Asymmetric Synthesis of β-Lactams by Staudinger Ketene-Imine Cycloaddition Reaction

Claudio Palomo,*[a] Jesus M. Aizpurua,[a] Iñaki Ganboa,[a] and Mikel Oiarbide[a]

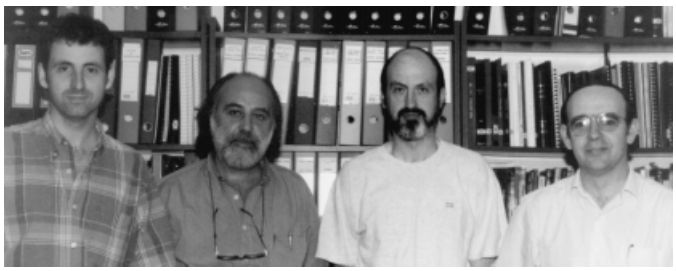
Keywords: Asymmetric synthesis / Cycloadditions / Lactams / Schiff bases

[2 + 2] Cycloaddition reactions between ketenes, bearing amino-, oxy-, or halo- groups, and imines are recognized as being amongst the most important and direct routes to β-lactams. Alkyl-substituted ketenes also furnished the corresponding β-lactams upon reaction with activated imines (iminoesters). In general, ketenes are generated from the appropriate acid chloride and a tertiary amine. The major or sole product of the cycloaddition is usually the *cis*-β-lactam, although a few exceptions showing *trans* selectivity are known. In this way β-lactams with a widely varying substitution pattern at the C-3 and C-4 positions of the ring are constructed stereoselectively. The diastereoselection of the cycloaddition process can be controlled with variable success from chiral groups attached to either the ketene or the imine component, or alternatively to both. This method, in turn, has proved to be valuable for the synthesis of precursors of important β-lactam antibiotics, and new successful applications can be expected in the near future.

Introduction

The β-lactam skeleton is the key structural element of the most widely employed family of antimicrobial agents to date, the β-lactam antibiotics, which include as representative structural classes (Figure 1) the penams **1**, cephems **2**, penems **3**, monobactams **4**, carbapenems **5**, and trinems **6**, among others.[1] The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat the microorganisms that have built up a resistance against the most traditional drugs,[2] have maintained the interest of chemists into β-lactams for decades. In addition, the understanding of the mechanism of action of β-lactam antibiotics by specific inhibition of bacterial transpeptidase enzymes has promoted

[a] Departamento de Química Orgánica,
Universidad del País Vasco,
Facultad de Química, Paseo Manuel Lardizabal-3,
20018-San Sebastián, Spain
Fax: (internat.) +34-943/212236
E-mail: qoppanic@sc.ehu.es



Claudio Palomo (center-left) was born in Barcelona (Spain) in 1951. He studied chemistry at the Instituto Químico de Sarriá, in Barcelona, where he received his Chemical Engeneering Degree in 1975. After spending two years in a pharmaceutical company (Gema S.A.) in Barcelona, he obtained his Licenciatura in chemistry in 1979 at the University of Barcelona. In the same year he joined the Organic Chemistry Department at the University of the Basque Country with Prof. R. Mestres. In 1983, he took his Ph.D. in Organic Chemistry and after two years of postdoctoral work at the same University, he became associate Professor. In 1989 he was promoted to full Professor in Organic Chemistry and two years later he joined, as visiting professor, the research group of Prof. H. Rapoport at the University of California at Berkeley. He has published more than 150 papers and reviews. Topics he is now interested in include diastereoselective carbon−carbon bond forming reactions, asymmetric catalysis in organic synthesis, combinatorial chemistry, and the design and implementation of new synthetic strategies to compounds of biological interest, including β-lactams, amino acids, peptidomimetics, and densely functionalized compounds.

Jesus M. Aizpurua (right) was born in 1959 and studied chemistry at the University of the Basque Country. He obtained his Licenciatura in 1982 and completed his Ph.D. in 1985 with Prof. C. Palomo on novel organosilicon reagents for organic synthesis. After a post-doctoral stay with J. Dunogues at Bordeaux University (France), he joined the Organic Chemistry Department of the University of the Basque Country as assistant Professor in 1987. Since 1997 he has been full Professor of Organic Chemistry at the same university and his current research interests include the application of organosilicon chemistry to the synthesis of β-lactams, peptides, and peptidomimetics.

José I. Ganboa (center-right), born in 1960, studied chemistry at the University of the Basque Country. He obtained his Ph.D. in 1986 with Prof. C. Palomo on β-lactam chemistry. From 1987 to 1990 he worked at the Faculty of Pharmacy of the University of the Basque Country at Vitoria. Currently he is assistant Professor of Organic Chemistry in the Chemistry Faculty at San Sebastian.

Mikel Oiarbide (left), born in 1963, studied chemistry at the University of the Basque Country. He obtained his Licenciatura in 1986 and completed his Doctorate in 1991 with Prof. Palomo on tributyl hydride additions to nitroalkenes. After a two-year post-doctoral stay with Prof. H. Rapoport at the University of California at Berkeley, he again joined the Department of Organic Chemistry at San Sebastian. Since 1994 he has been an assistant Professor of the University of the Basque Country. His research interests include β-lactam chemistry and the development of chiral auxiliaries and catalysts.

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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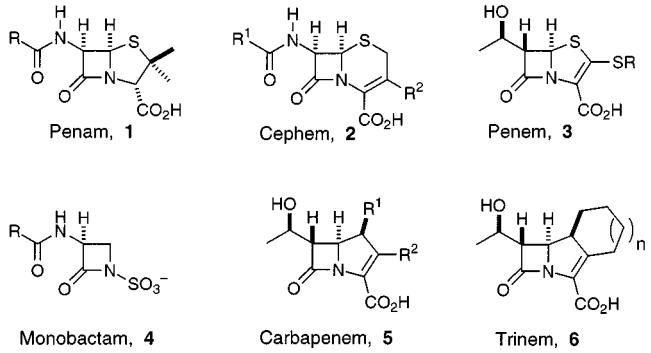


Figure 1. Some representative structural classes of β-lactam antibiotics

the development of new β-lactam inhibitors for related serine protease targets like β-lactamases and elastases.[3]

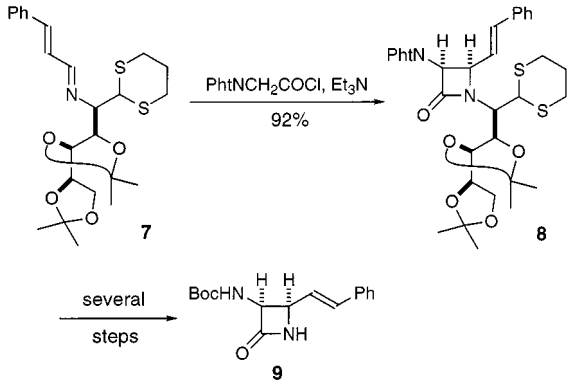
As a consequence, a large number of chemical methods for the production of β-lactams have been developed and the topic has been amply documented and reviewed several times.[4] The hydroxamate cyclization,[5] the metalloester enolate-imine condensation,[6] the chromium carbene-imine reaction,[7] the isocyanate-alkene cycloaddition,[8] and the ketene-imine cycloaddition, also known as the Staudinger reaction,[9] are the approaches most often employed for the construction of the azetidin-2-one ring. In particular, the latter method has provided useful and economical entries to β-lactams, mainly due to the ready availability of both Schiff bases and ketenes.[10] In this context, in spite of the high level of achievement reached in the Staudinger reaction, the subject still constitutes an active area of research, especially given the number of unsolved aspects related to either the control of the stereochemistry or the generality of the reaction.

The present account is intended to show the state of the art on the asymmetric Staudinger ketene-imine cycloaddition reaction[11] as one of the most direct approaches to the β-lactam nucleus. The material covered herein is ordered according to the type of functionalization of the β-lactam ring at the α position and the place from which asymmetric induction is exerted.

