Domino Reactions

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Control of the Regio- and Stereoselectivity in Diels–Alder Reactions with Quinone Boronic Acids**

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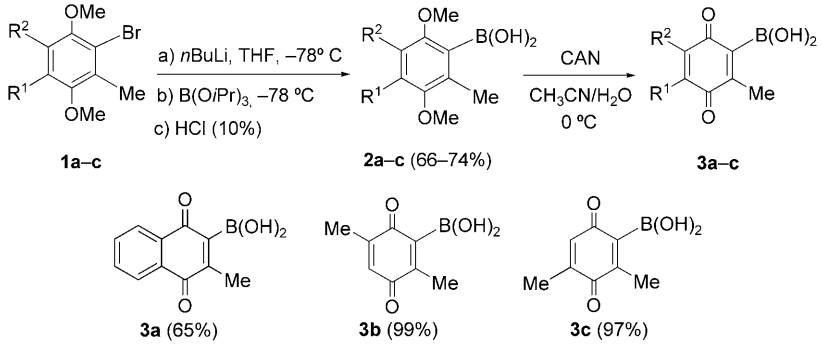
Dedicated to Prof. Dr. Josep Font on the occasion of his 70th birthday

Organoboron compounds are nowadays extensively used in organic synthesis.[1] Besides the cross-coupling reactions, alkenyl and dienyl boronic acids participate in Diels–Alder reactions leading to boron containing adducts, which can be easily transformed into highly functionalized systems. Dialkoxyboryl 1,3-butadiene derivatives, with the borate ester at C2[2] and C1,[3] have been reported to react with typical dienophiles and heterodienophiles,[4] whereas 3-boronoacrolein derivatives[5] and their imino analogues[6] behave as heterodienes. Alkenyl boranes[7] and boronates[8] reacted as dienophiles[9] leading to highly regio- and *endo*-selective cycloaddition products. The use of boronates as both internal[10] and external[11] Lewis acids have been reported to improve the reactivity and regioselectivity of dienophiles bearing a boron group.

Despite the well recognized utility of quinone Diels–Alder adducts in the synthesis of complex molecular targets,[12] to our knowledge, the effect of a boron substituent, which is directly linked to the quinone dienophile,[13] upon Diels–Alder reactions has never been reported. The synthesis and Suzuki cross-coupling reactions of 2-naphthoquinonyl boronic esters and other fused heterocyclic analogues had been published by Harrity and co-workers.[14] The methodology they developed involved the Dotz benzannulation of Fischer chromium carbene complexes and 2-substituted 1-alkynylboronates to yield hydroxy naphthyl boron pinacolates, which were further transformed into naphthoquinone derivatives by ceric ammonium nitrate (CAN) oxidation.[15]

Our interest in Diels–Alder reactions with quinones[16] led us to investigate the effect of a boronic acid, situated at C2 of the quinone framework, on its dienophilic behavior. Herein, we report our results showing that upon reaction with dienes, 2-quinonyl boronic acids evolve through a domino process involving a Diels–Alder reaction and a spontaneous protodeboronation, which leads, in one step, to quinone adducts. The *trans*-fused cycloadducts were formed from acyclic dienes. Moreover, when unsymmetrical dienes were used the regiochemical course of the cycloaddition was fully controlled by the boron substituent to finally yield regioisomers that have never been directly accessed from the quinone lacking the boron group.

Taking into account the poor reactivity of the methyl-substituted quinones as dienophiles and the expected increased reactivity of the boron-substituted systems, we focused our study on 3-methyl-2-quinonyl boronic acids. The required 3-methyl-2-benzoquinonyl or naphthoquinonyl boronic acids **3a–c** were synthesized from 1,4-dimethoxy aromatic precursors **1a–c** through a Br/Li exchange protocol and reaction with $B(OiPr)_3$, followed by acidic hydrolysis of the boronate ester (Scheme 1). Subsequent oxidative demethylation of the 1,4-dimethoxy aromatic 2-boronic acids **2a–c** with CAN gave the desired 2-quinonylboronic acids **3a–c**, which were isolated in good to excellent yields as pure and stable yellow crystalline solids.[17]



Scheme 1. Synthesis of 3-methyl-2-quinonylboronic acids **3a–c**.

