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Creation of New Boron–Carbon Bonds by Dichlorocarbene Insertion into the Boron–Hydrogen Bond of Amine– and Phosphine–Boranes

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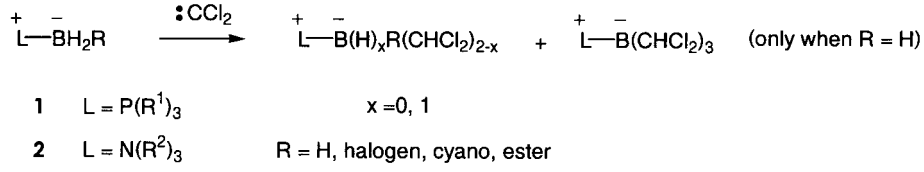
Abstract—A simple approach for constructing a new boron–carbon bond by direct insertion into the B–H bond of amine– and phosphine–borane complexes is described. The outcome of this reaction was studied according to the substituents and the experimental conditions. A preliminary investigation of the reactivity of some insertion products as well as their anti-proliferative activities is also reported.

Introduction

For nearly a century, amine– and phosphine–borane complexes have stimulated research interest from chemists. However, it is only in the last three decades that a better understanding of their basic reactions has been the starting point of new synthetic applications.[1] For example, significant advances have been made in the preparation of chiral non racemic phosphines by using borane both as a protecting and an activating group.[2] Promising results were also reported in various other areas, such as boron analogues of aminoacids and nucleotides,[3] boron-containing host molecules,[4] and in materials sciences.[5] In our laboratory, preliminary experiments using triphenylphosphine–borane as the starting material indicated that dichlorocarbene insertion into the boron–hydrogen bond should open a new route to hitherto unknown borane complexes.[6] The same reaction was carried out with 1,2-dihydro-1,2-λ^3-azaphosphinine–BH_3 and, later by other authors, with dihydro-1H-phosphole-BH_3.[7] More recently, methylene insertion with samarium carbenoids has been used to afford phosphine–monoalkylborane in good yields.[8] Following our initial results, we report here a more detailed study of the reactivity of various amine– and phosphine–borane complexes toward dichlorocarbene (Scheme 1) and a first investigation of some aspects of their reactivity and their anti-proliferative activity.

Results and Discussion

1a (R^1=Ph, R=H) and **2a** (R^2=Me, R=H) are commercially available. Phosphine–boranes **1b**–**1f** and amine–boranes **2b** and **2c** were prepared easily in almost quantitative yields by exchange reactions of dimethylsulfide by the corresponding amines or phosphines according to the literature (Table 1).[1] Addition of sodium cyanoborohydride to phosphine or amine hydrohalide afforded **1e** (R^1=Ph, X=CN) and **2d** (R^2=Me, X=CN).[9] **2e**–**2f** were obtained following the procedures first described by Spielvogel et al.[10] Alkylation



Scheme 1.

Keywords: carbene; amine–borane; phosphine–borane; insertion; rearrangement; anti-proliferative activity.
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Table 1. Phosphine and amine–boranes **1** and **2**

	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
R^1	Ph	*p*-Tol	*n*-Bu	*i*-PrO	Ph	Ph	Ph
R	H	H	H	H	CN	Cl	Br
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	
R^2	Me	Et	Et	Me	Me	Me	
R	H	Cl	Br	CN	CO_2H	CO_2Me	

of **2d** by triethyloxonium tetrafluoroborate yielded **2e** after treatment with water. Esterification of **2e** with trimethylorthoformate in the presence of boron trifluoride etherate gave **2f**.[11]

Insertion reactions

Dichlorocarbene was generated according to the Makosza procedure.[12] Deprotonation of chloroform by means of sodium hydroxide and a quarternary ammonium salt in a phase-transfer system affords initially sodium trichloromethylide, which dissociates into a dichlorocarbene.

First experiments using triphenylphosphine–borane **1a** as a model substrate indicated that the reaction was incomplete after 30 min at room temperature and revealed the presence of a di-insertion product (^{31}P and ^{1}H NMR, **1a/3a/4a**=30/62/8) (Scheme 2). **1a** was completely consumed after 15 h and a ratio **3a/4a**=90/5 was then measured. Small amounts of triphenylphosphine ($\delta^{31}P=-4.9$), triphenylphosphine oxide ($\delta^{31}P=29.8$) and another unknown phosphorus compound ($\delta^{31}P=49.9$) were also detected. When the reaction was performed at 50°C for 1 h, a single phosphine–borane complex **4a** was produced, but large amounts of Ph_3P and Ph_3PO were also observed. The generation of dichlorocarbene by addition of *n*-butyllithium in hexanes to a solution of bromotrichloromethane at −100°C[13] only slightly modified the course of the reaction (**1a/3a/4a**=44/54/2). Sodium trichloracetate was also tested as a source of dichlorocarbene[14] with no significant improvement. We never observed the formation of a tri-insertion product **5a** $Ph_3P–B(CHCl_2)_3$.

