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Recent Advances in the Synthesis of Spiro-β-Lactams and Spiro-δ-Lactams

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Abstract: Spirocyclic molecules are widely recognized for their complex three-dimensional features and structural rigidity. Among this class of molecules, the spiro-lactams subclass stands out, being extensively explored due to its bioactivity and utility in a variety of scientific fields such as drug design and organic synthesis. Given the recognition of spirocyclic lactams' broad potential, several efforts have been engaged on the pursuit of new synthetic strategies towards these molecules. The present review gathers advances on the synthesis of both spiro-β-lactams (spiroazetidin-2-ones) and spiro-δ-lactams (spiropiperidon-2-ones) reported since 2015. The work is divided into two distinct parts, each one dedicated to one of these types of spiro-lactam, with the approach used for building the spirocyclic system being extensively discussed, according to the method's scope, efficiency, selectivity, and reaction mechanism.

Keywords: β-lactams; δ-lactams; spiro-β-lactams; spiro-δ-lactams; penicillanates; spirocyclization

1. Introduction

Spirocyclic compounds are characterized by having two rings sharing the same atom, the quaternary spiro carbon.[1] This structural feature induces rigidity on a molecule and allows unique three-dimensional disposition of molecular functional groups. The inherent rigidity of spirocyclic compounds causes a decrease in conformational entropy penalty when it comes to an interaction between a potential bioactive spiro compound and its putative molecular target.[2] In this context, it is not surprising that several biologically active molecules possess a spirocyclic scaffold in its molecular structure.

Therefore, spirocyclic compounds have attracted a lot of attention within the area of natural products and medicinal chemistry. Among spirocyclic molecules of interest, spiro-lactams stand out as a prominent class, since it includes synthetic biologically active molecules such as antifungal spirooxindole β-lactam **1**,[3] cholesterol absorption inhibitor (+)-SCH 54016 (**2**),[4] antiplasmodial spiropenicillanate **3**,[5] NMDA receptor modulator NYX-2925 (**4**),[6] and 11β-HSD1 inhibitor (**5**).[7] The spirocyclic lactam scaffold is also present in the structure of naturally occurring molecules such as marine toxin surugatoxin (**6**)[8] (Figure 1). However, spiro-lactams importance exceeds the previous presented utility in medicinal chemistry and drug discovery. Its complex structural features have also led spirocyclic lactams to play a relevant role in organic and asymmetric synthesis, where this class of molecules have been extensively explored both as building blocks and chirality inducers, respectively. Given spirocyclic lactams relevance in several chemistry fields, the scientific community devoted serious efforts to the pursuit of alternative synthetic approaches for these molecules. Such efforts resulted on a considerable myriad of synthetic pathways which range from the well-known classical Staudinger β-lactam synthesis and its derivatizations to more recent strategies such as

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N-heterocyclic carbene (NHC)-catalyzed annulation or one-pot cascade reactions.

Currently, the available bibliography contains a panoply of solid reviews focused on synthetic approaches to β-lactams.[9] Although in less extent when compared to its four-membered ring analogues, δ-lactams synthesis has also been reviewed.[10] However, very few reviews concerning β-lactams are exclusively focused on the synthesis of its spirocyclic counterparts,[11] while none about spiro-δ-lactams synthesis is available.

In the follow-up of our group previous review on spiro-γ-lactams (spiropyrrolinin-2-ones) synthesis,[12] herein we cover the most recent advances regarding spiro-β-lactams (spiroazetidin-2-ones) and spiro-δ-lactams (spiropiperidon-2-ones) synthetic methodologies reported since 2015. Concomitantly, the present review gathers a noteworthy variety of structurally diverse spirocyclic lactams with the spiro carbon at different positions (C3 and/or C4 for spiro-β-lactams and C3, C4, C5 or C6 for spiro-δ-lactams) (Figures 2). The present review also includes the synthesis of more specific cases of spirocyclic lactams, such as unsaturated spiro-δ-lactams, spirocyclic lactams fused to aromatic or heteroaromatic systems (Figure 2), and spirocyclic bis-lactams (Figure 3). Different synthetic strategies will be tackled separately, primarily according to the size of the lactam ring, differentiating spiro-β-lactams and spiro-δ-lactams, and then according to the spirocyclic motif synthesis procedure namely if it relies on: a) the building of the lactam ring from precursors with a ring subunit in its structure; b) the construction of the second ring from a lactam precursor and; c) one-pot synthesis of both lactam and non-lactam rings.

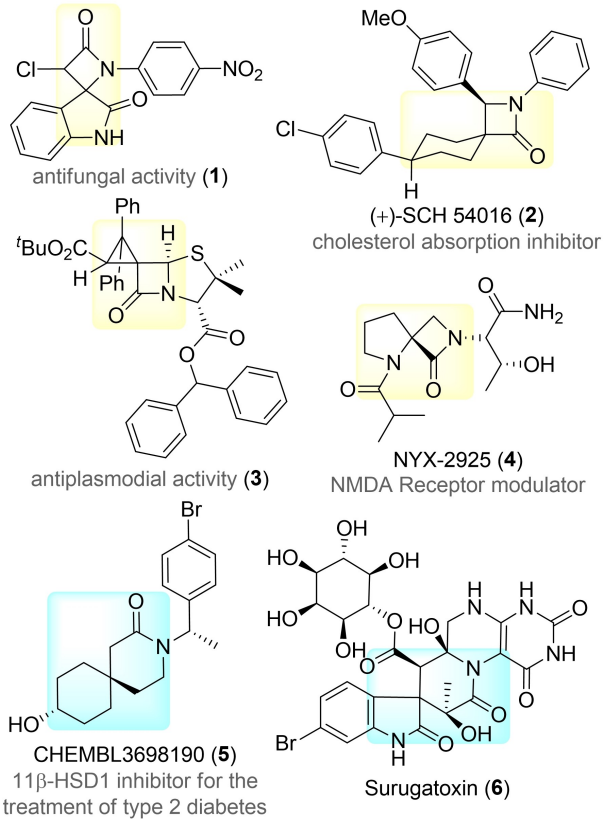


Figure 1. Representative examples of biologically active spirocyclic β- and δ-lactams.

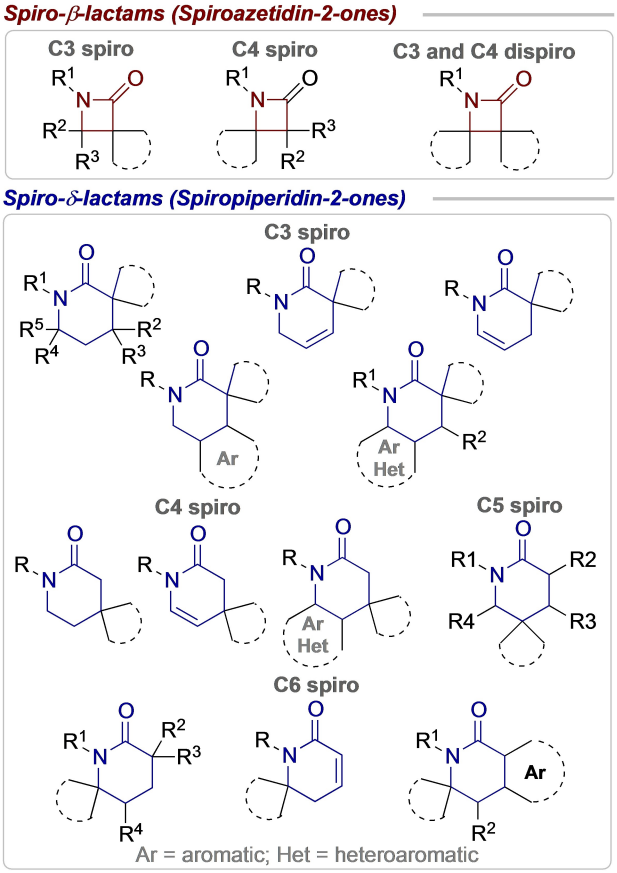


Figure 2. General structures of spirocyclic β- and δ-lactams.

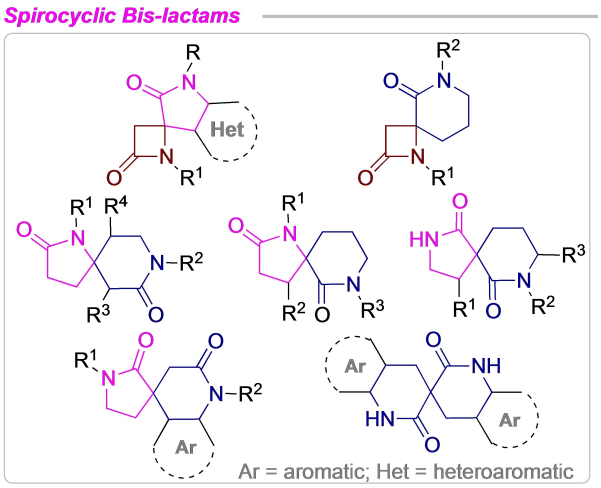


Figure 3. General structures of spirocyclic bis-lactams.

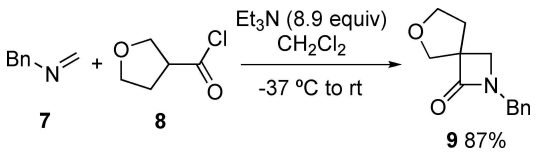
2. Spiro-β-Lactams

2.1. β-Lactam Ring Synthesis

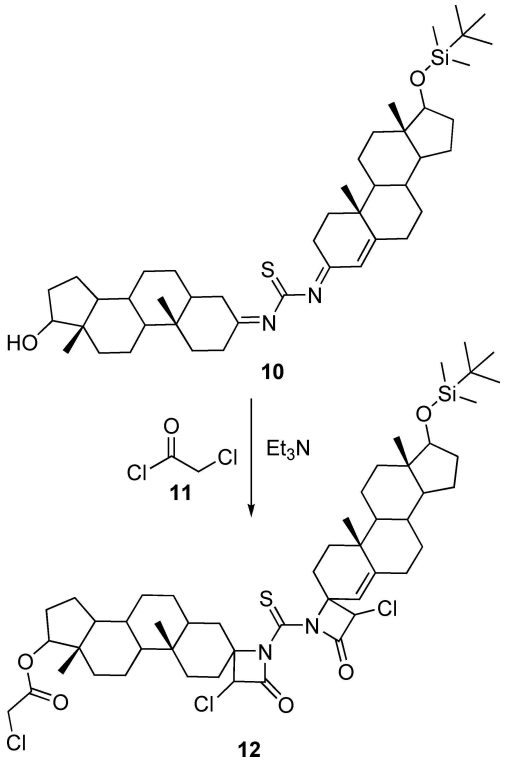
2.1.1. Staudinger Synthesis

The Staudinger reaction was reported in 1907 by Hermann Staudinger, introducing for the first time the synthesis of the 2-azetidinone ring.[13] The reaction occurs through a formal [2+2] cycloaddition (or cyclocondensation) between imines and ketenes, a two-step process involving zwitterionic intermediates. The reaction of acyl chlorides with triethylamine is commonly used for the *in situ* generation of ketenes, allowing to overcome their lack of stability. With the discovery and structural elucidation of the antibiotic penicillin, the Staudinger synthesis became of major importance in medicinal chemistry as this procedure allowed the synthesis of penicillin derivatives in the laboratory. Although several alternative methods have been developed, the Staudinger reaction remains as the most common method applied for the synthesis of β-lactams, including spiro-β-lactams.[14]

The classical Staudinger approach was used by Karlsson, Sörensen and co-workers in 2015 to synthesize a spiro-β-lactam, 2-benzyl-6-oxa-2-azaspiro[3.4]octan-1-one (**9**), through the cycloaddition between *N*-methylene-1-phenylmethanamine (**7**) and tetrahydrofuran-3-carbonyl chloride (**8**) in 87% yield (Scheme 1).[15] The procedure also proved to be suitable to be performed under flow conditions using *N*-methylpiperidine as the amine base. This Staudinger reaction under flow mode proved to be a safer



Scheme 1. Staudinger synthesis of a 6-oxa-2-azaspiro[3.4] octan-1-one.

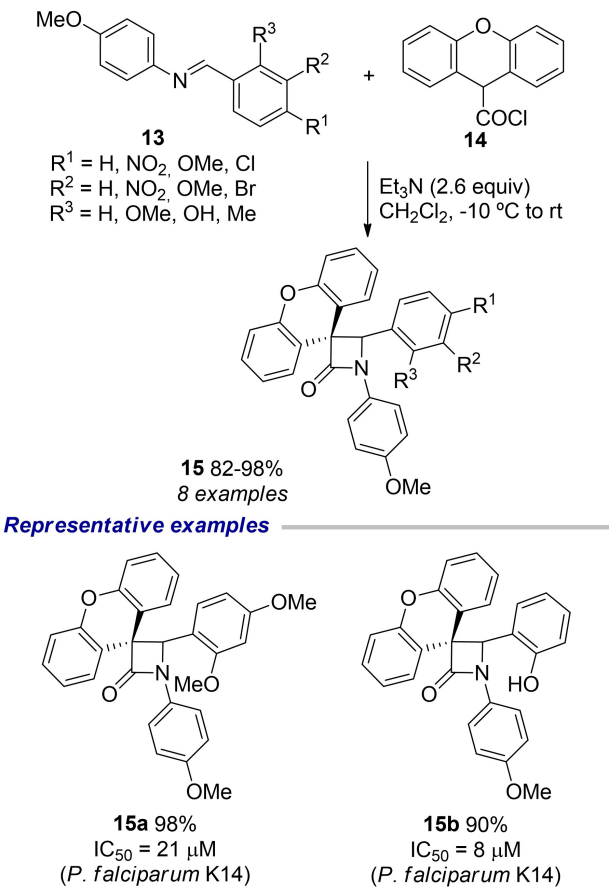


Scheme 2. Synthesis of an androgen derivative containing a spiro-β-lactam unit in its structure.

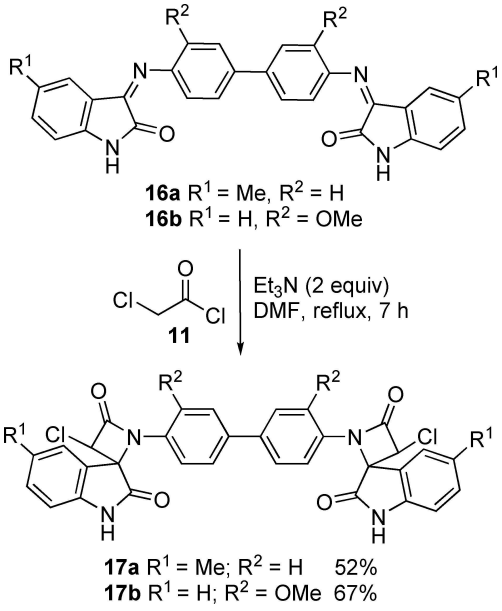
alternative, due to a more efficient transfer of the heat generated in this highly exothermic transformation despite affording spiro-azetidinone **9** in lower yield (56%).

Lauro *et al.* also used the Staudinger method on the synthesis of an androgen derivative **12** containing two spiro-β-lactam units in its structure.[16] The molecule was obtained from the reaction between a dihydrotestosterone derived diimine **10** and chloroacetyl chloride (**11**) in the presence of triethylamine giving the target molecule in 76% yield, in a process involving the construction of two β-lactam rings (Scheme 2).

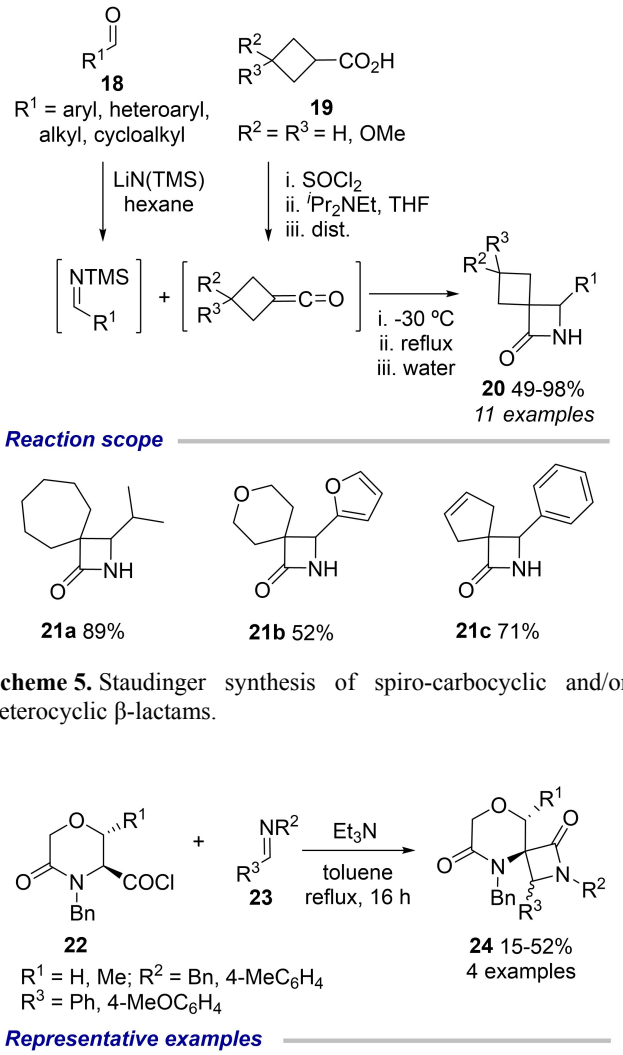
In 2016, Jarrahpour *et al.* used the conventional Staudinger reaction to explore the cycloaddition between 9*H*-xanthene-9-carbonyl chloride (**14**) and different aromatic imines **13** (Scheme 3).[17] This approach resulted in the synthesis of eight 1,4-diphenylspiro[azetidine-3,9′-xanthen]-2-ones **15** in high yields (82–98%), a class of C3 spiro-β-lactams



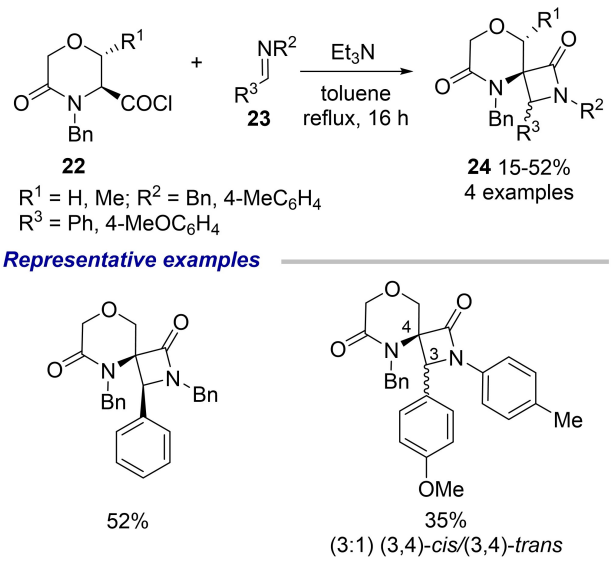
Scheme 3. Staudinger synthesis of 1,4-diphenylspiro[azetidine-3,9′-xanthen]-2-ones.



Scheme 4. Staudinger synthesis of bis-spiro-β-lactams.



Scheme 5. Staudinger synthesis of spiro-carbocyclic and/or heterocyclic β-lactams.



Scheme 6. Synthesis of peptidomimetic spiro-β-lactams from serine and threonine-derived morpholine derivatives.

containing a spiro-xantene moiety. The X-ray analysis of one derivative revealed that the β-lactam ring is nearly planar and the xanthene ring system is V-shaped with a dihedral angle between the benzene rings of 27.82° and with a folded central ring. These spirocyclic β-lactams were assayed for their activity against *Plasmodium falciparum* K14-resistant strain being identified two active molecules, where molecule **15b** stands out as being the most active ($IC_{50} = 8$ μM).

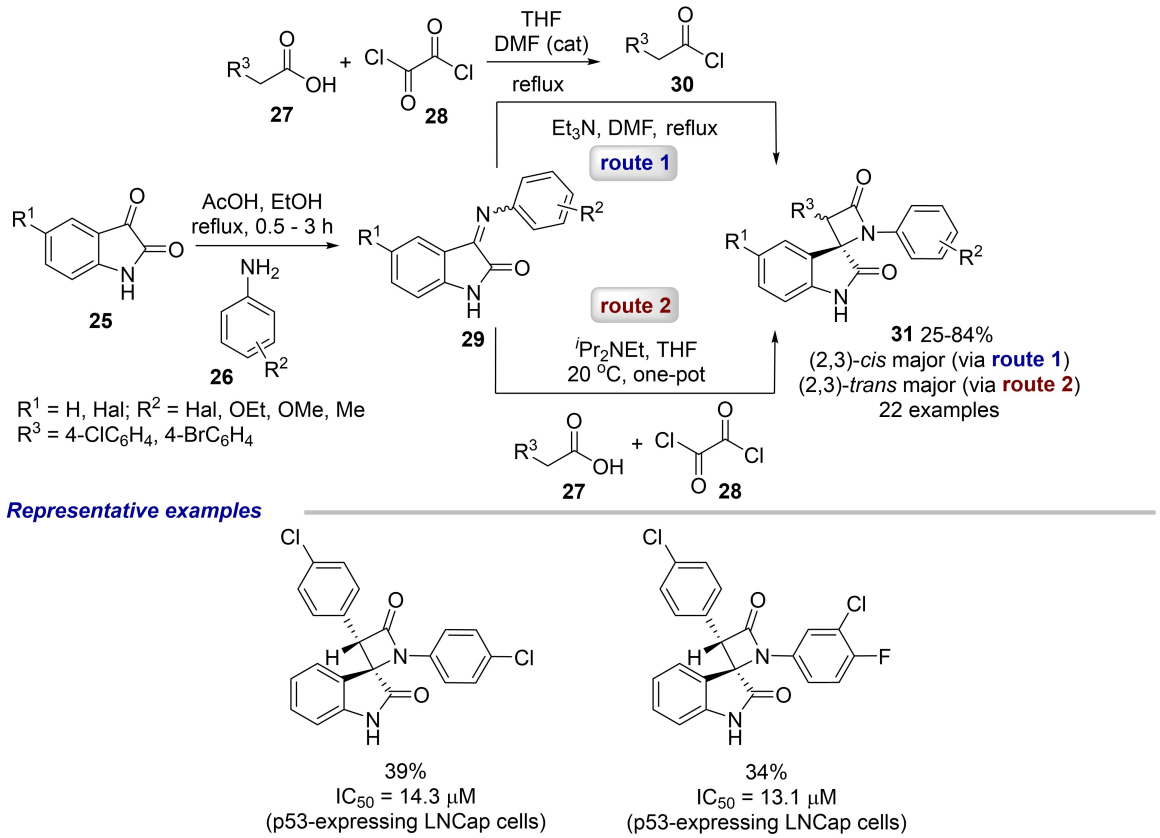
Using a similar approach, Kandile *et al.* synthesized two bis-spiro-β-lactams **17** containing two oxindole moieties, from the reaction carried out in refluxing DMF of chloroacetyl chloride (**11**) with bis-Schiff bases **16**, the latter obtained from the condensation of the corresponding 4,4′-diamino-1,1′-biphenyl and isatin derivatives (Scheme 4).[18] The target products were obtained in moderate yields (52–67%).

Mykhailiuk and co-workers also applied the Staudinger method to synthesize a library of eleven different spiro-β-lactams **20** containing a 2-azaspiro[3.3]heptan-2-one structural core (Scheme 5).[19] The formal [2 + 2] cycloaddition between ketenes derived from **19** and a set of different aromatic, heteroaromatic and aliphatic TMS-imines, generated *in situ* by condensation of aldehydes **18** with LiN(TMS), afforded the spirocyclic products in moderate to high yields (49–98%). The same research group extended the scope of the previous work by incorporating 5- to 7-membered carbocyclic and heterocyclic rings into the spirocyclic structure, obtaining seventeen spiro-β-lactams **21** in yields ranging from 14% to 89%. Three of the synthesized spiro-β-lactams and their respective yields are presented in Scheme 5.[20]

The conventional Staudinger reaction was also applied in the synthesis of four peptidomimetic spiro-β-lactams **24** (Scheme 6).[21] The molecules were obtained from the reaction between ketenes, generated from serine and threonine-derived morpholine derivatives **22** and aromatic imines **23**. The morpholine-derived spiro-β-lactams were obtained in low to moderate yields (15–52%). Nevertheless, the reaction occurred in a diastereoselective fashion with the *cis* products obtained as major or single stereoisomer.

The direct generation of ketenes from carboxylic acids in the presence of acid activator reagents, other than thionyl chloride or surrogate reagents, followed by the treatment with base has been used as a derivatization of the conventional Staudinger cycloaddition. This strategy overcomes problems associated with the use of acyl chlorides which can give inadequate results such as low yields and difficult purification procedures.

In this context, Beloglazkina and co-workers performed a comparative study on the Staudinger synthesis of racemic bis-aryl spiro[azetidine-2,3-indole]-2,4(1*H*)-diones **31** using two approaches which differ on the ketene precursor nature (Scheme 7).[22] One route uses previously prepared phenylacetyl chloride derivatives **30** as ketene precursor (route 1), while the other explores one-pot phenylacetic acid **27** activation with oxalyl chloride (**28**) via mixed anhydride (route 2). Notably, the different approaches afforded different diastereoselectivity. The *cis*-diastereoisomer or *trans*-diastereoisomer were respectively obtained as major product when an acyl chloride or an activated phenylacetic acid was used as ketene



Scheme 7. Staudinger synthesis of bis-aryl spiro[azetidine-2,3-indole]-2,4(1*H*)-diones.

