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Review

Synthesis of 2-Azetidinones via Cycloaddition Approaches: An Update

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Abstract: The present review is a comprehensive update of the synthesis of monocyclic ◎-lactams via cycloaddition reactions. According to the IUPAC definition of cycloaddition, both elementary and stepwise processes (formal cycloadditions) have been considered. The years 2019-2022 are covered by the cited literature. The focus of the review is on synthetic aspects with emphasis on the structural scope, reaction conditions, mechanistic aspects, and selectivity results. Selected significant data related to biological activities and synthetic applications are also highlighted.

Keywords: 2-azetidinone; β-lactam; cycloaddition; ketene; imine; isocyanate; nitrone

1. Introduction

2-Azetidinones, or monocyclic β-lactams or monobactams are a highly studied class of compounds.[1–5]. In addition to their well-documented antibacterial and anti-β-lactamase activities, β-lactams have attracted interest as promising drugs in other therapeutic areas, including neurodegenerative diseases and coagulation therapy[6–10]. β-Lactams are also useful synthetic intermediates for the synthesis of β-amino alcohols, β-amino acids, and nitrogen-containing compounds in general [11,12].

This review is an update of the CHEC-IV 2.01 Chapter 'Azetidines, Azetines and Azetes: Monocyclic' by Andresini, Degennaro and Luisi [1], as well as the *Chemical Review* article by Pitts and Lectka [3]. The purpose of this review focuses on ◎-lactam synthesis and, among the numerous synthetic methods reported in the literature, we provide here a comprehensive survey of monocyclic 2-azetidinones synthesized by a cycloaddition approach from 2019 to 2022 (articles that appeared as online publications in the above time interval are cited in this review according to the final publication date). The cycloaddition reactions covered in this review adhere to the IUPAC definition of a cycloaddition:"*A reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. ….. Cycloadditions may be pericyclic reactions or non-concerted stepwise reactions.*"[13] (pp. 1103-1104).

On this basis, the different types of cycloaddition processes applied in the synthetic assembly of 2-azetidinones are described and discussed, with a focus on structural scope, reaction conditions, mechanistic aspects, and related selectivity outcomes. Significant results related to various biological activities and applications are also highlighted.

2. Ketene-Imine Cycloaddition (Staudinger Synthesis)

Ketene-imine cycloaddition, known as Staudinger synthesis discovered in 1907, still remains the most general method to access variously substituted 2-azetidinones [1–5,14–18]. This reaction, which is quite simple from the practical point of view, has a rather complex mechanism, especially with regard to stereoselectivity. This depends largely on the nature of the reactants (mainly on the electronic and steric effects of the substituents) and the experimental conditions (solvent,

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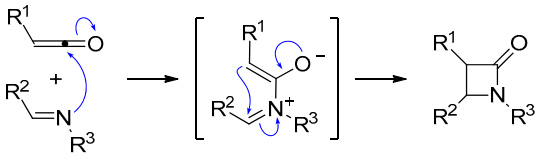
temperature) and for these reasons numerous theoretical and experimental studies on this topic are still present in the literature.

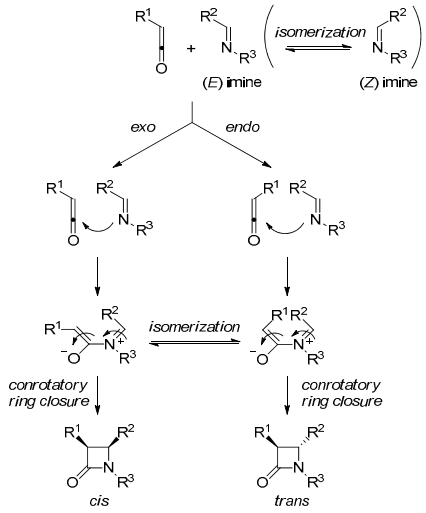
The process is a formal [2+2]-cycloaddition able to generate up to two chiral centers in the cyclic product. The concerted thermal approach requires the orbital symmetry allowed [⊚2s+⊚2a] pathway which is, unfortunately, geometrically demanding. Thus, a two-step mechanism involving a sequential formation of the N(1) – C(2) and C(3) – C(4) covalent bonds of the ⊚-lactam ring is commonly accepted. The first step of the reaction likely implies the nucleophilic addition of the imine nitrogen on the sp-hybridized carbon atom of the ketene to form a zwitterionic intermediate. The following four-electron conrotatory electrocyclization (that can be also viewed as an intramolecular Mannich-type reaction of the enolate on the electrophilic iminium moiety) gives rise to the four-membered cycloadduct (Scheme 1) [19,20].



Scheme 1. Ketene-imine cycloaddition (Staudinger synthesis of ⊚-lactams).

The scope of the Staudinger cycloaddition was computationally analyzed by considering a series of substituents placed at the ketene Cα and imine Cα and N positions. The results obtained by means of DFT calculations show that the reaction performance mainly depends on the electrocyclic step (rate-determining step), rather than the initial nucleophilic attack. In particular, the reaction outcomes are scarcely influenced by the substituents on the imine, while they are essentially determined by the steric and electronic nature of the substituents present at the α-position of the ketene. The latter has a dominant effect on the overall feasibility of the reaction [21].

One of the main critical aspects of the process is the *cis-trans* diastereoselectivity. In this regard, it is usually assumed that the first step takes place through the less hindered side of the ketene (*exo*-approach, that is favored with respect to the *endo*-approach) (Scheme 2). The second step, a conrotatory electrocyclization, is subject to torquoelectronic effects that depend on the relative in/out relationship between the C-3 and C-4 substituents. In general, (*E*)-imines give *cis* ⊚-lactams while (*Z*)-imines yield *trans* ⊚-lactams; however, recent studies, have shown that the stereochemical outcome may also depend on isomerization pathways at the level of the starting imine or in the zwitterionic intermediate (Scheme 2) [14].



Scheme 2. Thermal ketene-imine cycloaddition: *cis-trans* diastereoselectivity analysis [the same pathways can operate even for (*Z*)-imine].

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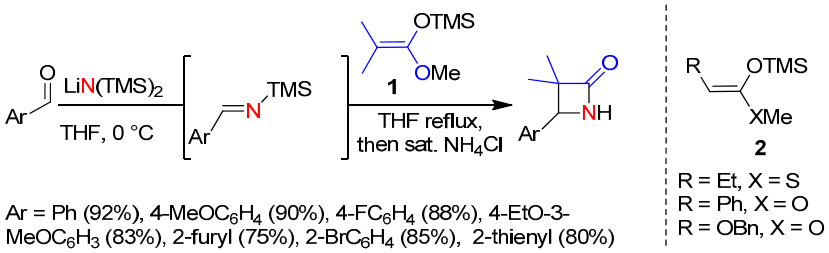
The use of preformed and isolated ketenes as reagents in the Staudinger synthesis is limited by the instability of these compounds. Commonly, ketenes are generated *in situ* from precursors such as acyl chlorides, carboxylic acids, diazo compounds, haloesters, and enolates.

The contents of this section are organized considering the different methods applied for ketene generation.

2.1. Ketene Generated In Situ from Ketene Acetals

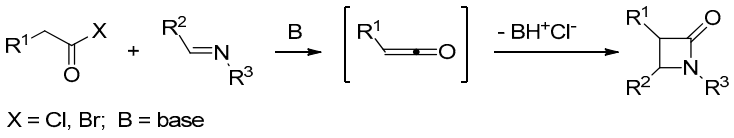
An example of the use of a masked ketene has been reported by Magriotis *et al.* 3,3-Dimethyl β-lactams with a 4-aryl/heteroaryl substituent were synthesized *via* an uncatalysed reaction between dimethylketene acetal **1** and *N*-trimethylsilyl imines, the latter generated *in situ* by treatment of benzaldehydes, furfural, and 2-thiophenecarboxaldehyde with lithium hexamethyldisilazide [LiN(TMS)$_2$]. It is worth noting that the process did not succeed when other similar ketene acetals were used, such as **2** (Scheme 3) [22].



Scheme 3. Synthesis of β-lactams from arylimines and TMS-ketene acetals.

2.2. Ketene Generated In Situ from Acyl Chlorides and Acyl Bromides

Ketenes are often generated from acyl chlorides by treatment with a tertiary amine and are trapped *in situ* by imines to give azetidinones via [2+2]-cycloaddition (Scheme 4, X = Cl; B = R$_3$N). Recently, several monocyclic β-lactams have been prepared using this protocol. This approach is often used to synthesize hybrid molecules,[23] that is, compounds containing the β-lactam ring linked to other bioactive heterocycles. The goal is to create new potential drug candidates with improved biological properties due to the synergistic action of the two or more heterocycles.



Scheme 4. General protocol to access ketenes from acyl chlorides/bromides and synthesis of azetidine-2-ones.

The contents of this section are organized by type of substituents on the C-2 of the acyl chloride (corresponding to the C-3 position of 2-azetidinones) and then, possibly, by substituents on the nitrogen atom of imine (corresponding to the N-1 position of 2-azetidinones). Schemes and charts show the structures of β-lactams, the conditions used to generate them and the yields by which they were obtained. When β-lactams were designed and tested for a particular bioactivity, the types of tests are also mentioned.

2.2.1. Ketene Generated In Situ from Acetyl Chloride

Staudinger cycloaddition of imines with ketenes generated from acetyl chloride affords 3-unsubstituted β-lactams.

As shown in Scheme 5, 2-azetidinones **3** variously decorated with oxadiazole and indole, quinazolin-(3*H*)-one and 11*H*-indeno-[1,2-*b*]-quinoxaline moieties, respectively, were prepared in

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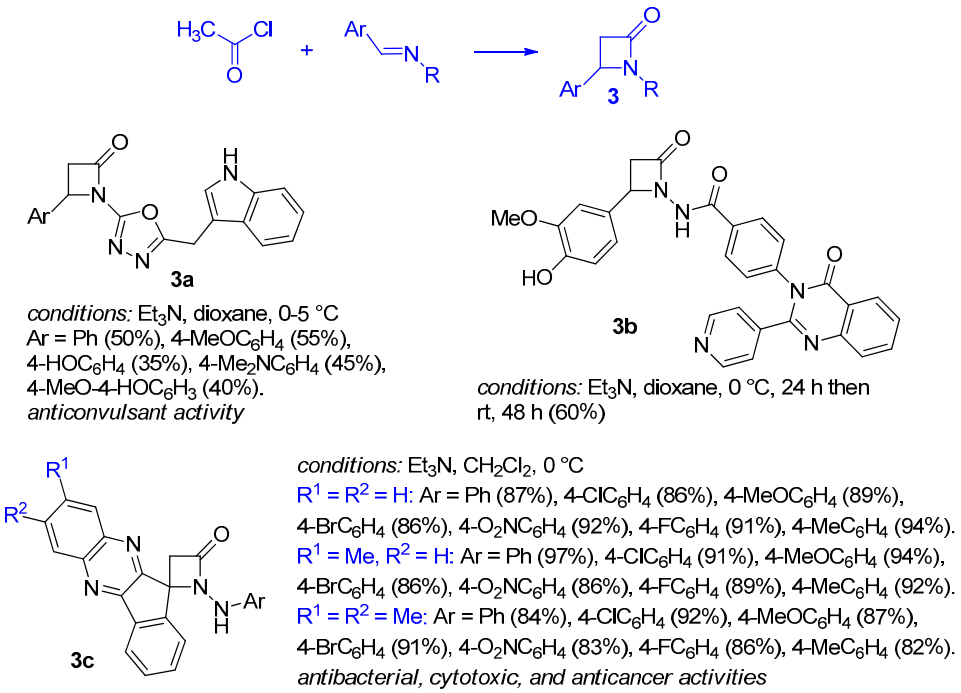
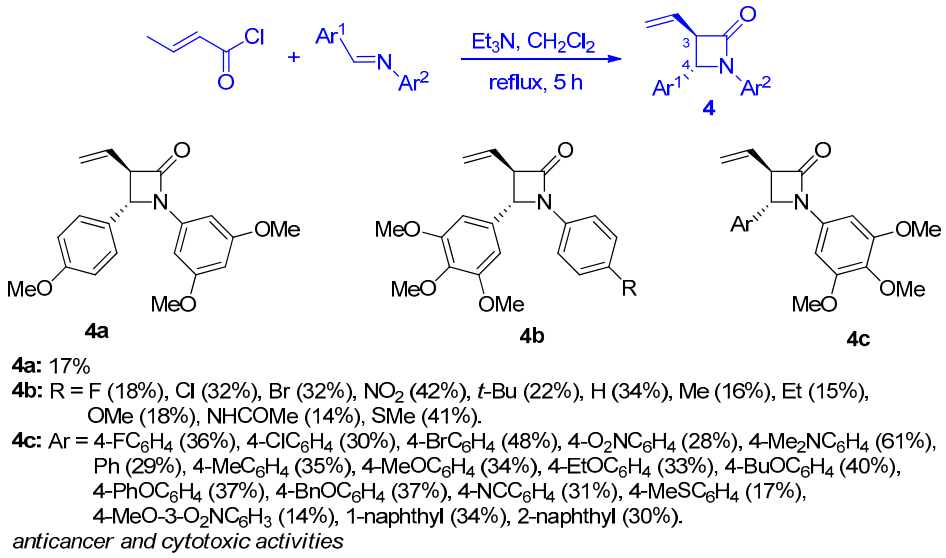
good yield from acetyl chloride and suitable aromatic imines in the presence of triethylamine as a base at low temperature [24–26].



Scheme 5. Synthesis of 3-unsubstituted-2-azetidinones. *(Tested activities are in italics)*.

2.2.2. Ketene Generated In Situ from 2-Alkyl-, 2-Vinyl-, and 2-Arylacetyl Chloride

3-Vinyl-2-azetidinones **4** were prepared by adding crotonyl chloride to a solution of suitable aromatic imines and triethylamine in dichloromethane under reflux conditions (Scheme 6) [27]. The reaction was highly diastereoselective with exclusive formation of *trans* adducts, as attested by a characteristic coupling constant between the 3-H and 4-H hydrogens of less than 3 Hz ($J_{3,4}$ = 1.0-2.5 Hz). Furthermore, the stereochemical assignment of **4b** (R = Et, OMe, SMe) and **4c** (Ar = 4-MeOC$_6$H$_4$) was confirmed by X-ray structural analysis. Derivative **4c** (Ar = 4-MeO-3-HOC$_6$H$_3$) showed potent activity in MCF-7 breast cancer cells (IC$_{50}$ = 8 nM) and minimal cytotoxicity against non-tumorigenic cells.



Scheme 6. Synthesis of 3-vinyl-2-azetidinones. *(Tested activities are in italics)*.

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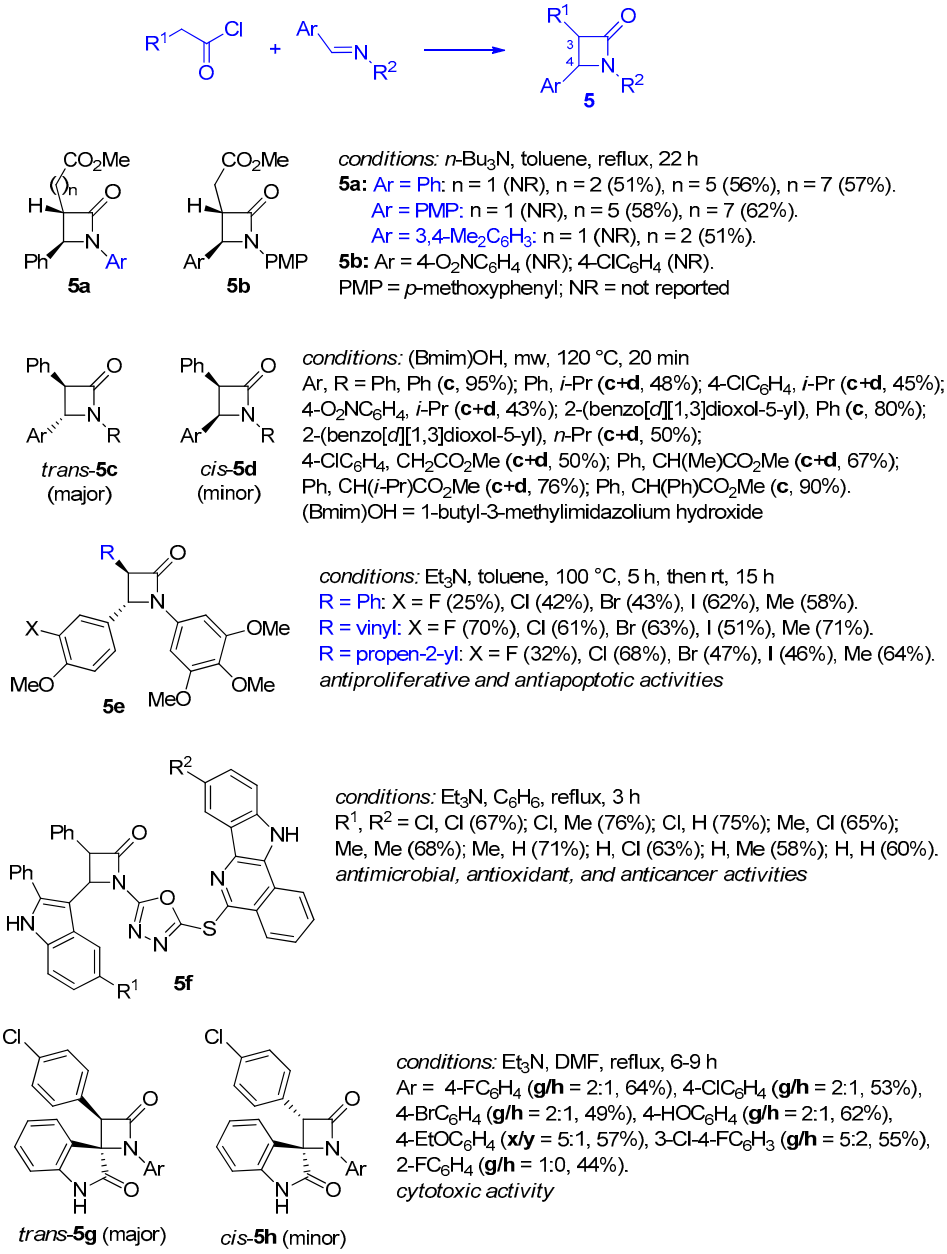
Some 3-alkyl- and 3-aryl-2-azetidinones prepared by Staudinger synthesis are shown in Scheme 7. *trans*-1,4-Diaryl-2-azetidin-2-ones **5a** and **5b** ($J_{3,4}$ = 2.0-2.3 Hz) were synthesized in refluxing toluene (Scheme 7) [28]. Ketenes were generated *in situ* from the monomethyl ester chloride of succinic, glutaric, suberic, and sebacic acids by treatment with tributylamine. The carboxyl moiety linked to C-3 of the β-lactam by a chain of variable length was then exploited to acylate the nitrogen atom of 7-aminocephalosporanic acid. The final compounds bearing two β-lactam rings were tested as antibiotics.

Hydroxide anion of the ionic liquid 1-*n*-butyl-3-methylimidazolium hydroxide [(Bmim)OH] was used as a base to promote the formation of phenyl ketene in the synthesis of **5c** and **5d** (Scheme 7) [29]. The reaction was conducted under microwave irradiation (mw) at 120 °C and provided the *trans* isomer **5c** as the main or sole product.



Scheme 7. Synthesis of 3-alkyl- and 3-aryl-2-azetidinones **5**. *(Tested activities are in italics).*

3-Phenyl-, 3-vinyl-, and 3-propenyl-β-lactams **5e** were prepared by Staudinger synthesis in toluene at 100 °C with complete *trans*-stereoselectivity ($J_{3,4}$ = ca 0-2.5 Hz) (Scheme 7) [30]. Structure of the 3-phenyl derivative **5e** (R = Ph, X = F) was confirmed by X-ray analysis. This β-lactam, which

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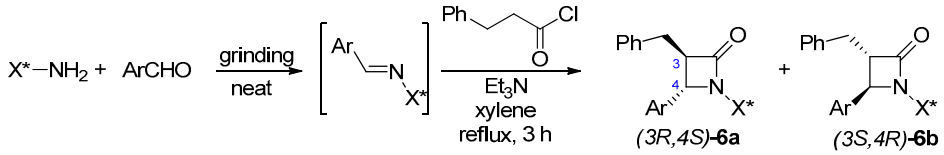
showed remarkable metabolic stability, was found to have high activity against HT-29 colon cancer cells (IC_{50} = 9 nM) and MCF-7 breast cancer cells (IC_{50} = 17 nM).

3-Phenyl-2-azetidinone **5f** (R^1 = R^2 = Me) showed good cytotoxicity against MFC-7, A-589, and HeLa cancer cells (IC_{50} = 0.63-0.85 ◎M) (Scheme 7) [31].

4-Spirofused (2-oxoindolin-3-yl)-2-azetidinones **5g** and **5h** (Scheme 7) [32] were prepared from isatin-derived imines with 2-(4-chlorophenyl)acetyl chloride in the presence of triethylamine in refluxing DMF. Under these reaction conditions, the unwanted isomer *trans*-**5g** was mainly formed. Fortunately, the diastereoselectivity was reversed by forming acyl chloride *in situ* from 2-(4-chlorophenyl)acetic acid and oxalyl chloride and carrying out the reaction at room temperature (see Scheme 53).

In a recent review on electrochemically induced synthesis and functionalization of β-lactams, the application of this technique to the Staudinger synthesis was reported. In particular, 1-aryl-3,4-diphenyl-2-azetidinones were prepared via dehydrohalogenation of 2-phenylacetyl chloride with an electrogenerated *N*-heterocyclic carbene (NHC) to give the phenylketene, which was trapped *in situ* by an arylimine [33].

1-Aminoindane (IND-NH_2) and 1,2,3,4-tetrahydro-1-naphthylamine (THN-NH_2) in both enantiomeric forms were used as chiral auxiliaries in the synthesis of 3-benzyl-β-lactams **6a** and **6b** (Scheme 8) [34]. The chiral imines, prepared by grinding amines and aromatic aldehydes, were treated directly with 3-phenylpropionyl chloride and triethylamine in xylene at high temperature (140 °C). Under the reported reaction conditions, *trans*-diastereoselectivity was complete ($J_{3,4}$ = 2.0-2.4 Hz), while the control of the absolute configuration of the newly generated C-3 and C-4 stereocenters ranged from 59 to 76%. In general, THN-NH_2 was a more efficient chiral auxiliary than IND-NH_2, and the highest selectivity was obtained with Ar = 3,4,5-$(MeO)_3C_6H_2$.



X* = (*S*)- and (*R*)-1-indanyl (IND); (*S*)- and (*R*)-1-(1,2,3,4-tetrahydronaphthyl) (THN)

X*	Ar	Yield (%)[a,b]	ds (%)[b]
(*S*)-IND	2-$MeOC_6H_4$	73	59
(*S*)-THN		78	65
(*S*)-IND	2,3-$(MeO)_2C_6H_3$	74	59
(*S*)-THN		79	65
(*S*)-IND	3,4-$(MeO)_2C_6H_3$	83	58
(*S*)-THN		81	73
(*S*)-IND	2,4,6-$(MeO)_3C_6H_2$	86	66
(*S*)-THN		82	59
(*S*)-IND	3,4,5-$(MeO)_3C_6H_2$	75	67
(*S*)-THN		77	76

[a]Isolated yield (calculated from aromatic aldehyde).

[b]Analogous results were observed using the enantiomeric chiral auxiliaries (*R*)-IND and (*R*)-THN.

Scheme 8. Synthesis of optically active 3-benzyl-2-azetidinones.

2.2.3. Ketene Generated In Situ from 2-Amidoacetyl Chloride

N-Propargyl-2-azetidinone **9** was prepared in enantiopure form from (*S*)-2-(2-oxo-4-phenyloxazolidin-3-yl)acetyl chloride **7**, imine **8**, and trietylamine at low temperature (Scheme 9) [35]. The reaction was completely *cis*-stereoselective ($J_{3,4}$ = 4.9 Hz). The terminal alkyne moiety was exploited to introduce a 1,2,3-triazole ring, which in turn was converted into a triazolium salt. The corresponding Au complex having a 1,2,3-triazolydene-β-lactam hybrid ligand was used as a catalyst in the cycloisomerization of enynes (see also **10b**, Scheme 10 and **22**, Scheme 17).

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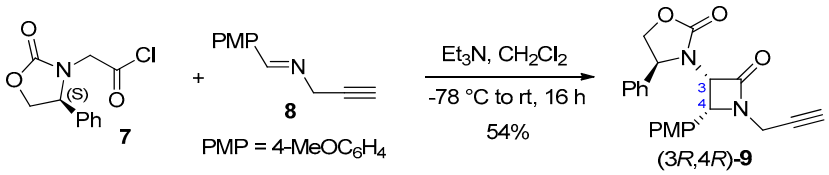
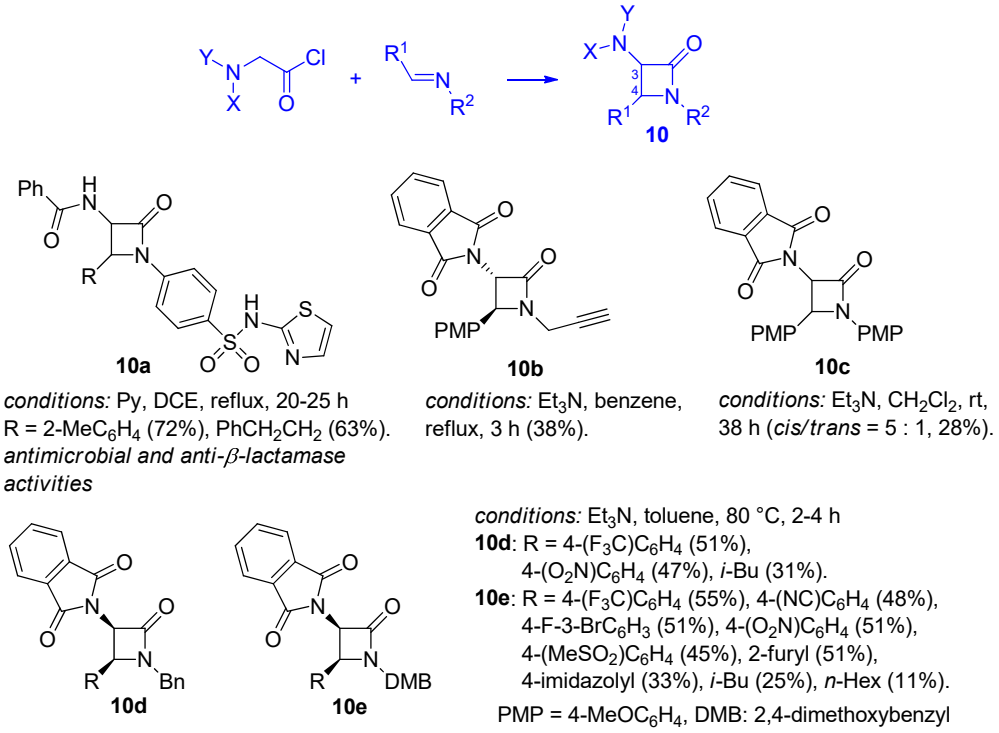


Scheme 9. Synthesis of enantiopure-3-oxazolidinyl-2-azetidinone **9**.

3-Benzamido- and 3-phthalimido-2-azetidinones **10a**-**10e** were prepared by Staudinger synthesis starting from the corresponding 2-amidoacetyl chlorides (Scheme 10) [35–38].



Scheme 10. Synthesis of 3-amido-2-azetidinones. *(Tested activities are in italics*).

The reaction of propargylimine **8** with phthalimidoacetyl chloride and trietylamine at 80 °C gave *trans*-2-azetidinone **10b** ($J_{3,4}$ = 2.5 Hz) as the only product.[35] Compound **10b** was used as a precursor of β-lactam substituted mesoionic metal carbene complexes, which were tested as catalysts in the cycloisomerization of enynes (Au-carbene complexes) and in the hydrosilylation of phenyl acetylene (Pt-carbene complexes) (see also **9**, Scheme 9 and **22**, Scheme 17)

Orthogonally protected azetidinone **10c** was obtained as a *cis*/*trans* mixture ($J_{3,4\ cis}$ = 5.4 Hz, $J_{3,4\ trans}$ = 2.4 Hz) [37]. The *N*-(4-methoxyphenyl) protecting group was selectively removed by treatment with cerium ammonium nitrate (CAN). Then, the 3-N exocyclic nitrogen atom was first deprotected using hydrazine and then acylated with 4-chlorophenyl isocyanate to generate a 3-ureido-2-azetidinone.

β-Lactams **10d** and **10e** were obtained mainly as *cis*-isomers ($J_{3,4}$ = 5.0-5.5 Hz) and used to study the selective deprotection of N-1 and 3-N nitrogen atoms [38]. Oxidative cleavage with CAN and ammonia-free Birch reduction were effective in removing 2,4-dimethoxybenzyl and benzyl groups from N-1, respectively. Hydrazine easily removed the phthalimido group in 4-alkyl substituted lactams (R = alkyl), but in the case of 4-aryl derivatives (R = aryl and heteroaryl), the addition of HCl was necessary to obtain satisfactory conversions. β-Lactams having a carbamate group on C-3 were also examined (see **96**, Figure 6).

Chiral imines **12** derived from α-amino acids **11** were reacted with phthalimidoacetyl chloride and a base to obtain dipeptidic 4-phenyl β-lactams **13** (Scheme 11) [39]. The reaction carried out at low temperature (method **A**) gave low yields. Better results were obtained at 110 °C in toluene in the presence of 2,6-lutidine as the base (method **B**). Under these reaction conditions, mainly 3,4-*trans*-

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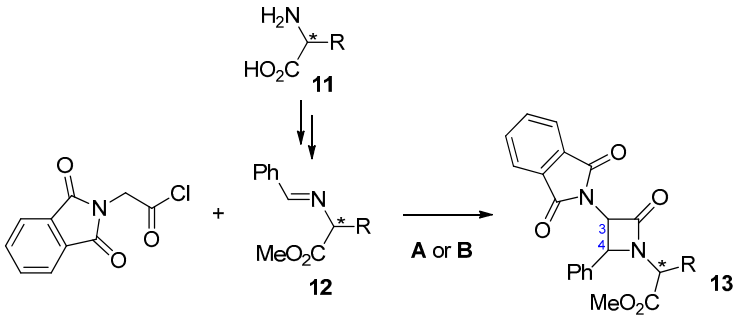
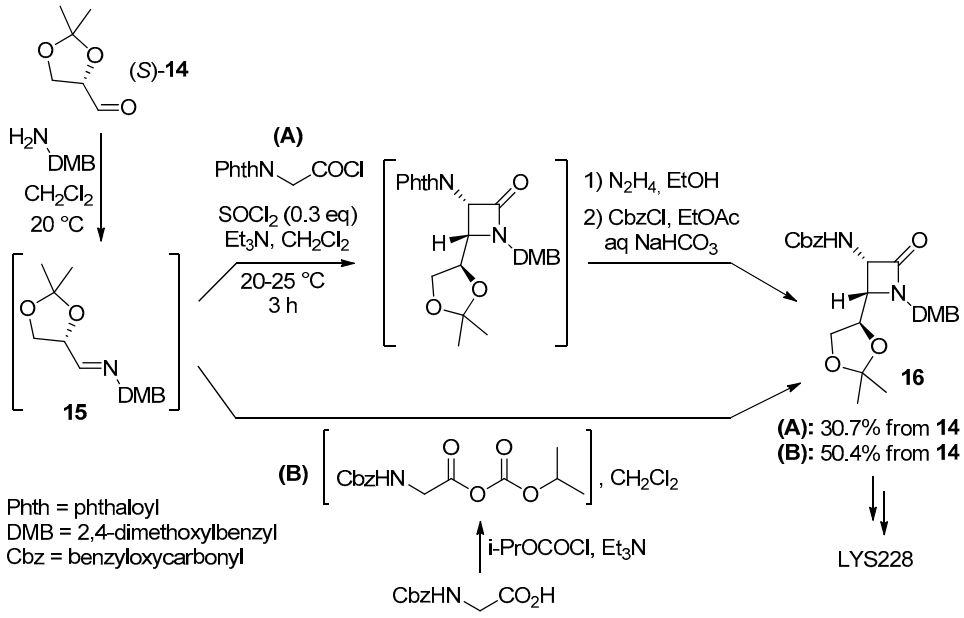
disubstituted β-lactams were formed ($J_{3,4\ cis}$ = 5.4-5.6 Hz, $J_{3,4\ trans}$ = 2.5-2.7 Hz) with low control of the absolute configuration of C-3 and C-4 stereocenters. The 3-N nitrogen atom was deprotected with hydrazine and then coupled with 2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetic acid in search of novel inhibitors of penicillin-binding protein (PBP).



conditions: **A:** Et_3N, CH_2Cl_2, -78 °C then rt, 2 h; **B:** 2,6-lutidine, toluene, rt then reflux, 16-96 h
11 = L-Phe (**A**, *cis*, dr = 58/42, 5%), DL-Phe (**B**, *cis*, dr = 59/41, 6% + *trans*, dr = 55/45, 64%), L-Glu (**B**, *trans*, dr = 52/48, 89%), L-Trp (**B**, *trans*, dr = 59/41, 85%), L-Met (**B**, *trans*, dr = 56/44, 64%), D-Met (**B**, *trans*, dr = 57/43, 60%).

Scheme 11. Synthesis of dipeptidic 4-phenyl-2-azetidinones.

A scalable process for the production of the monobactam antibiotic LYS228 on a multi-kilogram scale was described (Scheme 12) [40]. Two approaches to the key intermediate **15** were investigated, both starting from enantiopure (*S*)-glyceraldehyde acetonide **14**. Aldehyde **14** was condensed with 2,4-dimethoxybenzylamine, and imine **15** was reacted directly with phthalimidoacetyl chloride in the presence of triethylamine as a base and $SOCl_2$ as a trace water scavenger (method **A**). Then the phthalimido group was removed by treatment with hydrazine, and the free 3-N amino group was protected with benzyl chloroformate to obtain **16** (91.9 Kg, 99.8% ee) with an overall yield of 30.7% from **14**. To avoid exchange of protecting-groups, *N*-Cbz glycine was activated as mixed anhydride with isopropyl chloroformate in the presence of triethylamine and reacted with imine **15** to directly obtain **14** with an overall yield of 50.4% (method **B**).



Scheme 12. Synthesis of 3-phenylthio-2-azetidinones.

