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ADDITION-ELIMINATION STRATEGY FOR ASYMMETRIC INDUCTION: A CHIRAL SULFOXIDE AS A LEAVING GROUP

Kaoru Fuji,* Manabu Node, and Hitoshi Abe,
Institute for Chemical Research, Kyoto University
Uji, Kyoto 611, Japan
Akichika Itoh and Yukio Masaki
Gifu Pharmaceutical University, Mitahora, Gifu 502, Japan
Motoo Shiro
Shionogi Research Laboratories Shionogi & Co. Ltd.
Fukushima-ku, Osaka 553, Japan

Abstract: The reaction of β-nitro-α,β-unsaturated sulfoxide **7** with δ-lactam enolates **11** - **15** afforded **20** - **24**, respectively, in good chemical yields with high enantiomeric excesses.

Chiral induction based on the addition-elimination reaction possessing a chiral leaving group is an attracting method, which affords enantiomers directly. Cram *et al.* first introduced this strategy to synthesize the optically active atrop isomers.[1] Recently, we reported a new method for the nitroolefination of δ-lactones with chiral nitro enamines **1** based on the addition-elimination reaction[2] and the application of this methodology to the total syntheses of indole alkaloids.[3] As an extention of this work, we describe here the efficient chiral induction with an optically active β-nitro-α,β-unsaturated sulfoxide **2**, where the sulfoxide group functions as a leaving group.

Scheme I.

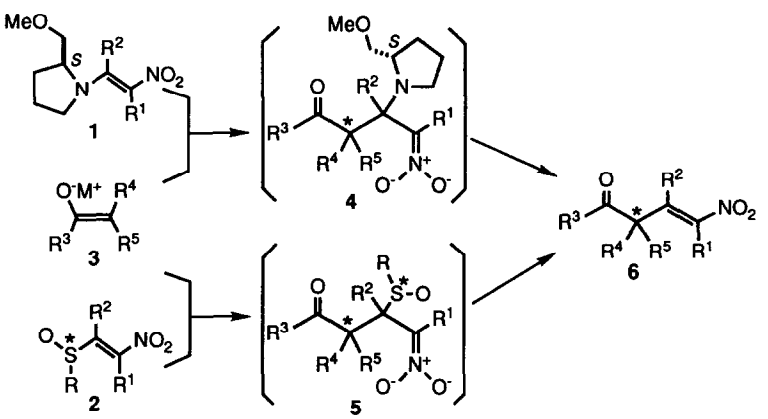
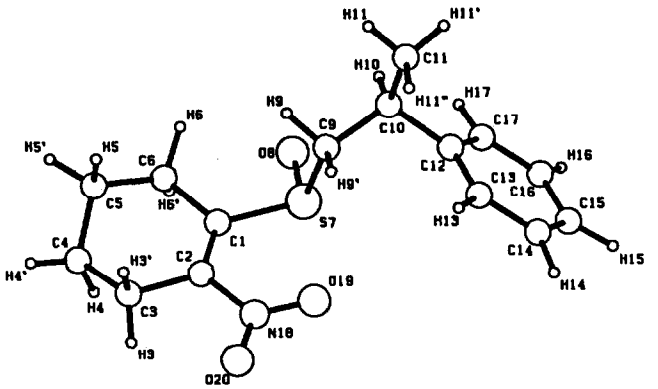
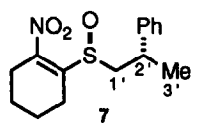


Figure 1. Perspective view of **7** showing the atom numbering schemes.



As shown in structure **4**, the 1,4-chiral induction occurs at the addition step followed by the elimination of the prolinol moiety to give the chiral product **6**, when an enolate **3** reacts with the chiral nitro enamine **1**. More efficient chiral transfer could be expected with a chiral β-nitro-α,β-unsaturated sulfoxide **2**, because the 1,3-relationship is attained between the chiral sulfur atom and the chiral center introduced in the intermediate adduct **5**. Moreover, since the sulfinyl group is more efficient as a nucleofuge than the substituted amino group, the reaction should proceed more smoothly with the sulfinyl group than with the amino group. We chose a cyclic olefin **7** as a chiral transfer agent to avoid complexity due to geometrical isomers. (*SS*,2'*S*)-Nitroolefin **7** was prepared from 1-ethylthio-2-nitrocyclohexene (**10**)[4] through a three step sequence including oxidation with OXONE, replacement of ethylsulfinyl group with (*S*)-2-phenylpropanethiol,[5] and the OXONE oxidation in 65 - 70% overall yield along with (*SR*,2'*S*)-isomer **8** (30 - 35%). Stereochemistry including absolute configuration of the major sulfoxide **7** was determined by an X-ray analysis[6] whose perspective view is shown in Figure 1.



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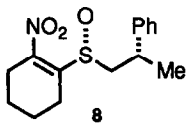

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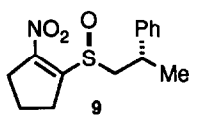

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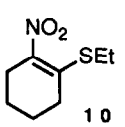

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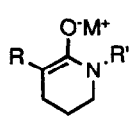
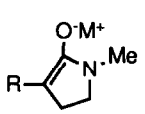
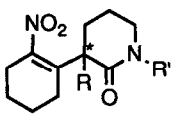
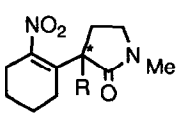








