

II. 1,3-Dipolar cycloadditions to unsaturated boronic esters [☆]. Synthesis of borylated 2-isoxazolines. Conversion of some cycloadducts to 5-hydroxy-2-isoxazolines, 5-hydroxymethyl-2-isoxazolines and isoxazoles

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Abstract

A variety of borylated 2-isoxazolines was prepared by 1,3-cycloaddition reactions of nitrile oxides to vinyl- and allylboronic esters. The influence of substituents on the reactivity, the regio- and stereoselectivity was examined and some examples of cycloadduct oxidation were described.

Keywords: Boron; 2-Isxazolines; Synthesis; Cycloaddition; Isoxazoles

1. Introduction

1,3-Dipolar cycloaddition is one of the most powerful methods for the construction of five-membered heterocycles [2]. In particular, nitrile oxide reactions have proven particularly useful in the synthesis of 2-isoxazolines and isoxazoles and the subsequent conversions of these heterocycles, for example, to β -hydroxyketones or γ -aminoalcohols, has provided important synthetic alternatives to the stereoselective aldol and related reactions [2,3]. Much attention has been also focused on unsaturated organoboranes. The reactivity of the double bond is greatly influenced by the presence of the boron atom and, moreover, organoboranes are also versatile precursors of alcohols, aldehydes, carboxylic acids, amines, etc. [4].

We have recently shown that alkenylboranes were good partners in Diels-Alder [5], cyclopropanation [6], iodosulfonation [7] reactions, and diazoalkane 1,3-dipolar cycloadditions [1,8a]. Thirty years ago, Grünanger et al. reported very briefly the cycloaddition of three

arylnitrile oxides to dibutylvinyl boronic ester [9]. Since then, to the best of our knowledge, no supplementary data has been published. This led us to begin a more detailed study of this promising route to borylated 2-oxazolines [8a,8b]. The recent publications of Wallace et al. on this subject prompted us to report our results in this field [10].

2. Results and discussion

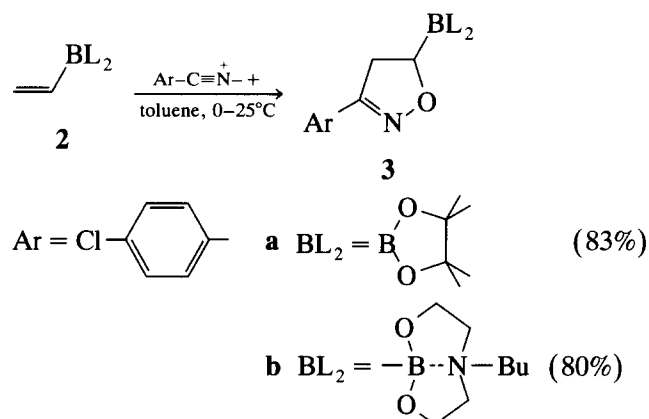
Nitrile oxides **1** were generated either by treatment of the hydroxamic acid chlorides with triethylamines [11] or by dehydration of primary nitroalkanes [12]. Alkenylboronic esters **2** were prepared by hydroboration of the corresponding alkynes with dibromoborane-dimethylsulfide complex [13], pinacolborane [14], diisopinocampheylborane [15], catecholborane [16] or by borylation of alkenyl organometallic derivatives [17].

For our study of the cycloaddition of nitrile oxides to unsaturated organoboranes, we selected boronic esters **2** ($BL_2 = B(OR)_2$) which are easy to prepare and to handle. Several attempts to increase the reactivity of the double bond by introducing of a better electron-withdrawing group, such as 9-BBN, $-BX_2$ ($X = \text{halogen}$)

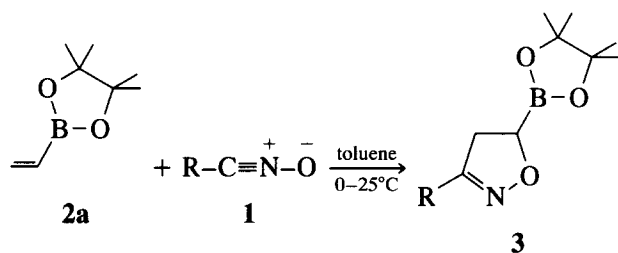
[☆] For part I see Ref. [1].

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or *B*-catechol [18–20] were unsuccessful. This suggests that the Lewis acidity of such derivatives is responsible for preferential decomposition of the 1,3 dipole, rather than favouring cycloaddition reaction. However, a good yield was obtained with the boratrane **2b** that could be useful, for example, if it was necessary to generate or to use an organolithium in a further transformation of the cycloadduct [21].

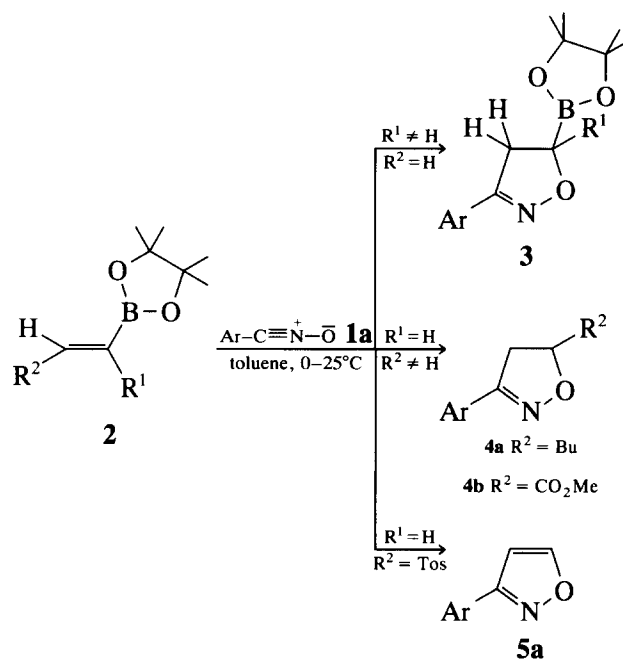


We began our investigation with the cycloaddition of various nitrile oxides to the parent vinylboronate **2a**, derived from pinacol. The corresponding 5-boronic ester-2-isoxazolines were obtained regioselectively in good yields (Table 1).

