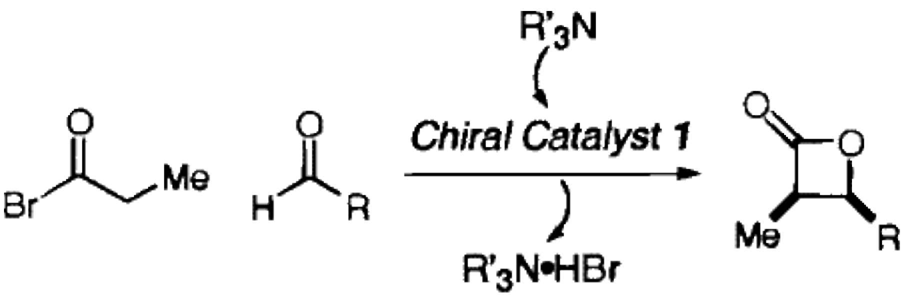
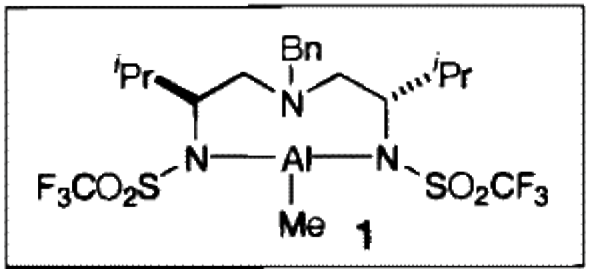
Catalytic Asymmetric Acyl Halide-Aldehyde Cyclocondensation Reactions of Substituted Ketenes

Scott G. Nelson, Cheng Zhu, and Xiaoqiang Shen
J. Am. Chem Soc. **2004**, *126*, 14-15.



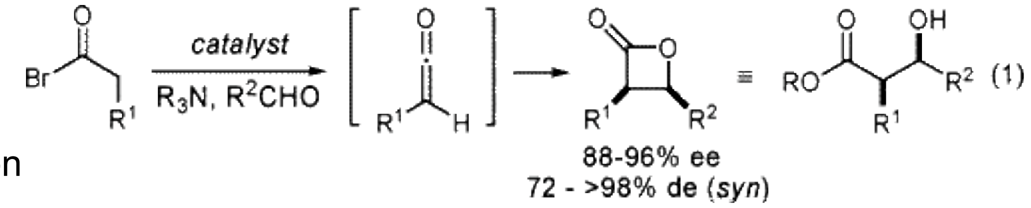
(1)



Michael C. Myers, Literature Presentation, January 27, 2004

The Cyclocondensation Reaction

- *Kinetically Complex Processes: 4 Competing Reaction Pathways*
    1. Cyclocondensation
    2. Ketene Dimerization
    3. Ketene Trimerization
    4. Aldehyde Homoaldol Addition

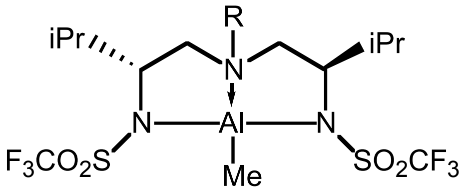


- *Woodward-Hofmann Rules Govern **Syn** Selectivity: [2+2] Cyclocondensation Reaction*
- *Aluminum$^{(III)}$ Lewis Acid Catalysts: Catalyze Cyclocondensation / Limit Other Pathways*

1st Generation

$Al(SbF_6)_3$

2nd Generation (Chiral)



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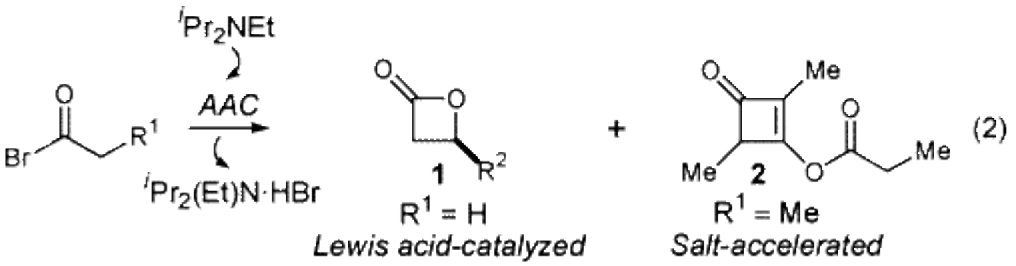
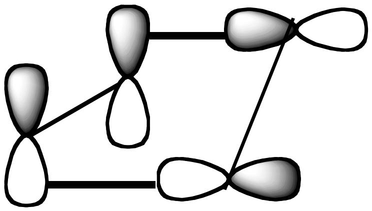


