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Generalization, Alteration, and Enhancement of the Stereoselectivity in the Cieplak-Mode Reductions of 4-Alkoxy(or Silyloxy)cyclohexanones

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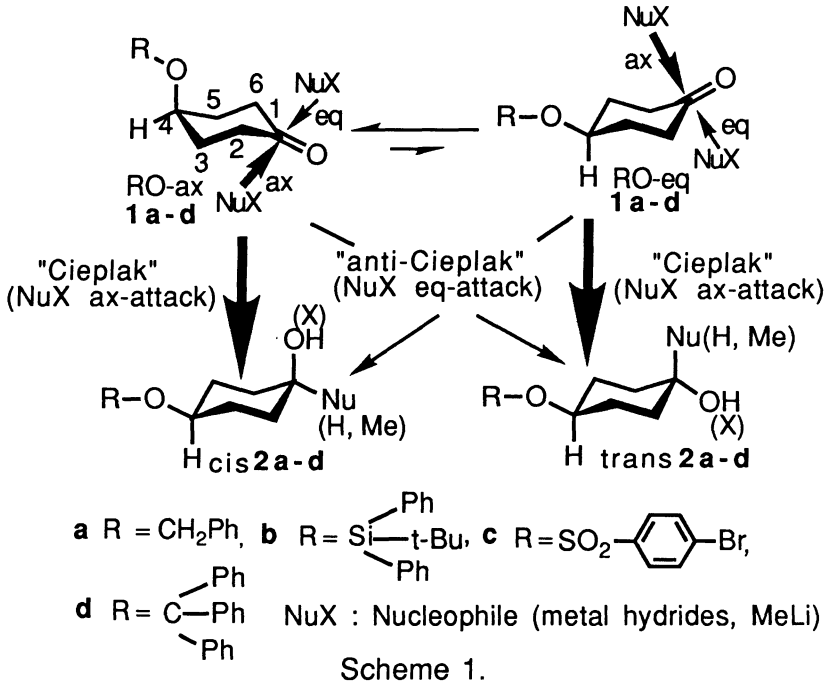
Reductions of 4-alkoxy(or silyloxy)cyclohexanones with $LiAlH_4$, $AlH(i\text{-}Bu)_2$, and $Li(s\text{-}Bu)_3BH$ afforded the corresponding cis alcohols in 73-80% selectivities. Similar reduction of 4-benzyloxy- and 4-*t*-butyldiphenylsilyloxy-cyclohexanones with $AlH(i\text{-}Bu)_2$ in the presence of $EtAlCl_2$ gave trans alcohol (93% selectivity) from the former and cis alcohol (94% selectivity) from the latter, respectively.

Stereocontrolled reactions based on an elaborate fixation method for conformationally flexible ring systems possessing mono- or di-substituent group(s) seem promising. Recently, we have reported fixation of the disubstituted cyclohexene ring to a 1,3-diaxial conformer utilizing an intramolecular Sn-O hypervalent interaction and its application to the highly stereocontrolled osmylation.[1] Here we descrive a general aspect and the Lewis acid-directed alteration and enhancement of the alkoxy or silyloxy substituent-controlled stereoselectivity in the reductions of 4-alkoxy(or silyloxy)cyclohexanones **1a-d**.

In 1981, Cieplak reported a remarkable postulation with the stereochemistry of nucleophilic addition to cyclohexanone based on a two-electron stabilizing interaction.[2] Since then, attractive and suggestive experimental results consistent with the Cieplak postulation were reported independently by le Noble,[3] Johnson,[4] Meyers,[5] and Laube[6] groups.[7] There have been independent reports on metal hydride reductions of a few 4-heteroatom-substituted cyclohexanones by Henbest and Combe[8] and by Kwart and Takeshita.[9,10] However, their explanation for the unusual stereochemical outcome had been wrong[8,9] or impertinent.[10] Hence, we attempted the systematic reductions with small and bulky reagents onto various 4-alkoxy(or silyloxy)cyclohexanones **1a-d** predominantly adopting an alkoxy(or silyloxy) axial conformer in the solution.

In the nucleophilic addition reaction in a conformational equilibrium between RO-ax **1** and RO-eq **1**, cis **2** can be preferentially obtained by axial attack of nucleophile(NuX) onto RO-ax **1** in a "Cieplak" mode (n, $\sigma^*_{\neq}$ orbital overlap control between oxygen lone-pair electron and the transition state $\sigma^*_{\neq}$ bond)[2] and a small amount may result from equatorial attack of NuX onto RO-eq **1** in an "anti-Cieplak" mode (steric control) (Scheme 1). On the other hand, trans **2** can be mainly produced from RO-eq **1** in another "Cieplak" mode (electronic control)[2] and a little can result

from RO-ax **1** in the "anti-Cieplak" mode (steric control) (Scheme 1). Since 4-alkoxy(or silyloxy)cyclohexanones **1a-d** can predominantly occupy the RO-ax form in a solution especially at low temperature,[10-12] nucleophilic addition reactions toward 4-alkoxy(or silyloxy)cyclohexanones are expected to afford cis alcohols **2** stereoselectively. In this case, the rate for nucleophilic addition of NuX onto both conformers RO-ax **1** and RO-eq **1** must be almost the same.



