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Diastereoselective [3 + 1] Cyclization Reaction of Oxindolyl Azaoxyallyl Cations with Sulfur Ylides: Assembly of 3,3′-Spiro[β-lactam]-oxindoles

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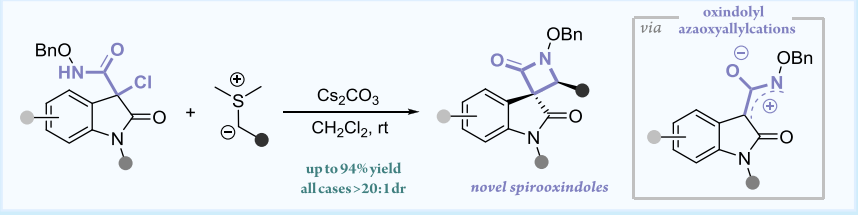

ABSTRACT: Oxindoles and β-lactams are attractive structural motifs because of their unique biological importance. However, the fusion of the two moieties featuring 3,3′-spirocyclic scaffolds is a challenging task in organic synthesis. Herein we designed a novel type of oxindole-based azaoxyallyl cation synthons, which could readily participate in the [3 + 1] cyclization with sulfur ylides. With this protocol, a collection of 3,3-spiro[β-lactam]-oxindoles were facilely produced in up to 94% yield with perfect diastereoselectivity.

Nitrogen-containing heterocyclic frameworks are widely distributed in many bioactive natural products and medicinally relevant molecules.[1] Among them, β-lactams, representing a unique type of four-membered azacycles, are well known for their significant antibiotic bioactivities.[2] In addition, oxindole-based natural alkaloids and pharmaceutical molecules have also exhibited a broad range of biological activities, including antitumor, anti-HIV, antimicrobial, and antimalarial activities.[3,4] According to the theory of combination principles in medicinal chemistry,[5] merging β-lactam and oxindole moieties into a rigid spirocyclic scaffold might provide a great opportunity for discovering valuable lead compounds. For example, molecules bearing a 3,2′-spiro[β-lactam]-oxindole skeleton could act as promising antipoliovirus agents and human rhinovirus 3C-proteinase inhibitors.[6] Therefore, the exploration of diverse spiro[β-lactam]-oxindoles for drug discovery could be an emerging dynamic research field (Figure 1).

In fact, the development of efficient synthetic strategies to construct spiro[β-lactam]-oxindoles has already attracted considerable attention from the synthesis community. A number of methods have been established to synthesize 3,2′-spiro[β-lactam]-oxindole skeletons through [2 + 2] annulations, which are typically based on the isatin-derived ketimines as key building blocks.[7] However, a similar 3,3′-spiro[β-lactam]-oxindole scaffold, featuring the spiro-center at C3′ position, has rarely been investigated, probably because of the synthetic challenge to utilize the existing substrates to prepare this unique skeleton. Consequently, it is highly desirable to

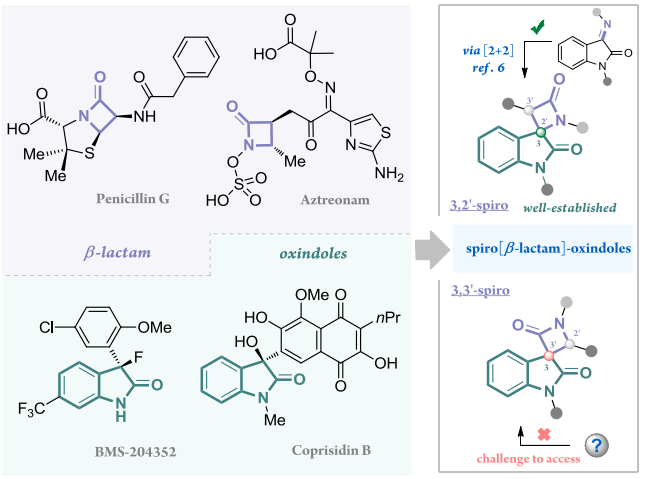

Figure 1. Motivation and state-of-the-art for constructing spiro[β-lactam]-oxindole scaffolds.

