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Asymmetric ring opening of *meso*-epoxides with *B*-halobis(2-isocaranyl)boranes 2-$^{d}Icr_2BX$

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This paper is dedicated to Professor Herbert C. Brown

Abstract—Hydroboration of commercially available (+)-2-carene (96% ee) with either $BH_2Cl{\cdot}SMe_2$ or BCl_3/Me_3SiH, provides chemically pure *B*-chlorobis(2-isocaranyl)borane (2-$^{d}Icr_2BCl$) whereas *B*-bromobis(2-isocaranyl)borane (2-$^{d}Icr_2BBr$) could only be prepared by Matteson's BBr_3/Me_3SiH procedure in high chemical yield and purity. The enantiomeric excess achieved with 2-$^{d}Icr_2BCl$ (78%), was significantly higher than those realized with the previously explored reagent, $^{d}Ipc_2BCl$ (41%), especially for *meso*-cyclohexene oxide. The new reagent, 2-$^{d}Icr_2BBr$ also showed considerable improvements in enantiomeric excesses, in the cases of *meso*-cyclopentene oxide (67%) and *meso*-*cis*-2,3-butene oxide (78%) than those achieved with the previously reported reagent, $^{d}Ipc_2BBr$ (57% and 61%, respectively).

1. Introduction

Asymmetric synthesis starting from *meso*-compounds is an effective and attractive approach to the synthesis of complex optically active organic compounds of chemical and biological interest.[1] Vicinal halohydrins, are also very useful synthetic intermediates for the synthesis of halogenated marine natural products (laurenyne, isodactylyne), antibiotics (thienamycin), and immuno-suppressant ISP-1.[2] Desymmetrization of either *meso*- or racemic-epoxides has been successfully accomplished with a wide variety of nucleophiles, such as, carbon nucleophiles,[3] phenols,[4] thiols,[5] carboxylic acids,[6] aromatic amines,[7] azide,[8] and cyanide.[9] Although halides have been extensively used as nucleophiles[10] in the enantioselective cleavage of epoxides, including *B*-halodiisopinocampheylboranes (Ipc_2BX)[11] from our laboratory, there have only been a couple of reports available in the literature by Denmark[12] and Buono[13] which provide highly enantiomerically enriched chlorohydrins utilizing chiral organophosphorus Lewis base catalysts.

Although $^{d}Ipc_2BX$ succeeded in cleaving the *meso*-epoxides enantioselectively, the moderate enantioselectivities achieved in many cases, especially with $^{d}Ipc_2BCl$ and $^{d}Ipc_2BBr$, pressed the need for development of superior reagents which could achieve enantioselectivities approaching 100%. In the asymmetric allylboration, significant improvements in enantioselectivity were realized with *B*-allylbis(2-isocaranyl)borane (2-$^{d}Icr_2BAll$)[14] over $^{d}Ipc_2BAll$. This persuaded us to synthesize and test these new chiral reagents, *B*-chlorobis(2-isocaranyl)borane (2-$^{d}Icr_2BCl$) and *B*-bromobis(2-isocaranyl)borane (2-$^{d}Icr_2BBr$) for the asymmetric cleavage of *meso*-epoxides. Herein, we report our results on the enantioselective cleavage of *meso*-epoxides with 2-$^{d}Icr_2BCl$ and 2-$^{d}Icr_2BBr$.[15]

2. Results and discussion

At first, we decided to reexamine some of our earlier work on the enantioselective ring opening of a few representative *meso*-epoxides with $^{d}Ipc_2BX$. A slight variation in the reaction conditions (little longer reaction time and slow warming after addition of *n*-butyraldehyde) and quick analysis of the halohydrins on Chiraldex-GTA analytical column, 10–20% higher enantiomeric excess is realized (Table 1).

