Some Recent Applications of Hydroboration/Organoborane Chemistry to Heterocycles

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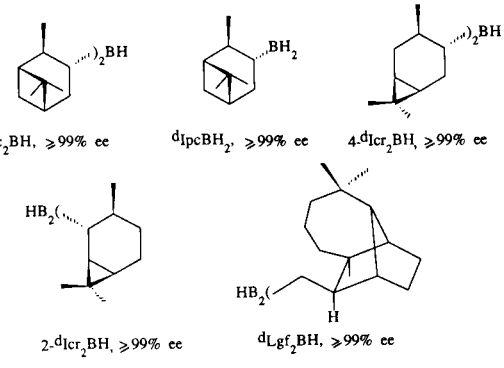
Since the discovery of the ether catalyzed addition of diborane to carbon-carbon multiple bonds [1], hydroboration has become a highly powerful and versatile reaction for organic synthesis[2-4]. The organoboranes thus prepared by hydroboration are among the most versatile organometallic intermediates, making possible a wide variety of carbon-carbon bond forming reactions to afford almost all types of organic compounds [5,6]. Numerous reports of the hydroboration of *cis*-olefins, *trans*-olefins, dienes, acetylenic compounds and functionalized unsaturated substrates have appeared. To achieve the desired hydroboration in an appropriate and convenient manner, a wide variety of hydroborating agents, such as borane-methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), disiamylborane (Sia_2BH), thexylborane ($ThxBH_2$), catecholborane and haloboranes, were developed and their hydroboration properties studied systematically [7]. These hydroborating characteristics often proved to be complementary, providing valuable procedures to the synthetic organic chemist for achieving the selective hydroboration of multifunctional compounds.

Recently intense interest has been aroused in the development of efficient methods for asymmetric synthesis [8]. Of these procedures, asymmetric hydroboration is an especially promising process for the synthesis of chiral compounds [9]. Various chiral hydroborating agents, derived from naturally abundant, low cost terpenes, of various steric requirements, have been developed to hydroborate different classes of prochiral olefins (Scheme 1).

Scheme 1



d_{Ipc_2BH}, ≥99% ee d_{IpcBH_2}, ≥99% ee 4-d_{Icr_2BH}, ≥99% ee

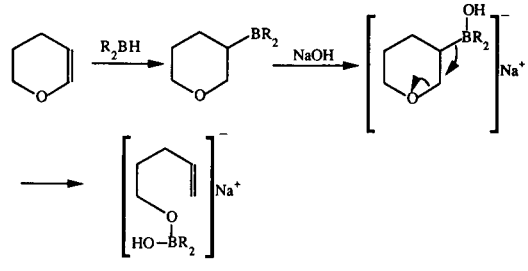
2-d_{Icr_2BH}, ≥99% ee d_{Lgf_2BH}, ≥99% ee

Diisopinocampheylborane (Ipc_2BH) hydroborates cis-alkenes, resulting in asymmetric induction in the range of 80-99% ee [10]. Similarly, monoisopinocampheylborane ($IpcBH_2$) hydroborates *trans*-alkenes and trisubstituted alkenes with optical induction ranging from 53-98% ee [11]. Both *cis*- and trisubstituted olefins have been hydroborated with dilongifolylborane (Lgf_2BH) and dicaranylboranes (4-Icr_2BH and 2-Icr_2BH), realizing moderate to good asymmetric induction [12,13].

The early studies largely utilized hydrocarbon alkenes and alkynes to establish the characteristics of the hydroboration reaction and the utility of the organoborane products for organic synthesis. But heterocyclic derivatives constitute an even larger segment of organic chemistry. Consequently, it was desirable to explore the extension of hydroboration/organoborane chemistry to heterocyclic derivatives.

Heterocyclic derivatives introduce some major differences in hydroboration/organoborane reactions. First, the heterocyclic group plays a major role in controlling the direction of hydroboration of double (and triple) bonds. Secondly the presence of a boron atom β- to the heteroatom can result in facile elimination (Scheme 2). Fortunately, it has proven possible to control both of these effects to achieve the desired utilization of hydroboration/organoborane chemistry for organic synthesis involving heterocyclic derivatives. This article presents a review of the developments in this area, as well as a recent application of organoborane chemistry which made possible the first successful synthesis of the heterocyclic boracyclanes in the strained medium-ring range.

Scheme 2

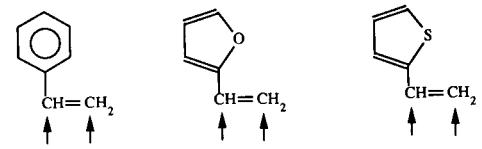


I] Hydroboration of Heterocyclic Olefins.

a) Hydroboration of Heterocyclic Disubstituted Olefins.

The hydroboration of representative vinyl and propenyl heterocycles with BMS, 9-BBN, Chx_2BH and Sia_2BH was studied to establish directive effects in the hydroboration

HYDROBORATION OF 2-VINYL HETEROCYCLES



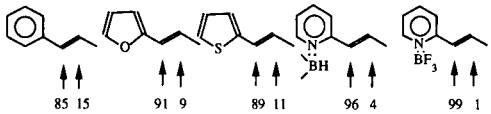
BMS	19	81	16	84	12	88
9-BBN	2	98	3	97	2	98
Chx_2BH			0	100	0	100
Sia_2BH	2	98	0	100	0	100

Table 1

[14]. The directive effects observed for 2-vinylfuran and 2-vinylthiophene are similar to those realized in the case of styrene (Table 1).

A systematic study of the hydroboration of *trans*-(2-propenyl)heterocycles with BMS, 9-BBN, Chx_2BH and Sia_2BH shows the preferred formation of α-bora derivatives [14]. A comparison of the behaviour of *trans*-(2-propenyl) heterocyclics with that of *trans*-(2-propenyl)benzene in the hydroboration reveals that the effect of heterocycles is comparable to that of phenyl in directing the boron atom to the α-carbon atom of the side chain (Table 2).

HYDROBORATION OF 2-PROPENYL HETEROCYCLES



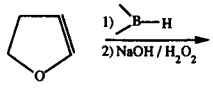
BMS	85	15	91	9	89	11	96	4	99	1
9-BBN	97	3	96	4	94	6	93	7	99	1
Chx_2BH			98	2	95	5	95	5	99	1
Sia_2BH			95	5	96	4	99	1	100	0

Table 2

b) Heterocycles Containing the Double Bond Inside the Ring (endocyclic double bond).

The hydroboration of representative heterocyclic olefins bearing an endocyclic double bond with BMS, 9-BBN, Chx_2BH and Sia_2BH was investigated systematically and the optimum conditions for clean, quantitative hydroboration have been established (Tables 3, 4, 5, 6).

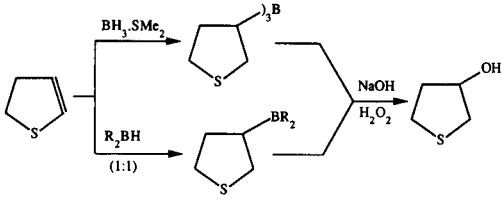
HYDROBORATION OF 2,3-DIHYDROFURAN



Hydroborating agent	Reaction conditions	Product distribution, mole %		
		3- Hydroxy-THF	3-Buten-1-ol	1,3- and 1,4-Butanediols
$BH_3.SMe_2$	3:1, 0°C, 3h	88	4	6
	3:1, 25°C, 1h	98	trace	trace
	3:1, 25°C, 4h	65	27	4
	2:1, 0°C, 8h	54	19	5
9- BBN	1:1, 25°C, 1h	100	0	0
Chx_2BH	1:1, 25°C, 1h	100	0	0
Sia_2BH	1:1, 0°C, 2h	100	0	0

