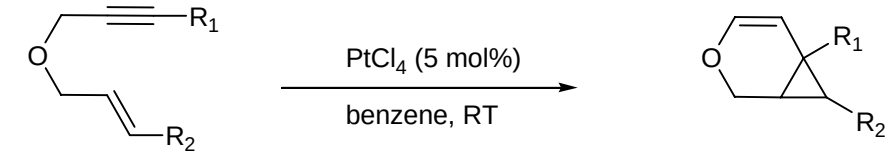
Platinum- and Gold-Catalyzed Rearrangement Reactions of Propargyl Acetates: Total Synthesis of (-)-α-Cubebene, (-)-Cubebol, Sesquicarene and related Tepenes

A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, ASAP

Stephan Elzner, Current Literature March 04 2006

Transition Metal Catalyzed Cycloisomerisation of Enynes

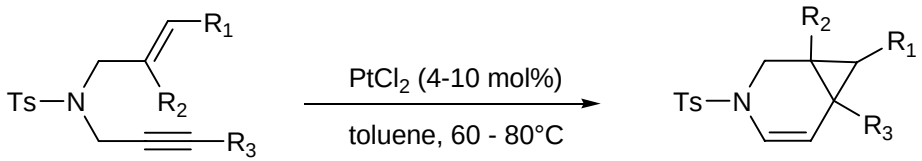
Synthesis of Cyclopropanes



R_1 = Ph, Me
R_2 = H, Me, Ph, Naphtyl

20 - 97%

J. Blum, H. Beer-Kraft, Y. Badrieh, *J. Org. Chem.* **1995**, *60*, 5567-5569.



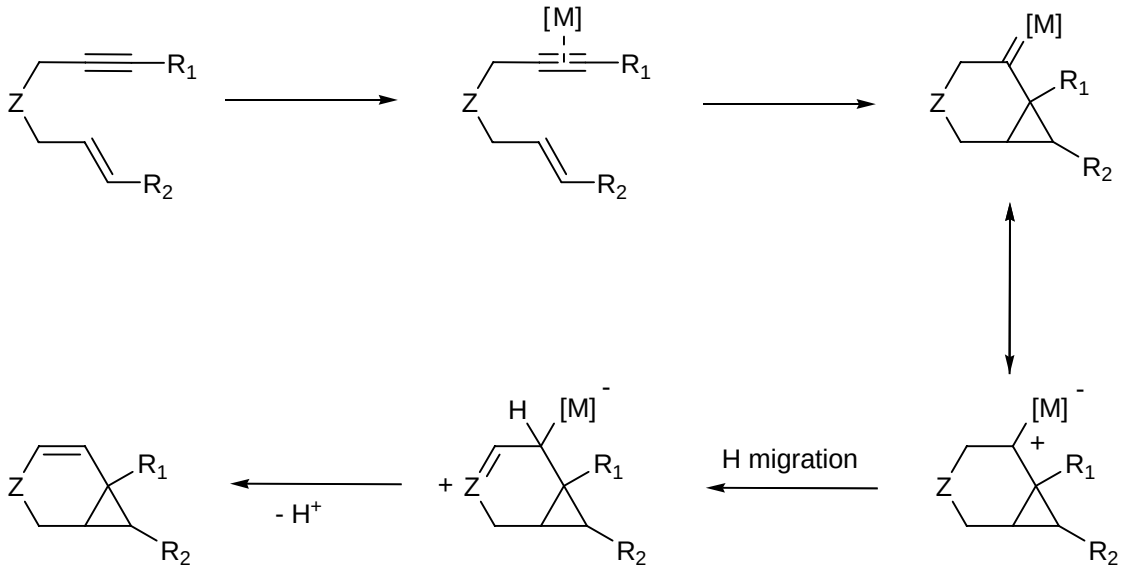
R_1 = H, Ph, $SiMe_3$
R_2 = H, Me
R_3 = H, Me, Ph

47 - 87%

Fürstner, F. Stelzer, H. Sziliat, *J. Am. Chem. Soc.* **2001**, *123*, 11863 - 11869.
Review: C. Bruneau, *Angew. Chem. Int. Ed.* **2005**, *44*, 2328 - 2334.

