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Chiral Synthesis *Via* Organoboranes. 38. Selective Reductions. 48. Asymmetric Reduction of Trifluoromethyl Ketones by *B*-Chlorodiisopinocampheylborane in High Enantiomeric Purity†

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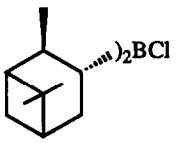
Abstract: (–)-*B*-Chlorodiisopinocampheylborane [(–)-DIP-Chloride™, **1**], introduced by us several years ago, has been shown to reduce prochiral aryl and alkyl perfluorinated ketones to the corresponding optically active alcohols in very high ee. For example, 2,2,2-trifluoroacetophenone, trifluoroacetyl-1-naphthalene, and trifluoroacetyl-2-naphthalene are all reduced with **1** within 1-3 d at rt in 90% ee, 78% ee and 91% ee, respectively. The optical purity of 1-phenyl-2,2,2-trifluoroethanol is upgraded to ≥99% ee by crystallizing the initially formed product from pentane. 1,1,2,2,2-Pentafluoropropiophenone and 1,1,2,2,3,3,3-heptafluorobutyrophenone are reduced in 3 d with **1** to the corresponding alcohols in 92% ee and 87% ee, respectively. The reagent reduces alkyl trifluoromethyl ketones at a rate faster than that of the aryl derivatives, while still providing the product alcohols in very high ee. Thus, 1,1,1-trifluoroacetone, 1,1,1-trifluorononan-2-one, and 1,1,1-trifluorodecan-2-one are all reduced within 4-8 h in 89% ee, 92% ee, and 91% ee, respectively. Even α-*sec*-alkyl trifluoromethyl ketones are handled by **1** very efficiently. Thus cyclohexyl trifluoromethyl ketone is reduced by **1** at rt in 12 h to the product alcohol in 87% ee. In all of these cases the trifluoromethyl group acts as the enantiocontrolling larger group as compared to the aryl or alkyl group. This produces alcohol products with stereochemistry opposite to those obtained for the corresponding hydrogen analogs. The steric and electronic influence of the trifluoromethyl group in achieving enantiocontrol in asymmetric reductions is discussed.

Asymmetry in organic molecules was recognized more than a century ago.[2] The concept of asymmetric synthesis is also known for nearly a century.[3] The tragedies of the Thalidomide babies highlighted the importance of producing enantiomerically pure pharmaceuticals, emphasizing the desirability of achieving asymmetric synthesis.[4] This area of organic synthesis has received considerable attention in the past decade, with promising success. While the medicinal chemists and pharmacologists emphasized the structure-activity relationships (SAR)[5] between molecules and man, the organic chemists developed efficient strategies to synthesize optically pure molecules, making the SAR studies worth-while. The new guidelines of the Food And Drug Administration[6] for manufacturing pharmaceuticals have provided an added impetus to the chiral synthesis program.

A number of research groups around the world have explored their own unique strategies for synthesizing such molecules in enantiomerically pure form.[7] We approached this project *via* chiral organoboranes.[8] Our strategy involves a three-pronged approach to asymmetric synthesis. They are (1) asymmetric hydroboration and related reactions, (2) asymmetric reduction, and (3) asymmetric allyl- and crotylboration. Using these three approaches we can now synthesize thousands of pure enantiomers.

†Dedicated to Professor Shun-ichi Yamada in appreciation of his outstanding contributions to chiral synthesis.

As part of our asymmetric reduction program, we have developed several efficient chiral reducing agents that can achieve the asymmetric reduction of several classes of ketones.[9] One of the successful reagents, *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™, **1**)[10] is applicable to the synthesis of several pharmaceuticals.[11] One class of *secondary* alcohol that is potentially very important in the synthesis of certain pharmaceuticals is the fluoro alcohol. The importance of chiral compounds containing fluorine atoms in organic and medicinal chemistry has been summarized in several reviews.[12] Compounds containing a carbon-fluorine bond constitute 6.2% of the ten million registered by Chemical Abstracts.[13] The brisk activity in the field of organofluorine chemistry with the surprizes that often emerge from research in this area led Professor Dieter Seebach to coin a new term, *Flustrates* (Fluorine-containing substrates).[14] We decided to extend our ongoing project in chiral reductions, to "flustrates". Accordingly, we undertook a study of the asymmetric reduction of representative prochiral fluorinated aromatic and aliphatic ketones using **1**.

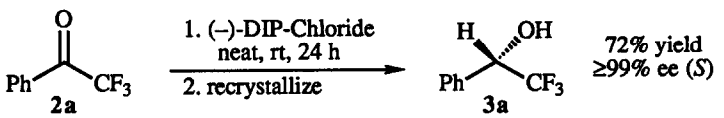


(–)-DIP-Chloride™, **1**

The asymmetric reduction of prochiral trifluoromethyl ketones has interested many organic chemists in the past.[15] The major electronic influence of the trifluoromethyl group in achieving enantiocontrol of chiral reductions have been considered by Mosher,[16] Nasipuri,[17] and Kobayashi.[18] A discussion of the stable conformations undergoing reduction[19a] and the entropy factors[19b] explaining the observed behavior of the trifluoromethyl group in chiral reduction was made by Lardicci. However, all of the above discussions are based on reductions which achieved relatively poor enantiomeric excess (ee). Mosher studied this aspect in great detail, but could not arrive at any conclusion rather than some mechanism is operative different from that which provided enantiocontrol in the reduction of hydrocarbon ketones.[16] He states that postulating that the $-CF_3$ group acts as though it were a group larger than phenyl would be incompatible with other evidence.