Table 3

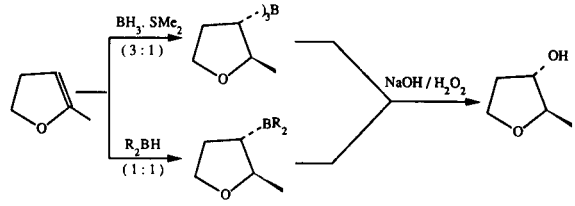
HYDROBORATION OF 2,3-DIHYDROTHIOPHENE



Hydroborating agent	Reaction conditions	Yield, %
$BH_3.SMe_2$	3 : 1, 25°C, 1h	94
9-BBN	1 : 1, 25°C, 1h	98
Chx_2BH	1 : 1, 25°C, 1h	100
Sia_2BH	1 : 1, 0°C, 2h	100

Table 4

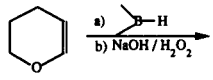
HYDROBORATION OF 2-METHYL-4,5-DIHYDROFURAN



Hydroborating agent	Reaction conditions	Yield, %
$BH_3.SMe_2$	3 : 1, 25°C, 1h	100
9-BBN	1 : 1, 25°C, 1h	93
Chx_2BH	1 : 1, 25°C, 1h	98
Sia_2BH	1 : 1, 0°C, 2h	97

Table 5

HYDROBORATION OF 3,4-DIHYDROPYRAN



Hydroborating agent	Reaction conditions	Product distribution, %		
		3-Hydroxy-THP	4-Penten-1-ol	1,4- and 1,5-Pentanediol
$BH_3.SMe_2$	3:1, 25°C, 1h	82	15	3
	3:1, 25°C, 4h	51	1	20
	3:1, 65°C, 4h	47	4	22
	2:1, 25°C, 4h	37	0	56
	2:1, 0°C, 4h	44	0	50
$BH_3.THF$	2:1, 0°C, 3h	90	0	0
9-BBN	1:1, 25°C, 2h	92	0	0
Chx_2BH	1:1, 25°C, 1.5h	98	0	0
Sia_2BH	1:1, 0°C, 18h	96	0	0

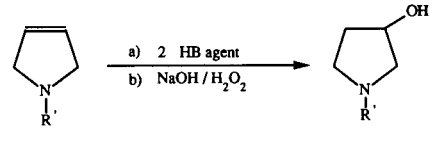
Table 6

In the case of heterocycles containing the double bond adjacent to the heteroatom, the hydroboration is regioselective, furnishing β-organoboranes exclusively. Oxidation of such β-organoboranes furnishes β-hydroxy heterocycles, valuable intermediates in organic synthesis.

Hydroboration of nitrogen heterocycles with various hydroborating agents could not be achieved with the nitrogen atom unprotected [15,16]. Such hydroborations have been accomplished by protecting the nitrogen atom with an alkyl,

Scheme 3

HYDROBORATION OF FIVE MEMBERED NITROGEN HETEROCYCLES

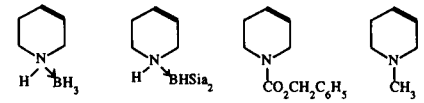


R' = $-CH_3$, $-CH_2C_6H_5$, $-CO_2CH_2C_6H_5$

HB agent : BH_3, 9-BBN, Chx_2BH, Sia_2BH

benzyl [17,18] or carbobenzyloxy group. The intermediate trialkylboranes are readily converted to their corresponding alcohols (Scheme 3, Table 7).

HYDROBORATION OF SIX-MEMBERED NITROGEN HETEROCYCLES



HYDROBORATION OF BENZYLOXYCARBONYL 1,2,5,6-TETRAHYDRO-PYRIDINE

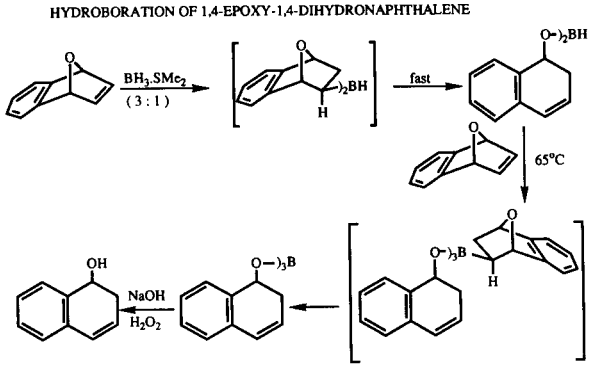
Hydroborating agent	Reaction conditions	Yield %	Product distribution, % 3-ol	4-ol
$BH_3.SMe_2$	3:1, 25°C, 1h	80	85	15
9-BBN	1:1, 25°C, 24h	75	85	15
Chx_2BH	1:1, 25°C, 6h	84	75	25
Sia_2BH	1:1, 0°C, 96h	69	75	25

Table 7

Excess hydride and prolonged reaction time can cause the cleavage of the intermediate trialkylborane to yield first unsaturated products, which then undergo further hydroboration. 1,4-Epoxy-1,4-dihydronaphthalene, an unusual heterocycle, was hydroborated with BMS, 9-BBN, Chx_2BH and Sia_2BH [19]. It was discovered that the organoboranes derived from BMS and 9-BBN are very unstable, yielding upon oxidation 1-hydroxy-1,2-dihydronaphthalene in quantitative yield. On the other hand, organoboranes derived from Chx_2BH and Sia_2BH are stable, yielding upon oxidation 7-oxa-2-benzonorborneol, in quantitative yield. Evidently, in the case of BMS (with lower steric requirements), the oxygen heteroatom chelates with the boron atom, opening the ring (Scheme 4). On the contrary, by the proper choice of hydroborating agents with greater steric requirements, such as Chx_2BH and Sia_2BH, coordination of the boron atom with the hetero atom is considerably hindered, circumventing ring opening, providing a stable organoborane intermediate (Scheme 5). Thus, this example demonstrates the complementary nature of these different hydroborating agents.

Scheme 4

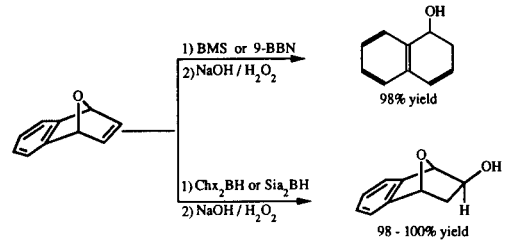
HYDROBORATION OF 1,4-EPOXY-1,4-DIHYDRONAPHTHALENE



The relative reactivities of representative heterocyclic olefins with 9-BBN and Sia_2BH have been determined [20] (Scheme 6). From this study it is quite evident that dihydrofuran with a double bond adjacent to oxygen is more reactive and can be hydroborated selectively in the presence of either 6-membered heterocyclic or carbocyclic olefins. Also, carbocyclic olefins can be hydroborated selectively in the presence of nitrogen heterocycles. These differences in reactivity can be of considerable importance in synthetic organic chemistry. However, related heterocycles containing larger rings do not show such rate enhancement relative to the corresponding carbocycle. Similarly sulfur heterocycles containing the double bond adjacent to the sulfur atom do not show higher reactivities compared to the carbocyclic analogs.

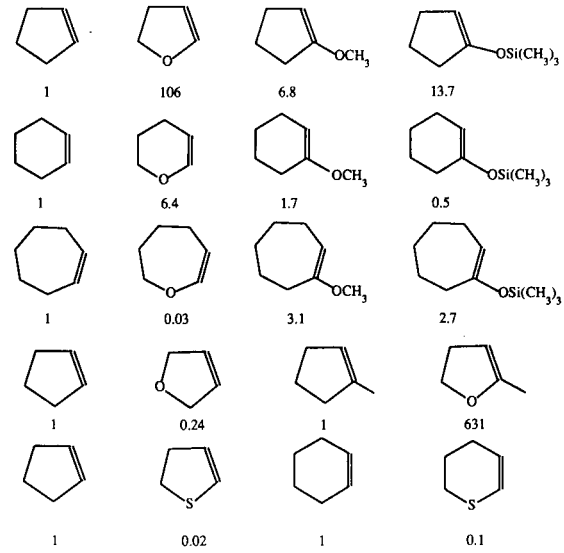
Scheme 5

HYDROBORATION OF 1,4-EPOXY-1,4-DIHYDRONAPHTHALENE



Scheme 6

RELATIVE REACTIVITIES OF HETEROCYCLIC OLEFINS WITH 9-BBN



II] Asymmetric Hydrororation of Heterocyclic Olefins.

a) Asymmetric Hydroboration of Five-membered Heterocyclic Olefins.

