

Ynamide Chemistry

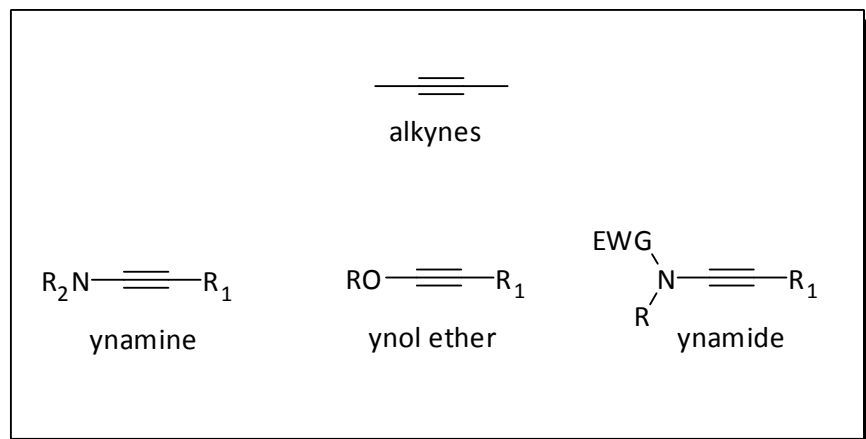
Wednesday Group Meeting

Crimmins Group

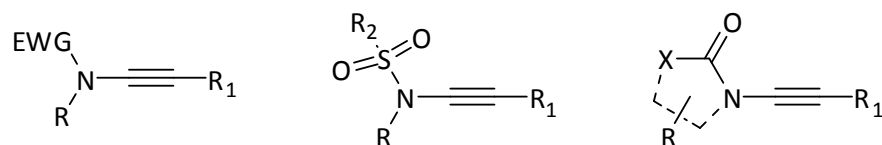
Philip Williams

June 17, 2009

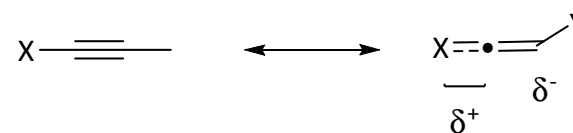
What is an Ynamide?



Typical ynamides

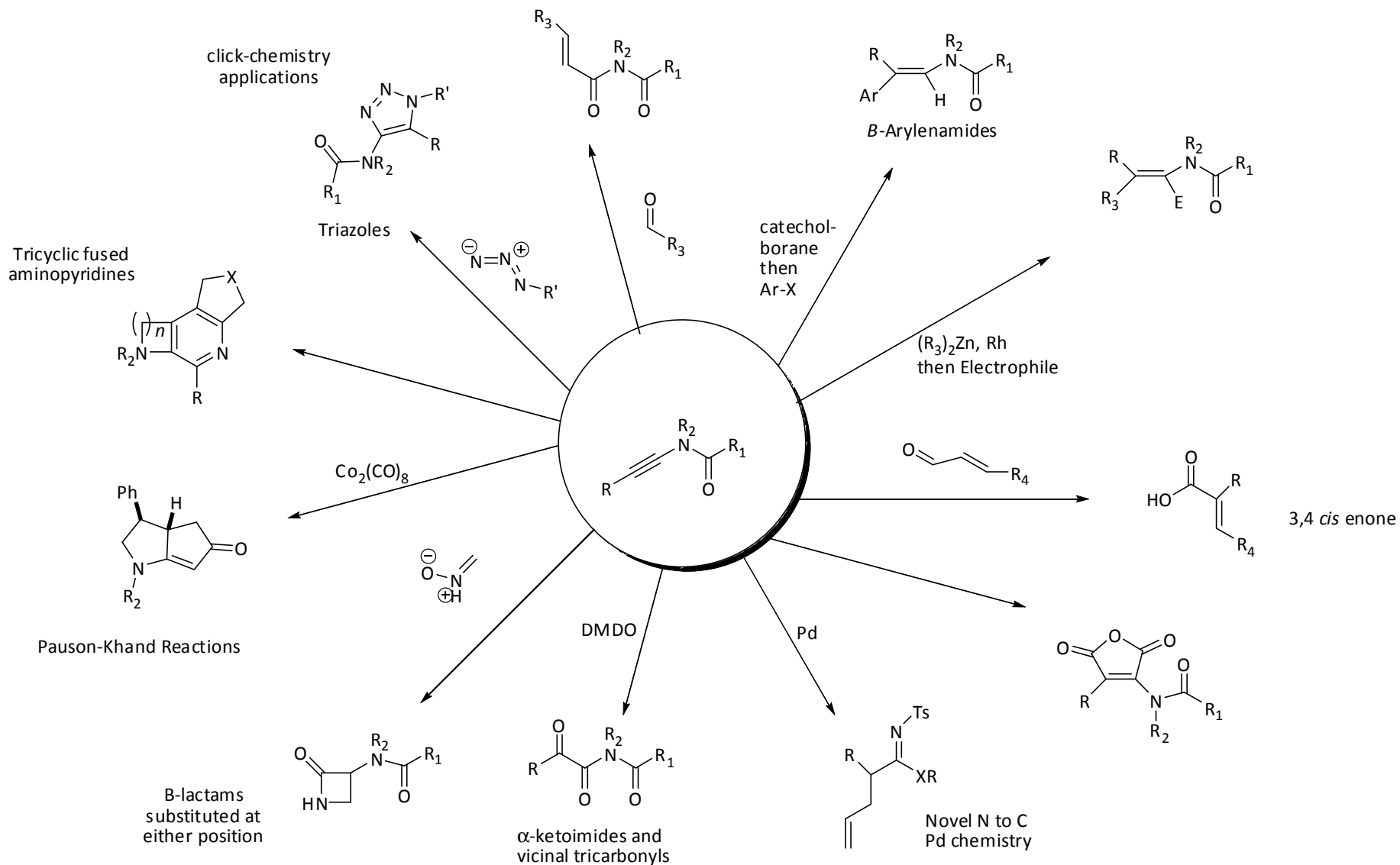


Electronics



- Ynamines were first reported in 1892 but not characterized until 1958-1960. The first useful route to ynamines was published in 1963 by Viehe.
- Due to the instability of ynamines, ynamides were seen as the alternative because of their stability. They were first synthesized in 1972 by Viehe.

What can we do with Ynamides?

