Bull Soc Chim Fr (1995) 132, 1003-1008

Review

Useful synthetic transformations *via* organoboranes. I. Amination reactions

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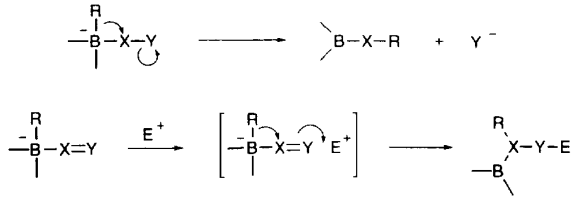
(received 20 June 1995, accepted 5 September 1995)

Summary – Simple and convenient procedures have been developed to prepare primary RNH_2 and secondary amines $RNHR'$ from organoboranes RBXY. These reactions proceed with complete retention of configuration for *R* and have found valuable applications in the syntheses of amines of high enantiomeric purity. Intramolecular additions of azides to organoboranes also open attractive routes to nitrogen heterocycles.

primary amine / secondary amine / organoborane / chloramine / azide / enantiomerically pure compound / polyamine / heterocycle

Since the pioneering studies of Brown *et al*, the role of organoboron compounds in organic synthesis has continued to grow at a spectacular rate. The hydroboration reaction remains the most frequent route to these interesting and versatile intermediates, and several complementary approaches now allow access to a still larger variety of structures [1].

Tricoordinate organoboranes may be strong Lewis acids due to the presence of an empty *p* orbital on the boron atom. They react easily with nucleophiles to form organoborates which, in most cases, do not undergo any further spontaneous reaction. However, the presence of a leaving group in a position α to the boron or the creation of an electron-deficient center induces an intramolecular 1,2-transfer with complete retention of the configuration at the migrating group and, when the adjacent atom is a sp^3 carbon atom, with clean inversion at this center (scheme 1).



R migration with retention of stereochemistry.

Scheme 1

These rearrangements dominate most of the ionic reactivity of organoboranes. These transformations are more useful synthetically in the chiral series since the replacement of the boron with other elements occurs in a stereospecific manner. Thus, amination of organoboranes represents an attractive, but in our opinion undervalued, route to primary and secondary amines, two particularly important classes of organic compounds with numerous synthetic applications and biological properties. The present review is aimed at presenting more prominent results in this field.

Synthesis of primary amines

The replacement of a boron atom by an amino group was first reported 30 years ago by Brown *et al* [2]. Organoboranes, prepared by hydroboration of alkenes, reacted with chloramine to afford the corresponding primary alkylamines (scheme 2).

$$\text{alkene} \xrightarrow{BH_3} R_3B \quad \text{or} \quad R_2BH \xrightarrow[NaOH]{NH_2Cl} RNH_2$$

Scheme 2

This reaction proceeded with complete retention of configuration, very likely *via* an ionic 1,2-migration which constituted a supplementary example of the general mechanism described in scheme 1. The transfer of one of the three alkyl groups was followed by a second similar reaction of the dialkylborinic derivative R_2BOH produced. No further evolution was observed, probably because of the low electrophilicity of $RB(OH)_2$ which made the essential prior coordination with chloramine difficult (scheme 3) [3].

Maximum yields were therefore limited to 66% for R_3B and 50% for R_2BH. The *in situ* generation

* Correspondence and reprints

$$R_3B + NH_2Cl \rightleftarrows [R_3\overset{-}{B}\text{–}\overset{+}{N}H_2Cl] \overset{OH^-}{\rightleftharpoons} [R_3\overset{-}{B}\text{–}NHCl]$$

$$\rightarrow R_2B\text{–}NHR + Cl^- \xrightarrow{\text{hydrolysis}} RNH_2 + R_2BOH$$

$$R_2BOH \xrightarrow{NH_2Cl} RNH_2 + RB(OH)_2$$

Scheme 3

of chloramine from sodium hypochlorite and ammonium hydroxide [4], the use of hydroxylamine-*O*-sulfonic acid [3, 5, 6] or *O*-mesitylenesulfonylhydroxylamine [7] slightly improved the results. Finally, the best solution was found by using organodimethylboranes, readily accessible from alkenes and dimethylborane [4, 8]. The methyl group has a low migratory aptitude and the small amount of methylamine produced was easily eliminated under the experimental conditions (scheme 4).

