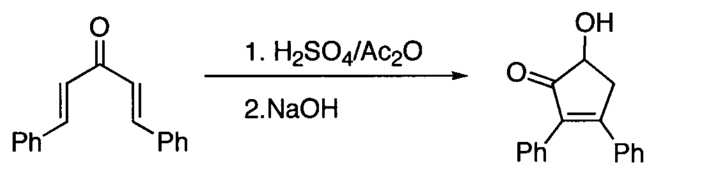
Interrupted Nazarov Cyclization on Silica Gel

Francis Dhoro and Marcus Tius
University of Hawaii

J. Am. Chem. Soc. ASAP

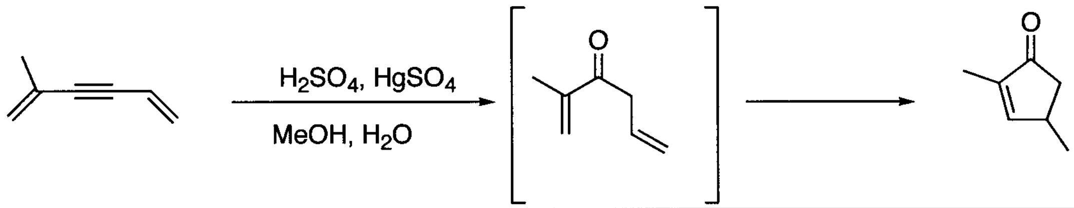
Nazarov Cyclization

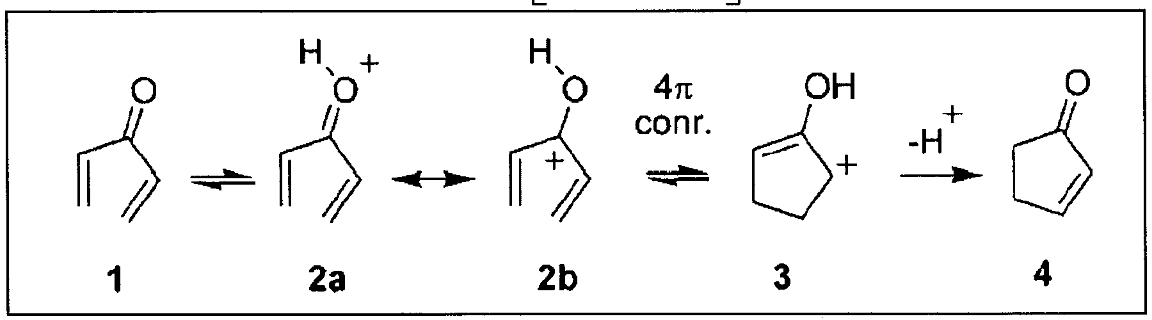
Vorlander & Schroeter (1903)



"structure unknown"

Nazarov (1940-1950s)





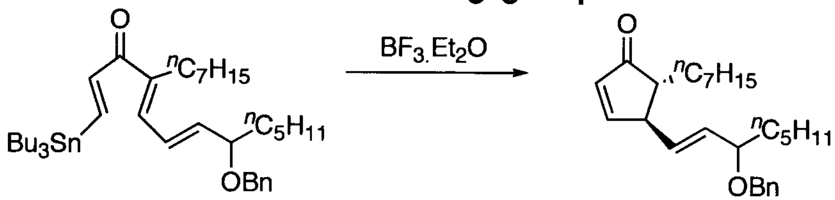
Initiation occurs with protic or Lewis acids
Under *hv*, ring closure is disrotatory

Opportunity for bond forming rxns

Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193.

Control the location of the α,β-unsaturation in the termination step

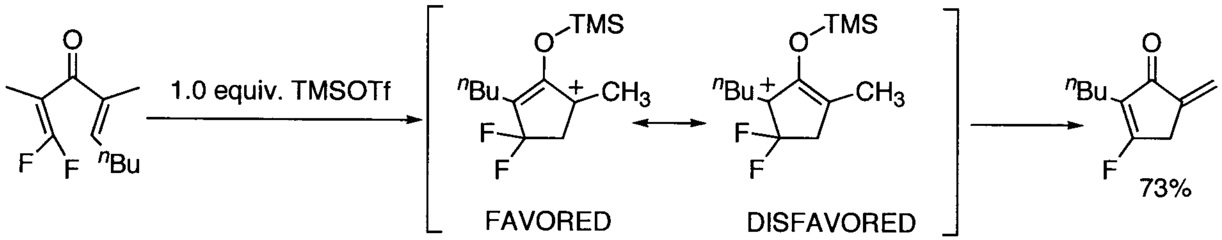
- Stable carbocation leaving groups



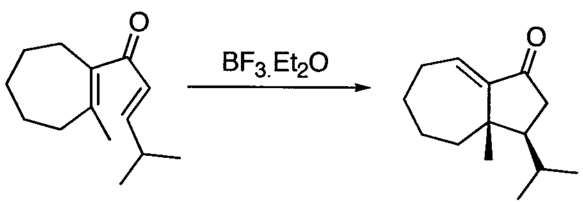
Johnson, C. R.; M. R. Peel *Tetrahedron Lett.* **1986**, *27*, *5947*.

