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# Stereoselective synthesis of $\beta$ -lactams: recent examples

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The synthesis of  $\beta$ -lactam derivatives is a research topic of great interest due to the biological activity of these molecules. Indeed, there are several antibiotics which include a  $\beta$ -lactam core in their structures, such as penicilins, monobactams, carbacephems and cephamycins. The development of stereoselective approaches to access these molecular architectures turns out to be necessary in order to take advantage of the distinct properties provided by the different stereoisomers. This review covers recent advances towards the stereoselective synthesis of  $\beta$ -lactams, including Staudinger syntheses, cascade reactions, metal-catalyzed syntheses and base-promoted cyclizations. Within these methods, some particularly novel synthetic approaches are highlighted, such as the induction of chirality through bimetallic synergistic catalysis or the transfer of chirality between components in mechanically interlocked molecules. Additionally, a critical opinion on the state of the art of this research field is offered, remarking key points on which the future research should be focused on.

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## 1. Introduction

$\beta$ -Lactams are organic compounds well known for their biological activity, highlighting their antibiotic properties. Although the discovery of this type of ring arose with the development of penicillin, there are several natural products containing this four-membered ring.<sup>1</sup> Thus,  $\beta$ -lactams are privileged scaffolds for the preparation of a vast range of antibiotics, including penicillins, cephalosporins, monobactams and carbacephems, among others. This extensive presence in a wide range of antibiotics has led to an increased interest of several synthetic chemists in the development of methodologies to access this type of compounds.<sup>2</sup>

The traditional approaches to synthesize  $\beta$ -lactams followed the method developed by Hermann Staudinger in 1907, in which an imine reacts with a ketene *via* a [2 + 2] cycloaddition to afford the target product.<sup>3</sup> But the development of new synthetic methodologies has allowed to obtain these bioactive molecules in several ways.<sup>4–21</sup>

Progress in the preparation of  $\beta$ -lactams ran parallel with the development of stereoselective synthetic methodologies, allowing to access to the different isomers (*cis* or *trans*) and also to obtain enantioenriched products.<sup>22–26</sup> This review is focused on recent advances towards the stereoselective synthesis of  $\beta$ -lactams, dividing the manuscript into three main sections: (i) metal-free cycloaddition reactions; (ii) transition

metal-catalysis; and (iii) base-promoted synthesis. In addition to highlighting selected examples, a critical opinion on the state of the art is provided.

The examples highlighted in this review have been carefully selected from literature published from 2018, when Hosseyni and Jarrahpour published a review on the synthesis of  $\beta$ -lactams.<sup>2</sup> For details of the exact chronology of the synthesis of  $\beta$ -lactams and specific synthetic approaches towards their preparation, we refer readers to previously reported reviews.<sup>1,9,22,23,25–27</sup>

## 2. Metal-free cycloaddition reactions

Multicomponent cycloaddition reactions have been the most widely employed methods in order to obtain  $\beta$ -lactam derivatives, highlighting the synthesis based on the Staudinger ketene-imine cycloaddition.<sup>2,28–33</sup> This section discusses selected recent examples of metal-free stereoselective cycloaddition syntheses of  $\beta$ -lactams.

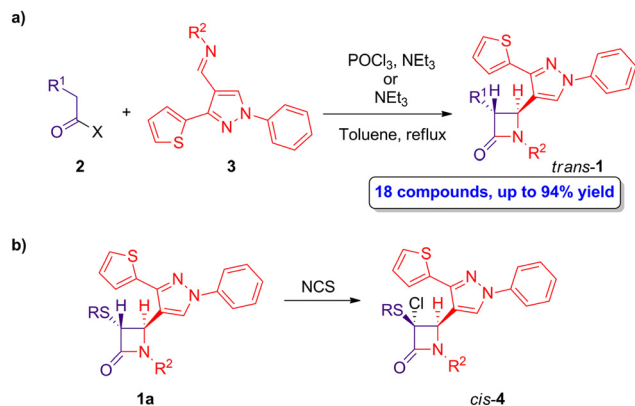
### 2.1. Ketene-imine cycloaddition reactions

As abovementioned, the ketene-imine cycloaddition has been widely employed in the preparation of  $\beta$ -lactams. A representative example reported by Bhalla and coworkers describes the synthesis of a series of *trans*-4-(thiophenyl)pyrazolylyl  $\beta$ -lactams **1**.<sup>34</sup> The synthesis proceeds through a Staudinger cycloaddition reaction of (thiophenyl)pyrazol substituted Schiff's bases **2** and 2-substituted ethanoic acid or acid chloride derivatives **3** (Scheme 1a) in the presence of  $\text{NEt}_3$  or  $\text{POCl}_3$ /

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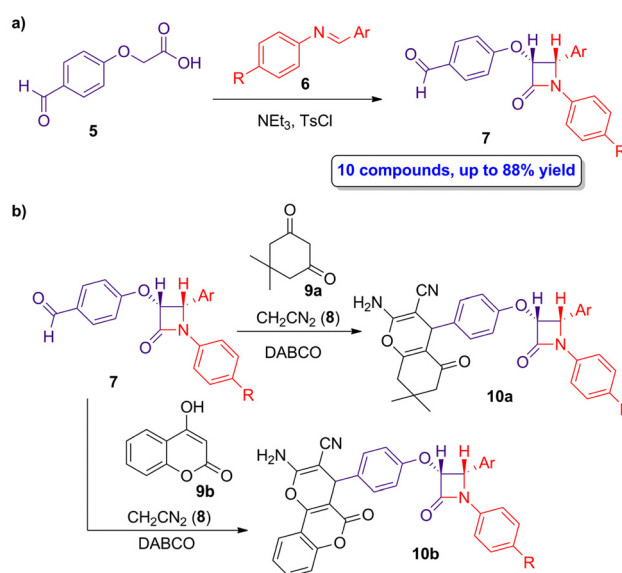


**Scheme 1** (a) Diastereoselective ketene-imine cycloaddition reaction of **2** and **3** to afford *trans*- $\beta$ -lactams **1**; and (b) preparation of *cis*- $\beta$ -lactams **4**. The original results were reported by Bhalla and colleagues.<sup>34</sup>

$\text{NEt}_3$ . The ketene intermediates are generated *in situ* through the deprotonation of carboxylic acid derivatives **1** ( $\text{X} = \text{OH}$ ) by using  $\text{NEt}_3$ , followed by the formation of an active ester with  $\text{POCl}_3$ , which subsequently reacts with  $\text{NEt}_3$ , or by direct reaction with  $\text{NEt}_3$  if ethanoyl chloride derivatives **1** ( $\text{X} = \text{Cl}$ ) are employed. When the reaction was carried out in chloroform, tetrahydrofuran or toluene at reflux, only the *trans*- $\beta$ -lactams **1** were obtained in high yield (67–94%). Interestingly, one *cis* derivative ( $\text{R}^1 = \text{acetyl}$ ,  $\text{R}^2 = p$ -methoxyphenyl) could be obtained using  $\text{CH}_2\text{Cl}_2$  as solvent and setting the temperature from 0 °C to room temperature.

Noteworthy, the treatment of *trans*- $\beta$ -lactams **1a** having sulfonyl substituents with *N*-chlorosuccinimide (NCS) afforded *cis*- $\beta$ -lactams **4** (Scheme 1b), which can further react through nucleophilic substitution to afford a series of functionalized *cis*- $\beta$ -lactams.

