Pure & Appl. Chem., Vol. 66, No. 2, pp. 235–244, 1994.
Printed in Great Britain.

Reductive mono- and *trans*-α, α'-diallylation of aromatic nitrogen heterocycles by allylboranes

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Abstract Reductive *trans*-α,α'-diallylation of pyridines, 4,4'-dipyridyl, pyrrole and isoquinoline as well as reductive monoallylation of pyrrole, indole, quinolines, isoquinoline and phenanthridine by allylic boranes were discovered. A convenient method for *trans*- → *cis*-isomerization of *trans*-2,6-diallyl-Δ^3-piperideines and *trans*-2,5-diallylpyrrolidine was found.

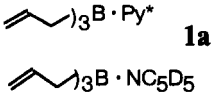
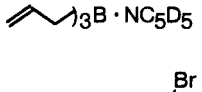
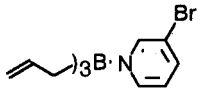
Last two decades have seen dramatic development in synthetic application of β,γ-unsaturated (allylic) boron compounds [1,2]. One of the most important types of allylborane reactions is the additions to organic compounds with multiple bonds (C=O, C=S, C=N, C≡N, C=C, C≡C). Such allylboration reactions proceed regio- and stereoselectively ($2\pi+2\pi+2\sigma$ processes) and, with a proper choice of reagents, enantioselectively [1,2]. Deboration of the boron-containing adducts results in homoallylic alcohols, thiols, amines, 1,4-dienes, 1,4-enynes, etc.

As a part of our program on the use of organoboranes in synthesis [2—4], we have studied the transformations of certain aromatic nitrogen heterocycles under the action of allylic boranes and have found a series of new reactions [5,6], that unite heterocyclic and organoboron chemistries on the novel basis.

1. REDUCTIVE *trans*-DIALLYLATION OF PYRIDINES

Triallylborane reacts readily with pyridine [7a], C_5D_5N and 3-bromopyridine to form the corresponding complexes **1a—c** (Table 1). Adduct **1a** left unchanged on heating at 160°C for 20 hrs. Its IR-, Raman- [7d] and NMR spectra [7b,c] have been previously described.

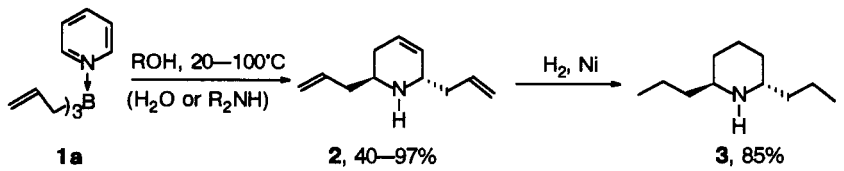
Table 1. Triallylborane complexes

Complex	b.p., °C (torr)	n_D^{20}	$\delta^{11}B$
 **1a**	102 (1)	1.4535	0
 **1b**	103—104 (1)	1.5409	—0.60
 **1c**	106 (1)	1.5643	—0.3

* d_4^{20} 0.932; μ=4.97D [7c]; m.p. 14—15°C.

We have found that pyridine adduct **1a** is easily transformed into *trans*-2,6-diallyl-1,2,5,6-tetrahydropyridine (*trans*-2,6-diallyl-Δ^3-piperideine) **2** in a 40—92% yield on treatment with alcohols, water or Et_2NH at 40—100°C for 2—8 hrs. Admixture of *cis*-isomer (0.5—3%) in **2** thus obtained is easily separated by chromatography on SiO_2. The yield of **2** reaches 97% if **1a** is heated (80—100°C) with *t*-BuOH or *i*-PrOH (4 equ) in the presence of pyridine (1 equ).

Scheme 1



The reaction can be carried out in ether, THF, hydrocarbons, CCl_4, etc., or without any solvent (Table 2).

