

## REVIEW

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# Recent advances in the accessibility, synthetic utility, and biological applications of aziridines

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Compounds featuring aziridine moieties are widely known and extensively reported in the literature. Due to their great potential from both synthetic and pharmacological points of view, many researchers have focused their efforts on the development of new methodologies for the preparation and transformation of these interesting compounds. Over the years, more and more ways to obtain molecules bearing these three-membered functional groups, which are challenging due to their inherent reactivity, have been described. Among them, several are more sustainable. In this review, we report the recent advances in the biological and chemical evolution of aziridine derivatives, in particular, the variety of methodologies described for the synthesis of aziridines and their chemical transformations leading to the formation of interesting derivatives, such as 4–7 membered heterocycles of pharmaceutical interest due to their promising biological activities.

## 1. Introduction

Aziridines are the simplest class of three-membered saturated nitrogen-containing heterocycles. They are less basic than alkylamines but more basic than arylamines. The strain caused by the geometric constraints of the trigonal ring confers high reactivity.<sup>1</sup> Indeed, aziridines enable various intri-

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guing synthetic opportunities that can be harnessed. Among these are reactions such as ring-opening, ring enlargement, tandem<sup>2</sup> and multicomponent reactions.<sup>3</sup> In the past, aziridines were considered to be difficult compounds to synthesize due to their instability, which is caused by their reactivity. Nevertheless, a variety of methodologies have been reported for preparing these interesting compounds including catalysis, annulation, and cycloaddition reactions, and organometallic chemistry. Lately, more sustainable conditions have been developed in good agreement with the principles of green chemistry including flow chemistry applications. Furthermore, aziridines are useful building blocks for the preparation of more complex heterocycles or amino acids which are also interesting from biological and pharmacological points of view due to their various biological activities.<sup>4</sup> For these reasons, the interest of the scientific community in these small and fascinating compounds is ever increasing. Therefore, we herein report an overview of the recently developed methodologies regarding the syntheses, synthetic uses, and biological applications of aziridines. We have focused our attention on the past three years, trying to describe the most important breakthroughs that have been made after the publication of other reviews covering this field.<sup>5</sup>

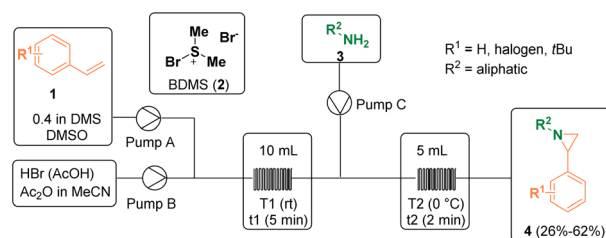
## 2. Preparations of aziridines

### 2.1 Aziridination of olefins

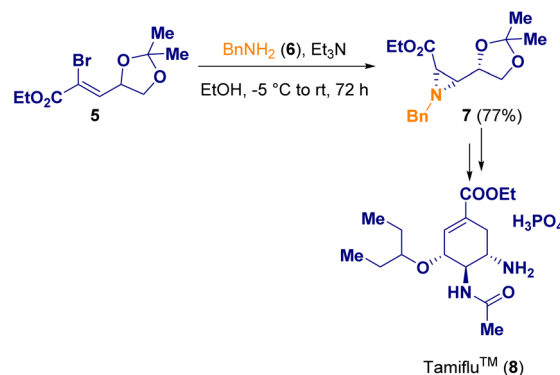
Several methodologies have been described for the preparation of aziridine derivatives. Kappe and co-workers reported a continuous flow bromodimethylsulfonium bromide (**2**, BDMS) generation/alkene sulfobromination/aziridination sequence for preparing functionalized aziridines (**4**). BDMS (**2**) is a versatile reagent employed in organic synthesis as a stoichiometric reagent or as a catalyst. However, upon storage, it has to be treated as a hazard since it is corrosive and sensitive to heat and moisture, releasing molecular bromine (Br<sub>2</sub>) upon contact with water. For this reason, the authors decided to develop a continuous flow procedure for the safe generation and utilization of BDMS (**2**). In addition, by using a flow chemistry approach, the potential hazard from the accumulation of this reagent in batch can be overcome, as the reagent is immediately consumed upon generation. Thus, BDMS (**2**) was prepared for the first time in flow, starting from HBr and DMSO, and was then further reacted with primary amines (**3**) to yield 2-phenyl aziridines (**4**) in a 3-step sequential process (Scheme 1).<sup>6</sup>

Gonnade and co-workers documented the syntheses of aziridine **7** which was then used for the preparation of the well-known Tamiflu (**8**), also called oseltamivir phosphate, which is used as a medicine to cure both influenza A and B and to prevent the spread of influenza. In one of the described procedures, *cis*-aziridine (**7**) was employed as a chiral synthon (Scheme 2).<sup>7</sup>

Watson and co-workers reported in 2022 the asymmetric synthesis of aziridines (**13**) *via* enantioselective protonation of



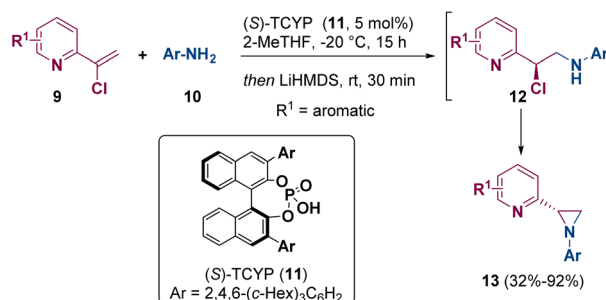
**Scheme 1** Flow BDMS generation/alkene sulfobromination/aziridination sequence.



**Scheme 2** Aziridination of vinyl bromide **5** for preparing Tamiflu (**8**).

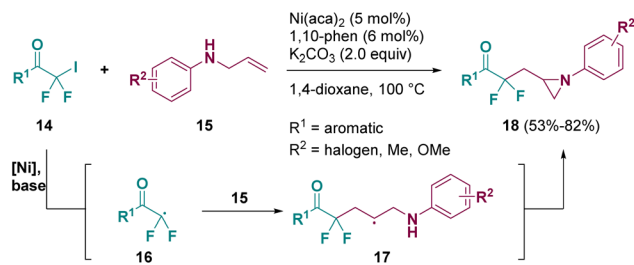
catalytically generated enamines by using chiral Brønsted acids such as **11** ((*S*)-TCYP). The aziridine ring (**13**) is achieved after treating the so-formed  $\alpha$ -chloroamine **12** with a base in a one-pot process (Scheme 3).<sup>8</sup>

Catalysis is one of the most used methodologies for preparing aziridine derivatives. Indeed, a lot of pathways have been described by using different catalysts.<sup>9</sup> Among them, nickel was employed and in 2022 Wu and co-workers reported a nickel-catalyzed aminofluoroalkylative cyclization of unactive alkenes (**15**) with iododifluoromethyl ketones (**14**) to afford versatile difluoroalkylated nitrogen-containing heterocycles including aziridines (**18**), as shown in Scheme 4.<sup>10</sup> According to the authors, the transformation proceeds through a radical mechanism. Upon treatment with the Ni-catalyst and base, iododifluoromethyl ketones (**14**) are transformed into inter-



**Scheme 3** Asymmetric synthesis of aziridines.



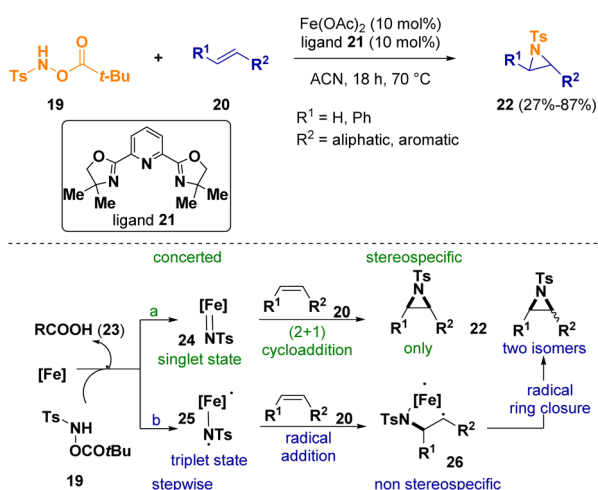


Scheme 4 Nickel catalyzed aziridination of unactive alkenes.

mediates such as **16**, which react with *N*-allyl anilines (**15**) to give radical species **17**, from which the aziridine products (**18**) are obtained.

Berhal *et al.* documented the iron-catalyzed reaction between alkenes (**20**) and hydroxylamine derivatives (**19**) to give aziridines **22**. In particular, they used simple iron(II) sources and readily available ligands rendering the reaction conditions more sustainable (Scheme 5).<sup>11</sup> Considering the mechanism of the reaction, the *in situ* generated iron catalyst [Fe] provides an iron–nitrene intermediate (**24** or **25**) after reacting with the hydroxylamine derivative **19**, releasing an equivalent amount of carboxylic acid (**23**). Since metal–nitrene complexes exist in two different spin states, the authors consider two possible reaction pathways. If the metal–nitrene complex predominantly exists in its singlet state (**24**), a concerted (2 + 1) cycloaddition could take place, leading to a stereospecific process (Scheme 5 – path a). On the other hand, if the iron–nitrene complex is in its triplet state (**25**), a radical addition followed by a radical-based ring closure could occur (Scheme 5 – path b). In this case, due to the multistep procedure, no stereoselectivity should be observed.

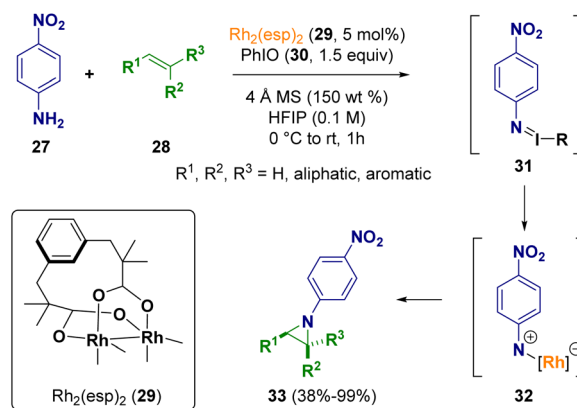
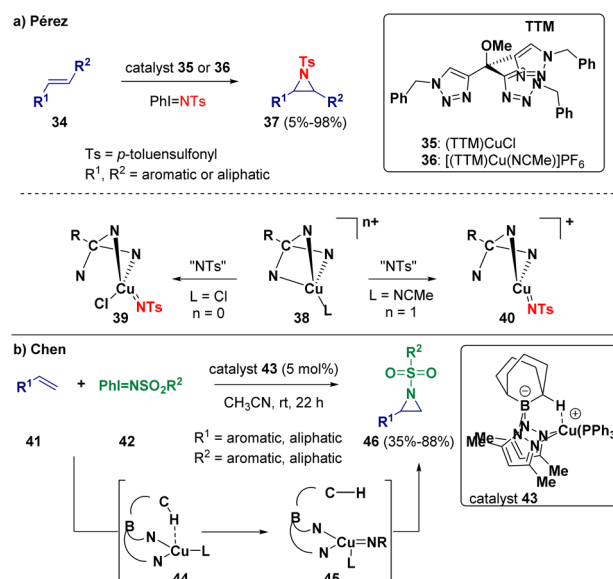
Driver *et al.* described an intermolecular  $\text{Rh}_2(\text{II})$ -catalyzed aziridination of olefins (**28**) using anilines (**27**) as non-activated nitrogen atom precursors and an iodine(III) reagent (**30**)



Scheme 5 Reaction of alkenes with hydroxylamines for preparing aziridines.

as the stoichiometric oxidant. During the process, the *N*-aryl nitrene fragment is transferred from the intermediate iminoiodane (**31**) to the  $\text{Rh}(\text{II})$  carboxylate catalyst **29**. The reaction proved to be stereospecific and chemo- and diastereoselective to produce *N*-aryl aziridine **33** as the only amination product (Scheme 6).<sup>12</sup>

After describing in 2022 the use of  $(\text{NHC})\text{M}$  ( $\text{M} = \text{Cu}, \text{Ag}, \text{Au}$ ) cores as catalysts for the olefin aziridination reaction,<sup>13</sup> recently, Pérez and co-workers reported the copper-catalyzed aziridination of olefins.<sup>14</sup> The authors highlighted the important role of the halide characterizing the copper catalyst (Scheme 7 – path a). Indeed, they demonstrated *via* mechanistic studies that the employed copper(I) complexes  $(\text{TTM})\text{CuCl}$  (**35**) and  $[(\text{TTM})\text{Cu}(\text{NCMe})]\text{PF}_6$  (**36**) (TTM = tris(triazolyl) methane ligand) possess different behaviors, from catalytic and mechanistic points of view, depending on the presence or absence of the chloride ligand bonded to the metal center. If

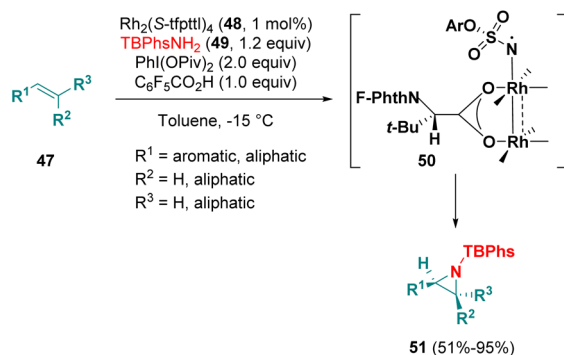
Scheme 6 Intermolecular  $\text{Rh}_2(\text{II})$ -catalyzed aziridination of olefins.