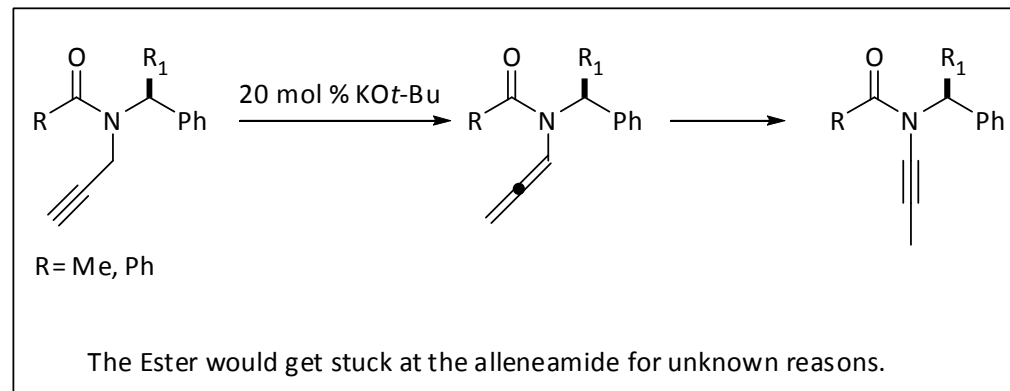


Overview

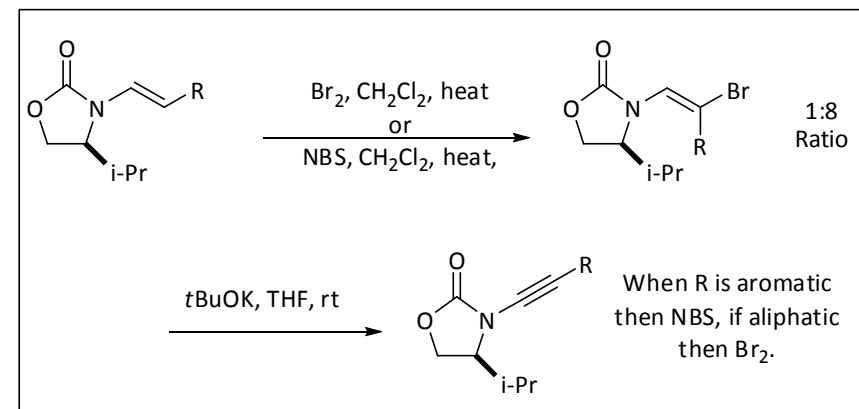
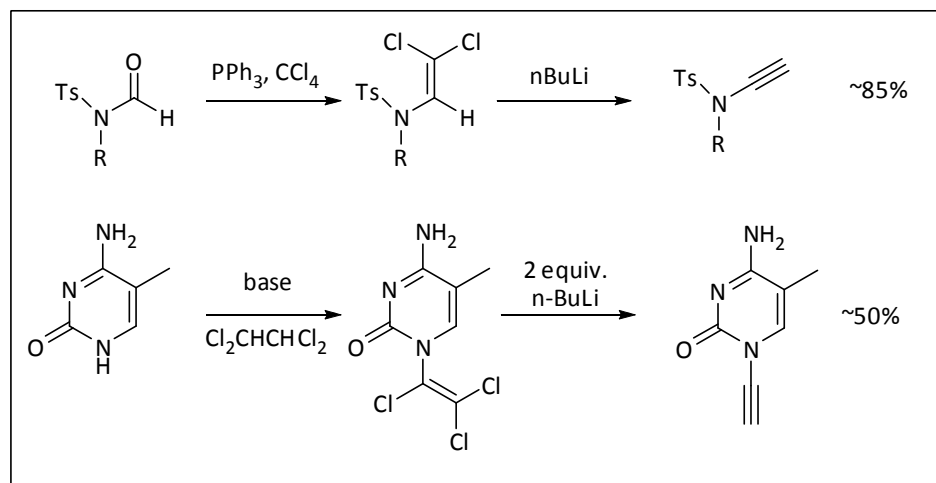
- Syntheses of Ynamides
 - Isomerization
 - Elimination
 - N-alkynylation
- Cycloaddition Chemistry
 - [2+2+2] pyridine synthesis
 - [2+2] cyclobutanones
 - [3+2] Kinugasa reaction
 - [2+2] 'Metathesis'
- Ynamides in Total Synthesis
 - Lennoxamine
 - Desbromoarborscidines A and C
 - Antiostatin A₁
- Other reactivity of Ynamides
 - Enamides synthesis
 - Sonogashira cross couplings
 - Oxidation and Vicinal Tricarbonyls

Let's make some Ynamides!

Isomerization:

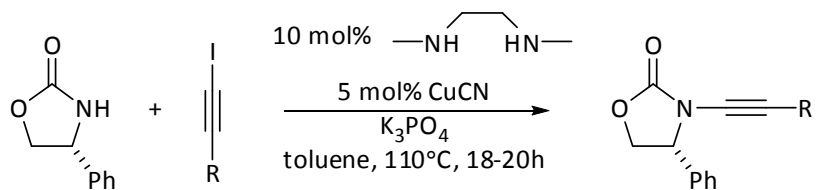
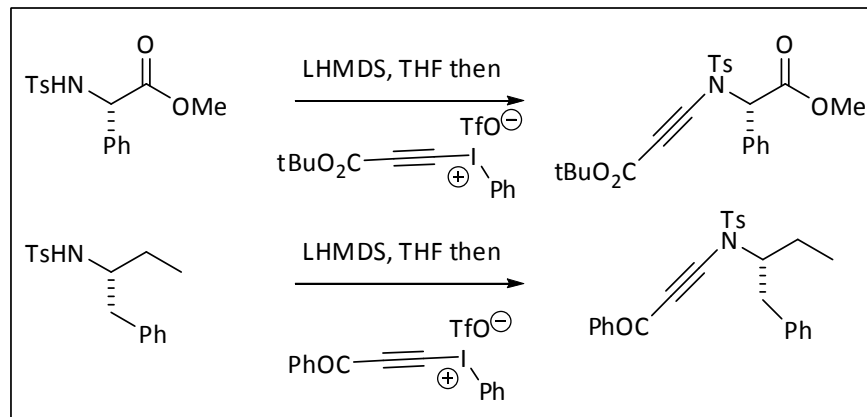


Elimination:

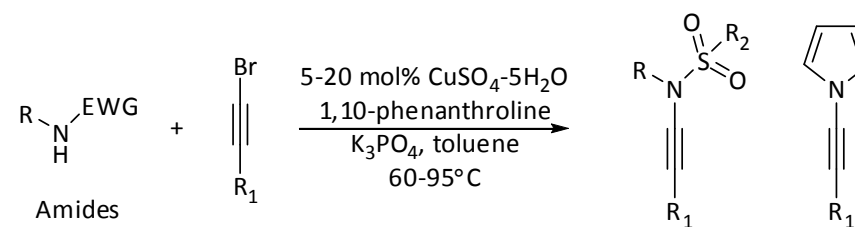
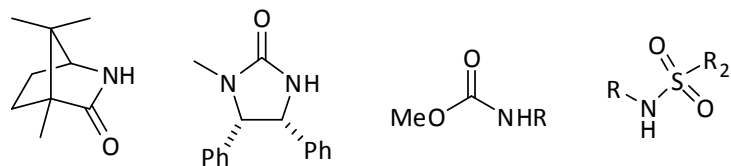


Let's make some Ynamides!

Direct N-alkylation Methods:

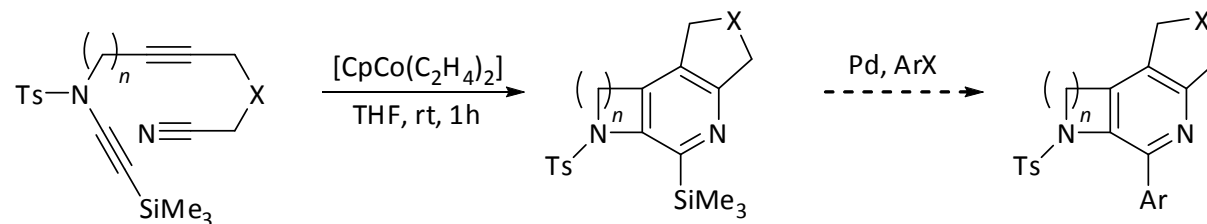


Looks great, but works pretty much only with sterically accessible amides. Sulfonamides didn't work at all. This is a problem because of how often Tosylamides are used in the future methodologies.

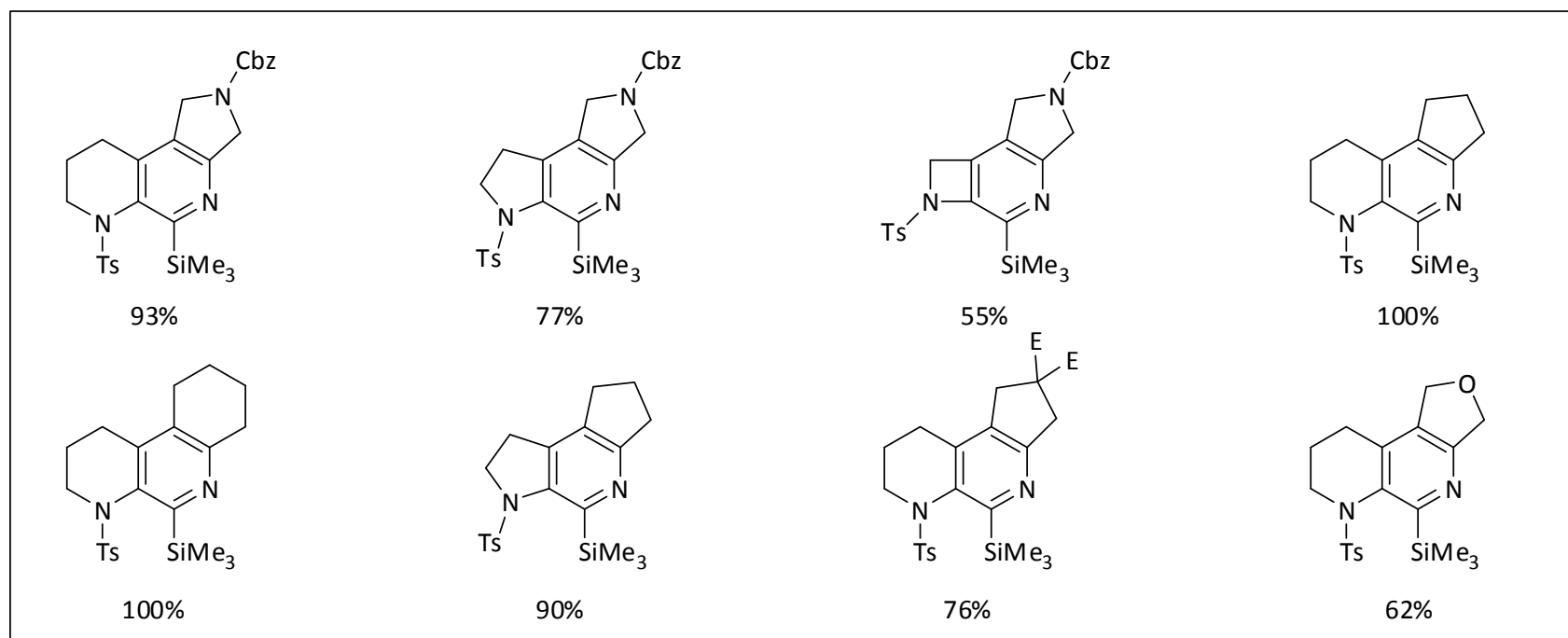


More of the various useful ynamides are accessible via this greener alkylation strategy.

