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Derivatives of tetrahedral boronic acids

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Abstract

A series of aliphatic and benzylic bifunctional boronate esters have been prepared as potential ligands for affinity chromatography. α-Acetamido, picolino, thioureido and acetamidino boronates have the hetero atom coordinated with the boron, creating a tetrahedral structure. The ^{1}H, ^{13}C and ^{11}B NMR for these compounds confirm the structure, as well as the hetero atom–boron coordination, and show that the bonding of the internal Lewis base with boron increases in order of coordination strength: pyridine < acetamido < thiourea < acetamidine. Bifunctional boronate esters containing these α-substituents and phenoxy ether or dimethylaminophenoxy ether groups, which can be coupled to a solid matrix via a diazonium bond, were prepared.

Introduction

Aromatic boronic acids have been immobilized on several different matrices to perform affinity chromatography of carbohydrates, nucleosides, oligonucleotides, RNA, catecholamines, glycoproteins, serine proteinases, and many other investigations which illustrate the utility of chromatography on immobilized aromatic boronic acids [1–3]. Aliphatic boronic acids have not been employed in boronate chromatography or in enzyme/antibody conjugation methods even though they, like aromatic boronic acids, form diol esters in high pH solutions.

In organic solvents, boronate diol esters are formed with a resulting trigonal boron (**1**), while in aqueous solution they exist as tetrahedral anions (**2**) [4].

Matteson and co-workers have prepared a tetrahedral aliphatic boronic ester containing a thiourea moiety as an internal Lewis base and used it to form an ester with catechol [5,6] and an anhydride with malonic acid [7], both of which were stable under acidic conditions. Later, Matteson and co-workers synthesized a series of compounds with properties similar to these thiourea derivatives [8].

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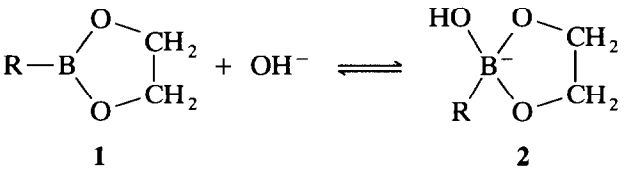


Scheme 1.

Among them were (+)-pinanediol (*R*)-1-acetamido-2-phenylethane-1-boronate and pinacol 1-acetamidino-2-phenylethane-1-boronate. The tetrahedral structure proposed for the above compounds were not, however, confirmed by X-ray or ^{11}B NMR analysis.

Recently, Lauer and Wulff [9] prepared a series of aromatic boronic acids in which coordination of an intermolecular dimethylamino group was indicated by ^{11}B NMR spectroscopy. The cyclic esters of these acids showed ^{11}B NMR absorption between 5 and 14 ppm, relative to boron trifluoride etherate. The same authors have investigated the intramolecular complexation of arylboronates with nitrogen-containing bases using ^{1}H NMR, polarimetry and calorimetry, and found that the degree of complexation was highly sensitive to their steric environment [10].

Brown and co-workers [11] investigated aliphatic boronic esters complexed with amino diols. ^{11}B NMR showed that coupling with the amine function gives a chemical shift of 12–14 ppm. These investigations demonstrated that electronic and steric factors are influential in forming the boron–nitrogen bond.

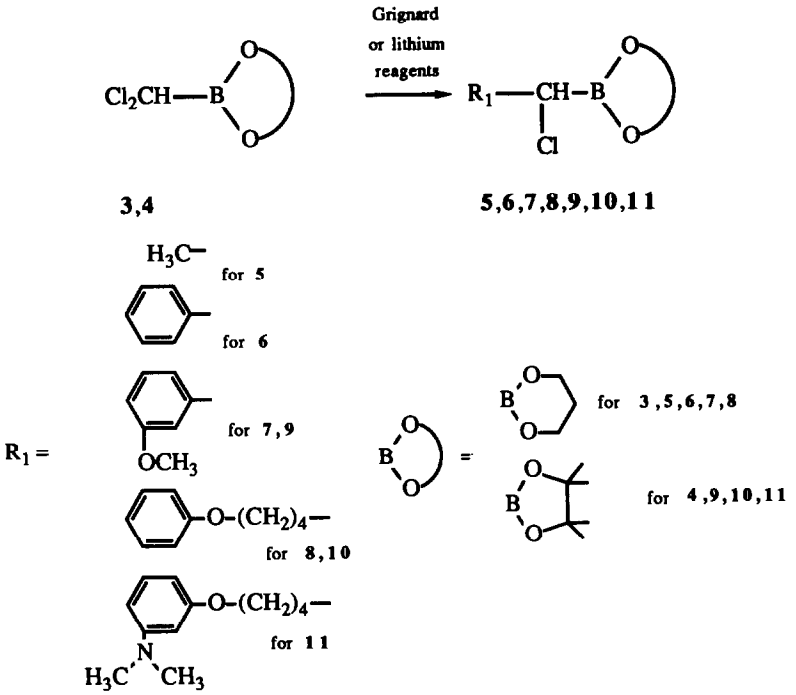
^{11}B NMR for phenylboronates in solution indicate the presence of specific chemical shift for the neutral (δ 30), the boronate anions (δ 3) and *cis*–diol complexed boronate species (δ 7.5) [12].

From the above, it is apparent that the natural tendency of boron to accept an electron pair favors the stability of tetrahedral boronic esters in contrast to trigonal forms, particularly under neutral or acidic conditions. For this reason, internally coordinated tetrahedral boronic acids may be very useful for affinity chromatography. The desired compound should have a functional group which is easy to immobilize on a solid phase and, at the same time, should also possess an internal Lewis base to coordinate with boron. Such bifunctional aliphatic boronate esters are unknown. Among aromatic boronate esters, 5-vinyl-2-dimethylaminomethylbenzeneboronic acid [13] is one example of such a bifunctional structure.

Results and discussion

Aliphatic boronic esters are useful as intermediates in general organic synthesis [14] and, particularly, in asymmetric synthesis [15–17]. This paper is the first approach to the investigation of aliphatic boronic esters fulfilling the requirements of affinity chromatography.

Because we wished eventually to immobilize these compounds, we synthesized boronic esters containing an aromatic ether or an aromatic ether with dimethylamino group which could be coupled via a diazo bond, to a solid matrix. We have prepared the series of bifunctional aliphatic boronate esters containing neighbor-



Scheme 2.

ing groups such as acetamido, pyridine, thiurea and acetamidine, which by electron donation to the empty *p*-orbital of boron, may be able to increase the rate of formation of diol esters in lower pH solution and also may increase their stability. Most boronic esters synthesized to date have been monofunctional derivatives. The number of known bifunctional derivatives have been limited by synthetic difficulties.

