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

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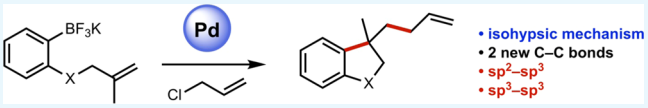
Supporting Information

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 sp^3-rich scaffolds are of particular importance. Although there are methods for combining heterocyclization and formation of new sp^3−sp^3 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.[1] Palladium-catalyzed methods are among the most widely used, due to the versatility and functional group tolerance of these cycles.[2] 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 difunctionalisation of alkenes by heteroallylation can be used to generate a range of O- and N-containing heterocycles (Figure 1a).[3] A lesser-used set of reactions utilizes starting materials where the carbon−heteroatom bonds are already in place.[4] For example, Pd-promoted cyclization of aryl bromide **3**, followed by Sonogashira−type coupling affords oxindole **4** (Figure 1b).[5]

The inclusion of more sp^3-hybridized carbons in medicinal chemistry programmes has been shown to correlate to increased clinical success.[6] As a complement to our earlier alkene heteroallylation work that generates heterocycles substituted with a new $C(sp^3)$−$C(sp^3)$ bond at the 2 position (Figure 1a), we became interested in developing a Pd-catalyzed synthesis of 3,3-disubstituted heterocycles with accompanying $C(sp^3)$−$C(sp^3)$ 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 daledalin, or the neurokinin receptor antagonist **7** (Figure 2).[7]

A single literature report describes Pd-catalyzed heterocycle synthesis from aryl boronic acids (**8** → **9**, Scheme 1).[8] 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 sp^3−sp^3 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 $PdCl_2$ 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**[9] 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

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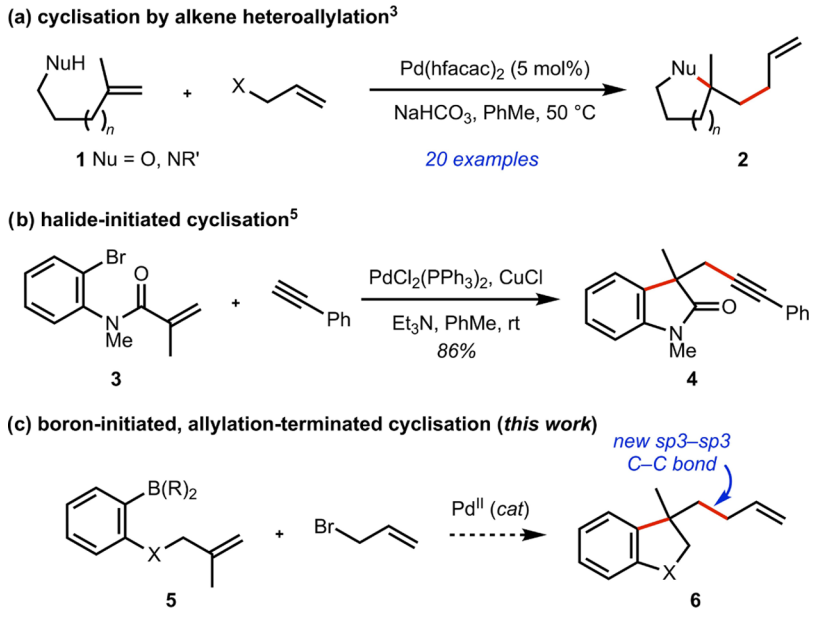


Figure 1. Examples of Pd-catalyzed heterocycle formation and our plan for a new synthesis of 3,3-disubstituted heterocycles.

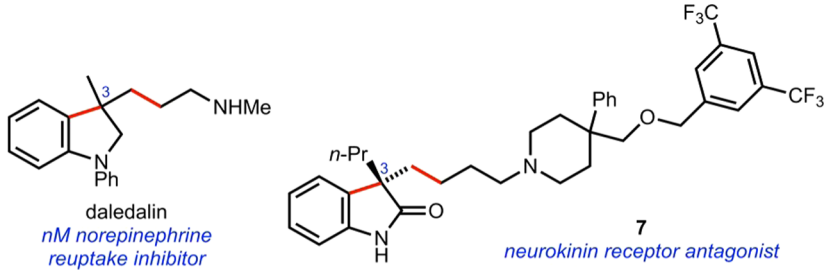
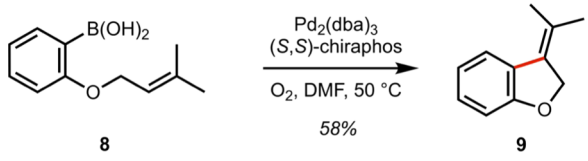


Figure 2. Biologically active 3,3-disubstituted heterocycles.

Scheme 1. Heterocyclization of Boronic Acid 8

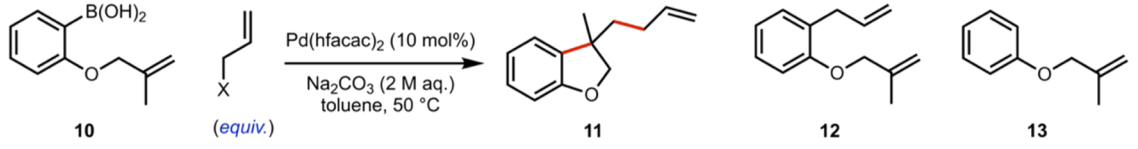


fluoride, caused lower or zero conversion to the desired product (entries 3 and 4). Use of organic bases, such as triethylamine, also resulted in formation of the desired product as a minor component (entry 5).