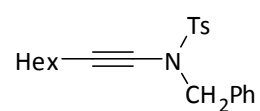
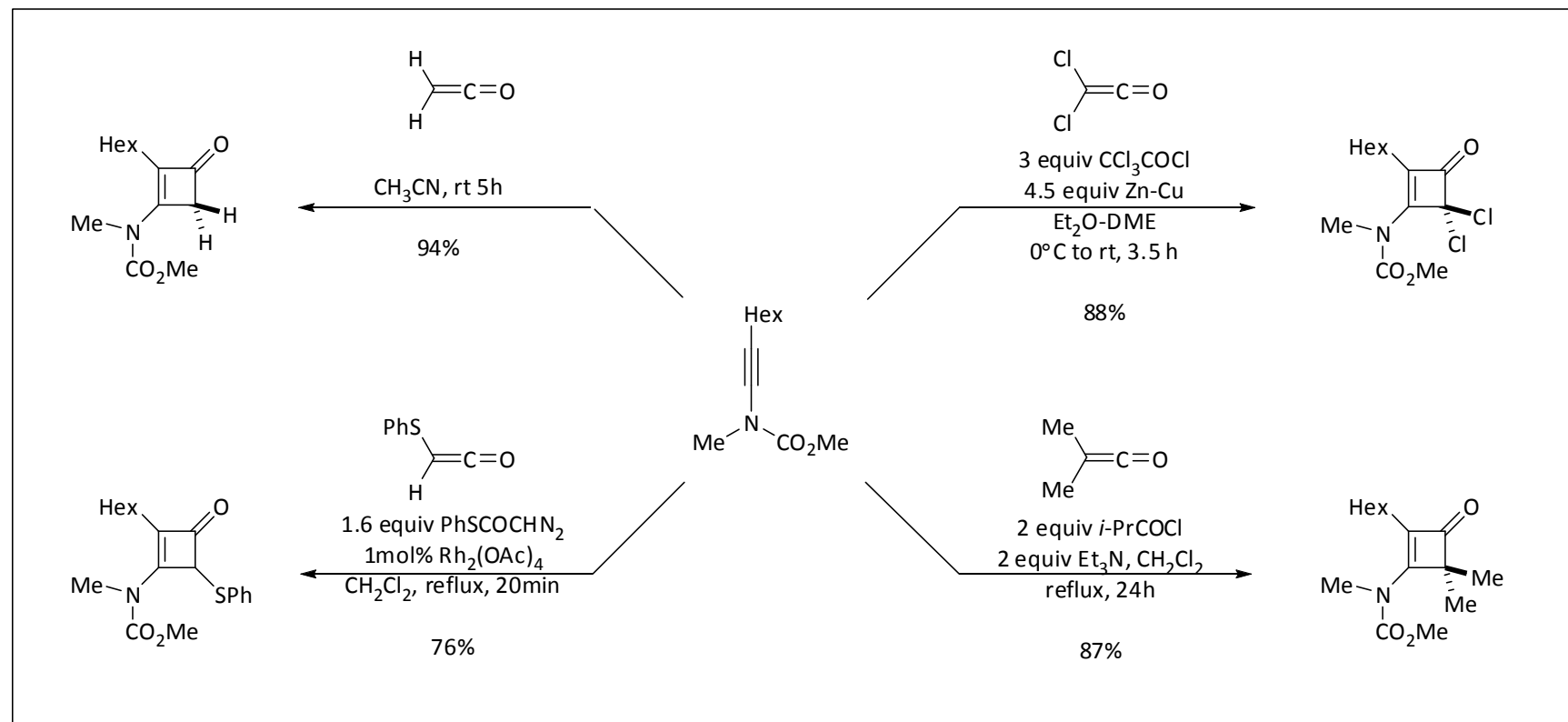
Easy Access to Substituted Pyridines!



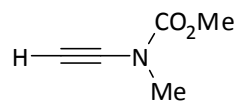
ynamide + alkyne + nitrile = pyridine!



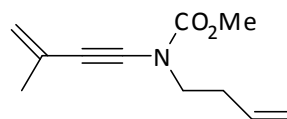
Synthesis of Cyclobutanones



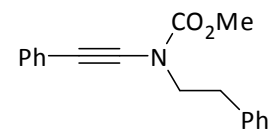
79%



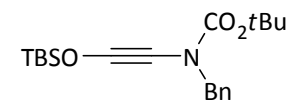
80%



65%

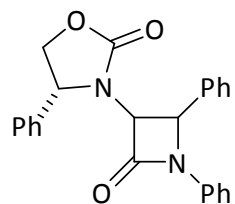
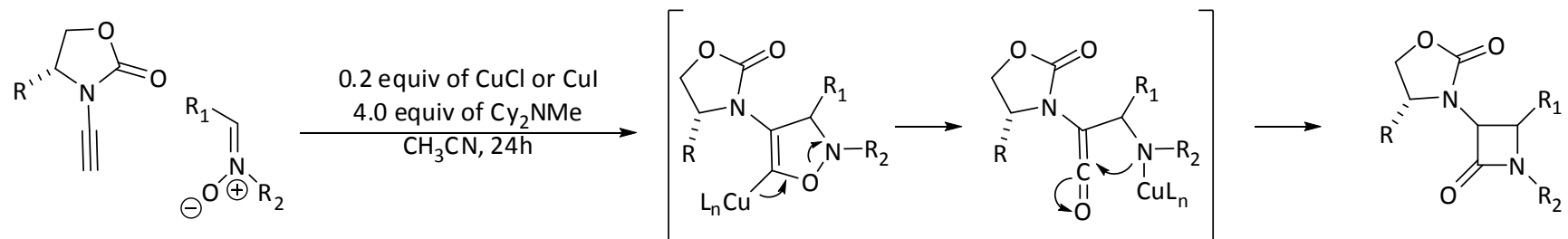


83%
brsm

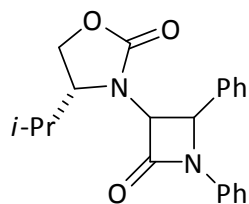


86%

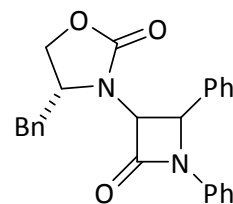
Let's make some *B*-lactams!



