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Construction of nitrogen bicyclic and cage compounds with the use of allylic organoboranes*

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Abstract: It is shown that reactions of triallylborane with pyrrole, pyridines, isoquinolines, lactams, 1-pyrroline, and acetylenes offer versatile methodology for the construction of various bicyclic and polycyclic nitrogen compounds, some of which are skeletally related to important classes of alkaloids. Optically active 3-borabicyclo[3.3.1]non-6-enes are useful precursors for synthesis of chiral 3-aza- and 3-thiabicyclo[3.3.1]non-6-enes, as well as derived chiral cyclohexenoid systems. The convenient methodology for the transformation of 1-boraadamantanes into 1-azaadamantanes is also discussed.

Keywords: nitrogen bicyclic compounds; nitrogen cage compounds; allylic organoboranes; alkaloid synthesis; chiral cyclohexene derivatives; boraadamantanes; azaadamantanes.

INTRODUCTION

Nitrogen heterocyclic compounds are widely distributed in Nature and play a vital role in the metabolism of all living cells. A vast number of natural and synthetic nitrogen heterocycles are in regular clinical use and have other important practical applications. In this paper, novel approaches to nitrogen bicyclic and cage compounds (Fig. 1) are discussed. These new methods are based on the high reactivity of allylic organoboranes and their unique reactions developed in our team.

The following five general reactions have been applied in a course of this investigation:

- reductive trans-α,α'-diallylation of pyridines, isoquinoline, and pyrrole with allylic boranes [1,2]
- reductive diallylation of lactams with triallylborane [3]
- allylboron-acetylene condensation [4,5]
- allylboration of imines [6,7]
- transformation of 1-boraadamantanes into 1-azaadamantanes [5b,8]

The preparation of alkaloids and related nitrogen compounds through the use of allylboranes has been reviewed in 1999 [9].

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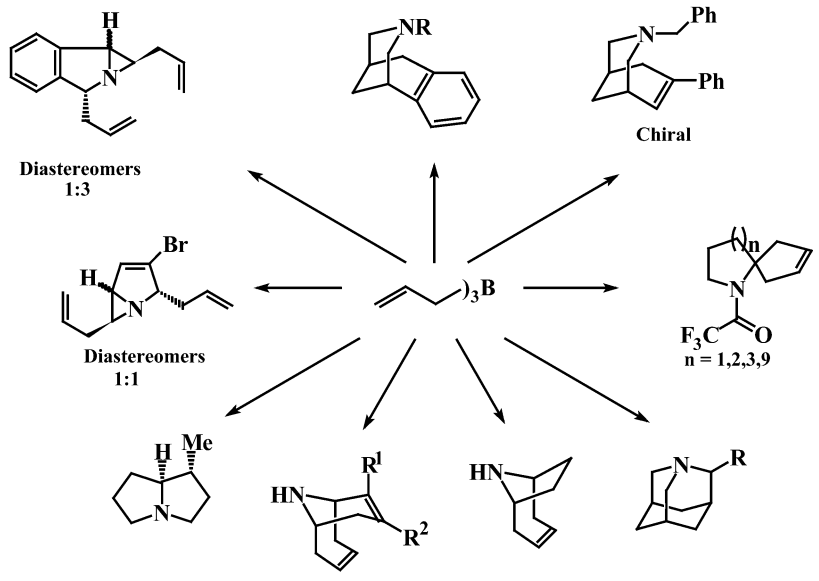


Fig. 1 Novel approaches to nitrogen bicyclic and cage compounds.

