Synthesis, Regioselective Deprotonation, and Stereoselective Alkylation of Fluoro Ketimines

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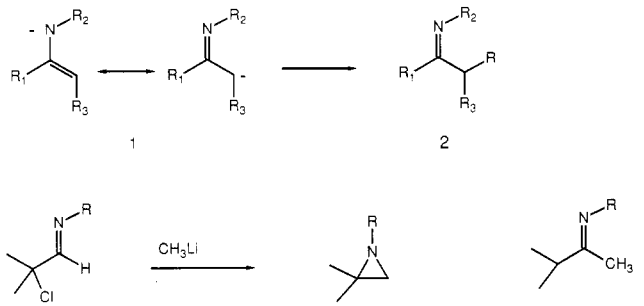
Received August 3, 1987

Fluoroacetone imines of cyclohexylamine, valinol *O*-methyl ether, and phenylalaninol *O*-methyl ether and 2-fluorocyclohexanone imines of cyclohexylamine and phenylalaninol *O*-methyl ether were prepared. The temperature-dependent, regioselective deprotonation of these imines was employed in highly regioselective alkylation reactions. The deprotonation of fluoroacetone cyclohexylimine on the carbon bearing fluorine yielded only a single stereoisomer as determined by low temperature ^{19}F NMR. In contrast, deprotonation of fluoroacetone *O*-benzyloximes was not regiospecific under any of the conditions examined.

Deprotonated imines[1] and the related reagents deprotonated hydrazones,[2] oximes, oxime ethers,[3] and isoxazolines[4] are important reactants for the formation of new carbon–carbon bonds via alkylation or addition to carbonyl groups.[1]

Deprotonated imines 1 may be alkylated with primary or secondary halides or with epoxides or may be condensed with aldehydes or ketones to form aldolates or α,β-unsaturated carbonyl compounds.[5] They have also been employed in the syntheses of β-sinensals,[6] nuciferal,[7] and Δ^2-tetrahydropyridines.[8] α-Halo ketimines show markedly different reactivity from the α-halo ketones[9] from which they are derived. α-Chloro aldimines may form aziridines or may undergo addition reactions.[9]



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α-Fluorinated imines are postulated as intermediates in the reaction of several suicide enzyme inhibitors;[10] however, very little is known about their chemistry. NMR studies of the pyridoxal 5′-phosphate imine of fluoroaspartic acid derivatives have been reported.[11] It was only very recently that the imines of 2′-fluoroacetophenone[12] and fluoroacetone[13] have been described.

The selective reaction of inexpensive, readily available compounds such as fluoroacetone, is the cornerstone of our approach to the preparation of complex fluorinated molecules. In order to utilize deprotonated asymmetric, fluorinated imines as synthons, it was necessary to develop a high yield method for α-fluoro ketimine formation and to develop methods for regioselective deprotonation of the fluorinated ketimine.

Results and Discussion

Synthesis of Fluoro Ketimines. Fluoroacetone, prepared in 10–15% yield from bromoacetone,[14] failed to form fluoroacetone cyclohexylimine by simple azeotropic distillation of water. However, dropwise addition of fluoroacetone in carbon tetrachloride (CCl_4) to a CCl_4 solution of cyclohexylamine in the presence of activated 4A molecular sieves at 0 °C yielded the desired fluoro imine 4.

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This method was highly successful with 2-fluorocyclohexanone and cyclohexylamine but failed with bulky amines such as *tert*-butylamine or with slightly more encumbered α-fluoro carbonyl compounds such as 2′-fluoroacetophenone.

Surprisingly, the condensation of cyclohexylamine with fluoroacetone yielded a single isomer about the carbon–nitrogen double bond as judged by ^{19}F, ^{13}C, and ^1H NMR. *E* stereochemistry was assigned on the basis of ^1H NMR NOE measurements. Irradiation of the methine resonance of the cyclohexyl group resulted in a 4–6% enhancement of the methyl signal. 2-Fluorocyclohexanone similarly

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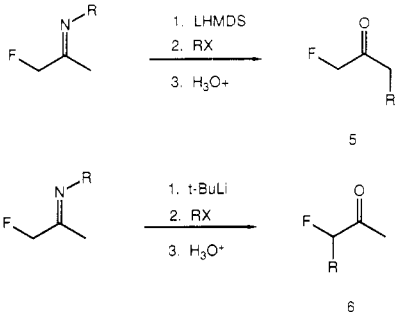
Table I. Regioselective Alkylation of Fluoroacetone Cyclohexylimine



alkyl halide	temp, °C	base[a]	product composition[a] 6	5	yield,[c] %
CH_3I	−30	A	11	89	48[d]
CH_3I	−80	B	96	4	43[d]
CH_2=$CHCH_2Br$	−30	A	9	91	62
CH_2=$CHCH_2Br$	−80	B	97	3	69
$CH_3CH_2CH_2CH_2I$	−30	A	3	97	30
$CH_3CH_2CH_2CH_2I$	−80	B	97	3	64
$C_6H_5CH_2Br$	−30	A	30	70	71
$C_6H_5CH_2Br$	−80	B	97	3	81
(*E*)-C_6H_5CH=$CHCH_2Br$	−30	A	7	93	88
(*E*)-C_6H_5CH=$CHCH_2Br$	−80	B	94	6	73

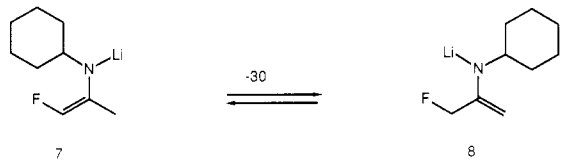
[a] A = LHMDS, B = *tert*-butyllithium. [b] Product composition determined by GC and integration of ^{19}F signals. [c] Isolated, purified yield. [d] Crude yield.

formed only a single C=N isomer **9**.

Regioselective Deprotonation and Alkylation of α-Fluoro Ketimines. The deprotonation and alkylation of the cyclohexylimine of fluoroacetone can be achieved regioselectively and this regioselectivity appears to be temperature dependent. Slow addition of the fluoro ketimine to lithium hexamethyldisilazide (LHMDS) in THF containing hexamethylphosphoramide (HMPA) at −30 °C followed by addition of an alkyl halide resulted in regioselective alkylation of the methyl group. In contrast, dropwise addition of *tert*-butyllithium to a THF solution of the fluoroimine at −80 °C followed by addition of an alkyl halide led to regioselective alkylation of the fluoromethyl group (Table I).[13]

Selective deprotonation of the fluoromethyl group at low temperature may result from the increased acidity of the fluoromethyl protons acting in concert with the steric interactions of the *N*-alkyl substituent with *tert*-butyllithium. Deprotonation of the carbon anti to the *N*-alkyl substituent has been reported in the deprotonation of dialkyl ketimines.[1]

Alkylation of the methyl group syn to the *N*-cyclohexyl group at higher temperature is not as easily rationalized. Methyl deprotonation at higher temperature is not due to isomerization of imine anion **7**. In a control experiment, the imine anion **7** was formed at −85 °C with *tert*-butyllithium, and an aliquot of the solution was allowed to react with an alkyl halide. The remainder of the imine anion



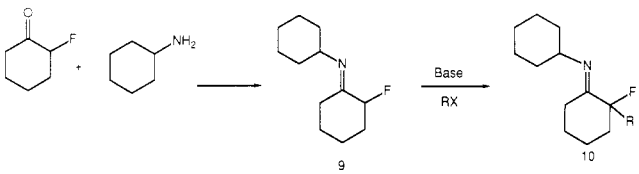
was warmed to −30 °C for 2 h and then was treated with the same alkyl halide. There was no evidence for isomerization of the deprotonated imine; however, considerable decomposition did occur. The high yield of **5** at higher temperatures argues against self-destruction of anion **7** and the preservation of anion **8** to account for the observed regioselectivity.

Table II. Regioselective Alkylation of Fluoroacetone *O*-Benzyloxime

alkyl halide	temp, °C	base	product composition[a] 13	14
CH_3I	−78	BuLi	1.5	1.0
CH_3I	−78	LDA	1.6	1.0
CH_2=$CHCH_2Br$	−100	LDA	1.6	1.00
CH_3I	−78	*t*-BuLi	1.6	1.0

[a] Determined by ^{19}F NMR spectroscopy.

Finally, the alkylation of 2-fluorocyclohexanone cyclohexylimine (**9**), whose structure was confirmed by 2D NOE experiments, with iodomethane, iodobutane, and benzyl bromide was performed. The ^{19}F NMR spectra of the alkylated ketimines **10** revealed a single resonance, possible only with excellent regioselectivity on deprotonation and alkylation.



Comparable regioselective deprotonation of α-fluoro ketone oxime ethers was not observed. The required oxime ethers were prepared by condensation of *O*-benzylhydroxylamine, prepared in two steps from *N*-hydroxyphthalimide and benzyl bromide with fluoroacetone forming the *E* and *Z* oxime ethers **11** and **12**, in a ratio of 1.6:1.0, in 70% yield.

Varying the temperature of deprotonation or changing the base had little effect on the ratio of regioisomeric products that were formed (Table II), suggesting that fluorination has no effect on the regioselectivity of deprotonation. Apparently under these conditions, the carbon syn[15] to the oxygen is deprotonated, while the carbon anti is not.