We chose α-chloro-boronic esters (**5–11**) as starting compounds for further synthetic evaluation. It is known that dichloromethane boronic acid forms 1,3-propanediol esters (**3**) [18] or pinacol esters (**4**) [19]. These esters, or pinanediol dichloromethane boronate [20], can react with lithium or Grignard reagents and form α-chloro-boronic esters [18]. Using appropriate lithium or Grignard reagents in reaction with **3** or **4** we have prepared a series of α-chloro-boronic esters (**5–11**) containing either an aromatic ether group or a 3-dimethylaminophenoxy group and have examined their structures by ^{1}H, ^{13}C and ^{11}B NMR.

Low molecular weight chlorides **5** and **6** were purified by distillation and correct elementary analysis were obtained for both compounds. Other chlorides were unstable during distillation (for example **7** began boiling at 165°C, 0.1 Torr; **8** at 170°C, 0.02 Torr and polymerization occurred in both), and during chromatography on silica gel. We found that extraction with hexane removed polymeric impurities and after evaporation of hexane led to oils of high purity as seen in the proton NMR of these components. High resolution mass spectrometry gave the correct molecular ion for all compounds.

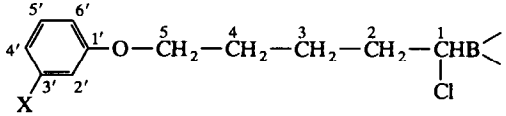
Pasto [21] found that purification of 1-bromo-1-phenylethane-1-boronate was impossible. We similarly encountered this problem (decomposition after removing

Table 1

^{13}C NMR data of compounds **4–11**, in $CDCl_3$, chemical shifts (δ ^{13}C) in ppm with TMS as internal standard

	Aliphatic chain [a]					Aromatic ring [a]						Propanediol group		Pinacol group	
	C1	C2	C3	C4	C5	C1′	C2′	C3′	C4′	C5′	C6′	OCH_2	CH_2	C	CH_3
4	64.6													85.8	24.4
5	42.2	20.4										62.2	27.1		
6	31.8					139.8	128.3	128.5	127.4	128.5	128.3	62.4	27.0		
7 [b]	32.1					141.2	115.1	159.7	113.3	129.4	121.7	62.0	27.0		
8	42.1	28.9	24.1	33.8	67.7	158.7	114.6	129.5	120.6	129.5	114.6	62.3	27.1		
9 [c]	32.2					140.2	115.0	159.7	113.8	129.6	121.9			84.6	24.6
10	42.3	28.8	24.4	33.8	67.4	159.0	114.5	129.2	120.5	129.2	114.5			84.4	24.6
11 [d]	42.0	28.8	23.9	33.7	67.3	160.1	102.5	151.8	105.8	129.5	100.0			84.3	24.5

[a] Carbon atoms are numbered as follows:



X = H, OCH_3, $N(CH_3)_2$. [b] $\delta(^{13}C)$ in OCH_3, 55.3. [c] $\delta(^{13}C)$ in OCH_3, 55.2. [d] $\delta(^{13}C)$ in $N(CH_3)_2$, 42.0.

Table 2

^1H and ^{11}B NMR data of compounds **4–11**

	^1H NMR ($CDCl_3$) δ (ppm *versus* TMS)	^{11}B NMR ($CDCl_3$) δ (ppm *versus* external $BF_3 \cdot OEt_2$)
4	1.35 (s, 12, CH_3C), 5.37 (s, 1 H, HCB)	29.7
5	1.49 (d, J = 7.5 Hz, 3H, CH_3), 1.99 (quint., J = 5.4 Hz, 2H, CH_2), 3.44 (quart., J = 7.5 Hz, 1H, CHB), 4.08 (t, J = 5.4 Hz, 4H, OCH_2)	28.3
6	1.92 (quint., J = 5.4 Hz, 2H, CH_2), 4.02 (t, J = 5.4 Hz, 4H, OCH_2), 4.36 (s, 1H, CHB), 7.38 (m, 5H arom.)	28.1
7	1.96 (quint., J = 5.4 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.17 (m, 4H, OCH_2), 4.25 (s, 1H, CHB), 6.62–7.40 (m, 4H arom.)	28.2
8	1.46–2.09 (m, 8H, pentane and propanediol CH_2), 3.24 (t, J = 7.2 Hz, 1H, CHB), 3.80–4.10 (m, 6H, OCH_2), 6.65–7.37 (m, 5H arom.)	28.9
9	1.29 (s, 12H, CH_3C), 3.79 (s, 3H, OCH_3), 4.41 (s, 1H, CHB), 6.78–7.43 (m, 4H arom.)	30.7
10	1.28 (s, 12H, CH_3C), 1.47–2.07 (m, 6H, CH_2), 3.43 (t, J = 7.5 Hz, 1H, CHB), 3.94 (t, J = 6.2 Hz, OCH_2), 6.75–7.37 (m, 5H arom.)	29.8
11	1.30 (s, 12H, CH_3C), 1.50–2.10 (m, 6H, CH_2), 2.93 (s, 6H, NCH_3), 3.42 (t, J = 7.2 Hz, 1H, CHB), 3.95 (t, J = 6.2 Hz, 2H, OCH_2), 6.10–7.30 (m, 4H arom.)	29.9

THF) when we attempted to prepare 4-methoxy analogs of **7** and **9**. Attempts to prepare **7** and **9** via lithium derivatives (after lithiation of the starting bromides with *n*-butyl-lithium), instead of Grignard reagents, failed. Synthesis of **11** was done using the Grignard reagent prepared from 1-chloro-4-(3-dimethylaminophenoxy)butane (**12**), which was synthesized by Williamson reaction of 3-dimethylaminophenol with 1-bromo-4-chlorobutane. NMR data for compounds **5–11** are given in Tables 1 and 2.