Our interest in the reduction of these fluorinated ketones was aroused by the fact that the product chiral fluorinated alcohols are potentially of immense importance in biological and medicinal chemistry[12] and for materials in non-linear optics.[20] Optically pure aryl trifluoromethyl alcohols are widely used for chiral stationary phases in liquid chromatography[21] and as chiral solvating agents both in NMR and Mass Spectrometry.[22] In addition, we were interested in understanding the puzzles provided by trifluoromethyl ketones during their asymmetric reduction.[15-19]

DIP-Chloride is an excellent reagent for the reduction of aralkyl ketones.[10] Based on this we anticipated very high ee for the product alcohols in the reduction of aryl fluoroalkyl ketones. When we treated 2,2,2-trifluoroacetophenone (**2a**) with **1** under our standard conditions (ethyl ether (EE), 1*M*, –25 °C), the reaction was very slow. At room temperature (rt), without solvent, the reaction was complete in 24 h providing 90% yield of the *S*-alcohol[23] (**3a**) in 90% ee. Crystallization from pentane at 0 °C upgraded the ee to ≥99% with 80% recovery of **3a** (eq 1).



(1)

The % ee is high, as anticipated. But, the slow rate of reduction was unexpected. So was the inversion in the observed stereochemistry of **3a**. The tentative mechanism of reduction (Scheme I) and the results realized in the reduction of acetophenone[10] had led us to expect the *R*-alcohol. If the direction of reduction is controlled by steric interactions, as proposed for the reaction of acetophenone with **1**, it follows that the CF_3 group must be

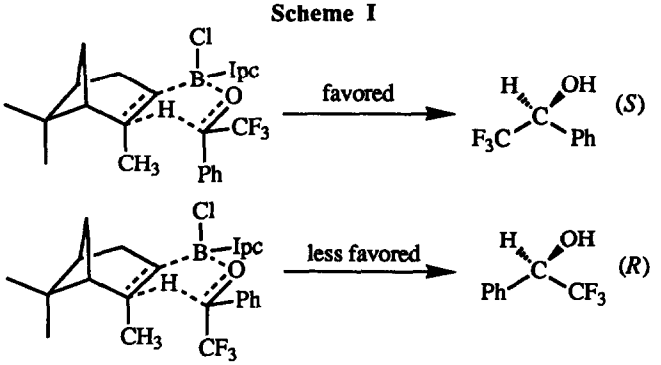
bulkier than the phenyl group. This is the problem that Professor Mosher encountered three decades ago.[15] Apart from studying the efficiency of **1** in the chiral reduction of trifluoromethyl ketones, we undertook this project in the hope of realizing a better understanding of the reasons for the inversion of the stereochemistry. The results are presented in this paper.

RESULTS AND DISCUSSIONS

Reduction of Aryl Perfluoroalkyl Ketones

The reaction of **2a** with **1** at rt without solvent is complete within 24 h as determined by ^{11}B NMR spectrometry. We used our modified workup procedure using acetaldehyde[24] to isolate the product alcohol in 90% yield, and in 90% ee in the (*S*)-isomer, determined as the menthyloxy carbonyl (MCF) derivative[25] on a capillary GC. Crystallizing the product from pentane at 0 °C, 80% of the alcohol was recovered in ≥99% ee. Based on the capability of **1** in reducing aralkyl ketones in high ee, we were pleased with the ee obtained, especially for a reaction at rt. However, the inversion in stereochemistry for **3a** as compared to the reduction product of acetophenone was unexpected. The proposed transition state model[10] for chiral reductions with **1** that accounts for the (*S*) isomer for the product **3a** shows that the $-CF_3$ group must be more enantiocontrolling than the phenyl group (Scheme I). In the reduction of hydrocarbon ketones with **1**, the bulkier of the two groups attached to the prochiral ketone, RR'CO, controls the stereochemistry of the reduction process. The question then arises whether $-CF_3$ can be bulkier than Ph.

Scheme I



Transition State Models for the Asymmetric Reduction of Trifluoroacetophenone with (–)-DIP-Chloride

It was recognized previously that the $-CF_3$ group behaves as though it is bulkier than a phenyl group in asymmetric reductions.[15] A search of the recent literature was undertaken to see whether the behavior of a $-CF_3$ versus an aryl group is the same for all the chiral reducing agents that have been utilized for the asymmetric reduction of this type of ketone. The data comparing the reduction of $ArCOCH_3$ and $ArCOCF_3$ with various asymmetric reagents is summarized in Table 1. As can be seen the trend is not general. However, it must be noted that all hydride reagents, aluminum or boron based, give the same stereochemistry for the product alcohols derived from the reduction of $ArCOCH_3$ and $ArCOCF_3$. Chong et. al. studied Binal-H[26] which reduces **2a** in 27% ee at –60 °C, whereas 9-anthryl trifluoromethyl ketone (**2d**) is reduced in very high ee (56%-98%) depending on the stoichiometry and the temperature of the reaction.[27] Both of the alcohols **3a** and **3d** show no inversion in stereochemistry. Another hydride reagent derived by modifying $LiAlH_4$ with a chiral sulfamide also gives trifluoromethyl 9-anthryl methanol of 55% ee with the same stereochemistry as the methyl analogue.[28] Midland's NB-Enantride provides **3a** in 50% ee without any inversion in stereochemistry as compared to phenethyl alcohol obtained by reduction with the same reagent.[29] Another borohydride reagent, K-Glucoride, also provides **3a** in 48% ee without inversion of stereochemistry.[30] Chong reports that Corey's CBS catalyst-BH_3 mixture[31a] gives very poor ee (16% yield, 18% ee) for a reaction of **2a**.[27] The product alcohol is obtained

in opposite stereochemistry as compared to the methyl analogue. However, Corey recently reported that changing the hydride donor to catecholborane, very high ee (90%) for **3a** can be obtained.[31b] Again the alcohol obtained is of the opposite stereochemistry. The reduction of aryl trifluoromethyl ketones with bakers' yeast gives the product alcohols in 44-66% ee with the same stereochemistry as that of the methyl analogue.[32] It is surprizing to note that the first successful chiral organoborane reducing agent, Midland's Alpine-Borane, gives **3a** of the same stereochemistry when compared to a reduction of acetophenone.[33] The mechanism of reduction for Alpine-Borane[34] and DIP-Chloride[10] is essentially similar. Yet, they provide the alcohols of opposite configuration. This may indicate that the presence of a chlorine atom in the reagents[10,16,17] exerts a significant influence on the stereochemistry of the trifluoromethyl alcohols produced.

