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COMMUNICATION

Palladium-Catalyzed Dearomatizing Alkoxydiarylation of Furan Rings by Coupling with Arylboronic Acids: Access to Polysubstituted Oxabicyclic Compounds

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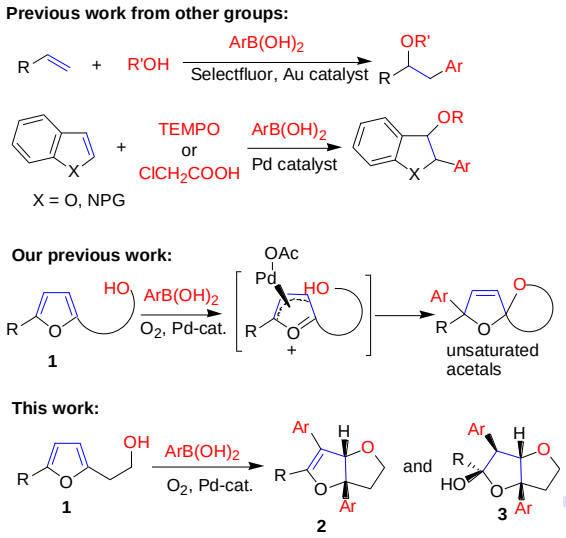
Abstract: We report a protocol for palladium-catalyzed dearomatizing alkoxydiarylation of furan rings via aerobic oxidative coupling between arylboronic acids and 5-aryl-2-hydroxyalkylfurans. This green protocol starting from furan derivatives, which can be sustainably sourced, provides rapid access to polysubstituted 2,3,3a,6a-tetrahydrofuro[3,2-*b*]furans and hexahydrofuro[3,2-*b*]furans, oxabicyclic frameworks that are shared by various natural products and synthetic molecules with important biological activities.

Keywords: aerobic oxidation, fused-ring systems, green chemistry, regioselectivity

Selective introduction of two functional groups into an alkene in a single operation is a powerful method for the rapid construction of complex molecules.[1] In recent years, numerous protocols for transition-metal-catalyzed difunctionalization of alkenes have been reported, such as dioxygenation,[2] oxyamidation,[3] diboration,[4] and diamination.[5] These step-economical protocols have provided a wide range of structurally diverse functionalized compounds that are of great importance in organic synthesis.

Alkene carboalkoxylation is a useful subclass of alkene difunctionalization and has been used to construct biologically valuable tetrahydrofurans, dihydrobenzofurans, and other oxygen-containing heterocycles.[6] This transformation usually involves coupling between an exogenous carbon electrophile or nucleophile and an alcohol that bears a pendant alkene. However, the transformation is limited to structurally simple alkenes, and extension to aromatic alkenes is challenging because of the chemical inertness of the aromatic ring. Recently, Pd-catalyzed dearomatizing 2,3-alkoxyarylation reactions of heteroarenes such as indoles and benzofurans have been reported to efficiently and stereoselectively afford indolines and 2,3-dihydrobenzofurans (Scheme 1);[7] in these cases, the chemical properties of the destroyed aromatic alkene substrates are similar to those of simple monoalkenes. To our knowledge, efficient methods for transition-metal-catalyzed dearomatizing difunctionalization of diene-like aromatic rings, such as furans, with regioselectivity and stereoselectivity are limited.



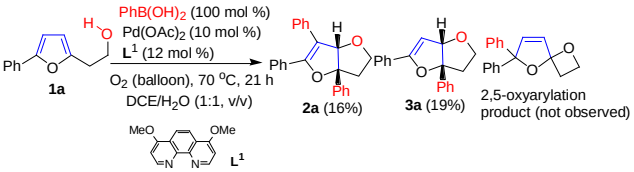
Scheme 1. Alkoxydiarylation of alkenes and arenes with boronic acids as carbon nucleophiles

