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The Preparation of Optically Active Δ2-Isoxazolines via Addition of Nitrile Oxides to Chiral Acryloyl Esters Bearing Cyclitols as Auxiliaries

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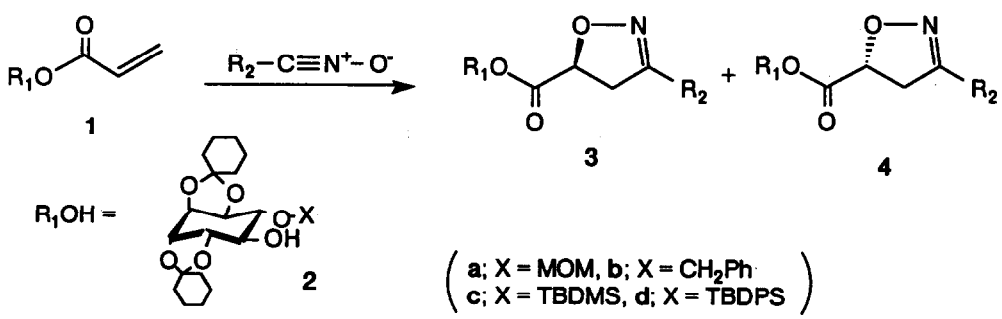
Abstract: An acryloyl ester derived from (1L)-3-*t*-butyldiphenylsilyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol underwent 1,3-dipolar cycloaddition with nitrile oxide to give Δ2-isoxazolines of high diastereomeric excess (up to 90% de).

Δ2-Isoxazolines are of great importance as intermediates in the preparation of β-hydroxy carbonyl compounds, and asymmetric induction in nitrile oxide 1,3-dipolar cycloadditions have hence attracted considerable attention for their synthesis.[1] Although Lewis acid promoted asymmetric Diels-Alder reaction with chiral acrylate derivatives have resulted in high levels of induction,[2] asymmetric induction in nitrile oxide cycloaddition to acryloyl derivatives have limited success because Lewis acid does not generally promote the cycloaddition.[3] Thus development of a new chiral auxiliary group which permit high levels of asymmetric induction in thermal addition is still of great importance. Curran[4] and other groups[5] have recently reported highly diastereoselective 1,3-dipolar cycloaddition of nitrile oxide to chiral acryloyl amides, but diastereoselective cycloaddition to chiral acryloyl ester provided unsatisfactory results[6] because the ester linkage is more flexible than amide linkage and hence the control of the conformation of ester moiety is more difficult than that of amides.



In previous papers, we reported that highly diastereoselective addition of organometallics to α-keto esters having the chiral cyclitol **2c** moiety,[7] which was derived from naturally abundant L-quebrachitol ((1L)-2-*O*-methyl-*chiro*-inositol),[8,9] as an auxiliary group. We wish to describe here highly diastereoselective 1,3-dipolar cycloaddition of nitrile oxide to acryloyl esters bearing *chiro*-inositol derivatives as chiral auxiliaries.

Table 1. Results of the Cycloaddition of PhCNO with **1**

Entry	Ester	Reaction time /h	Yield / %	3 : 4
1	**1a**	2.5	87	37 : 63
2	**1b**	1.5	89	55 : 45[a)]
3	**1c**	1.5	88	84 : 16
4	**1d**	1.1	81	95 : 5

a) Stereochemistry was not determined.

In the first place, acryloyl esters (**1a,b,c,d**)[10] were treated with PhCNO in benzene at room temperature to afford Δ^2-isoxazolines **3** and **4**, and the results are shown in Table 1. The nitrile oxide was generated by the Huisgen method by 1,3-dehydochlorination of the hydroximic acid chloride. The acryloyl esters **1a** and **1b**, bearing methoxymethyl (MOM) and benzyl resulted in low diastereoselection. The ester **1c** having bulkier *t*-butyldimethylsilyl (TBDMS) ether was found to be effective, upgrading the selectivity to 68% de (Entry 3), and **1d** with *t*-butyldiphenylsilyl (TBDPS) ether underwent smooth, highly π-face selective cycloaddition to afford Δ^2-isoxazolines in 90% de (Entry 4).

