spectra of the individual components. In the ^1H NMR spectrum, all signals of the phenol are shifted downfield, most significantly the hydroxyl proton (Table II). In the ^{13}C spectrum, the principal changes are observed for the ipso carbon. For benzophenone we observed no change in the ^1H NMR spectrum but a downfield shift of the carbonyl carbon resonance. These shifts suggest a weak interaction between the hydroxyl proton and the carbonyl group in benzene-d_6 solutions.

Due to the close proximity of the carbonyl moiety and the phenolic hydrogen in the aggregate, it is not impossible that the photoexcited benzophenone molecules react with the phenol predominantly in the singlet state before intersystem crossing to the triplet state can occur. The resulting change in spin multiplicity ($\mu > 0 \rightarrow \mu < 0$) would explain the observed change in signal directions [ortho, para (meta): E(A) → A(E)].

The concept of singlet quenching in a complex suggests several control experiments. For example, complex formation should be sensitive to steric hinderance. This is confirmed by the system 2,6-di-*tert*-butylphenol–benzophenone–benzene-d_6. Neither the ^1H NMR nor the ^{13}C NMR spectrum of 2,6-di-*tert*-butylphenol is affected by admixture of benzophenone (Table II), and the observed polarization is that expected for triplet quenching. However, other attempts to support this concept did not produce unambigous results. Since the observed effects represent a competition between singlet and triplet state reactions, the addition of a triplet quencher such as biphenyl should enhance the effects due to the singlet reaction.[15] Also the relative intensity of the CIDNP effects as a function of phenol concentration should provide information about the relative amounts of singlet and triplet reaction. The results in both experiments are ambiguous, perhaps suggesting additional interactions.

All of the CIDNP results discussed thus far reflect the hyperfine coupling pattern of the phenoxyl radical. In certain experiments, however, the polarization observed for the phenol does not reflect the spin densities of this intermediate. For example, the irradiation of DDBP in a CD_3CN solution containing 4-*tert*-butylphenol led to a CIDNP spectrum which showed both ortho and meta protons in emission (Table I). The polarization of the ortho protons is that expected for a phenoxy radical, but the polarization of the meta protons appears to be inconsistent with that intermediate. In order to explain this effect, we invoke the cross-polarization mechanism previously delineated for anilinium radical cations[16] and for phenoxyl radicals.[17] This mechanism involves transfer of polarization from a strongly polarized nucleus to a nucleus having weak or negligible hyperfine interaction. In order for the polarization transfer to occur these nuclei must be coupled indirectly and must experience a periodic exchange between paramagnetic and diamagnetic states. In the case of 4-*tert*-butylphenol, the polarization of the ortho protons (strong hfc) is transferred to the meta protons (weak hfc) so that both are observed in emission. The occurrence of polarization transfer will depend critically on factors which influence the rate of exchange such as solution acidity. Accordingly, the cross-polarization mechanism cannot be expected to be generally operative.

By applying CIDNP techniques we have been able to identify phenoxyl radicals as intermediates in the quenching of photoexcited ketones by simple phenols and have elucidated several facets of the reaction as well as the polarization mechanism. We are extending the application of these techniques to phenolic resin systems in order to determine the composition of mixed resins.

Acknowledgment. The author is indebted to H. D. Roth for helpful discussions.

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(16) (a) Closs, G. L.; Czeropski, M. S. *J. Am. Chem. Soc.* **1977**, *99*, 6127. (b) Closs, G. L.; Czeropski, M. S. *Chem. Phys. Lett.*, **1978**, *53*, 321. (c) Hendricks, B. M. P.; Walter, R. I.; Fischer, H. *J. Am. Chem. Soc.* **1979**, *101*, 2378.

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Enantioselective Alkylation of Ketones via Chiral, Nonracemic Lithioenamines. An Asymmetric Synthesis of α-Alkyl and α,α'-Dialkyl Cyclic Ketones

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Abstract: Chiral imines (*S*)-**2** are readily prepared from cyclic ketones and the chiral methoxyamine, (*S*)-**1**. Metalation and alkylation followed by imine hydrolysis lead to 2-alkylcycloalkanones **5** in 87–100% enantiomeric purity. A method to determine % ee of 2-alkylcyclohexanones via their diastereomeric acetals by ^{13}C NMR is also described. Dialkylation of the chiral imines (*S*)-**2** has produced 2,6-dialkylcyclohexanones, which for the dimethyl case were formed in 85% ee.

The alkylation of ketone enolates is among the most fundamental and widely used methods for carbon–carbon bond formation. Unfortunately, this process does not lend itself to enantioselective control due to the symmetric nature of the enolate π-system, and, thus, asymmetric C–C bond-forming reactions in simple, flexible, structures is not feasible. From Scheme I nucleophilic attack by the enolate would generally be expected to introduce an electrophile above and below the π-system with equal facility and thus provide equal amounts of the enantiomeric ketones ($k_1 \simeq k_2$; $\Delta\Delta G^{\ddagger} \simeq 0$). With the advent of metalloenamines[2] as enolate equivalents came the opportunity to introduce a chiral environment which could influence the direction and the rate of

(1) (a) Taken in part from the Ph.D. Thesis of D.R.W. 1978; (b) National Institutes of Health Postdoctoral Fellow, 1978–1980.

(2) (a) Stork, G.; Dowd, S. *J. Am. Chem. Soc.* **1963**, *85*, 2178. (b) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem.* **1963**, *75*, 978.

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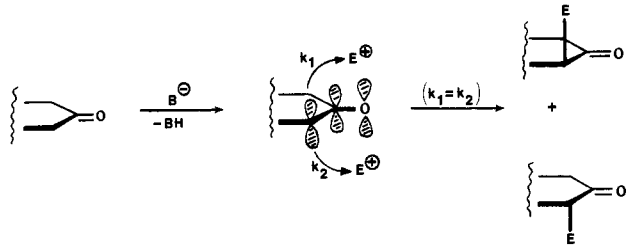
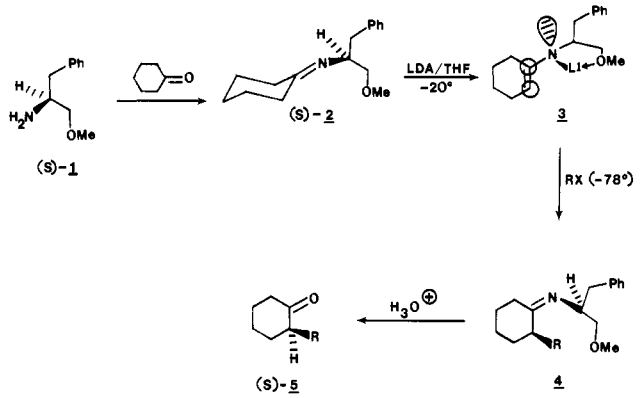
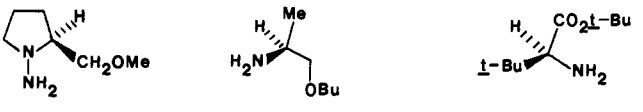
Scheme I