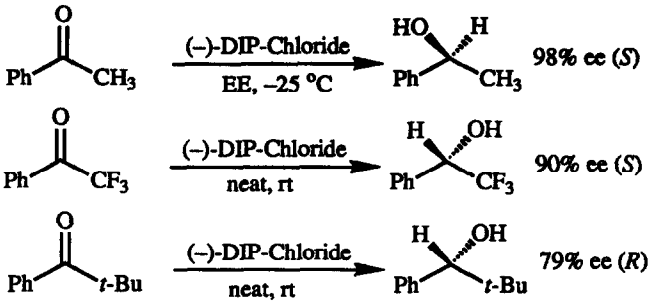
Table 1. Comparison of the Stereochemistry of Product Alcohols from the Asymmetric Reduction of Aryl Trifluoromethyl Ketones With Several Reagents

Ar-CO-CF_3 Ar	reagent	reactn condn	% ee (isomer)	stereochem compared to Ar-CO-Me	ref
Ph	Mosher's reagent	THF, 0 °C	50 (*S*)	opposite	16
Ph	Nasipuri's reagent	THF, –78 °C	77 (*S*)	opposite	17
Ph	*R*-Binal-H	THF, –60 °C	27 (*S*)	same	27
9-anthryl	*R*-Binal-H	THF, –20 °C	98 (*S*)	same	27
9-anthryl	LAH-sulfamide	THF, –78 °C	55 (*S*)	same	28
Ph	NB-Enantride	THF, –78 °C	50 (*S*)	same	29
Ph	K-Glucoride	THF, –78 °C	48 (*S*)	same	30
Ph	CBS cat/BH_3	THF, –78 °C	18 (*R*)	opposite	27
Ph	CBS cat/catecholborane	THF, –78 °C, 15 h	90 (*R*)	opposite	31b
9-anthryl	CBS cat/catecholborane	THF, –78 °C, 72 h	94 (*R*)	opposite	31b
Ph	Bakers' yeast	H_2O, rt, 2 d[a]	44 (*S*)	same	32
Ph	Alpine-Borane	neat, rt, 45 d[b]	35 (*R*)	same	33a
Ph	Alpine-Borane	6000 atm, rt, 3 d	54 (*R*)	same	33b
Ph	DIP-Chloride	neat, rt, 24 h	90 (*S*)	opposite	
9-anthryl	DIP-Chloride	neat, rt, 30 d[c]	82 (*S*)	opposite	

[a] 80% reaction complete. [b] 90% reaction complete. [c] 60% reaction complete.

The above comparison did not lead to a fixed pattern in the reduction wherein the inversion in stereochemistry could be ascribed either to the steric size of the –CF_3 group or to its electronic influence, or both. Earlier we had shown that a product of opposite configuration is produced in the reduction of pivalophenone with **1** (Scheme II).[10] In this case, the opposite configuration of the product alcohol is attributed to the steric crowding of the *tert*-butyl group.[35] A comparison of this kind indirectly states that a –CF_3 group is similar to a *tert*-butyl group in terms of enantiocontrolling capability. (A recent report in the literature involving the kinetic resolution of fluoroalkyl vinyl carbinols also suggests that a –CF_3 group tends to be like a *tert*-alkyl group.[36]) The rate of reduction of **2a** with **1** (24 h) is considerably faster than that of pivalophenone (60% reaction in 12 d). In general sterically hindered ketones are reduced at a slower rate.[10,25] If we assume that the –CF_3 group is as bulky as a *tert*-butyl group, then the fast reaction of the trifluoromethyl ketone might be due to the electron-withdrawing effect of the –CF_3 group, as has been observed in the case of α-keto esters and α,β-acetylenic ketones.[33a, 37] In the literature, studies of the size of a –CF_3 group have shown it to be only as bulky as an isopropyl group.[38a] An isopropyl group acts as a smaller moiety, less enantiocontrolling, compared to a phenyl group in chiral reductions.[10]

Scheme II



The above facts warrant a comparison of the physical nature of the $-CH_3$, $-CF_3$ and $-C(CH_3)_3$ groups. In Table 2 we have compiled the effective van der Waals radii and diameter of these three groups from two different studies.[38] A crude way of comparison of these three groups would be to compare the molar volumes of similar compounds bearing these moieties. Thus while the molar volume for acetophenone is 116.5 mL, the molar volume of **2a** is 138.8 mL and pivalophenone is 167.25 mL, respectively.[39] A similar trend can be seen if one compares the molar volumes of acetone (73.43 mL), 1,1,1-trifluoroacetone (89.5 mL), and pinacolone (125.04 mL) also. The values in Table 2 show that the steric requirements of a *tert*-butyl group is much more than those of a $-CF_3$ group and in fact, the latter is much closer to a $-CH_3$ group than a $-C(CH_3)_3$ group in its steric requirements. This suggests that the inversion in configuration of the product trifluoromethyl alcohol in the reduction with DIP-Chloride might probably be due to a combined steric and electronic effect, the latter assuming more influence. But before making any conclusion we decided to treat a series of trifluoromethyl ketones with **1**.

