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Syntheses of 3-Amino-2-azetidinones: A Literature Survey

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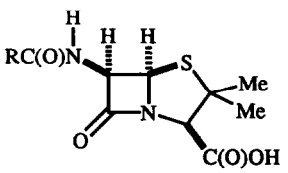
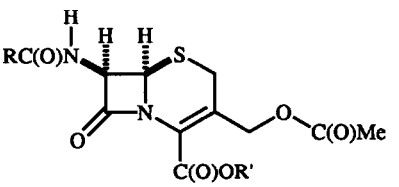
INTRODUCTION

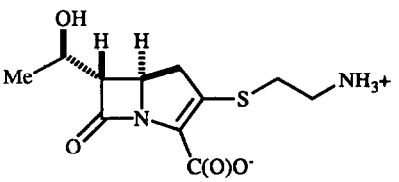
2-Azetidinones (β-lactams) are four-membered cyclic amides derived from 3-amino-propanoic acids The first member of this class of compounds was synthesized by Staudinger in 1907 [1] However, until the discovery of penicillin (Fig 1) by Fleming in 1929, the importance of β-lactams as antibiotics was not recognized [2] Penicillin and its derivatives are still the most widely used antibiotics After the discovery of the antibacterial activity of penicillin, thousands of compounds containing the β-lactam ring have been either isolated from natural sources or synthesized by chemical means [3] Figure 1 presents the structures of several β-lactam antibiotics that have been applied clinically



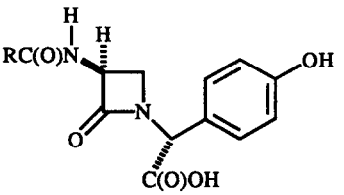
Penicillin (natural, 1929)



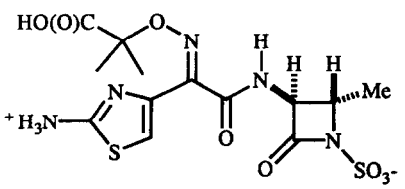
Cephalosporin (natural, 1945)



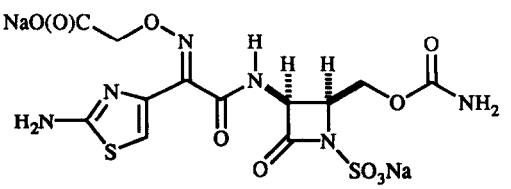
Thienamycin (natural, 1976)



Nocardicin (natural, 1976)



Aztreonam (synthetic, 1981)



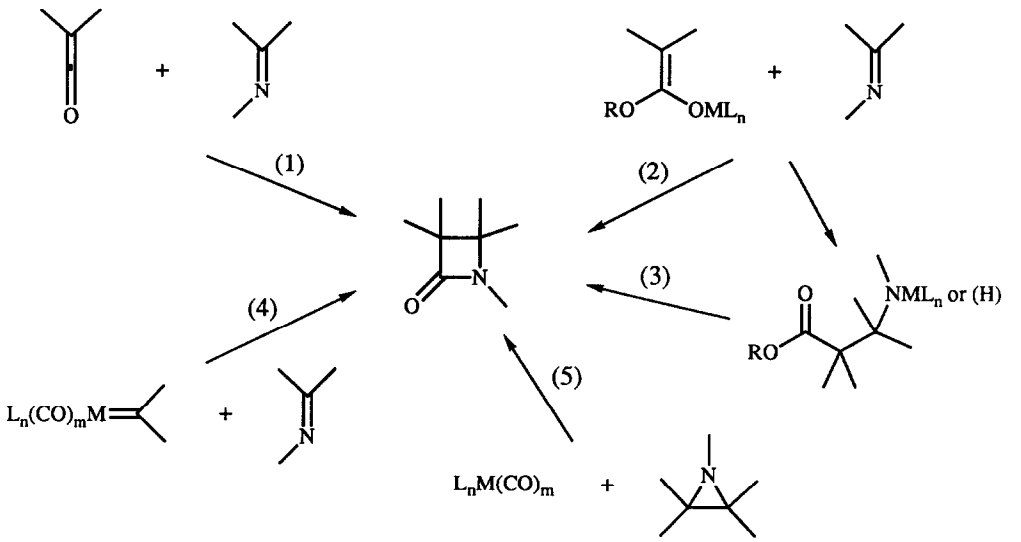
Carumonam (synthetic, 1982)

Figure 1. Important β-lactam antibiotics

Most of the penicillins and cephalosporins are obtained by biosynthesis or by chemical modification of intermediates that are produced *via* biosynthesis However, because the growing resistance of bacteria against penicillins and cephalosporins and the need for medicines with a more specific antibacterial activity, several synthetic and semi-synthetic β-lactam antibiotics have been developed by the pharmaceutical industry The most important compounds among these are given in Figure 1

The commonly applied routes for the direct construction of the 2-azetidinone ring are outlined in Scheme I The Staudinger cycloaddition (1) is the reaction which has been the most extensively developed [3] However, in most cases the products obtained *via* this reaction are mixtures of all of the possible stereoisomers Noteworthy in this respect is the recent work of several research groups that have, independently, developed highly stereoselective syntheses of several 2-azetidinones based upon the ketene - imine cycloaddition (*vide infra*)

Scheme 1



The progress of modern organometallic chemistry has shown that by using organometallic reagents organic reactions can be selectively tuned, giving control over reactivity, regio-, diastereo- and enantio-selectivity [4] Based on this knowledge, several metal-mediated synthetic routes to β-lactams have been developed including the ester enolate - imine condensation (2) and subsequent ring-closure of the formed β-amino esters (3), the ketene - imine cycloaddition using metallo-carbene intermediates (4), and the annelation of aziridines by transition-metal catalysts (5) Reviews concerning several of these separate routes have appeared in literature [5,6,7]

This report gives an overview of the recent advances in the synthesis of 3-amino-2-azetidinones and will deal only with synthetic methods directed towards the construction of the β-lactam ring

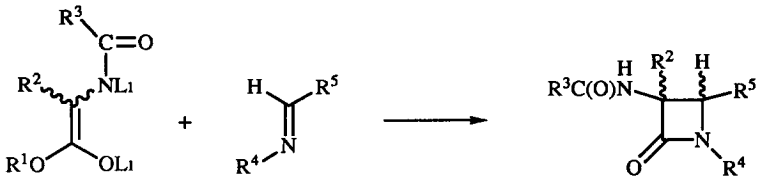
THE ESTER ENOLATE - IMINE CONDENSATION

Gilman and Speeter were the first to report the preparation of a β-lactam by the condensation of Reformatsky reagents (*i e* zinc ester enolates) with simple imines [8] Development of this ester enolate - imine condensation started in the late 1970's when enolate chemistry had become standard for organic synthesis In the last decade several research groups have studied the synthesis of β-lactams *via* metal ester enolates [5,6,9]

This report will focus on the construction of the 3-amino-substituted β-lactam ring from metal ester enolates and imines and includes the Lewis-acid catalyzed condensation of silylketene acetals with imines In most cases a

direct conversion to a β-lactam is observed, but in some instances the reactions provide non-cyclized β-amino esters which require cyclization to the β-lactam.

The first strategy that has been applied for the synthesis of 3-amino-2-azetidinones is shown in equation 6 The amino-function of the starting glycine esters is protected by an acyl or carbamate group Treatment of the protected α-amino esters with two equivalents of lithium amide (usually lithium di-*iso*-propylamide = LDA) afford the lithium dianions that react with appropriate imines giving 3-(protected)amino-2-azetidinones (Table 1)



(6)

Table 1 Reactions of α-Amido Ester Enolates (Lithium Dianions) with Imines.

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	*cis* *trans*[a] (*e e*)	ref
1	Et	H	Ph	Ph	Ph	45	0 100	10
2	Et	Me	Ph	Ph	Ph	91	0 100	10
3	(-) menthyl	Me	Ph	Ph	Ph	75	0 100 (4)	10
4	Me	OMe	Ph	Ph	Ph	84	0 100	11
5	Me	OMe	Ph	1-naphthyl	Ph	88	0 100	11
6	Me	OMe	Ph	Ph	p-ClC_6H_4	91	0 · 100	11
7	Me	OMe	BnO	1-naphthyl	Ph	84	0 100	11
8	Me	OMe	BnO	Ph	p-ClC_6H_4	91	0 100	11
9	Et	H	BnO	2,4-$(MeO)_2$Bn	H[b]	63		12
10	Et	Me	BnO	2,4-$(MeO)_2$Bn	H[b]	74		12
11	Et	Me	*t*-BuO	2,4-$(MeO)_2$Bn	H[b]	60		12
12	Et	*t*-Pr	*t*-BuO	2,4-$(MeO)_2$Bn	H[b]	45		12
13	Et	H	*t*-BuO	(*R*)-(4-BnOPh)C(H)OBn	H[b]	51	(33)	12
14	Me	Me	Ph	p-$MeOC_6H_4$	C(H)=N-Ar[c]	80	55 45	13

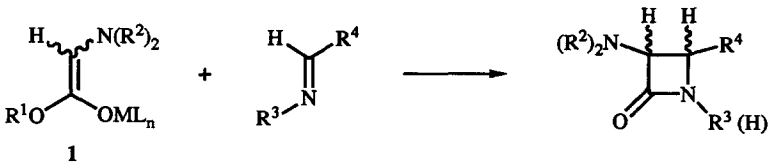
[a] Refers to the relative position of the $R^3C(O)N(H)$- and R^5-substituents, irrespective of the priority of the R^2-substituent [b] The imine was generated *in situ* from the secondary *N*-(cyanomethyl)amine [c] Ar = p-$MeOC_6H_4$

Gluchowski and Bose and coworkers (Entries 1-8) synthesized 3-methyl- and 3-methoxy-substituted 2-azetidinones they used only *N*-aryl- and *C*-aryl-substituted imines so that no useful intermediates for the synthesis of β-lactam antibiotics were obtained Noteworthy is the excellent diastereoselectivity of these reactions in that only *trans*-3-amino-4-aryl-2-azetidinones were obtained This is rather surprising, since monoanionic lithium ester enolates usually yield *cis*-2-azetidinones or mixtures of both *cis*- and *trans*-isomers (*vide infra*) The use of a chiral menthyl ester as a starting material resulted in a disappointingly low induction (4% *e e* , Entry 3)

