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Asymmetric Synthesis using Organoboranes. Relative Effectiveness of the *B*-Halobis(terpenyl)boranes for the Enantioselective Halogenative Cleavage of Representative *meso*-Epoxides*

Chandra D. Roy[A,B,C] *and Herbert C. Brown*[A]

[A]Department of Chemistry, Herbert C. Brown Center for Borane Research, Purdue University, West Lafayette, IN 47907-2084, USA.

[B]Present address: EMD Biosciences, Inc., 10394 Pacific Center Court, San Diego, CA 92121, USA.

[C]Corresponding author. Email: chandra0919@gmail.com

A comparative study of the relative effectiveness of various Ter_2BX, such as $^{d}Eap_2BX$, $^{l}Eap_2BX$, 2-$^{d}Icr_2BX$, 4-$^{d}Icr_2BX$, and $^{l}Cleap_2BX$ along with $^{d}Ipc_2BX$ for the asymmetric ring opening of three representative *meso*-epoxides (cyclohexene, cyclopentene, and *cis*-2,3-butene oxides) is reported. Among all the reagents studied, 2-$^{d}Icr_2BCl$ (78–80%) demonstrated significant improvement in enantiomeric excess over a previously explored reagent, $^{d}Ipc_2BCl$ (41%), especially for *meso*-cyclohexene oxide. Although all these three reagents, $^{d}Ipc_2BBr$, $^{d}Eap_2BBr$, and 2-$^{d}Icr_2BBr$ provided comparable enantiomerically enriched 2-bromocyclohexan-1-ol (76–86%) from *meso*-cyclohexene oxide, the carene-based reagent, 2-$^{d}Icr_2BBr$ 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 previously reported reagent, $^{d}Ipc_2BBr$ (57 and 61%, respectively). The enantioselectivity of the reaction was observed to be highly substrate dependent. The present study represents a significant advance in asymmetric synthesis using the chiral organoborane chemistry.

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Introduction

The desymmetrization of *meso*-epoxides by an enantioselective addition of nucleophiles is a very efficient strategy in asymmetric synthesis since it creates and establishes two contiguous stereogenic centers simultaneously.[1] Vicinal halohydrins are very important key intermediates in the syntheses of many halogenated marine natural products (e.g., aplysiapyranoid A, laurenyne, dactylyne, isodactylyne, 2-bromo-β-chamigrene) and pharmaceuticals (e.g., thienamycin, immunosuppressants ISP-1, cryptophycin 1, epothilone, antiviral nucleosides).[2] The asymmetric ring openings (AROs) of *meso*- or racemic epoxides have been successfully achieved with a variety of nucleophiles, such as aromatic amines,[3] carbon nucleophiles,[4] phenols,[5] thiols,[6] carboxylic acids,[7] azides,[8] cyanides,[9] and halides.[10–13] Among the myriad of nucleophiles studied, halides have drawn considerable attention. In 1988, the first general synthesis of optically active β-halohydrins using stoichiometric amounts of chiral Lewis acid halides, *B*-halodiisopinocampheylboranes (Ipc_2BX) was reported from this laboratory.[11] Nugent used the trimethylsilyl azide ($TMSN_3$)/allyl halide in the presence of a zirconium complex in the ARO of different epoxides to afford the corresponding vicinal halohydrins in high chemical and optical yields.[12] Denmark et al.[13] reported the first catalytic ARO of epoxides to provide enantiomerically enriched chlorohydrins using $SiCl_4$ in the presence of a chiral phosphoramide Lewis base. Later Fu and coworkers[14] and Nakajima et al.[15] published the enantioselective cleavage of epoxides with $SiCl_4$ using η^5-C_5Ar_5-based planar-chiral pyridine *N*-oxides. These catalytic methods (developed by the groups of Fu and Nakajima) provided the best results only with acyclic epoxides. Even the catalytic method of Denmark et al. appeared to be highly substrate dependent (highly effective only with certain substrates, such as stilbene oxide and benzyloxy-substituted 2,3-butene oxide). In the past decades, several valuable chiral organoboron reagents derived from the naturally occurring terpene-based chiral auxiliaries, especially the super chiral auxiliary, α-pinene, were developed by Brown[16–18] and their synthetic applications were successfully demonstrated in many asymmetric transformations, such as hydroboration, reduction, homologation, allylboration, enolboration, and ring opening of *meso*-epoxides (Fig. 1).

Although the α-pinene-based reagents, $^{d}Ipc_2BX$ (X = Br, I) demonstrated good to excellent enantioselectivities in the ARO reactions with most of the epoxides studied, the lower enantiomeric excesses (ee's) achieved with $^{d}Ipc_2BCl$ persuaded us to undertake the syntheses of structurally modified terpene-based chiral boron reagents, Ter_2BX, and test these chiral reagents, in the hope of improving enantioselectivities. Earlier, Brown and coworkers[16–18] had succeeded in finding improved steric and electronic matches between the

* This paper is dedicated to the memory of my mentor, the late Professor Herbert C. Brown (1912–2004). The work described herein was carried out at Purdue University as a post-doctoral research associate.

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terpene-based reagent and the substrate, thereby achieving higher enantioselectivity in many reactions. Hydroborating agents ($RapBH_2$)[16] and reducing agents (Rap_2BCl),[17] derived from these structurally modified terpenes as well as allylborating agent (2-^{d}Icr$_2$BAll),[18] prepared from (+)-Δ^2-carene, have shown considerable improvements in enantioselectivities over α-pinene-based reagents. Consequently, we synthesized a series of structurally modified chiral *B*-halobis(terpenyl)boranes that can act as chiral Lewis acids bearing halides (as nucleophilic units) and examined their effectiveness in the enantioselective desymmetrization of *meso*-epoxides. In a continuation of our research work to develop new methods and reagents for the regio-, chemo-, and enantioselective ring opening of epoxides,[19] we recently communicated our preliminary results on the ARO of *meso*-epoxides with special emphasis on *meso*-cyclohexene oxide using structurally modified *B*-halobis(terpenyl)boranes.[20] The success with 2-^{d}Icr$_2$BX prompted us to extend our comprehensive study on the enantioselective halogenative cleavage of three representative *meso*-epoxides with Ter_2BX (X = Cl, Br) and the results of such study are described herein.

