The *S*-Thioester Enolate/Imine Condensation: A Shortcut to β-Lactams

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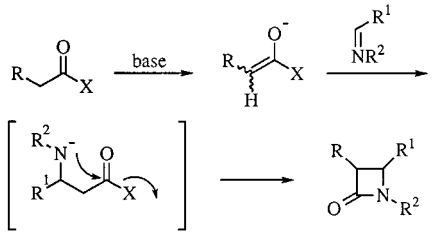
The condensation between imines and *S*thioester metal enolates provides a mild, efficient, and straightforward route to the preparation of β-lactams. The synthetic applications and the stereochemical aspects of this reaction are discussed.

Introduction

The condensation between imines and metal ester enolates (or their synthetic equivalents, the silylketene acetals) represents one of the most popular entries to β-lactams.[1] Since its original discovery,[2] this reaction has been constantly refined to become a powerful and reliable synthetic tool. This result originated from the improved ability of organic chemists to master the reactivity of the enolate by the use of various compounds as its precursors, and of different bases for its generation.[3]

The ideal enolate precursor for β-lactam synthesis should have some characteristic properties. In particular, it should: (i) undergo rapid and complete enolization under mild conditions; (ii) allow good control of the enolate geometry; (iii) react smoothly with imines; and last but not least, (iv) give an easy additon/elimination reaction between the carbonyl carbon and the former imine nitrogen to directly deliver the β-lactam ring (Scheme 1).



Scheme 1

In principle *S*-thioesters fulfill all these requirements. They are readily available compounds[4] that feature an enhanced acidity at C-α with respect to simple esters.[5][6] *S*-thioester enolization has been extensively studied, and can be carried out in a highly stereoselective fashion under a variety of conditions.[7] Finally, the sulfur-containing substituent of a *S*-thioester is more readily displaced from the carbonyl carbon than the oxygen-containing substituent of an ester.[6]

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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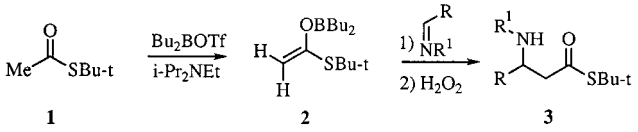
The great potential of *S*-thioesters for β-lactam synthesis was recognized in the early 1980′s, and it is the aim of this *Microreview* to illustrate the developments of the *S*-thioester enolate/imine condensation reaction from the first attempts to the more recent achievements. Special emphasis will be placed on the stereochemical aspects of the process.

Two-Step Synthesis of β-Lactams

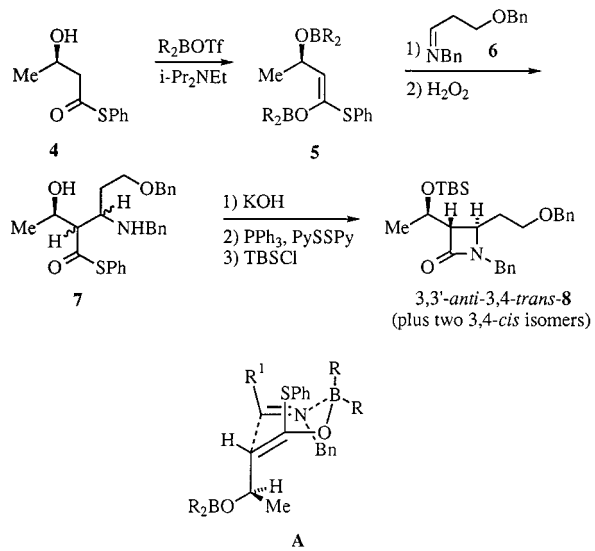
Boron Enolates

The first condensation of a *S*-thioester enolate with an imine was reported by Ohno in 1981.[8] This reaction took advantage of the α-acidity of *S*-thioesters that allows for enolate generation simply by the addition of a tertiary amine (typically diisopropylethylamine) to a mixture of *S*-*tert*-butyl thioacetate **1** and di-*n*-butylboron triflate at 0°C (Scheme 2).[7a]



Scheme 2

The resulting boron enolate **2** reacted smoothly with a variety of imines to afford the corresponding β-amino *S*-thioester in 40−80% yields. Even if **3** was not ring-closed to the azetidinone, the *S*-thioester enolate route to β-lactams was virtually opened, and in 1985 Shibasaki fully exploited this methodology in a stereoselective synthesis of (+)-thienamycin (Scheme 3).[7a]

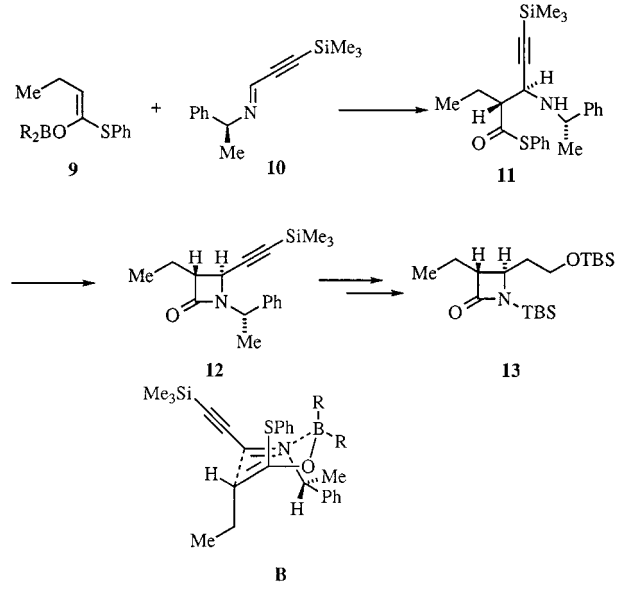


Scheme 3

(*R*)-*S*-Phenyl 3-hydroxythiobutanoate **4**, obtained in four steps from readily available methyl (*R*)-3-hydroxybutanoate, was transformed into the boron enolate **5** by reaction with 9-BBN and diisopropylethylamine. Condensation of **5** with imine **6** gave adduct **7** as a mixture of isomers of undetermined composition in 36% yield. Conversion of this mixture into β-lactam **8** using Ohno′s method (72% yield),[10] followed by further protecting groups manipulation, established that the major component (88%) of the stereoisomeric mixture had the required configuration to be transformed into (+)-thienamycin. In the same paper, it was also demonstrated that the condensation of the lithium enolate of methyl (*R*)-3-hydroxybutanoate with imine **6** failed, thus showing the advantages provided by the use of a *S*-thio- versus a normal ester in this reaction.

