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Synthesis of 2-Arylphenol Derivatives through a One-Pot Suzuki–Miyaura Coupling/Dehydrogenative Aromatization Sequence with Pd/C Catalysis

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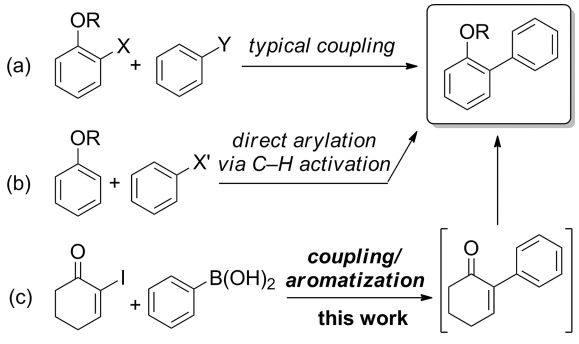
One-pot synthesis of 2-arylphenols starting from 2-iodo-2-cyclohexen-1-one and arylboronic acids through sequential Suzuki–Miyaura coupling/dehydrogenative aromatization with Pd/C catalysis has been developed. A range of arylboronic acids serve as substrates, including those containing electron-donating or electron-withdrawing groups. Additionally, one-pot synthesis of di- or trisubstituted phenols bearing a phenyl group at the *ortho* position are also generated by using 2-iodo-2-cyclohexen-1-one derivatives as substrate. In the present method, commercially available and easily removable Pd/C was employed as a catalyst without any ligands. The operationally simple procedure and accessible conditions were used to provide modified phenols as the sole product in moderate to high yields.

Introduction

Phenol derivatives are important core structures that are found in natural products, pharmaceuticals, and polymers, and are useful precursors in synthetic chemistry.[1] In particular, 2-arylphenols exist as bioactive compounds,[2] ligands for homogeneous catalysts,[3,4] and substrates for the synthesis of dibenzofurans,[5] which are the structural motifs of optoelectronically and biologically active compounds. The most commonly used approach to access 2-arylphenols is coupling reactions starting from the 2-halophenol or its derivatives as substrate (Scheme 1, a). However, 2-halophenols are difficult to prepare because the typical electrophilic halogenations of phenols produce a mixture of *ortho*- and/or *para*-halogenated phenols, promoted by the strong resonance effect of the hydroxyl group. Although direct *ortho*-metalation of O-modified phenol such as *O*-phenylcarbamates with alkyllithium followed by halogenation can provide 2-halophenol derivatives, multiple steps are required and the reaction is restricted to substrates that are tolerant of the alkyllithium reagent. Direct *ortho*-arylation of phenols through transition-metal-catalyzed C–H activation is a more straightforward approach (Scheme 1, b). However, *ortho*-selective arylation of naked phenols is limited to a few examples.[6] The *ortho*-arylation of phenols in the presence of phosphinite or phosphoramidite has also been demonstrated,[7] wherein the introduction of a directing group into the substrate in situ is required to promote the *ortho*-metalation. Additionally, direct *ortho*-arylation using isolated O-modified phenols as substrates, such as phenylpivalates or *O*-phenylcarbamates, has been reported.[8] In these cases, functional groups on the oxygen serve as protecting and directing groups. Major drawbacks of these direct *ortho*-C–H activation/arylation reactions are: (1) multiple arylation could occur to give the corresponding mono- and/or di-arylated phenols, and (2) expensive catalysts are required in some cases.



Scheme 1. Access to 2-arylphenol derivatives; R = H or protecting group, X = halogen, Y = $B(OR)_2$, SnR_3, etc. X′ = H or halogen.

As an alternative approach to the synthesis of phenol derivatives, the transition-metal-catalyzed oxidative aromatization of 2-cyclohexenone is an attractive strategy.[9–11] By taking this route, various phenols could be obtained, including not only *ortho*- and *para*- but also *meta*-substituted phenols without concerns about selectivity. We have reported a copper-catalyzed oxidative aromatization of 2-cyclohexenones to prepare various phenols, combined with aqueous hydrogen bromide and molecular oxygen under simple conditions.[9d] In the course of our study, we found

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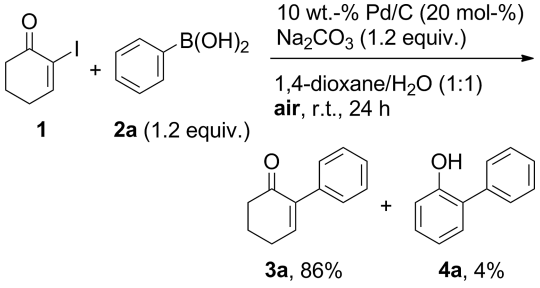
that the Suzuki–Miyaura coupling reaction of 2-iodocyclohexenone (**1**) and phenylboronic acid (**2a**) in the presence of Pd/C catalyst under air, afforded 2-phenylcyclohexenone (**3a**) with a small amount of 2-phenylphenol (**4a**),[12] which is considered to be generated by oxidation of the coupling product; see Equation (1). Palladium-catalyzed aerobic dehydrogenative aromatization has been studied and developed by the Stahl group.[9b,9c,9e,13] We hypothesized that a Suzuki–Miyaura coupling reaction followed by sequential dehydrogenative aromatization under optimal conditions could provide a one-pot synthesis of 2-arylphenols **4** from 2-iodocyclohexenone (**1**) and arylboronic acid **2** (Scheme 1, c).[14] Pd/C is an attractive palladium source because of its availability and because of the ease with which it can be removed from the reaction media. Moreover, 2-iodocyclohexenone (**1**) and its derivatives can be prepared in a single step from cyclohexenone derivatives[15] and boronic acids are stable, nontoxic, and commercially available reagents. With the present method, 2-arylphenols **4** could be easily obtained without problems of regioselectivity and multiple arylation reactions. In this report, a one-pot Suzuki–Miyaura coupling/dehydrogenative aromatization sequence producing 2-arylphenols **4** in the presence of Pd/C catalyst under simple conditions is described.

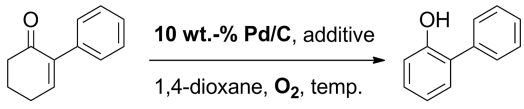


(1)

Results and Discussion

We commenced our study by optimizing the reaction conditions for the dehydrogenative aromatization of 2-phenylcyclohexenone (**3a**) in the presence of Pd/C catalyst under molecular oxygen (Table 1). Initially, the reaction of 2-phenylcyclohexenone (**3a**) was examined in the presence of 10 mol-% Pd/C (10 wt.-%) in 1,4-dioxane at 100 °C for 20 h under molecular oxygen to give the corresponding phenol **4a**, but only a trace amount of product was detected (entry 1). The addition of Na_2CO_3 as a base proved to be ineffective (entry 2). On the other hand, the yield was improved slightly when a catalytic amount of *p*TsOH was added (entry 3). Although the addition of a suitable ligand could be effective,[9c] we chose to screen acids without any ligands to simplify the reaction conditions. The use of catalytic $CuBr_2$ as a Lewis acid was ineffective (entry 4). Although the use of stoichiometric amounts of AcOH or CF_3COOH was not helpful (entries 5 and 6), the addition of aqueous 48% HBr or 37% HCl produced 2-phenylphenol (**4a**) in 90 and 94%, respectively (entries 7 and 8). When the reaction was conducted at room temperature or with catalytic acid, the yields were reduced (entries 9–12).

Table 1. Optimization of reaction conditions for dehydrogenative aromatization with catalytic Pd/C.[a]

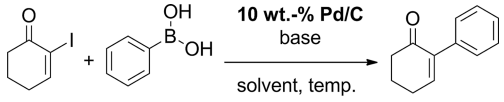


Entry	Additive [mol-%]	Temp. [°C]	Yield [%][b]
1	–	100	2
2	Na_2CO_3 (200)	100	2
3	*p*TsOH (10)	100	27
4	$CuBr_2$ (10)	100	2
5	AcOH (100)	100	3
6	CF_3COOH (100)	100	10
7	48% HBr aq. (100)	100	90
8	36% HCl aq. (100)	100	94
9	48% HBr aq. (100)	30	12
10	36% HCl aq. (100)	30	13
11	48% HBr aq. (10)	100	4
12	36% HCl aq. (10)	100	3

[a] Reaction conditions: 2-phenylcyclohexen-1-one (0.25 mmol), 10 wt.-% Pd/C (10 mol-%), additive, 1,4-dioxane (1.0 mL), 20 h, O_2. [b] GC yield by using dodecane as internal standard.

Following the results mentioned above, we then carried out a re-examination of the reaction conditions of Suzuki–Miyaura coupling using the Pd/C catalyst (Table 2). The reaction of 2-iodocyclohexenone (**1**) and phenylboronic acid (**2a**) in the presence of 10 mol-% Pd/C (10 wt.-%) and Na_2CO_3 in anhydrous 1,4-dioxane at room temperature for 18 h gave only a trace amount of the corresponding cou-

Table 2. Re-examination of Suzuki–Miyaura coupling under various conditions.[a]

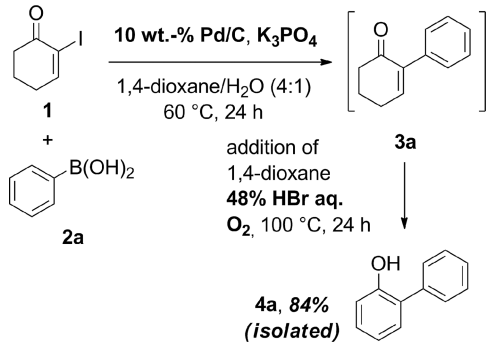


Entry	Base	Solvent	Temp. [°C]	Yield [%][b]
1	Na_2CO_3	1,4-dioxane	30	trace
2	Na_2CO_3	1,4-dioxane	60	10
3	K_2CO_3	1,4-dioxane	60	31
4	$Na_3PO_4{\cdot}12H_2O$	1,4-dioxane	60	33
5	K_3PO_4	1,4-dioxane	60	47
6	K_3PO_4	1,4-dioxane/H_2O (9:1)	60	72
7	K_3PO_4	1,4-dioxane/H_2O (4:1)	60	85
8	K_3PO_4	1,4-dioxane/H_2O (4:1)	30	64
9	K_3PO_4	1,4-dioxane/H_2O (4:1)	40	74
10	K_3PO_4	1,4-dioxane/H_2O (4:1)	80	64
11	K_3PO_4	1,4-dioxane/H_2O (4:1)	100	59

[a] Reaction conditions: 2-iodocyclohexen-1-one (0.25 mmol), phenylboronic acid (1.2 equiv.), 10 wt.-% Pd/C (10 mol-%), base (2.0 equiv.), solvent (1.0 mL), 18 h, argon. [b] GC yield by using dodecane as internal standard.

pling product **3a** (entry 1). After screening of the base and reaction temperature, we found that the desired product was obtained in moderate yield when the reaction was conducted at 60 °C with K_3PO_4 as base (entry 5). Additionally, performing the reaction in a mixed solvent of 1,4-dioxane/H_2O (9:1) gave the desired product in 72% yield (entry 6); when a 4:1 ratio was used, the product yield was improved to 85% (entry 7). The reactivity was reduced when the reaction was carried out at either lower or higher temperature (entries 8–11).

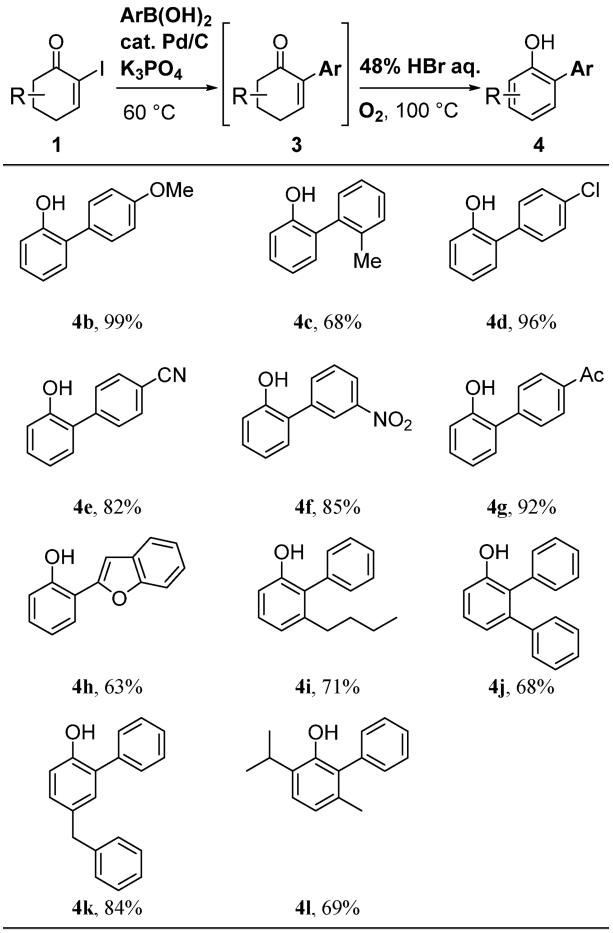
Finally, the one-pot Suzuki–Miyaura coupling/dehydrogenative aromatization sequence was tested (Scheme 2). Thus, a mixture of 2-iodocyclohexenone (**1**) and 1.2 equiv. phenyl boronic acid (**2a**) with 10 mol-% Pd/C (10 wt.-%) and K_3PO_4 in 1,4-dioxane/H_2O (4:1) was stirred at 60 °C for 24 h, and then aqueous 48% HBr and 1,4-dioxane were added[16] together with a flow of molecular oxygen, followed by stirring at 100 °C for 24 h. After purification, the desired 2-phenylphenol (**4a**) was isolated in 84% yield. In this reaction, only 0.9% palladium (24.8 μg) leached into the reaction mixture, based on atomic absorption analysis.



Scheme 2. One-pot synthesis of 2-phenylphenol through Suzuki–Miyaura coupling/dehydrogenative aromatization. Reaction conditions: i. 2-iodocyclohexen-1-one (0.25 mmol), phenylboronic acid (1.2 equiv.), 10 wt.-% Pd/C (10 mol-%), K_3PO_4 (2.0 equiv.), 1,4-dioxane/H_2O (4:1, 1.0 mL), 60 °C, 24 h, argon; ii. 1,4-dioxane (1.0 mL), 48% HBr aq. (8.0 equiv.), 100 °C, 24 h, O_2.

The present one-pot system could be applied to the synthesis of various 2-arylphenols (Table 3). When (4-methoxyphenyl)boronic acid was employed as substrate, the desired product **4b** was obtained in 99% yield. The use of (2-methylphenyl)boronic acid resulted in a moderate yield due to steric hindrance. The reaction starting from (4-chlorophenyl)boronic acid also produced the corresponding phenol **4d** in high yield. The present reaction system worked well even in the presence of a cyano (**4e**), a nitro (**4f**), and an acetyl group (**4g**), for which further transformations could be performed for the preparation of functionalized phenols. Furthermore, phenol derivative **4h**, bearing a benzofuran group, which is an important heteroaryl framework that is contained in a wide range of biologically active compounds, was afforded from the corresponding boronic acid, albeit in moderate yield. We then focused on the synthesis of di- or trisubstituted phenol derivatives with the

Table 3. Synthesis of 2-arylphenol derivatives through one-pot Suzuki/Miyaura coupling/dehydrogenative aromatization.[a]



[a] Reaction conditions: i. 2-iodocyclohexen-1-one derivative (0.25 mmol), phenylboronic acid (2.0 equiv.), 10 wt.-% Pd/C (10 mol-%), K_3PO_4 (2.0 equiv.), 1,4-dioxane/H_2O (4:1, 1.0 mL), 60 °C, 24 h, argon; ii. 1,4-dioxane (1.0 mL), 48% HBr aq. (8.0 equiv.), 100 °C, 24 h, O_2. Isolated yields.

aryl substituent at the *ortho*-positions. 2-Iodocyclohexen-1-one derivatives were prepared from the corresponding 2-cyclohexen-1-ones by following reported procedures.[15] 2-Phenyl-3-*n*-butylphenol (**4i**) was obtained in 71% yield by using the corresponding iodide (**1i**) under the standard conditions. The reaction with 3-phenyl-2-iodo-2-cyclohexen-1-one (**1j**) produced terphenyl derivative 2,3-diphenylphenol (**4j**) in 68% yield. In these cases, substitution at the 3-position of 2-iodo-2-cyclohexen-1-one is considered to decrease the yield of the first coupling step due to steric hindrance. On the other hand, 2-iodocyclohexen-1-one **1k**, bearing a benzyl group at the 4-position, produced the corresponding phenol **4k** in 84% yield, wherein bromination or oxidation at the benzyl position did not occur even under oxidative conditions. The present reaction system could be adapted to the synthesis of trisubstituted phenol. 2-Phenyl-3-methyl-6-isopropylphenol (**4l**) was isolated in 69% yield from the reaction of the corresponding iodide **1l** and phenylboronic acid under similar conditions.

Conclusions

We have demonstrated a one-pot Suzuki–Miyaura coupling/dehydrogenative aromatization sequence to give 2-arylphenols from 2-iodocyclohexenone and arylboronic acids under Pd/C catalysis. Additionally, 2-phenylphenol derivatives bearing substitution groups at the *meta* or *para* positions could be produced by using the corresponding iodide. In this method, the generation of the regioisomers or multiple arylation products that could occur in direct C–H arylation of phenols were avoided. Moreover, the present reaction system did not require any ligands and proceeded under operationally simple and accessible conditions.

Experimental Section

General Information: All commercially available compounds were purchased and used as received. Solvents 1,4-dioxane, THF, and Et_2O were purchased from Wako Pure Chemical Industries and used as received. Palladium on carbon (10 wt.-%) was purchased from Sigma–Aldrich (product number: 205699). 2-Iodo-2-cyclohexen-1-one derivatives were synthesized by reported methods. Thin-layer chromatography was performed using Merck TLC silica gel 60 F254 Aluminum sheets and visualized by UV irradiation and phosphomolybdic acid staining. Flash chromatography separations were performed on Kanto Chemical Silica Gel 60 (spherical, 40–50 mesh). Gas chromatographic analysis was conducted with a Shimadzu GC-2014 instrument equipped with an FID detector and the chemical yields were determined by using dodecane as an internal standard. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with a JEOL JNM-LA400 spectrometer. Proton chemical shifts are reported relative to residual solvent peak $CDCl_3$ at δ = 7.26 ppm. Carbon chemical shifts are reported relative to $CDCl_3$ at δ = 77.00 ppm. NMR spectra are reported as: chemical shift (multiplicity, coupling constants, relative integral). High-resolution mass spectra (HRMS) was measured with a JEOL JMS-700 MStation FAB-MS.

General Procedure for the One-Pot Synthesis of 2-Arylphenols: A screw-capped test tube was charged with 2-iodocyclohexenone (0.25 mmol), phenylboronic acid (2.0 equiv.), 10 wt.-% Pd/C (10 mol-%), K_3PO_4 (2.0 equiv.), and 1,4-dioxane/H_2O (4:1, 1 mL). The tube was filled with nitrogen and sealed with a screw-cap and the reaction mixture was stirred at 60 °C for 24 h. After the addition of 1,4-dioxane (1 mL) and 48% HBr aq. (8.0 equiv.), the tube was filled with molecular oxygen and again sealed with a screw-cap. The reaction mixture was stirred at 100 °C for 24 h, then the insoluble materials were removed through a Celite plug and washed with EtOAc and the mixture was transferred to separating funnel with satd. aq $Na_2S_2O_3$. The organic layer was separated and extracted with EtOAc three times, and then washed with brine, dried with Na_2SO_4, filtered, and the solvents were evaporated. The desired product was purified by column chromatography (SiO_2; EtOAc/hexane).

Biphenyl-2-ol (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 4 H), 7.44–7.40 (m, 1 H), 7.31–7.27 (m, 2 H), 7.05–7.01 (m, 2 H), 5.28 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.37, 137.04, 130.21, 129.22, 129.11, 129.06, 128.09, 127.82, 120.81, 115.79 ppm.

4′-Methoxybiphenyl-2-ol (4b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.3 Hz, 2 H), 7.24–7.20 (m, 2 H), 7.02 (d, J = 8.3 Hz, 2 H), 6.99–6.96 (m, 2 H), 5.15 (s, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.22, 152.48, 130.22, 129.17, 128.73, 127.79, 120.72, 116.67, 115.63, 114.62, 55.30 ppm.

2′-Methylbiphenyl-2-ol (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 2 H), 7.32–7.21 (m, 3 H), 7.12 (dd, J = 1.6, 7.7 Hz, 1 H), 7.01–6.96 (m, 2 H), 4.74 (s, 1 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.46, 137.39, 135.67, 130.64, 130.45, 130.11, 129.09, 128.49, 127.67, 126.42, 120.42, 115.26, 19.72 ppm.

4′-Chlorobiphenyl-2-ol (4d): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.29–7.22 (m, 2 H), 7.00 (dt, J = 1.2, 3.5 Hz, 1 H), 6.96 (dd, J = 1.1, 8.1 Hz, 1 H), 5.09 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.27, 135.61, 133.79, 130.47, 130.24, 129.37, 129.23, 127.01, 121.05, 116.01 ppm.

4′-Cyanobiphenyl-2-ol (4e): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.5 Hz, 2 H), 7.66 (d, J = 8.5 Hz, 2 H), 7.32–7.26 (m, 2 H), 7.04 (dt, J = 0.9, 7.7 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 5.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.35, 142.59, 132.41, 130.43, 130.07, 129.94, 126.50, 121.39, 118.82, 116.39, 110.95 ppm.

3′-Nitrobiphenyl-2-ol (4f): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (t, J = 1.9 Hz, 1 H), 8.22 (ddd, J = 1.1, 2.3, 8.3 Hz, 1 H), 7.89 (ddd, J = 1.2, 1.6, 7.7 Hz, 1 H), 7.63 (t, J = 8.0 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.06 (dt, J = 1.2, 7.2 Hz, 1 H), 6.95 (dd, J = 1.1, 8.1 Hz, 1 H), 4.96 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.31, 139.39, 135.32, 130.58, 129.98, 129.43, 125.98, 124.25, 122.16, 121.48, 116.36 ppm. HRMS (EI): m/z calcd. for $C_{12}H_9O_3N$ $[M]^+$ 215.0582; found 215.0578.

4′-Acethylbiphenyl-2-ol (4g): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.3 Hz, 2 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.31–7.27 (m, 2 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 5.45 (s, 1 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.92, 152.51, 142.55, 135.98, 130.31, 129.75, 129.35, 128.94, 127.12, 121.10, 116.25, 26.64 ppm.

2-(Benzofuran-2-yl)phenol (4h): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, J = 1.6, 8.0 Hz, 1 H), 7.62 (dd, J = 1.6, 6.7 Hz, 1 H), 7.55 (dd, J = 1.6, 7.2 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.18 (s, 1 H), 7.11 (d, J = 0.9 Hz, 1 H), 7.04–7.00 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.27, 153.95, 153.29, 130.26, 128.48, 127.14, 124.43, 123.41, 120.98, 120.76, 117.37, 116.05, 110.98, 103.31 ppm.

6-*n*-Butylbiphenyl-2-ol (4i): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.46 (m, 2 H), 7.46–7.40 (m, 1 H), 7.33–7.27 (m, 2 H), 7.24–7.16 (m, 1 H), 6.91–6.81 (m, 2 H), 4.67 (s, 1 H), 2.40–2.32 (m, 2 H), 1.44–1.34 (m, 2 H), 1.22–1.12 (m, 2 H), 0.76 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.73, 142.03, 135.01, 130.49, 129.21, 128.54, 128.09, 127.78, 120.99, 112.43, 33.25, 32.94, 22.38, 13.73 ppm. HRMS (EI): m/z calcd. for $C_{16}H_{18}O$ $[M]^+$ 226.1358; found 226.1354.

2,3-Diphenylphenol (4j): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 4 H), 7.20–7.12 (m, 5 H), 7.11–7.01 (m, 4 H), 5.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.87, 142.20, 141.00, 134.96, 130.90, 129.59, 128.97, 128.76, 127.67, 127.57, 126.69, 126.36, 122.32, 114.42 ppm. HRMS (EI): m/z calcd. for $C_{18}H_{14}O$ $[M]^+$ 246.1045; found 246.1043.

5-Benzylbiphenyl-2-ol (4k): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.40 (m, 4 H), 7.39–7.33 (m, 1 H), 7.30–7.23 (m, 2 H), 7.22–7.16 (m, 3 H), 7.09–7.03 (m, 2 H), 6.92–6.86 (m, 1 H), 5.12 (s, 1 H), 3.93 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.70, 141.37, 137.13, 133.45, 130.57, 129.50, 129.17, 129.04, 128.79, 128.43, 127.99, 127.76, 126.00, 115.83, 41.08 ppm. HRMS (EI): m/z calcd. for $C_{19}H_{16}O$ $[M]^+$ 260.1201; found 260.1201.

3-Isopropyl-6-methylbiphenyl-2-ol (4l): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.48 (m, 2 H), 7.47–7.40 (m, 1 H), 7.35–7.28 (m, 2 H), 7.13 (d, J = 7.7 Hz, 1 H), 6.84 (d, J = 7.7 Hz, 1 H), 4.77 (s, 1 H), 3.28 (sep, J = 6.8 Hz, 1 H), 2.03 (s, 3 H), 1.27 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.86, 135.67, 134.11, 131.95, 130.39, 129.47, 128.12, 127.70, 125.22, 121.49, 27.08, 22.64, 20.13 ppm. HRMS (EI): *m*/*z* calcd. for $C_{16}H_{18}O$ $[M]^+$ 226.1358; found 226.1359.

Acknowledgments

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[1] For example, see: J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, **1996**.

[2] For example, see: a) M.-E. Million, J. Boiziau, F. Parker, B. Tocque, B. P. Roques, C. Garbay, *J. Med. Chem.* **1995**, *38*, 4693–4703; b) T.-S. Jeong, K. S. Kim, J.-R. Kim, K.-H. Cho, S. Lee, W. S. Lee, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2719–2723; c) T.-S. Jeong, K. S. Kim, S.-J. An, K.-H. Cho, S. Lee, W. S. Lee, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2715–2717; d) X. He, A. Alian, R. Stroud, P. R. Ortiz de Montellano, *J. Med. Chem.* **2006**, *49*, 6308–6323.

[3] For example, see: a) S. Ishikawa, K. Manabe, *Chem. Lett.* **2007**, *36*, 1302–1303; b) S. Ishikawa, K. Manabe, *Chem. Lett.* **2007**, *36*, 1304–1305.

[4] For reviews on BINOL, see: a) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3212; b) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–898.

[5] a) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253; b) Y. Wei, N. Yoshikai, *Org. Lett.* **2011**, *13*, 5504–5507; c) J. Zhao, