

Enantioselective Michael Additions in Natural Products Synthesis

MacMillan Group Meeting

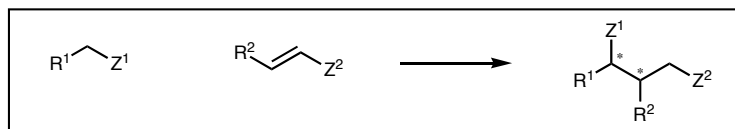
12 December 2001

Julie Y. Park

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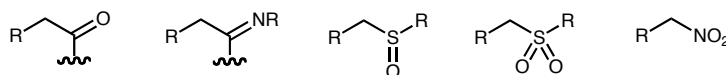
Introduction

Definition of Michael addition:

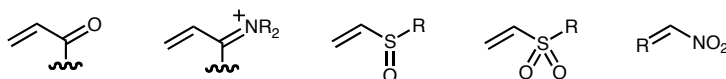


- Carbon-carbon bond-forming reaction
- Addition of a compound with an electron-withdrawing group (Z) to an activated C-C multiple bond
- Excludes metal-mediated 1,4-conjugate addition (cuprates, Grignards, lithiates, etc.)
- Excludes heteroatom conjugate addition

Representative Michael donors:



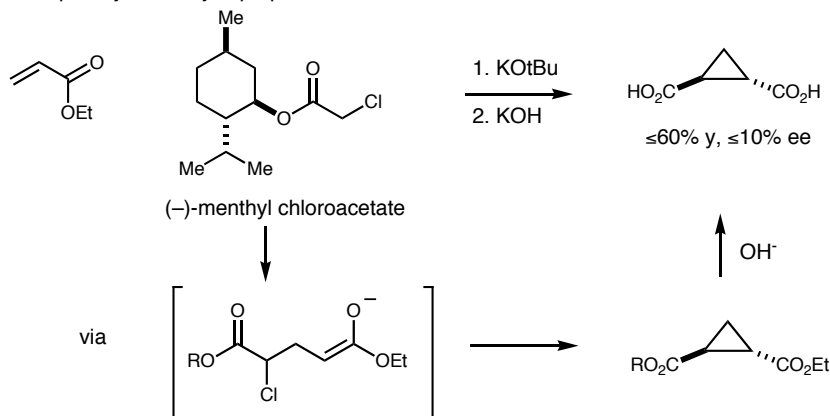
Representative Michael acceptors:



- The same functional groups serve to activate either the nucleophile or the electrophile
- A wide variety of functional handles that can be further elaborated in synthesis

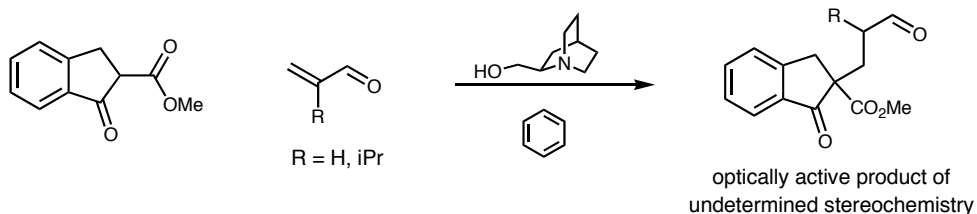
Early Examples of Enantioselective Michael Reactions

Synthesis of optically active cyclopropanes:



Inouye, Y.; Inamasu, S.; Ohno, M.; Sugita, T.; Walborsky, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 2962.

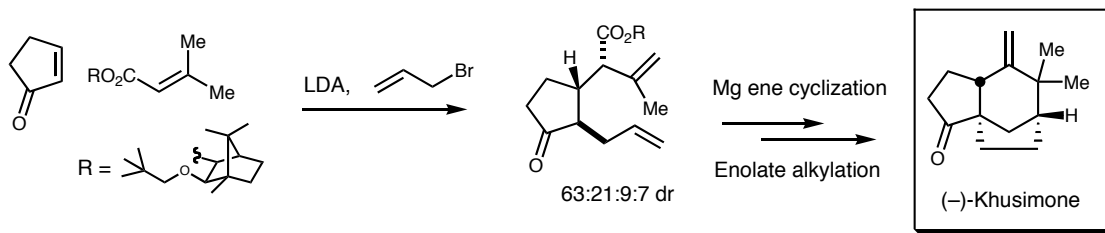
Chiral base catalyzed Michael addition forms chiral quaternary center:



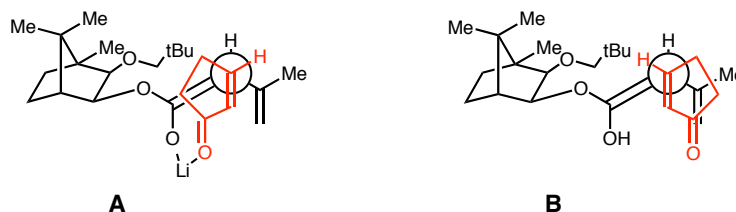
Langstrom, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.

Auxiliary-Controlled Asymmetric Induction

Oppolzer's synthesis of (-)-khusimone:



Stereochemical rationale:

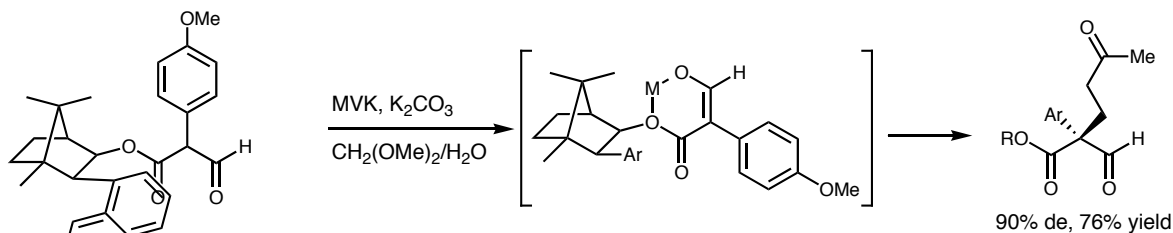


- Alpha face of enolate is shielded by the auxiliary
- Enantiofacial discrimination of the enone determined by sterics and chelating factors which favor model **A**.

Oppolzer, W.; Pitteloud, R.; Bernardinelli, G.; Baettig, K. *Tetrahedron Lett.* **1983**, 45, 4975.

Auxiliary Control: Enantioselective Robinson Annulation

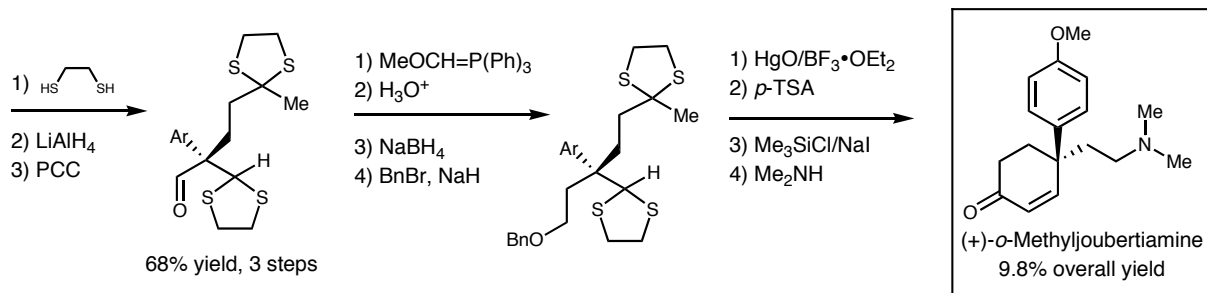
Taber's synthesis of (+)-*o*-methyljoubertiamine



Factors in choosing K₂CO₃ as base:

- weak base to quench intermediate ketone enolate
- chelating counterion

Auxiliary-aided Michael donor

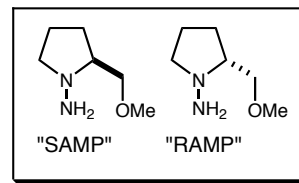


Taber, D. F.; Mack, J. F.; Rheingold, A. L.; Geib, S. J. *J. Org. Chem.* **1989**, 54, 3831.