Analogously with TMS group

- Stability of Carbocation



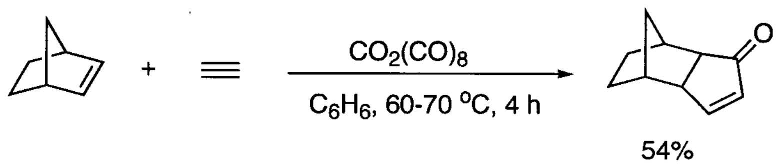
Ichikawa, J.; Miyazaki, S.; Fujiwara, T.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320.



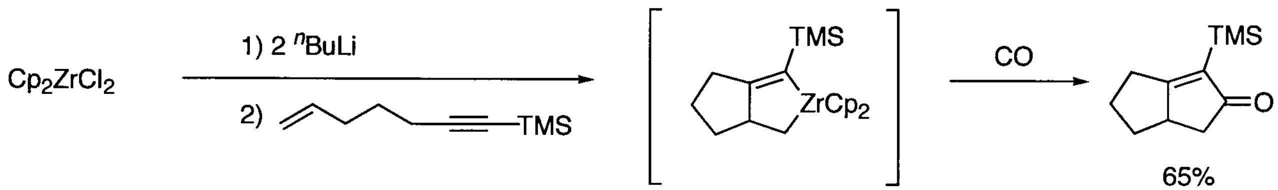
Chui, P.; Li, S. *Org. Lett.* **2004**, 6, 613.

Synthesis of Cyclopentenones

Pauson-Khand

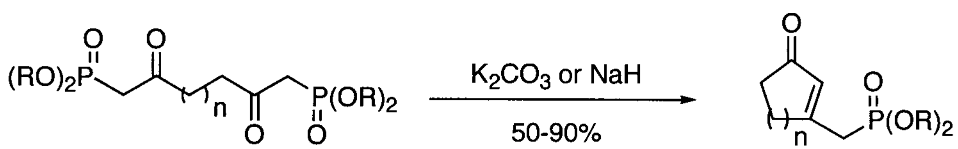


Zirconium-promoted bicyclization



zirconium metalacycle.

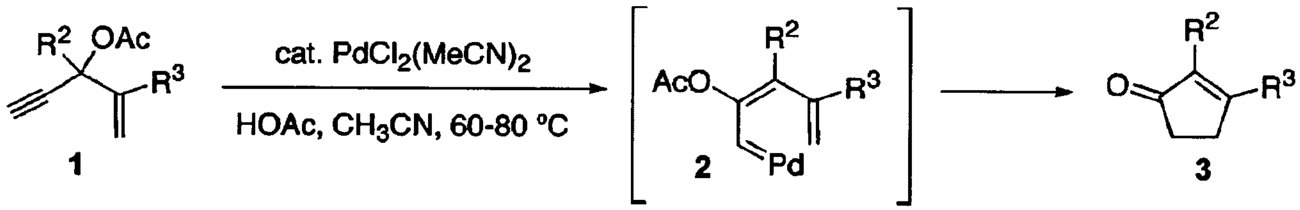
Phosphonate-mediated



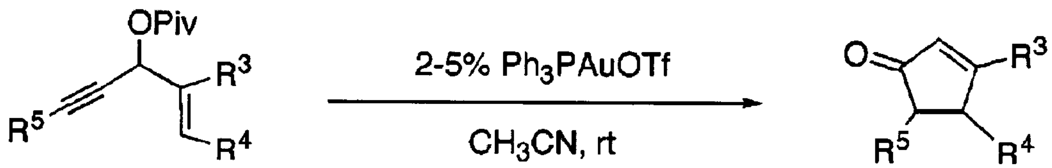
Schore, N. *Chem. Rev.* **1988**, *88*, 1081-1119.

Mikolajczyk, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, *71*, 473.

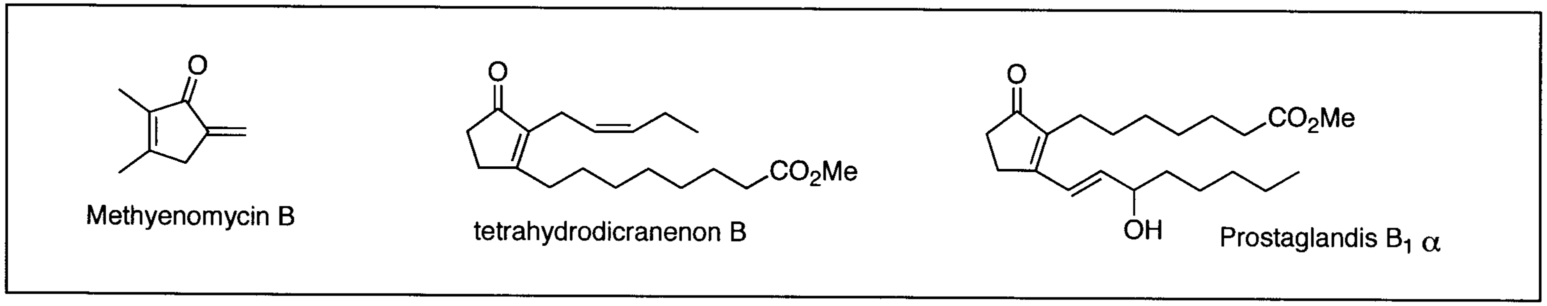
Rautenstrauch Rearrangment



Rautenstrauch, V. J. *J. Org. Chem.* **1984**, *49*, 950.