Overman and Osawa (Entries 9-13) have applied *in situ* generated imines derived from formaldehyde, giving 4-unsubstituted-2-azetidinones which are intermediates for the synthesis of nocardicins (Fig 1) With increasing bulk of the R^2-substituent, the yields of the 2-azetidinones drop markedly (Entries 9-12) The use of a chiral imine derived from (*R*)-phenylglycine (Entry 13), affords an intermediate for nocardicin in a moderate yield and modest enantioselectivity

Alcaide and coworkers were the first to report about the use of α-diimines as imine components, providing a protected aldehyde function at the 4-position of the 2-azetidinone 4-Formyl-2-azetidinones are versatile synthons for several monobactam and penem antibiotics [3,6,9] However, the reaction of the lithium enediolate of methyl 2-(benzoylamino)propionate with *N,N'*-1,4-di(*p*-methoxyphenyl)-1,4-diaza-1,3-butadiene is unselective, affording almost equal amounts of the *cis*- and *trans*-2-azetidinone (Entry 14)

Other means of protection of the amino-function as diallyl, dibenzyl, and disilyl derivatives have been extensively studied (eqn 7) In most cases special attention was given to 2-azetidinone products that would be useful intermediates for the synthesis of known β-lactam antibiotics For example, imines *N*-substituted with easily removable group, *e g* trimethylsilyl, benzyl, etc., were used. The results of these studies are summarized (Table 2)



(7)

1

1a R^1 = Me, R^2 = allyl, **1b** R^1 = Et, R^2 = $Me_2SiCH_2CH_2SiMe_2$
1c R^1 = Et, R^2 = benzyl, **1d.** R^1 = Et, R^2 = Me_3Si

The application of 1,2-bis(dimethylsilyl)ethane as cyclic protecting disilyl group (as in **1b**) proved to be the most suitable because the protecting reagent is readily available, cheap, and easily removed by acid or base catalyzed hydrolysis Overman and Osawa have applied this group to obtain intermediates for nocardicins and obtained reasonable to good yields of the 3-amino-4-unsubstituted-2-azetidinones (Entries 3-5) Cainelli and coworkers have studied the reactions of lithium enolate **1b** with several *in situ* prepared *N*-(trimethylsilyl)imines to afford 3-amino-4-substituted-2-azetidinones in moderate yields (Entries 10-14) These reactions generally display a high *cis*-stereoselectivity (*d e* 80-90%) An exception is the reaction of the imine derived from *iso*-butyraldehyde This displays a high *trans*-stereoselectivity (*d e* 84%, Entry 12)

Our research-group has extensively studied the reactions of several metal enolates derived from *N,N*-diprotected glycine esters with imines [22-27] The most important results are shown in Table 2, Entries 15-36 As observed by Cainelli and coworkers, the lithium enolate **1b** (and **1c**) reacts with *N*-(trimethylsilyl)imines to afford *cis*-3-amino-2-azetidinones in excellent yields and with a good stereoselectivity (*d e* 68-94%, Entries 15, 25, 31, 33, and 36) However, when an appropriate metal compound, *e g* $ZnCl_2$ or $alkyl_2AlCl$, is added to the lithium enolates, which are then converted into the corresponding zinc and aluminum enolates, respectively, the reactions with imines then yields *trans*-3-amino-2-azetidinones in excellent yields with a good stereoselectivity (*d e* 34-100%) Furthermore, the zinc and aluminum mediated reactions permit the use of *N*-(alkyl)imines which are usually easier to prepare and are more stable By proper choice of substituents, metal, and reaction conditions we are able to synthesize selectively either the *cis*- or *trans*-isomers of several useful 3-amino-4-substituted-2-azetidinones in excellent yields

Noteworthy in this respect are the syntheses of *i*) *trans*-3-amino-4-(trimethylsilyl)ethynyl-2-azetidinone (Entry 22), a versatile intermediate for the synthesis of mono- as well as bicyclic-β-lactam antibiotics, *ii*) *trans*-1-benzyl-3-amino-4-methyl-2-azetidinone (Entries 23 and 24), an intermediate for the synthesis of aztreonam and related monobactam antibiotics (see Fig 1), *iii*) both *cis*- and *trans*-3-amino-4-(2-furyl)-2-azetidinones (Entries 34-36) The furyl group can be readily oxidized to a carboxyl group,[28] resulting in a versatile intermediate for the synthesis of monocyclic- and bicyclic-β-lactam antibiotics

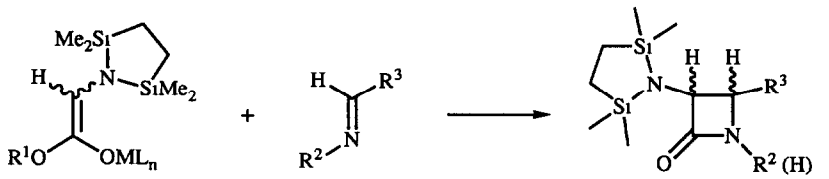
The results summarized in Table 2 show that control of the diastereoselectivity of the metal ester enolate - imine condensation has been well-documented However, complete control of the enantioselectivity is also required in an efficient approach towards the synthesis of known β-lactam antiobiotics that have a specific absolute configuration To our knowledge, only those reactions using the cyclic disilyl derivate as protection of the amino-function have been studied for the enantioselective synthesis of 3-amino-2-azetidinones (eqn 8)

Table 2 Reactions of *N,N*-Protected α-Amino Ester Enolates with Imines.

Entry	Ester	R^3	R^4	ML_n^+	Yield (%)	*cis* *trans*	ref
1	**1a**	OBn	H	$SiMe_3$[a]	52[b]		14
2	**1b**	5-(2-Bn)2*H*-tetrazole	Me	Li	59[b]	76 26	15
3	**1b**	Bn	H[c]	Li	43[d]		12
4	**1b**	2,4-$(MeO)_2$Bn	H[c]	Li	80[d]		12
5	**1b**	2,5-$(MeO)_2C_6H_3$	H[c]	Li	47[d]		12
6	**1c**	*p*-$MeOC_6H_4$	CF_3	Li	63	0 100	16
7	**1b**	$SCPh_3$	Me	Li	78	83 17	17
8	**1b**	*p*-$MeOC_6H_4$	C(H)Me[e]	Li	34		18
9	**1b**	c-hexyl	C(H)Ph[e]	Li	45		18
10	**1b**	$SiMe_3$ / H[f]	Me[g]	Li	40[h]	90 10	19
11	**1b**	$SiMe_3$ / H[f]	Et[g]	Li	57[h]	90 10	19
12	**1b**	$SiMe_3$ / H[f]	*i*-Pr[g]	Li	28[h]	8 92	19
13	**1b**	$SiMe_3$ / H[f]	2-furyl[i]	Li	43[d]	95 5	20, 21
14	**1b**	$SiMe_3$ / H[f]	2-thienyl[i]	Li	35[d,h]	90 10	21
15	**1b**	$SiMe_3$ / H[f]	Ph	Li	99	96 4	22
16	**1b**	Me	Ph	ZnCl[j]	97	8 92	22, 23
17	**1d**	Me	Ph	ZnCl[j]	75	0 100	22, 23
18	**1b**	Me	Ph	$AlEt_2$[k]	96	8 92	24
19	**1b**	$SiMe_3$ / H[f]	Ph	ZnCl[j]	96	14 86	22, 23
20	**1d**	$SiMe_3$ / H[f]	Ph	ZnCl[j]	70	0 100	22, 23
21	**1b**	$SiMe_3$ / H[f]	Ph	$AlEt_2$[k]	94	10 90	24
22	**1b**	$SiMe_3$ / H[f]	C≡C$SiMe_3$	ZnCl[j]	93	3 97	22, 23
23	**1b**	Bn	Me	ZnCl[j]	98	9 91	22, 23
24	**1b**	Bn	Me	$AlEt_2$[k]	96	5 95	24
25	**1c**	$SiMe_3$ / H[f]	Ph	Li	91	84 16	22
26	**1c**	$SiMe_3$ / H[f]	Ph	ZnCl[j]	94	0 100	22
27	**1c**	Me	Ph	ZnCl[j]	80	33 67	22, 25
28	**1b**	*t*-Bu	C(H)=N*t*-Bu	ZnCl[j]	94	0 100	26, 27
29	**1b**	*t*-Bu	2-pyridyl	ZnCl[j]	99	0 100	27
30	**1b**	$SiMe_3$ / H[f]	2-pyridyl	ZnCl[j]	96	0 100	27
31	**1b**	$SiMe_3$ / H[f]	2-pyridyl	Li	92	91 9	27
32	**1b**	$SiMe_3$ / H[f]	2-thienyl[l]	ZnCl[j]	87	15 85	27
33	**1b**	$SiMe_3$ / H[f]	2-thienyl	Li	99	94 6	27
34	**1b**	$SiMe_3$ / H[f]	2-furyl	ZnCl[j]	92	8 92	27
35	**1b**	$SiMe_3$ / H[f]	2-furyl	$AlMe_2$[m]	87	4 96	24
36	**1b**	$SiMe_3$ / H[f]	2-furyl	Li	95	97 3	27

[a] Catalyzed by Me_3SiOTf [b] Yield of the non-cyclized aldolate An additional ring-closure to the β-lactam product is required [c] The imine was generated *in situ* from the secondary *N*-(cyanomethyl)amine [d] Ratio enolate : imine = 2 : 1 [e] The substituent is attached as alkylidene to the β-lactam ring [f] Upon hydrolysis replaced by a proton [g] The imine was prepared *in situ* from the aldehyde and LiHMDS [h] Isolated as the BnOC(O)N derivative [i] The imine was prepared *in situ* by reduction of the nitrile derivative [j] The enolate was prepared by transmetalation of the lithium enolate with $ZnCl_2$ [k] The enolate was prepared by transmetalation of the lithium enolate with two equivalents of Et_2AlCl [l] Reaction performed with the $ZnCl_2$-complex of the imine [m] The enolate was prepared by transmetalation of the lithium enolate with 1 2 equivalents of Me_2AlCl

Several approaches towards the enantioselective synthesis of 2-azetidinones are obvious Chiral information can be either put into the starting ester (R^1) or into the imine (either R^2 or R^3) These approaches have been studied by several groups (Table 3)



(8)

Table 3. Enantioselective Syntheses of 3-Amino-2-azetidinones *via* the Ester Enolate - Imine Condensation.

