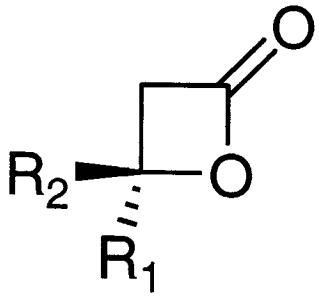
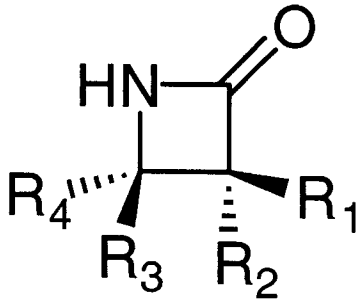
# Synthesis of $\beta$-Lactones and $\beta$-Lactams By Catalytic Asymmetric [2+2] Cycloadditions

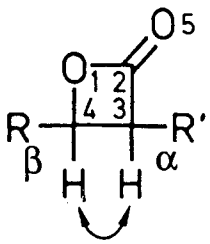



**John Baird**

April 16, 2002

# Structure of $\beta$-Lactones (2-oxetanones)



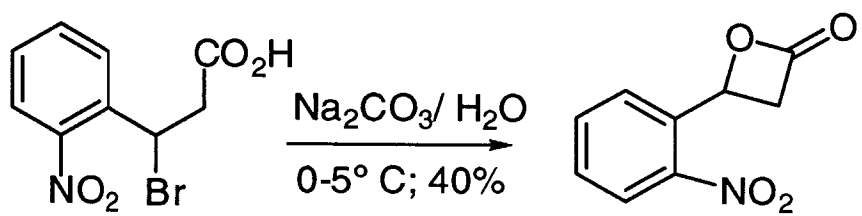

$^3J_{trans}$ = 4 - 4.5 Hz
$^3J_{cis}$ = 6.5 Hz

Display intense carbonyl IR absorption at $\nu$ = 1840-1810 cm.$^{-1}$

NMR Spectroscopy can allow for the attribution of a cis or trans relation to 3,4-disubstituted 2-oxetanones.

X-ray strucures as well as MM2 calculations show that 2-oxetanones adopts a planar conformation.

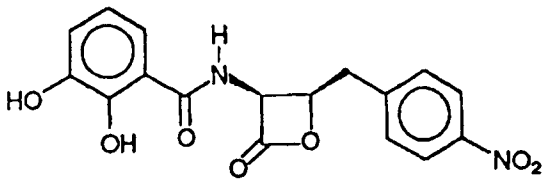
First isolated and purified $\beta$-Lactone reported in the literature was by Einhorn in 1883



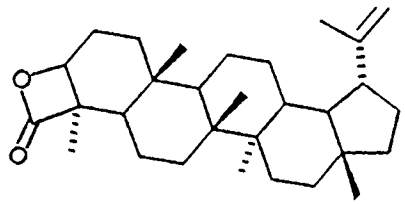


Pommier, A.; Pons*, J.M. *Synthesis* **1993**, 441-459.
Einhorn, A. *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2208.

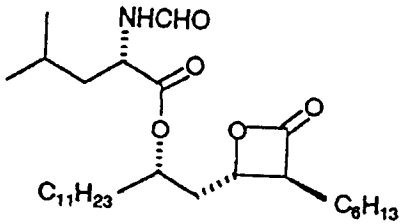
# Natural Products Containing β-Lactones




Obafluorin
(antibiotic)



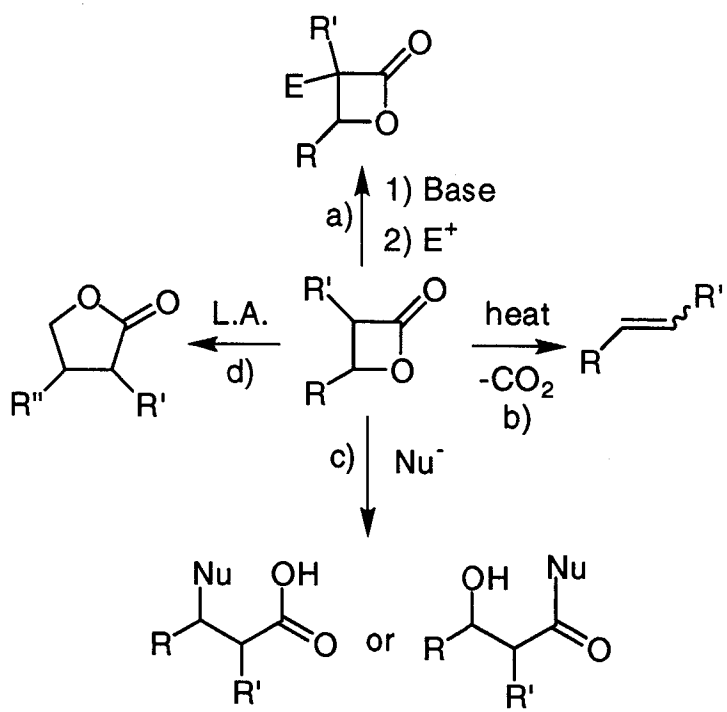

Lupeolactone
(Has been shown to lower serum cholesterol




Tetrahydrolipstatin
(potent pancreatic lipase inhibitor and shows promise for the treatment of obesity)

Pommier, A.; Pons*, J.M. *Synthesis* **1995**, 729-744.

# Reactivity of $\beta$-Lactones




## Common Reactions:

a) Enolate formation and attack of electrophiles.

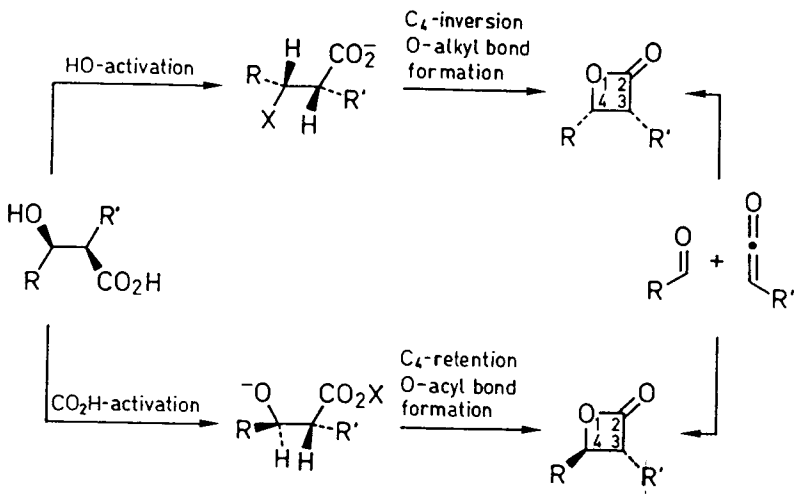
b) Decarboxylation

c) Attack by nucleophiles (with ring opening)
Functions as a masked Aldol equivalent

d) Lewis acid promoted rearrangement

Pommier, A.; Pons*, J.M. *Synthesis* **1993**, 451.

# Common Methods of Preparation




[2+2] Cycloaddition

Lactonization by oxygen-acyl bond formation

Lactonization by oxygen-alkyl bond formation

Pommier, A.; Pons*, J.M. *Synthesis* **1993**, 443.

