The Ester Enolate–Imine Condensation Route to β-Lactams

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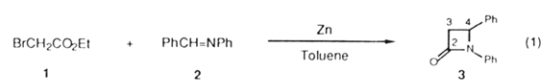
Contents

I. Introduction

The first preparation of a β-lactam was described in 1907 when Staudinger described the cycloaddition between ketenes and imines.[1] During the next four decades several other methods for preparing β-lactams were described. These included a communication by Gilman and Speeter in 1943 describing the preparation of 1,4-diphenyl-2-azetidinone (**3**) by condensation of the Reformatsky reagent derived from ethyl α-bromoacetate (**1**) with *N*-phenylbenzaldimine (**2**).[2] In spite of con-



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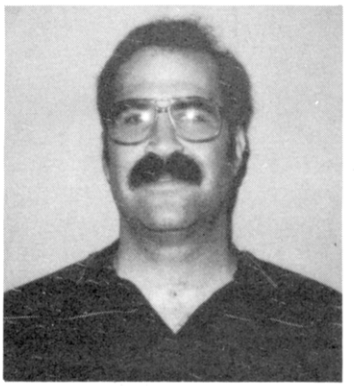
siderable interest in the area of β-lactam synthesis, stimulated by the structure elucidation of penicillin (**4**) in 1945 and cephalosporin C (**5**) in 1959, development of the ester–imine condensation was slow to occur.[3,4] One can only speculate as to why this was so, but a combination of factors comes to mind. For example, the ability of the synthetic chemist to manipulate the reactivity patterns of enolates has become sophisticated only within the last 20 years.[5] In addition, it was felt for some time that a sulfur substituent was needed at



David J. Hart was born in 1948 and grew up in Okemos, MI. He received his B.S. in 1972 from the University of Michigan and his Ph.D. in 1976 from the University of California at Berkeley, where he studied with William G. Dauben. He then spent 2 years as an NIH postdoctoral fellow in the laboratory of David A. Evans at the California Institute of Technology. He joined the faculty of The Ohio State University in 1978, where he is currently Professor of Chemistry. His research interests include natural product synthesis, free radical chemistry, stereochemical problems in synthesis, and the development of synthetic methods.

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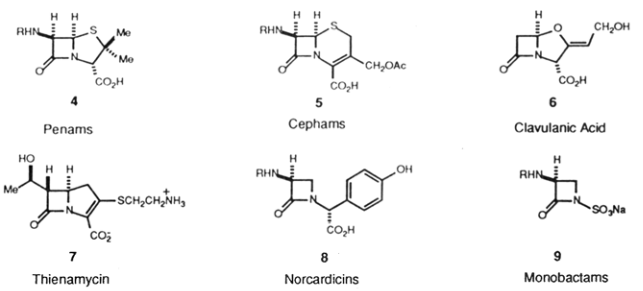

4 5 6 7 8 9

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C(4) of the β-lactam nucleus for potent antibiotic activity to be observed, and such compounds did not appear to be accessible via ester–imine condensations. This view changed in the 1970s, however, as analogue programs and the isolation of new potent β-lactam antibiotics (e.g., **6**–**9**) from fermentation broths revealed that C(4) sulfur substituents were unnecessary for activity.[6] Thus, it is probable that the development of enolate technology and the realization that β-lactams carrying C(4) alkyl substituents were pharmacologically interesting are responsible for the research activity that has surrounded ester–imine condensations during the past decade.

This article will provide a comprehensive review of the development of the one-pot ester–imine condensation route to β-lactams dating from the Gilman–Speeter communication in 1943.[2] The review will focus on the scope, limitations, and mechanism of the reaction, although selected applications to β-lactam antibiotic synthesis will also be presented. In addition, some space will be devoted to related two-step processes that involve initial generation of a β-amino ester followed by β-lactam generation in a second step.

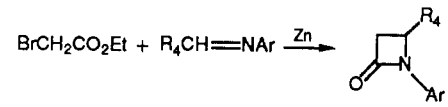
II. Early Studies with Zinc Enolates: Reformatsky Reagents

A. Scope and Limitations

Following the initial report of Gilman and Speeter, 15 years passed before studies exploring the generality of the ester–imine condensation route to β-lactams began to appear. A number of studies showed that ethyl α-bromoacetate would react with a variety of *N*-aryl nonenolizable aldimines to give good yields of 3,4-diaryl-2-azetidinones (Table I).[7-11] The use of ultrasound appears to increase yields relative to those obtained under standard Reformatsky conditions.[9] Although Gilman and Blicke[7] examined a few reactions between ethyl α-bromopropionate and aldimines, the stereochemical course of such reactions was first investigated by Kagan and Luche.[12,13] It was determined that the stereochemical course of reactions involving α-substituted acetates was a function of the solvent, α-substituent, and alkyl portion of the ester. The following general trends emerge from the data presented in Table II:[7,10-14] (1) When the α-substituent is an alkyl group (R_3 = Me, Et, *i*-Pr, Cy, *t*-Bu), the major product almost always has cis geometry. (2) The use of tetrahydrofuran as solvent renders the cis isomer the only product when the substituent is branched (R_3 = *i*-Pr, Cy, *t*-Bu). (3) In toluene, the type of ester (Me vs *i*-Pr) seems to have some effect on the partitioning between geometrical isomers, with the secondary ester favoring the trans geometrical isomer. Comparable studies in tetrahydrofuran were not performed. (4) The limited data available on phenyl acetates (R_3 = Ph) suggest that the trans isomer is favored regardless of solvent.

All the examples presented in Tables I and II afford β-lactams with aryl substituents on nitrogen and nonenolizable substituents on C(4). Although not well studied even to this day, it appears that enolizable and *N*-alkylaldimines can also be used in this process (Table III).[7,15-17] No information regarding the stereochemical course of these reactions is available.

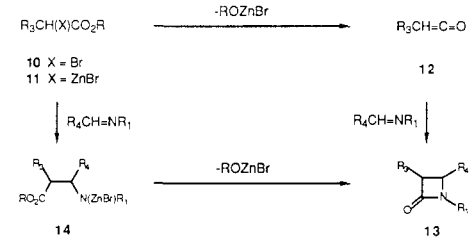
TABLE I. Reactions between Reformatsky Reagents from α-Bromoacetates and *N*-Arylaldimines



R_4	Ar	conditions[a]	% yield	ref
Ph	Ph	A	52–58	2, 7, 8
Ph	Ph	C	70	9
Ph	*p*-ClPh	A	54	8
Ph	*p*-BrPh	A	59	8
Ph	*p*-EtOPh	A	60	8
p-ClPh	Ph	A	64	8
p-ClPh	*p*-BrPh	A	57	8
p-ClPh	*p*-ClPh	A	63	8
o-ClPh	*p*-BrPh	A	68	8
p-MePh	*p*-MeOPh	C	95	9
Ph	*p*-MeOPh	C	82	9
p-ClPh	*p*-MeOPh	C	77	9
$C_5H_5FeC_5H_4$	Ph	B	57	10
$C_5H_5FeC_5H_4$	*p*-MeOPh	B	28	10
$C_5H_5FeC_5H_4$	*p*-EtOPh	B	43	10
$C_5H_5FeC_5H_4$	*p*-ClPh	B	5	10
$C_5H_5FeC_5H_4$	*p*-MePh	B	30	10
$C_5H_5FeC_5H_4$	$C_5H_5FeC_5H_4$	B	62	10
Ph	$C_5H_5FeC_5H_4$	B	66	10
$(CO)_3MnC_5H_4$	$C_5H_5FeC_5H_4$	B	62	10
$(CO)_3MnC_5H_4$	Ph	B	35	10
trans-PhCH=C(Me)	*p*-MeOPh	A	53	11

[a] Conditions: A = Zn, toluene, reflux. B = Zn, THF, reflux. C = Zn, dioxane, ultrasound, 25 °C.

SCHEME I



B. Mechanistic and Stereochemical Studies

Several mechanisms can be considered for the aforementioned reactions (Scheme I). For example, the initially formed Reformatsky reagent (**11**) could fragment to afford a ketene (**12**). A subsequent cycloaddition between the ketene and imine would afford a β-lactam (**13**). This is a variant of the mechanism originally proposed for the Staudinger β-lactam synthesis.[1,18] Alternatively, the Reformatsky reagent could add to the imine to afford a β-amido ester (**14**) followed by cyclization to afford **13**.

Several studies addressing these mechanistic possibilities have appeared. In a thorough series of experiments Gaudemar showed that "preformed" Reformatsky reagents reacted with *N*-arylaldimines to afford β-amino esters or β-lactams, depending on the reaction conditions (eq 2).[15,16,19,20] For example, treatment of Reformatsky reagent **15** with imine **2** at 20 °C for 3 h

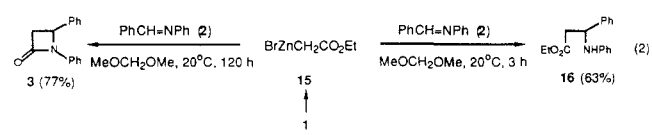
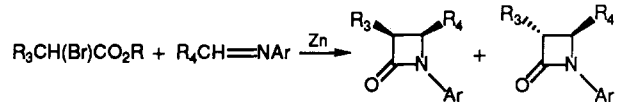


TABLE II. Reactions between Reformatsky Reagents from α-Substituted α-Bromoacetates and *N*-Arylaldimines

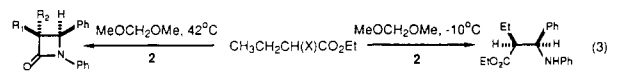


R_3	R	R_4	Ar	conditions[b]	% yield (cis:trans)	ref
Me	Me	Ph	Ph	A	75 (73:27)	12, 13
Me	*i*-Pr	Ph	Ph	A	>75 (66:34)	12, 13
Me	Me	Ph	Ph	B	94 (80:20)	12, 13
Me	Me	Ph	*p*-BrPh	B	90 (100:0)	12, 13
Me	Me	*trans*-PhC=C(Me)	*p*-MeOPh	A	50 (50:50)	11
Me	Et	$C_5H_5FeC_5H_4$	*p*-MeOPh	B	36 (—)	10
Me	Et	$C_5H_5FeC_5H_4$	*p*-EtOPh	B	34 (—)	10
Me	Et	$C_5H_5FeC_5H_4$	*p*-ClPh	B	31 (—)	10
Me	Et	$C_5H_5FeC_5H_4$	*p*-MePh	B	53 (—)	10
Me	Et	$C_5H_5FeC_5H_4$	*m*-MePh	B	33 (—)	10
Et	Me	Ph	Ph	A	94 (64:36)	13
Et	Me	Ph	Ph	B	96 (74:26)	13
Et	Me	Ph	Ph	C	94 (63:37)	13
Et	Me	*trans*-PhC=C(Me)	*p*-MeOPh	A	80 (80:20)	11
i-Pr	Me	Ph	Ph	A	98 (55:45)	13
i-Pr	*i*-Pr	Ph	Ph	A	93 (34:66)	13
i-Pr	Me	Ph	Ph	B	92 (100:0)	13
i-Pr	Me	Ph	Ph	C	98 (80:20)	13
i-Pr	Me	Ph	*p*-MePh	B	97 (100:0)	13
i-Pr	Me	Ph	*p*-ClPh	B	98 (100:0)	13
i-Pr	Me	Ph	*p*-BrPh	B	98 (100:0)	13
i-Pr	Me	Ph	*p*-BrPh	A	95 (—)	13
i-Pr	Me	*p*-MeOPh	Ph	A	70 (—)	13
Cy	Me	Ph	Ph	A	92 (45:55)	13
Cy	Me	Ph	Ph	B	96 (100:0)	13
Cy	Me	Ph	Ph	C	98 (75:25)	13
t-Bu	Me	Ph	Ph	A	71 (25:75)	13
t-Bu	*i*-Pr	Ph	Ph	A	95 (2:98)	13
t-Bu	Me	Ph	Ph	B	96 (100:0)	13
t-Bu	Me	Ph	*p*-BrPh	A	98 (—)	13
t-Bu	Me	Ph	*p*-BrPh	B	98 (100:0)	13
Ph	Me	Ph	Ph	A	>75 (5:95)	12, 13
Ph	Et	Ph	Ph	A	7 (—)	7
Et, CO_2Et[a]	Et	Ph	Ph	A	(—)	14

[a] Diethyl 2-ethylmalonate. [b] Conditions: A = Zn, toluene, reflux. B = Zn, THF, reflux. C = Zn, benzene–diethyl ether (1:1), reflux.

gave only ester **16** (63%). When the reaction was allowed to proceed for 120 h, β-lactam **3** (77%) was obtained. The same observations were recorded with *N*-alkylaldimines, although the onset of β-lactam formation took place at lower temperatures and shorter reaction times. These results were interpreted as evidence for a condensation–cyclization mechanism in which the cyclization was rate determining.