Entry	R^1	R^2	R^3	ML_n^+	Yield (%)	*cis trans* (*e e*)[a]	ref
1	Et	(*R*)-(4-BnOPh)C(H)Bn	H[b]	Li	72[c]	(83)	12
2	Et	(*R*)-(4-BnOPh)C(H)OMEM	H[b]	Li	54[c]	(83)	12
3	Et	(*S*)-(Ph)C(H)OBn	H[b]	Li	65[c]	(82)	12
4	(-) menthyl	*p*-MeOC$_6$H$_4$	Ph	Li	65[d]	0 100 (99)	29
5	(+) neomenthyl	*p*-MeOC$_6$H$_4$	Ph	Li	65[d]	74 26 (21)	29
6	(-) bornyl	*p*-MeOC$_6$H$_4$	Ph	Li	53[d]	63 37 (2)	29
7	(-) 2-Ph-1-c-hexyl[e]	*p*-MeOC$_6$H$_4$	Ph	Li	58[d]	0 100 (99)	29
8	(+) 2-Ph-1-c-hexyl[e]	*p*-MeOC$_6$H$_4$	Ph	Li	58[d]	0 100 (99)	29
9	(-) menthyl	SiMe$_3$ / H[f]	Ph	Li	38[d]	0 100 (68)	29
10	(-) menthyl	SiMe$_3$ / H[f]	C(H)=C(H)Ph	Li	48[d]	100 0 (11)	29
11	(-) 2-Ph-1-c-hexyl[e]	SiMe$_3$ / H[f]	C(H)=C(H)Ph	Li	46[d]	100 0 (78)	29
12	(-) menthyl	*p*-MeOC$_6$H$_4$	*p*-FC$_6$H$_4$	Li	55[d]	0 100 (99)	29
13	(-) menthyl	*p*-MeOC$_6$H$_4$	*p*-CF$_3$C$_6$H$_4$	Li	59[d]	0 100 (99)	29
14	(-) menthyl	*p*-MeOC$_6$H$_4$	*p*-MeOC$_6$H$_4$	Li	70[d]	11 89 (99)	29
15	(-) menthyl	*p*-MeOC$_6$H$_4$	3,4-(MeO)$_2$C$_6$H$_3$	Li	54[d]	9 91 (99)	29
16	Et	(*R*)-C(H)(Me)Ph	C(H)=NC(H)(Me)Ph	Li	50	0 100 (40)	30
17	Et	(*R*)-C(H)(Me)Ph	C(H)=NC(H)(Me)Ph	ZnCl[g]	91	0 100 (91)	30
18	Et	(*R*)-C(H)(Me)Ph	2-pyridyl	Li	67	0 100 (50)	30
19	Et	(*R*)-C(H)(Me)Ph	2-pyridyl	ZnCl[g]	98	0 100 (99)	30
20	Et	(*R*)-C(H)(Me)Ph	2-pyridyl	AlMe$_2$[h]	93	7 93 (90)	30
21	Et	(*R*)-C(H)(Me)Ph	2-furyl	ZnCl[g]	50	0 100 (35)[i]	30
22	Et	(*R*)-C(H)(Me)Ph	2-furyl	ZnCl[g]	82	89 11 (99)[j]	30
23	Et	(*R*)-C(H)(Me)Ph	C≡CSiMe$_3$	Li	70	50 50 (0)	30
24	Et	(*R*)-C(H)(Me)Ph	C≡CSiMe$_3$	ZnCl[g]	93	12 88 (57)	30
25	Et	(*R*)-C(H)(Me)Ph	C≡CSiMe$_3$	AlMe$_2$[h]	95	30 70 (34)	30
26	Et	(*R*)-C(H)(Me)Ph	Me	ZnCl[g]	87	20 80 (99)[i]	30
27	Et	(*R*)-C(H)(Me)Ph	Me	ZnCl[g]	97	88 12 (99)[j]	30
28	Et	(*S*)-C(H)(Me)Ph	Et	ZnCl[g]	95	5 95 (99)[i]	30
29	Et	(*S*)-C(H)(Me)Ph	Et	ZnCl[g]	96	100 0 (99)[k]	30
30	Et	SiMe$_3$ / H[f]	(*R*)-C(H)(OTBDMS)Me	Li	80[l]	0 100 (96)	31[m]
31	Et	*p*-MeOC$_6$H$_4$	(*R*)-C(H)CH$_2$OC(Me$_2$)O	Li	93	88 12 (59)	30
32	Et	*p*-MeOC$_6$H$_4$	(*R*)-C(H)CH$_2$OC(Me$_2$)O	ZnCl[g]	94	6 94 (99)	30

[a] Refers to the *e e* of the major isomer [b] The imine was generated *in situ* from the secondary *N*-(cyanomethyl) amine [c] Ratio enolate imine = 2 1 [d] Isolated as the deprotected 3-amino-2-azetidinone [e] The pure *trans* cyclohexyl derivative was used [f] Upon hydrolysis replaced by a proton [g] The enolate was prepared by transmetalation of the lithium enolate with $ZnCl_2$ [h] The enolate was prepared by transmetalation of the lithium enolate with 1 2 equivalents of Me_2AlCl [i] Reaction performed in Et_2O [j] Reaction performed in THF [k] Reaction performed in THF/HMPA (4 1 v/v) [l] Isolated as the BnOC(O)N derivative [m] The imine was prepared *in situ* from the aldehyde and LiHMDS

Overman and Osawa were the first to report the application of chiral imines, *N*-substituted with a group containing chiral information, in the (lithium) ester enolate - imine approach to 3-amino-2-azetidinones They obtained several useful intermediates for the synthesis of nocardicins in moderate yields with a high enantioselectivity (Entries 1-3)

Whereas the use of chiral esters, readily prepared from glycine and chiral alcohols, did not result initially in very impressive chiral inductions (see Table 1, Entry 3 and ref 32), very recently Ojima and Habus reported that the use of chiral *N,N*-disilylprotected glycine esters results in high chiral inductions (Entries 4-15) The best results were obtained with chiral menthyl or *trans*-2-phenyl-1-cyclohexyl glycine esters Surprisingly, with *C*-aryl substituted imines *trans*-2-azetidinones almost exclusively are formed (Entries 4, 7-9, and 12-15), whereas with the imine derived from cinnamic aldehyde a *cis*-2-azetidinone is formed exclusively (Entries 10 and 11) *Cis*-3-amino-4-styryl-2-azetidinone, a useful intermediate for the synthesis of several β-lactam antibiotics, has been prepared (46%) with a reasonable selectivity (78% *e e* , Entry 11) However, no useful *trans*-2-azetidinone has been synthesized by the method of Ojima and Habus

We have directed most of our efforts towards the use of imines derived from the relatively cheap, readily available, and easily removable,[33] (*R*)- and (*S*)-α-methylbenzylamines (Entries 16-29) Whereas the lithium mediated reactions gave poor results (Entries 16, 18, and 23), the aluminum and zinc mediated reactions afforded useful 3-amino-2-azetidinones in high yields In some cases, depending upon the reaction conditions, excellent stereoselectivity was observed Noteworthy in this respect are the syntheses of *trans*-3-amino-4-imino-2-azetidinone (91% yield, 100% *d e* , 91% *e e* , Entry 17), *cis*-3-amino-4-(2-furyl)-2-azetidinone (82% yield, 78% *d e* , 99% *e e* , Entry 22) and all possible stereoisomers of 3-amino-4-alkyl-2-azetidinones (yields 87-96%, *d e* 60-100%, *e e* 99%, Entries 26-29), which are key-intermediates in the synthesis of aztreonam (Fig 1) and related monobactam antibiotics

Only a few examples for the application of imines derived from chiral aldehydes in the synthesis of 3-amino-2-azetidinones have been reported Cainelli and coworkers have applied the *N*-(trimethylsilyl)imine derived from (*S*)-mandelic aldehyde, that reacted with the lithium enolate to yield, quite surprisingly, the *trans*-2-azetidinone as a single stereoisomer in 80% yield (Entry 30) We have applied the *N*-(*p*-methoxyphenyl)imine derived from *D*-glyceraldehyde and obtained the *cis*-2-azetidinone in 93% yield (76% *d e* , 59% *e e* , Entry 31) for the lithium mediated reaction The zinc mediated reaction afforded the *trans*-isomer in 94% yield (88% *d e* , 99% *e e* , Entry 32) All three compounds can be readily converted into key-intermediates for the synthesis of carumonam and related antibiotics

From the examples given in this section, it is clear that the rapid progress in the field of enolate chemistry has enabled the organic chemist to selectively synthesize any stereoisomer of a given target molecule containing a 3-amino-2-azetidinone moiety, provided that a proper set of parameters (*i e* protective groups, metal, solvent, reaction conditions, etc) is chosen

THE KETENE - IMINE CYCLOADDITION

The ketene - imine cycloaddition (Staudinger reaction) was the first method by which a 2-azetidinone was synthesized,[1] and the discovery of penicillin and cephalosporin (Fig 1) necessitated further development of the Staudinger reaction

The most widely applied reagents for the formation of 3-amino-2-azetidinones are phthalimido- and azidoacetyl chlorides, which upon treatment with a mild base, usually triethylamine, are *in situ* converted to the corresponding ketenes, **2a** and **2b** Recently several other ketenes have been applied to introduce the 3-amino function (*vide infra*)

In contrast to the development of the ester enolate - imine condensation (see preceding section) that was initiated by the discovery of the carbapenem antibiotics, the development of the ketene - imine cycloaddition parallels the discovery and development of the β-lactam antibiotics right from the start Early studies were focussed on the preparation of intermediates for the synthesis of penicillins and cephalosporins, *i e* 3-amino-2-azetidinones that contain a sulfur atom directly attached to the 4-position of the β-lactam ring The general reaction

is shown (equation 9) and the results are summarized (Table 4) Entries 1-10 show the results obtained with acyclic thioformimidates and Entries 11-28 the results obtained with cyclic thiazoline derivatives

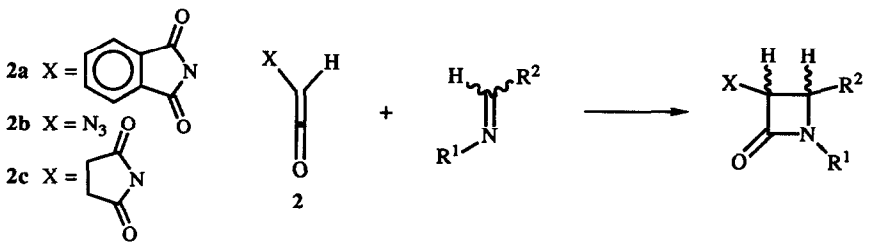


Table 4. The Synthesis of Intermediates for Penicillins and Cephalosporins (and Analogs) *via* the Ketene - Imine Cycloaddition.

