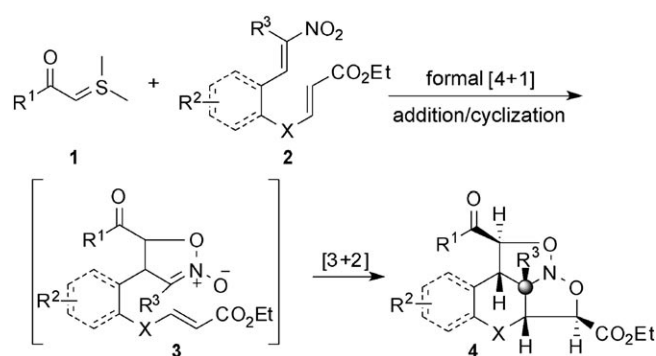


Construction of Fused Heterocyclic Architectures by Formal [4+1]/[3+2] Cycloaddition Cascade of Sulfur Ylides and Nitroolefins**

Liang-Qiu Lu, Fang Li, Jing An, Ji-Ji Zhang, Xiao-Lei An, Qiu-Lin Hua, and Wen-Jing Xiao*

Over the last 50 years, seminal research from the groups of Franzen,^[1] Corey,^[2] Trost,^[3] Aggarwal,^[4] and Dai^[5] have established sulfur ylides^[6] as valuable and versatile intermediates in synthetic chemistry. As a consequence, sulfur ylides are widely utilized for the construction of epoxide, aziridine, and cyclopropane architectures. Recently, studies by Tang and co-workers^[7] and others^[8] have significantly extended the scope of the ylide-initiated reactions and outlined the first examples of tandem reactions initiated by sulfur ylides to furnish a range of functionalized cyclic compounds beyond three-membered rings. Despite the advances, the search for unprecedented ylide-based multiple cascade reactions continues, with the goal of increasing the diversity of possible substrates and the architectural complexity of products in a step-economical fashion.^[9] Recently, our laboratory implemented a new reaction of sulfur ylides with nitroolefins to afford diverse and structurally complex oxazolidin-2-ones, wherein a transiently generated cyclic nitronate was involved.^[10] On this basis, we became interested in the possibility of using the above mentioned cyclic nitronate as a suitable 1,3-dipole to react with electron-deficient components in situ, and in doing so create multiple bonds, rings, and stereocenters in a single transformation. Herein, we report a successful execution of this idea and describe the first intermolecular [4+1]/intramolecular [3+2] cycloaddition cascade of sulfur ylides and alkene-tethered nitroolefins.^[11] This novel and catalyst-free strategy allows rapid access to functionalized 2,3-trioxa-2a-azapentaleno[1,6-*ab*]naphthalenes, 2,3-dioxa-5-thia-2a-azapentaleno[1,6-*ab*]naphthalenes, and isoxazolo[4,3,2-*hi*][2,1]benzisoxazoles in a highly concise fashion (Scheme 1); and these products are versatile synthons for the construction of densely functionalized chromans, thiochromans, amino acids, amino alcohols, and other important heterocycles.^[12]



Scheme 1. Concept of the formal [4+1]/[3+2] cycloaddition cascade. Four bonds, three rings, five consecutive stereogenic centers, and one quaternary carbon center are formed from versatile synthons. The products are densely functionalized rings.

We initially studied the reaction of dimethyl (2-oxo-2-phenylethyl)sulfonium ylide (**1a**) with (*E*)-ethyl 3-(2-((*E*)-2-nitrovinyl)phenoxy)acrylate (**2a**) in acetonitrile at 0°C for 12 hours, at which point the reaction mixture was warmed to room temperature and stirred for an additional eight hours. To our delight, the proposed cycloaddition cascade was indeed facile and afforded ethyl 1-(phenylcarbonyl)-4,4a,9b,9c-tetrahydro-1*H*-2,3,5-trioxa-2a-azapentaleno[1,6-*ab*]naphthalene-4-carboxylate (**4a**) as a major isolable product in 43% yield with great diastereocontrol (Table 1,

Table 1: Optimization of the reaction conditions for the cycloaddition cascade.^[a]

