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Construction of a Benzo[*b*]azepine Skeleton through Decarboxylative Ylide [6+1] Annulations with Modified Vinyl Benzoxazinanones

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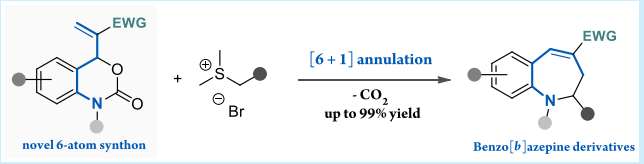
ABSTRACT: A Lewis acid-promoted [6+1] annulation between sulfur ylides and modified vinyl benzoxazinanones was described. In this reaction, the newly designed vinyl benzoxazinanones could serve as a novel six-atom synthon, and the key to success is the installation of an electron-withdrawing group on the alkene moiety of the benzoxazinanones. A broad range of substrates are compatible with this mild reaction system, thereby providing a facile and practical approach for constructing a benzo[*b*]azepine skeleton.



Nitrogen-containing heterocycles are key structural motifs in numerous natural products, pharmaceuticals, and agrochemicals.[1] In particular, the benzo[*b*]azepine skeleton represents an important class of benzannulated medium-sized N-heterocycles due to its broad bioactivity. For example, drugs such as Benazepril, Epinastine, and other related bioactive compounds all contain the benzo[*b*]azepine ring system (Figure 1).[2] Because of their significant pharmaceutical value, the development of straightforward synthetic methods for the construction of benzo[*b*]azepine scaffolds is urgent.

Intermolecular cyclization is considered as one of the most efficient methods for the construction of heterocycles, due to the formation of at least two chemical bonds in a single step.[3] Among various cyclization strategies, the ylide-mediated [*n*+1] annulations are of particular interest in organic chemistry.[4] In the past several decades, remarkable progress has been made in this field, and various annulation types, such as [2+1],[5] [3+1],[6] [4+1],[7] and [5+1][8] cyclizations, were successively developed by incorporating different *n*-atom reaction partners, thereby providing efficient protocols for accessing structurally complicated cyclic compounds. However, to the best of our knowledge, the type of ylide [6+1] annulation[9] that could construct seven-membered rings is yet to be established thus far. The main challenge of this annulation is probably the presence of inherent entropic factors and transannular interactions during the formation of a medium-sized ring system.[10] Another reason is the lack of an easily available and bench-stable six-atom synthon with ambiphilic properties. Theoretically, such 1,6-dipolar substrates might easily undergo intramolecular cyclization to furnish a six-membered ring, and therefore, the desired intermolecular [6+1] annulation pathway with an ylide partner might be hindered (Scheme 1a). In this scenario, it is of considerable significance to design a novel, bench-stable, and reactive six-atom synthon that could enable the challenging [6+1] annulation reactions for the synthesis of medicinally interesting seven-membered heterocycles.

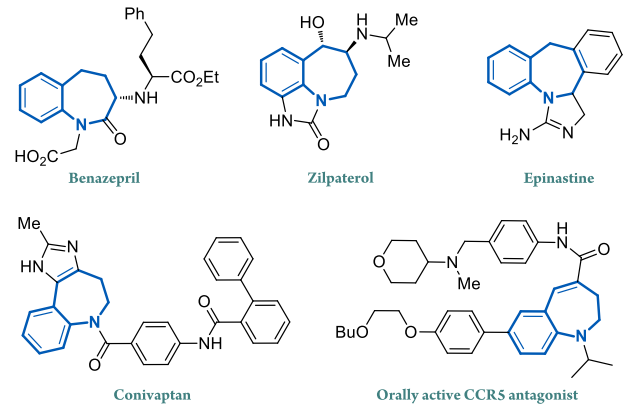


Figure 1. Selected examples of bioactive benzo[*b*]azepine derivatives.