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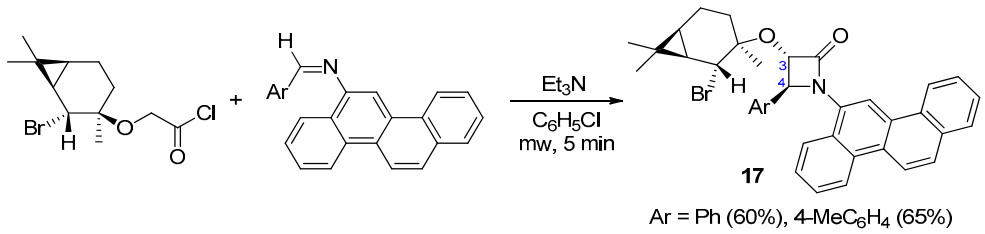
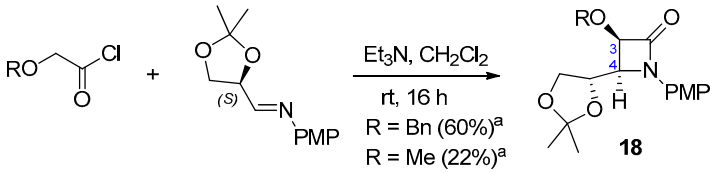
2.2.4. Ketene Generated In Situ from 2-Alkoxy-, 2-Aryloxy-, and 2-Acetoxyacetyl Chloride

Enantiopure acyl chlorides or imines have recently been used for the synthesis of optically active β-lactams. *trans*-Azetidinones **17** (Ar = Ph, $J_{3,4}$ = 2.0 Hz) were obtained by microwave-promoted cycloaddition of *N*-(chrysen-6-yl)imines with a ketene derived from naturally occurring (+)-car-3-ene (Scheme 13) [41]. An explanation for the high stereoselectivity of the Staudinger synthesis was proposed. Removal of the chiral auxiliary by treatment with Zn/AcOH gave the corresponding enantiopure 3-hydroxy-2-azetidinones, which were in turn acetylated.



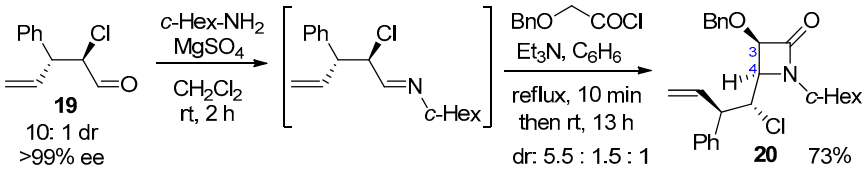
Scheme 13. Synthesis of optically active *N*-(chrysen-6-yl)-2-azetidinones.

D-Mannitol was used to prepare an enantiopure 1,3-dioxolan-4-yl)methanimine that was reacted with 2-benzyloxy- and 2-methoxyacethyl chloride in the presence of triethylamine at room temperature (Scheme 14) [42]. Under the reported reaction conditions, exclusive formation of the *cis* isomer of 4-(1,3-dioxolan-4-yl)azetidin-2-ones **18** was observed ($J_{3,4}$ = 4.4-5.6 Hz). Acetal hydrolysis with *p*-TsOH in THF/H_2O followed by oxidation of the glycol moiety with $NaIO_4$ afforded optically active 4-formyl-β-lactams in good yields.



Scheme 14. Synthesis of 3-alkoxy-4-(1,3-dioxolan-4-yl)azetidin-2-ones. ([a] Yield after recrystallization).

(2*R*,3*R*)-2-Chloro-3-phenylpent-4-enal (**19**) was prepared with high enantioselectivity by iridium-catalysed allylic substitution of chloroacetaldehyde. Aldehyde **19** was condensed with cyclohexylamine and the crude imine was reacted with 2-(benzyloxy)acetyl chloride in the presence of triethylamine in benzene (Scheme 15) [43]. Purification of the crude mixture (dr 5.5:1.5:1) afforded pure *cis*-β-lactam **20** ($J_{3,4}$ = 5.0 Hz) in 73% overall yield.



Scheme 15. Synthesis of optically active 3-benzyloxy-2-azetidinone **20**.

3-Methoxy-*N*-ethyl-*tert*-butylcarbamate β-lactams **21** were prepared by Staudinger synthesis at – 82 °C (Scheme 16) [44]. The reaction was highly stereoselective producing only *cis* adducts **21** ($J_{3,4}$ = 4.0-4.4 Hz). Treatment of **21** with TFA in CH_2Cl_2 at room temperature afforded the corresponding deprotected *N*-(2-aminoethyl) derivatives in 70-97% yields. All azetidinones were evaluated for antimicrobial and anticancer activities.

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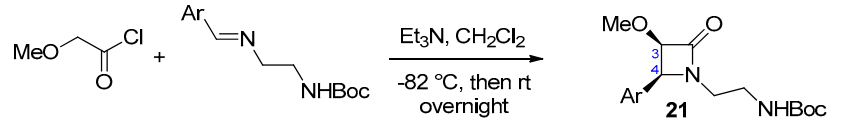
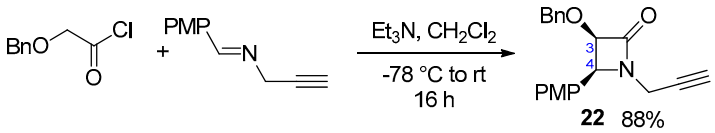


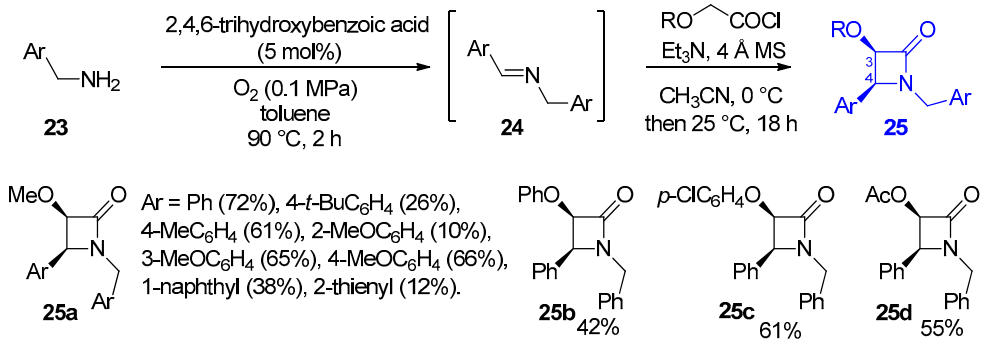
Scheme 16. Synthesis of 3-methoxy-2-azetidinones **21**.

cis-3-Benzyloxy-*N*-propargyl-2-azetidinone **22** ($J_{3,4}$ = 4.4 Hz) was prepared with high stereoselectivity and high yield under similar reaction conditions (Et_3N, CH_2Cl_2, -78 °C then rt) (Scheme 17) [35]. Lactam **22** was used for the preparation of β-lactam substituted 1,2,3-triazolin mesoionic carbene metal complexes as in the case of the analogues 3-amido-*N*-propargyl-β-lactams **9** and **10b** (see Schemes 9 and 10).



Scheme 17. Synthesis of 3-benzyloxy-1-propargyl-2-azetidinone **22**.

Organocatalytic oxidative condensation of primary amines to unstable imines was applied to the one-pot synthesis of *cis*-β-lactams **25** and **26** under mild conditions (Schemes 18 and 19) [45]. Imines **24** were generated *in situ* by homocondensation of benzylamines **23** using 4,6-dihydroxysalicyclic acid as an organocatalyst and molecular oxygen as a co-oxidant. Imines **24** were then treated with acyl chlorides and triethylamine in the presence of molecular sieves in acetonitrile at 0 °-rt to give *cis*-azetidinones **25** ($J_{3,4}$ = 4.1-4.6 Hz) with high selectivity. Gram scale syntheses of **25a** (Ar = Ph) and **25c** were carried out by this method.



Scheme 18. One-pot synthesis of 2-azetidinones by organocatalytic oxidative condensation of primary amines.

cis-Azetidin-2-ones **26** ($J_{3,4}$ = 3.6-4.6 Hz) bearing three different substituents were prepared by the 4,6-dihydroxysalicylic acid-catalyzed oxidative cross-condensation of two different amines followed by [2+2]-cycloaddition with ketenes under similar conditions (Scheme 19) [45]. β-Lactams **26a** and **26b** underwent acid catalyzed hydrolysis to afford the corresponding β-amino acids as single diastereomers.

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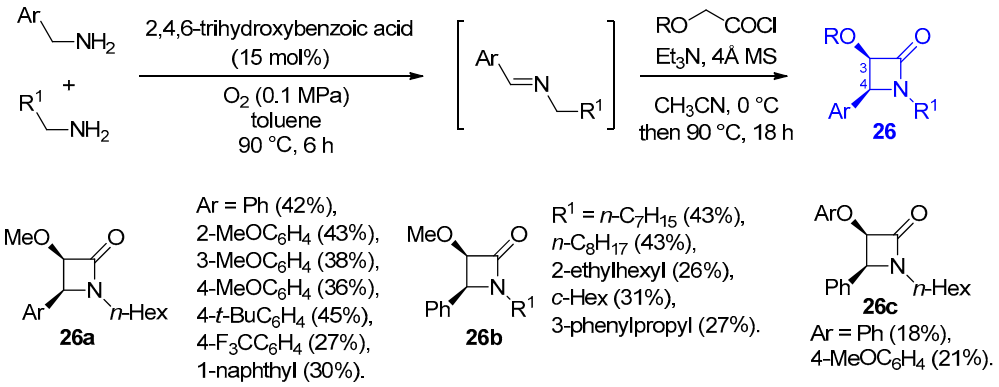
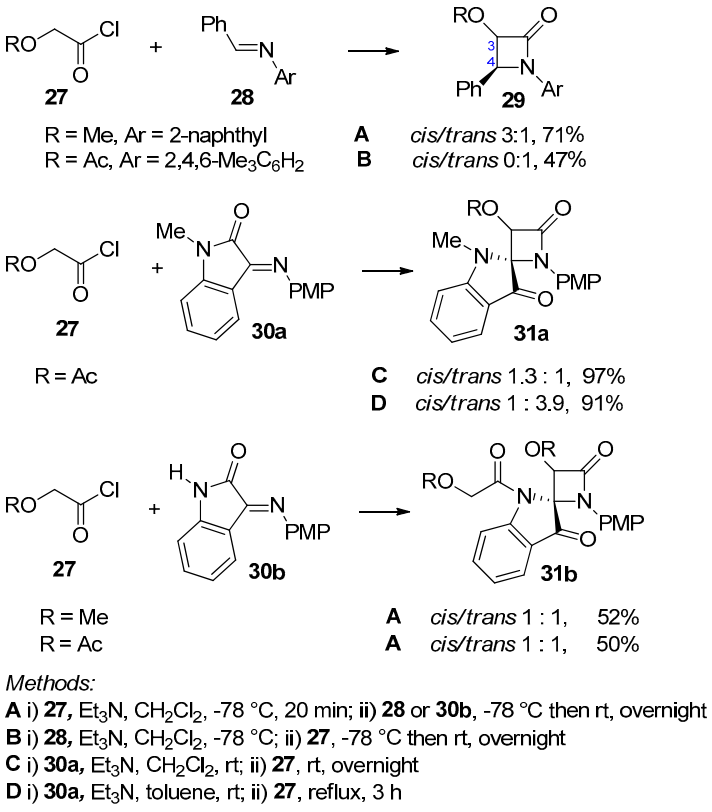


Scheme 19. One-pot synthesis of 2-azetidinones by organocatalytic oxidative condensation of primary amines.

The role of imine isomerization in the stereoselectivity of the Staudinger synthesis was investigated both computationally and experimentally. Different reaction conditions were considered, including more polar and less polar solvents (CH_2Cl_2 and toluene), different reaction temperatures (-78 °C and room temperature) and different order of reagent addition (acyl chloride first and imine first) (Scheme 20) [20]. The *cis* and *trans* stereochemistry of azetidine-2-ones **29** was determined by analysis of the coupling constants between 3-H and 4-H ($J_{3,4\ cis}$ = 4.9 Hz, $J_{3,4\ trans}$ = 1.8-2.0 Hz). The structure of the two isomers *cis*-**31a** and *trans*-**31a** (R = Ac) derived from *N*-methyl-isatin was confirmed by X-ray analysis. The *N'*-unsubstituted imine **30b** was reacted with an excess of acid chloride **27** (2.2 molar equiv). Under these conditions, the isatin nitrogen atom was acylated and azetidinones **31b** were obtained as an equimolar mixture of *cis* and *trans* isomers. On the basis of experimental data and DFT calculations, the isomerization of the starting imine was found to be critical for the stereoselectivity of the cases studied.



Scheme 20. Study of the stereoselectivity of the Staudinger synthesis under different reaction conditions.

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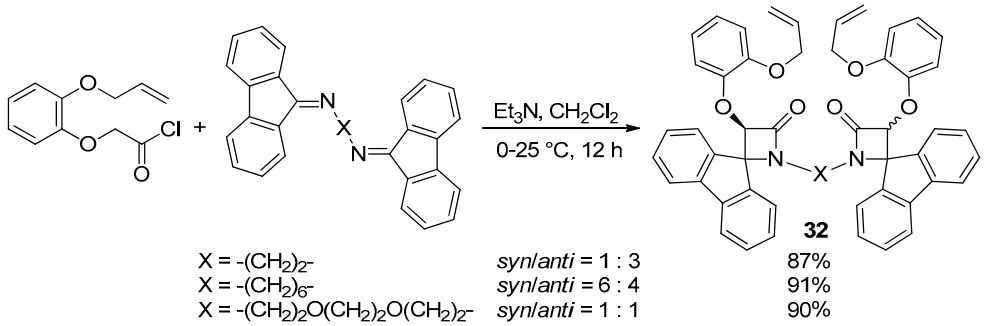
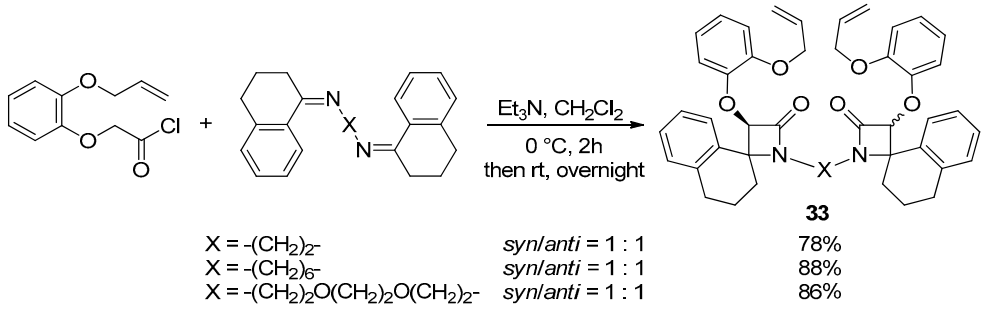
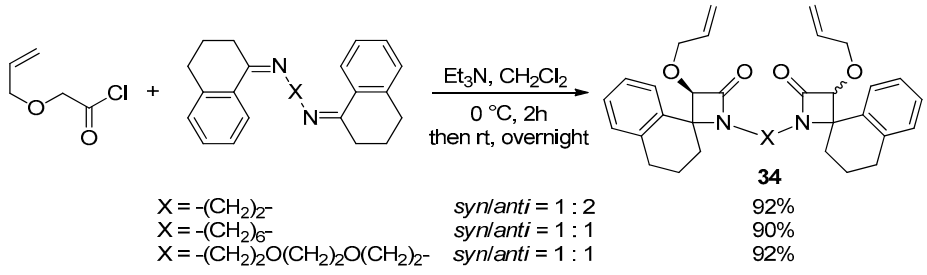
Bis-4-spiro-fused-β-lactams **32-35** were prepared by double Staudinger synthesis of 2-(2-(allyloxy)phenoxy)acetyl chloride and 2-allyloxyacetyl chloride with various diimines (Schemes 21–24) [46,47]. Diimines were synthesized by condensation of 9-fluorenone and 1-tetralone with 1,2-diaminoethane, 1,6-diaminohexane, and 1,8-diamino-3,6-dioxaoctane. Cycloadditions were carried out under standard conditions and afforded a mixture of *syn*/*anti* adducts in high yield. The structures of bis-azetidinones *anti*-**34** [X = -$(CH_2)_2$-] and *anti*-**35** [X = -$(CH_2)_2$-] were determined by single-crystal X-ray diffraction. Dienes **32-35** were then cyclized by ring-closing metathesis (RCM) to give macrocycles containing bis-4-spiro-β-lactams moieties in good yields, except for **34** [X = -$(CH_2)_2$-] and **35** [X = -$(CH_2)_2$-], which failed to undergo RCM because of the short ethylene linker.



Scheme 21. Synthesis of bis-4-spiro-fused-β-lactams **32**.



Scheme 22. Synthesis of bis-4-spiro-fused-β-lactams **33**.



Scheme 23. Synthesis of bis-4-spiro-fused-β-lactams **34**.

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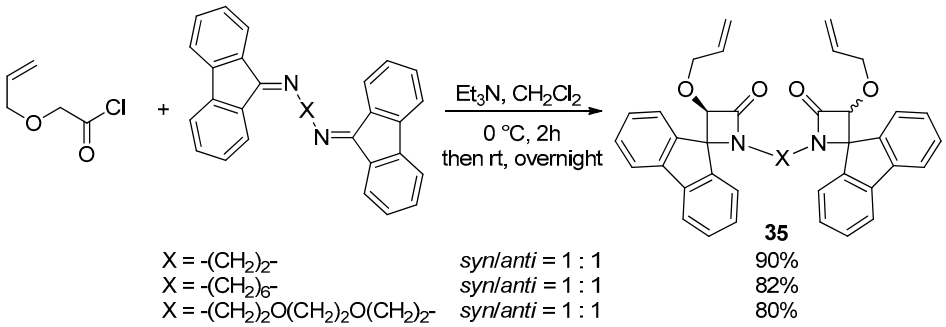

Scheme 24. Synthesis of bis-4-spiro-fused-β-lactams **35**.

Phenoxy- and *p*-chlorophenoxy-ketenes were generated by treating 2-aryloxyacetyl chloride with a base and trapped *in situ* with variously functionalized imines to generate 3-phenoxy- and 3-*p*-chlorophenoxy-2-azetidinones (Scheme 25) [30,36,42,44,48–51]. Condensation of aromatic aldehydes with 2-amino-1-phenylethanol afforded imines that were reacted with phenoxyketene without protection of the hydroxyl group. The reaction was performed at room temperature and provided *N*-(2-hydroxy-2-phenylethyl)-β-lactams **36a** with complete *cis* selectivity ($J_{3,4}$ = 4.4-4.8 Hz). After oxidation of the secondary benzyl alcohol to the corresponding ketone, treatment with phosphorus oxychloride converted the azetidinones into highly strained azetidine-fused oxazolium salts that underwent spontaneous opening to 2-vinyloxazole derivatives [48]. Phenoxyacetyl chloride was also used in the Staudinger synthesis of *cis*-4-(oxiran-2-yl)-β-lactams **36b** ($J_{3,4}$ = 4.6-5.2 Hz) [42].

3-Phenoxy-azetidinones **36c** bearing a *N*-Boc group were synthesized by ketene-imine cycloaddition at – 82 °C with complete *cis* selectivity ($J_{3,4}$ = 3.0-4.4 Hz) [44]. After recrystallization, the pure β-lactams **36c** were recovered in moderate to good yields (21-77%). Similarly to the corresponding 3-methoxy derivatives **21** (see Scheme 16), **36c** were treated with trifluoroacetic acid (TFA) to obtain the deprotected *N*-(2-aminoethyl) *cis*-azetidinones.

The synthesis of β-lactams **36d** was performed at high temperature (100 °C) in toluene [30]. Complete *trans* stereoselectivity was observed under these conditions ($J_{3,4}$ = ca 0-1.7 Hz), except for derivative **36d** (X = F), which was obtained as a mixture of *trans* and *cis* diastereomers ($J_{3,4\,cis}$ = 5.0 Hz). The structure of the *trans*-**36d** (X = F) and *cis*-**36d** (X = F) isomers was confirmed by X-ray analysis. The stability of β-lactam **36d** (X = Cl) was studied under acidic, neutral, and basic conditions. Its half-life ($t_{1/2}$) at pH 4, 7.4, and 9 was more than 15 hours.

β-Lactams **36e-36h** conjugated with 1,3,4-thiadiazole and imidazole nuclei, heterocycles present in various bioactive compounds, were prepared in high yields (75-89%). Ketenes generated *in situ* from 2-benzyloxy- or 2-(*p*-chlorobenzyloxy)acetyl chloride and trietylamine reacted with imines derived from β-tetralone in dichloromethane at 0 °C-rt [49,50]. All β-lactams **36e-36h** were purified by crystallization and were obtained with complete *cis* stereoselectivity ($J_{3,4}$ = 5.0-5.5 Hz). X-Ray analysis confirmed the structures of the two derivatives **36g** (Ar = 4-MeC_6H_4 and Ar = 4-ClC_6H_4).

The synthesis of azetidinones **36g** was carried out by dropwise addition of 2-(*p*-chlorobenzyloxy)acetyl chloride to an imine in the presence of pyridine as a base at 0 °C in dichloroethane (DCE), followed by heating to reflux temperature [36].

β-Lactam **36j** was obtained as a mixture of two diastereomers in 58:42 ratio by reacting a suitable hydrazone with *in situ* generated phenoxyketene [51].

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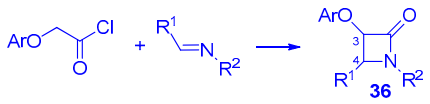

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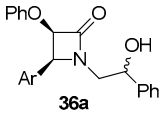
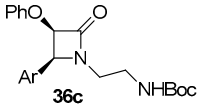


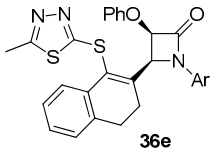
36a

conditions: Et_3N, CH_2Cl_2, rt, 12 h
Ar = Ph (30%), 4-MeC_6H_4 (47%), 4-ClC_6H_4 (44%).



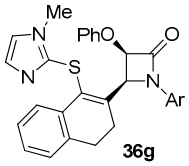
36c

conditions: Et_3N, CH_2Cl_2, -82 °C, then rt, overnight
Ar = 4-ClC_6H_4 (40%), 4-$O_2NC_6H_4$ (68%),
PhCH=CH (46%), 4-MeC_6H_4 (38%),
3-$MeOC_6H_4$ (21%), Ph (44%), 3-BrC_6H_4 (37%),
2-naphthyl (51%), 2,3-$(MeO)_2C_6H_3$ (77%),
3-$O_2NC_6H_4$ (67%).
antimalarial and antimicrobial activities



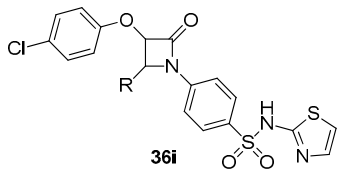
36e

conditions: Et_3N, CH_2Cl_2, rt, overnight
Ar = Ph (84%), 4-ClC_6H_4 (83%), 4-EtC_6H_4 (77%),
4-$O_2NC_6H_4$ (80%), 4-BrC_6H_4 (83%),
4-MeC_6H_4 (81%), 4-FC_6H_4 (84%),
4-$EtOC_6H_4$ (87%), 2-Cl-4-MeC_6H_3 (78%),
3,4-$Me_2C_6H_3$ (81%), 4-$MeOC_6H_4$ (89%).
antibacterial activity



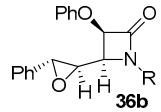
36g

conditions: Et_3N, CH_2Cl_2, 0 °C, overnight
Ar = 4-$MeOC_6H_4$ (84%), 3,4-$(MeO)_2C_6H_3$ (81%),
3,4,5-$(MeO)_3C_6H_2$ (89%), 4-MeC_6H_4 (87%),
4-ClC_6H_4 (84%), 4-$O_2NC_6H_4$ (86%),
3-$MeOC_6H_4$ (87%), 4-$EtOC_6H_4$ (89%),
4-BrC_6H_4 (84%).



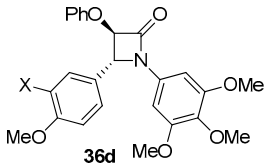
36i

conditions: Py, DCE, reflux, 20-25 h
R = Ph (67%), 4-ClC_6H_4 (75%), $PhCH_2CH_2$ (67%).
antibacterial and anti-β-lactamase activities



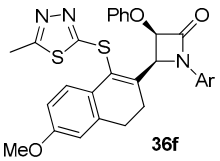
36b

conditions: Et_3N, CH_2Cl_2, rt, 2-3.5 h
R = CH_2CO_2Me (dr =9:1; 33%),
$CH(CO_2Me)CH_2OH$ (dr =9:1; 55%),
CH_2CH_2OH (dr =9:1; 14%).



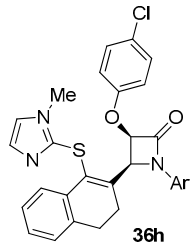
36d

conditions: Et_3N, toluene, 100 °C, 5 h, then rt, 15 h
X = F (*trans:* 33%, *cis:* 18%), Cl (28%), Br (61%),
I (67%), Me (62%)
antiproliferative and antiapoptotic activities



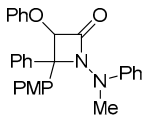
36f

conditions: Et_3N, CH_2Cl_2, rt, overnight
Ar = Ph (75%), 4-ClC_6H_4 (79%), 4-EtC_6H_4 (82%),
4-$O_2NC_6H_4$ (78%), 4-BrC_6H_4 (80%),
4-MeC_6H_4 (84%), 4-FC_6H_4 (75%),
4-$EtOC_6H_4$ (87%), 2-Cl-4-MeC_6H_3 (80%),
3,4-$Me_2C_6H_3$ (84%), 4-$MeOC_6H_4$ (87%).
antibacterial activity



36h

conditions: Et_3N, CH_2Cl_2, 0 °C, overnight
Ar = 4-$MeOC_6H_4$ (86%), 3,4-$(MeO)_2C_6H_3$ (85%),
3,4,5-$(MeO)_3C_6H_2$ (83%), 4-MeC_6H_4 (88%),
4-ClC_6H_4 (87%), 4-$O_2NC_6H_4$ (83%),
3-$MeOC_6H_4$ (88%), 4-$EtOC_6H_4$ (86%),
4-BrC_6H_4 (85%).



36j dr 58:42, 73%

conditions: Et_3N, CH_2Cl_2, 30 °C, 16 h

Scheme 25. Synthesis of 3-aryloxy-2-azetidinones. *(Tested activities are in italics).*

2-Acetoxyacetyl chloride is a useful building block for the synthesis of 3-acetoxy-2-azetidinones. The acetoxy group can be selectively hydrolyzed to 3-hydroxy-2-azetidinones. For example, β-lactams **37** were synthesized by Staudinger synthesis followed by treatment with hydrazine (Scheme 26) [30]. Lactams **37** retained the *trans* stereochemistry established in the cycloaddition step carried out at high temperature (100 °C) ($J_{3,4}$ = ca 0-1.7 Hz). X-ray crystallographic analysis confirmed the

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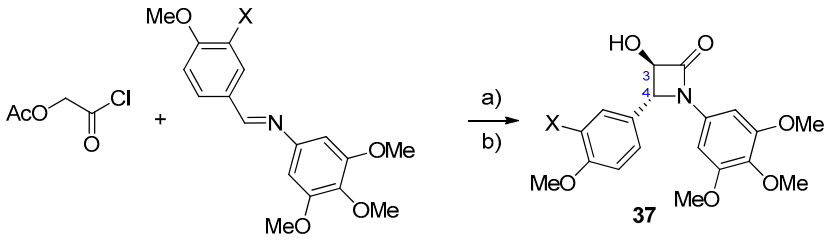
structure of 3-hydroxy-β-lactam **37** (X = F). Azetidinone **37** (X = F) showed potent activity in HT-29 (IC_{50} 3 nM) and MCF-7 (IC_{50} 22 nM) cell lines and strongly inhibited tubulin assembly. It also showed high stability towards hepatic enzymes, analogous to the corresponding 3-phenyl derivative **5e** (R = Ph, X = F) (Scheme 7).



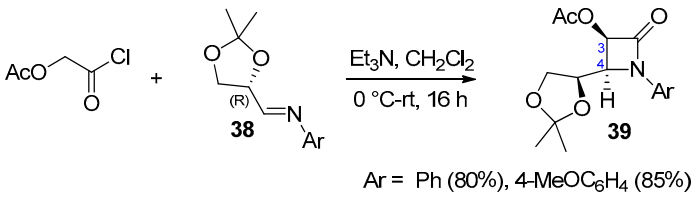
conditions: a) Et_3N, toluene, 100 °C, 5 h; b) NH_2NH_2·2HCl, Et_3N, MeOH, reflux, 2-4 h
X = F (29%), Cl (27%), Br (39%), I (46%), Me (40%).
antiproliferative and antiapoptotic activities

Scheme 26. Synthesis of 3-hydroxy-2-azetidinones. *(Tested activities are in italics*).

Chiral imines **38** derived from D-mannitol were subjected to Staudinger [2+2] cycloaddition with *in situ* generated acetoxyketene at low temperature (0 °C-rt) (Scheme 27) [52]. The reaction afforded *cis*-β-lactams **39**, which were hydrolyzed by treatment with LiOH to 3-hydroxy-2-azetidinones (90-95% yield) and then converted to optically active 2,3-fused β-lactams-1,4-dioxepane.

Scheme 28 shows some 3-acetoxy-2-azetidinones recently synthesized by the Staudinger synthesis using 2-acetoxyacetyl chloride and a base for *in situ* generation of the corresponding ketene [53–57].

The synthesis of azetidinone **40a** under microwave irradiation was investigated using a heterogeneous catalyst such as Mg-Al hydroxide (MAH) instead of an organic base [53]. In this case, both *cis*-**40a** and *trans*-**40a** were formed in low yields ($J_{3,4\ cis}$ = 5.0 Hz, $J_{3,4\ trans}$ = ca 0 Hz). Better results were observed when halogenated acyl chlorides were used (see: **47**, Scheme 33; **48**, Scheme 34; **58a**, Scheme 43; and **59b**, Scheme 44). Mixtures of diastereomeric β-lactams **40b** and **40c** were prepared by microwave-induced cycloaddition using *N*-methylmorpholine (NMM) as the base in CH_2Cl_2 [55].



Ar = Ph (80%), 4-$MeOC_6H_4$ (85%)

Scheme 27. Synthesis of optically active 3-acetoxy-2-azetidinones.

The 4-(thienyl)pyrazolyl- and 4-pyrazolo[5,1-*b*]thiazolyl-3-acethoxy-2-azetidinone hybrids **40d** and **40e** were synthesized by reacting a suitable aromatic imine with acetoxyacetyl chloride and triethylamine in toluene at reflux temperature [54,56]. Under these conditions, *trans* adducts were formed with complete selectivity ($J_{3,4}$ = 1.5-1.8 Hz). A similar reaction in CH_2Cl_2 at 0 °C afforded the *cis*-**40d** (Ar = 4-$MeOC_6H_4$) isomer in 25% yield ($J_{3,4}$ = 4.8 Hz).

Racemic 3-acetoxy-β-lactams **40f** and **40g** were synthesized via the Staudinger synthesis and converted into optically active 3-hydroxy-β-lactams (78-94% ee). In particular, **40f** and **40g** were sequentially hydrolyzed to 3-hydroxy-β-lactams, oxidized to azetidine-2,3-diones, and enantioselectively reduced to optically active 3-hydroxy-β-lactams by dynamic kinetic resolution (DKR) using Ni-catalyzed asymmetric hydrogenation (Schemes 28 and 29) [57].

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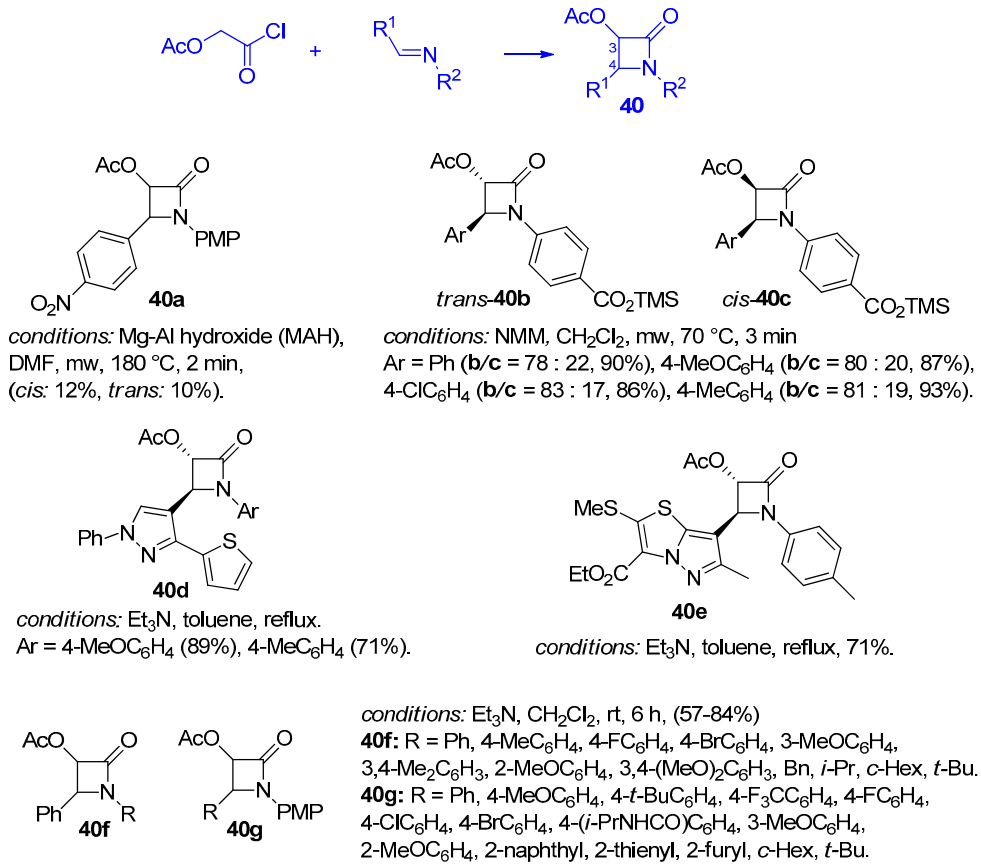
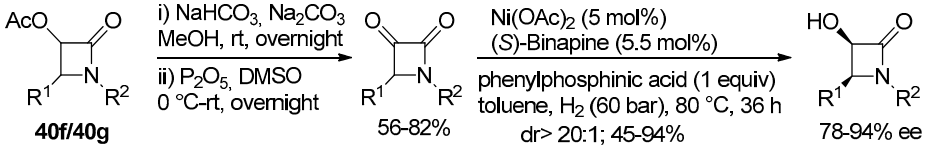
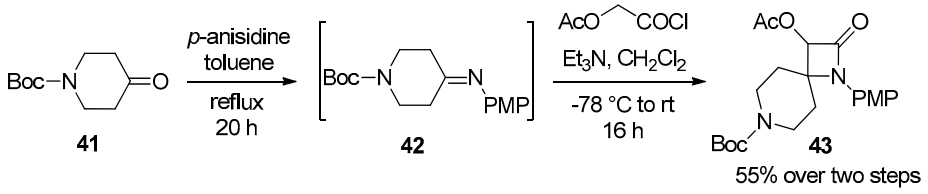


Scheme 28. Synthesis of 3-acetoxy-2-azetidinones.



Scheme 29. Synthesis of optically active 3-hydroxy-2-azetidinones

Condensation of piperidinone **41** with *p*-anisidine afforded the unstable imine **42**. This was directly reacted with 2-acetoxyacetyl chloride in the presence of triethylamine at -78 °C to give the spirofused β-lactam **43** in 55% yield over the two steps (Scheme 30) [58].



Scheme 30. Synthesis of 4-spirofused-3-acetoxy-2-azetidinone **43**.

