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Concise Asymmetric Synthesis of Fully Substituted Isoxazoline-*N*-Oxide through Lewis Base Catalyzed Nitroalkene Activation

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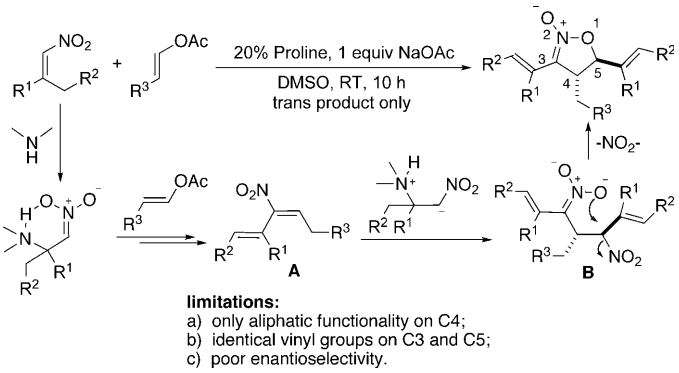
Structurally unique heterocycles are of great importance in chemical and biological related research.[1] The isoxazoline-*N*-oxide and its derivatives are an interesting class of compounds in this family[2] and have been applied as biologically active compounds[3] and drug candidates[4] in many research areas. Moreover, with the unique functionality-enriched structures, isoxazoline-*N*-oxides have also been recognized as versatile synthetic building blocks that could be readily converted into useful intermediates for complex molecules[5] and natural product syntheses.[6]

The conventional strategies for the preparation of isoxazoline frameworks include the intramolecular 5-*exo*-tet cyclization of nitro compounds[7] and intermolecular [3+2] cycloaddition.[8] However, both approaches suffered from limited substrate scope and low overall efficiency.[9] In addition, efficient asymmetric synthesis of isoxazoline-*N*-oxides is rare.[10,11] Thus, the practical synthesis of isoxazoline-*N*-oxides remains big challenge and new efficient methodologies are highly desirable.

Recently, our group reported the amine-catalyzed β-alkyl nitroalkene activation as a new approach in promoting complex-molecule cascade synthesis. Based on this strategy, several cascade processes have been successfully developed.[12,13] All of these new methods were carried out in a one-pot fashion, providing complex products with high efficiency and good stereoselectivity. Among these new methods, one particularly interesting reaction was the synthesis of isoxazoline-*N*-oxide through nitroalkene and vinyl ester condensation (Scheme 1).[14]

This cascade approach revealed an efficient strategy in producing active diene intermediate **A** in-situ, which allowed the preparation of isoxazoline-*N*-oxide without the challenging nitronate intermediate synthesis. However, this method possessed three limitations: 1) the C-4 position was limited to aliphatic groups, 2) two identical vinyl groups on C-3 and C-5 positions, and 3) poor enantioselectivity (<15% *ee* was observed in all cases with different chiral amines).



Scheme 1. Tandem isoxazoline-*N*-oxide synthesis through Lewis base catalyzed, nitroalkene activation.

Owing to the unique mechanism and strong desire for effective synthesis of enantiomerically enriched isoxazolines, we investigated the asymmetric synthesis of these fully substituted isoxazoline-*N*-oxides. Herein, we report a simple aldehyde condensation with amine-activated nitroalkene for the formation of diene intermediates and chemoselective condensation with chiral sulfide ylides, forming fully substituted isoxazoline-*N*-oxides in one-pot with excellent yields and stereoselectivity. Moreover, from the functional-group-enriched products, simple transformations gave the (−)-clausenamide analogue in four steps with good yield and excellent stereochemistry control.