Auxiliary Control: RAMP and SAMP Technology

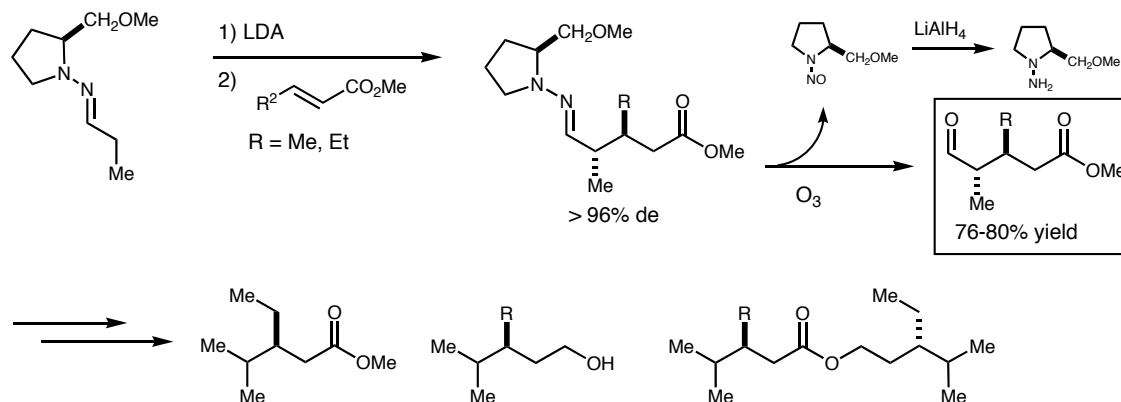
(*R*)- or (*S*)-1-amino-2-methoxymethylpyrrolidines

- Developed by Enders and coworkers
- Commercially available or easily prepared from (*S*)-prolinol or (*R*)-glutamic acid
- Form hydrazones in quantitative yield, even from sterically hindered ketones
- Anions are often more reactive than aldehyde or ketone enolates
- Auxiliary is easily cleaved and recycled



Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995.

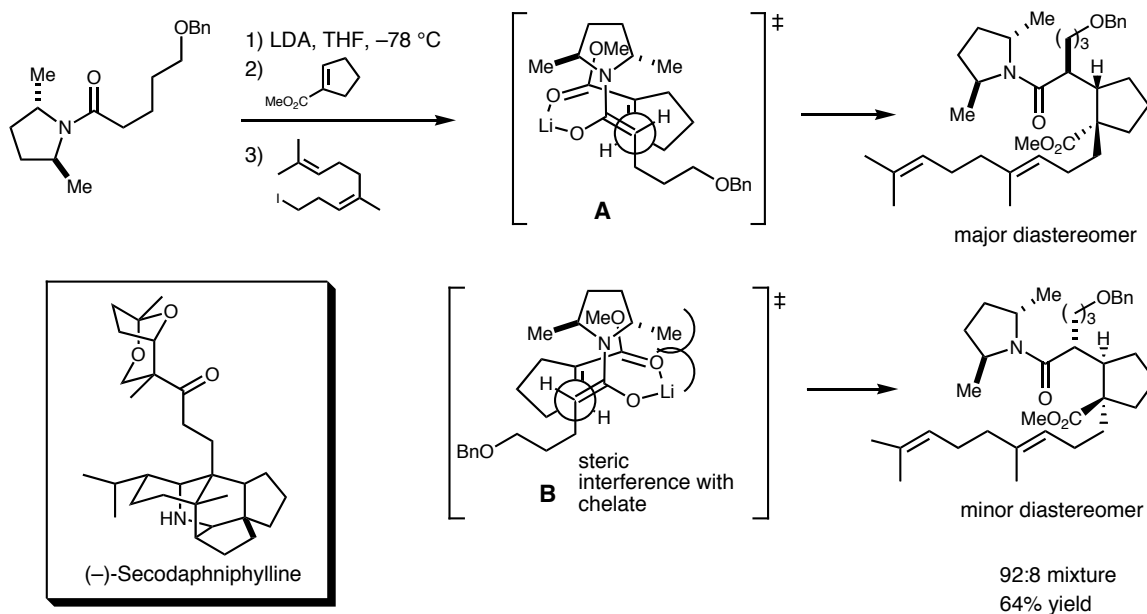
Application in the synthesis of ant pheromones:



Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235.

Auxiliary Control: Total Synthesis of (–)-Secodaphniphylline

Asymmetric induction using a C_2 -symmetric *N*-acyl pyrrolidine

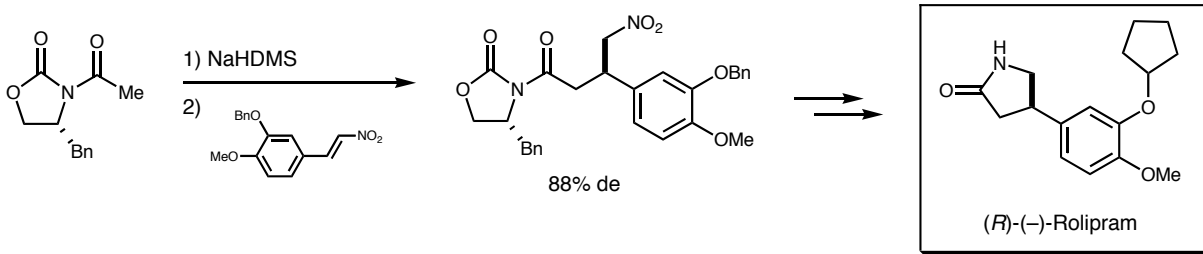


- Initial Michael addition–alkylation sets three contiguous stereocenters
- Stereochemistry of substituents on cyclopentane determine stereochemistry of methyl homosecodaphniphyllate

Heathcock, C. H.; Stafford, J. A.; *J. Org. Chem.* **1992**, *57*, 2566.
See also: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.

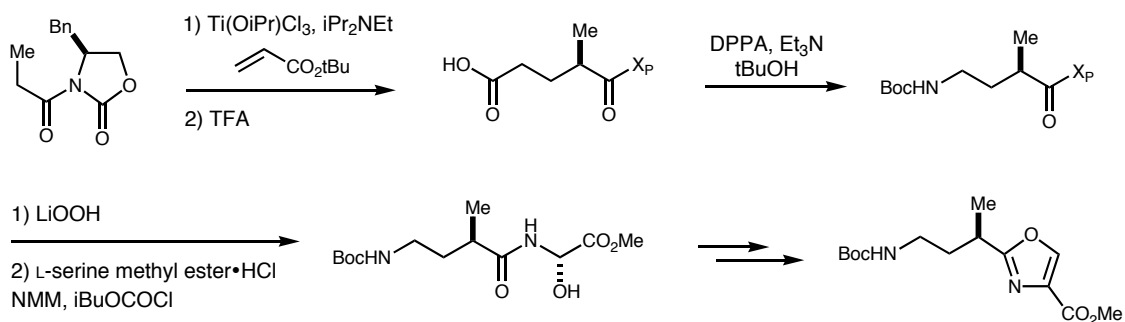
Evans Oxazolidinone

Evans acyl oxazolidone addition to nitroalkenes – α -amino stereocenter:



Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 870.