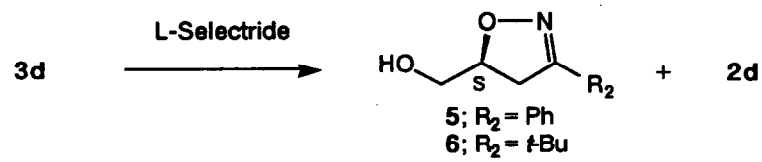
The solvent effect of the reaction of **1d** is shown in Table 2. The best diastereoselectivity was obtained in

Table 2. Results of the cycloaddition with **1d**

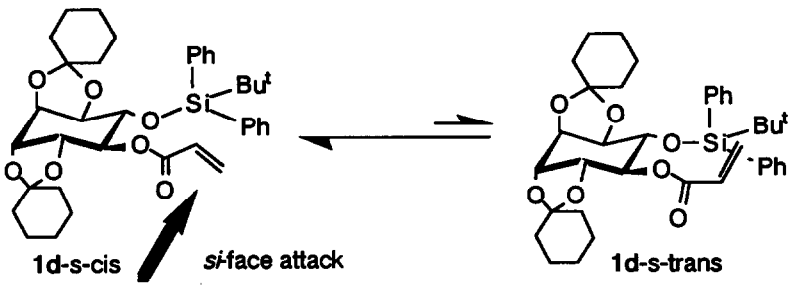
Entry	Nitrile Oxide R_2	Solvent	Reaction conditions	Yield / %	3 : 4
1	Ph	Benzene	r.t. 1.1 h	81	95 : 5
2	Ph	Et_2O	-70 °C, 1 h	73	91 : 9
3	Ph	Et_2O	r.t. 2.2 h	64	86 : 14
4	Ph	Toluene	-72 °C, 3.5 h	76	90 : 10
5	Ph	CH_2Cl_2	r.t. 2.2 h	58	88 : 12
6	Me	Benzene	r.t. 5.1 h	71	91 : 9[a)]
7	Et	Benzene	r.t. 2.6 h	80	90 : 10[a)]
8	*n*-C_5H_{11}	Benzene	r.t. 3.8 h	54	90 : 10[a)]
9	*tert*-Bu	Benzene	r.t. 2 h	95	91 : 9
10	Cl- 	Benzene	r.t. 4 h	73	90 : 10[a)]

a) Stereochemistry was assigned by analogy.

benzene (Entry 1). Toluene and CH_2Cl_2 showed good selectivity and lowering the temperature did not greatly improve the selectivity though the cycloaddition took place readily at low temperature (Entry 2). The cycloaddition with other nitrile oxides also showed good selectivity (Entries 6 -10). The diastereomers thus obtained were readily separable by SiO_2 column chromatography and the stereochemical outcome was ascertained by chemical correlation; reduction of the esters (3d; R_2=Ph and *t*-Bu) with L-Selectride™ (THF, 25 °C) provided easily separable mixture of optically pure Δ^2-isoxazoline (5 or 6) and a recovered alcohol (2d). The absolute configuration of the Δ^2-isoxazoline was assigned as S by comparison with the literature data 5; $[\alpha]_D^{22}$ +172 ° (c 0.87, $CHCl_3$), (lit. $[\alpha]_D^{25}$ +163 ° (c 1.0, $CHCl_3$))[5a], 6; $[\alpha]_D^{20}$ +121 ° (c 1.68, $CHCl_3$), (lit. $[\alpha]_D^{25}$ +124 ° (c 1.0, $CHCl_3$))[4a].



This stereochemical outcome can be rationalized by means of the following mechanism; the major 1,3-dipolar cycloadducts are derived from the s-cis conformer of the acrylate, while the minor ones from the s-trans conformer.[11] Bulky TBDPS group thus effectively hindered the attack from the *re*-face of the olefinic double bond.[7]



In summary, we have demonstrated that an acryloyl ester **1d**, derived from a chiral *chiro*-inositol, showed high diastereoselectivity in the 1,3-cycloaddition with nitrile oxide. This is the first example of the thermal cycloaddition of nitrile oxide to a chiral acryloyl ester which permits high π-facial selection.

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REFERENCES AND NOTES

1 (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410-416. (b) Curran, D. P. In *Advances in Cycloaddition*; JAI: Greenwich, CN, 1988; pp 129-189. (c) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press: Oxford. 1990; pp 285-297.

2 (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol.3, pp 455-501. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 261-306. (c) Ref 1c, pp 1-139.

