JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

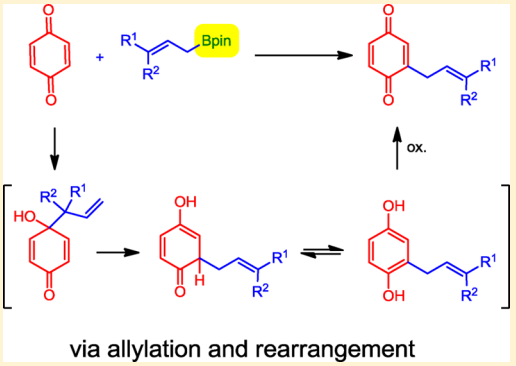
Direct Allylation of Quinones with Allylboronates

Hong-Ping Deng, Dong Wang, and Kálmán J. Szabó*

Department of Organic Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden

Supporting Information

ABSTRACT: Allylboronates undergo C−H allylation of unsubstituted or monosubstituted benzoquinone and naphthoquinone substrates. In the case of 2,5- or 2,6-disubstituted quinones addition involving the substituted carbon takes place. Allylation with stereodefined allylboronates occurs with retention of the configuration.



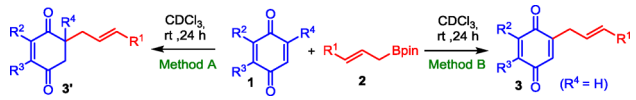
Allyl and isoprenoid quinones represent a very important class of bioactive compounds. These species are very important components of the cell membrane in living organisms. The benzoquinone (BQ) derivatives participate in the respiratory chain in eukaryotic mitochondria (such as ubiquinones) and are important components in the photosynthetic electron transport chains in plants (such as plastoquinones), while naphthoquinone based K-vitamins are essential in cell respiration.[1] The quinone core is very important in medicinal applications as well.[2] Quinone derivatives with antibiotic (such as bhimamycin),[3] anticancer (for example embelin derivatives),[4] and antimalarial[5] activities have received a lot of recent attention. In addition, quinone derivatives are also useful cocatalysts, usually as oxidants, in transition-metal-catalyzed reactions.[6]

Obviously, there is a considerable demand for development of new synthetic procedures to obtain functionalized quinones and related compounds. Recently, excellent procedures appeared in the literature for the synthesis of aryl and alkyl quinone derivatives.[7] In some of these procedures organoboranes are used as the coupling component.[7a,b,f,g] However, the synthesis of allyl and isoprenoid quinones is a somewhat less developed area. In most applications, allyl-stannanes[8] have been used to introduce the allyl moiety, but in some applications allyl-Ni,[9] allyl trifluorosilyl[10] and allyl-indium species[11] have also been applied. Surprisingly few applications have been reported for allylation of quinones with allylboron compounds.

As far as we know, the only example was published by Baran and co-workers[7b] on using farnesyl-BF_3K in the presence of Ag-catalyst for the synthesis of farnesyl-BQ. Allylboronates,[12] react with high selectivity and offer a benign alternative to allyl-stannanes and allyl-Ni derivatives. In addition, allyl-Bpin compounds are easily accessible from allyl-alcohols,[12c,13] alkenes,[14] and other allylic precursors.[12f,15] Therefore, we decided to explore the synthetic potential of allyl-Bpin compounds for synthesis of allyl and isoprenoid benzo- and naphthoquinone derivatives.

We have found that the reaction of BQ derivatives **1** and allylboronates **2** in a 2:1 ratio (method A) results in allyl-BQs **3** in high yield and in most cases with high selectivity (Scheme 1). In the case of 2,5-disubstituted quinones ($R^4 \neq H$), the addition product (**3′**) was formed by mixing equimolar amounts of the reaction components (Scheme 1).

Scheme 1. Allylation of Quinones with Allylboronates[a]



[a]For methods A and B see footnote "a" of Table 1.

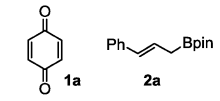
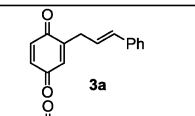
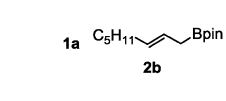
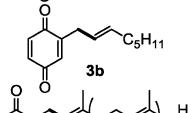
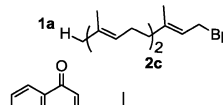
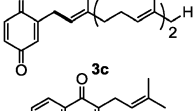
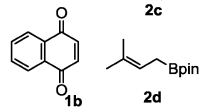
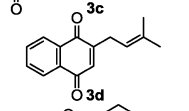
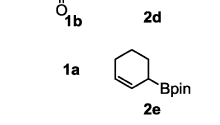
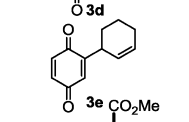
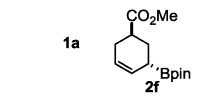
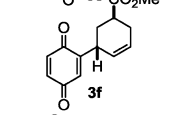
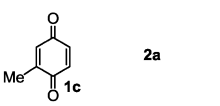
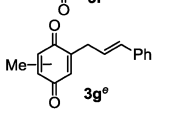
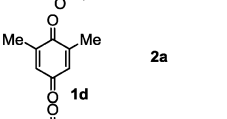
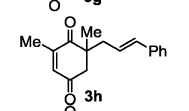
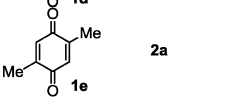
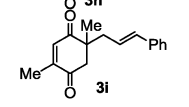
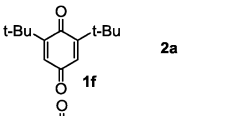
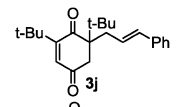
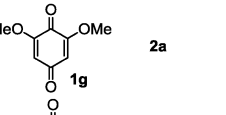
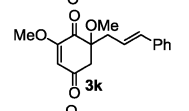
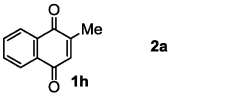
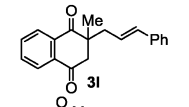
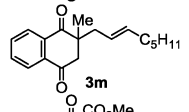
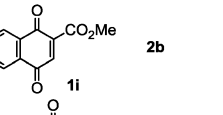
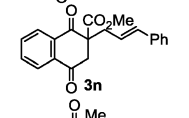
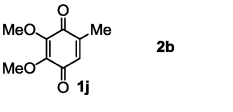
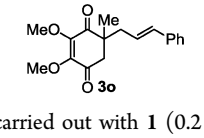
Benzoquinone **1a** (BQ) reacted readily with cinnamylboronate **2a** to give BQ-derivative **3a** with high yield and excellent regio- and stereoselectivity (Table 1). Exclusively the monosubstituted linear allyl species was formed, in which the double bond had an *E* geometry. A clean C−H functionalization reaction (entry 1) required the use of 2 equiv of BQ, otherwise a mixture of the hydroquinone and BQ products was formed. This suggested that 1 equiv of BQ **1a** was substituted to form a hydroquinone derivative, and the other equivalent of BQ was used as oxidant (see below).

