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ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 844–850
JOURNAL OF FLUORINE CHEMISTRY
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The influence of fluorine on the asymmetric reduction of fluoromethyl ketones

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Received 22 February 2007; received in revised form 10 April 2007; accepted 10 April 2007
Available online 19 April 2007

Abstract

A comparative study of the asymmetric reduction of representative aryl and alkyl α-fluoro- and α-chloromethyl ketones using (−)-diisopinocampheylchloroborane [(−)-DIP-Chloride™] and (−)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane [*R*-Alpine-Borane®] has been made. It was observed that DIP-Chloride™ is superior in terms of the rate and enantioselectivity for both classes of halo-ketones. While the reduction of monofluoroacetone and trifluoroacetone with DIP-Chloride™ provided the product alcohols in 61% ee and 96% ee, respectively, the reduction of difluoroacetone yielded only 5% ee. The influence of a lone halogen atom was not observed for monochloroacetone, all of which point towards a chelating effect of monofluoroacetone on the Lewis acidic chloroborane.

Keywords: Fluoroketones; Chloroketones; Asymmetric reduction; DIP-Chloride™; Enantioselectivity

1. Introduction

Examination of the effects of fluorine substitution in organic molecules is important for the successful development of pharmaceuticals, agrochemicals and novel materials [1]. Optically active fluorinated alcohols are important building blocks or end-products in organic synthesis [2] and the steric and electronic effects of fluorine substitution in ketones play a vital role in reactions involving them [3]. The reduction of fluoroacetophenones with (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP-Chloride™, **1**] [4] and *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane [*R*-Alpine-Borane®, **2**] [5] (Fig. 1) reported by us earlier [6] showed that the reagent **1** has more influence on the enantiomeric excesses achieved for the product fluoro-alcohols [7]. To further understand the influence of fluorine atoms on the reductions, we undertook a study of the rate and enantioselectivities in the reduction of the simplest of fluoroketones, mono-, di- and trifluoroacetones with **1** and **2** and compared them with chloroacetones. The earlier results on fluoroacetophenones were also compared with chloroacetophenones. Herein, we report the results of our study, which points to a fluorine-mediated chelation [8] with the stronger Lewis acidic reagent **1**.

2. Results and discussion

We began the study with the comparison of the reduction of chloro- and fluoroacetophenones with **1** and **2**. The reduction of 2,2-dichloroacetophenone (**5a**) with **1** in ethyl ether (Et_2O) at −25 °C is very slow, complete in only 5 days. The usual diethanolamine workup provides 2,2-dichloro-1-phenethanol (**6a**) in 78% yield and 82% ee in the (*R*)-isomer (Eq. (2)) [9]. This contrasts with the fast reduction (0.5 h) of 2-chloroacetophenone (**3a**) with **1**, which also provides (*R*)-2-chloro-1-phenethanol (**4a**) in 95% ee (Eq. (1)) [10]. It is worth noting that, in the case of fluoro-substituted acetophenones, the difluoro derivative (**5b**) reacted faster than the monofluoroacetophenone (**3b**) [6a]. Although, the two chlorine atoms in **5a** should make the carbonyl more reactive than in **3a**, the retarded rate of the reduction could be due to the increased steric bulk as is the norm with DIP-Chloride™ reductions. The reaction of 2,2,2-trichloroacetophenone (**7a**) with **1** is even slower at −25 °C, and was conducted under neat condition, at rt which require 22 days for near completion to provide (*S*)-2,2,2-trichloro-1-phenethanol (**8a**) (of

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0022-1139/$ – see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.jfluchem.2007.04.015

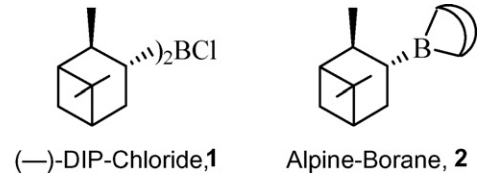
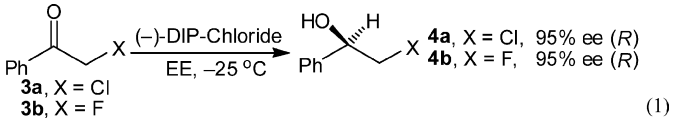


Fig. 1. Pinane-based asymmetric reducing agents.

opposite stereochemistry in contrast to **4a** and **6a**) in 91% ee (Eq. (3)). This is comparable to the product from the reduction of 2,2,2-trifluoroacetophenone (**7b**) when the reaction was complete in 24 h under neat condition at rt and provided the (*S*)-alcohol in 90% ee (Eq. (3)) [11]. The decreased rate in the case of **7a** might be due to the steric requirements of the three chlorine atoms.



