Synthesis of 3,3-Disubstituted Heterocycles by Pd-Catalyzed Arylallylation of Unactivated Alkenes

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ABSTRACT: Finding new methods of carbon–carbon bond formation is a key goal in expanding current methodology for heterocycle formation. Because of their inherently nonplanar shape, new methods of forming sp3-rich scaffolds are of particular importance. Although there are methods for combining heterocyclization and formation of new sp3–sp3 carbon–carbon bonds, these form the carbon–heteroatom bond rather than a carbon–carbon bond of the heterocycle. Here, we show a new alkene arylallylation reaction that generates a heterocycle with concomitant formation of two new carbon–carbon bonds. Furthermore, we demonstrate that this process occurs through an isohypsic (redox neutral) mechanism. Overall, this carboallylation reaction gives a new route to the synthesis of 3,3-disubstituted heterocycles.

1. INTRODUCTION

Heterocycles are found in a vast array of biologically active molecules and complex natural products. Consequently, many synthetic strategies have evolved to access these motifs. Palladium-catalyzed methods are among the most widely used, due to the versatility and functional group tolerance of these cycles. Most Pd-catalyzed heterocycle forming reactions take advantage of the nucleophilicity of the heteroatom as a key feature of the overall process. For example, we have previously shown that difunctionalization of alkenes by heteroallylation can be used to generate a range of O- and N-containing heterocycles (Figure 1a). A lesser-used set of reactions utilizes starting materials where the carbon–heteroatom bonds are already in place. For example, Pd-promoted cyclization of aryl bromide 3, followed by Sonogashira–type coupling affords oxindole 4 (Figure 1b). The inclusion of more sp3-hybridized carbons in medicinal chemistry programmes has been shown to correlate to increased clinical success. As a complement to our earlier alkene heteroallylation work that generates heterocycles substituted with a new C(sp3)−C(sp3) bond at the 2 position (Figure 1a), we became interested in developing a Pd-catalyzed synthesis of 3,3-disubstituted heterocycles with accompanying C(sp3)−C(sp3) bond formation (Figure 1c). The success of this transformation would provide a new potential strategy to access complex biologically active compounds, such as the nM norepinephrine reuptake inhibitor dalaedalin, or the neurokinin receptor antagonist 7 (Figure 2). A single literature report describes Pd-catalyzed heterocycle synthesis from aryl boronic acids (8→9, Scheme 1). This process likely proceeds through a Pd(0)→Pd(II) catalytic cycle, including β-hydride elimination and reoxidation of the Pd by oxygen. On the basis of this precedent as well as our experience on developing an isohypsic (redox neutral) heteroallylation of alkenes (Figure 1a), we set out to develop an alkene

carboallylation reaction that would generate 3,3-disubstituted heterocycles with concomitant sp3−sp3 C=C bond formation (Figure 1c).

2. RESULTS AND DISCUSSION

2.1. Optimization. An initial attempt at carboallylation was carried out using conditions similar to the heteroallylation (Table 1). Pleasingly, this resulted in formation of the desired dihydrobenzofuran 11, albeit as a minor component, with the main products being that of direct allylation 12 and deboronation 13 (entry 1). A change of the allyl halide from bromide to chloride resulted in decreased formation of the deboronation product 13 (entry 2). Lowering the number of the equivalents of allyl chloride caused an improvement in the ratio of 11:12, although the formation of 13 was also increased (entries 3 and 4). Continuing with 2 equivalents of allyl chloride, the effect of the catalyst system was examined (Table 2). The use of phosphine ligands proved detrimental, with none of the desired product formed (entries 2 and 3). Palladium(II) catalyst PdCl2 led to the slightly decreased formation of the desired product, along with lower formation of deboronation product 13 (entry 4), whereas palladium(0) catalysts did not result in formation of the desired product (entries 5–7). The use of phosphonite catalyst 14 resulted in an improved ratio between the desired and direct coupling products, but use of this catalyst was discontinued because of the formation of several additional unidentified side products (entry 8).

Moving from an aqueous base to a solid base greatly improved the ratio between 11:12 (Table 3, entries 1 and 2). Use of other solid bases, such as sodium hydroxide or cesium...
flouride, caused lower or zero conversion to the desired product (entries 3 and 4). Use of organic bases, such as triethylamine, also resulted in formation of the desired product as a minor component (entry 5).

