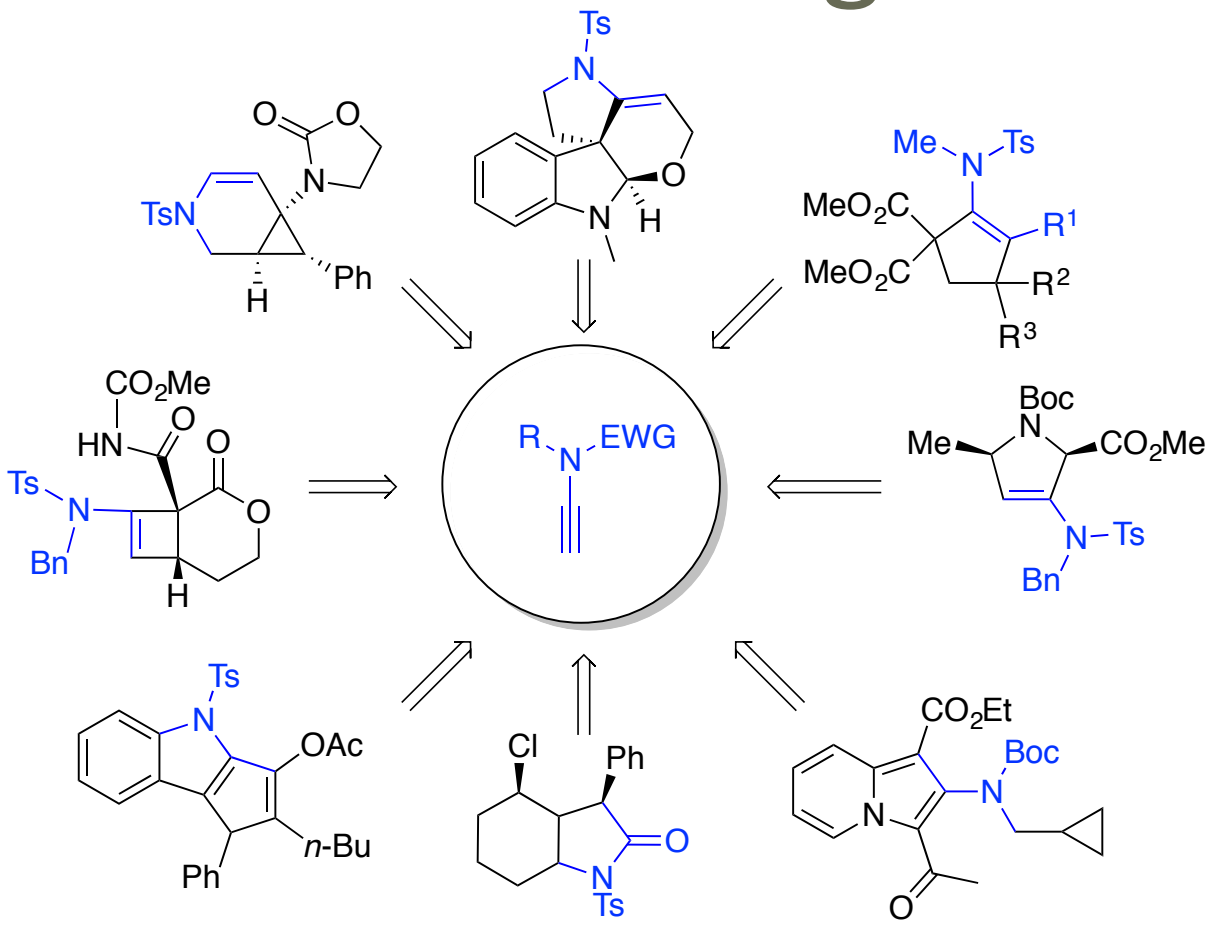
Cyclizations of Ynamides to Generate Novel Ring Structures



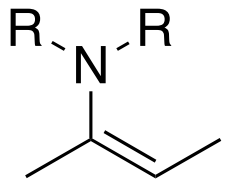
John Milligan

Wipf Group Meeting

Frontiers of Chemistry Seminar

July 23, 2016

Ynamides



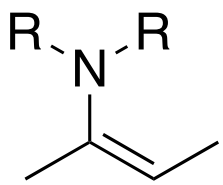
enamines:

First isolated in 1936

Storied history

Well understood reactivity

Ynamides



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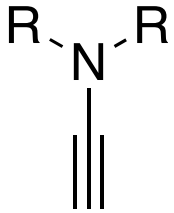


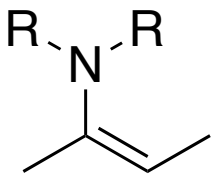
ynamines:

First isolated in 1958

Infrequent and sporadic in the literature

Major disadvantage: instability toward hydrolysis and polymerization

Ynamides

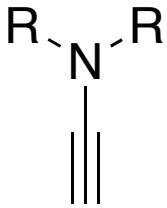


enamines:

First isolated in 1936

Storied history

Well understood reactivity

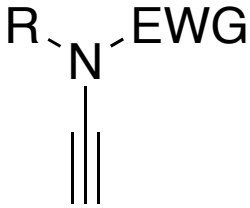


ynamines:

First isolated in 1958

Infrequent and sporadic in the literature

Major disadvantage: instability toward hydrolysis and polymerization



ynamides:

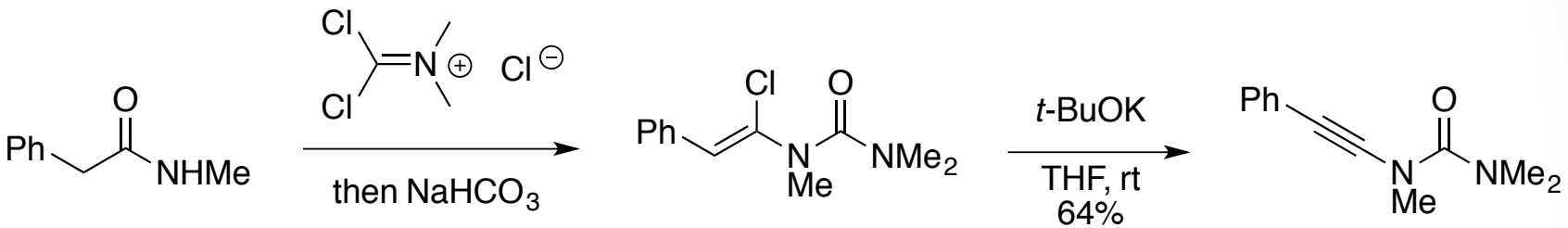
First isolated in 1972

Of great interest in recent years

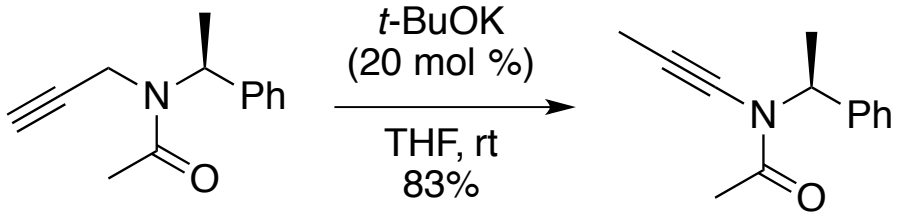
Bench stable!

Synthesis of Ynamides: State of the Art Before 2003

- Elimination



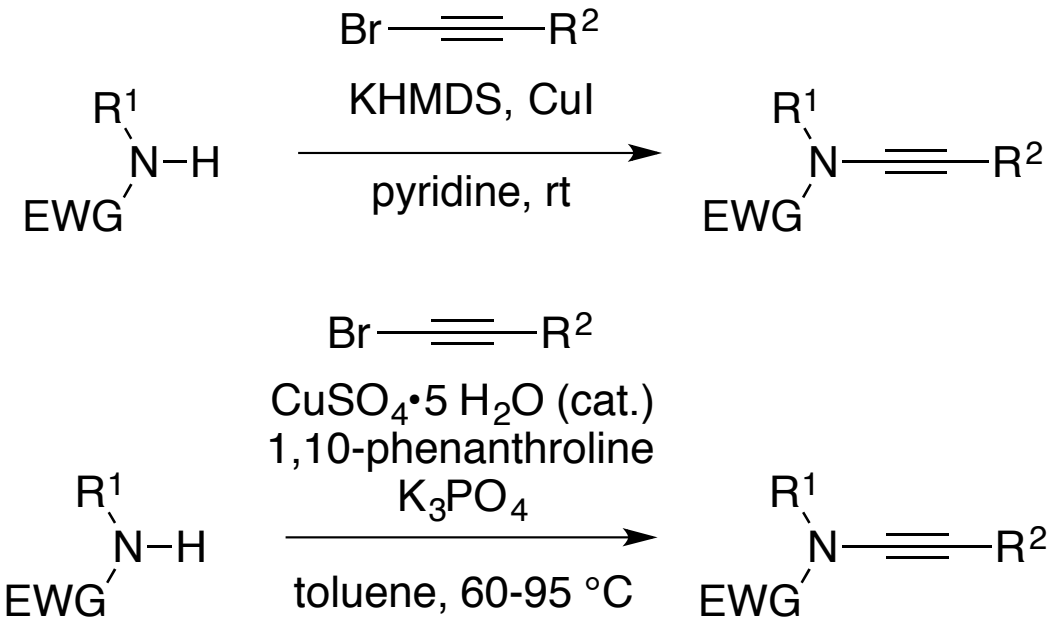
- Isomerization



Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem. Int. Ed.* **1972**, *11*, 917

Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A. Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417