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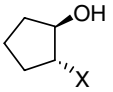
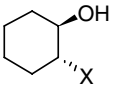
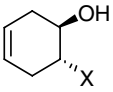
Table 1. Asymmetric ring opening of representative *meso*-epoxides with $^{d}Ipc_2BX$

Entry	Epoxide	Reagent, reaction conditions	Halohydrin	X	% Yield	% ee (Lit)[a]	Conf[b]
1		$^{d}Ipc_2BCl$, *n*-C_5H_{12}, −78 °C, 4 h $^{d}Ipc_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Cl Br	60 65	46 (44) 58 (48)	1*R*,2*R* 1*R*,2*R*
2		$^{d}Ipc_2BCl$, *n*-C_5H_{12}, −78°C, 4 h $^{d}Ipc_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Cl Br	70 75	41 (22) 92 (84)	1*R*,2*R* 1*R*,2*R*
3		$^{d}Ipc_2BCl$, *n*-C_5H_{12}, −78 °C, 4 h $^{d}Ipc_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Cl Br	55 65	40 (27) 77 (63)	1*R*,2*R* 1*R*,2*R*

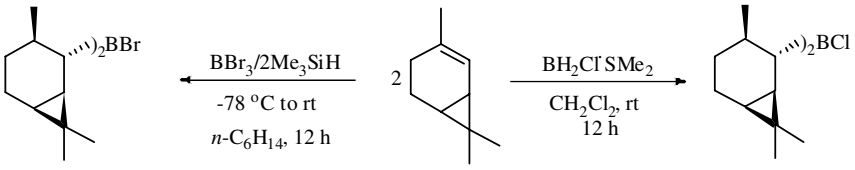
[a] Enantiomeric excess was determined on Chiraldex-GTA column as TFA derivatives.
[b] The absolute configurations of the halohydrins (1*R*,2*R*) were assigned based on the results obtained from previous Ipc_2BX reactions from this laboratory. The superscript 'd' indicates that the reagent is derived from (+)-α-pinene.

B-Chlorobis(2-isocaranyl)borane (2-$^{d}Icr_2BCl$) (96% ee) (^{11}B NMR: δ 74.5 ppm in *n*-pentane) was successfully prepared either by the hydroboration of 2-carene (96% ee) with $BH_2Cl{\cdot}SMe_2$ in CH_2Cl_2 for 12 h or by Matteson's BCl_3/Me_3SiH methodology in high yield and chemical purity (>95%) in *n*-hexanes.[16] Unlike 2-$^{d}Icr_2BCl$, 2-$^{d}Icr_2BBr$ could not be synthesized in high chemical purity either by direct hydroboration of 2-carene with $BH_2Br{\cdot}SMe_2$ in CH_2Cl_2 or by the reaction of 2-$^{d}Icr_2BH$ with Br_2 in CH_2Cl_2. Only Matteson's BBr_3/Me_3SiH procedure provided 2-$^{d}Icr_2BBr$ (96% ee; ^{11}B NMR: δ 78 ppm in *n*-pentane) in high chemical yield and purity (>95%) in *n*-hexanes or *n*-heptane (Scheme 1).

B-Chlorobis(2-isocaranyl)borane successfully cleaved representative *meso*-epoxides at −78 °C to vicinal chlorohydrins in reasonably good yields (Table 2); however, the enantioselectivity of the reaction was highly substrate dependent (Scheme 2). Only *meso*-cyclohexene oxide reacted with significant improved enantioselectivity.[17] No improvement in enantioselectivity was realised by lowering the reaction temperature to −100 °C. An improved enantiomeric excess achieved with 2-$^{d}Icr_2BCl$ (78%) was far superior to $^{d}Ipc_2BCl$ reported earlier by our research group (22–41%) and also by others. In the case of *meso*-*cis*-2,3-butene oxide also, 18–19% improvement was achieved in comparison with $^{d}Ipc_2BCl$. *meso*-Cyclopentene oxide appeared to be a problematic substrate possibly due to ring strain. It is quite evident from the literature that *meso*-cyclopentene oxide yields chlorohydrin of relatively lower enantiomeric excess. Even Buono's catalytic method, which appears to handle a wide variety of *meso*-epoxides (*meso*-cyclohexene oxide, 84% ee; *meso*-cycloheptene oxide, 98% ee; *meso*-cyclooctene oxide, >99% ee) very efficiently, fails in the case of *meso*-cyclopentene oxide (23% ee).

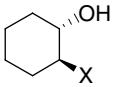
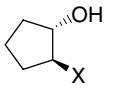
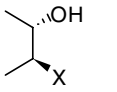
Although $^{d}Ipc_2BBr$ demonstrated its superiority over $^{d}Ipc_2BCl$ in the asymmetric opening of *meso*-epoxides (48–84% ee), there remained ample scope for further improvements due to the moderate enantioselectivity with many substrates. Therefore, it was of great interest to synthesize and examine new reagents having different chiral auxiliaries. Encouraged by the results obtained with 2-$^{d}Icr_2BCl$, we undertook the enantioselective ring opening of *meso*-epoxides with 2-$^{d}Icr_2BBr$. We were delighted to observe considerable improvements in enantiomeric excesses, especially with *meso*-cyclopentene- and *meso*-*cis*-2,3-butene oxides (68% and 78%, respectively). The conversion of the borinate ester to the boronate ester was observed to be sluggish when the 2-carene chiral auxiliary was present in comparison with the α-pinene. This problem was overcome by the addition of a small amount of $BF_3{\cdot}OEt_2$. With *meso*-cyclohexene oxide, only a comparable result (78% ee) was obtained. Considering the labile nature of the halohydrins toward racemization, we emphasized on the rapid isolation and quick analysis by chiral HPLC (with UV detector) by converting the hydroxyl group of the halohydrins into suitable UV sensitive esters (4-nitrobenzoate, 3,5-dinitrobenzoate, and 1-naphthoate). It is important to note that 2-$^{d}Icr_2BX$ produces vicinal halohydrins of the opposite configuration (1*S*,2*S*) in contrast to $^{d}Ipc_2BX$ (1*R*,2*R*). These results are summarized in Table 2.

Next, we decided to examine the enantioselective ring opening of *meso*-cyclohexene oxide as a model reaction with various Ter_2BCl reagents, such as $^{d}Eap_2BCl$ (97% ee),



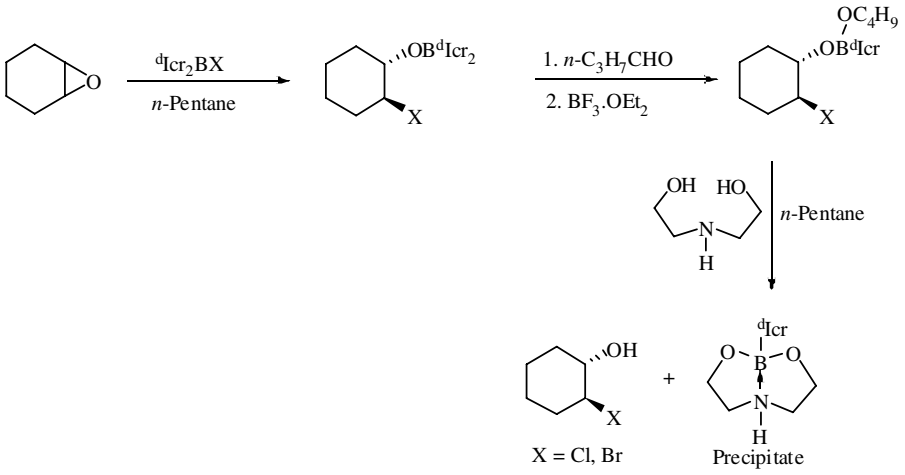
Scheme 1. Preparation of 2-$^{d}Icr_2BCl$ and 2-$^{d}Icr_2BBr$.

Table 2. Asymmetric ring opening of representative *meso*-epoxides with 2-$^{d}Icr_2BX$

Entry	Epoxide	Reagent, reaction conditions	Halohydrin	X	% Yield	% ee[a]	Conf[b]
1		2-$^{d}Icr_2BCl$, *n*-C_5H_{12}, −78 °C, 4 h		Cl	66	78	1*S*,2*S*
		2-$^{d}Icr_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Br	72	78	1*S*,2*S*
2		2-$^{d}Icr_2BCl$, *n*-C_5H_{12}, −78 °C, 4 h		Cl	60	12	1*S*,2*S*
		2-$^{d}Icr_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Br	69	68	1*S*,2*S*
3		2-$^{d}Icr_2BCl$, *n*-C_5H_{12}, −78 °C, 4 h		Cl	58	57	1*S*,2*S*
		2-$^{d}Icr_2BBr$, *n*-C_5H_{12}, −100 °C, 4 h		Br	70	78	1*S*,2*S*

[a] Enantiomeric excess values were determined by HPLC analysis on a Daicel Chiralcel OD-H column as aryl esters (4-nitrobenzoate, 3,5-dinitrobenzoate, and 1-naphthoate).