Entry	Ketene[a]	R^1	R^2	Yield (%)	*cis trans* (*e e*)	ref
1	2a	Ph	SEt	33	n d.[b]	34
2	2a	(*l*)-C(H)(COOMe)*i*-Pr	SMe	40	0 100 (0)	35
3	2a	(*l*)-C(H)(COOMe)*i*-Pr	SBn	39	0 100 (0)	35,36
4	2a	(*dl*)-C(H)(COOMe)CH_2CH_2SMe	S*p*-$NO_2C_6H_4$	22	0 100	37,38
5	2a	(*dl*)-C(H)(COOMe)CH_2CH_2SMe	STr	79	0 100	37,38
6	2a	C(COOMe)=CMe_2	S*p*-MeOBn	55	0 100	39
7	2b	(±)-C(H)(COOCPh$_2$)C(S[*p*-MeOBn)](CH_2)$_3$	SMe	55	0 100 (10)	40
8	2b	(±)-C(H)(COOBn)C[S(*p*-MeOBn)](CH_2)$_3$	SMe	39	0 100 (44)	40
9	2a	(*d*)-C(H)(COOMe)*p*-BnOC_6H_4	SMe	64	0 100 (20)	41
10	2b	(±)-C(H)(COOBn)P(OEt)$_2$O	SMe	42	0 100	42
11	2a	(±)-methyl 5,5-dimethyl-2-thiazoline-4-carboxylate[c]		8	0 100	43
12	2a	(±)-methyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate		58	n d[b]	44
13	2c	(±)-methyl 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylate		13	n d[b]	45
14	2a	2-phenyl-2-thiazoline		40	n d[b]	46
15	2b	2-phenyl-2-thiazoline		70	0 100	47
16	2c	2-phenyl-2-thiazoline		56	n d[b]	45
17	2a	2-phenyl-5,5-dimethyl-2-thiazoline		27	n d[b]	45
18	2b	2-phenyl-5,5-dimethyl-2-thiazoline		87	0 100	47
19	2c	2-phenyl-5,5-dimethyl-2-thiazoline		13	n d[b]	45
20	2b	2-phenyl-5-(methylthio)-4,4-dimethyl-2-thiazoline		50	0 100	48
21	2b	*cis*-2-phenyl-5-(methylthio)-4,4-(methyl, *iso*-propyl)-2-thiazoline		35	60 40	48
22	2b	*trans*-2-phenyl-5-(methylthio)-4,4-(*iso*-propyl, methyl)-2-thiazoline		84	0 100	48
23	2b	4-(*p*-methoxybenzylcarboxylate)-5-phenyl-1,3 2-thiazine		27	0 100	49
24	2b	4-(*p*-methoxybenzylcarboxylate)-5-*p*-methylbenzoate-1,3 2-thiazine		40	0 100	49
25	2b	4-(*p*-methoxybenzylcarboxylate)-5-(4-thiazolyl)-1,3 2-thiazine		28	0 100	49
26	2a	2-methyl-2-oxazoline		26	n d[b]	50
27	2a	2-phenyl-4,5-dihydro-1,3 2-thiazine		43	n d[b]	50
28	2b	1-(azidoacetyl)-2-phenyl-1,4,5,6-tetrahydropyrimidine[d]		n d[b]	n d[b]	51

[a] The ketene is generated *in situ* upon treatment of the acid chloride with Et_3N [b] Not determined or given [c] Prepared from (±)-*N*-formylpenicillamine [d] Generated *in situ* upon treatment of the 1-unsubstituted pyrimidine with azidoacetyl chloride

The first reaction of an acyclic thioformimidate with an imido-ketene was reported by Paul and coworkers (Entry 1) The 3-amino-4-ethylthio-2-azetidinone was obtained in moderate yield but unfortunately, no indication about the stereochemistry of the reaction has been reported. Bachi and coworkers have extensively studied the reactions of ketenes **2a** and **2b** with several thioformimidates, and obtained the *trans*-2-azetidinone products in reasonable yields (Entries 2-8) However, since these studies were directed towards the synthesis of penicillins and cephalolosporins, with a *cis*-configuration of the substituents attached to the 3- and 4-position of the β-lactam

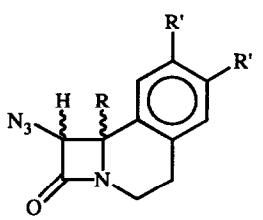
ring, an additional epimerization of the *trans*-products is necessary Two more examples of the reaction of thioformimidates with ketenes **2a** and **2b** have been reported (Entries 9 and 10), but no substantial progress with respect to the work of Bachi and coworkers has been made

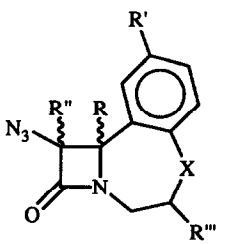
In 1951, the group of Sheehan performed pioneering studies towards the direct synthesis of penicillins [44,45,46] These studies were extended several years later by the group of Bose (Entries 11-19) [43,47] Although in the earlier reports by Sheehan and coworkers, no indication about the stereochemistry of the reactions was given, the results of Bose and coworkers indicate that in all these reactions only the undesired *trans*-2-azetidinones are formed. Furthermore, in order to obtain reasonable yields of the β-lactams, the thiazoline has to be substituted at the 2-position The best yields were obtained by Bose, using azidoacetyl chloride as the ketene precursor (Entries 15 and 18) A recent study by Jenny *et al* shows that the stereochemistry of the reaction can be directed to yield a *cis*-2-azetidinone as the major product (Entry 21) However, in this case no useful β-lactam intermediate was produced

Christensen and coworkers at the Merck-laboratories have studied the reactions of ketene **2b** with several thiazines, which in principle would provide useful intermediates for the synthesis of cephalosporins (Entries 23-25) However, as observed in all other reactions with imines *C*-substituted with a sulfur atom, only *trans*-2-azetidinones were formed

From the results given above, it must be concluded that the ketene - imine cycloaddition approach is not well-suited to synthesize penicillin- and cephalosporin intermediates [52]

Bose and coworkers have reported the syntheses of various, rather exotic, tricyclic 3-azido-2-azetidinones (see Figure 2), which were formed in reasonable yields (40-65%) [53,54,55] However, the applicability of these bicyclic 2-azetidinones as intermediates in the synthesis of known β-lactam antibiotics is rather premature





R = Ph, *p*-MePh, *p*-MeOPh, *p*-NO_2Ph
R' = H

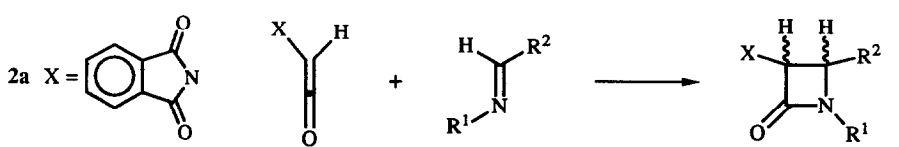
R = *p*-BrPh, *p*-CNPh, *p*-MeOPh, *p*-NO_2Ph
R' = OMe

X = O, R' = H, Cl, R" = H, R''' = H
R = SMe, SEt, S*i*-Pr

X = S, R' = H, R" = Me, R''' = H, Cl
R = SMe, S*i*-Pr

Figure 2. Examples of tricyclic 3-azido-2-azetidinones synthesized by Bose [53,54,55]

Although in the early days of the development of the ketene - imine cycloaddition reaction some examples of reactions with simple aldimines were reported, it was not until the discovery of the new class of monobactam antibiotics (nocardicins, aztreonam, carumonam, see Fig 1) that the reaction with simple aldimines was fully developed. The results of the explorative experiments (eqn 10) are summarized in Table 5



(10)

Table 5. Reactions of Azido- and Phthalimido-ketenes with Aldimines.

Entry	Ketene[a]	R^1	R^2	Yield (%)	*cis trans*	ref
1	**2b**	Ph	Ph	45	100 0[b]	54
2	**2b**	Ph	Ph	50	0 100[c]	54
3	**2b**	Ph	*p*-$NO_2C_6H_4$	35	100 0[b]	54
4	**2b**	Ph	*p*-$MeOC_6H_4$	30	100 0[b]	54
5	**2b**	Ph	*p*-$MeOC_6H_4$	53	0 100[c]	54
6	**2b**	*p*-BrC_6H_4	Ph	30	100 0[b]	54
7	**2b**	*p*-BrC_6H_4	Ph	65	0 100[c]	54
8	**2b**	*p*-BrC_6H_4	3,4-$(OCH_2O)C_6H_3$	35	100 0[b]	54
9	**2b**	*p*-BrC_6H_4	3,4-$(OCH_2O)C_6H_3$	31	0 100[c]	54
10	**2b**	Ph	OEt	n d[d]	0 100	54
11	**2a**	Ph	OEt	31	n d[d]	34
12	**2b**	*p*-FC_6H_4	Ph	23	100 0	54
13	**2b**	Ph	*p*-BrC_6H_4	30	100 0	54
14	**2b**	Ph	*p*-FC_6H_4	19	100 0	54
15	**2b**	C(H)(COOBn)P(OEt)$_2$O	$(CH_2)_2C(CH_2OAc)O(CH_2)_2O$	30	100 0	42
16	**2a**	2,4-$(MeO)_2Bn$	CH_2F	32	100 0	56
17	**2a**[e]	Ph	Ph	50	0 100	57
18	**2a**[e]	Ph	*p*-$MeOC_6H_4$	70	0 100	57
19	**2a**[e]	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	74	0 100	57
20	**2a**[e]	1-naphthyl	*p*-$MeOC_6H_4$	75	0 100	57
21	**2a**[e]	Bn	*p*-$MeOC_6H_4$	60	0 100	57
22	**2a**[f]	*p*-$MeOC_6H_4$	C(H)=C(H)Ph	45	95 5	58
23	**2a**[f]	*p*-$MeOC_6H_4$	C(Me)=C(H)Ph	64	100 0	58
24	**2a**[f]	*p*-$Me_3SiOC_6H_4$	C(H)=C(H)Ph	n d[d]	50 50	58
25	**2a**[f]	*p*-$Me_3SiOC_6H_4$	C(Me)=C(H)Ph	50	100 0	58
26	**2a**[f]	CH_2COOMe	C(Me)=C(H)Ph	66	100 0	58
27	**2a**	C(H)=CH_2	C(Me)=C(H)Ph	82	97 3	59
28	**2b**	$CH_2CH_2SiMe_3$	C(H)=C(H)Ph	≈ 75[d]	*cis*[d]	60
29	**2b**	$CH_2C(H)=CH_2$	C(H)=C(H)Ph	≈ 75[d]	*cis*[d]	60
30	**2b**	Bn	C(H)=C(H)Ph	≈ 75[d]	*cis*[d]	60
31	**2b**	CH(*p*-$MeOC_6H_4)_2$	C(H)=C(H)Ph	≈ 20[d]	*cis*[d]	60
32	**2a**[g]	*p*-$MeOC_6H_4$	C(H)=C(H)Ph	55	100 0	61
33	**2a**[g]	CH_2COOMe	C(Me)=C(H)Ph	50	100 0	61
34	**2a**[h]	CH_2SiMe_3	C(Me)=C(H)Ph	70	100 0	62
35	**2b**	Bn	Me	≈ 75[d]	*trans*[d]	60
36	**2b**	CH(*p*-$MeOC_6H_4)_2$	Me	≈ 75[d]	*cis*[d]	60

