Directly Generated Titanium Enolates

X = Ph
(Harrison, 1987)

X =

(Evans, 1990)

X = SAr
(Milano, 1991)

X =

(Anh, 1992; Yan, 1995)

X =

(Xiang, 1992; Ghosh,1996)

Synthesis of β-Lactams and a Possible Shortcut

A New One-Pot Synthesis of β-Lactams

R = H, Me, Et, i-Pr, OBn, OAc, $OSiR_3$, SPh, SMe, NHEWG, NPhth.

R^1= Ar, hetero-Ar, Ph-CH=CH, Ph-CH=C(Me), linear and branched alkyls, CH_2OR, CH_2CH_2OR, CH_2SR, COOR, COPh.

R^2= 4-MeOPh (PMP), Bn.

Applied to the synthesis of more than 300 β-lactams

<u>Stereoselectivity</u>: *trans* products with large and non-chelating R and R^1 groups;
cis products with chelating R and R^1 groups;
R^2 group has a limited influence.

Different Possibilities to Control Absolute Stereochemistry

Chiral Imines: Stereoselective Synthesis of a Precursor of (+)-PS-6

Chiral Imines: Stereoselective Synthesis of α-OH, β-NH_2 Acids

Bestatin

Chiral Thioester

R	Y%	ta	ts	ca+cs
Ar	80-90	86-91	2-14	0-11
Ph-CH=CH	42	84	16	0

Synthesis of 4-Acetoxy-3-(1-(TBSO)-ethyl)-2-azetidinone

TBSO
O
Spy
1) TiCl4/TEA
2)
PMPN
OAll
X
X = H, OMe
OTBS
H
H
N
PMP
OAll
X
X = H, ta : ts = 91 : 9
X = OMe, ta : ts = 86 : 3
1) CAN
2) Pd(PPh3)4
OH
1) Rh/C, H2
2) Swern
X = H, 20% o. y.
α : β = 80 : 20
X = OMe, 15% o. y.
α,α isomer only
OMe
COONa

(Bolm et al., 1990)

Looking for a Cheap and Efficient Chiral Auxiliary at the Imine Nitrogen

Amines, R* =

96/4 (80)

95/5 (79)

55/45 (65)

Aminoalcohols, R* =

>98/2 (25)

58/42 (75)

>98/2 (84)

α-Aminoesters, R* =

75/25 (54)

>98/ 2 (30)

>98/ 2 (21)

Renin Inhibitor

A Synthetically Promising Example of Double Stereoselection

1) R-enolate & R-imine are the matched pair.

2) The enolate is *stronger* than the imine in determining the stereoselectivity

3) The products have the configuration required by the thienamycin carbapenems

4) With imines derived from mono- and dialkoxyaryl, heteroaryl, unsaturated, and branched aliphatic aldehydes one out of four possible stereoisomers is formed (10 examples, yields from 30 to 83%).

Triple Stereoselection: Stereoselective Synthesis of a Precursor of 1β-Me Thienamycin

Lewis Acid Variation

Effective:	Uneffective:
$TiCl_4$ $TiBr_4$	TiF_4
$TiCl_3OPr\text{-}i$	$TiCl_2(OPr\text{-}i)_2$ $TiCl_2(NHSO_2R)_2$
$SnCl_4$ $SnBr_4$	$TiCl_2(OR^*)_2$ $TiCl_2(NR^*SO_2Ar)_2$
$ZrCl_4$	$SnCl_2$ $SnOTf_2$
BCl_3 BBr_3	$BF_3{\cdot}OEt_2$
$Al\,Br_3$ $EtAlCl_2$	Et_2AlCl R^*OAlCl_2
	$SbCl_3$ $SbCl_5$
	$BiCl_3$ $BiCl_5$
	$ZnCl_2$
	$MgBr_2$

A Different Mechanism with Al and B LA

Path B can occur with
0.25 mol equiv of LA

Base	Yield%	e.e.%
TEA	70	38
Quinuclidine	61	45
DABCO	60	65
DBU	37	40
Pyridine	32	57
	74	78

(1S,2R)-NME gave better results than other 15 amino-alcohols tested.

No correlation between the e.e. and the configuration of β-lactams and the structure of aminoalcohols was observed.

A Different Approach: Mukaiyama-Type Condensation

R= Me, Et, Pr-i, CH(Me)OTBS, OBn, $OSiR_3$, NBn_2, PhS

Chemically stable (SiO_2, temperature, water, LA)

Alkyl substituted derivatives are configurationally stable (E)-isomers

Heterosusbstituted derivatives isomerize when exposed to light

Configuration determined by 2D-NOESY NMR experiments

(E)-SKTA adopt pin-wheel conformation in solution

A Different Approach: Mukaiyama-Type Condensation

R	LA	Y%	trans : cis
Me	$TiCl_4$	81	96 : 4
Me	$BF_3{\cdot}OEt_2$	68	83 : 17
Me	$EtAlCl_2$	96	90 : 10
Me	$ZnCl_2$	44	90 : 10
Me	TBSOTf	88	90 : 10
Me	$Yb(OTf)_3$	68	78 : 22
Et	$TiCl_4$	63	94 : 6
Pr-i	$TiCl_4$	60	98 : 2
BnO	$TiCl_4$	66	79 : 21

Two obvious questions: a) enantioselective with a chiral LA? b) catalytic in LA?

Chiral LA promoted Mukaiyama-Type Condensation

LA	Y%	trans : cis	e.e.%trans	e.e.%cis
$BinolTiCl_2$	15	57 : 43	0	0
$TADDOLTiCl_2$	27	58 : 42	23	0
NME/BCl_3	86	58 : 42	50	24

A Catalytic One-Pot Synthesis of β-Lactams: Solvent Variation

Solvent	Y%	trans : cis
CH_2Cl_2	77	66 : 34
CH_3CN	63	97 : 3
CH_3CN*	62	95 : 5
CH_3NO_2	99	89 : 11
CH_3OH	58	77 : 23
CH_3NO_2[§]	22	-

* With a sample of $Yb(OTf)_3$ recovered from water during work-up

[§] Without catalyst

A Catalytic One-Pot Synthesis of β-Lactams: Imine Variation

R	Y%	trans : cis
Ph	63 (99)	97 : 3 (89 : 11)
Ph-CH=CH	27 (90)	98 : 2 (60 : 40)
2-Thienyl	29 (57)	96 : 4 (87 : 13)
C_6H_{11} - c	89 (-)	37 : 63 (-)
Bu - i	- (37)	- (63 : 37)

A Catalytic One-Pot Synthesis of β-Lactams: SKTA Variation

R	SKTA E : Z	Y%	trans : cis
Me	> 98 : 2	63	97 : 3
Et	> 98 : 2	62	95 : 5
Pr-i	> 98 : 2	16	>98 : 2
BnO	40 : 60	49	60 : 40
TBDPSO	90 : 10	21	40 : 60

Making Simple Things Simpler: A 3-Component Reaction

Solvent	$Yb(OTf)_3$	$MgSO_4$	Y%	trans : cis
CH_3CN	yes	yes	49	96 : 4
CH_3CN	yes	no	48	96 : 4
CH_3NO_2	yes	no	82	90 : 10
CH_3NO_2	no	no	8	-

Generality of the 3-Component Reaction

R	R	Y%	trans : cis
Me	Ph	82	90 : 10
Me	Ph-CH=CH	69	60 : 40
Me	2-Thienyl	54	83 : 17
Me	C_6H_{11}-c	90	40 : 60
Et	Ph	78	95 : 5
BnO	Ph	59	69 : 31

A Catalytic, 3-Component β-Lactam Synthesis on Solid Phase