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Preparation of β-lactams by [2+2] cycloaddition of ketenes and imines☆

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Contents

1. Introduction

The report by Staudinger in 1907 of the reactions of diphenylketene (**1**) with benzylideneaniline (**2**), benzaldehyde, and cyclopentadiene forming [2+2] adducts **3**–**5**, respectively, marked not only the beginning of cycloaddition chemistry, but also that of the chemistry of β-lactams.[1] There was, however, little interest in the preparation of β-lactams (2-azetidinones) for many years, as these materials possessed no apparent utility. By contrast β-lactones were useful for the preparation of alkenes upon decarboxylation (Scheme 1), while cyclobutanones attracted significant preparative and theoretical interest.

The β-lactam antibiotic penicillin was discovered by Fleming in 1928,[2a,b] although the appreciation of its seemingly miraculous medicinal properties was rather slow to develop. However, once these became known on the eve of World War II there was a great effort not only to prepare large quantities of the drug using biological processes, but also to elucidate the structure of penicillin and to devise laboratory syntheses. The determination of the β-lactam structure took the concentrated efforts of many of the

☆ Dedicated to Professor Ajay K. Bose, a pioneer in β-lactam chemistry for 60 years since his doctoral studies at MIT from 1946 – 1950 with John Sheehan when the first synthetic penicillin analogues were prepared. He received the B.Sc. and M.Sc. degrees at the University of Allahabad, India, and after postdoctoral work at Harvard University and the University of Pennsylvania and teaching at the Indian Institute of Technology, Kharagpur, he joined the Stevens Institute of Technology, Hoboken, NJ, in 1959, and became Professor Emeritus in 2007. He has published very extensively not only on β-lactams but also microwave-assisted synthesis and numerous other topics, and has received many awards, including US Presidential Award for Excellence in Science Mentoring and the Lifetime Achievement Award of The Indian Chemical Society.

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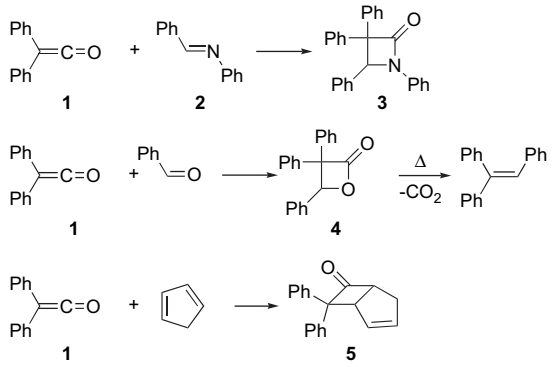


Scheme 1. [2+2] Cycloaddition reactions of diphenylketene.[1]

world's leading chemists, and this problem was solved by 1944,[2c] with a major contribution from R. B. Woodward among others, as has been described.[2d] Even with the full report of this effort in 1949[2c] and the proof of the structure by X-ray by Dorothy Crowfoot Hodgkin, there were still doubts, as expressed by Sir Robert Robinson,[2e] regarding the β-lactam structure. He advocated 'a protonomer' of the β-lactam which, "provides a simple relation between the oxazolone and β-lactam structures. A pendulum-like swing involves their interconversion." He represented the structures as shown in Figure 1, and the phrasing suggests a movement of atoms between the structures.

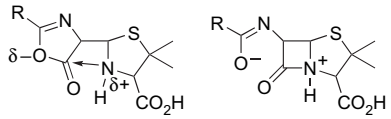
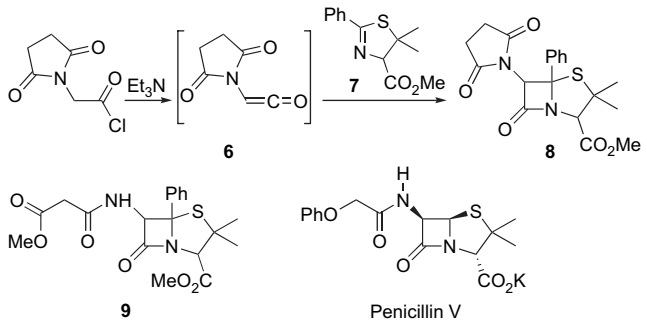


Figure 1. Proposed β-lactam 'protonomers'.[2e]

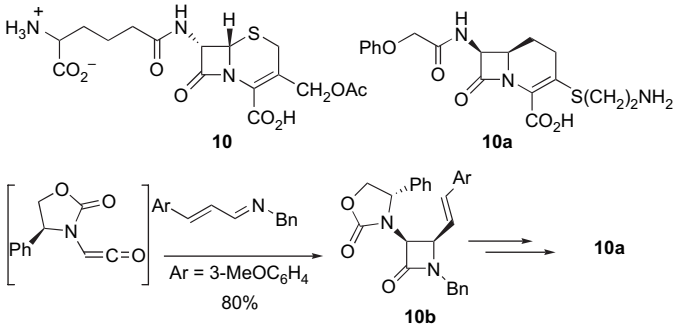
Methods for biological preparation of penicillin for clinical use were already in wide use, but development of laboratory syntheses followed a more tortuous path. The synthesis of a penicillin analogue, the penam **9**, by Sheehan and co-workers using the [2+2] cycloaddition of in situ generated ketene **6** with imine **7** forming the precursor **8** was accomplished in 1950 (Scheme 2),[2f] confirming Woodward's prescient structural assignment, and showing the way for the extensive future development of this reaction. The total synthesis of natural penicillin V was completed by Sheehan in 1957, but did not utilize a ketene cycloaddition.[2g]

The preparation and chemistry of β-lactams have been the subject of frequent reviews,[3] including not only [2+2] cycloadditions of ketenes with imines, but also other routes as well. The use of β-lactams as synthons for a wide variety of further useful products has also been extensively studied.[3n] The goal of the current review is to consider recent work on the synthesis and mechanism of β-lactam formation by [2+2] cycloadditions of ketenes with imines, especially those published since the last update[3d] in 2003, and to consider some aspects in greater detail, including the mechanism of the reaction, and the preparation of bis(β-lactams).



Scheme 2. Synthesis of the penicillin analogue **9**, and the structure of natural penicillin V.

The cephalosporins are another family of β-lactam antibiotics, and the first example came with the discovery of cephalosporin *p* by Guiseppi Brotzu from the sea near a sewer outlet in Caligari, Italy, in 1948.[4a,b] This set off another chain of chemical investigations, with the elucidation of the structure of cephalosporin *C* (**10**) in 1955.[4c] Woodward announced the first synthesis of cephalosporin *C* in his Nobel award address in 1965,[4d,e] but this was also not achieved using a [2+2] cycloaddition. Analogs of **10** with significant antibiotic activity have, however, been prepared using β-lactam formation by ketene–imine reactions,[4f–h] including enantioselective formation of the carbacephalosporin analog **10a** beginning with cycloaddition of a chiral ketene (Scheme 3).[4h] One of the difficulties in this area is that cyclic imines usually form trans products on cycloaddition with imines, but cycloaddition with an acyclic imine followed by ring closure leads to the desired cis product **10a**.[4h] Stereochemical control remains a major concern in β-lactam synthesis.



Scheme 3. Cephalosporin *C* and enantioselective synthesis of a carbacephalosporin nucleus.

Ketene chemistry has been the subject of recent reviews,[5a–c] and imines, or Schiff bases, are the other necessary components for β-lactam synthesis by [2+2] cycloaddition. These were first characterized by Schiff in 1864,[5d,e] and have a multitude of uses, with their role in β-lactam synthesis remaining as an essential part of current synthetic and mechanistic chemistry. Ketene–imine cycloadditions have also been extensively examined,[3,5] with an emphasis on variations in imine structure, including chiral and cyclic imines.

2. Mechanistic studies

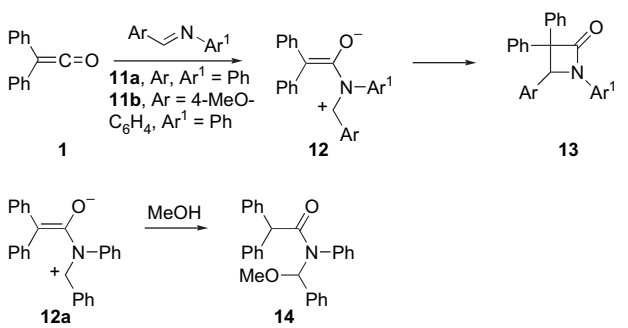
Early in the development of ketene–imine [2+2] cycloadditions forming β-lactams interest concentrated on the creation of synthetic methodology, with little attention to the mechanisms of these processes.[3,6] With the appearance of the Woodward–Hoffmann selection rules governing cycloaddition reactions and the realization that concerted [2+2] cycloadditions are controlled by orbital symmetry the question arose as to how this applied to ketene cycloadditions.[7] It was originally suggested that 'it must be concluded that those cycloadditions, which do occur in cases prohibited by our selection rules for concerted reactions must proceed through multistep mechanisms (e.g., formation of cyclobutane

derivatives by dimerization of allenes and ketenes…)'.[7a] Upon further consideration it was concluded that such concerted reactions were allowed by $[\pi 2_a+\pi 2_s]$ mechanisms, but this was not initially applied to ketene–imine cycloadditions.[7c,d] Mechanistic study of ketene–imine reactions concentrated on the stereochemistry observed, and the results were somewhat contradictory, in that in some cases reactions of aldoketenes (RCH=C=O) with imines gave high selectivity for formation of the less stable cis products, while in others mixtures of cis and trans products, or even exclusively trans products were formed.[3f] An empirical classification of the ketenes favoring different stereochemical outcomes was devised, [3f] grouped as Bose–Evans[8a,b] ketenes with small substituents favoring formation of *cis* β-lactams, Sheehan[2f] ketenes with medium sized substituents favoring cis products, except for reactions with diarylimines forming trans products, and Moore ketenes with large substituents favoring *trans* lactams.[3f,8c,d]

2.1. Mechanistic studies of uncatalyzed ketene–imine cycloadditions

β-Lactam formation by ketene–imine [2+2] cycloaddition presents many mechanistic problems, and is still far from being completely understood. A recent report asks "The Mechanism of the Ketene–Imine (Staudinger) Reaction in its Centennial: Still an Unsolved Problem?"[9] Reaction occurs by both uncatalyzed and catalyzed processes, and can follow complex mechanistic pathways, and even the involvement of ketenes in some examples is not always certain. The first example was the uncatalyzed process observed by Staudinger in 1907,[1] and this and other early examples of the uncatalyzed reaction generally used isolable ketenes such as $Ph_2C=C=O$ or $Me_2C=C=O$, which did not form stereoisomeric products. Initial studies of the reactions of ketenes with vinyl ethers found the reactions to be stereoselective, and ketene–alkene reactions forming cyclobutanones were classified as concerted reactions.[7c–e,10]

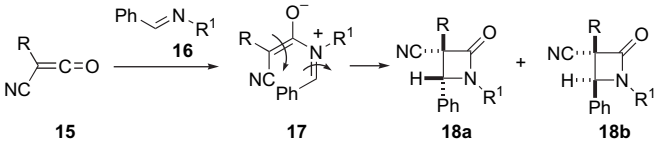
Kagan and Luche[11] already in 1968 observed that competitive reactions forming β-lactams **13** from diphenylketene (**1**) and imines (**11**) were faster in the more polar solvent butyronitrile compared to toluene, and that when MeOH was added after partial reaction that a portion of the product was diverted to formation of **14**. These results were interpreted as showing the reactions were stepwise, with the formation of zwitterion **12** (Scheme 4). In further competition experiments, the reaction of 1 equiv of $Ph_2C=C=O$ (**1**) with a mixture of 1 equiv each of PhCH=NPh (**11a**) and 4-$MeOC_6H_4CH$=NPh (**11b**) or **11a** and PhCH=NC_6H_4OMe-4 (**11c**) in toluene gave a preference for reaction **11b**/**11a** and of **11c**/**11a** of 2.3, also consistent with preferential attack of the more electron-rich and nucleophilic imine, and the formation of a zwitterionic intermediate **12** in the reaction.[11]



Scheme 4. Zwitterionic intermediates in ketene–imine cycloadditions.

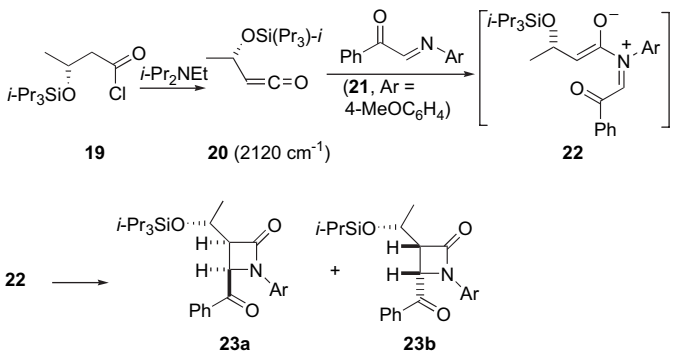
Cycloadditions of more reactive monosubstituted ketenes, which could form cis and trans products were, however, usually carried out by in situ dehydrochlorination of acyl chlorides with triethylamine in the presence of the imine, and these reactions resulted in variable stereochemical results.[8a] The question arose as to whether ketenes were always involved in these reactions, as direct reaction of the acyl chloride with the imine was also shown to occur in some cases, and this process could not always be excluded as a path for β-lactam formation.[8a]

To circumvent these problems, reactions of unsymmetrically substituted cyano ketenes **15** (R=*t*-Bu, Me, Cl, Br, and I) generated in situ by thermal reactions forming only inert byproducts were undertaken.[8c,d] These reactions usually showed stereoselective formation of products with a trans arrangement **18a** of CN and H in the product β-lactams (Scheme 5). The product **18b** became significant when R^1 was a bulky group such as *tert*-butyl. This formation of the more stable cycloadduct is counter to the usual finding for concerted $[\pi 2_s+\pi 2_a]$ reactions,[7c–e] while the stereoselectivity is unusual for a two-step mechanism. It was shown, however, that zwitterions **17** generated independently also gave products **18** with the same stereochemistry as the ketene–imine reactions. Capture of the zwitterions with alcohols was also demonstrated.[8c,d] Therefore, the results were interpreted in terms of two-step reactions with stereoselective attack of the imine on the cyano substituted side of the ketene forming zwitterionic intermediates **17**, which underwent conrotatory bond formation of β-lactams **18** (Scheme 5).[8c,d] Further product studies of the stereochemistry of such reactions have increasingly favored this mechanism involving formation of initial zwitterions, which then close to the product with conrotatory bond rotation.



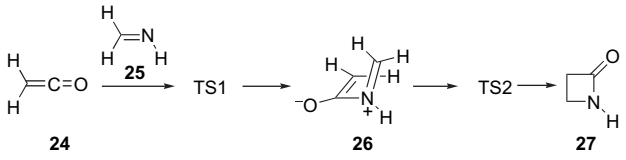
Scheme 5. Stereochemistry of cyanoketene–imine [2+2] cycloaddition.

Experimental study of the mechanism with direct observation during the course of ketene [2+2] cycloadditions with imines is made difficult both because the ketenes are often generated in situ for reaction with imines, and also because the ketene reactions are usually quite rapid. Photochemical generation of a ketene in a solid matrix in the presence of imidazole at 10 K revealed the ketene IR absorption at 2110 cm^{-1} together with the imidazole, and upon warming to 140 K the ketene and imidazole absorption diminished and an IR absorption appeared at 1635 cm^{-1}, and was attributed to zwitterion formation.[12a] In a pioneering study, reaction of the chiral acyl chloride **19** with the imine **21** catalyzed by *i*-Pr_2NEt gave *cis* β-lactams **23** with a **23a**/**23b** ratio of 1:4 (Scheme 6).[12b] The reaction of **19** with *i*-Pr_2NEt gave a strong IR band at 2120 cm^{-1} assigned to the ketene intermediate **20**, and the reaction of **19** with **21** at different concentrations of *i*-Pr_2NEt was monitored by IR at −22 °C, with simultaneous observation of all reactants and products. It was found that there was an initial rapid formation of ketene **20**, which reached a steady state, and that the consumption of **19** and **21** was concurrent with the formation of **23** and was first order in the concentration of *i*-Pr_2NEt (Scheme 6).[12b] No ketene was formed when reaction was attempted using Et_3N as the base, and deprotonation of an acylamine intermediate was excluded by the first order dependence on *i*-Pr_2NEt concentration. The conversion of **19** and **21** to **23** was interpreted as being exclusively through the intermediacy of ketene **20**, with initial nucleophilic attack of the imine nitrogen on the ketene carbonyl forming intermediate zwitterion **22**, which closed to the products **23**.[12b]



Scheme 6. Zwitterion formation in ketene–imine reaction.

Since kinetic studies of ketene–imine reactions are difficult to carry out further such investigations have been mainly limited so far to competition studies. The reaction is, however, amenable to computational study. The first ab initio computations were reported in 1992 for the reaction of ketene (**24**) with methylenimine (**25**), and at the HF/3-21G level the reaction was predicted to proceed by an asynchronous but concerted reaction, contrary to experimental results.[13] However, computations at the HF/6-31G*//HF/6-31G* and MP2/6-31G*//MP2/6-31G* levels found an initial twisted transition state (TS1) giving a zwitterionic intermediate **26**, which closes through TS2 to β-lactam **27** (Scheme 7).[13b] Energies (kcal/mol) relative to the reactants were 3.7 (TS1), 3.5 (**26**), 21.3 (TS2), and −41.2 (**27**). Further AM1 computations in 1993 agreed that the reaction was stepwise.[14a] Thus, the reaction was indicated to proceed through an initial reversible nucleophilic attack by nitrogen on the carbonyl carbon forming a zwitterionic intermediate, which passes through a higher barrier to the product in a strongly exothermic overall reaction.



Scheme 7. Computational studies of ketene–imine [2+2] cycloaddition.

A contrary view was presented[13a,14b] from computational studies of the cycloaddition reaction of ketene (**24**) and methylenimine (**25**), leading to 2-azetidinone (**27**) using RHF/3-21G and IRC. This reaction was suggested to be concerted but non-synchronous, taking place through a twisted transition state. Four p orbitals were involved in this reaction, described as a '2×[1+1]'-type cycloaddition.[14b] The activation barrier was calculated to be 33.9 kcal/mol. Substituted derivatives were also studied.[14b] A separate analysis of one center frontier-orbitals also supported a concerted pathway for the ketene and methylenimine reaction, but this was not compared to the stepwise pathway.[14c] Further analysis suggested that the consideration of solvent effects favored the two-step mechanisms, and that because of the strong basis set dependence that care should be taken in interpretations, but that the preponderance of experimental and computational evidence favored the latter pathway.[14d]

Subsequent computational studies have supported the two-step mechanism, and have concentrated on efforts to explain the stereochemistry of the reaction. Computational studies indicate the torquoselectivity of ketene–imine interconversion with β-lactams parallels that seen in electrocyclization of 1,3-butadienes to cyclobutenes, with π electron donating substituents (F, Cl, OH, and CH_3) preferentially occupying the outer positions in the transition state with conrotation to form cis products.[15] For the reaction of chloroketene with $CH_3CH{=}NH$, the cis transition state in dichloromethane was found to be favored by 11.57 kcal/mol at the B3LYP/6-31G* level (Fig. 2).[15b]

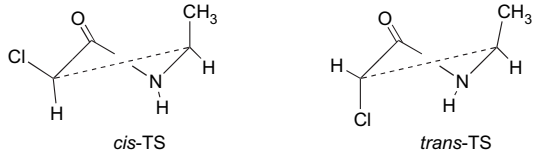
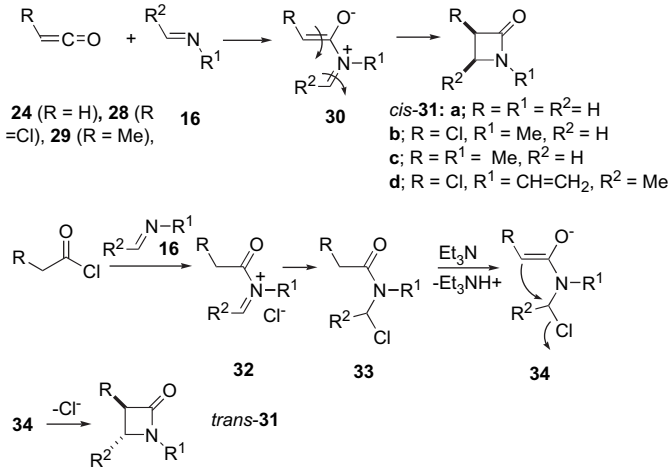


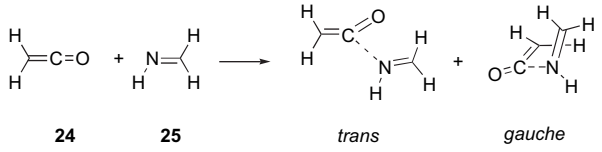
Figure 2. Torquoselective effects in β-lactam formation.

Calculations at the B3LYP/6-31G* level indicated that for various combinations of substituents, ketenes give stepwise reaction with imines **16** with formation of zwitterions **30** followed by conrotatory ring closure giving cis products **31**, in agreement with experiment.[15] For reaction of these imines with acyl chlorides in the presence of Et_3N it was calculated that direct reaction of the acyl chloride with the imine forming **32** took place, followed by chloride addition to give **33** leading to enolate **34**, and then intramolecular S_N2 reaction formed *trans* β-lactams **31** (Scheme 8).[15b]



Scheme 8. Computational studies of ketene–imine cycloaddition.