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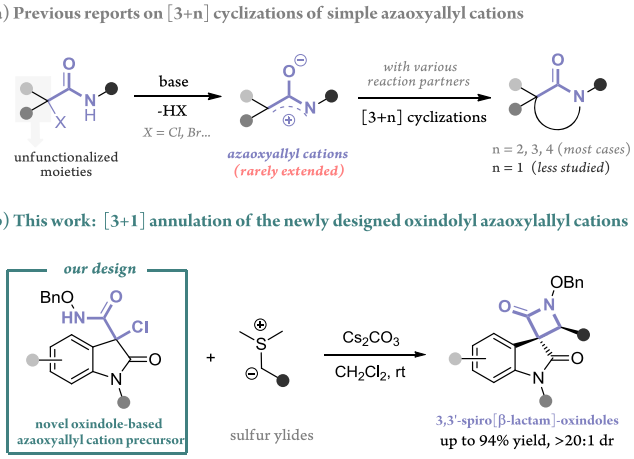
design a novel and suitable building block that could refresh the retrosynthetic planning and streamline the whole reaction process.

Azaoxyallyl cations, generated from α-halo hydroxamates, have emerged as a highly reactive three-atomic synthon for preparing structurally diverse lactam heterocycles.[8] In 2011, Jeffrey and coworkers reported the first synthetic application of azaoxyallyl cations in [4 + 3] cycloadditions by using furan or cyclopentadiene, and they also provided experimental evidence to demonstrate the existence of this transient intermediate.[9] Since then, the chemistry of azaoxyallyl cations has been extensively explored by organic chemists, and a variety of [3 + 2][10] and [3 + 3][11] cyclizations have been continuously developed during the past decade (Scheme 1a). Recently, the

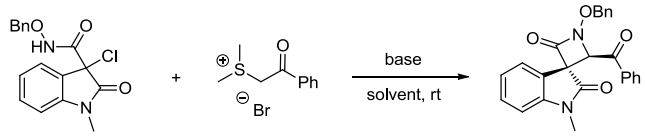
Scheme 1. Design of the Oxindole-based Azaoxyallyl Cations



Chen and Liu group reported an elegant [3 + 1] annulation by using Jeffrey's azaoxyallyl cations in the presence of sulfur ylides, and a collection of lactams were obtained in moderate to good yields.[10e] Despite these advancements, previous reports mostly relied on the use of simple α-halo hydroxamates as the key azaoxyallyl cation precursor. We envisioned that the design of a novel azaoxyallyl cation based on an oxindole skeleton might be quite interesting because the high reactivity of the azaoxylallyl cation intermediate could allow for rapid access to structurally challenging molecules, such as 3,3′-spiro[β-lactam]-oxindoles. On the basis of these considerations and our continuous interest in assembling biologically relevant heterocycles,[12] we herein report a highly diastereoselective [3 + 1] annulation of the newly designed oxindolyl azaoxyallyl cations with sulfur ylides. The present reaction could reach completion within a very short period of time, which further demonstrates the high reactivity of this new synthon. This protocol could afford a range of functionalized 3,3′-spiro[β-lactam]-oxindoles (Scheme 1b).

First, we prepared the designed oxindolyl azaoxyallyl cation precursors **1** in an efficient manner. (For details, see the Supporting Information.) Then, the model reaction of **1a** and sulfonium salt **2a** was investigated under alkaline conditions at room temperature. As illustrated in Table 1, hexafluoroisopropanol could not promote this reaction, despite the fact that it was frequently utilized as a privileged solvent because of its ability to stabilize the highly reactive azaoxyallyl cations (entry 1).[8−10] A poor conversion rate was still observed by using K_2CO_3 as the base in various solvents (entries 2−5). To our

Table 1. Optimization Studies[a]