1. Asymmetric Synthesis of α-Amino β-Lactams

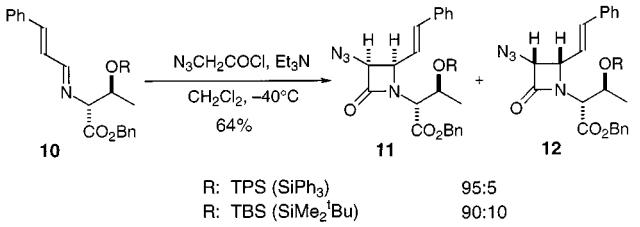
1.1. Asymmetric Induction from the Imine Component

The asymmetric induction in the reaction of achiral ketenes with chiral imines has been effected from imines derived from chiral aldehydes and achiral amines and also from imines derived from chiral amines and achiral aldehydes. In the latter case, β-lactams are often produced, if at all, with low levels of diastereoselectivity.[11b,c] It has been reported, however, that reaction of the imine **7**, derived from D-glucosamine[12] and cinnamaldehyde, with phthalimidoacetyl chloride and triethylamine furnished the β-lactam **8** as a single isomer. This compound was then transformed into the β-lactam **9** in several steps.[12a]



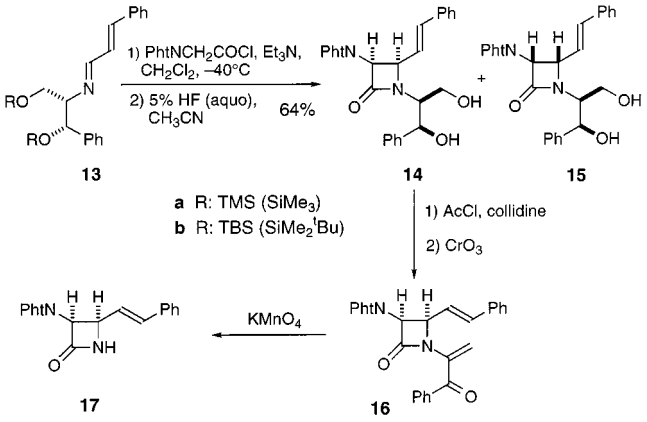
Scheme 1

The most recent examples exploiting the use of imines derived from chiral amines have been reported independently by Bose[13] and Gunda.[14] For instance (Scheme 2), it has been found that the imine **10**, derived from the amino acid D-threonine, upon treatment with azidoacetyl chloride and triethylamine affords β-lactams **11/12** in a 95:5 stereoisomeric ratio.[13] Changing the TPS group for the less bulky TBS leads to a slight decrease in diastereoselectivity, whereas changing the benzyl group of the ester function for other groups, such as methyl, ethyl, and *p*-nitrobenzyl, does not alter the observed diastereoselectivity.



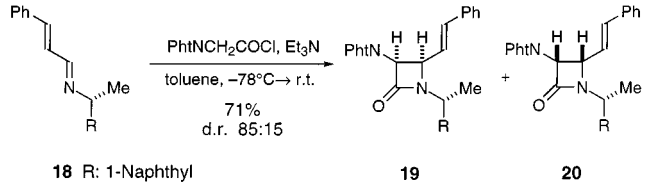
Scheme 2

As reported by Gunda,[14] the imine **13a** gave β-lactams **14/15** with very low diastereoselectivity (2:1) and the imine **13b**, bearing a bulkier *O*-protecting group, provided β-lactams **14/15** with higher diastereoselectivity (8:1), albeit modest. Removal of the substituent at N1 in **14** was accomplished in three steps, through the β-lactam **16**, to give **17** in 52% yield.



Scheme 3

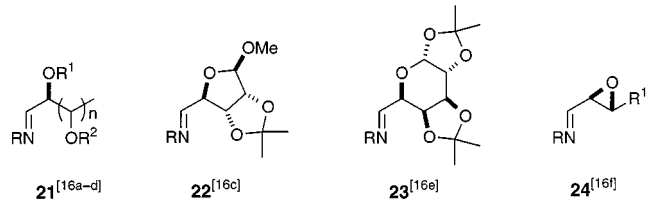
Imines derived from both (*R*)-1-(phenyl)ethylamine and (*R*)-1-(1-naphthyl)ethylamine have also been employed in the Staudinger reaction.[11c] The latter often produces the best results in terms of stereoselectivity. For instance, the reaction of **18** with phthalimidoacetyl chloride and triethylamine provided β-lactams **19/20** in a ratio of 85:15.[15]



18 R: 1-Naphthyl **19** **20**

Scheme 4

Better stereoselectivities are attained when imines derived from chiral aldehydes are used. The most common approaches involve (Figure 2) the use of α-oxyaldehyde-derived imines **21**, sugar aldehyde-derived imines **22** and **23**, and α,β-epoxyimines **24**.[16] In these cases, the β-lactams often present a relative *cis* configuration and both *cis*-dia-

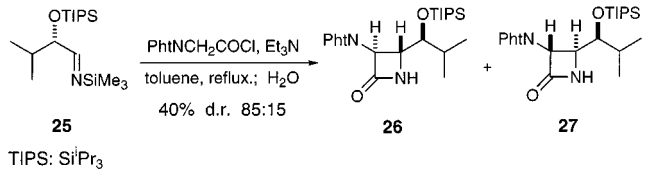


21[16a–d] **22**[16c] **23**[16e] **24**[16f]

Figure 2. Representative α-oxyaldehyde-derived imines employed in the Staudinger reaction

stereomers are usually obtained in ratios higher than 90:10.

Recently, Panunzio and co-workers[17] have reported a case of a *trans*-stereoselectivity preference. The method, shown in Scheme 5, involves the reaction of phthalimidoacetyl chloride with *N*-trimethylsilyl imines, such as **25**, and triethylamine under reflux in toluene.

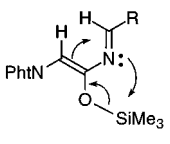


25 **26** **27**

TIPS: Si^iPr_3

Scheme 5

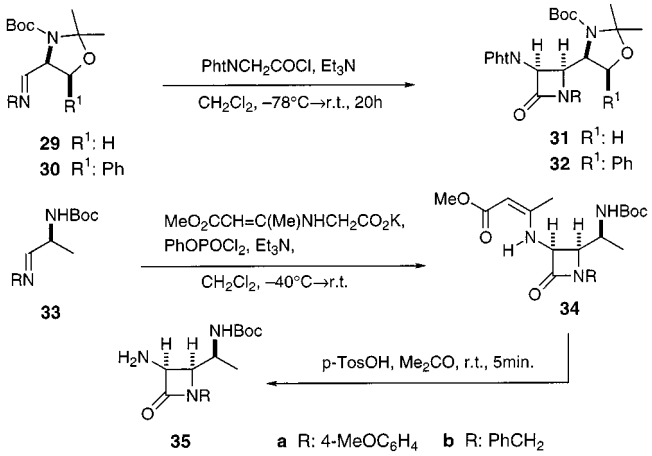
Apparently, β-lactams **26** and **27** are formed through the intermediate **28**.



28

Figure 3. Proposed intermediate for β-lactam formation. When R = CH_3, the intermediate was isolated and, upon heating at reflux in toluene, it afforded the corresponding β-lactams as an equimolar mixture of *trans*-diastereomers

Alternatively, the use of *N*-Boc-α-amino imines in the Staudinger reaction (Scheme 6) also leads to the corresponding β-lactams with high diastereoselectivity.[18] For example, the reaction of **29** with phthalimidoacetyl chloride and triethylamine afforded the respective β-lactams **31a**, **b** as single diastereomers in yields of 41% and 85%, respectively. Likewise, the reaction of the Dane salt of glycine with imines **33a**, **b** in the presence of phenyl phosphorodichloridate and triethylamine gives the corresponding vinylamino β-lactams **34a**, **b** in yields of 48% and 46%, respectively. Each compound **34**, on treatment with two equivalents of *p*-toluenesulfonic acid at room temperature for 5 min, furnishes the corresponding 3-amino β-lactams **35** in yields of 85% and 98%, respectively. In a similar manner, it has recently been found that imines **30**, upon treatment with phthalimidoketene, provide **32a**, **b** in yields of 73% and 91%, respectively.[19] In general, a wide variety of *N*-Boc-α-amino imines can be employed in such a cycloaddition reaction to give β-lactams, which are either potential monobactam precursors or synthetic intermediates for the construction of other heterocycles of interest.[20]



29 R^1: H
30 R^1: Ph
31 R^1: H
32 R^1: Ph
33
34
35
a R: 4-$MeOC_6H_4$ **b** R: $PhCH_2$

Scheme 6

The origin of the extremely efficient asymmetric induction observed in these reactions can be rationalized (Figure 4) on the basis of the magnitude of the stereoelectronic effect exerted by the σ* (C−X) orbital (X being an electronegative atom and C a stereogenic carbon atom) over the HOMO in the transition states leading to the formation of both diastereomeric products.[18]

α-Alkylaldehyde-derived imines, on the other hand, have not been successful in the Staudinger reaction in terms of both chemical reactivity and diastereoselectivity. Nonetheless, Bhawal[21] has shown that the imine **36** (Scheme 7), upon treatment with phthalimidoacetyl chloride and triethylamine, leads to a mixture of β-lactams **37/38** in good yield and acceptable diastereoselectivity. Azidoacetyl chloride also gives the corresponding β-lactams, albeit with a somewhat lower stereoselectivity.