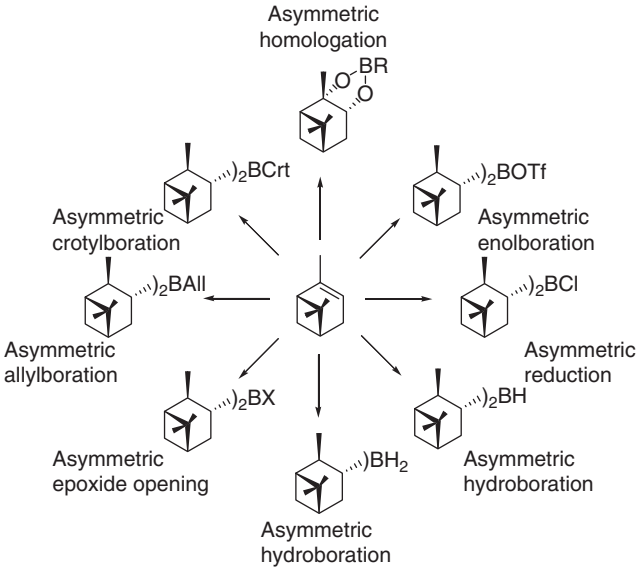
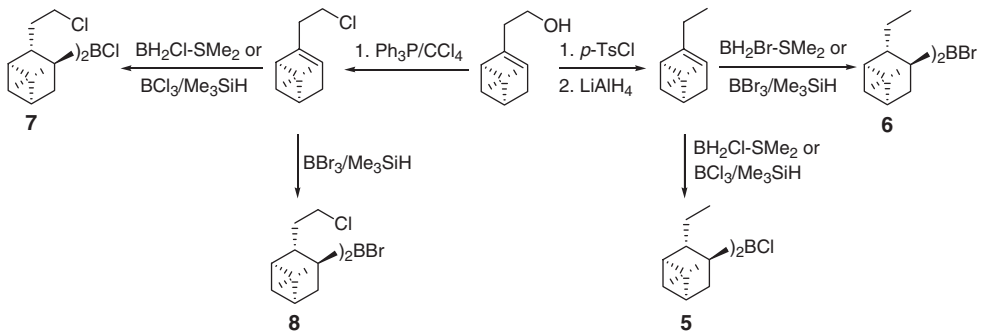


Fig. 1. α-Pinene, the super chiral auxiliary.

Results and Discussion

Synthesis of C_2-Symmetric Chiral B-Halobis(terpenyl)borane Reagents

The C_2-symmetric Ter_2BX reagents were prepared by the hydroboration of the corresponding olefins with suitable *B*-haloboranes.[17] Both (−)-2-ethylapopinene (^{l}Eap, 92–93% ee) and (−)-β-chloroethylapopinene (^{l}Cleap, 92–93% ee) were prepared from the commercially available (*R*)-(−)-nopol (92–93% ee). The (−)-nopol (92–93% ee) was refluxed with Ph_3P in CCl_4 for 7 h to obtain (−)-β-chloroethylapopinene. The (−)-2-ethylapopinene was obtained either by reducing the (−)-β-chloroethylapopinene with $LiEt_3BH$ (Aldrich: Super Hydride) or reducing the nopol tosylate (prepared from (−)-nopol) with $LiAlH_4$. The (+)-ethylapopinene (>99% ee) was prepared by the metallation of (+)-α-pinene (>99%) with *tert*-BuOK/*n*-BuLi, followed by alkylation with CH_3I. Finally, Ter_2BX **3**–**12** (X = Cl, Br) were obtained either by direct hydroboration of the corresponding olefins with BH_2X–SMe_2 or by Matteson's BX_3/Me_3SiH methodology (Scheme 1, Fig. 2). The hydroboration of (+)-Δ^2-carene and (+)-Δ^3-carene (96% ee) with either commercially available BH_2Cl–SMe_2 in CH_2Cl_2 or BCl_3/Me_3SiH in *n*-hexanes, afforded *B*-chlorobis(2-isocaranyl)borane **9** (2-^{d}Icr$_2$BCl) (^{11}B: δ 74.5) and *B*-chlorobis(4-isocaranyl)borane **11** (4-^{d}Icr$_2$BCl) in high chemical yield and purity. Hydroboration of (+)-Δ^2-carene with BH_2Br–SMe_2 in CH_2Cl_2 gave a mixture of products (2-^{d}Icr$_2$BBr and 2-^{d}IcrBHBr). The bromination of 2-^{d}Icr$_2$BH (prepared by the hydroboration of (+)-Δ^2-carene with BH_3) with Br_2 in CH_2Cl_2 also could not provide pure 2-^{d}Icr$_2$BBr. Only Matteson's BBr_3/Me_3SiH procedure yielded 2-^{d}Icr$_2$BBr **10** (96% ee, ^{11}B: δ 78) and 4-^{d}Icr$_2$BBr **12** in high chemical yield and purity.



Scheme 1. Synthesis of structurally modified terpenes and Ter_2BX.

