

Tandem Reaction Sequences

Chris Borths
MacMillan Group Meeting
November 21, 2000

- I. Cationic Transformations
- II. Anionic Transformations
- III. Pericyclic Transformations
- IV. Metal-catalyzed Transformations

Reviews: Ho, T.L. *Tandem Organic Reactions*; Wiley: New York, 1992.
Tietze, L.F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.
Tietze, L.F. *CHem. Rev.* **1996**, *96*, 115.

Why Tandem Reactions?

Practical Considerations

- Reduction of waste
- Avoids isolation of intermediates
- Reduces labor, time to effect given transformation

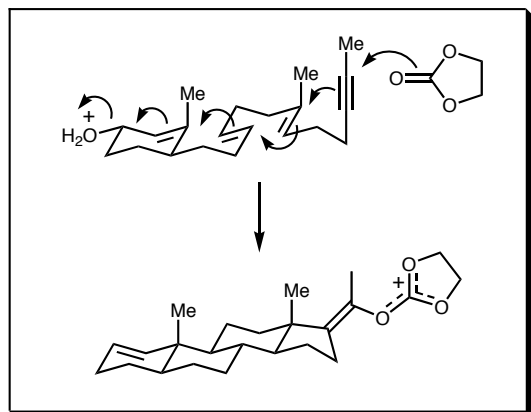
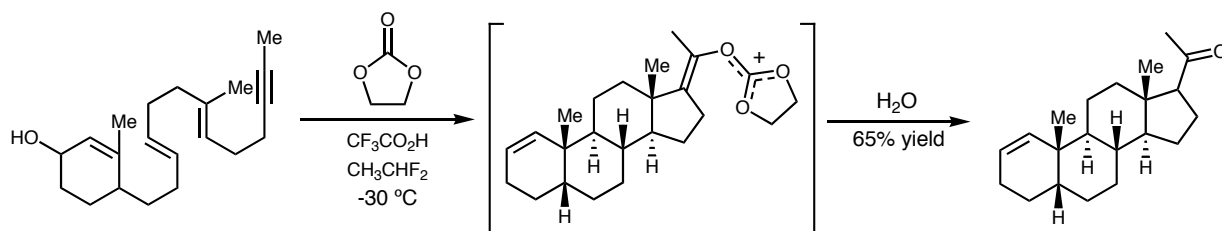
Academic Considerations

- Builds a large degree of complexity in one transformation
- Novel avenues of research, new reaction development

A Definition:

- A tandem reaction is a reaction in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents.

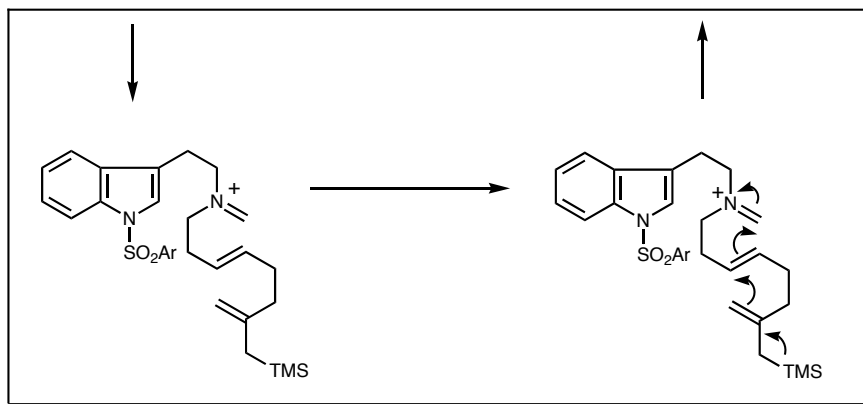
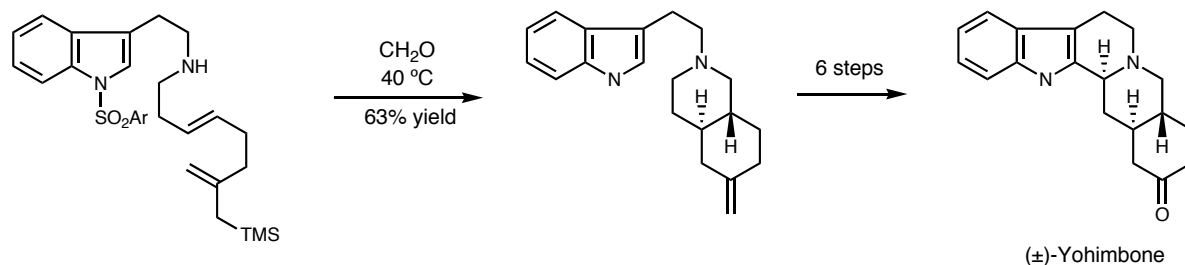
Polyene Cationic Cyclization



- Acetals and allylic alcohols are good initiators
- Only one out of 32 possible diastereomers formed
- Double bond geometry controls stereochemistry of product
- Vinyl fluorides can increase yield by stabilizing intermediate carbocations

Johnson, W.S. *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 9.
Fish, P.V.; Johnson, W.S. *J. Org. Chem.* **1994**, 59, 2324.

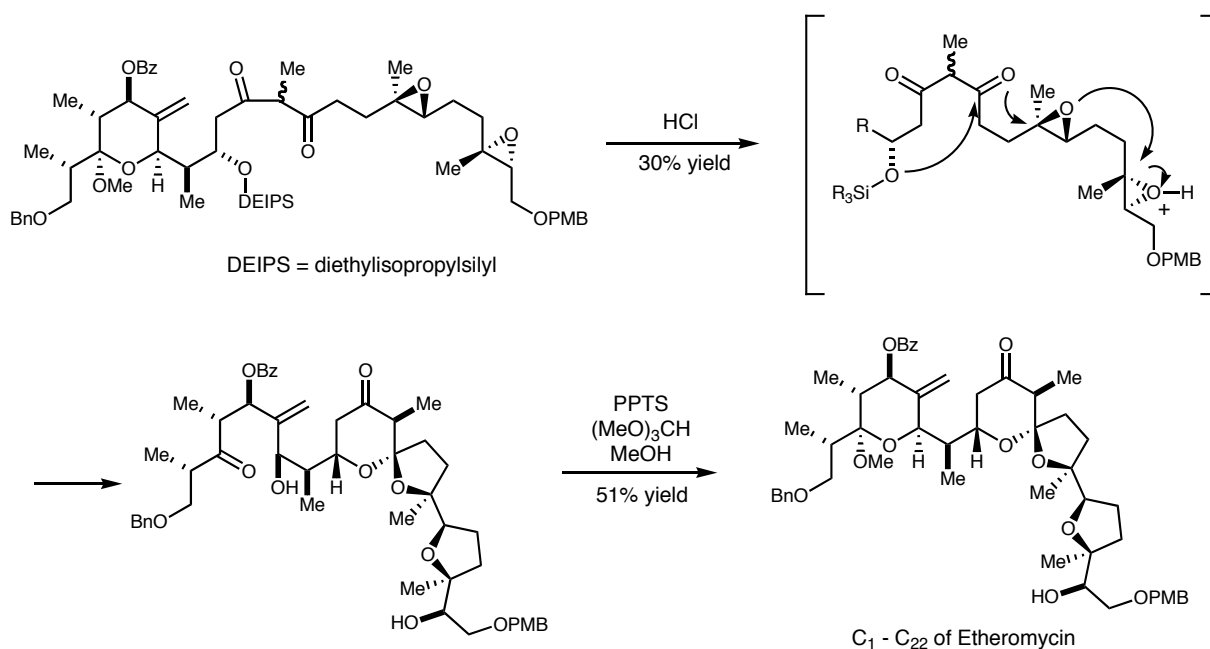
Mannich-Cation Olefin Cyclization



- Allylsilanes are common terminators of cationic olefin cyclizations
- This is the first example of an iminium ion as the initiator

Grieco, P.A.; Fobare, W.F. *J. Chem. Soc. Chem. Commun.* **1987**, 185.

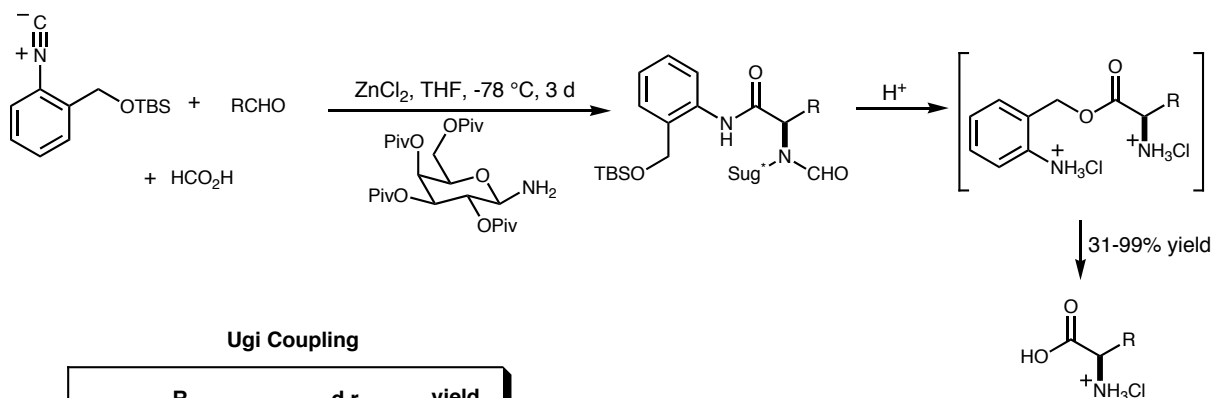
Cascade Polyether Cyclization



■ Stereochemistry of epoxide determines the stereochemistry of the polyether

Paterson, I.; Tillyer, R.D.; Smail, J.B. *Tet. Lett.* **1993**, *34*, 7137.
Review: Koert, U. *Synthesis* **1995**, 115.

