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(1R, 2R)-2-Nitroxycyclohexan-1-ol : First Example of a Cyclohexyl Based Chiral Auxiliary with Nitroxy Function as Diastereoface Discriminating Group

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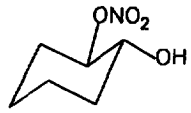
Abstract: Application of nitroxy substituent as diastereoface discriminating group in a cyclohexyl based chiral auxiliary has been described.

Applications of 2-substituted cyclohexan-1-ol based chiral auxiliaries in a variety of stereoselective processes have been well documented.[1-7] In all these processes alkyl, aryl and aryloxy substituents which are mainly based on a carbon frame work, have been employed as diastereoface discriminating groups to induce high levels of enantioselectivities.[1-7] However, application of the completely heteroatom (non-carbon) based nitroxy substituent as a diastereoface discriminating group in cyclohexyl based chiral auxiliaries has not been reported in the literature. We herein disclose application of the nitroxy function, for the first time, as a diastereoface discriminating group, thus demonstrating the potential of (1R,2R)-2-nitroxycyclohexan-1-ol as a novel chiral auxiliary.

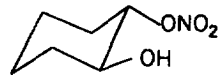
The ever increasing demand for the chiral drugs is due to the fact that chiral recognition by the bioorganism varies enormously with of little variation in the structural motif of the molecule.[8,9] However, such structural variations in nitrate based drugs have not been well explored although they find widespread therapeutical importance as drugs[10,11] for heart and vascular diseases. Recently we have developed a simple and convenient synthesis of (1R,2R)-2-nitroxycyclohexan-1-ol **1** and (1S,2S)-2-nitroxycyclohexan-1-ol **2** in enantiomerically pure form.[12] This easy accessibility of **1** & **2** has led us to examine the potential of

the nitroxy function as a diastereoface discriminating group. Thus, we investigated the diastereoselective addition of RZnCl to (1R,2R)-2-nitroxycyclohexyl phenylglyoxylate with a view to providing a simple and convenient synthesis of nitrate tethered atrolactic esters, *i.e.* (1R,2R)-2-nitroxycyclohexyl 2-hydroxy-2-phenylalkanoates, a novel class of molecules with structural variation in nitrate based chiral drugs.



(1R,2R)

1

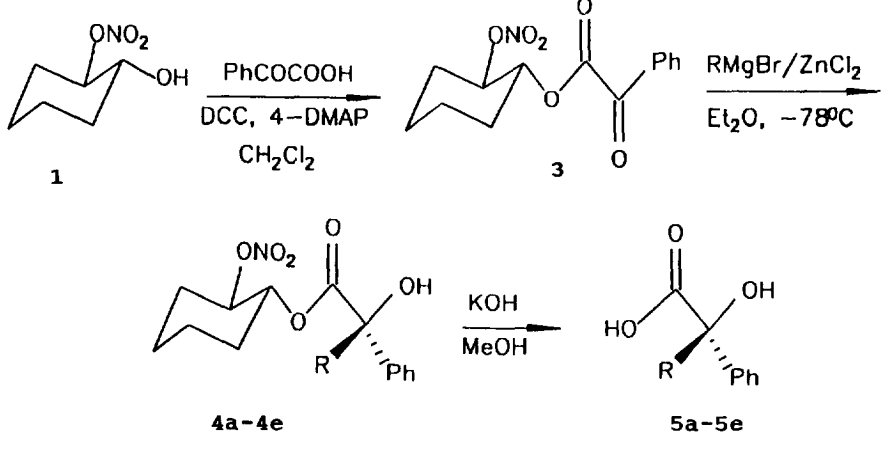


(1S,2S)

2

Accordingly, the required (1R,2R)-2-nitroxycyclohexyl phenylglyoxylate[13] **3** was prepared (47% yield) by the reaction of **1** (25 mM) with benzoylformic acid (27 mM) in the presence of dicyclohexylcarbodiimide (DCC) (27 mM) and 4-dimethylaminopyridine (4-DMAP) (5 mg catalyst) in CH_2Cl_2 (45 mL) at 0°C. Treatment of this glyoxylate **3** (2.5 mM) with i-PrZnCl (7.5 mM) in ether (15 mL) at -78°C under N_2 atm. for 3 h provided (1R,2R)-2-nitroxycyclohexyl 2-hydroxy-3-methyl-2-phenylbutanoate **4a** ($[\alpha]_D^{22}$ -117.1 (c 1.08, CH_2Cl_2)), after usual workup, in 90% yield. Interestingly, this reaction was found to be totally chemoselective, *i.e.* the nitroxy function was completely intact. The diastereoselectivity in this reaction was found to be 88% as indicated by the ^1H NMR spectral analysis.[14] ^{13}C NMR spectrum also indicates the presence of minor diastereomer. We have further confirmed the diastereoselectivity of this reaction by saponifying **4a** to provide (R)-2-hydroxy-3-methyl-2-phenylbutanoic acid[15] **5a** ($[\alpha]_D^{22}$-27.9 (c 0.85, EtOH) m.p. 104°C; lit.[16] $[\alpha]_D^{25}$ +32.5 (c 2, EtOH), >99% ee, Conf. (S), m.p. 103-105°C) in 86% ee.