Entry	Solvent	Conc. [M]	t [h]	Yield [%] ^[b]	d.r. ^[c]
1	CH ₃ OH	0.1	15	26	n.d. ^[d]
2	CH ₃ CN	0.1	20	43	> 95:5
3	THF	0.1	18	68	> 95:5
4	toluene	0.1	24	32	n.d.
5	CH ₂ Cl ₂	0.1	20	79	> 95:5
6	CHCl ₃	0.1	20	81	> 95:5
7	CHCl ₃	0.05	20	86	> 95:5
8	CHCl ₃	0.02	24	89	> 95:5
9 ^[e]	CHCl ₃	0.02	18	85	> 95:5

[a] Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), and solvent (5–25 mL). [b] Yield of isolated product. [c] Determined by ¹H NMR methods. [d] n.d. = not determined. [e] 1-(2-Chlorophenyl)thiourea (20 mol%) was used.

[*] L.-Q. Lu, Dr. F. Li, J. An, J.-J. Zhang, X.-L. An, Q.-L. Hua, Prof. Dr. W.-J. Xiao
Key Laboratory of Pesticide & Chemical Biology
Ministry of Education, College of Chemistry
Central China Normal University
152 Luoyu Road, Wuhan, Hubei 430079 (China)
Fax: (+86) 027-6786-2041
E-mail: wxiao@mail.ccnu.edu.cn
Homepage: <http://chem-xiao.ccnu.edu.cn/>

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entry 2). The structure and relative configuration of **4a** were unambiguously established by X-ray crystallographic analysis.^[13]

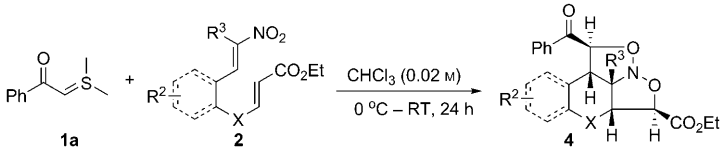
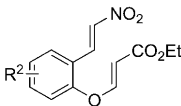
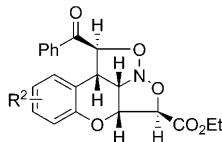
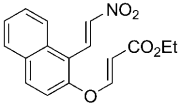
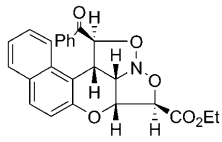
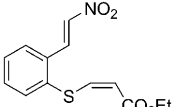
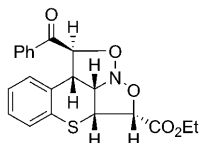
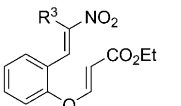
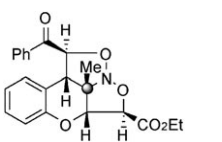
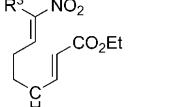
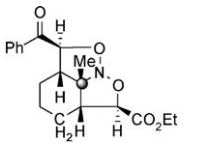
As shown in Table 1, the use of different solvents has a pronounced effect on the reaction efficiency, although excellent levels of diastereoselectivity were observed for a diverse range of reaction media (Table 1, entries 1–6). Notably, this cascade sequence worked very well in chloroform (CHCl₃) to afford **4a** in 81 % yield (Table 1, entry 6). A brief survey of substrate concentrations indicated that 0.02 M was ideal (Table 1, entry 8). As expected, an improved reaction rate was observed when an hydrogen-bonding donor catalyst, 1-(2-chlorophenyl)thiourea,^[10] was employed; however, the yield of the product was slightly decreased in this case (Table 1, entry 9).

