Electronic Control of Stereoselectivity in the Metal Hydride Reductions of a Series of Substituted 3,4-Dihydro-1,4-ethanonaphthalen-2(1*H*)-ones

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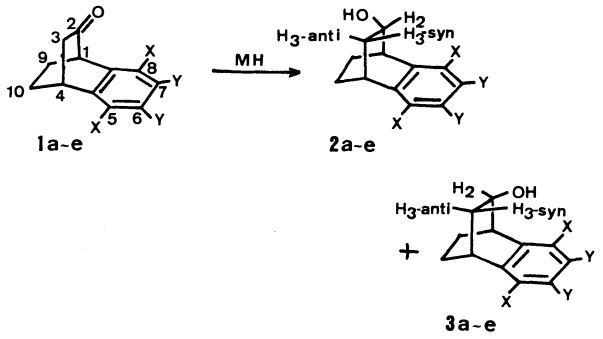
The anti/syn stereoselectivity in the metal hydride reductions of a series of substituted 3,4-dihydro-1,4-ethanonaphthalen-2(1*H*)-ones was studied. The observed steroselectivity sequence was found to be parallel with the homoconjugation sequence except for the case of 5,8-dimethoxy-substituted derivative: the portion of anti attack increases as the benzene ring becomes electron-rich. The results were rationalized by Cieplak's transition state model or by the nonclassical carboncation model. A special coordinated transition state was considered to explain the results for 5,8-dimethoxy-substituted compound.

Because of the homoconjugation interaction between the carbonyl group and the endocyclic double bond, bicyclo[2.2.2]oct-5-en-2-one has attracted considerable attention. This interaction has been investigated in terms of ^{13}C NMR,[1] PES,[2] and CD[3] studies. The homoconjugation interaction may also be revealed by chemical reactions especially by the stereoselectivity in nucleophilic additions. Hitherto, several experimental data in the nucleophilic additions toward this substrate have been reported. Metal hydrides such as sodium borohydride[4] or lithium aluminum hydride[5] are known to attack the carbonyl group predominantly from the anti side of the double bond, whereas Grignard reagents such as alkyl- or vinylmagnesium halides[6,7] mainly attack from the syn side. The origin of the stereoselectivity has not been considered in most cases. However, Snowden and co-workers speculated a steric factor in the Grignard reactions.[6] Brown and Muzzio considered a steric effect between attacking hydride and the π-electrons of C_5–C_6 double bond.[4] We have recently reported the anti/syn stereoselectivity of metal hydride reductions of a series of substituted 1,2,3,4-tetrahydro-1,4-methanonaphthalen-9-ones and have found that the electron-donating substituents on the benzene ring increase the portion of anti attack.[8] In order to know whether this substituent effect in bicyclic systems is general or not, we have extended our study to bicyclo[2.2.2]oct-5-en-2-one. In this paper, the metal hydride reductions of a series of substituted 3,4-dihydro-1,4-ethanonaphthalen-2(1*H*)-ones (**1a—e**) are investigated.



a: X=Y=F, b: X=Y=Cl, c: X=Y=H,
d: X=OMe; Y=H, e: X=H; Y=OMe

Results and Discussion

Stereochemistry of Anti- (2a—e) and Syn-Alcohols (3a—e). The reduction of substituted 3,4-dihydro-1,4-ethanonaphthalen-2(1*H*)-ones (**1a—e**) with various metal hydrides gave the corresponding anti- (**2a—e**) and syn-alcohols (**3a—e**) in high yields (>78%). The produced alcohols can be separated by preparative TLC or gas chromatography. In Table 1, the ^{1}H NMR data of the alcohols are listed. Among the methylene protons, the H_3-anti proton appears in the range of δ 2.2—2.4 as a d-d-d like multiplet for the anti-alcohols (**2a—e**) or a d-d-d pattern (typically, J=14, 9, and 3 Hz) for the syn-alcohols (**3a—e**). The H_3-syn proton and other four methylene protons appear in the higher field (δ 1.0—2.2) as multiplets. By addition of a NMR shift reagent, Eu(fod)$_3$, the H_3-syn proton of the syn-alcohols (**3a—e**) becomes separable as a multiplet having a geminal coupling of J=ca. 14 Hz from other methylene protons. The lower chemical shift of the H_3-syn proton compared with that of the H_3-anti proton is probably due to the anisotropic effect of the benzene ring.

