

# Asymmetric 1,3-Dipolar Cycloaddition of Chiral $\alpha$ , $\beta$ -Unsaturated- $\gamma$ -Sultams with Nitrile Oxides and Nitrones

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**Abstract:** The scope and limitations of 1,3-dipolar cycloaddition reactions between nitrile oxides and chiral  $\alpha$ , $\beta$ -unsaturated- $\gamma$ -sultams **2a** and **2b** have been investigated. Only very marginal diastereoselectivity was observed for the reaction. In contrast, using double asymmetric induction strategy, the cycloaddition products from **2a** and chiral nitrones were obtained in better diastereomeric ratios (up to 7.1:1).

**Key Words:** 1,3-Dipolar cycloaddition, chiral sultams, nitrile oxides, nitrones.

Sulfonamides have long been recognized for their wide-range of biological activities [1]. Recently, much interest has been directed to their cyclic counterparts, the sultams, which also exhibit a vast variety of biological activities. A number of substituted sultams have proven to be useful heterocycles for medicinal applications [2]. As a consequence, chemical syntheses towards sultams have continued to be an attractive topic for intense research [3]. On the other hand, structural rigid chiral sultams were developed and have served as efficient chiral auxiliaries [4]. The most noticeable example is Oppolzer's camphor sultam, which was derived from natural chiral pools [5]. Asymmetric induction in a chemical transformation is extremely sensitive to the exact structure of the auxiliaries. Although natural products are convenient sources of chiral auxiliaries, there is not much room to optimize their effectiveness via systematic structural modifications. In contrast, chiral auxiliaries based on rational design provide greater flexibility for optimization through structural variations. In that connection, we have demonstrated the developed tricyclic chiral sultams and its effectiveness in promoting enantioselective synthesis [6]. Recently, Chiacchio *et al.* reported a four-step synthetic sequence of chiral bicyclic sultams incorporating isoxazolidine moiety as the control unit in their design of auxiliaries [7]. In this communication, we wish to report a direct access of bicyclic chiral sultams via 1,3-dipolar cycloaddition of nitrile oxides/chiral nitron to chiral 1-propene-1,3-sultams.

The requisite unsaturated chiral sultam **2a** was obtained from prop-1-ene-1,3-sultone and (*S*)-(-)- $\alpha$ -methylbenzylamine in a two-step protocol established in our laboratory [3b]. Nitrile oxides **1a** – **1e** were synthesized efficiently from the corresponding hydroxymoyl chlorides via triethylamine induced dehydrochlorination [8]. The nitrile oxides generated

could be purified by column chromatography on silica gel. The 1,3-dipolar cycloaddition reaction between the nitrile oxides and **2a** took place smoothly in toluene at room temperature, giving a pair of diastereomers as the products in moderate to good yield as shown in Table 1. The activation of the double bond in **2a** by the sultam functionality is strong enough to render its cycloaddition reaction with nitrile oxides possible at room temperature. On the other hand, the cycloaddition reaction is seemingly not susceptible to the steric effect, nitrile oxides **1a** and **1e** possessing a sterically demanding *tert*-butyl and pyrenyl substituent, respectively underwent a smooth reaction with the dipolarophile to give rise to the corresponding cycloadducts in good isolated yield (Table 1, Entries 1,5). Nitrile oxide **1c** incorporating phenyl substituent with two electron-donating methoxy groups exhibited a higher reactivity towards **2a**, giving the adducts **3c** and **4c** with the highest yield among all cases. In principle, four cycloadducts could be formed in each of the cycloaddition reactions. However, as indicated by TLC method, in all cases, the cycloaddition reaction produced only two diastereomers. Moreover, it was gratifying to find that the two optically active diastereomers generated can be purified cleanly by column chromatography on silica. Careful examination of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the adducts revealed that the cycloaddition reaction is highly regioselective. The regiochemistry of the bicyclic isoxazolines was established as depicted in Table 1, which is in full accord with the direction of bond polarization of both dipoles and the dipolarophile. Based on the <sup>1</sup>H NMR analysis, the diastereoselectivity of the reaction was found to be quite disappointing with the diastereoselectivity ratio (dr) ranging from 1.1 to 1.5. However, the results were not out of our expectation as the chiral control element of the sultam is far away from the bond formation sites of the reaction. The <sup>1</sup>H NMR spectra of the two diastereomers obtained from each of the reactions are quite distinguishable. Furthermore, the absolute configuration of the stereogenic centers of **3b** was firmly established by X-ray crystallographic analysis as depicted in Fig. (1). By inference, the configuration of other adducts was confirmed. We envisioned that one way to enhance the diastereoselectivity of the chiral dipolarophile may be to replace the chiral inducing group with a more