# The Importance of Asymmetric Catalysis

I. Provides an elegant route for synthesis

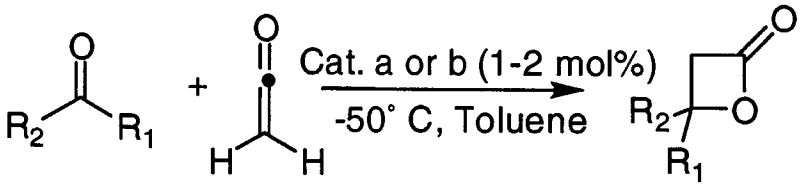
II. Possesses a high degree of efficiency

III. Allows access to chiral products

Single isomer drugs accounted for 32% of all drug sales worldwide in 1999

Analysts predict that chiral drug sales will be 146 billion dollars in 2003

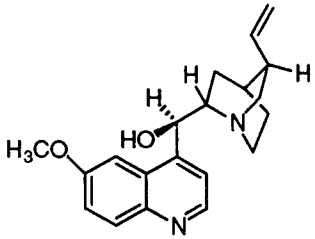
# Cinchona Alkaloids as Nucleophilic Catalysts-Early Work

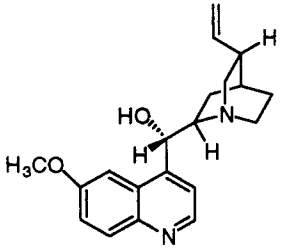



Catalyst a = quinidine
Catalyst b = quinine

| β-Lactone | | | % ee (yield,Configuration at C4) | |
|---|---|---|---|---|
| | R1 | R2 | a | b |
| 1 | H | $CCl_3$ | 98(89%,R) | 76(NR,S) |
| 2 | H | $CCl_2H$ | 45(67%,R) | NR |
| 3 | H | $CCl_2Me$ | 91(95%,R) | 76(95%,S) |
| 4 | H | $CCl_2Et$ | 89(87%,R) | 70(NR,S) |
| 5 | H | $CCl_2Ph$ | 90(89%,R) | 68(NR,S) |
| 6 | $CCl_3$ | Me | 94(72%,R) | 85(72%,S) |
| 7 | $CCl_3$ | Et | NR(1%,NR) | NR(1%,NR) |
| 8 | $CCl_3$ | p-ClPh | 90(68%,R) | 65(68%,S) |
| 9 | $CCl_3$ | p-$NO_2$Ph | 89(95%,R) | 65(95%,S) |

NR denotes that the information was not reported

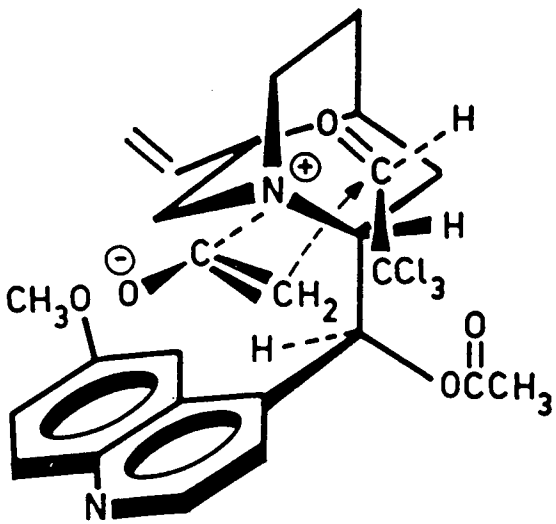

Quinine


Quinidine

Using either quinine or quinidine gives the optically active β-lactone in good to high ee

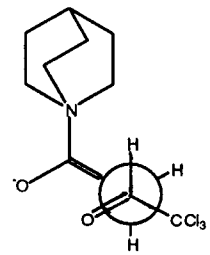
Wynberg, H.; Staring, E.G. *J. Am. Chem. Soc.* **1982**, 104, 166-168.
Wynberg, H.; Staring, E.G. *J. Org. Chem.* **1985**, 50, 1977-1979.

# Proposed Transition State

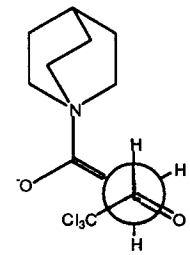



Ketene–chloral–quinidine acetate transition state.

Wynberg R Product is observed

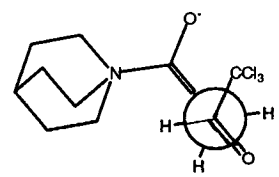



Gives R Product
syn clinal

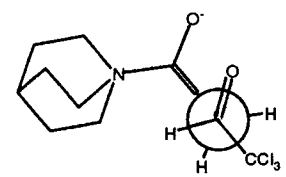



Gives S Product
anti-periplanar

Perhaps Another Reasonable TS




Gives R Product



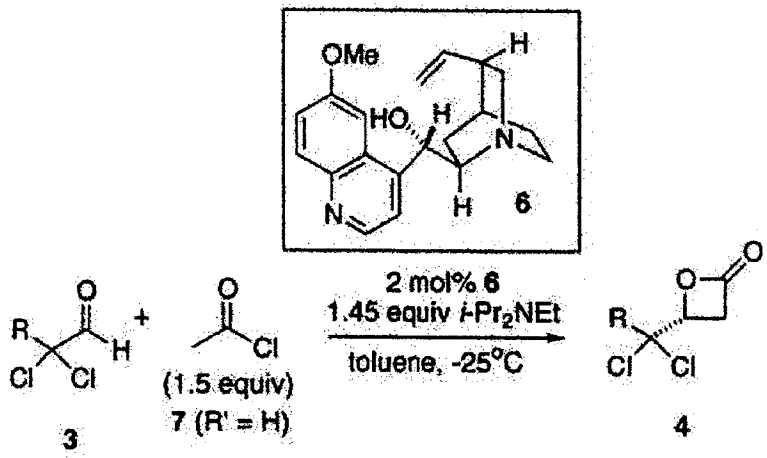

Gives S Product

Stepwise process via an ammonium enolate intermediate

Method relies on using a ketene generator, and an α-substituted aldehyde

Wynberg, H. in *Topics in Stereochemistry* **1986**, 16, 87-130.

# In Situ Generated Ketene for the Wynberg Synthesis of $\beta$-Lactones



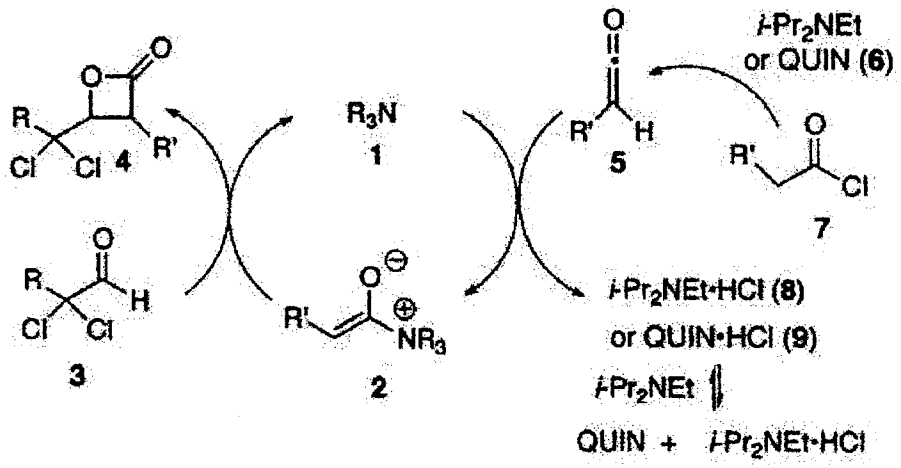

| entry | carbonyl precursor | β-lactone[a] | % yield[b] | % ee[c] |
|---|---|---|---|---|
| 1 | 3a | 4a | 85 | 94 |
| 2 | 3b | 4b | 73 | 93 |
| 3 | 3c | 4c | 80 | 94 |
| 4 | 3d | 4d | 40 | 98 |
| 5 | 3e | 4e | 25 | ND[d] |