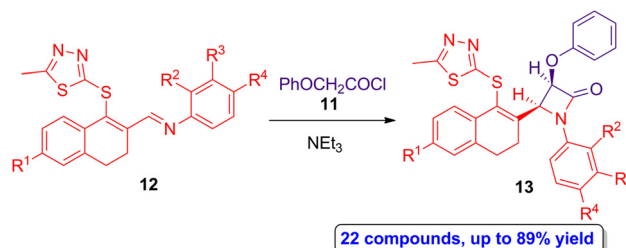
The pharmacophore hybridization approach, in which two distinct bioactive functions are combined into a single molecule, was employed by Jarrahpour and coworkers in the synthesis of hybrid molecules combining fused chromenes and  $\beta$ -lactams.<sup>35</sup> Both chromenes and  $\beta$ -lactams are well-known for their biological applications, such as the development of antibacterial, antifungal or anticancer products, among others. Through pharmacophore hybridization is possible to improve some parameters, such as therapeutic potential, mode of action and pharmacokinetics. A diastereoselective ketene-imine cycloaddition reaction between 2-(4-formylphenoxy) acetic acid (**5**) and imine **6** using  $\text{NEt}_3$  as base and *p*-toluenesulfonyl chloride afforded the target aldehyde-functionalized  $\beta$ -lactams **7** in high yields (up to 88%), showing only *cis* geometry (Scheme 2a). The subsequent functionalization of  $\beta$ -lactams **7** through a multicomponent reaction with the chromene precursors **8** and **9a,b** in the presence of triethylenediamine (DABCO) yielded the chromeno  $\beta$ -lactam hybrids **10a,b** (Scheme 2b). Interestingly, anti-inflammatory and anticancer functions of both aldehyde-functionalized  $\beta$ -lactams **7** and chromeno  $\beta$ -lactams **10a,b** were evaluated, observing good



**Scheme 2** (a) Diastereoselective ketene-imine cycloaddition reaction of **5** and **6** to afford  $\beta$ -lactams **7**; and (b) preparation of chromeno  $\beta$ -lactams hybrids **10a,b**. The original results were reported by Jarrahpour and colleagues.<sup>35</sup>

anti-inflammatory ratios (up to 53.4), whose activity depends on the different substitution at the N1 and C2 atoms of the lactam ring, and an anticancer response *in vitro* against SW1116 colon cancer cells.

The Staudinger synthesis was also employed by Sharma and colleagues in the preparation of monocyclic  $\beta$ -lactams having a 1,3,4-thiadiazole motif, which also has important biological properties *per se*.<sup>36</sup> Phenoxyacetyl chloride **11** was employed as source of ketene and thiadiazol-functionalized imines **12** as Schiff bases in the [2 + 2] cycloaddition reaction, which afforded a wide range of a monocyclic  $\beta$ -lactams **13** in high yield (up to 89%) and in a diastereoselective manner (Scheme 3), showing *cis* geometry as it was determined by the coupling constants of the hydrogens of the lactam ring using  $^1\text{H-NMR}$ . Interestingly, *in vitro* assays demonstrated antibacterial activity against the *Staphylococcus aureus* ATCC 25904 (Gram-positive) and *Escherichia coli* ATCC 12435 (Gram-negative) pathogens of mostly of the monocyclic *cis*- $\beta$ -lactams **13**



**Scheme 3** Diastereoselective ketene-imine cycloaddition reaction of **11** and **12** to afford thiadiazol-functionalized monocyclic  $\beta$ -lactams **13**. The original results were reported by Sharma and colleagues.<sup>36</sup>



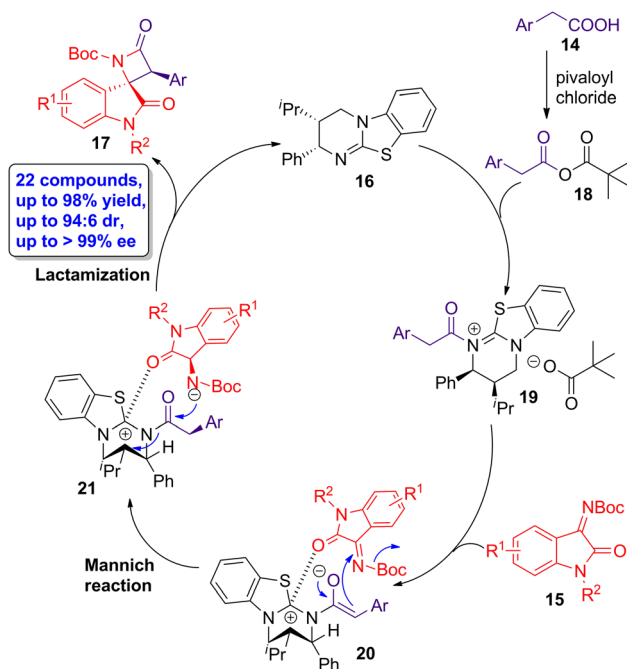
products, using ciprofloxacin as the reference control. In addition, the presence of electron-withdrawing groups placed at the aryl motif from the imine scaffold increased the antibacterial activity. Due to the stereoselectivity, high yield and easy purification step of this protocol, as well as the vast possibility of functionalization, this synthetic approach paves the way to the obtention of new monocyclic  $\beta$ -lactams having potential applications in medicinal chemistry.

The same research group also employed an analogous strategy using acid anhydrides as ketene precursors to obtain a series of monocyclic *cis*- $\beta$ -lactams.<sup>37</sup>

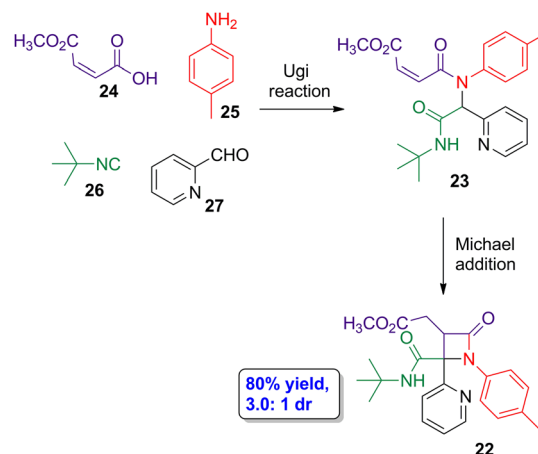
## 2.2. Mannich lactamization reactions

The Mannich reaction has been successfully employed in the synthesis of several heterocycles.<sup>38–42</sup>

Through an isothiourea-catalyzed Mannich/lactamization cascade reaction, Zhao, Deng and colleagues reported the asymmetric preparation of  $\beta$ -lactam derivatives.<sup>43</sup> Bench stable carboxylic acids **14** and isatin-derived ketimines **15** were employed as substrates and the chiral homobenzotetramisole **16** as catalyst in the presence of pivaloyl chloride, affording spirooxindole  $\beta$ -lactams **17** in high yields (up to 98%), showing excellent diastereo- and enantioselectivities (up to 94 : 6 dr and >99% ee, respectively). The proposed mechanism starts with the reaction *in situ* of carboxylic acid **14** and pivaloyl chloride, leading to the formation of acid anhydride intermediate **18** (Scheme 4). The subsequent acylation of **16** affords intermediate **19**, whose subsequent deprotonation yields intermediate **20**. Then, a Si-face attack Mannich reaction takes places,



**Scheme 4** Proposed catalytic cycle for the synthesis of enantio-enriched spirooxindole  $\beta$ -lactams **17** from carboxylic acids **14** and isatin-derived ketimines **15**. The original results were reported by Zhao, Deng and colleagues.<sup>43</sup>



**Scheme 5** Diastereoselective Ugi-Michael cascade reaction to synthesize  $\beta$ -lactam **22** from carboxylic acid **24**, aniline **25**, isocyanide **26** and aldehyde **27**. The original results were reported by Galons, Lu and colleagues.<sup>44</sup>

leading to intermediate **21**. A final intramolecular cyclization leads to the obtention of the target enantioenriched spirooxindole  $\beta$ -lactams **17** showing *cis* geometry.