Hydroboration of representative heterocyclic olefins bearing an endocyclic double bond with various hydroborating agents reveals clean hydroboration of these heterocyclic olefins with disiamylborane Sia_2BH, constituting a model for possible asymmetric hydroboration with Ipc_2BH. Therefore, the chiral hydroboration of representative heterocyclic olefins was undertaken in the hope of developing a simple, efficient method for the synthesis of pure heterocyclic enantiomers. 2,3-Dihydrofuran was chosen as a representative prochiral olefin. Thus, 2,3-dihydrofuran was hydroborated with various chiral dialkylboranes derived from naturally abundant and low cost terpenes (Table 8). Of the dialkylboranes studied, diisopinocampheylborane, Ipc_2BH, proved to be the best, giving quantitative asymmetric induction.

HYDROBORATION OF 2,3-DIHYDROFURAN WITH VARIOUS CHIRAL DIALKYLBORANES

Chiral Dialkylborane	Reaction Temp.,°C.	% ee	Absolute Configuration
$^{d}Ipc_2BH$	-25	≥99	R
4-$^{d}Icr_2BH$	0	39	R
2-$^{d}Icr_2BH$	0	51	S
$^{d}Lgf_2BH$	25	54	R

The optical purities of the reagents are of ≥99% ee and are derived from (+) enantiomer of the terpene

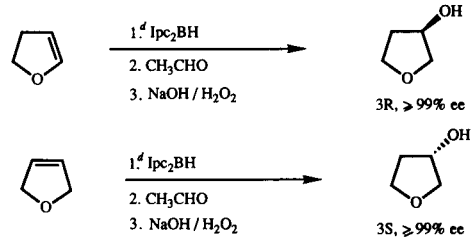
Table 8

The hydroboration of 2,3-dihydrofuran with $^{d}Ipc_2BH$ (prepared from (+)-α-pinene) proceeded rapidly even at –25°C to furnish the desired trialkylborane. Treatment of this trialkylborane with acetaldehyde displaces the α-pinene to furnish diethyl 3-tetrahydrofuranylboronate, which upon oxidation with alkaline hydrogen peroxide, affords *R*-3-hydroxytetrahydrofuran in nearly quantitative yield and excellent optical purity (≥ 99% ee). The chiral auxiliary, α-pinene can be readily recovered and recycled. This asymmetric hydroboration procedure constitutes an elegant, simple, efficient method for synthesizing 3-hydroxytetrahydrofuran in high yield and optical purity (Table 8). As anticipated, the hydroboration of 2,3-dihydrofuran with $^{l}Ipc_2BH$ (prepared from (-)-α-pinene) furnishes the other enantiomer, *i.e. S*-3-hydroxytetrahydrofuran in equally high optical purity (≥ 99% ee) [21].

Asymmetric hydroboration of 2,5-dihydrofuran with $^{d}Ipc_2BH$ under identical conditions furnishes *S*-3-hydroxytetrahydrofuran in excellent yield and very high optical purity (≥ 99% ee). Thus, merely by changing the position of the double bond in a five membered heterocycle, hydroboration with Ipc_2BH derived from the same chiral auxiliary leads to the opposite enantiomer. Thus, 2,3-dihydrofuran and 2,5-dihydrofuran, on hydroboration with $^{d}Ipc_2BH$ followed by oxidation, yield *R*- and *S*-3-hydroxytetrahydrofuran respectively [21] (Scheme 7).

Scheme 7

CHIRAL HYDROBORATION OF DIHYDROFURANS WITH $^{d}Ipc_2BH$

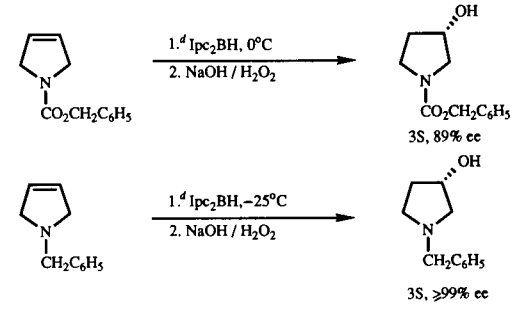


Similarly other five membered heterocyclic olefins on hydroboration with $^{d}Ipc_2BH$, followed by oxidation, yield the corresponding alcohols in very high optical purity and excellent yields [17,21] (Scheme 8,9).

Asymmetric hydroboration of 1,4-epoxy-1,4-dihydronaphthalene with $^{d}Ipc_2BH$ at –25°C followed by treatment of the resulting trialkylborane with acetaldehyde and oxidation furnishes 1*R*,2*S*,4*R*-7-oxa-*exo*-benzonorborneol in high optical purity (≥ 99% ee). Literature methods for the synthesis of such optically active 5-membered heterocyclic alcohols are tedious and often provide products with only low to moderate optical induction [22,23] (Scheme 10).

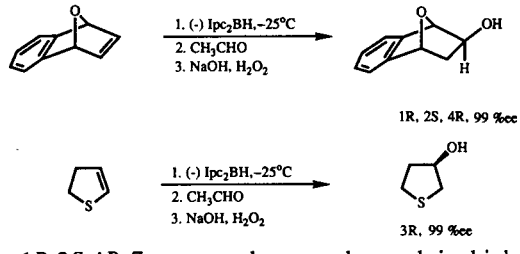
Scheme 8

CHIRAL HYDROBORATION OF FIVE- MEMBERED NITROGEN HETEROCYCLES



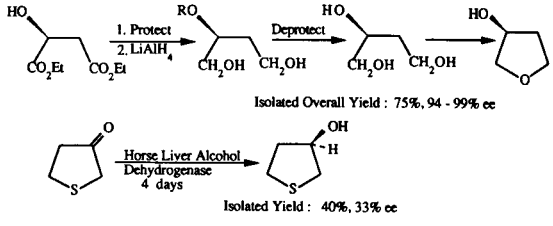
Scheme 9

CHIRAL HYDROBORATION OF HETEROCYCLIC OLEFINS



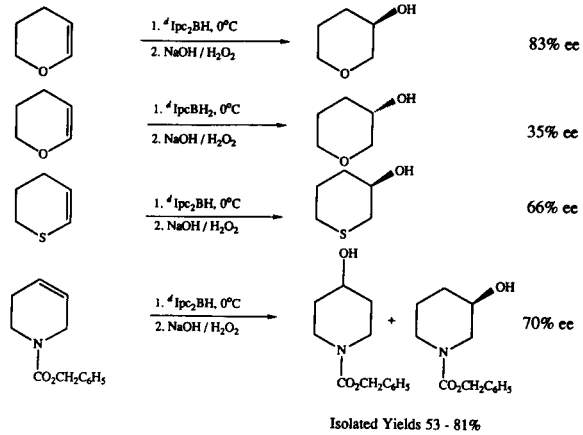
Scheme 10

SYNTHESIS OF CHIRAL HETEROCYCLIC ALCOHOLS : LITERATURE METHODS



Scheme 11

CHIRAL HYDROBORATION OF SIX- MEMBERED HETEROCYCLIC OLEFINS

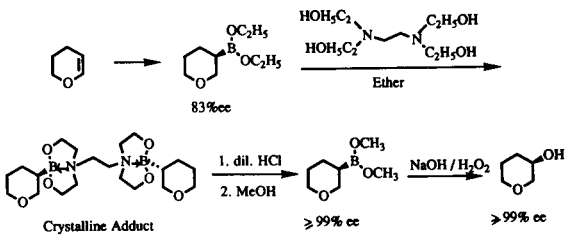


b) Asymmetric Hydroboration of Six-membered Heterocyclic Olefins.

