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Regioisomeric and Substituent Effects upon the Outcome of the Reaction of 1-Borodienes with Nitrosoarene Compounds

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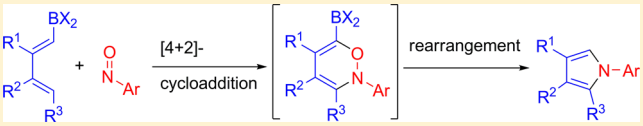
Supporting Information

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 yields 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 the cases, in moderate to good yields. ^{1}H and ^{11}B NMR studies on two boro-oxazine regioisomers showed that selective deprotection can be performed. Formation of either the pyrrole or the 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.

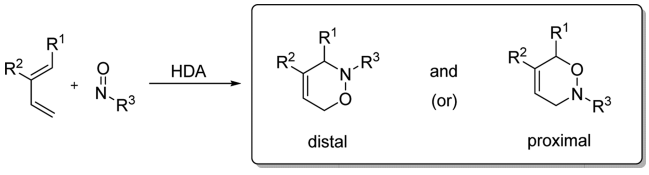


INTRODUCTION

The hetero-Diels–Alder reaction between a nitroso heterodienophile 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, 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 alkaloid derivatives,[3] heterocycles,[4] 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 the diene partners. For example, Houk et al. examined monosubstituted dienes and their addition to numerous nitroso derivatives[6] and established a correlation between regioselectivity and (1) the properties and position of substituents on the diene and (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 C_1 and an electron-donating group at the C_2 position. For the proximal isomer, a nonbulky substituent at C_1 and an electron-withdrawing group at C_2 are required. Nevertheless, regioselectivity is also dependent upon the nature of the nitroso compound.

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, R^1 = Bpin) with aryl nitroso derivatives **2**.[9] In addition to the possible postfunctionalization of the resulting cycloadducts, we expected that tuning of the electronic properties of the boronated group through the introduction of various substituents on boron[10] 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

Scheme 1. Regioselectivity of Nitroso Diels–Alder Reaction with Mono- and Disubstituted Dienes



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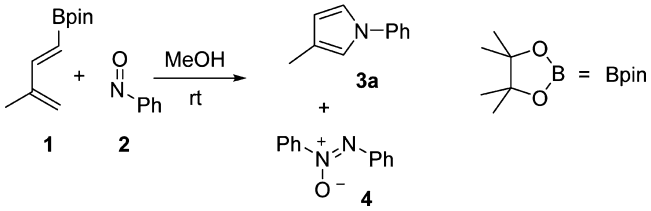
these studies, especially the impact of varying the nature of both the borodiene and the dienophile substituents upon the reaction outcome, and, hence, discuss the mechanistic implications of the results.

RESULTS AND DISCUSSION

Reaction of 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

Scheme 2. *N*-Phenylpyrrole Formation from the Reaction of Boronated Diene 1 and Nitrosobenzene 2



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 ^{1}H 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).

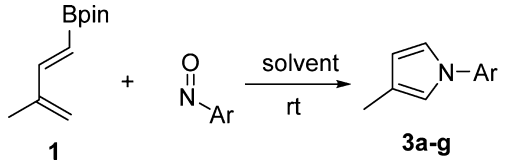
Further studies to address the scope of this reaction were conducted, the results of which are summarized in Table 1.

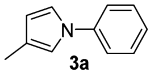
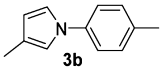
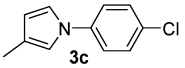
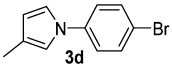
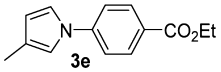
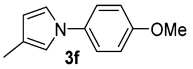
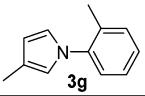
Differently substituted nitrosoarene compounds were reacted with borodiene **1** to afford *N*-arylpyrroles **3** in moderate to good yields. Use of either a protic solvent (MeOH) or an aprotic solvent (DCM) had no significant effect (entries 1 and 2, Table 1). Because of the formation of the azoxybenzene byproduct, an excess of nitrosoarene reagent (2.5 equiv) 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 52–82% yields (entries 4–9, Table 1). Other dienes, prepared according to literature procedures,[11] were also examined, as summarized in Table 2.

