Enantio- and Diastereoselective Synthesis of Isoxazolidines by Asymmetric 1,3-Dipolar Cycloaddition of Nitrones

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(Received February 27, 1997; CL-970144)

The asymmetric 1,3-dipolar cycloaddition of nitrones possessing electron withdrawing group to an achiral allyl alcohol was achieved by the use of diisopropyl (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding isoxazolidines with high regio-, diastereo- and enantioselectivity.

The 1,3-dipolar cycloadditions are important methods for the synthesis of various kinds of 5-membered ring compounds. Among the 1,3-dipolar cycloadditions, the asymmetric one of nitrone with olefin seems to be a useful reaction to prepare isoxazolidine which is a key building block for the synthesis of optically active nitrogen-containing chemicals such as γ-amino alcohols.[1] However, enantioselective 1,3-dipolar cycloaddition of nitrones was scarcely reported.[2,3] Recently, we reported an efficient enantioselective 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol using diisopropyl (*R,R*)-tartrate [(*R,R*)-DIPT] as a chiral auxiliary to give the optically active 2-isoxazolines.[4] Herein, we describe the enantioselective 1,3-dipolar cycloaddition of nitrones possessing electron withdrawing groups using (*R,R*)-DIPT as a chiral auxiliary.

Firstly, the enantioselective 1,3-dipolar cycloaddition of a nitrone **2a**[5,6] possessing cyano group to allyl alcohol (**1**) was examined. When allyl alcohol was treated with each 1.0 molar amount of diethylzinc, (*R,R*)-DIPT, additional diethylzinc, and **2a** successively, the corresponding isoxazolidine could not be obtained (Table 1, Entry 1). This result would be due to the weak Lewis acidity of ethylzinc moiety of the speculative intermediate **3** (X=Et), which could not be coordinated by the nitrone. In order to increase the Lewis acidity, chlorozinc intermediate **3** (X=Cl) was tried to generate alternatively. After the several attempts, using ethylzinc chloride instead of diethylzinc was found to be effective; that is, after allyl alcohol (**1**) was treated with diethylzinc, (*R,R*)-DIPT, and ethylzinc chloride, prepared from diethylzinc and zinc chloride (1/1) *in situ*,[7] **2a** was added to the reaction mixture to afford *trans*-isoxazolidine **4a** and *cis*-isomer **5a** in 13% and 11% yields with optical yields of 90% ee and 7% ee, respectively (Entry 2).[6] In this reaction, the formation of the regioisomer was not observed. When 1.5 molar amounts of diethylzinc was employed to **1** at the first step of the reaction procedure, the production of *cis*-isoxazolidine was inclined to decrease (Entries 3, 4). It was found that the slow addition of 3.0 molar amounts of **2a** at 45 °C afforded *trans*-isoxazolidine **4a** in 42% yield with the excellent enantioselectivity of 94% ee (Entry 5).

Next, the enantioselective 1,3-dipolar cycloaddition of the nitrone **2b**[5,6] possessing *t*-butoxycarbonyl group as an electron withdrawing group was carried out. The nitrone **2b** was more reactive than **2a**; that is, by the reaction with 1.0 molar amount of **2b** at 25 °C, *trans*-isoxazolidine **4b** was obtained in 40% yield with the selectivity of 76% ee accompanied with 7% of *cis*-isoxazolidine **5b** (Entry 6).[6] Using 2.0 molar amounts of **2b**, the yield was increased to 60% (Entry 7). When the reaction was carried out at higher temperature, not only the yield but also diastereo- and enantioselectivities were improved (Entry 8). The cycloaddition of **2b** at 60 °C selectively afforded **4b** with higher selectivity of 92% ee (Entry 9).

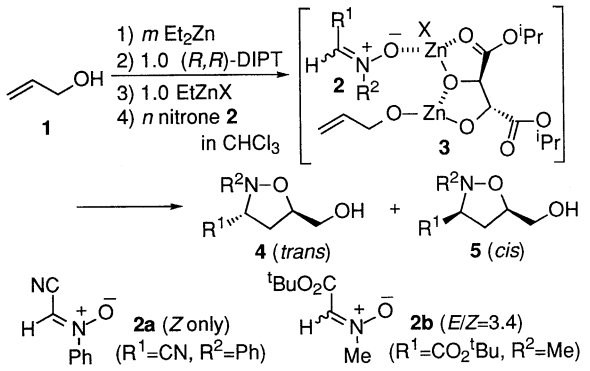


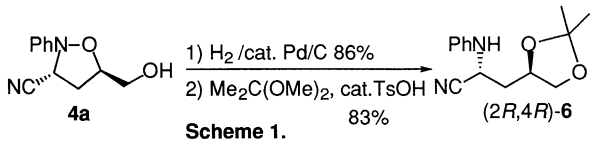
Table 1. The asymmetric 1,3-dipolar cycloaddition of nitrones **2a, b** to allyl alcohol (**1**) using (*R,R*)-DIPT