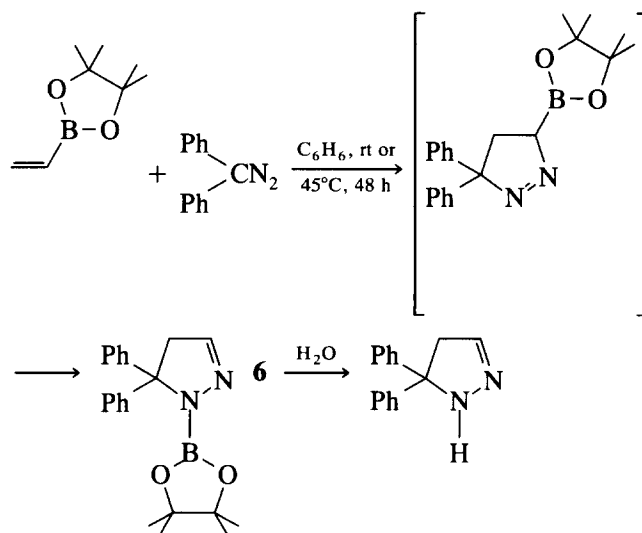


Our next goal was to investigate the 1,3-dipolar cycloaddition of a selected nitrile oxide, 4-chlorobenzonitrile oxide, **1a**, to various alkenylboronic esters (Table 2). Mono- and 1,1-di-substituted olefins produced a single 5-boronic ester-2-isoxazoline (entries 1–3). With a trisubstituted compound no adduct was isolated (entry

4). 1,2-Disubstituted alkenylboronates ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bu}^n$, CO_2Me , or SO_2Ar) yielded no corresponding cycloadducts, and only 2-isoxazolines **4a**, **4b** and isoxazole **5a** were obtained after work up.



The production of **3a**, **3i** and **3j** is consistent with the usual regioselectivity observed in nitrile oxide cycloadditions [3]. The results of the other cycloadditions were more surprising, mainly because of the loss of the boronic ester functionality. We and others [22] have already mentioned a similar behaviour when diazocompounds react with the vinylboronic ester, **2a**. After formation of a primary cycloadduct, a spontaneous 1,3-boratrophy occurred giving a 1-borylated 2-pyrazoline. The structure of **6** was established unambiguously by X-ray diffraction analysis [1].



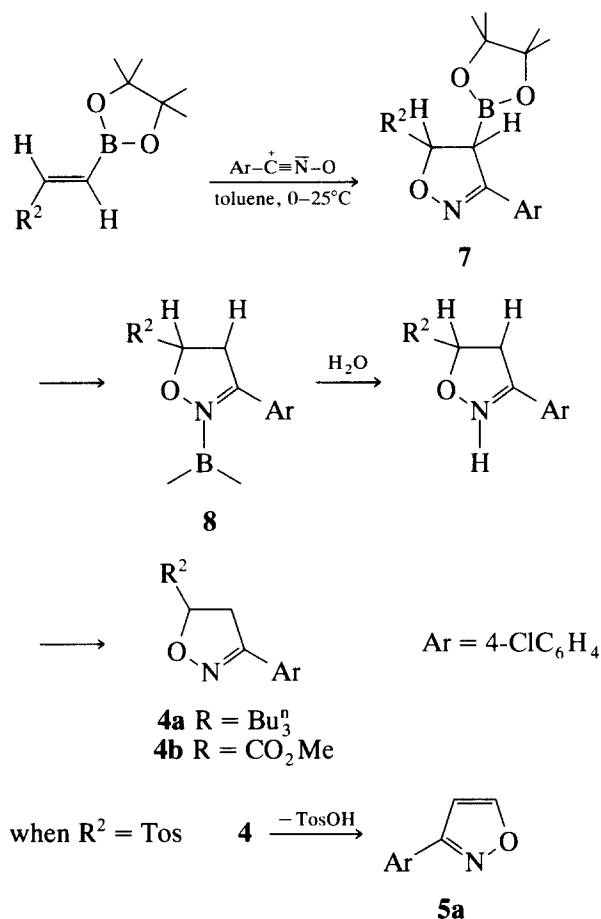
We therefore rationalized the production of **4a**, **4b** and **5a** by a highly regioselective cyclization of 4-chlo-

Table 1
Cycloadditions of nitrile oxides to vinylboronic ester **2a**

Entry	2-Isxazoline	R	Method ^a	Yield (%) ^b
1	3a	4-Cl-C ₆ H ₄	A	83
2	3c	Me	B	66
3	3d	<i>t</i> -Bu	B	61
4	3e	CO ₂ Et	B	70
5	3f	COMe	B	61
6	3g	(CH ₂) ₃ -CO ₂ Me	B	67
7	3h	CH ₂ CH(OCH ₃) ₂	C	70

^a Method A, isolated nitrile oxide generated from hydroxamic acid chloride and triethylamine; method B, in situ generation from the same reagents; method C, in situ generation from nitroalkane, phenylisocyanate, triethylamine. ^b Isolated yield.

robenzonitrile oxide to alkenylboronic esters **2** ($R^1 = H$, $R^2 = Bu^n$, CO_2Me , or $ArSO_2$) which afforded 4-boronic ester-2-isoxazoline **7** [23]. A spontaneous 1,3 boron migration then occurred, giving **8**, very labile to protonolysis. After work-up, only **4a** and **4b** were isolated. When $R^1 = Tos$ and $R^2 = H$, the additional elimination of $TosOH$ yielded the isoxazole **5a** as only boronic ester [24]. Such a high regioselectivity in a nitrile oxide cycloaddition to a 1,2-disubstituted alkene was quite unexpected since electron-withdrawing groups usually show smaller directing effect [3]. Further investigations are necessary to rationalize these experimental results.



