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Selective Reductions. 53. Asymmetric Reduction of α-Fluoromethyl Ketones with *B*-Chlorodiisopinocampheylborane and *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane. Combined Electronic and Steric Contributions to the Enantiocontrol Process[1]

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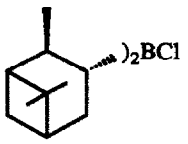
Abstract: A systematic study of the asymmetric reduction of aryl and alkyl α-fluoroalkyl ketones with (–)-diisopinocampheylchloroborane ((–)-DIP-Chloride, **1**), and (–)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane, **2**) has been made. In the case of reagent **1**, the direction of asymmetric induction in the chiral reduction of aryl trifluoromethyl ketones differs from that of the corresponding mono- and difluoromethyl ketones. For example, while 2-fluoro, and 2,2-difluoroacetophenones are reduced with **1** to the *R*-alcohols in 95% and 85% ee, respectively, 2,2,2-trifluoroacetophenone is reduced, under neat conditions at room temperature, to the *S*-alcohol in 90% ee. Though DIP-Chloride reduces unhindered prochiral dialkyl ketones in poor ee, alkyl α-fluoroalkyl ketones are reduced in improved ee depending on the number of α-fluorine atoms present in the ketone. While monofluoromethyl ketones provide moderate ee in the *R*-isomer, the di- and trifluoromethyl ketones are reduced in moderate to excellent ee in the opposite isomer. For example, 1-fluoro-2-octanone is reduced in 40% ee (*R*), whereas 1,1-difluoro- and 1,1,1-trifluoro-2-octanone are reduced in 32% (*S*), and 91% ee (*S*), respectively. In the case of the asymmetric reduction of the above series of ketones with **2**, the results are different. There is no change in the direction of chiral induction in the reduction of α-fluoroacetophenones with **2**. 2-Fluoroacetophenone and 2,2-difluoroacetophenone are reduced with **2** to the *R*-alcohol in 89% and 97% ee, respectively. The reaction of 2,2,2-trifluoroacetophenone is very slow, only 90% complete in 45 d, and provides the *R*-alcohol in 32% ee. In contrast, while 1-fluoro- and 1,1-difluoro-2-octanone are reduced by **2** in 65% (*R*) and 50% ee (*R*), respectively, 1,1,1-trifluoro-2-octanone is reduced in 60% ee (*S*), raising the question of which factors other than the steric size of the trifluoromethyl group, control the enantioselectivity of these reductions. The effect of steric versus electronic influence in such chiral reductions is discussed.

INTRODUCTION

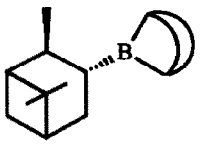
Asymmetric reduction is becoming a mature field in the area of asymmetric synthesis[3] with the development of several efficient reagents and procedures.[4] In the past decade, we have been involved in the syntheses of several chiral reagents for asymmetric reduction. From these, *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™, **1**) has emerged as one of the best reagents for the reduction of aralkyl ketones, α-hindered ketones, etc.[5]

Influenced by the growing importance[6] of fluoroorganic molecules in agricultural, materials, medicinal, and organic chemistry, we carried out the reduction of aryl and alkyl trifluoromethyl ketones with **1** and obtained generally ≥90% ee for the product alcohols.[7] These were of stereochemistry opposite to those produced in the reduction of the corresponding hydrogen analogs. We extended the study to the reduction of α-acetylenic α'-

fluoroalkyl ketones and observed that the perfluorinated acetylenic ketones can be reduced in very high ee with **1**.[8] On the other hand, α-acetylenic α'-mono- and difluoromethyl ketones are reduced to provide the product alcohols in moderate ee only. However, a similar organoborane reducing agent, Midland's *B*-isopinocampheyl-



DIP-Chloride, **1**



Alpine-Borane, **2**

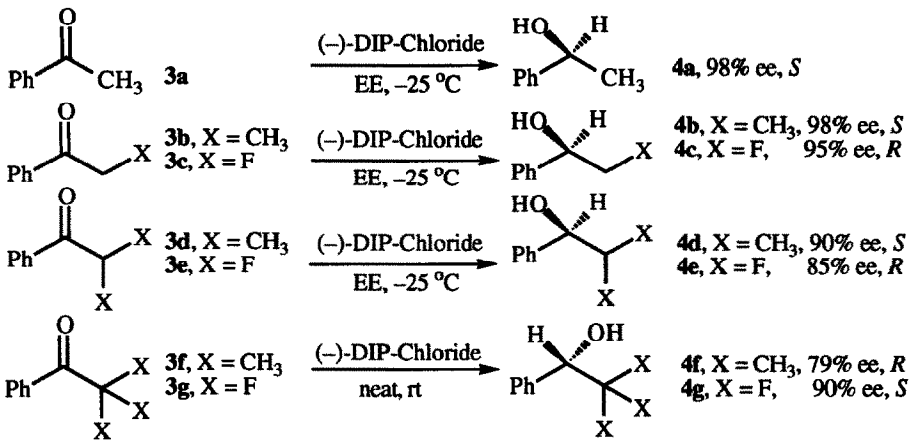
9-borabicyclo[3.3.1]nonane (Aldrich: Alpine-Borane®, **2**)[9] derived from the same chiral auxiliary, α-pinene, reduces all types of α-acetylenic α'-fluoroalkyl ketones in very high ee. We also know that **2** reduces aryl perfluorinated ketones at only a very slow rate providing the products in poor ee.[7] In order to understand the effect of fluorine atoms on the enantiomeric outcome during the asymmetric reduction of aryl and alkyl ketones, we carried out the reaction of a corresponding series of α-fluoro-, α,α-difluoro-, and α,α,α-trifluoromethyl ketones with **1** and **2**. The results of this study are presented in this paper.[10]