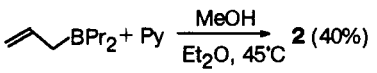
Table 2. Yield of **2** (All_3B:Py:ROH = 1:1:4)

Entry	ROH (4 equ)	Solvent	T, °C	Reaction time (hs)	Yield of **2** (%)
1	MeOH	THF	20	96	57
2	MeOH	ether	40—50	2—6	35—50
3	MeOH	C_6H_6	80	4	43
4	MeOH[a]	ether	45	4	63
5	EtOH	ether	60	3	50
6	EtOH	—	85	4	53
7	EtOH[a]	ether	45	4	60
8	i-PrOH	—	90	8	70
9	i-PrOH[a]	—	100	2	97
10	t-BuOH	—	95	6	85
11	t-BuOH	—	95	8	92
12	$(CH_2OH)_2$	—	90	6	36
13	Et_2NH	—	70	16	23
14	H_2O	THF	40	8	40
15	(-)-Menthol[b]	ether	45	10	66
16	MeOH[c]	ether	45	4	40

[a] Ratio triallylborane:Py:ROH = 1:2:4;
[b] For **2** obtained $[\alpha]_D^{23}$ −7.30° (c = 10.00, CH_2Cl_2);
[c] Allyl(dipropyl)borane was used instead of triallylborane.

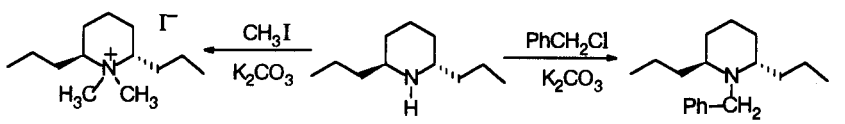
More convenient preparation of **2** consists in one-pot procedure without isolation of complex **1a** as well as **1b** or **1c** (see below). A mixture of triallylborane and pyridine (1:1 or 1:2) is usually heated with 3—4 equivalents of an alcohol. After the reaction is completed, the reaction mixture is stirred with 1.2—1.3 equ. of 10% NaOH, all boron compounds (allylboronic acid and others) being transferred into aqueous layer. The product is extracted by ether or hexane. Another procedure consists in a treatment of a reaction mixture (All_3B, Py, 4 ROH) with mono- or triethanolamine followed by distilling off **2** or its extraction with a hydrocarbon solvent.

Compound **2** is also obtained in 40% yield by interaction of pyridine with allyl(dipropyl)borane in the presence of methanol (4 equ) in ether (45°C, 4 h) (entry 16).



Hydrogenation of **2** in CH_3COOH over Raney nickel (100 at. H_2, 90—100°C, 6 h) leads to *trans*-2,6-dipropylpiperidine **3** (85%).

Scheme 2

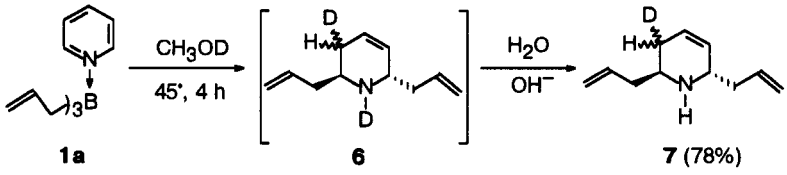


From the latter, N,N-dimethyl (**4**, 70%) and N-benzyl derivatives (**5**, 84%) were obtained by the action of CH_3I [8a] and $PhCH_2Cl$ [8b], correspondingly.

The magnetic equivalence of both methyl groups in salt **4** was shown by NMR spectroscopy. A sharp singlet in ^1H (δ 3.38) and the only signal in ^{13}C (δ 70.08) NMR are observed. In addition, the benzyl methylene protons ($PhCH_2N$) in ^1H NMR spectra of **5** appear as an AB quartet with $\delta_A = 3.60$ and $\delta_B = 3.70$ ($J = 14.04$ Hz) showing their non-equivalence. These data confirm *trans*-stereochemistry of 2,6-dipropyl compound **3** and — consequently — *trans*-configuration of 2,6-diallyl compound **2**. Similar ^1H NMR patterns have been observed in the cases of N,N-dimethylpiperidinium salt [9] and N-benzyl derivative [10] of trans-2,6-dimethylpiperidine.

Reaction of **1a** with CH_3OD followed by deboration with sodium hydroxide solution leads to 5-deuterio-compound **7** (78%).

Scheme 3

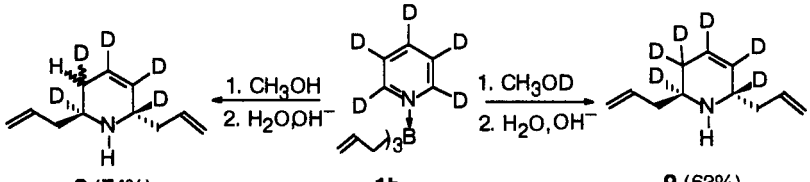


1a **6** **7** (78%)

There is no doubt that the 1,5-dideuterio compound **6** is the primary product of the reaction, which is converted into **7** in the course of work-up (N—D to N—H exchange).