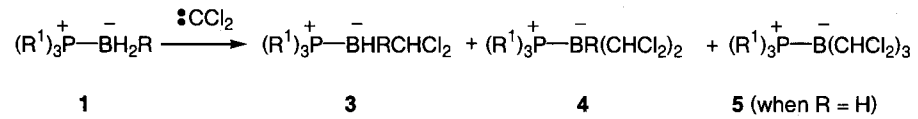
Following these preliminary observations, we then turned our attention to other phosphine–borane complexes **1**. Unless otherwise specified, we chose to generate dichlorocarbene from chloroform and sodium hydroxide in a phase-transfer system.

Tritolylphosphine–BH_3 **1b** appeared to be slightly more reactive than **1a** since total consumption of **1b** required approximately 1.5 h at 25°C (**3b/4b**=65/35). After 18 h, **4b** was the only detected insertion product. Tributylphosphine–borane **1c** has a similar reactivity**,** except that the formation of a tri-insertion product $(n\text{-Bu})_3P–B(CHCl_2)_3$ **5c** was observed after 3 h at 25°C (**3c/4c/5c**=31/63/6). **3c** was completely transformed after 18 h (**4c/5c**=28/72). The insertion reaction proceeded more slowly with $(i\text{-PrO})_3P–BH_3$ **1d** (30 min, 25°C, **1d/3d**=70/30) and there were only small amounts of a di-insertion product **4d** after 90 min at the same temperature (**3d/4d**=93/7. When the reaction was carried out at room temperature for 18 h, we obtained a mixture of mono-, di- and tri-insertion products (**3d/4d/5d**=23/65/12). After 5 h at 25°C, 80% of the monosubstituted borane complex $Ph_3P–BH_2CN$ **1e** has been consumed giving a 7/3 mixture of mono- and di-insertion products. In contrast, the introduction of a halogen on the boron moiety resulted in the formation of a single product. $Ph_3P–BH(CHCl_2)Cl$ **3f** or $Ph_3P–BH(CHCl_2)Br$ **3g**.

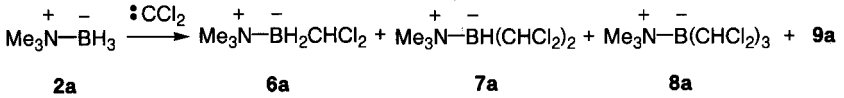
The same experiments were then performed on amine–borane. $Me_3N–BH_3$. **2a** was found to be completely transformed after 15 min at 0°C. A mixture of $Me_3N–BH_2CHCl_2$ **6a** and $Me_3N–BH(CHCl_2)_2$ **7a** was obtained together with an additional compound **9a**, whose structure will be discussed later (**6a/7a/9a**=40/40/20) (Scheme 3).

After 2 h at room temperature, the monoinsertion product was completely consumed. **7a** and the triinsertion complex **8a** were the only detected products. When *n*-butyllithium and bromotrichloromethane were used to generate dichlorocarbene, we observed the formation of a major monoinsertion product **7a** (**2a/7a/8a/9a**=9/61/9/21). Attempt to purify this crude mixture by distillation resulted in the obtention of **9a** without any contaminant in a 40% yield. We then verified by heating of the crude reaction mixture at reflux of chloroform that it was the result of the rearrangement of **6a** (Scheme 4). The NMR spectroscopic data, ^{1}H, ^{13}C, ^{11}B, were in agreement with the proposed structure. This transformation is discussed in the next paragraph.

As described previously for the phosphine complexes, the addition of dichlorocarbene on monohalogenoborane–triethylamine complexes only resulted in the formation of monoinsertion products **6b** (R=Cl) and **6c** (R=Br) while, for the cyanoborane derivative **2d**, a small amount of a di-insertion product was observed after 1 h 30 at room temperature (**6d/7d**=92/8). With the carbomethoxyborane



Scheme 2.



Scheme 3.

Scheme 4.

Table 2. Isolated insertion products **3**, **4**, **6** and **7**

Entry	Complex	Yield (%)	Entry	Complex	Yield (%)
3a	$Ph_3P–BH_2CHCl_2$	46	**3g**	$Ph_3P–BHBrCHCl_2$	56
4a	$Ph_3P–BH(CHCl_2)_2$	25	**7a**	$Me_3N–BH(CHCl_2)_2$	50
4b	$Tol_3P–BH(CHCl_2)_2$	21	**6b**	$Et_3N–BHClCHCl_2$	65
3d	$(i\text{-PrO})_3P–BH_2CHCl_2$	40	**6c**	$Et_3N–BHBrCHCl_2$	58
3e	$Ph_3P–BH(CN)CHCl_2$	24	**6d**	$Me_3N–BH(CN)CHCl_2$	55
4e	$Ph_3P–B(CN)(CHCl_2)_2$	35	**6f**	$Me_3N–BH(CHCl_2)(CO_2Me)$	45
3f	$Ph_3P–BHClCHCl_2$	48	**7f**	$Me_3N–B(CHCl_2)_2(CO_2Me)$	30

complex **2f** (R=CO_2Me), under the same experimental conditions, the mono-and the di-insertion products were formed in a 60/40 ratio. They were easily separated by careful distillation.