Owing to its low aromaticity, the diene moiety of a furan ring is chemically similar to a nonaromatic alkene or diene. Therefore, furans can be readily dearomatized. A number of reactions capitalize on this property and have been used to synthesize other useful compounds.[8] Recently, we reported a protocol for Pd-catalyzed intra- and intermolecular 2,5-oxyarylation reactions of furans for diastereospecific synthesis of spirooxindoles.[9] We also reported a protocol for 2,5-oxyarylation of furan rings *via* Pd-catalyzed oxidative coupling of boronic acids with α-hydroxyalkylfurans to synthesize spiroacetals using O_2 as a green oxidant.[10] These protocols can be viewed as a difunctionalization of the diene segment of the furan rings and provide new strategies for expanding the synthetic utility of furans for the construction of polycyclic dihydrofurans. As part of our ongoing work on dearomatizing transformations of furans,[11] which can be sustainably sourced, we herein report a protocol for Pd-catalyzed dearomatizing alkoxydiarylation of furan rings *via* the oxidative coupling of arylboronic acids with 5-aryl-2-hydroxyalkylfurans **1**, providing access to two types of oxa-bicyclic skeletons **2** and **3**.

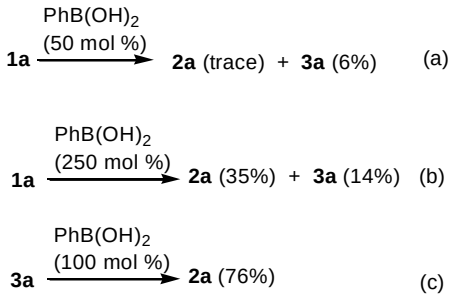
To our knowledge, the tri-functionalization of the furans *via* a one-pot protocol has never been reported.

The success of the alkoxydiarylation of **1** to provide **2** relies on suppression of 2,5-oxyarylation by the choice of suitable substrates **1**. We suspected that an aryl group of R would suppress the undesired 2,5-oxyarylation. To confirm this possibility, we investigated the reaction of 2-(5-phenyl-furan-2-yl)-ethanol (**1a**) with $PhB(OH)_2$ (100 mol %) by using $Pd(OAc)_2$ (10 mol %) as the catalyst, $\mathbf{L^1}$ as the ligand, O_2 (balloon) as the oxidant, 70 °C as the reaction temperature, and 1:1 (v/v) DCE/H_2O as the solvent (Scheme 2). Under these conditions, reaction for 21 h provided alkoxydiarylated product of furo[3,2-*b*]furan **2a** in 16% yield, along with a 19% yield of alkoxyarylated furo[3,2-*b*]furan **3a**. The 2,5-oxyarylation product was not observed.

To gain insight into this transformation, we conducted three control experiments (Scheme 3). When we carried out the reaction of **1a** under identical conditions except that we used less $PhB(OH)_2$ (50 mol %) and added it in portions, the yield of **3a** dropped to 6% (Scheme 3a). Carrying out the reaction of **1a** with more $PhB(OH)_2$ (250 mol %) elevated the yield of **2a** (35%) and reduced the yield of **3a** (14%) (Scheme 3b), relative to the yield under the standard conditions. These results suggested that increasing the amount of $PhB(OH)_2$ and tuning the reaction conditions would afford efficient access to **2a**. In the presence of 100 mol % $PhB(OH)_2$ but otherwise identical conditions, reaction of **3a** provided **2a** in 76% yield (Scheme 3c), indicating that **2a** may be formed by direct phenylation of **3a**.[12] The furo[3,2-*b*]furan is shared by various natural products and synthetic compounds with important biological activities (Figure 1),[13] so we directed our efforts at developing a route to this skeleton by means of 2,3-oxydiarylation of furans.