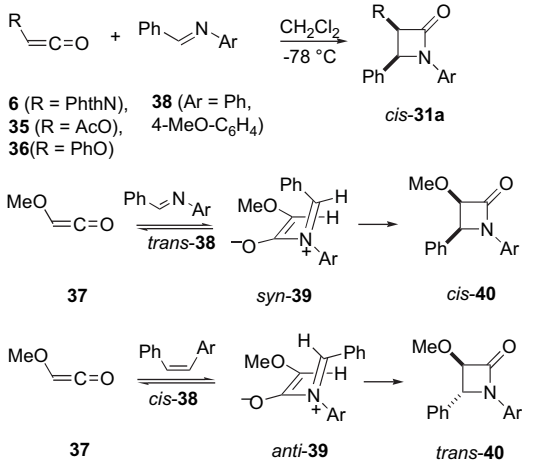
A mechanistic scheme derived using CASSCF and CASPT2 methods identified two directions of approach of ketene **24** and imine **25** in the reaction, with a near coplanar arrangement of the ketene and imine in the trans approach, and a 39.0° dihedral angle between the two in the intermediate for the *gauche* approach (Scheme 9).[16] This was proposed as a useful method for more detailed calculations, including substituent and solvent effects to successfully predict the product stereochemistry.[16]



Scheme 9. Geometry of ketene–imine complexation.

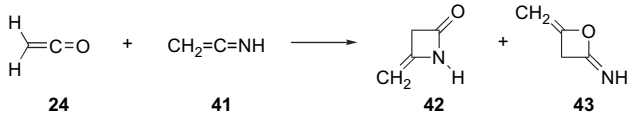
Steric effects also influence the stereochemistry of β-lactam formation, and experimentally ketenes generated by dehydrochlorination of carbonyl chlorides with Et_3N or dehydration of

carboxylic acids at −78 °C reacted with imines **38** to form exclusively *cis* β-lactams **31a** when Ar = Ph or 4-MeOC$_6$H$_4$, but with Ar = 1-naphthyl, 1-anthracenyl, 9-phenanthrenyl, 1-pyrenyl, and 6-chrysenyl these gave exclusively trans products (Scheme 10).[17a] In a computational study of this reaction at the B3LYP(PCM)/6-31+G*+ΔZPVE level,[17b] the reactivities were compared for *N*-arylimines **38** (aryl = phenyl or 1-naphthyl) with methoxyketene (**37**) to explain the divergent stereochemistry of the product β-lactams **40** (Scheme 10). Reactions of **37** with *cis*- and *trans*-**38** were considered, and it was concluded that for Ar = 1-naphthyl that the lowest energy pathway to the product **40** involved initial trans to cis isomerization of *trans*-**38** to *cis*-**38**, which added to ketene **37** giving zwitterion *anti*-**39** followed by conrotatory cyclization to form *trans*-**40**.[17b] The highest barrier for the latter route was 0.7 kcal/mol less than that for the path involving initial reaction of **37** with *trans*-**38**. For Ar = Ph the pathway with reaction of *trans*-**38** leading to *cis*-**40** had a lower barrier than that leading to *trans*-**40**.



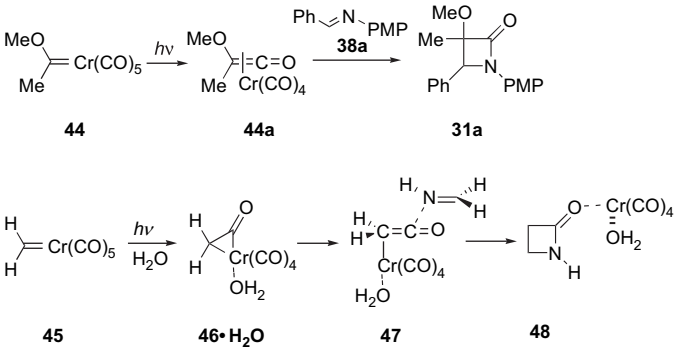
Scheme 10. Formation of *cis* and *trans* β-lactams **40** with imine isomerization.

Computational studies using the atoms in molecules (AIM) method for the reaction of ketene (**24**) with vinylimine (**41**) found concerted pseudopericyclic [2+2] pathways to the more stable β-lactam **42** and the less stable iminooxetane **43**, although there was a lower barrier for formation of **43** (Scheme 11).[18] Further study of the ellipticity changes in the reactions confirmed the previous conclusions, and led to the introduction of new criteria for pericyclic and pseudopericyclic reactions.[18b]



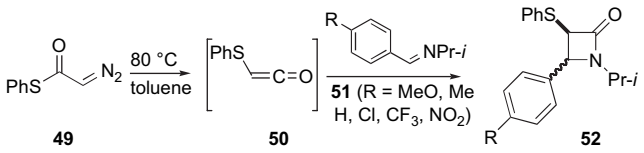
Scheme 11. Computational studies β-lactam and iminooxetane formation.

The formation of β-lactams by the photolysis of metal–carbene complexes in the presence of imines is a valuable synthetic method that has long been the subject of mechanistic speculation. Irradiation with visible light of the complex **44** was proposed to form the ketene complex **44a**, which in the presence of imine **38a** gave the β-lactam **31a** as a cis/trans mixture (Scheme 12).[19a] A DFT study using B3LYP/6-31G* level computations found a pathway for carbonylation of CH$_2$=Cr(CO)$_5$ (**45**) in solvent water forming the solvated ketene complex (H$_2$O)(OC)$_4$Cr·CH$_2$=C=O (**46**), which led to a new complex **47** with the imine CH$_2$=NH, and then the transition state for [2+2] cycloaddition which led to **48** (Scheme 12).[19a] Further computational studies examined the photochemistry of metal–carbene complexes in non-ketene forming reactions.[19b]



Scheme 12. β-Lactam formation from chromium–carbene complexes.

Systematic experimental studies of the mechanism of the uncatalyzed formation of β-lactams have been carried out by Xu and co-workers[20] by determining the cis/trans product ratio as a function of structural variation of the ketene as well as at both positions on the imine. This work has been reviewed,[20b] and greatly clarifies this process. To eliminate effects due to the presence of reagents used in ketene formation these reactants were generated by thermal Wolff rearrangements, which are clean reactions with only N$_2$ as a byproduct. In one set of experiments thermolysis of phenylthio diazoacetate **49** was used for in situ generation of phenylthioketene (**50**) in the presence of aryl substituted imines **51** to form cis/trans mixtures of β-lactams **52** (Scheme 13). The yields of the products were determined by NMR analysis of the product mixture, and the respective products were then separated by column chromatography for identification.[20] A linear correlation of log(cis/trans) with the Hammett σ constants was observed, with a slope $\rho = 1.62$, and $r^2 = 0.98$. The increase in percentage of trans product as the electron donor ability of the substituent at the imine carbon increased was interpreted as indicating formation of a zwitterionic intermediate, which was stabilized by the electron donation and therefore had a longer lifetime, which allowed isomerization to an intermediate, which could form trans product (vide infra, Scheme 15).



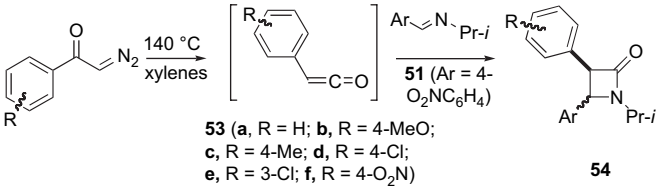
R	Yield **52** (%)	*cis*/*trans*	R	Yield **52** (%)	*cis*/*trans*
MeO	87	4:96	Cl	75	17:83
Me	80	7:93	CF_3	81	42:58
H	92	12:88	NO_2	79	73:27

Scheme 13. Selectivity in β-lactam formation.

The steric effect at the nitrogen substituent in imines PhCH=NR^1 was examined by reaction with ketene **50** and gave cis/trans ratios of <2:98, 12:88, and >98:2 for R^1=Bn, *i*-Pr, and *t*-Bu, respectively.[20] The increase in cis product with increasing bulk of the substituent paralleled earlier studies by Moore and co-workers.[8c,d]

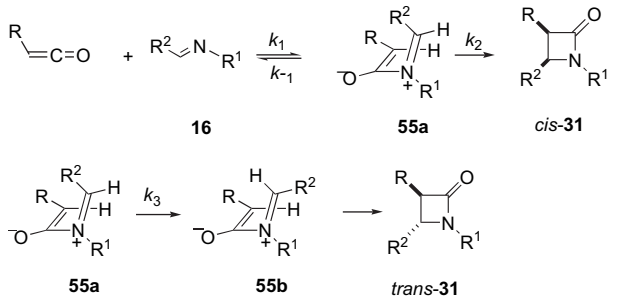
Substituted arylketenes **53** generated similarly from diazo ketones reacted with imine **51** (R = NO$_2$) to give cis/trans mixtures of

β-lactams **54**, and these gave a linear correlation of log(cis/trans) with the Hammett σ constants with a slope $\rho = -0.63$ and $r^2 = 0.93$ at 140 °C, and an estimated $\rho = -1.1$ at 80 °C (Scheme 14).[20] Electron withdrawing substituents R on the ketenyl aryl ring were proposed to stabilize a zwitterionic intermediate permitting greater conversion to the more stable conformation of the zwitterion leading to the *trans* product **54** (vide infra, Scheme 15).



R	Yield **54** (%)	*cis*/*trans*	R	Yield **54** (%)	*cis*/*trans*
4-MeO	93	66:34	4-Cl	65	40:60
4-Me	68	55:45	3-Cl	56	38:62
H	52	47:53	4-O_2N	60	27:73

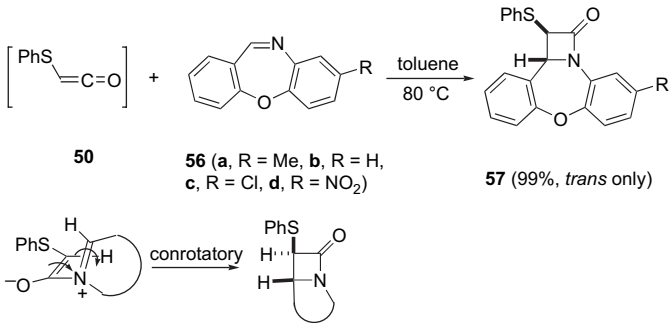
Scheme 14. Aryl substituent effects on formation of β-lactams.



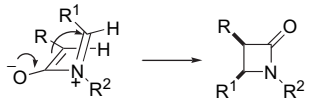
Scheme 15. Proposed mechanism for formation of *cis* and *trans* β-lactams.[20]

These reactions were interpreted as involving a mechanism in which for the major product determining pathway the imine approaches the ketene from the side opposite to the ketene substituent to form a zwitterion **55a**, and this either undergoes direct ring closure to form β-lactam *cis*-**31** or isomerizes by bond rotation to give intermediate zwitterion **55b**, which undergoes ring closure to *trans*-**31** (Scheme 15). Electron donating ketene substituents R and electron withdrawing imine substituents R^2 destabilize the intermediate zwitterion **55a**, and favor direct ring closure forming the *cis* β-lactam. Electron withdrawing ketene substituents R and electron donating imine substituents R^2 stabilize the zwitterions **55a**, and increase the probability of isomerization to zwitterion **55b**, thereby enhancing formation of the *trans* β-lactam. The cyclization step was proposed to involve a nucleophilic attack of the enolate on the imine moiety (vide infra, Scheme 17), and not an electrocyclic reaction. The higher yield of cis product with increasing bulk of the substituent on nitrogen was attributed to steric hindrance in the intermediate **55b**, which inhibits formation of this intermediate leading to trans product.

Xu and co-workers,[20] proposed that the conversion of **55a** to *trans*-**31** did not occur by an electrocyclic disrotatory process because analogous *cis*-cyclic imines **56** formed exclusively *trans* β-lactams **57** in 99% yield by conrotatory processes independent of their electronic character (Scheme 16), and therefore concluded that ketene–imine cycloadditions all proceeded by conrotatory processes, or by non-electrocyclic nucleophilic attack of the enolate on the imine moiety, which is stereochemically equivalent (Scheme 17).

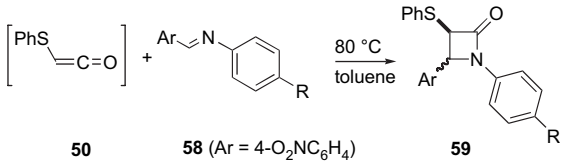


Scheme 16. β-Lactam formation from ketene **50** and cyclic imines **56**.



Scheme 17. β-Lactam formation by direct nucleophilic attack by the enolate.

Phenylthioketene (**50**) reaction in situ with *N*-aryl substituted imines **58** to form cis/trans mixtures of β-lactams **59** was also examined (Scheme 18). The effect of substituents R on the cis/trans ratio was a small decrease in trans product with electron withdrawing R groups, consistent with the intermediacy of a shorter-lived intermediate.[20]



R	Yield **59** (%)	*cis*/*trans*	R	Yield **59** (%)	*cis*/*trans*
MeO	75	27:73	Cl	72	35:65
Me	76	33:67	Ac	52	38:62
H	85	34:66	O_2N	5	48:52

Scheme 18. β-Lactam formation from ketene **50** and imines **58**.

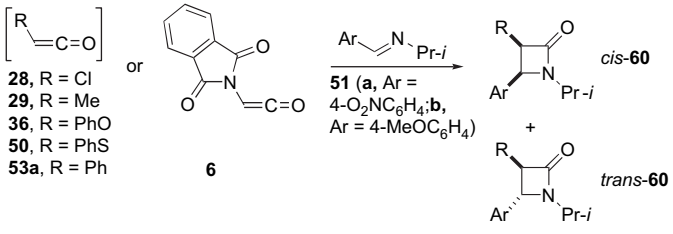
These results argue persuasively for a two-step mechanism for β-lactam formation from [2+2] cycloaddition of ketenes and imines with approach of the imine from the side opposite to the larger ketene substituent, and formation of a zwitterionic intermediate, which may form the product by a conrotatory process (Scheme 15) or the stereochemically equivalent intramolecular nucleophilic attack (Scheme 17) with rate constant k_2 (Scheme 15). If k_2 is faster than k_{-1} then the initial attack k_1 is likely rate-limiting, with no return to starting material. However, if the first step is reversible, then **55a** can undergo *syn*/*anti* interconversion, and k_3 is likely to be irreversible and rate-limiting, as reformation of the less stable zwitterion *syn*-**55a** is unlikely, and ring closure to the *trans* β-lactam will occur. There may be no need to propose torquoelectronic effects (Fig. 2)[15] in an electrocyclic ring closure, as direct

nucleophilic attack can explain the results (Scheme 17). Stabilization of the zwitterionic intermediate prolongs its lifetime and promotes isomerization and formation of a trans product.[20]

Comparison of β-lactam formation using ketenes generated from diazo ketones by either photochemical or microwave induced Wolff rearrangements and reaction with acyclic or cyclic imines show that both processes give similar product compositions. The results can be explained as involving zwitterionic intermediates that can isomerize in some cases leading to trans products, although side reactions are more likely in the photochemical reactions.[21a]

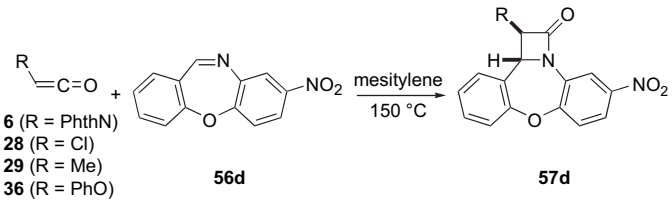
A study of reaction conditions showed that the more polar solvents toluene or acetonitrile modestly favored the formation of trans relative to *cis* β-lactam product, a result attributed to stabilization of the zwitterionic intermediate in the reaction, allowing a greater degree of isomerization of the imine moiety, and leading to the trans product.[21b] The presence of additives such as amine salts did not significantly affect the product stereochemistry, and neither did the mode of ketene generation.[21b] With ketene generation by dehydrochlorination the product stereochemistry was affected by the order of addition of the reagents, and this was attributed to the intermediacy of chloro amides **33** (Scheme 8) in some cases.[21b]

The temperature dependence of the cis/trans selectivity in the [2+2] cycloaddition of ketenes with imines **50** forming β-lactams **60** has been examined (Scheme 19).[22a] The ketenes were chosen as tending to favor *trans* β-lactams (Moore ketenes: **28**, **29**, **50**, and **53a**), or *cis* β-lactams (Sheehan and Bose–Evans ketenes: **6** and **36**, respectively), while imines **51a** and **51b** tend to favor *cis* and *trans* β-lactams **60**, respectively. Ketenes **28**, **29**, and **36** with imine **51a** or **51b** showed a change in the cis/trans product ratio from between 42:58 and 66:34 at 150 °C to between 91:9 and 100:0 at 40 °C, while for ketene **6** with imine **51b** the ratio varied from 4:96 to 87:13. Ketene **50** had ratios of 75:25 and 77:23 at 150 °C, with 73:27 and 70:30 at 40 °C, for imines **51a** and **51b**, respectively, with a maximum near 110 °C of 90:10. In most cases the cis-selectivities decreased with increasing temperature, a result that may be attributed to increase in the rates of isomerization in the zwitterion. In certain cases, increases in the selectivities were interpreted as due to favorable p–π and π–π interactions between the ketene and imine substituents, which increase the rate of direct ring closure more than the rate of isomerization of the zwitterions.



Scheme 19. Stereochemistry of β-lactam formation.

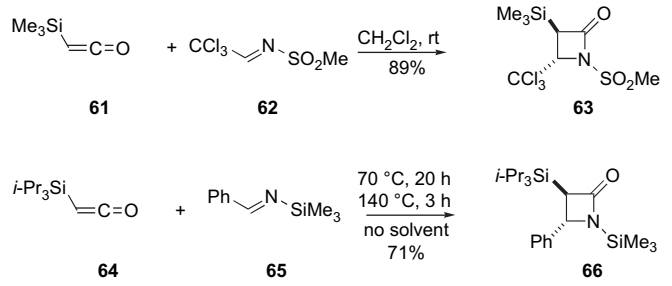
Reaction of ketenes **6** (R=PhthN), **28** (R=Cl), **29** (R=Me), and **36** (R=PhO) with the cyclic imine **56d** formed only *trans* β-lactams **57** (Scheme 20). This result rules out the possibility that formation of trans products at higher temperature is due to addition to the more hindered side of the ketene, which would lead to *cis* β-lactams.[22a] Ketene–imine cycloadditions enhanced by microwave irradiation were found to show no significant difference in the stereoselectivity than the same reactions conducted at the same temperature with thermal activation.[22b]



Scheme 20. β-Lactam formation from cyclic imine **56d**.

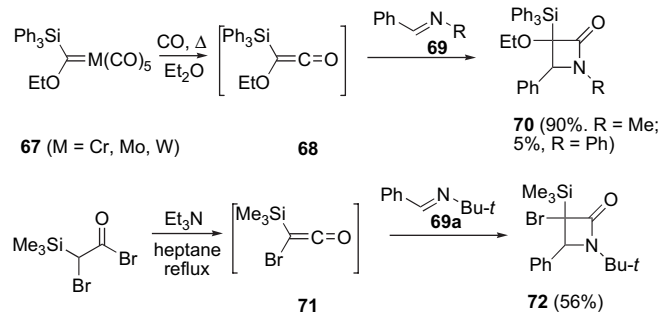
2.1.1. *β-Lactams from silyl substituted ketenes*

Ketenes bearing silyl substituents are remarkably less reactive compared to other ketenes, and provide useful mechanistic insights into reactions of ketenes with imines, which are normally too rapid for convenient reactivity studies. Trimethylsilylketene (**61**) is a unique isolable ketene that is quite unreactive, but does undergo cyclization with the highly nucleophilic imine **62** to form **63** (Scheme 21).[23] Tri(isopropyl)silylketene **64** reacted with imine **65** forming β-lactam **66** upon prolonged heating in a reaction proposed to involve a stepwise process forming a zwitterionic intermediate, which closed to the product (Scheme 21).[24]



Scheme 21. [2+2] Cycloaddition of silylketenes imines.

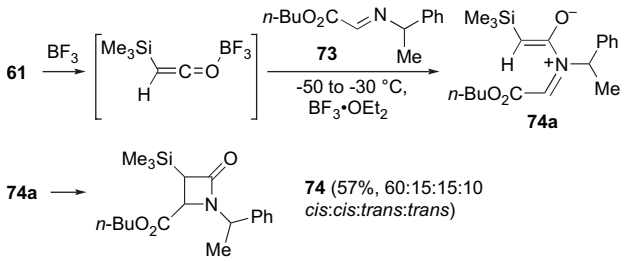
Ketene **68** generated thermally as an unobserved intermediate from metal–carbene complexes **67** reacted in situ with imines **69** forming β-lactams **70** as 4:1 mixtures of cis/trans isomers (Scheme 22).[25] Ketene **71** generated in situ by dehydrohalogenation in refluxing heptane in the presence of imine **69a** underwent [2+2] cycloaddition forming β-lactam **72** as a single isomer of unknown stereochemistry (Scheme 22).[26] In the absence of **69a**, ketene **71** was identified as a product of this reaction by the IR absorption at 2114 cm^{-1} but could not be isolated (Scheme 22).[26]



Scheme 22. β-Lactams from silylketenes.