All these insertion products were air- and moisture-stable compounds, except **3c–5c** and **3d–5d**. They were readily characterised by ^1H, ^{11}B, ^{31}P NMR, mass spectroscopy and (or) elemental analysis. In particular, the δ ^{11}B were found in the range 1.6 to −26.3 indicating a significant charge transfer from the nitrogen or phosphorus to the boron atom and, therefore, corroborate the presence of a tetracoordinate boron atom.[15] Isolated insertion products are listed in Table 2.

The previous results bring the following comments:

- The change in the method of generation of dichlorocarbene from phase transfer to a reaction performed in anhydrous medium starting from $BrCCl_3$ and *n*-BuLi did not cause any major modification. However, the second method is in general more selective, affording lower amounts of di-insertion products, probably because the carbene was present during a shorter time and was not in excess.
- We never succeeded to stop the reaction after the first insertion for all amine– and phosphine–BH_3 complexes. The presence of an halogen (chlorine or bromine) substituent on boron prevented a second insertion of the carbene and allowed the obtention of a single compound.
- Whatever the method used to generate the carbene and the boron substituents, the amine–boranes complexes are more reactive than the phosphine–boranes. For a same borylated moiety, BH_3 for example, the order of reactivity is the following:

$$Me_3N > Bu_3P \sim Ph_3P \sim Tol_3P > (i\text{-PrO})_3P$$

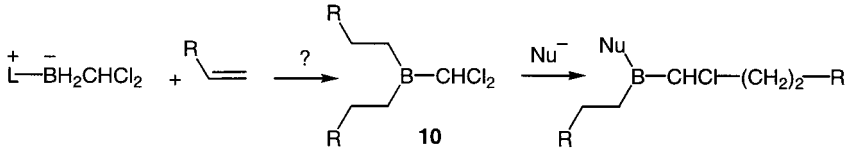
For a same Lewis base, for example PPh_3, the boranes can also be classified by increased reactivity.

$$BH_3 > BH_2Cl > BH_2Br \sim BH_2CN$$

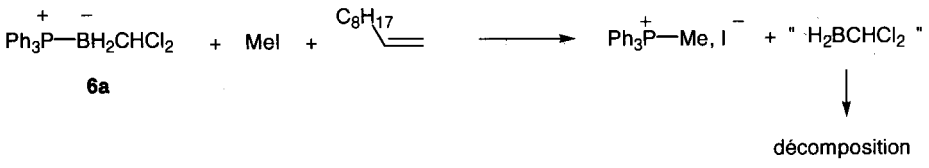
Reactivity

Decomplexation reactions. We envisaged that some of the previously prepared insertion products could be good precursors of new hydroborating agents and, for example, could give access to new dichloromethyl boranes **10** (Scheme 5). The chemistry of such species is extremely developed, due to the halogen atom α to the boron that induces an easy intramolecular 1,2 migration in the presence of a nucleophile (Scheme 5).[16]

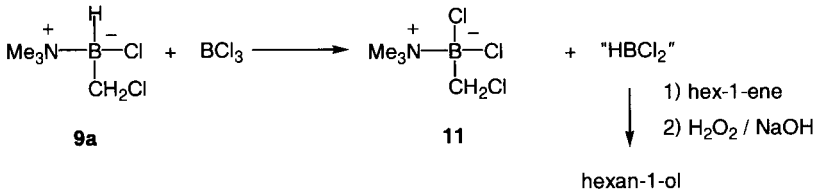
In order to test this reaction, we first heated unsuccessfully a



Scheme 5.



Scheme 6.



Scheme 7.

mixture of complex **6a** and dec-1-ene. We then decided to use methyl iodide in excess to generate in situ the free borane.[17] The formation of the phosphonium salt was actually observed, but, whatever the conditions, no hydroboration product was obtained. These results were not improved by using other electrophiles ($MeOSO_2CF_3$, HBF_4, Et_2O/BF_3), Thus it seems that, if decomplexation indeed occurred, H_2BCHCl_2 was too unstable in these conditions to hydroborate an alkene (Scheme 6).

In contrast, if decomplexation did not occur when **9a** was treated with boron trichloride, a new complex **11** was obtained instead of the expected boron trichloride–trimethylamine adduct (Scheme 7). The hydrogen atom carried by the boron atom was replaced by a chlorine atom. **11** was characterised by NMR ^{1}H, ^{13}C, ^{11}B and elementary analysis.

Such redistribution reactions between an amine–borane complex and a trihalogenoborane, without cleavage of the boron–nitrogen bond, were already described in the literature.[18] The formation of dichloroborane was confirmed by carrying out the reaction in the presence of hex-1-ene. After oxidation, hexan-1-ol was recovered in a good yield.