Enantioselective Alkylation of Stereogenic α-Fluoro Imines. (*S*)-Valinol *O*-methyl ether (**15**) and (*S*)-phenylalaninol *O*-methyl ether (**16**), derived from their corresponding α-amino acids, have previously been employed in highly efficient asymmetric syntheses.[16] These chiral amines were condensed with fluoroacetone by the

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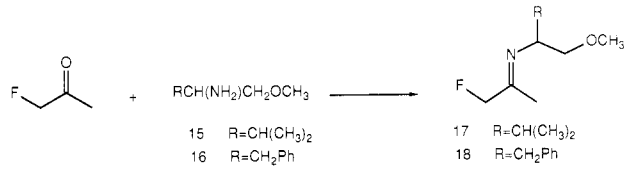
Table III. Alkylation of Chiral Fluoroketone Imine Anions

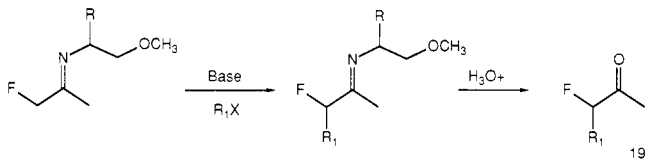
alkyl halide	amine	parent ketone	yield,[a] g		de,[b] %	
			method A	method B	method A	method B
CH_3I	ph[c]	fluoroacetone	26[d]	39[d]	58	64
$CH_2{=}CHCH_2Br$	ph	fluoroacetone	58	64	34	32
$C_6H_5CH_2Br$	ph	fluoroacetone	52	52	35	55
$CH_3CH_2CH_2CH_2I$	ph	fluoroacetone	64[d]	50[d]	26	11
$CH{\equiv}CCH_2Br$	ph	fluoroacetone		10[d]		40
$CH_2{=}CHCH_2Br$	va[e]	fluoroacetone	60		37	
$C_6H_5CH_2Br$	va	fluoroacetone	64		32	
$CH_3CH_2CH_2CH_2I$	va	fluoroacetone	58		33	
$CH{\equiv}CCH_2Br$	va	fluoroacetone	36[d]		46	
CH_3I	ph	fluorocyclohexanone	81	68	65	67
$C_6H_5CH_2Br$	ph	fluorocyclohexanone	62	74	38	33
$CH_3CH_2CH_2CH_2I$	ph	fluorocyclohexanone	40	77	33	58

[a] Method A: THF solvent. Method B: THF solvent, 1 equiv of 1,3-dimethyl-3,4,5,6-tetrahydropyrimidone added before deprotonation. [b] Determined by ^{19}F NMR spectroscopy. [c] (*S*)-phenylalaninol *O*-methyl ether. [d] Crude yield of alkylated imine. [e] (*S*)-Valinol *O*-methyl ether.

previously described method. Inspection of ^1H, ^{19}F, and ^{13}C NMR revealed that a single isomeric ketimine was formed. Comparison of ^{13}C shifts for the methyl carbon of the stereogenic imines **17** and **18** with the methyl ^{13}C shift for fluoroacetone cyclohexylimine suggested these fluoro ketimines also had *E* stereochemistry.

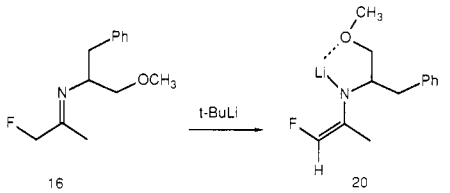


Deprotonation of ketimines **17** and **18** at temperatures between −85 and −90 °C was effected by the dropwise addition of *tert*-butyllithium to a THF solution of the imine. The regiochemical control of deprotonation was excellent. Upon hydrolysis of the alkylated imine, only the 3-fluoro ketones **19** could be detected by ^{19}F NMR.

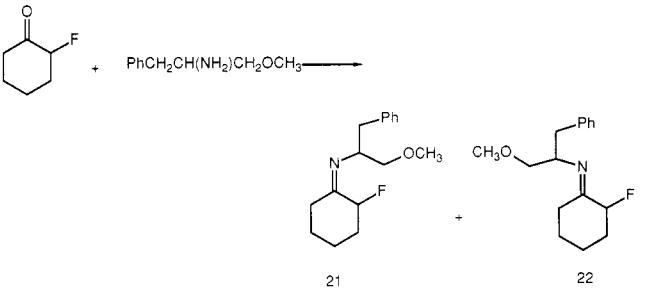


Alkylated ketimines were analyzed by ^{19}F NMR spectroscopy to determine the diastereoselectivity of the alkylation (Table III). Even though the yields of isolated ketones continued to be good, the transfer of asymmetry was only fair and was independent of the chiral auxiliary employed.

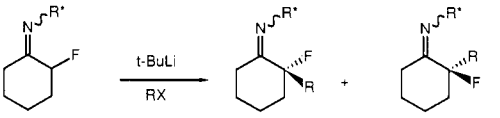
Our failure to observe better asymmetric induction in the alkylation of the deprotonated stereogenic α-fluoro imines was not due to an inability to control the geometry of the azaallylic carbon–carbon double bond. Direct observation of the ^{19}F spectrum of the aza enolate **20** indicated that only one isomer was formed to the limits of detection by NMR. The geminal J_{H-F} coupling constant for the anion is 80 Hz, suggesting that the carbon bearing fluorine retained considerable sp^2 character.



The imine prepared from phenylalaninol *O*-methyl ether and 2-fluorocyclohexanone was synthesized to learn more about the factors that control asymmetric induction. Interestingly, the condensation of the *O*-methylphenylalaninol with 2-fluorocyclohexanone gave rise to two C=N stereoisomers, **21** and **22**, in equal amounts as determined by NMR analysis. Regioselective deprotonation of **21** and



22 at −90 °C with *tert*-butyllithium of the fluorine-substituted carbon occurred irrespective of the carbon–nitrogen double bond geometry. Alkylation of this anion with iodomethane, iodobutane, and benzyl bromide occurred with only a modest improvement in asymmetric induction relative to the alkylation of fluoroacetone imines (Table III).



Reliability of Diastereomeric Excess Determination Using ^{19}F NMR Spectroscopy. Previously integration of diastereomeric proton resonances formed on alkylation of chiral aldimines has been employed for the determination of optical activity.[17] The ^{19}F NMR spectrum of alkylated fluoroacetone and 2-fluorocyclohexanone ketimines consistently displayed a resonance attributed to the major diastereomer at lower field than the resonance attributed to the minor isomer. Integration of these widely separated resonances was used to determine the optical purity of the alkylated ketimine products. To determine the reliability of this approach, the benzylated ketimine of fluoroacetone *O*-methylphenylalaninol imine was carefully hydrolyzed in a buffered acetic acid solution to yield ketone **23**. The optical purity was then determined to be 35% by ^1H NMR spectroscopy, employing tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphonato]europium(III), in good agreement with the value determined by the ^{19}F NMR method.

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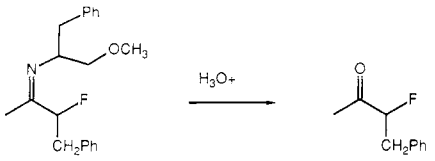

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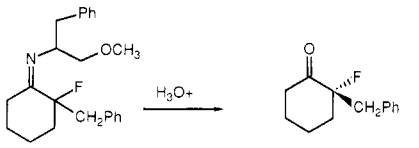
Similarly the product of benzylation of the *O*-methylphenylalaninol imine of 2-fluorocyclohexanone was studied. Twice recrystallized 2-benzyl-2-fluorocyclohexanone (**24**) was subjected to analysis with the chiral shift reagent, indicating synthesis in 34% enantiomeric excess, in agreement with the value obtained by integration of the diastereomeric fluorine resonances of the crude benzylated cyclohexanone imine barring accidental resolution of the enantiomeric mixture of **24**.



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The fluoro ketone **24**, $[\alpha]^{25}_{D}$ +9.6° (*c* 5, ethanol), showed a strong positive curve when the circular dichroism spectrum was determined, as does the nonfluorinated 2-benzylcyclohexanone. If it is assumed that fluorine has little effect on the sign of the CD curve,[18] the product is predicted to have the same absolute configuration as found in the nonfluorinated examples of Meyers,[16] which in this case would be the *S* configuration. Presumably, the chiral auxiliary directed the approach of the electrophile in the same manner for each alkylating agent.

Solvent Effects. The addition of *N,N'*-dimethylpropyleneurea (DMPU) before deprotonation of the ketimine usually enhanced the yield of alkylation product but did not have a significant effect on the asymmetric induction on alkylation.

Conclusion

General methods for the formation of α-fluoro imines and oxime ethers have been developed. Exclusive formation of the *E* C=N isomer for fluoroacetone imines has been confirmed by ^{1}H NMR NOE experiments. In contrast, the condensation of primary amines with 2-fluorocyclohexanone leads to formation of equal amounts of *E* and *Z* isomers. Likewise, the condensation of fluoroacetone with amino ethers lead to mixtures of *E* and *Z* fluoroacetone oxime ethers.

It has been demonstrated that fluoroacetone cyclohexylimine may be regioselectively deprotonated and alkylated at either the methyl or fluoromethyl position in moderate to good yield. Whereupon, asymmetric alkylation of stereogenic fluoroacetone and 2-fluorocylohexanone imine anions resulted in the formation of optically enriched 3-fluoroalkanones and 2-fluoro-2-alkylcyclohexanones in modest to good enantiomeric excess. The extent of asymmetric induction was influenced by solvent and alkylating agent. The best transfer of chirality was observed with small alkylating agents. The addition of DMPU, to dissociate any lithium aggregates which may be present, had only a modest effect on the degree of asymmetric induction but did improve the yield of alkylation products in most cases.

The direct observation of a single imine anion in the low-temperature ^{19}F NMR spectrum demonstrated that the ketimine may be selectively deprotonated. The vicinal J_{H-F} coupling constant for this anion was 80 Hz, indicating the fluorination is not having a significant effect on the planar geometry of the anion.

Because the aza enolate is formed stereoselectively the modest enantioselectivity is difficult to rationalize. However, lack of stereoselectivity may be due to electron donation of the C=C π system to the fourth unoccupied coordination site of the lithium atom.[19] Other explanations which may not be ruled out are possible metal–fluorine bridging in the aza enolate, reducing the percent of syn aza enolate, or that the percent of syn aza enolate is lowered because fluorine substitution is reducing the nitrogen lone pair–C=C π system repulsion by inductively lowering the electron density at the carbon terminus.

Direct observation of diastereomeric fluorine signals due to the presence of the chiral auxiliary was proved to be a viable method to determine the extent of asymmetric induction. Two examples of the hydrolyzed ketimines gave nearly the same enantiomeric excess when either a chiral shift reagent was used with the ketones or when the ^{19}F NMR of the diastereomeric ketimines was compared.