RESULTS AND DISCUSSION

The reaction of 2-fluoroacetophenone (**3c**) with **1** in EE at – 25 °C is complete in 1 h and the usual diethanolamine workup provides the product alcohol (**4c**, *R*) in 80% yield and in 95% enantiomeric excess (ee) (The *R* configuration, a consequence of the Cahn-Ingold-Prelog convention, is stereochemically equivalent to the *S*-alcohol of the corresponding hydrocarbon analog).[11] The configuration of the product is as expected from the proposed mechanism of the reduction.[5] A similar reaction of 2,2-difluoroacetophenone (**3e**) with **1** provides the product *R*-alcohol **4e** in 60% yield in 85% ee. We had reported earlier that 2,2,2-trifluoroacetophenone (**3g**) reacts with **1** only very slowly at –25 °C, but the reaction is complete within 24 h at room temperature (rt) providing the product alcohol (**4g**), 90% ee in the *S*-isomer (Scheme I).[7] The stereochemistry of this product is opposite to that obtained from the reduction of the corresponding hydrogen analog, acetophenone (**3a**)[11] and the above two ketones **3c** and **3e**. In other words, in asymmetric reduction with **1**, a trifluoromethyl group exerts an enantioselective control similar to that of the *tert*-butyl group.[7] A comparison of the results of asymmetric reduction of 2-methylacetophenone (propiophenone, **3b**), 2,2-dimethylacetophenone (isobutyrophenone, **3d**) and 2,2,2-trimethylacetophenone (pivalophenone, **3f**) shows a very similar trend (Scheme I).[5] We had compared the physical properties of the $-CH_3$, the $-CF_3$ and the $-C(CH_3)_3$ group and found that the steric requirements of the $-CF_3$ group is closer to those of the $-CH_3$ group than to those of the $-C(CH_3)_3$ group.[7]

It is very interesting to note that substituting the hydrogens of the methyl group of acetophenone with fluorine atoms, one at a time, does not change the direction of optical induction gradually. A major change occurs when the fluorine substitution is increased from two to three. This is true also for the ketones where the hydrogens are substituted with $-CH_3$ groups (X = CH_3). The comparison in scheme I shows that the $-CF_3$ group is very similar to a *tert*-butyl group, *albeit* for different influences, in factors that control the enantioselectivity. This indirectly suggests that a fluorine atom must exert similar steric influences as those of the $-CH_3$ group.[12] But the steric size of a fluorine atom is only modestly larger than that of a hydrogen atom, even though the electronic environment is different.[13] This suggests that the results observed in the asymmetric

reduction of fluoroalkyl ketones must be due to a combined effect involving both the steric and the electronic influences of the fluoroalkyl groups.



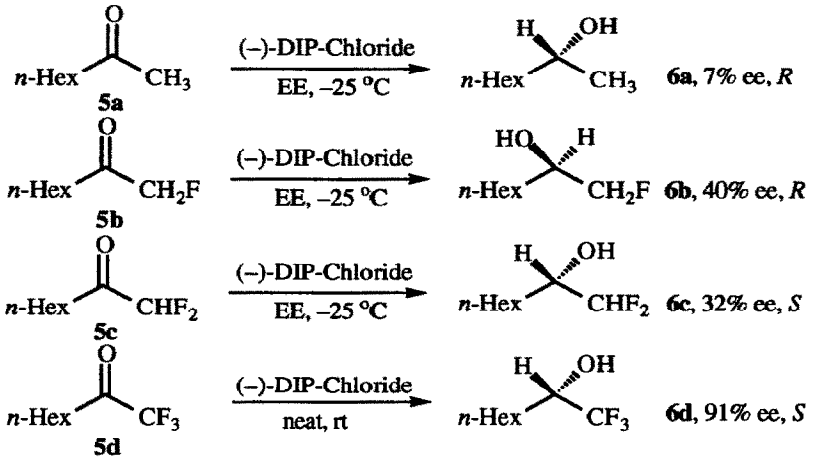
Scheme I

Since **1** is an excellent reducing agent for aralkyl ketones, the above substrates do not reveal the real effects of fluorine atoms in asymmetric reductions with this reagent. We know that **1** fails to reduce unhindered aliphatic ketones in satisfactory ee. This prompted us to study the asymmetric reduction of a series of aliphatic α-fluoro-, α,α-difluoro- and α,α,α-trifluoromethyl ketones with DIP-Chloride. We felt that the differences in the % ee and the configuration of the product alcohols from such a reaction should provide us with a better understanding of the electronic and/or steric effects since the electronic influences of the phenyl ring are absent here. Accordingly, we synthesized 1-fluoro-2-octanone (**5b**), 1,1-difluoro-2-octanone (**5c**), and 1,1,1-trifluoro-2-octanone (**5d**) using a literature procedure [14] for reduction with **1**.