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

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

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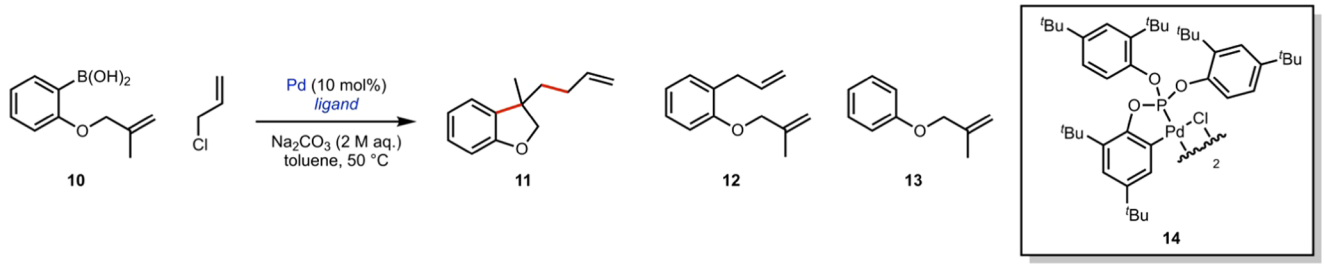
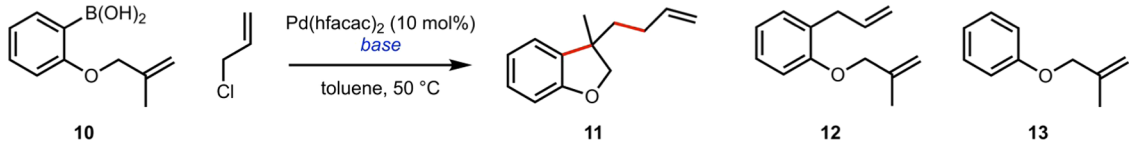
Table 2. Effect of Palladium-Catalyst System



entry	Pd source	additive	10	11	12	13
1	$Pd(hfacac)_2$		0.1	0.3	1	0.7
2	$Pd(hfacac)_2$	PPh_3 (1 equiv.)	0	0	1	0.2
3	$Pd(hfacac)_2$	PPh_3 (2 equiv.)	0.3	0	1	0
4	$PdCl_2$		0	0.2	1	0.1
5	$PdCl_2$(dppf)		0.3	0	1	0.1
6	$Pd(OAc)_2$		0	0	1	0.2
7	Pd_2dba_3		0	0	1	0
8[a]	**14**		0	0.7	1	0.1

[a]In addition to **11** and **13**, several additional side products were observed by ^{1}H NMR.

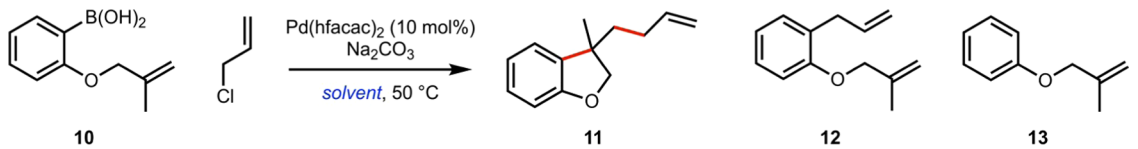
Table 3. Effect of Base



entry	base	10	11	12	13
1	Na_2CO_3 (2 M aq.)	0.1	0.3	1	0.7
2	Na_2CO_3[a]	3.2	6.7	1	10
3	NaOH[a]	0	0.1	1	0.2
4	CsF[a]	0	0	1	0.2
5	NEt_3	0.1	0.3	1	3.1

[a]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

trifluoroborate **15**, however, gave full conversion of the starting material while maintaining the ratio of desired/direct allylated products, forming the desired dihydrobenzofuran in 48% isolated yield (entry 4).

2.2. Reaction Scope. As the competition between desired **11** and direct coupling **12** products involves a cyclization step, the "reactive rotomer" effect[10] can have an important influence on product ratio (Scheme 2). After transmetallation to form Pd(II) intermediate **16**, the proximity of the *O*-methallyl chain determines how easily direct coupling or cyclization can occur. For cyclization to occur, the *O*-methallyl chain must be in close proximity to the Pd(II). As it is less sterically favorable for the *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

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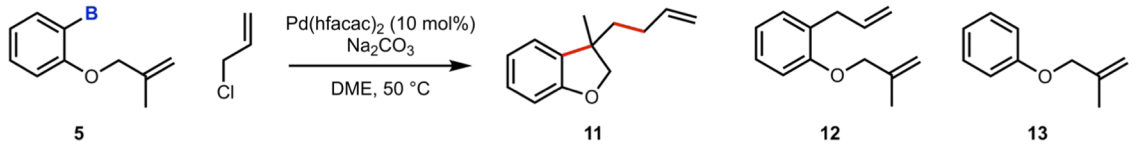
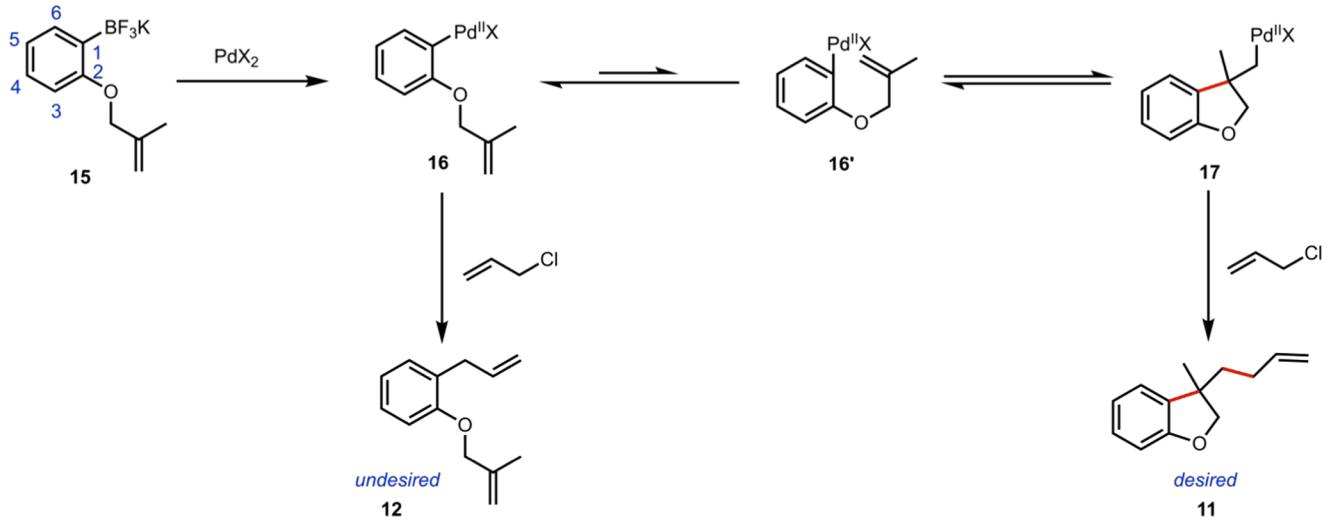
Table 5. Effect of Boronic Acid Source