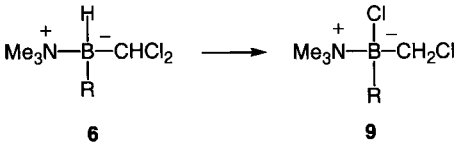
Thermal rearrangement. We described previously the presence of **9a** in the crude mixture besides **6a**, when Me_3NBH_3 was submitted to the insertion reaction of dichlorocarbene. Distillation caused the complete conversion of the expected product **6a** to **9a**. This rearrangement was the result of an exchange between the hydrogen carried by boron and one of the chlorine. It could be extended to other trimethylamine–borane complexes **6d** (9 days, reflux, MeOH) and **6f** (15 h, reflux, MeOH). The structures of these new compounds were established on the basis of NMR, mass spectroscopy and elementary analysis (Scheme 8).

This transformation presumably occurred through an intramolecular migration of one hydrogen from boron to the α-carbon, followed by the addition of the chloride anion generated in situ to the borylated moiety (Scheme 9).

Anti-proliferative activity. Previously, a series of trimethylamine cyanoboranes, trimethylamine carboxyboranes, their derivatives, and related compounds were reported to afford antineoplastic activities.[19] A preliminary study of the anti-proliferative activity of seven insertion products (**3a**, **3e**, **3f**, **3g**, **4e**, **6d** and **6e**) and five starting complexes (**1e**, **1f**, **1g**, **2d** and **2f**) against murine L1210 leukaemia has been carried out. Among all compounds tested at concentrations ranging from 0.5 to 50 μM, only **4e** impaired cell growth. An IC50 of 2.9±0.25 μM was calculated after 2 days of culture with this compound. At concentrations >5 μM, cells lost viability. Further investigations are required to determine the exact potential of **4e** as an anti-proliferative drug.

Conclusion

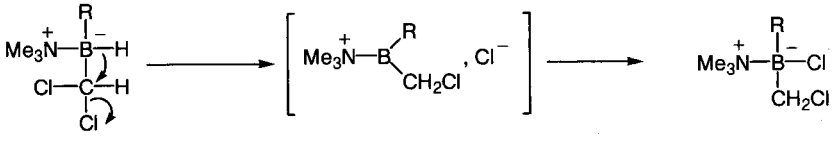
In summary, we have described the insertion reactions of a dichlorocarbene into the hydrogen–boron bond of phosphine– and amine–borane complexes. Although a second insertion of the carbene was sometimes difficult to prevent, hitherto unknown organoboranes were isolated successfully in acceptable to good yields. Preliminary aspects of the reactivity of these compounds as well as of their anti-proliferative activities were also reported. Further studies are in



Compound	9a	9d	9f
R	H	CN	CO_2Me
Yd (%)	40 [a]	70	60

[a] Yield calulated from Me_3NBH_3, without isolation of the intermediate **6a**

Scheme 8.



Scheme 9.

progress to elucidate the exact mechanism of this insertion reaction and to test other carbenes in order to synthesise new functionalized amine– and phosphine–borane complexes.

Experimental

Chloroform was first shaken with conc. H_2SO_4, washed with water, dried with $CaCl_2$ before filtering and distilling. All melting points were determined on a Kofler apparatus and are uncorrected. NMR spectra were measured on a Bruker AC 200 (200 MHz for ^1H and 50.3 MHz for ^{13}C) and a Bruker AC 300 (300 MHz for ^1H, 75.5 MHz for ^{13}C, 121 MHz for ^{31}P and 96 MHz for ^{11}B). For ^1H and ^{13}C NMR, TMS was used as internal standard (δ=0 ppm) and the J values are given in Hz. For ^{31}P and ^{11}B NMR, H_3PO_4 (85%, aq.) and Et_2OBF_3 were, respectively, used as external standard. High resolution mass spectra were obtained on a Varian MAT 311 (Centre Régional de Mesures Physiques, Université de Rennes 1, France). Elemental analyses were performed at the Central Laboratory for Analysis, CNRS, Lyon, (France). Silica gel 60F254 (Merck) was used for column chromatography.

General procedure for the insertion of a dichlorocarbene generated by phase transfer

To a solution of 10 mmol of a phosphine– or amine–borane complex in 70 ml of $CHCl_3$ were added 500 ml of triethylbenzylammonium chloride and 32 g of a 50% aqueous solution of sodium hydroxide (40 equiv.). The mixture was stirred mechanically very vigorously for the time and at the temperature, which were given below for each complex. The organic layer was washed with water (2×10 ml), dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by recrystallization or bulb to bulb distillation.

Triphenylphosphine–(dichloromethyl)borane 3a. 46% (after 15 h at r.t. and precipitation with diethylether). Mp=134°C (dichloromethane). ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.52 (q, J_{H-P}=5.9 and J_{H-H}=5.3 Hz, 1H), 7.26–7.71 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 71.9 (CH), 126.6 (d, J_{C-P}=59.0 Hz, C), 129.0 (d, J_{C-P}=10.9 Hz, CH), 131.8 (d, J_{C-P}=2.1 Hz, CH), 133.6 (d, J_{C-P}=9.6 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 10.8. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −22.3. $C_{19}H_{18}BCl_2P$ (359.0): calcd C, 63.56; H, 5.01; found C, 63.4; H, 5.1.