The asymmetric hydroboration of six-membered representative heterocyclic olefins with $^{d}Ipc_2BH$ could be achieved only at 0°C to yield the corresponding trialkylborane. 3-Hydroxy heterocyclic derivatives, obtained from the trialkylborane by treatment with acetaldehyde followed by oxidation, had optical purities in the range of 35%-83% ee [21]. (Scheme 11). However, the optical purity of the intermediate boronate ester (83% ee) has been upgraded to ≥ 99% ee by chelation with 0.5 equivalent of *N,N,N',N'*-tetrakis(2-hydroxyethyl)-ethylenediamine [24] followed by recrystallization. Regeneration of the boronate ester was achieved by treatment with methanolic hydrogen chloride. Oxidation of the boronate ester with alkaline hydrogen peroxide furnished 3-hydroxytetrahydropyran in high optical purity (≥ 99% ee) (Scheme 12).

Scheme 12

UPGRADING THE OPTICAL PURITY OF ETHYL-TETRAHYDRO-3-PYRANYL BORONATE



c) Asymmetric Hydroboration of Heterocyclic Trisubstituted Olefins.

i) Heterocycles containing double bonds inside the ring.

The asymmetric hydroboration of 2-methyl-4,5-dihydrofuran with various dialkylboranes *via* $^{d}Ipc_2BH$, 4-$^{d}Icr_2BH$, 2-$^{d}ICr_2BH$ and $^{d}Lgf_2BH$ has been studied [21] (Table 9). Surprisingly, $^{d}Ipc_2BH$ and 4-^{d} and 2-$^{d}Icr_2BH$ could hydroborate the compound without either disproportionation, or elimination of the reagent, furnishing the corresponding trialkylborane. These upon oxidation, give optically active alcohols (Table 9). This constitutes the first example of the hydroboration of a trisubstituted olefin with Ipc_2BH without disproportionation of the reagent. Possibly, it is attributable to the exceptional reactivity of this trisubstituted heterocyclic olefin [20].

HYDROBORATION OF 2-METHYL-4,5-DIHYDROFURAN WITH VARIOUS CHIRAL DIALKYLBORANES

Chiral dialkylborane	Reaction temp.,°C	% ee	Absolute configuration
$^{d}Ipc_2BH$	-25	83	2S,3R
4-$^{d}Icr_2BH$	0	70	2S,3R
2-$^{d}Icr_2BH$	0	27	3R,4S
$^{d}Lgf_2BH$	25	46	2S,3R

The optical purities of the reagents are of ≥ 99% ee and are derived from (+) enantiomer of the terpene

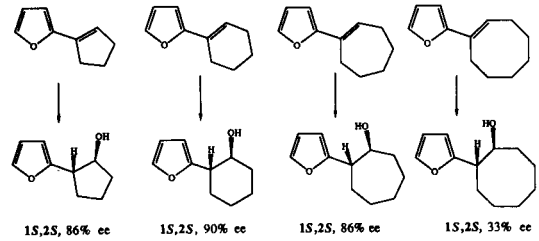
Table 9

ii) Hydroboration of Olefinic Heterocycles (heterocycles containing a double bond outside the ring).

The asymmetric hydroboration of representative furanyl-, thienyl-, and pyridyl-1-cycloalkenes has been achieved with $^{d}IpcBH_2$ [25]. In the case of 2-furanyl-1-cycloalkenes, the asymmetric induction during the hydroboration with $IpcBH_2$ increases slightly from the five-membered to the six-membered ring. The asymmetric induction in the seven-membered ring is, as expected similar to that observed for the five-membered ring. However, the asymmetric induction dropped dramatically in the case of the eight-membered ring (Scheme 13).

Scheme 13

HYDROBORATION OF HETEROCYCLIC CYCLOALKENES WITH $^{d}IpcBH_2$

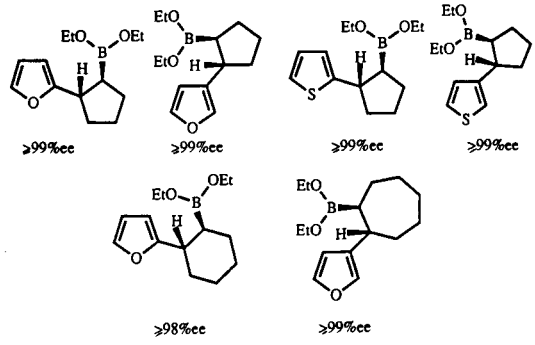


In the case of the furanyl- and thienyl-1-cyclopentenes, no change was observed in the asymmetric induction achieved by hydroboration with $IpcBH_2$, either by altering the position of the attachment of the cyclopentene moiety to the heterocyclic system, or by introducing substituents into the heterocyclic ring. However, a change in the thienyl-1-cyclohexene decreases the asymmetric induction modestly to a range of 76% to 90%.

Such dialkylboranes, isopinocampheylheterocyclicborane, derived from $IpcBH_2$ and the heterocyclic olefin are crystalline dimeric compounds. Products of lower optical purity could be upgraded to materials approaching ≥ 99% ee by simple crystallization of the intermediate, *e.g.* (2-furanyl)-cyclopentylisopinocampheylborane of 86% ee, was upgraded to ≥ 99% ee by a single crystallization from ether. The resulting ≥99% ee material was then converted to the more synthetically useful boronate of ≥ 99% ee, by treatment with acetaldehyde. By following this procedure, various heterocyclic dialkylboranes R *IpcBH have been upgraded and transformed into boronate esters of ≥ 99% ee [25] (Scheme 14).

Scheme 14

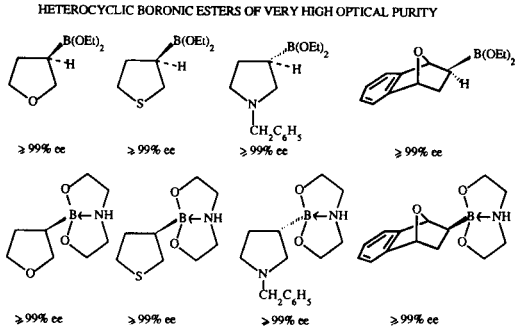
HETEROCYCLIC BORONATES OF HIGH OPTICAL PURITIES



III] Synthesis of Enantiomeric Heterocyclic Boronic Esters.

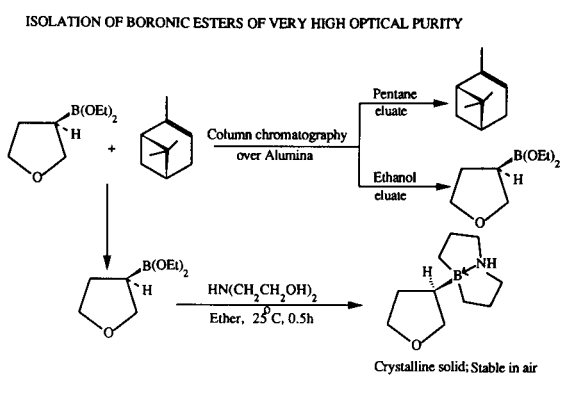
Chiral alkyl boronic esters containing only one alkyl group attached to boron are highly promising intermediates for asymmetric synthesis proceeding through organoborane chemistry [26]. Previously we have shown that diisopinocampheylalkylborane, on treatment with acetaldehyde, liberates α-pinene quantitatively, providing optically active diethyl alkylboronate [27]. By adopting a similar procedure, various representative diethyl heterocyclic boronate esters have been prepared (Scheme 14,15).

