Strategies and methodologies for the construction of spiro-fused γ-lactams: an update

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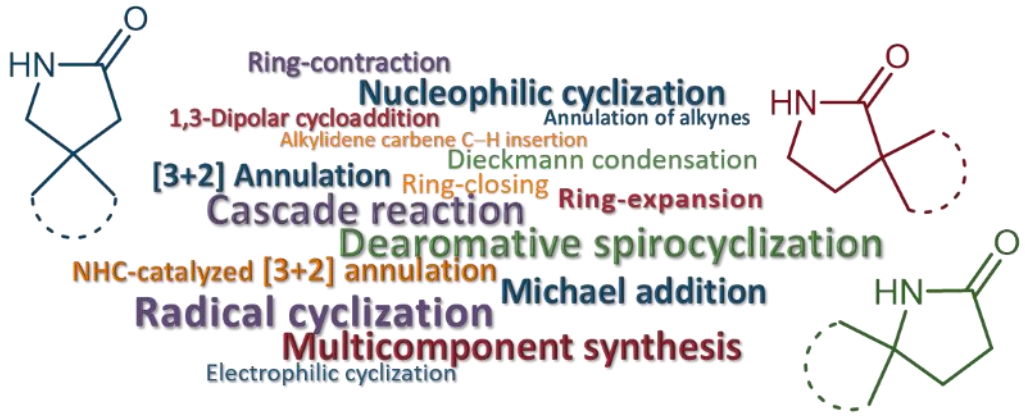


Abstract - Spiro-γ-lactams (spiropyrrolinin-2-ones) are a class of spirocyclic compounds that are present in a wide range of synthetic bioactive and naturally occurring molecules. The increasing attention to spirocyclic lactams in drug discovery has been accompanied by a growing interest in these compounds from a synthetic point of view, namely as synthetic building blocks in organic chemistry, due to their inherent rigidity and complexity. Herein, an insight into the most relevant advances in the synthesis of the spiro-γ-lactam scaffold since 2015 is provided, addressing issues such as scope, efficiency, selectivity and mechanistic insights.

Keywords: γ-lactams, spiro-γ-lactams, spiropyrrolinin-2-ones, spirocyclic compounds, spirocyclization

CONTENTS

1. INTRODUCTION

Spirocycles are privileged scaffolds in organic synthesis and drug design due to their vast existence as a key structural unit in a panoply of molecules of interest. Among them, spirocyclic ring systems containing a γ-lactam ring (spiropyrrolinin-2-ones) are present in several functional molecules, including biologically active molecules such as the antivomiting drug rolapitant (**1**).[1] The spirocyclic γ-lactam motif is also present in several naturally occurring molecules such as elmenol H (**2**),[2] alkaloid annosqualine (**3**) and spirostaphylotrichin A (**4**) (Figure 1).

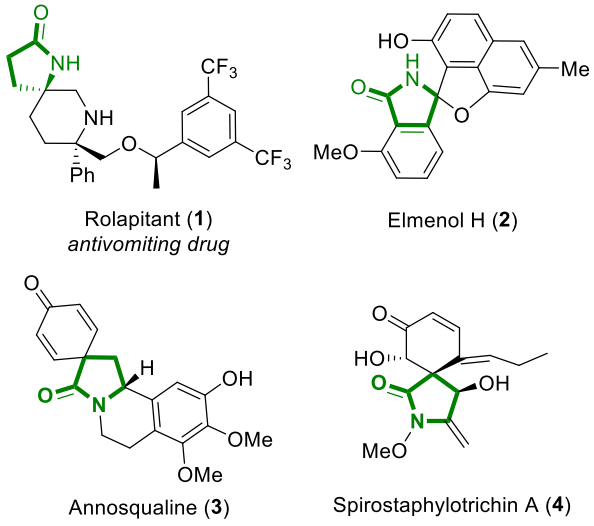


Figure 1. Representative biologically active spirocyclic γ-lactams.

Along with the increasing attention of spirocyclic lactams in drug discovery, the inherent rigidity and complexity of these scaffolds makes them very attractive compounds from a synthetic point of view, namely as synthetic building blocks in organic chemistry and even as chiral counterparts in asymmetric synthesis. Therefore, many efficient methods for the synthesis of spirocyclic γ-lactams have been developed, ranging from classical cyclization reactions to more recent

strategies such as N-heterocyclic carbene (NHC)-catalyzed annulation or photo-mediated radical cyclization reactions.

The literature contains a variety of comprehensive reviews addressing synthetic approaches to γ-lactams,[3] but none of them are dedicated exclusively to the synthesis of spirocyclic γ-lactams.

In this review, the most relevant advances in synthetic methodologies towards spirocyclic fused γ-lactams since 2015 are covered. The plethora of available methods has enabled the synthesis of a wide variety of spirocyclic lactams with the carbon fusion at different positions (C3, C4 or C5) as well as spiro-fused bis-lactams (Figure 2). Spiro-succinimides have not been included in the current review. The synthesis of spirocyclic unsaturated γ-lactams and spiro-γ-lactams fused to an aromatic/heteroaromatic system are also covered in this review, with the exception of those γ-lactams embodied in a spirooxindole core structure. The spirooxindole motif is a key unit present in a large number of bioactive alkaloids and several other compounds with relevance in medicinal chemistry, which inspire the continuous advent of comprehensive reviews covering both synthesis and biological activity of this family of compounds.[4] Nevertheless, the current review includes systems in which the oxindole moiety is fused with another γ-lactam ring.

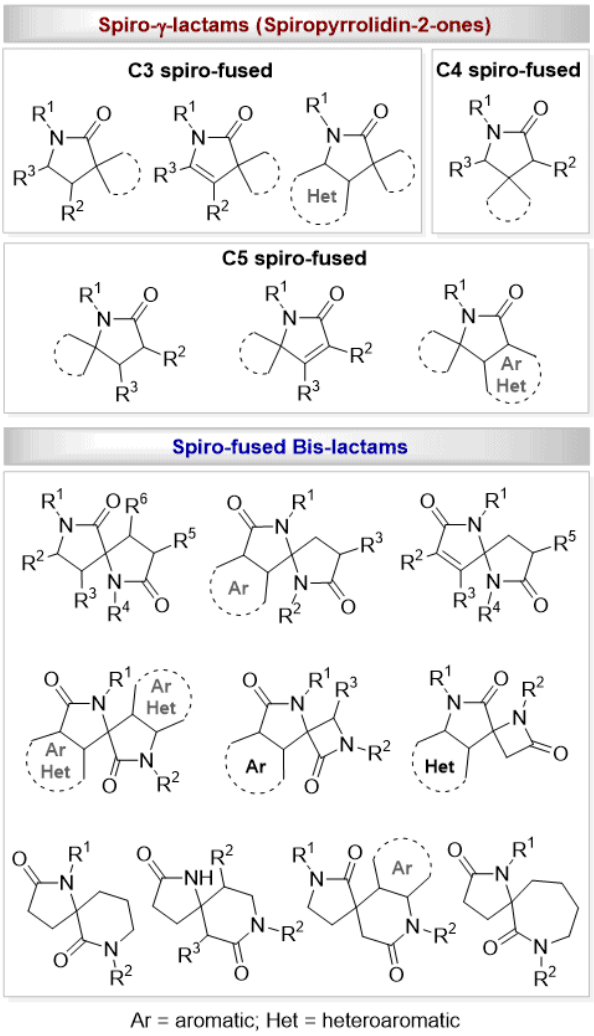


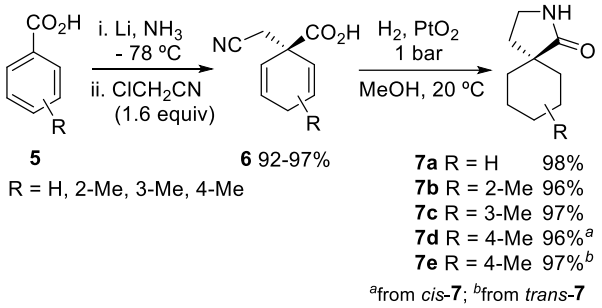
Figure 2. General structures of spirocyclic γ-lactams.

The most common synthetic strategies for obtaining spirocyclic lactams are comprised of two general strategies: a) the construction of the lactam ring starting from building blocks containing a ring subunit, and b) the construction of the second ring starting from lactam-containing precursors. Additionally, spirocyclic lactams can be obtained through less common processes involving the one-pot synthesis of both lactam and non-lactam rings. Herein, these three synthetic strategies will be addressed separately.

2. LACTAM RING SYNTHESIS

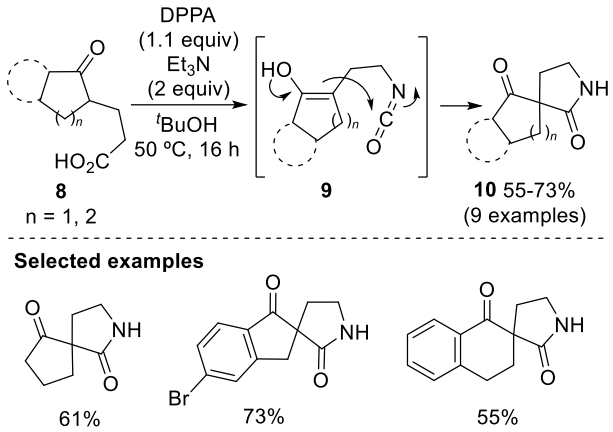
2.1 Nucleophilic cyclization reaction

Linker and co-workers developed a two-step protocol for the synthesis of cyclohexane-based spiro-γ-lactams starting from readily available building blocks.[5] The methodology involved a Birch reduction of benzoic acids **5** followed by direct alkylation with chloroacetonitrile to give cyclohexadienes **6** in high yields (92-97%) (Scheme 1). Catalytic hydrogenation of **6** using platinum (IV) oxide conveniently reduced, in the same step, the nitrile group and the double bonds generating *in situ* γ-aminobutanoic acids. Under these conditions, lactamization occured directly to give spiro-γ-lactams **7** in high yields (96-98%) as single diastereomers.



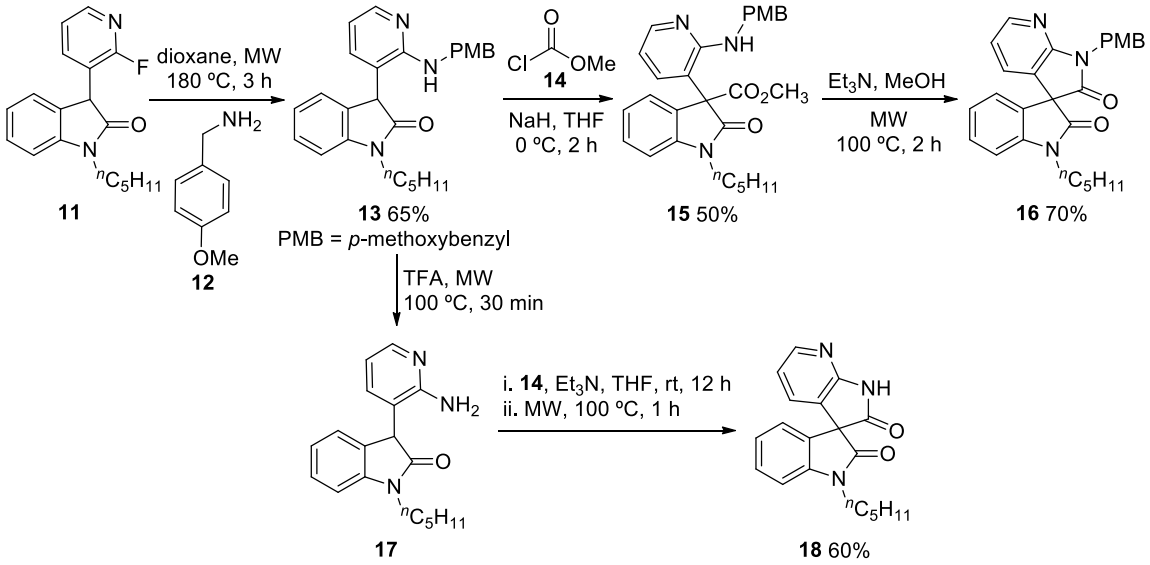
Scheme 1. Two-step approach to spiro-γ-lactams from benzoic acids via Birch reduction.

A straightforward one-pot protocol for the synthesis of spirocyclic β-keto-γ-lactams **10** using δ-keto carboxylic acids **8** as suitable precursors has been reported (Scheme 2).[6] The synthetic methodology started with a Curtius rearrangement, induced by the reaction of **8** with diphenylphosphoryl azide (DPPA) which led to the generation of isocyanate intermediates **9**. Subsequent intramolecular nucleophilic addition of the enolic form of the cyclic ketone to the isocyanate affords spirocyclic γ-lactams **10** in good yields (55-73%). When cyclohexanone β-keto carboxylic acids were used, modest yields of the corresponding spirocyclic γ-lactams were achieved. This was rationalized using molecular dynamics simulations which demonstrated that the isocyanate carbon to ring carbon distances are shorter for isocyanates derived from cyclopentanone δ-keto acids. Further post-functionalization reactions demonstrated the synthetic utility of the methodology.



Scheme 2. Spiro-γ-lactams from δ-keto carboxylic acids via one-pot cascade reaction involving a Curtius rearrangement followed by a nucleophilic cyclization.

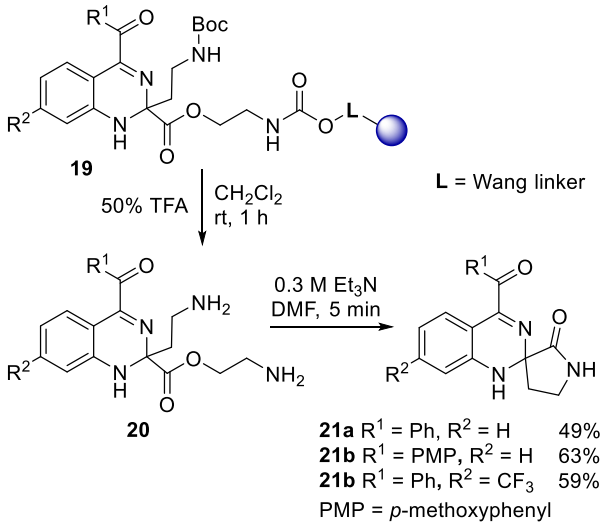
Guillaumet and co-workers reported a microwave-assisted cyclization of conveniently substituted *N*-pentyl-3-pyridinyl-oxindoles (Scheme 3).[7] Oxindole **13**, bearing a protected amine functionality at the pyridyl group, was prepared by the reaction of **11** with 4-methoxybenzylamine (**12**). Compound **13** was functionalized upon reaction with methyl chloroformate (**14**) in the presence of NaH to furnish C-3 disubstituted oxindole **15** which cyclized under microwave-assisted conditions in methanol in the presence of NEt_3 to give tetracyclic spiro-γ-lactam oxindole **16** in 70% yield. The *N*-deprotection of **13** was also carried out providing compound **17**, which could also be converted into spirocyclic γ-lactam **18** in 60% yield. It is noteworthy that the use of methyl bromoacetate instead of methyl chloroformate allowed the synthesis of analogous spirocyclic δ-lactam oxindoles**.**



Scheme 3. Microwave-assisted intramolecular cyclization of *N*-protected-3-methoxycarbonyl-3-(2-aminopyridinyl)-oxindoles.

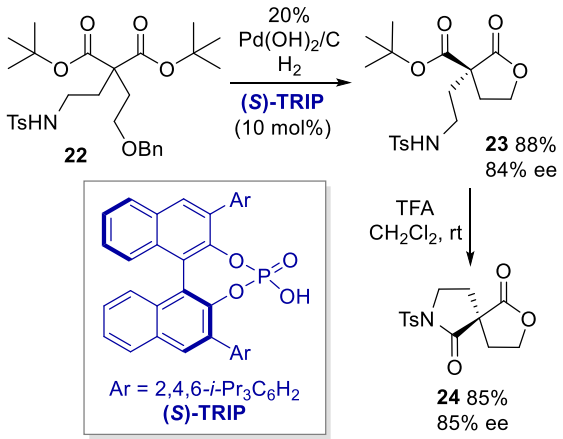
Schütznerová and co-workers reported the synthesis of spirocyclic quinazoline γ-lactams **21** via lactamization of quinazoline substrates **20**, bearing an ester and an aminoalkyl substituents at the quaternary carbon C-2, derived from resin-bound precursors **19** (Scheme 4).[8] Compounds **19** were prepared by a solid-phase synthesis using protected amino acids, 2-nitrobenzensulfonyl chlorides

and α-bromoacetophenones. Solution treatment of **19** with TFA (trifluoroacetic acid) promotes the cleavage of the quinazoline from the solid support as well as the deprotection of the amine group necessary for the amide bond formation, affording 1,2-dihydroquinazoline-2-carboxylates **20** which were isolated and fully characterized. Triethylamine-mediated cyclization of **20** in DMF led to the synthesis of spirocyclic lactams **21** in moderate yields (49-63%). The methodology was also used in the synthesis of spirocyclic quinazoline δ-lactams.



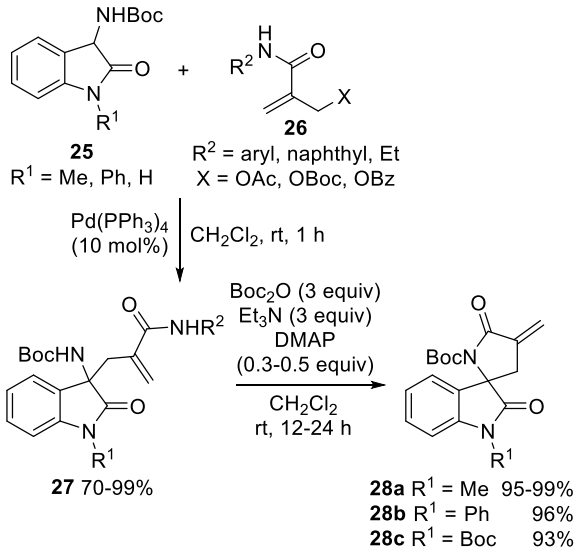
Scheme 4. Lactamization of 1,2-dihydroquinazoline-2-carboxylates.

Spiro-γ-lactone γ-lactam **24** was prepared by a two-step protocol in 75% overall yield from di-*tert*-butyl malonate derivative **22** bearing, at the α-carbon, two alkyl chains with terminal nucleophiles (Scheme 5).[9] The reaction involved the deprotection of the hydroxyl group of **22** under hydrogen atmosphere with 20% $Pd(OH)_2/C$, followed by desymmetrization via intramolecular lactonization using a chiral BINOL-phosphoric acid catalyst [(*S*)-TRIP]. This afforded enantioenriched γ-lactone **23** that subsequently underwent amine deprotection and lactamization in the presence of TFA to give spirocyclic compound **24** in 85% yield and 85% ee. A similar approach was applied to the synthesis of an analogous spiro-γ-lactone-δ-lactam.



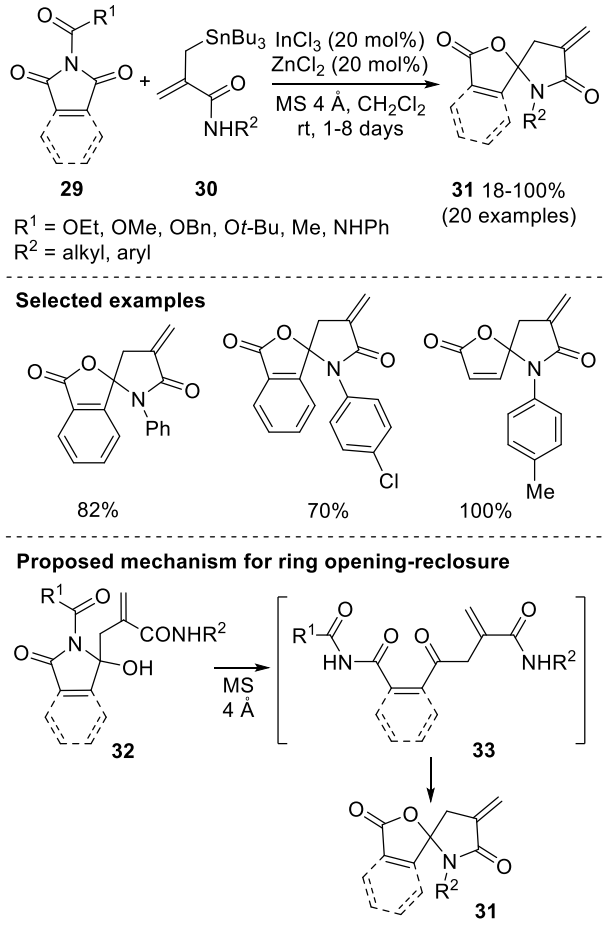
Scheme 5. Chiral spiro-γ-lactam from α-functionalized malonates via chiral phosphoric acid catalyzed lactonization followed by a lactamization reaction.

Yoda and co-workers described an efficient methodology for the synthesis of spirooxindole α-methylene-γ-lactams **28** by the cyclization of amide allylated oxindoles **27** (Scheme 6).[10] The key step of this strategy is an electrophilic amide allylation of 3-Boc-aminooxindoles **25** using acetoxy methacrylamides **26** and tetrakis(triphenylphosphine)palladium as catalyst. The cyclization of amide allylated oxindoles **27** was achieved by using Boc_2O, triethylamine, and *N*,*N*-dimethyl-4-aminopyridine (DMAP) in dichloromethane at room temperature. A range of substituents on the terminal amide were well tolerated, leading to the formation of products **28** in high yield (93-99%).



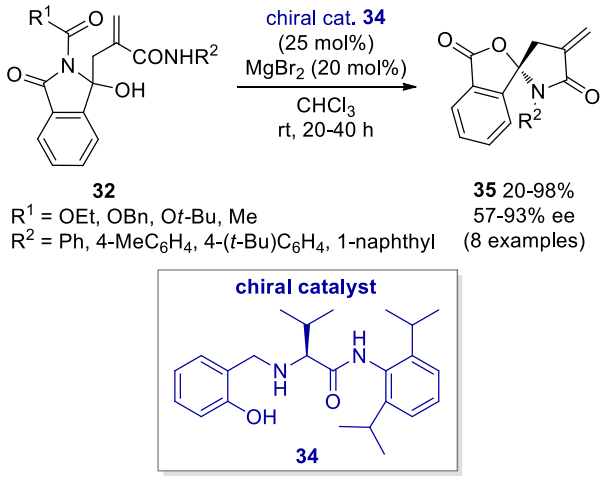
Scheme 6. Cyclization of amide allylated 3-Boc-aminooxindoles.

A two-step protocol for the synthesis of spiro-γ-lactone α-methylene-γ-lactams **31** involving the intermediacy of an amide allylated *N*-carbonyl imide (phthalimide or maleimide) has been also reported (Scheme 7).[11] Under the optimized conditions, *O*,*N*-spirocyclic compounds **31** were obtained in moderate to excellent yields (55-100%). However, in the case of *N*-carboxamide-substituted maleimide (**29**, R^1 = NHPh), the yield decreased dramatically to 18%. Mechanistic studies provided evidence for a two-step process involving a $ZnCl_2$-assisted addition of β-amido allylindium species, generated by the transmetalation of β-amido allyltributylstannanes **30** with $InCl_3$, to produce amide allylated *N*-carbonyl imide intermediate **32**. This is followed by a molecular-sieves mediated ring opening-reclosure with loss of the *N*-carbonyl unit. The use of β-amido allylboronates as nucleophilic reagent in the $ZnCl_2$-promoted amide allylation of *N*-carbonyl imides was later reported, disclosing an environmentally compatible and easy-to-handle synthetic alternative.[12] The reaction displays good functional group tolerance with both maleimide and phthalimide substrates, furnishing the corresponding spirocyclic γ-lactone α-methylene-γ-lactams in moderate to high yields (59-100%).



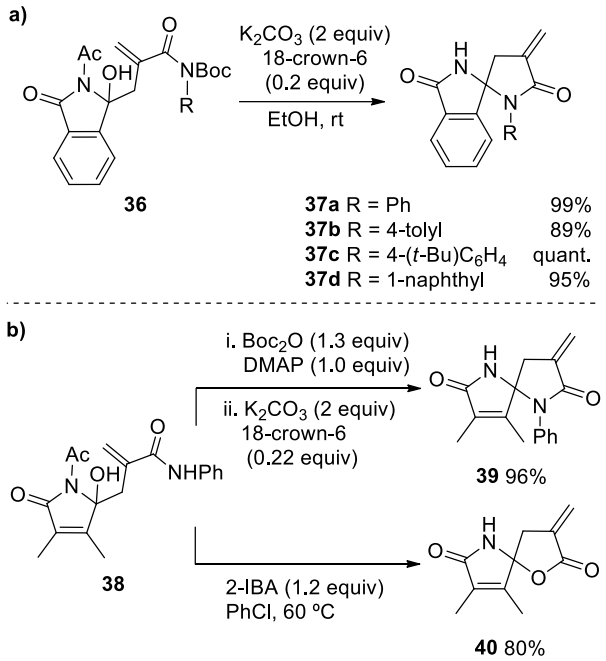
Scheme 7. Cyclization of amide allylated imides by ring opening-reclosure reactions.

Recently, the same research group described the enantioselective synthesis of *O*,*N*-spirocyclic compounds **35** catalyzed by $MgBr_2$ and chiral aminomethylphenol **34** (Scheme 8).[13] Amide allylated *N*-carbonyl imides **32**, derived from the reaction of *N*-carbonyl phthalimides with β-amido allylboronates, underwent asymmetric ring opening-reclosure to give the corresponding spirocyclic γ-lactams in good yields (up to 98%) and enantioselectivities (up to 93% ee).



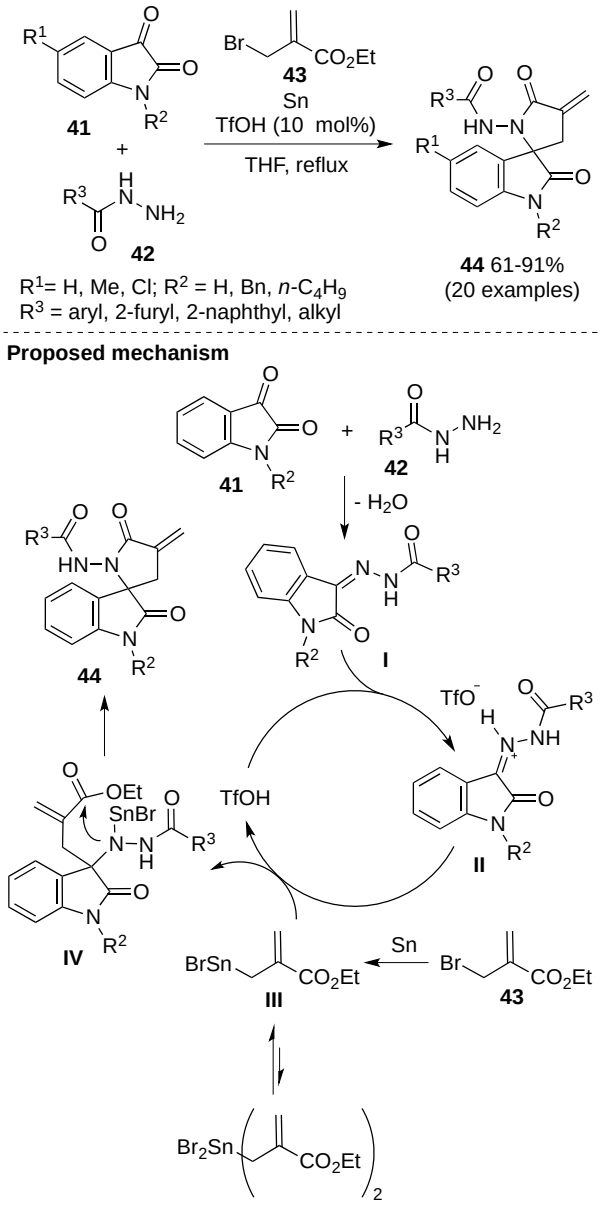
Scheme 8. Enantioseletive cyclization of amide allylated imides by ring opening-reclosure reactions.

Cyclization of *N*-Boc-protected amide allylated *N*-acetylisoindolinones **36**, derived from phthalimide, affords *N*,*N*-spirocyclic α-methylene-γ-lactams **37** (Scheme 9a).[14] The protection of the terminal amide moiety with Boc proved to be crucial, since when using unprotected precursors, under the same conditions, the formation of *O*,*N*-spirocyclic products was favored (see Scheme 7). *N*-Ethoxycarbonyl and benzyloxycarbonyl substituents on the isoindolinone moiety are also well tolerated, affording spiro-γ-lactam isoindolinones **37** in high yields (89% to 99%). The scope of the methodology was extended to the synthesis of maleimide-derived *N*,*N*- and *N*,*O*-spirocycles. Bis-lactam **39** was obtained in 96% yield by a two-step sequence using the same reaction conditions used for phthalimide derivatives, whereas unsaturated spiro-γ-lactone γ-lactam **40** was obtained by an iodobenzoic acid (IBA)-mediated cyclization in 80% yield (Scheme 9b).



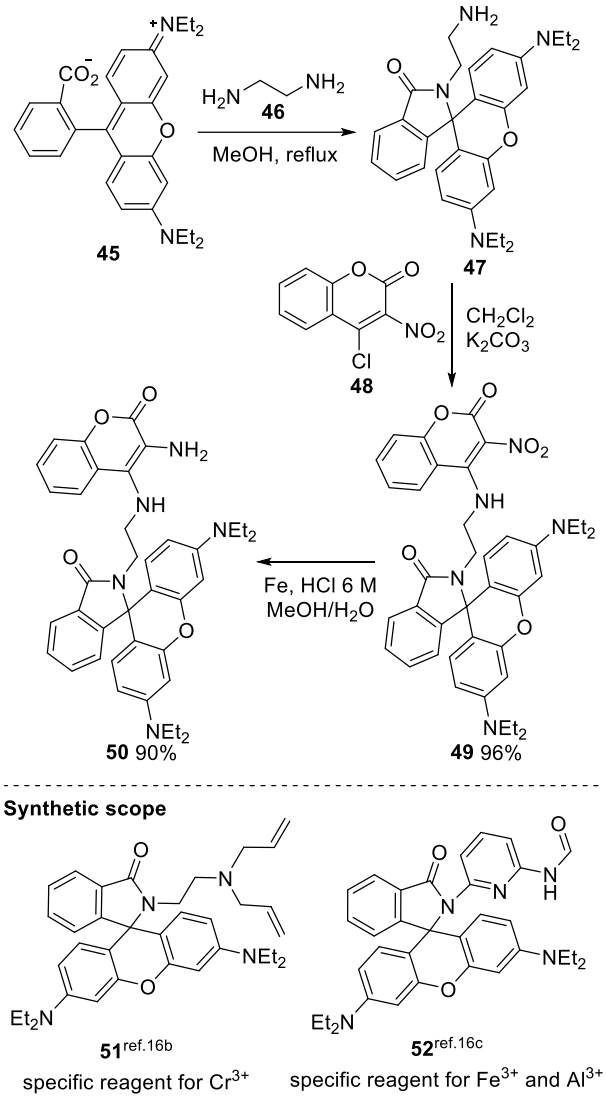
Scheme 9. Cyclization of amide allylated phthalimide-derived substrates.

Wang *et al*. reported a tin powder-promoted one-pot synthesis of spirooxindole α-methylene-γ-lactams **44** starting from isatin derivatives **41** (Scheme 10).[15] Isatins were condensed with aromatic and aliphatic hydrazides **42** to give *N*-acylhydrazones **I**, which were protonated with triflic acid to generate the more reactive intermediates **II**. Reaction of **II** with the *in situ* generated stannanes **III** afforded the allylated intermediates **IV** which underwent cyclization to give spirooxindole γ-lactams **44** in good yields (61-91%) with good substrate scope. Moreover, the use of tin powder avoids problems associated with the handling of toxic stannanes. No cyclization products were observed when aromatic amines were used instead of hydrazides. In this case, cyclization was unfavorable, leading to the exclusive formation of allylated products.



Scheme 10. Cyclization of ester allylated isatin-derived substrates.

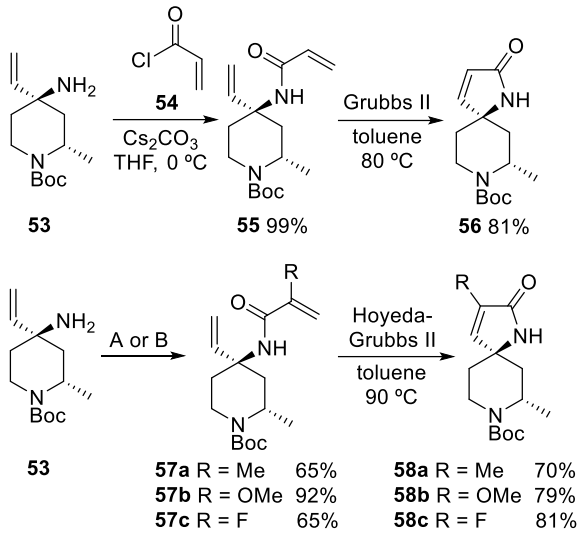
The synthesis of spirocyclic rhodamine-γ-lactam conjugates (*e.g.* **50**) suitable to act as fluorescent probes for the recognition of different metal ions of biological importance has been reported.[16] The key-step of these synthesis involved the reaction of a rhodamine-derived carboxylic acid or acid chloride (*e.g.* **45**) with an appropriate diamine (**46**) to provide the corresponding spirocyclic rhodamine-γ-lactam (*e.g.* **47**). The reaction of **47** with 4-chloro-3-nitro-2*H*-chromen-2-one (**48**) provided **49** which was further reduced to give rhodamine-γ-lactam conjugate **50**, a selective probe for Pd(II) cations (Scheme 11).[16a] In fact, upon specific binding to Pd^{2+} ions, the non-luminescent spirocyclic lactam form undergoes lactam ring-opening to give an acyclic luminescent xanthene form. Due to the non-toxicity towards Hct116 colon cancer cells and efficient cellular internalization, demonstrated by laser confocal microscopic studies, compound **50** can be used as imaging reagent for the detection of cellular uptake of Pd^{2+} in these cell lines.



Scheme 11. Synthesis of a coumarin-based sirocyclic rhodamine-γ-lactam molecular probe.

2.2 Ring-closing Grubbs metathesis

Martinez-Alsina *et al.* reported the synthesis of spiropiperidine α,β-unsaturated γ-lactams via ring-closing metathesis (Scheme 12).[17] The protocol included the initial acylation of allylic amine **53** with acryloyl chloride (**54**). The 4-acrylamido-4-vinylpiperidine **55** underwent catalyzed ring-closing metathesis using the second-generation Grubbs catalyst to give spiro-γ-lactam **56** in 81% yield. For the synthesis of 3-substituted spiro-γ-lactams **58**, amine **53** was acylated with an acid chloride (*e.g.* **57a**) or via amide coupling using an α-substituted acid (*e.g.* **57b** and **57c**). For these more hindered dialkenes, the Hoyeda-Grubbs second generation catalyst was used for the ring-closing metathesis, rendering spiro-γ-lactams **58** in good yields (70-81%). Spirocyclic lactams can be further arylated at the N-H via the Goldberg reaction with diamine ligand *N*,*N*′-dimethylethylenediamine (DMEDA), copper (I) iodide and aryl halides.