- *Substituting CH_2Cl_2 for Benzotrifluoride (BTF): Ammonium Bromide Salts Insoluble in BTF*

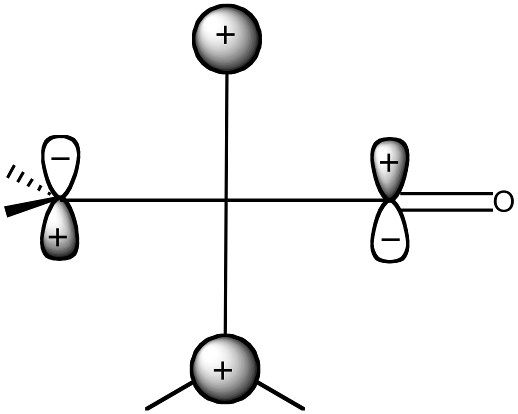
Woodward-Hofmann Implications

- *"The orbital requirements for concerted thermal ketene-aldehyde cycloaddition would ensure that substituted ketenes would afford the contrasteric cis-substituted 4-oxetanones, thereby providing the equivalent of a* ***syn****-selective propionate aldol."*
- *Few Systems Meet the Geometrical Limits: Most [2π + 2π] Additions Involve Ketenes*

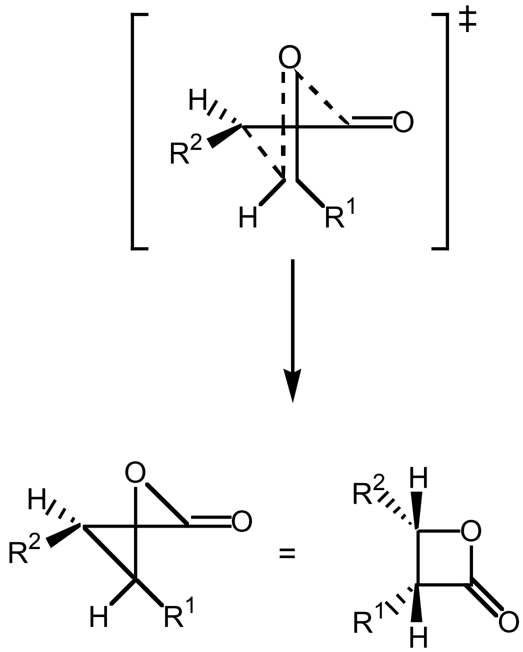


Supra/Antara
Mobius System
4 Electrons
Aromatic
Allowed

or



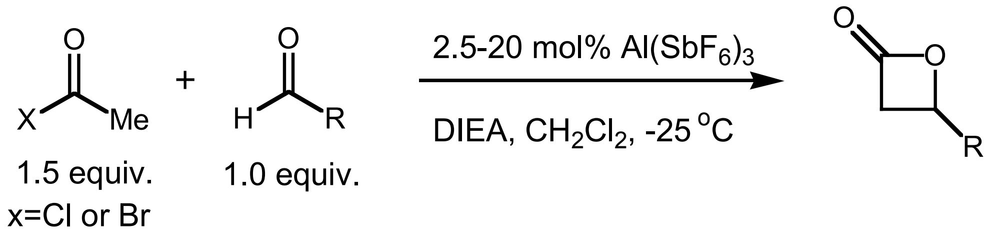
HOMO-*Aldehyde*
LUMO-*Ketene*



Woodward, R. B.; Hoffmann, R. *The conservation of Orbital Symmetry*; VCH: Weinheim, 1970.
Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883-1886.

Generation I and II $Al^{(III)}$ Catalysts

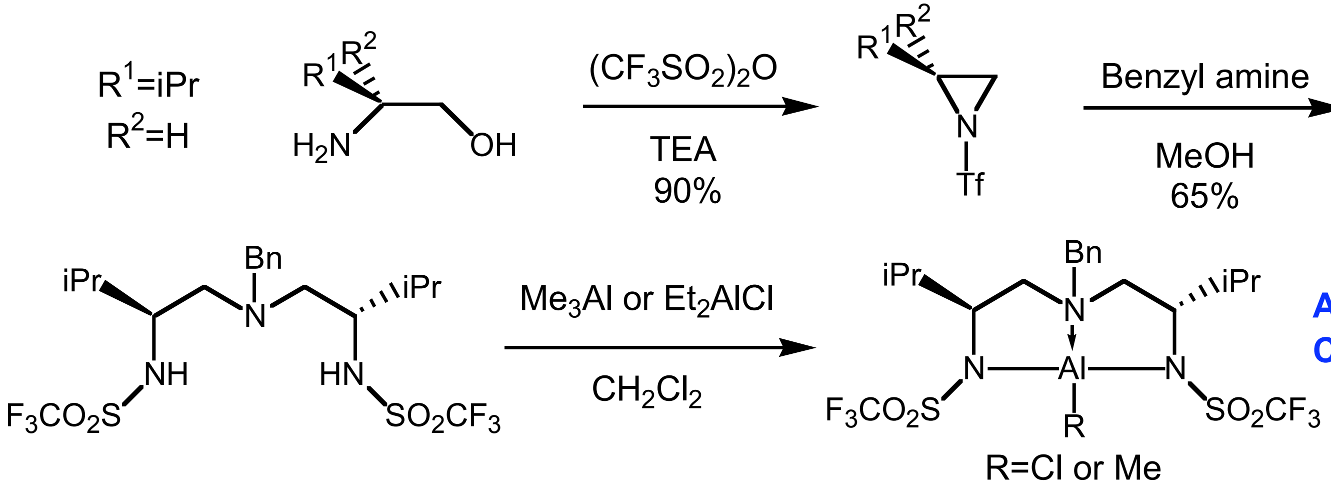
- *Empirically Found that $Al(SbF_6)_3$ Catalyzed the AAC Reactions*