Addresses the shortcoming of Wynberg's method and bypasses the need to use a ketene generator

Affords the net [2+2] cycloaddition of activated aldehydes and ketenes via a stepwise process

Tennyson, R.; Romo,* D. *J. Org. Chem.* **2000**, 65, 7248-7252

# Proposed Catalytic Cycle




Crucial to the catalytic cycle in this type of reaction is a solubility differential between the hydochloride salts of the base and catalyst

Protonation of the catalyst would poison the catalytic cycle

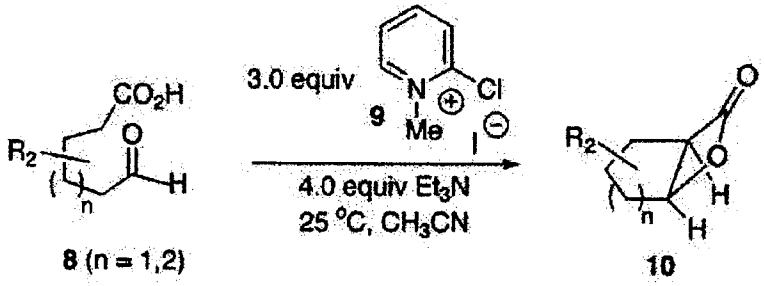
Used toluene to precipitate hydrochloride salt of Hunig's base thus relying on solubility differential as opposed to a $pK_a$ differential

Hunig's base does not catalyze formation of the β-lactone

Still requires an activated (dichloronated) aldehyde

Tennyson, R.; Romo,* D. *J. Org. Chem.* **2000**, 65, 7248-7252

# Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions

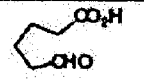
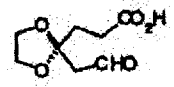
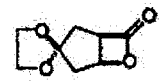
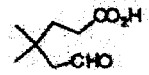
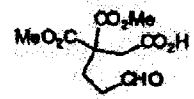
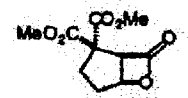
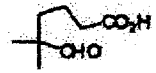
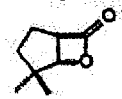
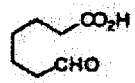
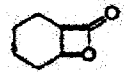
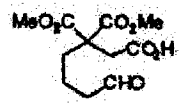
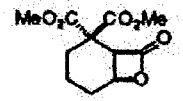



Catalyst a = O-acetyl quinidine
Catalyst b = O-acetyl quinine

**Catalytic, Asymmetric NCAL Reactions**

| entry | bicyclic β-lactone | | %yield | %ee | config |
|---|---|---|---|---|---|
| Cat.(10 mol%) | | | | | |
| 1 | a | (+)-10a | 54 | 92 | (1R,2S) |
| 2 | b | (- )-10a | 51 | 86 | (1S,2R) |
| 3 | a | (+)-10b | 37 | 92 | (3R,4S) |
| 4 | a | (+)-10c | 45 | 90 | (1R,2S) |

**Racemic Bicyclic Products via NCAL Reaction**

| entry | oxo-acid precursor | cmpd. no. | bicyclic-β-lactones | cmpd. no. | % yield[a] |
|---|---|---|---|---|---|
| 1 |  | 8a |  | 10a | 55 |
| 2 |  | 8b |  | 10b | 66 |
| 3 |  | 8c |  | 10c | 68 |
| 4 |  | 8d |  | 10d | 62 |
| 5 |  | 8e |  | 10e | 62 |
| 6 |  | 8f |  | 10f | 36[b] |
| 7 |  | 8g |  | 10g | 57 |

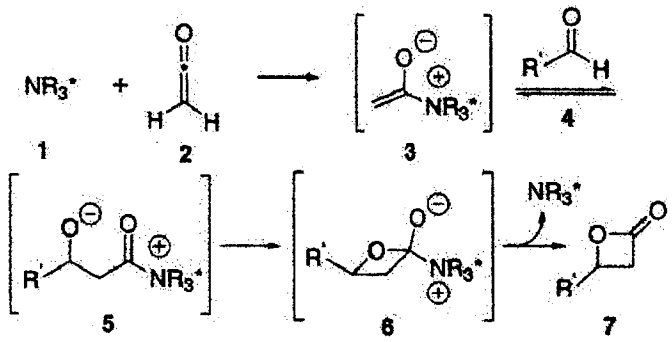
Developed to extend the methodology of Wynberg, and use nonactivated carbonyl compounds

Mukaiyama's reagent was used to generate the ketene in-situ

Yields are poor to moderate, but in catalytic examples ee's are quite high

Cortez, G; Tennyson, R.; Romo,* D. *J. Am. Chem. Soc.* **2001**, 123, 7945-7946.

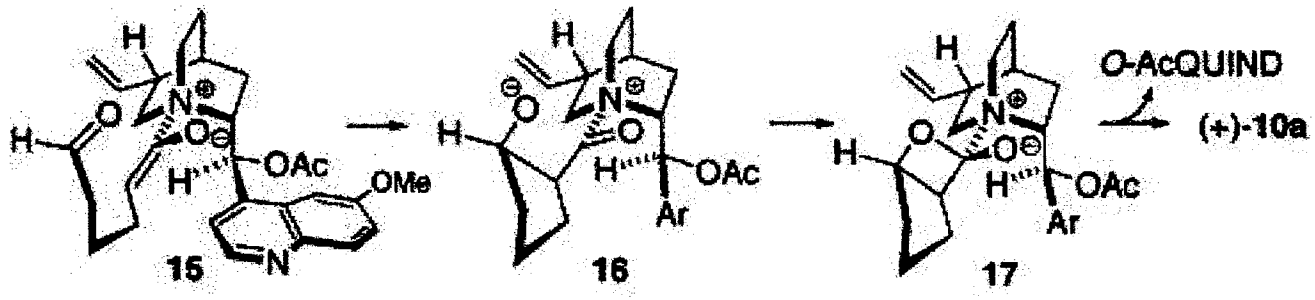
# Proposed Mechanism for the NCAL Reaction



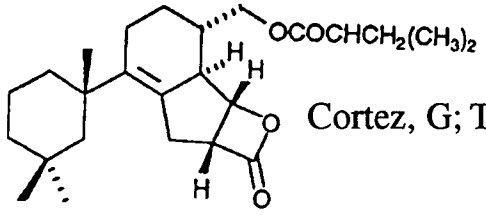

Proposed mechanism involves an aldol-lactonization process proceeding in a stepwise manner

# Proposed Transition State

*si* face approach of the aldehyde to the ammonium enolate proceeds opposite the quinoline ring



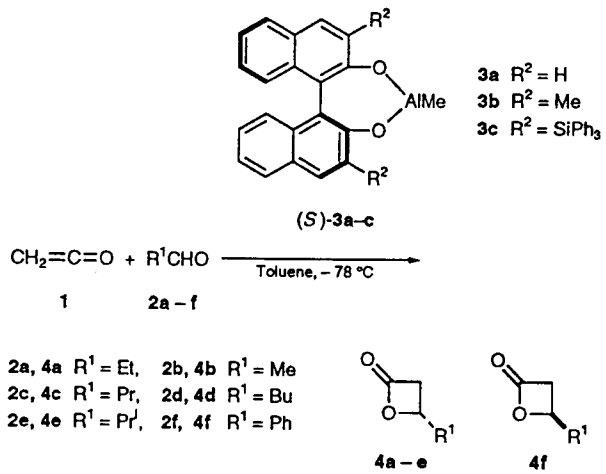

Intramolecular variant chosen to minimize unfavorable entropic barriers




**Spongiolactone (160)**

Cortez, G; Tennyson, R.; Romo,* D. *J. Am. Chem. Soc.* **2001**, 123, 7945-7946.

# Chiral $Me_3Al$ Complexes As Catalysts- Early Studies




Scheme 1

Stoichiometric addition of Al complex which presumably allows coordination to adehyde and activation in thermal [2+2] manner

Catalytic activity may be lost by preferential coordination of ketene or product oxetanone to the Lewis acid

Monoacetylation of the phenolic hydroxy groups of the Al complex was observed in the reactions

The preferred enantiomer depended on the structure of the catalyst as well as the aldehydes

**Table 1** Cycloaddition of ketene **1** with the aldehydes **2a–f** catalysed by axially chiral Lewis acids (*S*)-**3a–c**

| Run | Aldehyde 2 ($R^1$) | Catalyst 3 ($R^2$) | Product 4 | Yield[a] (%) | E.e.[a] (%) | Abs. Confign. |
|---|---|---|---|---|---|---|
| 1 | **2a** (Et) | **3a** (H) | **4a** | 45 (15[b]) | 36 | *S* |
| 2 | **2a** (Et) | **3b** (Me) | **4a** | 63 | 28 | *R* |
| 3 | **2a** (Et) | **3c** ($SiPh_3$) | **4a** | 67 | 56 | *S* |
| 4[c] | **2a** (Et) | **3c** ($SiPh_3$) | **4a** | < 5 | — | — |
| 5[d] | **2a** (Et) | **3c** ($SiPh_3$) | **4a** | 33 | 45 | *S* |
| 6[e] | **2a** (Et) | **3c** ($SiPh_3$) | **4a** | 91 | 20 | *R* |
| 7 | **2b** (Me) | **3c** ($SiPh_3$) | **4b** | 78 | 23 | *S* |
| 8 | **2c** (Pr) | **3c** ($SiPh_3$) | **4c** | 69 | 45 | *S* |
| 9 | **2d** (Bu) | **3c** ($SiPh_3$) | **4d** | 80 | 17 | *S* |
| 10 | **2e** ($Pr^i$) | **3c** ($SiPh_3$) | **4e** | 59 | 28 | *R* |
| 11 | **2f** (Ph) | **3c** ($SiPh_3$) | **4f** | 76[f] | 21[g] | *S* |

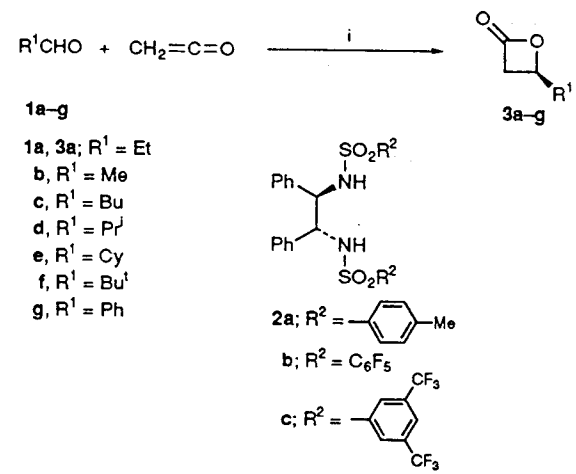
Tamai, Y.; Someya, M.; Fukumoto, J.; Miyano*, S. *J. Chem. Soc. Perkin Trans.* **1994**, 1549-1550.

# Second Generation Catalysts- Bissulfonamide-Trialkylaluminum Complexes

Weakly basic sulfonamide groups were installed to resist the acylative deactivation of the catalyst by the ketene

Acylation of the catalyst did not occur

## Reaction Scheme




**Scheme 1** *Reagents and conditions*: i, **2a–c**-$R_3{}^3Al$ (10 mol%), toluene, −78 °C. Cy = cyclohexyl.

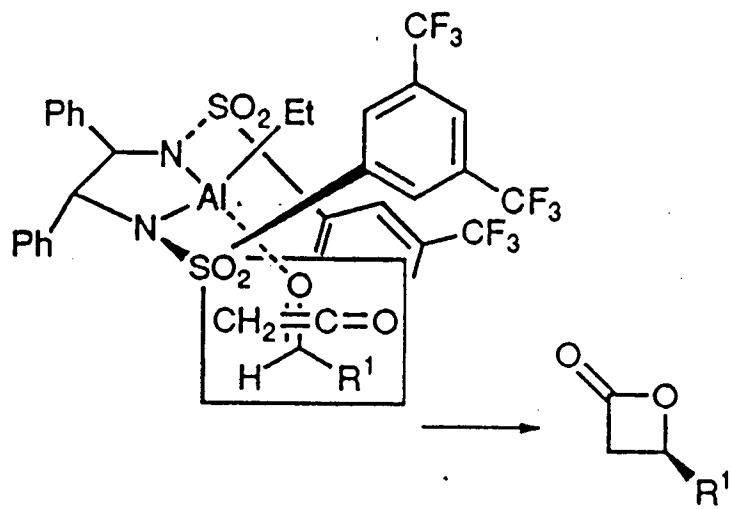
**Table 1** Cycloaddition of ketene with aldehydes **1a–g** catalysed by chirally modified Lewis acids[a]

| Run | Aldehyde 1 ($R^1$) | Catalyst 2-$R^3{}_3Al$ | Product 3 | Yield (%)[b] | Ec (%)[b] | Abs. confign.[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** (Et) | **2a**-$Me_3Al$ | **3a** | 13 | 0 | — |
| 2 | **1a** (Et) | **2b**-$Me_3Al$ | **3a** | 94 | 10 | *S* |
| 3 | **1a** (Et) | **2c**-$Me_3Al$ | **3a** | 55 | 20 | *S* |
| 4 | **1a** (Et) | **2c**-$Et_3Al$ | **3a** | 77 | 33 | *S* |
| 5 | **1a** (Et) | **2c**-$Bu^i{}_3Al$ | **3a** | 72 | 23 | *S* |
| 6 | **1b** (Me) | **2c**-$Et_3Al$ | **3b** | 59 | 30 | *S* |
| 7 | **1c** (Bu) | **2c**-$Et_3Al$ | **3c** | 82 | 41 | *S* |
| 8 | **1d** ($Pr^i$) | **2c**-$Et_3Al$ | **3d** | 76 | 56 | *R*[d] |
| 9 | **1e** (Cyclohexyl) | **2c**-$Et_3Al$ | **3e** | 75[e] | 74 | *R*[d,f] |
| 10 | **1f** ($Bu^t$) | **2c**-$Et_3Al$ | **3f** | 77 | 65 | *R*[d,g] |
| 11 | **1g** (Ph) | **2c**-$Et_3Al$ | **3g** | 11[h] | 14[i] | *R*[d] |

Bulky aldehydes gave higher enantioselectivities than the small aldehydes

Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano*, S. *J. Chem. Soc., Chem Commun.* **1994**, 2281-2282.

# Proposed Rationale for the Observed Stereochemistry of the Product



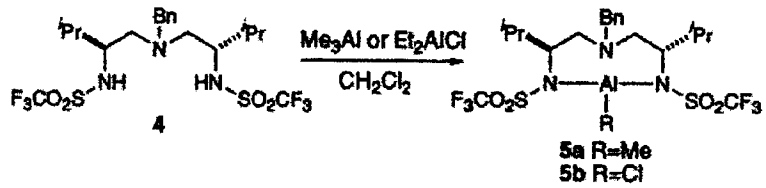

Preferred enantiomers were those generated via ketene addition from the *re*-face of the aldehydes

Lone pair electrons of the carbonyl oxygen of the aldehyde coordinate to the catalyst anti to the substituent $R_1$

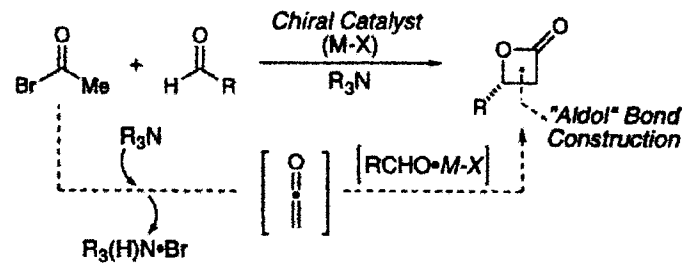
Higher enantioselectivities for the bulky aldehydes can be rationalized by avoiding the steric repulsion between $R_1$ and the diazaaluminolidine moiety

Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano*, S. *J. Chem. Soc., Chem Commun.* **1994**, 2281-2282.

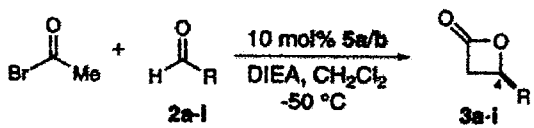
# Aluminum Complexes- Catalytic Asymmetric Acyl Halide-Aldehyde Cyclocondensations




(3)




(1)




(4)

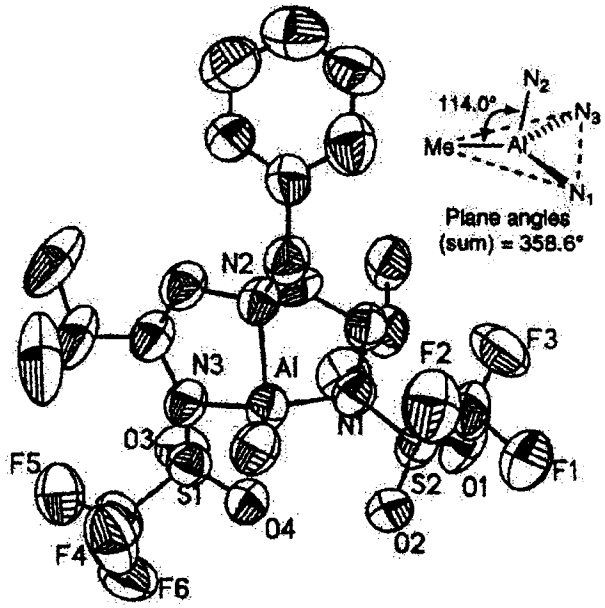
| entry | Aldehyde 2 (R) | catalyst [time (h), temp (°C)] | % yield[b] | % ee 3[d] (configuration) |
|---|---|---|---|---|
| a | $BnOCH_2$— | 5b (8, -40) | 91 | 92 (*R*) |
| b | $PhCH_2CH_2$— | 5a (16, -50) | 93 | 92 (*S*) |
| | $PhCH_2CH_2$— | 5a (72, -78) | 89 | 95 (*S*) |
| c | $CH_2CH(CH_2)_8$— | 5b (16, -50) | 91 | 91 (*S*) |
| d | $Me_2CHCH_2$— | 5a (24, -50) | 80[c] | 93 (*S*) |
| e | $BnOCH_2CH_2$— | 5b (16, -40) | 90 | 91 (*S*) |
| f | $TBDPSOCH_2$— | 5b (16, -40) | 74 | 89 (*R*) |
| g | $BnOCH_2$—≡— | 5a (16, -50) | 86 | 93 (*R*) |
| h | $Me_3C$—≡— | 5a (16, -50) | 91 | 85 (*R*) |
| i | $C_6H_{11}$— | 5b (24, -40) | 56 | 54 (*R*) |

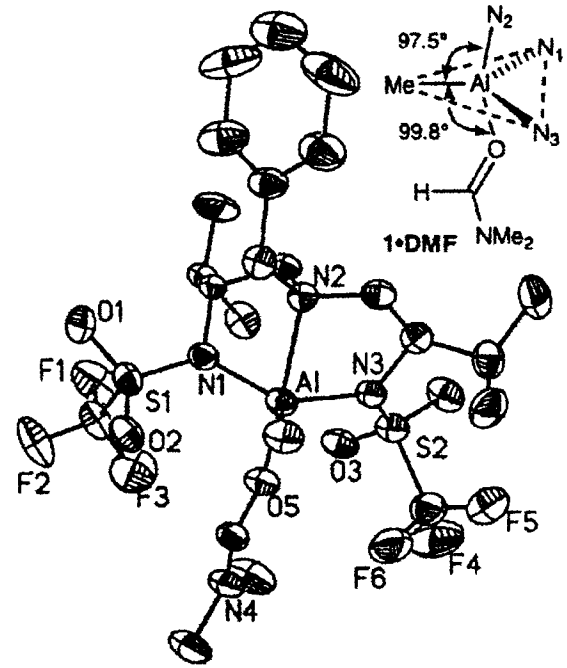
Developed a catalyst system that merges in situ ketene formation with enantioselective aldehyde addition

Generally good overall yields and excellent % ee for a variety of aldehydes

Nelson*, S,; Peelen, T.; Wan, Z. *J. Am. Chem. Soc.* **1999**, 121, 9742-9743.

# Crystal Structure of Aluminum (III) Triamine Complex




Crystal structure shows a four-coordinate complex that adopts a trigonal monopyramidal geometry

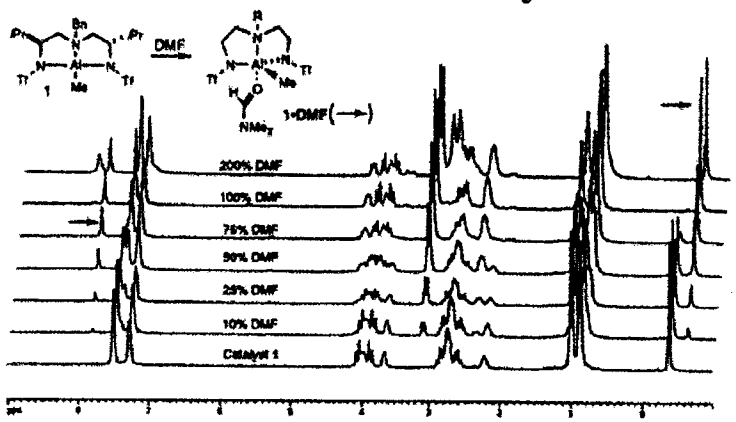
Distorted coordination geometry provides a vacant $d_{z^2}p$ orbital which is able to accept a 5th ligand and form a five-coordinate Lewis acid-base complex

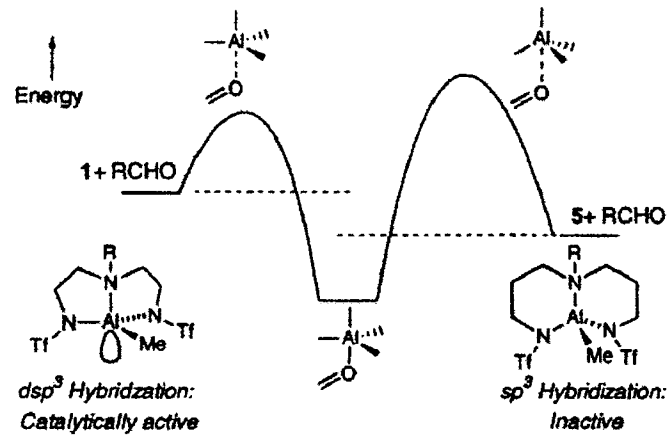
Notably, complexes without the heteroatom tether lack catalytic activity

Nelson*, S,; Kim, B.; Peelen, T. *Am. Chem. Soc.* **2000**, 122, 9318-9319.