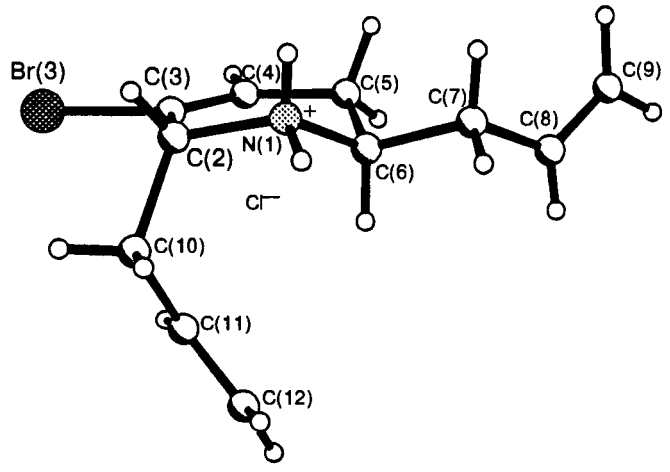
From C_5D_5N and triallylborane, the pentadeuteriated compound **8** (74%) and *trans*-2,6-diallyl-1,2,3,4,5,5-hexadeuterio-1,2,5,6-tetrahydropyridine **9** (63%) were synthesized by heating complex **1b** with methanol (40°C, 4 h) and CH_3OD (70°C, 5 h), correspondingly.

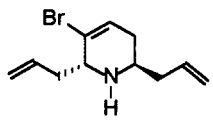
Scheme 4



8 (74%) **1b** **9** (63%)

trans-Diallylation of 3-bromopyridine with triallylborane in the presence of *t*-BuOH (4 equ) also proceeds smoothly (95°C, 5 h) to give the product **10** (83%), in which bromine atom is bound to vinylic carbon atom. The structure of **10** was confirmed by X-ray analysis of its hydrochloride (**10**·HCl) [11] (Fig.1).

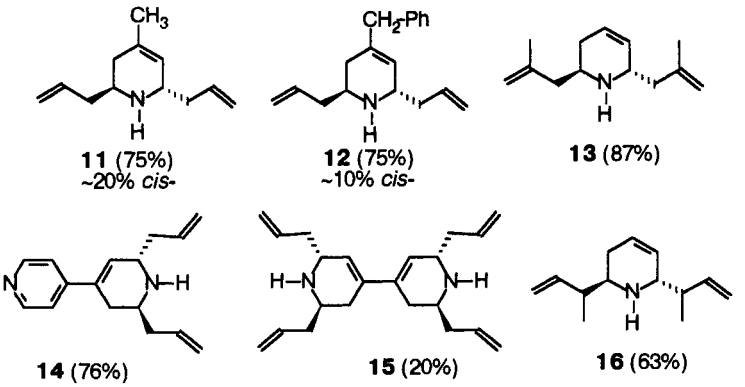




10 (83%)

Figure 1. Crystal structure of **10** · HCl

This methodology was applied for efficient one-pot synthesis of compounds **11**, **12**, **14**, and **15** from 4-methyl-, 4-benzylpyridines and 4,4'-dipyridyl, correspondingly, as well as of **13** using trimethallylborane as the allylborating reagent.



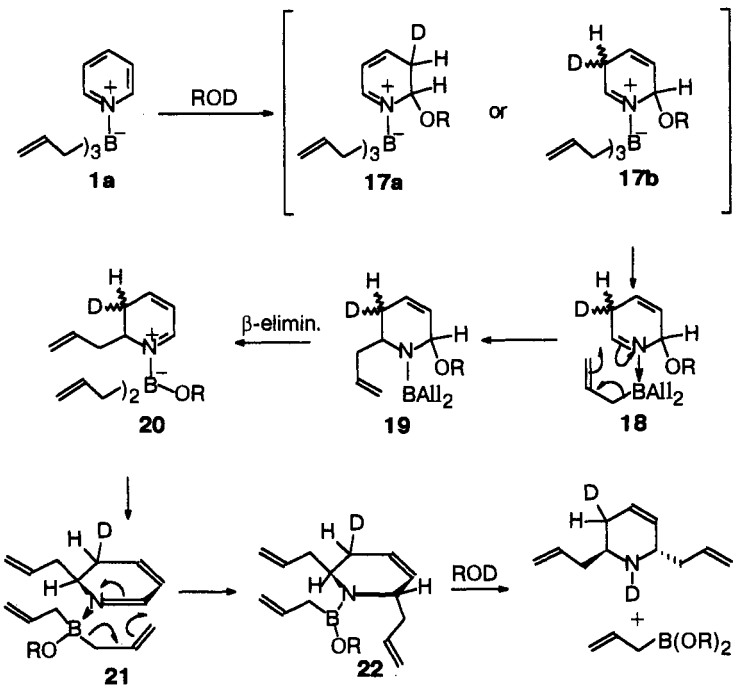
Reaction of tricrotylborane with pyridine under above conditions was found to proceed with rearrangements of the both allylic moieties to give the product with terminal double bonds **16** (63%).

Actually, the presented results demonstrate that reductive *trans*-diallylation of pyridines by allylic boranes is a general reaction leading to very useful products. Two new C—C bonds are created in the process.

What is the mechanism of the reaction?

As soon as complex **1a** is not changed on prolonged heating at 160°C, it is clear that alcohol (water or R_2NH) plays a dramatic role in the course of the process. Reactions of **1a,b** with CH_3OD (Schemes 3 and 4) and of **1b** with CH_3OH (Scheme 4) show definitely that proton (deuterium) from alcohol molecule is incorporated in position 5 of nitrogen heterocycle.

Scheme 5



Nevertheless, the first step of the reaction is very nebulous at best.

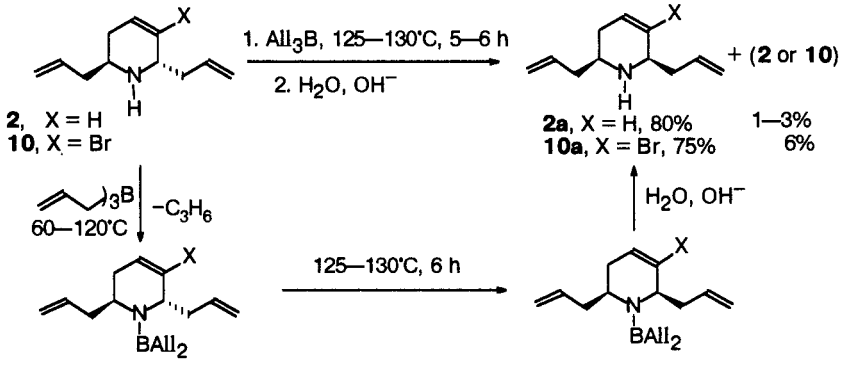
Nitrogen atom in pyridine—triallylborane complexes of type **1** is positively charged and their behavior in some cases should be familiar to that of pyridinium salts. It has been well documented [12—14] that the positive charge in pyridinium ions favors nucleophilic attack at ring carbon atom α to nitrogen atom under mild conditions to give the corresponding adducts. Examples of such nucleophiles are hydroxide, alkoxide, sulfide, cyanide, amine, and some organometallic compounds. Sometimes these adducts can be isolated, but they normally undergo further reactions very rapidly. Typical example is the well-known oxidation of pyridinium salts with hydroxide in the presence of ferricyanide to give 2-pyridones.

A plausible mechanism of our reaction is presented in Scheme 5.

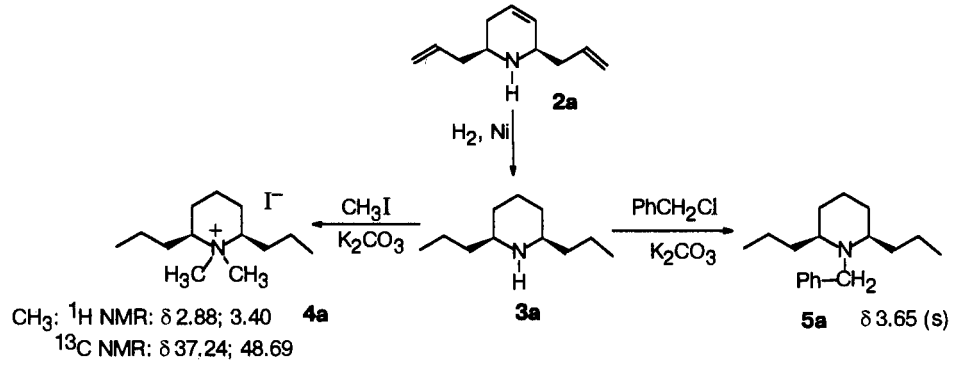
We suggest that the initial stage involves the nucleophilic alkoxide attack at ring C-2 atom to form adduct **17a** or, more likely, **17b** (1,2- or 1,4-addition of ROD to heterocycle, correspondingly). Both **17a** and **17b** contain a localized C=N bond, which immediately undergoes allylboration via six-membered transition state (**12**) to give the compound **19**. The latter is unstable and undergoes β-elimination giving rise to the complex **20**. The next stage, allylboration of the second C=N double bond, proceeds *trans*-stereoselectively with respect to the first allyl group in the ring (**21**) and this step is responsible for *trans*-stereochemistry of the final product. In aminoborane thus formed (**22**), B-N bond is cleaved at once by alcohol used in excess.