$Al(SbF_6)_3$ Represents the **$AlCl_3$:$AgSbF_6$** Stoichiometry *(1:3)*
Used to Generate the Catalyst

Nelson, S. G.; Wan, Z.; Peelen, T. J.; Spencer, K. L. *Tet. Lett.* **1999**, *40*, 6535-6539.

……



$Al^{(III)}$ Triamine Chiral Catalyst

Cernerud, M.; Skrinning, A.; Bergere, I.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 3437-3441.
Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742-9743.

Aluminum$^{(III)}$ Catalyst Role

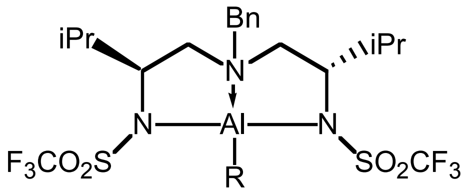
- *4-Coordinate Complex Adopting a Trigonal Monopyramidal (tmp) Geometry*
- *Balance Between Lewis Acidity of the Metal and Lewis Basicity of the Amine*

Distorted 4-Coordinate Geometry

↓

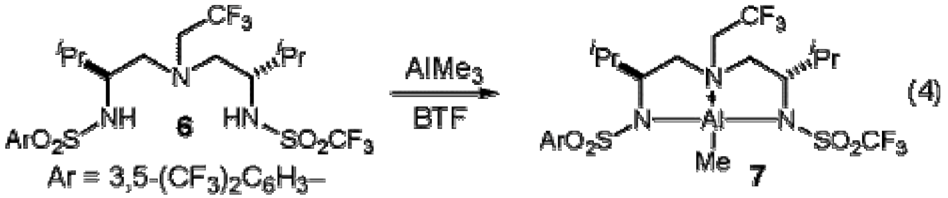
Access Pentacoordiante Species

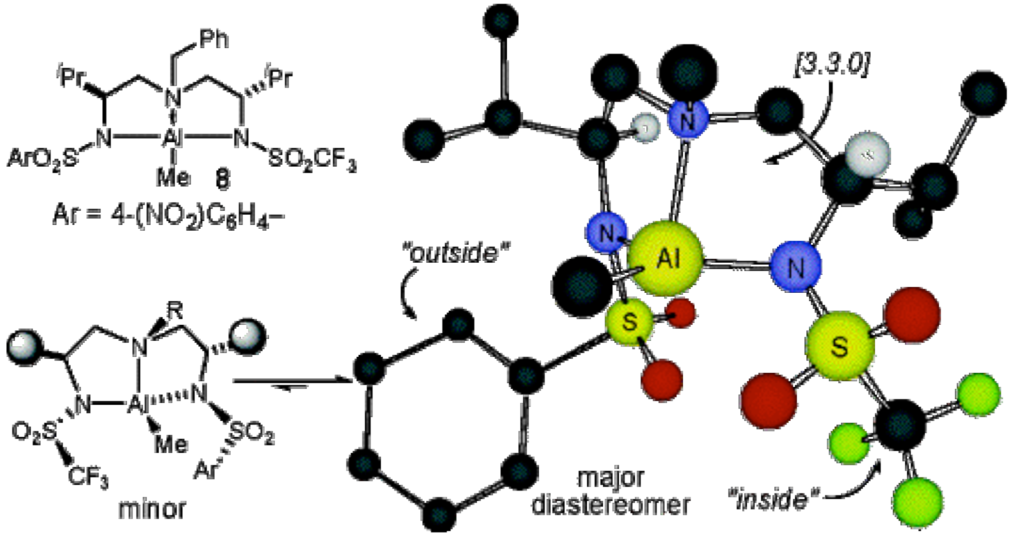
(KEY To Reactivity)