The structures of 2-isoxazolines **3a–3h** were determined on the basis of diagnostic 1H and ^{13}C NMR data and elemental analysis or mass spectra. **4a** and **4b** were prepared unequivocally by reaction of 4-chlorobenzonitrile oxide **1a** with hex-1-ene and methyl acrylate, respectively [3]. **5a** was obtained by oxidation of **3a** (vide infra).

We were interested in extending this work and exploring the reactivity of allylorganoboranes. Allylboronic esters **9** were synthesized from the appropriate allylmagnesium compound [25] or by reaction of α -chloroboronic esters with vinylmagnesium chloride [26]. Like their alkenyl analogues, boronic esters are good

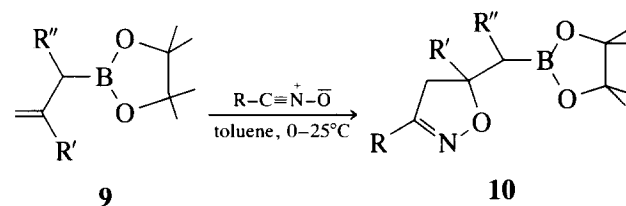
Table 2

Cycloaddition of 4-chlorobenzonitrile oxide to vinylboronic esters **2**

Entry	Cycloadducts	R^1	R^2	Yield (%) ^a
1	3a	H	H	83
2	3i	Me	H	84
3	3j	Ph	H	88
4	3k		$(CH_2)_4$	0
5	4a	H	Bu	60
6	4b	H	MeOCO	58
7	5a	H	Tos	^b

^a Isolated yield. ^b Not determined. **5a** was the only boronic ester detected in the crude mixture.

candidates for such cycloadditions. Yields after purification are moderate-to-good and single regioisomers were obtained. Mixtures of diastereoisomers **10'** + **10''** were produced in cycloadditions of 4-chlorobenzonitrile oxide to α -chiral allylboronic esters whether $R'' = Cl$, n -Hex or c -Pent (Table 3). The structures of 2-isoxazolines **10a–10f** were determined on the basis of diagnostic 1H , ^{13}C NMR data and elemental analysis or mass spectra. For **10d–10f**, we did not try to assign the exact stereochemistry of the major isomers.



3. Oxidation of 2-isoxazolines **3** and **10**

Previous studies had established the ready cleavage of B–C bonds by oxidation giving alcohols. Our products are no exception. The 2-isoxazolines **3** and **10** were subjected to oxidation with 30% w/w H_2O_2 in THF in the presence of a phosphate buffer and afforded 5-hydroxy- or 5-hydroxymethyl-2-isoxazolines **11**. Analo-

Table 3

Cycloaddition of nitrile oxide to allylboronic esters **9**

Entry	2-Isoxazoline	R	R'	R''	Yield (%) ^a	10' / 10'' ^b
1	10a	$Cl-C_6H_4$	H	H	91	–
2	10b	t -Bu	H	H	58	–
3	10c	$Cl-C_6H_4$	Me	H	67	–
4	10'd + 10''d	$Cl-C_6H_4$	H	Cl	70	65/35
5	10'e + 10''e	$Cl-C_6H_4$	H	n -Hex	67	55/45
6	10'f + 10''f	$Cl-C_6H_4$	H	c -Pent	60	65/35

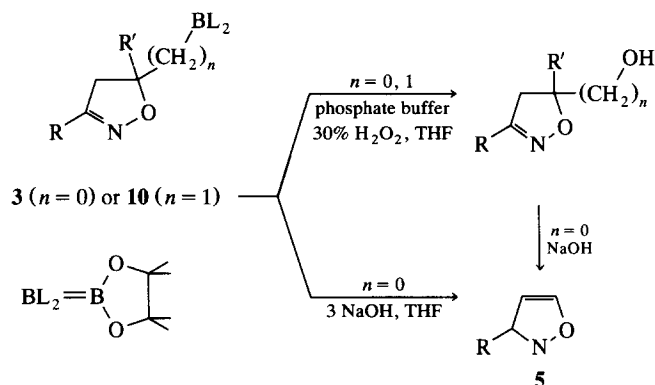
^a Isolated yield. ^b Determined by 300 MHz 1H NMR analysis.

Table 4
Oxidation of 2-isoxazolines **3** and **10**

Entry	2-Isoxazoline	R	R'	n	Yield (%) ^a
1	11a	4-ClC ₆ H ₄	H	0	62
2	11b	CH ₃	H	0	61
3	11c	(CH ₃) ₃ C	H	0	59
4	11d	CO ₂ CH ₃	H	0	62
5	11e	(CH ₂) ₃ CO ₂ CH ₃	H	0	63
6	11f	CH ₂ CH(OCH ₂) ₃	H	0	60
7	11g	4-ClC ₆ H ₄	H	1	71
8	11h	4-ClC ₆ H ₄	Me	1	68
9	5a	4-ClC ₆ H ₄	H	0	62
10	5b	(CH ₂) ₂ CH ₂ CO ₂ H ^b	H	0	65
11	5c	CH ₂ CH(OCH ₃) ₂	H	0	61

^a Isolated yield. ^b Under these experimental conditions, the ester was saponified.

gous treatment of **3** in the presence of 3-M NaOH instead of a buffer afforded isoxazoles **5** (Table 4).



In conclusion, we have prepared various 2-isoxazolines by 1,3-dipolar cycloaddition of nitrile oxides to the corresponding α,β - or β,γ -unsaturated boronic esters. Oxidative deborylation of these cycloadducts provided an efficient route to 5-hydroxy- or 5-hydroxyalkyl-2-isoxazolines, or to isoxazoles depending on the experimental conditions. Other studies involving both boron and isoxazolines are now in progress in our laboratory.