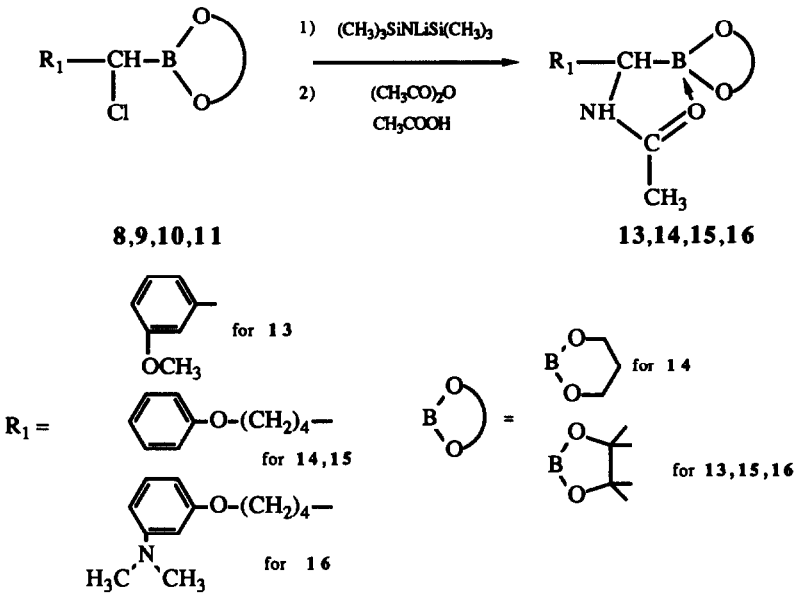
Acetamido derivatives **13, 14, 15** and **16** were prepared utilizing the procedure of Matteson *et al.* [8,22]. The reaction of **8, 9, 10** and **11** with *N*-lithiohexamethyldisilazane gave 1-aminosilyl derivatives which were acetylated *in situ* with acetic anhydride.

The solid compounds **13** and **15** were purified by crystallization in high yield, while the liquids, **14** and **16**, were difficult to purify with a resulting low overall yield. NMR data for compounds **13–16** are given in Tables 3 and 4.

The α-chloro-boronic esters **9** and **10** also undergo nucleophilic substitution with the lithium derivative of 2-picoline [23] forming pyridyl derivatives **17** and **18**, containing a potentially tetrahedral boron.

NMR data for compounds **17** and **18** are given in Tables 3 and 4.

Compounds **13–18** are examples of substitution of α-chloro boronate esters by strong nucleophiles containing Lewis bases. For reaction with weaker nucleophiles, such as acetamidine and thiourea, these chlorides (even the benzylic chlorides **6, 7, 9**) are not reactive enough. We found that when chlorides **5–10** are exchanged with



Scheme 3.

iodide using an acetonitrile solution of NaI, the resulting iodides react *in situ* with acetamidine to produce acetamidino derivatives **19, 20** and **21**.

Acetamidino compounds **19, 20, 21** were deliquescent, which made elemental analyses more difficult, although they gave good NMR and high resolution mass spectra.

Procedures similar to those used for producing acetamidino derivatives were applied to prepare the thiourea derivative. The iodide formed from chloride **10** was reacted with thiourea in acetonitrile solution at room temperature. The resulting salt was decomposed under anhydrous conditions using solid sodium carbonate, yielding **22**.

Benzylic chlorides **6, 7, 9** reacted with thiourea under similar conditions (iodide-assisted alkylation) to yield several products. ^{13}C NMR showed no carbon–boron bond in any of the products formed.

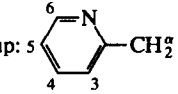
As a reference compound, we prepared 4-phenoxybutaneboronate (**23**), not containing a neighboring coordinating group, using the following general synthetic method [24]. The Grignard reagent formed from 4-phenoxybutyl bromide was allowed to react with trimethyl borate and after hydrolysis of the crude boronic acid, esterification with pinacol gave **23**. A second reference compound, 1,3-propanediol 1-(3-methoxyphenyl)ethane-1-boronate (**24**), was prepared by reaction of **5** with the Grignard reagent synthesized from 3-bromoanisole. NMR data for compounds **19–24** are given in Tables 5 and 6.

Matteson [17] reported that, of all boronate esters, pinanediol esters are the most stable and routinely survive chromatography on silica gel. We found that the propanediol and pinacol esters described in this paper were unstable on silica gel. On the other hand, pinanediol esters did not hydrolyze to the parent acids in acidic or basic conditions [25], a property which may be useful for preparing

Table 3

^{13}C NMR data of compounds [a] **13–18**, chemical shifts ($\delta(^{13}C)$) in ppm with TMS as internal standard

	Aliphatic chain					Aromatic ring						Acetamide group		Pinanediol group		Pinacol group		
	C1	C2	C3	C4	C5	C1′	C2′	C3′	C4′	C5′	C6′	C=O	CH_3	OCH_2	CH_2	C	CH_3	
13 [b]	52.5					142.7	111.1	159.5	112.6	128.9	119.1	176.8	17.1			80.6	24.6	25.0
14	46.7	29.3	24.2	30.3	67.6	159.1	114.4	129.4	120.4	129.4	114.4	174.3	18.1	61.0	28.3			
15	46.1	29.5	25.5	31.0	67.5	159.0	114.4	129.3	120.4	129.3	114.4	175.2	17.1			80.2	25.0	
16 [c]	45.8	29.6	24.8	30.9	67.6	160.1	102.6	151.9	105.8	129.6	100.0	175.2	17.4			80.4	25.0	25.5
17 [d,e]	37.2					147.5	113.4	159.2	110.1	128.5	120.7					80.4	26.0	26.5
18 [e]	37.8	29.5	25.6	30.7	67.8	159.1	114.2	129.3	120.3	129.3	114.2					80.8	25.6	

[a] Carbon atoms are numbered as in Table 1. [b] $\delta(^{13}C)$ in OCH_3, 55.3. [c] $\delta(^{13}C)$ in $N(CH_3)_2$, 40.6. [d] $\delta(^{13}C)$ in OCH_3, 55.1. [e] $\delta(^{13}C)$ in picoline group: 

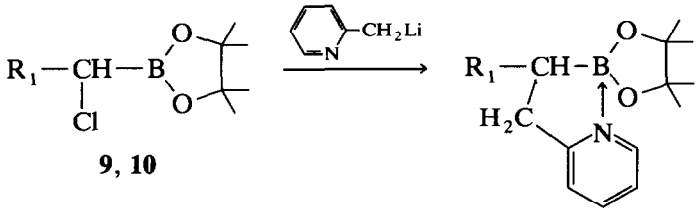
in **17**: C2, 162.0; C3, 122.7; C4, 104.4; C5, 123.7; C6, 142.5; Cα, 39.2. in **18**: C2, 162.3; C3, 121.6; C4, 138.5; C5, 123.4; C6, 144.5; Cα, 38.0.