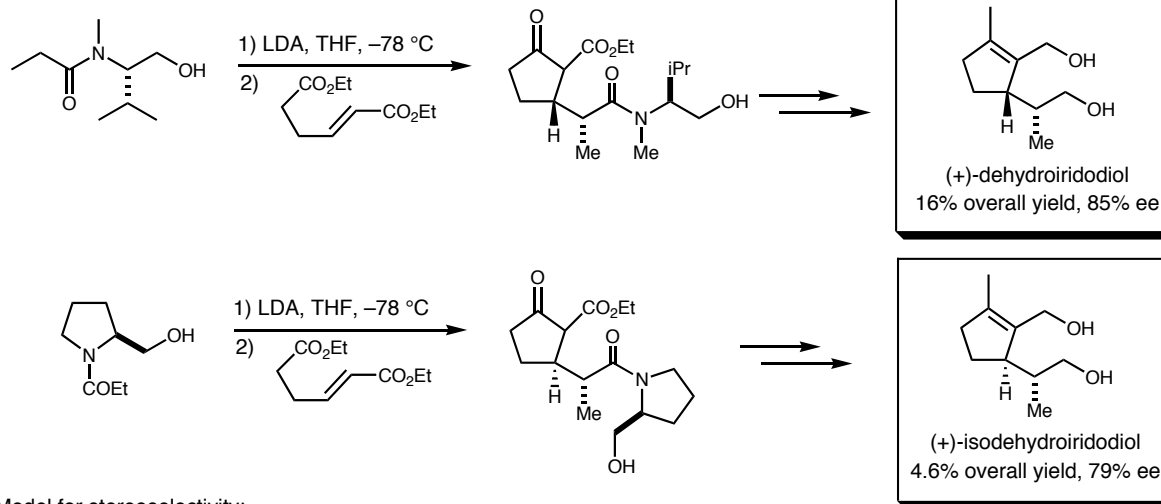
C₂₆-C₃₂ fragment of calyculin A – 1,4-functionality via Curtius rearrangement:



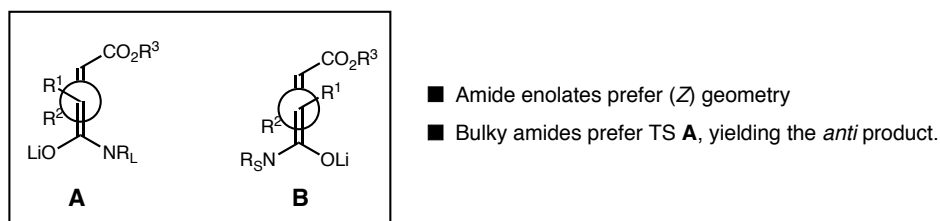
Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

Chiral Amide Enolates

Vicinal stereocontrol:



Model for stereoselectivity:

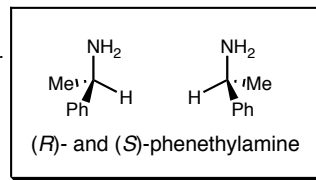


Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959.

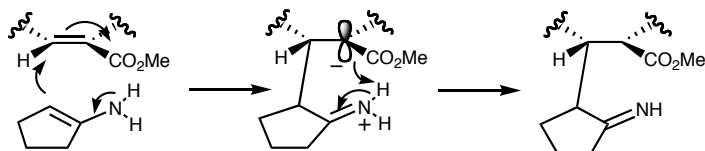
Chiral Imines and Enamines

(*R*)- or (*S*)-phenethylamine as a source of chiral induction:

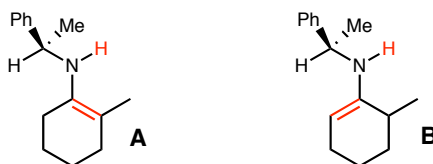
- Effects conversion of racemic stereocenters into enantiomerically enriched products.
- Construction of asymmetric quaternary carbon centers.
- Chiral amine is inexpensive (< \$1/g).
- Amine is easily recovered with no loss of optical purity.



Regio- and stereoselectivity affected by cyclic transition state – *syn* approach of substituents:



- Internal proton transfer only allowed for the more substituted enamine:

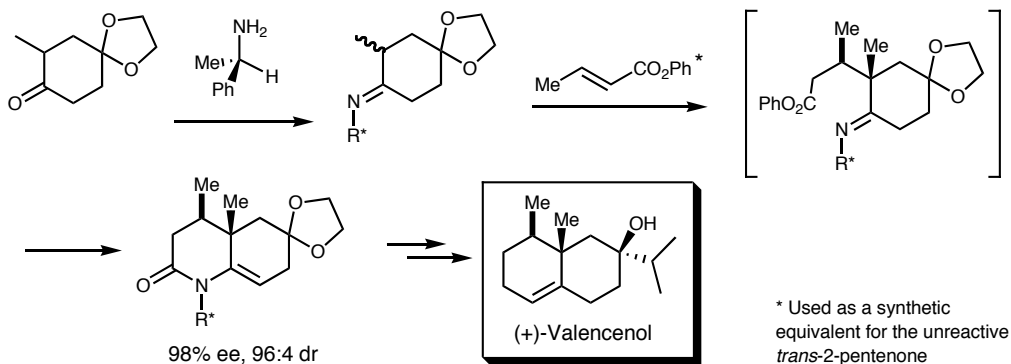


- Only enamine **A** has *syn* orientation of enamine and proton

A review on chiral imines in Michael additions: d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymm.* **1992**, *3*, 459.

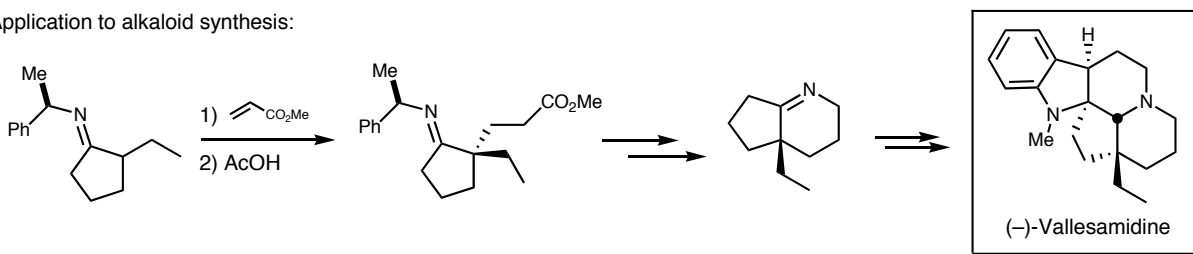
Chiral Imines and Enamines

Application in the synthesis of (+)-valencenol via Robinson annulation:



Pfau, M.; Reviel, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.
 Reviel, G.; Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymm.* **2001**, *12*, 1683.

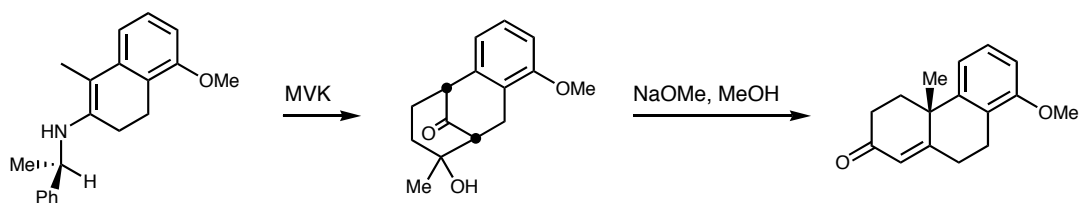
Application to alkaloid synthesis:



Costa, P. R. R.; Castro, R. N.; Farias, M. C.; Antunes, O. A. C.; Bergter, L. *Tetrahedron: Asymm.* **1993**, *4*, 1499.
 Total synthesis: a) Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798.
 b) Dickman, D. A.; Heathcock, C. H. *J. Chem. Soc.* **1989**, *111*, 1528.