The reduction of 1-fluoro-2-octanone (**5b**) in EE at –25 °C is complete in 6 h and the product is obtained in 40% ee in the *R*-isomer (Scheme II). The configuration of the product alcohol was determined by hydrogenating the corresponding acetylenic alcohol of known configuration, produced from the reduction of the fluoro acetylenic ketone.[8] If we compare the configuration of the product from the reduction of **5b** with that obtained from 2-octanone (**5a**) (7% ee, *R*),[5] we observe a reversal in stereochemistry. This represents a change of 47% in the asymmetric induction due to the substitution of a hydrogen with a fluorine atom. This leads to the conclusion that the lone fluorine atom exerts an enormous effect upon the chiral outcome.

The presence of two fluorine atoms influences the reduction in a major way, achieving a change in the direction of induction. The reduction of 1,1-difluoro-2-octanone (**5c**) with **1** provides the *S*-alcohol in 32% ee. In contrast to the aryl series, the change in the direction of enantioselection occurs when the fluorine substitution is increased from one to two. This effect is enhanced by substituting the third hydrogen atom of the α-methyl group of the ketone with yet another fluorine atom. The reaction of 1,1,1-trifluoro-2-octanone (**5d**), under neat conditions at rt, with **1** produces the *S*-alcohol (**6d**) in 91% ee. This is expected from our earlier results[7] which revealed a cumulative effect of the electronic and steric environment of the perfluoroalkyl group. The results of the reduction of all of the above fluoromethyl ketones with **1** are summarized in Table 1.

The configuration of the products **6c** and **6d** were determined by comparing their rotations with those reported in the literature, confirmed by hydrogenating the corresponding acetylenic alcohols of known configuration, produced by reduction of the fluoro acetylenic ketones.[8]



Scheme II

Table 1. Asymmetric Reduction of Fluoroalkyl Ketones With (–)-DIP-Chloride at –25 °C

ketone	R-CO-R_F R	R_F	react time, h	yield, isol.	%ee[a]	isomer	enantiocontrolling group preference[b]
3a[c]	Ph	CH_3	5	72	98	*S*	Ph > CH_3
3c	Ph	CH_2F	1	80	95	*R*[d]	Ph > CH_2F
3e	Ph	CHF_2	0.5	60	85	*R*[d]	Ph > CHF_2
3g[e]	Ph	CF_3	24[f]	90	90	*S*[g]	CF_3 > Ph
5a	*n*-C_6H_{13}	CH_3	5	72	7	*R*	CH_3 > *n*-Hex
5b	*n*-C_6H_{13}	CH_2F	6	72	40	*R*	*n*-Hex > CH_2F
5c	*n*-C_6H_{13}	CHF_2	6	72	32	*S*	CHF_2 > *n*-Hex
5d	*n*-C_6H_{13}	CF_3	8[f]	74	91	*S*	CF_3 > *n*-Hex

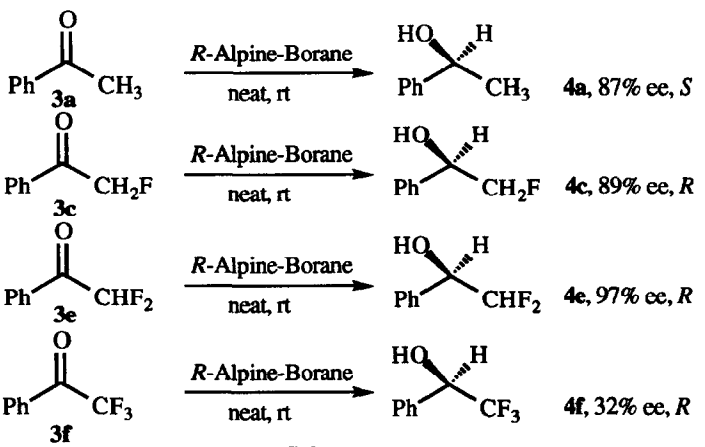
[a] ee determined as their MTPA derivative on a capillary GC. [b] Based on the proposed mechanism of the reduction (ref. 5). [c] From ref. 5. [d] The *R*-configuration is a consequence of the Cahn-Ingold-Prelog rules. [e] From ref. 7 [f] For a reaction at rt. [g] The *S*-configuration is a consequence of the Cahn-Ingold-Prelog rules.

Thus, the results of the reduction of a series of aliphatic α-fluoro-, α,α-difluoro- and α,α,α-trifluoromethyl ketones (without the electronic influence of the phenyl ring) with **1** show that substitution of one, two or all of the three hydrogens of the methyl group with fluorine atoms has considerable effect on the chiral outcome. In sharp contrast to the reduction of the phenyl ketones with **1**, the change in the direction of enantioselection is more gradual.

We sought to delineate the individual steric and electronic effects of the fluoroalkyl groups more precisely, if possible. The approach adopted was to study the reduction of the above series of ketones with Alpine-Borane, which is known to differentiate between the two groups of the ketones, RCOR', on the basis of the steric environment around the carbonyl group.[9] We felt that the absence of the chlorine atom in reagent **2** in contrast to **1** must decrease the electronic influences of the reagent, hopefully providing a clearer understanding

of the relative significance of the steric versus electronic effects of these ketones in these asymmetric reductions. This assumption is supported by the observation that in the reduction of **3g** with **2** we obtain the product of the same stereochemistry as compared to the hydrogen analog (**3a**), while reduction with **1** provides the alcohol of opposite stereochemistry.[7]