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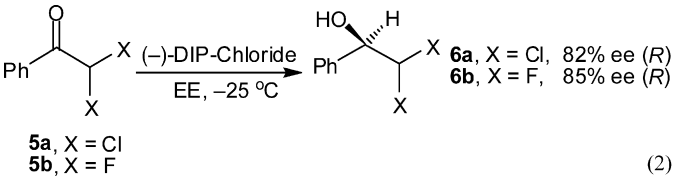

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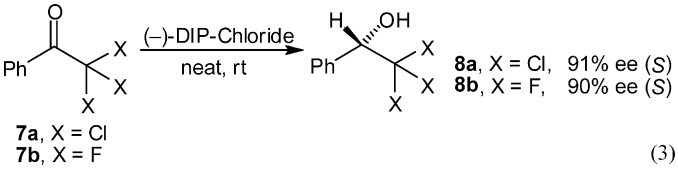
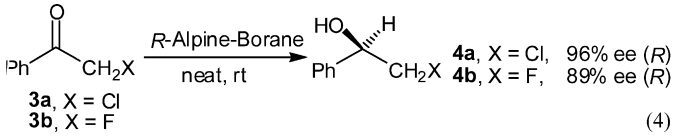


(3)

The reduction with **1** is believed to follow a six-membered transition state [4] with the hydride transfer as the rate-limiting step. The coordination of the carbonyl oxygen to the boron atom of the reagent is also equally important. Our results show that the trichloromethyl group is probably sterically more demanding than even a *tert*-butyl group since the reduction of pivalophenone is relatively faster than the reduction of **7a**. Corey et al. have made a detailed analysis of the structure and reduction of a series of trichloromethyl ketones including *tert*-butyl and adamantyl trichloromethyl ketones and have concluded that the trichloromethyl group effectively screens the lone pair of the carbonyl oxygen more than even the rigid adamantyl group [12].

The reduction of chloroacetophenones with **2** was then undertaken to compare with the above results and, probably, delineate the electronic and steric effects in this reduction. Since both **1** and **2** have similar reaction mechanism, any difference in the rate and configuration may be attributed to the electronic environment of the reagent due to the chlorine atom in **1**. Unlike the relatively fast reduction of **3a** with **2**, complete in 3 days, to produce **4a** in 96% ee (*R*) (Eq. (4)), the presence of two chlorine atoms in **5a** retards the rate and the reduction is only 70% complete in 22 days (Eq. (5)). Thirty percent of unreacted **5a** is recovered and the product **6a** with (*R*)-configuration is obtained in 83% ee. The reduction of **7a** with **2** is even slower, only 45% complete in 22 days (Eq. (6)). The product **8a** obtained after recovering 55% of **7a** showed an ee of 27% in the (*R*)-isomer, similar to the reduction of **7b** with **2** (32% ee) [6a]. The (*R*)-configuration of the trichlorophenethanol **8a** and trifluorophenethanol **8b** from Alpine-Borane reduction is in contrast to the (*S*)-**8a** and (*S*)-**8b** obtained from reduction of **7a** and **7b**, respectively, with DIP-Chloride™. Clearly, the net effect of the steric and electronic factors of the halogens in the ketone affects the rate of the reduction and influences the configuration of the product as well. The results of the reduction of all of the above aryl (phenyl) halomethyl ketones with **1** and **2** are summarized in Table 1.



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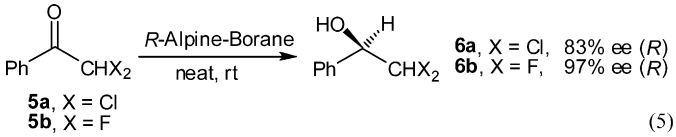

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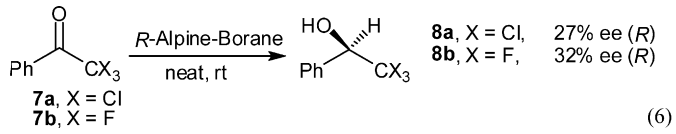


(6)

We now chose chloroacetone (**9a**), 1,1-dichloroacetone (**11a**) and 1,1,1-trichloroacetone (**13a**) for this study since a methyl group should be sterically smaller than the chloromethyl groups and the effect of the sterics versus electronics can probably be differentiated. In addition, the differences in the % ee and the configuration of the product alcohols from the reduction of the chloracetones and corresponding fluoroacetones, 1-fluoroacetone (**9b**), 1,1-difluoroacetone (**11b**) and 1,1,1-trifluoroacetone (**13b**), should provide a better picture of the electronic and/or steric effects due to the absence of the phenyl ring.