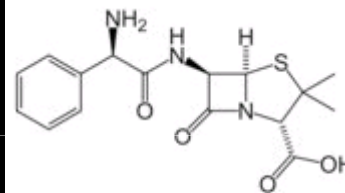
80%



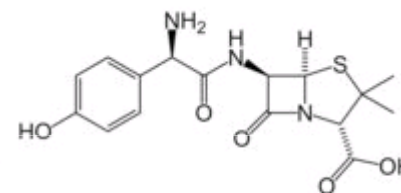
36%



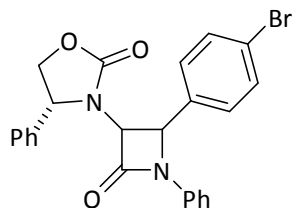
28%



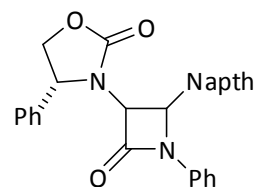
ampicillin



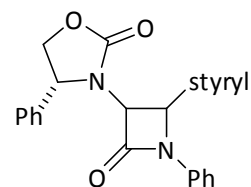
amoxicillin



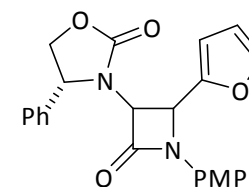
77%
>95:5



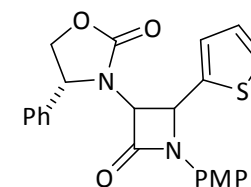
71%
90:10



72%
93:7

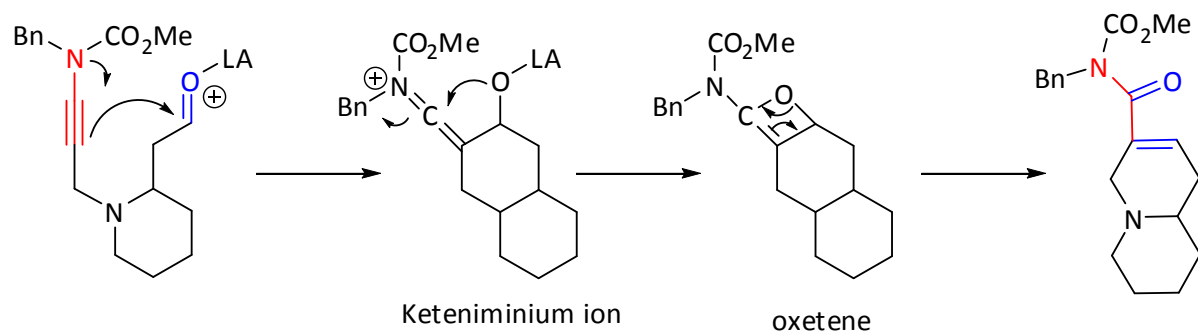
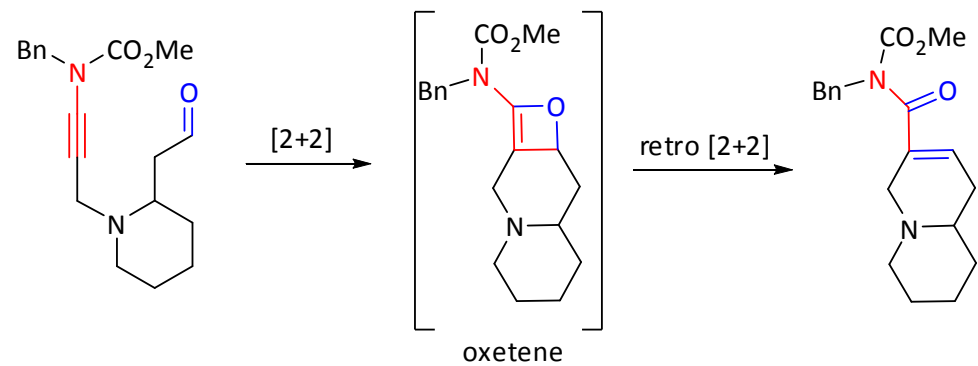


61%
82:18

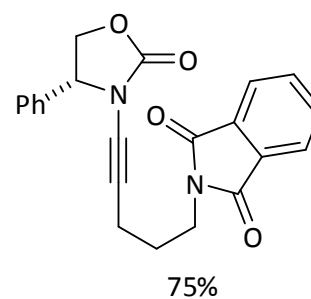
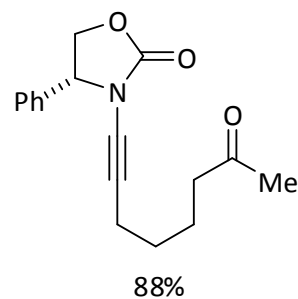
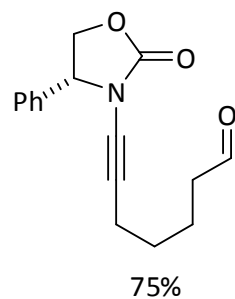
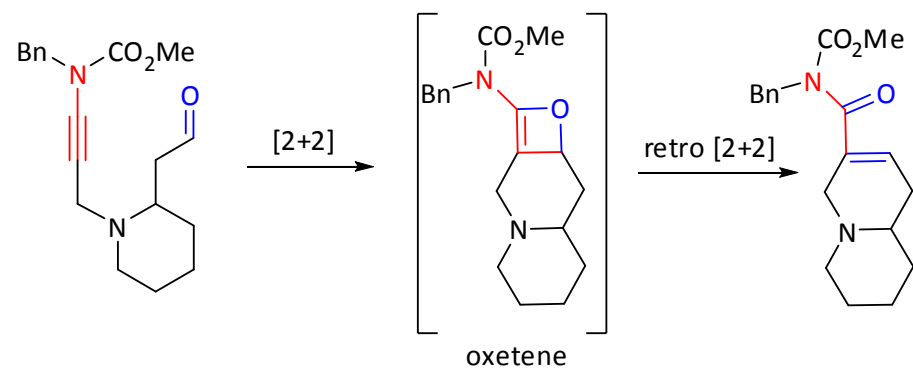


60%
>95:5

Cycloadditions with Ynamides

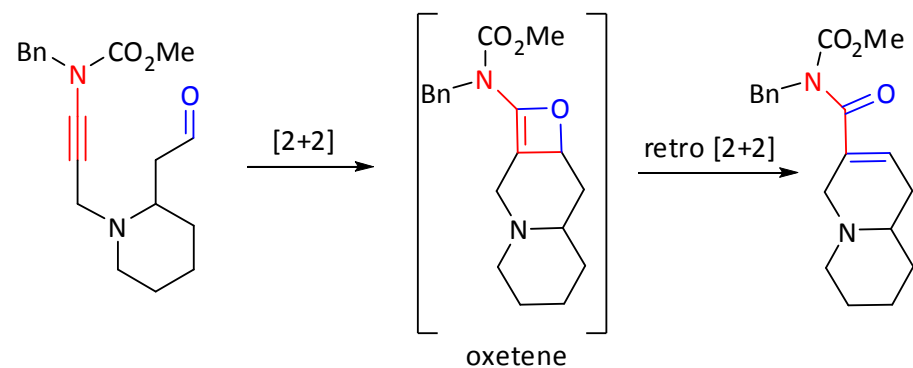


Cycloadditions with Ynamides

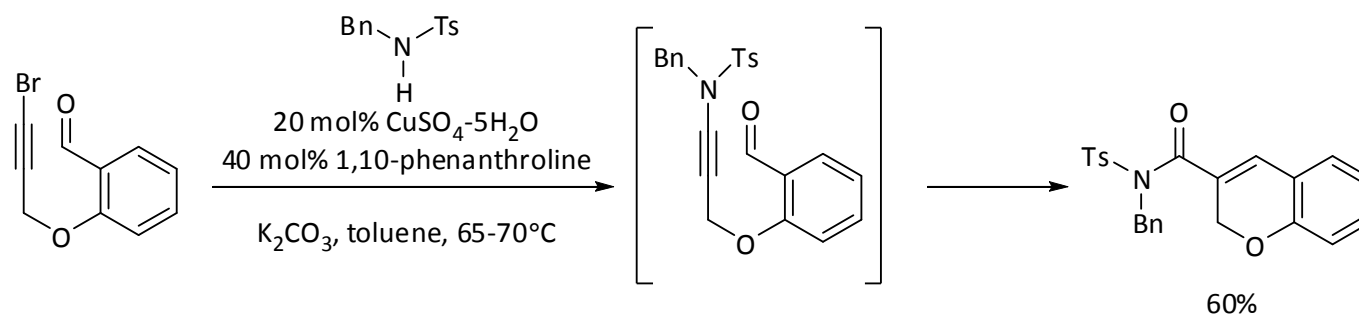


Best yields are with oxazolidinone ynamides.
Ring sizes 7 and up have diminished yields.
Camphor and tosylamides have significantly poorer yields.

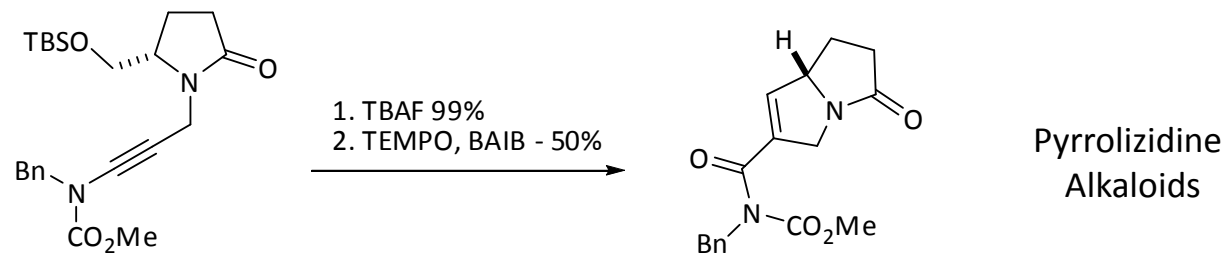
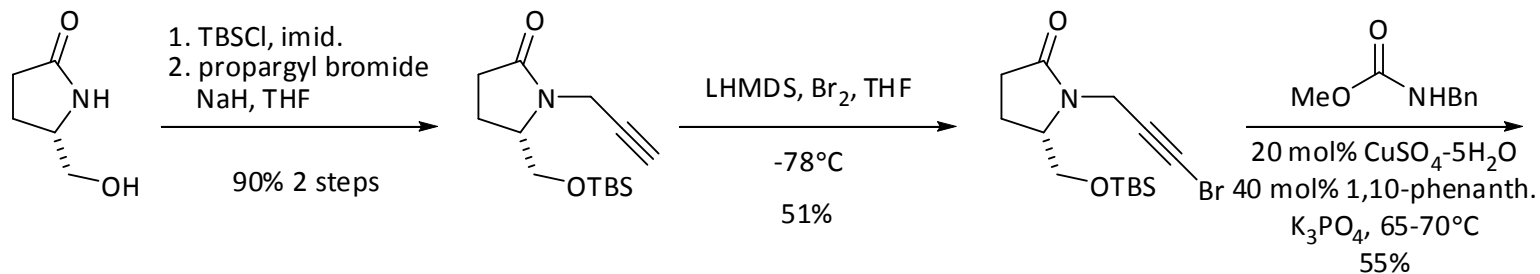
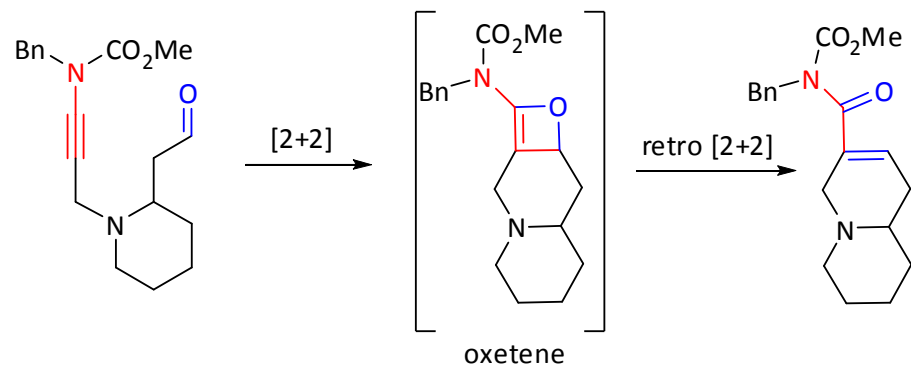
Cycloadditions with Ynamides



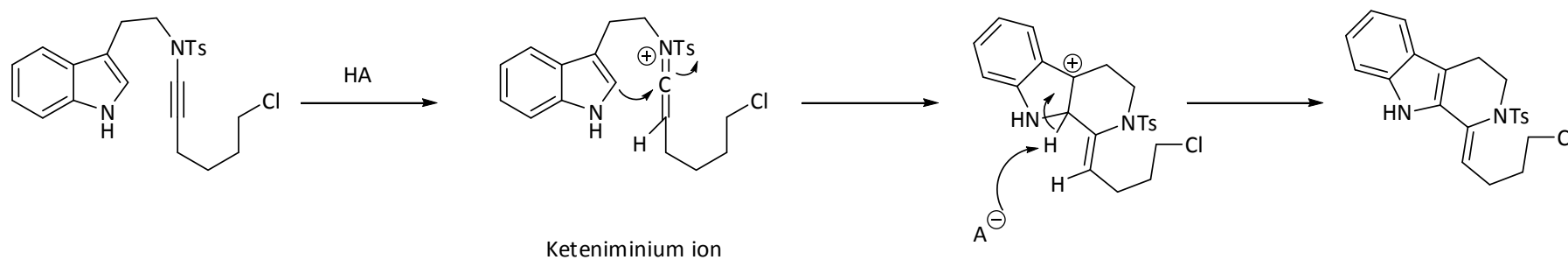
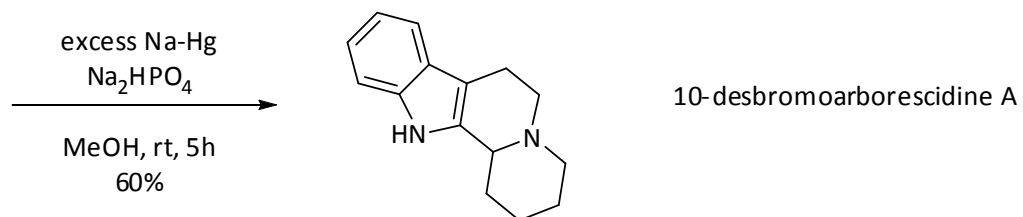
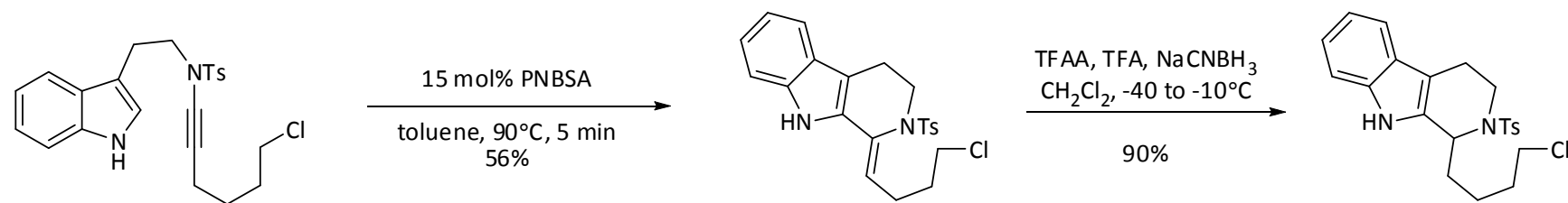
Tandem amidation-hetero metathesis