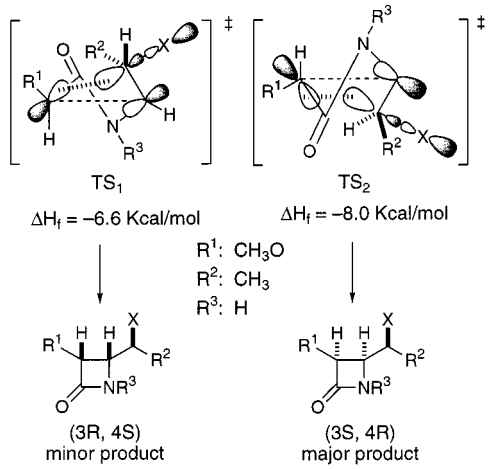
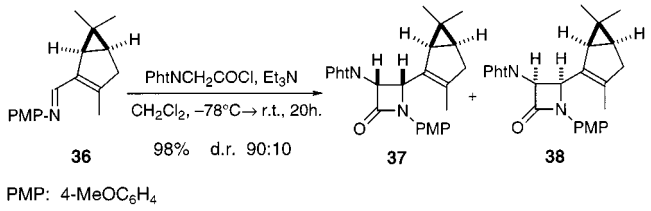


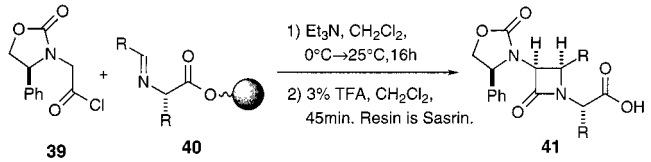
Figure 4. AM1 calculated transition states correponding to the formation of *cis*-(3*R*,4*S*)- and *cis*-(3*S*,4*R*)-4-[(*S*)-1-aminoethyl]-3-methoxyazetidin-2-ones (X: NH_2). TS_1 exhibits an angular arrangement between C3 and the exocyclic C−X bond, whereas TS_2 corresponding to the major product has a linear disposition for the same atoms; the reason for the angular arrangement in TS_1 is the steric interaction between the methyl group (R^2) and the forming β-lactam ring; in TS_2 this steric interaction does not occur and, as a consequence, the HOMO-σ* stabilization takes place more efficiently



Scheme 7

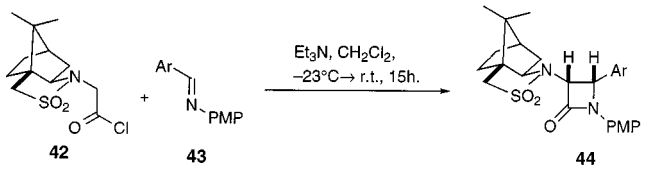
1.2. Asymmetric Induction from the Ketene Component

Another important strategy for the synthesis of nonracemic α-amino β-lactams involves the reaction of the Evans−Sjögren ketenes,[22][23] generated from their corresponding oxazolidinylacetyl chlorides and triethylamine, with aldimines. This strategy has also been successfully applied to solid-phase β-lactam synthesis.[24] As an example, the treatment of **39** with the resin-bound imines **40** in the presence of triethylamine afforded, after removal of the resin, the corresponding β-lactams **41** in 70−90% yields.[24a]



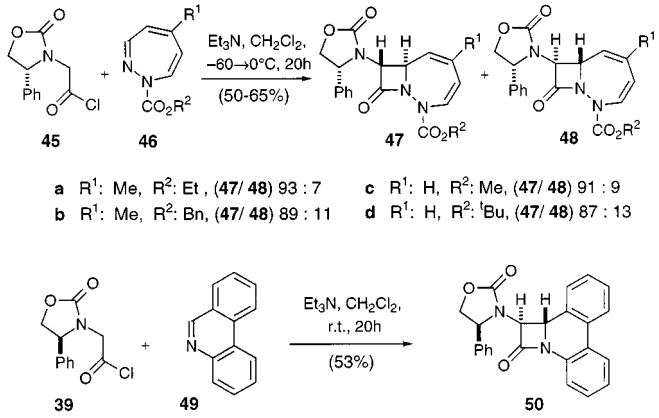
Scheme 8

The acid chloride **42**, on treatment with aldimines **43** and triethylamine, has also been found (Scheme 9) to produce β-lactams **44** as single diastereomeric products. Nonetheless, either acid/basic hydrolysis or reductive techniques failed to remove the camphorsultam moiety.[25]



Scheme 9

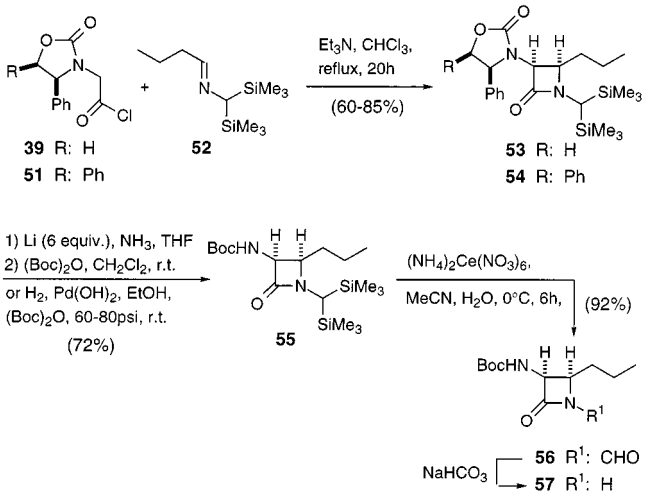
A number of cyclic (*Z*) imine derivatives, like 1*H*-1,2-diazepines **46**[26] or phenantridine **49**,[27] have also been cyclized with the Evans−Sjögren ketenes derived from **45** and its enantiomer **39**, to afford the corresponding polycyclic β-lactam compounds as exclusively *trans* isomers. In the former case, the diastereomeric ratios of adducts **47**/**48** were dictated by the steric effects of the substituents R^1 and R^2, whilst in the second case only the β-lactam **50** was obtained.



Scheme 10

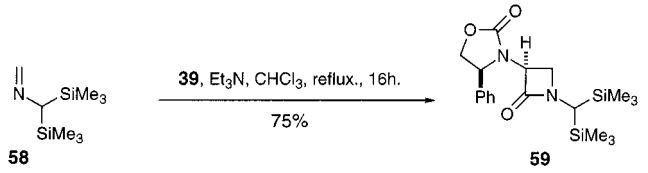
The majority of the investigations into the stereoselective production of 3-amino β-lactams from chiral ketenes deal with the use of non-enolizable aldehyde-derived imines. Enolizable imines cannot be employed in such reactions because of their facile isomerization to enamines. Recently, it has been found that *N*-bis(trimethylsilyl)methyl imines circumvent this problem.[28] For example (Scheme 11), the reaction of **39** with **52** and triethylamine in refluxing chloroform gives **53** in 75% yield along with its *trans*-diastereomer, which is epimeric at the C4 position, in the ratio 90:10. The major isomer **53** could be transformed into the *N*-Boc derivative **55** through removal of the oxazolidinone moiety according to the Evans procedure and subsequent introduction of the Boc group. Alternatively, better yields were achieved from the β-lactam **54**, obtained by reaction of the aminoketene precursor **51**[29] with **52**. In this instance, simple exposure of **54** to hydrogen over Perlman's catalyst in the presence of di-*tert*-butyl dicarbonate afforded the same β-lactam **55** in 96% yield. As Scheme 11 shows, the bis(trimethylsilyl)methyl group was removed from the cycloadduct **55** by treatment with cerium(IV) ammonium nitrate (CAN) and subsequent *N*-hydrodeformylation of the re-

sulting intermediate **56**. In this way, the product, **57**, was formed in 88% yield.



