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DIASTEREOSELECTIVE PREPARATION OF ANTI-β-AMINO ALCOHOLS VIA MICHAEL ADDITION OF ALKOXIDE ANIONS TO NITROOLEFINS AND SUBSEQUENT HYDROGENATION REACTION

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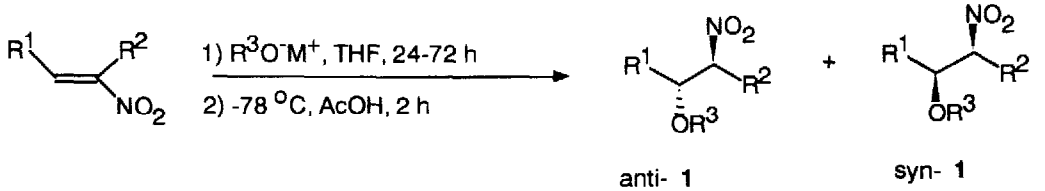
Summary: Diastereoselective conjugate addition of benzylalkoxide anion to nitroolefins and subsequent hydrogenation reaction provide a new convenient method for the preparation of anti-β-amino alcohols.

As nitroolefins are remarkably electron deficient owing to strong electron withdrawing ability of the nitro group, they are powerful synthetic intermediates in organic reactions.[1] For example, Michael type addition of various kinds of nucleophiles to nitroolefins is one of versatile synthetic methods in organic chemistry. This reaction has been used very frequently.[2] and metal enolates[3,4], enamines,[5] trialkyl aluminums,[6] allyl silanes,[7] and allyl stannanes[8] serve as effective carbon nucleophiles to form carbon-carbon bonds. Stereochemical investigation of this reaction has been of interest. Recently, Seebach[5] and Mukaiyama[4] have succeeded in the stereo control of Michael addition to nitroolefins using enamines and tin(II) enolates, respectively. Although nitrogen-, oxygen-, sulfur, and phosphor-atom centered nucleophiles are also effective nucleophiles to nitroolefins, there have been a few reports concerning stereochemical control in the reation of these nucleophiles.[1] Previously, we reported stereocontrolled Michael type addition of thiols[9] or selenols[10] to nitroolefins. In this paper, we report stereoselective Michael type addition of alkoxide anions to nitroolefins to give anti-β-nitro ethers **1**. Further, as **1** can be readily converted into *O*-protected β-amino alcohols **3** or free β-amino alcohols **4**, this method provides a new preparation of anti-β-amino alcohols from nitroolefins. β-Amino alcohols exist widely in natural compounds and they have been often synthetic targets or used as chiral auxiliary for asymmetric synthesis.[11]

2-Nitro-2-butene (1.185 g, 11.7 mmol) was added to the solution of sodium benzylalkoxide (3 equiv.), which was generated *in situ* by 60% sodium hydride (1.41 g) and benzylalcohol (3.90 g), in tetrahydrofuran (THF, 20 mL), then the resulting solution was stirred at room temperature for 48 h. The solution was cooled at -78 °C and acetic acid (5 mL) was added. After stirring for 2 h, the reaction mixture was poured into water. Following usual work up and purification by flush column chromatography (silica gel; hexane-ethyl acetate 20:1) gave 2-benzyloxy-3-nitrobutane **1a** (1.172 g, 72%). Other β-nitro ethers **1** were prepared by this procedure (Scheme 1). The results are summarized in Table 1.



anti- **1** syn- **1**

Scheme 1

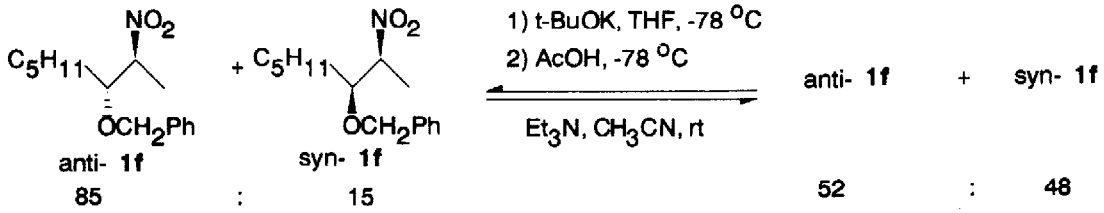
Table 1. Preparation of β-nitro ethers **1**

run	R^1	R^2	R^3	M^+	time (h)	yield(%)[a]	ratio anti/syn[b]
1	Me	Me	$PhCH_2$	Na	48	**1a** 72	88/12
2	Me	Me	$PhCH_2$	Li	48	**1a** 55	88/12
3	Me	Me	$PhCH_2$	K	48	**1a** 49	88/12
4	Me	Me	$PhCH_2CH_2$	Na	36	**1b** 63	90/10
5	Me	Me	$PhCH_2CH_2CH_2$	Na	48	**1c** 61	93/ 7
6	$PhCH_2CH_2$	Me	Me	Na	24	**1d** 42	90/10
7	Et	Me	$PhCH_2$	Na	36	**1e** 62	86/14
8	C_5H_{11}	Me	$PhCH_2$	Na	72	**1f** 68	85/15
9	Ph	Me	$PhCH_2$	Na	36	**1g** 70	67/33
10	i-Pr	Me	$PhCH_2$	Na	24	**1h** 54	66/34
11	Et	Et	$PhCH_2$	Na	36	**1i** 61	94/6
12	Me	Ph	$PhCH_2$	Na	36	**1j** 73	91/9[c]
13	Me	C_5H_{11}	$PhCH_2$	Na	48	**1k** 42	92/8
14	$-(CH_2)_4-$		$PhCH_2$	Na	48	**1l** 71	96/4[d]

a) Isolated yield. b) Determined by HPLC. c) Determined by 250 MHz ^{1}H-NMR. d) Ratio of cis/trans.