Scheme 7 Copper-catalyzed olefin aziridination.

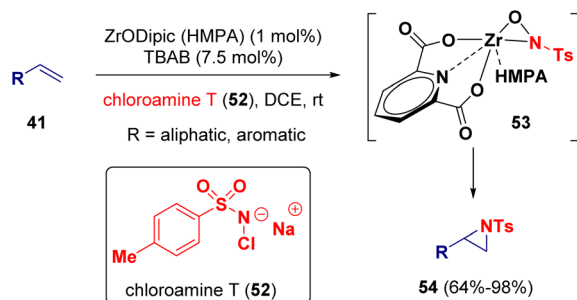
coordination is present, the limiting step of the reaction concerns the formation of the carbon–nitrene bond (**39**). In case the chlorine atom is not present, the highest barrier corresponds to the formation of the copper–nitrene intermediate (**40**). Chen and co-workers selected bis(pyrazolyl)borate Cu(I) complexes (**43**) as catalysts for the aziridination of olefins (Scheme 7 – path b). The reaction was carried out starting from a suitable styrene (**41**) and *N*-(sulfonyl)imino]phenyliodine (**42**). During the catalytic process, a nitrene is generated and added to the double bond.<sup>15</sup>

Dauban *et al.* employed C<sub>4</sub>-symmetrical dirhodium(II) tetracarboxylates (**48**) as catalysts for the asymmetric intermolecular aziridination of substituted alkenes (**47**) with *p*-*t*Bu-phenylsulfamates **49** (TBPhsNH<sub>2</sub>) (Scheme 8). The authors proposed a two-spin-state mechanism, involving a triplet Rh–nitrene species as the key intermediate (**50**) to direct the approach with stereocontrol and for the activation of the substrate. DFT studies support the proposed mechanism. An enantiomeric excess of up to 99% was observed.<sup>16</sup>

Zirconium has also been employed as a catalyst for the synthesis of aziridine derivatives. Moura-Letts and co-workers described the aziridination of alkenes (**41**) by using chloramine T<sup>17</sup> (**52**) as the quantitative source of nitrogen (Scheme 9). Supported by kinetics and model reaction studies, the authors propose that the reaction mechanism involves the formation of a zirconooxaziridine complex (**53**) as the active catalyst.<sup>18</sup>



**Scheme 8** Asymmetric intermolecular aziridination of substituted alkenes.

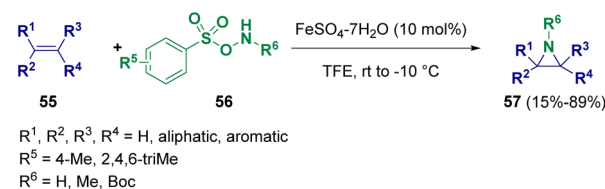


**Scheme 9** Zirconium catalyzed synthesis of aziridines.

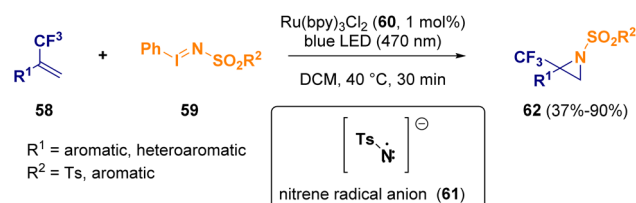
Jat and co-workers reported the iron(II) catalyzed direct N–H/N–Me aziridination of olefins (**55**) employing *O*-arylsulfonyl hydroxylamines (**56**). The one-pot methodology proved to be stereo- and regioselective, yielding a variety of unactivated aziridines (**57**) in good to excellent yields (Scheme 10).<sup>19</sup>

Mixed approaches of photo- and metal-catalysis have also been reported for the synthesis of aziridines.<sup>20</sup> Koenigs *et al.* described the preparation of trifluoromethylated aziridines (**62**) starting from fluorinated olefins (**58**) and iodine (**59**), which undergo oxidative quenching in the presence of a Ru (bpy)<sub>3</sub>Cl<sub>2</sub> catalyst (**60**), releasing a nitrene radical anion (**61**) (Scheme 11). Computational studies confirmed that the nitrene radical (**61**) serves as a reactive intermediate in direct aziridination reactions.<sup>21</sup>

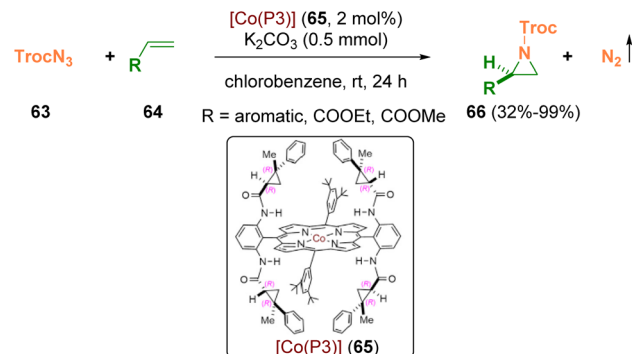
Zhang and co-workers employed the carbonyl azide TrocN<sub>3</sub> (**65**, 2,2,2-trichloroethoxycarbonyl azide), which is a potent nitrogen radical precursor for the aziridination of olefins (**64**) via Co(II)-based metalloradical catalysis (**65**) (Scheme 12). Chiral *N*-carbonyl aziridines (**66**) were prepared at room temp-



**Scheme 10** Iron(II) catalyzed direct N–H/N–Me aziridination of olefins.



**Scheme 11** Photocatalytic amination reaction for preparing trifluoromethylated aziridines.



**Scheme 12** Olefin aziridination via Co(II)-based metalloradical catalysis.





erature in high yields with excellent enantioselectivities. The obtained *N*-Troc-aziridines (**66**) can be opened by different nucleophiles, achieving a variety of chiral amines with excellent stereospecificity (89–100% es).<sup>22</sup>

The major part of the reported methodologies for synthesizing aziridines rely on the transition-metal catalyzed reactions of alkenes with nitrene precursors or imines with carbene precursors.<sup>23</sup> However, these pathways are limited by the use of hazardous and explosive carbene and nitrene precursors as well as additional steps for diazo synthesis and transition-metal residue removal. For these reasons, the development of more sustainable methodologies has been pursued by scientists.<sup>24</sup> Different pathways employing electrochemical activation to facilitate oxidative cyclization were developed.<sup>25</sup> Nevertheless, significant limitations and challenges are still to be overcome. Recently, the employment of thianthrenium salts was reported to be an alternative methodology.<sup>26</sup> In 2021, Wickens *et al.* documented the electrochemical transformation of non-activated alkenes (**67**) into metastable, dicationic intermediates **69** and **70** that undergo aziridination with primary amines (**71**) under basic conditions (Scheme 13). This new approach allows the preparation of diverse aziridine building blocks (**72**) bearing sensitive functional groups, such as allyl and cyano groups, that are challenging to access through more conventional approaches.<sup>26</sup>

In 2022, Shu and co-workers developed a straightforward aziridination pathway using primary amines (**73**) with alkenes substituted with thianthrenes (**74**). The methodology works well for terminal, internal, aromatic, and aliphatic alkenes (Scheme 14).<sup>27</sup> In comparison with the electrochemical thianthrene-mediated aziridine formation, which only allows

functionalization of terminal olefins with primary amines<sup>26</sup> (Scheme 13), this conventional approach allows aziridination of both terminal and internal alkenes. Furthermore it is not limited to the use of primary amines, but also tolerates primary amides, carbamates, and sulfonamides. The use of active methylenes instead leads to cyclopropanation, making the methodology even more versatile.<sup>27</sup>

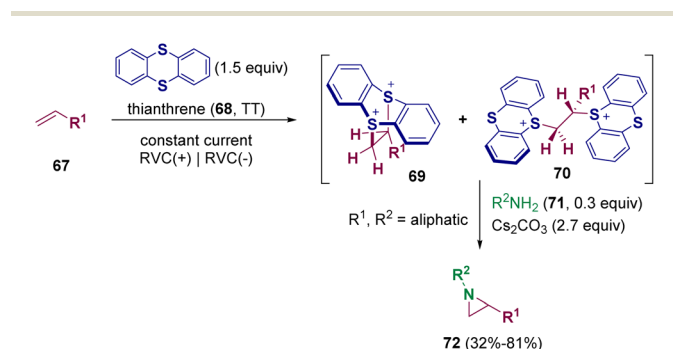
The chemoselective aziridination of styrenes (**76**) performed in the presence of hydroxylamine derivatives (**77**) *via* cobalt single-atom catalysis was reported by Tang and co-workers in 2023 (Scheme 15). The developed methodology is carried out under mild conditions and has a wide scope and high atom economy. Catalyst **78** is recyclable and not air-sensitive. Several natural products and drug-derived olefins have also been subjected to aziridination.<sup>28</sup>

Díez-González and co-workers reported the preparation of aziridines (**82**) from readily available azides (**80**) and alkenes (**81**). The reaction was carried out without any further additive by using technical solvents without the need for an inert atmosphere as the reaction can proceed in reaction vessels open to air (Scheme 16). The so-prepared aziridines (**82**) were then subjected to ring opening and ring enlargement reactions.<sup>29</sup>

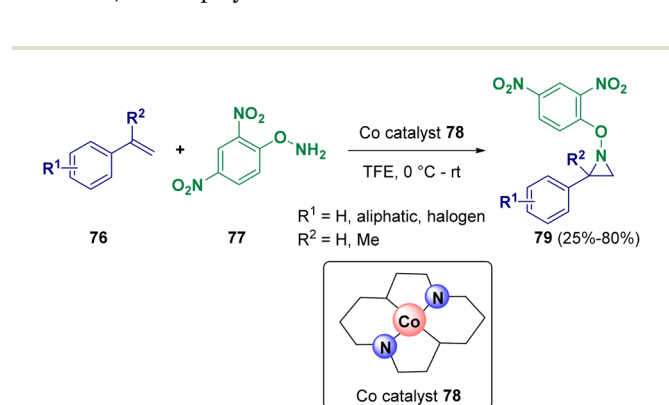
## 2.2 Aziridination of imines

Another common way for synthesizing aziridines is the addition of organometallics or other reagents to imine surrogates or amines.<sup>30</sup> Different methodologies have been reported and some of them allowed the preparation of interesting heterocycles under even more sustainable conditions.<sup>31</sup>

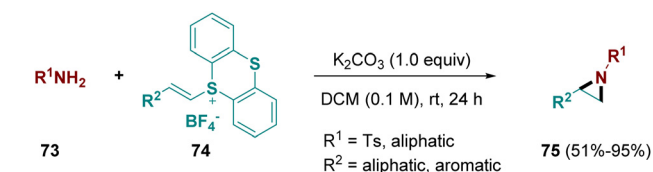
The presence of fluorine atoms within an organic compound can modulate its physico-chemical properties.<sup>32</sup> Therefore, the employment of fluorinated derivatives in medic-



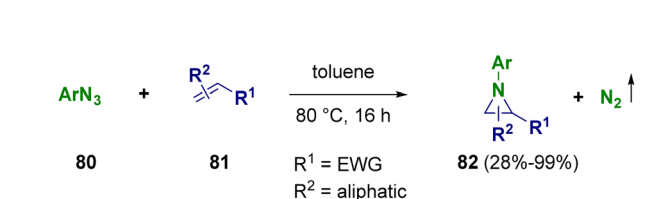
**Scheme 13** Electrochemical transformation of unactivated alkenes into aziridines.



**Scheme 15** Aziridination pathway *via* cobalt single atom catalysis.



**Scheme 14** Aziridination pathway using free primary amines and alkenes substituted with thianthrenes.



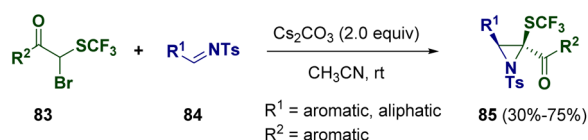
**Scheme 16** Preparation of aziridines from azides and alkenes.