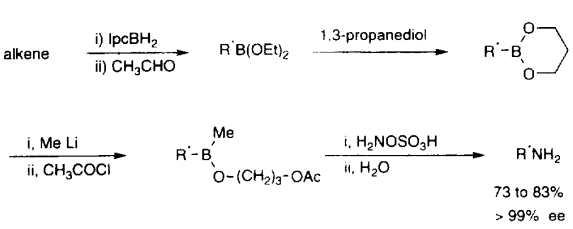
$$\text{alkene} \xrightarrow[\text{TMSCl}]{LiMe_2BH_2} RBMe_2 \xrightarrow[\text{ii) hydrolysis}]{\text{i) } H_2NOSO_3H} RNH_2$$

73 to 95%

Scheme 4

Isomerically pure ^{13}N- and ^{15}N-labelled primary amines have been synthesized from the corresponding organodimethylboranes [9] or triorganoboranes [10] and labelled chloramine. Tritiated methylborane was used to prepare [2-^{3}H]-*trans*-2-phenylcyclopentylamine from 1-phenylcyclopentene [11].

The synthesis of primary amines of very high enantiomeric purities has been achieved from a diisopinocampheylalkylborane [12] or from the corresponding boronic ester, which was prepared by asymmetric hydroboration of prochiral olefins (scheme 5) [13, 14].

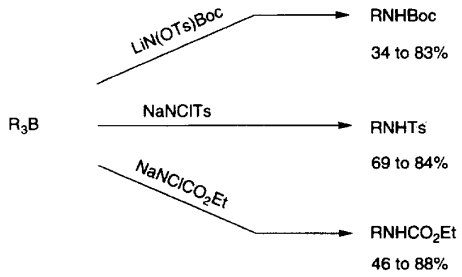


Scheme 5

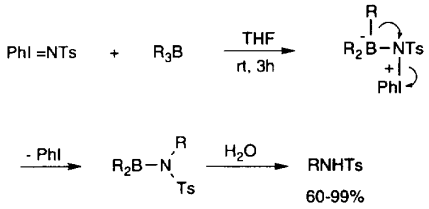
Trialkylboranes also reacted rapidly at low temperature with lithium or potassium *t*-butyl-*N*-tosyloxycarbamate to give the corresponding *N*-Boc protected primary amines [15]. In a similar way, *N*-alkylcarbamates and *N*-substituted sulfonamides were obtained respectively from *N*-chloro-*N*-sodiocarbamates [16] or chloramine-T: $MeC_6H_4SO_2NCl^-, Na^+$ (scheme 6) [17].

Interestingly, *N*-(*p*-toluenesulfonyl) protected primary amines were prepared by reaction of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane, a hypervalent iodonium ylide, with trialkylboranes (scheme 7) [18].

Hydrazoic acid, HN_3, generated either from sodium azide and an aqueous acid [19] or from trimethylsilyl



Scheme 6



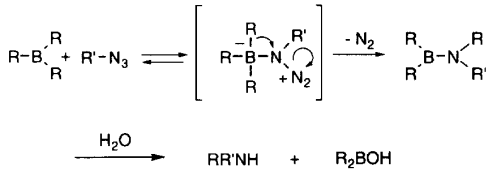
Scheme 7

azide and methanol [20], reacts with trialkylboranes to give primary amines in good to excellent yields (43–87%). The mechanism of these reactions is described in the next section.

Synthesis of secondary amines

From azides

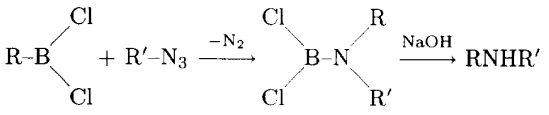
Triorganoboranes react in boiling xylene with azides with evolution of nitrogen and formation of dialkylaminodiorganoboranes. Such an intermediate readily undergoes solvolysis to the corresponding secondary amine and a borinic acid derivative [21]. Only one of the three alkyl groups is utilized (scheme 8).