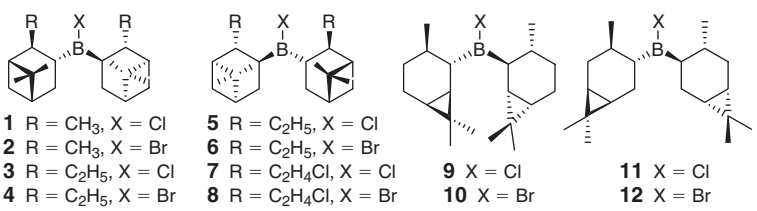


Fig. 2. Structurally modified chiral reagents, Ter_2BX.

ARO of meso*-Cyclohexene Oxide* ***13*** *with* Ter_2BX

For the comparative study, we chose to examine the enantioselective ring opening of three representative *meso*-epoxides, e.g., *meso*-cyclohexene oxide **13**, *meso*-cyclopentene oxide **14**, and *cis*-2,3-butene oxide **15** (Fig. 3), with Ter_2BX. In order to compare the relative effectiveness of these reagents, we selected *meso*-cyclohexene oxide as a standard substrate, which was subjected to ARO reactions with $^{d}Eap_2BCl$ **3** (97% ee), $^{l}Eap_2BCl$ **5** (91–92% ee), $^{l}Cleap_2BCl$ **7** (91–92% ee), 2-$^{d}Icr_2BCl$ **9** (97% ee), and 4-$^{d}Icr_2BCl$ **11** (97%) along with the previously studied $^{d}Ipc_2BCl$ **1** (99% ee) (Fig. 2) at −78°C. Previous studies involving $^{d}Eap_2BCl$[15] and $^{l}Cleap_2BCl$[15] have demonstrated their superiority over $^{d}Ipc_2BCl$ with certain carbonyl compounds in asymmetric reduction. In the case of $^{d}Ipc_2BCl$ **1**, a minor change in reaction conditions (slightly longer reaction time, slow elevation of the reaction temperature after addition of an aldehyde) and quick analysis of the chlorohydrins on a Chiraldex-GTA analytical column, provided enantiomerically

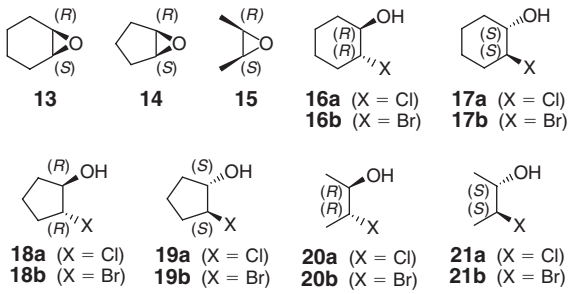


Fig. 3. Representative *meso*-epoxides and the chiral halohydrins.

enriched 2-chlorocyclohexan-1-ol (41% ee, conf. 1*R*,2*R*), whereas $^{l}Ipc_2BCl$ afforded 2-chlorocyclohexan-1-ol of 38.5% ee with opposite configuration (1*S*,2*S*). These ee values are considerably higher than the previously reported values (22%) (Table 1). These two experimental results were also highly informative to compare and establish the relative configurations of the various product chlorohydrins.

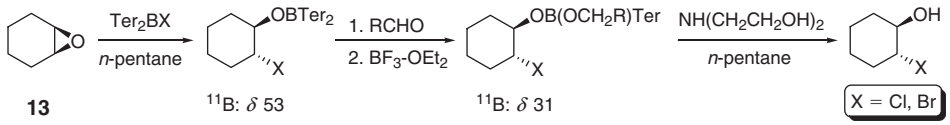
Among the various Ter_2BCl examined, 2-$^{d}Icr_2BCl$ **9** was demonstrated to be the most effective reagent in the enantioselective ring opening of *meso*-cyclohexene oxide (78–80% ee with **9**, 41% ee with **1**) (Scheme 2, Fig. 3). By changing the $–CH_3$ group to the $–C_2H_5$ group at the C-2 position in the apopinene structure, only 32% ee was observed in the case of $^{d}Eap_2BCl$ **3**. Both 4-$^{d}Icr_2BCl$ **11** and $^{l}Cleap_2BCl$ **7** provided 2-chlorocyclohexan-1-ol of 18 and 25% ee, respectively. It is also interesting to note that **9** yielded 2-chlorocyclohexan-1-ol of opposite configuration (1*S*,2*S*). No improvement in enantioselectivity was observed when the reaction was conducted at −100°C for 4 h. The chemical yield of the 2-chlorocyclohexan-1-ol in all cases ranged between 60 and 70%.

Although the ARO of representative *meso*-epoxides with **2** provided relatively higher enantiomerically enriched bromohydrins (48–84% ee) in comparison with **1** (40–46% ee), there remained considerable opportunity for further improvements with many substrates. Consequently, we undertook the asymmetric cleavage of *meso*-epoxides with Ter_2BBr along with previously examined **2** (for comparison). Except for $^{l}Cleap_2BBr$ **8**, all the Ter_2BBr provided *trans*-2-bromocyclohexan-1-ol of comparable ee (76–86% ee, Table 1). In the case of α-pinene-based reagents, the conversion of the borinate ester into the boronate ester was observed to be relatively fast (<2 h). The

Table 1. ARO of *meso*-cyclohexene oxide 13 with various Ter_2BX (X = Cl, Br)