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 that 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 was examined, possessing aromatic or electron-withdrawing groups in position 4. Diene **8** was prepared via a three-step pathway, involving a Sonogashira reaction of *β*-bromostyrene with

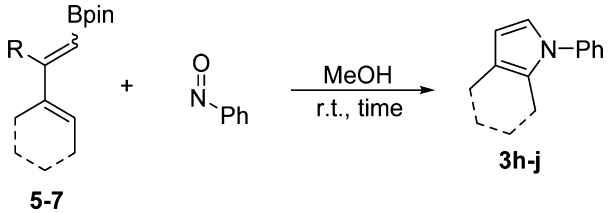
Table 1. Pyrrole Formation from the Reaction of Nitrosoarenes with Diene 1

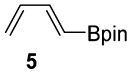
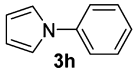
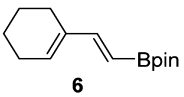
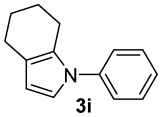
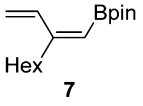
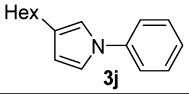


Entry	Nitroso compound	Product	Yield (%)
1[a]	C_6H_5NO	 **3a**	67
2[b]	C_6H_5NO	**3a**	61
3[c]	C_6H_5NO	**3a**	82
4[c]	*p*-Me-C_6H_4NO	 **3b**	60
5[c]	*p*-Cl-C_6H_4NO	 **3c**	68
6[c]	*p*-Br-C_6H_4NO	 **3d**	65
7[c]	*p*-EtO_2C-C_6H_4NO	 **3e**	57
8[c]	*p*-MeO-C_6H_4NO	 **3f**	77
9[c]	*o*-Me-C_6H_4NO	 **3g**	69

[a]Reaction with 1.5 equiv of ArNO in MeOH at rt for 5 h. [b]Reaction with 1.5 equiv of ArNO in DCM at rt for 48 h. [c]Reaction with 2.5 equiv of ArNO in MeOH at rt for 5 h.

Table 2. Reaction of Dienes 5–7 with Nitrosobenzene



Entry	Diene	Product	Yield (%)
1[a]	 **5**	 **3h**	78
2[b]	 **6**	 **3i**	16
3[b]	 **7**	 **3j**	34

[a]Reaction with 2.5 equiv of ArNO in MeOH at rt for 5 h. [b]Reaction with 2.5 equiv of ArNO in MeOH at rt for 16 h.

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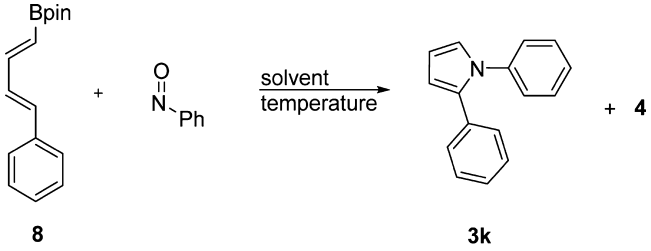
trimethylsilylacetylene, followed by proto-desilylation, to give 4-phenyl-3-buten-1-yne as an *E*/*Z* mixture (91/9).[12] Hydroboration using pinacolborane and Schwartz's catalyst[11a] provided the desired diene **8** as a mixture of two stereoisomers (*E*,*E*:*E*,*Z* = 91:9) in a 56% overall yield. The subsequent reactions of diene **8** with nitrosobenzene are shown in Table 3.

Table 3. Study of the Reactivity of Diene 8 with Nitrosobenzene



8 **3k**

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)

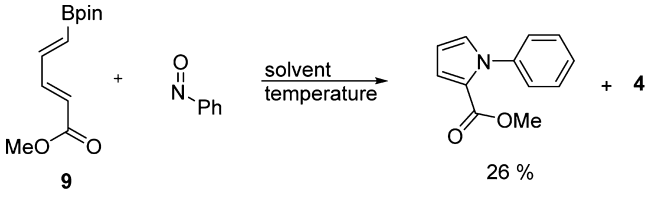
[a]Reactions with 2.5 equiv of nitrosobenzene. [b]Reaction with 2.5 equiv of nitrosobenzene added in portions. [c]Reaction with 2.5 equiv of nitrosobenzene added slowly by syringe pump. [d]Reaction with 3.5 equiv of nitrosobenzene.

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 ^{1}H 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-byproduct formation (1 equiv at the outset - 1 equiv after 4 h - 0.5 equiv after 4 h), or by slow addition of a MeOH solution by syringe pump (see entries 6 and 7, Table 3). Finally, the use of 3.5 equiv 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 of 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-stabilized ylide and *β*-borylacrolein pinacol ester, resulting in a mixture of three stereoisomers (*E*,*E*:*E*,*Z*:*Z*,*E* = 83:10:7) in an unoptimized 30% overall yield.[13] The subsequent reactions of diene **9** are shown in Table 4.