Chiral Imines and Enamines

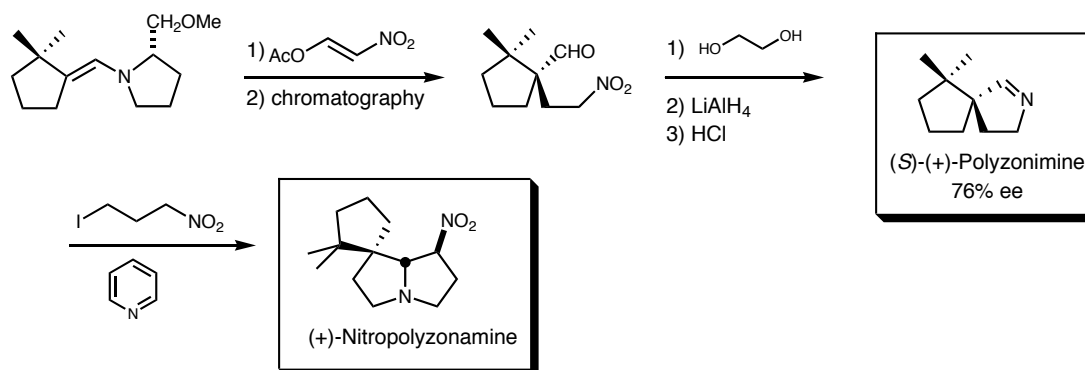
Enantioselective route to steroid precursors:



d'Angelo, J.; Reviel, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* **1988**, 35, 4427.

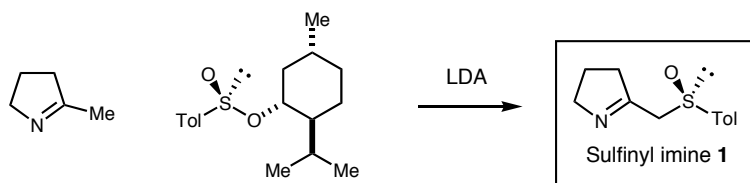
For a racemic steroid synthesis see: Cornforth, J. W.; Kauder, O.; Pike, J. E.; Robinson, R. *J. Chem. Soc.* **1955**, 3348.

Synthesis of spirocycles:



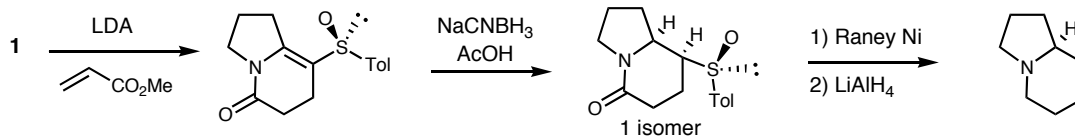
Mori, K.; Takagi, Y. *Tetrahedron Lett.* **2000**, 41, 6623.

Chiral Sulfinyl Imines

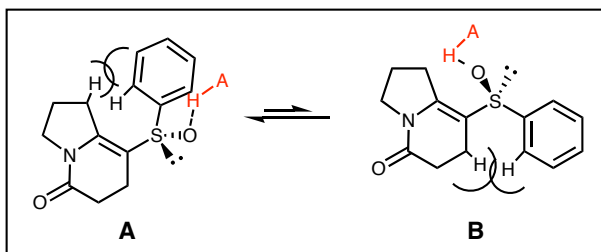


■ Displacement of the menthyl group occurs with complete inversion of configuration.

Asymmetric entry into alkaloid synthesis:



Proposed stereochemical rationale for selective reduction:

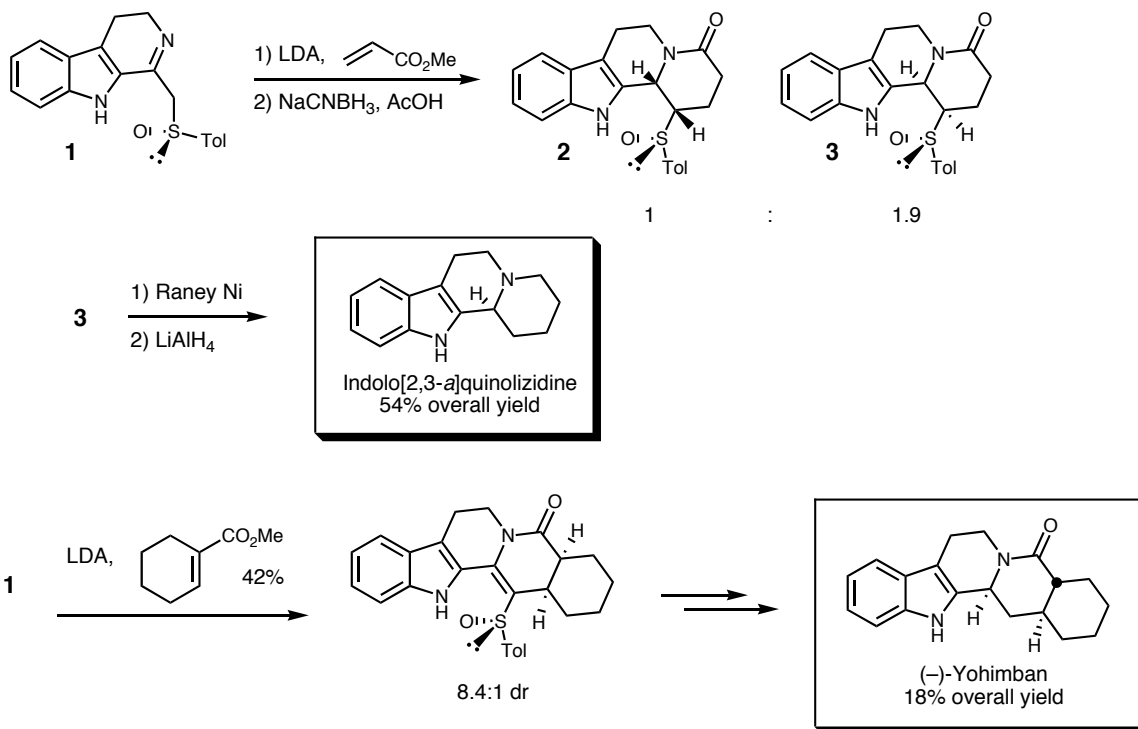


Factors governing stereoselectivity:

- Hydride delivery occurs from the less hindered face, resulting in overall *syn* selectivity.
- Delivery of a proton from the coordinated acid creates a stereocenter adjacent to the bulky sulfinyl group.
- Steric interference between aryl protons and vicinal protons favor conformation **A**.

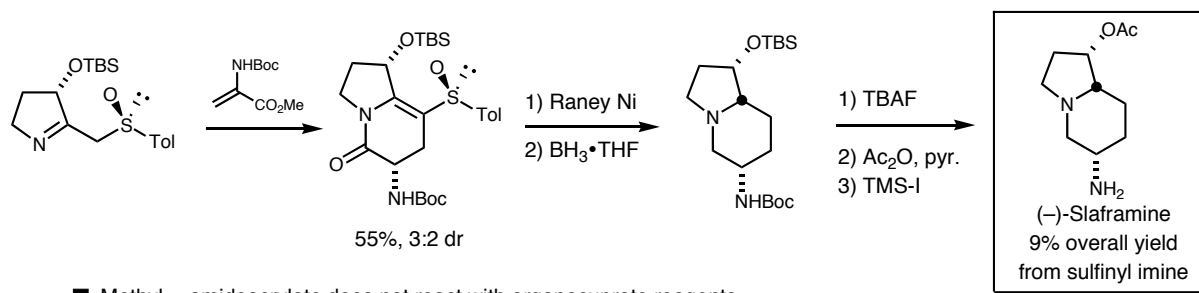
Hua, D. H.; Bharathi, S. N.; Panagadan, A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, 56, 6998.