## 2.3. Ugi and Michael addition cascade reactions

Diversity-oriented synthesis (DOS) through cascade reactions has turned out to be useful approaches towards the synthesis of different nitrogen-containing heterocyclic compounds. Galons, Lu and coworkers employed the DOS approach carrying out an Ugi-Michael addition cascade reaction to synthesize  $\beta$ -lactams **22** *via* the previous formation of Ugi-adduct intermediate **23** (Scheme 5).<sup>44</sup> In the model reaction, maleic acid derivative **24**, amine **25**, isocyanide **26** and nitrogen heterocyclic aldehyde **27** were employed as substrates. In the optimized conditions, **22** was obtained in 80% yield, having a good diastereoselectivity (3.0 : 1 dr). X-ray analysis and bidimensional NMR spectra allowed to determine that the main diastereoisomer is the lactam having pyridine ring and methyl ester group in *cis*-conformation. Different substrates were tested, observing a good tolerance for different hydrogen bond acceptor substituents placed at the aldehyde scaffold, thus even being possible to use 2-oxo-2-phenylacetaldehyde and ethyl 2-oxoacetate as aldehyde derivatives. Thus, control over the reaction can be provided by carbonyl groups acting as hydrogen bond acceptors. Interestingly, the use of fumaric acid derivatives, which are the geometric isomers of the maleic ones, also leads to the target lactams but affecting the diastereoselectivity of the Michael addition step, which is the one determining the chemo- and diastereoselectivities according to DFT calculations.

## 3. Metal-assisted synthesis

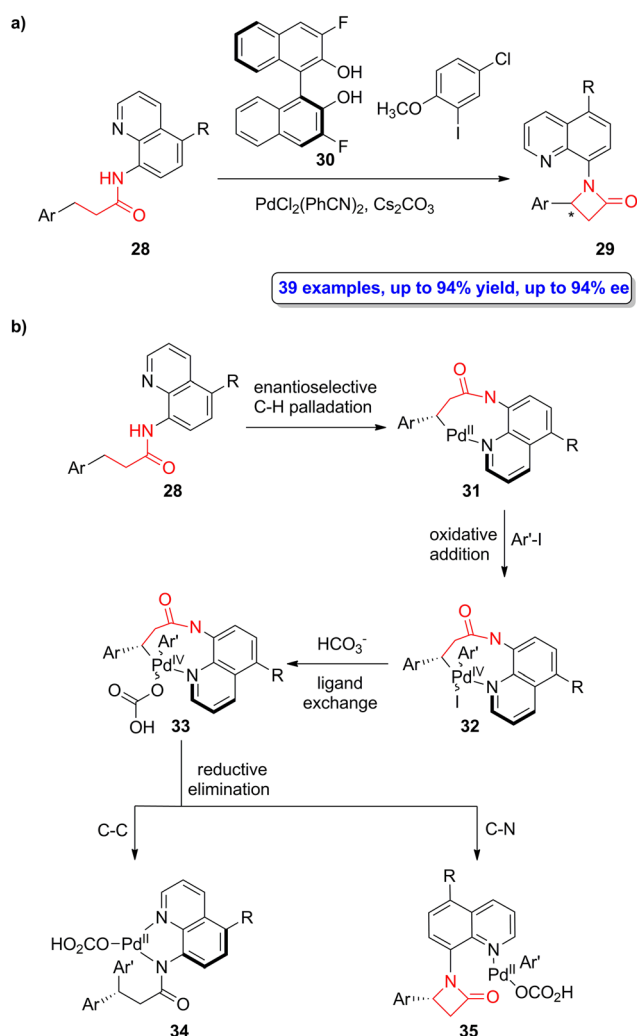
The use of transition-metal-catalysis has turned out to be a suitable strategy to access to a vast range of heterocyclic



compounds.<sup>45–49</sup> Thus, through metal-assisted synthesis, several  $\beta$ -lactams could be synthesized. This section covers recent selected examples on the use of transition-metals to catalyze the formation of the target lactams.

### 3.1. Palladium-assisted reactions

A palladium-catalyzed enantioselective intramolecular C(sp<sup>3</sup>)-H amidation of quinoline-functionalized amides **28** was recently employed by He, Liu, Chen and colleagues in the asymmetric synthesis of  $\beta$ -lactams **29**.<sup>50</sup> The chiral fluorinated BINOL **30** was employed as the ligand, PdCl<sub>2</sub>(PhCN)<sub>2</sub> as the catalyst and Cs<sub>2</sub>CO<sub>3</sub> as the base in the optimized cyclization reaction of **28** in the presence of 2-methoxy-5-chlorophenyl iodide as oxidant (Scheme 6a). A series of  $\beta$ -lactams bearing quinoline-based motifs were synthesized in good to high yields (up to 94%) with high enantioselectivity (up to 94% ee). Interestingly, the removal of the quinoline motifs was feasible



**Scheme 6** (a) Palladium-catalyzed enantioselective synthesis of  $\beta$ -lactams **29**; and (b) proposed mechanism for the formation of  $\beta$ -lactams **29**. The original results were reported by He, Liu, Chen and colleagues.<sup>50</sup>

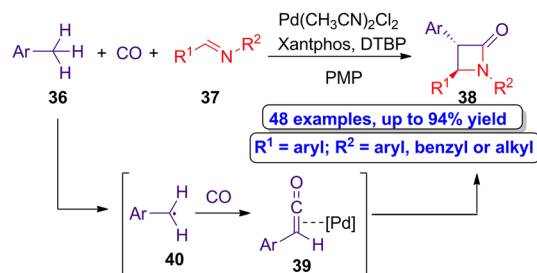
by treatment with cerium ammonium nitrate, retaining the enantiomeric excess of the product. The reaction proceeds forming an enantioenriched Pd(II)-palladacycle **31** whose enantioselectivity is controlled by the fluorinated BINOL-based ligand **30** (Scheme 6b). The subsequent oxidative addition of the aryl iodide affords the intermediate **32**, which can then experience a ligand exchange with HCO<sub>3</sub><sup>-</sup> leading to palladacycle **33**. This cycle can undergo either C-C or C-N reductive elimination. Computational studies allowed to conclude that the use of the nonconventional aryl iodide oxidant leads to high chemoselectivity due to electronic and steric effects, thus favouring the C-N reductive elimination over the C-C one. This synthetic methodology allows to access to a wide range of  $\beta$ -aryl- $\beta$ -lactams in high yields and excellent enantioselectivities.

