Formation of Four-membered Heterocycles

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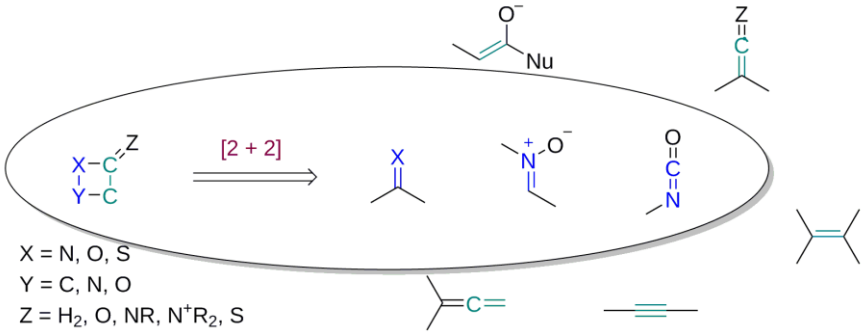
Abstract: This Chapter focuses on developments in [2 + 2] cycloadditions leading to four-membered heterocycles (β-lactams, β-lactones, β-sultams, azetidines,...). A special attention is drawn to the mechanistic aspects of the reactions and their consequences on the stereochemical outcome of the cycloaddition processes. Accordingly, the subdivision in sections reflects this point of view: the entries are related to reactions of various reagents (ketenes, enolates, ynolates, isocyanates, etc) with C=X bonds instead of a list of types of heterocycles. The emphasis is also put on asymmetric catalysis, which is of particular interest for the enantioselective synthesis of biologically active compounds or their precursors.

Graphical abstract:



Keywords: [2 + 2] cycloaddition, enolate, heteroallene, heterocycle, imine, ketene, β-lactam, β-lactone, Staudinger reaction, ynolate.

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Glossary:

- **Allene**: Compounds having two double bonds from one atom to two others. It can be a hydrocarbon ($R_2C=C=CR_2$) or a derivatives formed by substitution ($R_2X=Y=ZR_2$).

- **Hünig's base**: Organic compound having the structure *N*,*N*-diisopropylethylamine (DIPEA). It is used as a sterically hindered, hence poorly nucleophilic, base in organic chemistry.

- **Ketene**: Organic compound in which a carbonyl group is connected by a double bond to an alkylidene group, $R_2C=C=O$.

- **β-Lactam**: four-membered cyclic amide having a 1-azacyclobutan-2-one (2-azetidinone) structure.

- **β-Lactone**: four-membered cyclic ester having a 1-oxacyclobutan-2-one (oxetan-2-one) structure.

- **Zwitterion**: Neutral compound having formal unit electrical charges of opposite sign at different locations within that compound, sometimes referred to as inner salts or dipolar anion.

Key points:

- Synthetic strategies toward β-lactams using [2 + 2] cycloadditions
- Synthetic strategies toward β- lactones using [2 + 2] cycloadditions
- Synthetic strategies toward β- sultams using [2 + 2] cycloadditions
- Synthetic strategies toward β- sultones using [2 + 2] cycloadditions
- Mechanisms of the [2 + 2] cycloadditions leading to four-membered heterocycles
- Applications

Abbreviations:

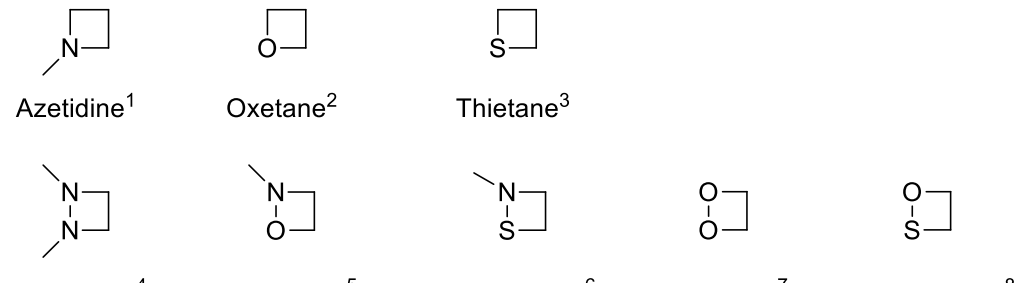
3CR	Three components reaction
All	Allyl
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bz	Benzoyl
Cbz	Carbobenzyloxy
CSI	Chlorosulfonyl isocyanate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DHQ	Dihydroquinine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
Dppb	1,4-*Bis*(diphenylphosphino)butane
EDG	Electron-donating group
EWG	Electron-withdrawing group
Fm	Fluoromethyl
Fmoc	9-Fluoromethoxycarbonyl
MAGL	Monoacylglycerol lipase
mCPBA	*m*-Chloroperbenzoic acid
MRSA	Methicillin resistant *Staphylococcus aureus*
Ms	Mesyl
NAAA	*N*-Acylethanolamine-hydrolyzing acid amidase
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
Nu	Nucleophile
OMP	*o*-Methoxyphenyl
PASP	Polymer-assisted solution-phase
PBP	Penicillin binding protein
PHB	Poly-(*R*)-3-hydroxybutyrate
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl ether
PMP	1,2,2,6,6-Pentamethylpiperidine
PTSA	*p*-Toluenesulfonic acid
Pyr	Pyridine
RGD	Arg-Gly-Asp
TBDMS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TMDA	Tetramethylamine azodicarboxylate
TMS	Trimethylsilyl
Tol-BINAP	2,2'-*Bis*(di-*p*-tolylphosphino)-1,1'-binaphthyl
Ts	Tosyl

Table of Contents

1. Introduction

This chapter is devoted to the formation of four-membered cycles containing at least one heteroatom, and obtained by combining π-systems through formal [2 + 2] cycloaddition reactions. Heat-activated and metal-, acid- or base-catalyzed reactions will be considered here, while the photochemical cycloadditions are discussed in another Chapter.

There are several classes of four-membered heterocycles (Scheme 1).[1,2,3,4,5,6,7,8] The considerable attention focused on these heterocycles originates from the discovery of penicillins,[9] cephalosporins,[10] and related antibiotics[11] which feature a β-lactam (azetidin-2-one) ring in their core structures. The β-lactone (oxetan-2-one) ring is also found as an important structural feature in several biologically active compounds.



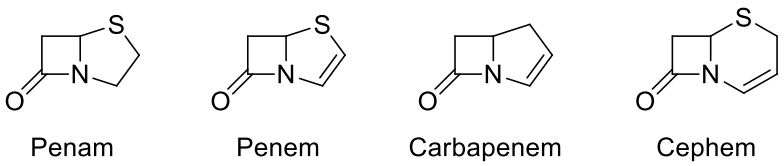
< **Scheme 1** near here>

The functionalities involved in four-membered heterocycles are endowed with increased reactivity resulting from the ring strain.[12,13,14] Accordingly these molecules can be exploited as building blocks in organic synthesis, in particular when regio-, stereo-, and enantio-selectivities have to be controlled.[15,16,17,18,19]

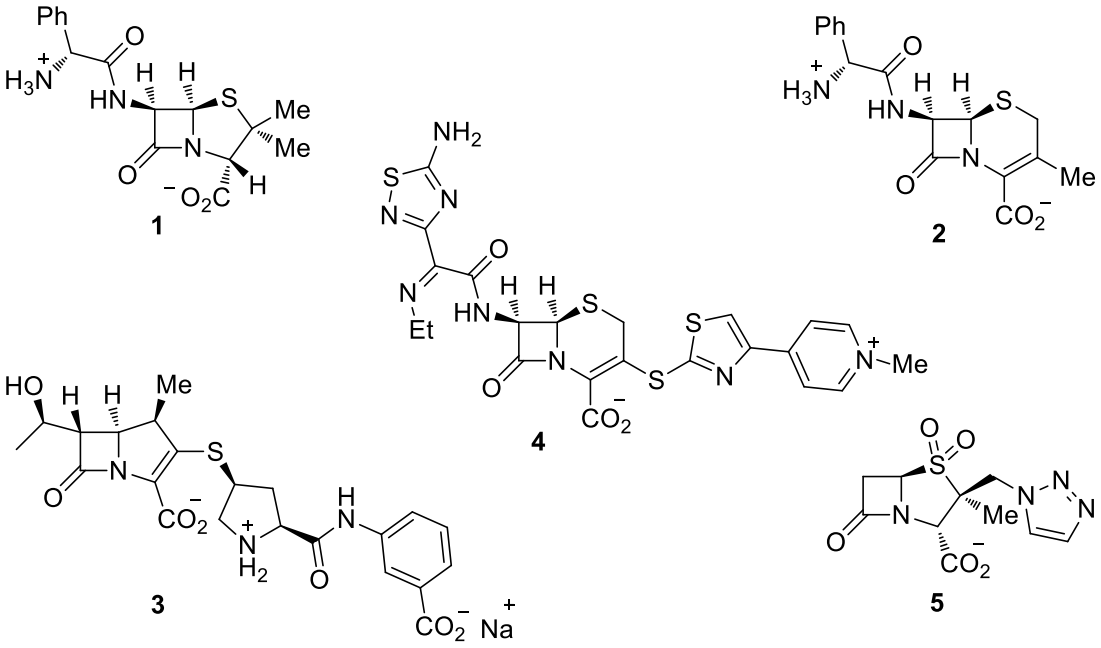
A brief survey of the above mentioned important aspects, lying outside the scope of this section, is presented as the introduction.

1.1. Four membered heterocycles as biologically active compounds

The antibiotics belonging to the so-called β-lactam class are still the most prescribed ones against bacterial infections.[20] Several sub-classes exist depending on the nature of the five- or six-membered fused rings (Scheme 2).[9,10,11] Due to the increasing bacterial resistance to early drugs, such as ampicillin **1** and cephalexin **2**, increasingly sophisticated derivatives have been developed as illustrated with ertapenam **3**[21] and ceftarolin **4**.[22] These β-lactams are active against MRSA (methicillin resistant *Staphylococcus aureus*) responsible of nocosomial infections in hospitals (Scheme 3). Another way to fight resistant bacteria is the administration of a traditional penicillin (ampicillin for instance) together with an inhibitor of β-lactamases (*i.e.* bacterial defense enzymes), such as tazobactam **5**.[23,24]

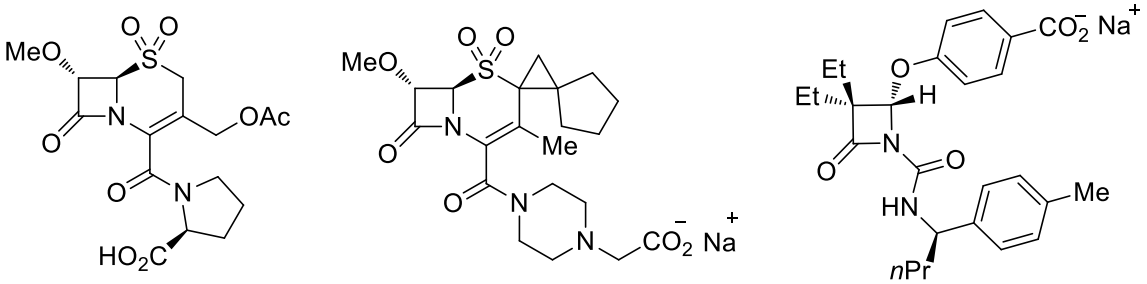


< **Scheme 2** near here>



< **Scheme 3** near here>

The mode of action of the β-lactam antibiotics as well as the resistance mechanisms have been intensively studied.[20,25] The structures of several bacterial target-enzymes are known at the atomic level, thus allowing the rational design of novel β-lactams acting as inhibitors of the so-called PBPs (Penicillin Binding Proteins).[26,27] Since these enzymes are serine proteases (DD, transpeptidases-carboxypeptidases involved in the bacterial cell wall biosynthesis), the β-lactam motif became considered by the medicinal chemists as a common pharmacophore for the inhibition of other serine-enzymes playing a key role in numerous diseases. For instance, human leukocyte elastase inhibitors L-658,758 (**6**)[28] and SYN-1390 (**7**)[29], used in aerosols for the treatment of allergy, are structurally related to the cephem antibiotics (Scheme 4). Orally bioavailable anti-inflammatory drugs, such as L-680,833 (**8**) are simple monocyclic β-lactams.[30]



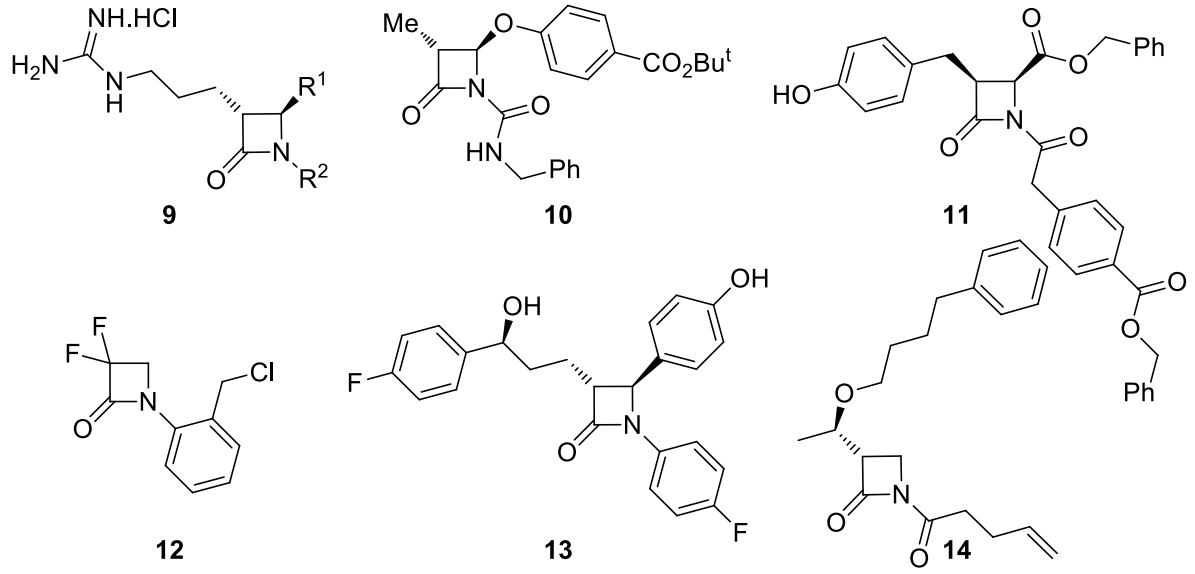
L-658, 758
6

Syn-1390
7

L-680, 833
8

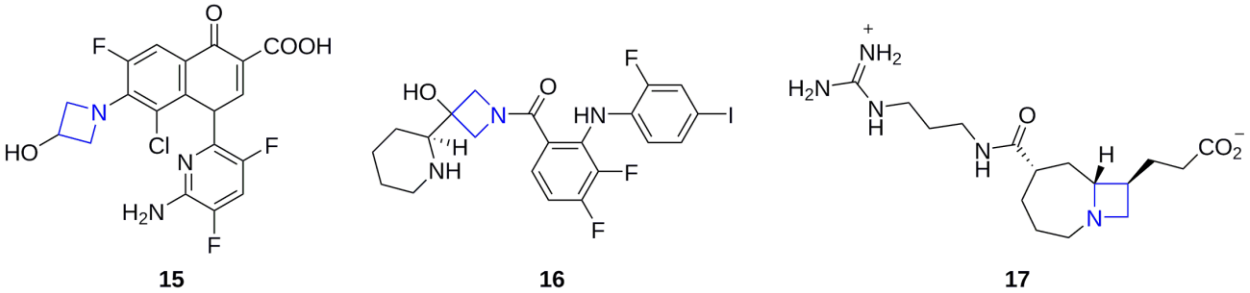
< **Scheme 4** near here>

A lot of monocyclic β-lactams[31,32,33,34,35,36,37] have been disclosed for the inhibition of thrombin (for example, **9**),[38] human cytomegalovirus protease (for example, **10**),[39] prostate specific antigen (for example, **11**),[40] β-lactamases (for example, **12**),[41] cholesterol absorption (for example, **13**)[42] and fatty acid amide hydrolase (for example, **14**),[43,44,45] among others (Scheme 5).



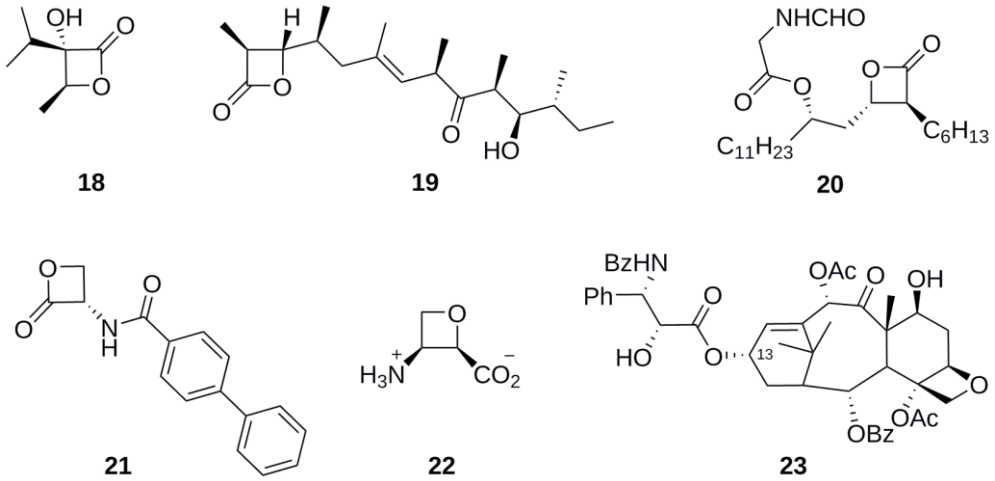
< **Scheme 5** near here>

Azetidine structure is also a privileged motif in medicinal chemistry showing mostly antibacterial (for example, **15**)[46] or anticancer (for example, **16**)[47] activities (Scheme 6). β-Turn mimicks for the construction of Arg-Gly-Asp (RGD) peptidomimetics are based on bicyclic azetines **17**.[48]



< **Scheme 6** near here>

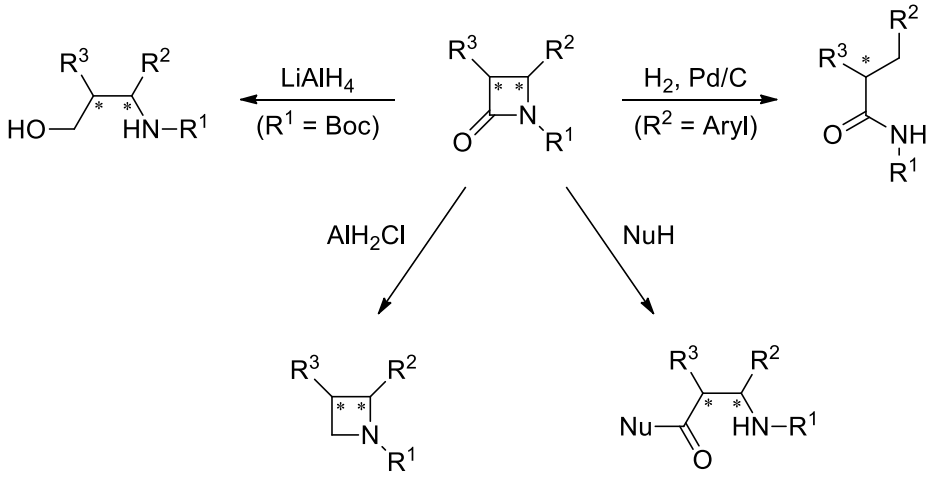
β-Lactones found in nature are pheromones (**18**),[49] esterase inhibitors (**19**),[50] etc. Synthetic derivatives have been designed for the inhibition of pancreatic lipase,[51] monoacylglycerol lipase (MAGL) (**20**),[52] and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) (**21**),[53] as examples (Scheme 7). Antimicrobial (**22**)[54] and anti-cancer drugs (**23**, paclitaxel)[55] feature an oxetane ring. The synthetic analog with a thietane ring (Taxol-thietane) has also been prepared.[56]



< **Scheme 7** near here>

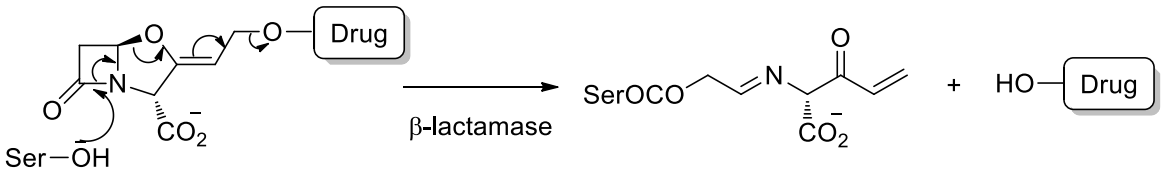
1.2. Four-membered heterocycles as reactive intermediates

Chiral β-lactams are useful precursors of azetines, amides, and 1,3-aminoalcohols, with preserved chirality, by selective reduction of the C_2 carbonyl, N_1-C_4 bond (R^2 = aryl) and C_2-N_1 bond (R^1 = Boc), respectively (Scheme 8).[57,58] Nevertheless, the main applications concern the nucleophilic addition on the C_2 carbonyl group accompanied with the C_2-N_1 bond cleavage leading to chiral β-aminoacid derivatives (Scheme 8).[1,15] The β-lactam function can also be broken by basic or acidic hydrolysis. A general strategy to produce enantiopure, non proteogenic α,β-diaminoacids makes use of β-lactam precursors.[59]

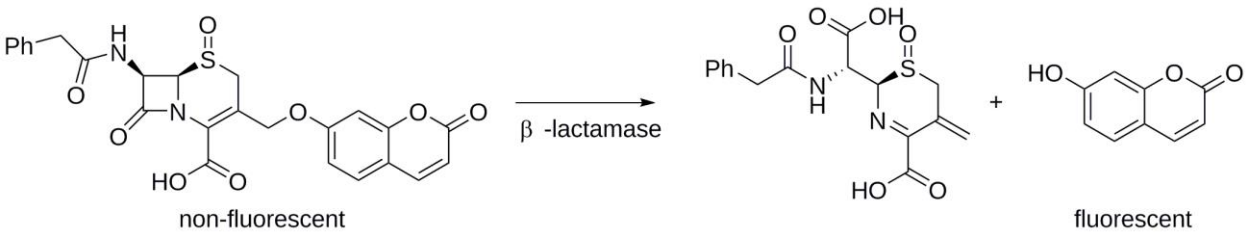


< **Scheme 8** near here>

The processing of β-lactams by serine-enzymes has been used for the design of pro-drugs. The drug of interest is coupled to a bicyclic β-lactam that is sensitive to β-lactamases; this conjugate is inactive. The enzymatic hydrolysis of the β-lactam core liberates the active drug on the site of infection. Equation 1 illustrates one example of drug delivery based on this strategy.[60,61] A similar approach is also used to release a chromophore enabling to probe β-lactamase activity and inhibition (Equation 2).[62]

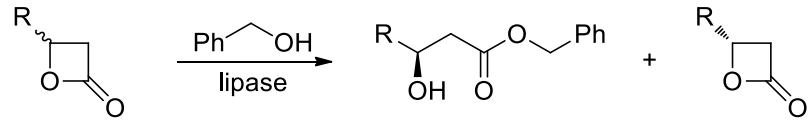


< **Equation 1** near here>

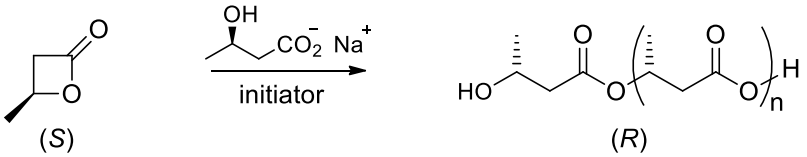


< **Equation 2** near here>

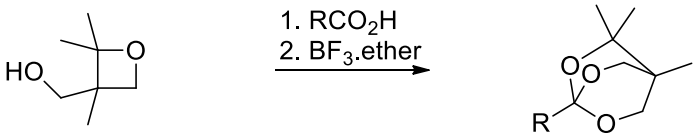
β-Lactones are very sensitive to nucleophilic attack and ring opening. An interesting kinetic resolution has been achieved *via* a lipase-promoted asymmetric transesterification with benzyl alcohol (O_1-C_2 bond cleavage) (Equation 3).[63] Anionic polymerization of β-lactones occurs *via* the O_1-C_4 bond cleavage. The nucleophilic attack on C_4 (S_N2 reaction) has been established by the inversion of configuration at this stereocenter: (*S*)-β-butyrolactone leads to the formation of poly-(*R*)-3-hydroxybutyrate (PHB) (Equation 4).[64] The most commonly used method to synthesize polyethers is the cationic ring opening polymerization of oxetanes.[65] Another example of acid-catalyzed ring opening of oxetanes is given by the synthesis of *ortho*-esters as the protection of carboxylic acids (Equation 5).[66,67]



< **Equation 3** near here>



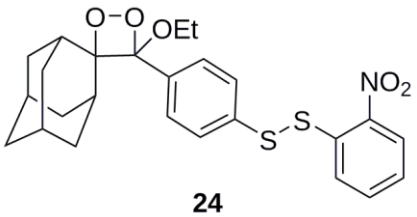
< **Equation 4** near here>



< **Equation 5** near here>

Chemiluminescent probes based on the dioxetane moiety are commonly used in molecular biology.[68] The simultaneous O_1-O_2 and C_3-C_4 bond cleavage give carbonyl species at the excited state, the deactivation of which produces light. Scheme 9 depicts the molecules **24** and **25** behind the bioassays for detection of cholin esterase and alkaline phosphatase activities, respectively.[69,70] Bioluminescent assays using a luciferase substrate are based on the

in situ formation of a dioxetanone, which decomposes into CO_2 and an excited carbonyl species emitting light under decay.[71]



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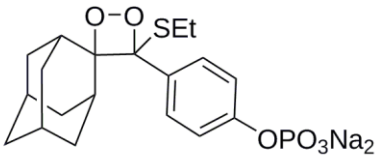