Triphenylphosphine–bis(dichloromethyl)borane 4a. 25% (after 1 h at 50°C and precipitation with diethylether). Mp=116°C (dichloromethane). ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.73 (dd, J_{H-P}=9.7 Hz, J_{H-H}=3.7 Hz, 2H), 7.31–7.72 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 66.0 (CH), 124.9 (d, J_{C-P}=59.8 Hz, C), 129.0 (d, J_{C-P}=10.9 Hz, CH), 132.1 (d, J_{C-P}=3.2 Hz, CH), 133.6 (d, J_{C-P}=9.6 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 9.9. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −11.4. $C_{20}H_{18}BCl_4P$ (441.9): calcd C, 54.35; H, 4.11; found C, 54.3; H, 4.1.

Tritolylphosphine–(dichloromethyl)borane 3b. All attempts of purification by recrystallization or chromatography on silica gel failed. The NMR data were measured from the spectrum of a 80/20 mixture of **3b/4b** (mp=101°C). ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 9H), 5.50 (q, J_{H-P} and J_{H-H}=5.3 Hz, 1H), 7.11–7.52 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.5 (s, CH_3), 72.0 ($CHCl_2$), 123.5 (d, J_{C-P}=61.6 Hz, C), 129.7 (d, J_{C-P}=10.6 Hz, CH), 133.4 (d, J_{C-P}=9.8 Hz, CH), 142.1 (d, J_{C-P}=2.3 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 8.8. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −22.3.

Tritolylphosphine–bis(dichloromethyl)borane 4b. 21% (after 15 h at r.t. and precipitation with diethylether/heptane 3/1). Mp=157°C (dichloromethane). ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.41 (s, 9H), 5.70 (dd, J_{H-P}=9.3 Hz, J_{H-H}=3.6 Hz, 2H), 7.22–7.61 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.5 (s, CH_3), 70.9 (CH), 121.8 (d, J_{C-P}=62.2 Hz, C), 129.7 (d, J_{C-P}=11.0 Hz, CH), 134.3 (d, J_{C-P}=9.5 Hz, CH), 142.5 (d, J_{C-P}=2.7 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 8.6. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −11.8. $C_{23}H_{24}BCl_4P$ (447.1): calcd: C, 57.02; H, 4.96; found C, 56.8; H, 5.0.

Tri-(*n*-butyl)phosphine–dichloromethylborane 3c. All attempts of purification by distillation or chromatography on silica gel failed. The NMR data were measured from the spectrum of a crude mixture of **3c/4c** (4/1) after 30 min at r.t. Other phosphorus derivatives without a borane moiety were also present. ^1H NMR ([d_8]-toluene, 300 MHz) δ: 0.81 (t, J_{H-H}=7.2 Hz, 9H); 1.10–1.85 (m, 18H); 5.78 (dt, J_{H-P}=22.7 Hz, J_{H-H}=4.0 Hz, 1H). ^{13}C NMR ([d_8]-toluene, 75 MHz) δ: 13.7 (s, CH_3); 21.1 (d, J_{C-P}=34.2 Hz, CH_2); 24.5 (s, CH_2); 24.7 (d, J_{C-P}=2.4 Hz, CH_2); 73.5 (CH). ^{31}P NMR ([d_8-toluene, 121 MHz) δ: 6.6. ^{11}B NMR ([d_8]-toluene, 96 MHz) δ: −24.1 (dt, J_{B-P}=61.2 Hz, J_{B-H}=82.1 Hz).

Tri-(*n*-butyl)phosphine–bis(dichloromethyl)borane 4c. All attempts of purification by distillation or chromatography on silica gel failed. The NMR data were measured from the spectrum of a crude mixture of **3c/4c/5c** (31/63/6) after 3 h at r.t. Other phosphorus derivatives without a borane moiety were also present. ^1H NMR ([d_8]-toluene, 300 MHz) δ: 0.81 (t, J_{H-H}=7.2 Hz, 9H); 1.10–1.85 (m, 18H); 6.06 (dd, J_{H-P}=19.2 Hz, J_{H-H}=4.0 Hz, 2H). ^{13}C NMR ([d_8]-toluene, 75 MHz) δ: 13.7 (s, CH_3); 20.5 (d, J_{C-P}=34.2 Hz, CH_2); 24.6 (s, CH_2); 24.8 (d, J_{C-P}=3.7 Hz, CH_2); 72.9 (CH). ^{31}P NMR ([d_8]-toluene, 121 MHz) δ: 1.8. ^{11}B NMR ([d_8]-toluene, 96 MHz) δ: −13.5 (dd, J_{B-P}=73.8, J_{B-H}=67.2 Hz).