2.2.5. Ketene Generated In Situ from 2-Phenylthioacetyl Chloride

Phenylthioacetyl chloride was used to prepare 3-phenylthio-2-azetidinones via Staudinger [2+2] cycloaddition (Scheme 31) [59,60]. *Trans*-β-lactams **44** were obtained with complete diastereoselectivity by microwave-induced reaction of diarylimines with phenylthioacetyl chloride in the presence of *N*-methylmorfoline (NMM). Under similar conditions, imines derived from the condensation of diethyl-2-oxomalonate with aromatic amines afforded β-lactams **45**. Decarboxylation

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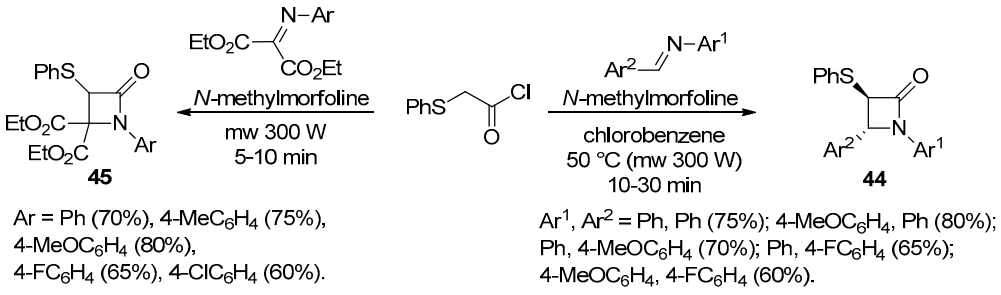
of **45** under Krapcho's reaction conditions (LiCl, DMSO, 120-130 °C, mw) provided an equimolar mixture of *cis*- and *trans*-3-phenylthio-4-carboethoxy-2-azetidinones.



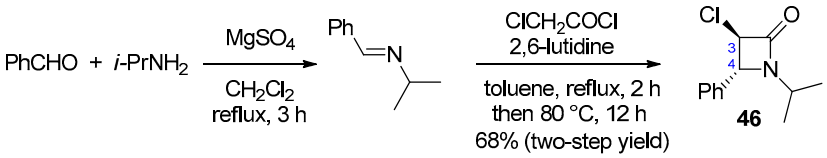
Scheme 31. Synthesis of 3-phenylthio-2-azetidinones.

2.2.6. Ketene Generated In Situ from 2-Chloroacetyl Chloride

Many differently decorated 3-chloro-azetidinones have been synthesized using commercially available and inexpensive chloroacetyl chloride with an imine in the presence of a base. In this section, the structures of the 3-chloro-⌾-lactams are grouped according to the type of N-substituent (alkyl, aryl, heteroaryl, heteroarylamino, carboxamido, ureido, and tosyl groups) (Schemes 32–42). The bioactivity assays described in the cited articles are listed together with the corresponding β-lactam structures.

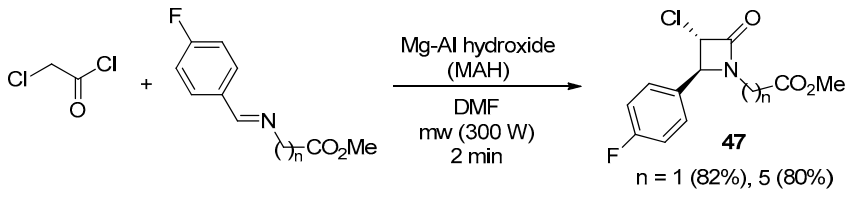
In the search for molecules with enhanced bioactivity, hybrid compounds with more than one bioactive moiety have often been synthesized. Considering that many heterocyclic derivatives are among the most biologically active compounds and possess important pharmacological properties, the design of 3-chloro-azetidinones variously linked to different heterocyclic nuclei is not surprising. Indeed, there are many examples of such compounds in this section. Although these molecules are racemic, promising bioactivity has been observed in some cases.

Benzaldehyde and isopropylamine were condensed in the presence of $MgSO_4$ to give the corresponding imine, which was filtered on Celite® and then reacted directly with chloroacetyl chloride using 2,6-lutidine as the base (Scheme 32). *Trans*-azetidinone **46** was obtained in 68% yield after recrystallization ($J_{3,4}$ = 1.8 Hz). The 3-chloro-⌾-lactam **46** was found to be inferior to 3-bromo analogues **59d** (see Scheme 44) as a substrate in cobalt-catalyzed ⌾-arylation with aryl Grignard reagents [61].



Scheme 32. Synthesis of 3-chloro-1-isopropylalkylazetidin-2-one **46**.

Solid MAH was used as a heterogeneous catalyst in the Staudinger synthesis of azetidinones under microwave irradiation (Scheme 33, see also **40a**, Scheme 28; **48**, Scheme 34; **58a**, Scheme 43; and **59b**, Scheme 44). The reaction was fast and afforded **47** in good yields with complete *trans* selectivity ($J_{3,4}$ = 1.2-1.9 Hz) [53].



Scheme 33. Synthesis of *N*-acetate- and *N*-hexanoate-3-chloro-azetidin-2-ones **47**.

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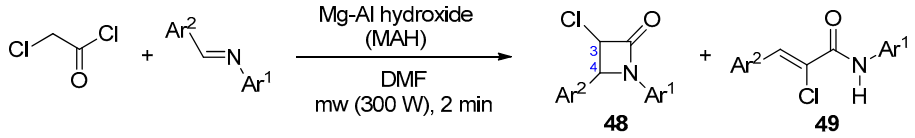
Under the same conditions, *N*-aryl azetidinones **48** were formed as a mixture of *cis* and *trans* isomers ($J_{3,4\ cis}$ = 5.0-5.4 Hz, $J_{3,4\ trans}$ = 0-2.0 Hz) (Scheme 34). The MAH catalyst could be recovered and reused up to 6 times without any significant loss of catalytic activity. In some cases, MAH induced partial or complete cleavage of the N-C4 bond of adducts **48** with formation of enones **49**. The structure of the isomeric ⍟-lactams *cis*-**48** and *trans*-**48** (Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-$O_2NC_6H_4$) as well as of the enone **49** (Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$) was confirmed by X-ray analysis [53].

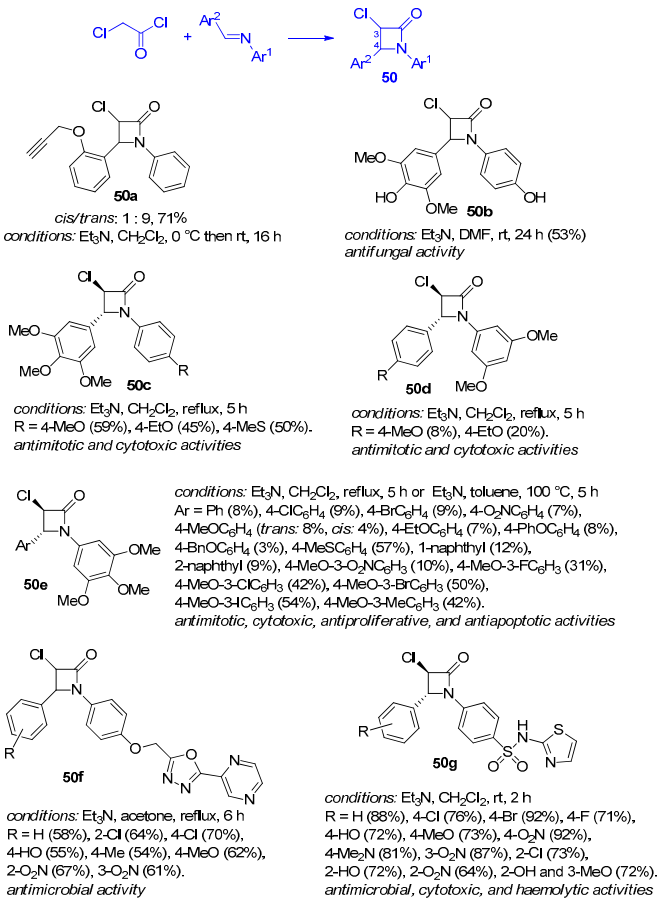


Ar^1	Ar^2	*cis*-**48**	*trans*-**48**	**49**
Ph	Ph	40%	52%	n.d.
Ph	4-$MeOC_6H_4$	36%	53%	10%
Ph	4-$O_2NC_6H_4$	47%	38%	n.d.
Ph	4-FC_6H_4	39%	54%	n.d.
4-$O_2NC_6H_4$	Ph	29%	29%	25%
4-BrC_6H_4	Ph	25%	33%	34%
4-ClC_6H_4	3-ClC_6H_4	55%	32%	n.d.

Ar^1	Ar^2	*cis*-**48**	*trans*-**48**	**49**
4-ClC_6H_4	2-thienyl	22%	22%	39%
4-ClC_6H_4	2-furyl	0%	0%	40%
4-$MeOC_6H_4$	4-$O_2NC_6H_4$	55%,	40%	n.d.
4-$MeOC_6H_4$	4-$MeOC_6H_4$	46%	31%	12%
4-ClC_6H_4	4-$MeOC_6H_4$	46%	40%	n.d.
4-ClC_6H_4	2,4-$Cl_2C_6H_3$	42%	43%	n.d.
4-$MeOC_6H_4$	PhCH=CH	26%	32%	38%

Scheme 34. Synthesis of *N*-aryl-3-chloro-azetidin-2-ones **48**.

1,4-Diaryl-3-chloro-2-azetidinones **50** were prepared by reaction of chloroacetyl chloride and aromatic imines using Et_3N as a base in different solvents (Scheme 35) [30,42,62–65].



Scheme 35. Synthesis of 1,4-diaryl-3-chloro-2-azetidinones **50**. *(Tested activities are in italics)*.

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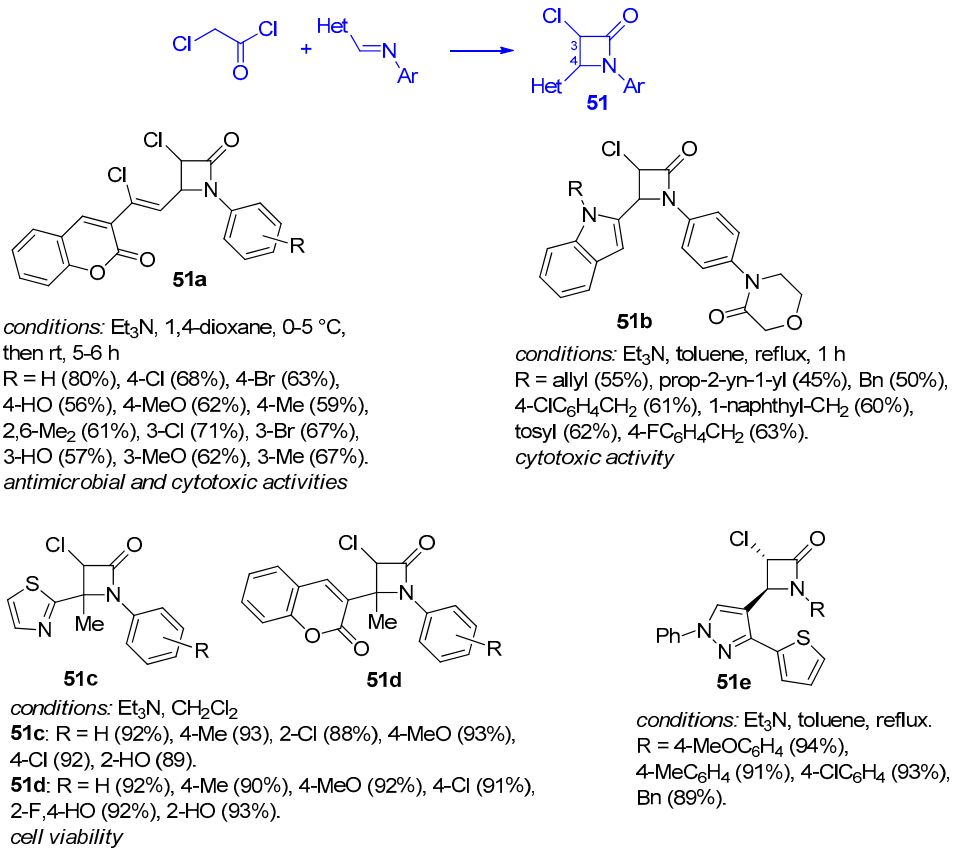
The 4-propargyloxyphenyl substituted ◎-lactam **50a** was formed as a *cis*/*trans* mixture in CH_2Cl_2 at room temperature. The reaction of **50a** with NaN_3 and KI in DMF at 150 °C afforded a ◎-lactam-fused benzotriazolo-oxazocane derivative via conversion of **50a** into the corresponding 3-azido-2-azetidinone followed by a spontaneous intramolecular azide-alkyne click reaction (83%) [42].

3-Chloro-azetidinones **50b-50g** were designed and synthesized to test their potential bioactivity. In most cases, the Staudinger synthesis was carried out at room temperature or in refluxing CH_2Cl_2. As shown in Scheme 35, the yields range from very low to very good (3-92%), but it must be said that in some cases the yields were not optimized, as the main aim of the research was the biological tests. Compound **50b** was synthesized from the syringic imine of 4-aminophenol with chloroacetyl chloride [62]. 1,4-Diaryl-2-azetidinones **50c-50e** were isolated exclusively as the *trans*-isomer ($J_{3,4}$ = 0-2.4 Hz). The only exception was **50e** (Ar = 4-$MeOC_6H_4$), which was formed as a *cis*/*trans* mixture (ratio 1:1.9) ($J_{3,4\ cis}$ = 5.0 Hz, $J_{3,4\ trans}$ = 2.0 Hz). The stereochemistry of these two diastereomers as well as of the two *trans*-azetidinones **50e** (Ar = 4-MeO-3FC_6H_3 and Ar = 4-MeO-3ClC_6H_3) was confirmed by X-ray analysis [30,63].

Hybrid adducts **50f** featuring a pyrazine, a 1,3,4-oxadiazole, and an azetidinone moiety showed interesting antimicrobial activity. In particular, a high antitubercular activity of the two derivatives **50f** (R = 4-Cl and R = 4-MeO) was reported (MIC 3.12 μg/ml against *Mycobacterium tuberculosis*) [64]. β-Lactams **50g** presenting a thiazolyl nucleus were synthesized with complete *trans* selectivity and evaluated as antimicrobial agents [65].

Heterocyclic hybrids of β-lactams **51a-51e** were prepared via the Staudinger synthesis by reaction of chloroacetyl chloride with heterocyclic imines in the presence of Et_3N as a base (Scheme 36) [54,66–68]. Azetidinones with coumarin [66,68], indole [67], thiazole [68], and (thienyl)pyrazole moieties [54] were formed in good yields. Several conditions were tested for the synthesis of β-lactams **51e**. No product formation was observed in CH_2Cl_2 at 0 °C. In refluxing $CHCl_3$, THF, 1,4-dioxane, and toluene the reaction was completely selective in favor of *trans*-β-lactams ($J_{3,4}$ = 1.4-1.7 Hz). The structure of **51e** (R = 4-MeC_6H_4) was confirmed by X-ray analysis [54].



Scheme 36. Synthesis of 1-aryl-3-chloro-4-heteroaryl-2-azetidinones **51**. (*Tested activities are in italics*).

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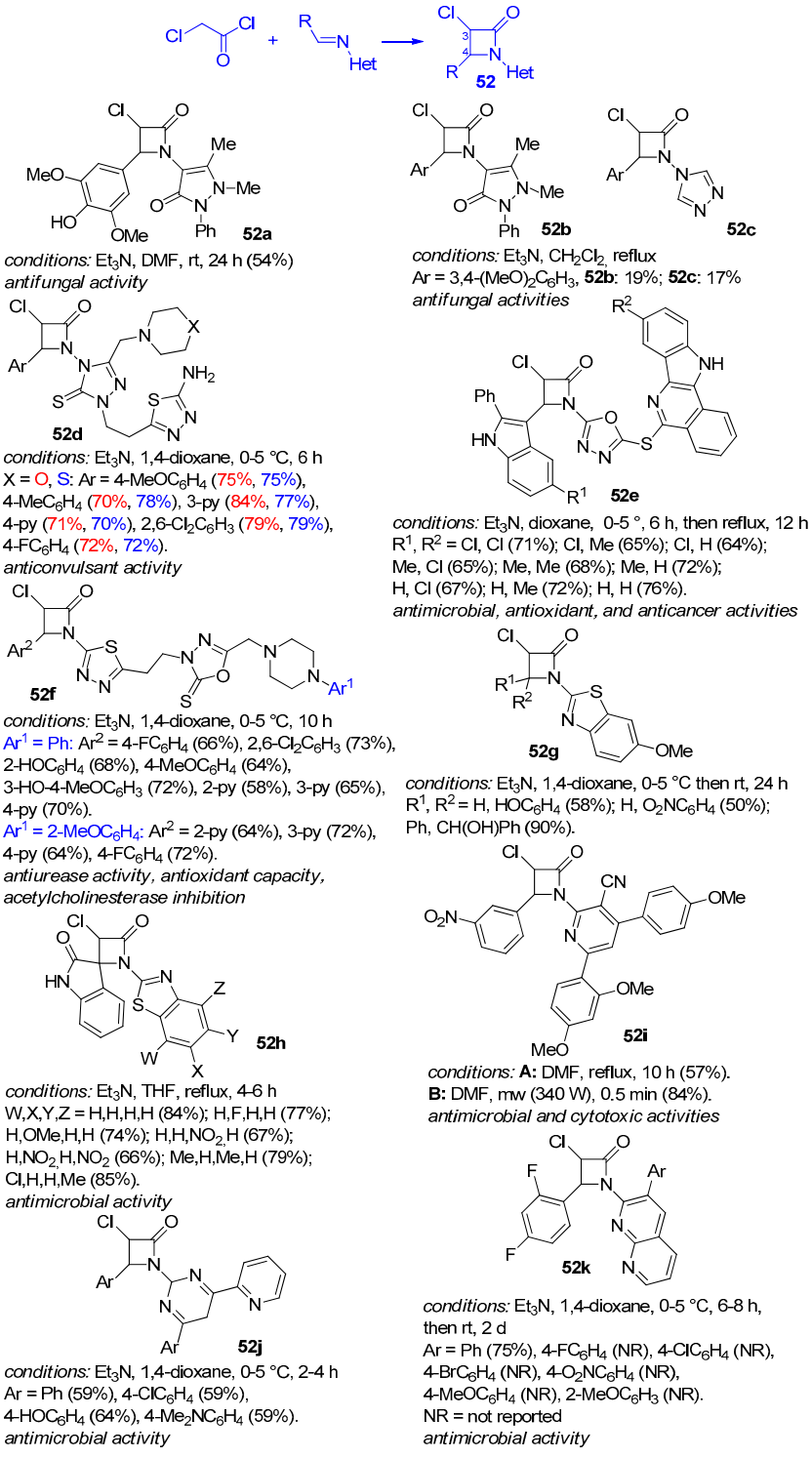
The structures of hybrid compounds with heterocyclic moieties directly linked to the nitrogen atom of the 3-chloro-β-lactam ring are shown in Scheme 37, [31,62,69–78]. Triethylamine was used as the base in all the syntheses, except for the pyridine derivative **52i.** Indeed, 2-((3-nitrobenzylidene)amino)-4,6-diarylnicotinonitrile was reacted with chloroacetyl chloride at a high temperature (DMF, reflux) without any base. In this case, the use of microwave heating reduced the reaction time (0.5 min versus 10 h) and increased the yield (84% versus 57%) [76].



Scheme 37. Synthesis of 3-chloro-1-heteroaryl-2-azetidinones. *(Tested activities are in italics).*

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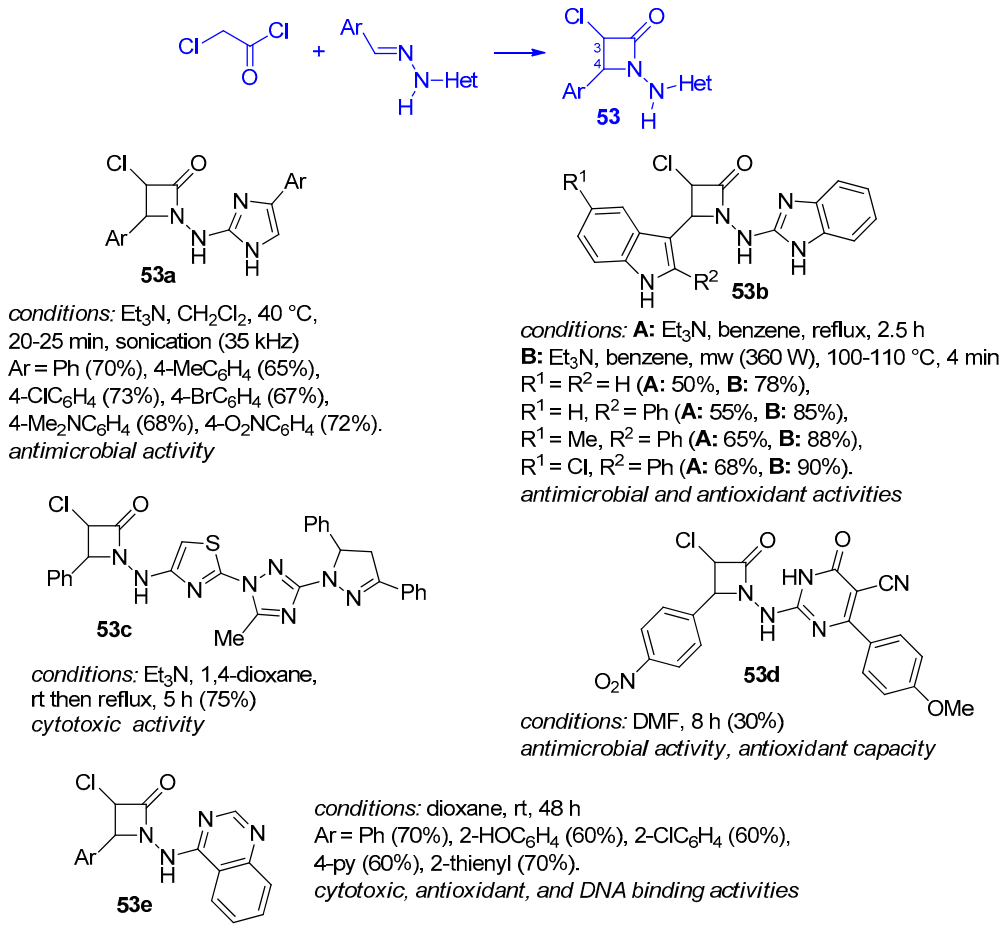
Adducts **52a** and **52b** were prepared from 4-amino-antipyrine [62,69]. The triazole derivative **52c** was obtained in low yield by reaction in refluxing CH_2Cl_2 [69]. Azetidinones **52d** with a 1*H*-1,2,4-triazole-5(4*H*)-thione as a heterocyclic linker for attachment of morpholine (or thiomorpholine) and thiadiazol-2-amine moieties were obtained in good yields (70-84%) [70]. Staudinger approach was also applied to the synthesis of oxadiazole [31], thiadiazole [69–71], benzothiazole [74,75], pyrimidine [77], and naphthyridine [78] derivatives **52f,g,h,j,k**.

Aryl/heteroaryl hydrazones prepared from aryl/heteroaryl aldehydes and heteroaryl hydrazines were reacted with chloroacetyl chloride to give 3-chloro-*N*-heteroarylamino-2-azetidinones (Scheme 38) [79–83]. The synthesis of imidazole derivatives **53a** was carried out under ultrasonication at a frequency of 35 kHz [79]. Both conventional and microwave (mw) heating were used for the preparation of azetidinones **53b** (conditions **A** and **B**). The comparison showed that mw irradiation was a superior method. It afforded the products with higher yield and purity in a shorter reaction time [80]. Hybrid compound **53c**, which contains three other potential pharmacophores besides the β-lactam, i.e. a thiazole, a 1,2,4-triazole, and an pyrazole moiety, showed significant cytotoxic activity against the HeLa (human cervical cancer) tumor cell line (IC_{50} = 4.12 μg/mL) [81]. Pyrimidine and quinazoline derivatives **53d** [82] and **53e** [83] were obtained in moderate to good yields by Staudinger synthesis without the use of any base.



Scheme 38. Synthesis of 3-chloro-1-heteroarylamino-2-azetidinones. *(Tested activities are in italics).*

1-Acetamido-3-chloro-2-azetidinones **54** were prepared by Staudinger synthesis between chloroacetyl chloride and *N'*-arylidene acetohydrazide derivatives in the presence of Et_3N (Scheme 39) [84–89]. The syntheses of β-lactams **54a** were carried out under conventional and microwave (mw) heating (conditions **A** and **B**). The reactions promoted by mw irradiation were faster (**A:** 16-24 h; **B:** 30-45 min) and afforded the products with higher yields (**A:** 50-60% vs **B:** 81-96%) [84]. The acetamido linker was used to attach various cyclic moieties to the azetidinone, including thymol (**54b**, [85]), 2-

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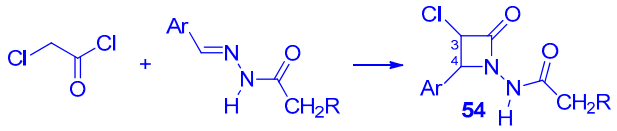
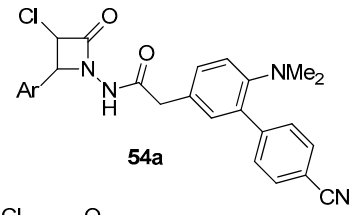
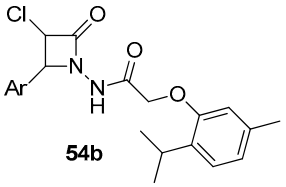
aminothiazole (**54c**, [86]), 2-(thien-2-yl)-2,3-dihydro-1*H*-benzo[*d*]imidazole (**54d**, [87]), and 1,4-benzoxazin-3-one (**54e**, [88]). Symmetrical bis-azetidinones **54f** with a central pyromellitic diimide tricyclic system were also prepared by the same approach [89].





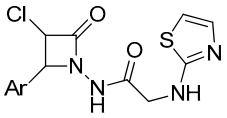
54a

conditions: **A:** Et_3N, MeCN, reflux, 16-24 h
B: Et_3N, MeCN, mw (600 W), 90 °C, 30-45 min
Ar = 4-FC_6H_4 (**A:** 58%, **B:** 81%), 4-ClC_6H_4 (**A:** 58%, **B:** 82%), 4-BrC_6H_4 (**A:** 55%, **B:**89%), 4-$F_3CC_6H_4$ (**A:** 50%, **B:** 96%), 3-BrC_6H_4 (**A:** 55%, **B:** 88%), 3-NCC_6H_4 (**A:** 60%, **B:** 84%), 2,4-$F_2C_6H_3$ (**A:** 50%, **B:** 82%), 2,4-$Me_2C_6H_3$ (**A:** 60%, **B:** 92%).
antimicrobial activity



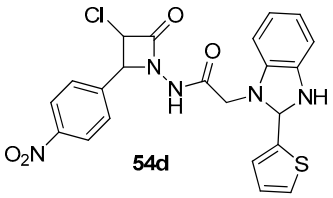
54b

conditions: Et_3N, DMF, rt, 24 h then 37 °C, 2 d
Ar = 4-$O_2NC_6H_4$ (50%), 3-$O_2NC_6H_4$ (53%), 2-$O_2NC_6H_4$ (49%).
antifungal and insecticidal activities



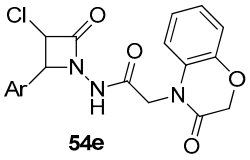
54c

conditions: Et_3N, dioxane, rt, 20 min, then reflux, 8 h
Ar = Ph (63%), 4-HOC_6H_4 (65%), 4-$O_2NC_6H_4$ (52%), 2-ClC_6H_4 (70%), 2-MeC_6H_4 (50%), 4-$MeOC_6H_4$ (45%) 4-$Me_2NC_6H_4$ (0%).
antimicrobial activity



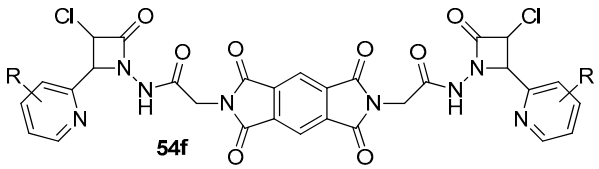
54d

conditions: Et_3N, dioxane, 0-5 °C, 9 h (42%)
antimicrobial activity



54e

conditions: Et_3N, dioxane, rt, 30 min
then reflux, 8 h
Ar = 2-ClC_6H_4 (65%), 2-thienyl (55%).
antimicrobial and antioxidant activities



54f

conditions: Et_3N, DMF, reflux, 4-5 h
R = H (55%), 5-Me (65%), 6-Me (64%), 5-MeO (71%), 3-MeO (73%), 3-OH (68%), 3-Cl (57%).
antimicrobial activity

Scheme 39. Synthesis of 1-acetamido-3-chloro-2-azetidinones. *(Tested activities are in italics).*

Staudinger synthesis of chloroacetyl chloride and *N'*-arylidene benzohydrazide derivatives in the presence of Et_3N afforded 1-benzamido-3-chloro-2-azetidinones **55a-55c** in good yields (Scheme 40) [24,90,91]. Adducts **55b** [24] and **55c** [91] contained a 2-(pyridin-4-yl)quinazolin-4(3*H*)-one and a thieno[3,2-*d*]pyrimidin-4-amine group, respectively, attached to the benzamido moiety. Hybrid β-lactams **55d** [92] and **55e** [93] were prepared analogously using substituted pyrazole-3-carbohydrazides and thieno[3,2-*b*]pyrrole-5-carbohydrazide, respectively (Scheme 40).

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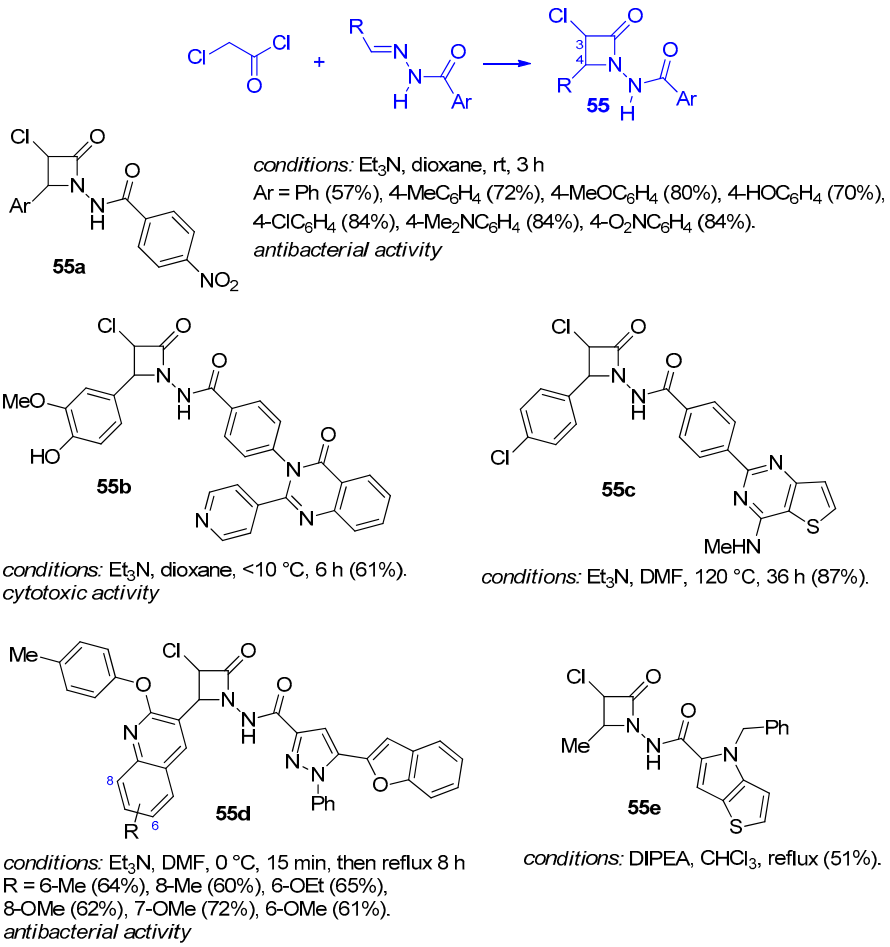
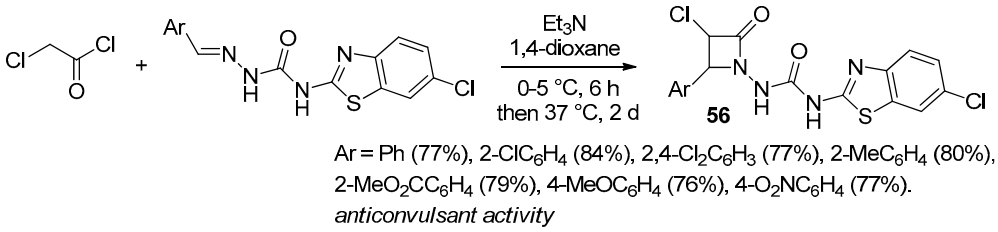
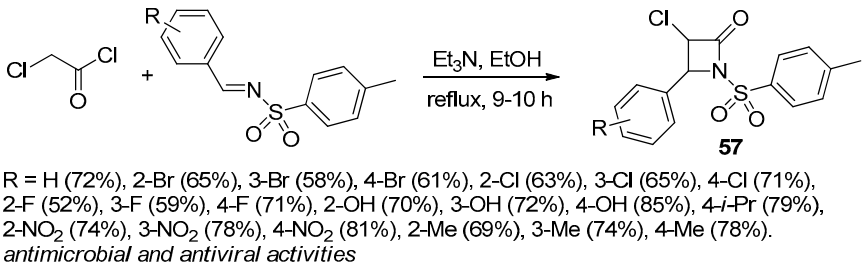


Scheme 40. Synthesis of 1-benzamido- and 1-(heteroarenecarboxamido)-3-chloro-2-azetidinones. *(Tested activities are in italics*).

Variously decorated 3-chloro-1-ureido-2-azetidinones **56** (Scheme 41) [94] and 3-chloro-1-tosyl-2-azetidinones **57** (Scheme 42) [95] were also obtained in good yields by Staudinger [2+2]-cycloaddition.



Scheme 41. Synthesis of 3-chloro-1-ureido-2-azetidinones. *(Tested activities are in italics*).



Scheme 42. Synthesis of 4-aryl-3-chloro-1-tosyl-2-azetidin-ones. *(Tested activities are in italics*).

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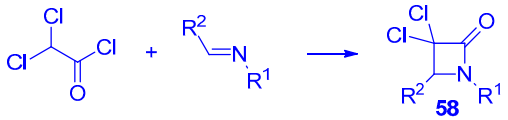
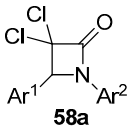
2.2.7. Ketene Generated In Situ from 2,2-Dichloroacetyl Chloride

2,2-Dichloroacetyl chloride was reacted with imines in the presence of a base to give 3,3-dichloro-2-azetidinones (Scheme 43) [30,53,63,93]. 1,4-Diaryl derivatives **58a** were obtained in high yields using solid MAH as heterogeneous base in DMF under microwave irradiation (see also **40a**, Scheme 28; **47**, Scheme 33; **48**, Scheme 34; and **59b**, Scheme 44). In contrast to the monochloro derivatives (Scheme 34), no formation of open by-products was observed [53].