[a] Ketene generated *in situ* by treatment of the acid chloride with Et_3N [b] Azidoacetyl chloride was added dropwise to a solution containing the imine and Et_3N, resulting in a *cis trans* ratio of *ca* 3 1 Yield and given stereochemistry are of the isolated isomer after chromatographic separation [c] Et_3N was added to a solution containing the imine and azidoacetyl chloride, resulting in a *cis.trans* ratio of *ca* 1 3 Yield and given stereochemistry are of the isolated isomer after chromatographic separation [d] Not determined or not given [e] Ketene generated *in situ* by treatment of phthaloylglycine with $Me_2N=C(H)OSOCl_2$ [f] Ketene generated *in situ* by treatment of the acid bromide with Et_3N [g] Ketene generated *in situ* from phthaloylglycine and $Me_2NP(O)Cl_2$ by treatment with Et_3N [h] Ketene generated *in situ* from phthaloylglycine and $PhOP(O)Cl_2$ by treatment with Et_3N

The most widely applied ketenes are still the phthalimido (**2a**)- and 2-azido (**2b**) derivatives (eqn 10), but several precursors and methods other than the treatment of the respective acetyl chlorides with triethylamine have been reported, *e g* the treatment of phthaloylglycine with $Me_2N=C(H)OSOCl_2$,[57] $Me_2NP(O)Cl_2$,[61] or $PhOP(O)Cl_2$,[62] under influence of a base

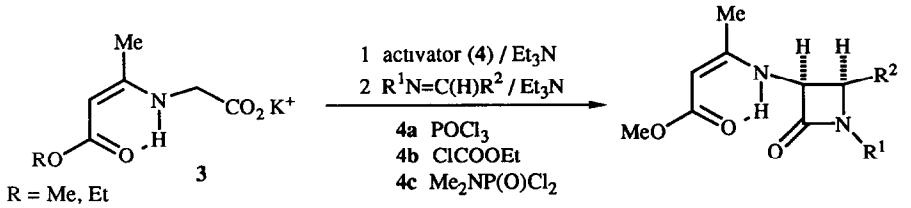
Bose and coworkers have demonstrated that for simple *N*-aryl imines the stereochemistry of the reaction with azido-ketene **2b** can be influenced by experimental conditions (Entries 1-9) Upon dropwise addition of the

azidoacetyl chloride to a solution containing the imine and triethylamine, the major products are the *cis*-2-azetidinones (*d e* ≈ 35%), while addition of triethylamine to a solution containing azidoacetyl chloride and the imine produces the *trans*-2-azetidinones as the major isomer (*d e* ≈ 35%)

Palomo and coworkers showed that generation of the phthalimido-ketene from phthaloylglycine and $Me_2N{=}C(H)OSOCl_2$ and subsequent treatment with simple *C*-aryl imines afforded exclusively *trans*-2-azetidinones in good yields (Entries 17-21) This contrasts to the results obtained for the reactions of **2a** and **2b**, generated by various means, with imines derived from cinnamic aldehyde and α-methylcinnamic aldehyde, that afford almost exclusively *cis*-2-azetidinones in moderate to good yields (Entries 22-34) Since the 4-styryl and 4-α-methylstyryl groups are readily converted into an acetyl group by ozonolysis, useful intermediates for the synthesis of *cis*-3-amino-β-lactam antibiotics are accessible

Just and coworkers have shown that with imines derived from acetaldehyde, depending on the nitrogen substituent, selectively *trans*- and *cis*- 3-azido-4-methyl-2-azetidinones (intermediates for the synthesis of aztreonam and derivatives) are obtained (Entries 35 and 36)

A new reagent to directly incorporate the 3-amino-substituent of the 2-azetidinone ring is the potassium salt (Dane's salt) of *N*-(α-methyl-β-(m)ethoxycarbonylvinyl)glycine (**3**), which in the presence of an appropriate activator and imine results in the formation of the 2-azetidinone product (eqn 11) The protected group is readily converted to an amino-function by treatment with hydrogen chloride in methanol The results obtained with this protecting group are summarized in Table 6



(11)

Table 6. Reactions of (α-Methyl-β-methoxycarbonylvinyl)amido-Ketenes with Imines.

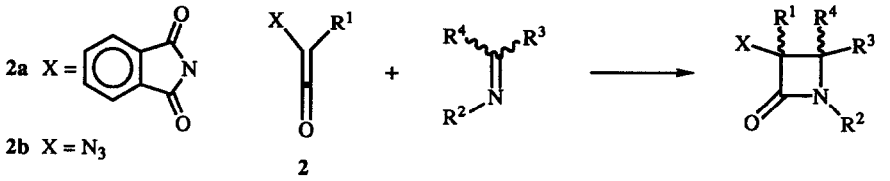
Entry	Reagent	R^1	R^2	Yield (%)	*cis trans*	ref
1	**4a**	Ph	Ph	≈ 40[a]	100 0	63
2	**4a**	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	35	100 0	63
3	**4a**	*p*-MeC_6H_4	3,4-$(OCH_2O)C_6H_3$	≈ 40[a]	100 0	63
4	**4a**	1-*p*-tolyl-3,4-dihydroisoquinoline		45	0 100	63
5	**4b**	3,4-$(MeO)_2$Bn	Ph	65	100 0	64
6	**4b**	2,4-$(MeO)_2C_6H_3$	Ph	60	100 0	64
7	**4b**	*p*-$MeOC_6H_4$	Ph	60	100 0	64
8	**4b**	3,4-$(MeO)_2$Bn	2-furyl	50	100 0	64
9	**4b**	2,4-$(MeO)_2$Bn	2-furyl	50	100 0	64
10	**4b**	*p*-$MeOC_6H_4$	2-furyl	50	100 0	64
11	**4b**	Ph	cyclopentyl	60	100 0	64
12	**4b**	*p*-$MeOC_6H_4$	C(H)=C(H)Ph	46	100 0	64
13	**4b**	1-*p*-methoxyphenyl-3,4-dihydroisoquinoline		80	0 100	64
14	**4c**	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	40	100 0	61
15	**4c**	2,4-$(MeO)_2$Bn	Ph	55[b]	100 0	61
16	**4c**	$CH_2C(H)(OH)Ph$	C(Me)=C(H)Ph	60[c]	100 0	61
17	**4c**	CH_2COOMe	C(O)Me	30[d]	100 0	61

[a] The exact yield is not given [b] Isolated as *N*-benzoyl derivative after deprotection with HCl in methanol and acylation with benzoylchloride [c] Isolated as *N*-benzylcarbamate [d] Isolated as *N*-chloroacetoxy derivative

Sharma and Gupta were the first who reported about the use of this protective group in the ketene - imine cycloaddition, but did not prepare very useful 2-azetidinone products (Entries 1-4) Bose and coworkers used the α-methyl-β-methoxycarbonylvinyl protecting group to synthesize more useful 2-azetidinone products in moderate yields (Entries 5-13) In all cases studied, except for the cyclic imine derived from quinoline (Entries 4 and 13),

exclusively the *cis*-isomer is formed. Recently, Palomo and coworkers reported four more examples, the most interesting being the 4-α-methylstyryl and 4-acetyl derivatives (Entries 14-17), which provide intermediates for the synthesis of *cis*-3-amino-β-lactam antibiotics

Several research groups have studied the reactions of phthalimido- and azido-ketenes with imines derived from ketones (eqn 12). The results of these studies have been summarized (Table 7)



(12)

Table 7. Reactions of Amino-Ketenes with Imines Derived from Ketones.

Entry	Ketene[a]	R^1	R^2	R^3	R^4	Yield (%)[b]	ref
1	**2b**	H	Ph	Me	Ph	30	54
2	**2b**	H	Ph	Ph	Ph	60	54
3	**2b'**	Me	Ph	H	Ph	10	54
4	**2b"**	Et	Ph	H	Ph	9	54
5	**2b'''**	Ph	Ph	H	Ph	7	54
6	**2a**	H	Ph	OMe	Ph	50	34
7	**2a**	H	Ph	OEt	Ph	55	34
8	**2a**	H	Ph	O*i*-Pr	Ph	51	34
9	**2a**	H	Ph	SMe	Ph	70	34
10	**2a**	H	Ph	$P(O)(MeO)_2$	Ph	18	65
11	**2a**	H	Ph	$P(O)(EtO)_2$	Ph	46	65
12	**2a**	H	Ph	$P(O)(MeO)_2$	*p*-MeC_6H_4	29	65
13	**2a**	H	Ph	$P(O)(EtO)_2$	*p*-MeC_6H_4	32	65
14	**2a**	H	Ph	$P(O)(MeO)_2$	*p*-ClC_6H_4	17	65
15	**2a**	H	Ph	$P(O)(EtO)_2$	*p*-ClC_6H_4	28	65
16	**2a**	H	Ph	$P(O)(MeO)_2$	*p*-BrC_6H_4	22	65
17	**2a**	H	Ph	$P(O)(EtO)_2$	*p*-BrC_6H_4	27	65
18	**2a**	H	Ph	$P(O)(MeO)_2$	*p*-$MeOC_6H_4$	36	65
19	**2a**	H	Ph	$P(O)(EtO)_2$	*p*-$MeOC_6H_4$	40	65
20	**2a**	H	Me	$P(O)(MeO)_2$	Ph	24	65
21	**2a**	H	Ph	C(O)Ph	Ph	25	66

[a] The ketene is generated *in situ* upon treatment of the acid chloride with Et_3N [b] The yields of the isolated products, the composition in terms of isomers (*cis* or *trans*) has not been determined or given

Although no really useful 2-azetidinones have been prepared in these studies, it is interesting to note that low to moderate yields of 2-azetidinone products are obtained To our knowledge, no successful reactions of ester enolates with imines derived from ketones have been reported (*vide supra*)

As in the case of the ester enolate - imine condensation (*vide supra*), several approaches towards the development of an enantioselective ketene - imine route to useful 3-amino-2-azetidinones have been studied The results of the studies on the reactions of phthalimido- and azido-ketenes with imines, *N*-substituted with a chiral auxiliary (eqn 13), are summarized in Table 8

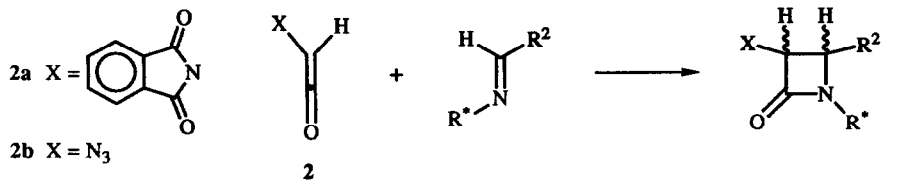


Table 8. Enantioselective Syntheses of 3-Amino-2-azetidinones from Ketenes and Imines, *N*-Substituted with a Chiral Auxiliary.