Table 4

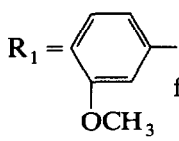
^1H and ^{11}B NMR data of compounds **13–18**

	^1H NMR ($CDCl_3$) δ (ppm *versus* TMS)	^{11}B NMR ($CDCl_3$) δ (ppm *versus* external $BF_3 \cdot OEt_2$)
13	0.88 (s, 6H, CH_3C), 1.01 (s, 6H, $CH_3'C$), 2.07 (s, 3H, CH_3CO), 3.59 (s, 1H, CHB), 3.74 (s, 3H, OCH_3), 6.67–7.32 (m, 4H, arom. and NHCO br. s ~ 7.15)	17.0
14	1.06–1.95 (m, 8H, aliphatic and propanediol CH_2), 2.07 (s, 3H, CH_3CO), 2.58 (br. m, 1H, CHB), 3.92 (m, 6H, $PhOCH_2$ and $BOCH_2$), 6.70–7.40 (m, 5H arom.), 8.50 (br. s, 1H, NH)	11.3
15	1.18 (s, 12H, CH_3C), 1.30–1.80 (m, 6H, CH_2), 2.06 (s, 3H, CH_3CO), 2.36 (br. m, 1H, CHB), 3.92 (t, J = 6.1 Hz, 2H, OCH_2), 6.82–6.92 (m, 3H arom.), 7.23 (m, 2H arom.), 9.90 (br. s, 1H, NH)	13.0
16	1.18 (s, 6H, CH_3C), 1.19 (s, 6H, $CH_3'C$), 1.31–1.76 (m, 6H, CH_2), 2.06 (s, 1H, CH_3CO), 2.38 (br. m, 1H, CHB), 2.90 (s, 6H, CH_3N), 3.92 (dt, J = 6.2 Hz, 2H, OCH_2), 6.24–6.36 (m, 3H arom.), 7.10 (t, J = 8.2 Hz, 1H arom.), 9.74 (br. s, 1H, NH)	14.6
17	1.05 (s, 6H, CH_3C), 1.20 (s, 6H, $CH_3'C$), 2.51 (t, J = 8.1 Hz, 1H, CHB), 3.38 (d, J = 8.1 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.62–7.87 (m, 7H arom.), 8.58 (d, J = 5.3 Hz, 1H pyrid.)	13.6
18	1.22 (s, 12H, CH_3C), 1.35–2.00 (m, 7H, $(CH_2)_3CHB$), 2.95 (m, 2H, CH_2-pyrid.), 3.92 (t, J = 6.2 Hz, 2H, OCH_2), 6.70–7.80 (m, 8H arom.), 8.50 (d, J = 5.3 Hz, 1H pyrid.)	24.8

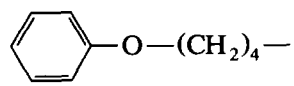
affinity chromatography materials. We purified compound **18** by chromatography on aluminum oxide, but the yield was very low, once again demonstrating that chromatographic methods are very limited when applied to these compounds. We



9, 10 **17, 18**

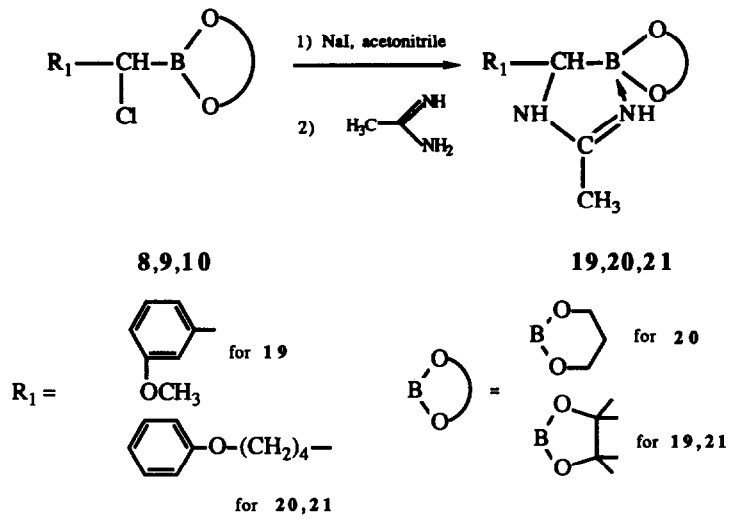


for **17**



for **18**

Scheme 4.

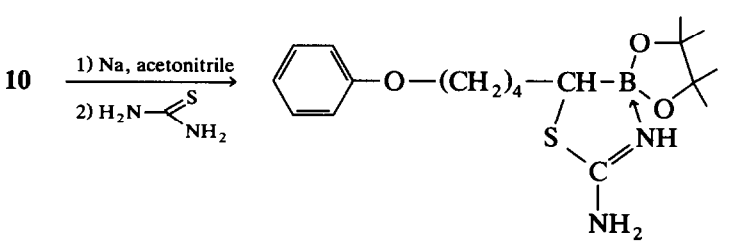


Scheme 5.

found that, in the case of liquids, extraction with hexane left a polymeric material and dissolved the desired compound. After evaporation of hexane, we obtained compounds of sufficient purity for spectral investigations and further synthetic modification.

The structure of these compounds was confirmed by ^{1}H, ^{13}C and ^{11}B NMR spectra, high resolution MS and elemental analyses. In ^{13}C NMR, the position and shape of the peak for the carbon bound to boron provided evidence for the existence of carbon–boron bonds, but did not indicate whether the boron is in a tetrahedral configuration, since the chemical shift of this carbon is determined more by the substituents it carries than by any internal coordination which might be present.

The potential tetrahedral structure of these compounds is, however, supported by ^{11}B NMR. The spectra of the reference organoborates (not containing internal Lewis bases) showed a ^{11}B chemical shift of 35.4 ppm (**23**) and 30.7 ppm (**24**) respectively (Table 6), and were also in the same range for α-chloro-boronic esters (28–31 ppm, Table 2). Similar values are given for aliphatic boronic esters [26]. For the other compounds described in this paper, ^{11}B chemical shifts are in the range 6.8 ppm (**20**) and 24.8 ppm (**18**) (Tables 6 and 4). The ^{11}B chemical shift decreases



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Scheme 6.

in the order: pyridine > acetamido > thiourea > acetamidine, which indicates an increase in coordination for those compounds with an upfield ^{11}B chemical shift. For acetamidine derivatives, the most coordinated compounds, the ^{11}B chemical shift amounts to 6.8 ppm (**20**) and 7 ppm (**19**) (Table 6). In case of pyridine derivatives, the coordination is very weak for compound **18** (24.8 ppm, δ ^{11}B) and stronger for **17** (13.6 ppm, δ ^{11}B) (Table 4).