Reagent **2** reacts with acetophenone under neat conditions within 14 d to provide *S*-phenethanol in 87% ee.[9b] However, 2-fluoroacetophenone (**3c**) is reduced faster, in 4 d, and the product *R*-alcohol[11] of 89% ee is obtained in 71% yield (Scheme III). 2,2-Difluoroacetophenone (**3e**) also reacts with **2** within 4 d yielding the *R*-alcohol in 97% ee. The enantioselectivity observed in this reaction is higher than normal. This is to be expected, because, when the reaction rate is increased, the dehydroboration of the reagent is decreased,[15] and the reduction occurs *via* the direct hydride transfer from the reagent rather than from the achiral 9-BBN. This is the first example of the reduction of an aralkyl ketone where Alpine-Borane provides product of higher ee than that obtained from the reduction with DIP-Chloride. As reported earlier, 2,2,2-trifluoroacetophenone (**3f**) is reduced slowly, only 90% in 45 d, providing the alcohol in 32% ee.[7] In all these cases the phenyl group acted as the group with larger steric requirements in the transition state model. The absence of inversion in stereochemistry for the product from the reduction of **3f** with **2** in comparison with the alcohol derived with **1** might be due to the absence of the electronic influence of the chlorine in the reagent. In contrast, pivalophenone is not reduced by **2**. This probably supports the argument that a $-CF_3$ group is not as bulky as a *tert*-butyl group.

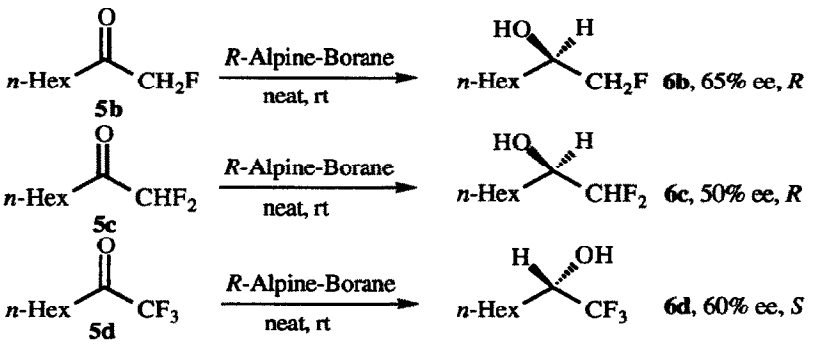


Scheme III

The rates of reduction of ketones **3c**, **3e** and **3f** with **2** are much slower when compared with the reduction with **1**. This can be attributed to the decreased Lewis acidity of **2** due to the absence of the chlorine atom in the reducing agent. The rates of reduction of **3c** and **3e** with **2** are much faster than that for **3a**. This is attributed to the increased electrophilicity (for hydride transfer) caused by the presence of the fluorine atoms. Midland has provided evidence that the hydride transfer is the rate limiting step.[15] However, we have seen that increasing the number of fluorine atoms to three has a negative effect on the rate with both the reagents. Probably, the presence of three fluorine atoms decreases the capability of the carbonyl oxygen to coordinate to the boron of the reagent, though the hydride transfer should be facilitated. This indicates that both the coordination of the carbonyl oxygen to the boron of the reagent as well as the activation of carbonyl carbon for

increased electrophilicity are important in these types of reductions. It appears that there has to be an optimum between the two to achieve best results, as in the reduction of **3a** with **1**, and **3e** with **2**.

The reduction of the fluorooctanones also showed interesting results (Scheme IV). 1-Fluoro-2-octanone (**5b**) is reduced by **2** in 9 d and the product alcohol (*R*) is obtained in 65% ee with the *n*-hexyl group controlling the stereoselection. A comparison of the reduction of **5b** with **1** and **2** shows an increase in % ee (40% –> 65%). The reduction of **5c** with **2** provides **6c** in 50% ee (*R*) showing that, in contrast to the reduction with **1**, there is not much effect of the second fluorine atom.



Scheme IV

Substituting all the hydrogens of the α-methyl group of 2-octanone with fluorine atoms decreases the rate of reduction with **2** (14 d) and provides the product alcohol in 60% ee in the opposite, *S*-isomer. The inversion of selectivity observed with the change of $-CHF_2$ to $-CF_3$ in **5c** and **5d** is not observed in the reduction of aryl fluoroalkyl ketones with **2**. In the proposed transition state model for reductions with **2**, an aryl group is the enantiocontrolling group compared to the $-CF_3$ group. But, compared to an alkyl group the $-CF_3$ group acts as the enantiocontroller. Once again, this shows that a $-CF_3$ group has unique influences that cannot be explained solely in terms of the physical size of the moiety.

The results of the reduction of all of the fluoroketones with **2** are summarized in Table 2.

Table 2. Asymmetric Reduction of Fluoroalkyl Ketones With *R*-Alpine-Borane at 25 °C

ketone	R-CO-R_F R	R_F	react time, d	yield, % isol.	%ee[a]	isomer	enantiocontrolling group preference[b]
3a[c]	Ph	CH_3	14	80	87	*S*	Ph > CH_3
3c	Ph	CH_2F	4	71	89	*R*[d]	Ph > CH_2F
3e	Ph	CHF_2	4	69	97	*R*[d]	Ph > CHF_2
3g[e]	Ph	CF_3	45	57	32	*R*[d]	Ph > CF_3
5a[f]	*n*-C_6H_{13}	CH_3	7	70	63	*S*	*n*-Hex > CH_3
5b	*n*-C_6H_{13}	CH_2F	9	82	65	*R*	*n*-Hex > CH_2F
5c	*n*-C_6H_{13}	CHF_2	10	78	50	*R*	*n*-Hex > CHF_2
5d	*n*-C_6H_{13}	CF_3	14	72	60	*S*	CF_3 > *n*-Hex

[a] ee determined as their MTPA derivative on a capillary GC. [b] Based on the tentative mechanism of the reduction (ref. 9). [c] From ref. 9b. [d] The *R*-configuration is a consequence of the Cahn-Ingold-Prelog rules. [e] From ref. 7. [f] From ref. 5.