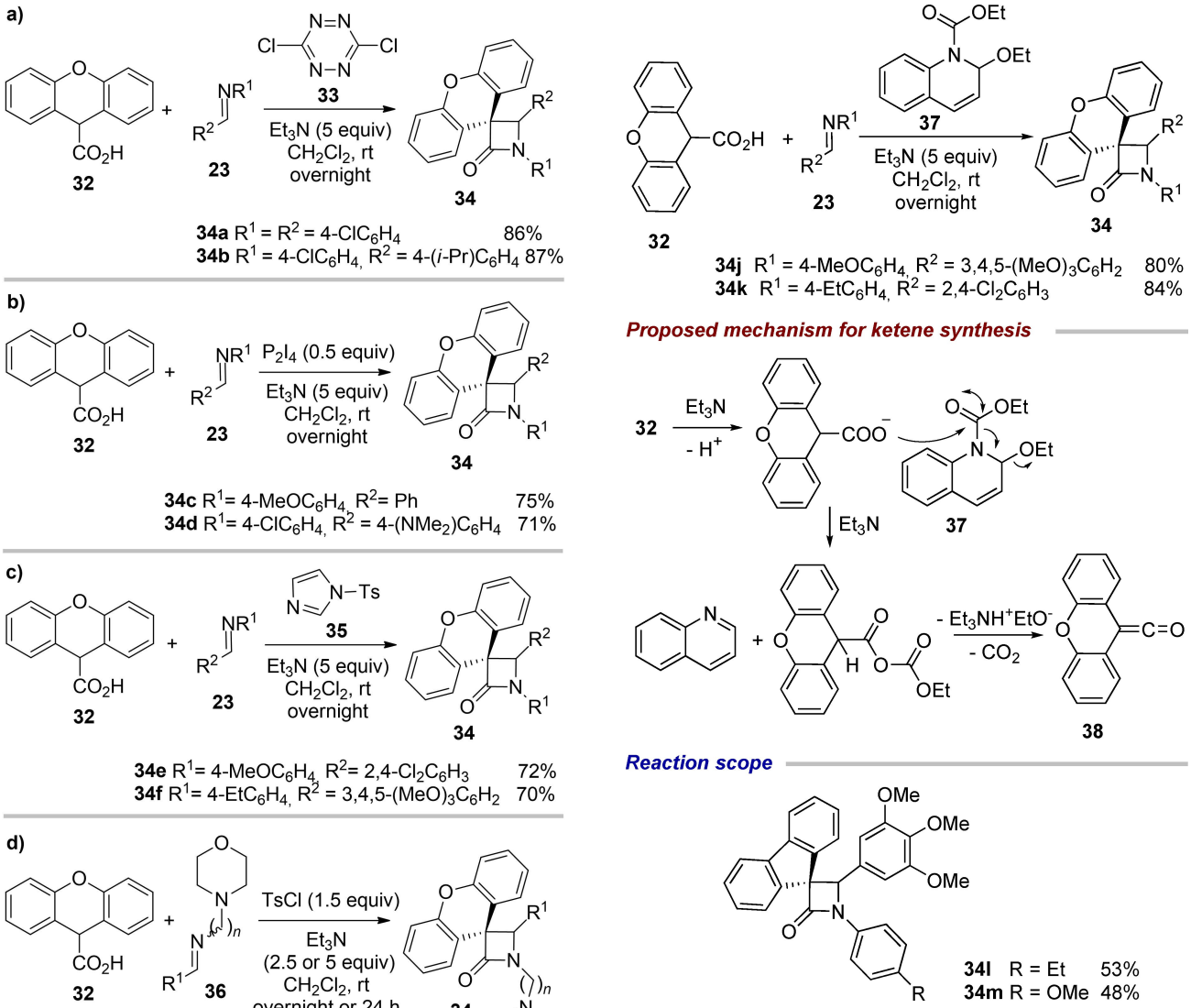
precursor. Based on insights gathered from molecular docking studies, four molecules were assayed for its potential cytotoxic activity, and two *trans*-isomeric spiro[azetidine-2,3-indole]-2,4(1*H*)-diones were identified as being cytotoxic against p53-expressing prostate cancer LNCap cells.

Zarei and co-workers synthesized C3 spiro-β-lactams **34 a** and **34 b**, containing the spiro-xanthene moiety, in high yields (86% and 87%, respectively) (Scheme 8a).[23] These molecules were obtained as products of the ketene-imine cycloaddition between xanthene-9-carboxylic acid (**32**) and aromatic imines **23** with 3,6-dichlorotetrazine (**33**) as the carboxylic acid activator. The use of diphosphorus tetraiodide as acid activator in the synthesis of two other xanthene-9-carboxylic acid derived C3 spiro-β-lactams, **34 c** and **34 d**, was also reported allowing the synthesis of the target molecules in good yields (71–75%) (Scheme 8b).[24] The same type of spiro-β-lactams **34 e,f** could also be prepared in good yields (70–72%) via cyclocondensation of xanthene-9-carboxylic acid (**32**) and aromatic imines in the presence of tosylimidazole (**35**) (Scheme 8c).[25] Tosyl chloride was also used for xanthene-9-carboxylic acid (**32**) activation, with this approach leading to the synthesis of C3 spiro-β-lactams **34 g,i** bearing a morpholine ring, in moderate to good yields (41–71%) (Scheme 8d).[26]

The same group reported the use of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (**37**, EEDQ) as the carboxylic acid activator for the *in situ* generation of ketene **38** (Scheme 9).[27] Spiro-xanthene spiro-β-lactams **34 j** and **34 k** were obtained in 80% and 84% yield, respectively. In the same study, by using fluorene-9-carboxylic acid as the ketene precursor, spiro-β-lactams **34 l** and **34 m** containing a spiro-fluorene moiety were also synthesized in 53% and 48% yield, respectively.

Sardarian and co-workers synthesized spiro-β-lactam **34 n** which was used for Fe_3O_4@SiO_2 nanoparticles functionalization.[28] This β-lactam was obtained from the Staudinger cycloaddition between xanthene-9-carboxylic acid (**32**), activated by tosyl chloride, and aromatic imine **39** (Scheme 10). By using the α,β-unsaturated Michael acceptor present in its structure, the spiro-β-lactam was conjugated with magnetic nanoparticles coated by 3-(triethoxysilyl)-propylamine (Fe_3O_4@SiO_2–$(CH_2)_3NH_2$).

The synthesis of a set of spirocyclic β-lactams **43** bearing a indeno[1,2-*b*]quinoxaline ring system has been reported.[29] The molecules were obtained as racemic mixtures by the ketene-imine Staudinger



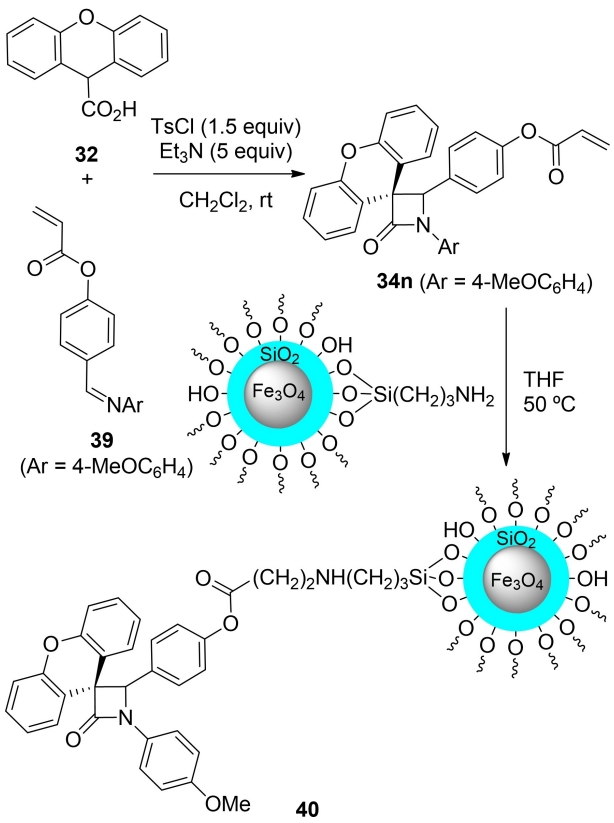
Scheme 8. Staudinger synthesis of spiro-β-lactams containing the xanthene moiety.

Scheme 9. Synthesis of spiro-β-lactams using EEDQ as the carboxylic acid activator.

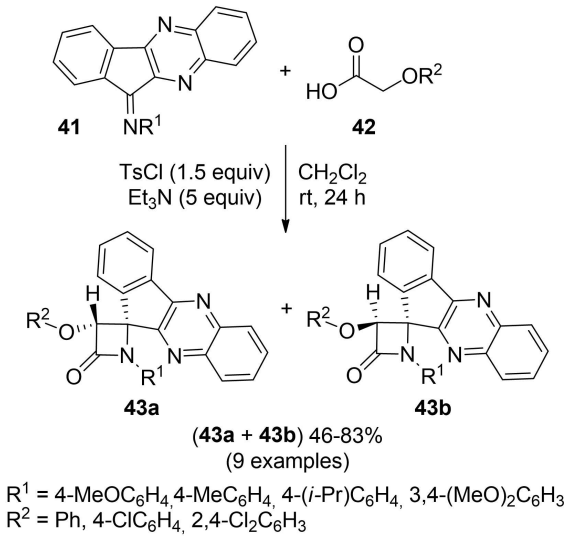
cycloaddition between four different *N*-phenyl-11*H*-indeno[1,2-*b*]quinoxalin-11-imine derivatives **41** and phenoxyacetic acid derivatives **42** in the presence of triethylamine and tosyl chloride (Scheme 11). The products were obtained as 50:50 mixtures of diastereoisomers and isolated in combined yields ranging from 46% to 83%. The stereochemistry assignment was supported by X-ray structure analysis of two spiro-β-lactam derivatives.

Alternatives to the common ketene-precursors acyl chlorides or activated carboxylic acids have been reported and used in the Staudinger cyclocondensation. Bengali, Arndtsen and co-workers reported the synthesis of spirocyclic β-lactams **45** containing an isoindolinone moiety through a methodology based on a multicomponent palladium-catalyzed reaction between an *ortho*-iodo-substituted aryl imine **44**, a second imine **23** and CO (Scheme 12).[30] Starting from *ortho*-iodo-substituted aryl imines, the synthesis of the spiro-β-lactams **45** proceeds via two palladium-catalyzed carbonylation reactions, with the first affording *in situ* acid chloride **I** which cyclizes to give *N*-acyl iminium salt **II** followed by a second carbonylation reaction to give ketene **III**. Finally, Staudinger reaction of this *in situ* generated ketene and an imine affords the spiro-β-lactam. This synthetic approach resulted in the synthesis of racemic spiro-β-lactams **45** in moderate to high yields (48–96%).

In 2019, Novikov and co-workers reported the domino synthesis of dispirocyclic *N*-vinyl β-lactams **49**

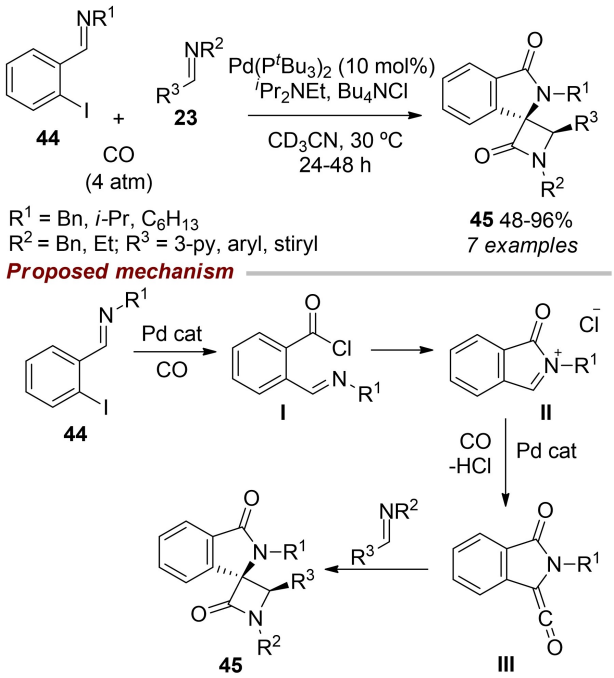


Scheme 10. Synthesis of a spiro-β-lactam functionalized Fe_3O_4@SiO_2 nanoparticle.



Scheme 11. Synthesis of spirocyclic β-lactams bearing a indeno [1,2-*b*]quinoxaline ring system.

from diazo-Meldrum's acid **48** and 2*H*-azirines **46** or 5-alkoxyisoxazoles **47** through a $Rh_2(Piv)_4$-catalyzed 2-azabuta-1,3-diene **IV** formation, and subsequent Staudinger ketene-imine cycloaddition (Scheme 13).[31]



Scheme 12. Spiro-β-lactams from ortho-iodo-substituted aryl imines via two palladium-catalyzed tandem carbonylation reactions followed by a Staudinger cyclocondensation.

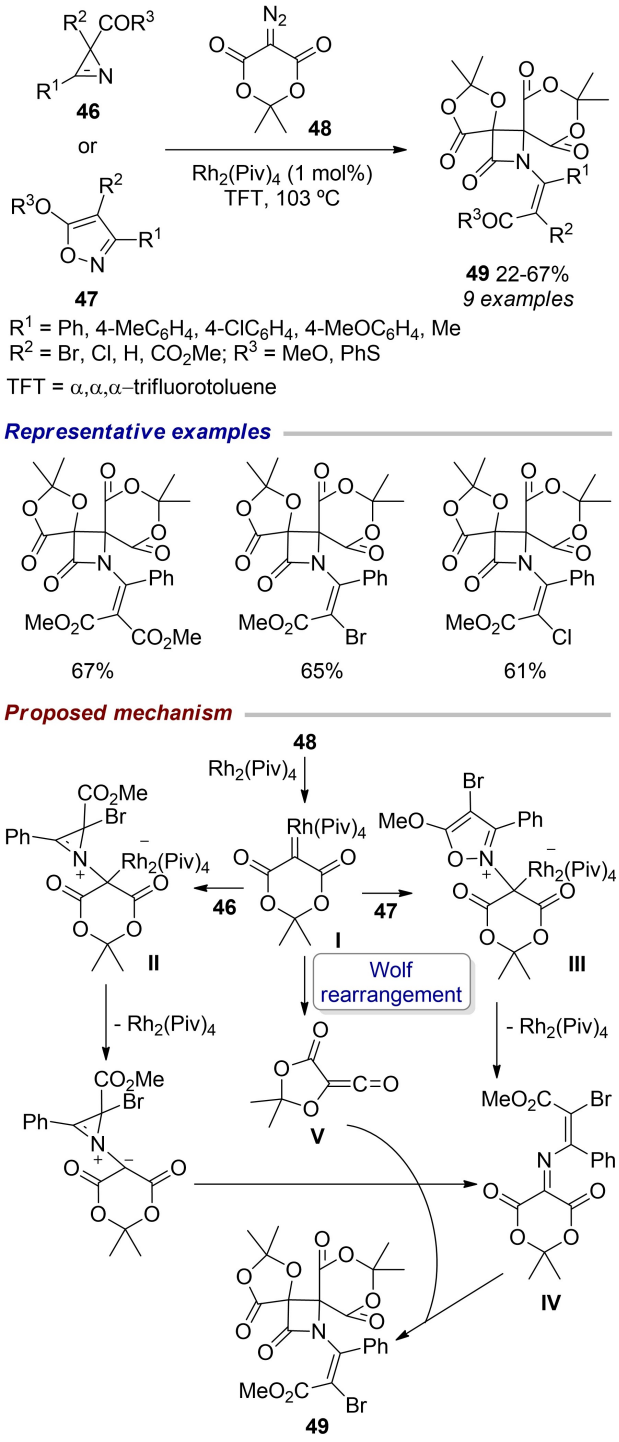
Concerning the reaction mechanism, the rhodium carbenoid **I** obtained from the Meldrum's acid derived diazo-compound **48**, adds to the azirines or isoxazoles forming a complex, with both pathways resulting on the same 2-azabuta-1,3-diene **IV** product. A parallel Meldrum's acid carbenoid Wolff rearrangement leads to the *in situ* generation of a ketene **V**, which undergoes a [2+2] Staudinger cycloaddition with the 2-azabuta-1,3-diene **IV** present in the reaction medium to give β-lactam **49**. By using different substituent groups on both azirine and isoxazole, nine different dispirocyclic *N*-vinyl β-lactams were obtained in low to moderate yields (22–67%).

The scope of the reaction was extended to the two-step synthesis of monospirocyclic β-lactams **54** by using acyclic α-diazocompounds **52** for the generation of the 2-azabuta-1,3-dienes and the diazo-Meldrum's acid to act solely as ketene precursor (Scheme 14).[31] This approach yielded nine spiro-β-lactams in low to good yields (21–75% yield).

2.1.2. Cascade Mannich/Lactamization Reaction

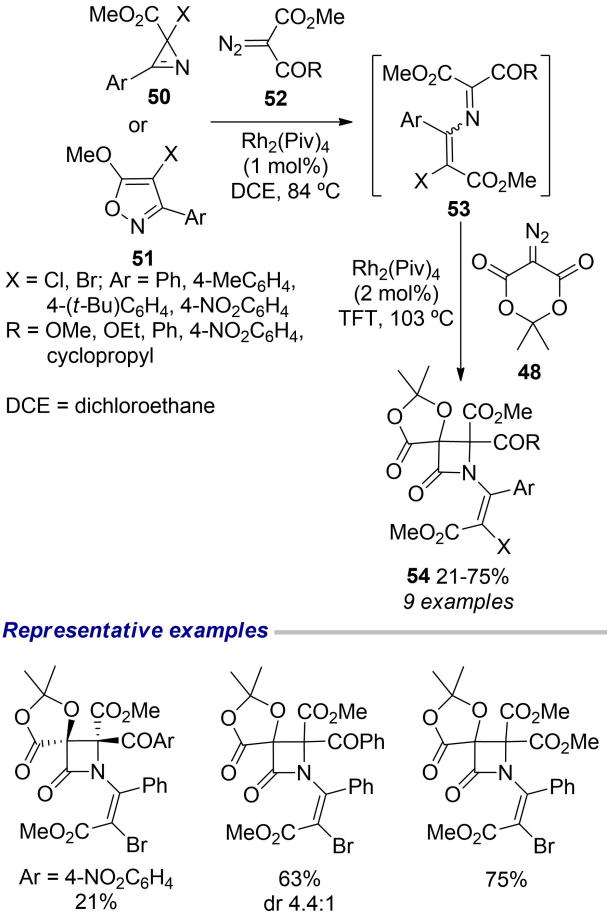
Although the use of imines for building 2-azetidinones is commonly related with the Staudinger method, these molecules have also been explored as building blocks on alternative synthesis of spiro-β-lactams namely in the Mannich/lactamization cascade reaction approach.

In this context, Ando and co-workers reported the synthesis of spiro-β-lactam **57** via the reductive



Scheme 13. Synthesis of dispirocyclic *N*-vinyl-β-lactams from diazo-Meldrum's acids and 2*H*-azirines or 5-alkoxyisoxazoles.

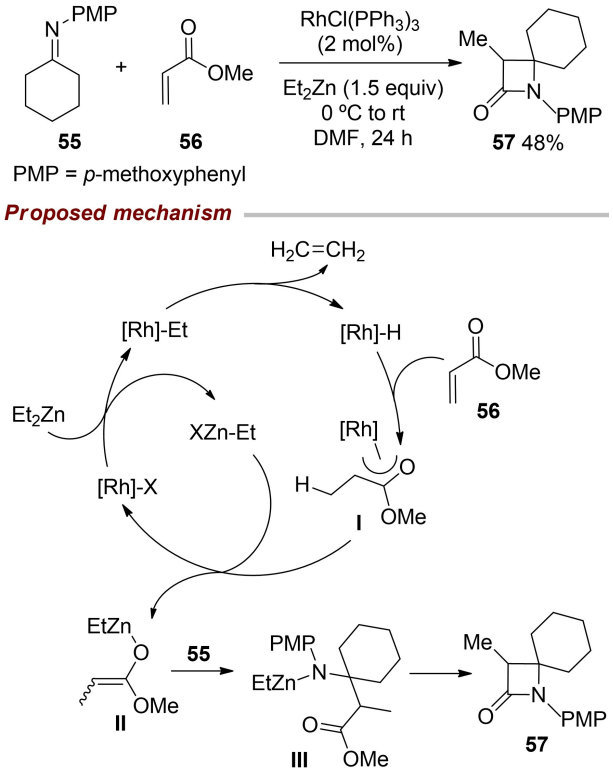
Mannich-type reaction of imine **55** with α,β-unsaturated ester **56**, in the presence of Et_2Zn and RhCl$(PPh_3)_3$ (Scheme 15).[32] The generated rhodium hydride complex (Rh–H) catalyzes the 1,4-reduction of the α,β-unsaturated ester producing rhodium enolate



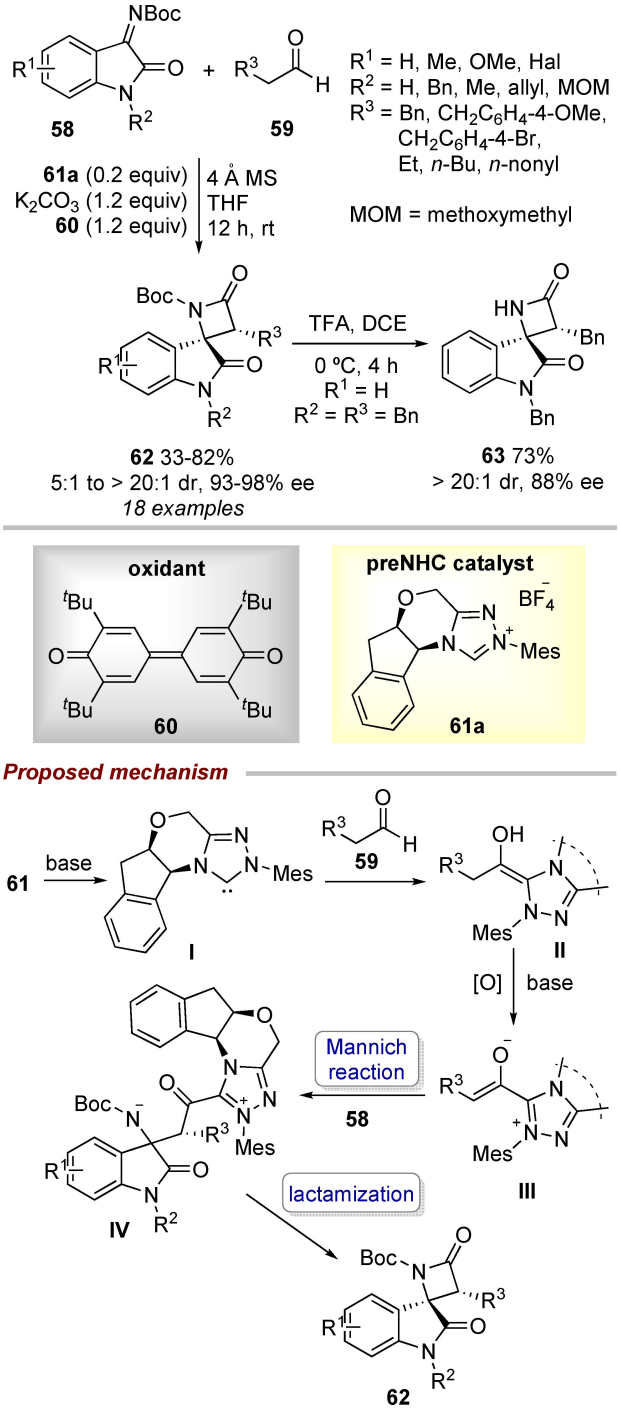
Scheme 14. Synthesis of spirocyclic *N*-vinyl-β-lactams from diazo-Meldrum's acids and acyclic α-diazocompounds and 2*H*-azirines or 5-alkoxyisoxazoles.

I which acts as a Reformatsky-type reagent on reacting with the imine to give spiro-β-lactam **57** in 48% yield.

Ren, Xu and co-workers synthesized a library of eighteen spiro-β-lactams **62** via the asymmetric [2+2] annulation of isatin derived imines **58** with simple aldehydes **59** (Scheme 16).[33] The reaction occurs through an oxidative N-heterocyclic carbene catalysis where the chiral triazolium enolate intermediate **III**, produced *in situ*, undergoes a highly stereoselective Mannich reaction with the isatin derived imines, being the enantioenriched spirooxindole-β-lactams generated by the subsequent intramolecular lactamization. The products of the reaction were obtained in moderate to good yields (33-82%) and with good to excellent diastereoselectivities and enantioselectivities (5:1 to > 20:1 and 93 to 98% ee, respectively). Further treatment of the spiro-β-lactams with trifluoroacetic acid (TFA) proved to be an effective method to remove the Boc protecting group, affording the free amine derived molecule without loss of diastereo- and enantioselectivity (*e.g.* spiro-β-lactam **63**).