Next, the choice of solvent was examined (Table 4). Use of dimethylformamide (DMF) showed no conversion to the desired product, with the only product being that of direct allylation (entry 2). Acetonitrile and tetrahydrofuran (THF) not only lowered the formation of the deboronated product but also resulted in the formation of less desired product (entries 3 and 4). Use of dimethoxyethane completely suppressed the formation of the deboronated product, although overall conversion was lowered (entry 5).

Carrying these conditions forward, the choice of boron reagent was examined (Table 5). Pinacol boronate ester proved ineffective, with only a small amount of the desired product formed, with direct allylation product 12 being the major result (entry 2). N-methyliminodiacetic acid (MIDA) boronate showed very low conversion, with the only product formed that of direct allylation (entry 3). Potassium

![Scheme 1. Heterocyclization of Boronic Acid 8](image)

**Table 1. Effect of Allyl Halide Equivalents on Product Ratios**

| entry | X  | equiv. | 10 | 11 | 12 | 13 |
|-------|----|--------|----|----|----|----|
| 1     | Br | 5      | 0  | 0.1| 1  | 1.2|
| 2     | Cl | 5      | 0.2| 0.1| 1  | 0.3|
| 3     | Cl | 2      | 0.1| 0.3| 1  | 0.7|
| 4     | Cl | 1.1    | 0  | 0.4| 1  | 0.9|

Figure 1. Examples of Pd-catalyzed heterocycle formation and our plan for a new synthesis of 3,3-disubstituted heterocycles.

Figure 2. Biologically active 3,3-disubstituted heterocycles.

Table 1. Effect of Allyl Halide Equivalents on Product Ratios
Table 2. Effect of Palladium-Catalyst System

| entry | Pd source | additive | 10 | 11 | 12 | 13 |
|-------|-----------|----------|----|----|----|----|
| 1     | Pd(hfacac)₂ |          | 0.1| 0.3| 1  | 0.7|
| 2     | Pd(hfacac)₂ | PPh₃ (1 equiv.) | 0  | 0  | 1  | 0.2|
| 3     | Pd(hfacac)₂ | PPh₃ (2 equiv.) | 0.3| 0  | 1  | 0  |
| 4     | PdCl₂     |          | 0  | 0.2| 1  | 0.1|
| 5     | PdCl₂(dppf) |        | 0.3| 0  | 1  | 0.1|
| 6     | Pd(OAc)₃  |          | 0  | 0  | 1  | 0.2|
| 7     | Pd₂dba₂   |          | 0  | 0  | 1  | 0  |
| 8     | Pd₂dba₂   |          | 0  | 0.7| 1  | 0.1|

“In addition to 11 and 13, several additional side products were observed by ¹H NMR.

Table 3. Effect of Base

| entry | base | 10 | 11 | 12 | 13 |
|-------|------|----|----|----|----|
| 1     | Na₂CO₃ (2 M aq.) | 0.1| 0.3| 1  | 0.7|
| 2     | Na₂CO₃ | 3.2| 6.7| 1  | 10 |
| 3     | NaOH | 0  | 0.1| 1  | 0.2|
| 4     | CsF | 0  | 0  | 1  | 0.2|
| 5     | NEt₃ | 0.1| 0.3| 1  | 3.1|

“Bases used as solids.

Table 4. Effect of Solvent

| entry | solvent | 10 | 11 | 12 | 13 |
|-------|---------|----|----|----|----|
| 1     | toluene | 3.2| 6.7| 1  | 10 |
| 2     | DMF     | 0  | 0  | 1  | 0  |
| 3     | MeCN    | 2.4| 1.1| 1  | 3.3|
| 4     | THF     | 3.6| 1.4| 1  | 0.7|
| 5     | DME     | 9.2| 3.4| 1  | 0  |

“O-methallyl chain to be close to the Pd(II) (conformer 16’), it will likely spend more time at a greater distance (conformer 17). This leaves the Pd(II) intermediate 16 more vulnerable to direct coupling. By replacing the hydrogen in the 3-position with another group, orientation of the O-methallyl chain toward the 3-position should become less favorable. This should result in the equilibrium being displaced toward 16’, therefore favoring cyclization.

To this end, the carboallylation conditions were applied to methyl-substituted potassium trifluoroborate 18 (Scheme 3). As predicted, the formation of direct allylation product 20 was greatly suppressed, with only a trace amount detected. The
desired dihydrobenzofuran 19 was formed in 46% isolated yield.