Scheme 2. Reaction of **1a** with $PhB(OH)_2$



Scheme 3. Control experiments

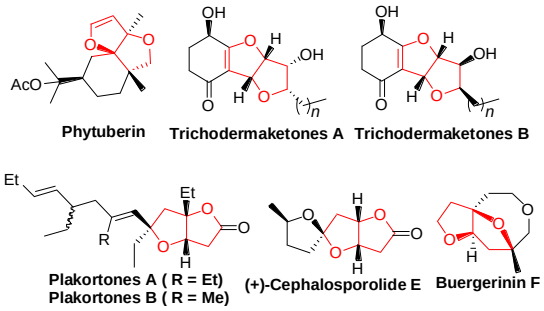
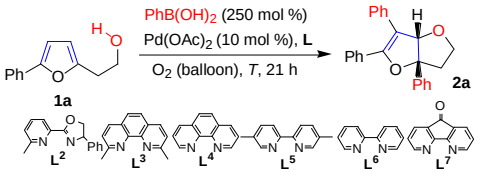


Figure 1. Representative furo[3,2-*b*]furans

To optimize the reaction condition for the production of **2a**, we began by allowing **1a** to react with $PhB(OH)_2$ (250 mol %) in the presence of a series of bidentate nitrogen-containing ligands (Table 1, entries 1–7). The electronic and steric properties of the ligand played an important role in the outcome of the reaction. Reactions with an electron-poor ligand ($\mathbf{L^7}$) and with sterically hindered ligands ($\mathbf{L^2}$ and $\mathbf{L^3}$) did not afford **2a**. Among the ligands examined, 1,10-phenanthroline ($\mathbf{L^4}$) was found to be optimal, giving **2a** in 74% yield. Various binary solvent systems were then screened (entries 8–11), and 1:1 (v/v) DCE/H_2O proved to be optimal. Increasing the DCE/H_2O ratio to 2:1 or lowering it to 1:2 did not improve the yield of **2a** (entries 12 and 13). When DCE was used as the sole solvent, the boronic acid did not dissolve well, and the yield of **2a** was only 17% (entry 14). Increasing the amount of **1a** to 350% mol reduced the yield (entry 15). Neither lowering the reaction temperature to 60 °C (entry 16) nor elevating it to 80 °C (entry 17) improved the yield. Thus, the optimal reaction conditions involved the use of $Pd(OAc)_2$ as the catalyst, O_2 as the oxidant, 1:1 DCE/H_2O as the solvent, and 70 °C as the reaction temperature.

Table 1. Optimization of reaction conditions for formation of **2a**[a]



entry	L	solvent	yield (%)[b]
1	$\mathbf{L^1}$	DCE/H_2O (1:1)	35
2	$\mathbf{L^2}$	DCE/H_2O (1:1)	0
3	$\mathbf{L^3}$	DCE/H_2O (1:1)	0
4	$\mathbf{L^4}$	DCE/H_2O (1:1)	74
5	$\mathbf{L^5}$	DCE/H_2O (1:1)	19
6	$\mathbf{L^6}$	DCE/H_2O (1:1)	45
7	$\mathbf{L^7}$	DCE/H_2O (1:1)	0
8	$\mathbf{L^4}$	MeCN/H_2O (1:1)	9
9	$\mathbf{L^4}$	THF/H_2O (1:1)	18
10	$\mathbf{L^4}$	DMF/H_2O (1:1)	trace
11	$\mathbf{L^4}$	MeOH/H_2O (1:1)	58

12	**L**^{4}	DCE/H_2O (2:1)	49
13	**L**^{4}	DCE/H_2O (1:2)	25
14	**L**^{4}	DCE	17
15[c]	**L**^{4}	DCE/H_2O (1:1)	21
16[d]	**L**^{4}	DCE/H_2O (1:1)	49
17[e]	**L**^{4}	DCE/H_2O (1:1)	55
18[f]	**L**^{4}	DCE/H_2O (1:1)	35

[a] Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), $PhB(OH)_2$ (0.5 mmol) (added in three equal portions at 4-h intervals), $Pd(OAc)_2$ (10 mol %), **L** (12 mol %), *T* = 70 °C, 21 h.