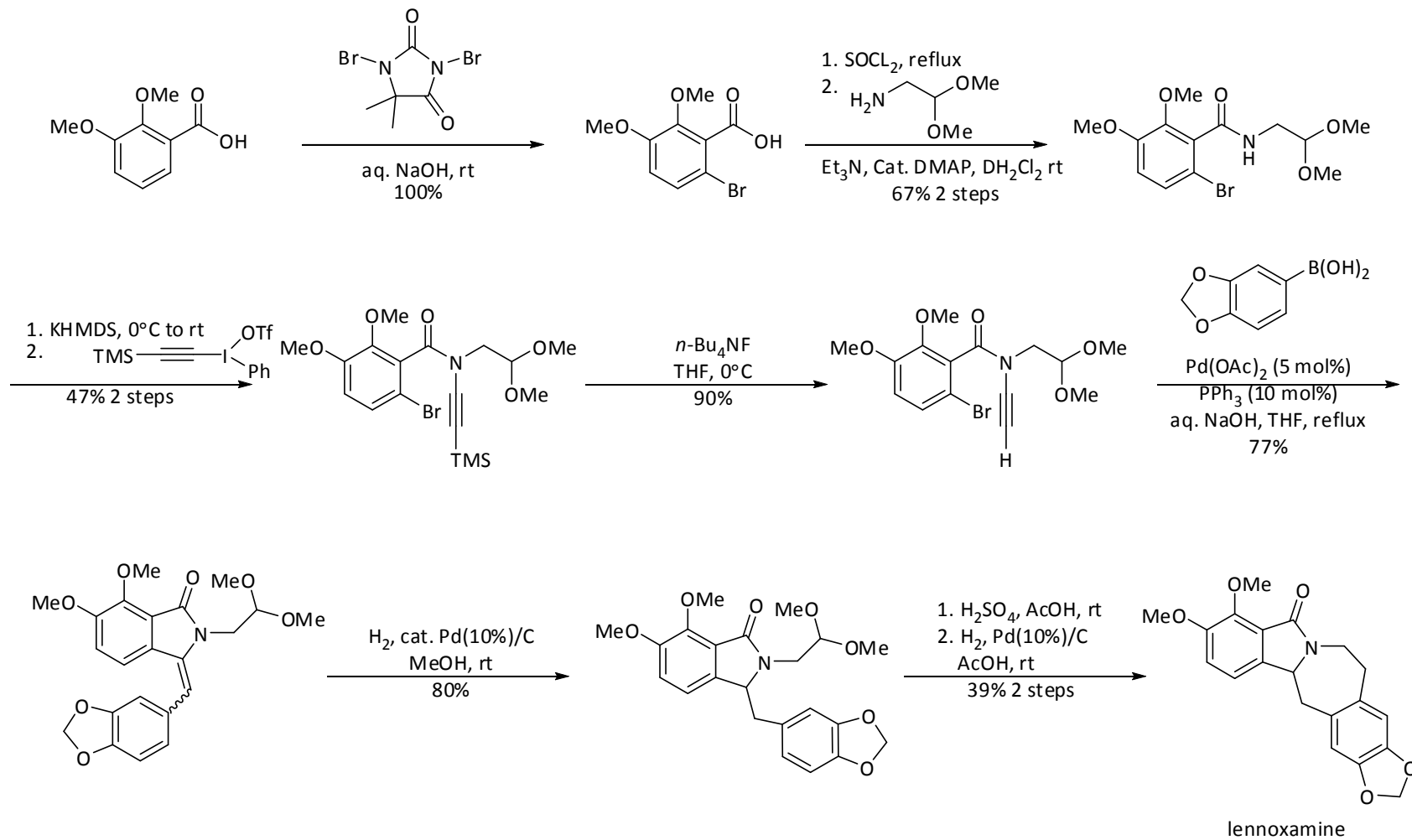
Cycloadditions with Ynamides



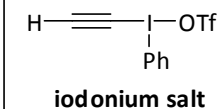
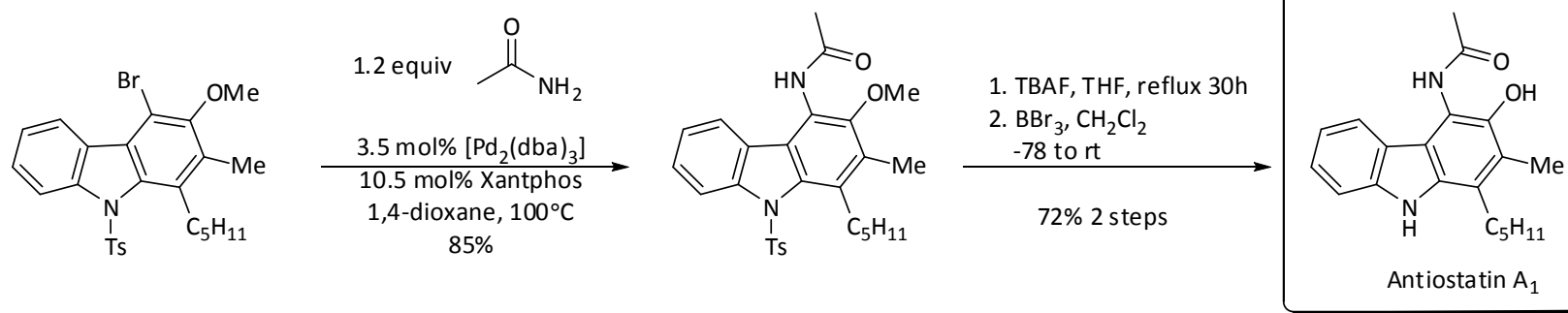
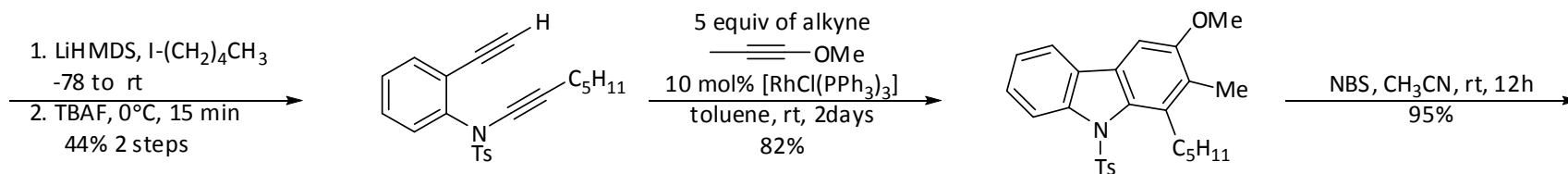
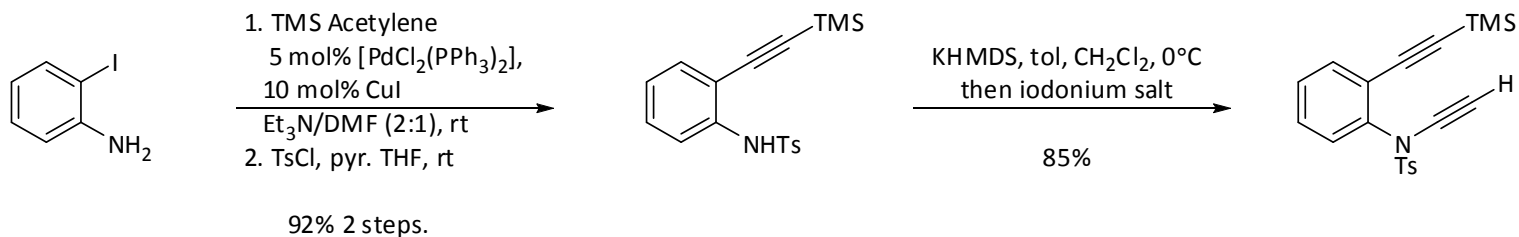
More Total Synthesis with Ynamides



More Total Synthesis with Ynamides



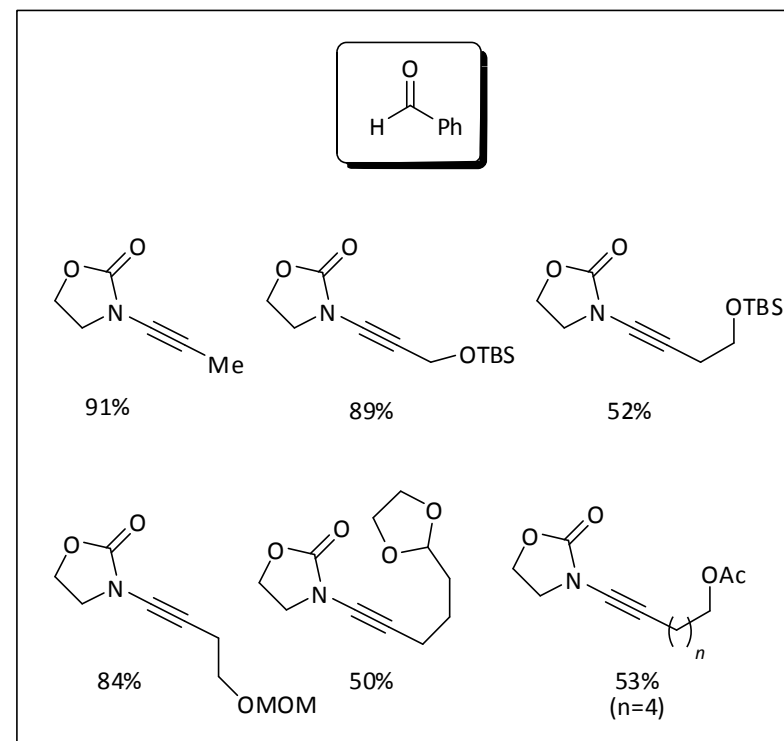
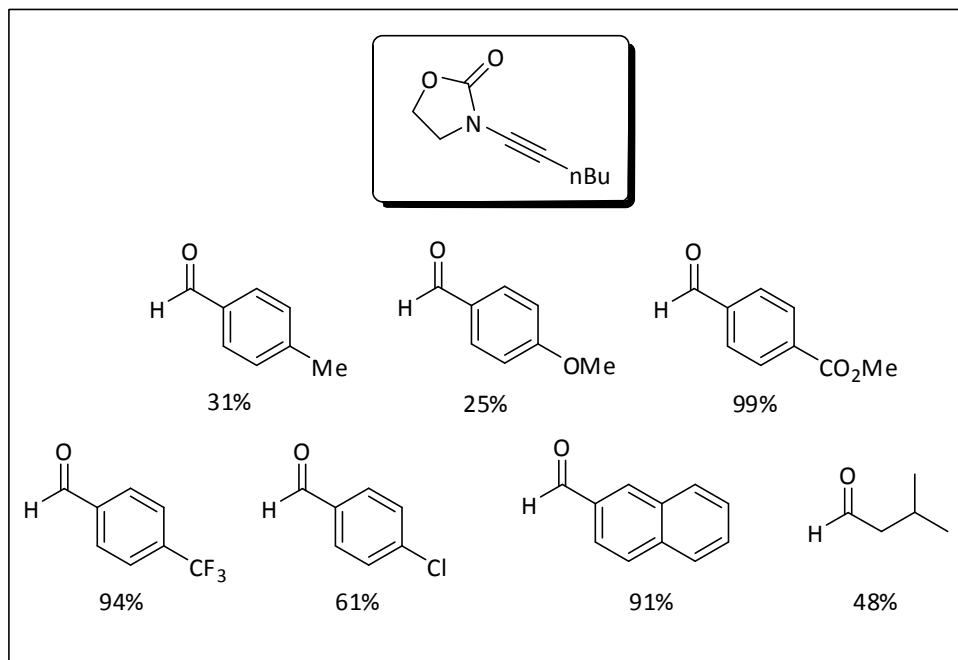
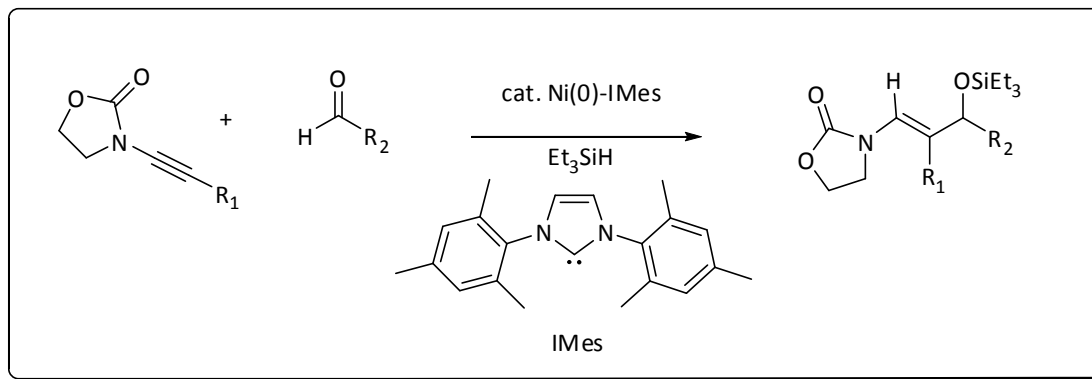
More Total Synthesis with Ynamides



What else can you do with ynamides?

