Asymmetric Synthesis of (+)- or (−)-2-Methyloctanal via the Metalloenamines of Chiral Alkoxy Amines

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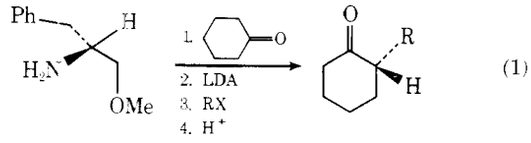
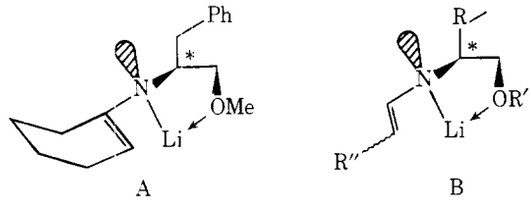
An asymmetric synthesis of the title aldehyde (**1**) was investigated using chiral amines derived from (*S*)- or (*R*)-phenylalanine, (*S*)-leucine, (*S*)-valine, and (*R*)-phenylglycine (**2**). These amino acids were transformed into their chiral amino alcohols (**3**) via reduction and then alkylated with various alkyl, alkoxyalkyl, and dimethylaminoalkyl halides. The alkoxy amines (**4**) were treated with propionaldehyde or octanal to afford the chiral aldimines **5** and **6**, respectively. Metalation of these aldimines followed by alkylation with *n*-hexyl iodide or methyl iodide gave, after hydrolysis, either optical antipode of 2-methyloctanal in enantiomeric excess as high as 58%. A study was made of the various parameters affecting this process, which included changing alkoxy (R′) and substituent R in the amino component **4**.

In recent years the desire for efficient asymmetric syntheses has resulted in a number of investigations which have lent some credence to the notion that modern synthetic methodology may have reached the level of sophistication to properly meet this challenge. A number of excellent reviews on this subject have appeared since 1971 and the progress toward efficient asymmetric synthesis becomes more evident as the reader proceeds from the reviews of Morrison and Mosher (1971),[3] to Scott and Valentine (1974),[4] to Kagan and Fiaud (1977).[5]

In 1976, this laboratory reported an asymmetric synthesis of 2-alkylcyclohexanones[6] using a chiral amine (eq 1), furnishing the products in 82–100% ee. The key feature in this process, which was deemed responsible for the high degree of asymmetric induction, was a suitably situated methoxy group which imparted rigidity to the chiral lithiated enamine (A).



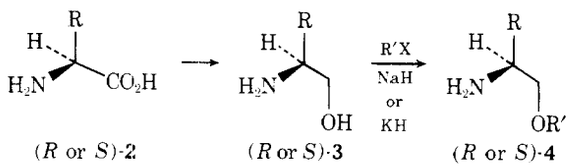
(1)



R″ = Me or *n*-Hex

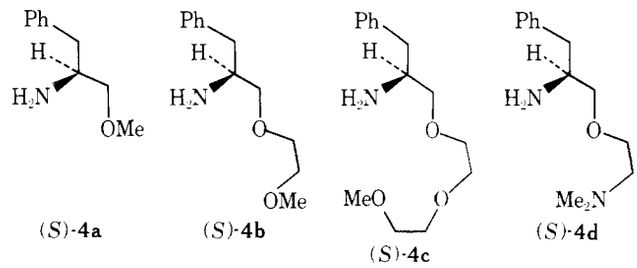
Additional studies by other laboratories[7,8] have since been reported and support the necessity of the alkoxyl group in metalloenamines during the crucial alkylating step.

We now describe the results of a study designed to extend this concept to the alkylation of aldehydes via the chiral lithio enamines B. A detailed study was carried out varying R, R′, base, and solvent and this system proved to be more complex and less efficient for arriving at a chiral aldehyde, e.g., 2-methyloctanal (**1**). The chiral amines **4** were all prepared (Experimental Section) from (*S*)- or (*R*)-acids **2** using hydride

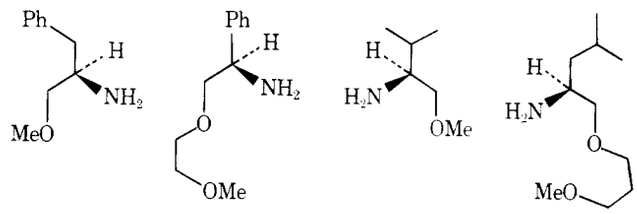


(*R* or *S*)-**2** (*R* or *S*)-**3** (*R* or *S*)-**4**

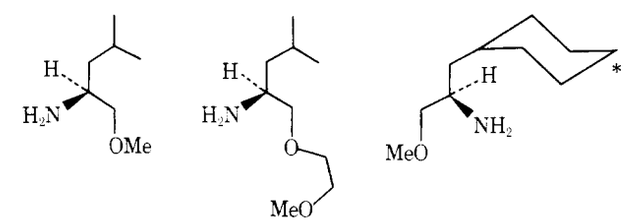
reagents, followed by alkylation of **3** with various alkyl halides. In all cases, the reduction of **2** to **3** proceeded with little or no racemization, as indicated by ^{19}F NMR data of diasteriomeric amides (Mosher amides)[9] and comparison with literature $[\alpha]_D$ values.[10] In order to assess the role of the alkyl and alkoxyl groups in **4** the series **4a–k** were prepared and subjected to the synthesis of the known (*R*)- or (*S*)-2-methyloctanal (**1**) via the aldimines **5** and **6**.



(*S*)-**4a** (*S*)-**4b** (*S*)-**4c** (*S*)-**4d**



(*R*)-**4e** (*R*)-**4f** (*S*)-**4g** (*S*)-**4h**



(*S*)-**4i** (*S*)-**4j** (*R*)-**4k**

The aldimines **5** and **6** were all prepared by treating equimolar quantities of amine and aldehyde in benzene with sodium sulfate. The sensitive aldimines were isolated in 95–100% yield and, although unstable as neat liquids, could be stored as 0.4 M solutions in THF at −30 °C. The purity of the aldimines were 95 ± 5% as determined by NMR and aliquots of their THF solutions were utilized in this study. Physical data for these aldimines are given in the Experimental Section. The aldimines were assumed to be in the *E* configuration based upon the report by Hine[11] and ^{13}C NMR studies which showed only a single resonance for the amino carbon (160–167 ppm). A mixture of (*E*,*Z*)-aldimines would be expected to exhibit different chemical shifts.