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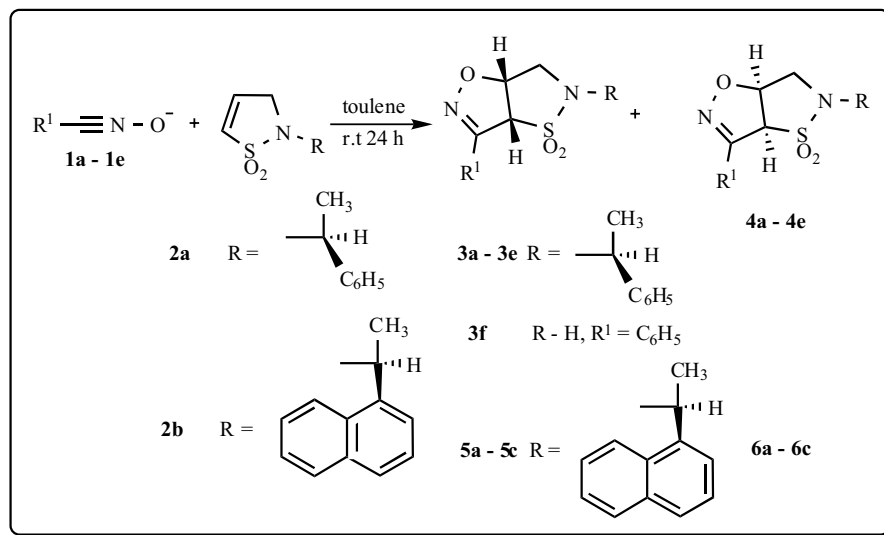
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bulky  $\alpha$ -methylnaphthylamino moiety. Thus, chiral sultam **2b** was prepared in 53% yield, starting from 1-propene-1,3-sultone via the ring opening reaction with (*S*)-(+)- $\alpha$ -methylnaphthylamine followed by the cyclization induced by  $\text{POCl}_3$ . When the structurally more demanded **2b** was allowed to react with selected nitrile oxides, mixtures of separable diastereomers were obtained in moderate yield (Table 1, Entries 6-8). To our disappointment, the diastereoselectivity of the reaction was again found to be not much different from those with **2a**. In spite of the relatively poor asymmetric induction observed for the reaction, the approach is highly effective in preparing homochiral sultams. For instance, debenzoylation of the adducts in refluxing formic acid followed by alkali treatment would afford the corresponding chiral sultams as exemplified by the formation of **3f** in an overall yield of 68% from **3a**.

To exploit further the synthetic utility of **2a** in asymmetric dipolar cycloaddition, its reaction with nitrones was undertaken. To set the stage for our study, achiral

nitronone **9a** obtained from benzylhydroxyamine (**7a**) and trimethylacetaldehyde (**8a**) was allowed to react with the unsaturated sultam **2a** in refluxing toluene for 24 h. A 1.2:1 diastereomeric mixture of the corresponding bicyclic isoxazolidines **10** was formed in 62% yield. Reminiscent to our recent finding [9], the reaction was highly regio- and stereoselective. It is noteworthy that only products, in which the alkyl group originated from the aldehyde is *cis* to the two ring juncture protons were formed stereoselectively. Again, the facial stereoselectivity exerted by the chiral element of the sultam was found to be insignificant, presumably due to its far distance from the reaction sites. The structural assignment of the adducts exemplified by **10a** was established by X-ray crystallographic analysis. As a measure to circumvent the lack of diastereoselectivity of the cycloaddition reaction, double asymmetric induction strategy was adopted. To this end, two different ways of preparing chiral nitrones were undertaken. Starting from the commercially available aldehyde **8b** and **8c**, the corresponding nitrones **9b** and **9c** were obtained in optically