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 **3l**, 5 equiv of nitrosobenzene and a 128 h

Table 4. Study of the Reactivity of Diene 9 with Nitrosobenzene



9 26 % **3l**

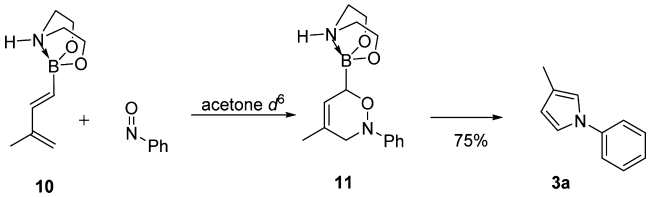
entry	solvent	temperature (°C)	time (h)	*E*,*E*-isomer conversion (isolated yield) (%)
1[a]	MeOH	rt	16	0
2[a]	MeOH	reflux	16	0
3[a]	toluene	rt	16	0
4[a]	toluene	reflux	64	15
5[b]	toluene	reflux	128	100 (26)

[a]Reactions with 2.5 equiv of nitrosobenzene. [b]Reaction with 5 equiv of nitrosobenzene.

reaction time were 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 **3l** 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, we 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



10 **11** **3a**

Reaction of 1-borodiene **10** with nitrosobenzene resulted in the identification of the [4 + 2]-cycloadduct **11** in the ^{1}H 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 eq 1 (compared with

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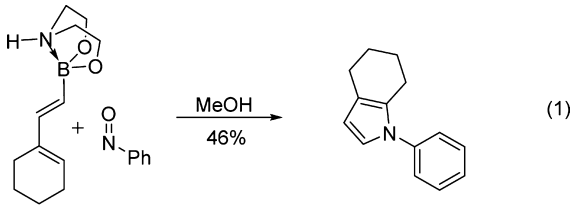
16% over 16 h for the corresponding pinacol ester derivative, entry 2, Table 2).



12 3i

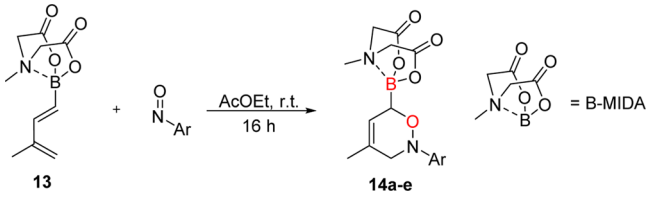
Most interestingly of course, the observation of the transient [4 + 2]-hetero-Diels–Alder cycloadduct **11** (Scheme 3) confirms the key role of the oxazine cycloadduct in the subsequent formation of the pyrrole. Diethanolamine esters are known for their facile hydrolysis or methanolysis to regenerate 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 then a pinacol ester, and, therefore, more reactive toward the electron-deficient dienophile.

Prompted by these results, we, therefore, examined the behavior of the corresponding MIDA (*N*-methyliminodiacetic)-borodiene derivatives. Because of their high stability toward 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 sp^3- versus an sp^2-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**.

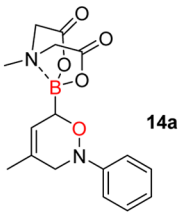
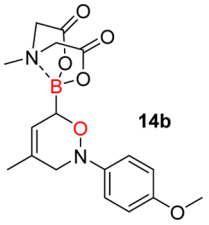
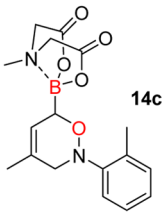
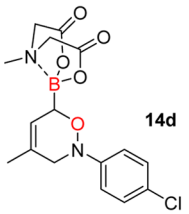
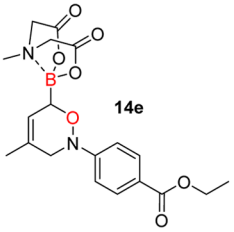
The reaction of the MIDA-borodiene **13** provided the corresponding oxazine cycloadducts in moderate to good yields with the different nitrosoarene compounds, without obvious electronic effects from the aryl substituent. However, single regioisomeric products were obtained, as exemplified by the formation 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% and 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 byproduct 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 summarized in Table 6.

