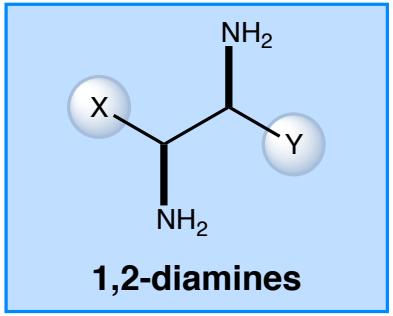
1,2-Diamines: Synthesis and Utility



1,2-diamines

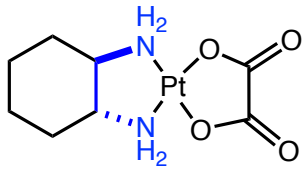
Wei Li

MacMillan Group Meeting

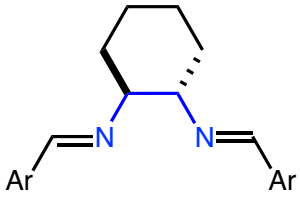
November 6, 2013

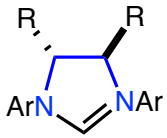
1,2-Diamines: Synthesis and Utility

- part 1: importance

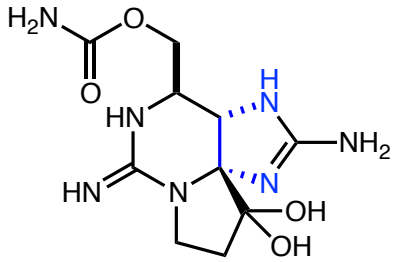


Medicinal agents



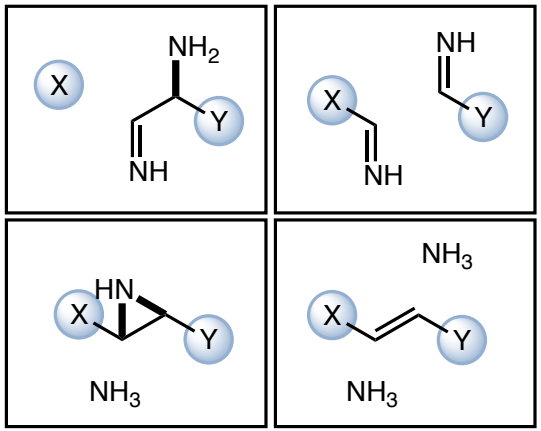


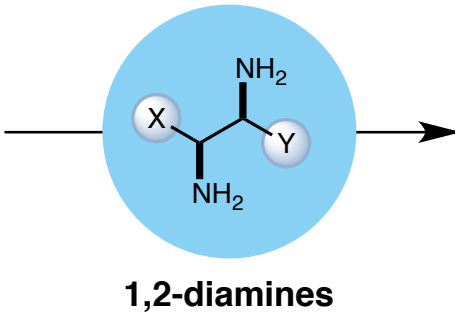
Ligands in catalysis



Natural product

- part 2: synthetic methods



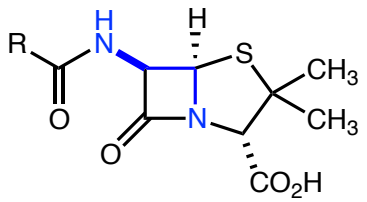


1,2-diamines

- part 3: utilization
  - resolution
  - chiral auxiliaries
  - chiral ligands
  - natural product synthesis
  - medicinal use

Importance of 1,2-Diamines in Chemical Fields

- Penicillin



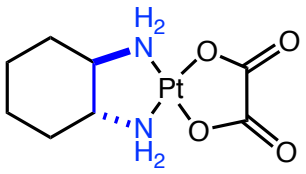
- **Penicillin: a group of antibiotics**
- *Penicillum* fungi
- Discovered by Sir Alexander Fleming in 1928
- Fleming, Florey and Chain - Nobel Prize, 1945
- saved millions of people from baterial infection

" When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bateria killer, but I suppose that was exactly what I did"

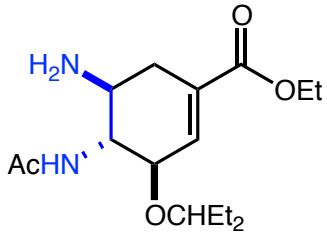
- Sir Alexander Fleming

Importance of 1,2-Diamines in Chemical Fields

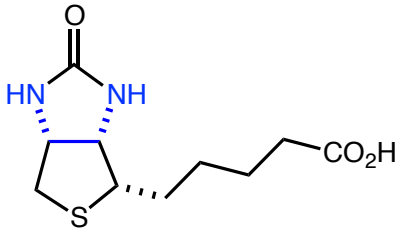
- Medicinal agents



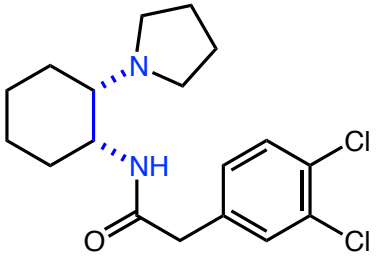
Eloxatin: anticancer drug



Tamiflu: antiviral drug



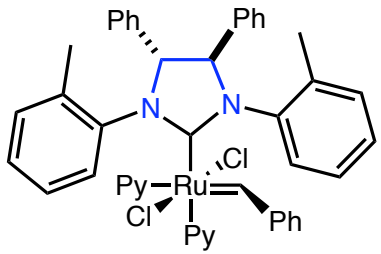
Biotin: vitamin H



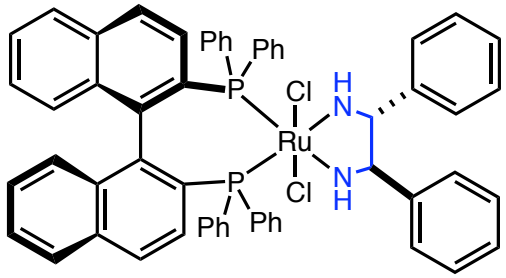
diaminocylcohexane: opioid receptor agonist

Importance of 1,2-Diamines in Chemical Fields

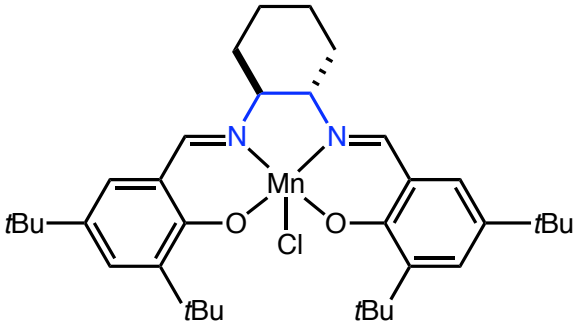
- Ligands in catalysis



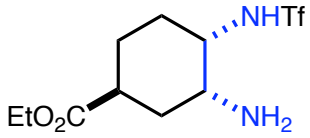
Grubbs metathesis catalyst



Noyori hydrogenation catalyst



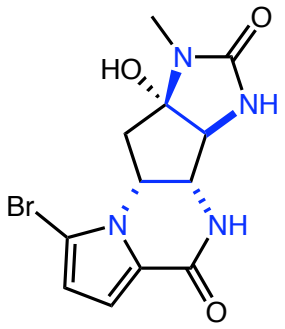
Jacobsen epoxidation catalyst



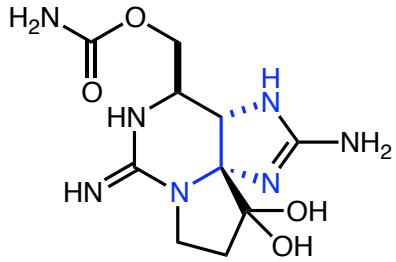
Maruoka organocatalyst

Importance of 1,2-Diamines in Chemical Fields

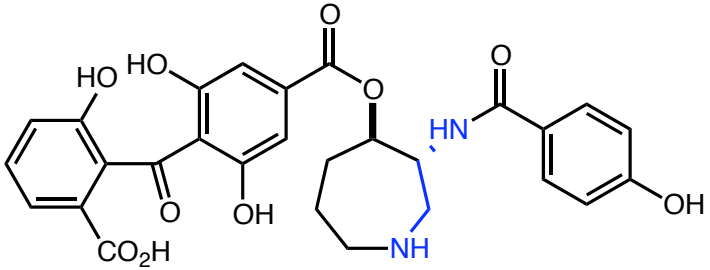
- Structural motif in natural products



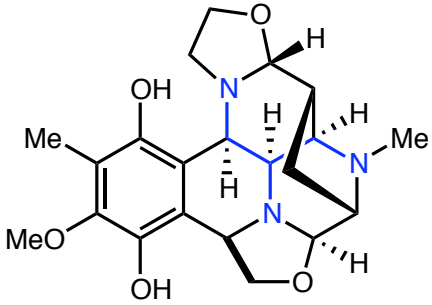
agelastatin A



Sexitoxin



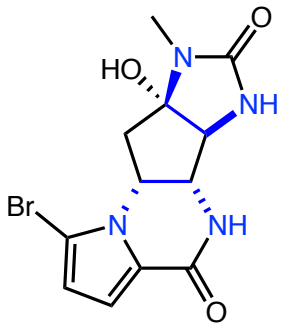
balanol



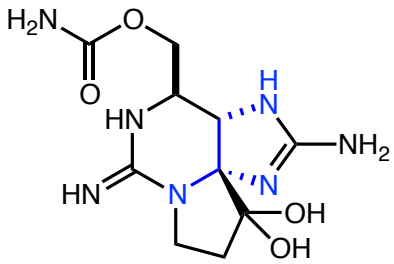
Bioxalomycin α2

Importance of 1,2-Diamines in Chemical Fields

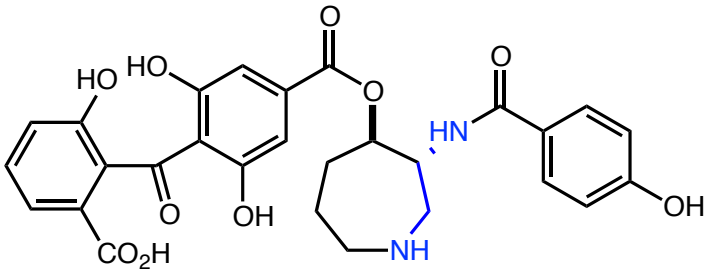
- Structural motif in natural products



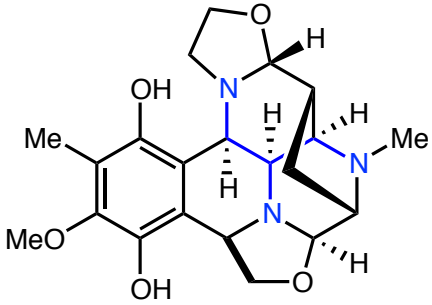
agelastatin A



Saxitoxin



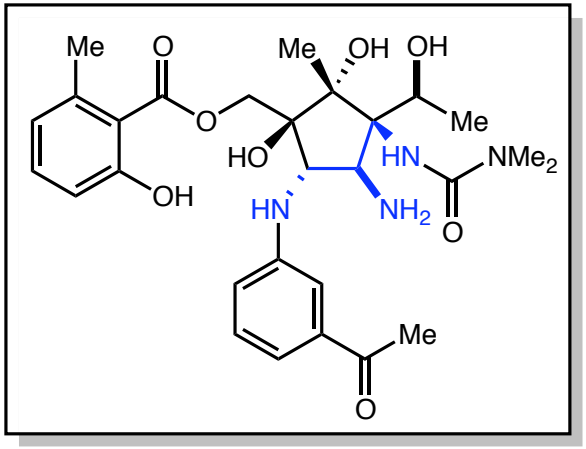
balanol



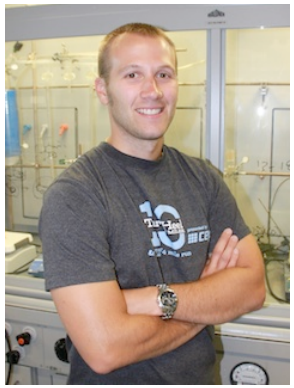
Bioxalomycin α2

Importance of 1,2-Diamines in Chemical Fields

- total synthesis of pactamycin



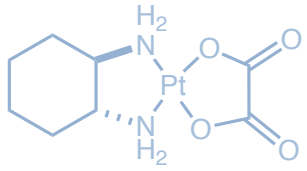
pactamycin



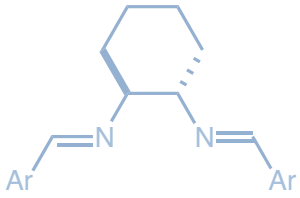
Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science.* **2013,** *340*, 180.