The nature of the enantiocontrolling factor

Midland introduced Alpine-Borane as an asymmetric reducing agent for prochiral ketones. The reagent reacts slowly with simple ketones and the enantioselection process is controlled by the steric requirements of the

groups flanking the carbonyl moiety. Electron-withdrawing groups increase the rate of reduction and the reagent is applied in the reduction of α-acetylenic-, α-halo-, and α-cyano ketones.

Later, we explored increasing the Lewis acidity of the reagent to achieve faster rates of reduction by more efficient coordination of the carbonyl oxygen with the boron of the reagent and introduced DIP-Chloride for asymmetric reductions. We observed that the enantiocontrol of the reduction of simple ketones with this reagent is based purely on the relative steric requirements of the R and R' groups in RCOR'. The electronic interactions favor some reactions while disfavoring others. For example, an aralkyl ketone is reduced in very high ee while an unhindered acetylenic ketone is reduced in low ee. In any particular class of ketones, we could predict the enantioselectivity based on the steric bulk of the R' group of the ketones, where R is the same, though bulky groups decrease the rate of reduction. Thus, 2-butanone, 3-methyl-2-butanone, and 3,3-dimethyl-2-butanone are reduced in 4%, 32%, and 95% in the *S*-isomer. Similarly, acetophenone, isobutyrophenone, and pivalophenone are reduced in 98% (*S*), 90% (*S*), and 79% (*R*) ee, respectively. The decrease in ee for isobutyrophenone and reversal in configuration for pivalophenone is reasonable in terms of steric control by the alkyl group. The *tert*-butyl group becomes the enantiocontrolling group in the reduction of pivalophenone. Even in the case of R-C≡C-CO-R' where DIP-Chloride usually provides poor ee, increasing the steric requirements of R' from Me –> Et –> *i*-Pr –> *t*-Bu increases the ee from 21% –> 28% –> 53% –> ≥99%, respectively.

However, such a prediction has become impossible in the case of the reduction of the fluoroalkyl ketones. The predictive capability holds good to some extent in reductions of fluoro ketones with Alpine-Borane. But, when there is the interaction between the chlorine of the reagent and the fluorine of the ketones, the enantiocontrol in the reduction must be based on a cumulative effect of the electronic and steric interactions.

Apart from the enantiocontrolling effect, the electron-withdrawing fluorine atom influences the rate of reduction, positively by increasing the electrophilicity of the carbonyl carbon of the ketone, but negatively by decreasing the coordination of the carbonyl oxygen to the boron of the reagent. An optimum between the two effects must be attained to achieve maximum enantioselection.

CONCLUSIONS

In conclusion, we have studied the asymmetric reduction of prochiral α-fluoroalkyl ketones to achieve an understanding of the steric and/or electronic influences of the fluorine atom on chiral reductions. DIP-Chloride and Alpine-Borane were selected as the reagents for this study since they differ in their electronic environments. A series of aryl and alkyl α-fluoro-, α,α-difluoro- and α,α,α-trifluoromethyl ketones were reduced for a clearer understanding of the effect of the fluorine substitution. As usual, all aryl fluorosubstituted ketones are reduced with **1** in very high ee. However, the trifluoromethyl ketone is reduced to the opposite isomer as compared with the mono- and difluoromethyl ketones. In the aliphatic series, **1** reduces 1-fluoro-2-octanone in moderate ee with the alkyl group as the enantiocontroller, providing the *R*-alcohol while 1,1-difluoro- and 1,1,1-trifluoro-2-octanone are reduced in moderate to excellent ee in the opposite isomer with the fluoroalkyl group acting as the enantiodirector. Reagent **2** reduces mono- and difluoroacetophenones in good to excellent ee, whereas trifluoroacetophenone is reduced very slowly, in poor ee. All of these alcohols are enriched in the *R*-isomer. The reduction of aliphatic series of fluoroalkyl ketones with **2** gives interesting results. While mono- and

difluoromethyl ketones are reduced to provide the *R*-alcohols, the corresponding trifluoromethyl ketone is reduced to the *S*-alcohol.

This study highlights the combined effect of the electronic and steric nature of a fluoromethyl group in asymmetric reduction and exposes a deficiency of the tentative transition state model currently used to explain the mechanism of reduction. We have understood that apart from the steric requirements of the reagent and the ketones, there is an optimum condition to be reached between the Lewis acidity of the boron of the reagent and the electrophilicity of the carbonyl carbon of the ketone to achieve fast rates of reduction and maximum enantioselectivity. We are continuing our experimental studies on the reduction of fluoro ketones with a simultaneous study of the molecular mechanics of these reactions to understand the unusual influence of fluorine atoms in asymmetric reductions. Modifications in the reagent to achieve improved asymmetric reduction of mono- and difluoromethyl ketones in high ee is also being made.