electrophilic entry and provide the bias necessary to form the alkylated products in disproportionate amounts (Scheme II). This concept has been tested earlier by Horeau[3] and Yamada[4] with varying degrees of success leading to enantiomerically enriched α-substituted ketones in 25–45% enantiomeric excess. In 1976, a preliminary report from this laboratory[5] described the asymmetric alkylation of cyclohexanones via certain lithioenamines furnishing α-alkylcyclohexanones in 90–100% ee. The basis for the efficient enantioselective alkylation rested on the induced rigidity of the lithioenamine by an internal ligand (OMe)[6] which was absent in the earlier work by Horeau and Yamada. Thus, starting from a readily available chiral amine **1** obtained by reduction of (*S*)-phenylalanine, we obtained and transformed the imine of cyclohexanone **2** into its lithioenamine **3** by using lithium

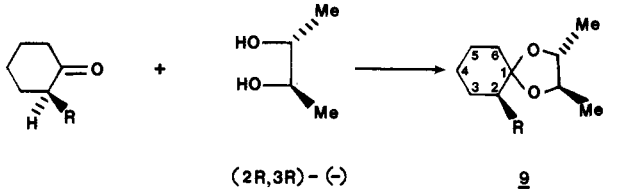


diisopropylamide. A key feature of **3** was the presumed formation of a rigid 5-membered chelate whose topology would influence the direction of entry by the alkyl halide, RX. Alkylation led to **4** by predominant entry from the *si* face (frontside) of the cyclohexenyl moiety producing, after hydrolysis, the (*S*)-2-alkyl ketone, **5**. Recovery of the chiral methoxyamine (*S*)-**1**, for recycling, was also possible since no racemization took place during the entire sequence. A number of other successes using the "rigid lithioenamine" concept have been described[7-9] since the original report in 1976 and have involved the use of various chiral amines **6–8**. In these instances, alkylation of the cyclohexanone imines,



as well as other imines, gave α-alkyl ketones in very high enantiomeric excesses (90–100%) attesting to the rather general nature of this asymmetric synthetic method. In the absence of an internal ligand, the degree of asymmetric induction fell considerably short of that observed above.[3,4,10] Recently, data has appeared[10,11] which indicate that other factors may also contribute to the high enantiomeric excess of the carbonyl products. These involve the use of various bases, added salts, geometry of the imines, and stereoelectronic effects in the deprotonation step. These aspects of the process and its true mechanistic pathway are still under active investigation and undoubtedly will be sorted out in the future. However, the synthetic practitioner need not await these findings in order to utilize this technique successfully.

We now describe in full our synthetic results concerning a large number of chiral α-substituted, as well as α,α′-disubstituted ketones in the cyclic series. Alkylation of acyclic and macrocyclic ketones are the subject of the adjoining paper since they involve another aspect, namely, *E*,*Z* isomerization of the lithioenamine which give rise to either (*S*)- or (*R*)-ketones. From Table I it is seen that enantioselective alkylation of a variety of cyclic ketones (via **2**) have been carried out. For the cyclohexanones, the enantiomeric excess ranges from 87 to 100% and furnishes the (*S*)-2-alkylcyclohexanones (entries 1–3). In a similar fashion, the 2-benzyl-, 2-alkyl-, 2-acetonyl-, and 2-(2-methoxyethyl)-cyclohexanones (entries 4–7) gave the (*R*)-enantiomer due to reversal of the Cahn–Ingold–Prelog priority assignment but possess the same sense of absolute stereochemistry as seen from their respective CD maxima. For those α-alkycycloalkanones in Table I which were not previously described, methods for determining the % ee were required. For 2-ethyl- and 2-benzylcyclohexanone their acetals **9** were prepared from (2*R*,3*R*)-(−)-2,3-butanediol in such a manner which precluded any racemization. On the basis



of a report by Wynberg,[12] diasteromeric ketals derived from 3-substituted cyclohexanones and (−)-2,3-butanediol gave ^{13}C NMR spectra which exhibited peak separation at the 2- and 6-carbons of ~1 ppm and allowed integration leading to diastereomeric ratios. On this basis we prepared **9** from the 2-substituted cyclohexanones. It was of prime importance that no epimerization occurred during the ketal formation. Initially, we examined racemic 2-methyl- and 2-(*n*-propyl)cyclohexanone and found that two peaks of equal intensity appeared at ~36–37 ppm (C-6) and another two peaks at ~40–44 ppm (C-2) with ΔΔδ of 0.4–0.8 ppm. In order to avoid kinetic resolution during the ketal formation, we utilized approximately 100% of excess diol. Next, to test the validity of this enantiomeric determination, we utilized 2-methyl- and 2-(*n*-propyl)cyclohexanone of known enantiomeric purity. The ketals were formed and, as seen from Table II, the diastereomeric ratios from ^{13}C NMR were in excellent agreement with the % ee via rotation data. This provided sufficient confidence that no epimerization was occurring during the ketal formation. In this manner, the enantiomeric purity of 2-ethyl- and 2-benzylcyclohexanone were determined, and the rotation expected for optically pure materials is given in the final column of the table. The other cyclohexanone derivatives in Table I readily succumbed to enantiomeric determinations by using chiral lanthanide-induced shift reagents and possess ee's which are within ±2%. Enantiomeric purities of the cycloheptanones, cyclooctanones, tetralones, and indanones were likewise determined by LISR techniques. Unfortunately, the chiral ketals from (−)-2,3-butanediol for ketones other than cyclohexanones did not lend themselves to ^{13}C NMR analysis since no reliable peak separations were observed. The same was found true for acyclic

(3) Mea-Jacheet, D.; Horeau, A. *Bull. Soc. Chim. Fr.* **1968**, 4571.
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(6) The use of methoxyl for chelaton has been demonstrated in oxazolines (Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375).
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Scheme II