Vinyl benzoxazinanones have been widely applied in synthetic methodology development. They typically serve as a transient 1,4-dipole in palladium-catalyzed cyclizations through decarboxylative generation of an ambiphilic *N*-anion-involved π-allyl palladium species.[11] With this key intermediate, multifarious [4+*n*] annulations have been achieved for

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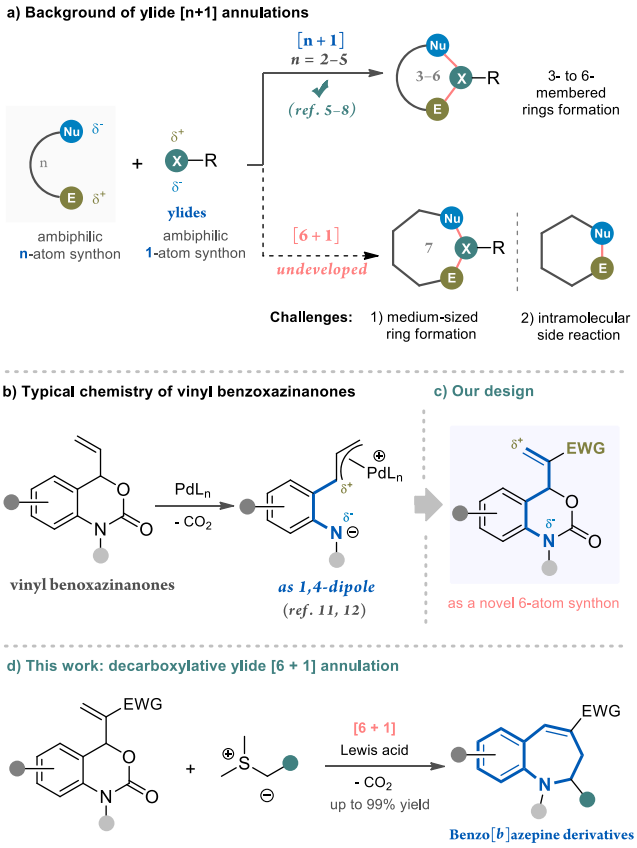
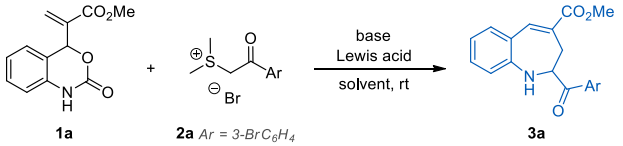
Scheme 1. Challenges in Ylide [6+1] Annulation and Our Design



assembling various interesting aza-heterocycles (Scheme 1b).[12] For example, Xiao's group pioneered the palladium-catalyzed [4+1] annulation of vinyl benzoxazinanones and sulfur ylides. To avoid the use of precious metal catalysts, we designed a new type of building block by simply introducing an electron-withdrawing group (EWG) on the olefin moiety, which might mimic the reactivity of the well-established Morita–Baylis–Hillman adducts.[13] Thus, the activated alkene moiety could be directly attacked by a nucleophile at the terminal carbon, and an *in situ*-generated *N*-anion could further react with electrophilic species. Notably, the electron-deficient alkene and *N*-nucleophile were spatially separated by a rigid aromatic structure, which could inhibit the intramolecular side reaction and make the substrates bench-stable. On the basis of this hypothesis, the newly designed vinyl benzoxazinanones could serve as an excellent 1,6-dipole in a palladium-free annulation (Scheme 1c). Herein, we report the design of modified vinyl benzoxazinanone substrates and the successful application in a Lewis acid-promoted decarboxylative [6+1] annulation with sulfur ylides, which provides an efficient protocol for accessing novel molecular structures (Scheme 1d).[14]

We started by investigating the reaction of the modified vinyl benzoxazinanones **1a** and sulfonium salts **2a** in the presence of a base at ambient temperature (Table 1).[15] To our satisfaction, the desired [6+1] annulation proceeded smoothly by using K_2CO_3 in toluene, affording product **3a** in 50% yield under transition metal-free conditions (entry 1). After various solvents had been screened, DCE led to the best result (entries 2–5). Moreover, the examination of bases resulted in inferior yields (entries 6–9). Then, a series of Lewis acids were tested