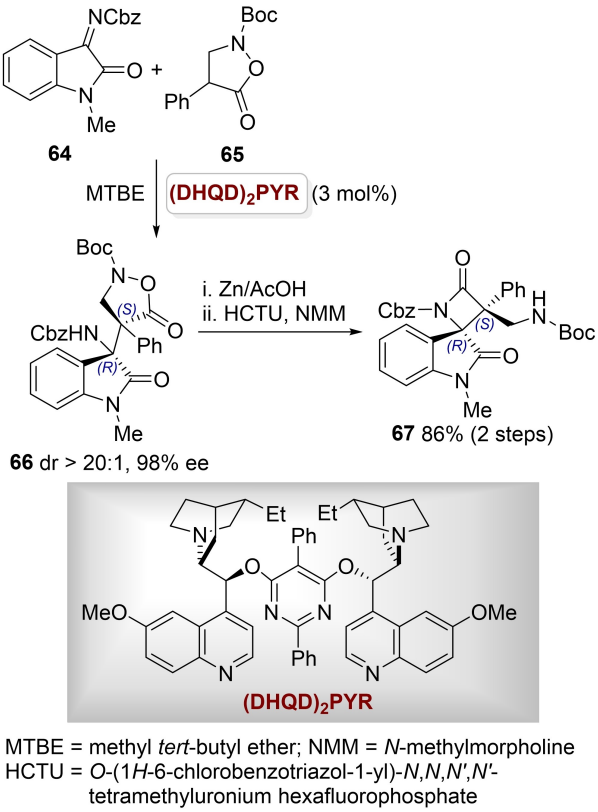
Scheme 15. Reductive Mannich-type reaction between an imine and an α,β-unsaturated ester.



Scheme 16. Oxidative NHC-catalyzed enantioselective [2+2] annulation of isatin derived imines with aldehydes.

The use of an isatin-derived Mannich adduct **66** for the synthesis of a spirooxindole-β-lactam **67** has also been reported (Scheme 17).[34] Racemic 4-substituted isoxazolidin-5-one **65** was used as precursor of the corresponding β-amino acid-type enolate which reacted with isatin derivative **64** via a catalytic Mannich reaction to give compound **66** in a process involving a diastereo- and enantioselective C–C bond-forming reaction with the construction of two adjacent stereocenters. The resultant Mannich adduct **66** had the N–O bond cleaved under reductive conditions affording a free carboxylic acid. In the presence of a coupling agent, the activated carboxylic acid underwent spontaneous intramolecular lactamization producing the spiro-β-lactam **67**. This molecule was obtained in 86% overall yield.

In 2019, Zhao, Deng and co-workers reported the synthesis of twenty-two enantioenriched spirooxindole-β-lactams **68** bearing two vicinal stereogenic centers.[35] The molecules were obtained in high yields (up to 98%), with good to high diastereoselectivities (up to 94:6) and excellent enantioselectivities (99 to > 99% ee) (Scheme 18). The reaction happens through a homobenzotetramisole (HBTM)-catalyzed Mannich/lactamization cascade reaction of isatin-derived imines **58** with aryl acetic acids **27**. Concerning the proposed reaction mechanism, the first step of the reaction involves a reaction between the aryl acetic acid **27** and pivaloyl chloride which generates a mixed anhydride **69**, responsible for the HBTM acylation which affords intermediate **I**. Intermediate **I** deprotonation results on C1-ammonium enolate intermediate **II** formation, which subsequent *si*-face-attack Mannich reaction affords intermediate **III**. On the last step of the



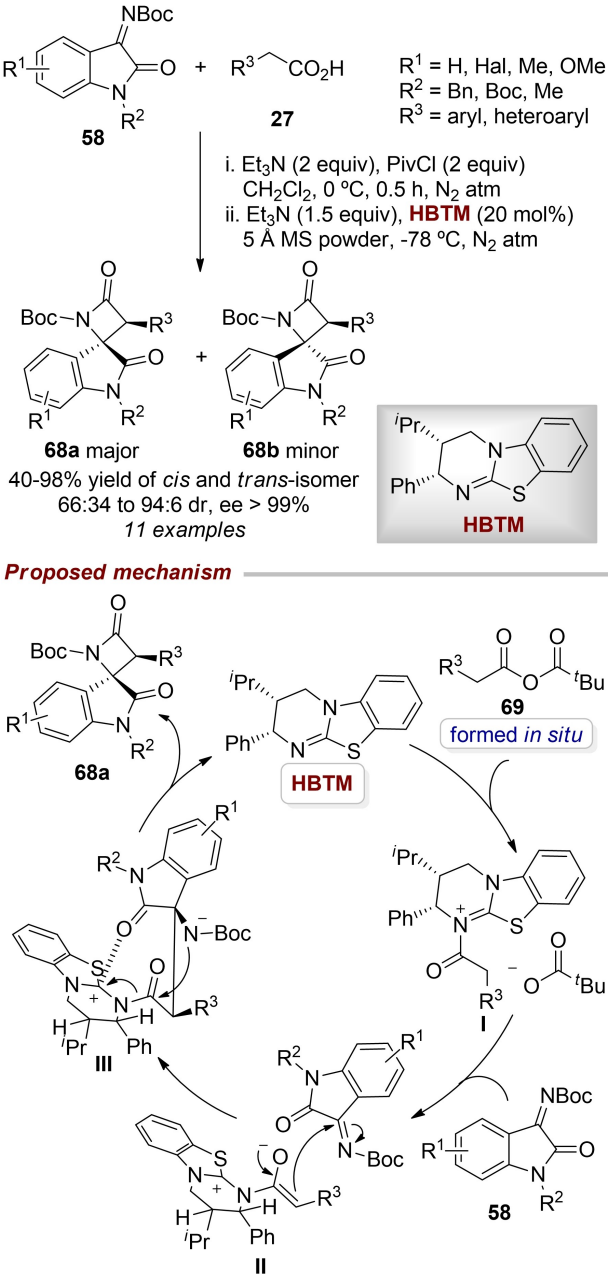
MTBE = methyl *tert*-butyl ether; NMM = *N*-methylmorpholine
HCTU = *O*-(1*H*-6-chlorobenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate

Scheme 17. Spiro-β-lactams synthesis from an isatin-derived Mannich adduct precursor.

catalytic cycle, intermediate **III** undergoes an intramolecular lactamization providing the desired *cis*-spirooxindole β-lactam product **68** and regenerating the HBTM catalyst.

2.1.3. Reformatsky Reaction

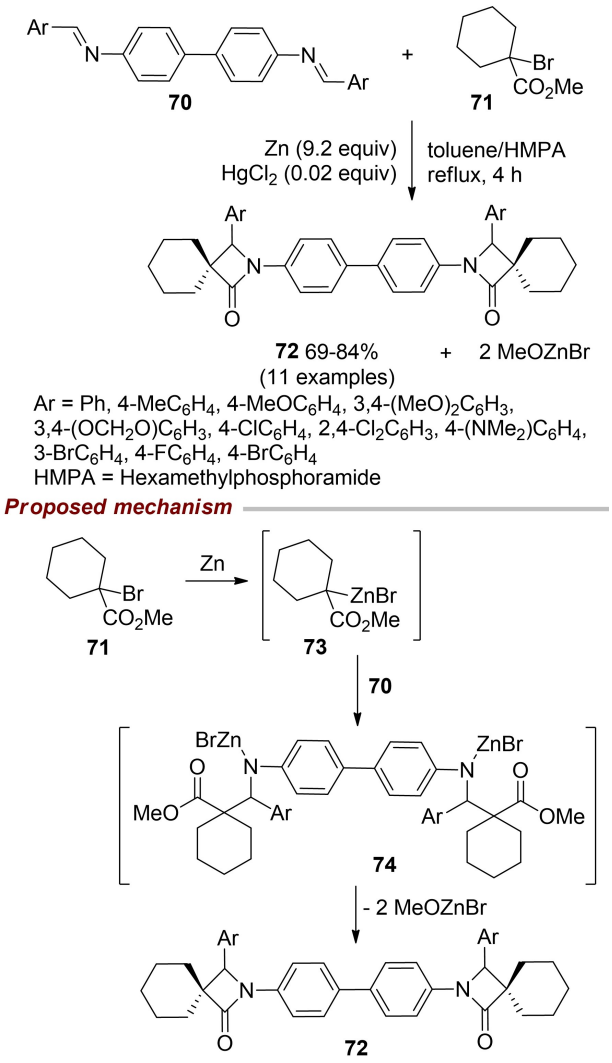
Apart from the conventional Staudinger cycloaddition and Mannich/lactamization cascade reactions, other synthetic approaches have been explored in order to synthesize spiro-β-lactams. Kirillov *et al.* synthesized a library of eleven bis(spiro-β-lactams) containing a spiro cyclohexane ring **72**, by exploring the Reformatsky reaction between methyl 1-bromocyclohexanecarboxylate **71** and *N*,*N*-bis(arylmethylidene)benzidines **70** as the first step (Scheme 19).[36] In the presence of Zn, methyl 1-bromocyclohexanecarboxylate forms Reformatsky reagent **73** which reacts with the bis-imine to form the corresponding adduct **74**. The adduct spontaneously cyclizes and forms the lactam ring, affording the bis-spiro-cyclohexane-β-lactam **72** with elimination of bromozinc methoxide. Bis(spiro-β-lactams) **72** were isolated in good yields (69-84%). The reaction was also expanded to synthesize nine spiro-cyclopentane containing β-lactams by using



Scheme 18. HBTM-catalyzed Mannich/lactamization cascade reaction of isatin-derived imines with aryl acetic acids.

methyl 1-bromocyclopentanecarboxylate as the starting carboxylate, in yields ranging from 54% to 84%.

The Reformatsky reaction was also used for the synthesis of spiro-β-lactam precursors. In this context, Zn/CuCl-mediated Reformatsky-type reaction of isatin-derived *N*-sulfinyl imine **75** was applied to the synthesis of the 2-oxoindolinyl-$\beta^{3,3}$-amino ester **76** in a diastereoselective fashion (Scheme 20).[37] Interestingly, the major product could be obtained in an enantiomeric pure form after column chromatography. The synthesis proceeds through three deprotection

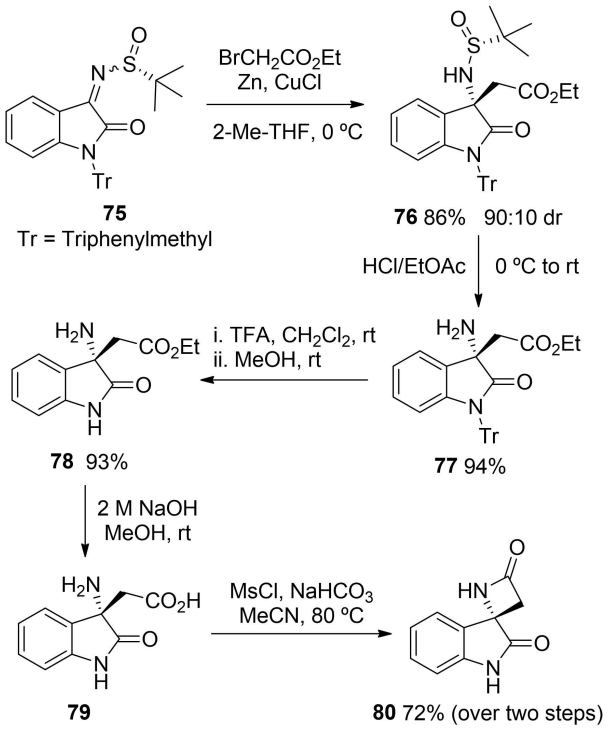


Scheme 19. Zinc-mediated reaction between a α-bromocycloalkanecarboxylate and *N*,*N*-bis(arylmethylidene)benzidines.

steps of 2-oxoindolinyl-$\beta^{3,3}$-amino ester **76** affording β-amino acid **79** which undergoes lactamization to give the alkaloid chartelline-core spirooxindole-β-lactam **80** in 63% overall yield.

2.1.4. Metal-Free Lactamization

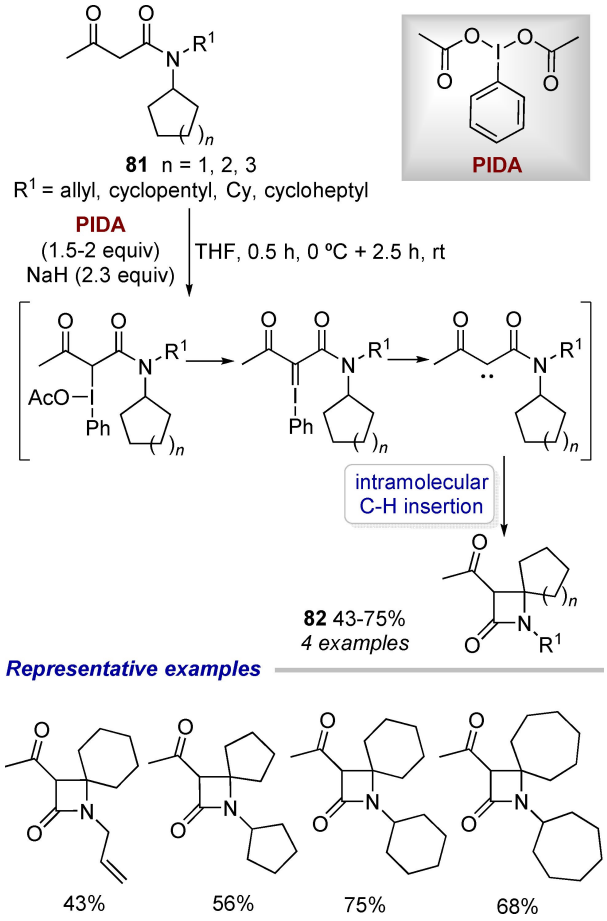
Afonso, Maulide and co-workers reported the synthesis of spirocyclic β-lactams **82** containing spiro-cycloalkanes moieties by a metal-free and diazo-free C–H insertion of simple β-ketoamide substrates **81**, through reaction with phenyliodine (III) diacetate (PIDA) in the presence of a base (Scheme 21).[38] The process starts with the formation of iodonium ylides, from the reaction of the β-ketoamide and PIDA, followed by loss of PhI resulting in the generation of carbene intermediates. DFT analysis of the reaction mechanism was consistent with the formation of reactive singlet



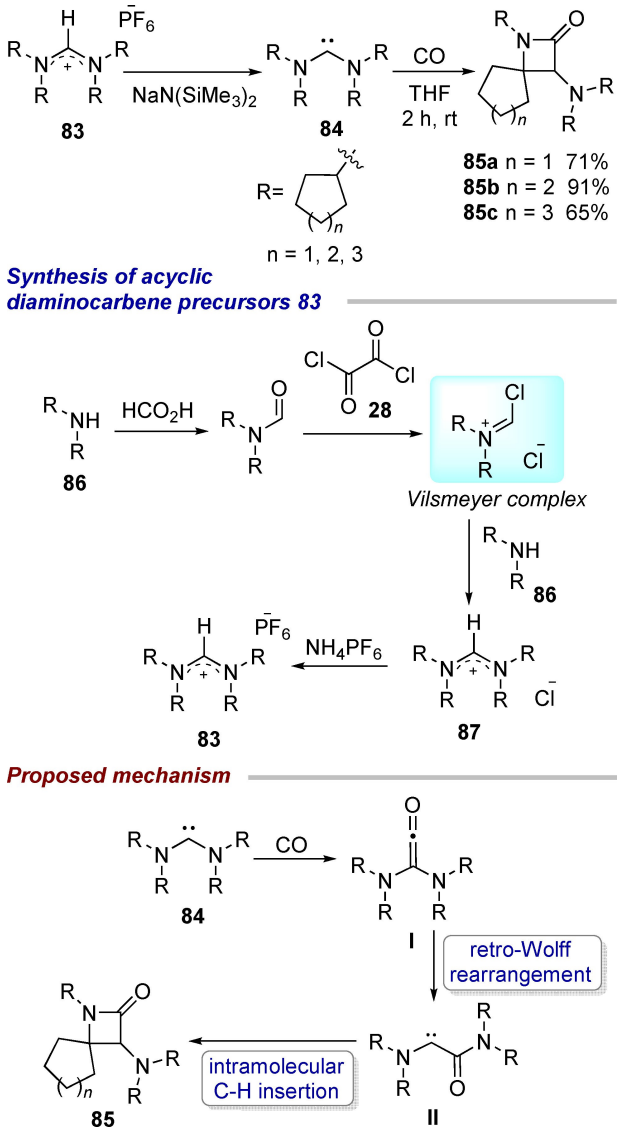
Scheme 20. Chartelline-core spirooxindole-β-lactam synthesis from a chiral 2-oxoindolinyl-$\beta^{3,3}$-amino ester.

carbenes as the limiting step. The lactamization was achieved via intramolecular C–H insertion reaction to give the corresponding racemic spiro-β-lactams in moderate to good yields (43–75% yield). The reported methodology circumvents the use of undesirable carbene precursors, such as diazo compounds, which disadvantage is their toxicity and potentially explosive behavior.

Siemeling *et al.* reported a metal-free synthetic methodology for the synthesis of racemic spiro-β-lactam derivatives **85** by exploring the reactivity of acyclic diaminocarbenes **84**, containing cycloalkyl substituents and using carbon monoxide as building block (Scheme 22).[39] The acyclic diaminocarbenes **84** were synthesized from secondary amines (*cyclo*-$C_nH_{2n-1})_2NH$ ($n = 5, 6, 7$). The amines were formylated with formic acid followed by the reaction with oxalyl chloride (**28**) to give the corresponding Vilsmeyer complex. The latter reacted with the secondary amines to afford formamidinium chlorides **87**. Anion exchange was performed with ammonium hexafluorophosphate to afford the corresponding formamidinium hexafluorophosphates **83** which were converted into carbenes **84** upon treatment with $NaN(SiMe_3)_2$. The synthesis of the spirocyclic β-lactams **85** is thought to proceed via carbonylation of the acyclic diaminocarbenes **84** leading to diaminoketenes **I** which undergo a retro-Wolff rearrangement to give (amido)(amino)carbenes **II** followed by an intramolecular C–H insertion to



Scheme 21. Metal-free C–H insertion of β-ketoamide substrates in the presence of PIDA and base.

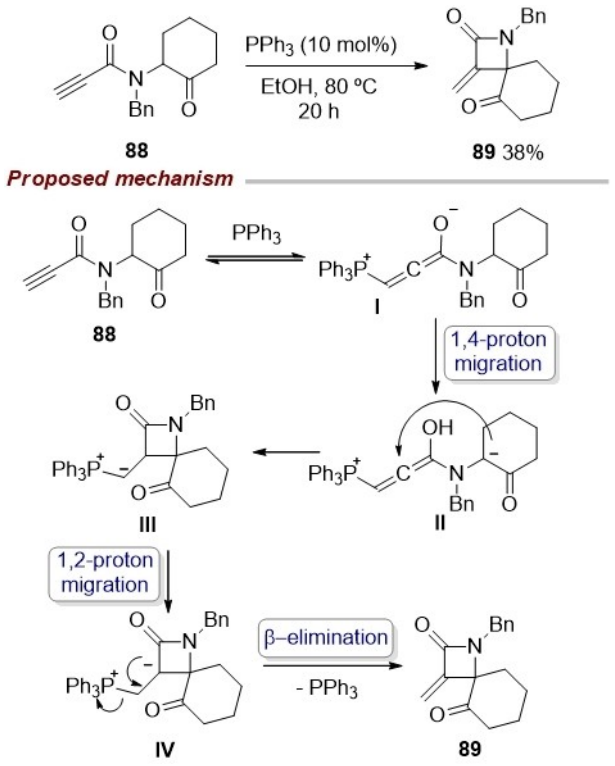


Scheme 22. Carbonylation of acyclic diaminocarbenes leading to spiro-β-lactams containing cycloalkyl substituents.

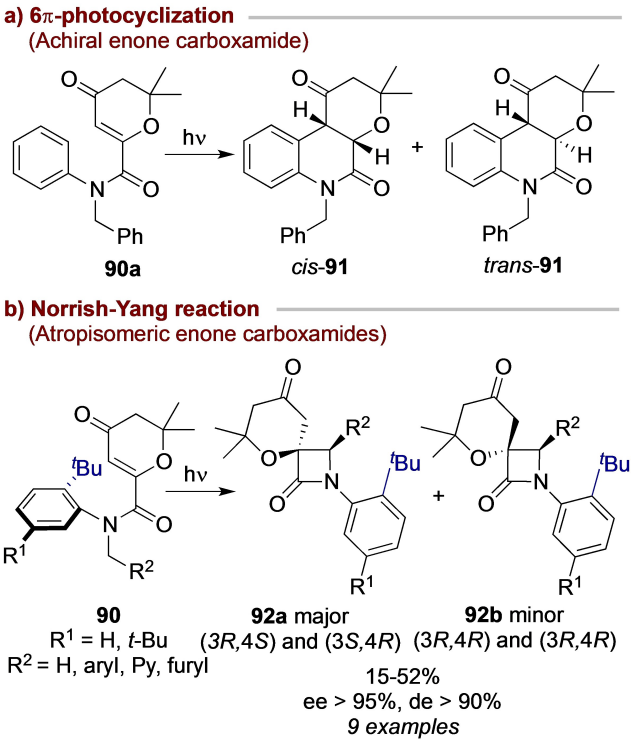
afford the final products in yields ranging from 65% to 91%.

Li and co-workers develop a route to α-methylene-β-lactams through a PPh_3-catalyzed umpolung cyclization of propiolamides. The reported methodology was applied to the synthesis of α-methylene-spiro-β-lactam **89** obtained in 38% yield (Scheme 23).[40] The proposed mechanism comprises the conjugated addition of triphenyl phosphine to the propiolamide ketone **88** generating zwitterionic intermediate **I** which undergoes a 1,4-proton migration to give anionic ketone **II**. This intermediate undergoes a 4-*exo* intramolecular conjugated addition generating spiro-β-lactam intermediate **III**, which is converted into α-methylene-spiro-β-lactam **IV** through 1,2-proton migration. The subsequent β-elimination affords the final product **89** and regenerates the phosphine.

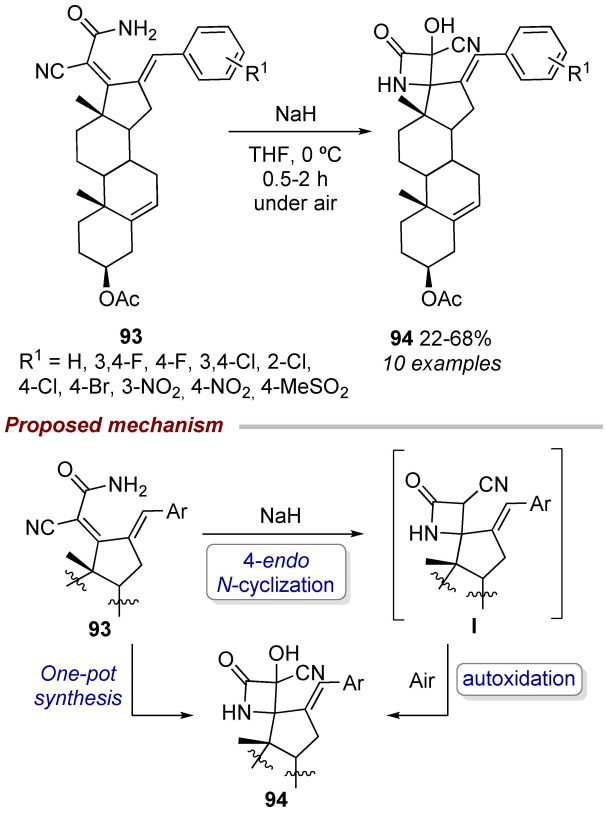
The Sivaguru group demonstrated that photo-induced reaction of achiral and atropisomeric enones **90** display divergent reactivity based on restricted bond rotations.[41] Photocyclization leading to 3,4-dihydroquinolin-2-one **91** via 6π-photocyclization was observed with achiral enone carboxamide **90 a** whereas atropisomeric enone carboxamides **90** underwent hydrogen abstraction leading to spiro-β-lactams **92** via Norrish-Yang reaction (Scheme 24). The restricted bond rotation in the atropisomeric systems, due to steric hindrance, allows these substrates to undergo chirally preorganization during the photochemical transformation and to translate their chiral information to the photoproducts, "axial to point chirality transfer". In fact, computational studies revealed that the synthesis of spiro-β-lactams **92** from atropisomeric enones was dictated by the relative orientations of the benzylic group and the bulky *ortho*-(*t*-butyl) substituent in the enones. Nine different spiro-β-lactam photoproducts **92** were obtained with ee > 95% and de > 90% by this synthetic strategy.



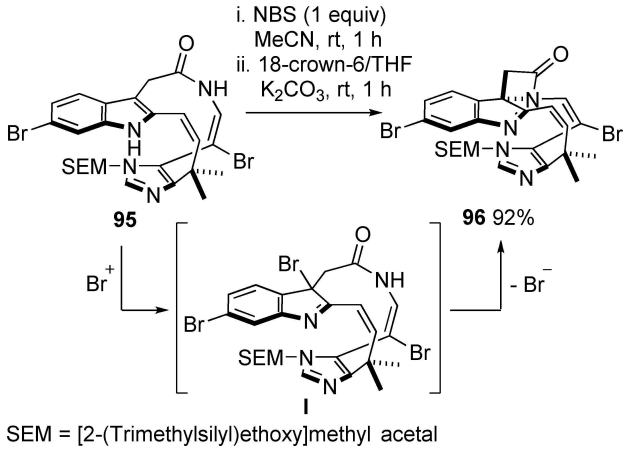
Scheme 23. PPh_3-Catalyzed umpolung cyclization of a propiolamide ketone.