[b] The absolute configurations of the halohydrins (1*S*,2*S*) were assigned based on the results obtained from Ipc_2BX reactions. The superscript 'd' indicates that the reagent is derived from (+)-2-carene.



Scheme 2. Enantioselective ring opening of *meso*-cyclohexene oxide with 2-$^{d}Icr_2BX$.

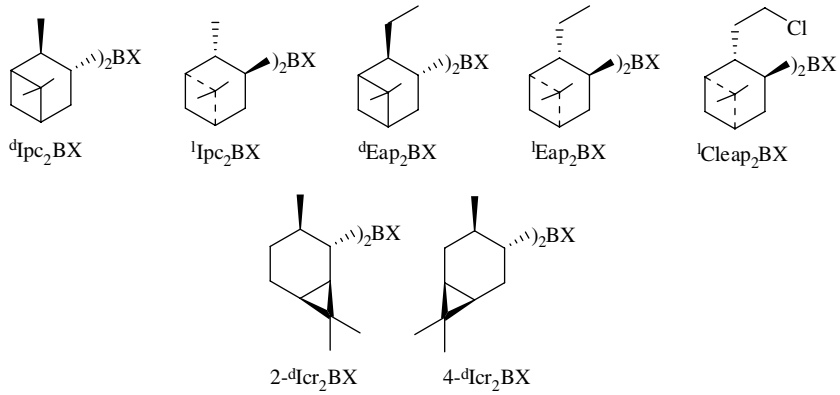


Figure 1. Various structurally modified chiral reagents, Ter_2BX.

$^{l}Eap_2BCl$ (91% ee), 4-$^{d}Icr_2BCl$ (97% ee), $^{l}Cleap_2BCl$ (91% ee), along with previously studied $^{d}Ipc_2BCl$ (99% ee) (Fig. 1). These chiral Ter_2BCl reagents were prepared by the hydroboration of the corresponding olefins with $BH_2Cl{\cdot}SMe_2$ in CH_2Cl_2 for 12–48 h. Two of these reagents, $^{d}Eap_2BCl$[18] and $^{l}Cleap_2BCl$[19] showed significant improvements in enantioselectivities with certain carbonyl compounds in asymmetric reduction over $^{d}Ipc_2BCl$. In order to compare the relative configurations of the product halohydrins, we reexamined the asymmetric ring opening of

Table 3. Asymmetric ring opening of *meso*-cyclohexene oxide with various Ter_2BCl

Entry	Ter_2BCl	Reaction conditions	Yield %	% ee[a]	Conf[b]
1	$^{d}Ipc_2BCl$	*n*-Pentane, −78 °C, 4 h	70	41	1*R*,2*R*
2	$^{l}Ipc_2BCl$	*n*-Pentane, −78 °C, 4 h	66	39	1*S*,2*S*
3	$^{d}Eap_2BCl$	*n*-Pentane, −78 °C, 4 h	65	32	1*R*,2*R*
4	$^{l}Eap_2BCl$	*n*-Pentane, −78 °C, 4 h	68	28	1*S*,2*S*
5	2-$^{d}Icr_2BCl$	*n*-Pentane, −78 °C, 4 h	66	78	1*S*,2*S*
6	4-$^{d}Icr_2BCl$	*n*-Pentane, −78 °C, 4 h	68	19	1*R*,2*R*
7	$^{l}Cleap_2BCl$	*n*-Pentane, −78 °C, 4 h	65	15	1*R*,2*R*

[a] Enantiomeric excess values were determined by HPLC analysis on a Daicel Chiralcel OD-H column as aryl esters (3,5-dinitrobenzoate and 1-naphthoate).