Using alkyl-Bpin substrate **2b** the reaction with BQ (**1a**) led to **3b** (entry 2), but the reaction was slower than with cinnamyl boronate **2a**. By addition of CF_3COOH (50 mol %) the reaction proceeded with acceptable rate and yield. The ratio of

Received: February 4, 2015
Published: March 1, 2015

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348

Table 1. Allylation of Quinones with Allylboronates

entry	substrate	method[a]	product	yield[b]	E:Z
1	 1a 2a	A	 3a	90%	>95:1
2[c]	 1a 2b	A	 3b	50%	5.8 :1
3	 1a 2c	A	 3c	83%	1.2 :1
4	 1b 2d	A	 3d	53%	
5[d]	 1a 2e	A	 3e	67%	
6[d]	 1a 2f	A	 3f	45%	
7	 1c 2a	A	 3g[e]	69%	
8	 1d 2a	B	 3h	94%	>95:1
9	 1e 2a	B	 3i	79%	>95:1
10	 1f 2a	B	 3j	68%	>95:1
11[f]	 1g 2a	B	 3k	63%	>95:1
12	 1h 2a	B	 3l	90%	>95:1
13[g]	1h 2b	B	 3m	67%	>95:1
14	 1i 2b	B	 3n	57%	>95:1
15	 1j 2b	B	 3o	87%	>95:1

[a]Method A: The reactions were carried out with **1** (0.2 mmol) and **2** (0.1 mmol) in $CDCl_3$ (0.5 mL) at room temperature for 24 h. Method B: The reactions were carried out with **1** (0.1 mmol) and **2** (0.12 mmol) in $CDCl_3$ (0.5 mL) for 24 h. [b]Isolated yield. [c]CF_3COOH (0.05 mmol) was used as an additive. [d]Diphenylphosphinic acid (0.05 mmol) was used as an additive. [e]The 5- and 6-Me-substituted regioisomers were formed in a 1:2.5 ratio. [f]**1** (0.15 mmol) was used. [g]CF_3COOH (0.1 mmol) was used as an additive.

E/*Z* isomers in **3b** was 6:1, indicating lower stereoselectivity than with cinnamylboronic acid **2a** (cf. entries 1 and 2). Interestingly, the reaction of alkyl-allylstanne analog of **2b** with BQ gives the branched regioisomer.[8d] A possible explanation is that the allylation with allylstannes requires Lewis acid (e.g., BF_3) catalysts, while the reaction with allylboronate proceeds without catalysts. The regio- and stereochemistry[16] of the Lewis acid-catalyzed process of allyl-stannanes of carbonyls is determined by a Type II (open) TS, while the allylation by allylboronates is determined by a Type I (six-membered ring) TS (see below the mechanistic rationalization of the reaction).

Farnesyl-Bpin **2c** also reacted easily with **1a** to give natural product, farnesyl-BQ **3c**. Interestingly, Baran and co-workers[7b] reported a sluggish reactivity for the $AgNO_3$-catalyzed process using $K_2S_2O_8$ as oxidant in CH_2Cl_2/water (1:1) mixture. Under our conditions, using **1a** as oxidant without any catalyst in chloroform the reaction gives **3c** smoothly. Baran and co-workers employed farnesyl-BF_3K instead of farnesyl-Bpin **2c** and obtained **3c** with essentially the same *E*/*Z* selectivity as we did (entry 3) but in somewhat lower yield. Naphthoquinone **1b** can be simply isoprenylated with **2d** to obtain **3d**.

