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Facile synthesis of novel spiroheterocycles *via* diastereoselective aziridination of cyclic enones†

Kai-Chuan Yang,[abc] Jun-Long Li,[*ab] Xu-Dong Shen,[b] Qiang Li,[b] Hai-Jun Leng,[b] Qian Huang,[b] Peng-Kun Zheng,[b] Xiao-Jun Gou[*b] and Yong-Gang Zhi[*ac]

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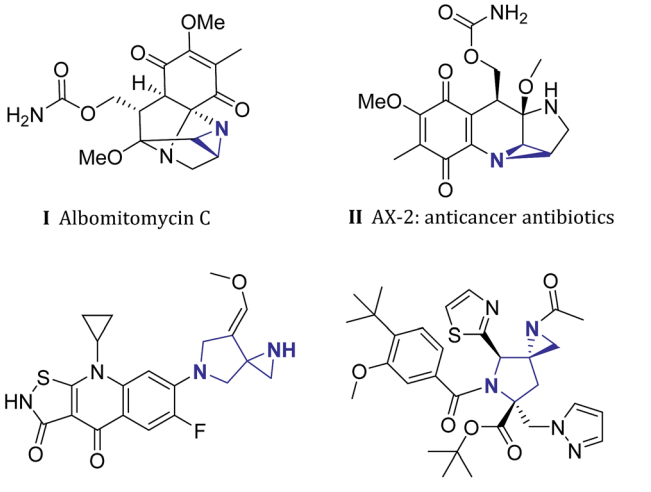
A collection of novel spiroheterocycles with strained aziridine moieties have been facilely synthesized by using easily accessible starting materials under mild reaction conditions. This procedure is robust, scalable and highly diastereoselective, and also features broad substrate scope. In addition, some of the products show promising *in vitro* biological activity against a spectrum of pathogens, which might be considered as a clue for the discovery of new antimicrobial agents.

Multifunctionalized aziridines, due to their unique and strained core structure, have provoked great interest in both pharmaceutical science and synthetic chemistry.[1] In particular, polycyclic heterocycles containing an aziridine moiety were frequently seen in many bioactive natural products and drug candidates.[2] For example, albomitomycin C, a representative aziridine alkaloid, was isolated from *Streptomyces caespitosus* culture broth, and can be used as a neoplasm inhibitor (Fig. 1, **I**). Antibiotic AX-2 which was derived from mitomycin C[3] shows significant anticancer activity (Fig. 1, **II**). On the other hand, spiropyrrolines have also been demonstrated to be a privileged pharmacophore among various therapeutic chemicals.[4] Merging these two interesting chemical building blocks can lead to a fascinating structural motif named spiro[aziridine-pyrrolines] (SAP), which has been successfully applied in the design of new antimicrobial agents in recent years (*e.g.* Fig. 1, **III** and **IV**).[5] However, efficient synthesis of such SAP derivatives has not received as much attention as other spirocycles,[6] despite their synthetic usefulness and great potential in medicinal chemistry.

Over the past decades, great efforts have been made to construct aziridines in a rapid and straightforward manner.[7] Significant advancement has been achieved in this adventure mostly based on three synthetic strategies: intramolecular substitution, direct aziridination of imines and aziridination of alkenes. Notably, it is necessary to pre-install two vicinal functional groups (an amine and a leaving group) in one molecule before using the intramolecular substitution strategy, which requires at least two chemical steps (Scheme 1a).[7a] The direct aziridination of imines, on the other hand, provides a variety of generally accepted and well-established methods for manufacturing the desired products; for example, the aza-Corey–Chaykovsky reaction, which involves the addition of sulfur ylides to imines, has been regarded as a robust and powerful protocol in the synthesis of aziridines since the middle of last century (Scheme 1b).[8] Alternatively, the aziridination of alkenes is also a particularly appealing synthetic strategy because of the ready availability of various olefinic starting materials; however, such a process is relatively less studied, and the organo-promoted or -catalyzed reactions with this strategy has not been systematically explored until the pioneering work of Loreto,[9a–f] Prabhakar[9g,h] and Córdova,[9i] respectively. Among these studies, there are still a lot of remaining problems[7] in terms of the



I Albomitomycin C **II** AX-2: anticancer antibiotics

III antibacterial agent **IV** inhibitors of Hepatitis C virus

Fig. 1 Selected natural products and bioactive molecules containing (spiro-)aziridine core structures.[3,5]

[a]*Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China. E-mail: zyggroup@hotmail.com*

[b]*Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, Chengdu 610052, PR China. E-mail: lijunlong709@hotmail.com; gouxj@163.com*

