

Regioisomeric and substituent effects upon the outcome of the reaction of 1-borodienes with nitrosoarene compounds.

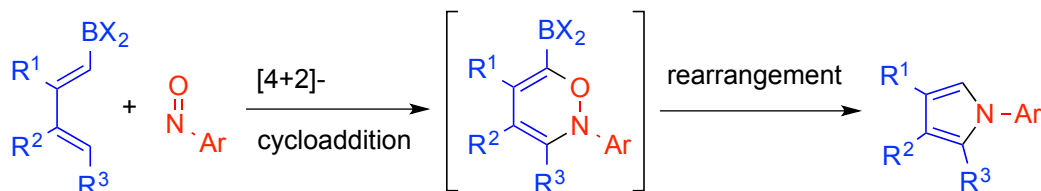
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Abstract

A study of the reactivity of 1-borodienes with nitrosoarene compounds has been carried out showing an outcome that differs according to the hybridization state of the boron moiety. Using an *sp*² boron substituent, a one-pot hetero-Diels-Alder/ring contraction cascade occurred to afford *N*-arylpyrroles with low to good yield depending on the electronic properties of the substituents on the borodiene. Whereas, an *sp*³ boron substituent led to the formation of stable boro-oxazines

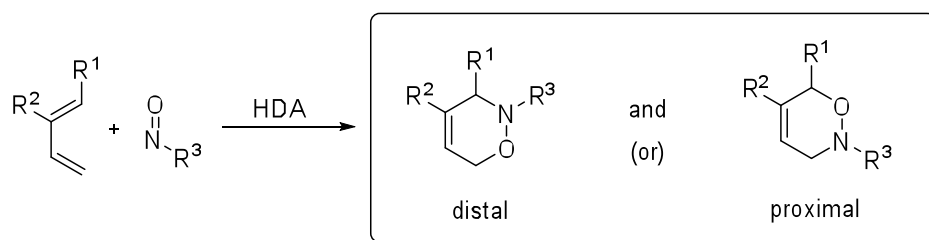
with high regioselectivity in most of cases, in moderate to good yield. ^1H and ^{11}B NMR studies on two boro-oxazine regioisomers showed that selective deprotection can be performed. Formation of either the pyrrole or furan derivative is pH and regioisomer-structure dependent. The results obtained, together with previous B3LYP calculations, support mechanistic proposals which suggest that pyrrole, or furan formation, proceeds *via* oxazine formation, followed by a boryl rearrangement and an intramolecular addition-elimination sequence.

Introduction

The hetero Diels-Alder reaction between a nitroso hetero dienophile and a diene is a useful tool in organic chemistry. Since 1947 and the pioneering work of Wichterle,¹ this reaction has been widely studied and numerous nitroso and diene partners have been used to enlarge its scope and efficiency. A large range of nitroso reagents, including acylnitroso, nitrosoarene and chloronitroso etc., have been used, as well as substituted acyclic, cyclic and heterocyclic dienes to provide 3,6-dihydro-1,2-oxazine scaffolds.² The resulting oxazine skeleton is a key intermediate in the synthesis of natural products, such as alkaloids derivatives,³ heterocycles⁴ and saccharide mimetics.⁵ However, the modest regioselectivity encountered with some types of unsymmetric dienes can constitute an important limitation for applications in organic synthesis. The nitroso [4+2]-cycloaddition can provide two regioisomers; the distal isomer (major substituent close to the nitrogen of the oxazine cycloadduct) and the proximal isomer (major substituent close to the oxygen of the oxazine cycloadduct) (Scheme 1). Several studies on the regiocontrol of this reaction have shown that it results from a combination of both steric and electronic effects on both the nitroso and diene partners. For example, Houk *et al.* examined monosubstituted dienes and their addition to numerous nitroso derivatives⁶ and established a

correlation between regioselectivity and: 1) the properties and position of substituents on the diene; 2) the nature of the nitroso compound. More recently, Kouklovsky *et al.* examined 1,2-disubstituted dienes and their reaction with Boc-nitroso compounds to derive nitroso Diels-Alder cycloadducts with high regioselectivity.⁷ To predominantly obtain the distal isomer, it is necessary for the diene to bear a bulky substituent at C₁ and an electron donating group at the C₂ position. For the proximal isomer, a non-bulky substituent at C₁ and an electron-withdrawing group at C₂ are required. Nevertheless, regioselectivity is also dependent upon the nature of the nitroso compound.

Scheme 1. Regioselectivity of nitroso Diels-Alder reaction with mono- and di-substituted dienes.



Despite the synthetic utility of borodienes,⁸ especially in multicomponent and cascade processes, no investigation of the reaction of borodienes has been carried out with nitroso compounds until our recent preliminary communication which focused on the reaction of 1,3-dienylboronic esters **1** (Scheme 1, R¹ = Bpin) with aryl nitroso derivatives **2**.⁹ In addition to the possible post-functionalisation of the resulting cycloadducts, we expected that tuning of the electronic properties of the boronated group through the introduction of various substituents on boron¹⁰ would provide an insight into the control of the regioselectivity of the [4+2] cycloaddition

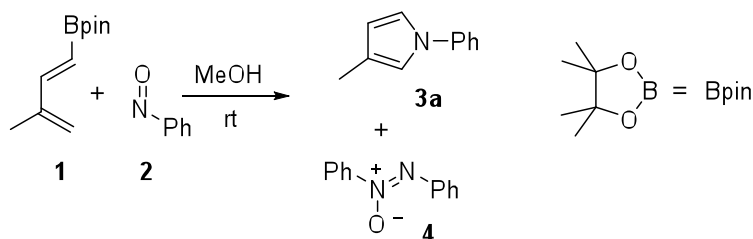
reaction, and therefore, the subsequent transformation of the resulting cycloadducts. Herein, we report the full details of these studies, especially the impact of varying the nature of both the borodiene and dienophile substituents upon the reaction outcome, and hence, discuss the mechanistic implications of the results.

Results and Discussion

Reaction 1-dienylboronate pinacolate esters with nitrosoarene compounds

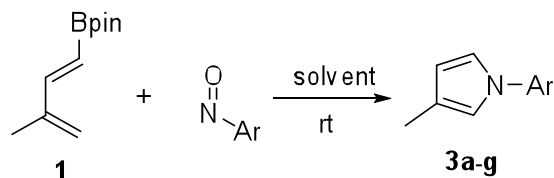
As reported previously,⁹ initial investigations into the reaction between the dienyl boronate **1** and nitrosobenzene **2** resulted in the formation of the unexpected *N*-phenylpyrrole **3a** instead of a mixture of regioisomeric oxazine cycloadducts (Scheme 2). Given that such reactions tend to lack high regiocontrol,² the efficiency of the pyrrole formation was intriguing and clearly required further study and explanation. Indeed, even when the reaction was followed by ¹H NMR, only 3-methyl-1-phenyl-pyrrole **3a**, together with some azoxybenzene **4**, was identified. There was a notable absence of any oxazine cycloadducts and the reaction was complete after 5 h to afford **3a** in 82% isolated yield (Table 1, Entry 3).

Scheme 2. *N*-Phenylpyrrole formation from the reaction of boronated diene **1 and nitrosobenzene **2**.**



Further studies to address the scope of this reaction were conducted, the results of which are summarized in Table 1.