Scheme 24. Divergent photo-induced transformation of achiral and atropisomeric enone carboxamides.

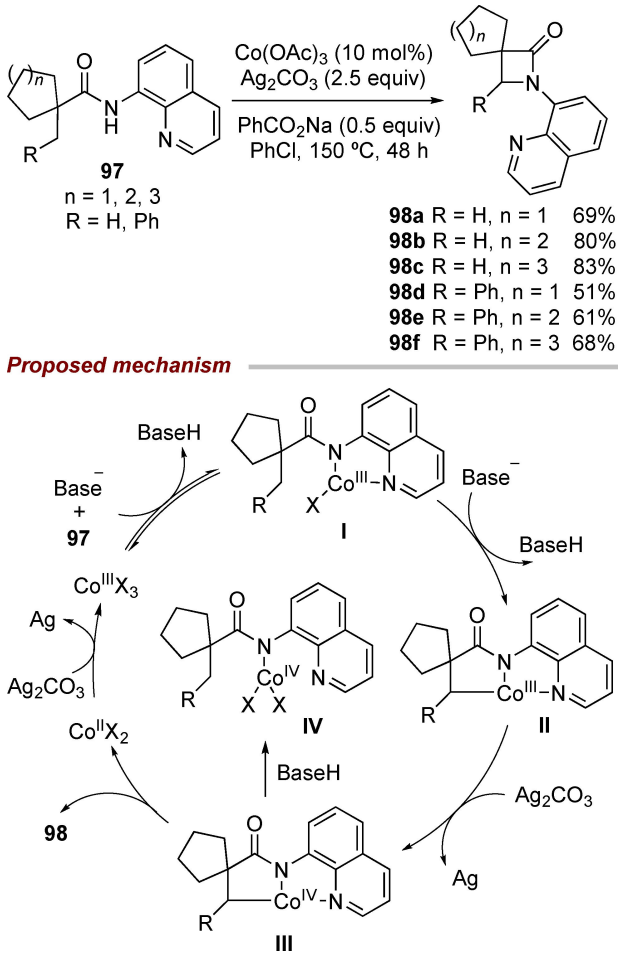


Scheme 25. Steroidal spiro-β-lactams synthesis from dienamides through a cascade 4-*endo* *N*-cyclization/aerobic oxidation sequence.

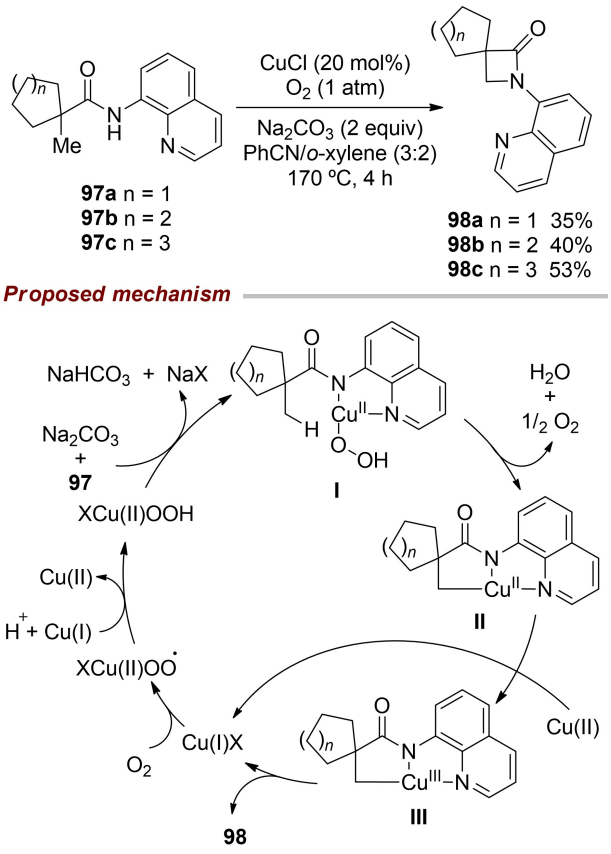


Scheme 26. Chartelline-core spiro-indolenine-β-lactam synthesis via bromide-mediated spiro-lactamization of a bromoenamide.

The synthesis of steroidal spiro-β-lactams **94**, bearing a cyanohydrin functional group, from steroidal dienamides **93** has been reported (Scheme 25).[42] The spirocyclic products were obtained in low to moderate yields (22–68%) under mild conditions and short reaction time in a one-pot procedure. The proposed



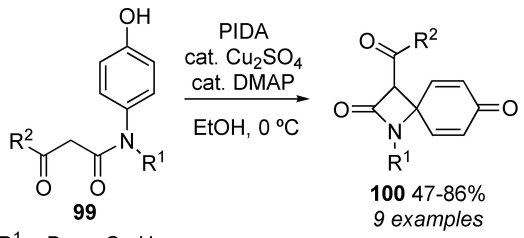
Scheme 27. Cobalt-catalyzed site-selective direct functionalization of unactivated C(sp^3)–H of aliphatic amides.



Scheme 28. Copper-catalyzed site-selective functionalization of unactivated C(sp^3)–H of aliphatic amides.

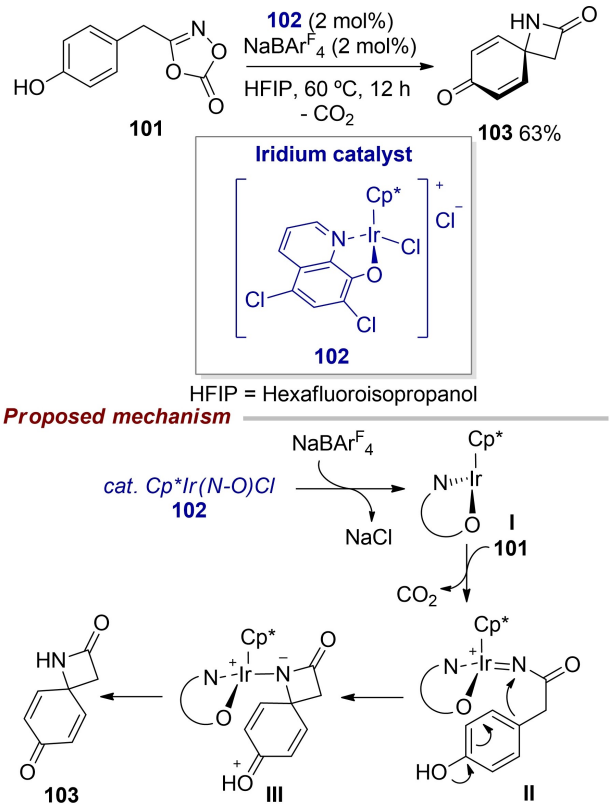
synthetic pathway involves an intramolecular lactamization of steroidal dienamides **93** via a selective 4-*endo* *N*-cyclization followed by a base-mediated aerobic oxidation which introduces a hydroxyl group at the α-position of the 2-azetidinone ring, generating the final spirocyclic product **94**. It is noteworthy that two continuous chiral centres are formed simultaneously upon the 2-azetidinone ring generation process and no 6-*endo* *N*-cyclization products were observed. However, no information regarding the stereochemistry of the spiro carbon is disclosed. Nevertheless, the present class of steroidal spiro-β-lactams having a cyanohydrin moiety on its structure is of major relevance for structural modulation purposes.

Recently, Nishikawa *et al.* disclosed the synthesis of a spiro-indolenine-β-lactam **96** analogue to alkaloid chartelline C (Scheme 26).[43] The two-step synthesis comprised the initial formation of a bromoindolenine intermediate **I** via a *N*-bromosuccinimide (NBS)-mediated chemoselective bromination of bromoenamide **95** at C3 followed by intramolecular lactamization in the presence of 18-crown-6 and K_2CO_3. The



Scheme 29. Spirocyclohexadienone-β-lactams from β-keto amides derived from 4-aminophenol.

target spirocyclic indolenine-β-lactam **96** was obtained in 92% yield.

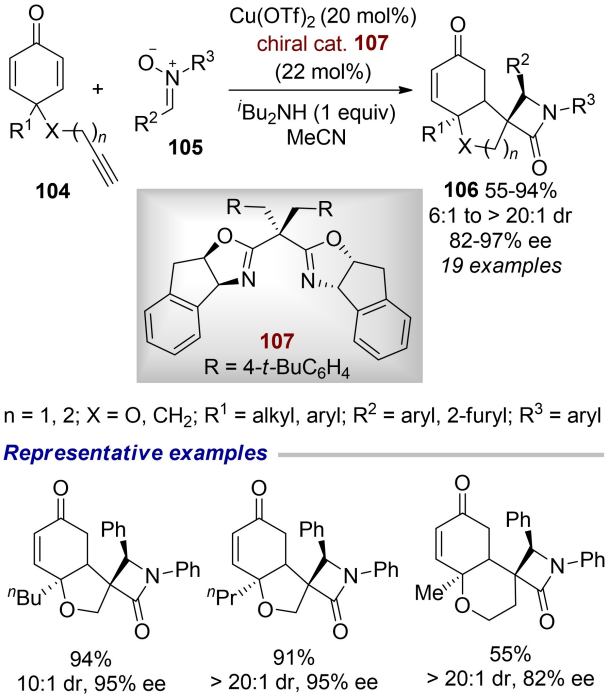


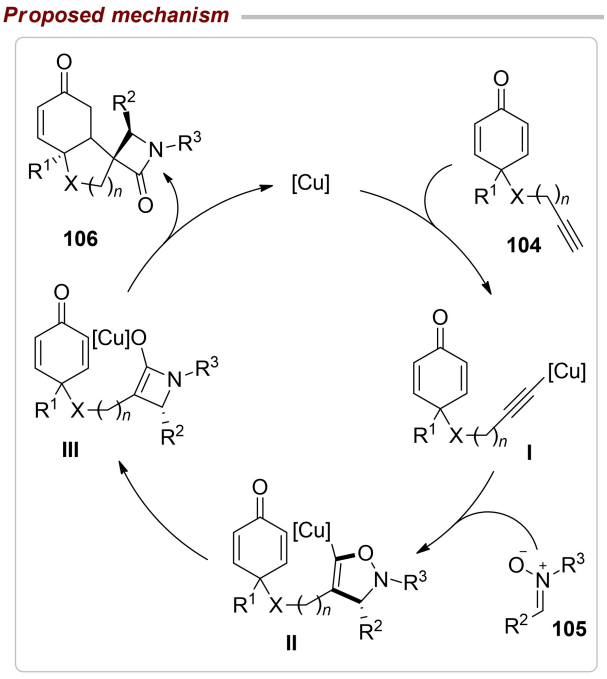
Scheme 30. Iridium-catalyzed dearomative spirocyclization of a phenol-based dioxazolone.

2.1.5. Metal-Catalyzed Lactamization

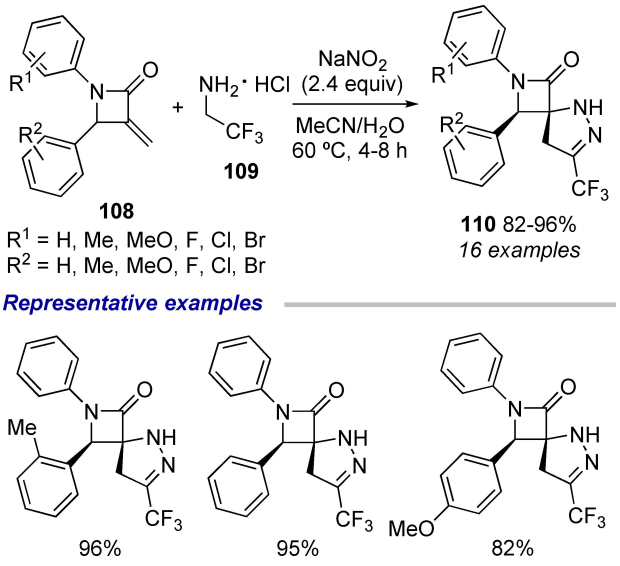
Li, Ge and co-workers reported a metal-catalyzed cyclization via dehydrogenative amidation of unactivated C(sp^3)–H for the synthesis of spirocyclic β-lactams.[44] In this context, spirocycloalkane β-lactams **98** containing a 8-quinolinyl functional group were obtained from the cobalt-catalyzed site-selective direct C(sp^3)–H functionalization of amides **97** with the aid of the quinolinyl group, a bidentate directing group (Scheme 27). The method affords the spirocyclic β-lactam products in moderate to good yields (51–83%) and it was proven that it can also be used for the synthesis of spiro-γ-lactams. A plausible catalytic cycle for the formation of the spiro-β-lactams is proposed in this work. The first step comprises the Co^{III} complex **I** generation where amide **97** coordinates with a cobalt species followed by a ligand exchange process under basic conditions. Intermediate **I** produces intermediate **II**, through cyclometallation in a presumably irreversible step. Oxidation of the latter intermediate with Ag_2CO_3 gives rise to the Co^{IV} complex **III**, affording the spiro-β-lactam product **98** upon reductive elimination. The produced Co^{II} species could then be re-oxidized to the Co^{III} species restarting the catalytic cycle.

In the same year, Yang, You and co-workers also synthesized the same 2-(quinolin-8-yl)-2-azaspiro[3.4] alkan-1-ones **98 a-c** through metal-catalyzed intramolecular amidation of unactivated C(sp^3)–H (Scheme 28).[45] However, in this approach the spiro-β-

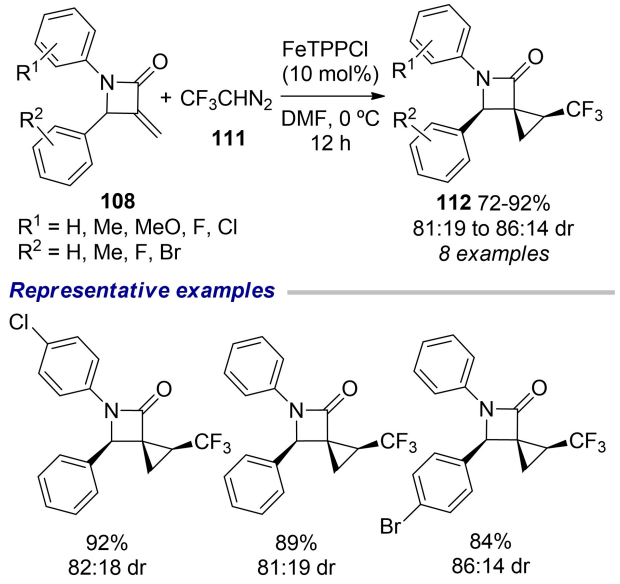




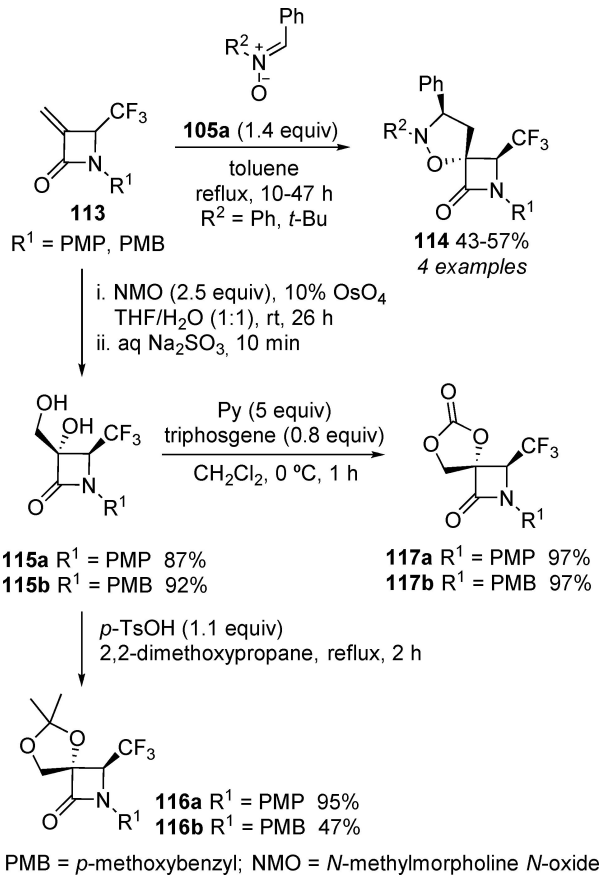
Scheme 31. Copper-catalyzed Kinugasa/Michael domino reaction between alkyne-tethered cyclohexadienones and nitrones.



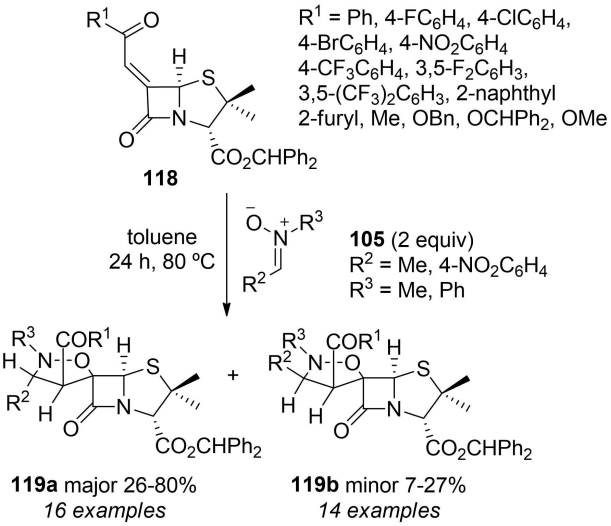
Scheme 32. [3+2] Cycloaddition of *in situ* generated 2,2,2-trifluorodiazoethane with α-methylene-β-lactams.



Scheme 33. Iron-catalyzed cyclopropanation of α-methylene-β-lactams with with 2,2,2-trifluorodiazoethane.

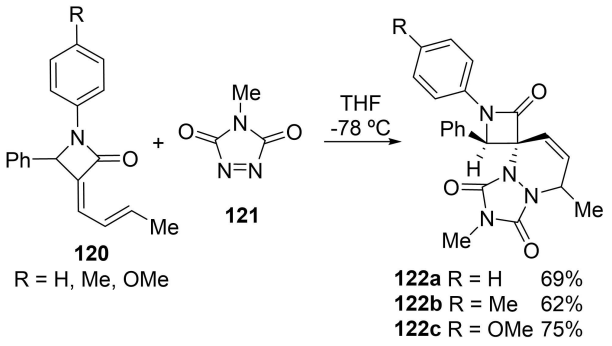


Scheme 34. 3-Methylene-4-(trifluoromethyl)azetidin-2-ones as building blocks for the synthesis of trifluoromethyl-containing spiro-β-lactams.

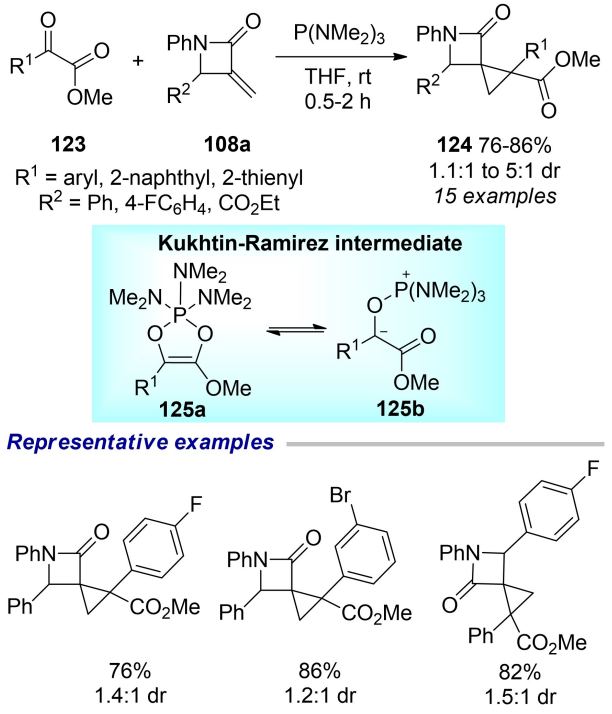


Scheme 35. 1,3-Dipolar cycloaddition between nitrones and 6-alkylidenepenicillanates.

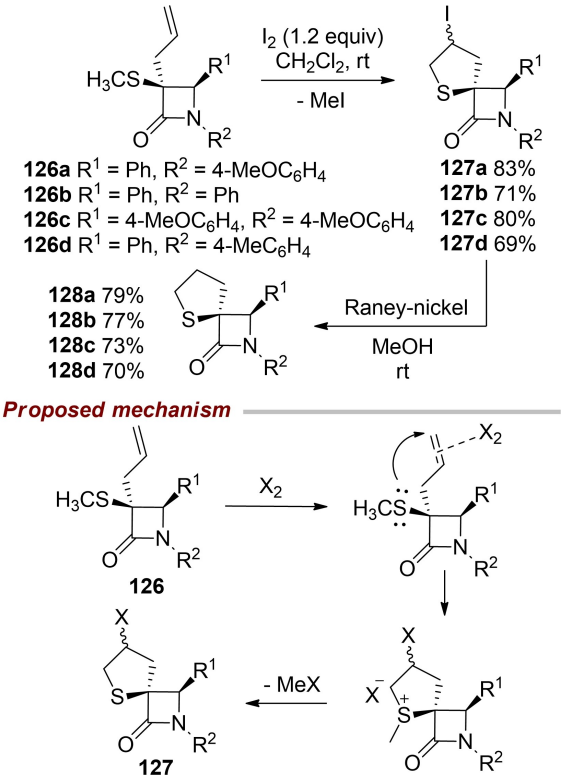
lactams **98** were obtained using oxygen as oxidant and Cu(II) as co-oxidant. Radical trapping experiments were carried, using 2,6-di-*tert*-butyl-*p*-cresol as radical inhibitor, indicating that a radical process may be involved. This observation supports the proposed mechanism, which starts with the reaction of Cu(I) with O_2 to afford a Cu(II)-superoxide radical, which undergoes electron transfer oxidation and H-abstraction to produce a Cu(II)-hydroperoxo species. Coordination with amide **97** affords *N*,*N*-chelated copper complex **I** which undergoes C(sp^3)–H cupration giving intermediate **II**, which is converted into Cu(III) complex **III** via a disproportionation process. Reduc-



Scheme 36. [4+2] Cycloaddition reaction between α-alkylidene-β-lactams and 4-methyl-[1,2,4]triazole-3,5-dione.



Scheme 37. $P(NMe_2)_3$-Mediated cyclopropanation of α-methylene-β-lactam.



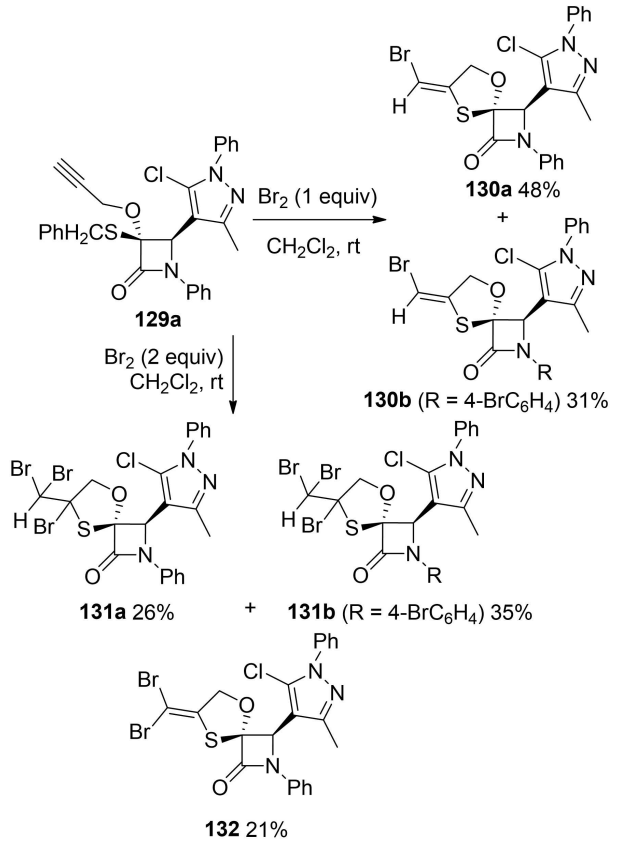
Scheme 38. Iodine-mediated intrasulfenyl cyclization reaction of 3-allyl-3-methylthio-β-lactams.

tive elimination of the latter gives spiro-β-lactam **98** together with the formation of Cu(I) species. This aerobic oxidative functionalization of $C(sp^3)$–H bonds presents itself as a more economical route, although it provides the target molecules in slightly lower yields (35–53%).

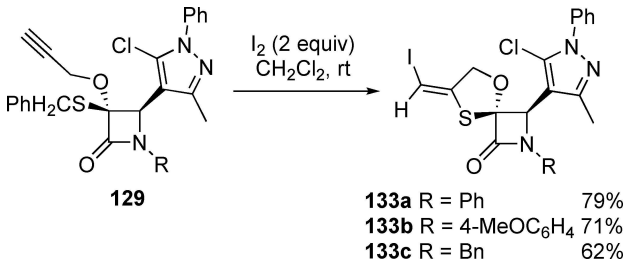
The synthesis of spirocyclohexadienone-β-lactams **100** with alkyl substituents from β-keto amides **99** derived from 4-aminophenol has been reported (Scheme 29).[46] The intramolecular lactamization occurs through a PIDA-mediated oxidative process catalyzed by *N*,*N*-dimethyl-4-aminopyridine (DMAP) and copper sulfate. Spiro-β-lactams **100** were obtained in moderate to good yields (47–86%). Four of these spirocyclic compounds proved to be active against *P. falciparum* 3D7 strain (IC_{50} = 1.35-9.78 μM). The synthetic methodology was also suitable for the synthesis of spiro-γ-lactams.

