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Preparation of 1,3-dienyl organotrifluoroborates and their Diels–Alder/cross-coupling reactions

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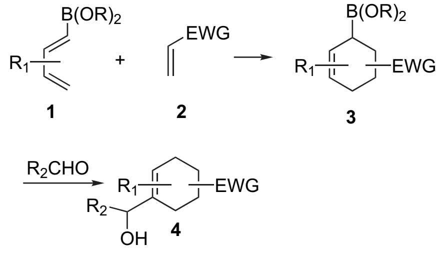
Abstract—2-BF_3-substituted 1,3-butadienes with potassium and tetrabutyl ammonium counterions have been prepared in gram quantities from chloroprene via a simple synthetic procedure. The potassium salt of this new main group element substituted diene has been characterized by ^1H, ^{13}C, ^{11}B, and ^{19}F NMR and the tetra *n*-butyl ammonium salt was also characterized by X-ray crystallography. Diels–Alder reactions of these dienes with dienophiles such as ethyl acrylate, methyl vinyl ketone, and *N*-phenylmaleimide are reported as well as subsequent Pd-catalyzed cross-coupling reactions of those Diels–Alder adducts. 4-Phenyl-2-BF_3-substituted 1,3-diene was prepared by magnesium–halogen exchange from the corresponding 2-bromo and iodo dienes. The 4-phenyl-2-bromo-1,3-butadiene was also characterized by X-ray crystallography. 4-Phenyl-2-BF_3-1,3-butadiene was used in Diels–Alder/cross-coupling reactions and the product of a Diels–Alder reaction with *N*-phenylmaleimide followed by cross-coupling with 4-bromo-benzonitrile was also characterized by X-ray crystallography.

1. Introduction

Reports of main group element substituted 1,3-dienes and their reaction chemistry are still fairly rare in organic chemistry. 2-Triethylsilyl-1,3-butadiene and a few of its Diels–Alder reactions were reported by Ganem and Batt in 1978.[1] Fleming and co-workers reported 1-trimethylsilyl-1,3-butadiene in 1976[2] and its Diels–Alder dimerization in 1981.[3] Paquette and Daniels reported some 2-silyl-substituted 1,3-cyclohexadienes in 1982 but none of their Diels–Alder chemistry.[4] Silyl-substituted diene chemistry was reviewed in 1993.[5] While not containing a diene carbon to silicon bond, related 2-trimethylsilyloxy-1,3-dienes have also been transmetallated to zirconium.[6] A 2-phenylseleno and 2-trialkylstannyl-1,3-butadiene and their Diels–Alder reactions were reported by Bates and co-workers in 1987.[7] Much less has been reported previously about aluminum-substituted 1,3-dienes. Eisch[8] and Hoberg[9] reported the preparation of alumina-1,3-cyclopentadienes decades ago, but very little has been done with them synthetically.[10]

Most work reported with main group-substituted dienes has been done with the 1-(dialkoxyboryl)-1,3-butadienes (**1**), sometimes termed 1,3-dienyl-1-boronates. These compounds were reported by Vaultier in 1987,[11] and numerous reports of their Diels–Alder chemistry have appeared from the laboratories of Vaultier,[12–15] Lallemand,[13,15–18] and others.[19–21] Most of these reports use the dienylboronates in [4+2]/allylation tandem reactions (**1**–**4**), and this sequence is now often called the Vaultier tandem sequence (Scheme 1). In general, the regioselectivities and *endo*/*exo* selectivities of the Diels–Alder reactions of these 1,3-dienyl-1-boronates are in the 4:1–9:1 range. One report also exists for a Suzuki coupling of a 1,3-dienyl-1-boronate (**1**)[22] and very recently a Diels–Alder/allylation using a silyl alkyne as dienophile[23] and a cycloisomerization/Diels–Alder/allylation sequence involving 1,3-dienyl-1-boronates have been reported.[24]



Scheme 1. Reactions of 1,3-dienyl-1-boronates.

In contrast to the 1,3-dienyl-1-boronates, few report the preparation and Diels–Alder chemistry of 1,3-dienyl-2-boronates (**6**).[25–28] Limited use of this class of compounds is presumably due to their high affinity toward dimerization, even at room temperature.[29] Suzuki and co-workers first

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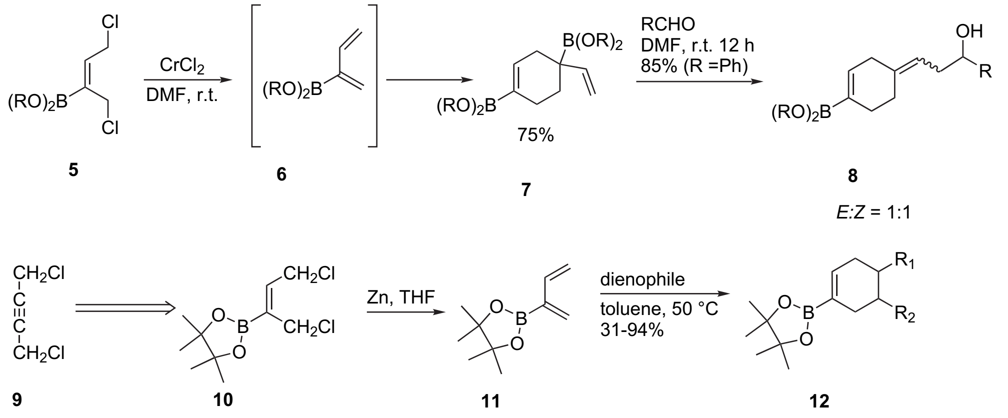


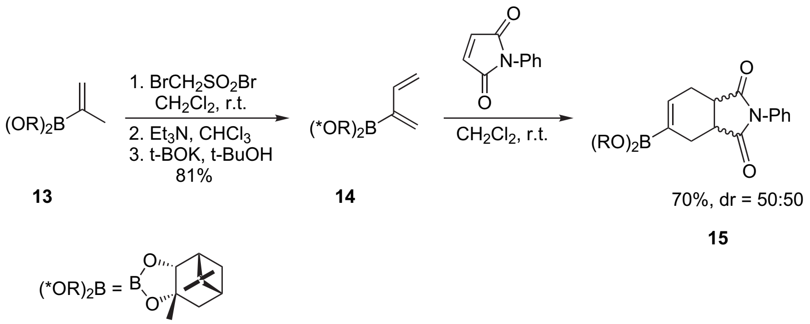
Scheme 2. Prior boron diene syntheses.

synthesized the unsubstituted diene (**11**), which could be isolated in a fast trap-to-trap distillation under high vacuum.[26] This diene (**11**) showed reasonable reactivity with both mono and disubstituted dienophiles at 50 °C (Scheme 2).