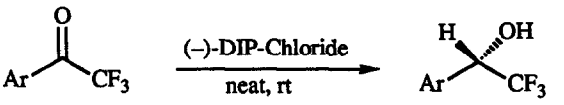
Table 2. Comparison of the Physical Properties of $-CH_3$, $-CF_3$, and $-C(CH_3)_3$ Groups

property	$-CH_3$	$-CF_3$	$-C(CH_3)_3$
van der Waals radius, Å[a]	1.8	2.2	3.6
van der Waals diameter, Å[b]	4.0	5.1	6.2
Energy barrier for rotation, Kcal/mol[c]	2.9	3.3	4.3
Conformational energy barrier, Kcal/mol[d]	1.7	2.4	5.3
Molar volume for a methyl ketone, mL[e]	73.43	89.5	125.04
Molar volume for a phenyl ketone, mL[e]	116.65	138.8	167.25

[a]derived from the rotational barriers in biphenyls.[38a] [b]considering the group as a spinning top.[15] [c]for rotation about a C–C bond in ethane.[15] [d]in a cyclohexane ring chair to boat conversion.[15] [e]ref. 39.

We prepared 1-naphthyl and 2-naphthyl trifluoromethyl ketones (**2b** and **2c**) from the corresponding naphthyllithium and ethyl trifluoroacetate by slightly modifying a literature procedure.[27] We used boron trifluoride etherate (BF_3·EE) as a catalyst for the reaction since the addition of BF_3·EE increases the yield of the ketone considerably.[40] We treated **2b** and **2c** with **1** without solvent at rt. The reaction is complete in 3 d and the product alcohols **3b** and **3c**, respectively are obtained in 93% and 92% isolated yields. The products were analyzed as their MCF derivative on a capillary GC to reveal 78% ee (*S*) and 91% ee (*S*), respectively (eq 2). Here again, the configuration of the product alcohols shows that the $-CF_3$ group controls the enantioselection. The decreased ee in the case of **3b** might be due to the increased steric interaction between the methyl group at the 2-position of the pinanyl moiety and the naphthyl group that it has to encounter when the $-CF_3$ group acts as the cotrolling group in our proposed transition state model (Scheme I). When 9-trifluoroacetyl anthracene (**2d**) was treated with **1**, the reaction was extremely slow.[27] Only 60% reaction was achieved in 30 d (^{11}B NMR).

We quenched the reaction with acetaldehyde, worked up, and separated the product alcohol from the unreacted ketone by chromatography. It was of 82% ee (eq 2). Again the $-CF_3$ group acts as the enantiodirector. The latter case also suggests that it might be the electronic effects of the trifluoromethyl group that play a more vital role than its steric requirements in controlling the enantioselectivity.

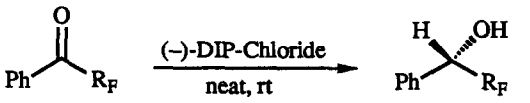


2b Ar: 1-naphthyl
2c Ar: 2-naphthyl
2d Ar: 9-anthryl

3b Ar: 1-naphthyl 78% ee
3c Ar: 2-naphthyl 91% ee
3d Ar: 9-anthryl 82% ee

(2)

In an effort to understand the effect of the fluorine substituent in asymmetric reduction better, we prepared 2,2,3,3,3-pentafluoropropiophenone (**2e**) and 2,2,3,3,4,4,4-heptafluorobutyrophenone (**2f**) from phenyllithium and the corresponding ethyl perfluoroalkanoate using a procedure similar to that used for the preparation of **2b** and **2c**. The reaction of these ketones with **1** is complete in 3 d and workup provided the alcohols in 82% and 81% yields and in 92% ee and 87% ee, repectively (eq 3). We obtain the (*S*) isomer in these cases also.



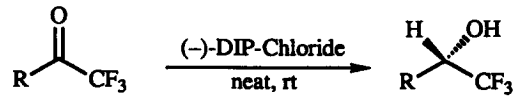
2a R_F: CF_3
2e R_F: C_2F_5
2f R_F: C_3F_7

3a R_F: CF_3 90% ee
3e R_F: C_2F_5 92% ee
3f R_F: C_3F_7 87% ee

(3)

Reduction of Alkyl Trifluoromethyl Ketones

In all the cases studied thus far, an aryl perfluoroalkyl ketone was treated with **1** and in each case we obtain the product alcohol wherein the perfluoroalkyl group acts like a *tert*-butyl group. We were curious to study alkyl perfluoroalkyl ketones with **1**. We expected high ee for the product alcohols, coupling the facts that (1) a *tert*-butyl alkyl ketone or any α-hindered ketone can be reduced with **1** in very high ee[10] and (2) a $-CF_3$ group acts like a *tert*-butyl group in asymmetric reduction with **1** as shown in the above discussion. When we treat the commercially available 1,1,1-trifluoroacetone (**2g**) with **1** at –25 °C, in EE we obtain the product alcohol **3g** in 72% yield and 96% ee. The reaction was slow and it takes 4 d for completion. The same reaction is complete within 4 h at rt without solvent and the product is obtained in 89% ee (eq 4). The electronic and steric effects should concur in this case and the product obtained is the (*S*) isomer as determined by comparing the sign of optical rotation with that reported in the literature.[16] In order to determine whether the high ee obtained is a norm for the reaction of a trifluoromethyl alkyl ketone with **1**, we synthesized *n*-alkyl trifluoromethyl ketones **2h** and **2i** using a literature procedure[41] and treated them with **1**. Since the reaction of **2g** was slow at –25 °C, we carried out the reaction of **2h** and **2i** at rt. It was complete in 8 h and provided the (*S*)-alcohol in 92% ee and 91% ee, respectively. It is noteworthy here that a Binal-H reduction of **2i** at –100 °C provides **3i** of only 61% ee.[42]



(4)

2g R: CH_3 **3g** R: CH_3 89% ee (*S*)
2h R: n-C_7H_{15} **3h** R: n-C_7H_{15} 92% ee (*S*)
2i R: n-C_8H_{17} **3i** R: n-C_8H_{17} 91% ee (*S*)