Chiral Sulfinyl Imines: Alkaloid Synthesis



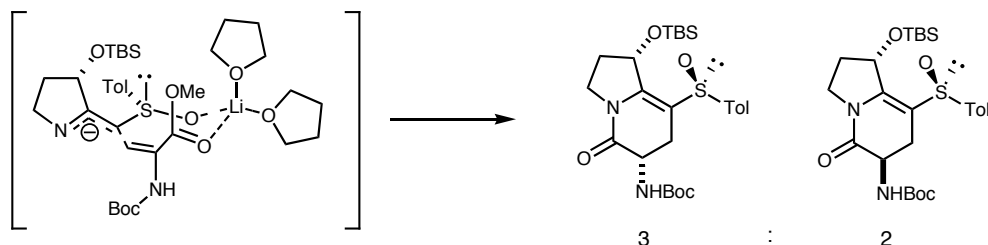
Hua, D. H.; Bharathi, S. N.; Panangadan, A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998.

Chiral Sulfinyl Imines: Functionalized Electrophiles



- Methyl α -amidoacrylate does not react with organocuprate reagents.
- Poor selectivities limit the utility of this methodology.

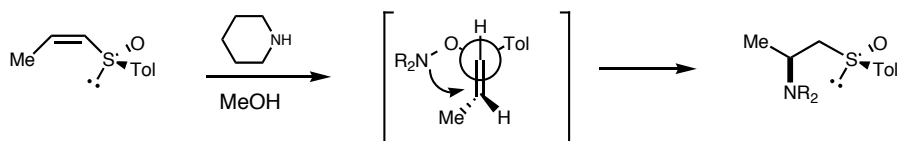
Stereochemical rationale:



Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144.

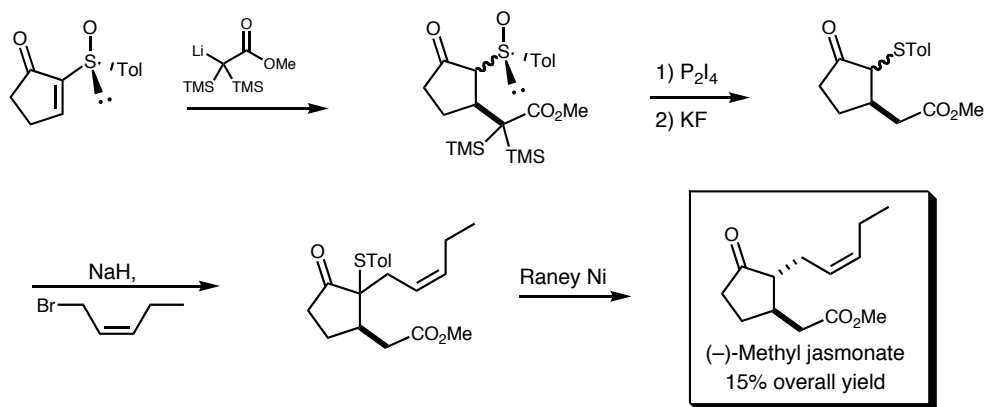
Chiral Vinyl Sulfoxides

First reported in literature in 1971:



Abbott, D. J.; Colonna, S.; Stirling, C. J. M. *Chem. Comm.* **1971**, 471.

Application in total synthesis:

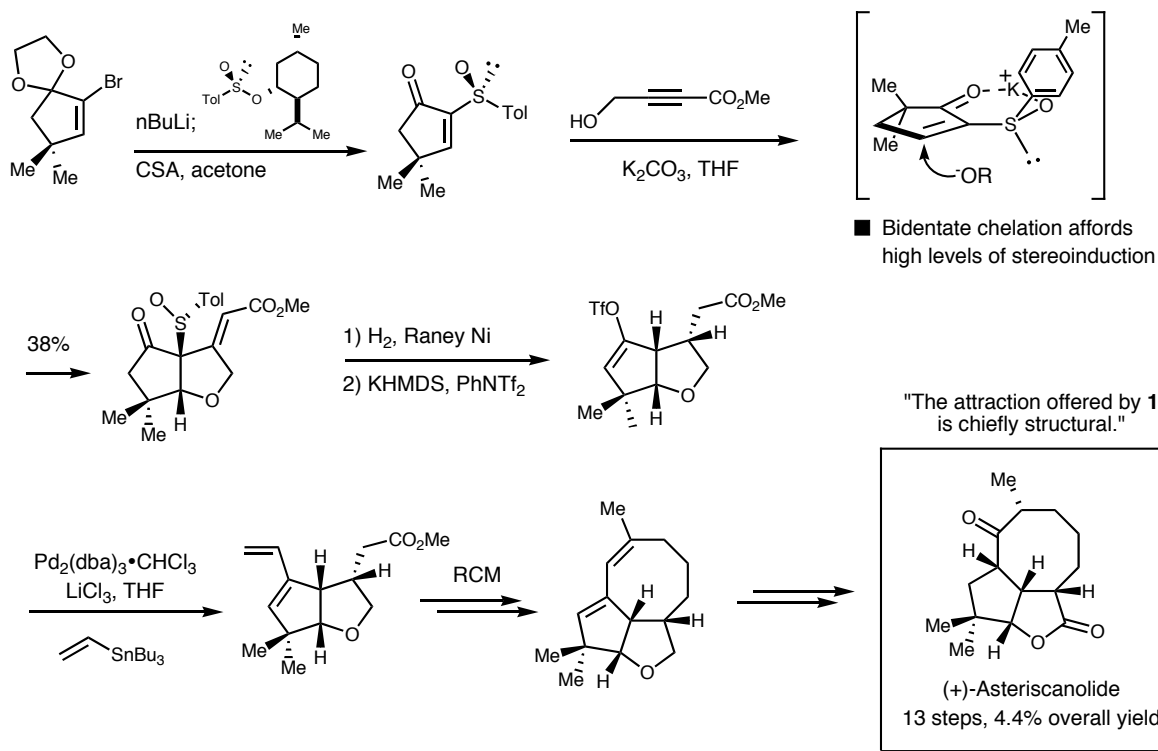


"of extremely high enantiomeric purity"

Posner, G. H.; Asirvatham, E. *J. Org. Chem.* **1985**, *50*, 2589.

Chiral Vinyl Sulfoxides: Tandem Hetero-Michael–Michael reaction

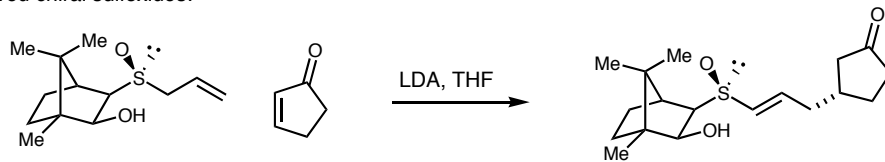
A new twist on Posner:



Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.