[b] Yields were determined by ^{1}H NMR spectroscopy of the crude products with dibromomethane as an internal standard.

[c] $PhB(OH)_2$ (0.7 mmol).

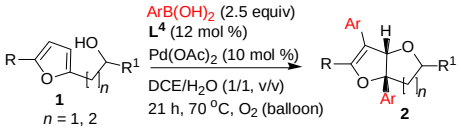
[d] *T* = 60 °C.

[e] *T* = 80 °C.

[f] *T* = 80 °C, $Pd(OAc)_2$ (5 mol %), **L**^{4} (6 mol %).

To investigate the scope of the reaction, we carried out reactions between various aryl boronic acids and α-hydroxyalkylfurans **1** with different *n* values and substitution patterns under the optimized conditions to synthesize 2,3,3a,6a-tetrahydrofuro[3,2-*b*]furans **2** (Table 2). When R was phenyl (entries 1–14), R^2 could be a phenyl group, either unsubstituted or with an electron-donating or electron-withdrawing substituent, and the corresponding products were obtained in good to excellent yields, except in the cases of **2c**, **2k**, and **2l**. The strongly electron-donating *para* MeO group and the strongly electron-withdrawing *para* NO_2 group may have been responsible for the very low yields of **2c** and **2l**, respectively (entries 3 and 12). The low yield of **2k** (entry 11) may have been due to the poor solubility of the corresponding boronic acid in the reaction solvent. Notably, the use of a bulky naphthyl boronic acid resulted in only a trace amount of product **2m** (entry 13). When R^2 was a vinyl group, none of the corresponding product (**2n**) was obtained. The R substituent could also be a phenyl group with an electron-donating or electron-withdrawing substituent (entries 15–18). However, when R was a 4-ClC_6H_4 group, the yield dropped to 40% (entry 18). When R^1 was a methyl group, the product **2s** was formed in a good yield (65%) with a diasteroselectivity of 1.3/1 (entry 19). A substrate with a methyl group as R gave a low yield (**2t**, 39%), owing to the formation of a significant amount of unverified by-product (entry 20). When R was ethyl or *i*-propyl group, none of the desired products were afforded (entries 21 and 22). Notably, when *n* was 2, product **2w** was obtained in 64% yield (entry 23). When *n* was 3, product **2x** was obtained but in a very low yield (21%, entry 24).

Table 2. Synthesis of tetrahydrofuro[3,2-*b*]furans **2**[a]



entry	R	Ar	R^1	*n*	**2** (yield [%])[b]
1	Ph	Ph	H	1	**2a** (71)
2	Ph	4-Me-C_6H_4	H	1	**2b** (78)
3	Ph	4-MeO-C_6H_4	H	1	**2c** (46)
4	Ph	4-F-C_6H_4	H	1	**2d** (61)
5	Ph	4-Cl-C_6H_4	H	1	**2e** (65)
6	Ph	4-Br-C_6H_4	H	1	**2f** (57)
7	Ph	3-Me-C_6H_4	H	1	**2g** (84)
8	Ph	3-F-C_6H_4	H	1	**2h** (70)
9	Ph	3-MeO-C_6H_4	H	1	**2i** (71)
10	Ph	3,5-di-Me-C_6H_3	H	1	**2j** (81)
11	Ph	3-Me-4-F-C_6H_3	H	1	**2k** (30)
12	Ph	4-NO_2-C_6H_4	H	1	**2l** (ND)
13	Ph	1-Np	H	1	**2m** (trace)
14	Ph	CH_2=CH	H	1	**2n** (ND)
15	4-Me-C_6H_4	3-Me-C_6H_4	H	1	**2o** (86)
16	2-Me-C_6H_4	3-Me-C_6H_4	H	1	**2p** (47)
17	3,5-di-Me-C_6H_3	3-Me-C_6H_4	H	1	**2q** (72)
18	4-Cl-C_6H_4	3-Me-C_6H_4	H	1	**2r** (40)[c]
19	Ph	3-Me-C_6H_4	Me	1	**2s** (65)[d]
20	Me	3-Me-C_6H_4	H	1	**2t** (39)
21	Et	3-Me-C_6H_4	H	1	**2u** (ND)
22	*i*-Pr	3-Me-C_6H_4	H	1	**2v** (ND)
23	Ph	3-Me-C_6H_4	H	2	**2w** (64)[e]
24	Ph	3-Me-C_6H_4	H	3	**2x** (21)[f]