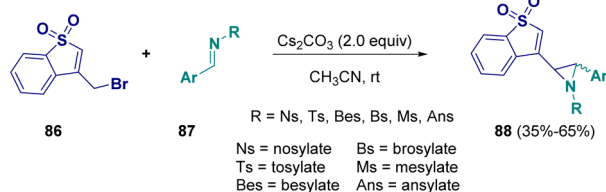
inal chemistry is very common and the development of new methodologies for the preparation of such interesting molecules is a central topic within the scientific community. In 2021, Njardarson and co-workers described the preparation of trisubstituted trifluoromethylthiolated ( $\text{SCF}_3$ ) aziridines (**85**) *via* the Darzens pathway. In particular, trisubstituted acetophenone nucleophiles (**83**) bearing  $\text{SCF}_3$  and bromine substituents at the  $\alpha$  position undergo reactions with tosyl-protected imines (**84**) under mild conditions to achieve the desired aziridine derivatives (**85**) (Scheme 17).<sup>33</sup>

In 2022, Njandanson and co-workers documented a reaction for preparing aziridines (**88**) starting from benzothiophene 1,1-dioxide (**86**) and imines (**87**). This vinylogous aza-Darzens reaction is base dependent ( $\text{Cs}_2\text{CO}_3$  is employed) and  $\gamma$ -selective, favouring the formation of *trans*-aziridines (Scheme 18).<sup>34</sup>

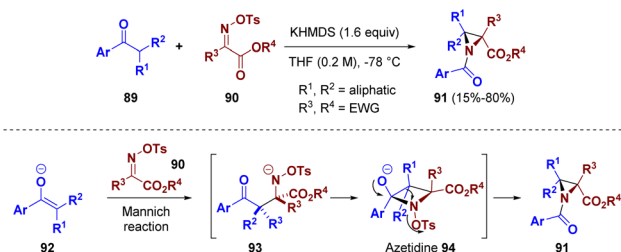
A telescoped reaction for the preparation of aziridines was described by Kürti and co-workers. Various electron-deficient *O*-sulfonyl oximes (**90**) were reacted with  $\alpha,\alpha$ -disubstituted acetophenone-derived enolates (**89**) to afford highly substituted aziridines (**91**) *via* an aza-quasi-Favorskii rearrangement (Scheme 19). This methodology was supported by computational studies which suggested a rearrangement pathway. The reaction of enolate **92** with imine **90** generates the *N*-activated  $\beta$ -aminoketone **93** which cyclizes to the *N*-activated



**Scheme 17** Preparation of trisubstituted trifluoromethylthiolated ( $\text{SCF}_3$ ) aziridines *via* the Darzens pathway.



**Scheme 18** The aza-Darzens reaction for the preparation of aziridines.



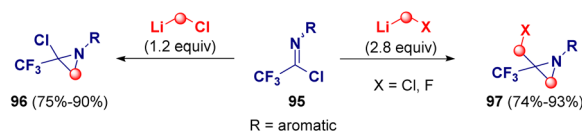
**Scheme 19** The aza-quasi-Favorskii rearrangement for the synthesis of aziridines.

azetidine **94**. The so-formed azetidine **94** undergoes an aza-quasi-Favorskii rearrangement to yield the highly strained and substituted aziridines **91**.<sup>35</sup>

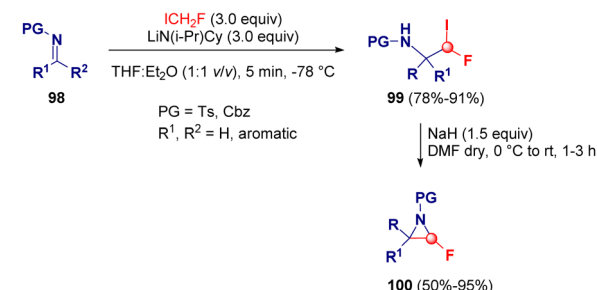
Pace and co-workers reported an unprecedented homologation reaction *via* lithium carbenoids for synthesizing mono- (**96**) and bis-homologated (**97**) trifluoromethyl-aziridine derivatives. The potency of this methodology relies on the selectivity of the reaction. Indeed, just by adjusting the stoichiometry of the employed carbenoid by using either 1.2 or 2.8 equivalents, the authors were able to selectively obtain chloro(trifluoromethyl)- (**96**) or chloromethyl(trifluoromethyl)aziridine derivatives (**97**), respectively.<sup>36</sup> A wide scope and full chemocontrol was observed by using  $\text{LiCH}_2\text{Cl}$  or  $\text{LiCH}_2\text{F}$  as the homologating agent, prepared *via* lithium-halogen exchange starting from  $\text{ICH}_2\text{Cl}$  or  $\text{ICH}_2\text{F}$  and  $\text{MeLi-LiBr}$  (Scheme 20 – path a).<sup>37</sup> Later on, the same group, in collaboration with Luisi and co-workers, described the preparation of rare  $\alpha$ -fluoroaziridines (**100**) by using the unknown  $\text{LiCHF}_2$  as the homologating agent. In this case, it was prepared *via* lithium-proton exchange (deprotonation) in the presence of the lithium amide base  $\text{LiN}(\text{i-Pr})\text{Cy}$  and  $\text{ICH}_2\text{F}$ . After the homologation of the imine derivatives (**98**) with  $\text{LiCHF}_2$ , a series of highly functionalized  $\beta$ -fluoroiodoamines (**99**) were isolated, which were subjected to deprotonation with  $\text{NaH}$  and after ring closure the desired  $\alpha$ -fluoroaziridines (**100**) were achieved (Scheme 20 – path b). Only in the case of **102**, the direct formation of the aziridine ring was observed (Scheme 20 – path c).<sup>38</sup>

In 2023, Aggarwal and co-workers described a two-step one-pot preparation of spirocyclic aziridines containing a cyclobutane motif. In the initial step, a bicyclo[1.1.0]butyl sulfoxide (**104**) is lithiated and added to a suitable imine (**103**).

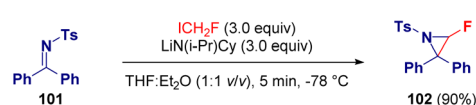
#### a) Mono- and bishomologated trifluoromethylaziridines



#### b) $\alpha$ -Fluoroaziridines: base-mediated ring closure

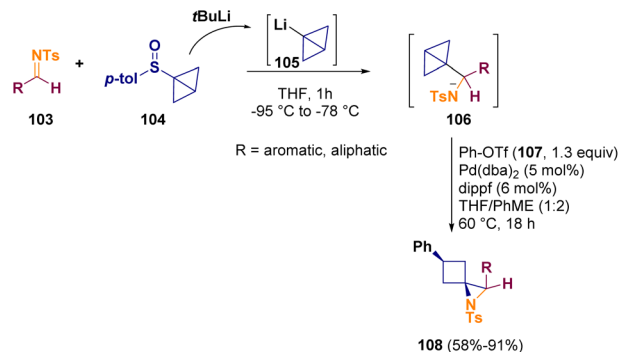


#### c) $\alpha$ -Fluoroaziridines: direct homologation-ring closure



**Scheme 20** Aziridine preparation *via* lithium carbenoids homologations.





**Scheme 21** Preparation of spirocyclic aziridines containing a cyclobutane motif.

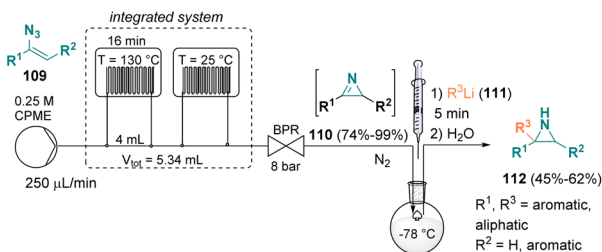
Afterward, the resulting intermediate (**106**) is cross-coupled with an aryl triflate (**107**) through a C–C  $\sigma$ -bond alkoxy- or aminopalladation, resulting in the related aziridine (**108**) formation (Scheme 21).<sup>39</sup>

### 2.3 Miscellaneous intramolecular aziridinations

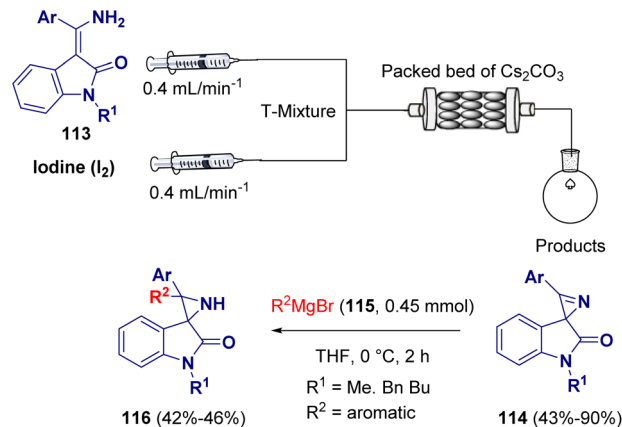
In 2021, Luisi *et al.* documented a sustainable mixed flow-batch approach for preparing functionalized NH-aziridines (**112**) from vinyl azides (**109**). The first part of the procedure was conducted under continuous flow conditions using CPME (cyclopentyl methyl ether) as the green solvent for obtaining a variety of 2H-azirines (**110**). Afterwards, the 2H-azirine (**110**) solution from the microfluidic system was collected in a round bottom flask, cooled to  $-78$  °C and reacted with various lithiated species (*e.g.*, phenyllithium, hexyllithium, *n*-butyllithium, and *i*-butyllithium, **111**), affording the desired NH-aziridines (**112**) (Scheme 22).<sup>40</sup>

Gnanaprakasam *et al.* described a mixed continuous flow/batch approach for the preparation of spiro-aziridines (**116**). In the first step of the reaction, a variety of spirooxindole 2H-azirines (**114**) were synthesized *via* intramolecular oxidative cyclization of 3-(amino(phenyl)methylene)-indolin-2-one derivatives (**113**) in the presence of  $I_2$  and  $Cs_2CO_3$ . The so-prepared spirooxindole 2H-azirines (**114**) were transformed into spiro-aziridine derivatives (**116**) *via* the addition of Grignard reagents (**115**) (Scheme 23).<sup>41</sup>

In 2022, Uchiyama *et al.* reported the aziridination of L-Val (**117**) by using the non-heme iron enzyme Fe(II)/

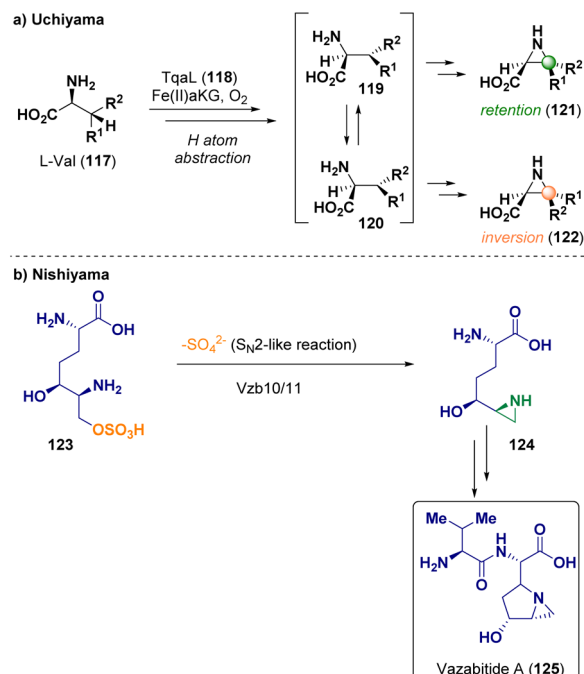


**Scheme 22** Mixed flow-batch approach for preparing functionalized NH-aziridines.



**Scheme 23** Mixed continuous flow/batch approach for preparing aziridines.

$\alpha$ -ketoglutarate-dependent oxygenase (**118**, TqaL) as catalyst, *via* cyclization proceeding through  $\beta$ -hydrogen abstraction (Scheme 24 – path a). This pathway proceeds through an unusual, diverse stereochemical route implying both retention (**121**) and inversion (**122**) of the C3(C $\beta$ ) stereocenter.<sup>42</sup> Nishiyama *et al.* described the biosynthesis of the aziridine derivative vazabotide A (**125**) catalyzed by Vzb10/11 *via* sulfate elimination to give aziridine **124** (Scheme 24 – path b). Vazabotide A (**125**) has a similar structure to azinomycin B, which shows antitumoral activity by alkylating the DNA *via* aziridine ring opening. Through structural analysis, the authors were able to elucidate the biosynthetic reaction mechanism.<sup>43</sup>