Electrophilic catalysis was also used to activate **61**, which in the presence of $BF_3{\cdot}OEt_2$ reacted with electrophilic imine **73** forming β-lactam **74** as a 75:25 mixture of cis and trans isomers (four diastereomers) in 57% yield even at −50 to −30 °C (Scheme 23).[27]

Examination of the reaction mixture by ^{13}C NMR at −40 °C revealed the presence of a BF_3–imine complex and formation of the β-lactam **74**, but no complexation of the ketene with BF_3 was detected. Computational studies at the B3LYP/6-311+G(d,p) level with incorporation of a solvent continuum for mechanisms involving BF_3 complexation either with the ketene carbonyl or with the imine nitrogen revealed that the lowest barrier pathway involved initial N–C bond formation between the imine and the ketene carbonyl carbon forming *syn* and *anti* intermediates, which converted to the trans and cis products with barriers of 9.1 and 8.7 kcal/mol, respectively, above the reactants (Scheme 23). Formation of the imine–BF_3 complex was calculated to be exothermic by 17.8 kcal/mol, consistent with the observation of this intermediate by NMR, but the lowest barrier for reaction of this complex with the ketene was 26.7 kcal/mol, and it was concluded that this pathway was not competitive.



Scheme 23. Computational and experimental studies of silylketene cycloadditions.

N-Silyl substituted imines have been found to react with ketenes in a two-step process with an isolable azadiene intermediate, which cyclizes to the product β-lactam as shown in Scheme 44 (vide infra).

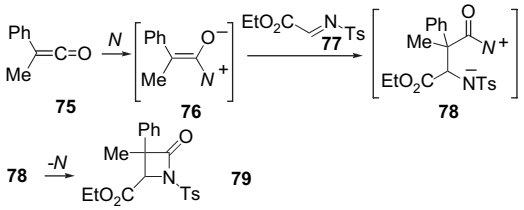
3. Steroselective β-lactam formation via ketene enolates

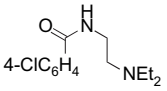
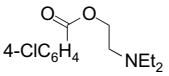
Ketene generation by dehydrohalogenation of acyl chlorides in the presence of tertiary amines often involves the generation of ketene enolates, which may be generated either by reaction of the tertiary amine with a first formed ketene, or by deprotonation of acyl ammonium ions formed by displacement of the halide by the amine. As described above (Scheme 6),[12] the presence of ketenes has been proven in some cases by detection of the characteristic ketenyl IR absorption, but in other examples the formation of discrete ketene intermediates is not certain.

The use of electrophilic imines and nucleophilic tertiary amine catalysts in β-lactam formation has been developed into a powerful synthetic method. As shown in Scheme 24 the nucleophilic catalyst adds to phenyl(methyl)ketene (**75**) forming the ketene enolate **76**, which reacts with the electrophilic imine **77** forming a further intermediate **78**, which cyclizes to the product **79**. The greatly enhanced yields in the presence of nucleophilic catalysts shows their efficacy in the procedure, while the variation in cis/trans product ratios shows a strong influence of the catalyst in the second step of the reaction.[28]

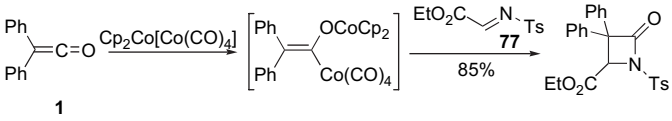
The cobalt carbonyl anion $Co(CO)_4^-$ from the catalyst cobaltocenium cobaltate ($Cp_2Co[Co(CO)_4]$) was also applied to reaction of **75** (Scheme 24) and for diphenylketene (**1**) with imine **77** (Scheme 25). No reaction was observed in the absence of the catalyst.[28c]

To extend the reaction to monosubstituted ketenes and their derived zwitterions from amine additions the ketenes were generated using a shuttle procedure in which tertiary amines served as kinetic bases, along with the stoichiometric base



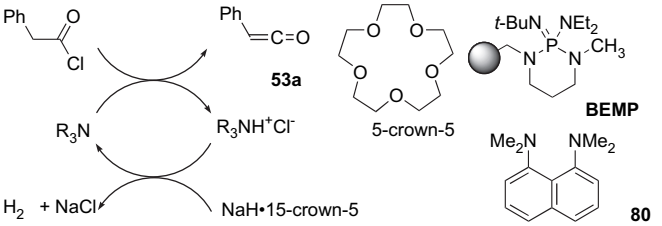
catalyst	Yield (%)[a]	*dr* (*cis*/*trans*)[b]	catalyst	Yield (%)[a]	*dr* (*cis*/*trans*)[b]
none	trace		Et_3N	83	55:45
	80	3:97		79	98:2
	77	34:66	 Dabco	62	66:33
$Cp_2Co[Co(CO)_4]$	55	25:75			

Scheme 24. β-Lactams by catalyzed ketene–imine cycloaddition in THF at −78 °C.[28a]



Scheme 25. Cobalt carbonyl anion catalysis of ketene–imine cycloaddition.

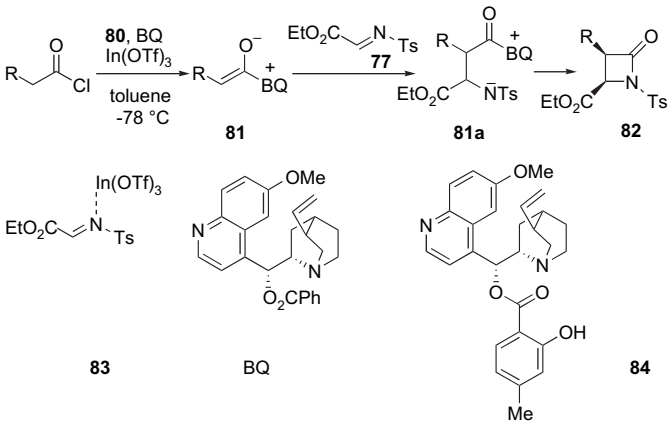
1,8-bis(dimethylamino)naphthalene (**80**, Proton Sponge) that scavenges the HCl generated.[28a,b] The tertiary amine rapidly effects the dehydrochlorination forming phenylketene (**53a**), and then transfers the proton to the stronger base, with regeneration of the catalytic base. Stoichiometric bases that react irreversibly include NaH with 15-crown-5, K_2CO_3, and the polymer bound base BEMP, which is a triaminophosphonamide imine bound to a polymer support (Scheme 26). In some cases, **80** may react reversibly with acyl chlorides so that the reactions proceed not by free ketenes but by acylation of the tertiary amine by the acyl chloride and then dehydrohalogenation.[28d]



Scheme 26. Shuttle mechanism for ketene generation using NaH·15-crown-5 and R_3N.

The use of chiral amine catalysts such as benzoylquinine (BQ) as the shuttle base to catalyze asymmetric reactions of the ketene, together with the electrophilic cocatalyst $In(OTf)_3$ and 1 equiv of **80** gave β-lactams **82** in very high yields, enantioselectivity, and cis/trans ratios (Scheme 27).[29] The use of $In(OTf)_3$ significantly increased the yields and based on a mechanistic analysis it was proposed that the chiral catalyst formed zwitterionic ketene enolates **81**, which reacted with the imine **77**, while $In(OTf)_3$ catalyzed the reaction by forming the imine complex **83**.[29] The bifunctional

salicylquinine catalyst **84** was also prepared, and when complexed with $In(OTf)_3$ in a 1:1 ratio effectively combined the nucleophilic and electrophilic functions in one molecule, and provided **82** (R=Ph) in 90% yield, 99% ee, and 10:1 dr.[29]



β-Lactam	Yield (%)	*ee* (*cis*/*trans*)	β-Lactam	Yield (%)	*ee* (*cis*/*trans*)
Ph, EtO_2C, Ts	95	98 (60:1)	AcO, EtO_2C, Ts	92	98 (34:1)
Bn, EtO_2C, Ts	94	98 (9:1)	BnO, EtO_2C, Ts	98	96 (11:1)
$PhOCH_2$, EtO_2C, Ts	93	96 (12:1)	Br, EtO_2C, Ts	91	96 (10:1)
$CH_2=CH$, EtO_2C, Ts	92	96 (10:1)	PhO, EtO_2C, Ts	93	97 (22:1)

Scheme 27. β-Lactam formation with combined nucleophilic and electrophilic catalysis.

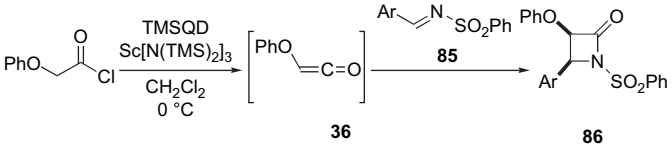
In reactions using **80** as the stoichiometric base, formation of ketene enolate **81** and of **81a** (Scheme 27) explains the observed catalysis, but the available evidence does not require the formation of free ketenes. In reactions halted after specified times by quenching with HCl the yield of β-lactam product depended upon the concentration of BQ, and increased by a factor of 3–5 in the presence of 10 mol % $In(OTf)_3$. That C–C bond formation giving intermediate **81a** (Scheme 27) was a rate-limiting step in the process was established by using $PhCD_2COCl$ as a precursor and comparing product yields after quenching upon partial reaction with those of a companion reaction using $PhCH_2COCl$. The yield of the deuterated β-lactam was higher, giving an inverse isotope effect $k(H)/k(D)$ value of 0.8, consistent with a slow step involving conversion of sp^2 to sp^3 hybridized carbon.[29]

When ketenes are first formed irreversibly from acyl chlorides by reaction with stoichiometric bases before contact with tertiary amines there is no doubt of their intermediacy. Ketene enolates formed by addition of tertiary amines to ketenes are expected to behave similarly to those generated by proton abstraction from acyl ammonium ions.

Competition studies of the stereoselective formation of β-lactams from reaction of acyl chlorides with bases in the presence of benzoylquinine led to the conclusion that these reactions involved formation of a zwitterionic benzoylquinine complex that reacted with the imine to form the product.[28d] Experiments in which phenylketene was generated by photochemical Wolff rearrangement of diazoacetylbenzene in the presence of benzoylquinine gave similar stereoselectivity in product formation, indicating that free ketenes formed enolates, which gave similar selectivity to the intermediates generated by acyl chloride dehydrohalogenation.[28d]

This procedure for β-lactam formation has also been adapted for use using solid phase reactants in sequential packed columns containing dehydrohalogenation reagents for ketene generation and chiral catalysts.[28d,30a] For example, the ketene is generated in the first column by stoichiometric reagents and flows into a second column containing the chiral catalyst that induces cycloaddition, and byproducts are scavenged in a further column.

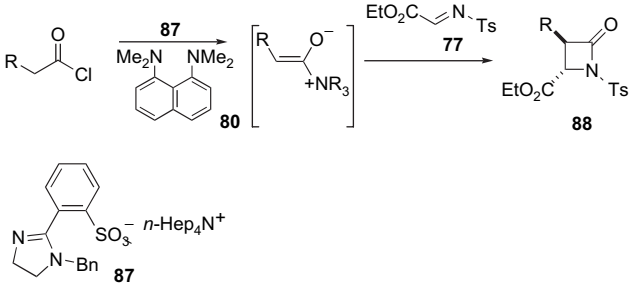
In another example of catalytic stereoselective [2+2] cycloaddition phenoxyacetyl chloride in the presence of TMS-quinidine (TMSQD) and imines **85** gave β-lactams **86** through the possible intermediacy of in situ generated phenoxyketene (**36**) reacting via the acyl ammonium enolate (Scheme 28).[30b]



Ar	Yield (%)	*cis*:*trans* (% *ee*)	Ar	Yield (%)	*cis*:*trans* (% *ee*)
$4\text{-}FC_6H_4$	47	19:1 (97)	$4\text{-}MeC_6H_4$	69	19:1 (95)
$4\text{-}ClC_6H_4$	57	28:1 (97)	$4\text{-}O_2NC_6H_4$	55	16:1 (94)
$4\text{-}BrC_6H_4$	70	14:1 (97)	$4\text{-}CF_3C_6H_4$	67	18:1 (95)
$4\text{-}NCC_6H_4$	52	12:1 (94)	$3.5\text{-}Cl_2C_6H_3$	66	14:1 (96)

Scheme 28. Catalytic enantioselective formation of β-lactams from phenoxyketene.

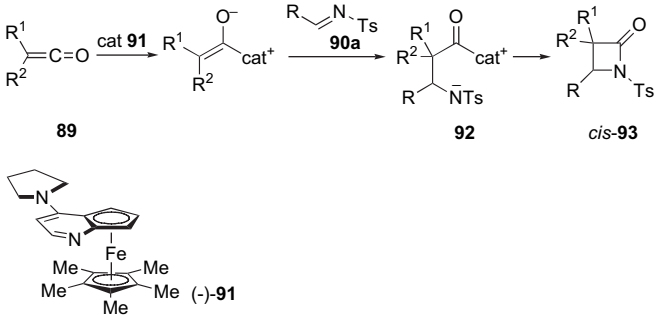
Procedures using cinchona alkaloids as amine catalysts gave a strong preference for the formation of *cis* β-lactams from monosubstituted ketene derived enolate intermediates upon reaction with *N*-sulfonylimines. However, the achiral anionic nucleophilic catalyst **87** gave preferentially *trans* β-lactams **88** from imine **77** and ketene enolates generated in situ from acyl chlorides and bis-1,8-(dimethylamino)naphthalene (**80**) (Scheme 29).[30c] This reversal in the stereochemistry was attributed to a steric effect of the bulky cation.

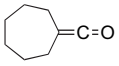
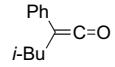
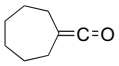
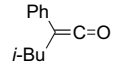
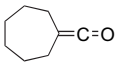
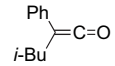
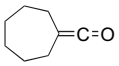
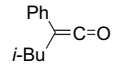
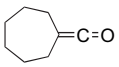
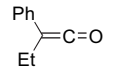
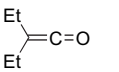
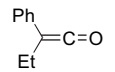
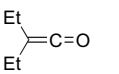


R	Yield %	*trans*/*cis*	R	Yield %	*trans*/*cis*	R	Yield %	*trans*/*cis*
Ph	50	37:1	$4\text{-}MeOC_6H_4$	70	13:1	$4\text{-}ClC_6H_4$	46	50:1
PhS	35	14:1	$3\text{-}MeOC_6H_4$	51	>50:1	2-Thienyl	69	5:1

Scheme 29. Catalytic trans-selective β-lactam formation.

Reactions of disubstituted ketenes **89** with *N*-tosylimines RCH=NTs (**90a**) catalyzed by the ferrocene derivative (−)-**91** give stereoselective formation of *cis* β-lactams **93** (Scheme 30).[31a,b]



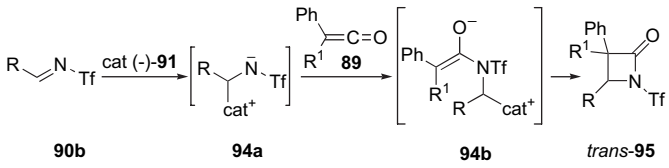
Ketene **89**	R	Yield, *ee* %	Ketene **89**	R	*cis*/*trans*	Yield, *ee*%
	Ph	84,81		Ph	8:1	88,98
	2-furyl	90,92		2-furyl	11:1	97,98
	*E*-Ph-CH=CH	82,91		*E*-Ph-CH=CH	10:1	95,98
	*c*-Pr	89,94		*c*-Pr	15:1	88,89
	*c*-hexyl	76,94		2-furyl	9:1	97,95
	2-furyl	93,92		*c*-Pr	10:1	98,98
	*E*-Ph-CH=CH	83,92				

Scheme 30. cis-Selective β-lactam formation from disubstituted ketenes and *N*-tosylimines.

By contrast reactions of ketenes **89** with *N*-trifylimines RCH=NTf (**90b**) and catalyst (−)-**91** preferentially formed *trans* β-lactams **95**. The reactions of **90a** were proposed to occur with initial catalyst coordination to the ketene, followed by C–C bond formation between the imine and the ketene, while *N*-trifylimines were thought to coordinate with the catalyst (−)-**91** followed by C–N bond formation with the ketene (Scheme 31).[31c]

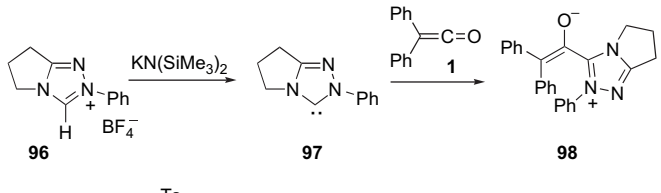
N-Heterocyclic carbene (NHC) **97** generated by deprotonation of the corresponding azolium salt **96** with potassium hexamethyldisilazide catalyzed reactions of diphenylketene (**1**) with *N*-tosylimines **90a** forming β-lactams **100** by [2+2] cycloaddition.[32] These reactions are proposed to involve deprotonation of the salt **96** and to proceed by attack of carbene **97** on the carbonyl carbon of ketene **1** forming an intermediate enolate **98**, which adds the imine **90a** forming the intermediate **99**, which gives the β-lactam **100** with regeneration of the catalyst **97** (Scheme 32).

Ketene **89a** reacted with imine **90a** with catalysis by carbene **97** giving mixtures of *syn*/*anti* β-lactams **101** (Scheme 33).[32]



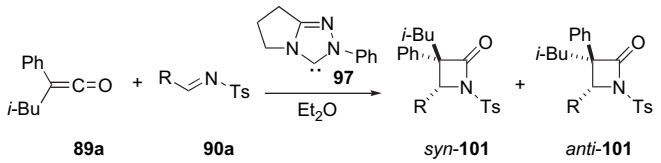
ee (%)[a]	R^1	R	Yield (%)	*trans*: *cis*	ee (%)[a]
63	Me	4-$CF_3C_6H_4$	80	97:3	69
81	Me	4-$MeOC_6H_4$	76	81:19	82
63	Me	2-MeC_6H_4	89	81:19	99
85	Me	2-BrC_6H_4	79	80:20	84
98	Me	2-naphthyl	76	98:2	94

Scheme 31. Nucleophilic catalysis of trans-selective ketene reaction with trifylimines.



R	Yield (%)	R	Yield (%)	R	Yield (%)
Ph	93	2-Naphthyl	92	4-BrC_6H_4	89
2-Furyl	85	4-$MeOC_6H_4$	59	*E*-PhCH=CH	94

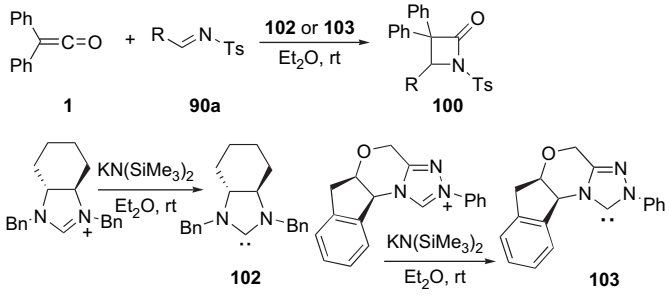
Scheme 32. Ketene–imine [2+2] cycloaddition catalyzed by *N*-heterocyclic carbene **97**.



R	*syn*:*anti*	Yield (%)	R	*syn*:*anti*	Yield (%)
Ph	68:32	89	4-BrC_6H_4	57:43	94
2-Naphthyl	63:37	89	*E*-PhCH=CH	76:24	72
2-Furyl	81:19	86			

Scheme 33. β-Lactams from ketene **89a** and imine **90a** catalyzed by NHCs.

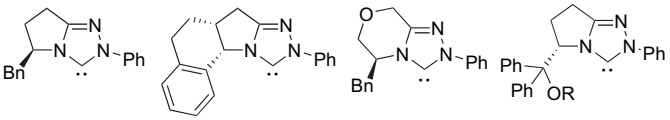
Chiral *N*-heterocyclic carbenes **102** or **103** formed by deprotonation of the corresponding triazolium salts catalyzed the cycloaddition of diphenylketene (**1**) with imine **90a** giving stereoselective formation of β-lactams **100** (Scheme 34).[32]



cat	R	Config **100**	Yield (%)	ee (%)	cat	R	Config **100**	Yield (%)	ee (%)
102	Ph	*R*	90	58	**102**	2-Furyl	*S*	85	61
103	Ph	*R*	96	64	**103**	2-Furyl	*S*	93	55
102	2-Np[a]	*R*	95	73	**102**	4-Br-C_6H_4	*R*	79	56
103	2-Np[a]	*R*	92	75	**103**	4-Br-C_6H_4	*R*	96	57

Scheme 34. Enantioselective β-lactam formation using chiral NHC catalysts.

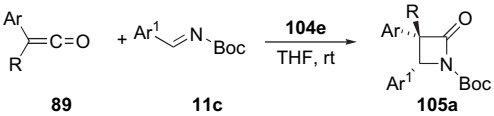
Chiral *N*-heterocyclic carbenes **104** generated by deprotonation of salts catalyzed the [2+2] cycloaddition of ketene **89b** with imines **11** forming β-lactams **105**.[33] The most effective catalyst proved to be **104a**, and mechanisms involving initial reaction of the catalyst with either the ketene or the imine were discussed, and either may be operative in different examples (Scheme 35). Arylalkylketenes **89** reacted with imine **11c** with catalysis by carbene **104e** forming β-lactams **105a** (Scheme 36).[33]



Cat **104**	Ar, R	*cis/trans*	Yield (%)	ee[a] (%)	Cat **104**	Ar, R	*cis/trans*	Yield, ee[a] (%)
a	2-furyl Ts	55:45	93	-38[b]	**e**	2-furyl Ts	67:33	98, 83
b	2-furyl Ts	62:38	99	42	**e**	4-ClC_6H_4 Ts	36:64	97,19
b	2-furyl Ts	78:22	99	63	**e**	4-ClC_6H_4 Cbz	60:40	53,89
c	2-furyl Ts	55:45	59	-9[b]	**e**	4-ClC_6H_4 Boc	75:25	68, 95
d	2-furyl Ts	50:50	99	58	**e**			

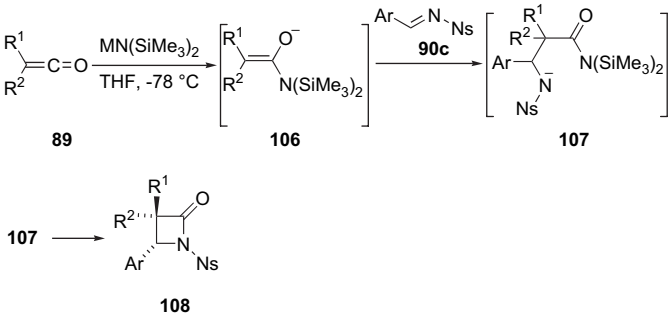
Scheme 35. Enantioselective catalysis of formation of β-lactams **105**.