EXPERIMENTAL SECTION

General Methods

Techniques for handling air-sensitive compounds have been previously described.[16] ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR (CF_3COOH at δ –76.5 ppm as an external standard) spectra were plotted on a Varian Gemini-300 spectrometer. IR spectra were plotted on a Perkin-Elmer 1420 ratio recording spectrophotometer. Mass spectra were recorded with a Finnigan gas chromatograph-mass spectrometer model 4000. GC analyses were done on a OV-3 column (1/8'x6') using a Varian 3400 gas chromatograph having a flame ionization detector and a built-in integrator. Analyses of the MTPA or MCF derivatives were performed on a Hewlett-Packard 5890A gas chromatograph using a Supelcowax glass capillary column (15 m), or a SPB-5 capillary column (30 m), at appropriate temperatures, and integrated using a Hewlett-Packard 3390 A integrator. Optical rotations were measured using a Rudolph Autopol III polarimeter.

Materials. Ethyl ether (Mallinckrodt) was used as such. DIP-Chloride, Alpine-Borane, *n*-hexylmagnesiumbromide, difluoroacetic acid, ethyl fluoroacetate, ethyl trifluoroacetate, palladium on activated carbon, phenyllithium, ethanolamine, diethanolamine, acetaldehyde, were all obtained from Aldrich Chemical Co. Fluoroacetyl chloride was purchased from Alfa. Ethyl difluoroacetate was purchased form Strem Chemicals. Preparation of the 2-fluoroacetophenone, 2,2-difluoroacetophenone, 1,1-difluoroacetone, 1-fluoro-2-octanone, 1,1-difluoro-2-octanone, and 1,1,1-trifluoro-2-octanone were all achieved according to the literature procedure. *R*-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure.[17]

2-Fluoroacetophenone, 3c. This ketone was prepared according to the literature procedure *via* Friedel-Crafts reaction using fluoroacetyl chloride and benzene in the presence of aluminum chloride. Yield: 56%. bp 68-70 °C/1 mm Hg (lit.[18] bp 65-70 °C/1 mm Hg); IR: ν_{max} cm^{-1} neat: 1704 (C=O); ^{1}H NMR δ (ppm) ($CDCl_3$): 5.54 (d, J = 46.9 Hz, 2H, CH_2F), 7.48-7.91 (m, 5H, Ph).

2,2-Difluoroacetophenone, 3e. Difluoroacetic acid (100 mmol) in 5 mL EE was added dropwise to a cold (0 °C) solution of phenylmagnesium bromide (128 mL of 2.0 *M* in THF) and heated under reflux for 1 h. The reaction mixture was then cooled, poured to ice and extracted with EE (3x60 mL). The combined ether

extracts were washed with water, dried ($MgSO_4$) and distilled to yield 60% of **3e**. bp 67-70 °C/ 11 mm (lit.[19] bp 61-62 °C/ 8 mm Hg); IR: ν_{max} cm^{-1} neat: 1700 (C=O).

1-Fluoro-2-octanone, 5b. To a stirred solution of ethyl fluoroacetate (100 mmol) in 100 mL EE cooled to –78 °C was added, dropwise, 50 mL of a 2.0 *M* hexane solution of *n*-hexylmagnesiumbromide (100 mmol). Stirring was continued at this temperatute for 1.5 h. The mixture was then warmed to –25 °C and saturated NH_4Cl (20 mL) was added, followed by, dil. HCl (20 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$, concentrated and distilled under aspirator vacuum to yield 63% of **5b**: bp 88-92/38 mm Hg (lit.[20] bp 59-60 °C/ 23 mm Hg); IR: ν_{max} cm^{-1} neat: 1729 (C=O) ; ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, *J* = 7.2 Hz, 3H, -CH_3), 1.2-1.4 (m, 6H, -$(CH_2)_3$-CH_3), 1.52-1.68 (m, 2H, -CH_2-C_4H_9), 2.54 (dt, *J* = 7.4, 2.8 Hz, 2H, -CO-CH_2-), 4.8 (d, *J* = 47.8 Hz, 2H, -CH_2F); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.92, 22.40, 22.63, 28.74, 31.45, 38.19, 84.88 (d, *J* = 184.9 Hz, C_1), 207.12 (d, *J* = 19.0 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –227.47 (t, *J* = 48.1 Hz).

1,1-Difluoro-2-octanone, 5c. This ketone was synthesized from ethyl difluoroacetate and *n*-hexylmagnesium bromide as described above. Yield: 78%, bp 74-77 °C/40 mm Hg (lit.[21] 71-73 °C/35 mm Hg); IR: ν_{max} cm^{-1} neat: 1744 (C=O) ; ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, *J* = 7.2 Hz, 3H, -CH_3), 1.22-1.40 (m, 6H, -$(CH_2)_3$-CH_3), 1.57-1.70 (m, 2H, -CH_2-C_4H_9), 2.66 (t, *J* = 7.4 Hz, 2H, -CO-CH_2-), 5.68 (t, *J* = 54.1 Hz, 1H, -CHF_2); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.80, 22.21, 22.36, 28.55, 31.40, 35.95, 109.88 (t, *J* = 252.6 Hz, C_1), 199.85 (t, *J* = 26.0 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –127.37 (d, *J* = 54.0 Hz).