First, we postulated that the diene intermediate **A**, besides the nitroalkene/vinyl ester condensation, could also be achieved through the Lewis based mediated Henry reaction between a nitroalkene and an aldehyde. Thus, the isoxazo-

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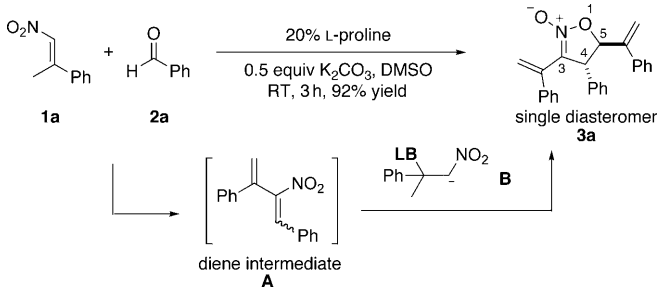
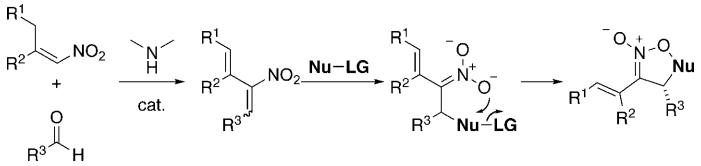
line-*N*-oxide could be prepared through a more general process with broader substrate scopes on the C-4 position. The reactions between nitroalkene **1a** and benzaldehyde **2a** were then performed. As expected, isoxazoline-*N*-oxide **3a** was obtained with excellent yields (Scheme 2).[15]



Scheme 2. Tandem nitroalkene/aldehyde condensation.

Encouraged by this result, we then moved toward the discovery of effective strategy for introducing different substituted groups on the C-3 and C-5 positions. Based on the reaction mechanism, we envisioned that functional molecules with both nucleophilic site and leaving groups (**Nu-LG**) could also be of possible reagents to give the hetero-isoxazoline-*N*-oxide (Scheme 3).



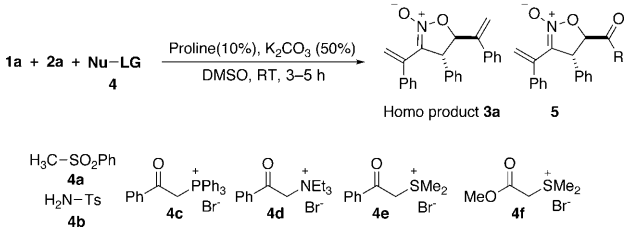
Scheme 3. Proposed alternative synthesis of C-3,C-5-unsymmetric isoxazoline-*N*-oxides.

The key for the success of this process is to identify an effective third component (**Nu-LG**) to compete with the addition of intermediate **B**, which gives the undesired homo-isoxazoline-*N*-oxide **3a**. Based on this hypothesis, compounds with **Nu-LG** functionality were employed to react with nitroalkene **1a** and aldehyde **2a** (Table 1).

Application of **4a** and **4b**, under previously developed optimal conditions, produced only the homo-isoxazoline-*N*-oxide **3a**, which was likely due to the low reactivity of the nucleophiles (entries 1 and 2). The phosphonium bromide **4c** and ammonium bromide **4d** did generate the desired product **5**. However, the reaction suffered from significant competition of homocondensation (entries 3 and 4). To our pleasure, application of sulfonium salts **4e** and **4f** gave compound **5** as the dominant product in excellent yields (entries 5 and 6). Only a trace amount of **3a** was detected.

At this stage, we then moved on to further investigate the enantioselective synthesis. Since all the chiral secondary amines did not provide good stereochemistry control,[16,17] we wondered whether chiral sulfur ylides could serve as auxiliaries to deliver the chirality. Several readily available camphor-derived sulfur ylides[18] were investigated to evaluate the stereoselectivity of these auxiliaries in this cascade process (Table 2).

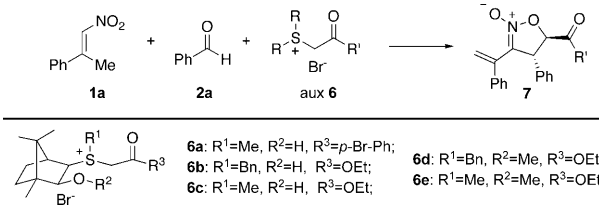
Table 1. Substrate screening for three-component condensation in the synthesis of hetero-isoxazoline-*N*-oxide.[a]



	Nu-LG	Product[b] 3a [%]	5 [%]
1	**4a**	76	<5
2	**4b**	85	<5
3	**4c**	58	35
4	**4d**	74	18
5	**4e**	<5	91[c]
6	**4f**	<5	92[c]

[a] Reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv, 0.5 M), **4** (1.1 equiv) and catalysts were mixed in solvent. [b] NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield.