[c]*University of Chinese Academy of Science, Beijing 100049, P. R. China*

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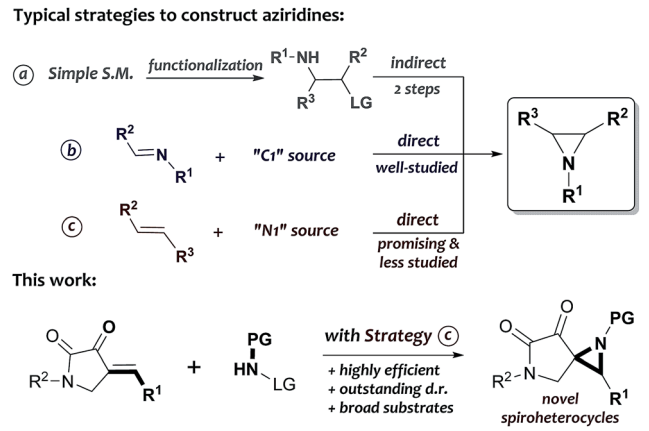


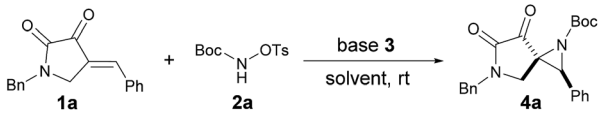
Scheme 1 Assembly of spiro[aziridine-pyrrolines] derivatives *via* aziridination of alkenes.

reaction efficiency, substrate compatibility and the stereoselectivity (Scheme 1c). Thus, the development of further efficient routes to novel structures of aziridines from easily accessible alkenes is highly desirable.

As part of our continuing interest in constructing medicinal relevant frameworks by using small nonmetal organic molecules,[10] we describe herein a base-promoted highly diastereoselective aziridination of cyclic electron-deficient alkenes, which leads to facile synthesis of novel SAP derivatives. Initially, we investigated the feasibility of this approach by evaluating the reaction between readily available enone **1a**[10a,b] and the modified carbamate **2a**. To our delight, the reaction proceeded smoothly in the presence of DABCO in DCM at room temperature, affording the desired product **4a** in 52% yield as a single diastereoisomer (Table 1, entry 1). This result encouraged us to further investigate the solvent effect (Table 1, entries 2–6), and chloroform was found to be the most appropriate (Table 1, entry 5). Changing other organic base (Table 1, entries 7–10) or using inorganic base (Table 1, entries 11 and 12) led to inferior results. Furthermore, the yield would be slightly dropped if less amount of base was used (Table 1, entry 13).

Having established the optimal reaction conditions (Table 1, entry 5), we set out to explore the generality of the [2 + 1] cycloadditions. Due to the ketone group that was adjacent to the aziridine moiety, some of the spiro-products were found to be somewhat unstable unless stored under low temperature, which limits the relevant biological study of such frameworks. Thus, a reliable Horner–Wadsworth–Emmons (HWE) reaction was utilized to transform this ketone group to the corresponding α,β-unsaturated ester as the final bench-stable product **5**. As summarized in Table 2, a variety of cyclic enones **1** bearing either electron-withdrawing (Table 2, entries 2–9) or electron-donating (Table 2, entries 10–12) groups at different positions

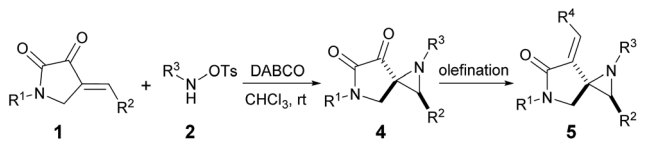
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Base **3**	d.r.[b]	Yield[c] (%)
1	DCM	DABCO	>95 : 5	52
2	DCE	DABCO	>95 : 5	57
3	CH_3CN	DABCO	>95 : 5	57
4	THF	DABCO	>95 : 5	82
5	**$CHCl_3$**	**DABCO**	**>95 : 5**	**93**
6	Toluene	DABCO	>95 : 5	89
7	$CHCl_3$	TMG	>95 : 5	91
8	$CHCl_3$	DBU	>95 : 5	60
9	$CHCl_3$	TEA	>95 : 5	83
10	$CHCl_3$	DIPEA	>95 : 5	85
11[d]	$CHCl_3$	K_2CO_3	>95 : 5	35
12[d]	$CHCl_3$	KOH	>95 : 5	50
13[e]	$CHCl_3$	DABCO	>95 : 5	85

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 0.15 mmol of base **3** in 1 mL solvent at room temperature overnight. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] 10 mol% of TBAB was added as phase transfer catalyst. [e] 0.1 mmol of DABCO was used as the base.