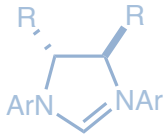
1,2-Diamines: Synthesis and Utility

- part 1: importance

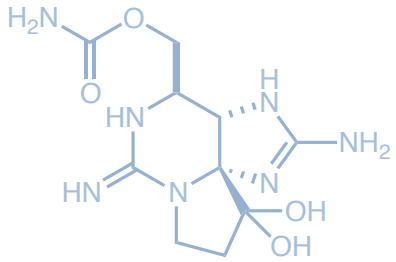


Medicinal agents



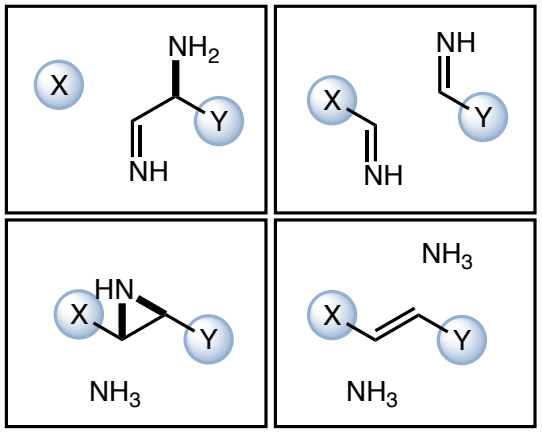


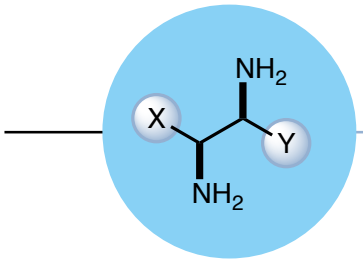
Ligands in catalysis



Natural product

- part 2: synthetic methods

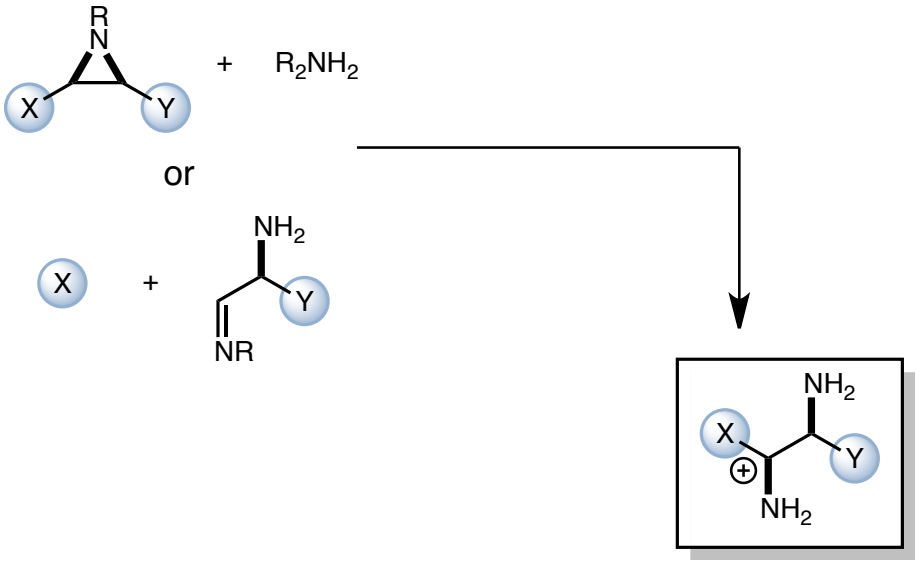




1,2-diamines

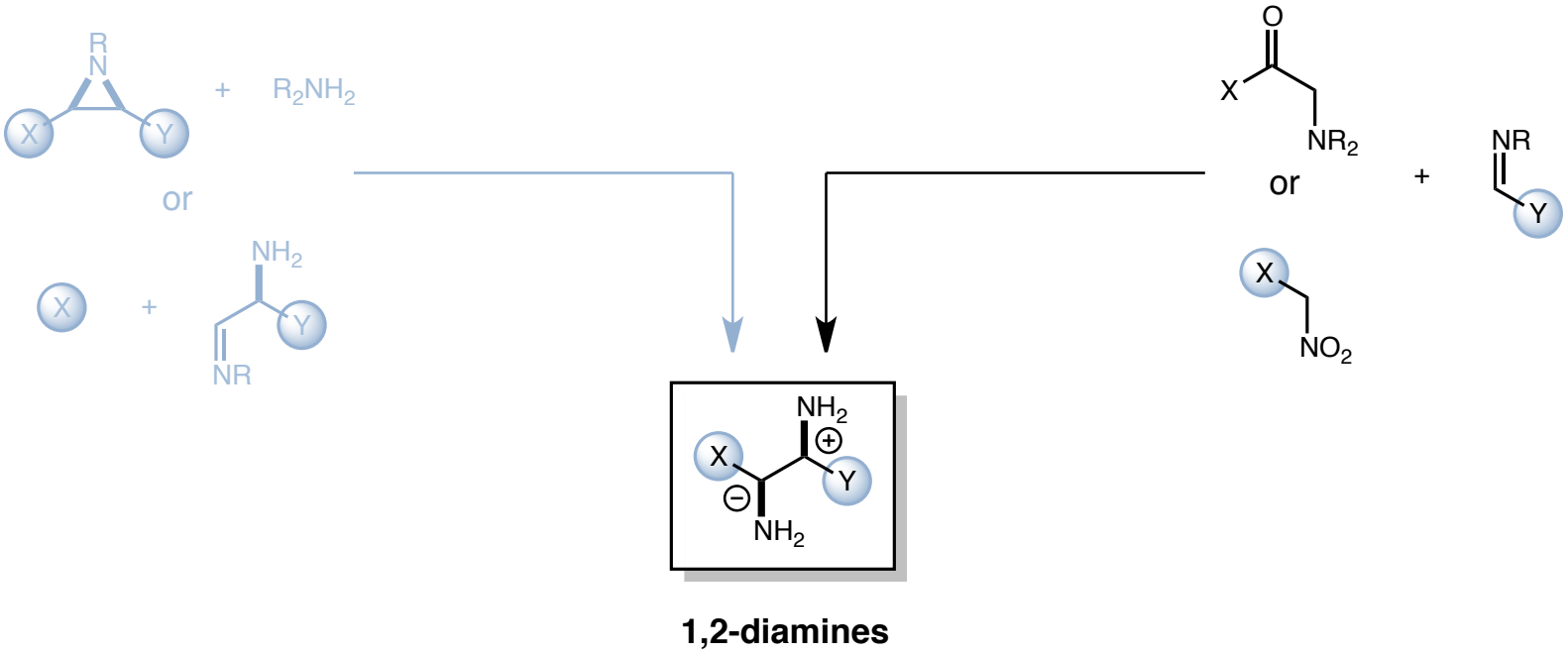
- part 3: utilization
  - resolution
  - chiral auxiliaries
  - chiral ligands
  - natural product synthesis
  - medicinal use