Table 2. Reaction condition screening of chiral auxiliaries for asymmetric isoxazoline-*N*-oxide synthesis.[a]



	Solvent	LB (20%)	Base (1.0 equiv)	Aux.	*T* [°C]	*t* [h]	yield [%][b] (*ee* [%])[c]
1	DMSO	L-proline	K_2CO_3	**6a**	RT	12	<5 (n.d.)[d]
2	DMSO	L-proline	K_2CO_3	**6b**	RT	6	19 (n.d.)[d]
3	acetone	L-proline	K_2CO_3	**6b**	RT	6	16 (n.d.)
4	THF	L-proline	K_2CO_3	**6b**	RT	24	13 (n.d.)
5	MeOH	L-proline	K_2CO_3	**6b**	RT	6	60[e] (36)
6	MeOH	L-proline	K_2CO_3	**6c**	RT	6	81[e] (75)
7	MeOH	L-proline	K_2CO_3	**6d**	RT	6	23 (40)
8	MeOH	L-proline	K_2CO_3	**6e**	RT	6	43 (59)
9	MeOH	L-proline	Cs_2CO_3	**6c**	RT	6	54 (76)
10	MeOH	L-proline	Cs_2CO_3	**6c**	−25	48	87[e] (82)
11	MeOH	L-proline	Cs_2CO_3	**6c**	−40	60	62[e] (82)
12	MeOH	D-proline	Cs_2CO_3	**6c**	−25	48	90[e] (86)
13	MeOH	pyrrolidine	Cs_2CO_3	**6c**	−25	48	86[e] (91)
14	MeOH	N-Me-Gly	Cs_2CO_3	**6c**	−25	48	51[e] (89)

[a] General reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv, 0.15 M) and auxiliary **6** (1.1 equiv). Ester exchange happened in MeOH, and only the methyl ester was detected. [b] NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] Determined by HPLC on chiral stationary phases. [d] Major products were homo-isoxazoline **3a** and the epoxide. [e] Isolated yield.

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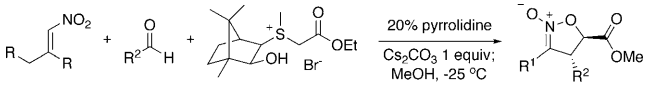
The ketone ylide **6a**[19] did not promote the heterocoupling reaction (entry 1), giving the homocoupling product **3a** (>85% yield) and epoxide product,[20] which was likely caused by the relatively low nucleophilicity associated with the more hindered chiral ylide in a polar solvent (compared to the simple ketone ylide **4e**). The ester-modified ylide **6b** produced the heterocoupling product 7 though with poor yield (entry 2). Solvent screening indicated that MeOH was the best solvent (entries 3–5). Further modification on the ylides revealed **6c** (R^1 = Me and R^2 = H) as the optimal auxiliary (entry 6) and Cs_2CO_3 as the preferred choice of base under lower temperature (entry 10), producing the desired product in excellent yield. Interestingly, the secondary amine Lewis base catalyst also influenced the stereochemistry of the products. With either L- or D-proline, the absolute stereochemistry of product **7** was identical (entries 10 and 12), which indicated that the ylide auxiliary dominated the stereochemistry control in the diene nucleophilic addition. However, to our surprise, slightly improved stereoselectivity was observed when D-proline was used as the catalyst (entry 12). Further investigation revealed that achiral secondary amine pyrrolidine gave improved stereoselectivity, without sacrificing much of the reactivity (entry 13, 86% yield and 91% *ee*). Application of *N*-methylglycine gave the similarly good enantioselectivity with moderate yield (entry 14). Notably, >50% of the camphor auxiliary was recovered during the purification. With the optimal conditions, various nitroalkenes **1** and aldehydes **2** were applied to investigate the reaction substrate scope.