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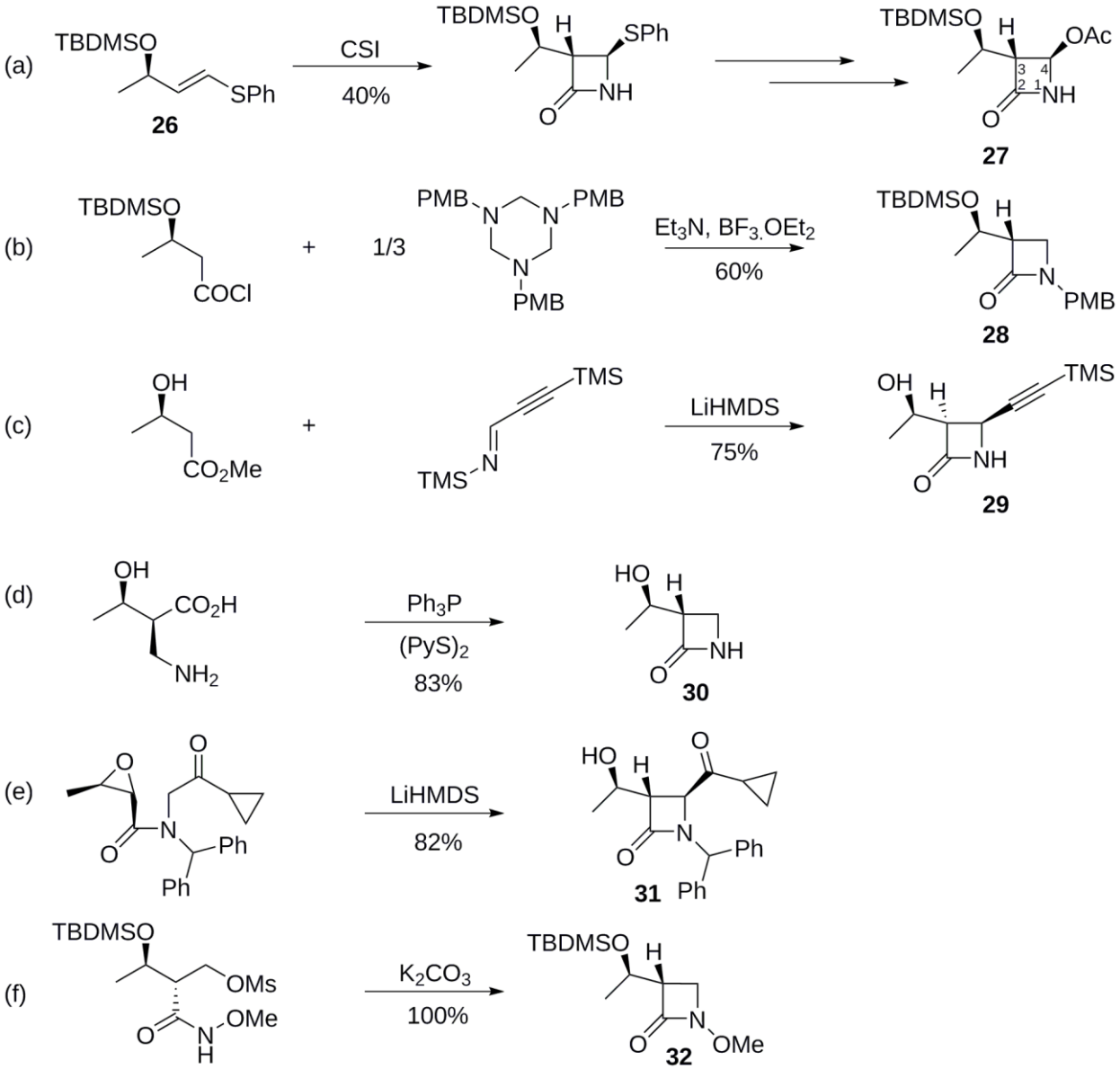
< **Scheme 9** near here>

1.3. Strategies for the preparation of four-membered heterocycles

The various strategies exploited for the synthesis of four-membered heterocycles are exemplified here with the preparation of acetoxy-azetidinone **27**, the industrial starting material of all the (carba)penem antibiotics (Scheme 10).[72,73,74] Usually, the chirality is introduced by using enantiomerically pure reagents and controlled reaction mechanisms. A first route (a) is based on the [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) onto the *trans*-phenylthio-alkene **26**,[75] thus forming concomitantly the C_2-C_3 and N_1-C_4 bonds. The [2 + 2] cycloaddition of ketenes or enolates to Schiff bases constitutes other main routes (b)[76] and (c),[77] leading to the simultaneous formation of C_3-C_4 and C_2-N_1 bonds. The cyclization reactions cover the C_2-N_1 bond formation from β-aminoacid precursors[78] (route (d)), the C_3-C_4 bond formation by intramolecular S_N2 reactions[79] (route (e)), and the Miller process for creating the N_1-C_4 bond (route (f)) from hydroxylamide derivatives.[80] All the chiral β-lactams **28** to **32** are precursors of the key building block **27**: the process (a) and (d) have been developed at pharmaceutical production scale.



< **Scheme 10** near here>

Beside these three [2 + 2] cycloaddition strategies and three cyclization approaches, the carbonylation of aziridines offers a practical access to β-lactams,[81,82,83,84] *via* a ring expansion reaction. Rearrangement of isoxazolidines (obtained by 1,3-dipolar cycloaddition of nitrones to alkynes, see Section 7) leads to β-lactams by a ring-contraction known as the Kinugasa reaction.[85,86,87,88]

Similarly, β-lactones are prepared by [2 + 2] cycloadditions of aldehydes to ketenes[89,90] or enolates,[91,92] and by lactonisation, *i.e.* O_1-C_2 cyclization from adequately β-substituted carboxylic derivatives,[93,94] as the principal strategies.

1.4. Aim of the review

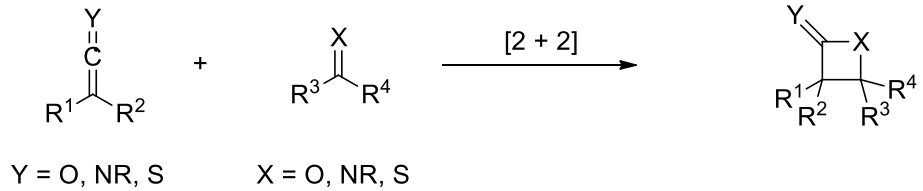
A recent volume of the CHC series (Comprehensive Heterocyclic Chemistry IV, 2022) edited by D. StC Black, J. Cossy and C. V. Stevens covers extensively the chemistry of four-membered heterocycles and all fused systems with a four-membered heterocyclic ring. The synthetic strategies other than the cycloadditions, namely various cyclization methods, ring

expansion and ring contraction methods, are discussed in an exhaustive manner for each class of compounds.

The present review, which is an updated version of the previous one in the second edition of this series (Comprehensive Organic Synthesis 2014, Vol. 5), focuses on new developments in [2 + 2] cycloadditions leading to four-membered heterocycles. A special attention is drawn to the mechanistic aspects of the reactions and their consequences on the stereochemical outcome of the cycloaddition processes. Accordingly, the subdivision in sections reflects this point of view: the entries are related to reactions of various reagents (ketenes, enolates, ynolates, isocyanates, etc) with C=X bonds instead of a list of types of heterocycles. The accent is also put on asymmetric catalysis which is of particular interest for the enantioselective synthesis of biologically active compounds or their precursors

2. Reaction of ketenes, ketenimines and thioketenes with C=X bonds

Heteroallenes of the type $R_2C=C=Y$ (Y = O, NR or S) are reactive intermediates which undergo [2 + 2] cycloaddition with C=X bonds to lead to the corresponding four-membered heterocycles (Equation 6).[95,96,97,98,99,100] Among these reactions, the most important is the [2 + 2] cycloaddition reaction between ketenes and imines, known as the Staudinger cycloaddition (Y = O; X = NR).[101,102] Ketenes are also reported to react with carbonyls and thiocarbonyls, leading to corresponding 2-oxetanones and 2-thietanones.[97]



< **Equation 6** near here>

Ketenimines and thioketenes (Y = NR and S) have received less attention.[103,104,105] In the former case, the reason is the low reactivity of such heteroallenes while, for thioketenes, it is their instability and the difficulty to prepare them which explain the dearth of examples.

Most disubstituted ketenes are stable intermediates which can be isolated. Monosubstituted and heterosubstituted ketenes on the contrary have limited stability (prone to polymerize).[106] Accordingly, ketenes are usually generated *in situ*, from the corresponding acyl chlorides or related derivatives in the presence of a base, by photolysis of metal-carbene complexes, or by rearrangement of α-diazocarbonyl compounds.[107,108,109] It is important to note however that the conditions for generating ketenes may have an influence on the mechanism and the stereochemical outcome of the reaction (vide infra).

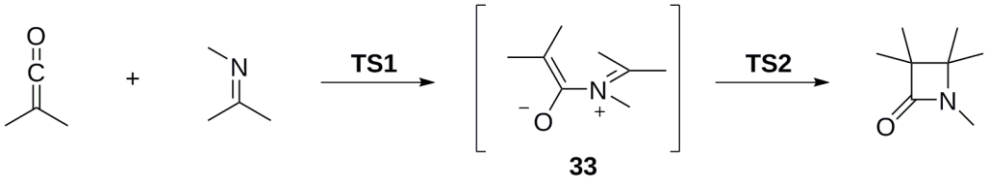
2.1. Reaction with imines

The most developed reaction of ketenes is their [2 + 2] cycloaddition with imines, known as the Staudinger cycloaddition.[101,102] This reaction is the most widely used strategy for the preparation of β-lactams.[110,111,112,113] The relevance of this method is due to its convergent nature, the readily access to reagents, and the wide range of β-lactams thus available.

2.1.1. Mechanism

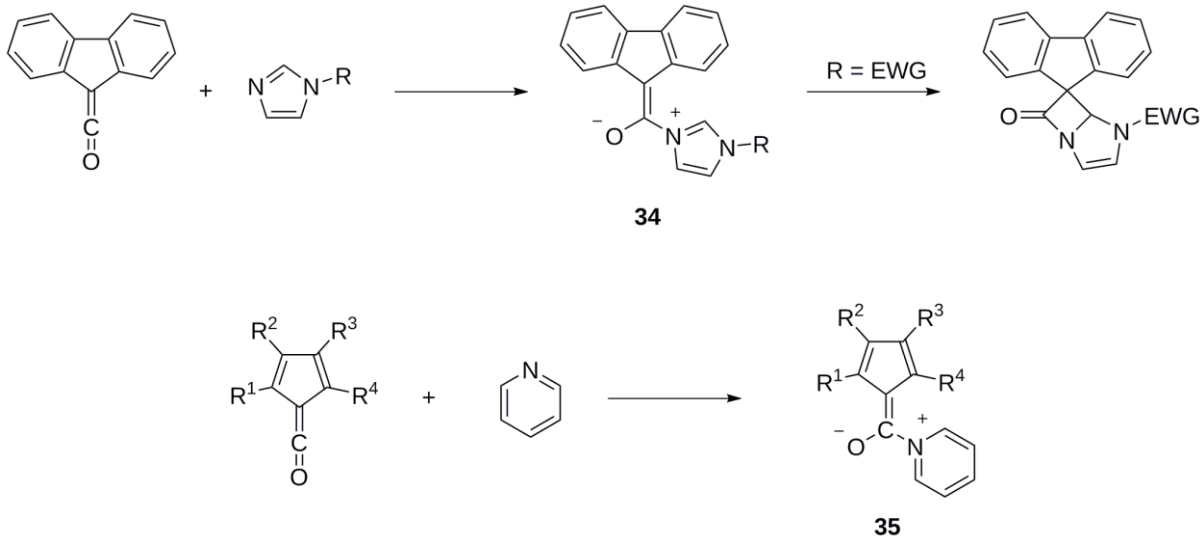
The ketene-imine Staudinger reaction is a [2 + 2] cycloaddition. These cycloadditions are allowed by the Woodward-Hoffmann rules, provided that the approach of the π-systems occurs in a *supra-antara* mode ($[_\pi2_s + _\pi2_a]$).[114] There are, however, abundant experimental evidences showing that the mechanism in solution is not concerted but is instead a stepwise process.[112,113]

The accepted mechanism for these reactions involves initial formation of a zwitterionic intermediate (**31**) by addition of the imine nitrogen atom to the central sp-hybridized carbon atom of the ketene (Scheme 11).[110,115] Subsequent intramolecular nucleophilic addition of the so-formed enolate function onto the iminium leads then to the β-lactam.

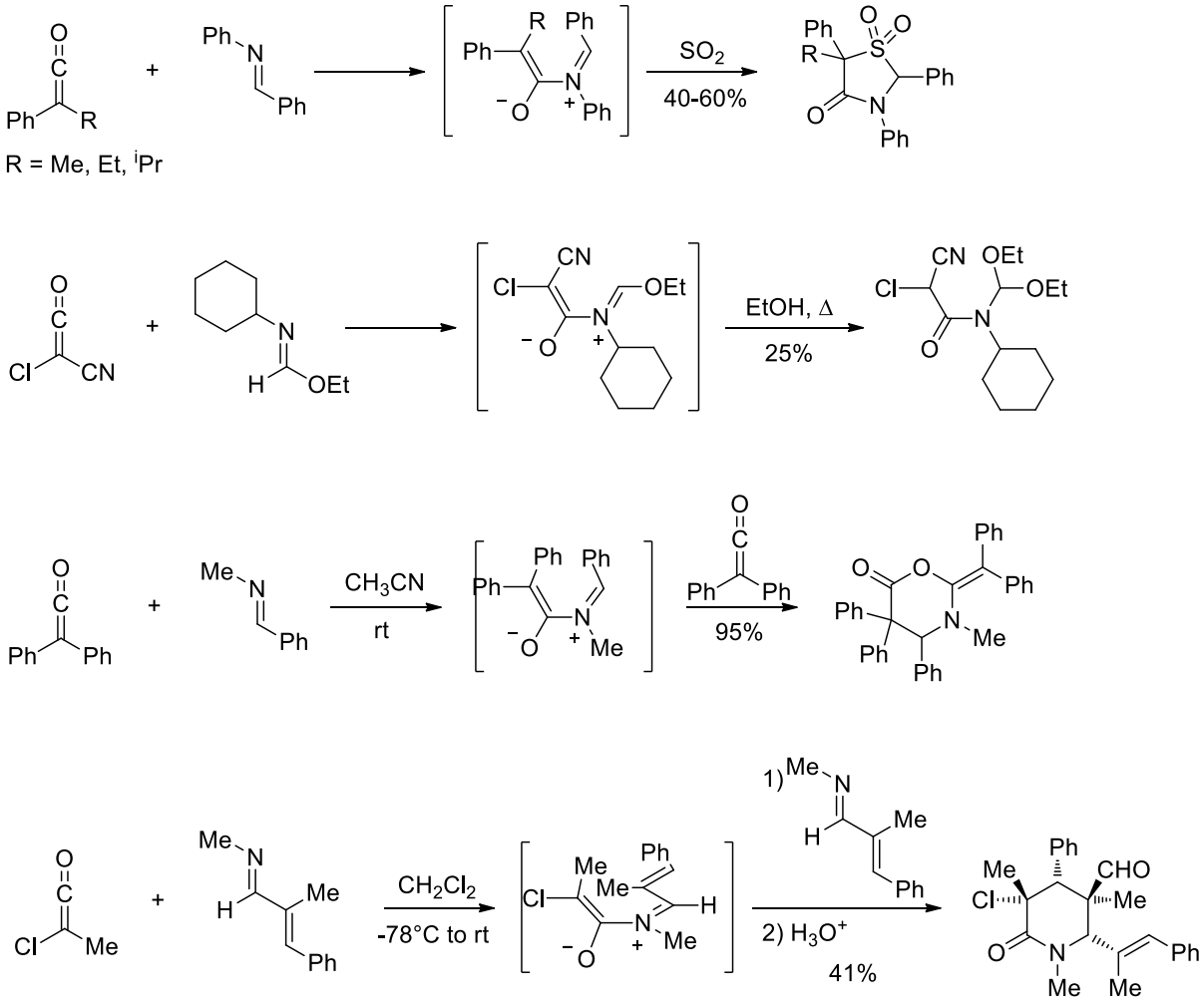


< **Scheme 11** near here>

This mechanism has been confirmed by isolation and characterization of zwitterionic intermediates **34** and **35** in the reaction of stabilized ketenes with imidazoles and pyridine, respectively (Scheme 12).[116,117] In several cases, the zwitterionic intermediate could also be trapped by sulfur dioxide,[118] ethanol,[119] a second equivalent of ketene,[120] or a dienophile[121] (Scheme 13).

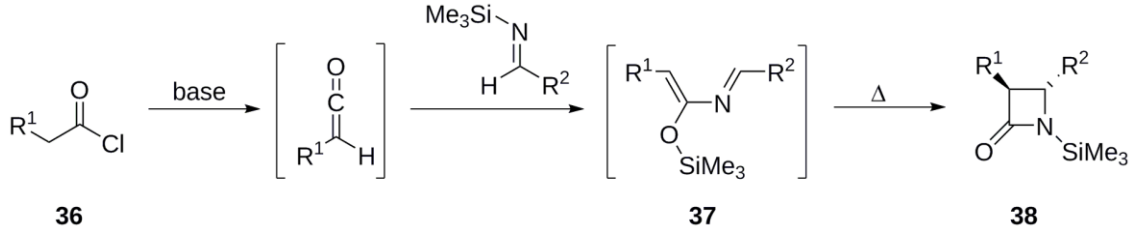


< **Scheme 12** near here>



< **Scheme 13** near here>

Additionally, in the reaction of monosubstituted ketenes and *N*-silylimines, the unambiguous formation of 3-aza-1,3-dienes **37** has been reported.[122,123,124,125] These intermediates were completely characterized and found to yield the corresponding *N*-silyl-β-lactams **38** upon heating (Scheme 14).

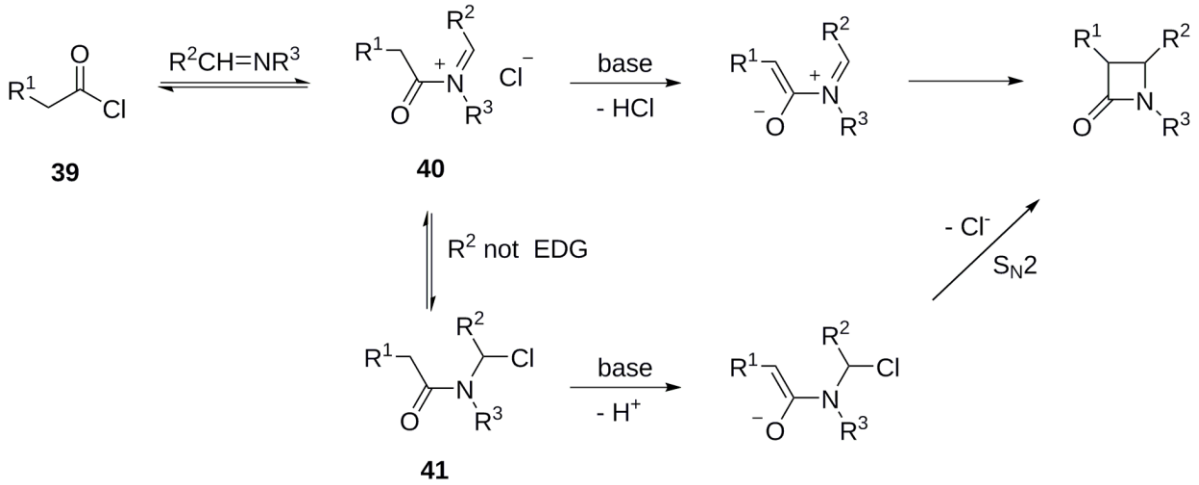


36 **37** **38**

< **Scheme 14** near here>

The two-step mechanism is also supported by computational results.[110,126] It is important to note that inclusion of solvent effects in the calculations of the mechanism was found to be crucial; calculations in the gas phase point to a concerted mechanism. It is also worth mentioning that calculations indicate that addition of the imine onto the ketene is reversible, with electrocyclization being the rate-determining step of the process.[127,128,126]

Xu *et al.* have shown that in some cases (when the acyl chloride is used as starting reactant), depending on the mode of addition of reagents, the mechanism may vary.[107,129] Indeed, when the acyl chloride is added to a solution of imine and a base, the ketene is directly formed and the reaction pathway follows the one described in Scheme 12. On the other hand, when the base is added to a solution of an imine and an acyl chloride, direct addition of the imine onto the acyl chloride (prior to ketene formation) produces an acyl iminium chloride **37** (Scheme 15). In most cases, this acyl iminium chloride undergoes a hydrogen abstraction to lead to the zwitterionic intermediate which further produces the β-lactam as in the general mechanism. In some specific cases (when the solution of the imine and the acyl chloride is stirred for several hours prior to addition of the base, and the imine is not substituted by a strong electron-donating substituent, EDG) addition of chloride has been shown to occur, producing the corresponding chloro amide (**38**). Subsequent deprotonation and intramolecular alkylation (via a S_N2 mechanism) then leads to the β-lactam.



39 **40** **41**

< **Scheme 15** near here>

The mechanism thus depends on the substitution of the reactants and on the reaction conditions. This is of particular importance since the nature of the pathway has an impact on the stereochemical outcome of the reaction (vide infra).

The reaction can also be catalyzed by Lewis acids or nucleophiles (tertiary amines or *N*-heterocyclic carbenes). In the former case, mechanistic studies indicate that activation occurs through complexation of the ketene (see Section 2.2.3.).[130] In nucleophile-catalyzed reactions, the nucleophile adds first to the ketene to form an enolate which then reacts with the imine.[131,132] The imine-enolate condensation will be discussed in Section 4.

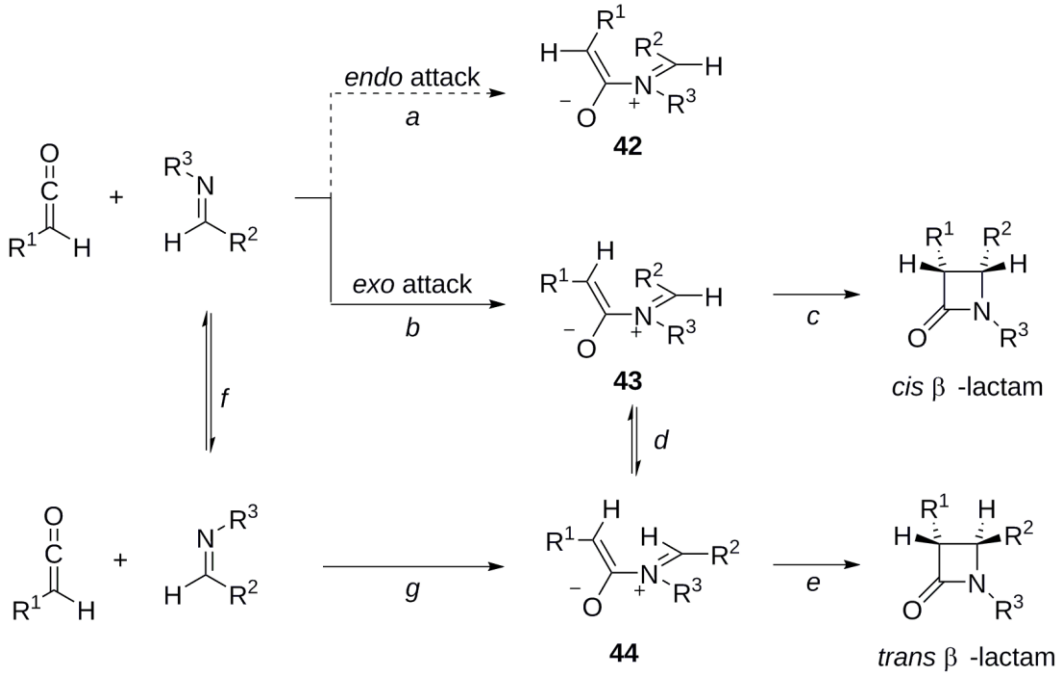
Reactions of ketenimines and thioketenes have been less studied.[133,134,135,136,137,138] On the other hand, mechanistic studies indicate that the [2 + 2] cycloaddition of these intermediates occurs via the same mechanism as for ketenes.[110]

2.1.2. Cis-trans Selectivity

The four-membered heterocycles formed by [2 + 2] cycloaddition of unsymmetrically substituted ketenes, ketenimines or thioketenes with imines possess two stereogenic centers, so four different stereoisomers can be produced. In order to obtain selectively one of these isomers, one needs to control both the relative (*cis/trans*) and the absolute stereochemistries of these two stereogenic centers.

The relative selectivity has been shown to depend on several factors such as the solvent used, the temperature, and the sequence of addition of the reactants.[110,127,129] Indeed, despite its formal simplicity, the stepwise mechanism of the reaction of ketenes and imines raises a complex stereochemical situation.

First, the initial nucleophilic attack of the nitrogen atom of the imine can occur either via the *endo* or the *exo* side of the ketene, leading to zwitterionic intermediate **42** or **43**, respectively (Scheme 16; pathway *a* or *b*).[139,115,110] Experimental studies showed, however, the exclusive formation of zwitterion **43**, resulting from an *exo* approach. This can be accounted for by steric considerations.[139]

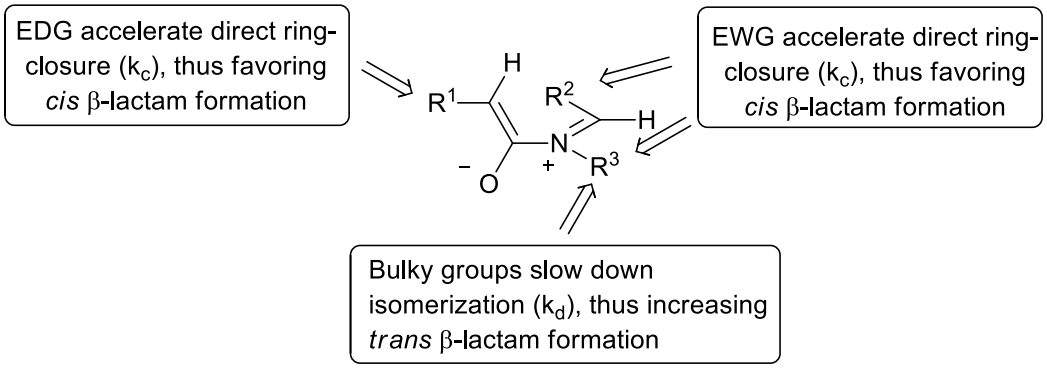


< **Scheme 16** near here>

Next, intermediates **43** and **44** undergo cyclization via an intramolecular nucleophilic addition[139,126] to form the corresponding *trans* and *cis* β-lactam, respectively.