Scheme 11

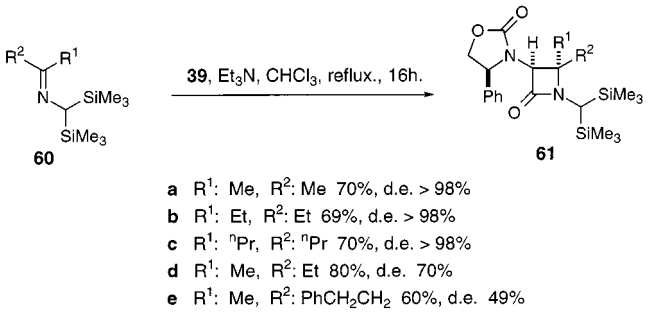
In general, a wide variety of *N*-alkylidene *C*,*C*-bis(trimethylsilyl)methyl amines can be employed in such a reaction. The resulting β-lactams are usually obtained with diastereomeric *cis*/*trans* ratios ranging from 70:30 to 98:2, with the only exception being glyoxylate imines, which led to very low diastereoselectivities regardless of the substituent attached to the imine nitrogen atom.[29a,30] On the other hand, the remarkable thermal stability of these imines becomes apparent in the reaction of ketenes with the imine **58**, which is the first isolable and stable methanimine that allows direct formation of 4-unsubstituted β-lactams. For example, the reaction of **39** with **58** leads to **59** in 75% isolated yield and with perfect asymmetric induction at the C3 position.[31]



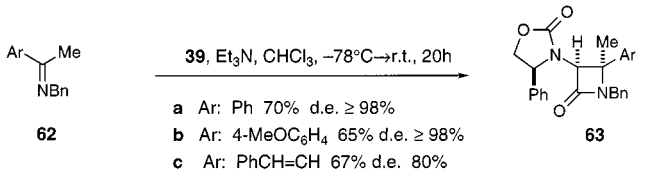
Scheme 12

The latter strategy could also be employed for the construction of β-lactams with quaternary stereogenic centers at the C4 position by simply using ketimines.[32] However, as Scheme 13 illustrates, whilst symmetrical ketimines **60a–c** gave **61a–c** with virtually total diastereoselectivity, unsymmetrical aliphatic ketimines **60d**, **e** led to β-lactams **61d**, **e** along with their epimers at the C4 position, with only low levels of diastereoselection.

On the other hand, imines derived from aralkyl ketones and benzylamine give β-lactams single diastereomers (Scheme 14). For instance, the reaction of **39** with ketimines **62a** and **62b** gave **63a**, **b** in good yields and with essentially total diastereoselectivity at the newly created stereogenic



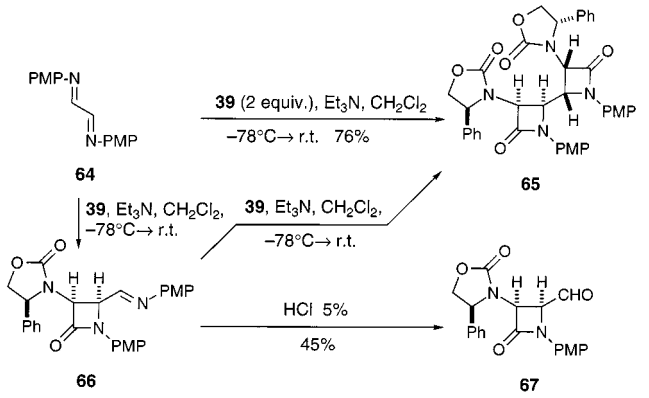
Scheme 13



Scheme 14

centers. Under the same conditions, however, **62c** provided **63c** along with its epimer at the C4 position.

Another approach to 3-amino β-lactams involves the use of bis-aldimines **64**.[33][34] As Scheme 15 illustrates, both β-lactams **65** and **66** are accessible by the Staudinger reaction. The latter can be converted easily into the 4-formyl azetidin-2-one **67**.

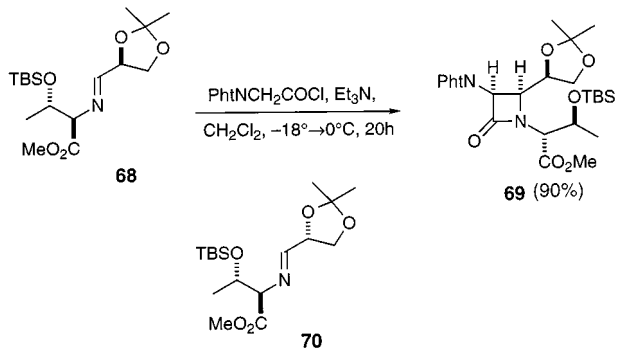


Scheme 15

1.3. Double Stereodifferentiating Cycloadditions

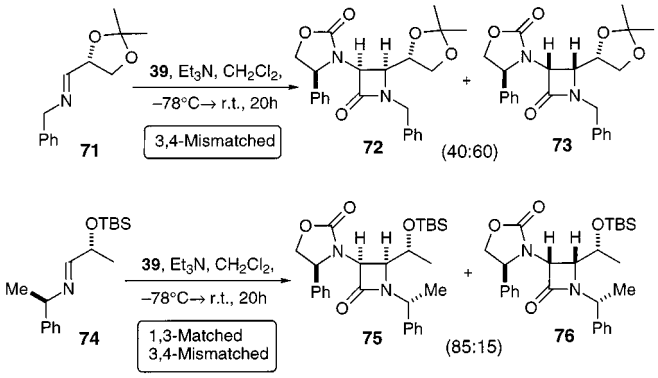
The concept of double asymmetric induction has been applied to [2 + 2] cycloadditions with variable success. Miller[35] found that the reaction of phthalimidoketene with the chiral imine **68**, in which aldehyde and amine units are in a matched relationship, affords the β-lactam **69** in 90% yield. This result represents a significant improvement over related reactions employing threonine imines derived from achiral aldehydes, vide supra. As expected, with mismatched imines like **70**, considerably lower levels of diastereoselectivity are attained.

High levels of double asymmetric induction in reactions between Evans–Sjögren ketenes and imines derived from



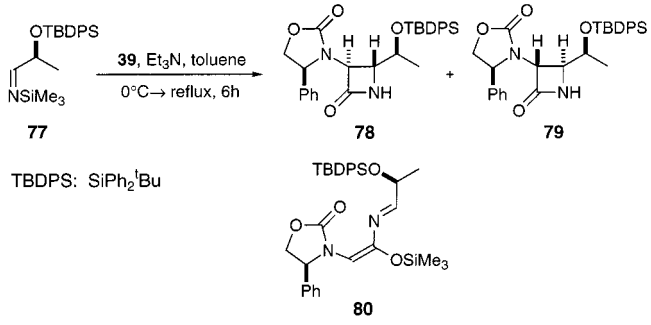
Scheme 16

(*R*)- and (*S*)-α-amino acid esters are documented.[23] Similarly, double induction effected by reaction between chiral ketenes and chiral aldehyde-derived imines has been studied.[36] For example, the reaction of imine **71** with the Evans−Sjögren ketene derived from **39**, in which both reactants are in a mismatched relationship, afforded a mixture of β-lactams **72/73** in a 40:60 ratio, whilst the reaction of imine **74** with the ketene derived from **39** afforded β-lactams **75/76** in an 85:15 ratio.



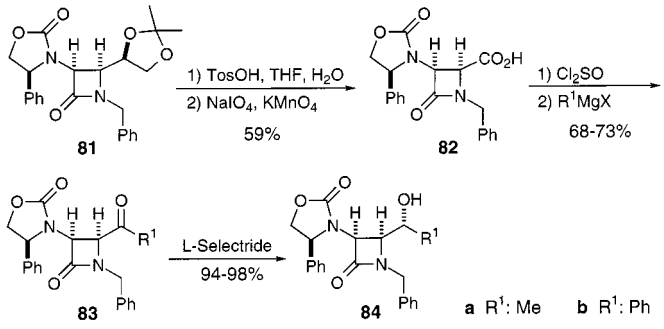
Scheme 17

An interesting variant of this reaction has been reported by Panunzio et al.[37] (Scheme 18), in which the imine **77**, upon treatment with the ketene from **39**, gave β-lactams **78/79** in the ratio 90:10. In this instance, the reaction is believed to occur through intermediate **80**. In any case, it should be noted that the configuration at the C4 position of the β-lactam ring in **78** is the opposite to that predicted by the imine partner, as indicated in Figure 4 (see also Scheme 5).