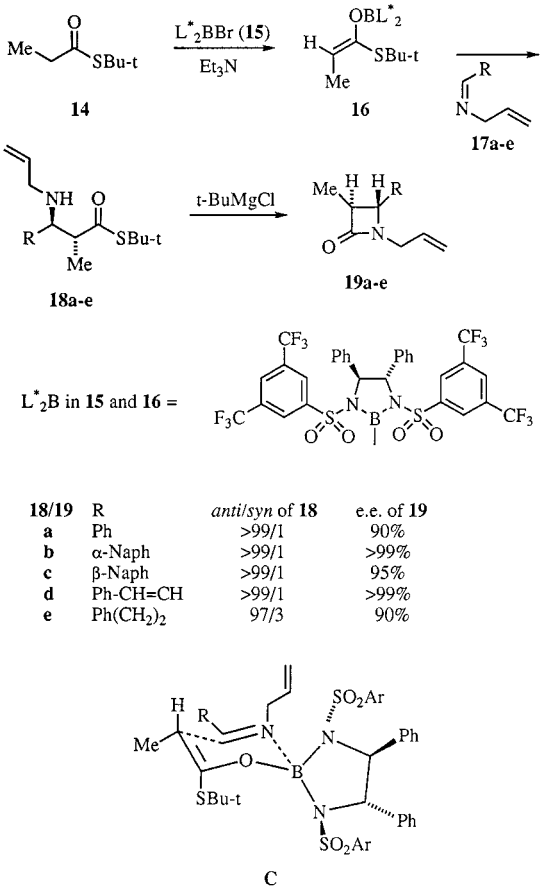
In a following series of papers, Shibasaki applied the methodology described in Scheme 3 to the preparation of 1-β-methylcarbapenem,[11] and proposed a model of stereoselection to explain the steric course of these enolate/imine condensations.[12] This model (**A** in Scheme 3) involved attack of the (*R*,*E*)-enolate **5** on the *Si* face of the (*E*)-imine in a cyclic transition state that is reminiscent of those proposed for the aldol condensation of *S*-thioester boron enolates.[7a,7b] Although this rationale is consistent with the observed configuration at the newly formed stereocenters in the predominant isomer, it must be noted that it features all the bulky substituents of both reagents in the unfavorable pseudo-axial positions.

While in the reaction of Scheme 3 the stereocontrol is provided by the stereocenter on the *S*-thioester, in that of Scheme 4 is the chiral auxiliary at the imine nitrogen that determines the steric course of the condensation.[13][14] The boron enolate of *S*-phenyl thiobutanoate reacted with (*S*)-α-methylbenzylamine derived imine **10** to afford a 62.5:25.0:12.5 mixture of β-amino *S*-thioesters in 69% yield. By *t*BuMgCl-promoted ring closure, the major component of this mixture, **11**, gave β-lactam **12** in 68% yield.[15] From this compound, the precursor of the (+)-PS-5 carbapenem antibiotic **13** was obtained in six steps.[16] Model **B**, clearly related to **A**, served to explain the preferential formation of adduct **11**.



Scheme 4

A more general entry to enantiomerically enriched β-lactams was accomplished by Corey with the reaction sequence described in Scheme 5.[17] In this approach, chiral ligands at boron were used as the elements of stereocontrol to give β-amino *S*-thioesters with high stereoselectivity.



18/19	R	*anti/syn* of **18**	e.e. of **19**
a	Ph	>99/1	90%
b	α-Naph	>99/1	>99%
c	β-Naph	>99/1	95%
d	Ph-CH=CH	>99/1	>99%
e	$Ph(CH_2)_2$	97/3	90%

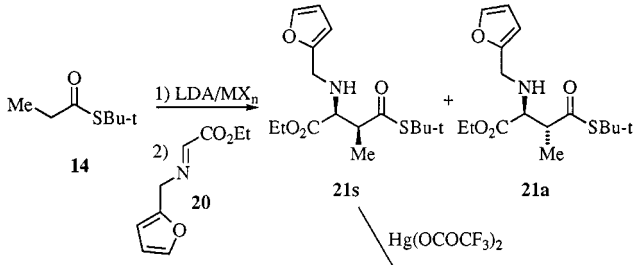
Scheme 5

(*Z*)-Enolate **16**, generated by the addition of triethylamine to the mixture of *S*-thioester **14** and the chiral boron reagent **15**, reacted with imines **17a−e** to afford β-amino *S*-thioesters **18a−e** (67−77% yield) with very high *anti* stereoselectivity. Treatment of these with *t*BuMgCl gave *trans*-β-lactams **19a−e** in 90 to > 99% *ee*.

This methodology, representing the first enantioselective synthesis of azetidinones from achiral esters and imines,[18] exploited the stereodirecting ability of the C_2 symmetric diazaborolidine **15**. In the proposed model of stereoselection **C**, the chirotopic, nonstereogenic boron atom coordinates the imine nitrogen to give a 6-membered chair-like transition state; attack of the *Si* face of the (*Z*)-enolate on the *Si* face of the (*Z*)-imine is believed to be favored because of the relative position of the arylsulfonyl groups and of the allyl and *tert*-butylthio substituents. It must be noted that this is one of the very few models of stereoselection for this type of reaction that involves enolate additon to a (*Z*)-configured imine.

Tin Enolates

In a systematic study by Mukaiyama and co-workers, the condensation of the highly reactive imine **20** with various metal enolates of *S*-thioester **14** was investigated (Scheme 6).[19] While the lithium, magnesium, and zinc enolates did not afford any product, the titanium, aluminum, and tin[20] species gave the expected β-amino *S*-thioesters **21** in low to good yields.