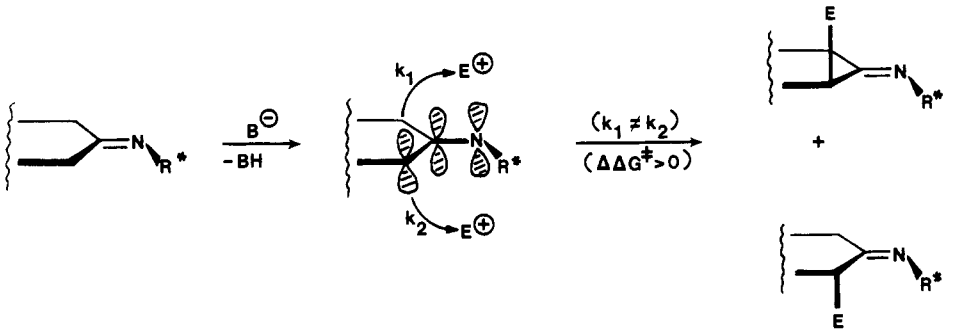
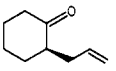
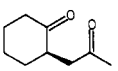
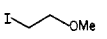
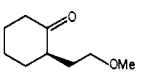
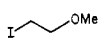
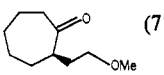
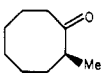
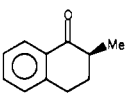
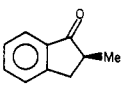


Table I. Chiral 2-Substituted Cycloalkanones 5

entry	ketone	RX	2-alkyl ketone (% yield)[a]	$[\alpha]_D$ (c, sol)	% ee (confn)	CD $[\theta]_{287}^{MeOH}$
1	cyclohexanone	MeI	 (65)	+12.2 (4, MeOH)	87 (*S*)[b]	+2120
2	cyclohexanone	EtI	 (82)	+24.1 (4, MeOH)	94 (*S*)[c]	+2200
3	cyclohexanone	*n*-PrI	 (76)	+27.9 (4, MeOH)	99 (*S*)[d]	+2480
4	cyclohexanone	allyl Br	 (80)	+15.8 (3, MeOH)	99 (*R*)[e]	+2190
5	cyclohexanone	$PhCH_2Br$	 (87)	+41.4 (5, MeOH)	88 (*R*)[c]	+1750
6	cyclohexanone		 (62)	+23.5 (6, MeOH)	80 (*R*)[f]	
7	cyclohexanone		 (64)	+0.38 (9, $CHCl_3$)	90 (*R*)[f]	
8	cycloheptanone	MeI	 (90)	+71.5 (6, $CHCl_3$)	85 (*S*)[f,22]	+2830
9	cycloheptanone		 (77)	+36.4 (4, $CHCl_3$)	81 (*R*)[f]	+2158
10	cyclooctanone	MeI	 (65)	+8.07 (7, $CHCl_3$)	20 (*S*)[f]	+572
11	1-tetralone	MeI	 (75)	−40.5 (3, dioxane)	79 (*S*)[f,g]	−939[h]
12	1-indanone	MeI	 (75)	−7.2 (5, dioxane)	17 (*S*)[f,g]	+145[i]

[a] Yield based on imine 2. [b] Beard, C.; Djerassi, C.; Sicher, J.; Sipos, F.; Tichy, M. *Tetrahedron* 1963, *19*, 919 report $[\alpha]_D$ + 14°. [c] Determined by ^{13}C NMR on the chiral dioxolane 9. [d] Hiroi, K.; Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* 1972, *20*, 246 report $[\alpha]_D$ −28.2° for *R* enantiomer. [e] Kitomoto, M.; Hiroi, K.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* 1974, *22*, 459. [f] Determined by use of chiral shift reagent, tris[(3-(heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III). [g] Jaouen, G.; Meyer, A. *J. Am. Chem. Soc.* 1975, *97*, 4667 report −51.2° for (*S*)-(−)-2-methyl-1-tetralone and −42° for (*R*)-(−)-2-methylindanone. [h] At 333 nm. [i] At 316 nm.

Table II. Determination of Enantiomeric Purity of Ketals 9 via ^{13}C NMR

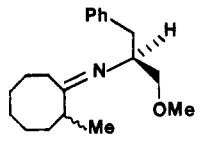
2-substituted cyclohexanone	$[\alpha]_D^{MeOH}$	% ee[a]	ketal (% yield)	^{13}C NMR C-2	^{13}C NMR C-6	^{13}C NMR % ee[d,e]	$[\alpha]_D^{max}$
Me	+11.4	81.6	92	39.7	36.5	82	+14.0
n-Pr	−19.9	71.4	84	44.5	36.5	72	−27.9[e]
Et	+24.2	*b*	85	46.6	36.5	94	+25.7
$PhCH_2$	+41.4	*c*	87	46.9	36.6	89	+46.5

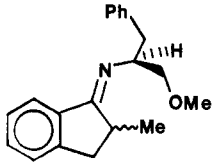
[a] Based on literature values, see Table I (ref *b*, *d*). [b] Helmchen-Zeier, R. E. thesis, ETH-Zurich, 1973 reports 2-ethylcyclohexanone as +19° (*c* 0.26, EtOH) for the (*S*)-(+)-ketone. [c] Not previously reported. [d] Determined by integration of the peaks at C-2 and C-6, see Table IV for complete spectral data. [e] This ketone was prepared by using (*R*)-1. [e] T_1 and NOE measurement showed no difference for C-2 and C-6 in each diastereomer or racemic ketals.

ketones which also failed to show diastereomeric splitting of carbon peaks.

As seen from Table I, all of the α-substituted ketones prepared possessed the absolute configuration in the major enantiomer consistent with the operational mechanism given earlier, namely, frontside entry of the alkyl halide on **3**. This heuristic sequence may be used with some confidence in predicting the absolute configuration of α-substituted cycloalkanones formed under these reaction conditions.[13]

The two examples shown in Table I which resulted in rather poor enantiomeric purity, 2-methylcyclooctanone and 2-methylindanone, were found to be victims of extensive racemization during the hydrolysis step to remove the imine (**4** → **5**). That the low ee's for these two examples is the result of the hydrolysis (NaOAc–HOAc, pentane–water) rather than poor selectivity in the alkylation step was shown by examining the H^1 NMR spectra of the diastereomers **10** and **11** prior to hydrolysis.