Diastereoselective Ugi Reaction



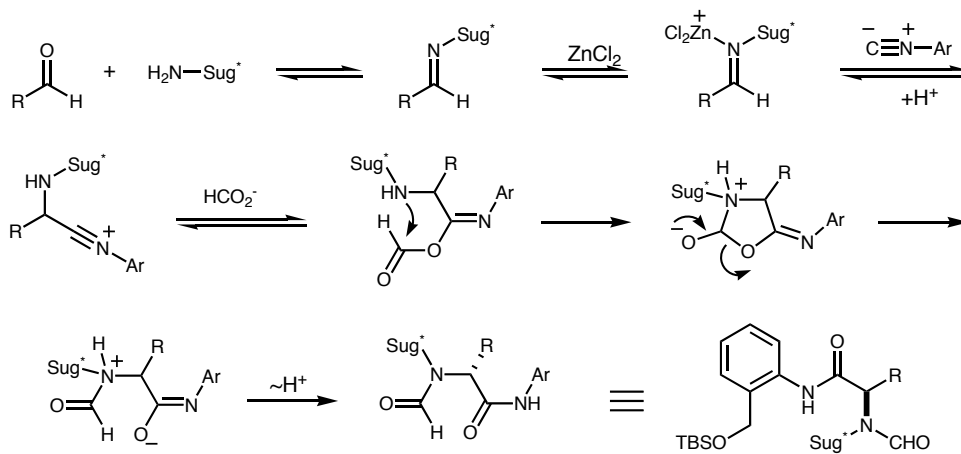
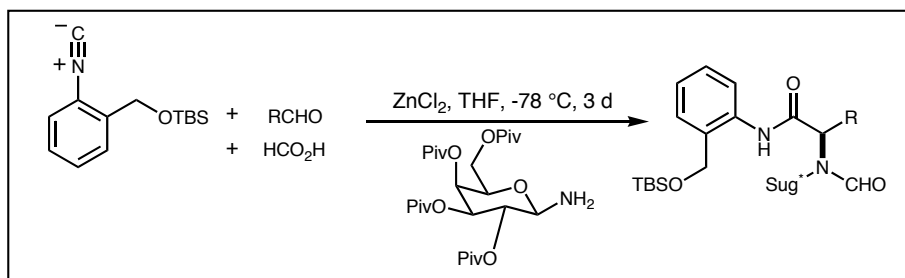
Ugi Coupling

R	d.r.	yield
Ph	90 : 10	61%
CH ₂ CH(CH ₃) ₂	97 : 3	80%
(CH ₂) ₄ CO ₂ CH ₃	98 : 2	80%
Bn	98 : 2	85%
(CH ₂) ₂ CF=CHC ₆ H ₅	98 : 2	65%

■ The opposite enantiomer can be accessed by using a different sugar auxiliary. Diastereoselectivities are similar (90:10 - 96:4); yields are lower (48 - 76%).

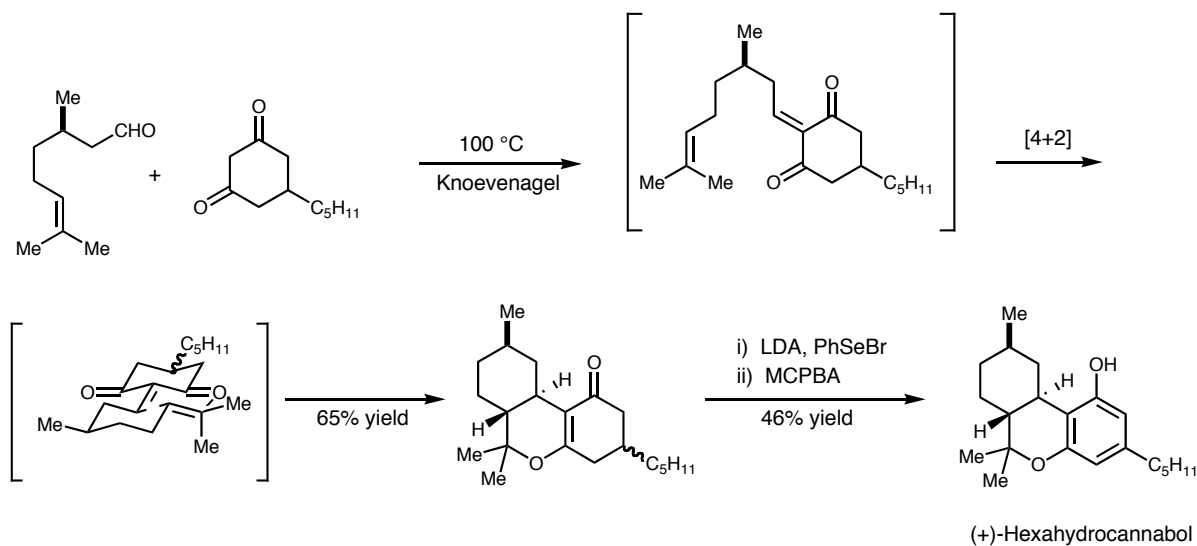
Linderman, R.J.; Binet, S.; Petrich, S.R. *J. Org. Chem.* **1999**, *64*, 336.

Ugi Reaction Mechanism



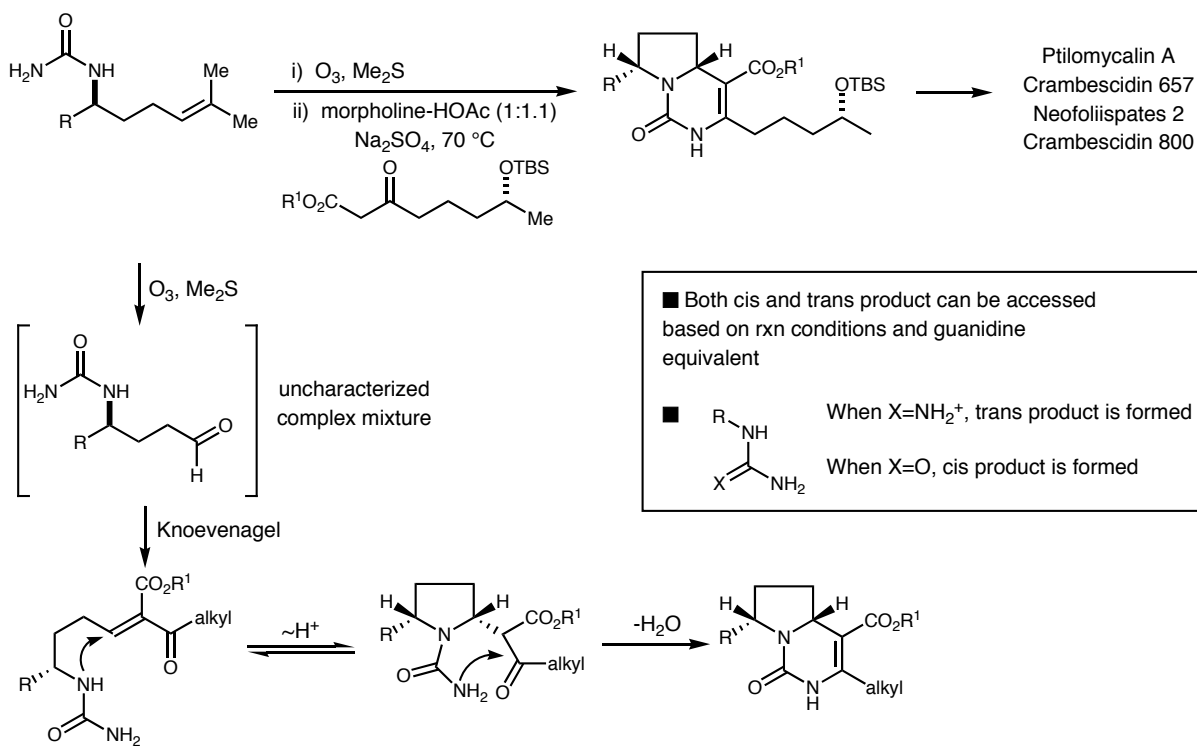
Linderman, R.J.; Binet, S.; Petrich, S.R. *J. Org. Chem.* **1999**, *64*, 336.
Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 8.

Tandem Knoevenagel Diels-Alder Reaction



- The Diels-Alder reaction is controlled by the chiral center in citronellal.
- The product is a 2:1 (α : β) mixture of diastereomers at the alkyl chain.

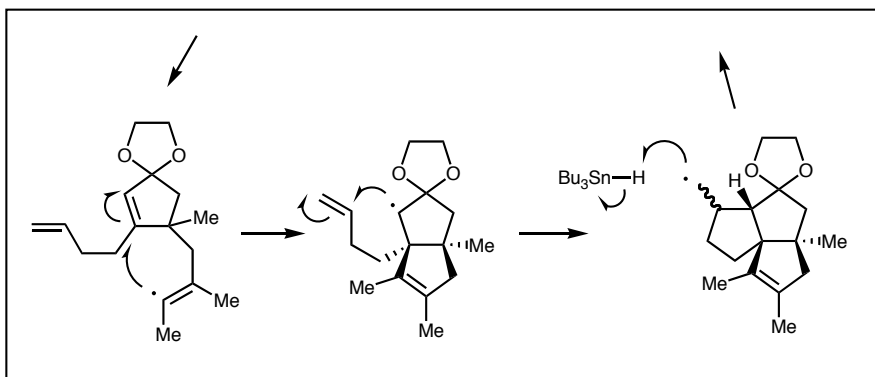
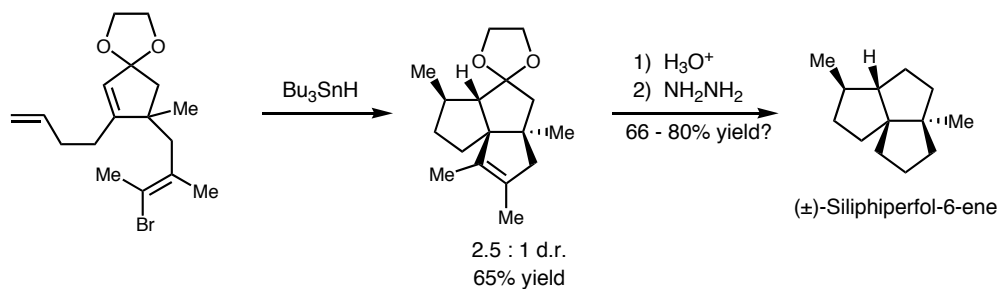
Tethered Biginelli Condensation



McDonald, A.I.; Overman, L.E. *J. Org. Chem.* **1999**, *64*, 1520.

Coffey, D.S.; McDonald, A.I.; Overman, L.E.; Rabinowitz, M.H.; Renhowe, P.A. *J. Am. Chem. Soc.* **2000**, *122*, 4893.