Metal hexamethyldisilazanes proved to be effective catalysts for reaction of ketenes **89** with imine **90c** in formation of β-lactams **108** (Scheme 37).[34] The reactions were proposed to proceed by nucleophilic catalysis by the silazide forming intermediates **106**, which react with the imines giving **107** leading to the products.



Ar, R	Ar^1	*cis/trans*	Yield, ee (%)	Ar, R	Ar^2	*cis/trans*	Yield ee[a](%)
Ph, Et	4-Cl-C_6H_4	75:25	72,96	Ph, Et	2-Furyl	83:17	57,98
Ph, Et	2-Cl-C_6H_4	91:9	71,99	Ph, Me	2,4-Cl_2-C_6H_3	86:14	53,93
Ph, Et	2-Br-C_6H_4	94:6	58,97	4-MeO-C_6H_4, Et	2-Cl-C6H4	93:7	78,91
Ph, Et	3-Cl-C_6H_4	80:20	66,99	4-MeO-C_6H_4, Et	2,4-Cl_2-C_6H_3	89:11	62,96
Ph, Et	4-Br-C_6H_4	78:22	71,99	4-Cl-C_6H_4, Et	2-Cl-C_6H_4	99:1	61,97
Ph, Et	4-O_2N-C_6H_4	71:29	75,99	4-Cl-C_6H_4, Et	4-Cl-C_6H_4	83:17	53,99
Ph, Et	Ph	75:25	64,99				

Scheme 36. Enantioselective catalysis of formation of β-lactams **105a**.

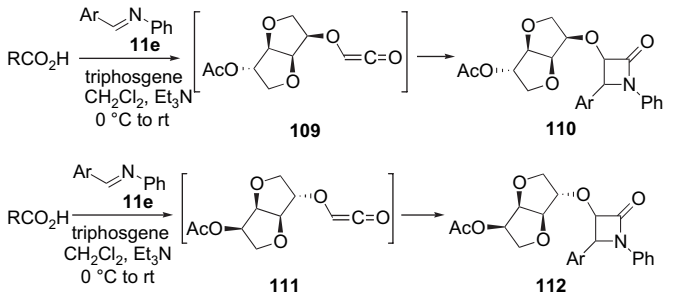


R^1, R^2, Ar	M	*cis/trans*	Yield **108** %	R^1, R^2	M	*cis/trans*	Yield **108** %
Ph, Et, Ph	K	4:1	85	Ph, Et, Ph	Na	4:1	99
Ph, Et, 1-Naph	K	6.4:1	89	Ph,Me, Ph	Na	2.3:1	72
Ph, Et, 2-ClC_6H_4	K	7:1	99	Ph,Et, Ph	Na	4:1	99
Ph, Et, 4-Tol	Na	2:1	87	Ph,Ph, Ph	Na	_	98
Ph, Et, 2-Thienyl	K	1.3:1	68	$(CH_2)_6$, Ph	Na	_	48
Ph,Et, 3,4-$(MeO)_2C_6H_3$	Na	3.5:1	88				

Scheme 37. Silazide catalysis of ketene–imine reaction.

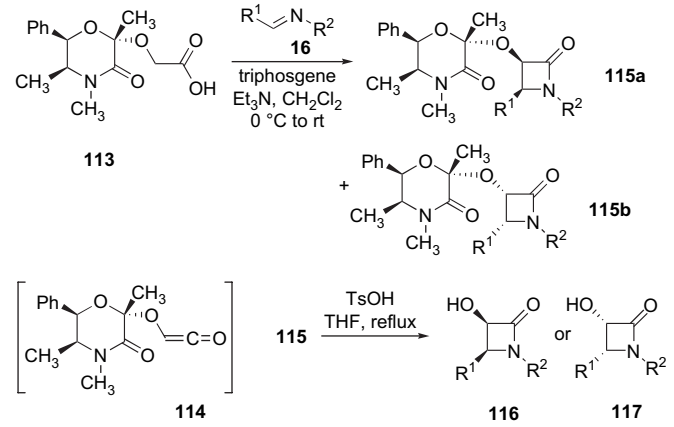
3.1. Enantioselective formation of β-lactams using chiral ketenes or chiral imines

Chiral substituents on the ketenes, or on either side of the imine, have been used in recent studies of stereoselective β-lactam formation from ketenes generated in situ by dehydrochlorination with subsequent reaction with imines. For example, chiral ketenes **109** and **111** derived in situ from carboxylic acids react with imines **11** (Ar=Ph, C_6H_4Cl) forming mixtures of *cis* β-lactams **110** and **112** in 65–71% yields with 4:1 and 1:1 diastereomeric ratios, respectively. The higher diastereoselectivity for **109** was attributed to the proximity of the side chain to the concave face of the sugar moiety (Scheme 38).[35]



Scheme 38. Stereoselective reaction of chiral 1,4:3,6-dianhydroglucitol-substituted ketenes with imines forming β-lactams.

The unobserved chiral ketene **114** derived in situ from the (−)-ephedrine substituted acid **113** reacted by [2+2] cycloaddition with imines **16** giving β-lactams **115a**,**b**, which were separated and after cleavage and recovery of the chiral auxiliary gave optically pure **116** or **117**, in 84–90% yields (Scheme 39).[36]



R^1	R^2	**115** (% yield)	dr	R^1	R^2	**115** (% yield)	dr
Ph	PMP	70	50:50	PMP	PMP	65	65:35
PMP	Ph	60	60:40	Ph	Ph	65	56:44

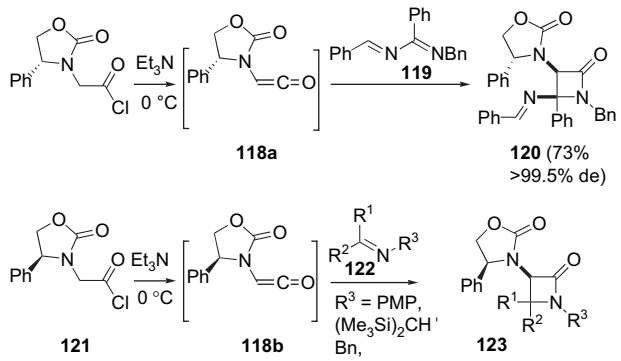
Scheme 39. Chiral ketene [2+2] cycloaddition forming β-lactams.

The chiral ketene **118a** generated in situ by dehydrochlorination reacted with 1,3-diazabuta-1,3-diene **119** by [2+2] cycloaddition forming β-lactam **120** with >99.5% diastereomeric excess, although the absolute configuration of the product was not determined (Scheme 40).[37] Chiral ketene **118b** also gave stereoselective [2+2] cycloadditions with imines **122** forming chiral β-lactams **123** with quaternary centers (Scheme 40).[38]

Chiral imines have been successfully applied in stereoselective synthesis, and **125** derived from 1,4:3,6-dianhydroglucitol reacts with ketenes **124** generated in situ by dehydrochlorination of acyl chlorides with Et_3N to give highly diastereoselective [2+2] cycloaddition forming *cis* β-lactams **126** with 96–98% enantioselectivity (Scheme 41).[35]

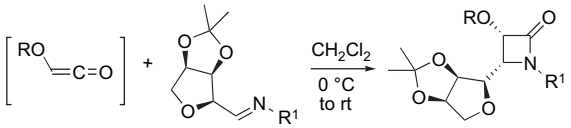
D-Glucose derived chiral imines **127** reacted with ketenes **124** generated by in situ dehydrochlorinations of acyl chlorides, and formed *cis* β-lactams **128** with high diastereoselectivity by [2+2] ketene cycloadditions (Scheme 42).[39]

Dehydrochlorination of acyl chlorides **129** forming ketenes **130** with in situ capture by optically active 5,6-dihydropyrazin-2(1*H*)-



R^1	R^2	R^3	Yield % de**123**	R^1	R^2	R^3	Yield % de**123**
Me	CO_2Me	4-MeO-C_6H_4	60 (20)	Me	Me	TMS_2CH	70 (>98)
Me	CO_2Me	TMS_2CH	39 (10)	Et	Et	TMS_2CH	69 (>98)
Me	$BnCH_2$	TMS_2CH	60 (44)	Me	Ph	Bn	65 (>98)
Me	CO_2Me	Bn	68 (20)	*n*-Pr	*n*-Pr	TMS_2CH	70 (>98)
H	$BnCH_2$	TMS_2CH	78 (66)	Me	Et	TMS_2CH	80 (70)
Me	4-MeO-C_6H_4	Bn	65 (>98)	H	Me	TM S_2CH	75 (40)
Me	*E*-Ph-CH=CH	Bn	77 (80)				

Scheme 40. Stereoselective β-lactam formation using chiral ketene **118b**.



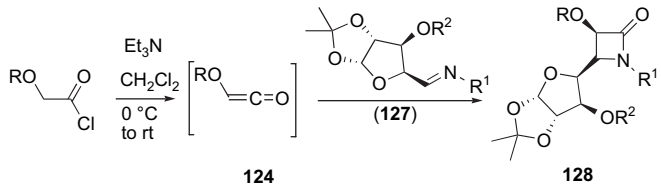
RO	R^1	Yield (%)	RO	R^1	Yield (%)	RO	R^1	Yield (%)
MeO	4-MeO-C_6H_4	74	MeO	Bn	67	MeO	4-ClC_6H_4	68
BnO	4-MeO-C_6H_4	78	BnO	Bn	70	BnO	4-ClC_6H_4	71
PhO	4-MeO-C_6H_4	75	PhO	Bn	60	PhO	4-ClC_6H_4	62
AcO	4-MeO-C_6H_4	75	AcO	Bn	61			

Scheme 41. Stereoselective reaction of ketenes with chiral imines.

ones **131** gave fused *trans* oxopiperazino-β-lactams **132** with complete control of diastereoselectivity (Scheme 43).[40]

Glycine derived ketenes **118** with chiral substituents generated in situ by dehydrochlorination in toluene or other solvents reacted with *N*-trimethylsilylimines **133** to give observable intermediates **134**, which at reflux cyclized to a mixture of *trans* β-lactams **135** with silyl migration (Scheme 44).[41] These two-step cycloadditions were also found to proceed with microwave assistance under solvent-free conditions.[42] Benzyloxyketene (**124**, RO = $PhCH_2O$) gave predominantly *cis*-β-lactams in cycloadditions with *N*-trimethylsilyl imines, while benzoyloxyketene (**124**, RO = $PhCO_2$) favored trans-stereochemistry.[43]

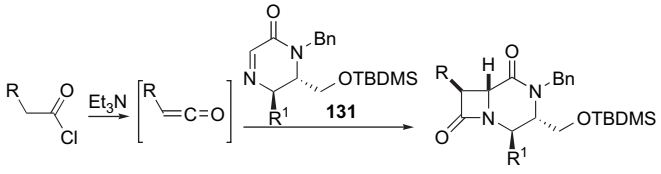
These reactions have been studied computationally, and silicon migration was found to be concerted with N–C bond formation



124 128

RO	R^1	R^2	Yield (%)	RO	R^1	R^2	Yield (%)
MeO	PMP	Bn	75	PhO	PMP	Allyl	79
PhO	PMP	Bn	75	AcO	PMP	Allyl	70
PhO	Ph	Bn	71	MeO	PMP	Allyl	72
AcO	Ph	Bn	72	PhO	Allyl	Allyl	69
PhO	Bn	Bn	74	AcO	Allyl	Allyl	68
AcO	Bn	Bn	70	PhO	PMP	AcO	75

Scheme 42. Glucose derived chiral imines in stereoselective reactions with ketenes.



129 130 132

R	R^1	Conditions	Yield (%)
Phthalimido	*i*-Pr	CH_2Cl_2, 0 °C to rt	99
AcO	*i*-Pr	CH_2Cl_2, 0 °C to rt	85
Cl	*i*-Pr	Toluene, 80 °C	74
BnO	*i*-Pr	Toluene, 40-80 °C	60
2,5-$(MeO)_2C_6H_3$	*i*-Pr	Toluene, 80 °C	74
Phthalimido	Naphthyl	Toluene, 80 °C	71
AcO	Naphthyl	CH_2Cl_2, 0 °C to rt	73
2,5-$(MeO)_2C_6H_3$	Naphthyl	Toluene, 80 °C	71

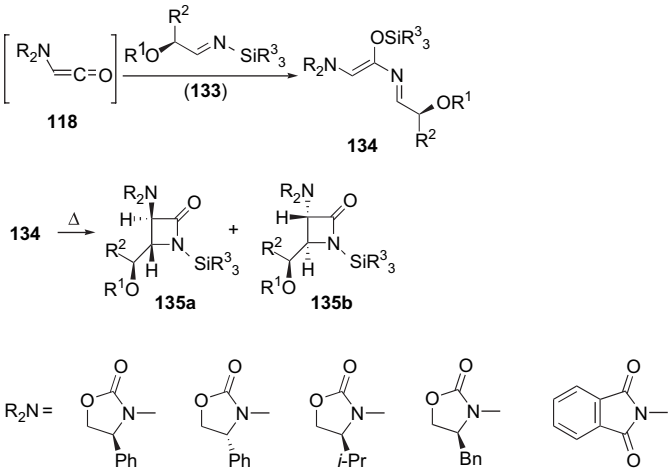
Scheme 43. Oxopiperazino-β-lactams by ketene–imine [2+2] cycloaddition.

leading to **134**, which then formed **135** as two trans diastereomers in a conrotatory cyclization.[41,44]

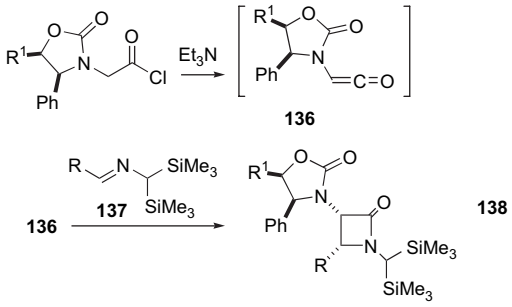
N-Bis(trimethylsilyl)methylimines **137** reacted in situ with ketenes **136** generated by dehydrochlorination to form β-lactams **138** in which the *N*-methyl group was subsequently functionalized with displacement of the silyl substituents (Scheme 45).[45]

Polymer supported imine **139** gave *cis* β-lactams **140** with high diastereoselectivities on reaction with ketenes generated by dehydrochlorination in solution, with removal of the β-lactams from the resin with 3% CF_3CO_2H (Scheme 46).[46a] The use of polymer supported synthesis using ketenes, including preparation of β-lactams, has been reviewed.[46b]

Chiral *N*,*N*-dialkylhydrazones **143** reacted in situ with the ketene **142** generated from the acid with Mukayama's salt **141** and *i*-Pr_2NEt to give the *trans*-azetidin-2-ones **144** as single



Scheme 44. Two-step Staudinger reactions with silyl group migration.



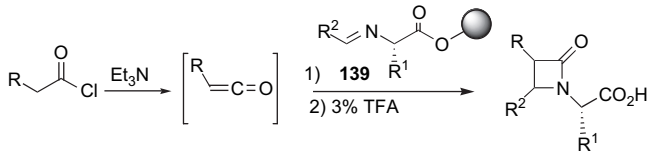
Scheme 45. *N*-Bis(trimethylsilyl)methyl substituted imines in β-lactam synthesis.

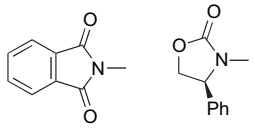
diastereomers (Scheme 47).[47a] The formation of trans products was in contrast to the cis-selectivity observed with benzyloxyketene,[47b] and was interpreted as involving formation of a zwitterionic intermediate, which because of a steric barrier to conrotatory closure to the cis-adduct instead underwent a C=N bond isomerization before conrotatory closing to the trans product (Scheme 47). For R^2=$BnOCH_2$, the trans/cis ratio changed from <1:99 at room temperature to 97:3 at 120 °C.[47a]

Imine **11b** containing a chiral chromium tricarbonyl biaryl complex as a substituent reacted with phenoxyketene (**36**) generated by dehydrochlorination forming the chiral β-lactam **145** (Scheme 48).[48a] Chiral chromium tricarbonyl complexed arylimines **146** reacted with phthalimidoketene **6** generated in situ from the acyl chloride in completely stereoselective [2+2] cycloadditions forming β-lactams **147**, with the absolute configuration shown (Scheme 48).[48b]

3.2. Other β-lactam forming reactions

Diphenylketene (**1**) reacted rapidly at −78 °C with transition metal substituted imine *N*-rhenaimine **148** by [2+2] cycloaddition forming β-lactam **149a** (Scheme 49).[49a] The structure of the product was confirmed by X-ray and examined by DFT computations. Ferrocenyl-substituted β-lactams have been made using either ferrocenylketenes to form **149b**[49b] or ferrocenylimines to form **149c**[49c] (Scheme 49).

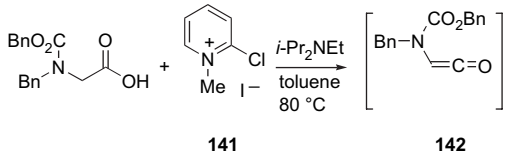


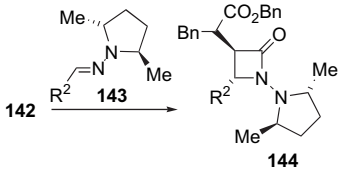


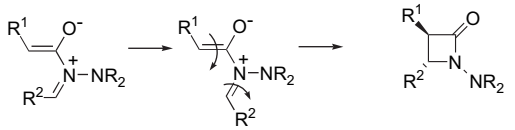
R	R^1	R^2	Yield (%)	dr	R	R^1	R^2	Yield (%)	dr
PhO	Me	Ph	80	57:43	*i*-Pr	2-furyl	PhO	80	67:33
PhthN	Me	Ph	69	55:45	*i*-Pr	2-furyl	PhthN	65	67:33
PhOx	Me	Ph	62	100:0	*i*-Pr	2-furyl	PhOx	73	100:0
CH_2=CMe	Me	Ph_2C=CH	91	55:45	*i*-Pr	2-thienyl	PhO	86	75:25
CH_2=CH	Me	Ph_2C=CH	58	55:45	*i*-Pr	2-thienyl	PhOx	81	100:0
PhO	$(CH_2)_4NH_2$	Ph	59	60:40	*i*-Pr	Ph_2C=CH	PhO	96	57:43
PhO	CH_2CO_2H	Ph	82	71:29	*i*-Pr	Ph_2C=CH	PhthN	96	55:45
PhO	CHOHMe	Ph	93	75:25	*i*-Pr	Ph_2C=CH	PhOx	97	100:0
PhO	Me	*c*-C_6H_{11}	66	67:33	*i*-Pr	2-pyridyl	PhO	80	*a*
PhO	*i*-Pr	Ph	80	67:33	*i*-Pr	2-pyridyl	PhthN	62	67:33
PhthN	*i*-Pr	Ph	55	67:33	*i*-Pr	2-pyridyl	PhOx	71	100:0
PhOx	*i*-Pr	Ph	91	100:0					

[a] *cis/trans* products 2:1 ratio

Scheme 46. Polymer bound chiral imines for β-lactam formation by [2+2] cycloaddition.

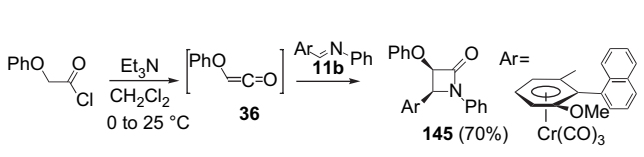


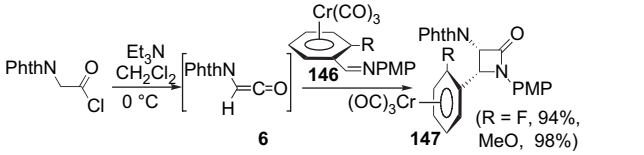




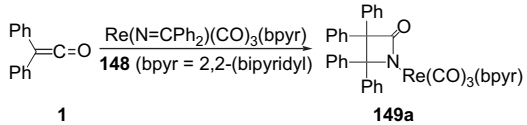
R^2	Yield (%)	*trans*/*cis*	R^2	Yield (%)	*trans*/*cis*
Me	74	>99:1	*i*-Bu	72	>99:1
i-Pr	66	>99:1	$BnCH_2$	70	>99:1
n-C_5H_{11}	58	98:2	$BnOCH_2$	66	54:46

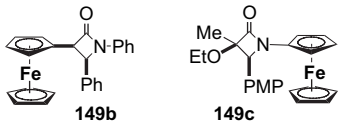
Scheme 47. Chiral *N*,*N*-dialkylhydrazones in β-lactam formation.





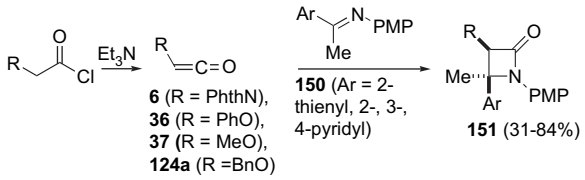
Scheme 48. Stereoselective [2+2] cycloaddition of chromium complexed imines.