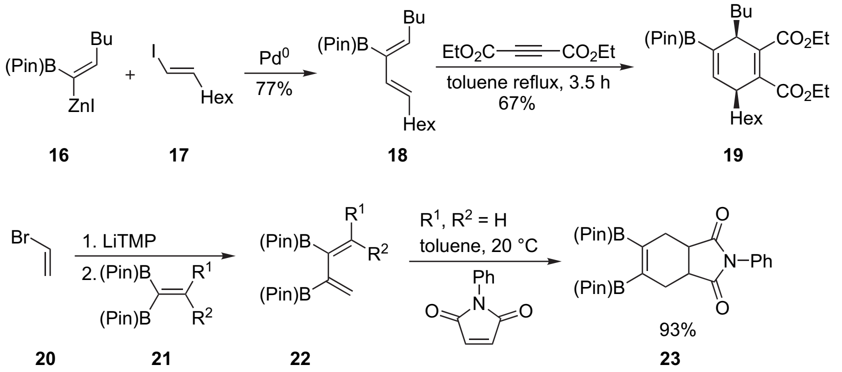
Related chiral diene (**14**) was synthesized in high yield (81%) via a free-radical addition of bromomethane sulfonyl bromide to **13** followed by vinylogous Ramberg–Backlund reaction (at room temperature slow dimerization of **14** occurred).[30] An attempted asymmetric version of a Diels–Alder reaction of **14** with *N*-phenylmaleimide produced **15** in a 70% yield with no diastereoselectivity (Scheme 3).

Following a Negishi-type cross-coupling reaction, Knochel and co-workers reported the synthesis of a stereochemically pure 2-boron functionalized 1,3-diene (**18**). The Diels–Alder reaction of diene (**18**) was performed with diethyl acetylene dicarboxylate to afford the cycloadduct (**19**) in 67% yield as a single diastereomer.[31] Diboronyl dienes (**22**) were synthesized by Shimizu et al. in a one-pot reaction.[32] Surprisingly, these dienes showed higher reactivity in cycloaddition than the corresponding mono-substituted boron diene (**11**). Carbene coupling to boryl alkynes has also been reported (Scheme 4).[33]

Recently, Renaud and co-workers have synthesized highly functionalized 1,3-dienyl-2-boronates (**24**) using enyne ring-closing metathesis reactions of boronate-substituted alkynes. These dienes undergo cycloaddition reactions with electron-deficient dienophiles (nitroethylene, acrolein, MVK) with high regio- and stereoselectivity. Unfortunately, many of these dienes turned out to be unstable due to

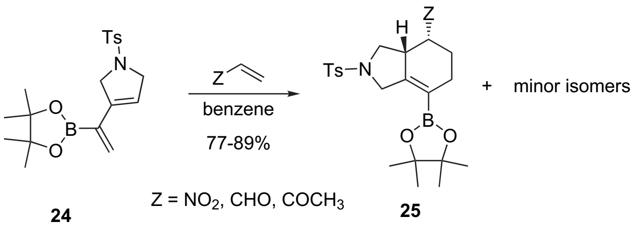


Scheme 3. A chiral boron diene synthesis.



Scheme 4. Pinacol boron diene reactions.

dimerization.[34] In 2005, Lee and Kim reported the preparation of a number of 2-boron substituted 1,3-dienes by enyne cross-metathesis.[35] A Diels–Alder reaction of one of these dienes was reported but the stereochemistry of the product of that reaction was not defined (Scheme 5).



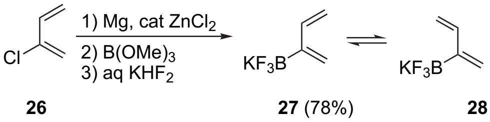
Scheme 5. Prior substituted boron diene Diels–Alder chemistry.

Because so much is now known about cross-coupling/transmetallation reactions of boron, aluminum, and silicon substituted alkenyl compounds, we were convinced that when we found a synthetic route to stable compounds in the 1,3-dienyl-2-main group element family, then these compounds would prove useful to synthetic organic chemists. Our experience in transition-metal dienyl complex chemistry had also been that 2-metal substituted 1,3-dienes were vastly superior to 1-metal substituted 1,3-dienes[36,37] both in rate enhancement and in stereoselectivity so we expected the same to be true for main group-substituted dienes if we could develop this chemistry. Our results in this area using boron substituted dienes are described below.

2. Results and discussion

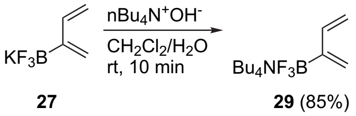
2.1. 2-Boron substituted 1,3-butadiene preparation

Potassium organotrifluoroborates were first introduced as alternatives to boronic esters and acids in 1995.[38] Since then, many have reported on their utility and advantages such as atom economy compared to boronic acids and esters, their ease of purification and disposal, their monomeric rather than trimeric nature, and their air stability.[39,40] Given the reported stability and utility of this class of compounds,[41] we recently set out to prepare the first 1,3-dienyl-2-trifluoroborates.[42] We chose to prepare the butadiene initially and used a route that involved preparing the Grignard reagent of chloroprene (**26**),[43,44] followed by its quenching with trimethylborate ($B(OMe)_3$) and aqueous KHF_2. This new boron substituted dienyl (**27**) is a white, air stable solid, and shows no propensity to dimerize.[45] It has now been prepared on several gram scale (78%), characterized by ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR, and appears by NOESY to be predominantly in a solution conformation close to *s-trans*-(**28**) (Scheme 6).



Scheme 6. BF_3 diene preparation.

We have also prepared the tetra *n*-butyl ammonium (TBA) salt of the BF_3-substituted diene (**29**) (85%) (Scheme 7).[46] TBA salts of other trifluoroborates have been shown to improve cross-coupling yields considerably, presumably due to their greater organic solvent solubility.[47] The bulkier ammonium salt should also increase organic solvent solubility of this class of dienes and may drive their solution conformation more toward *s*-cis and increase their Diels–Alder reactivity. The structure of the tetra *n*-butyl ammonium salt diene (**29**) was also confirmed by X-ray crystallography (Fig. 1).



Scheme 7. Cation exchange.