Table 1 also summarizes the relative shift values (1.00 for H_1 proton in both alcohols) induced by Eu(fod)$_3$ for the H_3 and other protons. It is clear from the table that the H_3-anti proton of the anti-alcohols has a larger relative shift (1.0—1.2) than that of the syn-alcohols (0.5—0.6). The relative shifts for other protons are reasonable except for the large induced shifts of the aromatic and methoxyl protons of **2e** and **3e**, the large shifts being ascribed to the partial coordination of Eu(fod)$_3$ onto the methoxyl groups. However,this coordination would not much affect the shift of H_3-anti proton because of the relatively long distance between the H_3-anti proton and the coordinated metal center. The assigned stereochemistry is

Table 1. Chemical Shift (δ)[a] and Relative Shift Values[b] Induced by Eu(fod)$_3$ for Protons of **2a—e** and **3a—e**

	H_2	H_1 and H_4	H_3-anti	H_3-syn and $H_{9,10}$	Aromatic protons	Methoxyl protons
X=Y=F	3.93	3.44[c]	ca. 2.40	1.05—2.15	—	—
2a	(1.78)	(1.00, 0.37)[d]	(1.11)			
X=Y=Cl	3.93	3.64[c]	ca. 2.40	1.05—2.15	—	—
2b	(1.83)	(1.00, 0.37)[d]	(1.10)			
X=Y=H	3.92	3.00[c]	ca. 2.29	1.10—2.15	7.15[c]	—
2c	(1.71)	(1.00, 0.41)[d]	(1.22)		(0.18)[c]	
X=OMe, Y=H	3.89	3.47[c]	ca. 2.28	0.98—2.10	6.67[c]	3.75, 3.76
2d	(2.00)	(1.00, 0.40)[d]	(1.13)		(0.13)[c]	(0.06, 0.09)
X=H, Y=OMe	3.92	2.92[c]	ca. 2.30	1.05—2.15	6.70, 6.74	3.87[c]
2e	(1.42)	(1.00, 0.66)[d]	(0.97)		(1.29, 1.24)[d]	(1.00)[c]
X=Y=F	4.21	3.50[c]	2.25	1.05—1.90	—	—
3a	(1.39)	(1.00, 0.36)[d]	(0.56)	(1.26)[e]		
X=Y=Cl	4.23	3.71[c]	2.25	1.05—1.90	—	—
3b	(1.38)	(1.00, 0.35)[d]	(0.49)	(1.07)[e]		
X=Y=H	4.08	3.06[c]	2.25	1.05—1.80	7.18[c]	—
3c	(1.56)	(1.00, 0.39)[d]	(0.57)	(1.44)[e]	(0.51,[f] 0.23[c])	
X=OMe, Y=H	4.10	3.61, 3.50	2.17	1.00—1.80	6.70[c]	3.76, 3.77
3d	(1.38)	(1.00, 0.41)[d]	(0.57)	(1.01)[e]	(0.20)[c]	(0.11, 0.19)
X=H, Y=OMe	4.08	3.01[c]	2.22	1.05—1.80	6.75, 6.80	3.88[c]
3e	(1.55)	(1.00, 0.49)[d]	(0.61)	(1.12)[e]	(0.57, 0.76)[d]	(0.34, 0.38)

a) Measured in $CDCl_3$ (ca. 25—30 mg/0.3 cm^3). b) In parenthesis; determined by successive addition of ca. 5 mg of Eu(fod)$_3$ up to ca. 20 mg. c) An averaged value. d) Respective values. e) For H_3-syn proton. f) For one of the aromatic protons.

Table 2. Product Ratios (**2a—e**:**3a—e**) in the Metal Hydride Reductions of **1a—e**[a]

Reagent	Solvent	**1a**	**1b**	**1c**	**1d**	**1e**
LAH	THF	43:57	35:65	14:86	13:87	15:85
LAH	Ether	40:60	36:64	27:73	38:62	30:70
DIBAL-H	Ether	54:46	53:47	28:72	29:71	21:79
LTBA[b]	Ether	53:47	52:48	54:46	55:45	59:41
$NaBH_4$	EtOH	63:37	61:39	27:73	38:62	27:73
$(BH_3)_2$	THF	84:16	90:10	52:48	65:35	45:55
Sia_2BH[c]	Diglyme	73:27	69:31	37:63	40:60	27:73

a) All reactions were performed at 0°C. b) Lithium tri-*t*-butoxyaluminum hydride. c) Bis(1,2-dimethylpropyl)borane (disiamylborane).