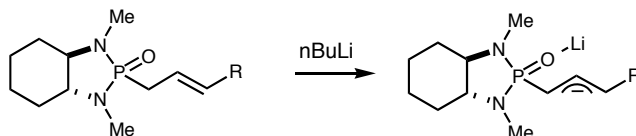
Chiral Allylic Sulfoxides: Vinylogous Michael Additions

Camphor-derived chiral sulfoxides:



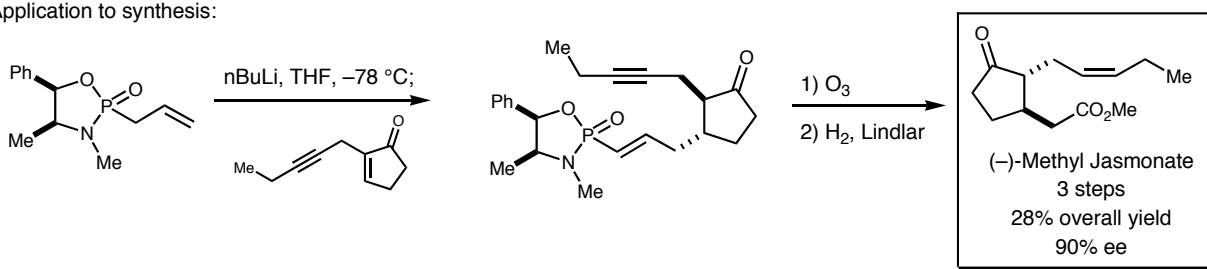
Binns, M. R.; Goodridge, R. J.; Haynes, R. K.; Ridley, D. D. *Tetrahedron Lett.* **1985**, 51, 6381.

Hanessian's chiral phosphonamides:



■ Phosphonamide anion adds to a variety of α,β -unsaturated enones, lactams, lactones and esters

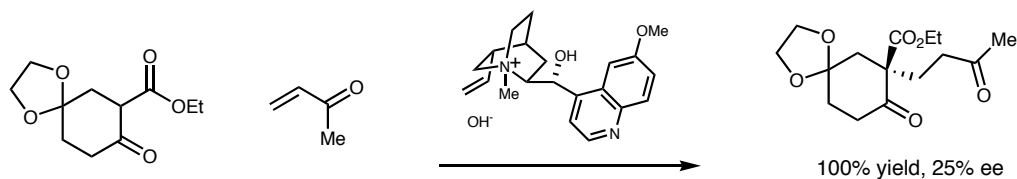
Application to synthesis:



Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, 65, 5623.
Hailes, H. D.; Isaac, B.; Javaid, M. H. *Tetrahedron Lett.* **2001**, 42, 7325.

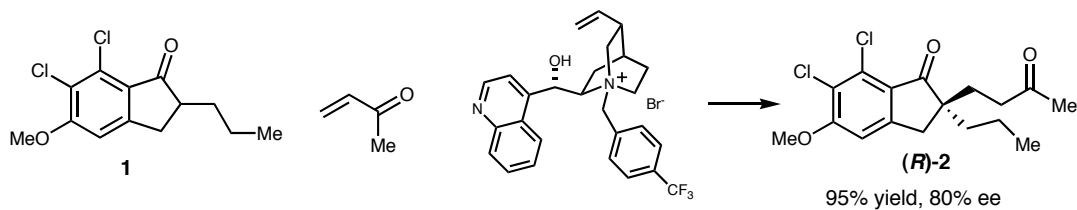
Phase-Transfer Catalysis: Chiral Quaternary Ammonium Salt

Early example of cinchona alkaloid catalyzed Michael addition:

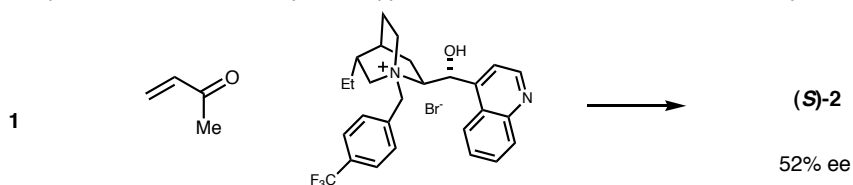


Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, 44, 2238.

Michael addition of an unactivated ketone:

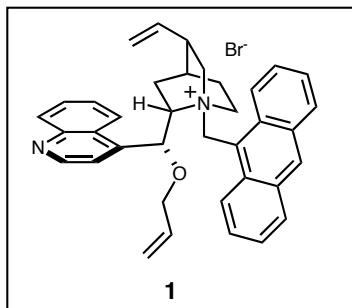


■ Using an epimeric cinchonidine catalyst, the opposite enantiomer can be obtained, but only with modest selectivity:



Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, 51, 4710.

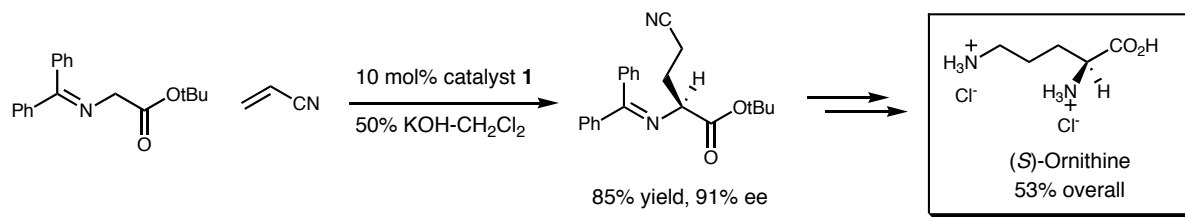
Phase-Transfer Catalysis: The Corey Approach



- Used in enolate alkylations, epoxidations, conjugate additions
- Shielding of three quadrants formed by tetrahedral ammonium ion
- Close ion pairing of the substrate in remaining quadrant provides selectivity
- Limited by strict substrate specificity

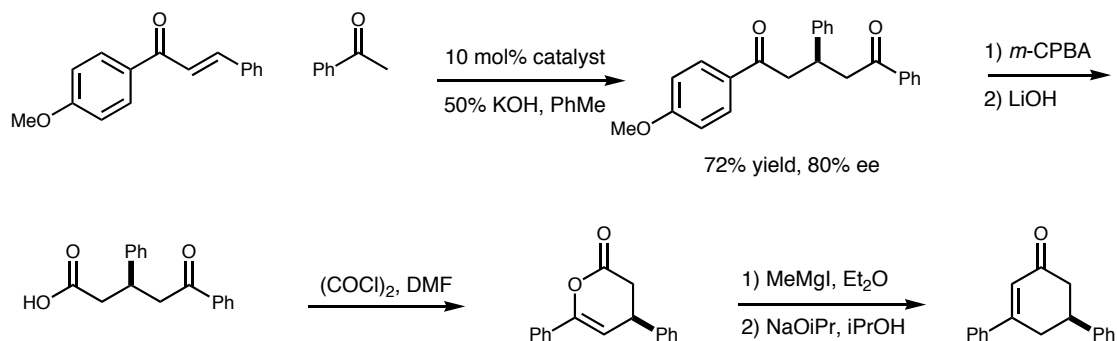
Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
 Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
 Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

Asymmetric Michael addition of Schiff base:

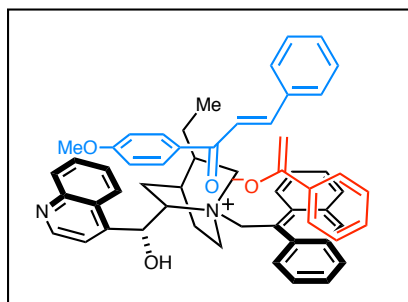


Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 1097.

