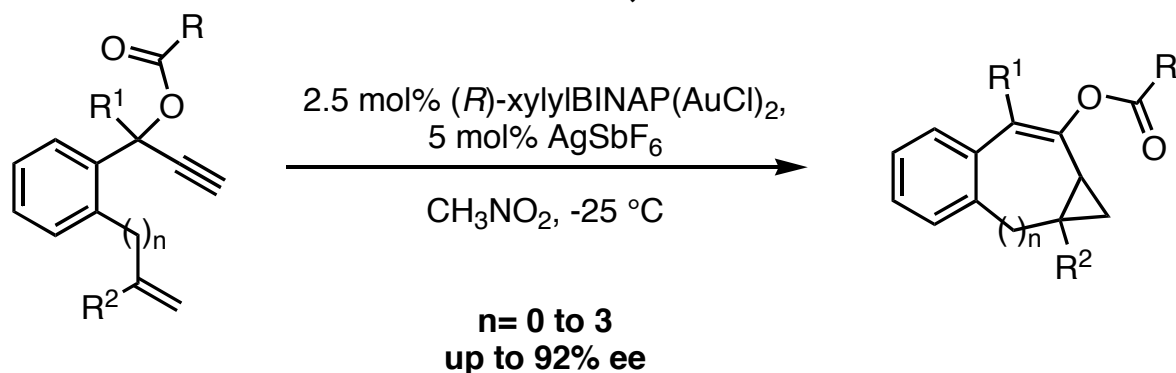


Asymmetric Synthesis of Medium-Sized Rings by Intramolecular Au(I)-Catalyzed Cyclopropanation

Iain D. G. Watson, Stefanie Ritter, and F. Dean Toste

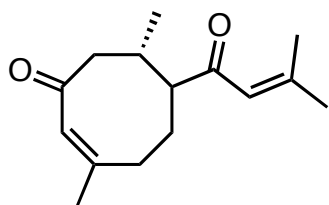
JACS, ASAP, 1/22/2009

DOI: 10.1021/ja8085005

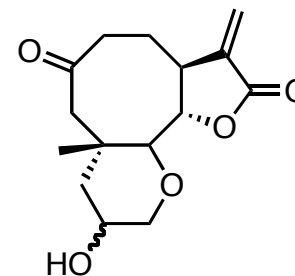
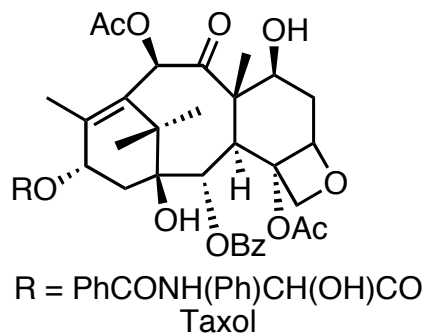