Discovery of Cu mediated coupling

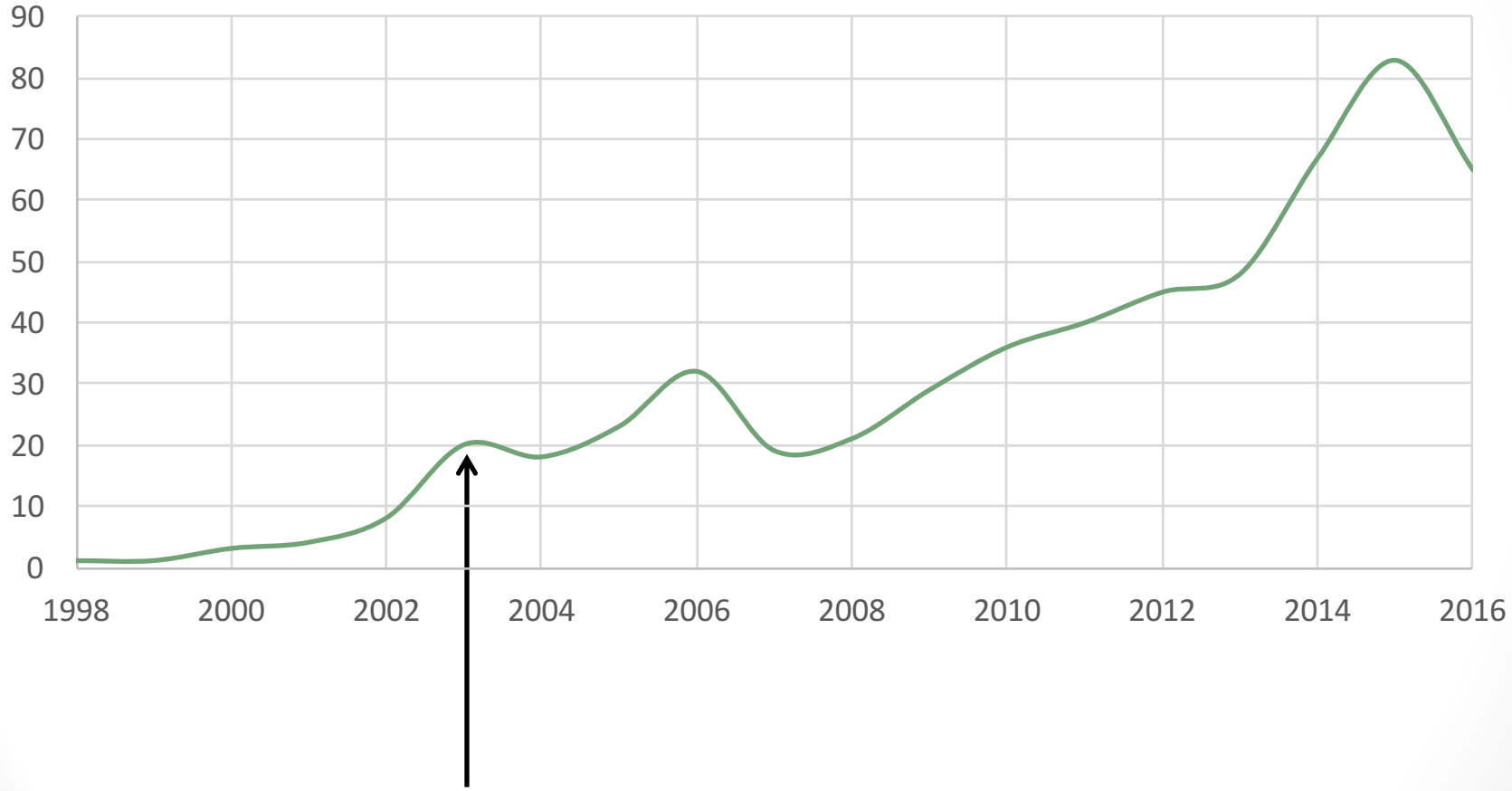


Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011

Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368

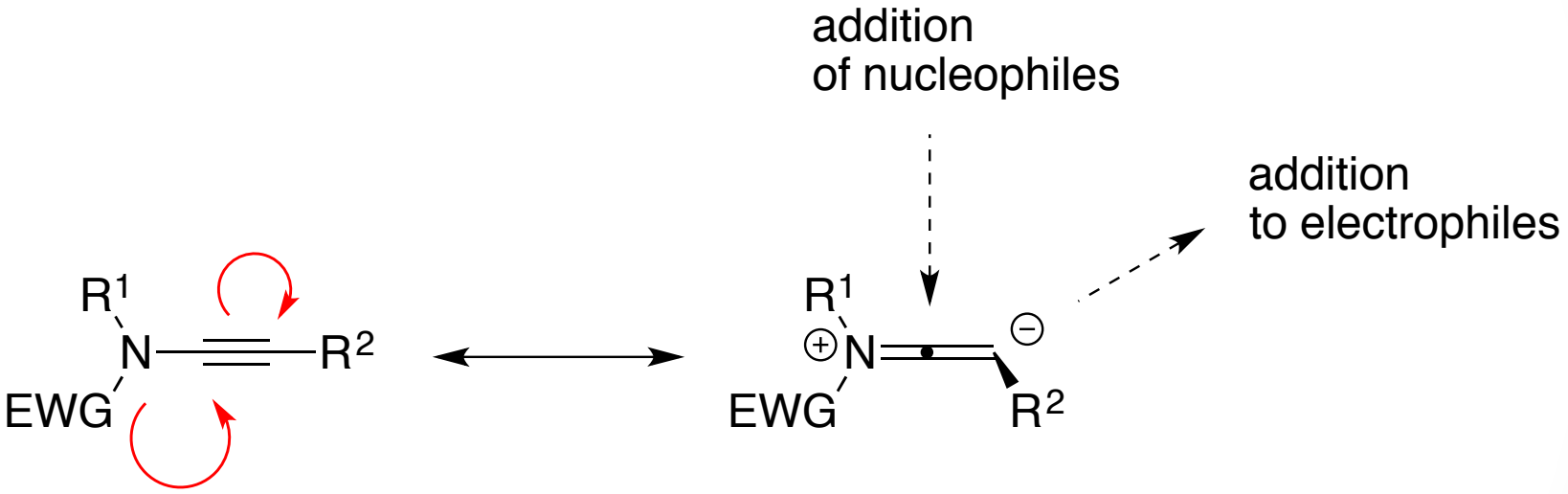
Zhang, Y.; Husng, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151

Occurrence of "Ynamides" in the Literature (SciFinder search, 7/18/16)



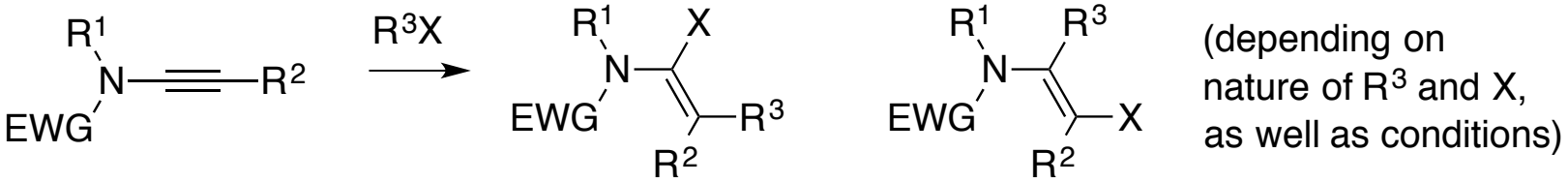
2003: Hsung and Danheiser each publish Cu-mediated ynamide syntheses

Reactivity of Ynamides



Major achievements: ca. 2002-2010

- Hydrofunctionalization
  - Hydroboration, hydrostannylation, etc.
- Additions
  - Control of regioselectivity



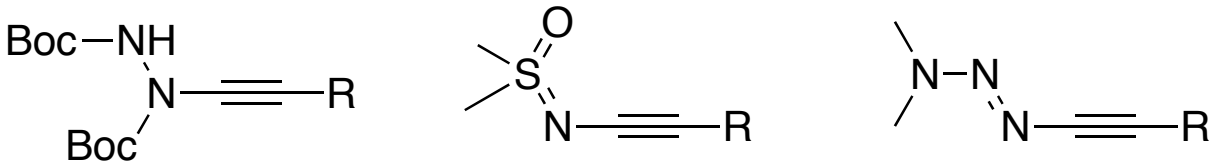
- Classic alkyne cycloaddition chemistry
  - [2+2]/[3+2]/[4+2]/[2+2+2]

DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064-5106

Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840-2859

Where has the ynamide frontier grown in the last 2-3 years?

- Development of functional analogs of ynamides:



- Increasing array of additions/hydrofunctionalizations

Lu, T.; Hsung, R. P. *ARKIVOC* **2014**, 127-141

Perrin, F. G.; Kiefer, G.; Jeanbourquin, L.; Racine, S.; Perrotta, D.; Waser, J.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2015**, *54 (45)*, 13393-13396

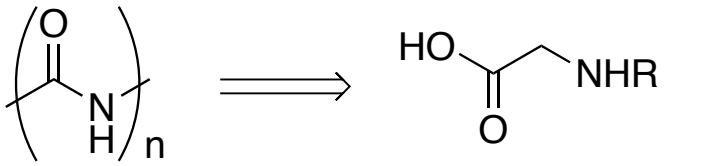
Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560-578

Where has the ynamide frontier grown in the last 2-3 years?

- **Development of Cycloadditions and Cyclizations: focus of present talk**
  - Cycloadducts of increasing complexity
  - Novel modes of reactivity/mechanistic aspects
  - Use of cheap and abundant catalysts/reagents

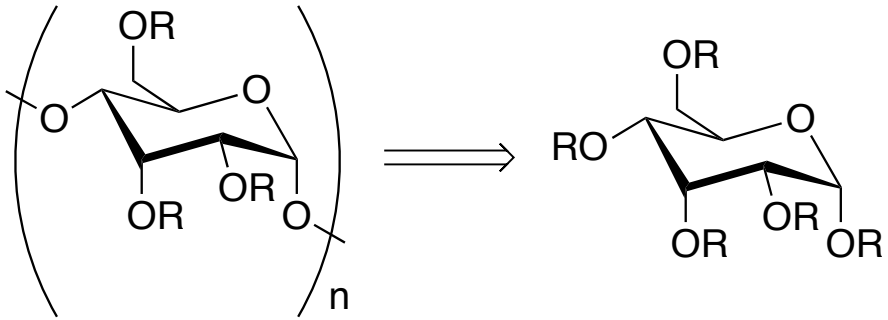
Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560-578

What is the overarching problem to which ynamide cyclizations contribute?



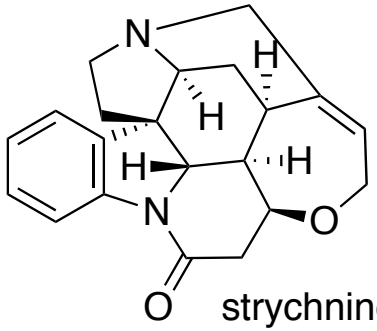
Solid phase peptide synthesis:

Established Methodology



Oligosaccharide synthesis:

Challenging but a constantly developing field



strychnine

?