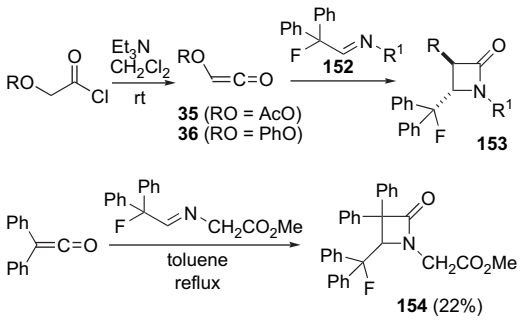
Scheme 49. Organometallic substituted β-lactams.

Ketenes generated in situ by dehydrochlorination of acyl chlorides react with heteroarylimines **150** (Ar=2-thienyl and 2-, 3-, and 4-pyridyl) with selective formation of *cis*-4-heteroaryl substituted β-lactams **151** (Scheme 50).[50]



Scheme 50. *cis*-Heteroaryl β-lactams by [2+2] cycloaddition.

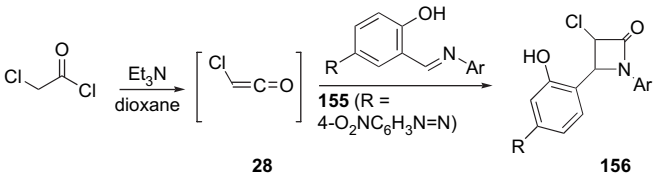
Ketenes generated by dehydrochlorination of acyl chlorides reacted with fluoroalkylimines **152** forming fluorine substituted β-lactams **153**, while diphenylketene (**1**) by reaction in toluene at reflux gave **154** (R^1=CH_2CO_2Me) in 22% yield (Scheme 51).[51]



R	R^1	Yield (%)	R	R^1	Yield (%)	R	R^1	Yield (%)
PhO	Bn	62	PhO	CH_2CO_2Me	42	PhO	Me	48
AcO	Bn	30	AcO	Me	46			

Scheme 51. Fluoroalkyl β-lactams by [2+2] cycloaddition.

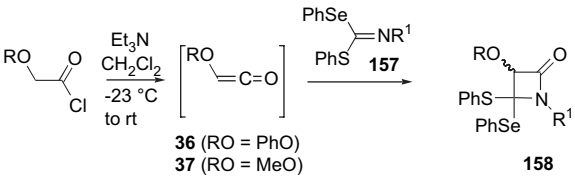
Chloroketene (**28**) generated in situ by dehydrochlorination reacted with imines **155** forming β-lactams **156** in 1,4-dioxane (Scheme 52).[52]



Scheme 52. Arylazo substituted β-lactams by [2+2] cycloaddition.

Mixed selenium and sulfur substituted imines **157** reacted with ketenes generated in situ by dehydrochlorination forming β-lactams **158** (Scheme 53). Two isomers were obtained in each case, but their stereochemistry was not determined.[53]

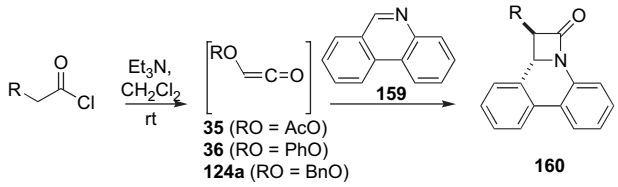
Ketene reactions with cyclic imines give β-lactams containing the ring structures of penicillins and cephalosporins, and there has been continuing interests in these reactions. Oxygen-substituted ketenes generated in situ by dehydrochlorination



RO	R^1	Yield %	Isomer ratio	RO	R^1	Yield %	Isomer ratio
PhO	2,6-Me_2-C_6H_3	52	89:11	MeO	4-MeO-C_6H_4	91	52:48
MeO	2,6-Me_2-C_6H_3	81	81:19	MeO	$(EtO)_2$-P(O)CH_2	79	64:36

Scheme 53. Formation of selenium substituted β-lactams by [2+2] cycloaddition.

reacted with phenanthridine (**159**) forming tetracyclic 2-azetidinones **160** as single trans isomers (Scheme 54).[54] However, less reactive alkylketenes failed to react with **159**. Reaction with ketene **118b** bearing a chiral substituent gave stereospecific formation of **160**.[54]



R	Yield	R	Yield
AcO	15%		53%
PhO	55%		
BnO	70%		

Scheme 54. Phenanthridine derived β-lactams by ketene [2+2] cycloaddition.

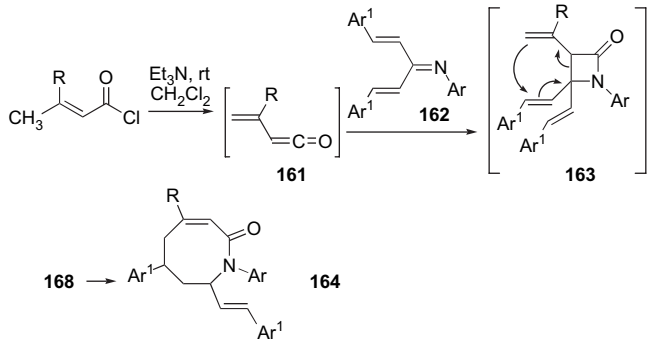
Alkenylketenes **161** generated by in situ dehydrohalogenation of unsaturated acyl chlorides reacted with azatrienes **162** forming azocinone derivatives **164** in reactions proposed to proceed by [2+2] cycloaddition forming β-lactams **163**, which then underwent Cope rearrangement (Scheme 55).[55] The pathway for the reaction was studied by AM1 computations.

Polymer bound imines **165** reacted with vinylketene **161a** generated by carboxylic acid dehydration with Mukaiyama's reagent **141** to form polymer bound vinylazetidinones **166** (Scheme 56) that were then subjected to solid phase olefin cross metathesis.[56] Cleavage of the β-lactam from the resin gave the product in 32% yield.

Ketenes **167** bearing electron withdrawing substituents were generated in situ from carboxylic acids and 1,1-carbonyldiimidazole, and underwent [2+2] cycloaddition with imines **16** to form β-lactams **31** (Scheme 57).[57]

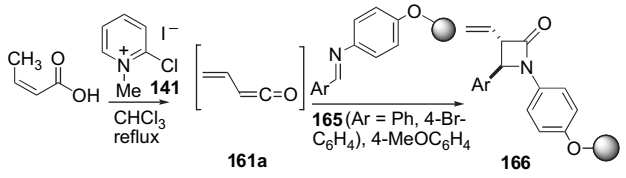
Imines **168** reacted with oxygen-substituted ketenes generated in situ by dehydrochlorination of acyl chlorides to give β-lactams **169** used in annulation reactions to form bicyclic systems (Scheme 58).[58]

β-Lactams **171** prepared similarly from imines **170** and oxygen-substituted ketenes were used to form annulated derivatives.[59a] Chloro substituted β-lactams **173** were prepared from imines **172** in

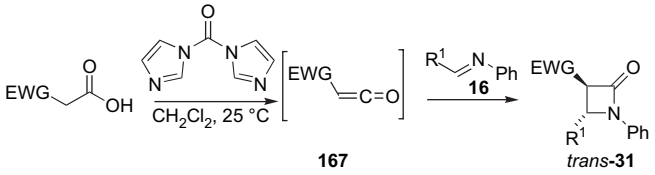


Ar^1	Ar	R	Yield %	Ar^1	Ar	R	Yield %
4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	85	Ph	4-$MeOC_6H_4$	Me	72
4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	82	Ph	4-$MeOC_6H_4$	H	78
4-$MeOC_6H_4$	4-MeC_6H_4	Me	81	Ph	4-MeC_6H_4	Me	86
4-MeC_6H_4	4-MeC_6H_4	H	88	Ph	4-MeC_6H_4	H	80
4-$MeOC_6H_4$	Ph	Me	89	Ph	Ph	Me	77
4-$MeOC_6H_4$	Ph	H	83	Ph	Ph	H	76

Scheme 55. Azocinones from tandem [2+2] cycloaddition and Cope rearrangement.



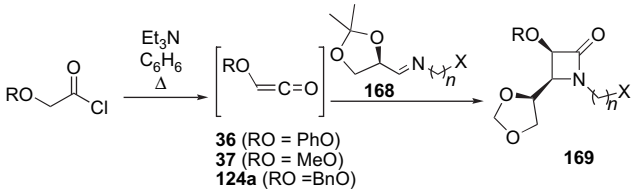
Scheme 56. Vinylketene [2+2] cycloaddition with polymer bound imines.



EWG	R^1	Yield (%)	EWG	R^1	Yield (%)
EtO_2C	Ph	98	$(EtO)_2P(O)$	4-BrC_6H_4	98
PhS(O)	Ph	97	$(EtO)_2P(O)$	4-NCC_6H_4	94
$PhSO_2$	Ph	96	$(EtO)_2P(O)$	4-ClC_6H_4	98
$(EtO)_2P(O)$	Ph	99			

Scheme 57. Imine [2+2] cycloaddition with ketenes from acid dehydration.

an analogous manner for conversion to alkenes, and alkenyl-substituted β-lactams **175** were prepared directly from alkenyl imines **174** (Scheme 59).[59b]



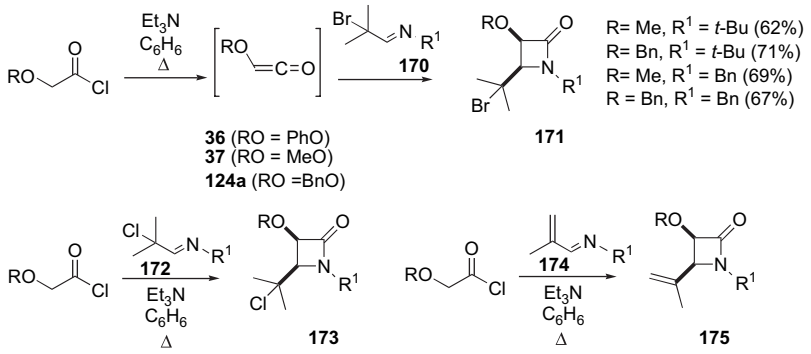
RO	X	*n*	*de* (%)	Yield (%)	RO	X	*n*	*de* (%)	Yield (%)
BnO	Cl	2	87	86	BnO	Br	3	88	77
PhO	Cl	2	88	87	MeO	Br	3	91	75
MeO	Cl	2	83	81					

Scheme 58. Stereoselective reactions of chiral imines.

Phenylthioketene **50** generated in situ from the acid salt reacted with imines **16** forming *trans* β-lactams **176** as the only observed products, and these were utilized in further synthetic transformations (Scheme 60).[60]

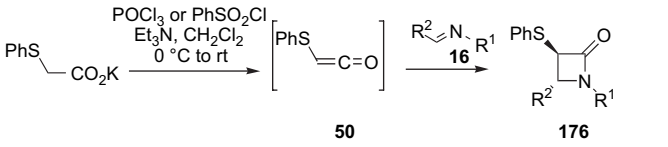
Thermal Wolff rearrangement at 80 °C without the need for rhodium catalysis also gave **50**, which was used for in situ [2+2] cycloaddition with cyclic imines forming β-lactams (Scheme 61).[61] Imine **179** did not react with **50**, while imine **180** gave a product from reaction with the dimer of ketene **50**. Yields were improved for reactions of less thermally stable imines by utilizing $Rh_2(OAc)_4$ catalysis.

Ketene **181** generated by catalysis with $Rh_2(OAc)_4$ showed significant thermal stability in solution, and addition of imines to solutions of **181** provides a route to β-lactams **182** substituted with CO_2Et groups (Scheme 62).[62a] Phenylthio imines **16a** react with oxygen-substituted ketenes giving *cis*/*trans* β-lactams with



R^1	RO	Yield **173** (%)	R^1	RO	Yield **173** (%)	R^1	RO	Yield **175** (%)
t-Bu	Me	75	*c*-Hex	Me	82	*t*-Bu	Bn	72
t-Bu	Bn	79	*c*-Hex	Bn	79	*c*-Hex	Bn	69
i-Pr	Me	72	allyl	Me	72	allyl	Bn	85
Bn	Bn	73						

Scheme 59. Preparation of chloroalkyl- and alkenyl-substituted β-lactams.



R^2	R^1	Yield %	R^2	R^1	Yield %
Ph	Ph	70	4-$MeOC_6H_4$	4-$MeOC_6H_4$	70
Ph	piperonyl	72	Ph	4-$MeOC_6H_4$	69
$HO_2CC_6H_4$	4-$MeOC_6H_4$	73	4-$MeOC_6H_4$	PhCH=CH	75

Scheme 60. Phenylthioketene reaction with imines.

moderate selectivity, which were oxidized to *N*-sulfinyl and *N*-sulfonyl derivatives (Scheme 62).[62b]

Aryloxyketenes **124** and ketenimines **184** generated together in situ react by an aza-Wittig reaction in the same pot, providing a route to alkyidene-β-lactams **185** (Scheme 63).[63]

3.3. Münchnone reactions

Amidoketenes **187** in equilibrium with Münchnones **186** are formed by Pd-catalyzed reaction of acyl chlorides with carbon monoxide and imines **16** and react in situ with excess imine forming β-lactams **188** (Scheme 64).[64] When 1 equiv of the imine is used initially the amidoketenes **187** formed can react upon addition of a second imine to form mixed β-lactams.[64]

4. Spiro lactam formation

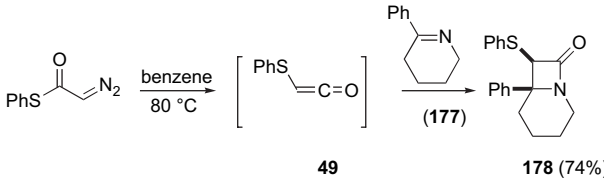
Spiro β-lactams may be formed by [2+2] cycloaddition between ketenes and imines when one of the reactants has an exocyclic functionality, and both exocyclic ketenes and imines have been utilized. In an early example of the application of exocyclic imines, reaction of ketenes **28** and **53g** generated by in situ dehydrochlorination with imine **189a** formed the *trans* spiro β-lactams **189b** (Scheme 65).[65a] The reaction of chloroketene **28** with imine **190a** has also been employed to prepare intermediates **190b** designed for use in the total synthesis of spirocyclic β-lactam chartelline alkaloids isolated from marine sources (Scheme 65).[65b,c] In related studies similar reactions were extended to formation of bis(spiro β-lactams) (vide infra).[65d]

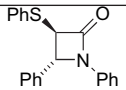
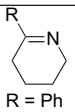
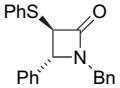
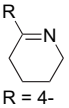
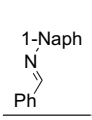
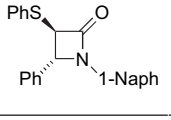
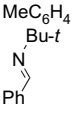
Ketene–isocyanide reactions have been known for more than 40 years, but the products were not completely elucidated.[66a] Further investigation has revealed that at low ketene concentrations, diphenylketene (**1**) reacts with isocyanides RN≡C (**191**) in two ways as illustrated[66] where **1** in both cases reacts as a nucleophilic component giving the intermediate **192**, which reacts further at lower concentrations of **1** and in the presence of Me_3SiCl in a second step in a net [3+2] cycloaddition forming **193** (Scheme 66). Cyclization of **192** is also proposed to occur to generate imine **194**, followed by [2+2] cycloaddition with **1** forming β-lactams **195**.[66] Ketenes serve two functions in these multi-component reactions, and were classified as privileged reagents. Products **195b** of acylation of enols of the ketone products were also observed.

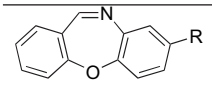
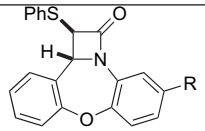
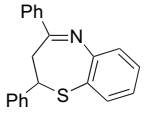
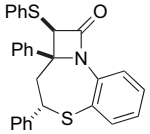
Exocyclic ketenes have also been exploited for formation of spiro lactams, including **196** generated in situ by dehydrochlorination reacting with imine **16** forming β-lactams **197** (Scheme 67).[67] The reactions were successful forming β-lactams with spiro chains with 5–7 carbon atoms in 57–70% yields, but not with three or four atoms.[67]

Tetrahydrofuran-derived exocyclic ketenes **198** generated in situ by dehydrochlorination formed spiro β-lactams **199** upon reaction with imine **16** (Scheme 68).[68] Imines bearing chiral substituents gave high diastereoselectivities up to 95:5.[68]

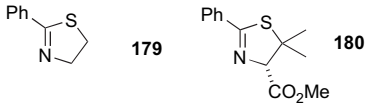
Computational modeling of the reaction at the MP2/6-31+G* level was also carried out with ketenes **198a**,**b** reacting with the imine **25** forming zwitterionic intermediates **200** (Scheme 69).[68] These studies suggested that for ketene **198a** there was a 3.4 kcal/mol preference for imine attack on the side of the ketene *syn* to oxygen, whereas for ketene **198b** there was a 0.5 kcal/mol preference for imine attack on the side of the ketene *anti* to oxygen. These



Imine	Product	Yield %	Imine	Product	Yield %
		98	 R = Ph		74 (96)[a]
		85	 R = 4-MeC_6H_4		76 (97)[a]
		71			93

Imine	Product	Yield %
		R = H 99 Me 99 NO_2 98
		70 (99)[a]

[a]Yield with $Rh_2(OAc)_4$ catalyzed reaction at room temperature



Scheme 61. Phenylthioketene reaction with cyclic imines.

formed β-lactams with preferences for conrotatory ring closure of 2.1 and 0.2 kcal/mol, respectively. This is in agreement with the experimentally observed greater preference for formation of cis product from **198a** (Scheme 69).[68]

The reaction of chiral proline derived ketenes **201a**,**b** with imine **11** (R^1=Ph, R^2=4-$MeOC_6H_4$) gave cis-stereoselectivity forming lactams **202** in equal amounts (Scheme 70).[69] Ketene **201c** (R=H) reaction with the chiral imines **203** and **204** gave the corresponding β-lactams with high cis-selectivity (Scheme 70).[69] Reaction of **201d** (R=MsO) with imines **11** forming **202** gave the product yields shown in Table 1.[70] Computational modeling of the reaction of an analogue of **201c** using DFT methods was also carried out for the analysis of the observed stereochemistry,[69] and in contrast to the results for **198**[68] there was a preference for attack *anti* to the ring hetero atom.

Spiro β-lactams **208** were obtained in 25–59% yields by reaction of ketene **201c** formed by acyl chloride dehydrochlorination with formaldehyde imines (CH_2=NR) generated in situ from triazines **207** (Scheme 71).[71] The ketene was generated at −40 °C followed by addition of the triazine and $BF_3{\cdot}OEt_2$ to depolymerize the triazine. The β-lactams **208** were resolved and used in further syntheses.

Ketene **209** from in situ acyl chloride dehydrochlorination underwent [2+2] cycloaddition with imine **210** forming the β-lactam **211** in 43% overall yield (Scheme 72).[72] The product was converted to a totally synthetic β-lactam with activity in proteasome inhibition.

Dehydration of the chiral 1,3-thiazolidine-2-carboxylic acid **212** with Mukaiyama's reagent (**141**) generated ketene **213**, which reacted in situ with imines **214** by [2+2] cycloaddition giving chiral spiro β-lactams **215** and **216**, which were separated by chromatography. Cleavage of the thiazolidine groups in **215** and **216** gave azetidine-2,3-diones (Scheme 73).[73]

Thermolysis of Meldrum's acid derivatives **217** in the presence of imines **16** resulted in the formation of spiro β-lactams **220** in a process proposed to proceed by oxiranyl ring opening forming dioxinones **218** as unobserved intermediates. These lost acetone giving intermediate acylketenes **219**, which reacted with the imines by [2+2] cycloaddition (Scheme 74).[74]

Dehydrochlorination of the glucose derived acyl chloride **221** formed the ketene **222**, which reacted in situ with imines **16** forming β-lactams **223** and **224** in ratios near 7:3 (Scheme 75).[75]

5. Bis(β-lactams)

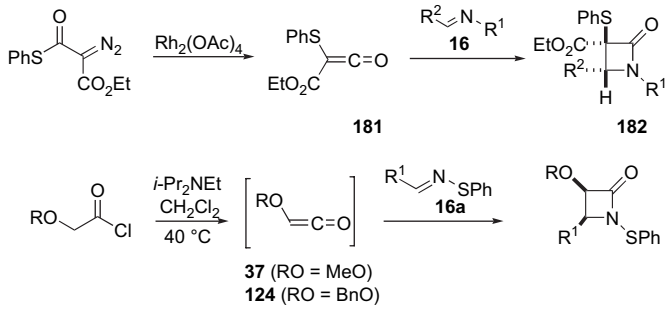
The possibility of cooperative effects from two therapeutic functionalities in drug molecules, as well as the possible use of these multifunctional substrates in further synthetic transformations, has prompted interest in the synthesis of bis(β-lactams). Syntheses of bis(β-lactams) have most often been carried out from reactions of monoketenes with bis(imines), although there have been recent studies involving reactions of the less accessible bis(ketenes). Many different arrangements of the bis(β-lactam) groups have been produced by different synthetic schemes.