Synthesis of 1,2-Diamines



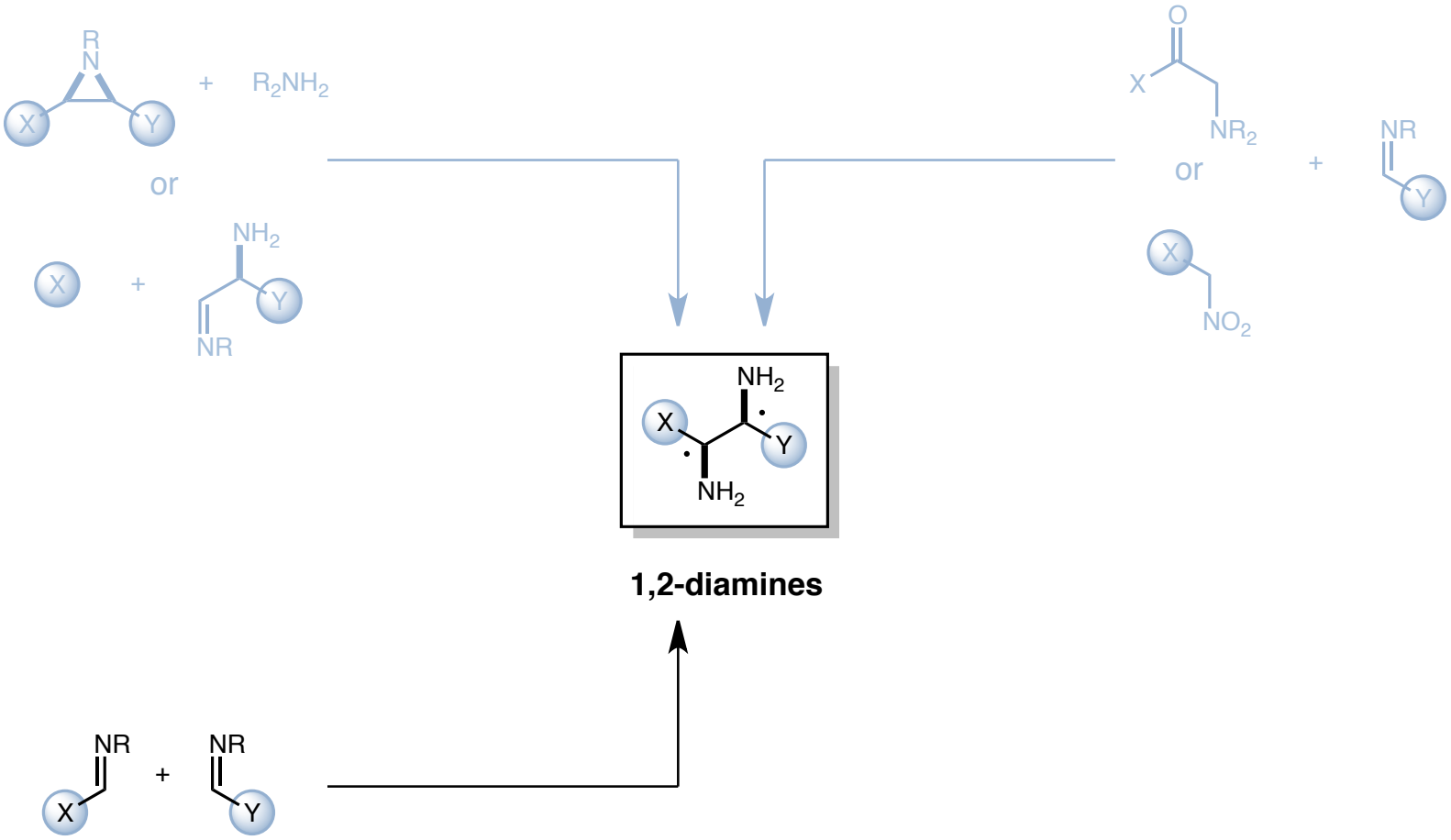
1,2-diamines

Synthesis of 1,2-Diamines

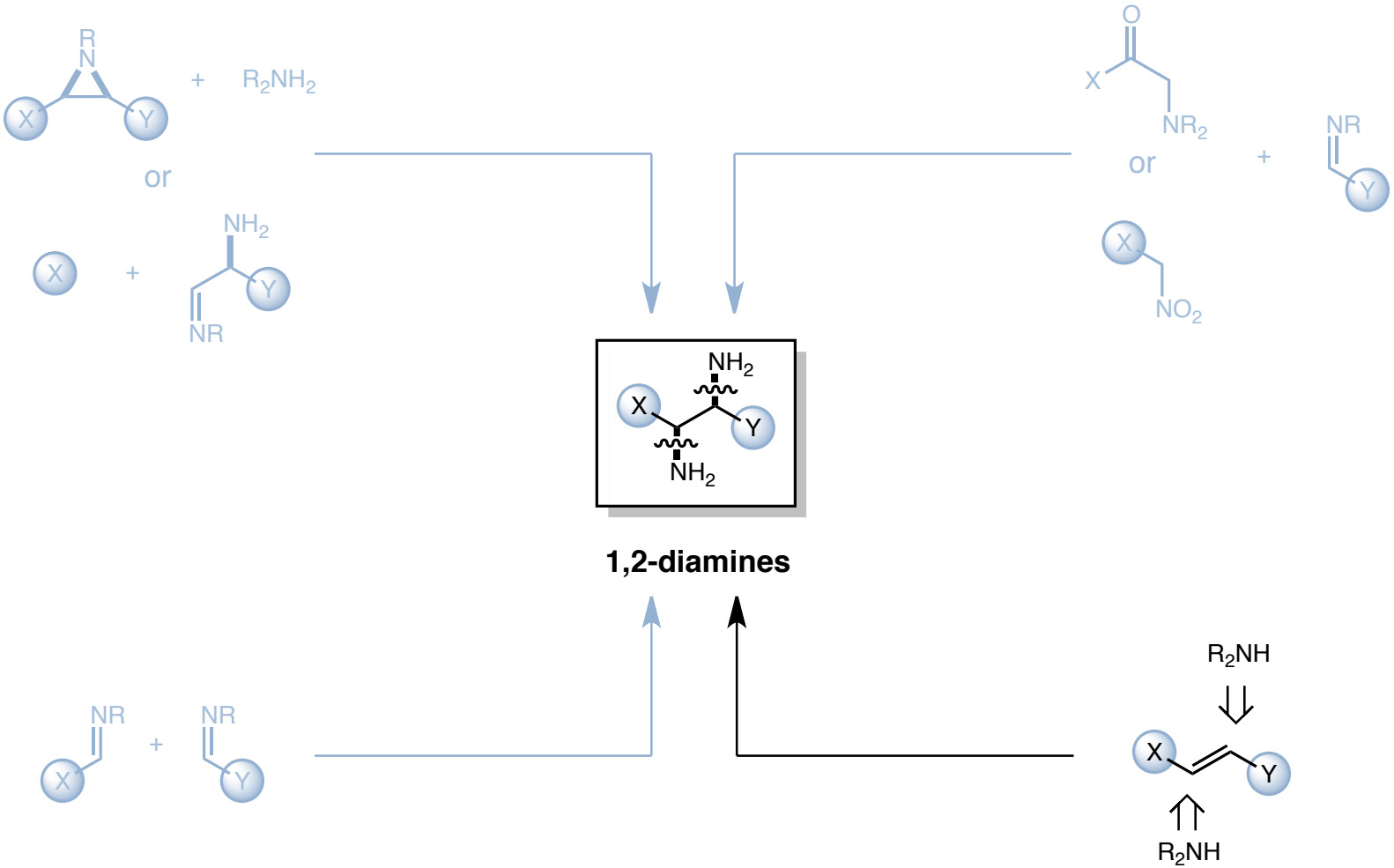


1,2-diamines

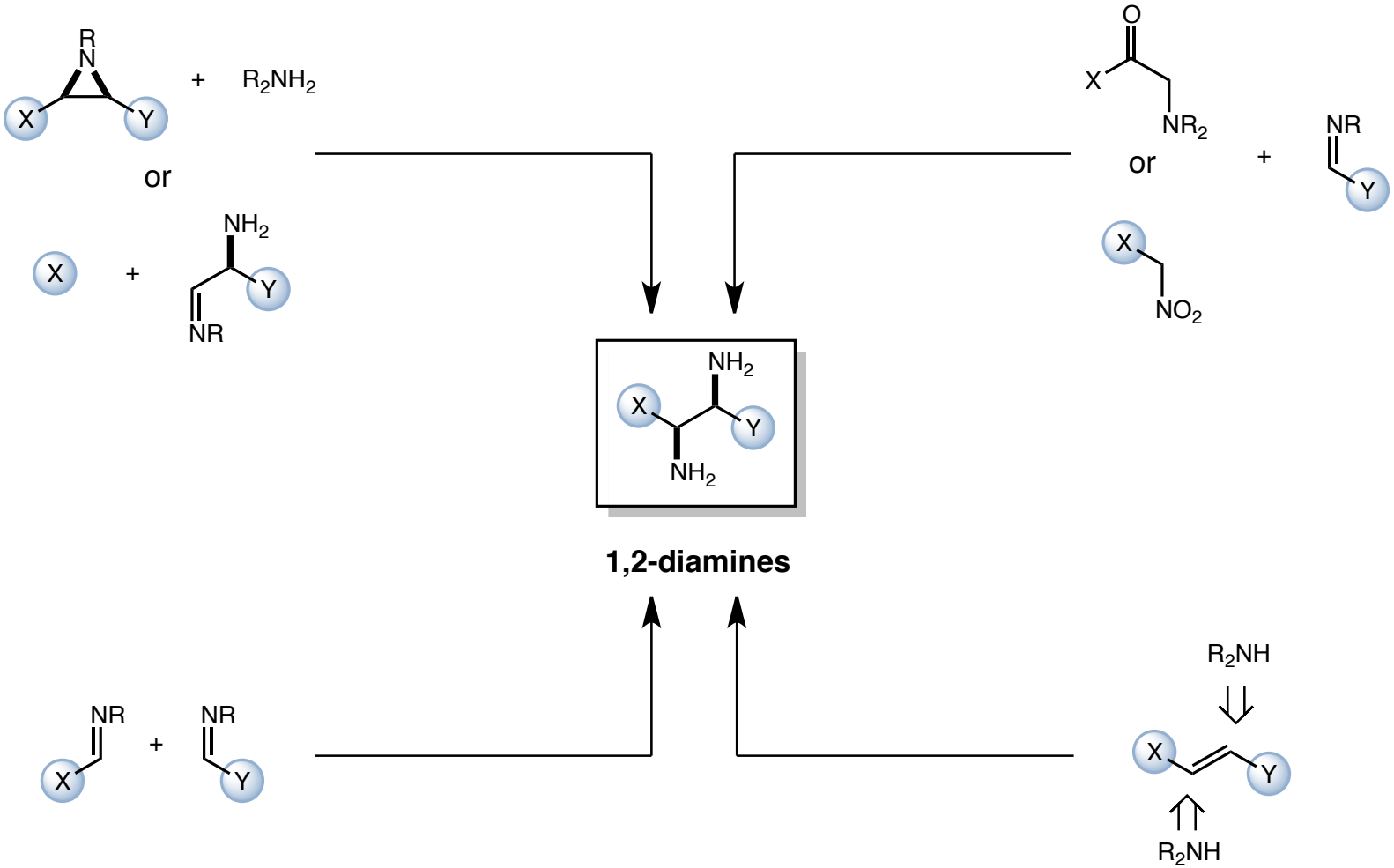
Synthesis of 1,2-Diamines



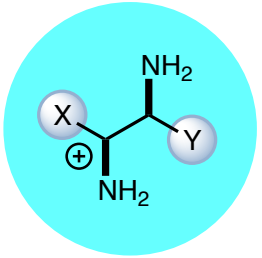
Synthesis of 1,2-Diamines



Synthesis of 1,2-Diamines

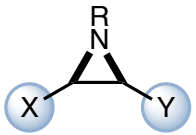


Synthesis of 1,2-Diamines



1,2-diamines

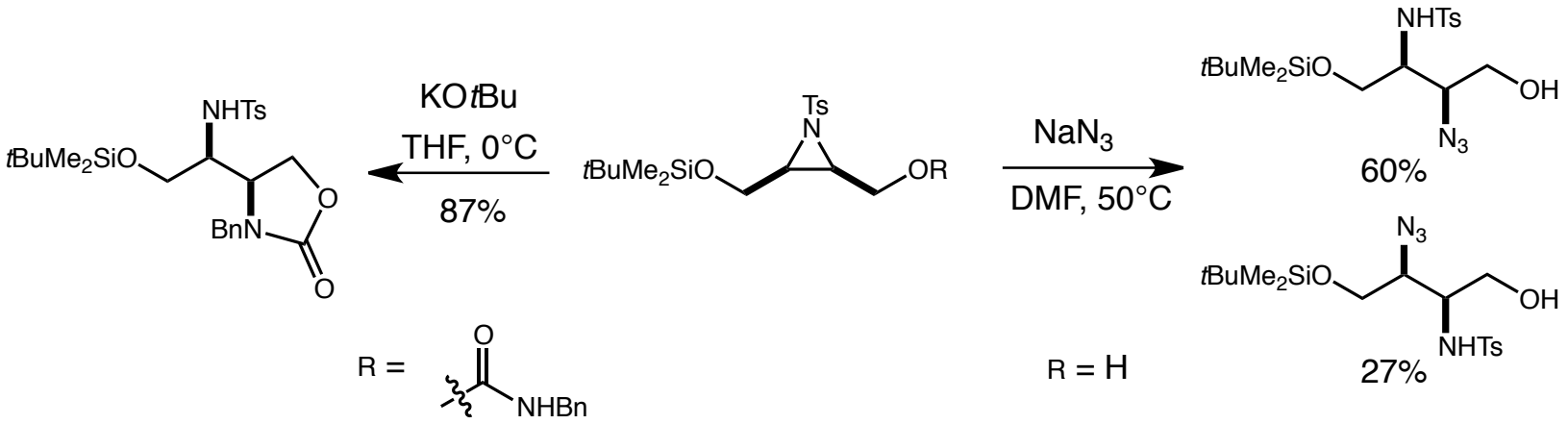
- aziridine openning by nitrogen nucleophiles



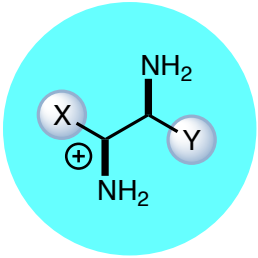
R_2NH

- *N*-aziridines protection is necessary
- "unactivated" aziridines - protonation, or quarternarization, or activation by a Lewis acid
- "activated" aziridines - Ts, Ns, Acyl, etc.
- regioselectivity

- aziridine openning by nitrogen nucleophiles

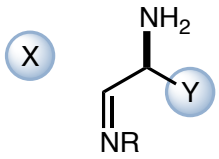


Synthesis of 1,2-Diamines



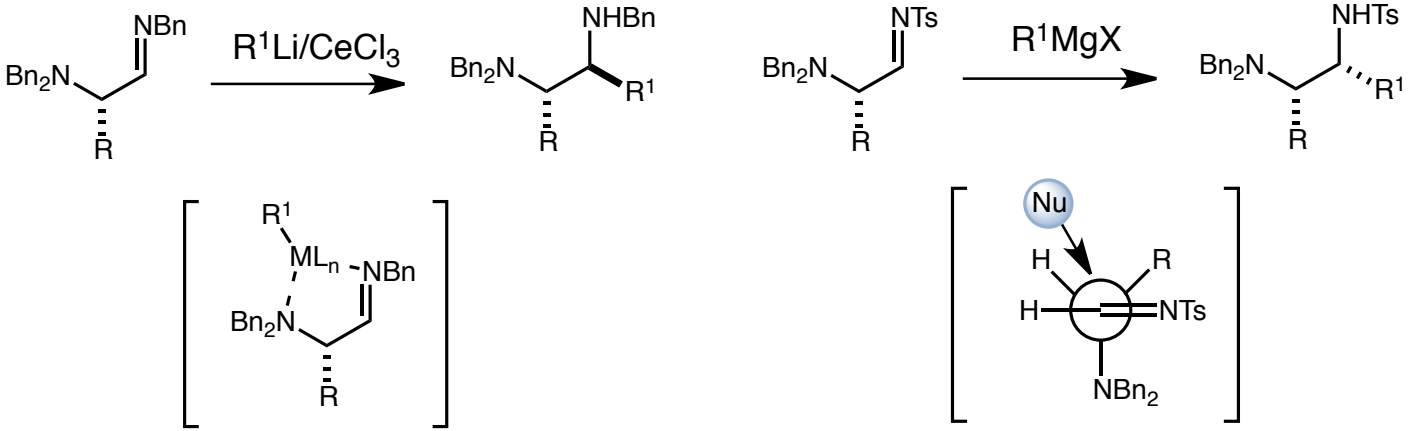
1,2-diamines

- nucleophile addition into α-amino imines



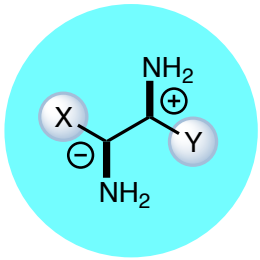
- chiral pool
- chelation control feasible
- non-chelation - Felkin-Anh model
- syn or anti diamine

- access to both syn and anti diamines



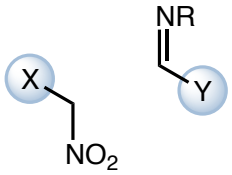
Reetz, M. T.; Jaeger, R.; Drewlies, M.; Hubel, M. *Angew. Chem. Int. Ed.* **1991,***30*, 103.