Table 5. Reactivity of MIDA-Substituted Diene 13 with Nitrosoarene Compounds



13 14a-e

Entry	Nitroso compound	Product	Yield (%)
1	C_6H_5NO	 14a	64
2	*p*-MeO-C_6H_4-NO	 14b	47
3	*o*-Me-C_6H_4-NO	 14c	56
4	*p*-Cl-C_6H_4-NO	 14d	77
5	*p*-EtO_2C-C_6H_4-NO	 14e	61

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 C_4 noticeably reduced the reactivity of the borodiene **18** with

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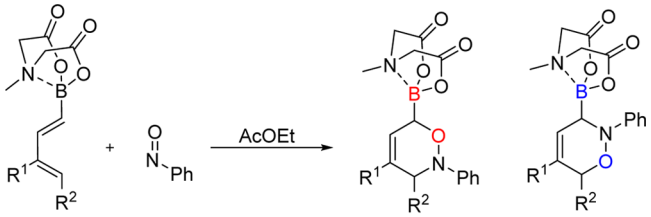
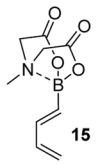
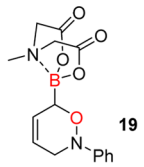
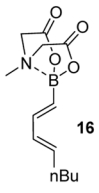
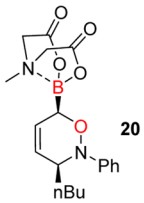
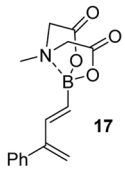
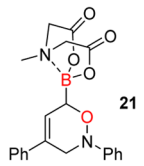
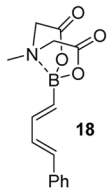
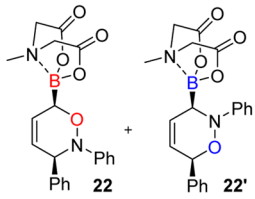
Table 6. Reactivity of MIDA-Substituted Dienes 15−18 with Nitrosobenzene



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)

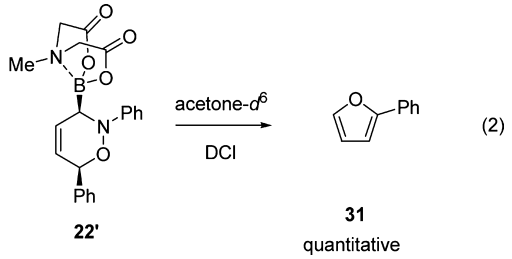
[a]Reaction with 2.5 equiv of nitrosobenzene in AcOEt at rt for 6 h. [b]Reaction with 5 equiv of nitrosobenzene AcOEt at reflux for 24 h.

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 the Supporting Information), 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-diene[20]).

Mechanistic Aspects of the Reaction of 1-Borodienes with Nitrosoarene Compounds. The mechanism which was hypothesized and subsequently supported by DFT calculations[9] 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 pyrroles **3a−l**.

Further investigations into this process to support our supposition and DFT calculations[9] 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 ^{1}H NMR spectrum of the crude mixture.[14] Reacting diene **10** or **12** with nitrosobenzene for 2 h resulted in complete diene consumption, and even the boro-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.

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. We, therefore, decided to test another method to deprotect the MIDA boronate ester function of these types of oxazine cycloadducts. Hence, under acidic conditions (DCl 1 M, 1 equiv) in acetone-d_6, 2-phenylfuran **31** was cleanly and quantitatively produced after 15 min at room temperature from regioisomer **22′**, as shown in eq 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.



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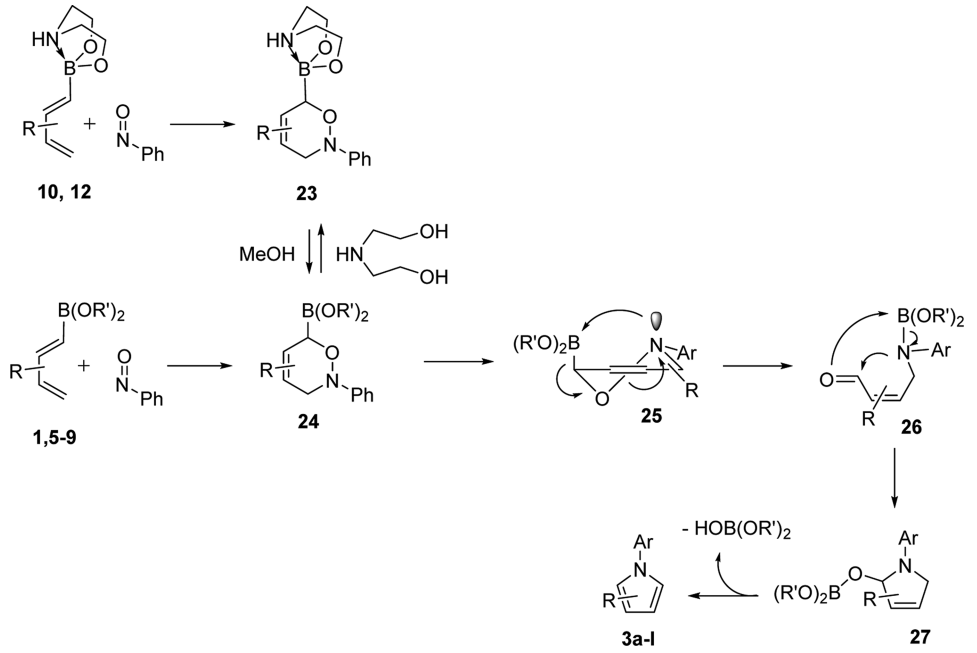
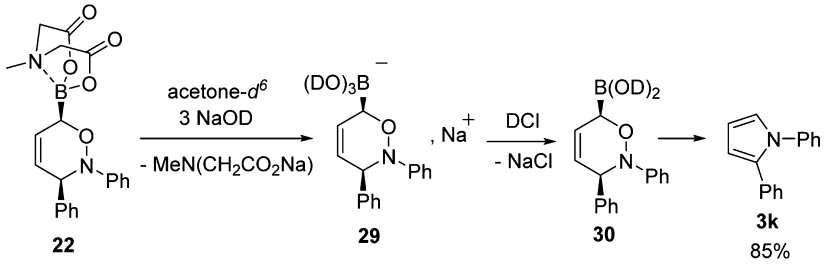
Scheme 4. Proposed Mechanism for the Formation of Pyrroles from the Reaction of 1-Borodienes with Nitrosoarene Compounds