In a pioneering example [2+2] cycloaddition of in situ generated azidoketene (**225**) with the chiral imine **226** gave the two diastereomeric azido-substituted *cis* β-lactams **227** as a 1:1 mixture (Scheme 76).[76] These were separated and as shown for **227a** converted to **228a**, and repetition of the cycloaddition with each of the separated diastereomers gave >99.5% stereoselectivity in formation of *cis*/*cis*-bis(β-lactams) **229**, with a 74% yield for **229a** from **228a** and 48% yield for the diastereomer **229b** from **228b**. Generation of the bis(β-lactam) **230a** confirmed that the stereoselectivity of ketene–imine cycloaddition was unaffected by the *N*-substituent. Both cis/cis diastereomers of **230b** were formed similarly with high stereoselectivity. These bis(β-lactams) all have an N1,C3′ linkage from the nitrogen of one azetidinone ring to C3 of the second azetidinone (Scheme 76).[76a,b] Preparation of bis(β-lactams) by coupling of two (β-lactams) has also been reported.[76c]

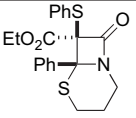
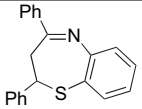
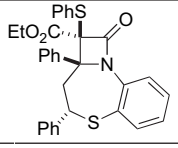
The reaction of in situ generated oxygen and phthalimido substituted ketenes with racemic imino-substituted β-lactam **231** formed *cis*,*cis*-bis(β-lactams) **232**, and for R=PhO this was separated using a chiral column into the enantiomers in a 1:1 ratio, showing the high stereoselectivity of the reaction (Scheme 77).[77]

Ketenes generated in situ reacted with optically active β-lactam substituted azadienes **233** and gave diastereomeric *cis*,*cis*-bis(β-lactams) **234**, which are linked by a chiral methylene group between N1 and C4′ (Scheme 78).[78]

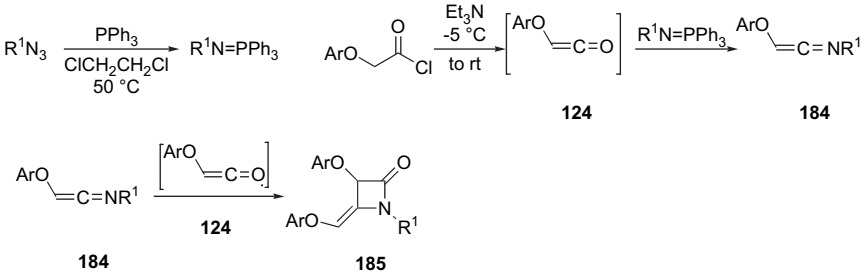
Two equivalents of ketenes generated in situ in the presence of methylene bridged bis(imines) **235** with initial reaction from 0 °C to room temperature followed by increasing the temperature to 70 °C gave two diastereomeric methylene *N*1,*N*1′ linked *cis*,*cis*-bis(β-lactams) **236** (Scheme 79).[79] Conducting the reaction with 1 equiv of ketene precursor from 0 °C to room temperature



R^2	R^1	Yield **182** %	R^2	R^1	Yield **182** %
Ph	Ph	89	Ph	Bn	70
PhCH=CH	PMP	96	Ph	*t*-Bu	67
2-Furyl	PMP	85	Ph	CH_2-CO_2Et	71

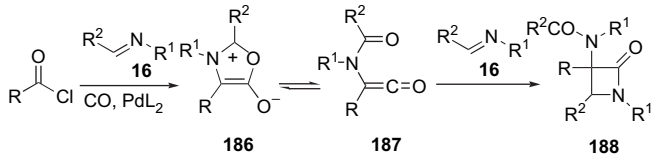
Imine	Product	Yield %	Imine	Product	Yield %
		88			79

Scheme 62. Imine reactions with **181**.



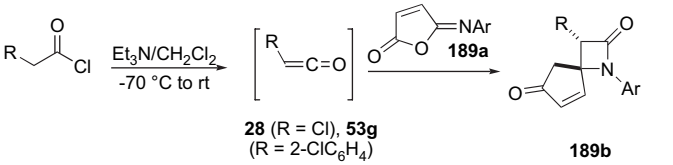
ArO	R^1	Yield %	ArO	R^1	Yield %
PhO	4-$MeOC_6H_4$	76	PhO	3-MeC_6H_4	88
PhO	4-MeC_6H_4	86	2-Me,4-ClC_6H_3O	4-$MeOC_6H_4$	79
PhO	2-MeC_6H_4	80	2-Me,4-ClC_6H_3O	4-MeC_6H_4	80
PhO	Ph	89	2-Me,4-ClC_6H_3O	2-MeC_6H_4	87
PhO	3,4-$Me_2C_6H_3$	83	2-Me,4-ClC_6H_3O	Ph	78
4-MeC_6H_4O	3-MeC_6H_4	85	2-Me,4-ClC_6H_3O	3-MeC_6H_4	81
PhO	4-$EtOC_6H_4$	78	2-Me,4-ClC_6H_3O	4-$EtOC_6H_4$	81
4-MeC_6H_4O	4-$EtOC_6H_4$	75	4-MeC_6H_4O	4-$MeOC_6H_4$	77
4-MeC_6H_4O	Ph	90	3-MeC_6H_4O	Ph	92
3-MeC_6H_4O	4-MeC_6H_4	87	PhO	2-BrC_6H_4	51
3-MeC_6H_4O	3-MeC_6H_4	91			

Scheme 63. One pot preparation of alkylidene-β-lactams.

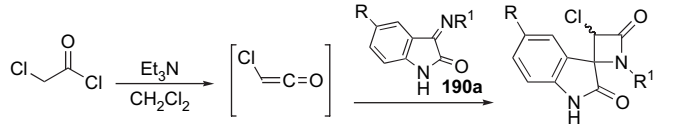


R	R^1	R^2	Yield %	R	R^1	R^2	Yield %
Ph	Bn	Ph	58	Ph	4-MeOBn	Ph	65
4-Tol	Bn	Ph	61	Ph	2-FurylCH_2	Ph	66
4-$MeSC_6H_4$	Bn	Ph	56	Ph	2-ThienylCH_2	Ph	62
4-$CF_3C_6H_4$	Bn	Ph	32	Ph	4-MeOPh	Ph	27
Ph	Bn	*i*-Pr	45	Ph	*n*-Hexyl	Ph	55
Ph	Et	Ph	56				

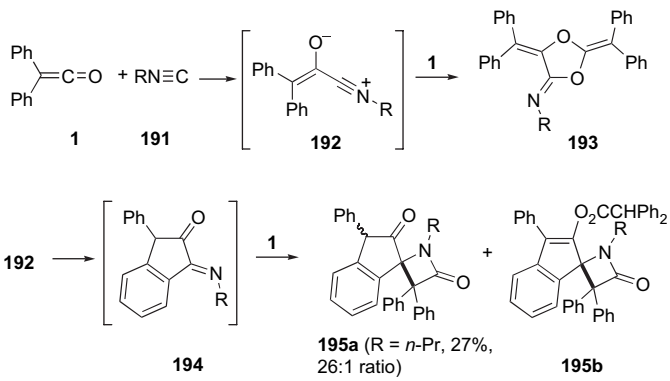
Scheme 64. β-Lactams from Münchone precursors.



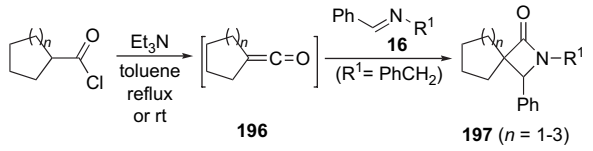
R	Ar	Yield (%)	R	Ar	Yield (%)
Cl	Ph	33	2-ClC_6H_4O	Ph	30
Cl	4-$MeOC_6H_4$	33	2-ClC_6H_4O	4-$MeOC_6H_4$	28
Cl	4-$AcOC_6H_4$	33	2-ClC_6H_4O	4-$AcOC_6H_4$	34



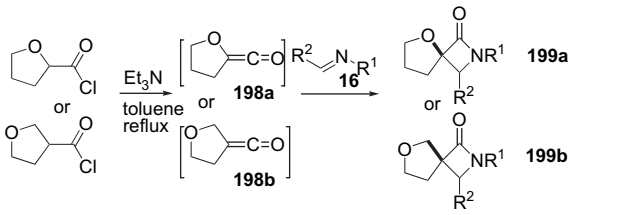
Scheme 65. Spiro β-lactams **189b** and **190b** from exocyclic imines.



Scheme 66. β-Lactams from diphenylketene reaction with isocyanides.



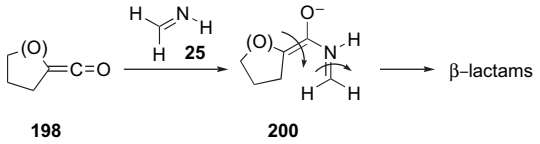
Scheme 67. Spiro β-lactams from carbocyclic ketenes.



R^2	R^1	Yield **199a** %(*cis*:*trans*)	R^2	R^1	Yield **199a** %(*cis*:*trans*)
4-MeO-C_6H_4	4-MeO-C_6H_4	76 (15:1)	4-$O_2NC_6H_4$	4-MeO-C_6H_4	74 (1:3)
Ph	Me	66 (14:1)	PhCH=CH	4-MeO-C_6H_4	56 (5:1)
Ph	4-MeO-C_6H_4	75 (12:1)	3-Pyridyl	4-MeO-C_6H_4	63 (4:1)
Ph	Ph	49 (6:1)	4-$O_2NC_6H_4$	Ph	58 (1:4)
2-Furyl	4-MeO-C_6H_4	64 (8:1)	4-$O_2NC_6H_4$	Me	71 (1:2)
Ph	4-O_2N-C_6H_4	66 (1:1)	4-$O_2NC_6H_4$	4-O_2N-C_6H_4	52 (1:5)
Ph	Bn	77 (5:1)			

R^2	R^1	Yield **199b** %(*cis*:*trans*)	R^2	R^1	Yield **199b** %(*cis*:*trans*)
4-MeO-C_6H_4	4-MeO-C_6H_4	69 (3:1)	Ph	Ph	69 (2:1)
Ph	4-MeO-C_6H_4	66 (3:1)	4-$O_2NC_6H_4$	Ph	68 (1:2)

Scheme 68. Spiro β-lactams from tetrahydrofuran-derived ketenes.

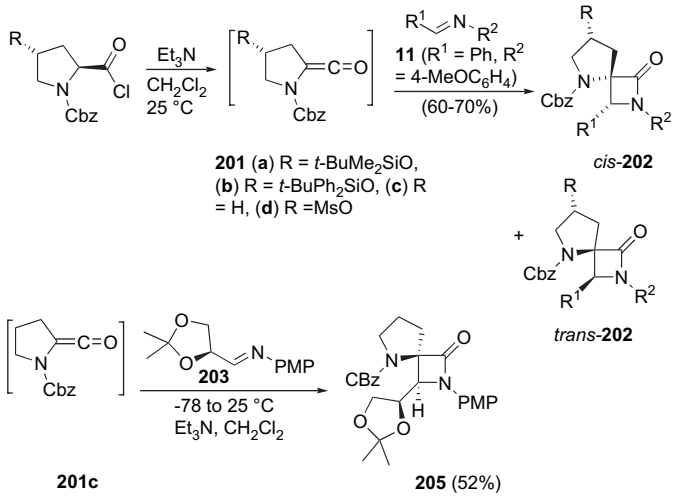


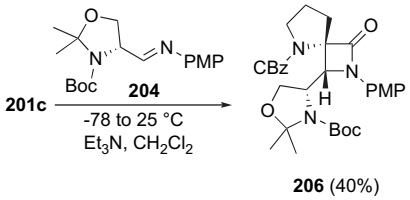
Scheme 69. Selectivity in formation of β-lactams.

followed by addition of 1 equiv of a second ketene precursor and increasing the temperature to 70 °C gave mixed bis(β-lactams).[79] The products were also prepared containing ^{15}N label as possible Taxol analogue synthons.

One-step preparation of *cis*,*cis*-bis(β-lactams) **238** with a C4,C4′ linkage was accomplished by reaction of bis(imines) **237** with ketenes generated in situ by dehydrochlorination of acyl chlorides (Scheme 80).[80] Syntheses of **238** were also carried out by stepwise processes. Base induced rearrangements of the bis(β-lactams) **238** gave fused *cis*,*cis*-bis(γ-lactams).

A single diastereomer of bis(β-lactam) **240** with a C4,C4′ linkage was obtained by reaction of the chiral ketene **118b** with bis(imine) **239** (Scheme 81).[80b] Reaction of ketenes with chiral bis(imine) **241** yielded the two isomers **242** and **243** (Scheme 81).[80b] Other optically

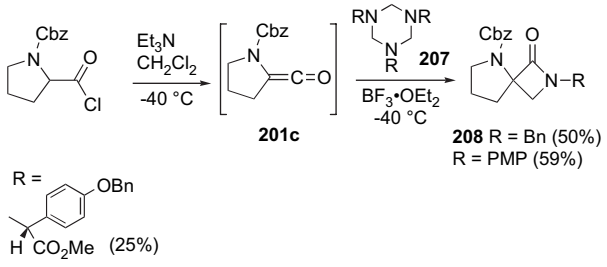




Scheme 70. Spiro β-lactams from ketene–imine cycloaddition.

Table 1
Spiro β-lactams from ketene **202d** (R=OMs) and imines **16**

R	R^1	R^2	Yield (%)		R	R^1	R^2	Yield (%)	
			cis	trans				cis	trans
MsO	Bn	Ph	51	20	MsO	*c*-Pr	4-$MeOC_6H_4$	41	12
MsO	PMB	4-FC_6H_4	54	9	MsO	PMB	4-$MeOC_6H_4$	50	6
MsO	*c*-Pr	4-FC_6H_4	58	—					

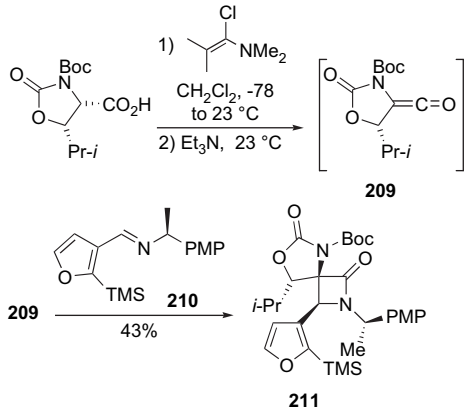


Scheme 71. Spiro β-lactams from triazines.

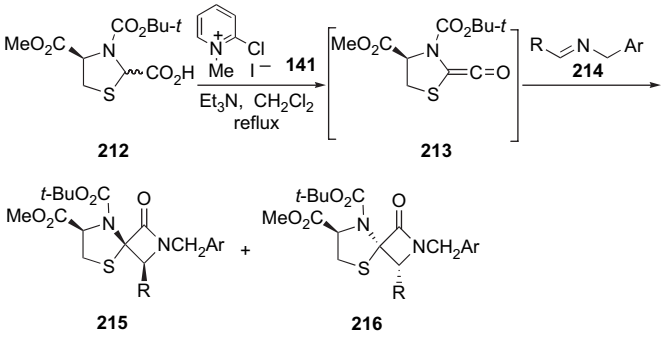
pure bis(β-lactams) were obtained by two-step procedures with initial preparation of imino-substituted monocyclic 2-azetidinones.

Reaction of chiral tartaric acid-derived bis(imines) **244** with ketenes generated in situ gave bis(β-lactams) **245** linked by a two carbon C4,C3′ chain in 52–73% yields, with only minor amounts of other diastereomers (Scheme 82).[81] For R=MeO the product was, however, **246**. These were hydrolyzed to diols, which were cleaved to mono β-lactams.

Ketenes generated in situ by dehydrochlorination of acyl chlorides reacted with dimethylene bridged bis(imines) **247** forming *N*1,*N*1′ linked bis(β-lactams) **248** as a mixture of *cis*/*cis meso* and DL



Scheme 72. Spiro β-lactam synthesis for proteasome inhibition.



R	Ar	Yield (%)	**215**: **216**	R	Ar	Yield (%)	**215**: **216**
Ph	Ph	63	64:36	PMP	2-furyl	60	46:54
PMP	Ph	62	56:44	PMP		72	69:31
PMP	2-thienyl	77	36:64				

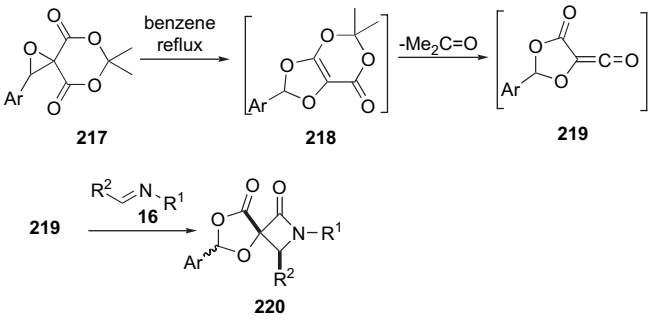
Scheme 73. Spiro thiazolidine β-lactams.

stereoisomers.[82] The chiral ketene **250** generated by in situ activation of the acid **249** reacted with bis(imine) **247** forming the bis(β-lactam) **251** in 93% yield as a single diastereomer (Scheme 83).[82]

1,2-*trans*-Bis(iminyl)cyclohexanes **252** reacted with an excess of ketenes generated in situ to form *meso* and DL substituted bis-(β-lactams) **253**, with a preference for the *meso*-isomer (Scheme 84).[83] The use of enantiomerically pure **252** (R^1=Ph) with **36** (RO=PhO) led to the pure diastereomers of **253** isolated by chromatography. Reaction of **252** with 1 equiv of in situ generated **124a** gave formation of equal amounts of mono(DL-β-lactams) **254**.[83]

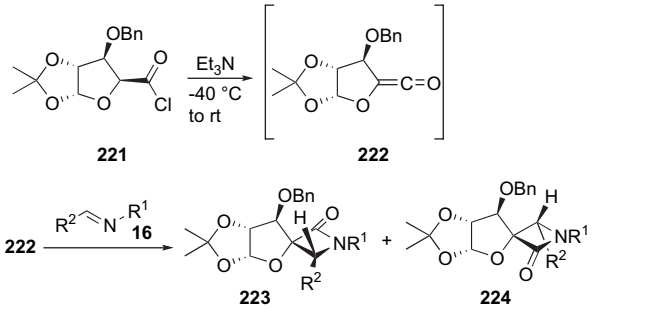
Stereoisomeric bis(β-lactams) **256** were formed in a similar manner from acylic 1,2-bis(imines) **255** by reaction with ketenes.[83] The use of enantiomerically pure **255** (R^1=R^2=Ph) with **36** (RO=PhO) led to the pure diastereomers of **256** isolated by chromatography (Scheme 85).[83]

Phenoxyketene (**36**) generated in situ by dehydrochlorination reacted with the bis(imine) **257** forming the bis(β-lactams) **258** with N1,N1′ and C4,C4′ linkages in 78% yield (Scheme 86).[84] Reactions of **259**, **261**, and **263** with **36** similarly formed bis(β-lactams) **260**, **262**, and **264**, respectively.[84] Reactions of **265** and **267** with **36** gave bis(β-lactams) **266** and **268** as mixtures of cis/cis diastereomers in a 58:42 dr.[85]



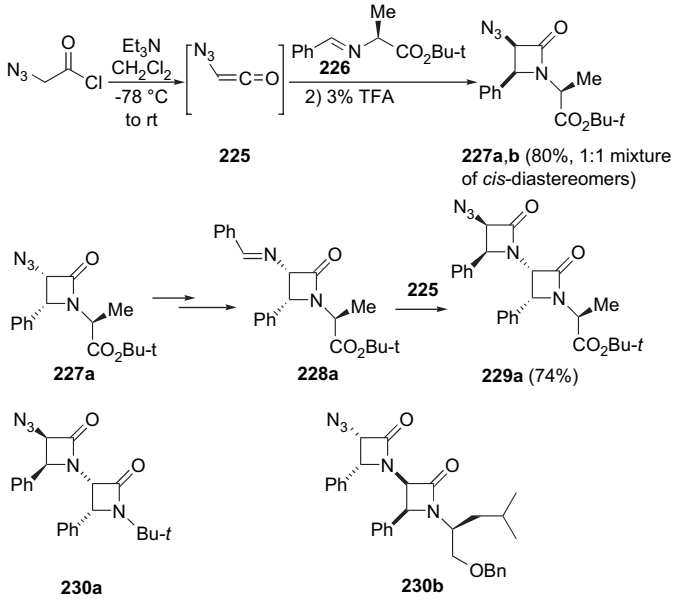
Ar	R^1	R^2	Yield % *trans*:*cis*	Ar	R^1	R^2	Yield % *trans*:*cis*
Ph	Ph	Ph	17:24	3-MeC_6H_4	Ph	4-ClC_6H_4	29:36
4-BrC_6H_4	Ph	Ph	16: 16	3-$MeOC_6H_4$	Ph	4-ClC_6H_4	32:40
4-ClC_6H_4	Ph	Ph	13:21	Ph	Ph	4-$MeOC_6H_4$	17:21
3-MeC_6H_4	Ph	Ph	22:37	3-MeC_6H_4	Ph	4-$MeOC_6H_4$	26:32
3-$MeOC_6H_4$	Ph	Ph	31:40	4-BrC_6H_4	4-MeC_6H_4	4-MeC_6H_4	20:27
Ph	Ph	4-ClC_6H_4	13:12	3-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	22:32
4-BrC_6H_4	Ph	4-ClC_6H_4	41:37				

Scheme 74. Spiro β-lactams from Meldrum's acid-derived ketenes.



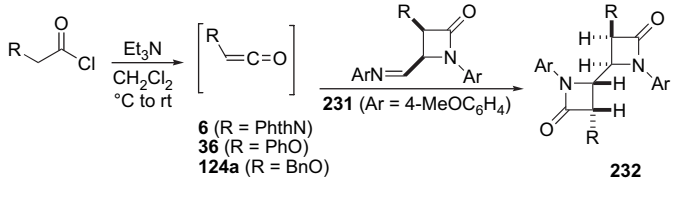
R^1	R^2	Yield %	*syn*/*anti*	R^1	R^2	Yield %	*syn*/*anti*
4-$MeOC_6H_4$	4-MeO-C_6H_4	65	70:30	Ph	PhCH=CH	69	71:29
Ph	4-MeO-C_6H_4	71	72:28	4-MeO-C_6H_4	PhCH=CH	67	68:32
Ph	Ph	62	70:30	4-Me-C_6H_4	Ph	72	64:36
4-$MeOC_6H_4$	Ph	62	68:32	Ph	4-MeC_6H_4	70	64:36
4-ClC_6H_4	Ph	59	65:35				

Scheme 75. Spiro β-lactams from a glucose derived ketene.