Experimental Section

General. Melting points were determined in open capillaries by using either a Mel-Temp or Buchi 510 melting point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 283 or 710B spectrometer. Proton nuclear magnetic resonance (^{1}H) spectra were determined on either a Varian EM-360A or Varian XL-300 NMR spectrometer. Solvents used were carbon tetrachloride (CCl_4), deuteriochloroform ($CDCl_3$), or deuterium oxide (D_2O). Chemical shifts are reported in parts per million (ppm; w values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, integration, and assignment. Carbon-13 nuclear magnetic resonance (^{13}C) spectra were recorded at 22.63 MHz on a Bruker WH-90D NMR spectrometer or at 75.429 MHz on a Varian XL-300 NMR spectrometer using $CDCl_3$ or D_2O as lock solvents. Chemical shifts are reported in ppm downfield from internal TMS. Fluorine-19 nuclear magnetic resonance (^{19}F) spectra were recorded at 282.203 MHz in $CDCl_3$ as lock solvent or in tetrahydrofuran (THF) with perdeuteriobenzene as a lock solvent. Chemical shifts are reported in ppm upfield from external fluorotrichloromethane. Optical rotations were recorded on a Pepol 60 polarimeter at the sodium D line. Circular dichroism spectra were recorded on a Cary 61 CD spectrometer scanning from 350 to 250 nm. Mass spectra were measured on an AEI MS-902B mass spectrometer. Analytical gas–liquid chromatography was carried out on a Perkin-Elmer 900 gas chromatograph equipped with a 50 m × 0.25 mm OV-101 fused silica capillary column and flame ionization detector. Preparative gas–liquid chromatography was carried out on an Aerograph A90P gas chromatograph equipped with a 6 ft × 0.25 in. column packed with 20% SE-30 on Chromosorb W. Thin-layer chromatography (TLC) was performed with silica gel F_{254} (Merck) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silica gel 60, 70–230 or 230–400 mesh (E. Merck). Flash chromatography refers to the method of Still. Combustion analyses were performed by either Galbraith Laboratories (Knoxville, TN) or by Mic-Anal (Tucson, AZ).

Methanol and hexanes were dried by distillation from calcium hydride. Acetone was dried by distillation from anhydrous potassium carbonate. Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Hexamethyldisilazane (HMDS), 1,3-dimethyl-3,4,5,6-tetrahydropyrimidone (DMPU),

(18) Cherbuliez, E.; Picciotto, A.; Rabinowitz, J. *Helv. Chim. Acta* **1960**, *43*, 1143.

(19) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462–468.

and hexamethylphosphoric triamide (HMPA) were purified by fractional distillation from calcium hydride. Cyclohexylamine and *tert*-butylamine were also distilled under a nitrogen atmosphere from calcium hydride before use.

A buffered acetic solution,[16a] prepared with 3.30 g of sodium acetate, 7.5 mL of glacial acetic acid, and 35 mL of distilled water, was used for hydrolyzing enolizable chiral α-fluoro ketimines. Determination of the enantiomeric excess by the use of tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphonato]europium(III) as the chiral shift reagent was accomplished by first purifying the ketone by preparative GC or by recrystallization. The purified ketone, 3–6 mg, was diluted with 1 mL of $CDCl_3$, whereupon 100-mL increments of a standard solution of 4.6 mmol/mL of chiral shift reagent was added. After the addition of 40–46 mol % of the chiral shift reagent the diastereomeric protons were resolved and were integrated.

1-Fluoro-2-propanone (3).[18] To 250 mL of anhydrous ethylene glycol and 168 g (3.0 mol) of anhydrous potassium fluoride in a mechanically stirred 1-L flask fitted with a distillation head and a pressure-equalizing addition funnel was added dropwise at 160 °C 102 g (0.75 mol) of 1-bromo-2-propanone.[14] The crude 1-fluoro-2-propanone distilled from the reaction over a 70–120 °C boiling point range. The crude distillate was dried over anhydrous potassium carbonate and then was fractionally distilled to yield 9.00 g (20%) of fluoroacetone (**3**): bp 75–77 °C (lit.[18] bp 77 °C); ^{1}H NMR (CCl_4) δ 4.52 (d, $J_{H,F}$ = 49 Hz, 2 H, CH_2F), 2.21 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 203.50 (d, $J_{C,F}$ = 18 Hz, C=O), 84.10 (d, $J_{C,F}$ = 181 Hz, CH_2F), 23.84 (s, CH_3); ^{19}F NMR ($CDCl_3$) δ −223.5 (t, $J_{H,F}$ = 48 Hz).

Fluoroacetone Cyclohexylimine (4). To a 100-mL flask were added 7.92 g (0.08 mol) of freshly distilled cyclohexylamine, 30 mL of CCl_4, and 1 g of anhydrous magnesium sulfate. On cooling to 0 °C, 5.78 g (0.08 mol) of **3**, dissolved in 10 mL of CCl_4, was added dropwise. After warming to room temperature over 2 h, the contents were stirred an additional 12 h. Filtration, followed by removal of the solvent in vacuo and bulb-to-bulb distillation, 90–110 °C (1.5 mm), yielded 11.2 g (90%) of the α-fluoro imine: IR (neat) ν 2950 (s), 2875 (m), 1680 (m), 1460 (m), 1380 (m), 1240 (w), 1015 (s) cm^{-1}; ^{1}H NMR (CCl_4) δ 4.52 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 3.41–3.10 (m, 1 H, NCH), 1.85 (d, $J_{H,F}$ = 3 Hz, 3 H, CH_3), 1.70–1.00 (m, 10 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 163.0 (d, $J_{C,F}$ = 20 Hz, C=N), 86.35 (d, $J_{C,F}$ = 178 Hz, CH_2F), 58.53 (NCH), 32.69 (CH_2), 25.08 (CH_2), 24.42 (CH_2), 12.78 (CH_3); ^{19}F NMR ($CDCl_3$) δ −223.6 ($J_{H,F}$ = 48 Hz). Anal. Calcd for $C_9H_{16}NF$: C, 68.75; H, 10.26. Found: C, 68.46; H, 10.46.

General Procedure for the Formation of 1-Fluoro-2-alkanones. To a magnetically stirred 50-mL three-necked flask containing lithium hexamethyldisilazide (LHMDS), prepared by the dropwise addition of 4.2 mL (0.007 mol) of methyllithium (1.6 M in ether) to 0.97 g (0.006 mol) of HMDS in 25 mL of THF at 0 °C, was added 1.07 g (0.006 mol) of HMPA followed by dropwise addition at −35 °C of 0.79 g (0.005 mol) of **4** in 10 mL of THF. After a half an hour, 0.005 mol of the alkyl halide in 5 mL of THF was added dropwise. After stirring another hour, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with distilled hexanes (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. The crude imine, dissolved in 20 mL of pentane, was hydrolyzed by treatment with 10 mL of 5% acetic acid solution for 2 h. The phases were separated, and the organic phase was washed with saturated sodium bicarbonate solution (2 × 10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed to yield the crude fluoro ketones (see Table I).

1-Fluoro-2-butanone was prepared by the addition of iodomethane (0.71 g, 0.005 mol) to **4** deprotonated with LHMDS. The reaction was worked up in the usual manner except that fluorotrichloromethane was used as solvent during the imine hydrolysis. The ketone was purified by preparative GC to yield 0.22 g (48%) of 1-fluoro-2-butanone: ^{1}H NMR (CCl_4) δ 4.68 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 2.61 (dq, $J_{H,F}$ = 5 Hz, J = 7 Hz, CH_2O), 1.20 (q, J = 7 Hz, CH_3), ^{13}C NMR ($CDCl_3$) δ 84.5 (d, $J_{C,F}$ = 178 Hz, CH_2F), 31.0, (CH_2), 13.6 (CH_3); ^{19}F NMR ($CDCl_3$) δ −228.3 (t, $J_{H,F}$ = 48 Hz).

1-Fluorohex-5-en-2-one was prepared by the addition of allyl bromide (0.61 g, 0.005 mol) to **4** deprotonated with LHMDS to yield, following isolation as described, 0.35 g (60%) of 1-fluorohex-5-en-2-one: IR (neat) ν 3100 (w), 2960 (m), 1725 (s), 1640 (w), 1385 (m), 1000 (m), 720 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 5.70–5.15 (m, 1 H, CH=CH_2), 5.05–4.45 (m, 2 H, CH=CH_2), 4.54 (d, $J_{H,F}$ = 47 Hz, 2 H, CH_2F), 3.00–2.51 (m, 2 H, CH_2CH=CH_2) 2.51 (dt, $J_{H,F}$ = 5 Hz, J = 6 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 206.3 (d, $J_{C,F}$ = 19 Hz, C=O), 131.1 (CH=CH_2), 119.0 (CH=CH_2), 85.0 (d, $J_{C,F}$ = 185 Hz, CH_2F), 37.6 (CH_2), 26.6 (CH_2); ^{19}F NMR ($CDCl_3$) δ −228.3 (t, $J_{H,F}$ = 48 Hz). Anal. Calcd for C_6H_9FO: C, 62.05; H, 7.81. Found: C, 62.16; H, 7.84.

1-Fluoro-2-heptanone was prepared by the addition of 1-iodobutane (0.92 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.20 g (30%) of 1-fluoro-2-heptanone. A sample for analysis was purified by preparative GC: IR (neat) ν 2960 (s), 2930 (m), 1725 (s), 1050 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 4.46 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 2.50 (d, $J_{H,F}$ = 3 Hz, CH_2CO), 1.63–1.56 (m, 2 H, CH_2), 1.35–1.22 (m, 4 H, CH_2CH_2), 0.87 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 84.9 (d, $J_{C,F}$ = 185 Hz, CH_2F), 31.2 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 13.8 (CH_3); ^{19}F NMR ($CDCl_3$) δ −227.9 (t, $J_{H,F}$ = 49 Hz). Anal. Calcd for $C_7H_{13}FO$: C, 63.61; H, 9.91. Found: C, 63.48; H, 9.97.

1-Fluoro-4-phenyl-2-butanone was prepared by the addition of benzyl bromide (0.86 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.58 g (70%) of 1-fluoro-4-phenyl-2-butanone. A sample for analysis was purified by preparative GC: IR (neat) ν 3150 (w), 3140 (w), 2950 (m), 1720 (s), 1600 (m), 1060 (s), 760 (s), 710 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 7.00 (br, 5 H, C_6H_5), 4.51 (d, $J_{H,F}$ = 49 Hz, 2 H, CH_2F), 2.82–2.50 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 134.0 (C-ipso), 129.3 (C-ortho), 128.3 (C-meta), 128.1 (C-para), 84.8 (d, $J_{C,F}$ = 184 Hz, CH_2F), 39.6 ($CH_2C_6H_5$), 26.4 (CH_2); ^{19}F NMR ($CDCl_3$) δ −227.7 (t, $J_{H,F}$ = 49 Hz). Anal. Calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 72.00; H, 6.49.

(*E*)-1-Fluoro-6-phenylhex-5-en-2-one was prepared by the addition of cinnamyl bromide (0.99 g, 0.005 mol) to **4** deprotonated with LHMDS. Workup in the normal manner yielded 0.84 g (88%) of (*E*)-1-fluoro-6-phenylhex-5-en-2-one. A sample for analysis was purified by preparative GC: IR (neat) ν 3140 (m), 3020 (m), 2950 (s), 1720 (s), 1600 (m), 1460 (w), 1340 (w), 1040 (m), 760 (s), 710 (m) cm^{-1}; ^{1}H NMR (CCl_4) δ 6.99 (br, 5 H, C_6H_5), 6.30-5.75 (m, 2 H, CH=CH), 4.48 (d, $J_{H,F}$ = 46 Hz, CH_2F), 2.80–2.15 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 205.9 (d, $J_{C,F}$ = 19 Hz, C=O), 136.9 (C-ipso), 131.1 (CH=CHC_6H_5), 128.4 (C-ortho), 127.3 (C-meta), 127.1 (C-ortho), 125.9 (CH=CHC_6H_5), 84.9 (d, $J_{C,F}$ = 184 Hz, CH_2F), 37.8 (CH_2CH=CHC_6H_5), 26.0 (CH_2); ^{19}F NMR ($CDCl_3$) δ −227.7 (t, $J_{H,F}$ = 49 Hz).

General Procedure for the Formation of 3-Fluoro-2-alkanones. To a magnetically stirred 50-mL three-necked flask under an inert atmosphere containing **4** (0.32 g, 0.002 mol) dissolved in 25 mL of dry THF was added dropwise at such a rate that the temperature did not exceed −80 °C 2.35 mL (0.004 mol) of *tert*-butyllithium (1.7 M in pentane). The solution was stirred at −85 °C for an additional 0.5 h, and then 0.002 mol of the alkyl halide dissolved in 5 mL of THF was added dropwise. After being stirred another hour, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with distilled hexanes (3 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. A pentane solution of the imine was hydrolyzed by treatment with 10 mL of 5% acetic acid solution for 2 h. Following separation, the organic phase was washed with saturated sodium bicarbonate solution (2 × 10 mL) until neutral and was dried over anhydrous magnesium sulfate and the solvent removed to yield the crude 3-fluoro ketone.

3-Fluoro-2-butanone[20] was prepared by the addition of iodomethane (1.14 g, 0.008 mol) to **4** deprotonated with *tert*-butyllithium and by being stirred for 0.5 h. On normal workup and hydrolysis in $CFCl_3$, 0.31 g (43%) of 3-fluoro-2-butanone was isolated: ^{1}H NMR (CCl_4) δ 4.78 (dq, $J_{H,F}$ = 49 Hz, J = 7 Hz, 1 H, CHF), 2.20 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3CO), 1.41 (dq, $J_{H,F}$ = 24 Hz, J = 7 Hz, 3 H, CH_3CF); ^{13}C NMR ($CDCl_3$) δ 208.5 (d, $J_{C,F}$

(20) Griesebaum, K.; Keul, H.; Kibar, R.; Pfeffer, S.; Sprawl, M. *Chem. Ber.* **1981**, *114*, 1858–1870.

= 25 Hz, C=O), 92.6 (d, $J_{C,F}$ = 181 Hz, CHF), 25.1 (d, $J_{C,F}$ = 3 Hz, CH_3CO), 17.4 (d, $J_{C,F}$ = 23 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −190.0 (dqq, $J_{H,F}$ = 49, 24, 4 Hz).

3-Fluorohex-5-en-2-one was prepared by the addition of allyl bromide (0.97 g, 0.008 mol) to 4 deprotonated with *tert*-butyllithium. Workup in the usual manner yielded 0.64 g (69%) of pure ketone: IR (neat) ν 3100 (w), 2965 (m), 1730 (s), 1645 (m), 1385 (m), 1260 (w), 1000 (s) cm^{-1}; ^1H NMR (CCl_4) δ 5.86–5.72 (m, 1 H, CH=CH_2), 5.25–5.01 (m, 2 H, CH=CH_2), 4.85 (dm, $J_{H,F}$ = 49 Hz, 1 H, CHF), 2.27 (m, 2 H, CH_2CF), 2.23 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 207.1 (d, $J_{C,F}$ = 25 Hz, C=O), 131.0 (d, $J_{C,F}$ = 3 Hz, CH=CH_2), 118.9 (CH=CH_2), 94.7 (d, $J_{C,F}$ = 186 Hz, CHF), 35.9 (d, $J_{C,F}$ = 20 Hz, CH_2), 25.8 (CH_3CO); ^{19}F NMR ($CDCl_3$) δ −189.9 (dt, $J_{H,F}$ = 49, 21 Hz). Anal. Calcd for C_6H_9FO: C, 62.05; H, 7.81. Found: C, 62.16; H, 7.84.

3-Fluoro-2-heptanone was prepared by the addition of 1-iodobutane (0.37 g, 0.002 mol) to 4 deprotonated with *tert*-butyllithium. Workup in the normal manner yielded 0.17 g (64%) of 3-fluoro-2-heptanone: IR (neat) ν 2955 (s), 2940 (m), 2860 (m), 1720 (s), 1460 (m), 1080 (m) cm^{-1}; ^1H NMR (CCl_4) δ 4.72 (ddd, $J_{H,F}$ = 49 Hz, J = 7, 4 Hz, 1 H, CHF), 2.25 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3), 1.85–1.73 (m, 2 H, CH_2), 1.46–1.29 (m, 4 H, CH_2CH_2), 0.91 (t, J = 6 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 208.3 (d, $J_{C,F}$ = 26 Hz, C=O), 95.9 (d, $J_{C,F}$ = 183 Hz, CHF), 31.5 (d, $J_{C,F}$ = 21 Hz, CH_2), 25.8 (CH_2), 22.2 (CH_2), 13.7 (CH_2); ^{19}F NMR ($CDCl_3$) δ −190.0 (dt, $J_{H,F}$ = 49, 24 Hz).

3-Fluoro-4-phenyl-2-butanone was prepared by the addition of benzyl bromide (0.34 g, 0.002 mol) to 4 deprotonated with *tert*-butyllithium. Workup in the normal manner yielded 0.25 g (75%) of 3-fluoro-4-phenyl-2-butanone, which was purified by column chromatography on 10 g of silica gel (ether/pentane, 1:9): IR (neat) ν 3080 (m), 3040 (m), 2940 (m), 2860 (m), 1728 (s), 1601 (w), 1500 (m), 1460 (m), 1035 (s), 710 (m) cm^{-1}; ^1H NMR (CCl_4) δ 7.35–7.20 (m, 5 H, C_6H_5), 4.84 (ddd, $J_{H,F}$ = 49 Hz, J = 8, 4 Hz, 1 H, CHF), 3.20–2.90 (m, 2 H, CH_2), 2.04 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 207.0 (d, $J_{C,F}$ = 20 Hz, C=O), 135.0 (C-ipso), 129.4 (C-ortho), 128.4 (C-meta), 126.9 (C-para), 95.6 (d, $J_{C,F}$ = 187 Hz, CHF), 38.0 (d, $J_{C,F}$ = 20 Hz, CH_2), 26.2 (CH_3CO); ^{19}F NMR ($CDCl_3$) δ −188.4 (dt, $J_{H,F}$ = 49 Hz, 24 Hz).

(*E*)-3-Fluoro-6-phenylhex-5-en-2-one was prepared by the addition of cinnamyl bromide (0.40 g, 0.002 mol) to 4 deprotonated with *tert*-butyllithium. Workup in the normal manner yielded 0.28 g (73%) of (*E*)-3-fluoro-6-phenylhex-5-en-2-one: IR (neat) ν 3050 (m), 3010 (m), 2980 (m), 1725 (s), 1610 (m), 1600 (w), 1420 (w), 1040 (s), 950 (s), 710 (m) cm^{-1}; ^1H NMR (CCl_4) δ 7.32–7.17 (m, 5 H, C_6H_5), 6.49–6.10 (m, 2 H, CH=CH), 4.76 (ddd, $J_{H,F}$ = 49 Hz, J = 7, 4 Hz, 1 H, CHF), 2.77–2.59 (m, 2 H, CH_2), 2.73 (d, $J_{H,F}$ = 5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 95.0 (d, $J_{C,F}$ = 187 Hz, CHF); ^{19}F NMR ($CDCl_3$) δ −189.3 (dt, $J_{H,F}$ = 49, 24 Hz).

2-Fluorocyclohexanol was prepared by the dropwise addition of 2.50 g, 0.025 mol) of cyclohexene oxide in 20 mL of methylene chloride to a stirred solution of 42% hydrogen fluoride in pyridine.[21] The mixture was stirred 2 h and then was poured over 10 g of ice. Upon separation, the aqueous phase was extracted with methylene chloride (2 × 10 mL). The combined organic phases were washed with 20 mL of water, 20 mL of a saturated sodium bicarbonate solution, and finally 20 mL of saturated copper(II) sulfate. After drying over anhydrous magnesium sulfate, fractional distillation yielded 1.94 g (66%) of 2-fluorocyclohexanol: bp 70–75 °C (15 mm) (lit.[21] mp 161 °C); mp 40–41 °C; IR (neat) ν 3370 (s), 2920 (s), 2840 (s), 1460 (s), 1380 (m), 1080 (s), 1040 (s), 925 (m), 860 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (ddt, $J_{H,F}$ = 51 Hz, J = 7, 3 Hz, 1 H, CHF), 3.57 (m, 1 H, C*H*OH), 3.05 (br, 1 H, OH), 2.10–1.90 (m, 2 H, CH_2), 1.75–1.60 (m, 2 H, CH_2), 1.48–1.10 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 105.66 (d, $J_{C,F}$ = 173 Hz, CHF), 82.14 (d, $J_{C,F}$ = 18 Hz, CHOH), 40.79 (d, $J_{C,F}$ = 7 Hz, CH_2), 39.35 (d, $J_{C,F}$ = 17 Hz, CH_2), 32.56 (d, $J_{C,F}$ = 4 Hz, CH_2), 32.48 (d, $J_{C,F}$ = 4 Hz, CH_2); ^{19}F NMR ($CDCl_3$) δ −181.35 (dm, $J_{H,F}$ = 51 Hz).