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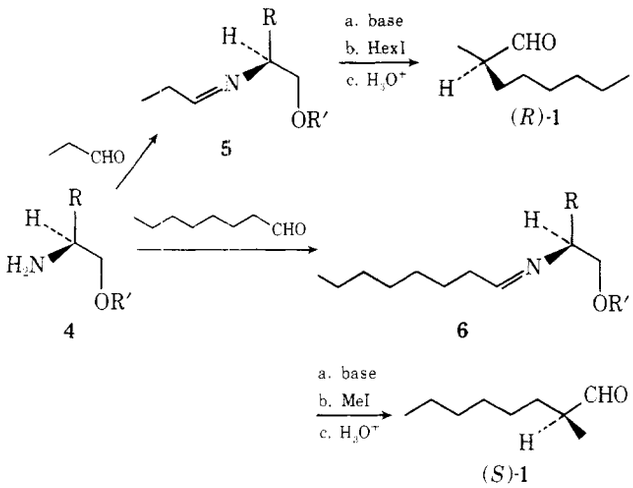
Table I. Asymmetric Synthesis of (*R*)- and (*S*)-2-Methyloctanal

		A. From Propylaldimine[a]				B. From *n*-Octylaldimine[a]			
Entry	Configuration of R	% yield[b]	$[\alpha]_D$[c] (neat)	%ee	Configuration	% yield[b]	$[\alpha]_D$[c] (neat)	%ee	Configuration
1	(*S*)-*i*-Pr (**5g**)	76	−7.73	26	*R*	67	+6.40	21	*S*
2	(*S*)-*i*-Bu (**5i**)	62	−8.64	29	*R*	72	+10.11	34	*S*
3	(*R*)-$C_6H_{11}CH_2$ (**5k**)	34	+5.06	17	*S*	62	−7.39	25	*R*
4	(*R*)-Phenyl (**5e**)	67	+11.0	37	*S*	59	−7.95	33	*R*
5	(*S*)-Benzyl (**5a**)	36	−12.55	42[d,e]	*R*	46	+14.05	47[d,e]	*S*

[a] All metalations performed at −23 °C in THF and all alkylations performed at −78 °C. [b] Distilled yields of pure aldehyde except for entry 5; see footnote *e*. [c] Based on $[\alpha]^{25}_D$ +29.9° (neat, *l* = 1) for pure (*S*)-(+)-2-methyloctanal. [d] Botteghi and C. Salamon, *Tetrahedron Lett.*, 4287 (1974). [d] Oxidized to 2-methyloctanoic acid to confirm %ee. [e] Extrapolated from ~70:30 mixture containing either *n*-hexyl iodide or octanal, see Experimental Section.

Metalation of chiral methoxyaldimines **5** and **6** with lithium diisopropylamide (LDA), followed by alkylation with *n*-hexyl



iodide or methyl iodide, respectively, gave, after hydrolysis (sodium acetate–acetic acid), (*R*)- or (*S*)-2-methyloctanal (**1**) in enantiomeric excess (ee) ranging from 17 to 47% (Table I).

The chemical yields of distilled products ranged from 34 to 76% based upon the starting aldimines. Thus, varying the nature of the R substituent in **4** from isoalkyl to benzyl to phenyl has a relatively small effect upon the %ee of the 2-methyloctanal.

It is of interest to note from Table I that the propyl aldimines derived from (*S*)-methoxyamines gave the aldehyde enriched in the *R* enantiomer, while those derived from the (*R*)-methoxyamine gave the aldehyde enriched in the *S* enantiomer. Furthermore, reversing the order of alkylating agent and aldimine gave the reverse enantiomers. Although the highest degree of asymmetric induction was observed for the benzylaldimines (entry 5, Table I), this was also accompanied by the lowest chemical yield due to 20–25% incomplete metalation. A variety of experiments (excess base, longer metalation time, variable temperatures of metalation) failed to increase the efficiency of metalation.

The moderate level of asymmetric synthesis for 2-methyloctanal may be due to several factors, the most important of which is the *E*/*Z* ratio of metalloenamines **7** and **8**. By considering the geometry of the *E*,*Z* isomers, it is possible to conceive of two conformers for each (**7A, 7B** and **8A, 8B**). The additional conformers, in which the alkenyl and R groups are

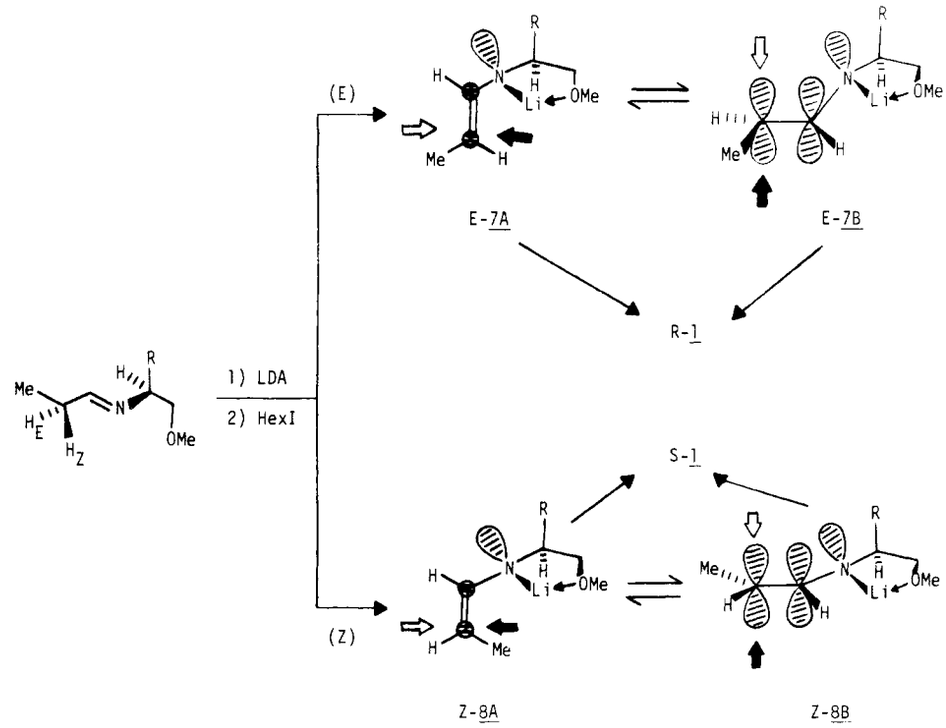
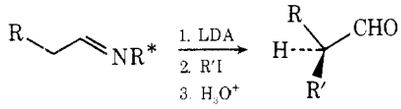


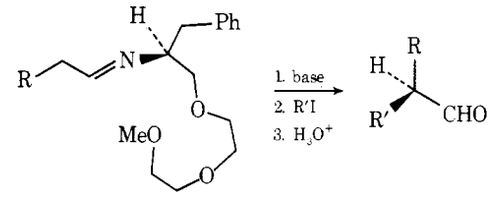
Table II. Alkoxy Effects in Chiral Aldimines[a]



Alkoxy-amines	Aldi-mine R	R'I	% yield[b]	$[\alpha]_D$[c]	%ee	Configu-ration
(*S*)-**4j**	Me	*n*-Hex	74	−12.6	42	R
(*S*)-**4j**	Hex	Me	73	+11.2	37	S
(*S*)-**4h**	Me	*n*-Hex	53	−6.12	20	R
(*R*)-**4f**	Me	*n*-Hex	70	+15.5	52	S
(*R*)-**4f**	*n*-Hex	Me	57	−10.3	31	R
(*S*)-**4b**	Me	*n*-Hex	70	−11.4[d,i]	39	R
(*S*)-**4c**	*n*-Hex	Me	48	+14.5[e,i]	48	S
(*S*)-**4c**	Me	*n*-Hex	60	−15.2[f,i]	51	R
(*S*)-**4d**	*n*-Hex	Me[h]	75	+16.3[g,i]	54	S

[a] All metalations performed at −23 °C in THF and all alkylations performed at −78 °C. [b] Distilled yields. [c] Rotations are as neat liquids unless stated otherwise. [d] *c* 8.6; $CHCl_3$. [e] *c* 8.8; $CHCl_3$. [f] *c* 11.4; $CHCl_3$. [g] *c* 9.1; $CHCl_3$. [h] Lithium 2,2,6,6-tetramethylpiperidide used as the base. [i] Extrapolated from mixtures (~75:25) of aldehyde and *n*-hexyl iodide or octanal (see Experimental Section).