For accurate investigation of the strength of coordination, we measured the ^{11}B chemical shift as a function of temperature. There were no changes in chemical shift during cooling of compounds **21** and **22** to $-50°C$ in CD_2Cl_2 and small changes for compounds **15** and **17** (^{11}B chemical shift decreases only 3 ppm). Only for the pyridine derivative **18**, which was weakly coordinated (24.8 ppm, δ ^{11}B), did a decrease in temperature cause an apparent increase in coordination (δ ^{11}B, 14 ppm at $-60°C$). These results show that compounds characterized by small (6.8–11.3 ppm) ^{11}B chemical shifts reach the maximum coordination, while an increase of this value indicates weaker coordination.

In compound **16**, boron can intramolecularly coordinate to the oxygen of the acetamide group or intermolecularly to the dimethylamino group. There can also exist a competition in coordination between these two different groups (an equilibrium can exist). However, ^{11}B NMR at room temperature shows the presence of one peak for boron at 14.6 ppm, similar to other acetamido derivatives. Decreasing the temperature does not split this signal, giving further evidence that only intramolecular boron–nitrogen coordination occurs. This is in agreement with our finding that reference compound **23** did not coordinate intermolecularly the *N,N*-dimethylamino group. There were no changes in the ^{11}B chemical shift after adding *N,N*-dimethylaniline to $CDCl_3$ solution of **23**.

The carbon-bound boron gives a small broadened ^{13}C signal which is only possible to observe after a long acquisition time. For 4-phenoxy boronic ester (**23**), the chemical shift of this carbon is 24.6 ppm; for compound **24**, where this carbon is benzylic, the chemical shift is 29.9 ppm (Table 5). In α-chloro-boronic esters (Table 1) the carbon next to boron is shifted to about 42 ppm for aliphatic carbons (compounds **5, 8, 10, 11**), and to 32 ppm for benzylic carbons (compounds **6, 7, 9**). The introduction of a second chlorine shifts this carbon downfield to about 64 ppm (compound **4**).

The introduction of groups like picoline, thiourea, acetamide and acetamidine on the carbon bound to boron causes a downfield shift of this carbon of 13.2 ppm (**18**), 18.6 ppm (**22**), 21.5 ppm (**15**) and 26.4 ppm (**21**), respectively, in comparison with unsubstituted aliphatic reference compound **23** (Tables 3 and 5). A similar change is observed for benzylic compounds. In comparison with compound **24** for the α-picoline derivative (**17**), the downfield shift of the carbon bound to boron is 7.3 ppm, for acetamide derivative (**13**) it is 22.6 ppm and for the acetamidine it is 27.2 ppm (**19**) (see Tables 3 and 5). The ^{13}C chemical shift in acetamido derivatives (**14**) and (**15**) are in agreement with values reported by Matteson and Sadhu [8] for similar compounds.

When 1,3-propanediol (6-membered rings) and pinacol esters (5-membered rings) are compared (compounds **8** and **10**, **7** and **9**, **14** and **15**, **20** and **21**, Tables 1, 3 and 5), there are no differences in ^{13}C chemical shift for the carbon attached to boron. Chemical shifts of the remaining carbons are in the range characteristic for their chemical surroundings. It is interesting that for derivative **19** (Table 5),

Table 5

^{13}C NMR data of compounds [a] **19' 24**, chemical shifts ($\delta(^{13}C)$) in ppm with TMS as internal standard

	Aliphatic chain					Aromatic ring						Acetamidine or thiorea group		Propanediol group		Pinacol group		
	C1	C2	C3	C4	C5	C1′	C2′	C3′	C4′	C5′	C6′	C=NH	CH_3	OCH_2	CH_2	C	CH_3	
19 [b]	57.1					145.1	110.1	159.1	112.8	128.5	119.4	168.0	16.1			78.6	24.4	24.8
																79.1	25.0	25.3
20	51.0	29.3	25.6	31.3	67.6	159.1	114.5	129.3	120.4	129.3	114.5	166.9	16.1	61.4	27.4			
21	51.0	29.4	25.4	31.3	67.9	159.0	114.4	129.4	120.5	129.4	114.4	166.9	16.2			78.5	25.1	
22	43.2	29.2	25.5	33.2	67.9	159.0	114.5	129.4	120.6	129.4	114.5	175.4				79.1	25.6	
23	24.6	24.1	31.8	67.6		159.2	114.5	129.3	120.4	129.3	114.5					83.0	24.8	
24 [c]	29.9					148.1	113.7	159.6	110.1	129.1	120.3			61.9	27.4			

[a] Carbon atoms are numbered as in Table 1. [b] $\delta(^{13}C)$ in OCH_3, 55.1. [c] $\delta(^{13}C)$ in OCH_3, 55.1; in CCH_3, 16.9.

Table 6

^1H and ^{11}B NMR data of compounds **19–24**

	^1H NMR ($CDCl_3$) δ (ppm *versus* TMS)	^{11}B NMR ($CDCl_3$) δ (ppm *versus* external $BF_3 \cdot OEt_2$)
19	0.98 (s, 12H, CH_3C), 1.97 (s, 3H, $NCCH_3$), 3.58 (s, 1H, CHB), 3.75 (s, 3H, OCH_3), 5.50 (br. s, 1H, NH), 6.50–7.40 (m, 4H arom.), 7.75 (br. s, 1H, NH′)	7.0
20	1.00–1.80 (m, 8H, pentane and propanediol CH_2), 1.99 (s, 3H, $NCCH_3$), 2.30 (s, 1H, CHB), 3.93 (m, 6H, $PhOCH_2$ and $BOCH_2$), 6.50 (br. s, 1H, NH), 6.70–7.40 (m, 5H arom.), 7.60 (br. s, 1H, NH′)	6.8
21	1.10 (s, 12H, CH_3C), 1.21–1.81 (m, 6H, CH_2), 2.00 (s, 3H, $NCCH_3$), 2.44 (m, 1H, CHB), 3.96 (t, $J = 6.1$ Hz, OCH_2), 5.75 (s broad, 1H, NH), 6.86–6.93 (m, 3H arom.), 7.10–7.30 (m, 3H, arom. and br. s NH ~ 7.18)	8.6
22	1.09 (s, 3H, CH_3C), 1.12 (s, 3H, CH_3C), 1.13 (s, 3H, CH_3C), 1.15 (s, 3H, CH_3C), 1.37–2.00 (m, 6H, CH_2), 2.38 (m, 1H, SCHB), 3.93 (dt, $J = 6.4$ Hz, 2H, OCH_2), 6.25 (s NH), 6.86–6.94 (m, 3H arom.), 7.23–7.28 (m, 2H arom.)	11.6
23	1.18 (s, 12H, CH_3C), 1.42–2.00 (m, 6H, CH_2), 3.90 (t, $J = 6.2$ Hz, 2H, OCH_2), 6.70–7.45 (m, 5H, arom.)	35.4
24	1.22 (d, $J = 7.7$ Hz, 3H, CH_3), 1.42–2.35 (m, 3H, CH, CH_2), 3.70 (s, 3H, OCH_3), 3.85 (t, $J = 5.4$ Hz, 4H, OCH_2), 6.50–7.40 (m, 4H arom.)	30.7