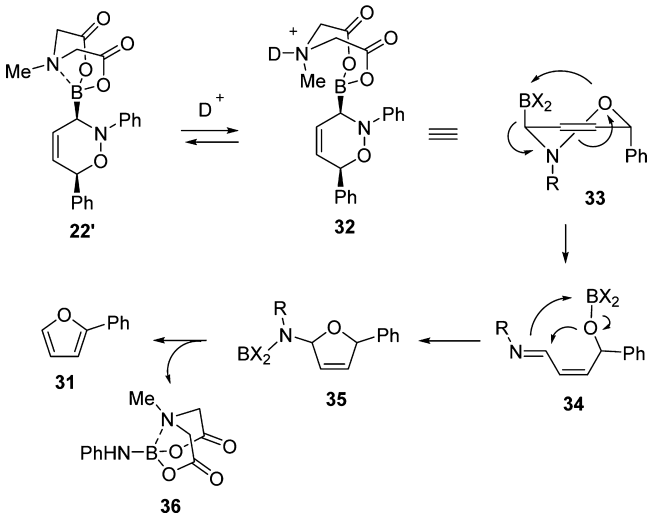


Scheme 5. Proposed Reaction Sequence for the Formation of Pyrrole 3k from MIDA Boronate Oxazine Derivative 22



Moreover, the byproduct **36** was isolated by extracting the reaction mixture with DCM (see Scheme 6) in 25% yield, whose structure was established by ^{1}H, ^{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 decoordination 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, ^{1}H NMR of the crude reaction mixture (see the Supporting Information) 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).

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.

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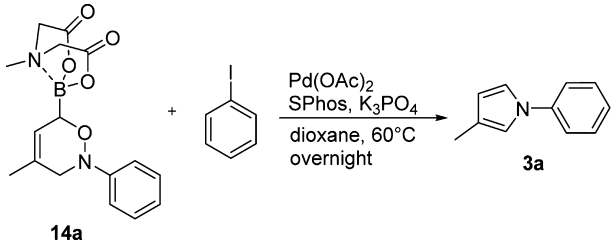
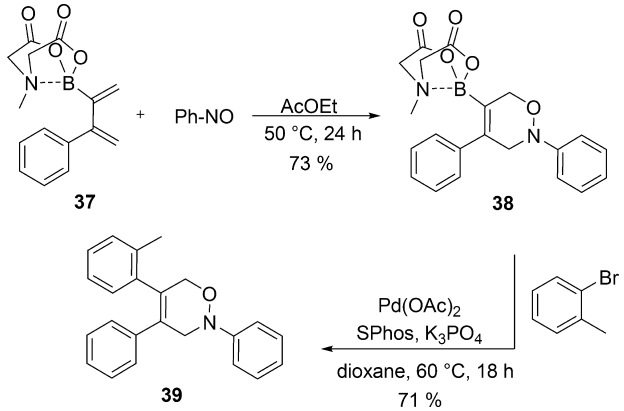
Scheme 7. Reactivity of Oxazine 14a and Iodobenzene under Suzuki−Miyaura Coupling Conditions



Scheme 8. Synthesis of Triarylated Oxazine 39 from the Nitrosobenzene Cycloadduct 38 after Suzuki−Miyaura Cross-Coupling Reaction Sequence



A NOESY NMR experiment (correlation between H's of the methyl group of the toluene moiety and H's on the oxazine ring at C_6) established the structure of this compound and consequently the orientation of the first cycloaddition. No ring contraction product was observed in this case.