R=Cl or Me

C_2-Symmetric
Al$^{(III)}$ Triamine
Chiral Catalyst



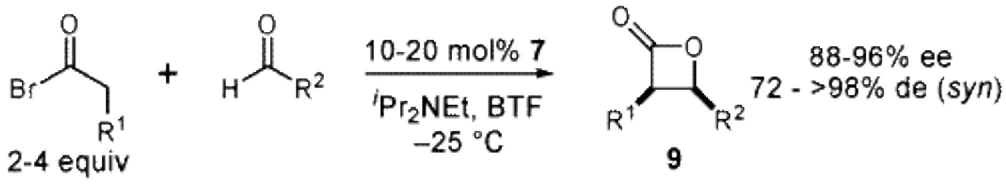


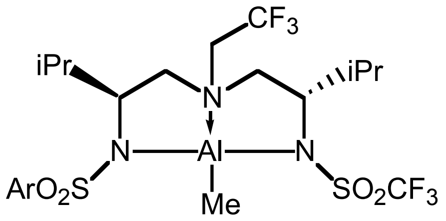
Best Performing Chiral Catalyst

Nelson, S. G.; Kim, B-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318-9319.
Scott G. Nelson, Cheng Zhu, and Xiaoqiang Shen *J. Am. Chem Soc.* **2004**, *126*, 14-15.

AAC Reaction Scope

entry	R^1	R^2	%ee **9**[a]	syn:anti [b,c]	% yield **9**[d]
a	Me	CH_2CH_2Ph	90	95:5	71
b	Me	$(CH_2)_8CHCH_2$	88	94:6	77
c	Me	CH_2CH_2OBn	91	86:14	75
d	Me	C_6H_5	96	>98:2	80
e	Me	$C\equiv CSiMe_3$	95	98:2	76[e]
f	Et	CH_2CH_2Ph	91	95:5	81
g	Et	CH_2CH_2OBn	91	88:12	83
h	Et	CH_2OBn	93	89:11	78
i	Et	C_6H_5	94	>98:2	83
j	^{n}Pr	CH_2CH_2OBn	91	91:9	88
k	^{n}Pr	C_6H_5	96	>98:2	85
l	^{i}Pr	$C\equiv CSiMe_3$	94	>98:2	71[e]
m	^{i}Pr	C_6H_5	96	>98:2	84





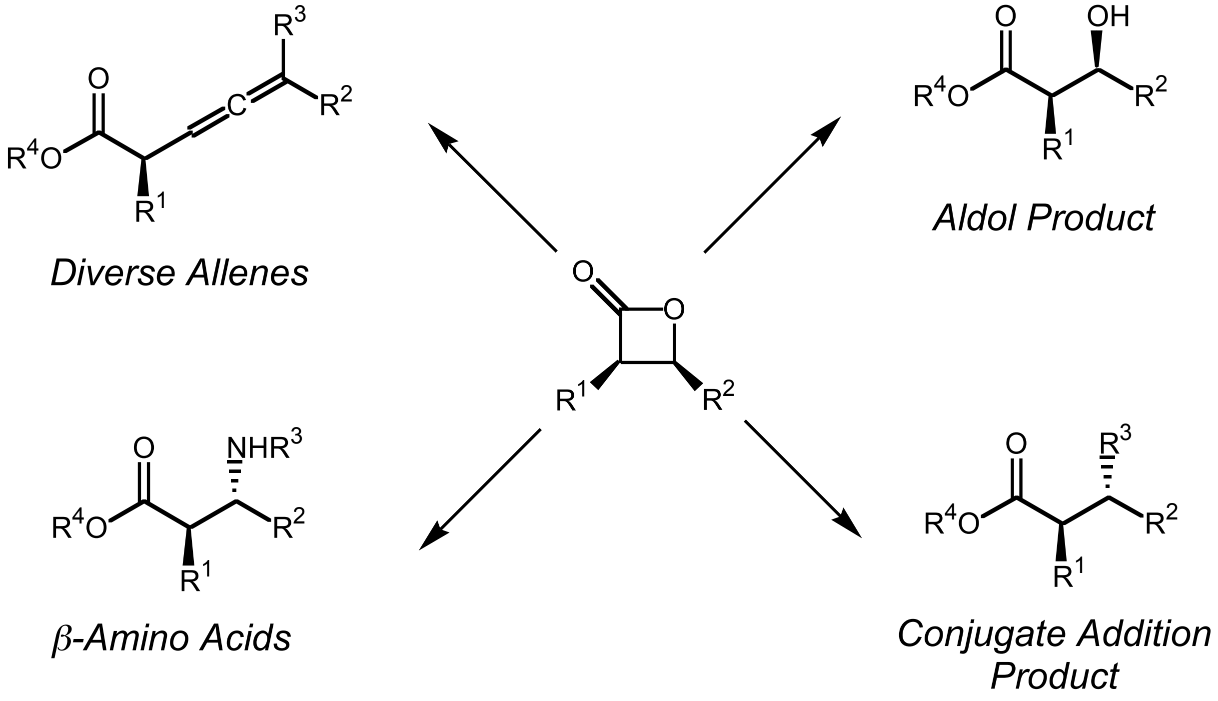
Second Generation
$Al^{(III)}$ Triamine
Unsymmetrical
Chiral Catalyst