# Titration Studies and Rationale

**NMR Titration Study**




Titration studies suggest that carbonyl binding is strongly favored and dissociation of the Lewis acid-base complex is slow

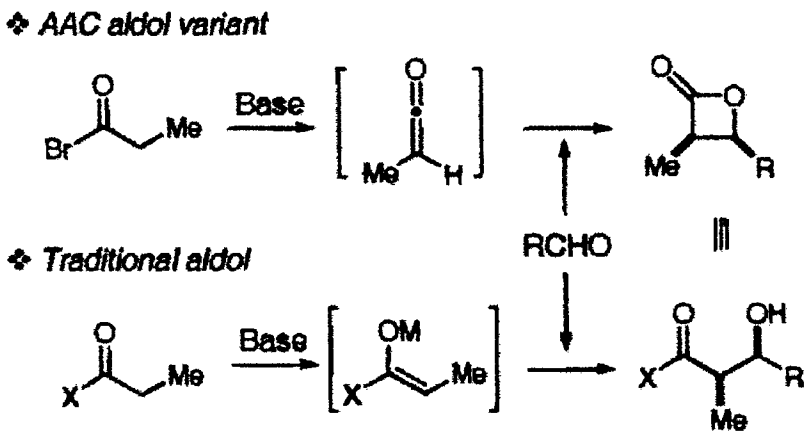
Neutral, pentacoordinate Lewis acid-base adduct is the catalytically active species

*dsp*$^3$ hybridization at Aluminum is required for catalytic activity

Distorted coordination geometry functions to decrease the energetic barrier associated with reorganizing tetrahedral geometry required to access the catalytically active pentacoordinate species

Nelson*, S,; Kim, B.; Peelen, T. *J. Am. Chem. Soc.* **2000**, 122, 9318-9319.

# Further Extensions of Al(III)-Triamine Catalyst-Propionate Aldol Reactions Via Acyl Halide-Aldehyde Cyclocondensations



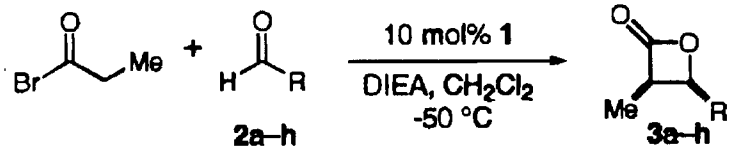




Table 1. Asymmetric Propionyl Bromide–Aldehyde Cyclocondensation Reactions

| entry | aldehyde 2 (R)[a] | % ee of 3 | *cis:trans* | % yield of 3[d] |
|---|---|---|---|---|
| a | $CH_2OBn$ | 94 | 88:12 | 78 |
| b | $C{\equiv}CCH_2OBn$ | 94 | 91:9 | 85 |
| c | $C{\equiv}CCH_2CH_2OPMB$ | 90 | 87:13 | 86 |
| d | $C{\equiv}CC_5H_{11}$[b] | 93 | 98:2 | 85 |
| e | $C{\equiv}CCMe_3$[c] | 90 | >99:1 | 90 |
| f | $C{\equiv}CSiMe_3$[c] | 93 | >99:1 | 90 |
| g | $C{\equiv}CPh$ | 91 | >99:1 | 83 |
| h | $4\text{-}(NO_2)C_6H_4$ | >98 | >99:1 | 90 |

[a] Stereoisomer ratios assayed by chiral HPLC (Chiralcel OD-H) unless otherwise indicated. [b] Stereoisomer ratios determined by chiral HPLC (Chiralcel OD-H) of the corresponding benzyl amide. [c] Stereoisomer ratios determined by chiral GC (Chiraldex G-TA). [d] Values are for purified materials.

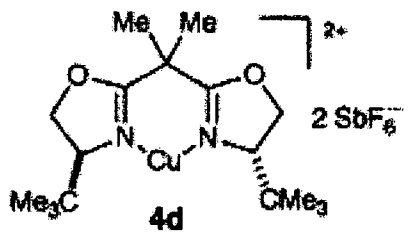
*Syn*-selective propionate aldol equivalents are generated in good yields and excellent *cis:trans* selectivity and ee

However, propionyl bromide-based AAC do not display the same generality as the respective acetyl bromide reactions

Aliphatic aldehydes and conjugated enals are not successful substrates

Nelson*, S,; Wan, Z. *Org. Lett.* **2000**, Vol. 2, No. 13, 1883-1886.

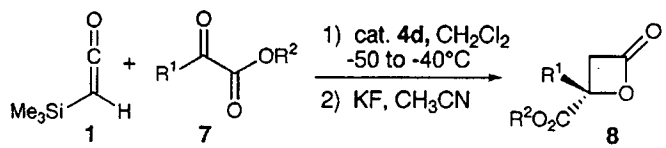
# C2-Symmetric Bis(oxazoline)-Cu(II) Complexes




Catalyze the enantioselective thermal [2+2] cycloaddition between (silyl) ketenes and chelating carbonyl substrates

bis(oxazoline)-Cu(II) catalyst

**Table 2.** Cycloadditions with α-Keto Esters (eq 5)



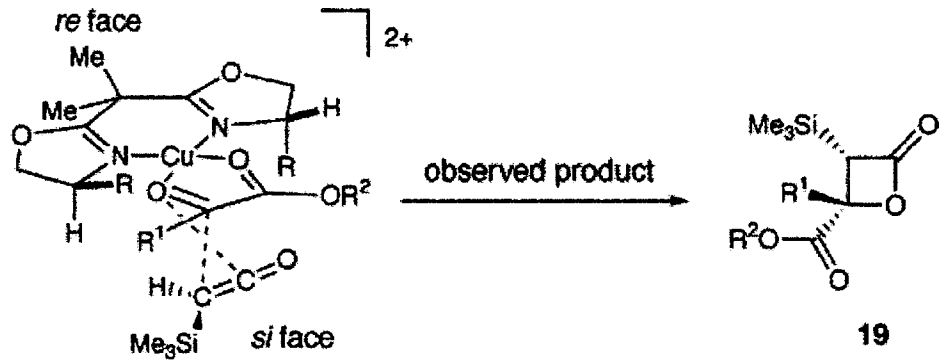

| α-keto ester | $R^1$ | $R^2$ | 20 mol % of **4d** % yield[a] (%ee[b,c]) | 10 mol % of **4d** % yield[d] (%ee[b,c]) |
|---|---|---|---|---|
| **a** | Me | Me | >99 (95) | 93[e] (95) |
| **b** | Et | Me | 92 (99) | 89 (93) |
| **c** | $^t$Bu | Me | 87 (83) | 89 (86) |
| **d** | $^i$Pr | Et | 86 (85) | 78 (88) |
| **e** | Ph | Me | 79[d] (87) | 76 (83) |
| **f** | $BrCH_2$ | Et | >99 (91) | 75 (91) |

[a] Reaction conducted over 24 h. [b] Enantiomeric excess determined by capillary GLC using a Cyclodex β column or by HPLC using a Chiralcel OD-H column. [c] Absolute configurations assigned by analogy. [d] Reaction conducted over 48 h. [e] Reaction conducted over 24 h with 1 mol % of **4d**.