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 for 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 byproducts. 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 this 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 distilled on sodium, benzophenone and DCM on P_2O_5. Reactions were monitored by TLC analysis using Silica Gel 60 F_{254} 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 ^{1}H, 75 or 101 MHz for ^{13}C, and 96 MHz for ^{11}B. ^{1}H and ^{13}C NMR chemical shifts were referenced to Me_4Si as internal reference, and ^{11}B NMR chemical shifts to external $BF_3{\cdot}OEt_2$ (0.0 ppm). Deuterated chloroform $CDCl_3$ 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 equiv) (pinacol boronate or diethanolamine esters) in the solvent was added nitrosoarene compound (2.5−5 equiv). 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 Compounds 3a−j.[9] *1,2-Diphenyl-1H-pyrrole* ***3k***.[23] 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%). ^{1}H 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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-1H-pyrrole-2-carboxylate ***3l***.[24] 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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$), 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 the procedure of Burke et al.[15] mp = 122 °C; ^{1}H 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); ^{13}C 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); ^{11}B NMR (96 MHz, acetone-d_6) δ ppm 10.8; HRMS (ESI) calcd. for $C_{16}H_{22}N$ $[M + H]^+$: 265.1485 found: 265.1484.

General Procedure for [4 + 2] Cycloaddition of B-MIDA Dienes to Nitrosoarene Compounds. To a solution of diene (1 equiv) (MIDA ester) in AcOEt was added aryl nitroso (2.5 equiv). 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.

14a. For oxazine **14a**, see ref 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 (Et_2O:MeCN 8/2, R_f = 0.4). **14b** (37.2 mg, 47%). mp = 164 °C; ^{1}H 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),

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3.57−3.51 (m, 1H), 3.27 (s, 3H), 1.79 (s, 3H); ^{13}C 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 $[M + Na]^+$ ($C_{17}H_{21}N_2O_6{}^{11}BNa$): 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 (Et_2O/MeCN 8/2, R_f = 0.5). **14c** (52 mg, 56%). mp = 169 °C; ^{1}H 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 $[M + Na]^+$ ($C_{17}H_{21}N_2O_5{}^{11}BNa$): 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 (Et_2O:MeCN 8/2, R_f = 0.5). **14d** (61 mg, 77%). mp = 224 °C; ^{1}H 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 $[M + Na]^+$ ($C_{16}H_{18}N_2O_5{}^{35}Cl{}^{11}BNa$): 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 (Et_2O:MeCN 8/2, R_f = 0.4). **14e** (31.9 mg, 61%). mp = 210 °C; ^{1}H 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 $[M + Na]^+$ ($C_{19}H_{23}N_2O_7{}^{11}BNa$): 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 (Et_2O:MeCN 8/2, R_f = 0.4). **19** (28 mg, 43%). mp = 161 °C; ^{1}H 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 $[M + Na]^+$ ($C_{15}H_{17}N_2O_5{}^{11}BNa$): 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 (Et_2O:MeCN 8/2, R_f = 0.7). **20** (61 mg, 68%). mp = 188 °C; ^{1}H 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 $[M + H]^+$ ($C_{19}H_{25}N_2O_5{}^{11}B$): 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 (Et_2O:MeCN 8/2, R_f = 0.4). **21** (32 mg, 78%). mp = 207 °C; ^{1}H 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 $[M + H]^+$ ($C_{21}H_{21}N_2O_5{}^{11}B$): 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 (Et_2O:MeCN 8/2, R_f = 0.4). **22** + **22′** (40/60) (62.8 mg, 89%). The mixture of isomer was solubilized 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 (1 M) (0.5 mL) was added, and the 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**: mp = 174 °C; ^{1}H 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 $[M + H]^+$ ($C_{21}H_{22}N_2O_5{}^{11}B$): 393.1622 found: 393.1624.