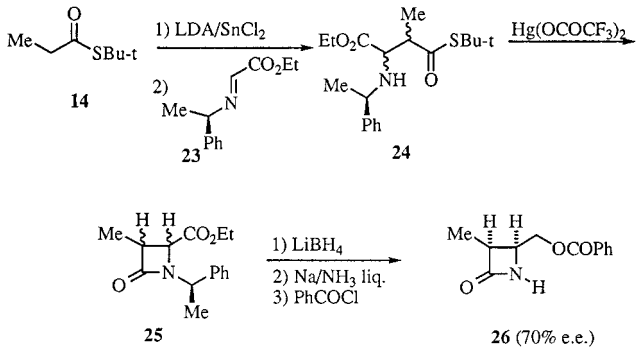


MX_n	Y%	**21s/21a**
none	0	-
$MgCl_2$	0	-
$ZnCl_2$	0	-
$TiOPr\text{-}iCl_3$	30	29/71
$EtAlCl_2$	25	50/50
$SnCl_2$	72	95/ 5
$SnBr_2$	53	93/ 3
$Sn(OTf)_2$	60	80/20

Scheme 6

Best results were obtained with the tin species generated by the addition of tin(II) chloride to the lithium enolate of **14** in diethyl ether: under these conditions a 95:5 mixture of *syn* (**s**) and *anti* (**a**) product **21** was obtained in 72% yield. Similar yields and stereoselectivities were observed using other *S*-thioesters. Cyclization of **21s** with mercury(II) trifluoroacetate in acetonitrile led to *cis*-β-lactam **22**.

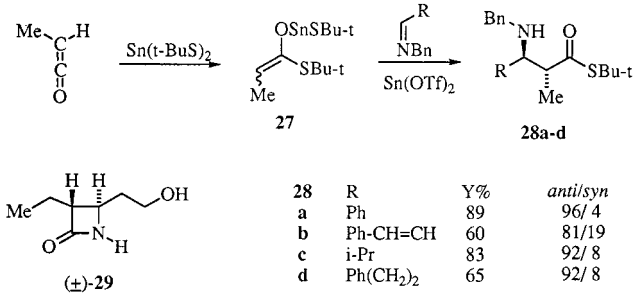
Control of absolute stereochemistry in the reaction of Scheme 6 was achieved by the introduction of a chiral auxiliary at the imine nitrogen as described in Scheme 7.[21] The stereoisomeric mixture of β-amino *S*-thioester **24**, obtained from **14** and **23**, was converted first into β-lactam **25** (*cis*/*trans* ratio 91:9), and then into azetidinone **26**, the major isomer of which had the indicated (3*S*,4*S*) configuration and a 70% *ee*. A model of stereoselection analogous to **B** (Scheme 4) was proposed to explain the observed stereochemical result.



26 (70% e.e.)

Scheme 7

Reversal of the stereoselectivity of the reaction described in Scheme 6 was obtained by generating the tin enolate of **14** under different conditions (Scheme 8).[22] Addition of tin(II) *tert*-butylthiolate to methylketene at −78°C gave enolate **27b**. This reacted with various *N*-benzylimines in the presence of tin(II) triflate to afford adducts **28a−d** largely in the *anti* configuration. Extension of this methodology to ethylketene and the *N*-benzylimine of 3-benzyloxypropanal led to **29**, the racemic precursor of PS-5 in three steps and 49% overall yield.

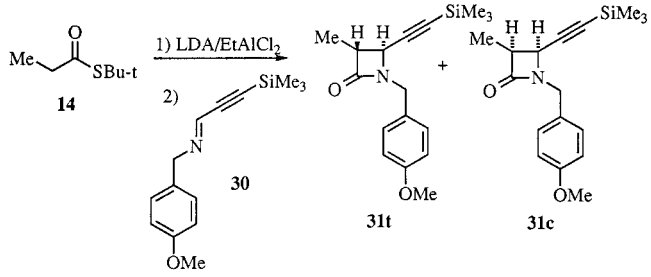


28	R	Y%	*anti/syn*
a	Ph	89	96/4
b	Ph-CH=CH	60	81/19
c	i-Pr	83	92/8
d	$Ph(CH_2)_2$	65	92/8

Scheme 8

Other Metal Enolates

In an investigation similar to the one carried out by Mukaiyama,[19] Shibasaki also found that the enolate generated from **14** by lithium/zirconium exchange reacted with imines to afford *syn*-β-amino *S*-thioesters.[23] More remarkable was the discovery that the diethylaluminum enolate of **14** condensed with imine **30** to give β-lactam **31** as a mixture of *trans* (**t**) and *cis* (**c**) isomers upon warming the crude reaction products (Scheme 9).



Scheme 9

This reaction represented the first one-pot synthesis of β-lactams by *S*-thioester enolate/imine condensation. Although this procedure suffered from unpredictable stereochemical results (e.g. *S*-thioesters more sterically hindered than **14** predominantly gave *cis*-azetidinones under the same conditions), it made the great potential of this route for the rapid preparation of β-lactams evident, and set the standards of efficiency that had to be matched by subsequent research in the field.

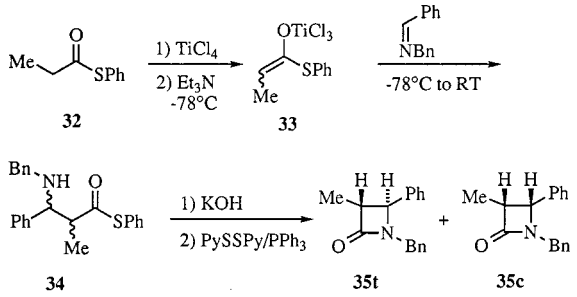
One-Step Synthesis of β-Lactams

Titanium Enolates

From the results reported so far it evidently appears that an ideal method for azetidinone synthesis based on the *S*-thioester enolate/imine condensation must combine the mild and easy protocol of boron enolate formation (Schemes 2−5) with the one-step generation of the β-lactam ring (Scheme 9).