- Commonly used catalysts: Pt^{II}, Au^{III}
- Outcome of the cycloisomerisation reactions using late transition metals depends on the reaction conditions and substrate structure
- Formation of Cyclopropanes requires an heteroatom at the propargylic position

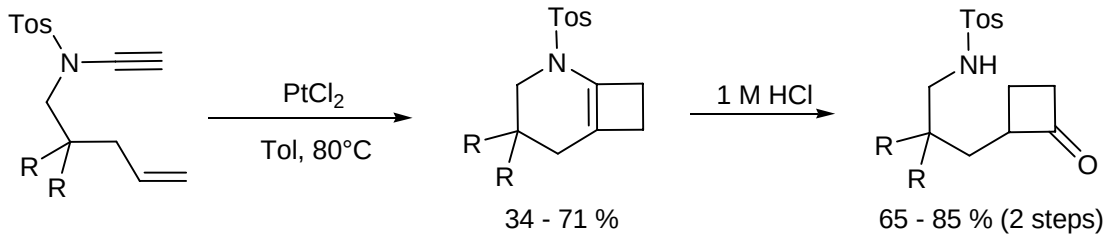
Proposed Mechanism



Heteroatom at the propargylic position facilitates H-migration

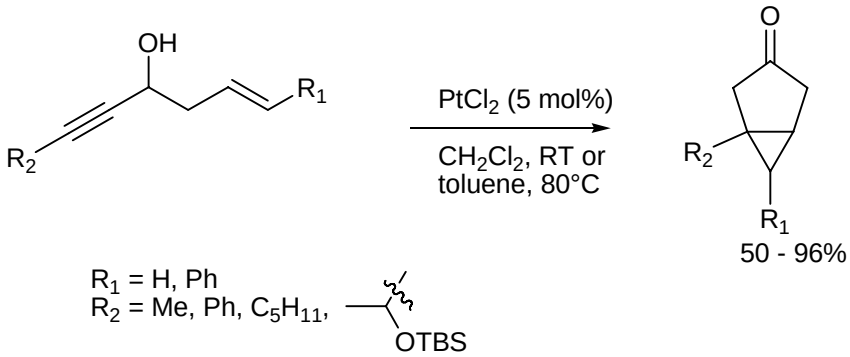
C. Bruneau, *Angew. Chem. Int. Ed.* **2005**, *44*, 2328 - 2334.

Cycloisomerisation to Cyclobutenes



F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509-1511

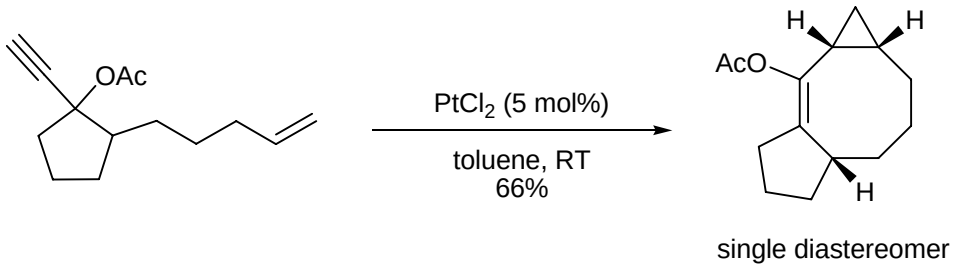
Propargylic alcohols as substrates



V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655
Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mourie, A. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2004**, *126*, 8656-8657

Ohloff-Rautenstrauch Rearrangement

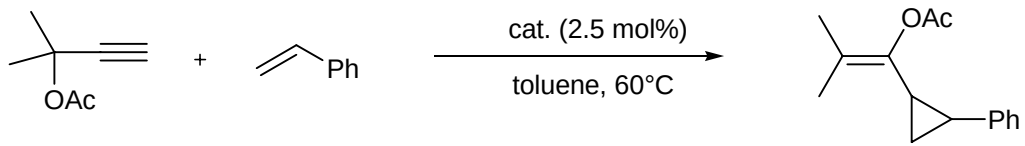
Intramolecular:



single diastereomer

E. Mainetti, V. Mourieres, L. Fensterbank, M. Malacria, J. Marco-Contelles, *Angew. Chem.* **2002**, *41*, 2132-2135.

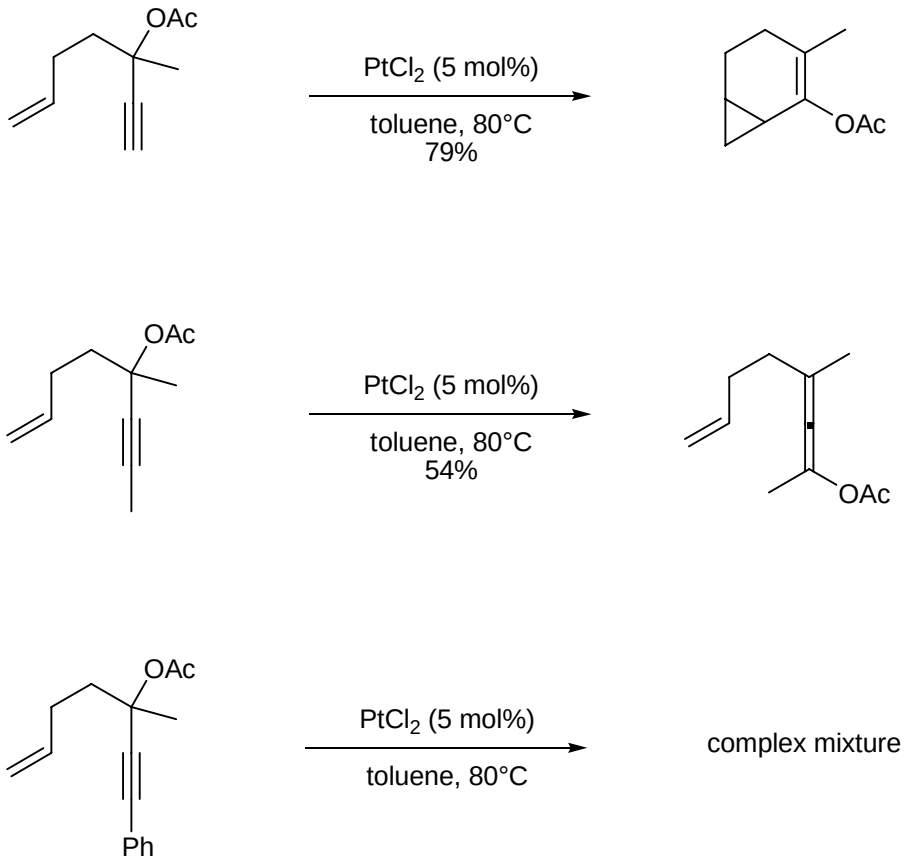
Intermolecular:



$IrCl_3$	24 h	45%
$[RuCl_2(CO)_3]_2$	15 h	90%
$PtCl_2$	1 h	93%
$AuCl_3$	10 min	63%

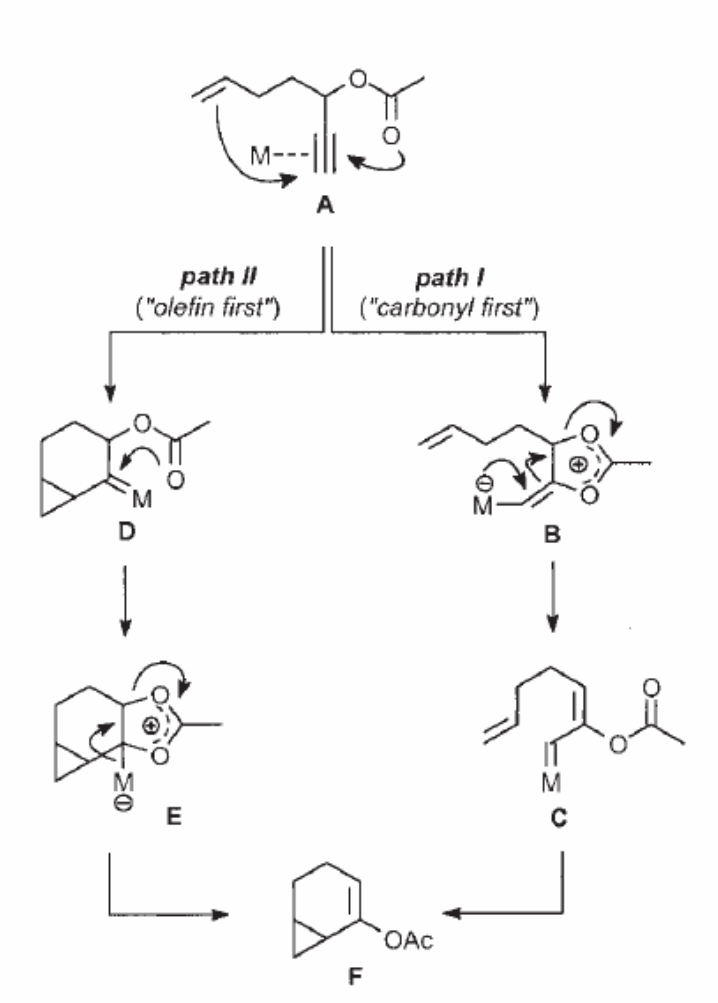
K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505-8513.