Table 3. Asymmetric Reduction of Fluorinated Ketones With DIP-Chloride at 25 °C

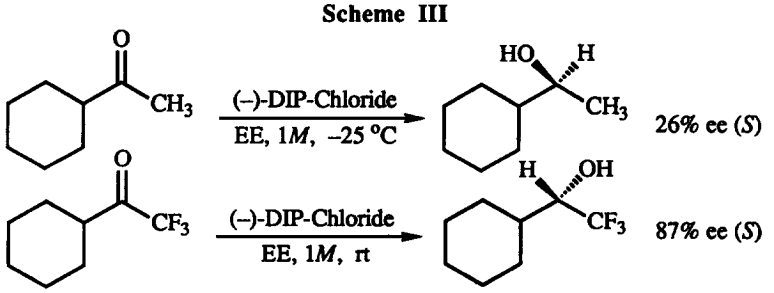
ketone	R-CO-R_F R	R_F	react time, h	yield, isol.	$[\alpha]_D$	% ee[a]	isomer
2a	Ph	CF_3	24	90	+37.64° (neat)[b]	90	*S*
2b	1-Naphth	CF_3	72	93	+20.35° (*c* 5.17, EtOH)	78	*S*
2c	2-Naphth	CF_3	72	92	+35.1° (*c* 4.14, EtOH)	91	*S*
2d	9-anthryl	CF_3	30 d[c]	48	+24.61° (*c* 6.1, $CHCl_3$)	82	*S*
2e	Ph	C_2F_5	72	82	+28.95° (*c* 2.69, EtOH)	92	*S*
2f	Ph	C_3F_7	72	81	+23.02° (*c* 2.32, EtOH)	87	*S*
2g	CH_3	CF_3	3	70	– 5.60° (neat)	89	*S*
2g	CH_3	CF_3	96	72	– 6.24° (neat)	96[d]	*S*
2h	n-C_7H_{15}	CF_3	8	80	–23.35 (*c* 2.6, $CHCl_3$)	92	*S*
2i	n-C_8H_{17}	CF_3	8	87	–20.44° (*c* 3.84, MeOH)	91	*S*
2j	Chx	CF_3	12	75	–17.82° (*c* 7.5, $CHCl_3$)	87	*S*
2k	*t*-Bu	CF_3	very slow reaction				

[a] ee determined as their MTPA or MCF derivative on a capillary GC. [b] α_D^{25}. On crystallization from pentane at 0 °C, α_D^{22} improved to +42.18° which corresponds to ≥99% ee. [c] 60% reaction was complete in 30 d. [d] For a reaction at –25 °C

Reduction of Branched-Alkyl Trifluoromethyl Ketones

Having obtained very high ee for the reduction of straight chain alkyl trifluoromethyl ketones with **1** we were now interested in testing the limits of the capability of the trifluoromethyl group in directing chirality in the product alcohols. We prepared cyclohexyl trifluoromethyl ketone (**2j**), a ketone with branching at the α-position of the carbonyl moiety, and treated it with **1**. The reaction is complete in 12 h at rt and the alcohol is obtained in 87% ee in the (*S*) isomer.[43] Considering that the reaction of the corresponding hydrogen analog acetylcyclohexane gives only 26% ee (*S*) with **1** at –25 °C for the product alcohol,[10] the high ee realized in the reduction of **2j** reveals the major influence of the $-CF_3$ group (Scheme III). This shows that *if the $-CF_3$ group is not sterically as bulky as a t-Bu group, it exerts enormous electronic influence in chiral reductions with 1.* Our attempts to compare the result with that of cyclohexyl *tert*-butyl ketone[44] failed since this ketone resists reduction with **1** at an appreciable rate. Using ^{11}B NMR spectrometry as the probe, we observed an insignificant amount of reaction after several months.

Scheme III



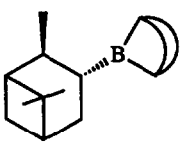
Limits of the Reagent

If we could compare the effect of a *tert*-butyl and a $-CF_3$ group in asymmetric reduction with **1** directly, i. e. reduce *tert*-butyl trifluoromethyl ketone with **1** and see the configuration of the product alcohol, we felt that we could obtain some insight into the puzzle. Since we believe that the *tert*-butyl group is considerably larger than a trifluoromethyl group (Table 2), this reaction would show the electronic influence in reduction with **1**. We prepared **2k** using a literature procedure.[45] However, the reaction of **2k** with **1** at rt without solvent is extremely slow, only <10% complete after 4 months. We did not pursue this reaction.

The results of the chiral reduction of fluorinated ketones are presented in Table 3. As can be seen from the Table, perfluoroalkyl ketones are reduced by **1** in very high ee in a consistent manner. As mentioned earlier several other reagents available for asymmetric reduction could not reduce this class of ketone in very high ee. Alpine-Borane reacts very slowly with perfluorinated ketones. Binal-H is not consistent in its results for aryl fluoroalkyl ketones[27] and alkyl fluoroalkyl ketones are reduced in only modest ee.[42] Other hydride reagents are a failure thus far. While CBS reduction requires catecholborane as the hydride source and the low temperature (–100 °C) for obtaining high ee, the reaction conditions for **1** (rt, neat) are considerably more convenient.