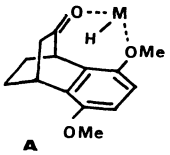
also in good accordance with the fact that the H_2-methine proton of the anti-alcohols has a lower chemical shift (δ ca. 3.9) than that (δ 4.1—4.2) of the syn-alcohols owing to the expectable anisotropy effect of the benzene ring. In our previous study,[8] we have observed that the syn-alcohols derived from a series of the related methanonaphthalen-9-ones have shorter GC retention time (OV-17) than the corresponding anti-alcohols. The GC retention time for these isomeric alcohols probably relates to their vapor pressure at the GC conditions. The higher vapor pressure of the syn alcohols can be expected from the possible intramolecular hydrogen bond between the hydroxyl group and the benzene π-bond. In the present system (**2a—e** and **3a—e**), the stereochemical assignment by this qualitative GC method resulted in a complete agreement with that from the NMR shift reagent study.

Stereoselective Metal Hydride Reductions of 1a—e. Table 2 shows the ratios of anti/syn-alcohols in the reductions using typical metal hydrides. Although some of these values differ only slightly and are nearly equal within the experimental error (±2%), there is apparently an overall trend that the portion of syn-alcohol (anti attack) increases in the sequence of **1a**⇄**b**→**d**⇄**c**→**e** in most cases despite of considerably different sizes and reactivities of the reagents. In particular, the reductions with sodium borohydride, diisobutylaluminum hydride, and bis(1,2-dimethylpropyl)borane (common name "disiamylborane" is used hereafter) follow this sequence. A small change in the sequence is observed with lithium aluminum hydride and diborane reductions. The anti/syn selectivity varies most widely in the reduction with disiamylborane. In this case, the main product is switched from the anti- to the syn-alcohol when the benzene ring becomes electron rich (**2a**/**3a**=73/27→**2e**/**3e**=27/73). Similar trends are observed for the reduction with diisobutylaluminum hydride, sodium borohydride, and diborane. With a very bulky

hydride, tri-*t*-butoxyaluminum hydride, the anti/syn ratio is almost constant (ca. 1:1) for **1a—e**; this result suggests that the electronic perturbation of the substituents is minimized for this bulky reagent and probably also suggests that the steric congestion in both the anti and syn sides would not be much different for **1a—e**.

Several comments on the results of Table 2 can be given. The selectivity is considerably dependent on the reagents for the each substrate; the anti/syn ratio varies from 40/60 (LAH in ether) to 84/16 (diborane in THF) for reduction of **1a**, from 35/65 (LAH in THF) to 90/10 (diborane in THF) for **1b**, from 13/87—15/85 (LAH in THF) to 54/46—65/35 (lithium tri-*t*-butoxyaluminum hydride in ether or diborane in THF) for **1c—e**. Among the reducing reagents used, the reductions with lithium aluminum hydride give the highest portion of anti attack for all the substrates. On the other hand, the reductions with borane reagents tend to produce the high portion of syn attack for **1a,b**. Although the reason for these selectivity change is not clear at present, it may relate with several factors such as the structure of reactive species,[9] the mode and degree of solvation,[9] Lewis acidity of the reagents,[10] and the ability of reagents for electron transfer.[11]

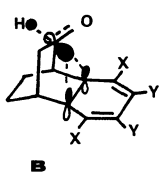
Obviously, the observed sequence of **1a≒b→d≒c→e** cannot be rationalized by steric effect of the substituents on the benzene ring. On the contrary, this sequence seems to be explicable by the electron-donating ability of the substituents on the benzene ring with the exception of **1d**. The electronic perturbation of the substituents to the reactive center would increase in the sequence of **1a→b→c→d→e**, in which methoxyl groups at C_6 and C_7 positions would have a larger electronic effect than those at C_5 and C_8 positions from the consideration of molecular orbitals of the benzo moieties. We have previously shown that the IR carbonyl stretching frequencies of a series of the related methanonaphthalenones are lined parallel with the electron donating ability of the benzene rings as well as the homoconjugation interaction.[8] The observed frequencies of the starting ketones (**1a—e**) follow the expected sequence [IR, ν_{CO} (cm^{-1}) in CCl_4; 1736 for **1a**, 1733 ($CDCl_3$) for **1b**, 1733 for **1c**, 1728 for **1d**, 1725 for **1e**]. Presumably, the deviation for **1d** in the sequence of stereoselectivity is due to the special coordination of the metal hydrides on the neighboring methoxyl group in the transition state as shown in structure **A** which would increase the portion of syn attack. As recognized from inspection of the molecular model, this type of coordination is much weak for **1e** and for the corresponding 1,2,3,4-tetrahydro-1,4-methano naphthalen-9-one derivatives in which such an anomalous effect was not observed in the metal hydride reductions,[8] because of the long distance between n-orbital of the carbonyl oxygen and the lone-pair electrons of the methoxyl group and because of the poor overlapping direction of these orbitals, respectively. Considering the above coordination factor for **1d**, we conclude that the variation of anti/syn stereoselectivity in the metal hydride reductions of **1a—e** is electronic in origin.