[b] The absolute configurations of the halohydrins (1*S*,2*S*) were assigned based on the results obtained from Ipc_2BX reactions.

meso-cyclohexene oxide with both commercially available reagents, $^{d}Ipc_2BCl$ and $^{l}Ipc_2BCl$. Among various Ter_2BCl examined, 2-$^{d}Icr_2BCl$ proved to be the best reagent of choice for the *meso*-cyclohexene oxide. The results are summarized in Table 3.

meso-Cyclopentene oxide appears to be a problematic substrate, possibly due to ring strain. It is quite evident from the literature that *meso*-cyclopentene oxide yields chlorohydrin of relatively lower enantiomeric excess. Even Buono's catalytic method, which handles a wide variety of *meso*-epoxides very efficiently, fails in the case of *meso*-cyclopentene oxide. It might be possible that either *meso*-cyclopentene oxide undergoes rapid cleavage even at lower temperatures or that the product could be undergoing comparatively rapid racemization under the reaction conditions considering the labile nature of halohydrins.[20]

Next, we decided to examine the enantioselective ring opening of *meso*-cyclohexene oxide as a model reaction with various Ter_2BBr, such as $^{d}Eap_2BBr$ (97% ee), $^{l}Eap_2BBr$ (91% ee), $^{l}Cleap_2BBr$ (91% ee), along with previously studied $^{d}Ipc_2BBr$ (99% ee) (Fig. 1). The reagents, $^{d}Eap_2BBr$ and $^{l}Eap_2BBr$ were successfully prepared either by the hydroboration with $BH_2Br{\cdot}SMe_2$ or by Matteson's Me_3SiH/BBr_3 procedure whereas $^{l}Cleap_2BBr$ (91% ee) could only be prepared by the hydroboration of 2-(β-chloroethyl)apopinene using the Me_3SiH/BBr_3 method. In order to compare the results, we reexamined the asymmetric ring opening of *meso*-cyclohexene oxide with the commercially available $^{d}Ipc_2BBr$. A slight modification in the reaction conditions (a longer reaction time with slow warming after addition of an aldehyde) followed by quick analysis of the bromohydrin on the GC (Chiraldex-GTA), achieved slightly higher enantiomeric excess (92%) (Table 1). It is important to note that the column purified 2-bromocyclohexan-1-ol showed slightly lower enantiomeric excess (86%) (in comparison with the crude bromohydrin). Except for $^{l}Cleap_2BBr$, all the four reagents, $^{d}Ipc_2BBr$, $^{d}Eap_2BBr$, $^{l}Eap_2BBr$, and 2-$^{d}Icr_2BBr$ showed comparable results for the *meso*-cyclohexene oxide (78–86% ee). The results are summarized in Table 4.

While determining the enantiomeric excess of the 2-bromo-1-trifluoroacetoxycyclohexane (obtained from $^{l}Eap_2BBr$ reaction) by an analytical GC on a Chiraldex-GTA column, we observed the racemization of the product TFA ester.[20] The HPLC analysis of various derivatives of β-bromohydrins either with 4-nitrobenzoyl chloride or 3,5-dinitrobenzoyl chloride or 1-naphthoyl chloride in CH_2Cl_2 in the presence of Et_3N provided consistent enantiomeric excess (ee). We believe that the enantiomeric excess values of the original β-bromohydrins must be higher than the observed ee values, considering the labile nature of the halohydrins (quick analysis of the TFA derivative of the crude product showed higher enantiomeric excess than the purified product, especially for the bromohydrin derived from *meso*-cyclohexene oxide). Buono et al. reported a drop in the specific rotation (α) of 2-chlorocyclohexan-1-ol from −30 to −20 after 4 h in CH_2Cl_2.[13]

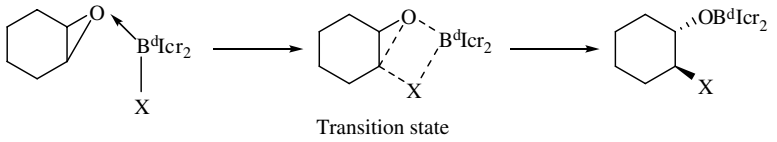
In the case of $^{d}Ipc_2BX$, experimental and stereochemical results supported an S_N2'-type reaction pathway involving a four-centered transition state, preceded by the complexation of boron with a lone pair on oxygen, and resulting in the selective cleavage of the enantiotopic *S* C–O bond in an antiperiplanar manner (Scheme 3). We believe that 2-$^{d}Icr_2BX$ also follows a similar reaction pathway, as previously proposed for the $^{d}Ipc_2BX$ reaction, but on the opposite enantiotopic *R* C–O bond resulting in the enantiomer of an opposite configuration. Presumably, steric factors are involved in the transition state as observed in the asymmetric hydroboration of *cis*-alkenes with $^{d}Ipc_2BH$.[21]