SYNTHESIS OF BRIDGED AZABICYCLO[4.n.1]ALKENES AND AZIRIDINE DERIVATIVES

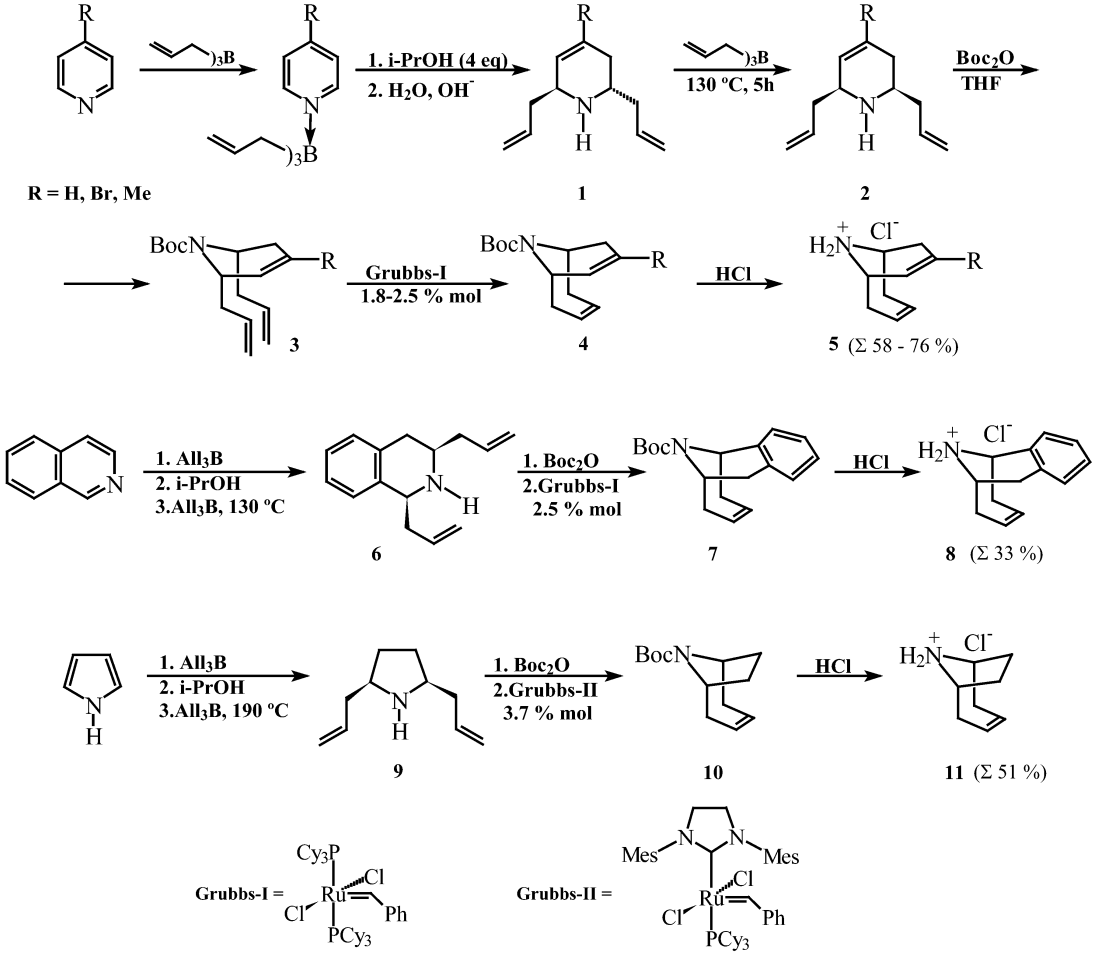
We have previously found that pyridines [1,2,10], isoquinolines [2a,11], and pyrrole [2a,12] undergo reductive *trans*-α,α'-diallylation on treatment with allylic boranes (triallyl-, trimethallyl-, tricrotyl-, or allyl(dipropyl)borane) and alcohol (1:1:4) to give the corresponding *trans*-α,α'-diallylated nitrogen heterocycles (e.g., **1**) in 70–97 % yields. These general reactions proceed stereoselectively under mild conditions (20–90 °C); two novel carbon–carbon bonds are formed in the process. It was also discovered that *trans*-2,6-diallyl-Δ^3-piperideines (*trans*-2,6-diallyl-1,2,3,6-tetrahydropyridines) **1** are transformed into the *cis*-isomers **2** on heating with triallylborane at 130 °C [1,2]. Similar isomerization of *trans*-2,5-diallylpyrrolidine proceeds at 185–190 °C to furnish a mixture of *cis*/*trans*-isomers (1:2.5-3) [2b,12], which was used for further transformations without separation. Solid *cis*-1,3-diallyl-1,2,3,4-tetrahydroisoquinoline **6** (m.p. 61 °C) was isolated by crystallization of a 1:1 mixture of *cis*/*trans*-isomers.

Martin [13] and Kibayashi [14] have recently demonstrated that *N*-acyl and *N*-Boc derivatives of *cis*-2,6-dialkenylpiperidines exist in a chair conformation with diaxial disposition of the alkenyl groups to avoid unfavorable $A^{1,3}$ strain between the carbonyl oxygen and substituents α to nitrogen. This unique property of piperidine compounds has been used for the creation of convenient methodology for the preparation of bicyclic nitrogen compounds through ring-closing metathesis (RCM). We reasoned that the same would apply to *N*-acylated *cis*-α,α'-diallylated heterocycles **2**, **6**, and **9**, and that they could also be utilized as precursors for construction of certain bridged azabicycles via RCM. In the presence of the 1st-generation Grubbs catalyst (Grubbs-I, 1.8–2.5 mol %), *N*-Boc-protected *cis*-2,6-diallyl-1,2,3,6-tetrahydropyridines **3** undergo facile and efficient RCM to give the corresponding nitrogen heterocycles **4** in nearly quantitative yields. The cyclizations were carried out in CH_2Cl_2 under reflux (4–6 h); the substrate concentration was as high as 0.26 M. We did not observe the formation of any side products during RCM. Insignificant impurities of *trans*-isomers (2–4 %) remained unchanged and were separated from the product by flash chromatography [15].