Synthesis of 1,2-Diamines



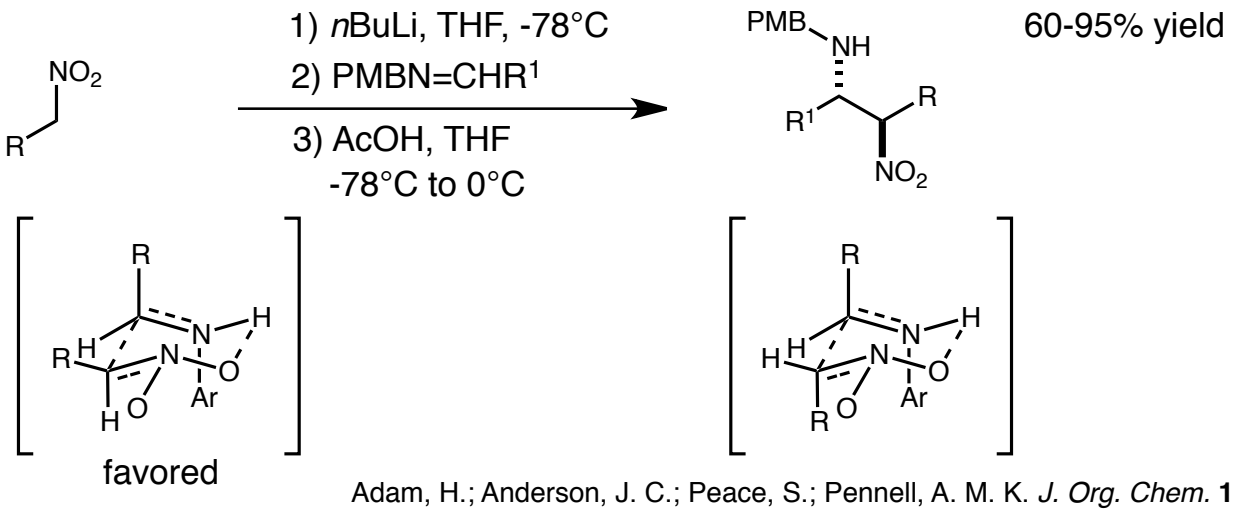
1,2-diamines

- nitro-Mannich or aza-Henry



Noble, A.; Anderson, J. C. *Chem. Rev.* **2013,***113*, 2887.

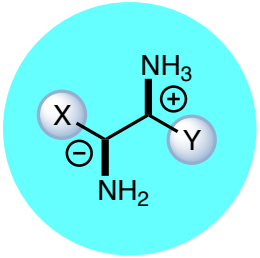
- diastereoselective example - Anderson



60-95% yield

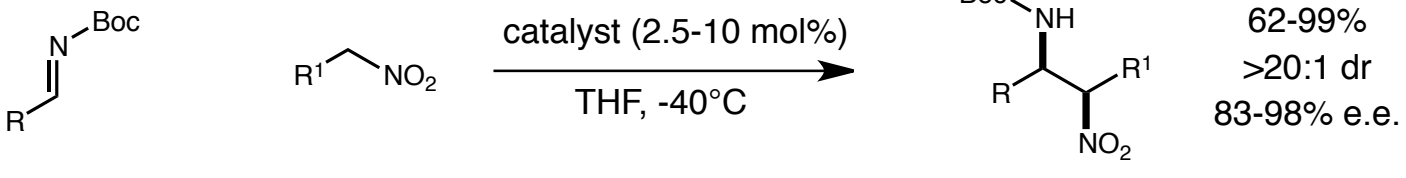
Adam, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998,** *63*, 9932.

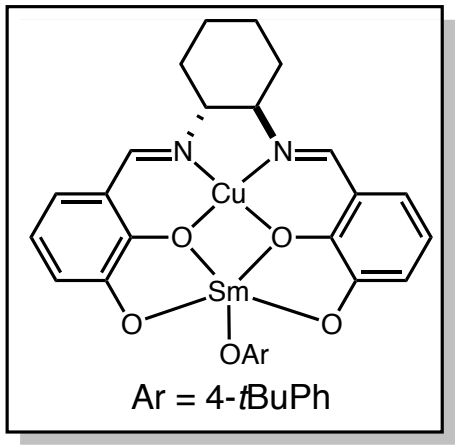
Synthesis of 1,2-Diamines



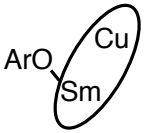
1,2-diamines

- enantioselective ***syn*** nitro-Mannich reaction - Shibasaki

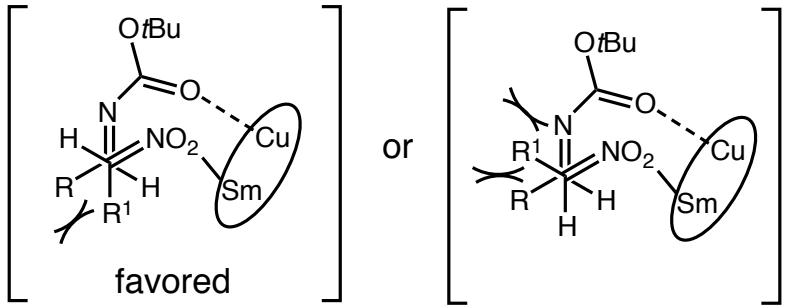




catalyst

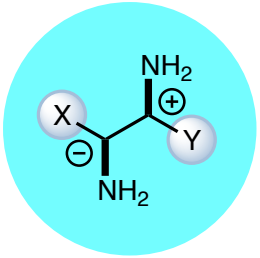


catalyst



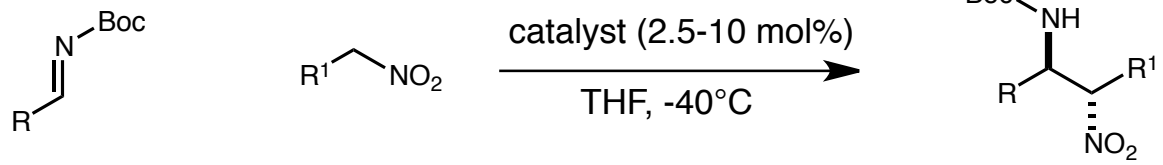
Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007,***129*, 4900.
Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010,***132*, 4925.

Synthesis of 1,2-Diamines

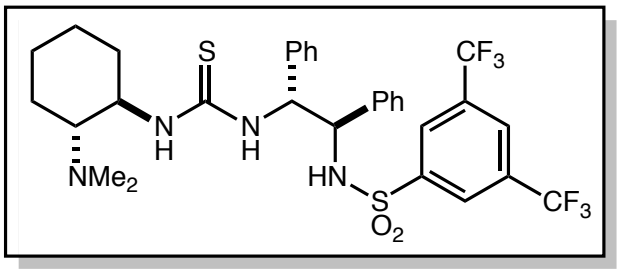


1,2-diamines

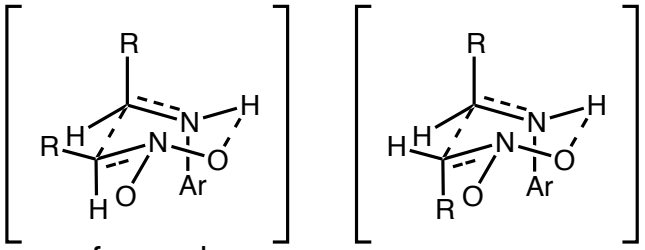
- enantioselective ***anti*** nitro-Mannich reaction - Wang



85-99%
>93:7 dr
96-99% e.e.



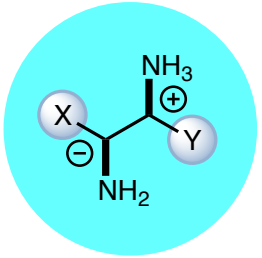
catalyst



favored

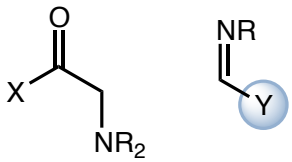
Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue. Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008,***130*, 8606.

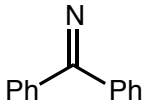
Synthesis of 1,2-Diamines



1,2-diamines

- Mannich reaction of α-aminol carbonyl with imines

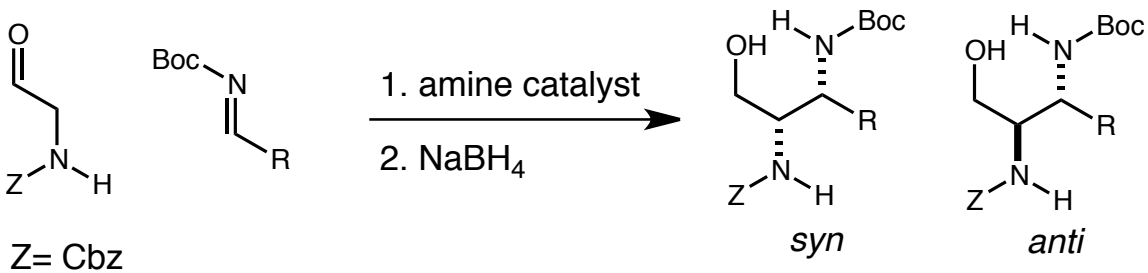


- NR_2 is often 

- *Syn*-diastereoselectivity
- both syn and anti can be obtained
- enantioselective processes - well precedented

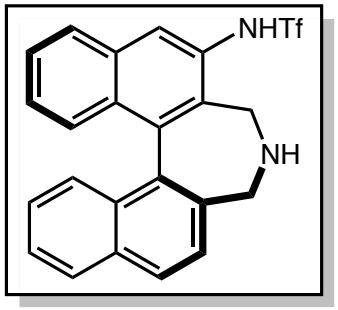
Arrayas. R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009,***38*, 1940.

- recent examples - Maruoka



L-proline : *syn* major, > 98% ee

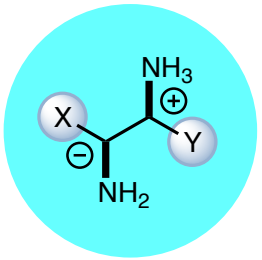
(S)-**1** : *anti* major, > 97% ee



(S)-**1**

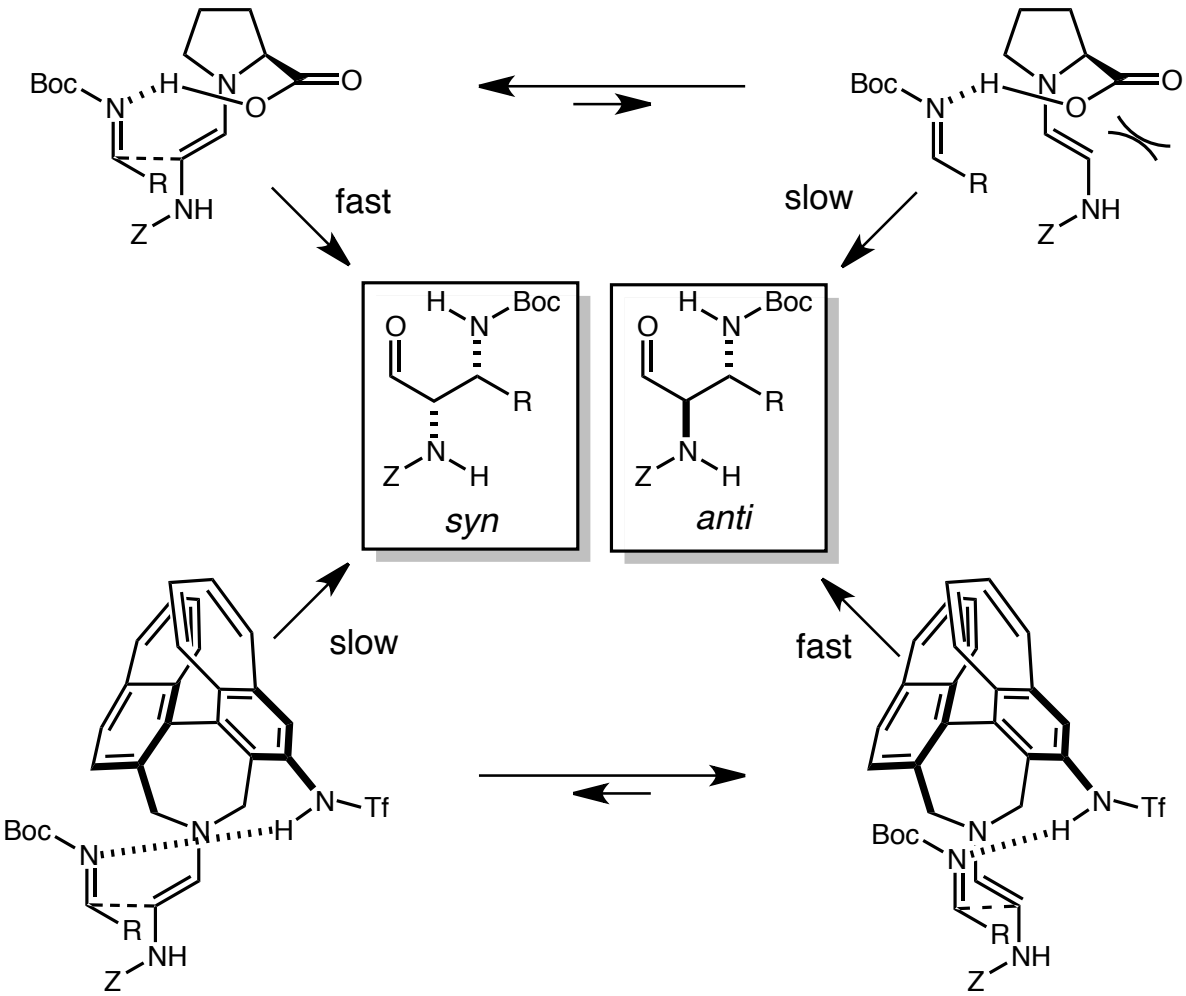
Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012,** *134*, 7516.

