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Zinc-mediated asymmetric epoxidation of nitro alkenes with oxygen

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Abstract

The asymmetric epoxidation of nitro alkenes using oxygen in the presence of diethylzinc and *N*-methyl pseudoephedrine as a chiral additive is reported. This method provides an access to 3-substituted *trans*-2-nitro oxiranes of excellent diastereomeric purity (de≥98%) and with medium to good enantiomeric excesses (ee=36–82%).

1. Introduction

The non-enantioselective epoxidation of nitro alkenes with hydrogen peroxide under base catalysis is a well known transformation,[1] with the reaction proceeding in moderate yields and complete diastereoselectivity. In addition, the diastereoselective synthesis of enantiomerically pure 2-nitro oxiranes, controlled by existing stereocentres within the chiral nitro alkene starting materials, has been demonstrated, with the work of Jackson et al. being of special note.[2–4]

The chemistry of racemic 2-nitro oxiranes has already been studied by several groups.[5] They have described them as useful starting materials for the synthesis of α-substituted aldehydes and ketones. Jackson et al. used enantiopure 2-nitro oxiranes carrying a phenylthio substituent at the α-carbon, which were accessed by diastereoselective synthesis and were shown to be useful in the synthesis of α-substituted *S*-phenylthioesters.[2–4]

Since further transformations of enantiopure 2-nitro oxiranes, which retain the stereochemical information, would give access to important classes of compounds, they are interesting targets for asymmetric synthesis.

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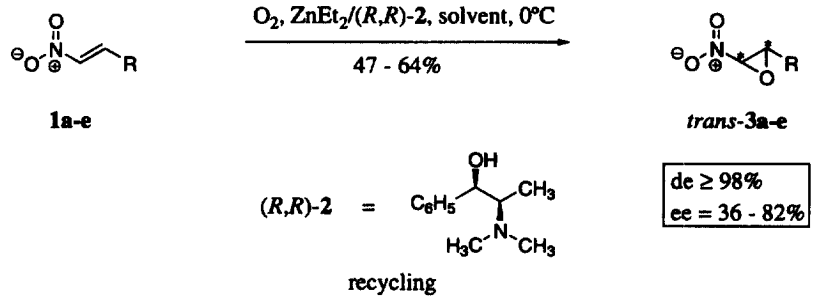
To our knowledge, there is only one published attempt to achieve enantioselective epoxidation of nitro alkenes by Colonna and Juliá et al. who obtained very low enantiomeric excesses (up to 7%) using $NaOH \cdot H_2O_2$ in the presence of polypeptides.[6,7]

2. Results and discussion

We have recently reported the asymmetric epoxidation of α-enones using oxygen in the presence of diethylzinc and *N*-methyl pseudo-ephedrine with good to exellent yields and enantiomeric excesses.[8,9] We now wish to report the extension of this protocol to the epoxidation of nitro alkenes. As is depicted in Scheme 1, the (*E*)-configured nitro alkenes **1** are treated with the inexpensive chemicals oxygen and diethylzinc in the presence of the enantiopure aminoalcohol (*R,R*)-**2** which is not consumed and can be recycled. The 3-substituted *trans*-2-nitro oxiranes **3** are obtained in yields of 47–64%, with complete diastereoselectivity (de≥98%) and medium to good enantiomeric excesses (ee=36–82%) (Scheme 1).[10,11]



Scheme 1.

The proposed active reagent is an ethylperoxyzinc compound, generated by the treatment of a mixture of *N*-methyl pseudo-ephedrine and diethylzinc with oxygen.[8] During the reaction it is converted into a zinc ethoxide species. Because nitro alkenes are much more electrophilic than α-enones as Michael acceptors, the zinc ethoxide can undergo addition to the nitro alkenes in an oxa-Michael type reaction. It was found to be very difficult to separate this 1,4-adduct from the 2-nitro oxiranes, especially in the case of the oxiranes **3a** and **3b**, which carry groups *R* of lower steric demand. In early experiments using ether or toluene as solvent, the materials contained up to 30% of this by-product. Only in the case of oxirane **3e** which carries a *t*-butyl group, was the selectivity satisfactory. In addition, the high steric demand of this group resulted in a high enantioselectivity for the epoxidation reaction (ee=82%). In the case of oxirane **3a** it was possible to carry out purification by HPLC. In the other cases the conditions therefore had to be optimised in order to avoid the oxa-Michael type reaction. The higher solubility of the alkylperoxyzinc compound in THF favoured the epoxidation reaction over the oxa-Michael type addition and gave satisfactory selectivity in the case of oxiranes **3b**, **3c** and **3d** (see Table 1).

The absolute configuration of the product nitro oxiranes **3** remains to be determined. According to the mechanism proposed for the related asymmetric epoxidation of enones,[8,9] we assumed that the (2*R*,3*S*)-oxiranes are formed in excess.

The advantages of the asymmetric epoxidation method are that the cheapest oxidant, namely oxygen or even air, can be used and that the chiral ligand can be recycled by extraction into acid (HCl_{aq}) with subsequent basification ($NaOH_{aq}$), and re-extraction into ether.