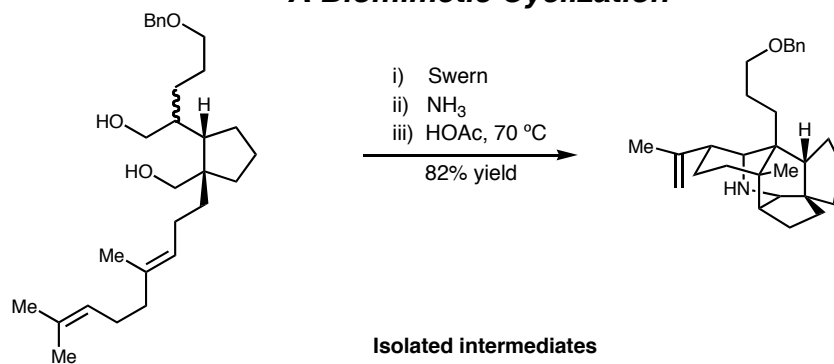
Tandem Radical Cyclization



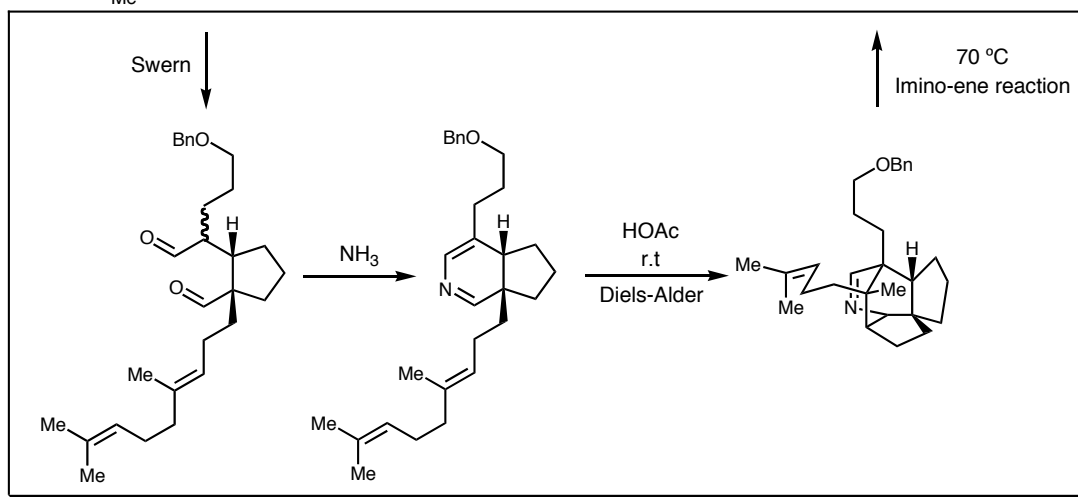
■ The stereochemistry of the vinyl bromide does not affect reaction outcome

■ Direct cyclization of the α,β -unsaturated ketone is possible, but favors the α -methyl diastereomer 3:1. The cyclic acetal shields the endo face of the bicyclic system and favors the β -methyl diastereomer.

A Biomimetic Cyclization

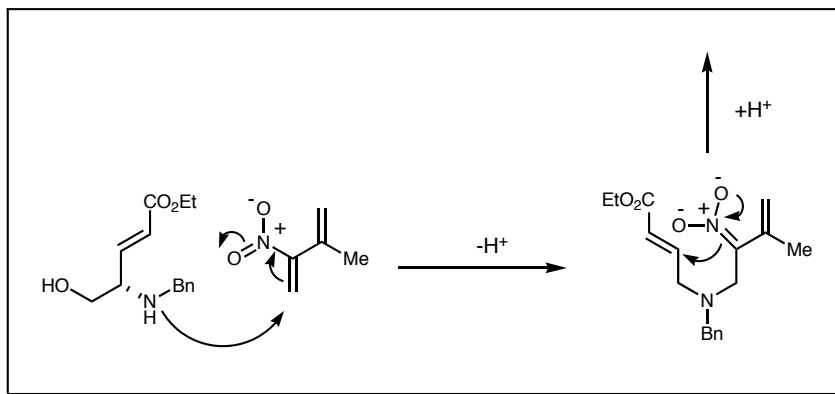
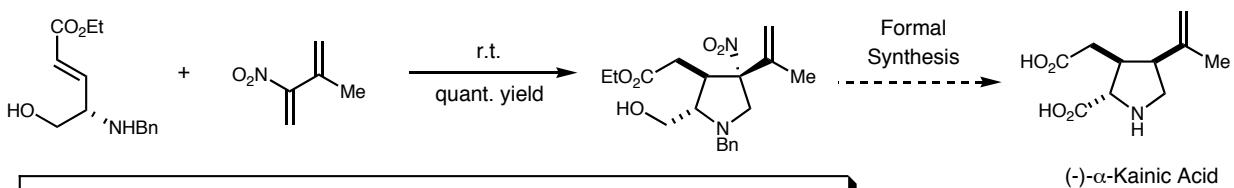


Isolated intermediates



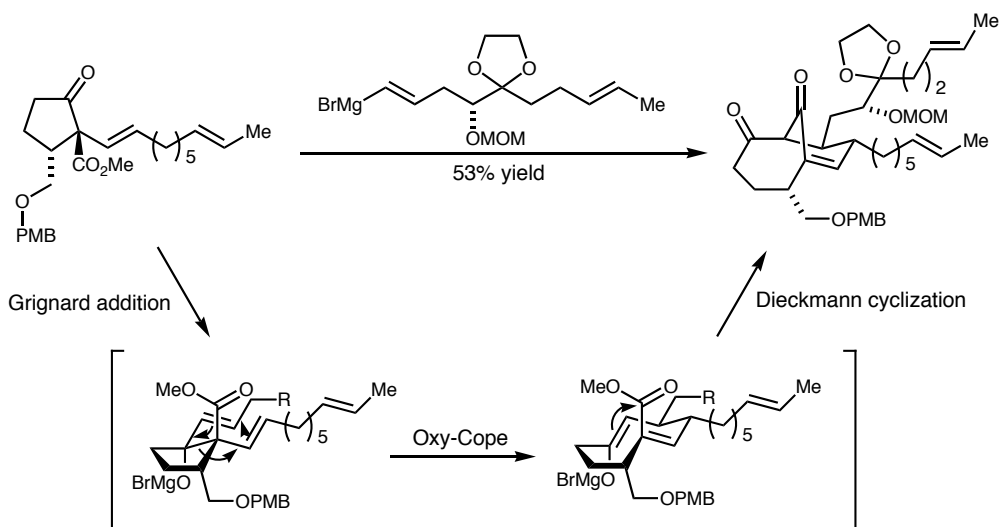
Heatchcock, C.H. *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 665.

Tandem Michael Reaction



■ Nitro group used as a removable electron-withdrawing group

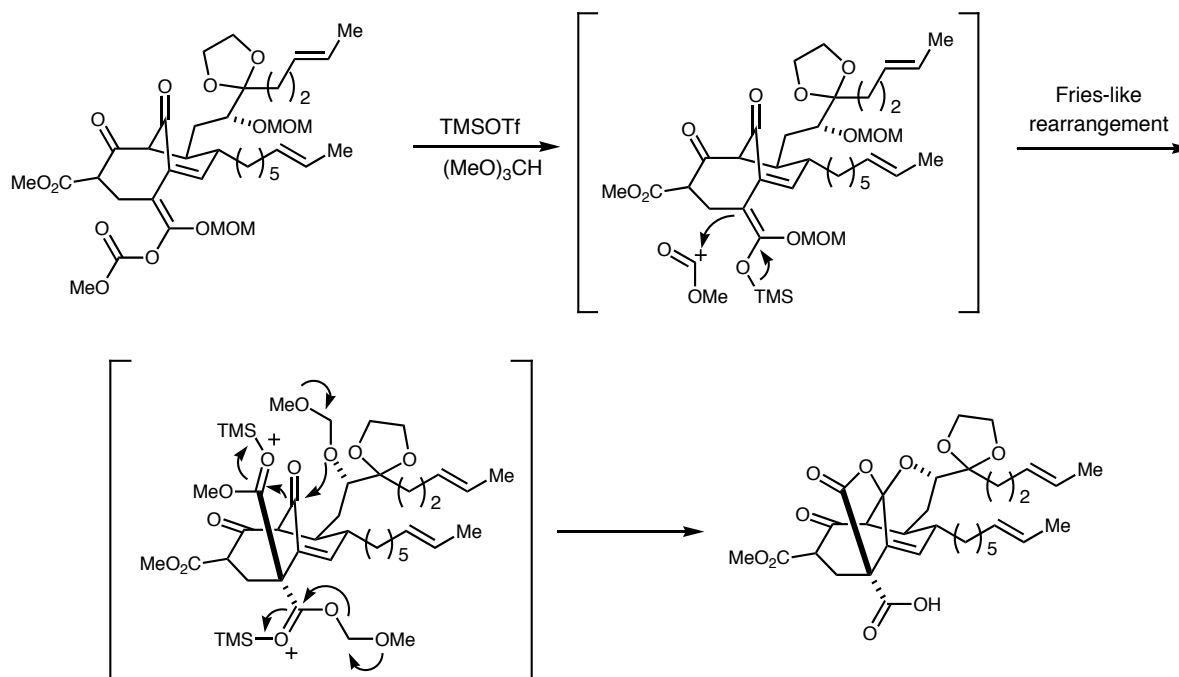
Tandem Alkylation, Oxy-Cope, Cyclization



- Grignard addition sets up an anion-accelerated oxy-Cope which rearranges through a chair transition state
- The enolate resulting from the oxy-Cope spontaneously cyclizes onto the methyl ester

Chen, C.; Layton, M.E.; Sheehan, S.M.; Shair, M.D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

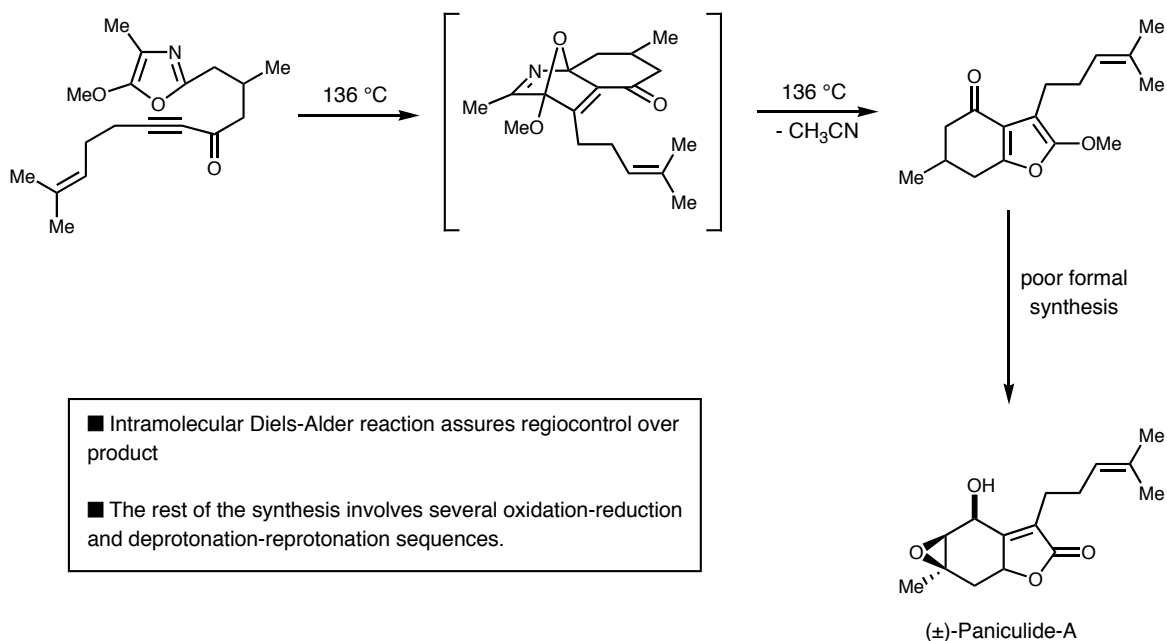
Tandem Fries rearrangement, Cyclization, Deprotection



- This intermediate was elaborated into (+)-CP-263,114.