Christopher Rosenker
Wipf Group - Current Literature
February 14, 2009

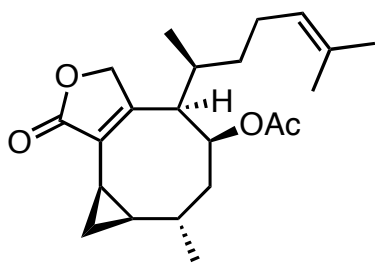
Medium-sized rings



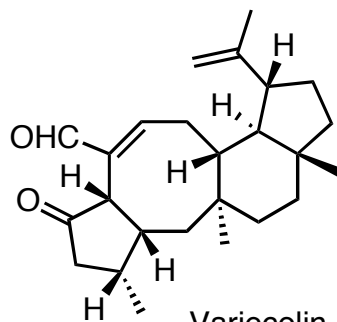
Spartidienedione



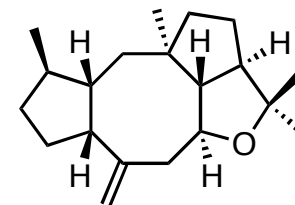
Vulgarolide



Acetoxycrenulide



Variocolin



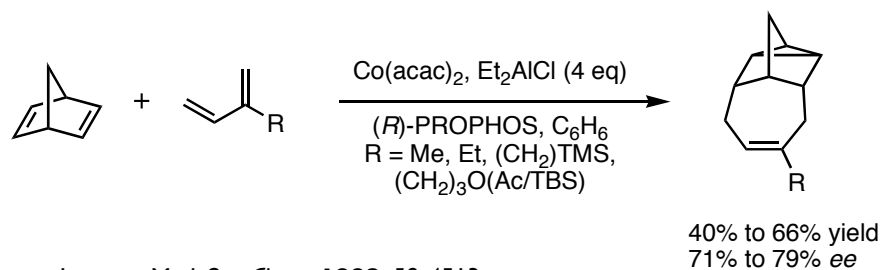
Epoxydictymene

- Synthetically obtained generally through various cycloaddition combinations; LA, radical, transition metal catalyzed cyclizations; and oxidative/reductive processes.
- Cyclization strategies for medium sized rings are difficult due to entropic factors and transannular interactions.

Mehta, G. & Singh, V. *Chem. Rev.* **1999**, 99, 881
Yet, L. *Chem. Rev.* **2000**, 100, 2963.

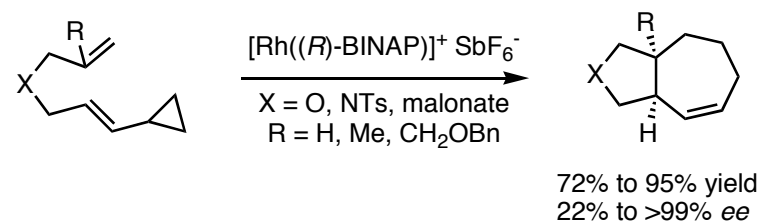
Enantioselective synthesis of medium-sized rings

Cobalt catalyzed [4 + 2 + 2] cycloaddition



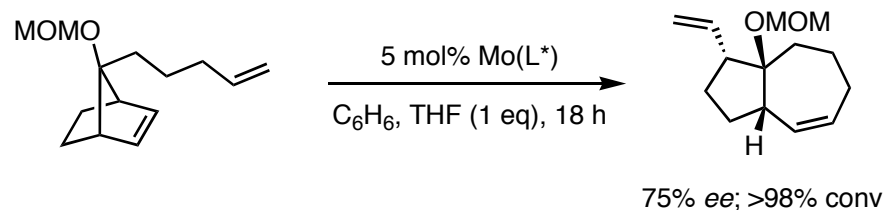
Lautens, M. *J. Org. Chem.* **1993**, *58*, 4513

[5 + 2] Cycloaddition of vinylcyclopropanes and π -systems



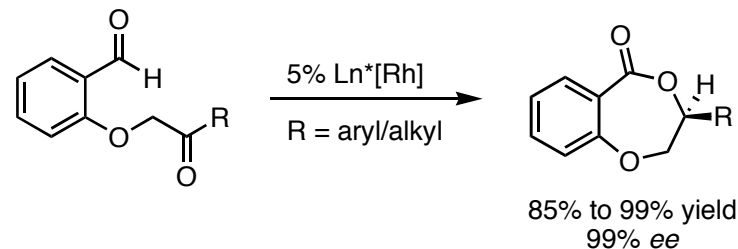
Wender, P.A. *J. Am. Chem. Soc.* **2006**, *128*, 6302.

Mo-catalyzed asymmetric olefin metathesis



Hoveyda, A. H. & Schrock, R. R. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5805

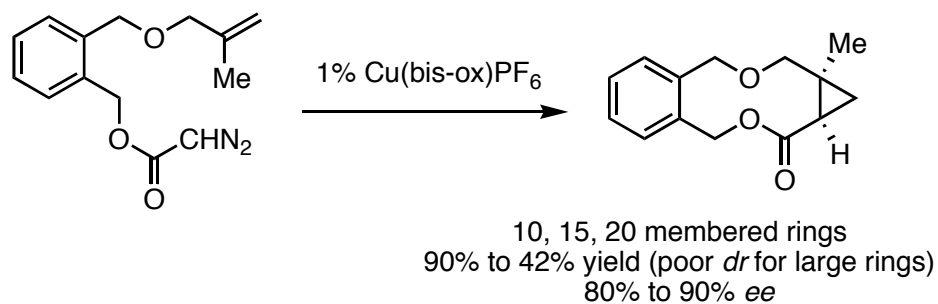
Rh-Catalyzed carbonyl hydroacylation to lactones



Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916

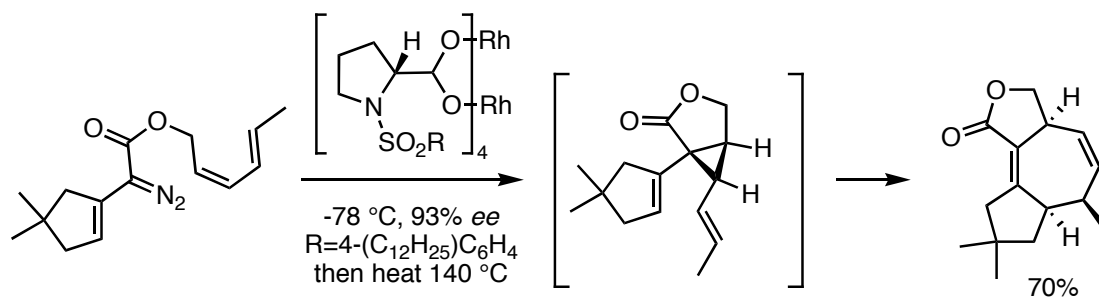
Enantioselective synthesis of medium-sized rings

Cu(I) catalyzed cyclopropanation to form macrocycles



Doyle, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 5718.

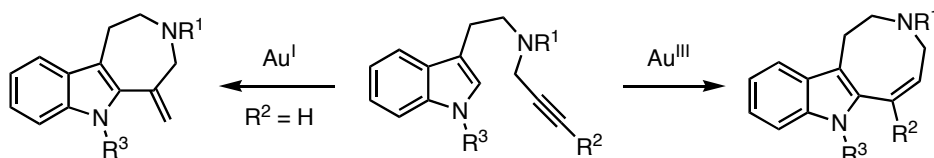
Asymmetric tandem cyclopropanation/Cope rearrangement



Davies, H. M. L. *Tet. Let.* **1996**, *37*, 3967.

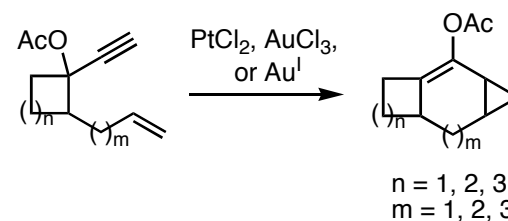
Intramolecular enyne cycloisomerizations

Hydroarylation of alkynes



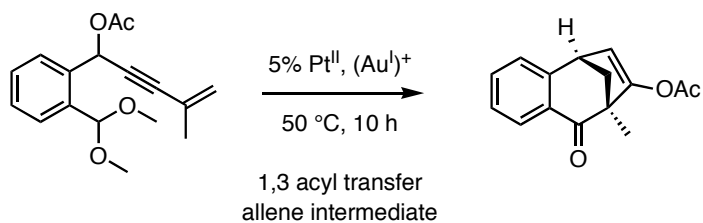
Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, 45, 1105.

Intramolecular cyclopropanation



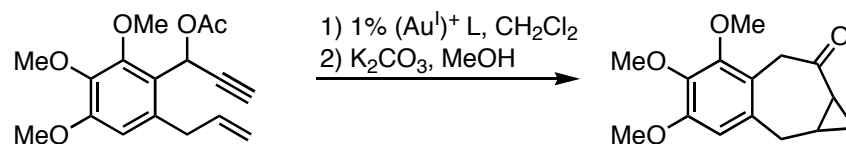
Fensterbank, L. & Malacria, M. *Adv. Synth. Catal.* **2008**, 350, 43.