With the optimal conditions in hand, the scope of the nitroolefins was explored. As highlighted in Table 2, the reaction displayed excellent generality and significant structural variation in the nitroolefin component was tolerated. Typically, methyl and methoxy substituents were incorporated onto the aryl ring at the *meta*- or *para*-positions, relative to the oxygen atom, without loss in reaction efficiency or diastereocontrol (Table 2, entries 2–4). Variation in the electronic contribution of the aryl architecture was also possible. Relatively electron-deficient *para*-chloro- or *para*-bromo-substituted substrates were successfully utilized in this reaction (Table 2, entries 5 and 6). Moreover, it was found that the aryl framework could be extended to naphthalene-derived substrates, generating product **4g** in 86 % yield (Table 2, entry 7). As expected, sulfur-tethered **2h** proved to be a viable reaction partner (Table 2, entry 8), affording a densely functionalized thiochroman. Notably, the nitroolefin bearing either *E* enoates (Table 2, entries 1–7, 9 and 10) or *Z* enoates (Table 2, entry 8) were utilized in this cascade reaction without significant loss in reaction efficiency.^[13] In addition to the substrates with an aryl framework, an aliphatic linear substrate was also tolerated (Table 2, entry 10). Therefore, in only one operation two simple, acyclic molecules (**1a** and **2j**) were converted into a fused tricyclic compound bearing five contiguous stereogenic centers in 83 % yield. The construction of the quaternary carbon center still remains a chal-

lenge in modern organic synthesis.^[14] As highlighted in entries 9 and 10 in Table 2 nitroolefins **2i** and **2j**, both having a methyl group in the α -position, can readily participate in this reaction and afford the corresponding quaternary carbon-containing adducts **4i** and **4j** in 75 and 83 % yields, respectively.

As exemplified in Table 3, a wide array of sulfur ylides was suitable for this cascade strategy. The electronic nature of the aryl ring of the sulfur ylides had little effect on the reaction efficiency and stereoselectivity (Table 3, entries 1–9). Incorporation of alkyl and alkoxy substituents at the *ortho* or *para* position revealed that steric variation of the ylide component can be tolerated (Table 3, entries 2–4). Furthermore, a heterocycle-derived ylide (Table 3, entry 10) was readily tolerated in this cascade cycloaddition. The scope of this reaction was also significantly extended to the use of alkyloxy- and alkyl-acyl ylides. For example, ethyloxyacyl

Table 2: [4+1]/[3+2] Cycloaddition cascade of sulfur ylide **1a** with representative nitroolefins.^[a]

							
Entry	Nitroolefin	Product	R ²	R ³	Yield [%] ^[b]	d.r. ^[c]	
1			4a	H	H	89	> 95:5
2			4b	4-MeO	H	91	> 95:5
3			4c	5-MeO	H	92	> 95:5
4			4d	4-Me	H	99	> 95:5
5			4e	4-Cl	H	94	> 95:5
6			4f	4-Br	H	97	> 95:5
7			4g			86	> 95:5
8 ^[d]			4h			85	> 95:5
9 ^[e]			4i	H	Me	75	> 95:5
10 ^[f]			4j	H	Me	83	> 95:5

[a] Reaction conditions: **1a** (0.55 mmol), **2** (0.5 mmol), and CHCl₃ (25 mL), 0 °C to RT, 24 h. [b] Yield of isolated product. [c] Determined by ¹H NMR methods. [d] The structure of **4h** was further confirmed by X-ray analysis; see reference [13]. [e] 0 °C for 4.5 h, and then 50 °C for 40 h. [f] 0 °C for 10 h, and then 62 °C for 4 days.

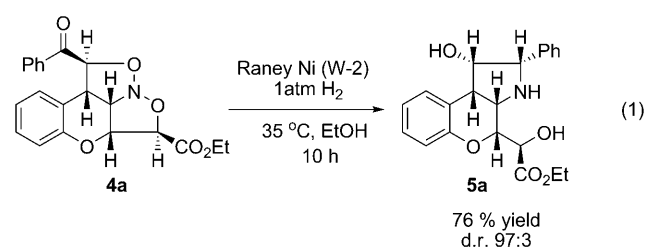
Table 3: [4+1]/[3+2] Cycloaddition cascade of representative sulfur ylides with nitroolefin **2a** or **2i**.^[a]