Table III. Effect of Base on Asymmetric Synthesis of 2-Methyloctanal

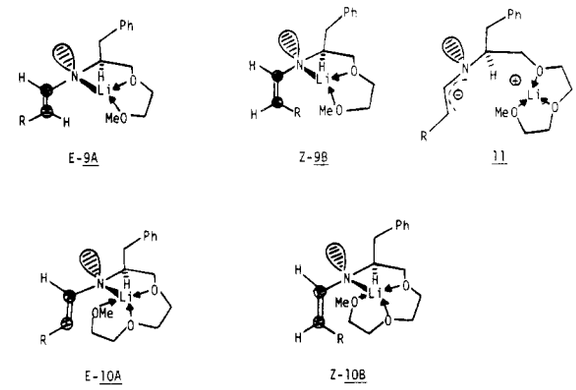


R	R'I	Base[a]	% yield[c]	$[\alpha]^{25}_D$ (*c*, $CHCl_3$)[d]	% ee (configu-ration)
Me	*n*-Hex	$KNEt_2$	13	−1.15 (12.7)	3.8 (*R*)
Me	*n*-Hex	$LiN(i\text{-}Pr)_2$	70	−11.4 (8.6)	39 (*R*)
n-Hex	Me	$(Me_3)_2SiN$-Li	9	+11.5 (3.4)	39 (*S*)
n-Hex	Me	LiTMP[b]	70	+17.3 (6.8)	58 (*S*)

[a] Metalations performed in THF at −23 °C (2–4 h) and alkyl iodide added at −78 °C (2–4 h). [b] LiTMP = lithium 2,2,6,6-tetramethylpiperidide. [c] All reagents added in equivalent amounts. [d] Extrapolated from mixtures (~75:25) of aldehydes and *n*-hexyl iodide or octanal (see Experimental Section).

cis (by inversion through the nitrogen lone pair), would exhibit severe 1,2-nonbonded interactions and are omitted from this argument. The black and white arrows for **7A** and **8A** indicate the possible approaches (above and below plane of paper, respectively) of hexyl iodide to the metalloenamines. For the *E* isomer (**7A, 7B**) approach via the black arrows would lead to the (*R*)-aldehyde which is observed in enantiomeric excess in all cases where the aldimine possesses the *S* configuration. Conformation **7A** would lead to the transition state where the N–Li orbital is parallel to the π orbital of the alkene, whereas **7B** is leading to the transition state involving developing overlap of the nonbonded pair on nitrogen with the π orbitals.[7] Which of these two alignments are in play is not known at this time. Entry of the alkyl halide from the opposite side (white arrows) is seemingly less attractive (space filling CPK models), but if it does occur, it would give the opposite antipode of 2-methyloctanal. Consideration of the *Z* isomers (**8A, 8B**), in two similar conformations leading to the transition state, would require approach of the hexyl iodide from the direction indicated by the black arrows and would lead to the (*S*)-aldehyde. The approach from the directions of the white arrow (again, less accessible) would furnish the enantiomeric aldehyde. If it is assumed that the metalation of **5** gives a mixture of *E* and *Z* metalloenamines[12] **7A** and **8A**, respectively, with *E* isomer predominating, then entry of the alkyl halide would follow the course depicted by the black arrows (more accessible entry route) and the %ee of the aldehyde would merely reflect the *E*/*Z* ratio of **7A** to **8A**. However, it would be expected to find different *E*/*Z* ratios of **7** and **8** with increasing size of the alkyl group on the alkene moiety and this simply was not the case as seen from addition of methyl iodide to the octenylaldimine **6**. Thus, there must be some approach of the alkyl halide from the side indicated by the white arrows. It is important to note that the %ee of the aldehyde generally increased when the substituent R on **7** or **8** was larger, supporting the assumption that topside (or inside) attack on **7** (**A, B**) and **8** (**A, B**) (white arrows) was becoming increasingly difficult.

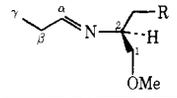
To gain further insight into those critical factors responsible for a high level of asymmetric induction, the nature of the alkoxy group was varied. Thus, aldimines derived from alkoxy amines **4** (**b, c, d, f, h,** and **j**) were prepared and subjected to the metalation–alkylation sequence leading to (*R*)- or (*S*)-2-methyloctanal. The results are summarized in Table II. The %ee of the product using polyoxy or aminooxy ligands was generally increased over the methoxyamines (**4a, 4e, 4g, 4i**), but only to the extent of 10–20%. This increase in asymmetric induction may be attributed to the increase in the *E* metalloenamine **9A** over the *Z* isomer (**9B**) or the *E* isomer **10A** over (*Z*)-**10B**. Models indicate that there is considerably more crowding in **9B** and **10B** due to the presence of a second or third ligand in the lithioenamine. However, the effect of these additional ligands was disappointingly small and it is also possible that the ligands are functioning as a "crown" which weakens the N–Li band resulting in a delocalized azaallyl anion **11**. This would cause a loss in rigidity and open up the lithio enamine to alkylation from several modes of approach. All that may be said of the results to data is that increasing the number of ligands to the lithium may result in the creation of opposing effects: (1) increasing *E*/*Z* ratio of **9** and **10**, which



is a favorable effect; and (2) furnishing a less rigid delocalized species **11**, which would be unfavorable. It is, nevertheless, important to state that the configuration of 2-methyloctanal obtained in ~50% ee is that derived from frontside (perpendicular to the page) entry of the alkyl halide to (*E*)-**9A** or (*E*)-**10A** (or its conformer analogous to **7B** and **8B**).

Finally, a study to determine whether the size or nature of the base was critical to this process was undertaken. If the *E*/*Z* ratio of the lithioenamine was determined by removal of the *pro-R* or *pro-S* proton in **12**, then the *E*/*Z* ratio for **13** would be kinetically controlled. No evidence in support of equlibrating lithioenamines **13** has been found, since the %ee of the

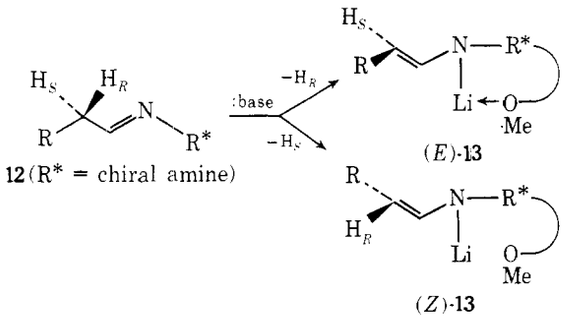
Table IV. ^{13}C NMR Chemical Shifts of Aldimines[a]



R	Carbon							
	α	β	γ	1	2	3	OMe	Other
Phenyl	166.9	28.9	10.3	76.1	72.0	39.2	59.0	ipso 139.0 ortho 129.9 meta 128.2 para 126.2
Isopropyl	166.0	29.1	10.5	76.9	68.3	41.4	58.9	H–C 24.3 $(CH_3)_2$ 23.7; 21.5
	160.3	32.5	10.7					56.5, 29.7

[a] All chemical shifts reported in parts per million relative to internal Me_4Si. Spectra were obtained on samples 1–3 M in $CDCl_3$ with 5% added Me_4Si. Assignments were confirmed by coupled spectra.