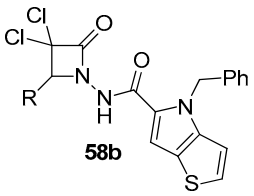


58



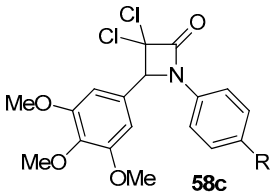
58a

conditions: Mg-Al hydroxide (MAH), DMF, mw, 180 °C, 2 min
Ar^1, Ar^2 = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$ (91%);
4-$MeOC_6H_4$, 4-$MeOC_6H_4$ (83%);
2,4-$Cl_2C_6H_3$, 4-ClC_6H_4 (89%).



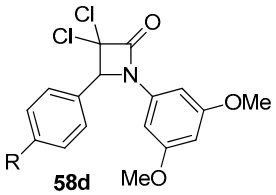
58b

conditions: DIPEA, $CHCl_3$, reflux
R = Me (68%), 2-furyl (59%).



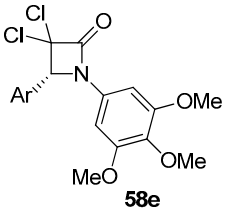
58c

conditions: Et_3N, CH_2Cl_2, reflux, 5 h
R = 4-OMe (18%), 4-OEt (25%), 4-SMe (47%).
antimitotic and cytotoxic activities



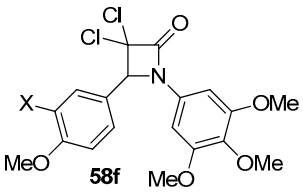
58d

conditions: Et_3N, CH_2Cl_2, reflux, 5 h
R = 4-OMe (13%), 4-OEt (7%).
antimitotic and cytotoxic activities



58e

conditions: Et_3N, CH_2Cl_2, reflux, 5 h
Ar = Ph (31%), 4-ClC_6H_4 (31%), 4-BrC_6H_4 (39%), 4-$O_2NC_6H_4$ (44%), 4-$MeOC_6H_4$ (28%), 4-$EtOC_6H_4$ (29%), 4-$PhOC_6H_4$ (24%), 4-$BnOC_6H_4$ (26%), 4-$MeSC_6H_4$ (63%), 1-naphthyl (32%), 2-naphthyl (35%), 4-MeO-3-$TBDMSOC_6H_3$ (NR), 4-MeO-3-$O_2NC_6H_3$ (17%), 4-MeO-3-MeC_6H_3 (50%).
NR = not reported
antimitotic and cytotoxic activities



58f

conditions: Et_3N, toluene, 100 °C, 5 h, then rt, 15 h
X = F (63%), Cl (63%), Br (45%), I (34%), Me (54%).
antiproliferative and antiapoptotic activities

Scheme 43. Synthesis of 1-aryl- and 1-amido-3,3-dichloro-2-azetidinones. *(Tested activities are in italics*).

The reaction of dichloroacetyl chloride with the condensation products of 4-benzylthieno[3,2-*b*]pyrrole-5-carbohydrazide with acetaldehyde and furfural in the presence of DIPEA gave β-lactams **58b** in higher yields than the analogous 3-chloro derivative **55e** (see Scheme 40). In contrast, the reaction with the corresponding isobutyraldehyde hydrazone did not give the [2+2] adduct and afforded the open isomer 4-benzyl-*N*′-(dichloroacetyl)-*N*′-(2-methylpropyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carbohydrazide in 52% yield [93].

1,4-Diaryl-3,3-dichloro-2-azetidinones **58c-58f** were prepared by the Staudinger synthesis in yields ranging from 7 to 63% [30,63]. Silyl derivative **58e** (Ar = 4-MeO-3-TBDMSO-C_6H_3) was not

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isolated but directly treated with TBAF to give the phenolic product **58e** (Ar = 4-MeO-3-HOC_6H_3). The structure of **58e** (Ar = 4-MeO-3-MeC_6H_3) was confirmed by X-ray analysis [63].

Instead of the expected 3,3-dichloro-β-lactams, the reaction of 2,2-dichloroacetyl chloride with 2,2-dimethyl-1,3-dioxolan-4-yl)methanimines yielded 2,2-dichloro-*N*-(chloromethyl)acetamides. This peculiar reactivity has been studied experimentally and by Density Functional Theory (DFT) calculations [96].

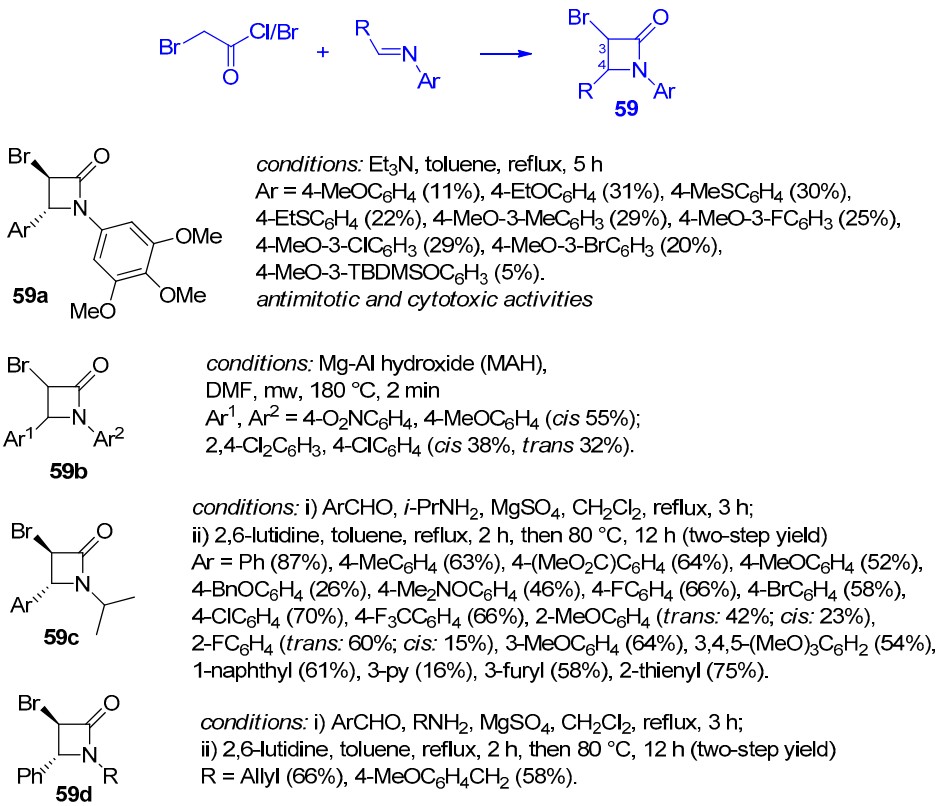
2.2.8. Ketene Generated In Situ from 2-Bromoacetyl Chloride/Bromide

Some 3-bromo-azetidin-2-ones have recently been synthesized by reaction of 2-bromoacetyl chloride or bromide with arylimines (Scheme 44) [53,61,63,97].

When the reaction was carried out in dichloromethane, the 3-bromo-β-lactams **59a** were obtained as a mixture with the corresponding 3-chloro-β-lactams in a ratio of 1:2, due to the halogen exchange with the chlorinated solvent. All adducts of **59a** were isolated as *trans*-isomers ($J_{3,4}$ = 0-2.1 Hz). The X-ray crystal structure of **59a** (Ar = 4-MeO-3-ClC_6H_3) was reported. In general, the 3-bromoazetidinones were less active than the corresponding 3-chloro derivatives [63].

Similar to 3-acetoxy-, 3-chloro- and 3,3-dichloro-2-azetidinones (see: **40a**, Scheme 28; **47**, Scheme 33; **48**, Scheme 34; **58a**, Scheme 43), 3-bromo-β-lactams **59b** were prepared by the use of solid MAH as a heterogeneous base in DMF under microwave heating. These derivatives were obtained in lower yields, mainly as *cis* adducts ($J_{3,4\ cis}$ = ca 5.0 Hz, $J_{3,4\ trans}$ = ca 0 Hz) [53].

Arylaldehyde and isopropylamine were condensed in the presence of $MgSO_4$ to give the corresponding imine, which was filtered on Celite® and directly reacted with bromoacetyl bromide using 2,6-lutidine as the base (Scheme 44). The reaction afforded *trans*-azetidinones **59c** as the sole adducts, except in the case of **59c** (Ar = 2-$MeOC_6H_4$) and **59c** (Ar = 2-FC_6H_4), which were obtained as a mixture of *cis*/*trans* isomers ($J_{3,4\ cis}$ = 4.9-5.1 Hz, $J_{3,4\ trans}$ = 1.6-1.9 Hz). Following the same protocol, *trans*-1-allyl- and *trans*-1-benzyl-3-bromo-β-lactams **59d** were also synthesized. 3-Bromo-2-azetidinones **59c** and **59d** were used to prepare *trans*-3,4-diaryl- and *trans*-3-allyl-4-aryl-β-lactams via a cobalt-catalyzed cross-coupling reaction with aryl Grignards and diallylzinc reagents [61,97].



Scheme 44. Synthesis of 3-bromo-azetidin-2-ones. *(Tested activities are in italics).*

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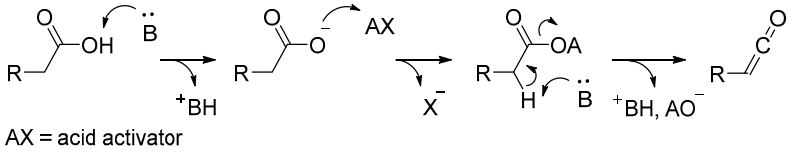
2.3. Ketene Generated In Situ from Carboxylic Acids

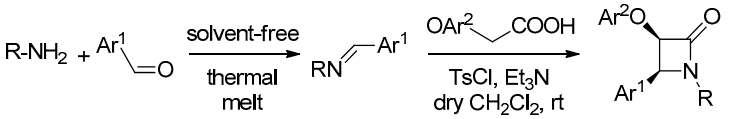
In general acyl chlorides are characterized by low stability and high toxicity, so in many synthetic approaches ketenes are generated *in situ* from carboxylic acids under different reaction conditions. Commonly, the process requires an acid activator (AX), such as *p*-TsCl, $POCl_3$; $SOCl_2$, acyl chlorides, Mukaiyama reagent, etc.… and a base (B) (Scheme 45).



Scheme 45. General protocol to access ketenes from carboxylic acids.

2.3.1. Ketene Generated In Situ from Carboxylic Acids and p-TsCl/Base

Jarrahpour and coworkers achieved the [2+2]-imine-ketene cycloaddition (Staudinger synthesis) in a one-pot sequential multicomponent fashion exploiting the efficient *in situ* generation of imines by thermal melting of equimolar amounts of aryl/heteroaryl aldehydes and primary amines. The freshly generated imines were then dissolved in dry CH_2Cl_2 and treated with aryloxyacetic acids and *p*-toluensulfonyl chloride, as acid activator, in the presence of triethylamine for ketenes generation, at room temperature. Substituted β-lactams **60** were synthesized in 70-93% yields, with exclusive *cis*-stereoselection (Scheme 46). The *cis* stereochemistry was determined by the coupling constants of the neighboring β-lactam ring protons ($J_{3,4} > 4.0$ Hz for the *cis* stereoisomer versus $J_{3,4} < 3.0$ Hz for the *trans* one) [98].



Scheme 46. One-pot sequential multicomponent synthesis of β-lactams **60**.

The same protocol was applied to previously prepared and purified imines. The use of *C*-aryl-*N*-aryl substituted Schiff bases and 2-(4-formylphenoxy)acetic acid gave rise to *cis* β-lactams **61**, containing a benzaldehyde moiety, in 70-88% yields. The further synthetic elaboration of the formyl group allowed to access chromeno β-lactam hybrids of type **62** (Scheme 47). All the azetidinone derivatives were screened for anti-inflammatory and anticancer activities evidencing good antitumour activity against the *SW1116* (colon cancer) cell lines, without notable cytotoxicity towards the *HepG2* control cell line. Compound **61** (Ar^1 = 4-ClC_6H_4, Ar^2 = 4-MeC_6H_4) resulted more active than the well-known dexamethasone corticosteroid used for the treatment of rheumatoid and skin inflammation [99].

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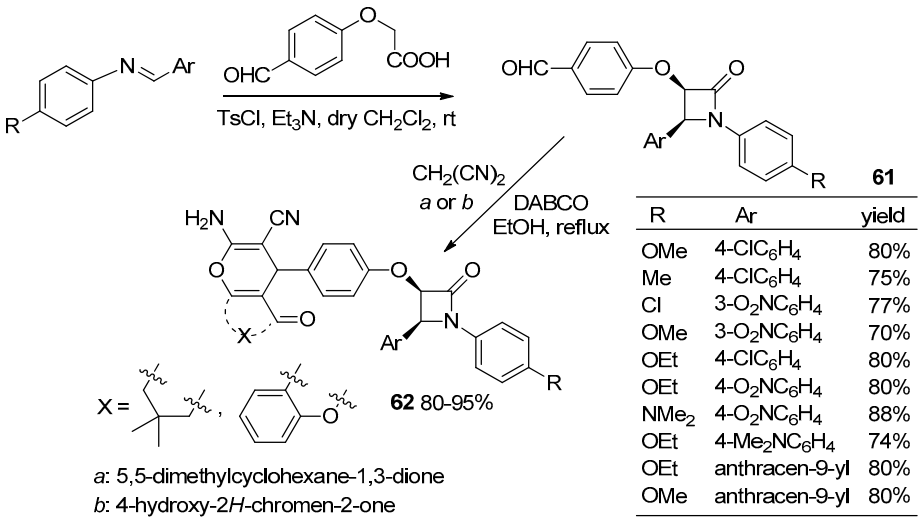
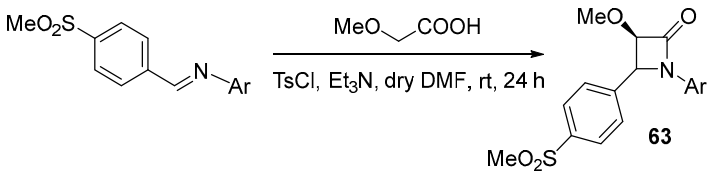


R	Ar	yield
OMe	4-ClC$_6$H$_4$	80%
Me	4-ClC$_6$H$_4$	75%
Cl	3-O$_2$NC$_6$H$_4$	77%
OMe	3-O$_2$NC$_6$H$_4$	70%
OEt	4-ClC$_6$H$_4$	80%
OEt	4-O$_2$NC$_6$H$_4$	80%
NMe$_2$	4-O$_2$NC$_6$H$_4$	88%
OEt	4-Me$_2$NC$_6$H$_4$	74%
OEt	anthracen-9-yl	80%
OMe	anthracen-9-yl	80%

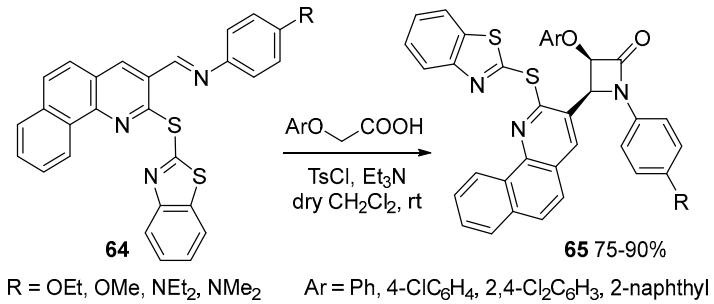
Scheme 47. Synthesis of 1,4-diaryl-3-aryloxy-2-azetidinones **61**.

In a similar way, operating in DMF as solvent, *cis* 1-aryl-4-(4-methylsulfonylphenyl)azetidine-2-ones **63** were synthesized (Scheme 48) and their biological activity as selective cyclooxygenase-2 (COX-2) inhibitors was evaluated. All compounds resulted selective inhibitors of the COX-2 isozyme and the 1-(3,4,5-trimethoxyphenyl) derivative showed the highest COX-2 inhibitory selectivity and potency. The analgesic activity was also investigated [100].



Scheme 48. Synthesis of 1-aryl-4-(4-methylsulfonylphenyl)azetidine-2-ones **63**.

The [2+2] cycloaddition of heteroaryl substituted imines, such as **64**, and different aryloxyacetic acids allowed the synthesis in 75-90% yields of *cis* β-lactam hybrids **65** containing 2-mercaptobenzothiazole and benzoquinoline systems (Scheme 49). Biological studies showed a good antibacterial activity against either the Gram-negatives *E. coli* and *P. aeruginosa* or the Gram-positive *S. aureus* mainly when Ar = Ph and low cytotoxicity effects on eukaryotic cells [101].



Scheme 49. Synthesis of *cis* β-lactam hybrids **65**.

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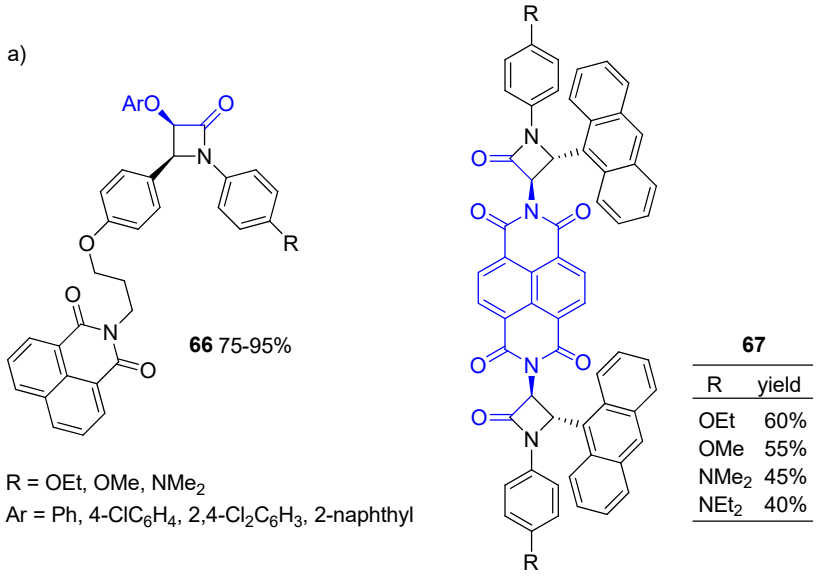
Applying this procedure to suitably substituted acetic acid derivatives and Schiff bases, structurally complex β-lactams bearing different heterocyclic systems were efficiently prepared (Figure 1).

On the basis of the mechanistic hypothesis outlined in Scheme 2 for the Staudinger [2+2] cycloaddition, it is difficult to predict the stereochemical outcome of the β-lactam adducts due to the influence of several factors, in particular when large polycyclic aryl substituents are present in the imine or ketene partners. These groups are responsible for larger or smaller steric interactions depending on spatial arrangements as well as ⊚⊚⊚ interactions that can be either attractive (⊚-stacking) or electronically repulsive in their nature. For instance, naphthalimido hybrids of type **66** were obtained from aryloxyacetic acids **e**xclusively as *cis*-stereoisomers (^{1}H NMR analysis: $J_{3,4}$ = 4.2-4.7 Hz; single crystal X-ray analysis on β-lactam with R = OMe and Ar = 4-ClC$_6$H$_4$). On the contrary, a bulky bis-arylimidoacetic acid derivative reacted with anthracenyl substituted imines leading to *trans* bis-β-lactams **67** (^{1}H NMR analysis: $J_{3,4}$ = 2.2-2.7 Hz) and the same stereochemical outcome was observed with aryl and fluorenyl imines (Figure 1a). Antioxidant and anticancer activities were evaluated as well as DNA interaction. In particular, bis-adducts **67** showed excellent antioxidant activity and *in vitro* anticancer activity against the *MCF-7* and *TC-1* cancer cell lines, without noticeable cytotoxicity towards healthy cells, as well as the ability to bind to calf-thymus DNA (CT-DNA) [102].

The synthesis of tripodal β-lactams **68** with 1,3,5-triazine core was performed using *s*-triazine-based tris-imines (Figure 1b). NMR analysis evidenced the all-*cis*-relative stereochemistry of the three β-lactam rings (even if the presence of different 'all-*cis*' diastereomers was not definitively established). The tris-β-lactams displayed good inhibitory behaviour against the K562 human leukemia cell line and antioxidant properties as radical scavengers while moderate antibacterial activity against Gram-positive bacteria *S. aureus* was observed for phenoxy derivatives with X = Y = H and Z = Me or OEt [103].

Completely stereoselective processes were also observed with different morpholino-1,3,5-triazine imines affording triazine-containing *cis*-β-lactam hybrids **69**, **70**, and **71** (Figure 1c). Some derivatives of type **69** and **70** showed excellent growth inhibitory activity (*in vitro* IC$_{50}$ < 5 ⊚M) against *SW1116* cells, comparable to that of the clinically used anticancer agent doxorubicin (IC$_{50}$ = 6.9 ⊚M). Strong interactions with CT-DNA were also observed for **69** [104].



67

R	yield
OEt	60%
OMe	55%
NMe_2	45%
NEt_2	40%

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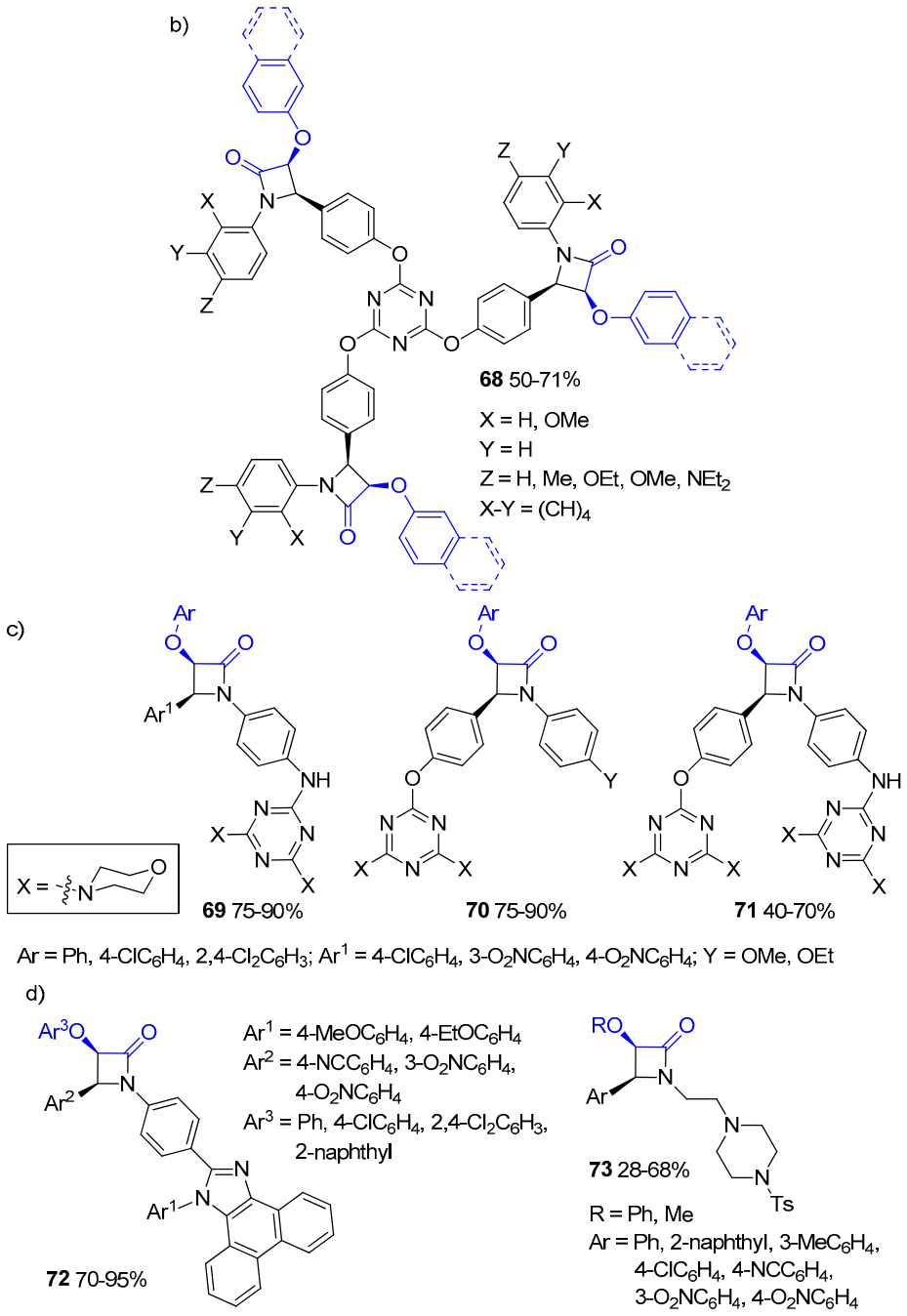

Figure 1. Structurally complex β-lactams **66**-**73** bearing different heterocyclic substituents. The blue part of the structure comes from the acetic acid derivative. For compounds **67** and **68** only one possible diastereomer is reported.

Moreover, monocyclic 1*H*-phenanthro[9,10-*d*]imidazole β-lactam conjugates **72** were synthesized exclusively as *cis* stereoisomers in 70-95% yields from 1*H*-phenanthro[9,10-*d*]imidazole imines and aryloxyacetic acids (Figure 1d). They exhibited significant cytotoxicity towards various mammalian cancer cell lines [105].

Cis-β-lactam rings **73** with a piperazine moiety in the appended side chain were also prepared in 28-68% yields from piperazinyl-substituted imines and 2-PhO/MeO-acetic acids (Figure 1d). High inhibitory effect on inducible nitric oxide synthase (iNOS) as well as anti-inflammatory activity were observed mainly when a naphthyl moiety is present at the C-4 position (Ar = 2-naphthyl). Good antibacterial activity against *S. aureus* and *E. coli* was also evidenced [106].

Applying the well-established protocol to morpholino-substituted imines **74**, the use of 2-ArO/MeO-acetic acids afforded *N*-morpholino-β-lactams **75** in 23-79% yields which *cis*

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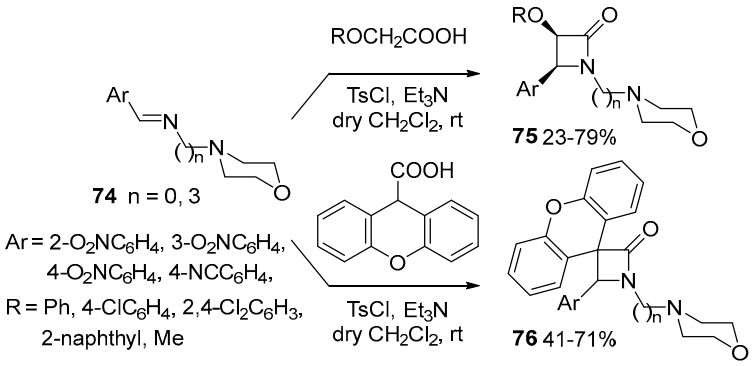
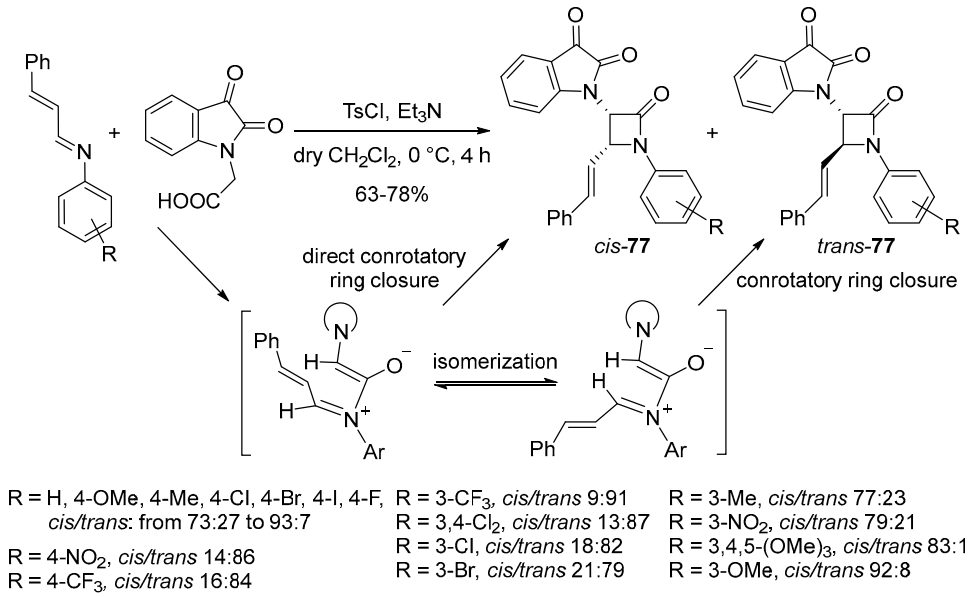
stereochemistry was confirmed by ^{1}H NMR analysis ($J_{3,4}$ = 4.6-5.1 Hz). When 9*H*-xanthene-9-carboxylic acid was applied as ketene precursor spiro derivatives **76** were obtained in 41-71% yields (Scheme 50). Compounds **75** showed high anti-inflammatory activity toward human inducible nitric oxide synthase (iNOS) and cytotoxic evaluation toward HepG2 cell lines evidenced their non toxicity and biocompatibility [107].



Scheme 50. Synthesis of *cis* β-lactams **75** and spirocyclic derivatives **76**.

β-Lactam-isatin conjugates **77** were synthesized from different *C*-styryl-*N*-aryl imines and 2-(2,3-dioxoindolin-1-yl) acetic acid by treatment with TsCl/Et$_3$N in dry CH_2Cl_2 at 0 °C (Scheme 51). The diastereoselectivity of the reaction is strongly dependent on the electronic nature of the substituents in the *N*-phenyl imine moiety. Strong electron-donating groups at the *para*-position promoted *cis*-selectivity likely due to the increased electron density on the imine nitrogen favoring the direct ring closure of the 2-azabutadiene intermediate. Strong electron-withdrawing groups at the same position reversed the diastereocontrol presumably by facilitating the isomerization of the intermediate. Variable results were observed for substituents at the *meta*-positions, probably depending on both electronic and steric factors. DFT-calculations supported the experimental outcome [108].



Scheme 51. Synthesis of β-lactam-isatin conjugates **77** and evaluation of stereochemical data.

Analogously, mono-spiro and bis-spiro isatin-tethered 2-azetidinones **78**, **79**, and **80** were prepared from isatin-based imines and bis-imines (Figure 2). For derivatives **78** the antimalarial activity was successfully evaluated against *P. falciparum* K1 strain, while compounds **79** and **80**

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showed moderate to excellent anti-cell proliferation behavior against two cancer cell lines (MCF-7 and HeLa). β-Lactams **79** were also able to interact with protein BSA and CT-DNA [109,110].

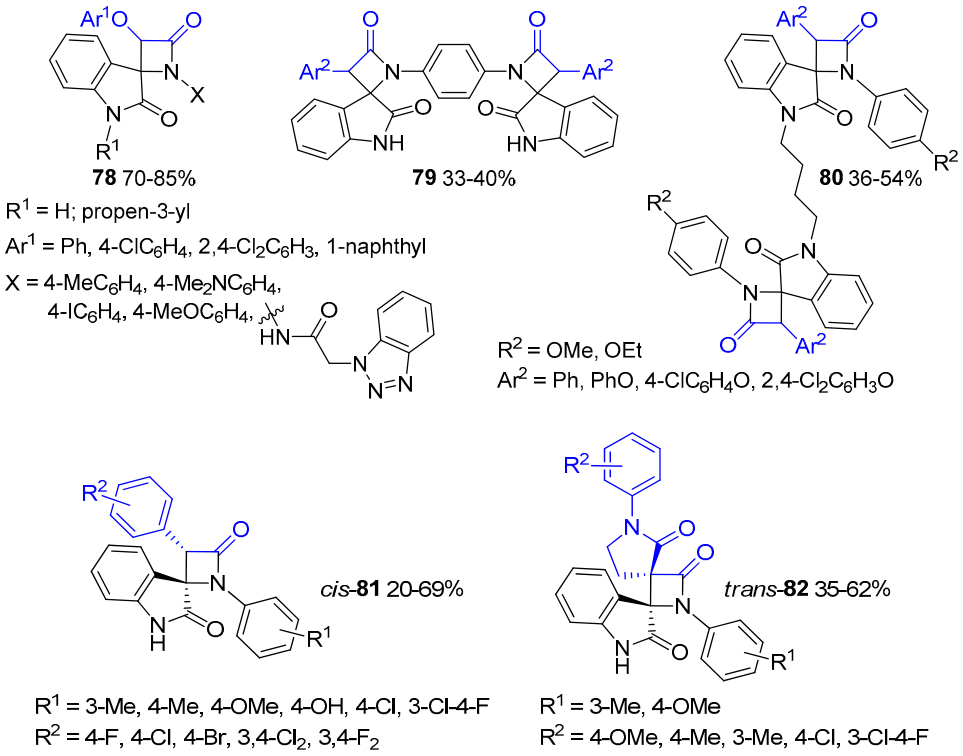

Figure 2. Mono-spiro and bis-spiro isatin-tethered 2-azetidinones **78**-**82**. The blue part of the structure comes from the acetic acid derivative.

A one-pot procedure led to 1,3-bis-aryl spirooxindolo-β-lactams **81** by treatment of substituted phenylacetic acids with TsCl and diisopropylethylamine (DIPEA) in dry *o*-xylene at 100 °C, for ketene generation, followed by isatin Schiff bases addition at room temperature. The reactions showed high diastereoselectivity in favor of the *cis*-isomers (except for 4-MeO-phenylacetic acid). An increase of *trans*-isomers was observed by raising temperature and solvent polarity. Using *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids as the ketene source and isatinimines, totally diastereoselective processes afforded *trans*-dispirooxindolo-β-lactams **82**, evaluated for cytotoxic and antibacterial activities (Figure 2) [111,112].

2.3.2. Ketene Generated In Situ from Carboxylic Acids and $POCl_3$/Base

Monocyclic β-lactams are generally more stable to hydrolysis by β-lactamases in comparison to other β-lactams. Thus, in the light of the search for new agents to fight the serious problem of antimicrobial resistance, monobactams are an attractive platform for studying the effects of synthetic modifications. In this context, 3-(*p*-substituted-phenylthio)-azetidin-2-ones **83** were prepared via [2+2] Staudinger cycloaddition and applied in Lewis acid catalyzed nucleophilic substitutions. 2-Arylthioacetic acids were reacted with *C*-aryl-*N*-aryl Schiff bases in the presence of triethylamine and phosphorous oxychloride in refluxing toluene to give *trans*-3-arylthio-β-lactams **83** ($J_{3,4}$ in the range 2.2-2.4 Hz) as the major products (minor amounts of the *cis* stereoisomers were also formed from 1,2-diphenylmethanimine) (Scheme 52) [113]. Compounds **83** were subjected to chlorination with sulfuryl chloride leading to *cis*-3-chloro-3-arylthio-β-lactams **84** which stereochemistry was confirmed by correlation of spectral data with those of compounds analyzed via X-ray crystallography. The following Lewis acid catalyzed C-3 functionalization allowed to prepare different derivatives such as *cis*-3-allyl-β-lactams **85** with allyltrimethylsilane. Oxidation with

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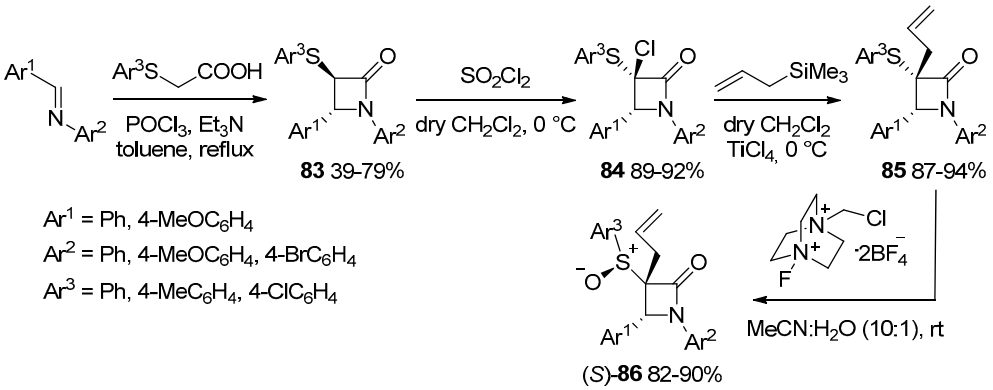
Selectfluor led to (*S*)-*cis*-3-allyl-3-arylsulfinyl-β-lactams **86** as single stereoisomers in excellent yields [114].