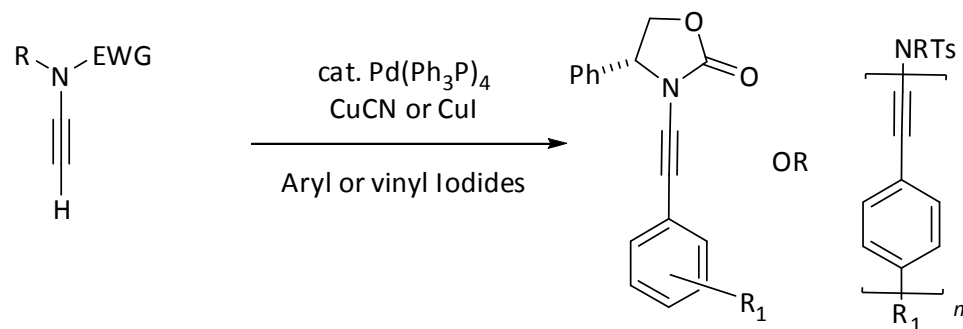
Enamide synthesis

- Order of addition turned out to be the important factor for this reaction. The ynamide is added over 7 hours to the stirring solution of the catalyst, ligand, and aldehyde to arrive at the optimum procedure.
- Electron deficient aldehydes work best.

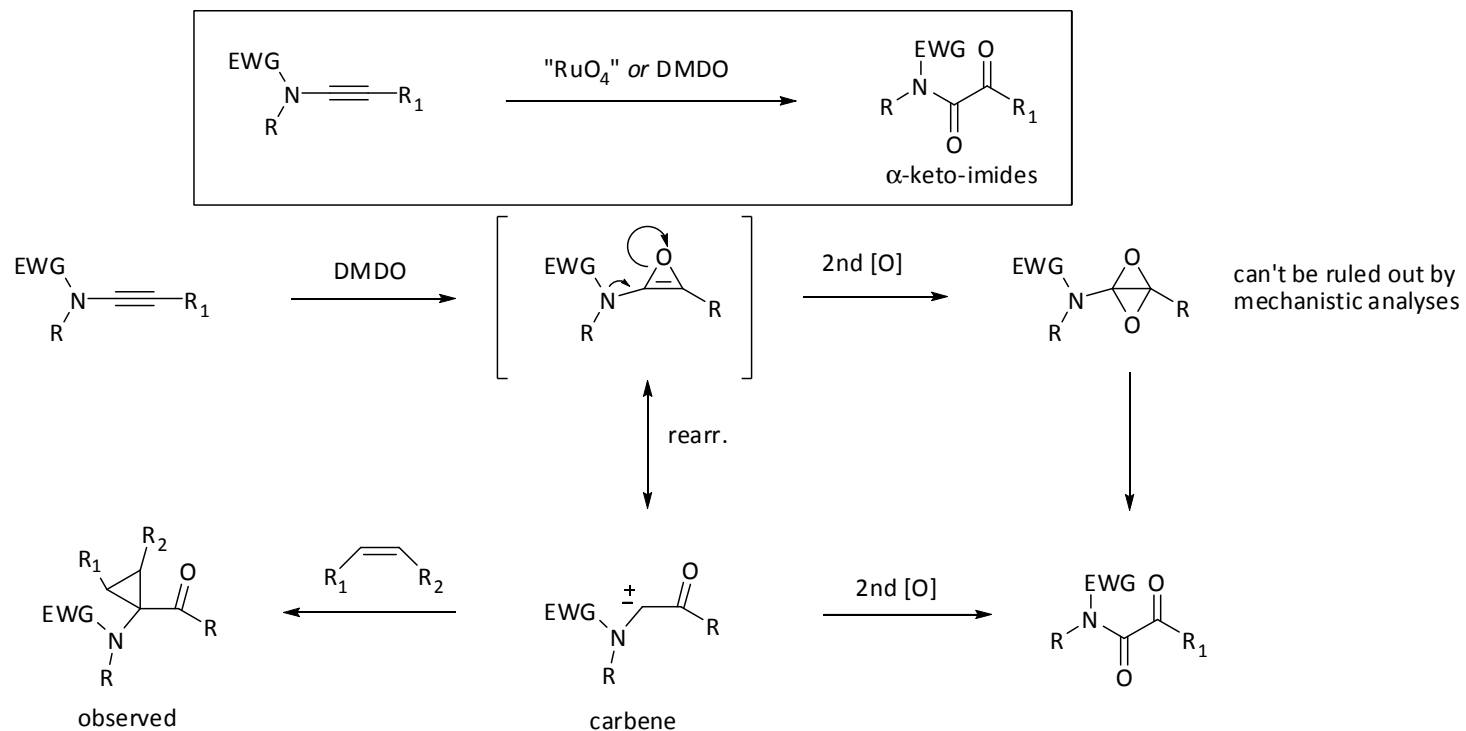


What else can you do with ynamides?

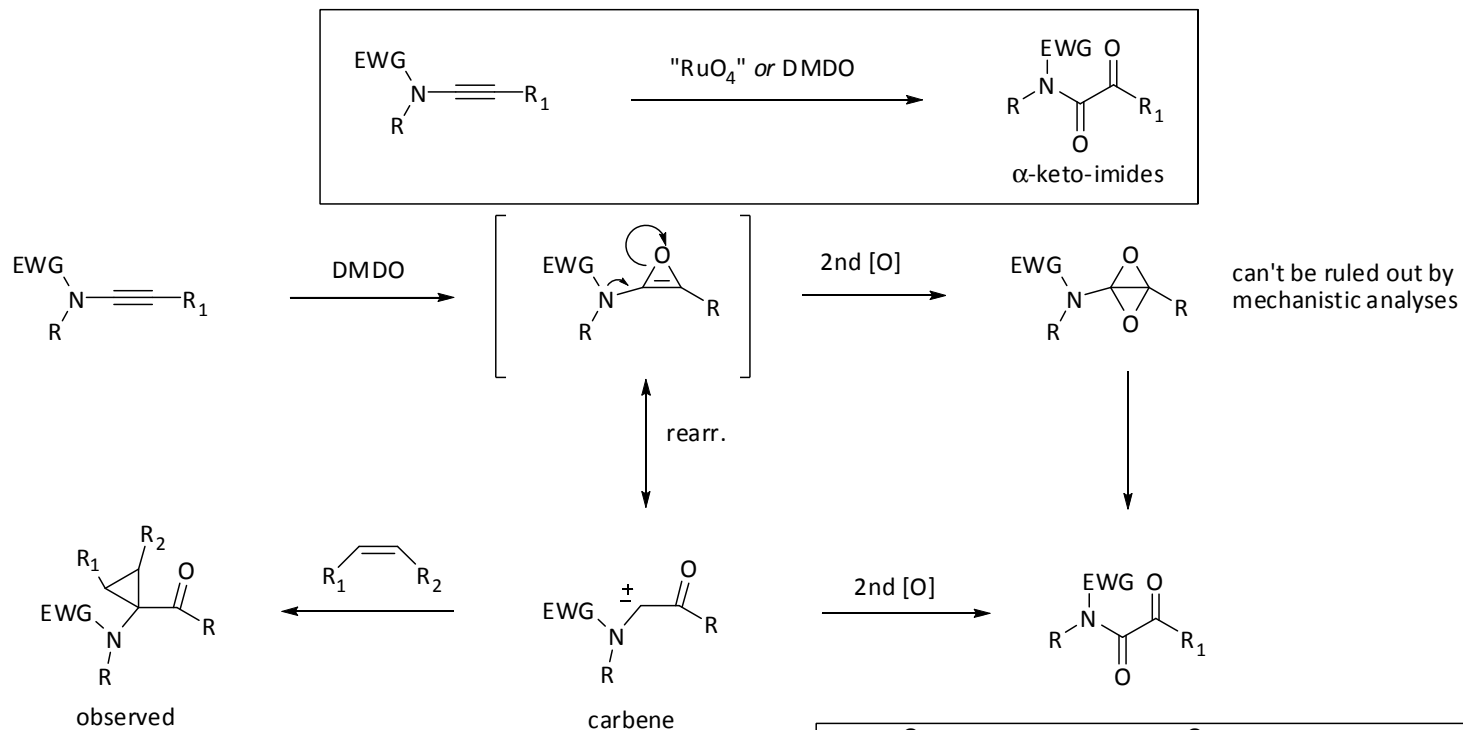
Sonagashira cross-coupling – analog synthesis