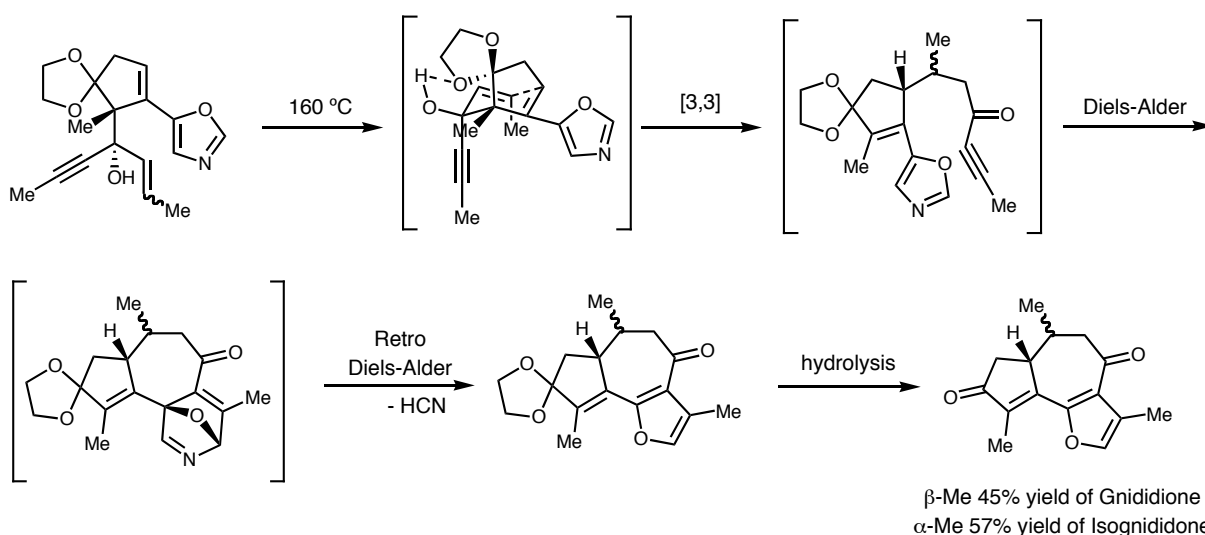
Chen, C.; Layton, M.E.; Sheehan, S.M.; Shair, M.D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

Tandem Diels-Alder Retro Diels-Alder



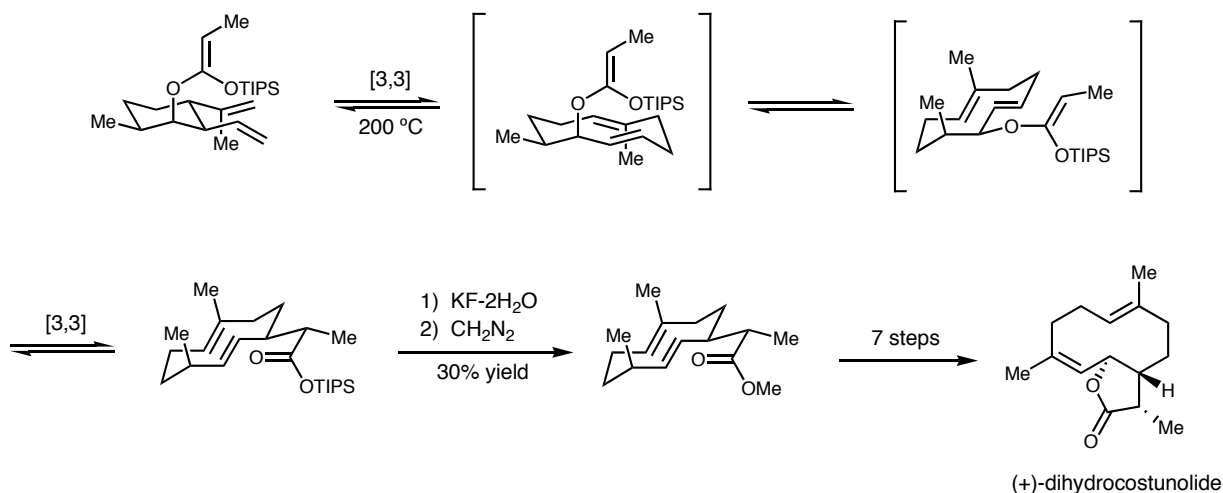
Jacobi, P.A.; Kaczmarek, C.S.R.; Udodong, U.E. *Tet. Lett.* **1984**, 25, 4859.

Oxy-Cope, Diels-Alder, Retro Diels-Alder



- Note: Each olefin geometry (E and Z) was prepared selectively and subjected to the reaction conditions
- Oxy-Cope rearrangement proceeds through a chair transition state, possibly stabilized by intramolecular hydrogen bonding. Analysis of crude reaction mixtures indicated that less than 2% of material rearranged through the boat conformation.
- Regiocontrol over the Diels-Alder reaction was established by geometrical constraints, and the retro Diels-Alder was entropically favored.

Tandem Oxy-Cope Claisen

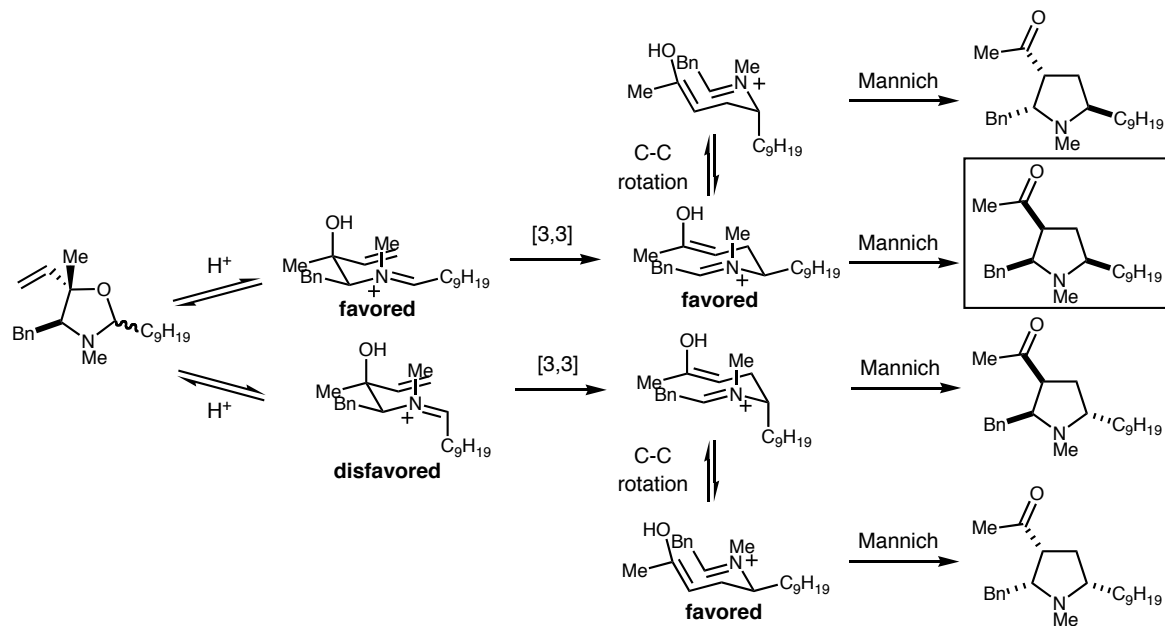
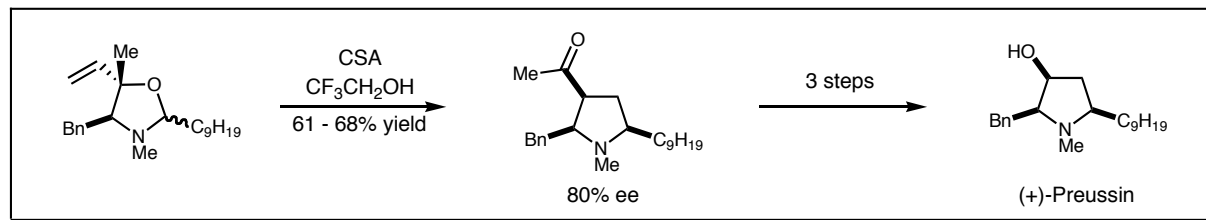


■ Rearrangement shows no evidence of silyl migration. When TBS is the silyl group, the rearrangement is complicated by silyl migration.

■ Both [3,3] rearrangements occur through chair transition states.