Table 1. Pyrrole formation from the reaction of nitrosoarenes with diene 1



Entry	Nitroso compound	Product	Yield (%)
1 ^[a]	C ₆ H ₅ NO		67
2 ^[b]	C ₆ H ₅ NO	3a	61
3 ^[c]	C ₆ H ₅ NO	3a	82
4 ^[c]	<i>p</i> -Me-C ₆ H ₄ NO		60
5 ^[c]	<i>p</i> -Cl-C ₆ H ₄ NO		68
6 ^[c]	<i>p</i> -Br-C ₆ H ₄ NO		65
7 ^[c]	<i>p</i> -EtO ₂ C-C ₆ H ₄ NO		57
8 ^[c]	<i>p</i> -MeO-C ₆ H ₄ NO		77
9 ^[c]	<i>o</i> -Me-C ₆ H ₄ NO		69

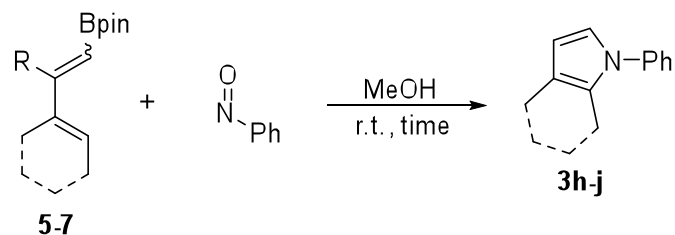
[a] Reaction with 1.5 eq of ArNO in MeOH at RT for 5 h.

[b] Reaction with 1.5 eq of ArNO in DCM at RT for 48 h.

[c] Reaction with 2.5 eq of ArNO in MeOH at RT for 5 h.

Differently substituted nitrosoarene compounds were reacted with borodiene **1** to afford *N*-arylpyrroles **3** in moderate to good yields. Use of either a protic solvent (MeOH) or an aprotic solvent (DCM), had no significant effect (Entries 1 and 2, Table 1). Due to the formation of the azoxybenzene by-product, an excess of nitrosoarene reagent (2.5 eq) was used in order to increase the isolated yield, for example, by 15% in the cases of comparing Entries 1 and 3 (Table 1). Modification of the nature or the location of the aromatic ring substituent on the nitrosoarene moiety showed no notable effect on the formation of the *N*-arylpyrrole products **3a-g**, which were isolated in 52 to 82% yields (Entries 4-9, Table 1). Other dienes, prepared according to literature procedures,¹¹ were also examined, as summarised in Table 2.

Table 2. Reaction of dienes 5-7 with nitrosobenzene



Entry	Diene	Product	Yield (%)
1 ^[a]			78
2 ^[b]			16
3 ^[b]			34

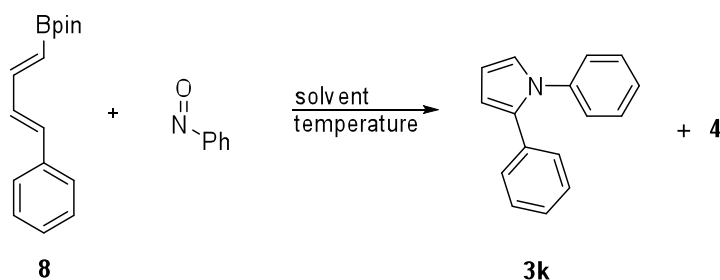
[a] Reaction with 2.5 eq of ArNO in MeOH at RT for 5 h.

[b] Reaction with 2.5 eq of ArNO in MeOH at RT for 16 h.

Unsubstituted 1-borobutadiene **5** reacted efficiently with nitrosobenzene to give the corresponding pyrrole **3h** in 78% yield (Entry 1, Table 2). However, there was a major decrease in yield observed in the case of the more substituted and cyclic borodiene **6** (Entry 2, Table 2). The acyclic, 2-substituted diene **7** also resulted in a reduced yield (Entry 3, Table 2), though the yield was not quite as low as for cyclic diene **6**. The corresponding pyrroles were nevertheless isolated in only 34% and 16% yields respectively, and despite the extended reaction times.

Next, the influence of substituents on the borodiene were examined, possessing aromatic or electron withdrawing groups in position 4. Diene **8** was prepared *via* a 3 step pathway, involving a Sonogashira reaction of β -bromostyrene with trimethylsilylacetylene, followed by protodesilylation, to give 4-phenyl-3-buten-1-yne as an *E/Z* mixture (91/9).¹² Hydroboration using pinacolborane and Schwartz' catalyst^{11a} provided the desired diene **8** as a mixture of two stereoisomers (*E,E*:*E,Z* = 91:9) in a 56% overall yield. The subsequent reactions of diene **8** with nitrosobenzene are shown in Table 3.

Table 3. Study of the reactivity of diene **8 with nitrosobenzene**



Entry	Solvent	Temperature (°C)	Time (h)	Conversion (Isolated yield) (%)
1 ^[a]	MeOH	rt	16	0
2 ^[a]	Toluene	rt	16	0
3 ^[a]	MeOH	reflux	5	50

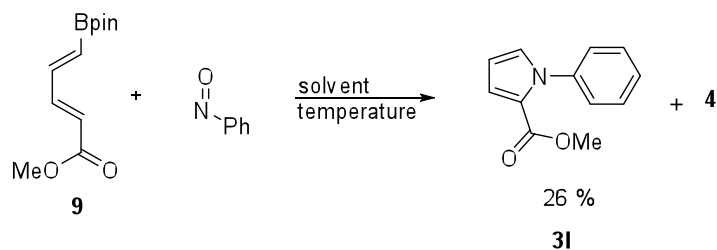
4 ^[a]	Toluene	70	16	50 (14)
5 ^[a]	MeOH	reflux	22	72 (19)
6 ^[b]	MeOH	reflux	22	77 (20)
7 ^[c]	MeOH	reflux	22	82 (24)
8 ^[d]	MeOH	reflux	22	100 (36)

[a] Reactions with 2.5 eq of nitrosobenzene.
[b] Reaction with 2.5 eq of nitrosobenzene added in portions.
[c] Reaction with 2.5 eq of nitrosobenzene added slowly by syringe pump.
[d] Reaction with 3.5 eq of nitrosobenzene.

In the presence of nitrosobenzene, no reaction of diene **8** was observed at room temperature in either toluene or MeOH (Entries 1 and 2, Table 3). Heating triggered reaction according to ¹H NMR in both MeOH and toluene (Entries 3 and 4, Table 3), and the starting nitrosobenzene was fully consumed after an extended 22 h reaction time, resulting in 72% conversion of diene **8** (Entry 5, Table 3). No further improvement was observed if the nitrosobenzene was added in portions in an attempt to decrease azo-by-product formation (1 eq at the outset - 1 eq after 4 h - 0.5 eq after 4 h), or by slowly addition of a MeOH solution by syringe pump (see Entries 6 and 7, Table 3). Finally, the use of 3.5 eq of nitrosobenzene (Entry 8, Table 3) was required in order to achieve the complete conversion of both stereoisomers of diene **8**, resulting in the formation pyrrole **3k** and a 36% isolated yield.

The introduction of an electron withdrawing group (methyl carboxylate function) in position 4 of the borodiene was next examined. Diene **9** was, therefore, synthesized by a Wittig route from an ester-stabilised ylide and β -borylacrolein pinacol ester, resulting in a mixture of three stereoisomers (*E,E:E,Z,E* = 83:10:7) in an unoptimized 30% overall yield.¹³ The subsequent reactions of diene **9** are shown in Table 4.

Table 4. Study of the reactivity of diene **9 with nitrosobenzene**



Entry	Solvent	Temperature (°C)	Time (h)	<i>E,E</i> -isomer conversion (Isolated yield) (%)
1 ^[a]	MeOH	rt	16	0
2 ^[a]	MeOH	reflux	16	0
3 ^[a]	Toluene	rt	16	0
4 ^[a]	Toluene	reflux	64	15
5 ^[b]	Toluene	reflux	128	100 (26)

[a] Reactions with 2.5 eq of nitrosobenzene.