1a 2a 3a

entry	solvent	base	yield (%)[b]	dr[c]
1	HFIP	K_2CO_3	<5	
2	toluene	K_2CO_3	<5	
3	THF	K_2CO_3	<5	
4	MeCN	K_2CO_3	<5	
5	CH_2Cl_2	K_2CO_3	<5	
6	CH_2Cl_2	Cs_2CO_3	58	>20:1
7	CH_2Cl_2	Na_2CO_3	<5	
8	CH_2Cl_2	NaOH	<5	
9	CH_2Cl_2	K_2HPO_4	7	
10	CH_2Cl_2	Et_3N	15	>20:1
11	CH_2Cl_2	iPr_2NEt	15	>20:1
12	CH_2Cl_2	DMAP	<5	
13	CH_2Cl_2	DABCO	<5	
14	CH_2Cl_2	TMG	<5	
15	CH_2Cl_2	DBU	<5	
16[d]	**CH_2Cl_2**	**Cs_2CO_3**	**85**	>20:1
17[e]	CH_2Cl_2	Cs_2CO_3	80	>20:1
18[f]	CH_2Cl_2	Cs_2CO_3	54	>20:1

[a]Unless otherwise noted, reactions were performed with oxindoles **1a** (0.10 mmol), sulfonium salts **2a** (0.05 mmol), and base (0.20 mmol) in 1.0 mL of solvent at room temperature for 15 min. [b]Isolated yield. [c]Determined by crude ^{1}H NMR analysis. [d]In 0.5 mL of CH_2Cl_2. [e]In 0.25 mL of CH_2Cl_2. [f]At 0 °C. HFIP: hexafluoroisopropanol; DMAP: 4-dimethylaminopyridine; TMG: tetramethylguanidine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

delight, the target [3 + 1] annulation could be triggered with Cs_2CO_3, which diastereoselectively offered the desired product **3a** in 58% isolated yield within a short time (entry 6). Encouraged by this result, we investigated a series of inorganic and organic bases, but no better results were obtained (entries 7−15). Fortunately, we found that the isolated yield could be improved to 85% by using a slightly higher concentration (entry 16). However, further increasing the concentration to 0.2 M afforded a lower yield (entry 17). Lowering the reaction temperature to 0 °C could not improve the results (entry 18).

Next, we evaluated the generality and limitation of this [3 + 1] cyclization under the optimized conditions by testing various substituted α-chloro hydroxamates **1** and sulfonium salts **2**. The results are summarized in Scheme 2. Sulfonium salts **2** bearing either electron-rich or electron-deficient substituents at the *para* or *meta* positions were well tolerated in this reaction system, affording the 3,3′-spiro[β-lactam]-oxindole derivatives **3a**−**3k** in good to excellent yields. However, a lower yield was obtained by testing the *ortho*-fluoro-substutited sulfonium salt (**3l**). The dichloro-substituted **2** could also be well compatible and gave the product **3m** in 70% yield. Moreover, the 2-naphthyl-substituted β-lactam **3n** was obtained in 75% yield. The [3 + 1] cyclization proceeded smoothly with sulfonium salts bearing a heteroarene, such as furan or thiophene, which delivered the corresponding products **3o** and **3p** in satisfying yields. Besides ketonic sulfonium salts, **2** incorporating an ester functionality could also be tolerated, and **3q** was produced in an acceptable yield. Furthermore, the hydroxamate **1** featuring a methyl substituent