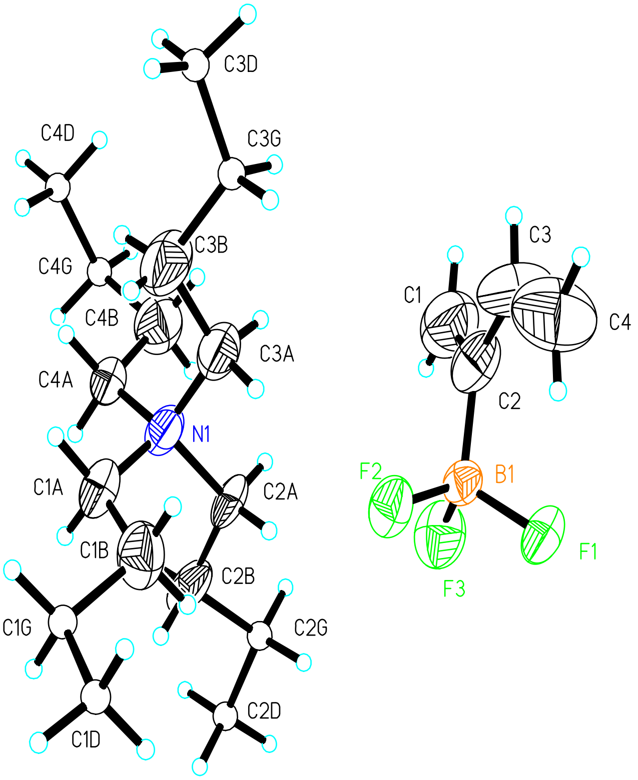
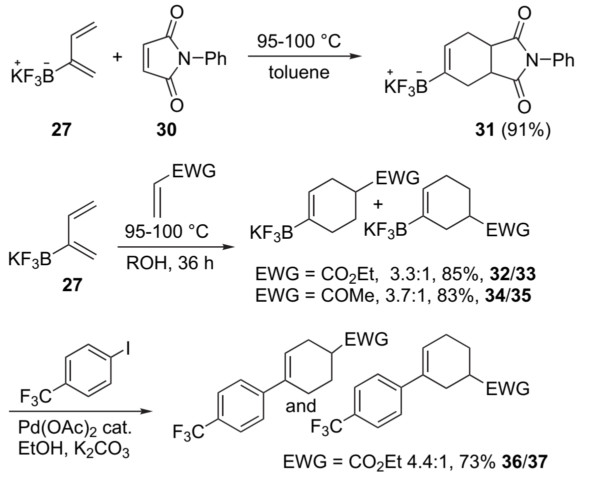


Figure 1. View of a molecule of **29**.

2.2. Diels–Alder reactions and Diels–Alder/cross-coupling tandem reactions of simple boron dienes

We first tried Diels–Alder reactions of diene (**27**) with *N*-phenylmaleimide (**30**) in toluene and ethyl acrylate and methyl vinyl ketone (MVK) in ethanol/methanol and found that boron containing cycloadducts (**31**–**35**) could be isolated in high yields. Those cycloadducts could then subsequently be cross-coupled using Pd catalysis to yield organic cycloadducts (**36** and **37**) (Scheme 8).

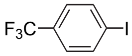
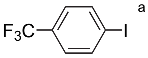
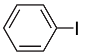
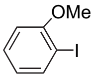
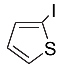
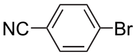
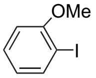
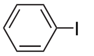
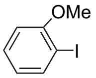
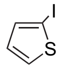
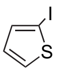
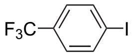
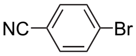
We then performed a series of tandem Diels–Alder/cross-coupling reactions without isolating and characterizing boron intermediates as shown in Table 1. We first heated the boron diene (**27** or **29**) and dienophile, then added $Pd(OAc)_2$ (0.5 mol %) and 3 equiv K_2CO_3, and refluxed in EtOH or



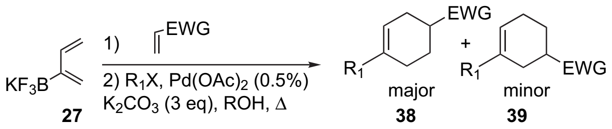
Scheme 8. Preliminary Diels–Alder chemistry followed by cross-coupling.

MeOH for 5 h. The sequence appears useful for unsubstituted phenyl halides (entries 3 and 8), phenyl halides substituted by electron donating (entries 4, 7, and 9) or withdrawing groups (entries 1, 2, 6, 12, and 13), and heteroaromatic halides (entries 5, 10, and 11). The yields for this tandem sequence are generally slightly higher for acrylate rather than MVK adducts (entries 1–7 versus 8–13). Phenyl halides with electron withdrawing groups (entries 1, 2, 6, 12, and 13) typically produce products in 5–10% higher isolated yield than those with electron donating groups (entries 4, 7, and 9). The preference for the *para* over *meta* regioisomer in these initial experiments ranges from 3 to 5:1. We wondered if the tetrabutyl ammonium counterion might have some effect on isolated yields (due to increased solubility) or regiochemical outcomes (due to steric effects) but comparison of entries 4 and 7 indicates that dienes **27** and **29** are almost identical in product outcome. Performing these reactions in a commercial microwave reactor drastically reduces the time required and produces a product in almost identical yield and regiochemistry to the one obtained from a classical thermal reaction (entries 1 and 2 and 10 and 11). Even in its limited form, Table 1 demonstrates that **27** or **29** can serve as a synthon for a host of 2-substituted 1,3-butadienes. We have not worried about regiochemistry here in these early studies, since we ultimately plan to transmetallate boron dienes to Rh prior to cycloadditions and we have already demonstrated that low valent transition metal substituted dienes participate in Diels–Alder reactions with excellent regio- and stereoselectivity (Scheme 9).[48]

Table 1. Tandem Diels–Alder/cross-coupling reactions of boron dienes

Entry	Diene	α,β-Unsaturated carbonyl	Aryl halide	Products	Ratios	Yields
1	**27**	$CH_2{=}CHCO_2Et$		**36/37**	2.9:1	62
2	**27**	$CH_2{=}CHCO_2Et$	 [a]	**36/37**	3.1:1	64
3	**27**	$CH_2{=}CHCO_2Et$		**38/39a**	2.5:1	60
4	**27**	$CH_2{=}CHCO_2Et$		**38/39b**	3.9:1	50
5	**27**	$CH_2{=}CHCO_2Et$		**38/39c**	3.8:1	55
6	**27**	$CH_2{=}CHCO_2Et$[b]		**38/39d**	5.7:1	60
7	**29**	$CH_2{=}CHCO_2Et$		**38/39b**	2.3:1	53
8	**27**	$CH_2{=}CHCOMe$		**38/39e**	2.7:1	56
9	**27**	$CH_2{=}CHCOMe$		**38/39f**	5.1:1	48
10	**27**	$CH_2{=}CHCOMe$		**38/39g**	5.2:1	50
11	**27**	$CH_2{=}CHCOMe$	 [a]	**38/39g**	4.8:1	54
12	**27**	$CH_2{=}CHCOMe$		**38/39h**	2.8:1	57
13	**27**	$CH_2{=}CHCOMe$[b]		**38/39i**	3.9:1	41

[a] Reactions run in a microwave.
[b] Pd catalyst of 1.5% was used.