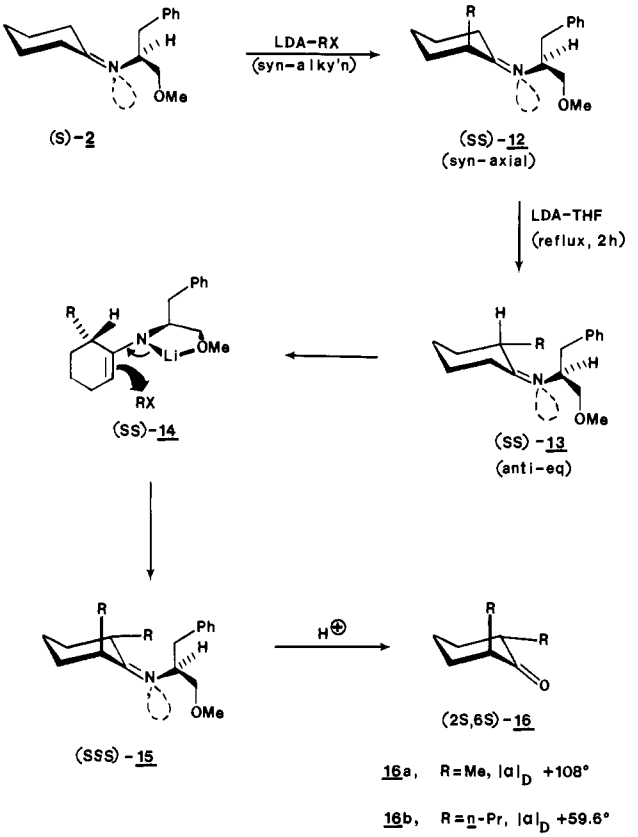




10a	SS, 96±2%	11a	SS, 93±3%
10b	SR, 4±2%	11b	SR, 7±3%

The newly introduced methyl groups showed doublets which integrated to >95% indicating the diastereomeric ratios were indeed quite high. Furthermore, racemic 2-methylcyclooctanone and 2-methyl-1-indanone as their imines **10** and **11** gave nicely separated pairs of doublets (1:1) for the methyl group. In order to validate the accuracy of the method, we made two further checks. The % ee of 2-methylcycloheptanone was found by using LISR (Table I, footnote *f*), to be within 5% of that found in the H^1 NMR spectra of diastereomeric imines as was the % ee for 2-methyl-1-tetralone when compared to that for its diastereomeric imine. Thus, hydrolytic conditions were the major cause of the low ee's observed for entries 11 and 12 in Table I.

We next turned our attention to asymmetric dialkylation of cyclohexanone in an effort to reach chiral, nonracemic 2,6-dialkyl derivatives. When (*S*)-**2** was metalated with LDA in THF, followed by addition of methyl iodide (−78 °C), the initial diastereomeric product (**12**) was assumed to be the syn-axial product on the basis of work of Fraser.[14] Addition of a second equivalent of LDA, followed by heating the solution to reflux (2 h), gave the isomerized imine (anti-equatorial) **13** which underwent efficient deprotonation to the metalloenamine **14**. Subsequent addition of methyl iodide (-78 °C) furnished the dialkylated imine **15** which was hydrolyzed in the acetic acid sodium acetate buffer to (2*S*,6*S*)-(+)-2,6-dimethylcyclohexanone (**16a**) in 85% ee.[15] It is important to note that without heating **12** in the presence of LDA prior to the addition of methyl iodide, considerable monoalkylated ketone (20–50%) is recovered. In a similar fashion, *n*-propyl iodide was utilized to dialkylate the chiral imine of cyclohexanone and gave (2*S*,6*S*)-(+)-2,6-bis(*n*-propyl)cyclohexanone (**16b**) in 91% yield.[16] Again, if the monoalkylated imine



12 was not heated with LDA prior to the second propyl iodide addition, 67% of 2-propylcyclohexanone was isolated along with only 33% of the 2,6-di-*n*-propyl derivative. The previously unreported enantiomeric purity of **16b** could not be assessed by any usual means (LISR, HPLC, or NMR of diastereomers) although its CD spectrum exhibited $[\theta]_{292}$ +3977 which is comparable both in sign and intensity to 2,6-dimethylcyclohexanone **16a** ($[\theta]_{292}$ +3868). This suggests that its enantiomeric purity and absolute configuration were closely related to those of **16a**.

This double alkylation may be seen as initially giving syn-axial alkylation to **12** (via syn-axial) deprotonation of **2** in accordance with the observations by Fraser.[14] Isomerization of **12** to **13** and ultimately to the metalloenamine **14** probably occurs via heat followed by metalation. Alternatively, it could take place by metalation of **12** followed by rapid isomerization. Choice between these alternate pathways is not possible at this time. However, one fact remains clear. The metalation of **12** appears to be very slow unless heat is applied in the presence of the base. This apparent stereoelectronic effect toward deprotonation is one which has received considerable attention in other weak organic acids and suggests that this phenomenon may become potentially very important for stereochemical and regiochemical control in synthesis.[17] This intriguing behavior prompted another experiment which was designed to provide further insight into this stereoelectronic effect. Metalation of **2** (LDA, −20 °C, THF), followed by isopropyl iodide gave the 2-isopropyl imine **17** which was treated with LDA at −20 °C, *or at reflux*, followed by addition of methyl iodide. To our surprise only 18% yield of 2-methyl-6-isopropylcyclohexanone (**19**) was obtained along with 80% of 2-isopropylcyclohexanone (**18**). The enantiomeric purity of the latter was only 5–10% due to considerable racemization during the hydrolysis of the imine. However, the significant result rested with the ratio of the mono- (**18**) to the dialkylated (**19**) product.

(13) Jaouen and Meyer (Table I, footnote *g*) report that the (−)-2-methyl-1-indanone possesses the *R* configuration, in contrast to our expectation that the (−)-enantiomer should be *S* based on all the examples in this and the following paper. Furthermore, Kagan et al. (*Tetrahedron* **1971**, *27*, 4737) report that (+)-2-methyl-1-tetralone possesses the *S* configuration in contrast to Jaouen and Meyer and our own assignment. This matter therefore remains unresolved and could represent a deviation from the predicted absolute configurations reported for all other examples in Table I.