**Scheme 24** Aziridination *via* biocatalysis.



With regard to copper-catalyzed aziridine formation, Oestreich *et al.* reported in 2023 the preparation of *C*-silylated unprotected aziridines (**130**) via an enantioselective copper-catalyzed (**127**) addition of a silicon nucleophile (**129**) to 3-substituted 2*H*-azirines (**126**). They employed an Si-B reagent<sup>44</sup> and in particular, a silyl boronic ester (**129**) as a silicon pronucleophile (Scheme 25).<sup>45</sup>

### 3. Reactions of aziridines

#### 3.1 Cycloadditions

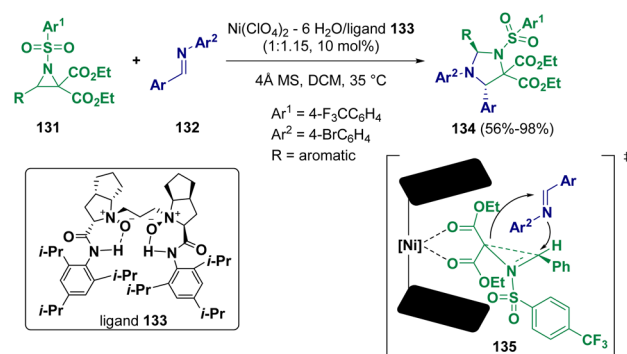
Aziridine derivatives are very important substrates and due to their high reactivity, they are largely employed in cycloaddition reactions<sup>46</sup> for the preparation of heterocycles and molecules that are important from a biological point of view.<sup>47</sup> Different methodologies have been applied and in recent years, more sustainable conditions have been reported for the preparation of such interesting derivatives.<sup>48</sup>

Several chiral *trans*-substituted imidazolidines (**134**) were synthesized by Feng and co-workers *via* the enantioselective reaction of donor-acceptor aziridines (**131**) with *N*-aryl protected imines (**132**) using Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O/*N,N'*-dioxide (**133**) as the catalytic system (Scheme 26).<sup>49</sup> The transformation appears to proceed through transition states such as **135**, where the ring formation starts with the attack from the imine from the *si*-face as the *re*-face is blocked by the *N*-arylsulfonyl moiety. Ring closure occurs subsequently by the attack on the bond that is broken, forming a bond with the carbon bearing the aryl group.

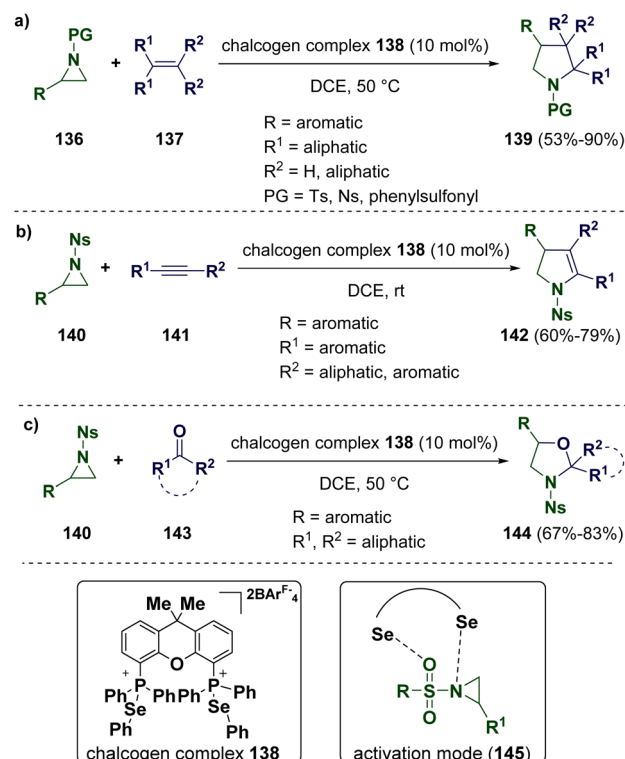
Usually, the activation of aziridines requires the employment of either a strong Lewis acid or transition metals. Recently, Wang and co-workers described a cycloaddition reaction of a weakly bonded aziridine-selenide complex with non-activated alkenes (**137**) by using phosphonium selenide-based chalcogen bonding catalysts (**138**) (Scheme 27 – path a). This study was supported by computational calculation and NMR, demonstrating that an activation mode (**145**) involving the cooperative Se–O and Se–N interactions is involved. The scope of the methodology was extended to alkynes (**141**) (Scheme 27 – path b) and ketones (**143**) (Scheme 27 – path c).<sup>50</sup>

#### 3.2 Ring enlargements

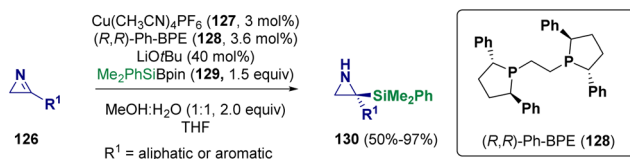
Ring-size manipulation has emerged as a powerful strategy to convert readily available cyclic structures into ring-expanded or ring-contracted compounds, which are more difficult to syn-



**Scheme 26** Enantioselective [3 + 2] cycloaddition of aziridines with *N*-aryl protected imines.



**Scheme 27** Cycloaddition of weakly bonded aziridine-selenide complexes with non-activated alkenes (a), alkynes (b), and ketones (c).



**Scheme 25** Preparation of *C*-silylated unprotected aziridines *via* an enantioselective copper-catalyzed addition.

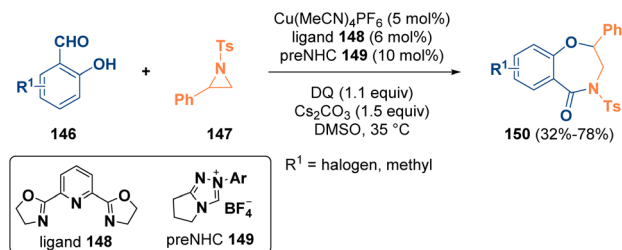
thesize. Many methodologies have been described for the preparation of interesting heterocycles starting from aziridines.<sup>51</sup>

Ye *et al.* reported in 2020 the synthesis of 4-benzoxazepinones (**150**) *via* a *N*-heterocyclic carbene/copper co-catalyzed reaction of salicylic aldehydes (**146**) with aziridines (**147**). The applied strategy allowed the authors to obtain compounds of this class, which are also interesting from a pharmaceutical viewpoint, in good yield and with full regioselectivity (Scheme 28).<sup>52</sup>

The spirooxindole-featuring azacycles have gained interest in the fields of synthetic as well as medicinal chemistry due to



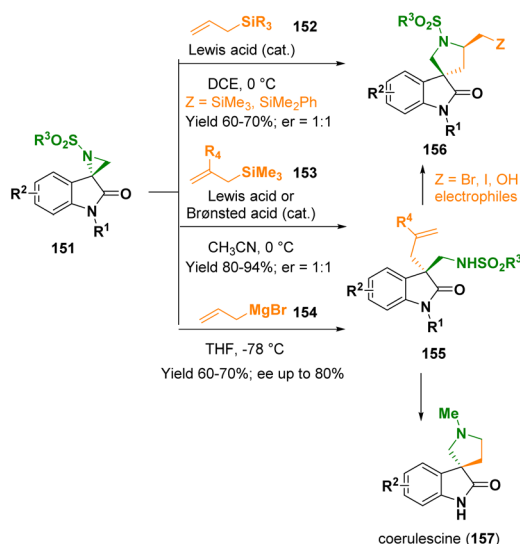




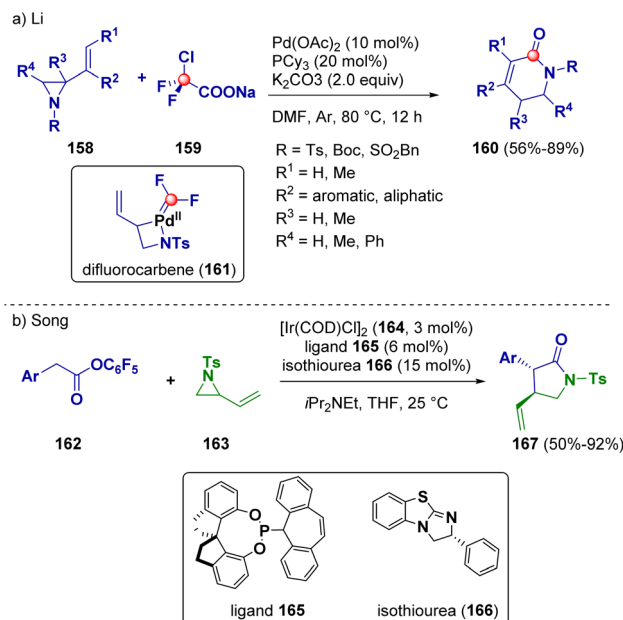
Scheme 28 Synthesis of 4-benzoxazepinones.

their peculiar three-dimensional architecture and interesting biological profiles. In 2022, Hajra and co-workers documented the Brønsted acid- and/or Lewis acid-catalyzed selective C3-allylation of spiro-aziridine oxindoles (**151**) with allyl silanes (**152** and **153**) or allyl Grignard reagents (**154**) to access 3-allyl-3-aminomethyl oxindoles (**155**) and 5-silyl methyl spiro[pyrrolidine-3,3'-oxindoles] (**156**), respectively (Scheme 29).<sup>53</sup> When chiral spiroaziridines were used, the methodology did not show any stereoselectivity. In contrast, the catalyst-free reaction of nonracemic spiroaziridines with allyl-Grignard reagents provided 3-allyl-3-aminomethyl oxindoles (**155**) with good stereoselectivity (ee up to 80%). The pathway was applied for preparing coerulescine (**157**) and various 5'-substituted spiro[pyrrolidine-3,3'-oxindoles] (**156**).

A ring enlargement pathway was described as a useful method for the preparation of  $\beta$ -lactams (**160**) by Li and co-workers. They reported a palladium-catalyzed ring expansion reaction of vinyl aziridines (**158**) with commercially available sodium 2-chloro-2,2-difluoroacetate ( $\text{ClCF}_2\text{COONa}$ , **159**), which serves as the carbonyl source of a difluorocarbene precursor. The authors reported a difluorocarbene-involved (**161**) reaction of  $\pi$ -allyl Pd(II) complexes (Scheme 30 – path a).<sup>54</sup>



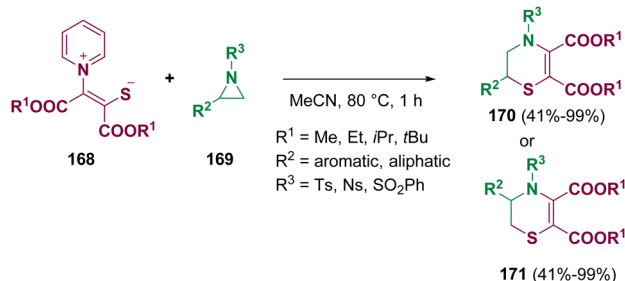
Scheme 29 Selective C3-allylation of spiro-aziridine oxindoles with allyl silanes and allyl Grignard reagents.

Scheme 30 Ring enlargement pathways for preparing  $\beta$ - and  $\gamma$ -lactams.