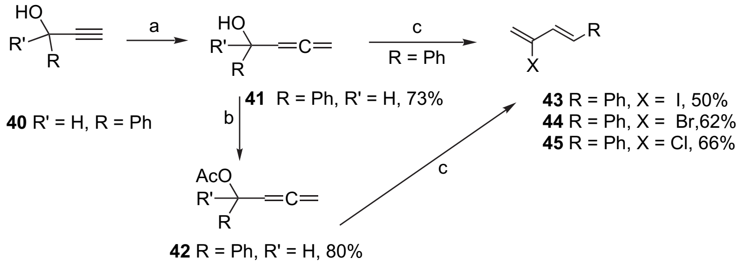


Scheme 9. Sequential Diels–Alder/cross-coupling chemistry.

2.3. Preparation of 4-aryl-2-boron substituted 1,3-butadiene and its Diels–Alder/cross-coupling reactions

Following these proof of principle experiments with the simplest 1,3-diene, we wanted to expand the scope of this chemistry to include more highly substituted boron dienes. Phenyl substituted halo dienes (**43–45**) were directly generated from the corresponding allenic alcohol (**41**) using the established protocol of Ma and Wang (Scheme 10).[49] We found that the temperature of the rearrangement reaction has significant impact on the product yield for the formation of the iodo-substituted diene (**43**). In the presence of 1.5 mol % Pd catalyst the reaction could be performed at 40 °C for both the bromo- and the chloro-substituted dienes (**44**, **45**).[50] Attempts to run the rearrangement reaction at temperatures even 10 °C higher than that for the iodo-substituted diene (**43**) resulted in product yields of <10% yield. Higher diastereoselectivity (>98–99% *E*-isomer) was also observed when these reactions were carried out at the lower temperature. The 2-bromo-4-phenyl-1,3-diene (**44**) was obtained as a crystalline solid and its structure was confirmed by X-ray crystallography (Fig. 2).

2.3.1. Initial attempts to make 4-substituted 1,3-dienyl-2-trifluoroborates. Newly formed halo dienes (**43–45**) were first subjected to the protocol (used for the formation of the unsubstituted 2-BF_3 diene (**27**)) to attempt to prepare the corresponding BF_3-substituted dienes. The first step was to generate the corresponding Grignard reagent followed by addition of trimethoxy borate and quenching by



Scheme 10. Halo diene preparation. Reagents: (a) paraformaldehyde, diisopropylamine, CuBr; (b) Ac_2O, pyridine; (c) LiX in acetic acid.

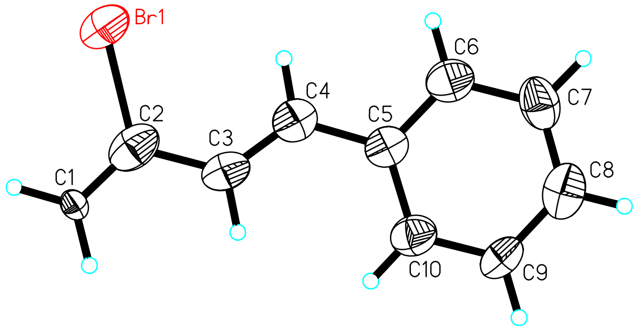


Figure 2. View of a molecule of **44**.

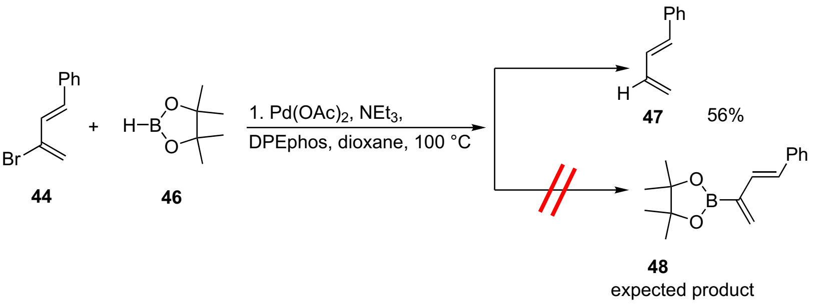
KHF_2/H_2O. Surprisingly, the desired products were not obtained via this route, instead a yellow solid was isolated. This solid was soluble in $CDCl_3$ but contained no alkenyl proton resonances in the ^1H NMR. This material had a complicated aromatic ^1H NMR spectrum, which could be due to the polymerization of the starting material, but further characterization was not continued.

Instead of making 2-BF_3-substituted dienes, efforts were initially made to prepare 2-substituted boronate dienes (such as **48**) via a cross-coupling route. First a phenyl substituted 2-halo diene (**44**) was subjected to the cross-coupling reaction with pinacolborane following a protocol similar to the one that Colobert and co-workers used in their arylboronates synthesis.[51] Reduced diene (**47**) was obtained as the major product in this process instead of the expected product (**48**) (Scheme 11).

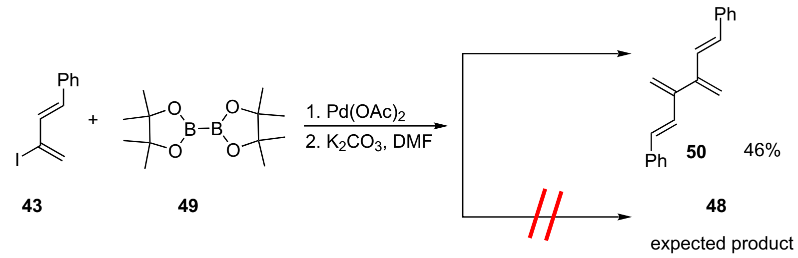
In a second attempt to overcome this problem, a diboryl reagent (**49**) was employed with ligandless palladium catalyst conditions, similar to the approach taken by Zhang and co-workers in their arylboronate synthesis.[52] But in this case, a homocoupled dimer (**50**) of the diene was obtained (Scheme 12).

Recently, Kabalka et al. reported the preparation of allyltrifluoroborate salts using Pd-catalyzed cross-coupling of Baylis–Hillman acetate adducts with bis(pinacolato)-diboron.[53] When 1-phenylbuta-2,3-dienyl acetate (**42**) was treated with bis(pinacolato)diboron (**49**) in the presence of palladium catalyst followed by quenching with aqueous KHF_2 this reaction also produced dimer (**50**) (Scheme 13).