Synthesis of 1,2-Diamines



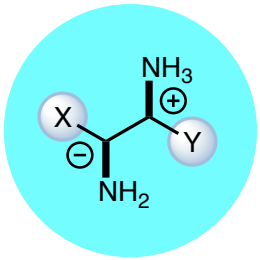
1,2-diamines

- stereoselectivity rationale



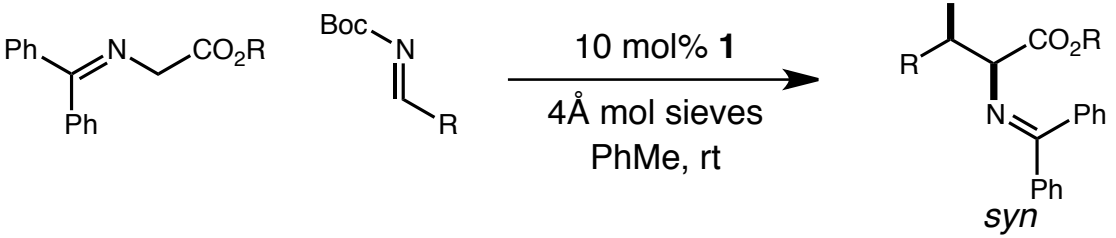
Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012,** *134*, 7516.

Synthesis of 1,2-Diamines



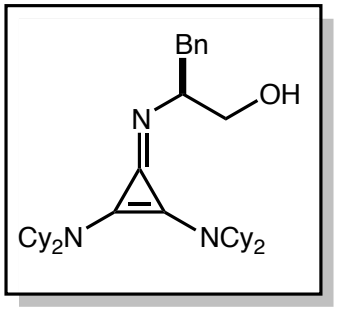
1,2-diamines

- Mannich reaction glycine ester Schiff bases with imines - Lambert



- gram scale
- alkyl and aryl imines

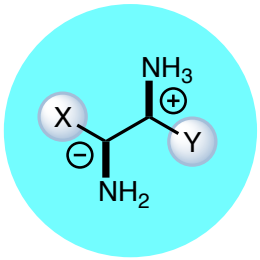
63-99% yield
>91:9 dr
38-97% ee



1

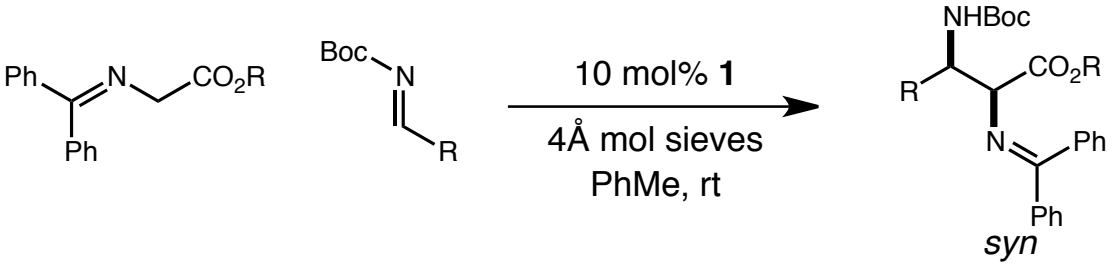
Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013,** *135*, 11799.

Synthesis of 1,2-Diamines



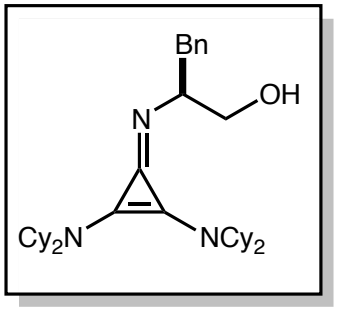
1,2-diamines

- Mannich reaction glycine ester Schiff bases with imines - Lambert



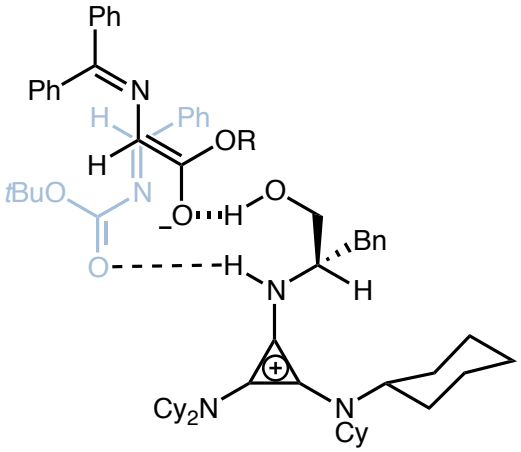
- gram scale
- alkyl and aryl imines

63-99% yield
>91:9 dr
38-97% ee



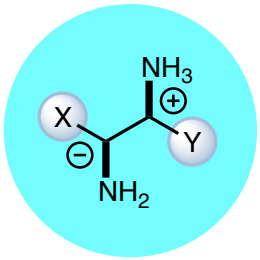
1

- Stereochemical rationale



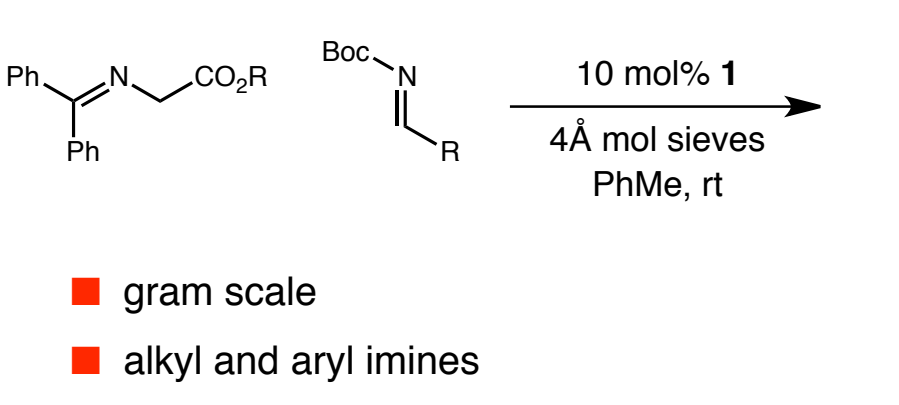
Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013,** *135*, 11799.

Synthesis of 1,2-Diamines



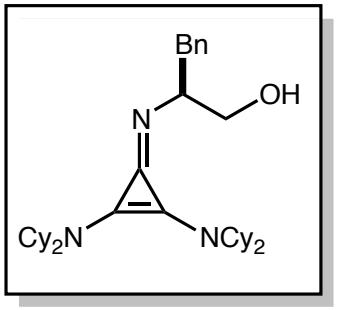
1,2-diamines

- Mannich reaction glycine ester Schiff bases with imines - Lambert



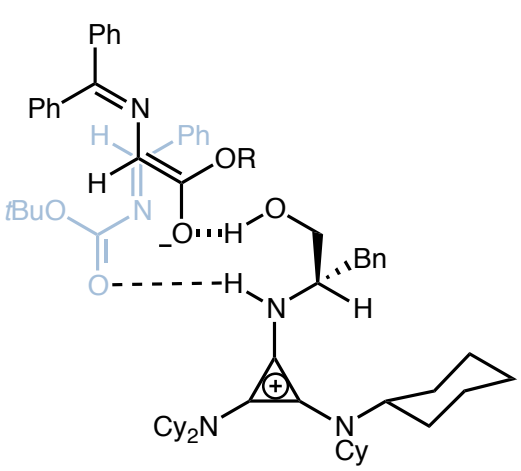
- gram scale
- alkyl and aryl imines

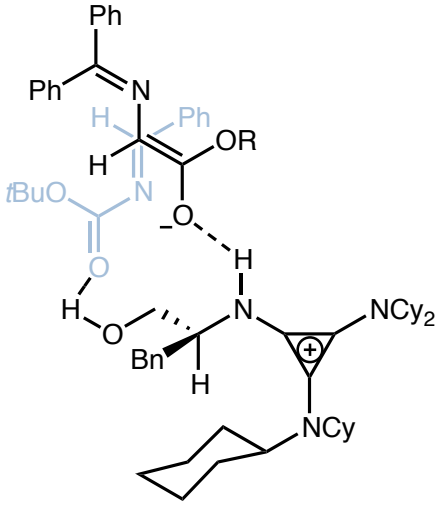
63-99% yield
>91:9 dr
38-97% ee



1

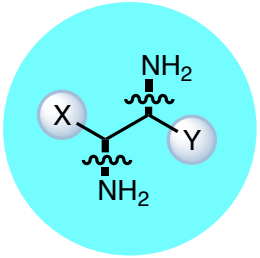
- Stereochemical rationale





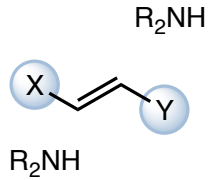
Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013,** *135*, 11799.

Synthesis of 1,2-Diamines



1,2-diamines

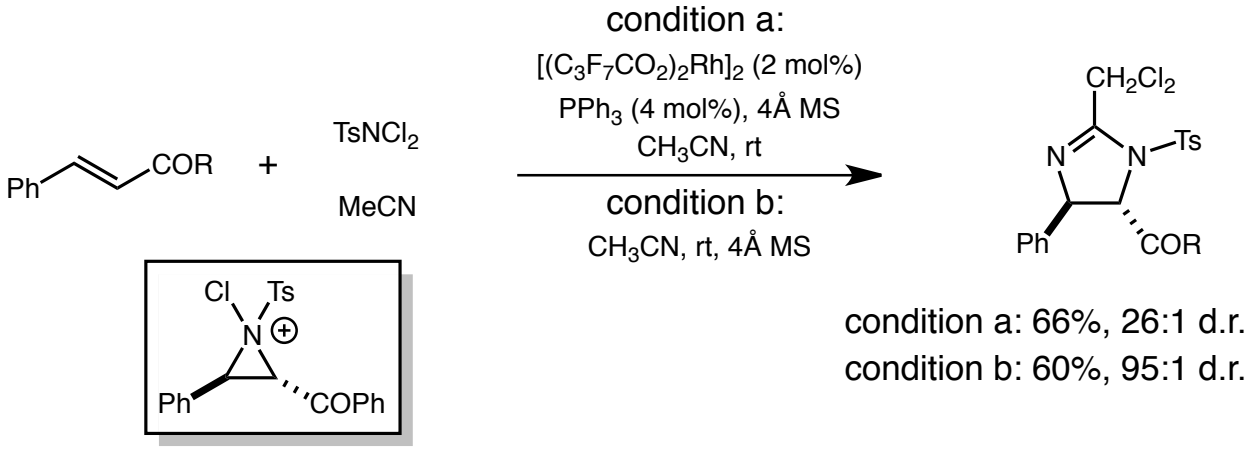
- transition metal catalyzed 1,2-diamination of alkenes



- stoichimetric examples with Osmium (VIII)
- relatively young field for catalytic processes
- alkene stereochemistry - product
- enantioselective processes are known

Muñiz, K. *New J. Chem.* **2005,** *29*, 1371.
Cardona, F.; Goti, A. *Nature Chemistry.* **2009,** *1*, 269.