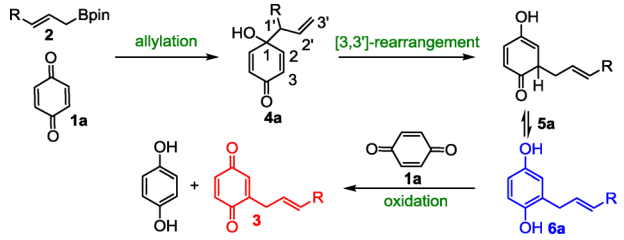
Not only allyl and isoprenyl boronates but also cyclic boronates, such as **2e** and **2f**, reacted with BQ **1a** (entries 5 and 6). The reactivity of the cyclic boronates **2e**,**f** was lower than for cinnamyl boronate **2a**. However, the addition of diphenylphosphonic acid accelerated the reaction, and **3e**,**f** were formed in acceptable yields. As **2f** is a stereodefined allylboronate, the reaction with **1a** (entry 6) gave insight about the stereochemistry of the allylation of quinones. The product **3f** was formed as a single diastereomer in which the COOMe and the BQ groups are on the different sides of the cyclohexenyl ring. Considering the fact that the COOMe and the Bpin groups had the same stereochemistry in substrate **2f**, the allylation process takes place with retention of the configuration of the Bpin leaving group. Although, several other allylating reagents have been employed for allylation of quinones,[8−11] as far as we know this is the first case (entry 6) when the stereochemistry of the allylation of BQ **1a** is determined.

The C−H functionalization of monosubstituted BQ derivative **1c** proceeds with high stereoselectivity but with a poor regioselectivity as the 5- and 6-cinnamyl derivatives were formed in a 1:2.5 ratio (entry 7). Surprisingly the 2,6-dimethyl-substituted derivative **1d** with **2a** gave a single addition product **3h** (entry 8). This product was formed in high yield even using about equimolar ratio of **1d** and **2a** (method B), indicating that the reaction does not involve an oxidation step. The 1,4-dimethyl-substituted quinone derivative **1e** also gave an addition product **3i** with **2a** (entry 9). The addition product (**3j**) was readily formed even in the presence of bulky alkyl substituents, such as ^{t}Bu groups (entry 10). Dimethoxy quinone **1g** reacted more reluctantly (entry 11) than its methyl-substituted counterpart **1d**. However, using a slight excess of **2a** an acceptable yield of the addition product **3k** could be obtained. Substituted naphthoquinones **1h** and **1i** reacted similarly to the corresponding BQ derivatives, affording the corresponding addition products **3l**−**o** (entries 12−14). Interestingly, the stereoselectivity is equally high with both cinnamyl (**2a**) and alkyl (**2b**) boronates (entries 12−13). The electronic character of the substituent did not influence the outcome of the reaction. Even in the case of a COOMe substituent (**1i**), the corresponding addition product **3n** was formed in excellent selectivity (entry 14). In the case of mixed OMe and Me substituents, such as in **1j**, the addition takes place at the Me substituent, such as in **3o** (entry 15).

The mechanism of the reaction is presumed to involve three major steps (Scheme 2) in the case of unsubstituted or monosubstituted quinones and naphthoquinone (such as **1a**−

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348

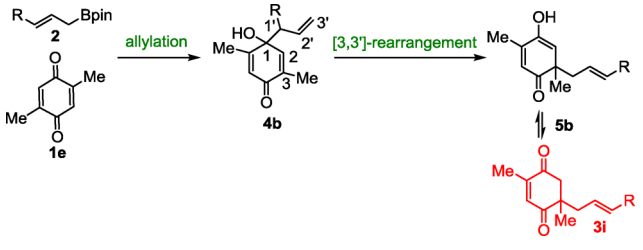
Scheme 2. C−H Allylation of BQ 1a by Allyl-Bpin



c). The first step is probably addition of the allylboronate to the carbonyl group via a six-membered ring TS structure,[16] affording the branched isomer **4a**.[12a,b,17] It is surprising that allyl-Bpin is added to a keto group under the present mild conditions.[12c,d,h,j,17b,18] However, the double bonds in the quinoid structure probably activate the carbonyl group for the addition reactions. We attempted to observe intermediate **4a** (and its methyl-substituted analogs) by monitoring the reaction with ^{1}H NMR spectroscopy. However, these attempts remained fruitless. This indicates that the allylborated initial intermediates (such as **4a**) are highly reactive species, which are rapidly consumed. The next reaction step is probably a fast Cope-type [3,3′]-rearrangement to **5a**. Similar rearrangements are known for adducts formed from BQ and allyl-indium and allyl-Ni species.[9,11] After tautomerization hydroquinone derivative **6a** is formed, which can be oxidized by another BQ molecule to quinone derivative **3**. This was also verified by reaction of isolated **6a** (R = Ph) with **1a**, which resulted in **3a** in a clean reaction. Thus, **1a** serves as both substrate and as oxidant in the C−H allylation of quinones. This is the reason for using quinones **1a−c** and allylboronates in a 2:1 ratio to obtain C−H allylated product **3**. The acid catalyst is supposed to accelerate two steps in the reaction. The Hall[16,19] and Miyaura[20] groups reported that allylboronates react faster with carbonyl compounds in the presence of Lewis and Brønsted acids.[12g,h,13b,18,21] As a consequence, the allylation process (**1a** → **4a**) is probably accelerated by proton catalysis. In addition, the oxidation potential of BQ is pH dependent.[22] Therefore, the acid catalysis probably accelerates the oxidation step (**6a** → **3**) as well.

When 2,4- or 2,6-disubstituted quinones are employed (Scheme 3), the same initial steps take place as above, i.e.,

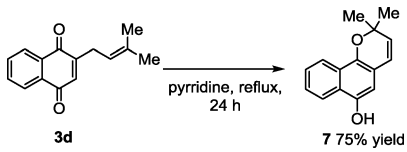
Scheme 3. Allylation of 2,4- (or 2,6-) Disubstituted Quinone Derivatives by Allyl-Bpin



addition to get **4b** followed by a [3,3′]-rearrangement to **5b**. However, after tautomerization **3i** is formed, which cannot be oxidized to quinone derivative (as compound **6a**) because of the presence of the Me (or other non-H) group.

