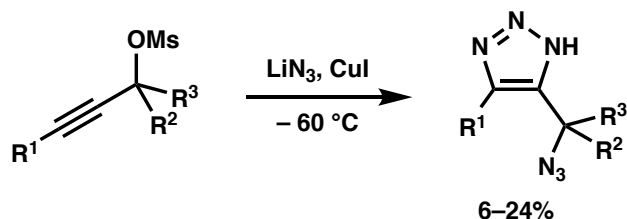
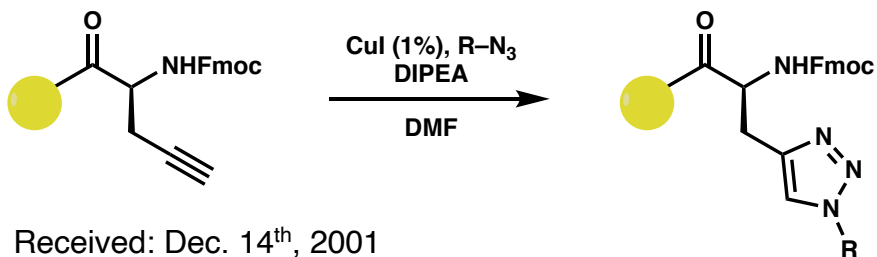


Background:

L'abbé (1984):

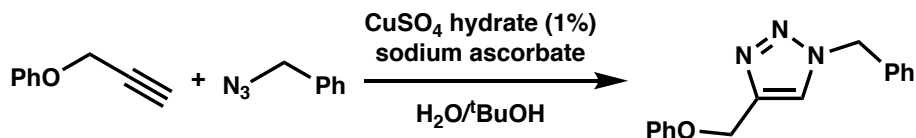
*Bull. Soc. Chim. Belg.* **1984**, 93, 579

Meldal (2002):

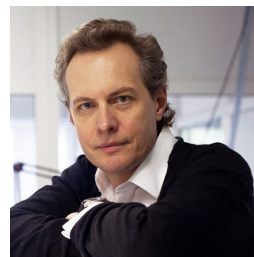
*J. Org. Chem.* **2002**, 67, 3057Received: Dec. 14th, 2001Published: Apr. 2nd, 2002

6.3k citations

Fokin and Sharpless (2002):

Received: Apr. 29th, 2002Published: Jul 15th, 2002

7.8k citations

Original Report: *ACIE* **2002**, 41, 2596Mechanism: *Science* **2013**, 340, 456

Valery Fokin



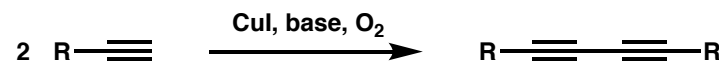
Barry Sharpless

“The fact that this ‘unstoppable’ reactivity of copper(I) acetylides with organic azides remained unrevealed until now, despite the great body of research on copper-mediated organic synthesis over the last seventy years, is extraordinary.”

“Despite this ‘azidophobia,’ we have learned to work safely with azides because they are the most crucial functional group for click chemistry endeavors.”

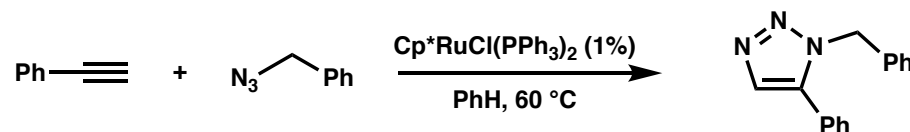
“a very robust catalytic process, which is so insensitive to the usual reaction parameters as to strain credulity.”

Glaser / Hay Coupling:



Cu(I) salts also useful: CuI , CuOTf , $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ *but* must use 2,6-lutidine and exclude O_2 to prevent byproducts

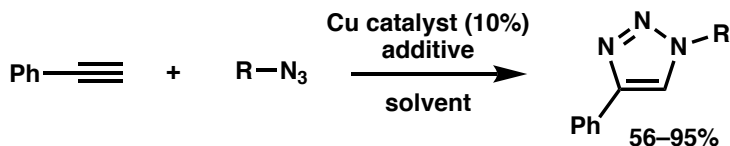
Fokin, Sharpless and Jia (2005):



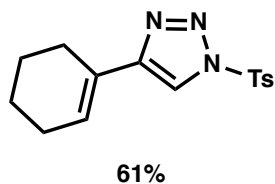
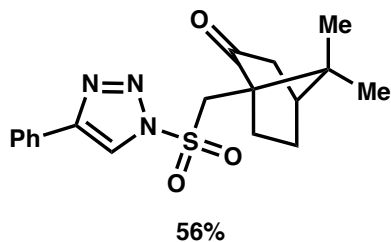
– internal alkynes are competent substrates as well

JACS **2005**, 127, 15998

Fokin, Sharpless and Chang (2007):

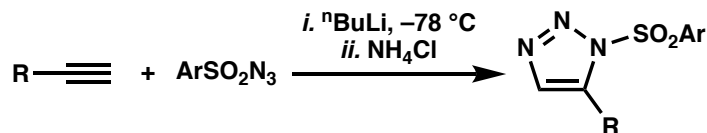


Catalyst	Additive	Solvent	Temperature	Yield (R = Ts)
CuSO ₄ hydrate	sodium ascorbate	H ₂ O ^t /BuOH	25 °C	12%
CuI	DIPEA	CHCl ₃	0 °C	<1%
CuI	2,6-lutidine	CHCl ₃	25 °C	37%
CuI	2,6-lutidine	CHCl ₃	0 °C	80%



ACIE 2007, 46, 1730

Croatt (2011):



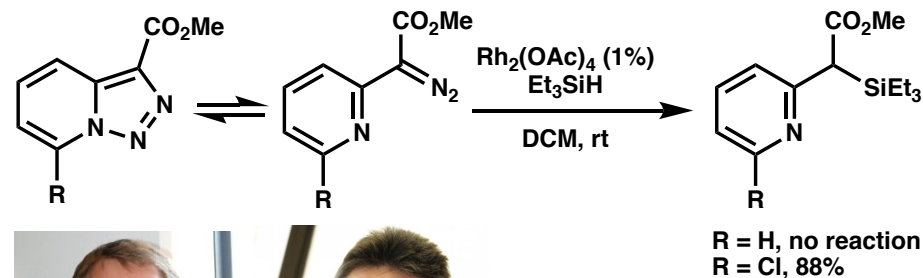
- 1,5-triazoles isomerize to 1,4-triazoles on silica gel
- crystallization can produce pure 1,5-triazoles
- storage at -20 °C for 1 week still results in isomerization to 1,4-triazoles

Org. Lett. 2011, 13, 2984

Early Studies:

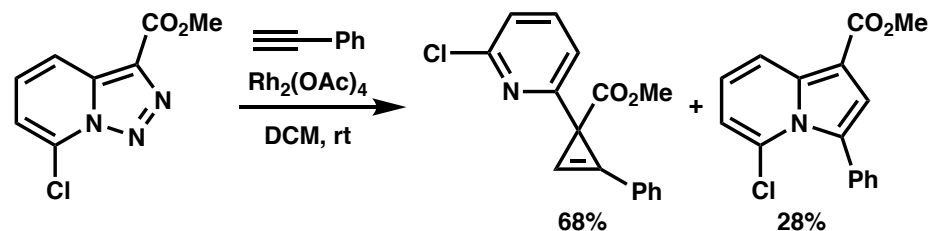
Gevorgyan (2007):

- follows up on a report from Davies (*J. Org. Chem.* **2001**, 66, 6595) and establishes triazoles as precursors of Rh carbenoids