Isomer **22′**: mp = 152 °C; ^{1}H 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 $[M + H]^+$ ($C_{21}H_{22}N_2O_5{}^{11}B$): 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 (1 M in water, 15 μL, 0.015 mmol) was then added, and the reaction was directly followed by ^{1}H 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 (1 M, 30 μL, 0.030 mmol) was finally added to observe complete consumption of the starting oxazine, followed by DCl (1 M 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×). The organic phase was dried over

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$MgSO_4$, 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), followed by the addition of DCl in D_2O (1 M, 18 μL, 0.018 mmol). After full conversion of the starting oxazine, the reaction mixture was poured into DCM (1 mL). NaOH (1M, 0.2 mL) was added. The aqueous layer was extracted with DCM (3×), dried over $MgSO_4$, filtered, and purified over a pad of silica (DCM). Furan **31** was isolated. (2.4 mg, quantitative)

Isolation of Byproduct 36. Oxazine **22′** (25.2 mg, 0.064 mmol) was dissolved in acetone-d_6 (0.7 mL). DCl (1 M in D_2O, 64 μL, 0.064 mmol) was then added, and the reaction was followed by ^1H and ^{11}B NMR. After full conversion of the starting oxazine, the reaction mixture was extracted with DCM (3×), dried over $MgSO_4$, filtered, and concentrated. The crude yellow solid was suspended in $CHCl_3$ (0.5 mL) and filtered. The resulting solid was washed with $CHCl_3$ (3×). (4 mg of **36**, 25%).

2-Phenylfuran ***31***.[25] ^1H NMR (400 MHz, $CDCl_3$) δ ppm ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, acetone-d_6) δ ppm 167.6, 147.2, 129.0, 117.4, 116.2, 62.1, 45.8, boron−carbon bound was not visible; ^{11}B NMR (96 MHz, acetone-d_6) δ ppm 9.9; HRMS (ESI) calcd. for $[M + H]^+$ ($C_{11}H_{14}N_2O_4{}^{11}B$): 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 (Et_2O:MeCN 8/2, R_f = 0.4). **38** (229 mg, 73%). mp = 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); ^{13}C 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); ^{11}B NMR (96 MHz, acetone-d_6) δ ppm 10.4; HRMS (ESI) calcd. for $[M + H]^+$ ($C_{21}H_{22}N_2O_5{}^{11}B$): 393.1618 found: 393.1622.

In a flask under an inert atmosphere were 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 K_3PO_4 (3 M, 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. Et_2O (5 mL) and NaOH (1M, 5 mL) were added in the reaction mixture. The aqueous phase was extracted with Et_2O (3×), and the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude compound was purified by silica gel chromatography (hexane/AcOEt 95/5, R_f = 0.4). **39** (27 mg, 71%). mp = 161 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40−6.83 (m, 14H), 4.58 (s, 2H), 4.12 (s, 2H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $[M + H]^+$ ($C_{23}H_{22}NO$): 328.1689 found: 328.1701.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data of all pyrrole and oxazine compounds; X-ray structural data of **22′**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00593.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wichterle, O. *Collect. Czech. Chem. Commun.* **1947**, *12*, 292−304.

(2) For reviews on HDA reactions of nitroso reagents, see: (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (b) Waldmann, H. *Synthesis* **1994**, 535−551. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. (d) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031−2043. (e) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630−5647.

(3) (a) Leonard, N. J.; Playtis, A. J.; Skoog, F.; Schmitz, R. Y. *J. Am. Chem. Soc.* **1971**, *16*, 3056−3058. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *50*, 1818−1825. (c) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 3135−3138. (d) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088−4097. (e) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083−6089. (f) Kobayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879. (g) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592. (h) Cabanal-Duvillard, I.; Berrienb, J. F.; Royer, J. *Tetrahedron Asymmetry* **2000**, *11*, 2525−2529. (i) Blakemore, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831−1845. (j) Zhu, L.; Lauchli, R.; Loo, M.; Shea, K. J. *Org. Lett.* **2007**, *12*, 2269−2271.

(4) (a) Judd, T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683−4685. (b) Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4686−4688. (c) Ding, P.; Miller, M. J.; Chen, Y.; Helquist, P.; Oliver, A. J.; Wiest, O. *Org. Lett.* **2004**, *11*, 1805−1808. (d) Wencewicz, T. A.; Yang, B.; Rudloff, J. R.; Oliver, A. G.; Miller, M. J. *J. Med. Chem.* **2011**, *54*, 6843−6858.

(5) (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089−5090. (b) Bressel, B.; Reissig, H. U. *Org. Lett.* **2007**, *3*, 527−530. (c) Pfrengle, F.; Reissig, H. U. *Chem. Soc. Rev.* **2010**, *39*, 549−557. (d) Moinizadeh, N.; Klemme, R.; Kansy, M.; Zimmer, R.; Reissig, H. U. *Synthesis* **2013**, *45*, 2752−2762.

(6) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192−5200.