Reduction with Alpine-Borane

The reduction of **2a** with the other widely used organoborane reagent Alpine-Borane (**4**) was extremely slow, requiring 45 d for 90% completion and provides the product alcohol in 32% ee with the same stereochemistry when compared to the product from the reduction of acetophenone. The decreased ee could be due to the dehydroboration of the reagent, followed by reduction with the 9-BBN.[34] To confirm the result



R-Alpine-Borane, **4**

obtained in the reduction of **2a** with **4**, we treated **2e** and **2f** also with **4**. The reactions were extremely slow. After 20 d, only 20% of **2e** and 15% of **2f** had reacted with **4** (^{11}B NMR). We worked up the reaction at this stage and analyzed for the % ee and the configuration of the partially formed product alcohol. We obtain 40% ee for **3d** and 48% ee for **3e**, respectively. In both the cases we have the (*R*)-alcohol showing that the approach of the ketones in the transition state for the reagents **1** and **3** are opposite. The results are summarized in Table 4. Assuming that a similar mechanism of reduction is operative in both the cases with a similar transition state model where the methyl group at the 2-position of the pinanyl group controls the chiral outcome, the inversion of configuration in the case of the reduction with **1** is puzzling. We have utilized this transition state model to design better chiral reducing agents, proving that this model is at least partially correct.[46] Most probably the inversion in stereochemistry could be attributed to the electronic interaction between the fluorine atoms of the ketone and the chlorine atom of the reagent.

Table 4. Asymmetric Reduction of Fluorinated Ketones With Alpine-Borane, **4** at 25 °C

ketone	R-CO-R_F		react time, d	% reactn[a]	% ee[b]	isomer
	R	R_F				
2a	Ph	CF_3	45	90	32	*R*
2e	Ph	C_2F_5	20	20	40	*R*
2f	Ph	C_3F_7	20	15	48	*R*

[a] determined by ^{11}B NMR. [b] % ee determined as their MCF or MTPA derivative on a capillary GC.

CONCLUSIONS

In conclusion, DIP-Chloride reduces trifluoromethyl ketones to the corresponding alcohols in very high ee in a consistent manner. Our strategy to modify the steric and electronic environment around boron to produce efficient chiral reducing agents has succeeded in the reduction of trifluoromethyl ketones also. DIP-Chloride is unique in reducing alkyl trifluoromethyl ketones in high ee. Other asymmetric reductions attempted for an alkyl trifluoromethyl ketone with Binal-H and baker's yeast gave the product alcohols in only moderate ee. The reasons forcing the trifluoromethyl group to act as the enantiodirector is not yet clear though we feel that it could be due to the combined steric and electronic influence of the fluorine atoms. We are currently studying this aspect in detail. Theoretical interests on the influence of the fluorine atom aside, we obtain chiral fluorinated alcohols in very high ee. These alcohols are potentially of considerable importance in organic, biological, pharmaceutical, and materials chemistry. Ready availability of both enantiomers of DIP-Chloride now makes these alcohols easily accessible. This widens further the utility and scope of DIP-Chloride.

EXPERIMENTAL SECTION

General Methods

Techniques for handling air-sensitive compounds have been previously described.[47] ^{1}H, ^{13}C and ^{11}B NMR spectra were plotted on a Varian Gemini-300 spectrometer and 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, 1,1,1-trifluoroacetone, 2,2,2-trifluoroacetophenone, 9-anthryl trifluoromethyl ketone, cyclohexylmagnesiumchloride, trifluoroacetic acid, ethyl trifluoroacetate, ethyl octanoate, ethyl nonanoate, boron trifluoride etherate, 1-naphthylbromide, 2-naphthylbromide, phenyllithium, ethanolamine, acetaldehyde, menthyl chloroformate, were all obtained from Aldrich Chemical Co. Preparation of the perfluoroalkyl ketones are detailed below. *R*-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure.[48]

Preparation of the Perfluoroalkyl Ketones

Method A. Reaction of aryllithium with ethyl perfluoroalkanoate in the presence of BF_3·EE.[27,40] ***General procedure.*** A cool (0 °C) ether solution of the aryllithium (50 mmol) was added to an ether solution of ethyl perfluoroalkanoate (1.4 equiv, 70 mmol) at –78 °C. This was followed by the addition of 7.5 mL of BF_3·EE and the mixture was stirred at –78 °C for 1.5 h. Saturated aqueous ammonium chloride (30 mL) was then added and the slurry was warmed to rt. The ether layer was washed with brine and dried over $MgSO_4$. The crude ketone was purified by distillation under vacuum.

Method B. Reaction of ethyl alkanoate with LDA and ethyl trifluoroacetate followed by reaction with H_2SO_4.[41] Preparation of 1,1,1-trifluorodecan-2-one (**2i**) is representative. Ethyl nonanoate (50 mol) in THF (50 mL) was added dropwise to a solution of LDA (75 mmol) in 150 mL of THF at –78 °C and stirred for 30 min. Ethyl trifluoroacetate (100 mmol) in 50 mL of THF was added and the reaction mixture was gradually warmed to rt and stirred for 24 h. The reaction was quenched with 5% aq HCl at rt. The organic phase was washed with water and brine and the aq layer was extracted with EE. The combined organics

were dried over $MgSO_4$ and concentrated. The crude reaction product was dissolved in 100 mL 40% aq H_2SO_4 and refluxed for 4 d. The reaction mixture was cooled, extracted with EE, washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvents were removed under aspirator and the ketone was distilled in vacuum.

Method C. Reaction of Grignard reagent with trifluoroacetic acid. Preparation of cyclohexyl trifluoromethyl ketone (**2j**) is representative. Trifluoroacetic acid (100 mmol) in 10 mL EE was added dropwise over 1 h to cyclohexylmagnesium chloride (300 mmol) and heated to reflux for 1 h. The reaction mixture was then cooled and poured to crushed ice containing 30 mL conc. HCl. The ether layer was separated and the aqueous layer was repeatedly extracted (3x) with EE. The combined EE layer was washed with sodium bicarbonate and water, and dried over $MgSO_4$. This was then concentrated and distilled for a 65% yield of cyclohexyl trifluoromethyl ketone.

1-Naphthyl trifluoromethyl ketone, 2b. This ketone was prepared from 1-naphthyllithium and ethyl trifluoroacetate as in method A. Yield: 91%; bp 88-89 °C/0.6 mm Hg (lit.[27] bp 80-100 °C/0.3 Torr).

