

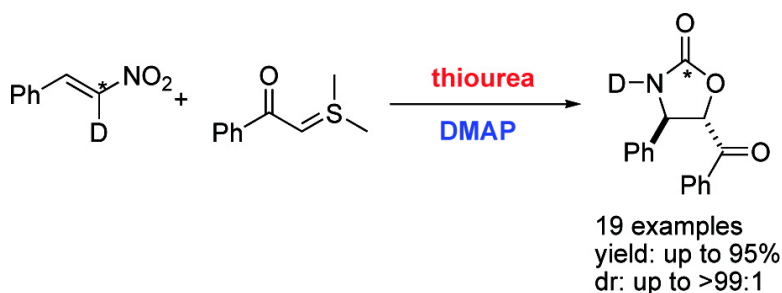
Communication

A New Entry to Cascade Organocatalysis: Reactions of Stable Sulfur Ylides and Nitroolefins Sequentially Catalyzed by Thiourea and DMAP

Liang-Qiu Lu, Yi-Ju Cao, Xiao-Peng Liu, Jing An, Chang-Jiang Yao, Zhi-Hui Ming, and Wen-Jing Xiao

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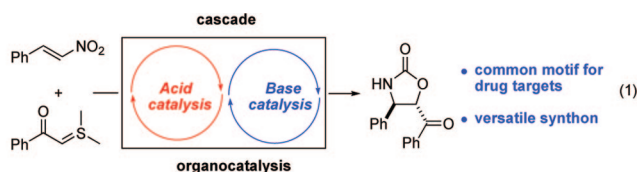
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The development of new methods that would rapidly transform readily accessible starting materials into complex molecules is of considerable current interest.¹ Advances in these methodologies have mainly focused on metal-catalyzed procedures with palladium, rhodium, nickel, ruthenium, and gold being the most prevalent.² Recently, significant efforts have been made to develop organocatalytic cascade reactions with the objective of mimicking the biosynthetic strategy, mainly based on enamine and/or iminium activation modes.³ Elegant examples have been reported which include secondary amine-catalyzed Robinson annulation,⁴ reductive Michael cyclization,⁵ conjugate addition–chlorination,⁶ conjugate addition–amination,⁷ Michael–aldol condensation,⁸ and Michael–Michael–aldol sequence.⁹ Although many catalytic systems have been developed for organocatalytic transformations, organocatalytic cascade chemistry has not achieved its full potential. The search for new strategies that increase compatibility and diversity of organocatalysts, reaction types, and starting materials is highly desirable.

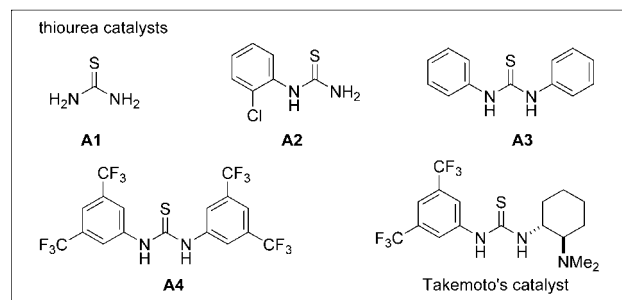
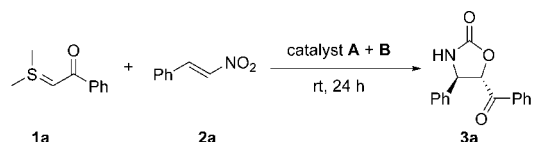
Sulfur ylides¹⁰ and nitroolefins¹¹ have proven to be extremely useful reagents in organic synthesis. Their reactivities and synthetic diversities provide an important platform for the development of novel cascade strategies. As part of an ongoing program to develop novel methodologies that are capable of building molecular complexity from simple substrates, we recently reported a new process combining a cross metathesis step with intramolecular hydroarylation.¹² In this communication, we describe a new cascade protocol: an unprecedented reaction of stable sulfur ylides and nitroolefins sequentially catalyzed by thiourea and DMAP to afford diverse and structurally complex oxazolidin-2-ones (eq 1). Oxazo-



lidin-2-ones are an important class of biologically active molecules¹³ and versatile intermediates¹⁴ in organic synthesis. They are now easily accessible in a highly concise fashion using our procedures.