With increased steric bulk of the acyl substituent, a slight decrease in % ee is seen in the β-lactone products

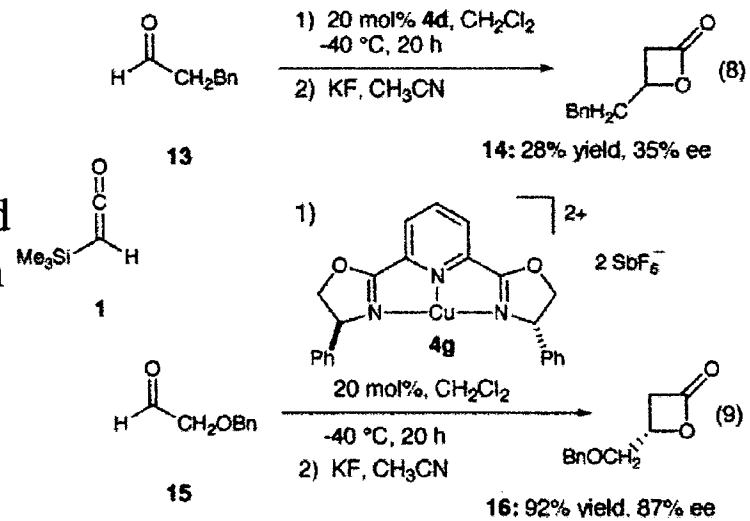
Evans*, D.; Janey, J. *Org. Lett.* **2001**. 13, 2125-2526.

# Proposed Chelation of the Carbonyl Electrophile




Ketene path of approach proceeds in an orthogonal manner onto the activated carbonyl

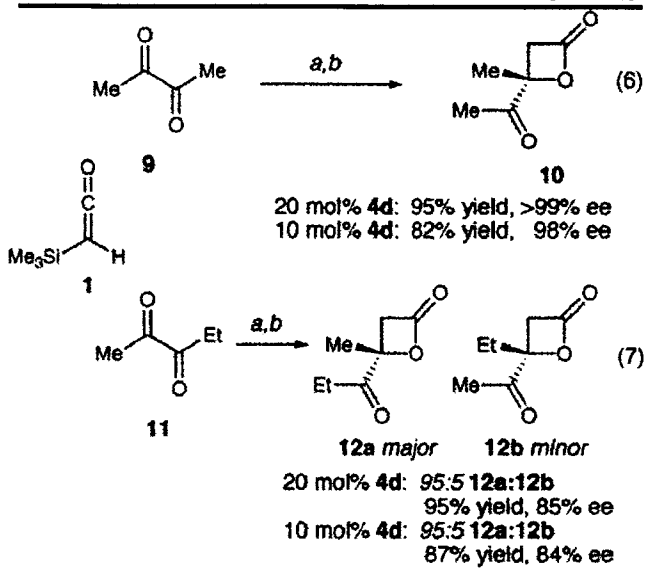
Chelating carbonyl functionality is required as hydrocinnamaldehyde gives β-lactone in poor yields and low ee's




Evans,* D.; Janey, J. *Org. Lett.* **2001**. 13, 2125-2526.

# Further Applications of Bis(oxazoline)-Cu(II) Complexes

## Reactions with α-Diketones

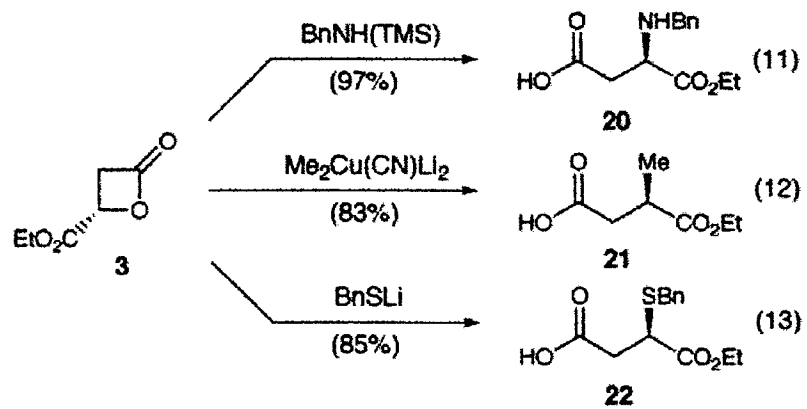



In the reactions with diketones, the catalyst is able to discriminate between the ethyl and methyl substituents

## β-lactone Ring Opening Reactions

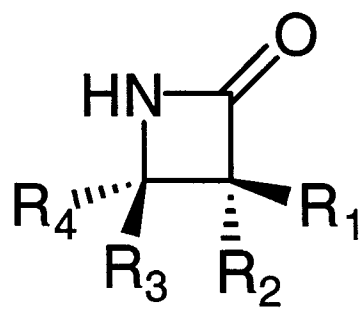
Opening proceeds via acyl-oxygen cleavage with "hard" nucleophiles

Opening proceeds via alkyl-oxygen cleavage with "soft" nucleophiles




Evans,* D.; Janey, J. *Org. Lett.* **2001**. 13, 2125-2526.

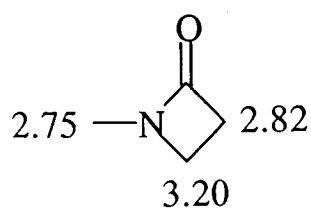
# β-Lactams (2-Azetidinones)




Useful synthetic intermediates and many are biologically active

β-lactam structure is a common motif in antibiotics

## Spectroscopic Information

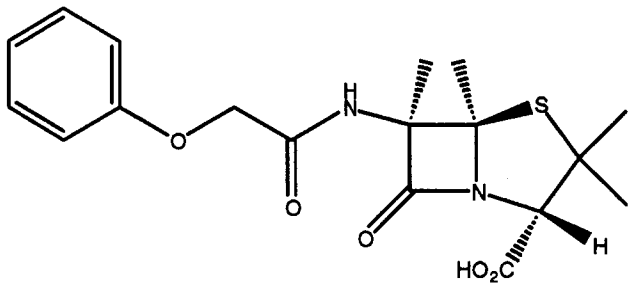



$^1$H NMR chemical shifts

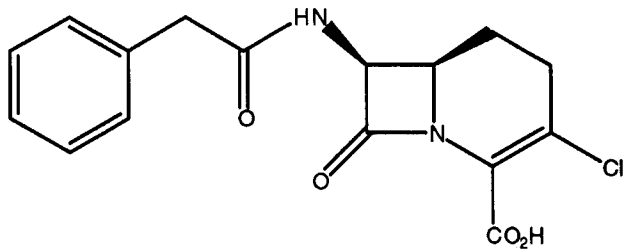
Display intense carbonyl IR absorption at $\nu = 1745\ cm^{-1}$

Pretsch, E; Buhlmann, P; Affolter, C. Structure Determination of Organic Compounds. **2000** 225.

# Interesting β-lactam Natural Products

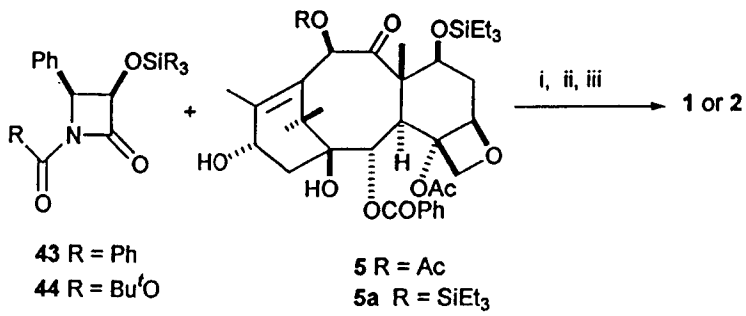


Penicillin V

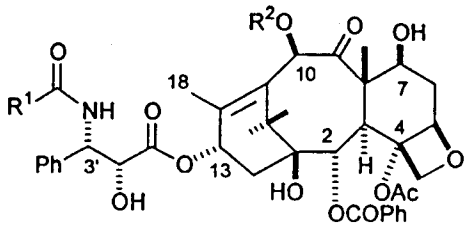


Laracarbef

# β-lactam in Synthesis- Preparation of Taxol




**Scheme 8** *Reagents and conditions*: i, **5** (0.1 M in THF), *n*-BuLi, −45 °C; ii, **43** or **44** (0.2 M in THF), warm to 0 °C, 2 h, 95%; iii, HF–pyridine, MeCN, 98%.