2. *trans*-TO *cis*-ISOMERIZATION OF *trans*-2,6-DIALLYL-Δ^3-PIPERIDINES

We have worked out a convenient method for isomerization of *trans*-compounds **2** and **10** into *cis*-isomers **2a** and **10a** which consists in their heating with triallylborane (125—130°C, 5—6 hrs) or with allyl(dipropyl)borane (140—150°C, 5 hrs) followed by deboration of aminoboranes formed.



Minor admixture of **2** and **10** in **2a** and **10a** (1—3% in **2a** and 6% in **10a**) is easily separated by chromatography on SiO_2 (pentane) and isomerically pure **2a** and **10a** were isolated in 80 and 75% yield, correspondingly.



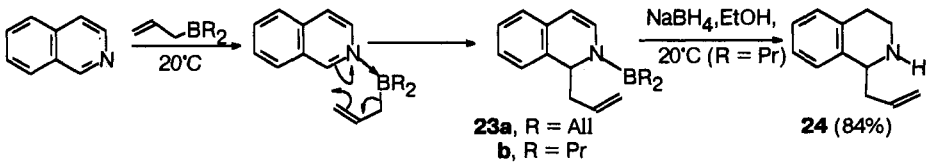
Hydrogenation of **2a** in acetic acid over Ra-Ni (90 atm. H_2, 90°C) lead to *cis*-2,6-dipropylpiperidine **3a** (90%), from which N,N-dimethylpiperidinium salt **4a** and N-benzyl derivative **5a** were obtained.

The magnetic non-equivalence of methyl groups bound to nitrogen atom in **4a** was demonstrated by NMR spectroscopy. Two sharp singlets in ^1H (δ 2.88 and 3.40) and two signals in ^{13}C NMR (at 37.24 and 48.69) were observed. Further evidence for *cis*-stereochemistry of **3a** and **2a** was obtained by ^1H NMR of **5a** in which benzyl methylene hydrogens (CH_2Ph) are enantiotopic and give a sharp singlet at 3.65 ppm. Similar patterns have been observed in the case of N,N-dimethyl [9] and N-benzyl derivatives [10] of *cis*-2,6-dimethylpiperidine.

In conclusion it should be stressed that the use of the only boron reagent, e.g. triallylborane, and the corresponding pyridine allows to synthesize both *trans*- and *cis*-2,6-diallyl-Δ^3-piperideines as well as *trans*- and *cis*-2,6-dipropylpiperidines in an isomerically pure state and in a large scale.

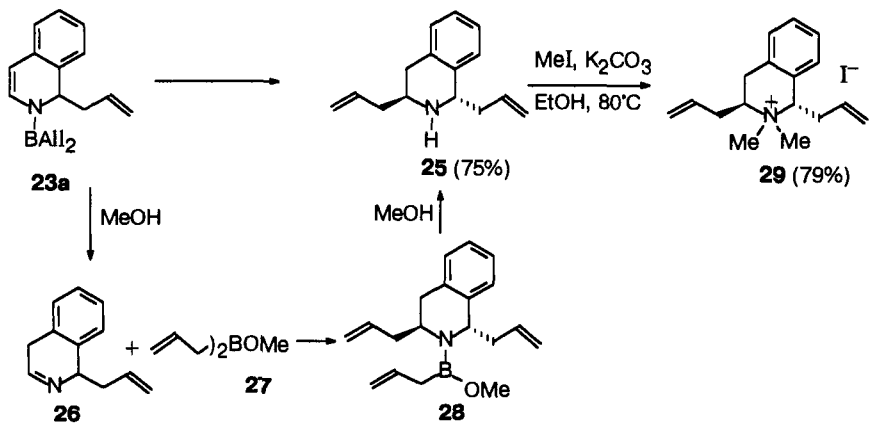
3. REDUCTIVE MONO- AND *trans*-1,3-DIALLYLATION OF ISOQUINOLINE