We initially studied the reaction of sulfur ylide **1a** with *trans*- β -nitrostyrene (**2a**) in the presence of 10 mol % of Takemoto's catalyst¹⁵ in dichloromethane at room temperature for 24 h. The reaction afforded *anti*-5-benzoyl-4-phenyloxazolidin-2-one (**3a**) as a major isolable product (35%) with great diastereoselectivity (dr >95:5) and low enantioselectivity (ee 6%). The structure of **3a** was proposed by NMR and unambiguously confirmed by X-ray diffraction.¹⁶ Encouraged by this result, we examined the reaction in detail under a variety of conditions in an attempt to increase the yield. The representative results are summarized in Table 1 (see

Table 1. Condition Optimization for the Reaction of Sulfur Ylide **1a** with Nitrostyrene **2a**^a

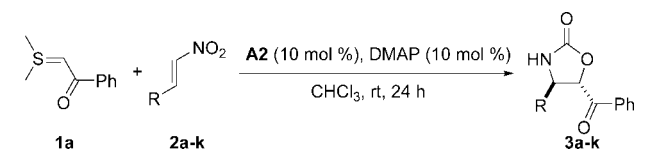


entry	catalyst		solvent	yield (%) ^b	dr ^c (anti/syn)
	A	B			
1	none	none	CH ₂ Cl ₂	trace	n.d. ^d
2	A2	none	CH ₂ Cl ₂	10	n.d. ^d
3	none	DMAP	CH ₂ Cl ₂	11	n.d. ^d
4	A1	DMAP	CH ₂ Cl ₂	60	95:5
5	A2	DMAP	CH ₂ Cl ₂	79	98:2
6	A3	DMAP	CH ₂ Cl ₂	44	98:2
7	A4	DMAP	CH ₂ Cl ₂	8	n.d. ^d
8	A2	DBU	CH ₂ Cl ₂	trace	n.d. ^d
9	A2	DABCO	CH ₂ Cl ₂	32	98:2
10	A2	NEt ₃	CH ₂ Cl ₂	43	99:1
11	A2	DMAP	CHCl₃	83	97:3
12	A2	DMAP	THF	13	n.d. ^d
13	A2	DMAP	toluene	11	n.d. ^d
14	A2	DMAP	DMF	27	n.d. ^d
15	A2	DMAP	CH ₃ CN	20	n.d. ^d

^a Reaction conditions: sulfur ylide **1a** (0.5 mmol), nitroolefin **2a** (0.4 mmol), catalyst **A** (10 mol % based on **2a**), catalyst **B** (10 mol % based on **2a**), solvent (1.6 mL), room temperature, 24 h. ^b Isolated yield. ^c Determined by ¹H NMR. ^d n.d. = not determined.

Supporting Information for more results). Among the catalysts examined in dichloromethane (Table 1, entries 2–10), the combination of 1-(2-chlorophenyl)thiourea (**A2**) and *N,N*-dimethylaminopyridine (DMAP) showed the highest activity for this cascade organocatalysis (Table 1, entry 5), while the reaction gave a complicated mixture in the absence of catalysts (Table 1, entry 1). With the use of **A2** or DMAP alone, the reaction gave **3a** in poor yields (Table 1, entries 2 and 3). Other catalyst combinations such as **A1**/DMAP, **A3–4**/DMAP, **A2**/DBU, **A2**/DABCO, and **A2**/NEt₃ were less effective (Table 1, entries 4 and 6–10).