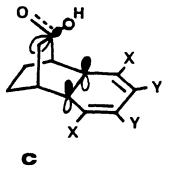
A

Several electronic factors in nucleophilic additions to cyclic ketones have been previously reported.[12,13] Among them, as we have pointed out in our previous report,[8] a qualitative transition state model developed by Cieplak seems to be attractive. Cieplak assumed that a newly formed bond between nucleophiles and carbonyl carbons is weak and intrinsically electron deficient in the transition state and therefore characterized as a low-lying antibonding σ*-orbital.[10] In his model, the transition state can be stabilized by the interaction between the σ*-orbital and electron-donating orbitals neighboring the carbonyl group, so that the favorable transition state is such that the nucleophiles approach to the carbonyl carbon from the anti side of donor orbital. More recently, le Noble and co-workers have reportd that the model developed by Cieplak reasonably explains the stereoselectivity in the reduction of a series of 5-substituted adamantanones.[14]

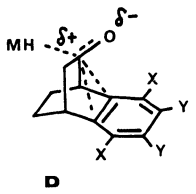
Application of Cieplak's model to our system gives satisfactory explanation. We show qualitative sketches of the transition states for the anti attack (**B**) and the syn attack (**C**). In the transition state **B**, the electron-deficient σ*-orbital can be much stabilized by the bonding interaction with π-orbital of the benzene ring with a larger overlap of back side lobe of the σ*-orbital. Electron donating substituents on the benzene ring would increase the stabilization gain in the transition state **B** and hence the anti attack. However, a similar explanation is afforded by the consideration of contribution of the nonclassical carbocation. As Cieplak pointed out, the incipient C–H bond is electron-deficient in nature, some positive charge remains on the carbonyl carbon with the greater extent than the ground state. When the benzene ring becomes electron-rich, the transition state for the anti attack would be stabilized as shown in **D**. Both the explanations are related to the stabilization



B



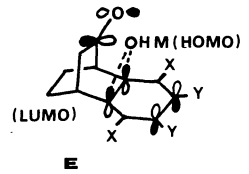
C



D

gain obtained by the HOMO–LUMO interaction between the benzene π-orbital and the p-orbital of the carbonyl carbon in the transition state. The interaction in the transition state must be parallel with that in the ground state (homoconjugation interaction).

Apart from the above explanations, it may be interesting to consider the role of secondary orbital interaction in the metal hydride reductions. As shown in **E**, incoming hydride would experience the antibonding repulsive secondary orbital interaction with



E

the benzene π-orbital. Although kinetic treatment was not investigated in this paper, this interaction predicts that the lower reactivity in the syn side should be observed as the benzene ring becomes electron-rich. In this context, Brown and Muzzio reported the rate study of sodium borohydride reduction of bicyclo[2.2.2]oct-5-en-2-one and its saturated analogue.[4] According to their study, the predominant anti attack is mainly due to the enhanced rate in the anti side. From this result, the antibonding secondary orbital interaction is not likely to be an origin of the stereoselectivity.

In summary, we have observed that the anti/syn stereoselectivity of a series of substituted 3,4-dihydro-1,4-ethano-naphthalen-2(1*H*)-ones is parallel with the homoconjugation interaction except for **1d**: the portion of anti attack increases as the benzene ring becomes electron-rich. A special coordinated transition state was considered to rationalize the results for **1d**. It should be noted that the variation of anti/syn stereoselectivity in the present system is considerably small when compared to the corresponding 1,2,3,4-tetrahydro-1,4-methanonaphthalen-9-one derivatives.[8] The reason would be simply due to the weaker interaction between the benzene π-orbital and the reactive center in **1a—e** in the transition state.