1,3-addition of alkenylcarbenoid intermediate



Liu, R. *J. Am. Chem. Soc.* **2008**, 130, 16488.

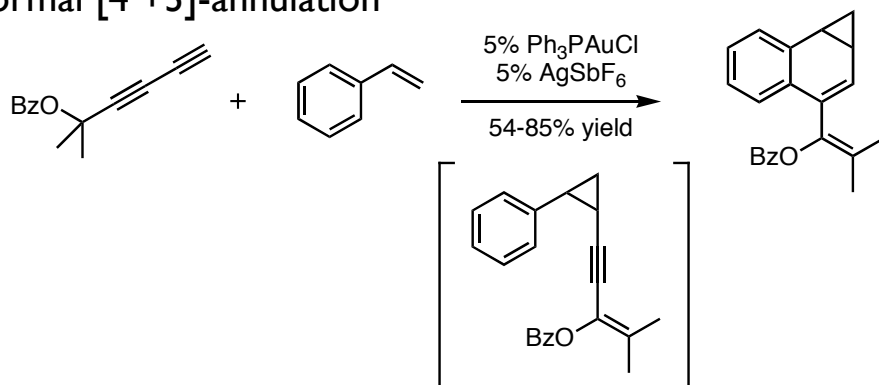
Olefin cyclopropanation to synthesize allocolchicinoid



Hanna, I. *J. Org. Chem.* **2008**, 73, 5163.

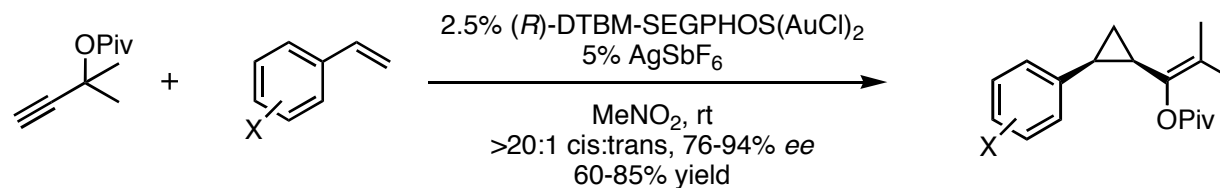
Au^I catalyzed cyclopropanation of olefins

Tandem cyclopropanation/hydroarylation:
formal [4 + 3]-annulation



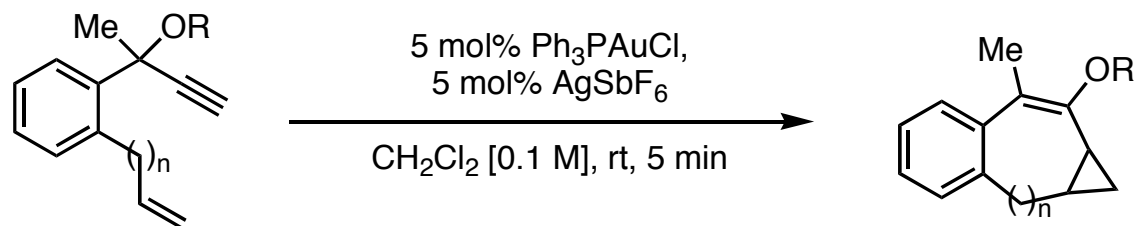
Toste, F.D. *J. Am. Chem. Soc.* **2006**. 128, 14480.

Intermolecular Stereoselective Olefin Cyclopropanation



Toste, F.D. *J. Am. Chem. Soc.* **2005**. 127, 18002.