Scheme 1:



1 **3**

4a-4e **5a-5e**

Table 1: Diastereoselective addition of RZnCl to (1R,2R)-2-nitroxycyclohexyl phenylglyoxylate[a,b]

R in RZnCl	Ester	Esters **4** Yield[c] (%)	$[\alpha]_D^{22}$ (c, CH_2Cl_2)	Acid	Acids **5** $[\alpha]_D^{22}$ (c, EtOH)	ee[d] (%)	Conf.[e]
i-Pr	**4a**	90	-117.1 (1.08)	**5a**	-27.9 (0.85)	86	(R)
i-Bu	**4b**	78	-56.9 (0.92)	**5b**	-16.7 (0.83)	83	(R)
n-Hex	**4c**	85	-85.9 (0.73)	**5c**	-16.3 (0.95)	84	(R)
n-Bu	**4d**	87	-93.1 (1.70)	**5d**	-19.1 (0.77)	82	(R)
Et	**4e**	81	-101.4 (3.46)	**5e**	-28.6 (1.81)	86	(R)

a). All reactions were carried out with 2.5 mM of **3** and 7.5 mM of RZnCl (prepared *in situ*) at -78°C under N_2 atm. for 3 h.

b). All products **4** & **5** were characterized by IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral analysis.

c). Isolated yield of the product after usual workup.

d). Based on specific rotation reported in the literature, *i.e.*,

5a : $[\alpha]_D^{25}$ +32.5 (c 2.0, EtOH), >99% ee, Conf. (S)[16]

5b : $[\alpha]_D^{25}$ +20.0 (c 2.0, EtOH), >99% ee, Conf. (S)[16]

5c : $[\alpha]_D^{22}$ -17.0 (c 2.2, EtOH), 88% ee, Conf. (R)[3]

5d : $[\alpha]_D^{22}$ -19.0 (c 2.2, EtOH), 82% ee, Conf. (R)[3]

5e : $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH), >99% ee, Conf. (S)[16]

e). Assigned on the basis of sign of specific rotation.[3,16]

Encouraged by this observation we have selected a variety of alkylzinc chlorides for the reaction with **3**. Thus atrolactic esters **4b-4e** were obtained in excellent chemo- and high diastereoselectivity (de 82-86%) as established by converting them into the corresponding atrolactic acids **5b-5e** (Table 1,Scheme 1).

In conclusion our report describes, for the first time, application of nitroxy function as diastereoface discriminating group in a cyclohexyl based chiral auxiliary and also provides a convenient synthesis of nitrate tethered atrolactic esters in high diastereoselectivity

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13. **Analytical data for 3:** m.p. 61-62°C; $[\alpha]_D^{22}$ -21.7 (c 0.56, CH_2Cl_2); IR (KBr)/ν_{max} cm^{-1}: 1597, 1635, 1693, 1739; ^1H NMR ($CDCl_3$) (200 MHz) δ 1.18-2.42 (m, 8H), 4.96-5.18 (m, 1H), 5.28-5.48 (m, 1H), 6.98-8.12 (m, 5H); ^{13}C NMR ($CDCl_3$) (50 MHz): 23.06, 23.20, 29.04, 30.25, 73.41, 82.36, 129.05, 129.90, 132.20, 135.12, 163.14, 185.97; Analysis calcd. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.15; N, 4.77 found C, 57.25, H, 5.17; N, 4.75.
14. **Spectral data for 4a**: IR (neat)/ν_{max} cm^{-1}: 1635, 1728, 3522; ^1H NMR ($CDCl_3$) (200 MHz): 0.69 & 0.72 (2d in the ratio 6 : 94, 3H, J = 6.8 Hz), 0.94 & 0.97 (2d in the ratio 6 : 94, 3H, J = 6.6 Hz) 1.22-2.38 (m, 8H), 2.64 (m, 1H), 3.65 (s, 1H, OH), 4.84 (m, 1H), 5.04 & 5.12 (2m, 1H), 7.18-7.38 (m, 3H), 7.52-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) (50 MHz): 15.77, 16.95, 22.93, 23.22, 29.00, 29.74, 30.16, 35.22, 35.47, 73.41, 74.33, 80.88, 81.99, 125.62, 125.93, 127.64, 128.12, 140.70, 175.00 (the underlined chemical shift values are due to the minor diastereomer).
15. **Spectral data for 5a:** IR (KBr) ν_{max}/cm^{-1}: 1720, 2600-3300, 3475; ^1H NMR ($CDCl_3$) (200 MHz): δ 0.71 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz), 2.66 (sept, 1H, J = 6.6 Hz), 3.28-5.26 (br, 2H, 2 OH), 7.22-7.46 (m, 3H), 7.62-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$) (50 MHz): δ 15.77, 17.27, 35.92, 81.10, 125.98, 127.86, 128.30, 140.41, 180.58.
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