Scheme 18

As Scheme 19 illustrates, the stereoselective reduction of 4-acyl β-lactams **83**, readily obtainable from the acid chloride of **82** and Grignard reagents, constitutes a practical alternative pathway to β-lactams **84** essentially as single isomers. Thus, starting from β-lactams with the configuration predicted by an imine partner such as **81** and/or its enantiomer, it is possible to obtain the remaining *cis*-diastereomers that are not directly accessible through simple and double stereodifferentiating cycloadditions.[36]



Scheme 19

1.4. Carbacephem Intermediates

An important application of the ketene-imine cycloaddition in recent years has been found in the synthesis of carbacephem intermediates.[38] An illustrative example is *Lorabide* (or *Loracarbef*), which possesses a range of biological activity similar to *Ceclor* but is substantially superior in terms of chemical stability. At present, this family of compounds is not directly accessible by fermentation processes or by the structural modification of naturally occurring β-lactam antibiotics.[39]

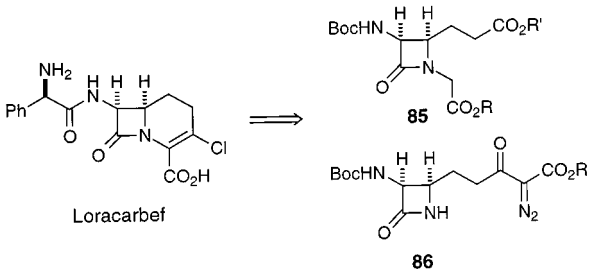
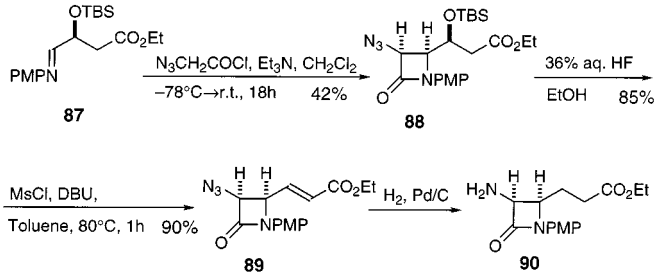


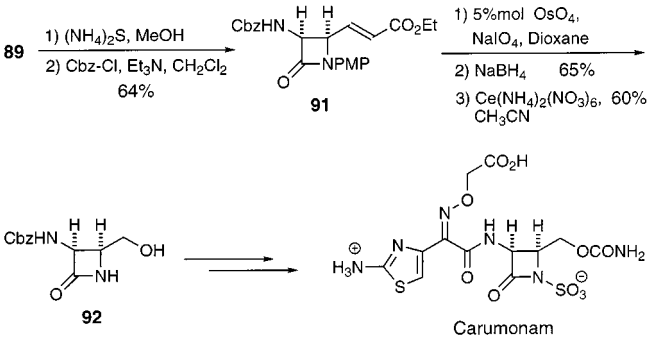
Figure 5. Synthetic approaches to *Loracarbef* antibiotic

The most convenient approaches to carbacephems have focused on the chemical synthesis of suitable monocyclic intermediates for subsequent intramolecular cyclization leading to the bicyclic carbacephem framework.[38][40] Two representative examples of the latter approach are the Dieckmann cyclization of **85**[41] and the rhodium(II) acetate-mediated carbene insertion into the N−H bond of the β-lactam **86**[42] among others.[43] Various syntheses of both **85** and **86** have employed the ketene-imine cycloaddition as the key step. For instance (Scheme 20), Fujisawa and Shimizu[44] have utilized the imine **87**, which upon treatment with azidoacetyl chloride and triethylamine gave **88** in 42%

yield. Dehydration of **88** and reduction of the azido group in **89** generated **90** as a suitable intermediate of *Loracarbef*. The same authors reported the synthesis of **92** as an intermediate of the antibiotic *Carumonam*[45] (Scheme 21) via β-lactam **91**.

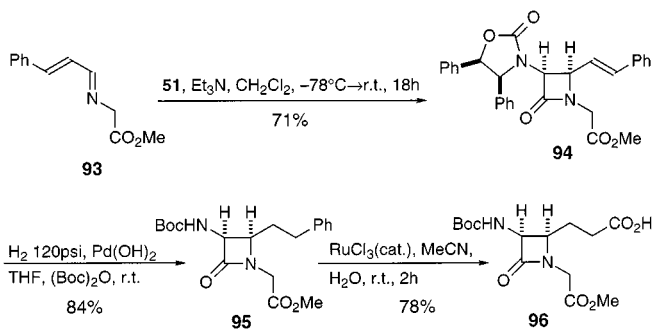


Scheme 20



Scheme 21

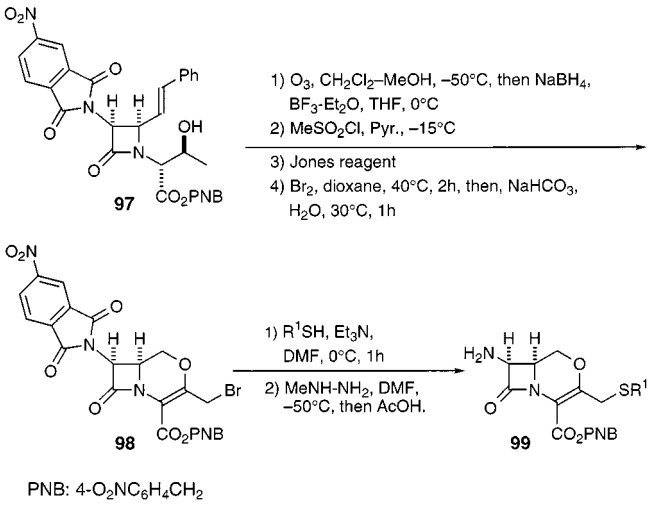
Other syntheses have involved the use of the Evans−Sjögren amino ketene derived from **39** to obtain the corresponding β-lactam in optically pure form. In these cases, two methods to remove the oxazolidinyl moiety from the resulting cycloadducts have been reported: namely a dissolving metal reduction[41] or treatment with trimethylsilyl iodide.[46] Alternatively, the use of **51** allows a more convenient access to *Loracarbef* intermediates.[47] For example, the reaction of **51** with the imine **93** gives the β-lactam adduct **94** in 71% yield. Exposure of **94** to hydrogen over Perlman′s catalyst in THF, as solvent, containing di-*tert*-butyl dicarbonate leads to the removal of the oxazolidinyl moiety together with the reduction of the double bond to give the *N*-Boc derivative **95** in 84% yield. This compound has been transformed easily into the *Loracarbef* intermediate **96**.