4. Experimental details

¹H and ¹³C NMR spectra were recorded on a Bruker AM 300 Spectrometer (75.5 MHz for carbon, 96.3 MHz for boron). Mass spectra were measured at 70 eV on a Varian MAT 311 (Centre Régional de Mesures Physiques de l'Quest). Starting materials were prepared according to reported procedures: for alkenylboronic esters, reaction of vinylmagnesium bromide, propen-2-yl-magnesium bromide, or 1-phenylvinylmagnesium bromide with trimethylborate followed by hydrolysis and treatment with pinacol [17] hydroboration of hex-1-ene with HBBR₂:SMe₂ followed by hydrolysis and treatment with pinacol [13] hydroboration of methylpropionate with diisopinocampheylborane followed by successive treatment with acetaldehyde and pinacol [15]

iodosulfonylation of vinylboronic ester **2a** followed by dehydrohalogenation with triethylamine [7]. For allylboronic esters, reaction of allylmagnesium bromide or metallylmagnesium chloride with trimethylborate followed by treatment with pinacol [25] addition of vinylmagnesium bromide to α -chloroalkylboronic esters [26]. Boratrane **2b** was obtained by mixing the parent vinylboronic ester derived from 1-butanol [17] and *N*-butyldiethanolamine (0.95 equiv.). After concentration under reduced pressure, **2b** was distilled at 10⁻² mm Hg. B.p. = 75–80°C, yield = 70%. ¹H NMR (CDCl₃): δ 0.96 (t, 3H, *J* = 7.4), 1.27–1.40 (m, 2H), 1.57–1.68 (m, 2H), 2.66–2.75 (m, 2H), 2.85–3.05 (m, 4H), 3.88–4.06 (m, 4H), 5.60 (dd, 1H, *J* = 4.9 and 12.7), 5.66 (dd, 1H, *J* = 4.9 and 19.5), 5.91 (dd, 1H, *J* = 12.7 and 19.5). ¹³C NMR (CDCl₃): δ 13.8 (CH₃), 20.3 (CH₂), 26.8 (CH₂), 57.2 (CH₂), 58.9 (CH₂), 62.4 (CH₂), 126.3 (CH₂), 140.8 (CH). ¹¹B NMR (CDCl₃): δ 11.6 ppm.

4.1. Cycloadditions of nitrile oxides

4.1.1. General procedure for the preparation of 2-isoxazolines **3** and **10** from hydroximoyl chlorides

A solution of 4-chlorobenzonitrile oxide [27] **1** (5 mmol) and alkenyl- or allylborane **2** or **9** (5 mmol) in dry toluene (10 ml) was stirred at 0°C for 1 h and at 25°C for 16 h. The nitrile oxide can also be generated *in situ* by addition of triethylamine (5 mmol) to a solution of hydroximoyl chloride [28] (5 mmol) in dry toluene (10 ml). The resultant mixture was washed with water and dried with magnesium sulfate. The solution was concentrated and the product purified by distillation, recrystallisation, or flash chromatography on silica gel.

4.1.2. General procedure for the preparation of 2-isoxazolines **3** and **10** from nitroalkanes

To a solution of alkenyl- or allylboronic ester **2** or **9** (5 mmol) and phenyl isocyanate (9 mmol) in dry toluene (10 ml) was added over 10 min a solution of nitroalkane (6 mmol) in 5 ml of dry toluene and several drops of triethylamine. After the mixture was stirred for 16 h at 25°C, it was diluted with ether (20 ml) and filtered. After concentration of the filtrate, the residue was purified by distillation or flash chromatography on silica gel.

3a: Yield 83%, m.p. 87°C. ¹H NMR (CDCl₃): δ 1.32 (s, 12H), 3.27 (dd, 1H, *J* = 14.7 and 15.9), 3.45 (dd, 1H, *J* = 11.8 and 15.9), 4.26 (dd, 1H, *J* = 11.8 and 14.7), 7.33–7.63 (AA'BB' system, 4H). ¹³C NMR (CDCl₃): δ 24.7 (CH₃), 24.8 (CH₃), 37.8 (CH₂), 68.7 (CH), 84.7 (C), 128.1 (CH), 128.3 (C), 128.9 (CH), 135.7 (C), 155.6 (C). Anal. Found: C, 58.9, H, 6.4, N, 4.6%. Calc. for C₁₅H₁₉BCINO₃ C, 58.57, H, 6.23, N, 4.55%.

3b: Yield 80%, m.p. 184°C. ¹H NMR (CDCl₃): δ

0.98 (t, 3H, $J = 7.3$), 1.32–1.47 (m, 2H), 1.60–1.74 (m, 2H), 2.92–3.44 (m, 8H), 3.91–4.10 (m, 5H), 7.32–7.62 (AA'BB' system, 4H). ^{13}C NMR (CDCl_3): δ 13.9 (CH_3), 20.3 (CH_2), 26.7 (CH_2), 38.5 (CH_2), 57.2 (CH_2), 57.4 (CH_2), 57.8 (CH_2), 62.1 (CH_2), 62.5 (CH_2), 75.8 (CH), 128.0 (CH), 128.9 (C), 129.1 (CH), 135.1 (C), 155.7 (C). Anal. Found: C, 57.9, H, 7.1, N, 7.7%. Calc. for $\text{C}_{17}\text{H}_{24}\text{BClN}_2\text{O}_3$: C, 58.23, H, 6.90, N, 7.99%.

3c: Yield 66%, b.p. 40–45°C at 10^{-2} mm Hg. ^1H NMR (CDCl_3): δ 1.29 (s, 12H), 2.02 (s, 3H), 2.89 (dd, 1H, $J = 14.8$ and 16.3), 3.02 (dd, 1H, $J = 11.4$ and 16.3), 4.03 (dd, 1H, $J = 11.4$ and 14.8). ^{13}C NMR (CDCl_3): δ 12.9 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 41.7 (CH_2), 67.2 (CH), 84.5 (C), 155.5 (C). Anal. Found: C, 56.6, H, 8.8, N, 6.4%. Calc. for $\text{C}_{10}\text{H}_{18}\text{BNO}_3$: C, 56.91, H, 8.60, N, 6.64%.