Entry	Ter_2BCl	Reaction conditions	Halohydrin no.	Yield [%]	ee [%]	Conf.[E]
1	$^{d}Ipc_2BCl$ **1**	−78°C, 4 h	**16a**	70	41[A]	1*R*,2*R*
2	$^{d}Ipc_2BBr$ **2**	−100°C, 4 h	**16b**	75	85–92[A]	1*R*,2*R*
3	$^{d}Eap_2BCl$ **3**	−78°C, 4 h	**16a**	65	32[C]	1*R*,2*R*
4	$^{d}Eap_2BBr$ **4**	−100°C, 4 h	**16b**	74	78[B]	1*R*,2*R*
5	$^{l}Eap_2BCl$ **5**	−78°C, 4 h	**17a**	68	28[A]	1*S*,2*S*
6	$^{l}Eap_2BBr$ **6**	−100°C, 4 h	**17b**	76	89–99[A,D]	1*R*,2*R*
7	$^{l}Cleap_2BCl$ **7**	−78°C, 4 h	**16a**	65	25[B]	1*R*,2*R*
8	$^{l}Cleap_2BBr$ **8**	−100°C, 4 h	**16b**	75	36[A]	1*R*,2*R*
9	2-$^{d}Icr_2BCl$ **9**	−78°C, 4 h	**17a**	66	78–80[B,C]	1*S*,2*S*
10	2-$^{d}Icr_2BBr$ **10**	−100°C, 4 h	**17b**	72	76[B]	1*S*,2*S*
11	4-$^{d}Icr_2BCl$ **11**	−78°C, 4 h	**16a**	68	18[B]	1*R*,2*R*
12	4-$^{d}Icr_2BBr$ **12**	−100°C, 4 h	**16b**	70	3[B]	1*R*,2*R*

[A]Enantiomeric excess values were determined by gas chromatographic analysis on a Chiraldex-GTA column as trifluoroacetate derivative.
[B]Enantiomeric ratios (er) were determined by HPLC analysis on a DAICEL Chiralcel OD-H column as 3,5-dintrobenzoate ester.
[C]Enantiomeric excess values were determined by HPLC analysis on a DAICEL Chiralcel OD-H column as 1-naphthoate ester.
[D]Racemization of the 2-bromocyclohexan-1-ol trifluoroacetate was observed.
[E]The absolute configurations of the major halohydrins (1*S*,2*S*) were assigned based on the results obtained from $^{d}Ipc_2BX$ reactions.



Scheme 2. ARO of *meso*-cyclohexene oxide with Ter_2BX.

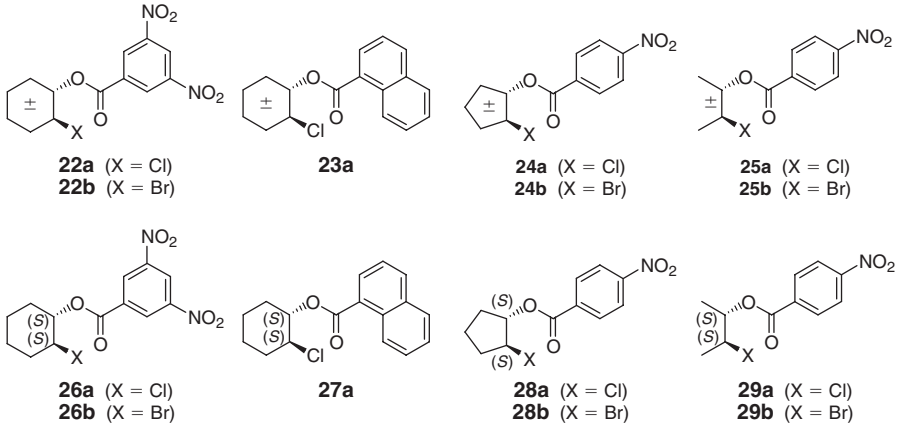


Fig. 4. Racemic and the chiral halohydrin derivatives.

slow conversion of the borinate ester (^{11}B: δ 53–56) into the boronate ester (^{11}B: δ 31) with other chiral reagents could be attributed to the steric nature of the chiral auxiliaries. Such conversion was accelerated by the addition of a small amount of BF_3–OEt_2. With *meso*-cyclohexene oxide, only 76% ee was achieved when analyzed by chiral high performance liquid chromatography (HPLC) after transforming the hydroxy group of the 2-bromocyclohexan-1-ol into a UV sensitive ester.

Considering the labile nature of these halohydrins, it was decided to analyze the crude bromohydrins obtained from $^{d}Ipc_2BBr$ **2** and $^{l}Eap_2BBr$ **6** reactions. In the case of **2**, the gas chromatographic analyses of the TFA (trifluoroacetyl) ester derivatives of both the crude and the purified 2-bromocyclohexan-1-ol (on Chiraldex-GTA column) revealed that the crude product had a slightly higher ee (92% ee) in comparison with the column-purified product (86% ee). Upon careful analysis of the TFA ester of the crude 2-bromocyclohexan-1-ol (obtained from reaction with **6**), it was obvious that the TFA derivative was undergoing slow racemization in solution (the ee of the product dropped from 99 to 89% in 1.5 h). The derivatization of halohydrins into UV sensitive esters (3,5-dinitrobenzoate and 1-naphthoate) and their analyses by chiral HPLC provided consistent and reproducible results (Fig. 4). It is believed that the ee's of the original β-bromohydrins are likely to be higher than the observed values. Vicinal halohydrins obtained from 2-$^{d}Icr_2BX$ have opposite configurations (1*S*,2*S*) in comparison with $^{d}Ipc_2BX$ (1*R*,2*R*).