Entry	2	X	*m*	*n*	Temp /°C	Time /h	**4** (*trans*) Yield /%	**4** (*trans*) ee /%	**5** (*cis*) Yield /%	**5** (*cis*) ee /%
1	**a**	Et	1.0	1.0	25	41	--	--	--	--
2	**a**	Cl	1.0	1.0	0	46	13	90[a]	11	7[a]
3	**a**	Cl	1.5	1.0	0	43	9	93[a]	5	7[a]
4	**a**	Cl	1.5	1.0	25	48	18	95[a]	6	6[a]
5	**a**	Cl	1.5	3.0	45	52[b]	42	94[a,c]	trace	--
6	**b**	Cl	1.5	1.0	25	28	40	76[d]	7	56[d,e]
7	**b**	Cl	1.5	2.0	25	22	60	82[d]	9	71[d,e]
8	**b**	Cl	1.5	2.0	40	22	68	87[d]	2	70[d,e]
9	**b**	Cl	1.5	2.0	60	22	68	92[d,f]	--	--

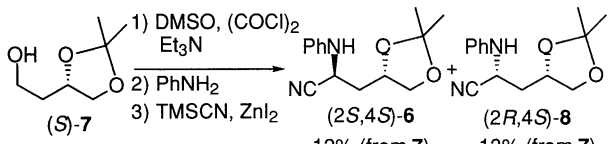
[a]Optical yields were determined by direct HPLC analysis (Daicel Chiralcel OB-H). [b]Nitrone **2a** was slowly added to the reaction mixture over a period of 43 h and the mixture was stirred for 9 h. [c]$[\alpha]_D^{25}$ +89° (c 0.43, MeOH). [d]Yields and optical yields were determined by ^{1}H NMR analysis of the (*R*)-MTPA esters derived from the mixture of **4b** and **5b**. [e]The opposite (*3R,5S*)-enantiomer was mainly obtained. [f]$[\alpha]_D^{25}$ +51° (c 0.62, MeOH).

The relative stereochemistry of the obtained isoxazolidines **4** and **5** was determined by NOE measurement.[8] Furthermore, the absolute configurations of the *trans*-isoxazolidines **4** were confirmed to be *3R,5R* by the chemical correlation between their derivatives and the stereochemically unambiguous authentic compounds; *i.e.*, **4a** (72% ee) was transformed to

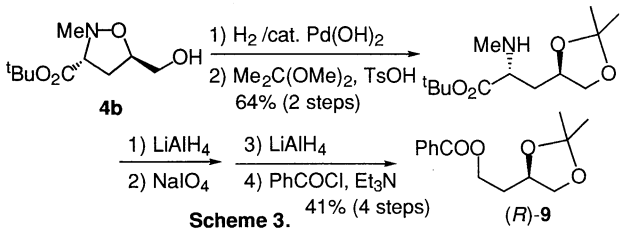
(*2R,4R*)-**6** ($[\alpha]_D^{25}$ +135° (c 0.83, MeOH)) (Scheme 1), whose specific optical rotation was opposite to that of the authentic (*2S,4S*)-**6** ($[\alpha]_D^{25}$ –199° (c 0.09, MeOH)) derived from (*S*)-**7**[9] (Scheme 2).[10] The *trans*-isoxazolidine **4b** (81% ee) was converted to (*R*)-**9** ($[\alpha]_D^{25}$ +16° (c 0.26, MeOH)) (Scheme 3), and compared with the authentic (*S*)-**9** ($[\alpha]_D^{25}$ –20° (c 0.73, MeOH)) prepared by benzoylation of (*S*)-**7**.[11]



Scheme 1.



Scheme 2.



Scheme 3.

Although the mechanism of the present reaction was not clear yet, the steric repulsion between the substituent R^2 on nitrogen and ester moiety in DIPT would disfavor bimetallic *exo* transition state as depicted in Figure 1. In the cycloaddition of *Z*-**2b** *via endo* transition state, coordination of carbonyl oxygen in **2b** to zinc could activate the cycloaddition (Figure 2) more than cycloaddition of *E*-**2b** *via endo* transition state in which such coordination is impossible. Higher reaction temperature might promote the isomerization of *E*-**2b** to *Z*-**2b** prior to the cycloaddition to give *trans*-(*3R,5R*)-isoxazolidine **4b** *via Z-endo* transition state diastereo- and enantioselectively.[3,12] Further, the intermediate **3** coordinated by **2b** would exist in the aggregated form, which would be dissociated to favorable monomeric or less aggregated form more smoothly at higher temperature resulting in the improvement of the enantioselectivity.[13] The cycloaddition of **2a** (*Z* only) might also proceed *via Z-endo* transition state (similar to Figure 2), in which though coordination of cyano group to zinc metal might not be allowed, to give *trans*-(*3R,5R*)-isoxazolidine **4a**.