Scheme 15



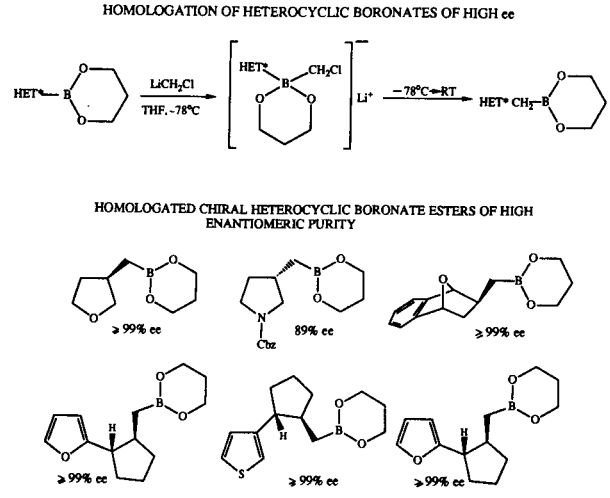
In some of the cases, difficulties are encountered in isolating the boronate in good yield because of its high water solubility. In addition, the boronates are often unstable to heat and can not be isolated by distillation under reduced pressure. However, the boronate can be freed from the liberated α-pinene at 25°C by pumping off the latter under high vacuum (0.05 mm Hg) or by column chromatography over alumina (Scheme 16). The pentane eluate furnishes α-pinene, subsequent elution with ethanol then provides the diethyl heterocyclic boronate. Since diethyl heterocyclic boronates possess low thermal stability, they were converted to the more stable, crystalline chelate esters [28] (Scheme 15,16). From such chelated derivatives, the boronic acids can be easily regenerated by treatment with 2*M* hydrochloric acid [28,29].

Scheme 16



Such heterocyclic boronate esters with a heteroatom in the β-position are known to be unstable with a tendency for elimination or rearrangement during synthetic transformation. To establish whether this side reaction is a serious problem, one-carbon homologation of these boronate esters was undertaken. The difficulty of elimination or rearrangement during synthetic transformation of heterocyclic boronate esters with a heteroatom in the β-position was circumvented by introducing a methylene group *via* one-carbon homologation, using (chloromethyl)lithium, $LiCH_2Cl$, generated *in situ*. This transformation would shift the position of the boron atom from β- to the heteroatom to γ-, thereby increasing the stability of these boronate esters. Indeed, one-carbon homologation of these representative optically active boronate esters has been demonstrated in high yields using (chloromethyl)lithium, $LiCH_2Cl$, generated *in situ* in THF at –78°C in the presence of the boronate ester [30]. It is a well known fact that the homologation transformation proceeds with retention of configuration at the chiral center. Hence by starting with an optically pure heterocyclic boronate ester it was possible to obtain one-carbon homologated boronic ester with retention of configuration at the chiral center. (Scheme 17).

Scheme 17



IV] Synthesis of Heterocyclic Enantiomers.

Optically pure alkynyl borinic esters R*BC≡CR"(OR') are cleanly obtained at low temperatures from optically pure heterocyclic boronic esters $R^*B(OR')_2$ and lithium acetylide followed by the treatment of the "ate" complex $LiR^*BC{\equiv}CR"(OR')_2$ with ethereal hydrogen chloride. These borinic esters react with α,α-dichloromethyl methyl ether, DCME, in the presence of a hindered base to furnish, after hydrogen peroxide oxidation, α-chiral α'-alkynyl ketones, R*COC≡CR" which exhibits the same high enantio- and stereoselectivity of the chiral boronic esters (Scheme 18,19). 3-Heterosubstituted(1-alkynyl)boronic esters, such as

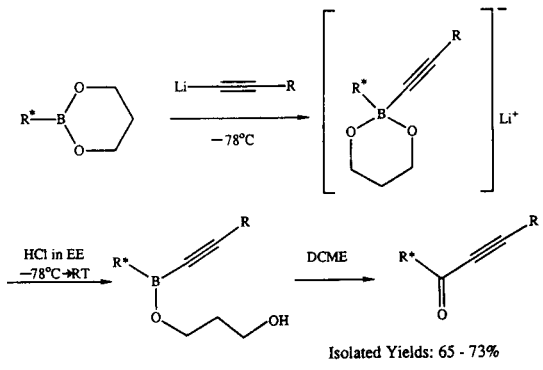
$$\overline{CH_2O\text{-}CH_2\text{-}CH_2}\text{-}CBC{\equiv}CR"(OR'),$$

despite their sensitivity to elimination reactions, have been converted into the corresponding ketones in excellent yields [31] (Scheme 19).

These α-chiral-α'-alkynyl ketones are potentially interesting intermediates for the synthesis of natural products [32]. We have developed a convenient preparation of this class of

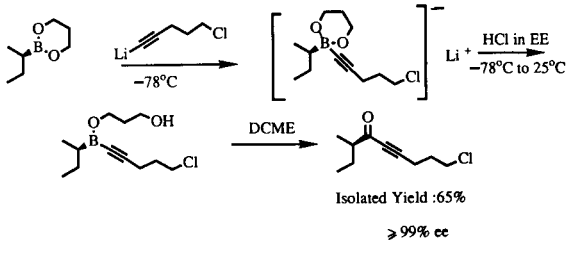
Scheme 18

PREPARATION OF ACETYLENIC KETONES OF HIGH ee



Scheme 19

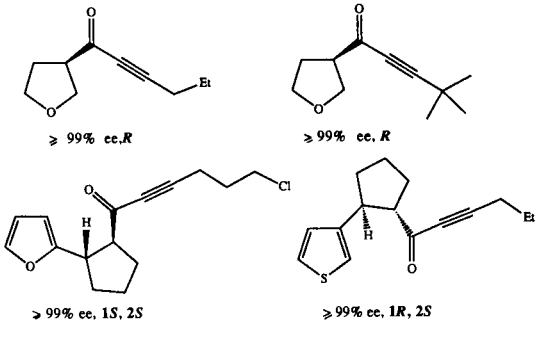
SYNTHESIS OF OPTICALLY PURE α-CHIRAL-α'-ALKYNYL KETONES



chiral compounds from optically pure heterocyclic boronate esters *via* the DCME reaction of the derived alkynyl borinates. The ketones obtained were of uniformly high enantiomeric excess (≥ 99% ee) (Scheme 20).

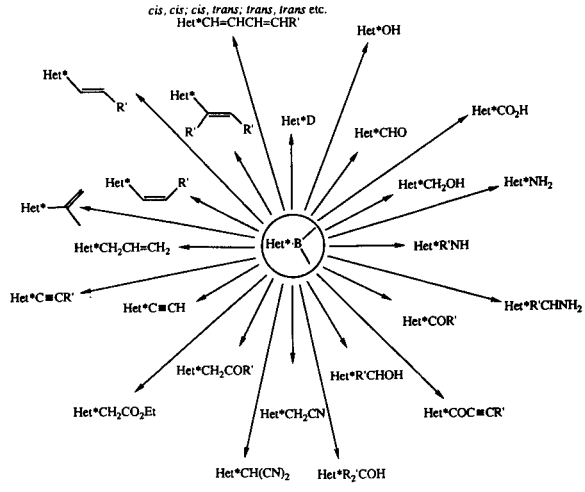
Scheme 20

HETEROCYCLIC ACETYLENIC KETONES OF HIGH OPTICAL PURITY



A systematic study of the hydroboration of various heterocyclic olefins has uncovered simple procedures for the preparation of various heterocyclic boranes. These organoboranes undergo the alkaline hydrogen peroxide oxidation normally, yielding the corresponding alcohols. This study has also made it possible to prepare, for the first time, a number of representative heterocyclic boronates of essentially ≥ 99% ee. Despite their sensitivity to elimination and rearrangement during synthetic transformations, such heterocyclic boronates (with boron β- to the heteroatom) have been successfully subjected to the one-carbon homologation reaction and to the preparation of ketones by the borinic ester/DCME reaction. Although this has not yet been investigated, it is probable that they undergo other known reactions of organoboranes. Consequently, there is a good reason to believe that these optically active boronates should also be transformable into many other enantiomerically pure derivatives, as indicated in (Scheme 21). Since both en-antiomers of α- pinene are readily available, the process makes it possible to synthesize both enantiomers. In this process, the chiral auxiliary, α-pinene, can also be readily recovered and recycled.