Table 1. Optimization Studies[a]



1a 2a Ar = 3-BrC6H4 3a

entry	base	solvent	Lewis acid	yield (%)[b]
1	toluene	K_2CO_3	–	50
2	MeCN	K_2CO_3	–	47
3	THF	K_2CO_3	–	25
4	DCM	K_2CO_3	–	45
5	DCE	K_2CO_3	–	66
6	DCE	Cs_2CO_3	–	50
7	DCE	$NaHCO_3$	–	<5
8	DCE	Et_3N	–	26
9	DCE	TMG[c]	–	34
10	DCE	K_2CO_3	$Sc(OTf)_3$	58
11	DCE	K_2CO_3	$Sn(OTf)_2$	77
12	DCE	K_2CO_3	$Al(OTf)_3$	31
13	DCE	K_2CO_3	$Fe(OTf)_2$	88
14	DCE	K_2CO_3	LiCl	56
15	DCE	K_2CO_3	$LiClO_4$	68
16	DCE	K_2CO_3	$BF_3{\cdot}Et_2O$	36

[a]Reactions were performed with vinyl benzoxazinanones **1a** (0.15 mmol), sulfonium salts **2a** (0.1 mmol), a base (0.12 mmol), and a Lewis acid (0.02 mol) in 1.0 mL of solvent at room temperature for 72 h. [b]Isolated yield. [c]Tetramethylguanidine.

as additives to improve the reaction efficiency, and $Fe(OTf)_2$ was found to be quite compatible with this reaction system to provide the highest yield (entries 10–16).

With the optimal conditions in hand, we set out to explore the generality of this [6+1] annulation with a combination of various substituted vinyl benzoxazinanones **1** and sulfonium salts **2**. As shown in Scheme 2, sulfonium salts featuring either an electron-donating or electron-withdrawing group on the benzene ring worked well under standard conditions, generating a range of benzo[*b*]azepine derivatives **3a–3m** in generally good yields. The reaction proceeded smoothly with a 2-naphthyl-substituted sulfonium salt, and an 87% yield of **3n** was obtained. Heteroaromatic sulfonium salts were also suitable substrates for producing furyl **3o** or thienyl **3p** in high yields. Besides ketones, other electron-withdrawing group on **2**, such as esters, could also be compatible with this reaction, delivering an ester-substituted product **3q** in moderate yield. Next, we examined the reaction of **2b** with various vinyl benzoxazinanones **1** under optimal conditions. As shown in the latter part of Scheme 2, this annulation was tolerant of electron-rich and electron-deficient substituents at position 5 or 6 of vinyl benzoxazinanones. The corresponding products **3r–3w** were produced in satisfying yields. The reactions also proceeded well for the 7,8-dimethyl-substituted **1**, providing **3x** in 85% yield. Furthermore, the different ester group on **1** has proven to show limited effects on the reaction outcome (**3y**).

Subsequently, we performed several experiments to demonstrate the versatility of this method. First, the direct sulfide-catalyzed [6+1] annulation of **1a** with 2-bromoacetophenone **4** was also achieved by employing tetrahydrothiophene **5** as the organocatalyst, giving the corresponding product **3b** in 65% yield (Scheme 3a). Then, synthetic derivatization of product **3b** was also extensively studied.