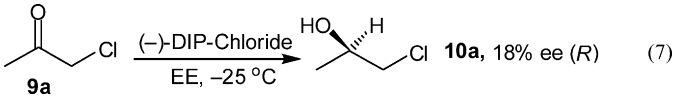
Reagent **1** reduces **9a** in Et_2O at −25 °C within 90 min to provide (*R*)-1-chloro-2-propanol (**10a**) in 65% yield and 18% ee (Eq. (7)). Surprisingly, the configuration of the product shows that the methyl group acts as the enantiocontrolling larger group in the tentative transition state model, probably due to the electronic effect of the chlorine atom on the reagent **1**. In comparison, the corresponding reduction of **9a** with **2** provides the (*S*)-alcohol in 16% ee, with the chloromethyl acting as the larger group. However, the reduction of the fluoroacetone, **9b**, with **1** in Et_2O at −25 °C is complete in 1 h providing 1-fluoro-2-propanol (**10b**) in a relatively high 61% ee in the (*S*)-isomer (Eq. (8)) [13], which is quite unexpected when compared with the 4% ee obtained for the reduction of 2-butanone [4b] and 18% ee obtained for of **10a**. A similar effect of a lone fluorine atom was also noticed in the reduction of

Table 1
Asymmetric reduction of α-fluoro- and α-chloroacetophenones with (−)-DIP-Chloride and *R*-Alpine-Borane

Entry	PhCOR		Reagent	Reaction condition			Haloalcohol			Control[b]
	#	R		Solv.	Temp.	Time	Yield (%)	ee (%)[a]	Conf.	
1	**3a**[c]	CH_2Cl	**1**	Et_2O	−25 °C	0.5 h	60	95	*R*	Ph
2	**3a**[d]	CH_2Cl	**2**	None	rt	8 h	75	96	*R*	Ph
3	**3b**[e]	CH_2F	**1**	Et_2O	−25 °C	1 h	80	95	*R*	Ph
4	**3b**[e]	CH_2F	**2**	None	rt	1 h	80	89	*R*	Ph
5	**5a**	$CHCl_2$	**1**	Et_2O	−25 °C	5 days	78	82	*R*	Ph
6	**5a**	$CHCl_2$	**2**	None	rt	22 days[f]	70	83	*R*	Ph
7	**5b**[e]	CHF_2	**1**	Et_2O	−25 °C	0.5 h	90	85	*R*	Ph
8	**5b**[e]	CHF_2	**2**	None	rt	4 days	69	97	*R*	Ph
9	**7a**	CCl_3	**1**	Et_2O	−25 °C	22 days	65	91	*S*	CCl_3
10	**7a**	CCl_3	**2**	None	rt	22 days[g]	62	27	*R*	Ph
11	**7b**[e]	CF_3	**1**	None	rt	24 h	90	90	*S*	CF_3
12	**7b**[e]	CF_3	**2**	None	rt	45 days[h]	57	32	*R*	Ph

[a] ee determined as their MTPA or TFA derivative on a capillary GC.
[b] Enantiocontrolling group based on the proposed mechanism of the reduction, ref. [4b].
[c] From ref. [5c].
[d] From ref. [4b].
[e] From ref. [6a].
[f] For 70% reaction, 30% ketone was recovered.
[g] For 45% reaction. 55% ketone was recovered.
[h] For 90% reaction.

monofluoromethyl acetylenic ketones [14] and 1-fluoro-2-octanone with **1** [6a] (Fig. 2). It is worthy to note that the interaction between the fluorine atom of the ketone **9b** and the chlorine atom of the reagent **1** has more effect on the chiral outcome than the interaction between the chlorine atoms of the ketone **9a** and **1**. This could be due to the chelating effect of the fluorine and the stronger Lewis acidic **1** (Fig. 3). This effect is further substantiated by the lack of dramatic configurational changes in Alpine-Borane reductions of fluoroketones as well.



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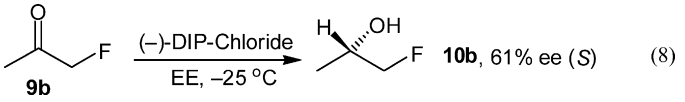
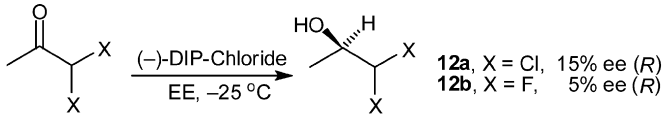


(8)

The reduction of dichloroacetone **11a** with **1** is complete within 2 h and provides the product 1,1-dichloroethanol (**12a**) in 72% yield and 15% ee (Eq. (9)). In comparison, the reduction of 1,1-difluoroacetone (**11b**) with **1** provides the alcohol in only 5% ee. A similar change in enantioselectivity for an α,α-difluoro compound compared to the α-fluoro compound was also observed for the reduction of α-fluorooctanones with **1** when the % ee changed from 40% (*R*) to 32% (*S*) (Fig. 2) [6a]. However, there is not much change in ee between the products from the reduction of monochloro- and dichloroacetone (**9a** and **11a**, respectively) with **2**.