Entry	Sulfur ylide 1	R ¹	Product 4	R ³	Yield [%] ^[b]	d.r. ^[c]
1	1a	Ph	4a	H	89	> 95:5
2	1b	4-MeOC ₆ H ₄	4k	H	92	> 95:5
3	1c	2-MeOC ₆ H ₄	4l	H	90	> 95:5
4	1d	4-MeC ₆ H ₄	4m	H	93	> 95:5
5	1e	4-FC ₆ H ₄	4n	H	90	> 95:5
6	1f	4-ClC ₆ H ₄	4o	H	90	> 95:5
7	1g	4-BrC ₆ H ₄	4p	H	90	> 95:5
8	1h	3-BrC ₆ H ₄	4q	H	94	> 95:5
9 ^[d]	1i	4-NO ₂ C ₆ H ₄	4r	H	90	95:5
10	1j	2-furanyl	4s	H	97	> 95:5
11 ^[e]	1k	EtO	4t	Me	82	> 95:5
12 ^[f]	1l	Me	4u	Me	75	> 95:5

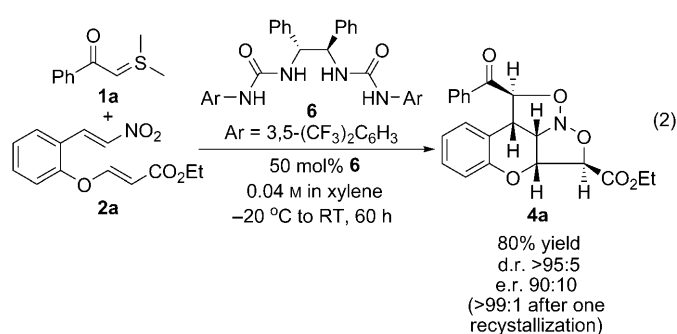
[a] Reaction conditions: **1** (0.55 mmol), **2a** or **2i** (0.5 mmol), and CHCl₃ (25 mL), 0 °C to RT, 24 h. [b] Yield of isolated product. [c] Determined by ¹H NMR methods. [d] 0 °C for 16 h, and then 62 °C for 4 days (1.2 equiv of **1i**). [e] 0 °C for 9 h, and then 50–55 °C for 36 h (2.0 equiv of **1k**). [f] 0 °C for 6 h, and then 62 °C for 36 h (12.5 equiv of **1l**).

ylide (**1k**) and acetyl ylide (**1l**) were employed in the reaction of **2i** and provided the corresponding **4t** and **4u** with a functionalized quaternary carbon center in high yields and excellent diastereoselectivities (Table 3, entries 11 and 12).

A demonstration of the synthetic manipulation of the cycloaddition products is presented in Equation (1). Azapentaleno[1,6-*ab*]naphthalene **4a** was subjected to hydrogenolysis with Raney Ni to readily cleave N–O bonds and to afford chroman **5** bearing an attractive pyrroline ring in high yield.^[12]



An initial attempt to carry out the asymmetric version of this reaction has also been examined. The simple C2-symmetric urea **6** was employed in the reaction of **1a** and **2a** [Eq. (2)]. Notably, this catalyst could effectively control the formation of one stereoisomer over the possible 32 (2⁵) stereoisomers in 80% yield with 90:10 e.r. and greater than 95:5 d.r. To our knowledge, this is the first successful example of chiral Brønsted acid promoted asymmetric reaction participated by sulfur ylides.



In summary, a new and powerful process combination of an intermolecular [4+1] and an intramolecular [3+2] cycloaddition has been developed for the rapid and selective construction of fused heterocyclic compounds. This mild and operationally simple cascade cycloaddition has been accomplished with a wide range of sulfur ylides and alkene-tethered nitroolefins. All five consecutive stereogenic centers could be stereospecifically controlled in this reaction. Complete diastereoselectivity and excellent reaction efficiency were obtained in all cases examined.

Experimental Section

Representative procedure: **2a** (0.5 mmol) and CHCl₃ (10 mL) were added to a 50 mL flask. The solution of **1a** (0.55 mmol) in CHCl₃ (15 mL) was then slowly added at 0 °C using a syringe pump, and the resulting reaction mixture was stirred at 0 °C for 12 h at which point **2a** was consumed as determined by TLC analysis. At this stage the reaction mixture was warmed up to room temperature and stirred for 12 h. Upon the completion of reaction, which was monitored by TLC analysis, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 10:1→5:1) to give pure **4a** in 89% yield with greater than 95:5 d.r.

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