Table 2 Substrate scope of the aziridination of cyclic enones[a]

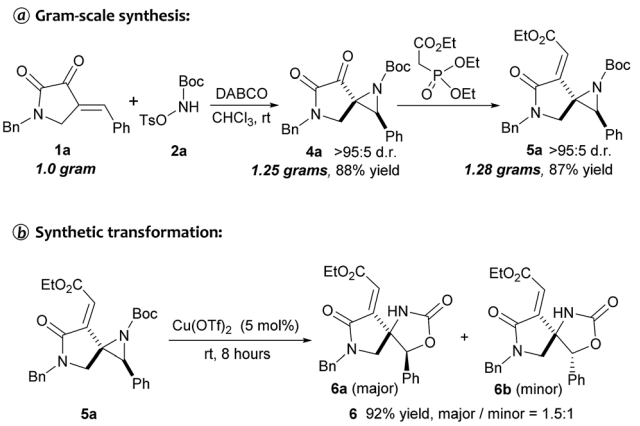


Entry	Product	R^1	R^2	R^3	R^4	Yield[b] (%)
1	**4a/5a**	Bn	C_6H_5	Boc	CO_2Et	93 (91)
2	**4b/5b**	Bn	4-FC_6H_4	Boc	CO_2Et	87 (88)
3	**4c/5c**	Bn	4-ClC_6H_4	Boc	CO_2Et	89 (91)
4[c]	**4d/5d**	Bn	4-BrC_6H_4	Boc	CO_2Et	88 (89)
5	**4e/5e**	Bn	4-$NO_2C_6H_4$	Boc	CO_2Et	89 (90)
6	**4f/5f**	Bn	3-ClC_6H_4	Boc	CO_2Et	85 (89)
7	**4g/5g**	Bn	3-BrC_6H_4	Boc	CO_2Et	87 (91)
8	**4h/5h**	Bn	2-ClC_6H_4	Boc	CO_2Et	81 (84)
9	**4i/5i**	Bn	2,4-$Cl_2C_6H_3$	Boc	CO_2Et	86 (89)
10	**4j/5j**	Bn	4-MeC_6H_4	Boc	CO_2Et	90 (89)
11	**4k/5k**	Bn	3-MeC_6H_4	Boc	CO_2Et	88 (90)
12	**4l/5l**	Bn	3-$MeOC_6H_4$	Boc	CO_2Et	84 (89)
13	**4m/5m**	Bn	1-Naphthyl	Boc	CO_2Et	80 (87)
14	**4n/5n**	Bn	2-Naphthyl	Boc	CO_2Et	86 (90)
15	**4o/5o**	PMB	C_6H_5	Boc	CO_2Et	89 (91)
16	**4p/5p**	Allyl	C_6H_5	Boc	CO_2Et	80 (81)
17	**4q/5q**	Bn	C_6H_5	Cbz	CO_2Et	90 (91)
18[d]	**4a/5r**	Bn	C_6H_5	Boc	H	93 (81)

[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **1**, 0.3 mmol of **2** and 0.3 mmol of DABCO in 2 mL $CHCl_3$ at rt overnight. The diastereomeric ratio of **4** was determined to be >95 : 5 by ^{1}H NMR spectroscopy of the crude reaction mixture. The HWE reaction was used for the olefination process, for details, see ESI. [b] Isolated yield of the aziridination product **4**, and the data in parentheses refers to the isolated yield of the olefination product **5**. [c] The structure of **5d** was determined by X-ray diffraction analysis, and others were determined by analogy. [d] Using methyltriphenylphosphonium bromide as the Wittig reagent for the olefination process, see ESI. Bn: benzyl; PMB: *p*-methoxybenzyl; Boc: *t*-butyloxy-carboryl; Cbz: carboxybenzyl.

of the phenyl ring reacted efficiently to afford the desired products **5b–5l** in excellent diastereoselectivities and nice isolated yields. The reaction was also suitable for enone substrates with polycyclic aromatics, such as 1-naphthyl and 2-naphthyl rings (Table 2, entries 13 and 14). It was revealed that the N-protecting groups of the enones have limited effect on the outcome of this reaction (Table 2, entries 15 and 16). On the other hand, in terms of the nucleophile, the Cbz group on the nitrogen atom could also be well tolerated (Table 2, entry 17). Furthermore, by using Wittig reaction, product **4a** could be easily transformed to the corresponding α,β-unsaturated lactam **5r** which contains an interesting exocyclic terminal alkenes (Table 2, entry 18).