2-Naphthyl trifluoromethyl ketone, 2c. This ketone was preapred from 2-naphthyllithium and ethyl trifluoroacetate as in method A. Yield: 91%; bp 86-88°C/1.0 mm Hg (lit.[49] bp 88 °C/ 1.1 mm Hg).

1,1,2,2,2-Pentafluoropropiophenone, 2e. The ketone **2e** was prepared from ethyl pentafluoropropionate and phenyllithium as in method A. Yield: 95%; bp 89-92 °C/70 mm Hg (lit.[50] bp 159-61 °C/740 mm Hg).

1,1,2,2,3,3,3-Heptafluorobutyrophenone, 2f. This ketone was prepared from phenyllithium and ethyl heptafluorobutyrate as in method A. Yield: 90%; bp 95-8 °C/68 mm Hg (lit.[51] bp 64 °C/12 mm Hg).

1,1,1-Trifluorononan-2-one, 2h. This was prepared as in method B from ethyloctanoate using LDA and ethyl trifluoroacetate. Yield: 60%; bp 160-62 °C (lit.[52] bp 160 °C/765 mm Hg).

1,1,1-Trifluorodecan-2-one, 2i. The procedure for **2j** is represented in the general procedure. Yield: 60%; bp 90-92 °C/20 mm Hg (lit.[53] bp 185-86 °C/760 mm Hg).

Cyclohexyl trifluoromethyl ketone, 2j. This was prepared as in method C from cyclohexylmagnesium chloride and trifluoroacetic acid in 65% yield: bp 52-54 °C/30 mm Hg (lit.[54] bp 53-54 °C/30 mm Hg).

3,3-Dimethyl-1,1,1-trifluoromethyl-2-butanone, 2k. This ketone was prepared as reported in the literature.[45] Yield: 54%; bp 57-78 °C (lit.[45] 57-78 °C).

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 (3.52 g, 11 mmol) was transferred to the flask in a glove bag and the ketone (10 mmol) was added at rt. The reagent went into solution and the reaction was followed by ^{11}B NMR spectrum after aliquots dissolved in EE and methanolyzed at periodic intervals. When the reaction was complete (^{11}B: δ 32 ppm), EE was added to the reaction mixture, cooled to 0 °C and 1.1 eq of acetaldehyde was added. The mixture was warmed to rt and left stirred overnight (8-24 h) when the second α-pinene was also liberated (^{11}B NMR of methanolyzed aliquot at δ 18 ppm). Aqueous sodium hydroxide was added and the organics separated. The aqueous layer was extracted with ether and the combined extracts were dried and concentrated. Distillation of the residue separated α-pinene and the product alcohol. The alcohol was further purified by preparative GC with appropriate columns (SE-30 or

Carbowax 20M). The rotation was measured. The MCF derivative or the MTPA ester of the alcohol was prepared by the standard procedure. Racemic alcohols of the ketones were obtained by reduction with $NaBH_4$. All the racemic alcohols were converted to the MCF derivatives or the MTPA esters and analyzed on a capillary GC to obtain the diastereomeric pairs of peaks. Then the optically active derivatives were analyzed to obtain the % ee.

(S)-(+)-1-Phenyl-2,2,2-trifluoroethanol, 3a. The reduction of **2a** with **1** under neat condition at rt was complete in 24 h. Workup gave the product **3a** in 90% yield. bp 64-65 °C/5 mm Hg (lit.[55] bp 99-105/17 mm Hg). α_D^{25} = +37.64° (neat) which showed an optical purity of 91.5% in the *S* isomer based on the literature α_D^{25} = +41.14° (neat) for the *S* isomer.[55] Analysis of the MCF derivative on a Supelcowax capillary column showed it to contain 95% of the *S*-isomer and 5% of the *R*-isomer, i. e. an ee of 90% in the *S* isomer. This product was crystallized from pentane at 0 °C to obtain solid **3a** with an overall yield of 72%; mp 27-28 °C. α_D^{22} = +42.18° (neat); $[\alpha]_D^{22}$ = +32.85° (*c* 2.6, $CHCl_3$). A capillary GC analysis of the MCF derivative now showed ≥99% ee.

(S)-(+)-2,2,2-Trifluoro-1-(1-naphthyl)ethanol, 3b. The reduction of **2b** was complete in 3 d. Workup provided the product alcohol in 93% yield. mp 52-53 °C (lit.[56] mp 51.6-53.2 °C). $[\alpha]_D^{22}$ = +20.35° (*c* 5.17, ethanol) which corresponds to an optical purity of 79% in the *S* isomer based on the reported maximum rotation[56] of $[\alpha]_D^{25}$ = 25.7° (*c* 5.1, ethanol). Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 78% ee.

(S)-(+)-2,2,2-Trifluoro-1-(2-naphthyl)ethanol, 3c. The reduction of **2c** with **1** was complete in 3 d. The alcohol **3c** was obtained in 92% yield; mp 91-93 °C (lit.[49] mp 83-84 °C for a racemic compound). $[\alpha]_D^{22}$ = +35.1° (*c* 4.14, ethanol); +28.63° (*c* 2.93, $CHCl_3$) which corresponds to an optical purity of 89% in the *S* isomer based on the reported rotation of $[\alpha]_D^{25}$ = –3.7° (*c* 17.2, $CHCl_3$) for 11.5% optical purity in *R* isomer.[57] However, analysis of the MTPA derivative on an SPB-5 capillary column showed an ee of 91%.