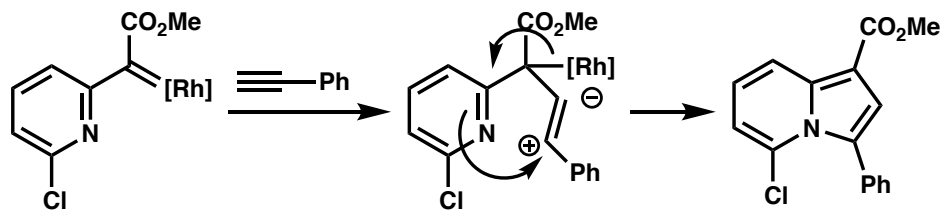


Stepan Chuprakov (Left)

Vladimir Gevorgyan (Right)

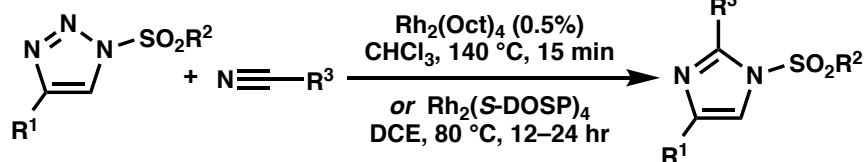
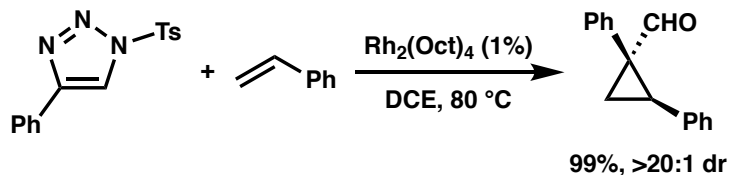


Proposed mechanism:

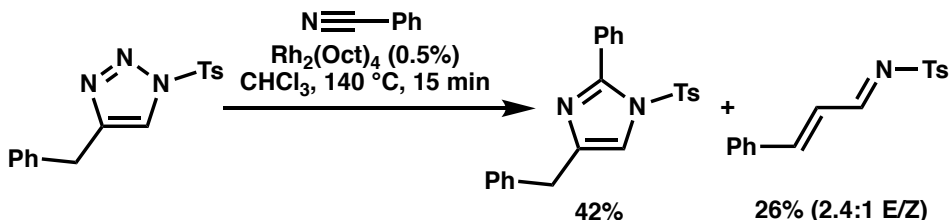
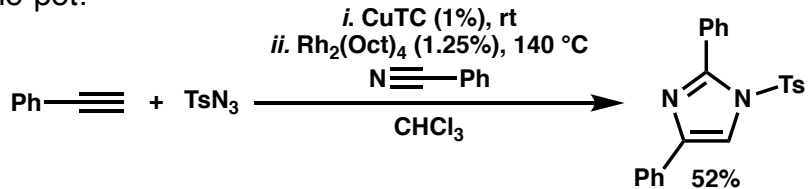


ACIE 2007, 46, 4757

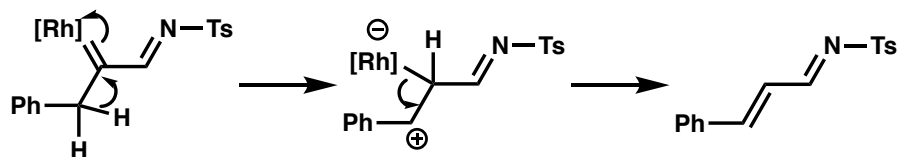
Gevorgyan and Fokin (2008):



one-pot:



via:

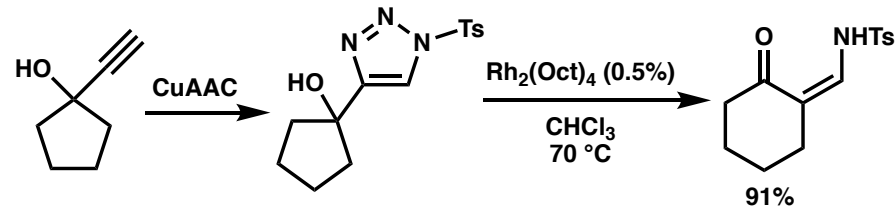


JACS 2008, 130, 14972

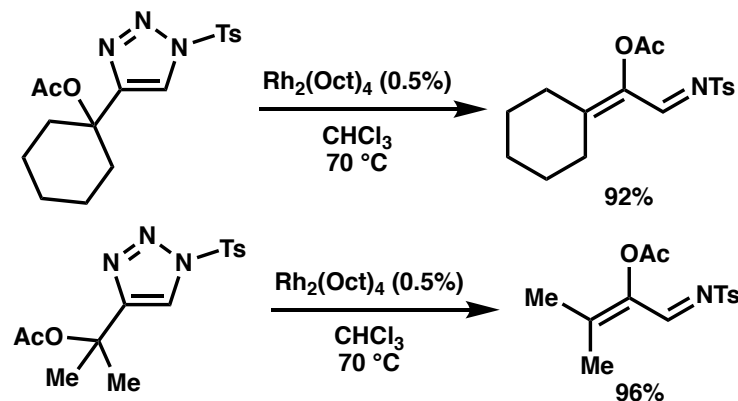
Rearrangements:

Fokin (2012):

Ring expansion:

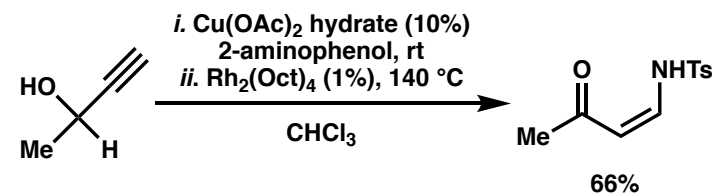


Rearrangement:



ACIE 2012, 51, 13054

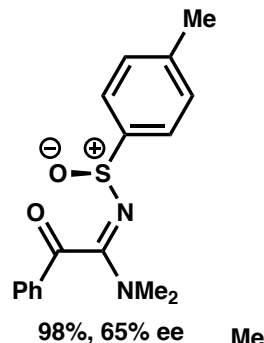
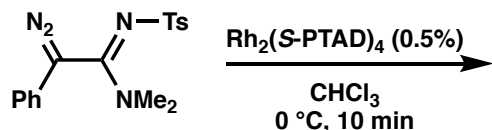
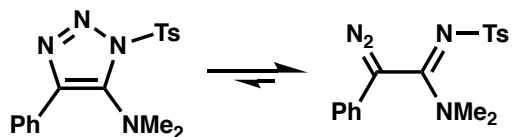
Murakami (2012):



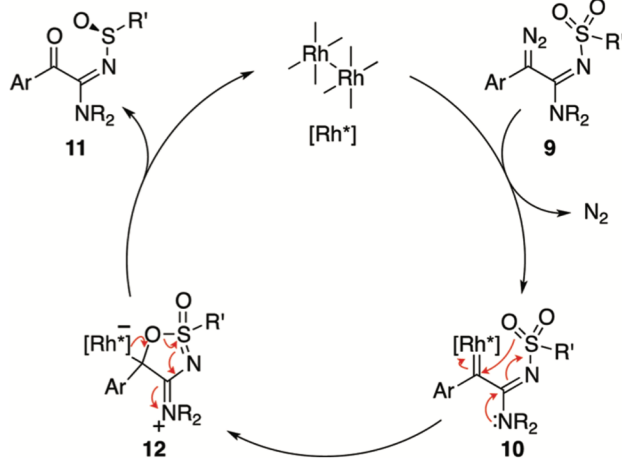
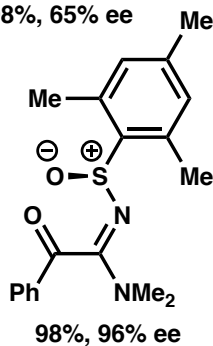
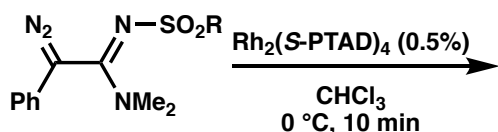
Masahiro Murakami