Deprotection of the Boc-derivatives **4** with 4 M HCl in dioxane at 60–70 °C gave rise to the corresponding hydrochlorides **5** (95–97 %). The structure of the parent bicycle **5** (R = H) was supported

by X-ray single-crystal analysis. The six-membered ring of **5** (R = H) has a sofa conformation, while the seven-membered ring exists in a chair conformation.

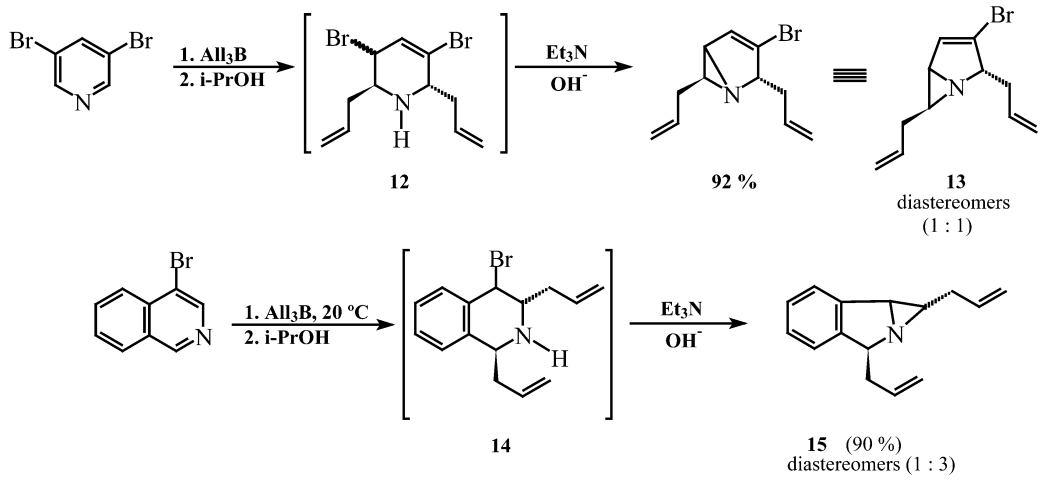
Similar methodology was used for the preparation of 7,8-benzo-10-azabicyclo[4.3.1]dec-3-ene hydrochloride **8** from isoquinoline. The pyrrolidine derivative **9** undergoes RCM only in the presence of the 2nd-generation Grubbs catalyst (Grubbs-II, 3.7 mol %) to give (after deprotection) 9-aza-bicyclo[4.2.1]non-3-ene hydrochloride **11** (Scheme 1) [15]. In both cases, ring closing proceeds in nearly quantitative yields (98–99 %).



Scheme 1

It should be mentioned that Brenneman and Martin [16] and Aggarwal's team [17] in 2004 have applied intramolecular enyne metathesis of *N*-Cbz- and *N*-Boc-protected *cis*-2,5-disubstituted pyrrolidines in asymmetric syntheses of (+)-anatoxin-a and (+)-ferruginine, respectively.

Interesting bicyclic and tricyclic compounds involving the aziridine cycle can be prepared by the reductive diallylation of 3,5-dibromopyridine and 4-bromoisoquinoline with triallylborane (Scheme 2) [11b]. This approach is based on lability of allylic or benzylic bromine in the products **12** and **14**. Their treatment with triethylamine and base give rise to aziridine derivatives **13** (b.p. 75–78 °C/0.5 Torr) and **15** (b.p. 95–96 °C/0.5 Torr).



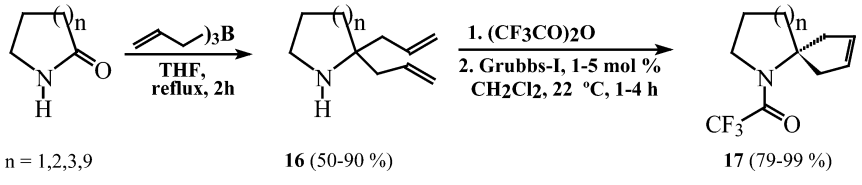
Scheme 2

SYNTHESIS OF 6-AZASPIRO[4.n]ALK-2-ENES

Many natural and biologically active compounds such as pinnaic acid, halichlorine, cephalotaxine, harringtonines [18,19], and others [20] contain azaspirocyclic frameworks. Consequently, the development of the convenient routes for the selective construction of the spiro fragments represents an important task.

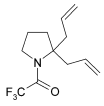
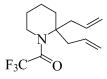
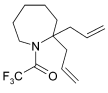
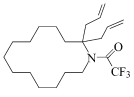
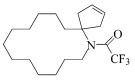
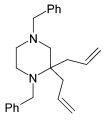
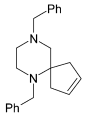
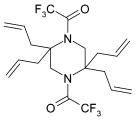
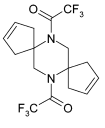
We have recently found that compounds **17** are available in high yields via RCM of N-acylated 2,2-diallylated nitrogen heterocycles **16** [21] which are readily obtained by the reductive allylation of lactams containing a N–H bond with triallyl- or trimethallylboranes [22] (see Scheme 3 and Table 1).