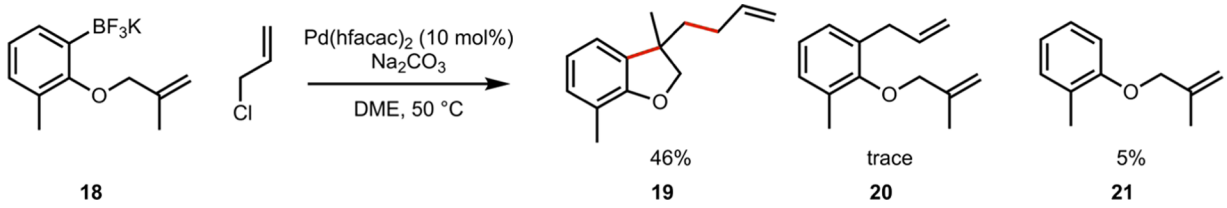
entry	B	10	11	12	13
1	$B(OH)_2$	9.2	3.4	1	0
2	BPin	0	0.1	1	0
3	BMIDA	8.8	0	1	0
4	BF_3K	0	3.5[a]	1	0.2

[a]48% isolated yield.

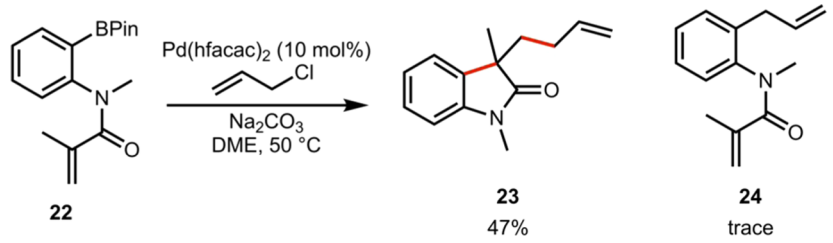
Scheme 2. Reactive Rotomer Effect on Carboallylation



Scheme 3. Carboallylation of Methyl-Substituted 18



Scheme 4. Carboallylation of Methylmethacrylamide 22



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.[5] 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 aryltrifluoroborate **15** using dideuteroallyl bromide (Scheme

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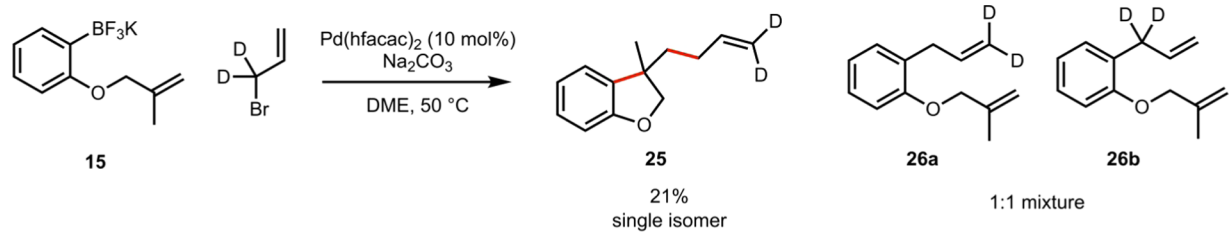
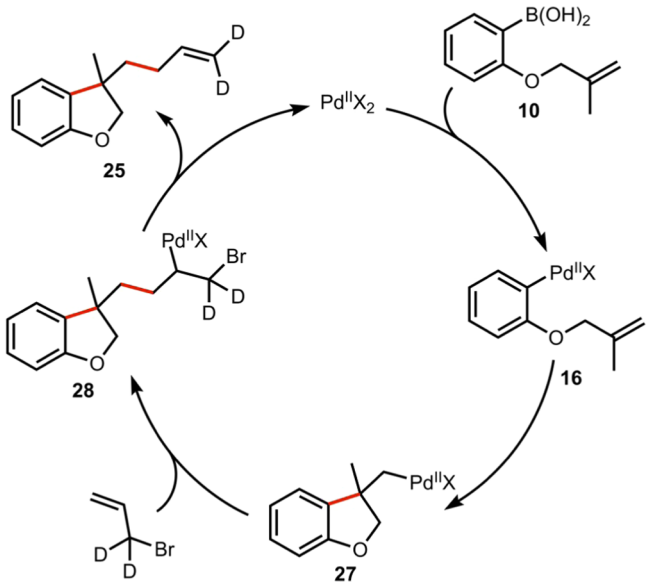
Scheme 5. Product Distribution of Carboallylation Using Deuterium-Labeled Allyl Bromide



5). This resulted in the formation of dihydrobenzofuran **25** as a single deuterated isomer, and direct allylation 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