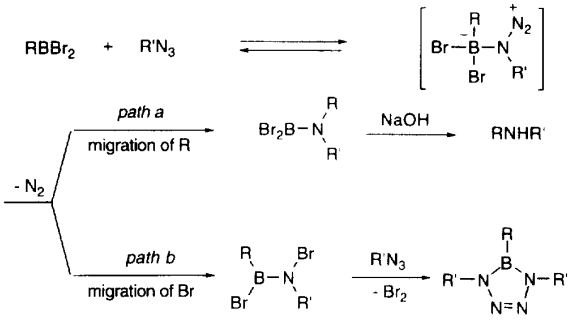
Scheme 8

A remarkable enhancement of reactivity was observed with the more electrophilic diorganochloroboranes [22]. However, organodichloroboranes, which can be easily prepared by hydroboration of alkenes [23, 24] or by treatment of organo-bis(dialkylamino)-boranes with dry HCl [25], proved to be better since they required milder conditions and no alkyl group was lost (scheme 9).

When dibromoboranes were used, competitive migrations of the alkyl group and bromine occurred which led to the simultaneous formation of the expected secondary amine and a tetraazaboroline (scheme 10) [26].

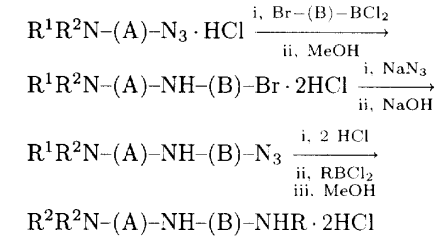


Scheme 9



Scheme 10

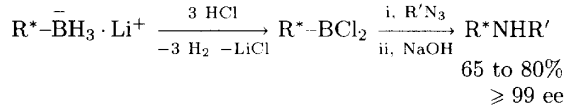
This secondary amine synthesis is highly efficient in terms of chemoselectivity [27], yields and has found valuable applications in the preparation of diamines [28, 29], ω-alkylaminoboronic esters [30] and in Diels–Alder-amination tandem reactions [31]. A convenient general new route to open-chain polyamines, which play major roles in cellular differentiative and proliferative processes, has also been developed using the reductive alkylation of aliphatic aminoazides by (ω-halogenoalkyl)dichloroboranes as a key step (scheme 11) [32].



(A), (B) = diversely substituted alkyl chains

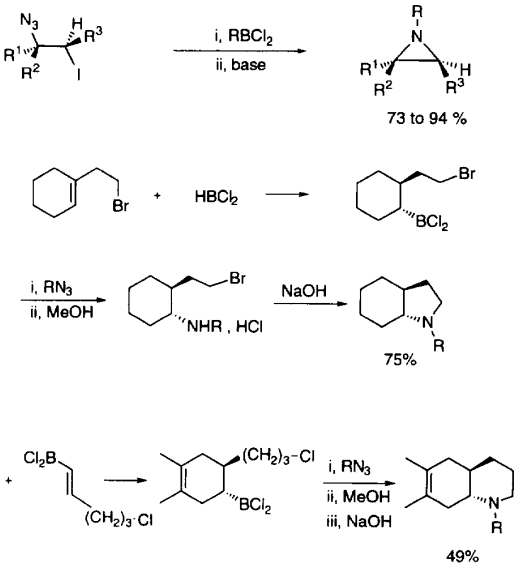
Scheme 11

These reactions proceed with retention of configuration at the migrating carbon. Consequently, it is now possible to synthesize secondary amines with high enantiomeric purity using α-chiral organodichloroboranes generated from the corresponding lithium monoalkylborohydride (scheme 12) [33].



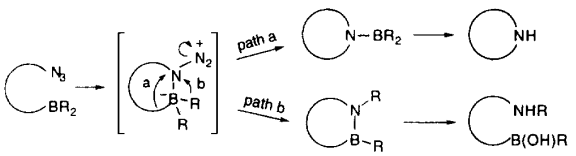
Scheme 12

With a halogen atom in the appropriate position, the ring closure of intermediate ω-halogenoalkylamines can be effected by treating with base. Aziridines [34] and bicyclic pyrrolidines and piperidines were efficiently prepared by this route (scheme 13) [35].



Scheme 13

The intramolecular version of this secondary amine synthesis turns out to be a general stereoselective route to nitrogen heterocycles. The successful execution of this approach requires there to be a selective migration of the ω-aminoalkyl chain (path a) *versus* the R substituent (path b). This has been achieved by using halogen [36] or cyclohexyl [37] as non-migrating groups (scheme 14).