Various protecting groups such as benzyl, acetyl, benzoyl, trifluoroacetyl, and Boc were tested. In the cases of acyl derivatives, 1 mol % of Grubbs-I catalyst was sufficient for full conversion to the corresponding metathesis products within 4 h, while metathesis of benzyl protected compounds required 4–5 mol % of the catalyst to achieve good conversation (94 % after 2 h). The trifluoroacetyl group was chosen as protecting group in most cases because of the higher volatility of derivatives, facilitating the gas chromatography (GC) analysis of the reaction mixtures.



Scheme 3

Table 1 Synthesis of nitrogen-containing azaspiro[4.n]alkenes[a].

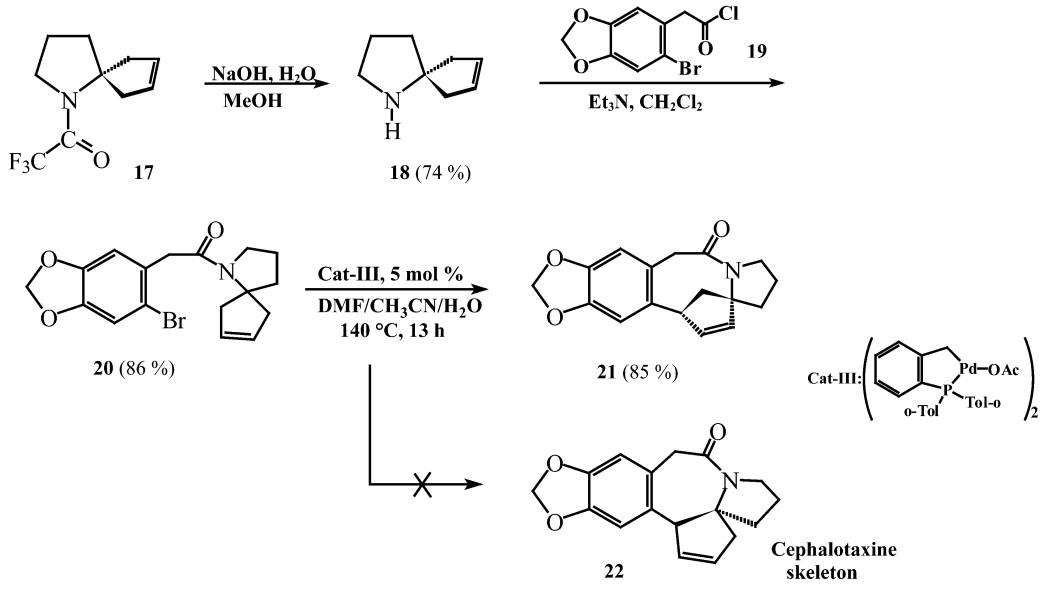
Substrate	Catalyst Grubbs-I mol %	Time h	Conversion[b] %	Product	Yield[c] %
	1	1 (4)	91 (100)		91
	1	2	97		98
Boc = $^{t}BuO_2C$					
	5	2	97		-
	1	4	97		98
	5	1	98		-
	1	1	100		95
	1	1	100		99
	1	4	30		-
	4	1	95		58
	2	2	100		89

[a]Conditions: indicated amount of catalyst, 22 °C, CH_2Cl_2, conc. of catalyst 5 mM, 4 h.
[b]Conversion determined by GC analysis of samples from the reaction mixture.
[c]Isolated yields after silica gel chromatography.

Pyrrolidine, piperidine, azepane, azacyclotridecane, and piperazine derivatives were isolated in nearly quantitative yields (Table 1). The structure of the dispiro-piperazine derivative was confirmed by X-ray analysis [21]. In this compound, the piperazine ring exists in a shallow twist-boat conformation to release strain in the dispiro system, while the cyclopentene rings are in a very shallow envelope-like orientation.

Free amine **18** was prepared in 74 % yield by treatment of **17** (n = 1) with base in methanol (Scheme 4). Further acylation of 6-azaspiro[4.4]non-6-ene **18** with **19** [18b] followed by cyclization of

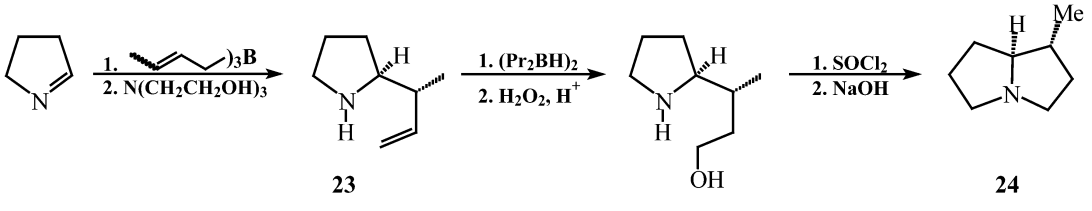
amide **20** in the presence of palladium catalyst-III (Heck reaction) gave rise to the pentacyclic compound **21**, the structure of which was confirmed crystallographically [23]. It is clear that the isomer of **20**, having a different location of the double bond, would be amenable to construction of the cephalotaxine skeleton **22** via Heck cyclization.