Scheme 6. Proposed Mechanism for the Formation of 25

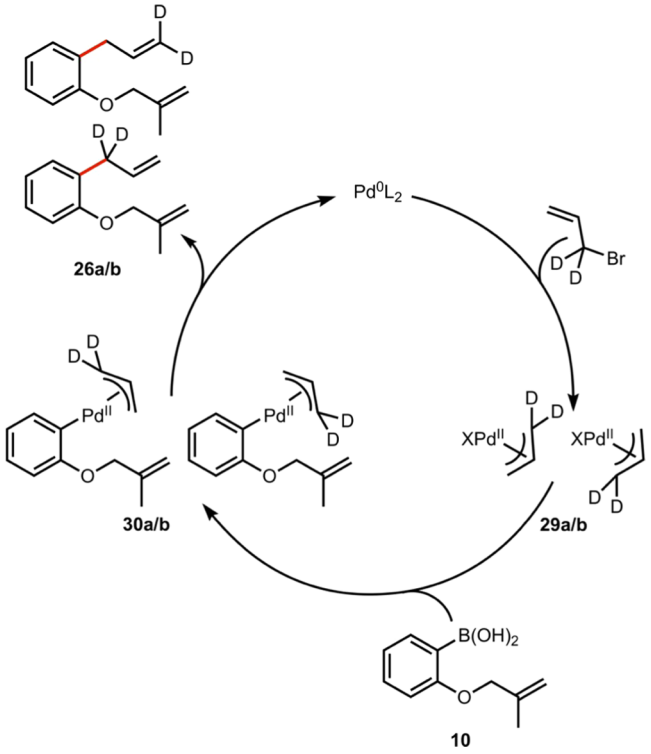


of boronic acid **10**, palladium(II) intermediate **16** is formed. Carbopalladation (olefin insertion) forms the C−C bond of the dihydrobenzofuran ring, giving **27**. A second carbopalladation can then occur, this time onto the allyl halide double bond giving palladium(II) intermediate **28**. Finally, 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 allylation products **26a**/**b**. This suggests that the direct allylation 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.

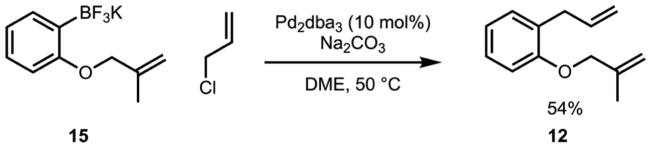
As the dihydrobenzofuran and direct allylation products appear to be formed by separate mechanisms, it should be possible to control, which product is formed by controlling the catalyst used. Having already shown the use of a palladium(II) catalyst to form a dihydrobenzofuran product from potassium trifluoroborate **15** (Table 5, entry 4), we chose to treat **15** with

Scheme 7. Proposed Mechanism for the Formation of 26a/b



a Pd(0) catalyst. As predicted, exposure of **15** to Pd_2dba_3 and allyl chloride resulted in the sole formation of direct coupling product **12** (Scheme 8).[11] Interestingly, use of several common oxidants, such as benzoquinone, DDQ, O_2, or Cu(II), did not favor the isohypsic cyclization process.

Scheme 8. Selective Formation of Direct Coupling Product 12



3. CONCLUSIONS

We have developed a new Pd-catalyzed arylallylation 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 arylallylation reaction was

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shown to proceed through an isohypsic 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 ($MgSO_4$), 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 procedure,[14] to a stirred solution of 1-(2-methylallyloxy)-2-iodobenzene (12 g, 43 mmol) and triisopropyl borate (12 mL, 52 mmol) in toluene/THF (4:1) (160 mL) at −78 °C, was added *n*BuLi (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 Et_2O (2 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), 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 solution of 2-(2-methylallyloxy)phenylboronic acid **10** (0.50 g, 2.6 mmol) in acetonitrile (11 mL), was added a solution of KF (0.60 g, 10 mmol) in water (1.2 mL). A solution of (L)-tartaric acid (0.80 g, 5.3 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%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.29 (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=*CHa*), 4.85−4.84 (1H, m, C=*CHb*), 4.27 (2H, s, OCH_2), 1.76 (3H, s, CH_3); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 161.6 (C), 142.1 (C), 138.7 (C, observed indirectly by heteronuclear multiple bond correlation (HMBC)), 133.4 (q, ^3J(C−F) = 3.1 Hz, CH), 126.3 (CH), 119.1 (CH), 110.99 (CH), 110.97 (CH_2), 70.5 (CH_2), 19.3 (CH_3); IR (solid) 1597, 1437, 1209, 1188, 922 cm^{-1}; high-resolution mass spectrometry (HRMS) (ESI) exact mass calculated for $C_{10}H_{11}F_3OB$ $[M - K]^-$ m/z 214.0897, found m/z 214.0858.

4.3. Potassium (2-(2-Methylallyloxy)-3-methylphenyl)trifluoroborate (18). Following a literature procedure,[12] 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 ($MgSO_4$), filtered, and concentrated in vacuo to give 2-(2-methylallyl)-3-bromotoluene as a yellow oil (1.3 g, quant.).

^{1}H NMR (500 MHz, $CDCl_3$) 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=*CHa*), 5.02−5.01 (1H, m, C=*CHb*), 4.31 (2H, s, OCH_2), 2.33 (3H, s, CH_3), 1.93 (3H, d, J = 0.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 154.4 (C), 141.4 (C), 133.6 (CH), 131.2 (CH), 130.5 (C), 125.3 (CH), 117.7 (C), 113.1 (CH_2), 76.2 (CH_2), 19.9 (CH_3), 16.8 (CH_3); IR (thin film) 2920, 1653, 1464, 1452, 1260, 1220 cm^{-1}; HRMS (EI) exact mass calculated for $C_{11}H_{13}OBr$ $[M]^+$ m/z 240.0150, found m/z 240.0153.