(7) Galvani, G.; Lett, R.; Kouklovsky, C. *Chem.—Eur. J.* **2013**, *19*, 15604−15614.

(8) (a) Hilt, G.; Bolze, P. *Synthesis* **2005**, *13*, 2091−2115. (b) Welker, M. E. *Tetrahedron* **2008**, *64*, 11529−11539. (c) Eberlin, L.; Tripoteau, F.; Carreaux, F.; Whiting, A.; Carboni, B. *Beilstein J. Org. Chem.* **2014**, *10*, 237−250.

(9) Tripoteau, F.; Eberlin, L.; Fox, M. A.; Carboni, B.; Whiting, A. *Chem. Commun.* **2013**, *49*, 5414−5416.

(10) Berionni, G.; Maji, B.; Knochel, P.; Mayr, H. *Chem. Sci.* **2012**, *3*, 878−882.

(11) (a) Dienes **5** and **6**: hydroboration of the corresponding enyne with pinBH according to: Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127−3128. (b) Diene **7**: bromoboration of 1-octyne, followed by Pd-catalyzed cross-coupling with vinylzinc bromide, according to: Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E.-I. *Org. Lett.* **2009**, *11*, 4092−4095.

(12) Schabel, T.; Plietker, B. *Chem.—Eur. J.* **2013**, *19*, 6938−6941.

(13) Rasset-Deloge, C.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1994**, *131*, 919−925.

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(14) The cycloadduct **11** was identified (NMR experiment, D_6-Me_2CO by comparison of its ^1H spectrum with that of the corresponding MIDA cycloadduct **14a**).
(15) For some examples of conversions of 3,6-dihydro-1,2-oxazines to pyrroles, after several steps, see: (a) Hart, H.; Ramaswami, S. K.; Willer, R. *J. Org. Chem.* **1979**, *44*, 1−7. (b) Blakemore, P. R.; Kim, S.-K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831−1847. (c) Pulz, R.; Schade, W.; Reissig, H.-U. *Synlett* **2003**, 405−407. (d) Krchnak, V.; Waring, K. R.; Noll, B. C.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 4559−4567. (e) Bressel, B.; Reissig, H.-U. *Org. Lett.* **2009**, *11*, 527−530. (f) Al-Harrasi, A.; Bouché, L.; Zimmer, R.; Reissig, H.-U. *Synthesis* **2011**, 109−118. By photolysis, see: (g) Scheiner, P.; Chapman, O. L.; Lassila, J. D. *J. Org. Chem.* **1969**, *34*, 813−816. (h) Givens, R. S.; Choo, D. J.; Merchant, S. N.; Stitt, R. P.; Matuszewski, B. *Tetrahedron Lett.* **1982**, *23*, 1327−1330. In the case of specific substituents, see: (i) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 3135−3138. (j) Kefalas, P.; Grierson, D. S. *Tetrahedron Lett.* **1993**, *34*, 3555−3558. In the presence of basic or acid reagents, see: (k) Firl, J. *Chem. Ber.* **1968**, *101*, 218−225. (l) Shi, G.-Q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445−1456. (m) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1−5. In the presence of oxidants, see: (n) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Synthesis* **2005**, 3346−3354. In the presence of samarium diiodide, see: (o) Jasiński, M.; Watanabe, T.; Reissig, H.-U. *Eur. J. Org. Chem.* **2013**, 605−610. Under high temperatures, see: (p) Ragaini, F.; Cenini, S.; Brignoli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460−466.
(16) Thadani, A. N.; Batey, R. A.; Lough, A. J. *Acta Crystallogr., Sect. E* **2001**, *57*, O1010−O1011.
(17) (a) Cha, J. S.; Brown, H. C. *Bull. Korean Chem. Soc.* **2005**, *26*, 292−296. (b) Bonin, H.; Delacroix, T.; Gras, E. *Org. Biomol. Chem.* **2011**, *9*, 4714−4724.
(18) (a) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17−27 and references therein. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961−6963. (c) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029−1040.
(19) (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466−468. (b) Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333−4343.
(20) Tran, A. T.; Liu, P.; Houk, K. N.; Nicholas, K. M. *J. Org. Chem.* **2014**, *79*, 5617−5626.
(21) Woerly, E. M.; Miller, J. E.; Burke, M. D. *Tetrahedron* **2013**, *69*, 7732−7740.
(22) For similar approach involving Diels−Alder/cross-coupling reactions of 2-boron-substituted-1,3-dienes, see: Wang, L.; Welker, M. E. *J. Org. Chem.* **2012**, *77*, 8280−8286.
(23) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.
(24) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550−1560.
(25) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002−5005.

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