Scheme 21

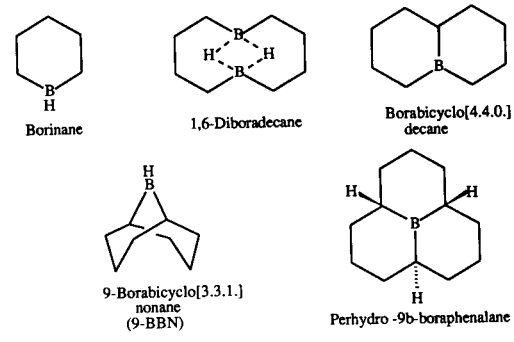


V] Heterocyclic Boracyclanes in the Strained Medium-Ring Range.

Heterocyclic boracyclanes may be defined as those cyclic species which contain at least one boron (hetero) atom in the ring structure. Although a number of boron-containing heterocycles have been known for some time [33], the discovery of hydroboration and the recent developments in organoborane chemistry [2,6,34] have remarkably widened this field (Scheme 22).

Scheme 22

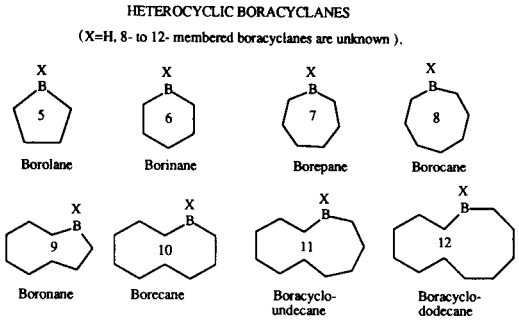
MONOCYCLIC, BICYCLIC AND TRICYCLIC BORACYCLANES



Heterocyclic boracyclanes, from five-membered through twelve-membered rings, are represented in Scheme 23. Only five-, six-, and seven-membered boracyclanes, *i.e.* borolane, borinane and borepane, have been prepared and characterised

in the literature [35]. The existence of boracyclanes, from eight- through twelve-membered rings, is totally unknown (Scheme 23).

Scheme 23

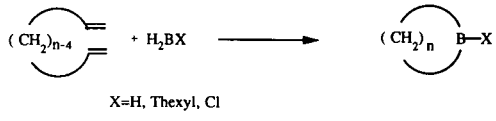


Methods available for the preparation of boracyclanes include cyclic hydroboration of dienes and polyenes [35,36], transmetallation [37], disproportionation [38], displacement reactions [38], substitution [39], and allylboration [40]. However, in cases where cyclic hydroboration is applicable, it is usually the method of choice, since it is simpler and more convenient than the other methods (Scheme 24). These approaches and their limitations have been discussed in detail elsewhere [35]. In the past few years, the cyclic hydroboration of dienes with various hydroborating agents such as diborane [41], thexylborane [42], BH_2Cl [43], and 9-BBN [41,44] has been actively investigated.

a) Hydroboration of Acyclic α,ω-Dienes.

The hydroboration of acyclic α,ω-dienes with suitable reagents under appropriate conditions leads to the formation of boracycloalkanes (Scheme 24).

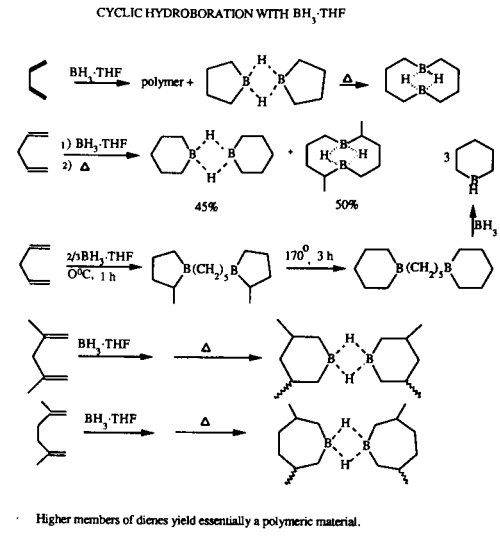
Scheme 24



i) Cyclic Hydroboration with Borane·THF [46].

Among acyclic α,ω-dienes, 1,3-butadiene is unique in that it is a simple conjugated diene. The primary hydroboration product of 1,3-butadiene with borane·THF is mainly polymeric. Thermal treatment converts the polymer into the highly stable 1,6-diboracyclodecane *via* a relatively labile intermediate, bisborolane. The reaction of 1,4-pentadiene with borane·THF followed by pyrrolysis furnishes cyclic dimeric borinane and methyl-substituted 1,6-diboracyclodecane in 45% and 55% yield respectively. However, hydroboration of 1,4-pentadiene with 2/3 BH_3·THF, followed by thermal treatment, produces a dumbell-shaped molecule which upon redistribution with borane furnishes the six-membered boracycle, borinane. Placement of two methyl groups at the two internal olefinic carbons of 1,4-pentadiene and 1,5-hexadiene greatly favors a cyclic course for the hydroboration to achieve the synthesis of boracyclanes. In these cases, the hydroboration product (a linear polymer) undergoes redistribution on standing to provide improved conversion to the desired methyl-substituted 6- and 7-membered boracycles [41] (Scheme 25).

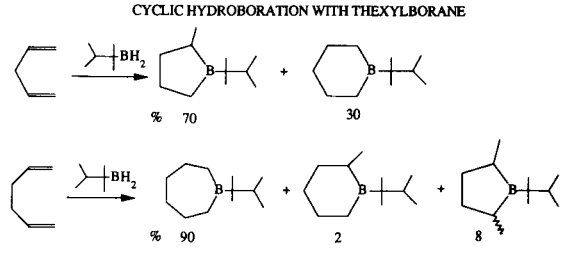
Scheme 25



ii) Cyclic Hydroboration with Thexylborane ($ThxBH_2$) [42].

The formation of boracycles is more efficient when thexylborane is used for the hydroboration of α,ω-dienes. Even in the case of 1,3-butadiene, 100% B-thexylborolane is formed. The results obtained in the hydroboration of 1,4-pentadiene with thexylborane indicate a strong kinetic preference for the formation of the five-membered ring over the corresponding six-membered ring. However, in the case of 1,5-hexadiene, it is the formation of the seven-membered ring that is strongly favored [46] (Scheme 26).

Scheme 26

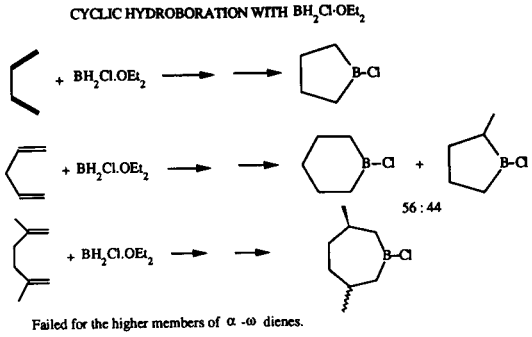


iii) Cyclic Hydroboration with Monochloroborane-Etherate ($BH_2Cl{\cdot}OEt_2$).

Application of monochloroborane-etherate ($BH_2Cl{\cdot}OEt_2$) in the cyclic hydroboration of α,ω-dienes appears to offer considerable advantage for the synthesis of organoborane heterocycles [43]. The initial hydroboration product in the case of 1,4-pentadiene and 1,5-hexadiene is partially polymeric and largely polymeric in case of higher dienes. Careful distillation of the polymeric material affords B-chloroboracyclanes in excellent yields. A great advantage is that no extensive isomerization was observed during depolymerisation of the products derived from C_5-C_7 olefins. Pure B-chloroborolane, B-chloroborinane and B-chloroborepane have been prepared following this method. An eight-membered ring boracyclane,

B-chloroborocane was prepared for the first time by the haloboration-depolymerization of 1,6-heptadiene. However, the products from the higher members of dienes and $BH_2Cl{:}OEt_2$ failed to undergo clean depolymerization into the desired boracyclanes [43] (Scheme 27).