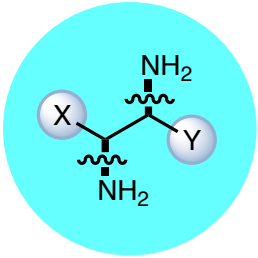
- early examples - Li



condition a: 66%, 26:1 d.r.
condition b: 60%, 95:1 d.r.

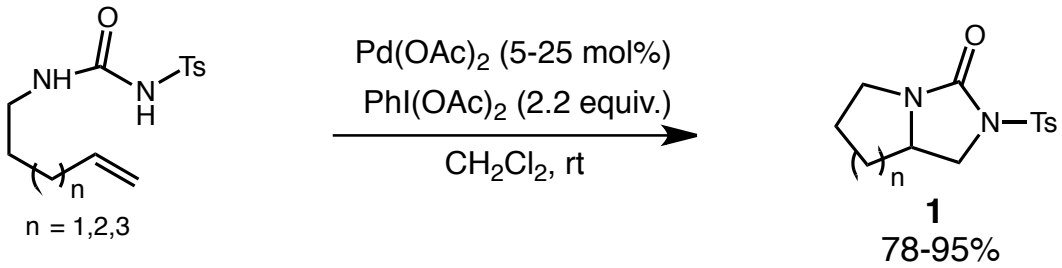
Li, G.; Wie, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem. Int. Ed.* **2001,** *40*, 4277.
Chen, D.; Timmons, C.; Wei, H.-X.; Li, G. *J. Org. Chem.* **2003,** *68*, 5742.

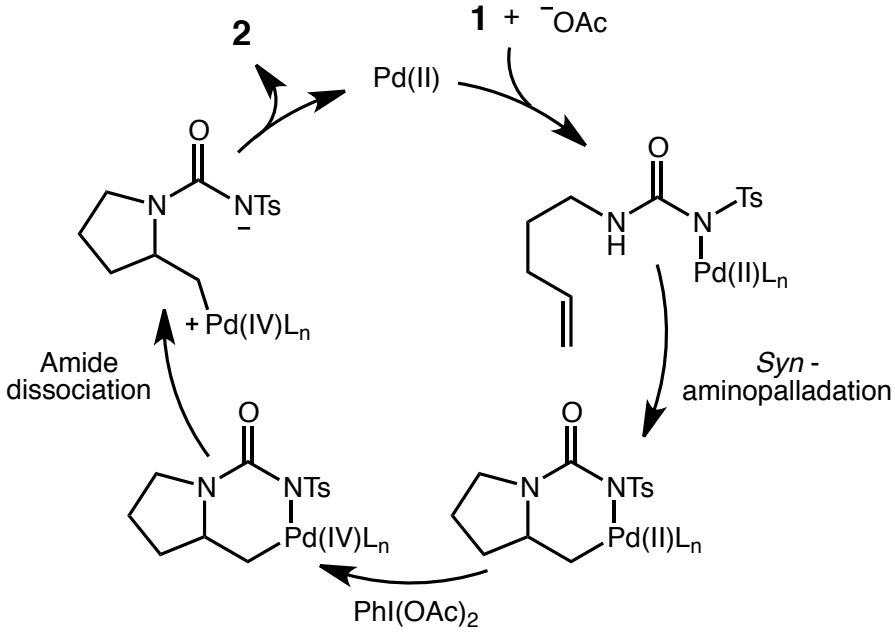
Synthesis of 1,2-Diamines



1,2-diamines

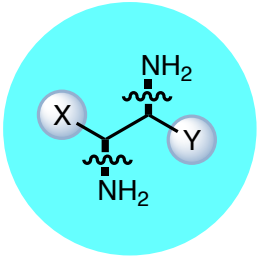
- metal-catalyzed intramolecular 1,2-diamination





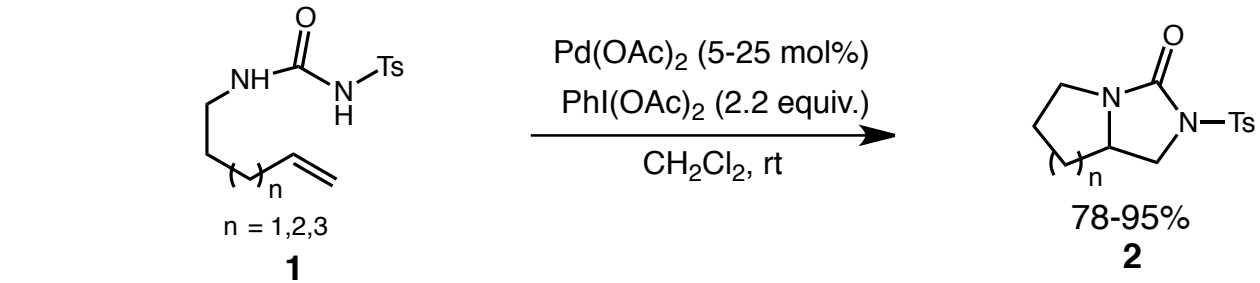
Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005,** *127*, 14586.

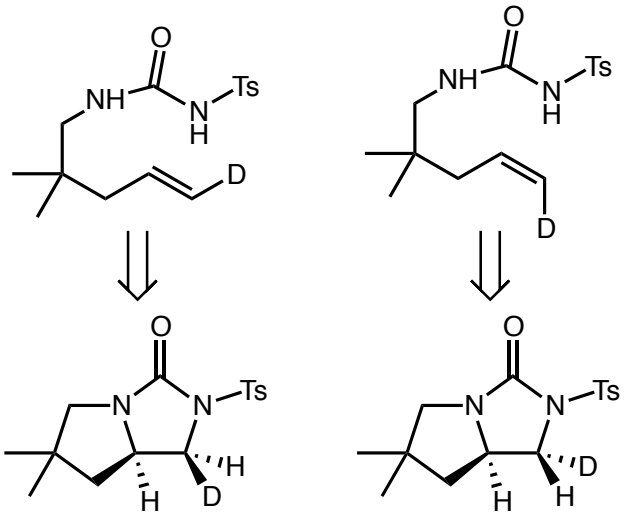
Synthesis of 1,2-Diamines



1,2-diamines

- *syn*-aminopalladation mis-assignment





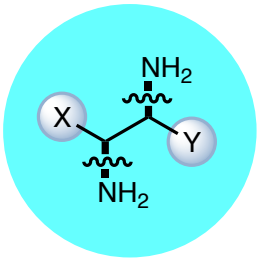
2005: J_{trans} = 8.6 Hz

2008: J_{cis} = 8.8 Hz J_{trans} = 4.4 Hz

Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005,** *127*, 14586.

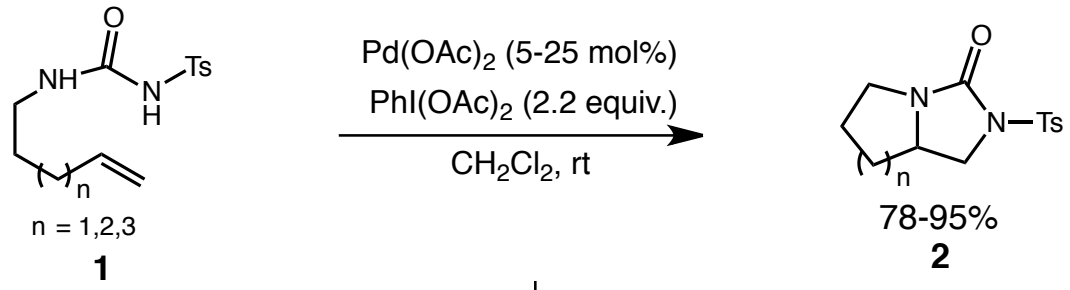
Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008,** *130*, 763.

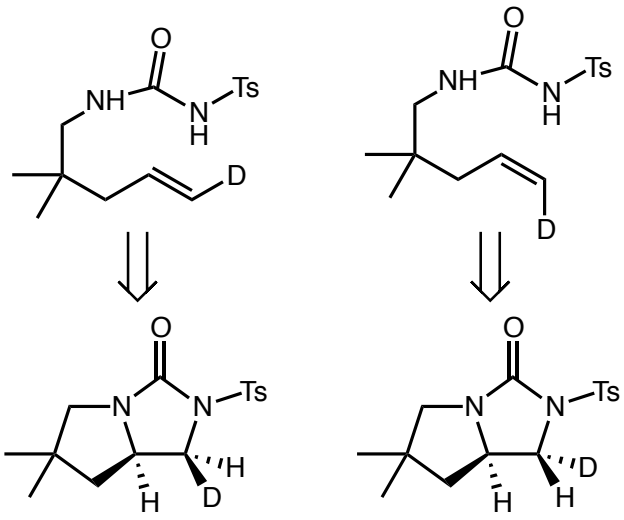
Synthesis of 1,2-Diamines



1,2-diamines

- *syn*-aminopalladation mis-assignment





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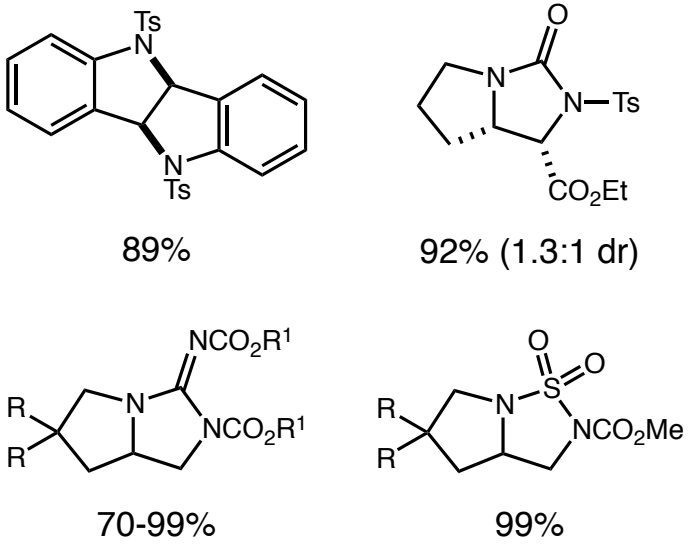
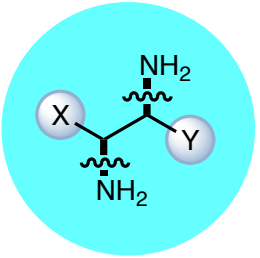


Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005,** *127*, 14586.

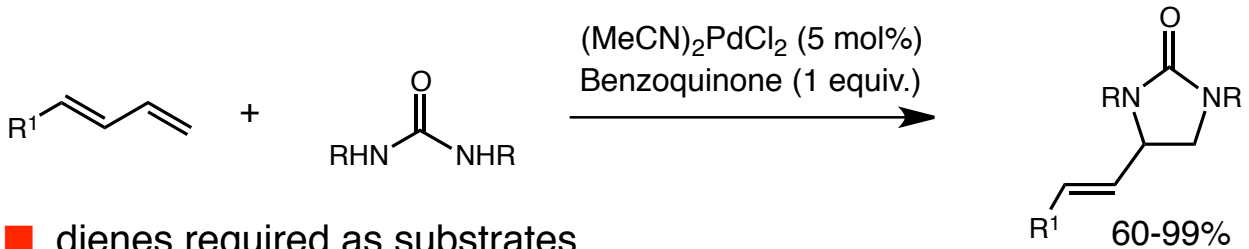
Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008,** *130*, 763.

Synthesis of 1,2-Diamines



1,2-diamines

- metal catalyzed intermolecular 1,2-diamination of alkenes

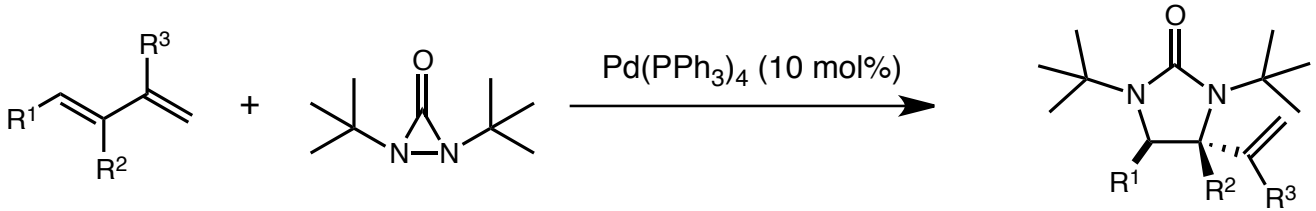


60-99%
>95% alkene regioselectivity

- dienes required as substrates
- least substituted alkene

Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005,** *127*, 7308.