Chang and co-workers explored an iridium-catalyzed dearomative spirocyclization reaction of phenol dioxazolone substrate **101** for the synthesis of spiro-β-lactam **103** (Scheme 30).[47] This synthetic strategy relies on an arene $C(sp^2)$–H amidation step through intramolecular transfer of iridium nitrenoids and afforded the spirocyclic product **103** in moderate yield (63%). The reaction mechanism was proposed based on both experimental and computational results and comprises a first step of coordination between the activated iridium catalyst **I** and phenol dioxazolone **101** and subsequent release of a carbon dioxide molecule, generating Ir-nitrene **II**. The latter intermediate **II** then affords the target spiro-β-lactam **103**, through amidation via electrophilic aromatic substitution followed by removal of the phenolic proton.

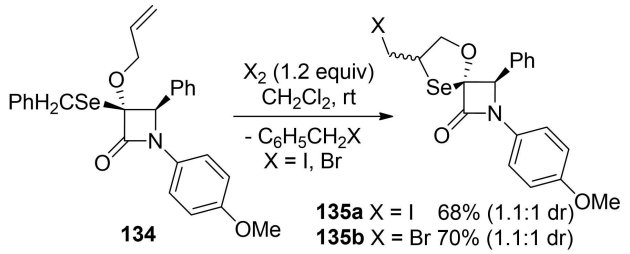
Enders *et al.* reported the synthesis of highly functionalized spirocyclic β-lactams **106** possessing four contiguous stereocenters, through a highly chemo-, regio-, diastereo-, and enantioselective copper-catalyzed Kinugasa/Michael domino reaction between alkyne-tethered cyclohexadienones **104** and nitrones **105** (Scheme 31).[48] The reaction uses $Cu(OTf)_2$ as a



Scheme 39. Bromine-mediated intrasulfenyl cyclization of *cis*-3-(prop-2'-ynyloxy)-4-pyrazolyl-β-lactams.



Scheme 40. Iodine-mediated intrasulfenyl cyclization of *cis*-3-(prop-2'-ynyloxy)-4-pyrazolyl-β-lactams.



Scheme 41. Halogen-mediated intraselenyl cyclization of a *cis*-3-allyloxy-3-benzylselenoazetidin-2-one.

copper source and indane-BOX chiral ligand **107**. The spiro-β-lactams were obtained in moderate to excellent yields (55–94%) and with excellent stereoselectivity (up to 97% ee, > 20:1 dr). The proposed reaction mechanism includes the initial *in situ* Cu(II) reduction to give copper acetylide intermediate **I**, which undergoes a [3 + 2] dipolar cycloaddition with the nitrone generating a copper-bound isoxazoline intermediate **II**. A rearrangement produces the tethered four-membered copper enolate intermediate **III**, which reacts by means of a desymmetric Michael addition, generating the spirocyclic β-lactam product **106** and regenerating the copper catalyst.

2.2. Non-β-Lactam Ring Synthesis

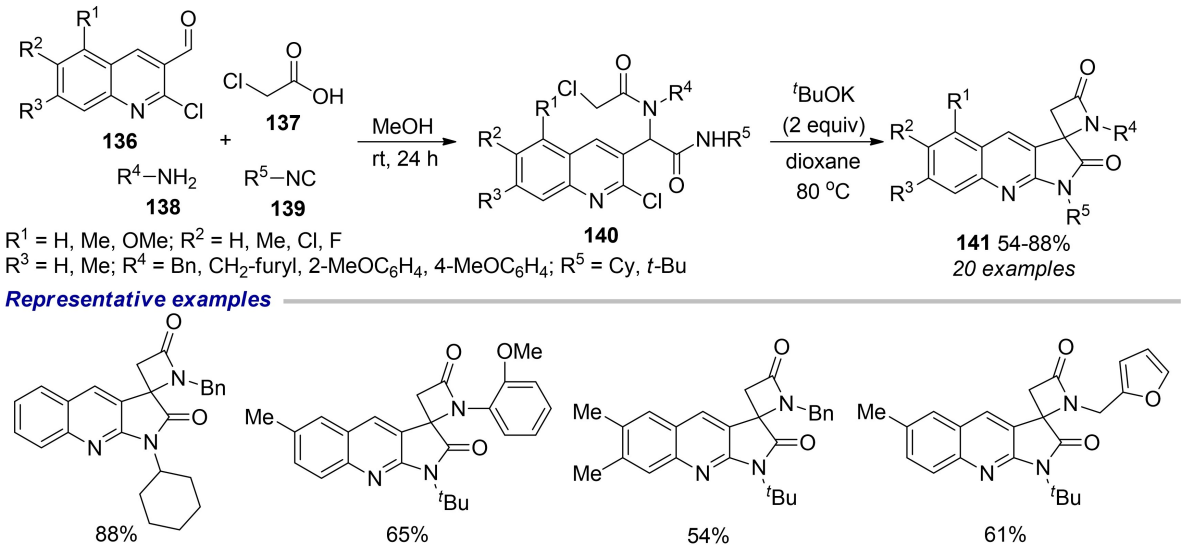
2.2.1. Spiro-β-lactams from α-Alkylidene-β-Lactams

The spirocyclic lactam scaffold can also be attained starting from lactam precursors, taking advantage of the reactivity of exocyclic substituents on the lactam ring, namely exocyclic double bonds. Given their double bond reactivity, α-alkylidene-β-lactams are prone to undergo epoxidation, cyclopropanation, Diels-Alder reactions, and 1,3-dipolar cycloaddition reactions, serving as precursor to numerous classes of spiro-β-lactams.

The [3 + 2] cycloaddition of *in situ* generated 2,2,2-trifluorodiazoethane with several α-methylene-β-lactams **108**, under metal-free conditions, affording trifluoromethyl-containing spirocyclic β-lactams has been reported (Scheme 32).[49] Various aromatic substituents proved to be well tolerated in this stereoselective transformation. The procedure resulted on the synthesis of sixteen different racemic 2-pyrazoline-containing spiro-β-lactams **110**, in good to excellent yields (82–96%).

It was observed that the use of an iron catalyst leads to a different reaction outcome. In fact, reacting α-methylene-β-lactams **108** with 2,2,2-trifluorodiazoethane (**111**) in the presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine iron(III) chloride (FeTPPCl) results in the formation of cyclopropanation products (Scheme 33).[49] The synthetic approach afforded racemic spiro-β-lactams **112** containing a spirocyclopropane moiety in good yields (79–92%) and good diastereoselectivity (81:19 dr to 86:14 dr).

D'hooghe and co-workers used 3-methylene-4-(trifluoromethyl)azetidin-2-ones **113** as building blocks for the synthesis of different classes of spiro-β-lactams (Scheme 34).[50] The 1,3-dipolar cycloaddition with *N*-phenyl- or *N*-*tert*-butyl-α-phenylnitrones **105a** in toluene under reflux afforded racemic 7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **114** in moderate yields (43–57% yield). On the other hand, 3-methylene-4-(trifluoromethyl)azetidin-2-ones **113** underwent OsO_4-mediated oxidation to give



Scheme 42. Synthesis of spirocyclic bis-α,γ-lactams from four-component Ugi-adducts precursors.

vicinal diols **115**. These molecules served as precursors in the synthesis of two classes of spiro-β-lactams, compounds **116** and **117**. Thus, acetalization with *p*-TsOH in 2,2-dimethoxypropane under reflux afforded 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-ones **116** in moderate to high yields. On the other hand, by reacting diols **115** with triphosgene in dichloromethane in the presence of pyridine, racemic CF_3-substituted spirocycles **117** were obtained in high overall yields.

The use of nitrones **105** as dipoles in 1,3-dipolar cycloadditions with 6-alkylidenepenicillanates **118** to synthesize spiro-β-lactams was explored by Pinho e Melo *et al.* (Scheme 35).[51] This approach, comprising the generation of three new consecutive stereogenic centers, proved to be regio- and stereoselective and afforded chiral spiroisoxazolidine-penicillanates **119** in moderate to good overall yields, using mild conditions. The major products **119a** were obtained through an *endo* 1,3-dipolar cycloaddition with addition of the nitrone to the α-side of the β-lactam and were obtained efficiently (26–80% yield). On the other hand, the stereoisomeric *exo*-cycloadducts **119b** were isolated as minor products (7–27% yield). It is noteworthy that the two cases were stereospecific as they only afforded the major product **119a**.

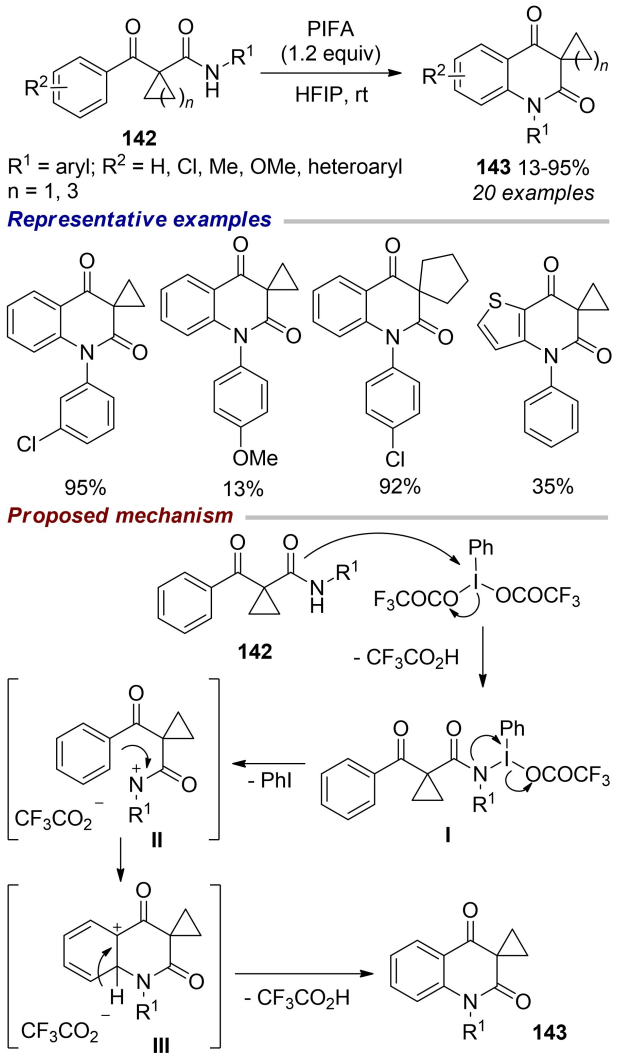
Bhargava *et al.* explored the synthesis of spiro-β-lactams through [4+2] cycloaddition reactions between α-alkylidene-β-lactams **120** and 4-methyl-[1,2,4]triazole-3,5-dione **121**, yielding racemic spiro[[1,2,4]triazolo[1,2-*a*]pyridazine-5,3'-azetidine]-1,2',3(2*H*,8*H*)-triones **122** in good yields (62–75%) (Scheme 36).[52]

Recently Luo *et al.* reported a phosphine-mediated reductive cyclopropanation reaction of α-methylene-β-lactams **108a** with α-keto esters **123** (Scheme 37).[53] This metal-free protocol provides the efficient synthesis of highly functionalized spirocyclopropyl β-lactams **124** through a mechanism involving the initial oxophilic addition of the phosphine to α-ketoester to generate Kukhtin-Ramirez intermediates (*e.g.* oxyphosphonium enolate **125b**), which dipolar structure can behave as a carbene surrogate. Subsequent Michael addition of these intermediates to the electron deficient β-lactam exocyclic double bond followed by a 3-*exo-tet* cyclization furnishes spirocyclic lactams as diastereoisomeric mixtures.

2.2.2. Halogen-Mediated Cyclization

Halogen-mediated (I_2, Br_2) cyclization reactions proved to be an alternative to building spirocyclic β-lactams from conventional β-lactams. Bari *et al.* synthesized halospiro-β-lactams **127** through *cis*-3-allyl-3-methylthio-β-lactams **126** intrasulfenyl cyclization reaction in the presence of molecular iodine, affording iodospirocyclic products isolated as diastereoisomeric mixtures in good yield (69–83%) (Scheme 38).[54] These diastereoisomeric mixtures were subjected to dehalogenation reaction using Raney-nickel to give **128** efficiently.

The synthesis of the spirocyclic brominated analogues was proven to be feasible in the presence of bromide as the halogen. However, a slight decrease in the yield was observed (*e.g.* 58% and 67%, for **127a** and **127b** brominated analogues, respectively). [54] A general mechanism proposed for the construction of the spirocyclic system relies on a first step of halogen interaction with the double bond followed by a stepwise nucleophilic addition-dealkylation sequence, which is in agreement with the seminal work of Turos and co-workers.[55]



Scheme 43. PIFA-mediated oxidative intramolecular cyclization of 2,2-disbustituted-2-benzoylacetamides.

Racemic halogenated 4-pyrazolylspiro-β-lactams have also been prepared through halogen-mediated intrasulfenyl cyclization of *cis*-3-(prop-2'-ynyloxy)-4-pyrazolyl-β-lactams **129** (Scheme 39).[56] Depending on the number of equivalents of Br_2 used, different halogenated spirocyclic β-lactams were obtained. These products result not only from de intrasulfenyl cyclization but also from polybromination, namely phenyl group electrophilic aromatic substitution reaction or double bond bromine electrophilic addition, and hydrobromic acid elimination events from the trihalogenated derivatives (*e.g.* **131 a**). The reaction was found to be general to other similar substrates such as the analogues containing a benzyl or a 4-methoxyphenyl amine protecting group instead of the phenyl group.

The reaction of *cis*-3-(prop-2'-ynyloxy)-4-pyrazolyl-β-lactams **129** performed with iodine proved to be more chemoselective, as monoiodinated 4-pyrazolyl-spirocyclic-β-lactams **133** were obtained efficiently as sole products (Scheme 40).[56]

Bhalla *et al.* used a similar method for the synthesis of 4-halomethyl-1,3-oxaselenolane substituted spiro-β-lactams **135** via intraselenyl cyclization of *cis*-3-allyloxy-3-benzylselenoazetidin-2-one **134** mediated by halogens, namely I_2 and Br_2 (Scheme 41).[57] Both halogens gave similar yields (68-70% yield). The mechanism involves the initial generation of a π-olefinic complex by coordination of the halogen to the alkene moiety followed by a stepwise nucleophilic addition-dealkylation sequence to provide spiroseleno-β-lactams, in a pathway similar to the one proposed for C3 halospiro-β-lactams **127** synthesis (see Scheme 38).

2.3. β-Lactam and Non-β-Lactam Ring Synthesis

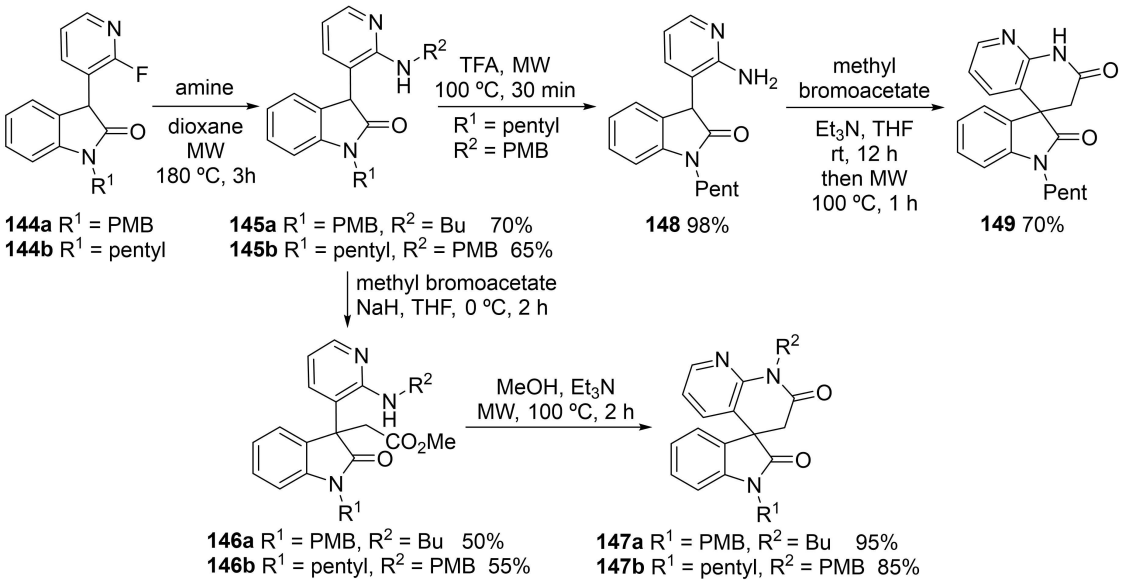
Al-Harrasi, Balalaie and co-workers described the synthesis of a library of spiropyrroloquinoline β-lactams **141** using four-component Ugi-adducts **140** as precursors (Scheme 42).[58] These spirocyclic bis-β,γ-lactams were obtained as racemic mixtures in moderate to high yields (54–88%). The Ugi-adducts **140** were synthesized through a four-component reaction of 2-chloro-3-formyl quinolines **136**, 2-chloroacetic acid (**137**), amines **138**, and isocyanides **139**. The proposed spirocyclization mechanism relies on two sequential cyclization steps of the Ugi-adduct, under basic conditions. The first cyclization involves the γ-lactam ring formation via intramolecular aromatic nucleophilic substitution, whereas the construction the β-lactam ring was achieved through a nucleophilic substitution.

3. Spiro-δ-Lactams

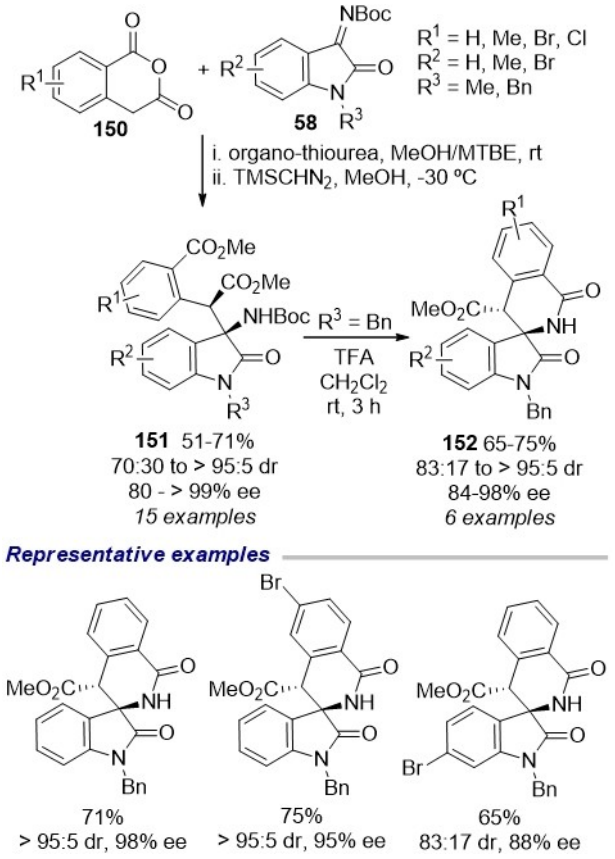
3.1. δ-Lactam Ring Synthesis

3.1.1. Nucleophilic Cyclization Reaction

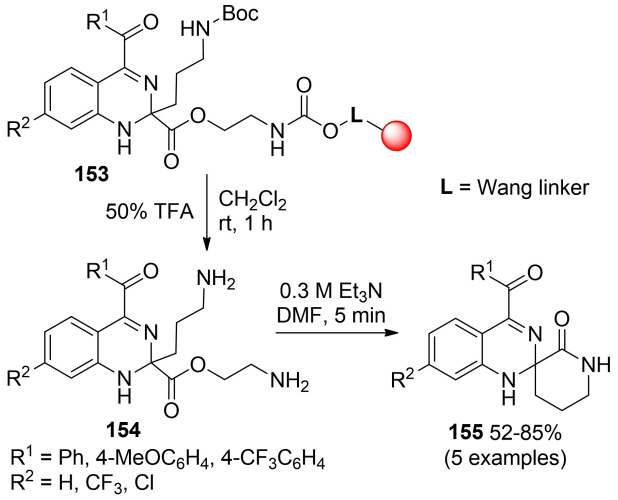
Spirocyclopropane- and spirocyclopentane-δ-lactams were obtained from 2-benzoylacetamides via an organoiodine-mediated oxidative ring-closing reaction.[59] The method involves the cyclization of 2,2-disubstituted-2-benzoylacetamides **142** in the presence of a non-metal oxidant, [bis(trifluoroacetoxy)iodo]benzene (PIFA), to give spirocarboxylic δ-lactams **143** in yields ranging from 13% to 95% (Scheme 43). The reaction displays good tolerance for aromatic amides, however no reaction was observed with aliphatic amides (R^1 = Bn, *n*-Bu). The proposed mechanism starts with the oxidation of substrate **142** with PIFA with the loss of a single molecule of trifluoroacetic acid. This step forms intermediate **I** which is converted into *N*-acylnitrenium ion **II** by iodobenzene release. Next, nucleophilic attack of the aryl moiety to the nitrenium ion **II**



Scheme 44. Microwave-assisted cyclization of *N*-protected-3-(2-aminopyridyl)oxindoles.



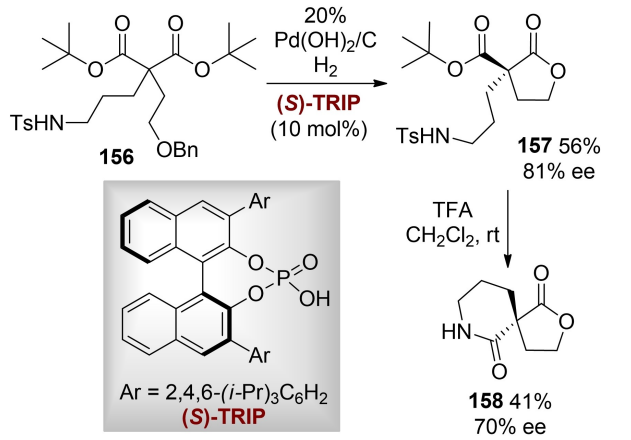
Scheme 45. TFA-mediated *N*-Boc deprotection/intramolecular *N*-acylation reaction of oxoindole-derived α-aryl-β-amino acids.



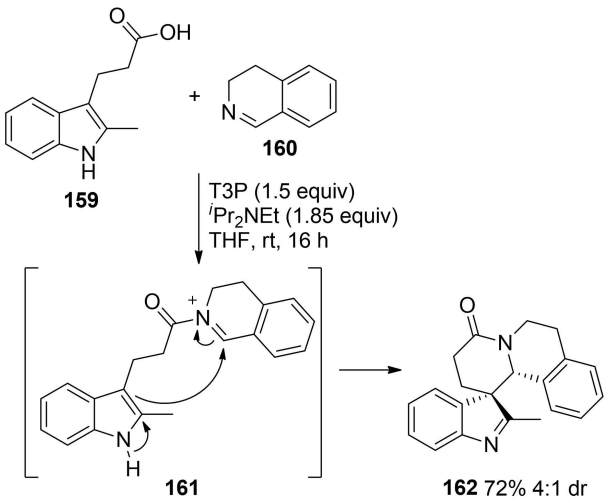
Scheme 46. Synthesis of spiroquinazoline-δ-lactams via lactamization of 1,2-dihydroquinazoline-2-carboxylates.

generates intermediate **III**, which undergoes further deprotonation to give the final product **143**.

The microwave-assisted cyclization of substituted *N*-protected-3-(2-aminopyridyl)oxindoles has been applied to the synthesis of spirooxindole-δ-lactams (Scheme 44).[60] Reaction of oxindoles **144** with an appropriate amine (butylamine or 4-methoxybenzylamine) furnished amine derivatives **145** which were converted into **146** by reacting with methyl bromoacetate in the presence of NaH. Compounds **146** underwent microwave-assisted cyclization to give spirooxindole-δ-lactams **147** in high yield by carrying out the reaction in methanol at 100 °C in the presence of NEt_3. *N*-Unprotected-3-aryl-oxindole **148** could also be used in the synthesis of corresponding spiro-δ-lactam. Thus, *N*-deprotection of **145b** with TFA led to



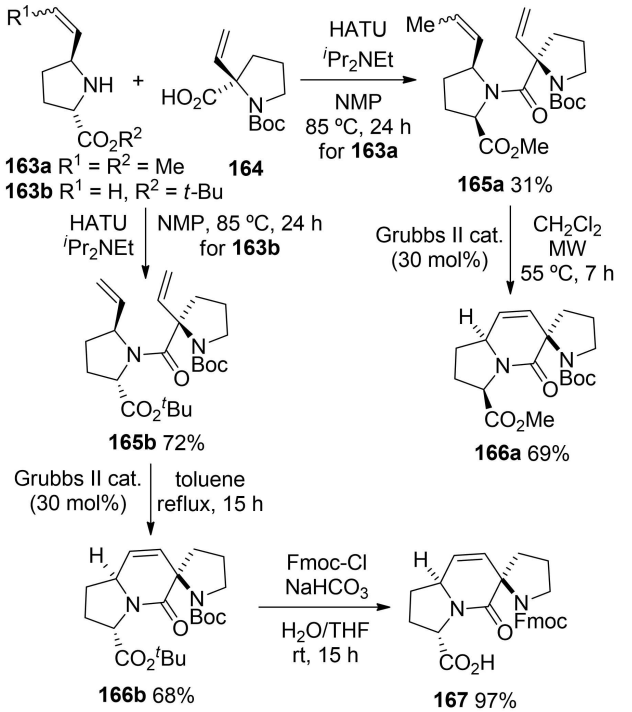
Scheme 47. Chiral spiro-δ-lactam synthesis from α-functionalized malonate through sequential chiral phosphoric acid catalyzed lactonization and lactamization reactions.