The reaction tolerates various nitroalkenes, including aryl, alkyl and cyclic structures (Table 3). Moreover, various aldehydes (aromatic, aliphatic and heteroaromatic) were suitable for this transformation. Compared to the nitroalkenes, the aldehyde substrates have stronger influence on the overall yield and stereoselectivity. With electron-deficient aldehydes (i.e., **7h**), excellent yields were obtained. However, the enantioselectivity was slightly decreased. This could be explained by the higher reactivity of the diene intermediate, which gave the lower efficiency in the stereoselectivity. Sterically hindered aldehydes (i.e., **7f**), on the other hand, promoted the stereoselectivity by providing better spatial control, and therefore led to the observed high enantioselectivity. Similar steric and electronic effects of the aldehyde were observed for all the other substrates that were tested.

This new enantioselective isoxazoline-*N*-oxides synthesis lit up our interest in its application towards the total synthesis of biological active, structurally unique natural products. Simple transformations would allow easy synthesis of complex molecules with high efficiency and good stereoselectivity. One great example is its application in the synthesis of *all-cis* γ-lactam, towards the synthesis of clausenamide derivatives (Scheme 4).[21]

Table 3. Asymmetric synthesis of substituted isoxazoline-*N*-oxides.[a]

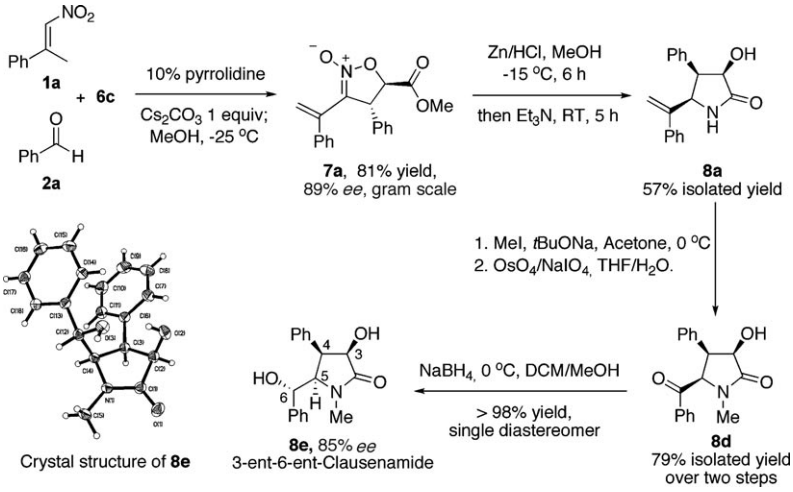


1 2 6c 7

	R^1	R^2		Yield [%][b]	*ee* [%][c]
1		C_6H_5	**7a**	86	91
2		*p*-OMe-C_6H_4	**7b**	82	94
3		*p*-Me-C_6H_4	**7c**	89	91
4		2-Py	**7d**	90	80
5		2-furanyl	**7e**	71	90
6	Ph	1-naphthyl	**7f**	86	96
7		*n*Pr	**7g**	63	88
8		*p*-NO_2-C_6H_4	**7h**	92	81
9		2-NO_2-C_6H_4	**7i**	82	70
10		2-OMe-C_6H_4	**7j**	84	88
11		2,4-di-Me-C_6H_3	**7k**	79	92
12		2-furanyl	**7l**	81	76
13		2-OMe-C_6H_4	**7m**	88	81
14	*p*-Cl-Ph	*p*-OMe-C_6H_4	**7n**	81	92
15		1-naphthyl	**7o**	91	93
16		2-OMe-C_6H_4	**7p**	75	81
17		1-naphthyl	**7q**	70	93
18		C_6H_5	**7r**	80	85
19		*p*-Me-C_6H_4	**7s**	80	90
20		1-naphthyl	**7t**	85	91
21		*p*-NO_2-C_6H_4	**7u**	93	65

[a] General reaction conditions: **1** (1.2 equiv), **2** (1.0 equiv, 0.15 M) and auxiliary **6c** (1.1 equiv). Ester exchange happened in MeOH and only the methyl ester was detected. [b] Isolated yield. [c] *ee* was determined by HPLC on chiral stationary phases.

The clausenamide derivatives **8e** was prepared in five steps from nitroalkene **1a** with 38% overall yield, on a gram scale. The synthesis involved neither exotic reagents nor protecting groups, giving high atomic efficiency. Moreover, excellent stereochemistry control was achieved in this



Scheme 4. Gram-scale synthesis of clausenamide derivatives.