Tri-(*n*-butyl)phosphine–tris(dichloromethyl)-borane 5c. All attempts of purification by distillation or chromatography on silica gel failed. The NMR data were measured from the spectrum of a crude mixture of **4c/5c** (28/72) after 15 h at r.t. Other phosphorus derivatives without a borane moiety were also present. ^1H NMR ([d_8]-toluene, 300 MHz) δ: 0.76 (t, J_{H-H}=7.2 Hz, 9H); 1.10–1.85 (m, 18H); 6.03 (d, J_{H-H}=10.5 Hz, 3H. ^{13}C NMR ([d_8]-toluene, 75 MHz) δ: 13.5 (s, CH_3); 20.8 (d, J_{C-P}=31.7 Hz, CH_2); 24.5 (s, CH_2); 25.7 (d, J_{C-P}=6.1 Hz, CH_2); 71.5 (CH). ^{31}P NMR ([d_8]-toluene, 121 MHz) δ: 0.9. ^{11}B NMR ([d_8]-toluene, 96 MHz) δ: −9.3 (d, J_{B-P}=70.2 Hz).

Triisopropylphosphite–(dichloromethyl)borane 3d. 40% (after 30 min at r.t. and distillation). $Bp_{0.01\ mmHg}$=70–75°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.33 (d, J_{H-H}=6.2 Hz, 18H), 1.75 (br q, J_{H-B}=90.0 Hz, 2H), 4.72 (d sept, J_{H-H}=6.2 Hz, J_{H-P}=1.8 Hz, 3H), 5.62 (dt, J_{H-P}=11.2 Hz, J_{H-H}=4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.9 (d, J_{C-P}=3.8 Hz, CH_3), 72.2 (d, J_{C-P}=6.3 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 89.1 (q, J_{P-B}=113.0 Hz). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −26.2 (dt, J_{P-B}=120.1 Hz, J_{B-H}=98.8 Hz).

Triisopropylphosphite–bis(dichloromethyl)borane 4d. The NMR data were measured from the spectrum of a 25/65/12 mixture of **3d/4d/5d** obtained after 18 h at r.t. and the spectrum of pure **3d**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.40 (d, J_{H-H}=6.2 Hz, 18H), 4.88 (d sept, J_{H-H}=6.2 Hz, J_{H-P}=0.9 Hz, 3H), 5.67 (dd, J_{H-P}=17.6 Hz, J_{H-H}=4.1 Hz, 2H. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.9 (d, J_{C-P}=4.1 Hz, CH_3), 70.0 (CH), 73.8 (d, J_{C-P}=8.9 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 75.5 (q, J_{P-B}=133.4 Hz). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −14;2 (dd, J_{P-B}=140.4, J_{B-H}=99.7 Hz).

Trisopropylphosphite–tris(dichloromethyl)borane 5d. As for **4d**, the NMR data were measured from the spectrum of a 23/65/12 mixture of **3d/4d/5d** and the spectrum of pure **3d**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (d, J_{H-H}=6.2 Hz, 18H), 4.98 (d sept, J_{H-H}=6.2 Hz, J_{H-P}=0.9 Hz, 3H), 5.89 (d, J_{H-P}=13.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.6 (d, J_{C-P}=4.9 Hz, CH_3), 75.5 (d, J_{C-P}=10.6 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 65.4 (q, J_{P-B}=93.5 Hz). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −8.8 (d, J_{P-B}=152.8 Hz).

Triphenylphosphine–(dichloromethyl)cyanoborane 3e. 24% (after 15 h at r.t. and precipitation with diethylether). Mp=172°C (dichloromethane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.28 (dd, J_{H-H} and J_{H-P}=3.6 Hz, 1H), 7.30–7.78 (m, 15H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 66.6 (CH), 123.6 (d, J_{C-P}=64.5 Hz, C), 129.5 (d, J_{C-P}=11.1 Hz, CH), 132.8 (d, J_{C-P}=2.7 Hz, CH), 133.7 (d, J_{C-P}=9.1 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 5.4. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −22.7 (dd, J_{B-P}=76.1 Hz, J_{B-H}=67.3 Hz).

Triphenylphosphine–bis(dichloromethyl)cyanoborane 4e. 35% (after 24 h at r.t. and precipitation with diethylether). Mp=158°C (dichloromethane). ^{1}H NMR ($CDCl_3$, $CDCl_3$, 200 MHz) δ: 5.57 (d, J_{H-P}=8.4 Hz, 2H), 7.31–7.87 (m, 15H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 66.6 (CH), 122.7 (d, J_{C-P}=62.9 Hz, C), 129.5 (d, J_{C-P}=11.1 Hz, CH), 133.0 (d, J_{C-P}=2.5 Hz, CH), 134.6 (d, J_{C-P}=9.5 Hz, CH. ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 7.2. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −13.0 (d, J_{P-B}=65.0 Hz). $C_{21}H_{17}BCl_4NP$ (467.0): calcd C, 54.01; H, 3.67; found C, 54.2; H, 3.9.