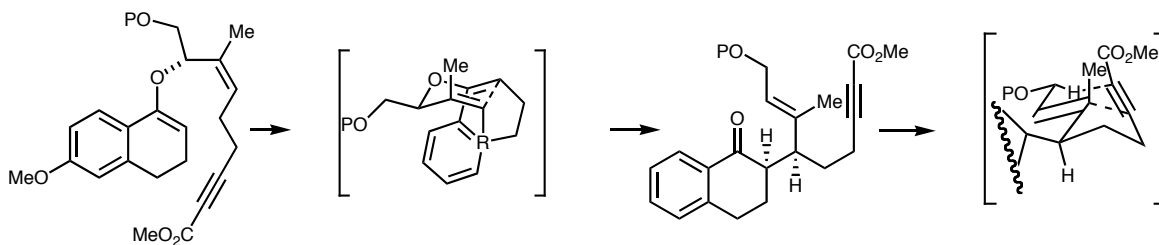
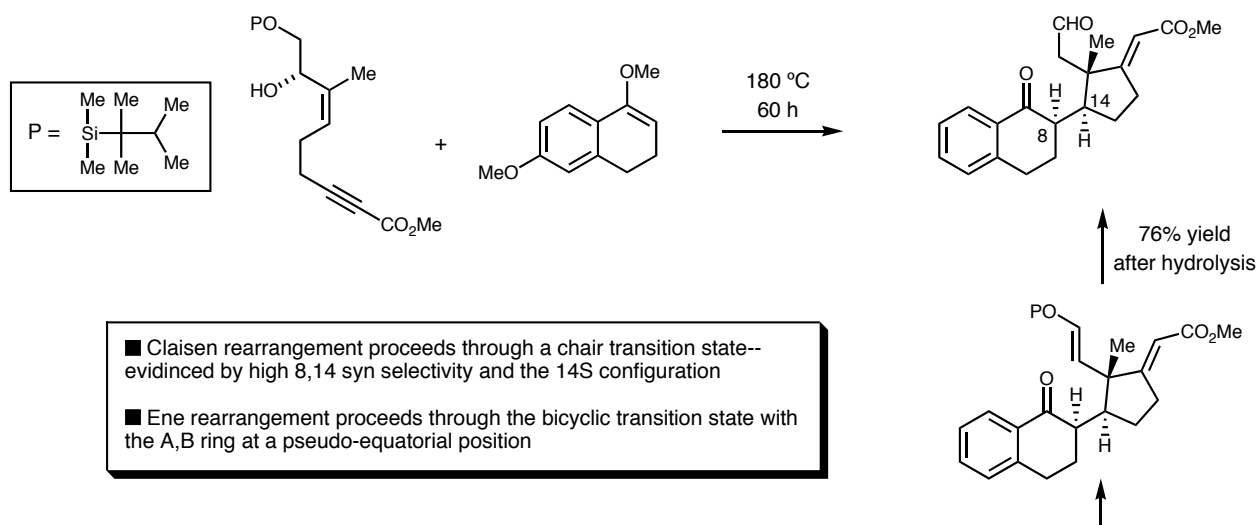
Raucher, S.; Chi, K.W.; Hwang, K.J.; Burks, J.E. *J. Org. Chem.* **1986**, *51*, 5503.

Aza-Cope Mannich Reaction



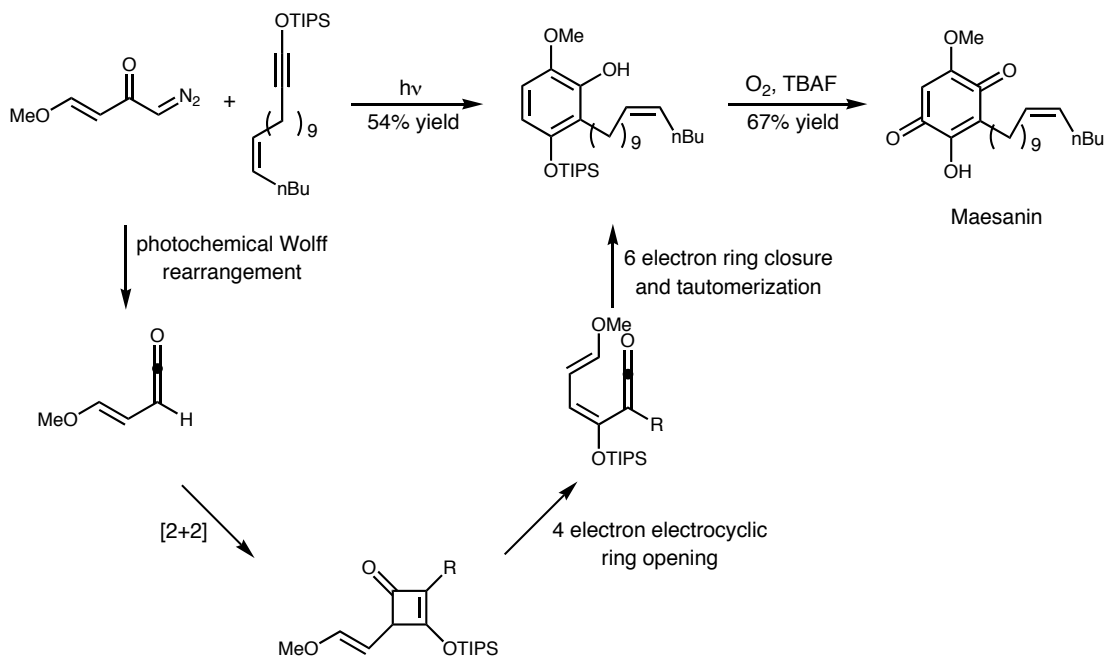
Deng, W.; Overman, L.E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

Tandem Claisen-Ene Reaction

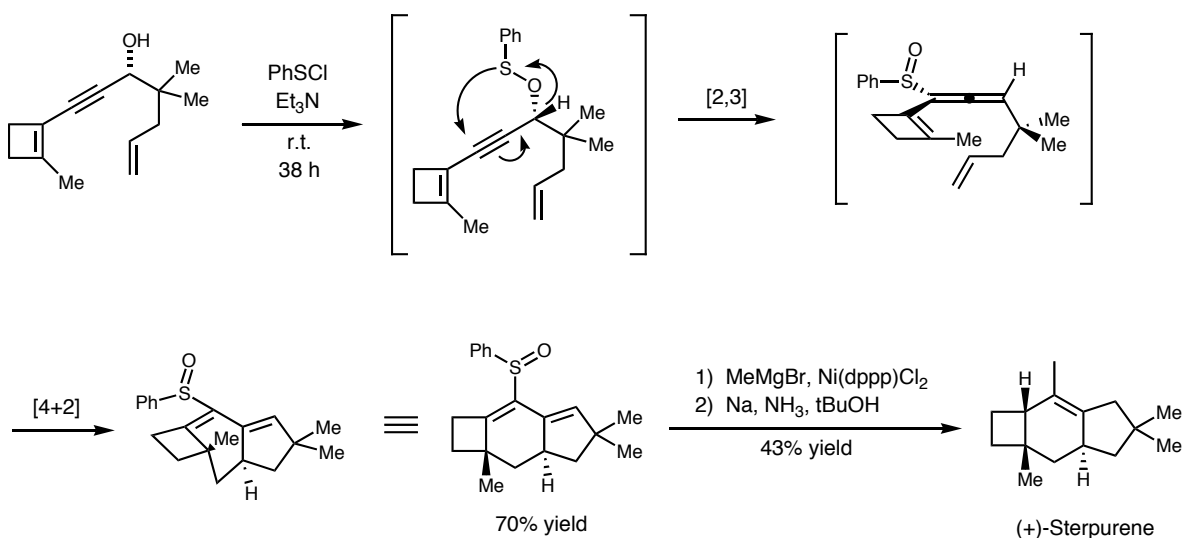


Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.
 Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948.

Cascade Aromatic Annulation



Tandem [2,3] Rearrangement, Diels-Alder

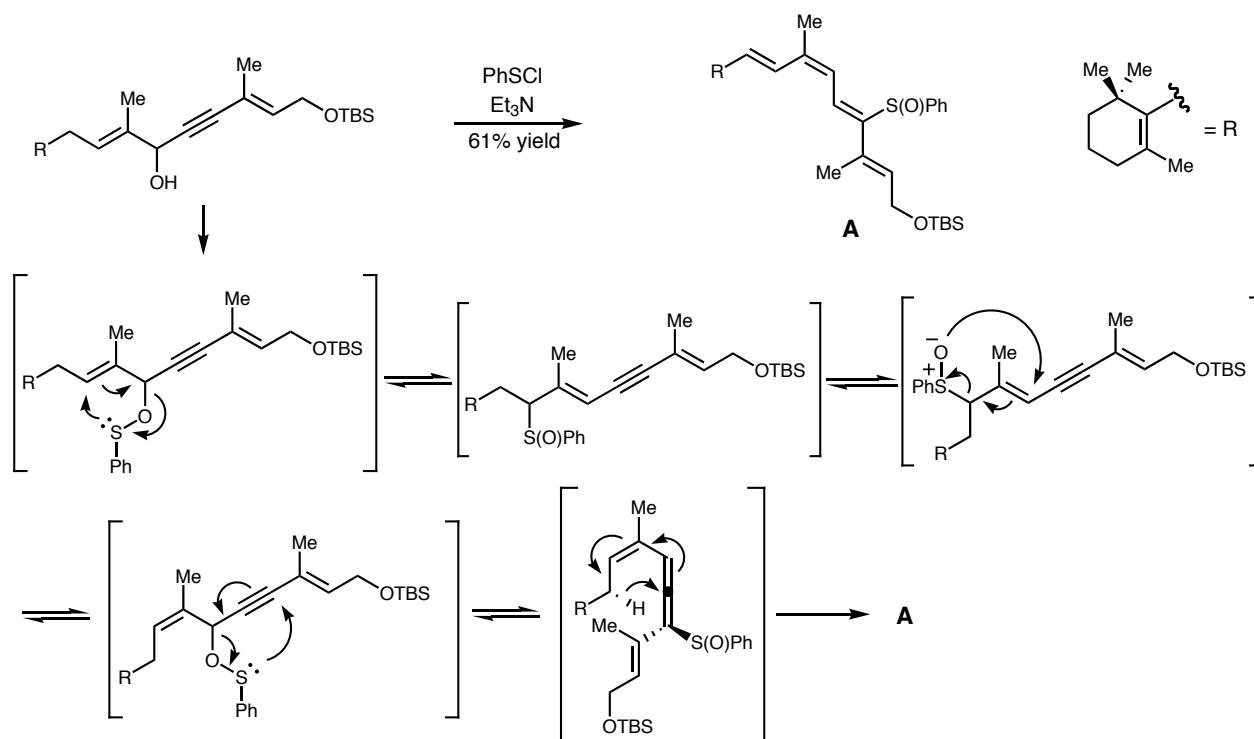


- Chirality of secondary alcohol is effectively transferred to the axial chirality of the allene intermediate
- The intramolecular Diels-Alder sets two stereocenters enatio- and diastereoselectively from the allene intermediate

Gibbs, R.A.; Okamura, W.H. *J. Am. Chem. Soc.* **1988**, *110*, 4062.