Scheme 52. Synthesis of *trans*-3-arylthio-β-lactams **83** and their synthetic elaboration.

Schiff bases prepared from amino-benzenesulfonamides and vanillin or salicylaldehyde were treated with thioglicolyc or 2-seleno-glycolic acid in the presence of Et_3N and $POCl_3$ in dry dichloromethane from 0 °C up to room temperature to afford 3-mercapto or 3-hydroseleno azetidine-2-ones **87** bearing benzenesulfonamido substituents at position 1 (Figure 3). The antibacterial activity was tested in vitro against *Staphylococcus aureus*, *Bacillus*, *Escherichia coli* and *Pseudomonas aeruginosa*, as well as the antioxidant and anticancer efficiency [115].

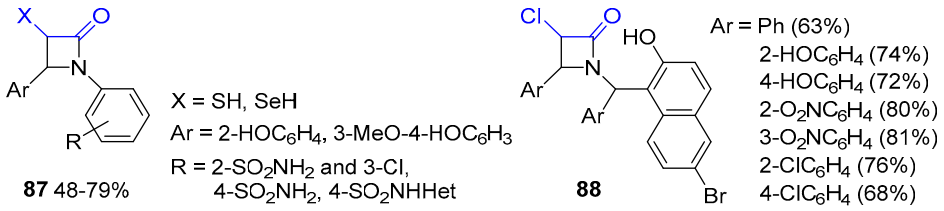


Figure 3. Synthesis of 3-mercapto-, 3-hydroseleno-, and 3-chloro-azetidine-2-ones **87** and **88**. The blue part of the structure comes from the acetic acid derivative.

The same protocol was applied to 2-hydroxynaphthyl substituted imines and chloroacetic acid to give 3-chloro-azetidin-2-ones **88** (Figure 3) which antibacterial activity was evaluated against different gram negative and gram positive bacteria. In compounds **87** and **88** the presence of hydroxyl groups seems very important in enhancing the antioxidant, anticancer, and antibacterial activities. Unfortunately, the relative stereochemistry was not determined for compounds **87** and **88** [116].

The treatment of Schiff bases bearing heterocyclic substituents and variously functionalized acetic acid derivatives (or acetyl chlorides) with $POCl_3/Et_3N$ (or simply Et_3N in the case of acetyl chlorides) in refluxing toluene allowed to access different β-lactam/heterocycle hybrids **89**-**92** (Figure 4) via almost exclusively *trans*-diastereoselective processes. The observed stereochemistry, determined on the basis of ^1H NMR analysis ($J_{3,4}$ in the range 0.8-2.6 Hz) and definitively confirmed via single crystal X-ray crystallography in representative cases, can be rationalized on the basis of both steric hindrance (bulky group at C-4 and N-1) and zwitterionic intermediate isomerization/electrocyclization pathway (see, Scheme 51), favoring the thermodynamically more stable product [54,56,117,118].

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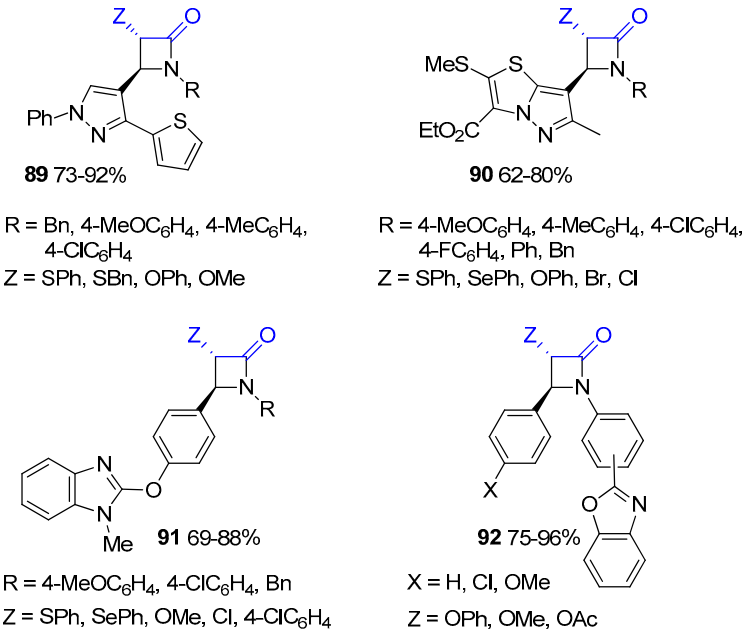

Figure 4. β-Lactam/heterocycle hybrids **89**-**92**. The blue part of the structure comes from the acetic acid derivative.

2.3.3. Ketene Generated In Situ from Carboxylic Acids and $SOCl_2$/Base

Azetidin-2-ones **93** and **94** bearing an oxazolidinone moiety were synthesized from (oxazolidin-3-yl)acetic acid derivatives and imines by treatment with $SOCl_2$ and Et_3N in MeOH at 40 °C (Figure 5). These compounds showed significant antibacterial activities against gram-positive and gram-negative bacteria like *B. Subtilis* and *E. Coli*. Moreover, fluorescence studies revealed excellent sensing capabilities for divalent metal cations [119,120].

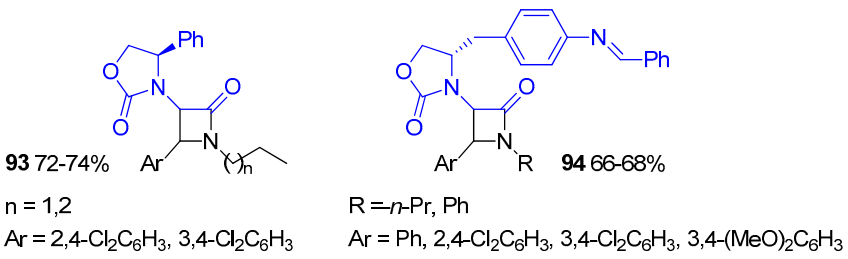

Figure 5. β-Lactam/oxazolidinone hybrids **93** and **94**. The blue part of the structure comes from the acetic acid derivative.

2.3.4. Ketene Generated In Situ from Carboxylic Acids and Acyl Chlorides/Base or Trifosgene/Base

Ketenes were also generated from carboxylic acids via activation with acyl chlorides, to generate mixed anhydrides as reactive precursors. For instance, spiroazetidine-2-ones of type **81** (see Figure 2), even substituted on the indoline moiety, were prepared in 27-84% yields, by a one-pot procedure involving addition of oxalyl chloride in dry THF to a solution of isatin imine, arylacetic acid, and DIPEA in the same solvent at room temperature (Scheme 53). Even in these conditions, compounds **81** were synthesized exclusively or mainly as *cis*-stereoisomers, as confirmed by X-ray diffraction analysis on specific products. The greatest diastereoselectivity was observed when electron donating substituents are present in the *N*-aryl moiety of the imine (R^1 = EDG). The same authors studied the above reaction using preformed aryl acetyl chloride (prepared from the acid by addition of oxalyl chloride in DMF/THF under reflux, purified by column chromatography and recrystallization), in the presence of Et_3N in refluxing DMF. An opposite stereochemical outcome was observed leading to the *trans*-stereoisomers as the major products (44-64% yields) (see **5g**, Scheme 7). The modified

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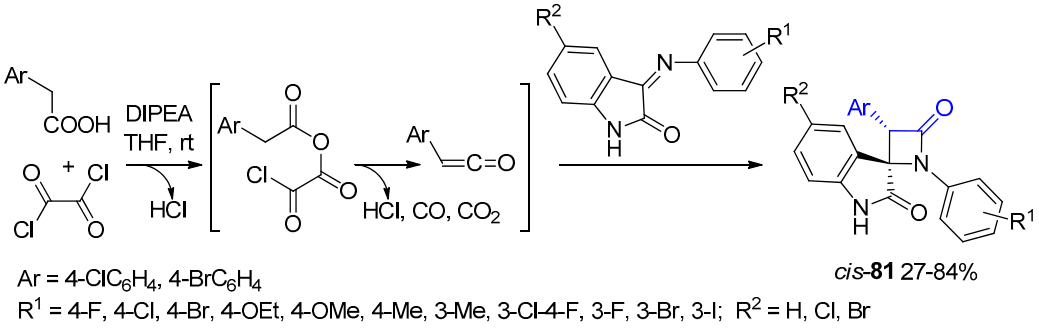
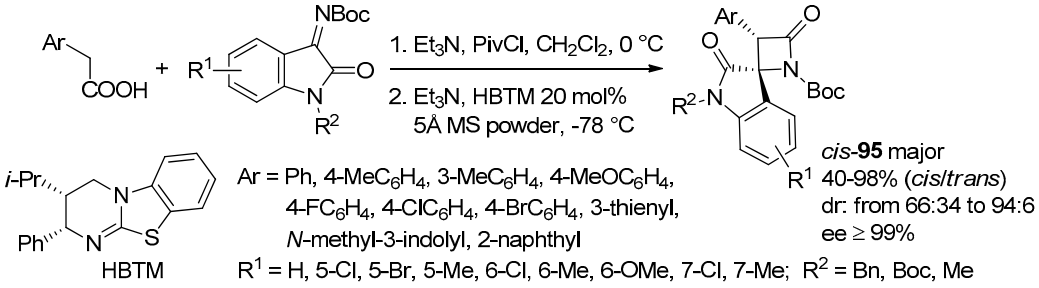
experimental conditions (likely the higher temperature) are responsible for the different stereoselectivity as well as lower yields. Preliminary *in vitro* cytotoxicity tests showed for *cis*-diastereomers a higher activity as inhibitors of the p53-MDM2 protein-protein interaction with respect to *trans* ones, according to molecular docking data [32].



Scheme 53. Synthesis of *cis*-spiroazetidine-2-ones **81** using oxalyl chloride as acid activator.

The asymmetric synthesis of spirooxindole ⍟-lactams **95**, analogous of **81**, was efficiently performed using pivaloyl chloride (PivCl) as acid activator, Et_3N as the base, and the enantiopure isothiourea organocatalyst homobenzotetramisole (HBTM) in dichloromethane at low temperature. Compounds **95** were prepared in 40-98% yields, as *cis*/*trans* mixtures where the *cis* stereoisomer was the major product (dr *cis*/*trans* from 66:34 to 93:7) with ee ≥ 99% (Scheme 54) [121].



Scheme 54. Synthesis of *cis*-spirooxindole ⍟-lactams **95** using pivaloyl chloride as acid activator.

An analogous method was applied to synthesize diprotected 3-amino-4-substituted monocyclic ⍟-lactams **96**. Ketenes were generated from *t*-butylcarbamate- or benzylcarbamate-protected glycine by treatment with ethyl chloroformate and Et_3N in dry THF at low temperature (from -60 to -40 °C) to form the mixed anhydride, then added to a solution of an aromatic imine. Compounds **96** were obtained mainly as *cis*-stereoisomers in 11-33% yields (Figure 6). This methodology was compared with those involving ketenes generation from acyl chlorides (see **10d** and **10e**, Scheme 10). Deprotection methods were also investigated [38].

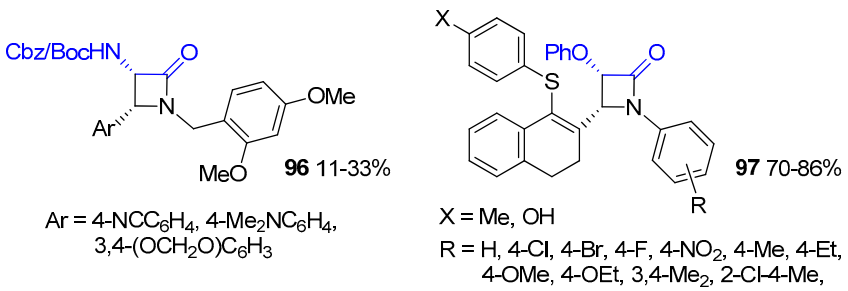


Figure 6. Monocyclic β-lactams **96** and **97**. The blue part of the structure comes from the acetic acid derivative.

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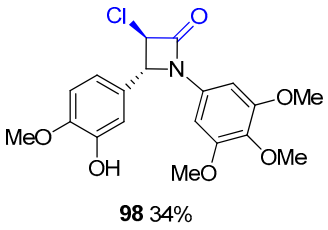
Even methyl 4,5-dichloro-6-oxopyridazine-1(6*H*)-carboxylate was applied as an activator of carboxylic acid for ketenes generation. The reaction with phenoxyacetic acid in refluxing toluene gave rise to a mixed anhydride with elimination of 4,5-dichloropyridazin-3(2*H*)-one that can be recovered and recycled. The following reaction with suitable Schiff bases and Et_3N in dry dichloromethane at room temperature gave monocyclic ◎-lactams **97** exclusively as *cis*-diastereomers, which stereochemistry was definitively confirmed via X-ray crystallographic analysis (Figure 6). The potential optical and nonlinear optical properties of these products were explored as well as their antimicrobial activities against some bacteria and fungi [122].

The system triphosgene (Cl_3C-O-COO-CCl_3)/Et_3N was also applied to activate carboxylic acids towards ketene generation, likely via formation of anhydride intermediates [123]. Operating with chloroacetic acid and the suitable imine in dry dichloromethane under reflux, this approach allowed the synthesis in 34% yield of *trans* 3-chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)azetidin-2-one (**98**), that is structurally related to the tubulin polymerization inhibitor and vascular targeting agent Combretastatin A-4 (CA-4) (Figure 7). This compound, as well as other 3-chloro/bromo- and 3,3-dichloro-azetidinones mainly synthesized from chloro/bromo-acetyl chloride and dichloroacetyl chloride (see **50e**, Scheme 35, **58c-e**, Scheme 43 and **59a**, Scheme 44), was evaluated as tubulin-targeting agent and showed significant antiproliferative activity at nanomolar concentrations in a range of human cancer cell lines [63].

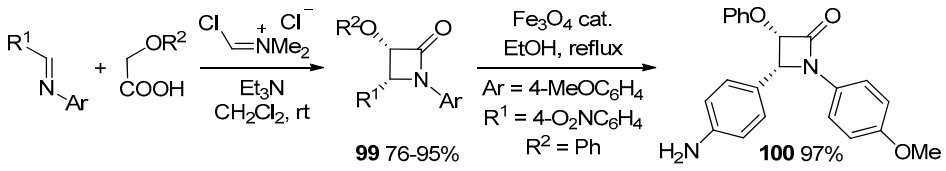


98 34%

Figure 7. 3-Chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)azetidin-2-one (**98**), structurally related to Combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

2.3.5. Ketene Generated In Situ from Carboxylic Acids and Vilsmeier Reagent/Base

(Chloromethylene)dimethyliminium chloride (Vilsmeier reagent) was used in the presence of a base as a carboxylic acid activator, to generate ketenes under mild reaction conditions. Aromatic Schiff bases and substituted acetic acids were treated with triethylamine and Vilsmeier reagent in dry dichloromethane at room temperature to afford monocyclic ◎-lactams **99**, exclusively as *cis*-stereoisomers (^{1}H NMR analyses). This protocol allowed the synthesis of different nitroaryl substituted 2-azetidinones in high yields, and the selective reduction of nitro to amino group was efficiently performed with Fe_3O_4 nanoparticles in refluxing EtOH, to give amino ◎-lactams, such as **100** (Scheme 55) [124].



99 76-95% **100** 97%

Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2-chloropyridin-3-yl

R^1 = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, styryl

R^2 = Ph, Me, 2,4-Cl$_2$C$_6$H$_3$, 4-O$_2$NC$_6$H$_4$, 2-naphthyl

Scheme 55. Synthesis of *cis*-monocyclic ◎◎lactams **99**, using Vilsmeier reagent as carboxylic acid activator.

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This protocol was applied to the synthesis of *N*-anthraquinon-2-yl-β-lactams **101** using imine derived from 2-aminoanthraquinone. Compounds **101** are in general synthesized as *cis*-diastereomers (^{1}H NMR data) but in some cases, probably due to electronic and steric effects of the substituents, *trans* derivatives were obtained (Figure 8). These compounds were evaluated for antibacterial, antifungal, and anticancer activities [125,126].

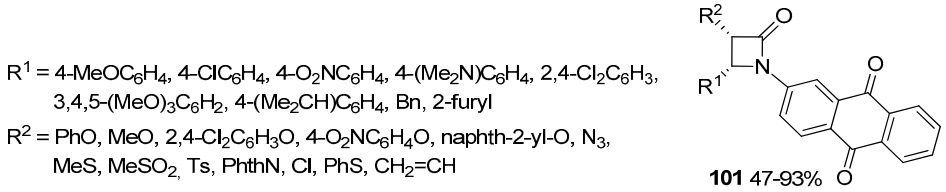
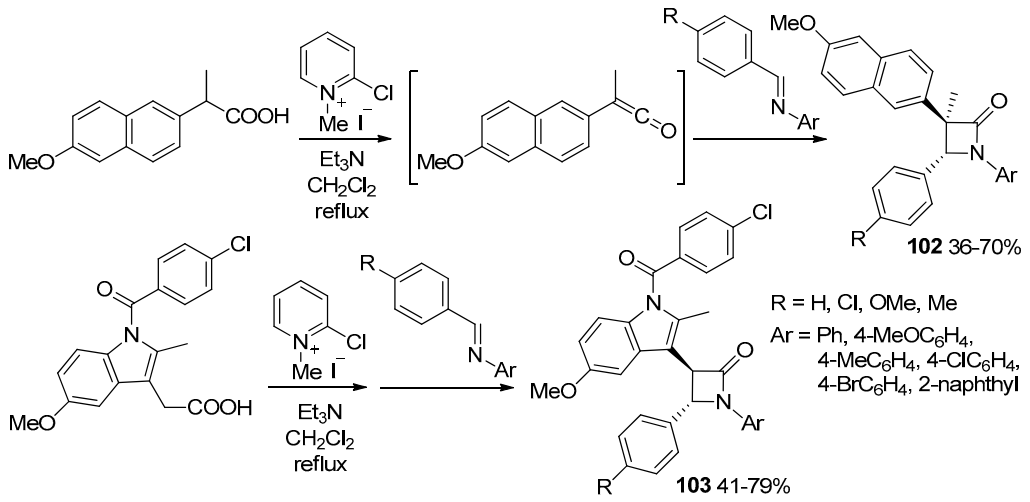


Figure 8. *N*-anthraquinon-2-yl-β-lactams **101**. The blue part of the structure comes from the acetic acid derivative.

2.3.6. Ketene Generated In Situ from Carboxylic Acids and Mukaiyama Reagent/Base

The *in situ* generation of ketenes from carboxylic acids was also achieved using 2-chloro-*N*-methylpyridinium iodide (Mukaiyama reagent) as the acid activator and triethylamine. The treatment of 2-(6-methoxy-2-naphthyl) propanoic acid (naprossen) with Mukaiyama reagent and Et_3N in dry CH_2Cl_2 under reflux was studied and resulted more efficient with respect to other systems for ketene generation. The presence of ketene intermediate was confirmed by its trapping with the stable free radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO). Subsequent addition of a *C*-aryl-*N*-aryl imine at the same temperature afforded 3-(6-methoxy-2-naphthyl)-3-methyl-1,4-diaryl-2-azetidinones **102** as diastereomeric mixtures containing mainly the *trans* isomer (Scheme 56). Applying the same protocol to indomethacin as ketene precursor, β-lactams **103** were synthesized exclusively as *trans* isomers. The steric hindrance aryl/naphthyl or aryl/indomethacinyl is probably responsible for the stereochemical outcomes. Derivatives **102** were tested for anticonvulsant activity [127,128].



Scheme 56. Synthesis of ⍟-lactams **102** and **103**, using Mukaiyama reagent as carboxylic acid activator.

Similarly, 3-amino-1,4-diaryl-2-azetidinones **104**, analogues of combretastatin A-4 (CA-4), were prepared from (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid (*N*-phthaloylglycine) using Mukaiyama reagent, exclusively as *trans* stereoisomers (Figure 9). Analogous derivatives with different substituents at position 3 were prepared starting from acyl chlorides (see **5e**, Scheme 7; **36d**, Scheme 25; **37**, Scheme 26; **50e**, Scheme 35; **58f**, Scheme 43) or ethyl bromoacetate in the presence of

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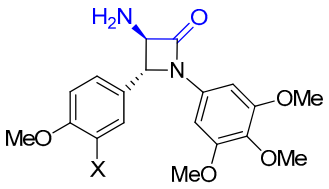
Zn (see Figure 11). They were evaluated *in vitro* for antiproliferative activity, antiapoptotic activity and inhibition of tubulin polymerization [30].

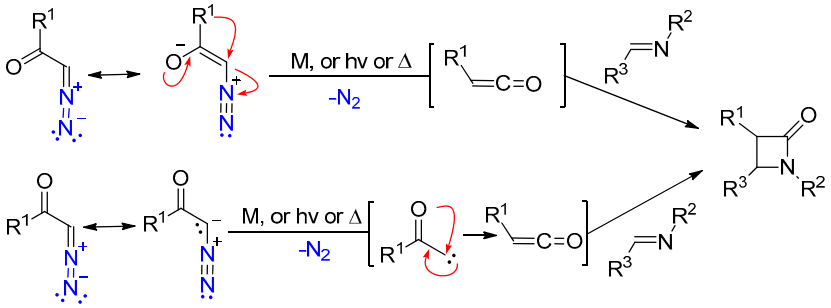


104 X = F (12%), Cl (96%)

Figure 9. 3-Amino-1,4-diaryl-2-azetidinones **104**, analogues of combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

2.4. Ketene Generated In Situ from Diazo Compounds

Diazo compounds are versatile substrates that readily undergo Wolff rearrangement to ketenes, which then undergo various transformations, including cycloaddition with imines to 2-azetidinones. These transformations are usually carried out under metal catalysis, although more recently both photoinduced and thermal decompositions have been used. The mechanistic pathway of the Wolff rearrangement can be described as either concerted or stepwise (Scheme 57).



Scheme 57. Wolff rearrangement–Staudinger cycloaddition.

A series of papers by Krasavin *et al.* describe the thermally promoted preparation of substituted 2-azetidones, combining the Wolff rearrangement and the Staudinger ketene-imine cycloaddition. Compared to previous methods, this approach does not require metal catalysts.

In a first paper, Kravasin *et al.* investigated the thermally assisted reaction of imines with α-acyl-α-diazoacetates **105**, which had previously been reported mainly in the presence of transition metal-catalysts. The reaction leads to the formation of densely substituted 2-alkoxycarbonyl-β-lactams **106** in moderate to good yields with excellent diastereoselectivities (single diastereomer except for R^2 = 2-FC_6H_4 and 4-$F_3CC_6H_4$ with R^3=R^4=Me and R^1=Bn). The reaction was carried out with imines prepared either *in situ* or in a separate step in refluxing toluene. Notably, mechanistic analysis of energetically feasible reaction pathways using DFT calculations evidenced 1,3-oxazin-4-one species as intriguing intermediates. This finding is novel as these intermediates have not previously been implicated in the Staudinger synthesis of β-lactams. Unfortunately, initial attempts to confirm this hypothesis with experimental data were unsuccessful (Scheme 58)[129].

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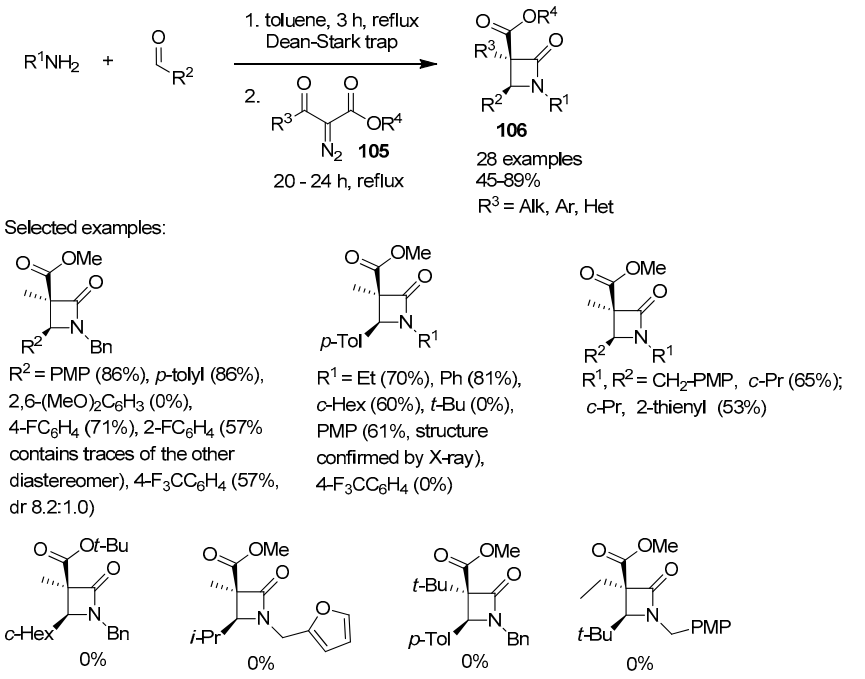
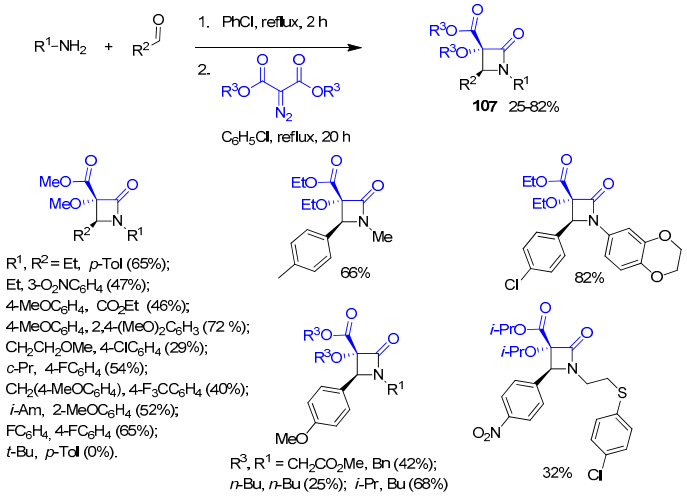


Scheme 58. 2-Alkoxycarbonyl-2-azetidinones by tandem Wolff rearrangement–Staudinger ketene-imine cycloaddition.

Later the reaction was extended to other types of diazo compounds such as dialkyl diazomalonates◎and◎◎-diazo-◎-ketosulfones as ketene precursors. The use of dialkyl diazomalonates gave 3-alkoxy-3-alkoxycarbonyl-2-azetidinones **107** with remarkable diastereoselectivity. The reaction failed with bulky amines such as *t*-butylamine (Scheme 59) [130].



Scheme 59. 3-Alkoxy-3-alkoxycarbonyl-2-azetidinones by tandem Wolff rearrangement–Staudinger synthesis.

A broad range of ◎-diazo-◎-ketosulfones **108** have been utilized in thermally promoted tandem Wolff rearrangement – Staudinger cycloaddition to afford polysubstituted ◎-lactam sulfones **109**. There was no significant effect of the type of migrant group (R^2) on the outcome of the response. Electron-withdrawing groups in the aldehyde portion (R^3) of the imine led to a poorer yield. The diastereoselectivity of the reaction seems to be mainly influenced by the nature of the amine substituent (R^4). There was a preference for the *cis* diastereomer and diastereomerically pure *cis*

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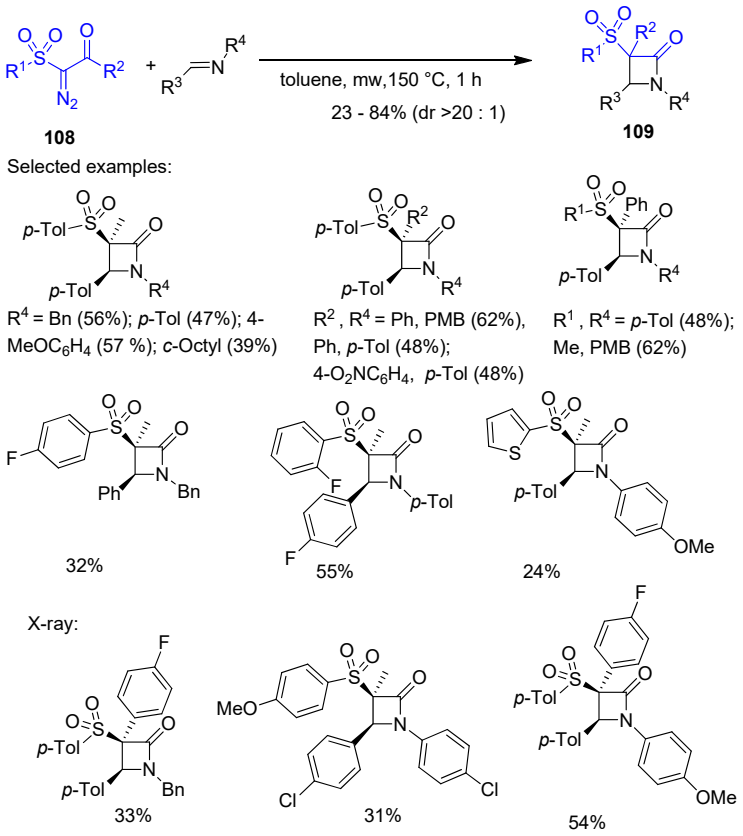
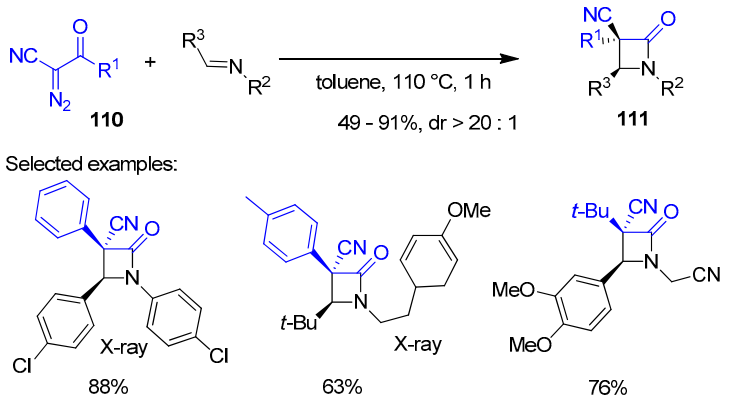
diastereomers were obtained in good yields after repeated chromatographies. The relative stereochemistry was confirmed by single crystal X-ray crystallography (Scheme 60) [131].



Scheme 60. 3-Sulfonylazetidin-2-ones by tandem Wolff rearrangement–Staudinger synthesis.

A thermally promoted tandem Wolff rearrangement – Staudinger cycloaddition has also been used to prepare 3-cyano-β-lactams **111** in good to excellent yields. The particularity of the process is the use for the first time of α-cyano-α-diazo ketones **110** for the generation of the corresponding ketenes. The process works well regardless of the substitution pattern in both reaction partners, and even imines with bulky tertiary alkyl substituents can lead to high product yields (Scheme 61) [132].



Scheme 61. 3-Cyano-2-azetidinones by tandem Wolff rearrangement–Staudinger cycloaddition.

In a similar thermal process, the imine was generated from the corresponding azide. Treatment of the azide **112** with triphenylphosphine leads to the formation of an iminophosphorane intermediate (Staudinger reaction), which subsequently reacts with the aldehyde (Aza wittig

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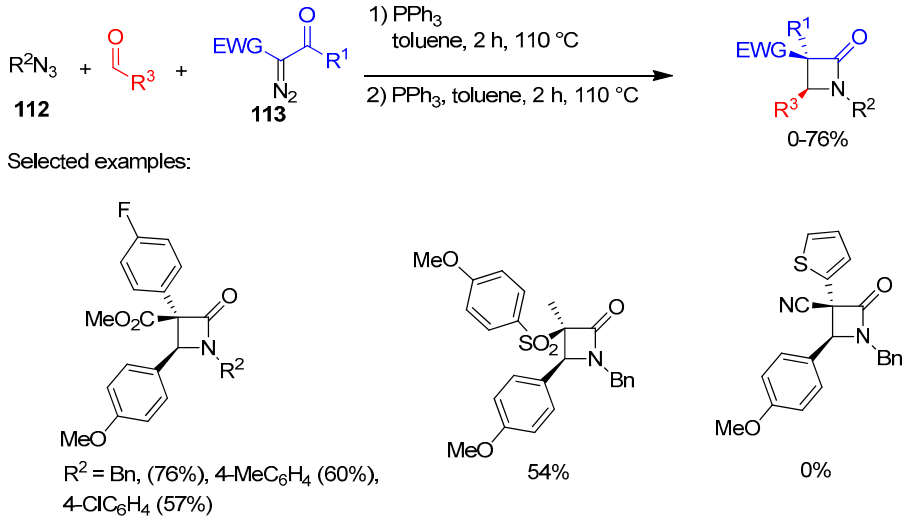
reaction) to give the imine. At the same time, ketene is generated from the diazo compound **113** (keto ester, keto nitrile, diketone, malonate) (Wolff rearrangement). A series of 24 novel structurally diverse β-lactams was prepared.

The *N*-benzyl β-lactams shown in Figure 10 were synthesized from Cbz-protected 1-amino-3-diazopropan-2-one and an imine in moderate yields. The reaction was carried out in 1,2-dimethoxyethane under microwave irradiation [38].

It was shown that this synthesis can be performed as a true multicomponent reaction (MCR) with simultaneous loading of all reactants, although with a somewhat lower yield compared with the two-step protocol (Scheme 62) [133].



Scheme 62. Diastereoselective three-component one-pot ◎-lactam synthesis from azides.

Another multicomponent Staudinger synthesis has been reported by Basso *et al.* The process involves mixing an aldehyde, an amine and a diazoketone in the dark and then switching on the light after the imine has formed. All of the ◎-lactams **114** were obtained exclusively as the *trans*-isomer and in moderate to good yields. The isolated yields of the three-component reaction products (shown in red) are slightly lower than those of the preformed imine reaction products. Aliphatic aldehydes gave no product (Scheme 63) [134].

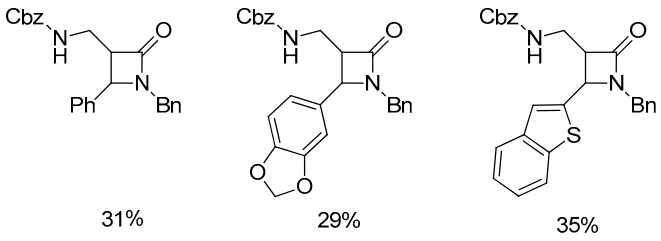


Figure 10. Preparation of Cbz protected 3-aminomethyl ◎-lactams.