Accordingly, variations in the selectivity can be accounted for by the relative rate of cyclization/isomerisation of the iminium in the zwitterions (k_c/k_d).[107,139]

In a series of systematic experimental studies, Xu *et al.* investigated the influence of several factors on the *cis/trans* selectivity in the reaction of ketenes with imines.[129139,140] These results showed that the nature of the substituents of the ketenes and imines (R^1, R^2 and R^3) is the crucial factor that determines the *cis/trans* selectivity of this reaction through their influence on the rate of the direct ring closure (k_c). Indeed, electron-donating groups on the ketene (R^1 = EDG) and electron-withdrawing imine substituents (R^2, R^3 = EWG) increase the nucleophilicity of the enolate moiety and the electrophilicity of the acyl-iminium group, respectively. This pattern of substitution thus accelerates the direct ring closure (increase k_c), and hence leads to a preference for *cis*-β-lactam formation (Figure 1). Conversely, electron-withdrawing ketene substituents and electron-donating substituents on the imine lower the rate of the ring closure (decrease k_c), thus allowing isomerisation (k_d) to take place before cyclization. In these cases, formation of the more stable *trans*-β-lactam is therefore observed (via pathway *e*). The electronic effect of the substituents on the rate of isomerization has been shown to be a minor factor in the stereoselectivity. On the contrary, the presence of a bulky group on the imine nitrogen (R^3) has a significant effect (slow down) on the rate of isomerization.



< **Figure 1** near here> : Factors influencing the *cis/trans* selectivity in the reaction of ketenes with imines

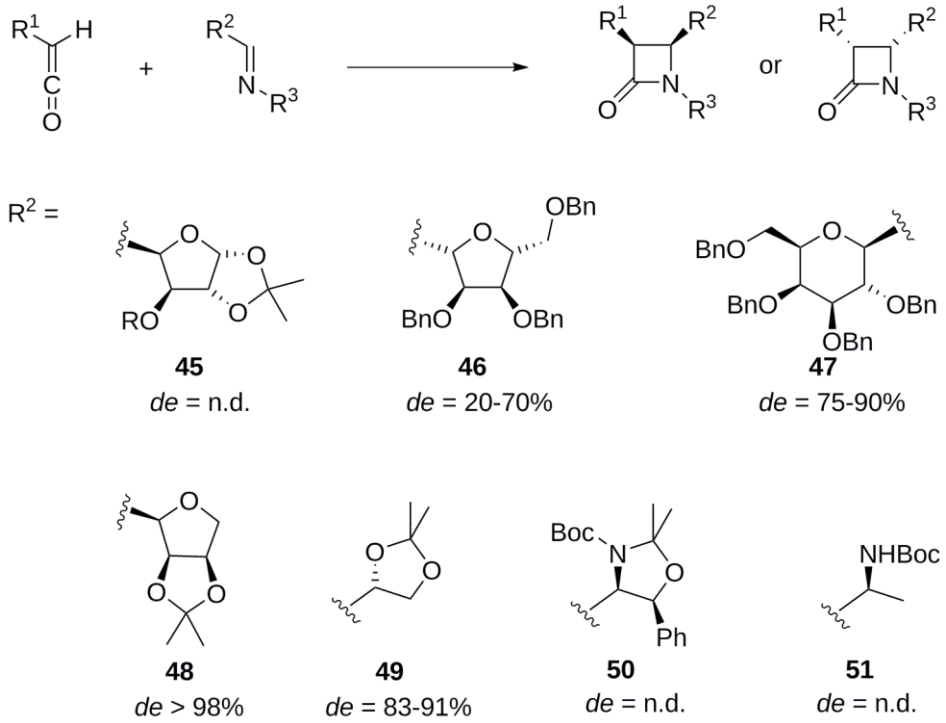
In some specific cases (when R^3 = anthracenyl), calculations have shown that the *E/Z* isomerization of the imine (pathway *f*) is faster than the addition ($k_f > k_b, k_g$). In these cases, the observed selective formation of *trans* isomer is thus accounted for by the addition of the more nucleophilic *Z*-imine onto the ketene yielding directly intermediate **41** (pathway *g*).[115,128]

Besides the main factor, which is the nature of the substituents, Xu *et al.* have shown that the reaction conditions (solvent, temperature, addition order of reagents, base,…) could also affect the stereochemical outcome of the Staudinger cycloaddition reaction.[107,129]

2.1.3. Reaction of chiral imines

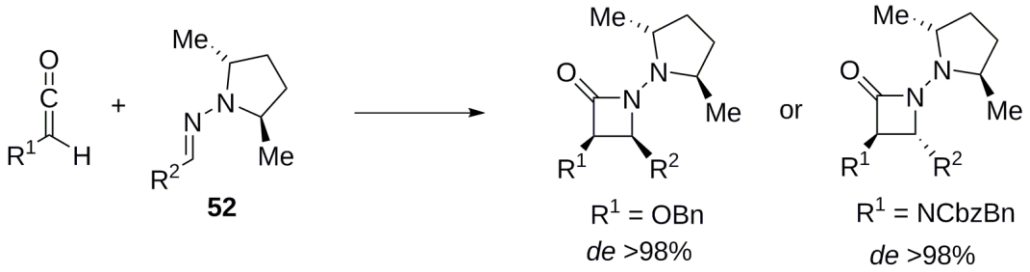
One of the strategies for controlling the absolute stereochemistry of the two stereocenters which are created in the reaction of unsymmetrically substituted ketenes and imines makes use of chiral imines, either derived from chiral aldehydes or from chiral amines.

In the former case, a common approach uses sugar aldehyde-derived imines such as **45**, **46**, and **47** (Scheme 17).[141,142] Other α-oxyimines, **48** and **49**, have also been used successfully.[127,143,144,145] Similarly, a wide variety of *N*-Boc-α-amino imines (such as **50** and **51**) have been reported to yield the corresponding *cis*-β-lactams with high diastereoselectivity.[113,146,147] The corresponding β-lactams are obtained in most cases as a single *cis* diastereoisomer after purification by column chromatography.



< **Scheme 17** near here>

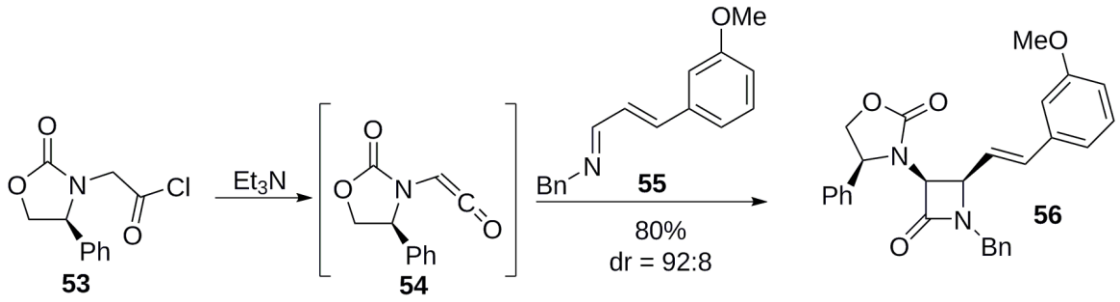
Imines bearing a chiral group on nitrogen have also been used for the asymmetric synthesis of chiral β-lactams (Equation 7). Enantiopure *N*,*N*-dialkylhydrazones **52** react with ketenes to yield the corresponding 3,4-disubstituted β-lactams as single diastereoisomers.[148,149] The *cis/trans* selectivity depends on the substitution of the ketene: alkoxyketenes lead to *cis* β-lactams with a very high selectivity, whereas cycloaddition of ketenes derived from *N*,*N*-disubstituted glycine occurs with a *trans* selectivity. Subsequent *N*-*N* bond cleavage under oxidative conditions allows the chiral auxiliary to be removed with formation of the corresponding NH β-lactams in high yields.



< **Equation 7** near here>

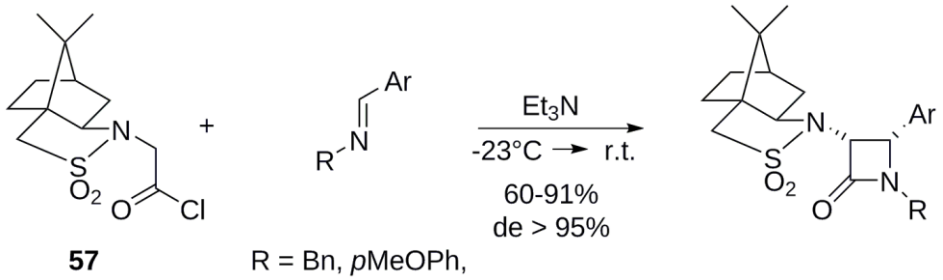
2.1.4. Reaction of chiral ketenes

Another strategy for the asymmetric synthesis of β-lactams is the [2 + 2] cycloaddition of imines with chiral ketenes.[111,113] The most widely used chiral ketene is 4-phenyloxazolidinylketene (**54**) (Evans-Sjögren ketene), generated from the corresponding oxazolidinylacetyl chloride (**53**) and triethylamine. As an example, the asymmetric synthesis of a carbasephem precursor from chiral ketene **54** and imine **55** has been described by D. Evans (Scheme 18).[150,151] After cycloaddition, the oxazolidinone auxiliary of β-lactam **56** can be reductively removed to give the unprotected 3-amino-β-lactam with a high enantiomeric excess.



< **Scheme 18** near here>

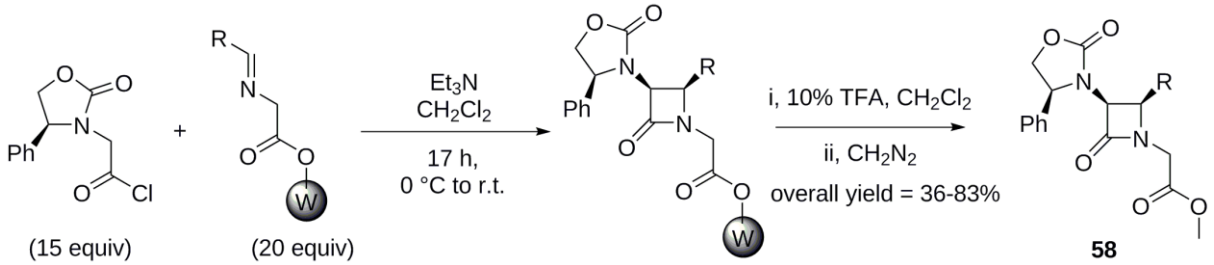
The ketene generated from acid chloride **57** has also been found to allow the formation of β-lactams with excellent diastereoselectivities (Equation 8).[152] Nonetheless, all attempts to remove the camphorsultam moiety failed.



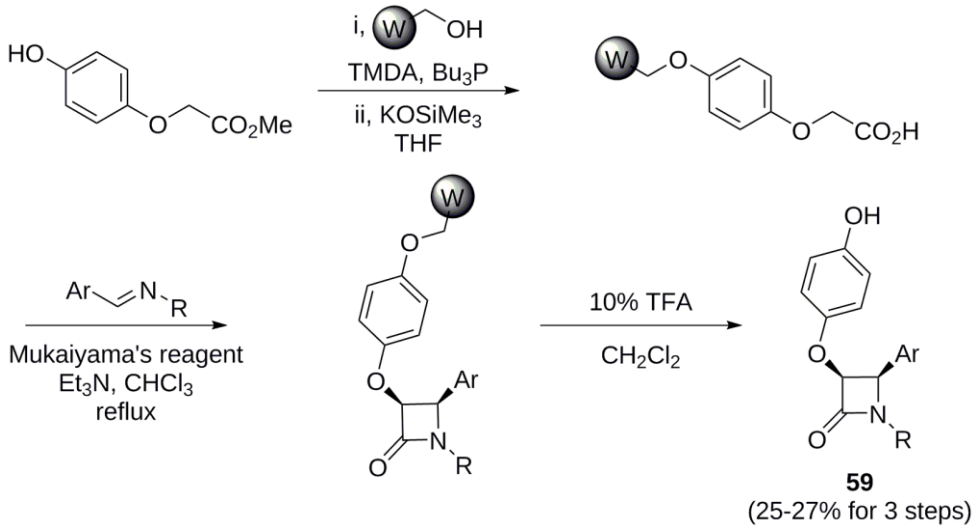
< **Equation 8** near here>

2.1.5. Applications

The large-scale production of β-lactams has required the development of solid phase techniques and polymer-supported synthesis. This has been reviewed,[153] with a special topic dedicated to the Staudinger reaction. Most often Wang resins are used and the imine partner is bound to the resin *via* its *N*-substituent (Scheme 19).[154] There are however few examples in which the ketene precursor is linked to the resin (Scheme 20).[155,156] The *cis* (chiral) β-lactams **58** and **59** are precursors of carbapenems and cholesterol absorption inhibitors, respectively.

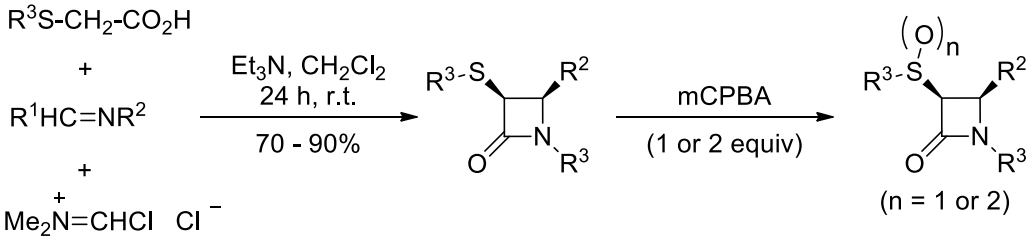


< **Scheme 19** near here>



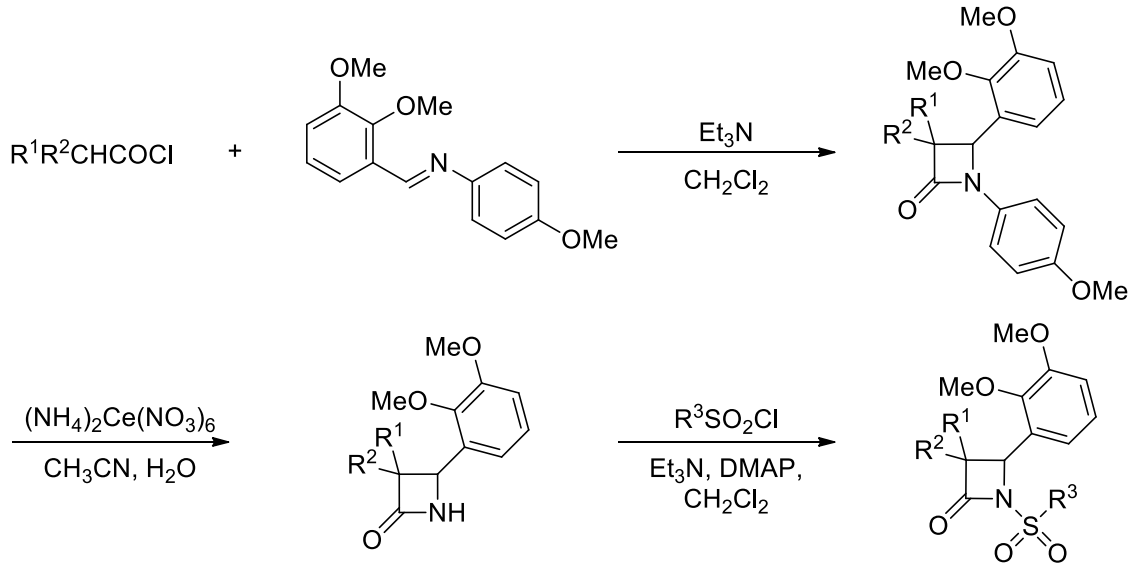
< **Scheme 20** near here>

Methods for the *in situ* activation of carboxylic acids worked efficiently, thus avoiding the isolation of acid chlorides as the ketene precursors. Beside the very popular Mukaiyama's reagent,[157] the Vilsmeier reagent (*i.e.* (chloromethylene)dimethylammonium chloride) was recently disclosed as a versatile activator of the [2 + 2] cycloaddition, directly from substituted acetic acids and imines.[158,159] 3-Thiolated-2-azetidinones endowed with antibacterial and antifungal activities have been prepared *via* this one-pot process for the cycloaddition step (Scheme 21).[160]

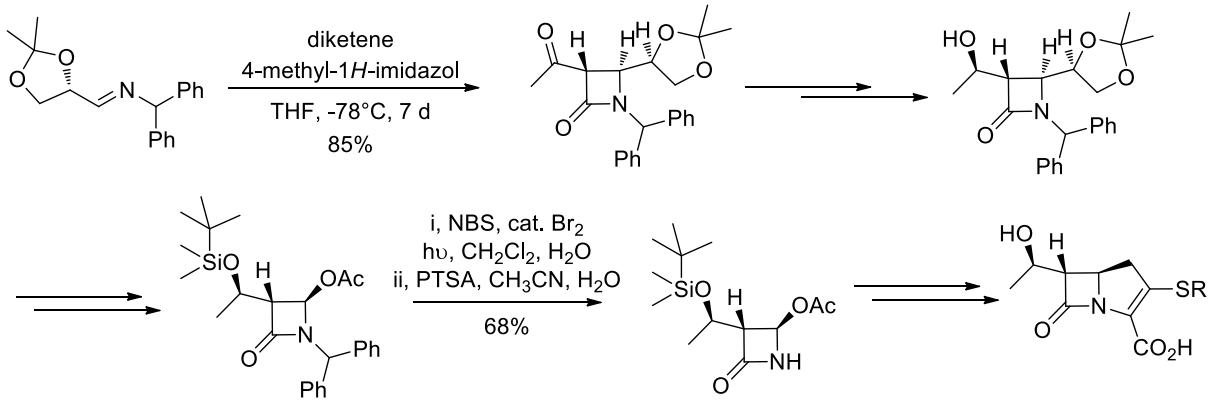


< **Scheme 21** near here>

N-Unsubstituted β-lactams are often desirable as key-intermediates in the synthesis of more elaborated antibiotics. For that purpose, imines bearing *N*-protecting groups are used. The deprotection conditions of *p*-methoxyphenyl and benzhydryl groups are compatible with the β-lactam ring. The former can be cleaved by oxidation with cerium ammonium nitrate on solid phase[161] and the latter by photoactivated bromination followed by smooth aqueous acid treatment.[162] Applications of the above methods to the synthesis of monobactams (*i.e. N*-sulfonyl monocyclic β-lactams)[163] and carbapenems[164] are described in Schemes 22 and 23 respectively.

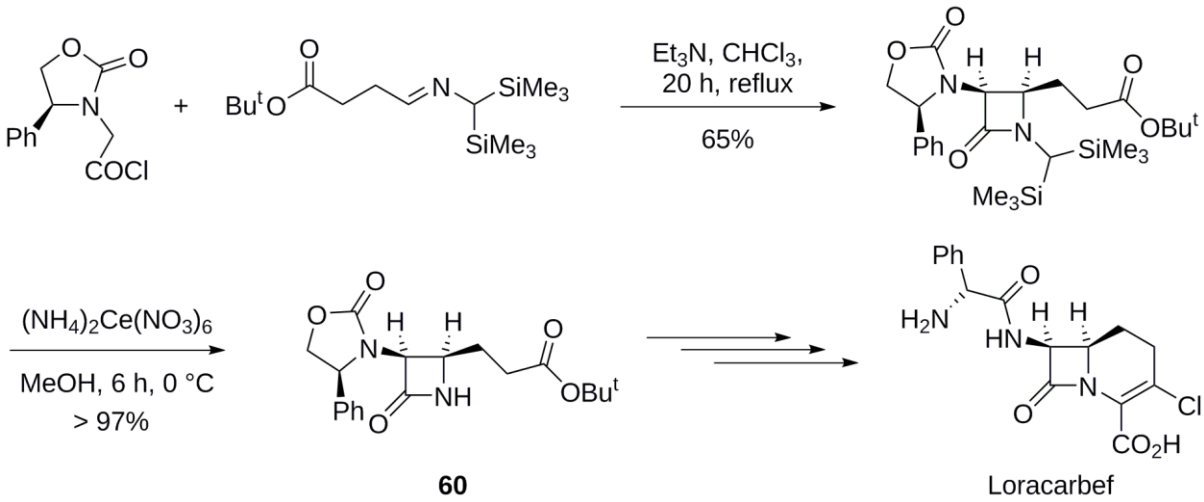


< **Scheme 22** near here>



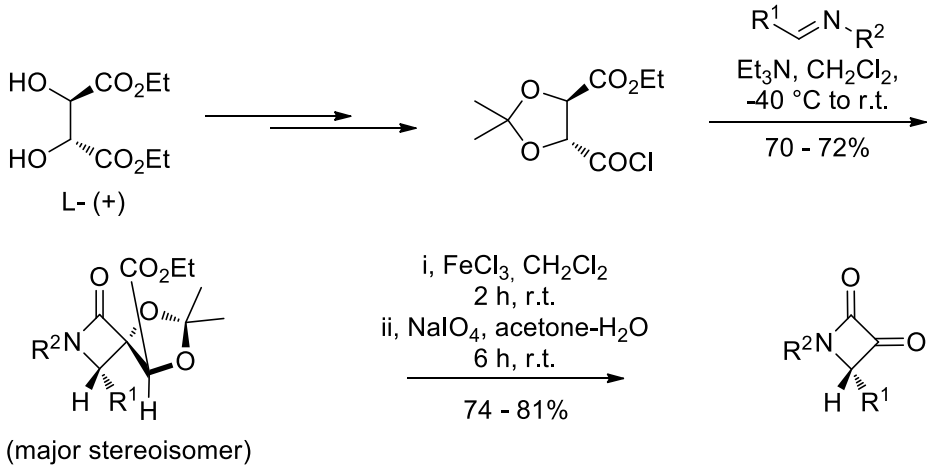
< **Scheme 23** near here>

Virtually all investigations about the Staudinger reaction have dealt with non-enolizable aldimines. Because of the instability of the corresponding imines, 4-alkyl-2-azetidinones were not readily accessible *via* the [2 + 2] cycloaddition strategy before the work of Palomo *et al*[165] who designed α-(trimethylsilyl)methyl imines as stable reagents, due to the ability of the silyl groups to stabilize electron-poor centers in the β- or γ-position. Deprotection of the *N*-*bis*(trimethylsilyl)methyl group from the cycloaddition products could be easily performed with cerium ammonium nitrate in methanol. The Loracarbef precursor **57** was prepared according to this strategy as a single enantiomer (Scheme 24).



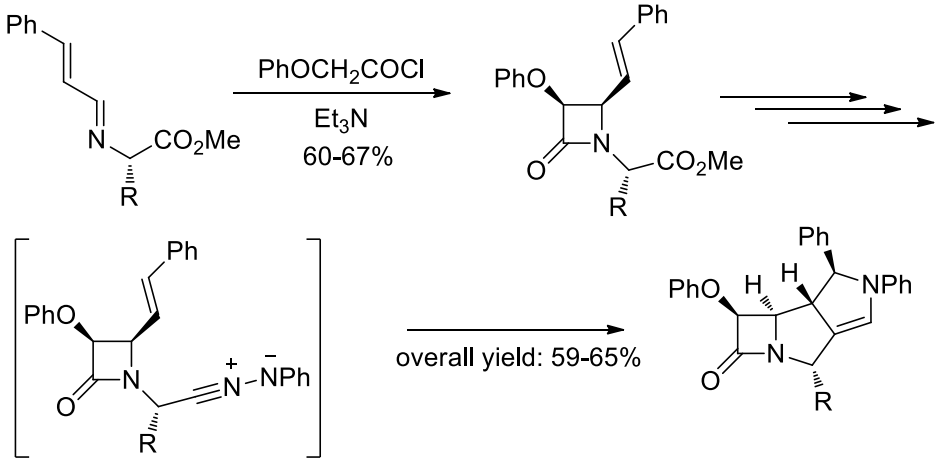
< **Scheme 24** near here>

Azetidine 2,3-diones constitute a useful class of synthons. Enantiopure derivatives were obtained by the Staudinger cycloaddition of the ketene derived from L-(+)-diethyl tartrate, giving spiro-β-lactams intermediates (Scheme 25).[166]



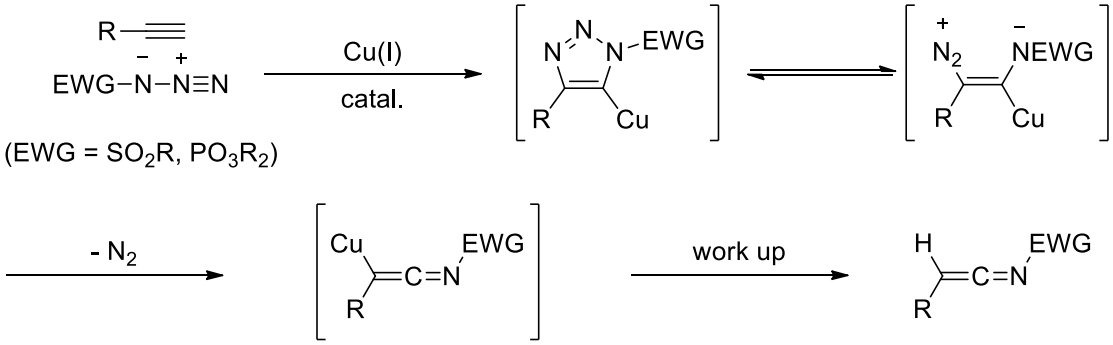
< **Scheme 25** near here>

Numerous polycyclic β-lactams of potential interest in medicinal chemistry resulted from a sequence of reactions including the Staudinger cycloaddition as the first step. Indeed, the β-lactam ring could play the role of a scaffold favoring the intramolecular reactions of functionalized chains on its backbone (Scheme 26).[167,168]

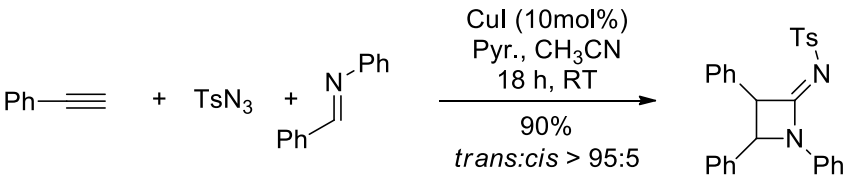


< **Scheme 26** near here>

Applications of ketenimine [2 + 2] cycloadditions are less abundant than the ketene analogues. A novel method for *in situ* generation of *N*-sulfonyl- (or *N*-phosphoryl-) ketenimines appears worthy of note because it allowed the development of inter- and intra-molecular cycloadditions with imines.[169] The well-known Cu(I)-catalyzed "click" reaction of aryl- or alkyl-azides with 1-alkynes, affording 1,4-disubstituted triazole adducts, gave a different outcome when using sulfonyl- (or phosphoryl-) azides: a ring-opening rearrangement of the initially formed *N*-sulfonyl- (or phosphoryl-) copper triazole species occurs rapidly (Scheme 27). Thus, *N*-sulfonyl ketenimines could be easily produced and quenched with a range of imines (Equation 9),[170,171] enlarging the scope of the initial reaction.[172]

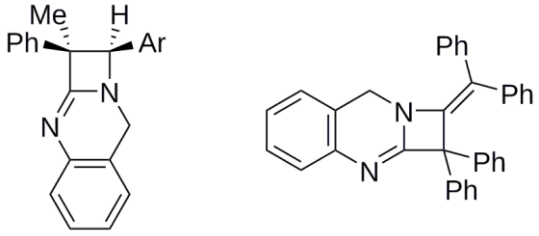


< **Scheme 27** near here>



< **Equation 9** near here>

Intramolecular ketenimine-imine [2 + 2] cycloadditions led to polycyclic systems such as **61**[173] and **62.**[174]



61 **62**

< **Molecules 58** and **59** near here>

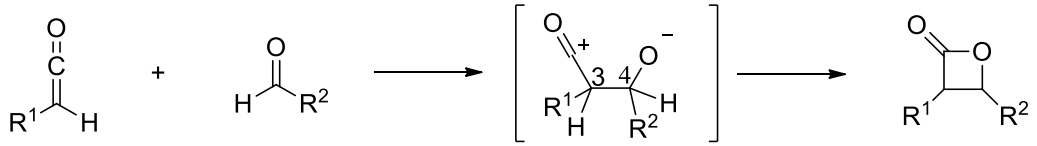
2.2. Reaction with carbonyl compounds

The carbonyl π-bond has been found to add also across the alkenic π-bond of ketenes to produce 2-oxetanones (β-lactones).[98] Unlike in the Staudinger ketene-imine cycloaddition, only highly activated systems (bearing strongly electron-withdrawing substituents) react readily with ketenes in the absence of catalyst (adducts decompose at the high temperatures necessary for their cycloaddition to occur). This lower reactivity can however be compensated

by using either a Lewis acid or a nucleophile (or both) as catalysts (**see** Sections 2.2.3 and 4.2.2).