Phase-Transfer Catalysis: Robinson Annulation



Stereochemical rationale:

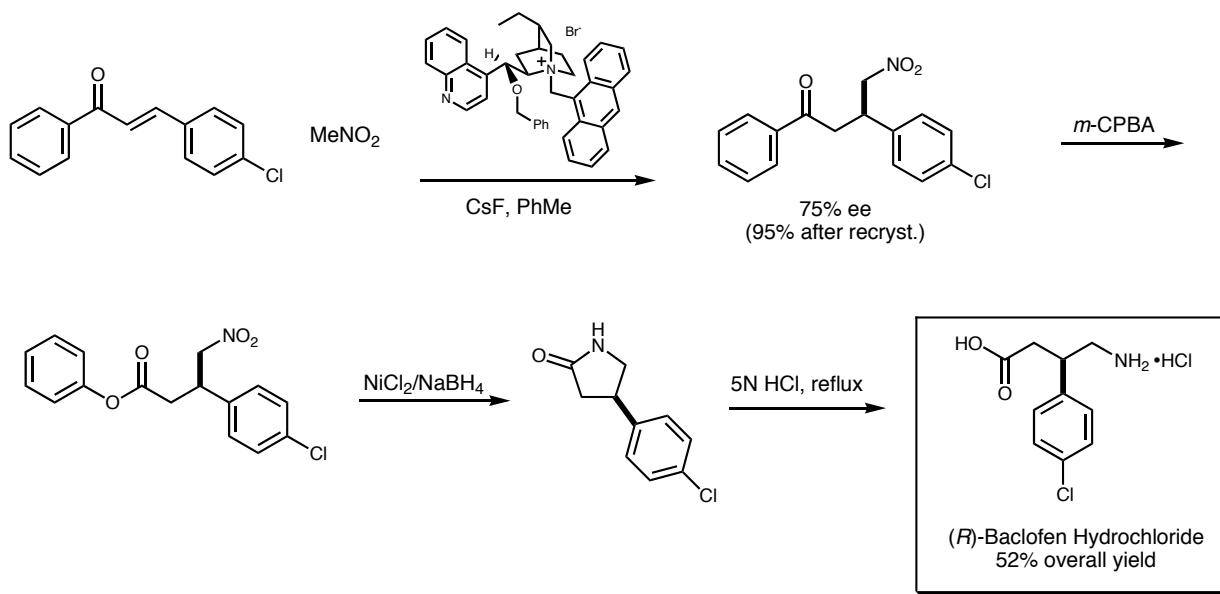


- Enolate is contact ion paired with N⁺
- α,β -ene is wedged between ethyl and quinoline substituents
- Carbonyl poised for ion pairing in enolate transition state

Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 1097.

Phase Transfer Catalysis

Synthesis of a chiral γ -amino acid:



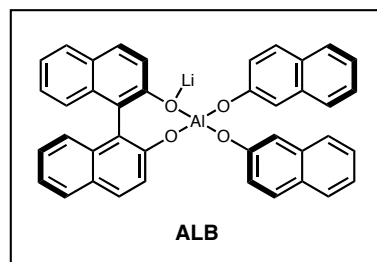
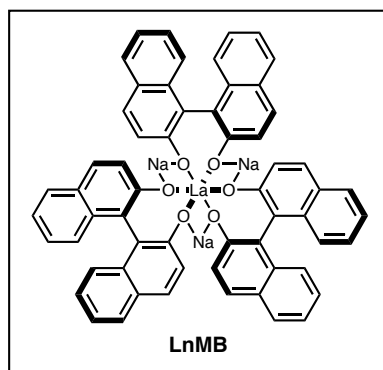
- Follows the same model for close ion pairing as the previous two examples

Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, 2, 4257.

Heterobimetallic Catalysts

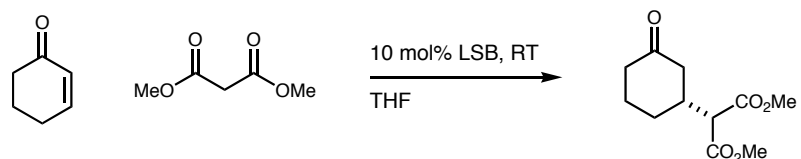
- Developed by Shibasaki and coworkers
- Catalysts function as both Brønsted base and Lewis acid and can catalyze a variety of reactions
- Complex between alkali metal (Na, Li) and either rare-earth (La, Eu, Pr, Ld) or Group 13 (Al, Ga)

Structures of complexes:



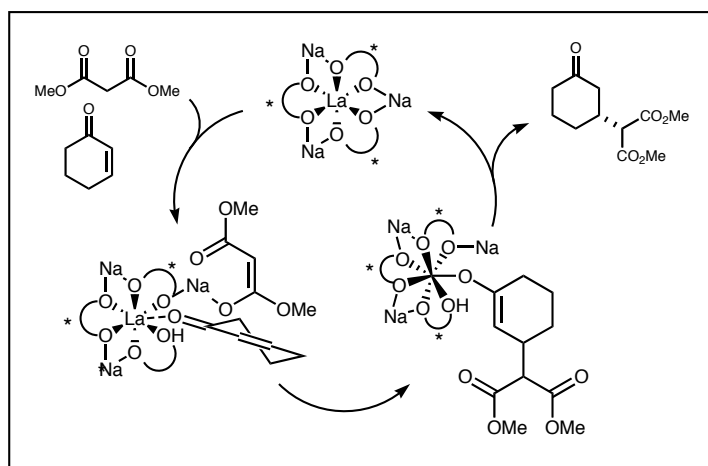
Acronyms: LnMB Ln = rare-earth metal M = alkali metal B = tris(binaphthoxide) ALB A = Al, L = Li

Heterobimetallic Catalysts: Asymmetric Michael Reaction



98% yield, 83% ee

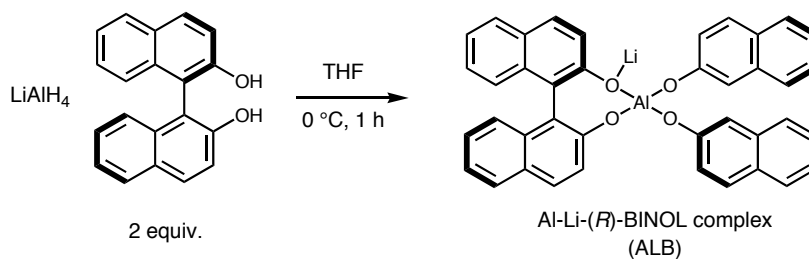
- LSB (Lithium sodium tris(binaphthoxide)) is the best complex for these transformations
- Excellent yields and good ee's (74-91%) for a range of substrates
- Proposed catalytic cycle:



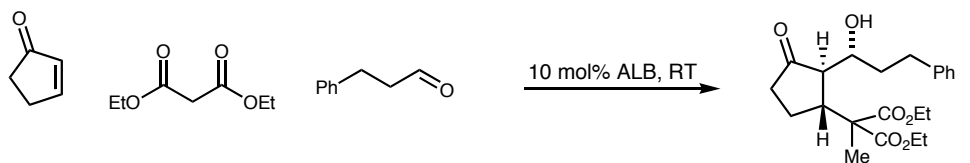
Shibasaki, M.; Sasai, H.; Arai, Y. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236.