Reaction of isoquinoline with triallylborane and allyl(dipropyl)borane proceeds under mild conditions (0—20°C) as a «thermal addition» of allyl-boron fragment to N=C-1 bond to give the corresponding aminoborane **23a** ($\delta^{11}B$ 47.4) and **23b** ($\delta^{11}B$ 51.6), further fate of which is determined by the conditions of work-up.



Reduction of **23b** by $NaBH_4$ in ethanol (20°C, 2 h) was found to give an 84% yield of 1-allyl-1,2,3,4-tetrahydroisoquinoline **24**.

On the other hand, treatment of aminoborane **23a** with methanol (3 equ, 20°C, 2 h) lead to *trans*-1,3-diallyl-1,2,3,4-tetrahydroisoquinoline **25** (75%). Possible mechanism of its formation is presented below.



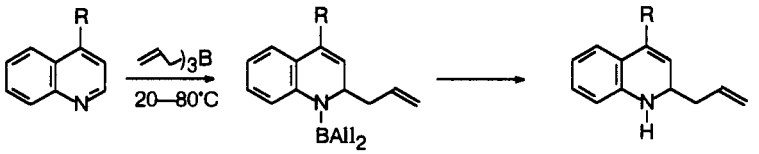
Alcoholysis of **23a** proceeds with migration of double bond (proton is added to C-4 of heterocycle) leading to imine **26** and methoxy(diallyl)borane **27**. The latter allylborates rapidly **26** to give **28** and the second allylic group is added *trans*- to the first one. In aminoborane **28** formed, B—N bond is immediately cleaved by methanol which is used in excess.

Trans-stereochemistry of **3** · HCl was confirmed by X-ray analysis (Yu.T.Struchkov and M.O.Dekaprilevich).

According to [15], AllMgBr reacts with isoquinoline to give 1-allylisoquinoline.

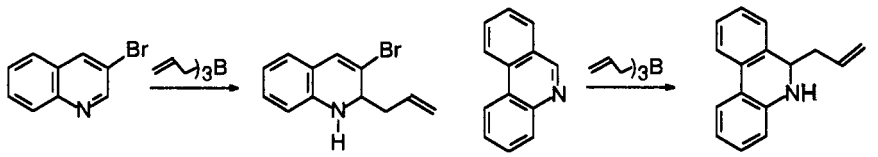
4. REDUCTIVE MONOALLYLATION OF QUINOLINES AND PHENANTHRIDINE

These reactions proceed at room temperature to afford aminoboranes **30** (**30a**, $\delta^{11}B$ 46.2), deboration of which leads to the corresponding α-allylated heterocycles **31a—c** and **32**.



30a, R = H
b, R = Me

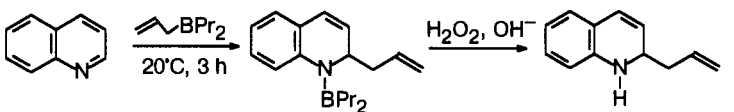
31a, R = H (93%)
b, R = Me (90%)



31c, (85%)

32 (98%)

Two B—C bonds of triallylborane are involved in the reaction with quinoline (ratio 1:2, 20—80°C, 1 h) to produce **31a** in 78% yield after hydrolysis of diaminoborane initially formed. Amine **31a** was also prepared with the use of allyl(dipropyl)borane as an allylborating reagent.



33

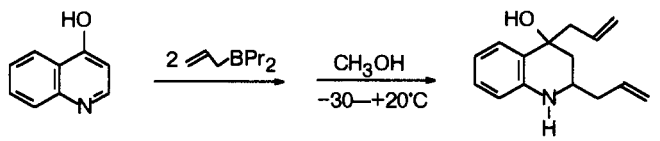
31a (46%)

Aminoborane **33** was isolated in a pure state (b.p. 112°C/1 torr, n_D^{20} 1.5376, $\delta^{11}B$ 56.9).