1,1,1-Trifluoro-2-octanone, 5d. This ketone was synthesized from ethyl trifluoroacetate and *n*-hexylmagnesium bromide as described above. Yield: 78%, bp 130-131 °C/750 mm Hg (lit.[22] bp 76 °C/88 mm Hg); IR: ν_{max} cm^{-1} neat: 1761 (C=O) ; ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, *J* = 7.2 Hz, 3H, -CH_3), 1.23-1.40 (m, 6H, -$(CH_2)_3$-CH_3), 1.61-1.72 (m, 2H, -CH_2-C_4H_9), 2.71 (t, *J* = 7.2 Hz, 2H, -CO-CH_2-); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.78, 22.33, 22.39, 28.43, 31.39, 36.30, 115.65 (q, *J* = 292.1 Hz, C_1), 191.53 (q, *J* = 34.7 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –79.60 (s).

Reduction of Ketones With (–)-DIP-Chloride. General Procedure. An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. (–)-DIP-Chloride (11 mmol was transferred to the flask in a glove bag and dissolved in EE (10 mL). The solution was cooled to –25 °C, and the ketone (10 mmol) was added using a syringe. The reaction was followed by ^{11}B NMR spectrum after aliquots were methanolyzed at –25 °C at periodic intervals. When the reaction was complete (^{11}B δ: 32 ppm), the mixture was raised to 0 °C and diethanolamine (22 mmol) was added dropwise. The mixture was warmed to rt and left stirred for 2 hours when the boranes precipitated as a complex which was filtered and washed with pentane. The filtrate was concentrated and distilled to collect the α-pinene and the product alcohol in separate flasks. The alcohol was further purified by preparative GC with appropriate columns (SE-30 or Carbowax 20M). The rotation was measured. The MTPA ester of the alcohol was prepared by standard procedure.[17] Racemic alcohols of the ketones were obtained by reducing with $NaBH_4$. All the racemic alcohols were converted to the MTPA esters and analyzed on a capillary GC to obtain the diastereomeric pairs of peaks. Then the optically active esters were analyzed to obtain the enantiomeric excess.

Reduction of Ketones with Alpine-Borane. General Procedure. To a 50-mL round-bottomed flask fitted as usual,[16] 12 mmol of the reagent was added, followed by the acetylenic ketone (10 mmol) and the mixture stirred at rt. The reaction was followed by ^{11}B NMR of an aliquot dissolved in EE. When the reaction was complete (^{11}B δ: 52 ppm), acetaldehyde (3 mmol) was added at 0 °C and stirred at rt for 30 min. EE (20 mL) was then added to the reaction mixture followed by ethanolamine (12 mmol) and stirred for 1 h. The precipitated boron component was filtered and washed with pentane. The filterate was concentrated and distilled to yield the alcohol. The MTPA ester was then prepared and analyzed on an appropriate capillary GC column to determine the % ee.

R-(−)-1-Phenyl-2-fluoroethanol, 4c.

(a) From reduction with 1. The reduction of **3c** in EE at −25 °C with **1** was complete in 1 h. Workup gave the product **4c** in 80% yield. bp 101-102 °C/12 mm Hg (lit.[20] bp 103 °C/12 mm Hg). IR: ν_{max} cm $^{-1}$ neat: 3379 (OH); $[\alpha]_D^{23}$ = −76.2 (*c* 3, MeOH) which corresponds to an optical purity of 96.2% in the *R* isomer based on the literature $[\alpha]_D$ = −67.3 (*c* 0.94, MeOH) for the 85% ee in the *R*-isomer.[20] Analysis of the MTPA derivative on a Supelcowax capillary column showed it to contain 97.7% of the *R*-isomer and 2.3% of the *S*-isomer, i. e. an ee of 95.4% in the *R* isomer.

(b) From reduction with 2. The reduction of **3c** with **2** was complete in 4 d. Workup provided 80% yield of **4c**. The analysis of the MTPA ester revealed 94.27% in the *R*-isomer and 5.73% in the *S*-isomer, i. e. an ee of 88.54% ee in the *R*-isomer.

R-(−)-1-Phenyl-2,2-difluoroethanol, 4e.

(a) From reduction with 1. The reduction of **3e** in EE at −25 °C with **1** was complete in 0.5 h. Workup gave **4e** in 60% yield. bp 64-65 °C/5 mm Hg (lit.[19] bp 97-99/9 mm Hg). $[\alpha]_D^{23}$ = −14.27 (*c* 3, CH_2Cl_2) which corresponds to an optical purity of 81% in the *R* isomer based on the literature $[\alpha]_D^{22}$ = −7.7 (*c* 3, CH_2Cl_2) for 43.7% ee in the *R*-isomer.[23] Analysis of the MTPA derivative on a Supelcowax capillary column showed it to contain 92.33% of the R-isomer and 7.67% of the S-isomer, i. e. an ee of 84.66% in the R isomer.

(b) From reduction with 2. The reduction of **3e** with **2** was complete in 4 d. Workup provided the product alcohol in 69% yield. $[\alpha]_D^{22}$ = −16.3 (*c* 3, CH_2Cl_2). Analysis of the MTPA derivative on a Supelcowax capillary column showed the product to be of 97% ee in the *R*-isomer.

R-(+)-1-fluoro-2-octanol, 6b.