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transformation, and **8e** was prepared in 85% *ee* (>99% *ee* after one recrystallization). The reduction of **8d** was highly diastereoselective to give **8e**.[22] Notably, **8e** was one of the most challenging isomers in the clausenamide family, since it possesses *all-cis*-substitution on the γ-lactam ring. With the reported synthetic route, preparation of different clausenamide derivatives, including different substitute groups on C-4 and C-5 positions and different stereoisomers at all four stereogenic centers, is feasible with simple modifications.

In conclusion, a one-pot asymmetric synthesis of fully substituted isoxazoline-*N*-oxides was developed. The methodology was based on a Lewis base catalyzed, multicomponent condensation, which allowed easy derivatization to achieve various substitutions at selected positions. Excellent yields and enantioselectivity were obtained. With the high efficiency and excellent chemo- and enantioselectivity, the reported method provides a new protocol for the preparation of isoxazoline derivatives, which could be applied both for the discovery of new drug candidates and for the construction of complex building blocks. Successful transformation of isoxazoline-*N*-oxide **7a** into a γ-lactam in a highly stereoselective fashion and gram-scale synthesis of clausenamide derivative **9e**, further highlights the advantages of the reported method as a powerful approach for the preparation of complex molecules with high atom efficiency and good stereoselectivity.

Experimental Section

General procedure for the synthesis of isoxazoline-*N*-oxide 3a: The nitroalkene **1a** (176 mg, 1.1 mmol, 1.1 equiv) was added to a solution of aldehyde **2a** (0.5 mmol, 1.0 equiv), L-proline (25 mg, 0.22 mmol, 0.2 equiv), and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv) in DMSO (5.5 mL), with aldehyde concentration as 0.1 M. The resulting mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (100 mL). The organic phase was washed with HCl (1.0 M), saturated $NaHCO_3$ (aq.), and brine, and then dried over anhydrous Na_2SO_4. Flash silica gel chromatography was then applied to give **3a** (169 mg, 92%) as clear oil.

General procedure for preparation of three-component isoxazoline-*N*-oxide 7a: The nitroalkene **1a** (114 mg, 0.7 mmol, 1.4 equiv) was added to a solution of the sulfur ylide **4d** (219 mg, 0.6 mmol, 1.2 equiv) in MeOH (0.4 M for nitroalkene), till the ylide dissolved. The mixture was cooled down to −25 °C. Pyrrolidine (7 mg, 0.1 mmol, 0.2 equiv) and K_2CO_3 (35 mg, 0.25 mmol, 0.5 equiv) were then added and the resulting mixture was stirred for 30 min. The aldehyde **2a** (0.5 mmol, 1.0 equiv) in MeOH (4.6 mL) was added dropwise over a period of 10 min. The resulting reaction mixture was stirred at −25 °C for 48 h. The mixture was then diluted with EtOAc (20 mL) and the water phase was extracted with EtOAc (20 mL × 3). The organic phase was washed with HCl (1.0 M), saturated $NaHCO_3$ (aq.), and brine, and then dried over anhydrous Na_2SO_4. Flash silica gel chromatography was then applied to give the product **7a** (144 mg, 89%) as clear oil.

For explicit experimental data, including spectroscopic data, see the Supporting Information.

Acknowledgements

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Keywords: asymmetric synthesis · clausenamide · enantioselectivity · isoxazoline-*N*-oxides · Lewis bases

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[15] See the Supporting Information for the detailed screening conditions.

[16] The detailed mechanistic study of the interaction between chiral secondary amine Lewis base and the nitro alkene or the intermediate is currently under investigation.

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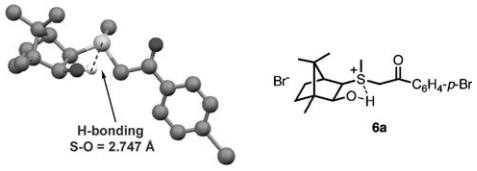

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[22] 2D NMR studies and the X-ray structure for **8e** are provided in the Supporting Information, and indicated the *all-cis* configuration of the γ-lectam.

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