3. Recently stereocontrolled 1,3-dipolar cycloadditions by the aid of metal chelation and hydrogen bonding were reported, see (a) Curran, D. P.; Choi, S-M.; Gothe, S. A.; Lin, F. *J. Org. Chem.* **1990**, *55*, 3710-3712. (b) Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett.* **1991**, *32*, 6367-6370.

4. (a) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555-3558. (b) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585-4595. (c) Curran, D. P.; Jeong, K-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238-9240.

5 (a) Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893-4896. For asymmetric induction in silyl nitronated cycloaddition, see: (b) Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron Asymmetry* **1991**, *2*, 27-30.

6. (a) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137-2141. For the cycloaddition with crotonates, see: (b) Kametani, T.; Nagahara, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3048-3052. (c) Olson, T.; Stern, K.; Sundell, S. *J. Org. Chem.* **1988**, *53*, 2468-2472. (d) Kanemasa, S.; Hayashi, T.; Yamamoto, H.; Wada, E.; Sakurai, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3274-3279.

7. For asymmetric reduction employing L-quebrachitol as a chiral auxiliary group, see: (a) Akiyama, T.; Nishimoto, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1335-1338. (b) Akiyama, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447-450.

8. For syntheses of natural products from L-quebrachitol, see: (a) Akiyama, T.; Takechi, N.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 1433-1434. (b) Akiyama, T.; Takechi, N.; Shima, H.; Ozaki, S. *Chem. Lett.* **1990**, 1881-1884. (c) Akiyama, T.; Shima, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 5593-5596. (d) Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett.* **1991**, 831-832. (e) Akiyama, T.; Takechi, N.; Ozaki, S.; Shiota, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 366-372.

9. For other syntheses of natural products utilizing L-quebrachitol as a starting material, see: a) Tegge, W.; Ballou, C. E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 94-98. b) Kozikowski, A. P.; Fauq, A. H.; Aksoy, I. A.; Seewald, M. J.; Powis, G. *J. Am. Chem. Soc.* **1990**, *112*, 4528-4531. c) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1990**, 994-995. d) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 1063-1066. (e) Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 588-590. See also references cited therein.

10. The esters were prepared starting from L-quebrachitol via (1L)-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol.[12]; **2d**; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.00 (9H, s, $C(CH_3)_3$), 1.10-1.80 (20H, m, $(CH_2)_{10}$), 3.64 (1H, dd, $J_{2,3}$=7.3 Hz, $J_{3,4}$=11.3 Hz, H-3), 3.97 (1H, dd, $J_{4,5}$=8.6 Hz, $J_{5,6}$=6.1 Hz, H-5), 4.26 (1H, dd, $J_{1,6}$=3.1 Hz, H-6), 4.34 (1H, dd, $J_{1,2}$=6.4 Hz, H-2), 4.43 (1H, dd, H-1), 5.17 (1H, dd, H-4), 5.59 (1H, dd, J=1.5 Hz, 10.4 Hz), 5.77 (1H, dd, J=10.4 Hz, 17.1 Hz), 6.18 (1H, dd, J=1.5 Hz, 17.1 Hz), 7.25-7.43 (6H, m, aromatic), 7.51-7.60 (2H, m, aromatic), 7.70-7.78 (2H, m, aromatic). $[\alpha]_D^{18}$ -44 ° (c 1.10, $CHCl_3$). See also ref. 7.

11 Curran et al. reported that the s-cis conformation of methyl acrylate is 0.7 kcal/mol more stable than the s-trans conformation in the gas phase.[6a)]

12. Angyal, S. J.; Irving, G. C.; Rutherford, D.; Tate, M. E. *J. Chem. Soc.* **1965**, 6662-6664.

13. A typical experiment procedure of the cycloaddition is as follows: To a solution of **1d** (54 mg, 0.085 mmol), phenyl hydroxymic acid chloride (66 mg, 0.43 mmol) in benzene (4.0 ml) was added a solution of triethylamine (60 µl, 0.43 mmol) in benzene (3.0 ml) at room temperature. Stirring was continued for 1.1 h at room temperature. The reaction mixture was quenched by addition of 10% HCl solution (5 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The remaining residue was purified by preparative TLC (ethyl acetate: hexane (v/v) = 1:10) to afford **3** (49 mg) and **4** (2.8 mg), the diastereomeric ratio of **3** and **4**, 95 : 5. The HPLC analysis (SiO_2, ethyl acetate: hexane (v/v) = 1:10) of the diastereomeric mixture before purification showed a 94 : 6 ratio of **3** and **4**.

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