From reduction with 1. The reduction of **5b** with **1** was complete in 6 h. Workup provided the product alcohol in 72% yield. bp 103 °C/12 mm Hg. IR: ν_{max} cm^{-1} (neat): 3431 (OH); ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, *J* = 6.6 Hz, 3H, -C<u>H</u>$_3$), 1.22-1.51 (m, 10H, -(C<u>H</u>$_2$)$_5$-CH$_3$), 2.32 (s, 1H, OH), 3.80-3.94 (m, 1H, C<u>H</u>OH), 4.30 (ddd, *J* = 47.9, 9.4, 6.8 Hz, 1H, C<u>H</u>H'F-), 4.39 (ddd, *J* = 46.6, 9.4, 3.0 Hz, 1H, CH<u>H</u>'F-); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.50, 23.03, 25.77, 29.67, 32.16, 32.28 (d, *J* = 6.4 Hz), 70.94 (d, *J* = 18.5 Hz, C_2), 87.51 (d, *J* =168.3 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): −228.11 (dt, *J* = 47.4, 18.3 Hz). Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 40% ee (*R*).

From reduction with 2. The reduction of **5b** with **2** was complete in 9 d and the usual ethanolamine workup provided the product **6b** in 82% yield. The MTPA ester of this product, on analysis using a GC with SPB-5 capillary column showed an ee of 65%. $[\alpha]_D^{21}$ = +7.41 (*c* 1.0, MeOH).[24] The configuration of the

product was assigned as *R* by comparing with the gas chromatogram of the MTPA of the product obtained by hydrogenating the corresponding acetylenic alcohol of known configuration as given below.

From hydrogenation of the acetylenic alcohol. A solution of *S*-1-fluoro-3-octyn-2-ol[8] (25 mmol) in THF was externally hydrogenated in the presence of 5% Pd on activated carbon in a Brown's hydrogenator[25] until no more hydrogen was abosorbed. The suspension was filtered through celite and washed with 2 mL of THF. The combined solution and washings were distilled to yield 94% of **6b**. Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 78% ee in the opposite isomer as obtained from the reduction with **2** above.

S-(−)-1,1-difluoro-2-octanol, 6c.

From reduction with 1. The reduction of **5c** with **1** was complete in 6 h. Workup provided the product alcohol in 72% yield. bp 103 °C/12 mm Hg (lit.[21] bp 106-08 °C/11 Torr). Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 32% ee (*S*). IR: ν_{max} cm^{-1} (neat): 3381 (OH); ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, *J* = 6.7 Hz, 3H, -CH_3), 1.20-1.70 (m, 10H, -(CH_2)$_5$-CH_3), 2.0 (d, *J* = 4.2 Hz, 1H, OH), 3.65-3.80 (m, 1H, CHOH), 5.61 (dt, *J* = 56.2, 4.2 Hz, 1H, CHF_2-); ^{13}C NMR δ (ppm) ($CDCl_3$): 14.51, 23.04, 25.30, 29.56, 30.48, 32.12, 71.64 (t, *J* = 23.2 Hz, C_2), 116.87 (t, *J* =243.5 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): −129.75 (ddd).

From hydrogenation of the acetylenic alcohol. A solution of *S*-1,1-Difluoro-3-octyn-2-ol[8] (25 mmol) in THF was externally hydrogenated as described above to yield 95% of **6c**. $[\alpha]_D^{21}$ = −21.63 (*c* 2.0, $CHCl_3$) which corresponds to ≥99% ee in the *S*-isomer based on the maximum rotation $[\alpha]_D$ = −20.1 (*c* 1.14) reported in the literature for 99% ee.[26] Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 88% ee in the same isomer as obtained above.

(R)-(+)-1,1-difluoro-2-octanol, 6c. The reduction of **5c** with **2** was complete in 10 d and the usual workup provided **6c** in 78% yield. The MTPA ester of this alcohol, on analysis, showed 50% ee in the *opposite* isomer as compared to the **6c** produced from the reduction with **1** and the hydrogrenation of the corresponding acetylenic alcohol of *S*-configuration.

(S)-(−)-1,1,1-trifluoro-2-octanol, 6d.

From reduction with 1. The reduction of **5d** with **1** was complete in 8 h. Workup provided the product alcohol in 74% yield. bp 167-68 °C/740 mm Hg. $[\alpha]_D^{21}$ = −24.19 (*c* 1.5, $CHCl_3$) which corresponds to an optical purity of 85.3% in the *S* isomer based on the reported maximum rotation[26] of $[\alpha]_D^{21}$ = −27.5 (*c* 1.49, $CHCl_3$) for 97.5% ee. Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 91% ee. IR: ν_{max} cm^{-1} (neat): 3367 (OH); ^1H NMR δ (ppm) ($CDCl_3$): 0.90 (t, *J* = 6.8 Hz, 3H, -CH_3), 1.21-1.78 (m, 10H, -(CH_2)$_5$-CH_3), 2.50 (d, *J* = 4.6 Hz, 1H, OH), 3.82-3.96 (m, 1H, CHOH); ^{13}C NMR δ (ppm) ($CDCl_3$): 14.47, 23.04, 25.36, 29.37, 30.06, 32.08, 71.05 (q, *J* = 30.9 Hz, C_2), 125.21 (q, *J* =281.9 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): −80.11 (d, *J* = 6.6 Hz).

From reduction with 2. The reduction of **5d** with **2** was complete in 14 d. The usual workup provided **8d** in 72% yield. Analysis of the MTPA ester of this product on a SPB- capillary column showed an ee of 60% in the same isomer as that obtained from reduction with **1** and the hydrogenation of the corresponding acetylenic alcohol of *S*-alcohol.

From hydrogenation of the acetylenic alcohol. A solution of *S*-1,1,1-trifluoro-3-octyn-2-ol[8] (25 mmol) in THF was externally hydrogenated as described above to yield 93% of **6d**. Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 98% ee in the same isomer as obtained above.

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