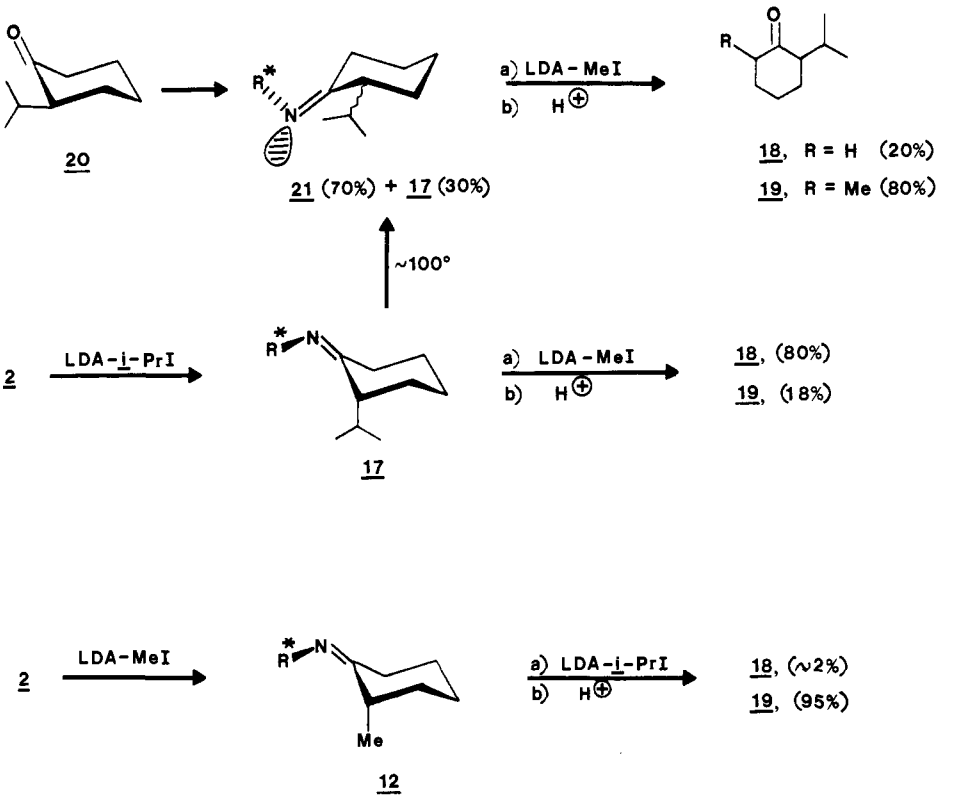
(14) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999.

(15) Beard, C.; Djerassi, C.; Snider, J.; Sipos, F.; Tichy, M. *Tetrahedron* **1963**, *19* report $[\alpha]^{23}_D$ +130°. Chiral LISR studies confirmed the enantiomeric purity; see Experimental Section.

(16) Only the 2-axial-6-equatorial cyclohexanones are chiral and would exhibit optical activity. The 2,6-diequatorial derivatives are meso compounds.

(17) Meyers, A. I.; Campbell, A. L.; Abatjoglou, A. G.; Eliel, E. L.; Kupyer, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262. Wolf, S. *Acc. Chem. Res.* **1972**, *5*, 102. Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. Streitweiser, A.; Williams, J. E. *Ibid.* **1975**, *97*, 191.

Scheme III



On the other hand, reversing the order of sequential metalation–alkylation on **2**—metalation and introduction of methyl iodide to **12** followed by metalation (reflux)—isopropyl iodide gave the dialkylated ketone **19** in 95% yield with only a trace of 2-methylcyclohexanone recovered. Once again, the % ee of the ketone **19** was low (20–30%) due to racemization during hydrolysis. Although the latter result was not unexpected, the former [**17** → **18** (80%)] was indeed surprising. The 2-isopropyl imine **17** was then isolated and its ^{13}C NMR spectrum examined which revealed the presence of a single syn-axial isomer.[25] Signals for the isopropyl-substituted carbon (C-2) at δ 45.0 and the α'-carbon at δ 37.0 are in agreement with previous assignments.[14] Heating **17** more drastically (80–100 °C) resulted in a major change in its ^{13}C NMR spectrum and indicated that **17** had isomerized into a 70:30 mixture of **21** and **17** (Scheme III). Metalation of this mixture (LDA, −20 °C, MeI) gave, in contrast to reaction of pure **17**, a 20:80 ratio of **18** and **19**, respectively. Furthermore, when racemic 2-isopropylcyclohexanone (**20**) was converted to its imine by using excess (*S*)-**1**, the product was virtually identical by ^{13}C NMR with that obtained after heating imine **17**. Metalation of this mixture from (±)-**20** gave **18** and **19** in the same ratio (20:80). One may conclude from this behavior that the isopropyl group enters in a syn-axial manner (**17**) but is simply too bulky to isomerize under mild conditions (refluxing THF) to the anti-equatorial isomer to allow metalation. Alternatively, metalation may be inhibited in **17** due to the presence of the axial isopropyl group. It is also of interest that the isopropyl imine formed from 2-isopropylcyclohexanone (**20**) gives rise to a thermodynamic mixture of imines by virtue of its method of formation which is indeed quite different than the kinetically controlled metalation–alkylation of cyclohexanone imine, **2**.

Experimental Section[18]

(*S*)-(−)-2-Amino-1-methyoxy-3-phenylpropane (1). Reduction of (*S*)-Phenylalanine. A modified procedure, previously reported[19a] and based on Yamada's[19b] technique, was employed. (*S*)-Phenylalanine (183.4 g, 1.11 mol) was suspended in 1 L of methanol (dried over Na_2SO_4). The solution was cooled to 0 °C (ice-water bath) and 200 mL (2.74 mol) of thionyl chloride was added dropwise over ca. 1 h. the solution was allowed to warm to room temperature and stirred overnight. Concentration gave a yellow solid which was stirred with 400 mL of Et_2O, filtered, and dried under high vacuum (to remove excess $SOCl_2$), to produce 236.5 g (101%) of the white solid hydrochloride salt of the methyl ester.

The ester (0.497 mol), without further purification, was dissolved in 500 mL of 50% aqueous EtOH. This was slowly added to a cooled (0 °C) solution of $NaBH_4$ (89.8 g, 2.38 mol) in 1500 mL of 50% aqueous EtOH over Ca. 1 h (gas evolution and insoluble liquid layer at bottom). The solution was stirred at room temperature for 4 h, then refluxed under N_2 for 6 h, and allowed to stir at room temperature overnight. The top layer was decanted and the ethanol removed in vacuo until a white solid appeared. The lower insoluble layer was extracted (3 × 150 mL) with EtOH and concentrated. The two concentrated aqueous layers were extracted (5 × 100 mL) with EtOAc. The combined EtOAc layers were dried over Na_2SO_4 and concentrated to yield a white solid. This was recrystallized in EtOAc (255 mL) and hexane (100 mL) to give 58.3 g (78%) of the desired alcohol: ^1H NMR ($CDCl_3$) δ 1.53 (s, 2 H), 2.78 (m, 2 H), 3.23 (d, 2 H), 3.45–3.70 (m, 1 H), 4.20 (s, 1 H), 7.15 (s, 5 H); mp 89–91 °C; $[\alpha]_D$ −24.2° (*c* 1.5, EtOH).