A survey of solvents¹⁶ indicated that this new reaction was sensitive to the solvent medium (Table 1, entries 5 and 11–15),

Table 2. Organocatalyzed Cascade Reaction of Sulfur Ylide **1a** with Representative Nitroolefins^a


entry	nitroolefin		product	yield (%) ^b	dr ^c (anti/syn)
	R	2			
1	Ph	2a	3a	83	97:3
2	4-MeOPh	2b	3b	95	94:6
3	4-ClPh	2c	3c	70	97:3
4	4-FPh	2d	3d	75	97:3
5	2-ClPh	2e	3e	89	95:5
6	2-NO ₂ Ph	2f	3f	73	97:3
7	3-BrPh	2g	3g	74	96:4
8	2,4-Cl ₂ Ph	2h	3h	82	99:1
9	1-naphthyl	2i	3i	84	99:1
10	<i>n</i> -Pr	2j	3j	47	95:5
11	<i>i</i> -Pr	2k	3k	68	99:1

^a Reaction conditions: sulfur ylide **1a** (0.5 mmol), nitroolefin (0.4 mmol), **A2** (10 mol %), DMAP (10 mol %), CHCl₃ (1.6 mL), room temperature, 24 h. ^b Isolated yield. ^c Determined by ¹H NMR.

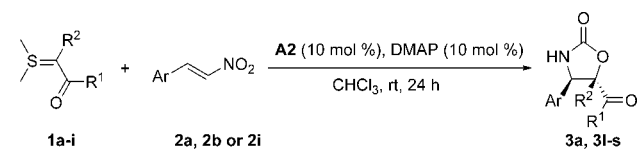
and great levels of reaction efficiency and diastereocontrol could be obtained in chloroform (Table 1, entry 11).

Experiments that study the scope of the nitroolefin substrate are outlined in Table 2. Under optimized conditions, a wide range of aromatic nitroolefins underwent reactions with sulfur ylide **1a** in high isolated yields and diastereoselectivities (Table 2, entries 1–11). The reaction appears quite tolerant with respect to the steric and electronic contribution of the substituent on the benzene ring of the nitroolefin (Table 2, entries 2–8). As revealed in entries 3–5, 7, and 8, *ortho*-, *meta*-, and *para*-halogen-substituted nitrostyrenes can be successfully utilized in this organocatalysis cascade reaction to produce the corresponding oxazolidin-2-one products in high yields (70–89%). Such halogenated oxazolidin-2-one derivatives should be valuable intermediates for further transformations.¹⁷

Perhaps more significant, the nitroolefin bearing an aliphatic β -substituent proved to be a viable reaction partner. Thus, (*E*)-1-nitropent-1-ene (**2j**) and (*E*)-3-methyl-1-nitrobut-1-ene (**2k**) were employed in the reaction of **1a** and efficiently provided *anti*-5-benzoyl-4-propyloxazolidin-2-one (**3j**) and *anti*-5-benzoyl-4-isopropyloxazolidin-2-one (**3k**) in good yields and excellent diastereoselectivities (Table 2, entries 10 and 11), respectively.

This organocatalysis cascade strategy appears to be well suitable for other stable sulfur ylides, too, therefore allowing for diastereoselective formation of substituted oxazolidin-2-ones in good to excellent isolated yields (Table 3). The electronic nature of the aryl ring of the sulfur ylides has little effect on the reaction efficiency and selectivity (Table 3, entries 1–4). Significantly, heterocycle-containing ylide (Table 3, entry 5, R¹ = 2-furanyl) and sterically encumbered ylide (Table 3, entry 7, R¹ = *tert*-butyl) are readily tolerated in this cascade transformation. Incorporation of a methyl group in the α -position of the phenylacetyl ylide proved to be feasible, as the reaction of **1f** resulted in the formation of 4,5,5-trisubstituted oxazolidin-2-one (**3p**) bearing a quaternary carbon center in 15% yield and 91:9 dr (Table 3, entry 6).