Entry	Ketene[a]	R*	R^2	Yield (%)	*cis trans* (*e e*)	ref
1	**2a**	(*d*)-C(H)(COOMe)Ph	H[b]	80	(56)	67
2	**2a**	(*d*)-C(H)(COOBn)*p*-BnOC$_6$H$_4$	H[b]	87	(50)	67
3	**2a**	(*dl*)-C(H)(COOMe)Naphthyl	H[b]	51	(82)	67
4	**2a**	(*d*)-C(H)(COOMe)-2-thienyl	H[b]	65	(56)	67
5	**2a**	(*dl*)-C(H)(COOMe)-2-furyl	H[b]	39	(50)	67
6	**2b**	(*l*)-C(H)(Me)Ph	C(H)=C(H)Ph	≈ 75[c]	*cis*[c] (n.d)[c]	60
7	**2b**	(*l*)-C(H)(Me)Ph	Me	≈ 75[c]	*trans*[c] (n d)[c]	60
8	**2a**	(*d*)-C(H)(Me)Ph	CH_2F	59	100 0 (62)	68
9	**2b**	(*d*)-C(H)(COOBn)C(H)(Me)OH	C(H)=C(H)Ph	60	100 0 (0)	69
10	**2b**	(*d*)-C(H)(COOBn)C(H)(Me)OTBDMS[d]	C(H)=C(H)Ph	60	100 0 (80)	70
11	**2b**	(*d*)-C(H)(COOBn)C(H)(Me)OTPS[d]	C(H)=C(H)Ph	55	100 0 (90)	69
12	**2a**	(*S,S*)-C(H)(CH_2OTMS)C(H)(OTMS)*p*-$NO_2C_6H_4$	C(H)=C(H)Ph	50	100 0 (43)	71
13	**2a**	(*S,S*)-C(H)(CH_2OTMS)C(H)(OTMS)Ph	C(H)=C(H)Ph	50	100 0 (43)	71
14	**2a**	(*S,S*)-C(H)$CH_2OSi(Me_2)$OC(H)Ph	C(H)=C(H)Ph	55	100 0 (43)	71
15	**2a**	(*S,S*)-C(H)(CH_2OTBDMS)C(H)(OTBDMS)Ph	C(H)=C(H)Ph	62	100 0 (82)	71
16	**2b**	protected *d*-glucosamine[e]	C(H)=C(H)Ph	92	100 0 (100)	72

[a] The ketene is generated *in situ* upon treatment of the acid chloride with Et_3N [b] The imine is generated *in situ* by treatment of the hexahydrotriazine with BF_3 OEt_2 [c] Not determined or given [d] TBDMS = *t*-butyldimethylsilyl, TPS = triphenylsilyl, TMS = trimethylsilyl [e] 3,4 5,6-di-*O*-isopropylidene-*d*-glucosamine propane dithioacetal

Kamiya and coworkers have reported about the enantioselective synthesis of useful intermediates for the synthesis of nocardicins (Entries 1-5) The chiral imines were prepared *in situ* upon treatment of hexahydrotriazines, derived from chiral glycines, with BF_3 OEt_2 The 4-unsubstituted-2-azetidinones were formed in reasonable to good yields with moderate to good enantioselectivity

Just and coworkers have reported about the use of chiral imines, derived from readily available chiral (*l*)-α-methylbenzylamine (Entries 6 and 7) Unfortunately, no details are given about the exact yields and composition of the products, but in both cases useful 2-azetidinones are formed The result of Teutsch and Bonnet with the imine derived from fluoroacetaldehyde and (*d*)-α-methylbenzylamine is quite remarkable (Entry 8) Just found that the *trans*-2-azetidinone was formed as the major isomer with the imine derived from acetaldehyde, whereas the *cis*-2-azetidinone, a key-intermediate for the synthesis of a known β-lactam antibiotic,[73] was the exclusive product in the case of fluoroacetaldehyde

Several research groups have reported about the enantioselective synthesis of useful *cis*-3-amino-4-styryl-2-azetidinones, using imines derived from cinnamic aldehyde and chiral modified α-amino esters (Entries 9-15) The best results in terms of enantioselectivity were obtained by Bellau and Bose (Entries 10 and 11, respectively), who obtained the *cis*-2-azetidinone products with a good enantioselectivity, albeit in moderate yields Barton and coworkers, used modified *d*-glucosamine to protect the imino-nitrogen and obtained enantiomerically pure *cis*-3-phthalimido-4-styryl-2-azetidinone in excellent yield However, efficient removal of the modified sugar has not yet been accomplished

A second approach towards the enantioselective synthesis of useful 3-amino-2-azetidinones is the use of imines, *C*-substituted with a useful chiral synthon (eqn 14) The results of the studies based on this approach are summarized in Table 9

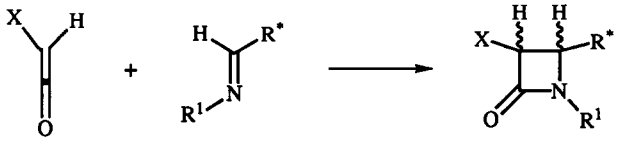


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Table 9. Enantioselective Syntheses of 3-Amino-2-azetidinones from Ketenes and Imines, *C*-Substituted with a Chiral Auxiliary.

Entry	X[a]	R^1	R^*	Yield (%)	*cis trans* (*e e*)	ref
1	Phthaloyl	2,4-$(MeO)_2$Bn	(*S*)-C(H)$CH_2OC(Me)_2O$	76	100 0 (99)	74
2	Phthaloyl	*p*-$MeOC_6H_4$	(*S*)-C(H)$CH_2OC(Me)_2O$	55	100 0 (99)	74
3	MeCOOC(H)=C(Me)NH	Bn	(*S*)-C(H)$CH_2OC(Me)_2O$	72	100 0 (99)	74
4	Phthaloyl	2,4-$(MeO)_2$Bn	(*S*)-C(H)(Me)OBn	69	100 0 (99)	74
5	Azido	*p*-$MeOC_6H_4$	(*R*)-C(H)$CH_2OC(Me)_2O$	55	100 0 (99)	75
6	Phthaloyl	*p*-$MeOC_6H_4$	(*R*)-C(H)$CH_2OC(Me)_2O$	57	100 0 (99)	75
7	Azido	CH_2COOMe	(*R*)-C(H)$CH_2OC(Me)_2O$	55	100 0 (99)	75
8	Phthaloyl	Bn	(*R,R*)-2-phenylepoxide	82	100 0 (86)	76
9	Phthaloyl	2,4-$(MeO)_2$Bn	(*R,R*)-2-phenylepoxide	85	100 0 (86)	76
10	Phthaloyl	CH_2COO*t*-Bu	(*R,R*)-2-phenylepoxide	65	100 0 (82)	76
11	Phthaloyl	$CH_2C(Me)=CH_2$	(*R,R*)-2-phenylepoxide	88	100 0 (84)	76
12	Phthaloyl	*p*-$MeOC_6H_4$	(*R,R*)-2-phenylepoxide	66	100 0 (80)	76
13	$BnCH_2OC(O)N(H)$	2,4-$(MeO)_2$Bn	(*R,R*)-2-phenylepoxide	60	100 0 (90)	76
14	Oxazolidinon[b]	2,4-$(MeO)_2$Bn	(*R,R*)-2-phenylepoxide	84	100 0 (82)	76
15	Phthaloyl	Bn	(*R*)-2,2-dimethylepoxide	84	100 0 (94)	76

[a] The ketenes are generated *in situ* upon treatment of the respective acetylchlorides with Et_3N [b] 4,5-diphenyloxazolin-2-on-3-yl

The first synthesis of a 3-amino-2-azetidinone, based on this approach was performed in the laboratories of Hoffmann-La Roche They used imines derived from readily available (*S*)-glyceraldehyde acetonide (Entries 1-3) This group can be converted into a formyl-substituent (oxidation with $NaIO_4$ or $Pb(OAc)_4$), providing 3-amino-2-azetidinone products, which can be used for the syntheses of several known β-lactam antibiotics Several enantiomerically pure *cis*-2-azetidinones have been prepared in moderate to good yields Some years later, Bose and coworkers reported similar results starting from (*R*)-glyceraldehyde acetonide (Entries 5-7)

Evans and Williams used chiral epoxyimines, derived from readily available α,β-epoxyaldehydes (Sharpless-oxidation of substituted allylic alcohols), for the enantioselective syntheses (*e e* 80-94%) of several useful *cis*-3-amino-4-epoxy-2-azetidinones, in good to excellent yields (Entries 8-15) The substituted epoxy group is readily oxidized to the useful formyl group, which has been mentioned earlier in this review (*vide supra*)

A third approach towards the enantioselective synthesis of useful 3-amino-2-azetidinones is to start from chiral ketene precursors Evans and Sjogren initiated the development of this method by making use of (4*S*)-phenyloxazolidylacetyl chloride, prepared from readily available (*S*)-phenylglycine, as precursor for a chiral ketene (eqn 15)