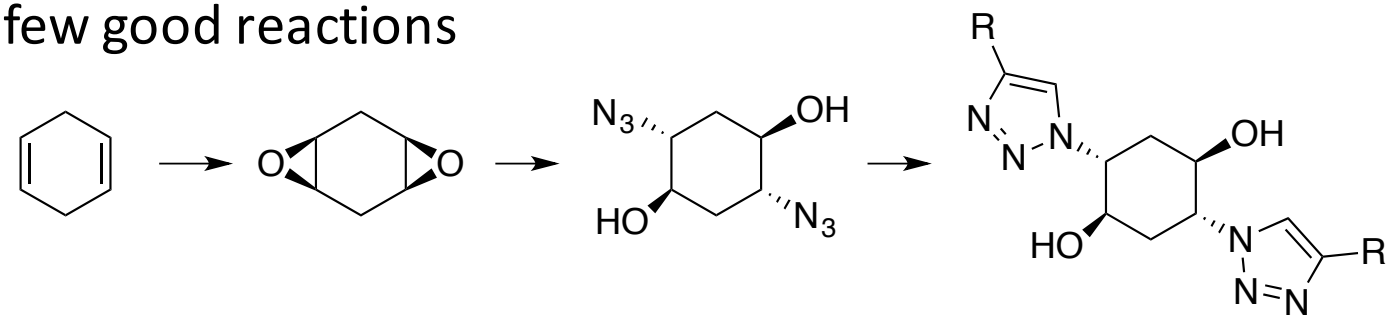
Polycyclic, complex molecules:

Strucure dependent, no general set of building blocks

A massive, long lasting problem!

What Paradigms Address this Problem?

- Schriber- Diversity Oriented Synthesis: Building Rapid Diversity into new chemical space
- Sharpless- Click Chemistry: Diverse Chemical Function through a few good reactions



Schriber, S. L. *Science* **2000**, *287*, 1964-1969.
Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021
Burke, M. D. et al. *Science* **2015**, *347*, 1221-1226.

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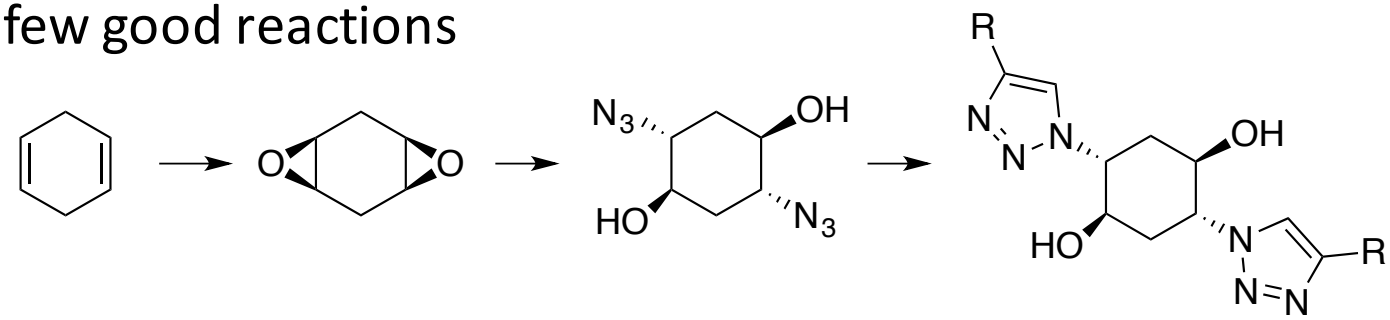
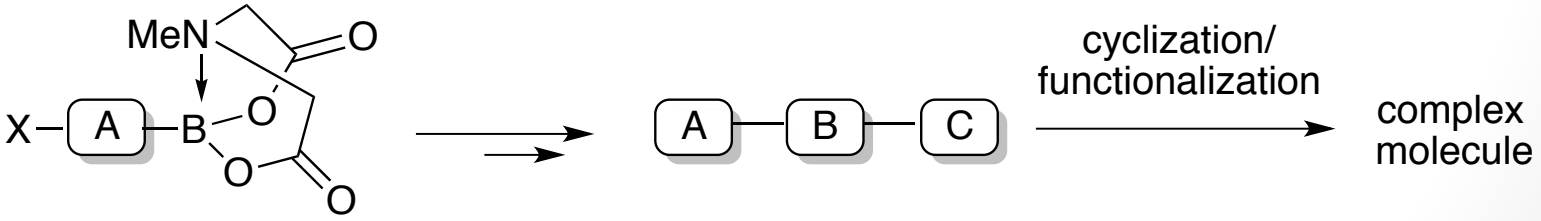


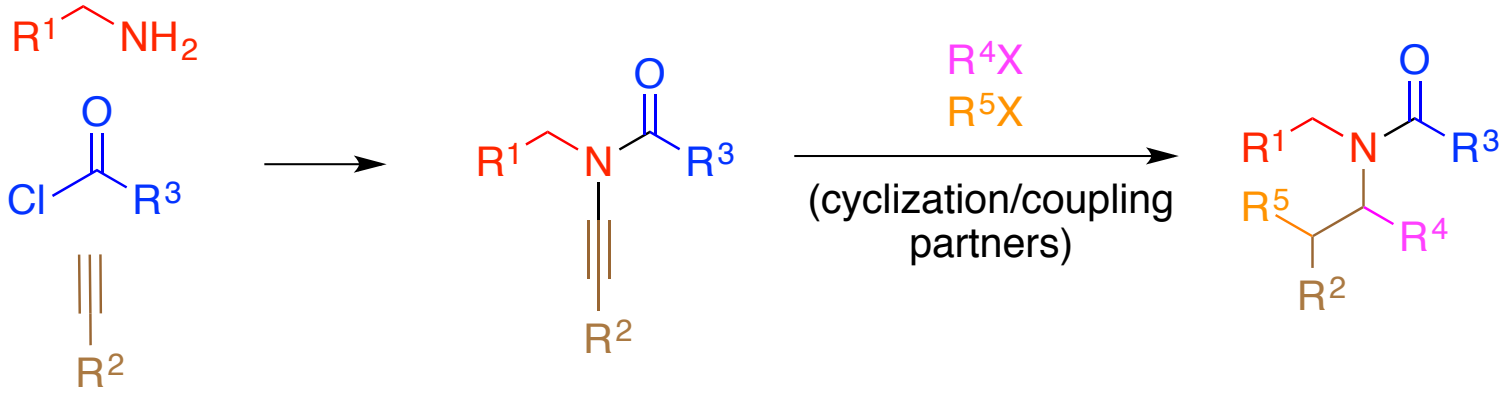
- Burke- "The Synthesis Machine": Breaking complex molecules into simple building blocks



Schriber, S. L. *Science* **2000**, *287*, 1964-1969.
Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021
Burke, M. D. et al. *Science* **2015**, *347*, 1221-1226.

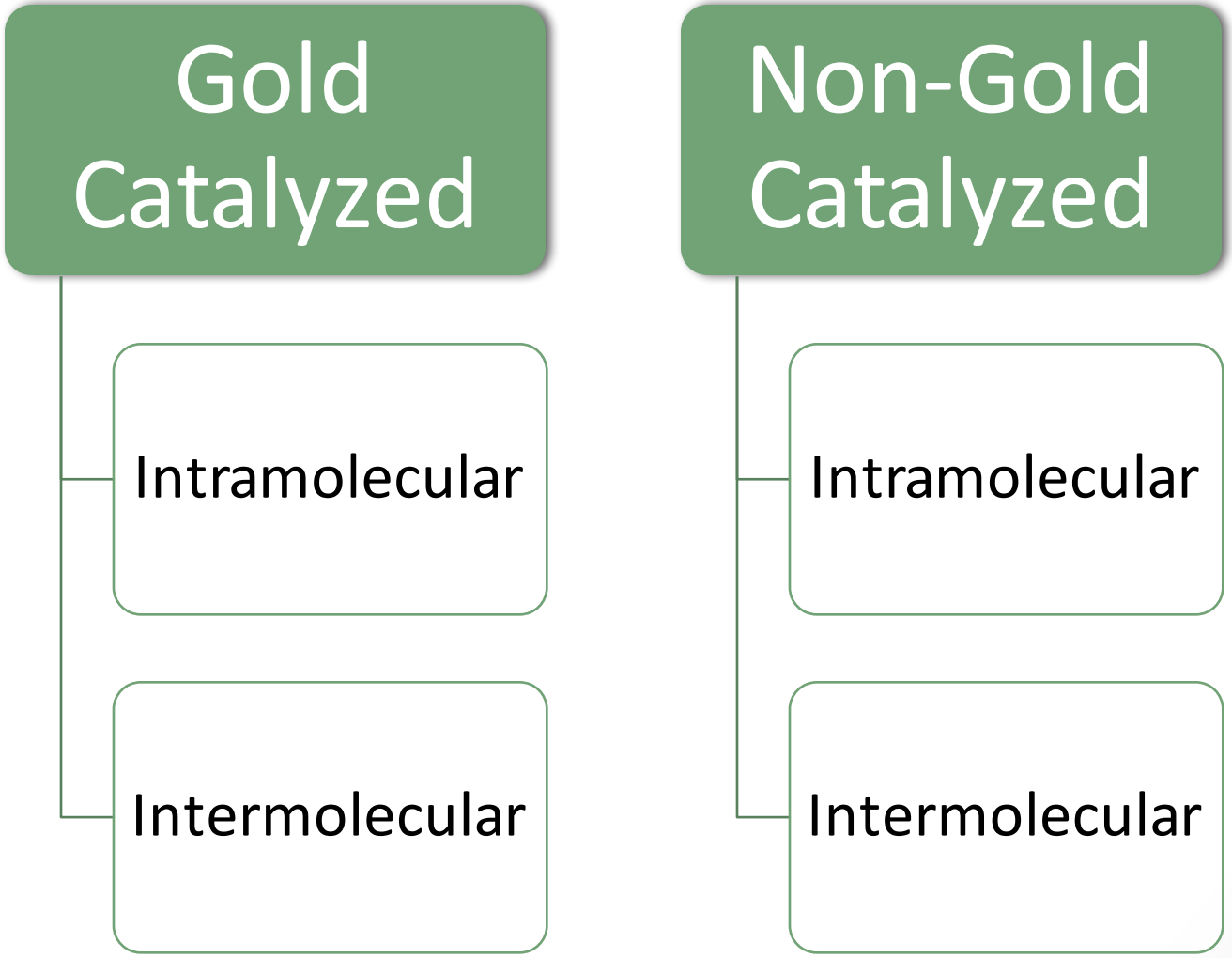
Ynamides: Potential Contributors as Tunable, Reactive Building Blocks

- A “building block” approach to to alkaloids and heterocycles



- R’s can be be linked in a variety of ways: many novel cyclic structures are possible