(9)

The reduction of trichloroacetone (**13a**) with **1** is very slow, compared to mono- and dichloroacetones at −25 °C in Et_2O. Even under neat condition, at rt, the reaction took 3 days for completion and the product is obtained in 78% yield and 91% ee (Eq. (10)). Yet, the reaction rate (3 days) is faster compared to the reduction of the phenyl analog (**7a**) (22 days), the reasons of which are unclear, at present. As is normal with the reduction of perfluoroalkyl ketones with **1**, the reduction of **13b**, at −25 °C, provides the (*S*)-alcohol in 96% ee.

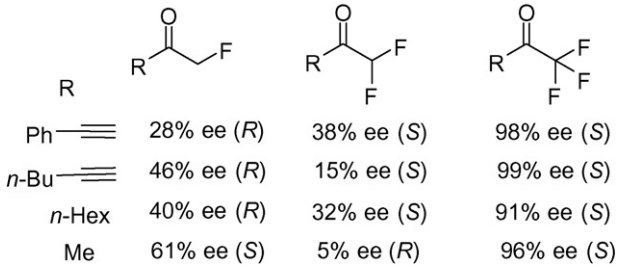


Fig. 2. The effect of fluorine on % ee in reductions of fluoromethyl ketones with **1**.

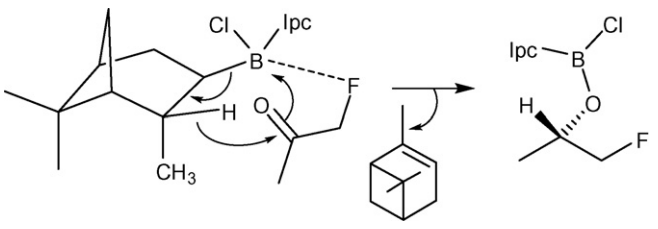
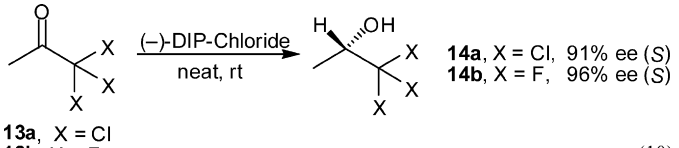


Fig. 3. Transition state model depicting the chelation effect in the reduction of fluoroacetone with DIP-Chloride.

Table 2
Asymmetric reduction of α-fluoro- and α-chloroacetones with (−)-DIP-Chloride and *R*-Alpine-Borane

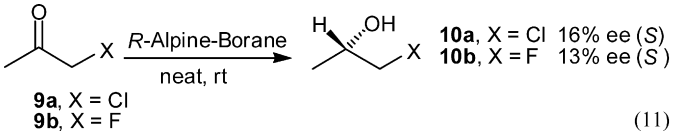
Entry	MeCOR		Reagent	Reaction condition			Haloalcohol			Control[b]
	#	R		Solv.	Temp.	Time	Yield (%)	ee (%)[a]	Conf.	
1	**9a**	CH_2Cl	**1**	Et_2O	−25 °C	1.5 h	65	18	*R*	Me
2	**9a**	CH_2Cl	**2**	None	rt	3 days	68	16	*S*	CH_2Cl
3	**9b**	CH_2F	**1**	Et_2O	−25 °C	1 h	80	61	*S*[c]	CH_2F
4	**9b**	CH_2F	**2**	None	rt	3 days	68	13	*S*[c]	CH_2F
5	**11a**	$CHCl_2$	**1**	Et_2O	−25 °C	2 h	72	15	*R*[c]	Me
6	**11a**	$CHCl_2$	**2**	None	rt	4 days	75	62	*S*[c]	$CHCl_2$
7	**11b**	CHF_2	**1**	Et_2O	−25 °C	2 h	80	5	*R*[c]	Me
8	**11b**	CHF_2	**2**	None	rt	3 days	54	16	*S*[c]	CHF_2
9	**13a**	CCl_3	**1**	Et_2O	−25 °C	3 days	78	91	*S*[c]	CCl_3
10	**13a**	CCl_3	**2**	None	rt	22 days	70	24	*S*	CCl_3
11	**13b**[d]	CF_3	**1**	None	rt	4 h	72	90	*S*	CF_3
12	**13b**	CF_3	**2**	None	rt	4 days	60	82	*S*	CF_3

[a] ee determined as their MTPA, benzoate or TFA derivative on a capillary GC.
[b] Based on the proposed mechanism of the reduction (ref. [4b]).
[c] Based on analogy.
[d] From ref. [11].