[b] Reaction with 5 eq of nitrosobenzene

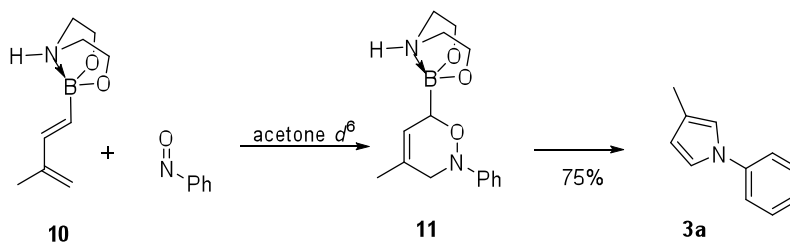
Diene **9** proved even less reactive than diene **8**, and longer reaction times and higher temperatures were required to give an improved conversion (see Table 4, Entries 1-5). In order to form the pyrrole **31**, 5 equivalents of nitrosobenzene and a 128 h reaction time was required in toluene at reflux, and only the *E,E*-stereoisomer reacted. Indeed, even under longer reaction times, the other isomers were still unreacted and present in the reaction mixture (Entry 5, Table 4). Nevertheless, 26% of the corresponding pyrrole **31** was isolated after silica gel chromatography (Entry 5, Table 4).

Reaction of tetracoordinated 1-borodienes to nitrosoarene compounds

Since the various 1-borodienes with pinacol esters all resulted in reactions in which the oxazine was not observed, our attention was turned our attention to the study of the influence of boron

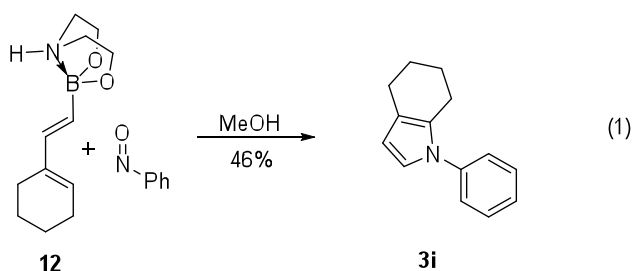
substituents that might result in the oxazine cycloadducts being isolated. The impact of replacing the pinacol ester of boronate **1** by diethanolamine was studied, as outlined in Scheme 3.

Scheme 3. Reactivity of dienyl diethanolamine esters **10 with nitrosobenzene.**



Reaction of 1-borodiene **10** with nitrosobenzene resulted in the identification of the [4+2]-cycloadduct **11** in the ^1H NMR spectrum of the crude mixture.¹⁴ After 2 h, all the diene **10** was consumed and the intermediate boro-1,2-oxazine **11** had also disappeared, resulting in only pyrrole **3a** formation, together with small amounts of azoxybenzene **4** (Scheme 3).¹⁵ This cycloaddition (Scheme 4) was notably faster with this tetracoordinated boron substituent (50% conversion after 5 min at room temperature compared with 5 h for complete conversion of the corresponding pinacol ester (Table 1, Entry 3).

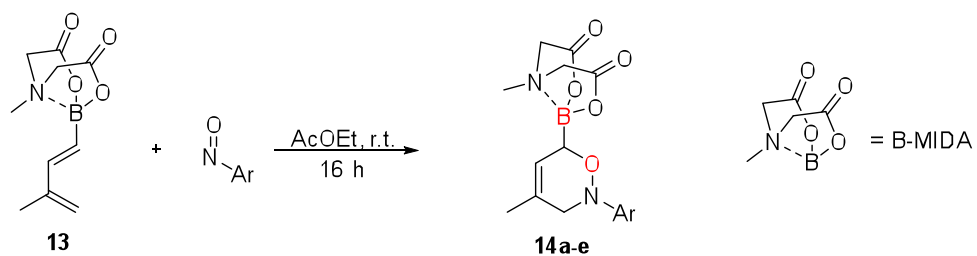
Indeed, this increased reactivity was confirmed by the reaction of cyclic diene **12**¹⁶ which provided pyrrole **3i** after only 2 h and in a 46% yield as shown in Equation 1 (compared with 16% over 16 h for the corresponding pinacol ester derivative, Entry 2, Table 2).

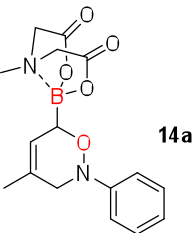
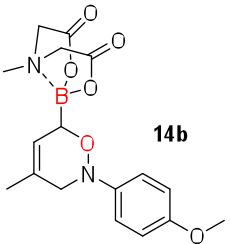
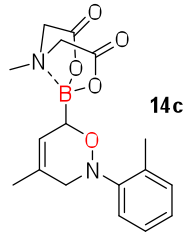
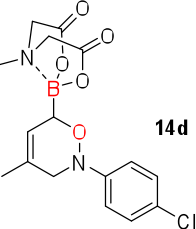


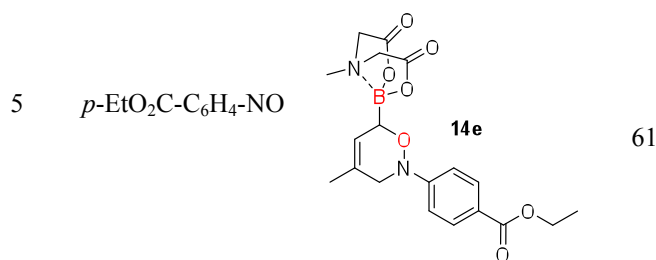
Most interestingly of course, the observation of the transient [4+2]-hetero-Diels-Alder cycloadduct **11** (Scheme 3) confirms the key role of the oxazine cycloadduct in the subsequent formation of the pyrrole. Diethanolamine esters are known for their facile hydrolysis or methanolysis to regenerate the corresponding boronic acid or ester,¹⁷ however, simply the reversibility of B-N chelation could be responsible for allowing the facile rearrangement to the pyrrole (*vide infra*). We can also observe in these results, the beneficial effect of the tetracoordinated boronate ester, which is presumably less electron withdrawing than a pinacol ester, and therefore, more reactive towards the electron deficient dienophile.

Prompted by these results, we therefore examined the behavior of corresponding MIDA (*N*-methyliminodiacetic)borodiene derivatives. Because of their high stability towards air and moisture, these compounds have been used as flexible scaffolds for the synthesis of a wide range of functionalized small molecules.¹⁸ It was our expectation that such dienes would make it possible to isolate and study the intermediate oxazine cycloadducts. The presence of an sp³-*versus* a sp²-hybridized borodiene would also be expected to be a useful tool to examine the regioselectivity of the cycloaddition reaction. The scope of the reaction of the MIDA diene **13** was, therefore, examined with various nitrosoarene compounds, as outlined in Table 5. Reactions were carried out in AcOEt for a better solubility of the diene B-MIDA **13**.

Table 5. Reactivity of MIDA-substituted diene 13 with nitrosoarene compounds



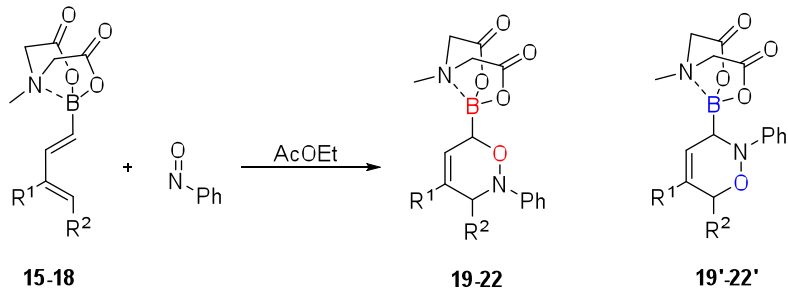
Entry	Nitroso compound	Product	Yield (%)
1	$\text{C}_6\text{H}_5\text{NO}$	 14a	64
2	$p\text{-MeO-C}_6\text{H}_4\text{-NO}$	 14b	47
3	$o\text{-Me-C}_6\text{H}_4\text{-NO}$	 14c	56
4	$p\text{-Cl-C}_6\text{H}_4\text{-NO}$	 14d	77



The reaction of the MIDA-borodiene **13** provided the corresponding oxazine cycloadducts in moderate to good yields with the different nitrosoarene compounds, without obvious electronic effects from the aryl substituent. However, single regioisomeric products were obtained, as exemplified by the formation of the stable [4+2]-cycloadduct **14a**, obtained from reaction of diene **13** with nitrosobenzene and isolated in 64% yield (Entry 1, Table 5). Only the boron-oxygen 1,2 related regioisomer (in red in Table 5) was observed and its structure was assigned by NOESY NMR by correlation between the *o*-phenyl Hs and one of the NCHs on the oxazine ring. The introduction of different nitrosoarene substituents, *i.e.* electron donating and withdrawing groups in positions 2 and 4, did not change the resulting regiochemical outcome (Entries 2-5, Table 5) and yields ranged between 47 to 77%. It is also noteworthy that little or no dimerization of the nitrosoarene took place during these reactions, reflecting the short reaction times and more reactive diene, reducing the potential for competitive by-product formation from the nitroso compound.