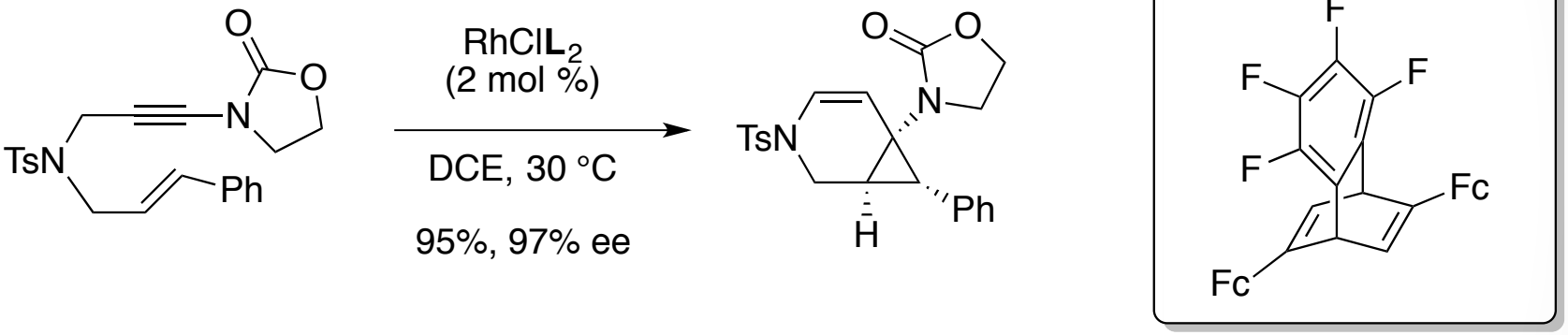
Cyclizations of Ynamides



Part 1A: “Gold Free”, intramolecular

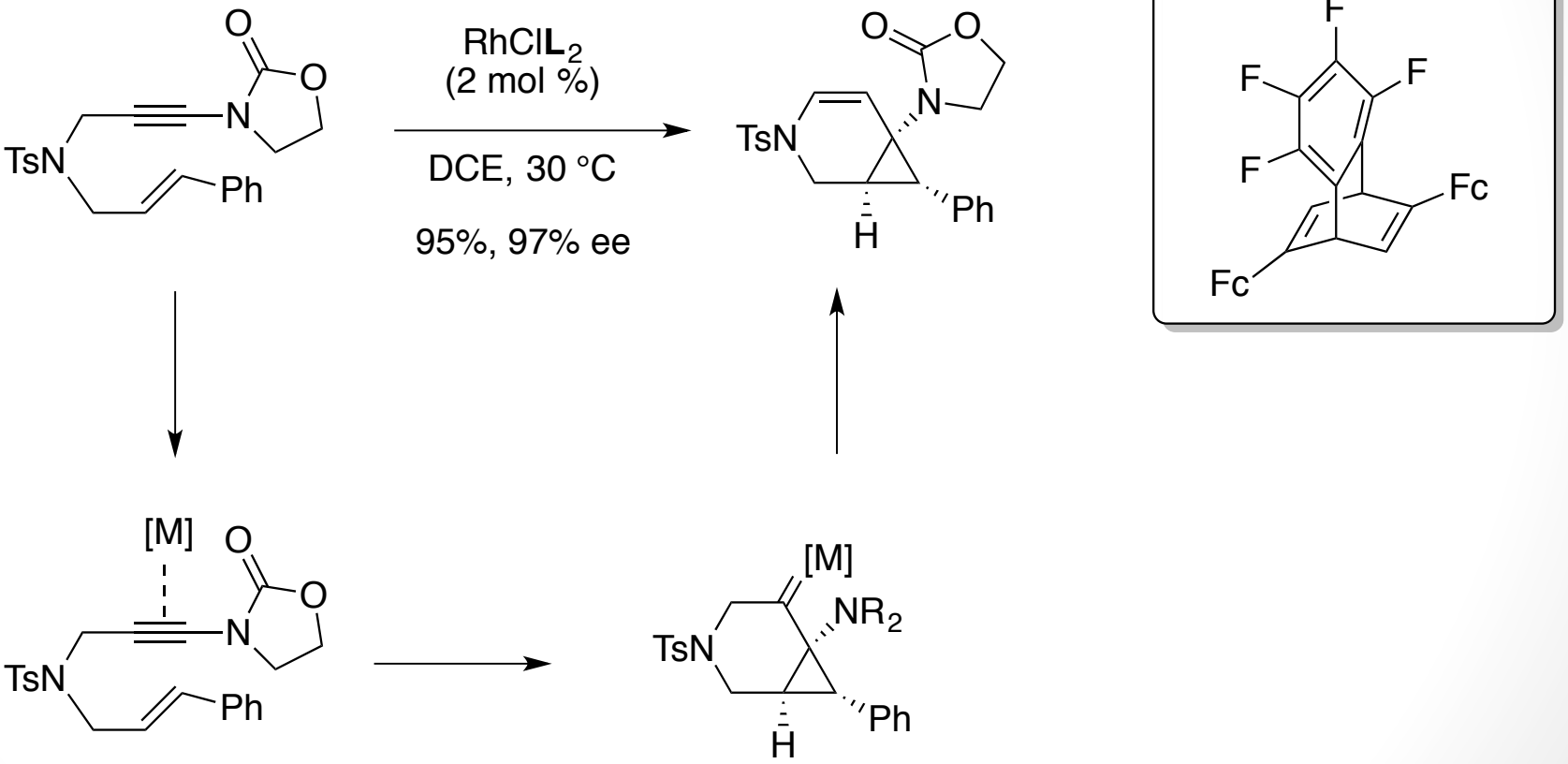
- Transition metal catalyzed enyne/diyne cyclizations
- Lewis acid mediated cyclizations

Rh-catalyzed asymmetric cyclization



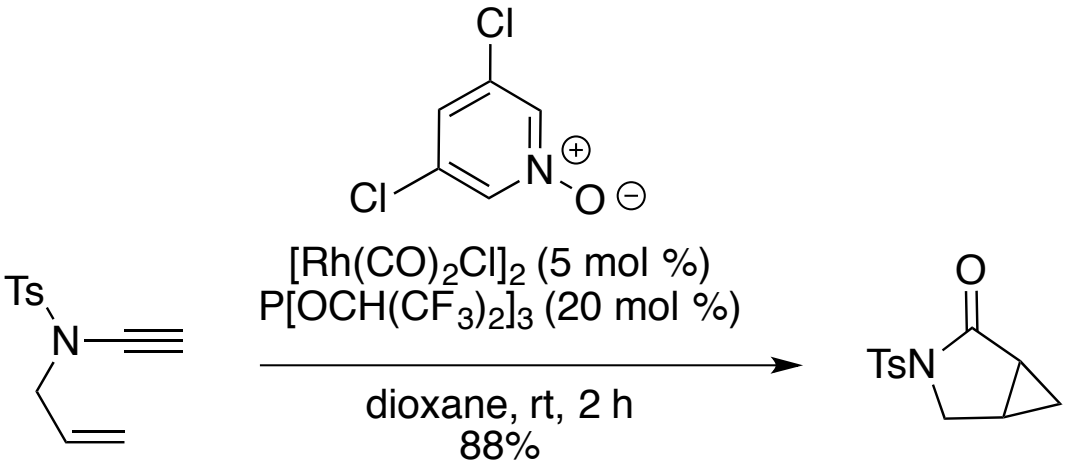
Nishimura, T.; Takiguchi, Y.; Maeda, Y.; Hayashi, T. *Adv. Synth. Catal.* **2013**, *355*, 1374-1382

Rh-catalyzed asymmetric cyclization



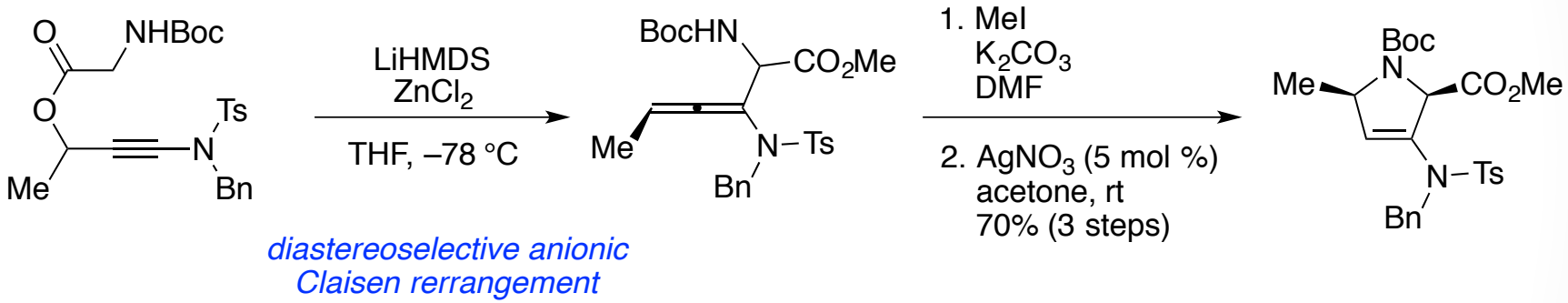
Nishimura, T.; Takiguchi, Y.; Maeda, Y.; Hayashi, T. *Adv. Synth. Catal.* **2013**, *355*, 1374-1382

Oxidative Rh-catalyzed cyclization



Liu, R.; Winston-McPherson, G. N.; Yang, Z-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013,** *135*, 8201-8204.