Scheme 4

(±)-PSEUDOHELIOTRIDANE

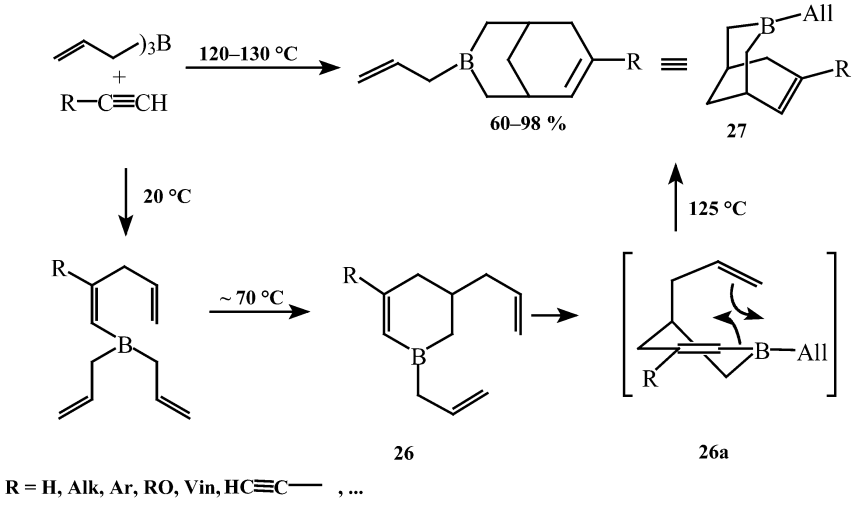
1,2-Allylboration of imines occurs with rearrangement to give the corresponding homoallyl amines [6]. Reaction of tricrotylborane (*E*:*Z* = 7:3) with 1-pyrroline was found to proceed stereoselectively to produce 2-(1-methylallyl)pyrrolidine **23** (Scheme 5). The latter was transformed into a pyrrolizidine alkaloid pseudoheliotridane **24** by a hydroboration-oxidation-cyclization sequence [7]. Oxidation was carried out in acidic media.



Scheme 5

ALLYLBORON-ACETYLENE CONDENSATION

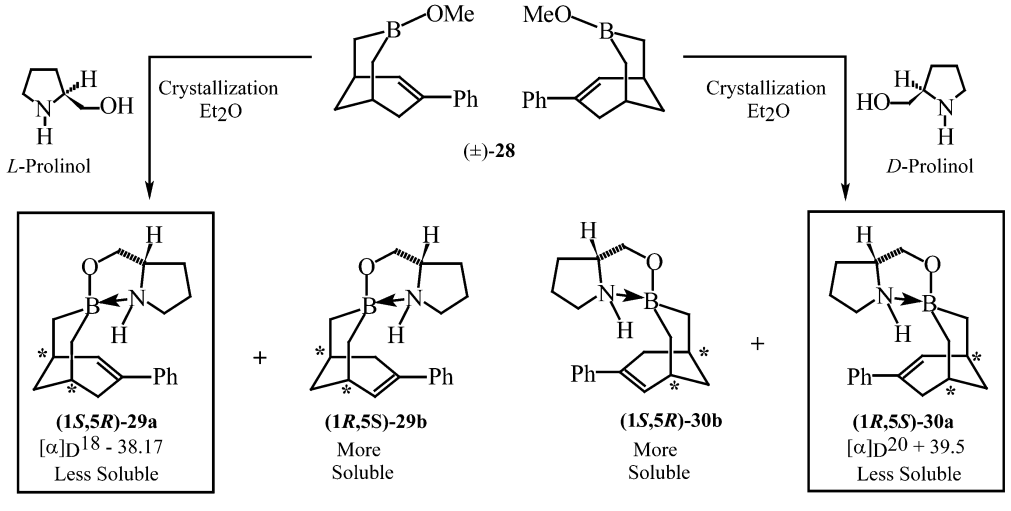
The thermal reaction of triallyl- or trimethallylborane (130–140 °C) with terminal acetylenes RC≡CH (allylboron-acetylene condensation), proceeding regio- and stereoselectively, presents a general approach to the corresponding 7-R-3-borabicyclo[3.3.1]non-6-enes **27** in 70–97 % yields (Scheme 6) [4,5]. The condensation was found to proceed in three stages: (1) *cis*-allylboration of the acetylene triple bond, (2) intramolecular allylboration of the terminal double bond, and (3) intramolecular *vinylbora-*



Scheme 6

tion of the terminal double bond in **26** (**26a**). The bicyclic boron compounds **27** have been used as starting materials for the preparation of various cyclohexane, 1-bora-, and 1-azaadamantane derivatives [5].