The impact of different MIDA borodiene substituents was then examined, *i.e.* dienes **15-18**, which were synthesized by Stille or Suzuki-Miyaura couplings of (*E*)-(2-bromovinyl)-MIDA boronate with either vinyltributyltin (72%), (*E*)-hex-1-ene boronic acid (79%), (1-bromovinyl)benzene (68%) or 1-phenylvinylboronic acid (76%), respectively.¹⁹ The resulting nitroso addition reactions are summarised in Table 6.

Table 6. Reactivity of MIDA-substituted dienes 15-18 with nitrosobenzene



Entry	Diene	Product	Yield (%) (Isomer ratio)
1 ^[a]			43 (100/0)
2 ^[a]			68 (100/0)
3 ^[a]			78 (100/0)
4 ^[b]			89 (40/60)

[a] Reaction with 2.5 eq of nitrosobenzene in AcOEt at rt for 6 h.

[b] Reaction with 5 eq of nitrosobenzene AcOEt at reflux for 24 h.

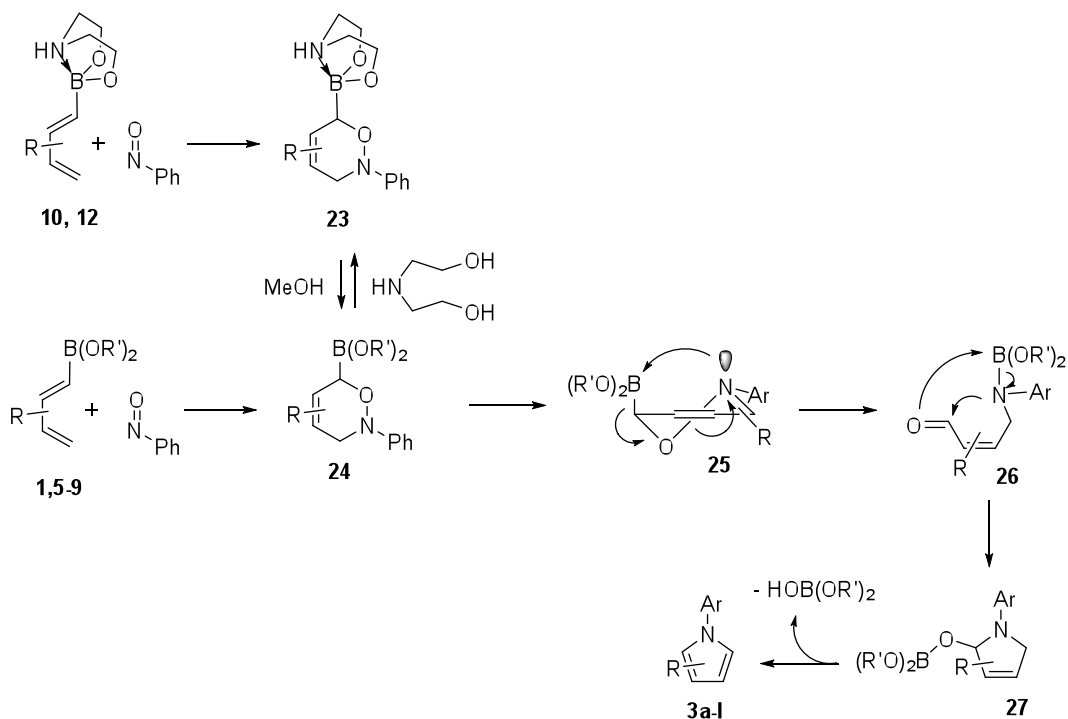
Similar to the results observed with the MIDA derivative **13**, the first three dienes (**15-17**) gave the same single regioisomeric boron-oxygen 1,2-related products at room temperature (in red in

Table 6), with the boron occupying the α -position relative to the ring oxygen of the oxazine (Entries 1-3, Table 6). The introduction of a phenyl group at C₄ noticeably reduced the reactivity of the borodiene **18** with reaction only occurring at reflux in EtOAc over 24 h. In addition, a mixture of regioisomers **22** and **22'** (ratio 40:60) was isolated in an 89% combined yield (Entry 4, Table 6). The structure of the major boron-oxygen 1,3-related regioisomer **22'** (in blue in Table 6) was secured by single crystal X-ray structure analysis (see SI), confirming the *cis*-stereochemistry of the boron and phenyl ring substituents. Both steric and electronic effects of the phenyl ring can explain this observed preferred regiochemistry (as discussed by Houk *et al.* for 1-phenylbutadiene compared with penta-1,3-diene²⁰).

Mechanistic aspects of the reaction 1-borodienes with nitrosoarene compounds

The mechanism which was hypothesized and subsequently supported by DFT calculations⁹ to rationalize the observed formation of pyrroles **3a-l** is shown in Scheme 4, which involves a [4+2]-Diels–Alder cycloaddition intermediate **23** or **24**, followed by rearrangement of the resulting oxazine. Consequently, borodienes **1**, **5-9** and dienyl diethanolamine esters **10**, **12** react with the nitroso compounds to afford the corresponding 3,6-dihydro-1,2-oxazines **24** and **23** respectively. The subsequent boryl rearrangement would give **26** followed by an intramolecular aza-boryl addition to the aldehyde generating **27** and finally, borate elimination provides the pyrrole **3a-l**.

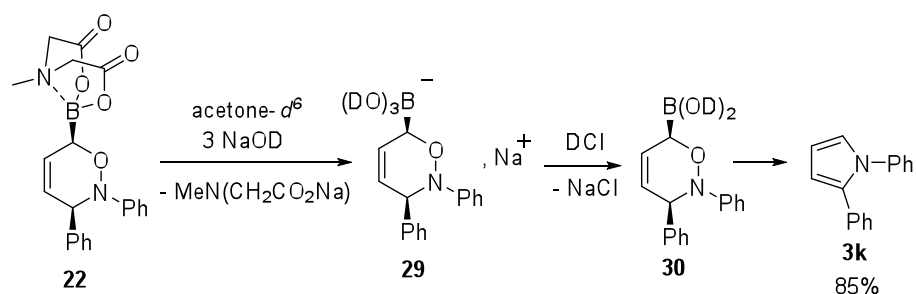
Scheme 4. Proposed mechanism for the formation of pyrroles from the reaction of 1-borodienes with nitrosoarene compounds.