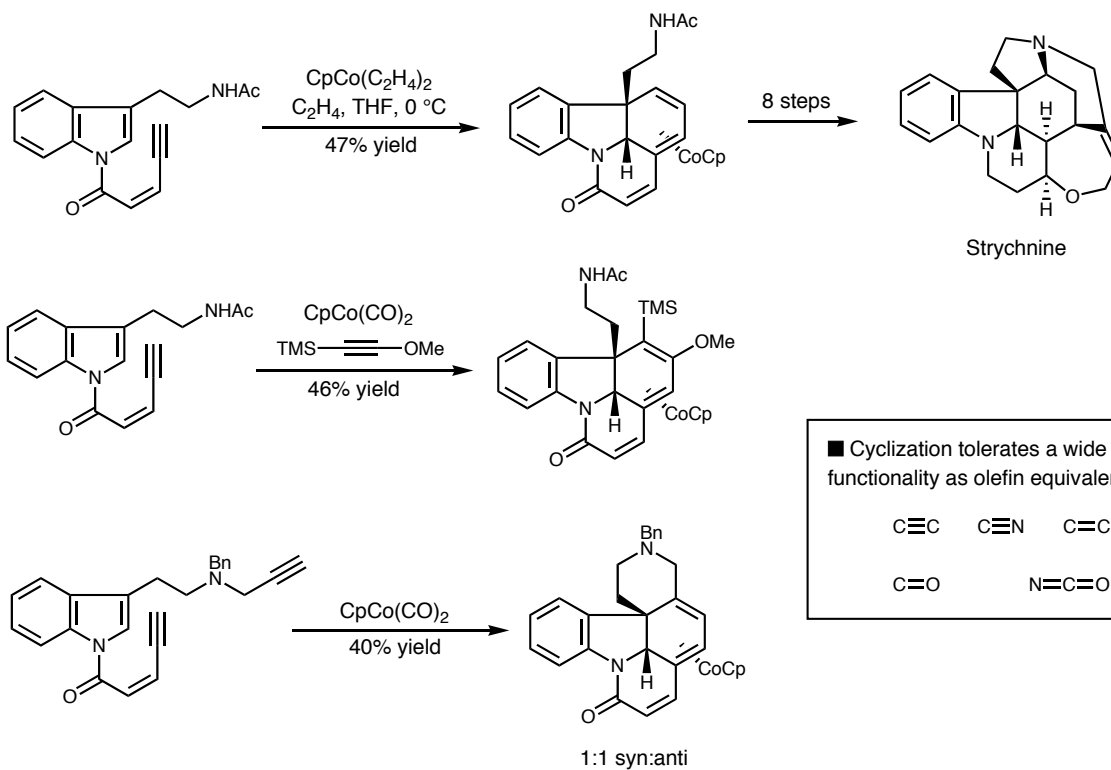
Pericyclic Domino Reaction

- [2,3]-allyl sulfonate and [2,3]-allyl sulfoxide shifts are reversible. The [1,5] sigmatropic hydride migration is the stereodifferentiating step in this reaction sequence.



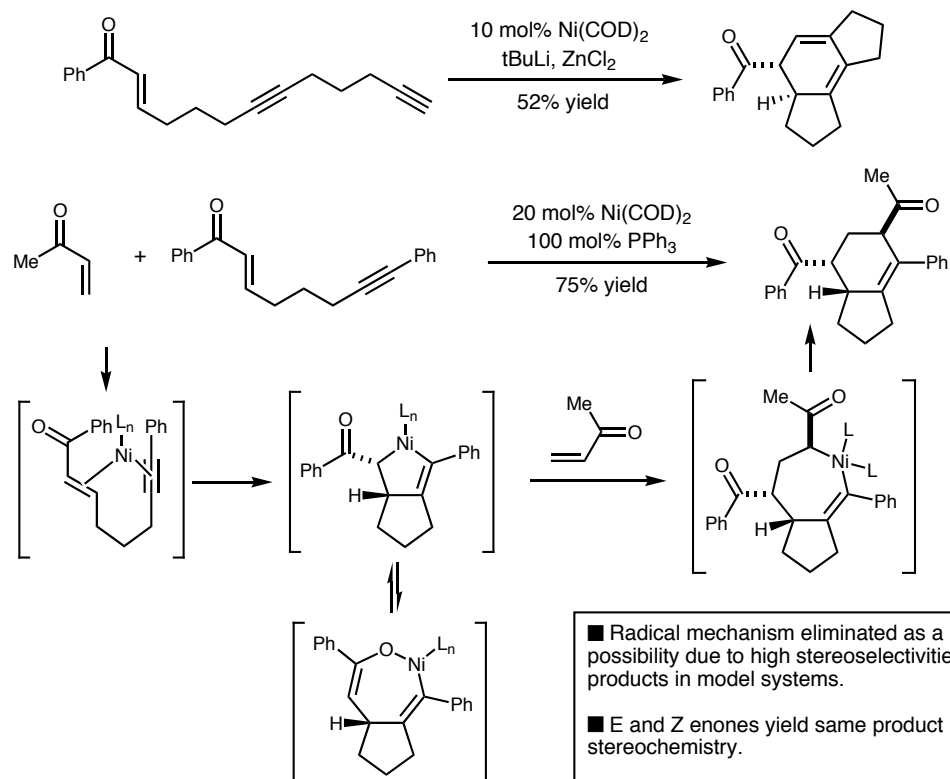
Iglesias, B.; Torrado, A.; de Lera, A.R. *J. Org. Chem.* **2000**, *65*, 2696.

Cobalt-Mediated [2+2+2] Cycloaddition



Eichberg, M.J.; Dorta, R.L.; Lamottke, K.; Vollhardt, K.P.C. *Org. Lett.* **2000**, *2*, 2479.

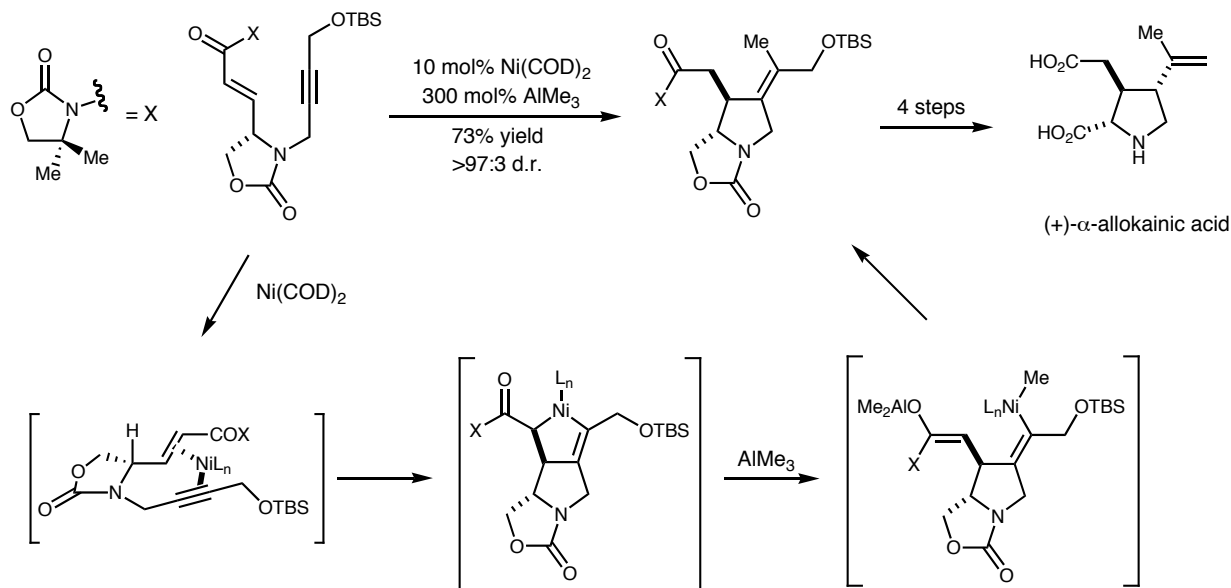
Nickel-Catalyzed [2+2+2] Cyclizations



Montgomery, J.; Seo, J. *Tetrahedron* **1998**, *54*, 1131.

Seo, J.; Chui, H.M.; Heeg, M.J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.

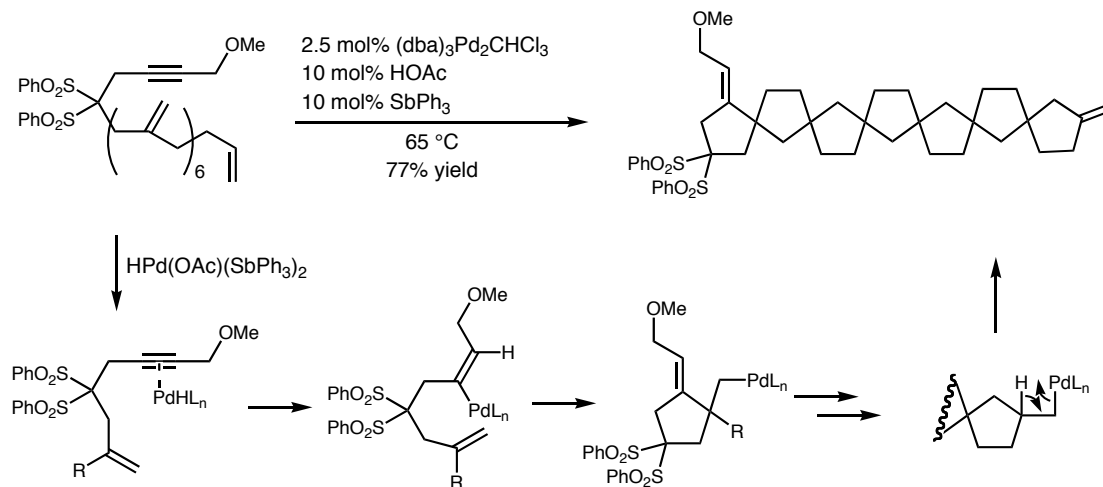
Nickel-Catalyzed Cyclization



- Metallocycle formation proceeds through a transition state with all substituents in a pseudo-equatorial configuration
- Unsaturated acyl oxazolidinones show greater reactivity and selectivity than unsaturated esters.

Chevliakov, M.V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.
Seo, J.; Fain, H.; Blanc, J.B.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 6060.