2-Fluorocyclohexanone was prepared by the dropwise addition over 30 min of 8 mL (0.020 mol) of Jones' reagent to a stirred solution of 2-fluorocyclohexanol (2.4 g, 0.020 mol) in 10 mL of acetone at 0 °C.[22] The mixture was then allowed to stir overnight. The reaction mixture was extracted with hexanes (2 × 10 mL) and 10 mL of diethyl ether. The combined organic phases were washed with a saturated sodium bicarbonate solution (2 × 10 mL), followed by 10 mL of brine. The product was chromatographed on 20 g silica gel (hexane/diethyl ether). Fractional distillation yielded 1.82 g (77%) of 2-fluorocyclohexanone bp 100–110 °C (70 mm): IR (neat) ν 2920 (m), 2850 (m), 1720 (s), 1450 (m), 1110 (s), 1090 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (ddd, $J_{H,F}$ = 49 Hz, J = 12, 6 Hz, 1 H, CHF), 2.60–2.45 (m, 1 H, CH_2CO axial), 2.45–2.25 (m, 2 H, CH_2), 2.10–1.35 (m, 6 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 92.59 (d, $J_{C,F}$ = 191 Hz, CHF), 40.13 (CH_2), 34.10 (d, $J_{C,F}$ = 18 Hz, CH_2CHF), 26.80 (CH_2), 22.64 (d, $J_{C,F}$ = 10 Hz, CH_2); ^{19}F NMR ($CDCl_3$) δ −188.18 (ddd, $J_{H,F}$ = 49, 12, 6 Hz); MS (70 eV), m/z 116 (16), 75 (24), 73 (25), 55 (100).

2-Fluorocyclohexanone Cyclohexylimine (9). To a 25-mL flask containing cyclohexylamine (0.51 g, 0.0052 mol), 10 mL of CCl_4, and 2 g of activated 4 A molecular sieves was added dropwise at 0 °C 2-fluorocyclohexanone (0.60 g, 0.0052 mol) dissolved in 5 mL of CCl_4. After being stirred for 12 h, the reaction mixture was filtered, and the solvent was removed in vacuo. Bulb-to-bulb distillation at 105–110 °C (0.75 mm) yielded 1.00 g (98%) of **9**: IR (neat) ν 2980 (s), 2920 (s), 1675 (s), 1460 (s), 1310 (m), 1200 (m), 1120 (m), 1000 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (ddd, $J_{H,F}$ = 50 Hz, J = 4, 2 Hz, 1 H, CHF), 3.37 (m, 1 H, NC*H*$(CH_2)_5$), 2.55 (dd, J = 5, 5 Hz, 1 H CH_2 axial), 2.51 (dd, J = 5, 5 Hz, 1 H CH_2 equatorial), 2.00–1.20 (m, 16 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 166.70 (d, $J_{C,F}$ = 19 Hz, C=N), 94.08 (d, $J_{C,F}$ = 174 Hz, CHF), 57.77 (NCH), 33.45 (CH_2), 33.29 (CH_2), 32.96 (d, $J_{C,F}$ = 24 Hz, CH_2CHF), 26.48 (CH_2), 25.61 (CH_2), 25.18 (CH_2), 24.42 (d, $J_{C,F}$ = 4 Hz, CH_2), 20.29 (d, $J_{C,F}$ = 2 Hz, CH_2); ^{19}F NMR ($CDCl_3$) δ −182.48 (ddd, $J_{H,F}$ = 50, 4, 2 Hz).

General Procedure for the Deprotonation/Alkylation of 2-Fluorocyclohexanone Imine (9). To a magnetically stirred 50-mL three-necked flask, under an inert atmosphere, was added **9** (0.49 g, 0.0025 mol) in 25 mL of dry THF. Upon cooling to −85 °C, 2.35 mL (0.004 mol) of *tert*-butyllithium (1.7 M in pentane) was added dropwise at such a rate that the temperature did not exceed −80 °C. The solution was stirred at −85 °C for 0.5 h, and then (0.002 mol) of the alkyl halide in 5 mL of THF was added dropwise. After being stirred for an hour, the reaction was quenched by pouring over 10 mL of a saturated sodium bicarbonate solution and extracting with distilled hexanes (3 × 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude imine in pentane was hydrolyzed by treatment with 10 mL of 5% acetic acid solution for 2 h. On separation, the organic phase was washed with a saturated sodium bicarbonate solution (2 × 10 mL) and was dried over anhydrous magnesium sulfate and the solvent removed to yield the crude 2-fluoro-2-alkylcyclohexanone.

2-Fluoro-2-methylcyclohexanone was prepared by the addition of iodomethane (0.36 g, 0.0025 mol) to the anion of **9**. Analysis of the crude alkylated imine by ^{19}F NMR showed a single resonance, δ −146.69 (m). Normal workup yielded 0.28 g (86%) of 2-fluoro-2-methylcyclohexanone: ^1H NMR ($CDCl_3$) δ 2.45–2.35 (m, 1 H, CHC=O), 2.12–2.04 (m, 1 H, CHC=O), 1.90–1.40 (m, 6 H, CH_2), 1.14 (d, $J_{H,F}$ = 21 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 96.68 (d, $J_{C,F}$ = 177 Hz, CF), 39.97 (d, $J_{C,F}$ = 23 Hz, CH_2), 39.02 (CH_2), 27.50 (CH_2), 21.60 (d, $J_{C,F}$ = 6 Hz, CH_2), 21.15 (d, $J_{C,F}$ = 25 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −150.85 (ddq, $J_{H,F}$ = 21, 12, 7 Hz).

2-Fluoro-2-butylcyclohexanone was prepared by the addition of 1-iodobutane (0.46 g, 0.0025 mol) to the anion of **9**. Analysis of the crude alkylated imine by ^{19}F NMR showed a single resonance, δ −154.14 (m). Normal workup yielded 0.24 g, (56%) of 2-fluoro-2-butylcyclohexanone: IR (neat) ν 2950 (s), 2860 (s), 1720 (s), 1460 (m), 1355 (m), 1120 (m), 905 (m), 725 cm^{-1}; ^1H NMR (CCl_4) δ 2.66–2.59 (m, 1 H, CH_2C=O), 2.43–2.32 (m, 1 H, CH_2C=O), 2.10–1.65 (m, 8 H, CH_2), 1.50–1.15 (m, 4 H, CH_2), 0.90 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 208.11 (d, $J_{C,F}$ = 21 Hz, C=O), 98.75 (d, $J_{C,F}$ = 184 Hz, CF), 39.54 (CH_2), 37.95 (d, $J_{C,F}$ = 22 Hz, CH_2), 34.25 (d, $J_{C,F}$ = 23 Hz, $CFCH_2$), 27.30 (CH_2), 24.46 (d, $J_{C,F}$ = 2 Hz, CH_2), 22.76 (CH_2), 22.00 (d, $J_{C,F}$ = 8 Hz, CH_2), 13.76 (CH_3); ^{19}F NMR ($CDCl_3$) δ −156.2(m); MS (70 eV),

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no parent, m/z 116 (100), 86 (28), 55 (40).

2-Fluoro-2-benzylcyclohexanone was prepared by the addition of benzyl bromide (0.43 g, 0.0025 mol) to the anion of **9**. Analysis of the crude alkylated imine by ^{19}F NMR showed a single resonance, δ −153.74 (m). Normal workup yielded 0.31 g (62%) of crude material, which was recrystallized from hexanes/ethanol (9:1): mp 110–111 °C; IR (KBr) ν 3040 (m), 3000 (s), 2900 (s), 2820 (m), 1715 (s), 1600 (m), 1590 (w), 1500 (m), 1460 (s), 1130 (s), 910 (m), 760 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (br, 5 H, C_6H_5), 3.16 (dd, $J_{H,F}$ = 20 Hz, J = 10 Hz, 1 H, CH_2), 3.10 (dd, $J_{H,F}$ = 20 Hz, J = 10 Hz, 1 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 207.49 (d, $J_{C,F}$ = 21 Hz, C=O), 134.50 (C-ipso), 130.46 (C-ortho), 128.18 (C-meta), 126.88 (C-para), 97.76 (d, $J_{C,F}$ = 184 Hz, CF), 39.76 (d, $J_{C,F}$ = 22 Hz, $CH_2C_6H_5$), 39.43 (CH_2), 36.91 (d, $J_{C,F}$ = 23 Hz, CH_2), 27.42 (CH_2), 21.42 (d, $J_{C,F}$ = 6 Hz, CH_2); ^{19}F NMR ($CDCl_3$) δ −155.7 (ddt, $J_{H,F}$ = 21, 14, 10 Hz). Anal. Calcd for $C_{13}H_{15}OF$: C, 75.70; H, 7.33. Found: C, 71.57; H, 6.71.

***N*-(Benzyloxy)phthalimide.**[23] To a 50-mL flask containing 1.96 g (0.012 mol) of *N*-hydroxyphthalimide and 2.05 g (0.012 mol) of benzyl bromide in 15 mL of acetonitrile was added 2.0 mL of triethylamine. The red solution was heated under reflux for 1 h while the red color discharged. The reaction was poured over 20 mL of distilled water and extracted with ether (3 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The off-white solid was recrystallized from methanol to yield 1.50 g (47%) of *N*-(benzyloxy)phthalimide: mp 132–134 °C (lit.[23] mp 141–142 °C); ^1H NMR ($CDCl_3$) δ 7.90 (br, 4 H, C_6H_4), 7.70–7.40 (br, 5 H, C_6H_5), 5.39 (s, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 134.39, 129.84, 129.32, 128.42, 123.45 (C-aryls), 79.84 (CH_2O).