In summary, we presented a useful synthetic method for allylation and isoprenylation of quinone derivatives. The process is suitable for simple C−H functionalization of BQ and naphthoquinone derivatives using allyl-Bpin reagents usually without using any catalysts or additives. In some reactions catalytic amounts of Brønsted acid was used to accelerate the process. This reaction may find useful applications in the synthesis of isoprenyl natural products and terpenes with a BQ core. For example, hemitectol[23] **7** can be synthesized in only three steps from naphthoquinone **1b** and allyl alcohol based isoprenyl-Bpin **2d** followed by biomimetic 6π-electrocyclization[8c] in pyridine (Scheme 4). The reactions

Scheme 4. Synthesis of Hemitectol from 3d



are highly regio- and stereoselective. Using stereodefined allylboronates, the reaction occurs with clean retention of the stereochemistry (entry 6). In the case of 2,4- and 2,6-substituted quinones the reaction gives addition products (such as **3h−p**) in high selectivity, which further extends the synthetic scope of preparation of quinone-based isoprenoids, which are important components of the cell membrane[1] and important motifs in drug intermediates.[2−5]

EXPERIMENTAL SECTION

General Information. **1i**[24] and **2a−f**[13d,e] were prepared according to literature procedures. All other chemicals were obtained from commercial sources and used as received. All operations were carried out under Ar. ^{1}H NMR and ^{13}C NMR spectra were recorded using 400 or 500 MHz spectrometers. Chemical shifts were reported using the residual solvent peak as internal standard. ESI or APCI technique and mass analyzer type TOF were used for the high-resolution mass (HRMS) measurements. For column chromatography, silica gel (35−70 μm) was used.

General Procedure for Allylation of Quinones. A solution of allylboronates **2** (0.1 mmol), BQ **1a** (21.6 mg, 0.2 mmol) in $CDCl_3$ (0.5 mL) was stirred at room temperature for 24 h. The product was purified by silica chromatography.

*2-Cinnamyl-1,4-benzoquinone (**3a**).* The product was prepared according to the above general procedure from **2a** (24.4 mg, 0.1 mmol) and BQ **1a** (21.6 mg, 0.2 mmol). After chromatography (pentane:Et_2O = 20:1) the product **3a** (20.2 mg, 90% yield) was obtained as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.37 (m, 2H), 7.29−7.33 (m, 2H), 7.23−7.26 (m, 1H), 6.79 (d, J = 10.0 Hz, 1H), 6.73 (dd, J = 10.0, 2.5 Hz, 1H), 6.64 (dt, J = 2.5, 1.6 Hz, 1H), 6.52 (d, J = 15.6 1H), 6.18 (dt, J = 15.8, 7.1 Hz, 1H), 3.34 (dt, J = 7.2, 1.5 Hz, 2H). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ 187.7, 187.2, 147.8, 136.7, 136.5, 134.2, 133.0, 128.6, 127.7, 126.2, 123.9, 32.3. The ^{13}C signals of C5 and C6 are probably overlapping. HRMS-APCI m/z: Calcd for $C_{15}H_{13}O_2$ [M + H]$^+$ 225.0910. Found 225.0901.

*2-(Oct-2-en-1-yl)-1,4-benzoquinone (**3b**).* The product was prepared according to above general procedure from **2b** (23.8 mg, 0.1 mmol), BQ **1a** (21.6 mg, 0.2 mmol), and CF_3CO_2H (0.05 mmol). After chromatography (pentane:Et_2O = 50:1) the product **3b** (11 mg, 50% yield, E:Z = 5.8:1) was obtained as a yellow oil. E isomer (major), ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, J = 10.0 Hz, 1H), 6.71 (dd, J = 2.4, 10.0 Hz, 1H), 6.56 (dt, J = 1.6, 2.4 Hz, 1H), 5.54−5.62 (m, 1H), 5.35−5.43 (m, 1H), 3.10−3.13 (m, 2H), 2.00−2.06 (m, 2H), 1.25−1.38 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 187.8, 187.3, 148.6, 136.7, 136.3, 135.7, 132.6, 123.6, 32.5, 31.8, 31.4, 28.9, 22.5, 14.0. HRMS-APCI m/z: Calcd for $C_{14}H_{19}O_2$ [M + H]$^+$ 219.1380. Found 219.1384.

*2-((6E)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)-1,4-benzoquinone (**3c**).* The product was prepared according to above general

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348

procedure from farnesyl-Bpin **2c** (33.2 mg, 0.1 mmol) and BQ **1a** (21.6 mg, 0.2 mmol). After chromatography (pentane:Et_2O = 20:1) the product (26 mg, 83% yield, *E*:*Z* = 1.2:1) was obtained as a colorless oil. The NMR shifts were determined from the spectra of the isomer mixture. These shift values agree with the published spectral data.[7b] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 10.0 Hz, 1H), 6.70 (dd, *J* = 2.4, 10.0 Hz, 1H), 6.54 (dd, *J* = 2.4, 4.0 Hz, 1H), 5.05−5.17 (m, 3H), 3.12−3.13 (m, 2H), 1.93−2.12 (m, 8H), 1.67 (s, 3H), 1.63 (d, *J* = 1.2 Hz, 1H), 1.59 (s, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 187.9, 187.6, 148.5, 140.2, 136.7, 136.3, 135.4, 132.4, 131.3, 124.3, 123.7, 117.6, 39.6, 27.4, 26.7, 26.3, 25.7, 17.7, 16.1, 16.0. Minor isomer, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 10.0 Hz, 1H), 6.70 (dd, *J* = 2.4, 10.0 Hz, 1H), 6.52 (dd, *J* = 2.4, 4.0 Hz, 1H), 5.05−5.17 (m, 3H), 3.12−3.13 (m, 2H), 1.93−2.12 (m, 8H), 1.77 (d, *J* = 1.2 Hz, 1H), 1.67 (s, 3H), 1.59 (s, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 187.9, 187.5, 148.8, 140.2, 136.7, 136.3, 135.4, 132.3, 131.3, 124.2, 123.5, 118.3, 39.7, 39.6, 31.9, 27.2, 26.6, 26.4, 25.7, 23.5, 16.0. HRMS-ESI *m*/*z*: Calcd for $C_{21}H_{28}NaO_2$ [M + Na]$^+$ 335.1982. Found 335.1975.