[a] Enantiomeric ratios determined by chiral GLC or HPLC. [b] Diastereomeric ratios determined by ^1H NMR of crude product mixtures except for entries b and e (GLC). [c] Relative and absolute stereochemical assignments based on prior literature precedent; see ref 2d. [d] Yields for diastereomerically pure materials except entries g and j (diastereomers were inseparable). [e] Yield for the amide derived from amine -mediated ring opening of the crude ?-lactone.

Scott G. Nelson, Cheng Zhu, and Xiaoqiang Shen *J. Am. Chem Soc.* **2004**, *126*, 14-15.

Building Blocks Derived from β-Lactones

- *β-Lactones are Direct Progenitors of Numerous Useful Building Blocks*



Diverse Allenes

Aldol Product

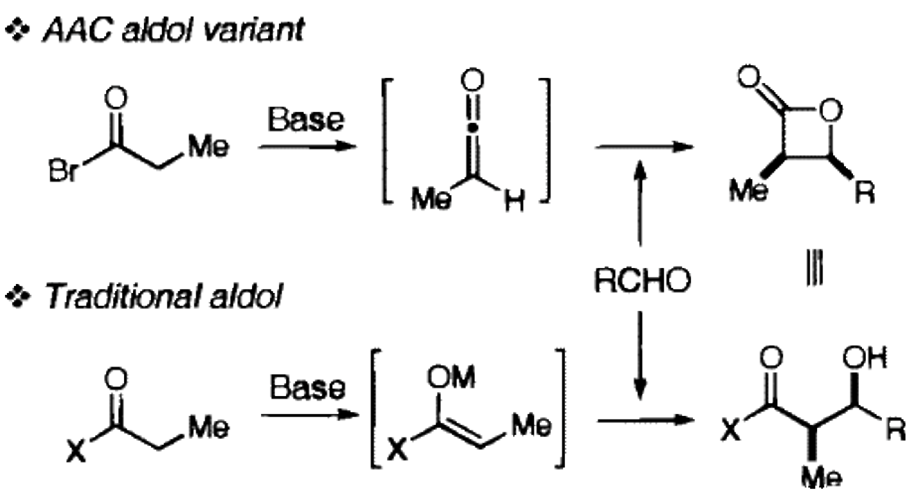
β-Amino Acids

Conjugate Addition Product

See References Within Presentation

Aldol Bond Construction Strategies

- *Typical Aldol Additions Successfully Relay Enolate Geometry to the Relative Stereochemistry at the Two Stereogenic Centers*
- *Obtain* ***Syn*** *Aldol Adducts*