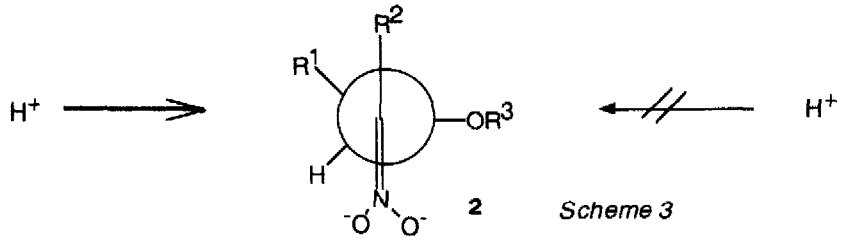
The stereochemistry of **1** was determined by ^{13}C-NMR spectra.[12] Potassium and lithium are also used as counter cation with the same extent of stereoselectivity as using sodium (run 1-3). Various kinds of alcohols, such as β-phenylethyl alcohol, γ-phenylpropyl alcohol, or methanol can be used for this reaction to give anti-**1** selectively (run 4-6). Sterically hindered R^1 groups, such as i-Pr or Ph group, diminish the anti-selectivity (run 9, 10). On the other hands, R^2 groups do not affect the anti-selectivity (run 11-13). The reaction of the alkoxide with a cyclic nitroolefin gave cis-**1l** with high stereoselectivity (run 14).

When anti-rich **1f** was treated with a catalytic amount of triethylamine in acetonitrile at room temperature for 24 h, the ratio of anti/syn was shifted to a thermodynamically controlled mixture of anti- and syn-**1f**. This mixture was readily converted into anti-rich **1f** by deprotonation-protonation at -78 °C (Scheme 2).



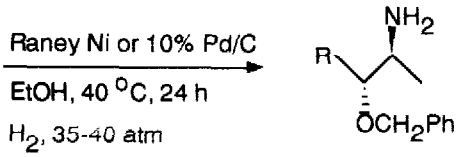
Scheme 2

The reason for this stereo selection may be explained as shown in Scheme 3. Namely, protonation to intermediate **2** can occur more preferentially from the less-hindered left site than the right site.[9,10]



2 *Scheme 3*

The nitro groups of **1** *were readily reduced to amino groups in the presence of a catalyst under* the conditions of hydrogen at 35-40 atm in ethanol in good yield. Neutral Raney-Ni or 10% Pd/C was effective as a catalyst. Epimerization on the carbon adjacent to the nitro group did not take place. It is noteworthy that *O*-benzyl group cannot be removed under these conditions (Scheme 4).[13]



3

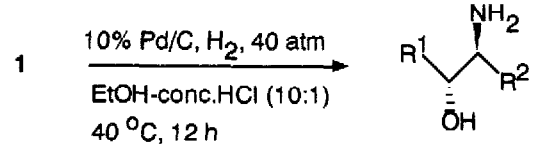
3	R	yield(%)[a]	anti/syn[b]
3a	Me	89	84/16
3b	Et	89	91/9
3c	C_5H_{11}	93	90/10

a) Isolated yield.

b) Determined by 250 MHz ^{1}H-NMR.

Scheme 4

One step conversion of **1** into β-amino alcohols **4** was achieved in good yield by the catalytic hydrogenation using ethanol-conc. HCl (10:1) as solvent (Scheme 5).[14] Anti configuration of **4** was assigned by ^{1}H-NMR.[15] Thus, **1** is converted into *O*-protected β-amino alcohols **3** or free β-amino alcohols **4** by the method shown in Scheme 4 or 5, respectively. As many kinds of nitroolefins are readily available, this method provides a new method for preparing anti-β-amino alcohols.



4

4	R^1	R^2	yield(%)[a]	anti/syn[b]
4a	C_5H_{11}	Me	64	86/14
4b	Et	Et	49	80/20
4c	Me	C_5H_{11}	72	88/12
4d	Me	Ph	72	91/9

a) Isolated yield.

b) Determined by 250 MHz ^{1}H-NMR.

Scheme 5

References and Notes

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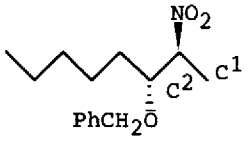
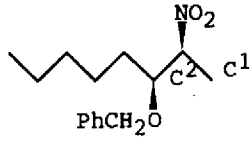
12. The stereochemistry of acyclic **1** is determined by ^{13}C-NMR spectra as following. C^1 signal for major isomer of **1f** appears at 12.884 ppm, and that of minor isomer of **1f** appears at 15.554 ppm. α-O_2N-C (C^2) signals at 84.668 ppm for major isomer of **1f** and 85.717 ppm for minor one. The same tendencies on ^{13}C-NMR spectra are also observed for Seebach's *O*-silylated nitroaldols. Thus, these data clearly establish the relative stereochemistries of major-**1f** and minor-**1f** as anti-**1f** and syn-**1f**, respectively. see; ref 16.





	anti **1f**	syn-**1f**
C^1 (ppm)	12.884	15.554
C^2 (ppm)	84.668	85.717

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15. For example, ^{1}H-NMR spectra of **4a** and **4b** were identical with literature data.[16]
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