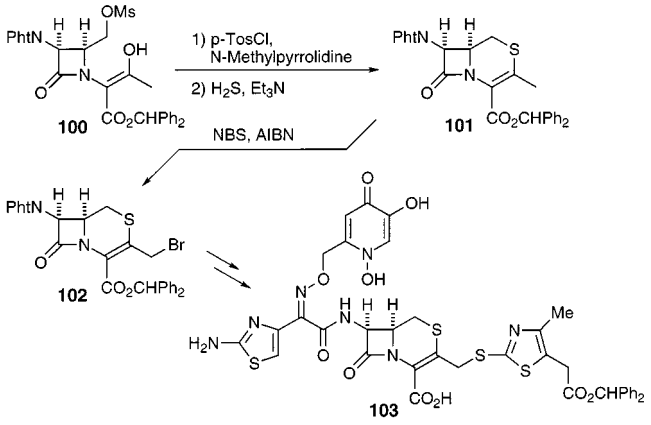
Scheme 22

1.5. 2-Oxaisocephems and 2-Isocephems

The ketene-imine cycloaddition has also been employed to prepare the β-lactam **97** (Scheme 23), which, by conventional manipulations, was transformed into the 2-oxaisocephems **98** and **99**.[48] Likewise, as Scheme 24 illustrates, **100** was transformed into the 2-isocephem **102** via **101**. Starting from both **99** and **102**, a series of 2-oxaisocephems and 2-isocephems, respectively, have been prepared and evaluated for antimicrobial activity. The most active compound is **103**, which exhibited potent in vitro activity against clinically isolated *P. aeruginosa* and *Acinetobacter baumanii* and good in vivo efficacy against clinically isolated *P. aeruginosa*.[49]



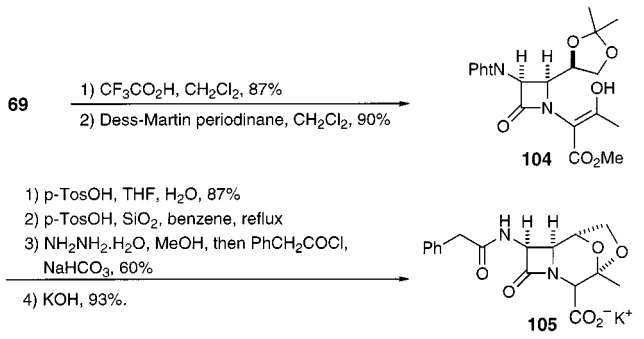
Scheme 23



Scheme 24

Tricyclic β-lactams, such as **105**, have also been prepared from the cycloadduct **69**, via **104**, as shown in Scheme 25. Compound **105** exhibited significant inhibitory activity

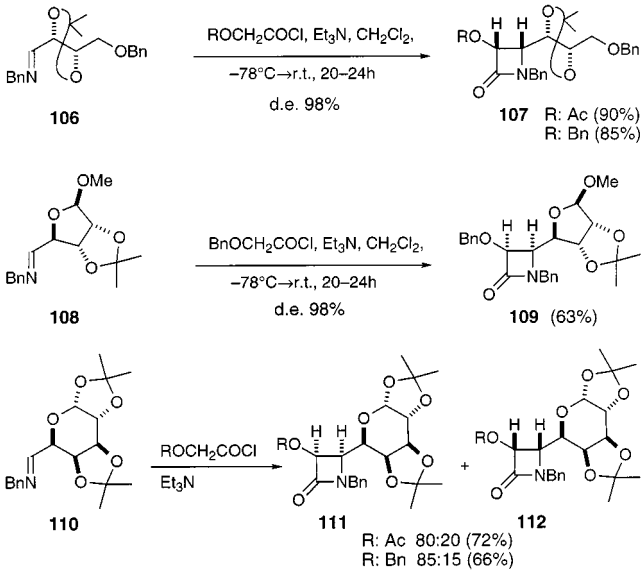
against *Streptococcus pyogenes*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.[35]



Scheme 25

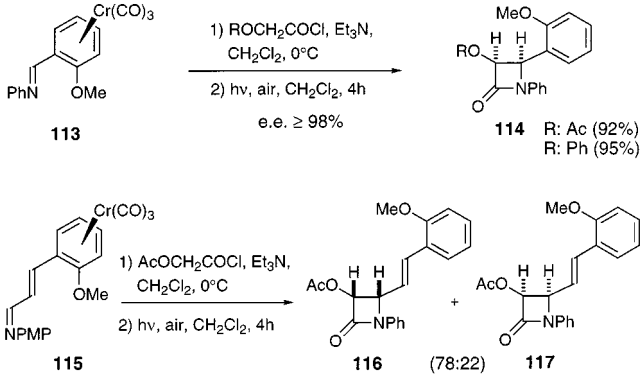
2. Asymmetric Synthesis of α-Hydroxy(alkoxy) β-Lactams

In contrast to the success achieved in cycloaddition reactions of aminoketene equivalents with imines, the analogous reaction of imines with hydroxyketene equivalents still needs further development.[11c] To date, only the reaction of achiral alkoxy ketenes with imines derived from both chiral α-oxy aldehydes[16][50] and chiral α-amino aldehydes[18][19] have provided stereoselective entries to α-hydroxy β-lactams. For example, the reaction of the imines **106** and **108** (Scheme 26) with acetoxyacetyl chloride or benzyloxyacetyl chloride and triethylamine furnished the corresponding β-lactams **107** and **109** as single diastereomers. In some instances, however, the level of diastereoselectivity has been found to be low, as in the case of the imine **110**, which upon treatment with both acetoxyketene and benzyloxyketene led to the corresponding mixture of β-lactams **111/112** in 80:20 and 85:15 ratios, respectively.[51]



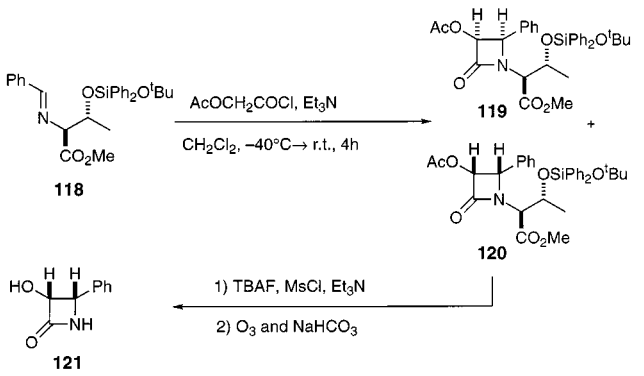
Scheme 26

A significative variation of the cycloaddition stereoselectivity has also been reported[52] for alkoxyketenes and tricarbonyl(η^6-arene)chromium(0) imines **113** and **115** (Scheme 27). Mild decomplexation upon exposure to air and sunlight of the initially formed 4-[tricarbonyl(η^6-arene)chromium(0)]azetidin-2-ones, afforded the respective α-alkoxy β-lactams **114** with e.e. > 98% and **116/117** in 78:22 ratio. The lower stereoselectivity attained in the latter reaction seems consistent with the remote position of the stereogenic arylchromium moiety in the cinnamyl imine **115**, but the reversal of the diastereomeric ratio of isomers remains intriguing.



Scheme 27

At present, the level of reaction diastereoselection attained from chiral imines derived from achiral aldehydes and chiral amines is, like in previous cases with amino ketenes, often very poor.[11c] Farina and co-workers[53] have reported a case (Scheme 28) of a highly diastereoselective cycloaddition on using the imine **118**, derived from benzaldehyde and L-threonine, with the latter bearing a bulky protective silyl group. The reaction of this imine with acetoxyacetyl chloride and triethylamine thus provides a mixture of β-lactams **119/120** in a ratio of 1:11.5. The major isomer **120** is then transformed in several steps into **121**, the cyclized form of the Taxol side chain.



Scheme 28

Other recent examples are shown in Figure 6. As can be seen, β-lactams **122**,[54] **123**,[55] and **124**[56] are produced with low diastereoselectivity.

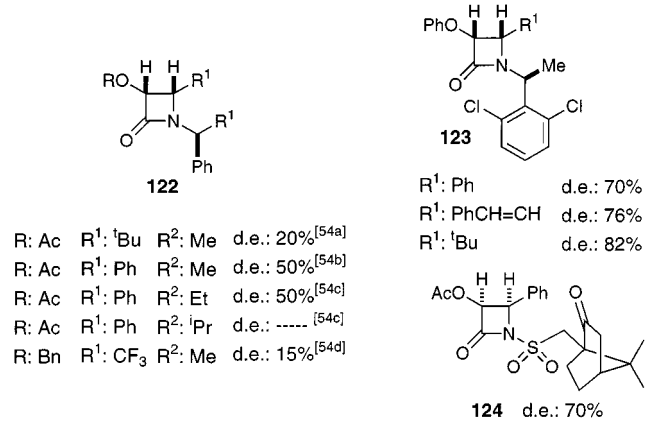
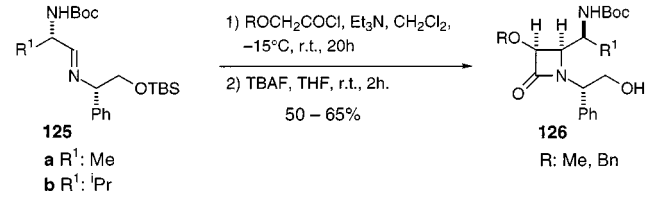