pinacol quaternary carbons and methyl groups are not magnetically equivalent, since we observed two peaks for quaternary carbons and four for methyl groups. This is a consequence of hindered rotation around the C–B bond and supports our conclusion that the adjacent heteroatom is coordinated in the compound.

Experimental

All reactions were carried out under argon using oven-dried glassware. Melting points are uncorrected. ^1H, ^{13}C and ^{11}B NMR spectra were recorded in $CDCl_3$ on a JEOL FX 90 MHz or Bruker AMX 360 MHz spectrometer. For ^1H and ^{13}C NMR, TMS was used as internal standard ($\delta = 0$ ppm), for ^{11}B NMR the chemical shifts are in ppm relative to $BF_3 \cdot OEt_2$. High resolution mass spectra were obtained on a VG (FISONS) ZAB 2-E mass spectrometer at the University of Texas, Austin, on a VG70770EQ-HF mass spectrometer at the University of Colorado, Boulder and on a KRATOS CONCEPT 1H mass spectrometer at James River Corporation, Neenah, WI. Microanalyses were performed by Atlantic Microlab., Inc., Norcross, GA.

Preparation of α-chloro-boronic esters 5–11

Equimolar amounts of commercial 1.4 *M* methyllithium, 1.8 *M* phenyllithium or Grignard reagents in 20 ml of THF prepared from the appropriate bromide or chloride utilizing accepted synthetic methods [27] were added dropwise with stirring at −75°C to a solution of 5 g (29.6 mmol) of **3** or 5 g (23.7 mmol) of **4** in 60 ml of THF. The mixture was allowed to reach room temperature for 1 h, was kept overnight at 20–25°C, and then was concentrated under vacuum. The residue was dissolved in ether, filtered, evaporated and again dissolved in hexane and filtered.

1,3-Propanediol-1-chloroethane-1-boronate (5). Distillation gave 2.1 g (47.86%) of **5**, b.p. 80–83°C (15 Torr). Anal. Found: C, 40.23; H, 6.58; Cl, 23.68. $C_5H_{10}BO_2Cl$ calc.: C, 40.47; H, 6.79; Cl, 23.89%.

1,3-Propanediol chloro(phenyl)methaneboronate (6). Distillation gave 4.75 g (76.3%) of **6**, b.p. 125–127°C (1 Torr). Anal. Found: C, 57.04; H, 5.75; Cl, 16.93. $C_{10}H_{12}BO_2Cl$: C, 57.07; H, 5.75; Cl, 16.85%.

1,3-Propanediol chloro(3-methoxyphenyl)methaneboronate (7). Evaporation gave 6.30 g (88.7%) of **7**. MS Found: *m/e* 240.0731. $C_{11}H_{14}BO_{11}Cl$ (M^+) calc.: *m/e* 240.0725.

1,3-Propanediol chloro-5-phenoxypentane-1-boronate (8). Evaporation gave 5.14 g (61.5%) of **8**. MS Found: *m/e* 282.1198. $C_{14}H_{20}BO_3Cl$ (M^+) calc.: *m/e* 282.1194.

Pinacol chloro(3-methoxyphenyl)methaneboronate (9). Evaporation gave 5.78 g (86.3%) of **9**. MS Found: *m/e* 282.1198. $C_{14}H_{20}BO_3Cl$ (M^+) calc.: *m/e* 282.1194.

Pinacol chloro-5-phenoxypentane-1-boronate (10). Evaporation gave 7.0 g (90.7%) of **10**. MS Found: *m/e* 324.1659. $C_{17}H_{26}BO_3Cl$ (M^+) calc.: *m/e* 324.1664.

Pinacol chloro-5-(3-dimethylaminophenoxy)pentane-1-boronate (11). Evaporation gave 7.1 g (81.4%) of **11**. MS Found: *m/e* 367.2070. $C_{19}H_{31}BO_3NCl$ (M^+) calc.: *m/e* 367.2086.

1-Chloro-4-(3-dimethylaminophenoxy)butane (12)

Sodium (1.17 g, 51.9 mmol) was added to 40 ml of absolute ethanol. When the reaction was completed, 7.0 g (51.03 mmol) of 3-dimethylaminophenol in 20 ml of absolute ethanol was added. The reaction was heated at reflux to 0.5 h, after which 1-bromo-4-chlorobutane (8.75 g, 51.03 mmol) in 10 ml of absolute ethanol was added to the resulting solution. The mixture was again refluxed for 9 h. After this, the ethanol was evaporated under reduced pressure and the liquid residue was purified by column chromatography on Aldrich silica gel (230–400 mesh ASTM) using a solvent system of ether/petroleum ether 40–60°C (1:5) to give 5.3 g (45.6%) of **12**. MS Found: *m/e* 227.1069. $C_{12}H_{18}ONCl$ (M^+) calc.: *m/e* 227.1077. 90 MHz ^1H NMR ($CDCl_3$): δ 1.92 (m, 4H, CH_2); 2.90 (s, 6H, $N(CH_3)_2$); 3.55 (t, $J = 6.4$ Hz, 2H, CH_2Cl); 3.94 (t, $J = 6.2$ Hz, 2H, OCH_2); 6.27 (m, 3H arom.); 7.12 (m, 1H arom.). 22.6 MHz ^{13}C NMR: δ 26.7, 29.3, 40.5 (NCH_3), 44.6(CH_2Cl), 66.7 (CH_2O), arom. 99.6, 101.9, 105.7, 129.6, 151.9, 159.2.