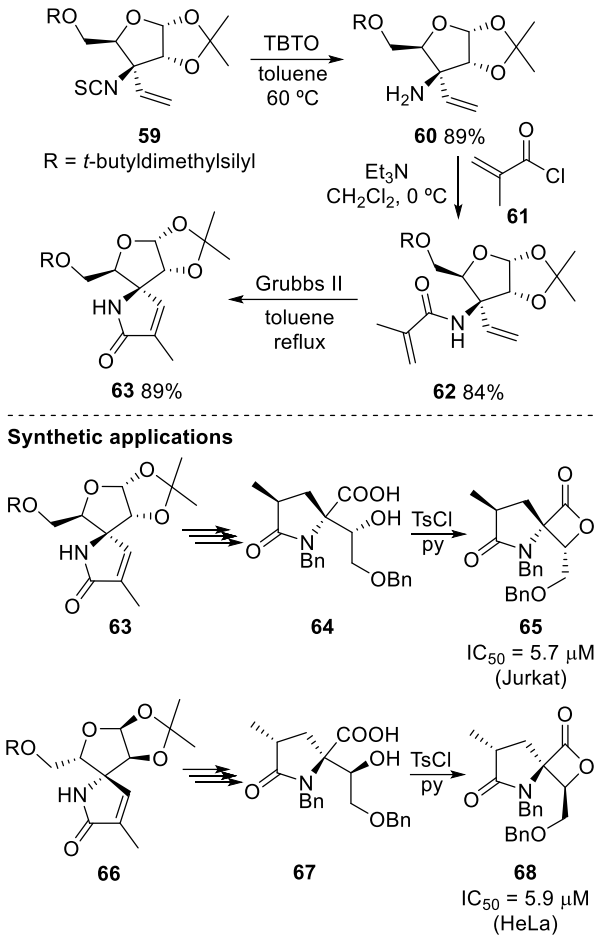


A: acid chloride, Cs_2CO_3, THF, 0 ºC (R = Me)
B: acid, DIPEA, TPTU, DMF (R = OMe, F)

DIPEA= N,N-Diisopropylethylamine; TPTU = *O*-(2-oxo-1(2*H*) pyridyl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate

Scheme 12. Ring-closing Grubbs metathesis of 4-acrylamido-4-vinylpiperidines.

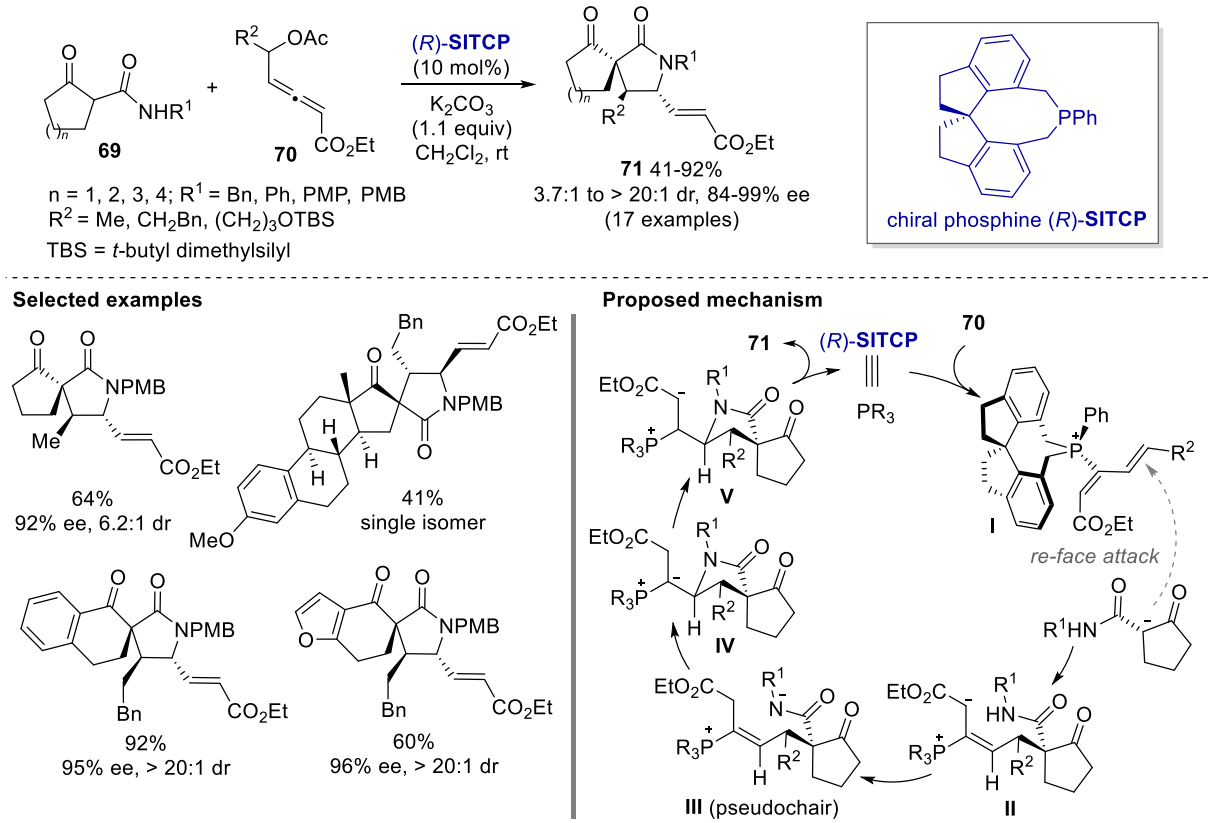
Recently, a similar ring-closing metathesis was applied in the synthesis of spiro-β-lactone γ-lactams starting from D- and L-xylose-derived isothiocyanates (Scheme 13).[18] Treatment of isothiocyanate **59** derived from D-xylose with bis(*n*-tributyltin) oxide (TBTO) afforded amine **60** which was converted into the sugar-derived vinyl acrylamide **62** by acylation with methacryloyl chloride (**61**). Subsequent ring-closing metathesis in the presence of Grubbs II afforded unsaturated spirocyclic γ-lactam **63** in 89% yield. The same strategy was used for the synthesis of the corresponding antipode **66** starting from L-xylose isothiocyanate. Lactams **63** and **66** were converted into spirocyclic β-lactone γ-lactams **65** and **68**, respectively, through a sequence of reactions which started with the reduction of the lactam moiety, involved opening of the non-lactam ring and ended with a β-lactonization reaction. The screening of compounds **65** and **68** for their *in vitro* cytotoxicity in human cancer cell lines showed that they possessed comparable or higher antiproliferative activity against Jurkat (human acute T-lympho-blastic leukaemia) and HeLa (cervical adenocarcinoma) cell lines than conventional chemotherapeutic drugs etoposide and cisplatin.



Scheme 13. Ring-closing Grubbs metathesis of sugar-derived vinyl acrylamides.

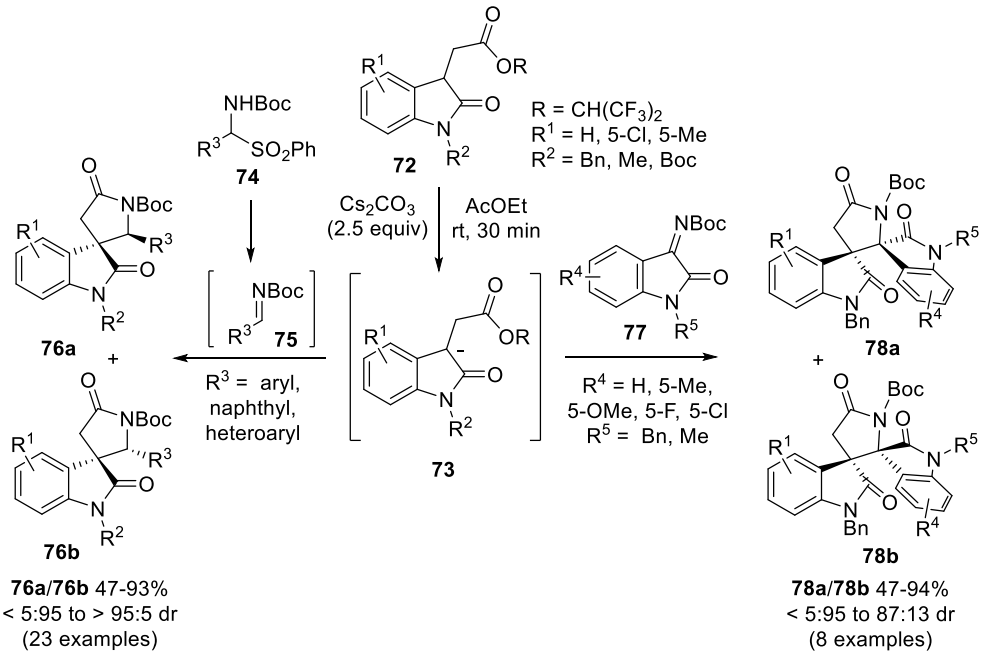
2.3 [3+2] Annulation reaction

Under phosphine catalysis, δ-acetoxy allenoates can behave as 2-carbon synthons in formal [3+2] cycloaddition reactions. Ni *et al.* explored the asymmetric [3+2] annulation of δ-acetoxy allenoates **70** with β-carbonyl amides **69** using chiral phosphine (*R*)-SITCP (Scheme 14).[19] Spirocyclic β-keto γ-lactams **71** were obtained in moderate to high yields (41-92%) and high stereoselectivity (> 20:1 dr and up to 99% ee). The reaction exhibits a broad substrate scope including steroidal substrates. In this annulation reaction, the C-γ and C-δ positions of the allenoates act as electrophilic sites on reacting with β-carbonyl amides **69** which behave as α-C,N-bisnucleophiles. The proposed mechanism involves the generation of 2-phosphonium diene intermediates **I** from **70** via a phosphine-catalyzed addition-elimination process. Since the *si*-face of the C-δ is shielded by the phenyl group of the phosphine, the nucleophilic attack of β-carbonyl amides **69** occurs by the *re*-face via a 1,6-additon providing intermediate **II**. Then, sequential proton transfer, intramolecular aza-Michael addition involving a pseudochair conformation, a second proton transfer and 1,2-elimination of the phosphine catalyst furnished the final products.



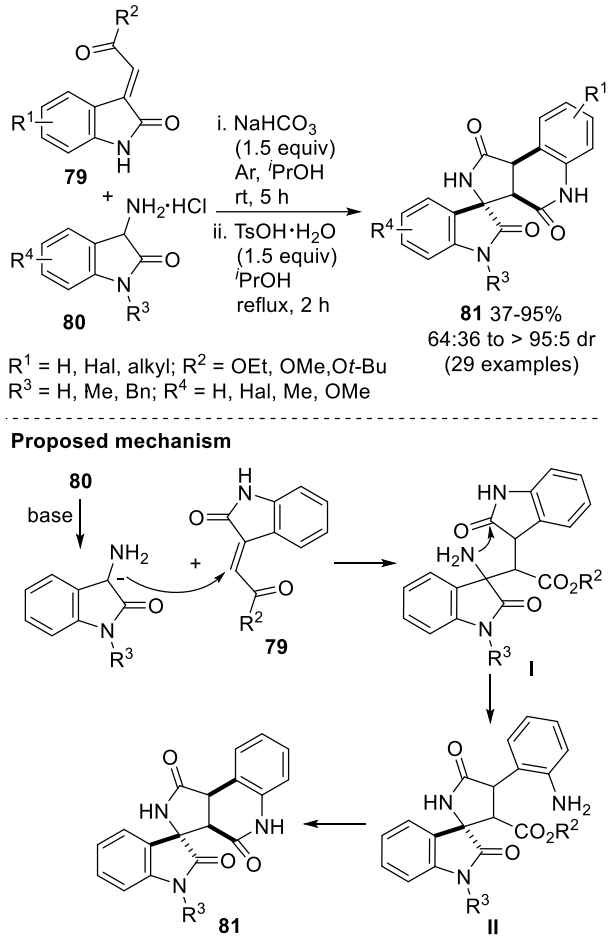
Scheme 14. [3+2] Annulation of δ-acetoxy allenoates with β-carbonyl amides.

Isatin-derived saturated esters **72** participate as 3-carbon synthons in base-promoted [3+2] annulation reactions with *N*-Boc imines to give 3,3'-spirooxindole γ-lactams under mild conditions (Scheme 15).[20] Starting from *N*-Boc aldimines derived from **74**, spirooxindole γ-lactams **76** were obtained in moderate to good yields. In general, this strategy led to the preferential formation of diastereomer **76a**, with the formation of the **76b** being favored only when aldimine precursors bearing *ortho*-substituted phenyl, 2-naphthyl or heteroaryl groups were used. The scope of the methodology was extended to *N*-Boc isatin ketimines **77**, providing the expected bispirooxindole γ-butyrolactams **78** in moderate to good yields and moderate diastereoselectivities.



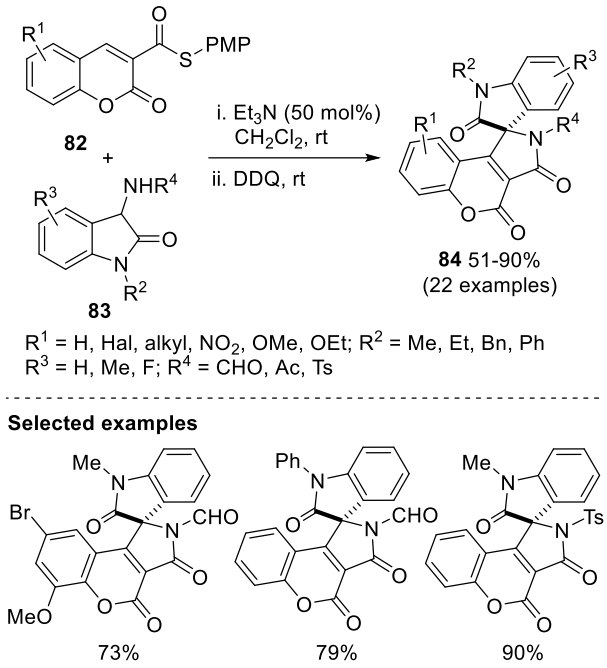
Scheme 15. Base-promoted [3+2] annulation of isatin saturated esters and *N*-Boc imines.

3-Aminooxindoles can be used as versatile nucleophiles for the construction of spirocyclic oxindoles via a cascade Michael addition/cyclization process.[4a] One example of this strategy is the synthesis of polycyclic spirooxindoles **81** featuring three lactam rings by a one-pot tandem ring-opening/ring-closure process combining methyleneindolinones **79** with 3-aminooxindoles **80** (Scheme 16).[21] The reaction started with the chemoselective Michael addition of 3-aminooxindole **80** to the double bond of methyleneindolinones **79** followed by lactam ring opening triggered by the cyclization of intermediate **I**. Subsequent lactamization afforded spirocyclic bis-γ-lactam adducts **81** fused with a δ-lactam moiety in moderate to high yields (37-95%) and diastereoselectivities (64:36 to > 95:5 dr) with good functional group tolerance. It's noteworthy, that these policyclic heterocycles could be isolated by simple filtration. Preliminary results on the asymmetric process using quinine, cinchona-derived thiourea and L-pyroglutamic sulphonamide as catalysts were also reported. Using these organocatalysts, the desired spirooxindoles **81** were obtained in high yields (91-93%) and diastereoselectivities (> 95:5 dr), however with low enatioselectivities (4-12% ee).



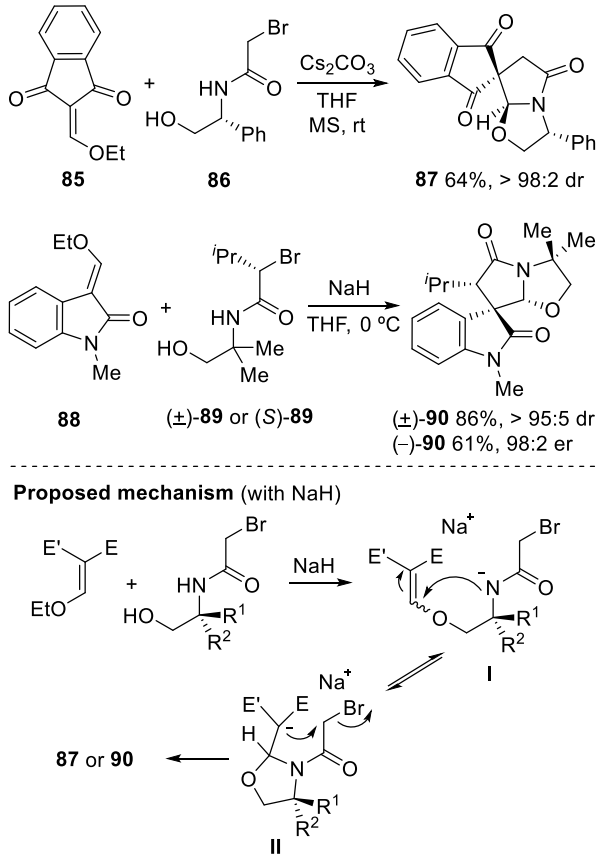
Scheme 16. Cascade ring-opening/ring-closure process between 3-aminooxindoles and methyleneindolinones.

Recently, Yuan and Zhao employed coumarin-3-thioformates as 3-carbon synthons for cyclocondensation with 3-aminooxindoles to the synthesis of pentaheterocyclic spirooxindole γ-lactams **84** (Scheme 17).[22] The reaction of coumarin-3-thioformates **82** with 4-aminooxindoles **83** via a one-pot tandem Michael addition/lactamization process followed by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) led to spirooxindole γ-lactams **84** in good yields (51-90%). Control experiments demonstrated that the 3-thioester moiety was crucial for the cyclocondensation process, since when using coumarin-3-carboxylate esters the expected spirocyclic products were not formed. This different reaction outcome was rationalized by the consideration of the higher lability of C(O)–S bond in thioesters.



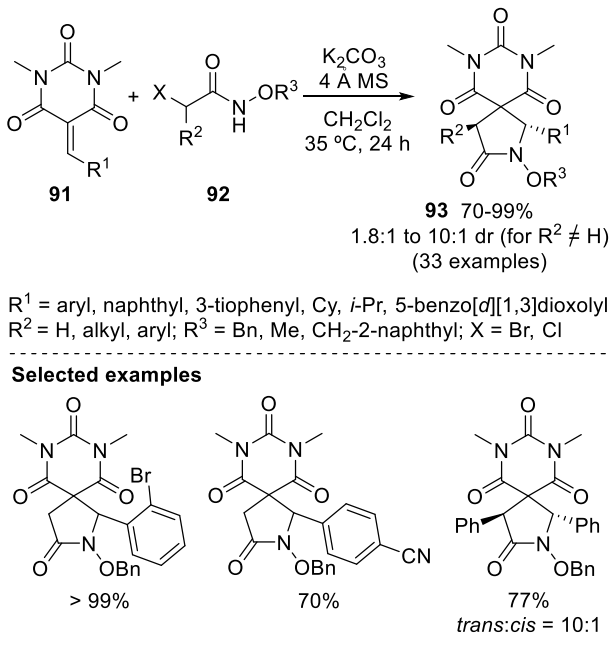
Scheme 17. Cascade Michael/cyclization reactions of 3-aminooxindoles with coumarin-3-thioformates.

Le Goff *et al.* reported a stereoselective cascade oxa-Michael/aza-Michael/cyclization process to access bicyclic γ-lactams, including bicyclic spiro-γ-lactams, using hydroxy haloamides and diverse Michael acceptors (Scheme18).[23] The reaction of 1,3-indanedione-derived alkene **85** and hydroxy bromoamide **86** led to the synthesis of spiro-1,3-indanedione γ-lactam **87** in 64% yield and high diastereoselectivity.[23a] When using oxindole-derived alkene **88** as Michael acceptor and racemic hydroxy bromoamide (±)-**89**, (±)-spirooxindole γ-lactam **90** was obtained in high yield and high diastereoselectivity (86%, > 95:5 dr). The use of enantioenriched hydroxy bromoamide (*S*)-**89**, led to the synthesis of the corresponding spirocyclic lactam (−)-**90** in 61% yield and high enantiomeric ratio (98:2).[23b] The proposed mechanism starts with a deprotonation by the base, followed by an addition-elimination process between the Michael acceptor and hydroxy bromoamide to furnish intermediate **I** which undergoes an aza-Michael addition to give **II**. Next, cyclization by intramolecular nucleophilic substitution leads to the formation of the spiro-γ-lactams.



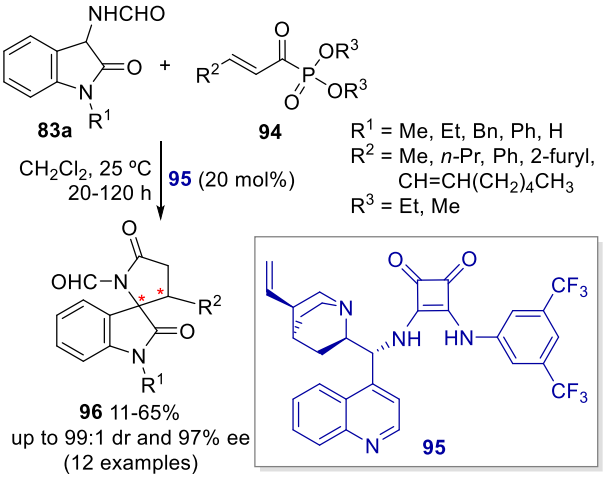
Scheme 18. Cascade oxo-Michael/aza-Michael/cyclization reactions of Michael acceptors with hydroxy bromoamides.

The efficient synthesis of spiro-barbiturate γ-lactams **93** was achieved by a base-promoted domino aza-Michael/S_N2 cyclization reaction between barbiturate-derived alkenes **91** and *N*-alkoxy α-haloamides **92** (Scheme 19).[24] This [3+2] annulation protocol tolerates diverse substituents on the terminal alkene position, including aromatic/heteroaromatic and alkyl groups, leading to spiro-γ-lactams **93** in high yields (70-99%).



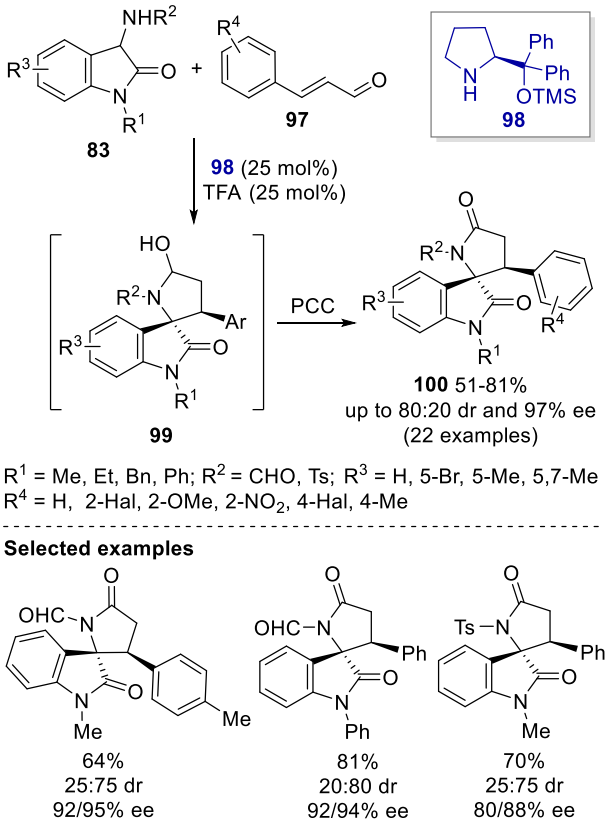
Scheme 19. Cascade aza-Michael/S_N2 cyclization reactions of barbiturate-derived alkenes with *N*-alkoxy α-haloamides.

Yuan, Xu and co-workers reported an organocatalytic enantioselective synthesis of spirocyclic γ-lactams **96** using α,β-unsaturated acyl phosphonates (Scheme 20).[25] Using cinchonine derived squaramide **95** as organocatalyst, the asymmetric Michael/cyclization cascade reaction of 3-aminooxindoles **83a** with α,β-unsaturated acyl phosphonates **94** afforded spirocyclic lactams **96** in moderate yields (11-65%) and stereoselectivities (up to 99:1 dr and up to 97% ee). Catalyst **95** plays a crucial role in this spiro-γ-lactam synthesis, activating both the Michael donor aminooxindole **83a** via enolization by the tertiary amine moiety and the Michael acceptor α,β-unsaturated acyl phosphonate **94** via an hydrogen-bonding interaction with the squaramide motif.



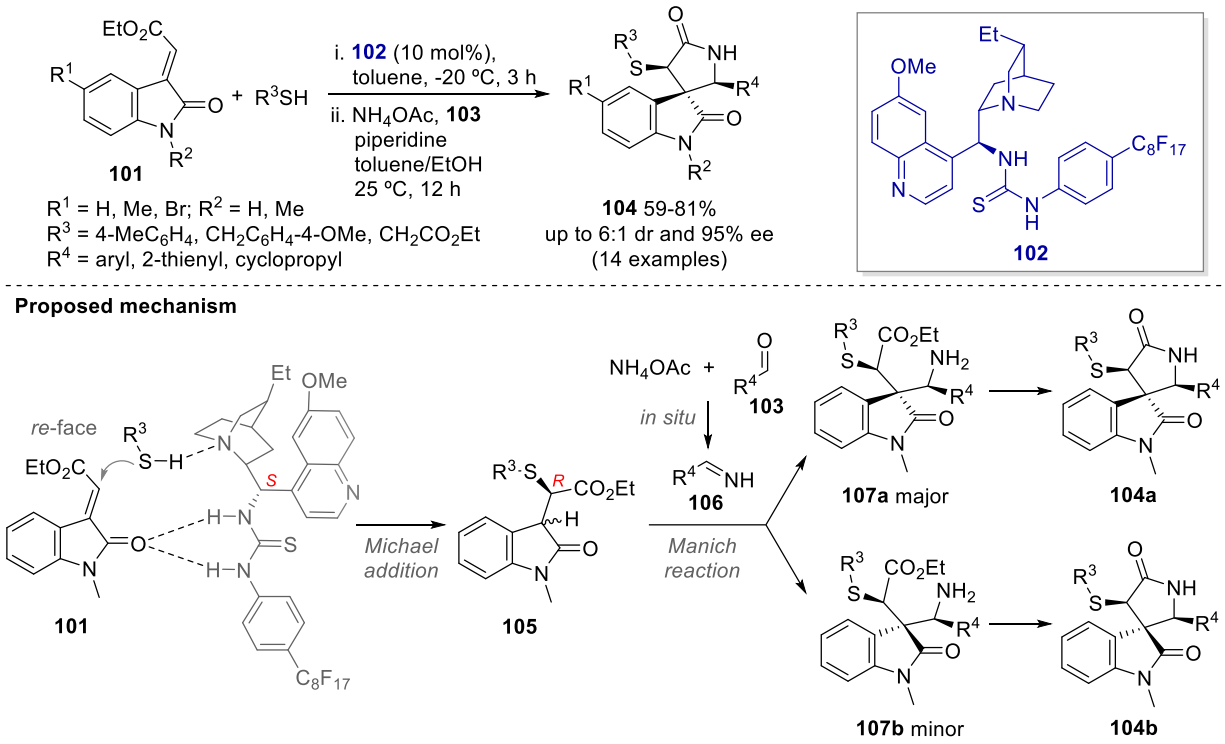
Scheme 20. Organocatalytic enantioselective cascade Michael/cyclization reactions between 3-aminooxindoles and α,β-unsaturated acyl phosphonates.

A similar enantioselective Michael/cyclization strategy was described by Wang and co-workers using α,β-unsaturated aldehydes as Michael acceptors.[26] The reaction of 3-amidooxindoles **83** with α,β-unsaturated aldehydes **97** in the presence of chiral α,α-diarylprolinol silyl ether catalyst **98** selectively afforded spirocyclic hemiaminals **99** which were oxidized with pyridinium chlorochromate (PCC) to give spirooxindole γ-lactams **100** in good yields (51-81%) with 75-97% ee and up to 80:20 dr (Scheme 21).



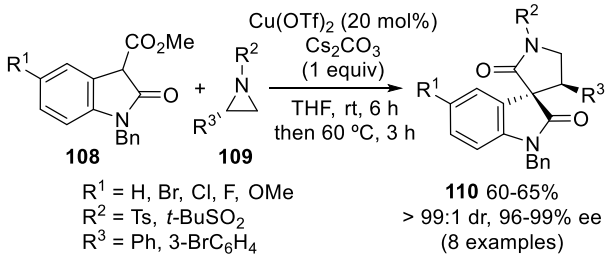
Scheme 21. Organocatalytic enantioselective cascade Michael/cyclization reactions between 3-aminooxindoles and α,β-unsaturated aldehydes.

In 2016, the Zhang's group reported the first asymmetric synthesis of spirooxindole γ-lactams bearing three contiguous stereocenters on the γ-lactam ring via a one-pot cascade thiol-Michael/Mannich/lactamization process (Scheme 22).[27] The reaction was initiated by a Michael addition of thiols to 2-oxoindolin-3-ylidenes **101**, catalyzed by recyclable fluorous bifunctional cinchona alkaloid-derived thiourea catalyst **102**, leading to the corresponding compound **104**. The stereochemical outcome was rationalized considering that the chiral catalyst forms a complex with the 2-oxoindolin-3-ylidene to induce the *re*-face Michael addition leading to the selective formation of a (*R*)-thiolated stereocenter. Subsequently, compounds **105** participate in a Mannich reaction with imine **106**, generated from aldehydes **103** and NH_4OAc, to give **107** which undergo further cyclization furnishing spirooxindole γ-lactams **104** in good yields (59-81%) with up to 95% ee and 6:1 dr.



Scheme 22. Cascade Michael/Mannich/cyclization reactions between oxoindolin-3-ylidenes and thiols.

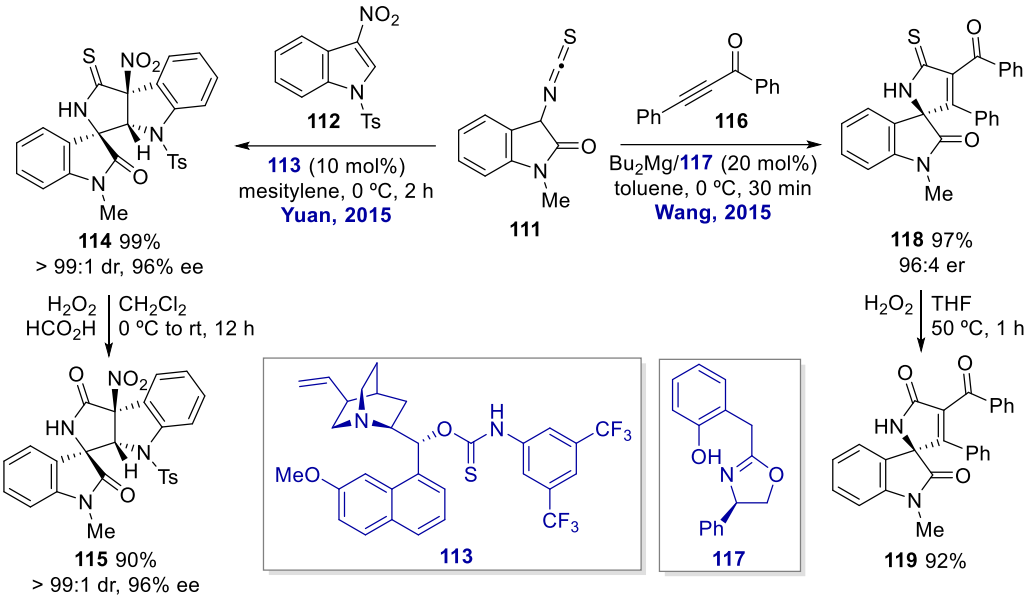
The synthesis of chiral spirooxindole γ-lactams via Lewis acid catalyzed cascade reaction involving aziridine ring opening and lactamization reactions has been reported.[28] The reaction between oxindole-3-carboxylates **108** and 2-aryl-aziridines, catalyzed by copper(II) triflate, afforded a range of spirooxindole γ-lactams in good yields (58-70%). Using enantiopure 2-aryl aziridines **109**, the corresponding spirocyclic lactams **110** were obtained in moderate yields (60-65%) with excellent stereoselectivities (dr > 99:1 and ee up to > 99%) (Scheme 23). The proposed mechanism involves $Cu(OTf)_2$ catalyzed selective aziridine ring-opening via N1–C2 bond cleavage triggered by nucleophilic attack of the enolate of the oxindole-3-carboxylates **108** and subsequent lactamization reaction.



Scheme 23. Copper-catalyzed domino aziridine ring opening/lactamization reactions.

Spirooxindole γ-lactams can be also obtained by oxidation of the corresponding spirocyclic γ-thiolactam precursors (Scheme 24). The asymmetric Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles (*e.g.* **111**) and 3-nitroindoles (*e.g.* **112**) catalyzed by amino-thiocarbamate catalyst **113** is one example of a strategy for the enantioselective synthesis of spirooxindoles bearing a thiolactam moiety (*e.g.* **114**).[29] Oxidation of compound **114**, employing aqueous hydrogen peroxide and formic acid, allowed the synthesis of spirooxindole γ-

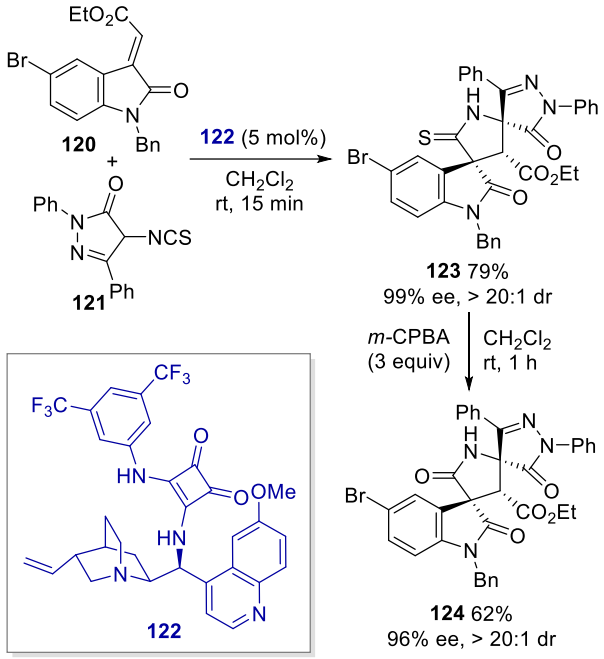
lactam **115** in 90% yield. On the other hand, the catalytic asymmetric [3+2] annulation of 3-isothiocyanoato oxindoles (*e.g.* **111**) and alkynyl ketones (*e.g.* **116**) affords a series of spirooxindoles (*e.g.* **118**) using a magnesium catalyst generated *in situ* from chiral oxazoline-OH ligand **117**. The C=S bond of the thiolactam ring was converted into a C=O bond by oxidation with hydrogen peroxide to give spirooxindole γ-lactam **119** in 92% yield.[30]



Scheme 24. Synthesis and oxidation of spirooxindole γ-thiolactams.