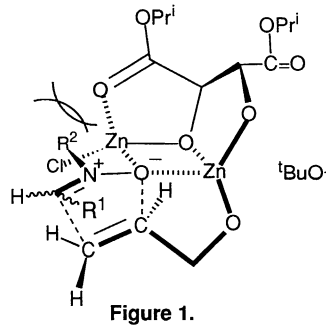


Figure 1.

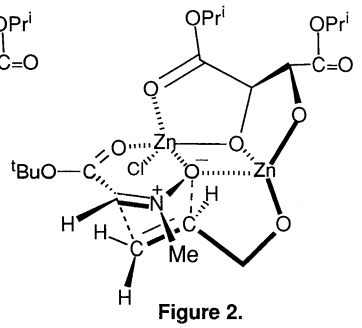


Figure 2.

As described above, the present method provides a useful entry for the stereoselective construction of optically active isoxazolidines. Further, easy availability of (*R,R*)- and (*S,S*)-DIPT has now made it possible the facile preparation of both enantiomers of isoxazolidines which are versatile synthetic intermediates for nitrogen-containing chemicals.

The authors are grateful to Daicel Chemical Industries Ltd. for the kind suggestion of HPLC analyses using Chiralcels. The present work was partially supported by Tanabe Seiyaku Co., Ltd. Award in Synthetic Organic Chemistry, Japan and Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture.

References and Notes

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2 Recently asymmetric 1,3-dipolar cycloadditions of nitrones were reported: J.-P. G. Seerden, M. M. M. Kuypers, and H. W. Scheeren, *Tetrahedron: Asymmetry*, **6**, 1441 (1995); K. V. Gothelf, I. Thomsen, and K. A. Jørgensen, *J. Am. Chem. Soc.*, **118**, 59 (1996); K. V. Gothelf, R. G. Hazell, and K. A. Jørgensen, *J. Org. Chem.*, **61**, 346 (1996); K. Hori, H. Kodama, T. Ohta, and I. Furukawa, *Tetrahedron Lett.*, **37**, 5947 (1996).

3 Diastereo- and regioselective 1,3-dipolar cycloadditions of nitrones mediated by metals were reported: a) S. Kanemasa, T. Tsuruoka, and E. Wada, *Tetrahedron Lett.*, **34**, 87 (1993); b) S. Kanemasa and T. Tsuruoka, *Chem. Lett.*, **1995**, 49; c) O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe, and M. Sakamoto, *Tetrahedron*, **51**, 107 (1995).

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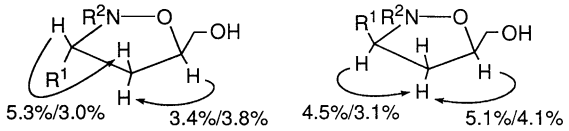
5 The reaction of *N*-(cyanomethyl)pyridinium bromide and nitrosobenzene in the presence of NaH gave (*Z*)-nitrone **2a** in a single isomer.[14] Nitrone **2b** (*E/Z* = 3.4 in $CDCl_3$) was prepared from *t*-butyl glyoxylate and MeNHOH·HCl by the treatment with Et_3N.[15]

6 All new compounds, such as nitrones **2** and isoxazolidines **4**, **5**, were characterized by ^1H NMR spectra, IR spectra, and elemental analyses or MS spectra.

7 J. Boersma and J. G. Noltes, *Tetrahedron Lett.*, **1966**, 1521. In our reaction, $ZnCl_2 \cdot OEt_2$ in CH_2Cl_2 was used.

8 NOE was observed for **4a,b** and **5a,b** as shown below.



4a/4b (*trans*) **5a/5b** (*cis*)

9 (*S*)-Alcohol **7** was prepared from (*S*)-malic acid: M. Barth, F. D. Bellamy, P. Renaut, S. Samreth, and F. Schuber, *Tetrahedron*, **46**, 6731 (1990).

10 The ^1H NMR spectrum of (*2R,4R*)-**6** was in accord with that of (*2S,4S*)-**6**, but not with that of (*2R,4S*)-**8**.

11 The absolute configurations of *cis*-isoxazolidines **5a** and **5b** were confirmed by the similar way described for *trans*-isomers. The specific optical rotations ($[\alpha]_D^{25}$ in MeOH) were as follows: (*2R,4S*)-**8**, +106° (c 0.10); (*2S,4R*)-**8**, –4° (c 0.80) [derived from (*3S,5R*)-**5a** (5% ee)]; (*S*)-**9**, –2° (c 0.93) [derived from (*3R,5S*)-**5b** (17% ee)].

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13 In the present reaction, the regioisomer was not produced in contrast to the case of the nitrone having benzoyl group even though zinc alkoxide of allyl alcohol was used, probably due to that the formation of orthoester from *t*-butylester moiety and allyl alcohol might be impossible; see, T. Tsuruoka and S. Kanemasa, 69th National Meeting of the Chemical Society of Japan, Kyoto, March 1995, Abstr., 2H831 and Ref. 3a.

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