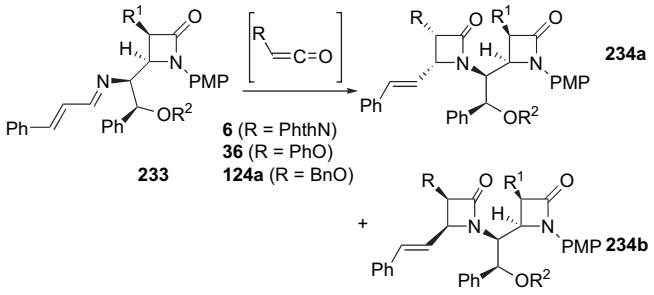


Scheme 76. N1,C3′ Linked bis(β-lactams) by successive [2+2] cycloaddition.

Imine **269** derived from benzylisatin reacted with ketenes generated in situ by Et_3N dehydrochlorination of acyl chlorides in CH_2Cl_2 from −10 °C to room temperature forming spiro β-lactams **270** in yields of 54–71% (Scheme 87).[86] Similar reactions of bis-(imines) **271** reacted similarly forming bis (spiro β-lactams) **272**.[65d]

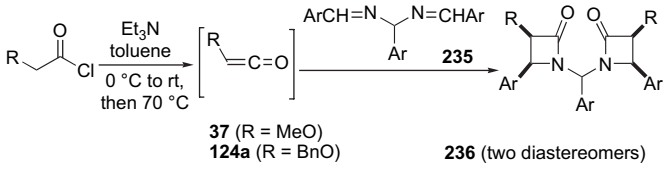


Scheme 77. Preparation of C4,C4′ linked bis(β-lactams) **232**.



R	R^1	R^2	Yield (%)	R	R^1	R^2	Yield (%)
BnO	TMS	PhO	82 77:23[a]	PhthN	TBDMS	PhO	70 66:34[a]
PhO	TMS	PhO	78 65:35[a]	PhthN	TBDMS	BnO	96 70:30[a]
PhthN	TMS	PhO	86 78:22[a]	PhthN	TBDMS	PhthN	69 >95:5[a]
PhthN	TMS	BnO	87 75:25[a]				

Scheme 78. Methylene N1,C4′ linked bis(β-lactams) by [2+2] cycloaddition.



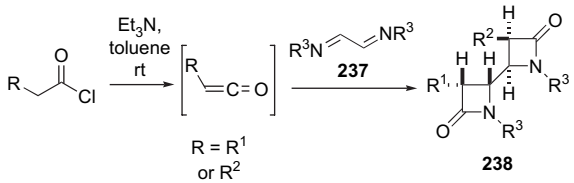
R,R	Ar	Yield %	*dr*	R,R	Ar	Yield %	*dr*
MeO,MeO	Ph	66	70:30	MeO,MeO	4-$MeOC_6H_4$	66	70:30
BnO,BnO	Ph	84	75:25	BnO,BnO	4-$MeOC_6H_4$	73	80:20
MeO,BnO	Ph	31	70:30	MeO,MeO	3-BrC_6H_4	74	70:30

Scheme 79. Methylene N1,N1′ linked *cis*,*cis*-bis(β-lactams).

An alternative approach to bis(β-lactam) synthesis utilized photolysis of bis(carbene) complexes **273** in the presence of imidazoline **275** to give bis(β-lactams) **276** as a 1:1 mixture of cis/cis diastereomers in 55–68% yields. This reaction could formally have proceeded through bisketene complexes **274**, which reacted with the imine functionality in a double [2+2] cycloaddition leading to the observed product **276**, but stepwise processes may be involved (Scheme 88).[86] A number of other examples were investigated, including those with poly(ethylene glycol) or hydrocarbon linkages, and those from optically active imidazolines.[87,88]

Formation of bis(lactam) **280** by bisketene reaction with imine **279** may occur upon treatment of diacid **277** with Mukaiyama's reagent **141** to generate the formal bisketene **278** that reacted with the imine (Scheme 89).[89] The ketenyl groups are not formed simultaneously and may be generated and react in a stepwise fashion. Reaction of **278** with bis(imine) **281** formed a polymer with β-lactams in the polymer chain.[89]

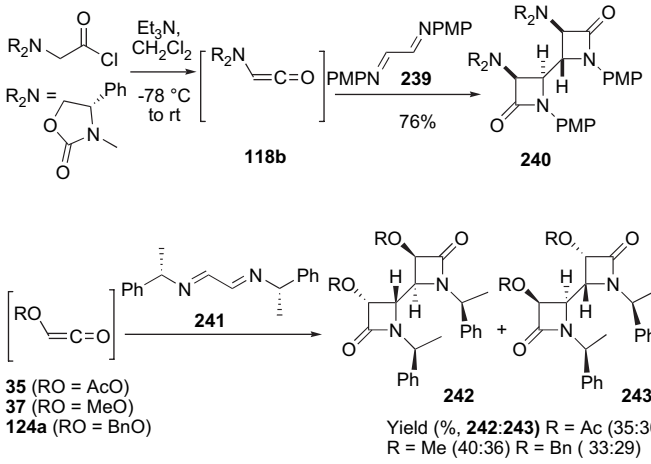
Bisketenes **282** are generated by photochemical Wolff rearrangement and directly observed by IR, and on reaction with imine **38a** gave *cis*,*cis*-bis(β-lactam) **283** as a mixture of *meso* and DL isomers (Scheme 90).[90] 1,2-Bisketenylbenzene (**284**) generated by a dehydrochlorination procedure also gave mixtures of *meso* and



Two step reaction				One step reaction			
R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
Me	PhO	PMP	90	MeO	MeO	PMP	85
Me	PhO	DAM	40	BnO	BnO	PMP	80
Ph	PhO	PMP	76	BnO	BnO	DAM	56
PhO	Md	PMP	70	PhO	PhO	PMP	90
PhO	Cl	PMP	85	Md	Md	PMP	82
PhS	Phth	PMP	62	Phth	Phth	PMP	89
PhO	PhS	PMP	70	Phth	Phth	DAM	44
				PhO	PhO	DAM	64

[a]PMP = 4-$MeOC_6H_4$, Phth = phthalimido, DAM = malimidyl

Scheme 80. C4,C4′ Linked bis(β-lactams) by [2+2] cycloaddition.



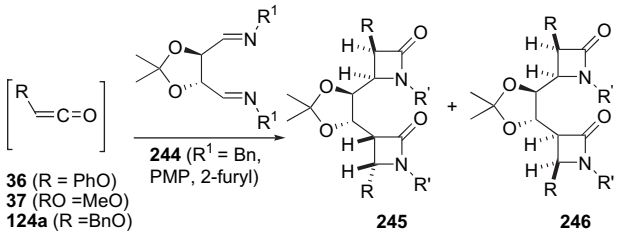
Scheme 81. C4,C4′-Bis(β-lactams) from a chiral ketene and from chiral bis(imines).

DL*cis*,*cis*-bis(β-lactams) **285**, and 1,4-bisketenylbenzene reacted similarly.[90]

1,2-Bisketenes **287** generated by photolysis of cyclobutenediones **286** reacted with imines **38**, but formed aziridines **288** rather than bis(β-lactams) (Scheme 91).[90] Computations indicated that this reaction involved rate-limiting ketene–imine reaction forming a zwitterion, which then closed to the product aziridine.[90]

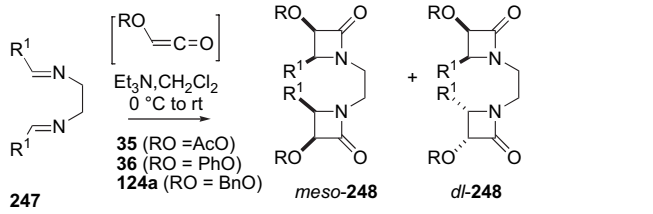
6. Ketene [3+2] and [4+2] cycloadditions with imines

Ketene reactions with conjugated imines have the potential of undergoing not only [2+2] but also [3+2] and [4+2] cycloadditions. In a recent example 2-arylthiocarbamoyl benzimidazolium (**289**),

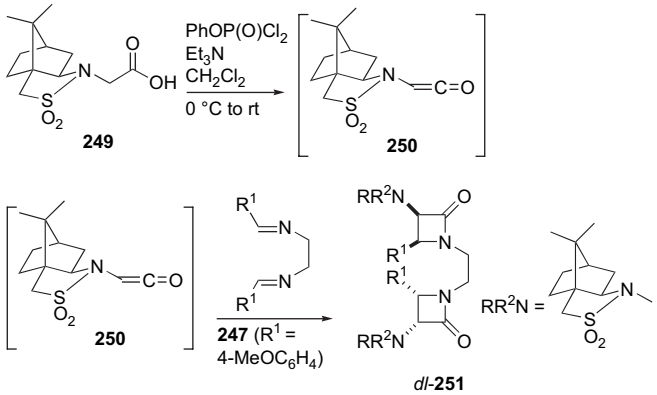


R	R1	Yield (%)	R	R1	Yield (%)	R	R1	Yield (%)
PhO	Bn	61	PhO	PMP	73	PhO	2-Furyl	63
BnO	Bn	53	BnO	PMP	52	BnO	2-Furyl	58
MeO	PMP	62						

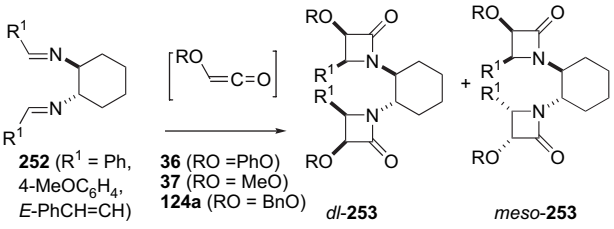
Scheme 82. *C*4,*C*3′ Bis(β-lactams) linked by two-carbon chains.



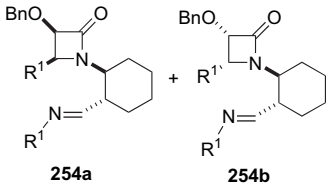
RO	R1	Yield %	*meso*:*dl*	RO	R1	Yield %	*meso*:*dl*
PhO	4-MeOC$_6$H$_4$	80	58:42	BnO	Ph	85	70:30
BnO	4-MeOC$_6$H$_4$	86	45:55	BnO	PhCH=CH	60	42:58
AcO	4-MeOC$_6$H$_4$	75	49:51	PhO	PhCH=CH	66	39:61
PhO	Ph	79	62:38				



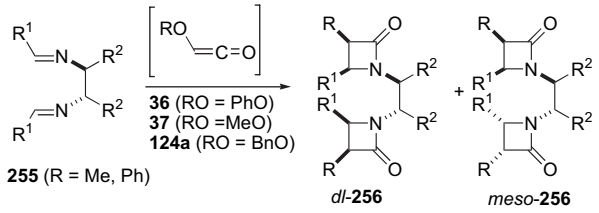
Scheme 83. N1,N1′ Linked bis(β-lactams) from bis(imines).



R, R^1	*meso*:*dl*	Yield (%)	R, R^1	*meso*:*dl*	Yield (%)
PhO,Ph	66:34	90	MeO,PMP	76:24	73
BnO,Ph	66:34	87	PhO,styryl	64:36	88
MeO,Ph	77:23	86	BnO,styryl	54:46	81
PhO,PMP	78:22	93	MeO,styryl	56:42	86
BnO,PMP	72:28	80			



Scheme 84. *N*1,*N*1′ 1,2-Cyclohexyl linked bis(β-lactams) from bis(imines).



R, R^1,R^2	*meso*:*dl*	Yield (%)	R, R^1,R^2	*meso*:*dl*	Yield (%)
PhO,Ph,Ph	58:42	81	MeO,Ph,Ph	60:40	88
BnO,Ph,Ph	56:44	84	PhO,Ph,Me	70:30	91

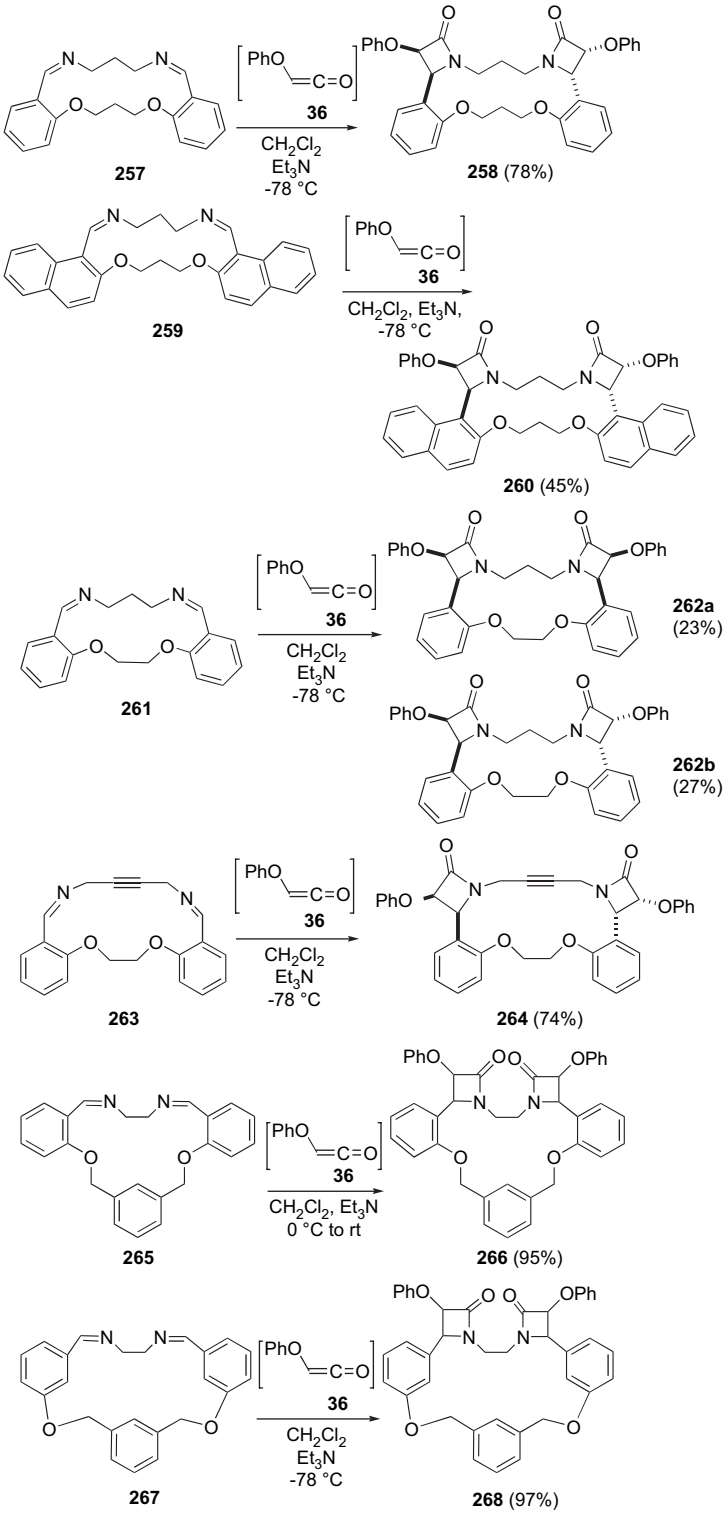
Scheme 85. *N*1,*N*1′ 1,2-Substituted ethyl-linked bis(β-lactams).

imidazolinium (**291**), and triazolium (**293**) inner salts containing 1,3-dipoles react by [3+2] cycloaddition with ketenes generated either by in situ dehydrochlorination or by $PhCO_2Ag$ induced Wolff rearrangement in highly site-selective processes to form benzimidazoline-, imidazolidine-, or triazoline spiro-pyrrolidones in 58–93% yields (Scheme 92).[91] Stable trimethylsilylketene (**61**) reacted with **289** giving an unstable adduct **290a**, which lost the trimethylsilyl group upon chromatography giving **290b** in 84% yield. Computations at the B3LYP/6-31G(d) level for reaction of **291** with $Me_2C{=}C{=}O$ suggest a stepwise mechanism is favored with nitrogen attack on the ketene carbonyl forming intermediate zwitterion **291a** as a shallow minimum (Tables 2–4).[91]

Possible [2+2] and [4+2] cycloaddition pathways of *N*-substituted 1,3-diazabuta-1,3-dienes **295** with ketenes have been studied by DFT methods (Scheme 93).[92] Initial nucleophilic attack forming zwitterions **296** and subsequent ring closure to β-lactams **297** and γ-lactams **298** were analyzed, and the choice of four- or six-membered ring formation was evaluated by the most favorable electrostatic interactions. Cyanoketene reactions with vinylimines also proceed by [4+2] cycloaddtions in some cases.[8c,d]

[4+2] Cycloadditions of ketenes and thioacylimines **299** both generated in situ are catalyzed by *O*-trimethylsilylquinine (TMSQ) to form enantio-enriched *cis*-4,5-disubstituted 1,3-thiazin-6-one heterocycles **300** with 95 to >98% ee and *c*is/trans 95:5 to >97:3 (Scheme 94).[93]

Silylated vinylketenes **301** generated by either Wolff rearrangement or cyclobutenone ring opening reacted by [4+2] cycloaddition with imines forming α,β-unsaturated δ-valerolactams **302**

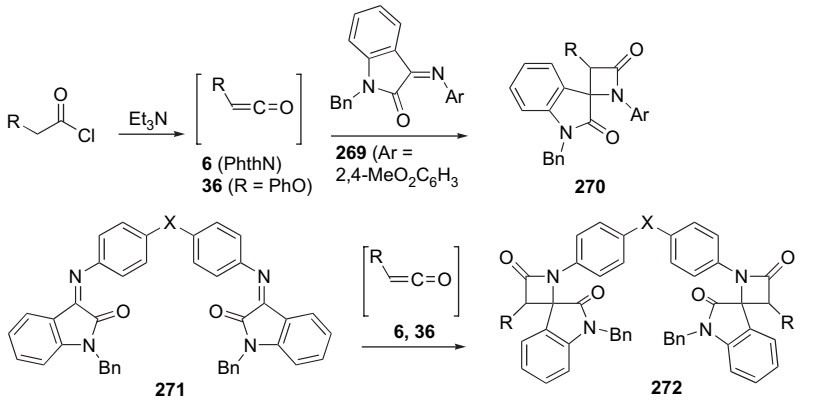


Scheme 86. Macrocyclic bis(β-lactam) formation with N1,N1′ linkages.

(Scheme 95).[24] The intermediate products underwent de(trimethylsilylation) upon chromatography. Both stepwise reactions involving zwitterions intermediates and concerted [4+2] reactions were considered as possible mechanisms for the reactions.

α-Bromo-α-alkenylketenes **303** generated by dehydrochlorination of acyl chorides reacted in situ with imines **16** by [2+2] cycloaddition giving bromo-substituted β-lactams **304** (Scheme 96).[94a,b] Many side chain modifications of the products have been carried out.[94] 3-Substituted alkenylketenes **305**, however, reacted by [4+2] cycloadditions with imines **16** forming 3-bromo-5,6-dihydropyridin-2-ones **306** (Scheme 96).[95] Reaction with a chiral imine proceeded stereoselectively.

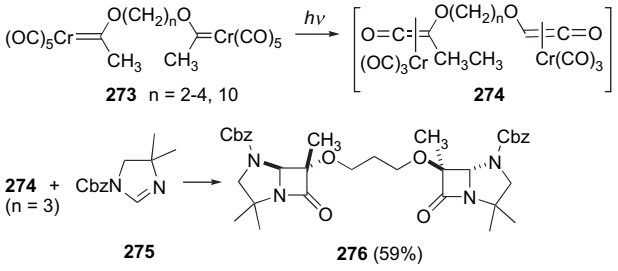
Ketene generation with 1,8-bis(dimethylamino)naphthalene (**80**) in the presence of benzoylquinidine (BQd) as a nucleophilic



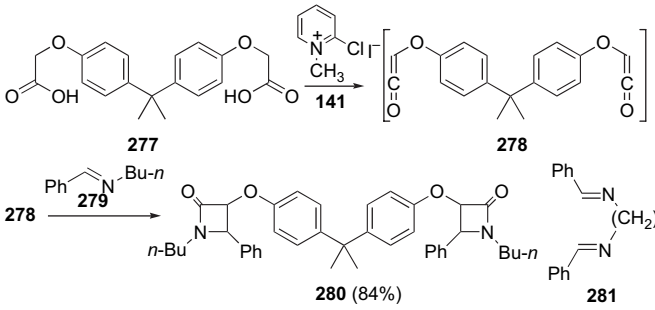
X	R	Yield (%) **272**	X	R	Yield (%) **272**	X	R	Yield (%) **272**
CH_2	PhO	67	CH_2[a]	PhO	70	O	PhO	66
CH_2	PhthN	63	CH_2[a]	PhthN	58	O	PhthN	66

[a] 1,3-isomer of **272** from 1,3-isomer of **27**

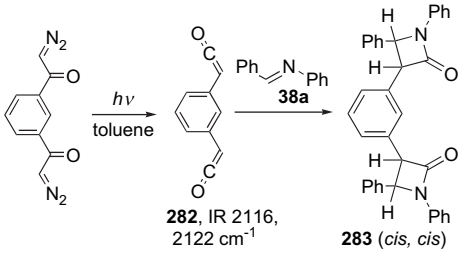
Scheme 87. Spiro bis(β-lactam) formation with N1,N1′ linkages.