We have found that monoallylated compounds **31a—c, 32** obtained via allylboration are stable up to 100°C in nitrogen atmosphere and compound **31a** is isomerized to 2-propylquinoline on heating at 170°C for 2 hrs.

2-Allyl-1,2-dihydroquinoline **31a** has been previously synthesized by Eisch and Comfort [16] by interaction of allylmagnesium chloride and quinoline, and **32** has been obtained similarly from phenanthridine by Gilman, Eisch and Soddy [15]. The authors have mentioned that compound **31a** is easily transformed into 2-propylquinoline through interesting hydrogen transfers even on work-up [16], and 5-allyl-5,6-dihydrophenanthridine **32** is extremely air-sensitive [15].

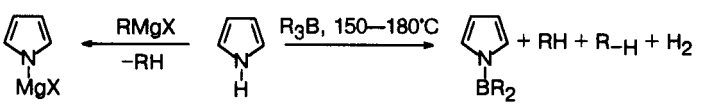
Carbinol **31d** was obtained from the reaction of allyl(dipropyl)borane with 4-hydroxyquinoline (2:1, 20°C) followed by treatment with methanol at −30°C.



31d (40%)

5. REDUCTIVE MONO- AND *trans*-DIALLYLATION OF PYRROLE

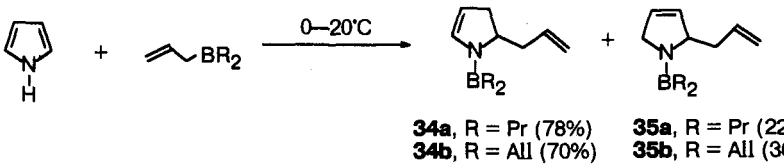
The cleavage of RLi and RMgX with pyrrole (pK_a 17.5) is well known [17]



Köster and Bellut [18,19] have shown that triethyl- and tripropylborane are also cleaved by pyrrole at 150—180°C to afford the corresponding N-dialkylborylpyrrole.

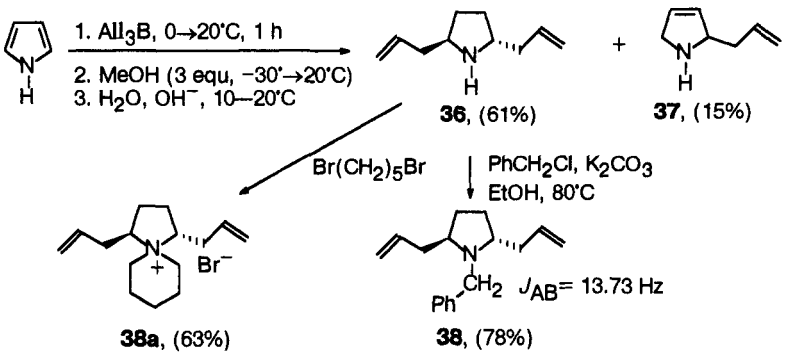
Another story with allylic boranes.

We have found that allyl(dipropyl)- and triallylborane react with pyrrole at 20°C to afford a mixture of addition products **34** and **35**.



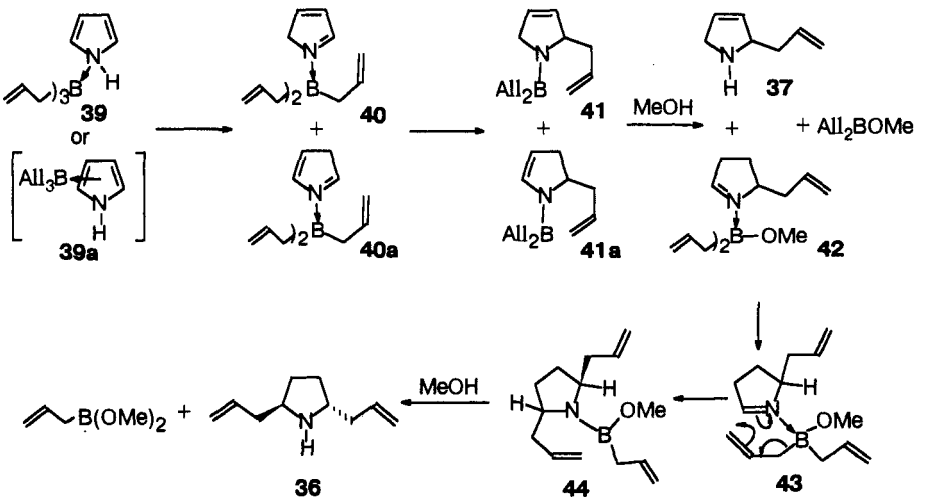
34a, R = Pr (78%) **35a**, R = Pr (22%)
34b, R = All (70%) **35b**, R = All (30%)

Treatment of the products formed from triallylborane (**34b** + **35b**) with methanol (3 equ, −30→20°C, 1 h) followed by NaOH (10—20%) leads to *trans*-2,5-diallylpyrrolidine **36** and 2-allyl-3-pyrroline **37** which were isolated in 61% and 15% yields, correspondingly.