Diels–Alder reactions of **3a–c** were initially conducted with cyclopentadiene. Addition of the diene to a solution of **3a** in CH_2Cl_2 led to **4a** (90% yield), whose structure corresponded to the *cis*-protodeboronated adduct (Scheme 2). This adduct was formed directly in the reaction vessel before workup. The reaction was completed in a short

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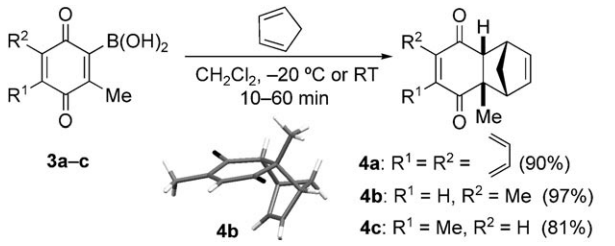
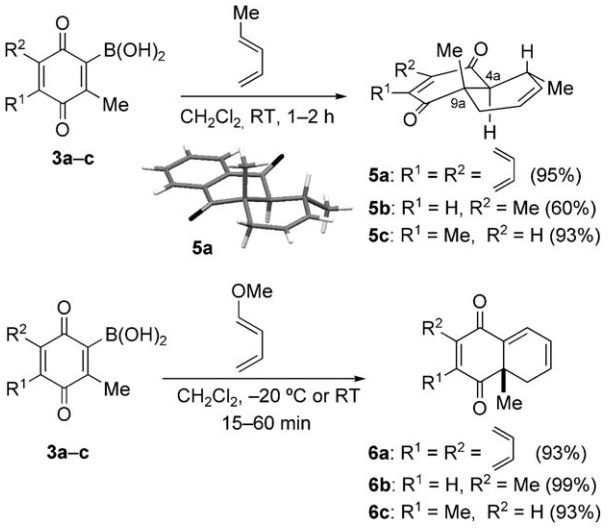


Scheme 2. Diels–Alder reactions of **3a–c** with cyclopentadiene and the X-ray structure of **4b**.

time (10 minutes) and under very mild reaction conditions (room temperature), and exhibited a significant increase of the dienophilic reactivity by the presence of the $B(OH)_2$ group.[18] Even more impressive was the increased reactivity of dimethyl-substituted benzoquinonyl boronic acids **3b** and **3c**, which afforded **4b** (1 hour) and **4c** (30 minutes) in 97% and 81% yields, respectively. The *endo* structure was confirmed by X-ray diffraction analysis of **4b**[19] (Scheme 2).

The reaction between boronic acid **3a** and piperylene was completed within 2 h at room temperature to exclusively afford the protodeboronated adduct **5a** in 95% yield (Scheme 3). Three aspects of this reaction are noteworthy.

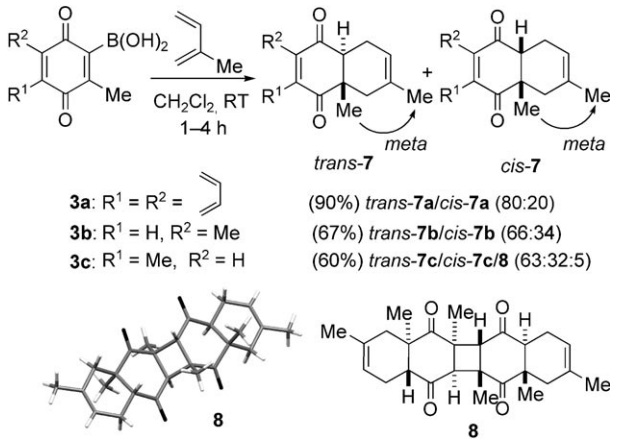


Scheme 3. Diels–Alder reactions of **3a–c** with 1-subtituted-1,3-butadienes and the X-ray structure of *trans*-fused **5a**.