Preparation of acetamido derivatives 13, 14, 15, 16

1,1,1,3,3,3-Hexamethyldisilazane (2.03 g, 12.6 mmol) in 40 ml of THF was treated with 12.6 mmol of butyllithium in hexane (5.0 ml of 2.5 *M* solution) at 0°C. The mixture was cooled to −70°C and 12 mmol of the appropriate chloride (**8**, **9**, **10**, or **11**) at 10 ml of THF was added at once. The mixture was allowed to reach

room temperature and after mixing for 5 h at this temperature, the mixture was cooled again to −70°C and 3.86 g (37.8 mmol) of acetic anhydride, followed by 0.81 g (12.6 mmol) of acetic acid was added. For compound **11**, a two-fold excess (25.2 mmol) of acetic acid was added. The mixture was kept overnight at 20–25°C and concentrated under vacuum. The residue was dried at 80°C under 0.02 Torr for 1 h and the resulting crude product was extracted with hexane and the extract discarded.

Pinacol acetamido(3-methoxyphenyl)methaneboronate (13). The residue was crystallized from ether to yield 2.6 g (71%) of **13**, m.p. 178–180°C. Anal. Found: C, 62.71, H, 8.00, N, 4.56. $C_{16}H_{24}BO_4N$ calc.: C, 62.97, H, 7.93, N, 4.59%.

1,3-Propanediol 1-acetamido-5-phenoxypentane-1-boronate (14). The residue was dissolved in dichloromethane, filtered, and crystallized from dichloromethane/hexane (1:5) at −10°C to yield 1.20 g (32.8%) of **14** (oil at room temp.). MS Found: *m/e* 305.1804. $C_{16}H_{24}BO_4N$ (M^+) calc.: *m/e* 305.1798. Anal. Found: C, 62.32; H, 7.91; N, 4.68. $C_{16}H_{24}BO_4N$ calc.: C, 62.97; H, 7.93; N, 4.59%.

Pinacol 1-acetamido-5-phenoxypentane-1-boronate (15). The residue was dissolved in ether, filtered, and crystallized from ether/hexane to yield 3.18 g (76.3%) of **15**, m.p. 110–112°C. Anal. Found: C, 65.82; H, 8.77; N, 4.08. $C_{19}H_{30}BO_4N$ calc.: C, 65.72; H, 8.77; N, 4.08%.

Pinacol 1-acetamido-5-(3-dimethylaminophenoxy)pentane-1-boronate (16). The residue was extracted three times with 10 ml of hexane. The first fraction was discarded, and the last two fractions were evaporated to yield 1.55 g (33.1%) of **16**. MS Found: *m/e* 390.2683. $C_{21}H_{35}BO_4N_2$ (M^+) calc.: *m/e* 390.2690.

Preparation of pyridyl substituted boronic esters 17 and 18

Phenyllithium in cyclohexane/ether (7:3) (5.3 mmol, 2.94 ml, 1.8 mol solution) was added to 0.49 g (5.3 mmol) of α-picoline dissolved in 5 ml of THF. The mixture was stirred at room temperature for 1 h [23]. This mixture was added dropwise with stirring to solution of 5.3 mmol of chloride **9** or **10** in 20 ml of THF at −70°C. The resulting solution was kept 20 h at 20–25°C and mixed for an additional 2 h with 2 g of sodium bicarbonate. The mixture was filtered and concentrated under vacuum. The residue was dissolved in chloroform, filtered and evaporated.

Pinacol 1-(3-methoxyphenyl)-2-(2-pyridyl)ethane-1-boronate (17). Crystallization from hexane gave 1.65 g (89.4%) of **17**, m.p. 70–72°C. Anal. Found: C, 68.99; H, 7.87; N, 4.05. $C_{20}H_{26}BO_3N \cdot 1/2\ H_2O$ calc.: C, 68.98; H, 7.81; N, 4.02%.

Pinacol 6-(phenoxy)-1-(2-pyridyl)-hexane-2-boronate (18). Extraction with ether, evaporation and a second extraction with hexane and evaporation gave 1.3 g (64.4%) of **18**. An analytical sample (0.3 g) was further purified by column chromatography on Aldrich aluminum oxide, activated neutral Brockman I (~ 150 mesh) using THF/ether (1:20) as the solvent system to give 0.05 g (16.6%) of **18**. MS Found: *m/e* 381.2458. $C_{23}H_{32}BO_3N$ (M^+) calc.: *m/e* 381.2475.

Preparation of acetamidino derivatives 19, 20, 21

Sodium iodide (3.6 g, 24 mmol) was added to a solution of 24 mmol of chloride **8**, **9**, or **10** in 40 ml of dry acetonitrile. The resulting suspension was mixed at room temperature for 8 h. In another flask, 55.2 mmol of butyllithium in hexane (22.1 ml of 2.5 *M* solution) was added to a suspension of 5.2 g (55.2 mmol) of acetamidine

hydrochloride in 50 ml of THF at −70°C. The mixture was stirred for 0.5 h at 0°C, was again cooled to −70°C and the iodide prepared from chloride **8**, **9** or **10** was added. The mixture was kept overnight at 20–25°C and concentrated under vacuum. The residue was then treated with 17 ml of water and extracted three times with 200 ml of methylene chloride. The organic phase was concentrated to give a solid residue, which was crystallized from ether/hexane to give the following.

*Pinacol acetamidino(3-methoxyphenyl)methaneboronate (**19**).* 4.1 g (56.2%) of **19**, m.p. 172–174°C. MS Found: *m/e* 304.1973. $C_{16}H_{25}BO_3N_2$ (M^+) calc.: *m/e* 304.1958. Anal. Found: C, 62.70; H, 8.32; N, 9.38. $C_{16}H_{25}BO_3N_2$ calc.: C, 63.18; H, 8.28; N, 9.21%.

*1,3-Propanediol 1-acetamidino-5-phenoxypentane-1-boronate (**20**).* 2.59 g (35.5%) of **20**, m.p. 85–88°C. MS Found: *m/e* 304.1976. $C_{16}H_{25}BO_3N_2$ (M^+) calc.: *m/e* 304.1958. Anal. Found: C, 62.54; H, 8.21; N, 9.40. $C_{16}H_{25}BO_3N_2$ calc.: C, 63.18; H, 8.28; N, 9.21%.

*Pinacol 1-acetamidino-5-phenoxypentane-1-boronate (**21**).* 3.51 g (42.2%) of **21**, m.p. 67–70°C. MS Found: *m/e* 346.2409. $C_{19}H_{31}BO_3N_2$ (M^+) calc.: *m/e* 346.2428. Anal. Found: C, 65.40; H, 8.83; N, 8.22. $C_{19}H_{31}BO_3N_2$ calc.: C, 65.90; H, 9.02; N, 8.09%.