Limitations



A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *ASAP*

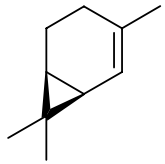
Proposed Mechanism



A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *ASAP*

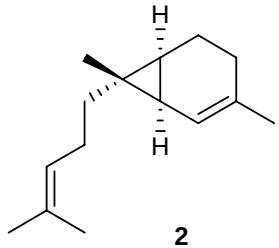
Application: Total Synthesis of Terpenes

Terpenes carrying functionalized cyclopropanes:



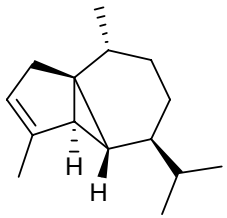
1

3-carene
isolated from pine tree oil



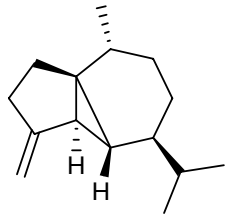
2

2-Sesquicarene
isolated from *Schisandra chinensis*
(Chinese Magnolia)



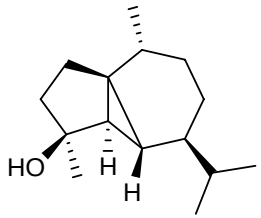
3

(-)-α-cubebene



4

(-)-β-cubebene



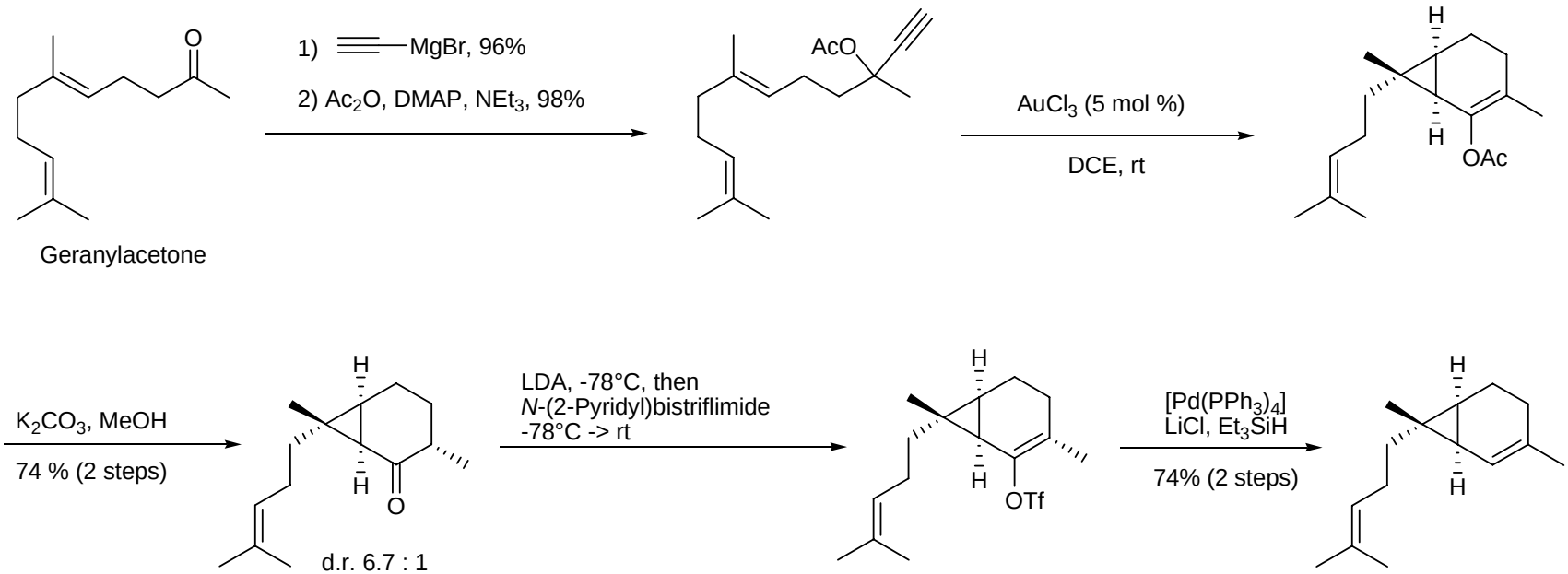
5

cubebol

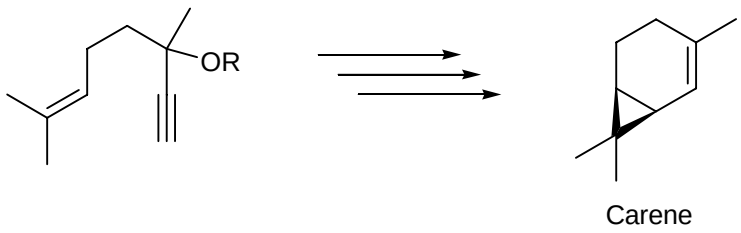
Isolated from *Piper cubeba* (tailed pepper)

Y. Ohta, T. Sakai, Y. Hirose, *Tetrahedron Lett.* **1966**, 6365 - 6370.
M. A. Sumathykutty, J. Madhusudana Rao, K. P. Padmakumari, C. S. Narayanan, *Flavour Fragr. J.* **1999**, 14, 279-282.
Racemic synthesis of **2**: K. Mori, M. Matsui, Tetrahedron Lett. **1969**, 2729-2732.
Racemic synthesis of **3** and **4**: E. Piers, R. W. Britton, W. de Waal, *Can. J. Chem.* **1971**, *49*, 12-19.