Yu and coworkers reported the mono-selective synthesis of a series of  $\beta$ -lactams using a related strategy, the  $\beta$ -C(sp<sup>3</sup>)-H lactamization of amides having commonly used protecting groups (tosyl, 4-nitrobenzenesulfonyl, 4-cyanobenzenesulfonyl, 2-trimethylsilylethanesulfonyl and mesyl) instead of quinoline-based substituents, thus diversifying the range of products that can be obtained through C(sp<sup>3</sup>)-H lactamization of amides.<sup>51</sup>

Huang and colleagues reported a novel palladium-catalyzed double C-H bond activation synthetic approach to access  $\beta$ -lactams *via* carbonylative formal cycloaddition.<sup>52</sup> Thus, the authors carried out the reaction of alkylarenes **36** and aldimines **37** in the presence of carbon monoxide, using Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> as the catalyst, Xantphos as the ligand, di-*tert*-butyl peroxide (DTBP) as the oxidant and 1,2,2,6,6-penta-methylpiperidine (PMP) as the base (Scheme 7). Through this synthetic approach, a series of *trans*- $\beta$ -lactams **38** were synthesized in moderate to high yields (up to 94%). The reaction proceeds through the prior formation of the palladium-ketene complexes **39** formed by the reaction of the radical intermediates **40** and carbon monoxide, which can subsequently react with aldimines **37** to afford the target heterocycles in a diastereoselective manner.

### 3.2. Rhodium-assisted reactions

Sun and coworkers reported the diastereoselective synthesis of highly functionalized  $\beta$ -lactams through a three-component rhodium-organo relay catalysis.<sup>53</sup> The reaction of

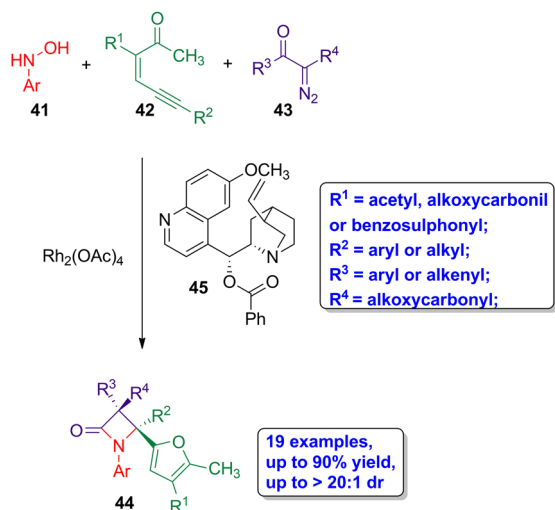


**Scheme 7** Diastereoselective carbonylative formal cycloaddition of alkylarenes **36** and aldimines **37** to afford *trans*- $\beta$ -lactams **38**. The original results were reported by Huang and colleagues.<sup>52</sup>

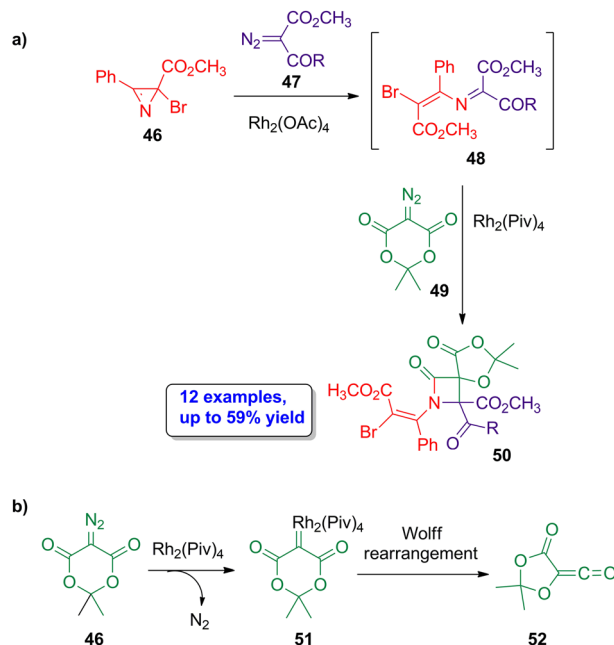


*N*-hydroxyanilines amphiphilic nucleophiles **41**, enynones **42** and diazo compounds **43** affords only furyl-functionalized *cis*- $\beta$ -lactams **44**, using  $\text{Rh}_2(\text{OAc})_4$  as catalyst and benzoylquinine **45** as organic base (Scheme 8). The target lactams were obtained in high yields (up to 90%) having an excellent diastereoselectivity (*dr* > 20 : 1). The reaction proceeds through the formation of an imine derivative from a 2-furyl rhodium carbene, generated *in situ* with the corresponding enynone **42**, and the amphiphilic nucleophile **41**. The sequential Wolff rearrangement of diazo **43** to the ketene, and the subsequent ketene-imine cycloaddition leads to the obtention of the four-membered ring lactams. Interestingly, this synthetic methodology is compatible with the functionalization of *N*-hydroxyamine, enynone and diazo compounds, with both electron-withdrawing or electron-donating groups, not affecting the yield of the reaction, affording the desired compounds in good to high yields and with high stereoselectivity. A mechanistic study allowed to conclude that the diastereoselectivity of the reaction arises during the course of an umpolung Staudinger cyclization, in which a ketene-based enolate acts as the nucleophile and the imine acts as the electrophile, thus leading to the formation of fully substituted  $\beta$ -lactams having exclusively *cis* geometry.

A rhodium-catalyzed approach was also employed by Novikov and coworkers in the assembly of spirocyclic  $\beta$ -lactams.<sup>54</sup> The reaction of the halogenated azirine derivatives **46** with diazocompounds **47** in the presence of  $\text{Rh}_2(\text{OAc})_4$  leads to the formation of azadienes **48** (Scheme 9a). The reaction of these azadienes with diazo-Meldrum's acid **49** using  $\text{Rh}_2(\text{Piv})_4$  as catalyst affords the spiro  $\beta$ -lactams **50** in moderate yields (21% to 59%) and with high stereoselectivity, showing a preferential formation of the (*1RS,4RS*) diastereoisomer. A possible mechanism could be the formation of the rhodium carbenoid **51**, from diazo-Meldrum's acid **49**, which acts as the ketene source (**52**) after a Wolff rearrangement (Scheme 9b),



**Scheme 8** Rhodium-catalyzed diastereoselective synthesis of *cis*- $\beta$ -lactams **44** from *N*-hydroxyanilines **41**, enynones **42** and diazo compounds **43**. The original results were reported by Sun and colleagues.<sup>53</sup>



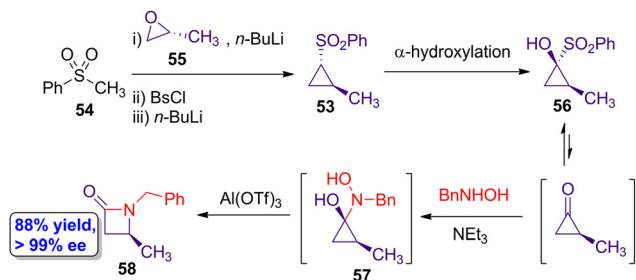
**Scheme 9** (a) Rhodium-catalyzed diastereoselective synthesis of spirocyclic  $\beta$ -lactams **50** from halogenated azirine derivatives **46**, diazocompounds **47** and diazo-Meldrum's acid **49**; and (b) possible mechanism pathway for the formation of the ketene **52**, involving the generation of the rhodium carbenoid **51**. The original results were reported by Novikov and colleagues.<sup>54</sup>

thus allowing a Staudinger cycloaddition in the final step. Therefore, the four-member ring skeleton of the lactam is assembled *via* two separate rhodium-catalyzed steps from two distinct diazo derivatives. Interestingly, the formation of the target lactams was also possible using isoxazoles derivatives as starting materials instead of azirines. Noteworthy, this work is the first reported example of the formation of diazo-Meldrum's acid-based iminium-type ylides.