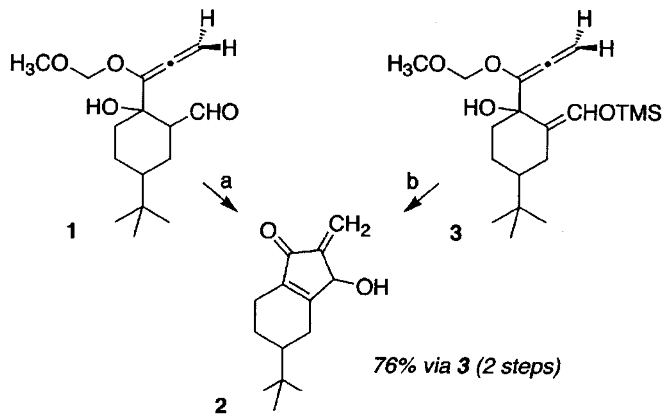


Toste, F. D.; Shi, X.; Gorin, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 5802.



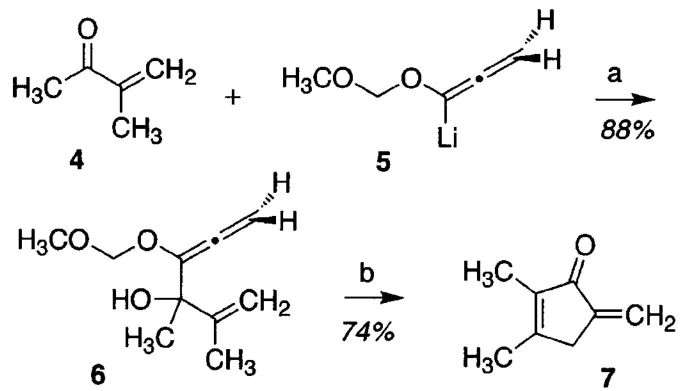
Nazarov- allene ethers

M. A. Tius - 1980's



(a) CH_2Cl_2, 3-chlorobenzoic acid, 25 °C; (b) CH_2Cl_2, BF_3•Et_2O, 0 °C.

Cyclization of a 3° alcohol

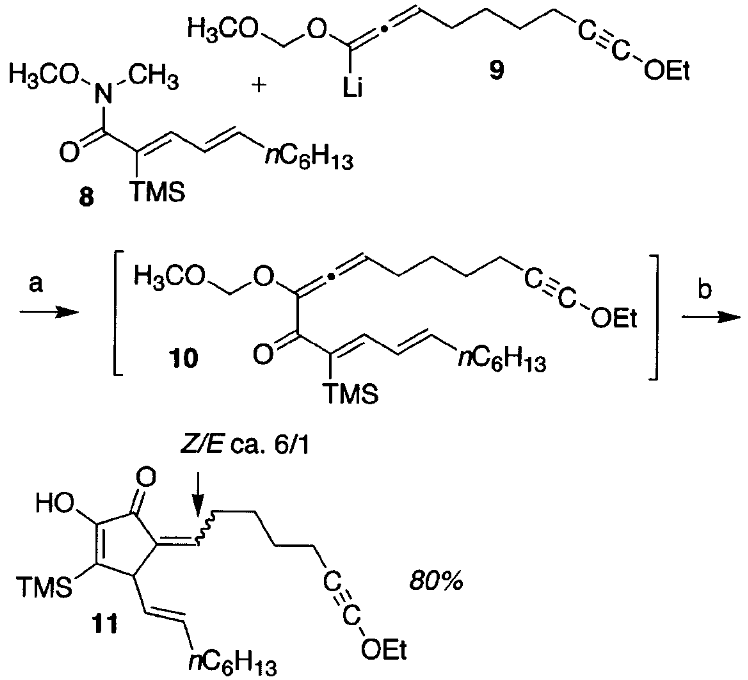


(a) 4 equiv **5**, THF, Et_2O, -78 °C; 88%; (b) 3 equiv TFAA, 5 equiv 2,6-lutidine, CH_2Cl_2, -20 °C; 74%.

Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.

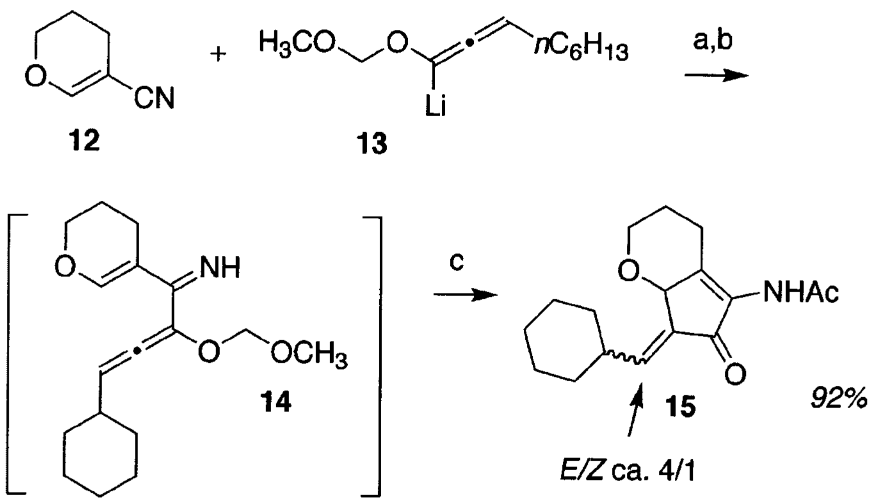
Nazarov- allene ethers

Allenyl ketones



(a) THF, Et_2O, -78 °C; (b) aq NaH_2PO_4; 80%.