In a separate study, Gaudemar noted that the Reformatsky reagent derived from ethyl α-bromobutyrate (**18**) reacted with **2** at −10 °C in methylal to give erythro β-amino ester **19** (85%). The corresponding threo diastereomer was not observed. When the reaction was run at 42 °C, a 4:1 mixture of **20** and **21**, respectively, was obtained (eq 3).[19,20] Thus, the stereoisomer ratio

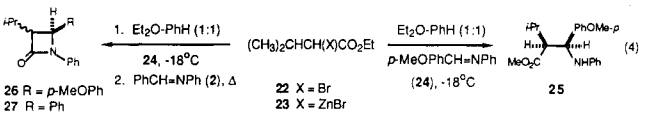


20 R_1 = Et R_2 = H
21 R_1 = H R_2 = Et

17 X = Br
18 X = ZnBr

19

observed in the β-lactams did not coincide with the observed kinetic ratio of β-amino ester diastereomers and some isomerization event was intervening. In a different study addressing this issue, Kagan and Luche showed that treatment of the "preformed" Reformatsky reagent **23** with imine **24** at −18 °C in ether–benzene (1:1) gave an 85% yield of β-amino ester **25**.[21] When *N*-phenylbenzaldimine (**2**) was added to the cold reaction mixture and the solution was brought to reflux, however, a mixture of four β-lactams (**26** and **27**) was obtained (eq 4). In conjunction with experiments that



26 R = *p*-MeOPh
27 R = Ph

22 X = Br
23 X = ZnBr

established the stability of the β-lactams to the reaction conditions,[12,22] these results were interpreted as evidence that the ester–imine condensation was reversible and suggested that the isomerization event might be associated with this process. These results, however, did not rule out the possibility that the isomerization was in part or totally due to base-catalyzed isomerization of **25** (**19**) or production of β-lactam via the ketene mechanism. The ketene mechanism was ruled out by the stereochemical study outlined in eq 5. Thus, pyrolysis of acetylene **28** in the presence of imine **2** gave only trans β-lactam **29** (78%), inconsistent with the stereochemical course of the corresponding ester–imine condensation. The stereochemical course of other presumed ketene–imine cycloadditions were consistent with this result.[23,24]

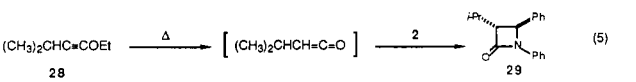


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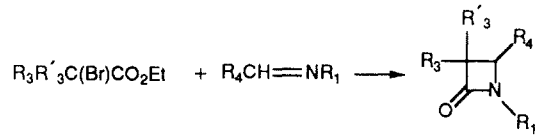
TABLE III. Reactions of Reformatsky Reagents with Enolizable Aldimines and *N*-Alkylaldimines



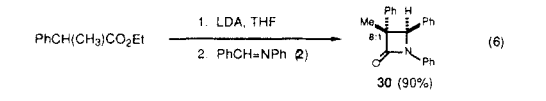
R_3	R'_3	R_4	R_1	conditions[a]	% yield[b]	ref
H	H	*i*-Pr	Me	A	34	15, 16
H	Et	*i*-Pr	Me	A	44	16
Me	Me	*i*-Pr	Me	A	52	16
H	H	*i*-Pr	*i*-Pr	A	58	16
H	Et	*i*-Pr	*i*-Pr	A	51	16
Me	Me	*i*-Pr	*i*-Pr	A	55	16
H	H	*i*-Pr	*n*-Bu	A	67	15, 16
H	H	Ph	*n*-Bu	A	60	16
H	H	Ph	Bn	A	20 (20)	16
H	Me	Ph	Bn	B	76	7
H	Et	Ph	Bn	A	20 (32)	16
Me	Me	Ph	Bn	A	15 (25)	16
Me	Me	Ph	Bn	B	84	7
H	H	Ph	Me	A	32 (15)	16
H	Et	Ph	Me	A	28 (12)	16
Me	Me	Ph	Me	A	31	16
Me	Me	Ph	Me	B	81	7
Me	Me	3,4,5-$(MeO)_3$Ph	Me	A	81	17
H	H	*i*-Pr	Ph	A	0 (48)	15
H	Et	*i*-Pr	Ph	A	0 (55)	16
Me	Me	*i*-Pr	Ph	A	0 (50)	16

[a] Conditions: A = Zn, MeOMe. B = Zn, toluene, reflux. [b] Yield in parentheses refers to β-amino ester byproduct [$R_4CH(NR_1)C(R_3)(R'_3)CO_2Et$].

III. Recent Developments: Studies with Lithium, Aluminum, Tin, Zirconium, and Boron Enolates

A. *N*-Aryl- and *N*-Alkylimines as the Azomethine Component

Following the studies from the Kagan and Gaudemar laboratories, this route to β-lactams lay dormant until Bergbreiter and Newcomb reported the reaction between lithium enolates of esters and imines in 1980.[25] It was shown that enolates derived from treatment of a variety of α,α-disubstituted acetates with lithium diisopropylamide (LDA) reacted with nonenolizable *N*-arylaldimines to afford β-lactams in good yields and in some cases with excellent diastereoselectivity (eq 6).



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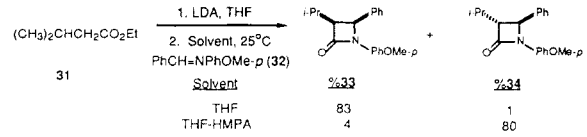
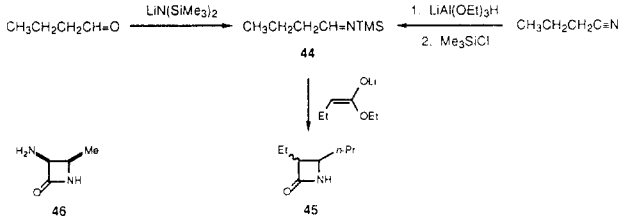


Solvent	%33	%34
THF	83	1
THF-HMPA	4	80

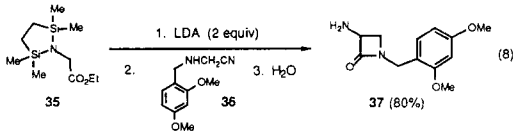
(7)

Because esters are more readily available than the corresponding α-bromo esters, this procedure can be more efficient than the Reformatsky route. A limitation of the procedure was that *N*-alkyl and enolizable aldimines failed to afford β-lactams. An additional limitation of the process appeared to be that reactions proceeded poorly when α-monoalkylated esters were used. It was later shown that some of these problems do not persist in all systems (vide infra).

SCHEME II



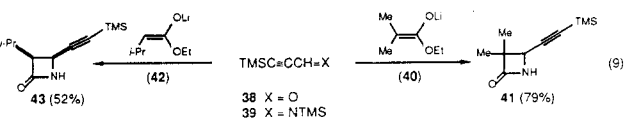
During the past decade, the scope of the lithium enolate condensation has been extended, and the following general statements are based on the data presented in Table IV:[25-29] (1) Conditions for incorporating heteroatomic, aromatic, and alkyl substituents at C(3) of the azetidinone have been developed. (2) Preparation of C(3)-unsubstituted azetidinones via this procedure is problematic and the Reformatsky route to such compounds is clearly superior. (3) When α-monosubstituted acetates are used, stereochemistry can frequently be controlled by appropriate choice of solvent. When tetrahydrofuran is the solvent, the stereochemical course of these reactions parallels that observed with the corresponding Reformatsky reagents (compare eq 4 and 7). Thus, treatment of the enolate of **31** with **32** in tetrahydrofuran affords **33**. When HMPA is added to the reaction mixture, **34** becomes the major stereoisomer (eq 7). In this case, it has been shown that HMPA merely increases the rate at which cis–trans isomerization occurs under the basic reaction conditions.[28] (4) *N*-Aryl- or *N*-alkylformaldimines, generated in situ from *N*-aryl- or *N*-alkyl-α-amino nitriles, can be used to prepare C(4)-unsubstituted β-lactams (**35** + **36** → **37**; eq 8).[26]



(8)

B. *N*-(Trialkylsilyl)imines as the Azomethine Component

Many routes to β-lactam antibiotics are designed to pass through N-unsubstituted β-lactam intermediates. A glance reveals that many of the nitrogen substituents of the imines used in Tables I–IV are not readily removable. Notable exceptions are *N*-*p*-methoxyphenyl and benzylic groups, which can be removed by using oxidative and reductive processes, respectively.[30,31] An alternative route to N-unsubstituted β-lactams was described in 1983 when it was discovered that *N*-(trimethylsilyl)imines would serve as the azomethine component.[32] For example, treatment of imine **39**, prepared from aldehyde **38** and lithium hexamethyldisilazide,[33] with the enolate derived from ethyl isobutyrate (**40**) gave **41** in 79% yield. The enolate of ethyl isovalerate (**42**) gave **43** (52%) along with 5% of the corresponding trans β-lactam (eq 9).[28a] Recent studies that extend

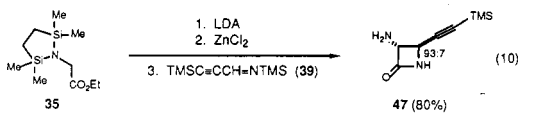


(9)

the scope of this process to include enolizable *N*-(trimethylsilyl)imines are shown in Scheme II.[34-36] Thus,

solutions of enolizable imine **44** were prepared from either *n*-butyronitrile or *n*-butyraldehyde. The preparation of **44** from the aldehyde is surprising on the surface, but the competitive addition of lithium hexamethyldisilazide to an enolizable aldehyde has precedent.[32] Treatment of **44** with the enolate of ethyl butyrate gave β-lactam **45** (28–40%) as a mixture of diastereomers. This method was also used to prepare monobactam precursor **46** in 40% yield.

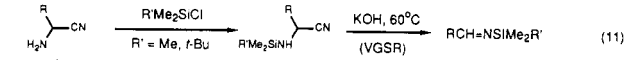
The reaction between zinc enolates of esters and *N*-(trimethylsilyl)imines has also been described (eq 10).[37] For example, treatment of the lithium enolate



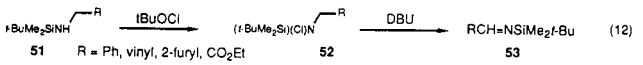
(10)

of **35** with zinc chloride in ether followed by imine **39** gave β-lactam **47** (80%) as a 93:7 mixture of trans and cis stereoisomers, respectively. This procedure was used to prepare a variety of 3-amino and 3-dimethylamino β-lactams in high yield, generally with high trans selectivity, as documented in Table V. This stereoselectivity complements the cis selectivity observed with the corresponding lithium enolates.

Although a few of the *N*-(trimethylsilyl)imines shown in Table V were purified prior to use, they were usually generated in situ and used in condensations without isolation. Two new procedures for the preparation and isolation of such imines have recently been described. Dehydrocyanation of *N*-(trialkylsilyl)-α-amino nitriles (**49**) with potassium hydroxide using vacuum gas–solid reaction techniques (VGSR) gave gram quantities of a variety of enolizable *N*-(trialkylsilyl)imines (**50**).[39] For example, imine **44** (**50**, where R = *n*-Pr, R′ = Me) was prepared in 69% yield (eq 11). These substances (**50**) were reported to undergo oligomerization at temperatures between −10 °C (R′ = Me) and −40 °C (R = *t*-Bu). Colvin recently described the preparation of nonenolizable *N*-(*tert*-butyldimethylsilyl)imines (**53**) by dehydrohalogenation of *N*-chloro-*N*-(*tert*-butyldimethylsilyl)amines (eq 12).[40] These procedures should eventually find use in β-lactam synthesis. Indeed, the use of imines of type **53** in a two-step route to β-lactams will be discussed below.



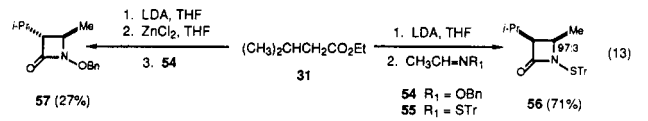
(11)



(12)

C. Other Azomethines

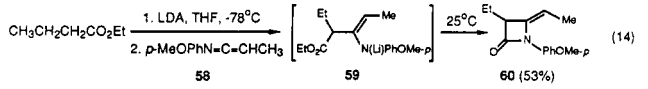
Other variants of the azomethine component of the title reaction have been studied. Oxime ethers and sulfenimines derived from enolizable and nonenolizable aldehydes react with both lithium and zinc enolates (Table VI).[41,42] Oxime ethers appear to be less electrophilic than the corresponding sulfenimines and the latter can be used with a broader spectrum of enolates. For example, the enolate of ethyl isovalerate fails to react with oxime ether **54** at room temperature in tetrahydrofuran as enolate fragmentation competes with azomethine addition. Under the same conditions, sulfenimine **55** gives β-lactam **56** (69%) and 2% of the corresponding trans isomer (eq 13). The corresponding



(13)

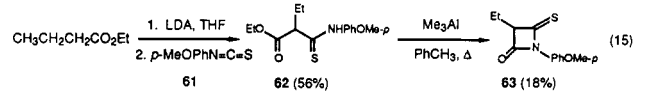
zinc enolate, however, does give a low yield of trans β-lactam **57** (27%) upon treatment with oxime ether **54**. Extension of this promising result to other enolates and oxime ethers, however, has not been extremely successful. Methods for removing both the *N*-benzyloxy and *N*-tritylsulfenyl groups from β-lactams of type **56** and **57** have been described.[42,43]

Azacumulenes have also been used as the azomethine component (Table VII).[44,45] Thus, treatment of the lithium enolate of ethyl butyrate with ketenimine **58** gives **60** (eq 14).[44] When the reaction was quenched



(14)

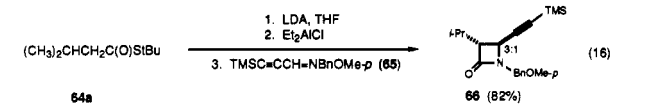
with aqueous acetic acid prior to warming to room temperature, ethyl 2-ethyl-3-oxopentanoate was obtained, demonstrating the intermediacy of metalated imine **59**. The observed *Z* stereoselectivity follows from the least hindered approach of the enolate to the ketenimine. Ester enolates also react with isothiocyanates (**61**) to afford malonic acid derivatives (**62**) that can be converted to 4-thiono-β-lactams (**63**) using trimethylaluminum[46] (eq 15).[45] A limitation of this method appears to be low yields in the cyclization when the intermediate malonate derivative is enolizable.