**1** $R^1$ = Ph, $R^2$ = Ac

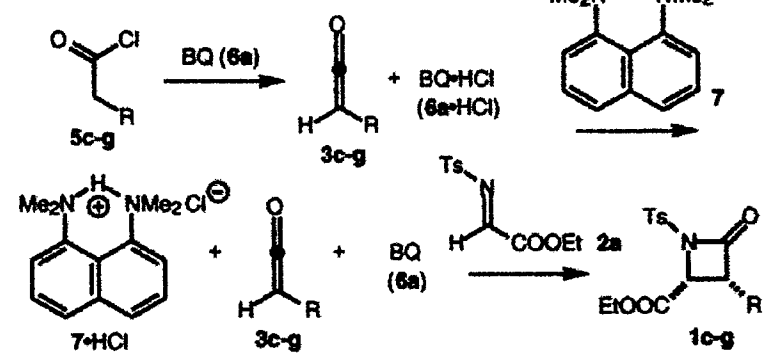
(paclitaxel or Taxol™, **1**)

Kingston, D. Chem. Commun. **2001**. 13, 872.

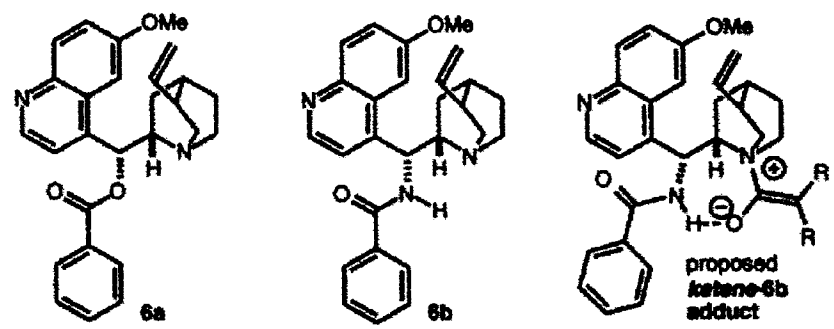
# Catalytic, Asymmetric Route To Optically Active β-Lactams

| entry | acid chloride | ketene | product | % ee | dr (cis/trans)[c] | % yield[d] |
|---|---|---|---|---|---|---|
| 1 | 5a[b] | 3a | 1a | 99 | -- | 36 |
| 2 | 5c | 3c | 1c | 96 | 99/1 | 65 |
| 3 | 5d | 3d | 1d | 99 | 99/1 | 57 |
| 4 | 5e | 3e | 1e | 99 | 99/1 | 45 |
| 5 | 5f | 3f | 1f | 98 | >99/1 | 61 |
| 6 | 5g | 3g | 1g | 95 | 99/1 | 56 |

## Reaction Scheme




## Catalysts

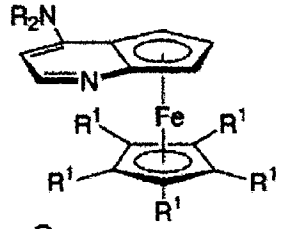



Method for the enantioselective synthesis of b-lactams using a nucleophile catalyzed reaction of electron deficient ketenes and imines to yield a net [2+2] cycloaddition

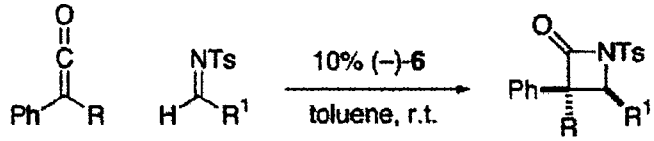
Benzoylquinine plays two roles: it acts as a dehydrohalogenation agent as well as a nucleophilic catalyst

Taggi, A.; Hafez, A.; Wack, H.; Young, B.;Drury, W.; Lectka*, T. *J. Am. Chem. Soc.* **2000**. 122, 7831-7832.

# Enantioselective Staudinger Synthesis of β-Lactams

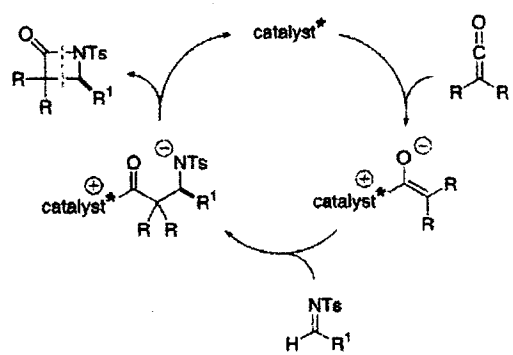


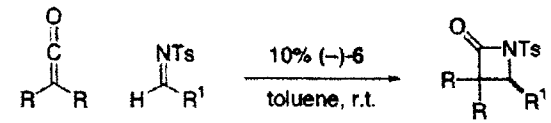

$NR_2$ = pyrrolidino  $R^1$ = Me  (–)-6




1.15 equiv

| Entry | R | $R^1$ | dr[a] | ee (%)[a] | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | *i*-Bu | -Ph | 8:1 | 98 | 88 |
| 2 | *i*-Bu | | 11:1 | 98 | 97 |
| 3 | *i*-Bu | -Ph | 10:1 | 98 | 95 |
| 4 | *i*-Bu | | 15:1 | 89 | 88 |
| 5 | Et | | 9:1 | 95 | 97 |
| 6 | Et | | 10:1 | 98 | 98 |




1.15 equiv

| Entry | R | $R^1$ | ee (%)[a] | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $-(CH_2)_5-$ | -Ph | 81 | 84 |
| 2 | $-(CH_2)_5-$ | | 92 | 90 |
| 3 | $-(CH_2)_5-$ | -Ph | 91 | 82 |
| 4 | $-(CH_2)_5-$ | | 94 | 89 |
| 5[b] | $-(CH_2)_5-$ | | 94 | 76 |
| 6[c] | Et | | 92 | 93 |
| 7[c] | Et | -Ph | 92 | 83 |

Addresses the limitations of Lectka's work where only one immine was used

Both the structure of the immine and ketene were varied to give a variety of β-lactams in generally good yields 76-97% and excellent ee's

Hodous, B.; Fu*, G. *J. Am. Chem. Soc.* **2002**. 124, 1578-1579.

# Conclusion

Catalytic, asymmetric [2+2] cycloadditions show great promise in the construction of valuable optically active β-lactones and β-lactams

The limitations of the Wynberg approach to β-lactones (activated aldehyde and ketene generator) have been addressed in the work of Romo

Miyano's bissulfononamide trialkylaluminum complexes can effectively catalyze β-lactones although the yields and % ee are variable

Nelson's system merges in situ ketene generation with enantioselective aldehyde addition in good yields and % ee while demonstrating the power of distorted coordination geometry in his Al catalysts

Evan's Cu box is the method of choice for α-keto esters and dicarbonyl substrates

While the methods used to generate β-lactams enantioselectively as well as catalytically are relatively new, the work of Lectka and Fu have shown great progress