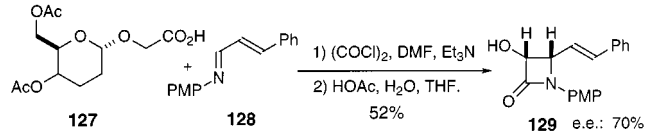
Figure 6. α-Hydroxy β-lactams from achiral α-hydroxy (alkoxy) ketene equivalents and imines derived from achiral aldehydes and chiral amines

When chiral imines **125** (Scheme 29), derived from chiral aldehydes and chiral amines (both of which are in a matched relationship), are involved in such a cycloaddition reaction, only one diastereomeric β-lactam, **126**, is produced.[57]



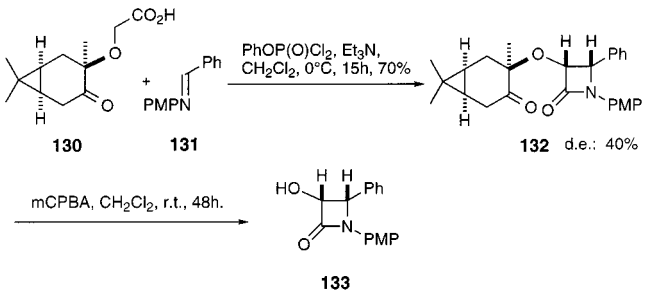
Scheme 29

Attempts to achieve efficient asymmetric induction from chiral alkoxyketenes all met with failure. For example, the reaction of the acid chloride of **127** with the imine **128** in the presence of base (Scheme 30) afforded, after *O*-deprotection, the β-lactam **129** with only 70% enantiomeric excess.[58] In a similar way (Scheme 31), the reaction of **130** with the imine **131**, promoted by phenyl phosphorodichloridate, led to the corresponding β-lactam **132** with a very low diastereomeric excess.[59]



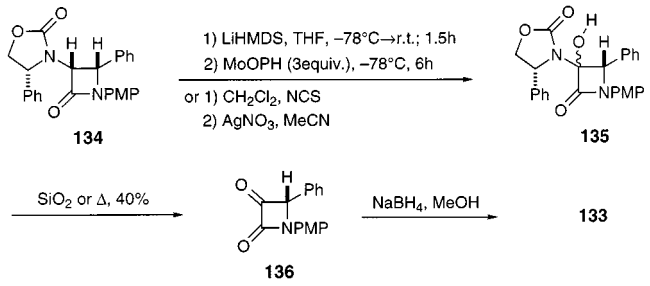
Scheme 30

A solution to this problem (Scheme 32) consists of the prior formation of the β-lactam **134**, which upon deprotonation and subsequent α-hydroxylation leads to the intermediate α-amidocarbinol **135**. This compound subsequently undergoes loss of the oxazolidinyl moiety to give the α-keto β-lactam **136**. The reduction of **136** with $NaBH_4$ proceeds with essentially complete stereoselectivity to give



Scheme 31

133.[60] An analogous approach has been reported by Holton[61] and this involves an α-chlorination of **134** followed by dechlorination with aqueous $AgNO_3$ to give **136**.

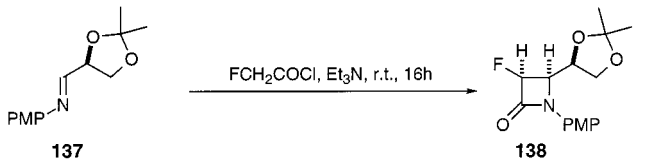


Scheme 32

Alternatively, optically active α-3-hydroxy β-lactams can also be obtained by both enzymatic[62] or chemical[63] resolution of the corresponding racemic derivatives.

3. Asymmetric Synthesis of α-Halo β-Lactams

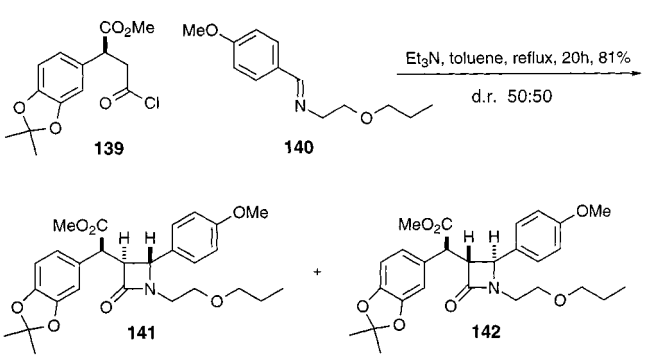
In general, the reaction of acid chlorides with imines in the presence of triethylamine also works well when the acid chloride bears electron-withdrawing groups other than nitrogen and oxygen at the α-position. A representative recent example is the reaction of fluoroacetyl chloride with the imine **137**, derived from *p*-anisidine and D-glyceraldehyde acetonide, to give the β-lactam **138** in 68% yield as a single diastereomer.[64]



Scheme 33

4. Asymmetric Synthesis of α-Alkyl β-Lactams

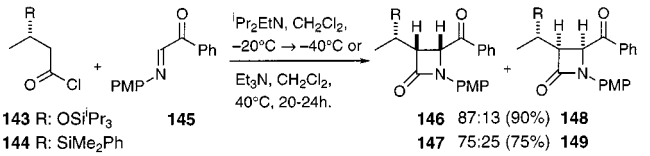
The direct preparation of α-alkyl β-lactams from monoalkylketenes and imines is often fraught with difficulties associated with the generation of the corresponding ketene from the acid chloride and a base, and also with the

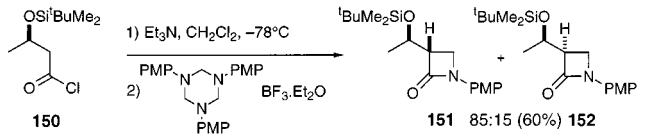


Scheme 34

usual instability of the monoalkyl ketene thus generated.[65] It has been found, however, that racemic 3-alkyl-1,4-diaryl azetidin-2-ones can be obtained from alkanoyl chlorides and imines in refluxing toluene by using tributylamine as base.[66] In a similar way, the reaction of the acid chloride **139** (Scheme 34) with the imine **140** and triethylamine, carried out in refluxing toluene, also proceeds satisfactorily to give **141/142**. However, no diastereofacial selectivity was observed in such a reaction.[67]

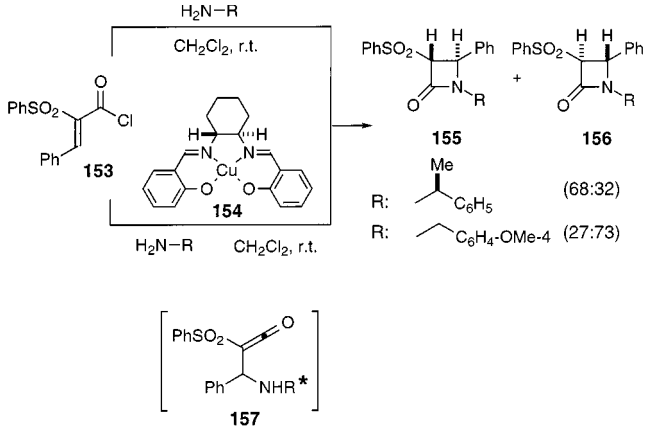
The most general access to α-alkyl β-lactams involving the Staudinger reaction probably involves the use of imines derived from glyoxylates, pyruvates, phenylglyoxal[30,68,69] or formaldimine trimers activated by boron trifluoride/diethyl ether.[70] These cycloadditions work nicely with ketenes derived from enantiomerically pure β-silyloxy- or β-(silyl)-butyric acid chlorides, albeit with moderate diastereoselectivity and nonuniform induction sense. For example, β-lactams **146** and **151**, with the same configuration at the C3 position, are obtained as the major isomers when the ketenes derived from (*S*)-3-(triisopropylsilyloxy)butanoyl chloride **143** and (*R*)-3-(*tert*-butyldimethylsilyloxy)butanoyl chloride **150** are treated, respectively, with the phenylglyoxal imine **145**[69e] and *N*,*N*,*N*-*p*-methoxyphenylhexahydro-1,3,5-triazine.[70]