(15)

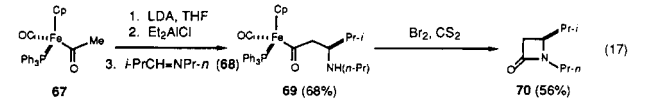
D. Other Enolates and Two-Step Sequences to β-Lactams

The condensation of imines with zinc enolates derived from lithium enolates was mentioned briefly above.[37,38] This method has been extended to aluminum enolates and may be particularly valuable when conducting condensations with enolizable *N*-alkylimines, a family of azomethines that does not generally give good yields of β-lactams in reactions with lithium enolates (Table VIII).[47,48] One example that involves the aluminum enolate derived from a thioester is outlined in eq 16 (**64a** + **65** → **66**).[48]



(16)

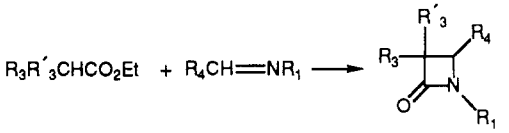
Some enolate–imine condensations do not directly afford β-lactams. In such cases, intermediate β-amino esters may be isolated and then converted to β-lactams in a second step. One relevant example that involves a metalated acyliron species[49–51] is shown in eq 17.[49] In



(17)

this case, the aluminum enolate derived from **67** affords (β-aminoacyl)iron species **69** (68%) with >20:1 diast-

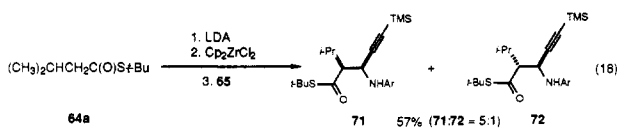
TABLE IV. Reactions of Lithium Enolates with *N*-Aryl- and *N*-Alkylaldimines



R	R_3	R'_3	R_4	R_1	conditions[a]	% yield (cis:trans)	ref
Et	Ph	OH	Ph	Ph	A	70 (0:100)	25
Et	Ph	Me	Ph	Ph	B	90 (11:89)	25
Et	Me	Me	Ph	Ph	B	75	25
Et	Me	Me	*p*-MeOPh	Ph	B	82	25
Et	Me	Me	*p*-ClPh	Ph	B	95	25
Et	Me	Me	Ph	*p*-MePh	B	84	25
Et	Me	Me	*p*-ClPh	*p*-MePh	B	80	25
Et	Me	Me	*p*-Me_2NPh	Ph	B	66	25
Et	Me	Me	2-furyl	Ph	B	67	25
Et	Me	Me	2-thienyl	Ph	B	89	25
Et	Me	Me	H	Ph	F	77	26
Et	Me	Me	H	Bn	F	66	26
Et	Me	Me	H	cyclohexyl	F	66	26
Et	Me	SPh	H	Bn	F	62	26
Et	$-(CH_2)_5-$		Ph	Ph	B	84	25
Et	$-(CH_2)_5-$		H	Bn	F	65	26
Et	$(CH_2)_3NCO_2$-*t*-Bu		H	2,4-$(MeO)_2$Bn	F	63	26
Et	PhCONH	Me	Ph	Ph	A	91 (0:100)	25
Et	BnOCONH	Me	H	2,4-$(MeO)_2$Bn	G	63	26
Et	*t*-BuOCONH	Me	H	2,4-$(MeO)_2$Bn	G	60	26
Et	*t*-BuOCONH	*i*-Pr	H	2,4-$(MeO)_2$Bn	G	45	26
Me	PhCONH	OMe	Ph	Ph	A	84 (100:0)	27
Me	PhCONH	OMe	Ph	1-naphthyl	A	88 (100:0)	27
Me	PhCONH	OMe	*p*-ClPh	Ph	A	91 (100:0)	27
Me	BnOCONH	OMe	Ph	1-naphthyl	A	84 (100:0)	27
Me	BnOCONH	OMe	*p*-ClPh	Ph	A	91 (100:0)	27
Et	BnOCONH	H	H	2,4-$(MeO)_2$Bn	G	74	26
Et	PhCONH	H	Ph	Ph	A	45 (0:100)	25
Et	Ph	H	Ph	Ph	B	35 (0:100)	25
Et	H	H	Ph	Ph	B	14	28a
Et	Me	H	Ph	Ph	B	47 (96:4)	28a
Et	Me	H	Ph	Ph	C	31 (31:69)	28a
Et	Me	H	Ph	Ph	D	30 (33:67)	28a
Et	Et	H	Ph	Ph	B	86 (80:20)	28a
Et	Et	H	Ph	Ph	C	47 (11:89)	28a
Et	Et	H	Ph	Ph	D	46 (11:89)	28a
Et	Et	H	*trans*-PhCH=CH	*p*-MeOPh	C	67 (15:85)	28b
Et	*i*-Pr	H	Ph	Ph	B	88 (99:1)	28a
Et	*i*-Pr	H	Ph	Ph	C	92 (5:95)	28a
Et	*i*-Pr	H	Ph	Ph	D	91 (5:95)	28a
Et	*i*-Pr	H	Ph	*p*-MeOPh	B	84 (97:3)	28a
Et	*i*-Pr	H	Ph	*p*-MeOPh	E	73 (56:44)	28a
Et	*i*-Pr	H	Ph	*p*-MeOPh	C	84 (5:95)	28a
Et	*i*-Pr	H	Ph	*p*-MeOPh	D	84 (6:96)	28a
Et	*i*-Pr	H	*trans*-PhCH=CH	*p*-MeOPh	C	78 (10:90)	28b
Et	*i*-Pr	H	(TMS)C≡C	*p*-MeOPh	B	71 (92:8)	28a
Et	Bn_2N	H	CF_3	*p*-MeOPh	B	69 (0:100)	29
Et	$[(Me_2SiCH_2)_2]N$	H	H	Bn	F	43	26
Et	$[(Me_2SiCH_2)_2]N$	H	H	2,4-$(MeO)_2$Bn	F	80	26
Et	$[(Me_2SiCH_2)_2]N$	H	H	2,5-$(MeO)_2$Bn	F	47	26

[a] Conditions (base, solvent, final temperature): A = LDA (2 equiv), THF, room temperature; B = LDA (1 equiv), THF, room temperature; C = LDA (1 equiv), HMPA–THF, room temperature; D = LDA in THF, add HMPA, room temperature; E = LDA, HMPA–THF, 0 °C; F = LDA, THF, (imine generated in situ from $R_4CH(CN)NHR_1$ and enolate:imine = 2:1); G = as conditions F only LHMDS used as base.

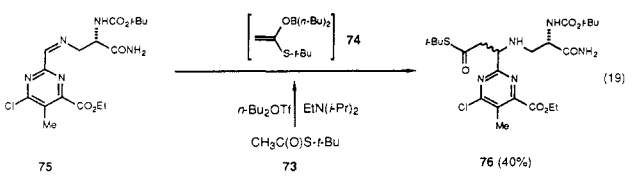
ereoselectivity. Oxidative conversion of **69** to β-lactam **70** was accomplished in 56% yield. The use of thioesters in the stepwise synthesis of β-lactams is illustrated in eq 18. For example, sequential treatment of



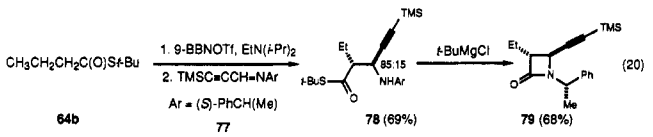
(18)

thioester **64a** with lithium diisopropylamide and bis(cyclopentadienyl)zirconium dichloride followed by imine **65** gave a 57% yield of β-amino thioesters **71** (syn) and **72** (anti) as a 5:1 mixture of stereoisomers, respectively.[48] Tin enolates derived from thioesters and stannous chloride give similar results (Table IX).[52]

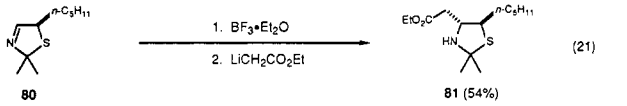
Condensations of imines with (vinyloxy)boranes derived from thioesters have also been reported.[53-55] For example, the reaction between **74** and **75** was used to prepare the pyrimidine portion (**76**) of bleomycin (eq 19).[53,54] The stereochemical course of (vinyloxy)bo-



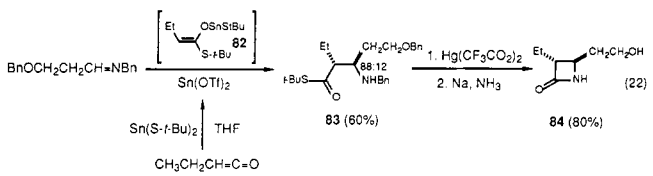
(19)



rane–imine condensations has been examined, and anti addition products are usually the major products, frequently with excellent diastereoselectivity (eq 20).[55a] Enolizable and nonenolizable *N*-alkyl- and *N*-arylaldimines have been used. The β-amino thioesters afford β-lactams upon treatment with *tert*-butylmagnesium chloride (**78** → **79**). A comparison of Tables VIII–X indicates that the boron chemistry complements the syn stereoselectivity usually observed in reactions between imines and related zinc, aluminum, zirconium, and tin enolates. In a process related to the aforementioned reactions of (vinyloxy)boranes, Volkmann showed that thiazolines precomplexed to boron trifluoride etherate would react with lithium enolates of esters to afford β-amino esters (eq 21).[56] This process has not been widely used but shows promise as the first step in a two-step route to β-lactams.

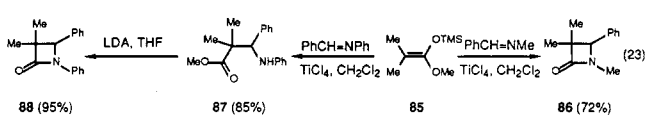


(Vinyloxy)stannanes derived from thioesters undergo stannous triflate catalyzed addition to imines to afford anti β-amino thioesters (eq 22 and Table X).[57] Thus,

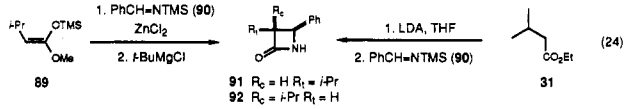


(vinyloxy)stannane **82** reacted with *N*-benzyl-β-(benzyloxy)propionaldimine to give **83** (60%) as an 88:12 mixture of anti and syn diastereomers, respectively. Conversion of **83** to β-lactam **84** was accomplished in 80% overall yield. It is notable that the stereochemical course of this condensation reaction differed from that reported for similar tin(II) enolates derived from lithium enolates (Table IX).

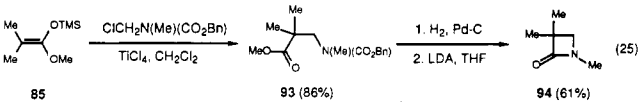
Equation 22 could be regarded as an acid-catalyzed reaction between a ketene acetal and an imine. Such reactions were introduced in 1977 when Ojima showed that *O*-alkyl-*O*-(trimethylsilyl)ketene acetals reacted with imines in the presence of titanium tetrachloride to afford β-lactams or β-amino esters (**85** → **86** or **87**), depending on the nature of the imine (eq 23).[58] *N*-



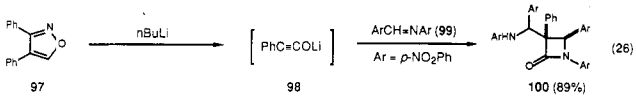
Alkylimines afforded β-lactams while *N*-arylimines gave β-amino esters. The β-amino esters were converted to β-lactams upon treatment with lithium diisopropylamide (**87** → **88**). This process has been extended to include oxime ethers[59] and *N*-(trimethylsilyl)imines[40,60] as the azomethine component and can be used with enolizable as well as nonenolizable azomethines. Zinc chloride has been used in place of titanium tetrachloride,[40,60] and trimethylsilyl triflate can also be used to catalyze such additions.[59,61] Modest stereoselectivity, usually favoring trans β-lactams (anti β-amino esters), is observed [**89** + **90** → **91** (56%) + **92** (12%)].[40] This complements the high cis selectivity observed in the corresponding reaction between the lithium enolate of **31** and **90** [**31** + **90** → **91** (1%) + **92** (84%)][28a] as shown in eq 24. Examples of Lewis acid mediated reactions between ketene acetals and azomethines are documented in Tables XI and XII.[58-63]



Ketene acetals have also been treated with iminium ions generated in situ as shown in eq 25.[64] The resulting β-amino esters can be converted to β-lactams by standard methodology (**85** → **93** → **94**). Additional examples are presented in Table XIII.[69,64-68]



In closing this section, we note that the reaction between lithium ynolates and imines has been briefly examined. Thus, ynolate **98** reacts with imine **99** to give 2:1 adduct **100** in 89% yield.[69] This process is interesting but limited to electron-deficient nonenolizable *N*-arylaldimines.

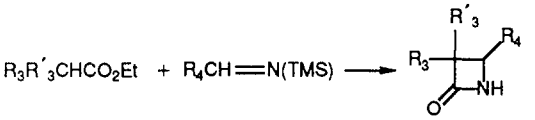


E. Mechanistic and Stereochemical Studies with Lithium Enolates

As with Reformatsky reagents, several mechanistic questions can be asked about the ester–azomethine condensations of lithium, aluminum, boron, zinc, tin, and zirconium enolates described above. On the basis of stereochemical studies alone, it is clear that ketenes are not intermediates in most or all of these reactions.[25,28a] It is probable that those reactions leading directly to β-lactams proceed by a two-step mechanism similar to that discussed in Scheme I. The issues of (1) the rate-determining step and (2) reversibility of the azomethine addition, however, have been well studied in only a few cases. These studies, all of which involve lithium enolates, will be described below.