- diaziridinone as source of diamine

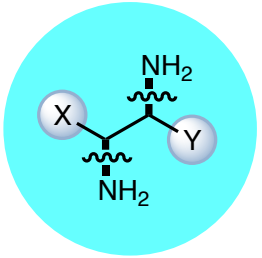


46-95%
>95% dr
>95% alkene regioselectivity

- no external oxidant necessary
- highly stereospecific
- more substituted alkenes

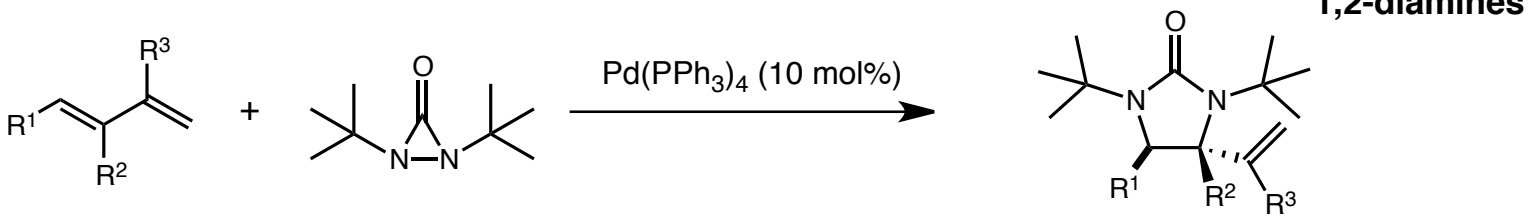
Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007,** *129*, 763.

Synthesis of 1,2-Diamines



1,2-diamines

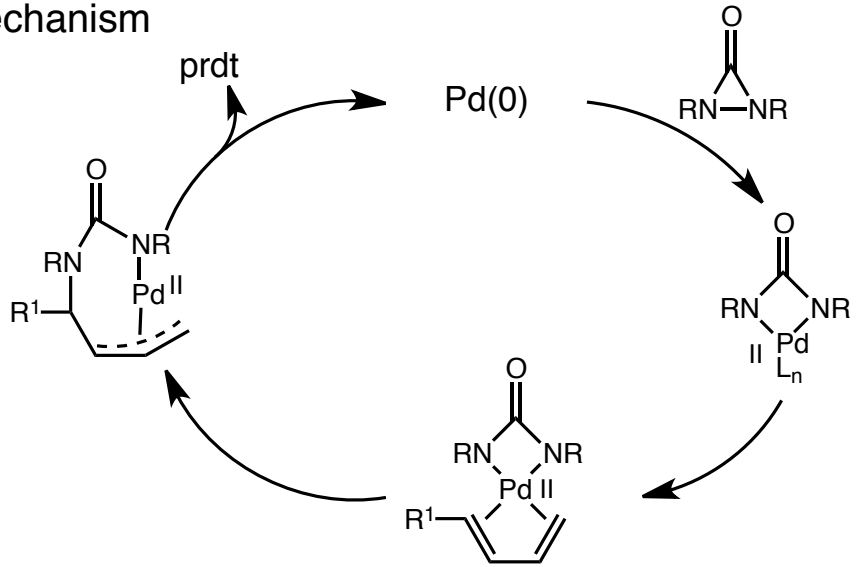
- metal catalyzed intermolecular 1,2-diamination of alkenes



46-95%
>95% dr
>95% alkene regioselectivity

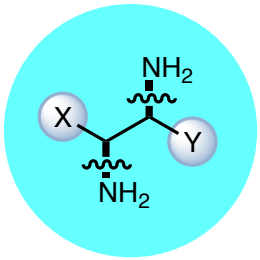
- no external oxidant necessary
- highly stereospecific
- more substituted alkenes

- proposed mechanism



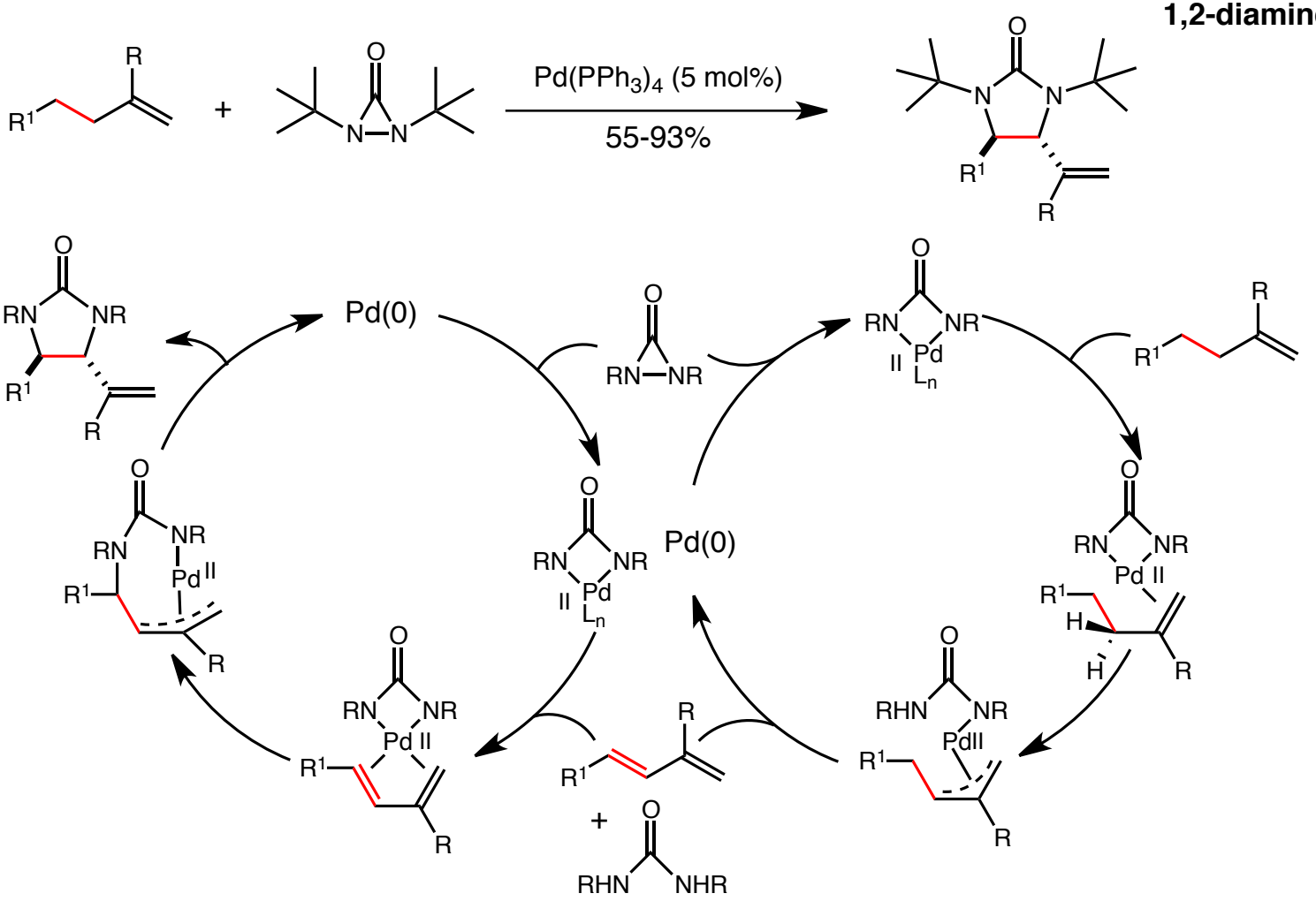
Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007,** *129*, 763.

Synthesis of 1,2-Diamines



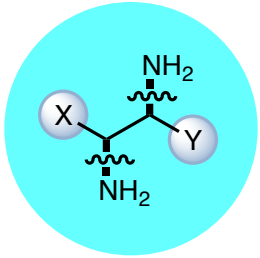
1,2-diamines

- 1,2-diamination of alkenes



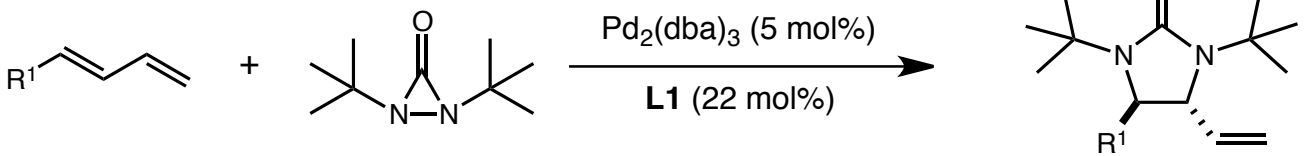
Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007,** *129*, 763.

Synthesis of 1,2-Diamines



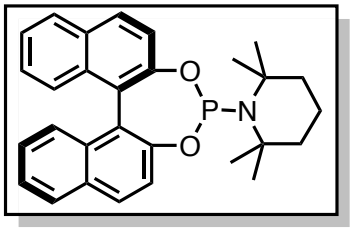
1,2-diamines

- enantioselective 1,2-diamination of alkenes



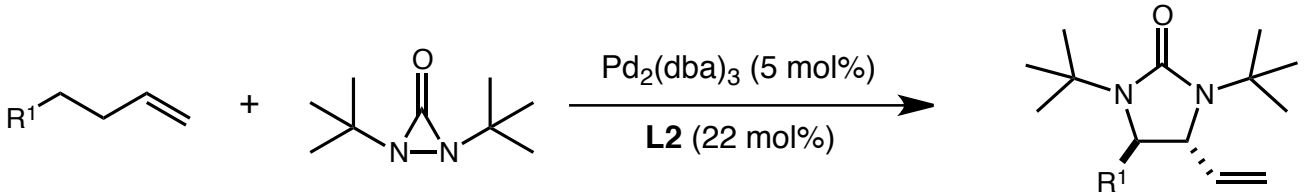
60-95%
91-95% e.e.

L1 =



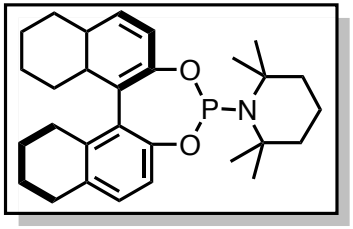
Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007,** *129*, 11688.

- enantioselective allylic and homoallylic diamination of terminal olefins



50-85%
89-94% e.e.

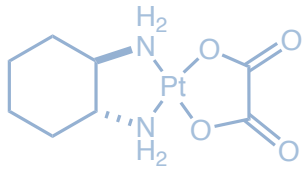
L2 =



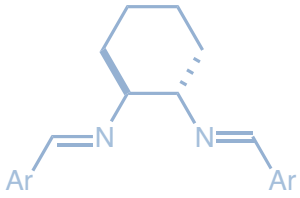
Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008,** *130*, 8590.

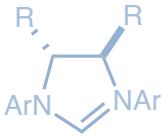
1,2-Diamines: Synthesis and Utility

- part 1: importance

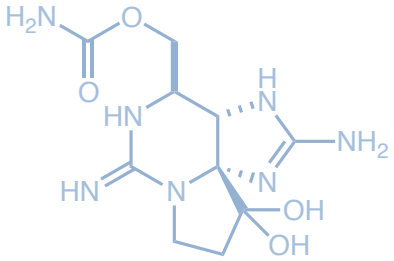


Medicinal agents



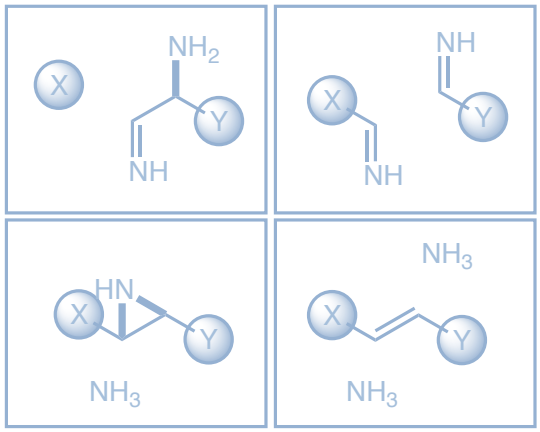


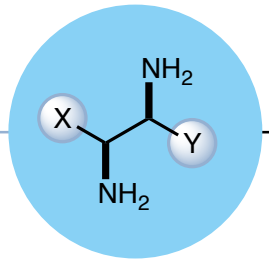
Ligands in catalysis



Natural product

- part 2: synthetic methods



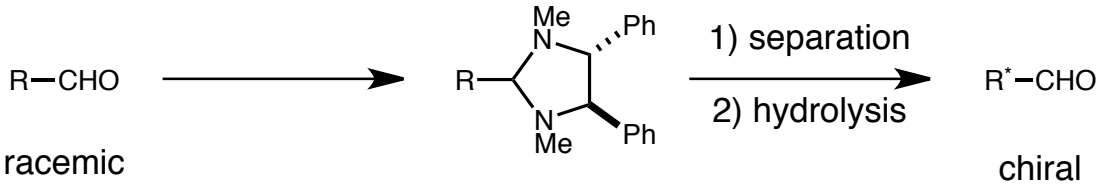


1,2-diamines

- part 3: utilization
  - resolution
  - chiral auxiliaries
  - chiral ligands
  - natural product synthesis
  - medicinal use

Utilization of 1,2-Diamines

- resolution of racemates



Alexakis, A.; Mangeney, P.; Marek, I.; Rose-Munch, F.; Rose, E.; Semra, A.; Robert, F. *J. Am. Chem. Soc.* **1992,** *114*, 8288.