Shi's[31] and Du's[32] groups used a similar tandem asymmetric Michael/cyclization process for the synthesis of spirocyclic oxindole γ-thiolactams starting from 3-isocyanato oxindoles and α,β-unsaturated imines or chalcones, respectively, and using cinchona-derived catalysts. Both groups demonstrated that spirooxindoles γ-thiolactams could be efficiently converted to the corresponding spirooxindoles γ-lactams upon oxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) without loss of diastereo- and enantioselectivity.

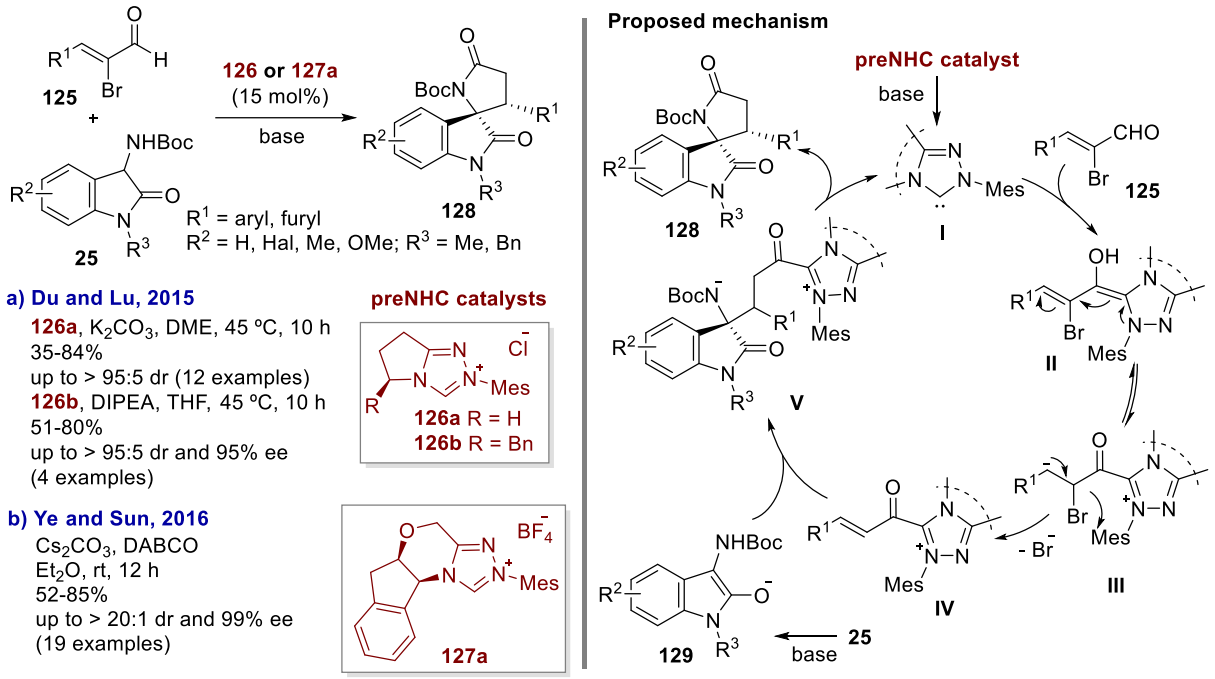
Recently, an interesting asymmetric synthesis of di-spiro-triheterocycles featuring a spirooxindole γ-thiolactam motif via a cascade Michael/cyclization reaction has been reported.[33] The construction of the spirooxindole γ-thiolactam core involved a quinine-derived squaramide-catalyzed reaction between 3-ylideneoxindoles (*e.g.* **120**), behaving as Michael acceptors, and 4-isothiocyanato pyrazolones (*e.g.* **121**) (Scheme 25). The synthetic utility of the protocol for the synthesis of spiro-γ-lactam oxindoles has been demonstrated by carrying out the oxidation of a spirooxindole γ-thiolactam **123** with *m*-CPBA which led to spirooxindole γ-lactam **124** in 62% yield without compromising the stereoselectivity (96% ee and dr > 20:1).



Scheme 25. Synthesis and oxidation of a spirooxindole γ-thiolactam.

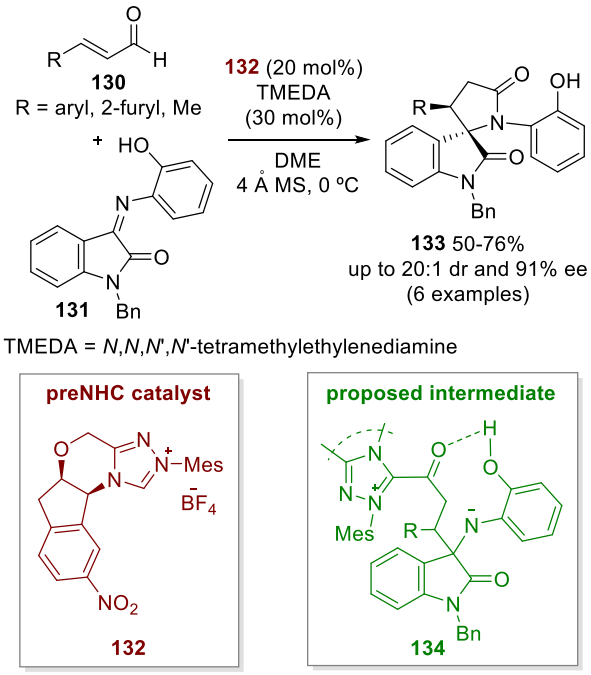
2.4 N-Heterocyclic carbene-catalyzed [3+2] annulation reaction

In recent years, N-heterocyclic carbenes have emerged as valuable organocatalysts and several examples of NHC-catalyzed annulation reactions have been reported for the synthesis of spirocyclic oxindole γ-lactams. In particular, NHC-catalyzed addition to α,β-unsaturated aldehydes generates α,β-unsaturated acylazoliums which are versatile intermediates, acting as biselectrophiles in the reaction with bisnucleophiles to give [3+n] annulation carbocyclic and heterocyclic products.[34] In this context, Lu, Du and co-workers have reported the stereoselective synthesis of spirooxindole γ-lactams by NHC-catalyzed [3+2] annulation of aromatic and heteroaromatic substituted α-bromoenals **125** with 3-aminooxindoles **25** (Scheme 26a).[35] The nucleophilic addition of **25** to α,β-unsaturated acylazoliums **IV**, generated from α-bromoenals **125** in the presence of preNHC catalyst **126a** and K_2CO_3, followed by lactam formation afforded a range of functionalized spirooxindole γ-lactams **128** in moderate to good yields (35-84%) and good diastereoselectivities. The asymmetric version of this methodology, using chiral NHC catalyst **126b**, was also explored by these authors, and later by Ye, Sun and co-workers.[36] In the latter case a mixed base of 1,4-diazabicyclo[2.2.2]octane (DABCO) and Cs_2CO_3 was used for the generation of a free NHC from chiral triazolium salt **127a** allowing the synthesis of the corresponding spirooxindole γ-lactams **128** in high diastereoselectivities and enantioselectivities (Scheme 26b). Mechanistically, the reaction proceeds through the generation of a carbene from the corresponding preNHC catalyst followed by its addition to α-bromoenal **125** to give the Breslow intermediate **II** which undergoes further tautomerization and debromination to give α,β-unsaturated acylazolium intermediate **IV**. Michael addition of 3-aminooxindole **25** via enolate **129** to intermediate **IV** affords **V** which undergoes lactamization giving **128**.



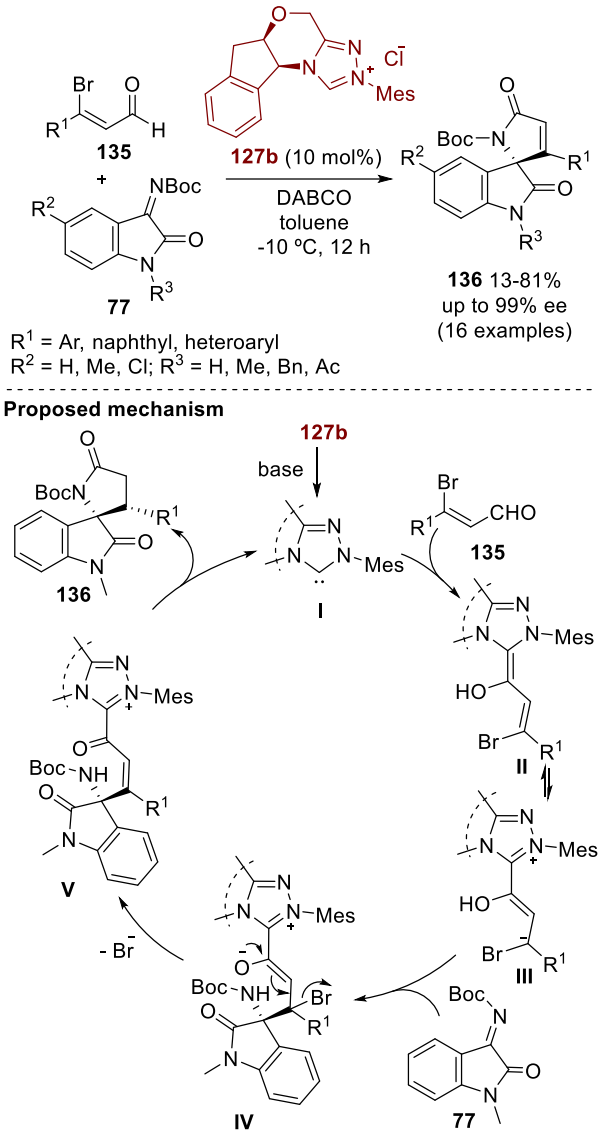
Scheme 26. NHC-Catalyzed [3+2] annulations of α-bromoenals with 3-aminooxindoles.

The asymmetric synthesis of spirocyclic oxindole γ-lactams was also achieved via NHC-catalyzed formal [3+2] cycloaddition of enals **130** with isatin-derived *N*-(*ortho*-hydroxyphenyl)imine **131** (Scheme 27).[37] The *ortho*-hydroxyphenyl group is a structural requirement for the synthesis of spirocyclic compounds, since derivatives bearing a phenyl group with substituents other than *ortho*-hydroxyl (*e.g.* H, Hal, Me) undergo a linear reaction affording the functionalized oxindole-γ-amino esters via NHC-catalyzed homo-Mannich reaction. The most likely mechanism for these transformations involves the addition of the carbene to the enal to give the corresponding Breslow intermediate which undergoes homo-addition to isatin imines followed by tautomerization. For the isatin-derived *N*-(*ortho*-hydroxyphenyl)imine **131** the lactamization process is favored due to an intramolecular hydrogen bridge (intermediate **134**) involving the *ortho*-hydroxyl group bringing the nitrogen nucleophile into close proximity with the acyl azolium. The use of a chiral NHC catalyst allowed to obtain spirooxindole γ-lactams **133** with good yields (50-76%) and high stereoselectivities (up to 20:1 dr and 91% ee).



Scheme 27. NHC-Catalyzed [3+2] annulation of enals with an isatin-derived *N*-(*ortho*-hydroxyphenyl)imine.

Hui and co-workers reported a NHC-catalyzed [3+2] annulation of 3-bromoenals **135** with isatin-derived *N*-Boc imines **77** affording spiro[indoline-3,2'-pyrrole] derivatives **136** with one chiral quaternary center (Scheme 28).[38] The use of a chiral NHC catalyst led to the formation of spirocyclic oxindoles **136** bearing an α,β-unsaturated γ-lactam moiety in moderate to good yields and with high enantioselectivities. The reaction conditions were compatible with a variety of substrates, however, higher yields and enantioselectivities were achieved when using isatin-derived imines bearing electron-donating *N*-protecting groups. A plausible catalytic cycle involves the generation of the Breslow intermediate **III** via 1,2-additon of chiral carbene **I** to 3-bromoenal **135** followed by 1,2-H migration. Intermolecular nucleophilic addition of **III** with isatin imine **77**, proton transfer and debromination affords **V** which undergoes intramolecular lactamization giving **136** and regenerating the NHC catalyst. The detailed mechanism and the origin of stereoselectivity have been theoretically investigated using density functional theory (DFT) calculations,[39] which indicated that the catalytic cycle was characterized by six steps, instead of the previously proposed five steps.[38] The debromination of intermediate **IV** followed by intramolecular cyclization triggered by bromine anion and subsequent regeneration of the catalyst were proposed as the three final steps. Moreover, it was found that the intermolecular nucleophilic addition of **III** to **77** was the stereoselectivity-determining step and the *S*-configuration product was the predominant product.

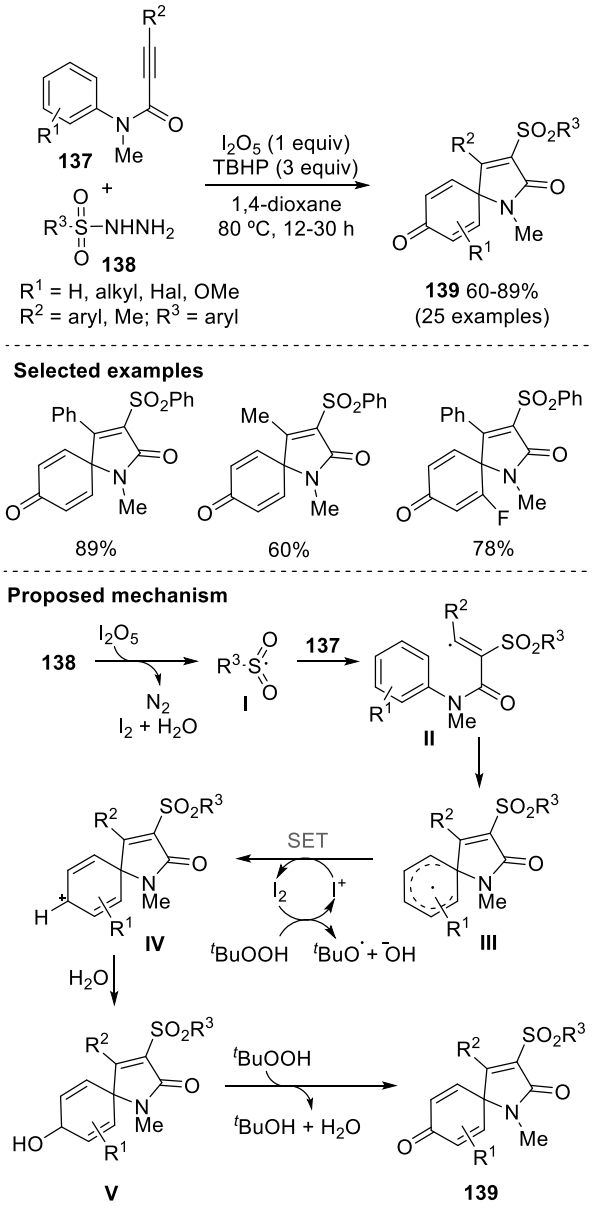


Scheme 28. NHC-Catalyzed [3+2] annulation of 3-bromoenals with isatin-derived *N*-Boc imines.

2.5 Dearomative spirocyclization

Electrophilic cyclization of heteroatom containing alkynes with a neighboring aromatic or heteroaromatic ring, such as *N*-aryl-alkynamides, provides a useful strategy to annulated heterocycles.[40] Depending on the reaction conditions and substrates, fused- or spiro-heterocycles can be attained if the cyclization involves the introduction of a substituent at the *ortho* or *ipso* positions of the aromatic ring, respectively. Wang, Wei and co-workers described a I_2O_5-mediated direct oxidative spirocyclization of *N*-arylpropiolamides **137** with sulfonylhydrazides **138** leading to 3-sulfonated azaspiro[4,5]trienones **139** (Scheme 29).[41] This involves a tandem process with sequential alkyne sulfonation, *ipso*-carbocyclization, dearomatization, hydration and oxidation reactions. Under the optimized conditions, using I_2O_5/*tert*-butyl hydroperoxide (TBHP) system in dioxane at 80 °C, unsaturated spiro-γ-lactams **139** were obtained in good yields (60-89%) with good functional group tolerance. The reaction also works with *para*-substituted *N*-arylpropiolamides **137** (*p*-MeO, *p*-F and *p*-I) affording the corresponding spiro-γ-lactams **139** by releasing the *para*-substituents. However, the reaction failed when the *N*-Me group was replaced

by *N*-H or *N*-Ac. The proposed mechanism starts with the single-electron oxidation of **138** mediated by I_2O_5 to generate aryl sulfonyl radical **I** followed by regioselective addition to *N*-arylpropiolamide **137** to give vinyl radical **II**. This intermediate undergoes intramolecular *ipso*-cyclization affording radical **III** which is then converted into cyclohexadienyl cation **IV** by a single-electron transfer (SET) process. Hydration, followed by TBHP-mediated oxidation leads to spiro-γ-lactams **139**. Recently, a similar metal-free approach has been reported where aryl sulfonyl radicals were generated *in situ* from 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) and aryl diazonium salts.[42] Sixteen spiro-3-sulfonated-γ-lactams were obtained in 76-90% yields.

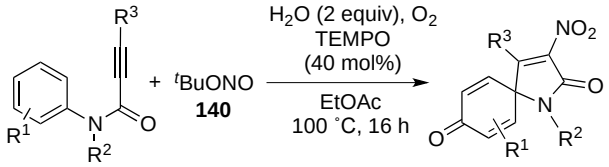


Scheme 29. I_2O_5-mediated direct oxidative spirocyclization of *N*-aryl-alkynamides.

The dearomative spirocyclization of *N*-aryl-alkynamides has become a valuable tool for the construction of diverse 3-substituted *para*-quinoid-based spiro-γ-lactam frameworks. Li, Song and co-workers reported a radical nitrative alkyne spirocyclization of *N*-aryl-alkynamides **137** employing a combined *t*-BuONO/water system as the nitro source, 2,2,6,6-tetramethylpiperidine

1-oxyl (TEMPO) as the initiator and O_2 as the oxidant (Scheme 30a).[43] The *para*-quinoid-based 3-nitro-spiro-γ-lactams **141** were obtained in good yields (43-86%) with good functional group tolerance and multigram-scale practicality. Soon after, Liu and co-workers employed $AgSCF_3$ as trifluoromethylthio radical source for the oxidative dearomatization of *N*-aryl-alkynamides **137** (Scheme 30b).[44] The reaction, promoted by the combination of $K_2S_2O_8$ and TBHP in the presence of hexamethylphosphoramide (HMPA), led to the synthesis of trifluoromethylthio-substituted spiro-γ-lactams **143** in good yields (52-95%) and good functional group tolerance, including *para*-substituted substrates (**137**, R^1 = 4-OMe, 4-Cl or 4-F).

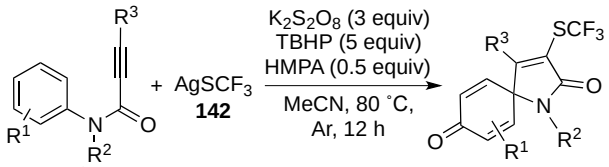
a) Li and Song, 2015



137 R^1 = H, alkyl, Hal, Ph, OMe, SMe, -$(CH)_4$-, 2,3-pyrido; R^2 = Me, Bn, Ph; R^3 = aryl, heteroaryl

141 43-86% (21 examples)

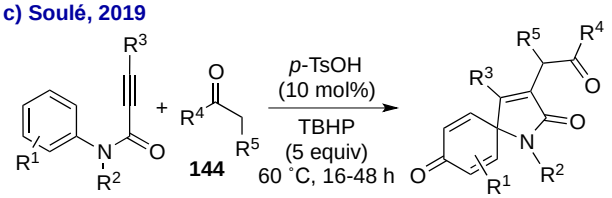
b) Liu, 2016



137 R^1 = H, alkyl, Hal, OMe, -$(CH)_4$-; R^2 = Me, Bn; R^3 = Me, aryl

143 52-95% (28 examples)

c) Soulé, 2019

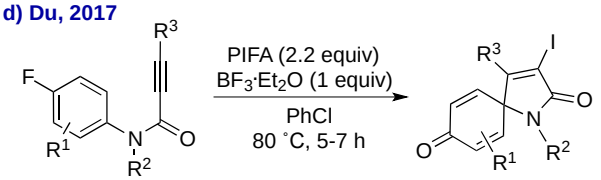


137

R^1 = H,alkyl, Hal; R^2 = Me, Et, Bn, allyl
R^3 = aryl, 1-naphthyl
R^4 = alkyl, cyclopropyl; R^5 = H, Me

145 42-86% (22 examples)

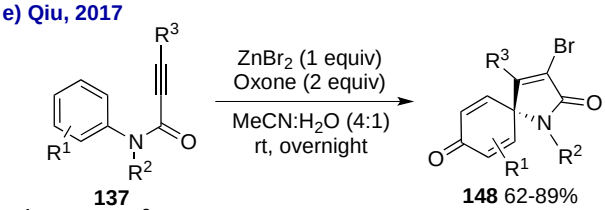
d) Du, 2017



146 R^1 = H, Hal; R^2 = Me, *i*-Pr; R^3 = aryl, 2-thienyl

147 43-82% (10 examples)

e) Qiu, 2017



137

R^1 = H, Me; R^2 = Me, Bn, $CH_2C_6H_4$-2-Br, CH_2CO_2Me, Ac, CHPhC(O)NH*t*-Bu
R^3 = Me, aryl, TMS

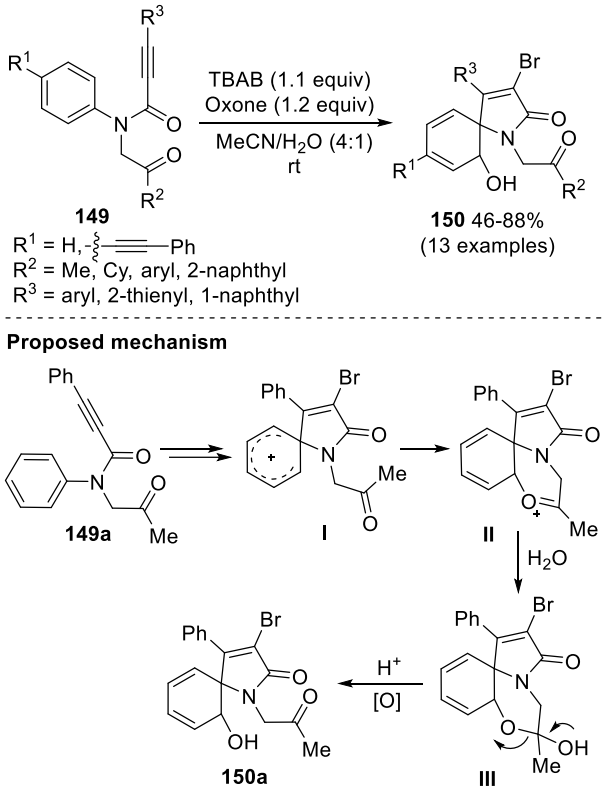
148 62-89% (19 examples)

Scheme 30. Dearomative oxidative spirocyclization of *N*-aryl-alkynamides.

The dearomative spirocyclization was also applied to the synthesis of spirocyclic γ-lactams **145** bearing ketone side chains at 3-position (42-86% yields), using ketones **144** as the counterpart of *N*-aryl-alkynamides **137** (Scheme 30c).[45] In this case the authors proposed the generation of a ketone radical from ketones **144** and TBHP in acidic medium, as the initial step of the cascade process comprising of addition, *ipso*-cyclization and dearomatization reactions.

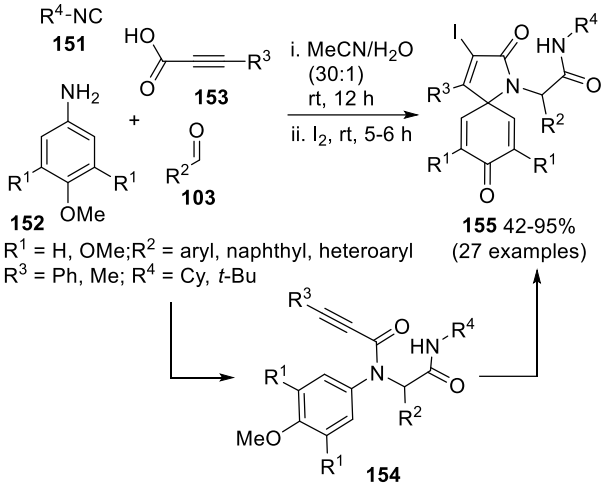
Iodo-spirocyclization of *N*-4-fluorophenylpropiolamides **146** mediated by an hypervalent iodine reagent has been also reported (Scheme 30d).[46] Using [bis(trifluoroacetoxy)iodo]benzene (PIFA) as oxidant and iodination reagent, 3-iodo-spiro-γ-lactams **147** were obtained in 43-82% yields via a defluorination pathway. In this case, an ionic mechanism was proposed involving the initial activation of the alkyne by $BF_3{\cdot}EtO_2$-activated PIFA and subsequent intramolecular electrophilic *ipso*-cyclization.

The use of zinc bromide or tetra-*n*-butylammonium bromide (TBAB) as bromine sources for radical oxidative bromocyclization of *N*-aryl-alkynamides has been also described.[47] Qiu and He reported the efficient synthesis of a range of spirocyclic 3-bromo-γ-lactams **148** using $ZnBr_2$ and Oxone® as the oxidant via sequential radical addition, 5-*exo*-trig *ipso*-cyclization and oxidation reactions (Scheme 30e).[47a] The same research group applied a TBAB/Oxone®-mediated protocol to the synthesis of 3-bromo-spiro-γ-lactams **150** via *ortho*-hydroxylative *ipso*-cyclization of *N*-aryl-alkynamides **149** (Scheme 31).[47c] A plausible mechanism involves the generation of a cyclohexadienyl cation **I** by α-addition, *ipso*-cyclization, and single-electron oxidation as key intermediate. The *ortho*-hydroxylation involves the intramolecular trapping of the **I** by the carbonyl group of the *N*-protecting group followed by nucleophilic addition of water and oxygen transfer. The scope of the reaction was extended to tetrabutylammonium iodide (TBAI) as iodine source with analogous efficiency.



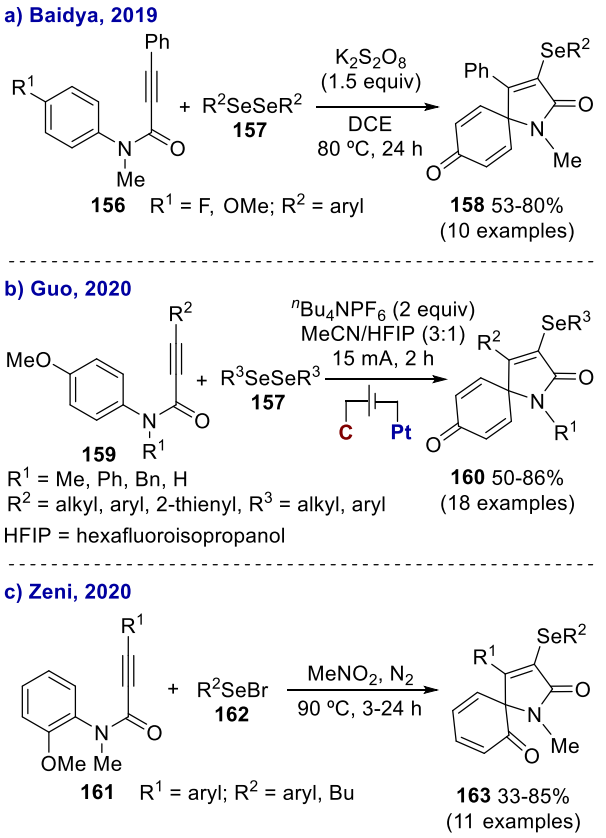
Scheme 31. TBAB-mediated oxidative bromospirocyclization of *N*-aryl-alkynamides.

Srivastava and Yugandhar reported the efficient synthesis of functionalized azaspiro[4,5]trienones by a tandem Ugi four-component reaction (Ugi-4CR) and intramolecular electrophilic *ipso*-iodocyclization in an one-pot and high atom economy process (Scheme 32).[48] The first stage of the protocol involves the reaction between isocyanides **151**, *p*-anisidines **152**, aromatic aldehydes **103**, and 3-alkyl- or 3-aryl-propiolic acids **153** to generate *in situ* the Ugi adducts, *N*-aryl-alkynamides **154**. Subsequent dearomative iodine-mediated *ipso*-cyclization afforded spirocyclic unsaturated 3-iodo-γ-lactams **155** in good yields (42-95%) A mixture of acetonitrile and water was found to be the best solvent system to perform the Ugi-4CR and *ipso*-iodocyclization by sequential addition of reagents and the product isolation was carried out by simple precipitation procedures. In 2018, Balalaie *et al.* reported a similar approach to the synthesis of 3-bromospiro-γ-lactams using *N*-bromosuccinimide as bromine source.[49] In this case, *ortho*-halogen substituted anilines were used and the oxidative spirocyclization of the Ugi adducts was carried out in the presence of $(NH_4)_2S_2O_8$/TBHP as oxidant system and *N*-methylmorpholine as base.



Scheme 32. One-pot Ugi-4CR/*ipso*-iodocyclization.

The scope of the metal-free oxidative *ipso*-cyclization of *N*-aryl-alkynamides was extended to the synthesis of selenyl-substituted spiro-γ-lactams (Scheme 33a).[50] Divergent synthesis of 3-selenyl quinolin-2-ones and spiro-γ-lactams was observed from the selenium radical triggered *ortho*- or *ipso*-cyclization cascade of *N*-aryl-alkynamides **156**, respectively, with the outcome of the reaction dependent on the substitution pattern of the *N*-aryl group. *N*-Aryl-alkynamides **156** bearing *para*-methoxy or *para*-fluoro substituents selectively afforded 3-selenyl-spiro-γ-lactams **158**. A similar reactivity was observed for an *ortho*-methoxy substituted substrate, giving rise to an unusual *ortho*-quinoid spiro-γ-lactam derivative.

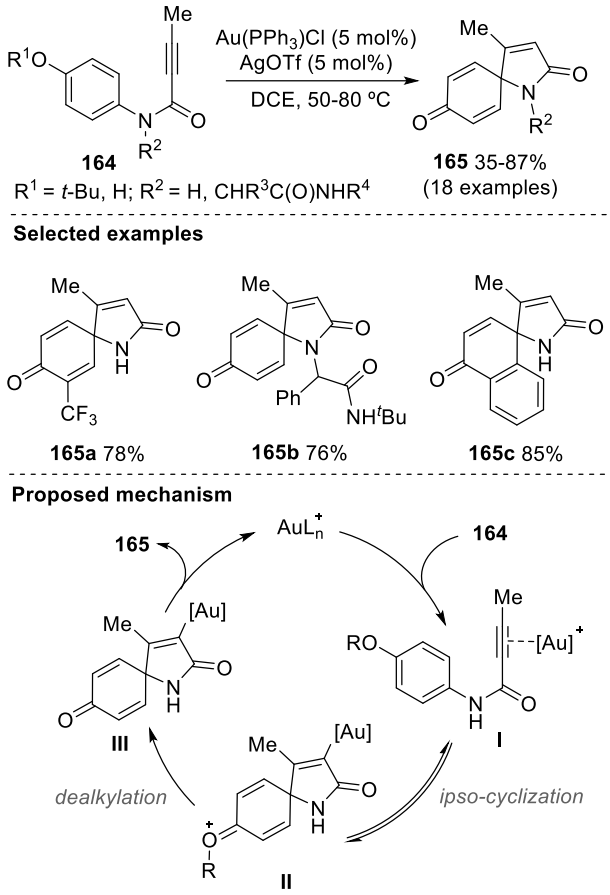


Scheme 33. Selenium-promoted spirocyclization of *N*-aryl-alkynamides.

Recently, Guo and co-workers disclosed a metal-free and oxidant-free radical dearomative spirocyclization of *para*-methoxy *N*-aryl-alkynamides **159** affording selenyl-substituted spiro-γ-lactams **160** in good yields (50-86%) (Scheme 33b).[51] The protocol involves electrochemical synthesis of the spiro-γ-lactams, in the presence of diselenides, by direct constant current electrolysis (15 mA) using a graphite anode and a platinum cathode, and *n*-Bu_4NPF_6 as the electrolyte. It is noteworthy that an electrochemical continuous-flow system was developed for scale-up purposes overcoming the low efficiency of traditional electrochemical scale-up strategies.

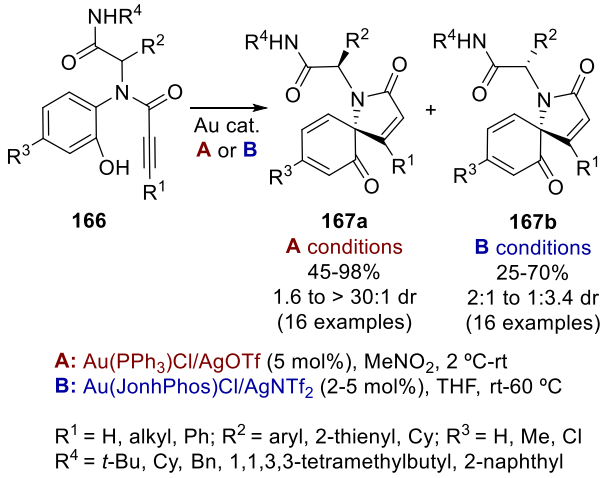
Zeni´s group described a metal-free selenium-promoted electrophilic cyclization of substituted *N*-aryl-alkynamides.[52] The reaction of *N*-(*ortho*-methoxyphenyl)alkynamides **161** with arylselenyl bromides **162**, acting as the electrophilic source, afforded *ortho*-quinoid 3-organoselenyl-spiro-γ-lactams **163** in moderate to good yields (33-85%) (Scheme 33c). The same type of derivatives was also previously reported by Baidya.[50] The scope of the reaction was extended to *N*-(*para*-methoxyphenyl)alkynamides giving rise to 3-organoselenyl-spiro-γ-lactams having a carbonyl group at C-8. Control experiments ruled out the involvement of a radical mechanism, and instead an ionic mechanism was proposed involving the arylselenyl bromide-promoted activation of the C–C triple bond by forming a seleniranium ion, followed by intramolecular *ipso*-attack on the activated alkyne. It is noteworthy that the use of these electrophilic organoselenium species prevents the formation of 3-selenyl quinolinone derivatives.