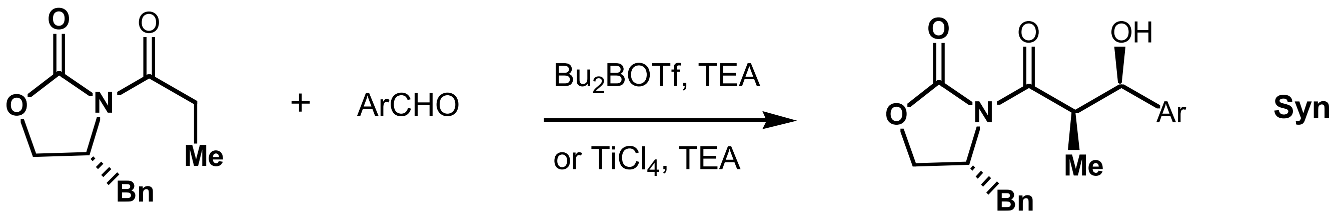


Stereochemistry

Relative
Woodward-Hofmann
Absolute
Chiral Lewis Acid

Relative
Enolate Geometry
Absolute
Chiral Oxazolidinone

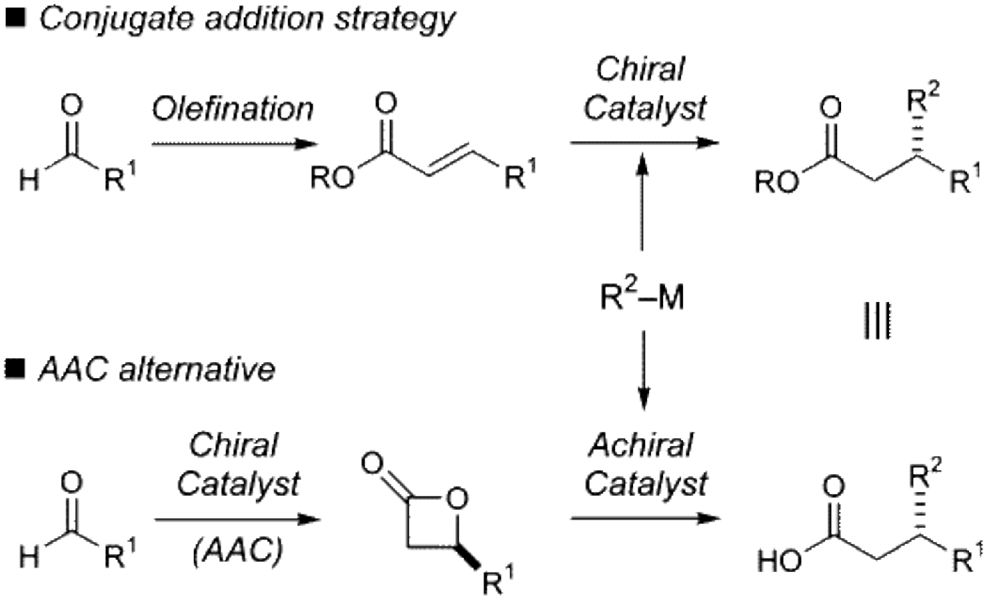
Example



Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883-1886.
Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; and Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049.

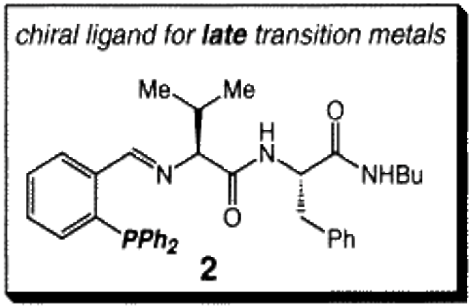
Asymmetic “Conjugate Addition” Strategies

- *Prototypical Conjugate Addition Reactions Use an Enone Electrophile*
- *β-Lactones Opened with $Cu^{(I)}$ Salts Give “Conjugate Addition” Products*

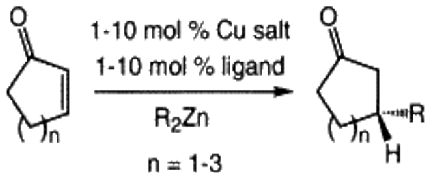


Stereochemistry
Based on Chiral Catalyst

Stereochemistry
Based on Stereocenter
(S_N2)