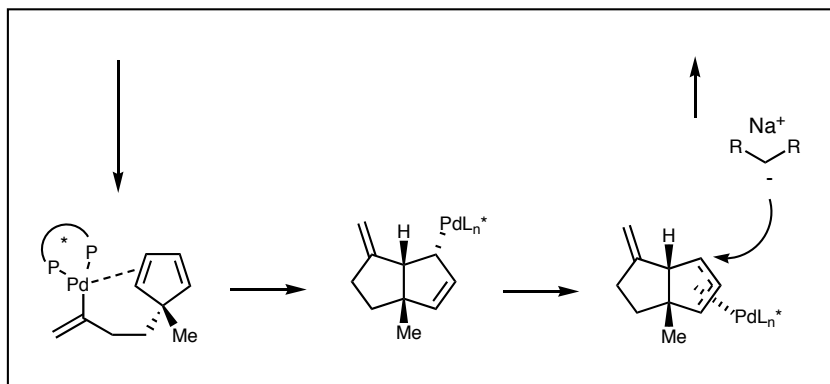
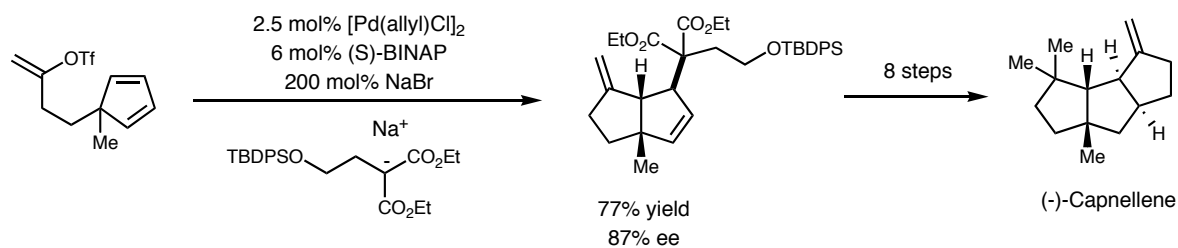
Palladium Polyene Cyclization



- The geometry of the double bonds controls the ring-fusion geometry. 1,1-disubstituted olefins form spiro ring systems - 1,2-disubstituted olefins form fused ring systems.
- The two new bonds formed with the π-system are cis to one another due to the syn addition of the Pd species.
- This tandem cyclization process can be initiated by an alkyne in the presence of HOAc or by a vinyl halide.

Trost, B.M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.
Review: Overman, L.E.; Abelman, M.M.; Kucera, D.J.; Tran, V.D.; Ricca, D.J. *Pure Appl. Chem.* **1992**, *64*, 1813.

Enantioselective Heck-Anion Addition



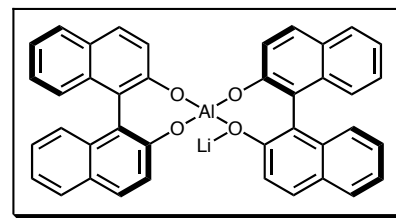
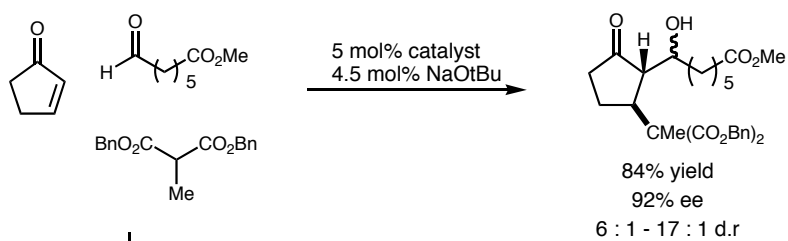
■ Heck reaction is enantiodifferentiating

■ Nucleophile adds to less hindered carbon

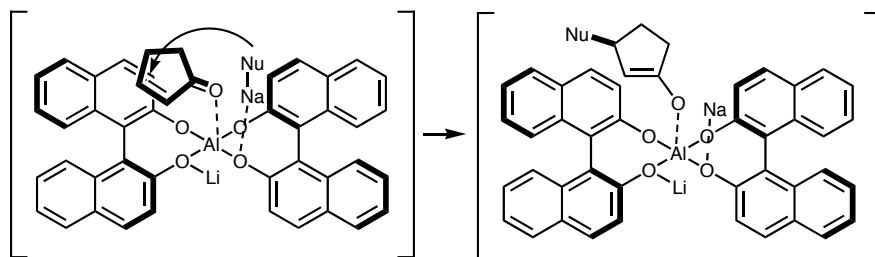
■ Wide range of soft nucleophiles will add to the π-allyl Pd species

Oshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108.

Enantioselective Michael Aldol



catalyst

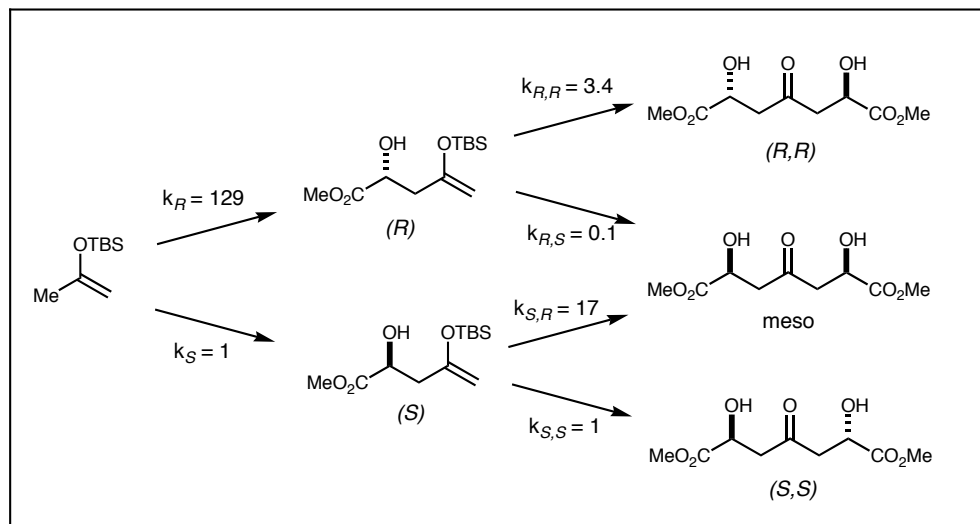
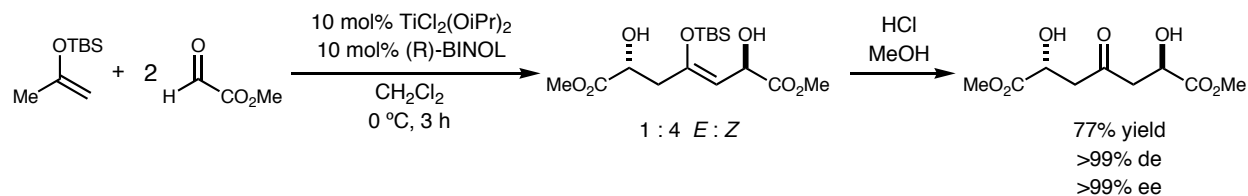


■ Enantioselectivity is determined in the Michael addition.

■ When simple malonates were used as nucleophiles, low yields resulted.

Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666.

Enantioselective Tandem Mukaiyama Aldol Reaction



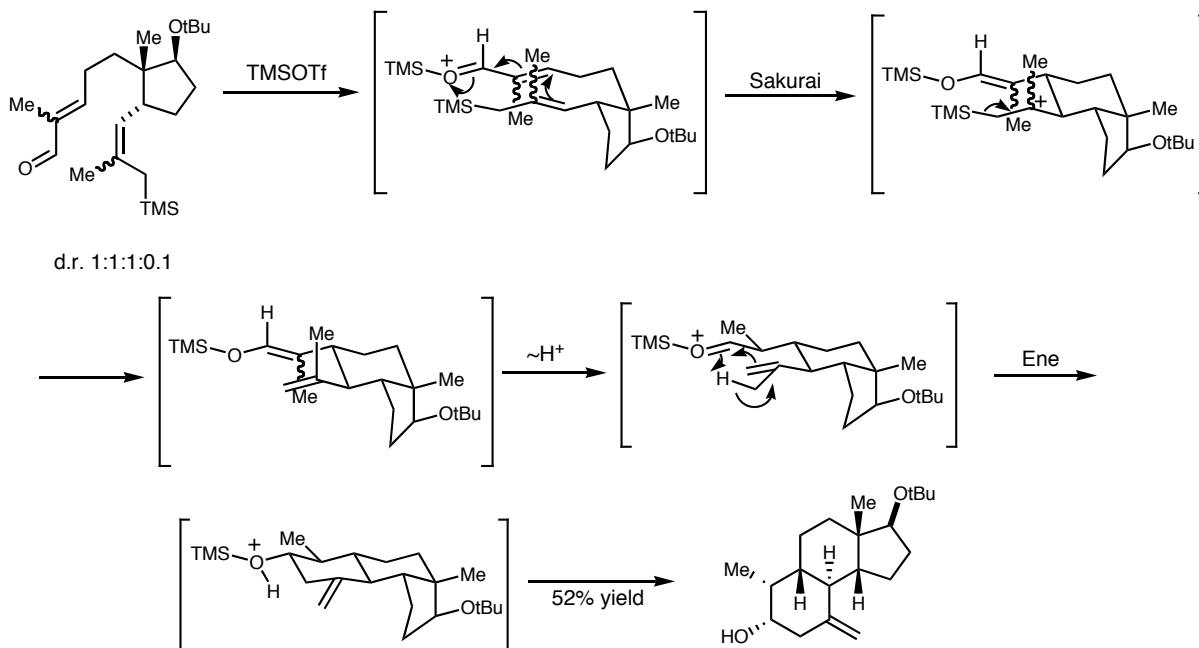
■ ee of major product of first reaction amplified

■ minor product of first aldol converted into meso product preferentially

Mikami, K.; Matsukawa, S.; Nagashima, M.; Funabashi, H.; Morisima, H. *Tet. Lett.* **1997**, *38*, 579.