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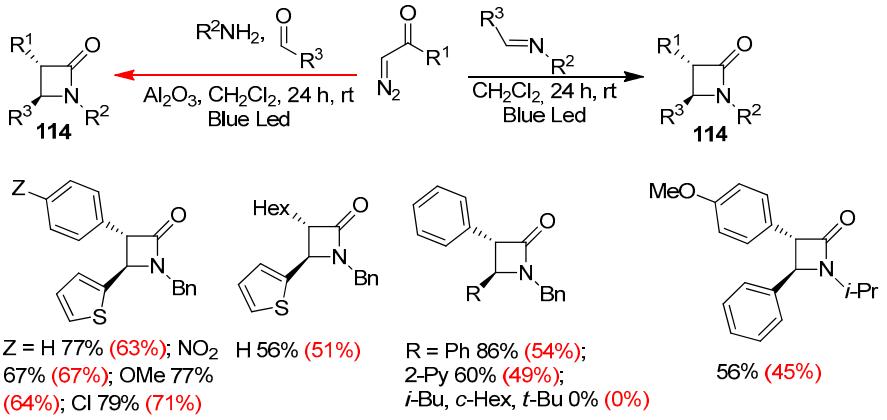
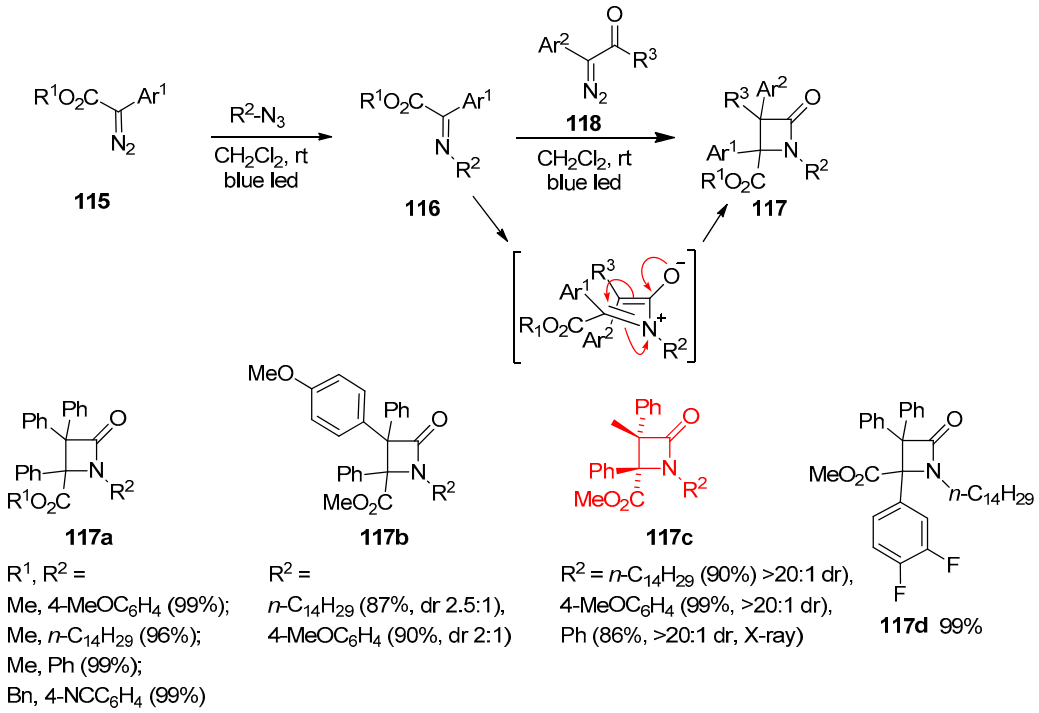


Scheme 63. Photoinduced Staudinger synthesis of ⍟-lactams.

In a report published by Munaretto and colleagues a two-step reaction was proposed in which aryl diazoacetates **115** were reacted with azides in the presence of blue light, resulting in the formation of imines **116**. The imines were then reacted with aryl diazoketones, even in the presence of blue light, yielding alkyl 4-carboxylate-β-lactams **117**. When two aryl substituents are present in the aryldiazoketone **118**, poor diastereoselectivities were observed (**117b**) while when a methyl and a phenyl group are present only one diastereomer of the β-lactam **117c** was observed (Scheme 64) [135]. A one-pot preparation of some β-lactams was also attempted, starting from the corresponding aryl diazoacetates and azides. The diazoketone partner was then added sequentially, but in a few cases competitive yields were obtained.



Scheme 64. Blue-light-mediated preparation of 4-alkoxycarbonyl-β-lactams **117**.

A three-component reaction of *N*-hydroxyanilines (stable, and readily available), enynones, and diazo compounds has been developed under rhodium catalysis, providing highly functionalized β-lactams **119** containing two quaternary carbon centers in good yields and with excellent diastereoselectivities (Scheme 65). This protocol involves a sequential reaction of Rh(II)-catalyzed

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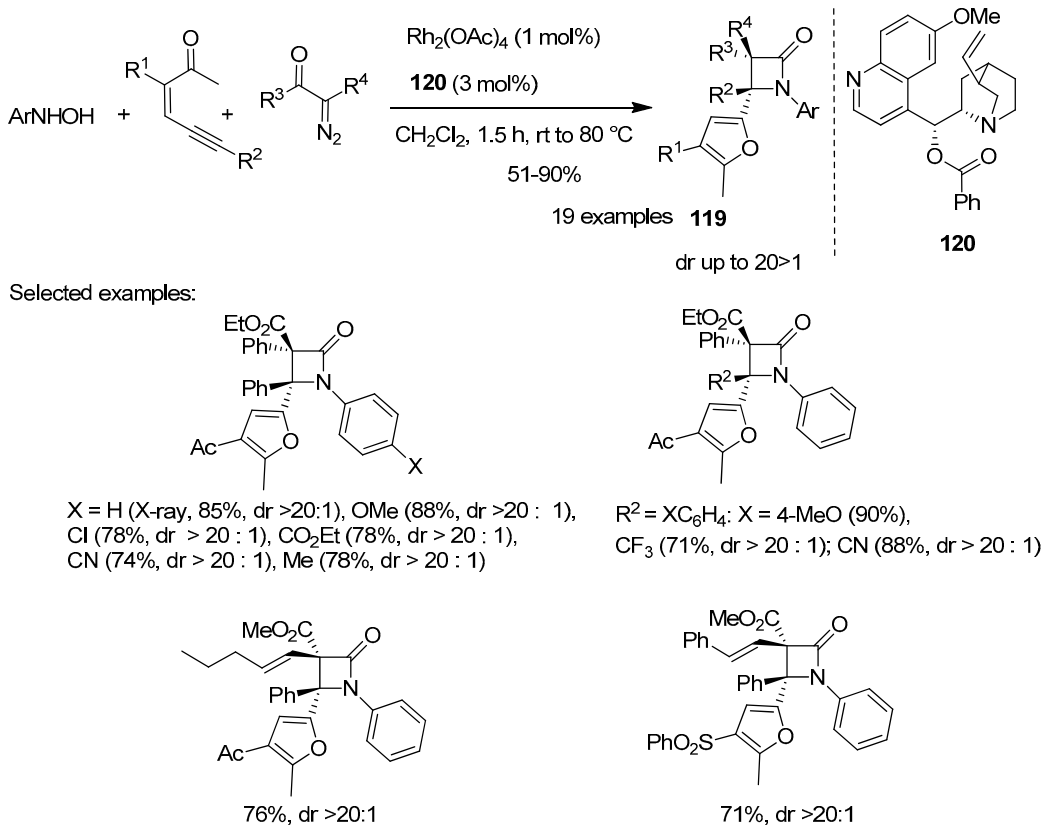
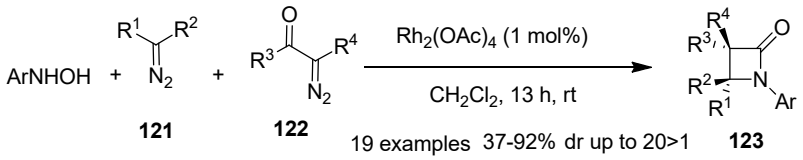
imine formation, Wolff rearrangement, and benzoylquinine **120** catalyzed Staudinger cycloaddition [136].



Scheme 65. Three-component reaction of *N*-hydroxyanilines, enynones, and diazo compounds.

A similar rhodium(II) catalyzed three-component reaction was explored for the synthesis of ◎-lactams **123** using, *N*-hydroxyanilines, and diazo compounds **121** and **122**, (Scheme 66) [137].



R^1, R^2= CO_2Me, Ph, CF_3, $P(O)(OMe)_2$, 3-thienyl, 4-Cl-3-pyridyl, $4\text{-}MeOC_6H_4$, $3\text{-}MeOC_6H_4$, $4\text{-}(F_3C)C_6H_4$

R^3, R^4 = CO_2Me, Ph, COPh, 3-thienyl, 1-pentenyl, styryl

Ar = Ph, $4\text{-}MeOC_6H_4$,$4\text{-}ClC_6H_4$, $4\text{-}NCC_6H_4$, $4\text{-}(EtO_2C)C_6H_4$, $2\text{-}MeC_6H_4$, $3\text{-}MeC_6H_4$, $2,4\text{-}di\text{-}Me_2C_6H_3$

Scheme 66. Rhodium catalysed three-component reaction to 2-azetidinones.

A new method for the synthesis of functionalized ◎-lactams has been developed based on a $Rh_2(esp)_2$-catalyzed redox/cycloaddition cascade reaction. The reaction was performed under very mild conditions, using only 0.5 mol% of the catalyst, and employing stable and readily available *N*-methyl nitrones as the precursors of *N*-methyl imines. The process is initiated by the reduction of the *N*-methylnitrone to the corresponding *N*-methylimine in the presence of a first molecule of the diazoacetoacetate enone which was plausibly oxidized to the corresponding tricarbonyl compound. A second molecule of the diazoacetoacetate enone then undergoes a Wolff rearrangement to form a vinyl ketene. This vinyl ketene then reacts with the *in situ* generated *N*-methyl imine to selectively produce a ◎ lactam with two contiguous stereogenic centers (Scheme 67) [138]. Complete

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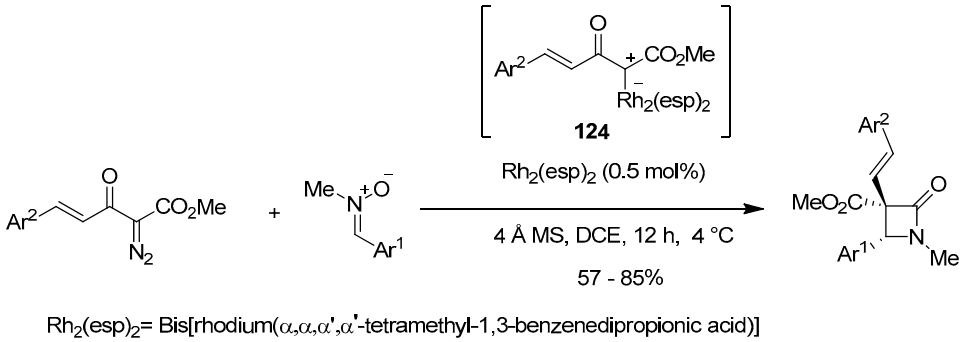
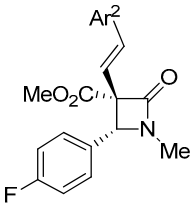
diastereoselectivity was observed in all the transformations. The rhodium catalyst, through the formation of the initial carbene **124**, has two fundamental roles: i) to promote the formation of the imine from the nitrone and ii) to promote the rearrangement of the diazoacetoacetate enone to the vinyl ketene.



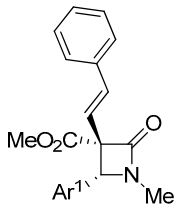
$Rh_2(esp)_2$= Bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]

diazoacetoacetate enones:



Ar^2 = 2-MeC_6H_4 (82%), 3,5-$Me_2C_6H_3$ (64%), 4-*i*-PrC_6H_4 (74%), 4-FC_6H_4 (73%), 2-ClC_6H_4 (80%), 3-ClC_6H_4 (74%), 4-ClC_6H_4 (60%), 3-BrC_6H_4 (63%), 4-BrC_6H_4 (83%), 4-IC_6H_4 (72%), 2-F-4-ClC_6H_3 (63%), 3-F-4-ClC_6H_3 (71%), 2-F-4-BrC_6H_3 (75%), 2,6-$Cl_2C_6H_3$ (32%), 2-$MeOC_6H_4$ (62%), 4-$MeOC_6H_4$ (56%), 3-$F_3CC_6H_4$ (63%)

N-methyl *C*-aryl nitrones:



Ar^1 = Ph (X-ray, 64%), 2-MeC_6H_4 (75%), 3,4-$Me_2C_6H_3$ (73%), 4-*i*-PrC_6H_4 (80%), 2-FC_6H_4 (80%), 3-FC_6H_4 (57%), 4-FC_6H_4 (82%), 2-ClC_6H_4 (80%), 4-BrC_6H_4 (82%), 2-F-4-ClC_6H_3 (85%), 3-F-4-ClC_6H_3 (79%), 3,4-di-ClC_6H_3 (79%), 2-F-4-BrC_6H_3 (78%), 2-Cl-5-BrC_6H_3 (74%), 3-$MeOC_6H_4$ (70%), 2-$MeOC_6H_4$ (75%), 3-$F_3CC_6H_4$ (73%),4-NCC_6H_4 (70%), 2-furyl (72%), 2-thienyl (79%),

Scheme 67. Rhodium catalysed ◎–lactams from *N*-methyl *C*-aryl nitrones.

Sivasankar *et al.* have proposed a convenient method to synthesize β-lactams. This method involves the carbonylation of diazo compounds using [$Co_2(CO)_8$] as a solid carbonyl source to produce corresponding ketenes, which are then subjected to cycloaddition with imines. This newly developed method proved successful in producing β-lactams from electronically and structurally diverse substrates under mild reaction conditions. FT-IR spectroscopy confirmed the ketene formation and the transformation of ketene into ◎-lactam (Scheme 68) [139].

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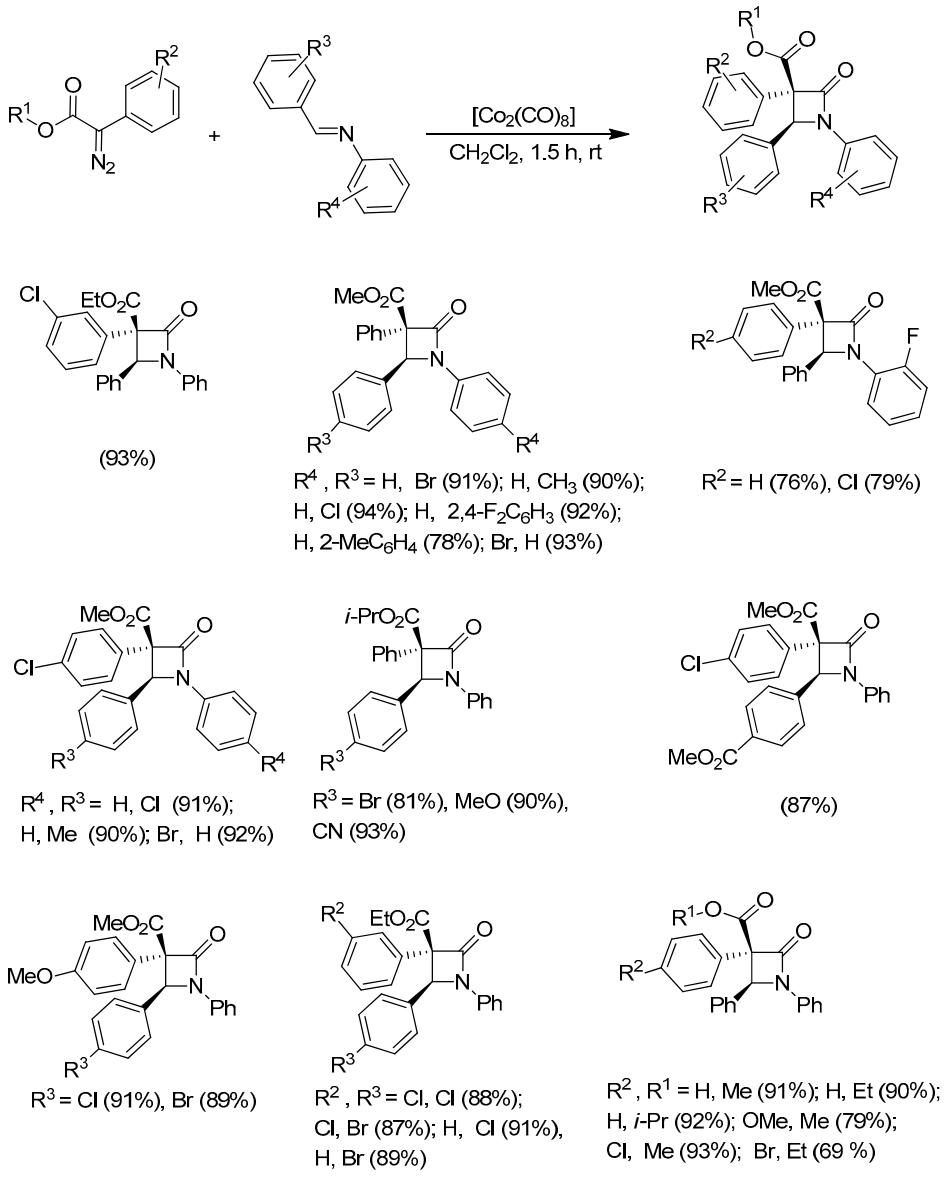
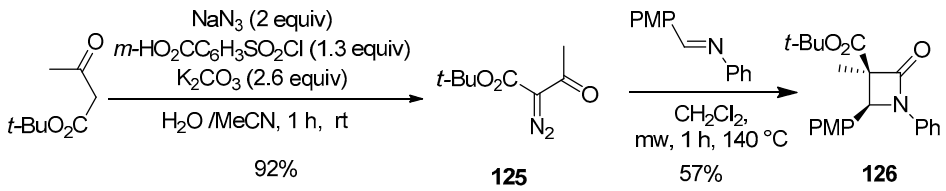


Scheme 68. [Co2(CO)8] preparation of ⌾ lactams from diazo compounds.

Diazo transfer reactions are well-known to involve the use of sulfonyl azides, which are potentially explosive. Interestingly, a sulfonyl azide-free protocol for diazo transfer in aqueous medium was applied to the preparation of diazaketone **125** from *in situ* generated *m*-carboxybenzenesulfonyl azide. Diazoketone **125** was then used as a substrate for a Staudinger synthesis to give ⌾-lactam **126**, the structure of which was confirmed by X-ray analysis (Scheme 69) [140].



Scheme 69. Synthesis of ⌾-lactam **126**.

Spirocyclic *N*-vinyl β-lactams **129** have been prepared by a two-step Rh(II)-catalyzed domino synthesis from 5-alkoxyisoxazoles **127** and acyclic α-diazomalonates. The process proceeds by the

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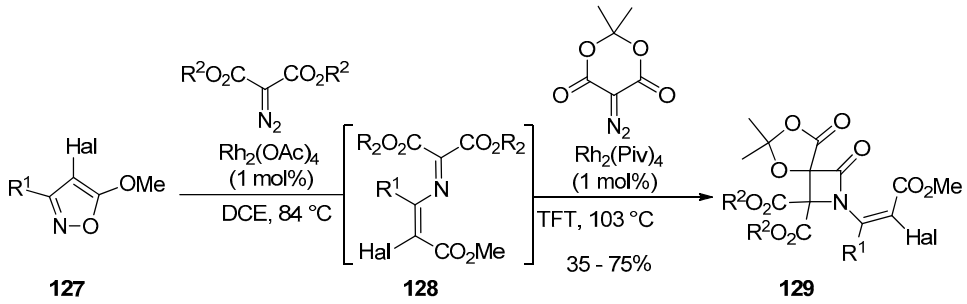
formation of 2-azabuta-1,3-dienes **128** in DCE (dichloroethane) followed by the addition of diazo-Meldrum's acid as ketene precursors for the subsequent Staudinger ketene-imine cycloaddition in TFT (trifluorotoluene) (Scheme 70). The reaction was also developed using azirines instead of isoxazoles combined with diazoketoesters [141].

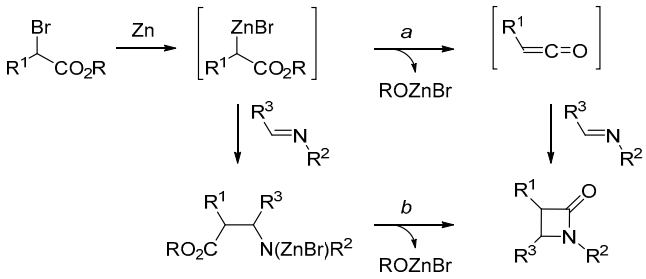


R^2, R^1, Hal = Me, Ph, Br (75%); Me, Ph, Cl (69%); Me, 4-MeC_6H_4, Br (40%); Me, 4-*t*-BuC_6H_4, Br (58%); Me, 4-$O_2NC_6H_4$, Br (35%); Et, Ph, Br (52%)

Scheme 70. Synthesis *N*-vinyl β-lactams from 5-alkoxyisoxazoles.

2.5. Ketene Generated In Situ from a-Haloesters (Reformatsky-Type Reaction)

The reaction between imines and Reformatsky reagents, obtained from a-haloesters and Zn, can be described as a variant of the ketene-imine Staudinger cycloaddition, where the fragmentation of the Reformatsky reagent allowed ketene generation (path *a*). Alternatively, a two-step process involving addition of the Reformatsky reagent to the imine and cyclization of the intermediate b-amido ester can be proposed (path *b*) (Scheme 71). Several studies supporting these different hypotheses have been reported [142]



Scheme 71. Mechanistic hypotheses for the Reformatsky-type b-lactam synthesis.

1,4-Diaryl-3-unsubstituted β-lactams **130a** (Figure 11), analogous to CA-4 (see Figure 9), were synthesized via the microwave assisted Reformatsky reaction in 22-37% yields, using *C*-aryl-*N*-aryl imines, ethyl bromoacetate, Zn dust, and trimethylchlorosilane in benzene at 100 °C [30].

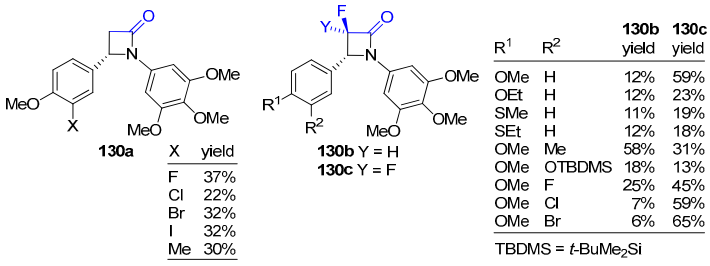


Figure 11. 1,4-Diaryl-2-azetidinones **130a-c**, analogues of combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

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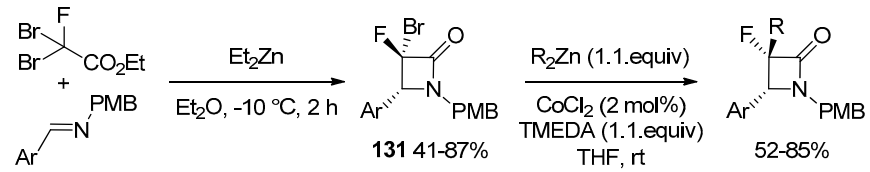
Applying the same protocol to ethyl bromofluoroacetate or ethyl bromodifluoroacetate, 3-fluoro- and 3,3-difluoro-azetidine-2-ones **130b** and **130c** (Figure 11), were synthesized in 6-65% yields with exclusive *trans* stereochemistry for the monofluoro derivatives, based on spectral and X-ray crystal analyses. The fluorinated compounds, as well as the 3-unsubstituted derivatives, were evaluated for in vitro antiproliferative activity in MCF-7 human breast cancer cells [143].

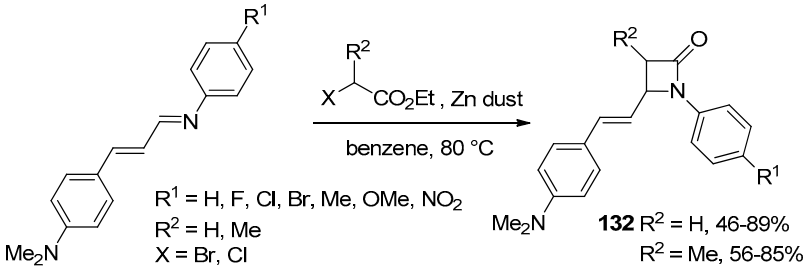
A Reformatsky-type reaction, involving the treatment of *N*-(4-methoxybenzyl)arylimines and ethyl dibromofluoroacetate with Et_2Zn in diethyl ether at -10 °C, allowed the synthesis of 3-bromo-3-fluoro ◎-lactams **131** in 41-87% yields (Scheme 72). The *cis* relative configuration (related to the position of fluorine and hydrogen atoms) was proposed on the base of the $^3J_{H,F}$ coupling constant (≈ 10.3 Hz) and confirmed via X-ray diffraction analysis on a selected derivative (R = 3,4,5-trifluorophenyl). The same authors reported the synthesis of *trans*-4-aryl-3-bromo-1-isopropyl ◎-lactams **59c** (see scheme 44) from ◎-bromo acetyl bromide and aryl imines. These 3-bromo derivatives were subjected to cobalt-catalyzed cross-coupling reactions with diarylzinc or diallylzinc reagents to perform the C-3 functionalization of ◎-lactams [97].



Scheme 72. Synthesis of of 3-bromo-3-fluoro ◎-lactams **131**.

The application of the imino-difluoro-Reformatsky reaction, involving α-halo-α,α-difluoro esters, imines, and Zn or Et_2Zn, to the asymmetric synthesis of α,α-difluoro-β-lactams has been reviewed [144].

Imines prepared from *p*-dimethylaminocinnamaldehyde and variously substituted anilines were reacted with ethyl bromoacetates or chloroacetates in the presence of Zn dust in dry benzene under reflux to give 3-unsubstituted and 3-methyl substituted azetidin-2-ones **132** (Scheme 73). The use of different Lewis acids was studied, but Zn catalysts gave the best results in terms of reaction rate and yields. These compounds were tested for antibacterial activity in vitro against different pathogenic bacteria and fungi [145].



Scheme 73. Synthesis of of 4-styryl-◎-lactams **132**.

The applicability of imines as nonclassical Reformatsky electrophiles was also briefly explored under ball-milling conditions that require no solvent, no inert gas, and no pre-activation of the zinc source. A mechanochemical Reformatsky reaction was performed with *N*-benzylidene aniline and ethyl bromoacetate in the presence of Zn flake. The not optimized reaction afforded 1,4-diphenylazetidin-2-one but in only 7% yields, along with the acyclic ◎-amino ester (48%) [146].

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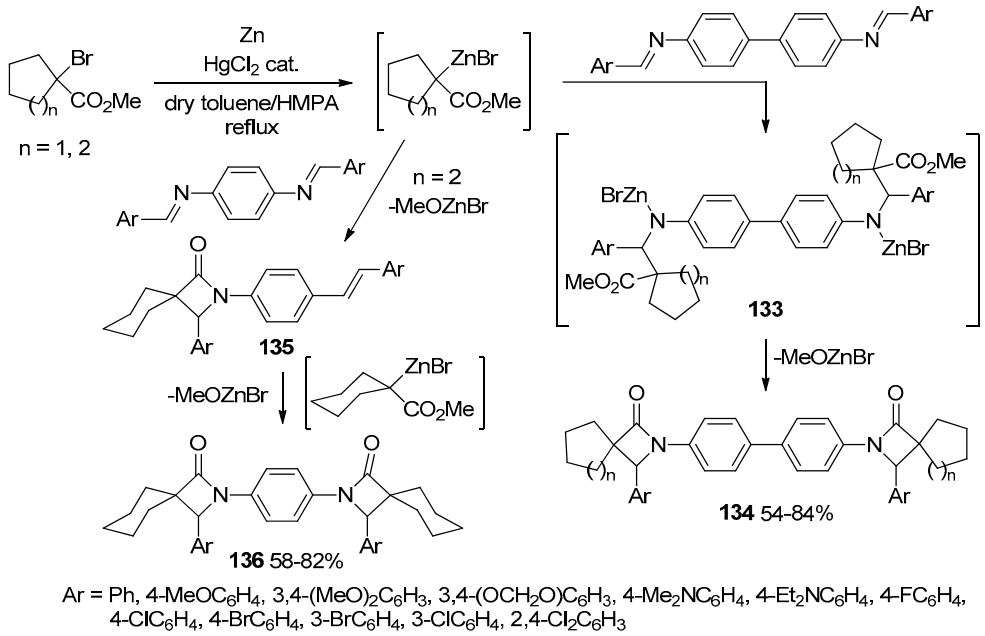
The Reformatsky reagents, prepared from methyl 1-bromocycloalkanecarboxylates and Zn, were reacted with *N*,*N*′-bis(arylmethylidene)benzidines in dry toluene with 10% HMPA and catalytic amounts of $HgCl_2$ under reflux. Bis(spiroazetidinones) **134** were then prepared in 54-84% yields, likely via nucleophilic addition to the imine C=N double bond and spontaneous cyclization of intermediates **133** with elimination of MeOZnBr (Scheme 74). The authors based this mechanistic hypothesis on previous results concerning the isolation of amino esters formed by hydrolysis of intermediates of type **133**. The spectral analyses (^{1}H NMR) evidenced the presence of only one diastereomer in solution [147].

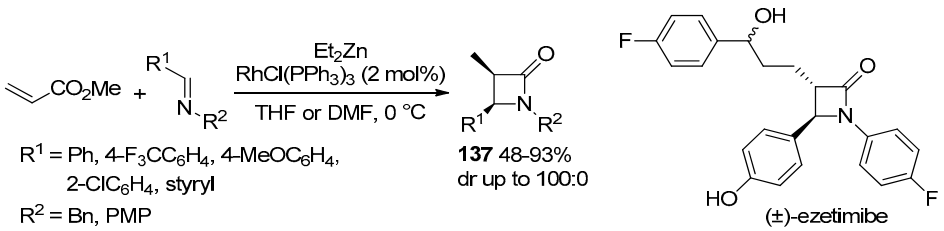


Scheme 74. Synthesis of of ◎-lactams **134**-**136**, using the Reformatsky reagent.

Analogously, the Reformatsky reagent prepared from methyl 1-bromocyclohexanecarboxylate reacted with *N*,*N*′-(1,4-phenylene)bis(1-arylmethanimines) to produce bis(spiro)-◎-lactams **136** in 58-82% yields (Scheme 74). The use of equimolar amounts of the Schiff base and Reformatsky reagent was also applied to isolate some mono(spiroazetidinones) **135** (Ar = 4-fluorophenyl 52% and 2,4-dichlorophenil 63%) [148].

2.6. Ketene Generated In Situ from Ester (or Amido) Enolates

A minireview by Sato and coworkers deals with the Rh-catalyzed reductive Mannich reaction, in which metal enolates obtained by 1,4-reduction of ◎,◎-unsaturated esters reacted with imines to give◎◎-lactams **137**, along with minor amounts of ◎-amino esters. Operating with methyl acrylate and Et_2Zn and $RhCl(PPh_3)_3$ as catalyst in THF at 0 °C a total *cis*-diastereoselectivity was observed (Scheme 75). However, steric factors associated with the use of different ◎,◎-unsaturated esters can determine the formation of *trans* ◎-lactams. For instance, the process was applied to the synthesis of (±)-ezetimibe, a cholesterol absorption inhibitor [149].



Scheme 75. Synthesis of ◎-lactams **137**.

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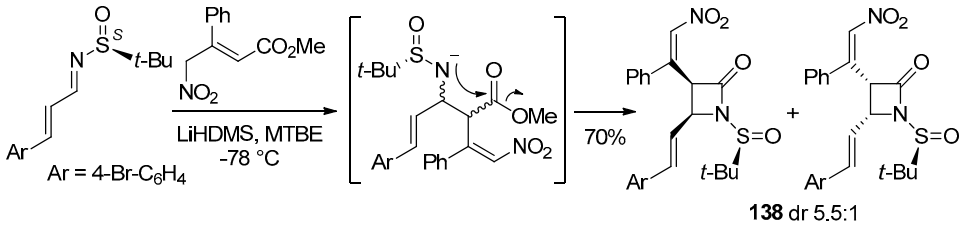
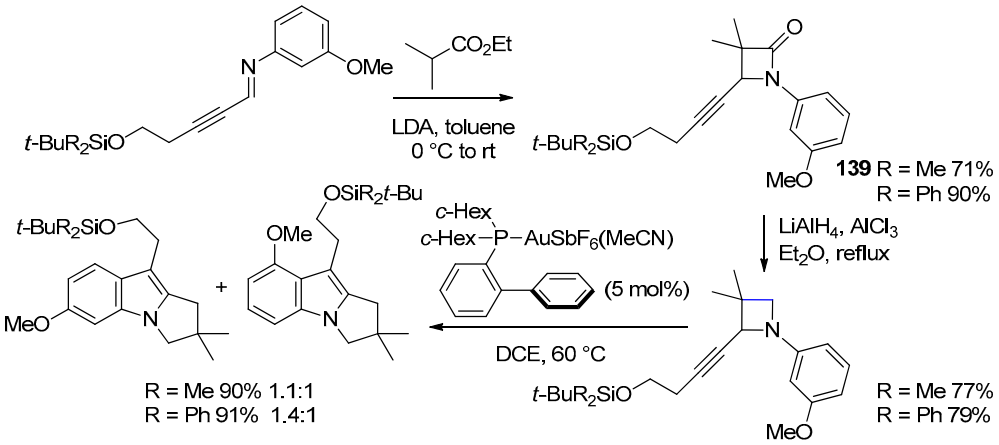
The reaction of (*E*)-methyl 4-nitro-3-phenylbut-2-enoate with optically pure (*E*,*E*)-cinnamaldehyde *tert*-butanesulfinyl imine, in the presence of lithium hexamethyldisilyl amide (LiHMDS) in methyl *tert*-butyl ether (MTBE) as solvent, gave rise to the mixture of enantiopure *cis* ◎-lactams **138** likely by cyclization of the intermediate Mannich adduct (Scheme 76). The presence of the strong electron-withdrawing nitro group can suppress the amino-Cope pathway favoring β-lactam formation. Nevertheless, a ketene intermediate cannot be ruled out [150].



Scheme 76. Synthesis of enantiopure *cis* ◎-lactams **138.**

N-Aryl-4-alkynylazetidin-2-ones **139** were prepared upon addition of alkynylimines to a lithium enolate solution derived from ethyl isobutyrate. Subsequent reduction afforded the corresponding azetidines, which were subjected to gold-catalyzed rearrangement to regioisomeric pyrrolo[1,2-*a*]indoles (Scheme 77) [151].



Scheme 77. Synthesis of *N*-aryl-4-alkynylazetidin-2-ones **139**.

The synthesis of ◎-lactams was performed from arylacetic esters, by treatment with isothiourea catalysts in basic medium, likely via C(1)-ammonium enolates as key intermediates. The reaction of pentafluorophenyl (Pfp) arylacetic acid esters with alkynylimines, in the presence of benzotetramisole (BTM) as chiral isothiourea organocatalyst, allowed to access optically pure 4-alkynylazetidine-2-ones **140** in high yields and high enantio- and diastereoselecivities (Scheme 78). The absolute configuration of some derivatives was determined by single-crystal X-ray diffraction analysis [152].