Scheme 27



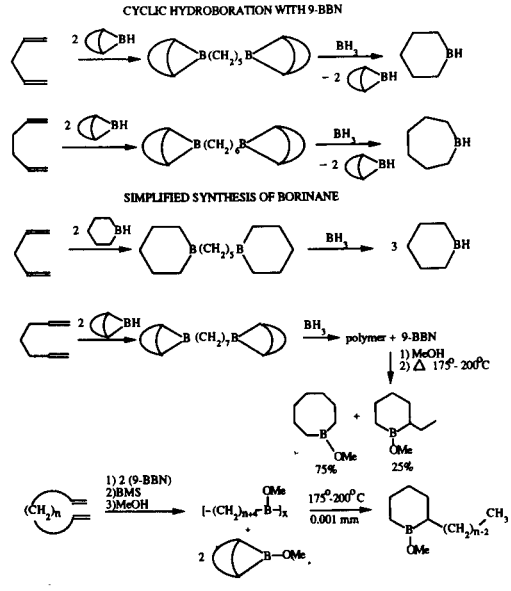
iv) Cyclic Hydroboration with 9-BBN [44].

Two major difficulties are encountered in the synthesis of pure boracyclanes *via* the cyclic hydroboration of unsubstituted acyclic dienes. Attack of borane on the first double-bond of a nonconjugated diene places the boron preferentially at C_1 of the chain. But reaction of the borane moiety with the remaining double bond appears to prefer the internal position, forming 2-methyl boracyclane moieties. Moreover, polymers are formed. Thermal depolymerization is frequently accompanied by isomerization, resulting in poor yields of the desired boracyclanes. This difficulty was circumvented by applying 9-BBN to the cyclic hydroboration of α,ω-dienes. Cyclic hydroboration of 1,4-pentadiene and 1,5-hexadiene with two equivalents of 9-BBN furnishes the corresponding dumbell-shaped molecule which upon redistribution with borane cleanly furnishes borinane and borepane in excellent yields. The hydroborating agent, *i.e.* 9-BBN, is readily recovered in this procedure. However, the cyclic hydroboration of 1,6-heptadiene with 9-BBN under identical conditions furnishes a dumbell-shaped molecule which upon redistribution with borane followed by depolymerisation, provides a product. Methanolysis of this product furnishes B-methoxyborocane in 75% yield, accompanied by 25% of the undesired by-product, 2-alkylsubstituted B-methoxyborinane. This procedure fails to achieve the synthesis of medium-ring boracycles in the case of the higher α,ω-dienes. These α,ω-dienes, upon cyclic hydroboration, followed by depolymerization, (with accompanying isomerization) essentially provide 2-alkyl substituted borinane derivatives [44] (Scheme 28).

Later, an excellent simplified procedure was developed for the preparation of borinane from 1,4-pentadiene, avoiding the need to separate 9-BBN from the desired product. 1,4-Pentadiene is cleanly hydroborated with two equivalents of borinane to furnish a dumbell-shaped molecule, which, upon redistribution with borane (BMS), furnished cleanly three equivalents of borinane. Since borinane also exhibits high regioselectivity in hydroboration, no other isomeric products are formed. By this method, two moles of borinane are converted into three (Scheme 28).

Cyclic hydroboration works well only for the synthesis of 5-,6- and 7-membered boracyclanes. However, in only two cases, (using $BH_2Cl{\cdot}OEt_2$ and 9-BBN) the formation of an

Scheme 28



eight-membered boracyclane in impure form have been achieved [43,44]. Thus far, cyclic hydroboration of α,ω-dienes has failed to achieve the synthesis of boracyclanes with more than eight-ring members. During attempts to achieve the cyclic hydroboration of higher members of α,ω-dienes, the dominant reaction is the formation of a non-cyclic, three-dimensional polymer, containing predominantly linear moieties, with very little if any cyclic moieties. Thermal depolymerization of these polymers proceed with isomerization to furnish isomeric boracycles containing one or two alkyl groups in the 2,2'-positions. Efforts to synthesize boracycles in the strained medium ring range, $HB(CH_2)_{n-1}$ (n = 9-12) *via* cyclic hydroboration procedures had all failed.

This long string of failures in the cyclic hydroboration of α,ω-dienes to synthesize medium ring systems containing a boron atom as one of the ring members implies that the strains in these medium ring boracyclanes are too large for the relatively labile boron-carbon bonds [45]. Because of the considerable success we had achieved in applying the Matteson homologation procedure [46] for lengthening the chain of optically active derivatives [47], we decided to explore this procedure as a means of enlarging the size of the ring in B-methoxyboracyclanes, thereby avoiding undesired ring opening and polymerisation. We were particularly interested in the possible synthesis of boracyclanes in the medium-ring range (9- to 12-membered), *via* the sequential one-carbon homologation procedure, since their existance is totally unknown. Not only would this provide the unknown boracyclanes in the medium-ring range, but it would also provide a convenient new route *via* the DCME reaction to the valuable medium-ring ketones and possibly other derivatives.

b) One-Carbon Homologation of B-alkoxyboracyclanes [50].

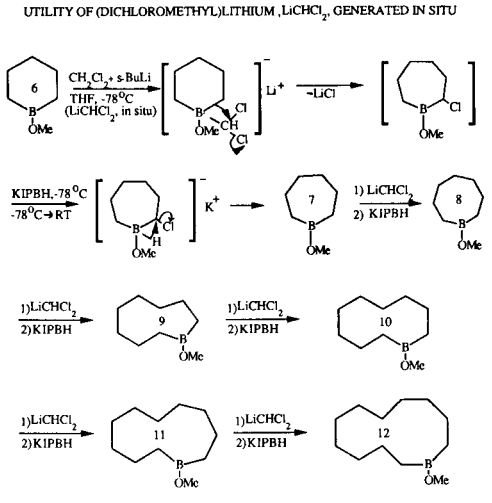
For the sequential one-carbon homologation of B-alkoxyboracyclanes, two procedures were explored: (dichloromethyl)lithium, $LiCHCl_2$, generated *in situ*, followed by potassium triisopropoxyborohydride (KIPBH) reduction of the α-chloro intermediate, and (chloromethyl)lithium, $LiCH_2Cl$,

generated *in situ* [49]. The six-membered boracyclane, B-methoxyborinane, was chosen as the starting boracyclane.

i) Utility of (dichloromethyl)lithium, $LiCHCl_2$, generated *in situ*/KIPBH reduction.

The reaction of (dichloromethyl)lithium, $LiCHCl_2$, generated *in situ* by reacting dichloromethane and *sec*-BuLi in THF at –78°C in the presence of B-methoxyborinane provides the desired α-chloro-B-methoxyborepane cleanly. The *in situ* reduction of α-chloro-B-methoxyborepane with KIPBH at -78°C furnishes the seven-membered boracyclane, borepane, in good yield. It is important to add the KIPBH at -78°C to minimize ionisation of the C-Cl bond leading to the related carbocycle [50]. Repetition of this process with B-methoxyborepane gave the eight-membered derivative, B-methoxyborocane. By continuing this sequential one-carbon homologation procedure, boracyclanes through the 12-membered derivative have been prepared [50] (Scheme 29).