JACS 2012, 134, 17440

Fokin (2012):



– increased steric demand on sulfonyl group improves ee

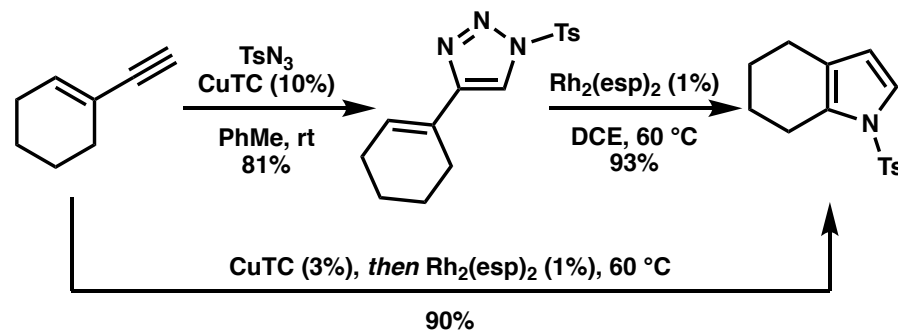


JACS 2012, 134, 2477

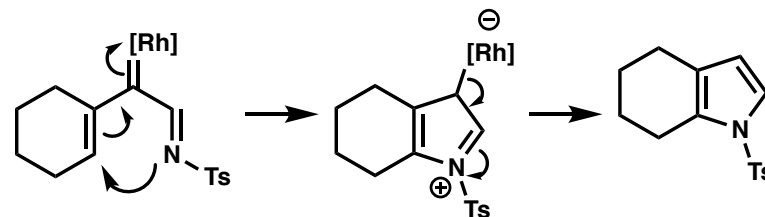
Huw Davies



Davies (2013):

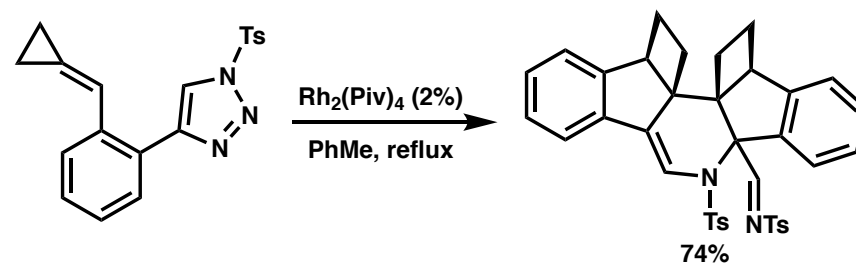


Proposed mechanism:



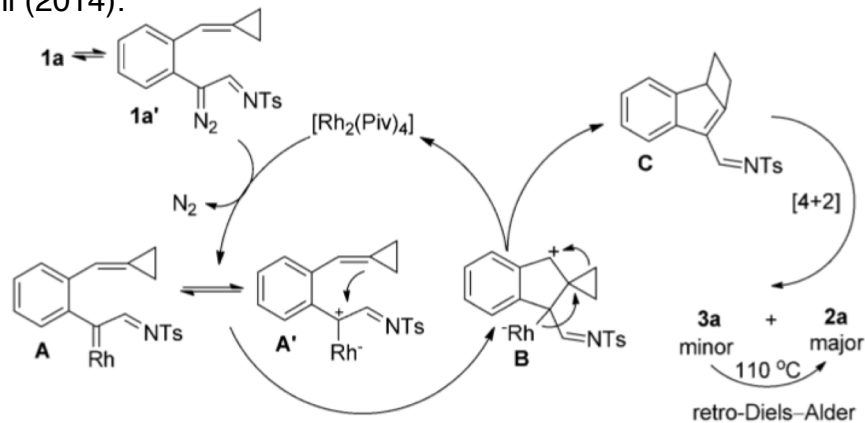
JACS 2013, 135, 11712

Shi (2014):



ACIE, 2014, 53, 6645

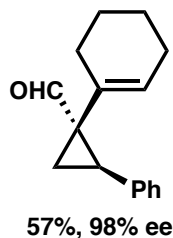
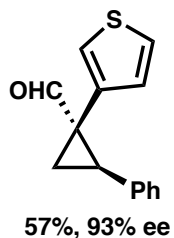
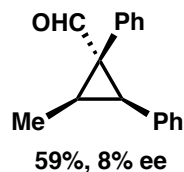
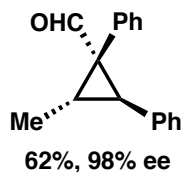
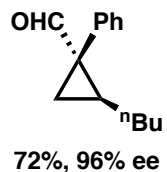
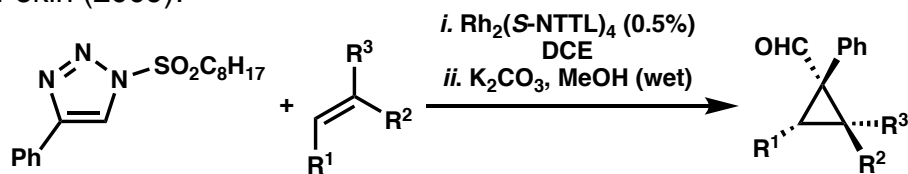
Shi (2014):



ACIE, 2014, 53, 6645

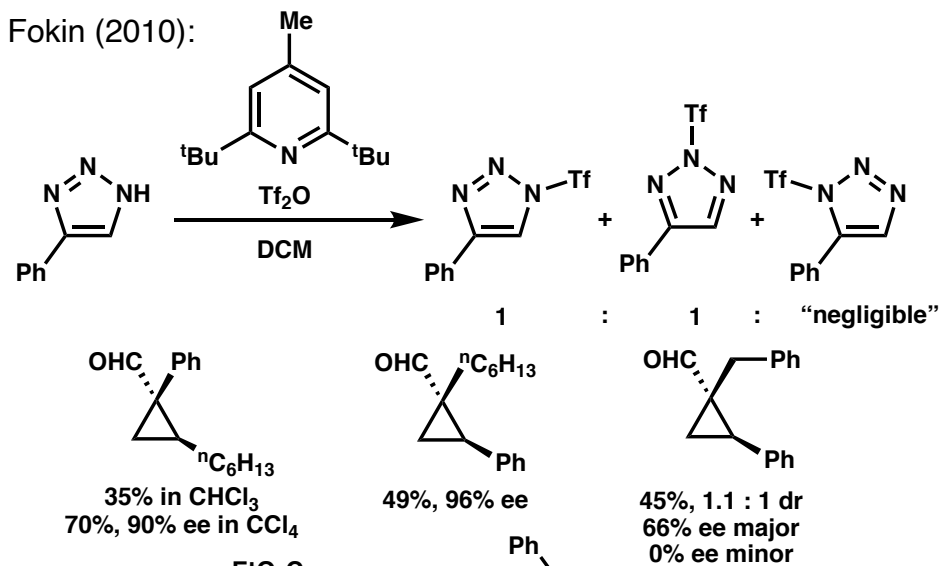
Cyclopropanation:

Fokin (2009):