Studies with β-amino esters **101** and **102** suggest that azomethine addition is the rate-determining step in many lithium enolate–imine condensations conducted in tetrahydrofuran. Thus, treatment of **101** and **102** with lithium diisopropylamide in tetrahydrofuran (−70 °C → room temperature) gave **33** and **34**, respectively, with no crossover in stereochemistry (Scheme III). The cyclizations even occurred to a certain extent when the reaction temperature was maintained at −70 °C. In addition, it was shown that enolate **42** did not react with **32** at −70 °C under conditions when some conversion of **101** (**102**) to **33** (**34**) was observed. These experiments demonstrate the kinetic competence of β-amido esters **103** and **104** to serve as intermediates in reactions affording β-lactams and suggest that, in this case, the azomethine addition is rate determining.[70] These re-

TABLE V. Reactions of Lithium and Zinc Enolates with *N*-(Trimethylsilyl)imines



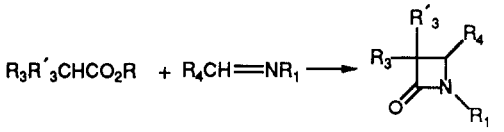
R_3	R'_3	R_4	conditions[a]	% yield	cis:trans	ref
Me	Me	Ph	A	72	(—)	32
Me	Me	*trans*-PhCH=CH	A	69	(—)	32
Me	Me	(TMS)C≡C	A	79	(—)	32
Me	Me	2-thienyl	D	45	(—)	35
Me	Me	Ph	E	57	(—)	34, 35
Me	Me	*trans*-PhCH=CH	E	20	(—)	34, 35
Me	Me	2-furyl	E	60	(—)	35
Me	Me	*i*-Pr	A	60	(—)	36
Me	Me	Et	A	40	(—)	36
Me	Me	Me_2C=CH	A	33	(—)	36
Me	PhS	Ph	A	58	29:71	32
Me	PhS	(TMS)C≡C	A	70	29:71	32
PhS	H	Ph	A	53	9:91	32
H	H	Ph	A	14	(—)	28
Me	H	Ph	A	44	93:7	28
Me	H	Ph	B	44	43:57	28
Me	H	Ph	C	38	71:29	28
Et	H	Ph	A	72	100:0	28
Et	H	Ph	B	64	44:56	28
Et	H	Ph	C	56	71:29	28
Et	H	*p*-MeOPh	D	68	89:11	35
Et	H	2-thienyl	E	50	50:50	34, 35
Et	H	2-furyl	E	56	70:30	34, 35
Et	H	*trans*-PhCH=CH	E	24	86:14	34
Et	H	*n*-Pr	E	40	50:50	34, 35
Et	H	*n*-Pr	A	28	72:28	36
Et	H	Me	A	38 (46)[b]	86:14 (78:22)[b]	36
Et	H	n-C_8H_{17}	A	44	92:8	36
Et	H	*i*-Pr	A	(29)[b]	(8:92)[b]	36
Et	H	Me_2C=CH	A	20	77:23	36
i-Pr	H	Ph	A	81	99:1	28
i-Pr	H	Ph	B	86	50:50	28
i-Pr	H	Ph	C	84	99:1	28
i-Pr	H	CH_2=CH	A	11	100:0	28
i-Pr	H	(TMS)C≡C	A	57	91:9	28
i-Pr	H	*trans*-PhSCH=CH	A	76	93:7	28
i-Pr	H	2-furyl	A	85	99:1	28
i-Pr	H	*p*-MeOPhC≡C	A	81	100:0	28
t-Bu	H	Ph	A	40	100:0	28
Me_2NCH_2	H	Ph	A	57	50:7	28
MeCH(SPh)CH_2	H	Ph	A	61	100:0[e]	28
MeC=CH_2	H	Ph	A	42	0:100	28
MeC=CH_2	H	2-furyl	D	30	10:90	35
$[(Me_2SiCH_2)_2]N$	H	2-furyl	E	43[c]	95:5	34, 35
$[(Me_2SiCH_2)_2]N$	H	2-thienyl	D	35[d]	90:10	35
$[(Me_2SiCH_2)_2]N$	H	Me	A	40[d]	90:10	36
$[(Me_2SiCH_2)_2]N$	H	Et	A	57[d]	90:10	36
$[(Me_2SiCH_2)_2]N$	H	*i*-Pr	A	28[d]	90:10	36
$[(Me_2SiCH_2)_2]N$	H	Ph	F	90	30:70	37
$[(Me_2SiCH_2)_2]N$	H	(TMS)C≡C	F	80	7:93	37
$(Me_3Si)_2N$	H	Ph	F	70	11:89	37
Bn_2N	H	Me	A	36	95:5	36
Et_2N	H	Ph	F	95	0:100	38
Et_2N	H	PhC≡C	F	98	0:100	38
Et_2N	H	(TMS)C≡C	F	97	0:100	38

[a] Conditions (preparation of R_4CH=N(TMS), base, solvent, final temperature): A = RCHO + $LiN(TMS)_2$, LDA, THF, room temperature; B = RCHO + $LiN(TMS)_2$, LDA, THF–HMPA, room temperature; C = RCHO + $LiN(TMS)_2$, LDA in THF, add HMPA, room temperature; D = RC≡N + Red-Al followed by Me_3SiCl, LDA, THF, room temperature; E = RC≡N + $LiAl(OEt)_3H$ followed by Me_3SiCl, LDA, THF, room temperature; F = RCHO + $LiN(TMS)_2$, LDA in Et_2O, then add $ZnCl_2$ in Et_2O, reflux; G = RCHO + $LiN(TMS)_2$, LDA in PhH, add $ZnCl_2$, reflux. [b] Yield (ratio) in parentheses refers to reaction using *tert*-butyl butyrate. [c] β-Lactam isolated as R_3 = NH_2. [d] β-Lactam isolated as R_3 = $NHCO_2Bn$. [e] 1:1 mixture of diastereomers at stereogenic center in R_3.

sults are not surprising since it had been known that (1) magnesium amides derived from diastereomeric β-amino esters cyclize without loss of stereochemistry[15,21] and (2) stereochemically undefined β-amino esters give β-lactams upon treatment with lithium diisopropylamide.[58,62] Nonetheless, these results define one difference between lithium and zinc enolates. A recent study suggests that care must be taken in extrapolating these results to other solvent systems.[71]

Although it is clear that enolate geometry should affect the stereochemical course of ester–imine condensations, this issue was not experimentally addressed until 1984.[28a] In a detailed study using aliphatic ester enolates and imines **2**, **32**, and **90**, it was demonstrated

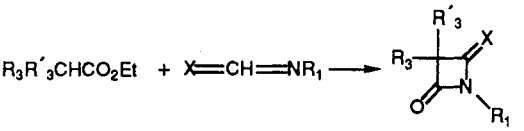
TABLE VI. Reactions of Lithium and Zinc Enolates with Oxime Ethers and Sulfenimines



R	R_3	R'_3	R_4	R_1	conditions[a]	% yield (cis:trans)	ref
Me	Me	Me	H	OBn	A	67	41
Me	Me	Me	Me	OBn	A	48	41
Me	Me	Me	Et	OBn	A	40	41
Et	Me	Me	Ph	SPh	A	35 (19)[b]	42
Et	Me	Me	Ph	STr	A	87	42
Et	Me	Me	Me	STr	A	76 (97:3)	42
Me	Ph	Me	H	OBn	A	82	41
Me	$-(CH_2)_4-$		H	OBn	A	40	41
Me	$-(CH_2)_5-$		H	OBn	A	65	41
Et	*i*-Pr	H	Ph	SPh	A	37 (30)[b]	42
Et	*i*-Pr	H	Ph	STr	A	70 (82:18)	42
Et	*i*-Pr	H	Me	SPh	A	8 (—)[b]	42
Et	*i*-Pr	H	Me	STr	A	71 (97:3)	42
Et	*i*-Pr	H	Me	OBn	A	0[c]	42
Et	*i*-Pr	H	Me	OBn	B or C	27 (0:100)	42
Et	$[(Me_2SiCH_2)_2]N$	H	Me	STr	A	78 (83:17)[d]	42

[a] Conditions (base, solvent, final temperature): A = LDA, THF, room temperature; B = LDA, add $ZnCl_2$ in THF, room temperature; C = Zn with ethyl 2-bromoisovalerate, THF, room temperature. [b] The β-lactam was isolated as R_1 = H. The yield in parentheses refers to α-phenylsulfenylated ester byproduct. [c] A 50% yield of ethyl 5-methyl-3-oxo-2-isopropylhexanoate was obtained. [d] The β-lactam was isolated as $R_3 = NH_2$.

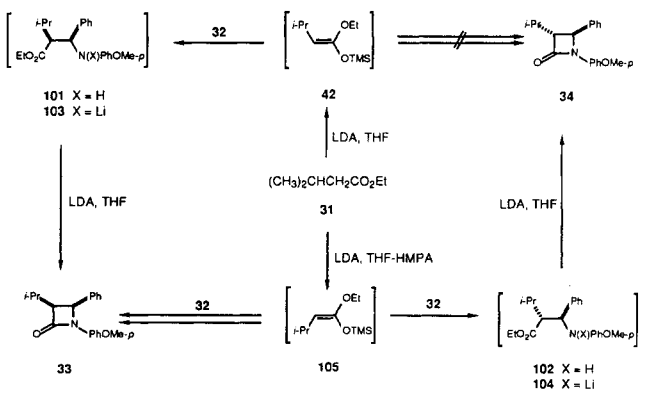
TABLE VII. Reactions of Lithium Enolates with Ketenimines, Isothiocyanates, and Isocyanates



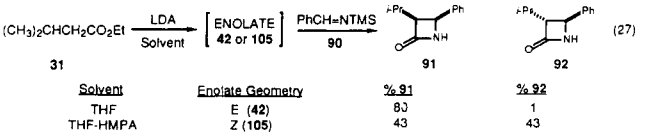
R_3	R'_3	X	R_1	conditions[a]	% yield	ref
Me	Me	CHMe	*p*-MeOPh	A	82	44
Me	Me	CHMe	cyclohexyl	A	98	44
Me	Me	S	*p*-MeOPh	B	80 (94)[b]	45
Me	Me	O	*p*-MeOPh	C	10 (40)[b]	45
Et	Me	CHMe	*p*-MeOPh	A	61	44
Et	Me	S	*p*-MeOPh	B	46 (64)[b]	45
Et	H	CHMe	*p*-MeOPh	A	53	44
Et	H	Ph	*p*-MeOPh	A	16	44
Et	H	Ph	cyclohexyl	A	54	44
Et	H	S	*p*-MeOPh	C	10 (50)[b]	45
$MeC{=}CH_2$	H	CHMe	*p*-MeOPh	A	32	44
$MeC{=}CH_2$	H	S	*p*-MeOPh	B	17 (68)[b]	45
$[(Me_2SiCH_2)_2]N$	H	CHMe	*p*-MeOPh	A	34	44
$[(Me_2SiCH_2)_2]N$	H	Ph	*p*-MeOPh	A	45	44
$[(Me_2SiCH_2)_2]N$	H	Ph	cyclohexyl	A	41	44

[a] Conditions (base, solvent, final temperature): A = LDA, THF, room temperature; B = (1) LDA, THF, room temperature, (2) Et_3Al, toluene, Δ; C = (1) LTMP, THF, room temperature, (2) Me_3Al, toluene, Δ. [b] All 4-alkylidene-β-lactams have *Z* geometry. Yields for two-step procedures involving isocyanates and isothiocyanates are overall yields. Yields of intermediate β-dicarbonyl compounds are in parentheses.

SCHEME III

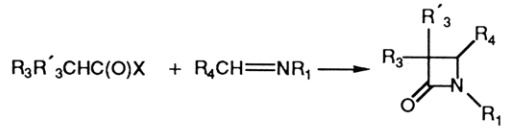


that (*E*)-enolates afford β-lactams with high diastereoselectivity while (*Z*)-enolates show little stereoselectivity. For example, sequential treatment of **31** with lithium diisopropylamide and **32** in tetrahydrofuran gave **33** (82%) and **34** (2%). A solution containing predominantly the (*Z*)-enolate of **31** (**105**) gave both **33** (41%) and **34** (32%) when the reaction was conducted at 0 °C. Similar results were obtained in the reactions of **42** and **105** with *N*-(trimethylsilyl)imine **90** (eq 27).[28a]



Solvent	Enolate Geometry	% 91	% 92
THF	E (**42**)	80	1
THF-HMPA	Z (**105**)	43	43

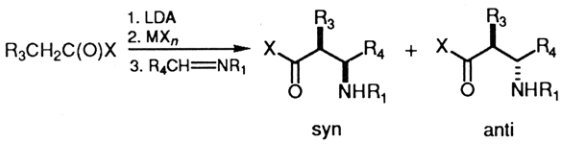
TABLE VIII. Reactions of Zinc and Aluminum Enolates (from Lithium Enolates) with *N*-Aryl- and *N*-Alkylaldimines



X	R_3	R'_3	R_4	R_1	conditions[a]	% yield (cis:trans)	ref
OMe	Me	Me	*n*-Pr	Bn	A	95	47
OMe	Me	Me	*n*-Pr	$BnCH_2$	A	61	47
S-*t*-Bu	Me	H	(TMS)C≡C	*p*-MeOBn	A	78 (20:80)	48
OEt	Me	H	*n*-Pr	Bn	A	69 (76:24)	47
OEt	Me	H	*n*-Pr	$BnCH_2$	A	81 (60:40)	47
OEt	Me	H	*i*-Pr	Bn	A	82 (83:17)	47
S-*t*-Bu	Et	H	(TMS)C≡C	*p*-MeOBn	A	82 (25:75)	48
OEt	*i*-Pr	H	*n*-Pr	Bn	A	50 (90:10)	47
S-*t*-Bu	*i*-Pr	H	(TMS)C≡C	*p*-MeOBn	A	73 (87:13)	48
OEt	H	H	*n*-Pr	$BnCH_2$	A	87	47
OEt	Et_2N	H	Ph	Me	B	95 (0:100)	38
OEt	Et_2N	H	Ph	Bn	B	98 (0:100)	38
OEt	$(Me_3Si)_2N$	H	Ph	Me	B	75 (0:100)	37
OEt	$[(Me_2SiCH_2)_2]N$	H	Ph	Bn	B	97 (0:100)	37
OEt	$[(Me_2SiCH_2)_2]N$	H	Ph	Me	B	98 (8:92)	37

[a] Conditions (base, solvent, final temperature): A = LDA, add Me_2AlCl in THF, room temperature; B = LDA, add $ZnCl_2$ in Et_2O, room temperature.