Amino benzyl ether was prepared by the addition of anhydrous hydrazine (0.13 g, 0.004 mol) to 20 mL of anhydrous ethanol and 1.0 g (0.004 mol) of *N*-(benzyloxy)phthalimide at room temperature.[24] After heating under reflux for 4 h, the solution was cooled and made acid (ca. pH 1) with 4 drops of concentrated hydrochloric acid and then was partitioned between methylene chloride and water. The aqueous phase was made basic to litmus by the addition of 0.1 g of solid KOH and was extracted with ether (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to yield 0.48 g (98%) of amino benzyl ether: IR (neat) ν 3050 (s), 2940 (w), 1625 (m), 1040 (s), 740 (s), 700 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.20 (br, 5 H, C_6H_5), 4.75 (s, 2 H, CH_2), 3.90 (br, 2 H, NH_2).

Fluoroacetone *O*-Benzyloxime (11 and 12). To a 25-mL flask containing of amino benzyl ether (0.49 g, 0.004 mol) in 10 mL of CCl_4 and 1 g of activated 4A molecular sieves was added dropwise at 0 °C fluoroacetone (0.30 g, 0.004 mol) in 5 mL of CCl_4. After being stirred overnight at room temperature, the reaction was filtered and the solvent removed in vacuo. The crude product was distilled bulb to bulb, bp 70–80 °C (0.25 mm), to yield 0.60 g (83%) as a mixture of *E* and *Z* isomers **11** and **12**: IR (neat) ν 2940 (w), 2850 (w), 1700 (m), 1250 (m), 1000 (s) cm^{-1}; ^1H NMR (CCl_4) [*E* and *Z*] δ 7.05 (br, 10 H, C_6H_5), 4.95 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 4.74 (s, 2 H, $CH_2C_6H_5$), 4.50 (s, 2 H, $CH_2C_6H_5$), 4.45 (d, $J_{H,F}$ = 48 Hz, 2 H, CH_2F), 1.90–1.80 (m, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) [*E*] δ 153.02 (d, $J_{C,F}$ = 20 Hz, C=N), 128.15 (C-ortho) 127.80 (C-meta), 127.69 (C-para), 83.05 (d, $J_{C,F}$ = 167 Hz, CH_2F), 75.80 ($C_6H_5CH_2O$), 22.47 (CH_3), [*Z*] 156.02 (d, $J_{C,F}$ = 20 Hz, C=N), 12815 (C-ortho), 127.80 (C-meta), 127.69 (C-para), 78.70 (d, $J_{C,F}$ = 167 Hz, CH_2F), 74.96 ($C_6H_5CH_2O$), 31.40 (CH_3); ^{19}F NMR ($CDCl_3$) [*Z*] δ −223.09 (t, $J_{H,F}$ = 50 Hz), [*E*] −235.25 (t, $J_{H,F}$ = 50 Hz).

General Procedure for Deprotonation/Alkylation of Fluoroacetone *O*-Benzyloxime (11 and 12). To a stirred solution of **11** and **12** (0.36 g, 0.002 mol) in 10 mL of THF was added 1 equiv of base (e.g., LDA, *n*-butyllithium, or *tert*-butyllithium). While the solution was stirred at −78 °C, 0.28 g (0.002 mol) of iodomethane in 5 mL of THF was added. After being stirred for 1 h at −78 °C, the reaction was worked in the normal manner to yield 0.30 g (77%) of mixture of the 1- and 3-fluoroalkanone *O*-benzyloxime (**13** and **14**) in a ratio of 1.6:1.0.

(*S*)-(−)-2-Amino-1-hydroxy-3-phenylpropane. The procedure of Koga was modified.[25] (*S*)-Phenylalanine (18.2 g, 0.11 mol) suspended in 200 mL of anhydrous ethanol was cooled to 0 °C, and 20 mL (0.27 mol) of thionyl chloride was added dropwise over a 1-h period. After completion of the addition, the mixture was stirred for 2 h at 20 °C and then was heated under reflux for 2 h. Concentration of the reaction mixture in vacuo yielded a light green solid, which was elutriated with 200 mL of diethyl ether. The resultant white solid was dried overnight in vacuo to yield 23.5 g of the ethyl ester hydrochloride.

The ethyl ester hydrochloride (23.5 g, 0.11 mol) in 100 mL of 50% aqueous ethanol was added dropwise to 24.95 g (0.66 mol) of sodium borohydride in 200 mL of 50% aqueous ethanol at 0 °C. After the addition was complete, the reaction mixture was heated under reflux for 4 h and then allowed to cool. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to yield a white solid. The crude product was recrystallized once from ethyl acetate/hexanes (3:1) to yield 6.64 g (40%) of phenylalaninol: mp 89–90 °C (lit. mp 89–91 °C); $[\alpha]_D$ −24° (*c* 1.5, ethanol) (lit.[25] $[\alpha]_D$ −24.2°); IR (KBr) ν 3360 (w), 3300 (m), 1580 (s), 1495 (w), 1455 (w), 1340 (m), 1070 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.05 (br, 5 H, C_6H_5), 4.20 (br, 1 H, OH), 3.70–3.45 (m, 1 H, CH), 3.23 (m, 2 H, CH_2OH), 2.78 (m, 2 H, $CH_2C_6H_5$), 1.53 (s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 138.58 (C-ipso), 129.13 (C-ortho), 128.52 (C-meta), 126.35 (C-para), 66.08 (CH_2OH), 54.13 ($CHNH_2$), 40.64 ($CH_2C_6H_5$).

(*S*)-(−)-2-Amino-1-methoxy-3-phenylpropane (16). To a dry, 250-mL flask was added of potassium hydride (2.86 g, 0.025 mol, 35% oil dispersion). After washing with pentane, 50 mL of THF and 4.08 g (0.027 mol) of (*S*)-(−)-2-amino-1-hydroxy-3-phenylpropane dissolved in an additional 50 mL of THF were added. After the mixture was stirred overnight and cooled to 0 °C, iodomethane (3.55 g, 0.025 mol) in 10 mL of THF was added dropwise. The reaction was stirred for 1 min then was poured over 10 g of ice and extracted with hexanes (3 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The product was fractionally distilled to yield 3.20 g (78%) of **16**: bp 95–100 °C (15 mm): IR (neat) ν 3350 (s), 3250 (s), 3040 (w), 2925 (s), 1600 (s), 1500 (m), 1460 (m), 1100 (s), 740 (s), 700 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.10 (br, 5 H, C_6H_5), 3.43 (s, 3 H, CH_3), 3.45–3.20 (m, 1 H, $CHNH_2$), 2.80–2.60 (m, 2 H, CH_2OCH_3), 2.45–2.30 (m, 2 H, CH_2Ph), 1.50 (s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 138.58 (C-ipso), 129.13 (C-ortho), 128.52 (C-meta), 126.35 (C-para), 66.08 (CH_2OH), 54.13 ($CHNH_2$), 40.65 ($CH_2C_6H_5$).

(*S*)-2-Amino-3-methyl-1-butanol.[26] To a magnetically stirred 250-mL three-necked flask were added L-valine (20 g, 0.17 mol), 40 mL of THF, and boron trifluoride–etherate (21.0 g, 0.17 mol). The mixture was heated to 50 °C and 18.8 mL (0.18 mol) borane–methyl sulfide complex added dropwise over 2 h. After the mixture was heated under reflux for 18 h and then cooled to room temperature, 20 mL of methanol was added. The solvent was removed by distillation. The residual white syrup was cautiously treated with 100 mL of 6 N sodium hydroxide and was heated under reflux 4 h. After filtration through Celite, the mixture was extracted with methylene chloride (3 × 100 mL). The organic phase was dried over anhydrous potassium carbonate, and the solvent was removed in vacuo. The crude product distilled to yield 8.2 g (47%) of valinol: bp 62–65 °C (2.5 mm) [lit. bp 62–65 °C (2.5 mm)]; $[\alpha]_D$ +14° (*c* 5.0, ethanol); IR (neat) ν 3300 (s), 2950 (s) 2860 (s), 1590 (s), 1465 (m), 1385 (s), 1365 (m), 1020 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42–3.34 (m, 1 H, CH_2OH), 3.11–3.05 (m, 1 H, CH_2OH), 2.60 (br, 3 H, OH, NH_2), 1.40 (s, J = 7 Hz, 1 H, CH), 0.60 (d, J = 7 Hz, 3 H), 0.55 (d, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 63.91 (CH_2), 57.96 (CH), 30.43 (CH), 18.91 (CH_3), 17.94 (CH_3).

(*S*)-2-Amino-3-methyl-1-methoxybutane (15). To potassium hydride (4.46 g, 0.039 mol, 35% oil dispersion), washed with

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pentane, in a 250-mL flask were added 50 mL of THF and (*S*)-2-amino-3-methyl-1-butanol (4.02 g, 0.039 mol) dissolved in an additional 50 mL of THF. After the mixture was stirred overnight and cooled to 0 °C, iodomethane (5.54 g, 0.039 mol) in 10 mL of THF was added dropwise. The reaction was stirred for 1 min, then was poured over 10 g of ice, and extracted with hexanes (3 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the product was fractionally distilled to yield 1.61 g (35%) of **15**: bp 55–60 °C (30 mm); IR (neat) ν 2950 (s), 2860 (s), 1590 (s), 1069 (s) cm^{-1}; ^1H NMR (CCl_4) δ 3.90 (br, 3 H, NH_2), 3.50-3.10 (m, 2 H, CH_2), 2.50–2.20 (m, 1 H, $CHNH_2$), 1.80–1.00 (m, 1 H, $CH(CH_3)_2$), 0.90 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$).

