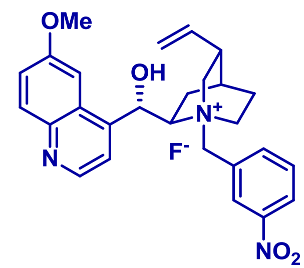
List, B. *et al. Angew. Chem. Int. Ed.* **2017**, *56* (18), 4936–4940.

Synthesis of dihydrocoumarins

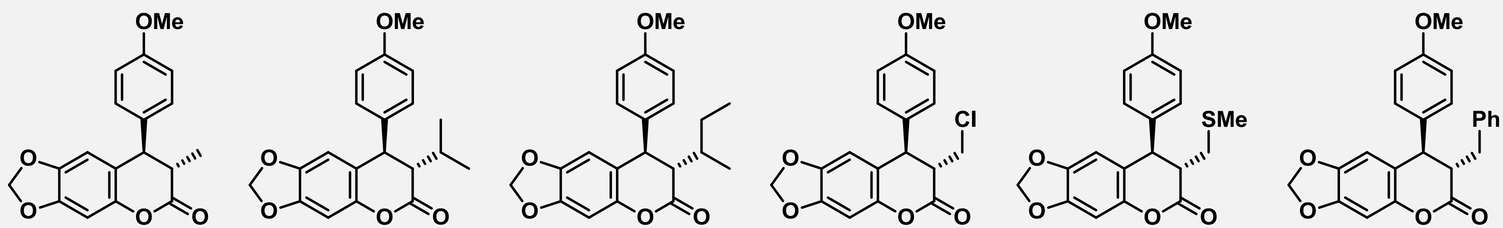
1st enantioselective [4+2] with oQM :



87%, ee = 80%



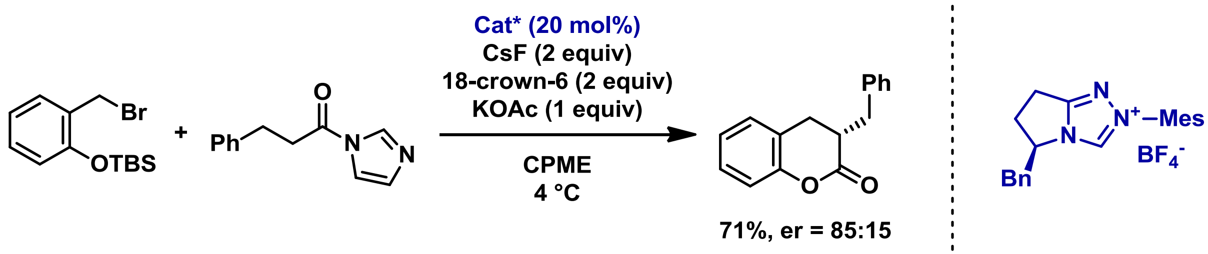
Complete scope :



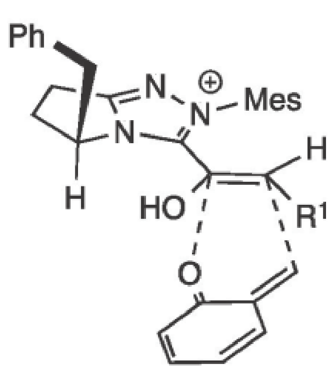
72%	79%	81%	90%	85%	80%
dr = 8:1	dr = 10:1	dr = 11:1	dr = 15:1	dr = 10:1	dr = 10:1
ee = 72%	ee = 88%	ee = 91%	ee = 88%	ee = 84%	ee = 86%

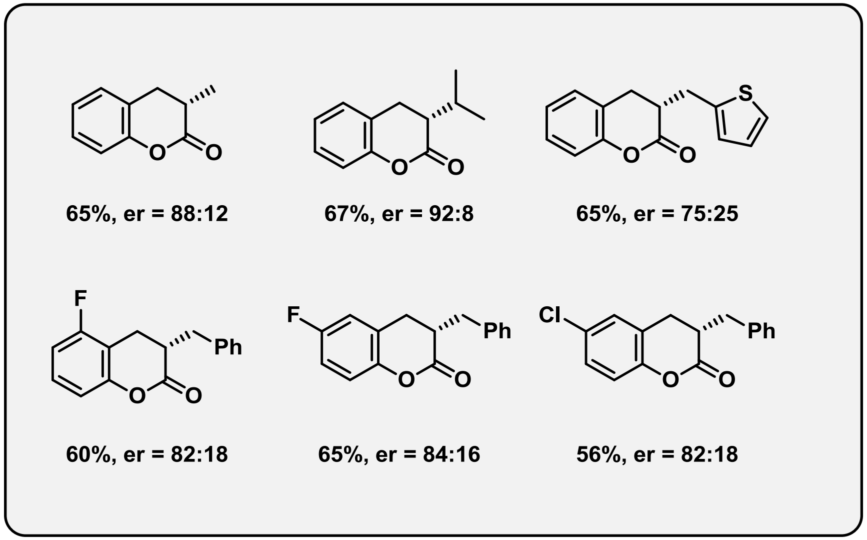
Lectka, T. *et al. Org. Lett.* **2008**, *10* (21), 4951–4953.

Synthesis of dihydrocoumarins



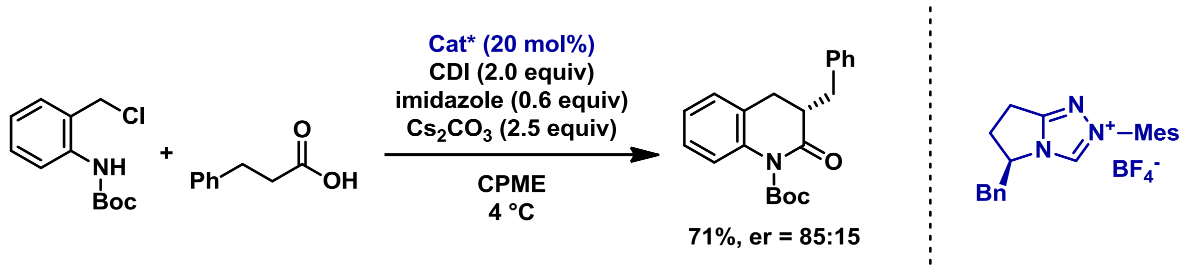
Proposed transition state :



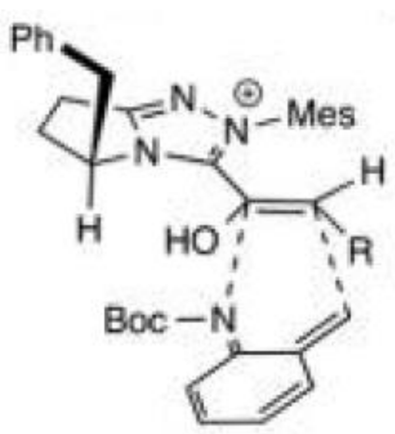


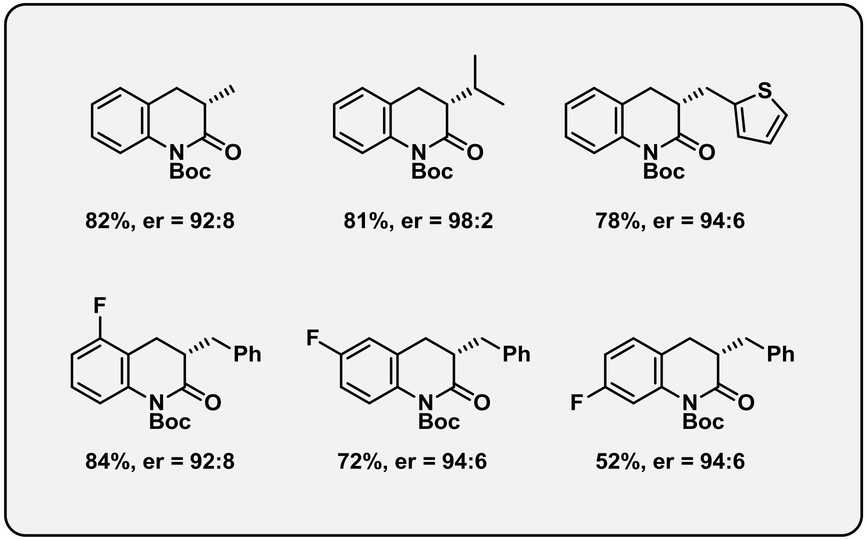
Scheidt, K. A. *et al. Chem. Commun.* **2015**, *51* (16), 3407–3410.

N-containing 6-membered heterocycles



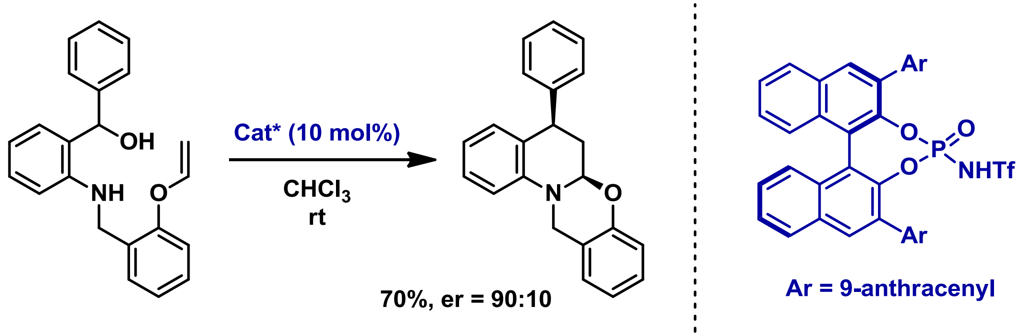
Proposed transition state :



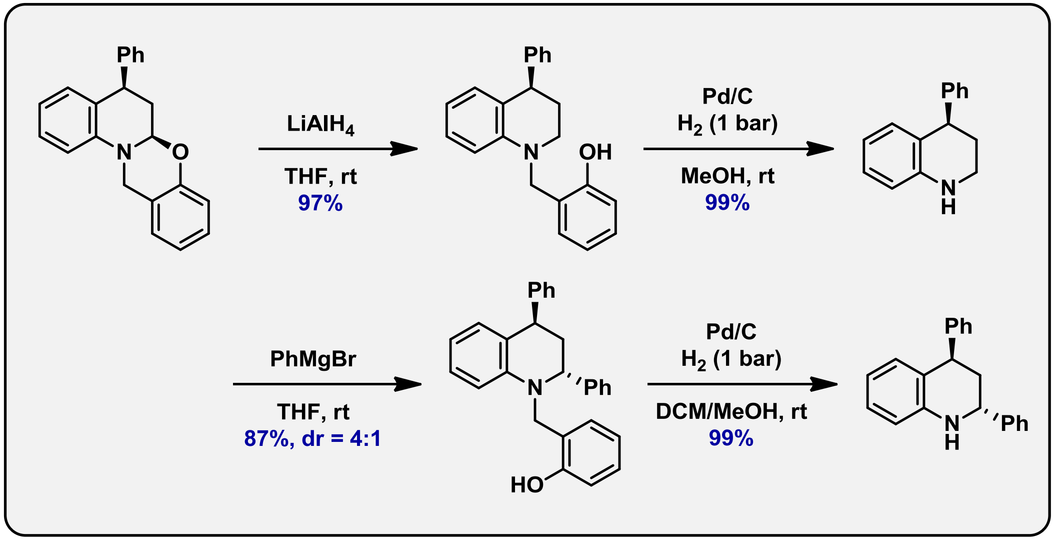


Scheidt, K. A. *et al. J. Am. Chem. Soc.* **2014**, *136* (30), 10589–10592.

_N_-containing 6-membered heterocycles



Derivatizations :



Schneider, C. *et al. Angew. Chem. Int. Ed.* **2018**, *57* (17), 4774–4778.

1) **Introduction**

2) **[4+1] Cycloadditions**

Dihydrobenzofurans

Indoles and indolines

3) **[4+2] Cycloadditions**

Chromenes, chromanes, dihydrocoumarins

N-containing 6-membered heterocycles

4) **[4+3] Cycloadditions**

Benzoxepin derivatives

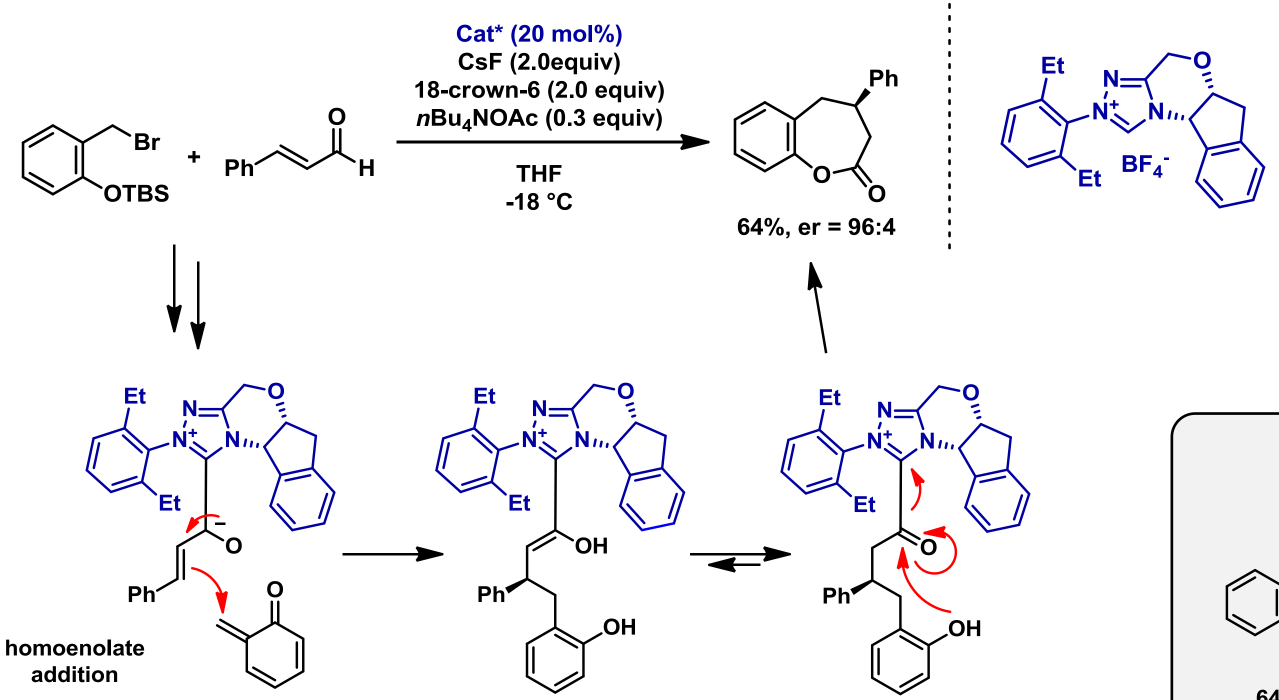
Benzazepin derivatives

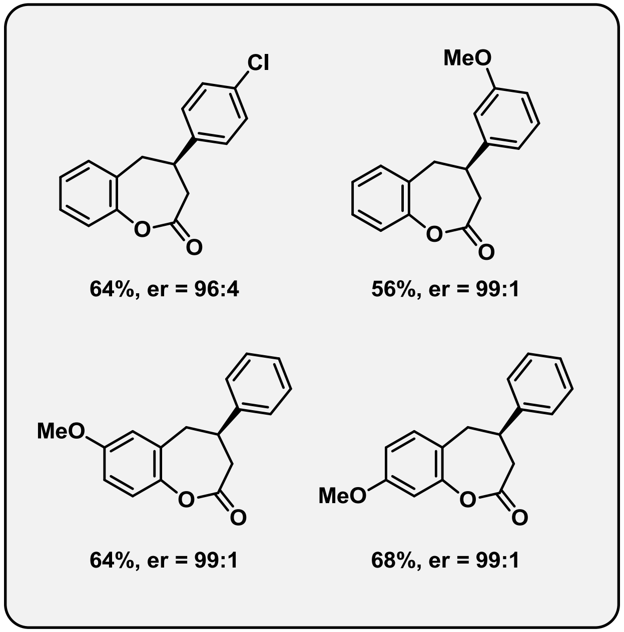
5) **[4+4] Cycloaddition**

6) **Applications in Total Synthesis**

7) **Conclusion & Questions**

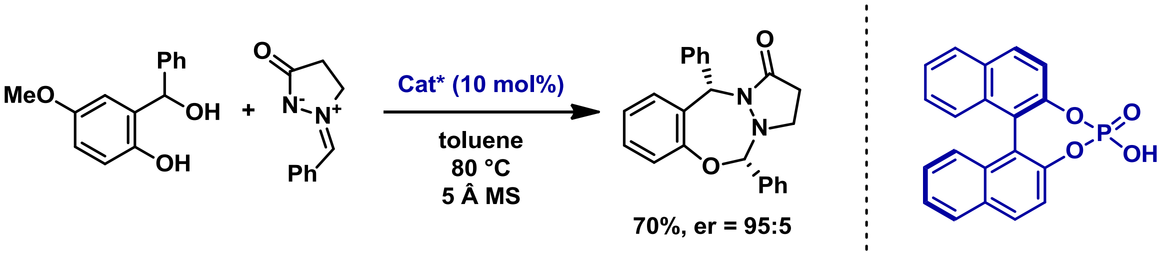
Benzoxepin derivatives



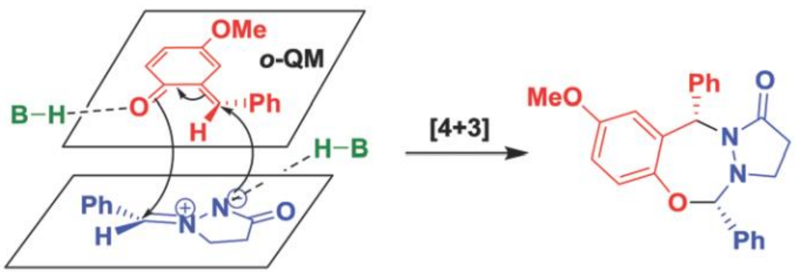


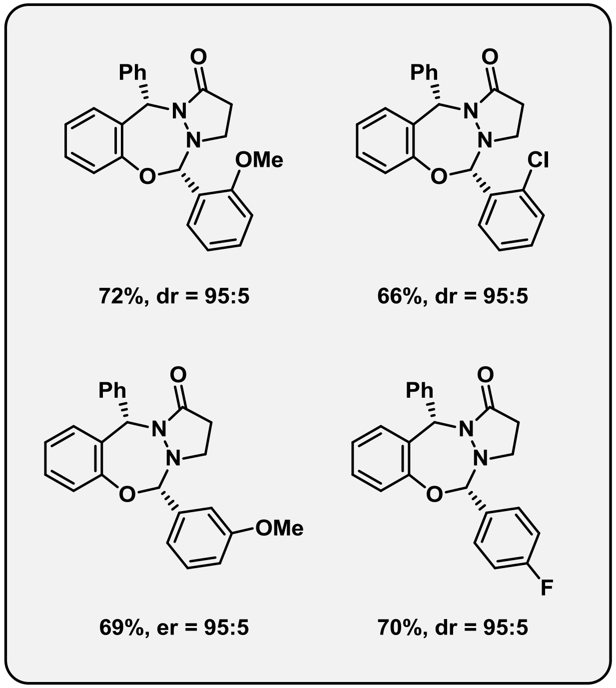
Scheidt, K. A. A *et al. J. Am. Chem. Soc.* **2013**, *135* (29), 10634–10637.
Ye, S. *et al. Angew. Chem. Int. Ed.* **2013**, *125* (33), 8769–8772. (similar)

Benzoxepin derivatives



Proposed transition state :





Shi, F. *et al. Chem. Commun.* **2017**, *53* (18), 2768–2771.

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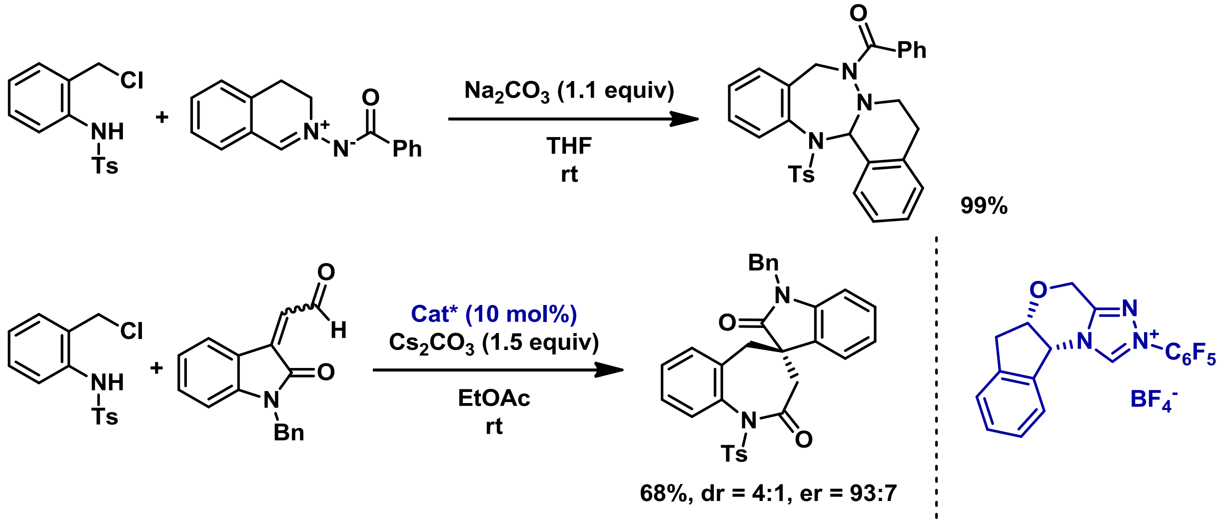

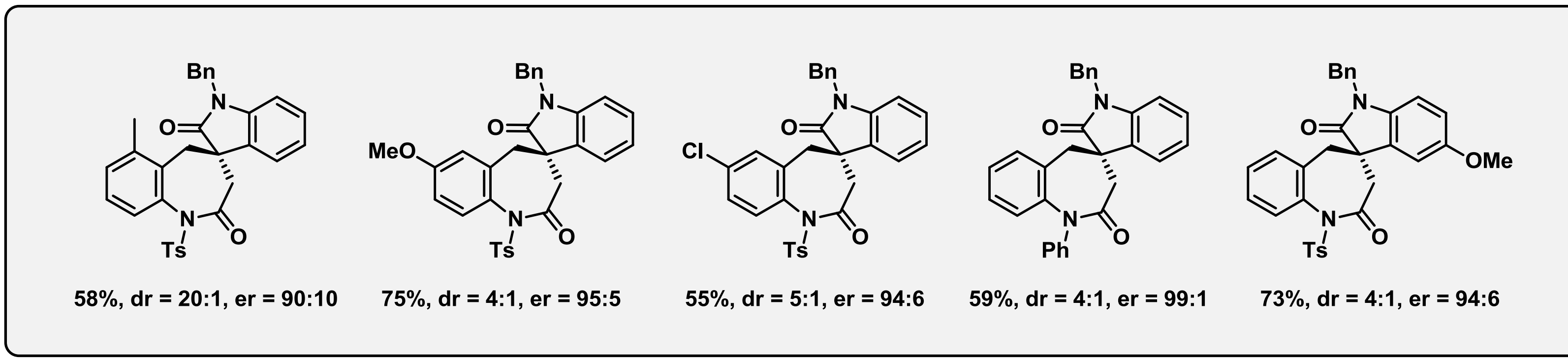

Du, Z. Y. *et al. RSC Adv.* **2015**, *5* (94), 76696–76699.
Enders, D. *et al. Angew. Chem. Int. Ed.* **2016**, *55* (37), 11110–11114.

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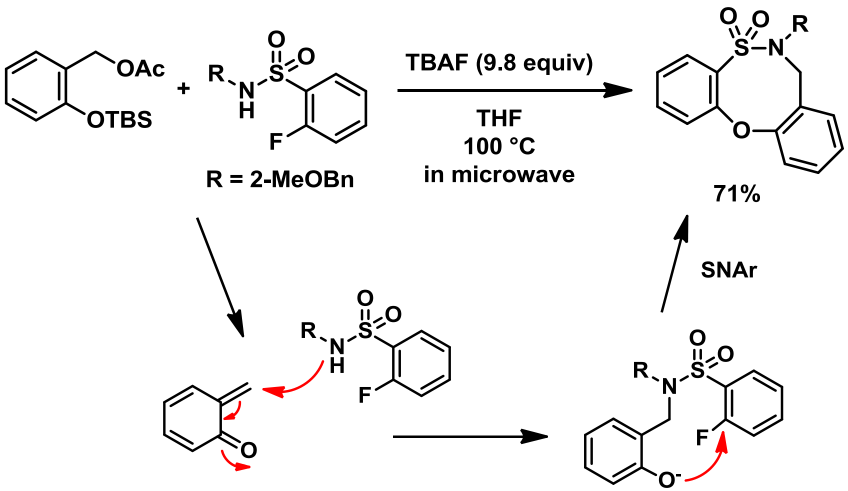
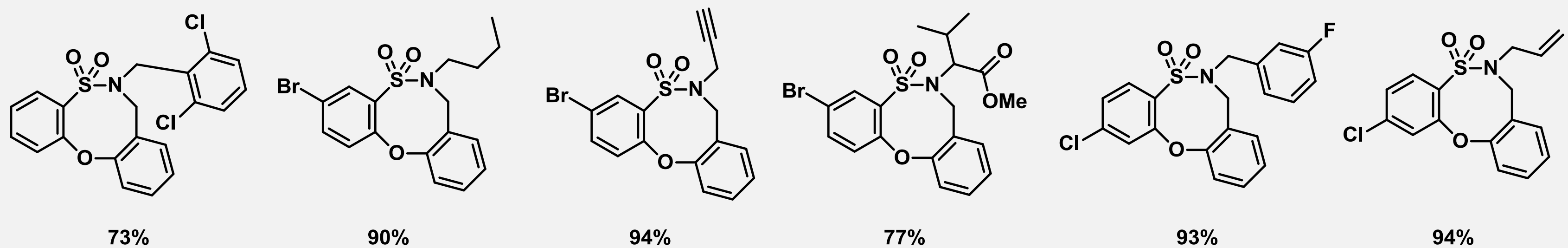
1st report of [4+4] cycloaddition with oQM





Hanson, P. R. *et al. Org. Lett.* **2010**, *12* (10), 2182–2185.

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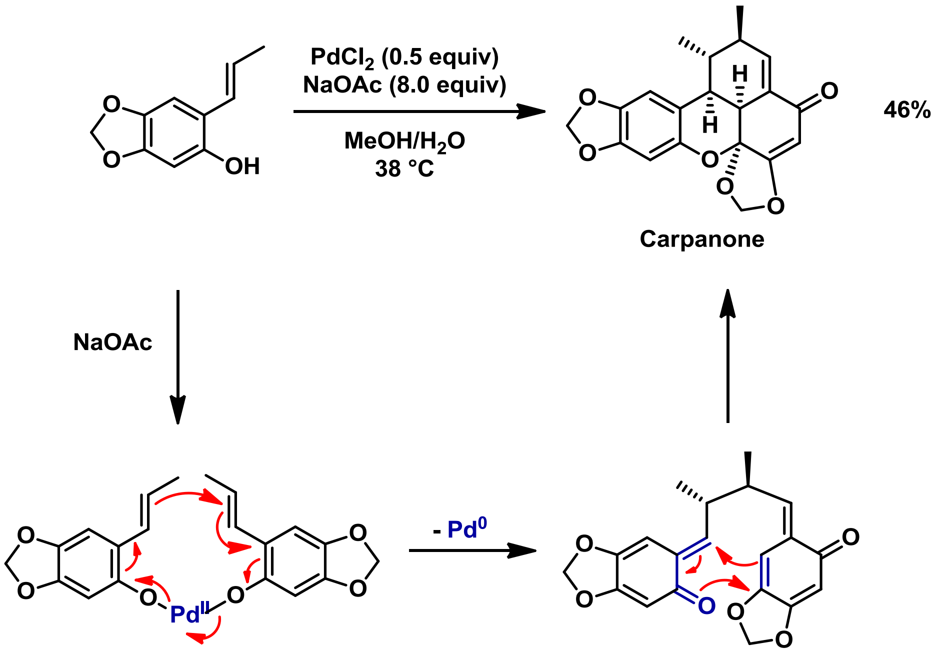
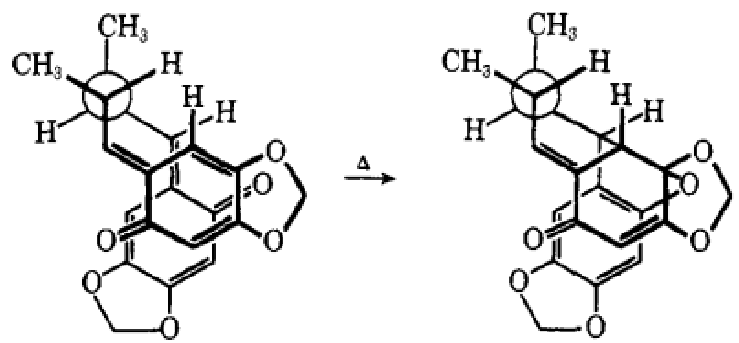
Carpanone (Clardy, 1971)



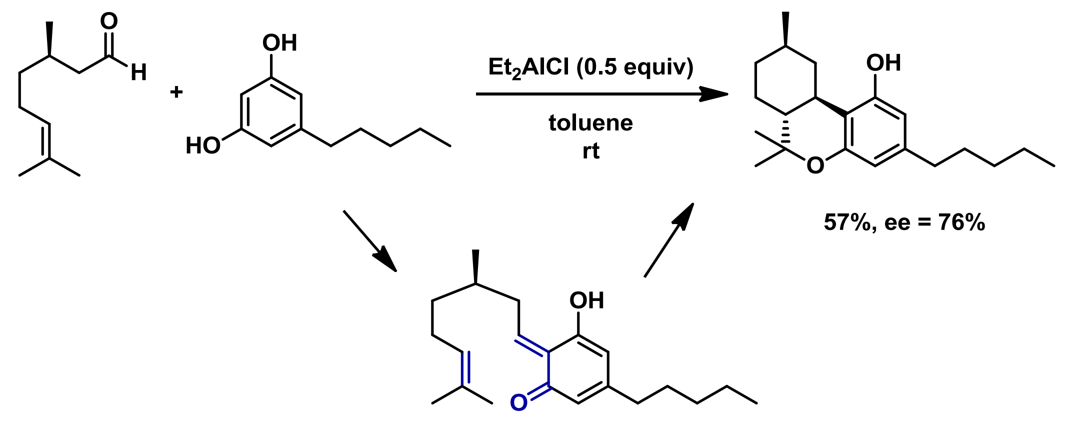
5 contiguous chiral centers

Proposed transition state :

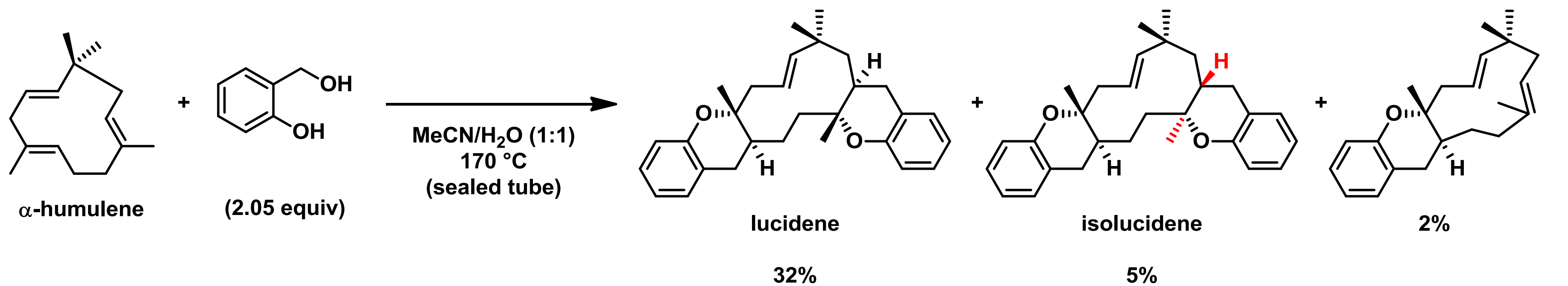


Clardy, J. C. *et al. J. Am. Chem. Soc.* **1971**, *93* (24), 6696–6698.

Hexahydrocannabinols HHC (Belicchi, 1986) :

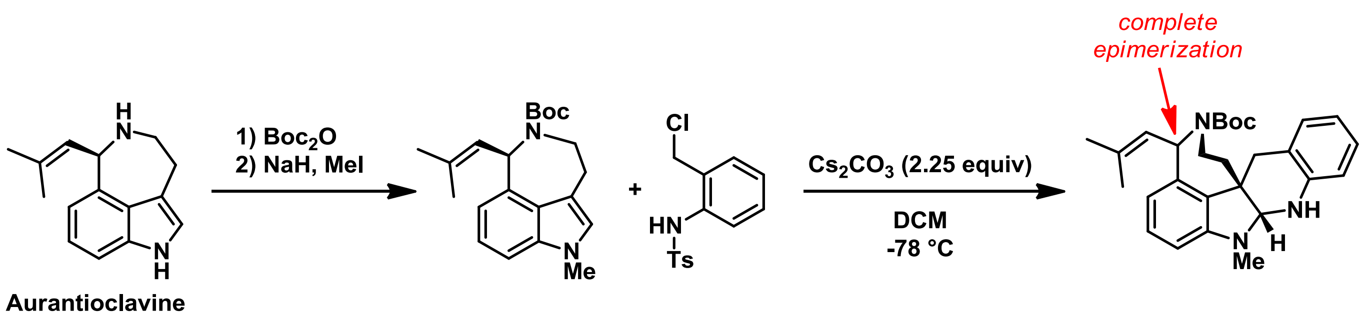


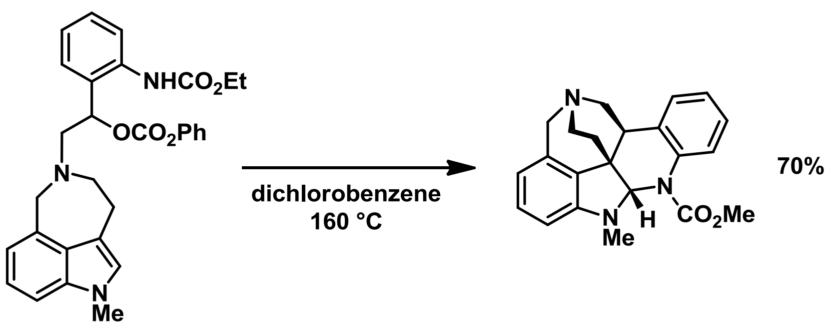
Lucidene (Watkin, 1999) :

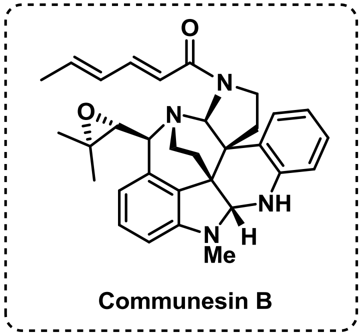


Belicchi, M. F. *et al. J. Chem. Soc., Chem. Commun.* **1986**, *0* (3), 271–273.
Watkin, D. J. *et al. Org. Lett.* **1999**, *1* (12), 1937–1939.

Approaches to Communesin B :

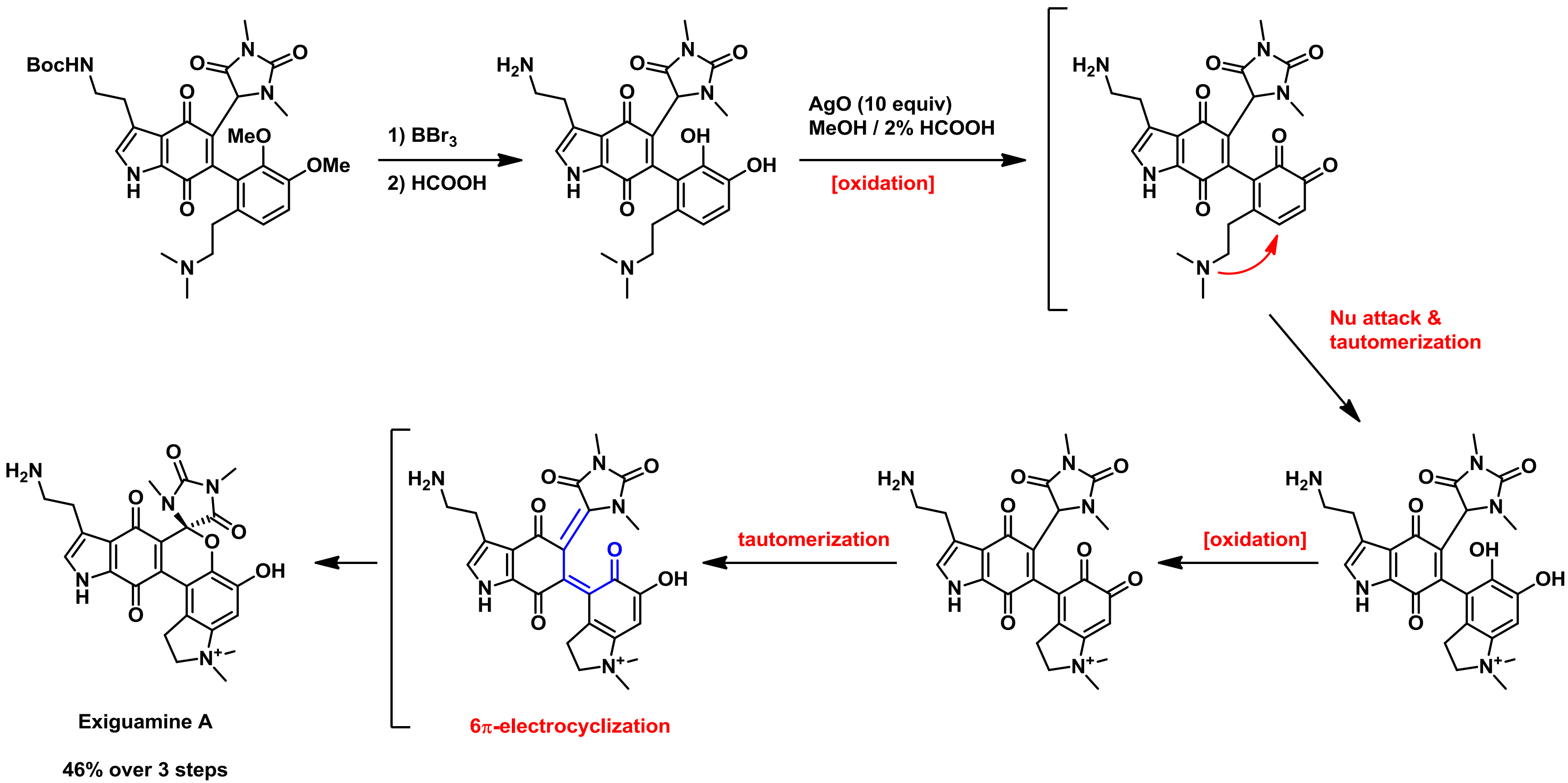






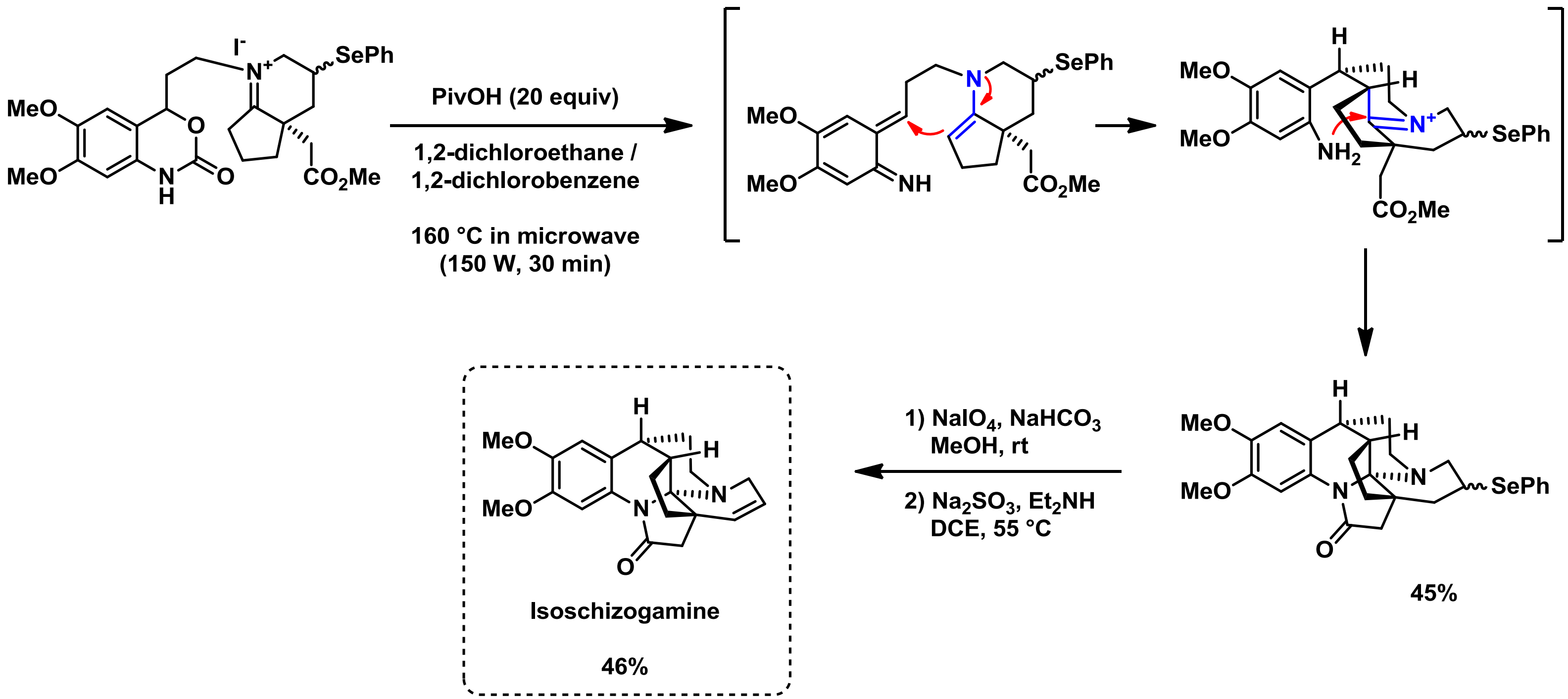
Stoltz, B. M. *et. al. Tet. Lett.* **2003**, *44* (6), 1203–1205.
Funk, R. L. *et. al. Org. Lett.* **2003**, *5* (18), 3169–3171.