Scheme 48. Direct coupling between an indole-derived carboxylic acid and an imine.

compound **148** which reacted with methyl bromoacetate in the presence of NEt_3 followed by microwave irradiation to give spiro-δ-lactam **149** in 70% yield. The methodology also applies to the synthesis of spirooxindole-γ-lactams using methyl chloroformate instead of methyl bromoacetate.

The synthesis of spirooxindole-δ-lactams from oxoindole-derived α-aryl-β-amino acids has been described.[61] Oxoindole derivatives **151** were obtained in a stereoselective fashion (up to >95:5 dr and up to 99% ee) by an organocatalyzed asymmetric Mannich reaction between homophthalic anhydride **150** and isatin-derived *N*-Boc imines **58** (Scheme 45). Treatment of oxoindoles **151** with TFA provided spiro-δ-lactams **152** in good yields (65-75%) with retention of the stereochemistry of the two adjacent carbon chiral centers (up to >95:5 dr and up to 98% ee). The

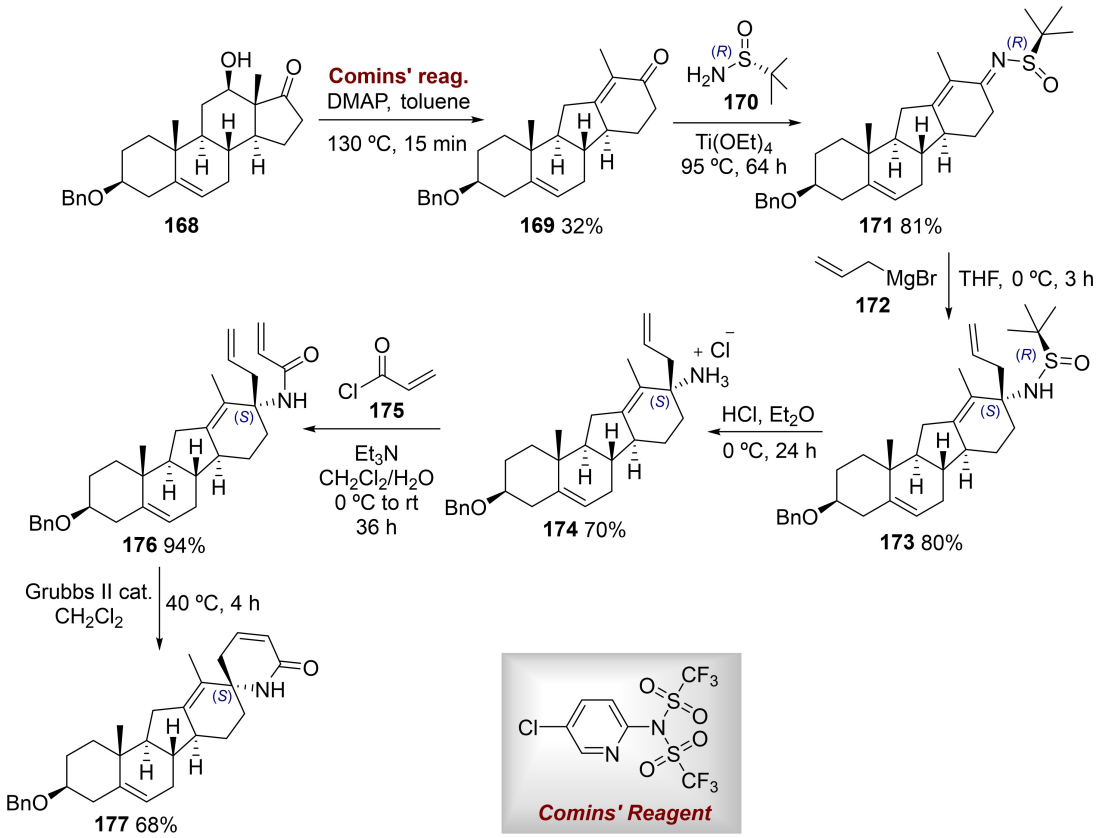


Scheme 49. Ruthenium-catalyzed ring-closing metathesis of vinyl-dipeptides.

reaction proceeds through deprotection of the amino group followed by intramolecular *N*-acylation to afford the spiro-δ-lactams.

The synthesis of spiroquinazoline-δ-lactams **155** was reported. The molecules were obtained through cyclization of substrates **154**, having a quinazoline moiety sharing the same quaternary carbon with both an ester and an aminoalkyl functional groups (Scheme 46).[62] Quinazoline substrates **154** are derived from the resin-bound precursors **153**, which treatment with TFA allows both the release of the quinazoline from the solid support and the two amide bonds cleavage affording 1,2-dihydroquinazoline-2-carboxylates **154** with two primary amine groups. Spirocyclic lactams **155** were obtained in moderate to good yields (52–85%), as products of the base-mediated lactamization of **154**.

Petersen and co-workers prepared spirocyclic γ-lactone-δ-lactam **158** from di-*tert*-butyl malonate derivative **156** which bears two alkyl chains containing terminal protected nucleophiles, at its α-carbon (Scheme 47).[63] Molecule **158** was synthesized through a two-step synthetic pathway in 23% overall yield. The reaction protocol comprises as first step the removal of the benzyl protecting group with 20% $Pd(OH)_2/C$. The resulting unprotected hydroxyl group undergoes desymmetrization via intramolecular lactonization, cata-



Scheme 50. Ruthenium-catalyzed ring-closing metathesis of steroidal acrylamides.

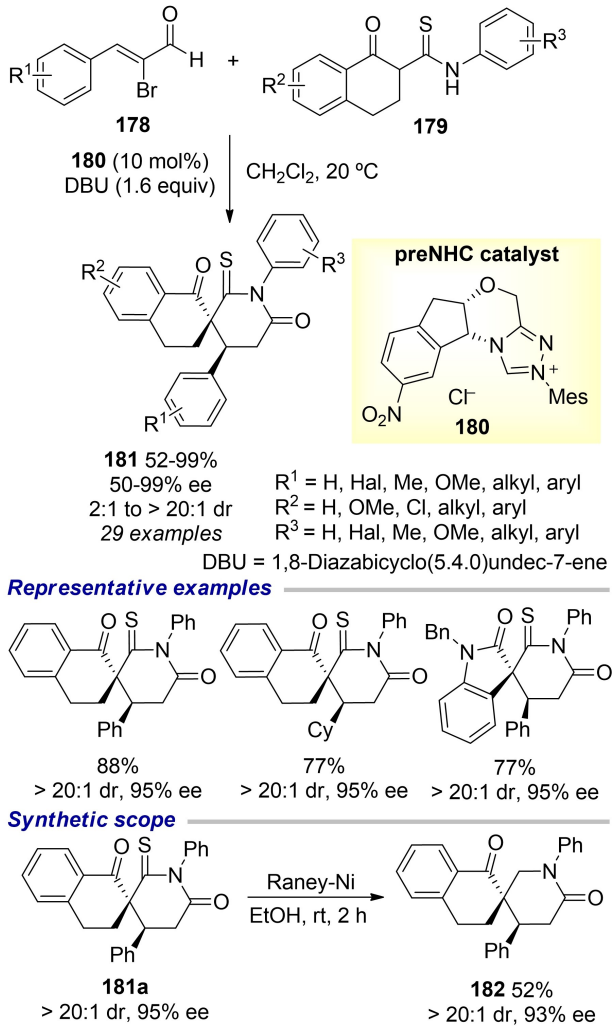
lyzed by a chiral BINOL-phosphoric acid [(*S*)-TRIP], affording enantioenriched γ-lactone **157**. Finally, γ-lactone **157** has its amine deprotected in the presence of TFA allowing the molecule to undergo a lactamization ring-closing process to afford spiro-γ-lactone-δ-lactam **158**.

The synthesis of spiro-δ-lactam indole **162**, was achieved from indolepropanoic acid **159** and 3,4-dihydroisoquinoline (**160**) (Scheme 48).[64] The reaction occurs through a direct coupling between these starting materials in the presence of propylphosphonic anhydride (T3P) and $^{i}Pr_2NEt$, in THF at room temperature, affording spirocyclic lactam **162** in 72% yield. The δ-lactam ring formation comprises an initial carboxylic acid activation with T3P and a subsequent *N*-acylation of 3,4-dihydroisoquinoline (**160**) leading to reactive *N*-acyliminium ion **161**. On the last reaction step, an intramolecular nucleophilic attack by the indole 3-carbon results in the dearomatization of this heterocyclic moiety with the formation of spiro-δ-lactam **162**.

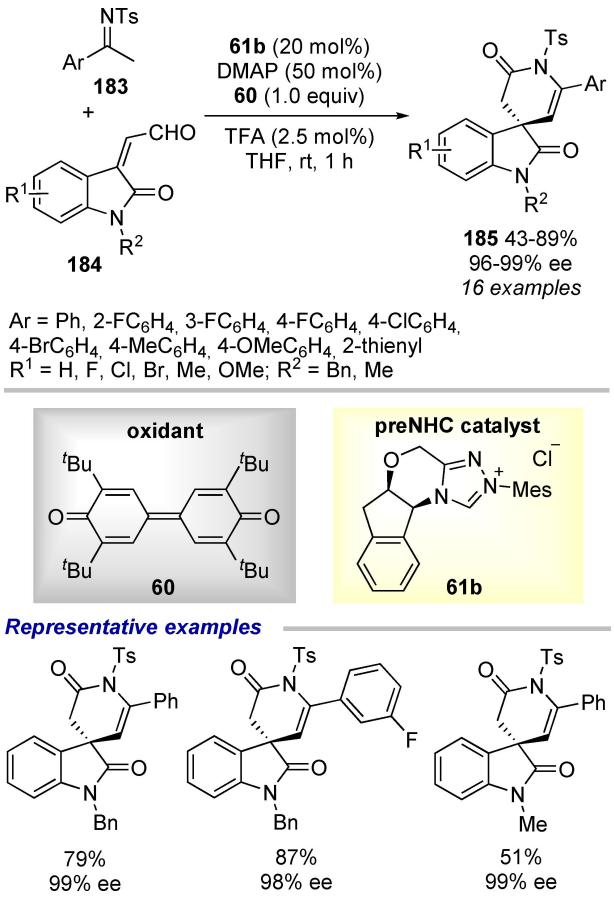
3.1.2. Ring-Closing Metathesis

Ruthenium-catalyzed ring-closing metathesis (RCM) was applied in the stereoselective synthesis of diproline scaffolds **166** (Scheme 49).[65] The synthetic approach relies on a peptide coupling of vinyl-substituted prolines to give dipeptides **165** followed by the RCM in the presence of 30 mol% Grubbs II catalyst. Curiously, the coupling of **163 a** with **164** led to an epimerization of the stereocenter in the α-ester position (**165 a**). Using a bulky substituent (R = CO_2t-Bu, **163 b**) and optimized reaction conditions, the epimerization was completely suppressed leading to compound **165 b** in 72% yield. The corresponding diproline-based spiro-δ-lactams **166** were obtained in good yield. Conversion of the *tert*-butyl ester derivative **166 b** to the free acid was also performed, leading to compound **167** in 97% yield.

The ring-closing metathesis reaction was also applied to the diastereoselective synthesis of C17 spiro-δ-lactam C-*nor*-D-*homo* steroids (Scheme 50).[66] The authors have explored two distinct synthetic approaches for the synthesis of the desired steroids starting from 3β-benzyloxy-12β-hydroxy-dehydroepiandrosterone **168**, however just one approach gave the diastereosisomeric pure compounds. The first step of the sequence involves a rearrangement of the steroidal skeleton via a Wagner-Meerwein-type rearrangement, in the presence of Comins' reagent and DMAP affording steroid **169** in 32% yield. Further



Scheme 51. NHC-catalyzed [3+3] spiroannulation of β-keto-thiaoamides and bromoenals.



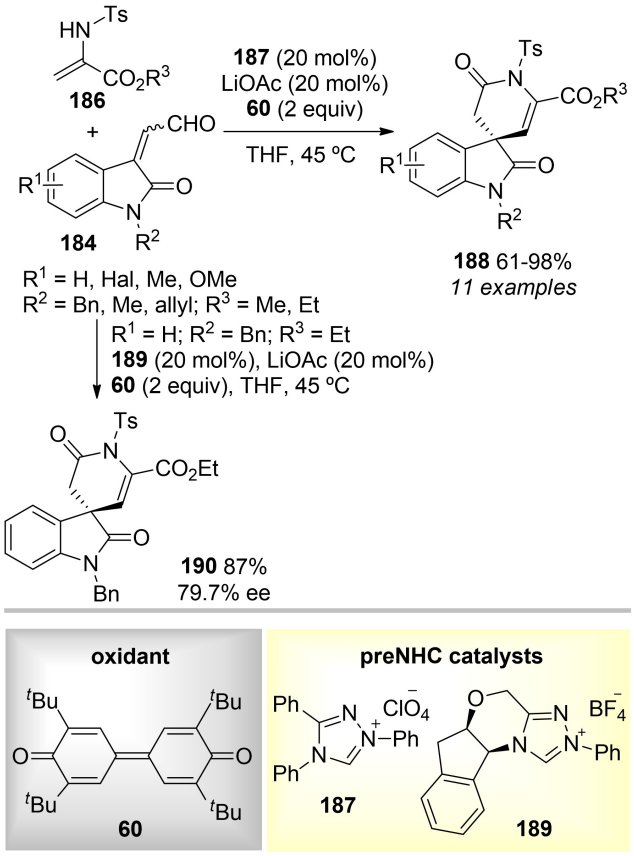
Scheme 52. NHC-catalyzed [3+3] spiroannulation of imines and isatin-derived enals.

condensation with an enantiopure sulfamide (**170**) as chiral auxiliary, and subsequent stereoselective nucleophilic addition of allylmagnesium bromide (**172**) to imine **171** provided compound **173** as a single diastereoisomer. Acidic treatment of **173** resulted in the cleavage of the sulfinyl moiety providing the corresponding amine hydrochloride **174**, which reacted with acryloyl chloride (**175**) in the presence of triethylamine to give arylamide **176**. Finally, a ruthenium-catalyzed RCM furnished the diastereosisomeric pure spiro-δ-lactam **177** in 68% yield.

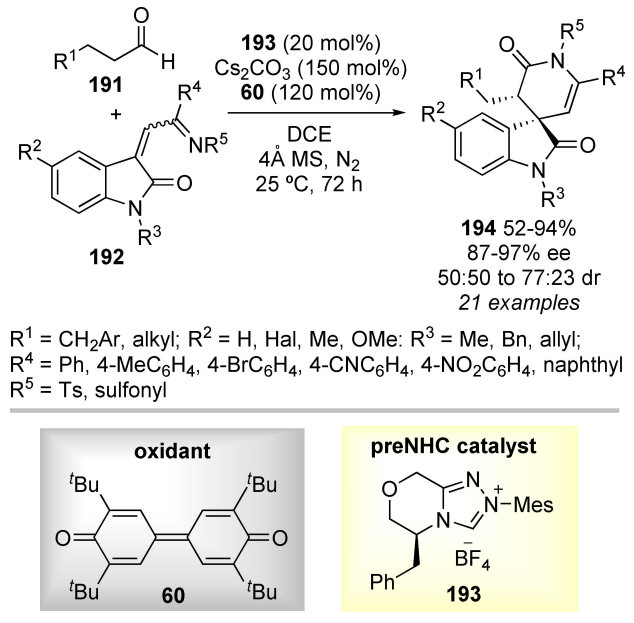
3.1.3. N-Heterocyclic Carbene-Catalyzed Annulation Reaction

Xu and co-workers reported the asymmetric synthesis of spiro-δ-lactams via NHC-catalyzed [3+3] spiroannulation of β-ketothiaoamides (KATs) acting as 1,3-C,N-dinucleophiles and bromoenals as the other three-atom counterpart (Scheme 51).[67] The reaction of bromoenals **178** and KATs **179** in the presence of chiral triazolium salt **180** as the N-heterocyclic carbene precursor, led to the synthesis of a range of spirocyclic derivatives **181** in good to excellent yields (52–99%) and excellent enantio- and diastereoselectivies (up to 99% ee and >20:1 dr). Structural modulation of spiro-δ-lactam **181 a** was also carried out, namely the removal of the thiocarbonyl group in the presence of Raney-Ni which afforded **182** keeping the stereochemical integrity.

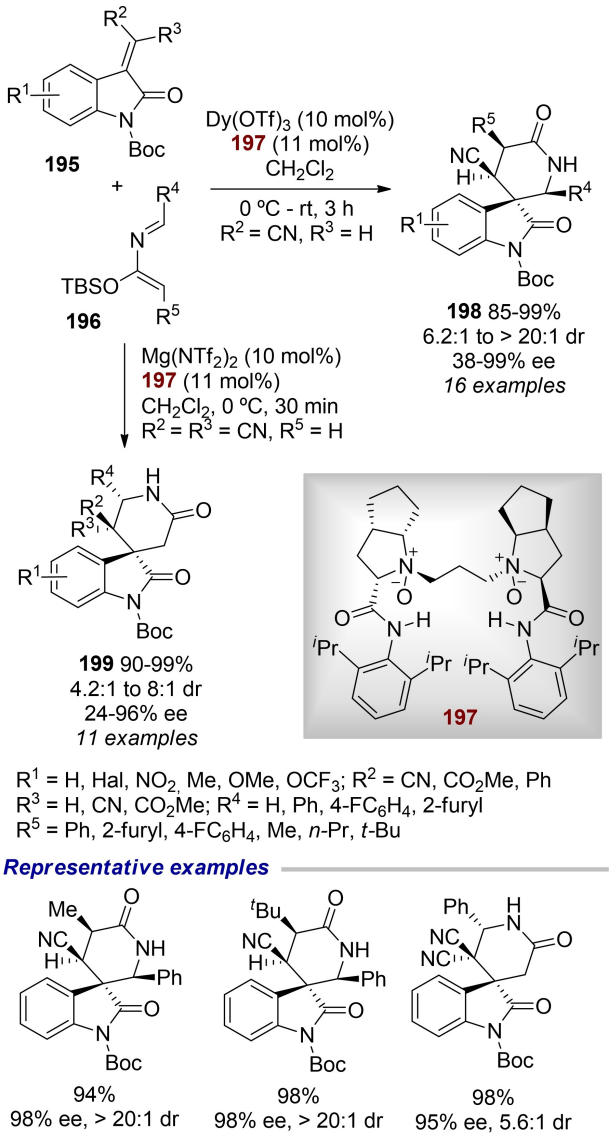
The NHC's chemistry was also applied in the enantioselective synthesis of spirocyclic unsaturated-δ-lactams through a [3+3] annulation reactions of imines **183** and isatin-derived enals **184**, in the presence chiral preNHC catalyst **61 b**, TFA, DMAP and oxidant **60** (Scheme 52).[68] The desired products **185** were obtained in yields ranging from 43% to 89% with excellent enantioselectivities (96–99% ee) carrying out the reaction at room temperature with short reaction time (1 hour). It is noteworthy that the enantioselectivity is not significantly affected by the nature of the isatin-derived enals' substituents (namely



Scheme 53. NHC-catalyzed [3+3] spiroannulation of 2-aminoacrylates and isatin-derived enals.



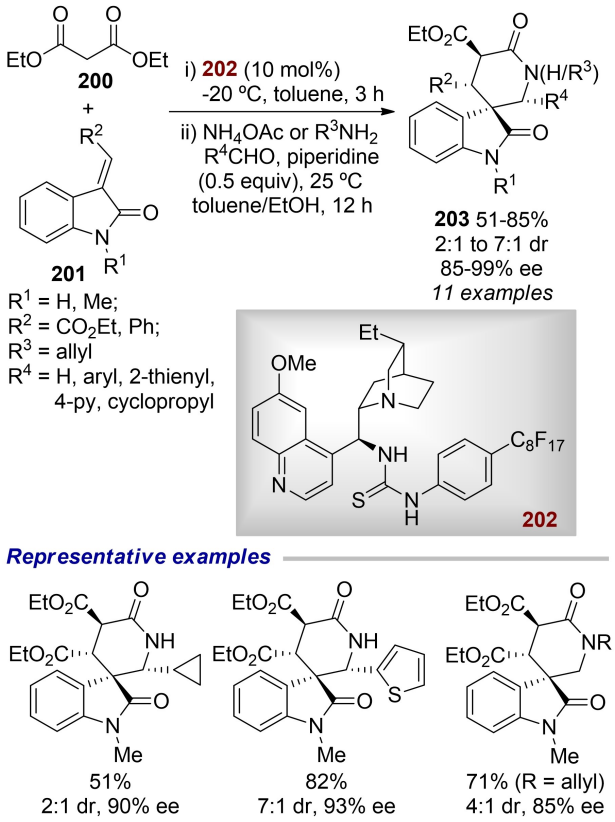
Scheme 54. NHC-catalyzed [2+4] spiroannulation of aliphatic aldehydes with oxoindole-derived α,β-unsaturated imines.



Scheme 55. Enantioselective hetero-Diels-Alder reaction between 2-aza-silyloxy-1,3-butadienes and oxoindole-derived alkylidenes.

R^1) although some influence on the reaction yields was observed.

NHC catalysis was also applied in the synthesis of racemic spirooxindole-δ-lactams **188** (Scheme 53).[69] In this case, the process involved the [3+3] spiroannulation reaction of 2-aminoacrylates **186** and isatin-derived enals **184** providing a wide range of spiro derivatives **188** in good to excellent yields (83–98%). A preliminary study on the asymmetric catalytic version of this methodology was also reported. Carrying out the reaction of **184** (R^1 = H; R^2 = Bn) with **186** (R^3 = Et) in the presence of 20 mol% of chiral triazolium salt **189**, using lithium acetate as the base, the corresponding spirooxindole **190** was obtained in 87% yield with high enantiomeric excess.



Scheme 56. One-pot four-component Michael/Mannich/cyclization sequence between oxoindole-derived alkylidenes, diethyl malonate, an aldehyde and ammonium acetate or a primary amine.

Spirooxoindole-δ-lactams **194** were synthesized via a NHC-catalyzed oxidative [4+2] annulation of aliphatic aldehydes **191** with oxoindole-derived α,β-unsaturated imines **192** using chiral preNHC catalyst **193** (Scheme 54).[70] The target spirocyclic lactams **194** were obtained in good yields (up to 94%) and good to excellent enantioselectivities (87-97% ee). However, the drawback of this approach was the observed poor to moderate diastereoselectivity. The reaction exhibits good functional group tolerance although attempts to carry out the reaction with *N*-Boc-imine or *N*-Ac-imine derivatives did not lead to the formation of the desired products.

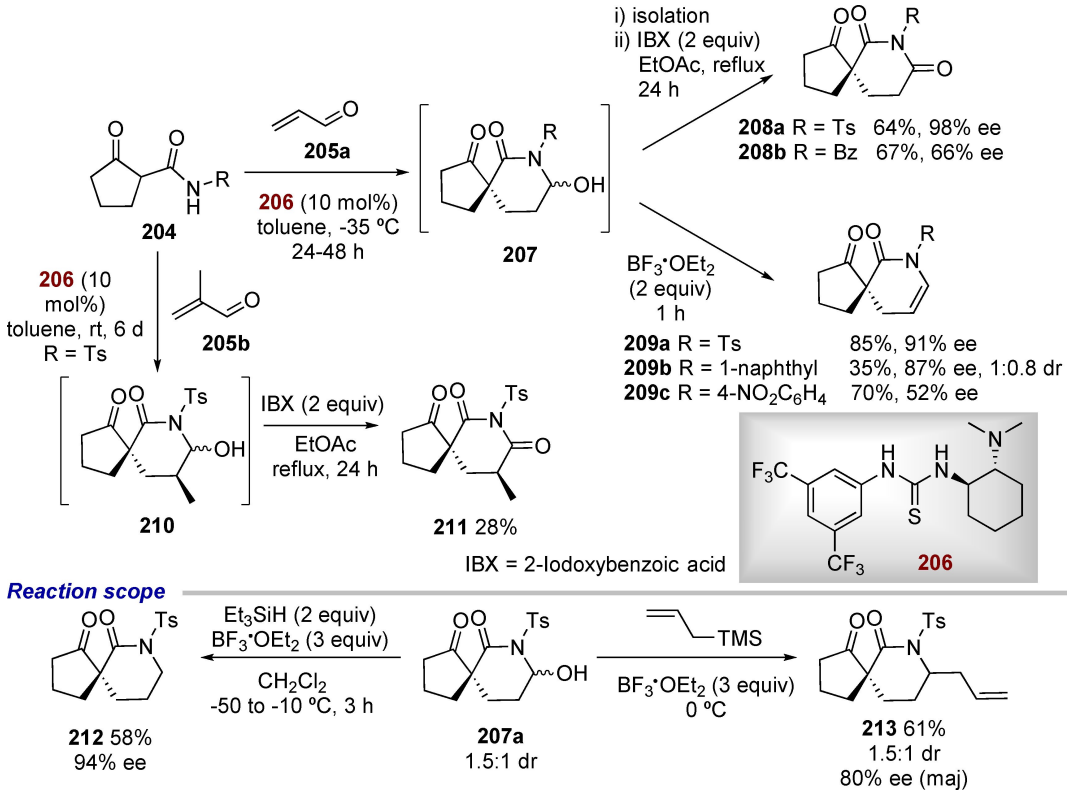
3.1.4. [4+2] Cycloaddition Reaction

The enantioselective hetero-Diels-Alder reaction of 2-aza-silyloxy-1,3-butadienes **196** with oxoindole-derived alkylidenes **195** has been described (Scheme 55).[71] The reaction relies on an *exo*-selective asymmetric cycloaddition catalyzed by complexes of chiral *N*,*N*'-dioxide ligands (**197**) providing C5 and C4 spirocyclic δ-lactams **198** and **199**, respectively. Carrying out the reaction with a dysprosium salt as catalyst, spiro-δ-lactams **198** were obtained in high yields (85–99%). Further studies have shown that starting from dicyano alkylidene oxoindoles **195** ($R^2=R^3=CN$), the use of a magnesium salt as catalyst favored the synthesis of C4 spiro-δ-lactams **199** (90–99% yield). Moreover, starting from alkylidenes bearing one cyano and/or one ester moiety the magnesium salt catalyst can also be used for the synthesis of C5 spiro-δ-lactams. The authors rationalized the observed selectivity considering that spiro adducts obtained via dysprosium salt-catalyzed reactions occurred through an approach of the azadiene to the *si*-face of the cyanoalkene leading to *exo*-adducts. On other hand, when the reactions were catalyzed with magnesium salts, the spiro adducts were obtained from the approach of the azadiene to the *re*-face. Both strategies led to the corresponding spirocyclic δ-lactams in moderate to good stereoselectivities (from 4.2:1 to >20:1 dr and 24–99% ee).

3.1.5. Michael Addition/Cyclization Reaction

In 2015, Zhang and co-workers reported an enantioselective strategy for the synthesis of spirooxindole-δ-lactams bearing multiple stereocenters (Scheme 56).[72] The reaction, catalyzed by a recyclable fluorous organocatalyst **202**, comprises a one-pot Michael addition of diethyl malonate (**200**) to alkylidenes **201** followed by a Mannich/cyclization sequence in the presence of an aldehyde and ammonium acetate or a primary amine. The resulting spirooxindole-δ-lactams **203** were obtained in moderate to high yields (51–85%) and with excellent enantioselectivities (up to 99%). However, this reaction presents a drawback concerning diastereoselectivity, with dr from 2:1 to 7:1.

Cyclopentanone-derived spiro-δ-lactams were synthesized via an organocatalytic enantioselective Michael addition of secondary β-ketoamides **204** to α,β-unsaturated aldehydes **205** (Scheme 57).[73] The reaction of **204** with acrolein (**205a**) in the presence of bifunctional Takemoto's thiourea catalyst **206** led to the formation of spiro-δ-lactams **207** which were directly derivatized by oxidation or dehydration to the corresponding enantioenriched glutarimides **208** or dihydropyridones **209**, respectively. The organocatalytic conjugate addition of β-ketoamide (R=Ts) **204** to methacrolein (**205b**) and subsequent oxidation led to the expected spiro-δ-lactam **211**, however in low yield (28%). The synthetic utility of the methodology was demonstrated with several post-functionalization reactions of **207a**, including reduction to give **212** and direct one-pot Lewis acid *N*-acyliminium generation followed by trapping with allyl trimethylsilane to provide **213**, both without loss of stereointegrity of the newly created stereocenters.



Scheme 57. Organocatalytic enantioselective conjugate addition of β-ketoamides to acroleins.

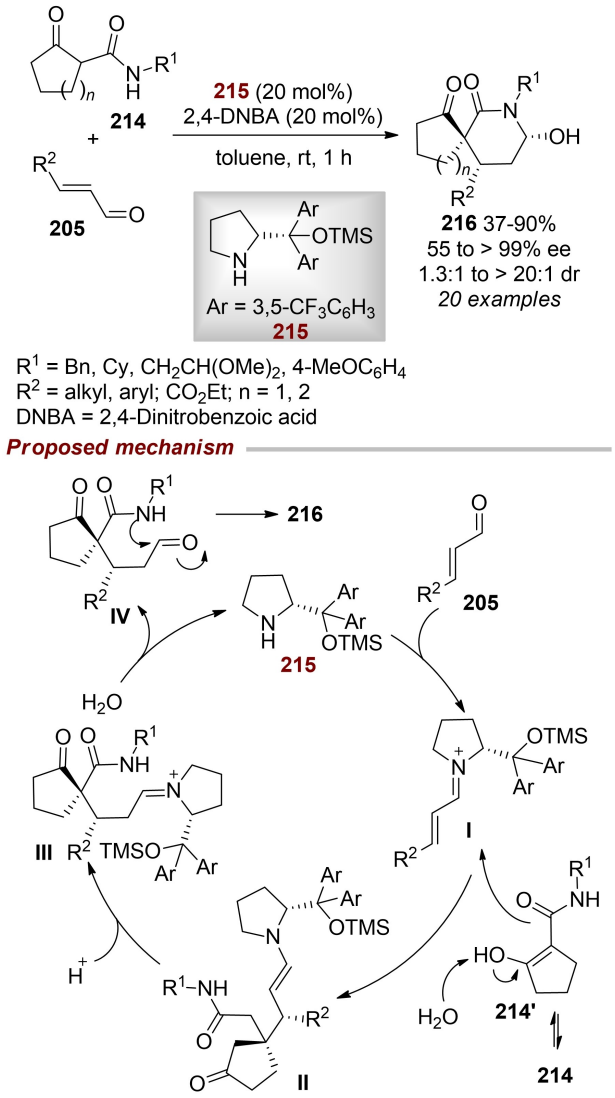
The asymmetric synthesis of spirocyclic δ-lactams **216** via an organocascade reaction has been described.[74] The reaction relies on a Michael addition of β-ketoamides **214** to α,β-unsaturated aldehydes **205** catalyzed by a chiral secondary amine catalyst (**215**) (Scheme 58). A library of twenty spirocyclic δ-lactams **216** was obtained in moderate to high yields (37–90%), with high stereoselectivities (up to >20:1 dr and 99% ee) and good functional group tolerance. In the proposed mechanism, the bulky groups in the structure of the catalyst **215** have a key role in the observed enantioselectivities. They can block the bottom face of the iminium ion **I**, forcing the Michael addition step to occur from the *si* face in an enantioselective fashion. Moreover, the diastereoselectivity can be rationalized considering the attack of **214'** to **I** in two distinct approaches, A and B. The major diastereomer is achieved via attack of *syn*-**214'** with the ketoamide substituent far away from the catalyst (approach A). However, carrying out the reaction with enals **205** bearing bulky substituents (R^2 = aromatic) the steric effect loses some relevance, leading to lower diastereoselectivities.

Spiro-δ-lactams **220** were prepared from *ortho*-quinone methide imines, generated *in situ* from propargylic alcohols **217**, and cyclic β-oxo esters **218** (Scheme 59).[75] The reaction was catalyzed by chiral BINOL-based phosphoric acid **219** and comprised a one-step domino Michael addition-lactamization process. The products were obtained in moderate to high yields (32–98%) with excellent stereoselectivities (up to >20:1 dr and up to >99:1 er). The reaction was tested on large-scale to establish its applicability.

3.1.6. Radical Cyclization Reaction

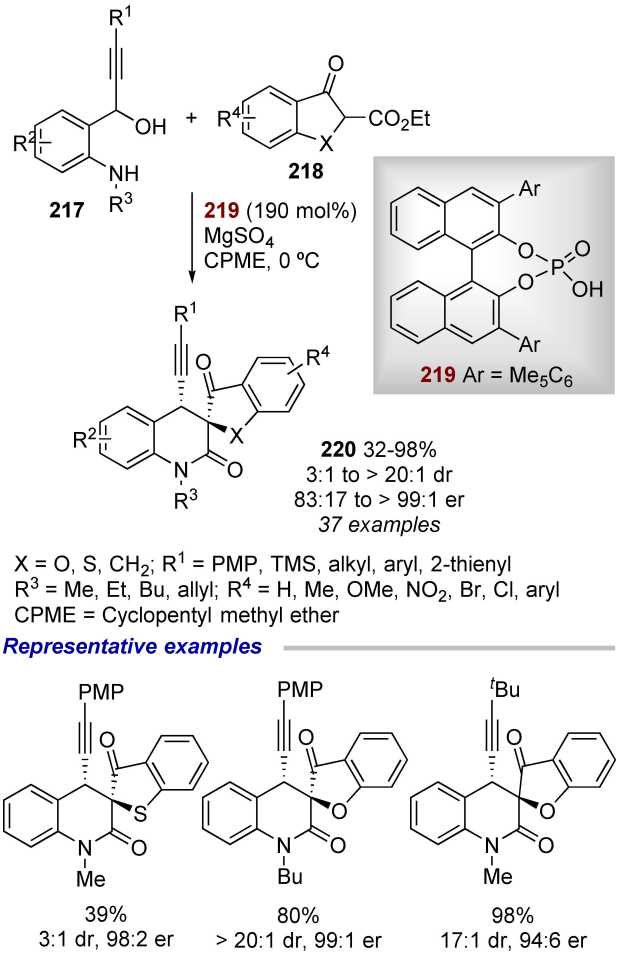
The synthesis of spiro-δ-lactams via free radical spirocyclization of xanthates has been described aiming at the synthesis of the lead σ-1 receptor ligand **L-687384** (**226**).[76] Cyclization of carbamoylmethyl radical **222**, generated from xanthate **221** in the presence of dilauroyl peroxide (DLP), which behaves as both chain reaction initiator and oxidant, led to the regioselective synthesis of spiro-δ-lactam **224** in 50% yield (Scheme 60). The observed selective *ipso*-spirocyclization was corroborated by DFT calculations. The synthesis of **L-687384** was achieved via reduction of compound **224** with $LiAlH_4$ affording **225** followed by the reduction of the carbonyl group under Wolff-Kishner conditions.

The reductive generation of carbamoyl radicals using photoredox catalysis with visible light was applied to the synthesis of benzo-fused spiro-δ-lactams.[77] Carbamoyl radicals (**230**), generated from *N*-hydroxyphthalimido oxamide precursors **227**, reacted with exocyclic electron deficient alkenes **228** via



Scheme 58. Organocatalytic enantioselective conjugate addition of β-ketoamides to α,β-unsaturated aldehydes.

an intermolecular addition/cyclization reaction to give a range of spirocyclic compounds **229**, namely, spirolactone-δ-lactams, spirocyclic bis-γ,δ-lactams and

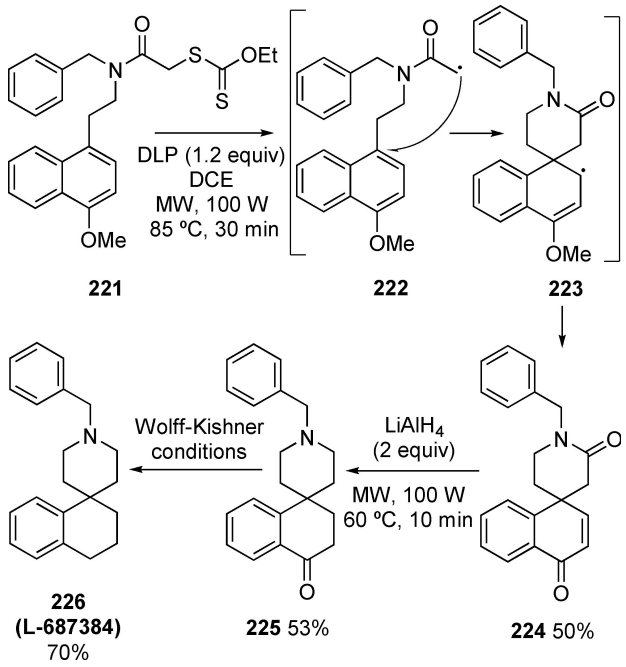


Scheme 59. Domino Michael addition-lactamization reaction of ortho-quinone methide imines and cyclic β-oxo esters.

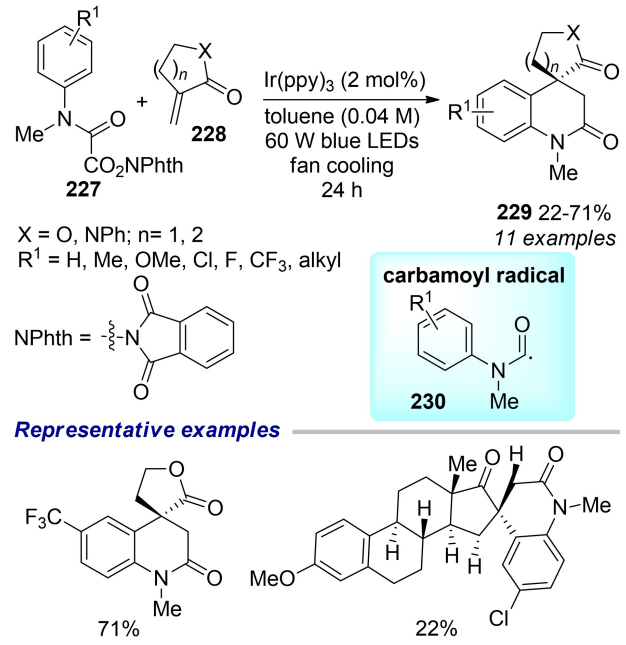
a steroidal spiro-δ-lactam derivative isolated as single enantiomer (Scheme 61).

3.1.7. Schmidt-Boyer Rearrangement

Spirocyclic bis-lactam **235** synthesis was reported by Dhavale and co-workers.[78] The molecule stands out as a spiro-iminosugar and was obtained through a two-step reaction in good overall yield (65%) (Scheme 62). The first reaction step comprises an oxidative cleavage of diol **231** followed by $NaBH_4$ reduction leading to compound **232** which was converted into azide **234** via tosylation of the primary hydroxyl group followed by the reaction with sodium azide. Further *in situ* hydrolysis of the 1,2-acetonide functional group of **234** by a one-pot TFA/water-promoted affords intermediate **I**. Concomitant intramolecular Schmidt-Boyer rearrangement of intermediate **I** generates bis-γ-lactam-δ-lactam **235**. Notably, spirocyclic bis-lactam **235** revealed to be a potent and selective inhibitor of glycosidade enzyme in single-target assay. Complementary docking studies

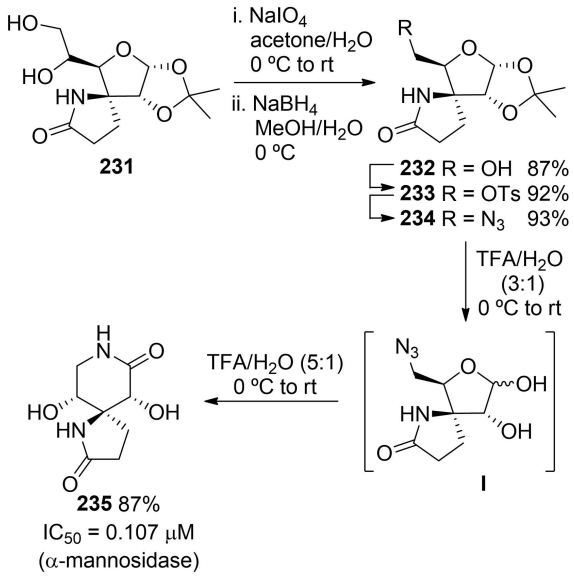


Scheme 60. Regioselective free radical-mediated cyclization of a xanthate.

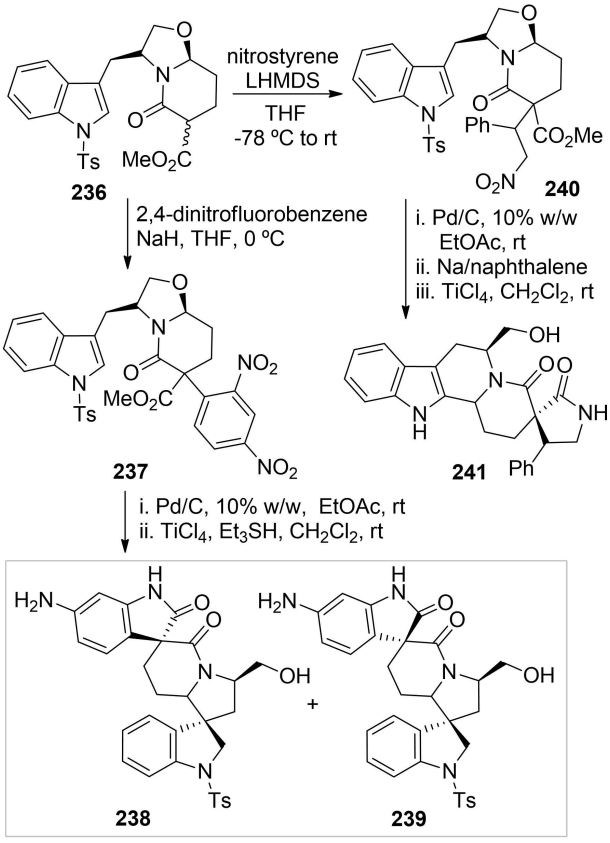


Scheme 61. Intermolecular addition/cyclization of carbamoyl radicals.

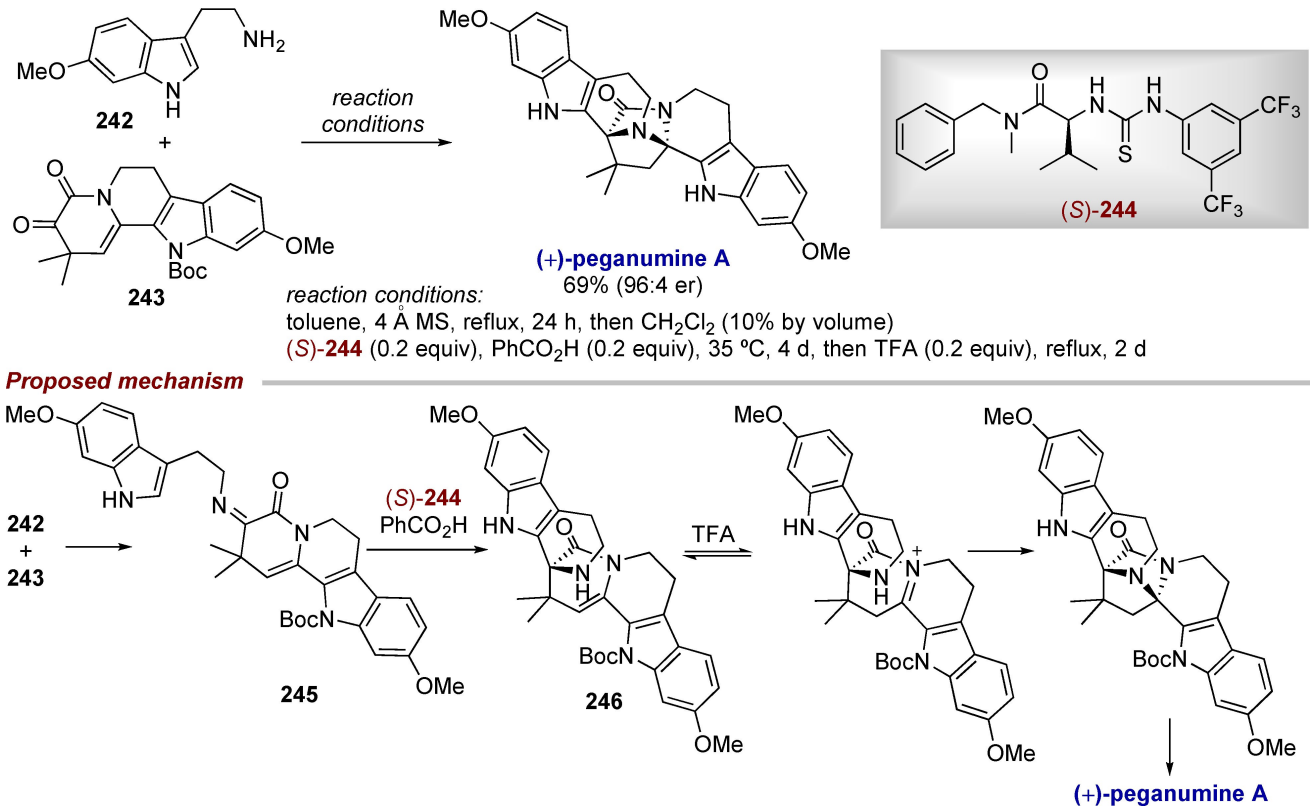
were in agreement with the observed bioactivity of spirocyclic bis-γ-lactam-δ-lactam **235**.



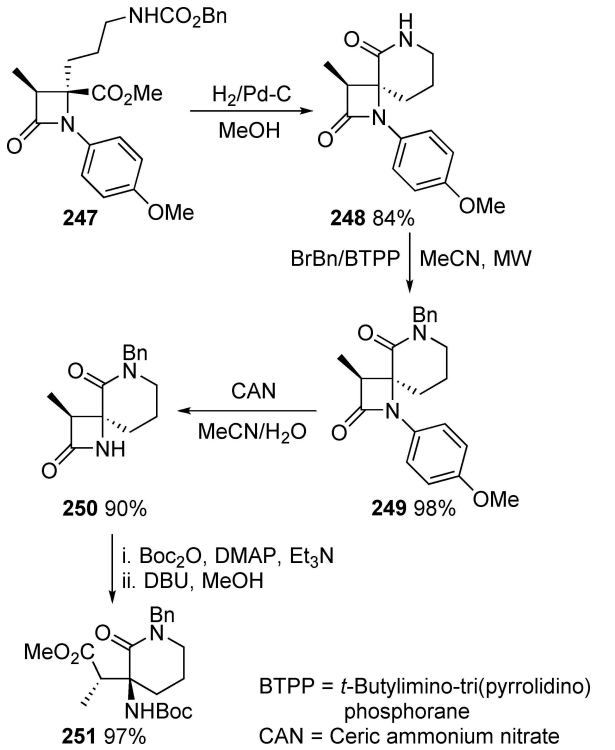
Scheme 62. Bis-γ-lactam-δ-lactam synthesis through Schmidt-Boyer rearrangement.



Scheme 63. Cyclization of a *S*-tryptophanol-derived chiral bicyclic δ-lactam.



Scheme 64. Cyclization of a *S*-tryptophanol-derived chiral bicyclic δ-lactam.



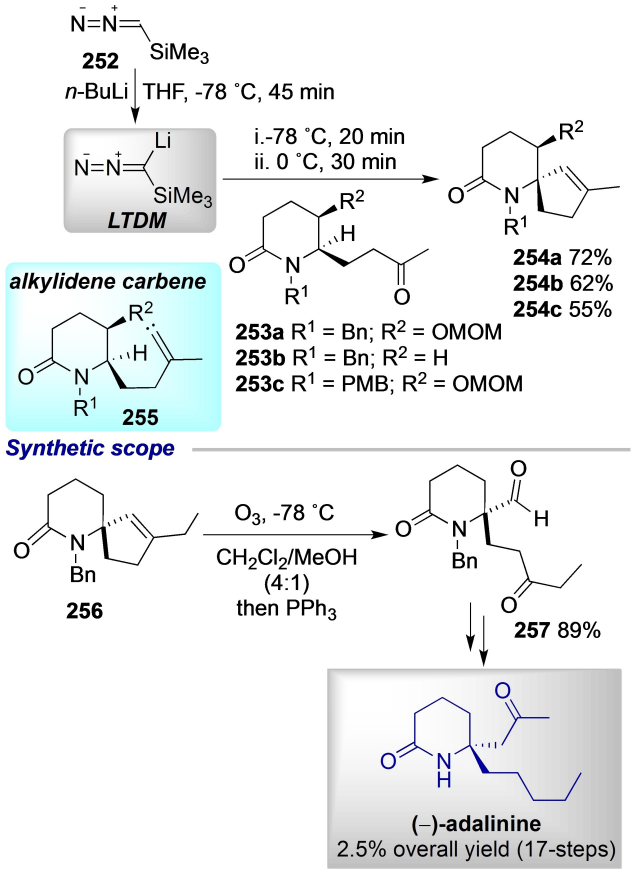
Scheme 65. Spirocyclization of an Orn-derived β-lactam leading to a spirocyclic bis-β,δ-lactam and further transformations of the latter.