ARO of meso-*Cyclopentene Oxide* ***14*** *with* Ter_2BX

Earlier, we reported the asymmetric cleavage of *meso*-cyclopentene oxide **14** with various $^{d}Ipc_2BX$ (X = Cl, Br, I). Interestingly, the enantioselectivity observed for all three halohydrins were very close (44% ee with $^{d}Ipc_2BCl$ **1**, 48% ee with $^{d}Ipc_2BBr$ **2**, and 52% ee with $^{d}Ipc_2BI$) which is in marked contrast to the results obtained with *meso*-cyclohexene oxide (22, 84, and 91% ee, respectively). During the catalytic enantioselective ring opening of epoxides with $SiCl_4$ in the presence of a chiral Lewis base (phosphoramide), Denmark and coworkers[13] also observed very low enantioselectivity with *meso*-cyclopentene oxide (2-chlorocyclopentan-1-ol, 7% ee), whereas *meso*-cyclohexene oxide afforded 2-chlorocyclohexan-1-ol (52% ee). It appears that *meso*-cyclopentene oxide is a highly reactive substrate possibly because of the ring strain. Therefore, it was of great interest to examine and compare the relative effectiveness of Ter_2BX in the asymmetric halogenative cleavage of *meso*-cyclopentene oxide.

First of all, we revisited the ring opening of *meso*-cyclopentene oxide with $^{d}Ipc_2BX$ (X = Cl, Br). No significant improvement was seen with $^{d}Ipc_2BCl$ **1** (46% ee). Among the various structurally modified Ter_2BCl studied, only $^{l}Cleap_2BCl$ **7** (entry 19) showed slightly improved results (49% ee). It was interesting to note that the configuration of the product chlorohydrin obtained from $^{l}Cleap_2BCl$ was similar to the chlorohydrin obtained from $^{d}Ipc_2BCl$ **1**. It appears that the β-chloroethyl side chain has a significant influence on the stereochemical outcome of the reaction. Next, we investigated the asymmetric epoxide opening reactions of *meso*-cyclopentene oxide **14** with Ter_2BBr. Upon reexamination of epoxide **14** with $^{d}Ipc_2BBr$ **2**, a slightly improved enantioselectivity (from 48 to 57% ee) was observed, under slightly different reaction conditions (Table 2, entry 14). Among all the reagents studied, only 2-$^{d}Icr_2BBr$ showed an encouraging result (67% ee, entry 22). The results are tabulated in Table 2.

ARO of cis-*2,3-Butene Oxide* ***15*** *with* Ter_2BX

After examining two representative cyclic epoxides **13** and **14**, attention was turned to test the effectiveness of these reagents with *cis*-2,3-butene oxide **15** and compare the results with $^{d}Ipc_2BX$. Considering the enantioselectivity achieved with $^{l}Cleap_2BX$ and 4-$^{d}Icr_2BX$, only four reagents, $^{d}Eap_2BX$ and 2-$^{d}Icr_2BX$ were examined. First we attempted to reproduce the previous work with $^{d}Ipc_2BX$. Although we obtained chlorohydrin of slightly improved enantiomeric excess (46% ee, lit.[11] 38% ee) with $^{d}Ipc_2BCl$ **1**, $^{d}Ipc_2BBr$ **2** provided bromohydrin of 57% ee (lit.[11] 61% ee) in our hand. Gratifyingly, both 2-$^{d}Icr_2BCl$ **9** and 2-$^{d}Icr_2BBr$ **10** turned out to be the most effective reagents (57 and 78% ee's, respectively) in the series. Interestingly, the acyclic epoxide, *cis*-2,3-butene oxide furnished halohydrins of relatively higher ee's than the results obtained from *meso*-cyclopentene oxide. These results are summarized in Table 3.

A Proposed Reaction Mechanism

Jacobsen's mechanistic studies on ARO reactions have revealed that the reaction is second order with respect to metal reagent (one metal center serves as a Lewis acid and the second metal center delivers the nucleophile).[8] Shibasaki's bimetallic catalytic process also follows the similar reaction pathway.[5]

Table 2. ARO of *meso*-cyclopentene oxide 14 with various Ter_2BX (X = Cl, Br)

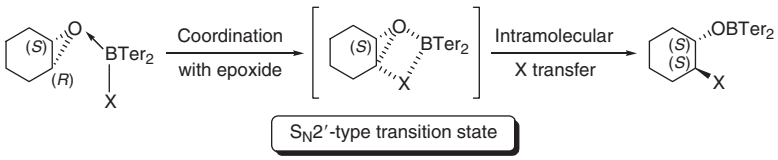
Entry	Ter_2BCl	Reaction conditions	Halohydrin no.	Yield [%]	ee [%]	Conf.[C]
13	$^{d}Ipc_2BCl$ **1**	−78°C, 4 h	**18a**	60	46[A]	1*R*,2*R*
14	$^{d}Ipc_2BBr$ **2**	−100°C, 4 h	**18b**	65	57[A]	1*R*,2*R*
15	$^{d}Eap_2BCl$ **3**	−78°C, 4 h	**18a**	65	32[B]	1*R*,2*R*
16	$^{d}Eap_2BBr$ **4**	−100°C, 4 h	**18b**	65	32[B]	1*R*,2*R*
17	$^{l}Eap_2BCl$ **5**	−78°C, 4 h	**19a**	68	28[B]	1*S*,2*S*
18	$^{l}Eap_2BBr$ **6**	−100°C, 4 h	**19b**	66	20[B]	1*R*,2*R*
19	$^{l}Cleap_2BCl$ **7**	−78°C, 4 h	**18a**	65	49[B]	1*R*,2*R*
20	$^{l}Cleap_2BBr$ **8**	−100°C, 4 h	**18b**	62	39[B]	1*R*,2*R*
21	2-$^{d}Icr_2BCl$ **9**	−78°C, 4 h	**19a**	68	12[B]	1*S*,2*S*
22	2-$^{d}Icr_2BBr$ **10**	−100°C, 4 h	**19b**	69	67[B]	1*S*,2*S*

[A]Enantiomeric excess values were determined by gas chromatographic analysis on a Chiraldex-GTA column as trifluoroacetate derivative.
[B]Enantiomeric excess values were determined by HPLC analysis on a DAICEL Chiralcel OD-H column as 4-nitrobenzoate ester.
[C]The absolute configurations of the halohydrins (1*S*,2*S*) were assigned based on the results obtained from Ipc_2BX reactions.