2-methyloctanal was unchanged by varing the temperature (−78 to 0 °C) or aging **13** (2–24 h) prior to the alkylation step.



The results of deprotonation using various bases are presented in Table III. The addition of alkyl- or aryllithium reagents such as *n*-BuLi, *sec*-BuLi, *t*-BuLi, and PhLi to the C=N bond precluded their use in this study. Therefore, only bulky nonnucleophilic bases could be employed. The highest %ee achieved in this study was derived from the use of the lithium 2,2,6,6-tetramethylpiperidide (LiTMP), which also produced the chiral aldehyde in 70% chemical yield. The use of potassium diethylamide gave the lowest enantiomeric purity of the aldehyde as well as a poor chemical yield. The low %ee observed for the aldehyde may be attributed to the poor chelating ability of potassium ion in the metalloenamine **10**. With respect to solvent effects in this reaction, THF was consistently the superior medium, while ether, dimethoxyethane, and hexane–ether and hexane–THF solvents gave poor chemical yield (12–30%) and poor enantiomeric purity of aldehyde (12–30%). Addition of DMF or HMPA to reaction mixtures did little to affect the asymmetric induction, presumably because of the strong intramolecular chelation of the alkoxy groups on the chiral amine. This lack of effect using HMPA was also observed by Enders using chiral methoxy derivatives of (*S*)-proline.[8]

In summary, an asymmetric synthesis of 2-methyloctanal was achieved in 58% ee (Table III). The factors controlling this process have been examined and complete understanding of the reaction is still incomplete. Undoubtedly, direct observation of the lithioenamines by NMR techniques would be desirable as well as a more accurate description of the transition state involved. These are the goals now being pursued as well as the synthesis of different chiral aldehydes and ketones.

Experimental Section[13]

(*S*)-(−)-Phenylalininol (3, R = $PhCH_2$) was prepared according to the method of Yamada:[14] mp 88–90 °C, $[\alpha]^{25}_D$ −25.4° (*c* 1.22, EtOH). Alternatively, **3** (R = $PhCH_2$) was prepared by the procedure of Brown[15] (B_2H_6) and that of Lane[16] and all three methods gave similar results. The latter method,[16] in our hands, proved to be the most convenient.

The enantiomeric purity was confirmed as >95% by preparing the Mosher amides as follows: A solution of 0.5 mmol of (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride ($[\alpha]^{24}_D$ −127° (5.41, CCl_4))[9] was added with stirring to an ice-cold solution of 0.5 mmol of (−)-phenylalininol containing 1.0 mmol of triethylamine. After several minutes, a solid appeared and the mixture was allowed to warm to ambient temperature and stirred overnight. After filtration to remove the solid, the filtrate was concentrated in vacuo to furnish the theoretical amount of amide as colorless solid: NMR ($CDCl_3$) δ 7.63–6.97 (m, 12), 4.55 (m, 1, NH), 3.91–2.99 (m, 6), 2.99 (d, 2). The ^{19}F NMR spectrum at 56.5 MHz using trifluoroacetic acid as an external standard showed only a single ^{19}F peak at 278 Hz.[17]

(*S*)-(+)-Valinol (3, R = *i*-Pr) was purchased from Aldrich, $[\alpha]^{25}_D$ 18.5° (*c* 7.83, EtOH); however, the literature value[18] is $[\alpha]^{25}_D$ +15.6° (EtOH). The Mosher amide prepared as above showed on ^{19}F NMR analysis a single peak at 280 Hz, indicating that the compound is at least >95% enantiomerically pure and that the rotational data is sensitive to some trace impurities.[10]

(*S*)-(+)-Leucinol (3, R = *i*-Bu) was purchased from Aldrich and had $[\alpha]^{25}_D$ +4.89° (neat). Leucinol was also prepared by the three methods described earlier[14–16] and gave widely varying $[\alpha]_D$ values between 1.2 and 4.9° (neat); $[\alpha]_D$ reported[19] was 1.57° (neat). The Mosher amides for (*S*)-(+)-leucinol have been prepared and all methods of its formation[14–16] gave material of >95% ee by ^{19}F NMR measurements.[10] To prepare (*S*)-(+)-leucinol of constant rotation from all three reduction methods, the hydrochloride salts were prepared. A solution of 100 mL of absolute ethanol containing 2.36 g of (*S*)-(+)-leucinol [Aldrich $[\alpha]^{25}_D$ +4.84° (neat, *l* = 1.0)] was treated with dry hydrogen chloride. The solvent was evaporated and the residue was recrystallized (ether–ethanol) twice to give a colorless solid: mp 124–126 °C (sealed capillary) with a crystal change at 95–98 °C; $[\alpha]^{20}_D$ +11.4°, $[\alpha]^{20}_{365}$ +31.8 (*c* 4.3, ethanol). The hydrochloride was neutralized in 3 N sodium hydroxide, extracted with ether, dried (Na_2SO_4), and distilled, bp 95 °C (9 mm), to a colorless oil: $[\alpha]^{20}_D$ +1.21° (neat, *l* = 1).

(*R*)-(−)-Phenylglycinol (3, R = Ph) was purchased from Aldrich: mp 75–78 °C; $[\alpha]^{20}_D$ −27.1° (*c* 5.36, MeOH): (lit.[20] $[\alpha]^{20}_D$ −25.8° (*c* 6.60, MeOH). The Mosher amide was prepared as above and ^{19}F NMR (acetone-d_6) showed a single peak at 680 Hz (trifluoroacetic acid used as external standard at 94.1 MHz).

(*S*)-(−)-2-Amino-1-methoxy-3-phenylpropane (4a). A solution of 18.4 g (0.122 mol) of (*S*)-(−)-phenylalininol in 250 mL of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of 5.23 g (0.130 mol) of potassium hydride (pentane washed) in 100 mL of tetrahydrofuran at 25 °C under nitrogen. The resulting pale yellow gelatinous mixture was allowed to stand overnight and then a solution of 17.0 g (0.119 mol) of methyl iodide in 150 mL of THF was added dropwise over 2 h. Mixing was accomplished by external shaking, since the gelatinous mixture would not stir with magnetic stirring bars. The reaction components were allowed to mix an additional 3 h and then poured into 1 L of cold saturated brine, extracted with ether (3×), dried with Na_2SO_4, and concentrated to give 24.9 g of crude product. Distillation gave 17.1 g, bp 55–59 °C (0.1 mm), of a clear oil which on standing became cloudy and rapidly produced a white precipitate

which was found to be the carbonate. It was subsequently found that conversion of the freshly distilled methoxyamine to its hydrochloride salt was a more convenient way to store the compound. Thus the methoxyamine (17.0 g), immediately after distillation, was dissolved in 700 mL of absolute ethanol and dry HCl bubbled in for 10 min. The resulting solution was concentrated, in vacuo, to furnish 20.5 g of a colorless solid which was recrystallized from ethanol–ether (13:1): mp 151–152 °C; $[\alpha]^{25}_{578}$ +19.7° (c 2.5, EtOH), $[\alpha]^{25}_{407}$ +41.8°; IR (KBr) 3600–2300, 1265, 1203, 1125, 1071, 1052, 953, 790, 698 cm^{-1}; NMR (D_2O) δ 7.37 (br s, 5), 3.59 (m, 1), 3.54 (s, 2), 3,34 (s, 3), 2.90 (d, 2).