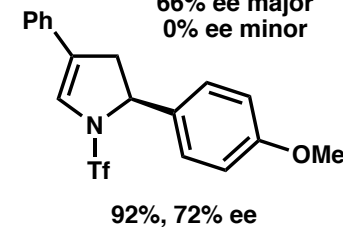
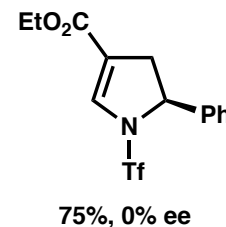
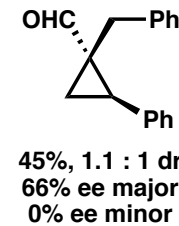
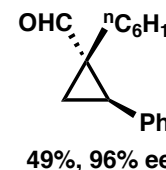
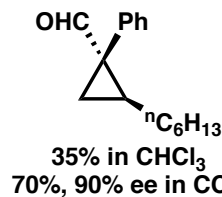


JACS 2009, 131, 18034

Fokin (2010):

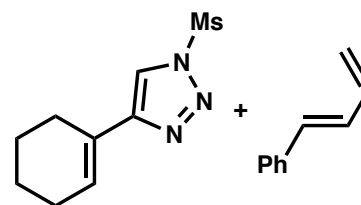
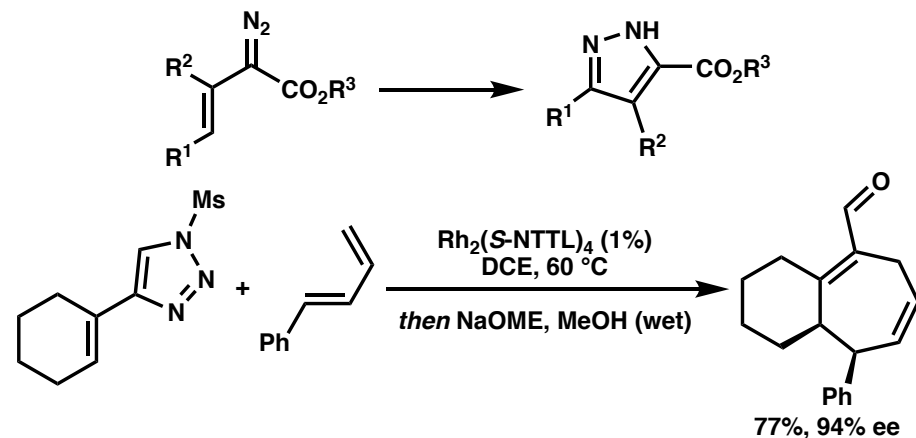


Conditions:
 i. $\text{Rh}_2(\text{S-NTTL})_4$ (0.5%), base, olefin, $-30\text{ }^\circ\text{C}$;
 ii. Tf_2O , $-30\text{ }^\circ\text{C}$ \rightarrow rt



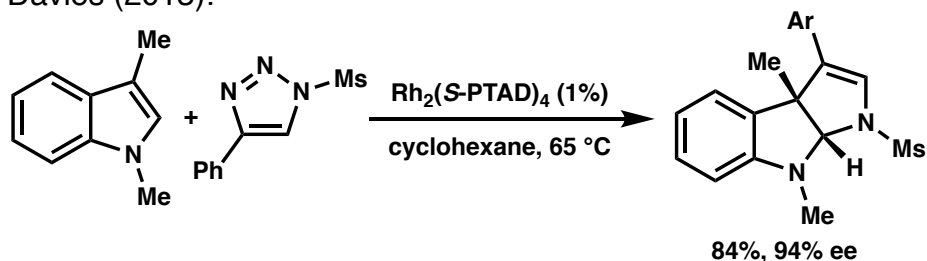
JACS 2010, 132, 2510

Davies (2013):

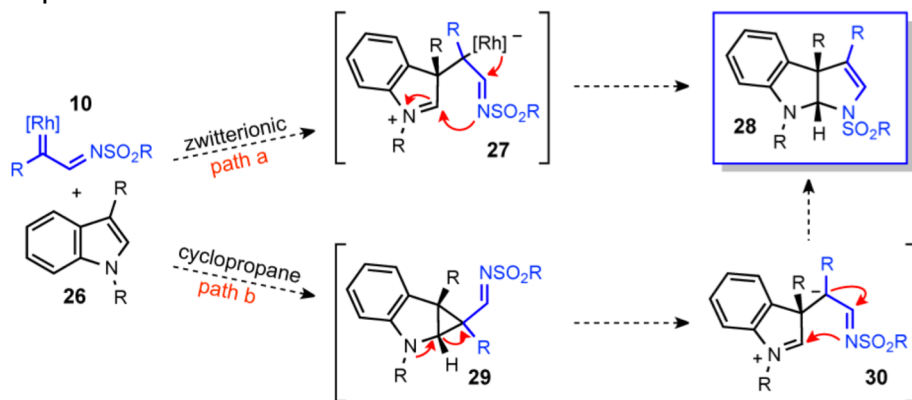


ACIE 2013, 52, 10044

Davies (2013):



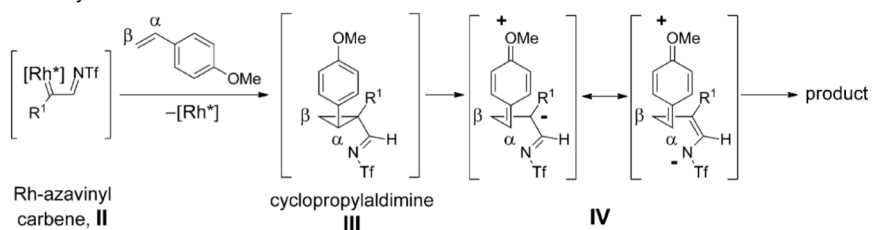
Proposed mechanism:



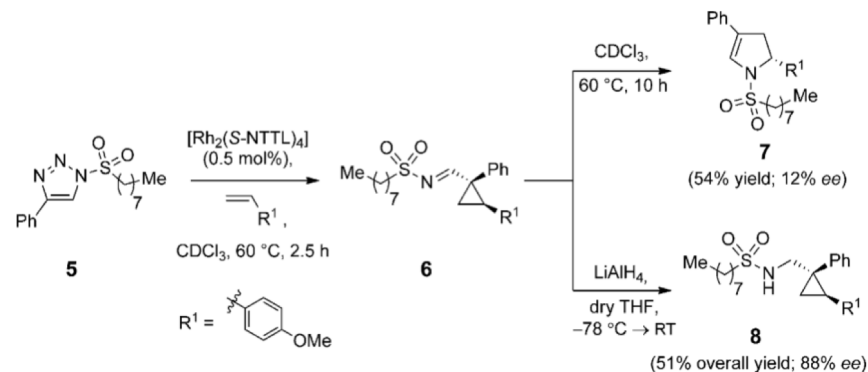
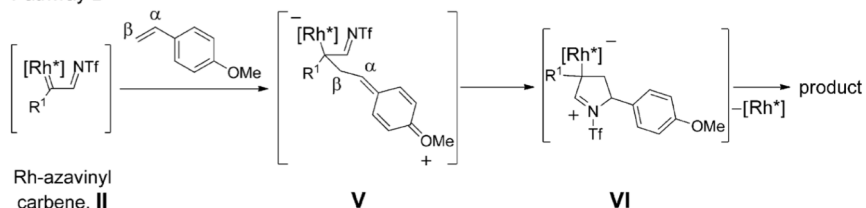
JACS 2013, 135, 6802

Fokin (2014):