Metal-promoted dearomatizing spirocyclization reactions of arenes/heteroarenes that can undergo intramolecular Friedel-Crafts reactions via an *ipso*-cyclization pathway have been also explored. Vadola and co-workers reported a gold-catalyzed non-oxidative dearomative spirocyclization of *para*-*tert*-butoxy- and *para*-hydroxy-substituted *N*-arylpropiolamides **164** (Scheme 34).[53] Under the optimized conditions, using 5 mol% $Au(PPh_3)Cl$ and AgOTf in dichloroethane at 50-80 ºC, spirodienone unsaturated γ-lactams **165** were obtained in moderate to high yields (35-87%). This synthetic approach tolerates both electron-donating and electron-withdrawing groups in the aromatic ring, as well as substitution at the amide nitrogen. Moreover, these conditions also enabled the synthesis of spiro-γ-lactam **165c** from an aminonaphthol derived *N*-aryl alkynamide. The proposed mechanism involves the initial formation of alkyne-gold complex **I** which undergoes *ipso*-cyclization to give intermediate **II** via nucleophilic attack of the aryl moiety to the activated triple bond. Subsequent dealkylation of **II**, followed by protodemetalation leads to the final product and catalyst regeneration.



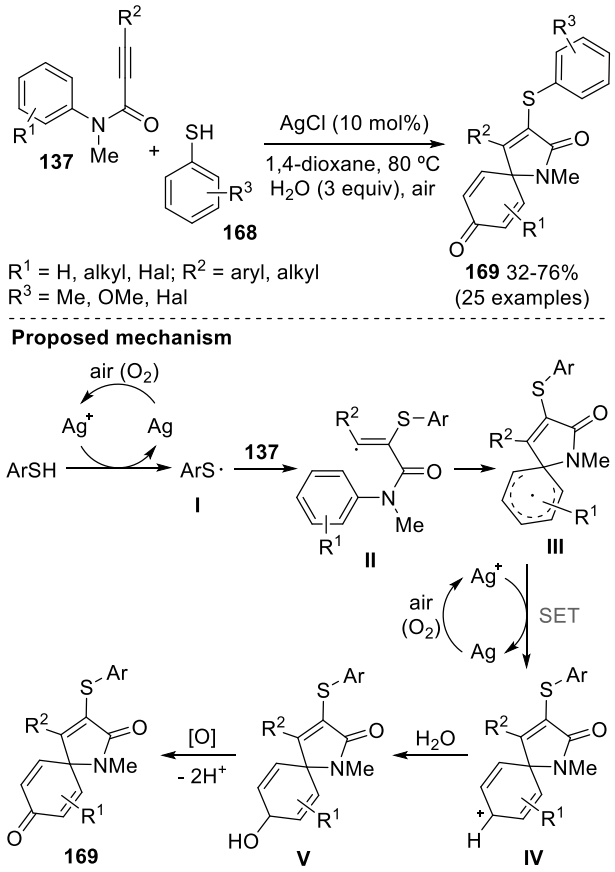
Scheme 34. Gold-catalyzed dearomative spirocyclization of *N*-aryl-alkynylamides.

Soon after, the Van der Eycken's group reported a similar gold-catalyzed *ipso*-cyclization reaction using Ugi adducts **166** as substrates (Scheme 35).[54] Spirodienone unsaturated γ-lactams **167** were obtained in moderate to high yields (43-98%) with the diastereoselectivity outcome controlled by tuning the catalytic system, solvent, and temperature (conditions A or B). The reaction exhibits good functional group tolerance, however conditions B have some limitations, namely the formation of a by-product when using more hindered internal alkynes (R^1 = Pr, Ph) and inversion of the dr for Ugi adduct bearing an aliphatic cyclohexyl group in R^2. Later, the same research group applied the gold-catalyzed post-Ugi *ipso*-cyclization/*ortho*-dearomative protocol for the cascade synthesis of complex fused polyheterocyclic scaffolds and bridged *N*-heterocycles.[55,56]



Scheme 35. Gold-catalyzed post-Ugi *ipso*-cyclization.

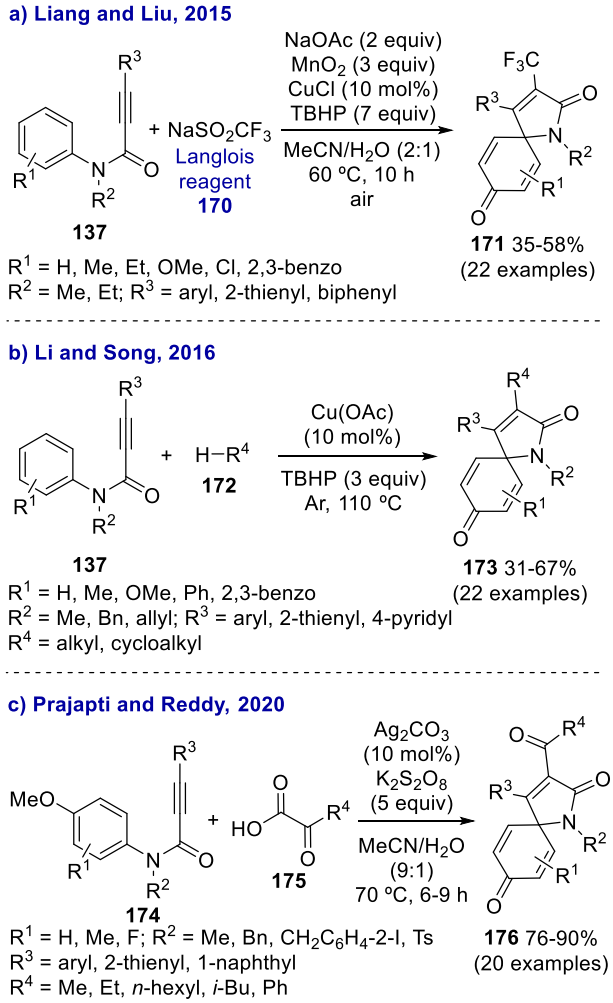
Unsaturated 3-(arylthio)-spiro-γ-lactams can be prepared by silver-catalyzed oxidative *ipso*-spirocyclization of *para*-unsubstituted *N*-aryl-alkynamides **137** with thiophenols **168** in the presence of water (Scheme 36).[57] Products **169** were obtained in moderate to good yields (32-76%) with high functional group tolerance by a cascade alkyne difunctionalization involving the sequential formation of C–S and C–C bonds and a dearomatization process. Mechanistic studies indicated that the reaction might involve a radical process and the carbonyl oxygen atom of spiro-γ-lactams **169** originated from the water. Thus, a plausible mechanism involves the addition of thiyl radical **I** to the α-position of the unsaturated amide to give vinyl radical **II**. Subsequent intramolecular *ipso*-cyclization followed by a single-electron transfer generates cyclohexadienyl cation **IV** which undergoes nucleophilic addition of water to give intermediate **V**. The final oxidative step delivers the final product.



Scheme 36. Silver-catalyzed dearomative spirocyclization of *N*-aryl-alkynylamides.

The synthesis of analogous spirocyclic 3-(arylthio)-γ-lactams via an oxidative *ipso*-cyclization of *para*-methoxyaryl *N*-arylpropiolamides with disulfides using an inexpensive catalytic system comprising of copper(II) chloride and molecular oxygen has been also reported.[58] The same research group reported an iron-catalyzed oxidative spirocyclization of *para*-unsubstituted *N*-arylpropiolamides with silanes and TBHP.[59] This radical-tandem cyclization/dearomatization protocol allowed the cascade formation of one C–Si bond, one C–C bond, and one C–O double bond. The 3-silyl-spiro-γ-lactams were obtained in yields ranging from 32% to 76%.

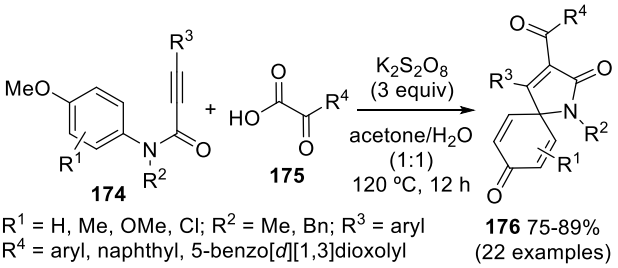
The metal-catalyzed radical oxidative *ipso*-annulation of *N*-aryl-alkynylamides has been also applied to the synthesis of azaspiro[4,5]trienones in which a new C–C bond is created at position 3 of the lactam ring.[60,61,62] The copper-catalyzed reaction of *N*-arylpropiolamides **137** with trifluoromethanesulfinate (Langlois reagent, **170**) allows the synthesis of spirocyclic 3-trifluoromethyl-γ-lactams **171** in moderate yields (35-58%) with good functional group tolerance (Scheme 37a).[60] On the other hand, 3-alkyl-spiro-γ-lactams **173** were obtained from *para*-unsubstituted *N*-arylpropiolamides **137** and unactivated alkanes (Scheme 37b).[61a] The reaction, catalyzed by copper, provided the final spirocyclic compounds in moderate yields (31-67%). Both strategies involve the alkyne difunctionalization via the formation of two carbon-carbon single bonds and one carbon-oxygen double bond initiated by the addition of a radical (CF_3 or alkyl radical) to the α-position of the triple bond. A nickel-catalyzed oxidative *ipso*-annulation of *N*-(*para*-methoxyaryl)propiolamides with α-carbonyl alkyl bromides to generate spirocyclic 3-alkyl-γ-lactams has been also disclosed in moderate yields.[61b]



Scheme 37. Metal-catalyzed dearomative spirocyclization of *N*-aryl-alkynylamides.

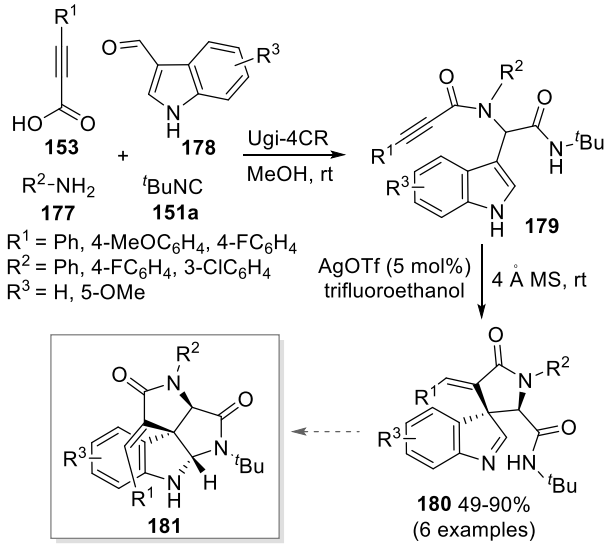
Recently, Prajapti, Reddy and co-workers reported a silver-catalyzed oxidative *ipso*-cyclization of substituted *N*-(*para*-methoxyphenyl)alkynylamides **174** with β-keto acids **175** (Scheme 37c).[62] The cascade transformation, which involves the generation of an acyl radical by a decarboxylative process, allows the formation of 3-acyl-spiro-γ-lactams **176** in good yields (76-90%) and good functional group tolerance. The synthetic scope was further extended to access 3-alkyl-spiro-γ-

lactams by using alkyl carboxylic acids. Almost simultaneously, Volla and co-workers disclosed a metal-free spirocyclization of *N*-(*para*-methoxyphenyl)alkynylamides **174** with β-keto acids **175** employing $K_2S_2O_8$ as the oxidant.[63] Following a similar mechanistic pathway to the last example, the reaction afforded the corresponding spirocyclic 3-acyl-γ-lactams **176** with good yields (75-89%) without the need of a metal catalyst (Scheme 38).



Scheme 38. Metal-free dearomative spirocyclization of *N*-aryl-alkynylamides.

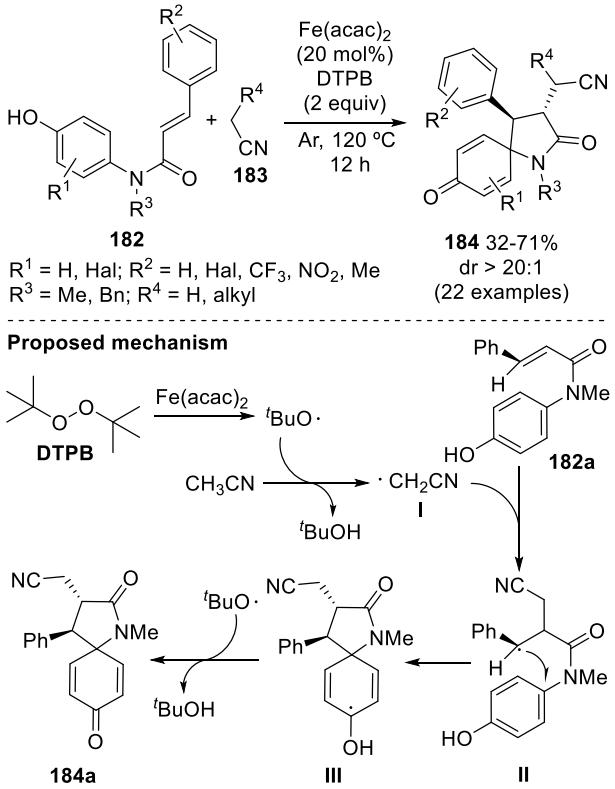
The synthesis of spiro-3*H*-indole γ-lactams via a post-Ugi protocol has been reported.[64] 3-Aryl propiolic acids **153**, anilines **177**, indole-3-carboxaldehydes **178** and *tert*-butyl isocyanide (**151a**) were employed as substrates for the Ugi-4CR (Scheme 39). Then, the Ugi adducts **179** were converted into spiro-3*H*-indole γ-lactams **180** in the presence of silver(I) triflate and 4 Å molecular sieves. The most likely mechanism of this transformation involves a AgOTf-catalyzed Friedel-Crafts *ipso*-cyclization of the indole onto the triple bond. It is noteworthy that in the presence of Brønsted acid additive (TFA) the reaction evolves to tetracyclic spiroindolines **181**. This event, resulting from an acid-mediated trapping of the imine generated after the *ipso*-cyclization by the amide nitrogen, is blocked under acid free conditions.



Scheme 39. Four-component Ugi reaction followed by AgOTf-catalyzed Friedel Crafts *ipso*-cyclization leading to spiro-3*H*-indole γ-lactams.

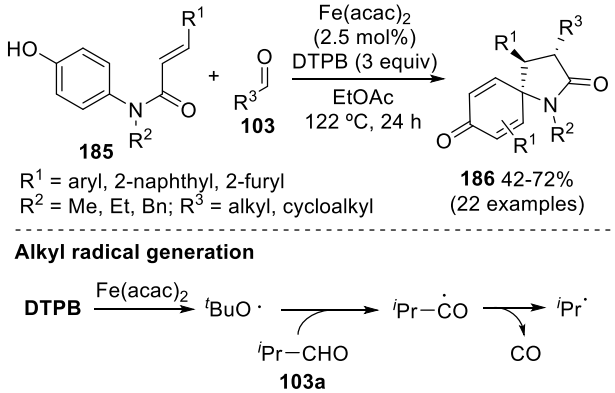
3-Cyanoalkyl-spiro-γ-lactams have been prepared via an iron-catalyzed radical dearomative spirocyclization of *N*-phenylcinnamamides **182** initiated by cyanoalkylation (Scheme 40).[65] By reacting **182** with alkyl cyanides **183**, in the presence of $Fe(acac)_2$ and di-*tert*-butyl peroxide (DTPB), the target molecules **184** were obtained in moderate to good yields (32-71%) and high diastereoselectivities (dr > 20:1). Selective radical cyanoalkylation of *N*-phenylcinnamamides

182 (*e.g.* **182a**) led to intermediates **II** which was followed by a 5-*exo*-cyclization giving spirocyclic intermediate **III**; a thermodynamically controlled cyclization favoring the *trans*-configuration of the phenyl and cyanomethyl groups. Hydrogen abstraction from radical intermediate **III** by *tert*-butoxy radical affords spiro-γ-lactams **184**.



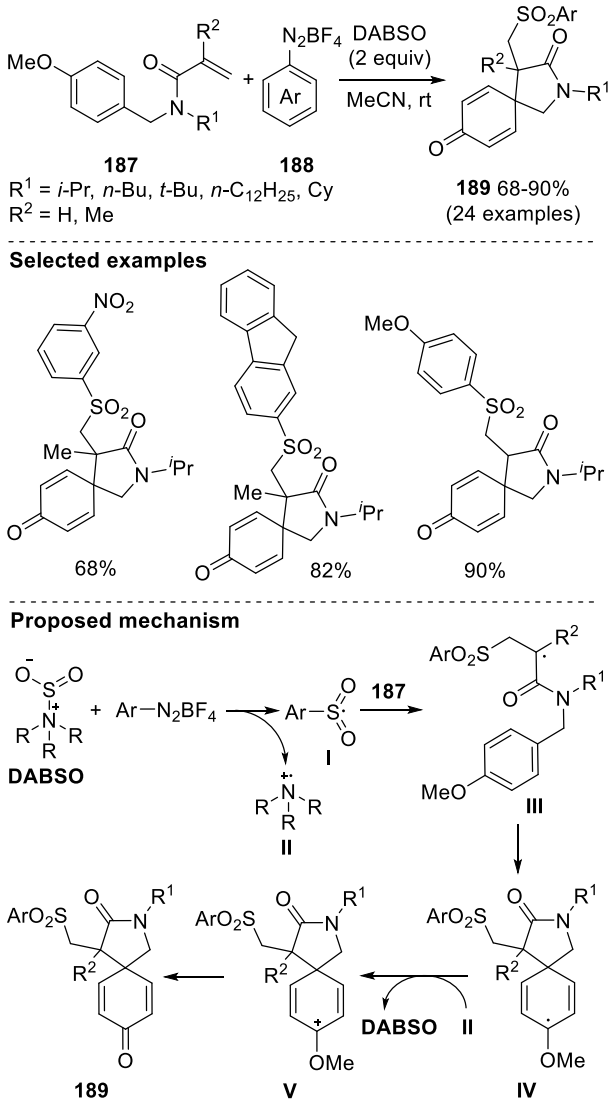
Scheme 40. Iron-catalyzed dearomative spirocyclization of *N*-phenylcinnamamides.

The iron-catalyzed decarbonylative alkylative spirocyclization of *N*-phenylcinnamamides **185** with aliphatic aldehydes **103** afforded 3-alkyl-spiro-γ-lactams **186** in moderate to good yields (42-72%) (Scheme 41).[66] This synthesis shows good functional group tolerance, allowing the use of substrates bearing a 2-naphthalenyl and 2-furanyl at the β-position of the unsaturated amide and a wide array of aliphatic aldehydes. The generation of alkyl radicals was rationalized by considering an oxidative decarbonylation of aliphatic aldehydes promoted by a $Fe(acac)_2$/DTPB catalytic system.



Scheme 41. Iron-catalyzed dearomative spirocyclization of *N*-phenylcinnamamides.

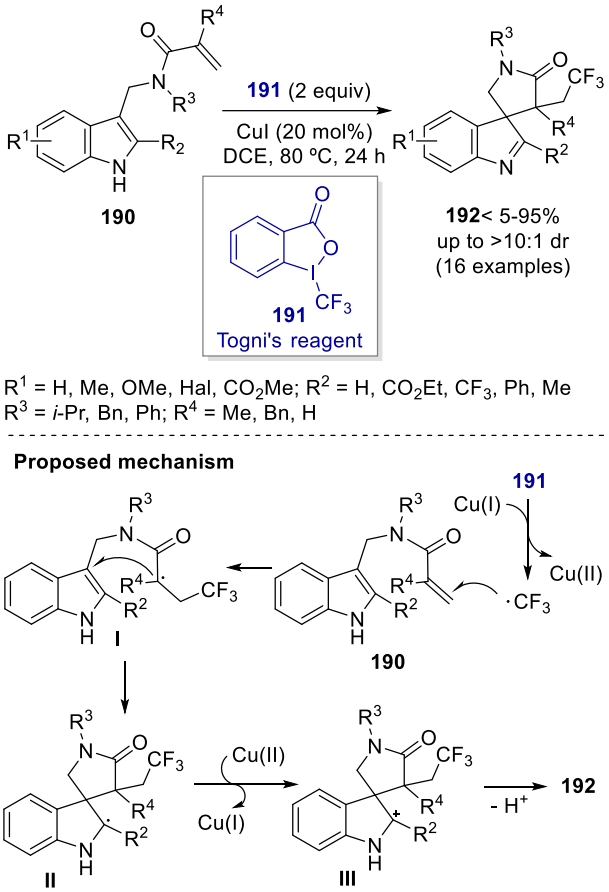
N-Benzyl-acrylamides are also suitable substrates for dearomative spirocyclization reactions. Thus, *N*-benzyl-acrylamides **187** reacted with aryldiazonium salts **188** in the presence of sulfur dioxide surrogate DABSO to give cyclohexadienone-based spiro-γ-lactams **189** via an insertion of sulfur dioxide/*ipso*-cyclization protocol (Scheme 42).[42] The reaction displays good functional group tolerance, affording the products in good to high yields (68-90%) as well as gram-scale reproducibility. The authors proposed the *in situ* generation of aryl sulfonyl radicals **I**, from DABSO and aryl diazonium salts, followed by regioselective addition of radical **I** onto benzyl-acrylamides **187**, affording intermediates **III**. Subsequent *ipso*-cyclization gives **IV** which undergo a single-electron oxidation by the radical cation **II** followed by demethylation leading to the final products.



Scheme 42. Metal-free sulfonative spirocyclization of *N*-benzyl-acrylamides.

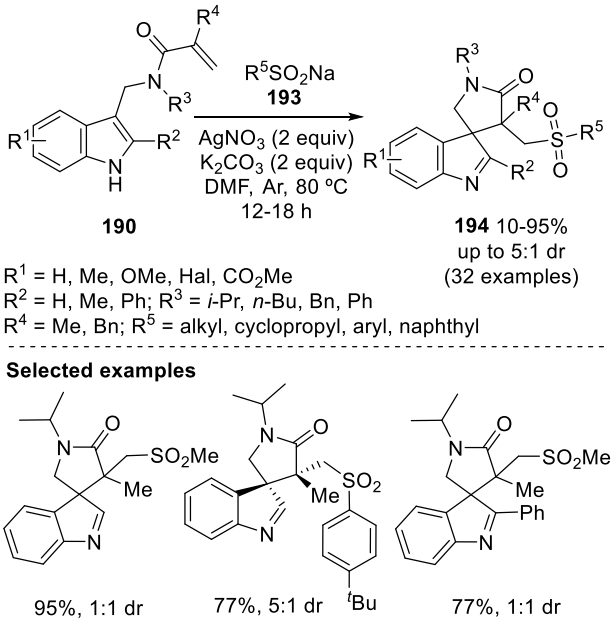
Wang and co-workers reported the synthesis of spiro-3*H*-indole γ-lactams **192** by copper-catalyzed trifluoromethylation of indole-based acrylamides **190** coupled with ring-closure and indole dearomatization (Scheme 43).[67] The optimized reaction conditions employ Togni's reagent (**191**) as the source of CF_3 and CuI as the catalyst in DCE at 80 ºC. Spiro-3*H*-indole γ-lactams

192 were obtained in moderate to high yields (15 examples, 50-95%). Except for a C-2 methyl-substituted indole precursor (< 5% yield), various substituents on the indole and acrylamide moieties are well tolerated. To gain insight into the reaction mechanism, the synthesis of one trifluoromethyl-substituted spiro-γ-lactam was carried out in the presence of radical scavenger TEMPO leading to a significant decrease in the yield, which indicates that free-radical intermediates are involved. Thus, the proposed mechanism initiates with the reduction of Togni's reagent by CuI to generate the CF_3 radical and Cu(II). Selective attack of the CF_3 radical to the acrylamide group at the β-position generates carbon-centered radical **I** followed by 5-*exo* cyclization at the C-3 position of indole to give **II**. Oxidation of this radical intermediate by Cu(II) gives carbocation **III** which is then converted into the final products by deprotonation.



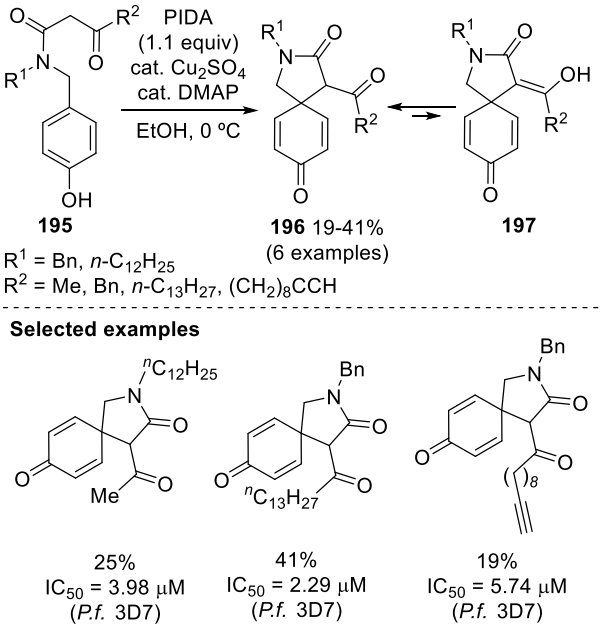
Scheme 43. Copper-catalyzed cascade trifluoromethylation, cyclization and indole dearomatization.

A similar cascade sulfonation, cyclization and indole dearomatization of acrylamides using sodium sulfinates in the presence of $AgNO_3$ and K_2CO_3 was reported recently by Li and Wang.[68] Sulfonylated spiro-3*H*-indole γ-lactams **194** were obtained from indole-based acrylamides **190** in moderate to high yields (10-95%) (Scheme 44). In this case, the generation on a sulfonyl radical from the reaction between sodium sulfinates **193** and $AgNO_3$ was proposed. Attempts to apply the copper- or silver-promoted strategies to the synthesis of analogous spiro-3*H*-indole δ-lactams using substrates with one more carbon between the indole and acrylamide nitrogen atom, were unsuccessful.[67,68]



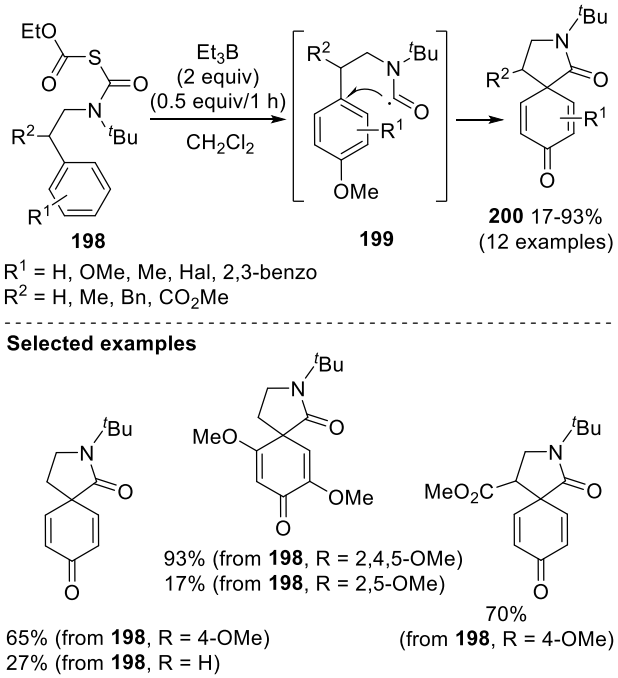
Scheme 44. Silver-promoted cascade sulfonation, cyclization and indole dearomatization.

Wong *et al.* described the synthesis of *N*-alkylated spirocyclohexadienone β- and γ-lactams from β-keto amides derived from 4-aminophenol or 4-(aminomethyl)phenol, respectively.[69] The intermolecular lactamization occurs through an oxidative process mediated by phenyliodine(III) diacetate (PIDA) and catalyzed by DMAP and copper sulfate. Spiro-β-lactams were obtained in moderate to good yields (47-86%) whereas spiro-γ-lactams **196** were obtained in low to moderate yields (19-41%) (Scheme 45). NMR spectra has shown that most spiro-γ-lactams are present in solution in both keto-enol tautomeric forms. Bioactivity assays were performed, revealing that four of these spirocyclic compounds were active against *P. falciparum* 3D7 strain (IC_{50} = 2.29-7.09 μM).



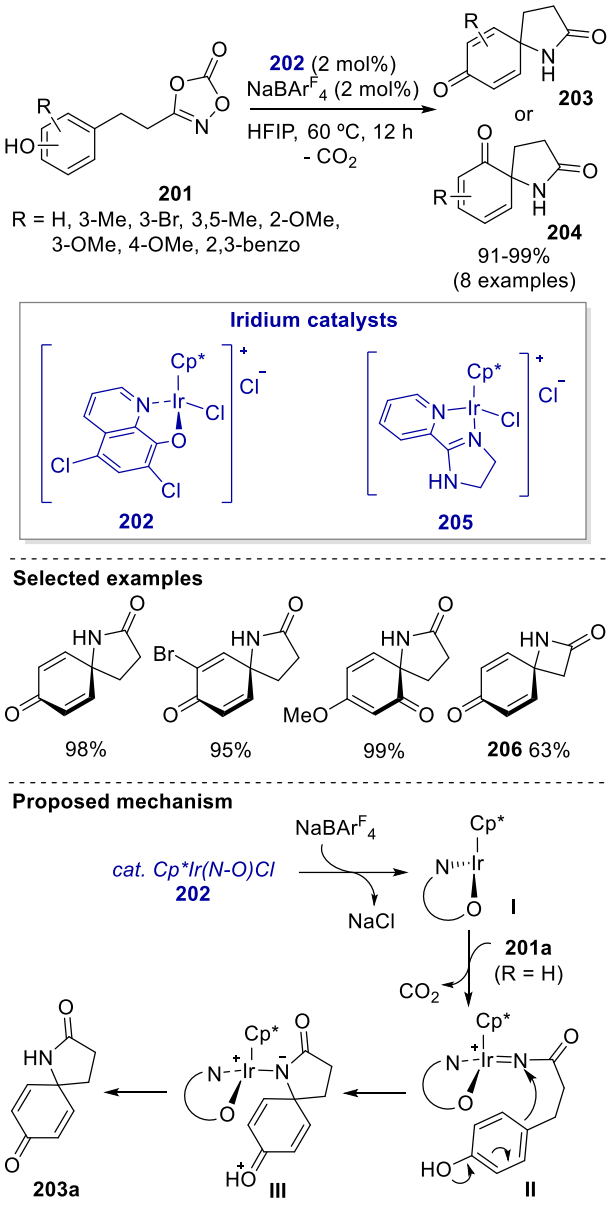
Scheme 45. DMAP/Cu_2SO_4-Catalyzed dearomative spirocyclization of β-keto amides derived from 4-aminophenol.

Dearomative spiroacylation leading to cyclohexadienone spiro-γ-lactams **200** based on the generation of carbamoyl radical intermediates has been disclosed (Scheme 46).[70] Previous studies have demonstrated that the stability of carbamoyl radicals, generated from the corresponding carbamoylxanthates, was dependent on the presence of an *N*-*t*-butyl group on the amine moiety.[71] Therefore, carbamoylxanthates **198** were selected as starting materials and underwent a Et_3B-mediated reaction to afford spiro-γ-lactams **200** in moderate to high yields (17-93%) via *ipso*-cyclization of carbamoyl radicals **199**.



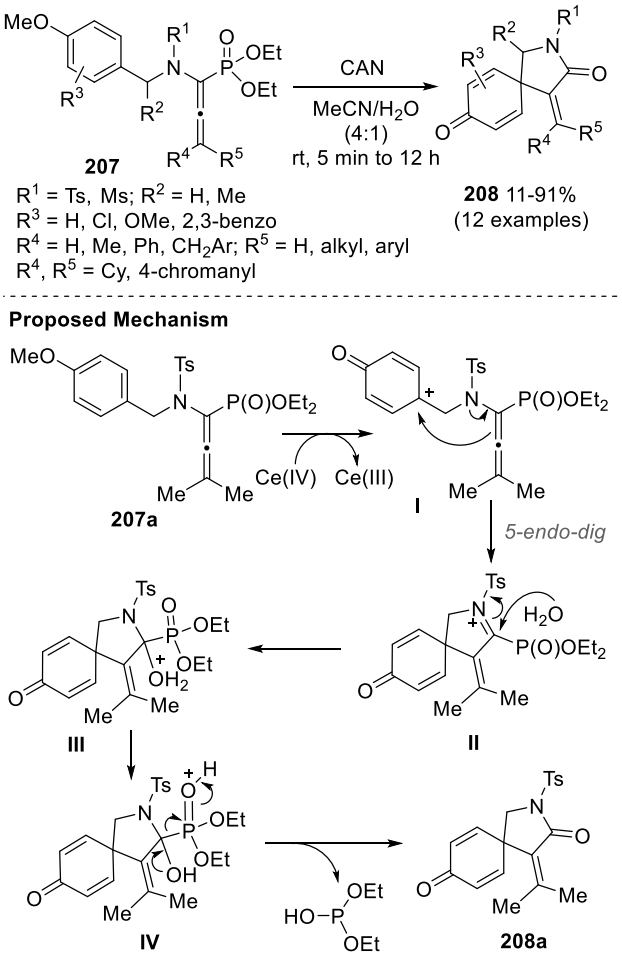
Scheme 46. Et_3B-Mediated radical dearomative spiroacylation.

In 2018, Chang and co-workers developed a synthetic route to spiro-γ-lactams **203** and **204** via an iridium-catalyzed dearomative spirocyclization reaction of phenol-based dioxazolone substrates **201** (Scheme 47).[72] Under the optimized reaction conditions, using 2 mol% of Ir-catalyst **202** and an equal amount of additive sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F_4$) in HFIP, the target spiro-γ-lactams were obtained in high yields (91-99%), either from *para*- or *ortho*-phenol dioxazolone substrates. The protocol involves an arene C(sp^2)–H amidation via intramolecular transfer of iridium nitrenoids. The reported mechanism, supported by experimental and computational analysis, starts with the coordination of the activated iridium catalyst **I** to dioxazolone **201** to generate Ir-nitrene **II** by the release of a molecule of carbon dioxide. Subsequent amidation via electrophilic aromatic substitution followed by removal of the phenolic proton afforded the target spiro-γ-lactam. The methodology was further extended to the synthesis of spiro-β-lactam **206**. Recently, this synthetic methodology was further explored using iridium catalyst **205**.[73] Under these conditions, spiro-γ-lactams **203** were obtained in high yields (92-99%); the only exception was the *ortho*-phenol substrate **201** (R = 4-OMe), which gave the corresponding spiro-γ-lactam **204** in moderate yield (52%). Moreover, gram-scale experiments demonstrated the practicability of the methodology.



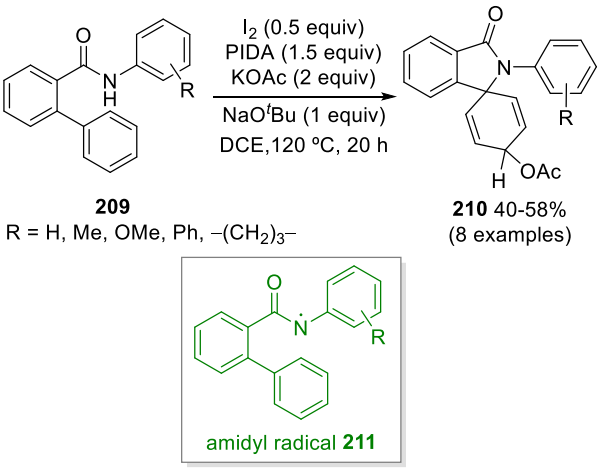
Scheme 47. Iridium-catalyzed dearomative spirocyclization of phenol-based dioxazolones.