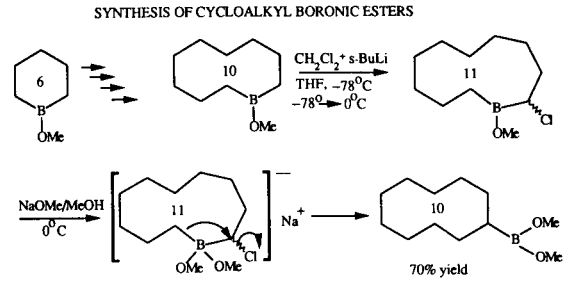
Scheme 29



This homologation sequence essentially proceeds *via* the formation of an ate-complex, which, upon warming to room-temperature, undergoes the migration of a boron-carbon bond with the displacement of chloride to furnish α-chloro-B-methoxyboracyclane. It was observed that some part of this α-chloro-borinate ester undergoes a partial ionisation of a carbon-chlo-rine bond, assisted by the solvent THF, to furnish ~ 25% of cycloalkylboronate ester. Increase in the bulk of the alkoxy group in B-alkoxyboracyclane did not help to prevent this side reaction. However, it could be controlled by adding the KIPBH at -78°C reducing the intermediate α-chloroborinate ester *in situ* and suppressing the ionisation of the C-Cl bond [50].

These observations indicate the possibility of preparing the higher cycloalkylboronic esters from the intermediate α-chloro-B-methoxyboracyclane by a slight modification of the present procedure. Indeed, treatment of the intermediate α-chloro-B-methoxyboracycloundecane (obtained *via* the one-carbon homologation of B-methoxyborecane with $LiCHCl_2$) with an equivalent of NaOMe in methanol at 0°C facilitated ionisation of the carbon-chlorine bond to furnish the cyclodecylboronate ester in 70% yield [50] (Scheme 30). This procedure provided various cycloalkylboronic acids, otherwise difficult to prepare *via* hydroboration, in good yield. The importance of such boronic acids/esters for both general and asymmetric synthesis is well recognized [51].

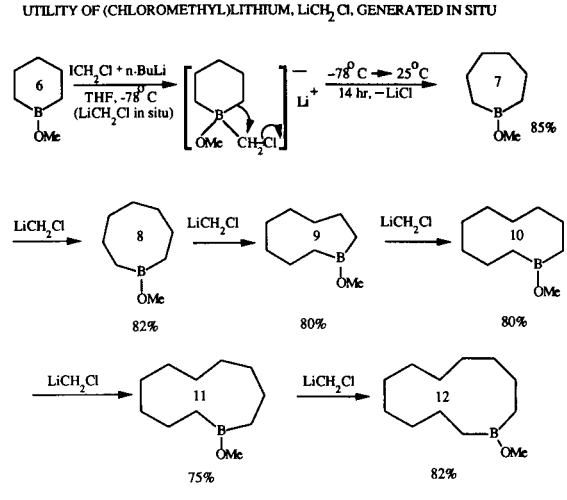
Scheme 30



ii) Utility of (Chloromethyl)lithium, $LiCH_2Cl$, Generated *In Situ*.

One-carbon homologation of B-methoxyborinane with (chloromethyl)lithium, $LiCH_2Cl$, generated in situ by reacting either ICH_2Cl or $BrCH_2Cl$ and n-BuLi in THF at -78°C in the presence of B-methoxyborinane proceeds smoothly to furnish B-methoxyborepane in excellent yield. By following this sequential one-carbon homologation procedure, boracyclanes through the 12-membered derivative have been prepared in excellent yield [50] (Scheme 31).

Scheme 31

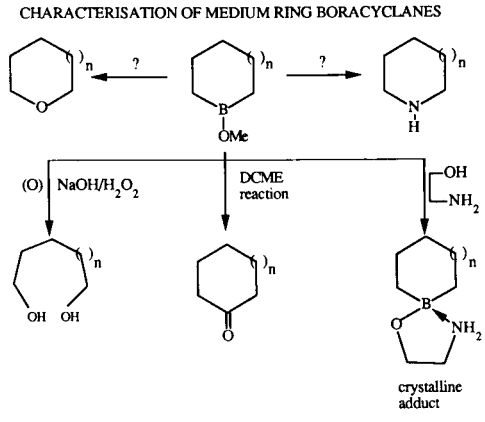


However, the fact that the $LiCH_2Cl$ procedure involves only a single step, as compared to the two steps involved in the $LiCHCl_2$ procedure, persuaded us to adopt this route for the synthesis of medium-ring boracyclanes. In each case the product boracyclane was purified by fractional distillation. The fact that no significant deterioration or isomerization was observed clearly shows the thermal stability of these medium-ring boracyclanes.

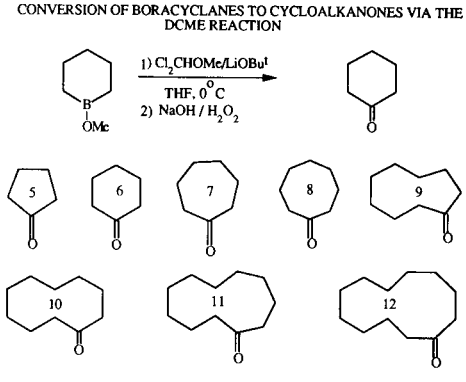
The formation of these medium-ring boracycles was confirmed by converting them to the corresponding diols *via* oxidation using alkaline hydrogen peroxide and analyzing the product diols by GC as their bis(trimethylsilyl)ethers, pre-

pared by treating the product diols with bis(trimethylsilyl)-acetamide, BSA [52]. These boracycles from five- to twelve-membered rings were converted to the corresponding crystalline ethanolamine adducts and characterised by ^{11}B NMR, ^{1}H NMR and mass spectra. These crystalline ethanolamine adducts are a convenient means for storing these medium-ring boracyclanes over a prolonged period of time. These medium-ring boracyclanes could be readily converted into the corresponding medium-ring cycloalkanones *via* the DCME reaction [50] (Scheme 32,33). The ease of preparing these cycloalkanones in the medium-ring range in good yields *via* the DCME reaction under mild conditions indicates the value of these boracyclanes for synthesis [50] (Scheme 33).

Scheme 32



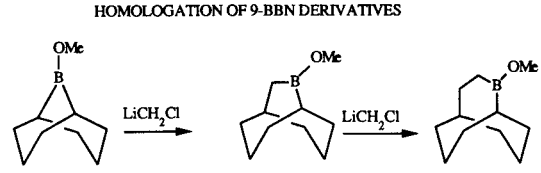
Scheme 33



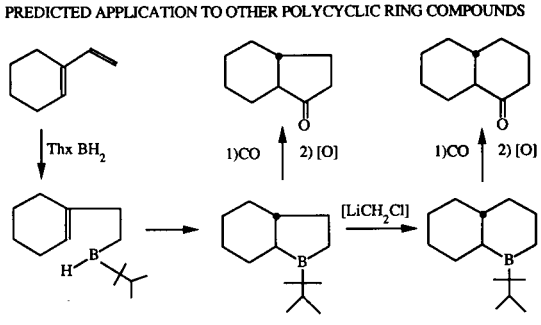
This development has also opened up the possibility of increasing the size of the ring in bi- and polycyclic systems. One-carbon homologation of B-methoxy 9-BBN with (chloromethyl)lithium, $LiCH_2Cl$, generated *in situ* in THF at -78°C afforded cleanly B-methoxyborabicyclo[3.3.2]decane. As anticipated, because of the greater migratory aptitude of the primary over the secondary alkyl group, the second homologation with $LiCH_2Cl$, *in situ* exclusively formed B-methoxyborabicyclo[3.3.3]undecane in good yield (Scheme 34).

Based on these facts, the one-carbon homologation of the trialkylborane derived from the hydroboration of 1-vinyl-1-cyclohexene with thexylborane should furnish a boradecalin derivative. Carbonylation and oxidation of this boradecalin derivative should furnish decalone (Scheme 35).

Scheme 34



Scheme 35



It is evident that considerable progress has been made in developing a simple and convenient method for the synthesis of strained medium-ring boracycles without any contamination of isomeric boracyclanes. This development has revealed a number of fascinating theoretical questions worthy of exploration.

Acknowledgements.

This review summarises research done over a period of years with a group of very able coworkers, whose names appear in the references. We thank them for their efforts. We gratefully acknowledge the financial support for this work from the National Institutes of Health (GM 10937-22) and the National Science Foundation (CHE-87 06102).

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