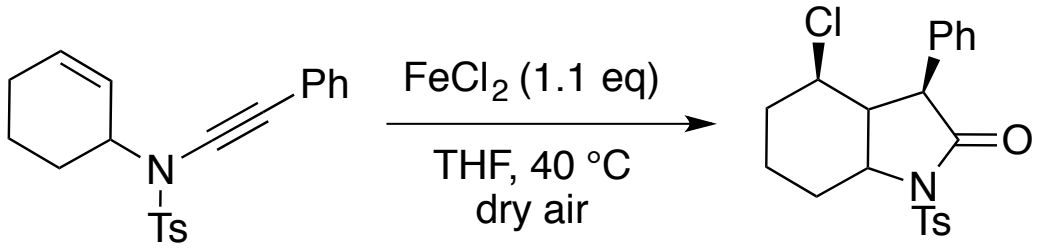
Anionic rearrangement



diastereoselective anionic Claisen rerrangement

Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2013**, *15*, 1626-1629

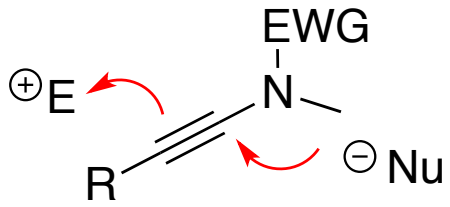
Lewis acid mediated cyclization



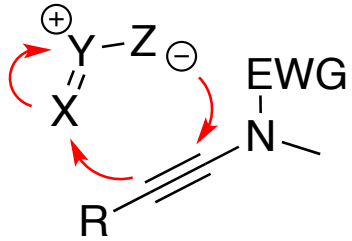
Yeh, M-C. P.; Shiue, Y.-S.; Lin, H.-H.; Yu, T-Y.; Hu, T.-C.; Hong, J.-J. *Org. Lett.* **2016**, *18*, 2407-2410

Part 1B: “Gold Free”, intermolecular

- [2+2] “Ficini” reactions
- Lewis/Bronsted acid mediated cyclizations

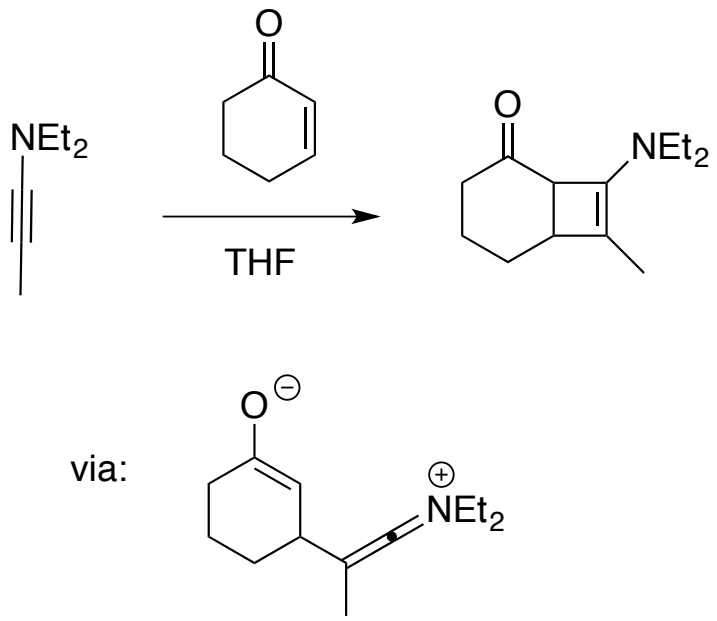


- Dipolar cycloadditions



- Cyclizations involving azides or diazo compounds

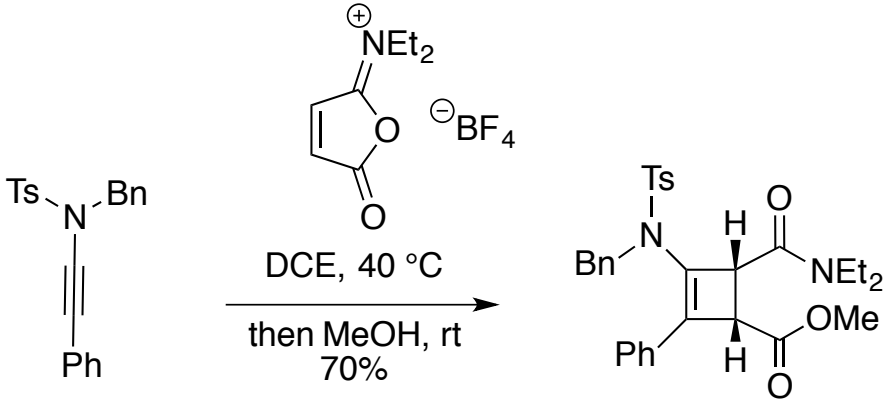
Ficini [2+2] addition



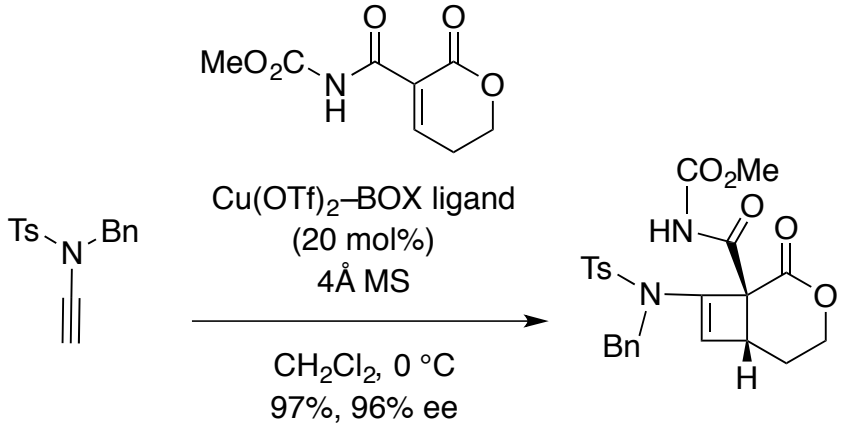
Ficini, J. *Tetrahedron* **1976**, *32*, 1449-1486

Modern ynamide Ficini reactions

- Facile addition with activated alkene partner:



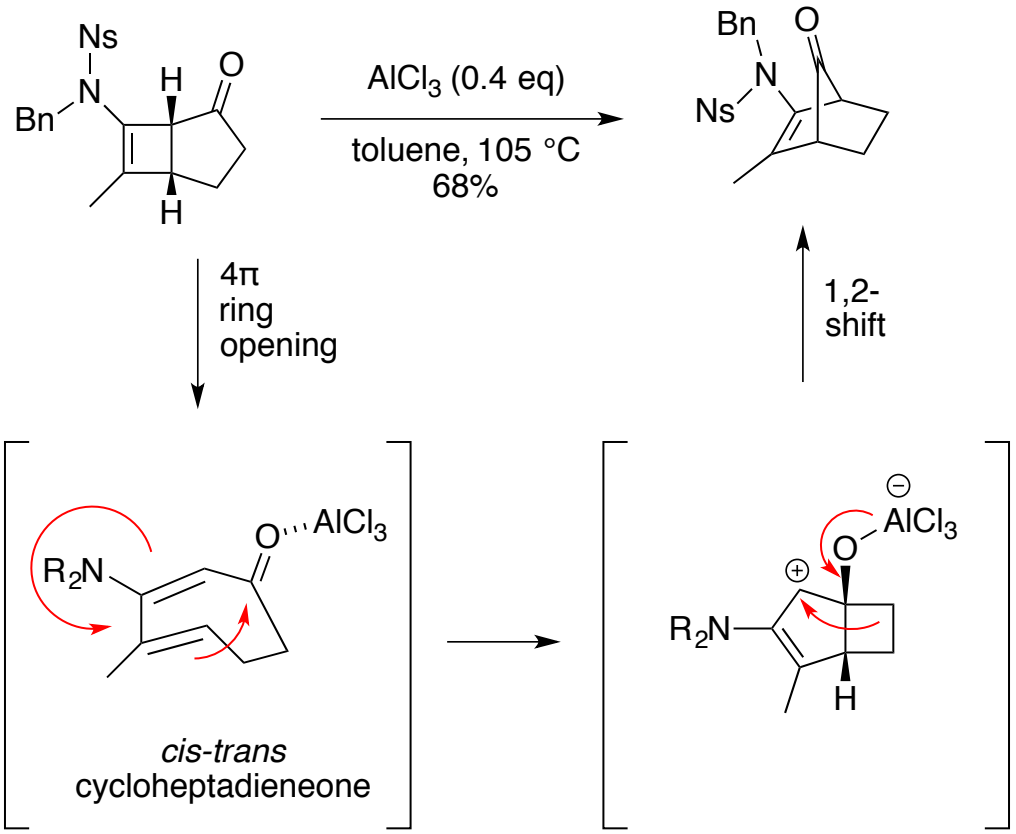
- Enantioselective addition:



Yuan, Y.; Bai, L.; Nan, J.; Liu, J.; Luan, X. *Org. Lett.* **2014**, *16*, 4316-4319

Enomoto, K.; Oyama, H.; Nakada, M. *Chem. Eur. J.* **2015**, *21*, 2798-2802

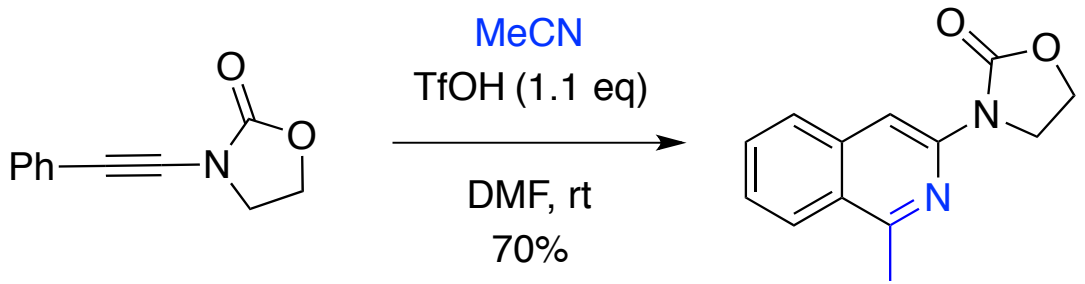
Ficini adduct opening

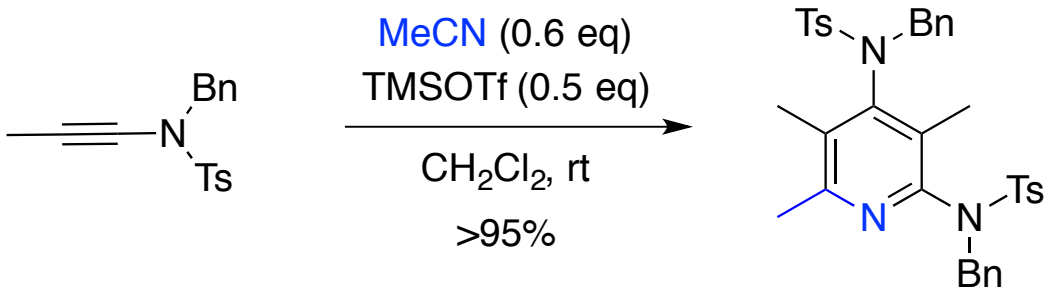


Wang, X.-N.; Krenske, E. H.; Johnston, R. C.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2014**, *136*, 9802-9805

Wang, X.-N.; Krenske, E. H.; Johnston, R. C.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2015**, *137*, 5596-5601