α,β- unsaturated nitrile



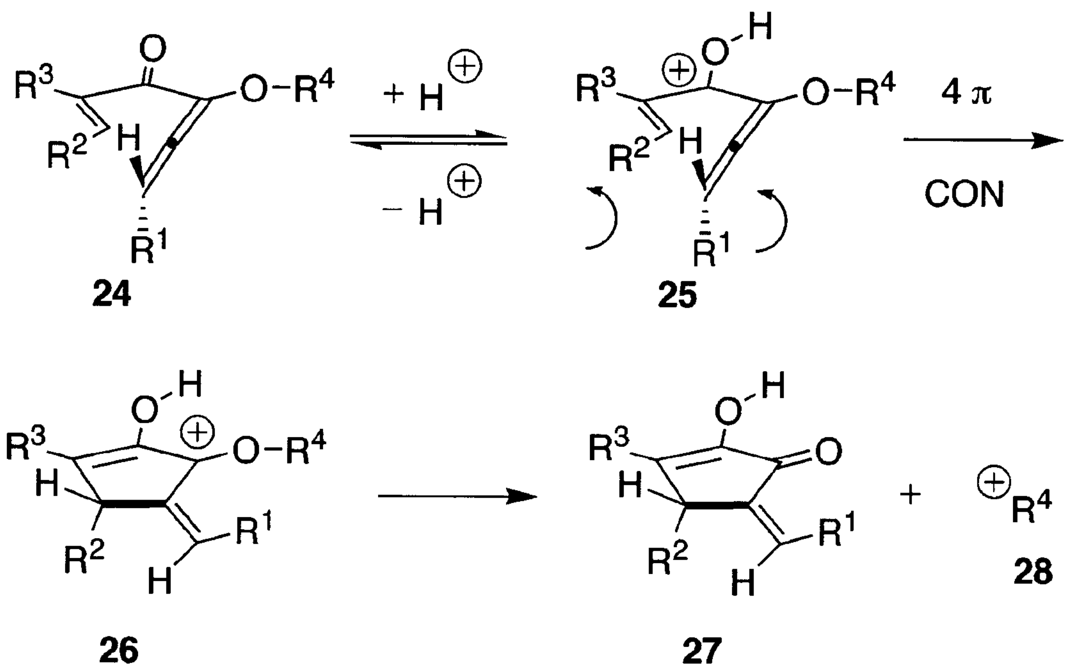
(a) THF, -78 °C; (b) aq $(NH_4)H_2PO_4$; (c) EtOAc, pyr, DMAP (cat.), Ac_2O; 92% (4/1 *E/Z*).

- Conditions are quite mild
- Kinetic preference for the z-isomer of the exocyclic bond

- First example of an imino-Nazarov cyclization
- Classical imino-Nazarov cyclizations are disfavored

Tius, M. A. *Acc. Chem. Res.* **2003**, 36, 284.

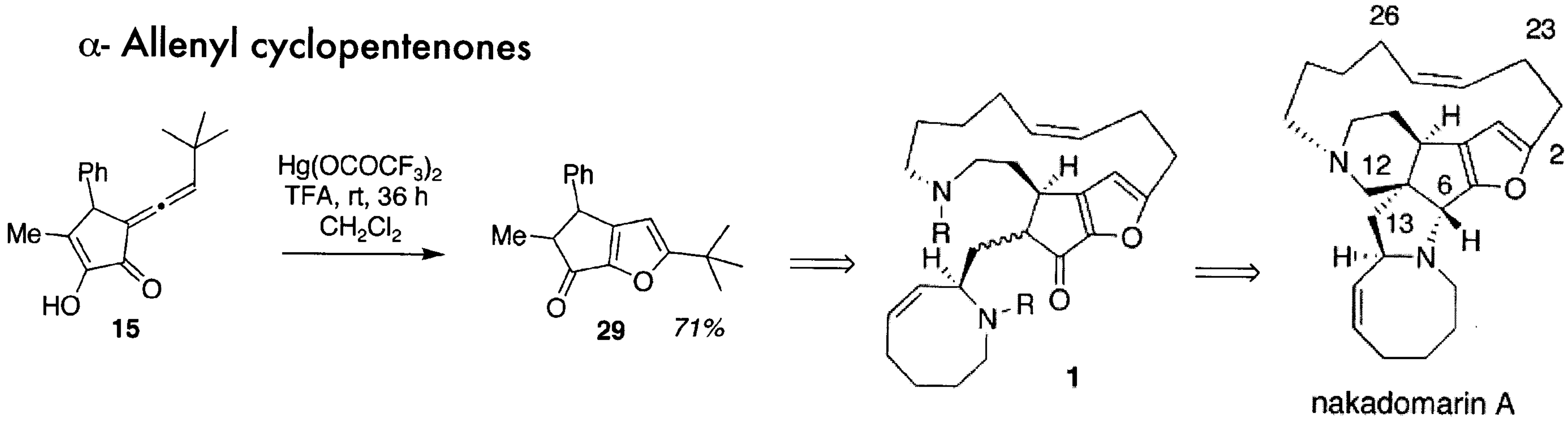
Mechanism



- Clockwise and counterclockwise rotation is allowed. But, preference is for counterclockwise due to sterics.
  - preference of exocyclic bond for *Z*-geometry

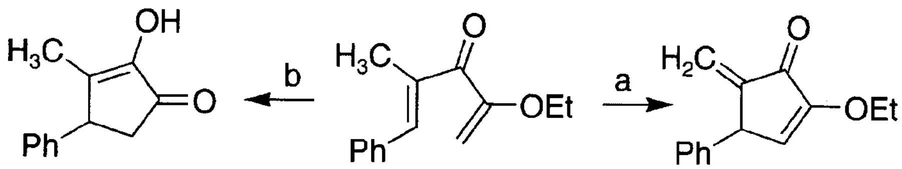
Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.