Methylation with KH–MeI to (*S*)-1. This was performed as previously described;[19a] $[\alpha]^{25}_D$ −13.8° (*c* 5.6, benzene). The product, (*S*)-**1**, is prone to carbon dioxide adsorption to form the carbonate and was either stored as its hydrochloride[19] ($[\alpha]^{25}_D$ +19.5° (*c* 2.5, EtOH) or kept

Table III. Chiral Imines from (*S*)-1 and Cyclic Ketones

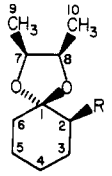
ketone[a]	Kugelrohr, °C (pressure, torr)	$[\alpha]^{25}_D(CHCl_3)$	$\nu_{C=N}$ (film), cm^{-1}
cycloheptanone	90–100 (0.1)	−42.91° (*c* 8.6)	1640
cyclooctanone	134–138 (0.025)	−53.62° (*c* 6.7)	1645
1-tetralone	160–164 (0.15)	−207.9° (*c* 6.64)	1630

[a] These ketones required 1–5% trifluoroacetic acid as a catalyst to form the imines. [b] The ^1H NMR spectra were recorded but were not of any unusual nature.

(18) Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Optical rotations were taken on a JASCO DIP-180 or a Perkin-Elmer 241 automatic polarimeter. ^1H NMR were taken on a Varian 360A or T-60 instrument and ^{13}C NMR were performed with a JEOL FX-100 instrument operating at 25.05 MHz. Gas chromatography was performed on a Hewlett-Packard 5750 FID chromatograph using SE-30, 6 ft × $^1/_8$ in. column.

(19) (a) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892. (b) Seki, H.; Koga, K.; Matsuo, S.; Ohki, I.; Matsuo, I.; Yamada, S. *Chem. Pharm. Bull.* **1965**, *13*, 995.

Table IV. ^{13}C Chemical Shifts of Acetals 9 and Diastereomers at C-2 and C-6



R	C-1	C-2	C-3[a]	C-4	C-5	C-6	others[b]
Me	109.7	39.6	24.9	32.2	23.7	37.2	2-CH_3, 14.4
		40.0				37.7	C-8, 79.6
							C-7, 77.6
							C-9, 16.2; C-10, 17.8
Et	109.8	46.7	24.7	28.1	23.6	37.2	CH_2, 20.9; CH_3, 11.9
		47.4	25.2			37.9	C-8, 79.3
							C-7, 77.3
							C-9, 16.2; C-10, 17.9
n-Pr	110.0[c]	44.5	24.1	28.6	23.6	36.5	CH_2, 20.5; CH_2, 30.2
		45.2	24.6			37.1	CH_3, 14.4
							C-8, 78.9
							C-7, 77.5
							C-9, 16.1; C-10, 17.8
$PhCH_2$	109.5	46.9	24.8	28.1	23.6	36.6	CH_2Ar, 34.8
		47.6				37.4	Ar, 121, 128, 125, 141
							C-8, 79.2
							C-7, 77.5
							C-9, 16.3; C-10, 17.9

[a] Diastereomers were also discernible at C-3 but were not generally useful due to small $\Delta\Delta\delta$ values in some cases. [b] Spectra of these compounds may be found with supplementary material. [c] Diastereomers could also be seen at C-1, but the $\Delta\Delta\delta$ were too small to be useful and these peaks did not separate in all cases.

tightly sealed under argon or nitrogen immediately after distillation, bp 57–59 °C (0.02 torr).

Cyclohexanone Imine of (*S*)-(−)-2-Amino-1-methoxy-3-phenylpropane (2). In a system containing a Dean–Stark trap arranged for azeotropic removal of water, the methoxy amine **1** (9.3 g, 56.4 mmol) and cyclohexanone (6.5 g, 66.4 mmol) were dissolved in 100 mL of benzene or toluene and heated to reflux until the theoretical amount of water was collected in the trap. Removal of the solvent and distillation of the oily residue gave 13.0 g (93%) of a clear viscous oil: Kugelrohr 95–100 °C (0.5 torr); $[\alpha]_D$ −46.2° (*c* 6.7, MeOH).

In a similar fashion the other cyclic ketones were converted to their imines by using **1** (Table III).

Metalation and Alkylation of Cyclohexanone Imines. Asymmetric Synthesis of 2-Alkylcyclohexanones 5. An oven-dried 50-mL flask equipped with a magnetic stir bar, a pressure-equalized addition funnel, and a rubber serum cap was charged with 20 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere. Freshly distilled diisopropylamine (1.47 mL, 10.5 mmol) was added via syringe and the solution cooled to 0 °C. Butyllithium (4.4 mL of a 2.4 M solution in hexane) was added and the solution stirred at 0 °C for 15 min and then cooled to −30 °C. The chiral imine of the various ketones (10 mmol) in 10 mL of THF (dry) was added over 15 min and allowed to stir for 1–1.5 h. The solution was then cooled to −78 °C and the alkyl halide (10.5 mmol) was added in a solution of THF (3–4 volumes) over a period of 1 h and the mixture allowed to stir at −78 °C for 1.5 h. The total volume of THF was such as to make the final concentration of the imine ~0.25 M. The light yellow cold solution was poured into 100 mL of saturated salt solution and extracted with ether (3×). The combined ether extracts were washed with brine, then dried (Na_2SO_4), and concentrated in vacuo, and the amber oil was subjected to hydrolysis immediately. Delay of the hydrolysis step (e.g., overnight) results in ~10–15% racemization. A buffer solution[20] comprised of 3.30 g of sodium acetate, 7.5 mL of acetic acid, and 35 mL of water was added to the crude imine in 50 mL of pentane and shaken for 30 min and the aqueous layer removed and saved to recover **1** (see below). The aqueous layer was washed with pentane, and the pentane solutions were combined and washed with 1 *N* HCl (to remove any unhydrolyzed imine), water, 5% sodium bicarbonate, water, and brine. The pentane solution was then dried (Na_2SO_4), filtered, concentrated, and bulb-to-bulb distilled to yield the 2-substituted ketone.