Triphenylphosphine–(dichloromethyl)chloroborane 3f. 48% (after 15 h at r.t. and precipitation with diethylether). Mp=187°C (dichloromethane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.44 (t, J_{H-H} and J_{H-P}=3.3 Hz, 1H), 7.29–7.78 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 70.1 (CH), 124.4 (d, J_{C-P}=61.8 Hz, C), 129.1 (d, J_{C-P}=10.9 Hz, CH), 132.3 (d, J_{C-P}=2.3 Hz, CH), 134.0 (d, J_{C-P}=9.1 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 1.7. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −7.8. $C_{19}H_{17}BCl_3P$ (393.5): calcd C, 58.00; H, 4.35; found C, 58.2; H, 4.5.

Triphenylphosphine–(dichloromethyl)bromoborane 3g. 56% (after 15 h at r.t. and precipitation with diethylether). Mp=172°C (dichloromethane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.36 (m, 1H), 5.48 (t, J_{H-H} and J_{H-P}=3.7 Hz, 1H), 7.35–7.80 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 69.0 (CH), 124.4 (d, J_{C-P}=63.5 Hz, C), 129.2 (d, J_{C-P}=10.7 Hz, CH), 132.4 (d, J_{C-P}=2.3 Hz, CH), 134.1 (d, J_{C-P}=8.9 Hz, CH). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 1.5. ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −11.5. $C_{19}H_{17}BBrCl_2P$ (437.9): calcd C, 52.11; H, 3.91; found C, 52.0; H, 4.0.

Trimethylamine–(dichloromethyl)borane 6a. The NMR data were measured from the spectra of the crude mixture of **6a**, **7a** and **9a** (4/4/2) obtained after 15 min at 0°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.74 (s, 9H), 5.59 (t, J_{H-H}=4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 52.8 (CH_3), 70.0 (CH).

Trimethylamine–bis(dichloromethyl)borane 7a. 50% (after 1 h at r.t. and precipitation with diethylether). Mp=91°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.00 (s, 9H), 5.80 (d, J_{H-H}=2.3 Hz, 2H,). ^{13}C NMR ($CDCl_3$, 75 MHz): 53.2 (CH_3), 70.0 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −1.1 (d, J_{B-H}=110.0). $C_5H_{12}BCl_4N$ (238.8): calcd C, 25.15; H, 5.06; found C, 25.7; H, 5.1.

Trimethylamine–tris(dichloromethyl)-borane 8a. The NMR data were measured from the spectra of the crude mixture **7a** and **8a** (8/2) obtained after 2 h at r.t. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.24 (s, 9H), 5.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): 53.5 (CH_3): 70.0 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −4.0.

Triethylamine–(dichloromethyl)chloroborane 6b. 65% (after 1.5 h at r.t.). Oil which decomposed during the distillation. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.30 (t, J=7.3 Hz, 9H), 3.20 (m, 6H), 5.59 (d, J_{H-H}=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 9.7 (CH_3), 51.2 (CH_2): 71.1 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: 1.6 (d, J_{B-H}=124.5 Hz).

Triethylamine–(dichloromethyl)bromoborane 6c. 58% (after 15 h at r.t.). Oil which decomposed during the distillation. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.32 (t, J_{H-H}=7.3 Hz, 9H), 3.28 (m, 6H), 5.64 (d, J_{H-H}=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 9.6 (CH_3), 51.7 (CH_2), 69.0 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: 0.4 (d, J_{B-H}=121.4 Hz).

Trimethylamine–(dichloromethyl)cyanoborane 6d. 55% (after 15 h at r.t. and precipitation with diethylether). Mp=126°C (sublimation). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.28 (m, 1H), 2.88 (s, 9H), 5.49 (d, J_{H-H}=2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 52.3 (CH_3), 63.0 (CH), 129.0 (C). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −8.0 (d, J_{B-H}=110.0 Hz). $C_5H_{11}BCl_2N_2$ (180.9): calcd C, 33.20; H, 6.13; found C, 33.5; H 6.0.

Trimethylamine–(dichloromethyl)carbomethoxyborane 6f. 45% (after 2 h at r.t. and distillation). $Bp_{0.05\ mmHg}$=55°C. Mp=71°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (m, 1H), 2.95 (s, 9H), 3.59 (s, 3H), 5.87 (d, J_{H-H}=2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 48.7 (CH_3), 52.5 (CH_3), 65.0 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −4.5 (d, J_{B-H}=103.4 Hz). IR (nujol): ν=2405 cm^{-1} (B–H); 1650 (CO). $C_6H_{14}BCl_2NO_2$

(213.9): calcd C, 33.69; H, 6.60; N, 6.55; found C, 33.6; H 6.4; N 6.6.