Fluoroacetone (*S*)-(3-Methyl-1-methoxybut-2-yl)imine (17). To a 25-mL flask containing **15** (0.59 g, 0.005 mol) in 10 mL of CCl_4 and 1 g of activated 4A molecular sieves at 0 °C was added a solution of fluoroacetone (0.30 g, 0.005 mol) in 5 mL of CCl_4. After being stirred at room temperature overnight, the reaction mixture was filtered, and the solvent was removed in vacuo. Bulb-to-bulb distillation, 90–100 °C (0.5 mm), yielded 0.75 g (86%) of the imine as a single isomer: IR (neat) ν 2960 (s), 2920 (s) 2860 (s), 1675 (s), 1460 (s), 1350 (s), 1200 (m), 1120 (s), 1000 (m), 740 (s) cm^{-1}; ^1H NMR (CCl_4) δ 4.68 (d, $J_{H,F}$ = 47 Hz, 2 H, CH_2F), 3.50–3.30 (m, 3 H, NCH, CH_2), 3.26 (s, 3 H, OCH_3), 2.10–1.70 (m, 1 H, CH), 1.90 (d, $J_{H,F}$ = 3 Hz, 3 H, CH_3), 0.90 (d, J = 6 Hz, 6 H, $(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 86.81 (d, $J_{C,F}$ = 172 Hz, CH_2F), 74.82 (OCH_2), 65.01 (CH), 58.60 (OCH_3), 30.51 (CH_3), 19.61 (CH_3); ^{19}F NMR ($CDCl_3$) δ -227.5 (d, $J_{H,F}$ = 49 Hz); exact mass, cald for $C_9H_{18}NOF$ 175.1368, found, 175.1382.

Fluoroacetone (*S*)-(-)-(1-Methoxy-3-phenylprop-2-yl)imine (18). To a 25-mL flask containing **16** (0.66 g, 0.004 mol) in 10 mL of CCl_4 and 1 g of activated 4A molecular sieves at 0 °C was added a solution of fluoroacetone (0.30 g, 0.004 mol) in 5 mL of CCl_4. After being stirred at room temperature overnight, the reaction mixture was filtered, and the solvent was removed in vacuo. Bulb-to-bulb distillation, 120–130 °C (0.5 mm), yielded 0.75 g (84%) of the imine as a single isomer: IR (neat) ν 3105 (w), 3060 (m), 2940 (s), 1685 (s), 1601 (m), 1510 (m), 1400 (m), 1380 (m), 1120 (s), 915 (s), 750 (s), 715 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.10–7.00 (br, 5 H, C_6H_5), 4.71 (d, $J_{H,F}$ = 49 Hz, 2 H, CH_2F), 3.80–3.50 (m, 2 H, CH_2), 3.30–3.00 (m, 1 H, CH), 3.23 (s, 3 H, CH_3), 2.80–2.40 (m, 2 H, CH_2), 1.46 (d, $J_{H,F}$ = 2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.95 (d, $J_{C,F}$ = 20 Hz, C=N), 138.65 (C-ipso), 129.42 (C-ortho), 128.11 (C-meta), 126.07 (C-para), 86.27 (d, $J_{C,F}$ = 172 Hz, CHF), 76.09 (CH_2), 61.52 (CH), 58.96 (OCH_3), 38.76 (CH_2), 13.71 (CH_3); ^{19}F NMR ($CDCl_3$) δ -222.2 (t, $J_{H,F}$ = 50 Hz); exact mass, calcd for $C_{13}H_{18}NOF$ 223.1404, found 223.1416.

^{19}F NMR Spectrum of Aza Enolate 20. To 0.1 mL of *tert*-butyllithium (1.7 M in pentane) in a dry NMR tube under an inert atmosphere at -195 °C was added approximately 1 mL of a solution containing 0.25 g of **18** and 0.1 g of perdeuteriobenzene. The sample was allowed to warm to -100 °C in the NMR probe. The ^{19}F NMR spectrum of the aza enolate at -90 °C showed a single resonance: ^{19}F NMR (THF/C_6D_6) δ -201.7 (dq, $J_{H,F}$ = 85, 5 Hz).

Method A. Preparation of Optically Enriched α-Fluoro Ketones. To a 50-mL three-necked flask containing 0.002 mol of α-fluoro imine **17** or **18** at -90 °C was added dropwise at such a rate that the temperature did not exceed -80 °C 2.4 mL (0.004 mol) of *tert*-butyllithium (1.7 M in pentane). After the mixture was stirred for 0.5 h, 0.004 mol of an alkyl halide in 5 mL of THF was added dropwise. After being stirred 0.5 h at -85 °C, the reaction mixture was poured over 10 mL of a saturated solution of sodium bicarbonate and was extracted with distilled hexanes (3 × 10 mL). The crude, alkylated ketimine was immediately analyzed by ^{19}F NMR to determine the extent of asymmetric induction. The crude fluoro ketone **19** was obtained by hydrolysis of the alkylated ketimine in pentane with a buffered acetic acid solution for 2 h. The phases were separated, and the organic phase was washed with 10 mL of a saturated sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation.

Method B. Preparation of Optically Enriched α-Fluoro Ketones. To a 50-mL three-necked flask containing 0.004 mol of α-fluoro imine **17** or **18** and DMPU (0.41 g, 0.0032 mol) at -90 °C was added dropwise at such a rate that the temperature did not exceed -80 °C 2.4 mL (0.004 mol) of *tert*-butyllithium (1.7 M in pentane). After the mixture was stirred 0.5 h, 0.004 mol of an alkyl halide in 5 mL of THF was added dropwise. After being stirred 0.5 h at -85 °C, the reaction mixture was poured over 10 mL of a saturated solution of sodium bicarbonate and was extracted with distilled hexanes (3 × 10 mL). The crude, alkylated ketimine was immediately analyzed by ^{19}F NMR to determine the extent of asymmetric induction. The crude fluoro ketone, **19**, was obtained by hydrolysis of the alkylated ketimine in pentane with a buffered acetic acid solution for 2 h. The phases were separated, and the organic phase was washed with 10 mL of a saturated sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation.

3-Fluoro-2-butanone (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imine was prepared from **18** and iodomethane. Workup in the normal manner yielded 0.25 g (26%) of the imine: ^{19}F NMR ($CDCl_3$) [major] δ -179.80 (dq, $J_{H,F}$ = 48, 24 Hz), [minor] -181.67 (dq, $J_{H,F}$ = 48, 24 Hz); methox A, de = 65%; method B, de = 58%.

3-Fluorohex-5-en-2-one (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imine was prepared from **18** and allyl bromide. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -186.1 (dt, $J_{H,F}$ = 48, 19 Hz), [major] -186.6 (dt, $J_{H,F}$ = 48, 24 Hz); method A, de = 34%; method B, de = 32%.

Hydrolysis yielded 0.28 g (64%) of crude ketone.

3-Fluorohex-5-en-2-one (*S*)-(3-methyl-1-methoxybut-2-yl)imine was prepared from **17** and allyl bromide. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -185.65 (ddd, $J_{H,F}$ = 48, 21, 14 Hz), [major] -185.60 (dt, $J_{H,F}$ = 48, 24 Hz); method A, de = 37%.

Hydrolysis yielded 0.27 g (60%) of crude ketone.

3-Fluoro-2-heptanone (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imine was prepared from **18** and iodobutane. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -185.70 (ddd, $J_{H,F}$ = 49, 21, 20 Hz), [major] -185.50 (ddd, $J_{H,F}$ = 47, 22, 21 Hz); method A (0.004-mol scale), de = 26%; method B (0.002-mol scale), de = 11%.

3-Fluoro-2-heptanone (*S*)-(3-methyl-1-methoxybut-2-yl)imine was prepared from **17** and iodobutane. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -186.1 (dt, $J_{H,F}$ = 49, 22 Hz), [major] -187.3 (dt, $J_{H,F}$ = 47, 24 Hz); method A, de = 33%.

Hydrolysis yielded 0.30 g (58%) crude ketone.

3-Fluoro-4-phenyl-2-butanone (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imine was prepared from **18** and benzyl bromide. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -185.10 (dt, $J_{H,F}$ = 48, 24 Hz), [major] -186.00 (ddd, $J_{H,F}$ = 48, 26, 18 Hz); method A (0.004-mol scale), de = 35%; method B (0.002-mol scale), de = 58%.

Hydrolysis yielded 0.34 g (52%) of crude ketone from method A.

3-Fluoro-4-phenyl-2-butanone (*S*)-(3-methyl-1-methoxybut-2-yl)imine was prepared from **17** and benzyl bromide. Workup in the normal manner yielded the diastereomeric ketimines: ^{19}F NMR ($CDCl_3$) [minor] δ -184.2 (dt, $J_{H,F}$ = 48, 21 Hz), [major] -185.9 (dt, $J_{H,F}$ = 47, 26 Hz); method A, de = 32%.

Hydrolysis yielded 0.34 g (52%) of crude ketone.

3-Fluorohex-5-yn-2-one (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imine was prepared from **18** and propargyl bromide. Following normal workup the yield of crude product by ^{19}F NMR was 12%: ^{19}F NMR ($CDCl_3$) [minor] δ -183.40 (dt, $J_{H,F}$ = 48, 22 Hz), [major] -184.0 (dt, $J_{H,F}$ = 48, 24 Hz); method B, (0.0038-mol scale), de = 40%.

Hydrolysis yielded only a trace of desired ketone: ^{19}F NMR ($CDCl_3$) [ketone] δ -184.7 (dt, $J_{H,F}$ = 48, 24 Hz).