Scheme 1.

Thus, reduction of compounds **1a-d** with $LiAlH_4$ (LAH) in Et_2O at -78 °C gave, with fairly high cis-isomer selectivity in the range of 80:20-73:27 ratios, the corresponding cis alcohols **2a-d** (Nu=H)[13] in 53-96% yields (entries 1, 6, 10, and 12 in Table 1) as we expected.[14] Surprisingly, the reduction of **1a,c** with highly bulky Li(*s*-Bu)$_3$BH (L-selectride) at -78 °C similarly afforded cis alcohols **2a,c** (Nu=H) in a cis-isomer selective manner (80:20 and 82:18 ratios) (entries 2 and 11).[14] Tentative alkylation of **1a,b** with MeLi in Et_2O at -78 or -100 °C also gave cis alcohols **2a,b** (Nu=Me) in a cis-isomer selective manner (entries 3 and 7).[15] Thus, we were able to clarify that all nucleophilic addition reactions including AlH(*i*-Bu)$_2$ (DIBAH)-reductions (entries 4, 8, and 13) toward the equilibrium system between RO-ax **1** and RO-eq **1** generally proceed under the Cieplak mode (electronic) regulation regardless of bulkiness of the reagents and the RO groups of compounds **1**.

Subsequently, the DIBAH reduction of **1a** and **1b** was examined in the presence of various amounts of $EtAlCl_2$. 4-Benzyloxycyclohexanone (**1a**) exhibited totally different behavior to the common DIBAH reduction from the case of 4-*t*-butyldiphenylsilyloxycyclohexanone (**1b**). Compound **1a** could be converted to the trans alcohol **2a** (Nu=H) in larger amounts by increasing the amounts of $EtAlCl_2$.[16] The optimum result (cis **2a** : trans **2a** = 7 : 93) is listed in entry 5 of Table 1. Inversely, compound **1b** could be converted to the cis alcohol **2b** (Nu=H) in larger amounts by increasing the amounts of $EtAlCl_2$ [see the optimum result (cis **2b** : trans **2b** = 94 : 6) shown in

entry 9].[17] Thus, alteration and enhancement of the original selectivity in the DIBAH reduction of **1a** and **1b** were successfully achieved. These stereochemical outcome may be understood in terms of two kinds of hypothetic transition states (A and B shown in Fig. 1) involving the Lewis acid-directed ring conversion of RO-ax **1a** toward RO-eq **1a** or of RO-eq **1b** toward RO-ax **1b**.[18]

Table 1. Nucleophilic addition onto 4-alkoxycyclohexanones

Entry	C4-Alkoxycyclohexanone (R=)	Nucleophile[a]	Conditions[b]	Yield/%[c]	Ratio[d] cis **2** : trans **2**
1	CH_2Ph	LAH[e]	Et_2O, 0.5 h	74	80 : 20
2	"	L-select.[e]	Et_2O-THF(6:1), 0.5 h	74	80 : 20
3	"	MeLi[f]	Et_2O, 0.6 h	88	67 : 33
4	"	DIBAH[g]	CH_2Cl_2, 1 h	88	73 : 27
5	"	"	CH_2Cl_2, $EtAlCl_2$,[h] 3 h	75	7 : 93
6	$Si(Ph)_2t$-Bu	LAH[e]	Et_2O, 3 h, -100 °C	76	73 : 27
7	"	MeLi[f]	Et_2O, 2.5 h, -100 °C	87	62 : 38
8	"	DIBAH[g]	CH_2Cl_2, 0.8 h	76	62 : 38
9	"	DIBAH[j]	CH_2Cl_2, $EtAlCl_2$,[i] 1.5 h	79	94 : 6
10	$SO_2C_6H_4(p$-Br)	LAH[e]	Et_2O, 0.5 h	53	75 : 25
11	"	L-select.[e]	Et_2O-THF(6:1), 0.5 h	60	82 : 18
12	$C(Ph)_3$	LAH[k]	Et_2O, 0.5 h	96	75 : 25
13	"	DIBAH[g]	CH_2Cl_2, 0.7 h	84	67 : 33

a)Amount(mol equiv.) of nucleophile or additive employed to C4-alkoxycyclohexanones was as followes: e)1.0, f)1.1, g)1.2, h)5.2, i)3.2, j)7.2, and k)2.2. b)Unless otherwise noted, the reaction was carried out at -78 °C. c)Total yield of both alcohol products. d)Determined by 200 MHz or 400 MHz ^{1}H-NMR analysis.