α- Allenyl cyclopentenones



Tius, M. A.; Leclerc, E. *Org. Lett.* **2003**, *5*(8), 1171.

Pd(II)-catalyzed Nazarov



91%

(a) $Pd(OAc)_2$; (b) $PdCl_2(MeCN)_2$

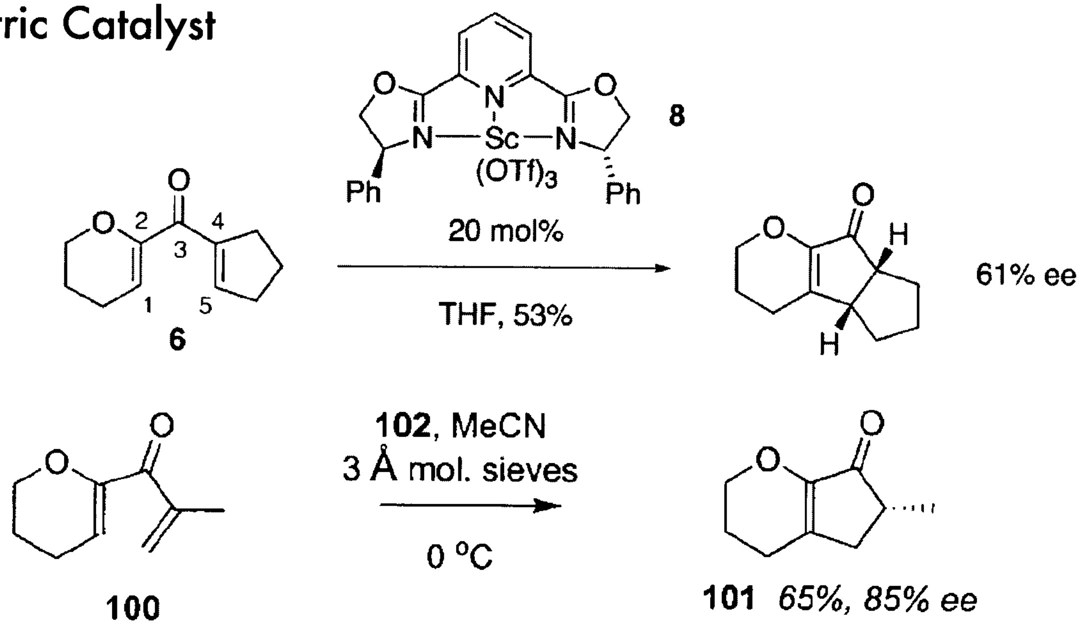
50%

Tius, M. A.; Bee, C.; Leclerc, E. *Org. Lett.* **2003**, *5*(26), 4927.

Asymmetric Nazarov cyclization

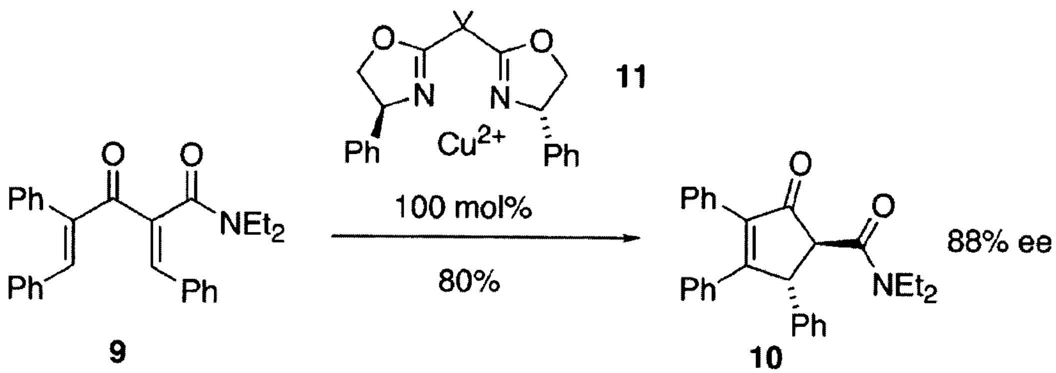
- Asymmetric Catalyst

D. Trauner



Trauner, D.; Liang, g. *J. Am. Chem. Soc.* **2004**, *126*, 9544.

V. K. Aggarwal

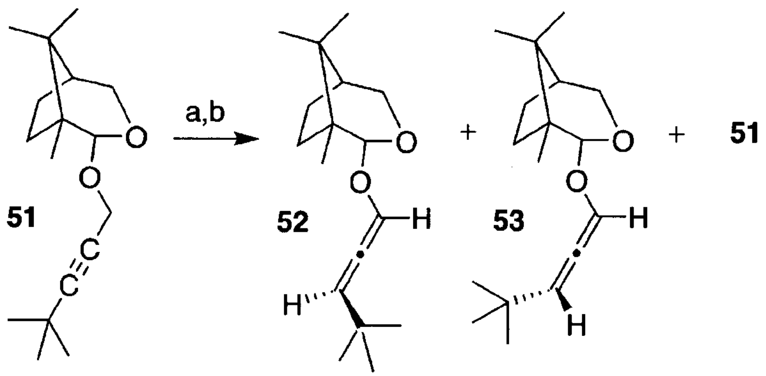


Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075.