Utilization of 1,2-Diamines

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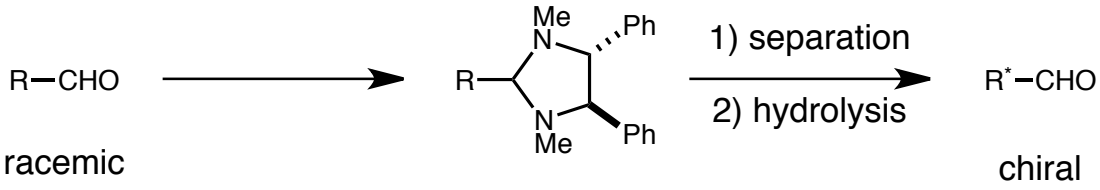

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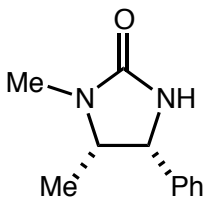
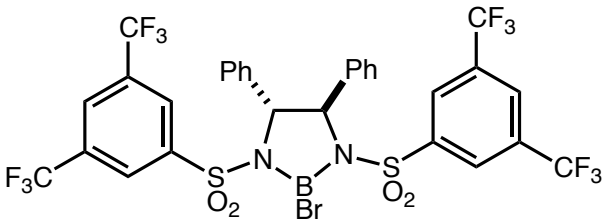
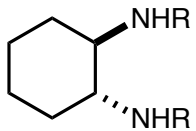
- chiral auxiliaries



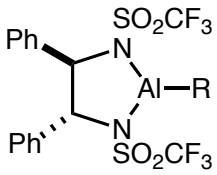


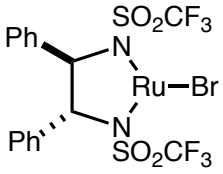


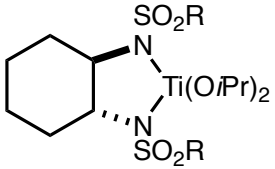
Lucet, D.; Gall, T. L.; Mioskowski, C. *J. Angew. Chem. Int. Ed.* **1998,** *37*, 2580.

Utilization of 1,2-Diamines

- chiral ligands
  - Lewis acid derivatives







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Utilization of 1,2-Diamines

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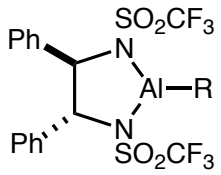
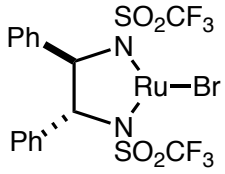
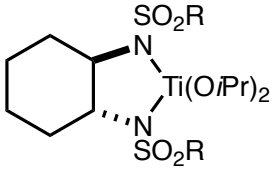
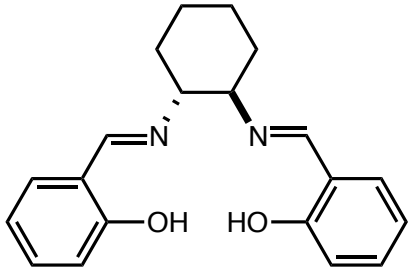
  - Lewis acid derivatives







  - salen-type ligands from 1,2 diamines and aromatic aldehydes



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Utilization of 1,2-Diamines

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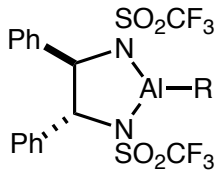
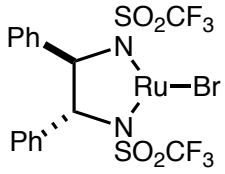
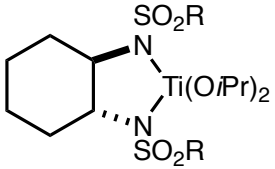
  - Lewis acid derivatives







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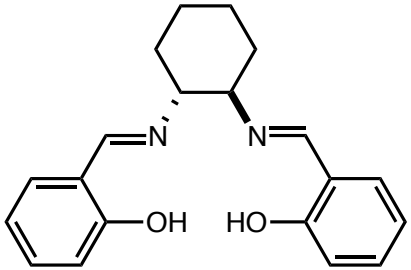
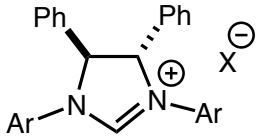
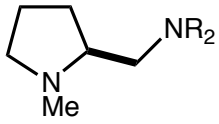


  - *N*-heterocyclic carbene ligands



  - Miscellaneous



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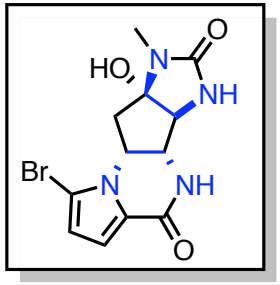
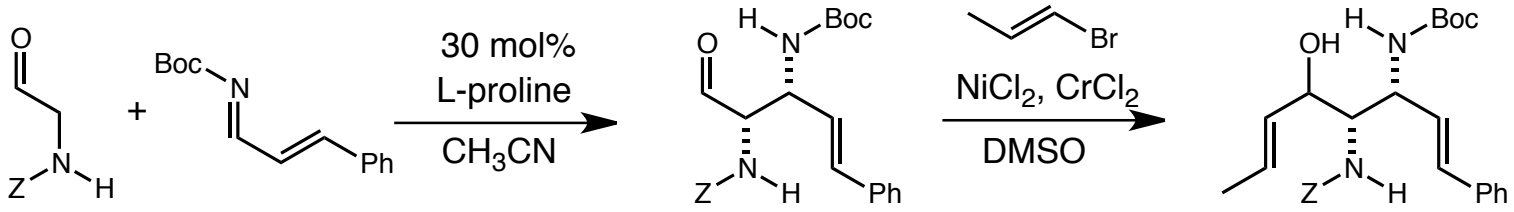
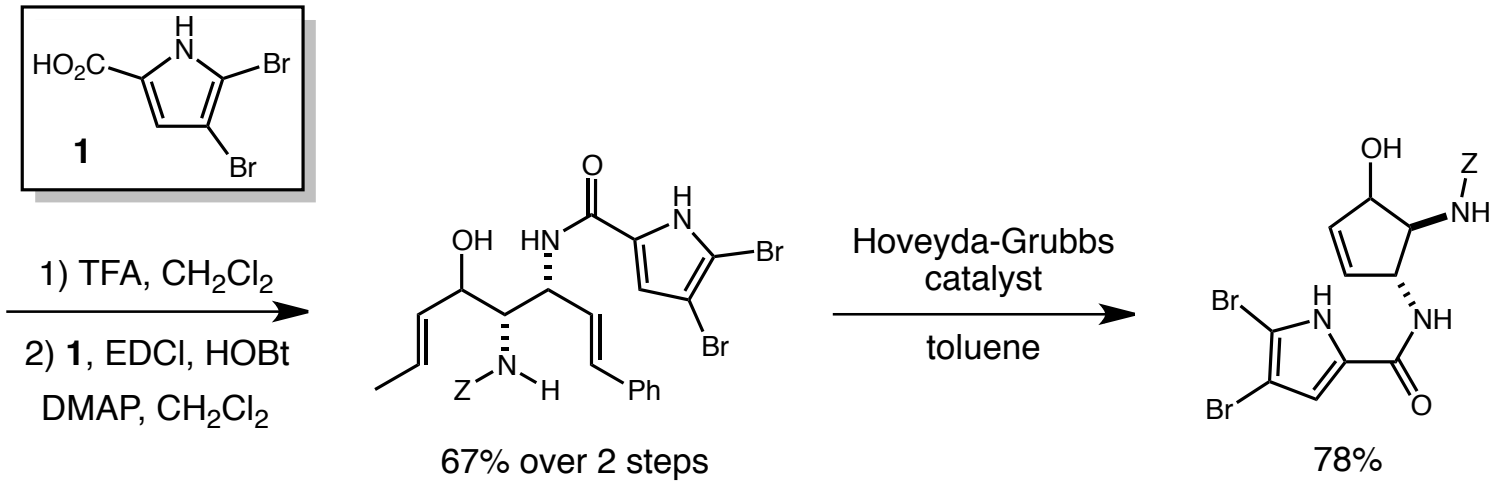
1,2-Diamines in Synthesis



- formal synthesis of (-)-Agelastatin A





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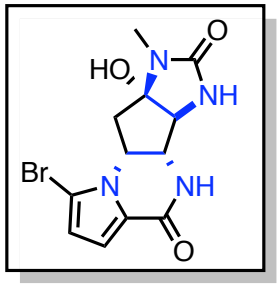
1,2-Diamines in Synthesis



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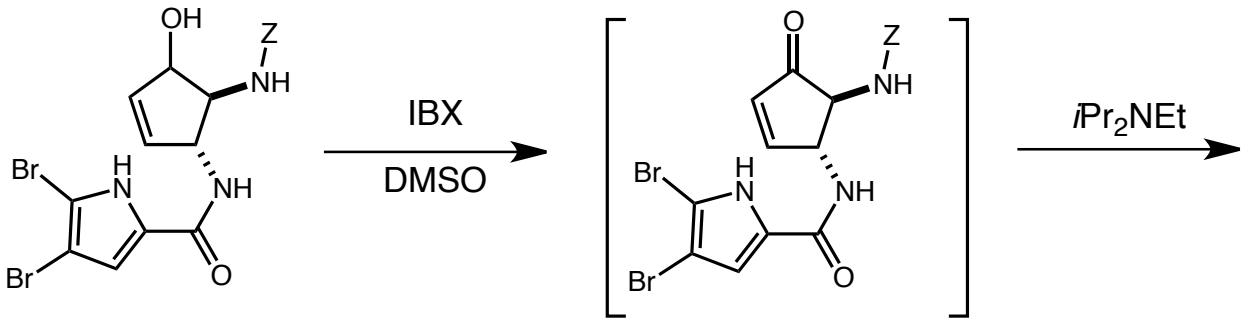

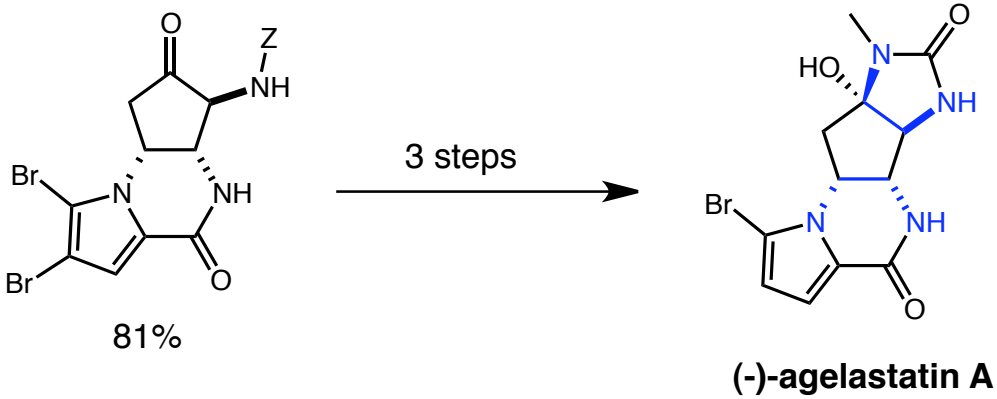

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