Further investigations into this process to support our supposition and DFT calculations⁹ have now been provided by experimental investigations. Therefore, the replacement of the boronate pinacol ester on the diene component by diethanolamine (*vide supra*) resulted in the identification of the [4+2]-cycloadduct in the ^1H NMR spectrum of the crude mixture.¹⁴ Reacting diene **10** or **12** with nitrosobenzene for 2 hours, resulted in complete diene consumption and even the boron-1,2-oxazine **11** had totally disappeared to afford only pyrrole **3a** with only small amounts of azoxybenzene **4** (Scheme 4) produced. The pyrrole formation under these conditions can be explained by an facile equilibrium between the dioxazaborocane **23** and the corresponding methyl ester **24** due to solvolysis.¹⁷ This equilibrium releases the vacant orbital on boron, and consequently, the subsequent rearrangement occurs to access the pyrrole (Scheme 4). The enhanced reactivity of the borodiene possessing a diethanolamine ester (50% conversion after 5 min at rt for **10** vs. 5 h for complete conversion for **1**, Table 1, Entry 1) is consistent with similar

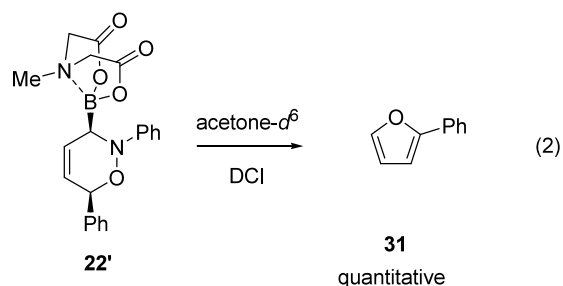
observations already reported in the literature,¹⁷ *i.e.* a more electron rich diene, reacting with an electron deficient nitroso compound, in a 'normal' electron, frontier-orbital-controlled [4+2]-cycloaddition reaction. It is noteworthy that even diene **12** provided a 48% yield of pyrrole **3i** after 2 h at rt (*c.f.* 16% in 16 h, Entry 2, Table 2) which further demonstrates the advantages of the more electron rich diene. Indeed, these conclusions are further supported by the MIDA boronate ester derivatives, as outlined in Scheme 5.

Scheme 5. Proposed reaction sequence for the formation of pyrrole 3k from MIDA boronate oxazine derivative 22



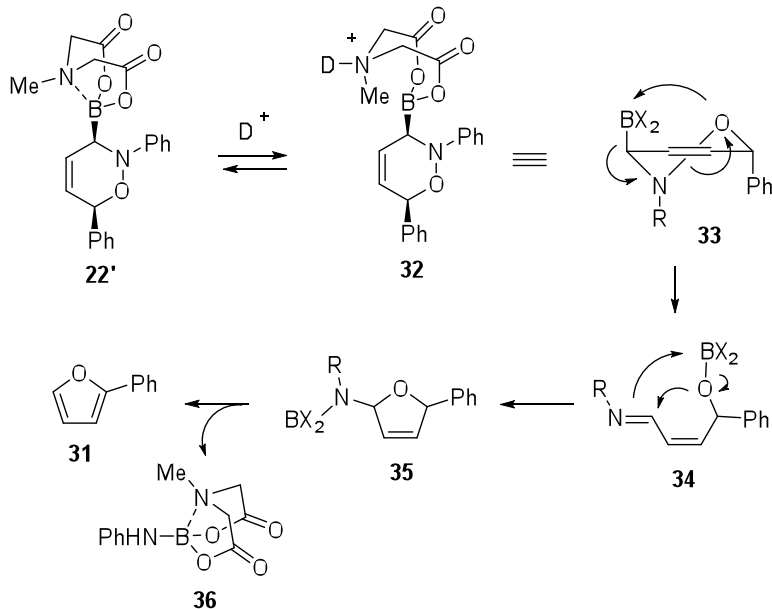
The reaction of nitrosobenzene with the MIDA boronate **18** results in the formation of the two regioisomers **22** and **22'** (*vide supra*). Under the same conditions (Scheme 5), regioisomer **22** reacted cleanly to give the pyrrole **3k**, whereas the other regioisomer **22'** gave a mixture of unidentified products. It was, therefore, decided to test another method to deprotect the MIDA boronate ester function of these types of oxazine cycloadducts. Hence, under acidic conditions (DCl 1M, 1 eq) in acetone-*d*₆, 2-phenylfuran **31** was cleanly and quantitatively produced after 15 minutes at room temperature from regioisomer **22'**, as shown in Equation 2. Under the same acidic conditions, the regioisomer **22** did not lead to the formation of the pyrrole **3k**. Instead, only the hydrochloride salt of the MIDA system was clearly identified. Thus, it is possible to

selectively, and cleanly deprotect, each regioisomer depending on the conditions. Pyrrole formation requires a regioisomer like **22**, and to be released in a basic medium, whereas furan formation requires a regioisomer like **22'** and an acidic medium.



Moreover, the by-product **36** was isolated by extracting the reaction mixture with DCM (see Scheme 6) in 25% yield, whose structure was established by ^1H , ^{13}C and ^{11}B NMR, and mass spectroscopy. These experimental observations are in agreement with the proposed mechanism outlined in Scheme 4. In addition, a preliminary and essential protonation of the nitrogen atom of the MIDA boronate **22'** results in the de-coordination of the nitrogen from boron, leading to the intermediate **32**. Formation of this BX_2 moiety **32** enables the facile boryl rearrangement **33-35** to take place, and in this case, to form the furan **31** (Scheme 6).

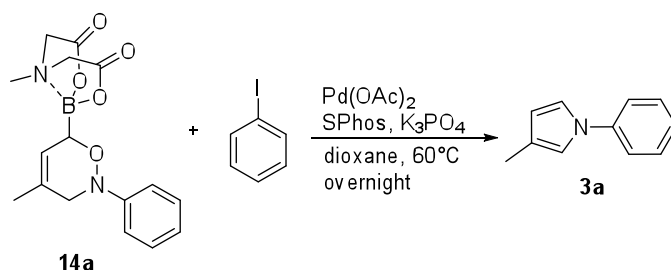
Scheme 6. Proposed mechanism for the formation of furan 31 from 22'



Transformations of boro-1,6-dihydro-1,2-oxazine derivatives

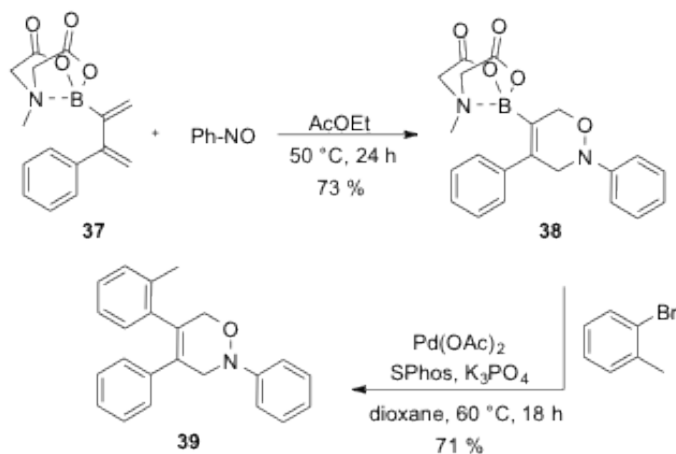
To explore the synthetic importance of B-MIDA oxazine derivatives, we decided to carry out a Suzuki-Miyaura coupling with the cycloadduct **14a** as a model substrate. Under classical experimental conditions for this class of reaction, ¹H NMR of the crude reaction mixture (see ESI) shows a full conversion of the starting material into the pyrrole **3a** that showed that **14a** is not stable enough to survive under Suzuki-Miyaura coupling conditions (Scheme 7).

Scheme 7. Reactivity of oxazine 14a and iodobenzene under Suzuki-Miyaura coupling conditions



To confirm that this is indeed the location of the boronated group that is responsible for this failure, the diene **37** was synthesized from (1-bromovinyl)-MIDA boronate and 1-bromostyrene.²¹ The reaction with nitrosobenzene regioselectively provided the cycloadduct **38** in a 73% isolated yield with only traces of the second isomer.²² To confirm the structure of the major regioisomer, it was engaged in a Suzuki-Miyaura cross-coupling with 1-bromotoluene in the presence of palladium acetate and SPhos (Scheme 8). The 2,4,5-trisubstituted dihydrooxazine **39** was isolated in a 71% yield. A NOESY NMR experiment (correlation between Hs of the methyl group of the toluene moiety and Hs on the oxazine ring at C₆) established the structure of this compound and consequently the orientation of the first cycloaddition. No ring contraction product was observed in this case.