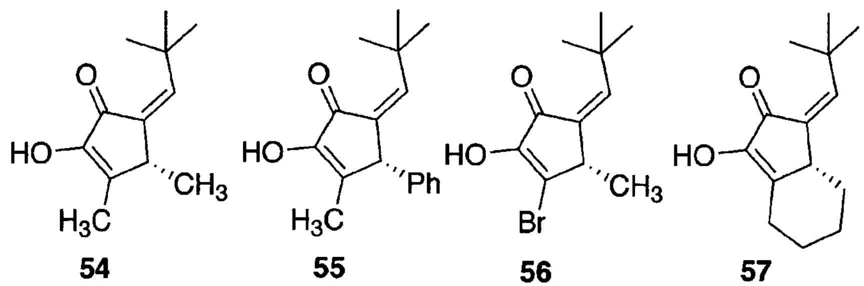
Asymmetric Nazarov cyclization

- Camphor- derived auxillary

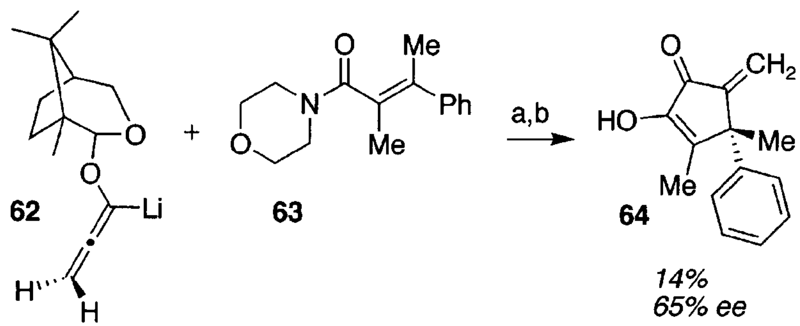
M. A. Tius



(a) 2 equiv *t*-BuLi, -78 °C, 2 h; (b) *t*-BuOH
65% of **52**.



61% yield	*80% yield*	*42% yield*	*60% yield*
92% ee	*96% ee*	*93% ee*	*92% ee*



(a) THF, -78 °C; warm to -30 °C; 1 h; (b) HCl, HFIP/TFE (1/1), -78 °C.

Quat. Centers??

^{t}-butyl group replaced with R_3Si

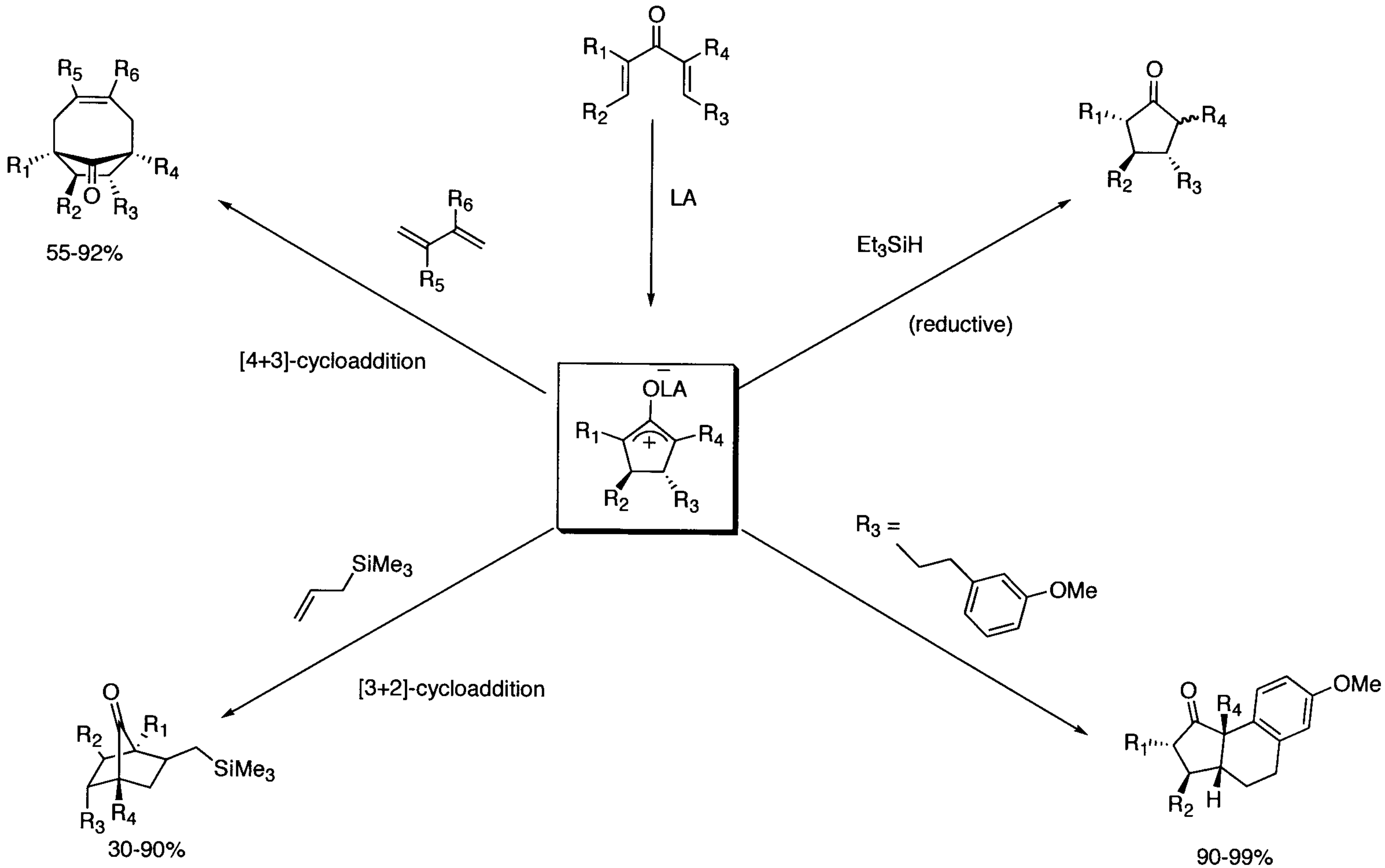
Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284.