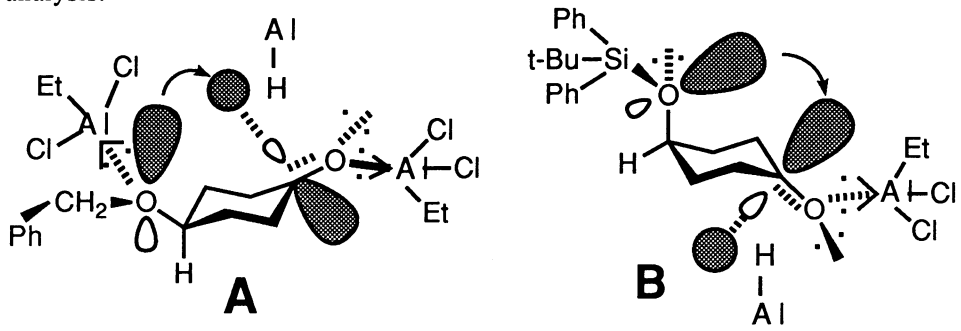


Fig. 1. Possible transition state for stereoselective reduction of **1a** (A) and **1b** (B) with DIBAH in the presence of $EtAlCl_2$.

Direction of the different ring conversion would be controlled by the bulkiness of the R group of C4-alkoxy (RO) substituents. ^{1}H-NMR analysis of **1a** and **1b** in the presence of $EtAlCl_2$ in $CDCl_3$ may support these plausible ring conversion.[19] Thus, alteration and enhancement of the original stereoselectivity in the DIBAH reduction of **1a** and **1b** were successfully achieved without perturbation of the Cieplak mode by utilizing manipulation of the ring conformation with a suitable Lewis acid.

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13) The stereochemistry of cis and trans alcohols **2** (Nu = H) can be readily assigned by the half-band width of HO-C<u>H</u> peaks on their 400 MHz ^{1}H-NMR($CDCl_3$) spectra [cis **2** (Nu = H) : W1/2 = 10.7-13.5 Hz, trans **2** (Nu = H) : W1/2 = 18.5-21.0 Hz].

14) Reduction of 4-*t*-butylcyclohexanone with LAH (1.0 mol equiv.) in Et_2O at -78 °C for 0.5 h gave cis and trans alcohols in a 4:96 ratio and in 73% yield. Its reduction with L-selectride (1.0 mol equiv.) in Et_2O-THF (6:1) under similar conditions afforded cis and trans alcohols in a 94:6 ratio and in 78% yield.

15) Cis and trans alcohols **2** (Nu = Me) could be assigned from the half-band width of RO-C<u>H</u> peaks on their 400 MHz ^{1}H-NMR($CDCl_3$) charts [cis **2** (Nu = Me) : W1/2 = 18.3 Hz, trans **2** (Nu = Me) ; W1/2 = 11.7 and 13.5 Hz].

16) $EtAlCl_2$ = 1.2 mol equiv. (cis **2** : trans **2** = 50;50), 2.2 mol equiv. (27:73), 3.2 mol equiv. (18:82), 4.2 mol equiv. (8:92), and 6.2 mol equiv. (7:93).

17) $EtAlCl_2$ and DIBAH = 2.2 mol equiv. (cis **2** : trans **2** = 77:23), 4.2 mol equiv. (90:10), and 8.2 mol equiv. (90:10).

18) Cf. H. C. Brown and G. Zweifel, *J. Org. Chem.*, **27**, 4708 (1962); E. L. Eliel and T. J. Brett, *ibid.*, **28**, 1923 (1963); K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 3588 (1988).

19) ^{1}H-NMR(200 MHz, $CDCl_3$, 25 °C) signal of C4-H of **1a** (R = CH_2Ph) : δ 3.82 ppm, W(bandwidth) = 22.5 Hz(without $EtAlCl_2$) → δ 4.80 ppm, W = 76.0 Hz [in the presence of $EtAlCl_2$ (2mol equiv.)]. ^{1}H-NMR signal of C4-H of **1b** [R = $Si(Ph)_2t$-Bu : δ 4.15 ppm, W = 20.7 Hz(without $EtAlCl_2$) → δ 4.30 ppm, W = 19.1 Hz [in the presence of $EtAlCl_2$ (2 mol equiv.)].

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