TABLE IX. Reactions of Acyliron and Thioester Enolates with *N*-Aryl- and *N*-Alkylaldimines



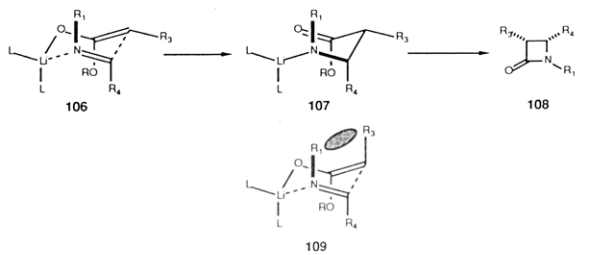
X[a]	R_3	R_4	R_1	MX_n (solvent)	% yield	syn:anti[d]	ref
L_3Fe	H	Ph	Ph	(THF)[b]	(—)	98:2 (*SS*:*SR*)	51
L_3Fe	H	Ph	Ph	(THF)[b]	79	93:7 (*SS*:*SR*)	50
L_3Fe	H	Ph	Ph	Et_2AlCl (THF)	55	85:15 (*SS*:*SR*) [80]	49
L_3Fe	H	Ph	*n*-Pr	Et_2AlCl (THF)	80	95:5 (*SS*:*SR*) [82]	49, 50
L_3Fe	H	*i*-Pr	*n*-Pr	Et_2AlCl (THF)	68	95:5 (*SS*:*SR*) [56]	49, 50
L_3Fe	H	Ph	Cy	Et_2AlCl (THF)	54	95:5 (*SS*:*SR*) [66]	49, 50
L_3Fe	H	*i*-Pr	Cy	Et_2AlCl (THF)	57	95:5 (*SS*:*SR*)	49, 50
L_3Fe	H	Ph	Bn	Et_2AlCl (THF)	75	96:4 (*SS*:*SR*)	50
L_3Fe	H	Et	Bn	Et_2AlCl (THF)	36	93:7 (*SS*:*SR*)	49
L_3Fe	H	*trans*-*n*-PrCH=CH	*p*-MeOPh	Et_2AlCl (THF)	68	56:44 (*SS*:*SR*)	49, 50
L_3Fe	H	*trans*-PhCH=CH	*n*-Pr	Et_2AlCl (THF)	44	71:29 (*SS*:*SR*)	49, 50
L_3Fe	H	*trans*-PhCH=C(Me)	*n*-Pr	Et_2AlCl (THF)	53	92:8 (*SS*:*SR*) [62]	49, 50
L_3Fe	H	*trans*-EtCH=C(Me)	*n*-Pr	Et_2AlCl (THF)	37	95:5 (*SS*:*SR*)	49, 50
S-*t*-Bu	Me	(TMS)C≡C	*p*-MeOBn	Cp_2ZrCl_2 (THF–hexane)	58	80:20	48
S-*t*-Bu	Et	(TMS)C≡C	*p*-MeOBn	Cp_2ZrCl_2 (THF–hexane)	57	83:17	48
S-*t*-Bu	*i*-Pr	(TMS)C≡C	*p*-MeOBn	Cp_2ZrCl_2 (THF–hexane)	43	95:5	48
S-*t*-Bu	Me	CO_2Et	CH_2(2-furyl)	$SnCl_2$ (Et_2O)[c]	72	95:5	52
S-*t*-Bu	Et	CO_2Et	CH_2(2-furyl)	$SnCl_2$ (Et_2O)	61	95:5	52
S-*t*-Bu	*i*-Pr	CO_2Et	CH_2(2-furyl)	$SnCl_2$ (Et_2O)	60	95:5	52
S-*t*-Bu	Ph	CO_2Et	CH_2(2-furyl)	$SnCl_2$ (Et_2O)	68	93:7	52

[a] L_3 = (*S*)-(Cp)(CO)(Ph_3P). [b] Lithium enolate. [c] When other solvents (THF, DME, CH_2Cl_2, PhMe) were used, β-amino esters were obtained with reduced diastereoselectivity. [d] Reactions where X = L_3Fe were run with racemic acyliron species. Syn:anti ratios refer to the relative ratios of [*SS* + *RR*] to [*SR* + *RS*] diastereomers. Several of the (β-aminoacyl)iron products were converted to β-lactams using procedures similar to that described in eq 17 in the yields shown in brackets.

These facts are consistent with transition-state models for ester–imine condensations discussed by Evans.[72] Thus, addition of an (*E*)-enolate to an (*E*)-imine via a chair-like transition state (**106**) should afford a cis β-lactam as observed (Scheme IV). The lack of selectivity with (*Z*)-enolates could be attributed to an additional steric interaction in hypothetical transition state **109**. Although this model has predictive value, it obviously does not take into account the aggregation state of the enolate. As with related aldol condensations, this proposal awaits experimental scrutiny.[73]

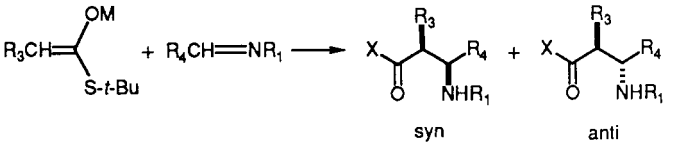
In addition to the kinetic diastereoselection issues discussed above, it is necessary to consider the ease with

SCHEME IV



which the product β-lactams isomerize under the basic reaction conditions. This appears to be a function of

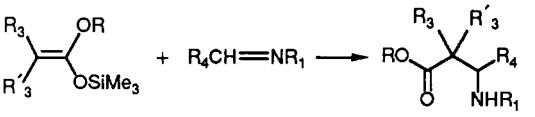
TABLE X. Reactions of Boron and Tin Enolates of Thioesters with *N*-Aryl- and *N*-Alkylaldimines



M[a,b]	R_3	R_4	R_1	conditions[c]	% yield	syn:anti	ref
n-Bu_2B	H	Ph	Bn	A	80 (26, 33, 35)[d]	(—)	54
n-Bu_2B	H	*trans*-PhCH=CH	Bn	A	63	(—)	54
n-Bu_2B	H	Ph	CH_2CO_2Me	A	52	(—)	54
n-Bu_2B	H	Ph	$CH_2CH_2CO_2Me$	A	86	(—)	54
n-Bu_2B	H	Et	Bn	A	43	(—)	54
n-Bu_2B	H	*i*-Pr	Bn	A	45	(—)	54
9-BBN	Me	$BnOCH_2CH_2$	Bn	B	73[e]	14:86 (89)[f]	55b
9-BBN	*i*-Pr	$BnOCH_2CH_2$	Bn	B	36[e]	10:90 (88)[f]	55b
9-BBN	Et	(TMS)C≡C	(*S*)-PhCH(Me)	C	69	15:85 (68)[g]	55a
SnS-*t*-Bu	Me	Bn	Ph	D	42	27:73	57
SnS-*t*-Bu	Me	Ph	Ph	D	59	42:58	57
SnS-*t*-Bu	Me	Ph_2CH	Ph	D	89	4:96	57
SnS-*t*-Bu	Me	Ph	Bn	D	89	4:96	57
SnS-*t*-Bu	Me	*trans*-PhCH=CH	Bn	D	60	19:81	57
SnS-*t*-Bu	Me	*trans*-PhCH=CH	Bn	E	55	16:84	57
SnS-*t*-Bu	Me	*i*-Pr	Bn	D	83	8:92	57
SnS-*t*-Bu	Me	$BnCH_2$	Bn	D	65	8:92	57

[a] Boron enolates were generated from the appropriate thioester (R_2BOTf, *i*-Pr_2NEt, CH_2Cl_2) and used directly in condensations. [b] Tin enolates were generated by treating methylketene with $Sn(S\text{-}t\text{-}Bu)_2$ in THF and used directly in condensations. [c] Conditions (solvent, final temperature, workup): A = Et_2O, room temperature, $NaOH\text{–}H_2O_2$; B = CH_2Cl_2, room temperature, HCl–MeOH–Et_2O, then KOH: C = CH_2Cl_2, room temperature, HCl–Et_2O–MeOH; D = THF with catalytic $Sn(OTf)_2$, room temperature, H_2O; E = THF with catalytic $SnBr_2$, room temperature, H_2O. [d] Yields in parentheses refer to reactions run in toluene, dichloromethane, and THF, respectively. [e] Isolated as carboxylic acids (X = OH). [f] Stereoisomer analysis performed after conversion to β-lactams [Ph_3P, $(PyS)_2$, CH_3CN]; yield in parentheses. [g] Major isomer was converted to a β-lactam (*t*-BuMgCl); yield in parentheses.

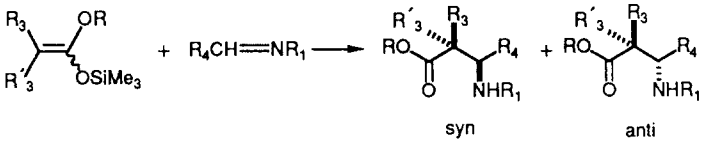
TABLE XI. Reactions of Ketene Acetals with *N*-Aryl- and *N*-Alkylaldimines



R	R_3	R'_3	R_4	R_1	conditions[a]	% yield	ref
Me	Me	Me	Ph	Me	A	(72)[b]	58
Me	Me	Me	*i*-Pr	Bn	A	(43)[b]	58
Me	Me	Me	Et	PhCH(Me)	A	(54)[b]	58
Me	Me	Me	Ph	Ph	A	85 (95)[c]	58
Me	Me	Me	Ph	Bn	A	92 (77)[c]	58
Me	$-(CH_2)_5-$		Ph	Ph	A	70 (91)[c]	59
Me	Me	Me	2-furyl	Ph	A	62 (84)[c]	62
Me	Me	Me	2-thienyl	Ph	A	54 (79)[c]	62
Me	Me	Me	2-pyridyl	Ph	A	81 (91)[c]	62
Me	Me	Me	Ph	3,4-Cl_2Ph	A	86 (98)[c]	62
Me	Me	Me	H	OBn	B	89	59
Me	Me	Me	Me	OBn	C	52	59
Me	$-(CH_2)_5-$		H	OBn	B	95	59
Me	Me	H	H	OBn	B	76	59
Me	Ph	H	H	OBn	B	93	59
Me	PhO	H	H	OBn	B	88	59
Me	$(CH_2{=}CHCH_2)_2N$	H	H	OBn	B	52	59
Me	H	H	H	OBn	B	42	59
Me	H	H	Me	OBn	C	61	59
$SiMe_3$	Me	Me	Ph	Ph	A	(75)[b]	63
$SiMe_3$	Me	Me	*i*-Pr	Ph	A	(66)[b]	63
$SiMe_3$	$-(CH_2)_5-$		Ph	Ph	A	(60)[b]	63
Me	Me	Me	Ph	$SiMe_3$	D	(75)[d]	40, 60
Me	Me	Me	2-furyl	$SiMe_3$	D	(76)[d]	40, 60
Me	Me	Me	PhC≡C	$SiMe_3$	D	(78)[d]	40, 60
Me	Me	Me	*trans*-PhCH=CH	$SiMe_3$	D	(77)[d]	40, 60
Me	Me	Me	CO_2Et	*t*-$BuMe_2Si$	E	71 (85)[e]	60
Me	H	H	Ph	$SiMe_3$	D	(27)[f]	40, 60

[a] Conditions (Lewis acid, solvent): A = $TiCl_4$, CH_2Cl_2; B = (TMS)OTf (0.1 equiv), CH_2Cl_2; C = (TMS)OTf (0.1 equiv), CH_3CN; D = ZnI_2, Et_2O–*t*-BuOH; E = (TMS)OTf, CH_2Cl_2. [b] Reaction gave β-lactam in yield shown in parentheses. [c] β-Amino ester was converted to β-lactam upon treatment with LDA in yield shown in parentheses. [d] Addition of *t*-BuMgCl to reaction mixture converted crude β-amino ester to β-lactam in yield shown in parentheses. [e] β-Amino ester was converted β-lactam upon treatment with MeMgBr in yield shown in parentheses. [f] *O*-Methyl *O*-*tert*-butyldimethylsilyl ketene acetal used as starting material.