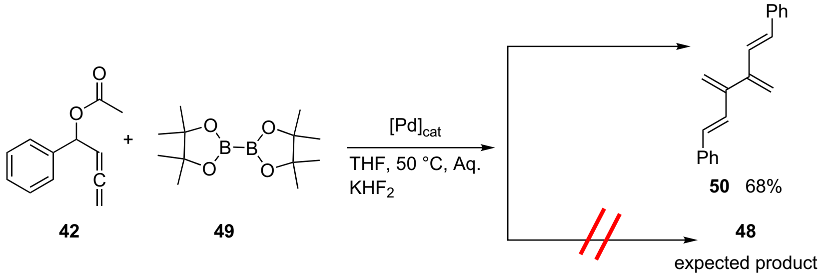
After these initial failures to make more highly substituted boron dienes from halo dienes, we tried milder procedures for preparing Grignard reagents from the corresponding alkenyl halides. Halogen–magnesium exchange reactions, mostly pioneered by Knochel and co-workers, have become



Scheme 11. Halo diene and borohydride.



Scheme 12. Halo diene and diboron reagent.



Scheme 13. Allenic acetate and diboron reagent.

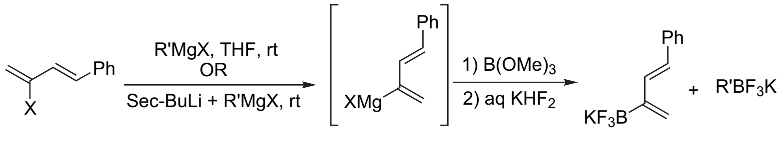
the method of choice for the preparation of organomagnesium reagents with high functional group tolerance.[54,55]

Several different reagents are commonly employed (e.g., ^{i}PrMgCl, ^{i}PrMgBr, *sec*-BuMgBr, ^{i}Pr$_2$Mg·LiCl, *sec*-Bu$_2$Mg·LiCl), which react interchangeably with the halo species to make the corresponding Grignard reagent.[55,56] In theory only 1 equiv of external Grignard reagent is required in a typical experimental procedure for halogen–Mg exchange reactions, but very slow transformations were observed to happen until excess reagents (1.6–2 equiv) were used. Similar observations were also reported by other workers in some related alkenyl halides–magnesium exchange reactions.[57,58] Moreover a competing side reaction, i.e., incorporation of the alkyl moiety from the external Grignard reagent into the 2-position of the diene was also observed during this process, which could be minimized with shorter reaction times. The conditions were optimized by employing 1.8–2 equiv of Grignard reagents to minimize the side reactions (<5%). It was also observed that the iodo-substituted diene (**43**) reacted faster than the corresponding bromo-diene (**44**) as expected. But with higher amounts of external Grignard reagent (1.8 or greater) the bromo-diene could also be converted in a similar fashion. It is noteworthy to mention that these reactions were only possible in THF since no transformation occurred when an external Grignard reagent in diethyl ether was used or diethyl ether was used as solvent for the reaction (Scheme 14).

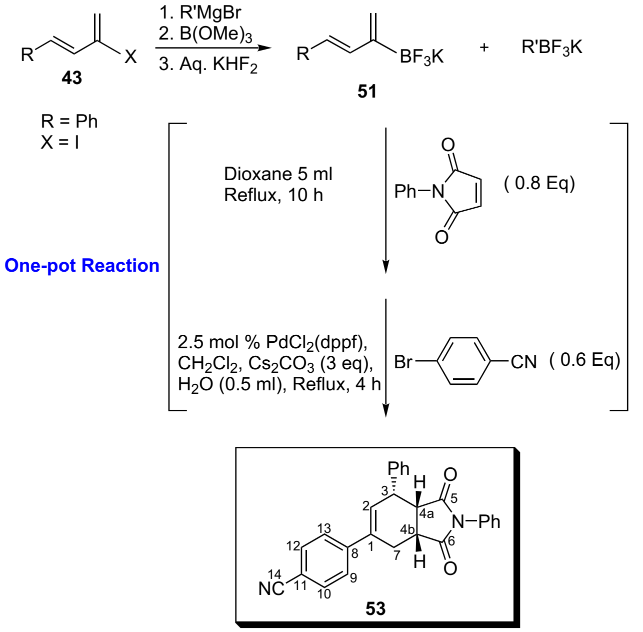
Isolating boron substituted diene (**51**) in analytically pure form, free of any **52**, was proved impossible even under optimized reaction conditions. Recognizing that the purity of diene (**51**) obtained from this sequence was inconsequential as long as **52** had limited impact on possible subsequent Diels–Alder cross-coupling chemistry, we decided to forge ahead and use this diene (**51**) in consecutive reactions. We also wanted to perform both the cycloaddition and the cross-coupling reactions in one-pot and thereby slightly modified our initial protocol used for the unsubstituted dienes (**27**, **29**) reported above. Recently, Molander and Kabalka have shown that organotrifluoroborates generally cross-couple well with a variety of coupling reagents under conventional Pd catalyst conditions in THF/H_2O, toluene/H_2O, alcohol/H_2O, or dioxane/H_2O.[59,60] We selected dioxane/H_2O as a choice of solvent system for the cross-coupling reaction with PdCl$_2$(dppf)·CH$_2$Cl$_2$ as catalyst and Cs$_2$CO$_3$ as a base. We performed the Diels–Alder reaction in dioxane and therefore the following step could be performed in the same pot without removing the solvent. A sequence of reactions have been performed to demonstrate the successful extension of the methodology as shown in Scheme 2. Interestingly, the reaction resulted in the formation of only the *endo* adduct, as presumably the BF$_3$ group is not bulky enough to direct the dienophile to approach in an *exo* fashion. The structure was confirmed both by NMR and by X-ray crystallography (Scheme 15).

The structure of **53** was first postulated by means of NMR spectroscopy. A COSY experiment allowed the unambiguous assignment of all the signals in the 500 MHz ^{1}H NMR spectrum of **53**. Proton H2 appeared at 6.63 ppm as a doublet of doublets (J=5.2 and 1.9 Hz) with the corresponding carbon (C2) signal at 129.2 ppm as confirmed by HMQC. The H2 proton showed two cross-peaks, one at 4.07 and the other at 2.84 ppm in the COSY. The proton at 2.84 ppm showed a strong cross-peak with a resonance at 3.54 ppm and both were attached to the same carbon atom (25.87 ppm) as confirmed by HMQC. It was then concluded that these two protons were the diastereotopic pair, H7 and H7′. The peak at 4.07 ppm was confirmed as H3 (corresponding carbon appeared at 42.66 ppm) as it showed three cross-peaks with H2, H4$_a$, and one of the H7 protons. Bridgehead protons (H4$_a$ and H4$_b$) appeared at the same chemical shift in the proton NMR but correlated clearly with two different carbon signals in the HMQC. Furthermore, one of the bridgehead protons showed a cross-peak with a proton at 2.84 ppm (H7) in the COSY as expected.