[a] Reaction conditions: **1** (0.4 mmol), $ArB(OH)_2$ (1.0 mmol, added in three equal portions at 4-h intervals), $Pd(OAc)_2$ (0.04 mmol), **L**^{4} (0.048 mmol), DCE (2 mL), H_2O (2 mL), 70 °C, under O_2 (balloon), 21 h.

[b] Isolated yields; ND, not detected.

[c] Yield was determined by ^{1}H NMR spectroscopy of the crude products with dibromomethane as an internal standard.

[d] Ratio *trans*/*cis* = 1.3/1. Diastereomer ratios were determined by ^{1}H NMR spectroscopy of the crude products.

[e] Ratio *trans*/*cis* = 6/1, as determined by ^{1}H NMR spectroscopy.

[f] Ratio *trans*/*cis* = 5/1, as determined by ^{1}H NMR spectroscopy.

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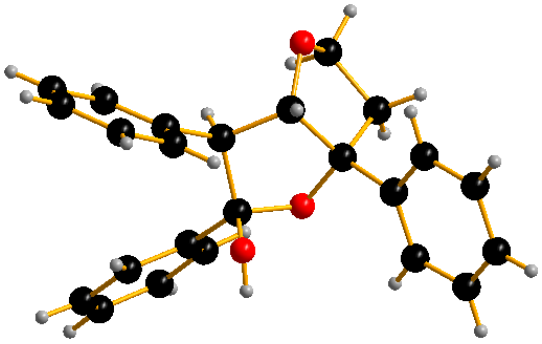
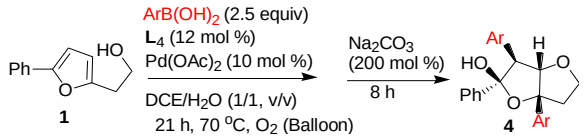


Figure 2. ORTEP diagram of **4a** with 30% ellipsoid probability.

Encouraged by the above-described results, we attempted the synthesis of hexahydrofuro[3,2-*b*]furans **4**, which have four chiral carbon centers, from **1**. As shown in Table 3, after completion of the reaction of **1** with boronic acids under the conditions described above for the formation of **2**, we added 200 mol % Na_2CO_3 without work-up and continued the reaction for an additional 8 h at 70 °C. As a result, products **4** were obtained diastereospecifically by means of a one-pot protocol in moderate to good yields. The stereochemistry of **4** was unambiguously determined by X-ray crystallographic analysis (**4a**, Figure 2).[14]

Table 3. One-pot formation of hexahydrofuro[3,2-*b*]furans **4**[a]

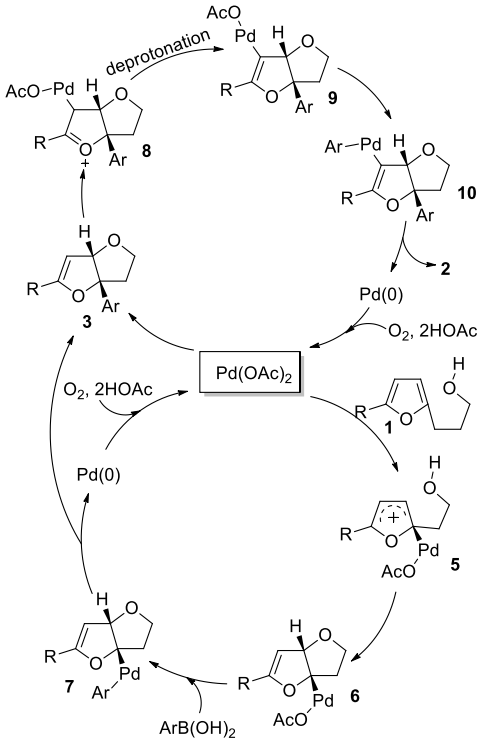


entry	Ar	**4** (yield [%])[b]
1	Ph	**4a** (78)
2	4-Me-C_6H_4	**4b** (62)
3	4-Cl-C_6H_4	**4c** (55)
4	4-Br-C_6H_4	**4d** (56)
5	4-Et-C_6H_4	**4e** (72)
6	4-*t*-Bu-C_6H_4	**4f** (71)
7	3-Me-C_6H_4	**4g** (60)
8	3-MeO-C_6H_4	**4h** (66)
9	3-F-C_6H_4	**4i** (44)
10	3,5-di-Cl-C_6H_4	**4j** (21)
11	3,5-di-Me-C_6H_4	**4k** (70)

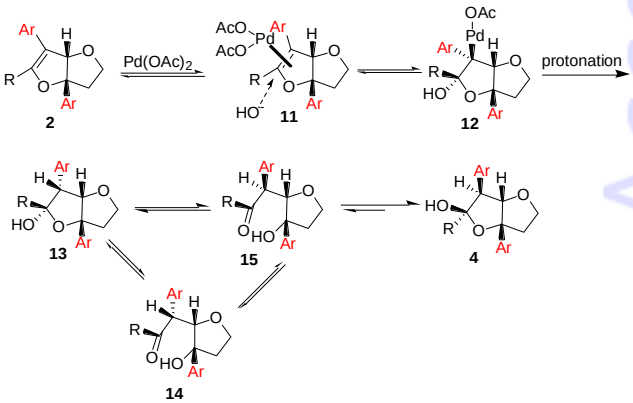
[a]Reaction conditions: **1** (0.4 mmol), $ArB(OH)_2$ (1.0 mmol), $Pd(OAc)_2$ (0.04 mmol), L_4 (0.048 mmol), DCE (2 ml), H_2O (2 ml), 70 °C, under O_2 (balloon), 21 h. Then Na_2CO_3 (0.8 mmol) was added to the same pot, and the reaction was continued for 8 h.
[b] Isolated yields.

On the basis of our previous studies and control experiments outcome, we propose the pathway for the formation of **2. As** outlined in Scheme 4, the electrophilic palladation of **1** with $Pd(OAc)_2$ produces complex **5. 5** then undergoes *O*-allylation to produce **6**, which is transformed into **3** via transmetalation followed by reduction elimination. The Pd(0) is oxidized into Pd(II) by O_2 to complete the catalytic recycle. Similarly, the electrophilic palladation of **3** with $Pd(OAc)_2$ produces complex **8**. **8** is deprotonated to form **9** which is transformed into **2** via transmetalation followed by reductive elimination.

To explain the stereochemistry of **4**, we propose the pathway outlined in Scheme **5**. Coordination of the palladium atom to the double bond of **2** from the same face of the Ar group provides complex **11**. Nucleophilic attack of a hydroxyl ion from the face opposite the palladium atom gives intermediate **12**, which then undergoes protonation to yield semiacetal **13**. Compound **13** can be isomerized into **14** and **15**. The cyclization of **15** provides the thermodynamic stable product **4** exclusively.



Scheme 4. Proposed pathway for formation of **2** from **1**



Scheme 5. Proposed pathway for formation of **4** from **2**

In summary, we have developed a protocol for palladium-catalyzed alkoxydiarylation of furan rings via aerobic oxidative coupling of boronic acids with

5-aryl-2-hydroxyalkylfurans, which can be sustainably sourced. This protocol constitutes a green, diastereoselective route to 2,3,3a,6a-tetrahydrofuro[3,2-*b*]furans and hexahydrofuro[3,2-*b*]furans), polysubstituted oxabicyclic compounds that may be biologically interesting and synthetically useful. This study can be expected to serve as a foundation for the design of new difunctionalization reactions of diene-like five-membered aromatic rings.