Table 1
3-Substituted *trans*-2-nitro oxiranes prepared by asymmetric epoxidation

3	R	solvent	yield [%]	$[\alpha]_D^{25}$ (c, CH_2Cl_2)	ee [%][a]
a[b]	2-phenylethyl	toluene	64	19.8 (1.05)	37[c]
b	propyl	THF	53	-16.8 (0.20)	43
c	*i*-propyl	THF	53	-11.7 (0.62)	42
d	*c*-hexyl	THF	47	-15.7 (0.92)	36
e	*t*-butyl	Et_2O	57	-21.8 (0.30)	82[d]

a) Determined by GC on a chiral stationary phase (Lipodex E 25m); b) (*S,S*)-*N*-Methyl *pseudo*-ephedrine was used as chiral additive; c) Determined by HPLC on a chiral stationary phase (Chiralcel OD (4.6 • 250mm)); d) Determined by GC on a chiral stationary phase (CP-Chirasil-dex CB 25m).

In summary, these initial results show the efficiency of the epoxidation with our system (O_2, Et_2Zn, enantiopure aminoalcohol). Experiments to achieve further improvements of the method and to test the applicability of the enantioenriched 2-nitro oxiranes are in progress.

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10. A typical procedure is the preparation of 2-nitro-3-(1-methyethyl)oxirane (**3c**): 1.2 mmol of diethylzinc (10% solution in hexane) was added to a solution of 430 mg (2.4 mmol) (*R,R*)-*N*-methyl pseudo-ephedrine in 5 ml THF under an argon atmosphere at 0°C. After 1 h, the flask was fitted with a balloon containing oxygen. 4 h later, 0.9 mmol (104 mg) of 3-methyl-1-nitro-but-1-ene (**1c**) were added. Then the solution was stirred for up to 3 h (TLC-control). After the reaction was complete, 10 ml of 3% hydrochloric acid were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo.

The residue was purified by column chromatography (SiO_2, petroleum ether:ether 20:1). The (*R,R*)-*N*-methyl pseudoephedrine could be recovered from the aqueous layer after basification (>90%).

11. 2-Nitro-3-(2-phenylethyl)oxirane (**3a**): mp=39–45°C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.89–2.08 (m, 2H, CH_2CH), 2.76 (dt, J=14.10 Hz, 7.72 Hz, 1H, C_6H_5CHH), 2.82 (dt, J=14.10 Hz, 7.38 Hz, 1H, C_6H_5CHH), 3.46 (ddd, J=5.04 Hz, 5.04 Hz, 0.67 Hz, 1H, CH_2CH), 5.10 (d, J=0.67 Hz 1H, $CHNO_2$), 7.15–7.34 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): 31.25, 31.29 (CH_2), 58.7 ($O_2NCHOCH$), 80.5 (O_2NC), 126.7 (*p*-C), 128.3, 128.8 (*o*-C, *m*-C), 139.5 (*i*-C). MS: 193 (M^+, 23%), 129 (11%), 117 (7%), 105 ($C_8H_8^+$, 6%), 92 (11%), 91 ($C_7H_7^+$, 100%), 77 ($C_6H_5^+$, 6), 65 (13%), 51 (8%), 41 (21%). IR (ν/cm^{-1}): 3070, 3030 (m), 2960, 2930 (m), 2860 (m), 1960, 1890, 1830 (w), 1655 (m) 1600 (m), 1570 (s), 1495, 1460, 1425, 1410 (m), 1360 (s), 1300, 1285, 1270, 1235, 1190, 1180, 1160, 1125, 1095, 1075, 1060, 1030, 1010 (m), 990 (s), 940, 915, 895, (m) 860, 825 (w), 790, 750, 730, 705 (s), 615 (m). $C_{10}H_{11}NO_3$ (193.2) calc. C, 62.17; H, 5.74; N, 7.25; found C, 62.51; H, 5.82; N, 7.40. 2-Nitro-3-cyclohexyloxirane (**3d**): ^{1}H NMR (300 MHz, $CDCl_3$): 1.00–1.90 (m, 11H, C_6H_{11}), 3.31 (1H, dd, J=0.8, 6.3, $O_2NCHOCH$), 5.25 (1H, d, J=0.6, O_2NCH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8, 24.9, 25.4, 28.0, 28.2 (CH_2), 37.3 ($O_2NCHOCHCH$), 62.9 ($O_2NCHOCH$), 79.5 (O_2NC). MS: 172 ($M+H^+$, 55%), 156 (12%), 154 (27%), 141 (32%), 125 (172−HNO_2, 100%), 107 (16%, 125−H_2O), 95 (7%), 81 (5%). IR (ν/cm^{-1}): 3068 (w), 2931, 2855, 1568 (s), 1451, 1368 (m), 1312, 1228, 1103 (w), 974, 948 (m), 927 (w) 805 (sh), 793 (m), 733 (s), 626, 552, 487 (w). $C_8H_{13}NO_3$ (171.20) calc. C, 56.13; H, 7.54; N, 8.18; found C, 56.39; H, 7.81; N, 8.21. The analytical data of **3b**, **3c** and **3e** are consistent with those reported in the literature.[1]