Experimental

General. Melting points were measured on a Mettler FP2 apparatus and are uncorrected. IR spectra were recorded with a Hitachi EPI-G3 grating spectrophotometer and wavenumbers were corrected with use of polystyrene film. The wavenumbers of the carbonyl stretching for **1a—e** were directly read from the spectrophotometer at their maximum absorptions. ^{1}H NMR spectra were obtained at 90 MHz on a JEOL FX-90Q or 100 MHz on a Varian XL-100. ^{13}C NMR spectra were taken with a JEOL FX-90Q (22.5 MHz). Mass spectra were measured on a JEOL JMS-01SG-2 mass spectrometer. GLC analysis were performed on a Hitachi 063 gas chromatography with a glass column packed with Silicone OV-17 (3%) on Chromosorb W AW DMCS (1 m). Column chromatography was carried out with Merck Kieselgel 60 and preparative TLC with Merck Kieselgel GF_{254} (Type 60). Lithium aluminum hydroide, sodium borohydride, lithium tri-*t*-butoxyaluminum hydride, and diisobutylaluminum hydride were commercial products. Diborane and disiamyborane were generated in situ prior to use.[15] Compounds **1a—d** were prepared according to the reported methods.[16] All the solvents were distilled before use.

Synthesis of 3,4-Dihydro-6,7-dimethoxy-1,4-ethanonaphthalen-2(1*H*)-one (1e). To a stirred solution of 280 mg (1.28 mmol) of 1,2,3,4-tetrahydro-6,7-dimethoxy-1,4-methanonaphthalen-9-one[8] in dichloromethane (6 cm^3) cooled at 0 °C under nitrogen, was sucessively added over 1 min boron trifluoride etherate (0.02 cm^3) and ethyl diazoacetate (217 mg, 1.90 mmol). After 4 h stirring at room temperature, the reaction mixture was treated with saturated aqueous sodium hydrogencarbonate (5 cm^3) and dichloromethane (20 cm^3). The separated organic layer was washed with brine (5 cm^3) and dried over magnesium sulfate. Purification with preparative TLC (hexane:ethyl acetate=3:1 (v/v)) gave 221 mg (57%) of a mixture of the syn and anti isomer (ca. 1:1 ratio) of the α-keto ester. The solution of 221 mg (0.727 mmol) of the α-keto ester in a mixture of dioxane (6 cm^3) and hydrochloric acid (2 mol dm^{-3}, 6 cm^3) was refluxed for 2 h. After cooling to room temperature, water (20 cm^3) was added and the mixture was extracted with ethyl acetate (20 cm^3) twice. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The resulting crude α-keto carboxylic acid was dissolved in 4 cm^3 of *o*-dichlorobenzene and the solution was refluxed for 1 h under nitrogen atmosphere. The solvent was evaporated under reduced pressure. Purification with preparative TLC (hexane:ethyl acetate=3:1 (v/v)) gave 93 mg (53%) of **1e**: colorless prisms from hexane; mp 100—101 °C; IR (CCl_4) 2925, 2850, 1725, 1504, 1466, 1348, 1290, 1260, 1233, 1011 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ=1.50—2.50 (m, 6H), 3.35 (m, 1H), 3.52 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 6.75 (s, 1H), 6.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=23.55, 25.34, 36.25, 42.13, 52.02, 56.11, 108.22, 109.55, 128.29, 135.23, 148.01, 148.37, 211.51; MS (75 eV) *m/z* (%) 232 (M^+; 100), 204 (30), 190 (55), 189 (57). Found: C, 72.35; H, 7.01%. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%.