In our attempt to solve this problem, we were influenced by a series of papers by Evans and co-workers[24] in which the facile enolization of ketones, *N*-acyloxazolidinones, and *N*-acylsultams by the addition of a tertiary amine to their titanium tetrachloride complexes in dichloromethane was reported. Since the acidity at the α-carbon of a ketone and of a *S*-thioester is very similar[5][6] we reasoned that Evans' procedure should apply to *S*-thioesters as well. This turned out to be the case, and we showed[25] that the titanium enolates[26] of *S*-aryl and *S*-*tert*-butyl thiopropanoate easily reacted with aldehydes.

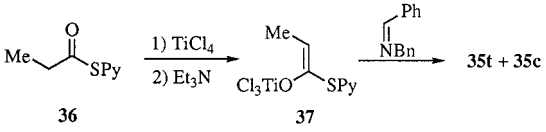
The condensation of these species with an imine was the next obvious step (Scheme 10). It was found that enolate **33** did react with *N*-benzylideneaniline in good yield (70%), but the resulting β-amino *S*-thioester **34** did not spontaneously cyclize to the azetidinone.



Scheme 10

In order to assess the stereoselectivity of the reaction, the crude diastereoisomeric mixture **34** was converted (70% yield) into a 70:30 mixture of *trans*- and *cis*-β-lactams **35t** and **35c** by Ohno's procedure. At this stage we had only a poorly *anti*-selective synthesis of β-amino *S*-thioesters, and not the desired one-pot synthesis of β-lactams. This goal was quite obviously accomplished by the formal "inversion" of the steps of Scheme 10.

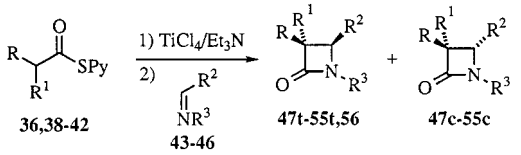
Replacement of the phenylthio group of **32** with the 2-pyridylthio group as in **36** generated a *S*-thioester that in principle is as ready enolizable as **32**, but much more prone to undergo addition/elimination,[27] and thus much more likely to directly deliver the β-lactam ring (Scheme 11).



Scheme 11

Indeed, when **36** was transformed into its titanium enolate (−78°C, dichloromethane, 30 min) and then reacted with *N*-benzylideneaniline for 6 h at −78°C, a 60:40 mixture of *trans*- and *cis*-β-lactams **37t** and **37c** was obtained in 60% yield.[28] Optimization of the reaction parameters (enolization at −78°C, condensation from −78 to 0°C) gave a 99% yield and a slightly improved diastereoselectivity (**37t/37c** = 75:25).

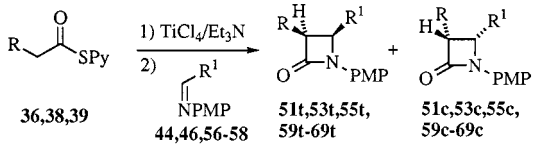
The scope of the reaction was established by the experiments collected in Scheme 12.[28] They showed that this methodology could be extended to sterically hindered (**39**, **42**) and heterosubstituted (**40**, **41**) *S*-thioesters, and to aromatic (**43** and **44**), unsaturated (**46**), and aliphatic (**45**) imines.



	R	R^1	R^2	R^3		Y%	*t/c*
38 + 43	Et	H	Ph	Bn	**47**	95	85/15
39 + 43	i-Pr	H	Ph	Bn	**48**	83	92/8
40 + 43	PhthN	H	Ph	Bn	**49**	40	98/2
41 + 43	BnO	H	Ph	Bn	**50**	64	9 /91
36 + 44	Me	H	Ph	pMeOPh	**51**	99	70/30
36 + 45	Me	H	Pr	Bn	**52**	90	30/70
36 + 46	Me	H	PhCH=CH	pMeOPh	**53**	99	60/40
38 + 46	Et	H	PhCH=CH	pMeOPh	**54**	91	70/30
39 + 46	i-Pr	H	PhCH=CH	pMeOPh	**55**	52	75/25
42 + 43	Me	Me	Ph	Bn	**56**	81	-

Scheme 12

The dependence of the *trans*/*cis* stereoselectivity on the structural features of the reaction partners was studied in detail by the experiments collected in Scheme 13,[29] where *S*-thioesters **36**, **38**, and **39** were condensed with imines **44**, **46**, and **56**−**58** in all the possible combinations.[30]

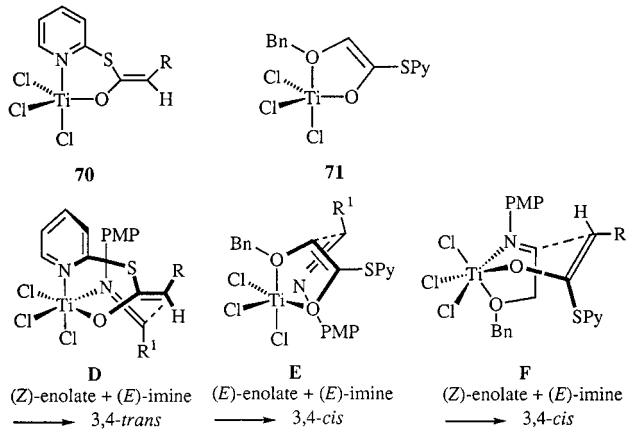


	R	R^1		Y%	*t/c*
36 + 44	Me	Ph	**51**	99	70/30
36 + 46	Me	PhCH=CH	**53**	99	60/40
36 + 56	Me	Pr	**59**	48	37/63
36 + 57	Me	CH_2OSiPh_2Bu-t	**60**	40	46/54
36 + 58	Me	CH_2OBn	**61**	40	23/77
38 + 44	Et	Ph	**62**	90	80/20
38 + 46	Et	PhCH=CH	**54**	91	70/30
38 + 56	Et	Pr	**63**	40	47/53
38 + 57	Et	CH_2OSiPh_2Bu-t	**64**	52	63/37
38 + 58	Et	CH_2OBn	**65**	43	24/76
39 + 44	i-Pr	Ph	**66**	91	85/15
39 + 46	i-Pr	PhCH=CH	**55**	52	75/25
39 + 56	i-Pr	Pr	**67**	45	83/17
39 + 57	i-Pr	CH_2OSiPh_2Bu-t	**68**	46	61/39
39 + 58	i-Pr	CH_2OBn	**69**	48	33/67