TABLE XII. Stereoselective Reactions of Ketene Acetal with *N*-Aryl- and *N*-Alkylaldimines



R	R_3	R'_3	R_4	R_1	conditions[a]	% yield[b]	ref
Me	PhO	Me	Ph	Ph	A	98 [92][c]	62
Et	PhS	Me	Ph	Ph	A	82 [98][c]	62
Et	PhS	Me	2-furyl	Ph	A	91 [84][c]	62
Et	PhS	Me	2-thienyl	Ph	A	90 [93][c]	62
Me	PhO	Me	2-furyl	Ph	A	92 [97][c]	62
Me	PhO	Me	2-thienyl	Ph	A	99 [90][c]	62
Me	Me	H	Ph	Ph	A	83 [90][c]	58
Me	PhO	H	Ph	Ph	A	72 [87][c]	62
$SiMe_3$	Ph	H	Ph	Ph	A	[69][d]	63
$SiMe_3$	Ph	H	*i*-Pr	Ph	A	[65][d]	63
Me	PhO	H	2-furyl	$SiMe_3$	B	[58] (63:37)[e]	40, 60
Me	Et	H	Ph	$SiMe_3$	B	[61] (10:90)[e]	40, 60
Me	Me	H	PhC≡C	$SiMe_3$	B	[82] (25:75)[e]	40, 60
Me	Me	H	(TMS)C≡C	$SiMe_3$	B	[62] (40:60)[e]	40, 60
Me	Ph	H	(TMS)C≡C	$SiMe_3$	B	[53] (7:93)[e]	40, 60
Me	Me	H	Ph	*t*-$BuMe_2Si$	B	[43] (15:85)[f]	60
Me	Me	H	2-furyl	*t*-$BuMe_2Si$	B	[49] (25:75)[g]	60
Me	Et	H	2-furyl	$SiMe_3$	B	[66] (33:67)[e]	60
Me	Et	H	(TMS)C≡C	$SiMe_3$	B	[44] (30:70)[e]	60
Me	*i*-Pr	H	Ph	$SiMe_3$	B	[68] (17:83)[e]	60
Me	Ph(*E*:*Z* = 1:2)	H	Ph	Ph	C	85 (14:86)	61
Me	Ph	H	*t*-$BuMe_2SiC$≡C	*p*-MeOPh	C	69 (44:56)	61
Me	Ph	H	*trans*-PhCH=CH	*p*-MeOPh	C	20 (—)	61
Me	Ph	H	*trans*-PhCH=CH	*p*-MeOPh	D	30 (—)	61
Me	Ph	H	*trans*-PhCH=CH	*p*-MeOPh	D	20 (—)	61
Me	Ph	H	*trans*-PhCH=CH	*p*-MeOPh	D	45 (15:85)	61
Me	Ph	H	*trans*-PhCH=CH	*p*-MeOPh	D	78 (15:85)	61
Me	Me (*E*:*Z* = 3:1)	H	Ph	Ph	C	85 (0:100)	61
Me	Me	H	*t*-$BuMe_2SiC$≡C	*p*-MeOPh	C	65 (37:63)	61

[a] Conditions (Lewis acid, solvent): A = $TiCl_4$, CH_2Cl_2; B = ZnI_2, Et_2O–*t*-BuOH; C = (TMS)OTf (0.1 equiv), CH_2Cl_2; D = (TMS)OTf (0.1 equiv), THF. [b] Numbers in brackets refer to yields of β-lactams. Numbers in parentheses refer to syn:anti (cis:trans) ratios where known. [c] β-Amino ester was converted to β-lactam upon treatment with LDA. [d] Reaction directly gave β-lactam. [e] Addition of *t*-BuMgCl to reaction mixture gave β-lactam (R_1 = H). [f] Addition of *t*-BuMgCl to reaction mixture gave β-lactam (R_1 = *t*-$BuMe_2Si$). A 12% yield of β-lactam (R_1 = H) was also obtained. [g] Addition of *t*-BuMgCl to reaction mixture gave β-lactam (R_1 = *t*-$BuMe_2Si$). A 24% yield of β-lactam (R_1 = H) was also obtained.

the nitrogen and C(3) substituents and the reaction medium. A glance at the tables and some experimental evidence[28a] suggest the following trends in reactions using lithium enolates: (1) *N*-aryl β-lactams isomerize more easily than *N*-protio or *N*-trialkylsilyl β-lactams. (2) Substituents at C(3) that enhance acidity render β-lactams more susceptible to isomerization. (3) The smaller the C(3) substituent, the faster the rate of isomerization. (4) The more polar the solvent (THF vs THF–HMPA), the faster the rate of isomerization.

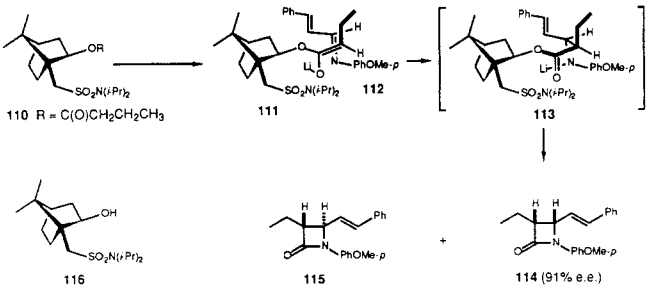
In closing this section, we note that the influence of azomethine geometry on the course of ester–imine condensations has not been addressed. For example, it would be interesting to examine the stereochemical course of enolate–cyclic imine condensations.

IV. Asymmetric Synthesis

A. Chiral Esters

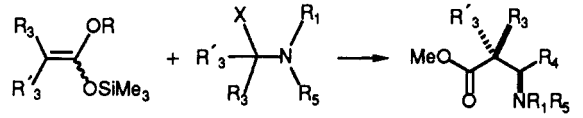
The first attempts to prepare optically active β-lactams using ester–imine condensations were reported by Kagan and Luche. They examined Reformatsky reactions between menthyl α-bromoacetate, α-bromopropionate, and α-bromoisovalerate and imine **2** and obtained racemic products.[13] This discouraging result was duplicated by Furukawa, who reported three reactions that gave β-lactams with 2–5% enantiomeric

SCHEME V



excess (ee).[74] In 1980 Bergbreiter and Newcomb examined lithium enolates derived from menthyl esters and were able to obtain β-lactams with up to 60% ee in reactions with **2**, although the sense of asymmetric induction was not determined (Table XIV).[25] The use of sodium enolates was described shortly thereafter.[75] The first examples of asymmetric induction using lithium enolates of α-monosubstituted esters were reported in 1986.[76–78] For example, the presumed (*E*)-enolate derived from **110** reacts with cinnamaldimine **112** to give β-lactams **114** (74%) and **115** (7%) along with a 95% yield of chiral auxiliary **116** (Scheme V).[76] The major product was formed with 91% ee and the absolute configuration of the major enantiomer was established by correlation with the β-lactam antibiotic PS-5 (vide infra). One rationale for the observed ste-

TABLE XIII. Reactions of Ketene Acetals with Iminium Ions Generated in Situ



R_3	R'_3	R_4	R_1	R_5	X	conditions[a]	% yield[b]	ref
Me	Me	H	Me	CO_2Bn	Cl	A	86 [61][c]	64
Me	Me	H	*i*-Pr	CO_2Bn	Cl	A	90 [56][c]	64
Me	H	H	Me	CO_2Bn	Cl	A	85 [5][c]	64
$-(CH_2)_5-$		Me	Me	CO_2Bn	Cl	A	83 [81][c]	64
Me	PhO	H	Me	CO_2Bn	Cl	A	81 [24][c]	64
Me	Me	H	$SiMe_3$	$SiMe_3$	OMe	B	84	65
$-(CH_2)_4-$		H	$SiMe_3$	$SiMe_3$	OMe	B	78	65
$-(CH_2)_5-$		H	$SiMe_3$	$SiMe_3$	OMe	B	85	65
Me	H	H	$SiMe_3$	$SiMe_3$	OMe	B	85	65
Ph	H	H	$SiMe_3$	$SiMe_3$	OMe	B	95	65
$[(Me_2SiCH_2)_2]N$	H	H	$SiMe_3$	$SiMe_3$	OMe	B	95	65
Me	Me	H	Me	CO_2Me	OMe	A	79 [—][d,e]	66
Me	Me	Me	H	CO_2Me	OMe	A	71 [—][d]	66
Me	Me		$-(CH_2)_3-$	CO_2Me	OMe	A	68 [—][d]	66
Me	Me		$-(CH_2)_4-$	CO_2Me	OMe	A	66 [—][d]	66
Me	Me		$-(CH_2)_5-$	CO_2Me	OMe	A	73 [—][d]	66
Me	Me	*i*-Bu	*i*-Pr	CO_2Me	OMe	A	85 [—][d]	66
Me	Me	H	*i*-Pr	CO_2Me	OMe	A	93 [—][d]	66
Me	Me	Ph	H	CO_2Me	OMe	A	81 [—][d]	66
Me	Me	Me	H	CO_2Me	OMe	A	78 (63:37) [—][d]	66
Me	Me	Me	H	CO_2Me	OMe	A	67 (63:37) [—][d]	66
Me	Me	H	*i*-Pr	CO_2Me	OMe	A	66 (50:50) [—][d]	66
Me	H	2-furyl	$SiMe_3$	$SiMe_3$	$OSiMe_3$	C	64 (33:67) [63][f]	60
Me	Me	H	*i*-Pr	(—)[a]		D	83[g]	67
Me	Me	H	Bn	(—)[a]		D	83[g]	67
Me	Me	H	Et	(—)[a]		D	58[g]	67
Me	Me	H	$CH_2{=}CHCH_2$	(—)[a]		D	76[g]	67
Me	Me	H	Ph	(—)[a]		D	67[g]	67
Me	Me	H	$PhCHCO_2Me$	(—)[a]		D	69[g]	67
Me	H	H	*i*-Pr	(—)[a]		D	87[g]	67
H	H	H	*i*-Pr	(—)[a]		D	41[g,h]	67

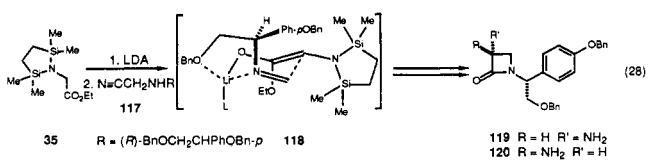
[a] Conditions (Lewis acid, solvent): A = $TiCl_4$, CH_2Cl_2; B = (TMS)OTf (0.01 equiv), CH_2Cl_2; C = (TMS)OTf (1 equiv), CH_2Cl_2; D = TFA (0.05 equiv), CH_2Cl_2. 1,3,5-Trialkylhexahydro-1,3,5-triazines were used as iminium ion precursors for reactions run using condition D. [b] Numbers in brackets refer to yields of β-lactams. Numbers in parentheses refer to syn:anti (cis:trans) ratios. [c] β-Amino ester was converted to β-lactam as described in eq 25. [d] β-Amino ester was converted to β-lactam using (1) HBr–AcOH and (2) *t*-BuMgCl. [e] Use of *O*-benzyl *O*-trimethylsilyl ketene acetal gave 91% β-amino ester. [f] β-Amino ester isolated as $R_1 = R_5 = H$ and converted to β-lactam using (1) Me_3SiCl, Et_3N and (2) MeMgBr. [g] β-Amino ester isolated as $R_5 = H$. [h] Started with *O*-benzyl *O*-trimethylsilyl ketene acetal.

reoselectivity is shown in Scheme V, and additional examples of this asymmetric synthesis are presented in Table XIV.

Chiral esters have also been examined in the ketene acetal route to β-amino esters.[71,79] Only a limited range of imines can be used, but modest to excellent stereoselectivity has been observed in a few cases.

B. Chiral Imines

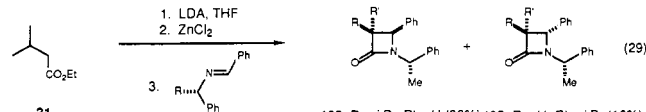
The first attempt to use chiral imines in ester–imine condensations was described by Furukawa, who was able to obtain 18–28% diastereomeric excess (de) in reactions between Reformatsky reagents and *N*-(α-methylbenzyl)imines.[74] This approach has been used with greater success by Overman and Osawa.[26] For example, treatment of 2 equiv of the enolate of **35** with α-cyano amine **117** gave a 72% yield of a 91:9 mixture of **119** and **120**, respectively. The authors pointed out that the observed stereoselectivity was consistent with chelated transition state **118** (eq 28).



(28)

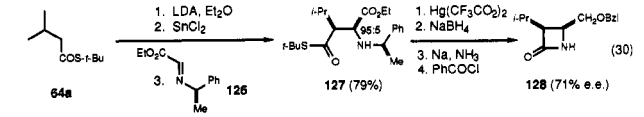
35 R = (*R*)-BnOCH$_2$CHPhOBn-*p* **118** **119** R = H R' = NH_2; **120** R = NH_2 R' = H

Zinc and tin enolates derived from lithium enolates have also been examined. Thus, the zinc enolate derived from **31** reacted with imine **121a** to give a 55% yield of β-lactams **122–125** (54:18:20:8, respectively) as shown in eq 29.[80] Less diastereoselectivity was observed when **121b** was used as the imine component. Tin enolates have been used with greater success and one example is shown in eq 30.[81] The authors invoke a chelated transition state involving an (*E*)-enolate and (*E*)-azomethine to rationalize this result.



(29)

31 **121a** R = Me, **121b** R = CH_2OMe **122** R = *i*-Pr R' = H (30%) **123** R = H R' = *i*-Pr (10%) **125** R = H R' = *i*-Pr (4%) **124** R = *i*-Pr R' = H (11%)

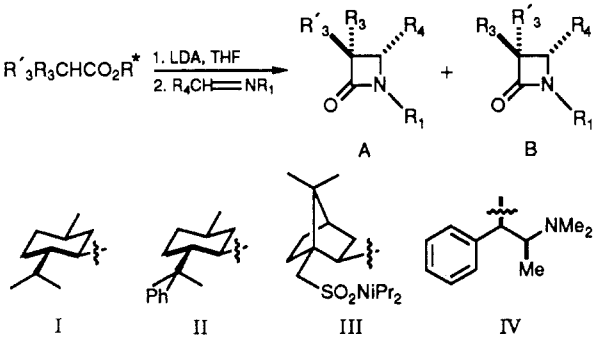


(30)

64a **126** **127** (79%) **128** (71% e.e.)