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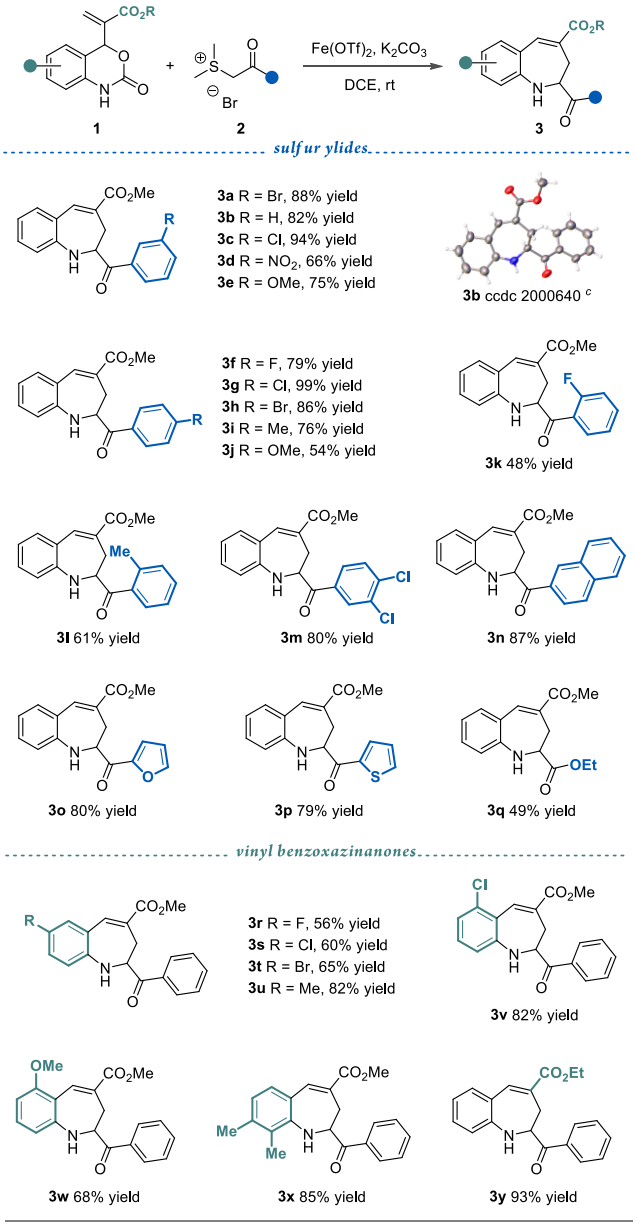
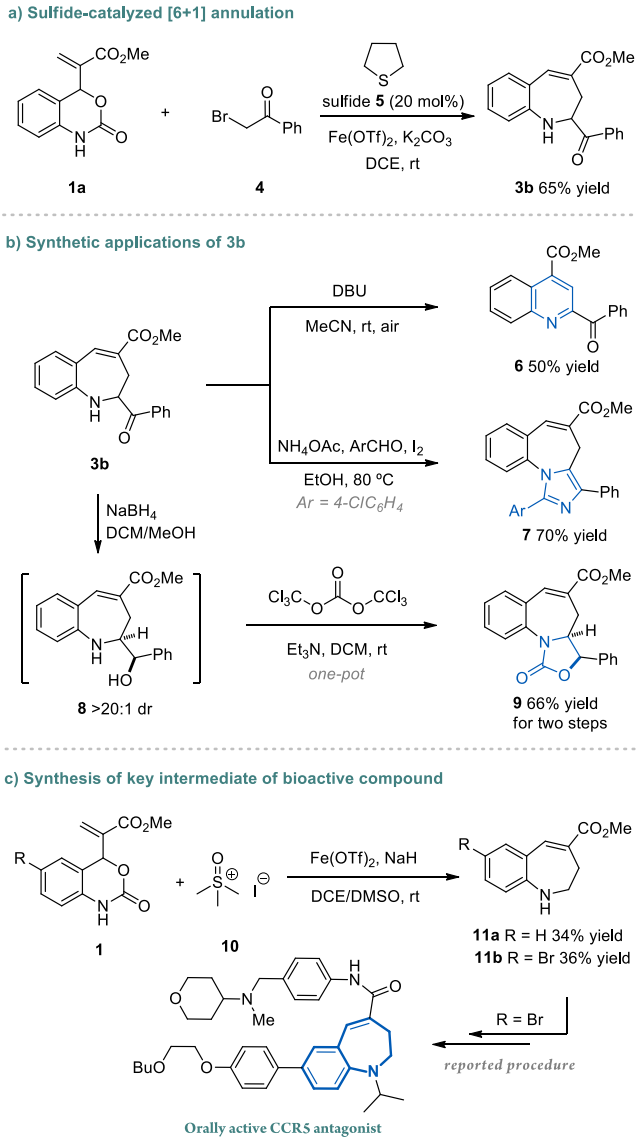
Scheme 2. Substrate Scope of the [6+1] Annulation[a,b]