*2-(3-Methylbut-2-en-1-yl)-1,4-naphthoquinone (**3d**).* The product was prepared according to the above general procedure from isoprenyl-Bpin **2d** (19.6 mg, 0.1 mmol) and naphthoquinone **1b** (31.6 mg, 0.2 mmol). After chromatography (pentane:Et_2O = 30:1) the product (12 mg, 53% yield) was obtained as a light yellow oil. The NMR data are in agreement with the literature values.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−8.12 (m, 2H), 7.69−7.74 (m, 2H), 6.76 (t, *J* = 1.6 Hz, 1H), 5.19−5.24 (m, 1H), 3.27 (d, *J* = 7.3 Hz, 2H), 1.78 (s, 3H), 1.66 (s, 3H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 185.4, 185.3, 150.8, 136.4, 134.7, 133.64, 133.59, 132.4, 132.2, 126.5, 126.1, 118.2, 28.0, 25.8, 17.8. HRMS-ESI *m*/*z*: Calcd for $C_{15}H_{15}O_2$ [M + H]$^+$ 227.1067. Found 227.1057.

*2-(Cyclohex-2-en-1-yl)-1,4-benzoquinone (**3e**).* The product was prepared according to the above general procedure from cyclohexenyl-Bpin **2e** (20.8 mg, 0.1 mmol), BQ **1a** (21.6 mg, 0.2 mmol) and diphenylphosphinic acid (12.5 mg, 0.05 mmol). After chromatography (pentane:Et_2O = 30:1) the product **3e** (13 mg, 69% yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, *J* = 10.0 Hz, 1H), 6.71 (dd, *J* = 2.4, 10.0 Hz, 1H), 6.56 (dd, *J* = 1.2, 2.4 Hz, 1H), 5.96−6.00 (m, 1H), 5.45−5.49 (m, 1H), 3.55−3.61 (m, 1H), 1.93−2.07 (m, 3H), 1.53−1.67 (m, 2H), 1.36−1.44 (m, 1H); ^{13}C-{^{1}H}NMR (100 MHz, $CDCl_3$): δ 188.0, 187.0, 152.5, 136.9, 136.2, 132.8, 130.9, 126.2, 33.8, 28.7, 24.8, 19.8. HRMS-APCI *m*/*z*: Calcd for $C_{12}H_{13}O_2$ [M + H]$^+$ 189.0910. Found 189.0910.

*trans-2-(Methyl-cyclohex-3-ene-1-carboxylate)-1,4-benzoquinone (**3f**).* The product was prepared according to the above general procedure from **2f** (*trans*:*cis* =12:1, 27.9 mg, 0.1 mmol), BQ **1a** (21.6 mg, 0.2 mmol), and diphenylphosphinic acid (12.5 mg, 0.05 mmol). After chromatography (pentane:Et_2O = 16:1−8:1) the product **3f** (11 mg, 45% yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 10.0 Hz, 1H), 6.73 (dd, *J* = 2.4, 10.0 Hz, 1H), 6.52 (dd, *J* = 1.2, 2.4 Hz, 1H), 6.01−6.06 (m, 1H), 5.49−5.54 (m, 1H), 3.69−3.73 (m, 1H), 3.66 (s, 3H), 2.38−2.46 (m, 1H), 2.23−2.33 (m, 2H), 2.05 (ddd, *J* = 6.8, 11.6, 13.6 Hz, 1H), 1.84−1.89 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 187.6, 186.6, 175.3, 150.6, 137.0, 136.3, 134.0, 129.5, 125.2, 51.8, 35.1, 32.6, 29.4, 27.3. HRMS-APCI *m*/*z*: Calcd for $C_{14}H_{14}NaO_4$ [M + Na]$^+$ 269.0784. Found 269.0791.

*2-Cinnamyl-5-methyl-1,4-benzoquinone (**3g**).* The product was prepared according to the above general procedure from **2a** (24.4 mg, 0.1 mmol) and 2-methyl-BQ **1c** (24.4 mg, 0.2 mmol). After chromatography (pentane:Et_2O = 50:1) the product **3g** together with the 6-Me isomer was obtained as a yellow oil (16.4 mg, 69% yield). The NMR data of the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.37 (m, 4H), 7.22−7.25 (m, 1H), 6.57 (s, 2H), 6.51 (d, *J* = 15.8, 1H), 6.18 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.33 (d, *J* = 7.1, 2H), 2.07 (d, *J* = 1.3 Hz, 2H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 187.9, 187.7, 147.8, 146.0, 136.7, 134.0, 133.3, 132.9, 128.7, 127.7, 126.2, 124.2, 32.6, 16.2. HRMS-APCI *m*/*z*: Calcd for $C_{16}H_{15}O_2$ [M + H]$^+$ 239.1067. Found 239.1070.