Anal. Calcd for $C_{10}H_{16}NOCl$: C, 59.55; H, 8.00. Found: C, 59.73; H, 7.98.

To release the free methoxyamine, it was dissolved in 5% potassium carbonate solution and extracted with ether, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation at 52 °C (0.1 mm) gave **4a** as a clear oil: $[\alpha]^{23}_{478}$ −14.7° (c 6, benzene), $[\alpha]^{23}_{407}$ −46.2; IR (neat) 3439, 3012, 1355, 1192, 1119, 1110, 913, 743, 699 cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 5), 3.35 (br s, 6), 2.68 (m, 2), 1.75 (br s, 2). The latter signal disappeared on shaking with D_2O. Analysis of the free methoxyamine was not performed due to its facile reaction with atmospheric carbon dioxide.

(*S*)-(−)-2-Amino-1-(2-methoxyethoxy)-3-phenylpropane (4b). A solution of 3.0 g (20 mmol) of (*S*)-(−)-phenylalininol in 7 mL of dry THF and 1.5 mL of acetonitrile was added to 0.6 g of NaH (hexane washed) and the mixture was heated to reflux for 6 h. The mixture was then treated with 2.8 g (30 mmol) of 1-chloro-2-methoxyethane[21] and heated at reflux for 120 h. After cooling, 50 mL of ether was added and then treated with 50 mL of water. The aqueous layer was extracted (2×) with 50 mL of ether and all the ethereal solutions were combined. The ether solution was washed (2×) with 50 mL of brine, dried (K_2CO_3), and concentrated. The residue was distilled to give 2.6 g (64%) of a colorless oil: bp 92–94 °C (0.03 mm); $[\alpha]^{25}_{D}$ −9.4°, $[\alpha]^{25}_{365}$ −29.90° (c 11.8, benzene); NMR ($CDCl_3$) δ 7.20 (m, 5), 3.73–2.00 (m, 9), 3.33 (s, 3), 1.80 (br s, 2); IR (neat) 3370, 3300, 1600, 1195, 1110, 1025 cm^{-1}. The product was >99% pure by VPC (UCW-98, 200 °C). This procedure also gave **4b** on 20-g scale.

Anal. Calcd for $C_{12}H_{19}O_2N$: C, 68.87; H, 9.15. Found: C, 68.98; H, 8.78.

(*S*)-(−)-2-Amino-1-(2-methoxyethoxyethoxy)-3-phenylpropane (4c) was prepared in an identical procedure as that described for **4b:** yield 13.2 g (62%); bp 142–145 °C (0.05 mm); $[\alpha]^{25}_{D}$ −3.5°, $[\alpha]^{25}_{365}$ −14.9° (c 10.7, benzene); IR (neat) 3370, 3300, 1195, 1110 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (m, 5), 3.66–2.13 (m, 13), 3.30 (s, 3), 1.53 (br s, 2). The product was >98.5% pure by VPC (UCW-98, 250 °C).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 65.94; H, 8.55.

(*S*)-(−)-2-Amino-1-(2-dimethylaminoethoxy)-3-phenylpropane (4d) was prepared by Mr. Donald R. Williams of this group and kindly provided for this study: bp 98–104 °C (0.05 mm); $[\alpha]^{25}_{D}$ −3.17° (c 2.33, benzene). Details of this preparation will be reported in the future.

(*R*)-(−)-1-Amino-1-phenyl-2-methoxyethane (4e)[22] was prepared according to the procedure for **4a** using potassium hydride–methyl iodide on a 10.0-g scale from (*R*)-(−)-phenylglycinol (Aldrich): yield 6.8 g (62%) of a clear oil; bp 47–50 °C (0.02 mm); $[\alpha]^{23}_{D}$ −51.4° (c 7.08, benzene), $[\alpha]_{365}$ −136°. As in the case of **4a**, the compound became cloudy after 1 h due to reaction with atmospheric carbon dioxide. It was characterized through its hydrochloride salt: mp 150–151 °C (ethyl acetate); $[\alpha]^{23}_{D}$ −28.7° (c 2.5, EtOH); IR (KBr) 3200–2400, 1590, 1500, 1450, 1385, 1200, 1090, 1030, 960, 915, 760, 700 cm^{-1}; NMR (D_2O, external Me_4Si) δ 7.45 (s, 5), 3.65 (s, 3), 4.60 (t, 1), 3.80 (d, 2), 3.40 (s, 3).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.50. Found: C, 57.52; H, 7.35.

(*R*)-(−)-1-Amino-1-phenyl-2-(2-methoxyethoxy)ethane (4f). A solution of 20 g of (*R*)-(−)-phenylglycinol (Aldrich) in 50 mL of dry THF and 11.0 mL of acetonitrile was added to 4.40 g of sodium hydride (hexane washed) and stirred at 25 °C for 1 h, then heated to reflux for 1 h. A solution of 34.2 g of 2-chloroethyl methyl ether in 25 mL of THF was added and the mixture heated for 70 h with occasional external shaking. The mixture was poured into 100 mL of water and extracted (3×) with 100-mL portions of dichloromethane. The organic extracts were washed three times with 50-mL portions of brine, dried (K_2CO_3), concentrated, and distilled to give 19.2 g (67%) of a colorless oil: bp 83–85 °C (0.05 mm); $[\alpha]^{25}_{D}$ −42.0°, $[\alpha]^{25}_{365}$ −116.3° (c 10.1, benzene); IR (neat) 3380, 3350, 1610, 1360, 1200, 1100, 860, 760, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (m, 5), 4.22 (d of d, 1, J = 3.7 and 8.5 Hz), 3.58 (m, 6), 3.35 (s, 3), 1.89 (br s, 2).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.43; H, 8.58.

(*S*)-(+)-1-Methoxy-2-amino-3-methylbutane (4g) was prepared as described previously for **4a** using 3.7 g of sodium hydride, 15.0 g of L-valinol (Aldrich), and 20.6 g of methyl iodide in THF. The crude product (12.8 g) was distilled, bp 57 °C (34 mm), affording 9.3 g of **4g** as a clear liquid containing a small amount of *N*-methyl by-product (NMR and VPC). Further purification was accomplished via the hydrochloride prepared by passing dry HCl into **4g** in absolute ethanol. Crystallization gave 12 g of a yellow solid which was recrystallized (ethanol–ether) furnishing 8.7 g (51%) of a colorless solid: mp 166–167 °C; $[\alpha]^{25}_{D}$ +11.8°, $[\alpha]^{25}_{407}$ +26.7 (c 2.7, EtOH); IR (KBr) 3500–2500, 1585, 1468, 1395, 1380, 1203, 1105, 948 cm^{-1}; NMR (D_2O) δ 4.71 (br s, 3), 3.68 (m, 3), 3.43 (s, 3), 2.01 (m, 1), 1.03 and 0.99 (d, 6, J = 8.4 Hz).

Anal. Calcd for $C_6H_{16}NOCl$: C, 46.91; H, 10.49. Found: C, 47.00; H, 10.29.

The free amine **4g** was liberated with 10% sodium hydroxide solution followed by extraction with ether. Distillation gave 5.21 g (31% from L-valinol) as a clear liquid: bp 56 °C (31 mm); $[\alpha]^{25}_{D}$ +23.7°, $[\alpha]^{25}_{407}$ +50.0 (c 6.2, benzene). Analysis was not performed on free methoxyamine due to its facile reaction with atmospheric carbon dioxide.