Table 4. Asymmetric ring opening of *meso*-cyclohexene oxide with various Ter_2BBr

Entry	Ter_2BBr	Reaction conditions	% Yield	% ee[a]	Conf[b]
1	$^{d}Ipc_2BBr$	*n*-Pentane, −100 °C, 4 h	75	86	1*R*,2*R*
2	$^{d}Eap_2BBr$	*n*-Pentane, −100 °C, 4 h	74	78	1*R*,2*R*
3	$^{l}Eap_2BBr$	*n*-Pentane, −100 °C, 4 h	76	78	1*S*,2*S*
4	2-$^{d}Icr_2BBr$	*n*-Pentane, −100 °C, 4 h	72	78	1*S*,2*S*
5	$^{l}Cleap_2BBr$	*n*-Pentane, −100 °C, 4 h	75	36	1*R*,2*R*

[a] Enantiomeric excess values were determined by HPLC analysis on a Daicel Chiralcel OD-H column as aryl esters (3,5-dinitrobenzoate and 1-naphthoate).

[b] The absolute configurations of the bromohydrins (1*S*,2*S*) were assigned based on the results obtained from Ipc_2BX reactions.



Scheme 3. Four-centered transition state for the cleavage of *meso*-cyclohexene oxide with 2-$^{d}Icr_2BX$.

3. Conclusions

In conclusion, we have synthesized two chiral reagents, 2-$^{d}Icr_2BCl$ and 2-$^{d}Icr_2BBr$ and tested them in the asymmetric cleavage of three representative *meso*-epoxides. *B*-Chlorobis(2-isocaranyl)-borane ($^{d}Icr_2BCl$) has significantly improved the enantiomeric excess of 2-chlorocyclohexan-1-ol from 41% to 78–79%. In the case of *meso-cis*-2,3-butene oxide also, 18–19% improvement was achieved in comparison with $^{d}Ipc_2BCl$. Unfortunately, this reagent is highly substrate dependent and fails to afford highly enantiomerically enriched 2-chlorocyclopentan-1-ol with *meso*-cyclopentene oxide. In the case of *B*-bromobis(2-isocaranyl)borane ($^{d}Icr_2BBr$), considerable improvements in enantiomeric excesses were realized with both *meso*-cyclopentene oxide (58–68%) and *meso-cis*-2,3-butene oxides (61–78%) whereas *meso*-cyclohexene oxide showed only comparable enantioselectivity (78%).

Acknowledgments

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17. *A representative procedure for the enantioselective opening of meso-cyclohexene oxide with 2-$^{d}Icr_2BCl$:* All operations are conducted under a nitrogen atmosphere. A 100 mL flask containing 2-$^{d}Icr_2BCl$ (6 mmol) in dry *n*-pentane (24 mL, 0.25 M) was cooled to −78 °C and *meso*-cyclohexene oxide (5 mmol, 0.5 mL) was slowly added dropwise with stirring. Stirring was continued for 4 h, then *n*-butyraldehyde (10 mmol) was added followed by $BF_3{\cdot}OEt_2$ (20 μl) and the reaction mixture was allowed to warm up slowly overnight. The conversion of the borinate to the boronate was followed by ^{11}B NMR (2–3 d). The resulting boronate was then treated with diethanolamine (5 mmol) to retrieve the 2-chlorocyclohexan-1-ol. The crude product was purified on silica gel column chromatography (5–10% ethyl ether in *n*-hexanes or *n*-pentane) and the enantiomeric excess (ee) was determined by HPLC analysis on a Daicel Chiralcel OD-H column after transforming the 2-chlorocyclohexan-1-ol into both 3,5-dinitrobenzoyl- and 1-naphthoyl esters. Enatiomeric excess: 78% (1*S*,2*S*).
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20. We had earlier noticed the racemization of the trifluoroacetate derivative of the 2-bromocyclohexan-1-ol while determining the enantiomeric excess by the analytical GC on a Chiraldex-GTA column. Buono and co-workers had also observed the racemization of 2-chlorocyclohexan-1-ol while recording the optical rotation in CH_2Cl_2 (Paper withdrawn, Buono, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4536; Buono, G. *Eur. J. Org. Chem.* **2002**, 218).
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