Oxyallyl Trapping

F. G. West - Universtiy of Alberta

West, F. G.; Wang, Y.; Schill, B. D.; Arif, A. *Org. Lett.* **2003**, *5*(15), 2747.

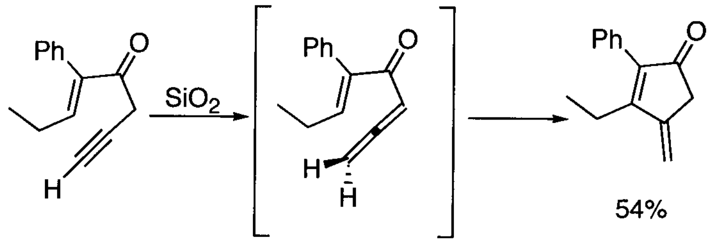
West, F. G. ; Giese, S. *Tetrahedron* **2000**, *56,* 10221.



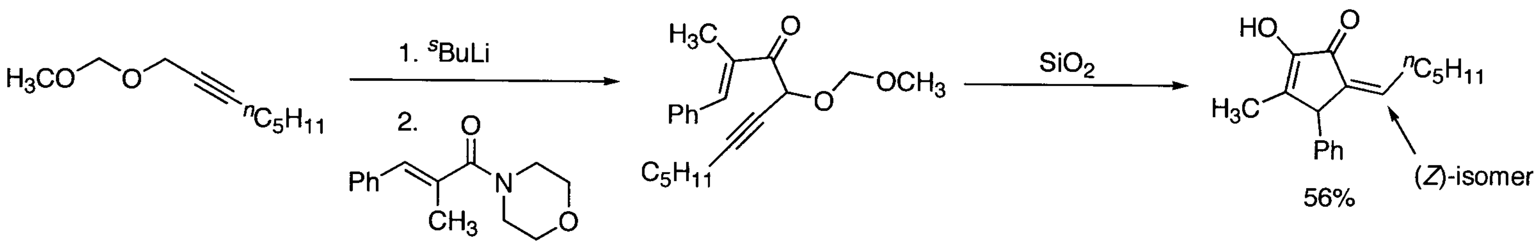
West, F. G.; Giese, S.; Kastrup, L.; Stiens, D. *Angew. Chem. Int. Ed.* **2000**, *39(11), 1970.*

West, F. H.; Browder, C.; Marmsater, F. P. *Org. Lett.* **2001,** *3*(19), 3033.

Inspiration.......

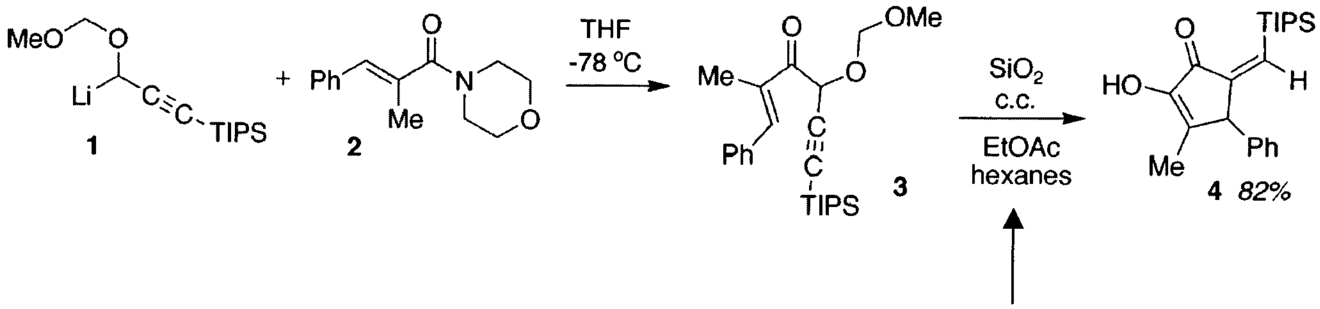


Hashimi, A. S. K.; Bats, J.; Choi, J-H.; Schwarz, L.*Tetrahedron Lett.* **1998**, *39*, *7491*.



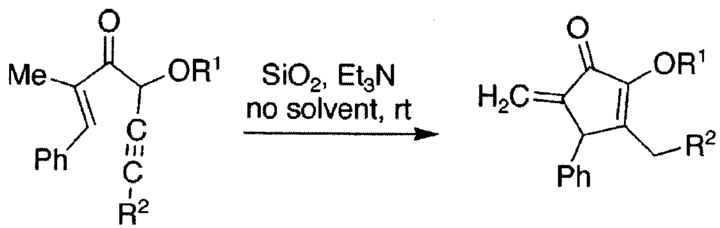
Tius, M.A. ; Frost, J.; Bee, C.; Cordaro, F. *Org. Lett.* **2003**, *5*(22), 4069.