(*S*)-(−)-1-Methoxy-2-amino-4-methylpentane (4i) was prepared from (*S*)-leucinol using NaH–methyl iodide in THF as described for **4a.** The hydrochloride was obtained in 35% yield as hygroscopic colorless crystals: mp 135–137 °C (chloroform–ether); $[\alpha]^{25}_{D}$ +15.3°, $[\alpha]^{25}_{407}$ +33.8° (c 4.0, EtOH).

Anal. Calcd for $C_7H_{18}NOCl$: C, 50.12; H, 10.84. Found: C, 50.08; H, 11.02.

The free amine **4i** was obtained by treatment of the hydrochloride with 10% potassium carbonate solution and ether extraction. The ethereal residue was distilled to furnish **4i** as a clear liquid: bp 72–73 °C (35 mm); $[\alpha]^{25}_{D}$ −3.35°, $[\alpha]^{25}_{407}$ −6.33 (c 6.7, benzene); IR (neat) 3360, 2945, 1585, 1469, 1385, 1365, 1199, 1167, 1112, 979, 875, 834 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 3), 3.05 (m, 3), 1.71 (m, 1), 1.44 (br s, 2), 1.18 (t, 2), 0.91 and 0.89 (d, 6); the peak at δ 1.44 disappeared on addition of D_2O.

Anal. Calcd for $C_7H_{17}NO$: C, 64.05; H, 13.08. Found: C, 63.85; H, 13.12.

(*S*)-(+)-1-(3-Methoxypropoxy)-2-amino-4-methylpentane (4h). A mixture of 15.0 g of (*S*)-(+)-leucinol and 20.0 g of phthalic anhydride was heated for 1 h at 140 °C and cooled before adding 200 mL of ether. The ether solution was washed successively with 10% potassium carbonate, water, 10% hydrochloric acid, water, and saturated salt solution. After drying (Na_2SO_4) and concentration, the crude phthalimide (27.8 g) was obtained (88%) as a viscous oil. Without further purification, a solution of 86 mmol of the phthalimide in 75 mL of THF was added to 104 mmol of sodium hydride and allowed to stir overnight. Allyl bromide (124 mmol) in 25 mL of THF was added and after 2 h, 200 mL of ether was added followed by 200 mL of water. The layers were separated and the organic phase was washed (brine) and dried (Na_2SO_4) to afford 20.6 g (83%) of the crude allyl ether. Without further purification, the allyl ether (20.0 g, 70 mmol) was dissolved in 80 mL of glyme and treated dropwise with 24 mL (24 mmol) of borane–THF (1 M solution) at room temperature. After stirring for 1 h, 8.5 mL of 3 N sodium hydroxide was carefully added followed by 8.5 mL of 30% hydrogen peroxide and the temperature kept below 40 °C by an external bath. Ether (100 mL) was added after 1 h and the layers separated. The aqueous layer was extracted with ether and the combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated to give 18.0 g (82%) of the alcohol. The crude product, as in the previous step, showed NMR and IR data consistent with structure. The crude phthalimido alcohol (59 mmol) was dissolved in 25 mL of THF and treated with 73 mmol of NaH and stirred for 15 h. A solution of 90 mmol of methyl iodide in 15 mL of THF was added and stirred for 24 h at room temperature. The usual workup (water, ether extraction, brine wash, drying concentration) gave 14.6 g (78%) of the methoxy ether, which was treated directly with 1.6 g of hydrazine in 75 mL of ethanol and heated to reflux for 2 h. The solid mass was removed by filtration and washed twice with cold ethanol. After concentration of the ethanol solutions, the residue was taken up in ether, filtered to remove solid material, and concentrated again to leave an oil, which was distilled, bp 77–82 °C (0.5 mm), to give 3.10 g of clear, colorless oil: $[\alpha]^{25}_{D}$ +1.96°, $[\alpha]^{25}_{365}$ +8.24° (c 5.93, benzene); IR (neat) 3370, 2925, 1470, 1388, 1360, 1193, 1109, 835 cm^{-1}; NMR ($CDCl_3$) δ 3.56 (m, 2), 3.32 (m, 6), 3.10 (d, 1), 1.82 (pentet, 2, J = 6.5 Hz), 1.25 (m, 3), 0.97 and 0.90 (d, 6, J = 6.1 Hz). VPC (UCW-98) indicated **4h** was >95% pure.

Anal. Calcd for $C_{10}H_{23}NO_2$: C, 63.43; H, 12.27. Found: C, 63.16; H, 11.99.

(*S*)-(+)-1-(2-Methoxyethoxy)-2-amino-4-methylpentane (4j).

A solution of 23.2 g (0.195 mol) of (*S*)-leucinol in 50 mL of THF and 12 mL of acetonitrile was treated with 5.6 g (0.23 mol) of NaH and stirred for 2 h at 55 °C. A solution of 19.0 g of 2-chloroethyl methyl ether (0.2 mol) in 25 mL of THF was added and the mixture heated to reflux for 90 h. After quenching in 100 mL of water and extracting with ether, the ethereal extracts were washed with brine, dried, and concentrated. The residual oil was distilled, bp 92–94 °C (10 mm), to obtain a clear colorless oil: $[\alpha]^{25}_{D}$ +4.41°, $[\alpha]^{25}_{407}$ +12.07° (*c* 5.6, benzene); IR (neat) 3300, 2950, 1589, 1466, 1384, 1200, 1090, 881 cm^{-1}; NMR ($CDCl_3$) δ 3.85–2.95 (m, 10), 2.20–1.36 (m, 4), 1.20 (t, 2, *J* = 7 Hz), 0.96 and 0.94 (d, 6).

Anal. Calcd for $C_9H_{21}NO_2$: C, 61.66; H, 12.10. Found: C, 61.94; H, 12.26.

(*R*)-(+)-1-Methoxy-2-amino-3-cyclohexylpropane (4k). A solution of (*R*)-**4a** ($[\alpha]^{25}_{578}$ −19.5°) was hydrogenated with 15% by weight of 5% $RhAl_2O_3$ in ethanol at 45 psi. Workup gave **4k:** bp 90–91 °C (2 mm); $[\alpha]^{25}_{D}$ + 5.74°, $[\alpha]^{25}_{407}$ +13.2° (*c* 5.5, benzene); IR (neat) 3360, 2890, 1580, 1443, 1363, 1187, 1101, 843, 820 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 3), 3.18 (m, 3), 1.73 (m, 6), 1.27(m, 9).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36. Found: C, 70.41; H, 12.25.

Formation of Aldimines 5 and 6. General Procedure. To a stirred solution (0 °C) of 10 mmol of the alkoxyamine dissolved in 30 mL of benzene (previously washed with concentrated sulfuric acid and distilled) was added 10 mmol of the pure aldehyde (propanal or octanal). An immediate cloudiness usually resulted on addition of the aldehyde. The mixture was allowed to warm to room temperature and ~15 g of anhydrous sodium sulfate added. After stirring the mixture an additional 30–40 min, it was filtered and the sodium sulfate washed thoroughly with dry ether. The solvent was removed by evaporation first with aspirator pressure and then with the vacuum pump (0.5 mm) to generally furnish 9.5–10 mmol of the aldimine as a colorless oil. Spectral data were immediately taken: IR (neat) 1662–1690 cm^{-1} (C=N); NMR ($CDCl_3$) δ 7.5–7.8 (t, 1, *J* = 4.9–5.1 Hz, –HC=N–). The aldimines were dissolved in THF (0.4 M) and stored at −20 to −30 °C. Attempts to store the aldimines as neat liquids resulted in deteriorations. As solutions, the aldimines were conveniently transferred via syringe to reaction vessels.