Following a literature procedure,[14] to a stirred solution of 2-(2-methylallyl)-3-bromotoluene (0.79 g, 3.3 mmol) and triisopropyl borate (0.90 mL, 3.9 mmol) in toluene/THF (4:1) (14 mL) at −78 °C was added *n*BuLi (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 Et_2O (2 × 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) 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-phenylboronic acid as a pale yellow crystalline solid (0.44 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) 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=*CHa*), 5.05 (1H, s, C=*CHb*), 4.23 (2H, s, OCH_2), 2.31 (3H, s, CH_3), 1.89 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.1 (C), 140.9 (C), 135.1 (CH), 134.3 (CH), 130.3 (C), 124.8 (CH), 123.0 (C, observed indirectly by HMBC), 113.3 (CH_2), 78.0 (CH_2), 19.8 (CH_3), 16.1 (CH_3); IR (thin film) 3412, 2910, 1464, 1435, 1383, 1344, 1084 cm^{-1}; HRMS (CI) exact mass calculated for $C_{11}H_{15}O_3B$ $[M]^+$ m/z 206.1229, found m/z 206.1232.

Following a literature procedure,[15] to a stirred solution of 2-(2-methylallyloxy)-3-methyl-phenylboronic acid (0.072 g, 0.35 mmol) in acetonitrile (1.4 mL), was added a solution of KF (0.081 g, 1.4 mmol) in water (0.15 mL). A solution of (L)-tartaric acid (0.11 g, 0.72 mmol) in THF (0.53 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 **18** as a fluffy white solid (0.084 g, 89%).

^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.20 (1H, dd, J = 7.2, 1.9 Hz, Ar−H), 6.87 (1H, ddd, J = 7.2, 2.0, 0.8 Hz, Ar−H), 6.73 (1H, t, J = 7.2 Hz, Ar−H), 5.05 (1H, dq, J = 2.4, 1.0 Hz, C=*CHa*), 4.83 (1H, dq, J = 2.7, 1.3 Hz, C=*CHb*), 4.23 (2H, s, OCH_2), 2.12 (3H, s, CH_3), 1.78 (3H, dd, J = 1.5, 0.8 Hz, CH_3); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 160.6 (C), 143.3 (C), 142.0 (C, observed indirectly by HMBC), 132.0 (q, ^3J(C−F) = 3.0 Hz, CH), 128.3 (CH), 128.2 (C), 121.8 (CH), 110.2 (CH_2), 75.5 (CH_2), 19.6 (CH_3), 16.5 (CH_3); IR (solid)

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1448, 1192, 993 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{11}H_{13}F_3OB$ $[M - K]^-$ m/z 228.1053, found m/z 228.1034.

4.4. *N*,2-Dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide (22). Following a modification of a literature procedure,[16] a mixture of bromoaniline (0.11 mL, 1.0 mmol) and bis(pinacolato)-diboron (0.38 g, 1.5 mmol) in dioxane (4 mL) was sparged with argon for 20 min. Potassium acetate (0.20 g, 2.0 mmol) and Pd(dppf)Cl_2 (0.041 g, 0.050 mmol) were added, and the reaction mixture was stirred at 80 °C. After 24 h, bis(pinacolato)diboron (0.38 g, 1.5 mmol) was added, and the reaction mixture was stirred at 80 °C for further 24 h. After cooling to room temperature, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 96:4) afforded 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as an orange crystalline solid (0.15 g, 67%). Analytical data were in accordance with literature values.[17]

Following a literature procedure,[17] to a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.10 g, 0.46 mmol) in toluene (15 mL) at 0 °C, was added triethylamine (0.50 mL, 0.46 mmol, 0.90 M) in toluene. A solution of methacryloyl chloride (0.50 mL, 0.46 mmol, 0.9 M) in toluene was added slowly (0.2 mL/min). The reaction mixture was stirred at 0 °C for 20 min and then allowed to warm to room temperature. The reaction mixture was washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 85:15) afforded 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide as a light brown crystalline solid (90 mg, 69%). Analytical data were in accordance with literature values.[17]

Following a literature procedure, to a stirred suspension of 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2-propenamide (0.73 g, 2.5 mmol) and potassium carbonate (0.40 g, 2.9 mmol) in DMF (41 mL), was added methyl iodide (0.22 mL, 3.6 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (100 mL) and water (100 mL), and extracted. The organic phase was washed with water (2 × 100 mL) and brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) afforded the title compound **22** as an orange crystalline solid (0.47 g, 62%).

^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) δ (ppm): 7.69 (1H, dd, J = 7.4, 1.7 Hz, Ar−H), 7.48 (1H, td, J = 7.7, 1.7 Hz, Ar−H), 7.31 (1H, td, J = 7.4, 1.1 Hz, Ar−H), 7.19 (1H, dd, J = 8.0, 1.1 Hz, Ar−H), 4.99 (2H, s, C=CH_2), 3.20 (3H, s, NCH_3), 1.73 (3H, s, CCH_3), 1.29 (12H, s, 4 × CCH_3); ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C) δ (ppm): 169.7 (C), 140.3 (C), 136.0 (C), 135.3 (CH), 132.5 (CH), 131.3 (C), 128.6 (CH), 126.2 (CH), 116.8 (CH_2), 82.9 (C), 37.7 (CH_3), 24.2 (CH_3), 19.5 (CH_3); IR (thin film) 2978, 1653, 1352, 1145 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{17}H_{24}BNNaO_3$ $[M + Na]^+$ m/z 324.1741, found m/z 324.1740.

4.5. 3-(But-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran (11). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **15** (76 mg, 0.30 mmol), Pd(hfacac)$_2$ (16 mg, 0.030 mmol), Na_2CO_3 (64 mg, 0.60 mmol), dimethoxyethane (1.2 mL), and allyl chloride (49 μL, 0.60 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 **11** as a colorless oil (27 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15−7.07 (2H, m, 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, ddt, J = 16.7, 10.2, 6.4 Hz, C*H*=CH_2), 4.98 (1H, dq, J = 17.1, 1.7 Hz, CH=C*H*H), 4.94−4.90 (1H, m, CH=CH*H*), 4.37 (1H, d, J = 8.7 Hz, O−C*H*H), 4.16 (1H, d, J = 8.6 Hz, O−CH*H*), 2.15−2.05 (1H, m, CH_2CH*H*CH=CH_2), 1.92−1.82 (1H, m, CH_2C*H*HCH=CH_2), 1.73−1.68 (2H, m, *C*$H_2$$CH_2$CH=$CH_2$), 1.36 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.9 (C), 138.5 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.7 (CH_2), 109.7 (CH), 82.6 (CH_2), 45.3 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3); IR (thin film) 2934, 1365, 1196 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}O$ $[M]^+$ m/z 188.1201, found m/z 188.1203.