3d: Yield 61%, b.p. 55–60°C at 10^{-2} mm Hg. ^1H NMR (CDCl_3): δ 1.29 (s, 12H), 2.02 (s, 9H), 2.89 (dd, 1H, $J = 14.9$ and 15.9), 3.02 (dd, 1H, $J = 10.9$ and 15.9), 4.03 (dd, 1H, $J = 10.9$ and 14.9). ^{13}C NMR (CDCl_3): δ 24.6 (CH_3), 28.2 (CH_3), 32.9 (C), 37.5 (CH_2), 67.9 (CH), 84.4 (C), 165.9 (C). HRMS m/z calc. for $\text{C}_{13}\text{H}_{24}^{11}\text{BNO}_3$: 253.1849; Found: 253.185.

3e: Yield 70%, b.p. 40–45°C at 10^{-3} mm Hg. ^1H NMR (CDCl_3): δ 1.29 (s, 12H), 1.36 (t, 3H, $J = 7.0$), 3.10 (dd, 1H, $J = 14.9$ and 16.8), 3.37 (dd, 1H, $J = 12.5$ and 16.8), 4.32 (dd, 1H, $J = 12.5$ and 14.9), 4.34 (q, 2H, $J = 7.0$). ^{13}C NMR (CDCl_3): δ 14.1 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 36.5 (CH_2), 61.9 (CH_2), 71.5 (CH), 84.1 (C), 151.2 (C), 160.8 (C). Anal. Found: C, 53.6, H, 7.5, N, 5.0%. Calc. for $\text{C}_{12}\text{H}_{20}\text{BNO}_5$: C 53.56, H 7.49, N 5.20%.

3f: Yield 61%, b.p. 40–45°C at 10^{-2} mm Hg. ^1H NMR (CDCl_3): δ 1.27 (s, 12H), 2.47 (s, 3H), 2.95 (dd, 1H, $J = 14.6$ and 16.8), 3.29 (dd, 1H, $J = 12.7$ and 16.9), 4.29 (dd, 1H, $J = 12.7$ and 14.6). ^{13}C NMR (CDCl_3): δ 24.7 (CH_3), 24.8 (CH_3), 26.2 (CH_3), 34.9 (CH_2), 71.9 (CH), 84.9 (C), 158.2 (C), 193.1 (C). Anal. Found: C 55.0, H 7.5, N 6.1%. Calc. for $\text{C}_{11}\text{H}_{18}\text{BNO}_4$: C 55.36, H 7.53, N 5.86%.

3g: Yield 67%. ^1H NMR (CDCl_3): δ 1.28 (s, 12H), 1.92 (quint, 2H, $J = 7.4$), 2.34–2.45 (m, 4H), 2.88 (dd, 1H, $J = 14.8$ and 16.1), 3.01 (dd, 1H, $J = 11.3$ and 16.1), 3.70 (s, 3H), 4.02 (dd, 1H, $J = 11.3$ and 14.8). ^{13}C NMR (CDCl_3): δ 21.5 (CH_2), 24.6 (CH_3), 24.7 (CH_3), 27.0 (CH_2), 33.1 (CH_2), 40.5 (CH_2), 51.5 (CH_3), 67.2 (CH), 84.5 (C), 157.9 (C), 173.4 (C). HRMS m/z Calc. for $\text{C}_{14}\text{H}_{24}^{11}\text{BNO}_5$: 297.1747. Found: 297.174.

3h: Yield 70%. ^1H NMR (CDCl_3): δ 1.29 (s, 12H), 2.68 (dd, 1H, $J = 5.6$ and 14.8), 2.75 (dd, 1H, $J = 5.6$ and 14.8), 3.08 (dd, 1H, $J = 15.0$ and 16.4), 3.08 (dd, 1H, $J = 11.3$ and 16.4), 3.35 (s, 3H), 3.36 (s, 3H), 4.04 (dd, 1H, $J = 11.3$ and 15.0), 4.59 (t, 1H, $J = 5.6$). ^{13}C NMR (CDCl_3): δ 24.6 (CH_3), 24.7 (CH_3), 31.4 (CH_2),

40.5 (CH_2), 53.3 (CH_3), 67.4 (CH), 84.4 (C), 102.3 (CH), 155.2 (C). HRMS m/z Calc. for $\text{C}_{13}\text{H}_{24}\text{BNO}_5$: 285.1747. Found: 285.174.

3i: Yield 84%, m.p. 98°C. ^1H NMR (CDCl_3): δ 1.30 (s, 12H), 1.35 (s, 3H), 3.00 (d, 1H, $J = 16.2$), 3.44 (d, 1H, $J = 16.2$), 7.33–7.62 (AA'BB' system, 4H). ^{13}C NMR (CDCl_3): δ 23.5 (CH_3), 24.7 (CH_3), 44.3 (CH_2), 84.7 (C), 128.0 (C), 128.6 (C), 128.8 (C), 135.6 (C), 154.2 (C) ppm (the resonance of the carbon α to boron was not detected). HRMS m/z Calc. for $\text{C}_{16}\text{H}_{21}^{11}\text{BClNO}_3$: 321.1303. Found: 321.133.

3j: Yield 88%, m.p. 154°C. ^1H NMR (CDCl_3): δ 1.25 (s, 6H), 1.27 (s, 6H), 3.42 (d, 1H, $J = 16.2$), 3.84 (d, 1H, $J = 16.2$), 7.19–7.25 (m, 1H), 7.29–7.36 (m, 4H), 7.42–7.49 (m, 2H), 7.55–7.59 (m, 2H). ^{13}C NMR (CDCl_3): δ 24.5 (CH_3), 24.6 (CH_3), 46.1 (CH_2), 85.0 (C), 124.3 (C), 127.0 (CH), 128.2 (C), 128.5 (CH), 128.8 (CH), 135.8 (C), 143.5 (C), 154.5 (C). (The resonance of the carbon α to boron was not detected). Anal. Found: C, 65.5; H, 6.2; N, 3.6%. Calc. for $\text{C}_{24}\text{H}_{23}\text{BClNO}_3$: C, 65.74; H, 6.04; N, 3.65%.

4a: Yield 60%, m.p. 74°C. ^1H NMR (CDCl_3): δ 0.92 (t, 3H, $J = 6.7$), 1.33–1.38 (m, 6H), 2.92 (dd, 1H, $J = 8.3$ and 16.4), 3.35 (dd, 1H, $J = 10.4$ and 16.4), 4.68–4.78 (m, 1H), 7.34–7.61 (AA'BB' system, 6H). ^{13}C NMR (CDCl_3): δ 13.9 (CH_3), 22.5 (CH_2), 27.6 (CH_2), 35.0 (CH_2), 39.8 (CH_2), 81.8 (CH), 127.8 (CH), 128.9 (C), 129.1 (CH), 134.5 (C), 155.5 (C). Anal. Found: C, 65.5; H, 6.6; N, 6.3%. Calc. for $\text{C}_{13}\text{H}_{16}\text{ClNO}$: C, 65.68; H, 6.73; N, 5.89%.

4b: Yield 58%, m.p. 68–70°C (lit. [29] m.p. = 69–70°C). ^1H NMR (CDCl_3): δ 3.60 (dd, 1H, $J = 7.6$ and 16.9), 3.65 (dd, $J = 10.7$ and 16.9), 3.80 (s, 3H), 5.20 (dd, 1H, $J = 7.6$ and 10.7), 7.35–7.62 (AA'BB' system, 2H). ^{13}C NMR (CDCl_3): δ 38.7 (CH_2), 52.9 (CH_3), 78.1 (CH), 127.8 (CH), 128.1 (C), 129.1 (CH), 136.5 (C), 155.2 (C), 170.5 (C).

10a: Yield 91%, m.p. 57°C. ^1H NMR (CDCl_3): δ 1.24 (s, 6H), 1.25 (s, 6H), 1.32 (dd, 1H, $J = 8.7$ and 15.6), 1.47 (dd, 1H, $J = 5.3$ and 15.6), 2.96 (dd, 1H, $J = 8.4$ and 16.5), 3.38 (dd, 1H, $J = 10.2$ and 16.5), 4.95 (dddd, $J = 5.3$, 8.4, 8.7 and 10.2), 7.32–7.60 (AA'BB system, 4H). ^{13}C NMR (CDCl_3): δ 18.8 (CH_2), 24.8 (CH_3), 41.3 (CH_2), 79.4 (CH), 83.5 (C), 127.8 (CH), 128.9 (C), 129.5 (CH), 135.6 (C), 155.7 (C). Anal. Found: C, 59.6; H, 6.6; N, 4.4%. Calc. for $\text{C}_{16}\text{H}_{21}\text{BClNO}_3$: C, 59.74; H, 6.58; N, 4.35%.

10b: Yield 58%, b.p. 70–75°C at 0.01 mm Hg. ^1H NMR (CDCl_3): δ 1.20 (s, 9H), 1.25 (s, 12H), 1.24 (dd, 1H, $J = 8.7$ and 15.6), 1.36 (dd, 1H, $J = 5.6$ and 15.6), 2.58 (dd, 1H, $J = 8.5$ and 16.6), 3.03 (dd, 1H, $J = 9.8$ and 16.6), 4.72 (dddd, 1H, $J = 5.6$, 8.5, 8.7 and 9.8). ^{13}C NMR (CDCl_3): δ 18.0 (CH_2), 24.8 (CH_3), 28.1 (CH_3), 32.9 (C), 40.8 (CH_2), 78.1 (CH), 83.4 (C), 166.1 (C). Anal. Found: C, 62.6; H, 9.8; N, 5.2%. Calc. for $\text{C}_{14}\text{H}_{26}\text{BNO}_3$: C, 62.93; H, 9.80; N, 5.24%.

10c: Yield 67%, m.p. 60°C. ^1H NMR (CDCl_3): δ 1.23 (12H), 1.44 (s, 2H), 1.50 (s, 3H), 3.04 (d, 1H, $J = 16.6$), 3.27 (d, 1H, $J = 16.6$), 7.33–7.60 (AA'BB' system, 4H). ^{13}C NMR (CDCl_3): δ 24.7 (CH_3), 27.8 (CH_3), 46.8 (CH_2), 83.5 (C), 87.1 (C), 127.7 (CH), 128.8 (C), 129.1 (CH), 135.4 (C), 155.6 (C) (the resonance of the carbon α to boron was not detected). Anal. Found: C, 60.6; H, 6.9; N, 4.2%. Calc. for $\text{C}_{17}\text{H}_{23}\text{BClNO}_3$: C, 60.83; H, 6.90; N, 4.17%.

10'd + 10''d: Yield 70% (mixture of two diastereoisomers 65/35). oil. ^1H NMR (CDCl_3): major diastereoisomer δ 1.29 (s, 6H), 1.30 (s, 6H), 3.34–3.47 (m, 2H), 3.59 (d, 1H, $J = 6.2$), 5.09 (ddd, 1H, $J = 6.2$, 7.8 and 9.8), 7.33–7.62 (AA'BB' system, 4H). Minor diastereoisomer δ 1.19 (s, 6H), 1.23 (s, 6H), 3.40–3.53 (m, 2H), 3.62 (d, 1H, $J = 5.4$), 5.13 (ddd, 1H, $J = 5.4$, 6.7 and 11.5), 7.33–7.62 (AA'BB' system, 4H). ^{13}C NMR (CDCl_3): major diastereoisomer δ 24.5 (CH_3), 24.6 (CH_3), 38.1 (CH_2), 44.0 (CH), 81.9 (CH), 84.9 (C), 127.9 (CH), 128.9 (C), 129.6 (CH), 136.1 (C), 155.4 (C). Minor diastereoisomer δ 24.6 (CH_3), 24.8 (CH_3), 38.1 (CH_2), 44.0 (CH), 81.9 (CH), 85.0 (C), 127.9 (CH), 128.9 (C), 129.6 (CH), 136.0 (C), 155.9 (C).