### 3.3. Aluminum-assisted reactions

Lindsay and colleagues reported the formation of a series of chiral  $\beta$ -lactams from enantioenriched cyclopropanone equivalents.<sup>55</sup> Noteworthy, the authors carried out a gram scale synthesis which allowed to obtain 1.25 g of a chiral lactam showing >99% enantiomeric excess. This large-scale synthesis started by the three-step formation of the chiral sulfonylcyclopropane **53** from methyl phenyl sulfone (**54**) and (*R*)-propylene oxide (**55**) (Scheme 10). Through this three-step protocol involving treatment with benzenesulfonyl chloride and *n*-BuLi, the target cyclopropane **53** was obtained in a 66% yield showing excellent enantioselectivity (>99% ee). A subsequent  $\alpha$ -hydroxylation protocol afforded the enantiopure cyclopropanone equivalent **56** in 80% yield, retaining the stereospecificity. Then, the cyclopropanone equivalent **56** reacted with *N*-benzylhydroxylamine chloride (BnNHOH) and  $\text{NEt}_3$  leading to the formation of the stable hemiaminal intermediate **57**, which experiences an *in situ* rearrangement after addition of  $\text{Al}(\text{OTf})_3$  to yield the target  $\beta$ -lactam **58** in 88% yield showing





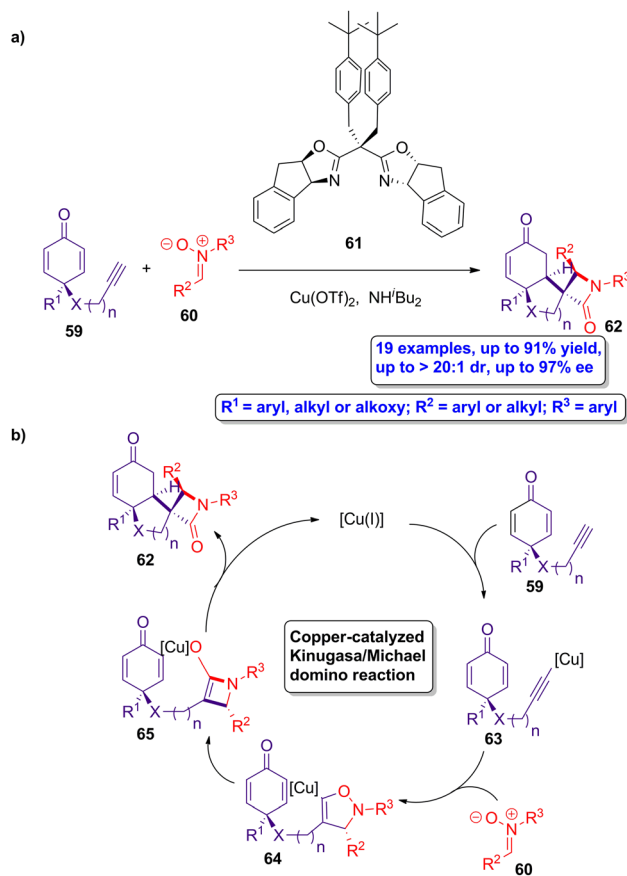
**Scheme 10** Gram scale synthesis of chiral  $\beta$ -lactam **58** through the formation of the cyclopropanone equivalent **56**. The original results were reported by Lindsay and colleagues.<sup>55</sup>

almost enantiopurity. Thus, the stereochemical information is completely transferred from the initial chiral cyclopropane to the prepared  $\beta$ -lactam. The employment of cyclopropanones as highly reactive intermediates leads to envision the use of this methodology to access a wide variety of chiral heterocycles that can be used in different implementations, such as development of new generations of antibiotics.

### 3.4. Copper-assisted reactions

Copper-catalyzed Kinugasa/Michael domino reactions were employed by Enders and colleagues in the asymmetric synthesis of a series of spirocyclic  $\beta$ -lactams.<sup>56</sup> The reaction of prochiral cyclohexadienone **59** and nitrones **60** using  $\text{Cu}(\text{OTf})_2$  as catalyst, ligand **61** and  $\text{NH}^t\text{Bu}_2$  as base (Scheme 11a), leads to the formation of the chiral spirocyclic  $\beta$ -lactams **62** in good yields, showing excellent diastereoselectivity (up to >20:1) and enantioselectivity (up to 97% ee). The proposed catalytic cycle starts with the formation of catalytically active copper(I) species by the *in situ* reduction of the catalyst (Scheme 11b). These active metallic species react with the prochiral cyclohexanodienone **59** to afford the copper acetylide intermediate **63**. A copper-isoxazoline intermediate **64** is then formed through a [3 + 2] dipolar cycloaddition of acetylide **63** and the corresponding nitron **60**. A rearrangement of **64** leads to the formation of the copper  $\beta$ -lactam-based enolate **65**, which subsequently experiences a desymmetrized Michael addition, yielding the target spirocyclic  $\beta$ -lactams **62**. Interestingly, the scale up of this protocol retains the excellent regio-, chemo-, diastereo- and enantioselectivities of the process. This methodology paves the way to the preparation of spirocyclic  $\beta$ -lactams having four neighbouring stereocenters in a versatile manner, allowing to access to improved bioactive compounds.

Copper(I)-catalyzed asymmetric interrupted Kinugasa reactions were employed by Xu and coworkers in the preparation of chiral  $\beta$ -lactams having sulfur groups in  $\alpha$ -position.<sup>57</sup> In this protocol, a sulfur-based electrophile is employed to capture the copper(I) four-membered enolate intermediate, thus avoiding the proton transfer process and affording the target sulfur-functionalized lactams. Thus, the reaction of alkynes **66**, nitrones **67** and benzenesulfonylthioates **68** using  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  as catalyst, ligand **69** and  $\text{K}_2\text{CO}_3$  as base



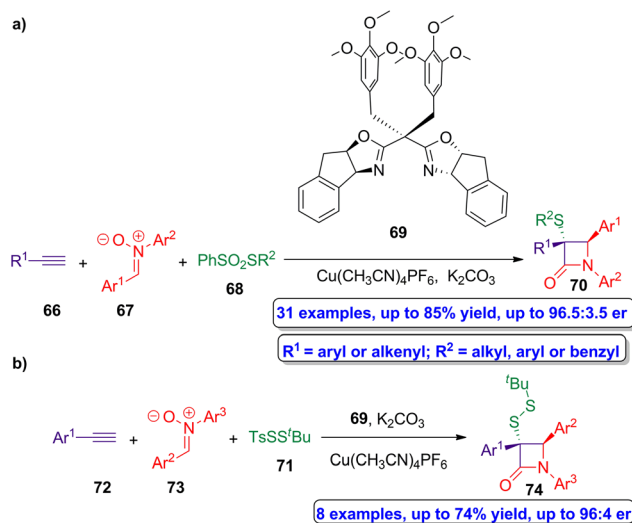
**Scheme 11** (a) Asymmetric synthesis of spirocyclic  $\beta$ -lactams **62** from cyclohexadienones **59** and nitrones **60**; and (b) catalytic cycle of the copper-catalyzed Kinugasa/Michael domino reaction. The original results were reported by Enders and colleagues.<sup>56</sup>