11 : R = H, R' = Me
12 : R = R' = Me
13 : R = $CH_2CH{=}CH_2$, R' = Me
14 : R = H, R' = CH_2Ph
15 : R = Me, R' = CH_2Ph

16 : R = H
17 : R = Me
18 : R = Et
19 : R = $CH_2CH{=}CH_2$

20 : R = H, R' = Me
21 : R = R' = Me
22 : R = $CH_2CH{=}CH_2$, R' = Me
23 : R = H, R' = CH_2Ph
24 : R = Me, R' = CH_2Ph

25 : R = H
26 : R = Me
27 : R = Et
28 : R = $CH_2CH{=}CH_2$

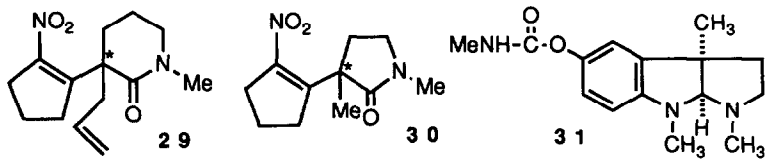
Various enolates generated from ketones, lactones, and esters underwent the Michael addition at the β-position to the nitro group followed by the elimination of the chiral sulfinyl group to afford the corresponding products **6** in good chemical yield but with poor enantiomeric excess (ee). Six-membered lactam enolates **11** - **15** afforded the corresponding products **20** - **24**, respectively, in good chemical and optical yields. The following is the typical procedure: To a stirred solution of zinc enolate **12** (6 mmol) in tetrahydrofuran (THF, 10 mL) was added the (*SS*, 2'*S*) sulfoxide **7** (1 mmol) in THF (10 mL) at -78 °C. After stirring for 1 h at the same temperature, extractive work up followed by column chromatography over silica gel with hexane-ethyl acetate afforded **21** in 93% yield. Enantiomeric excess was determined by ^{1}H NMR with (*R*)-(+)-binaphthol as a chiral shift reagent.[7]

Table I. Nitroolefination of Lactams with **7**.

run	enolate[a]	counter cation	temp. °C	time, h	product	yield, %	%ee[b,c]
1	**11**	Li^+	-78	1	**20**	70	44
2	**11**	Zn^{2+}	-78~-20	1	**20**	87	87
3	**12**	Li^+	-78	1	**21**	95	85
4	**12**	Zn^{2+}	-78	1	**21**	93	99
5	**13**	Li^+	-78	1	**22**	97	89
6	**13**	Zn^{2+}	-78	1	**22**	96	99
7	**14**	Zn^{2+}	-78	1	**23**	91	86
8	**15**	Li^+	-78	1	**24**	91	86
9	**16**	Zn^{2+}	- 78~-20	1	**25**	82	43
10	**17**	Li^+	-78	1	**26**	89	33
11	**17**	Li^+	-78	1	**26**	92	4[d]
12	**17**	Zn^{2+}	-78~-40	2	**26**	91	84
13	**18**	Zn^{2+}	-78~-10	0.5	**27**	96	73
14	**19**	Zn^{2+}	-78~-10	0.5	**28**	94	81

[a]Three mol equiv. for lithium enolates and 6 mol equiv. for zinc enolates. [b]Determined by ^{1}H NMR with (*R*)-(+)-binaphthol. [c]Absolute stereochemistry has not been determined. [d]With HMPA.

Table I lists the results of asymmetric nitroolefinations of 6- and 5-membered lactams with the chiral sulfoxide **7**. Zinc enolates gave better ee than the lithium enolate (runs 1-6). δ-Lactams afford better ee than γ-lactams though the chemical yields are comparable. The striking observation was that the nitroolefins **20** and **23** were obtained in 87% ee and 86% ee, respectively, though these compounds were supposed to have a hydrogen extremely labile to enolization.[8] Addition of hexamethylphosphoric triamide (HMPA) decreases ee dramatically (run 11). Though the detailed mechanism remains to be studied, this observation together with a high %ee with zinc enolate indicates the importance of the chelation of the metal cation in the addition step. Reactions of 5-membered chiral sulfoxide **9**[9] with zinc enolates **13** and **17** afforded **29** and **30** in good chemical yield, respectively, with low %ee (69 % for **29** and 9 % for **30**).



Although the usefulness of sulfoxides as a chiral auxiliary in the asymmetric synthesis such as the Diels-Alder reaction[10] and the conjugate addition[11] has been well documented, this is the first demonstration that the high degree of asymmetric induction has been achieved using a chiral sulfoxide as a leaving group. The product such as **26** is a suitable chiral building block for the synthesis of physiologically important alkaloids such as physostigmine (**31**). Syntheses of optically active alkaloids of this type are currently underway.

References and notes

1 (a) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (b) *J. Org. Chem.* **1984**, *49*, 4930.

2 Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855.

3 Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901.

4 Node, M.; Kawabata, T.; Fujimoto, M.; Fuji, K. *Synthesis* **1984**, 234.

5 Optically pure (S)-2-phenylpropanethiol was prepared from (S)-2-phenylpropanoic acid by the reduction with $LiAlH_4$ followed by the Mitsunobu reaction with thiolacetic acid, and then $LiAlH_4$ reduction.

6 Crystal data for **7** : $C_{15}H_{19}NO_3S$, space group $P2_12_12_1$ with a = 10.977 (1), b = 23.248 (1), c = 5.811 (1) Å and D_c = 1.314 g cm^{-3} for Z = 4. Bond lengths, bond angles, and atomic coordinates have been deposited with the Cambridge Crystallographic Data Center.

7 Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A ; Oomine, K.; Fuji, K. *Chem. Lett.* **1988**, 131.

8 Nonenolizable chiral β-dicarbonyl synthons have been reported: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

9 This compound was prepared from 1-ethylthio-2-nitrocyclopentene in a similar manner to the synthesis of **7**.

10 Takayama, H.; Iyobe, A.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1986**, 771 and references cited therein.

11 Posner, G. H. ; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383 and references cited therein.

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