Acid-mediated quinoline/ pyridine syntheses

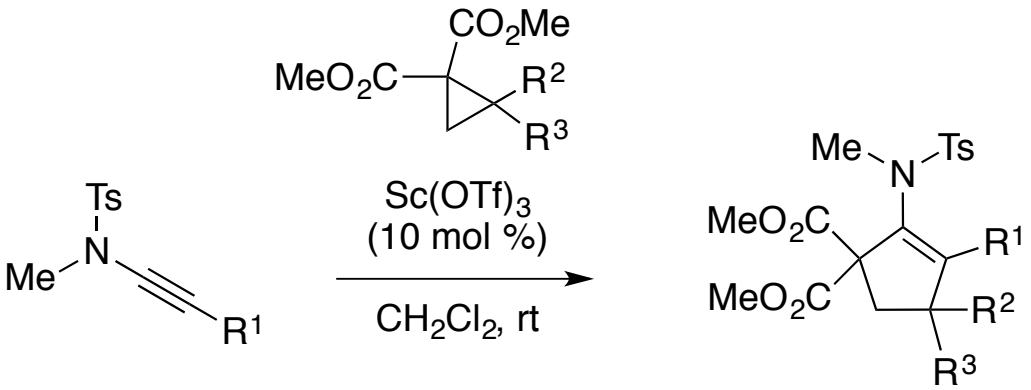




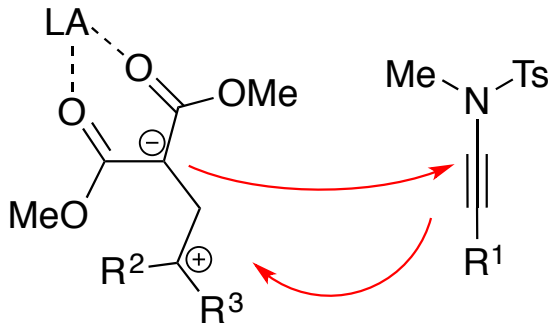
Xie, L.-G.; Niyomchon, S.; Mota, A. J.; Gonzalez, L.; Maulide, N. *Nat. Commun.* **2016**, DOI: 10.0138/ncomms10914

Zhang, J. Zhang, Q.; Xia, B.; Wu, J.; Wang, X.-N.; Chang, J. *Org. Lett.* **2016**, DOI: 10.1021/acs.orglett.6b

Lewis acids: DA cyclopropane activation

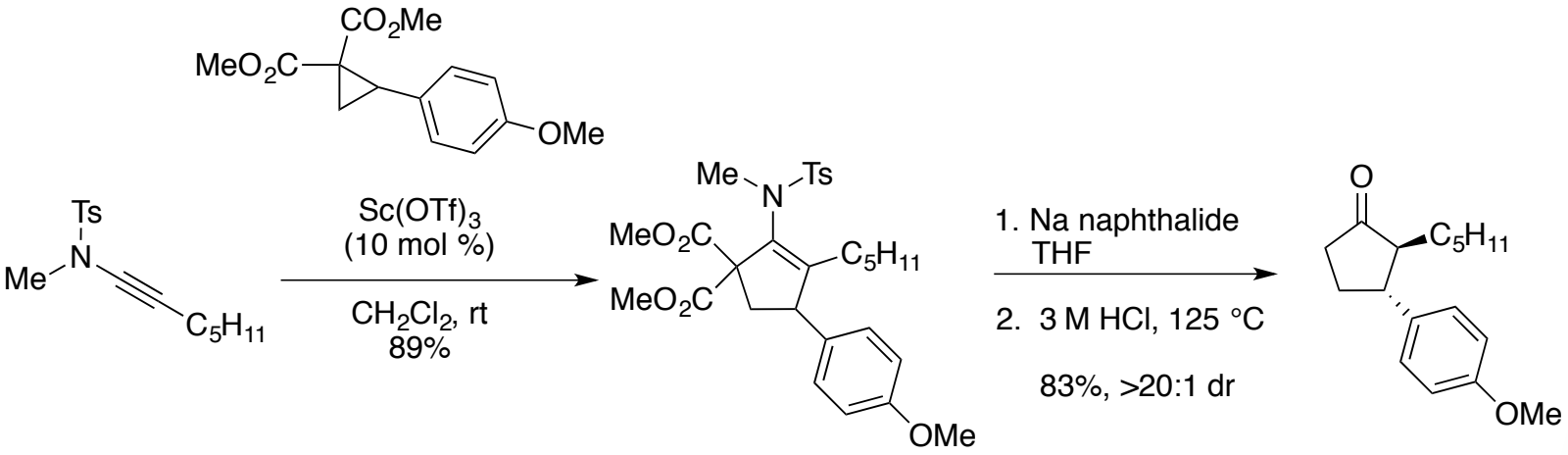


via:



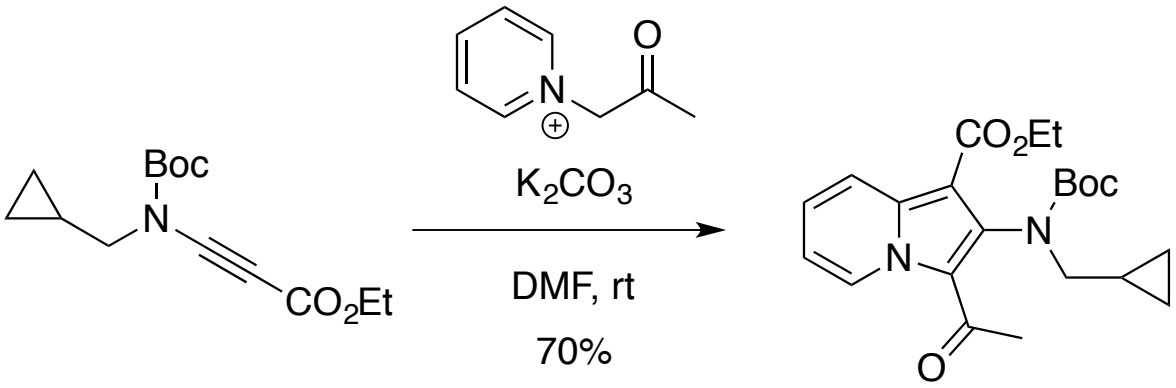
Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 1626-1629

Lewis acids: DA cyclopropane activation

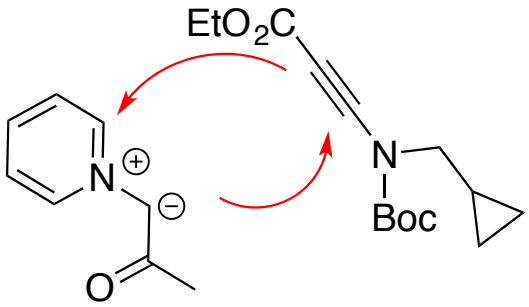


Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 1626-1629

Dipolar cycloaddition

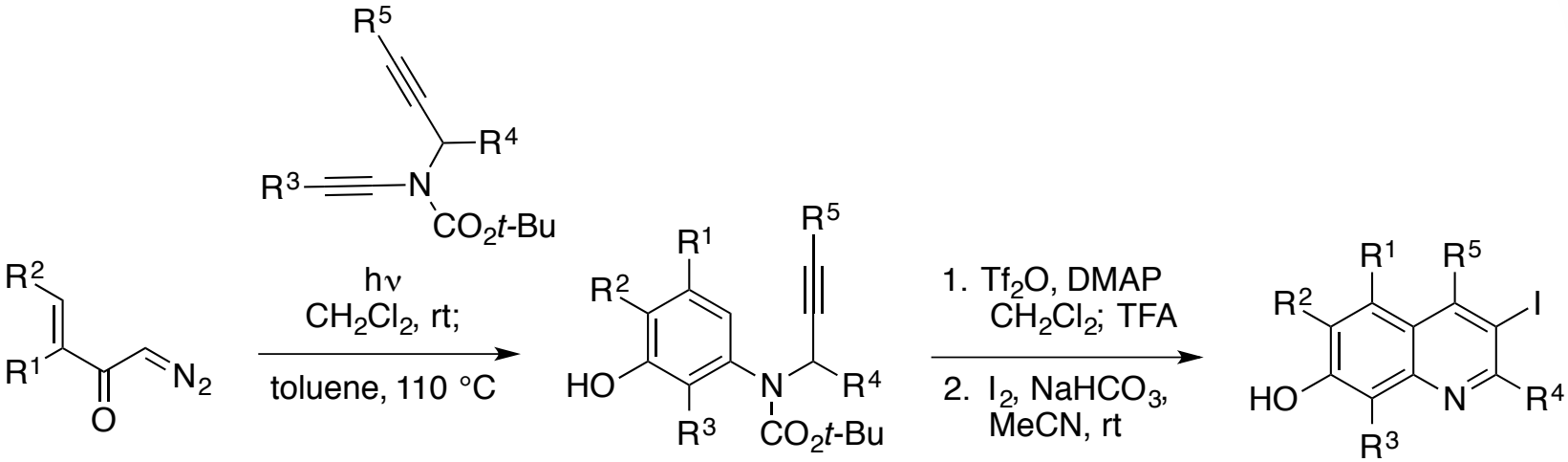


via:



Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2015**, *17*, 2800-2803.

Vinylketene cascade

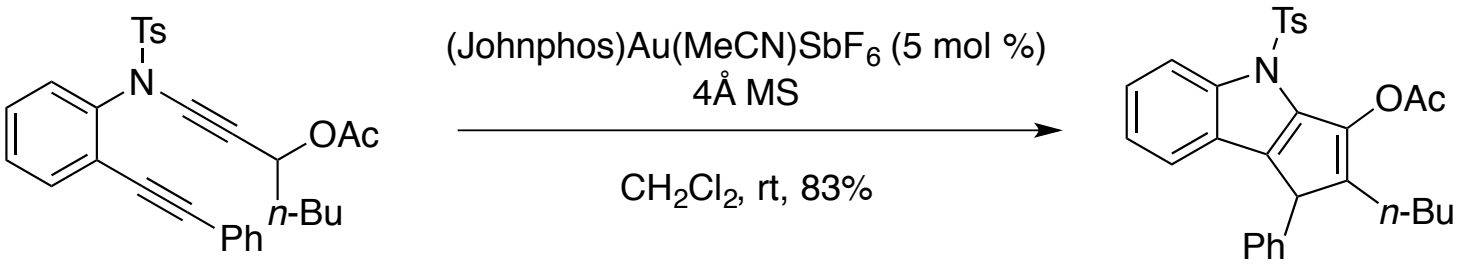


Willumstad, T. P. Bordreau, P. D.; Danheiser, R. L. *J. Org. Chem.* **2015**, *80*, 11794-11805.