(Scheme 12a), afforded chiral sulfur-functionalized  $\beta$ -lactams **70** in excellent enantioselectivity (up to 96.5:3.5 er). An analogous reaction using the disulfur transfer reagent  $\text{TsSS}^t\text{Bu}$  **71** as sulfur source, alkynes **72** and nitrones **73**, afforded the disulfur-functionalized  $\beta$ -lactam **74** showing up to 96:4 er (Scheme 12b). Both chiral products (**70** and **74**) can be easily functionalized to obtain bioactive molecules, turning out to be useful building blocks for the preparation of available products which can be employed in pharmaceutical chemistry, food chemistry and chemical biology.

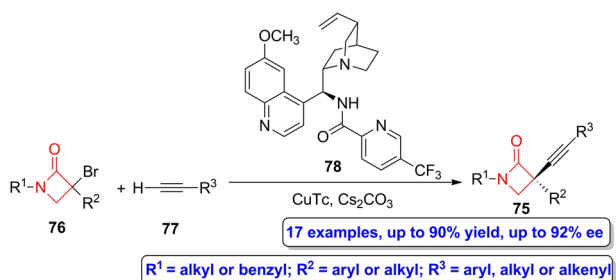
Cai and coworkers reported a copper-catalyzed interrupted asymmetric Kinugasa reaction of *N*-(2-iodo-aryl)-propiolamides and nitrones to obtain spirocyclic  $\beta$ -lactams.<sup>58</sup> In this example, an intramolecular aryl C–C coupling reaction was employed in order to trap the copper intermediate formed in the Kinugasa reaction.

Gu, Hong, Liu and colleagues reported the asymmetric synthesis of a series of alkyne-functionalized  $\beta$ -lactams **75** through a copper-catalyzed enantioconvergent  $\text{C}(\text{sp}^3)\text{--C}(\text{sp})$  cross-coupling of tertiary  $\alpha$ -bromo functionalized  $\beta$ -lactams **76**, which act as tertiary electrophiles, and alkynes **77** (Scheme 13).<sup>59</sup> In this synthetic approach,  $\text{CuTc}$  was employed





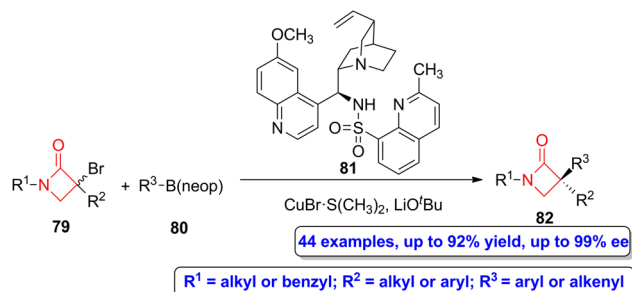
**Scheme 12** (a) Asymmetric synthesis of  $\beta$ -lactams **70** from alkynes **66**, nitrones **67** and benzenesulfonyl esters **68**; and (b) asymmetric synthesis of  $\beta$ -lactams **74** from alkynes **72**, nitrones **73** and disulfur transfer reagent **71**. The original results were reported by Xu and colleagues.<sup>57</sup>



**Scheme 13** Asymmetric copper-catalyzed enantioconvergent radical  $C(sp^3)$ - $C(sp)$  synthesis of alkyne-functionalized  $\beta$ -lactams **75** from bromo-functionalized  $\beta$ -lactams **76** and alkynes **77**. The original results were reported by Gu, Hong, Liu and colleagues.<sup>59</sup>

as the catalyst, compound **78** as the *N,N,N*-ligand and  $Cs_2CO_3$  as the base. The target four-membered heterocycles were obtained in high yields (up to 90%) showing excellent enantioselectivities (up to 92% ee). This synthetic strategy allows to access to enantioenriched  $\alpha$ -quaternary  $\beta$ -lactams, which turned out to be highly relevant due to the biological significance of this core motif and its underrepresentation in the literature.

Recently, a copper-catalyzed enantioconvergent radical  $C(sp^3)$ - $C(sp^2)$  cross coupling reaction was employed by Li, Liu and coworkers to synthesize  $\alpha$ -quaternary  $\beta$ -lactams.<sup>60</sup> The reaction of bromo-functionalized  $\beta$ -lactams **79** with organoboronate esters **80** using  $CuBr \cdot S(CH_3)_2$  as the catalyst, compound **81** as the *N,N,N*-ligand and  $LiO^tBu$  as the base afforded  $\alpha$ -quaternary  $\beta$ -lactams **82** (Scheme 14) in moderate to high yield (up to 92%) and excellent enantioselectivities (up to 99% ee). This synthetic strategy allows to access to a vast range of possible functionalization, covering both alkenyl- and (hetero)



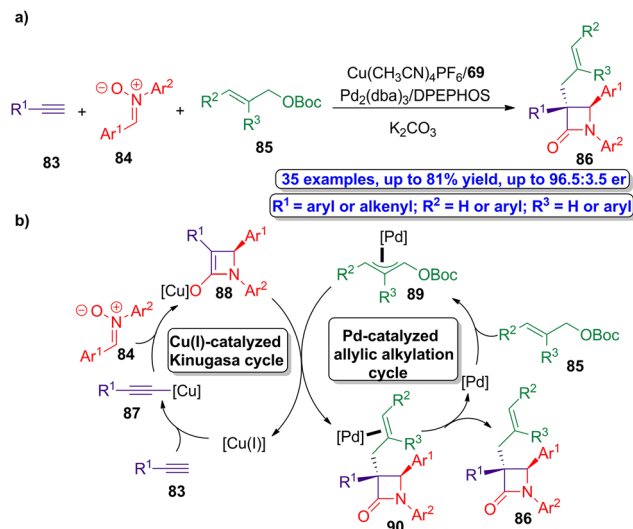
**Scheme 14** Asymmetric copper-catalyzed enantioconvergent radical  $C(sp^3)$ - $C(sp^2)$  synthesis of  $\alpha$ -quaternary  $\beta$ -lactams **82** from bromo-functionalized  $\beta$ -lactams **79** and organoboronate esters **80**. The original results were reported by Li, Liu and colleagues.<sup>60</sup>

arylboronate esters. Interestingly, the authors also tested a sequential cross-coupling followed by hydrogenation, thus being possible to synthesize a  $\alpha$ -quaternary- $\beta$ -lactam through a  $C(sp^3)$ - $C(sp^3)$  cross-coupling reaction.