(S)-(+)-2,2,2-trifluoromethyl-1-(9-anthryl)ethanol, 3d. The ketone **2d** in THF was added to a concentrated solution of **1** in THF at rt. After 1 h, most of the solvent was removed and the mixture was stirred at rt. ^{11}B NMR showed the reaction to be very slow. Solvents were completely removed after a few hours and the reaction was left stirred. Only 60% reduction was complete after 30 d (^{11}B NMR). Ethyl ether was added to the mixture followed by 1.5 equivalent of acetaldehyde. Aqueous NaOH workup was performed and the mixture of ketone and alcohol was chromatographed (silica, $CHCl_3$) to provide a 48% yield (80% based on the recovered ketone) of the alcohol: mp 130-32 °C (lit.[58] mp 130.5-133 °C); $[\alpha]_D^{22}$ = +24.61° (*c* 6.1, $CHCl_3$) which corresponds to an optical purity of 82% based on the reported maximum rotation.[57] The MTPA and MCF derivative could not be resolved on a capillary GC.

(S)-(+)-2,2,3,3,3-Pentafluoro-1-phenyl-1-propanol, 3e. The reaction was complete in 3 d. Yield: 82% ; bp 60-62 °C/16 mm Hg (lit.[59] bp for the racemic compound183-85 °C/760 mm Hg). Anal. Calcd for $C_9H_7F_5O$: C, 47.8; H, 3.12; F, 42.0. Found: C, 47.56; H, 3.16; F, 41.75. $[\alpha]_D^{22}$ = +28.95° (*c* 2.69, EtOH). Analysis of the MCF derivative on an SPB-5 capillary column showed an ee of 92%.

(S)-(+)-2,2,3,3,4,4,4-Heptafluoro-1-phenyl-1-butanol, 3f. The reduction of the ketone **2f** was complete in 3 d. Yield: 81%; bp 42 °C/0.03 mm Hg; $[\alpha]_D^{22}$ = +23.02° (*c* 2.32, EtOH) which corresponds to 86.2% optical purity in the *S* isomer based on the literature[60] value of $[\alpha]_D^{26.5}$ = –26.7±0.6° (*c* 6.93, EtOH) for optically pure *R* isomer. Analysis of the MTPA ester of the alcohol on an SPB-5 capillary column showed an ee of 87%.

(S)-(−)-1,1,1-Trifluoro-2-propanol, 3g. The reaction of **2g** with **1** in EE was complete in 4 d at −25 °C. The product alcohol **3g** was isolated in 72% yield; bp 77 °C (lit.[61] bp 77.8-77.9 °C/761 mm Hg). $[\alpha]_D^{23} = -6.24°$ (neat) which corresponds to 87.6% optical purity based on the reported maximum rotation of $[\alpha]_D^{25} = -7.14°$ for the *S* isomer.[61] However, a capillary GC (SPB-5) analysis of the MCF derivative of **3g** showed it to be of 96% ee.

The above reaction at rt was complete in 4 h. The alcohol **3g** was isolated in 70% yield; $[\alpha]_D^{25} = -5.6°$ (neat) which corresponds to 79% optical yield. The MCF derivative on analysis on a capillary GC showed an ee of 89% in the *S* isomer.

(S)-(−)-1,1,1-Trifluorononan-2-ol, 3h. The reaction of **2h** with **1** was complete in 8 h. The acetaldehyde work up provided **3h** in 80% yield: bp 185-88 °C (lit.[51] bp 186-8 °C). $[\alpha]_D^{25} = -23.35$ °C (*c* 2.6, $CHCl_3$). The MTPA derivative on capillary GC analysis on a SPB-5 column showed an ee of 92%.

(S)-(−)-1,1,1-Trifluorodecan-2-ol, 3i. The reduction of **2i** with **1** under neat condition was complete in 7.5 h. Yield: 87%; bp 65-70 °C/2 mm Hg (lit.[51] bp 69-71 °C/2 mm Hg); $[\alpha]_D^{25} = -20.44°$ (*c* 3.84, methanol) which corresponds to an optical purity of 88.3% based on the calculated maximum rotation reported,[42] $[\alpha]_D = 23.16°$ (*c* 1.5, methanol). The capillary GC analysis of the MTPA derivative of **3i** on a SPB-5 column showed it to be of 91% ee.

(S)-(−)-1-Cyclohexyl-1-trifluoromethyl methanol, 3j. The reduction of **2j** in EE at rt with **1** was complete in 12 h. Work up provided **3k** in 75% yield; bp 80-82 °C/23 mm Hg; $[\alpha]_D^{23} = -17.82°$ (*c* 9.5, $CHCl_3$) which corresponds to an optical purity of ≥100% in the *S* isomer based on the maximum rotation reported in the literature,[43] $[\alpha]_D = +17.8°$ ($CHCl_3$) for *R* isomer. Analysis of its MCF derivative on a Suplecowax capillary column showed an ee of 87%.

Reduction of Ketones with Alpine-Borane

The reduction of **2a** is representative. To a 50-mL round-bottomed flask fitted as usual, 14 mmol of the reagent was added, followed by **2a** (10 mmol) and the mixture was left stirred at rt. The reaction was followed by ^{11}B NMR of an aliquot dissolved in EE. When the reaction was 90% complete (45 d, ^{11}B: δ 52 ppm), acetaldehyde (0.28 mL, 5 mmol) was added at 0 °C and stirred for 30 min. The α-pinene liberated during the reaction was collected using a high vacuum pump (0.01 mm Hg, 6 h). EE (20 mL) was then added to the reaction mixture followed by ethanolamine (0.84 mL) and stirring continued for 1 h during which time the boron components precipitated. This was then filtered and washed with pentane. The filtrate was concentrated and distilled at high vacuum to obtain **3a**. Yield: 1.17 g (80%). The MCF derivative of the alcohol was prepared and analyzed on an SPB-5 (30 m) capillary GC column which indicated 32% ee.

The reaction of **2e** and **2f** with **4** were 20% and 15% complete, respectively in 20 d. The reaction was quenched by adding acetaldehyde. Work up as above provided the mixture of ketone and alcohol. This was derivatized as such and the % ee noted using a SPB-5 column on a capillary GC. The results are summarized in Table 4.

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