*Pinacol 1-thiourea-5-phenoxypentane-1-boronate (**22**)*

Sodium iodide (0.69 g, 4.61 mmol) was added to a solution of 1.5 g (4.61 mmol) of chloride **10** in 40 ml of dry acetonitrile. The resulting suspension was mixed for 4 h at room temperature, thiourea (0.35 g, 4.61 mmol) was added and mixing was continued at room temperature for 72 h. After this, 2 g of sodium carbonate was added and the resulting suspension was stirred for an additional 24 h. This mixture was then filtered and concentrated under vacuum. Extraction with ether, filtration and precipitation with hexane gave 1.22 (74.9%) of **22**. Anal. Found: C, 58.29; H, 8.15; N, 7.53; 8.69. $C_{18}H_{29}BO_3N_2S\ H_2O$ calc.: C, 58.20; H, 8.41; N, 7.54; S, 8.62%.

*Pinacol 4-phenoxybutane boronate (**23**)*

4-Phenoxybutyl bromide (10 g, 43.65 mmol) was dissolved in 20 ml of THF. To this solution, 1.06 g (43.65 mmol) of magnesium turnings was added. The resulting suspension was mixed and heated at reflux for 2 h, after which the magnesium was nearly consumed. The resulting Grignard reagent was diluted with 10 ml of THF and added dropwise to a solution of 4.96 g (47.7 mmol) of trimethyl borate in 40 ml of THF stirred at −75°C and stirring was continued for 4 h at 20–25°C. The reaction mixture was hydrolysed with 8 ml of 5 *N* hydrochloric acid. After addition of 20 ml of hexane, the organic layer was separated and the water layer was extracted 3×10 ml of ether. The combined organic layers were concentrated under vacuum. The residue was dissolved in 100 ml of ether and 4.56 g (38.6 mmol) of pinacol was added. The resulting solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Filtration, followed by vacuum distillation, gave 6.2 g (51.5%) of **23**, b.p. 118–120 (0.5 Torr). MS Found: *m/e* 276.1904. $C_{16}H_{25}BO_3$ (M^+) calc.: *m/e* 276.1897.

*1,3-Propanediol 1-(3-methoxyphenyl)ethane-1-boronate (**24**)*

3-Bromoanisole (1.279 g, 6.84 mmol) was dissolved in 5 ml of THF. One milliliter of this solution was added to 0.166 g (6.84 mmol) of magnesium turnings

with stirring. After a few minutes, the reaction was initiated and reflux started. Once the reaction had begun, a solution of 3-bromoanisole was added at a rapid dropwise rate, and the reaction allowed to proceed at reflux. Upon completion of addition, the reaction was further heated at reflux for 3 h, after which the magnesium was nearly consumed. The resulting Grignard reagent was diluted with 5 ml of THF and was added dropwise to a solution of 0.966 g (6.51 mmol) of 1,3-propanediol 1-chloroethane-1-boronate in 20 ml of THF stirred at −75°C. The mixture was kept overnight at 20–25°C and concentrated under vacuum. The residue was dissolved in ether, filtered and, after concentration, distilled. It yielded 0.9 g (67.7%) of **24**, b.p. 130°C (0.01 Torr). MS Found: *m/e* 220.1267. $C_{12}H_{17}BO_3$ (M^+) calc.: *m/e* 220.1271.

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References

1 A. Bergold and W.H. Scouten, in W.H. Scouten, Ed., Solid Phase Biochemistry, Wiley, New York, 1983, pp. 149–187.
2 J.R. Mazzero and J.S. Krull, Biochromatography, 4 (1989) 124.
3 R.J. Rotman and R.J. Waren, Biochim. Biophys. Acta, (1988) 143.
4 J.P. Lorand and J.O. Edwards, J. Org. Chem., 24 (1959) 769.
5 D.S. Matteson and Tai-Chun Cheng, J. Org. Chem., 33 (1968) 3055.
6 D.S. Matteson and G.D. Schaumberg, J. Org. Chem., 31 (1966) 726.
7 D.S. Matteson and G.D. Schaumberg, J. Organomet. Chem., 8 (1967) 359.
8 D.S. Matteson and K.M. Sadhu, Organometallics, 3 (1984) 614.
9 M. Lauer and G. Wulff, J. Organomet. Chem., 256 (1983) 1.
10 M. Lauer and G. Wulff, J. Chem. Soc., Perkin Trans. 2, (1987) 745.
11 H.C. Brown and J.V.N. Vara Prasad, J. Org. Chem., 51 (1986) 4526.
12 R.P. Singhal, B. Ramamurthy, N. Govindraj and Y. Sarwar, J. Chromatogr., 543 (1991) 17.
13 G. Wulff, Pure Appl. Chem., 54 (1982) 2093.
14 F. Negishi, Organic Reactions, 33 (1985) 1.
15 D.S. Matteson, K.M. Sadhu, R. Ray, M.L. Peterson, D. Majumdar, G.D. Hurst, P.K. Jesthi, D.J.S. Tsai and E. Edrik, Pure Appl. Chem., 57 (1985) 1741.
16 D.S. Matteson, K.M. Sadhu and M.L. Peterson, J. Am. Chem. Soc., 108 (1986) 810.
17 D.S. Matteson, Synthesis, (1986) 973.
18 M.W. Rathke, E. Chao and G. Wu, J. Organomet. Chem., 122 (1976) 145.
19 G.M. Wuts and P.A. Thompson, J. Organomet. Chem., 234 (1982) 137.
20 D.J.S. Tsai and P.K. Jesthi, Organometallics, 2 (1983) 1543.
21 D.J. Pasto, J. Chow and S.K. Arora, Tetrahedron, 25 (1969) 1557.
22 D.S. Matteson and P.K. Jesthi, K.M. Sadhu, Organometallics, 3 (1984) 1284.
23 L.A. Walter, Organic Syntheses, 3 (1955) 757.
24 K. Torsell and E.N. Larsson, Acta Chem. Scand., 2 (1957) 404.
25 D.S. Matteson, R. Ray, R.R. Rocks and D.J.S. Tsai, Organometallics, 2 (1983) 1536.
26 B. Wrackmeyer, Annu. Rep. NMR Spectrosc., 20 (1988) 61.
27 H.E. Ramsden, A.F. Balint, W.R. Whitfort, J.J. Wolburn and R. Cserr, J. Org. Chem., 22 (1957) 1202.