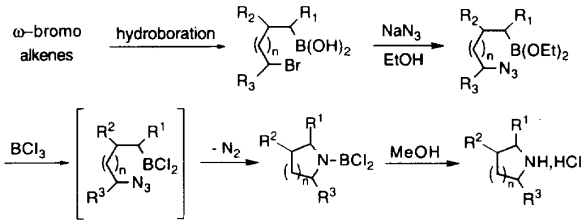


Scheme 14

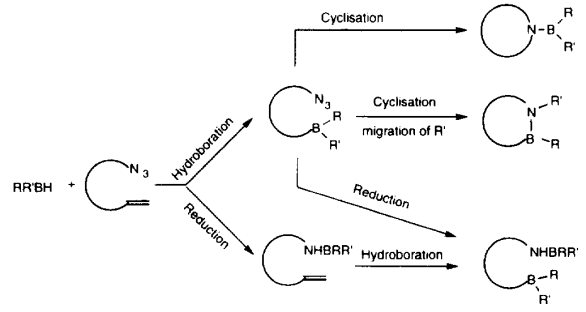
The treatment of ω-azidoalkylboronates with boron trichloride generated the corresponding chloroboranes which spontaneously cyclized to afford pyrrolidines and piperidines. Azetidine was obtained in a rather low yield, while attempts to prepare a seven-membered ring failed [38]. A stereoselective synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines has been achieved similarly (scheme 15) [39].

Another attractive route involves the application of a hydroboration–cycloalkylation sequence. Such an approach can lead to several competitive reactions [37, 38] (scheme 16). To be successful the alkene hydroboration must precede the reaction of the borane and the azide and a selective migration must occur.

An elegant preparation of a proline derivative exploiting successively the stereoselective bromoacetate

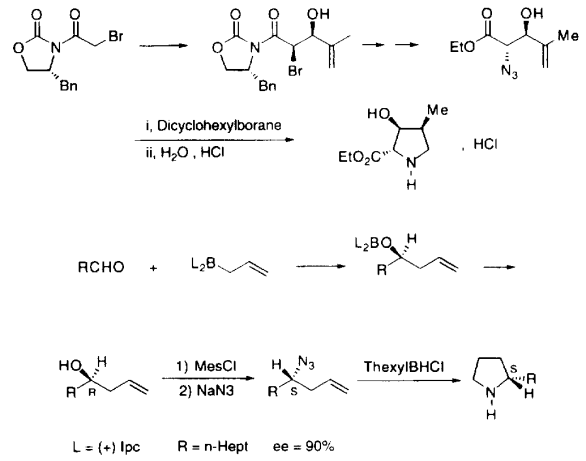


Scheme 15



Scheme 16

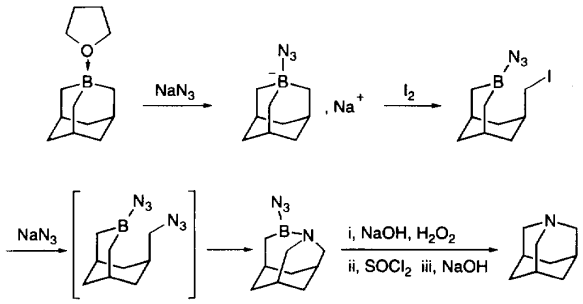
aldol reaction and the asymmetric induction in the hydroboration step was recently described [37]. Another synthesis using this intramolecular cycloalkylation was performed to prepare chiral non-racemic 2-substituted pyrrolidines. The starting homoallylic alcools was obtained from aldehydes and allyboranes (scheme 17) [40].



Scheme 17

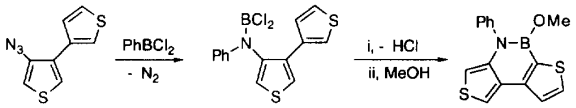
This method has also been applied to a novel and convenient synthesis of 1-azaadamantane from 1-boraadamantane-tetrahydrofuran complex [41]. As above, the key step is a 1,2-rearrangement which proceeds with elimination of nitrogen and migration of an organic moiety from boron to nitrogen (scheme 18).