During the development of their palladium-catalyzed cyclization of aryl halides, Zhou et al. also observed competition between cyclization and direct alkynylation. The direct alkynylation process could be largely suppressed by using N-methylmethacrylamides, as shown in Figure 1b. We thus employed N-methylmethacrylamide 22 (Scheme 4) as a boron analog of the aryl halide substrates used by Zhou et al. Pleasingly, the carboallylation conditions were successfully resulted in formation of oxindoline 23 in 47% yield, with only trace amounts of direct allylation product 24 formed.

**2.3. Mechanistic Study.** To examine the mechanism of the arylallylation process, a deuterium-labeling study was carried out. The heterocycle formation was carried out using ary trifluoroborates 15 using dideuterioallyl bromide (Scheme Table 5. Effect of Boronic Acid Source

| entry | B          | 10 | 11 | 12 | 13 |
|-------|------------|----|----|----|----|
| 1     | B(OH)$_2$  | 9.2| 3.4| 1  | 0  |
| 2     | BPin       | 0  | 0.1| 1  | 0  |
| 3     | BMIDA      | 8.8| 0  | 1  | 0  |
| 4     | BF$_3$K    | 0  | 3.5$^a$ | 1 | 0.2 |

$^a$48% isolated yield.

Scheme 2. Reactive Rotomer Effect on Carboallylation

Scheme 3. Carboallylation of Methyl-Substituted 18

Scheme 4. Carboallylation of Methylmethacrylamide 22
This resulted in the formation of dihydrobenzofuran 25 as a single deuterated isomer, and direct alkylation products 26a and 26b as a 1:1 mixture of deuterated isomers (in 21 and 1% isolated yields, respectively).

This is consistent with an isohypsic mechanism for the formation of 25 (Scheme 6). Beginning with transmetallation of boronic acid 10, palladium(II) intermediate 16 is formed. Carbopalladation (olefin insertion) forms the C–C bond of the dihydrobenzofuran ring, giving 27. A second carbopalladation can then occur, this time onto the allyl halide double bond giving palladium(II) intermediate 28. Finally, β-halide elimination gives the dihydrobenzofuran product 25 as a single deuterated isomer, and releases the palladium(II) catalyst.

However, an isohypsic mechanism is not consistent with the formation of a 1:1 mixture of deuterated isomers of the direct alkylation products 26a/b. This suggests that the direct alkylation products are formed via an alternative mechanism. Beginning with oxidative addition of palladium(0) into the allyl halide, π-allyl palladium(II) species 29a/b are formed (Scheme 7). Transmetallation of boronic acid 10 gives rise to palladium(II) intermediates 30a/b. Finally, reductive elimination forms the direct allylated products 26a/b and reforms the palladium(0) catalyst.

As the dihydrobenzofuran and direct alkylation products appear to be formed by separate mechanisms, it should be possible to control, which product is formed by controlling the catalyst used. Having already shown the use of a palladium(II) catalyst to form a dihydrobenzofuran product from potassium trifluoroborate 15 (Table 5, entry 4), we chose to treat 15 with a Pd(0) catalyst. As predicted, exposure of 15 to Pd2dba3 and allyl chloride resulted in the sole formation of direct coupling product 12 (Scheme 8). Interestingly, use of several common oxidants, such as benzoquinone, DDQ, O2, or Cu(II), did not favor the isohypsic cyclization process.

### 3. CONCLUSIONS

We have developed a new Pd-catalyzed arylation reaction of alkenes. This reaction has been demonstrated in the formation of heterocycles, such as dihydrobenzofurans and oxindolines, results in formation of two new carbon–carbon bonds, and generates a quaternary carbon center. After elimination of the deboronation side product and suppression of the direct coupling product, the arylation reaction was...
shown to proceed through an isolysptic palladium(II)-catalyzed mechanism. By controlling the reaction conditions, selective formation of either the cyclized or direct allylated product is possible.