In 2023, Song *et al.* synthesized chiral  $\gamma$ -lactams (**167**) through an isothiourea (**166**, ITU)/iridium (**164**) co-catalyzed reaction of vinyl aziridines (**163**) with pentafluorophenyl esters (**162**). This methodology allowed the achievement of several optically active compounds in good yields and with high asymmetric induction (up to 98% ee) (Scheme 30 – path b).<sup>55</sup>

Pyridinium 1,4-zwitterionic thiolates (**168**) were employed by Chen and co-workers for the regioselective and stereo-specific ring enlargement of aziridines (**169**). 3,4-Dihydro-2H-1,4-thiazines (**170** and **171**) were prepared *via* a domino  $\text{S}_{\text{N}}2$  ring-opening/*N*-Michael addition cyclization/retro-Michael addition/pyridine extrusion procedure under mild conditions without metal mediation or the need for a strong base (Scheme 31).<sup>108</sup>

Unprotected guanidine derivatives (**176** and **177**) were prepared *via* ring expansion of 2-substituted aziridines (**172**) and *N*-tosyl cyanamides (**173**) in a domino regioselective ring-opening/*5-exo-dig* cyclization. This metal-free methodology



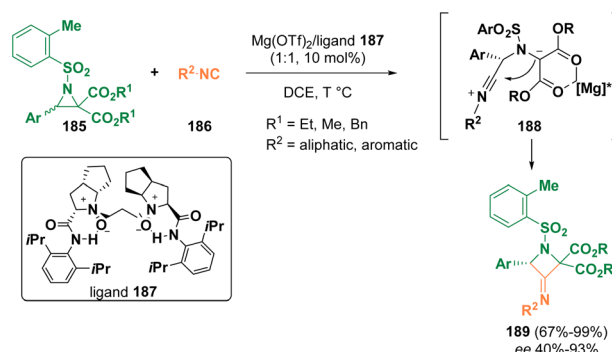
Scheme 31 Ring enlargement of aziridines with pyridinium 1,4-zwitterionic thiolates.



works well even with weaker bases such as cesium fluoride (CsF). Furthermore, the so-obtained compounds could be subjected to hydrolysis in order to obtain highly biologically interesting urea analogs (**178** and **179**) (Scheme 32).<sup>56</sup>

Schomaker *et al.* reported a [3 + 3] ring expansion of bicyclic aziridines (**180**) and rhodium-bound vinyl carbenes to synthesize a variety of dehydropiperidines (**184**). Supported by mechanistic studies, the authors supposed that the pathway proceeds *via* the formation of a vinyl aziridinium ylide (**183**) which undergoes a pseudo-[1,4]-sigmatropic rearrangement to yield heterocyclic products (**184**) with net retention of the configuration at the new CC bond (Scheme 33).<sup>57</sup>

In 2022, Feng *et al.* documented the ring enlargement of racemic donor-acceptor (D-A) aziridines (**185**) with isocyanides (**186**) catalyzed by a chiral *N,N*-dioxide (**187**)/Mg(II) complex, proceeding through ring opening *via* intermediates, such as **188**, to yield enantioenriched *exo*-imido azetidines (**189**) (Scheme 34).<sup>109</sup>



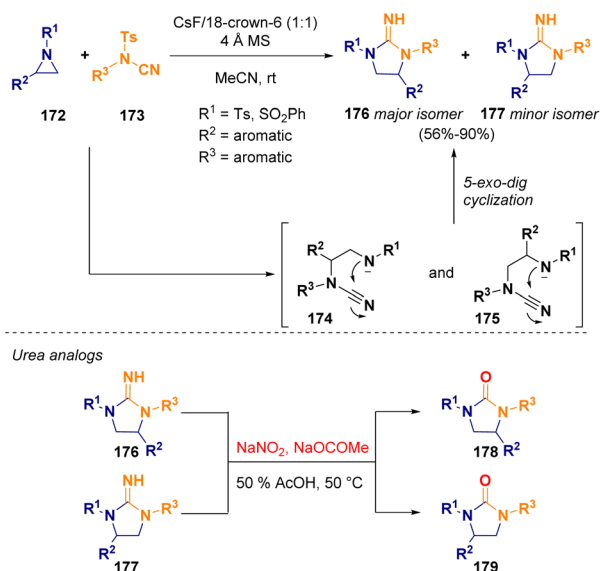
Scheme 34 Exo-imido azetidine preparation.

The preparation of 2-(2-oxoalkylidene)-1,3-oxazolidine derivatives (**193**) was described by Xu and co-workers in 2021 *via* the catalyst-free electrophilic ring expansion of *N*-unprotected aziridines (**191**) and the ketene C=O double bond of  $\alpha$ -oxoketenes (**192**).<sup>58</sup> Products **192** were prepared *in situ* through microwave-assisted Wolff rearrangement of 2-diazo-1,3-diketones (**190**) (Scheme 35). Products **193** were obtained with an *E* configuration *via* an S<sub>N</sub>1 mechanism.

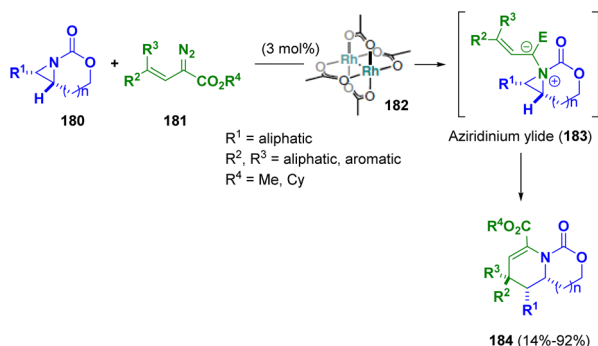
Alkoxy-carbonylketenes (**196**), generated from alkyl 2-diazo-3-oxoalkanoates (**194**), were employed as substrates for the electrophilic ring expansion of aziridines (**195**) in order to obtain alkyl 2-(oxazolin-2-yl)alkanoates (**197**) under microwave irradiation.<sup>59</sup> The corresponding final compounds (**197**) were obtained in good yields; in all cases, the formation of 1:1 mixtures of diastereomeric products was observed (Scheme 36).

In 2022, Arnold and co-workers documented the biocatalytic enantioselective one-carbon ring expansion of aziridines (**198**) to yield azetidines (**202**) *via* [1,2]-Stevens rearrangement by using “carbene transferase” as enzymes (Scheme 37). The employment of biocatalysts was crucial for controlling the reactivity of the formed aziridinium ylide intermediates (**201**), which could be not controlled by using other catalyst classes.<sup>60</sup>

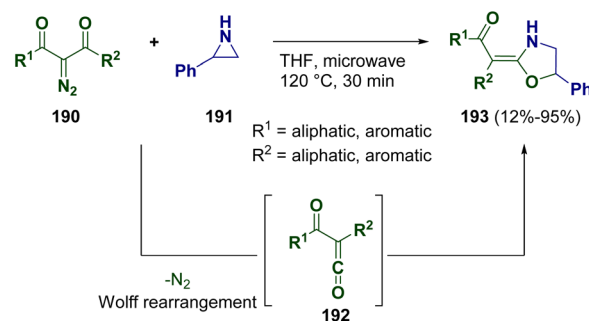
A typical ring enlargement reaction concerning aziridines is the one with CO<sub>2</sub> (**204**).<sup>61</sup> Indeed, different methodologies were described by using diverse catalysts.<sup>62</sup> Among them, Caselli and co-workers reported the preparation of 5-substi-



Scheme 32 Aziridine ring enlargements for preparing unprotected guanidine derivatives.

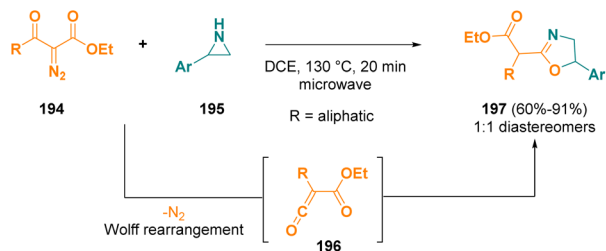


Scheme 33 Preparation of dehydropiperidines.

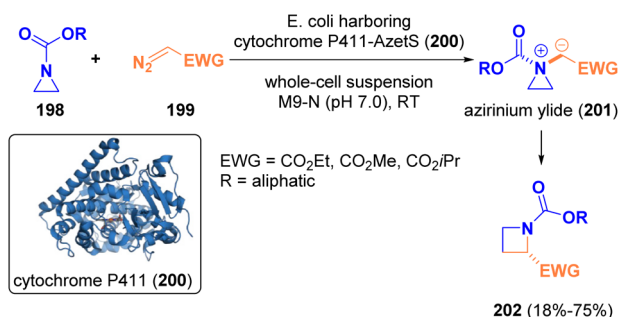


Scheme 35 Catalyst-free ring expansion of *N*-unprotected aziridines for preparing 2-(2-oxoalkylidene)-1,3-oxazolidine derivatives.





**Scheme 36** Microwave-assisted ring expansion of aziridines to obtain alkyl 2-(oxazolin-2-yl)alkanoates.

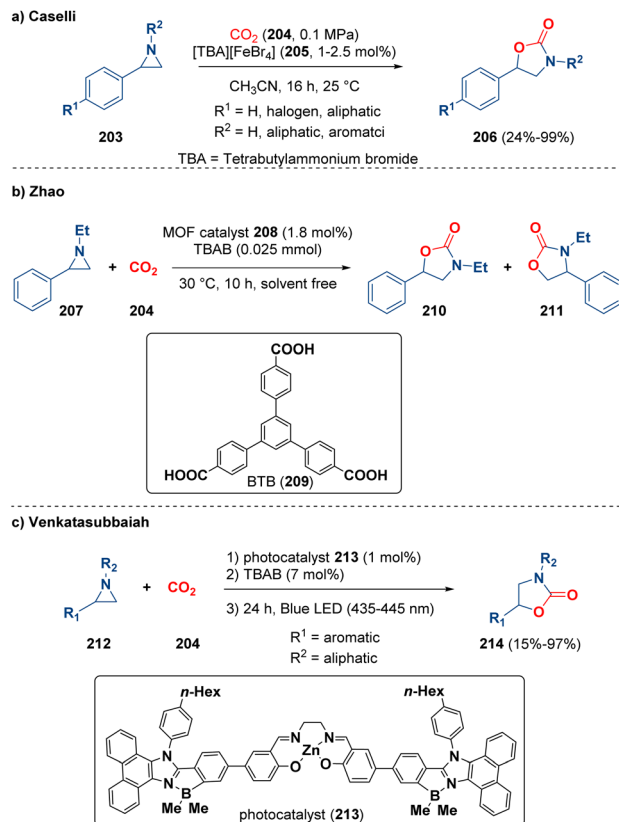


**Scheme 37** Azetidines from aziridines via ring enlargement.

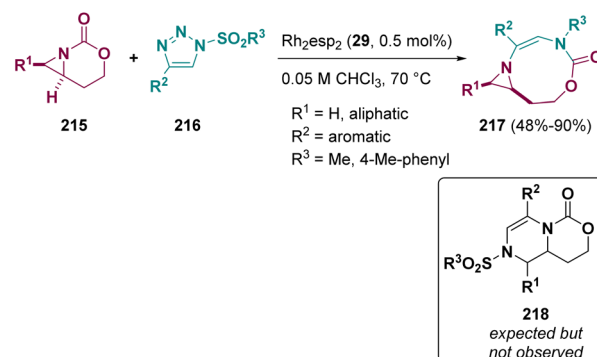
tuted 1,3-oxazolidin-2-ones (**206**) catalysed by ammonium ferrates (**205**) (Scheme 38 – path a). Theoretical calculations clarified that the reaction mechanism involves just one ferrate molecule and the rate determining step is the 1,3-oxazolidin-2-one ring closure.<sup>63</sup> Zhao and co-workers documented the reaction of CO<sub>2</sub> (**204**) and aziridines (**207**) catalyzed by MOFs (metal-organic frameworks). In particular, they prepared three-dimensional cluster-based MOF {(NH<sub>2</sub>Me<sub>2</sub>)[Co<sub>3</sub>(μ<sub>3</sub>-OH)(BTB)<sub>2</sub>(H<sub>2</sub>O)]·9H<sub>2</sub>O·5DMF}<sub>n</sub> (**208**) with large pores assembled by BTB ligands (**209**, BTB = 1,3,5-tri(4-carboxyphenyl)benzene) and [Co<sub>3</sub>] clusters (Scheme 38 – path b). With this methodology they achieved oxazolidinones (**210** and **211**) in up to 99% yield.<sup>64</sup> Recently, Venkatasubbaiah *et al.* described the solvent-free reaction of aziridines (**212**) and carbon dioxide (**204**), catalyzed by a zinc-salen having a B–N coordinated phenanthroimidazole motif (**213**) as a photocatalyst, for the synthesis of oxazolidinones (**214**) (Scheme 38 – path c).<sup>65</sup>

Schomaker *et al.* described a Rh catalyzed ring expansion of aziridines (**215**) and *N*-sulfonyl-1,2,3-triazoles (**216**). Instead of the expected dehydropiperazines (**218**), the authors observed the formation of [3,9]-bicyclic aziridines (**217**), see Scheme 39. The structure was confirmed by computational calculation and X-ray studies.<sup>66</sup>

A one-pot reaction for preparing benzoxepino-fused pyrrole derivatives (**221**) starting from substituted alkynyl aziridines (**219**) was reported by Sridhar and co-workers. In this metal-free procedure, two new CC bonds were established *via* the initial cleavage of the CC bond of the aziridine ring by the *in situ* generated azomethine ylides (**220**) (Scheme 40).<sup>67</sup>



**Scheme 38** Ring enlargement by the reaction of CO<sub>2</sub> and aziridines for preparing oxazolidinones.



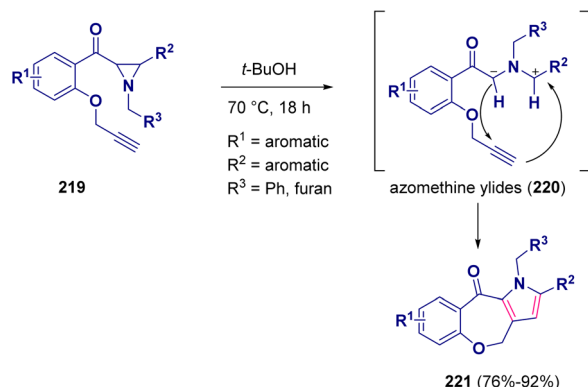
**Scheme 39** Rh catalyzed ring expansion of aziridines and *N*-sulfonyl-1,2,3-triazoles.