Racemic 3-methoxy-7-phenyl-3-borabicyclo[3.3.1]non-6-ene **28**, prepared by interaction of triallylborane and phenylacetylene at 130 °C, followed by treatment with methanol presents a 1:1 mixture of two enantiomers which differ only in location of the double bond (Scheme 7). For their resolution, we tested D-valinol, D-phenylalaninol, D- (98 % ee), and L-prolinol (99 % ee) and found prolinols to be chiral auxiliaries of choice [24].



Scheme 7

The reaction of the racemate **28** with L-prolinol led to the mixture of diastereomers (1*S*,5*R*)-**29a** and (1*R*,5*S*)-**29b**. Two successive crystallizations from diethyl ether resulted in the less soluble diastereomer (1*S*,5*R*)-**29a** with 96 % de. An absolute configuration of 3-borabicyclo[3.3.1]non-6-ene moiety in this compound was established by X-ray diffraction analysis on the base of the comparison

with known stereo structure of L-prolinol as a chiral ligand (Fig. 2). The conformation of boron cycle in **29a** is "distorted chair", while cyclohexene ring has "distorted sofa" conformation.

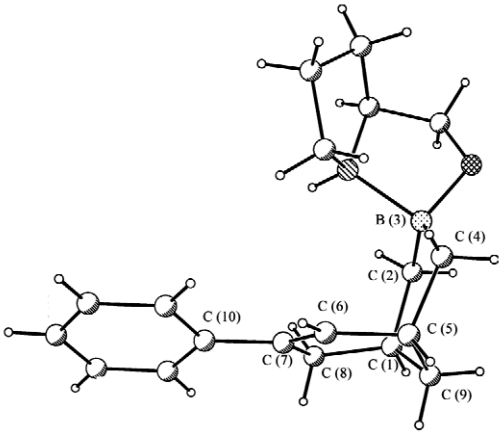
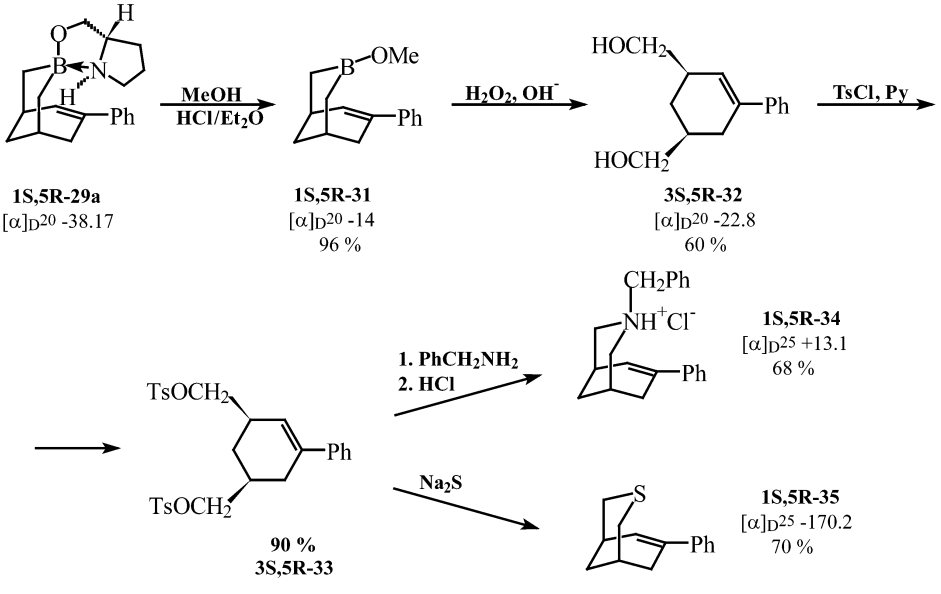


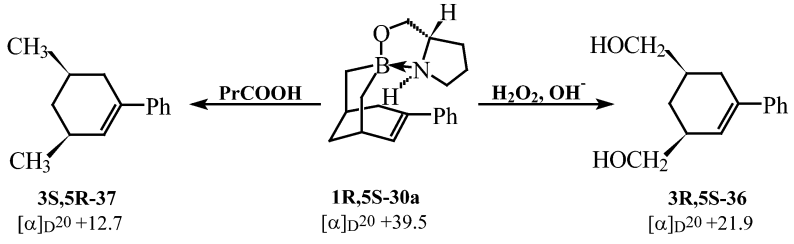
Fig. 2 X-ray crystal structure of the (1*S*,5*R*)-diastereomer **29a**.