**Table 1. Results of the 1,3-Dipolar Cycloaddition of Nitrile Oxides and Chiral Unsaturated Sultams**



entry	dipole	R <sup>1</sup>	dipolarophile	time (h)	products (dr) <sup>a</sup>	yield (%)
1	1a	(CH <sub>3</sub> ) <sub>3</sub> C	2a	36	3a : 4a (1.3)	50
2	1b	C <sub>6</sub> H <sub>5</sub>	2a	30	3b : 4b (1.5)	56
3	1c		2a	36	3c : 4c (1.3)	75
4	1d	9-anthracenyl	2a	36	3d : 4d (1.2)	58
5	1e	1-pyrenyl	2a	36	3e : 4e (1.1)	60
6	1a	(CH <sub>3</sub> ) <sub>3</sub> C	2b	36	5a : 6a (1.3)	42
7	1b	C <sub>6</sub> H <sub>5</sub>	2b	30	5b : 6b (1.2)	70
8	1d	9-anthracenyl	2b	30	5c : 6c (1.2)	55

<sup>a</sup>Estimated by <sup>1</sup>H NMR and the materials obtained from chromatography separation.

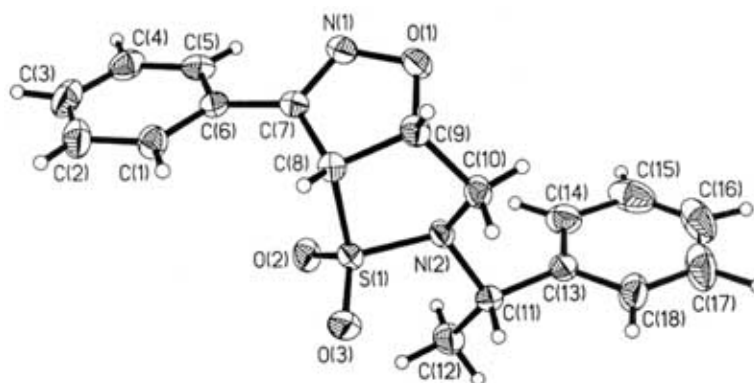
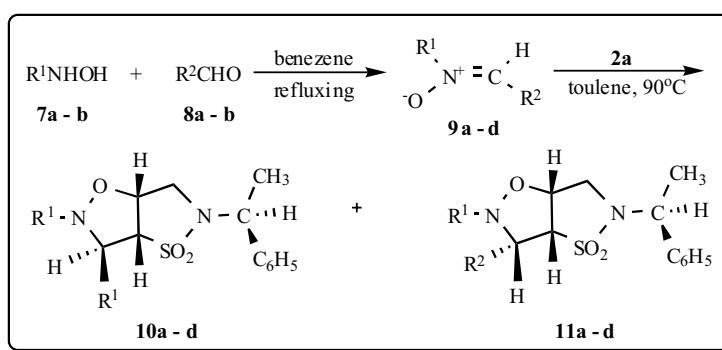
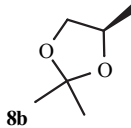
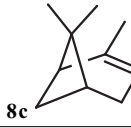
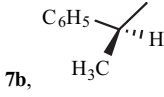
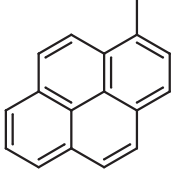


Fig. (1). X-ray Structure of 3b.

Table 2. 1,3-Dipolar Cycloaddition of Nitrones and Chiral Unsaturated Sultam 2a



entry	hydroxylamine 7, R <sup>1</sup> =	aldehyde 8, R <sup>2</sup> =	nitrones, yield % [ $\alpha$ ] <sub>0</sub> <sup>a</sup>	ratio (10/11) <sup>a</sup>	yield (10 + 11)
1	7a, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	8a (CH <sub>3</sub> ) <sub>2</sub> C-	9a, 72 -	1.2:1	62%
2	7a, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -		9b, 72 [+92.5 (C0.82, CHCl <sub>3</sub> )]	1.5:1	47%
3	7a, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -		9c, 68 [-47.1 (C1.5, CHCl <sub>3</sub> )]	1.8:1	67%
4	7b, 	8d 	9d, 64 [-241.3 (C2.0, CHCl <sub>3</sub> )]	7.1:1	65%

<sup>a</sup>Estimated by <sup>1</sup>H NMR and the materials obtained from chromatography separation.