### 3.3 Ring openings

Ring opening reactions are amongst the most important synthetic pathways of aziridines<sup>68</sup> as they can be transformed into many interesting compounds such as amino acids and natural products<sup>69</sup> that are very often useful for pharmacological applications.

Various *N*-(2,2-diphenylvinyl)-β-oxoamides (**225**) were prepared by Xu and co-workers, *via* a microwave-assisted catalyst-free methodology, starting from 2-diazo-1,3-dicarbonyl com-



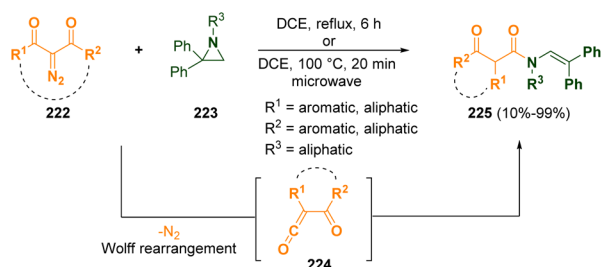
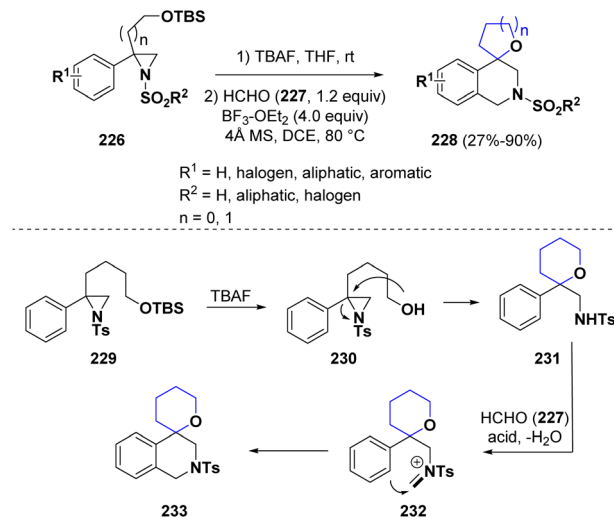
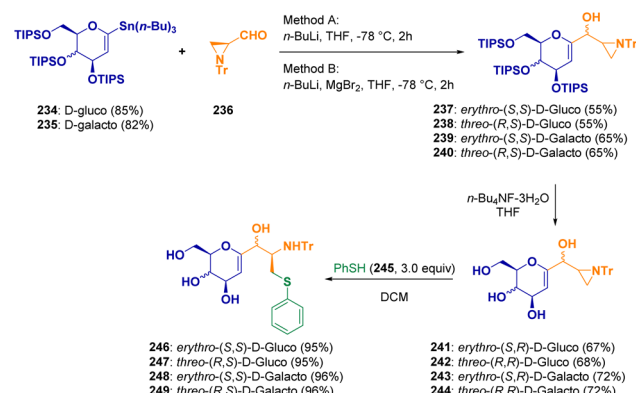


Scheme 40 Preparation of benzoxepino-fused pyrrole derivatives.

pounds (222) through an electrophilic ring opening of  $N$ -alkyl-2,2-diphenylaziridines (223).<sup>70</sup>  $\alpha$ -Oxoketenes (224), which then reacted with aziridines 223, were generated from 2-diazo-1,3-dicarbonyl derivatives (222) *via* a Wolff rearrangement (Scheme 41). The so-obtained  $N$ -(2,2-diphenylvinyl)- $\beta$ -oxoamides (225) are useful molecules as synthons for the preparation of  $\beta$ -lactams but also common structural motifs in biologically active compounds.

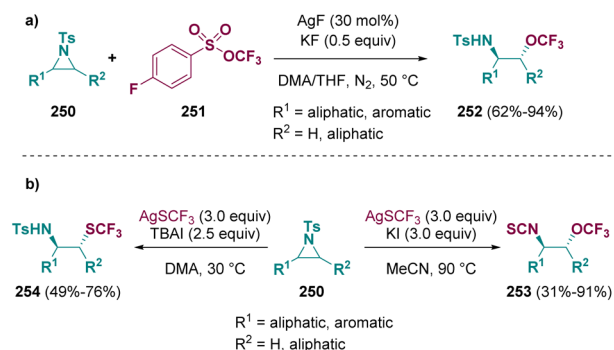
Zhu and co-workers reported the synthesis of 4-spiroannulated tetrahydroisoquinolines (228) *via* a multistep procedure involving a sequential ring opening of aziridines 226 and the subsequent Pictet–Spengler reaction.<sup>71</sup> The reaction proceeds under mild conditions with a broad scope. Considering the reaction mechanism, the TBS group is eliminated from derivative 229 by treatment with TBAF and the so-obtained free OH group (230) promoted an internal aziridine ring opening. The newly formed intermediate 231 reacted with formaldehyde (227) under acidic conditions to generate the iminium ion 232, which undergoes electrophilic cyclization to afford the final product 233 (Scheme 42).

C-Glycosyl-aminoethyl sulfide derivatives (246–249) were synthesized by Zawisza *et al.* *via* a reaction between tributyltin derivatives of glycals (234–235) and aziridinecarbaldehyde (236) and the regioselective ring opening of chiral aziridines (241–244) with thiophenol (245) (Scheme 43).<sup>72</sup> Glycoconjugates are very interesting derivatives due to their participation in many important biochemical processes.

Scheme 41  $N$ -(2,2-Diphenylvinyl)- $\beta$ -oxoamide generation from 2-diazo-1,3-dicarbonyl compounds and  $N$ -alkyl-2,2-diphenylaziridines.Scheme 42 Synthesis of 4-spiroannulated tetrahydroisoquinolines *via* a sequential ring opening of aziridines and the Pictet–Spengler reaction.

Scheme 43 Preparation of C-glycosyl-aminoethyl sulfide derivatives.

In 2022, Tang *et al.* described a methodology for the preparation of  $\beta$ -trifluoromethoxylated amines (252). This fascinating class of compounds was achieved *via* a silver-catalyzed ring opening of tosyl-aziridines (250) in the presence of trifluoromethyl arylsulfonate (251) (Scheme 44 – path a). A good



Scheme 44 Silver-catalyzed aziridine ring opening.

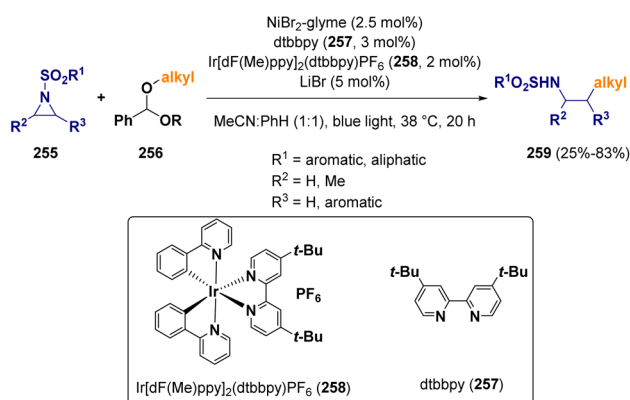




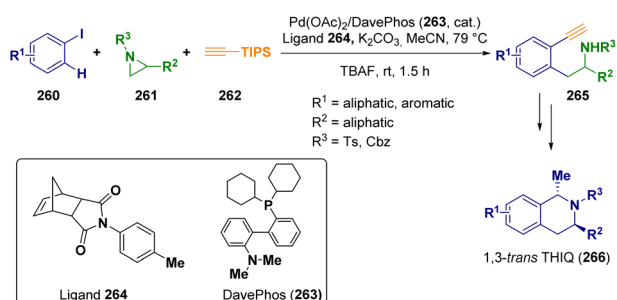
chemo- and regioselectivity was observed under mild conditions.<sup>110</sup> The same group accessed a series of  $\beta$ -trifluoromethylthiolated isothiocyanates (**253**) and amines (**254**) by using  $\text{AgSCF}_3$  and different iodine sources (TBAI, KI) (Scheme 44 – path b).<sup>73</sup>

In 2022, Doyle and co-workers reported an aziridine ring opening procedure with methyl/ $1^\circ/2^\circ$  aliphatic alcohols activated as benzaldehyde dialkyl acetals (**256**) via a Ni/photoredox cross-coupling.<sup>74</sup> The activation of the benzaldehyde dialkyl acetal (**256**) is carried out through hydrogen atom abstraction and  $\beta$ -scission via a bromine radical. The authors demonstrated that aziridine activation proceeds through oxidative addition to Ni(I) rather than a Ni(II)azametallacycle, as reported previously (Scheme 45).<sup>75</sup>

Palladium is the catalyst employed by Zhou and co-workers in a three-component Catellani reaction<sup>76</sup> starting from aryl iodides (**260**), typically for Catellani reactions with substituents at the *ortho*-position, aziridines (**261**), and (triisopropylsilyl) acetylene (**262**) as the building blocks. This first step of the reaction was useful for the preparation of the 2'-alkynylaryl-2-ethylamines (**265**), which were further reacted via a multistep procedure for preparing 1,3-*trans*-disubstituted tetrahydroisoquinolines **266** (THIQ), which is important from a biological point of view (Scheme 46).<sup>77</sup>



**Scheme 45** Aziridines ring opening via a Ni/photoredox cross-coupling.



**Scheme 46** Synthesis of 1,3-*trans*-disubstituted tetrahydroisoquinolines.

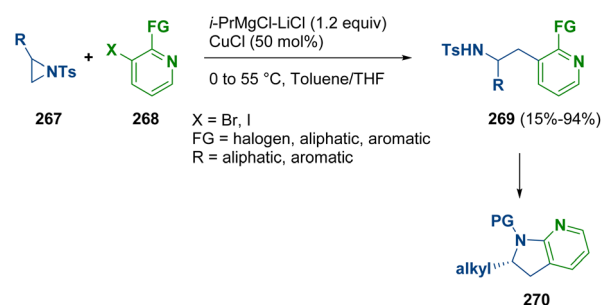
Han *et al.* instead documented the copper-catalyzed regioselective and stereospecific ring opening of aziridines with pyridinyl Grignard nucleophiles. With this methodology, the preparation of  $\beta$ -pyridylethylamines (**269**) was achieved, which are potential scaffolds for the synthesis of biologically active molecules. Challenging chiral dihydroazaindoles (**270**) were prepared via a mild one-pot aziridine opening followed by nucleophilic cyclization (Scheme 47).<sup>78</sup>

Hayla and co-workers described a catalyst-free regioselective ring-opening of aziridines (**274**), including spiroaziridine oxindoles (**271**), with commercially available 50% aqueous hydrogen peroxide (**272**). The reaction, which can be carried out without any additional organic solvents and reagents, gives rise to secondary benzylic  $\beta$ -hydroperoxy amines (**275**) and tertiary 3-hydroperoxy oxindoles (**273**) (Scheme 48).<sup>79</sup> The importance of this methodology relies on the utility of organic hydroperoxides, which are prevalent motifs in various biosynthetic intermediates, natural products, and bioactive compounds.<sup>80</sup>

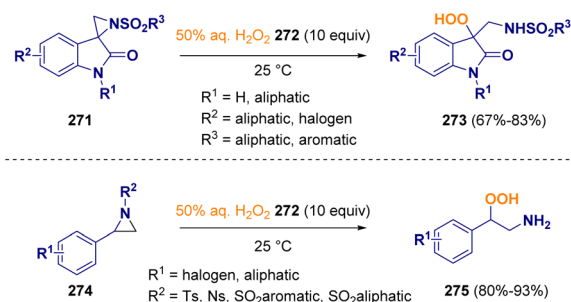
Hou *et al.* reported the ring opening of diastereomerically pure 2-oxazolidinone-fused aziridines (**276**) via fluoride anions. This methodology allows the preparation of optically active, primary, secondary, and tertiary organofluorides (**277**), which are precursors of interesting compounds such as fluorinated amino acids (Scheme 49).<sup>81</sup>

### 3.4 Catalysis

Most drugs are small molecules featuring heterocycles; therefore, they are ubiquitous in medicinal chemistry. Among them,