Treatment of the (1*S*,5*R*)-diastereomer **29a** with methanol and HCl in diethyl ether gave rise to (1*S*,5*R*)-3-methoxy-7-phenyl-3-borabicyclo[3.3.1]non-6-ene **31** ($[\alpha]_D^{20}$ –14, MeOH) (Scheme 8). Oxidation of the latter with hydrogen peroxide furnished (3*S*,5*R*)-3,5-dihydroxymethyl-1-phenylcyclohex-1-ene **32** ($[\alpha]_D^{20}$ –22.8, MeOH) in 60 % yield, while (3*S*,5*R*)-(*Z*)-3,5-dimethyl-1-phenylcyclohex-1-ene ($[\alpha]_D^{20}$ –9.52, hexene) was prepared in 78 % yield by the protolytic deboronation with butyric acid under reflux. From bis-tosylate **33**, chiral 3-benzyl-7-phenyl-3-azabicyclo[3.3.1]non-6-ene hydrochloride **34** and 7-phenyl-3-thiabicyclo[3.3.1]non-6-ene **35** were obtained by standard procedures.



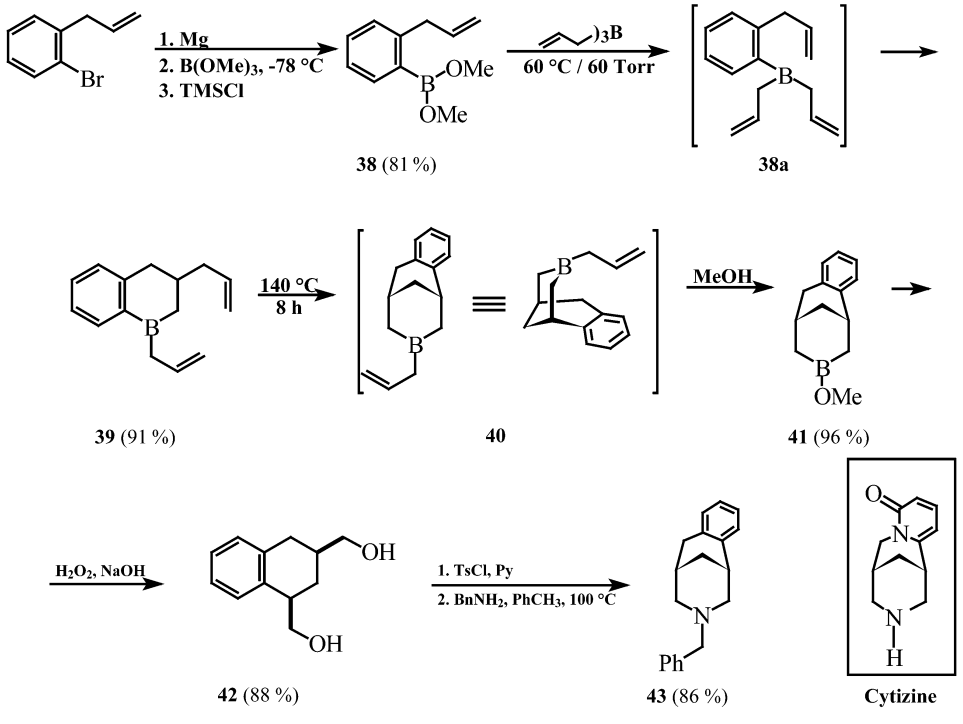
Scheme 8

A similar methodology was utilized for preparation of the (1*R*,5*S*)-diasteromer **30a** ($[\alpha]_D^{20}$ + 39.5, MeOH) using D-prolinol (Scheme 7) as a chiral auxiliary. Further oxidation of **30a** afforded optically active diol **36**, while (3*R*,5*S*)-3,5-dimethyl-1-phenylcyclohex-1-ene **37** ($[\alpha]_D^{20}$ 12.7, hexane) was obtained by deboration of **30a** with butyric acid (Scheme 9) [24].



Scheme 9

We have recently developed a novel version of the condensation (Scheme 10) wherein intramolecular *arylboration* of the terminal double bond (in **39**) takes place instead of *vinylboration* (Scheme 6) and thus worked out a convenient approach to 6,7-benzo-3-bora- **41** and 6,7-benzo-3-azabicyclo[3.3.1]nonane **43** [25].

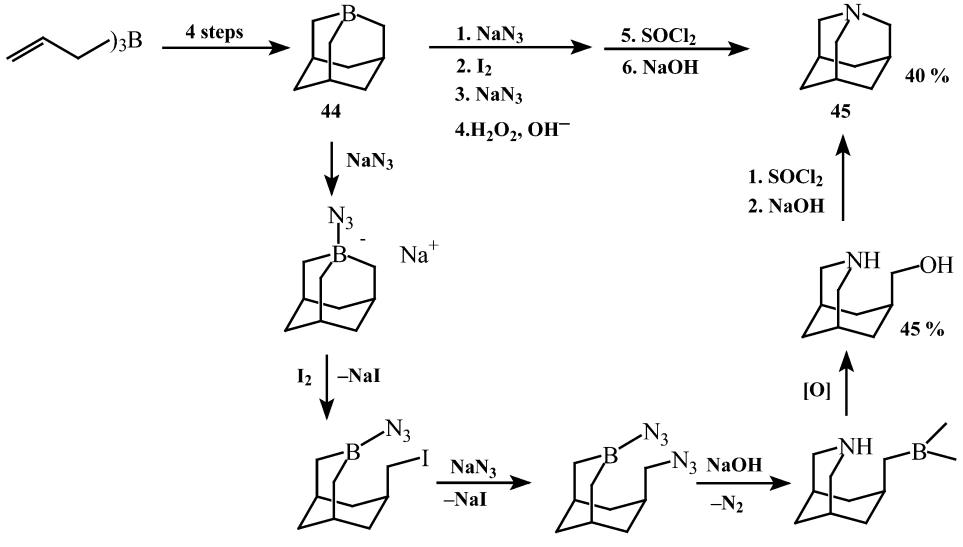


Scheme 10

An unsymmetrical 2-allylphenyl(diallyl)borane **38a** obtained by exchange reaction of dimethyl boronate **38** with triallylborane (1:2) undergoes intramolecular cyclization into **39** (via allylboration of the terminal double bond) under the reaction conditions (60 °C). The latter was transformed to the tricyclic compound **40** by heating at 140 °C for 8 h. Treatment of **40** with methanol gave rise to methyl borinate **41** (96 %), which was oxidized to the *cis*-diol **42**, the structure of which was confirmed by X-ray analysis. The diol **42** was then transformed in two steps into azocine **43** [25], a carbocyclic analog of cytizine.

1-AZAADAMANTANES FROM 1-BORAADAMANTANES

1-Boraadamantane **44** and various alkylated 1-boraadamantanes are available in four steps from triallylborane or trimethallylborane (a key step involve the hydroboration of the appropriate 7-substituted 3-methoxy-3-borabicyclo[3.3.1]non-6-enes) [5]. We worked out a convenient procedure for the conversion of 1-boraadamantanes into 1-azaadamantanes (e.g., **45**) consisting in the successive treatment with sodium azide, iodine, hydrogen peroxide, thionyl chloride, and base. The conversion is carried out as two-pot synthesis (Scheme 11) [26a,b].



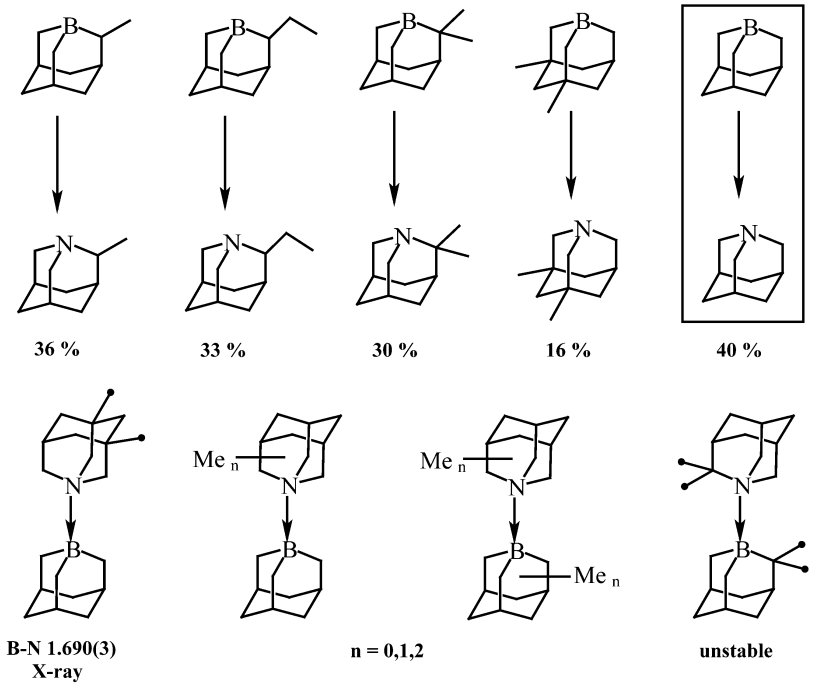
Scheme 11

From five 1-azaadamantanes and five 1-boraadamantanes, we have obtained many possible combinations of their complexes [26c].

Both (*S*)-(+)- and (*R*)-(–)-2-methyl-1-boraadamantanes were recently isolated by crystallization of the corresponding (*S*)-(–)- and (*R*)-(+)-phenylethylamine adducts from hexane, and transformed into optically active 1-hydroxy-2-methyladamantane by the carbonylation-oxidation sequence [27].

General methods for preparation of allylic boranes have recently been reviewed [28].

In conclusion, allylboranes present a useful class of reagents for the construction and modification of various types of nitrogen bicyclic and cage compounds.



Scheme 12

ACKNOWLEDGMENTS

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