### 3.4. Bimetallic-assisted reactions

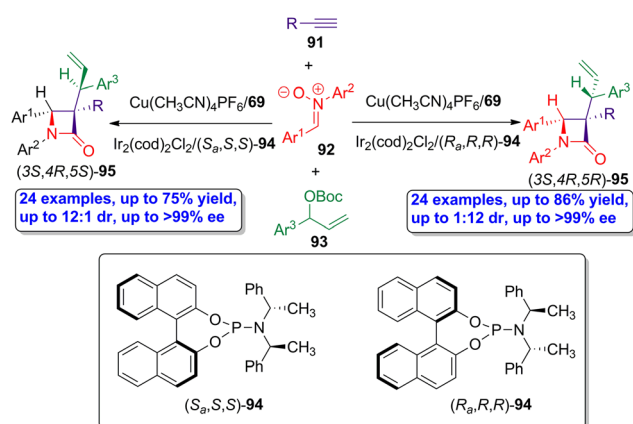
The research group of Xu went a step further and developed a one pot bimetallic catalysis methodology to access to a series of  $\alpha$ -quaternary chiral  $\beta$ -lactams.<sup>61</sup> The interesting point of this three-component synthetic protocol is the synergy of the asymmetric copper/palladium-catalyzed multicomponent reactions, which allow the modular preparation of the enantioenriched  $\beta$ -lactams by the coupling of transient organometallic species. The authors envision the simultaneously utilization of  $Cu(CH_3CN)_4PF_6$ /ligand **69** and  $Pd_2(dba)_3$ /bis[(2-diphenylphosphino)phenyl] ether (DPEPHOS) as combination of ligands and catalysts driving the process. However, in order to accomplish a synergistic bimetallic catalytic cycle, both individual catalytic cycles must be synchronized in order to afford the target product except the two-component Kinugasa adduct. Alkynes **83**, nitrones **84** and allylic electrophiles **85** were selected as the components of the reaction, leading to the target chiral allyl-functionalized  $\beta$ -lactams **86** (Scheme 15a). The proposed mechanism of this novel Kinugasa allylic alkylation reaction combines in a synergistic way a copper(i)-catalyzed Kinugasa cycle and a palladium-catalyzed allylic alkylation one (Scheme 15b). Thus, the reaction of active copper(i) species with alkynes **83** leads to the formation of copper(i)-acetylide **87**, which then accomplish a cycloaddition reaction with nitrones **84** affording the four-membered copper(i)-based enolate intermediate **88**. This enolate intermediate reacts with the corresponding allylic palladium intermediate **89**, which is formed from the reaction of palladium catalyst with allylic electrophiles **85** in the palladium-catalyzed cycle. The combination of both organometallic species (**88** and **89**) allows the formation of palladium-based  $\beta$ -lactam complexes **90**, that finally leads to the target  $\alpha$ -quaternary chiral  $\beta$ -lactams **86**. Noteworthy, these products are formed in good yields (up to 81%) showing excellent enantioselectivity (up to 96.5 : 3.5 er).





**Scheme 15** (a) Asymmetric synergistic synthesis of allyl-functionalized  $\beta$ -lactams **86** from alkynes **83**, nitrones **84** and allylic electrophiles **85**; and (b) proposed synergistic catalytic cycle of the Kinugasa allylic alkylation reaction. The original results were reported by Xu and colleagues.<sup>61</sup>

The same research group developed an analogous simultaneous dual bimetallic catalysis using copper- and iridium-based catalysts.<sup>62</sup> Through this stereodivergent methodology, chiral  $\beta$ -lactams having contiguous tertiary/quaternary/tertiary stereocenters were synthesized. As in the previous example, a three-component interrupted Kinugasa allylic alkylation reaction was accomplished, selecting alkynes **91**, nitrones **92** and allylic electrophiles **93** as the starting materials, and using the combination of  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6/\text{ligand } \mathbf{69}$  and  $\text{Ir}_2(\text{cod})_2\text{Cl}_2/(\text{S}_a, \text{S}, \text{S})\text{-}\mathbf{94}$  or  $\text{Ir}_2(\text{cod})_2\text{Cl}_2/(\text{R}_a, \text{R}, \text{R})\text{-}\mathbf{94}$  as catalysts (Scheme 16). The catalytic cycle is similar to that described in the previous example, but the iridium-catalyzed cycle provides an additional stereocenter in the allyl motif, whose configuration is determined by the



**Scheme 16** Asymmetric dual copper/iridium-catalyzed synthesis of allyl-functionalized  $\beta$ -lactams **95** having consecutive tertiary/quaternary/tertiary stereocenters, from alkynes **91**, nitrones **92** and allylic electrophiles **93**. The original results were reported by Xu and colleagues.<sup>62</sup>

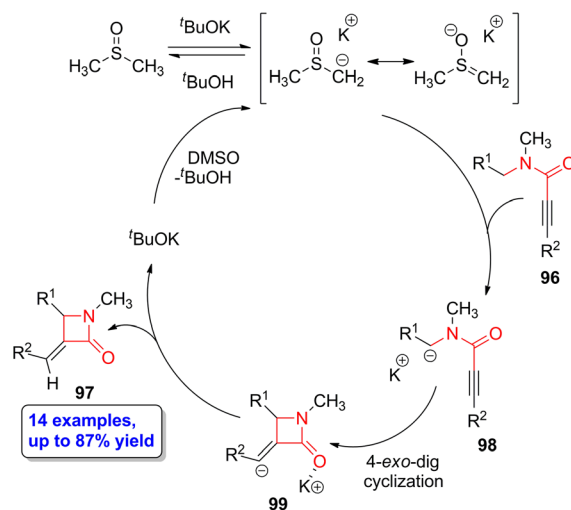
absolute configuration of the ligand **94**. Thus, when ligand  $(S_a, S, S)\text{-}\mathbf{94}$  was employed in the synergistic synthetic protocol,  $\beta$ -lactams  $(3S, 4R, 5S)\text{-}\mathbf{95}$  were obtained as main products in good yields (up to 75%) showing excellent diastereoselectivity (up to 12 : 1 dr) and enantioselectivity (up to >99% ee). When the ligand  $(R_a, R, R)\text{-}\mathbf{94}$  was used, the reaction afforded  $(3S, 4R, 5R)\text{-}\mathbf{95}$  as main products showing high diastereoselectivity (up to 1 : 12 dr) and enantioselectivity (up to >99% ee). This protocol further expands the application of asymmetric synchronized bimetallic-catalyzed cascade reaction in the synthesis of chiral bioactive  $\beta$ -lactams.

## 4. Base-promoted synthesis

Base-promoted cyclization reactions to afford  $\beta$ -lactams are also available synthetic approaches.<sup>63–66</sup> This section includes selected recent examples of cyclization reactions promoted by bases in order to prepare  $\beta$ -lactam derivatives.

### 4.1. Potassium *tert*-butoxide catalyzed reactions

Zeni and coworkers described a stereo- and regioselective base-catalyzed intramolecular cyclization of *N*-benzyl-*N*-methyl-propiolamides **96** to form  $\alpha$ -methylene- $\beta$ -lactam compounds **97** employing potassium *tert*-butoxide as the base and dimethylsulfoxide as the solvent.<sup>67</sup> The target lactams were obtained in yields up to 87% observing high selectivity for the 4-*exo*-dig cyclization over the 5-*endo*-dig process. The highest yields were observed when aryl motifs having electron-donating substituents in the *para* position were employed. The authors proposed a mechanism in which potassium *tert*-butoxide and dimethylsulfoxide first form a dimethyl sulfide ylide, thus allowing the abstraction of a hydrogen placed at the benzylic position of **96** (Scheme 17). The newly formed carbanion **98** experiences an intramolecular nucleophilic attack to the alkyne func-



**Scheme 17** Proposed potassium *tert*-butoxide-catalyzed cycle to obtain  $\beta$ -lactams **97** from *N*-benzyl-*N*-methyl-propiolamides **96**. The original results were reported by Zeni and colleagues.<sup>67</sup>



tionality in a 4-*exo*-dig manner, leading to the formation of the heterocyclic intermediate **99**. The subsequent protonation reaction leads to the target lactam **97**. Noteworthy, these heterocyclic scaffolds can be functionalized through Heck coupling with aryl iodide derivatives, thus paving the way to the incorporation of substituents having also biological activity.