The *endo* structure of the molecule was predicted on the basis of the coupling constant between H3 and H4$_a$ (triplet)



Scheme 14. Halogen–magnesium exchange followed by boron electrophile.



Only detected *endo* isomer

25% Overall Yield (based on limiting reagent) with an average yield of 63%/step over the 3 steps.

Scheme 15. Sequential halogen–magnesium exchange, boron electrophile quench, Diels–Alder/cross-coupling.

(J=5.4 Hz) at the H3 proton. Using the experimental $J_{3\text{–}4a}$ of 5.4 Hz in the electronegativity adjusted Karplus equation[61,62] predicted a dihedral angle between H3 and H4$_a$ of 45°. This closely matches the expected dihedral angle for the *endo* structure in molecular models. This was further confirmed by an X-ray crystallographic analysis where the observed dihedral angle was 57.5° (Fig. 3).

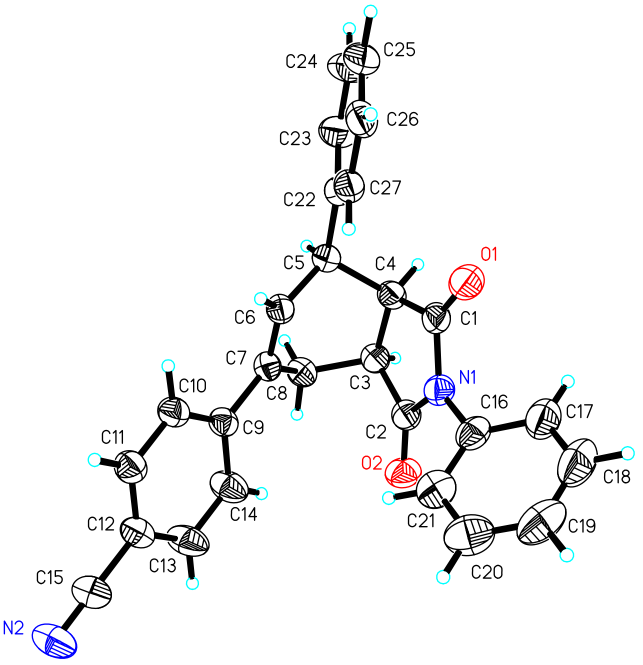


Figure 3. View of a molecule of **53**.

3. Conclusion

In summary, we have prepared new, stable, monomeric dienyl trifluoroborates in high yield and find that they readily participate in Diels–Alder/cross-coupling tandem reactions. We will report the rhodium catalyzed reaction chemistry of these main group element substituted dienes in due course.

4. Experimental section

4.1. General procedures

The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a 300 MHz spectrometer operating at 300.13 MHz or a 500 MHZ spectrometer operating at 500.13 MHz. ^{13}C NMR spectra were obtained using a 300 MHz spectrometer operating at 75.48 MHz. ^{11}B and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer at 96.29 and 282.38 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to the residual proton or carbon signals of the respective deuterated solvents. In the ^{13}C NMR spectrum, the signal of the quaternary carbon α to the tetravalent boron was not observed in organotrifluoroborates type of compounds as expected.[63] ^{11}B NMR chemical shifts were referenced to external $BF_3 \cdot OEt_2$ (0.0 ppm). All ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). All elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectrometry was performed at the Duke Mass Spectrometry Facility, Duke University in Durham, NC.

All reactions were carried out under an atmosphere of nitrogen. Methylene chloride was distilled from CaH_2; ether, THF, and pentane were distilled over Na. Water was deionized and distilled. Absolute ethanol, methanol, and dioxane (HPLC quality) were used without further purification. Deuterated solvents were dried over molecular sieves. Magnesium sulfate, magnesium small turnings, zinc chloride, 1,2-dibromoethane, iodobenzene, 4-bromobenzonitrile, 4-iodobenzotrifluoride, 2-iodoanisole, 2-iodothiophene, potassium hydrogenfluoride, cuprous bromide, diisopropylamine, potassium carbonate, [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with CH_2Cl_2, cesium carbonate, pinacolborane, bis(pinacolatodiboron), lithium chloride, *N*-phenylmaleimide, methyl vinyl ketone, and ethyl acrylate were purchased from Aldrich Chemical Company and used as received. Palladium acetate, bis(2-diphenylphosphinophenyl)ether, 98% DPEphos, and trimethylborate were purchased from Strem Chemicals and used as received. 1-Phenyl-2-propyn-1-ol, lithium iodide, trihydrate, and lithium bromide were purchased from GFS Chemicals and used as received. 2-Chloro-1,3-butadiene 50% in xylene (chloroprene) was purchased from Pafltz & Bauer, Inc. and used as received. Complete experimental details for the preparation of **27**, **29**, and **32–39** are available as supplementary material that accompanies Ref. 42.

4.1.1. Preparation of 5-potassiumtrifluoroborato-3a,4,7,7a-tetrahydro-2-phenyl-2*H*-isoindole-1,3-dione (31).

Potassium 1,3-dienyl trifluoroborate (**27**) (1.1 equiv, 176 mg, 1.1 mmol), *N*-phenylmaleimide (**30**) (173 mg, 1 mmol), and toluene (2.5 mL) were added to a thick walled pressure tube equipped with a magnetic stirring bar. The tube was heated to 95–100 °C for 16 h in a silicon oil bath. The reaction mixture was then cooled to room temperature and solvent was removed by rotary evaporation. The residual solid was washed with acetone and the acetone extracts were transferred to a round bottom flask. The solvents were removed by rotary evaporation and high vacuum. Compound **31** was obtained as a white solid in 91% yield (303 mg, 0.91 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.43–7.31 (m, 3H), 7.25 (dt, J=7.3, 1.7 Hz, 2H), 5.86 (br s, 1H), 3.18–3.04 (m, 2H), 2.64 (dd, J=14.5, 3.2 Hz, 1H), 2.46–2.37 (m, 1H), 2.25–2.10 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 180.9, 180.6, 134.5, 129.4, 128.6, 128.1, 124.4, 41.1, 40.8, 27.3, 24.8 (due to quadrupolar relaxation, the carbon attached to the boron atom was not detected). Negative ion ESI-MS: *m/z* calculated for $C_{14}H_{12}BF_3KNO_2$: (M^-) 333.2, found: 294.0 ($M-K^-$), 274.0 ($M-K-HF^-$), 253.9 ($M-K-2HF^-$).