4.6. 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-methylallyloxy)-3-methylphenyl)-trifluoroborate **18** (220 mg, 0.80 mmol), Pd(hfacac)$_2$ (42 mg, 0.080 mmol), Na_2CO_3 (170 mg, 1.6 mmol), dimethoxyethane (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, 9:1) afforded the title compound **19** as a colorless oil (74 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$) 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, ddt, J = 16.8, 10.2, 6.5 Hz, C*H*=CH_2), 4.99 (1H, dq, J = 17.1, 1.7 Hz, CH=C*H*H), 4.93−4.91 (1H, m, CH=CH*H*), 4.38 (1H, d, J = 8.7 Hz, O−C*H*H), 4.17 (1H, d, J = 8.7 Hz, O−CH*H*), 2.22 (3H, s, CH_3), 2.14−2.06 (1H, m, CH_2C*H*HCH=CH_2), 1.91−1.84 (1H, m, CH_2CH*H*CH=CH_2), 1.75−1.65 (2H, m, *C*$H_2$$CH_2$CH=$CH_2$), 1.35 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 82.4 (CH_2), 45.6 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3), 15.2 (CH_3); IR (thin film) 2965, 2922, 1456, 1188 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{18}O$ $[M]^+$ m/z 202.1358, found m/z 202.1357.

4.7. 3-(But-3-en-1-yl)-1,3-dimethylindolin-2-one (23). A screw-top glass vial (4 mL) was charged with *N*,2-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **22** (22 mg, 0.080 mmol), Pd(hfacac)$_2$ (4.2 mg, 0.0080 mmol), Na_2CO_3 (17 mg, 0.16 mmol), dimethoxyethane (0.32 mL), and allyl chloride (13 μL, 0.16 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%).

^{1}H NMR (500 MHz, $CDCl_3$) 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, C*H*=CH_2), 4.843−4.841 (1H, m, CH=C*H*H), 4.82−4.81 (1H, m, CH=CH*H*), 3.20 (3H, s, N-CH_3), 2.05−2.00 (1H, m, CH_2C*H*HCH=CH_2), 1.85−1.79 (1H, m, CH_2CH*H*CH=CH_2), 1.77−1.69 (1H, m,

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CHHCH$_2$CH=CH$_2$), 1.66−1.59 (1H, m, CHHCH$_2$CH=CH$_2$), 1.36 (3H, s, CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 180.7 (C), 143.5 (C), 137.9 (CH), 134.0 (C), 127.9 (CH), 122.7 (CH), 122.6 (CH), 114.7 (CH$_2$), 108.0 (CH), 48.3 (CH$_3$), 37.7 (CH$_2$), 29.1 (CH$_2$), 26.2 (CH$_3$); IR (thin film) 2974, 2929, 1705, 1614, 1379, 1352 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{17}ON$ [M]$^+$ m/z 215.1310, found m/z 215.1311.

4.8. 3-(4,4-Dideuteriobut-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran (25). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)-trifluoroborate **15** (64 mg, 0.25 mmol), Pd(hfacac)$_2$ (13 mg, 0.025 mmol), Na$_2$CO$_3$ (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL), and dideuteroallyl bromide[18] (0.37 mL, 1.3 M in Et$_2$O, 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%).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.13 (1H, ddd, J = 8.0, 7.4, 1.5 Hz, Ar−H), 7.08 (1H, ddd, 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, ddd, J = 8.0, 1.0, 0.5 Hz, Ar−H), 5.79−5.73 (1H, m, CH=CD$_2$), 4.38 (1H, d, J = 8.7 Hz, O−CHH), 4.17 (1H, d, J = 8.7 Hz, O−CHH), 2.15−2.06 (1H, m, CHHCH$_2$CH=CD$_2$), 1.92−1.83 (1H, m, CHHCH$_2$CH=CD$_2$), 1.73−1.69 (2H, m, CH$_2$CH$_2$CH=CD$_2$), 1.36 (3H, s, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ^1J(C−D) = 24.1 Hz, CD$_2$), 109.7 (CH), 82.6 (CH$_2$), 45.3 (C), 40.2 (CH$_2$), 29.1 (CH$_2$), 25.7 (CH$_3$); IR (thin film) 2926, 2237, 1600, 1481 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{14}D_2O$ [M]$^+$ m/z 190.1321, found m/z 190.1315.

4.9. 1-(Dideuterioallyl)-2-((2-methallyl)oxy)benzene (26a/b). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **15** (64 mg, 0.25 mmol), Pd(hfacac)$_2$ (13 mg, 0.025 mmol), Na$_2$CO$_3$ (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL), and dideuteroallyl bromide[18] (0.37 mL, 1.3 M in Et$_2$O, 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%).

^{1}H NMR (400 MHz, CDCl$_3$) 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=CD$_2$/CH=CH$_2$), 5.11 (1H, s, OCH$_2$C=CHa), 5.09−5.02 (2H, m, CD$_2$C=CH$_2$), 4.98 (1H, s, OCH$_2$C=CHb), 4.43 (2H, s, OCH$_2$), 3.43 (2H, d, J = 6.6 Hz, CH$_2$C=CD$_2$), 1.84 (3H, s, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ^1J(C−D) = 24.1 Hz, CD$_2$), 109.7 (CH), 82.6 (CH$_2$), 45.3 (C), 40.2 (CH$_2$), 29.1 (CH$_2$), 25.7 (CH$_3$); IR (thin film) 2926, 2237, 1600, 1481 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{14}D_2O$ [M]$^+$ m/z 190.1321, found m/z 190.1315.