Table 3. ARO of *meso-cis*-2,3-butene oxide 15 with various Ter_2BX (X = Cl, Br)

Entry	Ter_2BCl	Reaction conditions	Halohydrin no.	Yield [%]	ee [%]	Conf.[C]
23	$^{d}Ipc_2BCl$ **1**	−78°C, 4 h	**20a**	60	46[A]	1*R*,2*R*
24	$^{d}Ipc_2BBr$ **2**	−100°C, 4 h	**20b**	65	57[B]	1*R*,2*R*
25	$^{d}Eap_2BCl$ **3**	−78°C, 4 h	**20a**	60	32[B]	1*R*,2*R*
26	$^{d}Eap_2BBr$ **4**	−100°C, 4 h	**20b**	60	50[A]	1*R*,2*R*
27	2-$^{d}Icr_2BCl$ **9**	−78°C, 4 h	**21a**	58	57[B]	1*S*,2*S*
28	2-$^{d}Icr_2BBr$ **10**	−100°C, 4 h	**21b**	70	78[B]	1*R*,2*R*

[A]Enantiomeric excess values were determined by gas chromatographic analysis on a Chiraldex-GTA column as trifluoroacetate derivative.
[B]Enantiomeric excess values were determined by HPLC analysis on a DAICEL Chiralcel OD-H column as 4-ntrobenzoate ester.
[C]The absolute configurations of the halohydrins (1*S*,2*S*) were assigned based on the results obtained from Ipc_2BX reactions.



Scheme 3. A proposed reaction pathway for the asymmetric ring opening of a representative *meso*-epoxide with Ter_2BX.

Nugent has also proposed the involvement of two zirconium atoms during the enantioselective cleavage of epoxides.[12] Although a bimetallic activation pathway appears to be highly appealing, a plausible reaction mechanism for the ARO with $^{d}Ipc_2BX$ (Scheme 3) was proposed[11] based on the results obtained from the base-catalyzed closure of the chiral halohydrin to a *cis*-epoxide, the asymmetric cleavage of *meso*-cyclohexene oxide with $^{d}Ipc_2BBr$ **2** in the presence of *n*-Bu_4NBr, and the strong complexation with $^{d}Ipc_2BF$ without rupturing the epoxide in the presence of an external nucleophile. An enantiomeric discrimination is likely to be a two step event—activation of epoxide by binding with chiral boron reagent, followed by attack of halogen nucleophile in a S_N2' fashion that involves a four-centered transition state, to result in the selective cleavage of the enantiotopic *S* C–O bond in an anti-periplanar manner. We believe that 2-$^{d}Icr_2BX$ also follows a similar reaction pathway, but on the opposite enantiotopic *R* C–O bond resulting in an enantiomer of opposite configuration. The origin of chirality in ARO reactions may be a result of similar relative conformations of the two terpenyl structures as was proposed for asymmetric hydroboration.[21] Steric factors appear to play a significant role in the transition state, as envisioned in the asymmetric hydroboration of *cis*-alkenes with $^{d}Ipc_2BH$.

Conclusions

In summary, the relative effectiveness of several C_2-symmetric chiral *B*-halobis(terpenyl)boranes of diverse structural types, Ter_2BX, were tested in the asymmetric cleavage of three representative *meso*-epoxides. In all the cases studied, the halohydrins were obtained in reasonably good chemical yields. However, the enantioselective outcome of the reaction was observed to be highly substrate dependent. *B*-Chlorobis(2-isocaranyl)borane (2-$^{d}Icr_2BCl$) appeared to be the reagent of choice, especially

for *meso*-cyclohexene oxide, which significantly improved the enantiomeric excess of 2-chlorocyclohexan-1-ol from 41 to 78–80%. Except for $^{l}Cleap_2BBr$, all the Ter_2BBr showed comparable enantioselectivity (75–78% ee) with *meso*-cyclohexene oxide. Only moderate enantioselectivity was achieved with *meso*-cyclopentene oxide using Ter_2BX (X = Cl, Br). The highest enantiomeric excess (50%) of β-chlorohydrin was accomplished with $^{l}Cleap_2BCl$. Among the various Ter_2BBr tested, 2-$^{d}Icr_2BBr$ showed the best result (67% ee). In the case of acyclic *meso-cis*-2,3-butene oxide, only 2-$^{d}Icr_2BX$ showed marginal improvements (57 and 78% ee, respectively) over $^{d}Ipc_2BX$. It was interesting to note that 2-$^{d}Icr_2BBr$ produced halohydrins of opposite configuration (1*S*,2*S*) as compared to $^{d}Ipc_2BX$ (1*R*,2*R*). This study represents a significant advance in asymmetric synthesis using chiral organoborane chemistry.

Experimental

All operations and manipulations were carried out in oven-dried glassware that was assembled under nitrogen atmosphere. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a Varian-Gemini 300 MHz multinuclear NMR spectrometer. The ^{11}B NMR chemical shifts are in δ relative to BF_3–OEt_2. The enantiomeric excesses (ee's) of various halohydrins were determined either by analytical gas chromatographic analyses using a Chiraldex-GTA column (Hewlett–Packard 5890) or by analytical HPLC analyses on a DAICEL Chiralcel OD-H column with a built-in photometric detector (λ 254 nm). Column chromatography was performed using 230–400 mesh silica gel. All solvents were appropriately dried, degassed, and stored under nitrogen.

All the epoxides **13**–**15** were purchased from Aldrich and used as received. 2-(+)-Carene, 3-(+)-carene, α-pinene, boron tribromide, boron trichloride, monobromoborane–dimethyl sulfide, monochloroborane–dimethyl sulfide, and trimethylsilane were purchased from Aldrich and used as received. The chiral boron reagents, $^{d}Ipc_2BCl$ **1**, $^{l}Ipc_2BCl$, and $^{d}Ipc_2BBr$ **2**, were purchased from Aldrich. Following the procedures reported in the literature,[15] reagents **3**–**12** were prepared and used immediately in the ARO reactions. All the racemic halohydrins were prepared following the procedures reported in the literature[11,17] and these halohydrins were derivatized by suitable derivatizing agents for the determination of ee's. These racemic and chiral β-halohydrins have been thoroughly characterized in the literature.[11–13]

A Representative Procedure for the Enantioselective Ring Opening of meso*-Cyclohexene Oxide* ***13*** *with 2-*$^{d}Icr_2BCl$ ***9***

A 100 mL flask that contained 2-$^{d}Icr_2BCl$ **9** (6 mmol) in dry *n*-pentane (24 mL, 0.25 M) was cooled to −78°C and *meso*-cyclohexene oxide **13** (5 mmol, 0.5 mL) was slowly added drop wise with stirring. Stirring was continued for 4 h, and *n*-butyraldehyde (10 mmol) was then added followed by BF_3–OEt_2 (20 μL) and the reaction mixture was allowed to warm slowly overnight. The conversion of the borinate into the boronate was followed by ^{11}B NMR (δ 53–60 for borinate to δ 31 boronate, 2–3 days). The resulting boronate was then treated with diethanolamine (5 mmol) to retrieve the 2-chlorocyclohexan-1-ol **17a**. The crude product was purified on silica gel column chromatography (5–10% ethyl ether in *n*-hexanes or *n*-pentane) and the optical purity (ee) was determined by HPLC analysis on a DAICEL Chiralcel OD-H column after transforming the 2-chlorocyclohexan-1-ol into 3,5-dinitrobenzoate and 1-naphthoate esters. Enantiomeric excess: 78–80% (1*S*,2*S*).

(±)-*trans*-3,5-Dinitrobenzoic acid 2-chlorocyclohexyl ester **22a**: Yellow solid. δ_H ($CDCl_3$) 9.24 (s, 1H, ArH), 9.17 (s, 2H, ArH), 5.15 (m, 1H, –CHOCOAr), 4.05 (m, 1H, –CHCl), 2.50–2.20 (m, 2H, $–CH_2$), 1.90–1.30 (m, 6H, $–CH_2$). δ_C ($CDCl_3$) 163.8, 150.5, 135.6, 130.0, 123.5, 76.6, 60.5, 34.9, 30.9, 24.6, 23.3. HPLC retention time (area %) = 32.12 min (50.23%, 1*R*,2*R*) and 34.77 min (49.76%, 1*S*,2*S*).

(1*S*,2*S*)-*trans*-3,5-Dinitrobenzoic acid 2-chlorocyclohexyl ester **26a** (from 2-$^{d}Icr_2BCl$): HPLC analysis: hexane/propan-2-ol retention time (area %) = 30.19 min (11%, 1*R*,2*R*) and 32.37 min (89%, 1*S*,2*S*), 78% ee.

(±)-*trans*-Naphthalene-1-carboxylic acid 2-chlorocyclohexyl ester **23a**: White solid. δ_H ($CDCl_3$) 8.90 (d, 1H, ArH), 8.20 (d, 1H, ArH),7.95 (d, 1H, ArH), 7.80 (d, 1H, ArH), 7.50 (m, 1H, ArH), 7.45 (m, 2H, ArH), 5.16 (m, 1H, –CHOCOAr), 4.03 (m, 1H, –CHCl), 2.40–2.20 (m, 2H, $–CH_2$), 1.80–1.20 (m, 6H, $–CH_2$). δ_C ($CDCl_3$) 166.6, 133.7, 133.2, 131.2, 131.0, 128.4, 127.6, 127.3, 126.1, 125.7, 124.4, 76.5, 60.6, 34.8, 30.8, 24.5, 23.3. HPLC analysis: retention time (area %) = 9.34 min (51.70%, 1*R*,2*R*) and 10.36 min (48.29%, 1*S*,2*S*).

(1*S*,2*S*)-*trans*-Naphthalene-1-carboxylic acid 2-chlorocyclohexyl ester **27a** (from 2-$^{d}Icr_2BCl$): HPLC retention time (area %) = 13.86 min (10%, 1*R*,2*R*) and 15.56 min (90%, 1*S*,2*S*), 80% ee.

(±)-*trans*-4-Nitrobenzoic acid 2-chlorocyclopentyl ester **24a**: Yellow solid. δ_H ($CDCl_3$) 8.29 (d, 2H, ArH), 8.15 (d, 2H, ArH), 5.41 (m, 1H, –CHOCOAr), 4.35 (m, 1H, –CHCl), 2.50–2.20 (m, 2H, $–CH_2$), 2.20–1.70 (m, 4H, $–CH_2$). δ_C ($CDCl_3$) 163.7, 150.6, 135.3, 130.7, 123.5, 83.3, 62.1, 33.9, 29.5, 21.3. HPLC retention time (area %) = 13.12 min (50.28%, 1*R*,2*R*) and 14.71 (49.71%, 1*S*,2*S*).

(1*S*,2*S*)-*trans*-4-Nitrobenzoic acid 2-chlorocyclopentyl ester **28a** (from 2-$^{d}Icr_2BCl$): HPLC retention time (area %) = 13.30 min (44%, 1*R*,2*R*) and 15.01 min (56%), 12% ee.