Prototypical Procedure for Reductions with Lithium Aluminum Hydride. To a suspension of 20 mg (0.53 mmol) of lithium aluminum hydride in 5 cm^3 of dry ether under nitrogen at 0 °C was added dropwise over 2 min a solution of 100 mg (0.410 mmol) of **1a** in 5 cm^3 of dry ether. After 30 min, the reaction was quenched by addition of 0.08 cm^3 of water. The ether layer was dried over magnesium sulfate. Separation with preparative TLC (hexane:ethyl acetate=5:1 (v/v)) gave 38 mg of **2a** and 56 mg of **3a** in overall yield of 93% (**2a**:**3a**=40:60). The yields and product ratios for other derivatives were as follows, in ether: 93% (**2b**:**3b**=36:64) for **1b**, 81% (27:73) for **1c**, 90% (38:62) for **1d**,

and 99% (30:70) for **1e**, in THF: 79% (43:57) for **1a**, 87% (35:65) for **1b**, 85% (14:86) for **1c**, 95% (13:87) for **1d**, 85% (15:85) for **1e**. **2a**: colorless needles from hexane; mp 81—82 °C, IR (KBr) 3270, 2955, 1507, 1401, 1343, 1062, 1048, 1022, 1012, 1003, 952, 870, 819 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—2.15 (m, 6H), ca. 2.40 (m, 1H), 3.44 (m, 2H), 3.93 (m, 1H). Found: C, 58.43; H, 4.03%. Calcd for $C_{12}H_{10}OF_4$: C, 58.54; H, 4.09%. **3a**: colorless needles from hexane; mp 96—99 °C, IR (KBr) 3250, 1950, 1502, 1408, 1351, 1118, 1078, 1043, 1028, 935, 862, 832 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—1.90 (m, 6H), 2.25 (ddd, 1H, J=14.0, 9.0, and 3.0 Hz), 3.50 (m, 2H), 4.21 (m, 1H). Found: C, 58.72; H, 3.99%. Calcd for $C_{12}H_{10}F_4$: C, 58.58; H, 4.09%. **2b**: colorless needles from benzene-hexane; mp 138—141 °C, IR (KBr) 3300, 2950, 1394, 1380, 1340, 1279, 1224, 1172, 1078, 1050, 1010 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—2.15 (m, 6H), ca. 2.40 (m, 1H), 3.64 (m, 2H), 3.93 (m, 1H). Found: C, 46.58; H, 3.23%. Calcd for $C_{12}H_{10}OCl_4$: C, 46.19; H, 3.23%. **3b**: colorless prisms from benzene-hexane; mp 143—144 °C; IR (KBr) 3305, 2955, 2865, 1472, 1386, 1359, 1348, 1290, 1226, 1179, 1090, 1039 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—1.90 (m, 6H), 2.25 (ddd, 1H, J=14.0, 9.0, and 3.0 Hz), 3.71 (m, 2H), 4.23 (m, 1H). Found: C, 46.41; H, 3.28%. Calcd for $C_{12}H_{10}OCl_4$: C, 46.19; H, 3.23%. **2c**: colorles needles from hexane; mp 70—71 °C; IR (KBr) 3325, 2925, 1488, 1463, 1075, 1048, 1006, 754 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.10—2.15 (m, 6H), ca. 2.29 (m, 1H), 3.00 (m, 2H), 3.92 (m, 1H), 7.15 (s, 4H). Found: C, 82.68; H, 8.12%. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10%. **3c**: colorless needles from hexane; mp 102—104 °C; IR (KBr) 3265, 2930, 2855, 1488, 1460, 1349, 1332, 1081, 1033, 988, 750 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—1.80 (m, 6H), 2.25 (ddd, 1H, J=14.0, 9.0, and 3.0 Hz), 3.06 (m, 2H), 4.08 (m, 1H), 7.18 (s, 4H). Found: C, 82.61; H, 8.08%, Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10%. **2d**: colorless prisms from benzene-hexane; mp 115—116 °C; IR (KBr) 3275, 2940, 2825, 1499, 1464, 1453, 1340, 1323, 1280, 1261, 1239, 1112, 1088, 1071, 1054, 1010, 792, 712 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=0.98—2.10 (m, 6H), ca. 2.28 (m, 1H), 3.47 (m, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 3.89 (m, 1H), 6.67 (s, 2H). Found: C, 71.69; H, 7.80%. Calcd for $C_{14}H_{18}C_3$: C, 71.77; H, 7.74%. **3d**: colorless prisms from benzene-hexane; mp 92—93 °C; IR (KBr) 3465, 2935, 2860, 1499, 1439, 1339, 1261, 1243, 1115, 1087, 1052, 1035, 958, 800, 711 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.00—1.80 (m, 6H), 2.17 (ddd, 1H, J=14.0, 9.0, and 3.0 Hz), 3.50 (m, 1H), 3.61 (m, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 4.10 (m, 1H), 6.70 (s, 2H). Found: C, 71.67; H, 7.75%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. **2e**: colorless plates from benzene-hexane; mp 105—106 °C; IR (KBr) 3520, 3305, 2925, 2850, 1508, 1470, 1458, 1449, 1340, 1288, 1261, 1228, 1184, 1113, 1051, 1008, 992 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—2.15 (m, 6H), ca. 2.30 (m, 1H), 2.92 (m, 2H), 3.87 (s, 6H), 3.92 (m, 1H), 6.70 (s, 1H), 6.74 (s, 1H). Found: C, 71.54; H, 7.77%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. **3e**: colorless prisms from benzene-hexane; mp 122—123 °C; IR (KBr) 3980, 3400, 2915, 2840, 1510, 1461, 1364, 1280, 1232, 1208, 1075, 1030, 1009, 803 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ=1.05—1.80 (m, 6H), 2.22 (ddd, 1H, J=14.0, 9.0, and 3.0 Hz), 3.01 (m, 2H), 3.88 (s, 6H), 4.08 (m, 1H), 6.75 (s, 1H), 6.80 (s, 1H). Found: C, 71.81; C, 7.85%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%.