Initial Substrate Scope



$n = 0, R = \text{Ac}$

$n = 1, R = \text{Piv}$

$n = 2, R = \text{Piv}$

$n = 3, R = \text{Ac}$

* formation of indene byproducts

10%

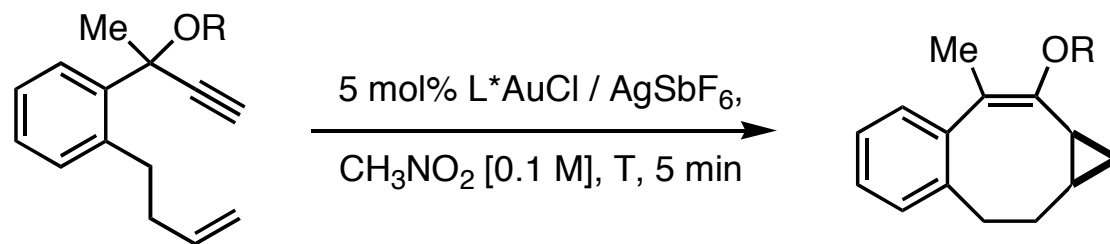
99%

99%

44% *

- Secondary propargylic esters cyclized in decreased yields for $n = 1$ and not at all for $n = 2$.
- Vinylic substitution generally decreases yield
- In the presence of 1,1-diphenylethylene, tertiary propargylic esters prefer intramolecular cyclization, whereas secondary propargylic esters prefer intermolecular cyclopropanation.

Intramolecular Enantioselective Cyclopropanation

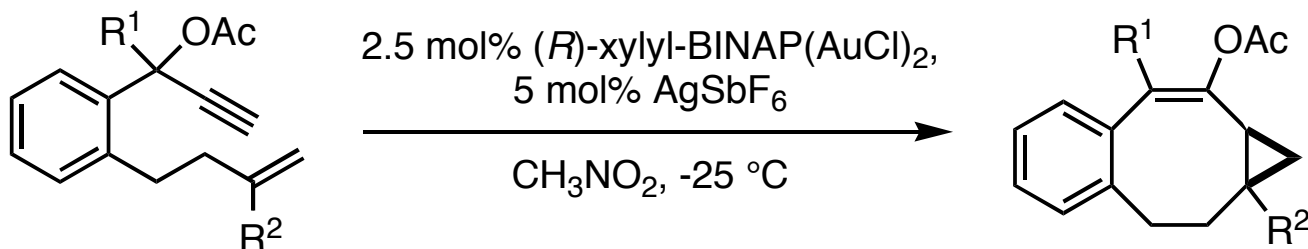


Entry	R	Ligand	T (°C)	ee (%)
1	Ac	(<i>R</i>)-DTBM-SEGPHOS	rt	3
2	Ac	(<i>R</i>)-xylyl-BINAP	rt	80
3	Piv	(<i>R</i>)-xylyl-BINAP	rt	49
4	Ac	(<i>R</i>)-xylyl-BINAP	-25	92

- Entry 1 conditions work well for intermolecular cyclopropanation
- Ligand screening showed (*R*)-xylyl-BINAP had best ee
- Acetate ester showed higher ee than pivaloate (49) and benzoate (63) esters (contrary to intermolecular cyclopropanation).
- Solvent screening included MeCN (69), CH₂Cl₂ (64), CDCl₃ (57), PhMe (20), THF (24), and EtOAc (29).
- Altering the ratios of gold to silver has no significant impact on ee (%).

Watson, Ritter, Toste. *J. Am. Chem. Soc.* **ASAP**. doi: 10.1021/ja8085005

Intramolecular Enantioselective Cyclopropanation



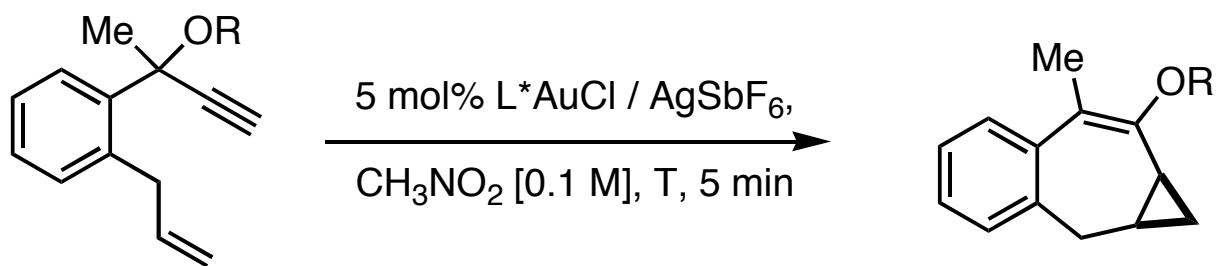
Entry	R ¹	R ²	Yield	ee (%)
1	Me	H	94	92
2	Et	H	91	92
3	Allyl	H	98	90
4	(CH ₂) ₂ Ph	H	80	90
5		H	96	90
6*	Me	Me	88	75