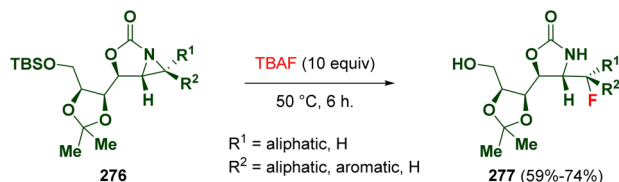


**Scheme 47** Aziridine ring opening with pyridyl Grignard nucleophiles.



**Scheme 48** Aziridine ring opening by using 50% aqueous  $\text{H}_2\text{O}_2$ .



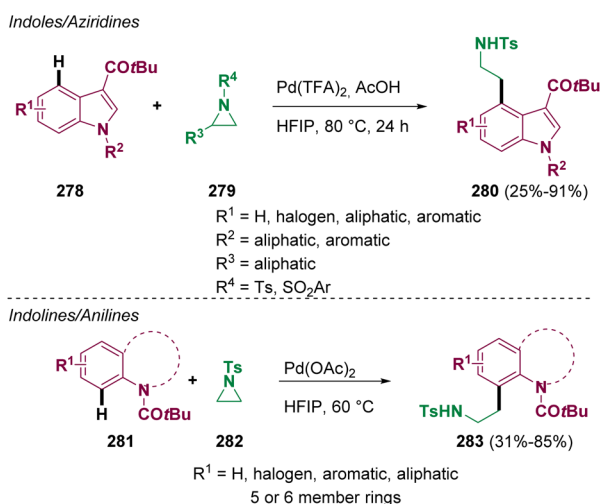


**Scheme 49** Ring opening of 2-oxazolidinone-fused aziridines via a fluoride anion.

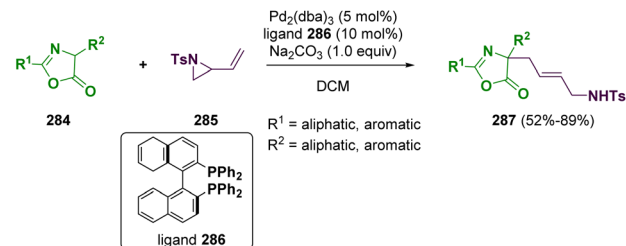
indole derivatives are common scaffolds used for the design of plausible “drug-like” compounds. For these reasons, scientists around the world have put in efforts for the development of novel methodologies that can be useful for preparing and modifying these heterocyclic compounds. Koley and co-workers reported in 2022 a palladium catalyzed cross-coupling of aliphatic aziridines (279 and 282) with indoles (278), indolines, tetrahydroquinolines, and anilines (281) for preparing  $\beta$ -arylethylamine derivatives (280 and 283) with a wide scope (Scheme 50).<sup>82</sup> These transformations proceed *via* CH activation.

Another important aspect is the preparation of amino acid derivatives from aziridine substrates. In recent years, the synthesis of functional quaternary amino acid derivatives has attracted considerable attention since they are key components in many active pharmaceutical ingredients. Among them, in 2022, Gao and co-workers reported the preparation of functionalized precursors of quaternary allylic amino acids (287) *via* a palladium-catalyzed allylic alkylation reaction of azalactones (284) with vinyl aziridine (285) (Scheme 51).<sup>83</sup>

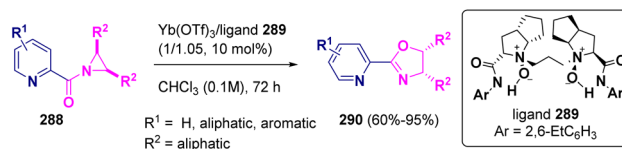
The preparation of chiral pyridine-oxazolines (290) starting from (*meso*)-*N*-(2-picolinoyl)-aziridines (288) catalyzed by a chiral ytterbium(III)-*N,N'*-dioxide (289) complex was reported by Liu and Feng in 2022. The reaction proceeds *via* an asymmetric Heine reaction, giving excellent yields with very good enantioselectivities (Scheme 52).<sup>84</sup>



**Scheme 50** Preparation of  $\beta$ -arylethylamine derivatives.

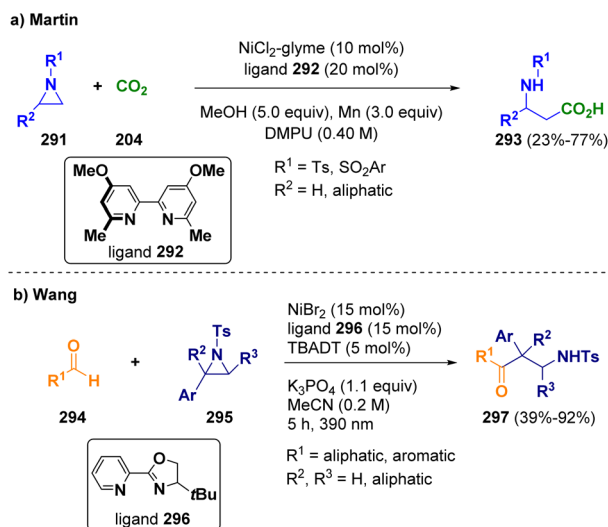


**Scheme 51** Preparation of functionalized quaternary allylic amino acid precursors.



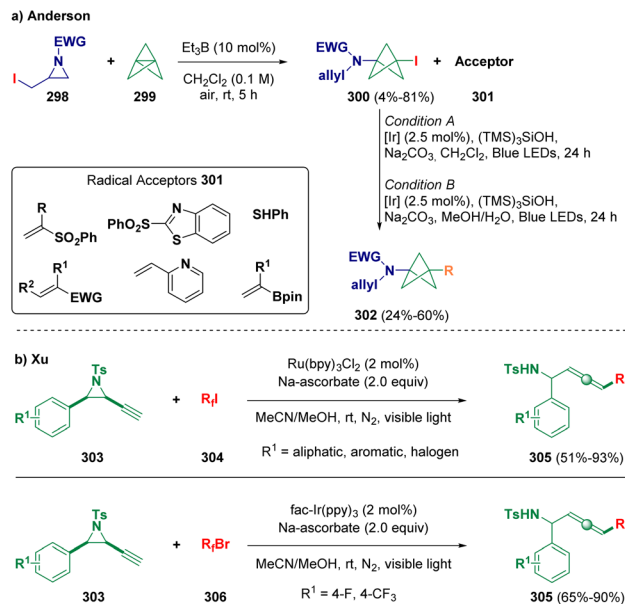
**Scheme 52** Ytterbium catalyzed synthesis of chiral pyridine-oxazolines.

Martin and co-workers reported a nickel-catalyzed reductive carboxylation of *N*-substituted aziridines (291) with CO<sub>2</sub> (204) at atmospheric pressure for accessing  $\beta$ -amino acids (293) (Scheme 53 – path a). The procedure works under mild conditions and exhibits high chemo- and regioselectivity.<sup>85</sup> Wang *et al.* applied a combined nickel/photoco-catalyzed hydrogen-atom-transfer in order to achieve the ring opening of *N*-tosyl styrenyl aziridines (295) with aldehydes (294). This method is a novel and atom-economical synthetic path towards a variety of  $\beta$ -amino ketones (297) with complete regiocontrol (Scheme 53 – path b). With this strategy, the difficult coupling between aldehydes and aziridines, which are both electrophilic species, can be facilitated.<sup>86</sup>



**Scheme 53** Nickel-catalyzed preparation of  $\beta$ -amino acids.





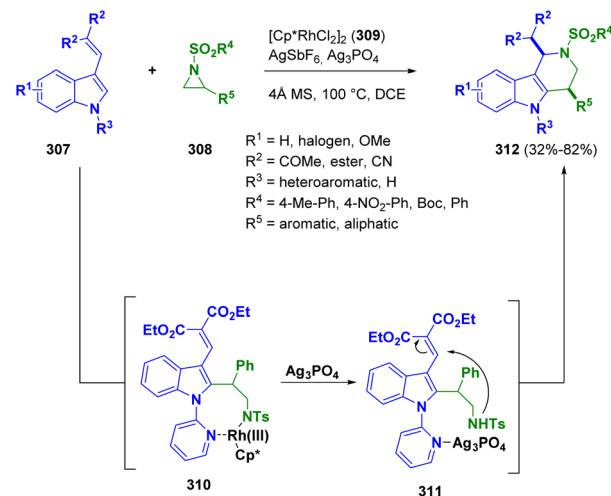
Scheme 54 Preparation of 1,3-disubstituted bicyclo[1.1.1]pentylamines.

Anderson and co-workers described the preparation of 1,3-disubstituted bicyclo[1.1.1]pentylamines (**302**, BCPAs) based on a radical functionalization strategy. In particular, sulfonamidyl radicals, obtained *via*  $\alpha$ -iodoaziridine (**298**) fragmentation, undergo initial addition with [1.1.1]propellane (**299**) to afford iodo-BCPAs (**300**). Afterwards, the so-formed CI bond is functionalized *via* a silyl-mediated Giese reaction (Scheme 54 – path a).<sup>87</sup> Xu *et al.* reported a radical addition/elimination strategy for preparing fluorinated allenes (**305**) starting from fluoroalkyl halides (**304** and **306**) and alkynyl aziridines (**303**) under visible-light irradiation (Scheme 54 – path b).<sup>88</sup>

Recently, the ring formation by the reaction of tosyl-aziridines (**308**) and indole derivatives (**307**) *via*  $[\text{Cp}^*\text{RhCl}_2]_2$  catalysis (**309**) was described by Zhu and co-workers. A series of *cis*-1,4-disubstituted tetrahydro- $\gamma$ -carbolines (**312**) was formed in high yields and excellent *cis*-diastereoselectivity under mild conditions. The authors postulated a stepwise mechanism, proceeding through the rhodacyclic intermediate **310**, which undergoes ring opening upon coordination of silver phosphate with nitrogen. The resulting intermediate **311** undergoes Michael addition to form a six-membered ring (Scheme 55).<sup>89</sup> According to the authors, only the formations of the *cis*-1,4-diastereomers was observed.

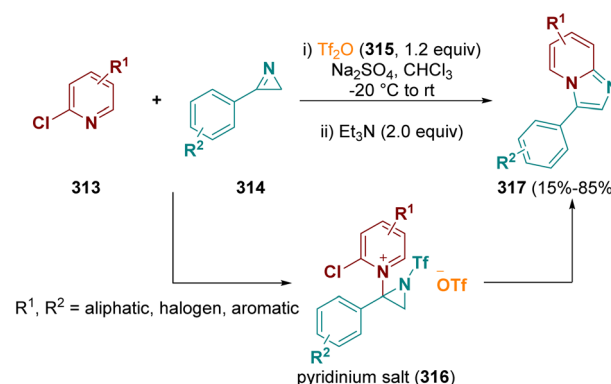
## 4. Aziridines as reaction intermediates and catalysts

Aziridines are very interesting reactions intermediates. Due to the ring strain, they are highly reactive and largely employed in multi-step reactions. Aziridines are useful for the preparation of fascinating organic compounds as well as for the synthesis of biologically active molecules.<sup>90</sup>

Scheme 55 Preparation of *cis*-1,4-disubstituted tetrahydro- $\gamma$ -carbolines from aziridines and 3-vinyl indoles substituted with EWGs.

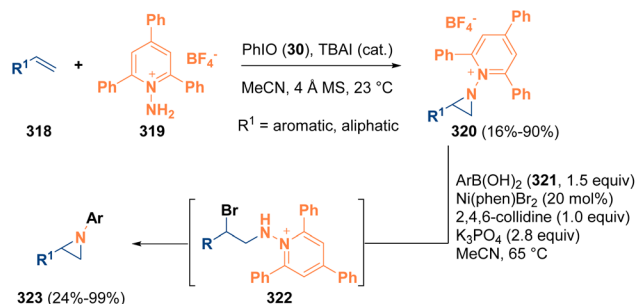
In 2021, Pelletier *et al.* documented the synthesis of imidazo[1,2-*a*]pyridines (**317**) by using 2-chloropyridines (**313**) and 2*H*-azirines (**314**) in the presence of triflic anhydride (**315**,  $\text{Trf}_2\text{O}$ ). An electrophilic 1-trifloyl-aziridin-2-yl triflate species is formed as the reaction intermediate which reacts *in situ* with the 2-halopyridines, forming transient pyridinium salts (**316**). These salts were treated in the same pot with triethylamine ( $\text{Et}_3\text{N}$ ), leading to the selective formation of the desired compounds (**317**) (Scheme 56).<sup>91</sup>

Another interesting example that highlights the use of aziridines as intermediates was reported in 2022 by Powers and co-workers. The authors described an olefin aziridination procedure by employing *N*-aminopyridinium reagents (**319**) as the activating group to afford *N*-pyridinium aziridines (**320**). The so-formed aziridines (**320**) then were subjected to a nickel-catalyzed C–N cross-coupling reaction with aryl boronic acids (**321**). The *N*-pyridinium aziridine intermediates (**320**) also participate in ring-opening chemistry with different nucleophiles to achieve 1,2-aminofunctionalization products. Mechanistic studies denote that the aziridine cross-coupling proceeds *via* a



Scheme 56 Aziridines used as intermediates.