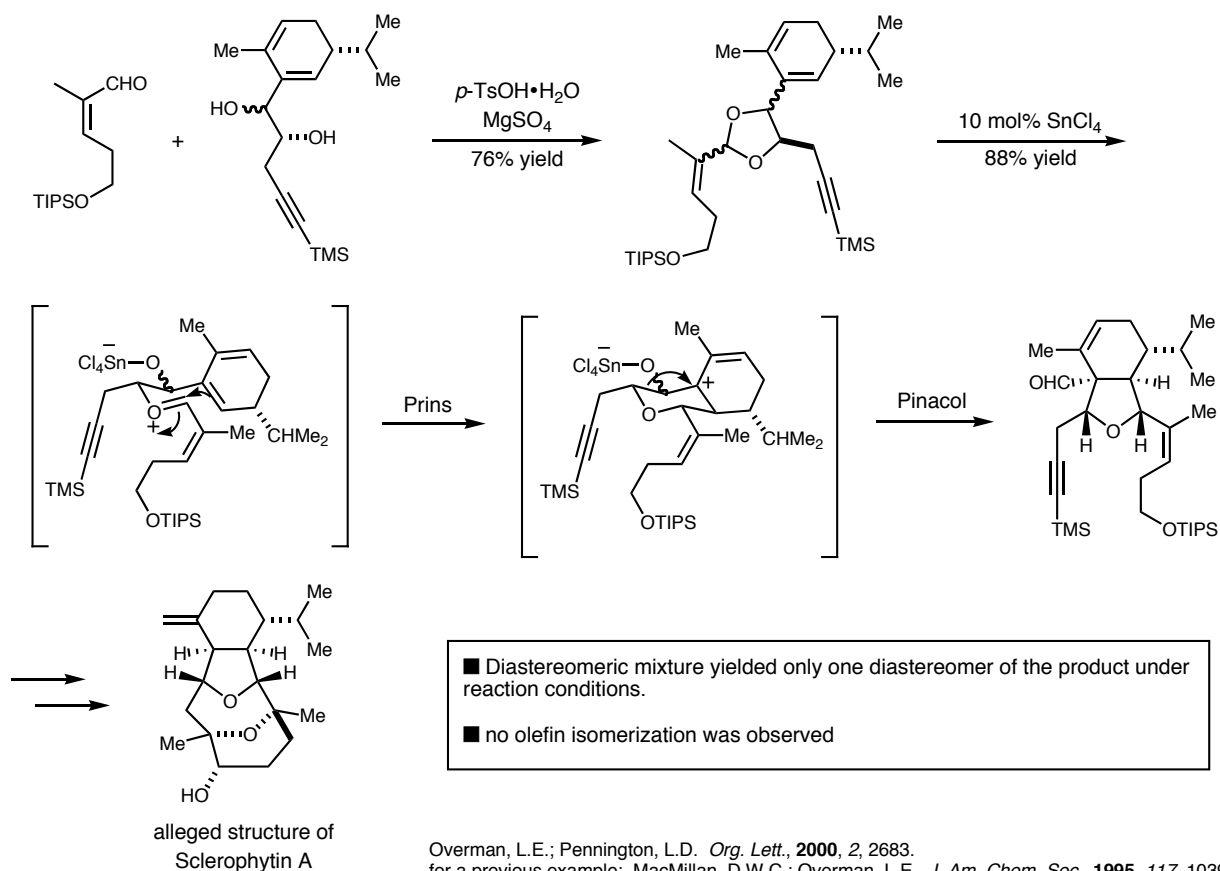
Tandem Sakurai Ene Reaction

■ High diastereoselectivity of the tandem sequence was observed when a mixture of all four olefin isomers was submitted to the reaction conditions.



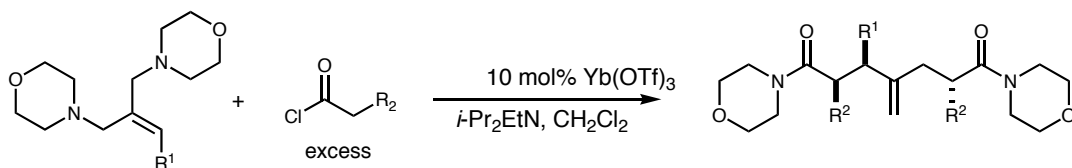
Tietze, L.F.; Rischer, M. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1221.

Prins-Pinacol Reaction



Tandem Acyl-Claisen Rearrangement

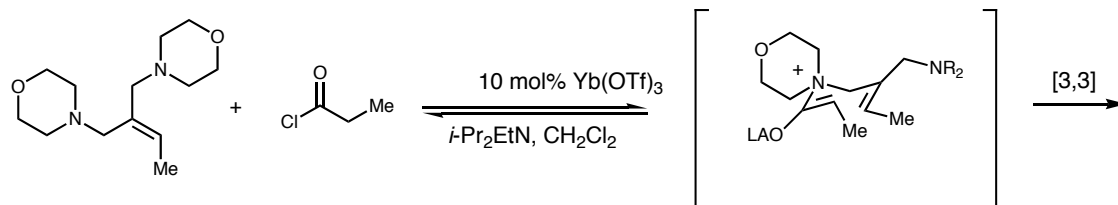
- The tandem acyl claisen tolerates a wide range of functionality with excellent yields and diastereocontrol.



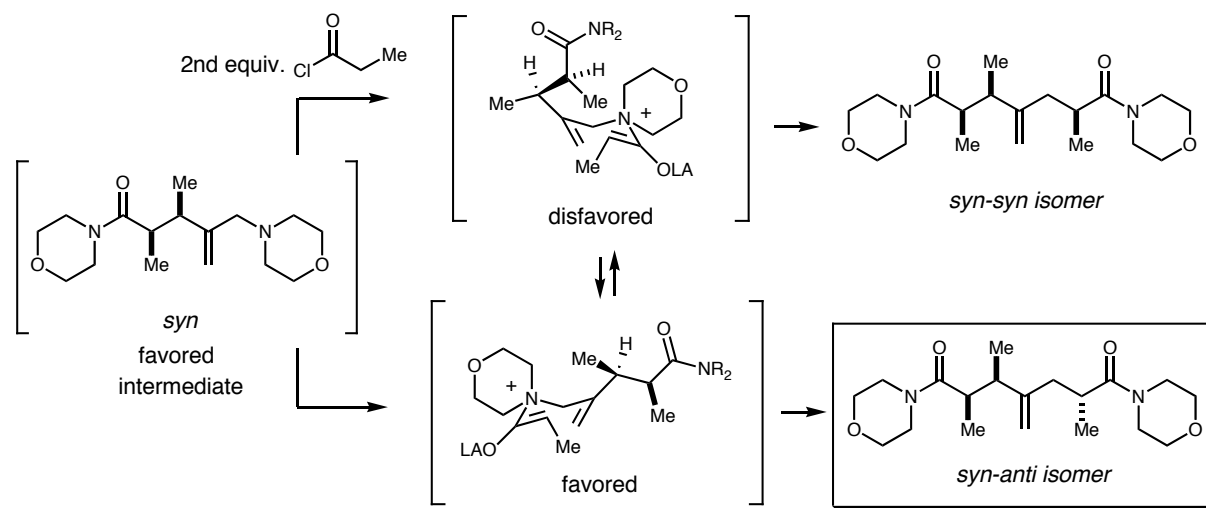
R^1	R^2	yield	d.r.
Me	Me	97%	97:3
Cl	Me	96%	>95:5
CN	Me	81%	>95:5
SPh	Me	70%	93:7
OBz	Me	86%	91:9
Me	NPhth	98%	95:5
Me	OPv	97%	97:3
Me	Bn	100%	94:6

Tandem Acyl-Claisen Rearrangement: Stereocontrol

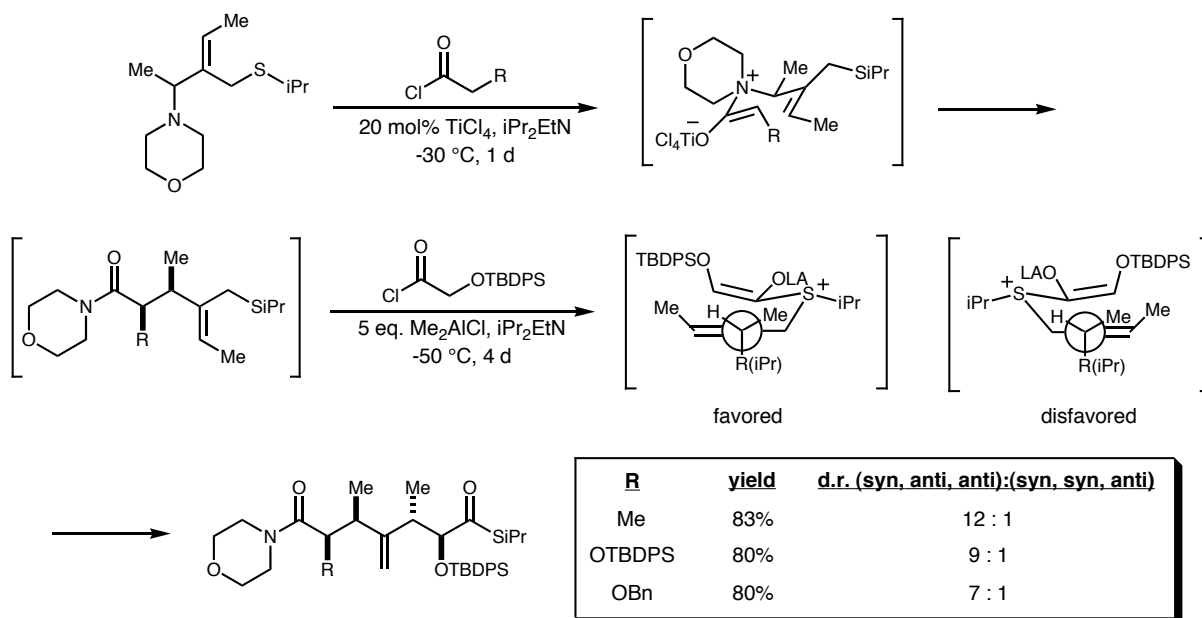
- Rearrangement via the trans morpholine is favored in the first rearrangement



- A^{1,2} strain controls the second rearrangement



Amino-Thio Tandem Acyl-Claisen



- Stereochemistry of first rearrangement is controlled by a chair transition state

- Stereochemistry of second rearrangement is dictated by "Felkin-Anh" type control

- When the OTBDPS group on the second acid chloride is substituted with a smaller substituent, the diastereoselectivity decreases

Seo, J.; MacMillan, D.W.C. *unpublished results*.

"Felkin-Anh" control in a [3,3] rearrangement: Hatakeyama, S.; Saijo, K.; Takano, S. *Tet. Lett.* **1985**, 26, 865.

The Conclusion Slide

- There are many tandem reaction sequences, grouping together almost any pair of reactions with compatible reaction conditions.
 - Tandem reactions are typically classified by the mechanism of each step.
 - Tandem reaction sequences can quickly build significant complexity into a molecule.
 - There are few enantioselective tandem reactions.
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