4. EXPERIMENTAL SECTION

4.1. 2-(2-Methylallyloxy)phenylboronic Acid (10). Following a literature procedure,12 to a stirred suspension of 2-iodophenol (12 g, 52 mmol) and potassium carbonate (14 g, 110 mmol) in DMF (260 mL), was added methallyl chloride (6.1 mL, 63 mmol). The reaction mixture was heated at 70 °C for 16 h, and then cooled to room temperature (RT), diluted with EtOAc (250 mL), and the phases were separated. The organic phase was washed with water (100 mL) and brine (3 × 100 mL), dried (MgSO4), filtered, and concentrated in vacuo to give 1-(2-methylallyloxy)-2-iodobenzene as a yellow oil (14 g, quant.). Analytical data were in accordance with literature values.13

Following a literature procedure14 to a stirred suspension of 1-(2-methylallyloxy)-2-iodobenzene (12 g, 43 mmol) and triisopropyl borate (12 mL, 52 mmol) in toluene/THF (4:1) (14 mL) at −78 °C, was added nBuLi (26 mL, 52 mmol). The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to −20 °C and quenched with 2 M aq. HCl (100 mL). The mixture was allowed to warm to room temperature and then extracted with Et2O (2 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) gave a pale yellow solid, which was boiled in water for 2 h. After cooling, the mixture was filtered to give the title compound 10 as a pale yellow crystalline solid (4.2 g, 51%). Analytical data were in accordance with literature values.14

4.2. Potassium (2-(2-Methylallyloxy)phenyl)-trifluoroborate (15). Following a literature procedure,15 to a stirred suspension of 2-(2-methylallyloxy)phenylboronic acid (12 g, 53 mmol) in THF (4.0 mL) was then added to the rapidly stirring solution, and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min, and then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated in vacuo to give the title compound 15 as a fluffy white solid (0.63 g, 95%).

1H NMR (400 MHz, DMSO-d6) δ (ppm): 7.94 (1H, dd, J = 7.1, 1.9 Hz, Ar−H), 6.96 (1H, ddd, J = 8.0, 7.2, 2.0 Hz, Ar−H), 6.66 (1H, t, J = 7.2 Hz, Ar−H), 6.62 (1H, d, J = 8.1 Hz, Ar−H), 5.16−5.14 (1H, m, C−CH3), 4.85−4.84 (1H, m, C−CH2), 4.27 (2H, s, OCH2), 1.76 (3H, s, CH3). 13C NMR (125 MHz, DMSO) δ (ppm): 161.7 (C), 140.9 (C), 137.7 (C), 133.1 (C), 131.2 (C, observed indirectly by HMBC).

4.3. Potassium (2-(2-Methylallyloxy)-3-methylphenyl)trifluoroborate (18). Following a literature procedure,16 to a stirred suspension of 6-bromo-o-cresol (0.66 mL, 5.4 mmol) and potassium carbonate (1.5 g, 11 mmol) in DMF (30 mL), was added methallyl chloride (0.62 mL, 6.4 mmol). The reaction mixture was heated at 70 °C for 16 h, and then cooled to room temperature, diluted with EtOAc (30 mL), and separated. The organic phase was washed with water (20 mL) and brine (3 × 20 mL), dried (MgSO4), filtered, and concentrated in vacuo to give 2-(2-methylallyl)-3-bromomethylbenzene as a yellow oil (1.3 g, quant.).

1H NMR (500 MHz, CDCl3) δ (ppm): 7.38 (1H, dd, J = 8.0, 1.5 Hz, Ar−H), 7.12 (1H, dq, J = 7.6, 0.7 Hz, Ar−H), 6.89 (1H, t, J = 7.8 Hz, Ar−H), 5.19−5.18 (1H, m, C−CH2), 5.02−5.01 (1H, m, C−CH2), 4.31 (2H, s, OCH2), 2.33 (3H, s, CH3). 13C NMR (125 MHz, CDCl3) δ (ppm): 152.8 (C), 130.9 (C, observed indirectly by HMBC), 113.3 (CH2), 78.0 (CH2), 19.9 (CH3), 16.8 (CH3); IR (thin film) 2920, 1653, 1464, 1452, 1260, 1220 cm−1; HRMS (EI) exact mass calculated for C11H15O3B [M]+ m/z 240.0150, found m/z 240.0153.

