Synthesis of Diastereomerically Pure Monoisopinocampheylcyanoborane Adducts of Phosphines. Direct Evidence of an S_N2 Substitution at a Boron Atom

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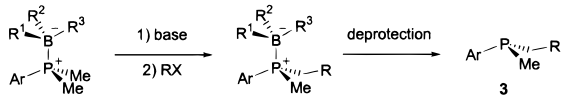
The synthesis of enantiomerically pure phosphines and diphosphines, in particular those having a chiral phosphorus atom,[1] is currently the subject of great interest, since these compounds find application as ligands in catalytic asymmetric reactions. Several methods for their synthesis involve the use of borane adducts of phosphorus compounds, in which the borane moiety serves mainly as a protecting group.[2] We reasoned that a chiral organoborane bound to an achiral phosphine could, at the same time, deliver an asymmetric induction in stereoselective processes, such as the selective formation of product **2** from complex **1**, which would serve as precursor to an enantiomerically enriched phosphine **3**.



However, to the best of our knowledge, no synthesis of an enantiomerically pure phosphorus compound containing a phosphorus−boron bond and a chiral boron atom has been reported. In this communication are described the first examples of such compounds. We also report experiments that provide direct evidence of an S_N2 substitution at a boron atom.

Since the preparation of enantiomerically pure complex **5** is well established,[3] we chose (1*R*)-(+)-α-pinene as the chiral source in the synthesis of compounds **10** and **11** (Scheme 1). Lithium monoisopinocampheylborohydride (**6**), prepared from **5**,[4] reacted with mercuric cyanide in THF at reflux to afford **7**.[5] Treatment of **7** with HCl in diethyl ether yielded monoisopinocampheylcyanoborane (**8**), which was directly converted in the presence of phosphines **9a**−**c** to the corresponding adducts. Two diastereomers, (R_B)-**10** and (S_B)-**11**, were produced at this stage. The ratio of these adducts depended strongly on the substitution pattern of the phosphine (Table 1).

Scheme 1

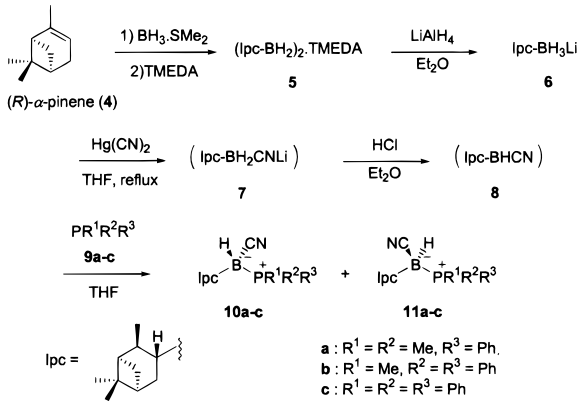


Table 1. Synthesis of Phosphine Adducts of Monoisopinocampheylcyanoborane

phosphine	time (days)	yield[a] (%)	**10**/**11** ratio[b]
9a	3	70	50/50
9b	3	62	65/35
9c	5	39	>98/2[c]

[a] Overall yield from $(IpcBH_2)_2$·TMEDA. [b] Determined by HPLC of the purified product. [c] Only one diastereomer observed in ^1H and ^{13}C NMR spectroscopy.

Mixtures were obtained from dimethylphenylphosphine (**9a**) and diphenylmethylphosphine (**9b**), while a single compound, **10c**, was isolated from triphenylphosphine (**9c**). Pure diastereomer **10a** was isolated by recrystallization (4/1 hexane/CH_2Cl_2), while pure **10b** was obtained by stirring the mixture of **10b** and **11b** in THF at room temperature for 10 days. The structures of **10a**[6] and **10c**[7] were determined by single-crystal X-ray analyses, allowing the attribution of the *R* configuration to the boron atom in both compounds. The conversion of **10c** to **10b** (Li, THF, 4 h, room temperature, then MeI; 43%)[8] permitted identification of **10b** as the major adduct from **9b**.

Thus, this method allowed us to prepare selectively several enantio- and diastereomerically pure monoisopinocampheylcyanoborane adducts having the *R* configuration at the boron atom. To obtain selectively the (S_B)-epimers, nucleophilic substitution

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(6) **10a** crystal data: $C_{19}H_{29}BNP$; space group $P2_12_12_1$; orthorhombic; a = 8.445(3) Å, b = 11.622(2) Å, c = 19.465(4) Å, V = 1911(1) Å^3, Z = 4; final R indices [$I > 2.0\sigma(I)$] R_1 = 0.035, wR_2 = 0.033 for 1569 absorption-corrected reflections.
(7) **10c** crystal data: $C_{29}H_{33}BNP$; space group $P2_1$; monoclinic; a = 9.844(2) Å, b = 14.396(3) Å, c = 9.842(2) Å, β = 114.22(6)°, V = 1272(1) Å^3, Z = 2; final R indices [$I > 2.0\sigma(I)$] R_1 = 0.039, wR_2 = 0.037 for 2284 absorption-corrected reflections.
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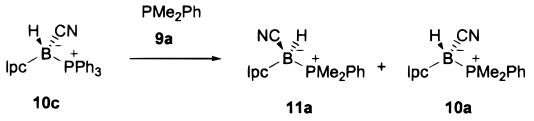
Table 2. Substitution of **10c** by Dimethylphenylphosphine (**9a**)



entry	solvent (equiv)	time	conversion rate[a] (%)	**11a**/**10a** ratio[a]
1	THF (1)	20 h	87	53/47
2	THF (1)	45 h	100	51/49
3	C_6D_6 (1)	15 days	88	62/38
4	C_6D_6 (10)	40 h	35	82/18
5	C_6D_6 (10)	4 days	71	75/25
6	C_6D_6 (10)	9 days	98	75/25
7	pure phosphine **9a**	2.5 h	75	92/8
8	pure phosphine **9a**	7 h	98	90/10
9	pure phosphine **9a**	20.5 h	100	80/20