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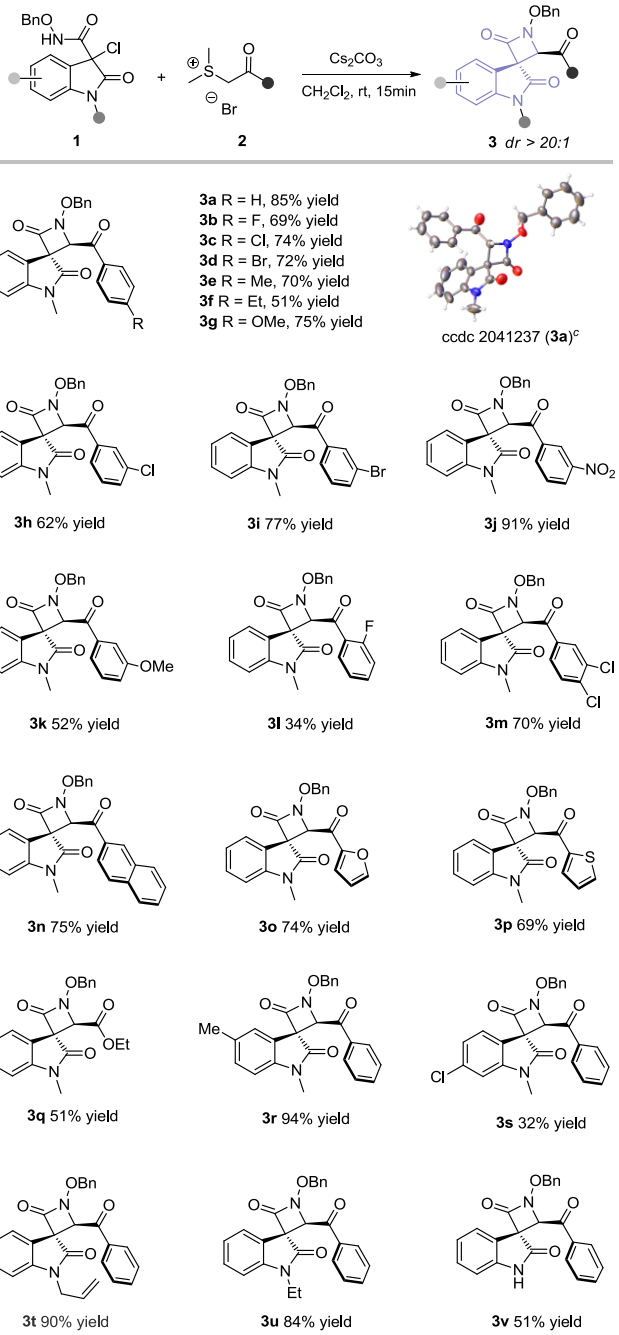
Scheme 2. Substrate Scope of the [3 + 1] Annulation[a,b]

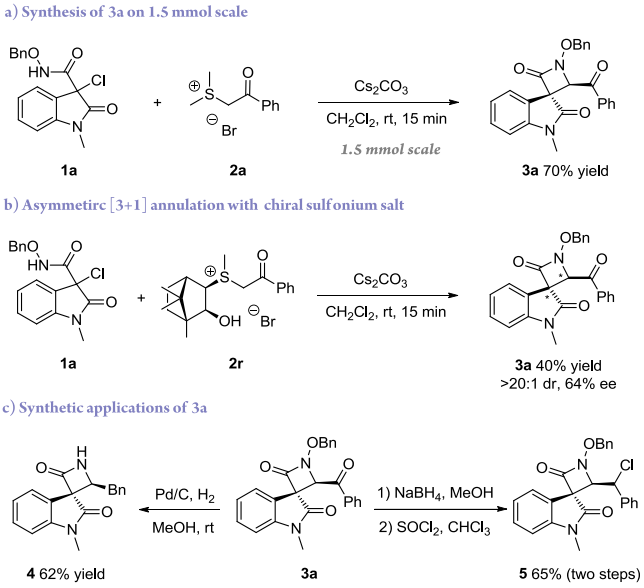


[a]Unless otherwise noted, reactions were performed with 0.20 mmol of **1**, 0.10 mmol of **2**, and 0.20 mmol of Cs_2CO_3 in 1.0 mL of CH_2Cl_2 at rt for 15 min. [b]Isolated yield. dr was determined to be >20:1 in all cases by crude ^1H NMR analysis. [c]Structure of **3a** was determined by X-ray diffraction analysis.

at the five-position on the oxindole skeleton was found to be highly reactive in the target reaction, which delivered **3r** in excellent yield. Nevertheless, the use of 6-chloro-substituted **1** resulted in lower reaction efficiency (**3s**). *N*-allyl- and *N*-ethyl-protected **1** could also well participate in this reaction and afforded the spirocyclic products **3t** and **3u** in excellent yields. Interestingly, this annulation could also proceed efficiently when the NH-free oxindolyl azaoxyallyl cation precursors were utilized (**3v**).

