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SYNTHESIS OF SECONDARY CARBINAMINE VIA N-BORYL IMINES GENERATED FROM NITRILES AND ALKYLBORANES

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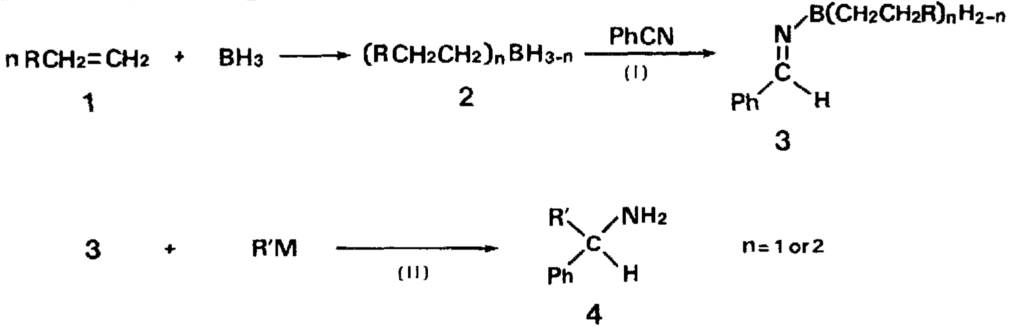
Abstract: The partial reduction of nitriles with several alkylboranes produced an addition product, N-boryl imine, which was readily converted to secondary carbinamine by treatment with organolithium or Grignard reagents. Optically active N-boryl imines were also prepared from chiral borane and nitrile for the chiral amine synthesis.

Masked imine derivatives of ammonia including metalloimines,[1] sulfenimines,[2] and sulfonyl imines[3] have been recently shown to be useful starting material for the synthesis of primary amines and β-lactams. Although N-metallo imines containing silicon, aluminium and tin, have been studied extensively, the corresponding N-boryl imines have found few synthetic applications.[4] We have found that N-boryl imines were easily obtained from the partial reduction of nitriles with alkyl boranes. Here we report that these electrophilic imines undergo clean reactions with organometallic reagents to give secondary carbinamines. Asymmetric induction in alkylation of chirally modified N-boryl imines was also investigated.

Nitriles are known to be reduced with an excess of borane-tetrahydrofuran to give primary carbinamines after acidic hydrolysis.[5] By using 1 equiv of borane-tetrahydrofuran, nitriles are reduced partially to give N-boryl imines which are often difficult to be isolated since the imine itself contains B-H bonds possessing reducing ability. On the other hand, dialkylboranes **2** (n=2) were found to result in partial reduction of nitrile to give N-boryl imine **3** (n=2) which has potential as alternative masked imine derivative of ammonia.

For example, benzonitrile was reduced with the dialkylborane (1 equiv) prepared from borane-tetrahydrofuran and 2 equiv of olefin (**1**) to yield N-dialkylboryl imine (**3**, n=2) quantitatively as monitored by TLC analysis and IR spectra. Typical IR spectra showed the absence of the C=N group and absorption assigned to C=N stretching near 1660 cm^{-1}. ^{1}H NMR spectra of **3** showed the presence of a vinylic proton at around 7.6 ppm. Alkylation of **3** with a variety of alkyl- aryl-lithium or Grignard reagents followed by an aqueous workup yielded the corresponding secondary carbinamines **4** (Scheme 1). Results of the synthesis of secondary carbinamine via N-boryl imine are summarized in Table 1.