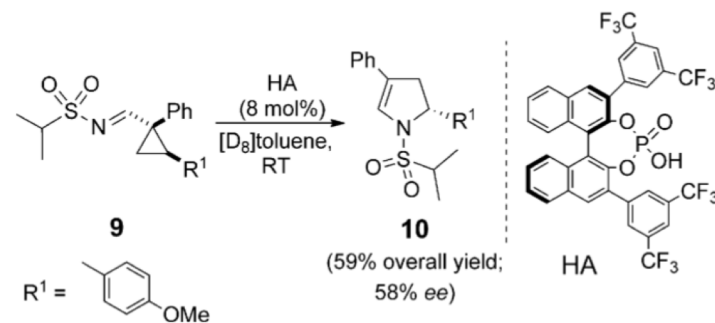
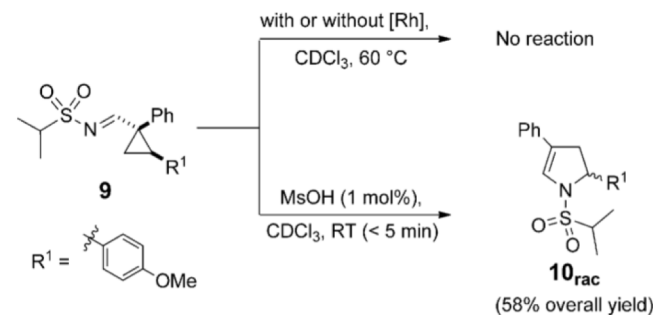
Pathway A



Pathway B



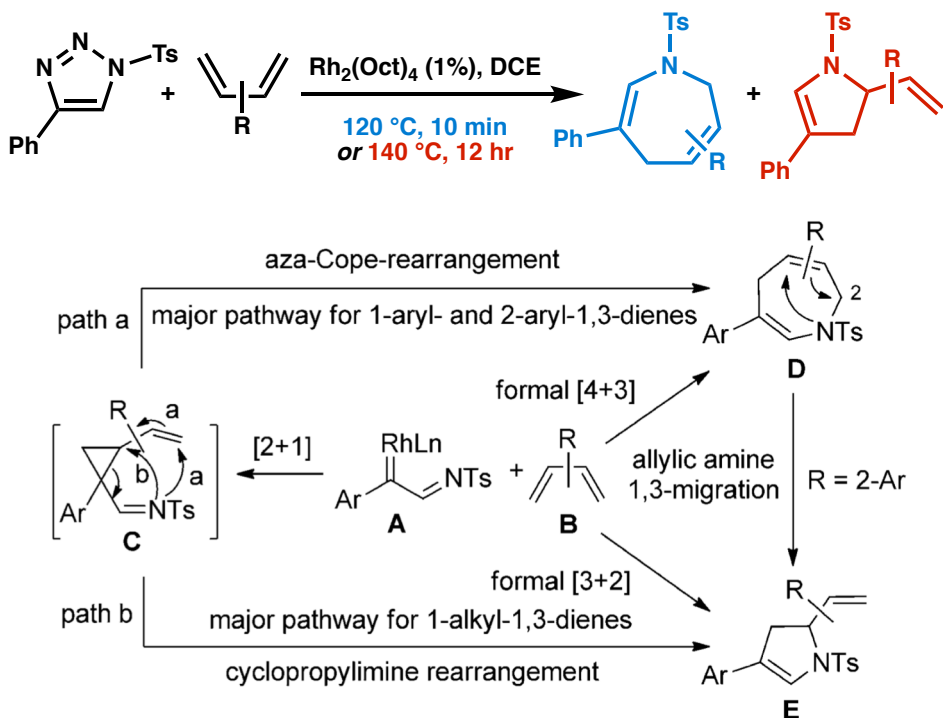
- 7 not detected prior to complete conversion of 5 to 6



“Proton activation, however, may have limited importance in the rearrangement of triflated cyclopropylimines, because of the increased electron-withdrawing power of the trifluoromethanesulfonyl group compared with alkyl-sulfonyl groups.”

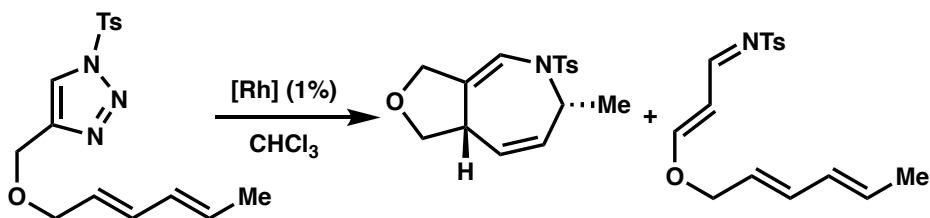
ACIE 2014, 53, 3452

Tang (2014):



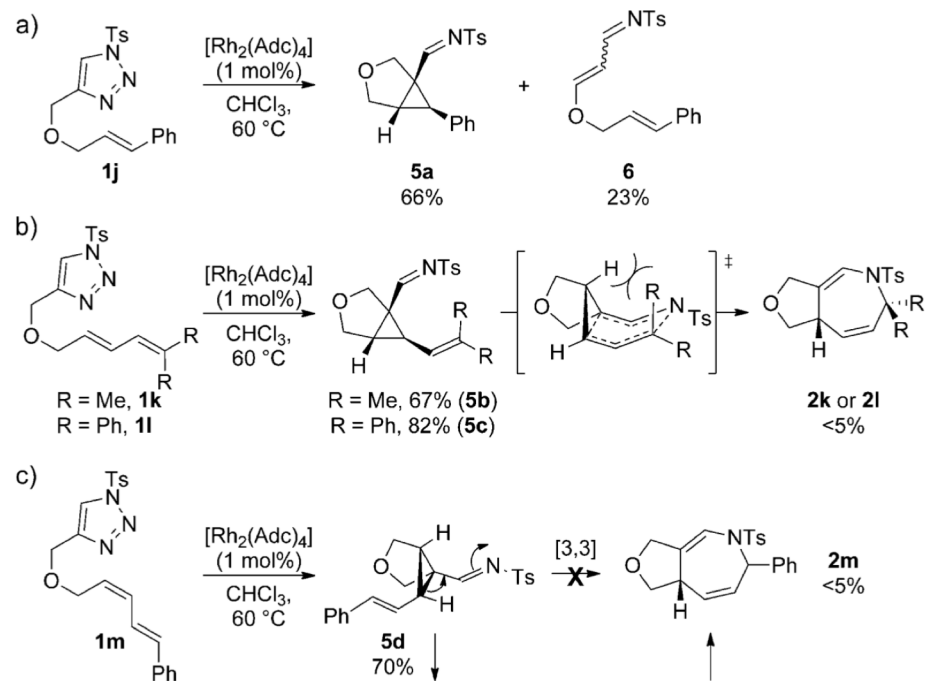
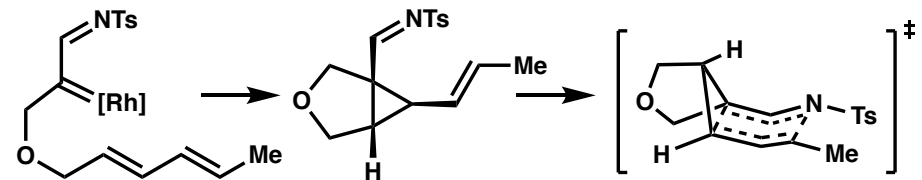
ACIE 2014, 53, 5662

Sarpong (2014):



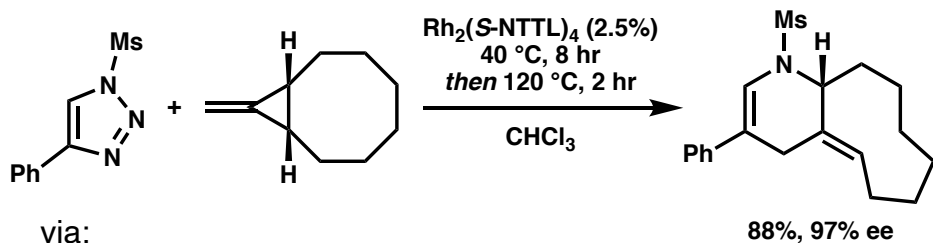
$\text{Rh}_2(\text{Oct})_4$, 140 °C, 15 min = 54% (34%)
 $\text{Rh}_2(\text{Adc})_4$, 140 °C, 15 min = 68% (17%)
 $\text{Rh}_2(\text{Adc})_4$, 60 °C, 16 hr = 74% (14%)