4.10. 2-(2-Methylallyloxy)phenylboronic acid pinacol ester. Following a modification of the reported procedure,[19] a mixture of 2-(2-methylallyloxy)phenylboronic acid **10** (500 mg, 2.6 mmol) and pinacol (307 mg, 2.6 mmol) in Et$_2$O (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 (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The ^{1}H NMR spectrum of the crude material indicated approximately 80% conversion, so the residue was refluxed with pinacol (92 mg, 0.8 mmol) in Et$_2$O (15 mL) for 16 h. The cooled reaction mixture was washed with water (25 mL), brine (2 × 25 mL), dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to afford the title compound as a colorless oil (650 mg, 92%).

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.68 (1H, dd, J = 7.3, 1.8 Hz, 6-H), 7.37 (1H, ddd, 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=CHa), 4.97−4.98 (1H, m, C=CHb), 4.42 (2H, s, OCH$_2$), 1.86 (3H, s, CH$_3$), 1.35 (12H, s, 2 × C(CH$_3$)$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) 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 (CH$_2$), 111.6 (CH), 83.5 (2 × C), 71.6 (CH$_2$), 25.1 (4 × CH$_3$), 19.6 (CH$_3$); IR (thin film) 1670, 1438, 1300, 1246, 1196, 1142; HRMS (ESI) exact mass calculated for $C_{16}H_{23}NaO_3B$ [M + Na]$^+$ m/z 296.1669, found m/z 296.1664.

4.11. 2-(2-Methylallyloxy)phenylboronic Acid Methyliminodiacetic Acid Ester. Following a modification of the reported procedure,[20] to a solution of 2-(2-methylallyloxy)-phenylboronic acid **10** (86 mg, 0.50 mmol) in DMF (1.5 mL), was added methylimindodiacetic acid (74 mg, 0.50 mmol). The resulting suspension was heated at 85 °C for 24 h and then filtered through an Isolute Si-Carbonate cartridge (500 mg), rinsing with MeCN. The filtrate was concentrated in vacuo and then partitioned between EtOAc (15 mL) and water (15 mL). The organic extracts were washed with brine (15 mL), dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 1:2 then 0:1) afforded the title compound as a colorless foam (100 mg, 66%).

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.69 (1H, dd, J = 7.4, 3.5 Hz, 6-H), 7.34 (1H, ddd, J = 8.2, 7.4, 1.8 Hz, 4-H), 6.99 (1H, td, J = 7.3, 0.8 Hz, 5-H), 6.87 (1H, d, J = 8.2 Hz, 3-H), 5.02 (2H, s, C=CH$_2$), 4.46 (2H, s, OCH$_2$), 3.96 (4H, s, CH$_2$N(CH$_3$)CH$_2$), 2.71 (3H, s, NCH$_3$), 1.80 (3H, s, C(CH$_3$)=CH$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 168.0 (2 × C), 161.7 (C), 141.2 (C), 135.3 (CH), 131.5 (CH), 123.3 (C, observed indirectly by HMBC), 121.5 (CH), 114.3 (CH$_2$), 111.9 (CH), 72.7 (CH$_2$), 63.9 (2 × CH$_2$), 47.5 (CH$_3$), 19.7 (CH$_3$); IR (solid) 1746, 1311, 1208, 1035, 1000; HRMS (ESI) exact mass calculated for $C_{15}H_{18}NNaO_5B$ [M + Na]$^+$ m/z 325.1207, found m/z 325.1195.

4.12. 1-Allyl-2-((2-methylallyl)oxy)benzene (12). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.19−7.16 (2H, m, 4-H, 6-H), 6.91 (1H, td, J = 7.4, 1.0 Hz, 5-H), 6.85 (1H, d, J = 8.1 Hz, 3-H), 6.07−5.98 (1H, m, CH$_2$CH=CH$_2$), 5.13 (1H, s, C(CH$_3$)=CHa), 5.10−5.03 (2H, m, CH$_2$CH=CH$_2$), 4.99 (1H, s, C(CH$_3$)=CHb), 4.44 (2H, s, OCH$_2$), 3.44 (2H, d, J = 6.7 Hz, CH$_2$CH=CH$_2$), 1.85 (3H, s, C(CH$_3$)=CH$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 156.4 (C), 141.2 (C), 137.2 (CH), 129.9 (CH), 129.0 (C), 127.3 (CH), 120.7 (CH), 115.5 (CH$_2$), 112.3 (CH$_2$), 111.6 (CH), 71.7 (CH$_2$), 34.6 (CH$_2$), 19.6 (CH$_3$); IR (thin film) 1491, 1451, 1238; HRMS (EI) exact mass calculated for $C_{13}H_{16}O$ [M]$^+$ m/z 188.1201, found m/z 188.1997.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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D.P. and J.F.M.H. performed the experiments. D.J.F. guided the research. All authors contributed to experimental design, data analysis, and manuscript preparation.

Notes

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■ REFERENCES

(1) (a) Rivera-Becerril, E.; Joseph-Nathan, P.; Pérez-Álvarez, V. M.; Morales-Ríos, M. S. Synthesis and Biological Evaluation of (−)- and (+)-Debromoflustramine B and Its Analogues as Selective Butyrylcholinesterase Inhibitors. *J. Med. Chem.* **2008**, *51*, 5271−5284. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell, 2010. (c) Sheppard, T. D. Strategies for the synthesis of 2,3-dihydrobenzofurans. *J. Chem. Res.* **2011**, *35*, 377−385.

(2) (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. Cyclisations Involving Attack of Carbo- and Heteronucleophiles on Carbon-Carbon π-Bonds Activated by Organopalladium Complexes. *Synthesis* **2003**, 2115−2134. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981−3019. (c) Smith, C. D.; France, D. J. 2-Alkenyl Furans from a Palladium-Catalyzed Cyclization and Coupling of Ene-Yne-Ketones. *ChemCatChem* **2014**, *6*, 711−712. (d) Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. Recent developments in the use of aza-Heck cyclizations for the synthesis of chiral N-heterocycles. *Chem. Sci.* **2017**, *8*, 5248−5260.