One example of asymmetric induction in a (vinyloxy)borane–imine condensation has already been described (eq 20). In this reaction, the anti:syn ratio of β-amino esters was 85:15, but the major product (**78**) was produced with an impressive 95% de. The authors account for this result by using the popular Zimmer-

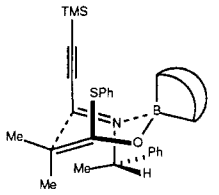
TABLE XIV. Asymmetric Synthesis of β-Lactams Using Lithium Enolates of Chiral Esters



R*	R_3	R'_3	R_4	R_1	% yield (A:B)	% ee A[a]	% ee B	ref
I	OH	Ph	Ph	Ph	74 (100:0)	14 (—)[b]	(—)	25
I	PhCONH	Me	Ph	Ph	72 (100:0)	4 (—)[b]	(—)	25
I	Me	Ph	Ph	Ph	85 (89:11)	60 (—)[b]	(—)	25
I	Et	H	Ph	*p*-MeOPh	80 (>95:5)	85 (3*R*,4*R*)[c,d]	(—)	78
II	Et	H	Ph	*p*-MeOPh	80 (83:17)	60 (3*R*,4*R*)[c,d]	(—)	78
III	Et	H	Ph	*p*-MeOPh	88 (>95:5)	92 (3*R*,4*R*)[c,d]	(—)	76
IV	Et	H	Ph	*p*-MeOPh	85 (>95:5)	20 (3*S*,4*S*)[c,d]	(—)	78
III	Et	H	*trans*-PhCH=CH	*p*-MeOPh	81 (91:9)	91 (3*R*,4*R*)[e,e]	(—)	76
III	Et	H	Ph	$SiMe_3$	34 (86:14)	62 (3*R*,4*S*)[c,d]	42 (—)[c,d]	78
III	*i*-Pr	H	Ph	*p*-MeOPh	70 (>98:2)	56 (3*R*,4*R*)[c,d]	(—)	76
III	*i*-Pr	H	*trans*-PhCH=CH	*p*-MeOPh	80 (95:5)	82 (3*R*,4*S*)[c,d]	(—)	76
III	*i*-Pr	H	*trans*-PhCH=CH	$SiMe_3$	51 (93:7)	65 (3*R*,4*S*)[c,d]	49 (—)[c,d]	78

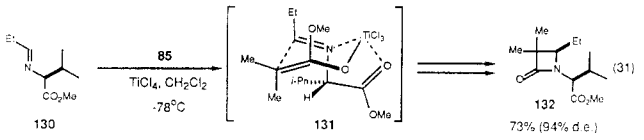
[a] Absolute configuration of major enantiomer shown in parentheses when known. [b] % ee determined by NMR using chiral shift reagents. [c] % ee determined by conversion to derivatives separable by chromatography over a chiral stationary phase (see ref 77). [d] Absolute configuration assigned by analogy with chromatographic behavior of 115 and other standard compounds (see ref 77). [e] Absolute configuration established by correlation experiments (see ref 76).

man–Traxler transition state (**129**).[55a] The syn β-amino esters obtained in this reaction (eq 20) exhibited only 13% de.



129

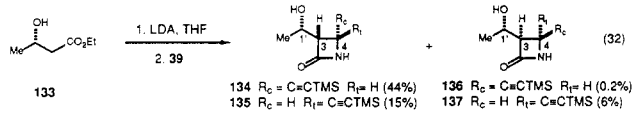
Finally, ketene acetal **85** has been treated with a variety of chiral imines.[82,83] The success of this approach varied widely depending on the imine, but excellent diastereoselectivity was observed with imines derived from the ethyl ester of valine (eq 31).[83] The sense of asymmetric induction can be accounted for by transition state **131**.



V. Studies with β-Hydroxybutyrates

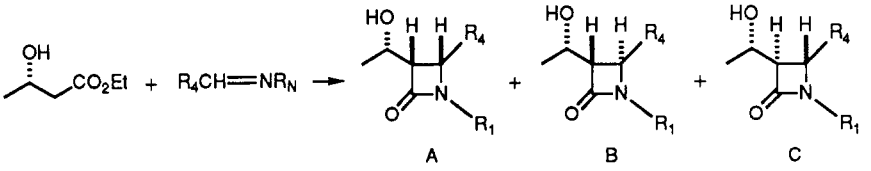
As mentioned in the Introduction, it is probable that the discovery of carbapenem antibiotics such as thienamycin (**7**) was partly responsible for the recent explosion of interest in the title reaction. It did not take long for several groups to recognize that the use of β-hydroxybutyrate as the ester component would lead to β-lactams with α-hydroxyethyl substitution at C(3), an important substructure of many carbapenem antibiotics, including thienamycin (**7**). The availability of both optical antipodes of β-hydroxybutyrate suggested that this strategy might provide enantioselective access to carbapenem antibiotics.

The results of a number of studies are documented in Table XV.[84-92] It is clear that most of these reactions proceed with good diastereoselectivity at C(3) relative to C(1′), but poor diastereoselectivity at C(4). For example, the reaction between ethyl β-hydroxybutyrate (**133**) and *N*-(trimethylsilyl)imine **39** has been reported to give **134** (44%), **135** (15%), **136** (0.2%), and **137** (6%) as shown in eq 32.[28a] This translates to 9:1 selectivity at C(3) and 2:1 selectivity at C(4) relative to C(1′).



To begin an attempt to rationalize the stereochemical course of the reactions shown in Table XV it is necessary, at a minimum, to know the geometry of the enolate derived from ethyl β-hydroxybutyrate. In fact, there is little hard evidence regarding the geometry of the dianion derived from **133**. Chelated (*Z*)-enolate **138** is cited most frequently, presumably based on the fact that reactions between this dianion and electrophiles display high anti selectivity (**133** → **140**).[93] Note that the reactions shown in Table VI are no exception to this trend. It is now appreciated, however, that chelated (*E*)-enolate **142** would also be expected to show anti selectivity, and thus, the stereochemical course of such reactions does not differentiate between enolate geometrical isomers (Scheme VI).[28a,94] There is some information, however, that suggests deprotonation of β-hydroxybutyrates by lithium diisopropylamide in tetrahydrofuran affords predominantly (*Z*)-enolate **139**. Kurth has reported that Claisen rearrangement of the enolates derived from esters **143** and **146** affords mainly **145** and **148**, respectively (Scheme VII).[95] The ste-

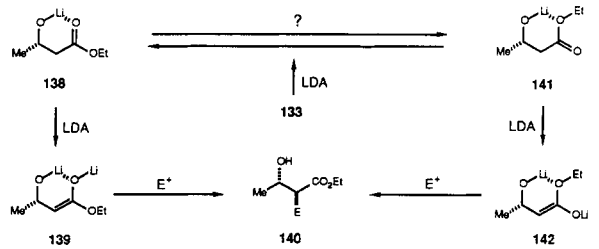
TABLE XV. Dianion of β-Hydroxybutyrate with Aldimines



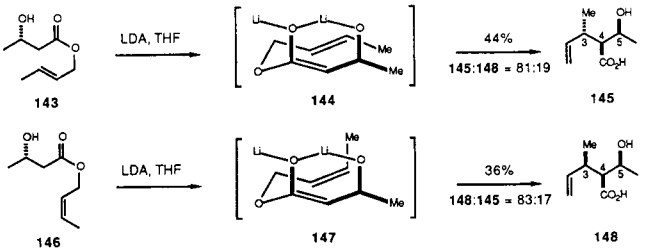
R	R_4	R_N	R_1	conditions[c]	% yield	A:B:C	ref
Et[a]	(TMS)C≡C	TMS	H	A	66	67:23:10	28a
Et	(TMS)C≡C	TMS	H	A	50	75:25:0	84
Et	(TMS)C≡C	TMS	H	B	66	75:25:0	84
Me	(TMS)C≡C	TMS	H	B	75	75:25:0	84
Me	(TMS)C≡C	TMS	H	C	52	43:57:0	84
Et	(TMS)C≡C	TMS	H	C	49	37:63:0	84
Et	*trans*-PhCH=CH	TMS	*t*-$BuMe_2Si$	A	43[d]	63:37:0	85
Et	*trans*-PhCH=CH	TMS	H	A	50	70:30:0	86
Et	*trans*-PhSCH=CH	TMS	*t*-$BuMe_2Si$	A	46[d]	78:22:0	28a, 87
Et	Ph	Ph	Ph	C	43	0:95:5	88–90
Et	Ph	Ph	Ph	D	41	40:60:0	89, 90
Et	Ph	*p*-MeOPh	*p*-MeOPh	C	59	0:50:50	89, 90
Et	Ph	*p*-MeOPh	*p*-MeOPh	D	50	80:20:0	89, 90
Et	2-furyl	*p*-MeOPh	*p*-MeOPh	C	50	0:50:50	89, 90
Et	2-furyl	*p*-MeOPh	*p*-MeOPh	E	65	15:65:20	89, 90
Et	2-furyl	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	C	29	0:80:20	89, 90
Et	2-furyl	3,4,5-$(MeO)_3$Ph	3,4,5-$(MeO)_3$Ph	C	59	0:95:5	89, 90
Me	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	A	67	35:60:5	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	C	77	25:50:25	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	C	30	21:79:0	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	D	67	40:50:10	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	F	77	40:50:10	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	E	77	50:50:0	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	G	66	50:50:0	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	A	59	39:46:15	92
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	A	81	35:55:10	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	H	60	60:35:5	91
Et	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	I	22	15:77:8	91
t-Bu	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	A	66	23:65:12	91
t-Bu	*trans*-PhCH=CH	*p*-MeOPh	*p*-MeOPh	I	15	21:62:17	91
Et	*trans*-PhCH=CH	3,4,5-$(MeO)_3$Ph	3,4,5-$(MeO)_3$Ph	C	20	30:70:0	89, 90
Et	*trans*-PhCH=C(Me)	*p*-MeOPh	*p*-MeOPh	C	35	30:70:0	89, 90
Et	Ph_2C=CH	*p*-MeOPh	*p*-MeOPh	C	77	30:70:0	89, 90

[a] Racemic ester used. [b] (*R*) ester used; products are enantiomers of those shown above. [c] Conditions (base, solvent, final temperature): A = LDA, THF, room temperature; B = LHMDS, THF, room temperature; C = LDA, HMPA–THF, room temperature; D = LDA, HMPA–THF, −20 °C; E = LDA, THF, 10 °C; F = LDA, THF–HMPA, 10 °C; G = LDA, THF, −20 °C; H = LDA, toluene, room temperature; I = LDA, toluene–HMPA, room temperature. [d] Crude product treated with (TBDMS)Cl–Et_3N.

SCHEME VI



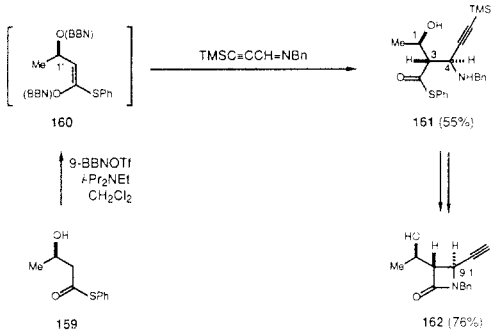
SCHEME VII



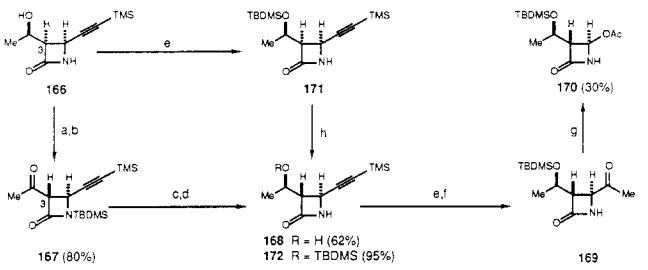
reochemical course of such rearrangements has generally provided a good measure of enolate geometry.[74,96] Thus, if (1) the enolate undergoing rearrangement is chelated, (2) anti selectivity, as discussed in Scheme VI, is maintained, and (3) the rearrangement proceeds principally through a chair-like transition state typical of most Claisen rearrangements, these stereochemical results imply that rearrangement occurs via (*Z*)-enolates **144** and **147**. Applying the same three criteria to the corresponding (*E*)-enolates predicts the opposite diastereoselection across the new carbon–carbon bond [C(3)–C(4)]. Of course, rearrangement of the (*E*)-enolates via boat-like conformations would also account for these results. Finally, it is notable that the experiments described by Kurth have also been reported using dimethoxyethane as solvent and lithium hexamethyldisilazide as the base and the authors came to entirely different conclusions regarding the stereochemistry of the products.[97] An examination of the methods used to determine product stereochemistry across C(4) and C(5) in the latter study, however, suggests that this relative stereochemical relationship may have been mistaken. If one inverts the assignment of stereochemistry at C(4) in this study, the results are in accord with those reported by Kurth. Thus, we feel that existing evidence points toward (*Z*)-enolate formation upon deprotonation of β-hydroxybutyrates in tetrahydrofuran.