Prototypical Procedure for Reduction with Diisobutylaluminum Hydride. To a solution of 100 mg (0.410 mmol) of **1a** in 10 cm^3 dry ether under nitrogen at 0 °C was dropwise a hexane solution (1.32 cm^3) of diisobutylaluminum hydride (2.30 mmol). After being stirred for 30 min at 0 °C, the mixture was treated with 2 cm^3 of ethanol, 8 cm^3 of aqueous hydrochloric acid (2 mol dm^{-3}), and 10 cm^3 of ether. The separated ether layer was washed with brine and dried over magnesium sulfate. The products were separated with preparative TLC (hexane:ethyl acetate=5:1 (v/v)) to give 50 mg of **2a** and 43 mg of **3a** in overall yield of 92% (**2a**:**3a**=54:46). The yields and the ratios of anti- and syn-alcohols were as follows; 93% (**2b**:**3b**=53:47) for **1b**, 93% (28:72) for **1c**, 89% (29:71) for **1d**, 89% (21:79) for **1e**.

Prototypical Procedure for Reductions with Lithium Tri-*t*-butoxyaluminum Hydride. To a suspension of 420 mg (1.65 mmol) of lithium tri-*t*-butoxyaluminum hydride in 5 cm^3 of dry ether under nitrogen at 0 °C was added a solution of 100 mg (0.410 mmol) of **1a** in dry ether (5 cm^3). After stirring overnight at 0 °C, the mixture was treated with 3 cm^3 of ethanol, 8 cm^3 of aqueous hydrochloric acid (2 mol dm^{-3}), and 10 cm^3 of ether. The separated ether layer was washed with brine, dried over magnesium sulfate. The products were purified with preparative TLC to give 47 mg of **2a** and 42 mg of **3a** in overall yield of 88% (**2a**:**3a**=53:47). The yields and rations of anti- and syn-alcohols were as follows, 91% (**2b**:**3b**=52:48) for **1b**, 94% (54:46) for **1c**, 98% (55:45) for **1d**, 93% (59:41) for **1e**.

Prototypical Procedure for Reductions with Diborane. To a suspension of 31 mg (0.82 mmol) of sodium borohydride in dry THF(10 cm^3) under nitrogen at 15—18 °C was added dropwise 0.13 cm^3 (1.0 mmol) of boron trifluoride etherate. After 30 min stirring, a solution of 100 mg (0.410 mmol) of **1a** in 5 cm^3 dry THF was added to the mixture and stirred for 30 min at 0 °C. The mixture was treated with 3 cm^3 of ethanol and 8 cm^3 of aqueous hydrochloric acid (2 mol dm^{-3}), and extracted with 15 cm^3 of ether twice. The ether layer was washed with brine and dried over magnesium sulfate. Separation with preparative TLC gave 62 mg of **2a** and 12 mg of **3a** in overall yield of 73% (**2a**:**3a**=84:16). The yields and ratios of anti- and syn-alcohols were as follows; 94% (**2b**:**3b**=90:10) for **1b**, 80% (52:48) for **1c**, 84% (65:35) for **1d**, 83% (45:55) for **1e**.