2.2.1. Mechanism

Lecea and Cossio have extensively explored the mechanism of uncatalyzed and Lewis acid catalyzed cycloadditions of ketene onto carbonyl compounds by computational means (*ab initio* and DFT).[175,176,177] These studies indicate that this cycloaddition occurs in fact via a two-step mechanism (Scheme 28). First, the ketene adds onto the carbonyl double bond, forming the C_3-C_4 bond and leading to a zwitterionic intermediate. Next, this intermediate undergoes cyclization to afford the β-lactones. This mechanism has been supported by kinetic isotope effect measurements.[178]



< **Scheme 28** near here>

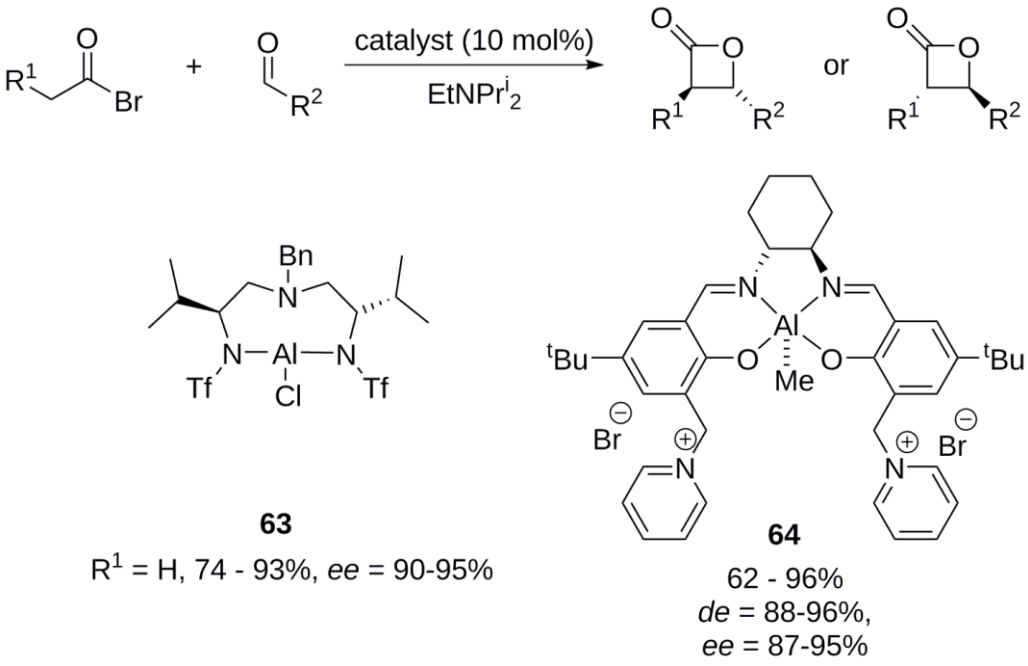
Alternatively, in the presence of a nucleophilic catalyst (an amine or a phosphine), the reaction occurs through formation of an enolate (by addition of the nucleophile onto the ketene) followed by addition of this later onto the carbonyl compound.[131] These reactions will be discussed in Section 4.

2.2.2. Cis-trans selectivity

In aldehyde cycloadditions with non-symmetrically substituted ketenes, mixtures of *cis* and *trans* isomers are generally obtained. In most cases, the ratio varies from 1:1 to 2:1.[116] Some Lewis acid catalyzed cycloadditions are however described to afford β-lactones with good diastereoselectivities (see Section 2.2.3).

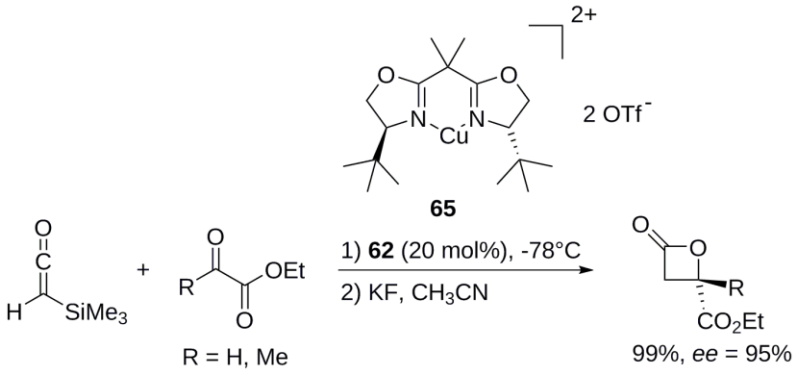
2.2.3. Enantioselectivity with chiral Lewis acids

Nelson and Peters developed the chiral C_2-symmetric aluminum complexes **63** and **64**, respectively, for the cycloaddition of mono-substituted ketenes with aldehydes (Scheme 29).[179,180] The corresponding *trans*-2-azetidinones are obtained in good enantiomeric excesses. The proposed mechanism is based on a contact ion pair-directed Lewis acid catalysis.[179]



< **Scheme 29** near here>

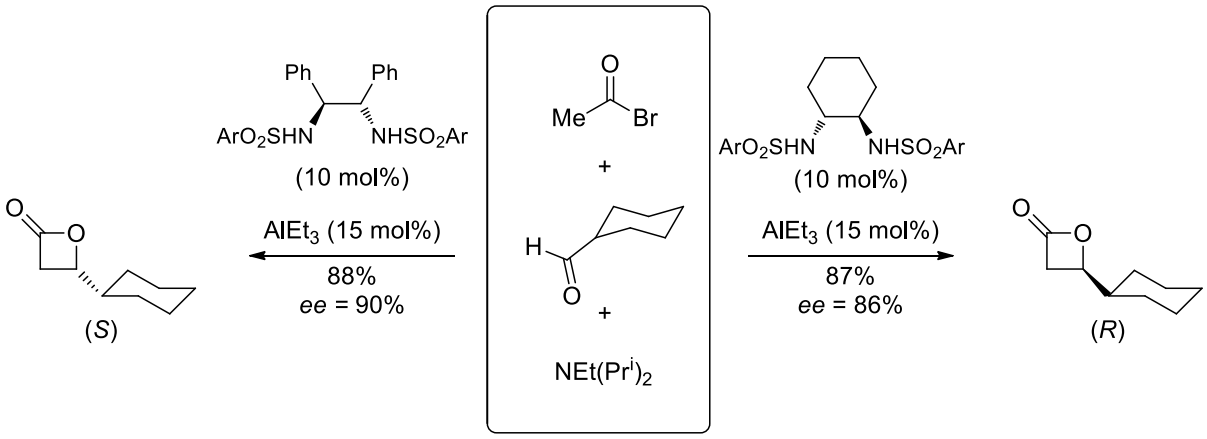
The asymmetric [2 + 2] cycloaddition of the more stable trimethylsilyl ketene has also been developed using different chiral Lewis acid catalysts (Scheme 30).[181,182,183,184] The best enantioselectivities are obtained with the C_2-symmetric copper(II)-bisoxazoline complex **65** and glyoxylate derivatives.[185]



< **Scheme 30** near here>

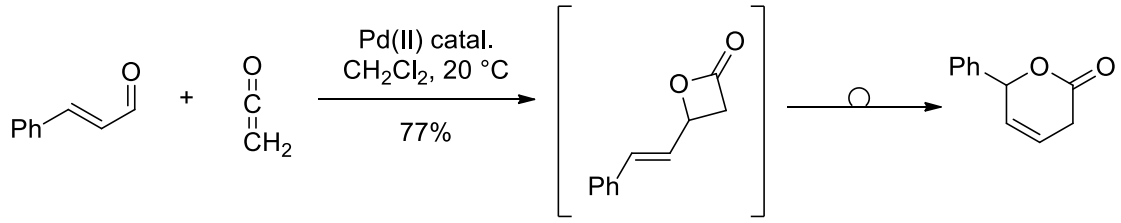
2.2.4. Applications

Ketene, generated *in situ* from acetyl bromide and Hünig's base, reacts with various α-unbranched and α-branched aliphatic aldehydes to give chiral β-lactones under catalysis by aluminum *bis*-sulfonamide complexes[186] formed *in situ* from (*R*, *R*)- or (*S*, *S*)-1,2-diamine derivatives and triethylaminium (Scheme 31).



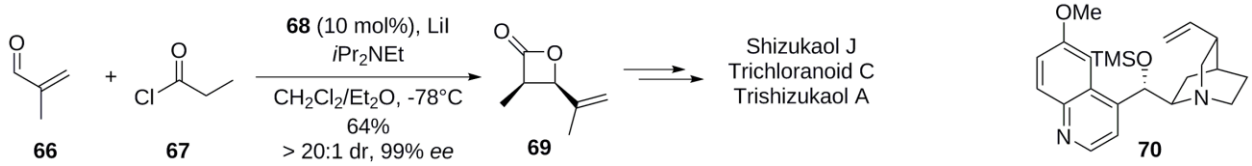
< **Scheme 31** near here>

3,6-Dihydro-*2H*-pyran-2-ones are obtained *via* tandem [2 + 2] cycloaddition/allylic rearrangement of ketene with α,β-unsaturated aldehydes and ketones; both reactions are catalyzed by the cationic palladium(II) complex $[Pd(dppb)(PhCN)_2]BF_4$ (where dppb = 1,4-*bis*-(diphenylphosphino)butane) (Scheme 32).[187]



< **Scheme 32** near here>

The asymmetric total synthesis of lindenane sesquiterpenoid oligomers (shizukaol J, trichloranoid C and trishizukaol A) developed by Liu *et al.* begins with the asymmetric [2 + 2] cycloaddition of methacrolein (**66**) and the ketene generated from propionyl chloride (**67**) (Scheme 33). The chiral catalyst is the trimethylsilyl quinidine (**70**) and the lactone (**69**) is obtained with an excellent stereocontrol (dr = 20:1 and *e.e.* = 99%).

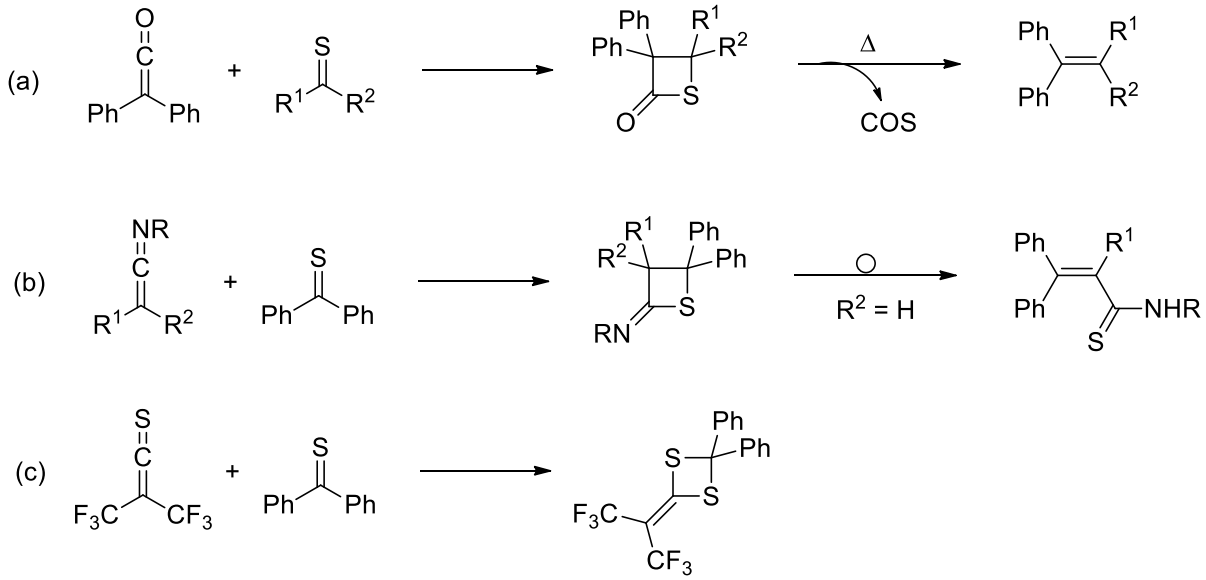


< **Scheme 33** near here>

2.3. Reaction with thiocarbonyl derivatives

Cycloadditions of heteroallenes onto C=S bonds are scarcely described, most probably because the corresponding cycloadducts have no real synthetic usefulness and are prone to decompose or rearrange.

Diphenylketene reacts with thiones, thioesters and thioamides to furnish thietane-2-ones (β-thiolactones), which lead to alkenes upon heating (Scheme 34 (a)).[188,189,190]



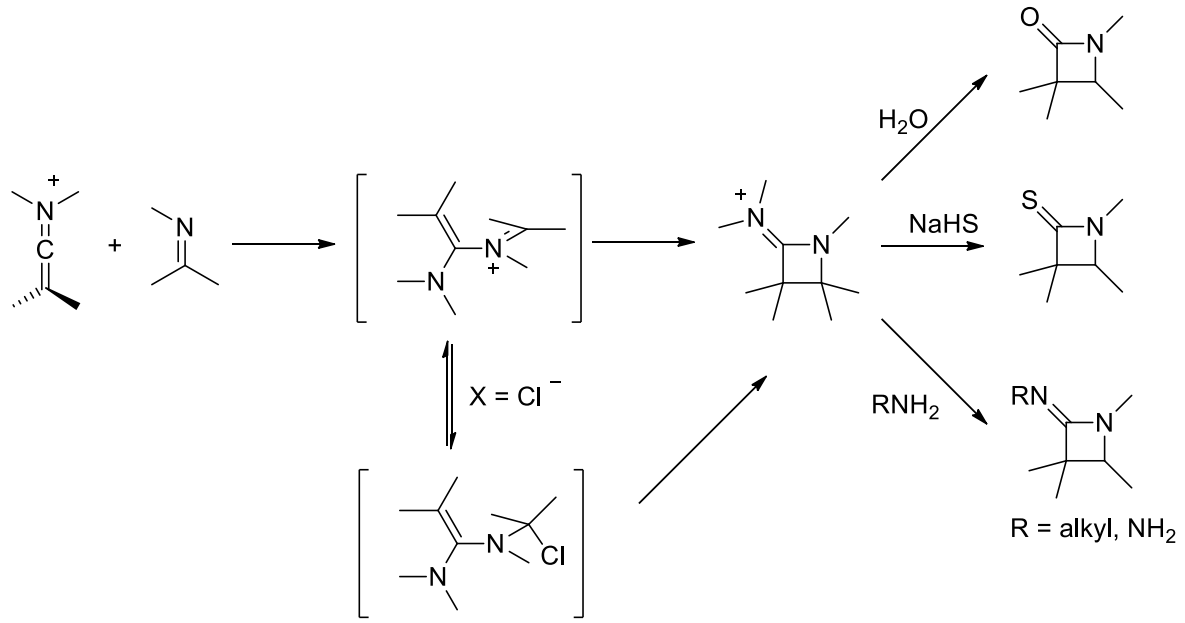
< **Scheme 34** near here>

The reaction of ketenimines with thiobenzophenone leads to thietane-2-imines; the enolizable cycloadducts undergoing a ring opening rearrangement into α,β-unsaturated thioamides (Scheme 34 (b)).[191,192]

Addition across the C=S bond of bis(trifluoromethyl)thioketene has been observed (Scheme 34 (c)) as a curiosity.[193]

3. Reaction of keteniminium salts with C=X bonds

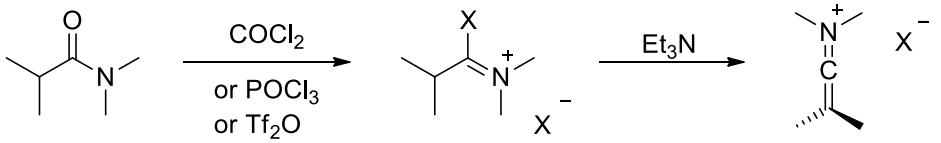
The [2 + 2] cycloaddition reaction of keteniminium salts with imines has been discovered by Ghosez in 1974.[134] It leads to the formation of 2-azetidinium salts which can be easily converted to 2-azetidin-ones, -thiones, or –imines (Scheme 35).[135,194,195] No example of cycloaddition of keteniminium salts with (thio)carbonyl compounds can be found in the literature.



< **Scheme 35** near here>

One advantage of keteniminiums salts is that they are highly reactive and can undergo cycloaddition reactions with imines which are unreactive with ketenes.

Due to their high reactivity, keteniminium salts are usually generated *in situ* by treatment of tertiary carboxamides with phosgene or triflic anhydride and a base (Scheme 36).[135]



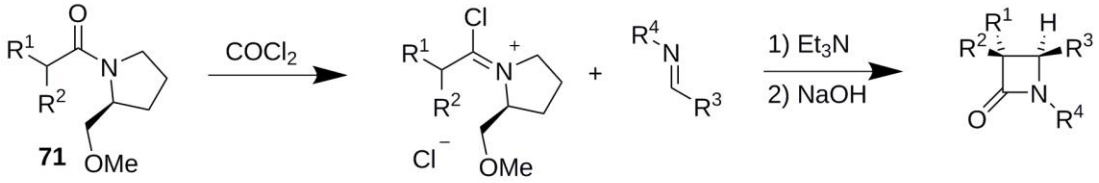
< **Scheme 36.** near here>

Similarly to the Staudinger reaction, the reaction between keteniminium salts and imines involves a two-step mechanism.[136] First, the imine adds onto the keteniminium to form the N_1-C_2 bond (Scheme 36). Next, this adduct undergoes an electrocyclic ring closure to form the C_3-C_4 bond leading to the 2-azetidinium salts.

The *cis/trans* stereoselectivity of the reaction is determined at the second step, when the C_3-C_4 bond is formed. It was found that the stereochemical outcome of the reaction depends on the nature of the anion, which in turn is related to the method used for generating the keteniminium intermediate. Indeed, the reaction is generally *cis* selective, but if the anion is nucleophilic, such as chloride, the ring closure preferentially takes place via intramolecular S_N2 reaction (similarly to the mechanism described in Scheme 15 for the Staudinger reaction) and *trans* selectivity is observed.[136]

An important advantage of the reaction of keteniminium salts as compared to that of ketenes, is that they provide another position for the incorporation of chirality. Indeed,

starting from the chiral amide **63**, the corresponding chiral β-lactams can be obtained after hydrolysis with excellent enantiomeric excesses (Scheme 37).[196] The nature of the keteniminium substituents R^1 and R^2 plays a decisive role in determining the stereoselectivity. When R^1 and R^2 are different from hydrogen, the stereoselectivity is very high, but it drops dramatically when R^1 and/or R^2 are hydrogen atoms.[196]



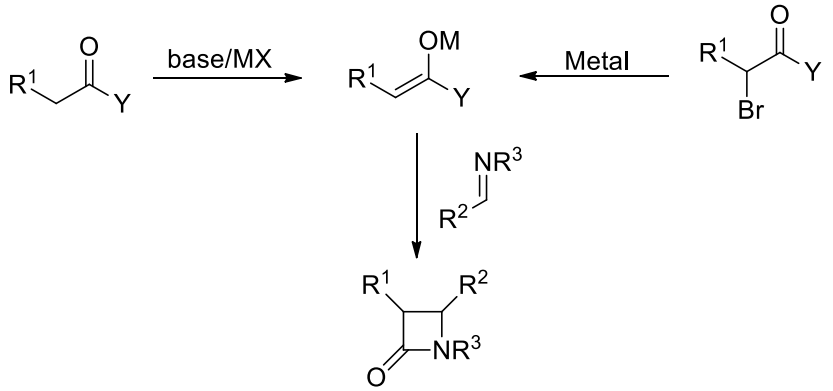
R^1	R^2	R^3	R^4	Yield (%)	*cis/trans*	*ee* (%)
Me	Me	Ph	C_3H_5	42	-	98
Me	Me	SPh	CH_2Ph	65	-	99
Ph	Me	Ph	Me	29	0/100	97
Me	H	Ph	Me	30	20/80	40
H	H	Ph	Me	47	-	4

< **Scheme 37** near here>

4. Reaction of enols and enolates with C=X bonds

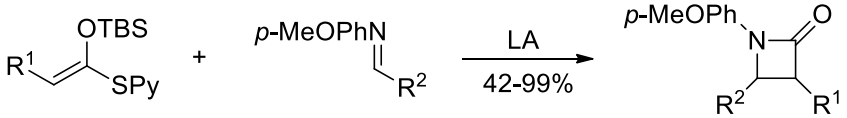
4.1. Scope and mechanism

Metal enolates derived from carboxylic acid derivatives have been reported to condense with imines to yield directly β-lactams (Scheme 38).[111] In this context, *S*-thioester enolates (Y = SR) serve particularly well.[197] Indeed, thiolates are more readily displaced from the carbonyl carbon than alkoxides. They are also more easily formed because of the enhanced acidity of the CH-α position as compared to that of simple esters. Several metals (MX) have been investigated for these transformations. Best results were obtained with titanium, aluminum, zinc, boron and tin.[198] Experiments demonstrated however that tin, aluminum and boron enolates had a more limited application to β-lactam synthesis than titanium enolates, and thus their chemistry was less developed.



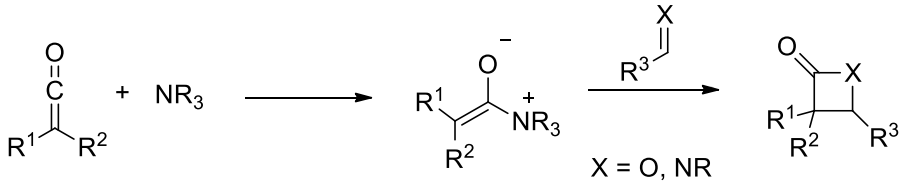
< **Scheme 38.** near here>

Although less studied, the reaction of silylketene thioacetals with imines in the presence of a Lewis acid has also been reported to yield β-lactams (Equation 10).[198]



< **Equation 10** near here>

Inspired by early works on the amine catalyzed dimerization of ketenes,[199] many groups have worked on the generation of zwitterionic ammonium enolates from ketenes and amines and their reaction with aldehydes and imines to give β-lactones and β-lactams respectively (Scheme 39).[96] In the case of imines, the overall process consists in the amine catalyzed Staudinger reaction.