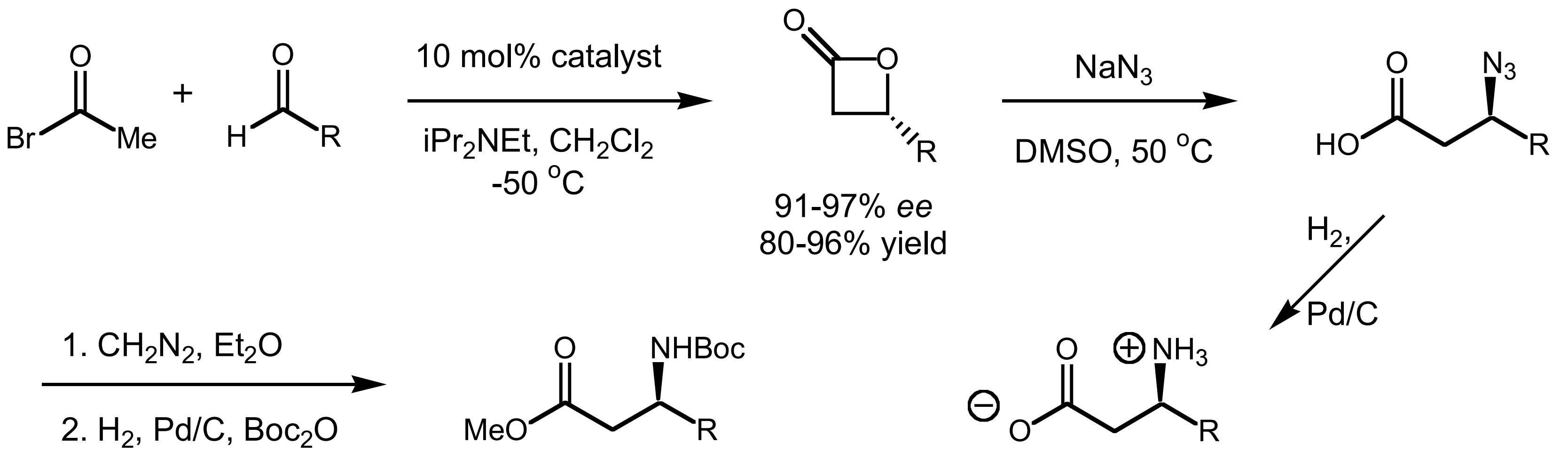
Example



Nelson, S. G., Wan, Z., Stan, M. A. *J. Org. Chem.* **2000**, *67*, 4680-4683
Degrado S. J., Mizutani H., Hoveyda A. H. *J. Am. Chem. Soc.* **2001**, *123,* 755-756.

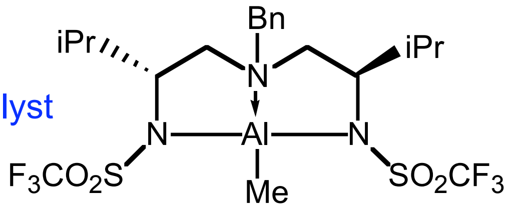
β-Amino Acid Synthesis

- *Amine-Mediated S_N2 Ring Opening of β-Lactones*



R = $BnOCH_2$, $PhCH_2CH_2$, Me_2CHCH_2, various alkyl chains
Ser ***Phe-like*** ***Val-like***

Al^{III} Triamine Catalyst



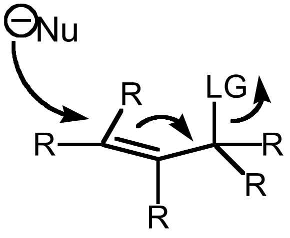
Nelson, S. G., Spencer, K. L., *Angew. Chem. Int. Ed.* **2000**, *39* , 1323-1325.

Allenes from β-Lactone Templates

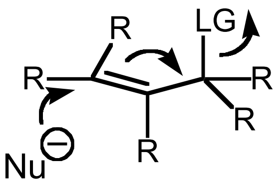
- *Structurally Diverse Allenes are Popular Intermediates for Asymmetric Synthesis*
- *S_N2` Ring Opening using Grignard Reagents and $Cu^{(I)}$ Catalysts*

S_N2` Mechanism

Syn Predominates

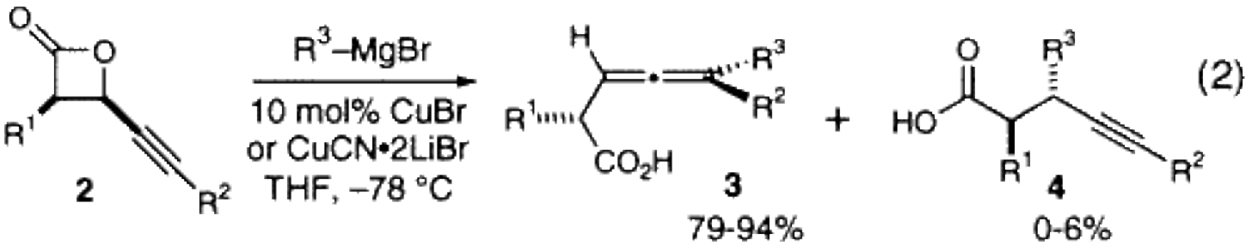


Syn



Anti

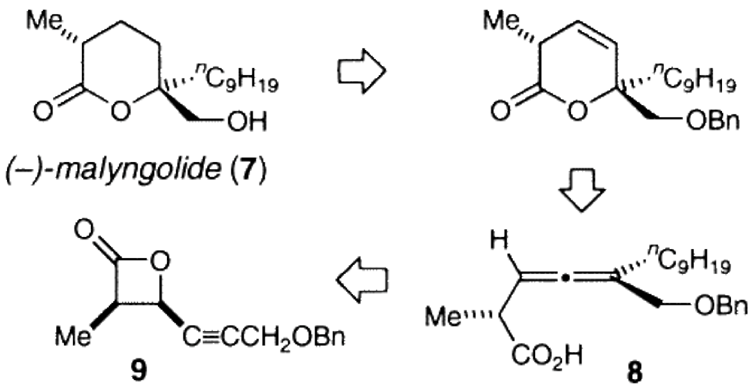
- *4-Alkynyl-β-Lactones Found to Undergo Sterospecific* ***Anti****-1,3-Substitution Reactions*
- *Minor Amounts of S_N2 Lactone Ring Opened Products When Using Unbranched Grignard Reagents*



Paquette, L. A.; Stirling, C. J. M. *Tetrahedron*, **1992**, *48*, 7383.-S_N2` Review
Wan, Z.; Nelson, G. S. *J. Am. Chem. Soc.* **2000**, *122,* 10470-10471.