pure form after purification by column chromatography. Alternatively, condensation of 1-pyrenecarboxaldehyde with chiral hydroxylamine **7b** at room temperature in dichloromethane using anhydrous magnesium sulfate as a desiccant gave nitrone **9d** in 64% yield [10]. With all these chiral nitrones in our disposal, the asymmetric DC reaction was examined. Due to the low reactivity of nitrones **9b-d**, their reaction with the sultam was required to conduct in refluxing toluene for 24 to 48 h affording the adducts in

good yield (Entries 2-4, Table 2). The diastereoselectivity of the reaction was found to be improved by utilizing chiral nitrones as the dipole. In particular, as a result of the interplay between the two chiral elements and the bulky pyrenyl group in the transition state of the reaction, excellent diastereoselectivity of 7.1:1 was observed for the reaction leading to the formation of **10d** and **11d** (Table 2, Entry 4) [11].

In summary, the scope of the asymmetric DC reaction of chiral unsaturated sultam **2a** to nitrile oxides and nitrones was examined. The synthetic route allows us to prepare a series of optically pure bicyclic isoxazolines and isoxazolidines. The exploration of their uses as chiral auxiliaries in asymmetric synthesis is underway.

## ACKNOWLEDGEMENTS

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- [11] Typical procedure: A mixture of chiral nitrones **9d** (3.0 mmol) and sultam **2a** (1.0 mmol) in 15 mL of dry toluene was stirred under nitrogen at 90°C for 24 h. The course of the reaction was monitored by TLC. When most of sultam was consumed, saturated ammonium chloride solution (10 mL) was added. Organic phase was separated, and aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel with ethyl acetate/petroleum ether (1 : 3) to afford cycloadducts **10d** and **11d** in a total 61% yield. **10d**: a white solid, mp 82-84°C; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): δ 1.36 (d, *J* = 7.0 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 2.96 (dd, *J* = 4.1, 11.6 Hz, 1H), 3.20 (d, *J* = 11.6 Hz, 1H), 3.81 (q, *J* = 7.0 Hz, 1H), 4.20 (brm, 1H), 4.65 (q, *J* = 6.5 Hz, 1H), 4.92 (dd, *J* = 4.2, 11.6 Hz, 1H), 5.03 (dd, *J* = 4.0, 11.6 Hz, 1H), 7.30-7.38 (m, 10H), 8.01-8.24 (m, 9H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>): δ 14.2, 19.5, 22.8, 29.8, 46.1, 54.0, 62.6, 74.5, 123.4, 124.6, 125.1, 125.3, 125.4, 126.0, 127.1, 127.2, 127.6, 127.8, 127.9, 128.6, 129.0, 129.1, 130.6, 131.2, 131.4, 139.2, 139.5, 140.1; IR (KBr): cm<sup>-1</sup> 3037, 2928, 2850, 1457, 1306, 1141, 1118, 856, 700; HRMS (ESI): *m/z*, found 572.2130, calcd for C<sub>36</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S 572.2134; [α]<sub>D</sub><sup>20</sup> -72.1 (C1.05, CHCl<sub>3</sub>).
- [12] **11d**: a white solid, mp 108-110°C; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): δ 1.43 (d, *J* = 6.2 Hz, 3H), 1.71 (d, *J* = 7.0 Hz, 3H), 3.21 (d, *J* = 11.1 Hz, 1H), 3.39 (dd, *J* = 4.1, 11.3 Hz, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 4.28 (brm, 1H), 5.11-5.19 (m, 2H), 5.52 (brm, 1H), 6.88-7.58 (m, 10H), 7.97-8.21 (m, 9H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>): δ 14.2, 17.1, 22.7, 31.7, 43.3, 50.5, 62.4, 75.2, 122.7, 124.6, 124.9, 125.0, 125.3, 125.4, 126.0, 126.9, 127.1, 127.2, 127.3, 127.7, 127.8, 128.1, 128.5, 128.8, 130.5, 131.1, 131.2, 139.6, 141.2; IR (KBr, cm<sup>-1</sup>): 3042, 2928, 2855, 1462, 1306, 1146, 1203, 856, 700; HRMS (ESI): *m/z*, found 572.2131, calcd for C<sub>36</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S 572.2134; [α]<sub>D</sub><sup>20</sup> -91.5 (C2.2, CHCl<sub>3</sub>).