Problem:



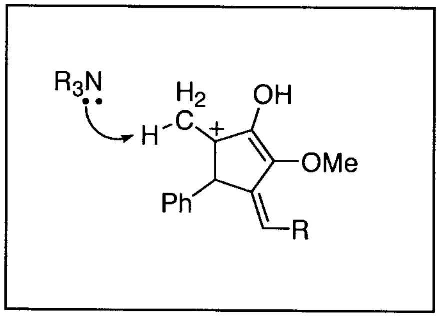
w/o solvent- no reaction

Solution:

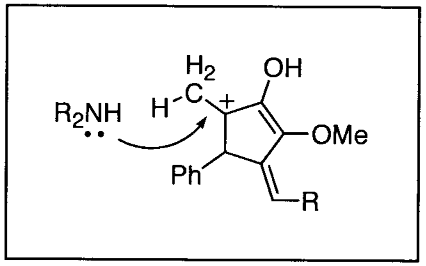


5 R^1 = Me, R^2 = TIPS
6 R^1 = MOM, R^2 = TMS

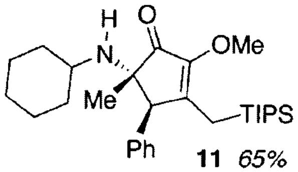
7 R^1 = Me, R^2 = TIPS *63%*
8 R^1 = MOM, R^2 = H *68%*



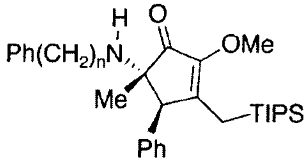
Cyclization–dry SiO_2 w/Lewis acids in the absence of solvent



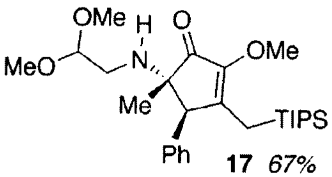
Aminocyclopentenones



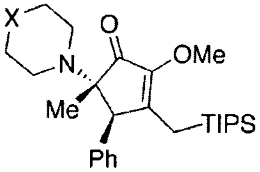
11 *65%*



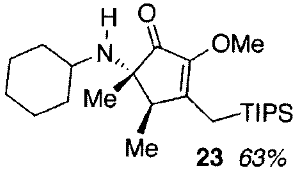
14 n = 1 *60%*
15 n = 2 *63%*



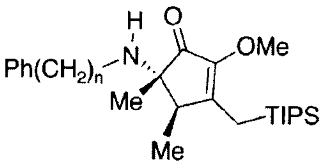
17 *67%*



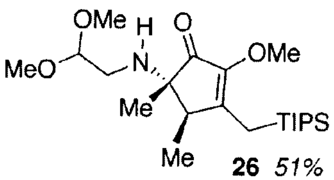
20 X = CH_2 *58%*
21 X = O *70%*



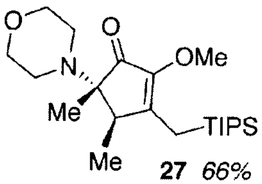
23 *63%*



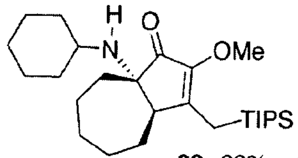
24 n = 1 *64%*
25 n = 2 *55%*



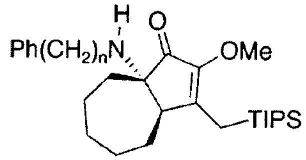
26 *51%*



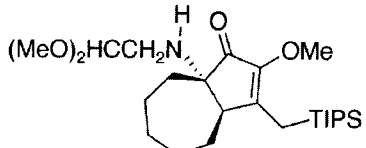
27 *66%*



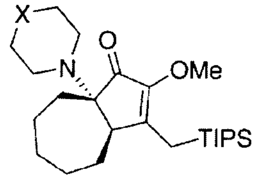
29 *68% + 13%*[b]



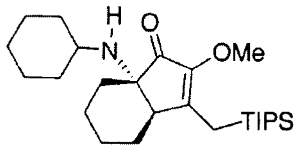
30 n = 1 *75% + 4%*[b]
31 n = 2 *71% + 4%*[b]



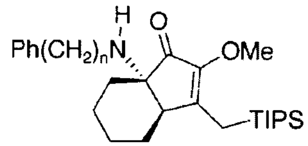
32 *60% + 10%*[b]



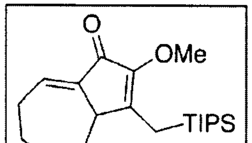
33 X = CH_2 *51% + 28%*[b]
34 X = O *61% + 20%*[b]



36 *59%*[c]



37 n = 1 *60%*[c]
38 n = 2 *64%*[c]



39

- 1° and 2° aliphatic amines
- Acetal tolerated

- Increase in sterics of α- substituent of the enone or of the amine result in some elimination

Summary:

• An economy and environmental friendly process using silical gel in the absence of solvent is presented for the Nazarov cyclization.

• The Interrrupted Nazarov cyclization by an amine as the nucleophile gives rise to new cyclopentenone scaffolds.

• Avoids the preparation of allenes

Future Work:

• Broaden scope with diverse amines–aromatic

• Optimize conditions where proton loss occurs