Trimethylamine–bis(dichloromethyl)carbomethoxyborane 7f. 30% (the residue obtained after distillation of **6e** was purified by sublimation). Mp=99°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.20 (s, 9H), 3.62 (s, 3H), 5.95 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 49.5 (CH_3), 53.0 (CH_3), 69.0 (CH). ^{11}B NMR ($CDCl_3$, 96 MHz) δ: −4.8. $C_7H_{14}BCl_4NO_2$ (296.8): C, 28.33; H, 4.75; found C, 28.6; H, 4.6.

Redistribution reaction of 9a with boron trichloride

0.64 mmol of BCl_3 (3.43 M in hexane, 186 μl) was added dropwise to a solution of **9a** (100 ml, 0.64 mmol) and 79 μl (0.64 mmol) of hex-1-ene in 0.5 ml of hexane at −78°C. After stirring for 15 min, the precipitate **11** was filtered. *m*=72 ml. 60%. Mp=111°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.97 (s, 9H), 3.15 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 37.4 (CH_2), 50.4 (CH_3). ^{11}B NMR ($CDCl_3$, 96 MHz): δ: 8.5. $C_4H_{11}BCl_3N$ (190.3): C, 25.25; H 5.83; N, 7.36; found C, 25.4; H, 5.8; N, 7.3.

Thermal rearrangement of 6

Trimethylamine–(chloromethyl)chloroborane 9a. To a solution of 7.4 mmol (730 μl) of bromotrichloromethane in 20 ml of THF cooled at −100°C was added dropwise 4.9 ml of *n*-BuLi (1.5 M in hexanes, 7.4 mmol). After 10 min, a solution of 500 ml of **2a** (6.76 mmol) in 50 ml of THF was added dropwise for 1 h. The mixture was kept one hour more at −100°C and was then allowed to warm slowly up to r.t. before the THF was evaporated under reduced pressure. The residue was treated with 5 ml of brine, extracted with methylene chloride (3×10 ml) and dried ($MgSO_4$). Evaporation of the solvent yielded a residue, which was purified by bulb to bulb distillation. *m*=424 ml. 40%. $Bp_{0.05\ mmHg}$=80–85°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (s, 9H), 2.97 (dd, *J*=2.3 and 13.5 Hz, 1H), 3.18 (dd, *J*=2.3 and 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 37.3 (CH_2), 50.4 (CH_3). ^{11}B NMR ($CDCl_3$, 96 MHz): 2.9.

Trimethylamine–(chloromethyl)chlorocyanoborane 9d. A solution of 80 ml (0.44 mmol) of $Me_3NBH(CN)(CHCl_2)$ **6d** in 6 ml of methanol and 2 ml of water was heated at reflux for 9 days. After extraction with chloroform (3×5 ml), the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel [R_f=0.6 (dichloromethane)]. 70%. Mp=136°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.95 (s, 9H); 2.97 (d, *J*=14.4 Hz, 1H), 3.09 (d, *J*=14.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 35.9 (CH_2), 50.4 (CH_3). ^{11}B NMR ($CDCl_3$, 96 MHz): −2.3.

Trimethylamine–(chloromethyl)chlorocarbomethoxyborane 9f. 9f was obtained from **6f** after 15 h of reflux according to the same experimental procedure as for **9d**. R_f=0.2 (heptane/ether: 1/1). 60%. Mp=134°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.00 (s, 9H), 3.04 (d, *J*=13.9 Hz, 1H), 3.28 (d, *J*=13.8 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 36.5 (CH_2), 49.4 (CH_3), 50.6 (CH_3), 207.0 (CO). ^{11}B NMR ($CDCl_3$, 96 MHz): 0.0. IR (KBr): ν=1687 cm^{-1} (CO). $C_6H_{14}BCl_2NO_2$ (213.9): calcd C, 33.69; H, 6.60; N, 6.55; found C, 33.8; H, 6.5; N, 6.5.

Anti-proliferative activity

Murine L1210 leukaemia cells were cultured in RPMI 1640 (Eurobio, Les Ulis, France) supplemented with 10% heat-inactivated foetal calf serum (Boehringer Mannheim, Mannheim, germany), 2 mM L-glutamine, penicillin (100 U/ml) and streptomycin (50 μg/ml) (Biomérieux, Marcy l'Etoile, France). Cell growth was monitored in 96 well-plates by determination of formazan formation from 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (Sigma Chemical Co., St Louis, MO, USA) (Mosmann, 1983).

Cells were seeded in 100 μl culture medium at a density of 2.5 104 cells/ml in presence of 10 μl of various concentrations of the drug to be tested. Ten millimolar stock solution of the various drugs were made in DMSO. Stock solutions were diluted in culture medium. Final concentration of DMSO did not overreach 0.2%, concentration above which DMSO exerts a cytotoxic effect. After 48 h of culture, 10 μl of an MTT solution at 5 mg/ml were added to each well. The plates were centrifuged 5 min at 1000 rpm after 4 h incubation. Supernatant was removed and formazan crystals were dissolved in 150 μl DMSO. Absorbance measurements were performed on a Titertek Multiskan microreader.

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