10'e + 10''e: Yield 67% (mixture of diastereoisomers 55/45). Oil, $R_f = 0.6$ (heptane–diethylether: 90–10). ^1H NMR (CDCl_3): major diastereoisomer δ 0.83–0.94 (m, 3H), 1.22–1.74 (m, 23H), 3.11 (dd, 1H, $J = 8.5$ and 16.4), 3.32 (dd, 1H, $J = 10.6$ and 16.4), 4.78–4.91 (m, 1H), 7.32–7.61 (AA'BB' system, 4H). Minor diastereoisomer δ 0.83–0.94 (m, 3H), 1.22–1.74 (m, 23H), 3.08 (dd, 1H, $J = 8.7$ and 16.4), 3.29 (dd, 1H, $J = 10.3$ and 16.4), 4.78–4.91 (m, 1H), 7.32–7.61 (AA'BB' system, 4H). ^{13}C NMR (CDCl_3): major diastereoisomer δ 14.1 (CH_3), 22.6 (CH_2), 24.8 (CH_3), 27.4 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 30.5 (CH), 31.7 (CH_2), 39.2 (CH_2), 83.4 (CH), 83.9 (CH), 127.8 (CH), 128.7 (C), 128.8 (CH), 135.6 (C), 155.5 (C). Minor diastereoisomer δ 14.1 (CH_3), 22.6 (CH_2), 24.7 (CH_3), 24.8 (CH_3), 28.0 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 30.5 (CH), 31.7 (CH_2), 39.2 (CH_2), 83.4 (CH), 83.9 (CH), 127.8 (CH), 128.7 (C), 128.8 (CH), 135.6 (C), 155.9 (C) ppm. Anal. Found: C, 64.9; H, 8.3; N, 3.4%. Calc. for $\text{C}_{22}\text{H}_{23}\text{BClNO}_3$: C, 65.12; H, 8.19; N, 3.45%.

10'f + 10''f: Yield 60% (mixture of diastereoisomers 65/35). Oil, $R_f = 0.5$ (heptane–diethylether 50/50). ^1H NMR (CDCl_3) major diastereoisomer: δ 1.24 (s, 12H), 1.28–1.87 (m, 10H), 3.14 (dd, 1H, $J = 9.2$ and 16.7), 3.35 (dd, 1H, $J = 10.5$ and 16.7), 4.82–4.95 (m, 1H), 7.32–7.66 (AA'BB' system, 4H). Minor diastereoisomer δ 1.13 (s, 6H), 1.20 (s, 6H), 1.21–2.05 (m, 10H), 3.26 (dd, 1H, $J = 9.6$ and 16.0), 3.28 (dd, 1H, $J = 9.6$ and 16.0), 4.85–4.95 (m, 1H), 7.32–7.62 (AA'BB' system, 4H). ^{13}C NMR: major diastereoisomer δ 24.7 (CH_3); 24.9 (CH_3); 26.8 (CH_2); 28.5 (CH_2); 32.0 (CH_2); 33.1 (CH_2); 36.7 (CH); 39.3 (CH); 40.3

(CH_2); 83.4 (CH); 83.8 (CH); 127.8 (CH); 128.6 (C); 128.9 (CH); 135.5 (C); 155.6 (C). Minor diastereoisomer δ 24.6 (CH_3); 24.7 (CH_3); 24.8 (CH_2); 25.0 (CH_2); 31.8 (CH_2); 32.7 (CH_2); 35.6 (CH); 38.7 (CH); 39.2 (CH_2); 83.3 (CH); 83.5 (CH); 127.8 (CH); 128.6 (C); 128.9 (CH); 135.5 (C); 155.9 (C). HRMS m/z Calc. for $\text{C}_{21}\text{H}_{29}\text{BClNO}_3$: 389.192. Found: 389.193.

4.2. Oxidation of 2-oxazolines 3 and 10

4.2.1. General procedure for the oxidation of 2-isoxazoline 3 and 10

A solution of 2-isoxazoline **3** or **10** (3 mmol) in 10 ml of THF was added to a well-stirred cooled mixture of a phosphate buffer (5 ml, prepared from a 1/1 mixture of solutions of KH_2PO_4 (34 g l^{-1}) and Na_2HPO_4 (35.5 g l^{-1})). 4 ml of 30% H_2O_2 was then dropwise added. The resulting mixture was stirred at 0°C for 1 h and at 25°C for 16 h. After separation, the aqueous layer was extracted twice with ether. The combined organic extract was dried with magnesium sulfate. The solution was concentrated and the product purified by flash chromatography on silica gel.

11a: Yield 62%, m.p. 129°C. ^1H NMR ($(\text{CD}_3)_2\text{CO}$): δ 3.18 (dd, 1H, $J = 1.8$ and 17.6), 3.20 (broad s, 1H), 3.49 (dd, 1H, $J = 6.9$ and 17.6), 6.09 (ddd, 1H, $J = 1.8$, 5.5 and 6.9), 6.18 (d, 1H, $J = 5.5$), 7.38–7.75 (AA'BB' system, 4H). ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$): δ 42.4 (CH_2), 99.3 (CH), 129.0 (C), 129.6 (C), 136.0 (C) (only three aromatic carbons were found), 156.0 (C). Anal. Found: C, 54.7; H, 4.2; N, 6.9%. Calc. for $\text{C}_9\text{H}_8\text{ClNO}_2$: C, 54.68; H, 4.05; N, 7.08%.

11b: Yield 61%. Oil, $R_f = 0.2$ (diethylether). ^1H NMR (CDCl_3): δ 2.05 (s, 3H), 2.76 (dd, 1H, $J = 6.2$ and 17.7), 3.09 (dd, 1H, $J = 5.8$ and 17.7), 5.35 (broad s, 1H). Anal. Found: C, 47.4; H, 7.1%; N, 13.7%. Calc. for $\text{C}_4\text{H}_7\text{NO}_2$: C, 47.52; H, 6.93; N, 13.86%.

11c: Yield 59% m.p. 68°C, $R_f = 0.5$ (heptane–diethylether: 50/50). ^1H NMR (CDCl_3): δ 1.02 (s, 9H), 2.74 (dd, 1H, $J = 2.4$ and 17.4), 3.00 (dd, 1H, $J = 5.6$ and 17.4), 5.02 (broad s, 1H), 5.80 (dd, $J = 2.4$ and 5.6). HRMS m/z Calc. for $\text{C}_7\text{H}_{13}\text{NO}_2$: 143.094. Found: 143.094.