Synthesis of Sesquicarene

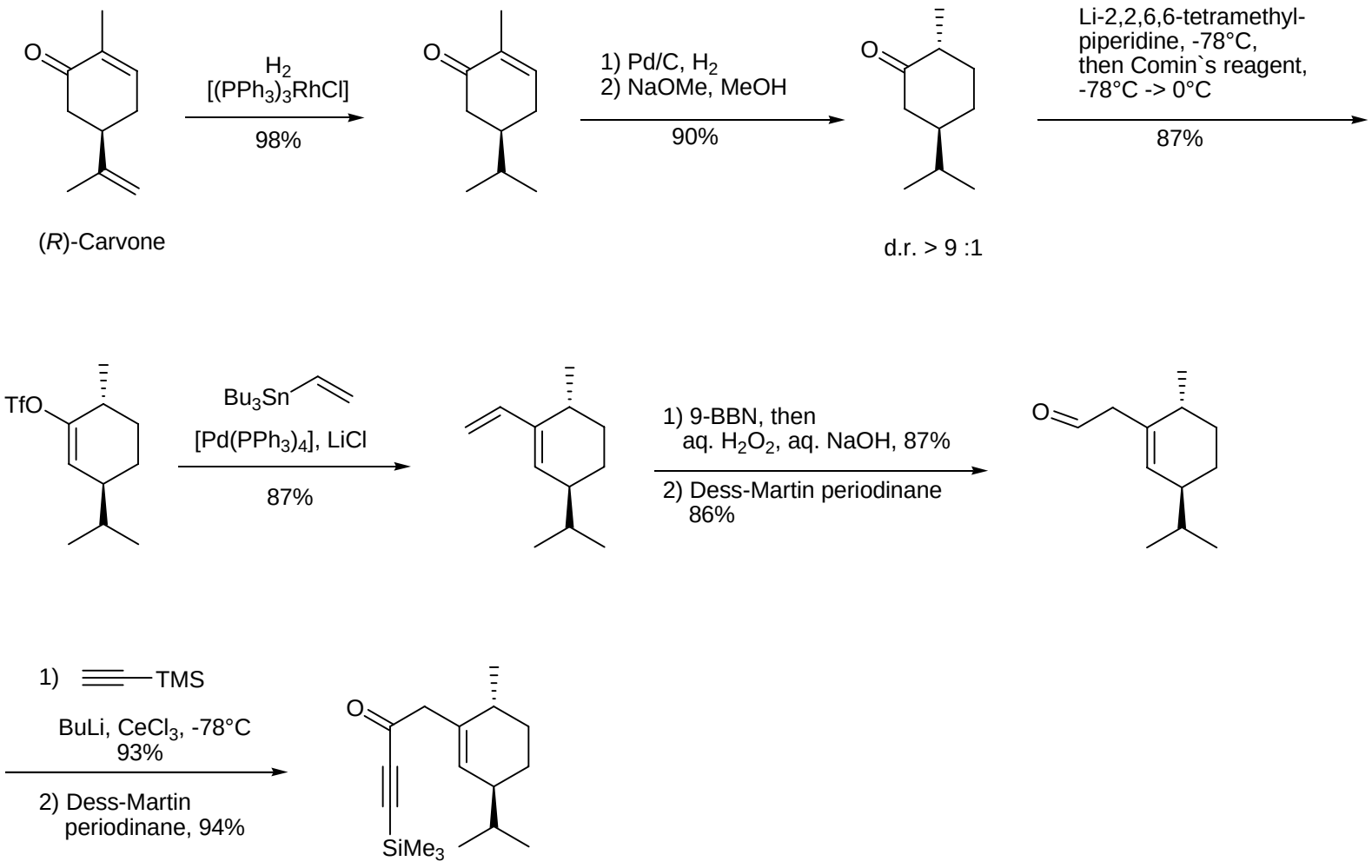


Analogous:



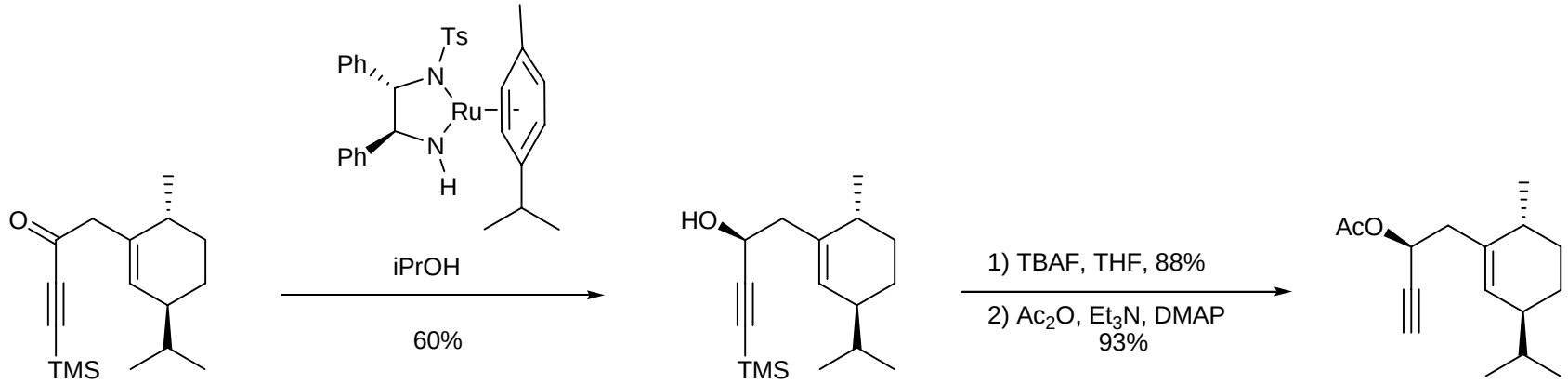
A. Fürstner, P. Hannen, *Chem. Commun.* **2004**, 2546-2547
A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *ASAP*

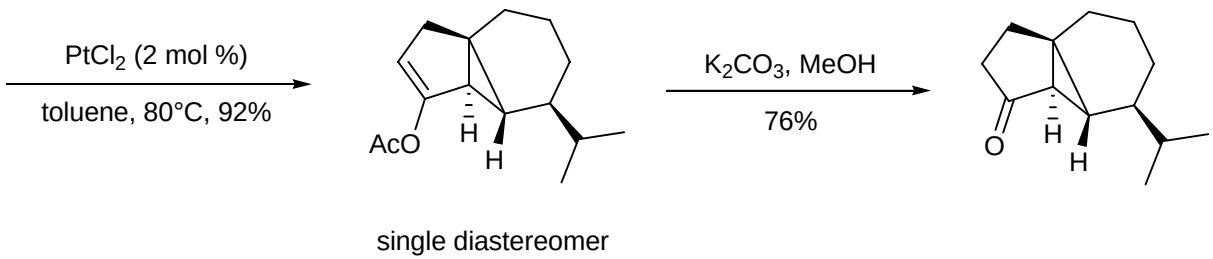
Total Synthesis of α-Cubebene, β-Cubebene and Cubebol