*6-Cinnamyl-2,6-dimethylcyclohex-2-ene-1,4-dione (**3h**).* The product was prepared according to above general procedure from **2a** (29.3 mg, 0.12 mmol) and 2,6-dimethyl-BQ **1d** (13.6 mg, 0.1 mmol). After chromatography (pentane:ethyl acetate =12:1) the product **3h** (24 mg, 94% yield) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.33 (m, 4H), 7.20−7.24 (m, 1H), 6.57 (d, *J* = 1.2 Hz, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.05 (ddd, *J* = 7.2, 8.0, 15.6 Hz, 1H), 2.91 (d, *J* = 16.4 Hz, 1H), 2.61−2.67 (m, 2H), 2.35 (ddd, *J* = 1.2, 8.0, 13.6 Hz, 1H), 2.01 (d, *J* = 1.2 Hz, 3H), 1.27 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 202.6, 197.7, 149.1, 137.2, 136.8, 134.4, 128.5, 127.5, 126.2, 124.3, 49.3, 48.9, 42.5, 24.6, 16.7. HRMS-ESI *m*/*z*: Calcd for $C_{17}H_{18}NaO_2$ [M + Na]$^+$ 277.1199. Found 277.1201.

*5-Cinnamyl-2,5-dimethylcyclohex-2-ene-1,4-dione (**3i**).* The product was prepared according to the above general procedure from **2a** (29.3 mg, 0.12 mmol) and 2,5-dimethyl-BQ **1e** (13.6 mg, 0.1 mmol) and without additives. After chromatography (pentane:ethyl acetate =8:1−4:1) the product (20 mg, 79% yield) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.33 (m, 4H), 7.19−7.23 (m, 1H), 6.52 (q, *J* = 1.6 Hz, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.05 (ddd, *J* = 7.2, 8.0, 15.6 Hz, 1H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.62−2.68 (m, 2H), 2.30 (ddd, *J* = 1.2, 8.0, 13.6 Hz, 1H), 1.98 (d, *J* = 1.6 Hz, 3H), 1.26 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 202.4, 198.6, 150.2, 136.8, 136.5, 134.4, 128.5, 127.5, 126.2, 124.4, 49.4, 49.1, 42.4, 24.7, 15.9. HRMS-ESI *m*/*z*: Calcd for $C_{17}H_{18}NaO_2$ [M + Na]$^+$ 277.1199. Found 277.1211.

*2,6-Di-tert-butyl-6-cinnamylcyclohex-2-ene-1,4-dione (**3j**).* The product was prepared according to the above general procedure **2a** (29.3 mg, 0.12 mmol) and 2,6-di-*tert*-butyl-BQ **1f** (22.0 mg, 0.1 mmol). After chromatography (pentane:ethyl acetate = 24:1) the product **3j** (23 mg, 68% yield) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.29 (m, 1H), 7.17−7.25 (m, 4H), 6.57 (s, 1H), 6.36 (d, *J* = 15.6 Hz, 1H), 5.94 (ddd, *J* = 6.0, 9.2, 15.6 Hz, 1H), 3.07 (ddd, *J* = 1.6, 6.0, 13.2 Hz, 1H), 2.82−2.92 (m, 2H), 2.04 (ddd, *J* = 0.8, 9.2, 13.2 Hz, 1H), 1.26 (s, 9H), 0.99(s, 9H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 201.6, 200.0, 161.8, 137.0, 136.4, 134.7, 128.5, 127.4, 126.3, 126.1, 57.8, 43.6, 38.4, 38.1, 35.8, 29.2, 26.8. HRMS-ESI *m*/*z*: Calcd for $C_{23}H_{30}NaO_2$ [M + Na]$^+$ 361.2138. Found 361.2152.

*6-Cinnamyl-2,6-dimethoxycyclohex-2-ene-1,4-dione (**3k**).* The product was prepared according to the above general procedure from **2a** (36.6 mg, 0.15 mmol) and 2,6-dimethoxyl-BQ **1g** (16.8 mg, 0.1 mmol). After chromatography (pentane:ethyl acetate = 4:1−2:1) the product **3k** (18 mg, 63% yield) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.34 (m, 4H), 7.20−7.23 (m, 1H), 6.57 (d, *J* = 1.2 Hz, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.07 (dd, *J* = 7.2, 15.6 Hz, 1H), 5.96 (s, 1H), 3.79 (s, 3H), 3.26 (s, 3H), 3.05 (dd, *J* = 1.2, 16.4 Hz, 1H), 2.88 (d, *J* = 16.4 Hz, 1H), 2.73 (dt, *J* = 1.2, 2.4 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 194.6, 191.8, 161.0, 136.7, 134.9, 128.5, 127.6, 126.2, 122.4, 112.1, 80.9, 56.5, 52.2, 46.8, 36.1. HRMS-ESI *m*/*z*: Calcd for $C_{17}H_{18}NaO_4$ [M + Na]$^+$ 309.1097. Found 309.1109.