* L = (R)-Difluorophos(AuCl)₂; -25 °C

- Substitution at R¹ is tolerated with out erosion of enantioselectivity
- In entry 3 preferential 8-member ring formation over 5-member ring.
- Substitution at R² causes decrease in enantioselectivity and alternate conditions

Watson, Ritter, Toste. *J. Am. Chem. Soc.* **ASAP**. doi: 10.1021/ja8085005

Intramolecular Enantioselective Cyclopropanation

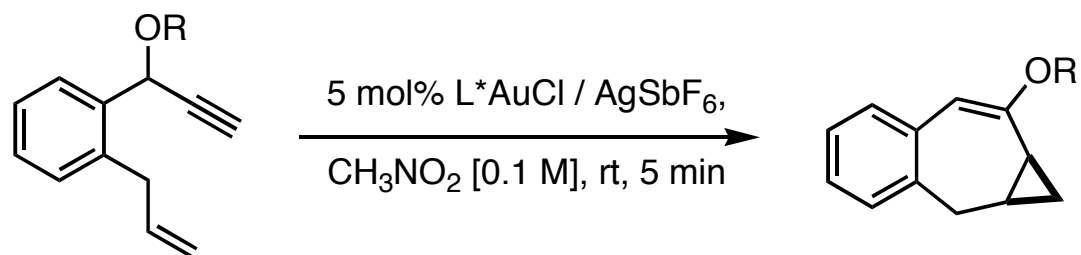


Entry	R	Ligand	ee (%)
1	Ac	(<i>R</i>)-xylyl-BINAP	49
2	Piv	(<i>R</i>)-xylyl-BINAP	44
3	Bz	(<i>R</i>)-xylyl-BINAP	42

- Change in R has little effect on ee
- Various chiral (L*) gold(I) chloride complexes were investigated including (*R*)-BINAP, (*R*)-DTBM-Segphos, and (*R*)-Cl-MeO-Biphep giving lower ee
- Lowering the reaction temperature does not have an impact on enantioselectivity.
- Much lower ee obtained compared to 8-member ring formation

Watson, Ritter, Toste. *J. Am. Chem. Soc.* **ASAP**. doi: 10.1021/ja8085005

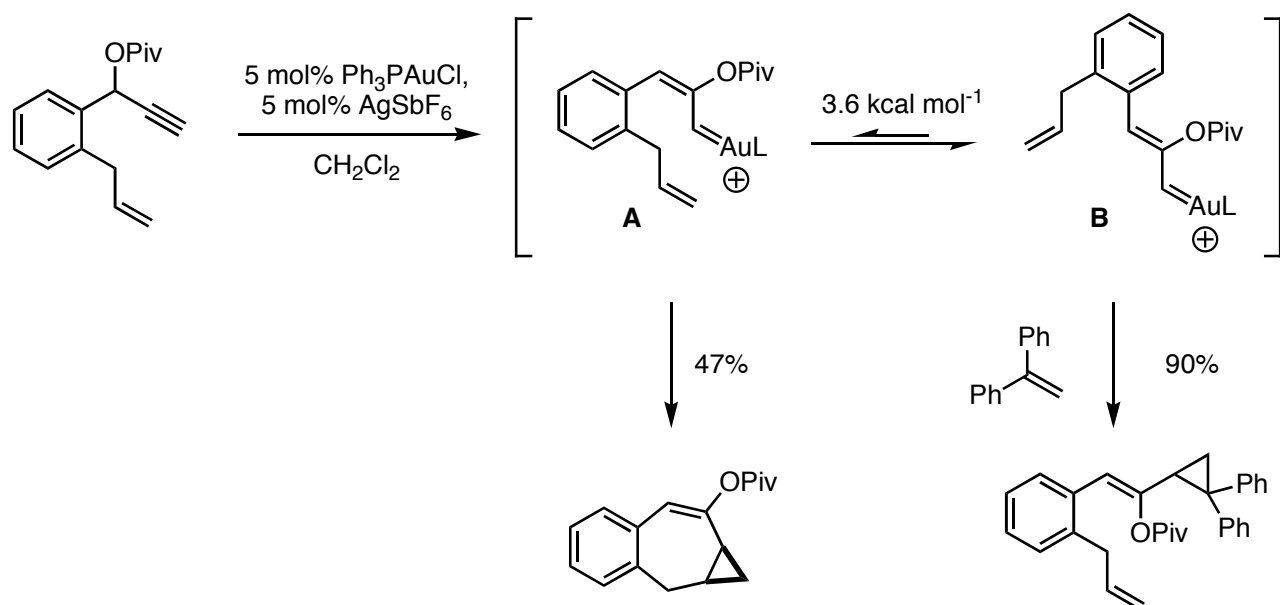
Intramolecular Enantioselective Cyclopropanation



Entry	R	Ligand	ee (%)
1	Ac	(<i>R</i>)-Cl-MeO-Biphep	37
2	Piv	(<i>R</i>)-xylyl-BINAP	85

- Various chiral (L*) gold(I) chloride complexes were investigated including (*R*)-BINAP, (*R*)-DTBM-Segphos, and (*R*)-Cl-MeO-Biphep (better for Ac, 37) giving decreased enantioselectivity compared to (*R*)-xylyl-BINAP.
- Change of R has dramatic effect on ee, R = Ac (21); Piv (85)
- No product is isolated at lower temperatures due to decomposition.

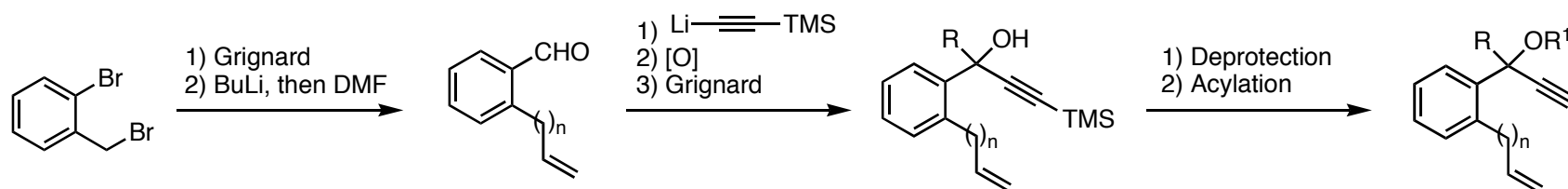
Isomeric Carbenoid Intermediates



- Selective intramolecular cyclopropanation is observed to form 7-membered ring without 1,1-diphenylethylene
- In the presence of 1,1-diphenylethylene the intermolecular product occurs exclusively
- Results indicate that Au(I)-stabilized vinyl carbenoids are “fluxional” and may even react through the thermodynamically disfavored isomer

Watson, Ritter, Toste. *J. Am. Chem. Soc.* **ASAP**. doi: 10.1021/ja8085005

Substrate synthesis



- Commercially available starting material (1-2\$ / gram)
- Straight forward synthesis that allows for various points of derivation
 - Although the reaction does not appear to be tolerant towards complex substitution

Conclusion

- Minor changes in substrate and/or ligand can have profound effects on the result
 - ie. Piv/Ac, 2° vs 3° propargylic esters, and ring size
 - usually involves ligand screening for every substrate
- The title paper extends the scope of the current methodology by performing asymmetric intramolecular cyclopropanation of enynes to form medium sized rings.
- Supports the notion of the fluxional nature of Au(I) stabilized vinyl carbenoid intermediates