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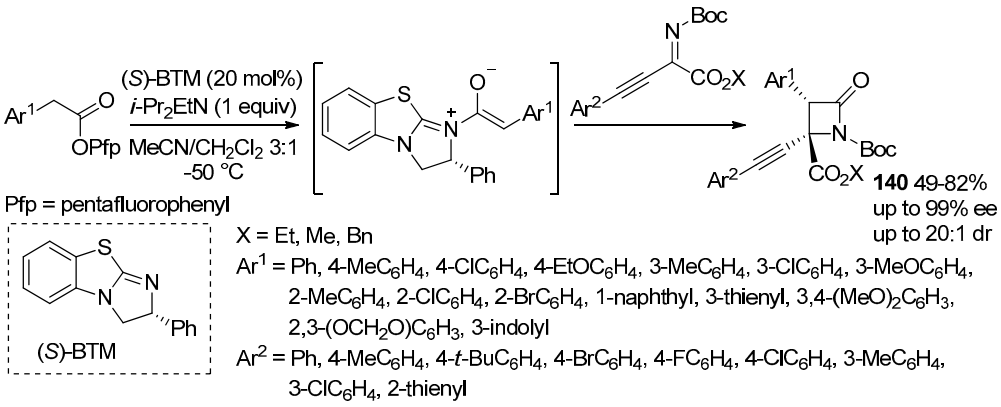
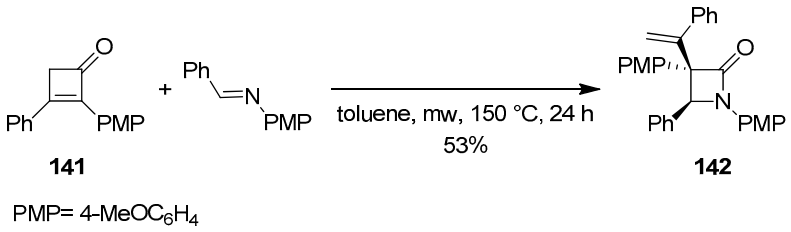


Scheme 78. Synthesis of optically pure 4-alkynylazetidine-2-ones **140**.

2.7. Ketene Generated In Situ from Cyclobutenones

2,3-Disubstituted-cyclobut-2-en-1-one **141** has been used as useful synthon for the stereoselective transannulation to ⌾-lactam **142.** Thermal ring opening and subsequent capture of the resulting ketene was achieved in the presence of *N*-(4-methoxyphenyl)-1-phenylmethanimine (Scheme 79) [153]**.**



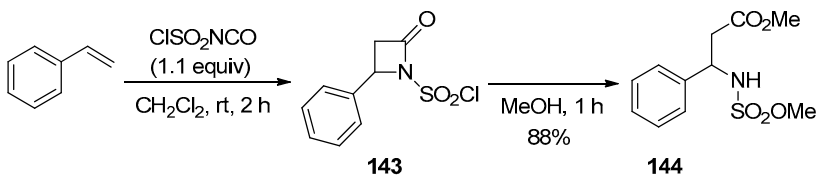
Scheme 79. Transannulation reaction of cyclobutenone **141**.

3. Alkene-Isocyanate Cycloaddition

The reaction between electron-deficient isocyanates, such as chlorosulfonyl isocyanate, and alkenes, particularly those with electron-rich properties, is a robust and relatively mild approach for the synthesis of β-lactams.

From a mechanistic point of view, this reaction can be described as a formal [2+2] cycloaddition allowed under thermal conditions with a supra-antara approach, analogous to the ketene-imine (Staudinger) cycloaddition. However, due to the sterically demanding factors involved in this process, unconcerted or pseudoconcerted mechanisms have also been proposed and some theoretical studies have even supported concerted suprafacial approaches [154]. Overall, the mechanism of this reaction (as well as the Staudinger cycloaddition) is still under investigation and discussion.

One-pot, two step reaction of styrene with chlorosulfonyl isocyanate at room temperature, yielded the β-lactam intermediate **143** which was directly hydrolyzed by dilution with methanol to the β-amino acid **144**. The latter contains a sulfamate group, which is the closest congener and bioisostere to the primary sulfonamide group (Scheme 80). Other examples involving endocyclic alkenes have been reported [155].



Scheme 80. Use of a ⌾-lactam intermediate for the preparation of a sulfamate β-amino acid.

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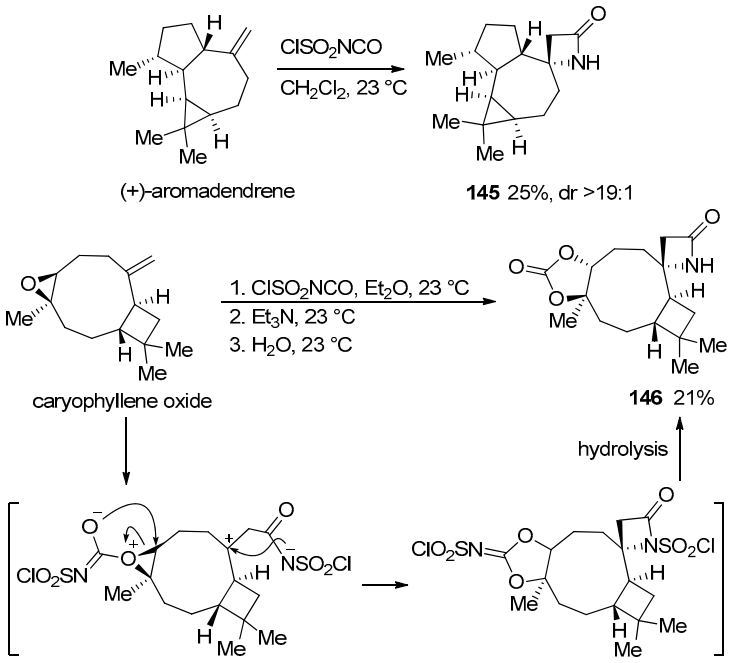
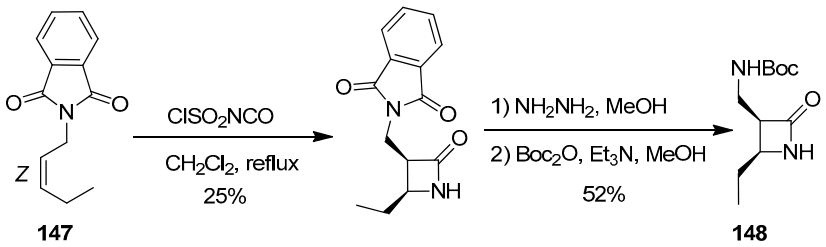
Chlorosulfonyl isocyanate has been used for ⌾-lactam annulations onto natural compounds bearing exocyclic double bonds. The reaction of aromadendrene, a sesquiterpene possessing a fused dimethylcyclopropane ring on a hydroazulene skeleton, with chlorosufonyl isocyanate resulted in the formation of spiro-⌾-lactam **145** in 25% yield with high diastereoselectivity. This cycloaddition proceeds with high selectivity likely controlled by the allylic stereocenter and overall topology of the tricyclic natural product, including a fused *gem*-dimethyl cyclopropane (Scheme 81). Similarly, the reaction of chlorosulfonyl isocyanate with caryophyllene oxide produced the spiro ⌾-lactam **146** by [2+2] cycloaddition on the exocyclic double bond. Notably, besides this reaction, *O*-acylation occurs, which leads to the opening of the epoxide ring, followed by its expansion to a cyclic carbonate, and hydrolysis (Scheme 81) [156].



Scheme 81. Annulation of a spiro-⌾-lactam onto large methylene cycloalkanes**.**

The racemic *cis* ⌾-lactam **148** was prepared from the alkene **147** by cycloaddition with chlorosulfonyl isocyanate followed by hydrolysis of the phthalimido protecting group and amine protection as carbamate (Scheme 82). The cycloaddition is stereospecific and the reaction with the corresponding *E* alkene gives rise to the *trans* ⌾-lactam isomer. Lactam **148** and its *trans* isomer have been used to prepare amphiphilic nylon-3 polymers. The interest in these polymers is related to their reported ability to mimic the biological activities of natural antimicrobial peptides, with strong activity against bacteria and low toxicity to eukaryotic cells [157].



Scheme 82. Synthesis of the β-lactam **148** subunit in nylon-3 polymers.

[1.1.1]Propellane, a highly strained small molecule, has been involved in processes for the preparation of spiro ⌾ lactams due to the exceptional reactivity of the central bond between the two

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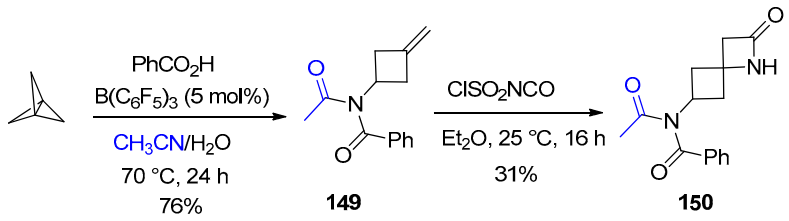
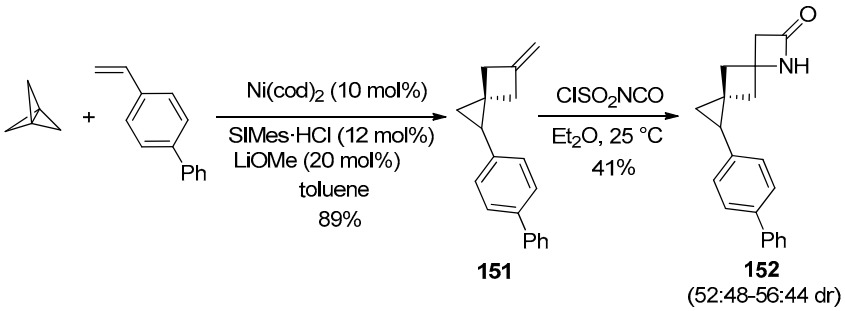
bridgehead carbons. Indeed, this property has allowed the preparation of interesting methylene-cyclobutane derivatives that reacted effectively with chlorosulfonyl isocyanate.

The synthesis of imidised methylenecyclobutane **149** was carried out in aqueous acetonitrile *via* a strain-release-driven addition reaction of [1,1,1]propellane with benzoic acid (Scheme 83). Subsequently, the reactivity of methylene cyclobutane **149** has been investigated by cycloaddition with chlorosulfonyl isocyanate to afford β-lactam **150** in 31% yield [158].



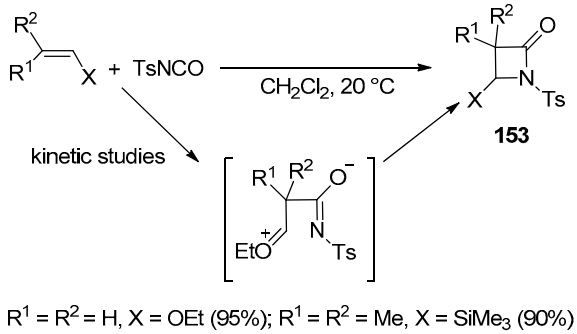
Scheme 83. Preparation of a spiro ◉-lactam.

A [2 + 2] cycloaddition with chlorosulfonyl isocyanate of methylenespiro[2.3]hexane **151** gave spiro β-lactam **152** in modest yield. Alkene **151** was prepared *via* a nickel-catalyzed cyclopropanation of 4-vinylbiphenyl with [1.1.1]propellane. The latter process involves cationic addition, which cleaves the cage system leading to an exo-methylenecyclobutane (Scheme 84) [159].



Scheme 84. Preparation of a spirocyclobutane ◉-lactam.

The kinetic of the reaction of tosyl isocyanate with ethyl vinyl ether and trimethyl-(2-methyl-propenyl)-silane was studied by ^{1}H NMR spectroscopy. Azetidinones **153** with the donor substituent in the 4-position were formed in good yields in CH_2Cl_2. However, the kinetic data showed that the reactions proceeded 5 times faster in CD_3CN than in CD_2Cl_2. These results indicated a moderate increase in polarity from the reactants to the transition state, likely supporting the formation of zwitterionic intermediates (Scheme 85) [160].



Scheme 85. Stepwise [2+2] cycloaddition of tosyl isocyanate with enol ethers.

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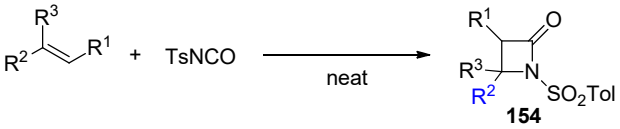
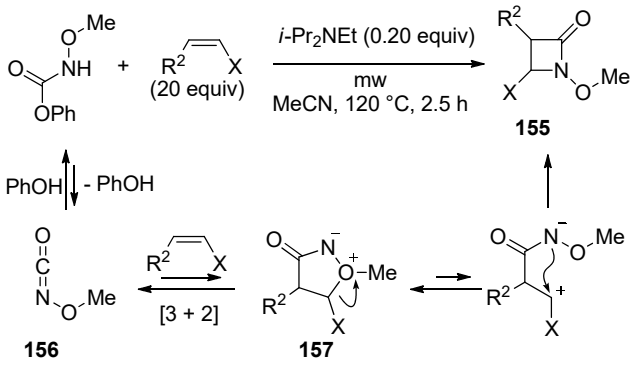
Reactions of *p*-toluenesulfonyl isocyanate (less reactive than chlorosulfonyl isocyanate) with electron-rich alkenes were investigated to prepare various ◎-lactams including interesting monofluoro-tosyl-β-lactams **154** (R^2 = F). The process was conducted under mild neat conditions which prevent the opening of the tosyl β-lactam products **154** (Scheme 86) [161].



R^1 = H, R^2–R^3 = *c*-Hex (98%, rt, 168 h)
R^1 = R^2 = H, R^3 = 4-MeC_6H_4 (59%, 50 °C, 10 days)
R^1 = R^2 = R^3 = Me (58%, 50 °C, 168 h)
R^1 = H, R^2 = F, R^3 = 4-MeC_6H_4 (68%, 50 °C, 114 h)
R^1 = H, R^2 = F, R^3 = 4-ClC_6H_4 (26%, 50 °C, 13 days)
R^1 = H, R^2 = F, R^3 = Ph (40%, 50 °C, 14 days)

Scheme 86. Preparation of *N*-tosyl-β-lactams.

Formation of ◎-lactams by cycloadditions of oxymethane isocyanates (*O*-isocyanates) **156** with allylsilane**s** and enol ethers has been the subject of both experimental and DFT (density functional theory) investigations. The results of these studies provide valuable insights into the mechanism involved in this transformation. Specifically, *O*-isocyanate **156** was generated from *O*-phenyl carbamate, by thermal loss of phenol, and involved in a [3+2] cycloaddition with alkenes and subsequent formation of the ylides **157**. The latter, through a ring opening-ring closure sequence, gives the ◎-lactams **155** (Scheme 87) [162]**.**The factors that determine the substrate reactivity (regio- and stereoselectivity) of electron rich alkenes (glycals) in isocyanate cycloaddition have been deeply investigated [163].



R^2 = H, X = O*n*-Pr (50%), O*c*-Hex (46%), CH_2SiMe_3 (30%)

Scheme 87. Synthesis of β-lactams by intermolecular [3+2] cycloaddition of enol ethers and *O*-isocyanate.

Azetidinones **160,** as well as dihydropyrimidinedione and oxazinone derivatives, were obtained from the reaction of isopropyl isocyanate with heterocumulene ylides **158** (Scheme 88). The reaction proceeded via the formation of a dipolar intermediate **159**, which in the case of (*N*-phenyliminovinylidene)triphenylphosphorane (**158**, X=NPh) cyclises to **160** or adds another molecule of isopropyl isocyanate to give dihydropyrimidinedione **161** and oxazinone **162**.

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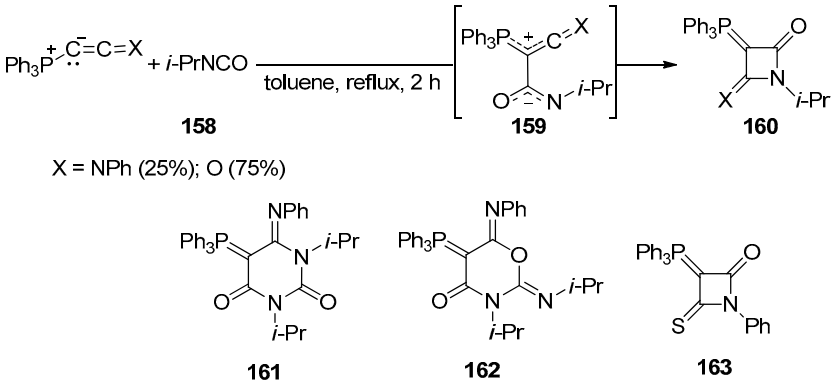


Scheme 88. Preparation of ◎-lactams from heterocumulene ylides.

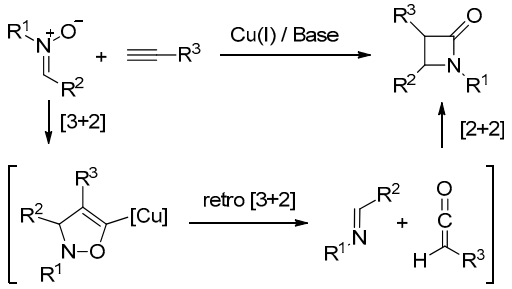
For (triphenylphosphoranylidene)ketene (**158**, X = O, Bestmann's ylide [164]), cyclisation was faster than addition and only ◎-lactam **160** was observed. The reaction was then extended to phenyl isothiocyanate which reacted with 2-oxovinylidene)triphenylphosphorane (**158**, X = O) to give the corresponding thioxoazetidinone **163** in 85% yield [165].

4. Azetidin-2-Ones from Nitrones

4.1. Nitrones and Alkynes (Kinugasa Reaction)

In 1972 Kinugasa and Hashimoto discovered that the reaction of copper acetylide with a nitrone affords β-lactams. Basically, the reaction is a cascade process that involves a 1,3-dipolar cycloaddition of a copper acetylide onto the nitrone, followed by a rearrangement step (Scheme 89) [166].

Since then, the "the acetylide reaction" (Kinugasa reaction) is used as a highly effective method for the synthesis of β-lactams. This is due to its high atom efficiency, use of easily accessible starting materials, and convergent approach. Additionally, the Kinugasa reaction has increased in utility through the implementation of asymmetric synthesis of β-lactams [167].



Scheme 89. Kinugasa reaction: mechanistic hypothesis.

The mechanism of the Kinugasa reaction has been re-evaluated using density functional theory (DFT) calculations and recent experimental results. According to the calculations, an isoxazoline intermediate is formed after a two-step cycloaddition initiated by two copper ions. This intermediate can undergo a rapid and irreversible cycloreversion to give an imine and a copper ketenyl intermediate. The reaction can then proceed by cyclization through an intramolecular nucleophilic attack of a copper amide on the ketene carbonyl. This is in contrast to the previous proposal of a [2 + 2)] Staudinger synthesis (in blue in Scheme 90). Importantly, the new mechanism is linked to the Staudinger pathway by a protonation event, which means that the relative energies of the two pathways depend on the strength of the base used in the experiments (or more precisely, on the strength of its conjugate acid) (Scheme 90) [168].

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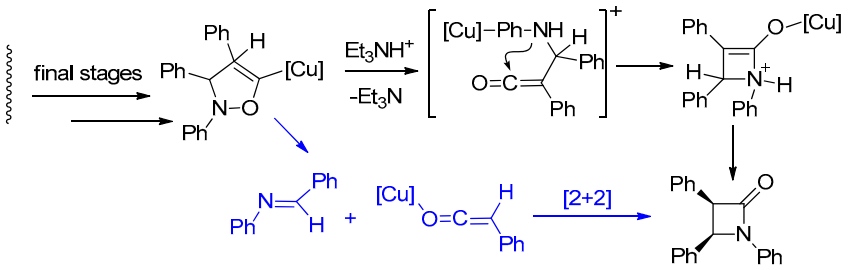
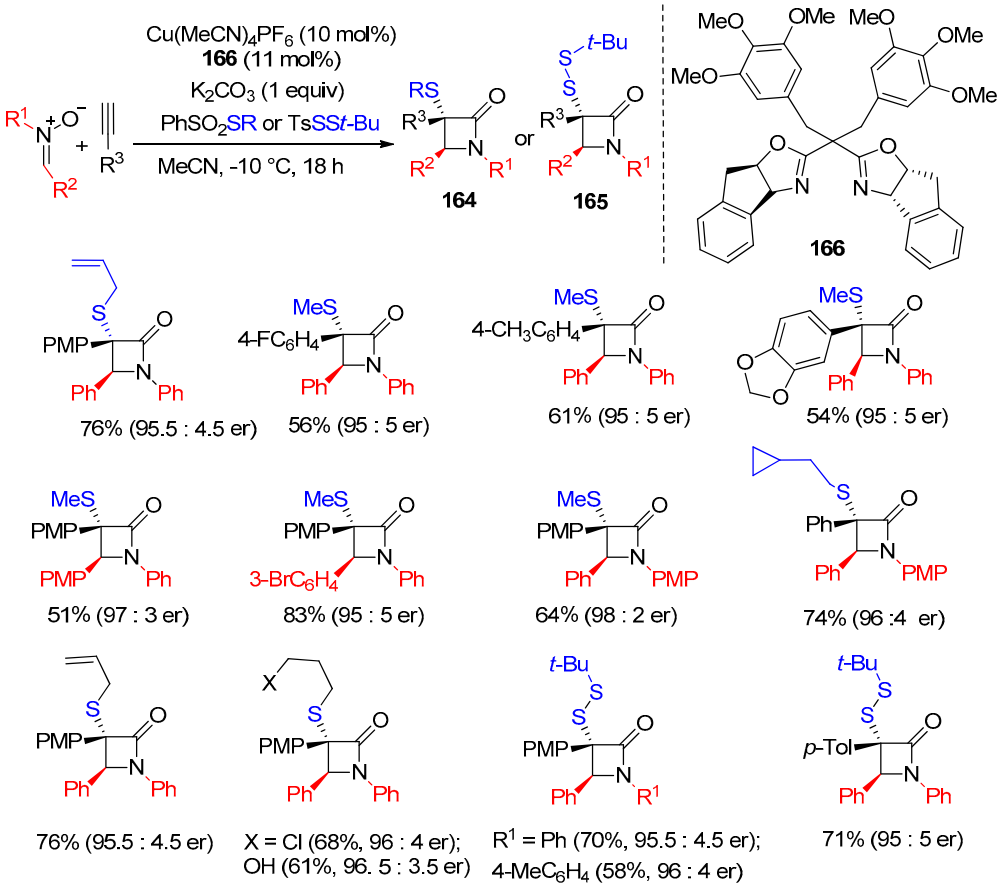


Scheme 90. Mechanism of the final stages of the Kinugasa reaction.

Various sulfur containing chiral ⌾-lactams **164** and **165** with two consecutive stereogenic centers have been synthesized by an asymmetric three-component interrupted Kinugasa reaction. In this process, $PhSO_2SR$ or TsSS*t*-Bu were used as a source of electrophilic sulfur, which competes with the proton for the copper(I) intermediate formed during the Kinugasa reaction. By using the box ligand **166** the chiral ⌾-lactams **164** and **165** were prepared with a wide substrate scope in modest to good yields, and excellent diastereo- and enantioselectivity (Scheme 91) [169].



Scheme 91. Preparation of chiral 3-alkylthio- and 3-*tert*-butyldisulfanyl-2-azetidinones **164** and **165**.

A similar process has been reported in which an interrupted Kinugasa reaction leads to the formation of a new C-C bond on the C-3 carbon of the 2-azetididinone. This reaction involves a synergistic system in which copper catalyzes the Kinugasa reaction while palladium catalyzes the allylic alkylation reaction in the presence of phosphine **168** (Scheme 92). As a result, 3,3′-disubstituted chiral ⌾-lactams **167** have been prepared in high yields and stereoselectivity. This method allows the synthesis of 2-azetidinones not available by other synthetic approaches [170].

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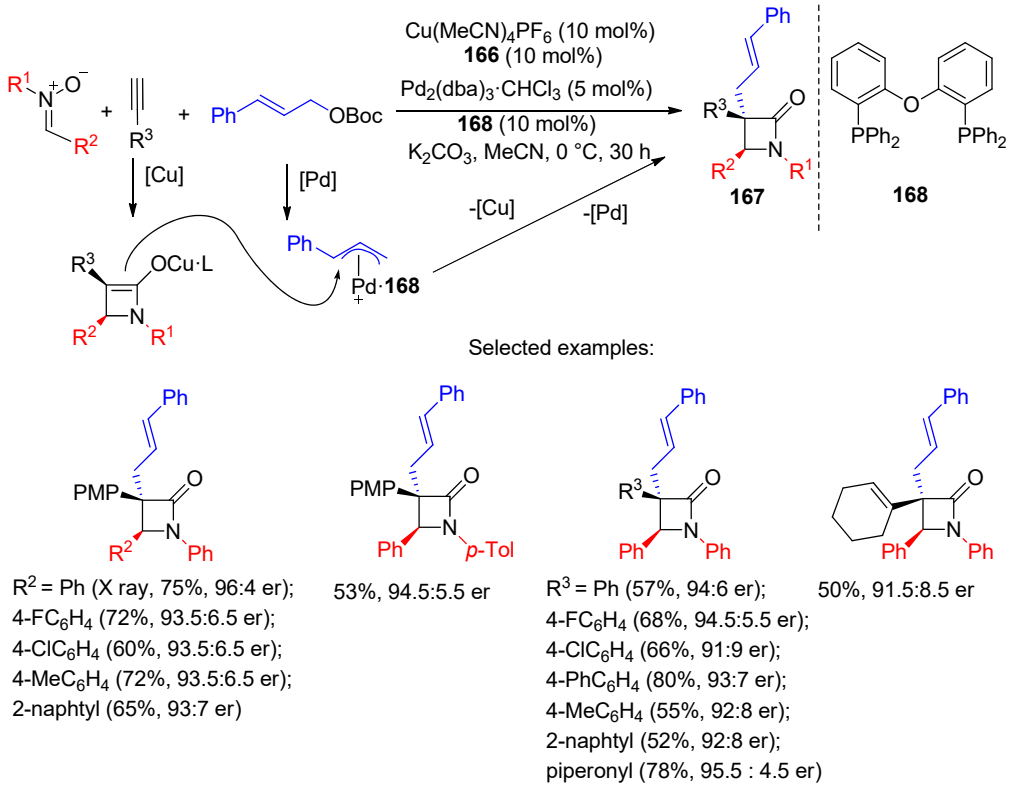

Scheme 92. Synthesis of ◎◎◎′-disubstituted chiral 2-azetidinones.

The scope of chiral ligands employed in Kinugasa reaction is limited and the highly enantioselective catalytic Kinugasa reaction is still a challenge. Recently, a novel class of chiral ligands such as **170** derived from TsDPEN [*N*-(*p*-tosyl)-1,2-diphenylethylene-1,2-diamine] has been developed and applied to the copper-catalyzed asymmetric Kinugasa reaction **(**Scheme 93**)**. This method provides an efficient way to synthesize -◎-lactams **169** in good to excellent yields (up to 93%) and with good to excellent diastereo- and enantioselectivities (dr up to 17.5 : 1, ee up to 91%). This Kinugasa reaction protocol is ineffective for aliphatic alkynes and phenylacetylenes with a strong electron-donating group. A proposed Cu complex working model, optimized by DFT calculations, has been suggested to explain the observed stereoselectivities. The model involves the [2 + 2]cycloaddition between ketene and imine as the stereocontrolling step [171].

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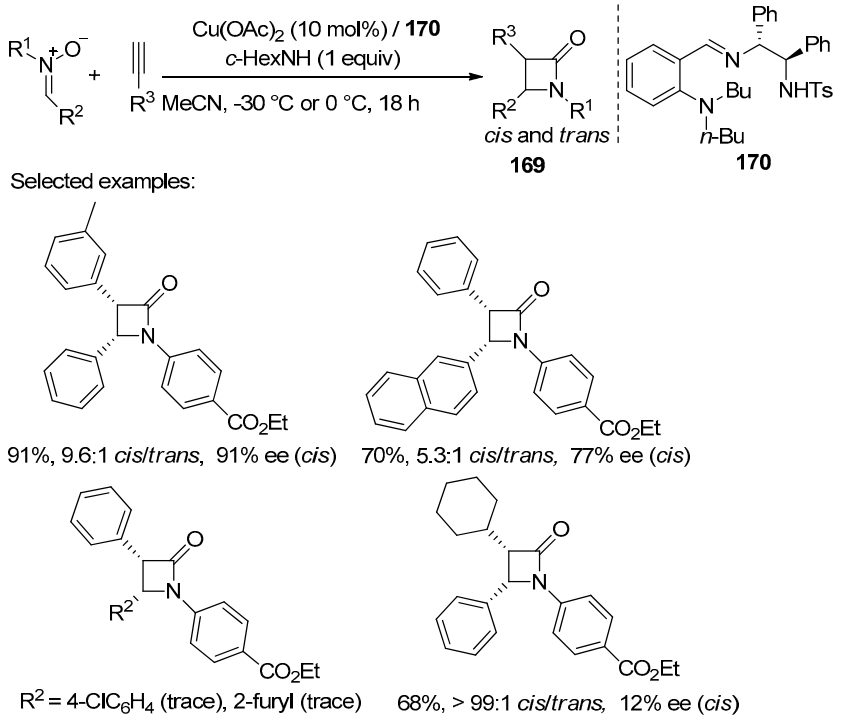
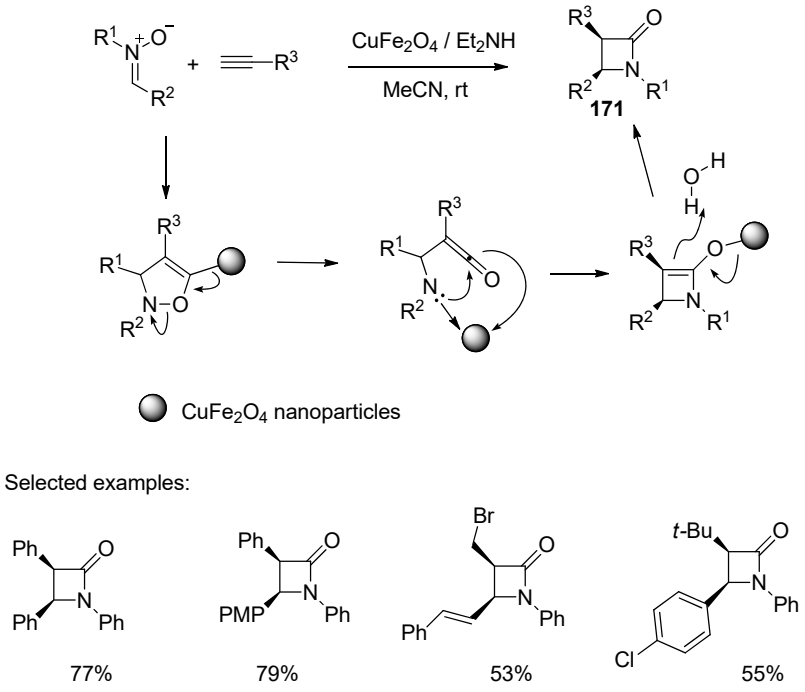


Scheme 93. Synthesis of chiral-2-azetidinones **169** with imine-containing ligands.

Application of magnetic copper ferrite ($CuFe_2O_4$) nanoparticles as a magnetically separable and recyclable heterogeneous catalyst in the Kinugasa reaction has been reported. Under mild conditions at room temperature, the reaction was efficient affording *cis* 2-azetidinones **171** with a wide range of functional-groups in good to excellent yields after crystallization (Scheme 94**)** [172].



Scheme 94. $CuFe_2O_4$ nanoparticles catalyzed synthesis of *cis* 2-azetidinones **171**.

Propargyl nitrones were generated using tartaric acid derivatives as substrates for intramolecular Kinugasa reactions. The dibenzyl ether of diethyl tartrate was easily converted to the corresponding propargyl aldehyde through a standard reaction sequence. The intramolecular

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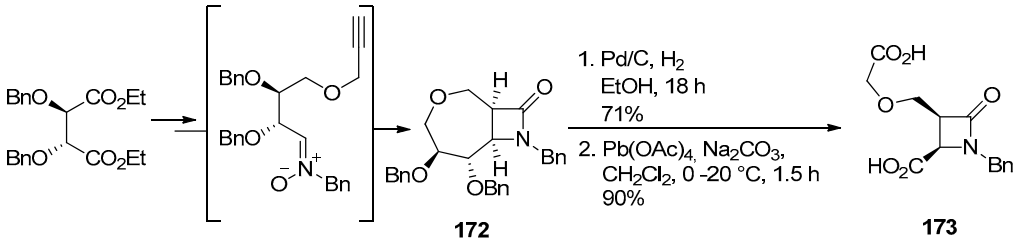
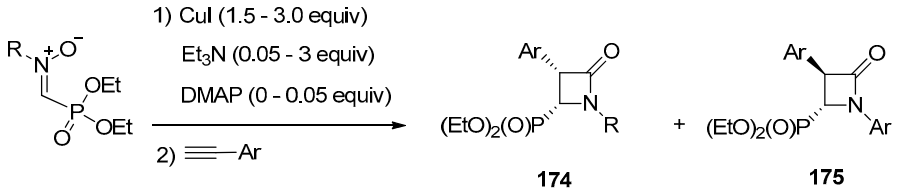
Kinugasa reaction, via *in situ* formation of the nitrone group, produced the bicyclic product **172** with the β-lactam fragment fused to the seven-membered ring in 54% yield. Finally, hydrogenative debenzylation was followed by the oxidative opening of the diol with lead tetraacetate, which afforded *cis*-β-lactam **173** as the only stereoisomer (Scheme 95) [173].



172 **173**

Scheme 95. Synthesis of monocyclic β-lactam **173** via an intramolecular Kinugasa reaction.

A series of *N*-substituted *cis*- and *trans*-3-aryl-4-(diethoxyphosphoryl)azetidin-2-ones **174** and **175** were synthesized by the Kinugasa reaction of *N*-methyl- or *N*-benzyl-*C*-(diethyoxyphosphoryl)nitrone and aryl alkynes (Scheme 96). All obtained azetidin-2-ones were tested against a wide range of DNA and RNA viruses to evaluate their antiviral activity [174].



174 **175**

R, Ar = Me, Ph (76-80%); Me, 2-FC_6H_4 (84-86%); Me, 3-FC_6H_4 (74-88%); Me, 4-FC_6H_4 (64-65%); Me, 2,4-$F_2C_6H_3$ (60-92%); Me, 3-Me-4-FC_6H_3 (65%); Bn, Ph (57-79%); Bn, 2-FC_6H_4 (65-78%); Bn, 3-FC_6H_4 (63-82%); Bn, 4-FC_6H_4 (54-66%); Bn, 2,4-$F_2C_6H_3$ (61-67%); Bn, 3-Me-4-FC_6H_3 (45-54%)

Scheme 96. Synthesis of 4-diethoxyphosphoryl)-2-azetidinones **174** and **175**.