To further illustrate the robustness and practicality of this methodology, the aziridination reaction with **1a** was scaled up to 1.0 gram under optimal conditions. Gratifyingly, the desired spiroaziridine **4a** and its derivative **5a** were smoothly obtained with excellent diastereoselectivity in 88% and 87% yield, respectively (Scheme 2a). It should be worth highlighting that such spiroaziridine skeleton could also be easily transformed to the spiro[lactam-oxazolidinone] core structure; as illustrated in Scheme 2b, in the presence of $Cu(OTf)_2$ as Lewis acid catalyst, the corresponding product **6** was synthesized in high yield, albeit with moderate diastereoselectivity. Moreover, structural correctness of the spiroaziridines and the relative configuration of the adjacent stereocenters were confirmed by X-ray diffraction analysis of the representative product **5d** (Fig. 2, for details, see ESI†).



Scheme 2 Gram-scale synthesis of spiroaziridines **4a** and **5a**, and the synthetic transformation of **5a**.

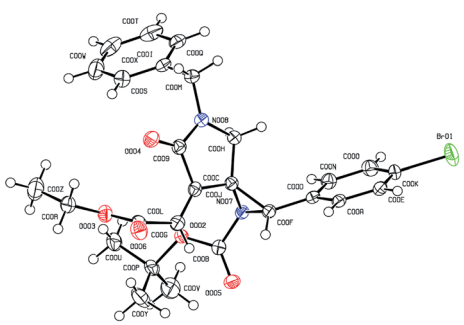
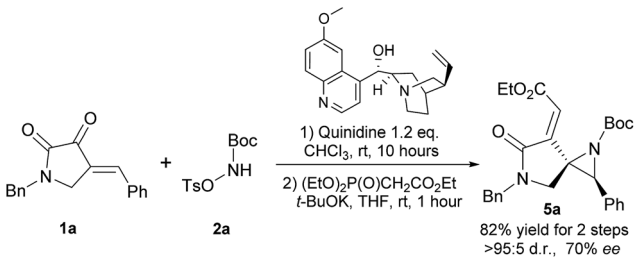


Fig. 2 Single crystal X-ray diffraction analysis of product **5d**.[11]

In addition, we have demonstrated that the enantioenriched spiroaziridine **5a** could be synthesized by using the readily available and relatively inexpensive quinidine as the chiral Brønsted base (Scheme 3). However, considering its moderate enantioselectivity and high loading of the chiral base, further optimization is still in urgent demand and currently underway in our lab.

The collection of new compounds **5a–5r** was screened for *in vitro* antibacterial activity against *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (MRSA, clinic isolates) and *Proteus mirabilis* (clinic isolates).[12] It was revealed that some of these spiroaziridines exhibited promising bioactivity, with the minimum inhibitory concentrations (MICs) value ranging from 8 to 128 μg mL^{-1}. Particularly, compound **5c**



Scheme 3 Asymmetric synthesis of chiral spiroaziridine **5a** by using commercially available quinidine.

Table 3 Preliminary studies of antibacterial activity of the racemic spiroaziridines **5a–5r**[a]

		MIC[b] (μg mL^{-1})		
Entry	Compound	*S. aureus*[c]	MRSA[d]	*P. mirabilis*[e]
1	**5a**	16	128	>128
2	**5b**	16	>128	>128
3	**5c**	8	16	64
4	**5d**	8	128	128
5	**5e**	8	>128	>128
6	**5f**	64	128	>128
7	**5g**	32	128	>128
8	**5h**	16	64	32
9	**5i**	8	64	128
10	**5j**	8	>128	>128
11	**5k**	16	>128	>128
12	**5l**	16	>128	>128
13	**5m**	8	128	64
14	**5n**	8	64	16
15	**5o**	16	128	>128
16	**5p**	128	>128	>128
17	**5q**	64	128	128
18	**5r**	32	128	>128

[a] Broth dilution method was used, for details, see ESI. [b] MIC: minimum inhibitory concentration. [c] *S. aureus*: Gram-positive, MIC of amoxicillin: 0.5 μg mL^{-1} (positive control). [d] MRSA: Gram-positive, MIC of amoxicillin: 16 μg mL^{-1} (positive control). [e] *P. mirabilis*: Gram-negative, MIC of amoxicillin: 4 μg mL^{-1} (positive control).

shows obvious *in vitro* antibacterial activity against MRSA which is regarded as a clinically important pathogen (Table 3).

Conclusions

In summary, we have successfully developed a highly diastereoselective aziridination reaction of cyclic enones under mild condition, giving an efficient access to a class of novel spiroaziridines. This approach is highly practical and functional group tolerant, which allows for large-scale synthesis and rapid assembly of substituent divergent products from simple, readily available starting materials. Preliminary biological studies of the synthesized compounds showed promising *in vitro* antibacterial activity against *S. aureus*, MRSA and *P. mirabilis*. Asymmetric organocatalysis of this aziridination process and further medicinal chemistry studies upon these novel structures are our current research interests, and the result will be reported in due course.

Acknowledgements

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