Alternatively, hydrolysis could be carried out with equally satisfactory results using 3 mL of saturated (±)-tartaric acid solution and 2 mL of pentane/mmol of imine obtained after solvent removal. The 2-alkyl ketones thus obtained were examined by gas chromatography and shown to be 98 ± 2% pure. Specific rotations and CD data are given in Table I.

Physical Data for 2-Alkyl Ketones. (a) **(*R*)-(+)-2-Acetonylcyclohexanone:**[21] bulb-to-bulb distillation 50–60 °C (0.05 torr); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3). VPC shows 99% purity.

(b) **(*R*)-(+)-2-(2-Methoxyethyl)cyclohexanone:** bulb-to-bulb distillation 80–90 °C (0.05 torr); IR (film) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.6 (m, 11), 3.20 (s, 3), 3.25 (t, 2). VPC shows 98% purity. Anal. Calcd for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 68.81; H, 10.27.

(c) **(*S*)-(+)-2-Methylcycloheptanone:**[22] bulb-to-bulb distillation 50 °C (8 torr); IR (film) 1695 cm^{-1}. VPC shows 99 ± 1% purity.

(d) **(*R*)-(+)-2-(2-Methoxyethyl)cycloheptanone:** bulb-to-bulb distillation 80–90 °C (0.05 torr); IR (film) 1700 cm^{-1}, NMR ($CDCl_3$) δ 1.20–2.50 (m, 13), 3.30 (s, 3), 3.35 (m, 2). VPC analysis shows 99% purity. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 69.91; H, 10.71.

(e) **(*S*)-(+)-2-Methylcyclooctanone:**[23] bulb-to-bulb distillation 50 °C (10 torr); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, 3), 1.10–2.00 (m, 10). VPC shows 3% unalkylated cyclooctanone, $[\alpha]_D$ +7.76, corrected for pure ketone, $[\alpha]_D$ +8.07.

(f) **(*S*)-(−)-2-Methyl-1-tetralone:**[24] bulb-to-bulb distillation 85–100 °C (0.1 torr); IR (film) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 3), 2.17 (m, 2), 2.75 (m, 1), 3.00 (m, 2), 7.40 (m, 3), 8.10 (m, 1). VPC showed 99% purity.

(g) **(*R*)-(−)-2-Methyl-1-indanone:**[13] bulb-to-bulb distillation 35–45 °C (0.005 torr); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, 3), 2.30–2.80 (m, 2), 3.10–3.60 (m, 1), 7.10–7.80 (m. 4). VPC showed 99% purity.

Recovery of *1*. The acidic aqueous layer from above was neutralized with solid KOH to pH 14 and then saturated with sodium chloride. This aqueous solution was extracted four times with ether, and the combined ether layers were washed with brine. Drying (K_2CO_3) and concentration gave an oil which was distilled: bp 57–59 °C (0.02 torr); $[\alpha]_D$ −13.75° (*c* 5.8, benzene). The recovery was ~85%. If the rotation of the distilled methoxyamine **1** was lower than 13.40 °C, it was purified via its hydrochloride. A solution of **1** in ice-cold ether was treated with dry HCl by bubbling through a fritted disk. The amine hydrochloride was collected by filtration and recrystallized from ethanol: mp 151–152 °C;

(20) Kieczykowski, G. R.; Schlessinger, R. H.; Salsky, R. B. *Tetrahedron Lett.* **1976**, 597.

(21) Islam. A. M.; Raphael, R. A. *J. Chem. Soc.* **1952**, 4086.

(22) Gutsche, C. D.; Cheng, C. T. *J. Am. Chem. Soc.* **1962**, *84*, 2263. These authors report (*S*)-(+)-2-methylcycloheptanone $[\alpha]_D$ +29° as 39% ee which would correspond to optically pure material having $[\alpha]_D$ 73.8°. On the basis of this value, 2-methylcycloheptanone would be 97% ee. The 85% ee reported in Table I was determined by LISR technique (see footnote *f*).

(23) Cope, A. C.; Ciganek, E.; Lazar, J. *J. Am. Chem. Soc.* **1962**, *84*, 2591.

(24) Jaouen, G.; Meyer, A. *J. Am. Soc.* **1975**, *97*, 4667.

$[\alpha]_D$ +19.50° (*c* 2.5, ethanol). Release of the amine **1** from its hydrochloride was accomplished by dissolving it in water containing 15% sodium chloride, adding solid KOH to pH 14, and extracting with ether (4×). Washing the ether solution with water and then with brine, and drying (K_2CO_3) gave, upon concentration, the amine $[\alpha]_D$ −13.75° in purity sufficient for imine formation.

Cyclic Acetals 9 of Cyclohexanone and (2*R*,3*R*)-2,3-Butanediol. The following procedure was used to prepare the cyclic acetals of 2-methyl-, 2-ethyl-, 2-*n*-propyl-, and 2-benzylcyclohexanones. The ketone (200 mg) and the (−)-diol (2 equiv) in 15 mL of methylene chloride containing 3–5 mg of *p*-toluenesulfonic acid were heated at reflux for 1–20 h depending on the 2-alkyl substituent. The reaction was followed by VPC (6 ft × $^1/_4$ in., SE-30 on 60–80 mesh Chromsorb W, 90–150 °C 10 °C/min), and heating continued until all of the ketone was gone. This avoided any kinetic resolution of the ketones. After being cooled, the methylene chloride solution was washed with water and then saturated bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The resulting products (VPC purity, 97–99%) were obtained in 85–95% yield, and their ^{13}C NMR spectra were examined as $CDCl_3$ solutions at 25.05 MHz (Table IV).