Scheme 35

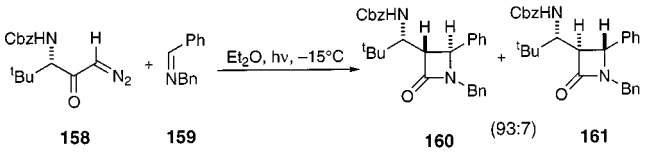
α,β-Unsaturated acid chlorides react with imines in the presence of base to give α-alkenyl β-lactams, although no examples of asymmetric versions have been described as yet.[71] In a related variant (Scheme 36), Detty has found that chiral amines, such as α-methylbenzylamine or the



Scheme 36

complex of 4-methoxybenzylamine and the copper imine **154**, react in a tandem Michael addition-cyclization process with (*Z*)-3-phenyl-2-(arylsulfonyl)propenoyl chloride **153** to afford *trans*-2-arylsulfonyl-3-phenyl-2-azetidinones **155/156**, albeit with low diastereoselectivity. The reaction is assumed to occur through the ketene intermediate **157**.[72]

Recently, the Wolff rearrangement of diazo ketones has been found to be a good alternative for ketene generation in [2 + 2] cycloadditions with imines.[73] For example, the reaction of **158**, generated from the α-amino acid *tert*-leucine, with the imine **159** produced a mixture of **160/161** in a 93:7 d.r. From this approach, a variety of α-amino acid-derived ketenes could be employed to form the corresponding α-(1′-aminoalkyl)-substituted β-lactams, albeit in some cases with modest diastereoselectivities.[74]



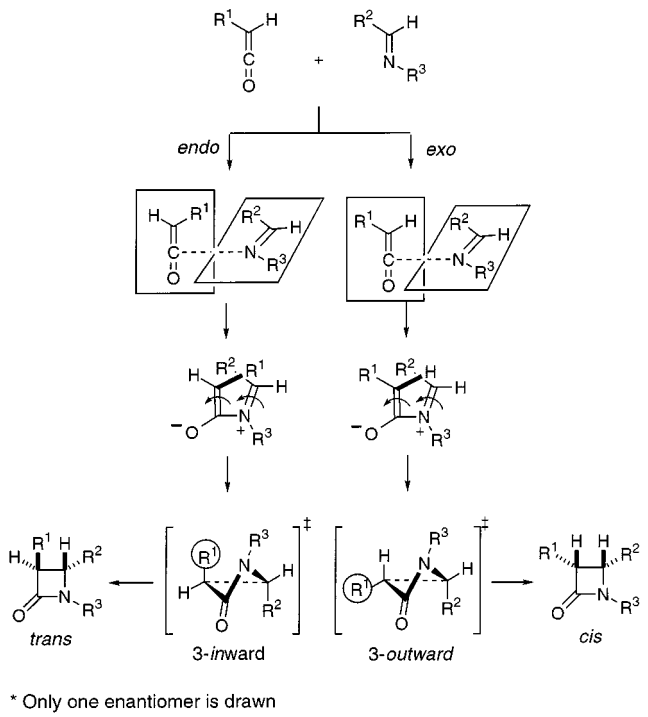
Scheme 37

Finally, it should be mentioned that the base-promoted reaction of acetyl chloride or equivalents with imines has not been viable for the preparation of α-unsubstituted β-lactams.[75] These compounds are suitable building blocks of *trans*-α-alkyl β-lactams.

5. Mechanistic Considerations

According to the accepted model (Scheme 38) the reaction between acyl chlorides and imines is assumed to proceed through in situ formation of a ketene,[68b] followed by interaction with the imine to form a zwitterionic intermediate, which undergoes an electrocyclic conrotatory ring closure to give the β-lactam ring. In general, (*E*) imines lead preferentially to the more hindered *cis*-β-lactams, while (*Z*) imines give predominantly the corresponding *trans* isomers.[11c,76] Theoretical studies undertaken to establish the origin of the *cis*/*trans* stereoselection reveal that the relative energies of the rate-determining transition states, leading

from zwitterions to β-lactams, are dictated not necessarily by steric effects, but by electronic torquoselectivity.[77] For instance, it has been calculated[77b] at the RHF/6-31G* level that the zwitterionic intermediate having an electron-donating group in the ketene fragment (R^1 = OH, CH_3) has a barrier for conrotatory closure to the β-lactam that is 8−12 kcal/mol lower when it adopts an "outward" rotation. This situation translates as a preference for the imine attack opposite (*exo*) to the R^1 group and, therefore, the formation of *cis*-β-lactams from (*E*) imines. According to the same study, this trend is reversed when R^1 is an electron-withdrawing group and, for instance, the "inward" rotation prevails by 12−15 kcal/mol for R^1 = BH_2, leading to a preference for an *endo* attack and, hence, the formation of *trans*-β-lactams from (*E*) imines. The origin of the chiral control of the Staudinger reaction, arising from the presence of chiral substituents (R^1, R^2 and/or R^3), has also been investigated at a semiempirical level (AM_1) for chiral amino ketenes and chiral α-hydroxy- and α-amino imines.[18,77c]



Scheme 38

Although the introduction of the torquoselectivity concept permits the rationalization of a substantial amount of the known experimental data concerning the Staudinger reaction, it is evident that further investigation in this area is required. For instance, a comparison of Schemes 35 and 37 shows that, under kinetic conditions, the alkyl ketene derived from **143** leads to the exclusive formation of *cis*-β-lactams **146** and **148**, whereas the alkyl ketene derived from **158** very predominantly leads to the *trans*-β-lactam **160**.

Conclusion and Outlook

In summary, the ketene-imine cycloaddition reaction shows high versatility for the direct access to diversely functionalized β-lactams in good chemical yields. In most of the cases, β-lactam rings with a relative *cis* configuration are the major or the sole products, although specific exceptions with *trans* selectivity are known. Many diastereoselective variants of the Staudinger reaction have been described for the control of the stereoselectivity. As illustrated here, there are, however, some unsolved problems that justify further investigation in this field. On the other hand, the recent discovery of new active β-lactam compounds (Figure 7), such as Thrombin,[78] Prostate Specific Antigen,[79] Human Cytomegalovirus Protease,[80] or the new Cholesterol Absorption Inhibitors,[81] guarantees renewed interest in the synthesis of azetidinones and, therefore, in the Staudinger reaction. Finally, taking into account the fact that functionalized β-lactams also constitute excellent building blocks for the synthesis of α- and β-amino acid derivatives,[23][82] it is to be expected that the improvements in the Staudinger reaction will contribute to making them the synthetic intermediates of choice for many chemists working in the fields of heterocyclic chemistry and peptide synthesis.

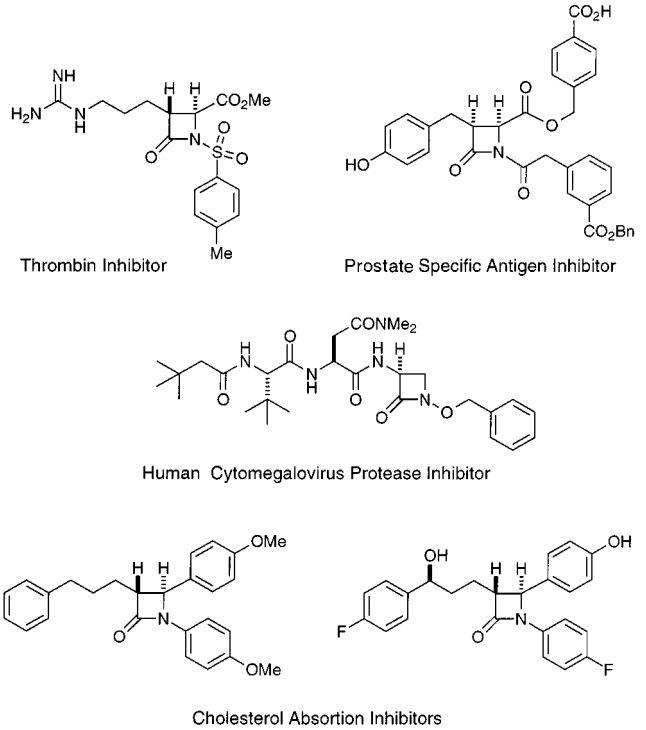


Figure 7. Some representative β-lactams displaying biological activities different from antibiotic

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(University of the Basque Country). All collaborators cited within the references are also acknowledged.

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