Prototypical Procedure for Reductions with Disiamylborane. To a suspension of 31 mg (0.82 mmol) of sodium borohydride and 0.21 cm^3 (2.0 mmol) of 2-methyl-2-butene in 10 cm^3 of dry diglyme under nitrogen at 0 °C was added 0.13 cm^3 (1.0 mmol) of boron trifluoride etherate. The mixture was stirred for 30 min at 0 °C. To this suspension was added over 2 min a solution of 100 mg (0.410 mmol) of **1a** in diglyme (5 cm^3) at 0 °C. After being stirred for 3 h, aqueous sodium hydroxide (3 mol dm^{-3}, 10 cm^3) and 30% aqueous hydrogen peroxide (8 cm^3) was added and the mixture was stirred overnight at room temperature. The mixture was treated with ice-water and extracted with 40 cm^3 of eter twice. The ether layer was washed with brine and dried over magnesium sulfate. Separation with preparative TLC gave 59 mg of **2a** and 22 mg of **3a** in overall yield of 80% (**2a**:**3a**=73:27). The yields and ratios of anti- and syn-alcohols were as follows; 78% (**2b**:**2b**=69:31) with 7% recovery of **1b**, 95% (37:63) for **1c**, 81% (40:60)for **1d**, 86% (27:73) for **1e**.

NMR Shift Reagent Study. The alcohols (**2a—e**, **3a—e**) were each dissolved in $CDCl_3$ (25—30 mg/ ca. 0.3 cm^3) in a NMR tube. The shift reagent, Eu(fod)$_3$, was weighed out and added into the solution four times in about 5 mg portions, and the ^1H NMR spectrum was measured each

time. The plots of the observed relative shift of each proton vs. the amount of added $Eu(fod)_3$ gave good straight lines. From the slope of each proton, the relative shift value was calculated.

References

1) Gurudate and J. B. Stothers, *Can. J. Chem.*, **47**, 3601 (1969); J. B. Stothers, J. R. Swenson, and C. T. Tan, *ibid.*, **53**, 581 (1975).

2) G. Hentrich, E. Gunkel, and M. Klessinger, *J. Mol. Struct.*, **21**, 231 (1974).

3) P.-A. Carrupt and P. Vogel, *Tetrahedron Lett.*, **22**, 4721 (1981).

4) H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

5) R. R. Fraser and S. O'Farrell, *Tetrahedron Lett.*, **1962**, 1143.

6) R. L. Snowden and K. H. Schulte-Elte, *Helv. Chim. Acta*, **64**, 2193 (1981).

7) A. P. Kozikowski and R. J. Schmiesing, *J. Org. Chem.*, **48**, 1000 (1983).

8) K. Okada, S. Tomita, and M. Oda, *Bull. Chem. Soc. Jpn.*, **62**, 459 (1989).

9) G. H. Heinsohn and E. C. Ashby, *J. Org. Chem.*, **38**, 4232 (1973); E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **97**, 3158 (1975); E. C. Ashby and J. R. Boone, *ibid.*, **98**, 5524 (1976); E. C. Ashby and J. R. Boone, *J. Org. Chem.*, **41**, 2890 (1976); E. C. Ashby and S. A. Noding, *ibid.*, **44**, 4371 (1979); J. Klein and E. Dunkelblum, *Tetrahedron*, **23**, 205 (1967); D. C. Wigfield and F. W. Gowland, *J. Org. Chem.*, **45**, 653 (1980).

10) A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981).

11) E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Am. Chem. Soc.*, **102**, 7779 (1980).

12) D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979) and references cited therein.

13) M. R. Giddings and J. Hudec, *Can. J. Chem.*, **59**, 459 (1981).

14) C. K. Cheung, L. T. Tseng, M.-H. Lin, S. Srivastava, and W. J. le Noble, *J. Am. Chem. Soc.*, **108**, 1598 (1986).

15) H. C. Brown and A. W. Moerikofer, *J. Am. Chem. Soc.*, **84**, 1478 (1962).

16) P. C. Buxton, N. J. Hales, B. Hankinson, H. Heaney, S. V. Ley, and R. P. Sharma, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2681; N. J. Hales, H. Heaney, and S. V. Ley, *ibid.*, **1974**, 2702; K. Kitahonoki and Y. Takano, *Tetrahedron Lett.*, **1963**, 1597; G. A. Russell, G. W. Holland, and K.-Y. Chang, *J. Am. Chem. Soc.*, **89**, 6629 (1967).