Scheme 1

Typical procedure for the preparation of secondary carbinamine from nitrile is as follows: Di(2-norbornyl)borane was prepared from borane and norbornene employing the method reported by Brown.[5] To tetrahydrofuran solution of di(2-norbornyl)borane (1.0 mol/L, 10 mL) was added a tetrahydrofuran (10 mL) solution of benzonitrile (10 mmol) at 20 °C. After the mixture had been stirred for 25 h at 20 °C, TLC analysis showed a single spot corresponding to the N-boryl imine instead of one for the nitrile. To the resulting solution containing N-boryl imine was added a 1.5 mol/L hexane solution (20 mL, 30 mmol) of butyllithium at -80 °C via a dropping funnel. The resulting red solution was stirred for a further 1 h at the same temperature, and then cautiously hydrolyzed with water and 2 mol/L HCl. The organic layer was removed and the aqueous layer was neutralized with NH$_4$OH and extracted with ether (3 x 30 mL). The combined extracts were dried (MgSO$_4$) and concentrated under reduced pressure to give an oil (1.4 g, 86%), identified as 1-phenylpentylamine. The amine obtained by this procedure prior to distillation was 95% pure as indicated by ^{1}H NMR and GLC.

Reaction time (I) required for the N-boryl imine formation depended on the structure of dialkylborane. Alkylation with alkyllithium reagents proceeded very rapidly even at -80 °C. Grignard reagent also yielded amine with relatively higher reaction temperature. Although enolizable silyl imines gave only poor yields of amine in alkylation,[1(c)] the desired amine was obtained with good yield from aliphatic N-boryl imine (Entry 8).

Table 1 Synthesis of Secondary Carbinamine from Nitrile

Entry	Olefin (1)	[Olefin] / $[BH_3]$	Nitrile	R'M	Reaction time (I) h	Reaction time (II)[a] h	Yield of amine **4** %
1	α-Methylstyrene	2	PhCN	BuLi	25	1	86
2		2	PhCN	sBuLi	25	1	54
3		2	PhCN	tBuLi	25	1	62
4		2	PhCN	PhLi	25	5[b]	61
5		2	PhCN	BuMgBr	25	5[c]	50
6	Isobutyl vinyl ether	2	PhCN	BuLi	50	1	80
7		2	o-MePhCN	BuLi	30	1	80
8		2	C_3H_7CN	BuLi	37	1	62
9	2-Methyl-2-butene	2	PhCN	BuLi	10	1	81
10	Norbornene	2	PhCN	BuLi	25	1	86
11	5-Vinyl-2-norbornene	1	PhCN	BuLi	25	1	73
12	α-Methylstyrene	1	PhCN	BuLi	7	1	84
13	Isobutyl vinyl ether	1	PhCN	BuLi	2	1	91
14	2-Methyl-2-butene	1	PhCN	BuLi	2	1	84
15	2,2-Dimethyl-2-butene	1	PhCN	BuLi	3	1	83
16	Norbornene	1	PhCN	BuLi	2	1	92

[a] Reaction at -80 °C. [b] Reaction at -80 - 0°C [c] Reaction at room temperature

Monoalkylboranes (**2**, n=1) were also found to be useful for the preparation of N-boryl imine followed by alkylation (Entries 12-16). Relatively shorter reaction time (I) (2 h to 7 h) was needed for the formation of N-monoalkylboryl imines. N-Monoalkylboryl imines contains disubstituted B-H which has almost no activity for the reduction of the imine. Alkylation of these imines gave secondary carbinamines in satisfactory isolated yields.

Several optically active alkylboranes have been known as chiral hydroboration reagent. These boranes could be used for the asymmetric synthesis of secondary carbinamines using the method described above. Indeed, as shown in Table 2, alkylation of the chiral boryl imine prepared from diisopinocampheylborane and benzonitrile provided chiral 1-phenylpentylamine in 24%ee. Chiral structure of the boryl imines and reaction conditions for the higher level of enantioselectivity in the alkylation are currently under investigation.

Table 2 Asymmetric Synthesis of 1-Phenylpentylamine

Entry	Chiral olefin	[Olefin] / [BH$_3$]	Reaction time (I)^a h	Reaction time (II)^b h	Yield %	Enantio-selectivity % ee (Config.)
1	α-Pinene	2	25	1	77	24 (S)
2	β-Pinene	2	25	1	88	0.8 (R)
3	Limonene	1	25	1	53	8.9 (R)
4	α-Pinene	1	2	1	70	7.7 (S)
5	β-Pinene	1	2	1	81	1.9 (S)

^{a} Reaction at 0 ^{o}C ^{b} Reaction at -80^{o}C

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