[a]Reactions were performed with 0.15 mmol of **1**, 0.10 mmol of **2**, 0.12 mmol of K_2CO_3, and 0.02 mmol of $Fe(OTf)_2$ in 1.0 mL of DCE at rt for 72 h. [b]Isolated yield. [c]The structure of **3b** was determined by X-ray diffraction analysis.[16]

Interestingly, the multifunctionalized quinoline **6** could be easily obtained from **3b** through a cascade reaction of aerobic dehydrogenation and oxidative ring contraction[17] in the presence of 1,8-dazabicyclo[5.4.0]undec-7-ene (DBU). Upon treatment of **3b** with ammonium acetate, aromatic aldehyde, and iodine in EtOH at 80 °C, imidazole-annulated product **7** was delivered in 70% yield.[18] Moreover, the diastereoselective reduction of **3b** could afford alcohol **8**, which could directly undergo further cyclization with triphosgene to produce a tricyclic product **9** in 66% total yield (Scheme 3b). In addition, Corey-chaykovsky reagent **10** could also react with modified vinyl benzoxazinanones, delivering the corresponding benzo-[*b*]azepine derivatives **11a** and **11b**. Notably, product **11b**

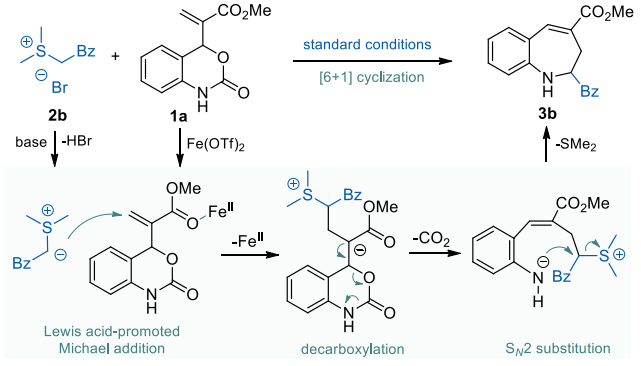
Scheme 3. Synthetic Application of 3b



could easily convert to a CCR5 antagonist through several established transformations (Scheme 3c).[2f]

The mechanism of this decarboxylative [6+1] annulation is proposed in Scheme 4. Sulfur ylide was initially generated in the presence of a base. With the assistance of a Lewis acid,

Scheme 4. Proposed Mechanism



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vinyl benzoxazinanone **1a** could be further activated and easily attacked by sulfur ylides at the terminal alkene position, thereby forming a betaine intermediate. Next, this intermediate released CO_2 gas to give an amino anion and then underwent an intramolecular cyclization to deliver the final cyclized product.

In conclusion, we have developed an unprecedented decarboxylative [6+1] annulation of vinyl benzoxazinanones and sulfur ylides. The success was greatly attributed to the design of electron-deficient vinyl benzoxazinanone substrates, which could serve as an excellent six-atom synthon. Promoted by Lewis acids, this annulation features advantages of mild conditions, high yields, and a broad substrate scope, thereby providing a facile route for producing benzo[*b*]azepine derivatives. In addition, this reaction pathway could also be realized by using direct sulfide organocatalysis. The synthetic utilization of the obtained benzene-annulated azepine products was demonstrated in various functional group derivatizations. Further investigations of the biological studies of these novel molecules 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.0c04041.

Complete experimental procedures, characterization of new products, NMR spectra, and HPLC chromatograms (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a**−**1i**, **3a**−**3y**, **6**, **7**, **9**, **11a**, and **11b** (ZIP)

Accession Codes

CCDC 2000640 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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(15) For more screening studies, see the Supporting Information.

(16) CCDC 2000640 (**3b**) contains the supplementary crystallographic data for this paper.

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