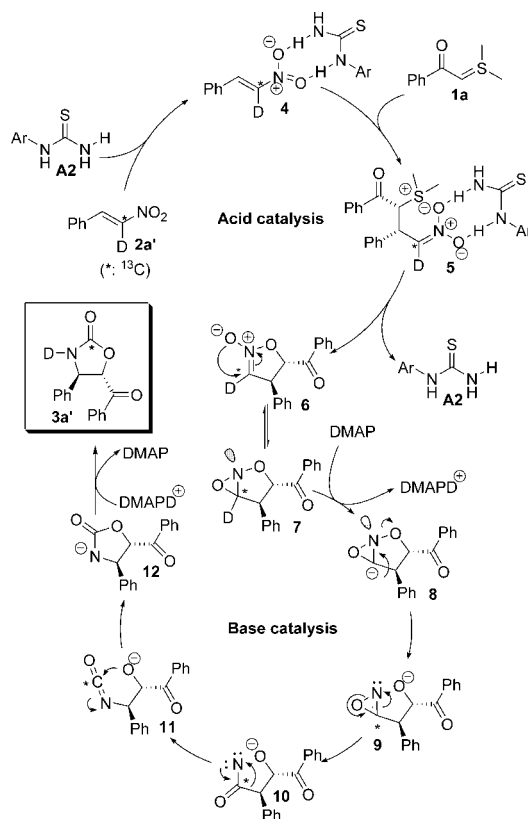
The scope of this reaction was also extended to the use of ethoxylacetyl ylide (**1h**) (Table 3, entry 8), and in principle, the product could be readily used in the synthesis of α -hydroxy- β -amino acids.¹⁸ Note that ylides that are too stable or too sterically hindered cannot be employed in this reaction, even at higher

Table 3. Organocatalyzed Cascade Reaction of Representative Stable Sulfur Ylides with Nitroolefins^a


entry	ylide		product	yield (%) ^b	dr ^c (anti/syn)
	R ¹	R ²			
1	Ph	H	1a 3a	83	97:3
2	4-MeOPh	H	1b 3l	76	>99:1
3	4-MePh	H	1c 3m	92	99:1
4	4-ClPh	H	1d 3n	81	95:5
5	2-furanyl	H	1e 3o	83	94:6
6	Ph	CH ₃	1f 3p	15	91:9
7	<i>t</i> -Bu	H	1g 3q	53	99:1
8	OEt	H	1h 3r	47	99:1
9	OEt	CO ₂ Et	1i 3s	0	n.d. ^d

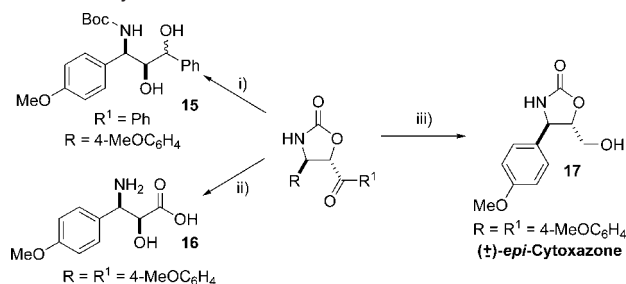
^a **2a** was employed in entries 1, 3–6, and 9; **2b** was employed in entry 2, and **2i** was employed in entries 7 and 8. ^b Isolated yield. ^c Determined by ¹H NMR. ^d n.d. = not determined.

Scheme 1. A Mechanistic Rationale for the Cascade Organocatalysis



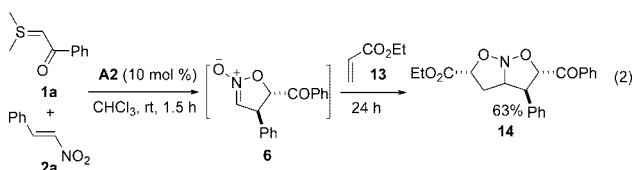
temperature (Table 3, entry 9). To demonstrate the preparative utility, the reaction of phenylacetyl ylide (**1a**, 4.51 g) with 4-methoxy nitrostyrene (**2b**, 3.58 g) was performed on a 20 mmol scale in the presence of 10 mol % of **A2** (0.37 g) and DMAP (0.24 g). One recrystallization gave the expected *anti*-**3b** (4.01 g) in 68% yield with >99:1 dr.

