Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides to γ-Substituted Allylic Alcohols

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The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to γ-substituted allylic alcohols was achieved by the use of diisopropyl (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding 3,4,5-trisubstituted-2-isoxazolines with high regio- and enantioselectivities. 4,5-*trans*-2-Isoxazolines derived from ethyl (*E*)-4-hydroxy-2-butenoate were transformed to the corresponding 4,5-*cis*-2-isoxazolines by the treatment with a base through isomerization and lactonization.

Asymmetric 1,3-dipolar cycloadditions have been the focus of great attention in synthetic organic chemistry.[1] The 1,3-dipolar cycloaddition is influenced by the steric interaction, and thus the control of the stereochemistry in the 1,3-dipolar cycloaddition to the internal olefin was difficult. For example, regio- and diastereoselectivities in the cycloaddition of nitrile oxide to crotonoyl derivatives of Oppolzer's chiral sultam were lower compared with those to acryloyl derivative.[2,3] Recently we reported highly enantioselective 1,3-dipolar cycloadditions of nitrile oxides and nitrones to a terminal olefin, 2-propen-1-ol.[4] Herein, we describe the regio- and enantioselective 1,3-dipolar cycloaddition of nitrile oxides to γ-substituted allylic alcohols utilizing (*R,R*)-diisopropyl tartrate (DIPT) as a chiral auxiliary.

First the 1,3-dipolar cycloaddition of *p*-methoxybenzonitrile oxide to (*E*)-2-buten-1-ol (**1*E***) using (*R,R*)-DIPT was examined paying attention to the molar amounts of the reagents and the reaction temperature. When **1*E*** was treated with Et_2Zn (1.0 molar amount), (*R,R*)-DIPT (1.0 molar amount), a second Et_2Zn (1.0 molar amount), and *p*-methoxybenzohydroximoyl chloride (1.0 molar amount) successively at 0 °C in $CHCl_3$, the corresponding optically active 4,5-*trans*-2-isoxazoline **2a** was obtained with high enantioselectivity, but in poor chemical yield (Entry 1 in Table 1). Increasing the molar amounts of hydroximoyl chloride and/or the reaction temperature slightly improved the chemical yield (Entries 2, 3). The enantioselective cycloaddition of benzonitrile oxide to **1*E*** also gave an optically active 2-isoxazoline **2b** in 59% yield with the selectivity of 94% ee (Entry 4). In the case of the 1,3-dipolar cycloaddition of *p*-methoxybenzonitrile oxide to (*Z*)-2-buten-1-ol (**1*Z***), 4,5-*cis*-2-isoxazoline **2c** was obtained in 63% yield with the selectivity of 96% ee when the reaction was carried out at 25 °C (Entry 6), but in lower chemical yield at 0 or 45 °C (Entries 5,7). Benzonitrile oxide also afforded the corresponding cycloaddition product **2d** with high enantioselectivity (Entry 8).[5] The regioisomer of **2** was scarcely produced in these reactions except for the reaction of benzonitrile oxide to **1*E*** (Entry 4).[6]

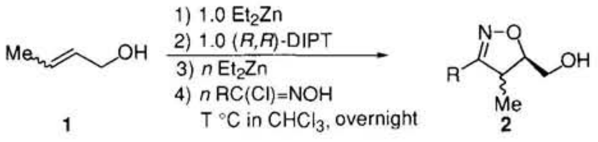


Table 1. The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to 2-buten-1-ol (**1**)

Entry	**1**	R	**2** (4,5-)	*n*	T	Yield/%	ee/%
1	*E*	*p*-$MeOC_6H_4$	**a** (*trans*)	1.0	0	20	93[a]
2				1.5	0	35	89[a]
3				1.5	25	37	88[a]
4	*E*	Ph	**b** (*trans*)	1.5	25	59[b]	94[b]
5	*Z*	*p*-$MeOC_6H_4$	**c** (*cis*)	1.5	0	30	97[a]
6				1.5	25	63	96[a]
7				1.5	45	44	94[a]
8	*Z*	Ph	**d** (*cis*)	1.5	25	51	98[a]

[a]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). [b]Chemical and optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H) of the mixture of **2b** and its regioisomer *trans*-4-(hydroxymethyl)-5-methyl-3-phenyl-2-isoxazoline (2% yield).