Following a literature procedure,14 to a stirred solution of 2-(2-methylallyl)-3-bromomethane (0.79 g, 3.3 mmol) and trimethyl borate (1.00 mL, 3.9 mmol) in toluene/THF (4:1) (14 mL) at −78 °C was added nBuLi (1.8 mL, 3.9 mmol). The reaction mixture was stirred at −78 °C for 1 h, and then allowed to warm to −20 °C, and quenched with 2 M aq. HCl (10 mL). The mixture was allowed to warm to room temperature and then extracted with Et2O (2 × 5 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave a pale yellow solid, which was boiled in water for 2 h. After cooling, the mixture was filtered to give 2-(2-methylallyloxy)-3-methyl-phenylborinic acid (18) as a pale yellow crystalline solid (0.44 g, 66%).

1H NMR (400 MHz, CDCl3) δ (ppm): 7.68 (1H, dd, J = 7.2, 1.6 Hz, Ar−H), 7.31 (1H, ddt, J = 7.5, 1.9, 0.7 Hz, Ar−H), 7.11 (1H, t, J = 7.4 Hz, Ar−H), 6.04 (2H, s, B(OH)2), 5.23 (1H, s, C−CH3), 5.05 (1H, s, C−CH2). 4.23 (2H, s, OCH2), 2.31 (3H, s, CH3), 1.89 (3H, s, CH3). 13C NMR (125 MHz, CDCl3) δ (ppm): 163.1 (C), 140.9 (C), 135.1 (C), 134.3 (C), 130.3 (C), 124.8 (CH2), 123.0 (C, observed indirectly by HMBC), 113.3 (CH3), 78.0 (CH3), 19.8 (CH3), 16.1 (CH3); IR (thin film) 3412, 2910, 1446, 1435, 1383, 1344, 1084 cm−1; HRMS (EI) exact mass calculated for C11H15O3B [M]+ m/z 206.1229, found m/z 206.1232.

Following a literature procedure,15 to a stirred solution of 2-(2-methylallyloxy)-3-methyl-phenylborinic acid (0.072 g, 0.35 mmol) and triisopropyl borate (0.90 mL, 3.9 mmol) in toluene/THF (4:1) (14 mL) at −78 °C was added nBuLi (1.8 mL, 3.9 mmol). The reaction mixture was stirred at −78 °C for 1 h, and then allowed to warm to −20 °C, and quenched with 2 M aq. HCl (10 mL). The mixture was allowed to warm to room temperature and then extracted with Et2O (2 × 5 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave a pale yellow solid, which was boiled in water for 2 h. After cooling, the mixture was filtered to give 2-(2-methylallyloxy)-3-methyl-phenylborinic acid as a pale yellow crystalline solid (0.44 g, 66%).
1.1 Hz, Ar), 7.31 (1H, td, J = 7.4, 0.7 Hz, Ar−H), 6.88 (1H, td, J = 7.4, 1.0 Hz, Ar−H), 6.79 (1H, dt, J = 8.0, 0.5 Hz, Ar−H), 5.76 (1H, dd, J = 16.7, 10.2, 6.4 Hz, CH−CH2), 4.98 (1H, dq, J = 17.1, 1.7 Hz, CH−CH2H), 4.94−4.90 (1H, m, CH=CH−H), 4.37 (1H, d, J = 8.7 Hz, O−CH2H), 4.16 (1H, d, J = 8.6 Hz, O−CH2H), 2.15−2.05 (1H, m, CH2CH2CH=CH2), 1.92−1.82 (1H, m, CH2CH2CH=CH2), 1.73−1.68 (2H, m, CH2CH2CH=CH2), 1.36 (3H, s, CH3); 13C NMR (125 MHz, CDCl3) δ (ppm): 159.9 (C), 138.5 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.7 (CH2), 109.7 (CH), 82.6 (CH2), 45.3 (C), 40.2 (CH2), 29.2 (CH2), 25.7 (CH3); IR (thin film) 2934, 1365, 1196 cm−1; HRMS (EI) exact mass calculated for C13H16O [M]+ m/z 188.1201, found m/z 188.1203.

4.3. 3-(But-3-en-1-yl)-3-methyl-7-methyl-2,3-dihydrobenzofuran (19). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallylloxy)-3-methylphenyl)-trifluoroborate 18 (220 mg, 0.80 mmol), Pd(hfacac)2 (42 mg, 0.080 mmol), Na2CO3 (170 mg, 1.6 mmol), dimethoxethane (3.2 mL), and allyl chloride (0.13 mL, 1.6 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane; 19:1) afforded the title compound 19 as a colorless oil (74 mg, 46%).