Rabasso and co-workers developed a cyclization of α-amino allenylphosphonates **207**, preceded by a cerium ammonium nitrate (CAN) mediated oxidation, as a route to spirodienone-γ-lactams **208** (Scheme 48).[74] The proposed mechanism starts with the oxidation of the *para*-methoxybenzyl ring with CAN to generate carbocation **I** followed by cyclization to give iminium ion **II**. Nucleophilic addition of water followed by prototropy and release of diethyl phosphite afforded spiro-γ-lactams **208** in yields ranging between 11% and 91%. The behavior of alcohols as nucleophile in the nucleophilic addition toward the iminium ion **II** was explored. The reaction with methanol and ethanol did not lead to the expected spiro-γ-lactams, however when using sterically hindered alcohols (*e.g. i*-PrOH, *t*-BuOH), the corresponding spiro-γ-lactams were obtained, albeit in lower yields (19-38%).



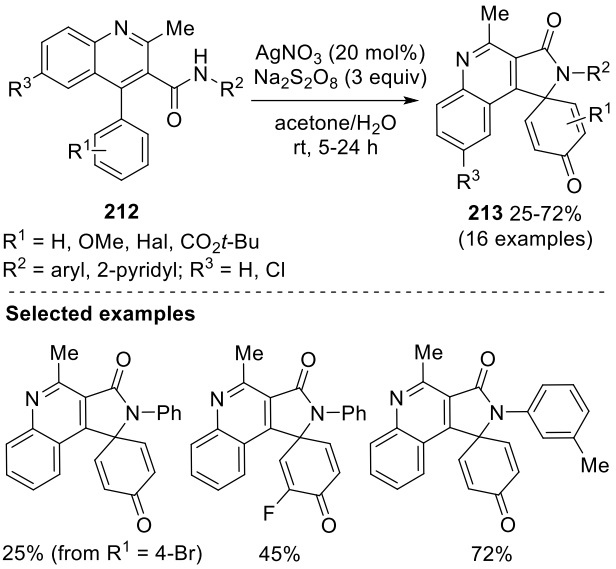
Scheme 48. CAN-Promoted spirocyclization of α-amino allenylphosphonates.

The iodine-mediated reaction of 2-phenyl-*N*-phenylbenzamides **209** in the presence of the oxidant PIDA afforded spiro-isoindolinones **210** in moderate yields (40-58%) (Scheme 49).[75] A plausible mechanism involves the generation of *N*-centered amidyl radicals **211** and subsequent cyclization leading to cyclohexadienyl intermediates which participate in an electron transfer to PhI·OAc (derived from PIDA and NaO*t*-Bu) followed by the transfer of the acetate to the cyclohexadienyl group.



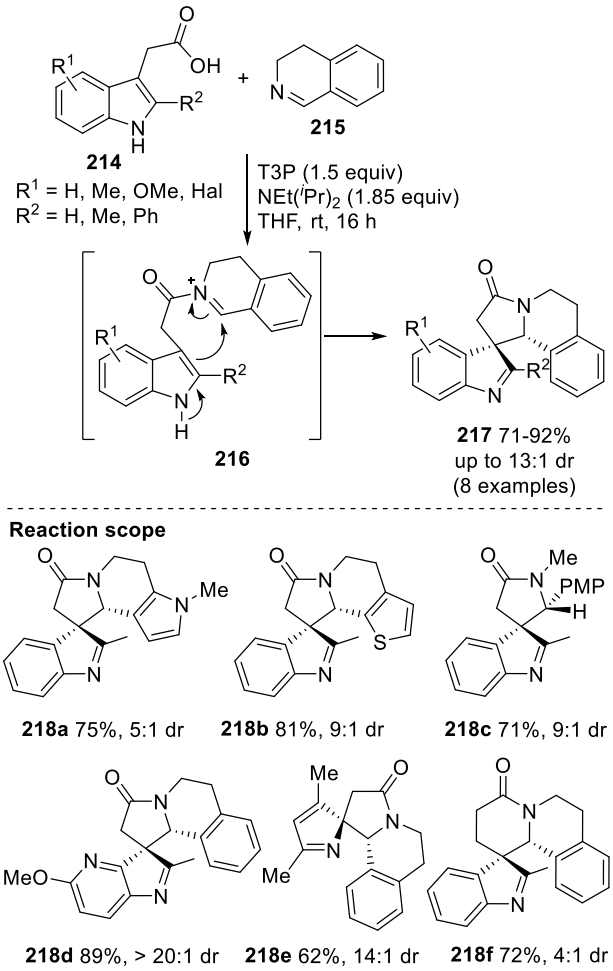
Scheme 49. Iodine-mediated dearomative spirocyclization of 2-phenyl-*N*-phenylbenzamides.

4-Arylquinoline-3-carboxamides **212** can be converted into dibenzo[*c*,*f*][2,7]naphthyridinones or spiro-γ-lactams through a switchable $Na_2S_2O_8$-mediated intramolecular oxidative amidation.[76] The former was obtained under catalyst-free conditions via *ortho*-cyclization, while spirodienone γ-lactams **213** were obtained under silver-catalyzed conditions via an *ipso*-cyclization pathway. The reaction proceeds through the generation of a *N*-centered amidyl radical prior to the spirocyclization step, affording spiro-γ-lactams **213** in moderate yields (25-72%) (Scheme 50). Several leaving groups at the *para*-position of the phenyl ring are tolerated, however, the reaction failed with *para*-methyl and *para*-ester substituted quinolines.



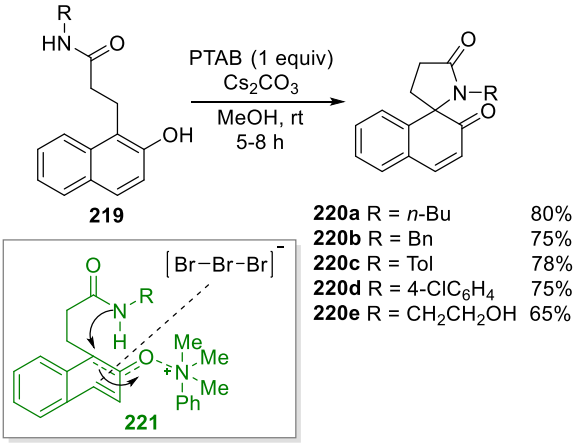
Scheme 50. Silver-catalyzed dearomative spirocyclization of 4-arylquinoline-3-carboxamides.

Spiro-3*H*-indole γ-lactams **217** were obtained in high yields (71-92%) by direct coupling between 3-indoleacetic acids **214** and 3,4-dihydroisoquinoline (**215**) (Scheme 51).[77] The optimized reaction conditions employ propylphosphonic anhydride (T3P) (1.5 equiv) and NEt(*i*-Pr)$_2$ (1.85 equiv) in THF at room temperature. The formation of spirocyclic lactams was rationalized by considering the activation of the carboxylic acid with T3P followed by *N*-acylation to generate reactive *N*-acyliminium ion **216**. Dearomatization via nucleophilic attack onto **216** gives the final products. The scope of this dearomative cyclization was extended to other heterocyclic acids (aza-indole- and pyrroleacetic acid) and imines (pyrrole- and thiophene-fused imines, and acyclic imines), giving access to a range of heterocyclic spiro-γ-lactams with two contiguous carbon stereocenters (*e.g.* **218a-e**) in good yields and diastereoselectivities (Scheme 51). Additionally, a six-membered lactam, spiro-3*H*-indole δ-lactam **218f**, was also obtained when using the appropriate indolepropanoic acid substrate.



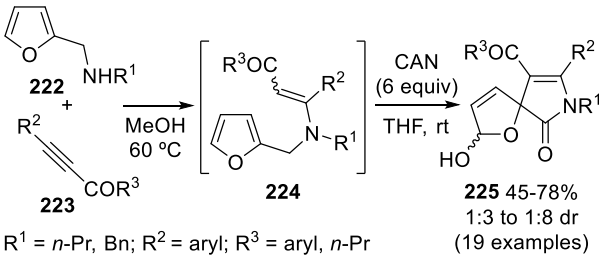
Scheme 51. Direct coupling between heteroaromatic carboxylic acids and imines.

Naphthalene-derived spiro-γ-lactams **220** have been prepared in yields ranging from 65% to 80% via a tribromide-mediated *ipso*-amidation (Scheme 52).[78] Under basic conditions, substituted naphthols **219** were converted into the corresponding naphthoxide ions which partially interact with the ammonium counter part of phenyl trimethyl ammonium tribromide (PTAB) to generate reactive intermediate **221**. Subsequent intramolecular spirocyclization via an oxidative dearomatization pathway furnishes the final products.



Scheme 52. Tribromide-mediated oxidative dearomatization of naphthol derivatives.

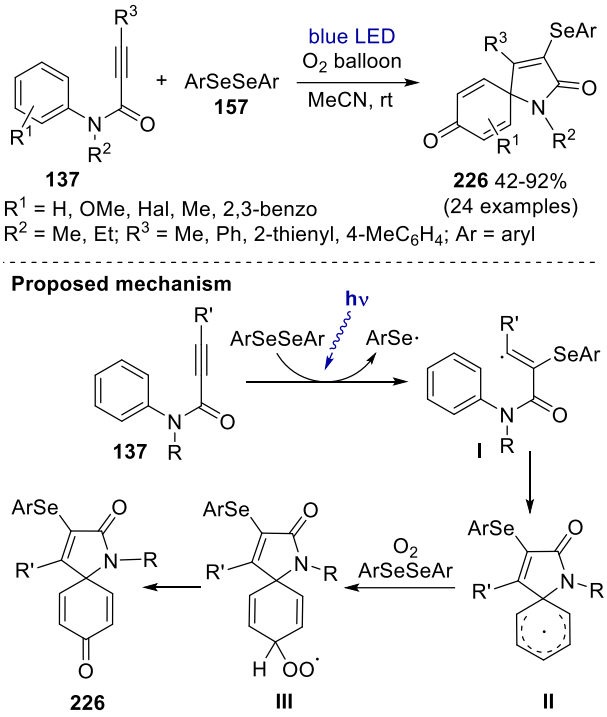
The synthesis of spiro-γ-lactam furans **225** *via* an oxidative cyclization reaction of furfurylamines **222** and ynones **223** mediated by CAN has been reported (Scheme 53).[79] This dearomative oxidation protocol involves the *in situ* generation of *N*-furan-2-ylmethyl-β-enaminone intermediates **224** followed by oxidative cyclization using CAN (6 equiv). Spirocyclic lactams **225** were obtained in moderate to good yields (45-78%) and good functional group tolerance. The authors proposed, as the most likely mechanism, a free-radical pathway for the oxidative cyclization process.



Scheme 53. CAN-Promoted oxidative cyclization reaction between furfurylamines and ynones.

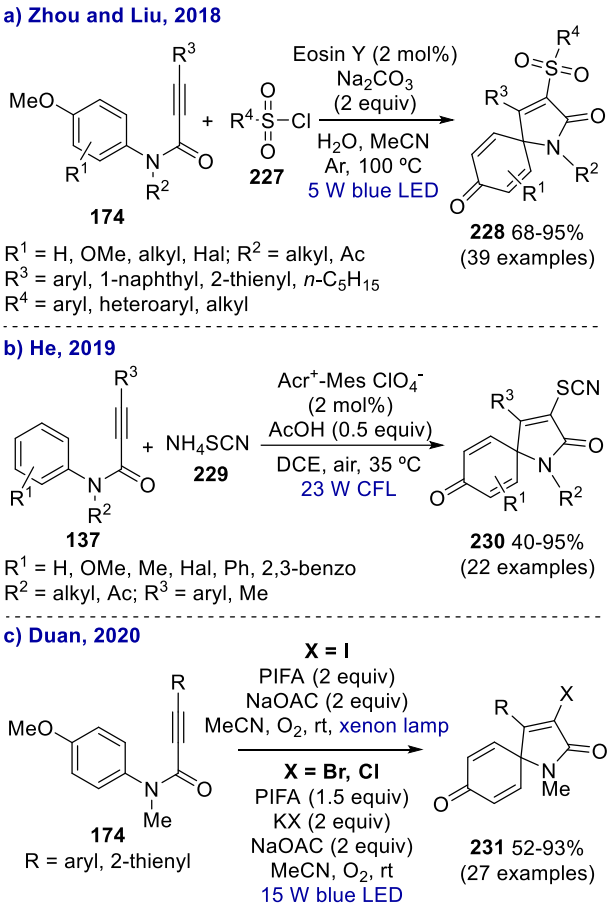
2.6 Photo-mediated radical cyclization

Visible-light mediated dearomative spirocyclization of *N*-aryl-alkynamides has been explored in recent years as an inexpensive and green methodology for the synthesis of unsaturated spiro-γ-lactams, azaspiro[4,5]trienones, under mild reaction conditions. In 2018, Baidya and co-workers developed a photocalyst-free protocol for the synthesis of 3-seleno-spiro-γ-lactams **226** taking advantage of the significant absorbance of diaryl selenides (**157**) in the visible region (Scheme 54).[80] Using blue LEDs (455 nm) and molecular oxygen as the oxidant, 3-selenospiro[4,5]trienones **226** were obtained in moderate to high yields (42-92%) and good functional group tolerance. The reaction is compatible with *N*-aryl-alkynamides bearing both electron-donating and electron withdrawing groups at *meta*- and *ortho*-positions of the *N*-aryl ring, as well as fluoro and methoxy *para*-substituted substrates. Based on control experiments indicating the involvement of radical species, a plausible mechanism was proposed with the initial photo-induced generation of aryl selenium radical, selective addition to the α-position of the unsaturated amide to give vinyl radical **I** and subsequent intramolecular *ipso*-cyclization to afford intermediate **II**. Under O_2 atmosphere and in the presence of aryl diselenide, the latter intermediate is converted into **III**, which after O–O bond cleavage gives the final products. A new *spiro-ring-opening* strategy to access unsymmetrical densely functionalized substituted acryl amides using allyl amine was also disclosed.



Scheme 54. Visible-light-induced selenylative dearomative spirocyclization of *N*-substituted alkynylamides.

In the same year, Zhou, Liu and co-workers reported a metal-free visible-light-induced radical sulfonylation and *ipso*-cyclization of *N*-substituted propiolamides **174** using 2 mol% Eosin Y as the photocatalyst, Na_2CO_3 as the base and H_2O (Scheme 55a).[81] The protocol allowed the synthesis of 3-sulfonyl-spiro-γ-lactams **228** in good to high yields (69-95%) and broad substrate scope, including the use of alkyl propiolamides and aliphatic sulfonyl chlorides. The proposed mechanistic pathway includes the generation of an aryl/alkyl sulfonyl radical, selective addition of the radical to the alkyne moiety and subsequent *ipso*-cyclization to afford the dearomatized products. Moreover, ^{18}O-isotope labelling experiments demonstrated that oxygen atom in the generated C–O double bond is derived from H_2O. Soon after, the same research group reported the synthesis of 3-sulfonyl-spiro-γ-lactams from *N*-substituted propiolamides using anilines and DABSO as aryl sulfonyl radical sources, and Eosin Y as the photocatalyst.[82] Recently, an analogous sulfonative dearomative spirocyclization of *N*-phenyl propiolamides was reported using diaryliodonium triflate salts and DABSO as aryl sulfonyl radical precursors under the irradiation with LEDs.[42]

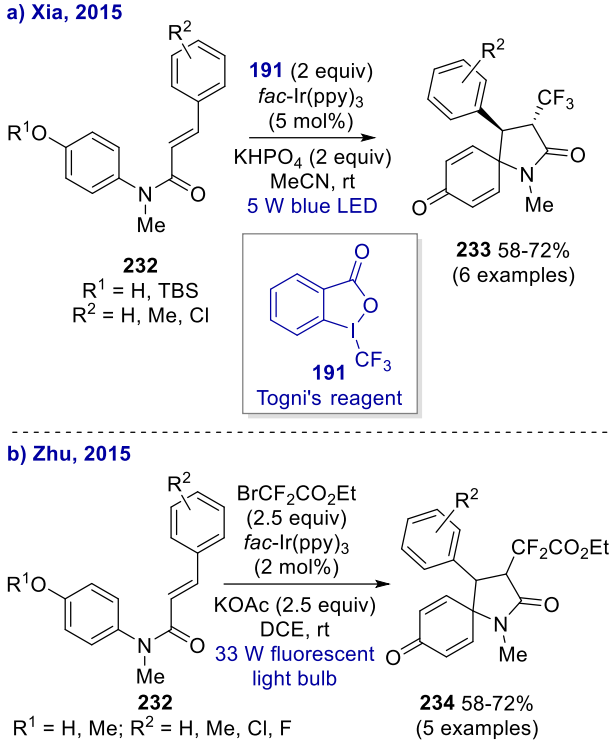


Scheme 55. Visible-light-induced dearomative spirocyclization of *N*-substituted alkynylamides.

A similar strategy was applied in the visible-light induced thiocyanation/*ipso*-cyclization/oxidation cascade reactions of *N*-substituted propiolamides **137** (Scheme 55b).[83] Using the organic dye acridinium perchlorate as photocatalyst and ammonium thiocyanate (**229**), spirocyclic 3-thiocyanate-γ-lactams **230** were obtained in moderate to high yields (40-95%). In this case, the oxygen atom in the newly generated carbonyl bond comes from air. The photo-mediated halogenative spirocyclization of *N*-(*p*-methoxyaryl)propiolamides **174** has been also reported, rendering 3-halogenated spiro-γ-lactams **231** in yields ranging from 52% to 93% (Scheme 55c).[84] 3-Iodinated products were obtained using PIFA as iodine free radical precursor under the irradiation of a xenon lamp, whereas chlorinated and brominated derivatives were obtained under blue LEDs using a mixture of PIFA and KCl/KBr as halogen radical precursors.

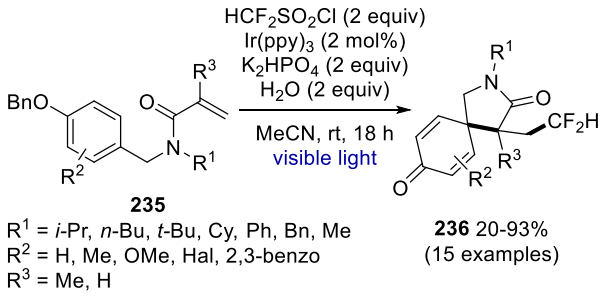
N-Arylcinnamamides can be converted into carbocyclic spiro-γ-lactams via photoredox visible-light-mediated radical dearomative spirocyclization reactions. Xia and co-workers reported the synthesis of 3-trifluoromethyl-spiro-γ-lactams **233** by the visible-light-induced trifluoromethylation of *N*-arylcinnamides **232** with Togni's reagent (**191**) in the presence of *fac*-^{III}Ir(ppy)$_3$ photocatalyst (Scheme 56a).[85] The proposed mechanism involves the initial generation of stable trifluoromethyl radical precursor by the excitement of *fac*-Ir^{III}(ppy)$_3$ to *fac*-Ir^{III}(ppy)$_3$* under visible-light irradiation followed by oxidative quenching with Togni's reagent to generate CF_3 radical along with *fac*-Ir^{IV}(ppy)$_3$. Subsequent selective addition of $\cdot CF_3$ to the double bond, intramolecular *ipso*-cyclization of the generated benzylic radical and oxidation by *fac*-Ir^{IV}(ppy)$_3$ lead to the final products. In the same year, Zhu and co-workers reported an analogous protocol for the synthesis of 3-difluroacetylated spiro-γ-lactams **234** using ethyl bromodifluoroacetate as

CF_2CO_2Et radical precursor and *fac*-$Ir^{III}(ppy)_3$ as the photoredox catalyst (Scheme 56b).[86] It should be noted that for *N*-arylcinnamamide substrates bearing substituents at the aniline moiety other than *para*-RO, divergent synthesis of quinolin-2-ones was observed.



Scheme 56. Visible-light-induced dearomative spirocyclization of *N*-arylcinnamamides.

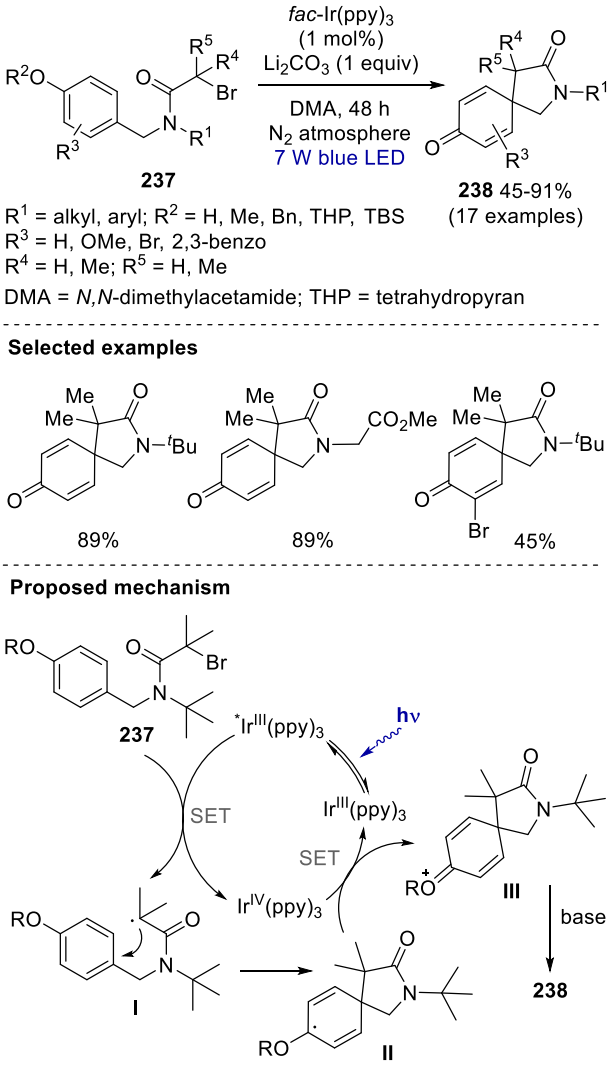
The visible-light-assisted dearomative spirocyclization of *N*-benzylacrylamides has been also reported.[87,88] CF_2H-Containing spiro-γ-lactams **236** bearing two adjacent quaternary stereocenters were obtained in 20-93% yields via a photoredox-catalyzed cascade intramolecular difluoromethylation/dearomative spirocyclization of *N*-benzyl-acrylamides **235** using difluoromethanesulfonyl chloride as the radical precursor (Scheme 57).[87] When CH_2FSO_2Cl or $CF_3CH_2SO_2Cl$ were used as radical sources, spiro-γ-lactams with retention of the SO_2 group were obtained. A similar reaction was reported using *N*-benzyl-acrylamides and R_f-X (X = I or Br) as the perfluorine radical source.[88] The reaction was catalyzed by *fac*-$Ir(ppy)_3$ to give spiro-γ-lactams bearing perfluorinated groups (*e.g.* CF_3, *n*-C_3F_7, *n*-C_8F_{17}, CF_2CO_2Et) in 28-84% yields.



Scheme 57. Visible-light-induced dearomative spirocyclization of *N*-benzyl-acrylamides.

Carbocyclic spiro-γ-lactams **238** have been constructed by the regioselective dearomative cyclization of α-bromo-*N*-benzyl-alkylamides **237** under visible-light irradiation using *fac*-

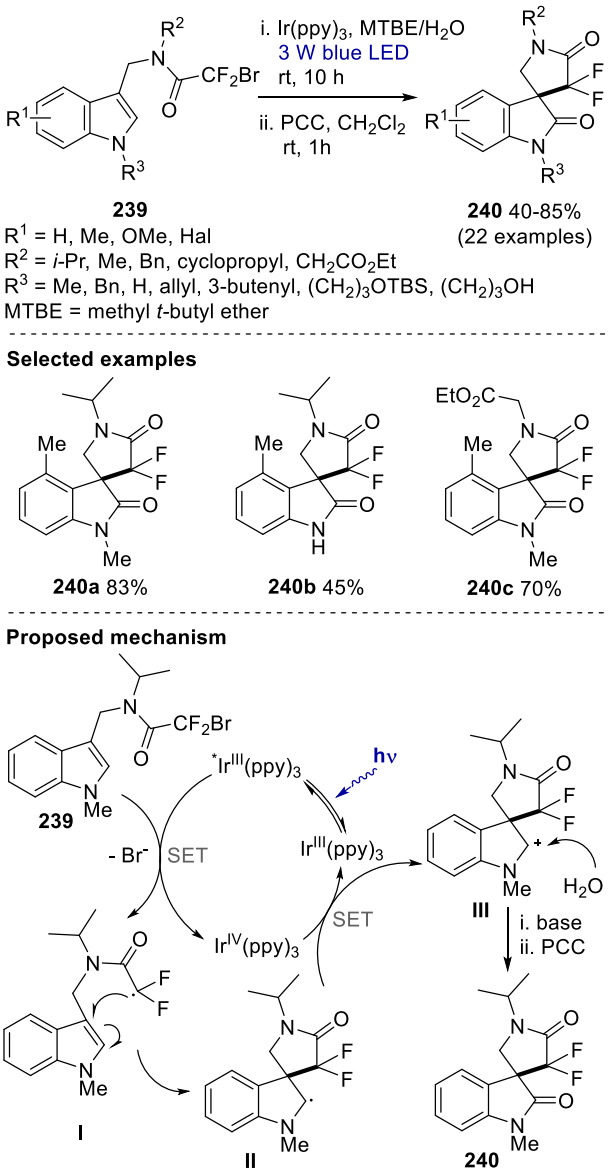
$Ir(ppy)_3$ as photoredox catalyst (Scheme 58).[89] In the proposed mechanism, the $Ir^{III}(ppy)_3$ is photoexcited to $^{*}Ir^{III}(ppy)_3$ and participate in a SET process with **237** to give electrophilic radical **I** and $Ir^{IV}(ppy)_3$. Regioselective *ipso*-cyclization of **I** affords radical intermediate **II** which is then oxidized to cation intermediate **III** via a second SET process with the *fac*-$Ir^{IV}(ppy)_3$, completing the photoredox catalytic cycle by regenerating $Ir^{III}(ppy)$. Base treatment gives the final products.



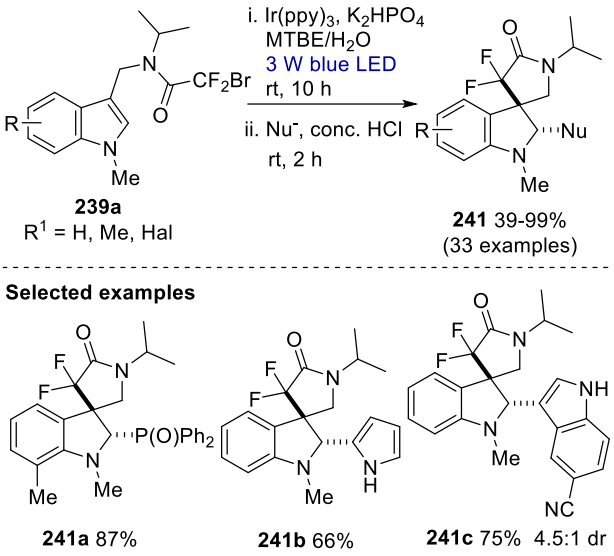
Scheme 58. Visible-light-induced dearomative spirocyclization of α-bromo-*N*-benzyl-alkylamides.

Wang and co-workers developed a visible light-mediated one-pot protocol for the synthesis of *gem*-difluorinated spirooxindole γ-lactams **240** starting from indole substrates **239** with a C-3 bromodifluroacetamide moiety as difluoromethyl radical precursor (Scheme 59).[90] The synthetic methodology, involving a cascade radical difluoromethylative dearomatization, hydroxylation and oxidation, features high chemo- and regioselectivity and is compatible with a wide range of indole subtrates. The proposed mechanism involves the nucleophilic capture of *in situ* generated carbocation **III** with water followed by oxidation with PCC. Having in mind these final steps, the authors expanded the scope of the reaction using nucleophiles other than water to capture intermediate **III** generated *in situ* (Scheme 60).[91] Diverse nucleophiles were used successfully, namely diarylphosphines, diethylphospine and electron-rich aromatic compounds (indole and pyrrole), leading to the efficient synthesis of a variety of functionalyzed spirooxindole γ-lactams

241 (39-99% yields). Some of the synthesized spirooxindole γ-lactams showed good antifungal activities, namely compounds **240a** and **241c** with inhibitory activity against *Rhizoctonia cerealis* comparable to commercial fungicide chlorothalonil.

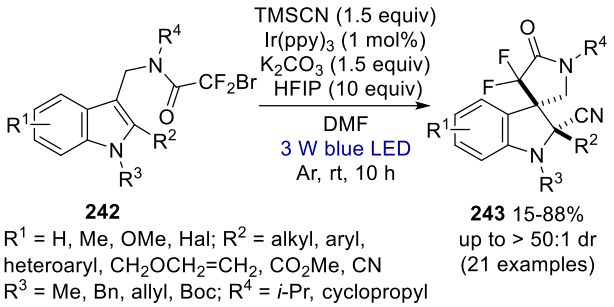


Scheme 59. Visible-light-induced cascade difluoromethylative dearomatization, hydroxylation and oxidation of indole derivatives.



Scheme 60. Photo-induced cascade difluoromethylative dearomatization, hydroxylation and substitution reactions of indole derivatives.

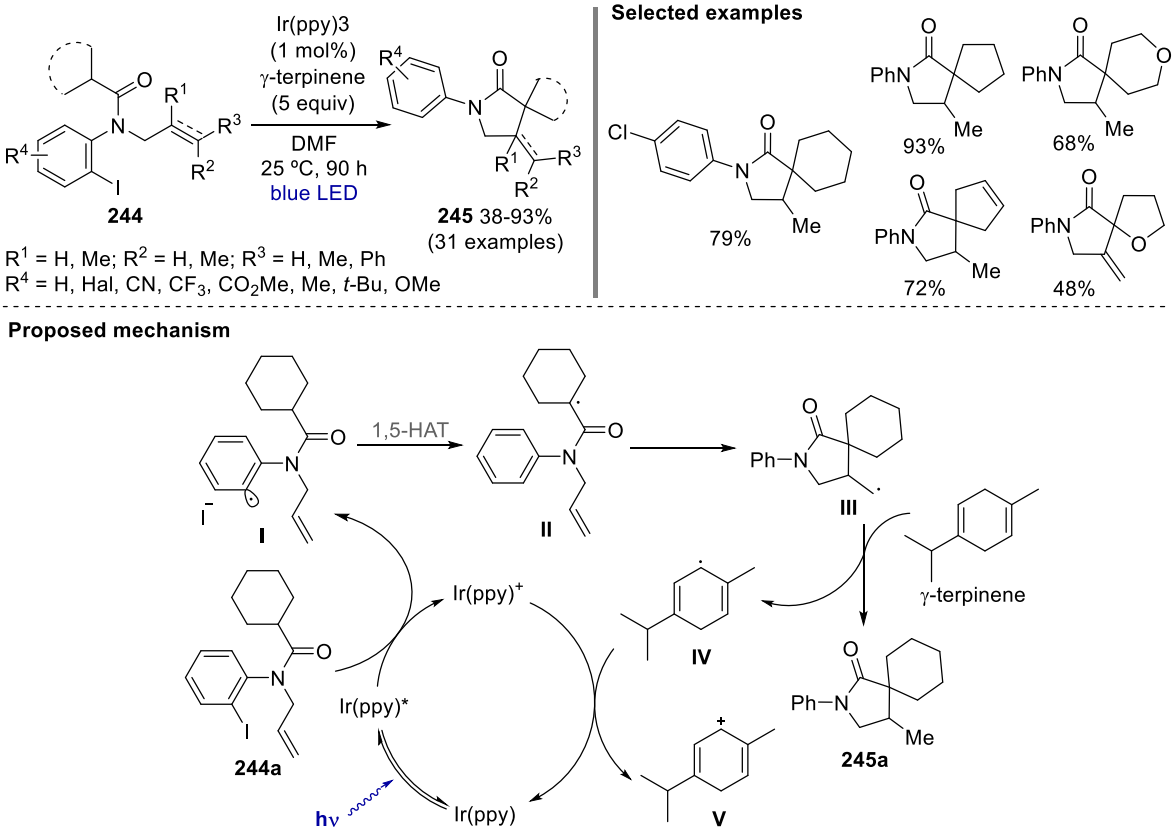
A similar strategy was applied in the synthesis of spiroindoline γ-lactams featuring two contiguous sterically congested quaternary carbon stereocenters starting from indole substrates **242** with substituents at both C-2 and C-3 (Scheme 61).[92] *gem*-Difluorinated and cyanated spirocyclic lactams **243** were obtained in 15-88% yields with moderate diastereoselectivities (up to > 50:1) by a visible-light-mediated difluoromethylative dearomatization/cyanation protocol using trimethylsilyl cyanide (TMSCN) as external nucleophile. The observed selectivity was rationalized by considering the more favorable nucleophilic addition of the cyano group to the less-hindered side of the carbocation intermediate. Attempts to promote the reaction using other external nucleophiles (*e.g.* TMS-N_3, TMS-NCS, TMS-allyl, indole, benzylamine) failed due to lower nucleophilicity and/or steric hindrance.



Scheme 61. Visible-light-induced cascade difluoromethylative dearomatization/cyanation of indole derivatives.

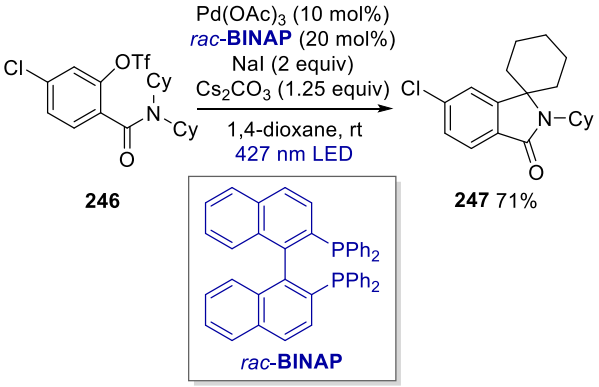
Tandem photoredox-induced intramolecular 1,5-H atom transfer (HAT) reaction-cyclization protocol of aryl iodides **244** furnishes a variety of spiro-γ-lactams **245** in moderate to high yields (38-93%) with good functional group tolerance (Scheme 62).[93] The best conditions were observed when γ-terpinene and $Ir(ppy)_3$ (1 mol%) were used as atom donor and photocatalyst, respectively. Control experiments demonstrated that both the visible light and the photocatalyst were crucial components of this cascade process. On the basis of these observations, the authors proposed a mechanism involving the photoactivation of $Ir(ppy)_3$ to generate $*Ir(ppy)_3$ which is quenched by aryl iodide **244**. The generated σ-radical **I** undergoes intramolecular 1,5-HAT giving the

stabilized tertiary carbon radical **II** which cyclizes via a 5-*exo*-trig (5-*exo*-dig for alkyne-substituted precursors **244**) to give spiro-γ-lactam radical **III**. Finally, hydrogen atom abstraction from γ-terpinene affords compounds **245** and radical **IV** which completes the photoredox catalytic cycle by reducing the photocatalyst to the ground state.