The enantioselective preparation of highly functionalized 2-isoxazolines, which are versatile synthetic intermediates, is strongly required. Then, asymmetric 1,3-dipolar cycloaddition to an allylic alcohol possessing an ethoxycarbonyl group was investigated. It was found that the asymmetric cycloaddition of nitrile oxides to ethyl (*E*)-4-hydroxy-2-butenoate (**3**) proceeded to afford the corresponding 4,5-*trans*-2-isoxazolines **4** with high enantioselectivity as shown in Table 2.[5]

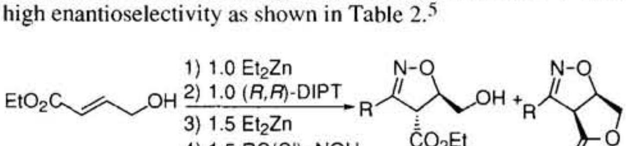


Table 2. The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to ethyl (*E*)-4-hydroxy-2-butenoate (**3**)

			4		**5**	
Entry	R		Yield/%	ee/%	Yield/%	ee/%
1	*p*-$MeOC_6H_4$	**a**	82	92[a]	--	--
2	Ph	**b**	75	92[b]	trace	--
3	*p*-BrC_6H_4	**c**	71	92[b]	trace	--
4[c]	Heptyl	**d**	35	96[b]	--	--
5	*t*-Bu	**e**	74	91[b]	--	--

[a]Optical yield was determined by HPLC analysis (Daicel Chiralcel OB-H). [b]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). [c] Two molar amounts of hydroximoyl chloride were used.

During the purification of the reaction products **4** by TLC on silica gel, the production of the lactone **5**, which was not observed before the purification, was confirmed. It indicated that the 4,5-*trans*-2-isoxazoline **4** could be readily isomerized to 4,5-*cis*-2-isoxazoline followed by lactonization to afford **5**. In order to promote the isomerization, *trans*-2-isoxazolines **4** were treated with a small amount of DBU to furnish the optically active 4,5-*cis*-2-isoxazolines **5** in high yields without loss of optical purity (Table 3).[5]

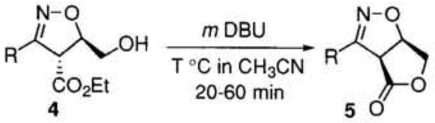
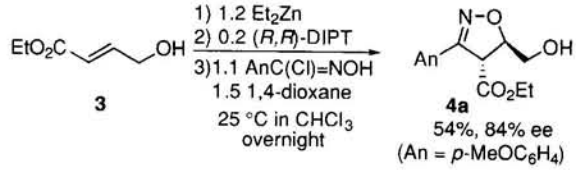


Table 3. The transformation of **4** to **5**

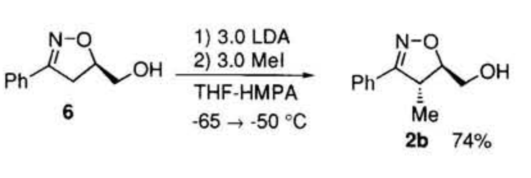
Entry	R		ee/% of **4**	*m*	T	Yield/%	ee/% of **5**
1	*p*-MeOC$_6$H$_4$	**a**	92	0.3	25	93	92[a]
2	Ph	**b**	91	0.1	0	98	91[a]
3	*p*-BrC$_6$H$_4$	**c**	92	0.1	-20→-10	97	92[a]
4	Heptyl	**d**	96	0.3	25	90	96[b]
5	*t*-Bu	**e**	91	0.3	25	92	94[a]

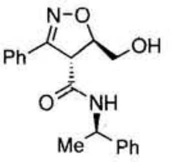
[a]Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). [b]Optical yield was determined by HPLC analysis (Daicel Chiralcel OB-H).

Catalytic asymmetric cycloaddition of *p*-methoxybenzonitrile oxide to **3** was also carried out[4b] to give the 2-isoxazoline **4a** with the enantioselectivity of 84% ee.



The absolute configuration of 4,5-*trans*-2-isoxazoline **2b** (98% ee; $[\alpha]_D^{25}$ -124° (c 0.14, MeOH)) was confirmed to be *4R,5R* by the comparison of specific optical rotation and the spectral data with those of the authentic sample **2b** (91% ee; $[\alpha]_D^{25}$ -113° (c 0.50, MeOH)) derived from the known (*R*)-2-isoxazoline **6**[4a] (91% ee).[7] On the other hand, the absolute configuration of **5b** was revealed to be *4S,5R* by X-ray crystallographic analysis of its derivative: The treatment of **5b** (87% ee) with (*R*)-1-phenylethylamine gave an amide **7** (69%) as a major product through ring opening and isomerization. The stereochemistry of **7** was determined to be *4R,5R* by X-ray crystallographic analysis of its single crystal as shown in Figure 1.[5,8]





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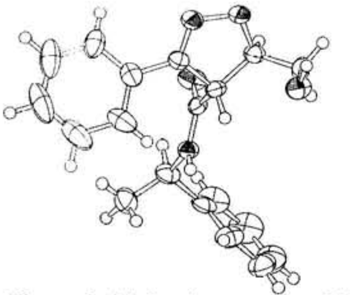

Figure 1. Molecular structure of **7**.