The aldimines were shown to be a single isomer by ^{13}C NMR of several representative examples (Table IV). *N-tert*-Butylpropylaldimine is included for reference.

(*R*)- or (*S*)-2-Methyloctanal (1). General Procedure. All the experiments described in Tables I–III were performed following the general procedure described below. All were conducted at approximately 0.25 M concentration (final concentration in THF only) and generally on aldimine solutions which had been stored in the freezer (−25 °C). Metalations and alkylations were monitored by withdrawing a 0.5-mL aliquot and quenching with methyl iodide and water, respectively. Determination of reaction course was made by NMR analysis. All the bases employed (Table III) were prepared in situ by addition of *n*-butyllithium or potassium hydride to an equimolar quantity of amine at 0 °C in THF. Stirring was continued for 30–60 min at 0 °C (or room temperature in the case of potassium diethylamide). Where appropriate (KH), the stoichiometric quantity of hydrogen was collected.

To a stirred solution of 11 mmol of base (−23 °C dry ice–CCl_4, under nitrogen atmosphere) in 10 mL of THF was added over 5 min 10 mmol of the aldimine (**5** or **6**) dissolved in 25 mL of THF. The resulting solution (generally yellow, but in some cases colorless) was stirred at −23 °C for 30 min and then cooled to −78 °C (dry ice–isopropyl alcohol). The halide (methyl or hexyl iodide, 10–12 mmol) dissolved in 5 mL of THF was then added and the reaction mixture stirred for 2–7 h at −78 °C and complete conversion was determined by removing aliquots. After warming to room temperature and addition of 50 mL of ether, the cloudy mixture was poured into 100 mL of water and the phases were separated. The aqueous phase was extracted with ether and the combined organic phases were washed with brine, dried (K_2CO_3 or Na_2SO_4), and concentrated. The crude alkylated aldimines were hydrolyzed by dissolving in 30 mL of pentane and shaking for 5 min in a separatory funnel with an aqueous acetic acid–sodium acetate solution (prepared from 37.5 mL of acetic acid, 37.5 mL of water, and 16.2 g of sodium acetate). The layers are separated and the aqueous acid layer is extracted once with 30 mL of fresh pentane. *Both layers are kept*, since the chiral alkoxy amine may be recovered from the aqueous phase. The combined pentane layers were washed successively with water, 10% sodium bicarbonate, and water and dried over sodium sulfate. Evaporation of the filtered pentane gave the crude aldehyde as a pale yellow liquid. Bulb-to-bulb distillation at 90 °C (4 mm) furnished a clear, colorless product which was free of impurities by VPC, NMR, and IR analysis. For the aldimine derived from alkoxyphenylalininols (**4a–d**) incomplete metalation always produced *n*-hexyl iodide or octanal from aldimines **5** and **6**, respectively. Thus, 2-methyloctanal could not be purified by distillation and VPC indicated only 70–75% product. The $[\alpha]_D$ for 2-methyloctanal (entry 5, Table I; last four entries in Table II, all entries in Table III) was therefore extrapolated from known prepared mixtures with octanal or hexyl iodide. That this extrapolation was valid was proven by starting with pure 2-methyloctanal (collected from VPC instrument), $[\alpha]^{25}_{D}$ −8.90°, and preparing (wt/wt) solutions of 12.7, 25.7, 44.6% *n*-hexyl iodide. Plotting weight percent vs. $[\alpha]_D$ gave a straight line. A similar check was made using octanal–2-methyloctanal solutions of 55.4, 74.3, 87.3% and the plot weight percent vs. $[\alpha]_D$ was again linear.

Recovery of Chiral Alkoxy Amines 4. The hydrolysis solution (NaOAc–HOAc) from above was neutralized with solid potassium hydroxide and extracted with ether (3×). The ethereal extracts were washed with brine, dried (K_2CO_3), and concentrated to yield the crude chiral amine in 80–88% yield. Distillation afforded the pure amine in 70–75% recovery and examination of the $[\alpha]_D$ values indicated, in every case, that no racemization had occurred.

(*R*)- or (*S*)-2-Methyloctanoic Acid. Further confirmation of the validity of the extrapolated rotation data in Table I (entry 5) was obtained by oxidizing 2-methyloctanal, $[\alpha]^{25}_{D}$ −12.55° and $[\alpha]^{25}_{D}$ +14.05°, with silver oxide according to the method of Shamma.[23] A solution of 1.49 g of (*R*)-(−)-2-methyloctanal (containing 30% *n*-hexyl iodide) in 40 mL of absolute ethanol was added to 5.0 g of silver nitrate in 5 mL of water. A solution of 2.8 g of KOH dissolved in 50 mL of water was added and a black precipitate formed immediately. The mixture was stirred for 1 h and filtered. The silver residue was washed with water and the combined filtrates were extracted with ether. The ether was discarded. Acidification of the filtrate (concentrated HCl) and several extractions with ether followed. The ethereal solution was washed with water, brine, and water, dried ($MgSO_4$), and concentrated. Distillation (bulb-to-bulb) of the residue gave the product: bp 95 °C (5 mm); 575 mg; $[\alpha]^{25}_{D}$ −6.94°; $[\alpha]^{25}_{407}$ −16.40° (neat, *l* = 1); d^{25} = 0.905; $[M]^{25}_{D}$ −11.0°. The literature[24] reports $[M]^{25}_{D}$ +26.0° for (*S*)-(+)-2-methyloctanoic acid. Thus, the ee for the acid derived from the aldehyde was 42%.

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Registry No.—(*S*)-**1**, 55352-42-6; (*R*)-**1**, 49642-49-1; (*S*)-**3** (R = $PhCH_2$), 3182-95-4; (*S*)-**3** (R = $PhCH_2$) Mosher amide, 64715-79-3; (*S*)-**3** (R = *i*-Pr), 2026-48-4; (*S*)-**3** (R = *i*-Bu), 7533-40-6; (*S*)-**3** (R = *i*-Bu) HCl, 17016-87-4; (*R*)-**3** (R = Ph), 56613-80-0; **4a**, 64715-80-6; **4a** HCl, 64715-81-7; **4b**, 64715-82-8; **4c**, 64715-83-9; **4d**, 64715-84-0; **4e**, 64715-85-1; **4e** HCl, 64715-86-2; **4f**, 64715-87-3; **4g**, 64715-88-4; **4g** HCl, 64715-89-5; **4h**, 64715-90-8; **4i**, 64715-91-9; **4i** HCl, 64715-92-0; **4j**, 64715-93-1; **4k**, 64715-57-7; **5a**, 64715-58-8; **5b**, 64715-59-9; **5c**, 64715-60-2; **5e**, 64715-61-3; **5f**, 64715-62-4; **5g**, 64715-63-5; **5h**, 64715-64-6; **5i**, 64740-18-7; **5j**, 64715-65-7; **5k**, 64715-66-8; **6a**, 64715-67-9; **6c**, 64715-68-0; **6d**, 64715-69-1; **6e**, 64715-70-4; **6f**, 64715-71-5; **6g**, 64715-72-6; **6i**, 64715-73-7; **6j**, 64715-74-8; **6k**, 64715-75-9; (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride, 39637-99-5; methyl iodide, 74-88-4; 1-chloro-2-methoxyethane, 627-42-9; phthalic anhydride, 85-44-9; (*S*)-(+)-leucinol phthalimide derivative, 64715-76-0; allyl bromide, 106-95-6; (*S*)-(+)-leucinol phthalimide derivative, allyl ether, 64715-77-1; (*S*)-(+)-leucinol phthalimide derivative, 3-hydroxypropyl ether, 64715-78-2; propanal, 123-38-6; octanal, 124-13-0; *N-tert*-butylpropylaldimine, 7020-81-7; hexyl iodide, 638-45-9; (*S*)-(+)-2-methyloctanoic acid, 61866-40-8.