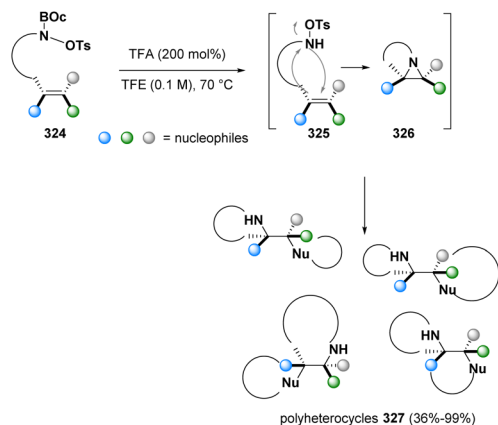


**Scheme 57** Aziridinations of alkenes and nickel-catalyzed cross-coupling.

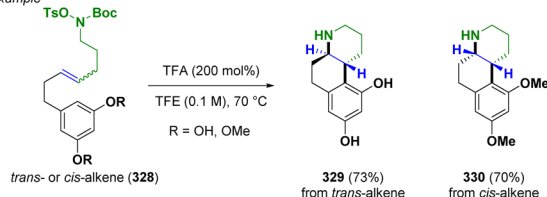
noncanonical mechanism involving initial aziridine opening (322), promoted by the bromide counterion of the nickel catalyst, and finally the formation of the aziridine moiety (323) by a ring-closing step (Scheme 57).<sup>92</sup>

In 2023, Bower and co-workers reported the preparation of stereochemically complex polyheterocyclic ring systems (327) *via* an aziridine intermediate (326). In particular, an intramolecular stereospecific aza-Prilezhaev aziridination occurs which is followed by a CN bond cleavage operated by a pendant nucleophile (Scheme 58). With this methodology, a variety of alkene *anti*-1,2-difunctionalizations (*i.e.*, diaminations, amino-oxygenations and amino-arylations) can be facilitated. The majority of the obtained structures are relevant in medicinal chemistry.<sup>93</sup>

Luisi *et al.* employed aziridines as chiral nucleophiles in the enantioselective synthesis of oxaspirohexane sulfonamide derivatives (338). In particular, (*S*)-*N*-*t*-butylsulfonyl-2-phenylaziridine (333) was prepared starting from (*S*)-phenyl-glycinol (332). The



An example



**Scheme 58** Preparation of stereochemically complex polyheterocycles.

lithiated intermediate 334 was trapped with 3-phenylcyclobutanone (331) to give a 90:10 *cis/trans* diastereomeric mixture of aziridino cyclobutanol (335 and 336). The *cis*-stereoisomer underwent Payne rearrangement under basic conditions, leading to the desired 1-azaspiro[2,3]hexane (338) (Scheme 59).<sup>94</sup>

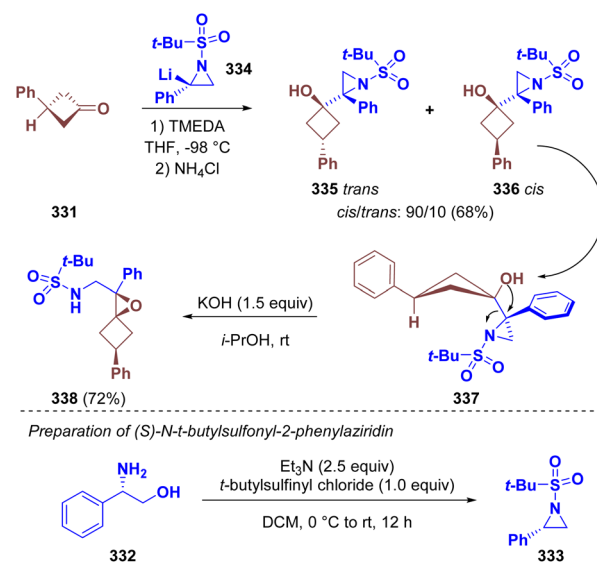
Aziridines were also reported to be useful catalysts.<sup>95</sup> Rachwalski and co-workers described an asymmetric Morita-Baylis-Hillman reaction of methyl vinyl ketone and methyl acrylate (339) with various aromatic aldehydes (340) using chiral aziridine-phosphines (341) as chiral catalysts (Scheme 60).<sup>96</sup>

## 5. Biological activities of aziridines

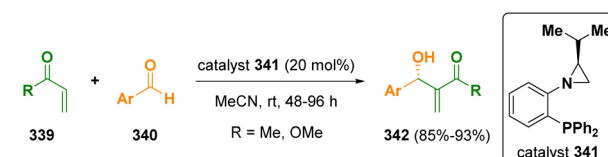
Aziridine derivatives possess different biological activities. Among them a large variety of compounds are active against various types of oncological diseases.<sup>97</sup> However, several molecules displayed inhibitory activity towards other biological targets such proving to be good glucocerebrosidase (GBA),<sup>98</sup> cysteine proteases,<sup>99</sup> tuberculosis,<sup>100</sup> microbial,<sup>101</sup> and *Leishmania*<sup>102</sup> inhibitors (Fig. 1).

### 5.1 Aziridines showing activity against GBA

Kuo and co-workers discovered a series of cyclophellitol aziridine derivatives as promising selective GBA inhibitors. Genetic defects in GBA determine Gaucher disease (GD) and also rep-



**Scheme 59** Synthesis of oxaspirohexane sulfonamide derivatives.



**Scheme 60** Chiral aziridines as chiral catalysts.





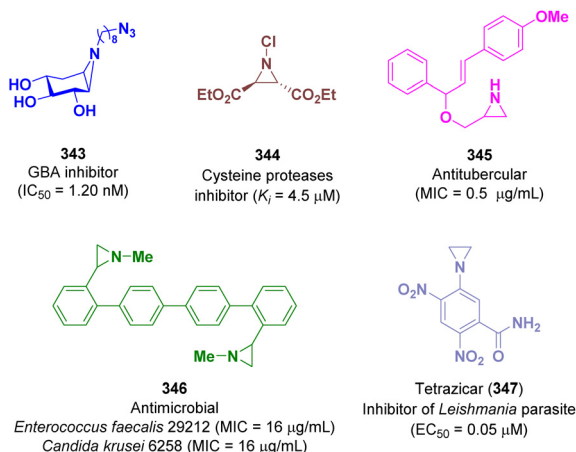


Fig. 1 Biological activity of aziridine derivatives.

represent a risk factor for developing Parkinson's disease. One of the most active compound of the series is derivative **343** with an IC<sub>50</sub> value of 1.20 nM on human GBA (Fig. 1).<sup>98</sup>

## 5.2 Aziridines showing activity against cysteine proteases

Schirmeister *et al.* reported a series of aziridine-2,3-dicarboxylate derivatives as potent irreversible inhibitors of cysteine proteases, which are involved in the life cycle of parasites that cause tropical disease such as malaria. The best activity was shown by compound **344** with a K<sub>i</sub> value of 4.5 μM (Fig. 1).<sup>99</sup>

## 5.3 Aziridines showing activity against tuberculosis

The *in vitro* antitubercular activity of aziridine derivatives against *Mycobacterium tuberculosis* was evaluated by Gandhimathi *et al.* in 2021. Promising activity was reported for derivative **345** with a minimum inhibitory concentration (MIC) value of 0.5 μg mL<sup>-1</sup> (Fig. 1).<sup>100</sup>

## 5.4 Aziridines showing antimicrobial activity

The antimicrobial activity of functionalized 2-arylaziridines was identified by Luisi and co-workers. The most interesting compound is derivative **346** which showed a selective antibacterial activity against *Enterococcus faecalis* 29212 (MIC = 16 μg mL<sup>-1</sup>) and an interesting antifungal action against *Candida krusei* 6258 (MIC = 16 μg mL<sup>-1</sup>) (Fig. 1).<sup>101a</sup>

## 5.5 Aziridines showing activity against Leishmania

Sharlow *et al.* described tretazicar (CB1954, 5-(aziridin-1-yl)-2,4-dinitrobenzamide, **347**) as a potent inhibitor of the *Leishmania* parasite. *In vivo* studies showed promising activity for curing cutaneous leishmaniasis, which is the most common form affecting humans (EC<sub>50</sub> = 0.05 μM in *L. major* cell-based amastigote) (Fig. 1).<sup>102</sup>

## 5.6 Aziridines showing activity against oncological targets

Aziridine derivatives are well-known for possessing anti-cancer activity. Great efforts over the years have made it possible to discover potent active molecules.

In 2021, Bulut and co-workers reported for the first time the synthesis of *N*-sugar substituted chiral aziridines *via* the Gabriel–Cromwell reaction. Among the newly prepared compounds were promising prodrug candidates for prostate (PC3) and cervical (HeLa) cancers. In particular, derivative **348** showed good activity with an IC<sub>50</sub> value of 23.55 μM for PC3 and 25.88 μM for HeLa (Fig. 2).<sup>103</sup>

Kalvins *et al.* documented a class of acyl derivatives of aziridine-2-carboxylic acid as weak to moderately active PDIA1 (protein disulfide isomerase) inhibitors. Derivative **349** showed good inhibitory activity with an IC<sub>50</sub> value of 26.0 μM. The *in vitro* cytotoxicity value toward a panel of cells was also evaluated and promising results were achieved (Fig. 2).<sup>104</sup>

In 2022, a series of trifluoromethyl-aziridine derivatives were reported as proteasome inhibitors, selective for the β5 subunit. The *in vitro* biological activity, both enzymatic inhibition and anti-proliferative profile against two leukemia cells lines, was evaluated and promising results were achieved. The best result was obtained for derivative **350** with an IC<sub>50</sub> value of 13.6 μM against the β5 subunit and 25.45 μM against drug-sensitive acute lymphocytic leukemia cells (CCRF-CEM) and 24.08 μM against a multidrug-resistant leukemia sub-cell line (CEM/ADR5000) (Fig. 2).<sup>105</sup>

Other anticancer aziridine bearing molecules were reported by Cheke *et al.* as inhibitors of the stem cell growth factor receptor often known as the c-KIT kinase domain. This is one of the 20 subfamilies of human receptor tyrosine kinases (RTKs) which is one of the main studied targets to fight cancer. The synthesized compounds were tested against the NCI-60 human cancer cell lines for a single-dose concentration. Derivative **351**, which was one of the most promising ones, was evaluated for a five-dose anticancer study showing an IC<sub>50</sub> value of 1.47 μM against different breast cancer cell lines (Fig. 2).<sup>106</sup>

Aziridines β-D-galactopyranoside derivatives were studied as anticancer agents by Calderón-Montaño and co-workers. The

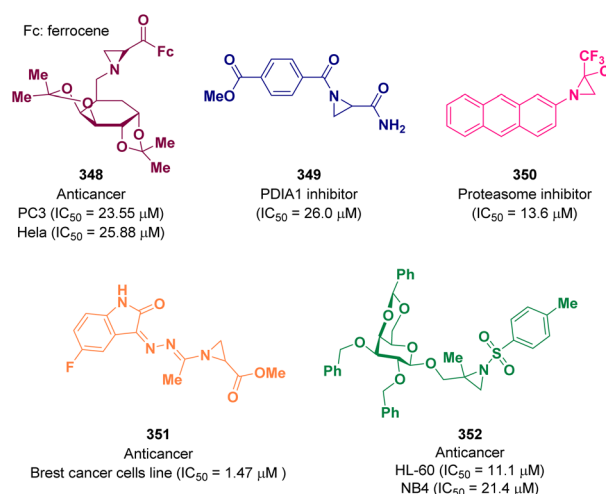


Fig. 2 Examples of aziridine derivatives with promising anticancer activity.



best result was obtained for compound **352**, which proved to induce DNA damage. The authors suggested that **352** has an anticancer therapeutic potential future since it showed selective cytotoxicity against different malignant cells in comparison with normal cells. In particular, the highest selectivity was observed for two acute promyelocytic leukemia cell lines, human acute promyelocytic leukemia cells (HL-60) and human acute promyelocytic leukemia cells (NB4) with an IC<sub>50</sub> value of 11.1 and 21.4  $\mu$ M, respectively (Fig. 2).<sup>107</sup>

## 6. Conclusions

In conclusion, this overview of the recent advances in the chemistry of aziridine derivatives highlights the syntheses and chemical transformations of compounds bearing aziridine moieties. The variety of methodologies developed to prepare aziridines in the last three years speak for the importance of these compounds. Aziridines have been used as building blocks, for example as precursors for the preparation of more complex heterocycles or amino acids which are interesting from biological and pharmacological points of view due to various biological applications related to this class of compounds. Furthermore, several aziridine-bearing compounds themselves show promising biological activities. For these reasons, the interest in aziridines will endure and occupy scientists in the future too. Thus, we can expect more scientific breakthroughs reported in a rapid manner and in large numbers.

## Conflicts of interest

The authors declare no conflict of interest.

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