(±)-4-Nitrobenzoic acid 2-chloro-1-methylpropyl ester **25a**: Yellow semi-solid. δ_H ($CDCl_3$) 8.29 (d, 2H, ArH), 8.25 (d, 2H, ArH), 5.31 (m, 1H, –CHOCOAr), 4.20 (m, 1H, –CHCl), 1.56 (d, 3H, $–CH(OCOAr)CH_3$), 1.46 (d, 3H, $–CH(Cl)CH_3$). δ_C ($CDCl_3$) 163.8, 150.5, 135.4, 130.8, 123.6, 74.5, 58.8, 20.9, 16.8. HPLC retention time (area %) = 12.59 min (48.98%, 2*R*,3*R*) and 13.33 min (51.01%, 2*S*,3*S*).

(2*S*,3*S*)-4-Nitrobenzoic acid 2-chloro-1-methylpropyl ester **29a** (from 2-$^{d}Icr_2BCl$): HPLC retention time (area %) = 12.57 min (21.70%, 2*R*,3*R*) and 13.34 min (78.29%, 2*S*,3*S*), 56.6% ee.

A Representative Procedure for the Enantioselective Ring Opening of meso*-Cyclohexene Oxide* ***13*** *with 2-*$^{d}Icr_2BBr$ ***10***

A 100 mL flask that contained 2-$^{d}Icr_2BBr$ **10** (6 mmol) in dry *n*-pentane (24 mL, 0.25 M) was cooled to −100°C and *meso*-cyclohexene oxide (5 mmol, 0.5 mL) was slowly added drop wise with stirring. Stirring was continued for 4 h, and *n*-butyraldehyde (10 mmol) was then added followed by BF_3–OEt_2 (20 μL) and the reaction mixture was allowed to warm slowly overnight. The conversion of the borinate into the boronate was followed by ^{11}B NMR (δ 53–60 for borinate to δ 31 boronate, 2–3 days). The resulting boronate was then treated with diethanolamine (5 mmol) to retrieve the 2-bromocyclohexan-1-ol. The crude product was purified on silica gel by column chromatography (5–10% ethyl ether in *n*-hexanes or *n*-pentane) and the optical purity (ee) was determined by HPLC analysis on a Daicel Chiralcel

OD-H column after benzoylating the 2-bromocyclohexan-1-ol with 3,5-dinitrobenzoyl chloride. Enantiomeric excess: 76% (1*S*,2*S*).

(±)-*trans*-3,5-Dinitrobenzoic acid 2-bromocyclohexyl ester **22b**: Yellow solid. δ_H ($CDCl_3$) 9.24 (s, 1H, ArH), 9.17 (s, 2H, ArH), 5.15 (m, 1H, –CHOCOAr), 4.05 (m, 1H, –CHBr), 2.50–2.20 (m, 2H, $–CH_2$), 1.90–1.30 (m, 6H, $–CH_2$). δ_C ($CDCl_3$) 163.8, 150.5, 135.0, 130.0, 123.5, 76.6, 60.5, 34.9, 30.8, 24.6, 23.3. HPLC retention time (area %) = 30.06 min (49.35%, 1*R*,2*R*) and 33.39 min (50.64%, 1*S*,2*S*).

(1*S*,2*S*)-*trans*-3,5-Dinitrobenzoic acid 2-bromocyclohexyl ester **26b** (from 2-$^{d}Icr_2BBr$): HPLC retention time (area %) = 30.40 min (12%, 1*R*,2*R*) and 33.50 min (88%, 1*S*,2*S*), 76% ee.

(±)-*trans*-4-Nitrobenzoic acid 2-bromocyclopentyl ester **24b**: Yellow solid. δ_H ($CDCl_3$) 8.30 (d, 2H, ArH), 8.15 (d, 2H, ArH), 5.41 (m, 1H, –CHOCOAr), 4.35 (m, 1H, –CHBr), 2.50–2.20 (m, 2H, $–CH_2$), 2.20–1.60 (m, 4H, $–CH_2$). δ_C ($CDCl_3$) 163.7, 150.6, 135.4, 130.7, 123.5, 83.6, 52.2, 34.6, 29.5, 21.7. HPLC retention time (area %) = 13.88 min (50.38%, 1*R*,2*R*) and 15.29 min (49.61%, 1*S*,2*S*).

(1*S*,2*S*)-*trans*-4-Nitrobenzoic acid 2-bromocyclopentyl ester **28b** (from 2-$^{d}Icr_2BBr$): HPLC retention time (area %) = 13.68 min (16.25%, 1*R*,2*R*) and 15.11 min (83.74%, 1*S*,2*S*), 67.5% ee.

(±)-4-Nitrobenzoic acid 2-bromo-1-methylpropyl ester **25b**: Yellow semi-solid. δ_H ($CDCl_3$) 8.29 (d, 2H, ArH), 8.26 (d, 2H, ArH), 5.31(m, 1H, –CHOCOAr), 4.30 (m, 1H, –CHBr), 1.75 (d, 3H, –CH(OCOAr)CH_3), 1.49 (d, 3H, –CH(Br)CH_3). δ_C ($CDCl_3$) 163.7, 150.6, 135.4, 130.8, 123.6, 74.5, 50.7, 22.1, 17.7. HPLC retention time (area %) = 12.86 min (50.48%, 2*R*,3*R*) and 13.71 min (49.51%, 2*S*,3*S*).

(2*S*,3*S*)-4-Nitrobenzoic acid 2-bromo-1-methylpropyl ester **29b** (from 2-$^{d}Icr_2BBr$): HPLC retention time (area %) = 13.72 min (11%, 2*R*,3*R*) and 14.71 min (89%, 2*S*,3*S*), 78% ee.

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