References and Notes

(1) National Research Service Award (NCI) Postdoctoral Fellow, 1976–1977.
(2) Swiss National Foundation for Scientific Research Fellowship, 1977.
(3) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.
(4) J. W. Scott and D. Valentine, *Science*, **184**, 943 (1974).
(5) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **10** (1977).
(6) A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am. Chem. Soc.*, **98**, 3032 (1976).
(7) J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, **42**, 377 (1977).
(8) D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, **15**, 549 (1976); D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 191 (1977).
(9) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(10) A. I. Meyers and G. S. Poindexter, *Tetrahedron Lett.* 3527 (1977).
(11) J. Hine and C. Y. Yeh, *J. Am. Chem. Soc.*, **89**, 2669 (1967).

(12) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976). These groups have observed and trapped *E,Z* ratios of kinetic enolates in aldehydes, ketones, and esters. To date, there are no reports of successful traping experiments involving *E* and *Z* metalloenamines (azaenolates).
(13) Microanalyses performed by Midwest Microlabs, Inc., Indianapolis, Ind. Optical rotations taken on a Perkin-Elmer automatic polarimeter, Model 241, or a JASCO DIP-180 automatic polarimeter. ^{1}H NMR were taken on a Varian T-60 and 360A instrument. ^{13}C NMR were taken on a Bruker HFX-90 operating at 22.6 MHz. Gas chromatographic analyses were performed on a Hewlett-Packard 5750 instrument using 6 ft × 8 in. UCW-98 (10%) column.
(14) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, **13**, 995 (1965).
(15) N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).
(16) C. F. Lane (Aldrich-Boranes, Inc.), U.S. Patent 3 935 280, *Chem. Abstr.*, **84**, 135101p (1976).
(17) The racemic phenylalininol as its Mosher amide gave two ^{19}F NMR signals at 277 and 280 Hz.
(18) P. Karrer, D. Portmann, and M. Suter, *Helv. Chim. Acta*, **32**, 1156 (1948).
(19) P. Karrer, D. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).
(20) C. C. Tseng, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* **25**, 166 (1977).
(21) K. Kurosawa, H. Obara, and H. Uda, *Bull. Chem. Soc. Jpn.*, **39**, 530 (1967).
(22) Prepared by Mr. Donald R. Williams of this group (research in progress).
(23) M. Shamma and H. R. Rodriguez, *Tetrahedron*, **24**, 6583 (1968).
(24) A. Rothen and P. A. Levene, *J. Chem. Phys.*, **7**, 975 (1939).

Stereochemical Aspects of Substitution Reactions of Stannyl and Germyl Anionoids with Cyclohexyl Derivatives

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The reactions of trimethyltinlithium (in THF) and trimethylgermaniumlithium (in HMPA) with some 4-alkylcyclohexyl bromides and tosylates have been conducted, and product stereochemistry has been established by ^{1}H and ^{13}C NMR spectroscopy. With the cis bromides both the stannyl and the germyl anionoids yield mixtures of *cis*- and *trans*-4-alkylcyclohexylstannanes and -germanes, respectively, whereas the stannyl anionoid reacts cleanly with inversion with *trans*-4-methylcyclohexyl tosylate. Both anionoids react in a straightforward way with cyclohexene oxide to yield the corresponding *trans*-2-hydroxycyclohexyl metalloids. Certain of our results contrast with some of those in a previous report. Variable-temperature ^{13}C NMR examination of *cis*-4-methylcyclohexyltrimethylgermane, and other considerations, yield a $-\Delta G°_{203}[Ge(CH_3)_3]$ of 2.1 ± 0.2 kcal/mol (*A* value), somewhat greater than the *A* value for CH_3 (1.74 kcal/mol).

Introduction

The reactions of organic halides with alkali metal derivatives of organometal anions have been extensively utilized for the formation of carbon–metal bonds as illustrated below:

$$R'_xM^-M_1^+ + RX \rightarrow R'_xMR + M_1X \ldots\ldots \quad (1)$$

This general area has been reviewed.[1]

This approach to carbon–metal bond formation has been particularly useful in group 4B chemistry, and many tetraorganostannanes have been synthesised in this manner.

$$R_3SnM + R'X \rightarrow R_3SnR' + MX \ldots\ldots \quad (2)$$

$$(R_3Sn = (CH_3)_3Sn, (C_6H_5)_3Sn;\ M = Na, K, Li)$$

Derivatives of silicon, germanium, and lead have also been obtained in the same general way.[1]

Stereochemical studies of the reaction (eq 2) have been reported and inversion of configuration at carbon was the general result, in keeping with the suspicion that the reaction was S_N2 in character.[2] Other transformations, however, indicated that other mechanisms must also be possible.[1d,3,4]

Recently, there has been great interest in the fine details of these anionoid substitutions, particularly for the systems in eq 2. In particular, Koermer, Hall, and Traylor[5] reported that whereas the 4-*tert*-butylcyclohexyl Grignard reagent on reaction with trimethyltin chloride provided overwhelmingly trans product, reaction of *cis*-4-*tert*-butylcyclohexyl bromide with $(CH_3)_3SnLi$ (in THF) yielded *cis*-4-*tert*-butylcyclohexyltrimethylstannane. The latter compound also resulted from the displacement of tosylate in the *trans*-4-*tert*-butylcyclohexyl derivative by $(CH_3)_3SnLi$ (in THF). These sequences seemed very attractive as they could provide geometric isomers of cyclohexyltin systems of high isomeric purity for other studies. Kuivila and co-workers[6] have also been conducting systematic studies of the reactions of stannyl anionoids under various conditions and have established that the stereochemistry of the reaction with certain bromonorbornenes (eq 2) is profoundly dependent upon the solvent and alkali metal counterion in $(CH_3)_3SnM$.

For some time we have been pursuing spectroscopic and conformational studies[7,8] of cyclohexyl derivatives of group 4B and have required 4-alkylcyclohexyl derivatives of tin and germanium of established stereochemistry. We have utilized reactions of $(CH_3)_3SnLi$ (in THF) and $(CH_3)_3GeLi$ (in HMPA) with cyclohexyl bromides and tosylates, as well as the Grignard route. In this report, we wish to present our conclusions concerning the stereochemistry of certain of these displacements (formally on carbon).

Results and Discussion

(A) Organotin Systems. The stereochemistry of the displacement of bromide and tosylate by $(CH_3)_3SnLi$ in the following cases (eq 3 and 4) has been examined.

In addition to tetraorganostannane product significant amounts of alkylcyclohexene (elimination) and hexamethyldistannane were also formed in these reactions.[5,6]

^{1}H NMR spectroscopy has been widely employed to determine the stereochemistry of substituted cyclohexyl sys-

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