1H NMR (500 MHz, CDCl3) δ (ppm): 6.96 (1H, dq, J = 7.4, 0.7 Hz, Ar−H), 6.92 (1H, dd, J = 7.4, 0.7 Hz, Ar−H), 6.80 (1H, t, J = 7.4 Hz, Ar−H), 5.75 (1H, dd, J = 16.8, 10.2, 6.5 Hz, CH=CH2), 4.99 (1H, dq, J = 17.1, 1.7 Hz, CH=CH2H), 4.93−4.91 (1H, m, CH=CH2), 4.38 (1H, d, J = 8.7 Hz, O−CH2H), 4.17 (1H, d, J = 8.7 Hz, O−CH2H), 2.22 (3H, s, CH3), 2.14−2.06 (1H, m, CH2CH2CH=CH2), 1.91−1.84 (1H, m, CH2CH2CH=CH2), 1.75−1.65 (2H, m, CH2CH2CH=CH2), 1.35 (3H, s, CH3); 13C NMR (125 MHz, CDCl3) δ (ppm): 158.0 (C), 138.6 (CH), 134.3 (C), 129.4 (CH), 120.5 (CH), 120.4 (CH), 119.9 (C), 114.6 (CH2), 82.4 (CH2), 45.6 (C), 40.2 (CH2), 29.2 (CH2), 25.7 (CH3), 15.2 (CH3); IR (thin film) 2965, 2922, 1456, 1188 cm−1; HRMS (EI) exact mass calculated for C14H18O [M]+ m/z 202.1358, found m/z 202.1357.

4.7. 3-(But-3-en-1-yl)-1,3-dimethylindolinol-2-one (23). A screw-top glass vial (4 mL) was charged with N2,N2-dimethyl-N-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)phenyl]-2-propenamide 22 (26 mg, 0.080 mmol), Pd(hfacac)2 (4.2 mg, 0.0080 mmol), Na2CO3 (17 mg, 0.16 mmol), dimethoxethane (0.32 mL), and allyl chloride (0.03 mL, 0.4 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) afforded the title compound 23 as a colorless oil (7.5 mg, 47%).

1H NMR (500 MHz, CDCl3) δ (ppm): 7.27 (1H, td, J = 7.7, 1.2 Hz, Ar−H), 7.17 (1H, dd, J = 7.3, 0.7 Hz, Ar−H), 7.07 (1H, td, J = 7.5, 0.8 Hz, Ar−H), 6.84 (1H, d, J = 7.8 Hz, Ar−H), 5.68−5.60 (1H, m, CH=CH2), 4.843−4.841 (1H, m, CH=CH2H), 4.82−4.81 (1H, m, CH=CH2H), 3.20 (3H, s, N−CH3), 2.05−2.00 (1H, m, CH2CH=CH2H), 1.85−1.79 (1H, m, CH2CH2CH=CH2), 1.77−1.69 (1H, m, CH2CH2CH=CH2).
4.8. 3-(4,4-Dideuterio-3-en-1-yl)-3-methyl-2,3-di-hydrobenzofuran (25). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methallyllyloxy)phenyl)trifluoroborate 15 (64 mg, 0.25 mmol), Pd[hfacac]2 (13 mg, 0.025 mmol), Na2CO3 (53 mg, 0.50 mmol), dimethyl ether (1.0 mL), and dideuteriobromide18 (0.37 mL, 1.3 M in Et2O, 0.50 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compound 25 as a colorless oil (8.8 mg, 19%).

1H NMR (400 MHz, CDCl3) δ (ppm): 7.13 (1H, dd, J = 8.0, 7.4, 1.5 Hz, Ar−H), 7.08 (1H, dd, J = 7.4, 1.5, 0.6 Hz, Ar−H), 6.88 (1H, td, J = 7.4, 1.0 Hz, Ar−H), 6.79 (1H, dd, J = 8.0, 1.0, 0.5 Hz, Ar−H), 5.79−5.73 (1H, m, CH=C=CD), 4.38 (1H, d, J = 8.7 Hz, O−CH2), 4.17 (1H, d, J = 8.7 Hz, O−CH2), 2.15−2.06 (1H, m, CH2CH=CH=CD=), 1.92−1.83 (1H, m, CH2CH=CH=CD=), 1.73−1.69 (2H, m, CH2CH=CH=CD), 1.36 (3H, s, CH3); 13C NMR (100 MHz, CDCl3) δ (ppm): 159.7 (C), 138.3 (CH3), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, 7j(C−D) = 24.1 Hz, CD2), 109.7 (CH), 82.6 (CH3), 45.3 (C), 40.2 (CH2), 29.1 (CH2), 25.7 (CH3); IR (thin film) 2926, 2237, 1600, 1481 cm−1; HRMS (EI) exact mass calculated for C13H16D2O [M+Na]+ m/z 296.1664, found m/z 296.1664.