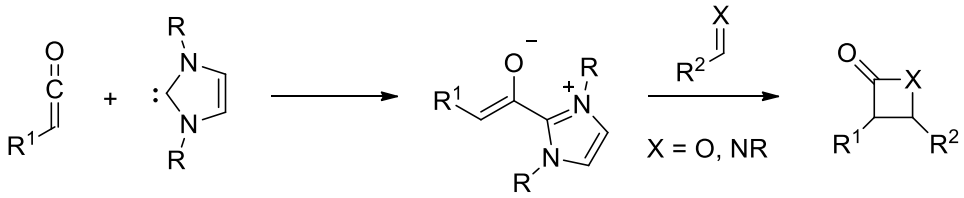


< **Scheme 39** near here>

Cinchona alkaloids have rapidly emerged as prominent catalysts for these transformations.[131] One drawback associated with this strategy, however, was the need for highly reactive aldehydes or imines, presumably to compete with ketene dimerization. It was shown that the low reactivity of ammonium enolates could be overcome and the scope of the reaction improved by using Lewis acid cocatalysts ($In(OTf)_3$, $LiClO_4$).[200,201,202] Later, Wilson

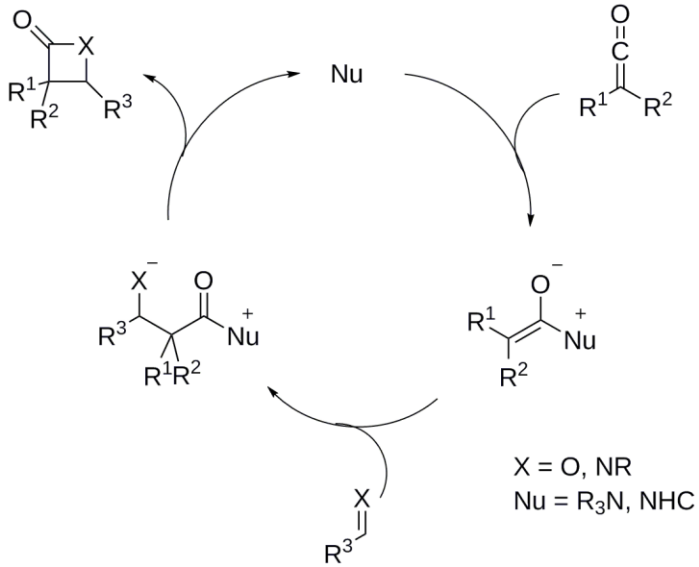
and Fu showed that ammonium enolates derived from planar chiral DMAP derivatives (see Section 4.2.) display increased reactivity as compared to cinchona derivatives.[203] These intermediates react with a large range of aldehydes and imines allowing to expand substrate scope of the reaction with the preparation of highly substituted β-lactones and β-lactams, respectively.

It was reported that *N*-heterocyclic carbenes (NHCs) are also efficient catalysts for the cycloaddition of ketenes with aldehydes and imines (Scheme 40).[204,205,206]



< **Scheme 40** near here>

The mechanism of the [2 + 2] cycloaddition of ketene with aldehydes or imines catalyzed by amines or NHCs involves three steps: addition of the amine to the ketene to form an ammonium enolate, addition of this later onto the aldehyde or imine electrophile, followed by cyclization of the newly formed alkoxide or amide onto the acylammonium species (Scheme 41).[96,207,208] Metal enolates of (thio)esters reactions have been shown to follow a similar mechanism.[197,209]

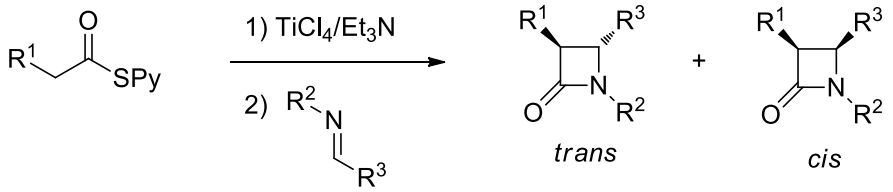


< **Scheme 41** near here>

4.2. Stereoselectivity

4.2.1. Reaction of metal enolates

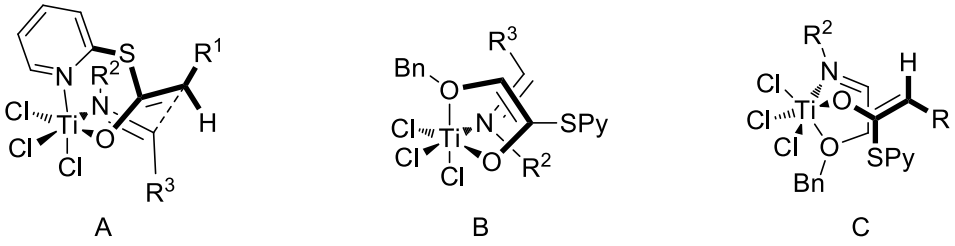
Systematic studies on titanium enolates have shown that the *cis/trans* selectivity depends highly on the substitution of the two partners (Scheme 42).[198] A few rules can however be drawn from the collected data: (1) large and nonchelating groups at the C2-postion of the *S*-thioester (R^1) and at the imine carbon (R^3) result in the formation of a *trans*-azetidinone, (2) the presence of a chelating substituent at either one of these positions results in a *cis*-selective reaction, (3) enolizable imines are more prone to produce a *cis*-β-lactam than conjugated imines.



R^1	R^2	R^3	Yield (%)	*trans*/*cis*
Me	*p*MeOPh	Ph	99	70/30
Et	*p*MeOPh	Ph	90	80/20
i-Pr	*p*MeOPh	Ph	91	85/15
Et	Bn	Ph	95	85/15
OBn	Bn	Ph	64	9/91
Me	*p*MeOPh	PhCH=CH	99	60/40
Me	*p*MeOPh	Pr	48	37/63
Me	*p*MeOPh	CH_2OBn	40	23/77

< **Scheme 42** near here>

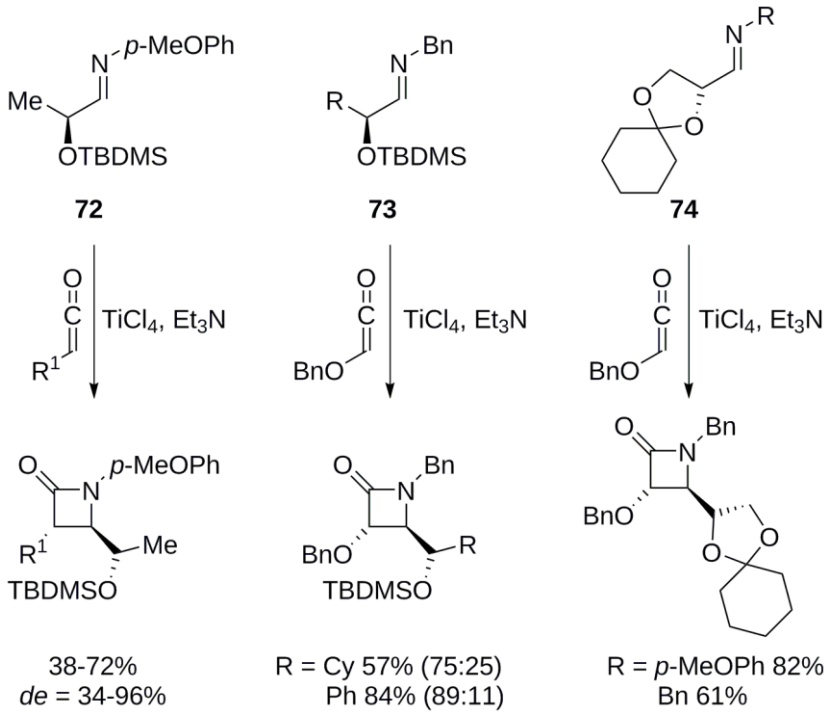
The proposed model to account for the observed *trans* selectivity involves a chair-like six-membered transition state (A) for the addition step in which the steric clash between the bulky R^1 and R^2 groups is minimized (Scheme 43).[197] In the case of small R^1 and R^2 groups, *cis*-β-lactams may be formed via similar transition structures involving either an (*E*)-enolate or a (*Z*)-imine. The *E/Z* imine equilibrium is also believed to be the origin of the tendency of alkyl-substituted imines to give more *cis*-azetidinones. Indeed, ^{1}H NMR experiments showed that conjugated imines exist predominantly in, and are likely to react from their (*E*) configuration, while aliphatic imines consist of almost equal mixtures of (*E*) and (*Z*) isomers.



< **Scheme 43** near here>

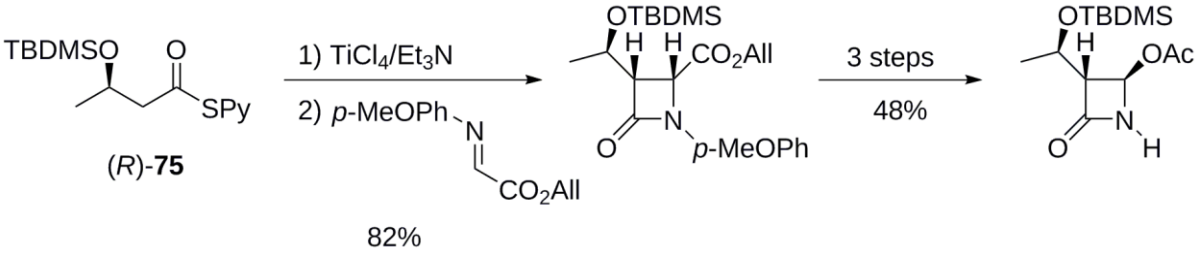
The formation of *cis*-β-lactams in the presence of a chelating substituent at either R^1 or R^2 position can be explained by the boat-like transition state models B and C, respectively (Scheme 43).

The absolute stereochemistry of the two chiral centers generated during the [2 + 2] cycloaddition is determined at the addition step and can be controlled by using either chiral imines or chiral enolates. The first of these strategies has been explored by several groups with α-alkoxy and α,β-dialkoxyimines such as **64**, **65** and **66** (Scheme 44).[210,211] When these imines were treated with the titanium enolates of 2-pyridyl thioesters, very high levels of stereocontrol were observed in the formation of β-lactams. Several imines bearing a chiral substituent on the nitrogen atom have also been studied but the obtained results were less satisfactory.[197]



< **Scheme 44** near here>

Cozzi investigated the reaction of the chiral 2-pyridyl thioester (*R*)-**67**.[212] Cycloaddition of the derived enolate with imines led to the corresponding β-lactams bearing the (*R*)-1-hydroxyethyl side chain at C3 present in the penem antibiotics with high diastereoselectivities (Scheme 45).

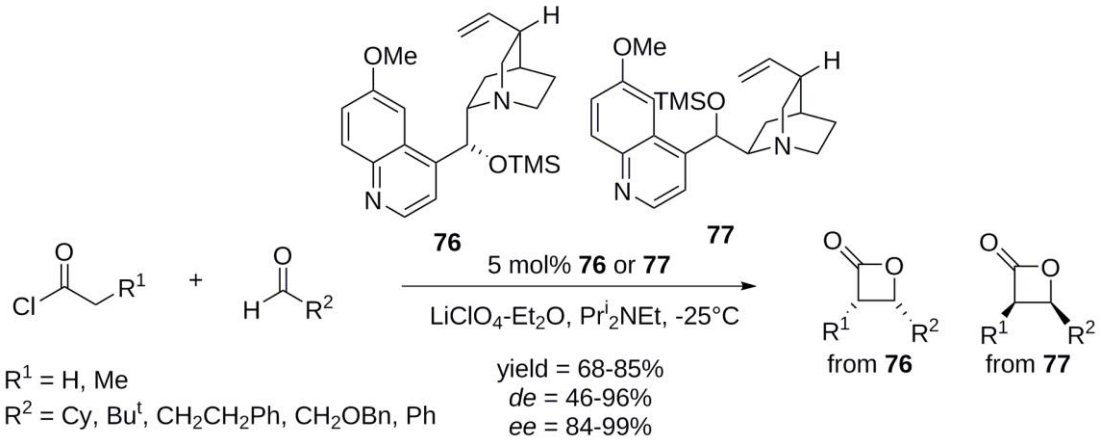


< **Scheme 45** near here>

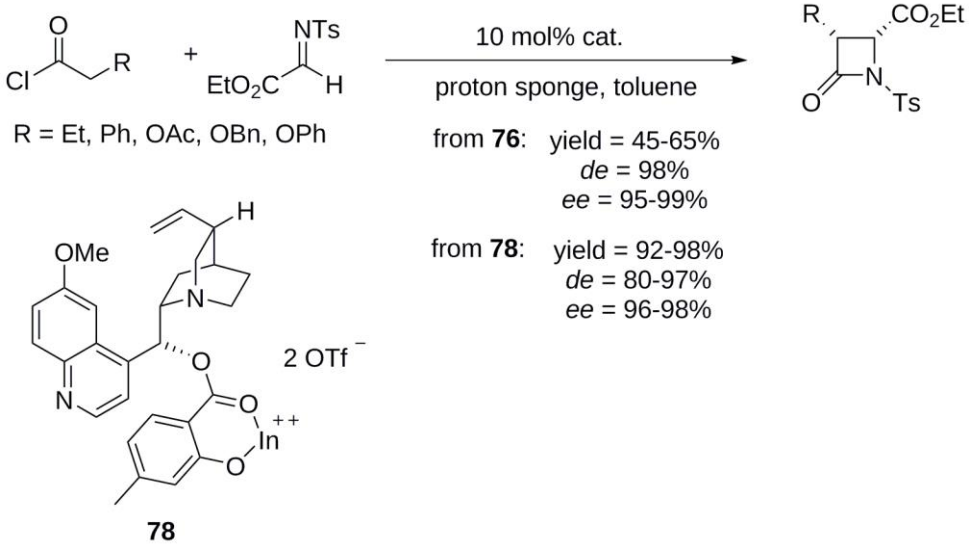
The possibility of using chiral metal complexes has also been investigated (with boron as metal), but the enantiomeric excesses never exceeded 78%.[213]

4.2.2. Reaction of ketenes

Both chiral NHCs and amines catalysts have been applied to the enantioselective synthesis of β-lactones and β-lactams from ketenes. The first chiral amines to be used in this context were cinchona alkaloids (Equation 11).[131] *Cis*-β-lactones and *cis*-β-lactams are obtained in moderate to good yields with excellent diastereo- and enantioselectivity (Scheme 46). Interestingly, by employing the diastereomeric alkaloids quinine (**76**) and quinidine (**77**) as catalysts one can access either enantiomer of a given product.



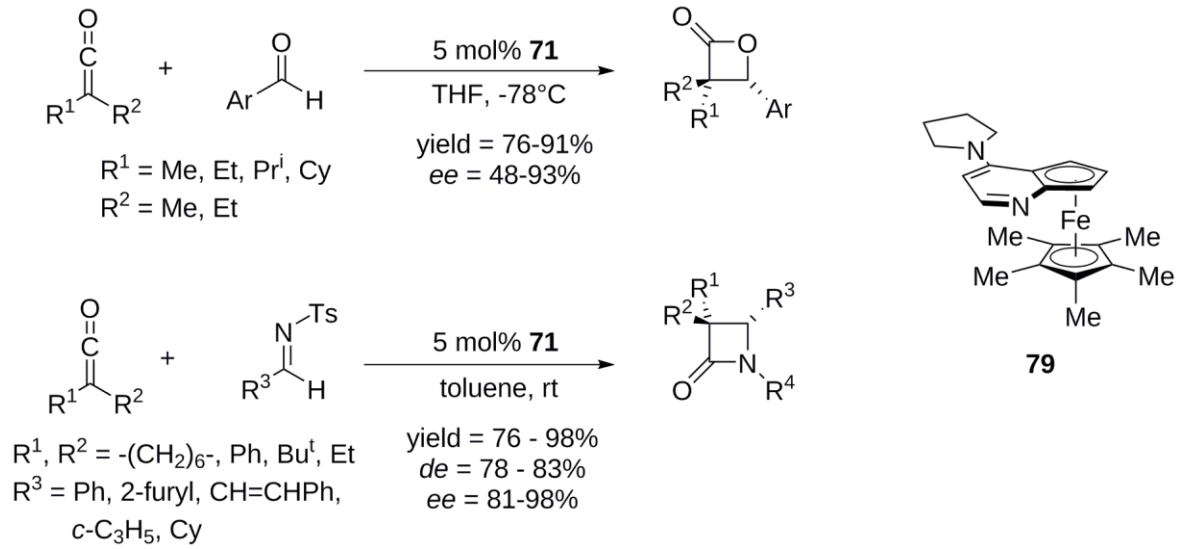
< **Equation 11** near here>



< **Scheme 46** near here>

Bifunctional catalysts in which the nucleophilic chiral amine is paired with a Lewis acid have also been developed (**78**; Scheme 46).[214,215,216,217,218]

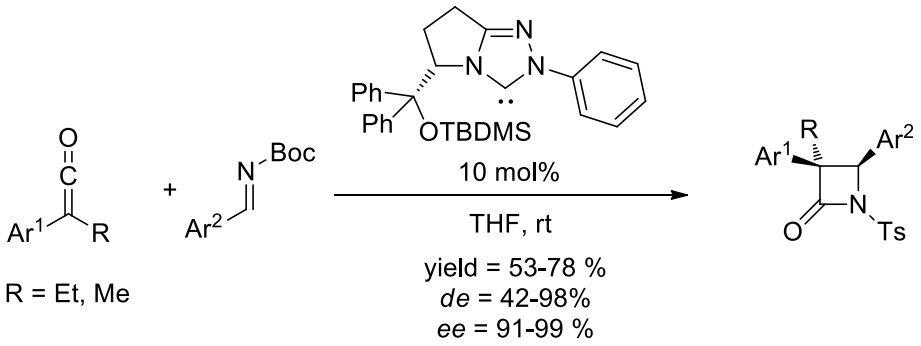
The limited scope of the reaction catalyzed by cinchona alkaloid prompted Fu and Wilson to investigate the application of planar chiral DMAP to these reactions. In the presence of 5 mol% of the chiral catalyst **79**, ketenes react with aldehydes and imines to yield [2 + 2] cycloadducts with excellent yields and stereoselectivities (Scheme 47).[203]



< **Scheme 47** near here>

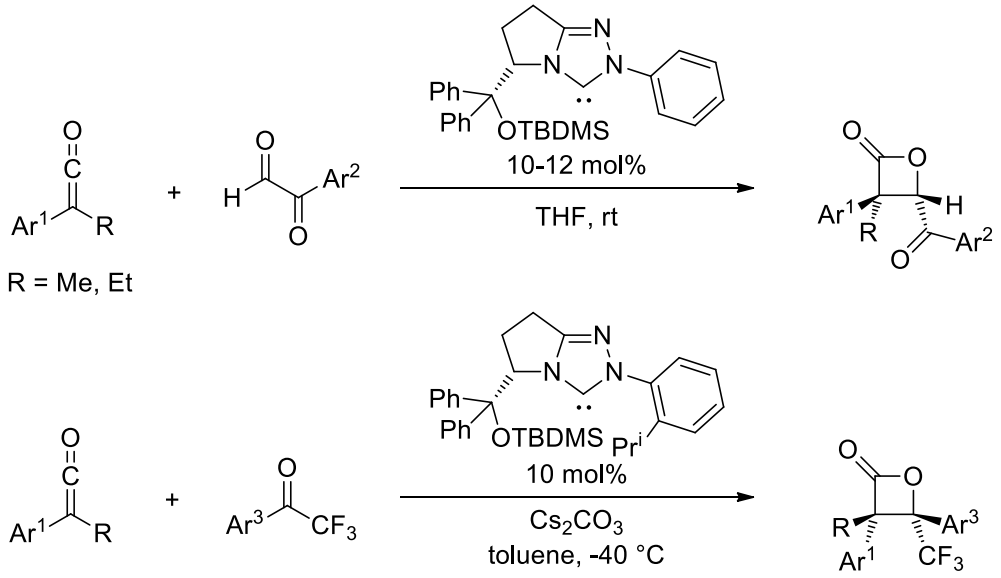
An interesting reversal in diastereoselectivity was observed by employing *N*-Tf-imines instead of *N*-Ts-imines.[153] The switch in selectivity is attributed to a change in mechanism.

Smith and Ye showed that enantioselective β-lactams formation can also be accomplished by chiral NHC catalysis (Scheme 48).[219,220] The catalytic cycle is similar to the one described for tertiary amine catalysts.[207,209] In this case, the steric hindrance of the NHC catalyst has been showed to be determinant for the *cis/trans* selectivity; bulky NHCs favoring *trans* isomer.[221]



< **Scheme 48** near here>

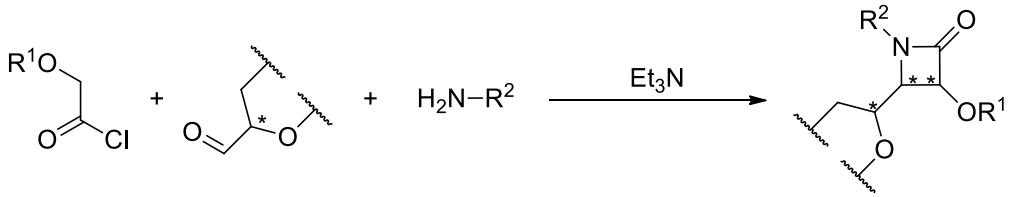
Later, this enantioselective strategy has been applied to the reaction of ketene with carbonyl compounds to form β-lactones bearing two contiguous stereocenters. Indeed, reaction of alkyl(aryl)ketenes with 2-oxoaldehydes or trifluoromethyl ketones leads to corresponding β-lactones in high yields, with good diastereoselectivities and excellent enantioselectivities (Scheme 49).[222,204,223] One drawback of this methodology, however, is the fact that it is limited to activated carbonyl compounds.



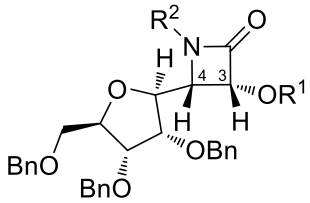
< **Scheme 49** near here>

4.3. Selected applications

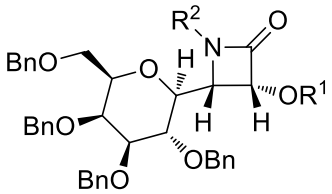
With the aim of simultaneously locking the transglycosidase and transpeptidase domains in PBP2a of resistant bacteria, Dondoni and Massi have synthesized sugar-decorated β-lactams. The C4-glycoconjugate β-lactams **72** and **73** are obtained by a 3CR-based methodology, *i.e.* the two-step one-pot amine-catalyze Staudinger reaction, combined with the PASP (polymer-assisted solution-phase) technique (Scheme 50).[224,225]



72 (C-ribosyl series)

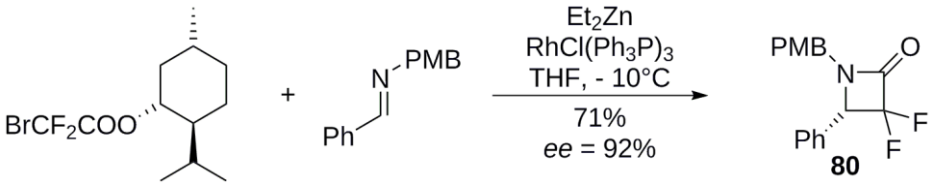


73 (C-galactosyl series)



< **Scheme 50** near here>

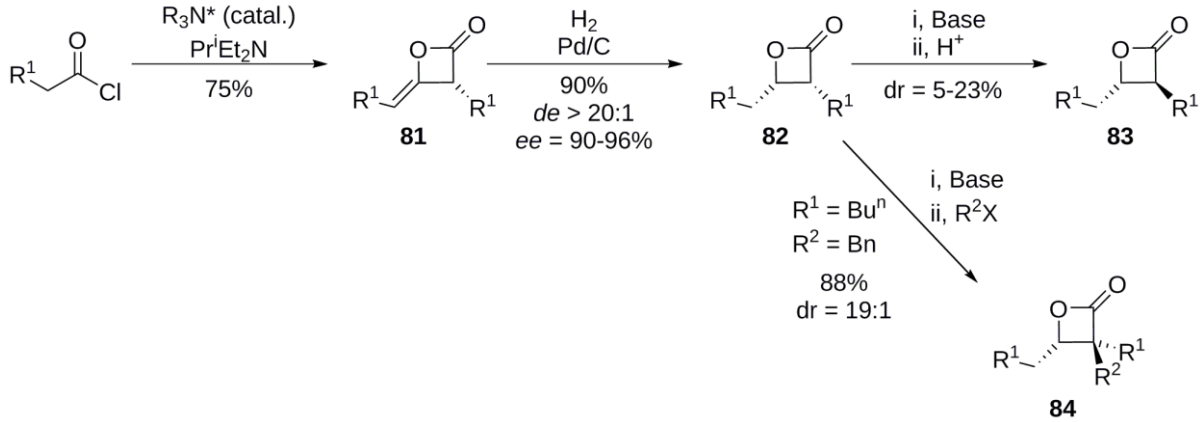
The Reformatzky-type reaction of imines and α-bromoesters with zinc dust[226,227] is the method of choice for the preparation of 3,3-difluoro-β-lactams,[228] and derivatives thereof such as α,α-difluoro-β-aminoacids. An asymmetric version using (-)-menthyl bromodifluoroacetate has been developed for the preparation of the chiral β-lactam **80** which was further reacted with taxane alcohol to give the 2,2'-difluoro analog of the anticancer drug docetaxel (Equation 12).[229]



< **Equation 12** near here>

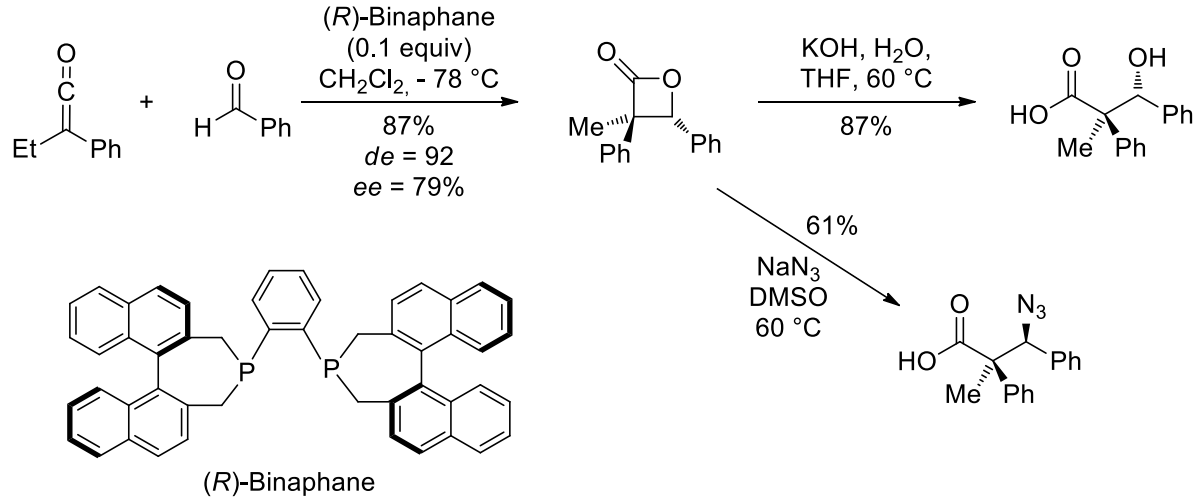
3,3-Dichloro β-lactones were obtained from trichloroacetyl chloride, α-oxyaldehydes or α-aminoaldehydes and zinc, and used as precursors of 1,2-diols or 1,2-amino alcohols subunits with predictable stereochemistry.[230]

The catalytic asymmetric synthesis of β-lactones *via* a sequential ketene dimerization / hydrogenation process allows an efficient access to inhibitors of the thio-esterase domain of fatty acid synthase (Scheme 51).[231] The facial-selective hydrogenation of the dimer **81** leads to the *cis*-substituted β-lactone **82**. The subsequent epimerization at C_3 under basic treatment gives the *trans* isomer **83** as the major compound. Alkylation of the enolate derived from **82** furnishes the β-lactone **84** with a C_4 quaternary center of controlled configuration.