Scheme 62. Photo-induced intramolecular HAT reaction-cyclization of aryl iodides.

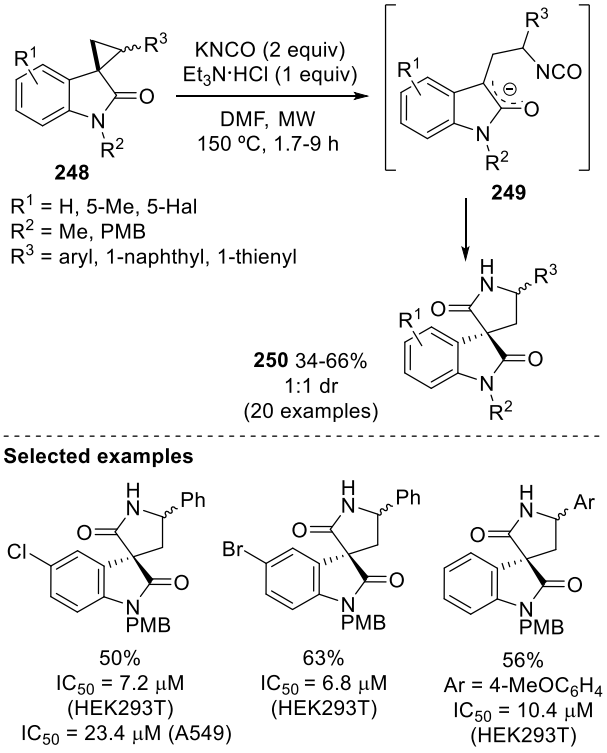
Recently, the Gevorgyan group reported the synthesis of oxindole and isoindolin-2-one scaffolds involving a visible-light-induced palladium-catalyzed intramolecular C−H arylation of amides.[94] The reaction of benzamide **246**, bearing a triflate substituent at the *ortho* position, using *rac*-BINAP as ligand and NaI as additive, under visible-light/Pd conditions, afforded spirocyclic isoindolin-2-one **247** in 71% yield (Scheme 63). The proposed mechanism involves the generation of a hybrid aryl Pd-radical intermediate by cleavage of the C(sp^2)−OTf bond, 1,5-HAT, intramolecular cyclization and rearomatization. Although the role of NaI has not been clarified, its presence proved to be crucial for the efficiency of the reaction.



Scheme 63. Visible-light-induced palladium-catalyzed intramolecular C−H arylation of a benzamide.

2.7 Ring-expansion / contraction

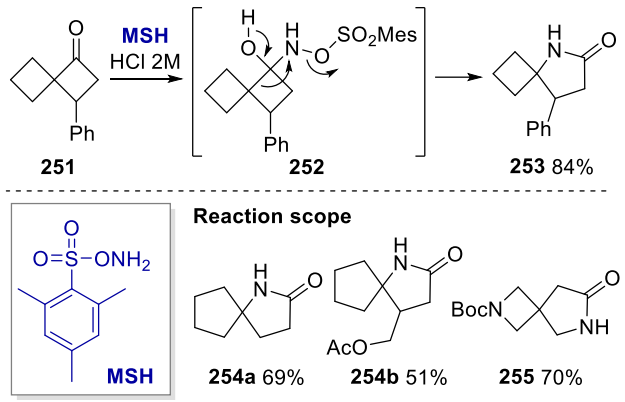
The synthesis of spirooxindole γ-lactams **250** via nucleophilic ring opening of spiro[cyclopropane-1,3′-oxindoles] **248** with cyanate ion has been reported (Scheme 64).[95] The ring-opening of cyclopropanes **248** was achieved upon treatment with potassium cyanate under microwave-assisted conditions giving spirooxindole γ-lactams **250** in moderate yields (34-66%). The effectiveness of this approach lies in the donor-acceptor character of the cyclopropane ring, activated by the oxindole fragment as an acceptor. The reaction proceeds through the formation of intermediate anion **249** followed by *ipso*-cyclization. *In vitro* cytotoxic assays of selected spiro-γ-lactams **250** revealed moderate antiproliferative activity against HEK293T, MCF7, and A549 cell lines.



Scheme 64. Nucleophilic ring opening of spiro[cyclopropane-1,3′-oxindoles].

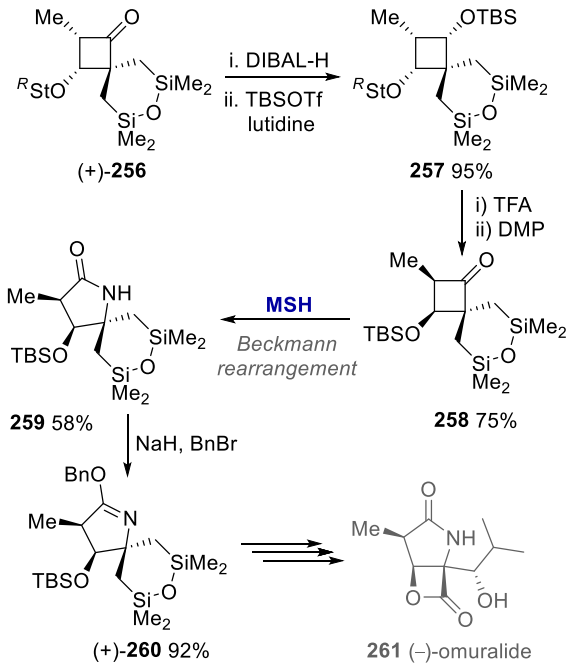
The Beckmann rearrangement of cyclobutanones is a straightforward method to the synthesis of γ-lactams. De Mesmaeker and co-workers reported an improved procedure for this rearrangement employing Tamura's reagent (*O*-mesitylenesulfonylhydroxylamine, MSH) and aqueous 2 M HCl.[96] This protocol suppresses the undesired Beckmann fragmentation pathway, where the oxime fragments to the corresponding nitrile and olefin, and allows the synthesis of a panoply of polycyclic lactams, including spiro-γ-lactams when using spiro-cyclobutanone substrates. The optimized reaction conditions led to the synthesis of spiro-γ-lactams **253-255** in good to high yields (51-84%) (Scheme 65). The authors proposed a mechanism involving the initial acid-promoted addition of MSH to the cyclobutanone to give tetrahedral intermediate **252**. Subsequent

elimination of mesitylene sulfonic acid, in a process similar to a Baeyer-Villiger reaction, leads to the formation of spiro products.



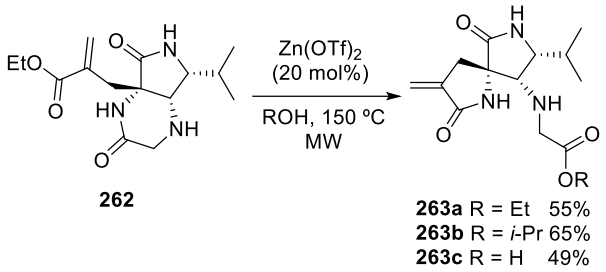
Scheme 65. Beckmann rearrangement of spiro-γ-lactams.

In the same year, Poisson and co-workers employed a two-step Beckmann transposition for the construction of the γ-lactam scaffold, as part of a strategy for the total synthesis of proteasome inhibitor (–)-omuralide (Scheme 66).[97] The direct Beckmann rearrangement of stericol-substituted cyclic oxadisilane spiro-cyclobutanone (+)-**256** using MSH was attempted, however low yields and regioisomeric lactams were obtained. The replacement of the bulky chiral auxiliary by a TBS ether via diastereoselective DIBAL-H reduction of **256** followed by TBS protection, stericol cleavage and subsequent Dess-Martin oxidation of the obtained alcohol, afforded cyclobutanone **258** as a suitable substrate for lactam formation. In fact, MSH-mediated Beckmann rearrangement of **258** provided spirocyclic oxadisilane γ-lactam **259** as a single regioisomer in 58% yield. The total synthesis of (–)-omuralide (**261**) was then achieved through a reaction sequence involving protection of the lactam moiety as benzyl imidate **260**, desymmetrization of cyclic oxadisilane via selective ring-opening by a proximal alcohol, and selective stepwise oxidation of silyl groups.



Scheme 66. Beckmann rearrangement of cyclic oxadisilane spiro-γ-lactams **256**.

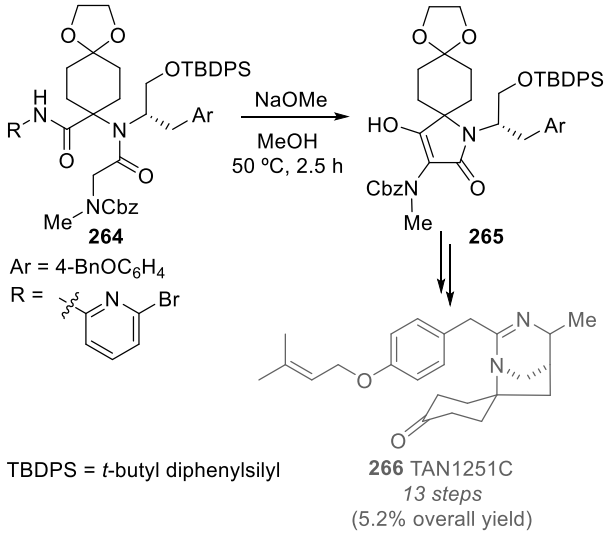
Microwave-induced zinc(II) triflate-catalyzed ring contraction/cyclization reactions of fused-γ-lactam **262** afford bis-spiro-γ-lactams **263**.[98] Using ethanol, isopropanol or water as solvents, the starting bicyclic compound **262** rearranges to the corresponding bis-lactam **263** in moderate yields (Scheme 67). A plausible mechanism for this rearrangement involves opening of the six-membered ring by the alcohol/water nucleophilic attack promoted by the zinc(II) triflate activation, followed by an intramolecular 5-*exo*-trig cyclization. Reactions carried out with methanol or allylic alcohol led to mixtures of bis-lactams **263** and transesterified starting material.



Scheme 67. Conversion of fused bis-lactams into spirocyclic lactams via zinc(II) triflate-catalyzed ring contraction/cyclization reactions.

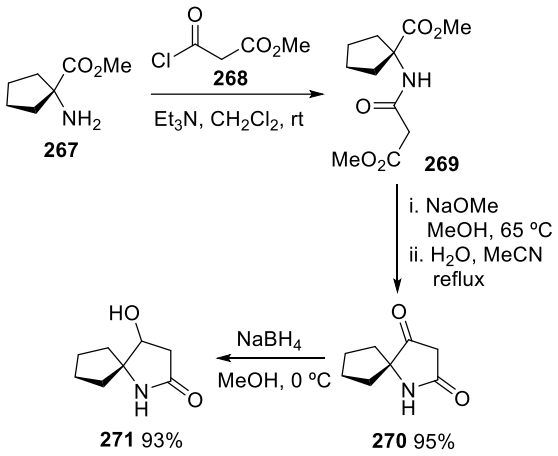
2.8 Dieckmann condensation

Kan's group reported a stereoselective total synthesis of muscarinic antagonist TAN1251C comprising of a Ugi-four component reaction and a Dieckmann condensation to construct a spiro-γ-lactam key intermediate (Scheme 68).[99] The synthetic strategy involved, as the first step, the synthesis of the Ugi product **264** followed by the Dieckmann condensation, carried out in methanol in the presence of sodium methoxide, to give unsaturated spiro-γ-lactam **265**. The total synthesis of TAN1251C (**266**) was achieved in 13 steps in an overall yield of 5.2%.



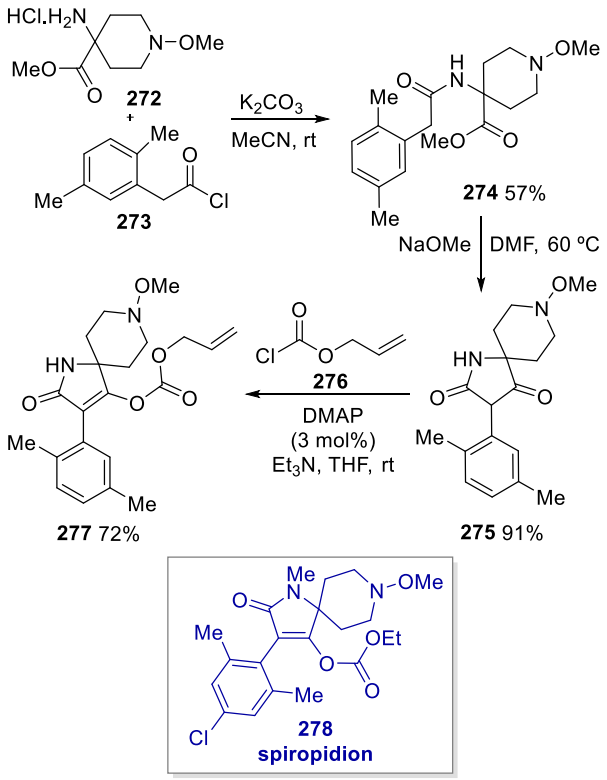
Scheme 68. Dieckmann condensation involved in the total synthesis of muscarinic antagonist TAN1251C.

An efficient strategy for the synthesis of spirocyclic diones (*e.g.* **270**) from cyclic α-amino acid substrates has been reported (Scheme 69).[100] Amide **269** was obtained by acylation of amino ester **267** with methyl malonyl choride (**268**) and was used without purification in the spirocyclization step. Spirocyclic dione **270** was obtained in high yield by an initial Dieckmann condensation of amide **269**, carried out in methanol in the presence of sodium methoxide, followed by hydrolysis and decarboxylation. Further reduction with $NaBH_4$ in methanol afforded 4-hydroxy-spiro-γ-lactam **271** in 93% yield.



Scheme 69. Synthesis of a spiro-γ-lactam via Dieckmann condensation.

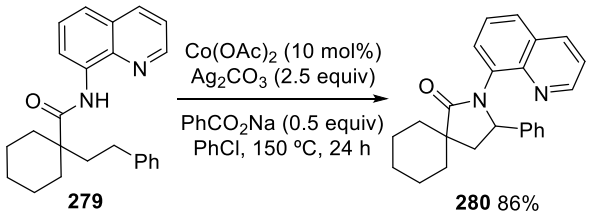
A similar Dieckmann condensation approach was recently employed by Muehlebach *et al.* in the synthesis of *N*-methoxy-piperidine-based spiro-γ-lactams (*e.g.* **277**), compounds with insecticidal activity for application in crop protection (Scheme 70).[101] The procedure involved the initial acylation of the α-amino ester **272** with aryl acid chloride **273** to give **274**. Subsequent methoxide-mediated Dieckmann-type cyclization affords spirocyclic compound **275** bearing a pyrrolidone-2,4-dione scaffold which is then acylated with allyl chloroformate (**276**) to give unsaturated spiro-γ-lactam **277** in 72% yield. A similar strategy was applied to the scalable synthesis of proinsecticide spiropidion (**278**).



Scheme 70. Synthesis of a *N*-methoxy-piperidine-based spiro-γ-lactam via Dieckmann condensation/acylation.

2.9 Other methods

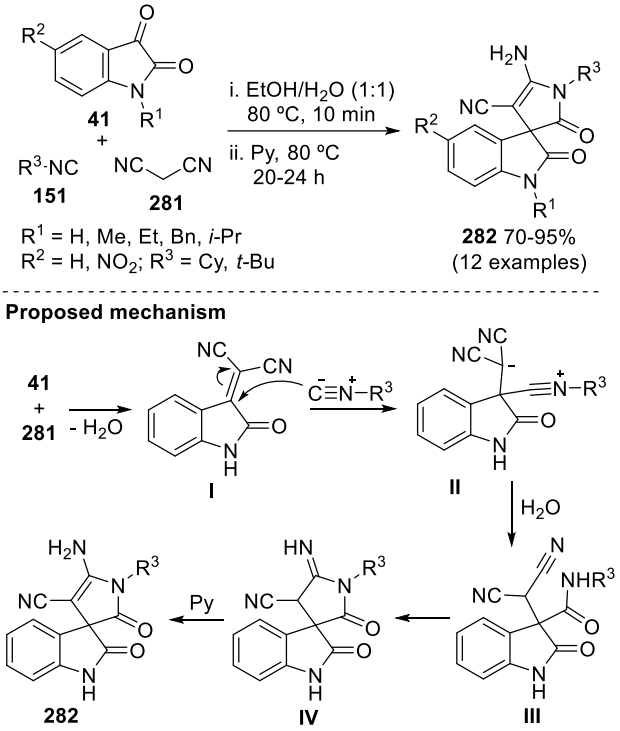
Metal-catalyzed cyclization through dehydrogenative amination of unactivated C(sp^3)−H bonds has been explored as a feasible method for spirocyclic lactam synthesis. In 2015, Li, Ge and co-workers reported the synthesis of spirocyclic β- and γ-lactams containing an 8-quinolinyl functional group and a cycloalkane spiro-ring on their structures.[102] In particular, spirocyclic γ-lactam **280** was obtained in high yield (86%) from the cobalt-catalyzed site-selective direct C(sp^3)–H functionalization of compound **279** with the aid of the quinolinyl group acting as a bidentate directing group (Scheme 71). A plausible mechanism for the formation of the spiro-γ-lactams involves the generation of an amide-Co^{III} complex, followed by cyclometallation and oxidation with Ag_2CO_3 giving γ-lactam **280** upon reductive elimination.



Scheme 71. Cobalt-catalyzed site-selective intramolecular dehydrogenative amination of unactivated C(sp^3)–H.

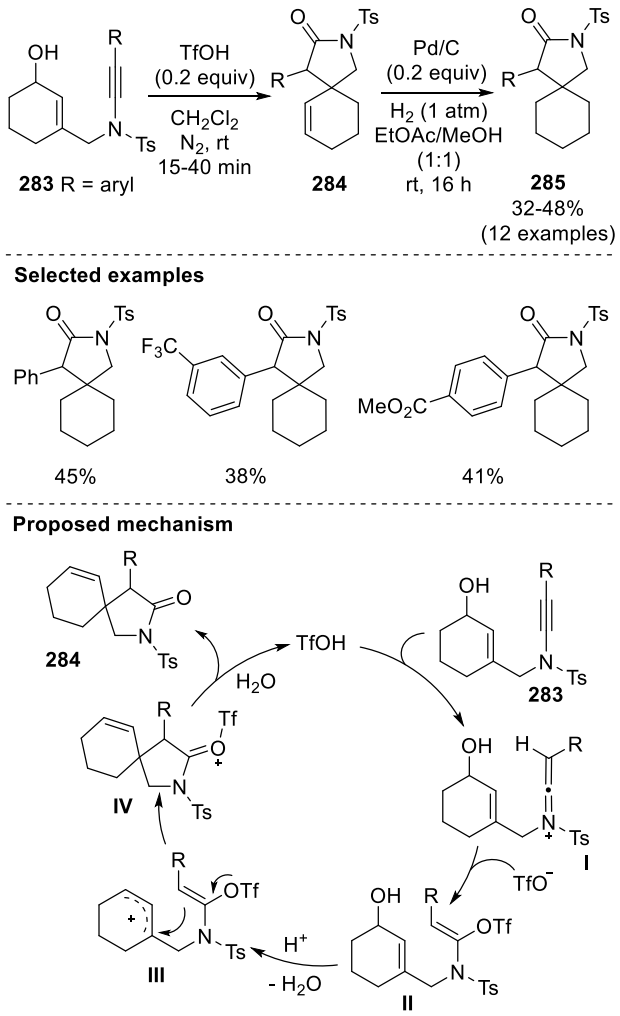
Adib and co-workers reported a one-pot multicomponent synthesis of spirooxindole γ-lactams **282** with two carbonyl groups located next to the spiro-carbon atom using isatins **41**, isocyanides

151, malononitrile (**281**) and pyridine (Scheme 72).[103] These spirocyclic compounds were obtained in high yields (70-95%) by a process involving the initial Knoevenagel condensation between isatins **41** and malononitrile. The resulting condensation product **I** undergoes nucleophilic addition of isocyanide **151** followed by the reaction with water to produce amide intermediate **III**. Pyridine-assisted cyclization via intramolecular nucleophilic addition of the amide functionality to one of the nitrile groups and subsequent tautomerization gives spirocyclic compounds **282**.



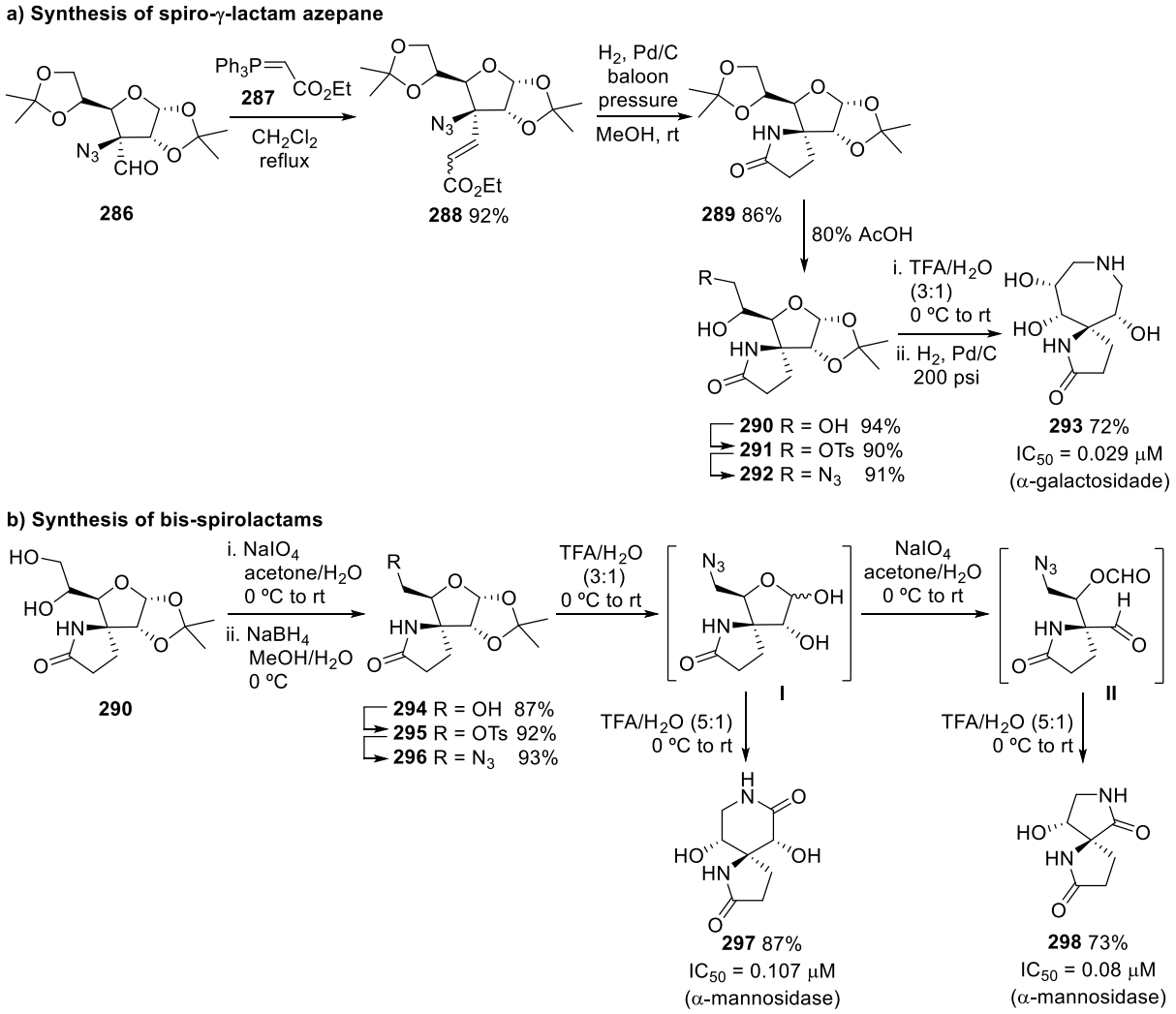
Scheme 72. Multicomponent synthesis using isatin precursors**.**

Yeh and co-workers reported a TfOH-catalyzed spirolactamization of cyclohex-2-enols **283** bearing a (arylethynyl(tosyl)amino)methyl tethered group (Scheme 73).[104] The protocol involved the initial spirocyclization of **283** in the presence of catalytic TfOH to give spiro-γ-lactams **284**. Subsequent hydrogenation reaction of the crude mixture afforded spiro-γ-lactams **285** in moderate overall yields (32-48%). The proposed mechanism for the construction of the spirocyclic system starts with the electrophilic activation of **283** with TfOH and subsequent trapping of the generated keteniminium intermediate **I** with triflate anion to give **II**. Further protonation/dehydration followed by attack of the vinyl triflate onto the tethered allylic carbocation furnished spirocyclic lactam intermediate **IV** which was hydrolyzed to **284** and regenerated the catalyst.



Scheme 73. TfOH-Catalyzed spirolactamization of (ethynyl(tosyl)amino)methyl tethered cyclohex-2-enols.

A multistep synthesis of D-glucose-derived spiro-γ-lactams was reported by Dhavale and co-workers (Scheme 74).[105] D-Glucose-derived α-azidoaldehyde **286** reacted with phosphorous ylide **287** to give α,β-unsaturated ester **288**. Subsequent reductive lactamization with H_2 and 10% Pd/C afforded spiro-γ-lactam **289** in 86% yield. The synthesis of the target spiroazepane-γ-lactam **293** was attained via sequential hydrolysis, selective tosylation, S_N2 displacement with sodium azide and TFA/water-mediated cleavage of the 1,2-*O*-acetamide functionality of compound **292** followed by reductive aminocyclization using again H_2 and 10% Pd/C. Spirocyclic bis-lactams **297** and **298** were obtained via oxidative cleavage of diol **290**, followed by tosylation and subsequent conversion into azide **296**. One-pot TFA/water-promoted *in situ* hydrolysis of the 1,2-acetonide functionality generates **I** which rearranges to spirocyclic bis-γ,δ-lactam **297** by a Schmidt-Boyer rearrangement. Bis-spiro-γ-lactam **298** was obtained via oxidative cleavage of **I** to give **II** followed by a Schmidt-Boyer rearrangement. Compounds **293** and **298** showed selective and potent glycosidase inhibitory activity. These results were supported by the molecular docking studies.

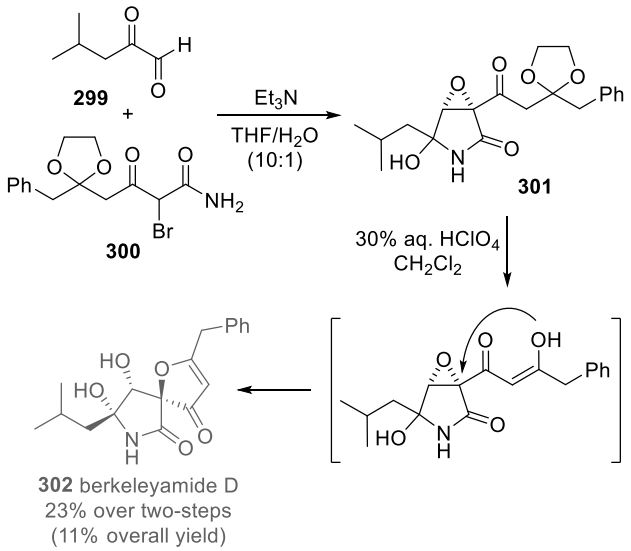


Scheme 74. Multistep synthesis of D-glucose-derived spiro-γ-lactams.

3. NON-LACTAM RING SYNTHESIS

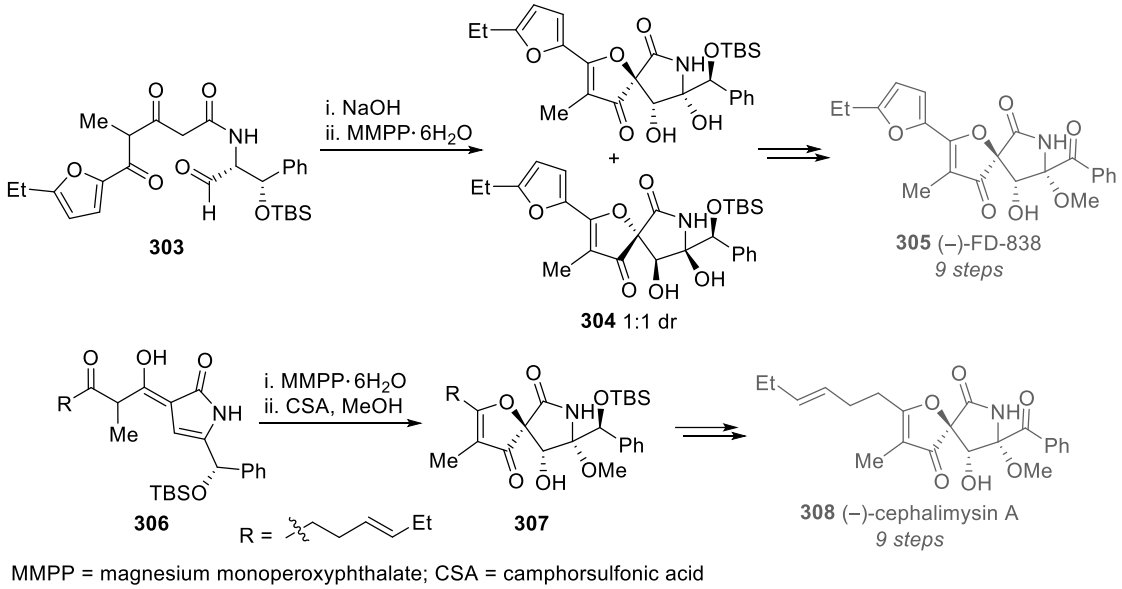
3.1 Nucleophilic cyclization reaction

An improved methodology for the synthesis of the metalloproteinase-3 and caspase-1 inhibitor, (±)-berkeleyamide D (**302**) has been reported by Kuramochi and co-workers (Scheme 75).[106] The protocol involves the synthesis of ketal **301** via a Darzens reaction of isobutylglyoxal (**299**) and α-bromo-β-ketoamide **300**. Deprotection of **301** followed by intramolecular spirocyclization via epoxide ring opening triggered by the enol moiety led to the target compound in 23% yield over a two-step sequence and in 11% overall yield, a 4-fold improvement of the overall yield of the previous reported synthesis.



Scheme 75. Final steps of the total synthesis of (±)-berkeleyamide D.

More recently, an analogous intramolecular spirocyclization step has been applied to the total synthesis of spirocyclic-γ-lactams, the PKS-NRPS-based secondary fungal metabolites (–)-FD-838 (**305**) and (–)-cephalimysin A (**308**) (Scheme 76).[107] Similar to the synthesis of (±)-berkeleyamide D, the spirocyclization step of the total synthesis of (–)-FD-838 involved the cyclization of a γ-lactam-fused epoxide intermediate.

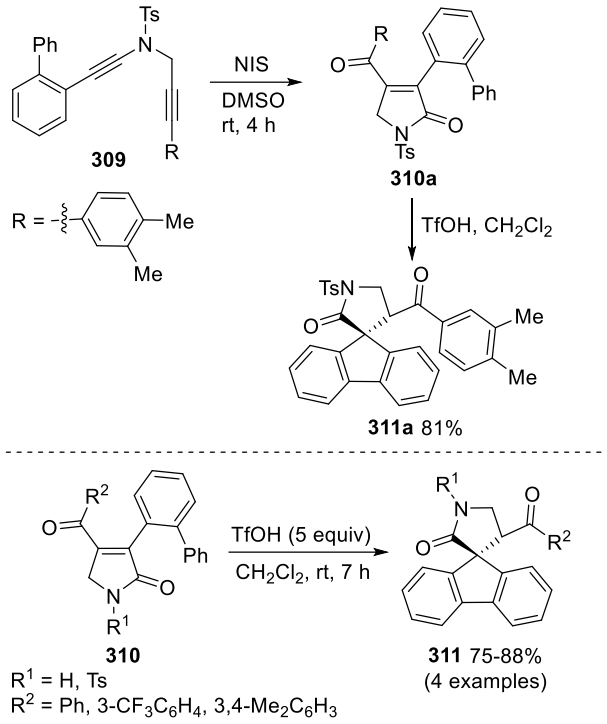


Scheme 76. Highlights of the total synthesis of metabolites (–)-FD-838 and (–)-cephalimysin A.

3.2 Electrophilic cyclization reaction

The synthesis of functionalized pyrrolidones via a metal-free dimethyl sulfoxide (DMSO)/*N*-iodosuccinimide (NIS)-promoted 5-*exo*-dig oxidative cyclization of ynamides bearing internal alkynes has been described by Sahoo and co-workers.[108] Following this protocol, the one-pot sequential 5-*exo*-dig cyclization of ynamide **309**, followed by electrophilic cyclization of the corresponding pyrrolidone furnished spiro adduct **311a** in 81% yield. In the presence of catalytic

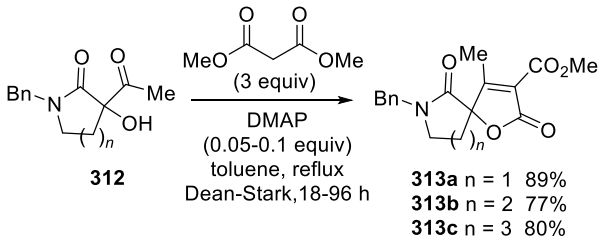
triflic acid (TfOH), pyrrolidones **310** having 3-*ortho*-biaryl motifs also underwent electrophilic cyclization with the alkene moiety to give spirocyclic γ-lactams **311** in good yields (75-88%) (Scheme 77).



Scheme 77. Oxidative cyclization of ynamides bearing internal alkynes and electrophilic cyclization of functionalized pyrrolidones.