As described above, the present method provides a useful way for the enantioselective synthesis of the 3,4,5-trisubstituted-2-isoxazolines. Especially by the asymmetric 1,3-dipolar cycloaddition of nitrile oxides to ethyl (*E*)-4-hydroxy-2-butenoate, not only 4,5-*trans*- but also 4,5-*cis*-2-isoxazolines were simply prepared with high enantioselectivity. Furthermore, this method provides a useful way to prepare both enantiomers of 3,4,5-trisubstituted-2-isoxazolines because of easy availability of (*R,R*)- and (*S,S*)-DIPT, ultimately allowing to provide all of the possible four optically active stereoisomers.

The present work was partially supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture.

References and Notes

1 Recently enantioselective 1,3-dipolar cycloadditions of nitrones and trimethylsilyldiazomethane were reported: K. V. Gothelf and K. A. Jørgensen, *Acta Chem. Scand.*, **50**, 652 (1996); A. I. Sanchez-Blanco, K. V. Gothelf, and K. A. Jørgensen, *Tetrahedron Lett.*, **38**, 7923 (1997); K. Hori, H. Kodama, T. Ohta, and I. Furukawa, *Tetrahedron Lett.*, **37**, 5947 (1996); S. Kobayashi, R. Akiyama, M. Kawamura, and H. Ishitani, *Chem. Lett.*, **1997**, 1039; S. Kanemasa and Y. Oderaotoshi, *J. Synth. Org. Chem. Jpn.*, **56**, 368 (1998); J.-P. G. Seerden, M. M. M. Kuypers, and H. W. Scheeren, *Tetrahedron: Asymmetry*, **6**, 1441 (1995).

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3 Diastereo- and regioselective 1,3-dipolar cycloaddition of nitrile oxides coordinated to magnesium to allylic alcohols was reported: a) S. Kanemasa, M. Nishiuchi, A. Kamimura, and K. Hori, *J. Am. Chem. Soc.*, **116**, 2324 (1994); b) S. Kanemasa, K. Okuda, H. Yamamoto, and S. Kaga, *Tetrahedron Lett.*, **38**, 4095 (1997).

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5 All new isoxazolines and the known isoxazoline **2b**[3a] were characterized by ^{1}H NMR spectra, IR spectra, and elemental analyses or MS spectra. Coupling constants $J_{4\text{-}5}$ of *trans*-isoxazolines **2a**,**2b**,**4**,**7** were smaller than those of the corresponding *cis*-isomers **2c**,**2d**,**5**. $J_{4\text{-}5}$/Hz ($CDCl_3$): 5.12 (**2a**), 9.27 (**2c**); 5.12 (**2b**), 9.27 (**2d**); 5.34 (**4a**), 9.27 (**5a**); 6.42 (**4b**), 9.54 (**5b**). 5.85 (**7**); 6.42 (**4c**), 9.51 (**5c**); 8.07 (**4d**), 9.72 (**5d**); 5.87 (**4e**), 9.54 (**5e**).

6 The regio- and enantioselectivities in the reaction of benzonitrile oxide to ***1E*** were improved by optimization of the molar amounts of reagents and the reaction temperature.[4a]

7 V. Jäger and W. Schwab, *Tetrahedron Lett.*, **1978**, 3129.

8 Single crystal of **7**, obtained by recrystallization from AcOEt, contained AcOEt (AcOEt/**7** was 1/5 by its ^{1}H NMR spectral analysis). mp: 129.5-130.0 °C. Found: C, 69.54; H, 6.39; N, 8.16%. Calcd for $C_{19}H_{20}N_2O_3 \cdot 1/5AcOEt$: C, 69.54; H, 6.37; N, 8.19%. The difference Fourier maxima revealed that the AcOEt was disordered along 6_5 axes. Taking AcOEt into account in each asymmetric unit with a scattering factor of one nitrogen atom improved the structure refinement: Crystal data: $C_{19}H_{20}N_3O_3$, *FW*. 338.39, hexagonal, $P6_5$, $a = 18.800(2)$ Å, $c = 8.871(1)$ Å, $V = 2715.1(5)$ Å^3, $Z = 6$. $D_{calc} = 1.242$ g/cm^3. $R = 0.054$ ($R_w = 0.071$) for 1012 reflections with $I > 3.00\sigma(I)$ and 222 variable parameters. Leaving AcOEt out of account, R value was 0.078 ($R_w = 0.117$).