Scheme 13

By considering the data of Scheme 12 and 13 as a whole, a few empirical rules were drawn to predict the *trans*/*cis* stereoselectivity of this β-lactam synthesis: (1) large and nonchelating groups at *S*-thioester C-2 and at the imine carbon result in a *trans*-selective reaction; (2) the presence of even one chelating substituent at either one of these positions induces the formation of *cis*-azetidinones; (3) imines derived from linear aliphatic aldehydes are more prone to produce a *cis*-β-lactam than those derived from unsaturated aldehydes.

The organization of all these experimental data in a single framework appeared very difficult, since many different factors can concur in determining the stereochemical results. Among these, the enolate and imine configuration, and the cyclic or acyclic nature of the transition state seemed decisive. A ^{1}H NMR study of the *S*-thioester/titanium tetrachloride complexation and of the enolization[31] strongly suggested that from *S*-thioesters **36**, **38**, and **39** (*Z*)-enolates such as **70** are predominantly formed, whereas compound **41** gives only the chelated (*E*) species **71** (Scheme 14).



Scheme 14

^{1}H NMR experiments also showed that aromatic and unsaturated imines such as **44** and **46** existed and were likely to react in their (*E*) configuration, while aliphatic or alkoxyalkyl-substituted imines such as **56**−**58** contained almost equal mixtures of (*E*) and (*Z*) isomers.[30]

In proposing models of stereoselection, we thought that cyclic rather than acyclic transition states should be considered, since in the poorly coordinating dichloromethane, the imine nitrogen should strongly bind a good Lewis acid such as the trichlorotitanium enolate. On these bases, the formation of *trans*-β-lactams from *S*-thioesters such as **36**, **38**, and **39** can be accounted for by the chair-like model **D**. This should be particularly favored when R^1 and R^2 are both bulky groups. That is the case when maximum *trans* selectivity is observed. From the same *S*-thioesters, *cis*-products can be formed via transition structures involving either an (*E*)-enolate or a (*Z*)-imine, a situation more likely to occur when R^1 and R^2 are small groups.

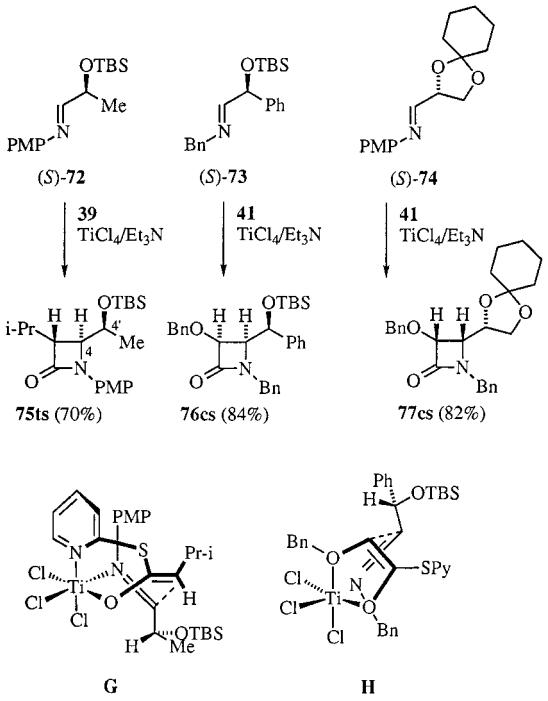
The formation of *cis*-azetidinones from *S*-thioesters such as **41** can be explained by model **E**, where the (*E*)-enolate reacts with an (*E*)-imine in a boat-like transition state. As shown by the data of Scheme 13, *cis* products are also predominantly obtained from chelating α-alkoxyimines such as **65**. In this case, it is possible that the imine alkoxy group

displaces the (*Z*)-enolate pyridyl residue from the coordination sphere of titanium. Addition of the enolate to the chelated (*E*)-imine, as in chair like model **F**, produces a *cis*-β-lactam.

With this versatile one-pot synthesis of azetidinones in hand, control of the absolute stereochemistry of the products was attempted using enantiomerically pure reagents.

Chiral Imines

Imines derived from chiral α-alkoxy and α,β-dialkoxyaldehydes such as **72**−**74** have been extensively used by several research groups for the preparation of enantiomerically pure β-lactams. When these imines were treated with the titanium enolates of 2-pyridyl thioesters, very high and often unprecedented levels of 4,4′-*syn* stereocontrol were observed in the formation of the azetidinones.[31] For instance, the condensation of (*S*)-**72** with *S*-thioester **39** (Scheme 15) gave 3,4-*trans*-4,4′-*syn*-β-lactam **75ts** in 70% yield as the only detected isomer. By *N*-deprotection of this compound (87% yield) a precursor of the carbapenem antibiotic (+)-PS-6 was obtained.[32]



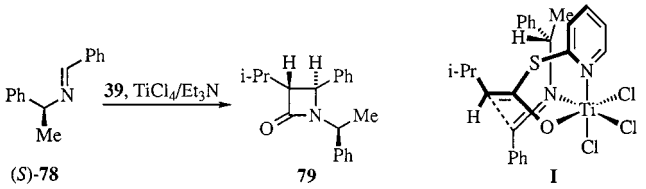
Scheme 15

Reaction of *S*-thioester **41** with imine (S)-**73** afforded 3,4-*cis*-4,4′-*syn*-azetidinone **76cs** in a large excess over the 3,4-*trans*-4,4′-*syn* isomer (84% yield, *dr* 94:6).[33] Functional group manipulation converted **76cs** into (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid, a bestatin component.[34]

3,4-*cis*-4,4′*syn*-β-Lactam **77cs**, obtained in 82% yield as a single isomer from imine **74** and *S*-thioester **41**,[33] was transformed first into the corresponding 4-formyl derivative, and then into a precursor of the renin inhibitor (2*S*,3*R*)-3-amino-2-hydroxy-4-cyclohexylbutanoic acid.[35]

The formation of *syn*-configured compounds **75** and **76** can be explained by models **G** and **H** derived from **D** and **E**, respectively, by replacement of the achiral R^2 group with the (*S*) residue of **72** and **73**. In both models, the small substituent at the stereocenter is located in the more sterically demanding position, and the enolate attacks *anti* to the bulkier group.