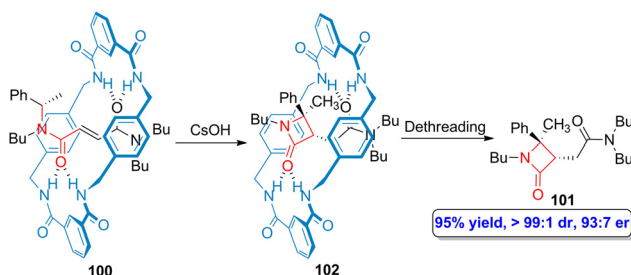
#### 4.2. Mechanical bond-activated reactions

Beyond the synthetic strategies described above, the use of *N*-(arylmethyl)fumaramide-based tetralactam [2]rotaxanes in the stereocontrolled synthesis of  $\beta$ -lactams, reported by Berna and colleagues, further expands the possibilities to access to this type of bioactive scaffolds.<sup>68–70</sup> This macrocycle-activated synthesis takes place through the base-promoted cyclization of the corresponding interlocked *N*-(arylmethyl)fumaramide linear counterparts within the confined space provided by the cavity of the macrocycle. The macrocycle is the activating element but also the element that dictates the diastereoselectivity, which leads to the obtention of the *trans*-adducts as the only products. In order to obtain the noninterlocked  $\beta$ -lactams, a dethreading process is carried out,<sup>71</sup> thus allowing the obtention of the target bioactive heterocycles.

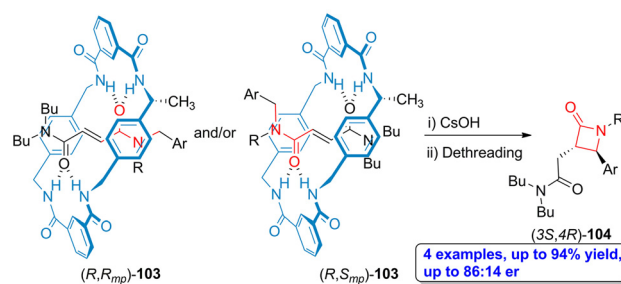
But in addition to the regio- and diastereoselections, this research group carried out a rational design incorporating stereocenters, either positioned in the linear counterpart<sup>72</sup> or in the cyclic one,<sup>73</sup> to induce enantioselection in the process.

The incorporation of a chiral  $\alpha$ -methyl benzyl group as one of the ends of the fumaramide linear counterpart (**100**) led to the preparation of enantioenriched  $\beta$ -lactam **101** after carrying out a dethreading process (Scheme 18).<sup>72</sup> Although the synthesis can be accomplished as a one pot protocol, it is possible to isolate the enantioenriched interlocked  $\beta$ -lactam **102** after the cesium hydroxide-promoted cyclization. The chiral information that the  $\alpha$ -methyl benzyl group provided to the thread is retained throughout the creation of the quaternary stereocenter in the target lactam **101**, showing high enantioselectivity (93 : 7 er) and excellent diastereoselectivity (>99 : 1 dr).

In a more recent example, one methyl group having *R* configuration was incorporated in the tetralactam macrocycle,



**Scheme 18** Base-promoted cyclization of *N*- $\alpha$ -(methylbenzyl)fumaramide-based tetralactam [2]rotaxanes **100** to afford enantioenriched  $\beta$ -lactams **101**. The original results were reported by Berna and colleagues.<sup>72</sup>



**Scheme 19** Base-promoted cyclization of *N*-(arylmethyl)fumaramide-based tetralactam [2]rotaxanes **103** to afford enantioenriched  $\beta$ -lactams **104**. The original results were reported by Berna and colleagues.<sup>73</sup>

thus affording *N*-(arylmethyl)fumaramide-based rotaxanes **103**, which are orientational mechanostereoisomers.<sup>73</sup> Through a one pot protocol involving cesium hydroxide-promoted cyclization and the subsequent dethreading process, the enantioenriched  $\beta$ -lactams **104** were obtained in high yield (up to 94%). Interestingly, the lactams (*3S,4R*)-**104** were obtained as the main products (up to 86 : 14 er) independently of the interlocked mechanical epimer [(*R,R*<sub>mp</sub>)-**103** or (*R,S*<sub>mp</sub>)-**103**] employed as starting material (Scheme 19). This result allows to conclude that the (*R*)-methyl stereocenter placed at the tetralactam macrocycle is the element directing the enantioselectivity of this process activated by the mechanical bond. Thus, the high level of enantioselectivity of this process is a consequence of the chirality transfer from the tetralactam macrocyclic counterpart to the linear one through the mechanical bond induced by the symmetry breaking generated by one small methyl group.

## 5. Conclusions

The synthesis of  $\beta$ -lactam derivatives is an important area of research due to their relevant bioactive properties. Indeed, there are several widely employed antibiotics having a  $\beta$ -lactam ring as a central core. Due to the major problem of antibiotic resistance,<sup>74</sup> the development of novel broad-spectrum antibiotics turns out to be necessary. In this scenario, the stereoselective synthesis of a vast range of  $\beta$ -lactams can contribute to avoiding a future antibiotic resistance crisis. This review article aims to highlight different suitable synthetic protocols to access to these heterocyclic molecules, highlighting selected recent examples.

As evidenced throughout the manuscript, the synthesis of  $\beta$ -lactams can be accomplished in diastereo- or/and enantioselective manners using a pool of different reactions, from the “traditional” syntheses to those using transition metal-catalysis or even through the activation of the mechanical bond in rotaxane-based systems. Through these protocols, high stereoselectivity has been obtained towards different functionalized  $\beta$ -lactams, allowing to incorporate several stereocenters. But despite these promising results, there is still a niche for future development. Synthetic efforts towards specific control over



the configuration of each individual stereocenters are envisioned as a key future research area in order to synthesize  $\beta$ -lactam compounds having enhanced biological activity.

The industrial scale up is also another milestone to overcome. Although for the utility of large-scale synthetic processes, it is not only required to reproduce yields and stereoselectivity, but also simple purification processes which lead to high purity and in a cost-effective manner. In this direction, the collaboration of academia and industrial sector, especially pharmaceutical industry, will lead to this end.

The privileged properties of  $\beta$ -lactams together with the continuous advances in organic synthesis lead to envision a great future development towards the stereoselective synthesis of these bioactive scaffolds. Thus, the preparation of highly functionalized  $\beta$ -lactams having multiple stereocenters with a precise control over the absolute configuration is anticipated.

## Author contributions

Conceptualization, L. A.-A. and A. S.-S.; writing – original draft preparation, L. A.-A. and A.-S. S.; writing – review and editing, A. S.-S.; visualization, L. A.-A. and A. S.-S.; supervision, A. S.-S.; funding acquisition, A. S.-S. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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