Experimental Section

General procedure for synthesis of 2 (2a)

To a stirred solution of **1a** (0.4 mmol) in 1:1 (v/v) DCE/H_2O (4 mL) in a Schlenk flask under a balloon of O_2 were added $Pd(OAc)_2$ (9.0 mg, 0.04 mmol, 10 mol %), 1,10-phenanthroline (8.6 mg, 0.048 mmol, 12 mol %), and $ArB(OH)_2$ (1.0 mmol, 250 mol %) (added in three equal portions at 4-h intervals). The reaction mixture was heated at 70 °C until TLC indicated the disappearance of the starting material. Then H_2O (5 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (with 30:1 petroleum ether/ethyl acetate as the eluent) to give **2a**.

2a: yellow solid (96.6 mg, 71%, mp 157.0 °C); IR (film): 3165, 3062, 2928, 2871, 1647, 1601, 1503, 1444, 1355, 1319, 1246, 1189, 1088, 1043, 790, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 4H), 7.33–7.20 (m, 8H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.09–7.03 (m, 1H), 5.33 (s, 1H), 4.16 (t, *J* = 7.9 Hz, 1H), 3.95–3.87 (m, 1H), 2.54–2.47 (m, 1H), 2.46–2.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 142.1, 134.6, 130.9, 129.5, 128.6, 128.4, 128.1, 127.7, 126.5, 124.8, 109.1, 96.6, 94.1, 66.5, 43.8; HRMS (ESI) *m*/*z* calculated for $C_{24}H_{21}O_2$ $[M+H]^+$: 341.1536, found: 341.1534.

General procedure for the synthesis of 4 (4a)

To a stirred solution of **1a** (0.4 mmol) in 1:1 DCE/H_2O (4 mL) in a Schlenk flask under a balloon of O_2 atmosphere were added $Pd(OAc)_2$ (9.0 mg, 0.04 mmol, 10 mol %), 1,10-phenanthroline (8.6 mg, 0.048 mmol, 12 mol %), and $ArB(OH)_2$ (1.0 mmol, added in three equal portions at 4-h intervals). The reaction mixture was heated at 70 °C until TLC indicated the disappearance of the starting material (~21 h). Then Na_2CO_3 (84.8 mg, 0.8 mmol) was added to the reaction mixture at 70 °C, and the reaction was continued for an additional 8 h. H_2O (5 mL) was then added, and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (with 30:1 petroleum ether/ethyl acetate as the eluent) to give **4a**.

4a: white solid (111.6 mg, 78%, mp 141.0 °C); IR (film): 3618, 3078, 2986, 2925, 2858, 1649, 1595, 1509, 1426, 1384, 1328, 1260, 1212, 1128, 1067, 856, 799, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.46–7.40 (m, 4H), 7.38–7.34 (m, 3H), 7.30 (m, 1H), 7.26–7.23 (m, 3H), 7.13 (m, 2H), 5.45 (d, *J* = 6.4 Hz, 1H), 4.31–4.21 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 1H), 2.71–2.64 (m, 1H), 2.35 (d, *J* = 1.6 Hz, 1H), 2.27–2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 142.2, 135.7, 129.8, 128.5, 128.3, 128.2, 127.9, 127.1, 126.8, 125.6, 124.6, 106.9, 96.0, 92.9, 67.4, 62.5, 45.9; HRMS (ESI) *m*/*z* calculated for $C_{24}H_{22}NaO_3$ $[M+Na]^+$: 381.1461, found: 381.1466.

Acknowledgements

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[14] CCDC-1517891 contains the supplementary crystallographic data for **4a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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COMMUNICATION

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