Exiguamine A & B (Trauner, 2008) :



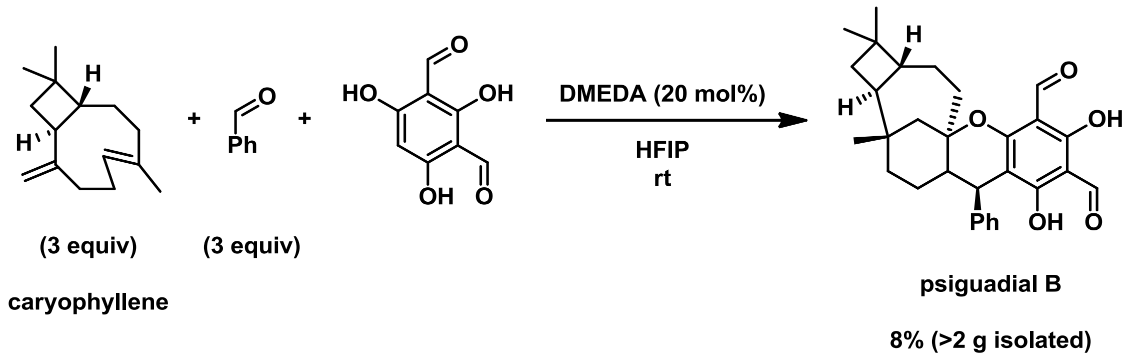
Trauner, D. *et al. Nature Chemical Biology* **2008**, *4* (9), 535–537.

Isoschizogamine (Zhu, 2015) :



Zhu, J. *et. al. Angew. Chem. Int. Ed.* **2015**, *54* (49), 14937–14940.

Approaches to Psiguadial B (Cramer, 2017) :



Propose a plausible mechanism for this transformation.

Cramer, N. *et. al. Angew. Chem. Int. Ed.* **2017**, *56* (44), 13776–13780.

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4) **[4+3] Cycloadditions**

Benzoxepin derivatives

Benzazepin derivatives

5) **[4+4] Cycloaddition**

6) **Applications in Total Synthesis**

7) **Conclusion & Questions**

Summary :

The reactions involving (a)oQMs intermediates…

… allow the synthesis of numerous heterocyclic scaffolds and natural products

… use simple and readily available starting materials

… are usually metal-free and run under mild conditions

Perspectives :

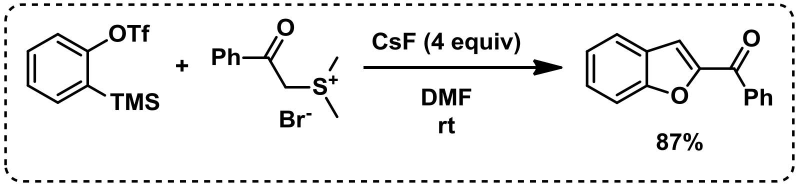
- Development of novel catalytic asymmetric reactions
- Exploitation of (a)oQM intermediates for the synthesis of complex natural product

Thank you for your attention !

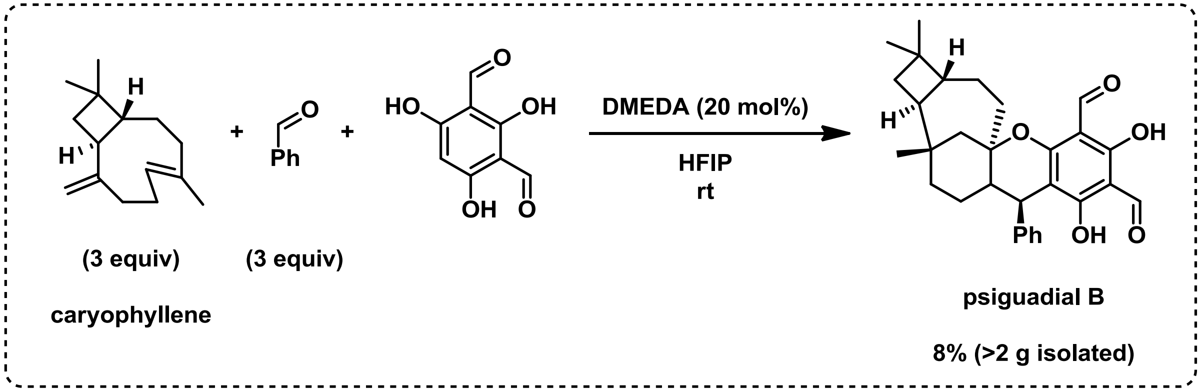
Questions ?

Questions :

Propose a mechanism for the following transformations :

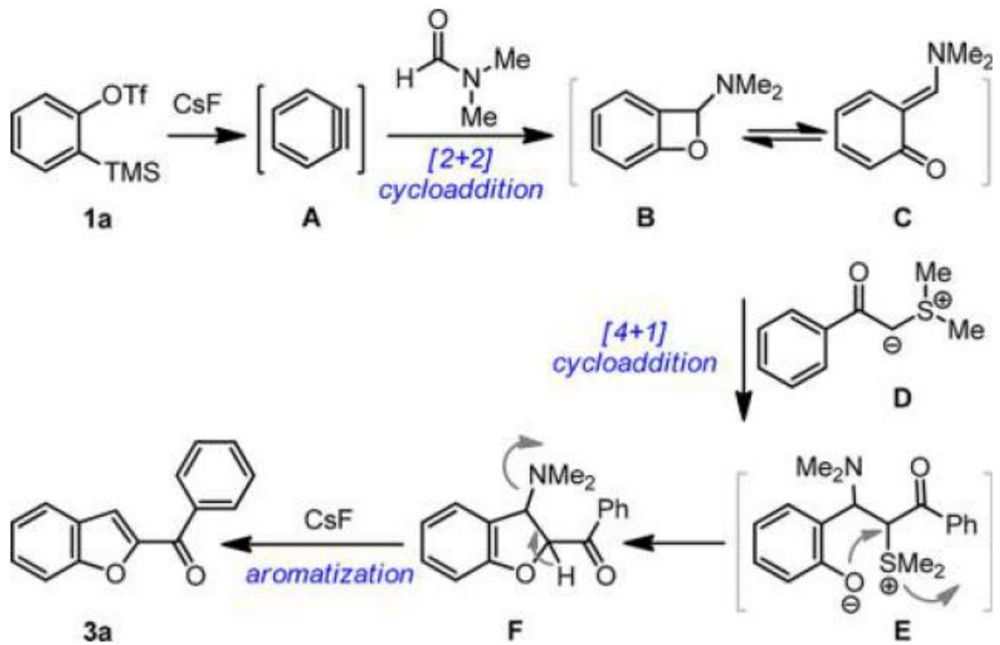


Chandrasekhar, S. *et al. J. Org. Chem.* **2018**, *83* (6), 3325–3332.



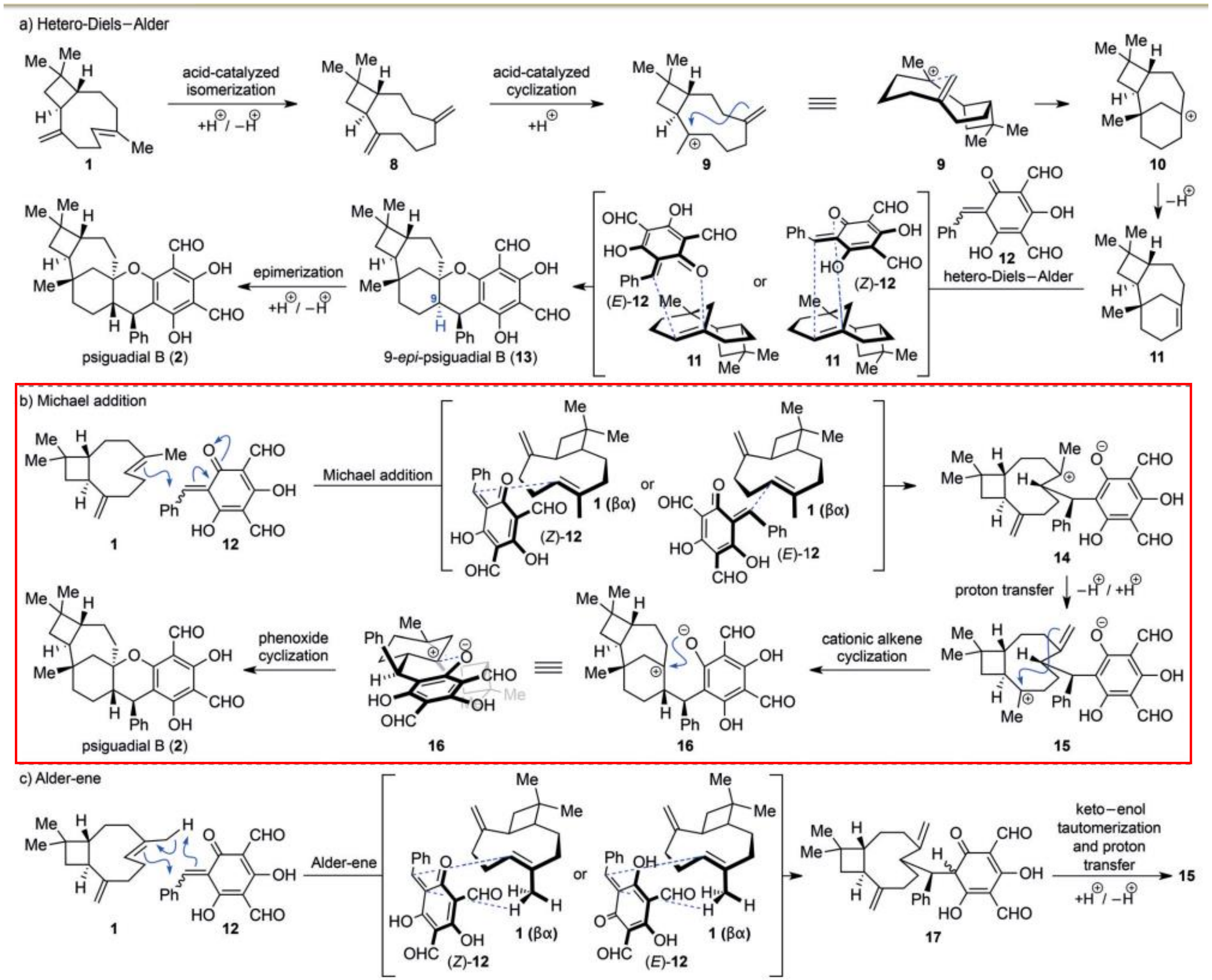
Cramer, N. *et. al. Angew. Chem. Int. Ed.* **2017**, *56* (44), 13776–13780.

Questions :



Chandrasekhar, S. *et al. J. Org. Chem.* **2018**, *83* (6), 3325–3332.

Questions :



Cramer, N. *et. al. Angew. Chem. Int. Ed.* **2017**, *56* (44), 13776–13780.

Qui-Hien Nguyen

Carbohydrate–NHC metal complexes: Synthesis, Structures and Applications in Catalysis and Medicinal Chemistry

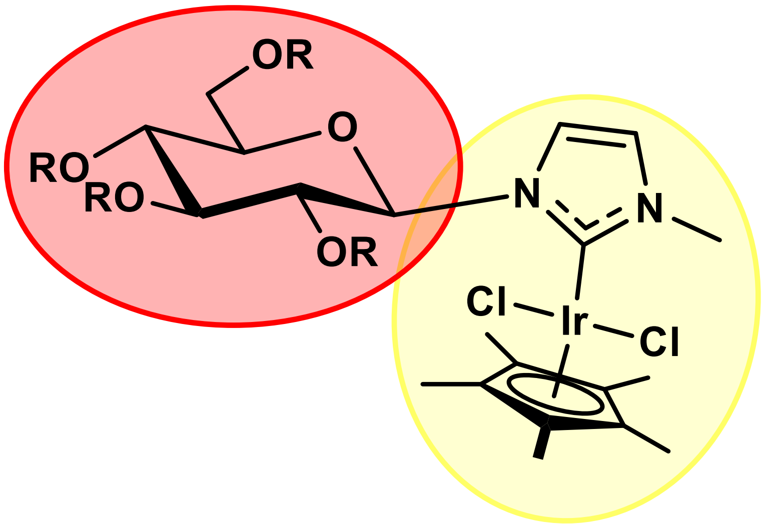
Frontiers in Chemical Synthesis II: *Heterocycle Chemistry*

(Prof. Jérôme Waser, Prof. Xile Hu)

Lausanne, May 17, 2018

1. Introduction
2. Synthesis of Carbohydrate–NHC complexes
3. Structural Complexity
4. Applications in Catalysis
5. Applications in Medicinal Chemistry

Why combine sugars and NHC?



NHC:

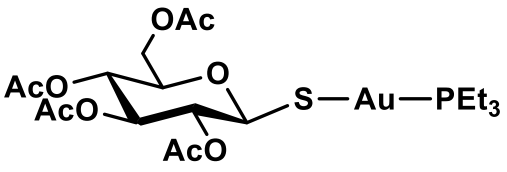
- Applications in catalysis.
- Strong e-donor but *not just phosphine-mimics.*
- Chiral NHC: a developing field.

Carbohydrates:

- Cheap, structural diverse, easily incorporating chiral motif.
- Increase water solubility.
- Biocompatible: applications in medicinal chemistry.

Why build analogues with carbohydrate and NHC?

- NHC: stabilizes metal center, ease of synthesis and derivatization.
- Carbohydrate: good biocompatibility, ease of tuning to achieve hydrophilicity and lipophilicity.
- Studies suggest increased carbohydrate uptake in cancer cells ("the Warburg effect").



Auranofin

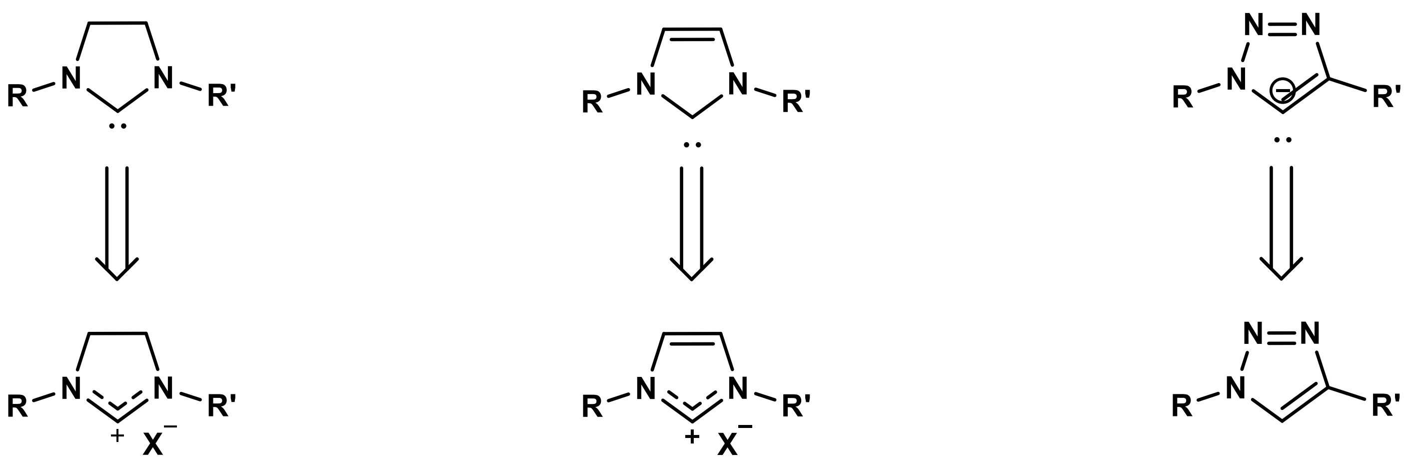
Auranofin:

- Well-known Au drugs, first used as anti-arthritic medicine then anti-cancer activity was found.
- Library of analogues can be built with NHC ligand, instead of phosphine.
- Sugar can be linked to NHC or acts as a ligand as in Auranofin.
- Other metal complexes are also discussed: Pt.

Reported carbohydrate–NHC complexes

NHC part: all 5-membered rings from 3 families.

imidazolidinylidene | imidazolylidene | 1,2,3-triazolylidene



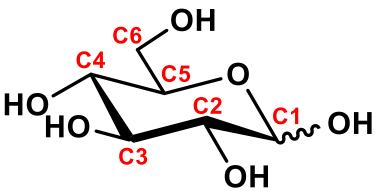
imidazolinium salt | imidazolium salt | 1,2,3-triazole

R: saccharide moiety or other substituent

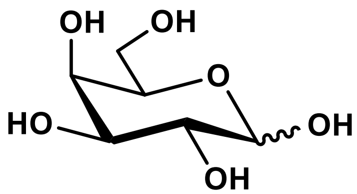
Coord. Chem. Rev. **2017**, *339*, 1–16.

Reported carbohydrate–NHC complexes

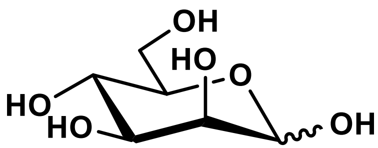
Carbohydrate part:



D-glucopyranose



D-galactopyranose



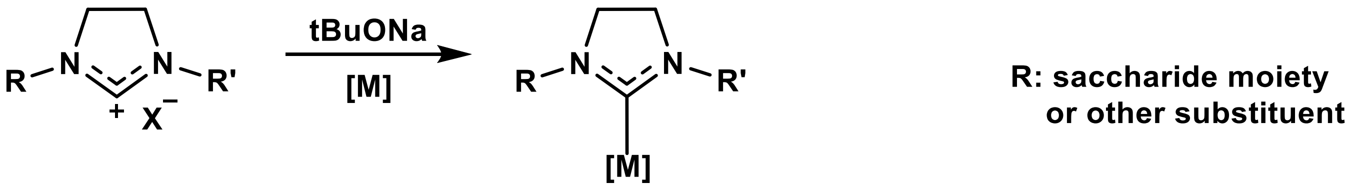
D-mannopyranose

and their derivatives

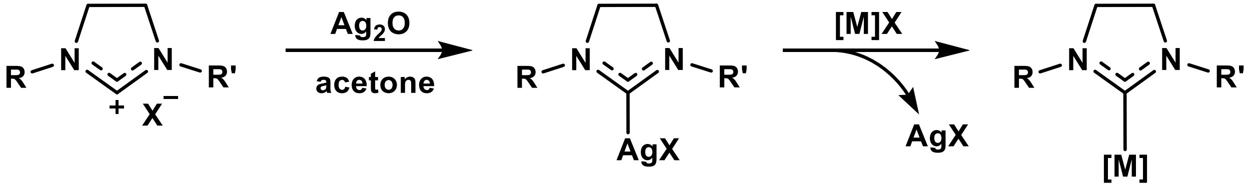
Linkage to NHC: C1, C2, C3 and C6.

Complexation of carbohydrate–NHC-metal complexes:

1. *In situ* deprotonation-complexation



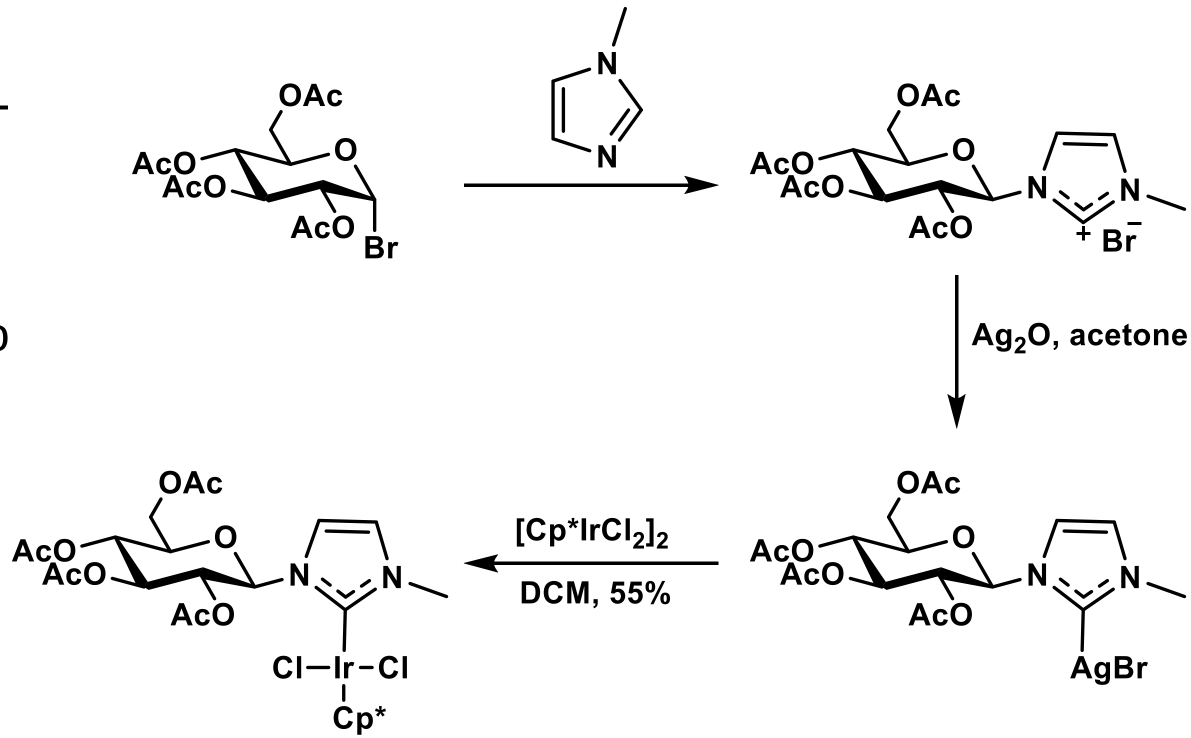
2. Ag-NHC transmetallation

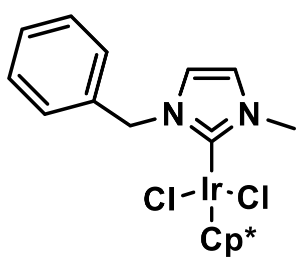


Angew. Chem. Int. Ed. **2008**, *47*, 3122–3172; *Organometallics* **1998**, *17*, 972–975.

Nishioka (2007)

- Stable carbene formed.
- IrCp* moiety points to α-face.
- X-ray diffraction studies suggests strong σ-donation, comparable to known Cp*Ir-carbene complexes.

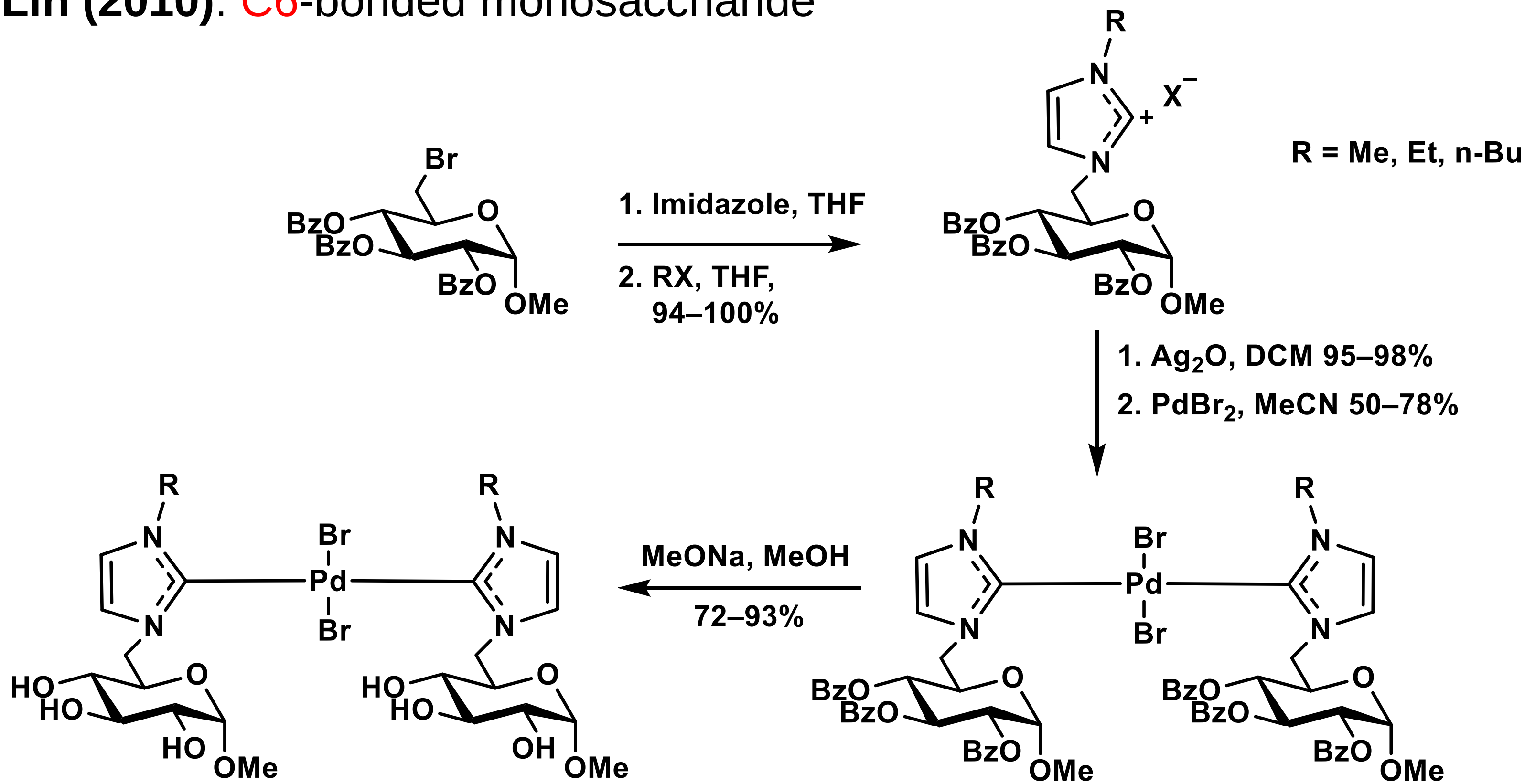




Organometallics **2007**, *26*, 1126–1128.

Trans-syn and *trans-anti* conformations

Lin (2010): C6-bonded monosaccharide

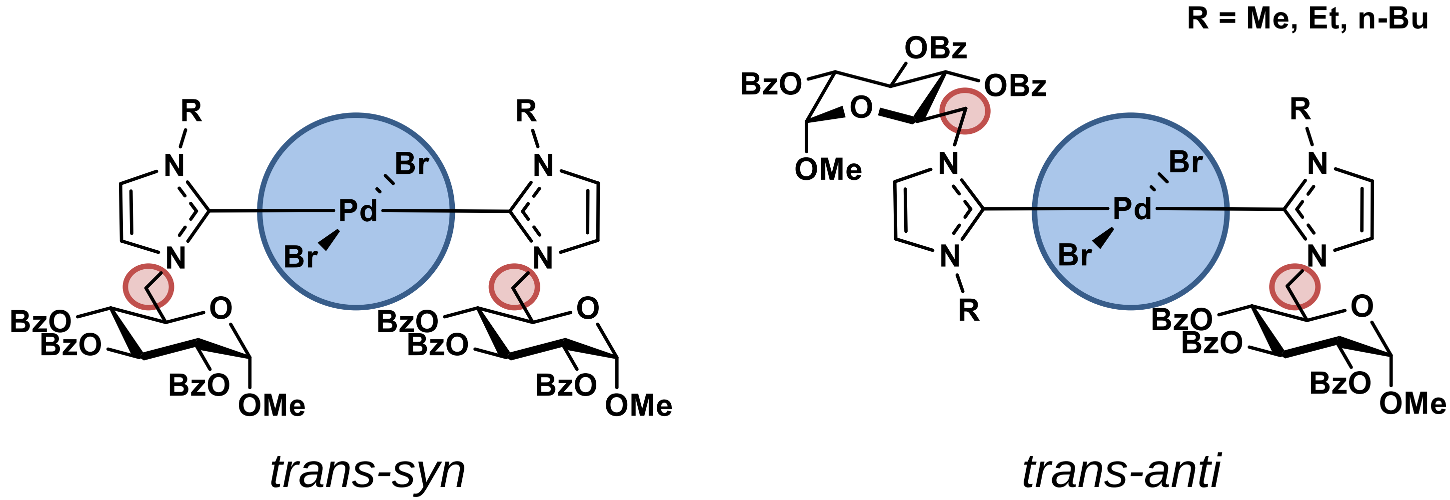


trans complex

Organometallics **2010**, *29*, 5959–5971.

Trans-syn and *trans-anti* conformations

Lin (2010): C6-bonded monosaccharide



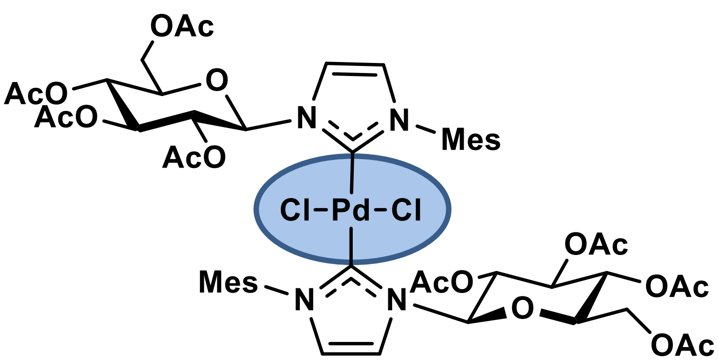
- In solution: two forms observed.
- Solid state: a slight twist between two NHC planes (15–33°).
- Core bulkiness: slows down NHC–Pd rotation on NMR timescale.
- C6 spacer: allows flexibility on NHC so two rotamers co-exist.

Organometallics **2010**, *29*, 5959–5971.

Structural Complexity

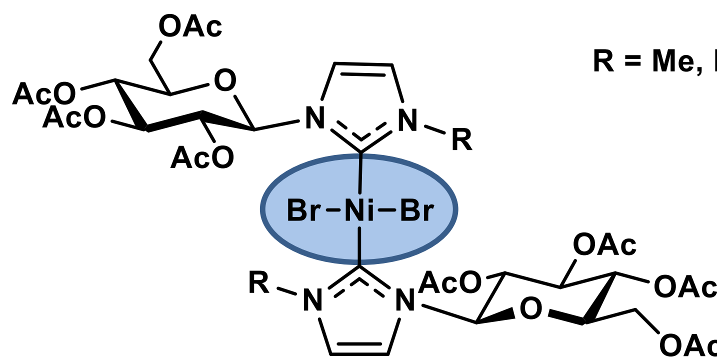
***Trans-syn* and *trans-anti* conformations**

Glorius (2007)



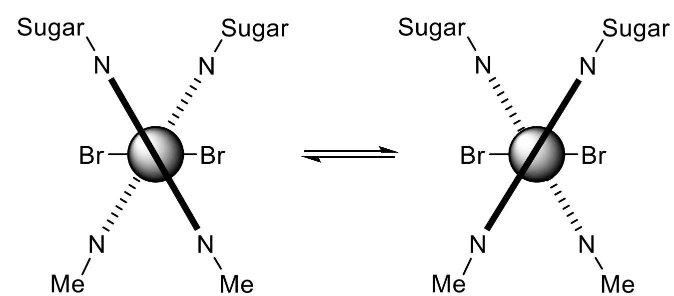
trans-anti only

Nishioka (2011)



both forms

- C1-bonded monosaccharide*:* no spacer effect.
- Core bulkiness: $[NiBr_2] > [PdCl_2]$.
- Nishioka: evidence of *syn-R*$_a$ and *syn-S*$_a$ diastereomers at low temperature.



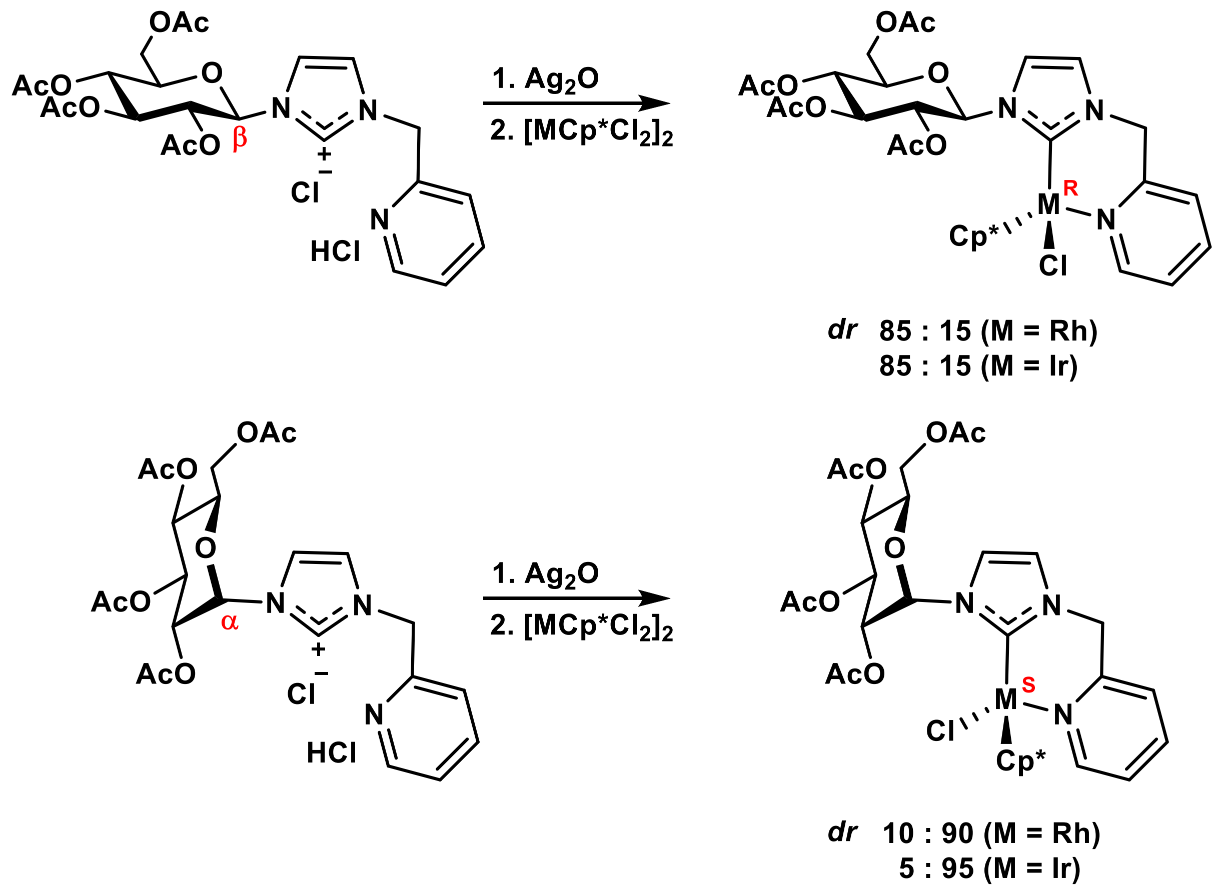
syn-S$_a$ *syn-R*$_a$

J. Organomet. Chem. **2007**, *692*, 4593–4602.
Dalton Trans. **2011**, *40*, 6778–6784.

Diastereoselective Synthesis

Nishioka (2011)

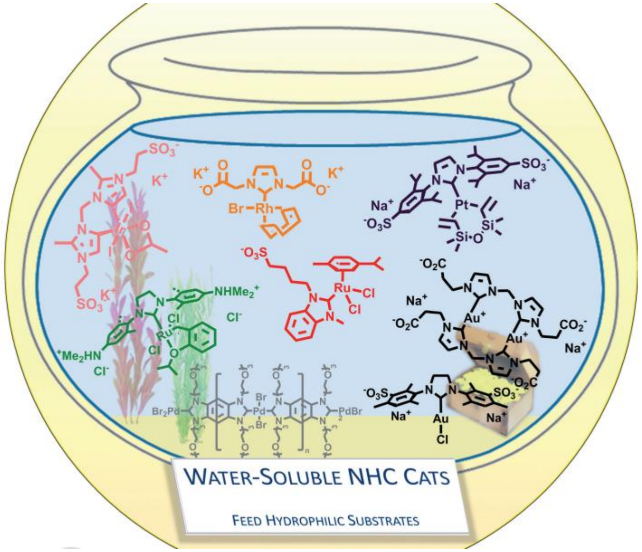
- Chelated NHC-metal complexes with pseudo-tetrahedral centre.
- Chirality controlled by anomeric isomerism of glucopyranoside.



Dalton Trans. **2011**, *40*, 4826–4829.

The "greenest" solvent

- Non-flammable, non-toxic, abundant.
- Easy separation of organic products.
- Easy homogeneous catalyst recycling.
- Applicable in industrial scale and in chemical biology (e.g. reaction on protein surface).



Water-soluble NHC complexes

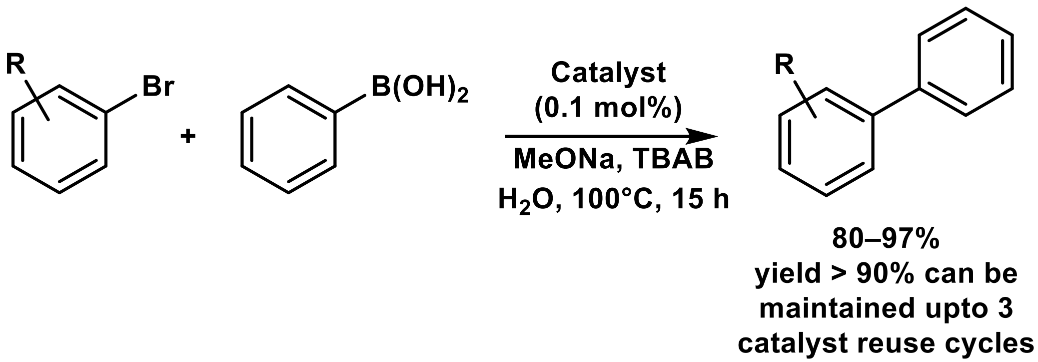
- Sugar moieties: greatly enhance hydrophilicity, easily incorporated, well-defined and tunable chirality.

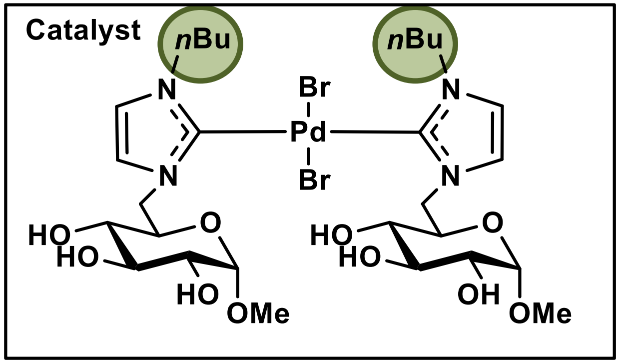
Review on Water-Soluble NHC-transition metal complexes: *Angew. Chem. Int. Ed.* **2013**, *52*, 270–289.

Water-Soluble Catalyst

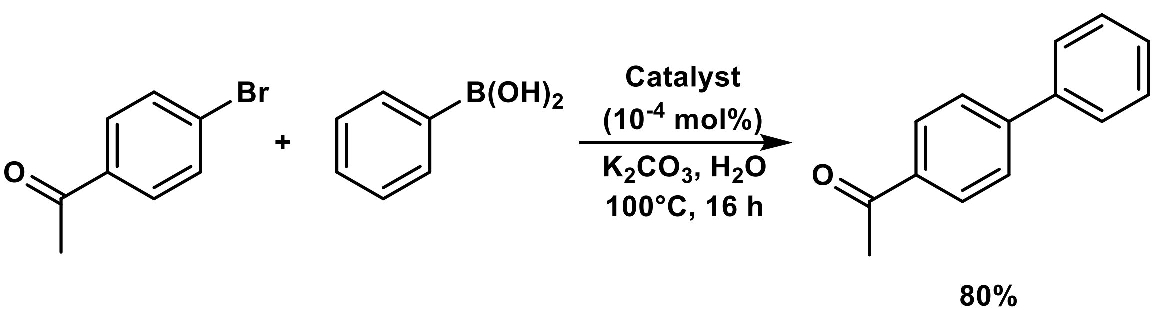
Suzuki–Miyaura Cross-Coupling:

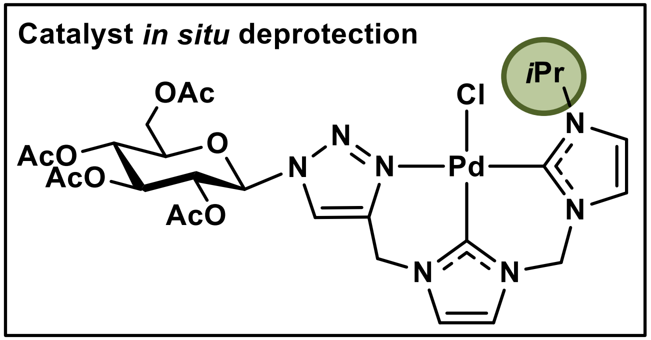
Lin (2010):





Nishioka (2015):



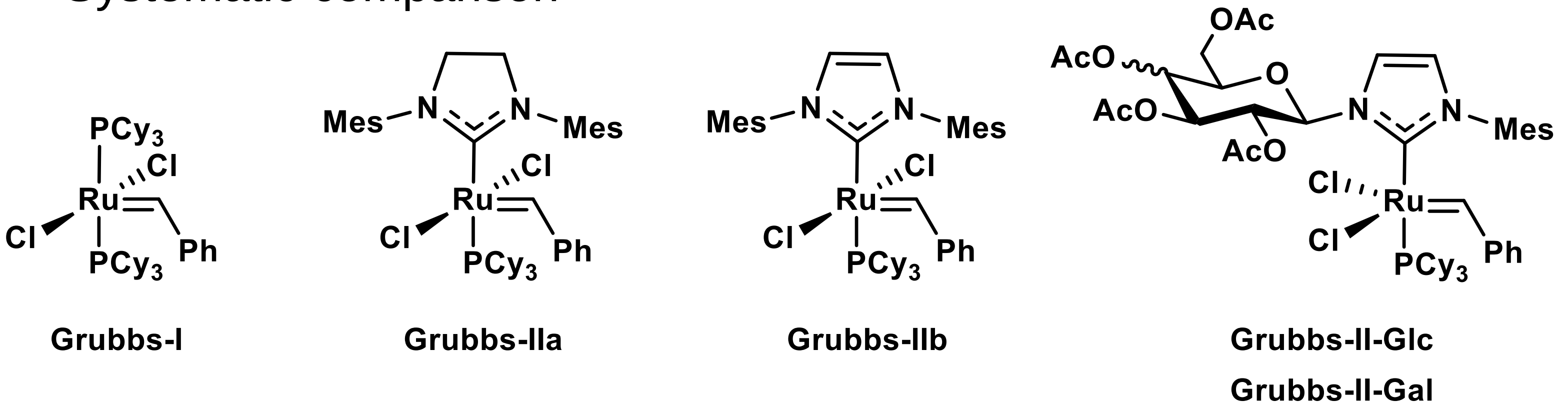


- In both cases: bulky, e-donating groups on NHC give optimal yield.

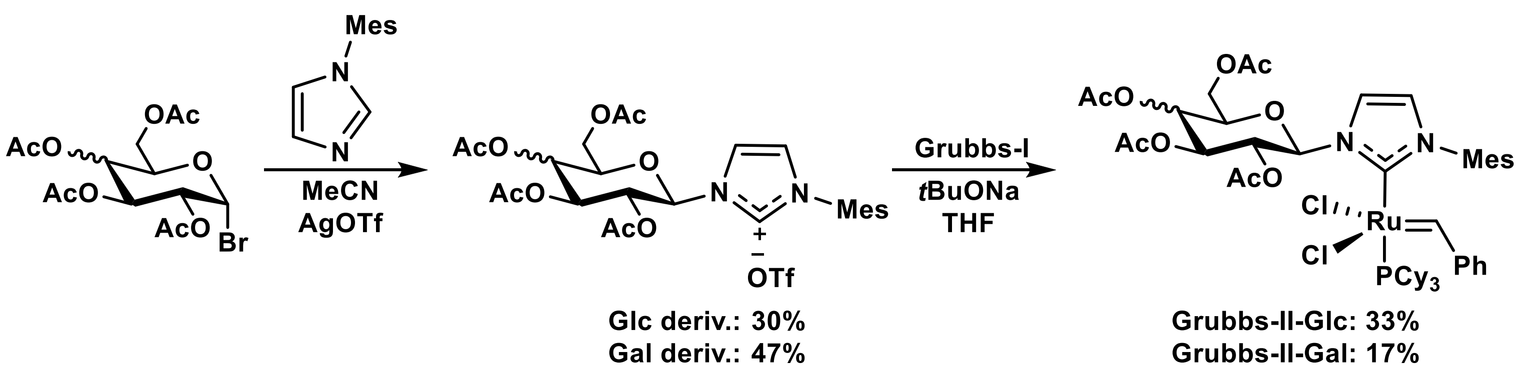
Organometallics **2010**, *29*, 5959–5971;
Bull. Chem. Soc. Jpn. **2015**, *88*, 1135–1143.

Grubbs (2009): Combining carbohydrate and 2nd generation Grubbs cat.

- Systematic comparison

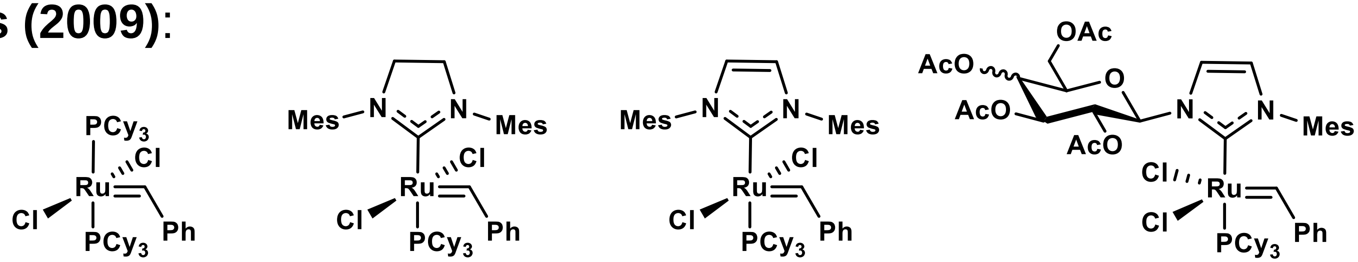


- Synthesis:



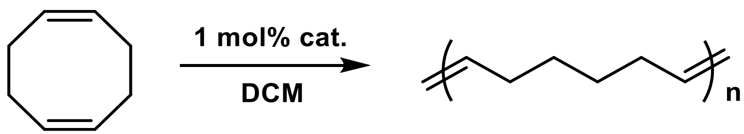
Organometallics **2010**, *29*, 403–408.

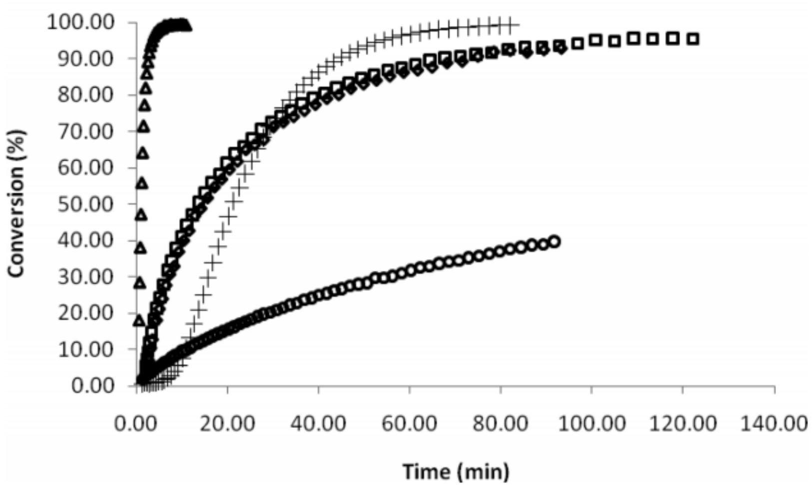
Grubbs (2009):



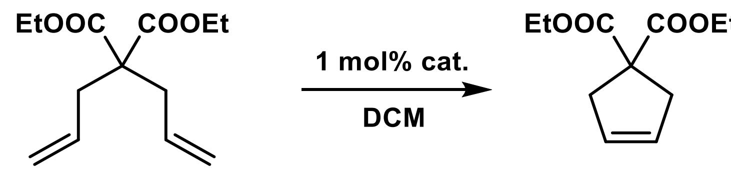
Grubbs-I ○ Grubbs-IIa △ Grubbs-IIb + Grubbs-II-Glc □ Grubbs-II-Gal ◇

- ROMP:





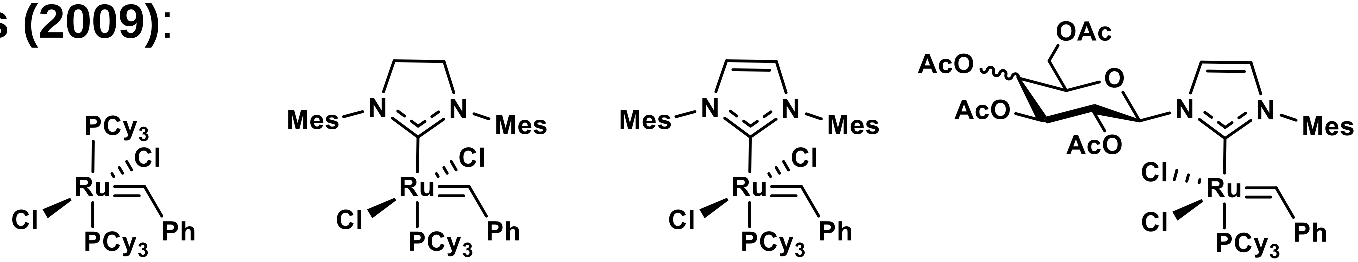
- RCM:



Grubbs-IIb: 90%
Grubbs-IIa: 80%
Grubbs-I: 60%
Grubbs-II-Gal: 60%
Grubbs-II-Glc: 30%

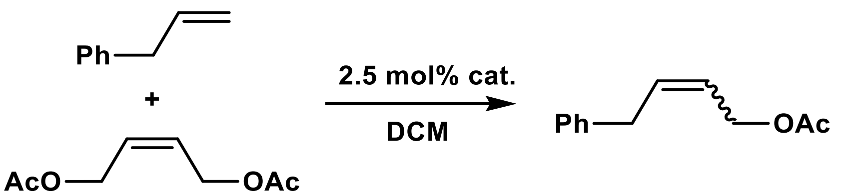
Organometallics **2010**, *29*, 403–408.

Grubbs (2009):



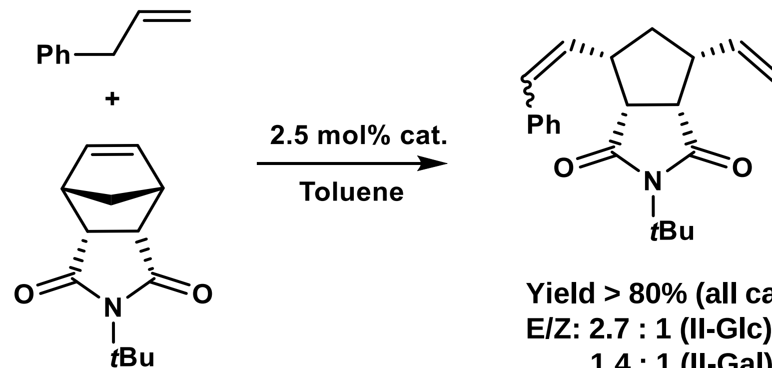
Grubbs-I | Grubbs-IIa | Grubbs-IIb | Grubbs-II-Glc / Grubbs-II-Gal

- CM:



Yield ~80% (all cases)
E/Z: 9:1 – 10:1 (I, IIa, IIb)
3:1 (II-Glc and Gal)

- AROCM:



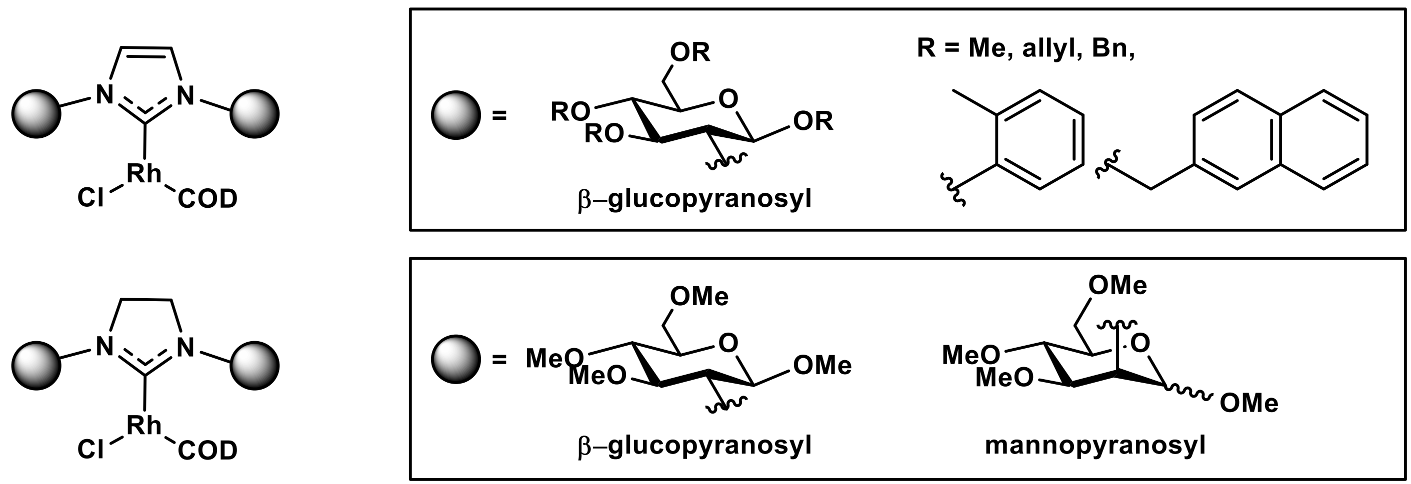
Yield > 80% (all cases)
E/Z: 2.7 : 1 (II-Glc)
1.4 : 1 (II-Gal)

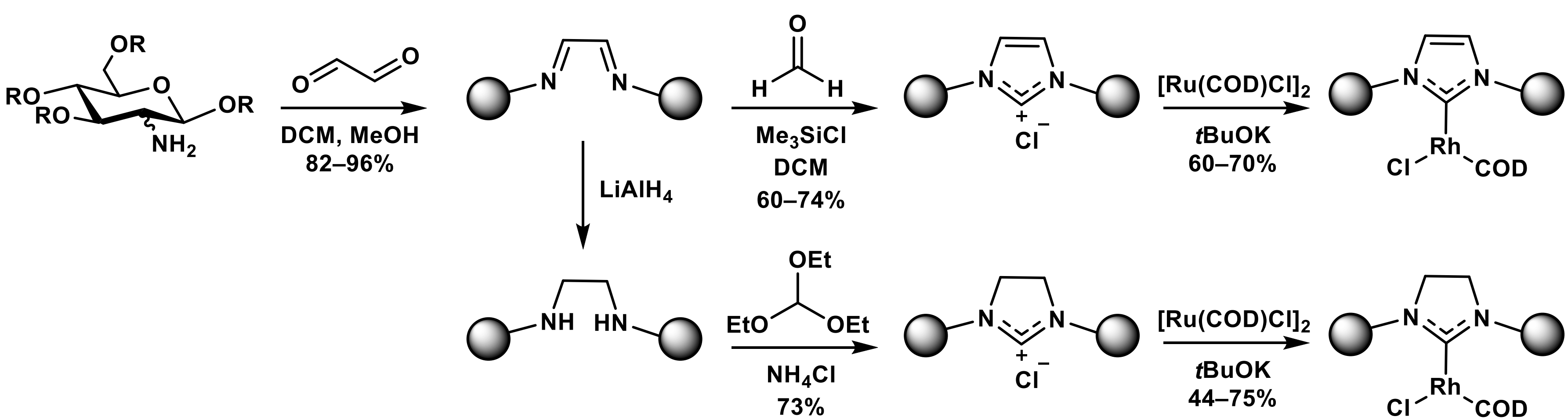
- II-Glc and II-Gal are inferior to IIa, comparable to IIb, in some case better than I.
- Speculation: decomposition of II-Glc and Gal; no evidence given though.
- No carbohydrate equivalent of IIa for comparison.

Organometallics **2010**, *29*, 403–408.

Asymmetric Ketone Reduction

Bower and Galan (2014): C2-bonded monosaccharide

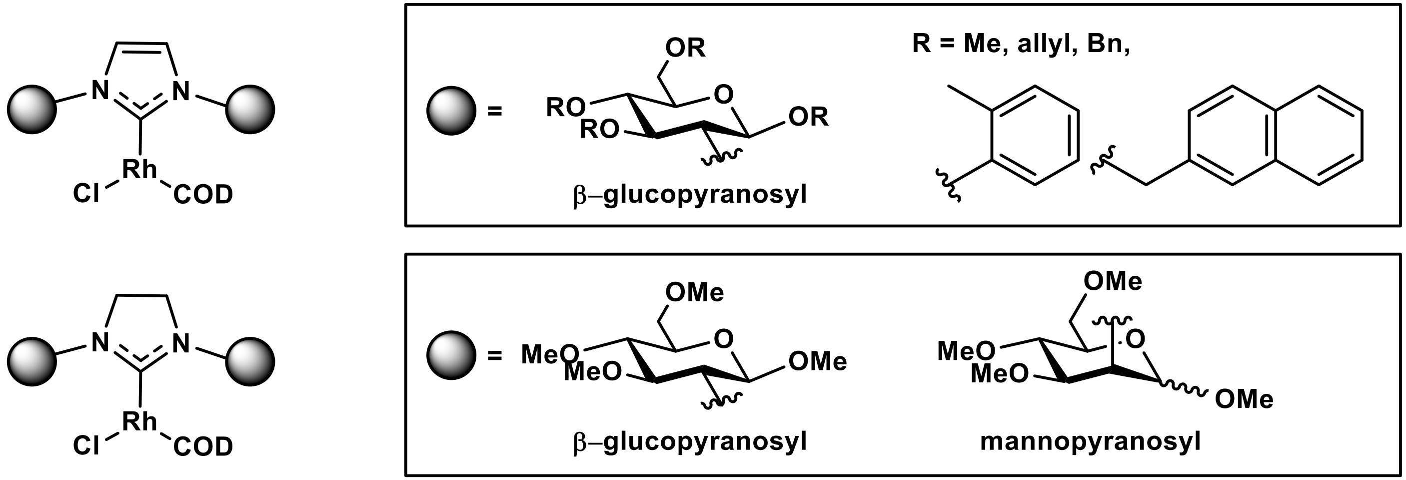


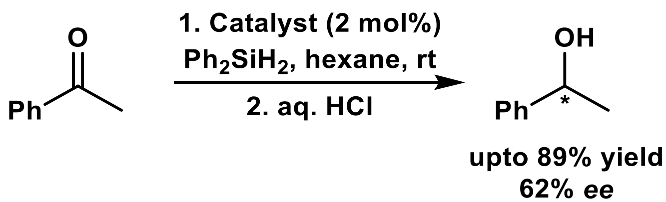


Org. Biomol. Chem. **2014**, *12*, 9180–9183.

Asymmetric Ketone Reduction

Bower and Galan (2014): C2-bonded monosaccharide

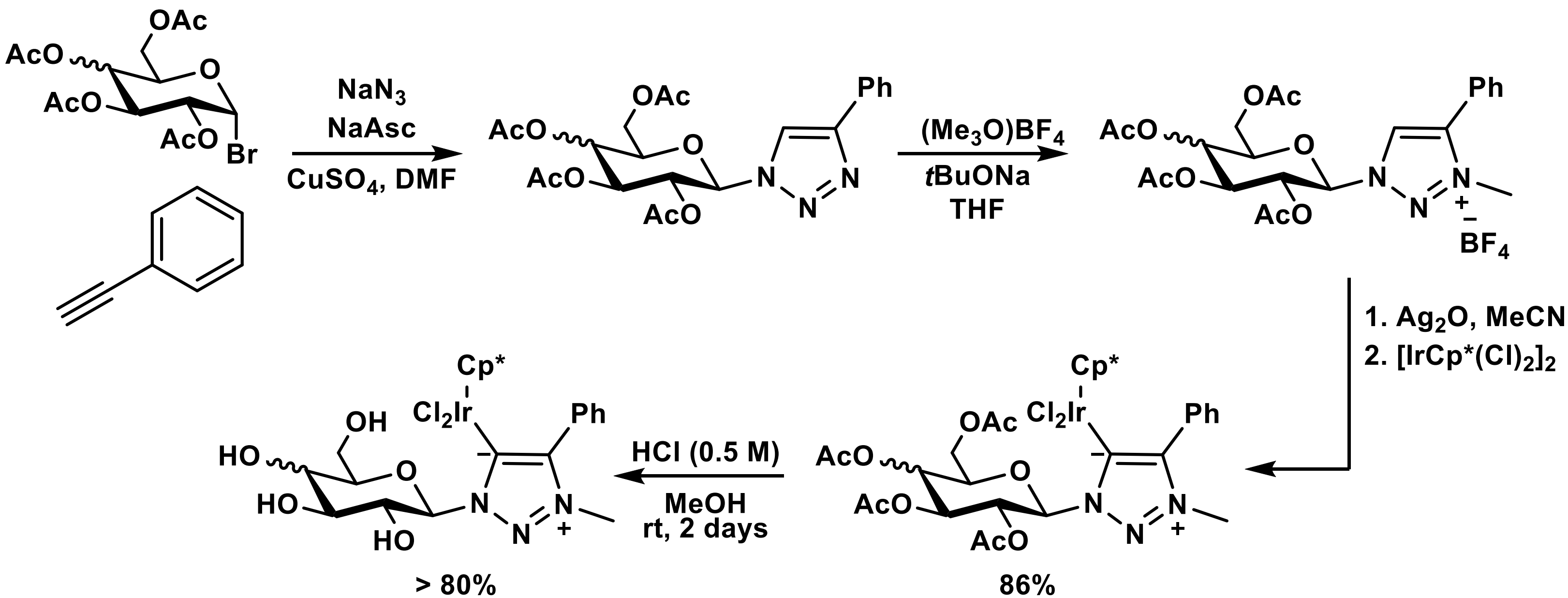


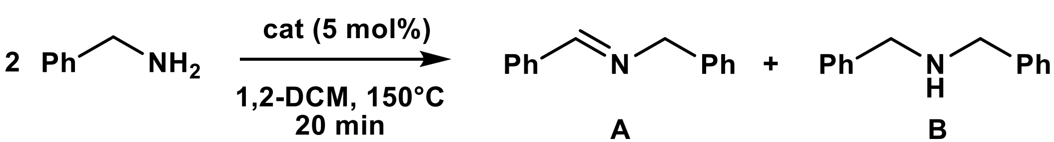


- Best reactivity and *ee* achieved with smallest R = Me.
- No difference between sat. and unsat. NHC.
- Glucopyranosyl-NHCs are more effective than mannopyranosyl-NHCs.

Org. Biomol. Chem. **2014**, *12*, 9180–9183.

Albrecht (2017): C1-bonded 1,2,3-Triazolylidene complexes

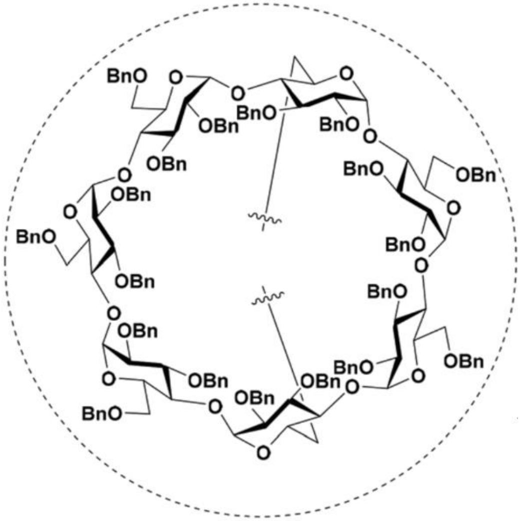


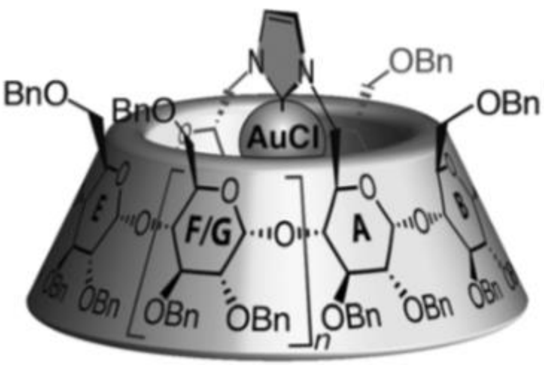


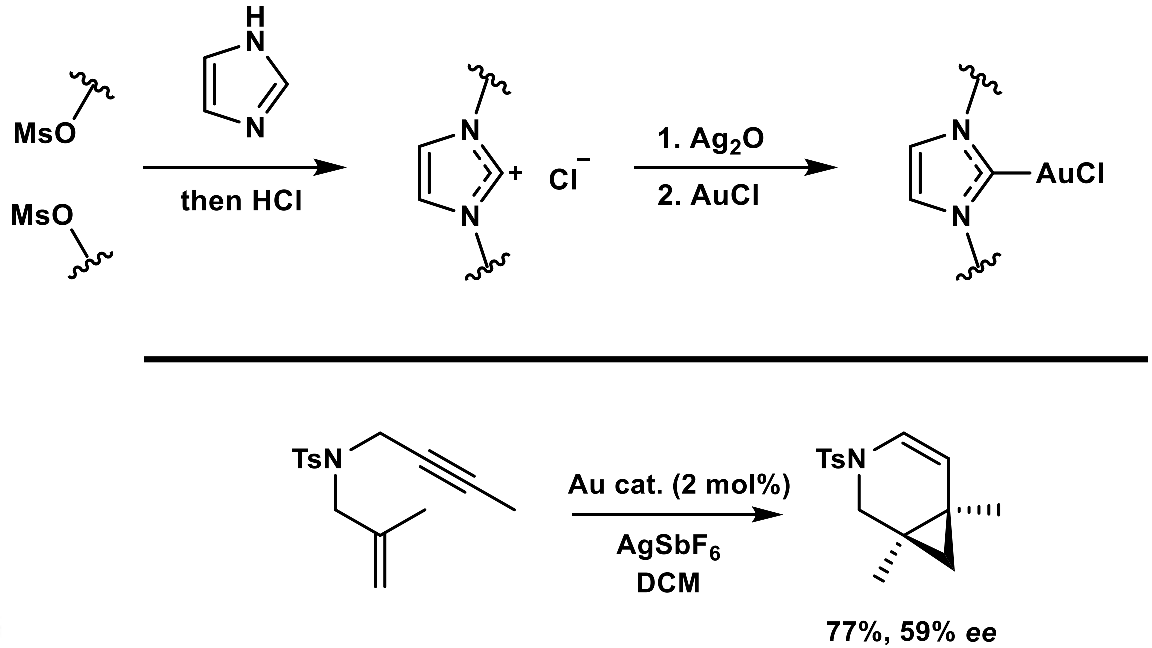
Catalyst	Yield	A : B
Protected Glc	90%	5 : 1
Protected Gal	77%	4 : 1
Deprotected Glc	> 95%	6 : 1
Deprotected Gal	> 95%	6 : 1
Ru complex	~ 60%	1 : 0

Inorg. Chem. **2017**, *56*, 12410–12420.

Sollogoub (2013): NHC-capped cyclodextrin Au complex







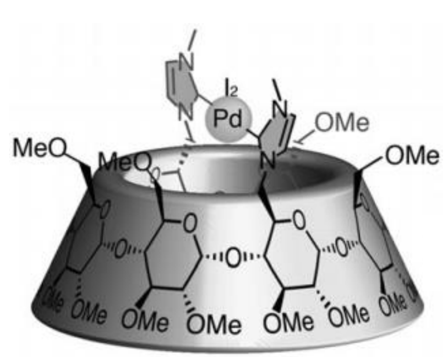
- 6-endo-dig product, structure selectivity is thought to be linked to cavity size.
- Promising stereoselectivity.
- More evidences needed.

Mechanism? Thank you.

Angew. Chem. Int. Ed. **2013**, *52*, 7213–7218; *Org. Biomol. Chem.* **2016**, *14*, 4008–4017.

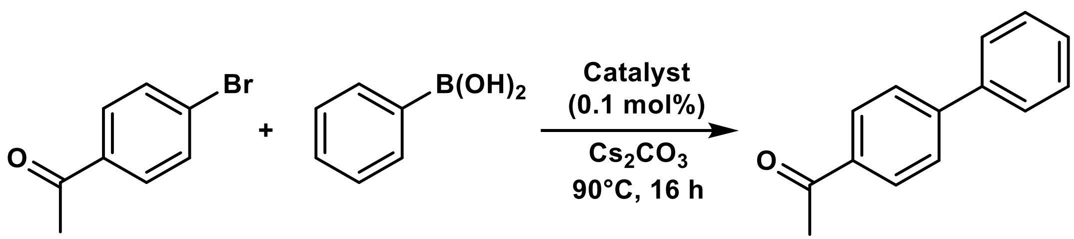
Sollogoub (2013): NHC-capped cyclodextrin Pd complex

A



B

C



Catalyst	Yield	Solvent
A	83%	EtOH
B	95%	H_2O
C	99%	EtOH

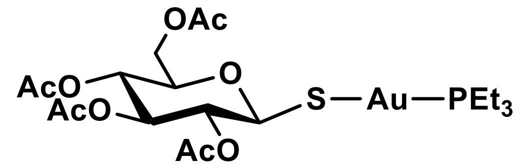
- Bis-NHC Pd complexes are needed for stablility (*cf.* Lin and Nishioka's works).

Eur. J. Org. Chem. **2013**, 3691–3699.

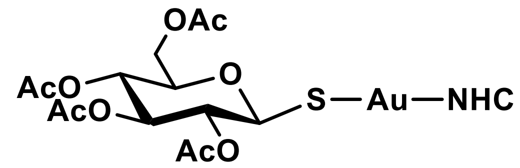
Auranofin and Au Drugs

Anti-cancer activity of Au drugs:

- Au binds to the selenocysteine residue at the active site of thioredoxin reductase (TrxR) protein.
- TrxR is needed in many processes that repair cells from oxidative damages.
- TrxR is overexpressed in cancer cells's mitochondria and some parasitic cells.
- Inhibiting TrxR leads to controlled cell death.



Auranofin



NHC analogues

Glucopyranosyl thiolate:

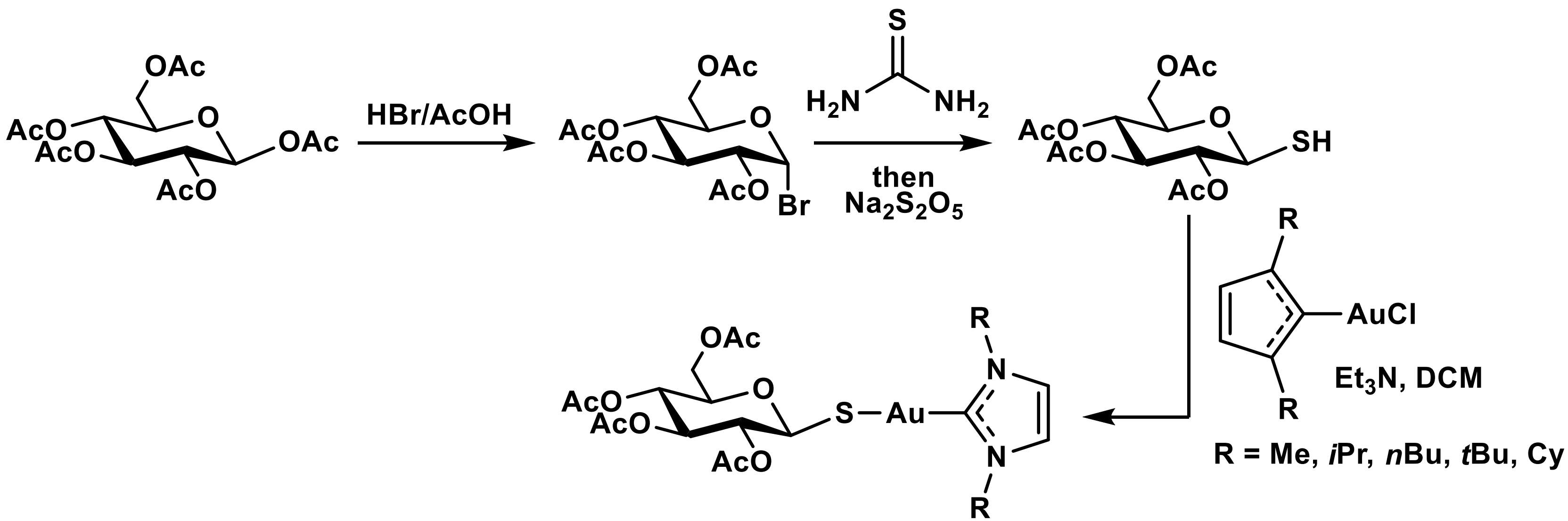
- Labile, displaced by biological thiols.
- Important for distributing Au drugs in blood stream.

NHC:

- Mimic binding of phosphine in Auranofin.
- Ease of synthesis.

Coord. Chem. Rev. **2009**, *253*, 1670–1681.
Coord. Chem. Rev. **2017**, *339*, 1–16.

Baker (2005):

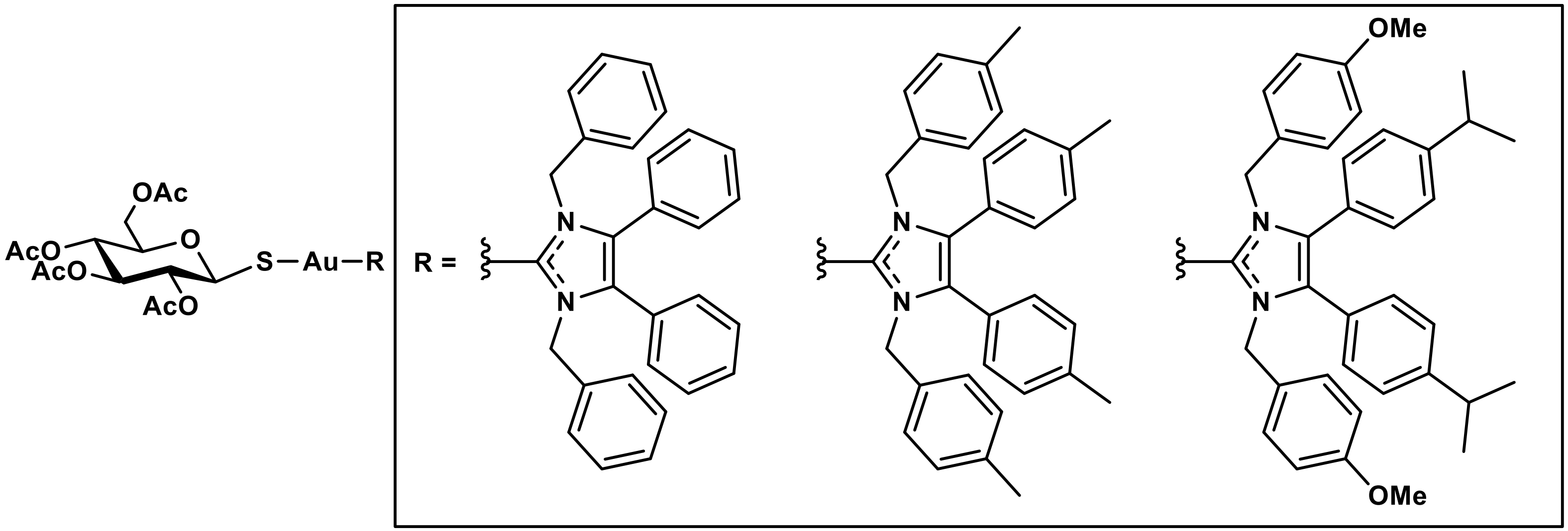


- Demonstrates the ease of synthesizing such complexes.
- Preliminary assay: no mitochondria swelling behaviour (i.e. no anti-mitochondrial activity). No assay on actual cancer cells provided.

J. Organometallic. Chem. **2005**, *690*, 5625–5635.

NHC-Analogues of Auranofin

Tacke (2013):

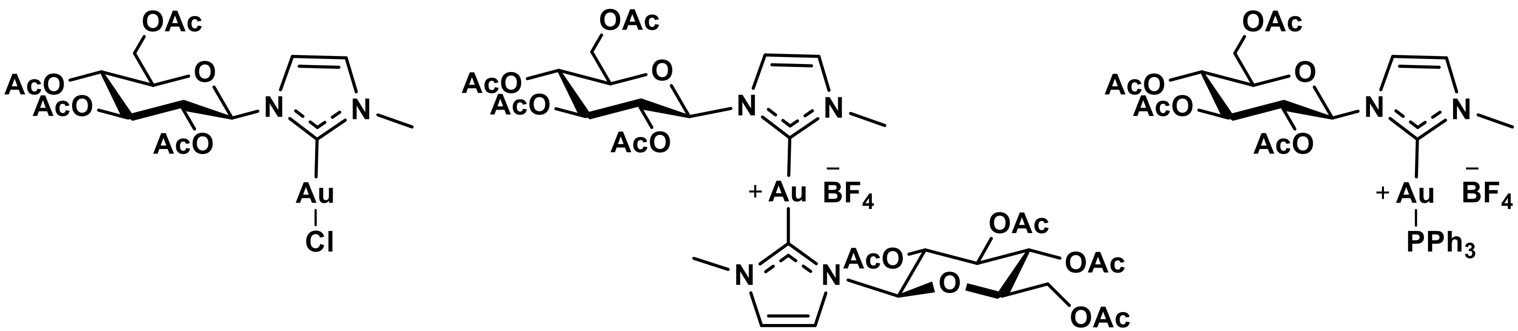


- Above 3 analogues show good IC_{50} value against cancer cell lines: renal (Caki-1) and breast (MCF-7), better than cisplatin.

Question: Suggest a reasonable explanation for the enhancement of anti-cancer activity of these highly substituted NHC complexes. Hint: intracellular environment is aqueous but the matrix of a mitochondrion is not.
What is the point of having a carbohydrate ligand?

Organometallics **2013**, *32*, 5551–5560.
Review: *Coord. Chem. Rev.* **2017**, *339*, 1–16.

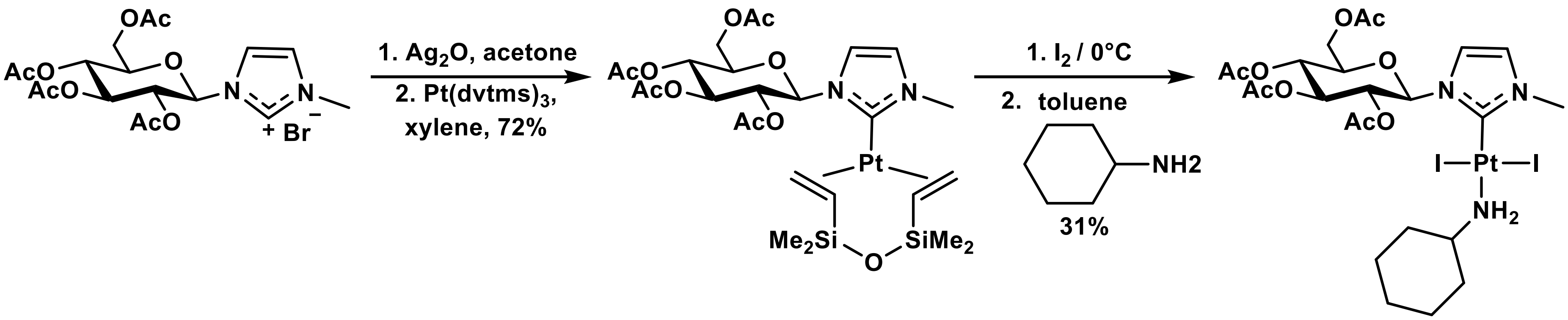
D'Amora (2017):



- Low mitochondrial uptake of many Au complexes is attributed to being chargeless.
- Against prostate cancer cells: neutral Au-Cl complex shows weak activity, [bis-Au]BF_4 less effective (too bulky), [$AuPPh_3$]BF_4 is comparable to cisplatin.

Eur. J. Inorg. Chem. **2017**, 4955–4961.

Skander (2010): Analogue of "transplatin"



- Demonstrate the synthesis of carbohydrate-NHC Pt complexes, amongst other "transplatin" NHC analogues.
- Assay for other complexes in the series revealed cytotoxic activity against cisplatin-sensitive and cisplatin-resistant cell lines. However, **NO** studies on the carbohydrate complex were reported.

J. Med. Chem. **2010**, *53*, 2146–2154.

Conclusion

Catalysis:

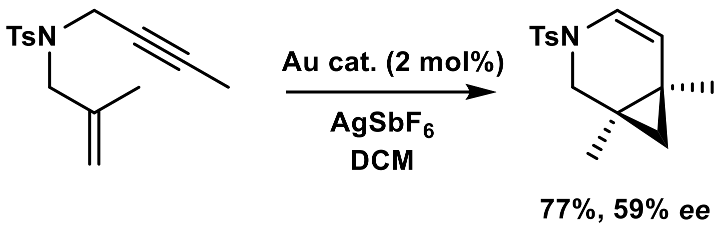
- Potentially provide cheap and simple methods for achieving water solubility and asymmetric synthesis.
- Both aspects are underdeveloped.
- Chirality transfer from the ligand to product is relatively poor.
- Future works: more complex carbohydrates, or better ligand design to direct the chiral moieties toward metal center.

Medicinal chemistry:

- Studies so far showed mixed results.
- Ease of modification on both carbohydrate and NHC parts open up vast possibility for tuning hydrophilicity and lipophilicity. No clear way of incorporating carbohydrate in metal complexes can be concluded just yet.

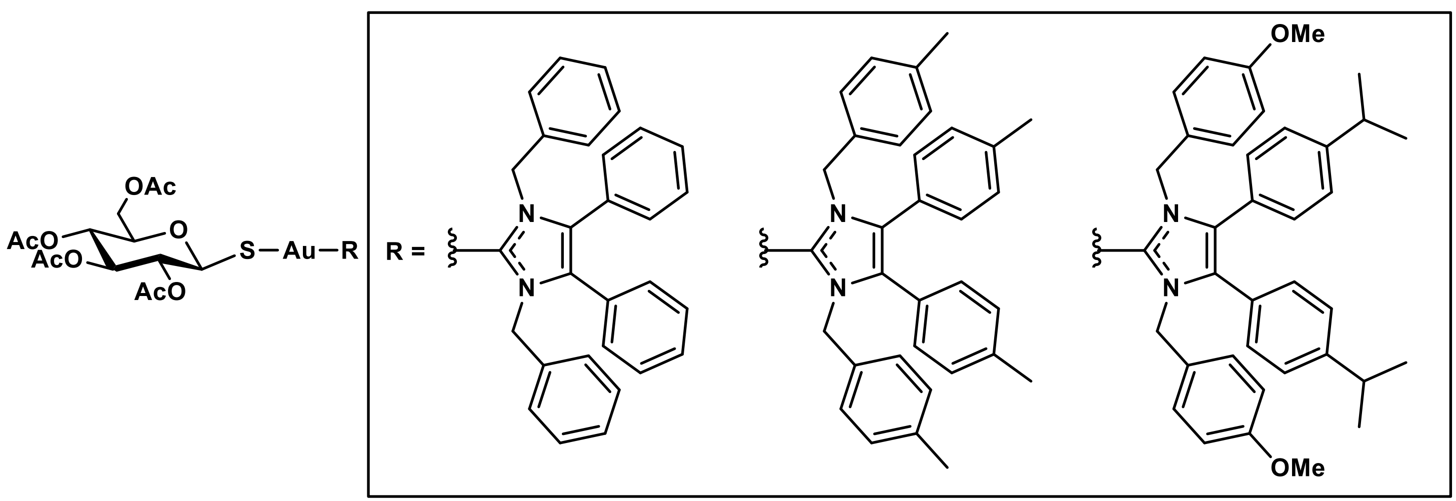
Thank you for you attention.

Questions

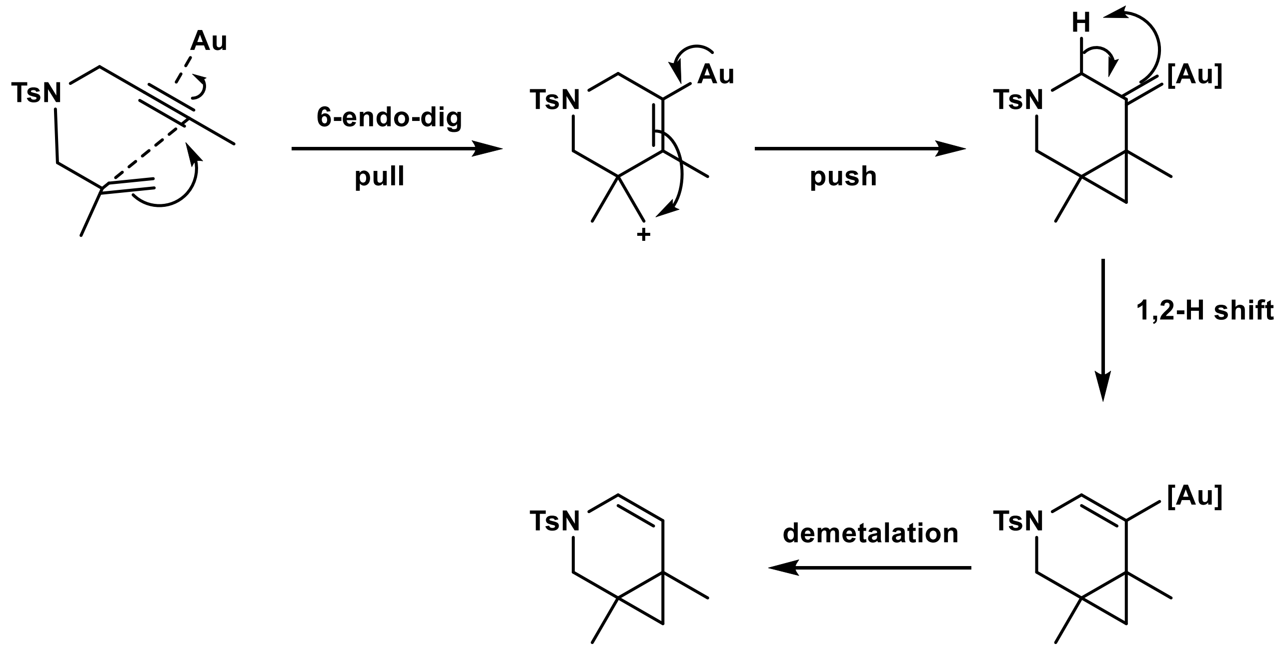


Mechanism?

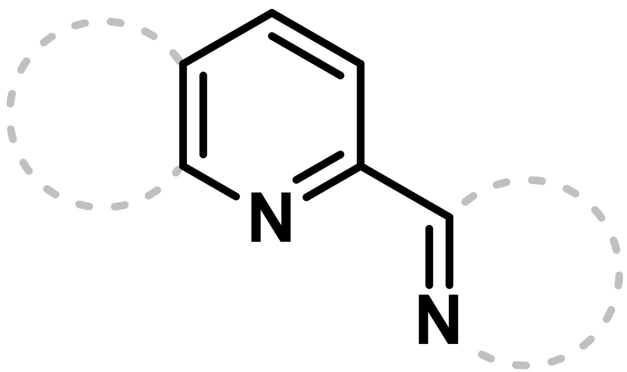
Question: Suggest a reasonable explanation for the enhancement of anti-cancer activity of these highly substituted NHC complexes. Hint: intracellular environment is aqueous but the matrix of a mitochondrion is not.
What is the point of having a carbohydrate ligand?



Answer


TsN
Au
6-endo-dig
pull
TsN
Au
+
push
H
TsN
[Au]
1,2-H shift
TsN
[Au]
demetalation
TsN

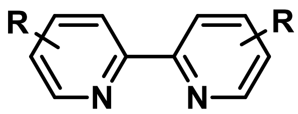
Mono-imino Pyridine and Derivatives as Ligands for Catalysis



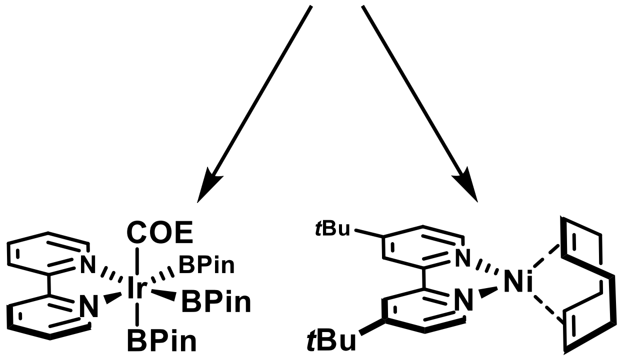
Frontier in Chemical Synthesis II: Heterocycle Chemistry

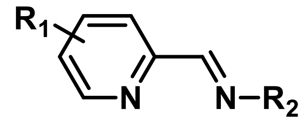
Benoît Audic - 18/05/2018

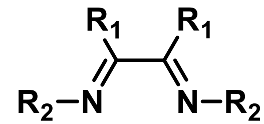
Related ligands



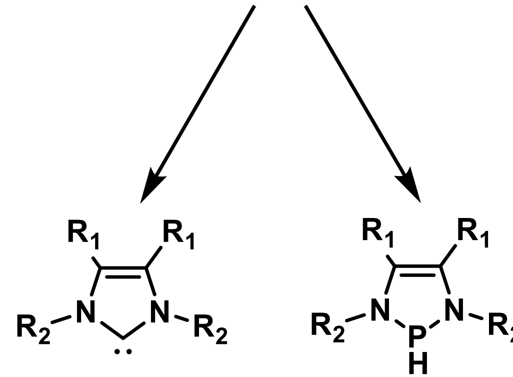
Ligand in C-H Activation and Photochemistry



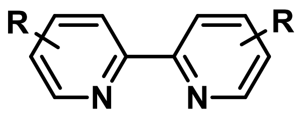




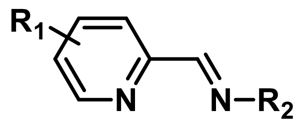
Precursors of NHC and 1,3,2-Diazaphospholenes
Chirik

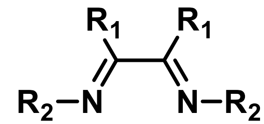


Related ligands

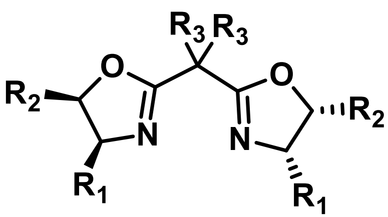


Ligand in C-H Activation and Photochemistry

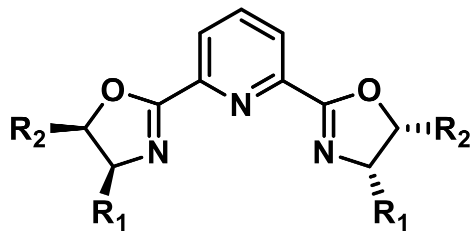




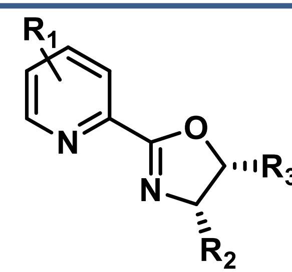
Precursors of NHC and 1,3,2-Diazaphospholenes
Chirik



Box ligands



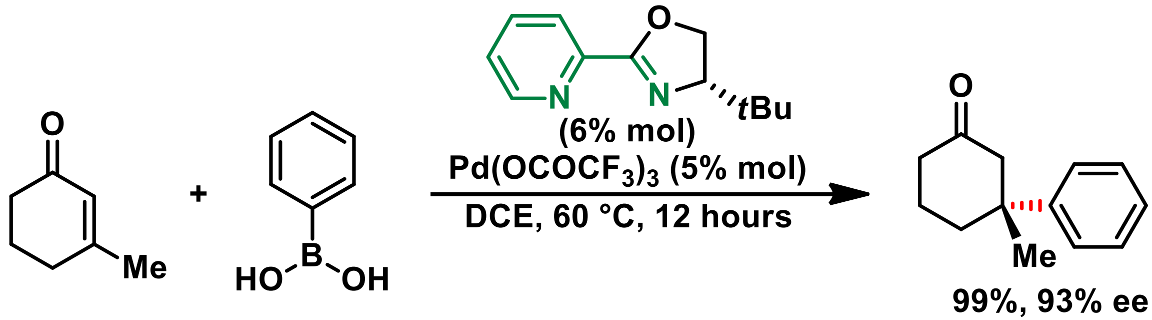
PyBox ligands



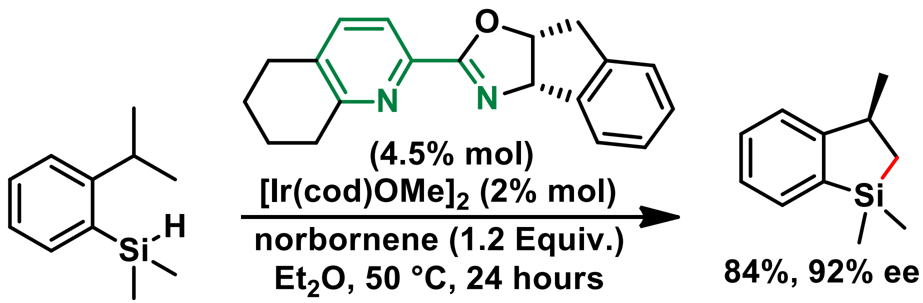
Stoltz, Hartwig, Sigman..

Related ligands

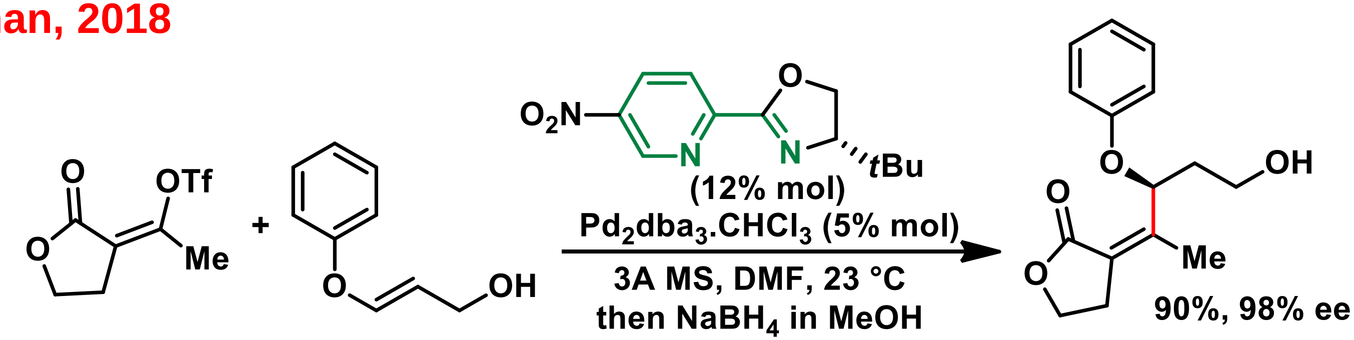
- **Stoltz, 2011**



- **Hartwig, 2017**

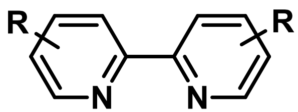


- **Sigman, 2018**

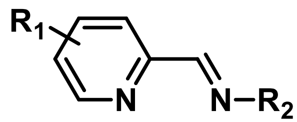


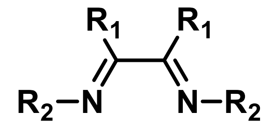
B. M. Stoltz, *J. Am. Chem. Soc.* **2011**, *133*, 6902
J. F. Hartwig, *J. Am. Chem. Soc.* **2017**, *139*, 12137
M. S. Sigman, *J. Am. Chem. Soc.* **2018**, DOI: 10.1021/jacs.8b02751

Related ligands

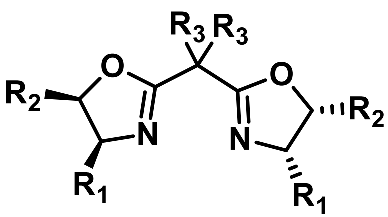


Ligand in C-H Activation and Photochemistry

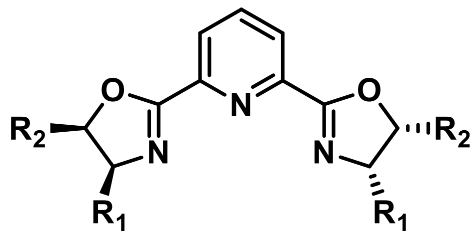




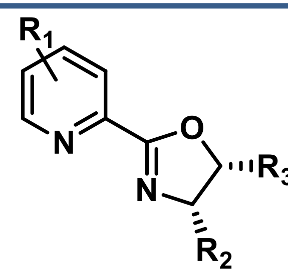
Precursors of NHC and 1,3,2-Diazaphospholenes
Chirik



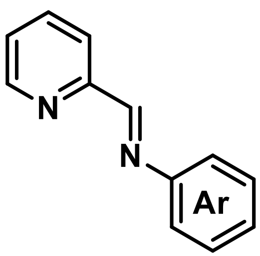
Box ligands



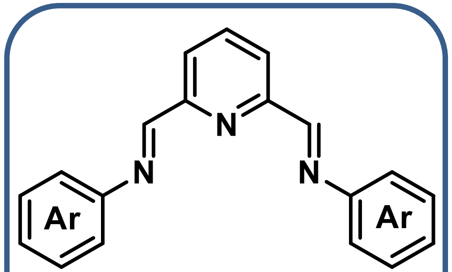
PyBox ligands



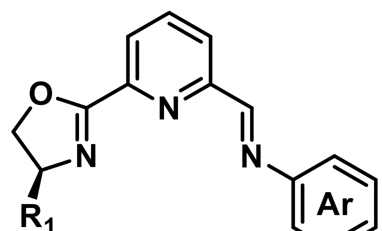
Stoltz, Hartwig, Sigman..



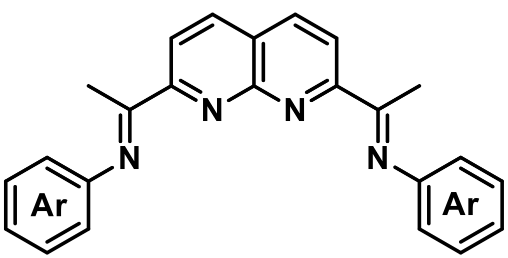
Ritter



Chirik

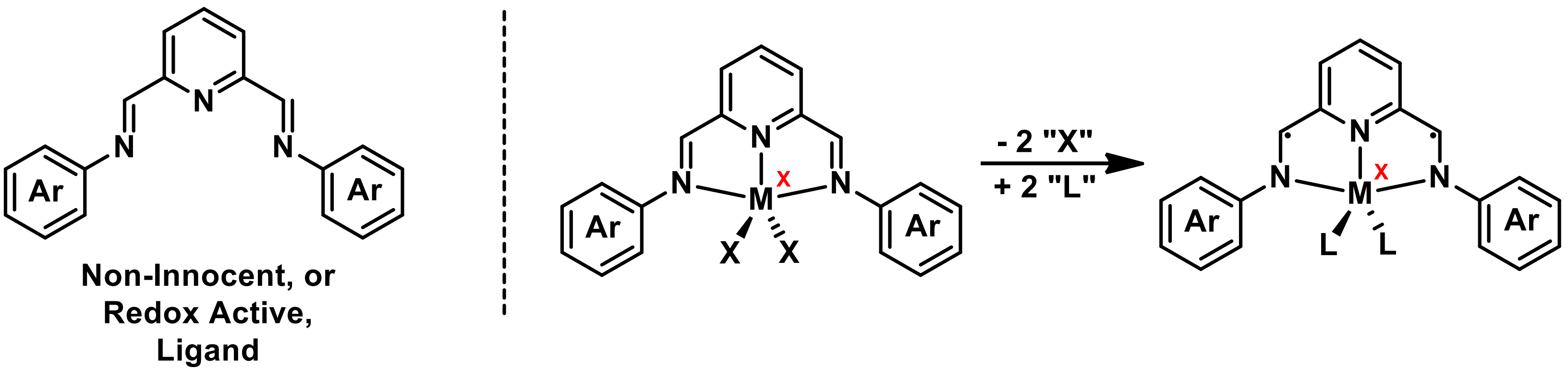


Huang, Lu

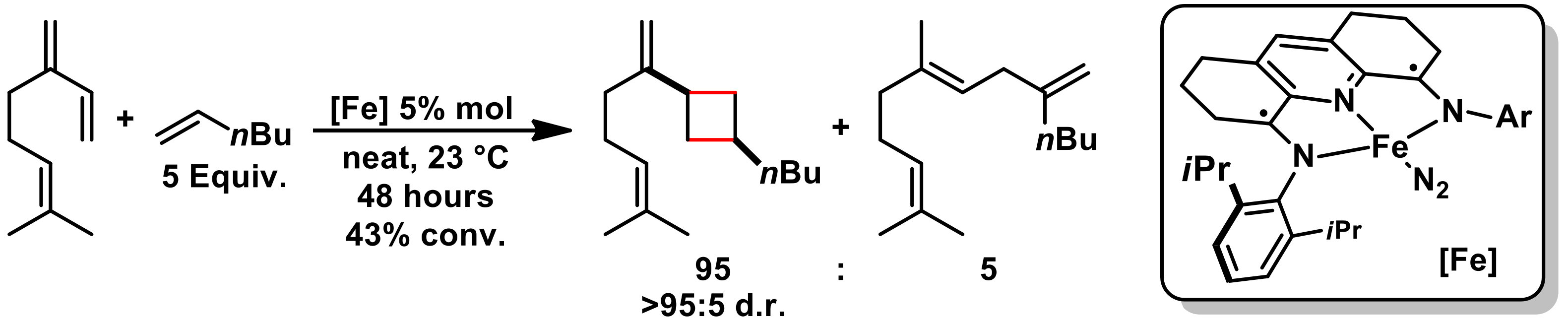


Uyeda

Related ligands

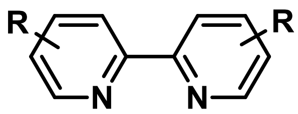


- **Chirik, 2015**

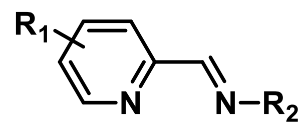


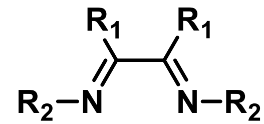
P. J. Chirik, *Science* **2015**, *349*, 960

Related ligands



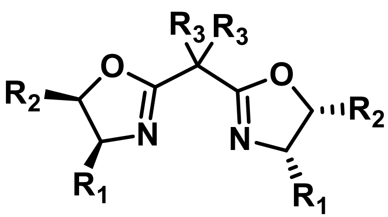
Ligand in C-H Activation and Photochemistry



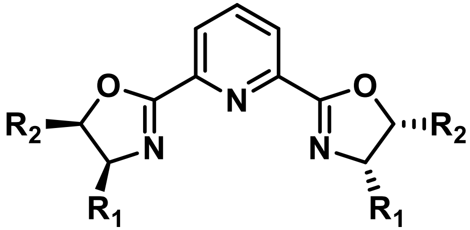


Precursors of NHC and 1,3,2-Diazaphospholenes

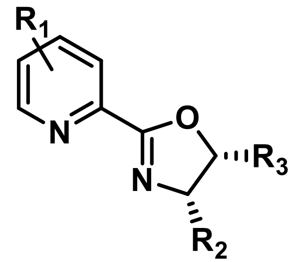
Chirik



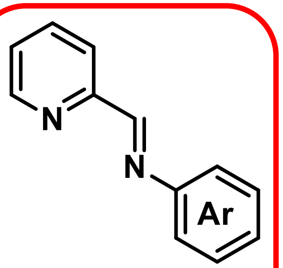
Box ligands



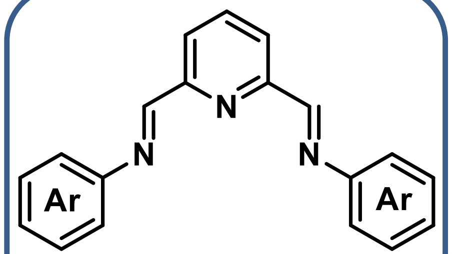
PyBox ligands



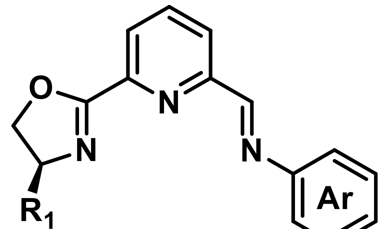
Stoltz, Hartwig, Sigman..



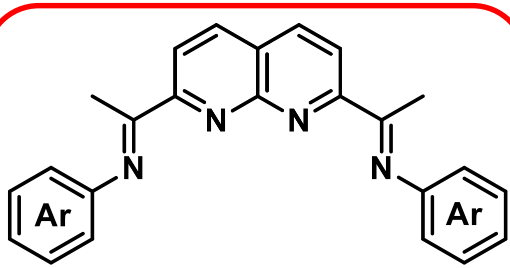
Ritter



Chirik



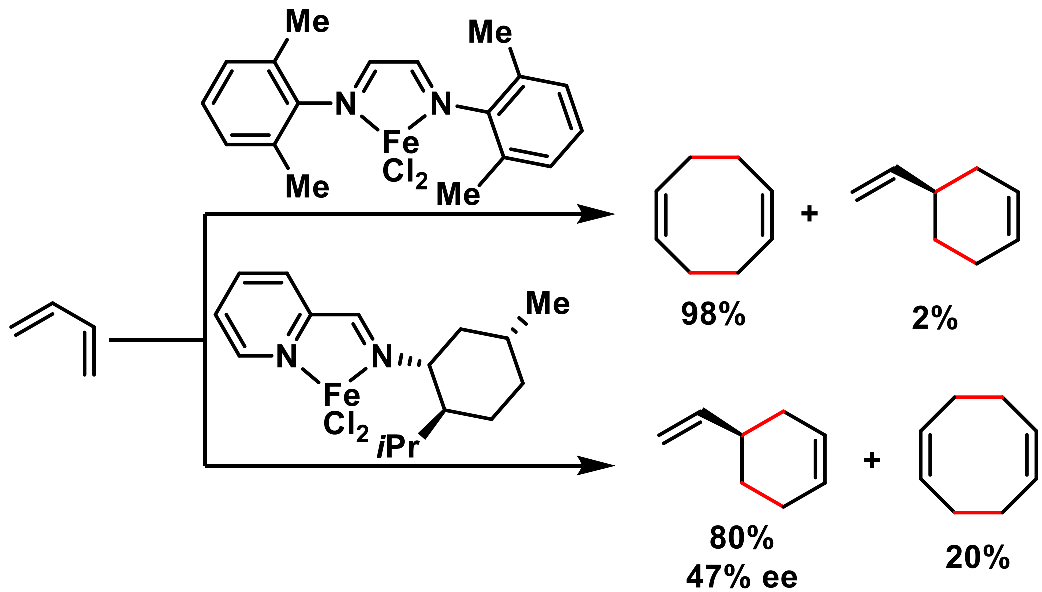
Huang, Lu



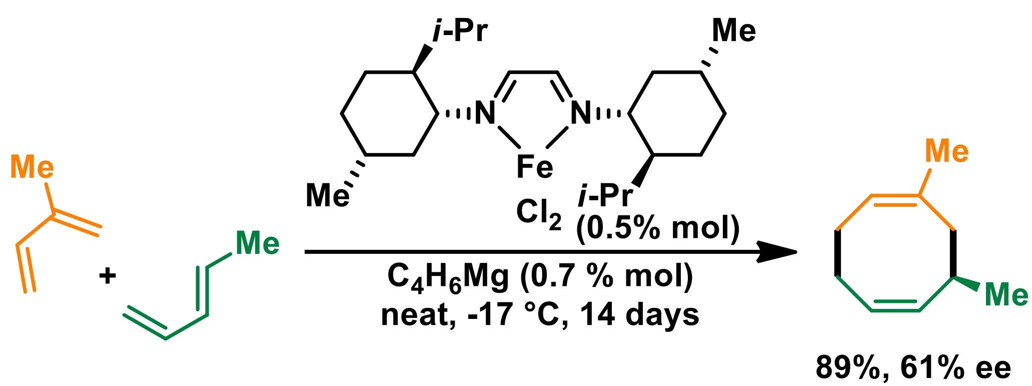
Uyeda

Pioneering work/Early examples

- **Dieck, 1985**



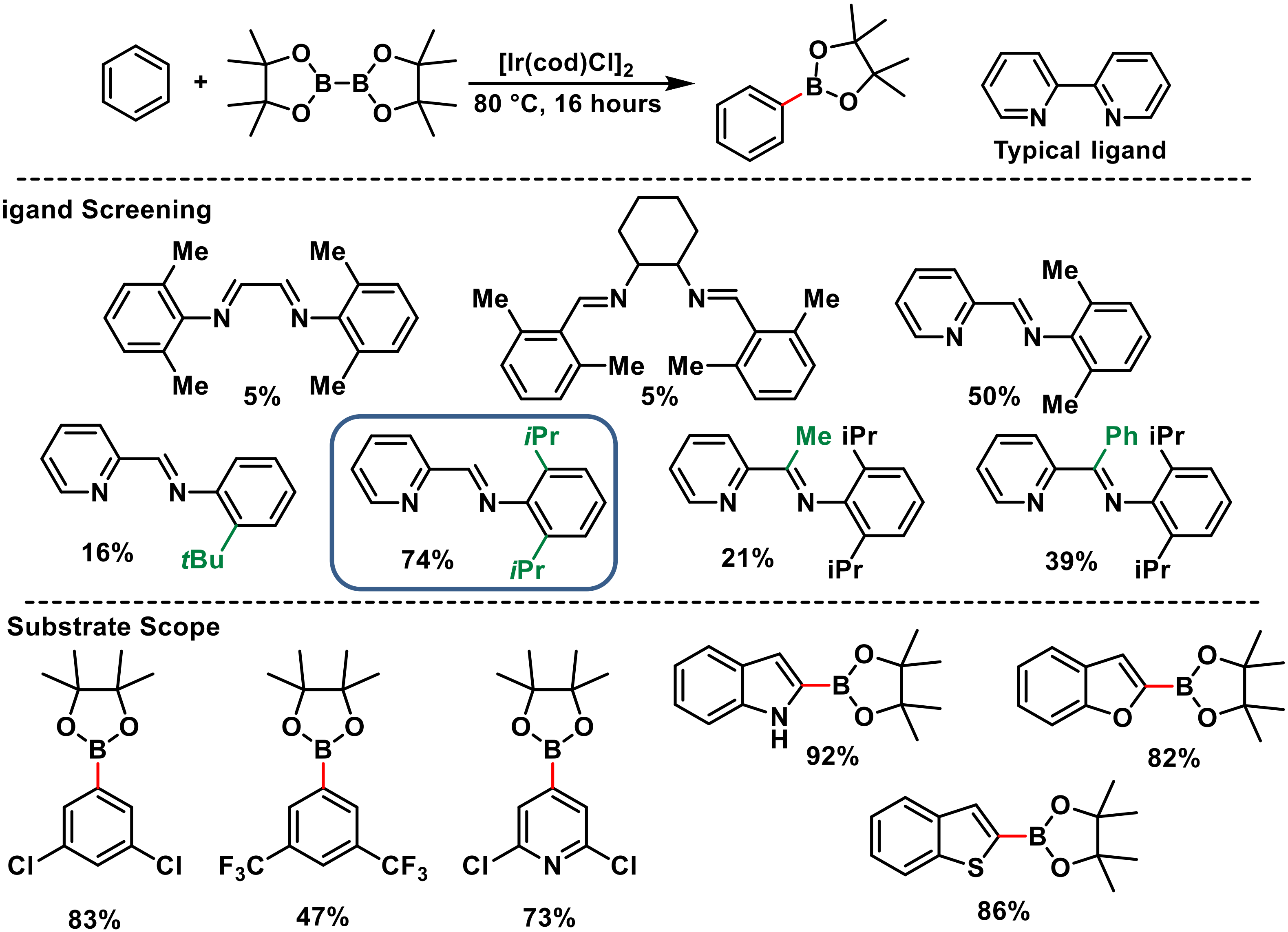
- **Dieck, 1992**



H. tom Dieck, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 781

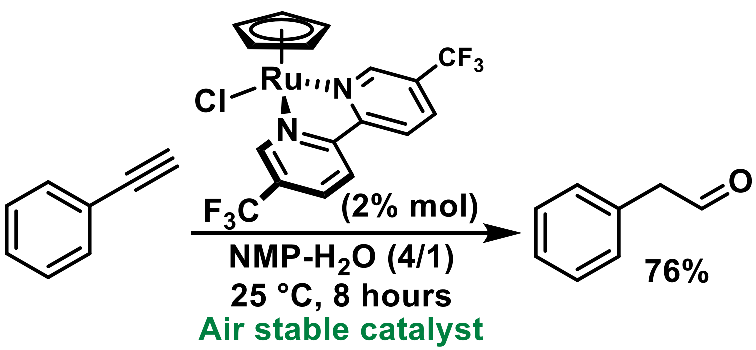
H. tom Dieck, *Angew. Chem. Int. Ed.* **1992**, *31*, 305

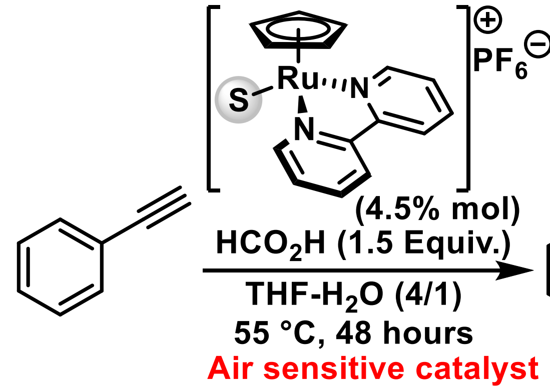
Iridium C-H activation

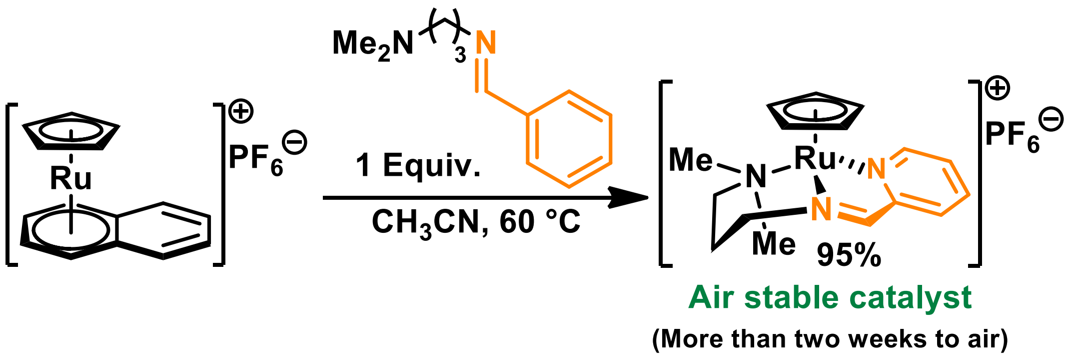


M. Nishida, *Adv. Synth. Catal.* **2004**, *346*, 1655

CpRu Catalysis with Iminopyridine





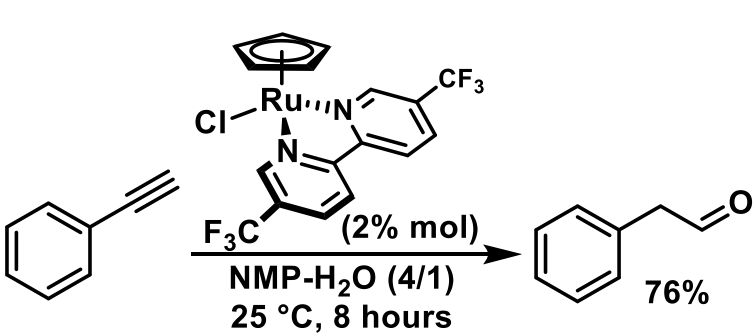


S. Herzon, *Angew. Chem. Int. Ed.* **2014**, *53*, 7892

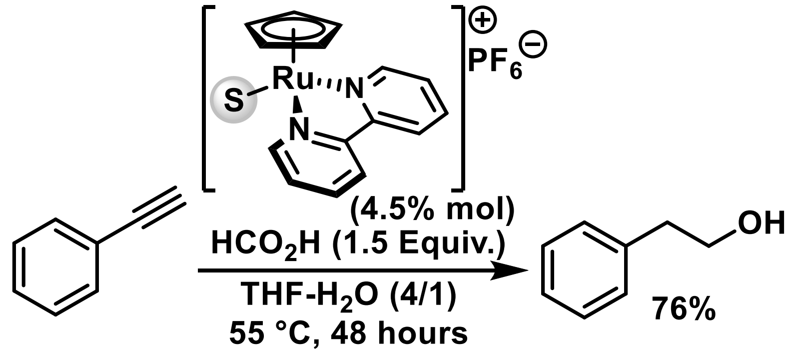
S. Herzon, Nature Chemistry **2014**, *6*, 22

S. Herzon, J. Am. Chem. Soc. **2014**, *136*, 7058

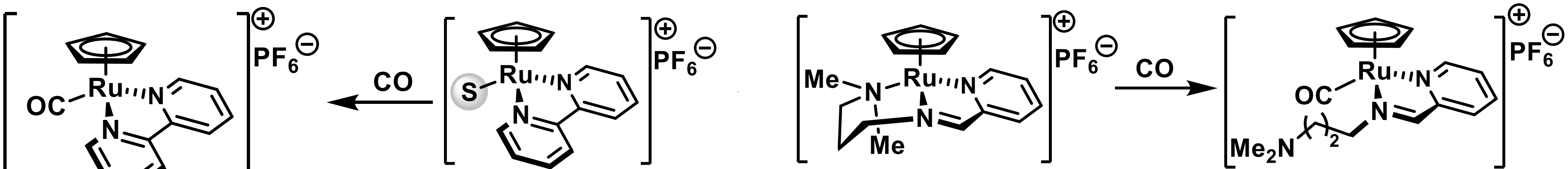
CpRu Catalysis with Iminopyridine



Air stable catalyst



Air sensitive catalyst



Complex A

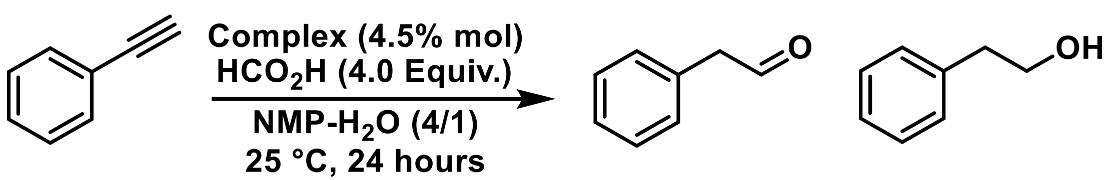
ν_{CO} (cm^{-1}) : 1962

Catalyst A

Catalyst B

Complex B

ν_{CO} (cm^{-1}) : 1972

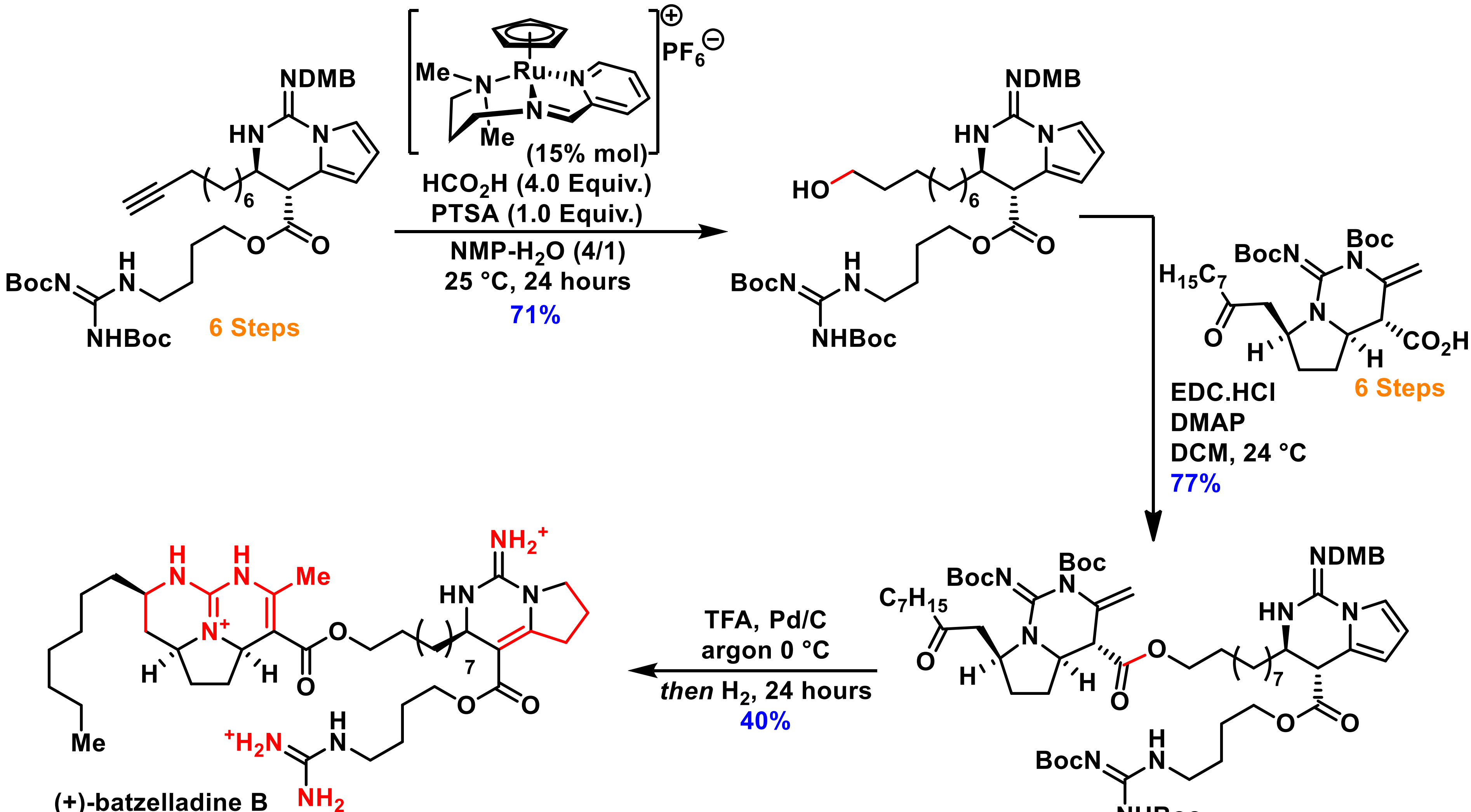


Catalyst A	>99%	<1%
Catalyst B	<1%	98%

S. Herzon, *Angew. Chem. Int. Ed.* **2014**, *53*, 7892
S. Herzon, Nature Chemistry **2014**, *6*, 22
S. Herzon, J. Am. Chem. Soc. **2014**, *136*, 7058

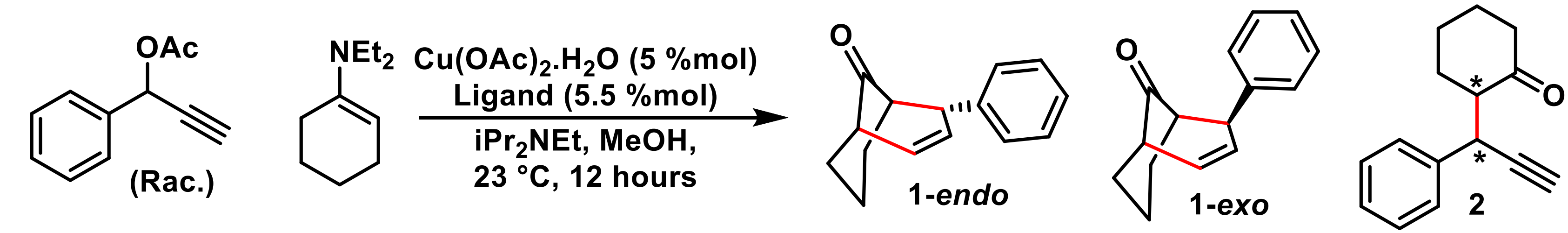
CpRu Catalysis with Iminopyridine

- Application in the synthesis of (+)-Batzelladine B

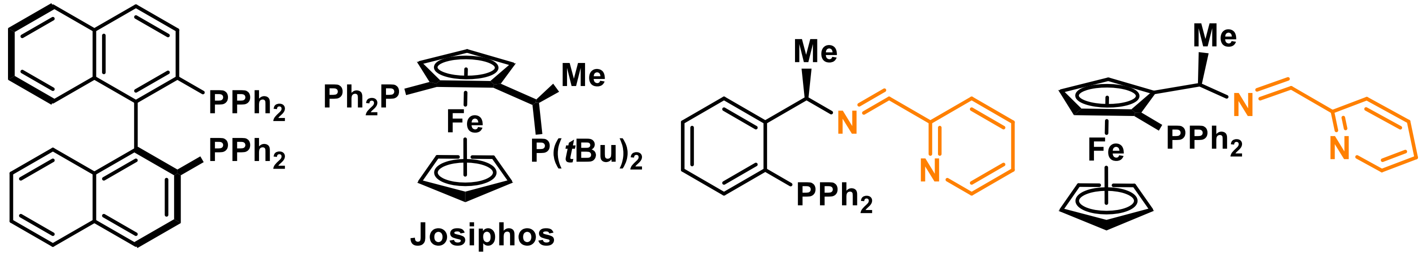


S. Herzon, *Nature*, ***2015***, *525*, 507

Enantioselective Cu-Catalyzed [3+3]

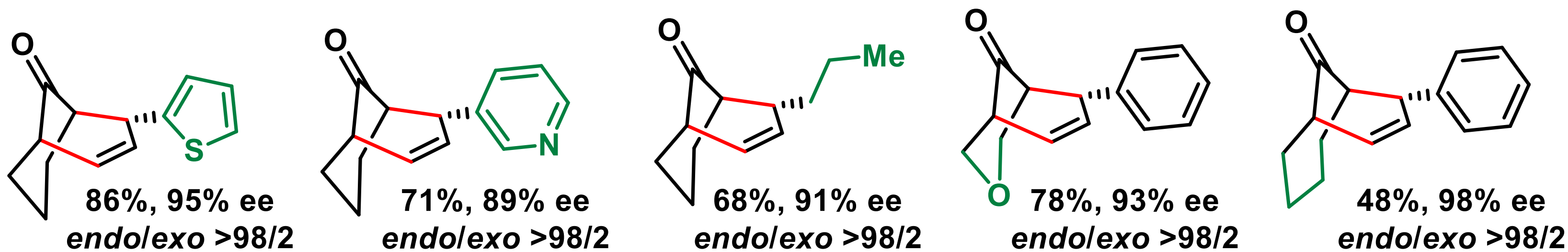


Ligand Screening



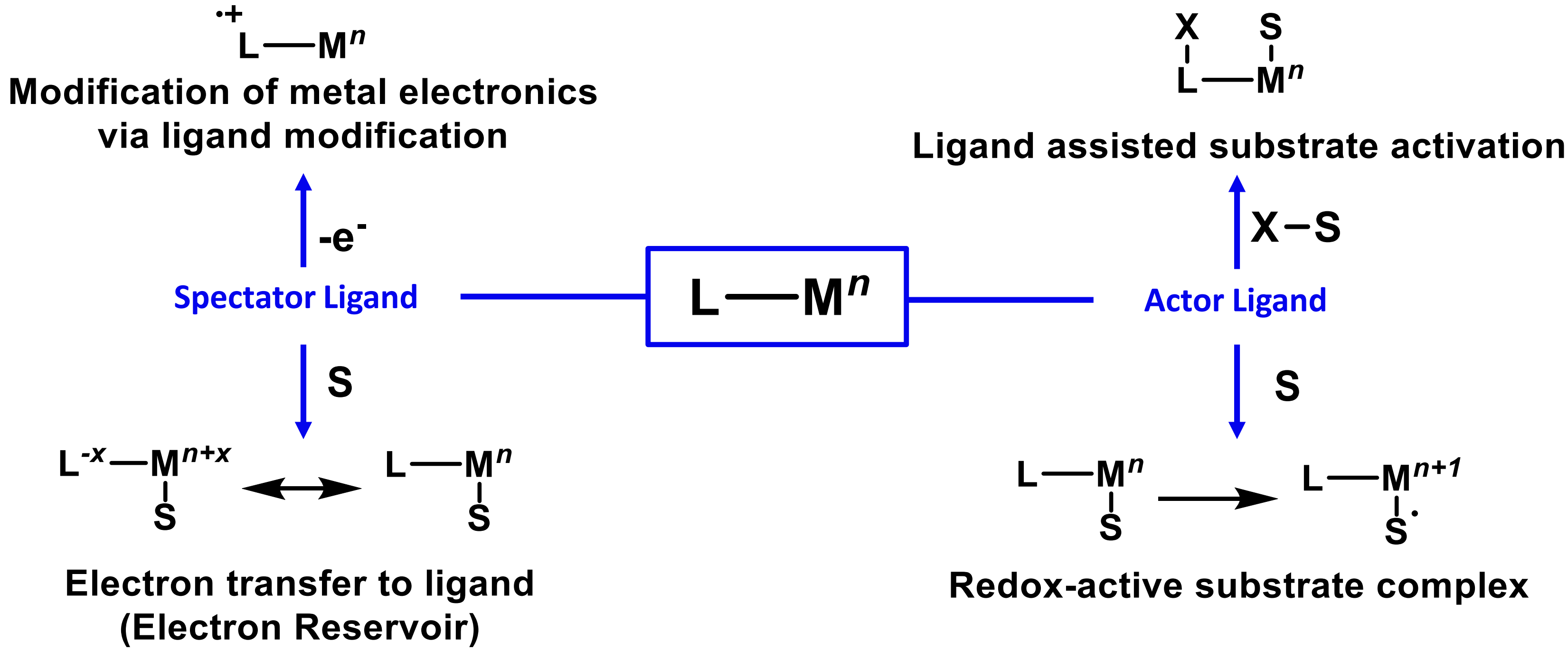
Yield of 1	58	62	82	86
Ratio : 1-*endo* / 1-*exo* / 2	61 / 12 / 27	78 / 6 / 16	97 / 3 / 0	>98 / <2 / 0
1-*endo* (ee%)	60	42	90	95

Selected examples



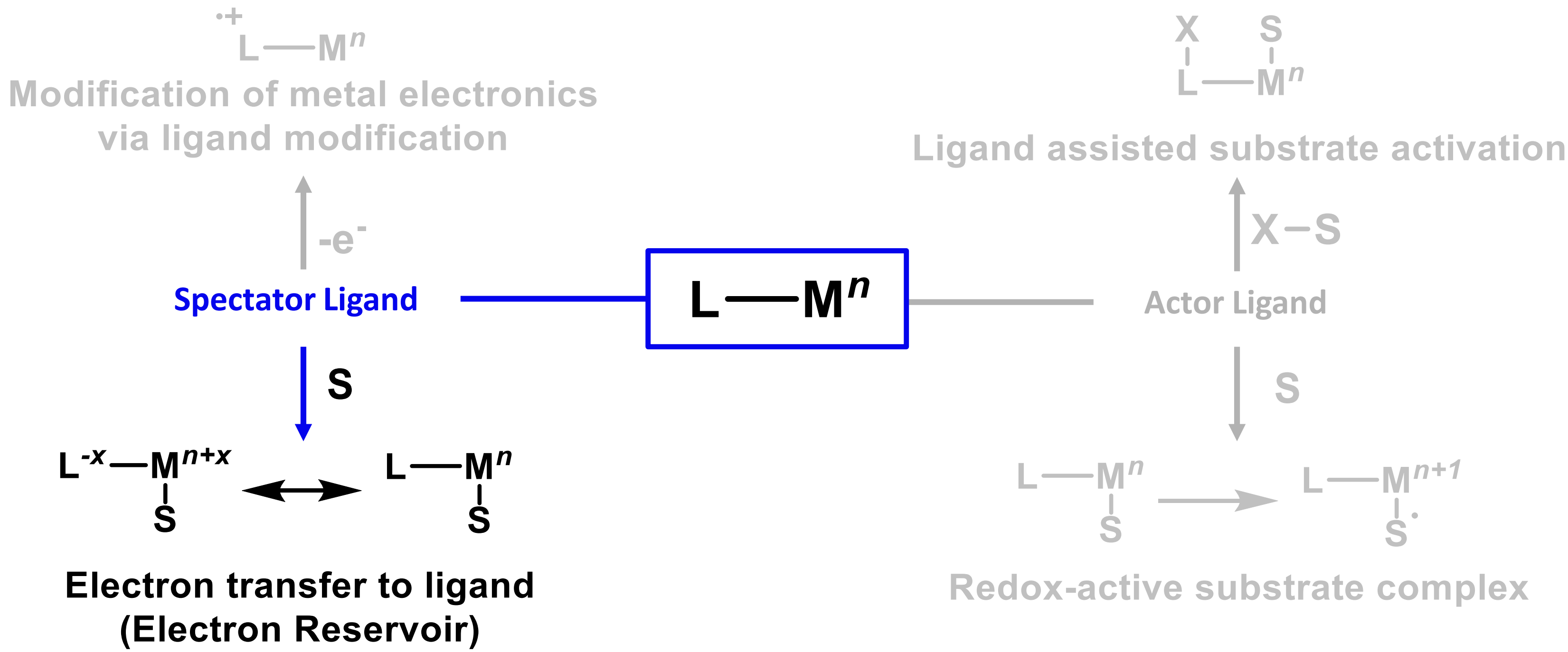
X.-P. Hu, *J. Am. Chem. Soc.*, **2012**, *134*, 9585

Redox-Active Ligand



For a perspective : B. de Bruin, *ACS Catal.* **2012**, *2*, 270

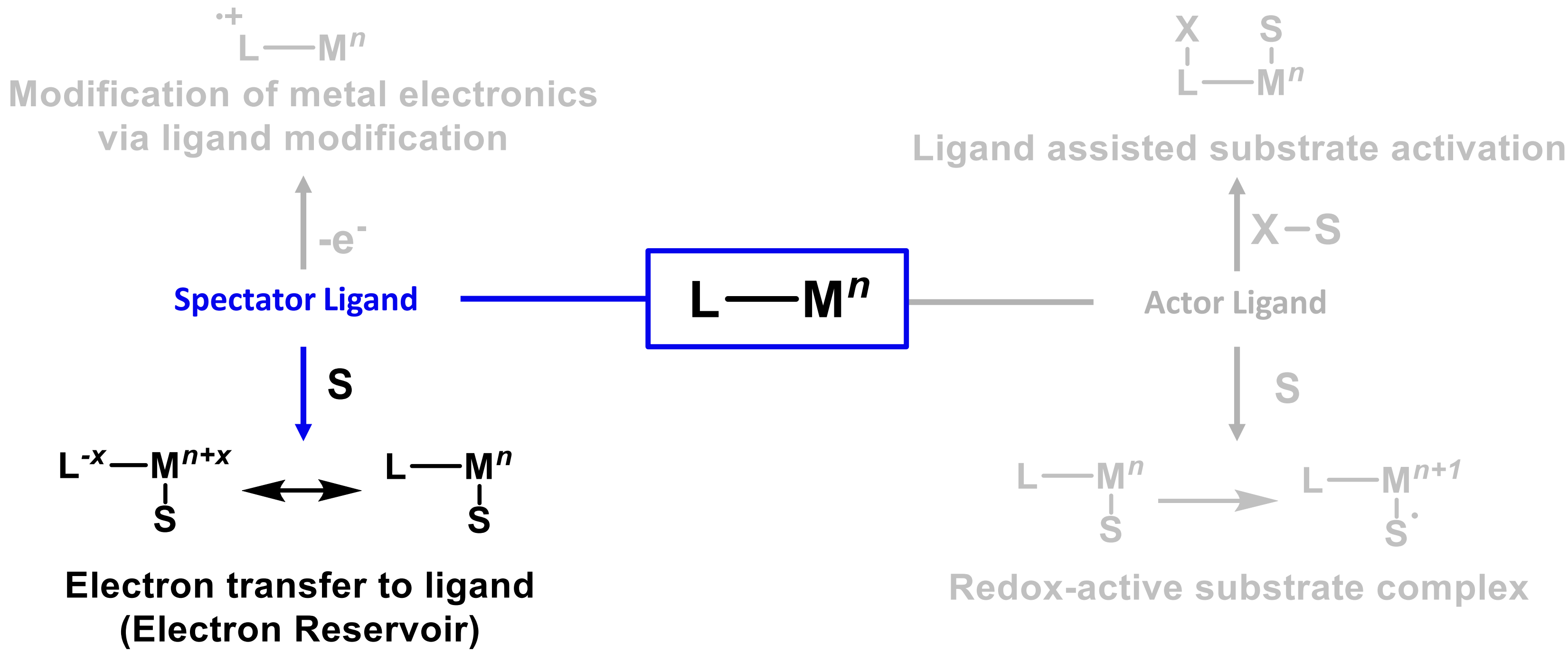
Redox-Active Ligand

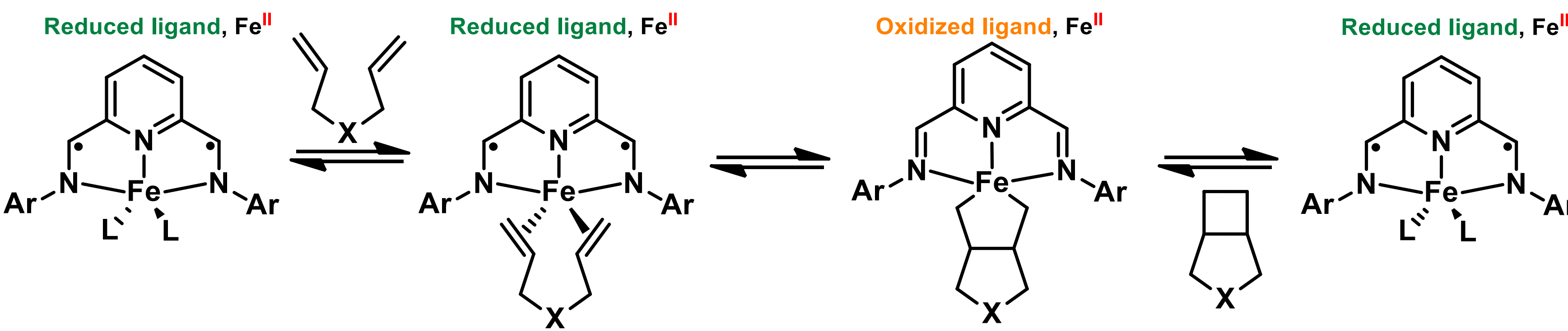


- Store electrons from the metal on the ligand
- 1st row-transition metals often prefer one-electron redox events
- Avoid uncommon oxidation states, brings nobility to the metals
- Can confer nobility by combination

For a perspective : B. de Bruin, *ACS Catal.* **2012**, *2*, 270

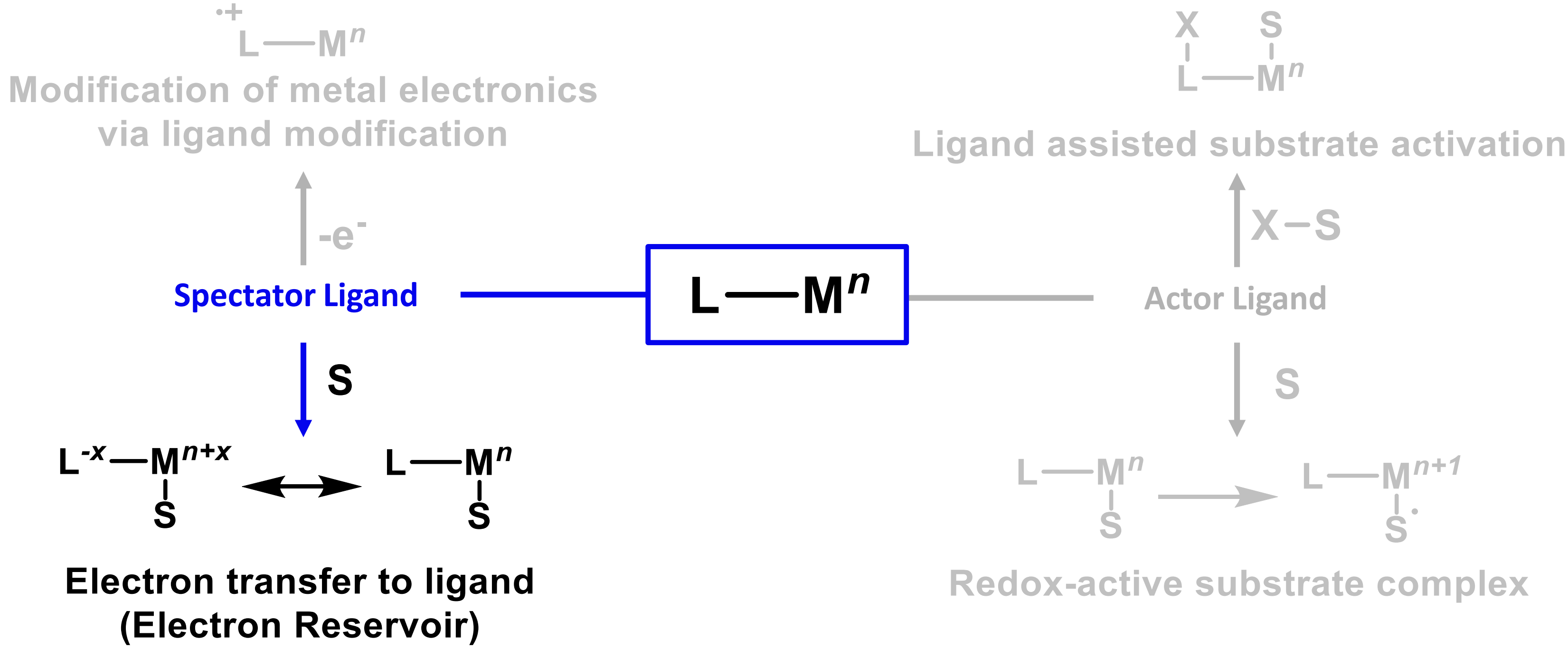
Redox-Active Ligand

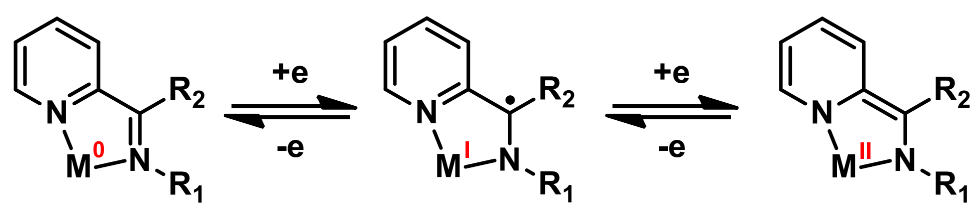




P. Chirik, *J. Am. Chem. Soc.*, **2006**, *128*, 13340

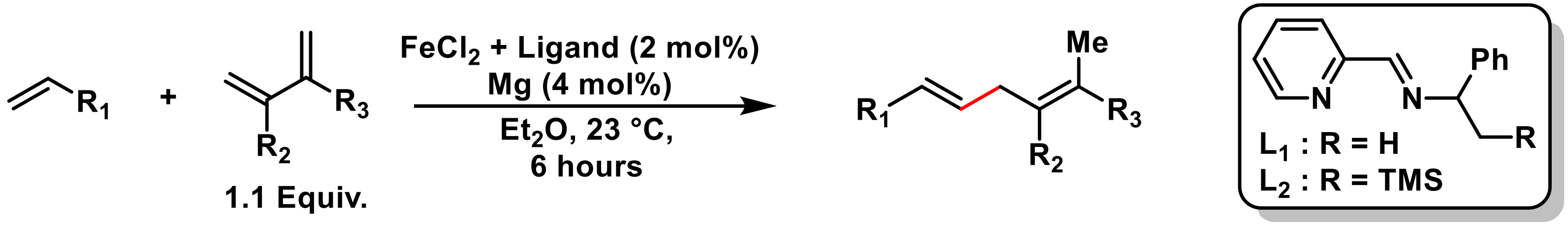
Redox-Active Ligand

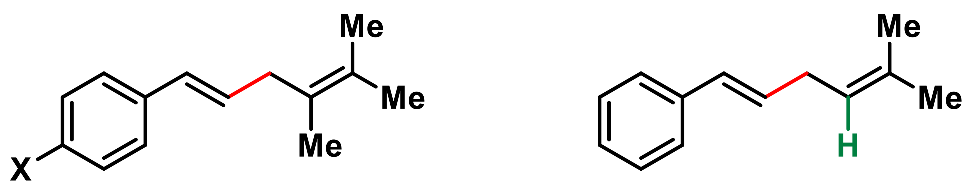




K. Wieghlard, *J. Am. Chem. Soc.*, **2008**, *130*, 3181

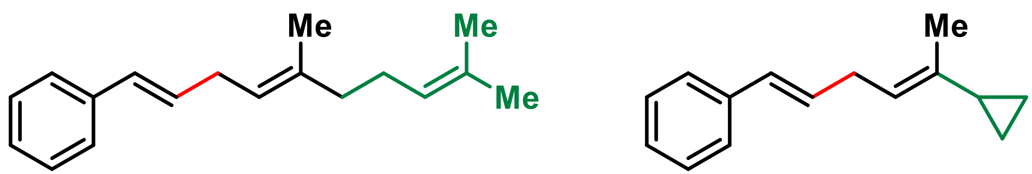
1,4 Addition of α-olefins to Dienes





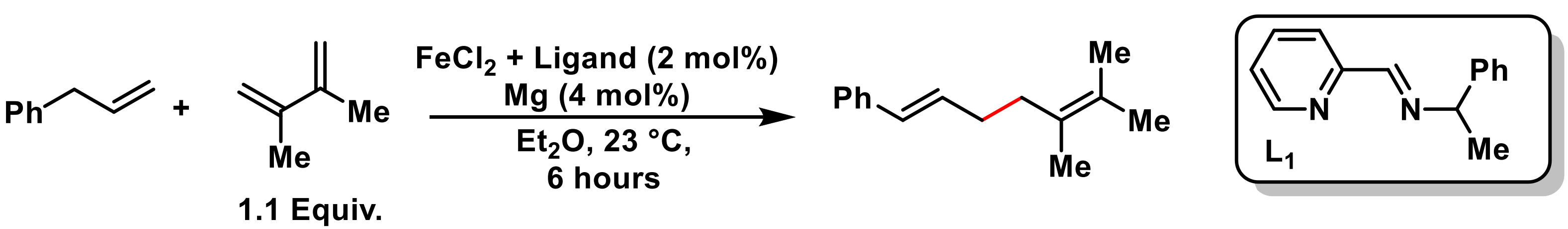
X : H = 94% ; Cl = 78%
F = 86% ; OAc = 85%

60%, Regio : 90/10



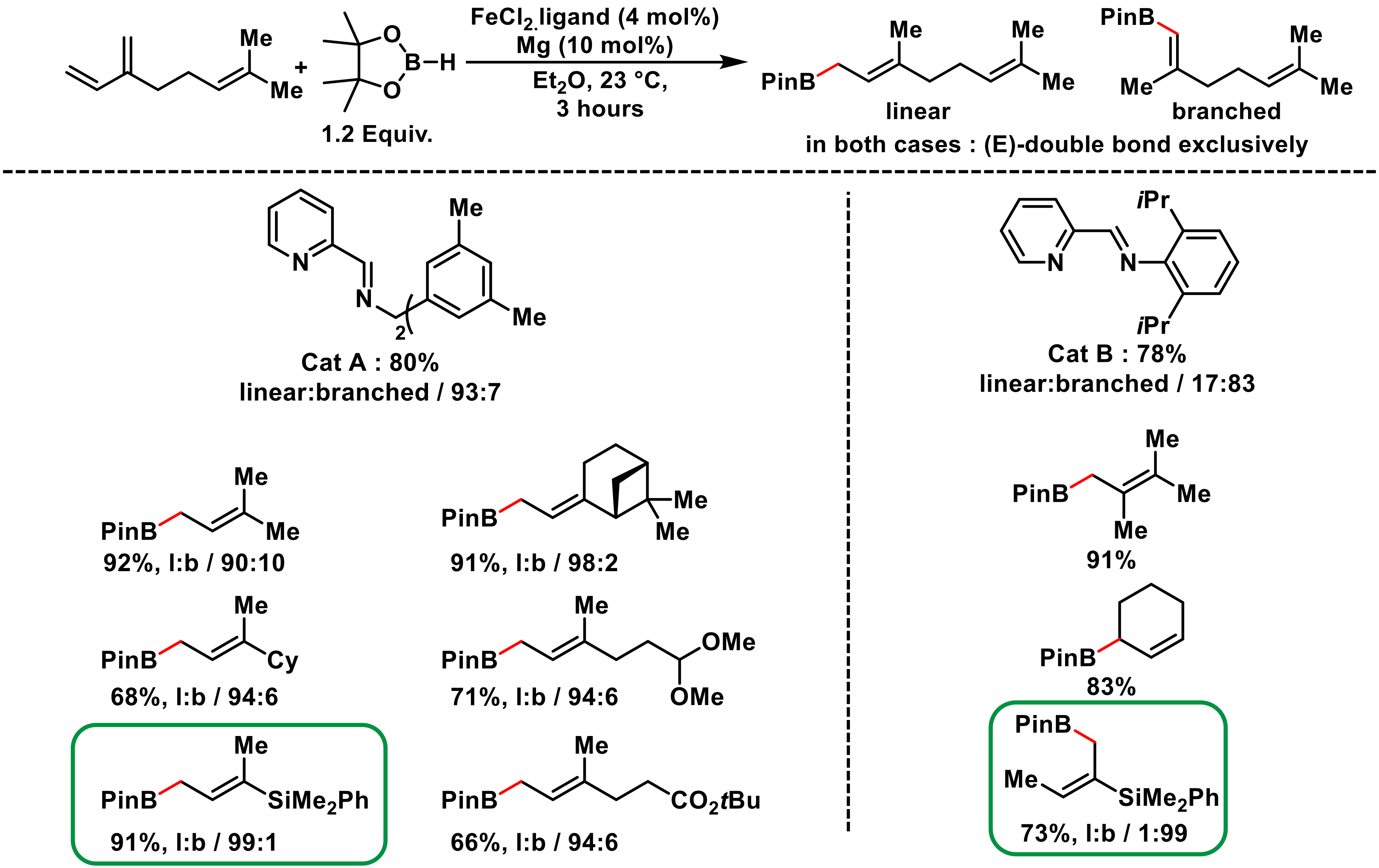
66%, Regio : 93/7

77%, Regio : >98/2



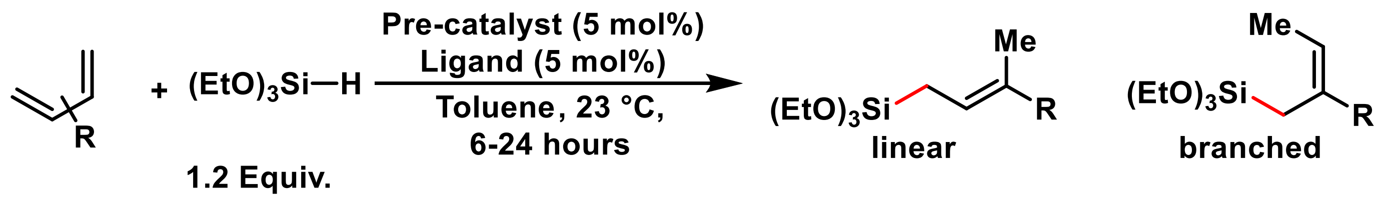
T. Ritter, *Org. Lett.* **2009**, *11*, 337

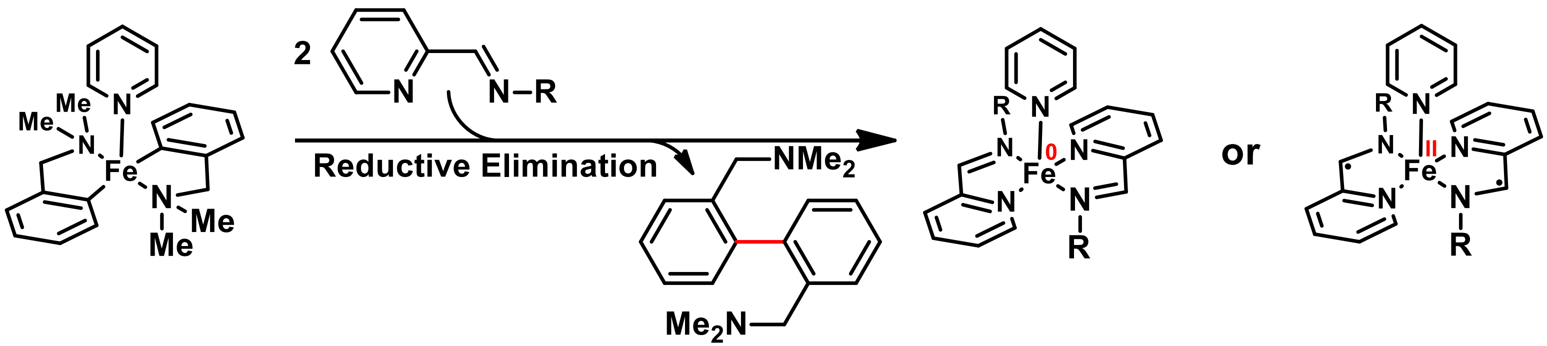
1,4-Hydroboration of 1,3-Dienes

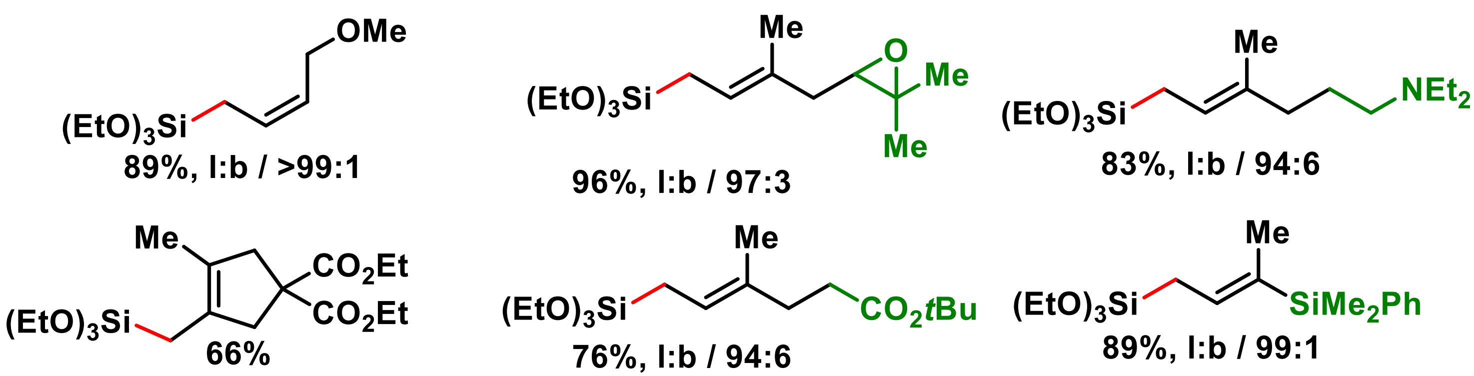


T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 12915

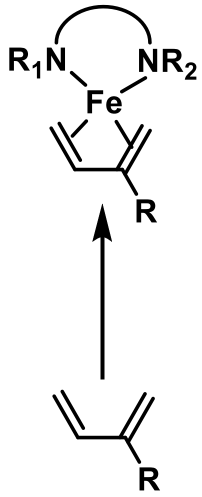
1,4-Hydrosilylation of 1,3-Dienes



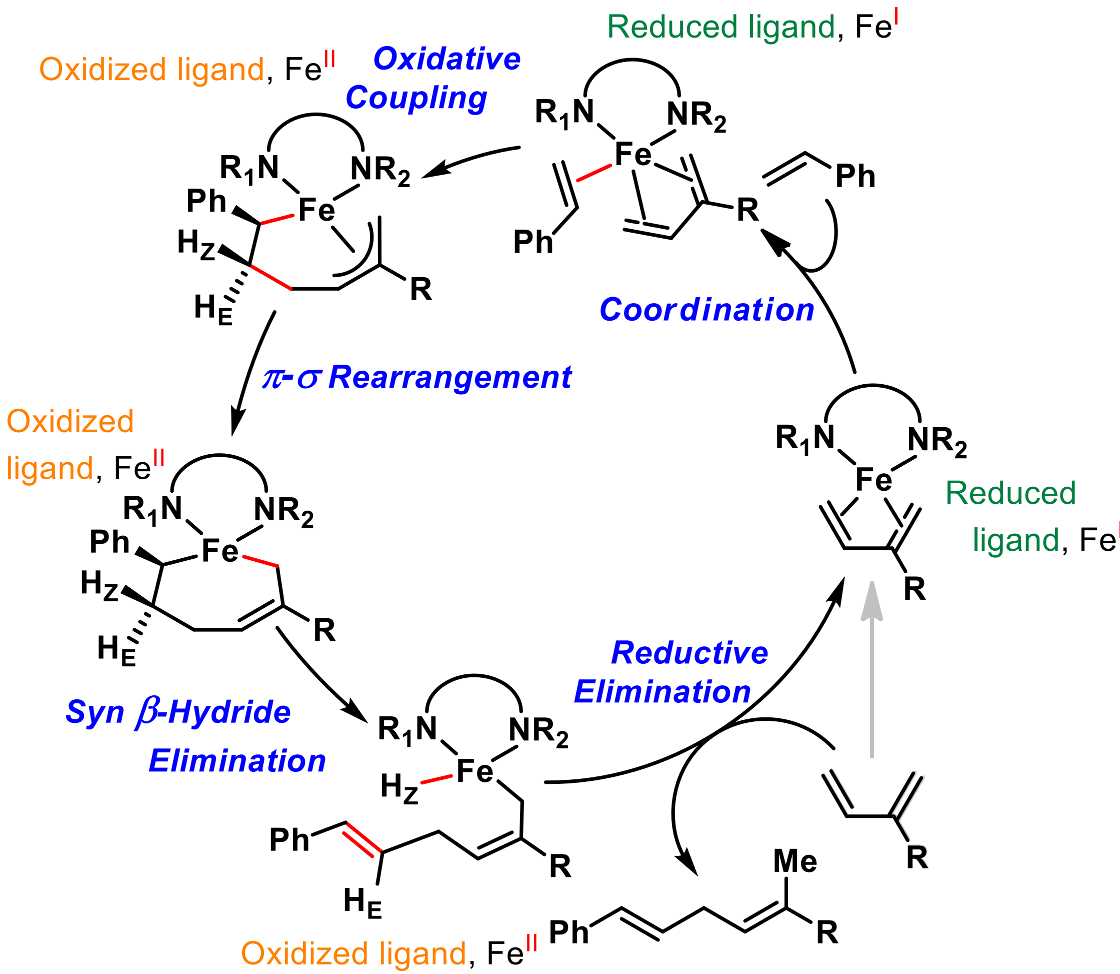


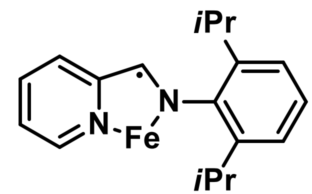


Proposed Mechanism for 1,4-Addition

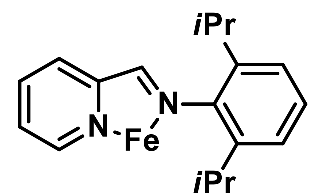


Proposed Mechanism for 1,4-Addition



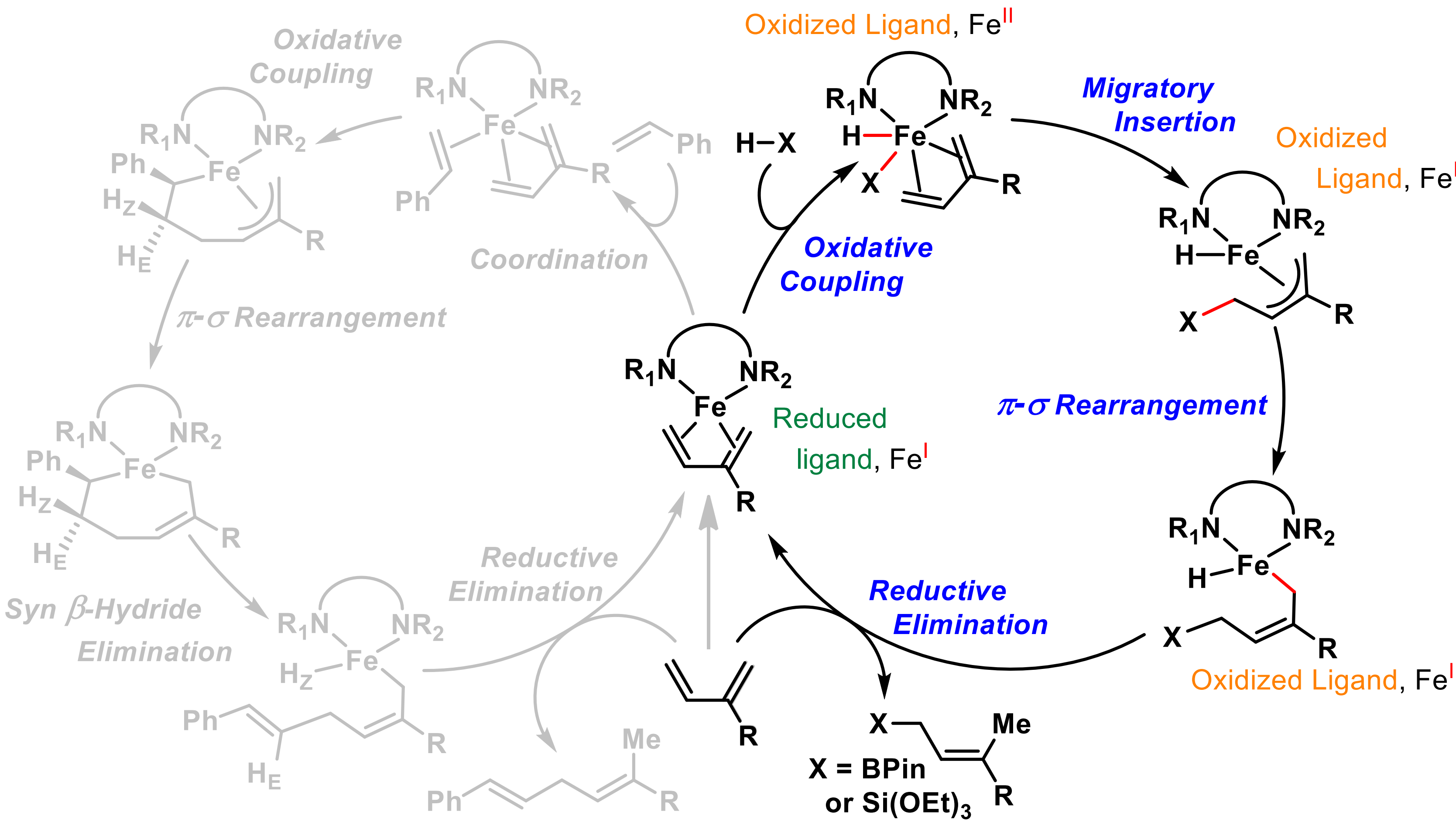


Reduced ligand

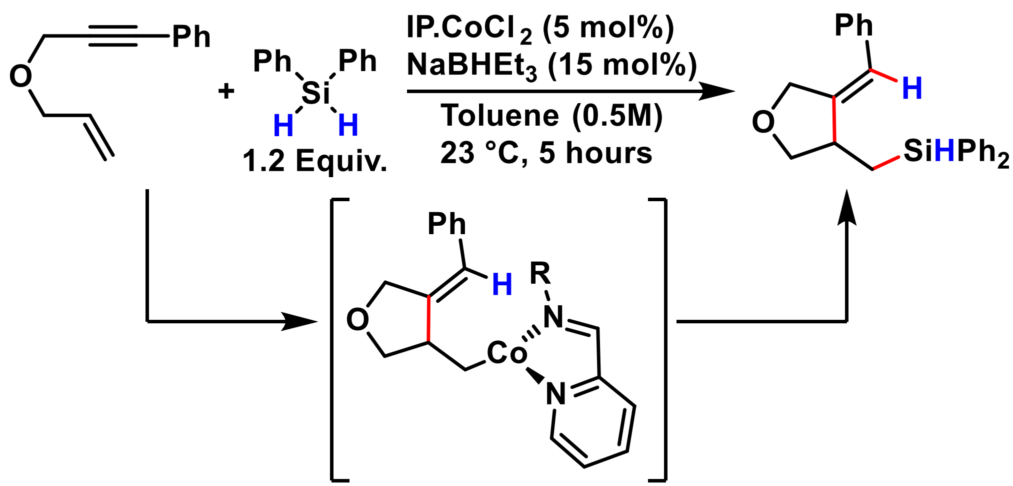


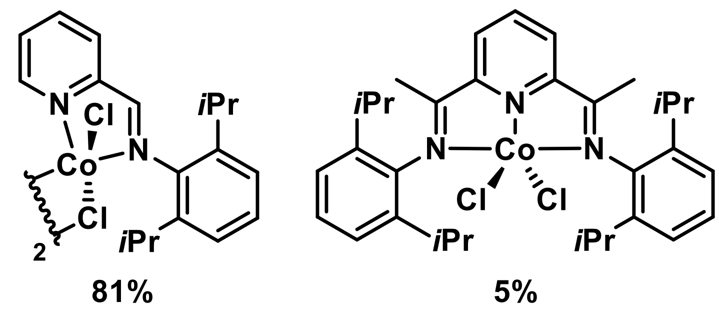
Oxidized ligand

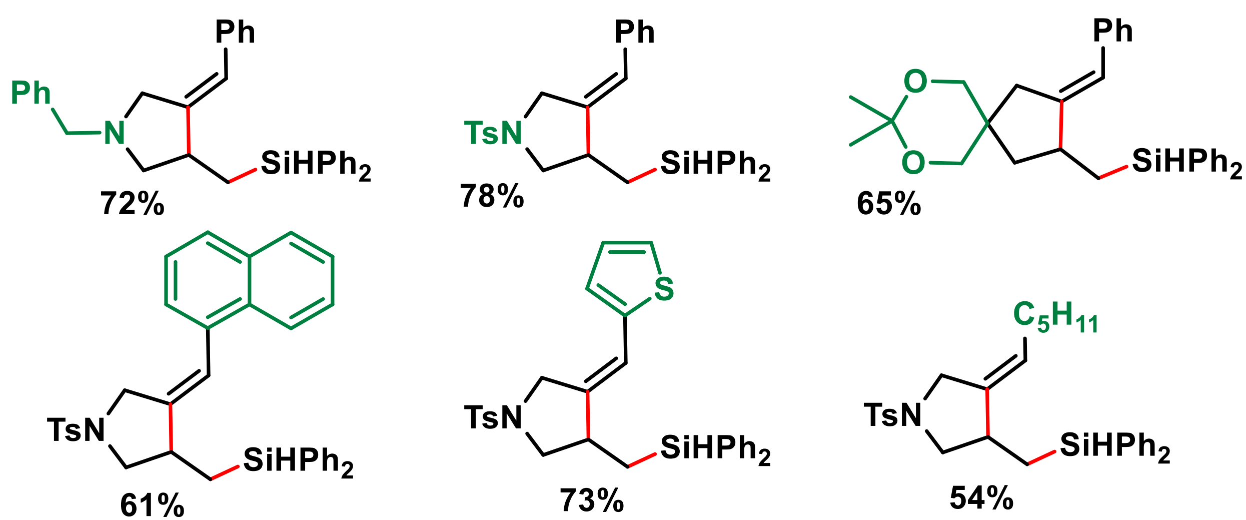
Proposed Mechanism for 1,4-Addition



Hydrosilylation of 1,6-Enyne

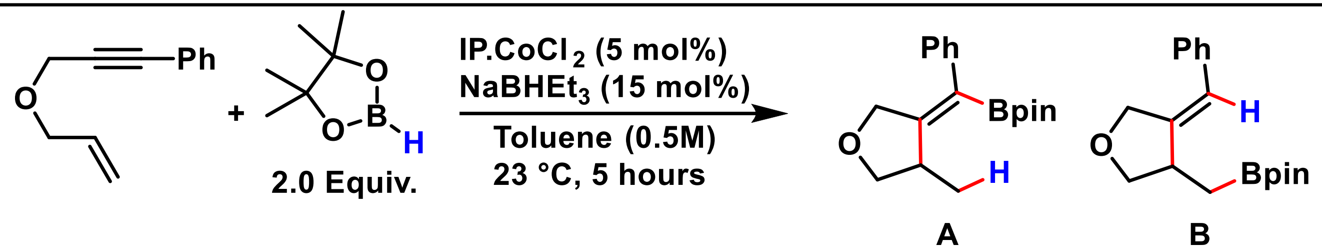


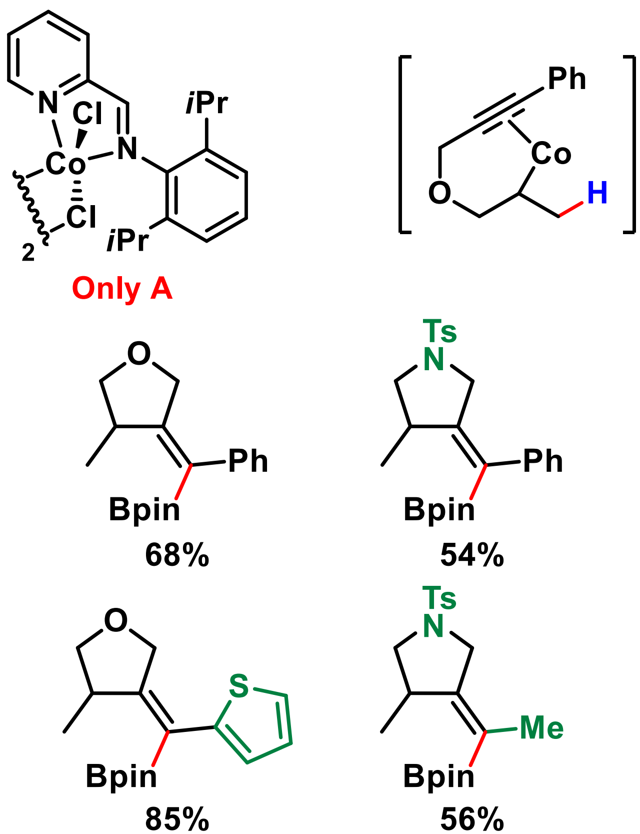


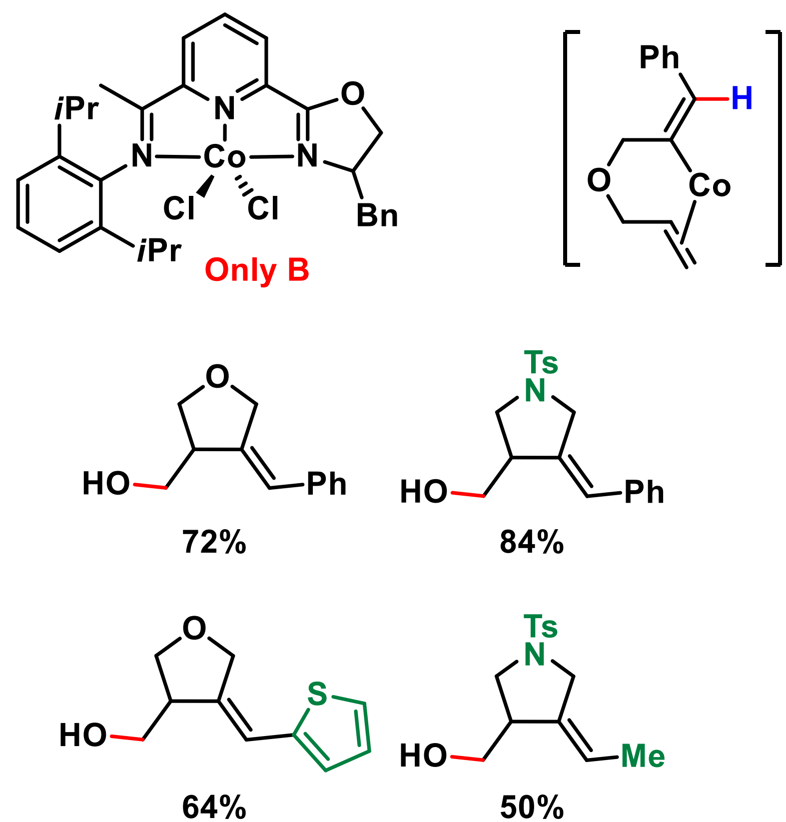


Z. Lu, *J. Org. Chem.* **2016**, 81, 8858

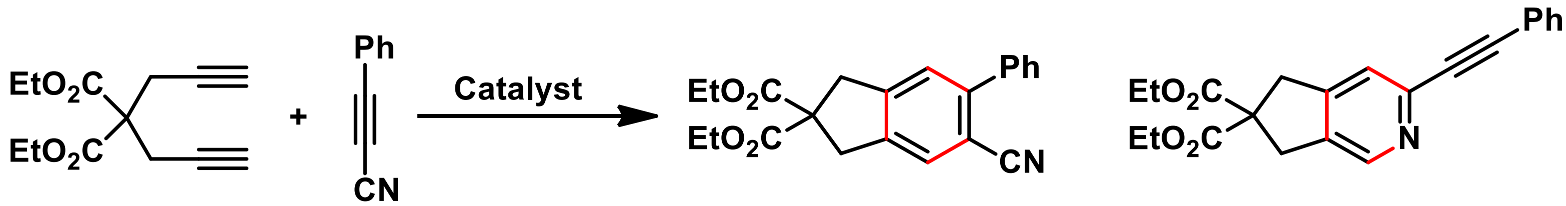
Hydroboration of 1,6-Enyne



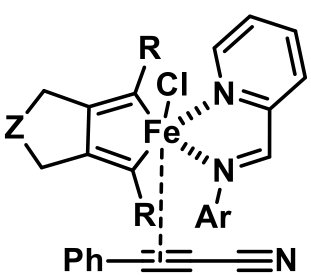




Chemoselective [2+2+2]

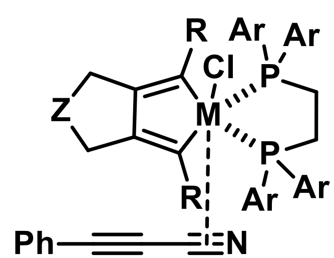


Entry	Catalyst (mol %) / Additive (mol %)	Yield A (%)	Yield B (%)
1	Cp*RuCl(cod) (5%)	58	21
2	CpCo(cod) (10%)	44	12
3	$[Ir(cod)Cl]_2$ (10%) / dppe (20%)	48	5
4	$(PPh_3)_3RhCl$ (10%)	47	Traces
5	$Ni(cod)_2$ (10%) / xantphos (20%)	21	Traces
6	$Pd_2(dba)_3$ (5%) / PPh_3 (10%)	Traces	Traces
7	$FeCl_2.4H_2O$ (5%) / $^{i\text{-}Pr}IP$ (6%) / Zn (10%)	86	Traces



Electron-deficient Metal

Electron-rich triple bond

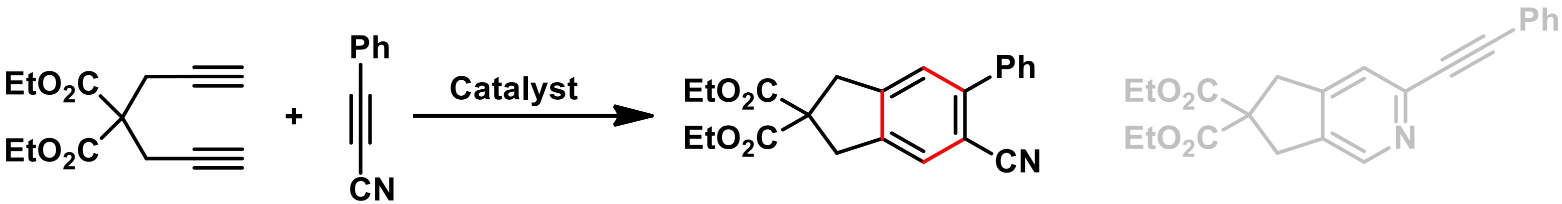


Electron-rich Metal

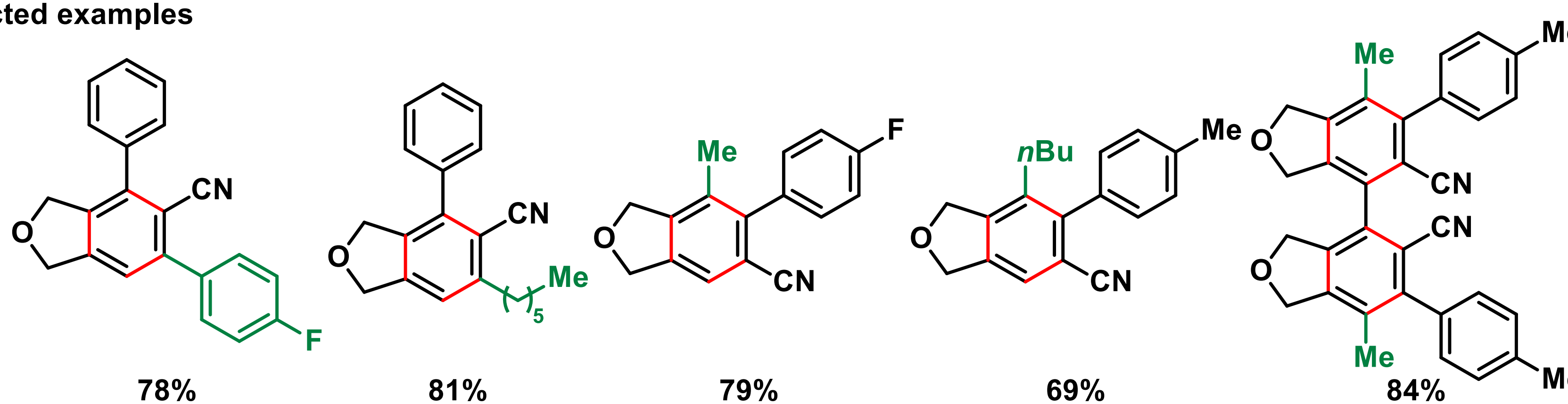
Electron-deficient triple bond

A. Goswami, *Org. Lett.* **2017**, 19, 3350

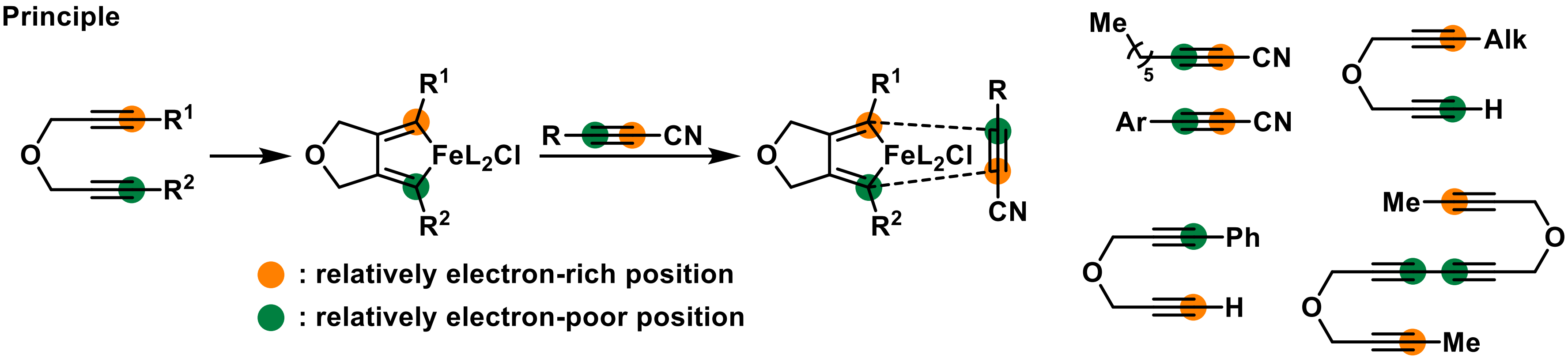
Chemoselective [2+2+2]



Selected examples

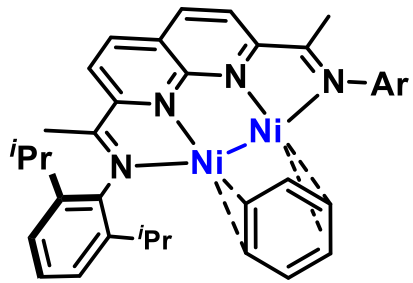


Principle

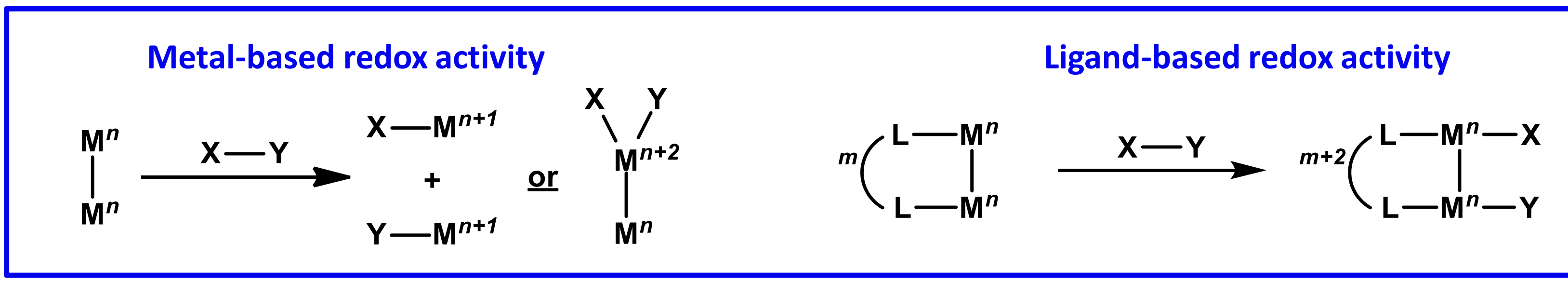


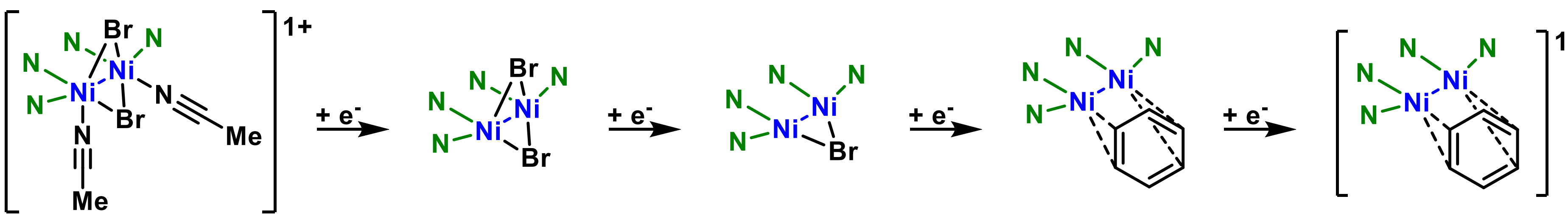
Dinuclear Naphthyridine-Diimine

- **Uyeda, 2014**



- Dinuclear Ni(I)–Ni(I) complex
- Different reactivity than mononuclear complexes
- Ligand-based redox activity

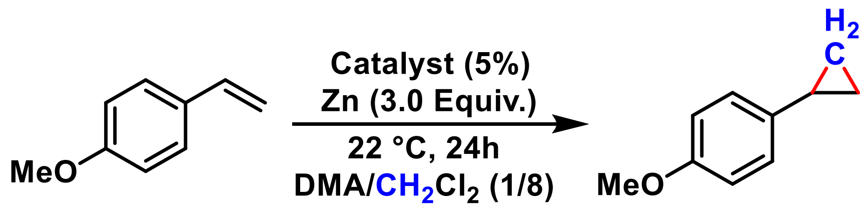


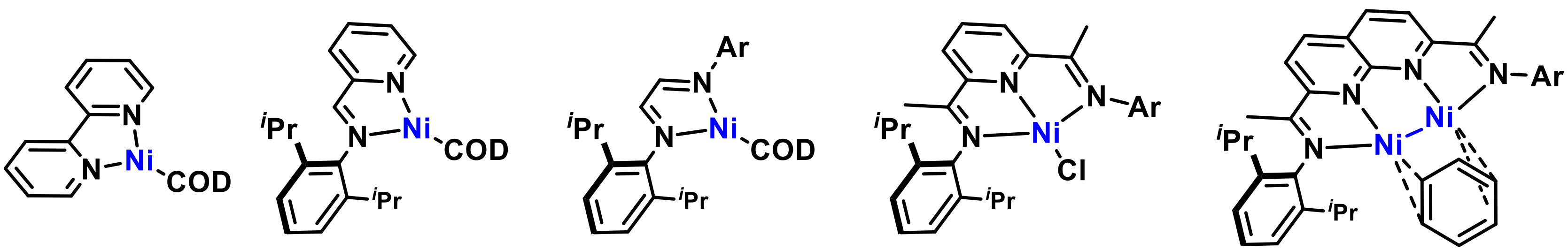


C. Uyeda, *Inorg. Chem.* **2014**, *53*, 11770

For a perspective on Metal-Metal Bonds in Catalysis : *ACS Catal.* **2017**, *7*, 936

Mild Cyclopropanation

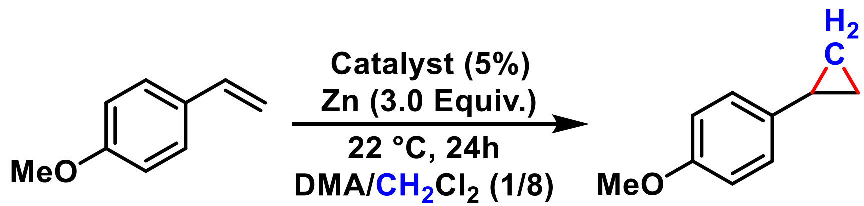




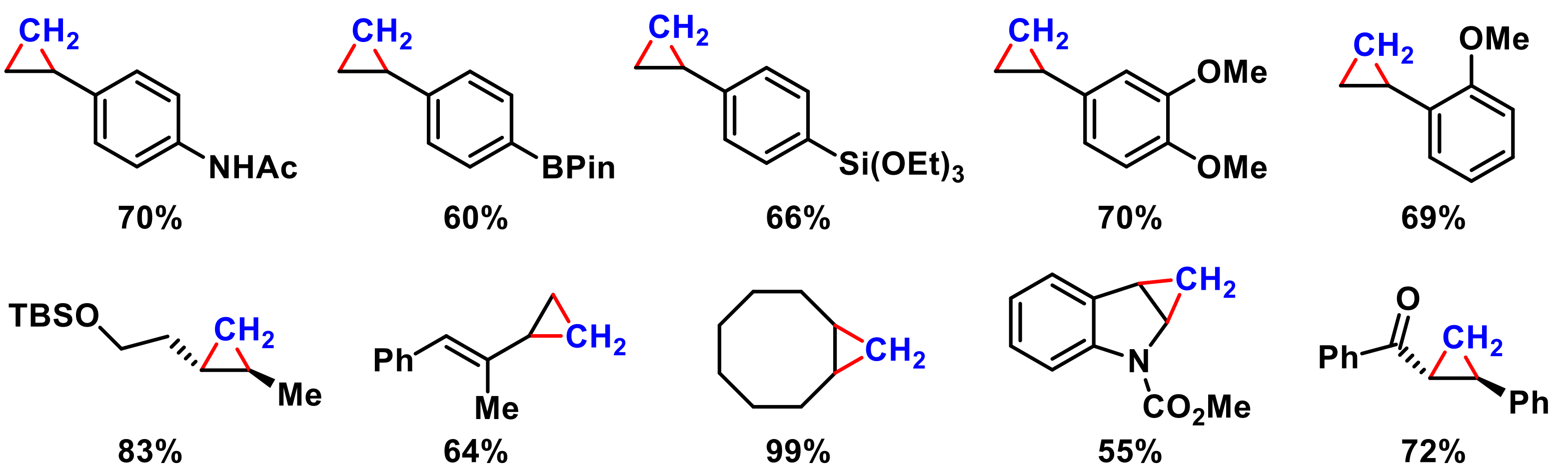
Conv. : 82%	Conv. : 52%	Conv. : 38%	Conv. : >99%	Conv. : >99%
Yield : 8%	Yield : 19%	Yield : 2%	Yield : 20%	Yield : 69%

C. Uyeda, *Angew. Chem. Int. Ed.* **2016**, *55*, 3171

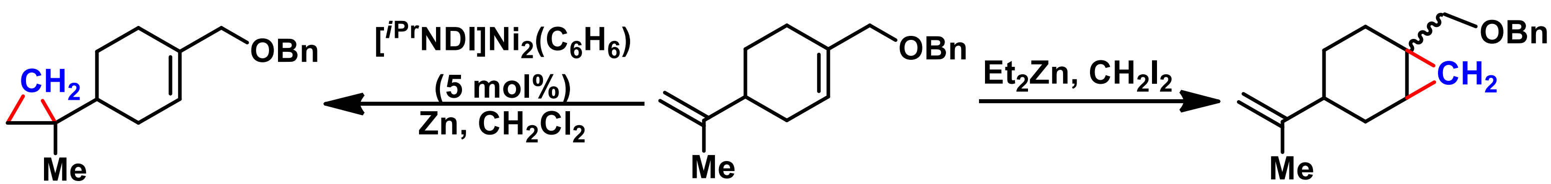
Mild Cyclopropanation



Selected examples

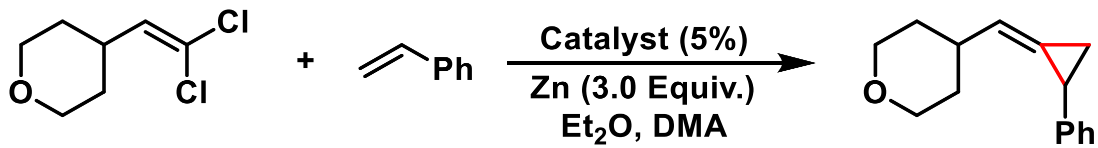


Comparison with Simmons-Smith

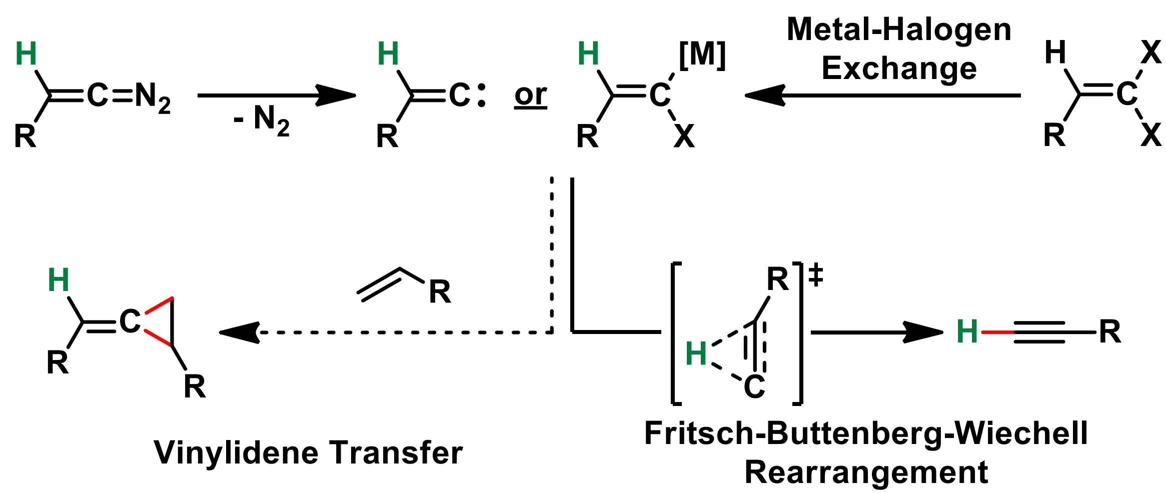


C. Uyeda, *Angew. Chem. Int. Ed.* **2016**, *55*, 3171

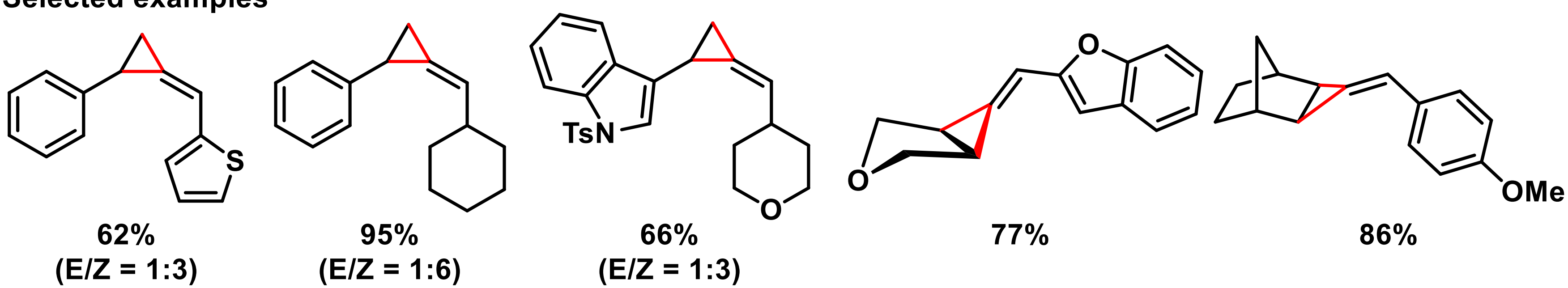
Vinylidene Transfer



Principle

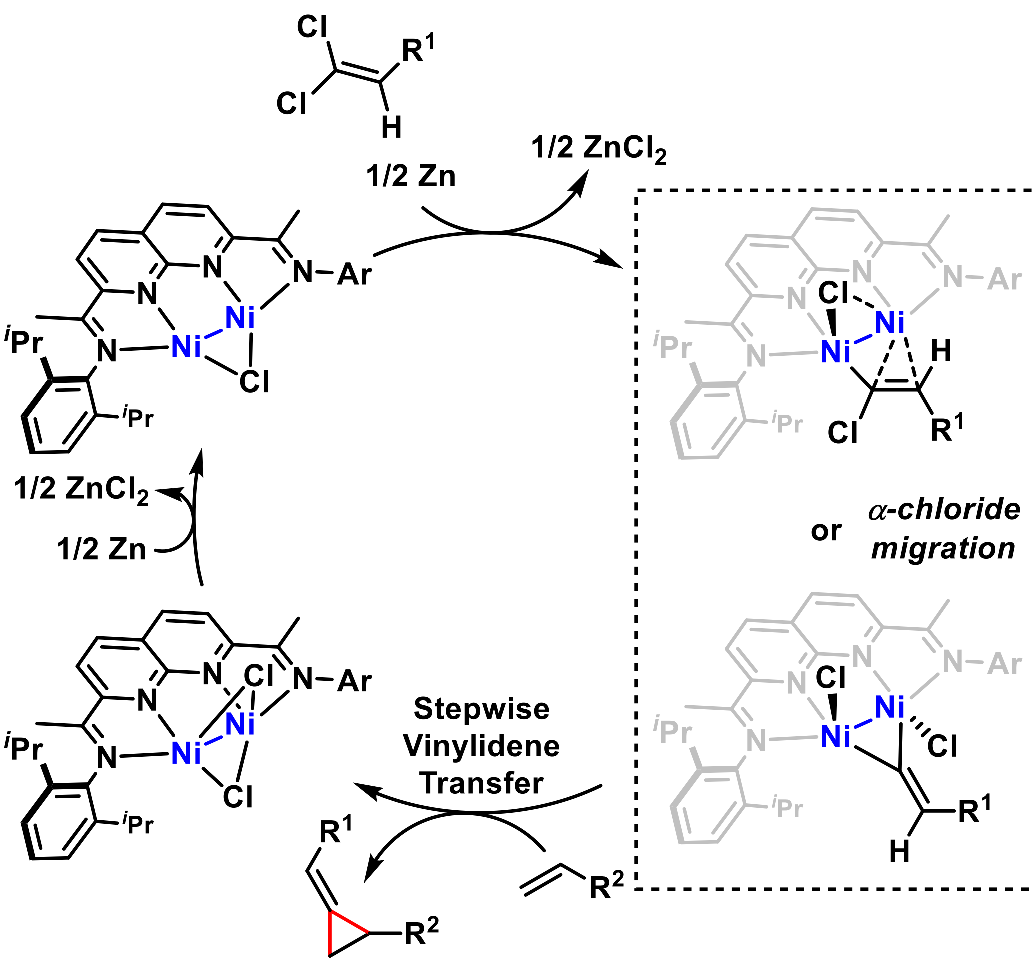


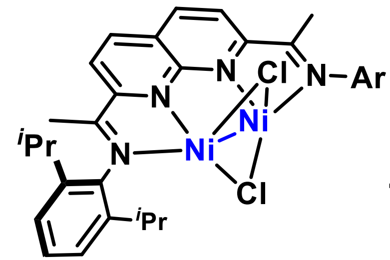
Selected examples



Vinylidene Transfer

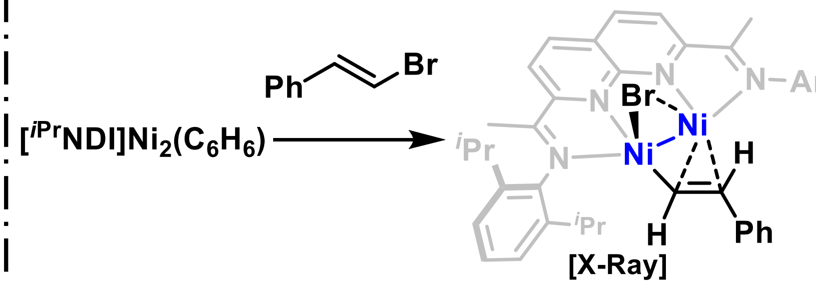
- **Mechanism**

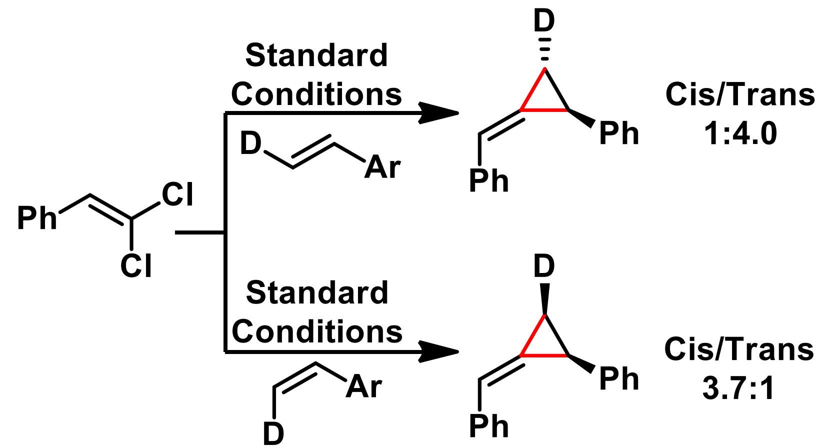




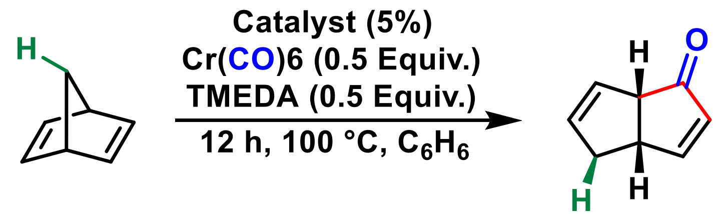
Two reversible reduction events : -1.15 and -1.72 V (F_c/F_c^+ couple)

Zn is capable of accessing only the first one

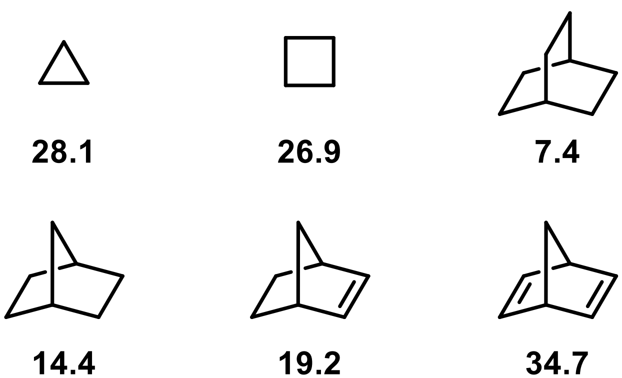




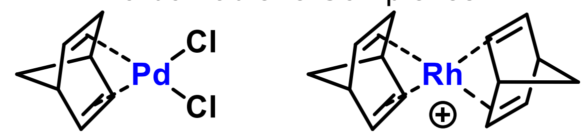
Carbonylative Rearrangement



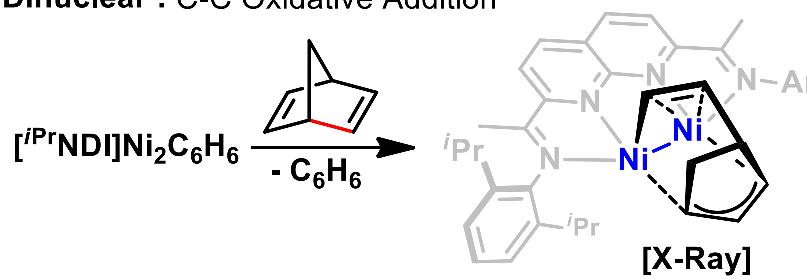
Ring Strain Energies (kcal/mol)



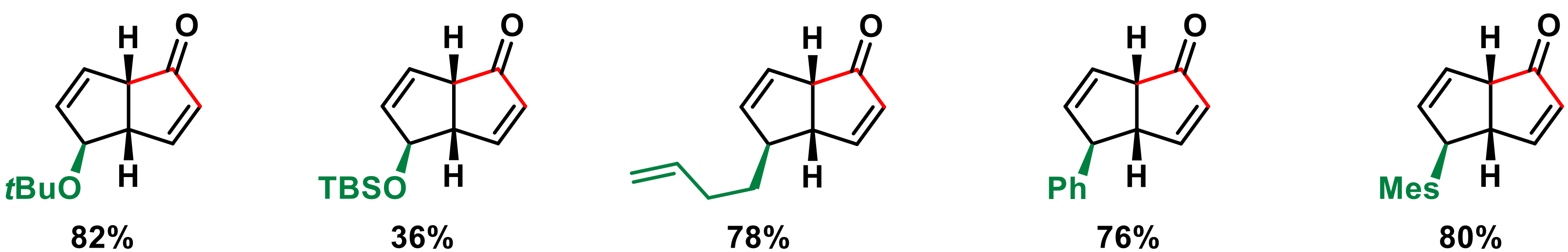
Mononuclear : Norbornadiene Complexes



Dinuclear : C-C Oxidative Addition

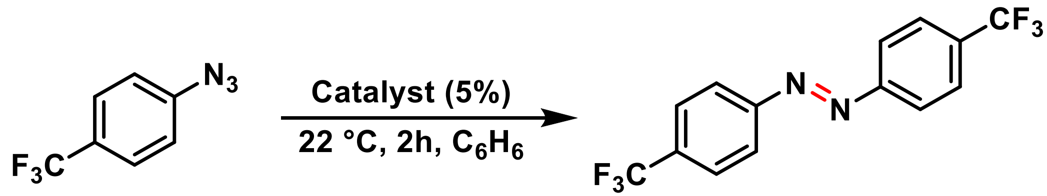


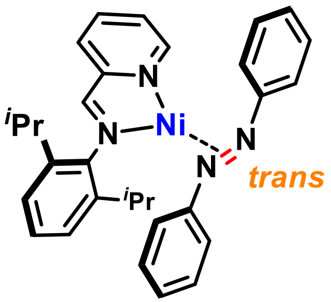
Selected examples



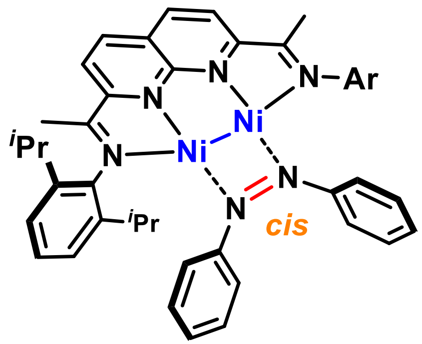
C. Uyeda, *J. Am. Chem. Soc.* **2017**, *139*, 13672

Azoarene Synthesis

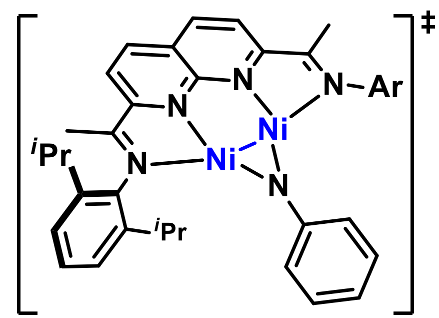




Strong Product Binding
No Catalyst Turnover

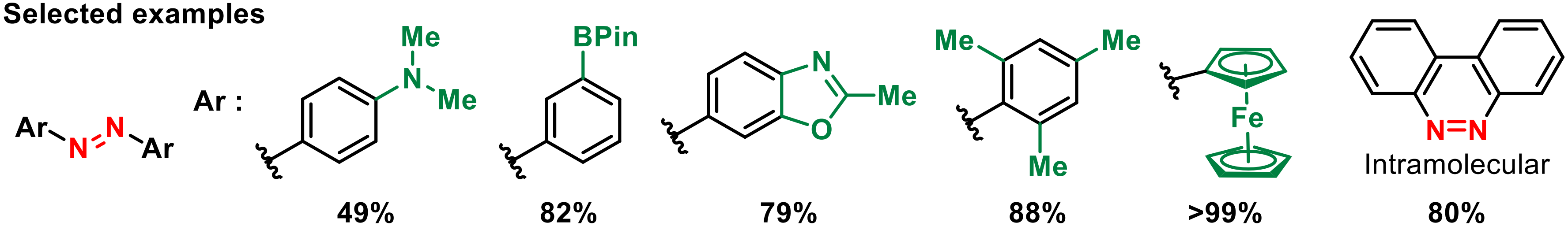


Weak Product Binding
Efficient Catalyst



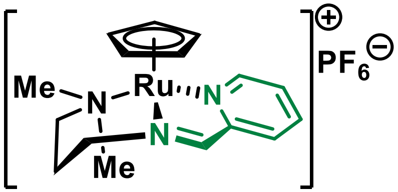
Proposed intermediate :
π-interactions with the Ni-Ni bond (No H-atom abstraction)

Selected examples

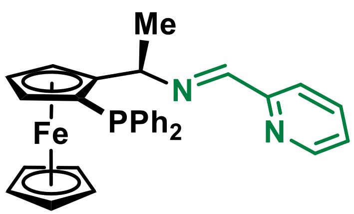


Conclusion / Future direction

- **Modification of known ligand**

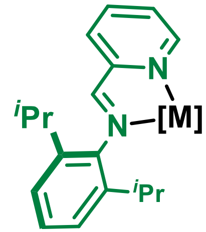


Anti-Markovnikov Hydration



[3+3] Cycloaddition

- **Redox-Active Ligands for catalysis**

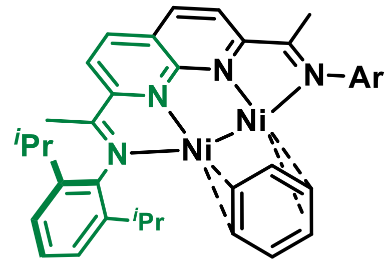


C-H Activation

1,4-Addition of Unactivated Alkenes

Hydroboration/Cyclization of 1,6-Enynes

Selective [2+2+2]

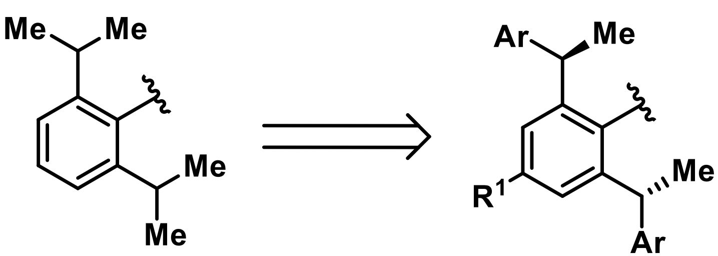


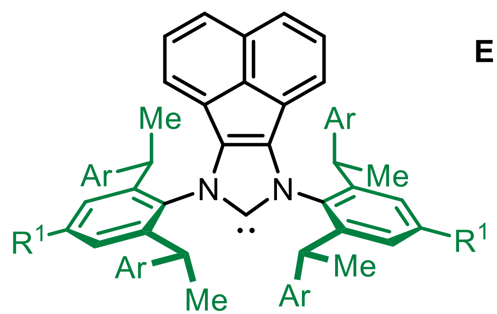
Mild cyclopropation

Vinylidene Transfer

Carbonylative Rearrangement *via* C-C Oxidative Addition

Azoarene synthesis



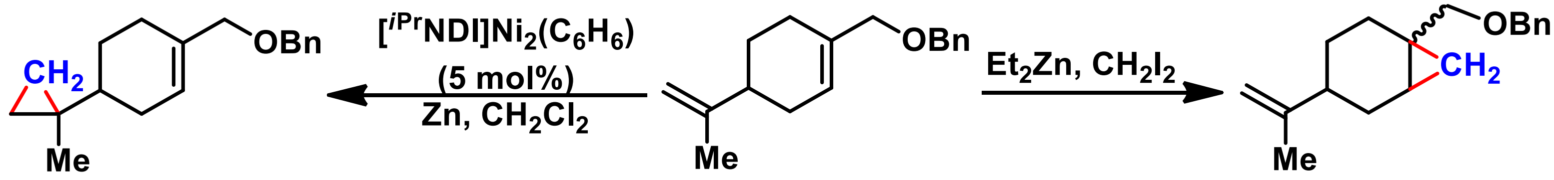


Enantioselective Markovnikov Protoboration of α-Olefins

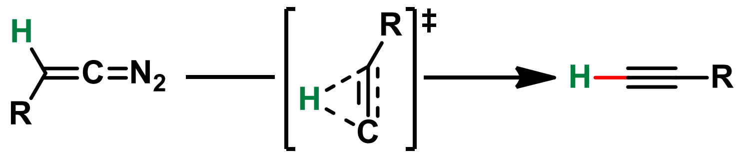
Enantioselective Pyridone C-H Functionalizations

S.-L. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 1376
N. Cramer, *J. Am. Chem. Soc.* **2018**, *140*, 4489

- **Question 1 : Explain the selectivity for both reactions**

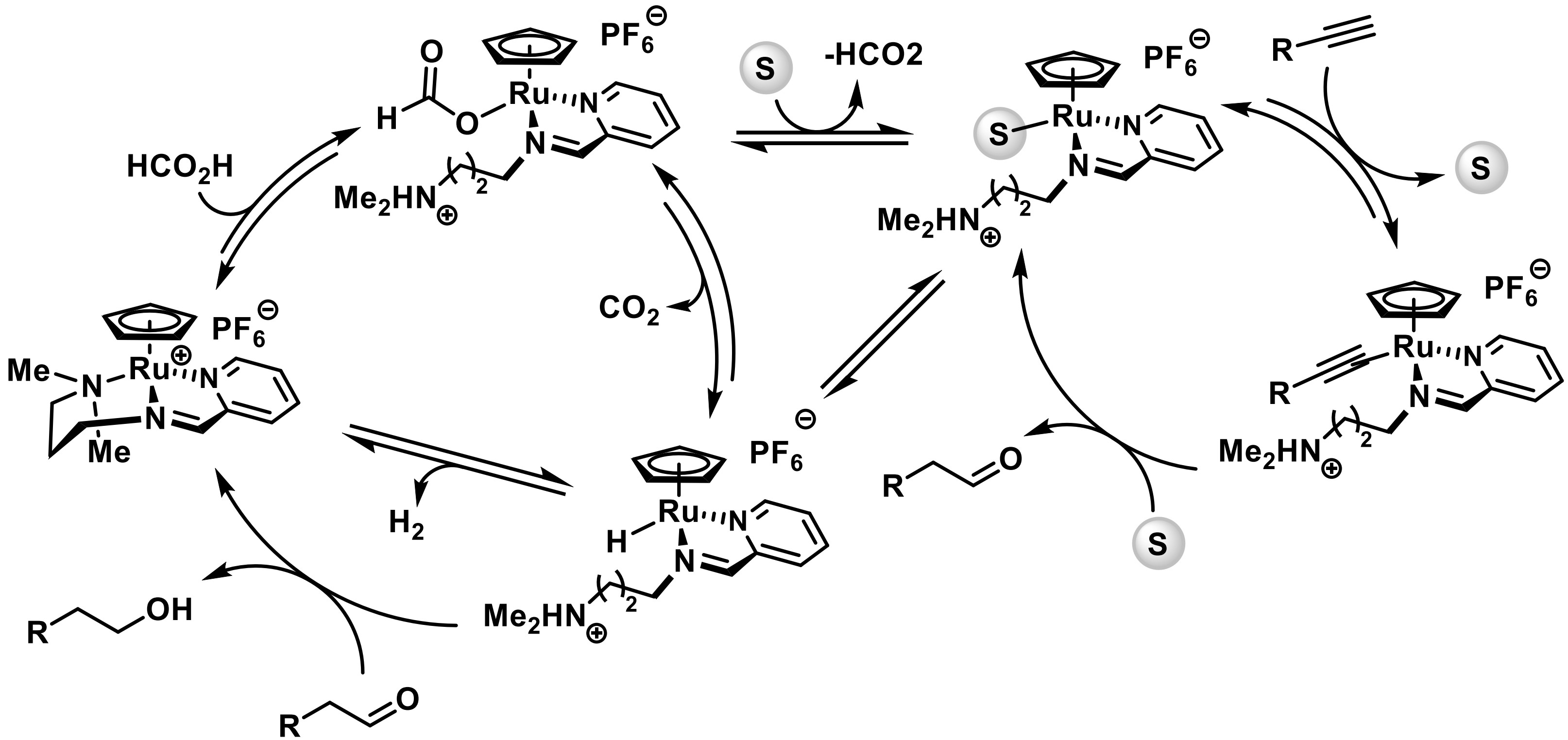


- **Question 2 : Which reaction/reagent is based on this principle ?**



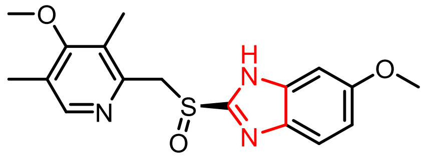
CpRu Catalysis with Iminopyridine

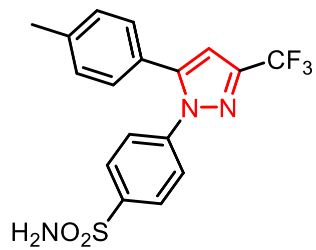
- **Mechanism**

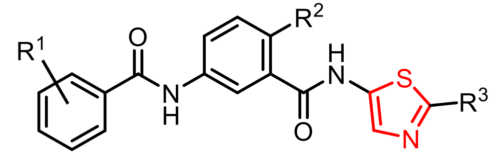


J. Am. Chem. Soc. 2014, 136, 7058,7067

Application and Synthesis of Imidazole, Pyrazole and Thiazole in Medicinal Chemistry



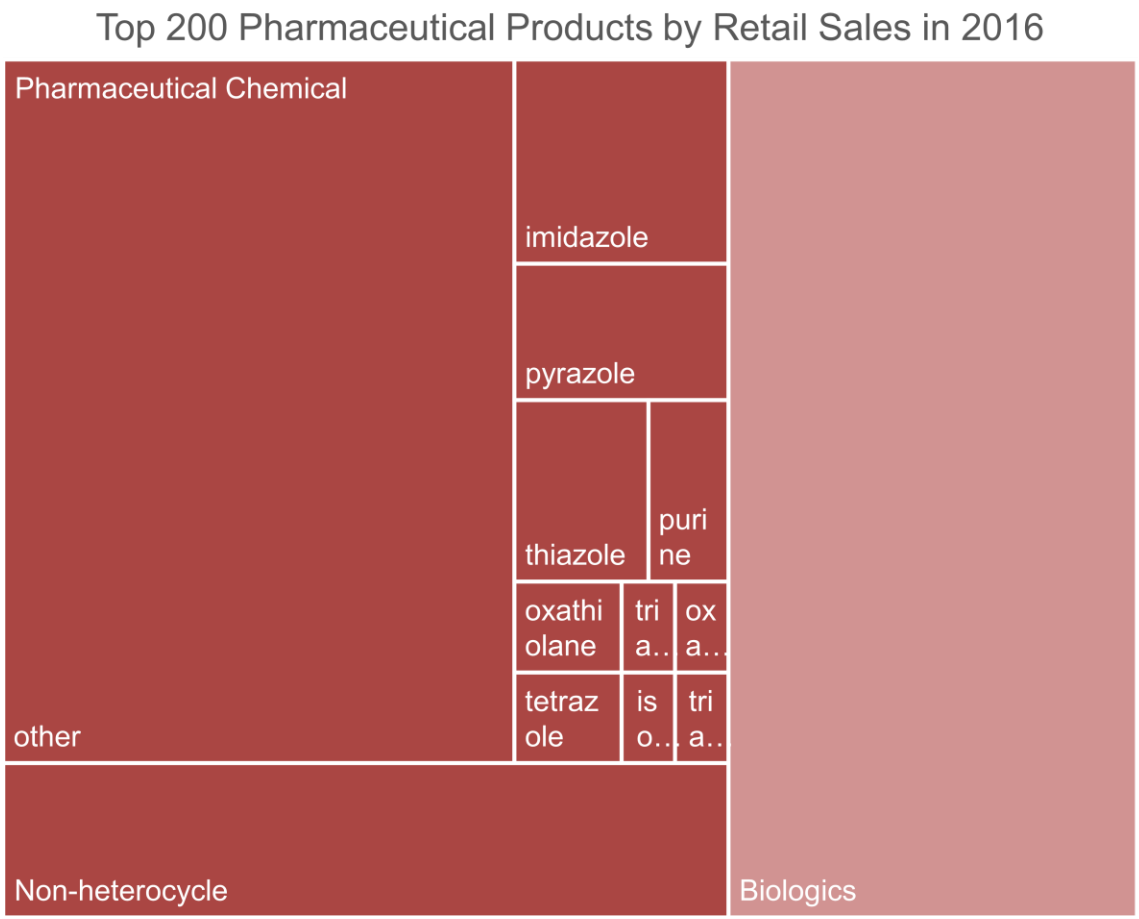




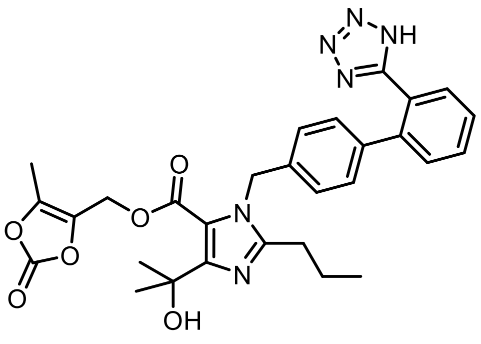
Sung Hwan Park

18.05.2018

- Pharmaceutical Chemical
  128 products (64%)
- Heterocycle in Chemicals
  105 product (82%)
- 5-membered ring with
  two heteroatoms
  31 products
- imidazole, pyrazole and thiazole



Medicinal Compound



olmesartan medoxomil (Benicar)

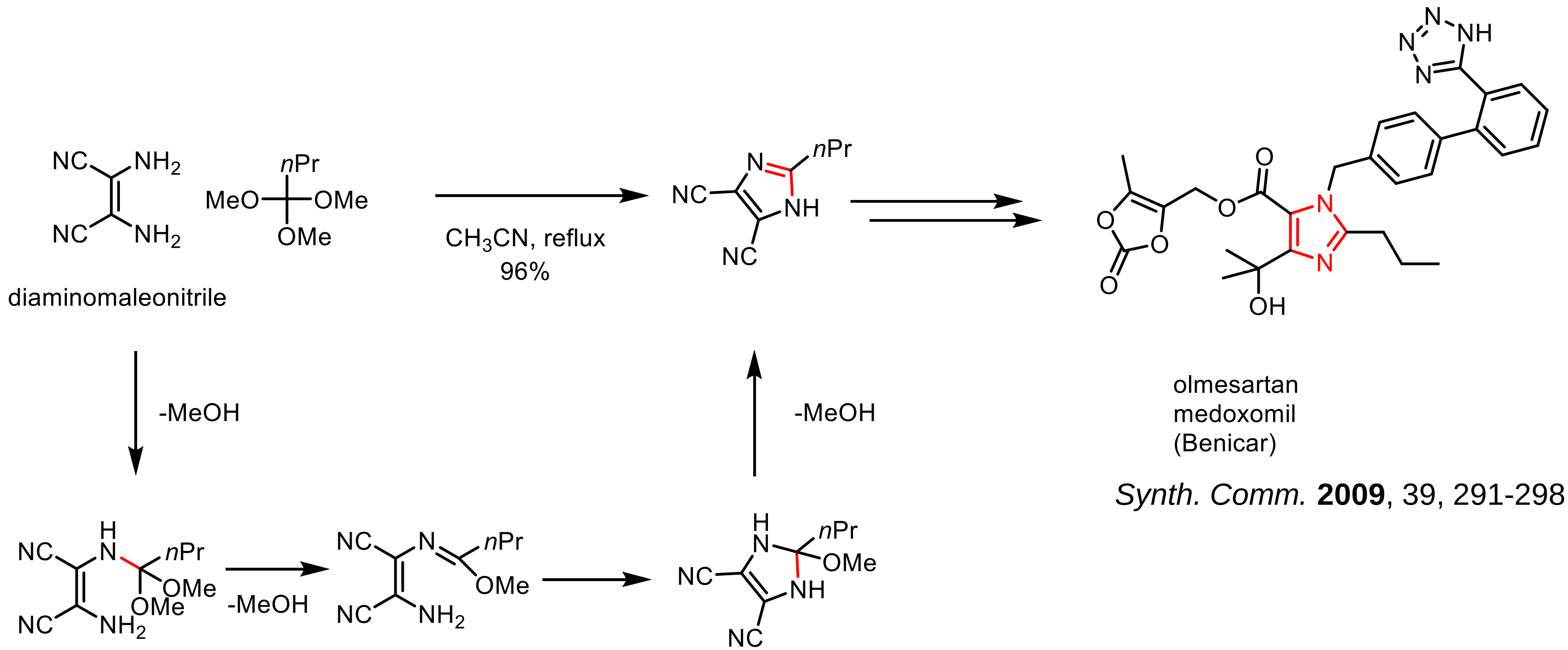
- Drug for high hypertension
- Inhibition of the angiotensin II-Induced Pressor Response

  83% inhibition
  (6 h, Rat, Oral administration)

H. Yanagisawa et al. *J. Med. Chem.* **1996,** *39,* 323-338

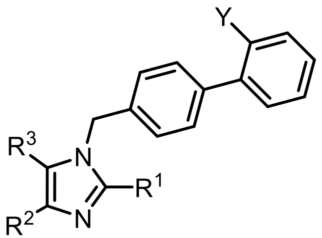
Construction of Imidazole in Med Chem

- diaminomaleonitrile (DAMN) reagent



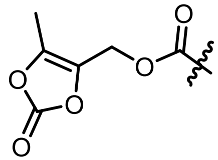
Synth. Comm. **2009**, 39, 291-298

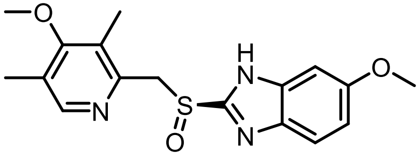
- Selected examples of *In vivo* tests, Inhibition of the AII-Induced Pressor Response



	R1	R2	R3	Y	dose (mg/kg)	% inhibition (1 h)	% inhibition (3 h)	% inhibition (6 h)	
1	Pr	CH_2OH	H	5-tetrazolyl	0.3	76	75	65	
2	Pr	CMe_2OH	H	5-tetrazolyl	0.3	83	77	78	
3	Pr	CMe_2OH	H	CO_2H	1	50	42	12	
4	Pr	CMe_2OH	MDO	CO_2H	1	72	70	70	
5	Pr	CMe_2OH	MDO	5-tetrazolyl	0.1	66	77	83	olmesartan medoxomil

MDO =

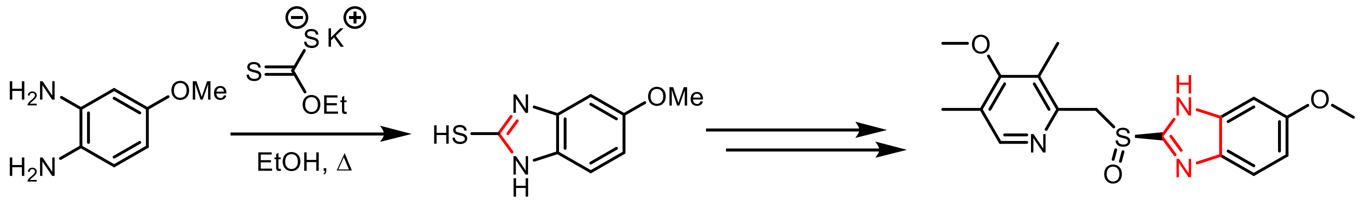




Esomeprazole (Nexium)

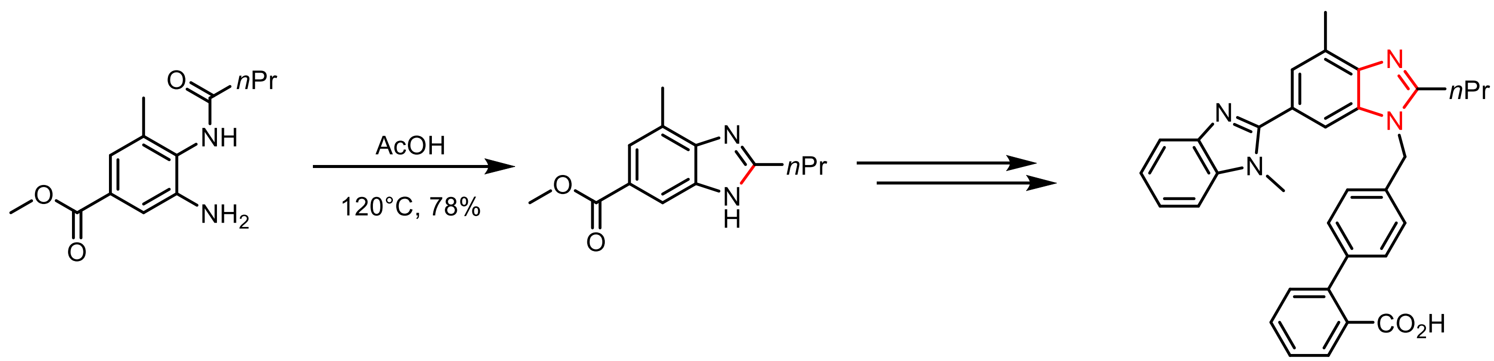
- Suppress gastric secretion
- $ 2,032 M sales in 2016 (51st rank)
- Inhibition of H^+/K^+-ATPase.

Construction of Imidazole in Med Chem



Esomeprazole (Nexium)

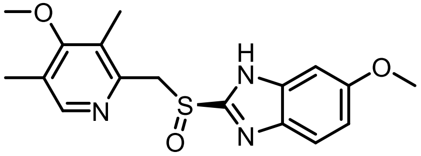
US 4255431 (Filed date: April. 05, 1979)
Org. Synth. **1950**, *30*, 56



telmisartan
(Micardis)

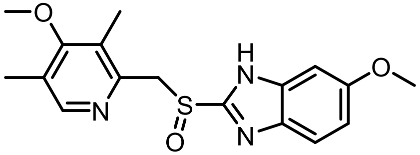
Beilstein J. Org. Chem. ***2010***, *6*, No.25

- *In vitro* tests



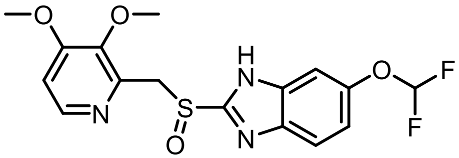
esomeprazole

140% inhibition
than omeprazole



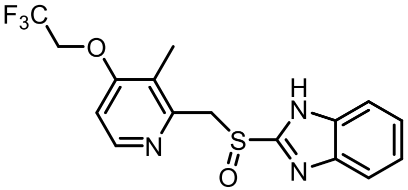
omeprazole
(racemic mixture of esomeprazole)

IC_{50} 0.5 µM (Rabbit gastric gland)



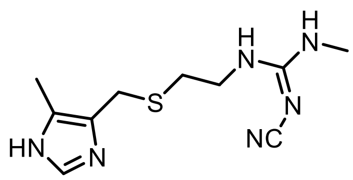
pantoprazole

IC_{50} 1.0 µM (Rabbit gastric gland)



lansoprazole

IC_{50} 0.4 µM (Rabbit gastric gland)



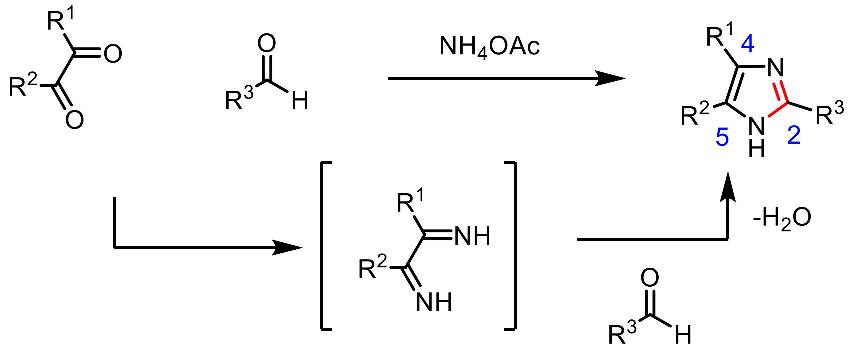
cimetidine (Tagamet)

- Suppress gastric secretion
- 1st Gen antihistamine drug
- Inhibitor of histamine type 2 receptor (H_2 receptor)

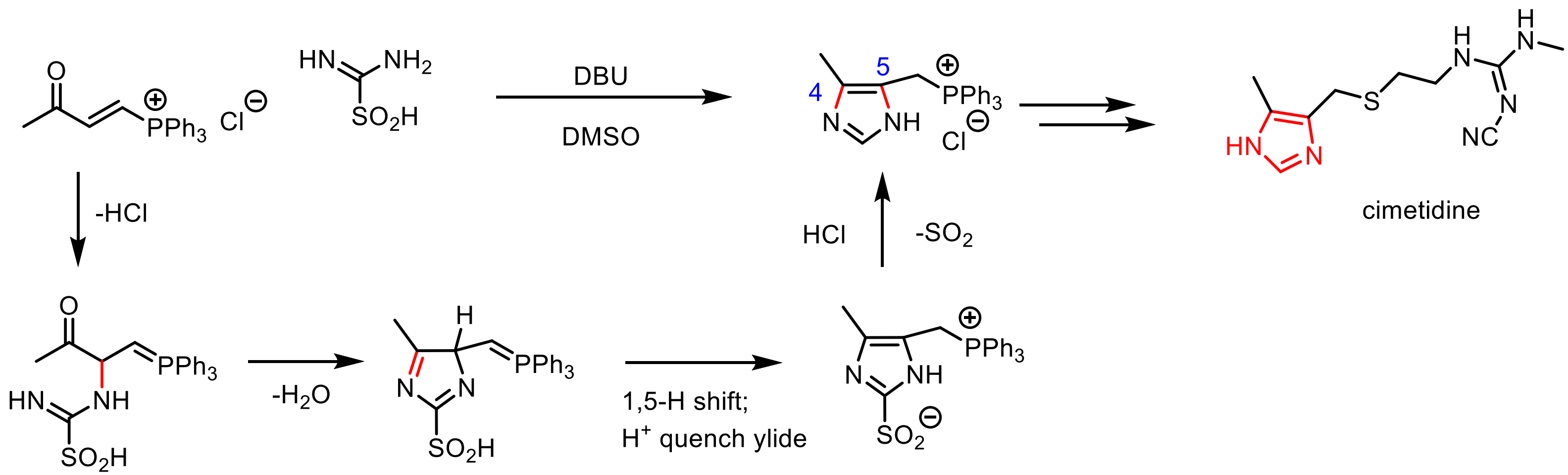
Synthesis of Essential Drugs **2006**, Elsevier, *1st ed.*, 231

Construction of Imidazole in Med Chem

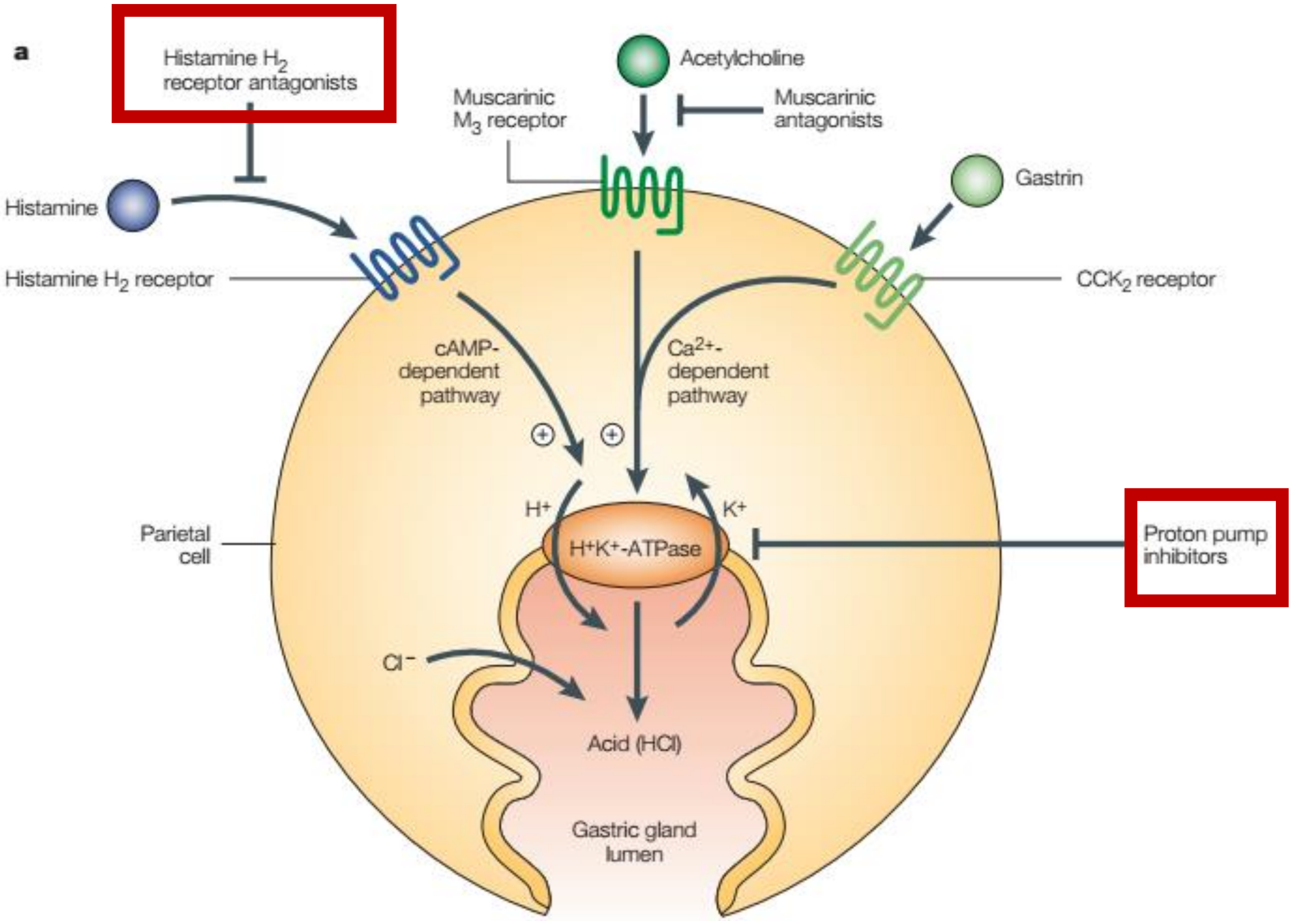
- Debus imidazole synthesis



- modified Debus imidazole synthesis



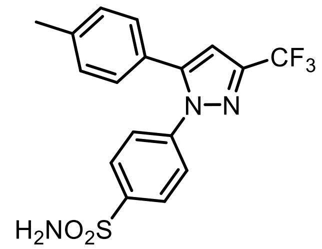
Biological Activities



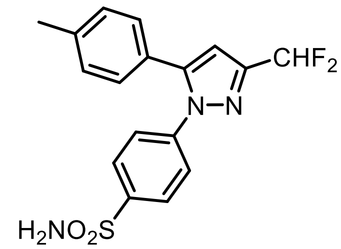
Nature Reviews Drug Discovery **2003**, *2*, 132–139

Medicinal Compound

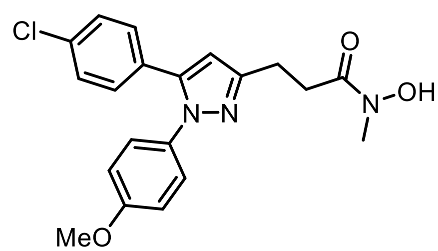
Pyrazole based medicinal molecules



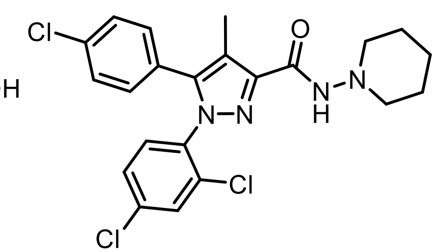
Celecoxib (Celebrex)



deracoxib (Deramaxx)

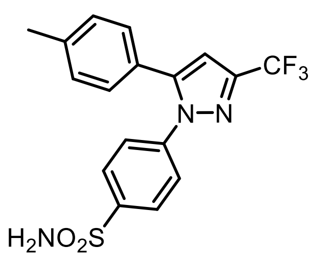


tepoxalin (Zubrin)



rimonabant (Acomplia, Zimulti)

Medicinal Compound



celecoxib (Celebrex)

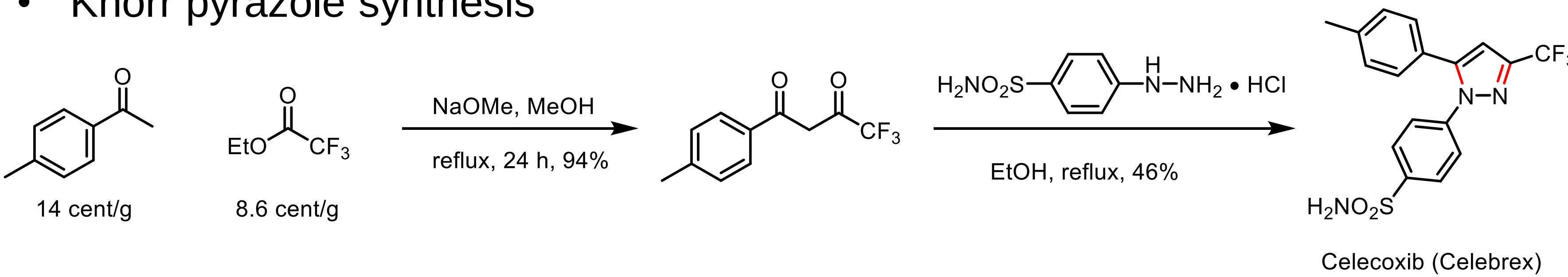
- Drugs for rheumatoid arthritis, osteoarthritis
- $ 733 M sales in 2016 (176th rank)
- Selective COX-2 (cyclooxygenase-2) inhibitor

IC_{50} = 40 nM on COX-2
IC_{50} = 15000 nM on COX-1

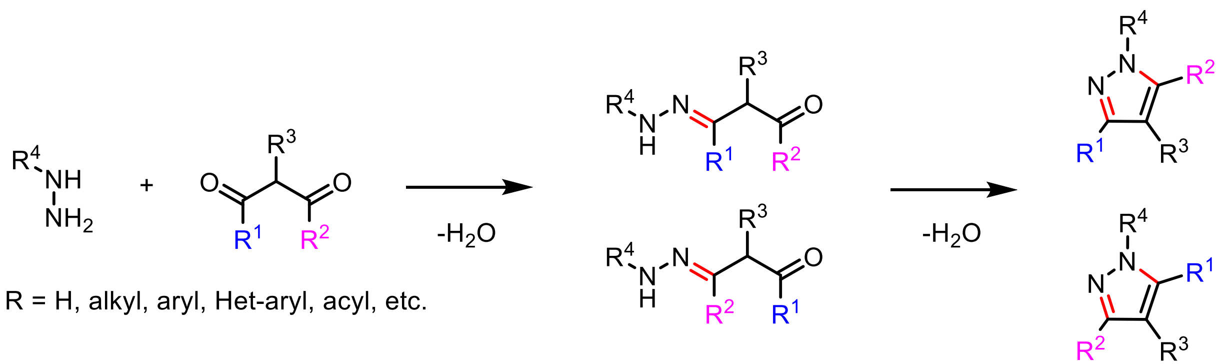
T. D. Penning et al. *J. Med. Chem.* **1997**, *40*, 1347-1365

Construction of Pyrazole in Med Chem

- Knorr pyrazole synthesis

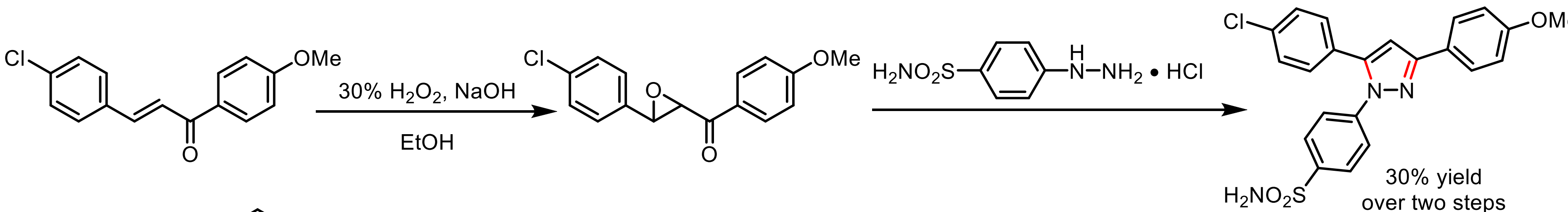


J. Med. Chem. **1997**, *40*, 1347-1365

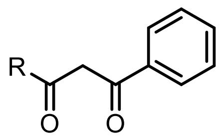


Construction of Pyrazole in Med Chem

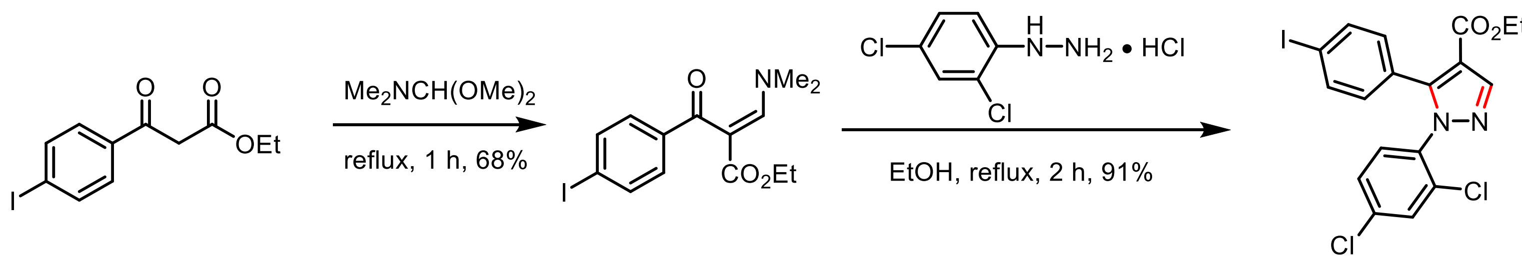
- Modified Knorr pyrazole synthesis



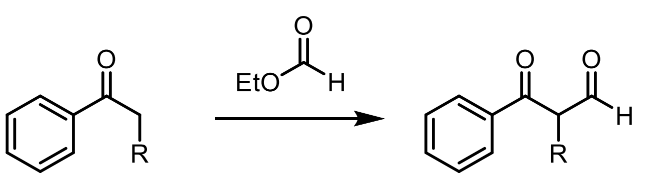
J. Med. Chem. **1997**, *40*, 1347-1365



R = alkyl, aryl

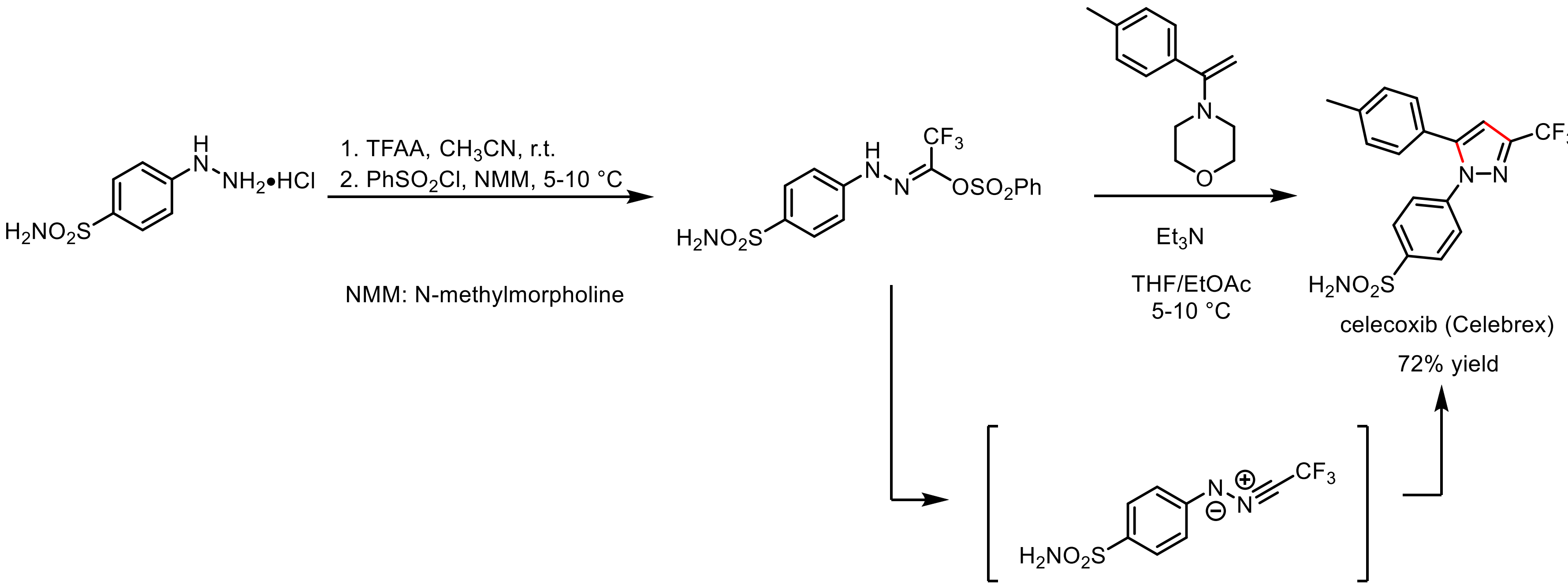


Eur. J. Med. Chem. **2008**, *43*, 2627-2638



Construction of Pyrazole in Med Chem

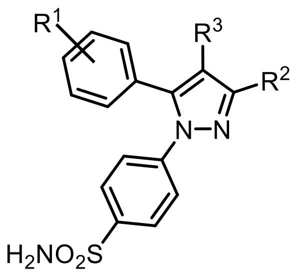
- Pechmann pyrazole synthesis (1,3-dipolar cycloaddition)



Tetrahedron Letters **2006**, *47*, 7943–7946

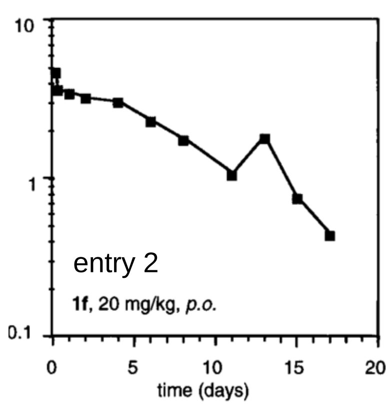
Biological Activities

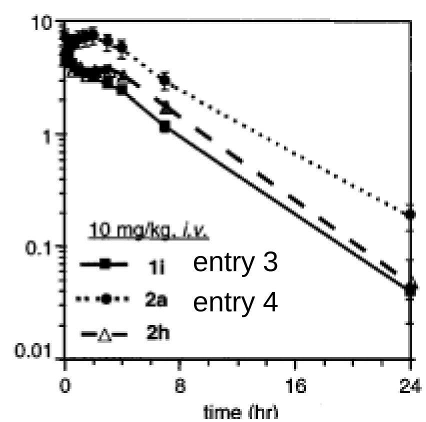
- Selected examples of *In vitro* tests on COX-1 and COX-2



	R1	R2	R3	IC_{50} (COX-1) nM	IC_{50} (COX-2) nM	Half-life in plasma	
1	4-Cl	CF_3	Cl	65	5.3		
2	4-Cl	CF_3	H	17800	10	a day	
3	4-Me	CF_3	H	15000	40	3-6 hr	celecoxib
4	4-Cl	CHF_2	H	5700	10	4.5 hr	

- Pharmacokinetics of selected pyrazoles in male rat

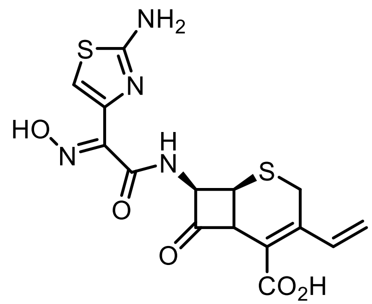




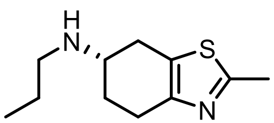
T. D. Penning et al. *J. Med. Chem.* **1997**, *40*, 1347-1365

Medicinal Compound

Thiazole based medicinal molecules

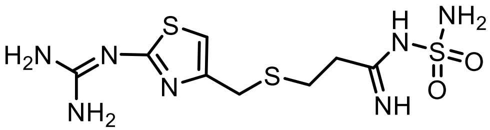


cefdinir (Omnicef)



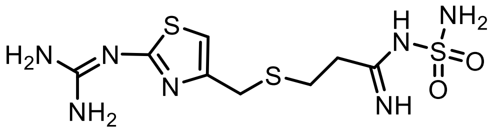
2HCl

pramipexole (Mirapex, Mirapexin, Sifrol)



famotidine (Pepcid)

Medicinal Compound



famotidine (Pepcid)

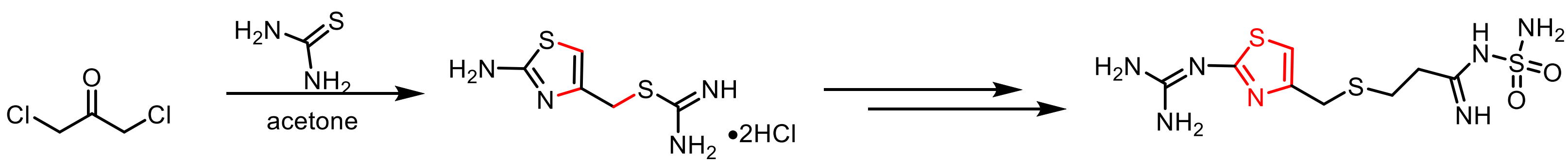
- Suppress gastric secretion
- Inhibitor of histamine type 2 receptor (H_2 Recepter)
- No interaction with P450 enzyme system

→ No interaction with other drugs

Aliment. Pharmacol. Ther. **1999**, *13, 18–26.*

Construction of Thiazole in Med Chem

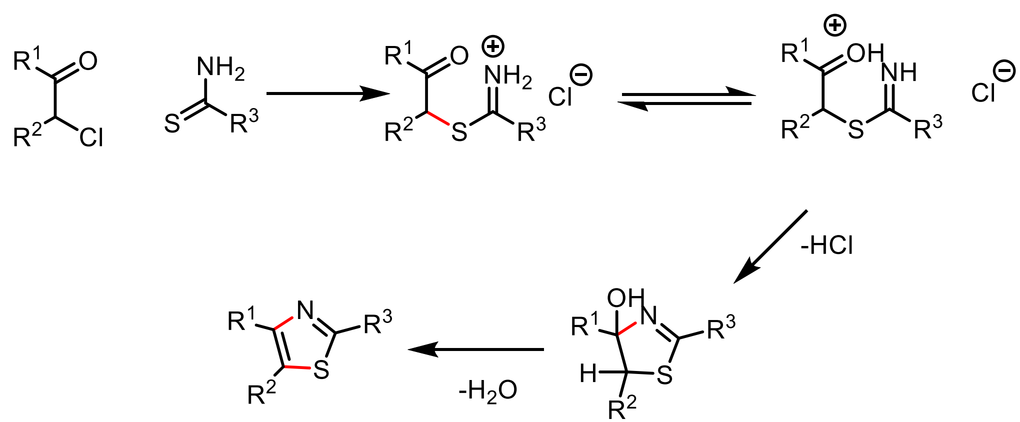
- Hantzsch thiazole synthesis



84%

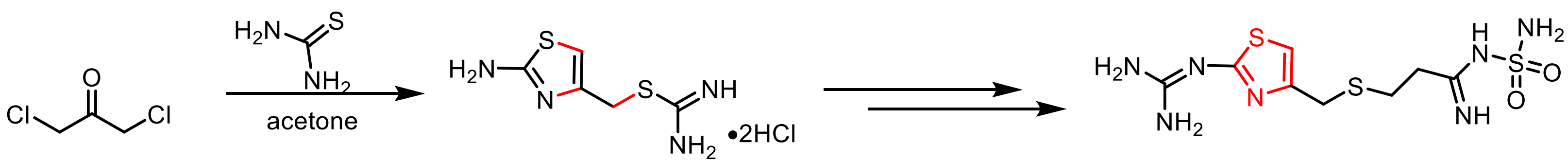
famotidine (Pepcid)

J. Am. Chem. Soc. **1946**, *68*, 2155-2159
US 4283408 (Filed date: Dec. 27, 1979)



Construction of Thiazole in Med Chem

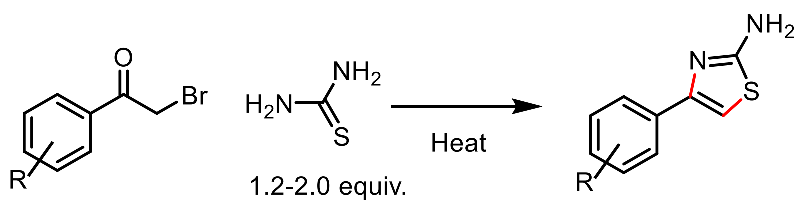
- Hantzsch thiazole synthesis



84%

famotidine (Pepcid)

J. Am. Chem. Soc. **1946**, *68*, 2155-2159
US 4283408 (Filed date: Dec. 27, 1979)



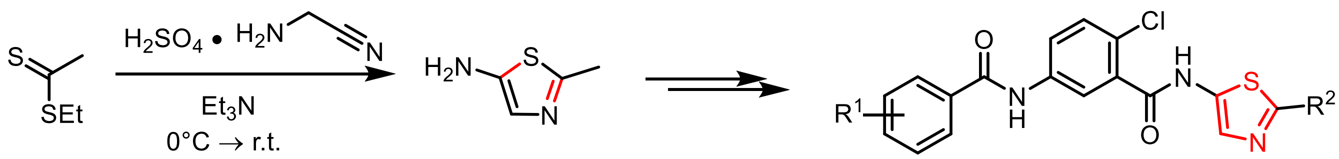
73-86%

Synthesis ***2016***, *48*, 437-440

R	2-Amino-thiazole	Proportion (**1**/**2**)	Time	Yield (%)	Mp (°C)
4-OMe	**3a**	2:1	instant	83	229–231
4-F	**3b**	1.2:1	10 s	73	236–238
4-Me	**3c**	2:1	20 s	80	286–287
4-NO_2	**3d**	2:1	instant	86	235–238
4-Cl	**3e**	2:1	15 s	79	236–239
4-Br	**3f**	2:1	instant	85	225–227
H	**3g**	1.2:1	10 s	77	220–222
4-CN	**3h**	2:1	instant	69	222–224

Construction of Thiazole in Med Chem

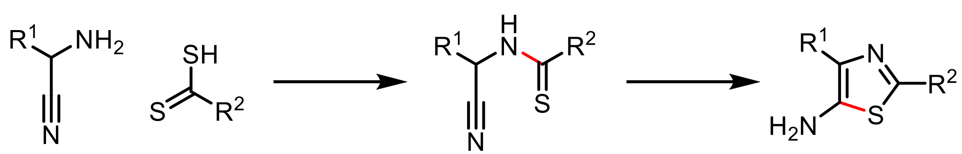
- Cook-Heilbron thiazole synthesis



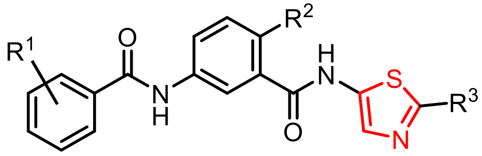
R^1= 3-CF_3, 3-Cl, 3,5-Me, etc

R^2= H, Me, *i*Pr,

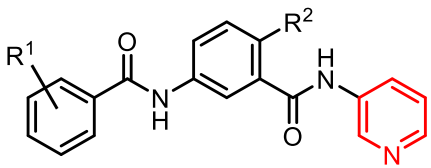
Bioorg. Med. Chem. Lett. **2008**, *18*, 4794-4797



- Selected examples of *In vitro* tests on CSF-1R and Cell activity



	R1	R2	R3	IC_{50} (CSF-1R) nM	IC_{50} (Cell) nM
1	3-CF_3	Me	Me	10	110
2	3-CF_3	Cl	Me	7	50
3	3,5-Me	Cl	Me	6	60
4	3-CF_3, 5-Me	Cl	Me	7	11

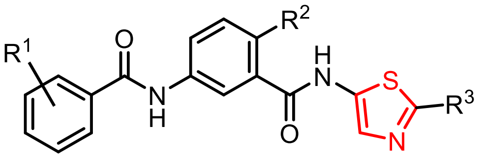


Average IC_{50} (CSF-1R): 13 nM
Average IC_{50} (Cell): 413 nM

D. A. Scott et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4794-4797

Biological Activities

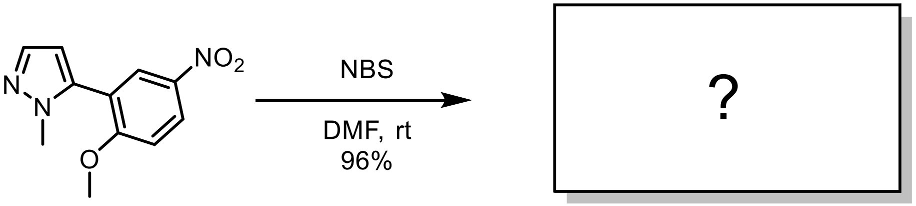
- *In vivo* tests on pCSF-1R



	R1	R2	R3	% Inhibition (2 h)	% inhibition (6 h)
1	3-CF_3	Cl	Me	70	35
2	3,5-Me	Cl	Me	90	60
3	3-CF_3, 5-Me	Cl	Me	100	100

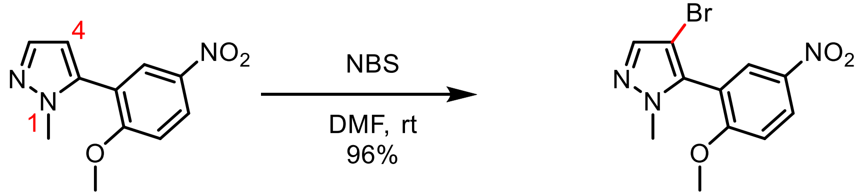
D. A. Scott et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4794-4797

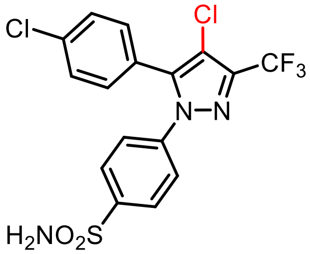
- Regioselectivity of electrophilic substitution on pyrazole



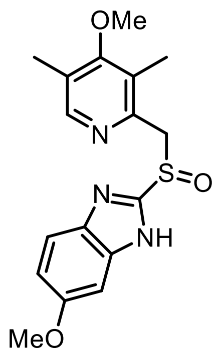
Answers

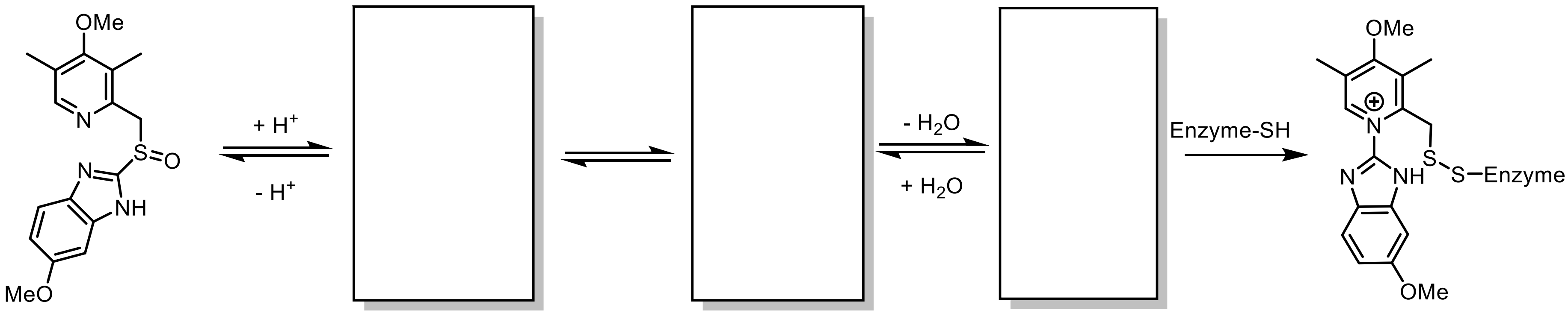
- Regioselectivity of electrophilic substitution on pyrazole



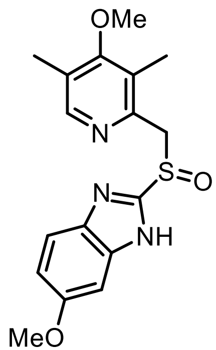


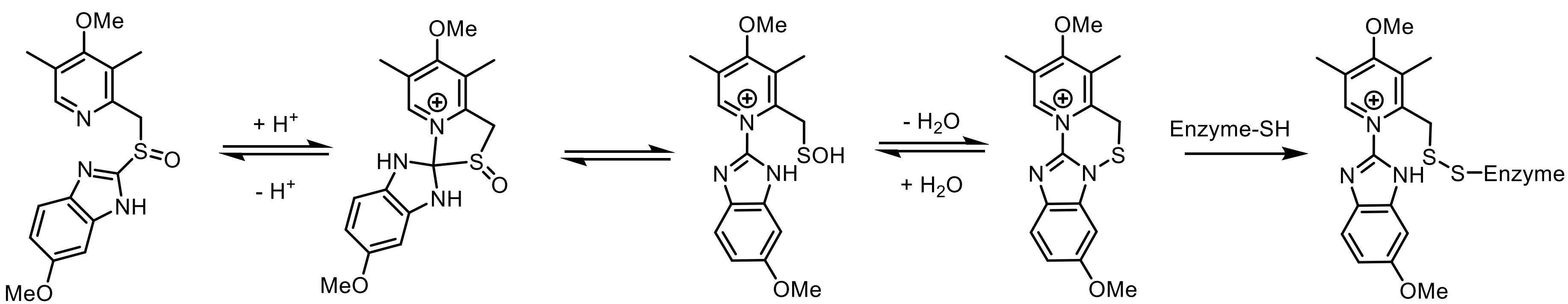
- Guess the reaction of esomeprazole in acidic condition



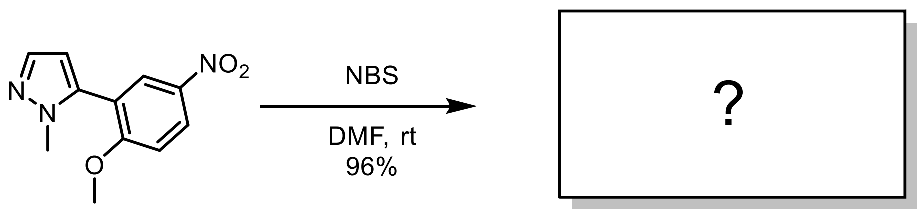


- Guess the reaction of esomeprazole in acidic condition

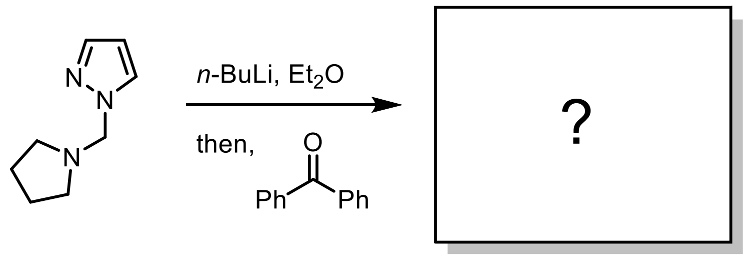




- Regioselectivity of electrophilic substitution on pyrazole

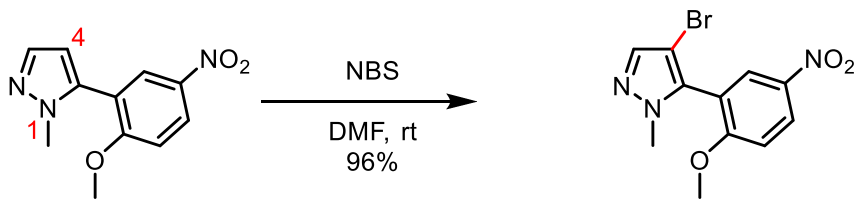


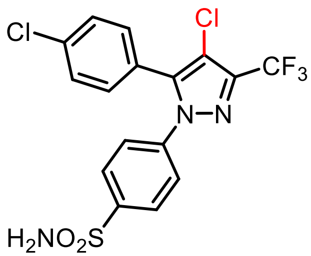
- Regioselectivity of metallation on 1-substituted pyrazole



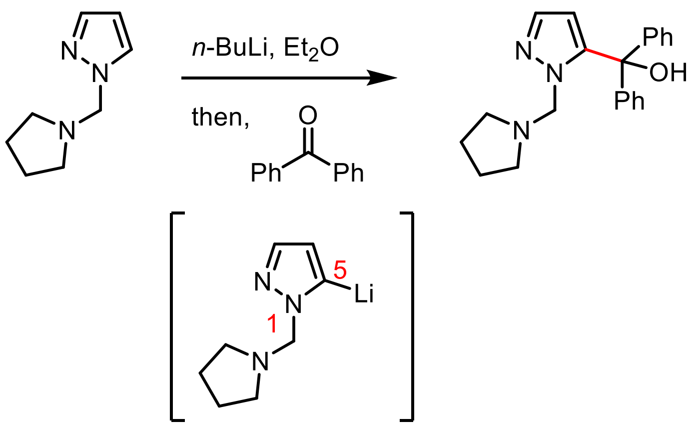
Answers

- Regioselectivity of electrophilic substitution on pyrazole

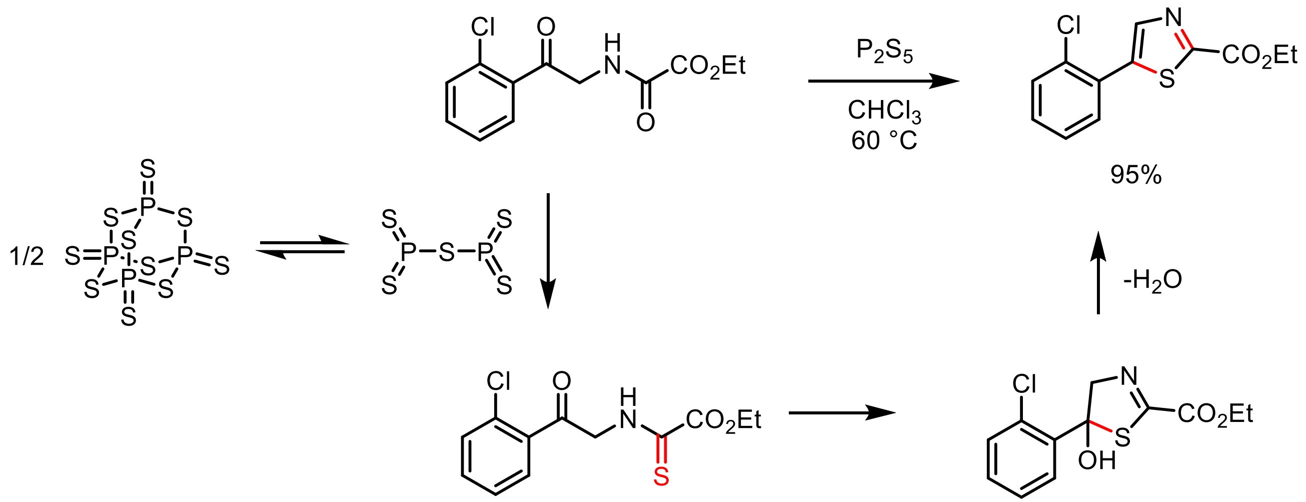




- Regioselectivity of metallation on 1-substituted pyrazole



- Gabriel thiazole synthesis



Bioorg. Med. Chem. Lett. **2005**, *15*, 2481-2486