4.1.2. 1-Phenylbuta-2,3-dien-1-ol (41).[64] Following a literature procedure with slight modification, 1-phenyl-2-propyn-1-ol (**40**) (12.6 g, 95.6 mmol), paraformaldehyde (3.30 g, 109.9 mmol), cuprous bromide (6.88 g, 48.0 mmol), and diisopropylamine (16.2 mL, 114.8 mmol) were refluxed in dry dioxane (350 mL) overnight. The mixture was allowed to cool to room temperature and the dioxane was carefully removed by rotary evaporation. The residue was then filtered through Celite, with addition of water (200 mL) and diethyl ether (250 mL). The filtrate was washed with water, and the collected organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford 1-phenylbuta-2,3-dien-1-ol (**41**) (10.2 g, 69.8 mmol) (73% yield) as a brown liquid. The alcohol was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.43–7.28 (m, 5H), 5.45 (q, J=6.6 Hz, 1H), 5.28 (pentet, J=2.8 Hz, 1H), 4.94 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 207.1, 142.8, 128.5, 127.8, 126.0, 95.2, 78.2, 71.9. GC/MS: *m/z* (relative, %): 146 (3) [M^+], 145 (18), 128 (6), 117 (6), 107 (100), 79 (51), 77 (38), 51 (10).

4.1.3. (*E*)-1-Phenyl-3-iodo-1,3-butadiene (43). A round bottom flask containing 1-phenylbuta-2,3-dien-1-ol (**41**) (2.55 g, 17.4 mmol) was charged with $Pd(OAc)_2$ (1.5 mol %) (58.6 mg, 0.26 mmol) and $LiI\cdot 3H_2O$ (3 equiv) (9.85 g, 52.3 mmol) in acetic acid (50 mL). The mixture was heated at 40 °C with stirring for 1 h (reaction was monitored either by ^{1}H NMR or by GC/MS). Water was added (125 mL) and the aqueous phase was extracted with pentane (2×150 mL). The organic layer was thoroughly washed with water (2×150 mL), satd $NaHCO_3$ (4×125 mL), and brine (2×50 mL) solution and was then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product obtained was passed through silica in a fritted funnel by eluting with pentane. Compound **43** was obtained as a light yellow crystalline solid after removal of pentane under reduced pressure (2.23 g, 8.7 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.45 (d, J=7.9 Hz, 2H), 7.37–7.23 (m, 3H), 6.75 (d, J=15.3 Hz, 1H), 6.44 (s, 1H), 6.27 (d, J=15.3 Hz, 1H), 6.03 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 139.2, 135.9, 129.6, 128.9, 128.7, 128.3, 127.2, 107.9. GC/MS: *m/z* (relative, %): 256 (21) [M^+], 129 (100), 128 (75), 127 (31), 102 (9), 77 (7), 63 (5), 51 (6). Anal. Calcd for $C_{10}H_9I$: C, 46.90; H, 3.54. Found: C, 47.00; H, 3.59.

4.1.4. (*E*)-1-Phenyl-3-bromo-1,3-butadiene (44). The title compound was prepared in 62% yield (2.25 g, 10.8 mmol) from allene **41** (2.55 g, 17.4 mmol) as a yellow solid following the general procedure outlined above with substitution of LiBr for LiI. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.45 (d, J=7.4 Hz, 2H), 7.38–7.24 (m, 3H), 6.94 (d, J=15.1 Hz, 1H), 6.72 (d, J=15.1 Hz, 1H), 5.92 (s, 1H), 5.70 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 135.9, 135.7, 129.9, 128.7, 128.4, 127.1, 126.7, 120.2. GC/MS: *m/z* (relative, %): 210 (10), 208 (11) [M^+], 129 (100), 128 (74), 127 (29), 102 (8), 77 (7), 64 (7), 51 (8).

4.1.5. (*E*)-1-Phenyl-3-chloro-1,3-butadiene (45). The title compound was prepared in 66% yield (1.89 g, 11.5 mmol) from allene **41** (2.55 g, 17.4 mmol) as a yellow solid following the general procedure outlined above with substitution of LiCl for LiI. NMR spectroscopic data were comparable to those previously reported.[65]

4.1.6. Attempted preparation of boronate diene (48) via cross-coupling reaction between a halo diene and pinacolborane. Diene **44** (208 mg, 1 mmol) was taken up in dioxane (2 mL), and triethylamine (558 μL, 4 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), DPEphos (53.8 mg, 0.10 mmol), and pinacolborane (3.00 mL, 1.0 M solution in THF, 3 mmol) were added slowly under nitrogen. The reaction mixture was heated at 100 °C for 5 h. Afterwards it was cooled to room temperature and quenched by a satd solution of NH_4Cl (10 mL). The aqueous phase was extracted with diethyl ether (3×15 mL) and dried over $MgSO_4$. The solution was filtered and removed under reduced pressure to obtain **47** (73 mg, 0.56 mmol) in 56% yield as a colorless liquid. NMR spectroscopic data were comparable to those previously reported.[66]

4.1.7. Attempted preparation of boronate diene (48) via cross-coupling reaction between a halo diene and bis(pinacolato)diboron. In a dry and nitrogen flushed 25-mL 2-neck flask were charged diene (**43**) (128 mg, 0.5 mmol), bis(pinacolatodiboron) (140 mg, 0.55 mmol), potassium carbonate (207.3 mg, 1.5 mmol), palladium acetate (17 mg, 0.05 mmol), and DMF (5 mL). The mixture was degassed by gently bubbling nitrogen for 10 min and then heated at 80 °C for 5 h in an oil bath. The reaction mixture was cooled to room temperature and diluted with water (50 mL). It was then extracted with ethyl acetate (3×25 mL). The organic layer was washed with brine (2×10 mL) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure to obtain a light yellowish solid. The product was purified by flash chromatography on silica gel (elution with hexane/ethylacetate 5:1) to yield a white solid (**50**) in 46% yield (59 mg, 23 mmol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.41–7.27 (m, 5H), 6.93 (d, J=16.0 Hz, 1H), 6.53 (d, J=16.2 Hz, 1H), 5.42 (d, J=1.5 Hz, 1H), 5.18 (d, J=2.3 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 146.6, 137.1, 131.5, 129.6, 128.5, 127.5, 126.5, 118.2. GC/MS: *m/z* (relative, %): 258 (48) [M^+], 243 (16), 228 (14), 215 (11), 202 (6), 129 (18), 165 (41), 154 (100), 141 (16), 128 (45), 115 (31), 102 (7), 91 (29), 77 (14), 63 (4), 51 (7).