2-Fluorocyclohexanone (*S*)-(-)-(1-methoxy-3-phenylprop-2-yl)imines (21 and 22) were prepared by the dropwise addition of 2-fluorocyclohexanone (0.70 g, 0.006 mol) to **16** (0.99 g, 0.006 mol) in 10 mL of CCl_4 and 3 g of activated 4A molecular sieves. Normal workup yielded 1.20 g (76%) of **21** and **22** as a 1:1 mixture of C=N isomers: bp 170–180 °C (0.25 mm); IR (neat) ν 3040 (w), 2950 (s)8 2860 (s), 1675 (s), 1605 (w), 1500 (m), 1460 (m), 1130 (s), 960 (s)8, 740 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–7.09 (br, 5 H, C_6H_5), 4.78 (dm, $J_{H,F}$ = 50 Hz, 1 H, CHF),

3.94–3.89 (m, 1 H, CH), 3.56–3.49 (m, 2 H, CH_2), 3.43 (dd, $J_{H,F}$ = 12 Hz, J = 6 Hz, 2 H, CH_2), 3.34 (s, 3 H, CH_3), 3.32 (s, 3 H, CH_3), 2.97 (m, 1 H, CH), 2.68 (m, 1 H, CH), 2.10–1.20 (m, 8 H, CH_2); ^{13}C NMR ($CDCl_3$) [*E*] δ 169.67 (d, $J_{C,F}$ = 11 Hz, C=N), 138.70 (C-ipso), 129.61 (C-ortho), 128.06 (C-meta), 125.98 (C-para), 93.79 (d, $J_{C,F}$ = 176 Hz, CHF), 76.19 (CH_2OCH_3), 60.49 (CH), 58.57 (CH_2OCH_3), 38.96 (CH_2), 33.37 (d, $J_{C,F}$ = 23 Hz, CH_2), 26.26 (d, $J_{C,F}$ = 6 Hz CH_2), 20.93 (d, $J_{C,F}$ = 5 Hz, CH_2), 20.17 (d, $J_{C,F}$ = 4 Hz, CH_2), [*Z*] 169.43 (d, $J_{C,F}$ = 9 Hz, C=N), 139.10 (C-ipso), 129.55 (C-ortho), 128.06 (C-meta), 125.98 (C-para), 94.40 (d, $J_{C,F}$ = 174 H, CHF), 76.19 (CH_2OCH_3), 60.59 (CH), 58.97 (CH_2OCH_3), 39.17 ($CH_2C_6H_5$), 33.05 (d, $J_{C,F}$ = 20 Hz, CH_2), 25.70 (d, $J_{C,F}$ = 32 Hz, CH_2), 20.93 (d, $J_{C,F}$ = 5 Hz, CH_2), 20.17 (d, $J_{C,F}$ = 4 Hz, CH_2); ^{19}F NMR ($CDCl_3$) [*E*] δ −183.61 ($J_{H,F}$ = 52, 27, 9 Hz), [*Z*] δ −183.22 ($J_{H,F}$ = 54, 28, 7 Hz).

(*S*)-(+)-2-Fluoro-2-benzylcyclohexanone (24) was prepared by the dropwise addition of 0.20 mL (0.0012 mol) of *tert*-butyllithium (1.7 M in pentane) to a mixture of **21** and **22** (0.21 g, 0.0008 mol) in 25 mL of THF at −90 °C. After the mixture was stirred for 1 h, benzyl bromide (0.068 g, 0.0004 mol) in 5 mL of THF was added dropwise. After another 0.5 h at −90 °C, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with hexanes (3 × 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo: ^{19}F NMR ($CDCl_3$) [minor] δ −153.5 (ddt, $J_{H,F}$ = 21, 10, 7 Hz), [major] −156.3 ($J_{H,F}$ = 21, 10, 7 Hz); de = 38%.

Hydrolysis of the imine and isolation in the usual manner yielded 0.10 g (61%) as a white solid. Recrystallization from hexane/ethanol (95:5) to yielded **24**: mp 109–110 °C; $[\alpha]_D$ +9.8° (*c* 5, ethanol).

Chiral Shift Study. 24 (3–5 mg), dried in vacuo, was dissolved in approximately 1 mL of deuteriochloroform. Upon addition of ca. 40 mol% of tris[(heptafluoropropyl)hydroxymethylene)-(+)-camphonato]europium(III) in $CDCl_3$, the benzyl proton resonances were resolved. Integration of these resonances indicated an optical purity of 31%.

Circular Dichroism Measurement. The circular dichroism spectrum of **24** of unknown concentration in ethanol showed a positive CD spectrum.[27]

2-Fluoro-2-methylcyclohexanone was prepared by the dropwise addition of 0.20 mL (0.0012 mol) of *tert*-butyllithium (1.7 M in pentane) to a mixture of **21** and **22** (0.21 g, 0.0008 mol) in 25 mL of THF at −90 °C. After the mixture was stirred for 1 h, iodomethane (0.11 g, 0.0008 mol) in 5 mL of THF was added. After another 0.5 h at −90 °C, the reaction mixture was poured over 10 mL of a saturated sodium bicarbonate solution and extracted with hexanes (3 × 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo: ^{19}F NMR ($CDCl_3$) [minor] δ −147.4 (tq, $J_{H,F}$ = 48, 22 Hz), [major] −148.6 (tq, $J_{H,F}$ = 47, 22 Hz); de = 65%.

Hydrolysis and normal workup yielded 0.40 g of the ketone, which was purified by preparative GC.

2-Fluoro-2-methylcyclohexanone (*S*)-(−)-(1-methoxy-3-phenylprop-2-yl)imine from **21** and **22**. Following normal workup, the title compound was obtained: ^{19}F NMR ($CDCl_3$) [minor] δ −147.4 (m), [major] −148.6 (m); method B (0.008-mol scale), de = 67%.

2-Fluoro-2-benzylcyclohexanone (*S*)-(−)-(1-methoxy-3-phenylprop-2-yl)imine from **21** and **22**. Following normal workup, the title compound was obtained: ^{19}F NMR ($CDCl_3$) [minor] δ −153.5 (ddt, $J_{H,F}$ = 21, 10, 7 Hz), [major] δ −156.3 ($J_{H,F}$ = 21, 10, 7 Hz); method B (0.004-mol scale), de = 33%.

Acknowledgment. Financial support of this work by National Science Foundation Grant CHE-8520875 is gratefully acknowledged.

Registry No. 3, 430-51-3; **4**, 114156-08-0; **5** (R = CH_3), 453-10-1; **5** (R = $CH_2CH{=}CH_2$), 114156-09-1; **5** (R = $CH_2CH_2CH_2CH_3$), 689-87-2; **5** (R = $CH_2C_6H_5$), 772-67-8; **5** (R = (*E*)-$CH_2CH{=}CHC_6H_5$), 114156-19-3; **6** (R = CH_3), 814-79-9; **6** (R = $CH_2CH{=}CH_2$), 2021-74-1; **6** (R = $CH_2CH_2CH_2CH_3$), 99687-74-8; **6** (R = $CH_2C_6H_5$), 99687-75-9; **6** (R = (*E*)-$CH_2CH{=}CHC_6H_5$), 114156-20-6; **9**, 114156-10-4; **11**, 114156-11-5; **12**, 114156-12-6; **13** (R = CH_3), 114156-13-7; **13** (R = $CH_2CH{=}CH_2$), 114156-23-9; **14** (R = CH_3), 114156-14-8; **14** (R = $CH_2CH{=}CH_2$), 114156-24-0; **15** (R = $CH(CH_3)_2$), 64715-88-4; **16** (R = CH_2Ph), 64715-80-6; **17** (R = $CH(CH_3)_2$), 114156-15-9; **18** (R = CH_2Ph), 114156-16-0; **19** (R_1 = $CH_2CH{=}CH_2$), 2021-74-1; **19** (R_1 = $CH_2CH_2CH_2CH_3$), 99687-74-8; **19** (R_1 = CH_2Ph), 99687-75-9; **19** (R_1 = $CH_2C{\equiv}CH$), 114156-31-9; **21**, 114156-17-1; **24**, 114156-18-2; CH_3I, 74-89-5; $HC{\equiv}CCH_2Br$, 106-96-7; $H_2C{=}CHCH_2Br$, 106-95-6; $CH_3CH_2CH_2CH_2I$, 542-69-8; $PhCH_2Br$, 100-39-0; (*E*)-$C_6H_5CH{=}CHCH_2Br$, 26146-77-0; 1-bromo-2-propone, 598-31-2; cyclohexylamine, 108-91-8; 2-fluorocyclohexanone, 694-82-6; 2-fluoro-2-methylcyclohexanone, 15344-32-8; 2-fluoro-2-butylcyclohexanone, 114156-21-7; 2-fluoro-2-benzylcyclohexanone, 114156-22-8; *N*-(benzyloxy)phthalimide, 16653-19-3; *N*-hydroxyphthalimide, 524-38-9; *O*-amino-*O*-benzyl ether, 622-33-3; (*S*)-2-amino-1-hydroxy-3-phenylpropanone, 3182-95-4; phenylalanine, 63-91-2; phenylalanine ethyl ester, hydrochloride, 3182-93-2; (*S*)-2-amino-3-methyl-1-butanol, 2026-48-4; L-valine, 72-18-4; 3-fluoro-2-heptanone (2-amino-1-methoxy-3-phenylprop-2-yl)imine, 114156-25-1; 3-fluorohex-5-yn-2-one (1-methoxy-3-phenylprop-2-yl)imine, 114156-26-2; 3-fluorohex-5-en-2-one (3-methyl-1-methoxybut-2-yl)imine, 114156-27-3; 3-fluoro-4-phenyl-2-butanone (3-methyl-1-methoxybut-2-yl)imine, 114156-28-4; 3-fluoro-2-heptanone (3-methyl-1-methoxybut-2-yl)imine, 114156-29-5; 3-fluorohex-5-yn-2-one (3-methyl-1-methoxybut-2-yl)imine, 114156-30-8; 2-fluorocyclohexanone (1-methoxy-3-phenylprop-2-yl)imine, 114156-32-0; 2-fluoro-2-benzylcyclohexanone (1-methoxy-3-phenylprop-2-yl)imine, 114156-33-1; 2-fluoro-2-benzylcyclohexanone (1-methoxyhex-2-yl)imine, 114156-34-2; 3-fluorohex-5-en-2-one (1-methoxy-3-phenylprop-2-yl)imine, 114156-35-3; 3-fluoro-4-phenyl-2-butanone (1-methoxy-3-phenylprop-2-yl)imine, 114156-36-4; 3-fluoro-2-butanone (1-methoxy-3-phenylprop-2-yl)imine, 114183-75-4.

(27) The circular dichroism spectrum was determined with the assistance of Dr. F. Maley of New York State Health Laboratories.