[a] Evaluated from HPLC chromatogram integration.

of the (R_B)-adduct of one phosphine by other phosphines was then considered. Kinetic studies on the substitution of Lewis base adducts of boron derivatives[9] suggest that both S_N1-B and S_N2-B pathways may be involved in such processes. However, only achiral or racemic chiral adducts were used in these works, so that the S_N2 mechanism, when assumed, could not be proven by simply establishing that a Walden inversion had happened.[10] The reactions of the triphenylphosphine adduct **10c** with **9a** under various conditions are summarized in the Table 2.

The reaction in THF (entries 1, 2) using 1 equiv of phosphine was complete after 45 h, according to HPLC monitoring, but nearly equimolar amounts of epimers were obtained. This outcome was attributed to an S_N1-B process. In deuterated benzene, a less dissociative solvent, the substitution with 1 equiv of **9a** (entry 3) was very sluggish; it was possible to accelerate it a little using 10 equiv of nucleophile (entries 4−6). The final diastereomer ratio **11a**/**10a** was 75/25 in that case. The occurrence of both mechanisms may account for this result in C_6D_6.

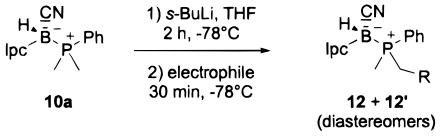
The reaction in pure **9a** proceeded much faster, being complete after 20.5 h (entries 7−9). More importantly, a high **11a**/**10a** ratio was observed after 2.5 h, and it was still 90/10 after 7 h, when 98% of the starting material had been converted.[11] Since the major isomer **11a** has an *S*-configuration at the boron atom, and since it was obtained from (R_B)-**10c**, it clearly resulted from an S_N2-type substitution at the boron atom. The ratio decreased to 80/20 after 20.5 h, probably because of an equilibration due to the excess of phosphine.

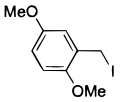
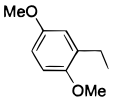
The reaction of **10c** with **9b** was then studied under similar conditions. In all cases, the equilibration of the adducts proceeded rapidly, favoring the epimer (R_B)-**10b**; for example, in pure phosphine, the ratio **11b**/**10b** changed from 78/22 after 3 h (45% conversion) to 49/51 after 1 day (91% conversion) and to 26/74 after 2 days (100% conversion).

To evaluate the synthetic potential of the substitution at boron atom, **11a** was prepared from **10c** (pure **9a**, 7 h, 59% after purification by HPLC).

Preliminary results on the alkylation of **10a** are reported in Table 3. Compound **10a** in THF was treated with *s*-BuLi at −78 °C. Then, after 2 h, the electrophile was added, and stirring was continued for 30 min at −78 °C.

Table 3. Diastereoselective Alkylation of Adduct **10a**



Electrophile	R	Products	Yield of **12** + **12'** (%)	*De* (%)
CH_3I	CH_3	**12a**, **12'a**	85	49[a]
$PhCH_2Br$	$PhCH_2$	**12b**, **12'b**	77	60[b]
		**12c**, **12'c**	92	51[c]
Ph_2CO	$Ph_2(HO)C$	**12d**, **12'd**	84	74[a]

[a] Determined from the amounts of diastereomers after separation by chromatography. [b] Determined by ^1H NMR spectroscopy in the presence of $Eu(FOD)_3$. [c] Determined by HPLC of the purified product.

The adducts **12** (major isomer) and **12′** were all stable and purified by column chromatography. In several cases, the diastereomers were separated. The best diastereomeric excess was observed in the reaction of benzophenone (74%). These results show that the monoisopinocampheylcyanoborane moiety acts as a good chiral auxiliary.

Adduct **12a** was converted, in two steps (treatment with DABCO, followed by oxidation of the resulting phosphine with hydrogen peroxide), to the known (*R*)-ethylmethylphenylphosphine oxide.[12] Therefore, **12a** has the *S*-configuration at the P atom. Some racemization occurred during the removal of the chiral auxiliary with DABCO in THF at reflux, but not when the reaction was performed at 40 °C. In this case, the phosphine was converted to the corresponding borane adduct, which was enantiomerically pure (ee > 99.5%, chiral-phase HPLC).

In conclusion, we have prepared enantiomerically pure phosphorus compounds containing a phosphorus−boron bond and a chiral boron atom, and showed that the substitution of **10c** with dimethylphenylphosphine proceeded with Walden inversion, thus providing direct evidence of an S_N2 substitution at the boron atom. Chiral induction was observed in the alkylation of **10a** with several electrophiles. Conversion to an enantiomerically pure phosphine was performed from a purified diastereomeric adduct.

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Supporting Information Available: Experimental procedures and characterization data for new compounds; X-ray structure determination and crystal data for **10a** and **10c** (PDF). See any current masthead page for Web access instructions.

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