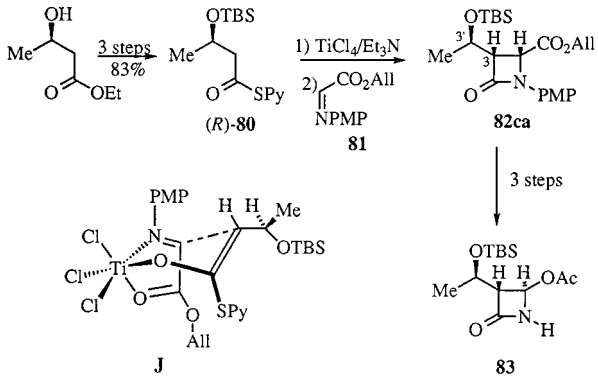
Several enantiomerically pure amines were screened as possible chiral auxiliaries for this β-lactam synthesis,[36] but only in some cases were good results obtained. For instance (Scheme 16), condensation of *S*-thioester **39** with imine (*S*)-**78** gave a 85:8:4:3 mixture of the four possible β-lactams. The major isomer, which has the indicated structure **79**, is believed to arise from model **I**, again derived from **D**.



Scheme 16

Chiral *S*-Thioesters

The pharmacological relevance of the β-lactams belonging to the thienamycin family led us to investigate the reaction of *S*-(2-pyridyl) thioester (*R*)-**80** (Scheme 17). This compound, which was easily prepared in three steps and 83% overall yield from ethyl (*R*)-3-hydroxybutanoate,[31] could deliver the (*R*)-1-hydroxyethyl side chain at C-3 of the azetidinone present in the structures of these powerful antibiotics.

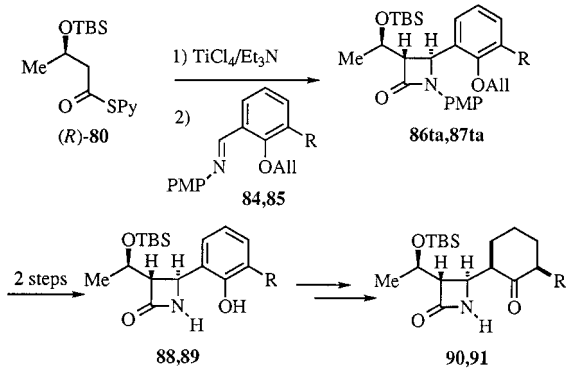


Scheme 17

As far as the *trans*/*cis* stereoselectivity of the condensations with a variety of imines is concerned, compound **80** behaved very similarly to its isosteric, achiral analogue **39**. In addition, it showed a very strong tendency to generate the *anti* configuration at C-3/C-3′ of the β-lactam ring, i.e. the same configuration of the bioactive azetidinones. For instance reaction of (*R*)-**80** with imine **81** gave a 94:6 mixture of the two *cis* products. The major product, the 3,4-*cis*-3,3′-*anti* compound **82ca**, was transformed in three steps

into the acetoxy derivative **83**.[37] This is the most common precursor for the synthesis of thienamycin and its congeners.[38] The formation of **82ca** was tentatively explained by model **J** in which the enolate attacks the chelated imine, placing the small hydrogen substituent in the more sterically crowded position to minimize steric repulsion.

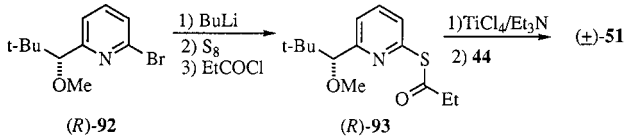
S-Thioester (*R*)-**80** was also used as starting material in the synthesis of some precursors of the powerful antibiotic Sanfetrinem (Scheme 18).[39] Reaction of (*R*)-**80** with imines **84** and **85** led to the stereoselective formation of β-lactams **86ta** and **87ta** in high yields (**86**: 91%, *dr* 91:9; **87**: 96%, *dr* 93: 7).[40]



Scheme 18

Removal of the allyl and 4-methoxyphenyl protecting groups gave compounds **88** and **89** in 58 and 56% yield, respectively; these were converted into the Sanfetrinem precursors **90** and **91** by a poorly-stereoselective dearomatization reaction, followed by Swern oxidation. Both these azetidinones, obtained as stereoisomeric mixtures, can be transformed into Sanfetrinem.

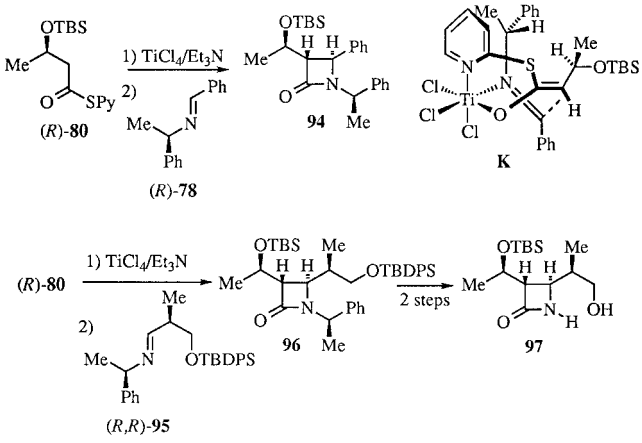
Chiral *S*-(2-pyridyl) thioesters can, in principle, also be obtained by replacement of the achiral pyridyl residue with an enantiomerically pure one. To this end, compound (R)-**92** was prepared following a described procedure[41] and then converted into *S*-thioester **93** (Scheme 19). Condensation with imine **44** gave β-lactam **51** in very high yield (90%, *trans*/*cis* = 70:30) but in virtually racemic form. The distance between the pre-existing stereocenter and the ones being formed is likely to be responsible for this poor stereoselectivity.[42]