4.1.8. Attempted preparation of 2-BF_3-substituted diene via Pd-catalyzed cross-coupling of allenic acetate with

bis(pinacolato)diboron. Acetic acid 1-phenyl-buta-2,3-dienyl ester (**42**) (188 mg, 1.0 mmol), bis(pinacolato)diboron (**49**) (280 mg, 1.1 mmol), and Pd(OAc)$_2$ (5 mol %) were taken in a dry nitrogen flushed 50 mL 2-neck flask equipped with a Schlenk tube, a magnetic stirrer, and a septum. THF (4 mL) was added using a syringe at room temperature. The mixture was heated at 50 °C for 4 h and the color of the solution changed to blackish red. The solution was then cooled to 0 °C and excess KHF$_2$ (468 mg, 6 mmol) was added all at once. Water (2 mL) was added drop by drop and the suspension was allowed to stir for an additional 20 min at room temperature. The solvents were removed on a rotary evaporator and the resulting white solids were subjected to high vacuum until dried completely. The solids were extracted with dry acetone (2×25 mL), and the acetone was evaporated to obtain a white solid (**50**) in 68% yield (175 mg, 0.68 mmol). Spectroscopic data matched with data reported above for this compound.

4.1.9. (*E*)-4-Phenyl-1,3-butadienyl-2-potassium trifluoroborate (51). Diene (**43**) (256 mg, 1 mmol) was dissolved in THF (5 mL) in a dry nitrogen flushed 50 mL 2-neck flask. Secondary butyl magnesium bromide (0.9–1.0 mL, 1.8–2 mmol, 2 M solution in THF) was added drop by drop (for over 5 min) using a syringe at room temperature. The color of the solution changed from light yellow to dark red and the mixture was stirred for 2/2.5 h depending upon the amount of Grignard reagent used at that temperature. The completion of the halogen–magnesium exchange was checked either by ^{1}H NMR or by GC/MS analysis of reaction aliquots. The reaction mixture was cooled to −78 °C and trimethylborate (~557 μL, 5 mmol) was added very slowly and stirring was continued at that temperature for 30 min. The solution was allowed to warm gradually to ambient temperature over a period of an hour (with slow change in color to white) and stirred for 30 min. The mixture was then cooled to 0 °C with additional stirring (30 min) and KHF$_2$ (930 mg, 12 mmol) was added all at once. Water (1.25 mL) and methanol (0.75 mL) were slowly added and the temperature of the reaction mixture was maintained around 0 °C. The resulting white suspension was allowed to warm to room temperature and stirred for half an hour. The solvents were removed on a rotary evaporator and the resulting white solids were subjected to high vacuum until dried completely. The solids were extracted with dry acetone (4×100 mL), and the acetone was evaporated to obtain a mixture of **51** and **52** as white solid (0.3 g). Diagnostic ^{1}H and ^{13}C NMR data are listed below.

Compound **51**: ^{1}H NMR (300 MHz, C_3D_6O, δ): 7.39 (dd, J=7.4, 1.3 Hz, 2H), 7.25 (t, J=7.5 Hz, 2H), 7.11 (tt, J=7.4, 1.3 Hz, 1H), 6.91 (d, J=16.0 Hz, 1H), 6.83 (d, J=16.0 Hz, 1H), 5.31 (d, J=5.1 Hz, 1H), 5.21 (br s, 1H). ^{13}C NMR (75.4 MHz, CDCl$_3$, δ): 138.3, 134.9, 128.2, 127.3, 125.2, 125.0, 120.3 (due to quadrupolar relaxation, the carbon attached to the boron atom was not detected).[63] LRMS (FAB$^-$) observed 236.15, (M−K)^{11}B 197.12, (M−K)^{10}B 196.12.

Compound **52**: ^{1}H NMR (300 MHz, C_3D_6O, δ): 1.54–1.38 (m, 1H), 1.06–0.89 (m, 2H), 0.83 (t, J=7.4 Hz, 3H), 0.74 (d, J=7.2 Hz, 2H). ^{13}C NMR (75.4 MHz, CDCl$_3$, δ): 29.0, 24.6, 13.7, 12.3.

4.1.10. One-pot tandem Diels–Alder/cross-coupling reaction: 4-(1,3-dioxo-2,7-diphenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-5-yl)-benzonitrile (53). 2-Substituted BF$_3$ phenyl diene (**51**) was first prepared from 2-iodo phenyl diene (**43**) (starting with 512.0 mg in a 2 mmol scale) as described above. The BF$_3$-substituted diene obtained was then dissolved in dioxane (5 mL), *N*-phenylmaleimide (277.0 mg, 1.6 mmol, 0.8 equiv with respect to the halo diene) was added, and refluxed for 10 h. The solution was then cooled down to room temperature and 4-bromobenzonitrile (218.4 mg, 1.2 mmol, 0.6 equiv with respect to the starting halo diene) was added with PdCl$_2$(dppf)·CH$_2$Cl$_2$ (19.6 mg, 0.024 mmol) and Cs$_2$CO$_3$ (1173.6 mg, 3.6 mmol) followed by addition of H$_2$O (0.5 mL). The reaction mixture was refluxed for 4 h and then cooled to room temperature. Water (10 mL) was added and extracted with CH$_2$Cl$_2$ (3×20 mL). The extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexane 5:1) to afford **53** as a white solid (120 mg, 0.3 mmol) in 25% overall yield with an average yield of 63% over each of the three steps. ^{1}H NMR (500 MHz, CDCl$_3$, δ): 7.67 (d, J=8.3 Hz, 2H), 7.57 (d, J=8.3 Hz, 2H), 7.37–7.26 (m, 8H), 6.78 (dd, J=6.7, 1.6 Hz, 2H), 6.63 (H2) (dd, J=3.2, 1.9 Hz, 1H), 4.07 (H3) (t, J=5.1 Hz, 1H), 3.59 (H4$_a$ and H4$_b$) (m, 2H), 3.48 (H7) (dd, J=16.1, 1.9 Hz, 1H), 2.84 (H7) (m, 1H). ^{13}C NMR (75.4 MHz, CDCl$_3$, δ): 177.9, 175.5, 144.5, 137.9, 137.7, 132.5, 131.4, 129.2, 129.1, 129.0, 128.6, 128.5, 127.7, 126.3, 126.1, 118.7, 111.4, 45.1, 42.6, 39.5, 25.8. HRMS (EI): *m/z* calculated for $C_{27}H_{20}N_2O_2$: (M$^+$) 404.1525, found: 404.1539.

4.1.11. Crystallographic data details. Crystallographic data for the structures of compounds **29**, **44**, and **53** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 655091–655093. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1#Z, UK.

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