*2-Cinnamyl-2-methyl-2,3-dihydronaphthalene-1,4-dione (**3l**).* The product was prepared according to the above general procedure from **2a** (29.3 mg, 0.12 mmol) and menadione **1h** (17.2 mg, 0.1 mmol) and without additives. After chromatography (pentane:ethyl acetate = 16:1−12:1) the product **3l** (26 mg, 90% yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.11 (m, 1H), 8.00−8.03 (m, 1H), 7.70−7.78 (m, 2H), 7.25−7.31 (m, 4H), 7.18−7.22 (m, 1H), 6.38 (dt, *J* = 1.2, 15.6 Hz, 1H), 6.11 (ddd, *J* = 7.2, 8.4, 15.6 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 2.88 (d, *J* = 16.0 Hz, 1H), 2.74 (ddd, *J* = 1.2, 7.2, 14.0 Hz, 1H), 2.41 (ddd, *J* = 1.2, 8.0, 14.0 Hz, 1H), 1.34 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 200.4, 196.3, 136.9, 134.9, 134.43, 134.38, 134.0, 133.8, 128.5, 127.5, 127.4, 126.2, 126.1, 124.3, 49.5, 49.3, 42.1, 24.1. HRMS-ESI *m*/*z*: Calcd for $C_{20}H_{18}NaO_2$ [M + Na]$^+$ 313.1199. Found 313.1203.

*(E)-2-Methyl-2-(oct-2-en-1-yl)-2,3-dihydronaphthalene-1,4-dione (**3m**).* The product was prepared according to the above general procedure from **2b** (28.6 mg, 0.12 mmol), menadione **1h** (17.2 mg, 0.1 mmol), and CF_3CO_2H (14.4 mg, 0.1 mmol). After chromatography (pentane:ethyl acetate =30:1) the product (18 mg, 63% yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05−

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348

8.08 (m, 1H), 8.00−8.02 (m, 1H), 7.69−7.76 (m, 2H), 5.37−5.44 (m, 1H), 5.23−5.32 (m, 1H), 3.02 (d, J = 16.0 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 2.47 (ddd, J = 0.8, 6.8, 13.6 Hz, 1H), 2.16−2.22 (m, 1H), 1.93 (dd, J = 6.8, 13.6 Hz, 2H), 1.16−1.32 (m, 9H), 0.85 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 200.8, 196.6, 136.0, 135.0, 134.4, 134.0, 133.9, 127.5, 126.0, 123.7, 49.5, 49.1, 42.0, 32.5, 31.3, 28.9, 23.7, 22.5, 14.0. HRMS-ESI m/z: Calcd for $C_{19}H_{24}NaO_2$ $[M + Na]^+$ 307.1669. Found 307.1658.

*Methyl 2-cinnamyl-1,4-dioxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**3n**).* The product was prepared according to the above general procedure from **2a** (29.3 mg, 0.12 mmol) and 2-(methyl)-carboxylate-1,4-naphthoquinone **1i** (21.6 mg, 0.1 mmol). After chromatography (pentane:ethyl acetate = 8:1−4:1) the product **3n** (19 mg, 57% yield) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04−8.09 (m, 2H), 7.73−7.77 (m, 2H), 7.20−7.33 (m, 5H),, 6.48 (d, J = 15.6 Hz, 1H), 6.12 (dt, J = 8.0, 15.6 Hz, 1H), 3.65 (s, 3H), 3.46 (d, J = 16.4 Hz, 1H), 2.93−3.04 (m, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 193.4, 192.8, 170.3, 136.6, 135.3, 134.9, 134.6, 134.4, 134.2, 128.5, 127.7, 127.6, 126.6, 126.3, 123.2, 60.9, 53.2, 44.8, 37.7. HRMS-ESI m/z: Calcd for $C_{21}H_{18}NaO_4$ $[M + Na]^+$ 357.1097. Found 357.1080.

*5-Cinnamyl-2,3-dimethoxy-5-methylcyclohex-2-ene-1,4-dione (**3o**).* The product was prepared according to the above general procedure from **2a** (29.3 mg, 0.12 mmol) and 2,3-dimethoxyl-5-methyl-BQ **1j** (18.2 mg, 0.1 mmol) and without additives. After chromatography (pentane:ethyl acetate = 8:1−4:1) the product (26 mg, 87% yield) was obtained as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−7.32 (m, 4H), 7.19−7.23 (m, 1H), 6.39 (d, J = 16.0 Hz, 1H), 6.05 (ddd, J = 7.2, 16.0 Hz, 1H), 3.953 (s, 3H), 3.946 (s, 3H), 2.86 (d, J = 16.0 Hz, 1H), 2.66 (ddd, J = 1.2, 6.8, 13.6 Hz, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.336 (ddd, J = 1.2, 8.0, 13.6 Hz, 1H), 1.28 (s, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 198.0, 193.4, 149.2, 148.3, 136.7, 134.5, 128.5, 127.6, 126.2, 124.2, 60.62, 60.59, 48.0, 47.9, 42.8, 24.8. HRMS-ESI m/z: Calcd for $C_{18}H_{20}NaO_4$ $[M + Na]^+$ 323.1254. Found 323.1268.

Hemitectol (7). A solution of **3d** (23 mg, 0.1 mmol) in pyrridine (0.5 mL) was refluxed for 24 h. The solution was then concentrated in vacuo, and the residue was purified by chromatography (pentane:ethyl-acetate = 18:1−12:1) to give dark yellow oil 17 mg, yield 75%. The spectral data agree with the corresponding literature values.[23] ^1H NMR (400 MHz, $CDCl_3$): δ 8.15−8.17 (m, 1H), 8.04−8.06 (m, 1H), 7.43−7.49 (m, 2H), 6.54 (s, 1H), 6.34 (d, J = 9.6 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 4.92 (s, 1H), 1.49 (s, 6H). Hemitectol easily undergoes dimerization,[23] and therefore the NMR spectra were recorded in diluted solutions. Because of this, some of the quaternary carbon atoms cannot be detected by ^{13}C spectroscopy. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 130.3, 125.8, 125.5, 122.6, 122.0, 121.4, 76.3, 27.6. HRMS-ESI m/z: Calcd for $C_{15}H_{15}O_2$ $[M + H]^+$ 227.1067. Found 227.1063.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all compounds. The material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kalman@organ.su.se; Web: http://www.organ.su.se/ks/; Fax: +46-8-15 49 08

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the financial support of the Swedish Research Council (VR) and the Knut och Alice Wallenbergs Foundation. H.-P.D. acknowledges a postoctoral position from the Wenner-Gren Foundation.

■ REFERENCES

(1) Nowicka, B.; Kruk, J. *Biochim. Biophys. Acta, Bioenerg.* **2010**, *1797*, 1587.

(2) Dandawate, P. R.; Vyas, A. C.; Padhye, S. B.; Singh, M. W.; Baruah, J. B. *Mini-Rev. Med. Chem.* **2010**, *10*, 436.

(3) Fotso, S.; Maskey, R. P.; Grün-Wollny, I.; Schulz, K.-P.; Munk, M.; Laatsch, H. *J. Antibiot.* **2003**, *24*, 1242.

(4) Viault, G.; Grée, D.; Das, S.; Yadav, J. S.; Grée, R. *Eur. J. Org. Chem.* **2011**, *7*, 1233.

(5) Lanfranchi, D. A.; Belorgey, D.; Muller, T.; Vezin, H.; Lanzer, M.; Davioud-Charvet, E. *Org. Biomol. Chem.* **2012**, *10*, 4795.

(6) (a) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (b) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149. (c) Young, A. J.; White, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6824.

(7) (a) Walker, S. E.; Jordan-Hore, J. A.; Johnson, D. G.; Macgregor, S. A.; Lee, A.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13876. (b) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292. (c) Lamblin, M.; Naturale, G.; Dessolin, J.; Felpin, F.-X. *Synlett* **2012**, *23*, 1621. (d) Molina, M. a. T.; Navarro, C.; Moreno, A.; Csákÿ, A. G. *Org. Lett.* **2009**, *11*, 4938. (e) Barton, D. H. R.; Bridon, D.; Zardb, S. Z. *Tetrahedron* **1987**, *43*, 5307. (f) Lüthy, M.; Darmency, V.; Renaud, P. *Eur. J. Org. Chem.* **2011**, *2011*, 547. (g) Kumli, E.; Montermini, F.; Renaud, P. *Org. Lett.* **2006**, *8*, 5861. (h) Ilchenko, N. O.; Janson, P. G.; Szabó, K. J. *Chem. Commun.* **2013**, *49*, 6614. (i) Wang, X.; Ye, Y.; Ji, G.; Xu, Y.; Zhang, S.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 3730.

(8) (a) Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774. (b) Uno, H. *J. Org. Chem.* **1986**, *51*, 350. (c) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865. (d) Takuwa, A.; Soga, O.; Mishima, T.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 1261.

(9) Hegedus, L. S.; Evans, B. R.; Korte, D. E.; Waterman, E. L.; Sjoberg, K. *J. Am. Chem. Soc.* **1976**, *98*, 3901.

(10) Hagiwara, E.; Hatanaka, Y.; Gohda, K.-i.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 2773.

(11) Araki, S.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1991**, *415*, 7.

(12) (a) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, 2011. (b) Hall, D.; Lachance, H. *Allylboration of Carbonyl Compounds*; Wiley: Hoboken, NJ, 2012. (c) Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 13050. (d) Alam, R.; Raducan, M.; Eriksson, L.; Szabó, K. J. *Org. Lett.* **2013**, *15*, 2546. (e) Alam, R.; Das, A.; Huang, G.; Eriksson, L.; Himo, F.; Szabo, K. J. *Chem. Sci.* **2014**, *5*, 2732. (f) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560. (g) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (h) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (i) Chen, J. L. Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316. (j) Chen, J. L. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 10992. (k) Böse, D.; Fernández, E.; Pietruszka, J. *J. Org. Chem.* **2011**, *76*, 3463. (l) Böse, D.; Niesobski, P.; Lübcke, M.; Pietruszka, J. *J. Org. Chem.* **2014**, *79*, 4699.

(13) (a) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (b) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723. (c) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, 2293. (d) Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409. (e) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc.* **2013**, *135*, 443.

(14) (a) Olsson, V. J.; Szabo, K. J. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 6891. (b) Olsson, V. J.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 3129. (c) Olsson, V. J.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 7715. (d) Deng, H.-P.; Eriksson, L.; Szabo, K. J. *Chem. Commun.* **2014**, *50*, 9207.

(15) (a) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (b) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (c) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (d) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416.

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348

(16) Kennedy, J. W.; Hall, D. G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4732.
(17) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1982**, *21*, 555. (b) Hoffmann, R. W.; Sander, T. *Chem. Ber.* **1990**, *123*, 145.
(18) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679.
(19) (a) Kennedy, J. W.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160.
(20) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.
(21) (a) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *73*, 1208. (b) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, 4085.
(22) (a) Grennberg, H.; Simon, V.; Bäckvall, J.-E. *J. Chem. Soc. Chem. Commun.* **1994**, 265. (b) Grennberg, H.; Gogoll, A.; Backvall, J. E. *Organometallics* **1993**, *12*, 1790.
(23) Cadelis, M. M.; Barker, D.; Copp, B. R. *Synlett* **2012**, *23*, 2939.
(24) Buccini, M.; Piggott, M. J. *Org. Lett.* **2014**, *16*, 2490.

DOI: 10.1021/acs.joc.5b00264
J. Org. Chem. 2015, 80, 3343−3348