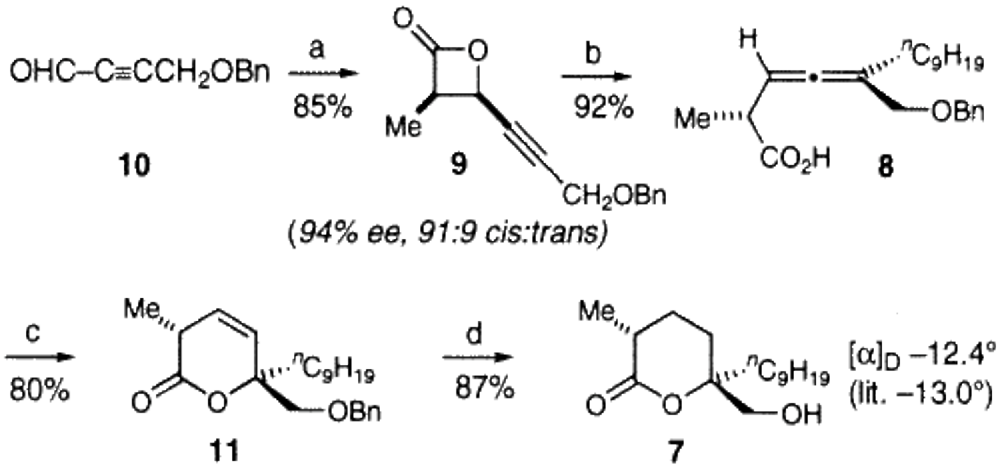
Stereocontrolled Synthesis of Malyngolide

- *(-)-Malyngolide is a Naturally Occurring Antibiotic*
- *Both Stereocenters Set in the Initial Asymmetric AAC Reaction*



Retrosynthesis

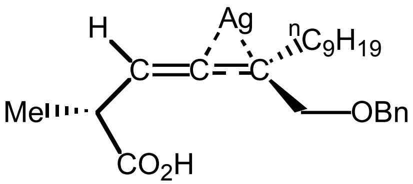
(a) 10 mol% **1**, EtCOBr, *i*Pr_2NEt, CH_2Cl_2, -50 °C.
(b) *n*C9H19MgBr, 10 mol % CuBr, THF, -78 °C.
(c) 10 mol%, $AgNO_3$, 5 mol% *i*Pr_2NEt, 80 °C, CH_3CN.
(d) H_2, Pd-C.



(*94% ee, 91:9 cis:trans*)

[α]$_D$ −12.4°
(lit. −13.0°)

Step c via



Four Steps / 54% Overall Yield

Asymmetric Synthesis

Wan, Z.; Nelson, G. S. *J. Am. Chem. Soc.* **2000**, *122,* 10470-10471.

Summary for Aldehyde Cyclocondensation (AAC) Reactions

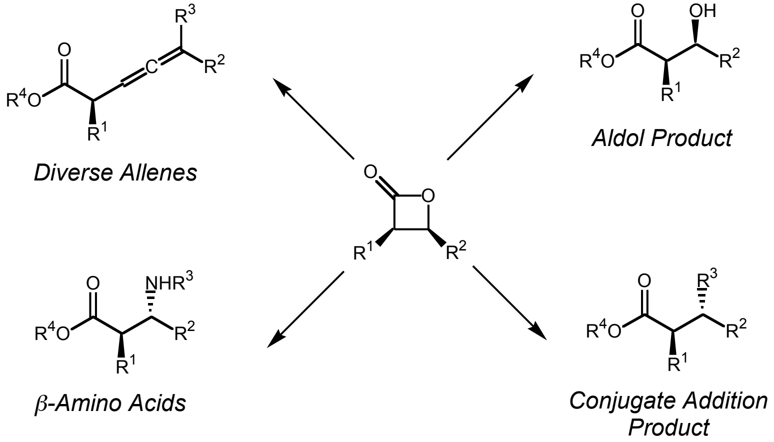
- Relative Stereochemistry is Set by Woodward-Hoffmann Rules: [2+2] Cycloaddition

- Absolute Stereochemistry is Set by a Chiral Triamine Al$^{(III)}$ Catalyst

- β-Lactones Act As Surrogates For Important Enantioenriched Building Blocks

- Can be Used to Prepare…

  1. Aldol Addition Products
  2. Conjugate Addition Products
  3. β-Amino Acids
  4. Diverse Allenes



- (AAC) Methodology Could be Used For Large Scale Preparation of Pharmaceutical Precursors if Approach is Competitive and Cost Effective Compared to Current Routes