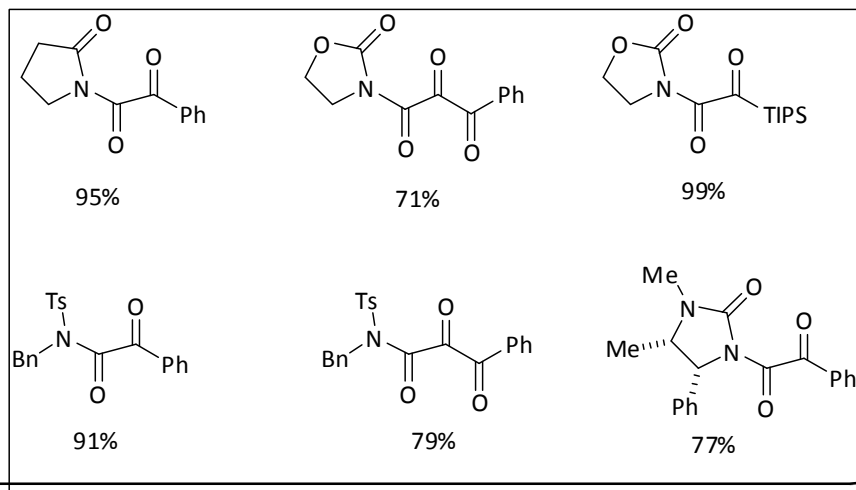
Oxidation



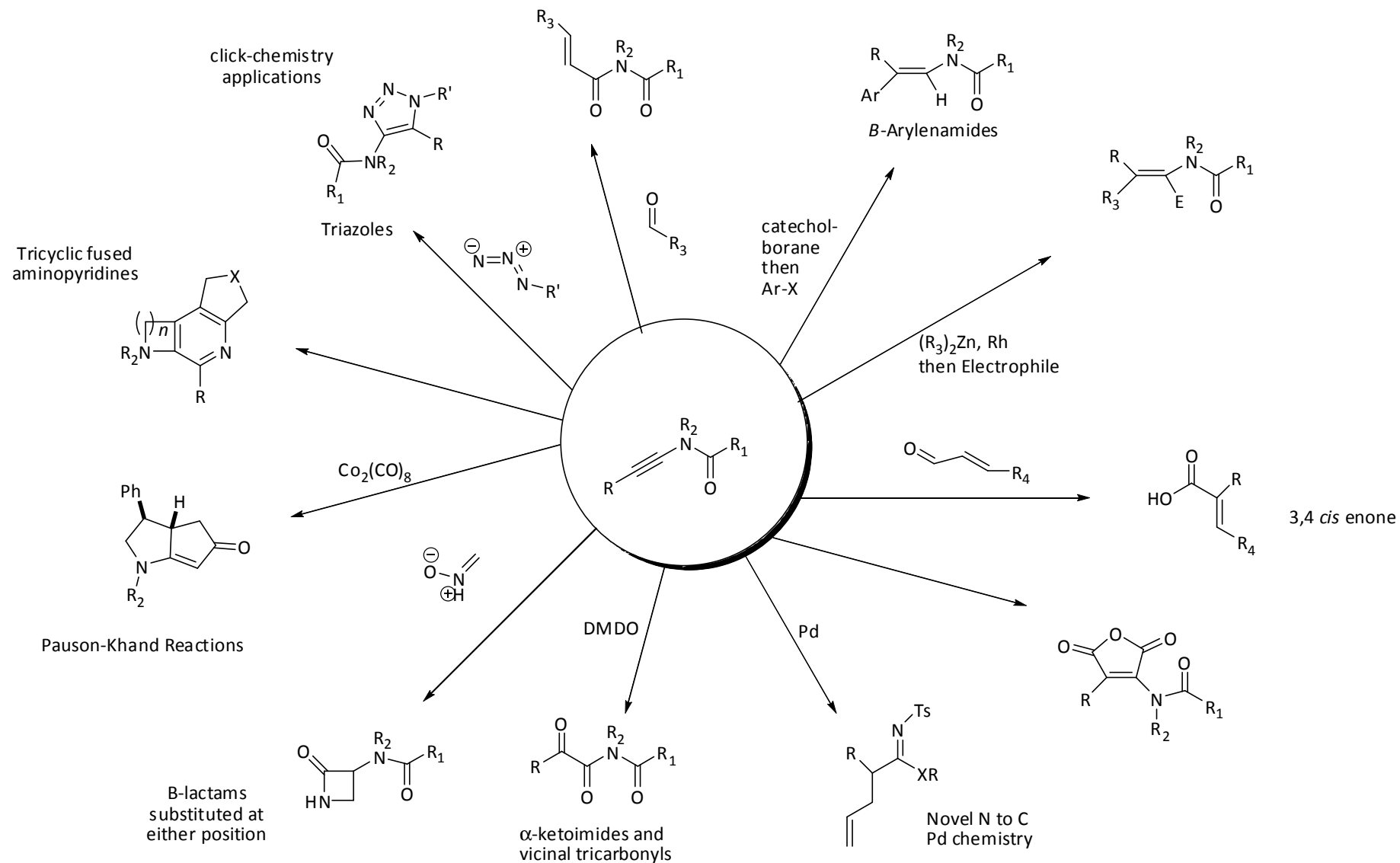
What else can you do with ynamides?



RuO₂-NaIO₄ is the better oxidant system, but DMDO works well too in cases where the ynamide is sensitive to oxidation at other functionalities. This oxidation gives extremely simple access to vicinal tricarbonyls (VTCs) which do some cool chemistry. (Ref 18) See the review in the references.



Ynamide Transformations



References:

Preparation of Ynamides:

- (1) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zifacsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459-466 %U <http://www.sciencedirect.com/science/article/B6THR-4233BFS-3/2/1f7ffcc63fdf35db900ad8be7bf70445>.
- (2) Zifacsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575-7606 %U <http://www.sciencedirect.com/science/article/B6THR-43T1K3J-3/2/024930a8ecd9d04e3bf5cabb3d31791f>.
- (3) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Organic Letters* **2002**, *4*, 2417-2420 %U <http://dx.doi.org/10.1021/ol020097p>.
- (4) Dunetz, J. R.; Danheiser, R. L. *Organic Letters* **2003**, *5*, 4011-4014 %U <http://dx.doi.org/10.1021/ol035647d>.
- (5) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *Journal of the American Chemical Society* **2003**, *125*, 2368-2369 %U <http://dx.doi.org/10.1021/ja021304j>.
- (6) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Organic Letters* **2004**, *6*, 1151-1154 %U <http://dx.doi.org/10.1021/ol049827e>.
- (7) Brückner, D. *Tetrahedron* **2006**, *62*, 3809-3814 %U <http://www.sciencedirect.com/science/article/B6THR-4JBGHVH-1/2/c7d54ff10cd0675c7f48e9beacc66960>.

Cycloaddition chemistry with Ynamides:

- (8) Ijsselstijn, M.; Cintrat, J.-C. *Tetrahedron* **2006**, *62*, 3837-3842 %U <http://www.sciencedirect.com/science/article/B6THR-4JCBN46-5/2/faa5002409483aa3a107a8bb4ced092c>.
- (9) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815-3822 %U <http://www.sciencedirect.com/science/article/B6THR-4JB9MPG-3/2/24080604f608f5bcf83b001687b7a5b7>.
- (10) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Organic Letters* **2006**, *8*, 231-234 %U <http://dx.doi.org/10.1021/ol052487s>.
- (11) Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Organic Letters* **2008**, *10*, 3477-3479 %U <http://dx.doi.org/10.1021/ol801257j>.
- (12) Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chemistry - A European Journal* **2009**, *15*, 2129-2139 %U <http://dx.doi.org/10.1002/chem.200802301>.

Interesting Ynamide chemistry:

- (13) Gourdet, B.; Lam, H. W. *Journal of the American Chemical Society* **2009**, *131*, 3802-3803 %U <http://dx.doi.org/10.1021/ja900946h>.
- (14) Saito, N.; Katayama, T.; Sato, Y. *Organic Letters* **2008**, *10*, 3829-3832 %U <http://dx.doi.org/10.1021/ol801534e>.
- (15) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *The Journal of Organic Chemistry* **2008**, *73*, 8780-8784 %U <http://dx.doi.org/10.1021/jo8015067>.
- (16) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *The Journal of Organic Chemistry* **2006**, *71*, 4170-4177 %U <http://dx.doi.org/10.1021/jo060230h>.
- (17) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Organic Letters* **2004**, *6*, 2209-2212 %U <http://dx.doi.org/10.1021/ol0493251>.
- (18) Wasserman, H. H.; Parr, J. *Accounts of Chemical Research* **2004**, *37*, 687-701 %U <http://dx.doi.org/10.1021/ar0300221>. (Vicinal Tricarbonyls)

Total Synthesis:

- (19) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chemical Communications* **2009**, 1464-1466 %U <http://dx.doi.org/10.1039/b820291e>.
- (20) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron Letters* **2006**, *47*, 767-769 %U <http://www.sciencedirect.com/science/article/B6THS-4HTCTC0-4/2/455de109d7997f96c5816d3d9dba950a>.
- (21) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Organic Letters* **2005**, *7*, 1047-1050 %U <http://dx.doi.org/10.1021/ol0473391>.