ALB catalysts in Michael Additions

- Prepared from BINOL and LiAlH₄:



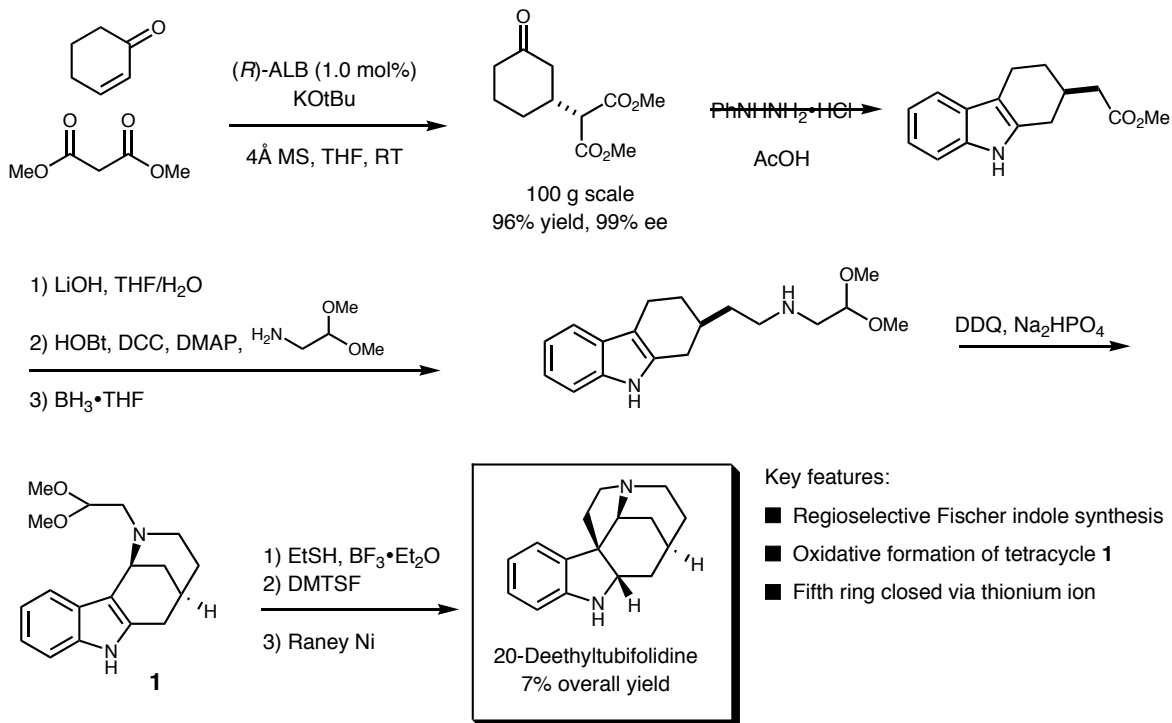
- Electropositive lithium should form lithium enolate preferentially over aluminum enolate
- NMR studies with ALB and 3 equiv. of cyclohexenone show that enones coordinate to aluminum center
- ALB acts as a *multifunctional catalyst*
- Reaction of lithium enolate with enone should generate aluminum enolate – potential for three-component coupling



64% yield, 91% ee
single diastereomer

Shibasaki, M.; Sasai, H.; Arai, Y. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236.

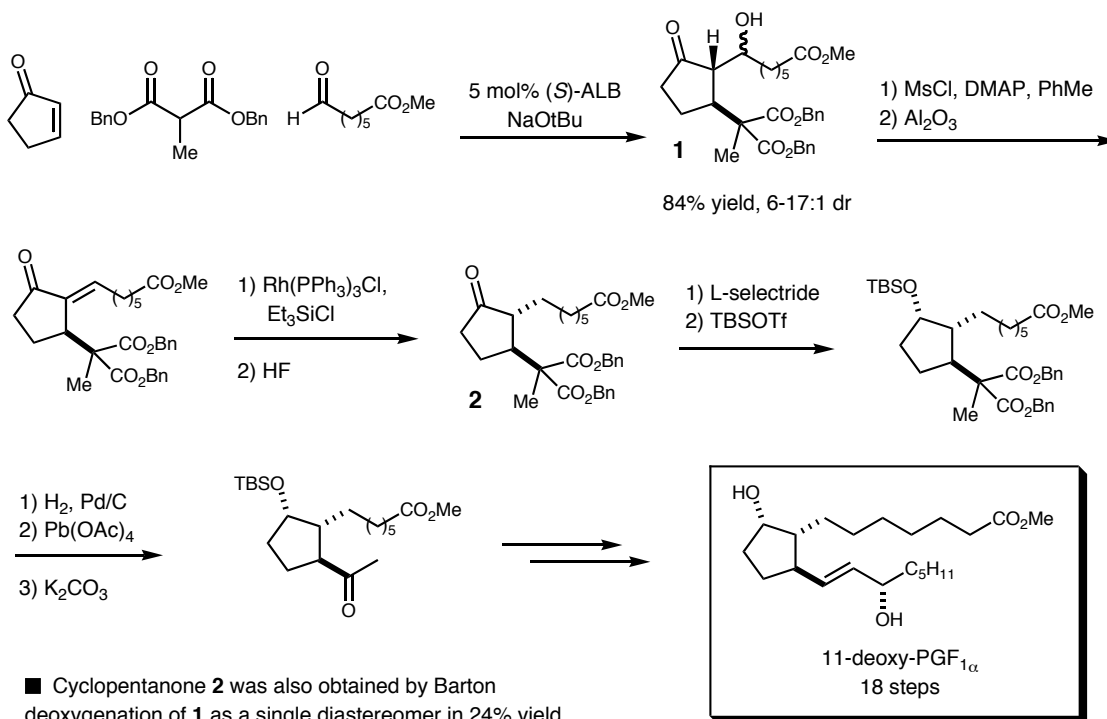
ALB: Application to Total Synthesis



Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547.
 Previous synthesis: Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.
 DDQ oxidation: Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
 Dimethyl(methylthio)sulfonium fluoroborate: Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.

ALB: Application to Total Synthesis

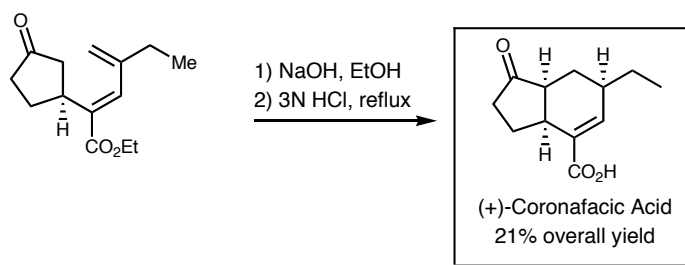
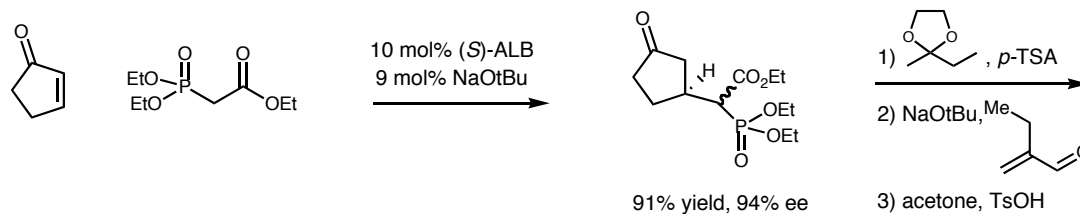
Three-component coupling as key step in synthesis of 11-deoxy-PGF_{1α}



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

ALB: Addition of Horner–Wadsworth–Emmons Reagents

- First catalytic asymmetric 1,4-addition of HWE reagent to enones



Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441.

For racemic and enantioselective total syntheses of coronafacic acid see: Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron*, **1997**, *53*, 9509.

Summary

- The Michael reaction is one of the most powerful carbon-carbon bond-forming reactions in organic synthesis
- Both the Michael donor and Michael acceptor have activating groups that can serve as functional handles
- Asymmetric induction can originate from either the donor or acceptor
- Enolate intermediate opens pathways for tandem Michael–electrophile trapping reactions
- Facile construction of vicinal and quaternary stereocenters, including spirocyclic and polycyclic structures
- Few examples of catalytic asymmetric reactions in total synthesis
- *A great deal of potential remains for the asymmetric Michael reaction to be used as a powerful tool in synthesis*