Scheme 8. Synthesis of triarylated oxazine 39 from the nitrosobenzene cycloadduct 38 after Suzuki-Miyaura cross-coupling reaction sequence



Conclusions

This study revealed that hetero Diels Alder cycloadditions of nitroso compounds and boronated dienes can afford either pyrrole derivatives or oxazine cycloadducts. The most critical parameter to guide these reactions remains the ability of the boron to keep, or not, its sp^3 hybridization state, the presence of a boronate function α to the oxygen or the nitrogen atom of the oxazine ring being responsible of the fate of the ring contraction. Different experimental observations led us to propose a mechanism to rationalize these results, also in agreement with previous theoretical investigations. In the case of 2-MIDA borodienes, the formation of the corresponding [4+2]-cycloadduct is highly regioselective, and notably, these more electron rich dienes react faster with the nitrosoarene compounds. Indeed, this increased reactivity directly results in a decrease in the amount of nitrosoarene compound which can competitively degrade to azo by-products. No decomposition of the oxazine ring was observed during a Suzuki-Miyaura coupling. A 2,4,5-triaryl-3,6-dihydro-1,2-oxazine was isolated in good yield, thus showing the interest of this

approach to prepare these class of heterocycles with complete control of the position of the different substituents.

EXPERIMENTAL SECTION

General information and materials.

Reagents and solvents were used as received from the supplier, unless specified. When specified, dried solvents were used; THF and toluene were distillate on sodium, benzophenone and DCM on P₂O₅. Reactions were monitored by TLC analysis using Silica Gel 60 F₂₅₄ plates. Purifications on silica gel were carried out on silica gel 0.060-0.200 mm, 60 Å. NMR Spectra were recorded on apparatus at 300, 400 or 500 MHz for ¹H, 75, or 101 MHz for ¹³C and 96 MHz for ¹¹B. ¹H and ¹³C NMR chemical shifts were referenced to Me₄Si as internal reference, and ¹¹B NMR chemical shifts to external BF₃.OEt₂ (0.0 ppm). Deuterated chloroform CDCl₃ and acetone-*d*₆ were used for NMR spectra. NMR data are reported as; chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, m = multiplet, b = broad), coupling constant J (Hz) and integration. High-resolution mass spectra (HMRS) were obtained on a Q-TOF instrument and measured using either electrospray ionization (ESI) or electron impact (EI). Melting points were measured and reported in °C.

General procedure for pyrrole synthesis.

To a solution of diene (1 eq) (pinacol boronate or diethanolamine esters) in the solvent was added nitrosoarene compound (2.5 to 5 eq). The reaction mixture was stirred at the temperature

indicated in the experimental procedure. The solvent was evaporated and the crude product was purified by silica gel chromatography.

Characterization and experimental procedure of compound 3a-j.⁹

1,2-Diphenyl-1*H*-pyrrole 3k.²⁷

To a solution of diene **8** (65 mg, 0.25 mmol) in MeOH (1 mL) was added nitrosobenzene (94.9 mg, 0.76 mmol). The reaction mixture was heated to boiling and stirred for 22 h. The solvent was evaporated and the crude product was purified by silica gel chromatography (cyclohexane/toluene 98/2, $R_f = 0.3$) to give compound **3k** (19.7 mg, 36%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 -7.31 (m, 2H), 7.28 - 7.26 (m, 1H), 7.21-7.14 (m, 7H), 6.99 (dd, $J = 2.7, 1.8$ Hz, 1H), 6.47 (dd, $J = 3.4, 1.8$ Hz, 1H), 6.41 (dd, $J = 3.4, 3.0$ Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 140.7, 134.0, 133.1, 129.1, 128.4, 128.2, 126.7, 126.4, 125.9, 124.5, 110.8, 109.4.

Methyl-1-phenyl-1*H*-pyrrole-2-carboxylate 3l.²⁸

To a solution of diene **9** (65 mg, 0.25 mmol) in MeOH (0.5 mL) was added nitrosobenzene (94.9 mg, 0.76 mmol). The reaction mixture was heated to boiling and stirred for 22 h. The solvent was evaporated and the crude product was purified by silica gel chromatography (cyclohexane/toluene 98/2, $R_f = 0.3$) to give compound **3l** (15 mg, 26%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 – 7.29 (m, 5H), 7.10 (dd, $J = 3.9, 1.8$ Hz, 1H), 6.95 (dd, $J = 2.7, 1.8$ Hz, 1H), 6.29 (dd, $J = 3.9, 2.7$ Hz, 1H), 3.71 (s, 3H); ¹³C NMR (101 MHz, CDCl₃), δ ppm 161.1, 140.6, 130.0, 128.7, 128.0, 126.5, 119.1, 109.3, 51.3.

(*E,E*)-1,3-Butadienyl-(4-butyl)-1-boronate MIDA ester 16.

Compound **16** was synthesized using procedure Burke *et al.* procedure¹⁵. M.p = 122°C; ¹H NMR (400 MHz, acetone-*d*₆) δ ppm 6.53 (dd, *J* = 17.5, 10.2 Hz, 1H), 6.18 – 6.07 (m, 1H), 5.81 – 5.72 (m, 1H), 5.54 (d, *J* = 17.5 Hz, 1H), 4.19 (d, *J* = 16.8 Hz, 2H), 4.01 (d, *J* = 16.8 Hz, 2H), 2.98 (s, 3H), 2.09 (q, *J* = 6.9 Hz, 2H), 1.45 – 1.27 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, acetone-*d*₆) δ ppm 169.1, 143.7, 136.4, 133.6, 62.2, 47.3, 32.9, 32.1, 22.9, 14.1 (boron-carbon bound was not visible); ¹¹B NMR (96 MHz, acetone-*d*₆) δ ppm 10.8; HRMS (ESI) calcd. for C₁₆H₂₂N [M+H]⁺: 265.1485 found: 265.1484.

General procedure for [4+2] cycloaddition of B-MIDA dienes to nitrosoarene compounds.

To a solution of diene (1 eq) (MIDA ester) in AcOEt was added aryl nitroso (2.5 eq). The reaction mixture was stirred at room temperature or in reflux conditions. The solvent was evaporated and the crude product was purified by silica gel chromatography.

For oxazine 14a, see reference 9.

Oxazine 14b.

To a suspension of diene **13** (50 mg, 0.22 mmol) in AcOEt (2 mL), was added 4-methoxynitrosobenzene (61.5 mg, 0.45 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. (Et₂O:MeCN 8/2, R_f = 0.4). **14b** (37.2 mg, 47%). M.p. = 164 °C; ¹H NMR (400 MHz, acetone-*d*₆) δ ppm 7.09-7.05 (m, 2H), 6.87-6.83 (m, 2H), 5.71 (ddd, *J* = 3.2, 1.7, 1.6 Hz, 1H), 4.47 (bs, 1H), 4.26 (dd, *J* = 16.8, 6.8 Hz, 2H), 4.01 (dd, *J* = 33.6, 16.8 Hz, 2H), 3.75 (s, 3H) 3.74-3.69 (m, 1H), 3.57-3.51 (m, 1H), 3.27 (s, 3H), 1.79 (s, 3H); ¹³C NMR (101 MHz, acetone-*d*₆) δ ppm 168.8, 168.5, 156.4, 145.6, 129.6, 122.3, 119.1, 114.8, 63.19, 63.17,

57.1, 55.7, 55.0, 46.8, 20.6 (boron-carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 9.9; HRMS (ESI) calcd. for $[\text{M}+\text{Na}]^+(\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_6^{11}\text{BNa})$: 383.1385 found: 383.1382.

Oxazine 14c.

To a suspension of diene **13** (60 mg, 0.27 mmol) in AcOEt (2 mL), was added 2-nitrosotoluene (48.9 mg, 0.40 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. ($\text{Et}_2\text{O}/\text{MeCN}$ 8/2, $R_f = 0.5$). **14c** (52 mg, 56%). M.p. = 169 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.23 (m, 1H), 7.16 (m, 2H), 7.15 (m, 1H), 5.74 (s, 1H), 4.51 (bs, 1H), 4.21 (dd, $J = 16.8, 11.1$ Hz, 2H), 3.94 (dd, $J = 19.5, 16.8$ Hz, 2H), 3.69-3.65 (m, 1H) 3.45-3.41 (m, 1H), 3.17 (s, 3H), 2.30 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 168.7, 168.6, 149.7, 133.6, 131.4, 130.2, 127.1, 125.7, 122.2, 119.0, 63.21, 63.16, 56.7, 46.8, 20.6, 18.5 (boron-carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 9.9; HRMS (ESI) calcd. for $[\text{M}+\text{Na}]^+(\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_5^{11}\text{BNa})$: 367.1436 found: 367.1439.