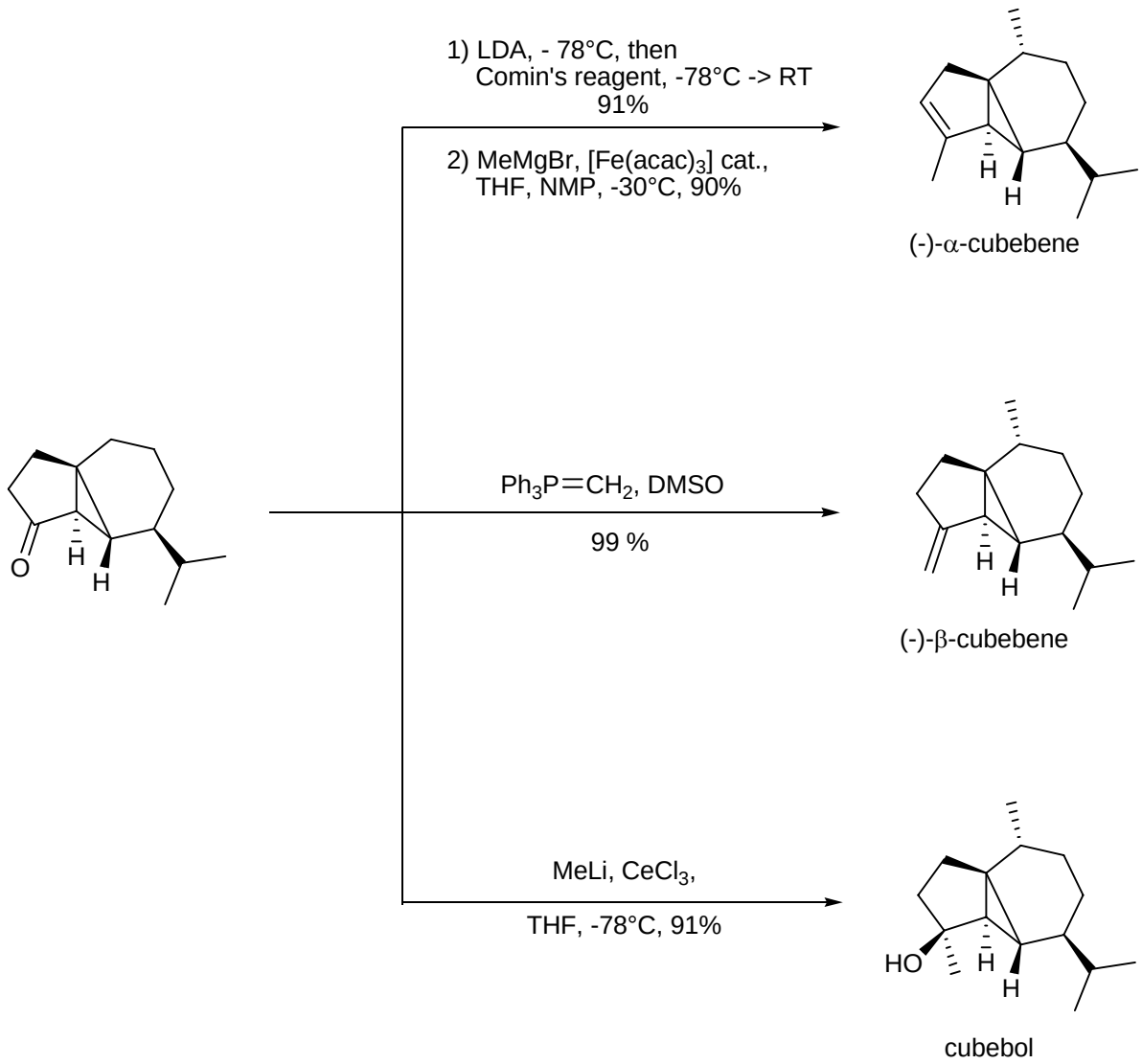


A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *ASAP*

Pt-catalyzed Cycloisomerization







Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *ASAP*
E. Piers, R. W. Britton, W. de Waal, *Can. J. Chem.* **1971**, *49*, 12-19.

Summary

- Late transition metal salts efficiently catalyze cycloligomerization reactions for the formation of substituted cyclopropyl compounds
- Pt and Au catalyzed Ohloff-Rautenstrauch rearrangement to afford tricyclic terpenes
- First stereoselective total synthesis of (-)-α-cubebene and (-)-Cubebol was achieved
- A better mechanistic understanding of the reaction and a more general protocol for these reactions is still needed