Scheme 19

Multiple Stereoselection

The condensation of *S*-thioester (R)-**80** with the enantiomers of imine **78** was studied to exploit the principle of multiple stereoselection[43] in this synthesis of azetidinones (Scheme 20). It was found that the (*R*)-**80** + (*R*)-**78** combination represented the matched pair, and that the condensation between these compounds led to the formation of a single β-lactam **94** in 65% yield. Several other imines derived from (*R*)-α-methylbenzylamine reacted with (*R*)-**80** with very high stereoselectivity, and often only one of the four possible products was formed in fair to high yields.

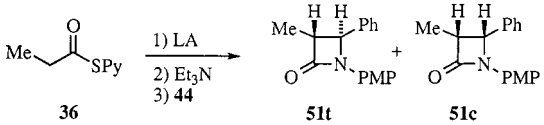


Scheme 20

These results were tentatively rationalized by model **K** in which both stereocenters adopt their less-hindered conformation, thus leading to the observed stereochemical result. The synthesis of the 1-β-methylthienamycin precursor **97** via adduct **96** [obtained as the only product from (*R*)-**80** and (*R*,*R*)-**95**] served to illustrate the scope of this approach.[44]

Tin, Aluminum, and Boron Enolates

In additon to titanium tetrachloride, several other Lewis acid were tested as activators for the enolization of *S*-(2-pyridyl) thioesters. Among the effective ones, tin tetrachloride,[45] aluminum tribromide and diethylaluminum chloride,[46] and boron trichloride[47] gave the best results. Using the synthesis of β-lactam **51** as a model reaction, it was shown that none of the enolates derived from these Lewis acid could compete with the titanium enolate in terms of chemical yields, while some improvements could be observed in terms of stereoselectivity (Scheme 21).

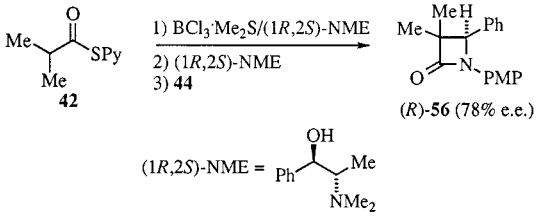


LA	Y%	51t/51c
$TiCl_4$	99	70/30
$SnCl_4$	71	77/23
$AlBr_3$	54	82/18
$EtAlCl_2$	60	92/ 8
BCl_3	43	75/25

Scheme 21

Further experiments demonstrated that tin, aluminum, and boron enolates had a more limited application to β-lactam synthesis than titanium enolates, and thus their chemistry was not further developed. Boron enolates, however, offered an interesting option that was not found with the other metal enolates, namely the possibility of controlling the stereochemistry of the reaction by the use of chiral metal ligands.[47]

It was found that the chiral Lewis acids prepared by mixing equimolar amounts of the boron trichloride−dimethyl sulfide complex and (1*R*,2*S*)-*N*-methylephedrine (NME)[48] could be used as an activator to promote the enolization of *S*-(2-pyridyl) thioesters, and that the resulting enolate reacted with achiral imines to afford enantiomerically enriched β-lactams. For instance (Scheme 22), the condensation of *S*-thioester **42** with imine **44** gave azetidinone (*R*)-**56** in 70% yield and 38% *ee*. This was increased to 78% by



Scheme 22

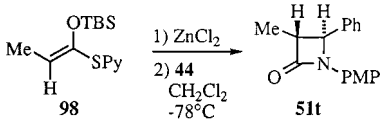
using NME both as the chiral ligand and the enolizing base.

Despite several attempts involving the use of about fifteen different amino alcohols and of various *S*-thioesters and imines, the 78% *ee* mark could not be improved. This was also attributed to the fact that the actual nature of the chiral Lewis acids and the structure of the transition state of the reaction remained unknown.

In concluding the discussion on the one-pot synthesis of β-lactams by the use of *S*-thioester metal enolates, it must be noted that the lithium enolate of *S*-phenyl 2-fluorothiopropanoate was reported to condense with aromatic imines to afford 3-fluoro-substituted azetidinones in fair to good yield and excellent *trans* stereoselectivity.[49]

Silyl Ketene Thioacetals

Hirai and co-workers were the first to report the one-pot synthesis of β-lactams by the Lewis acid promoted, Mukaiyama-type reaction of a series of silylketene thioacetals (SKTA) derived from *S*-(2-pyridyl) thioesters with nonenolizable imines (Scheme 23).[50]

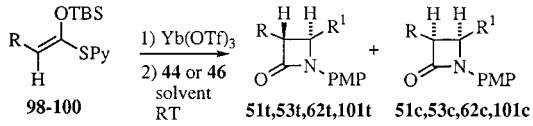


Scheme 23

For instance, in the presence of a stoichiometric amount of zinc chloride (the best promoter among the Lewis acids tested) SKTA **98** condensed with imine **44** to afford β-lactam **51** as a single *trans* isomer in 68% yield. In some cases, better yields were obtained by introducing a methyl substituent in the 3-position of the pyridyl residue of the SKTA.