While a precise reaction mechanism awaits further study, a plausible catalytic cycle is depicted in Scheme 1. The cascade sequence is initiated by the addition of sulfur ylide **1a** to nitroolefin **2a'** in the presence of thiourea catalyst **A2**, which results in the formation of double H-bonding stabilized nitronate **5**.¹⁹ Subsequent

Scheme 2. Synthetic Transformation of Oxazolidin-2-one Products^a

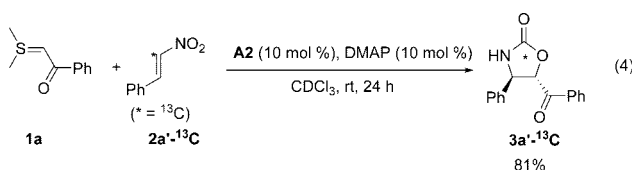
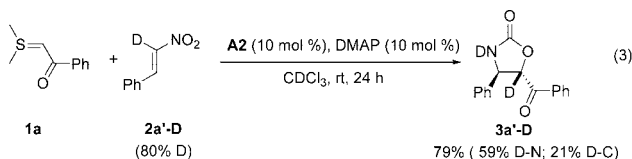
^a Reagents and conditions: (i) a. NaBH₄, MeOH, 91%; b. 20% aq KOH; c. (Boc)₂O, DMAP, 65% over two steps; (ii) a. MCPBA, NaH₂PO₄·H₂O, DCE, 62%; b. KOH, EtOH, reflux, 83%; (iii) a. MCPBA, NaH₂PO₄·H₂O, DCE, 62%; b. NaBH₄, HOAc, THF, 88%.

oxygen alkylation affords isoxazoline *N*-oxide **6**²⁰ and regenerates the thiourea catalyst. Attempts to isolate **6** in its pure form were unsuccessful; however, it could be trapped by the addition of ethyl acrylate to the reaction system (eq 2).



We assumed that isoxazoline *N*-oxide **6** would be converted into oxaziridine intermediate **7** under the reaction conditions,²¹ which then generates intermediate **8** upon deprotonation of the deuterium (D) by DMAP. The ring opening is driven by a release in ring strain that would yield nitrene **9**. Finally, the nitrene **10** would undergo Hofmann rearrangement to form isocyanate **11**.²² This would allow for intramolecular ring closing to provide **12**, which then reacts with DMAP-D⁺ to afford oxazolidin-2-one and regenerates DMAP.

To support this proposed mechanism, we have carried out D- and ¹³C-labeling experiments.¹⁶ When the deuterated nitrostyrene **2a**-D (80% D incorporation) was subjected to our standard conditions, oxazolidin-2-one **3a**-D with the deuterium bonding to nitrogen atom (59% D incorporation, and 21% deuterium at 5-position) was obtained in 79% yield (eq 3). Furthermore, when the reaction of ¹³C-labeled substrate **2a**-¹³C was examined, the oxazolidin-2-one **3a**-¹³C with the ¹³C at the 2-position was isolated in 81% yield (eq 4). These results are consistent with the proposed mechanism.



A demonstration of the synthetic manipulation of the products is presented in Scheme 2. As expected, oxazolidin-2-ones **3b** and **3l** can be readily converted into 1,2-amino alcohols (**15**) and α -hydroxyl- β -amino acid (**16**), respectively. Moreover, Baeyer–Villiger oxidation of **3l** with MCPBA followed by borohydride reduction provides *epi*-cytoxazone in 55% yield over two steps.

In summary, we have developed a new cascade organocatalytic reaction that allows efficient and rapid access to diverse and structurally complex oxazolidin-2-ones from simple starting materials and catalysts. Further investigation on the mechanism of the reaction as well as a catalytic asymmetric variant¹⁶ is ongoing.

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Supporting Information Available: Experimental details and spectral data for all unknown compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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