Part 2A: Gold catalyzed, intramolecular

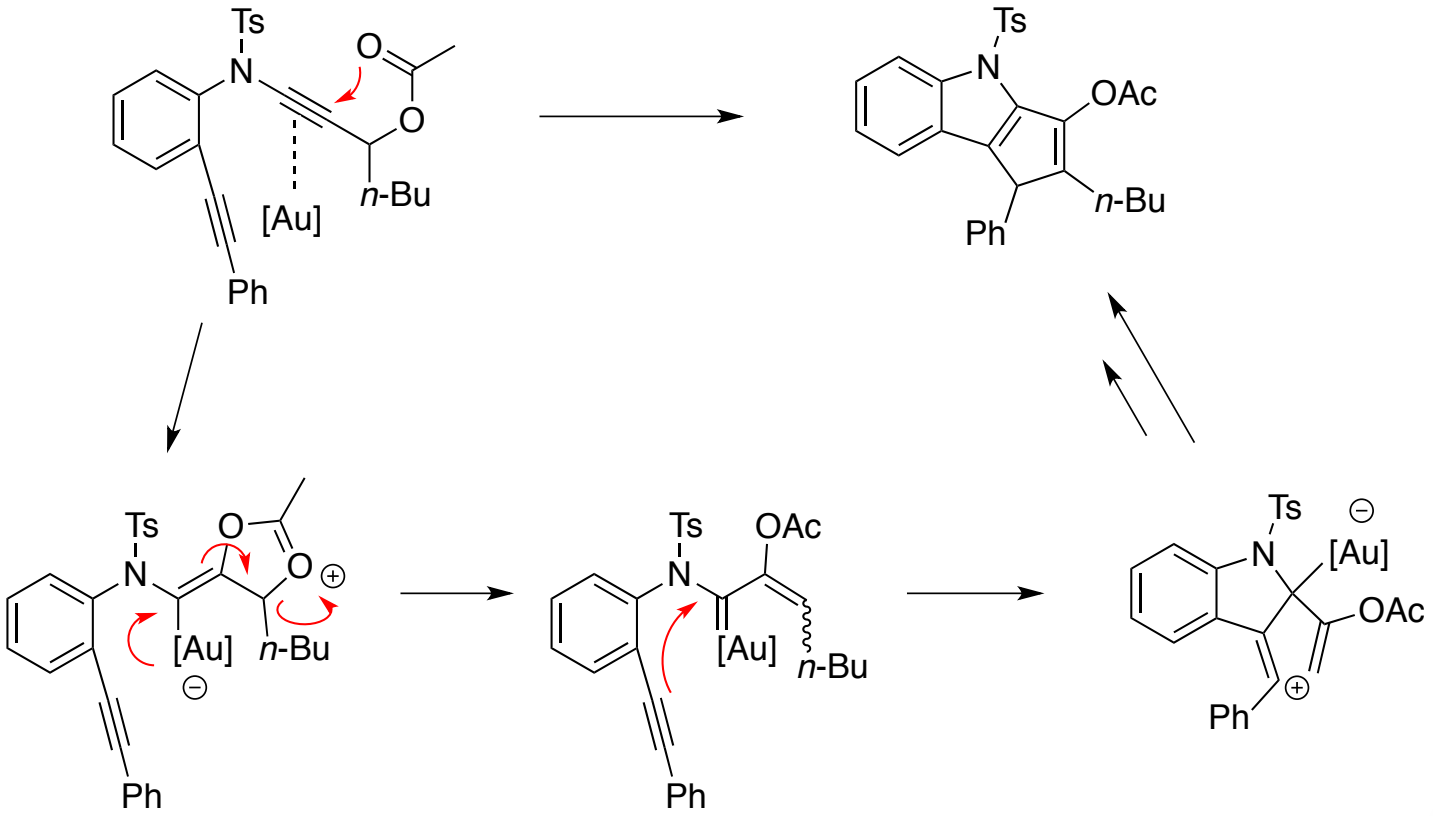
- Diyne cyclizations
- Enyne cyclizations
- Cyclizations involving azides

Diyne cyclization



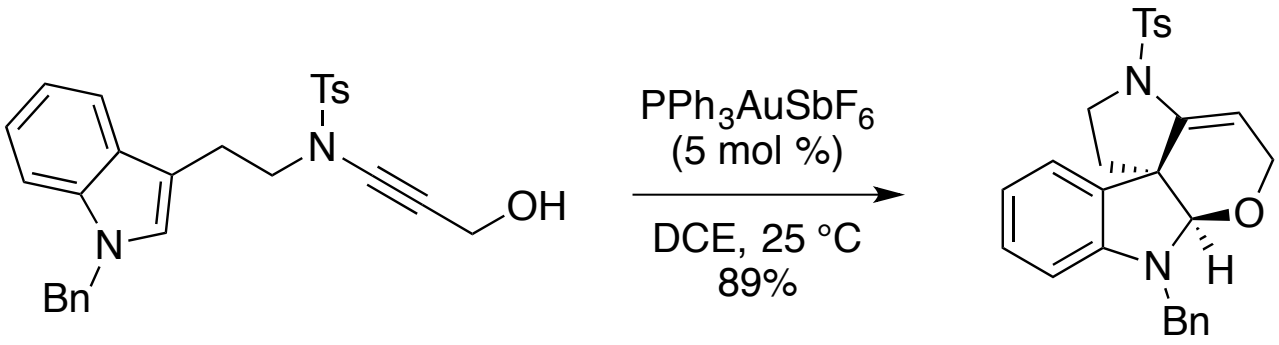
Liu, J.; Chen, M.; Zhang, L.; Liu, Y. *Chem. Eur. J.* **2015**, *21*, 1009-1013

Diyne cyclization



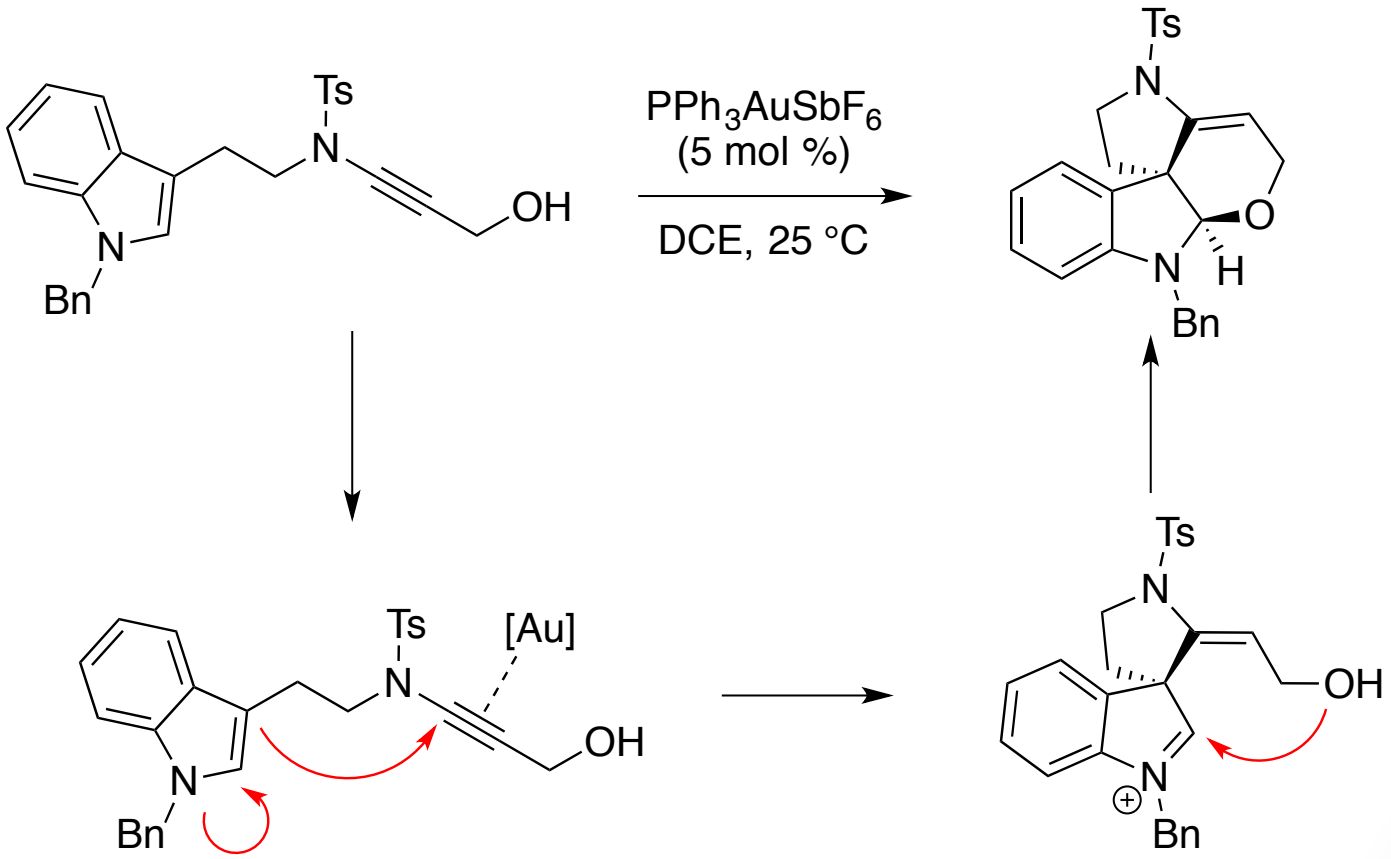
Liu, J.; Chen, M.; Zhang, L.; Liu, Y. *Chem. Eur. J.* **2015**, *21*, 1009-1013

Indole cyclization with tethered alcohol



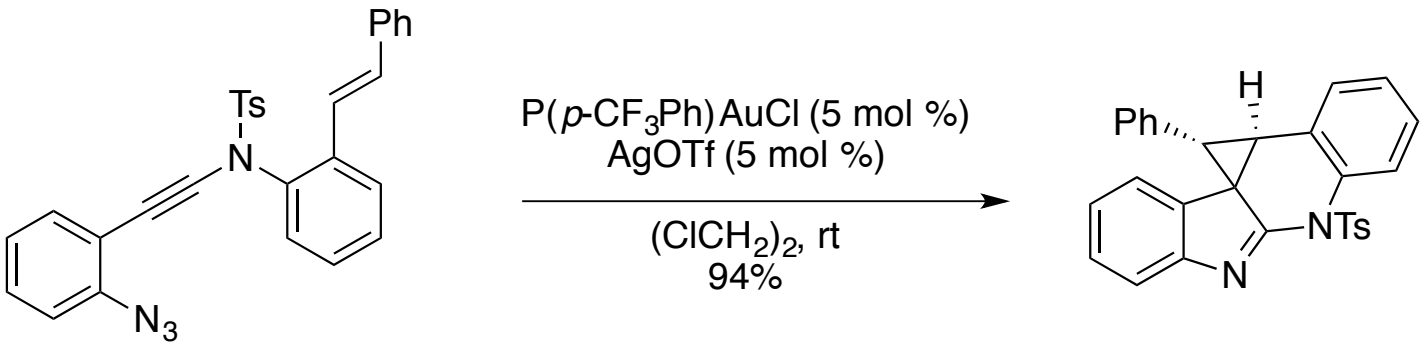
Zheng, N.; Chang, Y.-Y.; Zhang, L.-J.; Gong, J.-X.; Yang, Z. *Chem. Asian J.* **2016**, *11*, 371-375