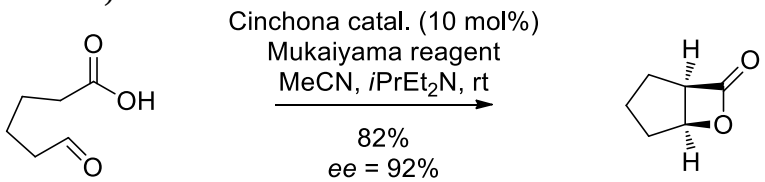
< **Scheme 51** near here>

Chiral β-lactones with a C_4 quaternary center can be directly obtained from disubstituted ketenes that cycloadd to aldehydes in the presence of a chiral phosphine catalyst. Further basic hydrolysis and nucleophilic opening of the cycloadducts afford β-hydroxy- and β-amino acid precursors featuring a controlled quaternary asymmetric carbon atom at the α-position (Scheme 52).[232] This reaction sequence illustrates well the use of chiral β-lactones as versatile building blocks.[233]



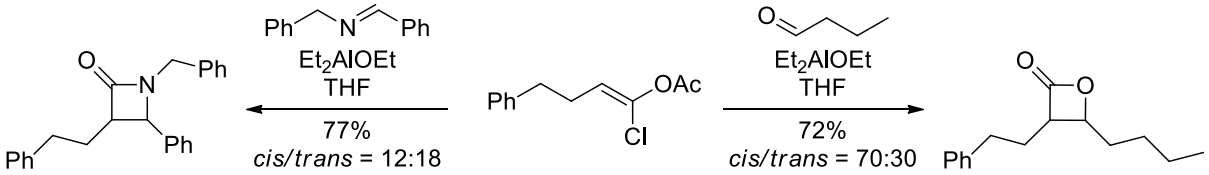
< **Scheme 52** near here>

An intramolecular version of the Wynberg synthesis of β-lactones is proposed by Romo and coworkers (Equation 13).[231,234]



< **Equation 13** near here>

Mioskowski has disclosed new ketene equivalents, namely α-haloenol acetates, for the practical synthesis of β-lactones and β-lactams. The [2 + 2] cycloaddition occurs readily in the presence of diethylaluminium ethoxide (Scheme 53).[235]

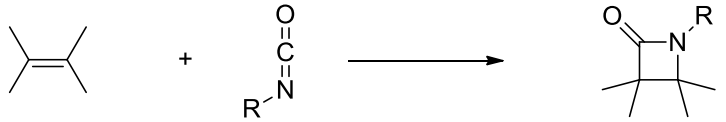


< **Scheme 53** near here>

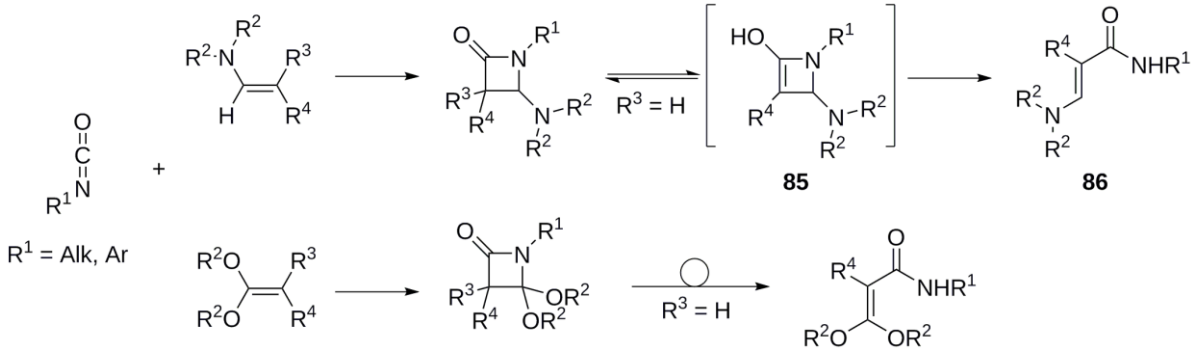
5. Reaction of isocyanates with alkenes

5.1. Scope

The cycloaddition of alkenes across the C=N bond of an isocyanate is a useful method for synthesizing β-lactams (Equation 14).[236] The reaction requires either activation of the alkene by electron-donating substituents or activation of the isocyanate by electron-withdrawing groups. Non-activated (alkyl or aryl) isocyanates react with enamines and ketene acetals (Scheme 54). The initial product is a β-lactam. However, when R^3 = H, enolization occurs and a fast electrocyclic rearrangement of the enol form (**85**) gives the open-chain isomer (**86**). In both cases, the rearrangement is driven by the release of ring-strain and the presence of an electron-donating group at C_4.

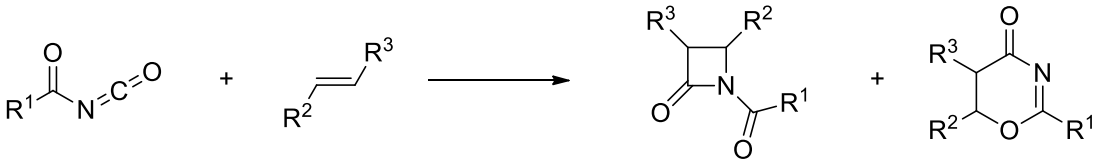


< **Equation 14** near here>



< **Scheme 54** near here>

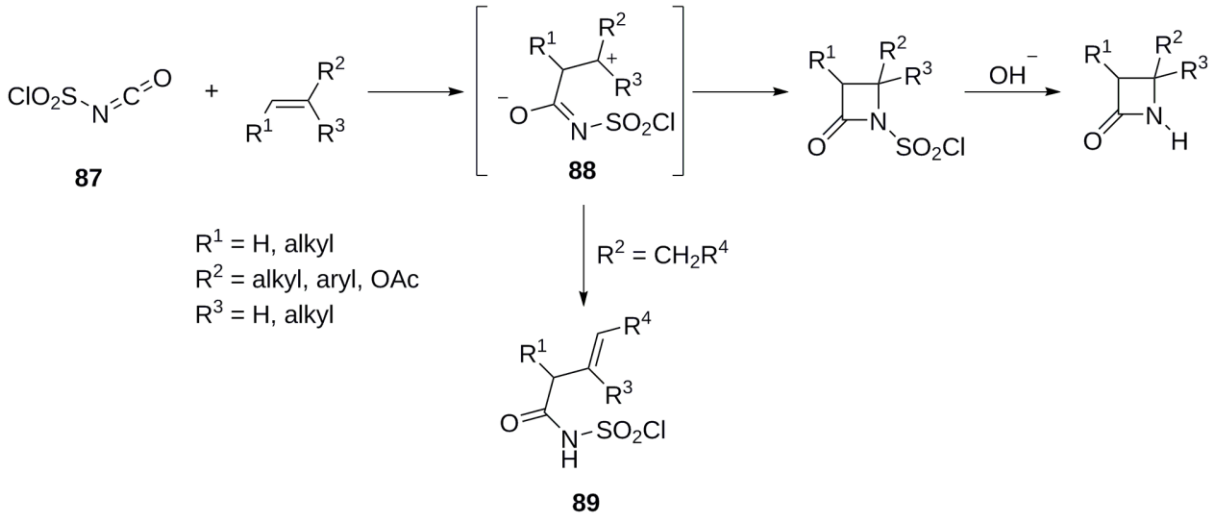
Acyl isocyanates are more reactive and can react with non-activated alkenes (Equation 15).[237,238,239] However, the presence of an additional π-bond conjugated to the C=N unit of the isocyanate opens the possibility for [4 + 2] cycloadditions to compete with normal [2 + 2] additions. The chemoselectivity varies with subtle changes in the structures of the reactants as well as the experimental conditions.



< **Equation 15** near here>

A more general and practical approach towards β-lactams from isocyantes uses the cheap chlorosulfonyl isocyante (CSI; **87**; Scheme 55).[240] This derivative, first described by Graf,[241] offers several advantages: (a) it has a strong activating effect on the cyanate function, (b) it does not lead to competing [4 + 2] cycloadditions, and (c) it can be smoothly removed by simple basic hydrolysis or reductive treatment. CSI reacts with a wide range of alkenes

under mild conditions to produce β-lactams together with variable but usually minor amounts of open-chain adducts (**89**).

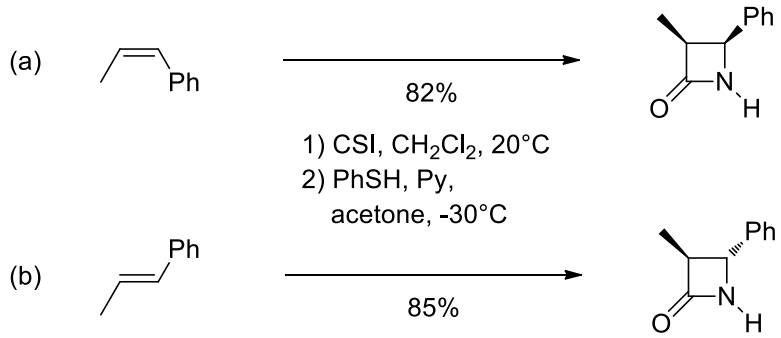


< **Scheme 55** near here>

Based on experimental results and computational studies, a stepwise mechanism via formation of a 1,4-dipolar intermediate (**88**) has been proposed for these reactions (Scheme 55).[242] In some specific cases, however, a concerted mechanism was shown to be preferred.[243] The reaction rates are markedly increased in polar solvents. The cycloadditions of isocyanates to alkenes are always regiospecific, the reaction taking place so as to form the most stable 1,4-dipole.

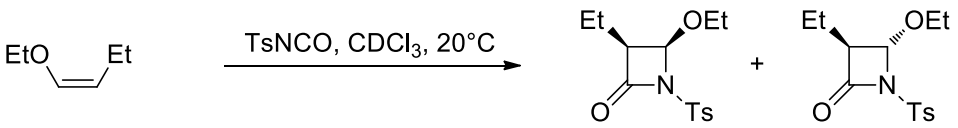
5.2. Stereochemical aspects

Reaction of activated isocyanates with alkenes are generally highly stereospecific (Scheme 56).[237,244,245]



< **Scheme 56** near here>

In a few cases, it was found that the primary adduct epimerizes under the reaction conditions (Scheme 57).[246]

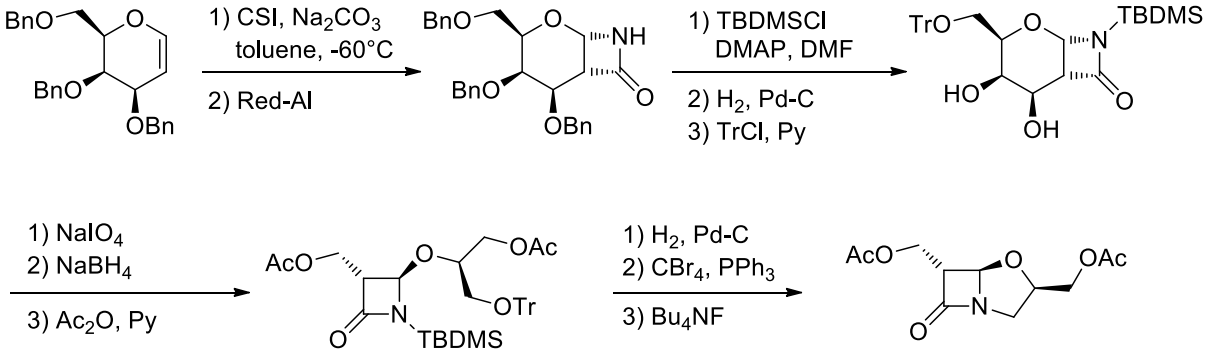


Reaction time	*cis*	*trans*
1 min	>95%	<5%
18 min	65	35
24 h	27	73

< **Scheme 57** near here>

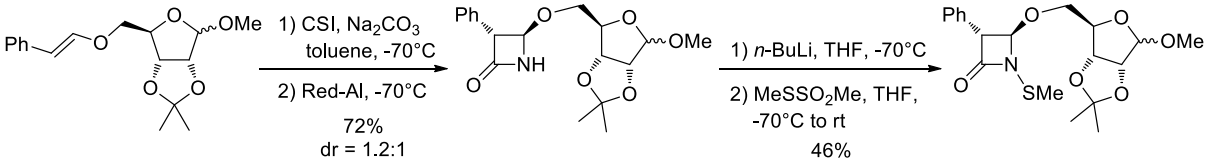
5.3. Selected applications

The main applications of the [2 + 2] cycloaddition of isocyanates with alkenes are related to the chemistry of antibiotics. A stereocontrolled synthesis of 1-oxabicyclic β-lactam antibiotics, using the cycloaddition of chlorosulfonyl (or trichloroacetyl) isocyanate to sugar vinyl ethers as the key step, has been developed by M. Chmielewski et al (Scheme 58).[247]



< **Scheme 58** near here>

Pyridinyl sulfones bearing carbohydrate moieties at the α-position have been used in the Julia-Lythgoe-Kocienski olefination with aldehydes, in a one-pot protocol affording glycosidic enol ethers with a (*E*)-stereoselectivity. Their [2 + 2] cycloaddition reaction with CSI provides glycosylated β-lactams regioselectively and with a exclusive *trans*-stereochemistry (Scheme 59).[248] After conversion into *N*-methylthio derivatives, these β-lactams showed antibacterial activity toward MRSA.

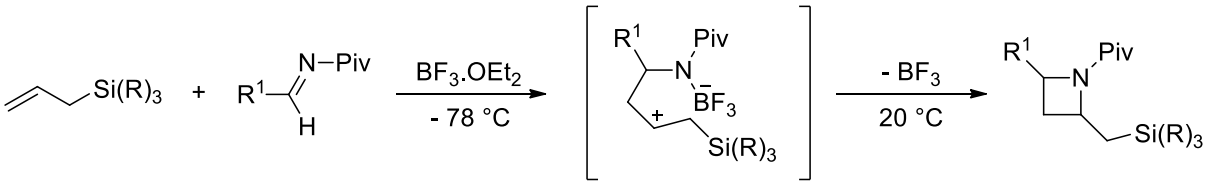


< **Scheme 59** near here>

6. Reaction of alkenes, allenes and alkynes with C=N bond

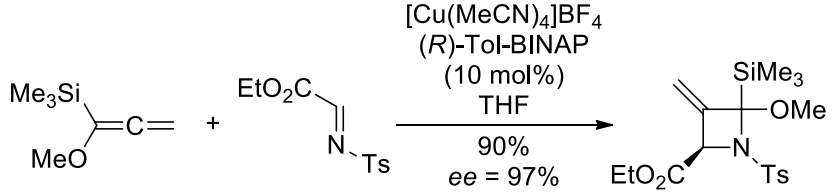
6.1. Lewis acid catalyzed reactions

N-Pivaloyl aldimines react with allylsilanes in the presence of boron trifluoride etherate or zinc chloride to give azetidines (Scheme 60).[249] This formal [2 + 2] cycloaddition most probably proceeds in two steps, *via* a β-silyl cation intermediate.



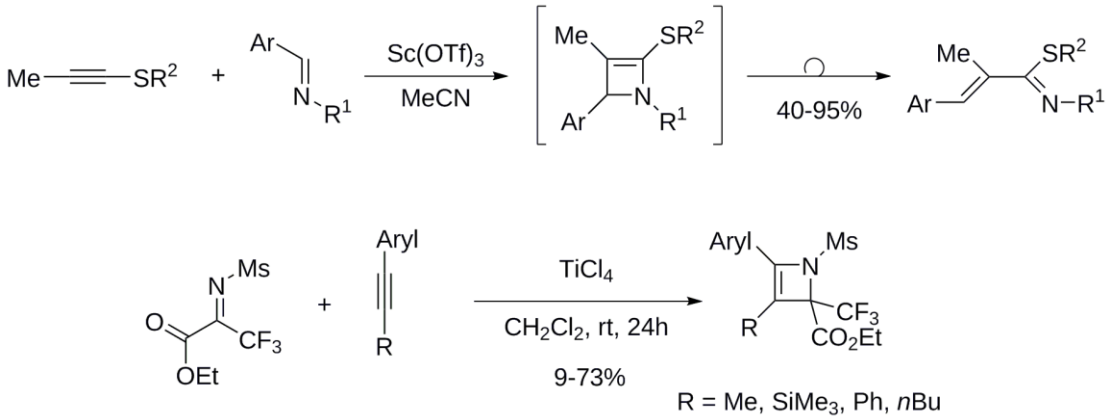
< **Scheme 60** near here>

The reaction of allenylsilanes with *N*-tosyl aldimines has been carried out in the presence of a chiral copper catalyst;[250] 3-exo-methylene azetidines were obtained in good enantiomeric excesses (Equation 16). An application to allenyl germanes is also described.[250]



< **Equation 16** near here>

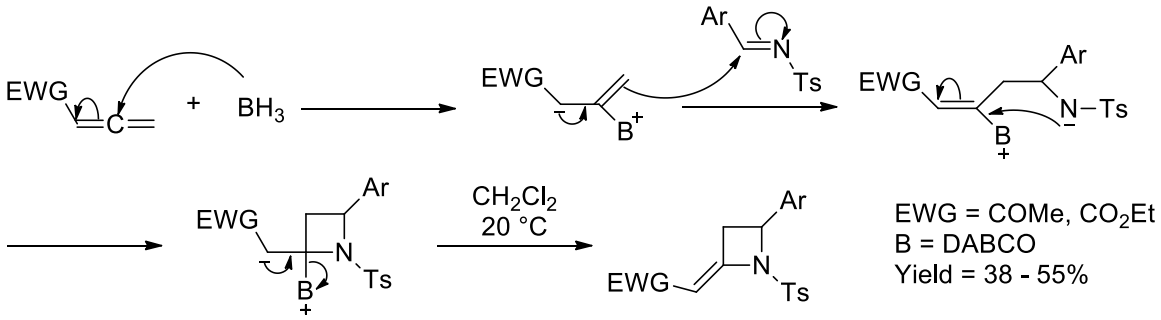
The reaction of imines with alkynes enables the synthesis of 2-azetine derivatives (Scheme 61).[251,252,253] 2-Azetines are however, in most cases, unstable, due to ring strain, and undergo ring opening to the corresponding 1-azadiene.



< **Scheme 61** near here>

6.2. Lewis base catalyzed reactions

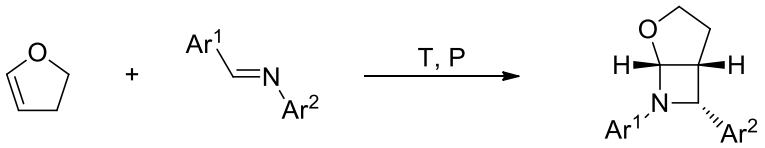
The [2 + 2] cycloaddition of allenes substituted with an electron-withdrawing group (EWG) to *N*-tosyl aldimines is catalyzed by DABCO (Scheme 62).[254] 2-Exomethylene azetidines are formed *via* a zwitterionic intermediate undergoing an intramolecular Michael addition.



< **Scheme 62** near here>

6.3. Thermic reactions

Upon heating under pressure, 2,3-dihydrofuran cycloadds onto (*E*)-benzylideneanilines to furnish bicyclic azetidines with high stereoselectivity (Equation 17).[255]

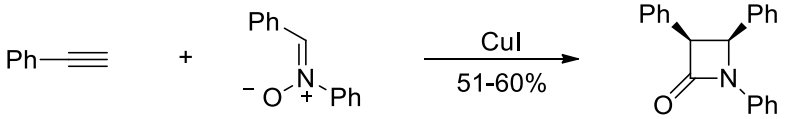


< **Equation 17** near here>

7. Reaction of alkynes with nitrones

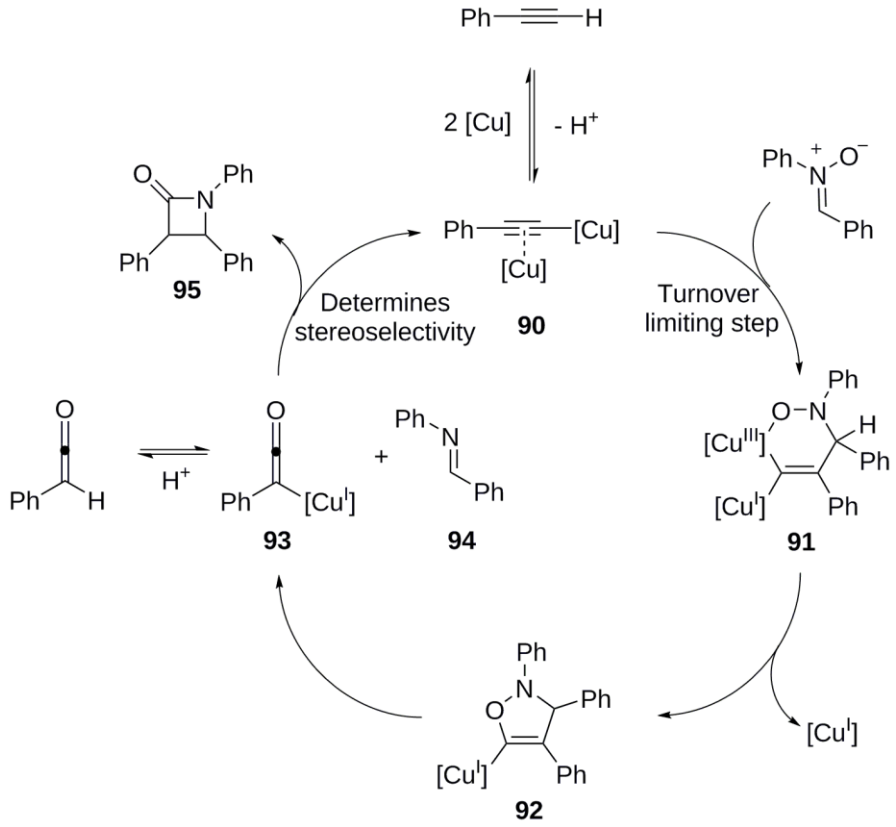
7.1. The Kinugasa reaction

The reaction of *C,N*-diphenylnitrone, phenylacetylene and a stoichiometric amount of a Cu(I) salt in dry pyridine was initially reported in 1972 by Kinugasa and Hashimito (Equation 18).[256] Later on, various terminal alkynes and substituted nitrones, both readily available starting materials, were used for the stereoselective synthesis of *cis*-β-lactams.[257] The Kinugasa reaction offers a high functional group tolerance and an atom-economical character since the catalytic version (sub-stoichiometric Cu(I)) could be developed by Miura *et al*,[258] and further optimized by Fu and Lo[259] with appropriate metal ligands. In most cases, the *cis* diastereomer of the β-lactam is favored.



< **Equation 18** near here>

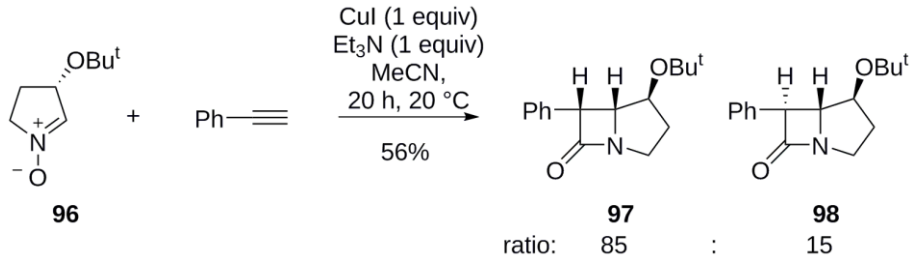
The proposed mechanism of β-lactam formation is outlined in Scheme 63: the reactive intermediate is the bis-Cu(I) acetylide **90** which undergoes a non-concerted 1,3-dipolar cycloaddition with the nitrone.[260,261,262,263] As indicated by recent kinetic studies, the mechanism proceeds then via a rapid (3+2) cycloreversion, providing copper ketenyl intermediate **93** and imine **94**, followed by a (2 + 2) cycloaddition to yield the desired β-lactam **95**.[259] Calculations suggest that, according to the strengths of the base, the second part of the mechanism can proceed either through protonation of **93** and a classical [2 + 2] cycloaddition or via nucleophilic addition of the ketenyl copper intermediate **93** onto the imine followed by a cyclization.[263]



< **Scheme 63** near here>

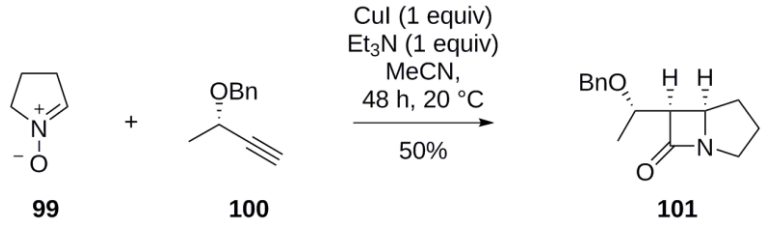
7.2. Asymmetric synthesis

The use of chiral non-racemic nitrones as partners of the Kinugasa reaction was explored by Chmielewski *et al*.[264] For instance, the cyclic nitrone **96** (available from (*S*)-malic acid) reacts with phenylacetylene in the presence of one equivalent of copper iodide and one equivalent of triethylamine to yield a 85:15 mixture of diastereoisomers **97** and **98** (Equation 19).



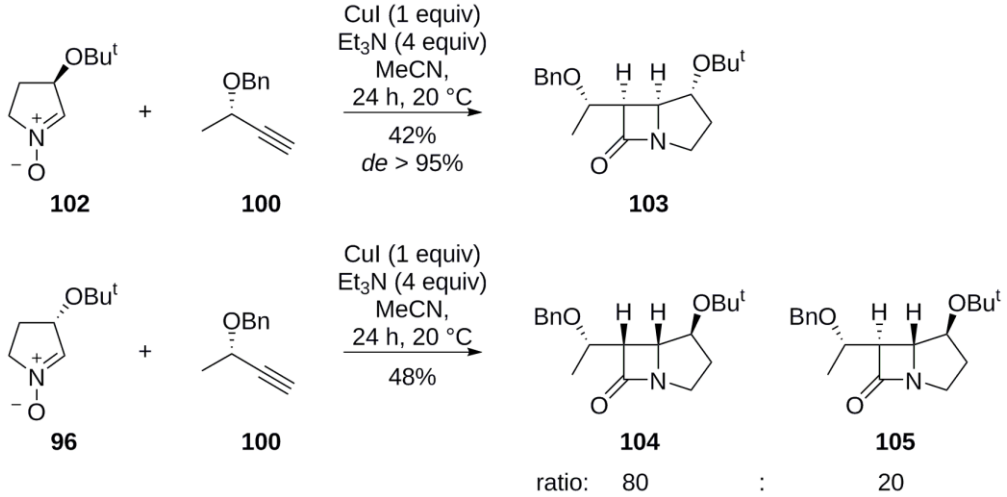
< **Equation 19** near here>

The copper(I)-mediated reaction between nitrones and chiral, non racemic terminal acetylenes was also studied by Chmielewski *et al*.[265] As shown in Equation 20, the reaction of cyclic nitrone **99** with alkyne **100** proceeds with excellent diastereoselectivity (de > 95%), affording the *cis* β-lactam **101**.



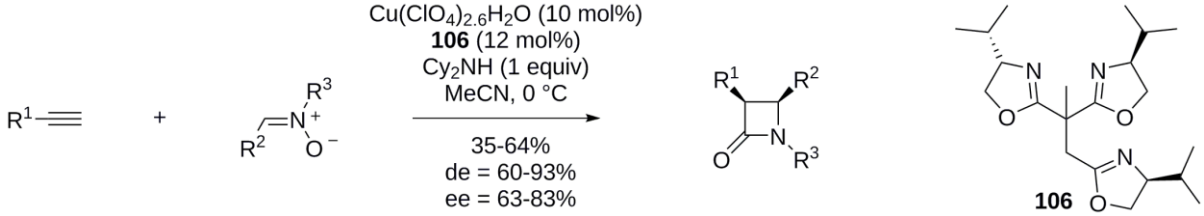
< **Equation 20** near here>

Using both enantiomerically pure reagents, *i.e.* nitrone and acetylene, matched and mismatched pairs have been identified (Scheme 64). Specifically, in reactions with acetylene **100**, the nitrone **102** leads to a quasi total diastereoselectivity, whereas its enantiomer **96** gives a 80:20 mixture of diastereoisomers.



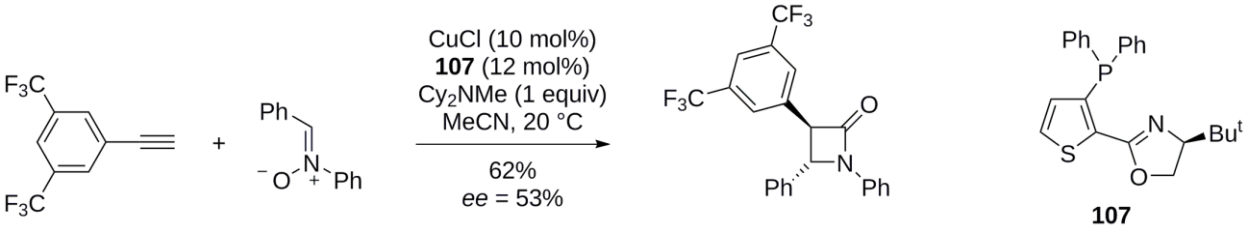
< **Scheme 64** near here>

Pioneering work on the catalytic asymmetric synthesis of β-lactams made use of *bis*-oxazolines as chiral ligands.[258] Later, other ligands such as *bis*-azaferrocenyl[259] and pseudo-C_3-symmetric *tris*-oxazoline[266] ligands enabled increasing enantioselectivities to to about 90% *ee* (Equation 21).[259] The presence of a base was shown to be essential to control the dia- and enantio-selectivities; compared to tertiary and primary amines, secondary amines gave the best results.



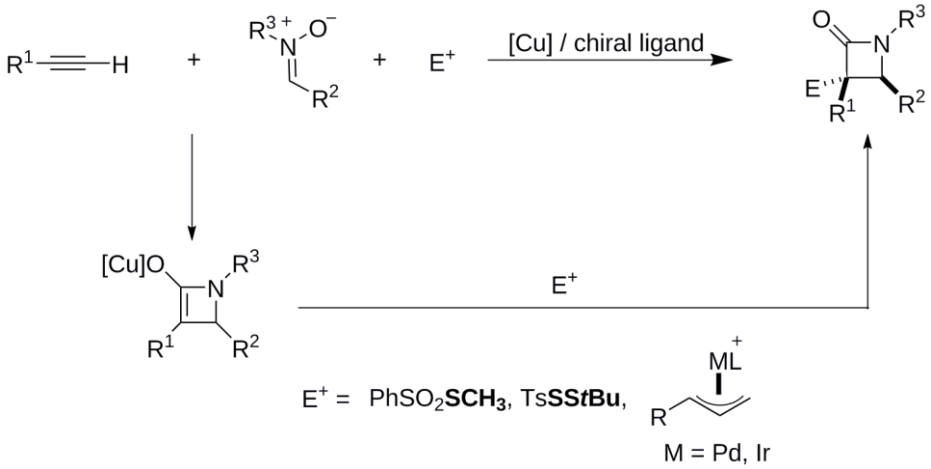
< **Equation 21** near here>

Beside the usual *N*,*N*-ligands, *P*,*N*-ligands, such as **107**, have also been applied to the enantioselective Kinugasa reaction (Equation 22).[267] High levels of enantioselectivity are obtained but with moderate diastereoselectivities.



< **Equation 22** near here>

In order to reach α-quaternary chiral β-lactams, many groups have developed strategies involving the interruption of the Kinugasa catalytic cycle by using an additional electrophile. Since the first example by Fu with allyl iodide,[268] many electrophiles have been studied such as sulfenylating[269] or allylic metal[270,271] reagents (Scheme 65).

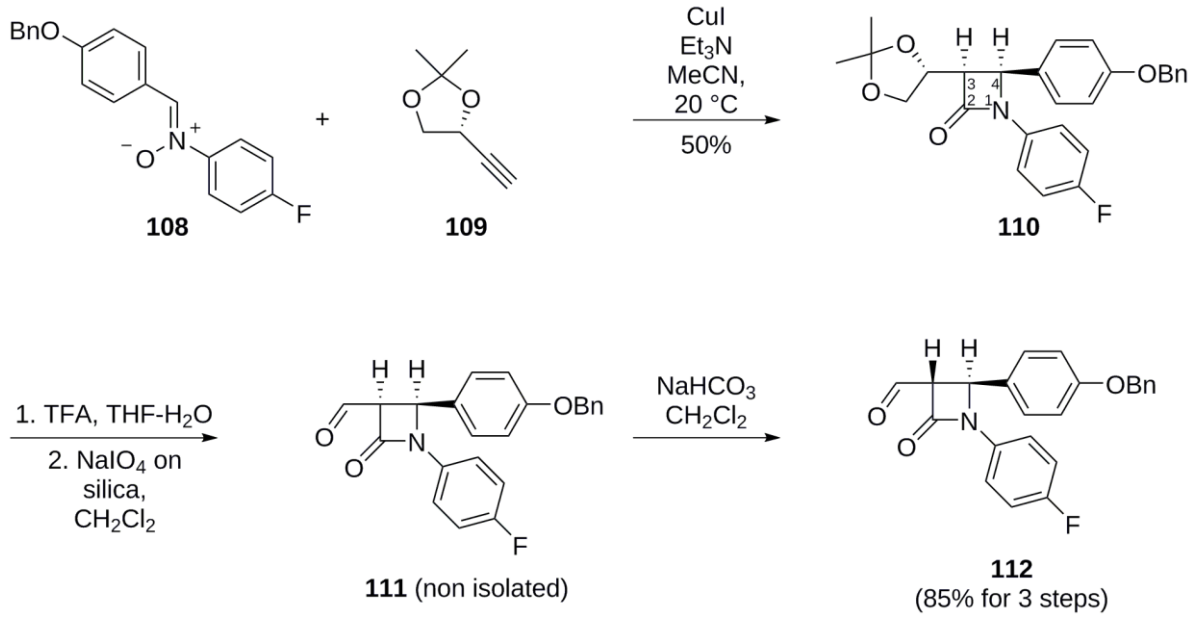


< **Scheme 65** near here>

7.3. Selected applications

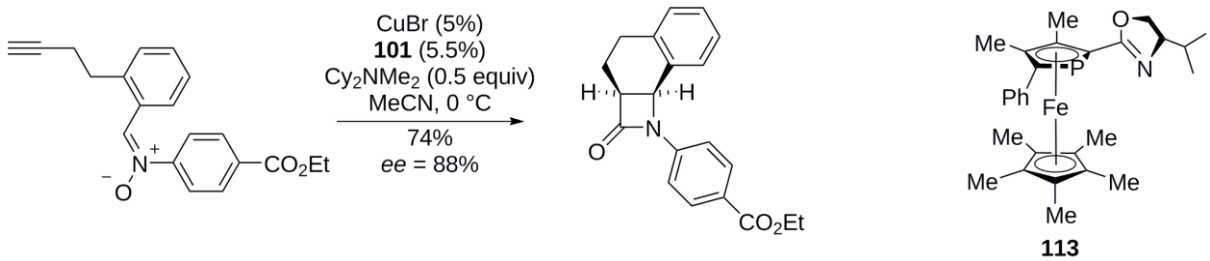
The key-intermediate **112** towards the cholesterol absorption inhibitor Ezetimibe has been synthesized from the nitrone **108** and the enantiomerically pure acetylene **109** (Scheme 66).[272] Under standard conditions (2 equivalents of **108** with respect to **109**, 1 equivalent of CuI and 4 equivalents of triethylamine), the Kinugasa reaction provides the desired *cis* β-

lactam **110** with the (4*S*)-configuration as the major diastereoisomer (separable from the (4*S*)-*trans*, (4*S*)-*cis* and (4*R*)-*trans* isomers). Acetonide deprotection, followed by oxidation to aldehyde **111** and C_3 epimerization lead to the (4*S*)-*trans* β-lactam **112** in 85% overall yield.



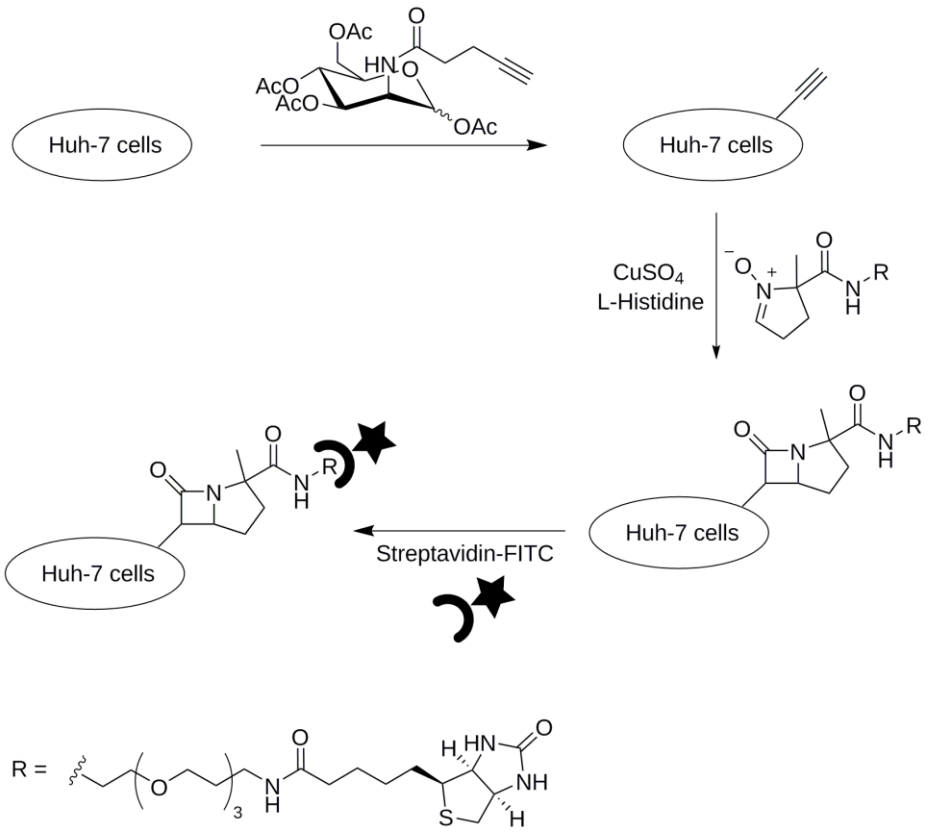
< **Scheme 66** near here>

The intramolecular version of the Kinugasa reaction has been applied to efficiently construct fused tricyclic ring systems with good enantioselectivities when using the chiral ferrocenyl derivative **113** as a catalyst (Equation 23).[273]



< **Equation 23** near here>

A biocompatible version of the Kinugasa reaction has been developed for grafting biotin on living mammalian cells and applications in bioorthogonal labeling with Streptavidin-fluorescein isothiocyanate (FITC) (Scheme 67).[274] The bioorthogonal Kinugasa reaction make use of L-histidine ligand and $CuSO_4$ as copper source.

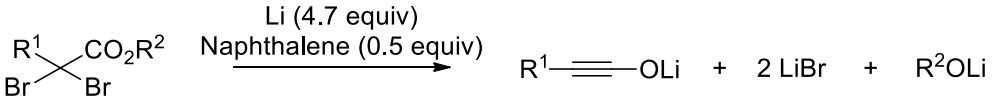


< **Scheme 67** near here>

8. Reaction of ynolates with C=X bonds

8.1. Synthesis of ynolates

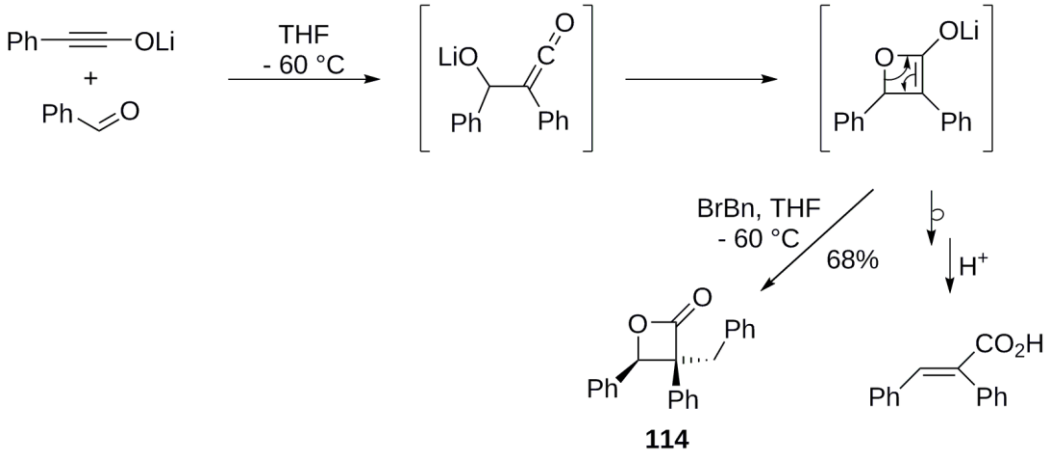
Contrary to enolates, which are well-established carbanions in synthetic organic chemistry, ynolates have attracted much less attention due to the lack of general and convenient methods[275] for their synthesis, until the works of Shindo *et al*.[276] They developed a safe and economical preparation of lithium ynolates by reductive lithiation of α,α'-dibromoesters in the presence of naphthalene (Equation 24).[277] Ynolates can be stored for a few days at room temperature.



< **Equation 24** near here>

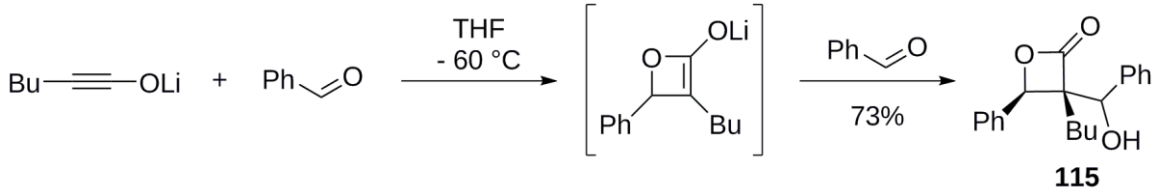
8.2. Reaction with aldehydes and ketones

Lithium phenylynolate reacts with benzaldehyde to give a β-hydroxy lithiated intermediate which cyclizes into a β-lactone enolate; it can be quenched at low temperature with an electrophile such as benzyl bromide to afford the stable β-lactone **114** with a high stereo-control (Scheme 68).[278]



< **Scheme 68** near here>

Lithium butylynolate and two equivalents of benzaldehyde yield the β-lactone **115** resulting from the quenching of the enolate intermediate with the aldehyde itself (Scheme 69).[279]



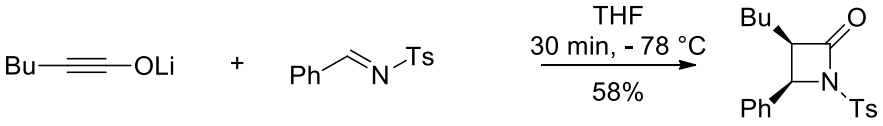
< **Scheme 69** near here>

In the absence of an electrophile, the β-lactone enolate intermediates are transformed upon heating into olefins with high stereoselectivity. Tri- and tetrasubstituted alkenes have been prepared; their configuration is controlled by the torquoselectivity of the electrocyclic ring-opening reaction (Scheme 68).[276]

The ynolate chemistry has been successfully applied to the synthesis of furanes, pyrroles and thiophenes *via* a cascade of reactions, namely cycloaddition, intramolecular cyclization, decarboxylation and dehydration.[280]

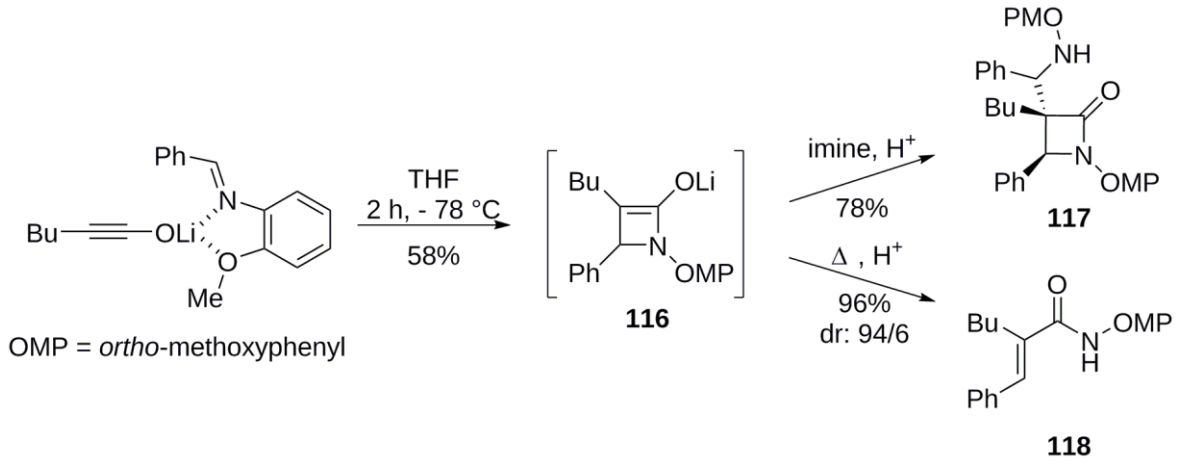
8.3. Reaction with imines

Barrett *et al*[281] and Murai *et al*[275] reported that phenyl- and silylynolates add to aldimines bearing an electron-withdrawing substituent to provide, respectively, β-lactams (2:1 adducts) at low temperature (-60 °C) and α,β-unsaturated amides at room temperature. Reaction of ynolates with *N*-sulfonyl imines leads to β-lactams (1:1 adducts) at -78 °C (Equation 25).[282]



< **Equation 25** near here>

Unactivated imines are not reactive, even in the presence of Lewis acids.[283] One exception is worthy of note: *N*-2-methoxyphenyl imine cycloadds to lithium ynolates as shown in Scheme 70. The authors propose an activation of the imino group by double chelation of the lithium ynolate. The isolated β-lactam **117** corresponds to the 2:1 adduct, because the nucleophilicity of the enolate intermediate **116** is higher than that of the ynolate. As a matter of fact, 1:1 adducts are obtained with the less nucleophilic *N*-tosyl imines (Equation 24). When heated to room temperature before aqueous work-up, the β-lactam enolate **116** suffers a ring-opening reaction leading to the α,β-unsaturated amide **118** in excellent *E*-selectivity.[284]



< **Scheme 70** near here>

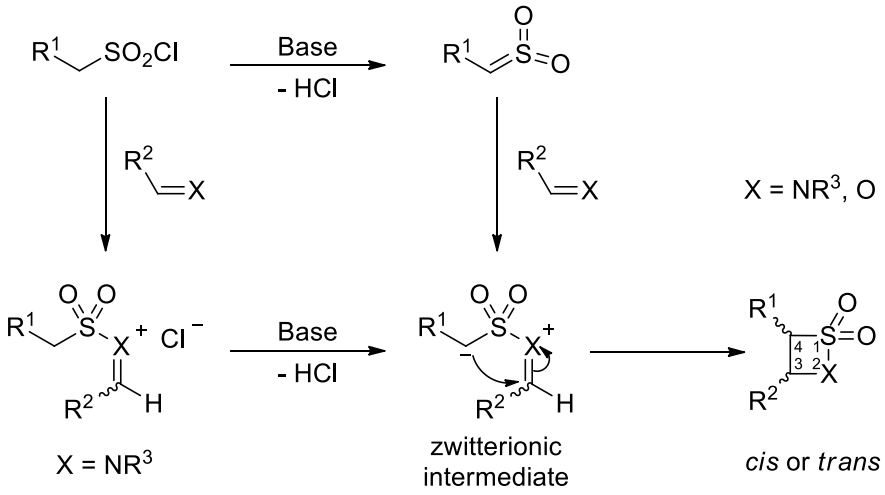
9. Reaction of sulfenes with C=X bonds

9.1. Analogy with the ketene chemistry

Similarly to β-lactams and β-lactones, β-sultams (1,2-thiazetidine-1,1-dioxides) and β-sultones (1,2-oxathietane-1,1-dioxides) have been studied for their potential properties in medicinal chemistry[285,286,287] and synthetic organic chemistry.[288,289]

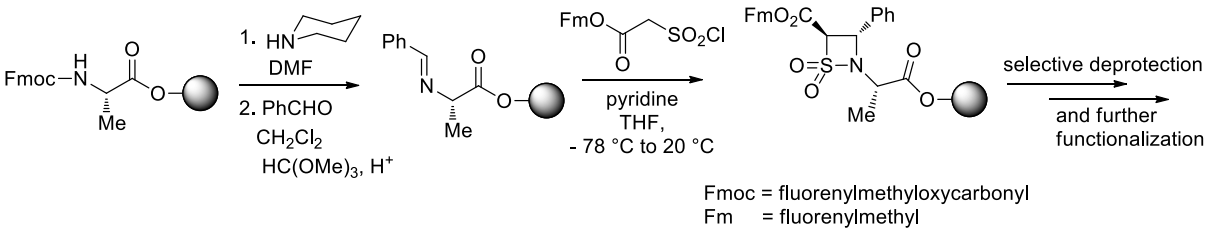
In particular, β-sultams are exploited for the discovery of active site directed inhibitors of serine enzymes such as elastases,[290] β-lactamases[291] and D,D-peptidases.[292] On the other hand, the high reactivity of β-sultams towards nucleophiles, leading to S-N bond cleavage, opens the route to taurine derivatives.[293]

Most often, β-sultams are obtained by cyclization reactions, mainly the formation of the N-S bond[294,295] or the C-C bond.[296] Another general route towards β-sultams is based on the formal [2 + 2] cycloaddition of sulfenes to imines.[285] Sulfenes are formed *in situ* by the dehydrochlorination of alkylsulfonylchlorides with a base at low temperature (Scheme 71).[297,298] Their existence was spectroscopically demonstrated,[299] but in contrast to ketenes, sulfenes cannot be isolated. The reaction with imines (Scheme 71, X = NR^3) has been described as a multi-step process with a zwitterionic intermediate.[300] Depending on the nature of the R^1, R^2 and R^3 substituents, formation of a zwitterionic intermediate *via* the initial reaction of the alkylsulfonyl chloride with the imine is also possible.



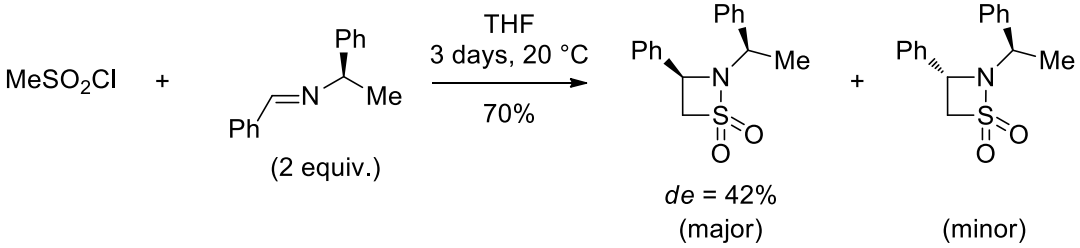
< **Scheme 71** near here>

The diastereoselectivity of the reaction is variable and depends mainly on the nature of R^1. Production of *trans* β-sultams has been reported for the reactions of benzoylmethanesulfonyl chloride (R^1 = PhCO);[301] mixtures of *cis* and *trans* isomers have been obtained with benzylsulfonyl chloride (R^1 = $PhCH_2$).[302] Combinatorial chemistry on solid phase allowed the synthesis of β-sultams libraries with a broad structural diversity.[285] In this application, the imine partner is produced *in situ* from a TentaGel resin derivatized with an aminoacid; the sulfene partner arises from chlorosulfonyl acetates as exemplified in Scheme 72 with the fluorenylmethyl ester (Fm).



< **Scheme 72** near here>

The 1,3-asymmetric induction in solution-phase has been studied using chiral imines derived from (*R*)- or (*S*)-α-methylbenzylamine.[303] The diastereoslectivities are moderate, in favor of the *syn*-stereoisomer, for the [2 + 2] cycloaddition of unsubstituted sulfene produced *in situ* from mesylchloride and 2 equivalents of imine (Equation 26).[304]

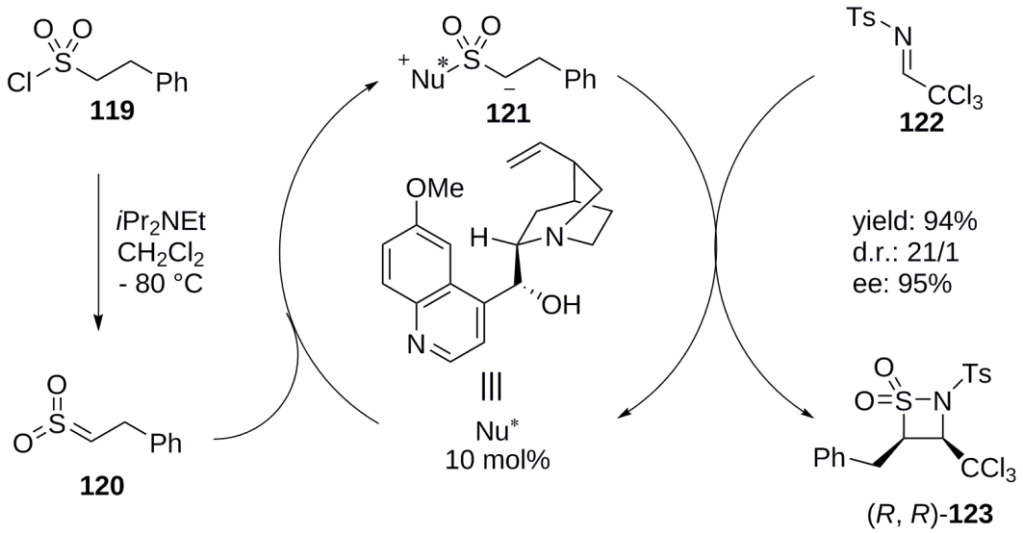


< **Equation 26** near here>

The number of accessible β-sultones, according to the strategy of Scheme 73 with aldehydes (X = O) as nucleophilic partners of the [2 + 2] cycloaddition, is rather limited because most β-sultones are unstable at room temperature. Indeed, the occurrence of proton shift, elimination and rearrangement reactions has been reported.[305,306] Derivatives holding an electron-withdrawing and sterically hindered group at the C_4 atom are the most stable ones (stabilization of the labile C-O bond).[286] For that reason, chloral is the privileged aldehyde for [2 + 2] additions to sulfenes (see Section 9.2.).

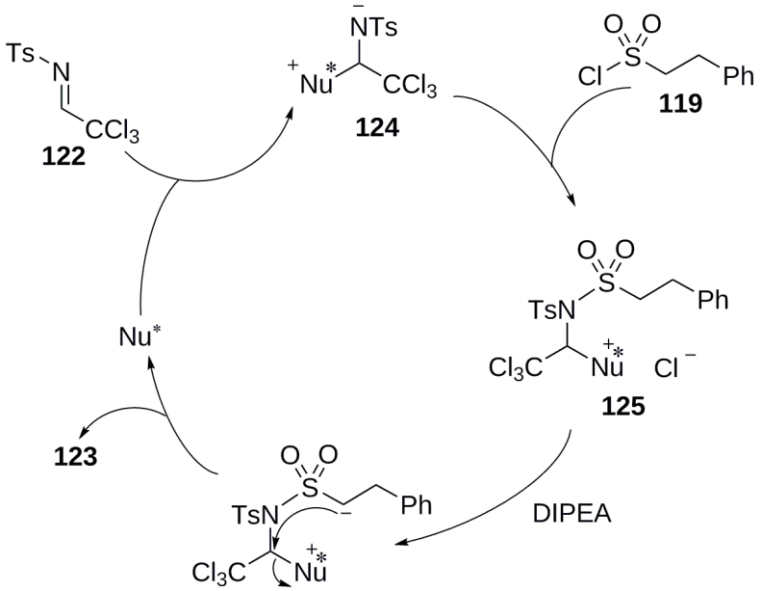
9.2. Catalytic asymmetric synthesis of β-sultams and β-sultones

In contrast to ketenes, the use of sulfenes in asymmetric catalysis is scarcely described and the major contribution in this field is due to R. Peters *et al.*[286,293,307,308] The main problem relies on the instability of sulfenes which have to be produced *in situ* at very low temperature. Nevertheless, reproducible protocols could be validated for the catalytic asymmetric synthesis of β-sultams and β-sultones, using electron-poor imines and aldehydes as highly activated partners of the [2 + 2] cycloadditions, and employing cinchona alkaloid derivatives as nucleophilic organocatalysts (Scheme 73).



< **Scheme 73** near here>

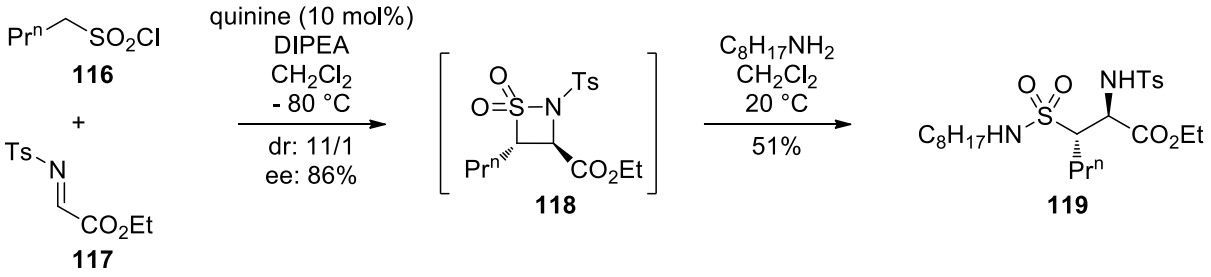
The sulfene **120**, produced *in situ* by dehydrochlorination of the corresponding sulfonyl chloride **119** by diisopropylethyl amine (DIPEA), reacts with the chiral nucleophilic catalyst (Nu*) to form the zwitterionic intermediate **121** capable of initiating the asymmetric [2 + 2] cycloaddition with the electron-poor *N*-tosyl imine (**112**) (Scheme 74). Indeed, **122** has to be non-nucleophilic to avoid the non-catalyzed competitive reaction between **122** and **120**. Using the cinchona alkaloid quinine as the catalyst, the *cis* β-sultam **122** is obtained in 94% yield with 95% of enantiomeric excess. Depending on the temperature and the order of addition of the reagents, another catalytic cycle has been proposed, involving the intermediate formation of an adduct (**124**) of the catalyst (Nu*) with the highly electrophilic imine **122**. The negatively charged N-Ts atom of **124** attacks the sulfonyl chloride (without prior formation of a sulfene) to give intermediate **125** which suffers deprotonation by DIPEA. Lastly, an intramolecular nucleophilic substitution leads to the β-sultam **123** and the release of the catalyst (Scheme 74).



< **Scheme 74** near here>

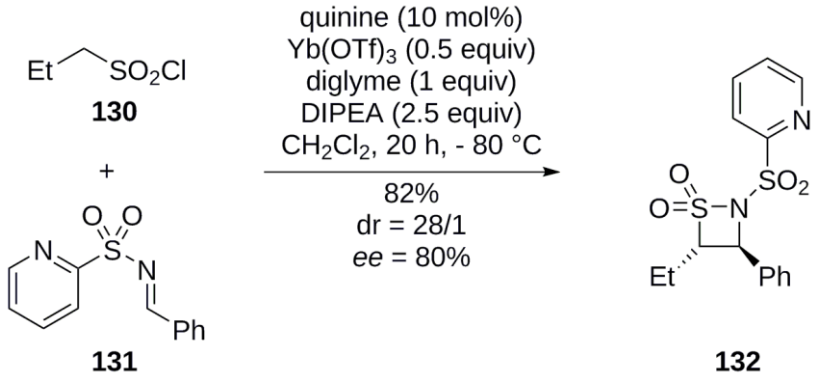
The methodology has been extended to α-iminoesters. Because these imines are prone to polymerize, the reagent **127** is added very slowly to a solution of catalyst (quinine), DIPEA

and sulfonyl chloride **126** at -80 °C to furnish the *trans*-β-sultam **128** in 86% *ee*. The tandem one-pot cycloaddition / nucleophilic ring opening sequence with octylamine leads to **128** in 51% yield (Scheme 75).



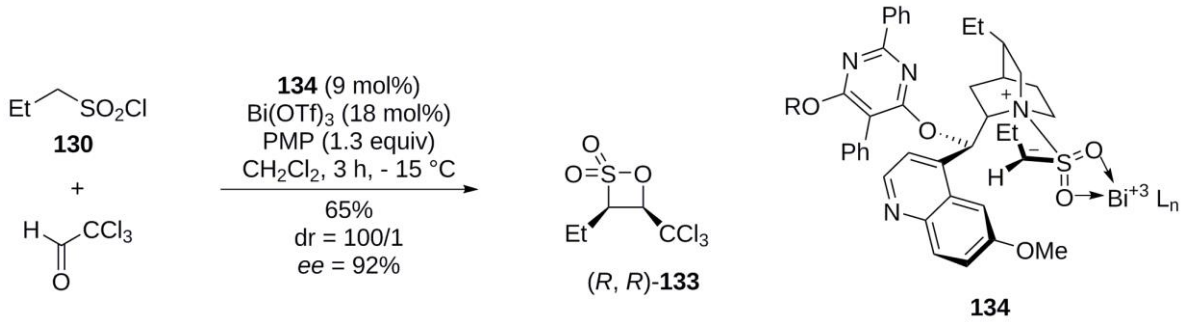
< **Scheme 75** near here>

Arylaldimines are less reactive towards sulfenes and therefore require the replacement of the tosyl group with the 2-pyridylsulfonyl group. Indeed, this moiety offers the possibility of bidentate coordination to a Lewis acid co-catalyst, giving an additional activation. For instance, the reaction of sulfonyl chloride **130** with imine **131** in the presence of DIPEA, quinine (10 mol%), ytterbium triflate as co-catalyst and diglyme as additive, yields the *trans*-β-sultam **132** in 82% yield and 80% *ee* (Equation 27)



< **Equation 27** near here>

The catalytic system developed for the asymmetric synthesis of β-sultams (Scheme 75) is not similarly efficient for the preparation of enantiomerically pure β-sultones (replacement of imine **117** with chloral).[286] The addition of a Lewis acid co-catalyst is required to enhance the performance. As the result of a large screening of reagents and experimental conditions, the selected catalytic system involves: (i) dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$) as the chiral nucleophilic catalyst; (ii) bismuth triflate as the Lewis acid co-catalyst; (iii) 1,2,2,6,6-pentamethylpiperidine (PMP) as the stoechiometric non-nucleophilic base; (iv) an excess of chloral (2.75 equivalents) (Equation 28). Under these reaction conditions, the cycloaddition of ethyl sulfene to chloral (trichloroacetaldehyde) affords the *cis*-β-sultone **133** with the *R*,*R*-configuration (established by X-ray diffraction analysis).[286] This result can be rationalized by the formation of a sulfene-$(DHQ)_2PYR$ adduct **124** coordinated to the Bi^{3+} salt, which is the reactive species for the addition to chloral. Another role attributed to the bismuth salt was the coordination of the aldehyde; the coordination of both reactants may lead to a highly organized transition state and consequently to high enantioselectivity.

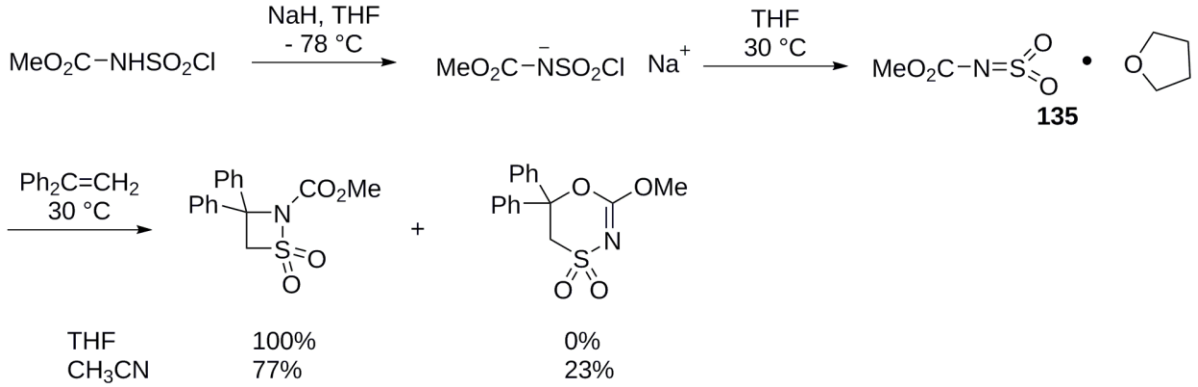


< **Equation 28** near here>

10. Miscellaneous

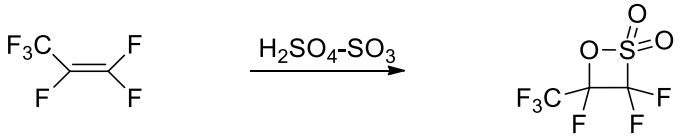
10.1. Four membered rings containing one sulfur atom

N-Sulfonylamines ($RN=SO_2$) are able to react with strained or nucleophilic alkenes to furnish β-sultams.[309] Methyl *N*-sulfonylurethan **135** cycloadds to non-activated alkenes, due to its high electrophilicity (Scheme 76).[310] This species is produced *in situ* from carbomethoxysulfamoyl chloride and is stabilized by complexation with tetrahydrofuran. A solvent dependent competition between [2 + 2] and [4 + 2] cycloadditions has been reported.[314]



< **Scheme 76** near here>

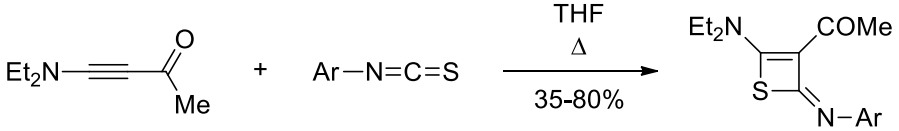
The similar [2 + 2] cycloaddition of sulfur trioxide with alkenes generates β-sultones, a method especially dedicated to the synthesis of perfluorinated derivatives (Equation 29). Perfluorinated β-sultones are used for the preparation of hybrid organic – inorganic mesoporous materials featuring terminal sulfonic acid groups; such materials are better catalysts than Nafion-silica® for the esterification of fatty acids.[311,312]



< **Equation 29** near here>

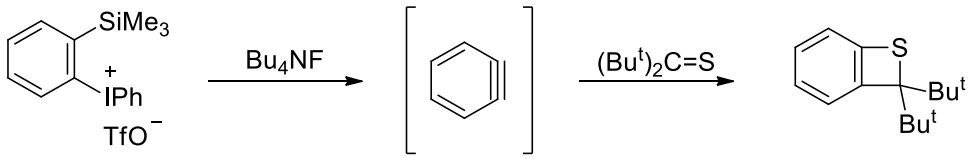
Oleum (fuming sulfuric acid) can be used as a source of SO_3.[313] Otherwise, the SO_3.pyridine complex is the usual source of SO_3. An alternative strategy to produce SO_3 *in situ* is based on the reaction of trimethylsilylsulfonyl chloride with iodosobenzene at low temperature; performed in the presence of alkenes, this method allows β-sultones to be isolated in moderate to good yields.[314]

The [2 + 2] cycloaddition of 4-diethylamino-3-butyn-2-one (ynamine) with aryl isothiocyanates leads to thietimine derivatives (Equation 30).[315]



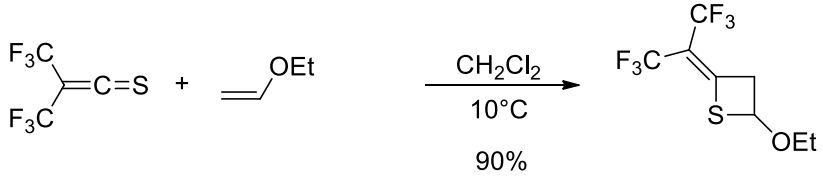
< **Equation 30** near here>

Fused thietes are obtained by the reaction of benzyne with thioketones (Scheme 77).[316]



< **Scheme 77** near here>

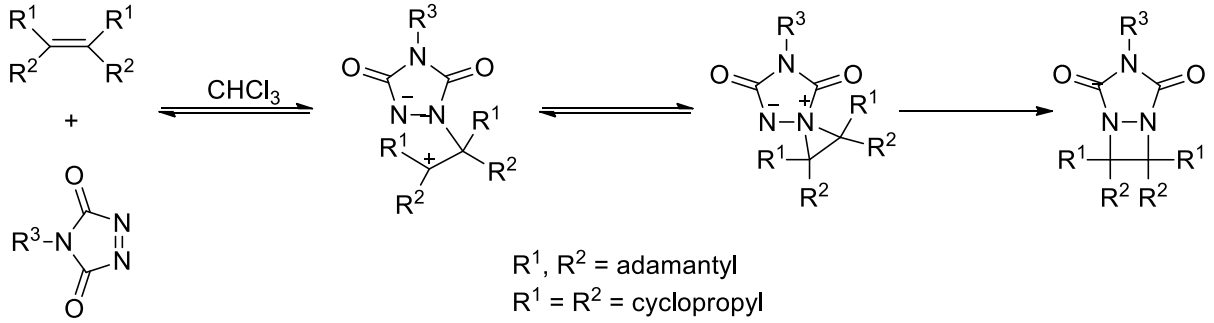
Since thioketenes are usually difficult to prepare, only reactions of bis(trifluoromethyl)thioketene as a stable representative with a range of C=C bonds have been studied. Unlike the other heterocumulenes, [2 + 2] cycloadditions occur across the cumulene C=X bond, leading to 2-exo-methylene-thietane derivatives (Equation 31).[193]



< **Equation 31** near here>

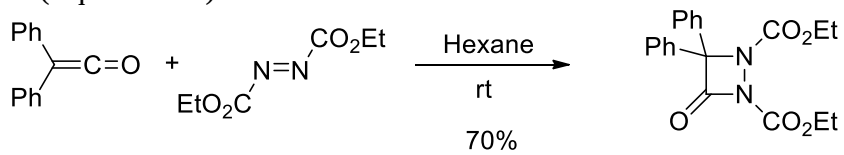
10.2. Four membered rings containing two nitrogen atoms

The formation of two C-N bonds by [2 + 2] cycloaddition between alkenes and azo compounds constitutes the general route towards 1,2-diazetidines.[317] Reactions between highly substituted alkenes and 1,2,4-triazoline-3,5-diones lead to bicyclic, N-N fused, diazetidine derivatives, most probably *via* zwitterionic intermediates (Scheme 78).[318,319,320]



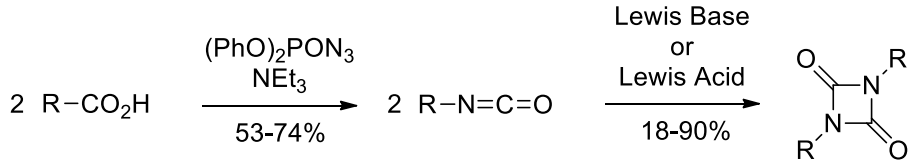
< **Scheme 78** near here>

1,2-Diazetidin-3-ones are obtained by [2 + 2] cycloaddition of ketenes to azobenzenes. Since only the *cis* stereoisomers are reactive, these reactions require light activation to isomerize the azobenzenes in situ.[321] In contrast, azodicarboxylates and azoketones react without irraditation (Equation 32).[322,323]



< **Equation 32** near here>

1,3-Azetidin-2,4-diones are classically obtained by dimerization of isocyanates under either Lewis base or Lewis acid catalysis. Non-commercially available isocyanates can be readily obtained from carboxylic acids by the Curtius rearrangement (Scheme 79).[324,325]

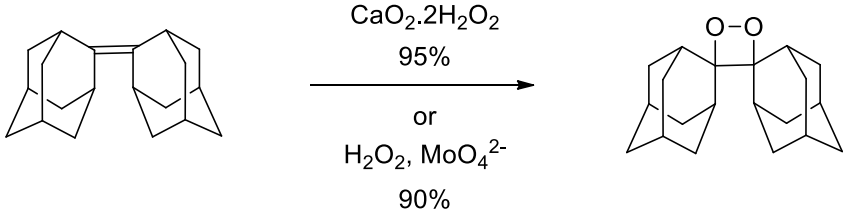


< **Scheme 79** near here>

Carbodiimide dimerization[326] and cross-dimerization between isocyanates and carbodiimides[327] have also been reported.

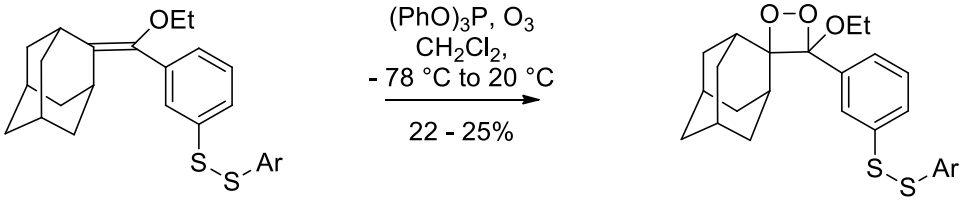
10.3. Four membered rings containing two oxygen atoms

In the past, 1,2-dioxetanes were prepared by cyclization methods, from β-halo hydroperoxides or from β-epoxy hydroperoxides. Presently, the cycloaddition of singlet oxygen to electron-rich alkenes is the most useful method, exemplified with a large number of compounds and employing a range of singlet oxygen sensitizers.[328,329,330,331,332] Environmentally friendly sources of singlet oxygen have been described, such as calcium peroxide diperoxohydrate[333,334] and hydrogen peroxide with molybdate ions in a reverse microemulsion (Equation 33).[335]



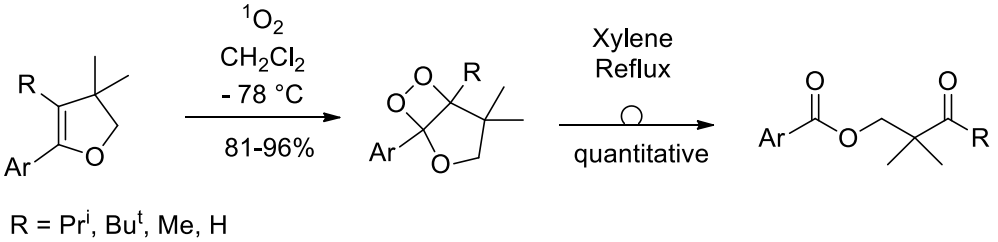
< **Equation 33** near here>

Beside the above general method, enol ethers could be transformed into 1,2-dioxetanes with triphenylphosphite and ozone (Equation 34);[336] this protocol is compatible with the sensitive disulfide function which is not oxidized.



< **Equation 34** near here>

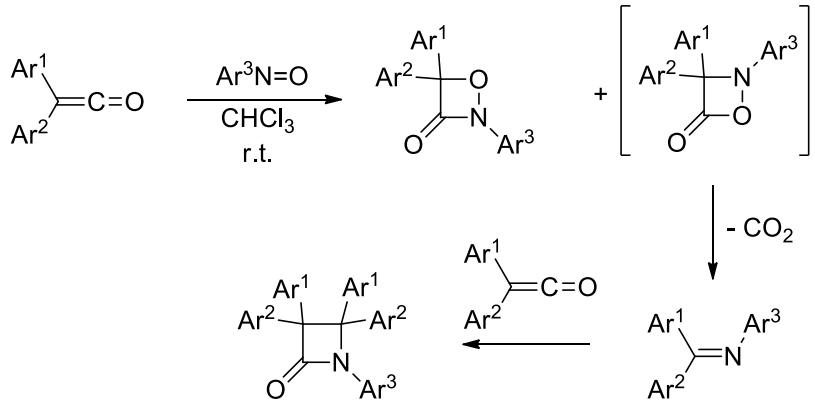
Singlet oxygen oxidation of cyclic enol ethers leads to the fused bicyclic 1,2-dioxetanes prone to rearrange into keto-esters when R = H (Scheme 80).[337]



< **Scheme 80** near here>

10.4. Four membered rings containing one nitrogen and one oxygen atom

The cycloaddition of diarylketenes onto arylnitroso derivatives occurs with poor regioselectivity: mixtures of 1,2-oxazetidin-3-ones and 1,2-oxazetidin-4-ones are obtained (Scheme 81). The latter is however unstable and decomposes into imines which are trapped by the ketene reagent to form β-lactams.



< **Scheme 81** near here>

11.Conclusion

The four-membered heterocycles are important building blocks in the synthesis of a wide range of biologically active molecules, including drugs and natural products. There are several classes of four-membered heterocycles that are valuable in organic synthesis and medicinal chemistry such as β-lactone, azetidine and oxetane but the considerable attention paid to these heterocycles originates from the discovery of β-lactams as antibiotics.

Accordingly, the synthesis of four-membered heterocycles via [2 + 2] cycloaddition has attracted significant interest. The [2 + 2] cycloaddition strategies toward β-lactams involve the reaction of imines with ketenes (Staudinger reaction), keteniminium, ynolates, enols or enolates as well as the cycloaddition of alkenes with isocyanates and the reaction between alkynes and nitrones (Kinugasa reaction). The [2 + 2] cycloaddition of imines with alkenes, allenes or alkynes is also described to lead to azetidine derivatives. Applied to carbonyl compounds, some of these reactions provide an access to β-lactones.

The use of a chiral catalyst (Lewis acid, NHC, organocatalyst) or a chiral auxiliary has enabled the development of enantioselective versions of some of these methodologies. Advances in the enantioselective synthesis of four-membered herterocycles are however still fundamental in order to drive innovation in synthesis and biology.

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