11d: Yield 62%. Oil, $R_f = 0.6$ (heptane–diethylether 30/70). ^1H NMR (CDCl_3): δ 1.41 (t, 3H, $J = 7.1$), 3.07 (dd, 1H, $J = 3.2$ and 18.7), 3.30 (dd, 1H, $J = 6.2$ and 18.7), 4.39 (q, 2H, $J = 7.1$), 5.52 (broad s, 1H), 6.07 (dd, 1H, $J = 3.2$ and 6.2). Anal. Found: C, 45.3; H, 5.7; N, 8.9%. Calc. for $\text{C}_6\text{H}_9\text{NO}_4$: C, 45.28; H, 5.66; N, 8.8%.

11e: Yield 63%. Oil, $R_f = 0.3$ (heptane–diethylether 50/50). ^1H NMR (CDCl_3): δ 1.88–2.04 (m, 2H), 2.42 (t, 2H, $J = 7.1$), 2.46 (t, 2H, $J = 7.3$), 2.82 (dd, 1H, $J = 0.7$ and 17.7), 3.07 (dd, 1H, $J = 6.5$ and 17.7), 3.68 (s, 3H), 4.90 (broad s, 1H), 5.85 (dd, 1H, $J = 0.7$ and 6.6). ^{13}C NMR (CDCl_3): δ 21.4 (CH_2), 27.1 (CH_2), 31.2 (CH_2), 44.3 (CH_2); 51.9 (CH_3), 97.1 (CH), 158.6

(C), 174.1 (C). HRMS m/z Calc. for $C_8H_{13}NO_4$: 187.0844. Found: 187.084.

11f: Yield 60%. Oil, R_f = 0.8 (heptane–diethylether 1/4). 1H NMR ($CDCl_3$): δ 2.69 (d, 2H, J = 5.5), 2.71 (dd, 1H, J = 1.5 and 18.1), 3.22 (dd, 1H, J = 6.6 and 18.1), 4.61 (t, 1H, J = 5.5), 4.85 (broad s, 1H), 5.81 (dd, 1H, J = 1.5 and 6.6). ^{13}C NMR ($CDCl_3$): δ 31.5 (CH_2), 50.0 (CH_2), 53.5 (CH_3), 53.6 (CH_3), 97.3 (CH), 102.2 (CH), 155.7 (C). HRMS m/z Calc. for $C_6H_{10}NO_3$, $M - CH_3O^{\cdot+}$: 144.0661. Found: 144.066.

10g: M.p. 110–111°C, Yield 71%. 1H NMR ($CDCl_3$): δ 3.23 (dd, 1H, J = 8.6 and 16.7), 3.29 (dd, 1H, J = 10.1 and 16.7), 3.62 (ddd, 1H, J = 4.2, 6.0 and 12.0), 3.68 (ddd, 1H, J = 4.6, 6.0 and 12.0), 4.51 (t, 1H, J = 6.0), 4.82 (dd, 1H, J = 4.2, 4.6, 8.6 and 10.1), 7.38–7.68 (AA'BB' system, 4H). ^{13}C NMR ($CDCl_3$): δ 36.1 (CH_2), 62.6 (CH_2), 82.1 (CH), 128.4 (CH), 128.5 (C), 129.1 (CH), 135.1 (C), 156.3 (C=N). Anal. Found: C, 56.6; H, 4.8; N, 6.4%. Calc. for $C_{11}H_{12}ClNO_2$: C, 56.75; H, 4.76; N, 6.62%.

11h: M.p. 80°C, yield 68%. 1H NMR ($CDCl_3$): δ 1.43 (s, 3H), 2.98 (d, 1H, J = 6.4), 3.47 (d, 1H, J = 6.4), 3.57 (d, 1H, J = 12.0), 3.75 (d, 1H, J = 12.0), 7.34–7.61 (AA'BB' system, 4H). Anal. Found: C, 58.3; H, 5.6; N, 6.3%. Calc. for $C_{11}H_{12}ClNO_2$: C, 58.55; H, 5.35; N, 6.20%.

5a: Yield 62%, m.p. 73°C (Lit. [30] m.p. = 76–78°C). 1H NMR ($CDCl_3$): δ 6.63 (d, 1H, J = 1.7), 7.38–7.76 (AA'BB' system, 4H), 8.45 (d, 1H, J = 1.7). ^{13}C NMR ($CDCl_3$): δ : 102.4 (CH), 127.3 (CH), 128.2 (C), 129.3 (CH), 136.1 (C), 159.2 (CH), 160.6 (C). HRMS m/z Calc. for C_9H_5ClNO : 179.0138. Found: 179.014.

5b: Yield 62%. Oil, R_f = 0.45 (diethylether). 1H NMR ($CDCl_3$): δ 1.71–2.20 (m, 2H), 2.45 (t, 1H, J = 7.1), 2.78 (t, J = 7.3), 6.21 (d, 1H, J = 1.6), 8.30 (d, 1H, J = 1.6), 8.50 (broad s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.1 (CH_2), 25.0 (CH_2), 33.1 (CH_2), 104.1 (CH), 158.4 (CH), 161.9 (C), 178.7 (C). Anal. found: C, 54.8; H, 6.0; N, 8.9%. Calc. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03%.

5c: Yield 61%. Oil, R_f = 0.3 (heptane–diethylether 1/1). 1H NMR ($CDCl_3$): δ 3.02 (d, 2H, J = 5.6), 3.31 (d, 6H), 4.10 (t, 1H, J = 5.6), 6.31 (d, 1H, J = 1.8), 8.29 (d, 1H, J = 1.8). ^{13}C NMR ($CDCl_3$): δ 30.0 (CH_2), 53.5 (CH_3), 103.0 (CH), 105.0 (CH), 158.2 (CH), 158.7 (C). Anal. Found: C, 53.5; H, 6.9; N, 8.9%. Calc. for $C_7H_{11}NO_3$: C, 53.50; H, 6.89; N, 8.91%.

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