The reactions betweeen α,β-unsaturated *ortho*-thienylazides and phenylboron dichloride afforded 1,2-dihydro-1-phenyl-2-chlorothieno[*b*]-, or thieno[*c*]-[1,2]azaborines in very good yields *via* the cyclization



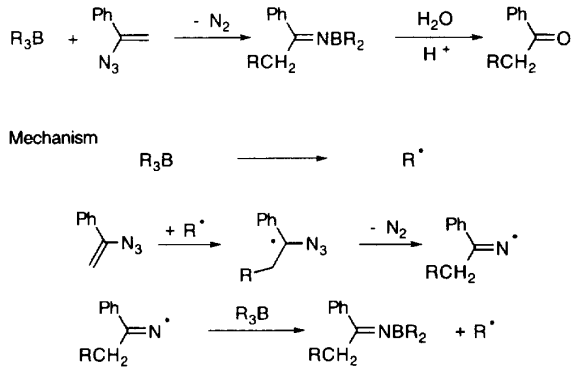
Scheme 18

of the intermediate *N*-dichloroborylamine (scheme 19) [42, 43]. Similar additions to 2-azidobiphenyl compounds led to carbazole or *N*-phenyl-[1,1'-biphenyl]-2-amine depending on the borane chosen [43, 44].



Scheme 19

Finally, we should note the synthesis of alkylaryl ketones from vinylic azides and trialkylboranes [45, 46]. To the best of our knowledge, this is the only example where a free radical mechanism involving intermediate α-azidoalkyl and iminyl radicals appears more likely than the usual ionic pathway (scheme 20).



Scheme 20

From chloroalkylamines

N-Chloroalkylamines react with triorganoboranes to give a wide variety of secondary amines. This set of reactions complements the azide method. These reactions presumably proceed *via* the usual anionotropic migration of an alkyl group from boron to nitrogen (see *Synthesis of primary amines*, above) (scheme 21) [47, 48].

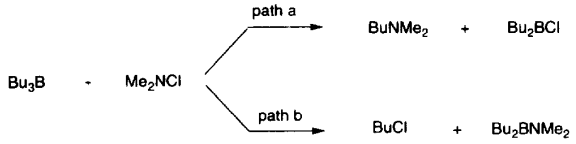
As regards chloramine, dimethylalkylboranes have been used to prevent the loss of two alkyl residues [49, 50]. These reactions tolerate functionality in

$$R_3B + R'NHCl \longrightarrow RNHR'$$

48 to 83%

Scheme 21

the organoborane, but the yields dramatically decrease in the presence of the sterically demanding *N*-chloroalkylamine. These results are consistent with a difficult formation of the intermediate complex. Thus, trialkylboranes showed a dichotomy in their behavior in reactions with *N*-chlorodialkylamines (scheme 22) [51, 52].



Scheme 22

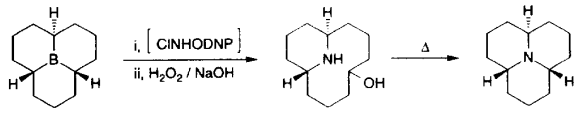
Concurrent polar (path a) and free radical (path b) processes occur in approximatively equal rates. The ionic reaction has been described previously and the homolytic reaction, which can be inhibited by a trace of galvinoxyl, involves the propagation steps shown in the following scheme (scheme 23).

$$Bu_3B + Me_2N^{\bullet} \longrightarrow Bu_2BNMe_2 + Bu^{\bullet}$$

$$Bu^{\bullet} + ClNMe_2 \longrightarrow BuCl + Me_2N^{\bullet}$$

Scheme 23

The transfer of two alkyl groups of an organoborane was accomplished with an appropriate reagent carrying two leaving groups on the nitrogen atom. *N*-Chloro-*O*-2,4-dinitrophenylhydroxylamine was prepared *in situ* and reacted with perhydroboraphenalene to afford 13-azabicyclo[7.3.1]tridecan-5-ol, which was then converted to perhydroazaphenalene (scheme 24) [53].



DNP = 2,4-dinitrophenyl

Scheme 24

To the best of our knowledge, this is the first and only reported example of such a reaction. Nitrogen trichloride, another candidate for the amination of organoboranes, only led the corresponding alkyl chlorides [54].

In summarizing, we wish to emphasize the usefulness of the amination reaction of organoborane in organic synthesis. Further developments in this area related, for example, to biologically active natural products, should be reported in the near future.

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