Oxazine 14d.

To a suspension of diene **13** (50 mg, 0.22 mmol) in AcOEt (2 mL), was added 4-chloronitrosobenzene (47.6 mg, 0.34 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.5$). **14d** (61 mg, 77%). M.p. = 224 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.31 – 7.23 (m, 2H), 7.16 – 7.08 (m, 2H), 5.74 (s, 1H), 4.51 (bs, 1H), 4.29 (dd, $J = 16.8, 0.7$ Hz, 2H), 4.05 (dd, $J = 20.8, 16.8$ Hz, 2H), 3.94-3.89 (m, 1H), 3.62 – 3.54 (m, 1H), 3.29 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 168.7, 168.5, 150.6, 129.4, 129.3, 126.9, 122.3, 118.1, 63.24, 63.23, 55.9, 46.9, 20.5 (boron-

carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 9.9; HRMS (ESI) calcd. for $[\text{M}+\text{Na}]^+(\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5^{35}\text{Cl}^{11}\text{BNa})$: 387.0889 found: 367.0888.

Oxazine 14e.

To a suspension of diene **13** (30 mg, 0.13 mmol) in AcOEt (1 ml), was added 4-nitrosobenzoate (33.9 mg, 0.19 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.4$). **14e** (31.9 mg, 61%). M.p. = 210 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.93-7.90 (m, 2H), 7.17-7.14 (m, 2H), 5.76 (s, 1H), 4.56 (bs, 1H), 4.35-4.29 (dd, $J = 16.8, 0.8$ Hz, 2H), 4.29 (q, $J = 7.1$ Hz, 2H), 4.14-4.04 (ddd, $J = 16.8, 10.1, 1.1$ Hz, 2H), 4.12-4.05 (m, 1H), 3.70-3.65 (m, 1H), 3.33 (s, 3H), 1.83 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 168.7, 168.5, 166.5, 155.0, 131.4, 129.1, 123.6, 122.2, 114.9, 63.28, 63.25, 60.9, 54.6, 47.0, 20.4, 14.7 (boron-carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 10.0; HRMS (ESI) calcd. for $[\text{M}+\text{Na}]^+(\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_7^{11}\text{BNa})$: 425.1490 found: 425.1491.

Oxazine 19.

To a suspension of diene **15** (40.0 mg, 2.21 mmol) in AcOEt (2 ml), was added nitrosobenzene (59.1 mg, 5.52 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.4$). **19** (28 mg, 43%). M.p. = 161 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.29-7.25 (m, 2H), 7.12-7.08 (m, 2H), 6.96-6.92 (m, 1H), 6.06 (dddd, $J = 10.1, 2.4, 1.7, 1.6$ Hz, 1H), 5.93 (dddd, $J = 10.1, 5.2, 2.8, 1.7$ Hz, 1H), 4.61(bs, 1H), 4.29 (dd, $J = 16.8, 0.7$ Hz, 2H), 4.10-4.04 (m, 1H), 4.06 (dd, $J = 22.6, 16.8$ Hz, 2H), 3.70-3.64 (m, 1H), 3.32 (s, 3H); ^{13}C NMR

(101 MHz, acetone- d_6) δ ppm 168.7, 168.5, 152.0, 129.6, 127.9, 122.6, 122.2, 116.5, 63.2, 52.6, 46.9 (boron-carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 9.9; HRMS (ESI) calcd. for $[\text{M}+\text{Na}]^+(\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_5^{11}\text{BNa})$: 339.1128 found: 339.1125.

Oxazine 20.

To a suspension of diene **16** (63 mg, 0.24 mmol) in AcOEt (3 mL), was added nitrosobenzene (64 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.7$). **20** (61 mg, 68%). M.p. = 188 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.28 – 7.21 (m, 2H), 7.02 (m, 1H), 6.86 (m, 1H), 6.06 (ddd, $J = 10.3, 5.2, 2.8$ Hz, 1H), 5.91 (dt, $J = 10.3, 1.4$ Hz, 1H), 4.37 (bd, $J = 1.4$ Hz, 1H), 4.31 (dd, $J = 19.2, 16.9$ Hz, 2H), 4.10 (dd, $J = 16.9, 10.7$ Hz, 2H), 4.10 – 4.07 (m, 1H), 3.35 (s, 3H), 1.68 – 1.62 (m, 2H), 1.44 – 1.21 (m, 4H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 169.0, 168.1, 149.9, 129.6, 127.6, 126.3, 121.4, 116.8, 69.6, 63.2, 58.1, 46.8, 31.9, 23.4, 14.3; ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 10.2; HRMS (ESI) calcd. for $[\text{M}+\text{H}]^+(\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_5^{11}\text{B})$: 373.1935 found: 373.1933.

Oxazine 21.

To a suspension of diene **17** (30 mg, 0.11 mmol) in AcOEt (2 mL), was added nitrosobenzene (23 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by silica gel chromatography. ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.4$). **21** (32 mg, 78%). M.p. = 207 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.59-7.57 (m, 2H), 7.40-7.36 (m, 2H), 7.33-7.23 (m, 5H), 7.00-6.96 (m, 1H), 6.51 (m, 1H), 4.74 (bs, 1H), 4.57 (ddd, $J = 15.8, 2.8, 1.8$ Hz, 1H), 4.33 (d, $J = 16.8$ Hz), 4.10 (dd, $J = 26.0, 16.8$ Hz) 4.01 (ddd, $J = 15.8, 2.8, 1.1$ Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 169.8, 169.6, 152.7,

140.4, 133.5, 130.6, 130.4, 129.2, 126.6, 126.2, 123.8, 118.0, 64.3, 54.8, 48.0 (boron-carbon bound was not visible); ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 10.2; HRMS (ESI) calcd. for $[\text{M}+\text{H}]^+(\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_5^{11}\text{B})$: 393.1622 found: 393.1618.

Oxazine 22 and 22'

To a suspension of diene **18** (50 mg, 0.18 mmol) in AcOEt (2 mL), was added nitrosobenzene (38 mg, 0.35 mmol). The reaction mixture was stirred under reflux during 24 h. The solvent was evaporated and the crude product was purified by solid phase silica gel chromatography. ($\text{Et}_2\text{O}:\text{MeCN}$ 8/2, $R_f = 0.4$). **22** + **22'** (40/60) (62.8 mg, 89%). The mixture of isomer was solubilised in the minimum amount of CHCl_3 , and left overnight in a fridge at +5 °C. The precipitate was filtered, washed with Et_2O and recrystallized in MeOH to afford pure isomer **22'** as white crystals. The filtrate was evaporated and diluted in CHCl_3 (1 mL). Aqueous HCl (1M) (0.5 mL) was added and heterogeneous mixture was vigorously stirred for 24 h to decompose the residual **22'**. The organic phase was separated, dried over MgSO_4 , filtered and concentrated under vacuum. After purification by silica gel chromatography, **22** was obtained as a pale yellow solid.

Isomer **22**: M.p. = 174 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.44-7.40 (m, 2H), 7.17-7.09 (m, 5H), 7.00-6.95 (m, 2H), 6.81-6.75 (m, 1H), 6.17 (ddd, $J = 10.0, 1.7, 1.6$ Hz, 1H), 6.04 (ddd, $J = 10.0, 5.2, 2.9$ Hz, 1H) 5.24 (ddd, $J = 4.8, 2.9, 1.7$ Hz, 1H), 4.59 (m, 1H), 4.36 (dd, $J = 29.6, 16.9$ Hz, 2H), 4.10 (dd, $J = 39.7, 16.9$ Hz, 2H), 3.33 (s, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 169.1, 167.9, 150.1, 139.1, 130.5, 129.2, 128.4, 127.9, 127.8, 125.9, 121.9, 117.3, 72.8, 64.3, 63.21, 63.16, 46.7; ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 10.3; HRMS (ESI) calcd. for $[\text{M}+\text{H}]^+(\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5^{11}\text{B})$: 393.1622 found: 393.1624.