Indole cyclization with tethered alcohol



Zheng, N.; Chang, Y.-Y.; Zhang, L.-J.; Gong, J.-X.; Yang, Z. *Chem. Asian J.* **2016**, *11*, 371-375

Gold Cyclization of Aryl Azide



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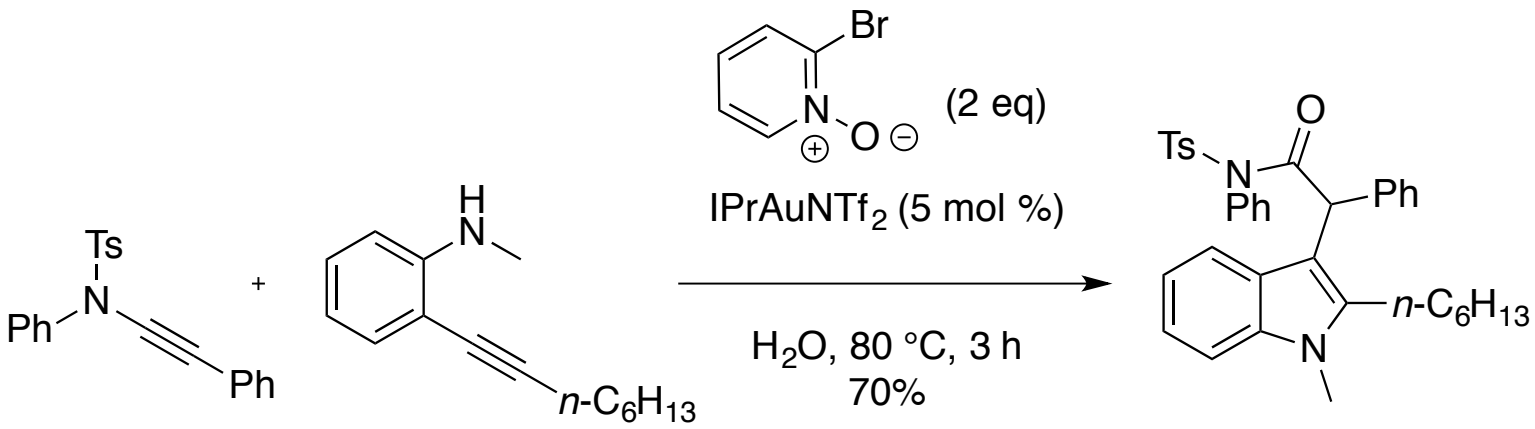
Part 2B: Gold catalyzed, intermolecular

- Alkyne partners
- Heterocyclic partners
- Azide partners

Alkyne coupling



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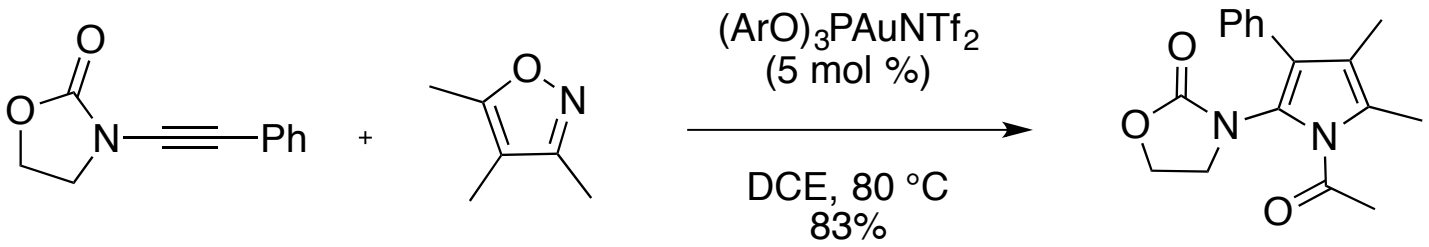
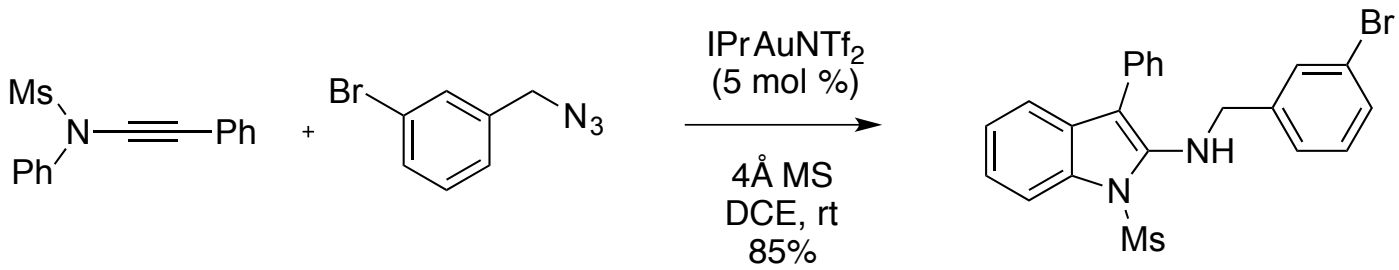
Isoxazole coupling



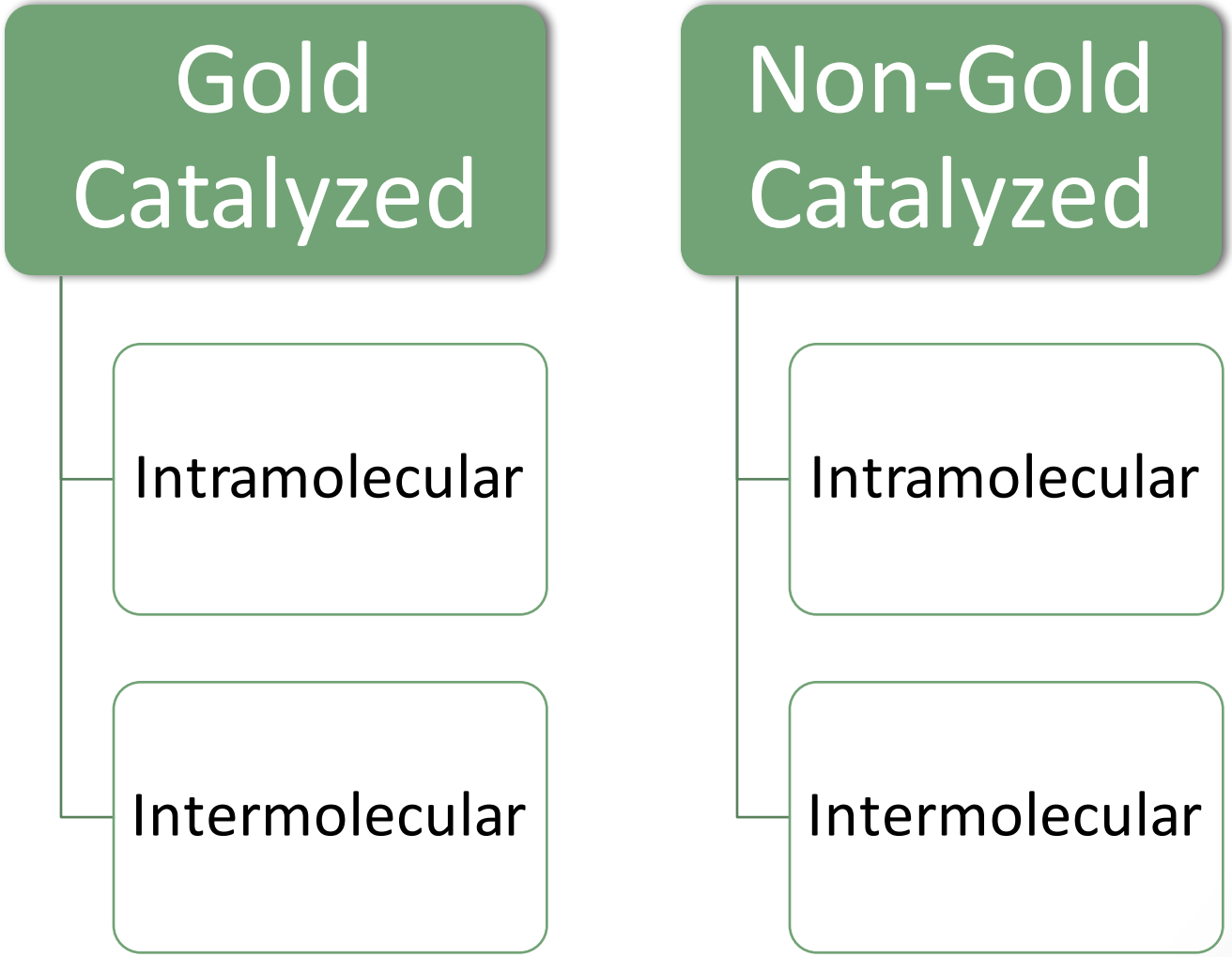
Xiao, X.- Y.; Zhou, A. H.; Shu, C.; Pan, F.; Li, T.; Ye, L.-W. *Chem. Asian J.* **2015**, *10*, 1854-1858

Azide coupling



Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F., Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567-9570

Summary


Gold Catalyzed
Intramolecular
Intermolecular
Non-Gold Catalyzed
Intramolecular
Intermolecular

Final thought: Black Swans

- Widely accepted conventional wisdom in 1976:
  - Gold is too unreactive to be of catalytic use
  - Palladium-catalyzed cross coupling can achieve C-C bond formation but not C-N bond formation
  - Olefin metathesis is an ill-defined reaction of olefinic hydrocarbons and is of little use in synthesis
  - **Plausible addition: Molecules with a nitrogen connected to a triple bond (aka ynamide) are too unstable and reactive for widespread adoption in practical synthetic chemistry**

Nugent, W. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8936-8949

Final thought: Black Swans

Nugent's concluding remark:

"One can only imagine what extraordinary developments those of you currently beginning your careers in chemistry will witness in the next 35 or 40 years. In this regard, I envy you."

Nugent, W. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8936-8949