Reactions with several *N*-benzyl-substituted imines afforded useful *cis*-2-azetidinone products, key-intermediates in the synthesis of carumonam, in good yields with a high chiral induction (Table X, Entries 1-4)

Ojima and coworkers extensively examined the reaction of (4*S*)-phenyloxazolidyl-ketene with imines, *C*-substituted with an aryl group and *N*-substituted with various substituents (Entries 5-13) The enantiomerically

pure *cis*-3-amino-4-aryl-2-azetidinones were obtained in good to excellent yields Quite remarkable is the fact that when imines derived from chiral α-amino acids are used, the same enantiomer of the 2-azetidinone product is formed, irrespective of the chirality present in the substituent of the imino-nitrogen (Entries 5-10) This implies that the stereoselectivity of these reactions is completely governed by the configuration of the starting ketene

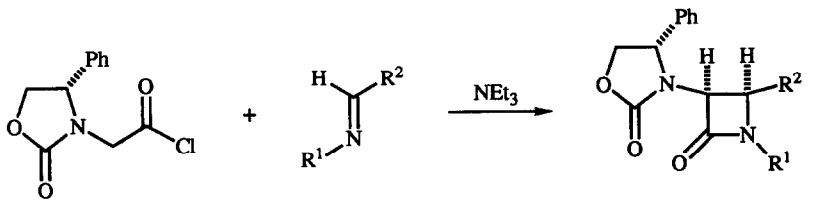

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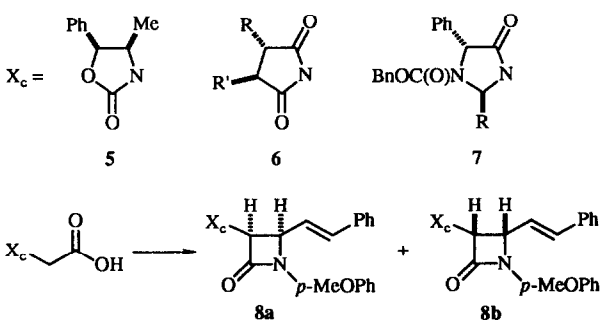
Table 10. Enantioselective Syntheses of 3-Amino-2-azetidinones from (4*S*)-Phenyloxazolidyl-Ketene and Imines.

Entry	R^1	R^2	Yield (%)	*cis trans* (*e e*)	ref
1	Bn	Ph	90	100 0 (94)	77
2	Bn	C(H)=C(H)Ph	82	100 0 (90)	77
3	Bn	C(H)=C(H)-3-MeOC$_6$H$_3$	80	100 0 (84)	77
4	Bn	C(H)=C(H)-2-furyl	80	100 0 (94)	77
5	(*S*)-C(H)(COOMe)Me	Ph	76	100 0 (99)[a]	78,79
6	(*R*)-C(H)(COOMe)Me	Ph	82	100 0 (99)[a]	78,79
7	(*S*)-C(H)(COOMe)*i*-Pr	Ph	92	100 0 (99)[a]	78,79
8	(*R*)-C(H)(COOMe)*i*-Pr	Ph	86	100 0 (99)[a]	78,79
9	(*S*)-C(H)(COOMe)Bn	Ph	91	100 0 (99)	78,79
10	(*S*)-C(H)(COOMe)CH$_2$CH$_2$SMe	Ph	79	100 0 (99)	78,79
11	Me	Ph	85	100 0 (99)	79
12	Bn	3,4-(MeO)$_2$C$_6$H$_3$	90	100 0 (99)	79,80
13	Me	3,4-(MeO)$_2$C$_6$H$_3$	95	100 0 (99)	79

[a] The same enantiomer is formed, irrespective of the chirality of R^1

Other research efforts concerning the application of chiral ketenes were conducted at the research laboratories of Lilly,[81] and by the group of Ikota and Hanaki [82] The results of these studies are summarized in Figure 3 In all these experiments *N*-(*p*-methoxyphenyl)-3-phenyl-2-propenylideneamine was used as the imine component, affording *cis*-3-amino-4-styryl-2-azetidinones **8a** and **8b** as products



Entry	X_c	8a	8b[a]
1	**5**	>95	5
2	**6a** (R = R' = PhC(O)O)	86	14
3	**6b** (R = R' = BnO)	86	14
4	**6c** (R = R' = MeC(O)O)	70	30
5	**6d** (R = MeC(O)O, R' = H)	55	45
6	**7a** (R = Ph)	70	30[b]
7	**7b** (R = 2,6-(Cl)$_2$C$_6$H$_3$)	0	100[b]
8	**7c** (R = 1-naphthyl)	60	40[b]
9	**7d** (R = *p*-NO$_2$C$_6$H$_4$)	70	30[b]
10	**7e** (R = *p*-MeOC$_6$H$_4$)	90	10[b]

[a] Yields are not given, see ref 79 [b] The same ratio as that of the isomers of **7**, each pure isomer gave better than 99% induction

Figure 3. Enantioselective Syntheses of *cis*-3-Amino-4-styryl-2-azetidinones Using Chiral Ketenes

The use of oxazolidinone **5**, derived from norephedrine, resulted in excellent chiral induction (Entry 1) The use of imides **6**, derived from *S,S*-tartraric acid, resulted in low to good chiral inductions, depending on the substituents R and R' (Entries 2-5) A complication that arises from the use of chiral imidazolones **7** derived from (*R*)-phenylglycine, is that these are formed as mixtures of *cis*- and *trans*-isomers, depending on the R substituent (Entries 6-10) Each pure isomer resulted in inductions better than 99% for the reactions of the respective ketenes with the imine

The examples given in the preceding section clearly demonstrate the usefulness of the ketene - imine cycloaddition approach to the synthesis of the 3-amino-2-azetidinone moiety It allows the use of a wide variety of differently substituted reagents (both ketene and imine) and in most cases the *cis*-2-azetidinone product is formed exclusively, although a few examples where a *trans*-2-azetidinone is obtained as the major isomer have been reported Syntheses of useful, enantiomerically pure *cis*-3-amino-2-azetidinones have been reported

THE CYCLOADDITION OF METALLO-CARBENE COMPLEXES WITH IMINES

The first synthesis of a 2-azetidinone *via* metallo-carbenes and imines was reported by Hegedus and coworkers in 1982 [83] Subsequent mechanistic studies,[84] indicated that when the starting chromium carbene (**9**) was subjected to irradiation, carbon monoxide insertion into the metal-carbon double bond produces a ketene complex, **10** (Scheme II) These complexes show typical ketene-reactivity, but the reactions with imines do not proceed *via* free ketenes, since the typical side-products, *e g* self-condensation products of the ketene or products containing one imine and two (or more) ketene fragments, are not observed.[84,85]

During the course of these studies several interesting 3-amino-2-azetidinones have been prepared using amino carbenes as starting material The route is very general and allows a wide variety of acyclic and cyclic imines (see Tables 11 and 12)

Scheme 2

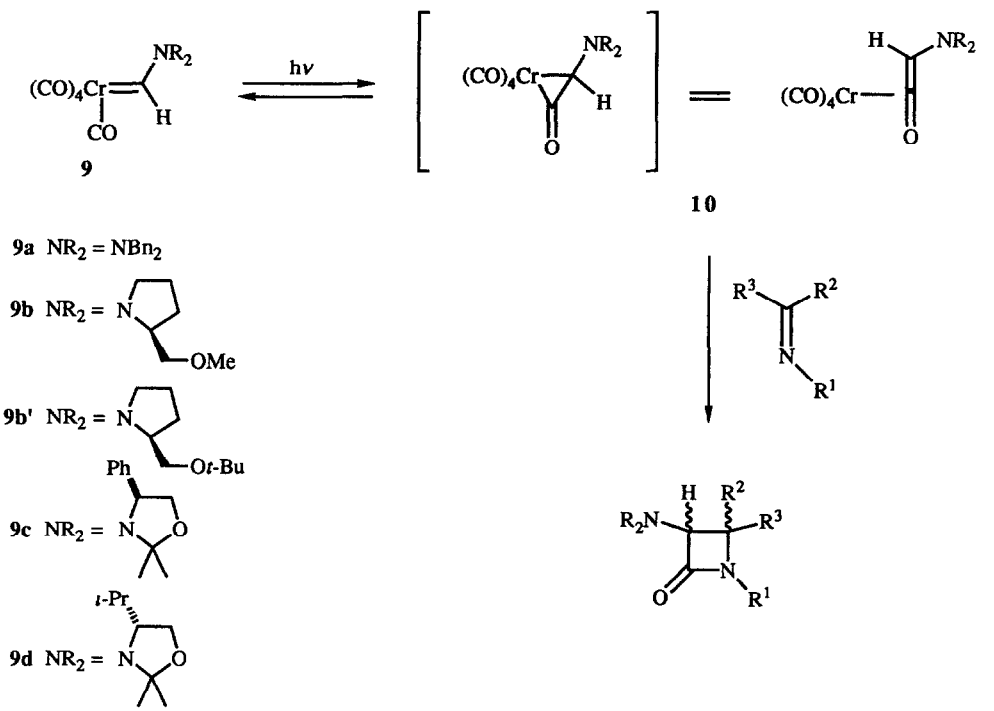


Table 11. The Syntheses of 3-Amino-2-azetidinones by Photolytic Reactions of Chromium Aminocarbene (9a) with Imines.