N-propargylated nucleobases have been heated, with *N*-substituted-*C*-(diethoxyphosphonyl)nitrones in the presence of copper iodide to afford a mixture of diastereoisomeric 3-substituted-(4-diethoxyphosphoryl)azetidin-2-ones *cis*-**176** and *trans*-**177,** always containing the *trans* isomer predominantly. The mixtures of the *cis*-**176** and *trans*-**177** were pre-purified on a silica gel column and then separated by HPLC. In most cases at least small amounts of both diastereoisomers were isolated, which were sufficient for biological screening. Of the 84 compounds obtained, some showed moderate activity against varicella-zoster (VZV). Among these, compounds **178** and **179** were found to be the most effective in inhibiting the thymidine kinase (TK)-VZV strain, with EC_{50} values of 13.4 and 10.5 μM, respectively (Scheme 97) [175].

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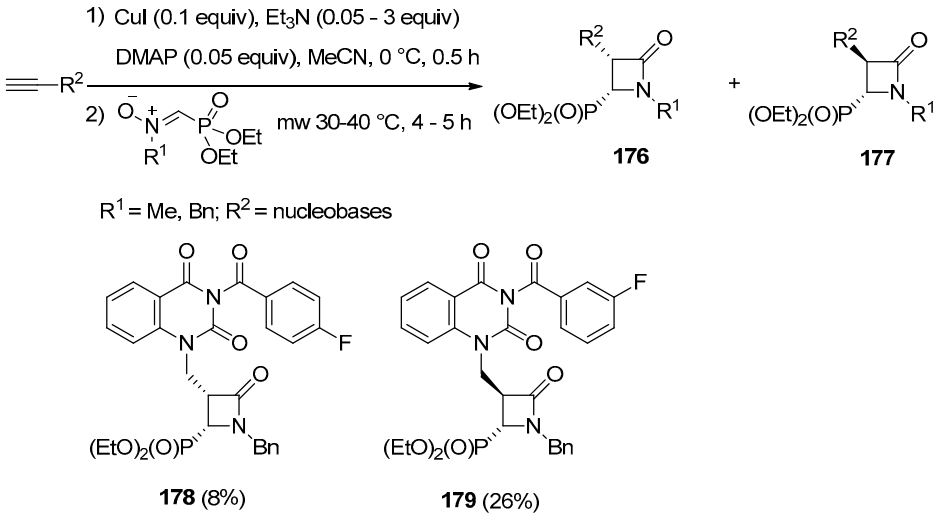
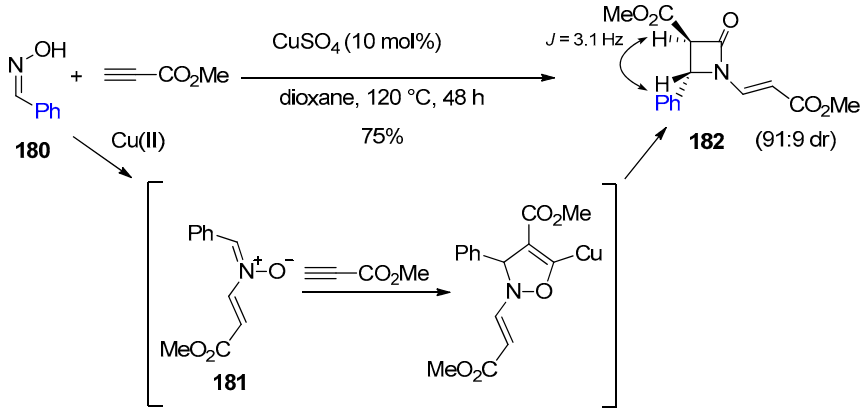


Scheme 97. Synthesis of 4-diethoxyphosphoryl-2-azetidinones **176** and **177**.

A copper(II)-catalyzed protocol has been developed for the construction of *trans*-β-lactams from oximes and methyl propiolate. This approach showed good substrate scope and diastereoselectivity (up to >99:1 dr). The method is based on a 1,3-dipolar cycloaddition of a copper acetylide onto the nitrone which is generated by 1,3-azaprotio transfer of oximes and methyl propiolate. For example, nitrone **181** was generated from oxime **180** to selectively give lactam **182** in good yield (Scheme 98).



Scheme 98. Synthesis of 2-azetidinones initiated by 1,3-azaprotio transfer of oximes and methyl propiolate.

The methods was extended to exocyclic ketoximes affording spirocyclic β-lactams **183-185** with various carbo and heterocyclic rings (Figure 12) [176].

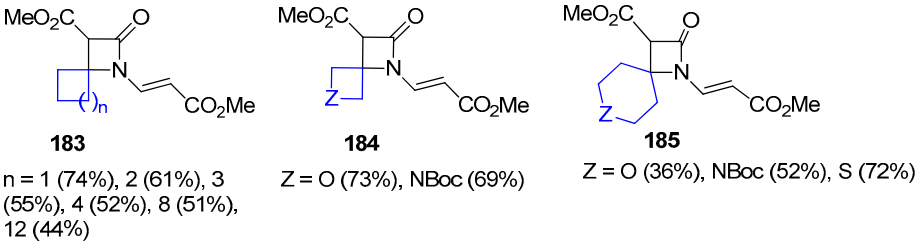


Figure 12. Synthesis of spirocyclic β-lactams **183-185**

A copper(I)-catalysed Kinugasa/aryl C-C coupling cascade reaction has been employed in the asymmetric synthesis of a series of spirocyclic β-lactams **186**. The reaction of *N*-(2-iodoaryl)propiolamides and nitrones using $Cu(MeCN)_4PF_6$ as the catalyst, a chiral bis-oxazoline

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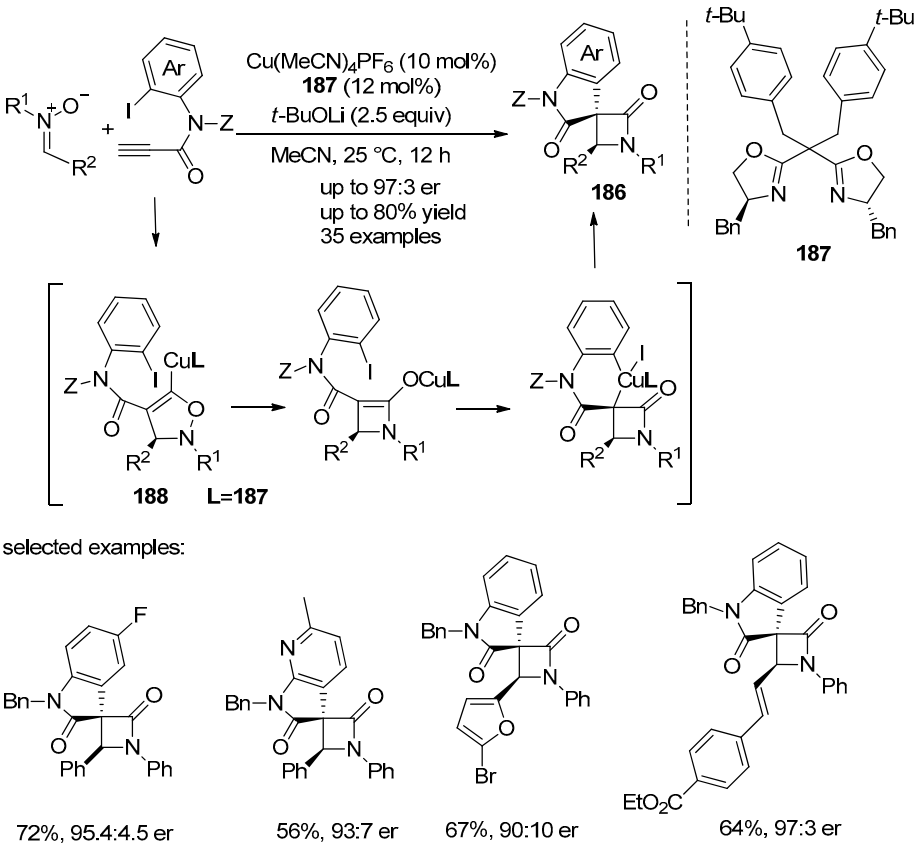
ligand **187** and *t*-BuOLi as a base, leads to the formation of functionalized chiral spiro[azetidine-3,3′-indoline]-2,2′-diones **186** as single diastereomers in good yields and with high enantiomeric ratios. No β-lactams were obtained in the presence of organic bases. Control experiments indicated that the diastereo- and enantio-determining step of this protocol is the Kinugasa reaction. This process uses intramolecular aryl-C coupling to capture the copper intermediate **188** formed during the Kinugasa reaction (Scheme 99) [177].



Scheme 99. Asymmetric Kinugasa/aryl C-C coupling cascade reaction of *N*-(2-iodoaryl)propiolamides with nitrones.

CuI catalyzed Kinugasa reaction of the nitrone **189** with methyl propiolate selectively afforded the *trans*-◎-lactam ***rac*-190**, which was reduced by sodium borohydride to the corresponding racemic ***rac*-191** which bears a hydroxymethyl group on the ◎-lactam nucleus. Subsequent optical resolution of racemic ***rac*-191** by esterification with Boc-L-proline and subsequent chromatographic separation of the two diastereomers, allowed isolation of the enantiopure alcohol **191** after ester hydrolysis. Treatment of the latter with diethylaminosulfur trifluoride (DAST) yielded the corresponding fluoride **192** with retention of the relative configuration. The ◎-lactam **192** was employed in the synthesis of a series of compounds, which were subsequently evaluated for their anticancer activity (Scheme 100) [178].

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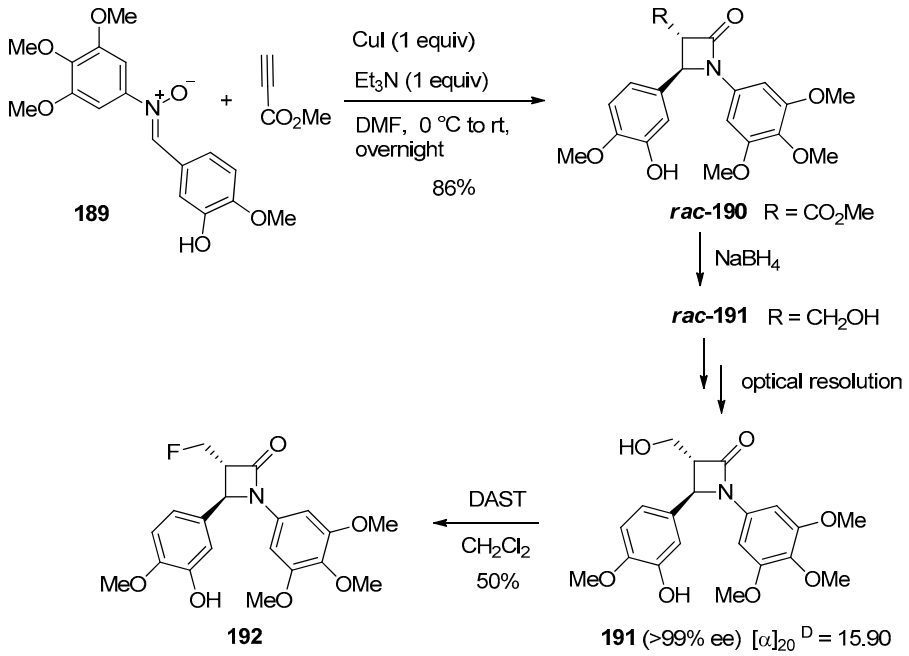
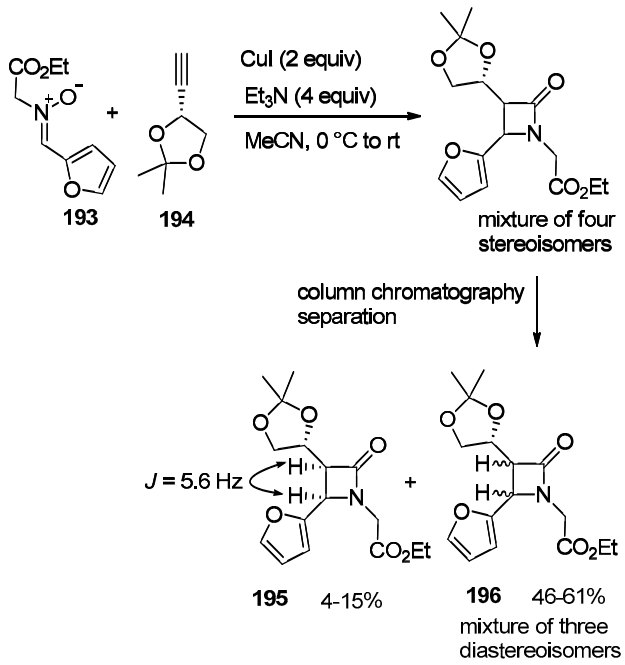


Scheme 100. Optical resolution of a racemic ◎-lactam ***rac*-191**.

Low stereoselectivity has been observed in reaction of chiral copper acetylides and non chiral, *C*-aryl acyclic nitrones. To circumvent this problem, the subsequent separation of Kinugasa adducts has been developed (Scheme 101). As a selected example, the reaction of nitrone **193** with acetylene **194** gave a mixture of four stereoisomers which after column chromatographyc provideded the *cis* adduct **195** ($J_{3\text{-}4}$ = 5.6 Hz) along with an inseparable mixture of the other three adducts **196** (Scheme 101). The absolute configuration at the C-4 carbon atom of **195** was established by electronic circular dichroism (ECD) spectroscopy [179].



Scheme 101. Kinugasa reaction with a chiral alkyne.

The aqueous Kinugasa reaction has been developed for bioorthogonal chemistry applications, with reaction rate acceleration made possible by the use of surfactant micelles. The reaction was optimised with acyclic nitrones using sodium lauril sulphate (SDS) as surfactant and L-Proline as

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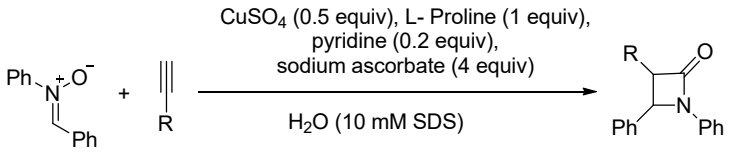
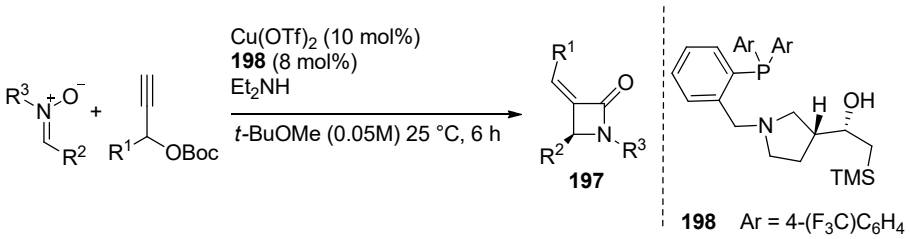
copper ligand (Scheme 102). The speed and efficiency of the reaction was found to be strongly influenced by the choice of alkyne. Biological lipids were found to be the most efficient surfactants. Alkynes with electron-withdrawing groups, such as propiolic esters and propiolamides, are the more reactive and give higher yields, while unactivated terminal and aryl alkynes led to lower yields of β-lactams. Membrane protein modification was possible using this process [180].

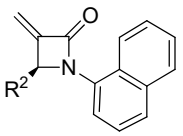


R = Ph (22%), 4-(F_3C)C_6H_4 (16%), $C(OEt)_2$ (20%), $(CH_2)_3CN$ (32%), $C(O)NH(CH_2)_2OMe$ (69%), $C(O)NHBn$ (64%), CO_2Et (65%)

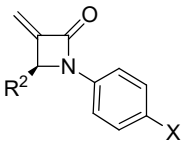
Scheme 102. Screening of alkynes in micelle-assisted Kinugasa reactions.

A chiral copper/prolinol-phosphine catalyst **198,** optimized for steric and electronic properties, allowed the highly enantioselective coupling of nitrones and propargyl alcohol derivatives (Scheme 103). The resulting chiral 3-alkylidene-◎-lactams **197** were obtained in moderate to high yields and served as precursors of other ◎-lactams through the transformation of their α,β-unsaturated carbonyl system [181].

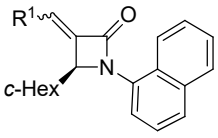




R^2 = *c*-Hex (94%, 92%ee), *i*-Pr (93%, 89%ee), Ph (69%, 93% ee), *p*-tol (63%, 91% ee), 3,5-di-$Me_2C_6H_3$ (67%, 94% ee), *o*-Tol (88%, 56% ee), PMB (60%, 93% ee), 4-(F_3C)C_6H_4 (41%, 90% ee)



R^2, X = *c*-Hex, H (57%, 98% ee); *N*-Boc-piperidin, H (63%, 97% ee); *c*-Hex, OMe (48%, 99% ee); *c*-Hex, X = CF_3(58%, 87% ee)



R^1 = Me 95% (*cis*/*trans* = 44:56), 90% ee (*cis*), 85% ee (*trans*); Bn 62% (*cis*/*trans* = 42:58), 66% ee (*cis*), 80% ee (*trans*); *i*-Pr 46% (*cis*/*trans* = 46:54), 46% ee (*cis*), 28% ee (*trans*)

Scheme 103. Synthesis of chiral 3-alkylidene-◎-lactams **197.**

A new protocol for the Kinugasa reaction has been developed for the one-pot synthesis of *N*-aryl-◎-lactams **200** using calcium carbide (CaC_2) as the acetylene source. CaC_2 was activated by tetra-*N*-butylammonium fluoride (TBFA) in the presence of CuCl/*N*-methylimidazole (NMI) (copper – fluoride catalysis). The facile synthesis and the utilisation of inexpensive chemicals enable quick and efficient access to substantial quantities of ◎-lactams unsubstituted on the C-3 position. The reaction failed with *N*-alkyl nitrones **199** (Scheme 104) [182].

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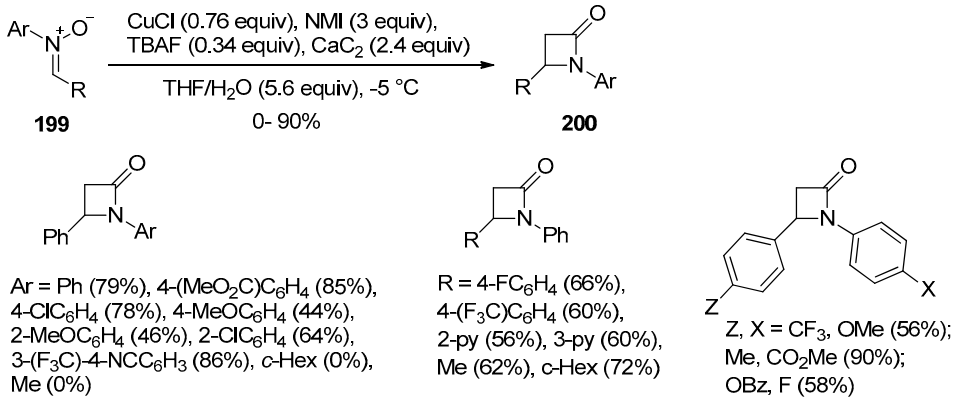
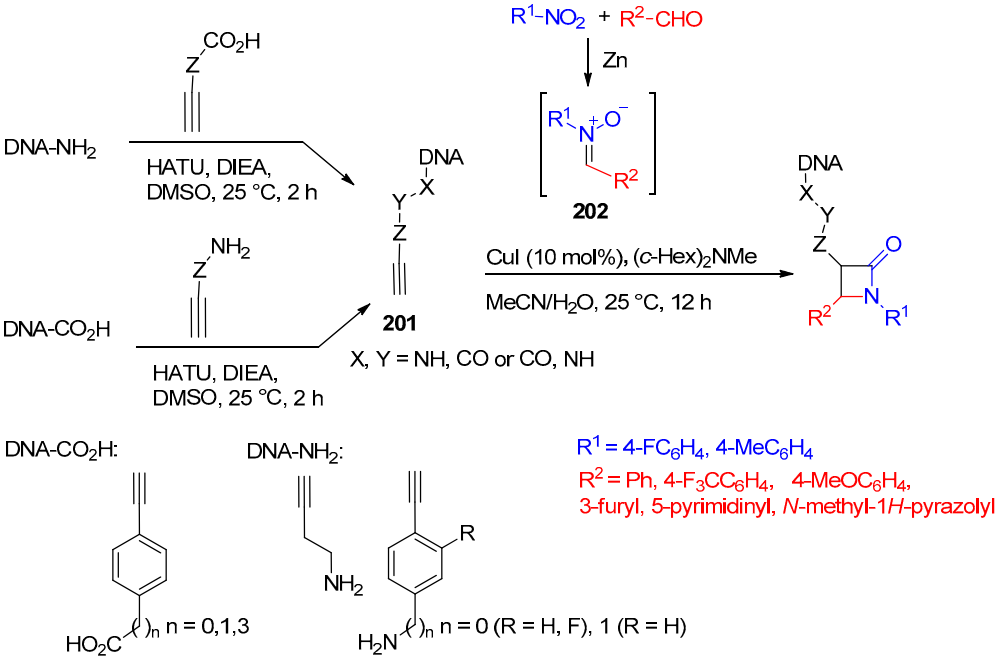


Scheme 104. Kinugasa reaction from calcium carbide.

The on-DNA combinatory synthesis of β-lactams through a copper-promoted Kinugasa reaction of nitrones **202** and DNA-conjugated alkynes **201** has been developed (Scheme 105). The alkynes were prepared by acylation of a double-stranded DNA oligonucleotide (DNA-NH_2) with alkynyl carboxylic acids or acylation of alkynyl amines with DNA-bound carboxylic acid (DNA-CO_2H), while nitrones are generated, *in situ* by reaction of nitro compounds with various aldehydes using zinc powder as a reductant (Scheme 105). Aromatic nitro compounds gave the ◎-lactams with conversions ranging from moderate to excellent while aliphatic nitro compounds were not effective[183].



Scheme 105. DNA-encoded library (DEL) for β-lactam synthesis.

A computational analysis of the Kinugasa reaction conducted with the presence of an unconventional catalyst, such as an oriented external electric field (OEEF), revealed that ◎-lactams can still be formed even without copper(I). However, no experimental data have been reported to support this hypothesis (Scheme 105) [184].

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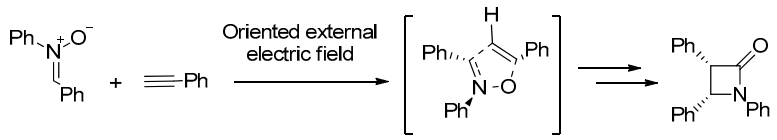
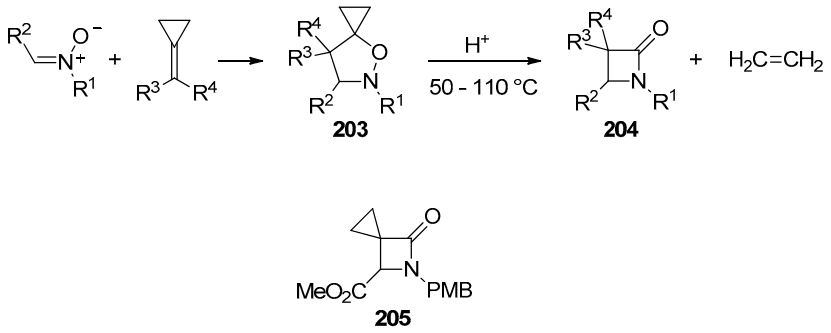


Scheme 106. Kinugasa reaction promoted by an oriented external electric field.

4.2. Nitrones and Methylenecyclopropanes

A recent report describes the development of an original protocol for the preparation of β-lactams **204** that are not readily accessible by conventional methods. The approach involves the use of 1,3-dipolar cycloaddition of nitrones and methylenecyclopropane derivatives, followed by thermal rearrangement of the resulting 5-spirocyclopropaneisoxazolidines **203** under acidic conditions (Scheme 107). The reaction also produces ethylene. Advantages of this strategy include the preservation of the relative and absolute configuration of the stereocenters established in the 1,3-dipolar cycloaddition and the possibility of obtaining highly strained spirofused β-lactams in good yields. For example, 3-spirocyclopropane-2-azetidinone **205** was synthesized via a one-pot three-component reaction from *N*-(4-methoxybenzyl)hydroxylamine], methyl glyoxalate, and bicyclopropylidene in 78% overall yield. Experimental and computational studies of the mechanism for this peculiar fragmentative rearrangement are described [185].



Scheme 107. Synthesis and thermal fragmentative rearrangement of 5-spirocyclopropaneisoxazolidines.

5. Miscellanea

5.1. Formal [1+1+2]-Cycloadditions

A general strategy for the asymmetric formal [1+1+2] reaction affording chiral ⌾-lactams **207** has been established. Azetidinones **207** were mainly synthesized as *trans*-isomers, with high yields and high enantio- and diastereoselectivities. In this approach, the key step is the catalytic generation of C(1)-ammonium enolates from benzyl bromides and CO, through the combination of Pd-catalyzed carbonylation (likely via acylpalladium intermediates converted by the base into ketenes) and chiral Lewis base organocatalysis using (*R*,*S*)-fused-BTM **206**, an isothiourea catalyst, for the subsequent asymmetric cascade reactions with *N*-tosylimines (Scheme 108). The process was applied to the synthesis of the antiproliferative ⌾-lactam **208** [186].

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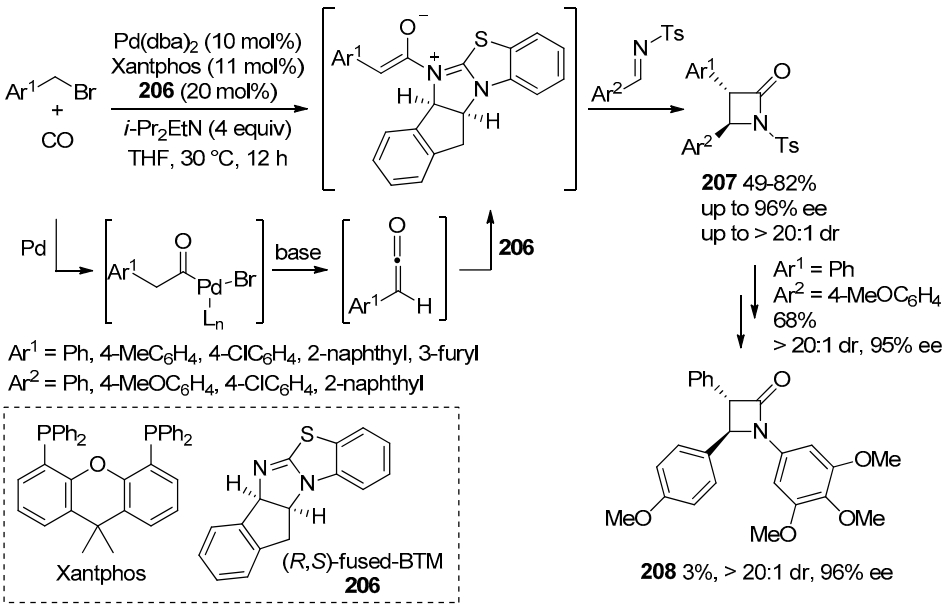
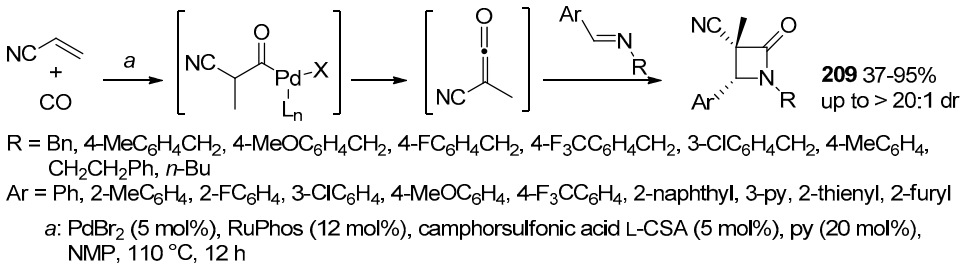


Scheme 108. Synthesis of optically pure b-lactams **207**.

Efficient palladium-catalyzed carbonylation/cycloaddition processes of alkenes and imines in the presence of CO have been described. A wide variety of alkenes and imines have been converted into variously substituted monocyclic and spirocyclic ◎-lactams in high yields, with complete regioselectivities and moderate to excellent diastereoselectivities usually in favor of the *cis* stereoisomer (determined by X-ray diffraction analyses on some derivatives). The success of this approach can be ascribed to the choice of a cooperative palladium/acid/base catalytic system (that depends on the type of alkene or diene employed) as well as the use of *N*-methyl-2-pyrrolidone (NMP) as solvent. The best results in terms of yields and stereoselectivities were observed with acrylonitrile leading to 3-cyanoazetidin-2-ones **209** in 37-95% yields (Scheme 109). From a mechanistic point of view, the reaction pathway involves acylpalladium intermediates, likely converted into ketenes by base [187].



Scheme 109. Synthesis of 3-cyanoazetidin-2-ones **209**.

Polysubstituted spirocyclic β-lactams **211** have been prepared in 47-90% yields through an efficient protocol involving the Pd-catalyzed carbonylation of *ortho*-bromoarylimines **210**. Likely, an alkylpalladium intermediate **I** is generated, via oxidative addition and subsequent CO and imine C=N bond insertion. Operating at 60 °C, a second CO insertion occurs leading to intermediate **II**, converted to the final compound by reaction with a second molecule of bromoarylimine, directly or via ketene formation (Scheme 110). The favored stereochemistry was determined on the basis of single crystal X-ray diffraction studies on some products [188].

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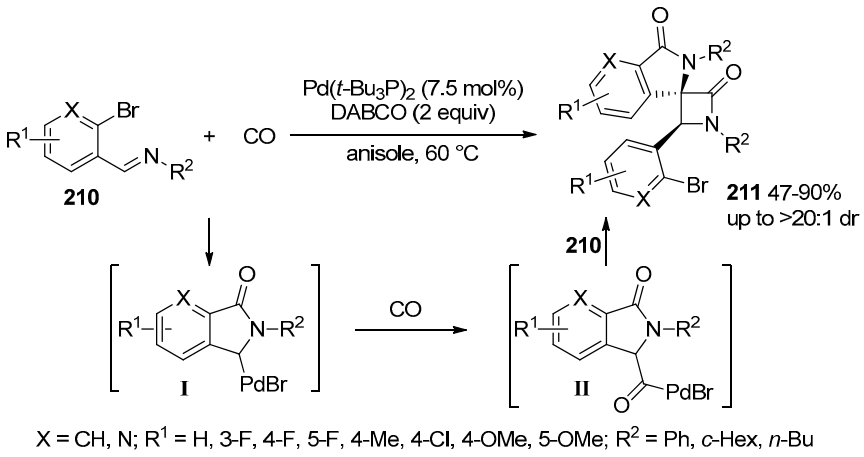
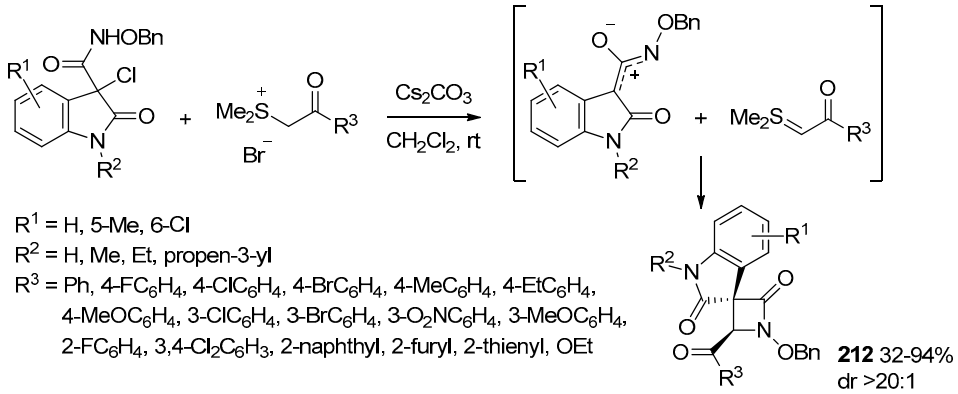


Scheme 110. Synthesis of polysubstituted spirocyclic β-lactams **211**.

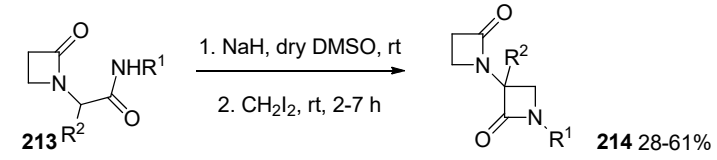
5.2. Formal [3+1]-Cycloadditions

The efficient and highly diastereoselective assembly of 3,3′-spiro[β-lactam]-oxindoles **212** has been reported (Scheme 111). The process can be described as a [3+1] cycloaddition of oxindole-based azoxyallyl cations and sulfur ylides, generated from *N*-(benzyloxy)-3-chloro-2-oxoindoline-3-carboxamides and sulfonium salts, respectively, by treatment with cesium carbonate [189]. The application of azoxyallyl cations in [3+m] cycloadditions has been reviewed by Singh et al. [190].



Scheme 111. Synthesis of 3,3′-spiro[β-lactam]-oxindoles **212**.

Mono-◎-lactams **213**, synthesized via 3-MCR Ugi reactions from ◎-amino acids, were converted into bis-◎-lactams **214** in moderate yields by NaH triggered diiodomethane addition (Scheme 112). The process was also performed in one pot conditions, starting from amino acid, aldehyde, and isocyanide, without isolation of the mono-◎-lactam species. The structure of compounds **214** was confirmed by X-ray diffraction analysis on one derivative (R^1 = *c*-Hex, R^2 = 4-PhC_6H_4) [191].



Scheme 112. Synthesis of bis-b-lactams **214**.

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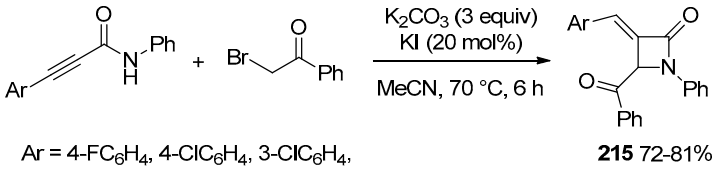
3-Methylene-β-lactams **215**, have shown interesting biological activities. When alkynylamides, obtained by alumination/amidation of terminal alkynes with isocyanates, were reacted with bromoacetophenone and potassium carbonate, in the presence of potassium iodide, compounds **215** were isolated in 72-81% yields (Scheme 113) [192].



Scheme 113. Synthesis of 3-methylene-β-lactams **215.**

5. Conclusions

Monobactams are molecules that continue to be of great interest because of their applications as potential drugs and as versatile intermediates in organic synthesis. In the field of their synthesis via cycloaddition reactions, the Staudinger [2+2]-cycloaddition is still the most widely used approach due to the easy accessibility of the reagents, its practical simplicity, the wide access to differently decorated β-lactams and the good control of the diastereoselectivity. An emerging field of research is the use of photocatalysis in the Staudinger synthesis of 2-azetidinones from diazo compounds. The recent application of asymmetric catalysts in the Kinugasa reaction is gaining importance for the enantioselective synthesis of β-lactams.

Most of these approaches are based on stepwise mechanisms, which are still under investigation because, although experimental and theoretical research is constantly providing new data, many aspects of these intriguing reactions remain to be elucidated.

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Conflicts of Interest: The authors declare no conflicts of interest.

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