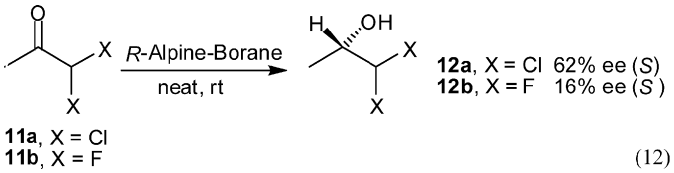
(10)

To unequivocally delineate the influence of the chlorine of the reagent on the reduction, the haloacetones were now reduced with **2**. The reduction of **9a** under neat conditions, at rt, is complete within 3 days and the product is obtained in 68% yield and 13% ee, with the same stereochemistry as obtained from the reduction with **1** (Eq. (11)). In contrast to the reduction of **9b** with **1** in 61% ee, the reduction with **2** provided only 13% ee for **10b** with the same configuration.



(11)

The reduction of **11a** with **2** is complete in 4 days and the product is obtained in 75% yield and 62% ee (Eq. (12)). As in the case of **9a**, the products from the reduction of **11a** with **1** and **2** had the opposite configurations. On the basis of the earlier results, we believe that we have obtained (*R*)-**12a** from the reduction with **1** and (*S*)-**12a** from the reduction with **2**. Again, the differences in the % ee for the reduction of **11a** with **1** and **2**, an overall change of 77% (15% *R* to 62% *S*), can probably be accounted for only by considering the electronic environment of reagent **1**. The reduction of difluoroacetone with **2**, complete in 3 days, provides the product of opposite configuration in 16% ee. Again on the basis of earlier results, we believe that we have obtained (*R*)-**12b** with **1** and (*S*)-**12b** from reduction with **2**.



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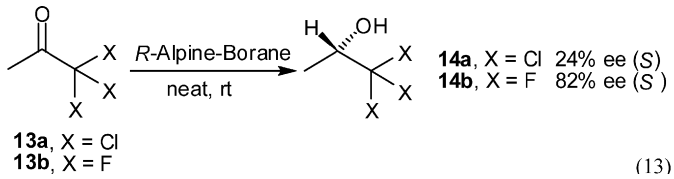

(13)

The rate of the reduction of **13a** with **2** is slower than the dichloro analog **11a**, complete within 22 days, producing **14a** in 70% yield and 24% ee. The product reveals the same configuration of the product obtained from a reduction of **13a** with **1**. We believe this to be the (*S*)-isomer. On the other hand, reduction of **13b** with **2** is little faster, complete in 7 days, and provides 60% of the product alcohol in 82% ee in the (*S*)-isomer (Eq. (13)).

The results of the reduction of all of the above alkyl halomethyl ketones with **1** and **2** are summarized in Table 2.

3. Conclusion

In summary, we have studied the asymmetric reduction of a representative series of aromatic and aliphatic α-halomethyl ketones to understand the steric and/or electronic influences of the fluorine atom on chiral reductions. DIP-Chloride™ and Alpine-Borane® are used as the reagents in this study as they differ in their electronic environments. As usual, all chloro- and fluorosubstituted acetophenones are reduced with **1** in very high ee. In the aliphatic series, **1** reduces trihaloketones in excellent ee with the trihalomethyl group acting as the enantio-controller. Surprisingly, we noticed a dramatic influence of the fluorine atom in the reduction of monofluoroacetone, possibly due to a

chelating effect with the Lewis acidic chloroborane. This effect is not noticeable in the reductions using **2** and in monochloroacetone reduction with **1**. Further molecular modeling studies will provide additional insight into this mechanism of fluoroketones.

4. Experimental

Unless otherwise noted, all manipulations were carried out under an inert atmosphere using flame-dried glassware. Techniques for handling air-sensitive compounds have been previously described [15]. Anhydrous ethyl ether (Mallinckrodt) was used as received. 2,2-Dichloroacetophenone [16], 2,2,2-trichloroacetophenone [17] and 1,1-difluoroacetone [18] were prepared according to the literature procedure. All other materials, including reagents **1** and **2** were obtained from Aldrich Chemical Co. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure [19].

The ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were plotted on a Varian Gemini-300 spectrometer (300, 75 and 282 MHz, respectively) with a Nalorac-quad probe. ^{1}H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: 0 ppm) or chloroform ($CHCl_3$: 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ or trifluoroacetic acid (TFA) as the internal standard. ^{1}H NMR data are reported as chemical shifts (δ ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz) and integration. Chromatography was performed on 40–60 μm silica gel (230–400 mesh). Analyses of the MTPA [19] or MCF [20] 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. Analysis of the trifluoroacetates or benzoates of alcohols were performed using a Chiraldex-GTA [21] (23 m) capillary column.

5. Experimental procedure and analytical data for products

5.1. Reduction of chloroalkyl ketones and fluoroalkyl ketones with (−)-DIP-Chloride™

5.1.1. General procedure

An oven-dried, 50-mL round-bottom flask equipped with a side arm, magnetic 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 dissolved in ee (15 mL). The solution was cooled to −25 °C, and the ketone (10 mmol) was added, dropwise, using a syringe. The reaction was followed by ^{11}B NMR spectrometry after aliquots were methanolyzed at −25 °C at periodic intervals. When the reaction was complete (^{11}B: δ 32 ppm), the mixture was warmed to 0 °C and diethanolamine (2.1 mL, 22 mmol) was added dropwise. The mixture was then warmed to rt and stirred for 3 h. The solid boron-amine complex was filtered, washed with pentane and the combined filtrate was concentrated. The residue was passed through a silica gel pad to separate α-pinene and the product (pentane and CH_2Cl_2 as eluents). The fraction containing the product was concentrated and distilled using a Kugelrohr apparatus. The alcohol was further purified by preparative GC using an SE-30 column. The rotation was measured. The MTPA, MCF or TFA derivative of the alcohol was prepared by the standard procedure. Racemic alcohols of the ketones were obtained by reduction with $NaBH_4$. All of the racemic alcohols were converted to the MTPA or MCF derivative and analyzed using a GC fitted with an appropriate capillary column to obtain the diastereomeric pairs of peaks. Then the derivatives of optically active alcohols were analyzed to obtain the enantiomeric excess.

5.2. Reduction of chloroalkyl ketones with (R)-Alpine-Borane

5.2.1. General procedure

A 12 mmol of a 0.5 M THF solution of **2** was added to a 50 mL round-bottomed flask fitted as described above and the solvent was removed under aspirator. The halomethyl ketone (10 mmol) was then added and the mixture was stirred at rt. The reaction was followed by ^{11}B NMR of an aliquot dissolved in ee. When the reaction was complete (^{11}B NMR: 52 ppm), acetaldehyde (3 mmol) was added at °C and stirred at rt for 30 min. ee (20 mL) was then added to the reaction mixture followed by enthanolamine (12 mmol) and stirred for 1 h. The solid complex was filtered and washed with pentane. The filtrate was concentrated and distilled to yield the alcohol. Further purification and analysis was carried out as described for reduction with **1**.

5.3. 2,2-Dichloro-1-phenylethanol, *6a*

5.3.1. (a) From reduction with (−)-1

2,2-Dichloroacetophenone (10 mmol) was treated with (−)-DIP-Chloride (11 mmol) in ee at −25 °C. The reaction was complete in 5 days. Workup as described in the general procedure provided **6a** in 78% yield. $[\alpha]_D^{21} = -30.17$ (ca. 3.0, CH_2Cl_2) which correspond to the (*R*)-isomer [22]. The GC analysis of its TFA derivative on a Chiraldex-GTA capillary column showed an ee of 82%. ^{1}H NMR δ ($CDCl_3$) 3.02 (sb, 1H), 4.93–4.96 (m, 1H), 5.80 (d, J = 5.4 Hz, 1H), 7.30–7.40 (m, 5H). ^{13}C NMR δ ($CDCl_3$) 76.16, 78.55, 127.03, 128.34, 128.86, 137.25.

5.3.2. (b) From reduction with *2*

A 10 mmol of **5a** was treated with (*R*)-Alpine-Borane (12 mmol) at rt in neat condition. The reaction was complete in 22 days. Workup as described above provided **6a** in 70% yield. The GC analysis of the TFA derivative on a Chiraldex-GTA capillary column showed an ee of 83% in the (*R*)-isomer.

5.4. 2,2,2-Trichloro-1-phenylethanol, **8a**

5.4.1. (a) From reduction with (−)-1

2,2,2-Trichloroacetophenone (10 mmol) was added to solid (−)-DIP-Chloride (11 mmol) at rt. The reaction was complete in 22 days. Workup as described above and distillation using a Kugelrohr apparatus (pot temperature 100–110 °C/0.5 mmHg) provided **8a** in 65% yield, after a recovery of 20% of **6a**. $[\alpha]_D^{25} = +35.80$ (ca. 3.0, CH_2Cl_2) correspond to the (*S*)-isomer [22]. GC analysis of the MTPA ester on a SPB-5 capillary column showed an ee of 91%. ^{1}H NMR δ ($CDCl_3$) 3.31 (d, J = 4.1 Hz, 1H), 5.20 (d, 4.1 Hz, 1H), 7.35–7.40 (m, Ph, 3H), 7.58–7.62 (m, Ph, 2H). ^{13}C NMR δ ($CDCl_3$) 84.31, 102.89, 127.72 129.11, 129.36, 134.80.