Entry	R^1	R^2	R^3	Yield (%)	*cis trans* (*e e*)	ref
1	Me	Ph	H	50	82 18	86
2	Bn	Me	H	74	64 36	86
3	*t*-Bu	H	H	72		87
4[a]	*p*-$MeOC_6H_4$	H	H	74		87
5[a]	Bn	Me	Me	56		87
6[a]	(*R*)-C(H)(COOMe)*p*-$BnOC_6H_4$	H	H	46	(0)	87
7	Bn	OMe	H	79	0 100	86
8	Ph	OEt	H	78	0 100	86
9	$-(CH_2)_3-$		Me	51	n d[b]	86
10[a]	$-(CH_2)_3-$		H	54	0 100	87
11[a]	$-(CH_2)_4-$		H	85	0 100	87
12	$-(CH_2)_3O-$		H	81	0 100	86
13	$-C(Me)_2CH_2O-$		H	32	0 100	86
14	$-(CH_2)_3S-$		H	73	0 100	86
15	$-CH(COOEt)C(Me)(OH)CH_2S-$		H	77	0 100	86
16	(*R*) $-CH(COOMe)C(Me)_2S-$		H	93	0 100 (99)	86

[a] The imine was used in the form of the hexahydrotriazine [b] A single diastereomer with unknown stereochemistry is formed

With simple acyclic imines, mixtures of *cis*- and *trans*-3-dibenzylamino-2-azetidinones are formed (Entries 1 and 2) Imines derived from formaldehyde, either as imine or in the form of the cyclic hexahydrotriazine, are also applicable, affording intermediates for nocardicins in reasonable yields (Entries 3-6) Quite surprisingly, unlike the reactions with free amino-ketenes (*vide supra*),[67] the use of the imine derived from (*R*)-phenylglycine did not result in any chiral induction (Entry 6) With imidates, *trans*-2-azetidinones are obtained as the single products in good yields (Entries 7 and 8)

The most notable feature of the metallo-carbene method is the comparative ease by which cyclic imines are converted into *trans*-2-azetidinones in moderate to excellent yields (Entries 9-16) This contrasts sharply with the reactions of free amino-ketenes with similar cyclic imines, that afford only low to moderate yields of *trans*-bicyclic-2-azetidinones (*vide supra*)

Thus several useful intermediates for the synthesis of penicillins, cephalosporins and related antibiotics have been prepared in high yields (in the case of penicillin even with an excellent enantioselectivity, Entry 16), but unfortunately with *trans*-stereochemistry concerning the 3- and 4-position of the β-lactam ring

A recent development reported by Hegedus and coworkers, is the use of chiral chromium aminocarbenes, derived from (*S*)-proline (**9b**), (*R*)-phenylglycinol (**9c**), and (*S*)-valinol (**9d**), in the enantioselective synthesis of useful 3-amino-2-azetidinones (Scheme II) The results of these efforts are summarized in Table 12

Reactions of the proline derived aminocarbenes **9b** and **9b'** with 5,6-dihydro-4*H*-1,3-oxazine (Entries 1 and 2) resulted in a moderate chiral induction, whereas the reaction of the phenylglycinol and valinol derived aminocarbenes **9c** and **9d** with the same imine resulted in an excellent chiral induction (Entries 13 and 14) As is the case for dibenzylaminocarbene **9a**, aminocarbenes **9c** and **9d** react smoothly with both acyclic- and bicyclic imines affording useful 3-amino-2-azetidinones with an excellent enantio- and diastereo-selectivity The reactions *via* carbene **9c** generally resulted in better yields of the 2-azetidinone products than *via* carbene **9d**

The reaction of carbene **9c** with the imine derived from cinnamic aldehyde afforded the racemic *cis*-2-azetidinone (Entry 15, *d e* 66%), whereas reactions of comparable *free* amino-ketenes with the same imine resulted in high chiral inductions (*vide supra*) [77]

Reaction of carbene **9d** with (±)-5-hydroxy-5-methyl-5,6-dihydro-4*H*-1,3-thiazine-4-methyl carboxylate afforded a key-intermediate for the synthesis of cephalosporins in good yields and with an excellent enantioselectivity, but unfortunately with the wrong *trans*-configuration of the 3- and 4-position

Table 12. The Syntheses of 3-Amino-2-azetidinones by Photolytic Reactions of Chiral Chromium Aminocarbenes with Imines.

Entry	Carbene	R^1	R^2	R^3	Yield (%)	*cis* *trans* (*e e*)	ref
1	**9b**	$-(CH_2)_3O-$		H	85	0 100 (60)	88
2	**9b'**	$-(CH_2)_3O-$		H	82	0 100 (67)	88
3	**9c**	Bn	H	H	74	(70)	88
4	**9c**	Bn	Me	Me	79	(70)	88
5	**9d**	Bn	Me	Me	59	(70)	88
6	**9c**	Bn	Me	H	61	33 67 (99)	88
7	**9d**	Bn	Me	H	54	26 74 (99)	88
8	**9c**	$-(CH_2)_3-$		H	75	0 100 (99)	88
9	**9c**	$-(CH_2)_4-$		H	91	0 100 (99)	88
10	**9d**	$-(CH_2)_4-$		H	55	0 100 (99)	88
11	**9c**	Bn	OMe	H	91	0 100 (99)	88
12	**9d**	Bn	OMe	H	76	0 100 (99)	88
13	**9c**	$-(CH_2)_3O-$		H	95	0 100 (99)	88
14	**9d**	$-(CH_2)_3O-$		H	70	0 100 (99)	88
15	**9c**	Bn	C(H)=C(H)*p*-$MeOC_6H_4$	H	53	83 17 (0)[a]	88
16	**9d**	(±)	$-CH(COOMe)C(Me)(OH)CH_2S-$	H	79	0 100 (99)[b]	88

[a] *E e* of the *cis*-isomer, the *trans*-isomer was formed with an *e e* of 99% [b] With respect to the configuration of the 3- and 4-position of the 2-azetidinone ring

The examples given in this section show that the synthesis of the 3-amino-2-azetidinone moiety *via* chromium amino-carbenes and imines is very promising, since it allows a wide variety of differently substituted reagents (both amino-carbene and imine) Especially the reactions of chiral amino-carbenes with cyclic imines, affording selectively enantiomerically pure *trans*-3-amino-2-azetidinones that may be used for the syntheses penicillins and cephalosporins in moderate to excellent yields, may become a method that could find application in the pharmaceutical industry

Major disadvantages of the metallo-carbene route is that use of irradiation to induce the reactions with imines is an expensive procedure and furthermore only *trans*-3-amino-bicyclic-β-lactam systems have been prepared by this route

MISCELLANEOUS

Besides the routes that have been reviewed in the preceding sections, several other approaches towards the synthesis of monobactam antibiotics have been described in the literature Some selected examples of the recent advances of these approaches will be briefly mentioned in this section

Most of these routes, mainly developed in the laboratories of pharmaceutical companies, involve multistep procedures (*i e* with overall yields form 0-10%), starting from readily available (natural) chiral synthons like (*S*)-serine, (*S*)-threonine and (*S*)-allo-threonine Most of these routes involve the intermediacy of hydroxamates (**11**), which are subjected to ring-closure conditions, resulting in the desired 3-amino-2-azetidinone products (Scheme 3) that can be readily converted into the monobactam antibiotics

Scheme 3

X = BnOC(O) or *t*-BuOC(O)
Y = OR or $SO_3^- M^+$
L = Leaving group, *e g* OR or Cl
R^1, R^2 = Hydrogen or alkyl

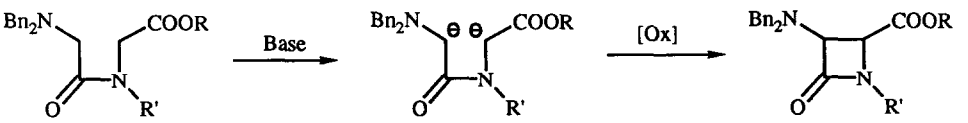
11

The first paper describing this hydroxamate-approach to the synthesis of monobactams was reported by Miller and coworkers in 1980 [89] In this paper the total synthesis of 3-aminonocardicinic acid, a key-intermediate in the synthesis of nocardicin A (see Fig 1), starting from β-chloro-(*S*)-alanine has been described Further studies by this group, in co-operation with the Lilly Research Laboratories, include the synthesis of key-intermediates in the synthesis of nocardicin A from (*S*)-serine,[89,90] aztreonam from (*S*)-threonine,[89] and more versatile intermediates, *cis*- and *trans*-3-amino-4-methoxycarbonyl-2-azetidinone, from *L-erythro*- and *DL-threo*-β-hydroxyaspartic acid, respectively [91] Several other modifications of this route have been reported by Cimarusti, Floyd, and Sykes and coworkers of the Squibb Institute of Medical Research [92] Recently, Herranz and cowokers reported a multistep procedure for the synthesis of aztreonam starting from (*D*)-glyceraldehyde acetonide following the hydroxamate procedure [93]

The total synthesis of carumonam, starting form either *L*-threonic acid or *L*-(+)-tartaric acid has been described by Wei and coworkers of the Hoffmann-La Roche Laboratories [94]

An isolated example of the syntheses of 3-amino-4-carboxylate-2-azetidinones, involving the oxidative coupling of the dianions of acyclic amides using Cu^{II}-salts or *N*-iodosuccinimide, has recently been reported by Hiyama and coworkers (Scheme 4) [95]

Scheme 4



Base = *n*-BuLi or *t*-BuLi
[Ox] = NIS, $Cu(OAc)_2$, $Cu(OCOPh)_2$

Following this method, *cis*-1-(α-methylbenzyl)-3-dibenzylamino-4-*t*-butoxycarbonyl-2-azetidinone (*d e* 90%, *e e* 90%), a key-intermediate in the synthesis of carumonam, has been prepared in 52% yield from (*R*)-α-methylbenzylamine

OUTLOOK

As shown in this report several general routes for the synthesis of useful 3-amino-2-azetidinones are nowadays available The latest developments of these routes have virtually all been focussed on the enantioselective synthesis of intermediates for monobactam antibiotics

An advantage of the ester enolate - imine condensation is the versatility of this route Using simple basic chemicals, a wide variety of 3-amino-2-azetidinones are accessible Moreover, with a proper choice of parameters (*i e* protective groups, metal, solvent(s), reaction conditions, etc) any enantiomer of a selected target molecule containing the 3-amino-2-azetidinone grouping can be selectively synthesized

The ketene - imine cycloaddition is even more versatile than the ester enolate - imine condensation, and works not only with imines derived from aldehydes as substrates, but with cyclic imines and imines derived from ketones as well Recent reports have shown that useful *cis*-3-amino-2-azetidinones can be obtained in high yields with excellent enantioselectivity Sofar no enantioselective routes to useful *trans*-3-amino-2-azetidinones have been reported

The cycloaddition of metallo-carbene complexes, in particular with cyclic imines, is a general and elegant route for the synthesis of bicyclic 3-amino-2-azetidinones Usually far better yields are obtained compared with the reactions of free ketenes with cyclic imines However, irradiation of the carbene complexes is required to produce the reactive metallo-ketene complexes and chromium salts are formed as waste material It is questionable therefore, whether pharmaceutical companies will apply this route for the synthesis of β-lactam antibiotics because of the high cost and ecological aspects

Several research groups have succeeded in the syntheses of intermediates for nocardicins, aztreonam, carumonam, and related monobactam antibiotics by relatively short and selective routes It will depend on cost aspects whether these routes will replace the total syntheses that are currently employed in the pharmaceutical industry

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