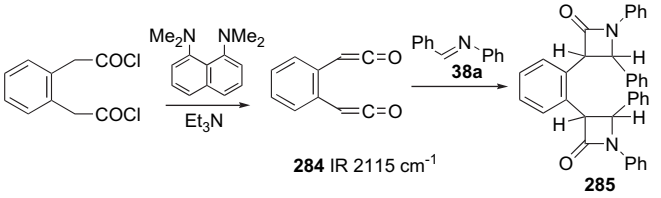


Scheme 88. C3,C3′ Linked bis(β-lactams) from chromium–carbene complexes.



Scheme 89. C3,C3′ Linked bis(β-lactams) from formal bisketenes.



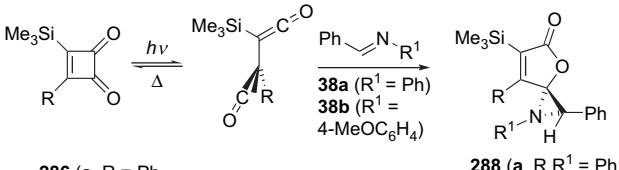


Scheme 90. Bisketenes in formation of bis(β-lactams) with C3,C3′ linkages.

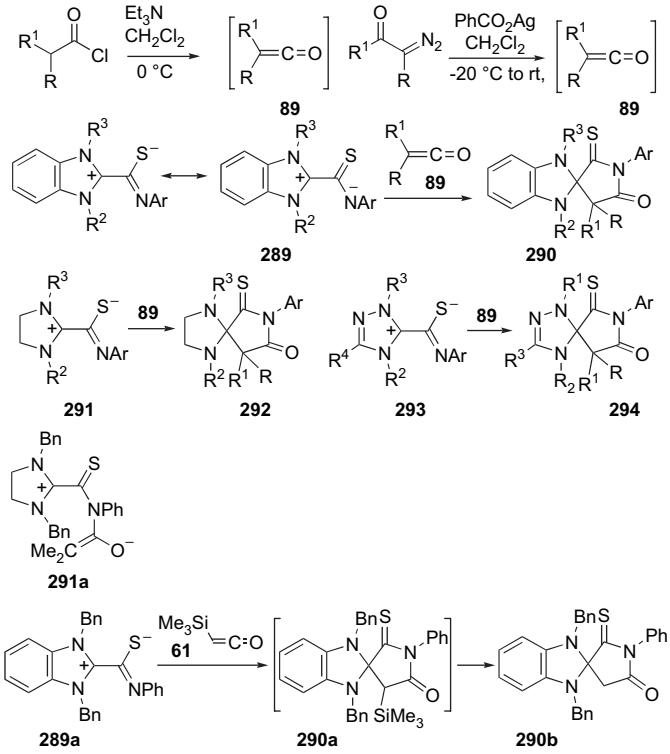
chiral catalyst and $Zn(OTf)_2$ as an electrophilic catalyst and *ortho*-benzoquinone diimides **307** as coreactants gave quinoxaline derivatives **309** with >99% ee in all cases (Scheme 97).[96] Ketene enolates **308** are proposed as the reaction intermediates. Conversion of the product **309** (R=Et) to **310** by reduction was also demonstrated.[96]

Ketene enolates **308** prepared as in Scheme 97 give enantioselective reactions with *ortho*-benzoquinone imides **311** forming 1,4-benzoxazines **312**, which could be converted to α-amino acids (Scheme 98).[97] These reactions proceed by alkylation at nitrogen and do not give amide products, and were found to be accelerated by Lewis acids catalysts, especially $Sc(OTf)_3$. A mechanism was proposed involving nucleophilic attack of the ketene enolate on the nitrogen of the catalyst activated *ortho*-benzoquinone imide.[97b]

Acylketenes **314** from furandiones **313** reacted with imines **16** to give quinoxalines **315**, while reaction with dicyclohexylcarbodiimide **316** gave **317** (Scheme 99).[98]



Scheme 91. Aziridine formation from 1,2-bisketene reaction with imines.



Scheme 92. 1,3-Cycloaddition of ketenes with 1,3-dipoles.

Table 2
Ketene reactions with benzimidazolium inner salts **289**[a]

R^2, R^3, Ar	R, R^1	Yield %	R^2, R^3, Ar	R, R^1	Yield (%)
Bn, Bn, Ph	Bn, H	91	*n*-Bu, Bn, Ph	Me, Me	83
Bn, Bn, 4-ClC_6H_4	Me, Me	85	Bn, Bn, Ph	CH_2CH_2Ph	66[b]
Bn, Bn, 4-$MeOC_6H_4$	Me, Me	85	Bn, Bn, Ph	$(CH_2)_5$	90
4-ClC_6H_4Bn, 4-ClC_6H_4Bn, Ph	*i*-Pr, H	58[b]	Bn, Bn, Ph	Bn, H	58[b]
4-ClC_6H_4Bn, 4-ClC_6H_4Bn, Ph	Me,Me	87	Bn, Bn, Ph	Me,Me	93
4-ClC_6H_4Bn, 4-ClC_6H_4Bn, Ph	Bn, H	85	Et, Bn, Ph	Me,Me	81

[a] Ketenes generated by dehydrochlorination unless indicated.
[b] Ketene generated by Wolff rearrangement.

Table 3
Ketene reactions with imidazolinium inner salts **291**[a]

R^2, R^3, Ar	R, R^1	Yield %	R^2, R^3, Ar	R, R^1	Yield (%)
4-ClC_6H_4Bn, 4-ClC_6H_4Bn, Ph	Me,Me	85	Bn, Bn, Ph	Me,Me	82
4-ClC_6H_4Bn, 4-ClC_6H_4Bn, Ph	H, Bn	83	Bn, Bn, Ph	$(CH_2)_5$	91

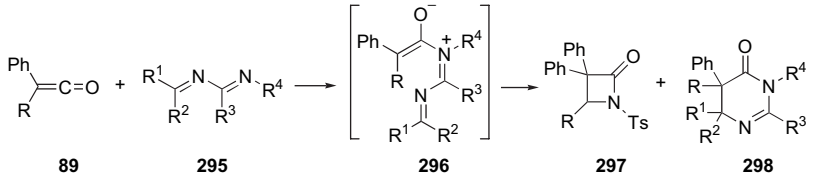
[a] Ketenes generated by dehydrochlorination unless indicated.

Table 4
Ketene reactions with triazolium inner salts **293**[a]

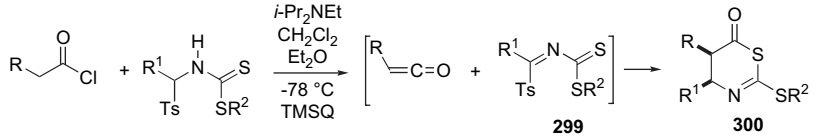
R^2, R^3, $R,^4$ Ar	R, R^1	Yield %	R^2, R^3, R^4, Ar	R^1, R^2	Yield %
4-Tol, Ph, Ph, 4-ClC_6H_4	Me, Me	60	Ph, Ph, Ph, Ph	Me, Me	71

[a] Ketenes generated by dehydrochlorination unless indicated.

In an extension[99] of earlier studies[100] diphenylketene (**1**) generated in situ by dehydrochlorination of diphenylacetyl chloride reacts with 1,2-dialkyldiaziridines (**318**) in benzene at 80 °C forming β-lactams **321** (41%, R=Et; 32%, R=*n*-Pr) together with

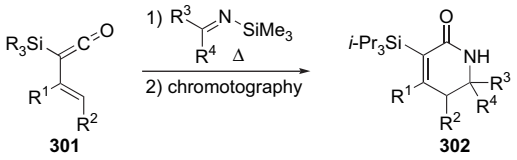


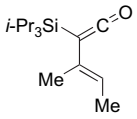
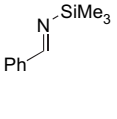
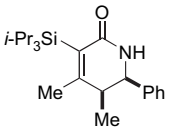
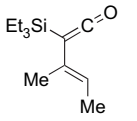
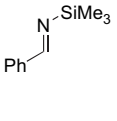
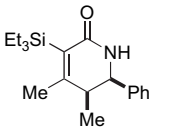
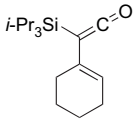
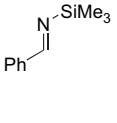
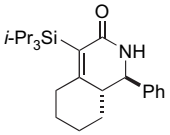
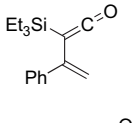
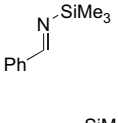
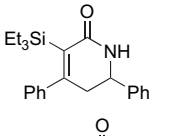
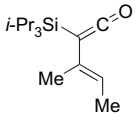
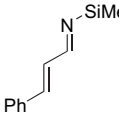
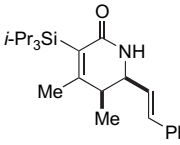
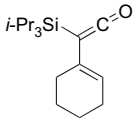
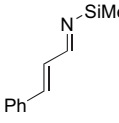
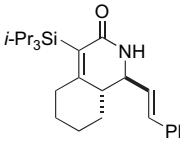
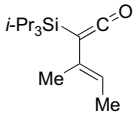
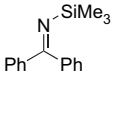
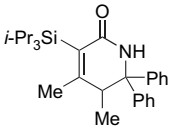
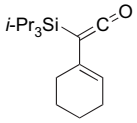
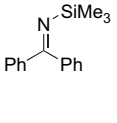
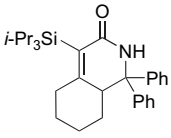
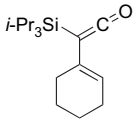
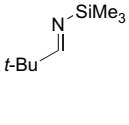
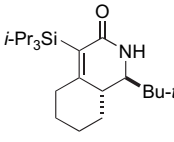
Scheme 93. β- and γ-Lactam formation from ketenes and 1,3-diaza-1,3-butadienes.



R	R^1	R^2	Yield %	R	R^1	R^2	Yield %
Me	$BnCH_2$	Et	76	Me	*n*-Pr	Bn	67
Me	*c*-C_6H_{11}	Et	75	Me	*i*-$PrCH_2$	Bn	74
Me	$BnOCH_2$	Et	51	Et	*i*-$PrCH_2$	Bn	72
Et	$BnCH_2$	Et	68	*n*-Pr	$BnCH_2$	Bn	58
Bn	$BnCH_2$	Et	65	*i*-Pr	$BnCH_2$	Bn	63
Me	Ph	Et	59	Et	Ph	Bn	59

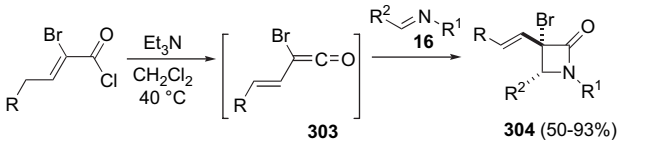
Scheme 94. Thiazin-6-one formation from ketenes and *N*-thioacylimines.

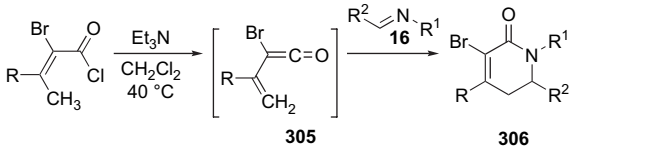


301	imine	302	Yield (%)
			79-83
			76
			91
			84
			78
			73
			79
			66
			56

Scheme 95. [4+2] Cycloaddition of vinylketenes with silyl imines.

1,3-dialkylimidazolidines **322** (21%, R=Et; 8%, R=*n*-Pr).[99a] The reaction was proposed to involve addition of the ketene to the diaziridine forming zwitterions **319**, which both cleaved to **320** followed by capture by **1** forming β-lactams **321**, and also underwent ring expansion forming 1,3-dialkylimidazolidines **322** (Scheme 100). Reactions of **1** or arylketenes **53** generated in

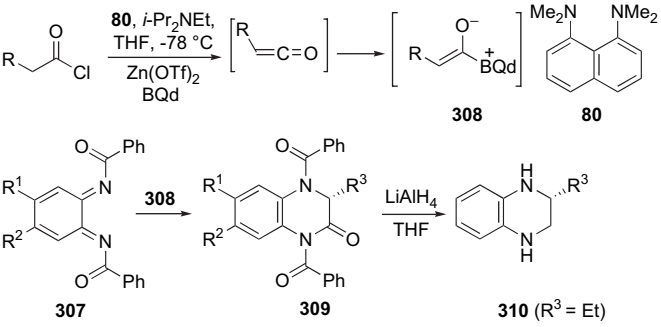




R	R^1	R^2	Yield % **306**	R	R^1	R^2	Yield % **306**
Me	Bn	Ph	92	Me	$(CH_2)_2CO_2Me$	Ph	64
Me	CH_2PMP	Ph	92	Me	$CH_2CH{=}CH_2$	Ph	96
Me	Bn	PMP	94	*n*-Pr	Bn	Ph	94
Me	CH_2CO_2Et	Ph	34				

Scheme 96. [4+2] Cycloaddition of bromo(vinyl)ketenes with imines.

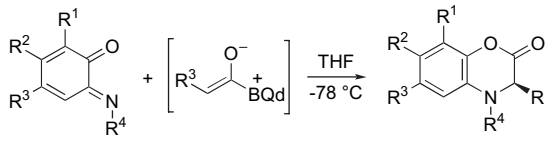
situ from −30 °C to room temperature with **318** gave only 1,3-dialkylimidazolidines **322** or **323**, respectively (Scheme 100).[99a] The reaction was also studied by computational methods.[99b]



R^1,R^2	R	% yield	R^1,R^2	R	% yield
Cl, Cl	Et	82	CF_3,H	*i*-Bu	83
Cl, Cl	*i*-Pr	79	CF_3,H	Bn	77
Cl, Cl	CH_2SMe	84	CF_3,H	4-BrBn	78
Cl, Cl	$(CH_2)_3Cl$	81	COPh,H	Et	84
Cl, Cl	Bn	85	COPh,H	*i*-Pr	84
Cl, Cl	CH_2NPhth	93	COPh,H	*i*-Bu	84
H,H	Et	76	COPh,H	CH_2SMe	92
H,H	*i*-Pr	71	COPh,H	$(CH_2)_3Cl$	87
H,H	*i*-Bu	73	COPh,H	Bn	86
H,H	Bn	83	COPh,H	CH_2NPhth	90
CF_3,H	Et	81	COPh,H	4-BrBn	69
CF_3,H	*i*-Pr	79	COPh,H	4-BrBn	72[a]

[a]Benzoylquinine catalyst

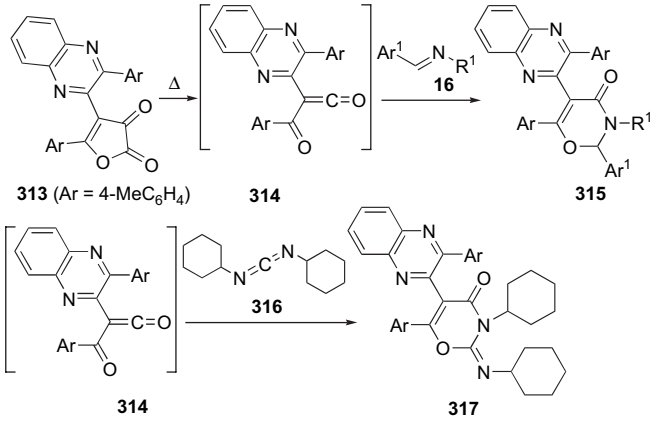
Scheme 97. [4+2] Cycloaddition of ketene enolates with *ortho*-benzoquinone diimides.



311 308 312

R	R^1	R^2	R^3	R^4	Yield (%) *ee* (%)	R	R^1	R^2	R^3	R^4	Yield (%) *ee* (%)
i-Bu	H	Cl	Cl	PNB	65, >99	Et	H	H	CF_3	PNB	62, >99
Bn	Cl	Me	Cl	Fmoc	63, >99	Bn	H	H	*t*-Bu	PNB	61, >99

Scheme 98. [4+2] Cycloaddition of ketene enolates with *ortho*-benzoquinone diimides.



Reaction with imines 16

Ar^1	R^1	Yield %	Ar^1	R^1	Yield %
4-BrC_6H_4	4-$MeOC_6H_4$	88	4-$MeOC_6H_4$	4-BrC_6H_4	86
4-FC_6H_4	4-MeC_6H_4	86			

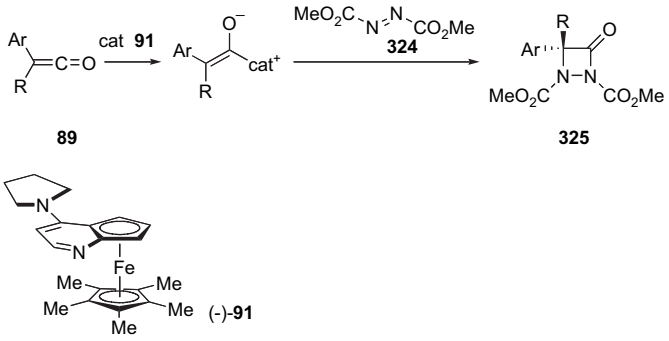
Reaction with carbodimide 316

Ar	Yield %	Ar	Yield (%)
Ph	82	4-MeC_6H_4	78

Scheme 99. Acylketene reaction with imines.

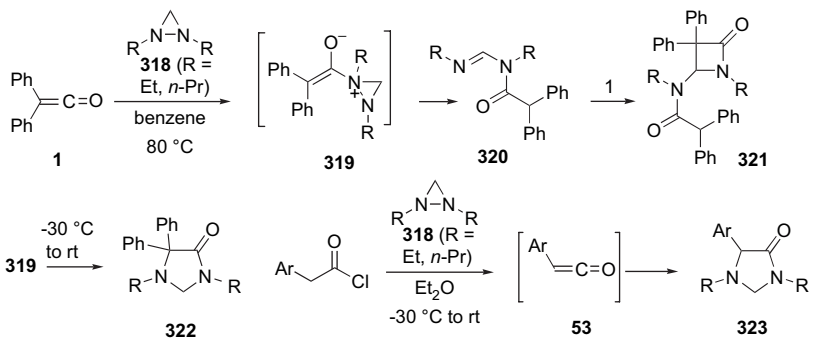
7. Ketene [2+2] cycloaddition with azo compounds

Ketene reactions with azo compounds (diazenes) forming aza-β-lactams were reported by Staudinger in 1912,[101a] and a number of examples have been reported.[101b-f] Recently the reaction of ketenes **89** with dimethyl azodicarboxylate (**324**) catalyzed by (-)-**91** has been found to give aza-β-lactams **325** in good yields and enantioselectivities (Scheme 101).[101g] The proposed mechanism corresponds to that for ketene-imine cycloadditions (Scheme 30).[31a,b]



Ar	R	*ee* (%)	Yield (%)	Ar	R	*ee* (%)	Yield (%)
Ph	Me	85	53	Ph	*c*-Pn	86	84
Ph	Et	86	89	Ph	*c*-Hx	94	90
3-MeC_6H_5	Et	85	79	Ph	*i*-Pr	95	91
2-MeC_6H_5	Et	67	46	4-$MeOC_6H_5$	*i*-Pr	96	91
2-$MeOC_6H_5$	Et	93	89	4-ClC_6H_5	*i*-Pr	92	90
Ph	Bn	81	73	3-Thienyl	*i*-Pr	96	90
Ph	*i*-Bu	83	87				

Scheme 101. Stereoselective ketene-diazene [2+2] cycloaddition.



Ar	R	Yield **319** (%)	Ar	R	Yield **319** (%)
4-MeC_6H_4	Et	40	4-BrC_6H_4	*n*-Pr	46
4-ClC_6H_4	Et	57	2-$O_2NC_6H_4$	Et	51

Scheme 100. β-Lactams and 1,3-imidazolidines from diaziridines and ketenes.

8. Outlook

As the [2+2] cycloaddition of ketenes and imines forming β-lactams and related structures enters its second century of active study the therapeutic and synthetic applications of this family combined with the investigative creativity of chemists worldwide guarantees a bright future for the study of this reaction. Many further studies of bis(β-lactams) and spiro β-lactams, as well as advances in both experimental and mechanistic study, may be anticipated.

Acknowledgements

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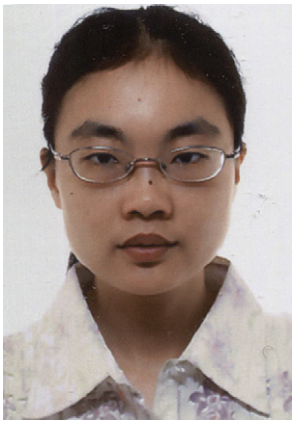
Biographical sketch



Nanyan Fu was born in 1973 in Quanzhou, Fujian, China, and studied chemistry at Nankai University, China, where she received B.Sc. degree in 1996. During 1996–1999 she studied organic chemistry at Perking University, China, under the direction of Professor Jiaxi Xu and received her M.Sc. degree in 1999 in the field of synthetic methodology of phosphonopeptides. She received her Ph.D. degree at Nankai University under the supervision of Professor Jitao Wang in 2002, completing her doctoral thesis on the application of indium tribromide, a green Lewis acid, in organic synthesis. She carried out postdoctoral research in Professor H.N.C. Wong's group at the Chinese University of Hong Kong, Hong Kong SAR, and with Professor T. T. Tidwell's group at the University of Toronto, Canada, where she initiated her research projects in the field of ketene chemistry. Since 2007 she has been professor in Fuzhou University, China, with research interests in ketene chemistry, reactive intermediate studies and synthetic methodology.

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