Proposed mechanism:

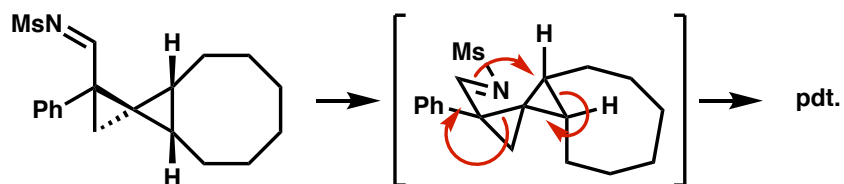


ACIE 2014, 53, 9904

Murakami (2014):

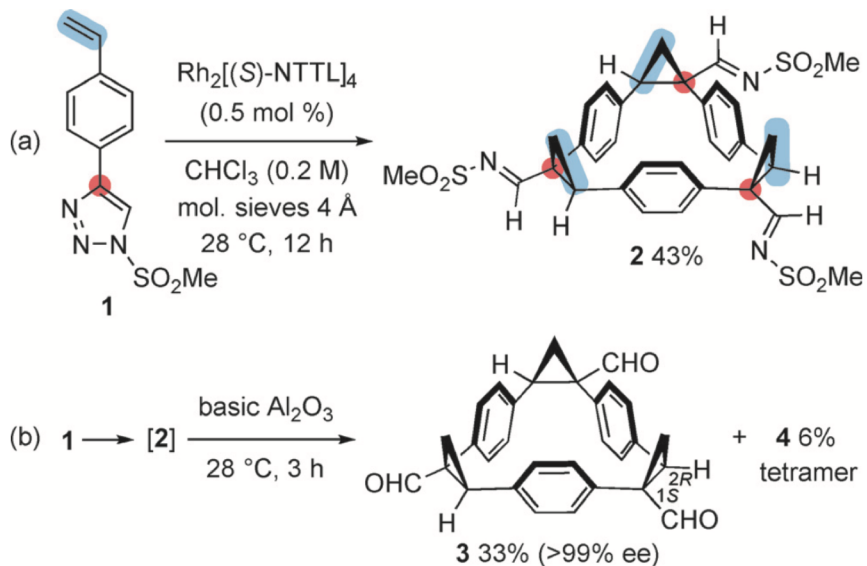


via:



JACS 2014, 136, 15905

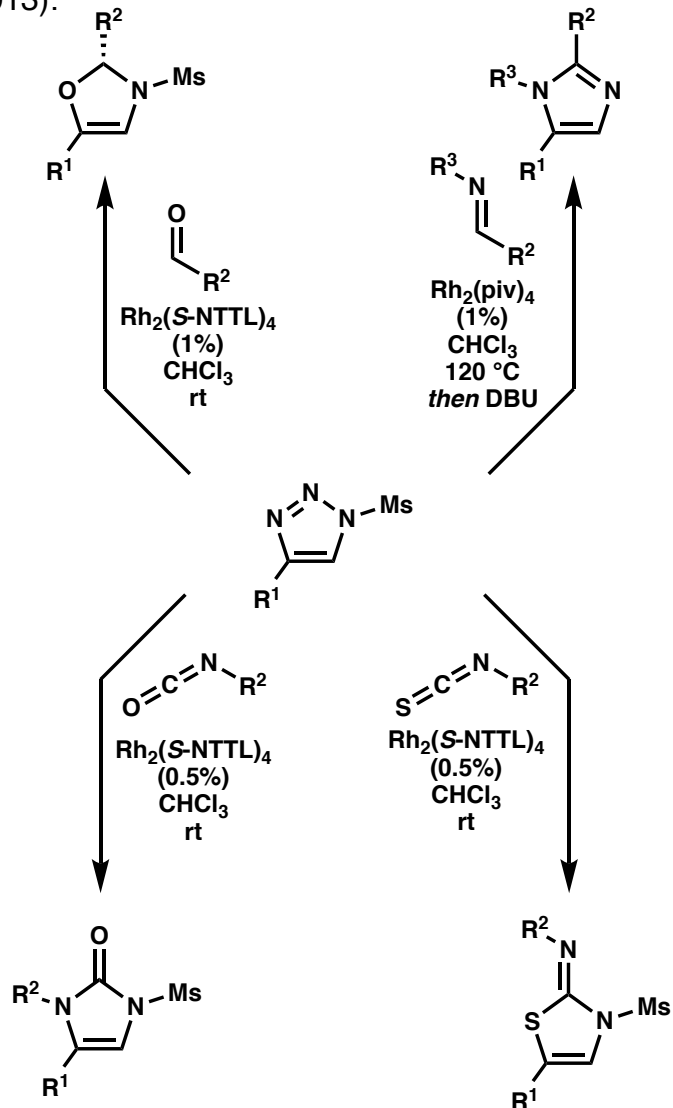
Murakami (2017):



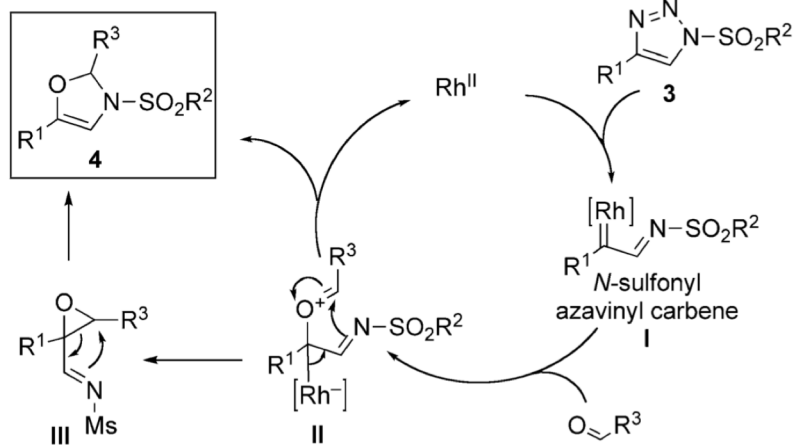
ACIE 2017, 56, 3334

Addition to Carbenoid:

Fokin (2013):

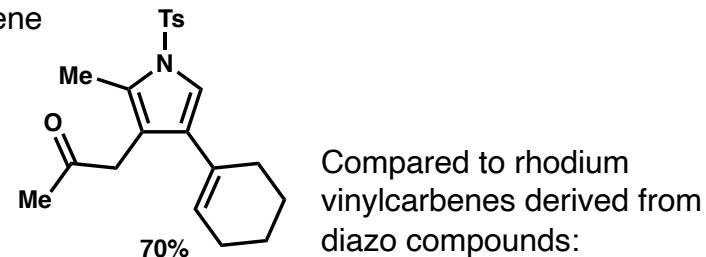
ACIE 2013, 52, 1507
JACS 2013, 135, 4652

Proposed mechanism:

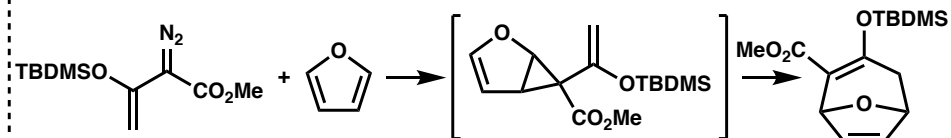


ACIE 2013, 52, 1507

via vinyl carbene from triazole:

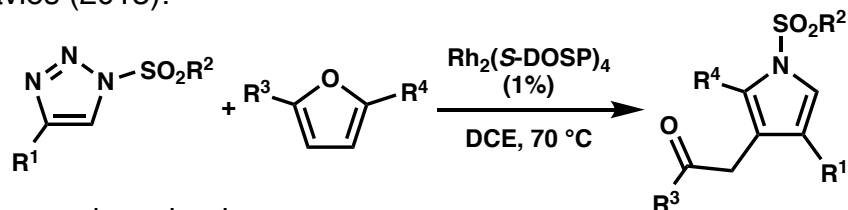


Compared to rhodium vinylcarbenes derived from diazo compounds:

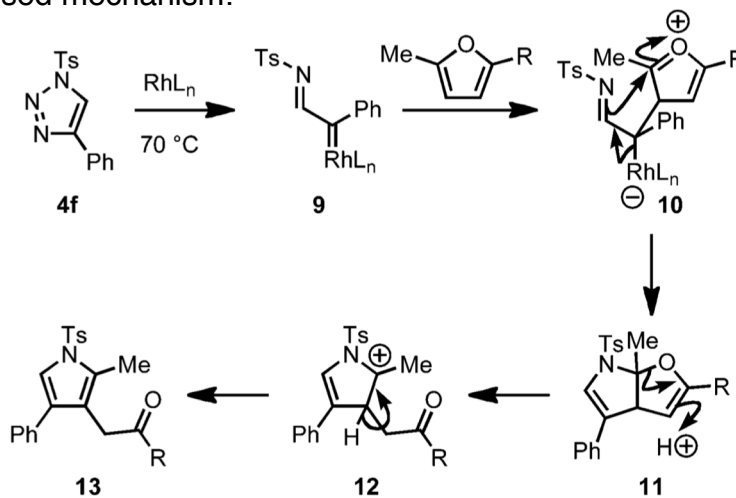


JACS 2013, 135, 4716

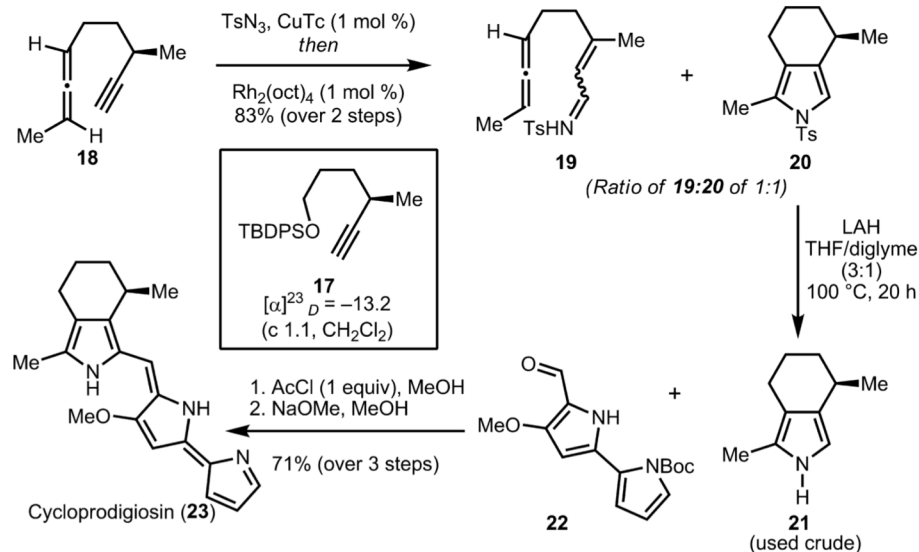
Davies (2013):



Proposed mechanism:

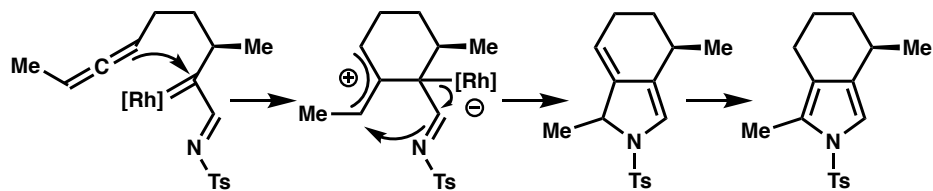


Sarpong (2013):



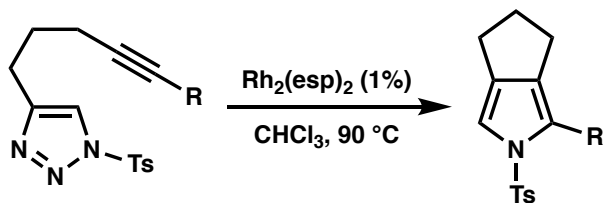
JACS 2013, 135, 4696

Proposed mechanism:

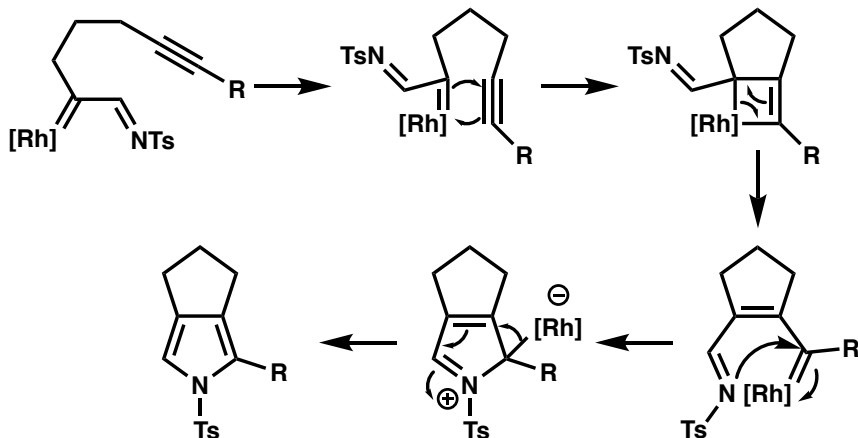


JACS 2013, 135, 4696

Gevorgyan (2013):

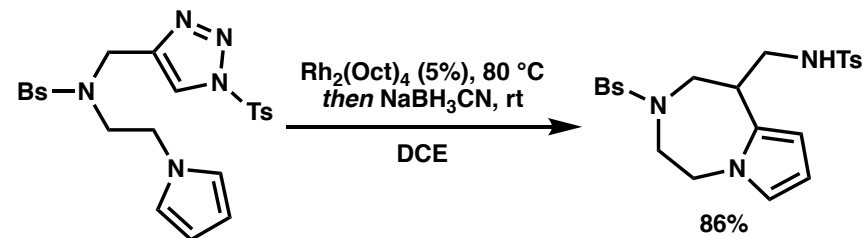


Proposed mechanism: Rh-carbene alkyne metathesis



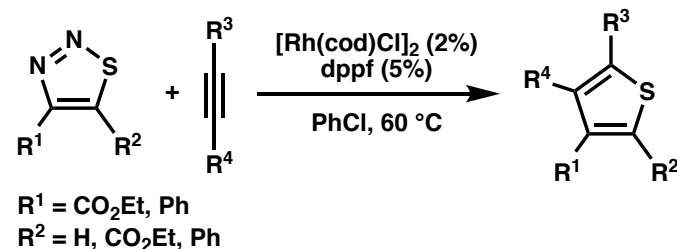
Org. Lett. 2013, 15, 5394

Shi (2014):

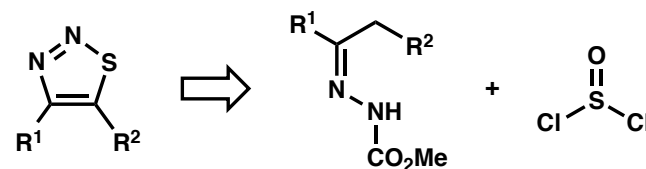


ACIE 2014, 53, 5142

Gevorgyan (2016):