First, the mild reaction conditions used and short reaction time required again revealed the high reactivity of the dienophile if compared with 2-methylnaphthoquinone.[20] Second, the exclusive formation of the 1,4a-dimethyl-substituted derivative **5a** indicated that the regiochemistry was fully controlled by the boron substituent. This result opens easy access to the *meta* adducts, which are not favored in cycloaddition reactions between 1-substituted dienes and 2-alkyl-substituted quinones. Third, the *trans* relative configuration of the C4a and C9a stereogenic centers in **5a**, which was confirmed by X-ray diffraction analysis,[21] indicated that the Diels–Alder reaction was followed by a *trans*-protodeboronation process. The *trans*-fused quinone cycloadducts are only accessible from the *cis*/*endo* Diels–Alder adducts that are directly formed from quinones by treatment with strong bases or acids,[22] and which generally gave different *trans*/*cis* mixtures.[23] Thus, the boronic acid acts as a temporary controller and therefore opens up straightforward access to the *trans*-fused *meta*-regioisomeric cycloadducts under mild reaction conditions. Dimethyl-substituted benzoquinonyl boronic acids **3b** and **3c** behave similarly in the Diels–Alder reactions with piperylene. Once again, the boronic acid directed the regiochemical outcome of the reaction[24] and promoted the formation of **5b** and **5c** in 60% and 93% yield, respectively, in short reaction times (Scheme 3). To compare the reactivity of **3c** with that of the analogue lacking the $B(OH)_2$ group, we tested the reaction of 3,5-dimethyl benzoquinone with piperylene. Under identical reaction conditions (CH_2Cl_2, room temperature), this reaction did not afford the adduct, even after 3 days. We also undertook the same experiment in the presence of $PhB(OH)_2$, to rule out a reaction catalyzed by a boron species,[25] and after 3 days no adduct was observed.

The reaction of **3a–c** with 1-methoxy-1,3-butadiene in CH_2Cl_2 occurred at −20 °C and led to **6a–c** in excellent yields. In this case the domino sequence, including the Diels–Alder reaction and protodeboronation, was followed by elimination of MeOH (Scheme 3). The regiochemical course of the initial cycloaddition, deduced from the position of the double bond generated in the elimination, was also directed by the $B(OH)_2$ group.

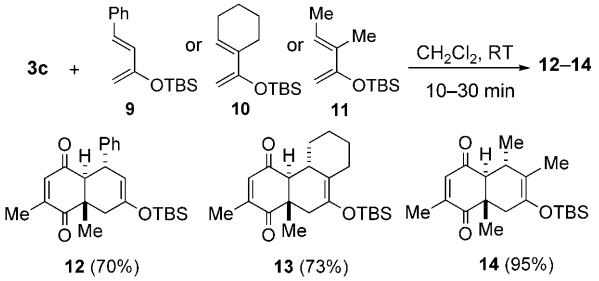
The cycloaddition of **3a–c** with isoprene occurred in a highly regioselective manner, and lead exclusively to the *meta* regioisomer.[26] Once again, the regiochemistry was fully controlled by the boronic acid. The spontaneous protodeboronation gave a mixture of *trans*/*cis*-fused adducts **7a** (80:20) and **7b** (66:34) from **3a** and **3b**, respectively (Scheme 4).[27,28] After flash chromatography, **3c** gave a 63:32:5 mixture of *trans*-**7c**, *cis*-**7c**, and **8**, as determined by ^1H NMR spectroscopy. Although we could not isolate them in diastereomerically pure form, to our surprise, the crystallization of the mixture from AcOEt/*n*-hexane gave a good quality single crystal of **8** whose unequivocal structure was estab-



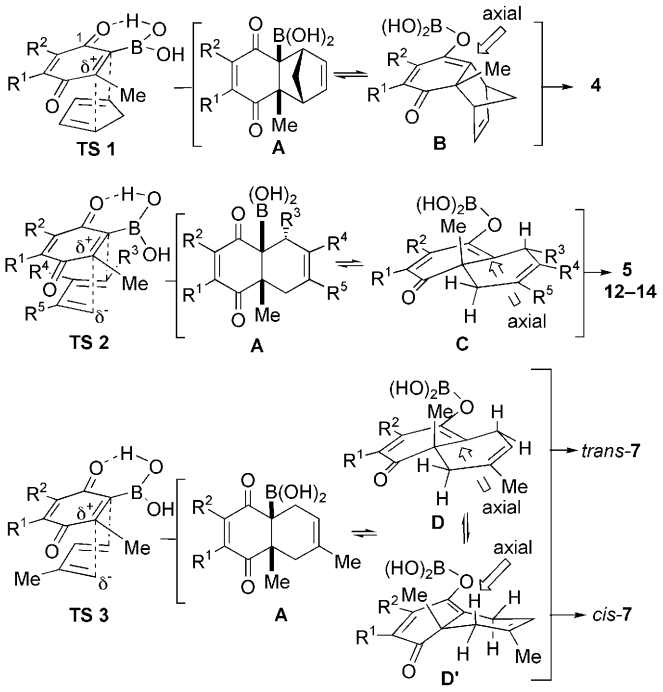
Scheme 4. Reaction of dimethylquinonyl boronic acids **3a–c** with isoprene and the X-ray structure of dimmer **8**.