3.2. Non-δ-Lactam Ring Synthesis

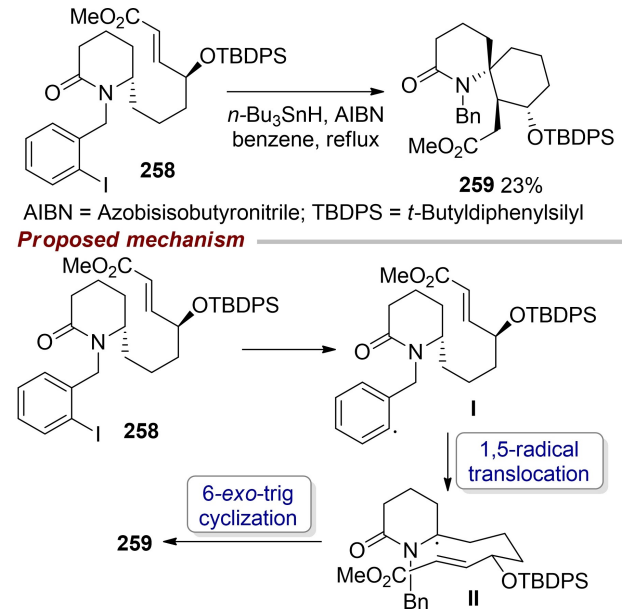
3.2.1. Nucleophilic Cyclization Reaction

The Singh's group reported the synthesis of chiral spiro-δ-lactams with antimalarial activity via two different strategies using bicyclic δ-lactam **236**, derived from *S*-tryptophanol, as building block (Scheme 63).[79] In the first approach, compound **236** reacted with 2,4-dinitrofluorobenzene via aromatic nucleophilic substitution reaction to afford compound **237**. Next, reduction with H_2/Pd–C followed by $TiCl_4$/triethylsilyl hydride promoted spirocyclization led to spirooxindole-δ-lactams **238** and **239**. The second approach involved an initial Michael addition with nitrostyrene to give compound **240**. Subsequent hydrogenolysis with H_2/Pd–C followed by detosylation with sodium/naphthalene and $TiCl_4$-induced 6-*endo*-*trig* cyclization gave spirocyclic bis-γ,δ-lactam **241**.

The enantioselective gram-scale total synthesis of (+)-peganumine A using two achiral building blocks has been reported (Scheme 64).[80] The reaction of indole-based compound, 6-methoxytryptamine (**242**) and tetracyclic α-ketoamide **243** in the presence of Jacobsen's chiral thiourea catalyst **244** and benzoic acid as co-catalyst furnished (+)-peganumine A in 69% yield in an enantioselective fashion (96:4 er). The reaction relies on a condensation of amine **242** with



Scheme 66. Alkylidene carbene generation-C–H insertion of δ-lactam ketones.



Scheme 67. Radical translocation-cyclization of a (+)-(*R*)-glycidol-derived substrate.

243 to give imine **245**. Next, enantioselective aza-Friedel-Crafts addition in the presence of (*S*)-**244** provided the enantioenriched spirocyclic **246**. TFA-Catalyzed enamine-imine tautomerization followed by stereospecific transannular addition of the secondary amine to iminium and removal of *N*-Boc protecting group furnished (+)-peganumine A.

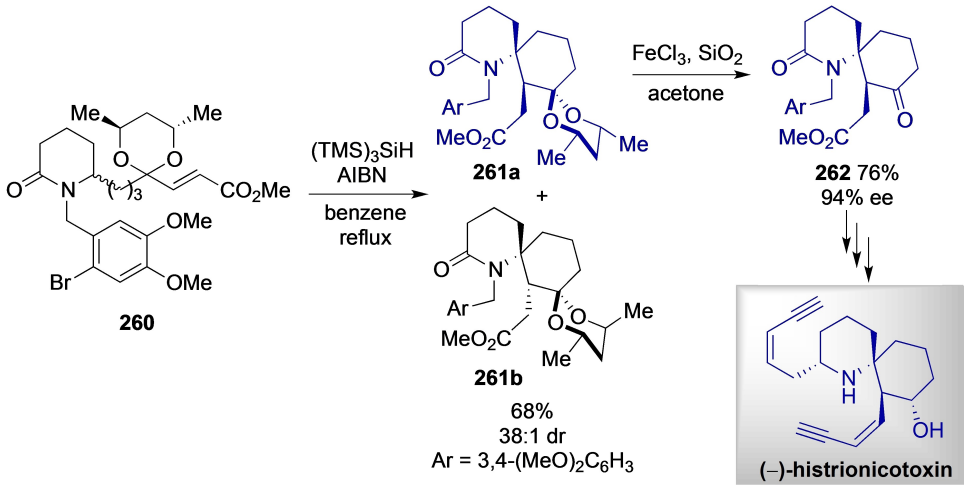
González-Muñiz and co-workers described the construction of the spirocyclic bis-β,δ-lactam scaffold **250** and its conversion into the corresponding 2-oxopiperidine amino ester **251** (Scheme 65).[81] Catalytic hydrogenation of enantiopure Orn-derived β-lactam **247** removed the protecting group, triggering the formation of the δ-lactam ring via a 6-*exo*-*trig* ring closure with the formation of spirocyclic bis-β,δ-lactam **248** in 84% yield. *N*-Protection of δ-lactam moiety followed by *N*-deprotection of the β-lactamic core provided spirocyclic compound **250**. The β-lactam *N*-Boc functionalization activated the four-membered ring to the subsequent intermolecular nucleophilic ring-opening which was carried out in the presence of DBU/MeOH affording 2-oxopiperidine amino ester **251** in 97% yield. It is noteworthy that the (3*S*,4*S*) configuration in **247** is maintained throughout the synthetic sequence and transferred to the final product.

3.2.2. Intramolecular Alkylidene Carbene C–H Insertion Reaction

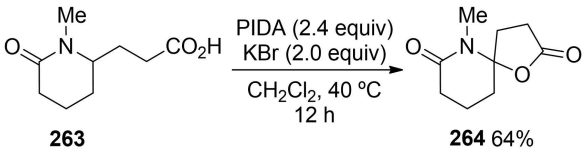
The alkylidene carbene generation-C–H insertion reaction of enantiopure lactam ketones and its application to the total synthesis of coccinellid alkaloid (−)-adalinine have been reported.[82] The protocol involves the generation of alkylidene carbenes **255** by treatment of δ-lactam ketones **253** with lithiotrimethylsilyldiazomethane (LTDM), obtained *in situ* by reaction of trimethylsilyldiazomethane (TMSDM) **252** and *n*-BuLi in THF at −78 °C (Scheme 66). Under the optimized reaction conditions, spiro-δ-lactams **254** were obtained in moderate yields (55–72%). The methodology was also applied to the synthesis of spiro-γ-lactams from γ-lactam ketones. The synthetic utility of the developed strategy was demonstrated by the successful conversion of spiro-δ-lactam **256** into (−)-adalinine.

3.2.3. Radical Cyclization Reaction

The stereoselective radical translocation-cyclization reaction of (+)-(*R*)-glycidol-derived substrate **258** was explored by Tokuyama and co-workers as a key step in the total synthesis of (−)-histrionicotoxin, a blocker of nicotinic acetylcholine receptors (Scheme 67).[83] The reaction of **258** under radical cyclization conditions led to the formation of spiro-δ-lactam **259** in 23% yield. Mechanistically, the reaction involves the generation of radical **I** which undergoes a 1,5-radical translocation to



Scheme 68. Radical translocation-cyclization of a substrate bearing a chiral cyclic acetal applied to the total synthesis of (–)-histrionicotoxin.



Scheme 69. PIDA/KBr-promoted C–H spirocyclization of δ-lactam carboxylic acids.

give intermediate **II** and subsequently a 6-*exo*-*trig* spirocyclization. The same compound (**259**) was obtained, also in 23% yield, when the C6 epimer of **258** was used, indicating an inversion of configuration after the 1,5-radical translocation step. The occurrence of a second undesired 1,5-radical translocation to generate an *O*-stabilized allyl radical was invoked by the authors to explain the low yield of the target compound.

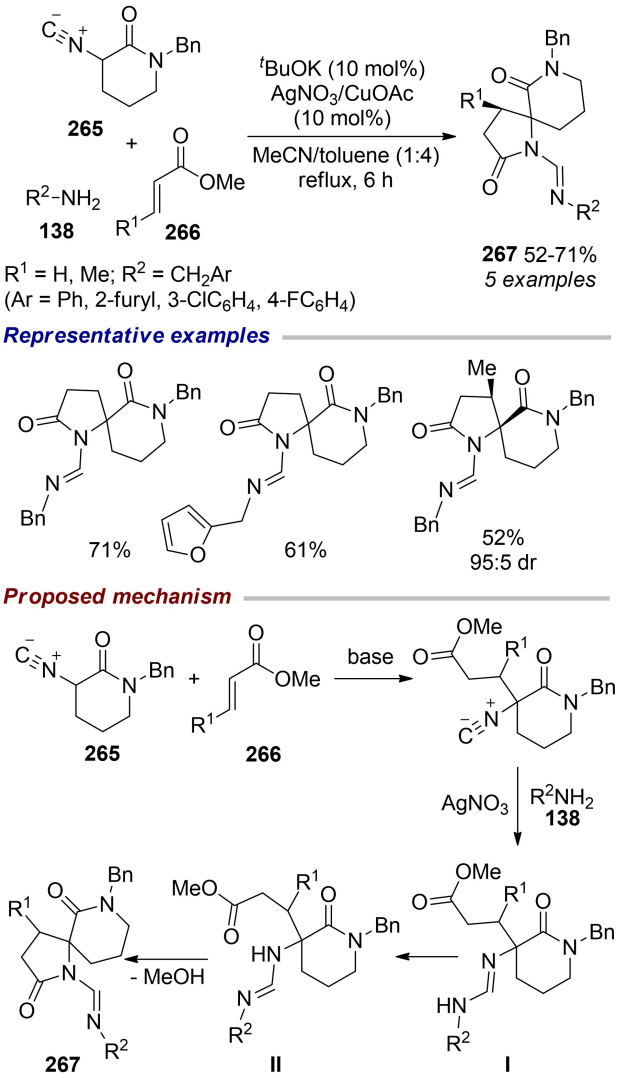
Due to the low yield of the previous reaction, an alternative strategy for the construction of the spiro-δ-lactam scaffold was disclosed using substrate **260** bearing a chiral cyclic acetal (Scheme 68).[83] Substrate **260**, having a chiral cyclic acetal, undergoes a radical translocation-cyclization reaction when reacted with $(TMS)_3SiH$ and AIBN in refluxing benzene, to give spirocyclic δ-lactam **261 a** as the major product. The practicality of the reaction was tested by carrying out the synthesis in a multigram-scale without loss of yield and selectivity. Deacetalization of **261 a** by treatment with $FeCl_3$ and silica gel in acetone afforded keto spiro-δ-lactam **262** in 76% yield with 94% ee. (−)-Histrionicotoxin was obtained from **262** through a 7-step synthetic sequence.

The synthesis of spiro-γ-lactone-δ-lactam **264** via spirocyclization of δ-lactam carboxylic acid **263** was reported by Yoda and co-workers (Scheme 69).[84] The proposed reaction mechanism comprises a C–H lactonization of the δ-lactam carboxylic acid **263** in the presence of PIDA and potassium bromide, through a radical-induced hydrogen abstraction pathway.

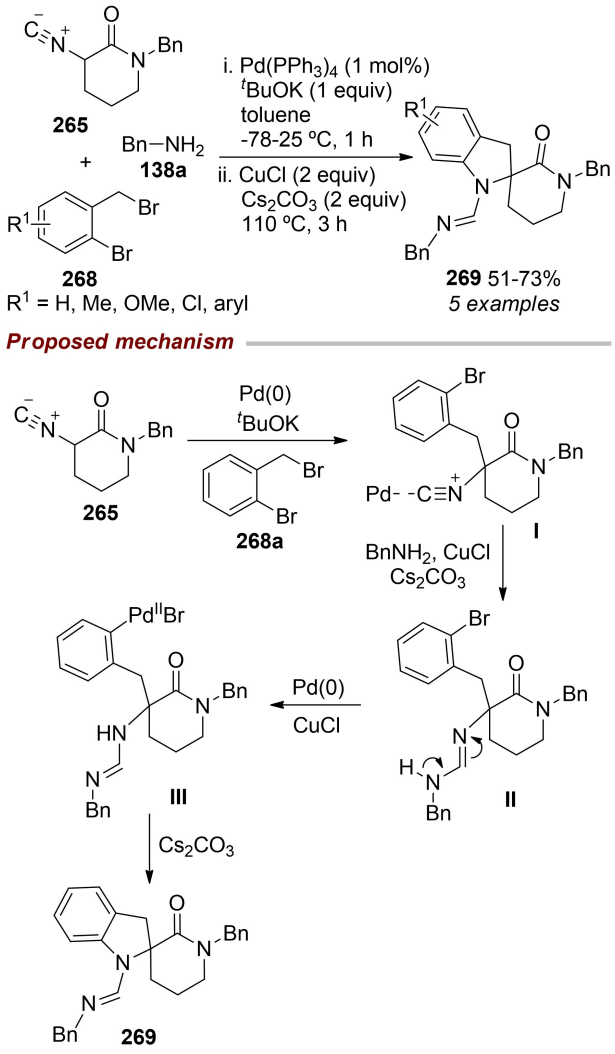
3.2.4. Tandem Three-Component Reaction

Two different three-component synthetic routes to spirocyclic δ-lactams were developed by Oh and co-workers, both exploring α-isocyano δ-lactams and amines as building blocks.[85] The first reported protocol used electron-deficient α,β-unsaturated methyl esters as the third component giving bis-γ-lactam-δ-lactams **267** in good yields (52–71%) via silver-catalyzed formal [3+2] cycloaddition reaction (Scheme 70).[85a] Preliminary reaction optimization studies demonstrated the need of the combined presence of both Ag and Cu catalysts for optimal yields and reaction time. The proposed mechanism comprises a conjugated addition of the α-isocyano δ-lactam **265** to the appropriated 2-butenoate **266** in the presence of *t*-BuOK and a subsequent Ag(I) salt-catalyzed amine addition to the isocyanide group. The generated intermediate **I** isomerizes to **II** and undergoes intramolecular lactamization to give the desired spirocyclic bis-γ-lactam-δ-lactam **267**.

The second three-component approach for the synthesis of spiroindoline δ-lactams **269**, used 2-bromobenzyl bromides **268** as the third reaction component, apart from α-isocyano δ-lactams **265** and benzylamine **138 a**, in the presence of a Pd/Cu catalytic system (Scheme 71).[85b] The proposed mechanism for this multicomponent reaction involves an initial Pd-catalyzed benzylation of α-isocyano δ-lactams **265** to give intermediate **I** which undergoes a copper-mediated *in situ* amine addition to the isocyanide moiety and finally isomerization to generate **II**. In the final step,



Scheme 70. Silver-catalyzed tandem three-component spirocyclization between isocyano δ-lactams, amines and electron-deficient 2-butenoates.



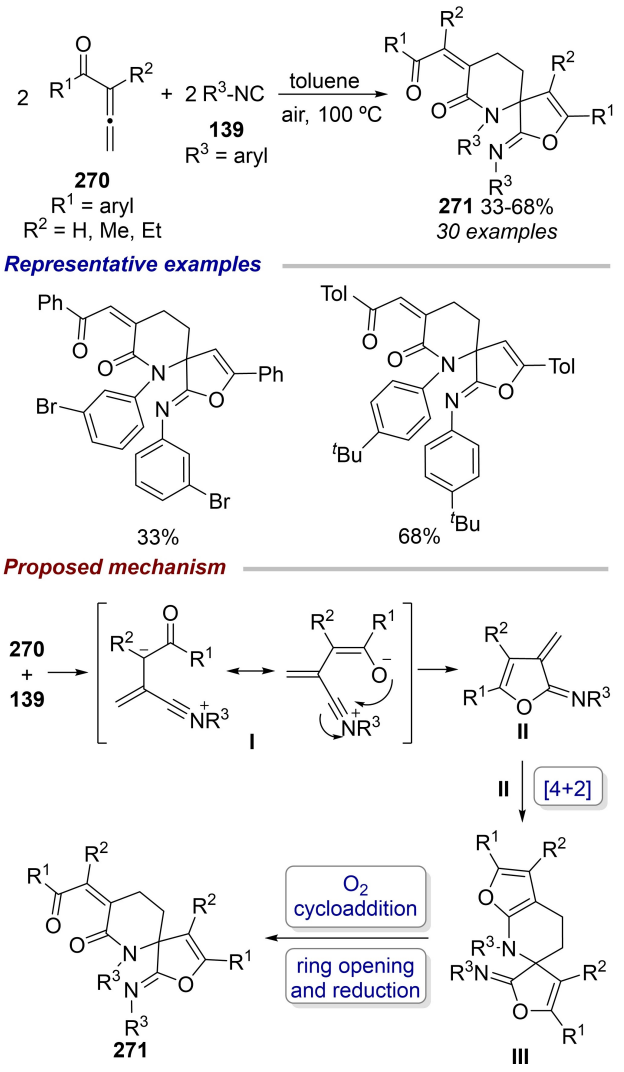
Scheme 71. Cooperative Pd/Cu-catalyzed tandem three-component reaction involving isocyano δ-lactams, amines and 2-bromobenzyl bromides.

the intramolecular *N*-arylation of palladium complex **III** via a key cooperative action of Pd/Cu catalysis generates the indoline core, affording spirocyclic δ-lactams **269** in moderate to good yields (51–73%).

3.3. δ-Lactam and Non-δ-lactam Ring Synthesis

Allenyl ketones **270** react with isocyanides **139** to generate spiro-δ-lactams **271** in moderate yields (33–68%) (Scheme 72).[86] This bicyclization protocol involves two molecular allenyl ketones and isocyanides and is distinguished by high atom economy and excellent functional group tolerance, with exception of bulky-substituted isocyanides (*e.g.* *t*-butyl). The proposed reaction mechanism comprises an initial Michael addition of isocyanide to the allenyl ketone followed by intramolecular cyclization to give intermediate **II**. [4+2] cycloaddition between two intermediates **II** takes place giving **III** which reacts with molecular oxygen to give the target compound.

Romo and co-workers described the enantioselective synthesis and reactivity of medium-size heterocyclic compounds containing the lactamic core (*e.g.* azepanones, benzazepinones, benzazocinones).[87] Benzazocinones **272**, obtained via the intermediacy of a chiral α,β-unsaturated acylammonium salt, were converted into spiro-δ-lactams **273** in moderate yields by addition of nucleophiles (Scheme 73). Tosylated benzazocinone **272 a** reacted with aliphatic amines to give non-spirocyclic products which were transformed into **273 a**,**b** by treatment with DBU. Detosylated benzazocinone **272 b** reacted with hydrazine giving directly the corresponding spiro-δ-lactam **273 c** in 30% yield as single (4*R*,4*R*')-enantiomer. These transformations presumably occur through a ring-cleavage of the benzazo-

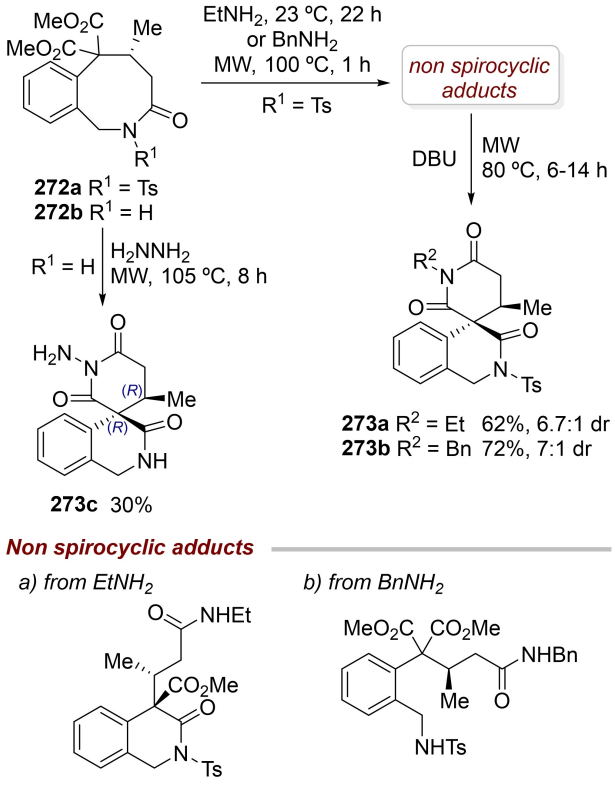


Scheme 72. Bicyclization reaction of two allenyl ketones and two isocyanides.

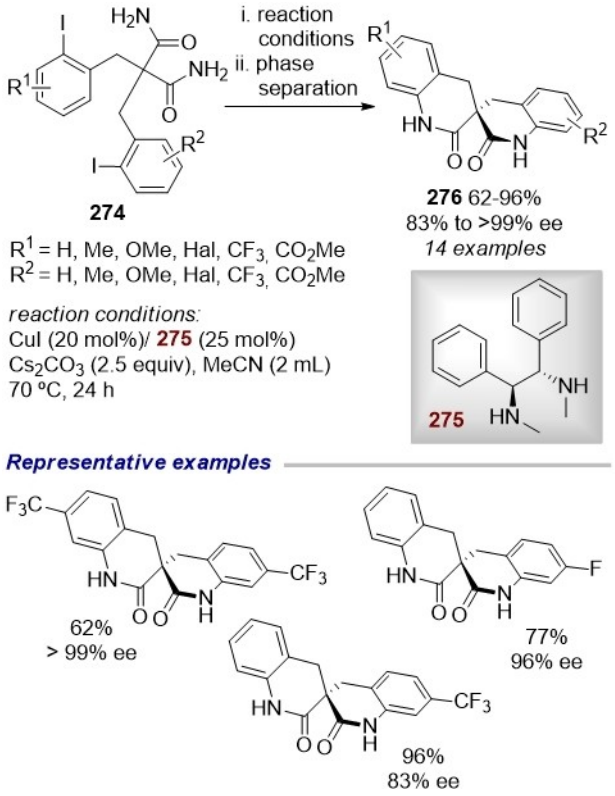
cinone ring, followed by lactamization and spirocyclization upon treatment with DBU.

Spirocyclic bis-lactams **276** were obtained via a copper-catalyzed double *N*-arylation of 2,2-bis(2-iodobenzyl)malonamides **274** followed by simple solid–solution phase separation (Scheme 74).[88] The reaction, catalyzed by copper in the presence of ligand **275** using Cs_2CO_3 as the base, allowed the synthesis of **276** in good yields (62–96%) and enantioselectivies (up to >99% ee). The double *N*-arylation comprises a two-step process, with enantioselectivity being established in the first desymmetric cyclization. The great breakthrough of this protocol was the observed enhancement of the solution enantiomeric excess through precipitation of racemates.

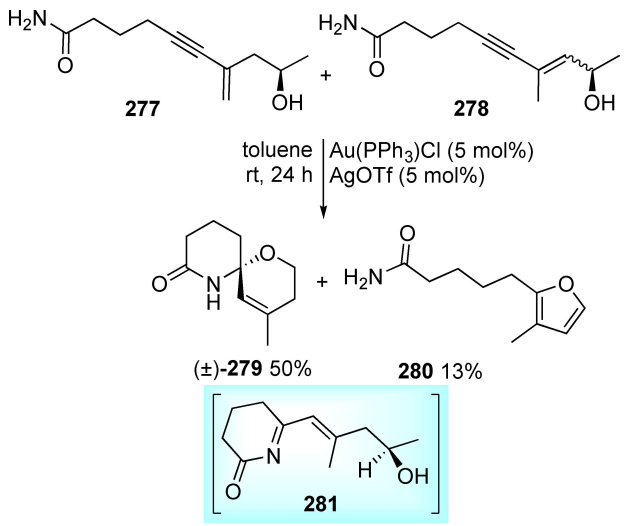
Sarli's group described the synthesis of spirodihydropyran-δ-lactam **279** through a gold-catalyzed spiroamidoketalization of alkynyl amidoalcohols



Scheme 73. Reactivity of benzazocinones towards nucleophiles.



Scheme 74. Copper-catalyzed double *N*-arylation of 2,2-bis(2-iodobenzyl)malonamides.



Scheme 75. Spiro-dihydropyran-δ-lactam via gold-catalyzed spirocyclization of alkynyl amidoalcohols.

(Scheme 75).[89] Spirocyclization of a mixture of ynamides **277** and **278** in the presence of 5 mol% Au catalyst afforded spiro-δ-lactam **279** in 50% yield along with furan derivative **280** (15%). A plausible mechanism for the synthesis of **279** involves a proton or gold-catalyzed intramolecular oxycyclization of intermediate **281**.

4. Conclusion

The present review focused on the most recent synthetic procedures developed towards the synthesis of spiro-β-lactam and spiro-δ-lactams. An extensive and comprehensive discussion about the methods' synthetic strategies, scope, efficiency, selectivity, and reaction mechanism is presented. The two classes of spirocyclic lactams discussed herein share the same general three strategies for building the spirocyclic core, namely, the construction of the lactam ring from a precursor containing a cyclic subunit, the construction of the second ring starting from a lactam-containing building-block or the one-pot synthesis of both rings.

Concerning spiro-β-lactams synthesis, the Staudinger cycloaddition approach remains the most widely explored methodology. However, several other methodologies have been alternatively applied such as, for example, the Reformatsky reaction for the β-lactam construction, or the 1,3-dipolar cycloaddition of α-alkylidene-β-lactams for the construction of the non-lactam ring. On the other hand, spiro-δ-lactams synthesis are mainly focused on nucleophilic cyclization reactions. However, other strategies, such as NHC-catalyzed annulation and cascade Mannich addition/cyclization reactions also found application in the synthesis of these scaffolds. The considerable efforts on the development of multicomponent and metal-free spiro-lactamization strategies are also remarkable.

Notwithstanding the considerable diversity of methods available for the synthesis of both spirocyclic β- and δ-lactams, the crescent interest towards these molecules with singular 3D properties in fields such as organic and medicinal chemistry requires a continuous investment on the development of new methodologies able to ensure the synthetic accessibility to new and more varied classes of spirocyclic lactams.

Acknowledgements

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