(2*S*,6*S*)-(+)-2,6-Dimethylcyclohexanone (16a). A solution of 1.23 g (5.0 mmol) of cyclohexanone imine **2** in 5 mL of THF was added to a solution of LDA (5.20 mmol) in 10 mL of THF at −20 °C over 15 min. The resulting yellow solution was stirred for 1 h under a nitrogen atmosphere and then cooled to −78 °C. To this was added 0.78 g (5.5 mmol) of methyl iodide in 5 mL of THF, and the clear mixture was stirred for 2 h at −78 °C and allowed to warm to ambient. This solution was transferred, via nitrogen pressure, through a cannula (double-edged syringe needle) into an addition funnel (pressure equalized attached to a three-necked flask containing 5.25 mmol of LDA in 10 mL of THF and equipped with both a nitrogen inlet tube, a reflux condenser, and a magnetic stir bar. The LDA solution was cooled to −20 °C and the imine solution added from the addition funnel over 15 min. The yellow solution was stirred for 1 h at −20 °C and then warmed to ambient and heated to reflux for 45 min. The somewhat darkened solution was cooled to −78 °C and a solution of 0.80 g (5.7 mmol) of methyl iodide in 5 mL of THF added, and the mixture was stirred at −78 °C for 2.5 h and warmed to ambient after which it was poured into 150 mL of saturated brine and worked up and hydrolyzed as described for the monoalkylation of cyclohexanones. Kugelrohr distillation gave 0.48 g (77%) of a clear colorless liquid: bp (bulb-to-bulb) 80–90 °C (9 torr); $[\alpha]^{25}_D$ +88.8° (*c* 7.8, MeOH) containing 18% *meso*-(2*R*,6*S*)-2,6-dimethylcyclohexanone. Correcting for the mesocontaminant gave $[\alpha]_D$ +108° which was 83% ee based on literature value[15] of $[\alpha]_D$ +130°; CD (MeOH) at 292, $[\theta]$ = +3868 (10^{-3} M). Verification of the meso compound was achieved by use of Resolve-Al (Aldrich) an achiral shift reagent (20 mg/0.025 g of cyclohexanone in 0.4 mL of CCl_4) which showed two doublets in 82:18 ratio. The % ee was also verified by use of europium shift reagent (footnote *f*, Table I): 18–20 mg/0.3 g of ketone in 0.4 mL of CCl_4 which gave integration of the doublets at 85 ± 2%.

(2*S*,6*S*)-(+)-2,6-Dipropylcyclohexanone (16b). In a manner similar to that above, 5 mmol of cyclohexanone imine **2** was treated with LDA and *n*-propyl iodide in sequential fashion and heating the monopropylated imine with LDA prior to addition of the second equivalent of *n*-propyl iodide. Workup and hydrolysis gave **16b** in 91% yield: bp (bulb-to-bulb) 80–90 °C (0.02 torr), $[\alpha]^{25}_D$ +59.6° (*c* 3.1, MeOH). VPC (UCW-98 on chromsorb W, 60–80 mesh) showed 2% mono-*n*-propylcyclohexanone: mass spectrum, (*m*/*e*) 182 (M+), 140, 111, 98, 91, 83, 77, 67, 55, 41; IR (film) 1715 cm^{-1}; ^1H NMR (CCl_4) δ 2.60–0.60 (m, 22); CD (MeOH) at 292, $[\theta]$ = +3977 (10^{-3} M). Anal. Calcd. for $C_{12}H_{22}O$: C, 79.20; H, 12.10. Found: C, 79.42; H, 12.17.

(*R*)-(+)-2-Isopropylcyclohexanone (18). To 4.4 mmol of LDA in 15 mL of THF at −20 °C contained in a flame-dried flask fitted with additional funnel, N_2 inlet, magnetic stirrer, and septum was added 0.98 g (4.0 mmol) of the imine **2** in 10 mL of THF. The resulting solution was stirred at −20 °C to 0 °C for 30 min and then cooled to −78 °C. The lithioenamine was alkylated with 1.02 g (6.0 mmol) of 2-iodopropane in 5 mL of THF. The resulting solution was allowed to warm to ambient over a 3-h period (NOTE: warming to ambient is necessary in this particular alkylation to obtain complete alkylation) and quenched with brine. The organic layer was separated and extracted 3× with ether, and the combined organics were washed with brine. The solvents were removed in vacuo, and the residue was examined by ^{13}C NMR. NMR analysis[25] indicated the syn isomer to be present in >95% diastereomeric purity. Hydrolysis of the imine with NaOAc/HOAc/pentane buffer for 13 h, pentane extraction, and subsequent Kugelrohr distillation (bp 50–80 °C (0.05 torr)) produced 0.46 g (83% yield) of the desired product **18**. VPC analysis ($^1/_4$ × 6 ft, SE-30, 100–175 °C) indicated the presence of only one peak. $[\alpha]^{25}_D$ +3.7° (*c* 6.13, $CHCl_3$). The enantiomeric excess was determined to be 5% of the *R* enantiomer on the basis of the maximum reported rotation[4] of $[\alpha]^{23}_D$ −75° (*c* 1.56, MeOH) for the *S* enantiomer.

2-Methyl-6-isopropylcyclohexanone (19). The imine (5.0 mmol, 1.22 g) from cyclohexanone and 2-amino-1-methoxy-3-phenylpropane in 5 mL of THF was added to 5.25 mmol of LDA at −20 °C in 5 mL of THF contained in a 50-mL flame-dried flask. The resulting solution was allowed to warm to 0 °C and stirred for 1 h before cooling to −78 °C. Methyl iodide (10 mmol) in 5 mL of THF was added dropwise and the solution allowed to warm to 0 °C. Another 6.0 mmol of LDA in 10 mL of THF was added to the reaction and the resulting solution heated to reflux for 45 min. The solution was then cooled to −78 °C and 2-iodopropane (7.0 mmol) in 5 mL of THF was added dropwise. The resulting soluton was allowed to slowly warm to room temperature and quenched with saturated NaCl. The organic layer was separated and the aqueous layer extracted three times with Et_2O. The organics were combined and washed twice with brine. The solvent was removed on a rotary evaporator and the residue hydrolyzed with NaOAc/HOAc/pentane buffer for 13 h. The organic layer was separated and the aqueous layer extracted with pentane. The organics were combined and washed with H_2O and dried over Na_2SO_4, and the solvent was removed on a rotary evaporator. Kugelrohr distillation of the residue (80–100 °C (0.05 mm)) gave 0.61 g (80% yield) of the desired product. VPC analysis (10% SE-30, 100–160 °C) indicated 3% of 2-isopropylcyclohexanone and 97% of 2-methyl-6-isopropylcyclohexanone. ^1H NMR ($CDCl_3$) δ 1.4–2.5 (8 H, overlapping signals), 0.6–1.3 (10 H, doublet at δ 1.0, *J* = Hz, doublet of doublets at δ 0.9, *J* = 4 Hz); $[\alpha]^{25}_D$ +21.96° (*c* 4.69, $CHCl_3$).

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Supplementary Material Available: The spectra for the ^{13}C NMR determination of enantiomeric excess of acetals 9 (12 pages). Ordering information is given on any current masthead page.

(25) ^{13}C NMR spectra of **17**, a mixture of **17** and **20** after heating, and deuterated compounds, as well as ^{13}C NMR spectra for actals **9**, are included as supplementary material.