Returning to ester–imine condensations, it was noted above that lithium (*Z*)-enolates add to azomethines with

SCHEME VIII

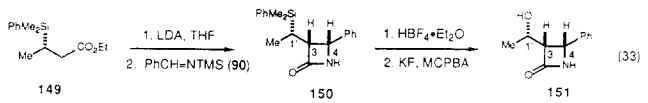


SCHEME IX

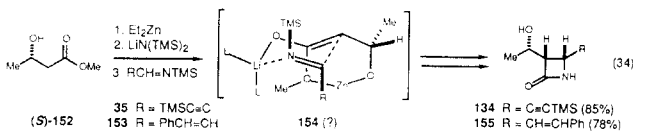


(a) LDA, THF; TBDMSCl (b) MnO_2, EtOAc (c) K-Selectride (d) HCl, MeOH (e) TBDMSCl, imidazole (f) $HgSO_4$, H_2SO_4, H_2O, THF (g) MCPBA, EtOAc (h) TMSOTf, Et_3N, CH_2Cl_2; HCl-H_2O

little or no stereoselectivity. Thus, the lack of stereoselectivity in reactions shown in Table XV and eq 32 also suggests that enolates derived from β-hydroxybutyrates may have *Z* geometry. Two notable attempts to improve overall diastereoselectivity in β-hydroxybutyrate and related reactions have been reported. It has been shown that β-trialkylsilyl ester **149** gives only β-lactam **150** (63%) upon treatment with imine **90** (eq 33).[98] This result is consistent with intermediacy of

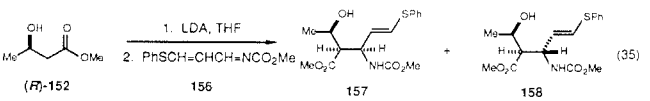


an (*E*)-enolate and known directing effects of β-trialkylsilyl groups on related aldol condensations and alkylations.[99] Although **150** has been converted to **151** in 48% yield, this sequence is not as practical or general as the aforementioned reactions of **133**. Recently, Oguni has described the reaction shown in eq 34.[100] Thus,



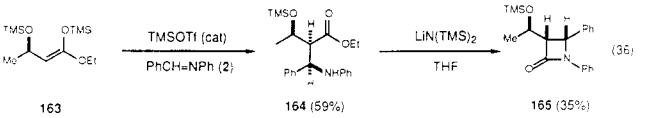
sequential treatment of β-hydroxybutyrate **152** with diethylzinc, lithium hexamethyldisilazide, and imine **35** or **153** affords β-lactams **134** (85%) and **156** (78%), respectively, to the exclusion of all other stereoisomers. This is a dramatic improvement over the reaction described in eq 32. Although a number of reasons for this improvement in stereoselectivity can be imagined, one possibility is that the (*E*)-enolate of **152** may be involved in this reaction. This suggestion awaits experimental scrutiny.

β-Hydroxybutyrate–imine condensations that only afford β-amino esters have also been described. For example, the lithium enolate of the *R* enantiomer of **152** reacts with *N*-acylimine **156** to give 96% of a 2:1 mixture of **157** and **158**, respectively (eq 35).[101] An improvement in diastereoselectivity was noted when the isopropyl ester related to **152** was used.



Reactions between imines and (vinyloxy)boranes derived from thioesters of β-hydroxybutyrate follow a different stereochemical course than reactions of lithium enolates.[55b,102-104] The major β-amino esters obtained from these reactions always provide trans-3,4-disubstituted β-lactams with a syn C(1′)–C(3) relationship. One example is shown in Scheme VIII.[102]

The stereochemical course of these reactions across C(1′) and C(3) is not readily explained by the models discussed above, and an alternative transition state in which the imine coordinates to the C(1′) alkoxyborane has been proposed. Finally, it has been reported that ketene acetal **163** reacts with imine **2** to give **164** (59%), which has been converted to β-lactam **165** in 35% yield (eq 36).[105] This provides access to yet another stereochemical array at C(1′), C(3), and C(4).



VI. Selected Applications of Ester–Imine Condensations to β-Lactam Antibiotic Synthesis

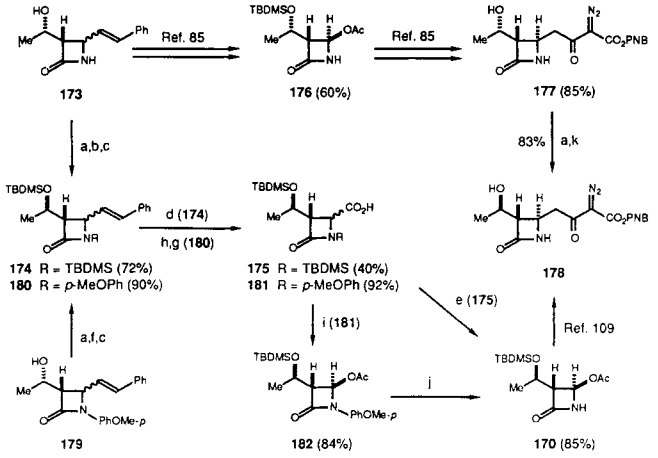
A. Preparation of Intermediates for the Synthesis of Carbapenem Antibiotics with 3-(1-Hydroxyethyl) Substituents

Several groups have used the aforementioned β-hydroxybutyrate condensations to prepare intermediates in the Merck syntheses of thienamycin and related carbapenem antibiotics. Since this topic has recently been reviewed,[106] the following discussion will focus only on examples that illustrate the different strategies that have been used.

The most popular strategy has been to prepare a β-lactam with a C(4) substituent that could be degraded to an acetoxy group. The use of such β-lactams in carbapenem synthesis has been amply demonstrated. Nakai has applied this strategy to **134**[84,107] as well as its enantiomer (**166**).[108,109] One approach to 4-acetoxy β-lactam **170**, a key intermediate in one synthesis of thienamycin (**7**),[110] is outlined in Scheme IX. Protection of the β-lactam nitrogen followed by side-chain oxidation converted **166** to **167**. Isomerization during the oxidation accomplished the necessary stereochemical adjustment at C(3). Reduction of **167** occurred with 9:1 diastereoselectivity, and blocking group removal gave **168**. O-Silylation, hydration of the triple bond, and a Bayer–Villiger oxidation completed the synthesis of **170**.[108] More efficient methodology for accomplishing the stereochemical adjustment at C(3) has also been reported (**166** → **171** → **172**).[109]

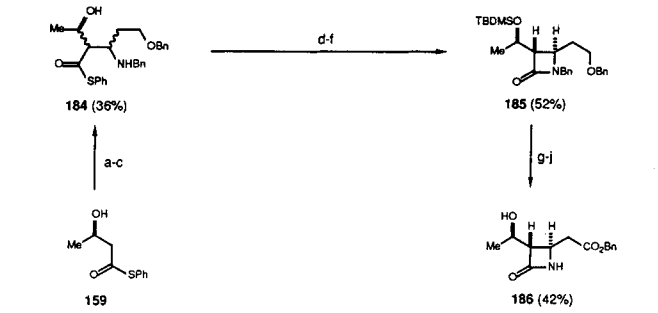
Three groups have focused on degradation of C(4)-Styryl groups as summarized in Scheme X. In each case **133** was used as the starting material, and thus, inversion of C(1′) stereochemistry was necessary. For example, β-lactam **173** (Table XV) was converted to **174** using a Mitsunobu reaction to adjust C(1′) stereochemistry.[86] The styryl group was then degraded to an

SCHEME X



(a) DEAD, Ph_3P, HCO_2H (b) HO^- (c) TBDMSCl, base (d) RuO_2, $NaIO_4$, aq. acetone (e) $Pb(OAc)_4$, $Cu(OAc)_2$, CH_3CN (f) MeOH, HCl (g) OsO_4, $NaIO_4$ (h) $KMnO_4$, THF, H_2O (i) $Pb(OAc)_4$, DMF, H_2O (j) CAN (k) $HSCH_2CH_2SH$, TsOH, CH_2Cl_2, *i*-PrOH

SCHEME XI



(a) 9-BBNOTf, iPr_2NEt (b) $BnOCH_2CH_2CH{=}NBn$ (**183**) (c) H_2O_2 (d) KOH, THF, H_2O (e) $(PyS)_2$, CH_3CN (f) TBDMSOTf, 2,6-lutidine (g) Na, NH_3 (h) $CrO_3{\cdot}2Py$ (i) DCC, 4-DMAP, $PhCH_2OH$ (j) AcOH, H_2O, THF

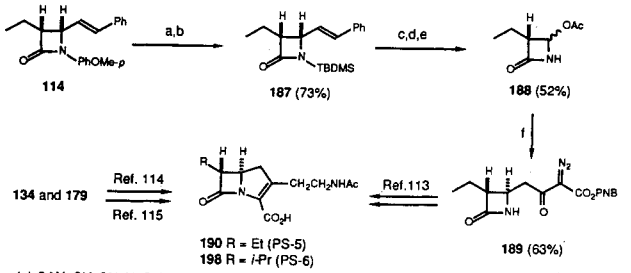
acetoxy group (**174** → **175** → **170**) via oxidative cleavage of the double bond followed by treatment of **175** with lead tetraacetate.[110] A similar sequence has been used to prepare the C(1′) isomer of **170** from **173**.[85] This isomer (**176**) has been used to prepare carbapenem precursors **177** and **178**.[85] *N*-Aryl β-lactams **179** have been used by Georg to prepare **170** (**179** → **180** → **181** → **182** → **170**) and **176**.[89,90,111] Similar sequences have been accomplished by others[85,91] and **179** has also been used in aminosaccharide synthesis.[92]

It is obvious that stereochemical adjustments were needed to prepare thienamycin precursors from the ester–imine condensation products described in Schemes IX and X. (Vinyloxy)borane–imine condensations, however, directly afford β-amino esters with the C(1′)–C(3)–C(4) stereochemical relationship required for thienamycin. One use of this approach is outlined in Scheme XI.[103] Thus, condensation of thioester **159** with imine **183** gave a mixture of β-amino esters **184** (36%). Thioester hydrolysis, cyclization of the intermediate amino acid, and protection of the C(1′) hydroxyl group gave **185** (52%) along with 7% of other stereoisomers. Finally, cleavage of the *N*-benzyl group and adjustment of C(4) side chain oxidation state gave thienamycin intermediate **186**. (Vinyloxy)borane–imine condensations have also been used to prepare **170**.[112]

B. Preparation of Intermediates for the Synthesis of PS-5

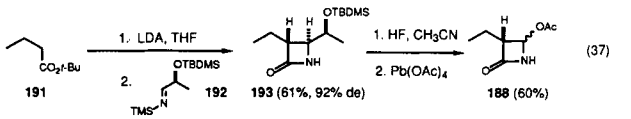
Ester–imine condensations have also been used to prepare intermediates in syntheses of the carbapenem

SCHEME XII



(a) CAN, CH_3CN, H_2O (b) TBDMSCl, Et_3N, DMF (c) O_3, CH_2Cl_2; Me_2S (d) $H_2Cr_2O_7$ (e) $Pb(OAc)_4$, DMF, AcOH (f) $CH_2{=}C(OTBDMS)C(=N_2)(CO_2PNB)$, $ZnCl_2$, CH_2Cl_2

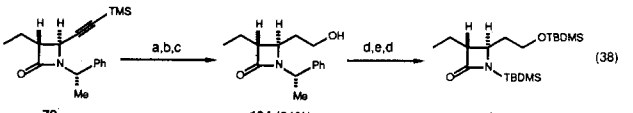
antibiotic PS-5 (**190**). A key intermediate in most of these approaches is 4-acetoxy β-lactam **188**, and degradative methods similar to those described in Schemes IX and X have been used to arrive at this point. One approach to **188**, involving an application of the asymmetric synthesis discussed in Scheme V, is shown in Scheme XII.[76,113] β-Lactams **134** and **179** have also been converted to **188**.[114,115] A third enantioselective approach to **188** is shown in eq 37.[116] This route uses



(37)

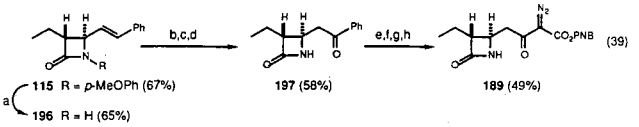
a chiral *N*-(trimethylsilyl)imine **192** as the original source of chirality. The stereochemical course of the azomethine addition is notable in that excellent trans selectivity is observed. This appears to be a trend for branched enolizable *N*-(trimethylsilyl)imines. Finally, one synthesis of *rac*-**188** has been reported that relies on a Reformatsky reagent–imine condensation for construction of the β-lactam.[11]

The aforementioned syntheses rely on degradation of a C(4) side chain, and once again, several alternative procedures have been developed. For example, β-lactam **79**, prepared with a (vinyloxy)borane–imine condensation as shown in eq 20, has been converted to PS-5 intermediate **195** as outlined in eq 38.[55a]



(38)

A synthesis of racemic PS-5 intermediate **189** that illustrates another procedure for transforming a C(4) styryl group into functionality useful for carbapenem synthesis is described in eq 39.[28b] Thus, *rac*-**115** was



(39)

(a) CAN, CH_3CN, H_2O (b) NBS, DMSO, H_2O (c) *n*-Bu_3SnH, AIBN, PhH, Δ (d) $H_2Cr_2O_7$ (e) CF_3CO_3H, CH_2Cl_2 Na_2HPO_4 (f) NaOH, EtOH; HCl, EtOH (g) CDI, THF; $Mg[OC(O)CH_2CO_2PNB)_2$ (h) TsN_3, Et_3N, CH_3CN

prepared from ethyl butyrate and imine **112** as described in Table IV. Oxidative removal of the *p*-methoxyphenyl group followed by formal hydration of the styryl double bond gave **197**. A Baeyer–Villiger reaction followed by chain extension of the resulting phenyl ester gave **189**. A similar sequence was also used to prepare racemic compounds related to PS-6 (**198**).[28b] Finally, for the purpose of comparison the reader is referred to two asymmetric syntheses of PS-5 that rely

on an aldol condensation–cyclization strategy.[117,118]

VII. Summary and Conclusions

It is clear that the ester–imine condensation route to β-lactams has been highly developed over the past decade. The behaviors of a broad spectrum of enolates and azomethines have been delineated and some mechanistic features of these reactions are understood, although it is in this area where in-depth understanding is still lacking. Nonetheless, the reaction has been developed to a stage where it has been applied to the synthesis of β-lactam antibiotics as illustrated herein by partial syntheses of carbapenems. Applications to monobactam substructures have also been reported,[26,36,38,42,119] and the use of this reaction in other areas of natural and nonnatural product synthesis can be anticipated.

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