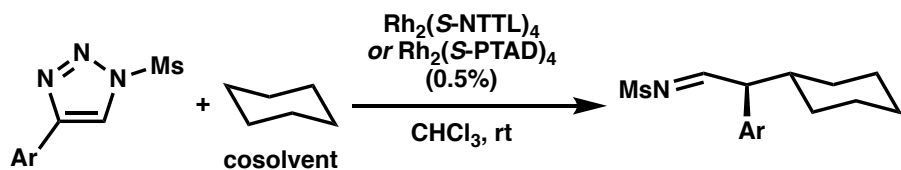
- Rh^{II} dimers proved to be ineffective
- Rh^I employed
- 4,5-substituted thiazoles more active than 4-substituted counterparts



Org. Lett. 2016, 18, 1804

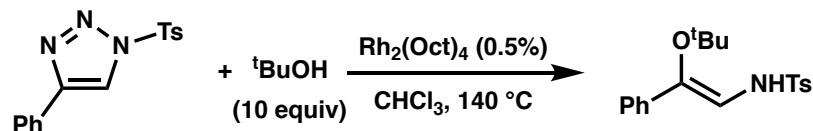
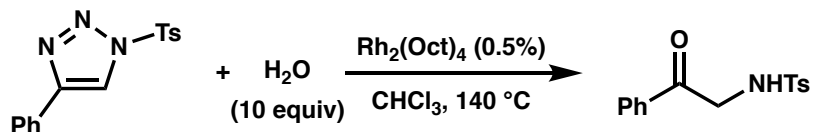
Insertions:

Fokin (2011):

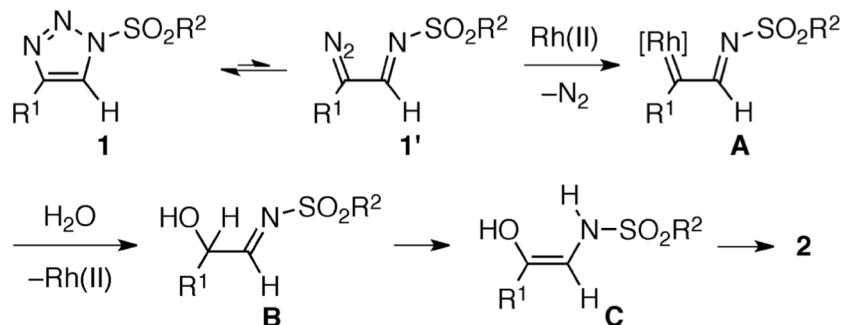


JACS 2011, 133, 10352

Murakami (2012):

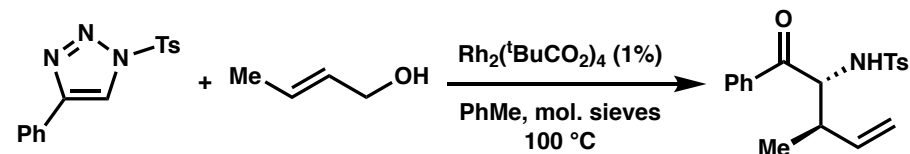


Proposed mechanism:

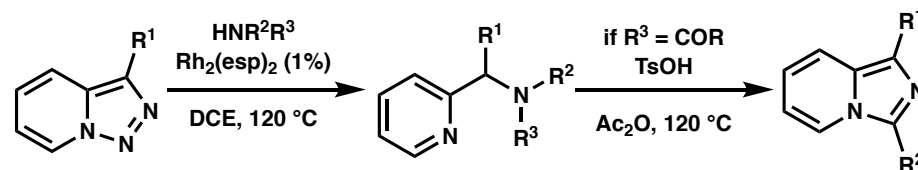


JACS 2012, 134, 194

Murakami (2013):

– OH insertion *then* Claisen rearrangement
ACIE 2013, 52, 3883

Gevorgyan (2014):

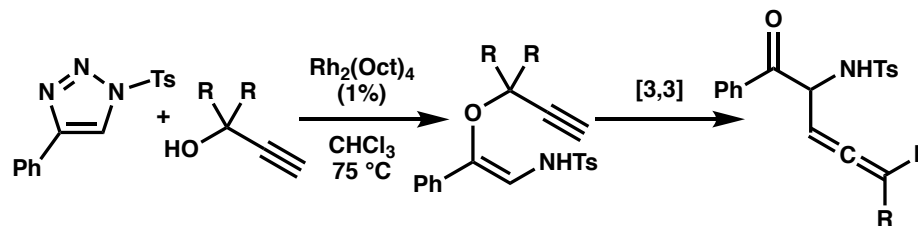
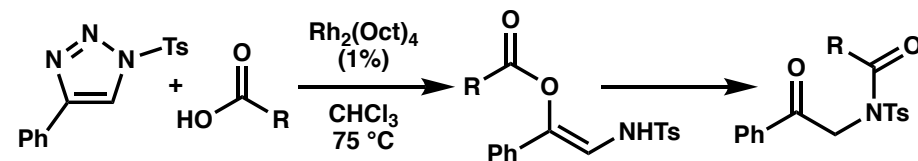
R¹ = CO₂R, Ph

- amides
- carbamates
- pyridazinones

– imidazopyridines formed
without activating group on
pyridine

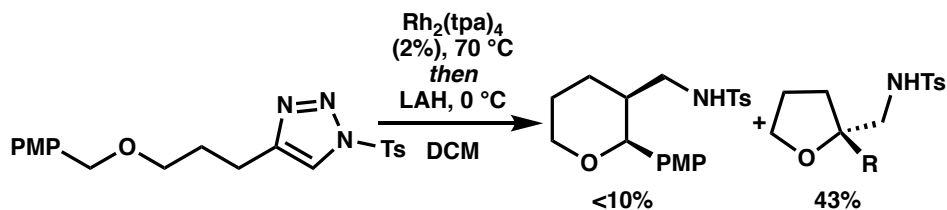
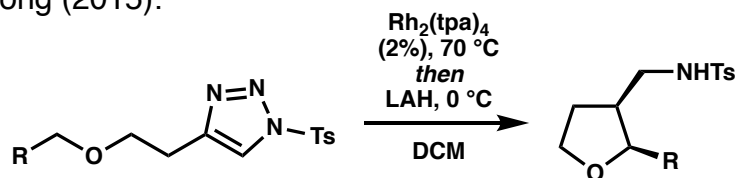
ACIE 2014, 53, 14191

Fokin (2014):

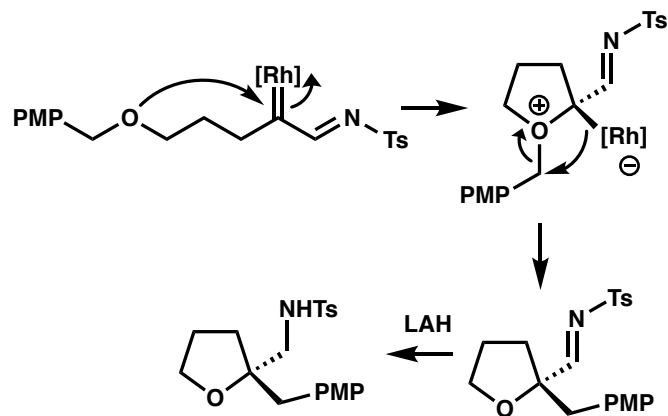


JACS 2014, 136, 195

Sarpong (2015):



Proposed mechanism:



JACS 2015, 137, 8368

The end

Non-Rh-mediated methods:

- Ni (*Chem. Commun.* **2009**, 1470)
- Cu (*Chem. Sci.* **2015**, 6, 1928; *Org. Lett.* **2020**, 22, 8500)
- hv (*Chem. Sci.* **2019**, 10, 8399)