Isomer **22'**: M.p. = 152 °C; ^1H NMR (400 MHz, acetone- d_6) δ ppm 7.60-7.58 (m, 2H), 7.37-7.31 (m, 5H), 7.22-7.20 (m, 2H), 6.98-6.94 (m, 1H), 6.19 (ddd, J = 10.5, 4.8, 2.4 Hz, 1H), 5.68 (ddd, J = 10.5, 1.7, 1.5 Hz, 1H), 5.11 (m, 1H), 4.19 (dd, J = 88.8, 16.9 Hz, 2H), 4.11 (dd, J = 54.0, 16.9 Hz, 2H), 4.11-4.07 (m, 1H), 3.13 (s, 3H); ^{13}C NMR (101 MHz, acetone- d_6) δ ppm 169.4, 167.8, 149.9, 139.9, 130.2, 129.6, 129.1, 129.0, 127.0, 125.1, 122.1, 117.1, 72.8, 63.08, 63.03, 49.8, 47.3, 45.4; ^{11}B NMR (96 MHz, acetone- d_6) δ ppm 10.6; HRMS (ESI) calcd. for $[\text{M}+\text{H}]^+(\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5^{11}\text{B})$: 393.1622 found: 393.1632.

Conversion of 22 to 1,2-diphenyl-1H-pyrrole 3k under basic conditions.

Oxazine **22** (6.0 mg, 0.015 mmol) was dissolved in acetone- d_6 (0.4 mL). NaOD (1M in water, 15 μL , 0.015 mmol) was then added and the reaction was directly followed by ^1H and ^{11}B NMR. After one night, a 32% conversion was observed with no further evolution if the reaction was left longer at room temperature. NaOD (1M, 30 μL , 0.030 mmol) was finally added to observe complete consumption of the starting oxazine, followed by DCl (1M in D_2O , 15 μL , 0.015 mmol). After 15 min, a full conversion into the corresponding pyrrole was observed. The reaction mixture was poured into DCM (2 mL), and water (1 mL) was added. The aqueous layer was extracted with DCM (3 x). The organic phase was dried over MgSO_4 , and filtered over a pad of silica gel and eluted with DCM to give pyrrole **3k** (2.8 mg, 85%).

Conversion of 22' to 2-phenylfuran 31 under acidic conditions

Oxazine **22'** (6.8 mg, 0.017 mmol) was dissolved in acetone- d_6 (0.4 mL). DCl in D_2O (1M, 18 μL , 0.018 mmol). After full conversion of the starting oxazine, reaction mixture was poured into DCM (1 mL). NaOH (1M, 0.2 mL) was added. The aqueous layer was extracted with DCM (3 x),

dried over MgSO₄, filtered and purified over a pad of silica (DCM). Furan **31** was isolated. (2.4 mg, quantitative)

Isolation of by-product **36**

Oxazine **22'** (25.2 mg, 0.064 mmol) was dissolved in acetone-*d*₆ (0.7 mL). DCl (1M in D₂O, 64 μL, 0.064 mmol) was then added and the reaction was followed by ¹H and ¹¹B NMR. After full conversion of the starting oxazine, the reaction mixture was extracted with DCM (3 x), dried over MgSO₄, filtered and concentrated. The crude yellow solid was suspended in CHCl₃ (0.5 mL) and filtered. The resulting solid was washed with CHCl₃ (3 x). (4 mg of **36**, 25%).

2-Phenylfuran **31**.²⁹

¹H NMR (400 MHz, CDCl₃) δ ppm ¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.66 (m, 2H), 7.48 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.27 (m, 1H), 6.66 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 154.1, 142.2, 131.0, 128.8, 127.5, 123.9, 111.8, 105.1.

6-Methyl-2-(phenylamino)-1,3,6,2-dioxazaborocane-4,8-dione **36**.

¹H NMR (400 MHz, acetone-*d*₆) δ ppm 7.07 (m, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 6.62 (m, 1H), 4.74 (bs, 1H), 4.25 (d, *J* = 17.2 Hz, 2H), 4.09 (d, *J* = 17.2 Hz, 2H), 3.01 (s, 3H); ¹³C NMR (101 MHz, acetone-*d*₆) δ ppm 167.6, 147.2, 129.0, 117.4, 116.2, 62.1, 45.8, boron-carbon bond was not visible; ¹¹B NMR (96 MHz, acetone-*d*₆) δ ppm 9.9; HRMS (ESI) calcd. for [M+H]⁺(C₁₁H₁₄N₂O₄¹¹B): 249.1047 found: 249.1042.

Synthesis and Suzuki-Miyaura coupling of boronated oxazine MIDA ester **38** with 2-bromotoluene

To a suspension of diene **37** (229 mg, 0.80 mmol) in AcOEt (10 mL), was added nitrosobenzene (221 mg, 2.06 mmol). The reaction mixture was stirred at 50 °C for 22 h. The solvent was evaporated and the crude product product was purified by solid phase silica gel chromatography (Et₂O:MeCN 8/2, R_f = 0.4). **38** (229 mg, 73%). M.p. = 153 °C; ¹H NMR (400 MHz, acetone-*d*₆) δ ppm 7.40 – 7.25 (m, 7H), 7.17 (m, 2H), 6.94 (m, 1H), 4.67 (t, *J* = 2.4 Hz, 2H), 3.97 (t, *J* = 2.4 Hz, 2H), 3.94 (d, *J* = 16.8 Hz, 2H), 3.43 (d, *J* = 16.8 Hz, 2H), 3.07 (s, 3H); ¹³C NMR (101 MHz, acetone-*d*₆) δ ppm 168.2, 151.5, 144.4, 141.9, 129.7, 129.5, 129.4, 128.2, 122.5, 116.2, 72.2, 63.0, 58.3, 47.3 (boron-carbon bound was not visible); ¹¹B NMR (96 MHz, acetone-*d*₆) δ ppm 10.4; HRMS (ESI) calcd. for [M+H]⁺(C₂₁H₂₂N₂O₅¹¹B): 393.1618 found: 393.1622.

In a flask under an inert atmosphere was added oxazine **38** (41 mg, 0.10 mmol), Pd(OAc)₂ (1.2 mg, 0.0053 mmol), SPhos (4.3 mg, 0.010 mmol) and 2-bromotoluene (14 μL, 0.11 mmol) in dioxane (2 mL). An aqueous solution of K₃PO₄ (3M, 190 mL, 0.57 mmol) previously degassed with Ar for 15 min was then added. The orange reaction mixture was stirred at 60 °C overnight. Et₂O (5 mL) and NaOH (1M, 5 mL) were added in the reaction mixture. Aqueous phase was extracted with Et₂O (3 x) and the organic layer was dried over MgSO₄, filtered and concentrated under vacuum. Crude compound was purified by silica gel chromatography (hexane/AcOEt 95/5, R_f = 0.4). **39** (27 mg, 71%). M.p. = 161 °C; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.40 – 6.83 (m, 14H), 4.58 (s, 2H), 4.12 (s, 2H), 2.00 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 150.2, 138.9, 137.1, 136.1, 134.1, 131.0, 130.3, 130.0, 129.1, 128.2, 128.1, 127.6, 127.2, 125.8, 122.8, 116.2, 72.0, 55.4, 19.7; HRMS (ESI) calcd. for [M+H]⁺(C₂₃H₂₂NO): 328.1689 found: 328.1701.

ASSOCIATED CONTENT

Supporting Information

Spectral data of all pyrrole and oxazine compounds; X-ray structural data of **22'**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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