lished by X-ray diffraction analysis.[29] The relative amounts of *trans*-**7c**, *cis*-**7c**, and **8** remained constant under different reaction conditions, including longer reaction times. Compound **8** (a dimer of *trans*-**7c**) was also formed in the dark, thus indicating a photochemically allowed [2+2] cycloaddition (as an explanation for the formation of the cyclobutane ring) was not the correct mechanistic pathway. Most probably, the [2+2] cycloaddition of *trans*-**7c** to form the cyclobutane ring[30,31] was catalyzed by the boron species present in the reaction medium.[32]

Reactions of **3c** with 1,3-disusbtitued diene **9** or 1,2,3-trisubstituted dienes **10** and **11** were also carried out. As shown in Scheme 5, the cycloaddition reactions were completed in very short reaction times, and led directly to the *trans*-fused *meta*-regioisomeric cycloadducts **12–14**, and thus is evidence of the regiochemical control exerted by the $B(OH)_2$ group in the dienophile and the cooperating effect of the C1 and C3 substituents in the diene partners. These results show the generality and potential utility of 2-quinonyl boronic acids as dienophiles.



Scheme 5. Diels–Alder reactions of **3c** with 1,3-disubtituted or 1,2,3-trisubstituted butadienes. TBS = *tert*-butyldimethylsilyl.



Scheme 6. Regio- and stereochemical course of the Diels–Alder reactions and protodeboronation (the domino process) of 3-methyl-2-quinonyl boronic acids **3** with cyclic and acyclic dienes.

The high dienophilic reactivity of 2-quinonyl boronic acids can be a consequence of the conjugation effect of the $B(OH)_2$ group, which must decrease the LUMO (lowest unoccupied molecular orbitals) energy of the $C_2{=}C_3$ quinonic bond, thus decreasing the HOMO (highest occupied molecular orbitals)–LUMO energy gap.[33] The high dienophilic reactivity must also be reinforced by hydrogen bonding between the boronic acid and the carbonyl group at C1 (**TS1** in Scheme 6).[34] The origin of the efficient regiocontrol exerted by the boronic acid can also be found in these features. As the coefficient values of the LUMO orbital for the carbonyl group at C1 becomes larger and the dienophilic double bond of **3** is polarized as shown, the regiochemistry is therefore expected by taking into account the C1,C2 or C1,C3 substitution of the diene partners.

A plausible explanation of the formation of *cis* or *trans* adducts is also summarized in Scheme 6. The evolution of the initially formed *endo* adduct **A** through the boron enolate intermediate could explain the formation of **4a–c**, which occurs by protonation and loss of the boron group.[35] When cyclopentadiene was used as the diene, the rigid and concave shaped boron enolate **B** could only undergo the protonation from the external face giving the *endo* adducts **4a–c**. The exclusive formation of the *trans*-fused adducts **5**, **12–14** from piperylene and dienes **9–11** can be explained by the stereoselective axial protonation of the boron enolate **C**, which occurs from the less hindered bottom face of the half-chair conformation shown. This conformation must be the most stable since the 1-(or 8-)methyl group is situated in the most favored pseudoequatorial disposition. In the case of the reaction between quinonyl boronic acids **3a–c** and isoprene, the formation of *trans*-fused adduct **7** as the major product can be explained on the basis of the above model, through the axial protonation of **D**. The minor product (*cis*-fused adduct **7**) could result from the axial protonation of the half-chair conformation **D′**. The relative stability of **D** (pseudoaxial Me group) and **D′** (pseudoaxial C=O group) conformers must be similar, thus explaining the formation of a *cis* and *trans* mixture of adducts **7** after protodeboronation.

In summary, we have shown that 3-methyl-2-quinonyl boronic acids are excellent dienophiles which behave as highly reactive synthetic equivalents of the quinone analogues lacking the boron group. The initially formed adducts evolved spontaneously into the products resulting from a protodeboronation process in a highly regio- and stereoselective manner. This process was dependant on the cyclic or acyclic nature of the diene partner. The methodology constitutes a new application of boronic acids as synthetic intermediates, thus expanding their utility to the straightforward access to *trans*-fused quinone adducts (which are not directly available from the latter) in excellent yields and under very mild reaction conditions. The overall regiochemical course of the reaction is the opposite to that which results form quinone

analogues without the boron group, thus leading to the otherwise elusive *meta* adducts.

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