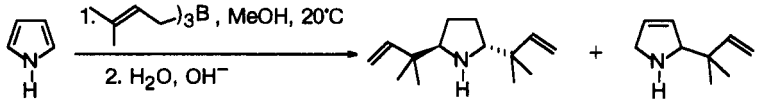
trans-Configuration of **36** was elucidated by the use of prochiral benzyl probe (**38**). As in 1-benzyl-*trans*-2,5-dimethylpyrrolidine [10], the benzyl methylene hydrogens of **38** are diastereotopic and give in the ^1H NMR an AB quartet, centered at 3.94 ppm (J = 13.73 Hz). Spiro compound **38a** was synthesized from **36**.

A possible mechanism of mono- and diallylation of pyrrole is presented below



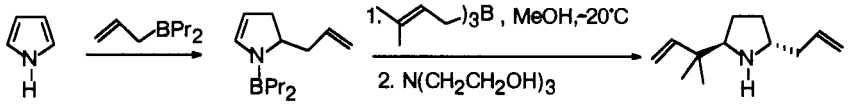
We suggest that N→B complex **39** (or π-complex **39a**) formed initially is isomerized by migration of hydrogen from nitrogen to C-3 and C-2 to give two imine adducts **40** and **40a** which undergo allylboration with the formation of monoallylated aminoboranes **41** and **41a**. Their cleavage by methanol produces the product **37** and the imine complex **42**. The latter is transformed into a new aminoborane **44** via **43** and the second allylboration reaction proceeds also *trans*-stereoselectively. Subsequent alcoholysis of **44** (the cleavage of B—N bond) affords the diallylated product **36** and dimethoxy(allyl)borane.

Both the allylborating stages of reductive *trans*-diallylation of pyrrole proceed with rearrangement. Thus, hindered amine **45** was synthesized from triprenylborane.



45 (65%) 20%

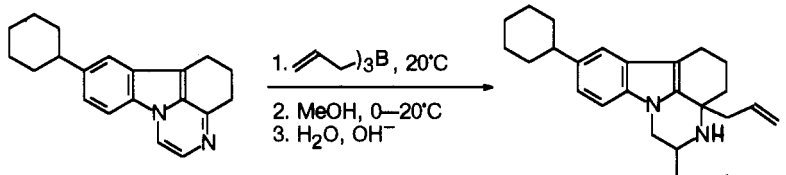
It should be stressed that reaction allows to introduce two different allylic groups into the heterocycle (**46**).



46, (65%)

The mixture of *cis*-2,5-diallylpyrrolidine (75%) and **36** (25%) was obtained by heating of **36** with triallylborane at 160°C for 10 hs.

Appendix. Reaction of compound **47** with triallylborane in $CHCl_3$ (20°C, 1 h) followed by treatment with methanol and base leads to diallylated compound **48**, m.p. 92—94°C.



47 **48** (25%)

Conclusion. The discovered reactions open new pathways and new rich possibilities in heterocyclic chemistry as well as in organoboron chemistry. There is no doubt that the reactions and compounds obtained by reductive mono- and α,α'-diallylation of nitrogen aromatic heterocycles with allylic boranes will find wide application in organic synthesis.

Acknowledgments. I wish to express my deep appreciation to Drs. E.A.Shagova, L.I.Lavrinovich and A.V.Ignatenko (NMR), and also to S.V.Evchenko, E.V.Klimkina and A.Yu.Zykov for the major contribution to this program. I am grateful to drs. M.E.Gursky, I.D.Gridnev and A.V.Geiderikh for stimulating discussions. I also wish to acknowledge the contribution to the preparation of this manuscript by my coworker Alex Geiderikh.

This work is partly supported (1993) by the Russian Fundamental Research Foundation (grant № 93-03-18193).

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