By exploring this condensation in great detail, we found that it could be extended to several SKTA and imines, and that the reaction could be promoted by many Lewis acids (titanium tetrachloride, boron trifluoride−diethyl ether, ethylaluminum dichloride, and *tert*-butyldimethylsilyl triflate), all of which performed better than zinc chloride.[51]

A more significant breakthrough in this reaction was achieved by the discovery that a catalytic amount (10% mol) of ytterbium triflate was enough to obtain many β-lactams in fair to good yields. A few examples are reported in Scheme 24.[52]



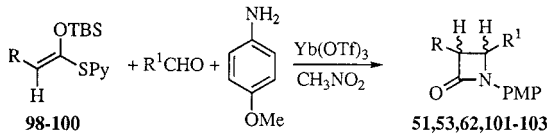
SKTA	R	Imine	R^1	solvent	Product	Y%	t/c
98	Me	**44**	Ph	CH_2Cl_2	**51**	77	66/34
98	Me	**44**	Ph	CH_3CN	**51**	63	97/3
98	Me	**44**	Ph	CH_3CN	**51**	62[a]	95/5
98	Me	**44**	Ph	CH_3NO_2	**51**	99	89/11
98	Me	**46**	PhCH=CH	CH_3CN	**53**	42	84/16
98	Me	**46**	PhCH=CH	CH_3NO_2	**53**	90	60/40
99	Et	**44**	Ph	CH_3CN	**62**	62	95/5
100	BnO	**44**	Ph	CH_3CN	**101**	49	60/40

Scheme 24

The results showed that the yields and the *trans*/*cis* ratios of the azetidinones depended on the solvent used, with acetonitrile giving the best stereoselection and nitromethane the best yield. The relatively expensive but easily recoverable catalyst performed satisfactorily when reused. This catalytic synthesis, however, turned out to be less general than the one based on the use of titanium enolates. For instance, the SKTA derived from *S*-thioester (*R*)-**80** reacted sluggishly with imines, and the condensation of some SKTA with imine (*S*)-**74** was poorly stereoselective.[52]

The use of ytterbium triflate as catalyst in these reactions, however, gave rise to an unprecedented result. This is described in Scheme 25.[52] Keeping in mind the ability of ytterbium triflate to activate imines toward nucleophilic attack,[53] a three-component β-lactam synthesis was performed in which the imine was generated in situ. Thus, when a mixture of the catalyst, an aldehyde, 4-methoxyaniline, and SKTA **98−100** in nitromethane was stirred for 15 h at room temp., azetidinones **51**, **53**, **62**, and **101−103** were obtained as mixtures of *trans*/*cis* isomers in good to high yields.

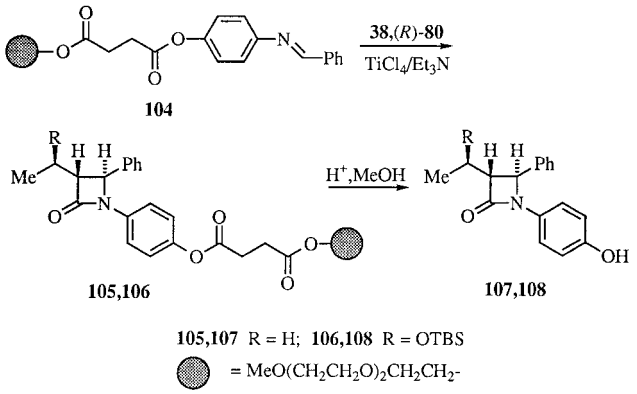
The multicomponent nature of this reaction could be useful in anticipation of a possible application to the field of combinatorial chemistry. With this in mind, the soluble polymer-supported synthesis of β-lactams described in Scheme 26 was developed.[54] Using the monomethyl ether of polyethylene glycol of MW 5000 as the polymer,[55] imine **104** was obtained in four easy steps. This reacted with the



SKTA	R	R^1	Product	Y%	t/c
98	Me	Ph	**51**	82	90/10
98	Me	PhCH=CH	**53**	69	60/40
98	Me	2-thienyl	**102**	54	87/13
98	Me	cyclohexyl	**103**	90	40/60
99	Et	Ph	**62**	78	95/5
100	BnO	Ph	**101**	59	69/31

Scheme 25

titanium enolates derived from *S*-thioesters **38** and (*R*)-**80** to afford the supported azetidinones **105** and **106**.



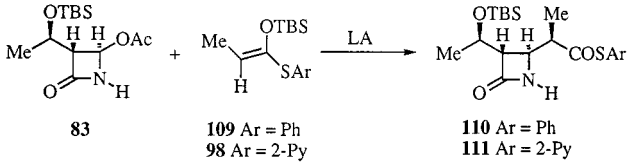
Scheme 26

Acid-catalyzed methanolysis of these compounds gave the polymer-free β-lactams **107** and **108** in 54 and 30% overall yield, respectively. Remarkably, the reactions carried out on the polymer-supported imine showed levels of stereoselectivity very similar to those observed for the nonsupported analogue **44**. Thus, **107** was obtained as a 85:15 mixture of *trans* and *cis* isomers, while **108** was isolated as a single 3,4-*trans*-3,3′-*anti* isomer.

Modification of the β-Lactam Nucleus by SKTA/Imine Reaction

The condensation between SKTA and an imine was also used to stereoselectively introduce a propionic acid sidechain at C-4 of the β-lactam ring en route to 1-β-methylthienamycin antibiotics (Scheme 27).

Bristol−Myers reseachers[56] found that the Lewis acid promoted reaction of acetoxyazetidinone **83** with SKTA **109** gave compound **110** in excellent yield (87%) and stereoselectivity (*dr* = 95:5) in favor of the desired β-methyl isomer. The reaction was believed to proceed *via* the cyclic imine obtained by formal elimination of acetic acid from **83**, followed by nucleophilic attack at C-4 by the SKTA. Replacement of **109** with **98**[57] led to **111** in slightly lower yield (72%) but with total β-stereocontrol. However, more



Scheme 27

complex derivatives of **98** failed to show the same efficiency in related reactions.[58]

Conclusions

S-Thioesters in general, and *S*-(2-pyridyl) thioesters in particular, have proved to be very versatile reagents for the efficient preparation of a variety of β-lactams by the enolate/imine condensation reaction. The remarkable levels of stereoselection observed in some of the reactions described in this *Microreview* make *S*-thioesters the reagents of choice for the synthesis of many biologically active azetidinones, and it can be anticipated that they will find widespread use in future.

Acknowledgments

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