5.4.2. (b) From reduction with **2**

2,2,2,-Trichloroacetophenone (10 mmol) was treated with 12 mmol (*R*)-Alpine-Borane without solvent at rt. The reaction was complete in 22 days. Workup as described above provided **8a** in 62% yield. The GC analysis of the MTPA derivative on a SPB-5 capillary column showed an ee of 27% in the (*R*)-isomer.

5.5. 2-Chloro-1-propanol, **10a**

5.5.1. (a) From reduction with (−)-1

1-Chloroacetone (10 mmol) was treated with (−)-DIP-Chloride (11 mmol) in ee at −25 °C. The reaction was complete in 1.5 h. Workup as described above and distillation using a Kugelrohr apparatus (pot temperature 75–85 °C/25 mmHg) provided **10a** in 65% yield, $[\alpha]_D^{25} = -3.49$ (ca. 5.6 $CHCl_3$) which correspond to the (*R*)-isomer [23]. GC analysis as the MCF derivative on a SPB-5 capillary column showed an ee of 18%. ^{1}H NMR δ ($CDCl_3$) 1.28 (d, J = 6.3 Hz, 3H), 2.35 (sb, 1H), 3.46 (dd, J = 11.0, 7.0 Hz, 1H), 3.66 (dd, J = 11.0, 3.6 Hz, 1H), 3.95–4.05 (m, 1H). ^{13}C NMR δ ($CDCl_3$) 20.06, 51.21, 67.54.

5.5.2. (b) From reduction with **2**

1-Chloroacetone (10 mmol) was treated with 12 mmol of (*R*)-Alpine-Borane under neat condition at rt. The reaction was complete in 3 days. Workup as above provided **10b** in 68% yield. GC analysis of the MCF derivative on a SPB-5 capillary column showed an ee of 16% in the (*S*) isomer.

5.6. 2,2-Dichloro-1-propanol, **12a**

5.6.1. (a) From reduction with (−)-1

1,1-Dichloroacetone (10 mmol) was treated with (−)-DIP-Chloride (11 mmol) in ee at −25 °C. The reaction was complete in 2 h. Workup as described above using a Kugelrohr apparatus (pot temperature 95–105 °C/25 mmHg) provided **12a** in 72% yield. GC analysis as the MTPA derivative on a SPB-5 capillary column revealed an ee of 15%. ^{1}H NMR δ ($CDCl_3$) 1.39 (d, J = 6.3 Hz, 3H), 2.46 (sb, 1H), 4.02–4.11 (m, 1H), 5.67 (d, J = 4.4 Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 17.89, 72.49, 77.15.

5.6.2. (b) From reduction with **2**

1,1,-Dichloroacetone (10 mmol) was treated with (*R*)-Alpine-Borane (12 mmol) at rt under neat condition. The reaction was complete in 4 days. Workup as described above provided **12a** in 75% yield. $[\alpha]_D^{21} = -2.92$ (ca. 3.2, $CHCl_3$). The GC analysis of the MTPA derivative on a SPB-5 capillary column showed an ee of 62% in the opposite isomer as compared to the product from (−)-DIP-Chloride™ reduction described above.

5.7. 2,2,2-Trichloro-1-propanol, **14a**

5.7.1. (a) From reduction with (−)-1

1,1,1-Trichloroacetone (10 mmol) was added to solid (−)-DIP-Chloride (11 mmol) at rt. The reaction was complete in 3 days. Workup as described above (pot temperature 110–120 °C/25 mmHg) provided **15a** in 78% yield. $[\alpha]_D^{21} = -4.68$ (ca. 1.26, $CHCl_3$). The GC analysis of the TFA derivative on a Chiraldex-GTA capillary column showed an ee of 91%. ^{1}H NMR δ ($CDCl_3$) 1.53 (d, J = 6.1 Hz, 3H), 2.90 (sb, 1H), 4.22–4.32 (m, 1H). ^{13}C NMR δ ($CDCl_3$) 17.75, 79.18, 104.41.

5.7.2. From reduction with **2**

1,1,1-Trichloroacetone (10 mmol) was treated with (*R*)-Alpine-Borane (12 mmol) at rt under neat condition. The reaction was complete in 22 days. Workup as above provided **14a** in 70% yield. The GC analysis of the TFA derivative on a Chiraldex-GTA capillary column showed an ee of 24% in the same isomer as obtained from (−)-DIP-Chloride™ reduction.