4.9. 1-(Dideuterioallyl)-2-(2-methallyloxy)benzene (26a/b). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methallyllyloxy)phenyl)trifluoroborate 15 (64 mg, 0.25 mmol), Pd[hfacac]2 (13 mg, 0.025 mmol), Na2CO3 (53 mg, 0.50 mmol), dimethyl ether (1.0 mL), and dideuteriobromide18 (0.37 mL, 1.3 M in Et2O, 0.50 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compounds in a 1:1 mixture as a colorless oil (1 mg, 1%).

1H NMR (400 MHz, CDCl3) δ (ppm): 7.19−7.14 (2H, m, Ar−H), 6.90 (1H, t, J = 7.4, Ar−H), 6.83 (1H, d, J = 8.1, Ar−H), 6.04−5.97 (1H, m, CH=C=CD=CH2), 5.11 (1H, s, OCH2C=C=CH2), 5.09−5.02 (2H, m, CD2C=CH2), 4.98 (1H, s, OCH2C=C=CH2), 4.43 (2H, s, OCH2), 3.43 (2H, d, J = 6.6 Hz, H2C=C=CD), 1.84 (3H, s, CH3); 13C NMR (100 MHz, CDCl3) δ (ppm): 159.7 (C), 138.3 (CH3), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, 7j(C−D) = 24.1 Hz, CD2), 109.7 (CH), 82.6 (CH3), 45.3 (C), 40.2 (CH2), 29.1 (CH2), 25.7 (CH3); IR (thin film) 2926, 2237, 1600, 1481 cm−1; HRMS (EI) exact mass calculated for C13H16D2O [M+Na]+ m/z 325.1207, found m/z 325.1195.

4.10. 2-(2-Methallyloxy)phenylboronic acid pinacol ester. Following a modification of the reported procedure,19 a mixture of 2-(2-methallyllyloxy)phenylboronic acid 10 (500 mg, 2.6 mmol) and pinacol (307 mg, 2.6 mmol) in Et2O (15 mL) was stirred at room temperature (RT) for 17 h and then heated at reflux for 4 h. The mixture was cooled to RT and washed with brine (3 × 25 mL). The organic extracts were dried (Na2SO4), filtered, and concentrated in vacuo. The 1H NMR spectrum of the crude material indicated approximately 80% conversion, so the residue was refluxed with pinacol (92 mg, 0.8 mmol) in Et2O (15 mL) for 16 h. The cooled reaction mixture was washed with water (25 mL), brine (2 × 25 mL), dried (Na2SO4), filtered, and concentrated in vacuo to afford the title compound as a colorless oil (650 mg, 92%).

1H NMR (500 MHz, CDCl3) δ (ppm): 7.68 (1H, dd, J = 7.3, 1.8 Hz, 6-H), 7.37 (1H, dd, J = 8.8, 6.9, 1.4 Hz, 4-H), 6.94 (1H, td, J = 7.3, 0.8 Hz, 5-H), 6.84 (1H, d, J = 8.3 Hz, 3-H), 5.34−5.35 (1H, m, C==CH2), 4.97−4.98 (1H, m, C==CH2), 4.42 (2H, s, OCH2), 1.86 (3H, s, CH3), 1.35 (12H, s, 2 × C(CH3)3); 13C NMR (125 MHz, CDCl3) δ (ppm): 163.4 (C), 141.1 (C), 136.9 (CH), 132.6 (CH), 120.4 (CH), 118.4 (C, observed indirectly by HMBC), 111.9 (CH3), 111.6 (CH), 83.5 (2 × C), 71.6 (CH2), 25.1 (4 × CH3), 19.6 (CH3); IR (thin film) 1670, 1438, 1300, 1246, 1196, 1142; HRMS (ESI) exact mass calculated for C14H15BNaO2 [M + Na]+ m/z 296.1669, found m/z 296.1664.
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Notes

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