3.3 Lactonization of functionalized lactams

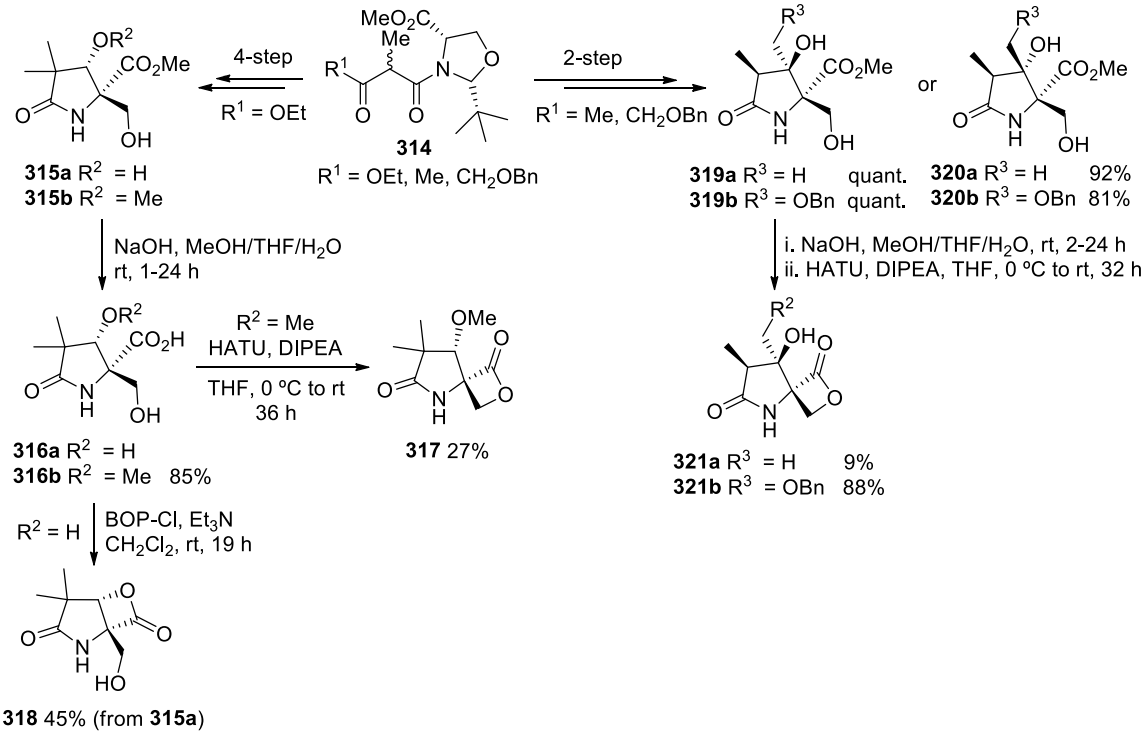
Christoffers and co-workers reported an efficient synthesis of spiro-γ-lactams starting from the appropriate lactam-containing precursors.[109] This synthetic methodology relies on a DMAP-catalyzed Knoevenagel condensation of α-hydroxy-α-acetyl-lactams **312** with dimethyl malonate followed by lactonization to afford spirocyclic γ-, δ-, or ε-lactams **313** in high yields (77-89%) (Scheme 78).



Scheme 78. Cyclocondensation of α-hydroxy-α-acetyl-lactams and dimethyl malonate.

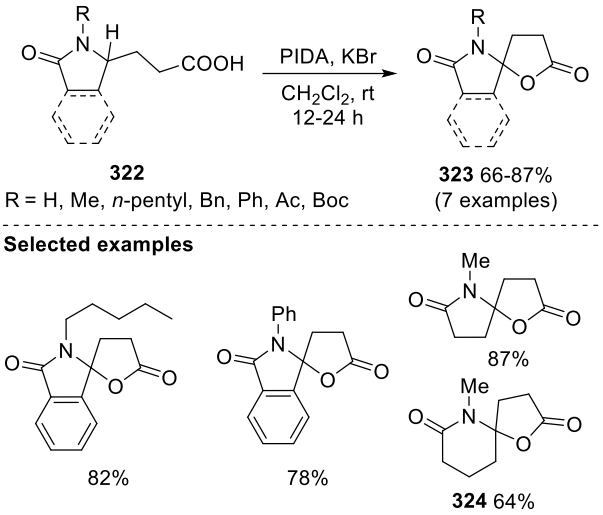
A synthetic approach to spiro-γ-lactams derived from oxazolidine precursors has been reported (Scheme 79).[110] Spiro-γ-lactam β-lactone **317** was synthesized by ring-closure of pyrrolidin-2-one **316** which was obtained through a five-step synthetic route involving a Dieckmann cyclization of malonamide **314**, followed by sequential reduction, methylation, deprotection and

hydrolysis reactions. The nature of the pyrrolidin-2-ones C-4 substituent plays a crucial role in the reaction outcome. Depending on the substitution pattern, spiro-β-lactone γ-lactams (*e.g.* **317**) or fused-β-lactone γ-lactams (*e.g.* **318**) may be obtained. Spiro-β-lactone γ-lactams are only obtained when the formation of the fused derivatives is blocked (*e.g.* substrates bearing a *cis* alkoxide and carboxyl groups at positions 4 and 5, respectively). Moreover, it is noteworthy that spiro-derivative **317** was not formed under standard conditions used in the synthesis of fused-γ-lactams (*N*,*N*'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride and triethylamine). Its synthesis was only possible by the treatment of the corresponding precursor with (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate) (HATU) and DIPEA. The synthesis of spiro-β-lactone γ-lactams **321**, bearing a hydroxyl group in the γ-lactamic core, was also achieved through a similar synthetic pathway.



Scheme 79. Lactonization of 2-(hydroxymethyl)-pyrrolidinone derivatives.

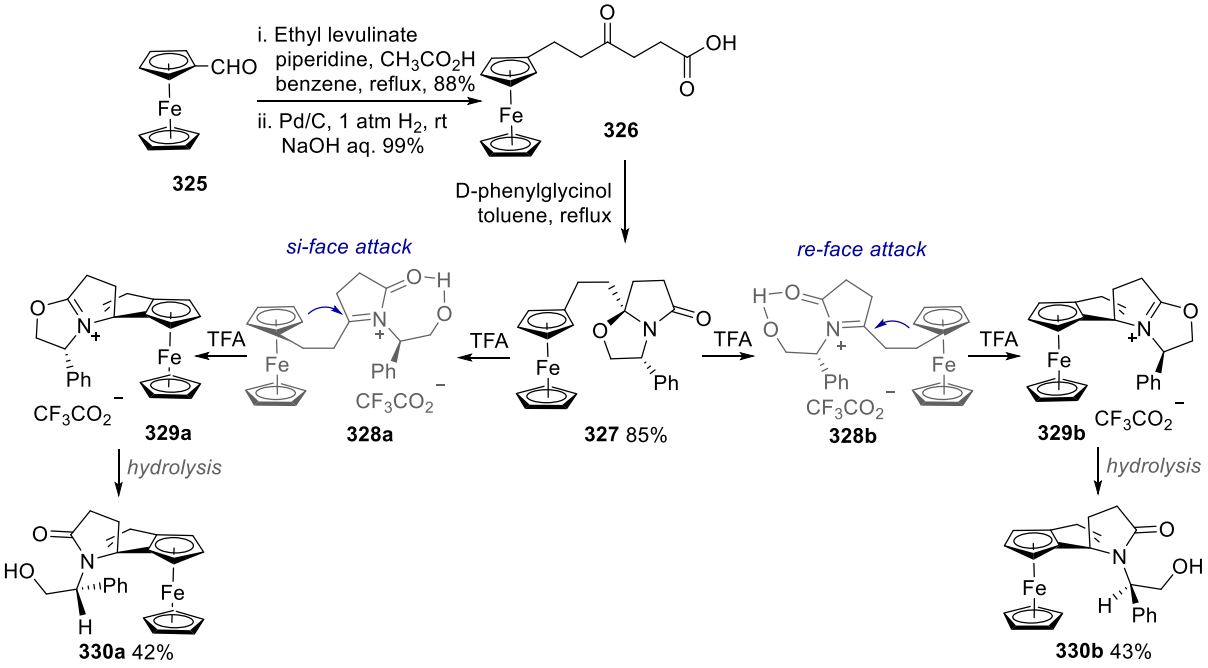
The Yoda's group reported a methodology for the synthesis of spiro-γ-lactone γ-lactams **323** involving a C–H spirolactonization as the key step (Scheme 78).[111] The reaction of γ-lactam carboxylic acids **322** in the presence of the hypervalent iodine (III) reagent PIDA and potassium bromide provided spirocyclic compounds **323** in good yields (66-87%). The authors found that the use of a bromide salt was essential to efficiently obtain the target spiro-γ-lactone γ-lactams. On the basis of this information, a radical-induced hydrogen abstraction pathway was proposed for the C–H spirocyclization. The methodology was also used in the synthesis of spiro-γ-lactone δ-lactam **324**.



Scheme 80. PIDA/KBr-promoted C–H spirocyclization of γ-lactam carboxylic acids.

3.4 Iminium ion cyclization

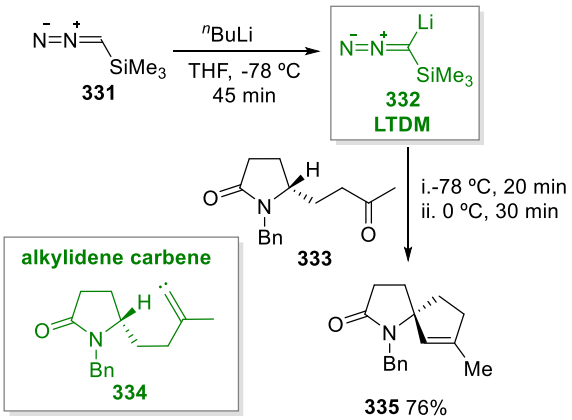
The simultaneous generation of planar, central, and axial chiralities in the synthesis of ferrocene derived spiro-γ-lactams via an iminium cyclization has been reported by Jiao and co-workers (Scheme 81).[112] The synthetic protocol included an initial aldolic condensation of ferrocenecarboxaldehyde (**325**) with ethyl levulinate followed by hydrogenation and hydrolysis reactions, affording compound **326** in high yield. Then, bicyclic ferrocene derivative **327** was synthesized, in 85% yield, through a condensation reaction of **326** with D-phenylglycinol. Treatment of compound **327** with TFA promoted an intramolecular spirocyclization reaction by the *si*- or *re*-face via acyl iminium intermediate (**328**) leading to compounds **329a** and **329b**, respectively. Subsequent hydrolysis of **329** leads to the corresponding spiro-γ-lactams **330a** and **330b** in 42% and 43% yield, respectively.



Scheme 81. Synthesis of ferrocene derived spiro-γ-lactams via iminium cyclization**.**

3.5 Intramolecular alkylidene carbene C–H insertion reaction

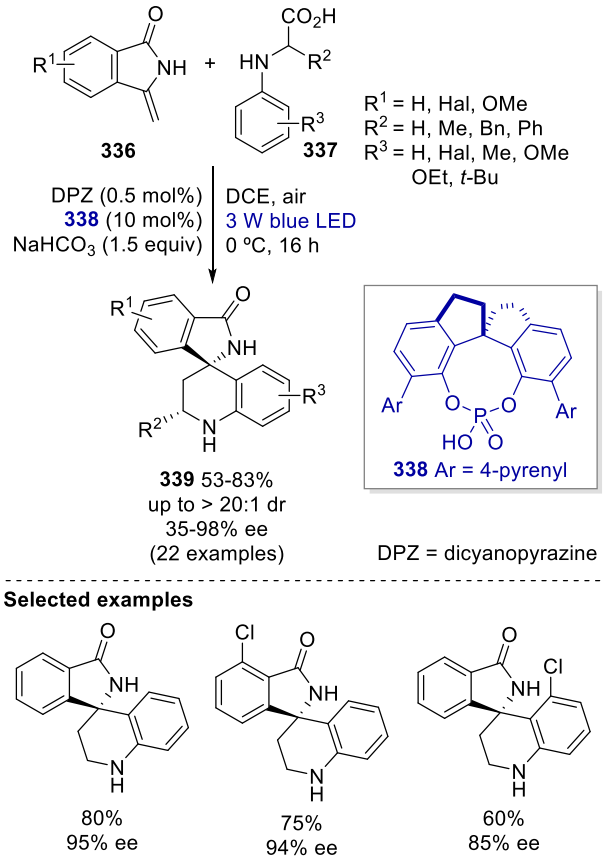
Alkylidene carbene C–H insertion reaction is an important synthetic tool for the functionalization of unactivated C–H bonds. This strategy is very useful for the formation of quaternary centers with stereochemical control since it usually occurs with retention of the stereochemistry at the tertiary centers. Wee and Annadi explored the alkylidene carbene generation followed by C–H insertion of enantiopure γ- or δ-lactam ketones for the synthesis of spirocyclic γ- and δ-lactams, respectively.[113] The protocol involves the generation of alkylidene carbenes (*e.g.* **334**) by treatment of γ- or δ-lactam ketones with lithiotrimethylsilyldiazomethane (LTDM) (Scheme 82). LTDM was obtained by reacting trimethylsilyldiazomethane (TMSDM) with *n*-BuLi in THF at -78 °C. After addition of a THF solution of γ-lactam ketone **333**, the reaction mixture was stirred at -78 ºC for 20 min, warmed to 0 ºC and further stirred for 30 min, giving spiro-γ-lactam **335** in 76% yield. The synthetic utility was demonstrated in the total synthesis of (–)-adalinine, a coccinellid alkaloid.



Scheme 82. Alkylidene carbene generation-C–H insertion of a γ-lactam ketone.

3.6 Decarboxylative Povarov reaction

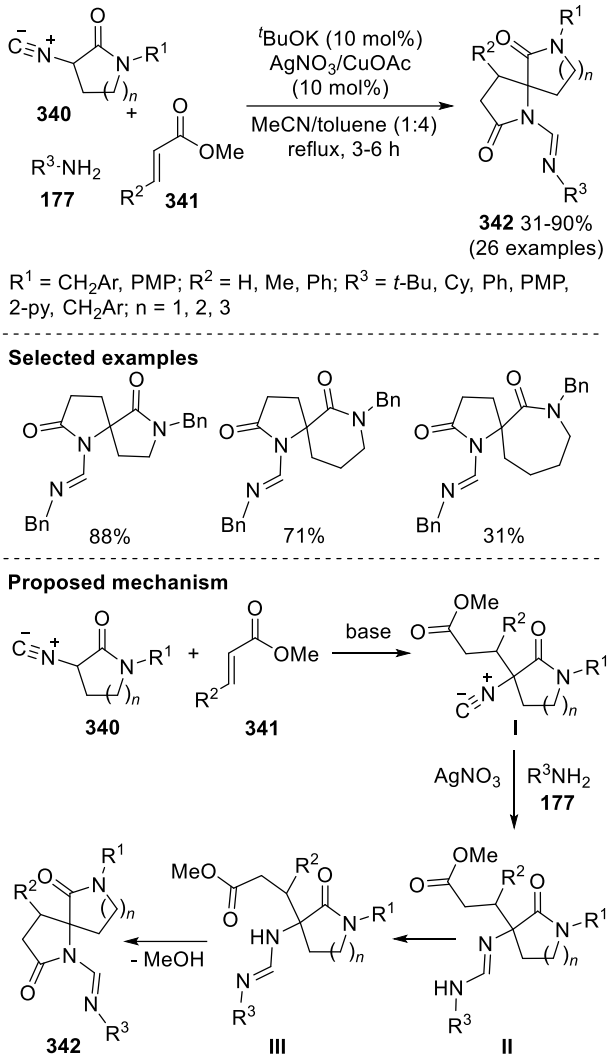
Jiang and co-workers employed an aerobic decarboxylative Povarov reaction of *N*-aryl α-amino acids with isoindolinones **336** for the synthesis of spiro-γ-lactams (Scheme 83).[114] The reaction was efficiently catalyzed through a metal-free cooperative catalytic system of photoredox and chiral Brønsted acid catalysis, providing spirocyclic adducts **339** in high yields with good to excellent diastereo- and enantioselectivities (> 20:1 dr and up to 99% ee).



Scheme 83. Asymmetric aerobic decarboxylative Povarov reaction.

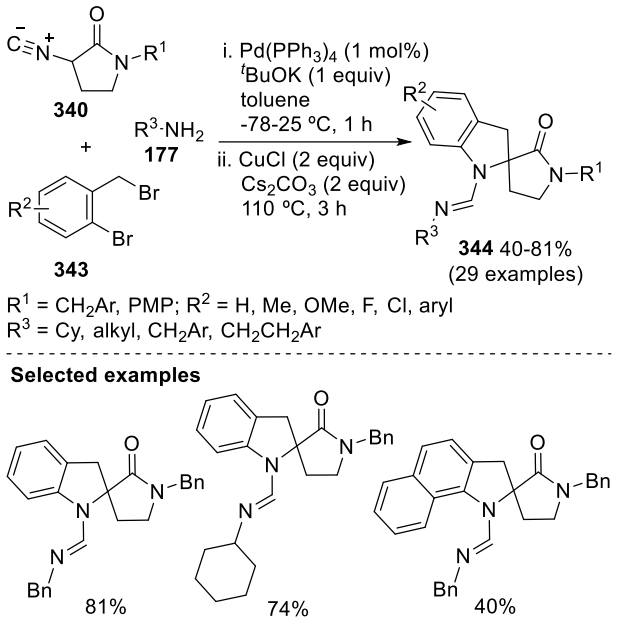
3.7 Tandem three-component reaction

Oh and co-workers developed two different three-component protocols leading to spiro-γ-lactams, both having in common isocyano lactams and amines as starting materials.[115] The silver-catalyzed formal [3+2] cycloaddition reaction involving isocyano lactams **340**, amines **177** and electron-deficient alkenes **341** as the third counterpart allowed the synthesis of spiro-fused bis-lactams **342** (Scheme 84).[115a] The reaction proceeded through a sequential conjugate addition of isocyano lactams **340** to alkenes **341** catalyzed by a Brønsted base followed by a silver-catalyzed amine insertion to the isocyanide moiety to give formamidine **II**. Isomerization of intermediate **II** into **III** followed by intramolecular lactamization gave bis-lactams **342** in moderate to excellent yields (31-90%) and good functional group tolerance.



Scheme 84. Silver-catalyzed tandem three-component spirocyclization involving isocyano lactams, amines and electron-deficient alkenes.

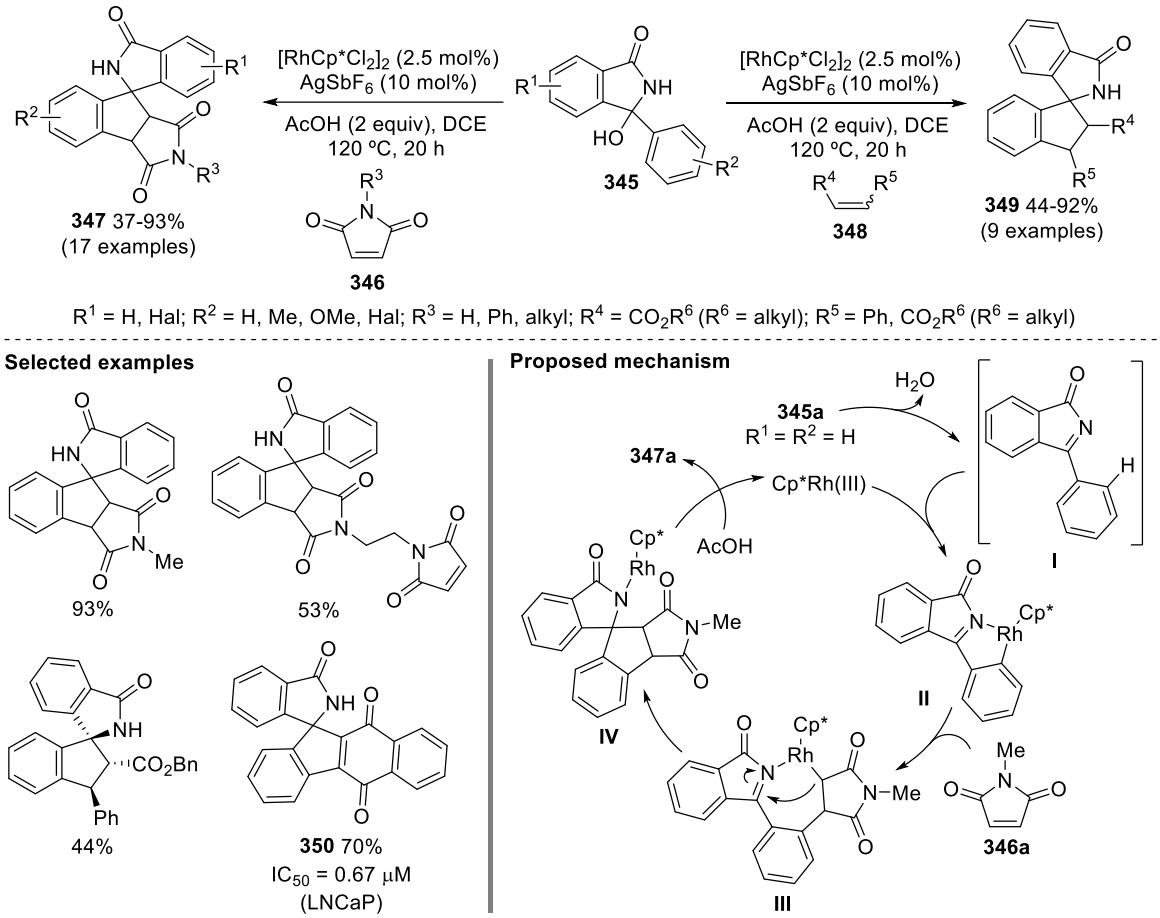
The second three-component methodology involved 2-bromobenzyl bromides **343** as the third reaction component (Scheme 85).[115b] This palladium/copper catalyzed reaction led to the synthesis of indole-based spiro-γ-lactams **344** in moderate to good yields (40-81%). The reaction relies on a Pd-catalyzed benzylation of α-isocyano lactams **340** with **343**, followed by *in situ* amine addition to the isocyanide moiety in the presence of a copper catalyst and subsequent intramolecular *N*-arylation via a key cooperative action of Pd/Cu catalysis.



Scheme 85. Cooperative Pd/Cu catalyzed tandem three-component reaction involving isocyano lactams, amines and 2-bromobenzyl bromides.

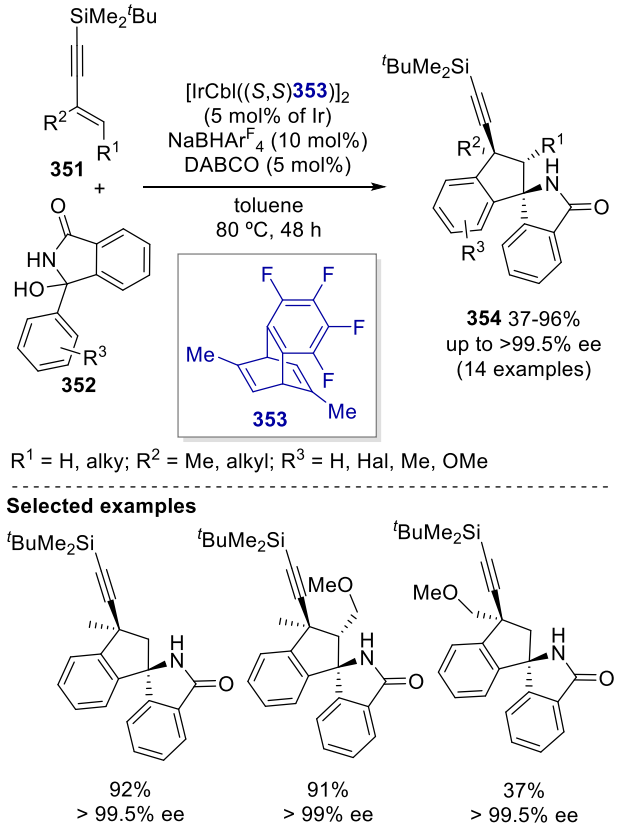
3.8 [3+2] Annulation reaction

Kim and co-workers reported a rhodium-catalyzed [3+2] annulation of *N*-acyl imines, generated *in situ* from 3-hydroxyisoindolinones **345**, with various activated alkenes (Scheme 86).[116] The reaction with maleimides, maleates, fumarates and cinnamates gave spiroisoindanes **347** and **349** in moderate to high yields (37-93%). The proposed mechanism involved the initial coordination of the cationic Rh(III) catalyst with intermediate **I** followed by C–H activation to generate rhodacycle intermediate **II**. Subsequent coordination with maleimide **346a** followed by a migratory insertion provided **III** which undergoes intramolecular nucleophilic addition to give **IV**. Protonation with AcOH generates spiro-γ-lactam **347a** and regenerates the catalyst. When using acrylates and quinones as activated alkenes, spiroindenes (*e.g.* **350**) were obtained instead of spiroindanes. In this case an alternative mechanistic pathway involving the formation of the equivalent intermediate **III** followed by β-H elimination and Prins-type cyclization was proposed. Bioactivity assays were performed, revealing that some quinone-derived spiroindenes were more active than the anticancer drug doxorubicin against human prostate cancer cells (*e.g.* **350**).



Scheme 86. Rhodium-catalyzed [3+2] annulation between *N*-acyl imines and activated olefins.

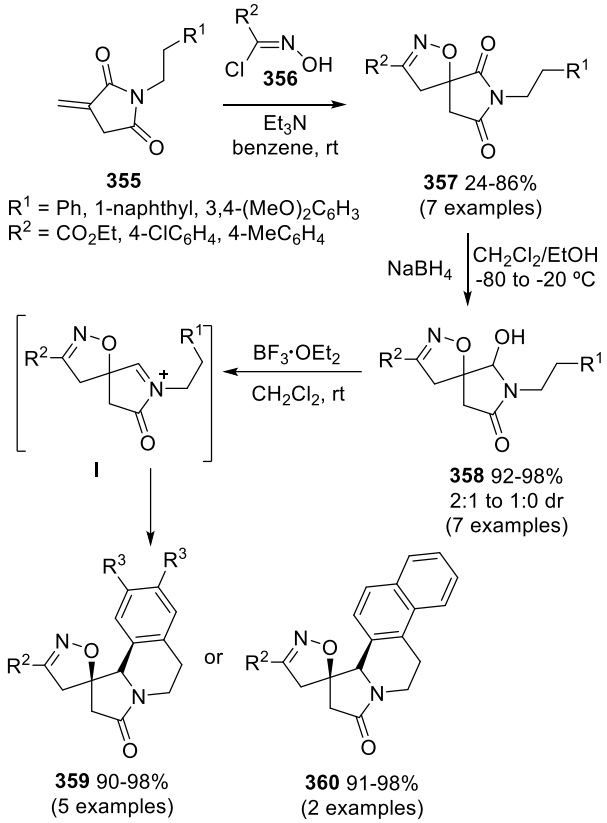
An enantioselective [3+2] annulation of *N*-acyl imines with 3-enynes catalyzed by an iridium/chiral diene complex was reported (Scheme 87).[117] *N*-Acyl ketimines were generated *in situ* from isoindolinones **352** and subsequent oxidative cyclization between aryliridium(I) species and 1,3-enynes **351** led to the desired spiro-γ-lactams **354** in high yields (up to 96%) and in a highly diastereo- and enantioselective fashion (over 98% ee).



Scheme 87. Enantioselective [3+2] annulation between *in situ* generated *N*-acyl imines and 3-enynes.

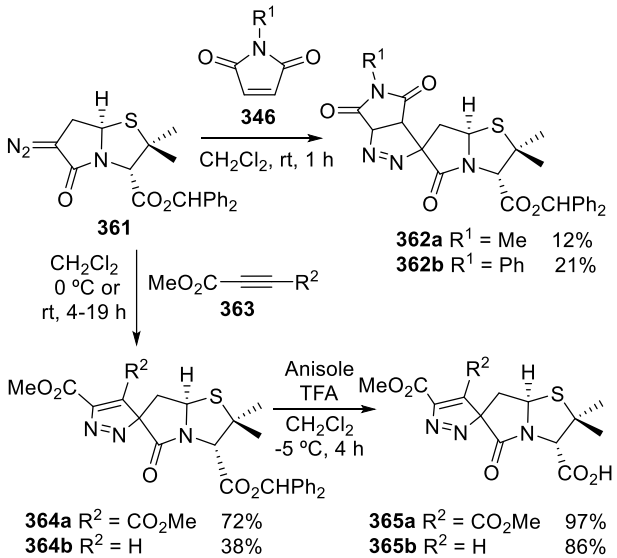
3.9 1,3-Dipolar cycloaddition reaction

Stepakov and co-workers described an efficient strategy for the synthesis of spiroisoxazoline-γ-lactams containing a tetrahydroisoquinoline core (Scheme 88).[118] The protocol involved an initial 1,3-dipolar cycloaddition between itaconimide derivatives **355** and nitrile oxides, generated *in situ* from the corresponding α-chlorinated oximes **356**, to furnish spiro-isoxazolines **357** in 24-86% yields. Selective reduction of one carbonyl with $NaBH_4$ gave the corresponding spirocyclic hydroxy-γ-lactam derivatives **358** in excellent yields (92-98%), isolated as diastereomeric mixtures or as single diastereomers (R^1 = 1-naphthyl). Treatment of spirocyclic lactams **358** with excess of $BF_3{\cdot}Et_2O$ led to the formation of *N*-acyliminium ion intermediates **I** which underwent cyclization via direct attack by the π-aromatic system to give spiro-γ-lactams **359** and **360** in high yields (90-98%).



Scheme 88. Synthesis of spiroisoxazoline-γ-lactams containing a tetrahydroisoquinoline core via a 1,3-dipolar cycloaddition.

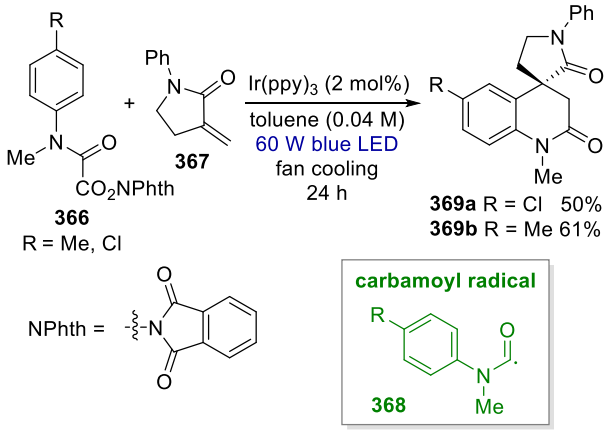
Recently, Pinho e Melo and co-workers established a novel synthetic route to chiral spiro-γ-lactams via 1,3-dipolar cycloaddition reaction of chiral diazo-γ-lactam **361** and electron-deficient dipolarophiles (Scheme 89).[119] Chiral diazo-γ-lactam **361** was synthesized through a multistep strategy starting from D-penicillamine and an L-aspartic acid derived aldehyde. The 1,3-dipolar cycloaddition reaction of **361** with electron-deficient dipolarophiles **346** and **363** afforded spiropyrazolo-fused γ-lactams **362** and **364**, respectively, under mild conditions in low to good yields (12-72%). Further conversion of the benzhydryl ester moiety into the corresponding carboxylic acid derivatives renders the spiro-γ-lactams **365** in excellent yields (86-97%).



Scheme 89. 1,3-Dipolar cycloaddition between a chiral diazo-γ-lactam and dipolarophiles.

3.10 Photo-mediated radical cyclization

Donald, Taylor and co-workers described for the first time the generation of carbamoyl radicals via a photo-catalyzed reductive process using visible light.[120] The nucleophilic carbamoyl radicals (**368**) were generated from *N*-hydroxyphthalimido oxamide precursors **366** and trapped with exocyclic electron deficient alkenes **367** via intermolecular addition/cyclization reactions to give spirocyclic bis-γ,δ-lactams **369** in moderate yields (Scheme 90).

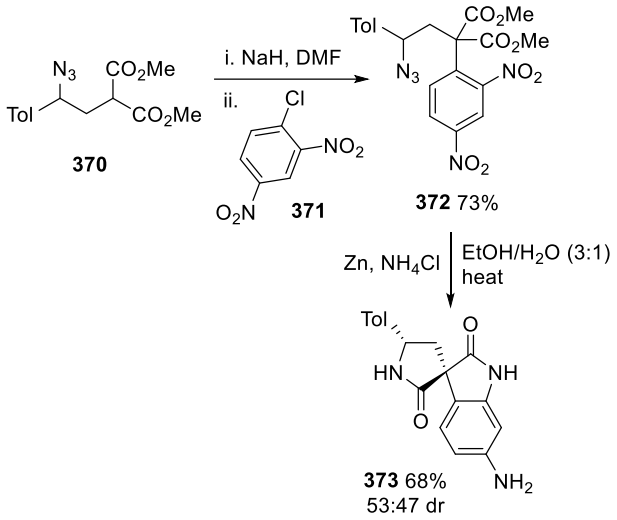


Scheme 90. Intermolecular addition/cyclization of carbamoyl radicals.

4. LACTAM AND NON-LACTAM RING SYNTHESIS

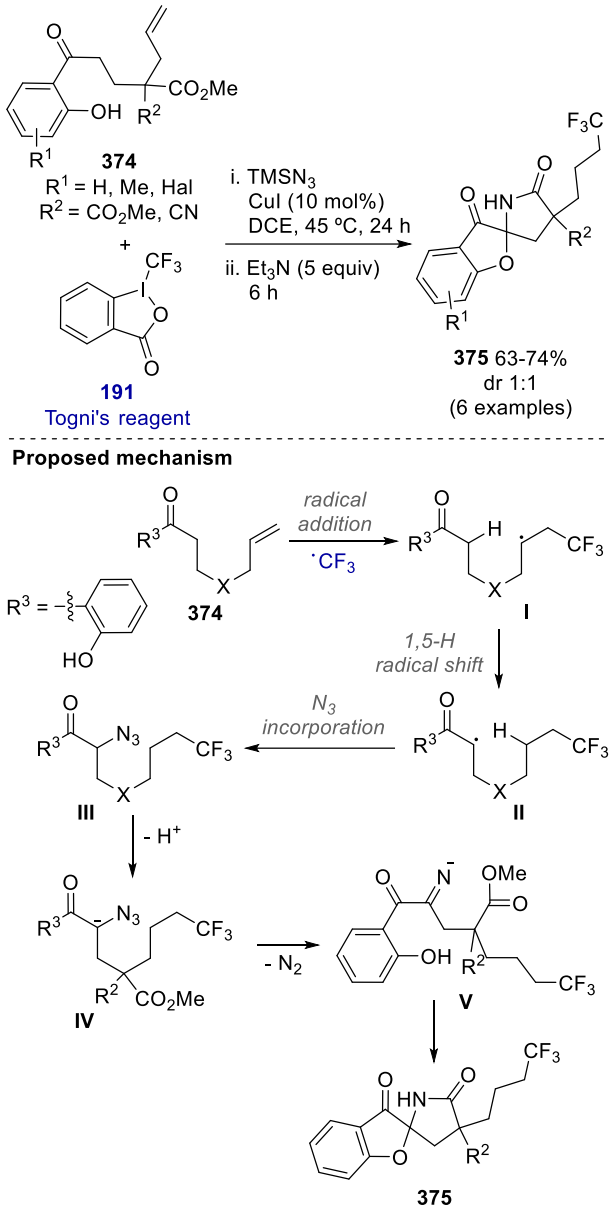
4.1 Spirocyclization via azide-containing substrates

Melnikov and co-workers described a method for the synthesis of highly functionalized azides through ring opening of cyclopropane substrates in the presence of sodium azide through an S_N2-type reaction.[121] These polyfunctional azides were used as building blocks in the synthesis of several *N*-heterocycles, including spirocyclic oxindole γ-lactam **373** (Scheme 91). Arylation of azide **370** with chloro-2,4-dinitrobenzene (**371**) led to compound **372** which was converted into spiro-γ-lactam **373** in 68% yield upon treatment with Zn in the presence of NH_4Cl. The latter is a tandem process consisting of a double domino sequence involving simultaneous N_3 and NO_2 reduction followed by double-lactamization reactions. The methodology towards polyfunctional azides could also be applied in the synthesis of natural products and synthetic drugs namely (-)-nicotine and atorvastatin.