Subsequently, we performed several experiments to demonstrate the potential utility of this synthetic method. First, the [3 + 1] annulation of azaoxyallyl cation precursor **1a** and sulfonium salt **2a** was conducted on a 1.5 mmol scale, which gave the desired **3a** in 70% yield (Scheme 3a). The

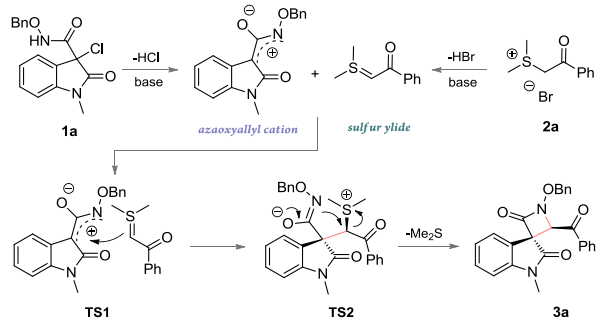
Scheme 3. Further Synthetic Investigations



asymmetric [3 + 1] annulation could also be achieved by using a champhor-derived chiral sulfonium salt **2r**, delivering **3a** in 40% yield with 64% enantioselectivity (Scheme 3b). Then, we explored the synthetic transformations to investigate the versatility of this *β*-lactam-incorporated spirooxindole **3a**. As shown in Scheme 3b, treating **3a** with Pd/C catalyst under a H_2 atmosphere led to the cleavage of the N−O bond as well as the reduction of the ketone moiety, delivering the benzyl-substituted *β*-lactam product **4** in satisfying yield. The chlorinated compound **5** could also be easily accessed in 65% overall yield through an efficient reduction/chlorination sequence (Scheme 3c).

The mechanism of this [3 + 1] annulation was speculated, as shown in Scheme 4. Initially, the highly reactive azaoxyallyl cation intermediate and sulfur yield species were both generated under alkaline conditions. Next, the nucleophilic attack of sulfur ylide to azaoxyallyl cation (the delocalization of positive charge via resonance through the aromatic ring probably contributes to the stabilization of the azaoxyallyl cation, **TS1**) provided a zwitterionic intermediate **TS2**. Finally,

Scheme 4. Proposed Mechanism of the [3 + 1] Annulation



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an intramolecular cyclization took place to release the dimethyl sulfide and delivered the spiro-β-lactam **3a**.

In conclusion, we have developed a novel azaoxyallyl cation precursor, which involved a biologically interesting spirooxindole motif. Such building blocks could be easily prepared and have been successfully applied in the [3 + 1] annulation with sulfur ylides. The 3,3′-spiro[β-lactam]-oxindole skeleton, which was previously difficult to access, could be easily constructed by using this protocol. A variety of novel spirooxindoles with diverse functional groups were obtained within a short period of time under mild conditions. The potential utility of this method was further demonstrated by synthetic transformations. A stepwise bond-formation mechanism was proposed based on previous ylide [3 + 1] annulation processes. Further applications of these new azaoxyallyl cation synthons and the biological evaluations of the corresponding spirooxindoles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00130.

Complete experimental procedures, characterization of new products, NMR spectra, HRMS data, and X-ray crystallographic data for **3a** (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a−1f**, **3a−3v**, **4**, **5**, **S3**, and **S4** (ZIP)

Accession Codes

CCDC 2041237 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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