5.8. (*R*)-1-Fluoro-2-propanol, **10b**

5.8.1. (a) From reduction with **1**

2-Fluoroacetone (10 mmol) was treated with (−)-DIP-Chloride (11 mmol) in ee at −25 °C. The reaction was complete in 1 h. The usual workup as described in the general procedure bp 98–105 °C (literature [24] bp 95–110 °C) provided **10b** in 80% yield, $[\alpha]_D^{21} = -10.21$ (ca. 1.9, CH_3OH). ^{1}H NMR δ ($CDCl_3$) 1.19 (dd, J = 6.5, 1.7 Hz, 3H), 2.42 (s, 1H), 4.00–4.15 (m, 1H), 4.26 (ddd, J = 48.0, 9.2, 7.0 Hz, 1H), 4.69 (ddd, J = 46.9, 9.2, 3.1 Hz, 1H). ^{13}C NMR δ ($CDCl_3$) 17.42 (d, J = 7.9 Hz), 66.49 (d, J = 19.1 Hz), 87.79 (d, J = 168.5 Hz).

The above product was converted to the benzoate ester in 92% yield. $[\alpha]_D^{21} = -4.88$ (ca. 1.0, $CHCl_3$) corresponds to the (*S*) isomer [13]. The GC analysis of the benzoate ester on a Chiraldex-GTA capillary column showed an ee of 61%. IR: $\upsilon_{max}^{cm^{-1}}$ (neat) 1715 (C=O). ^{1}H NMR δ ($CDCl_3$) 1.41 (dd, J = 6.6, 1.4 Hz, 3H), 4.42–4.67 (m, 2H), 5.30–5.45 (m, 1H), 7.40–7.60 (m, Ph, 3H), 8.04–8.10 (m, Ph, 2H). ^{13}C NMR δ ($CDCl_3$) 15.82 (d, J = 6.8 Hz), 70.02 (d, J = 19.8 Hz), 85.09 (d, J = 174.3 Hz), 128.84, 130.17, 130.58, 133.57, 166.42. ^{19}F NMR δ ($CDCl_3$) −228.81 (dt, J = 48.4, 20.9 Hz).

5.8.2. (b) From reduction with **2**

The reduction of **9b** with **2** was complete in 3 days. Workup provided the product alcohol in 68% yield. The analysis of the MTPA derivative on a Supelcowax capillary column showed

the product to be of 13% ee in the same isomer (*S*) as obtained from the reaction with **1**.

5.9. (S)-1,1-Difluoro-2-propanol, *12b*

5.9.1. (a) From reduction with *1*

The reduction of **11b** with **1** was complete in 2 h. Workup as above provided **12b** in 80% yield. bp 85–90 °C. IR $\upsilon_{max}^{cm^{-1}}$ neat: 3375 (OH); ^{1}H NMR δ (ppm) ($CDCl_3$): 1.27 (t, J = 6.6 Hz, 3H, C<u>H</u>$_3$), 2.67 (br s, 1H, CHO<u>H</u>), 3.8–4.0 (m, 1H, <u>H</u>-C-OH), 5.59 (dt, J = 56.3, 4.1 Hz, 1H, C<u>H</u>F$_2$); MS EI: *m/z*: 51 (M–$CH_3CHOH)^+$ (100%); CI: *m/z*: 97 $(MH)^+$ (100%). The GC analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 5% ee.

5.9.2. (b) From reduction with *2*

The reduction of **11b** with **2** was complete in 3 days. Workup provided the product alcohol in 54% yield. The GC analysis of the MTPA derivative on a Supelcowax capillary column showed the product to be of 16% ee in the *opposite* isomer as compared to the product from reduction with **1**. We believe that we obtain the (*R*)-isomer based on analogy with the reduction of **7c** with **2**.

5.10. (S)-(−)-1,1,1-trifluoro-2-propanol, *14b*

5.10.1. From reduction with *2*

The reduction of **13b** with **2** was complete in 4 days. Workup provided **6f** in 60% yield. bp 76–77 °C (literature [25] bp 77.8–77.9 °C). $[\alpha]_D^{22} = -5.23°$ (neat) which corresponds to an optical purity of 80.4% in the (*S*) isomer based on the reported maximum rotation [11] of $[\alpha]_D^{25} = -6.5°$ (neat). The GC analysis of the MCF derivative on a SPB-5 capillary column showed the product to be of 82% ee in the (*S*)-isomer.

Acknowledgement

We gratefully acknowledge Herbert C. Brown Center for Borane Research for support of this research.

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