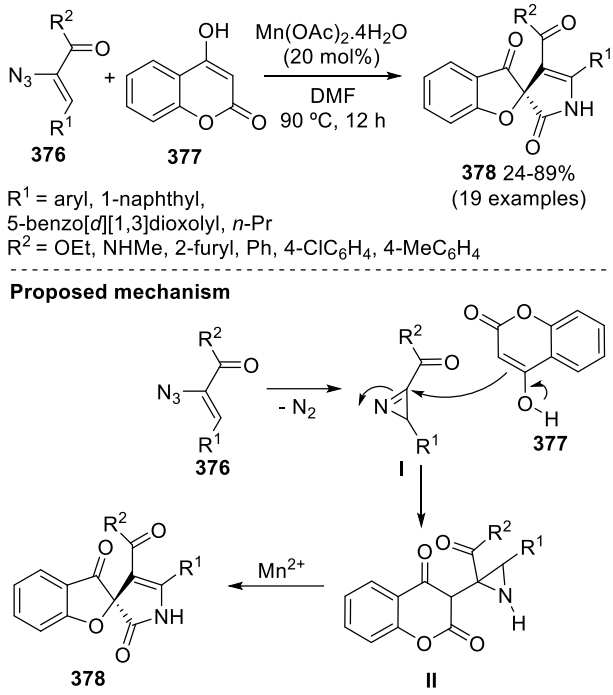
Scheme 91. S_NAr/reduction/γ-lactamization tandem reactions of a functionalized azide.

Alkenyl ketones **374** bearing a hydroxy group in the aromatic ring underwent a spirocyclization reaction leading to CF_3-containing spiro-γ-lactams **375** in good yields (63-74%) (Scheme 92).[122] The proposed mechanism starts with the generation of a CF_3 radical from the reaction of Togni's reagent with Cu(I), followed by radical addition to the terminal alkene to give **I** and subsequent 1,5-H radical shift to furnish intermediate **II**. The generation of α-azido ketone **III** in presence of $TMSN_3$ was rationalized considering two different copper-mediated pathways, a redox or a SET process, for the addition of the azide group. Finally, sequential base promoted deprotonation, nitrogen elimination and intramolecular nucleophilic trapping led to the final products. The synthetic utility of the developed strategy was demonstrated by the gram-scale synthesis of one of these spiro-γ-lactams.



Scheme 92. Synthesis of CF_3-containing spiro-γ-lactams via remote α-azidation of alkenyl ketones triggered by alkene trifluoromethylation.

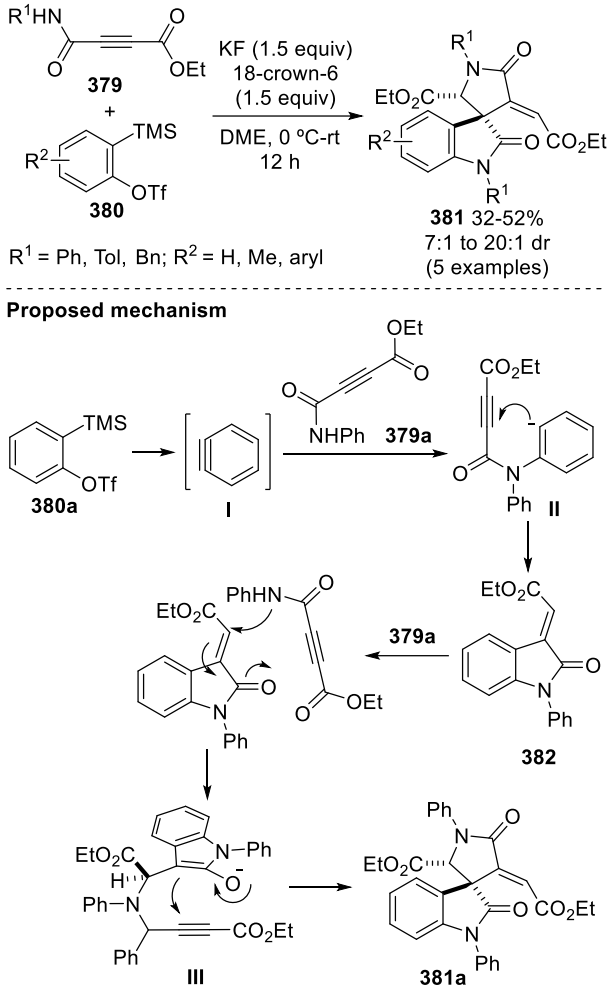
Zhang, Chen and co-workers described an efficient manganese-mediated synthesis of spirofuranonyl γ-lactams **378** via domino annulation reaction of vinyl azides **376** with 4-hydroxycoumarin **377** (Scheme 93**)**.[123] This methodology well tolerated a wide range of vinyl azides, allowing the synthesis of nineteen spiro-γ-lactams (24-89%). The transformation proceeded via thermal decomposition of the vinyl azides to give the corresponding 2*H*-azirines, followed by 4-hydroxycoumarin nucleophilic attack resulting in the formation of intermediates **II**. The latter undergoes a manganese-mediated rearrangement leading to the final products.



Scheme 93. Manganese-mediated annulation reaction of vinyl azides and 4-hydroxycoumarin.

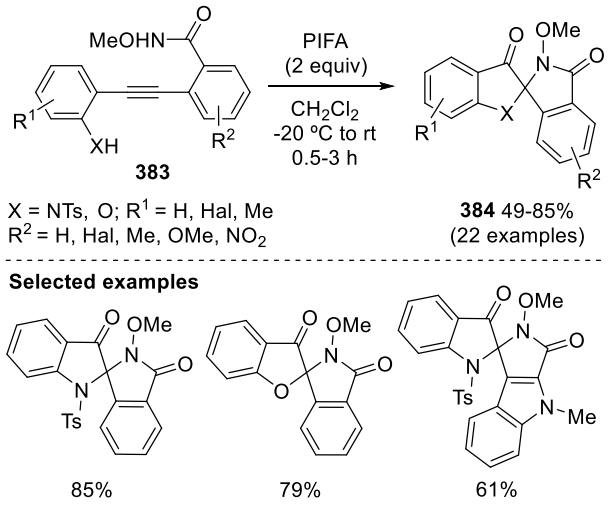
4.2 Annulation of alkynes

Pandya and Mhaske described a synthetic route to oxindolylidene acetates (*e.g.* **382**) and spirooxindole γ-lactam **381** from arynes and carbamoylpropiolates.[124] Thus, arynes (*e.g.* **I**) were generated *in situ* from **380** and underwent nucleophilic trapping by the carbamoylpropiolates followed by an intramolecular Michael addition to give oxindolylidene acetates (*e.g.* **382**) which could be isolated. When using excess of **379**, a second nucleophilic attack took place generating **III** which cyclized to provide **381**. The one-pot synthesis reaction between carbamoylpropiolates **379** and arynes provided spirooxindole γ-lactams **381** in moderate yields (32-52%) (Scheme 94).



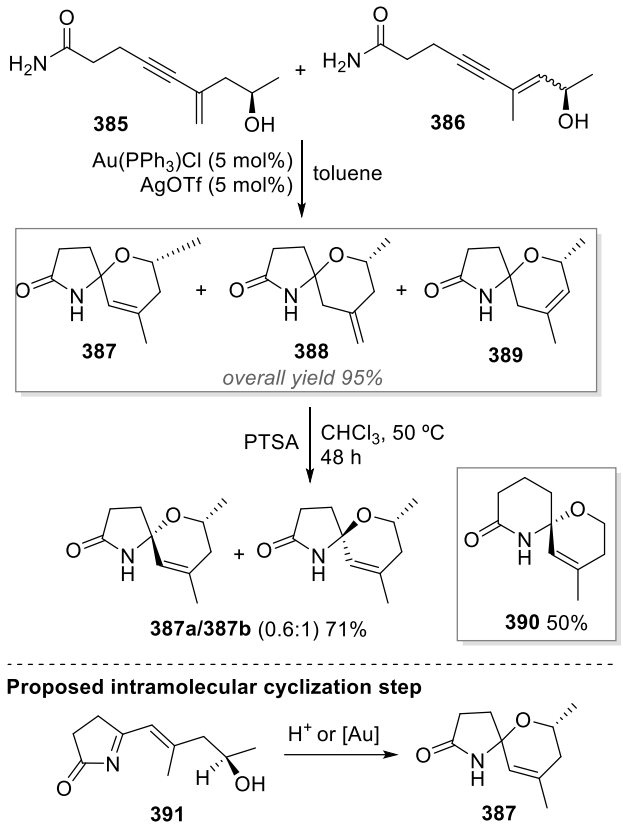
Scheme 94. Synthesis of spiro-γ-lactams from arynes and carbamoylpropiolates.

A hypervalent-iodine-mediated cascade annulation of internal alkynes was reported by Du and co-workers in 2015.[125] Di-*ortho*-substituted diarylacetylenes **383** were converted into spirocyclic lactams **384** in moderate to high yields (49-85%) in the presence of PIFA as the only oxidizing agent (Scheme 95). This unprecedented metal-free protocol involves two sequential C–N/C–O bond formations and one oxygen insertion.



Scheme 95. Hypervalent-iodine-mediated cascade annulation of internal alkynes leading to spirocyclic lactams.

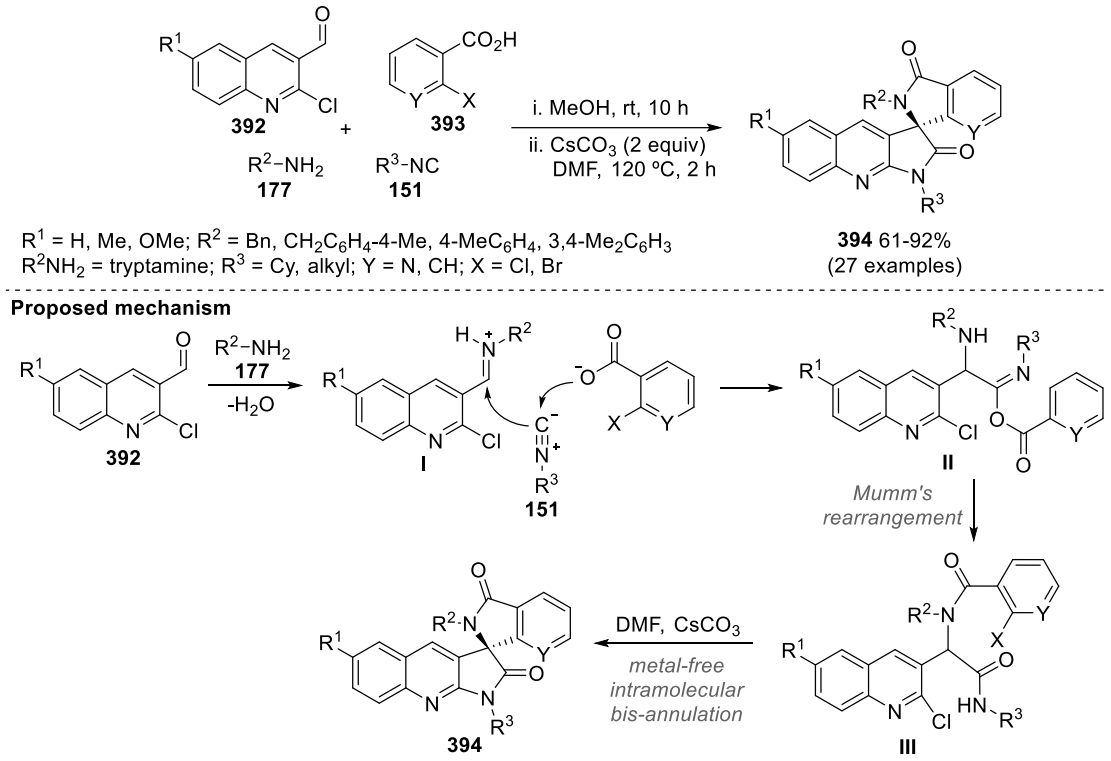
In the same year, the gold-catalyzed spirocyclization of internal alkynes was explored providing a route to spiro-γ-lactams **387** (Scheme 96).[126] The reaction of alkynyl amidoalcohols **385** and **386** in the presence of 5 mol% Au catalyst afforded a mixture of spiro-γ-lactams **387-389** in 95% yield. Upon treatment of this mixture with *p*-toluenesulfonic acid (PTSA), spiro-γ-lactams **388** and **389** isomerized to give **387** as an inseparable mixture of diastereomers. The synthesis of **387** was rationalized considering the formation of intermediate **391**, which was isolated under similar gold-catalyzed reaction conditions, through a proton or gold-catalyzed intramolecular oxycyclization. The use of alkynyl amidoalcohols with an extra methylene group allowed the synthesis of spiro-δ-lactam **390** in 50% yield.



Scheme 96. Gold-catalyzed spirocyclization of alkynyl amidoalcohols.

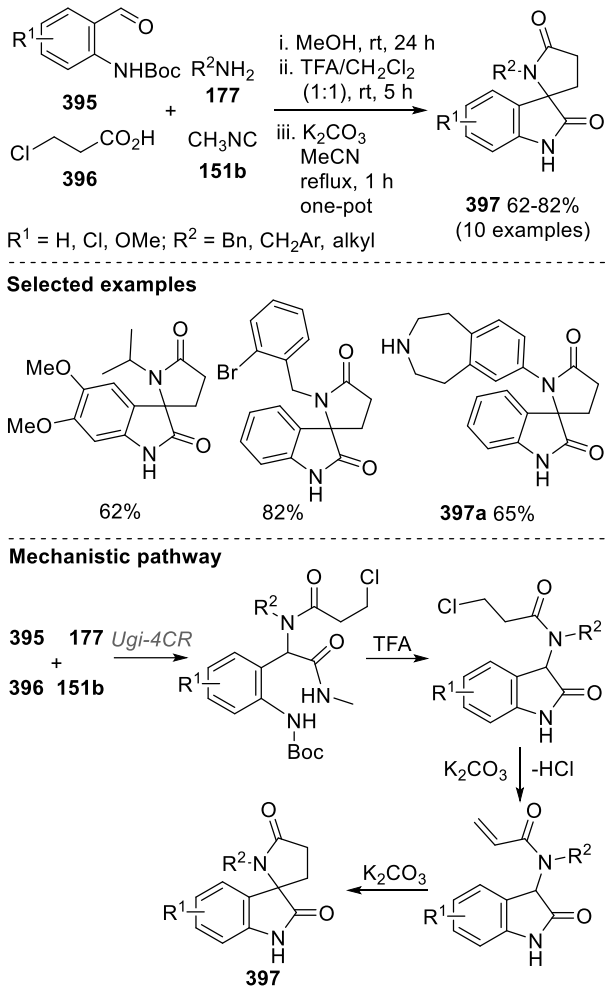
4.3 Multicomponent synthesis / cascade reaction

Ghandi *et al.* reported a one-pot synthesis of spiropyrroloquinoline, isoindolinone and aza-indolinone scaffolds by combining a Ugi-4CR with two metal-free cyclizations (Scheme 97).[127] Under the optimized conditions, the reaction between 2-chloroquinoline-3-carbaldehydes **392**, carboxylic acid **393**, amines **177** and isocyanides **151** furnishes bis-γ-lactams **394** in moderate to high yields (61-92%). The reported mechanism starts with the formation of iminium cation **I** followed by its electrophilic α-addition and nucleophilic carboxylate anion attack on isocyanide to generate **II**. Intramolecular acyl-transfer (Mumm's rearrangement) of intermediate **II** led to Ugi product **III** which underwent two annulations to give the final bis-γ-lactams.



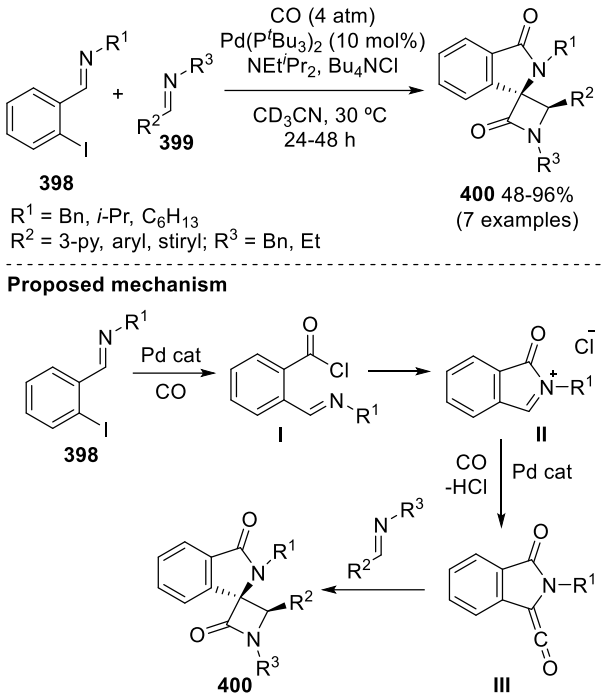
Scheme 97. Ugi-4CR/metal-free intramolecular bis-annulation.

A multicomponent synthesis of spirooxindole γ-lactams **397** was reported, starting from 2-*N*-Boc-benzaldehyde derivatives **395**, amines **177**, 3-chloropropanoic acid (**396**) and methyl isocyanide (**151b**) (Scheme 98).[128] The reaction, based on a post-Ugi 4CR tandem transamidation/cyclization protocol, affords spirocyclic lactams **397** in moderate to good yields (62-82%). The synthesis of 5-HT6 receptor antagonist **397a** is one example of the applicability of this process. The authors expanded this methodology to the use of 3-alkyl- or 3-aryl-propiolic acids instead of **396**. In this case, a small library of spirooxindolyl unsaturated-γ-lactams was obtained in 60-82% yields.



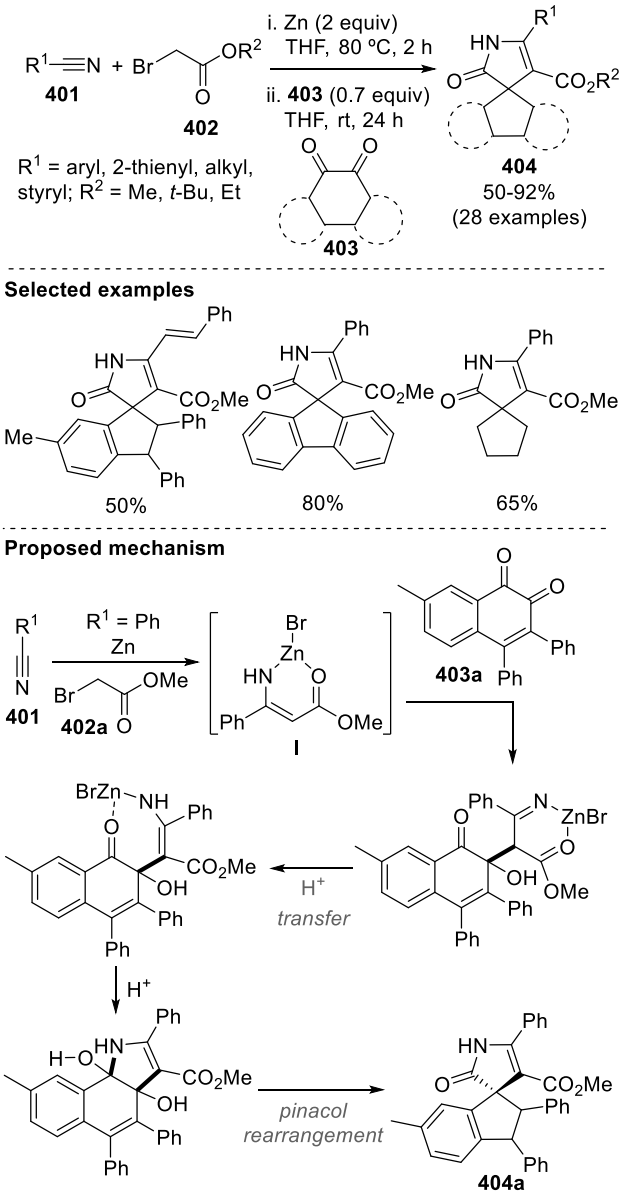
Scheme 98. Post-Ugi-4CR/transamidation/cyclization.

A palladium-catalyzed multicomponent reaction between *ortho*-iodo-substituted aryl imines **398**, a second imine **399** and CO was applied to the synthesis of spirocyclic bis-β,γ-lactams **400** (Scheme 99).[129] The construction of the γ-lactam ring involves a palladium-catalyzed carbonylation of *ortho*-iodo-substituted aryl imine **398** to generate *in situ* acid chloride **I** followed by cyclization to give *N*-acyl iminium salt **II**. Next, a second carbonylation led to ketene **III** which reacted with imine **399** via Staudinger reaction to give bis-β,γ-lactams **400** in moderate to high yields (48-96%).



Scheme 99. Spirocyclic lactams from *ortho*-iodo-substituted aryl imines via two palladium-catalyzed tandem carbonylation reactions followed by a Staudinger cyclocondensation.

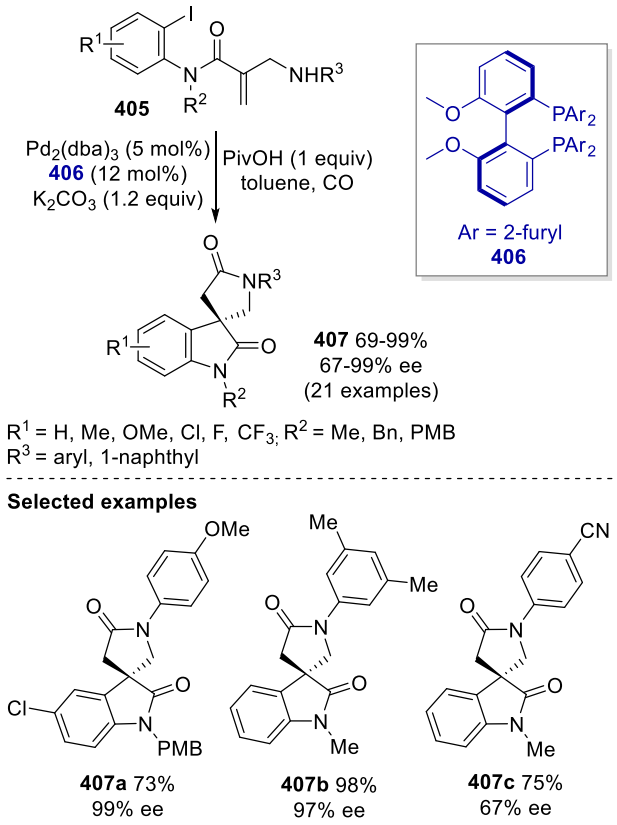
Spiro-γ-lactams have been prepared from Blaise reaction intermediates and 1,2-dicarbonyl compounds via one-pot cascade reaction.[130] Blaise reaction intermediates (*e.g.* **I**) were generated via zinc-mediated reaction of nitriles **401** and α-bromoesters **402** and participated in sequential nucleophilic addition/cyclization/pinacol rearrangement reactions upon reaction with dicarbonyl compounds **403** (Scheme 100). Spiro-γ-lactams **404** were obtained under mild reaction conditions in moderate to good yields (50-92%) and good functional group tolerance.



Scheme 100. Spiro-γ-lactams via cascade reaction between Blaise reaction intermediates and 1,2-dicarbonyl compounds.

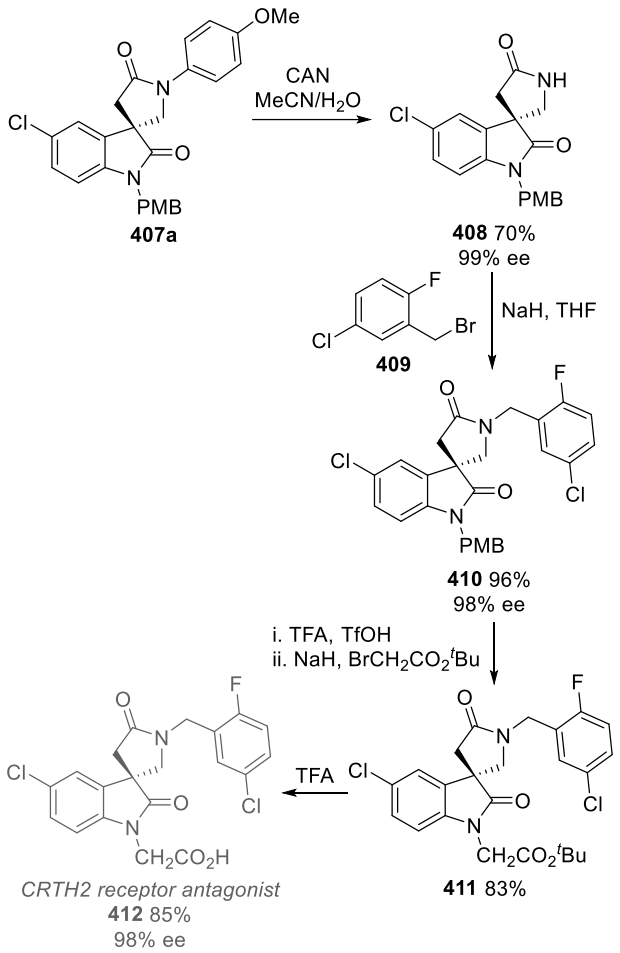
4.4 Heck / carbonylative cyclization reaction

Zhu, Luo and co-workers developed a one-pot synthesis of spiro-γ-lactams through a palladium-catalyzed asymmetric Heck/carbonylative cyclization sequence.[131] A Pd-catalyzed carbonylation of *N*-(2-iodophenyl)-*N*-acrylamide derivatives **405** was studied in the presence of a chiral bidentate phosphine ligand (**406**) within a CO rich atmosphere (Scheme 101). This approach allowed the synthesis of a library of spirooxindole γ-lactams **407** in high yields (69-99%) and with good to excellent enantioselectivities (67-99% ee). The observed asymmetric induction could be rationalized by considering that, due to steric hindrance and repulsion factors, the most favorable approach occurred when the amine moiety was on the opposite side of the chiral ligand. Subsequent migratory and CO insertions led to the formation of spirooxindole γ-lactams **407.**



Scheme 101. Heck/carbonylative cyclization of *N*-(2-iodophenyl)-*N*-methyl-acrylamides.

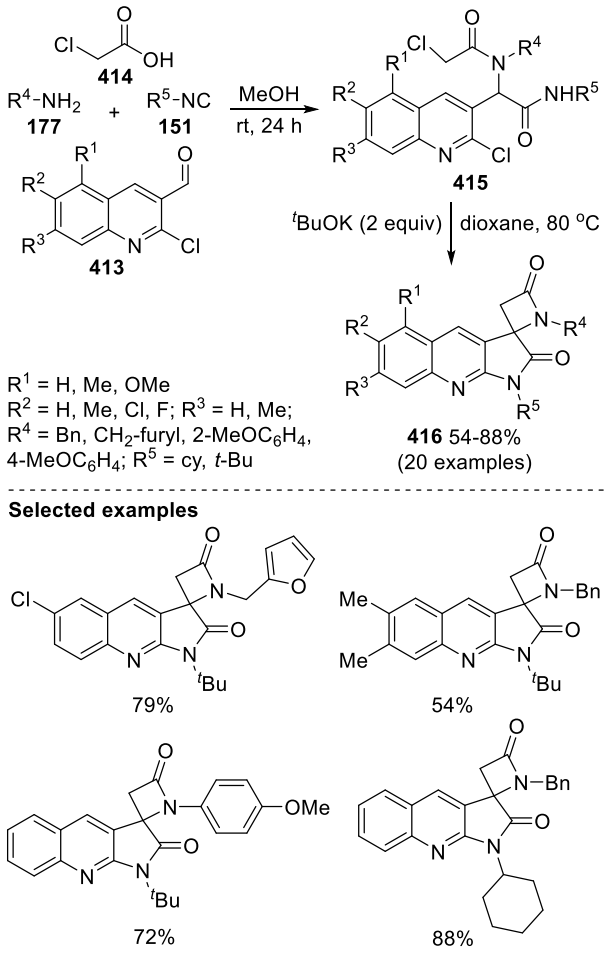
The synthetic route, outlined in Scheme 102 allied with excellent yields and enantioselectivities, shows the utility of the developed methodology.[131] Lactam **407a** served as key intermediate for the synthesis of **412**, an antagonist on the CRTH2 receptor, via a four-step synthetic route involving benzylation, deprotection and alkylation reactions, with a final hydrolysis of compound **411** affording **412** in 85% yield and 98% ee.



Scheme 102. Synthetic applications of the Heck/carbonylative cyclization of *N*-(2-iodophenyl)-*N*-methyl-acrylamides.

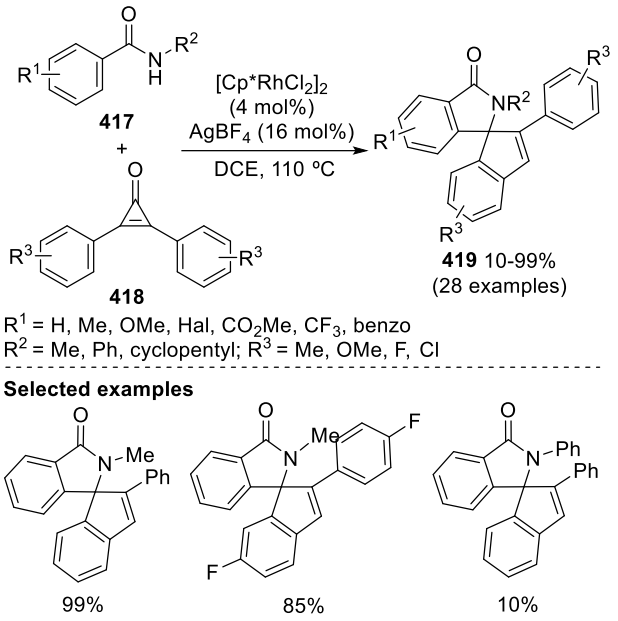
4.5 Other methods

The synthesis of spirocyclic bis-α,γ-lactams by two sequential intramolecular nucleophilic substitution reactions of Ugi adducts has been reported.[132] Compounds **415** were obtained via a Ugi-4CR between 2-chloro-3-formyl quinolines **413**, amines **177**, isocyanides **151** and chloroacetic acid (**414**) (Scheme 103). Cyclization of compounds **415** under basic conditions, in the presence of *t*-BuOK, gave spiro-bis-α,γ-lactams **416** in moderate to high yields (54-88%). It is noteworthy that the lowest yields were observed for quinoline derivatives bearing electron-donating groups and no cyclized products were observed for methoxy-substituted quinoline-derived Ugi adducts. Due to the high electrophilicity at 2-position of the quinoline ring, the authors proposed a S_NAr/S_N2 mechanism for the sequential construction of the γ- and β-lactam rings.



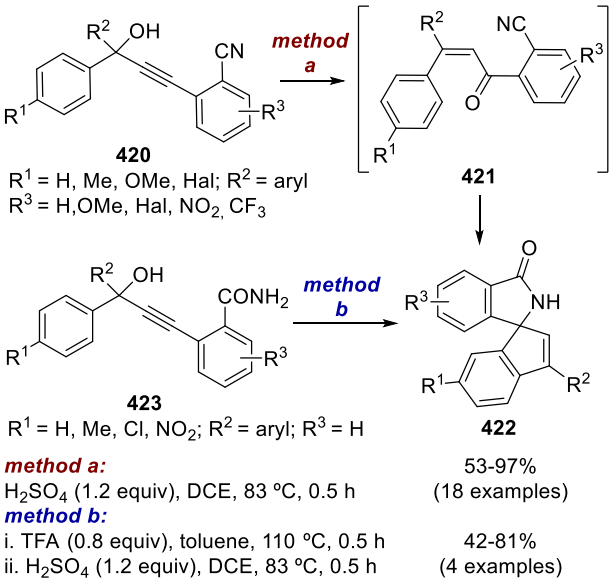
Scheme 103. Post-Ugi-4CR sequential nucleophilic substitution reaction.

Spiro-γ-lactams **419** were obtained by a rhodium(III)-catalyzed redox-neutral double C–H activation/cyclization cascade protocol comprising the reaction between benzamides **417** and cyclopropenones **418** (Scheme 104).[133] The spiroisoindolinones **419** were obtained in 10-90% yields via an environmentally friendly and atom economical strategy, involving the sequential one-pot creation of two new C–C bonds, one C–N bond and an *N*-substituted quaternary carbon center, and the formation of water as the sole by-product.



Scheme 104. Rhodium-catalyzed domino reaction between benzamides and cyclopropenones.

The sulfuric acid-promoted cascade cyclization of 2-(3-hydroxyprop-1-ynyl)benzonitriles **420** was also successfully employed in the synthesis of the spiroisoindolinone scaffold (Scheme 105).[134] The proposed mechanism involves an initial Meyer-Schuster rearrangement to generate α,β-unsaturated ketone **421** followed by nitrile hydrolysis, construction of the heterocyclic ring via imide formation and intramolecular Friedel-Crafts alkylation to form spiro-γ-lactams **422** in moderate to high yields (53-97%). A similar reactivity was observed when 2-(3-hydroxyprop-1-ynyl)benzamides **423** were used as starting materials. Spiro-γ-lactams **422** were obtained in moderate to high yields (42-81%) via a two-step one-pot protocol involving the generation of intermediate **421** in the presence of a catalytic amount of TFA. The authors also found that treatment of **422** with a halogen source (NIS or NBS) provided the corresponding C-2 halogenated products which could be further arylated via conventional Pd-catalyzed Susuki coupling reaction.



Scheme 105. Acid-promoted cascade cyclization of 2-(3-hydroxyprop-1-ynyl)benzonitriles and benzamides.

5. CONCLUSION

This review gives an insight into the most recent synthetic methodologies towards spirocyclic fused γ-lactams. Three synthetic methodologies have been generally used, namely, the construction of the lactam ring from building blocks with the second ring subunit, the construction of the second ring starting from lactam-containing precursors or the one-pot synthesis of both lactam and non-lactam rings. The first strategy has been by far the most widely explored.

Reports on the asymmetric synthesis of spiro-γ-lactams have been disclosed being the enantioselective organocatalysis a clear trend. Developments on multicomponent strategies and metal-free conditions are also highlighted.

Despite the plethora of methods available, which allowed the synthesis of a wide variety of spiro-γ-lactams, some synthetic challenges must be overcome regarding the development of general asymmetric methodologies and more sustainable synthesis in order to fully explore the potential of the spiro-γ-lactam motif in organic and medicinal chemistry.

Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgments

The authors thank Coimbra Chemistry Centre (CQC), supported by the Portuguese Agency for Scientific Research, "Fundação para a Ciência e a Tecnologia" (FCT) through project UIDB/00313/2020 and UIDP/QUI/00313/2020, co-funded by COMPETE2020-UE. Américo J. S. Alves and Nuno G. Alves thank FCT for fellowships SFRH/BD/128910/2017 and PD/BD/135287/2017, respectively.

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