(3) Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. Palladium-catalyzed heteroallylation of unactivated alkenes − synthesis of citalopram. *Chem. Sci.* **2013**, *4*, 3538−3543.

(4) Phillips, D.; France, D. J. Palladium-Catalyzed Heterocyclization: A Carbon-Centered Approach. *Asian J. Org. Chem.* **2017**, *6*, 27−40.

(5) Zhou, M. B.; Huang, X. C.; Liu, Y. Y.; Song, R. J.; Li, J. H. Alkylation of Terminal Alkynes with Transient σ-Alkylpalladium(II) Complexes: A Carboalkynylation Route to Alkyl-Substituted Alkynes. *Chem. - Eur. J.* **2014**, *20*, 1843−1846.

(6) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756. (b) Morley, A. D.; Pugliese, A.; Birchall, K.; Bower, J.; Brennan, P.; Brown, N.; Chapman, T.; Drysdale, M.; Gilbert, I. H.; Hoelder, S.; Jordan, A.; Ley, S. V.; Merritt, A.; Miller, D.; Swarbrick, M. E.; Wyatt, P. G. Fragment-based hit identification: thinking in 3D. *Drug Discovery Today* **2013**, *18*, 1221−1227. (c) Schneider, P.; Schneider, G. Privileged Structures Revisited. *Angew. Chem., Int. Ed.* **2017**, *56*, 7971−7974.

(7) (a) Koe, B. K. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649. (b) Gautier, C.; Aletru, M.; Bovy, P. Oxindole Derivatives Used as Neurokinin Receptor Antagonists. WO19990629001999.

(8) Akiyama, K.; Mikami, K. Pd(II)-Catalyzed Enantioselective Intramolecular Heck-Type Reaction to Construct Chiral Sulfonamide Rings. *Heterocycles* **2007**, *74*, 827−834.

(9) Williams, F. J.; Jarvo, E. R. Palladium-Catalyzed Cascade Reaction for the Synthesis of Substituted Isoindolines. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459−4462.

(10) Jung, M. E.; Piizzi, G. *gem*-Disubstituent Effect: Theoretical Basis and Synthetic Applications. *Chem. Rev.* **2005**, *105*, 1735−1766.

(11) (a) Bumagin, N. A.; Bykov, V. V. Ligandless palladium catalyzed reactions of arylboronic acids and sodium tetraphenylborate with aryl halides in aqueous media. *Tetrahedron* **1997**, *53*, 14437−14450. (b) Ghosh, R.; Adarsh, N. N.; Sarkar, A. A Novel, Air-Stable Phosphine Ligand for the Palladium- Catalyzed Suzuki−Miyaura Cross-Coupling Reaction of Chloro Arenes. *J. Org. Chem.* **2010**, *75*, 5320−5322. (c) Cívicos, J. F.; Alonso, D. A.; Nájera, C. Oxime Palladacycle-Catalyzed Suzuki−Miyaura Alkenylation of Aryl, Heteroaryl, Benzyl, and Allyl Chlorides under Microwave Irradiation Conditions. *Adv. Synth. Catal.* **2011**, *353*, 1683−1687.

(12) Newman, S. G.; Lautens, M. Palladium-Catalyzed Carboiodination of Alkenes: Carbon−Carbon Bond Formation with Retention of Reactive Functionality. *J. Am. Chem. Soc.* **2011**, *133*, 1778−1780.

(13) Casaschi, A.; Grigg, R.; Sansano, J. M. Palladium Catalysed Tandem Cyclisation−Anion Capture. Part 6: Synthesis of Sugar, Nucleoside, Purine, Benzodiazepinone and β-lactam Analogues via Capture of in situ Generated Vinylstannanes. *Tetrahedron* **2000**, *56*, 7553−7560.

(14) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. Practical Radical Cyclizations with Arylboronic Acids and Trifluoroborates. *Org. Lett.* **2011**, *13*, 5628−5631.

(15) Lennox, A. J.; Lloyd-Jones, G. C. Preparation of Organotrifluoroborate Salts: Precipitation- Driven Equilibrium under Non-Etching Conditions. *Angew. Chem., Int. Ed.* **2012**, *51*, 9385−9388.

(16) Xiao, D.; Li, J.; Zhu, Y.; Hu, Y.; Wang, H.; Wang, Z.; Wang, Z.; Wei, Y.; Sun, Y.; Wu, Q. Kinase Modulating Compounds, Compositions Containing the Same and Use thereof WIPO. WO2013/071865A12013.

(17) D'Hooge, F.; Rogalle, D.; Thatcher, M. J.; Perera, S. P.; van den Elsen, J. M. H.; Jenkins, A. T. A.; James, T. D.; Fossey, J. S. Polymerisation resistant synthesis of methacrylamido phenylboronic acids. *Polymer* **2008**, *49*, 3362−3365.

(18) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. Highly Asymmetric NHC- Catalyzed Hydroacylation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983−4987.

(19) Oehlke, A.; Auer, A. A.; Jahre, I.; Walfort, B.; Rüffer, T.; Zoufalá, P.; Lang, H.; Spange, S. Nitro- Substituted Stilbeneboronate Pinacol Esters and Their Fluoro-Adducts. Fluoride Ion Induced Polarity Enhancement of Arylboronate Esters. *J. Org. Chem.* **2007**, *72*, 4328−4339.

(20) Grob, J. E.; Nunez, J.; Dechantsreiter, M. A.; Hamann, L. G. One-Pot Reductive Amination and Suzuki−Miyaura Cross-Coupling of Formyl Aryl and Heteroaryl MIDA Boronates in Array Format. *J. Org. Chem.* **2011**, *76*, 4930−4940.

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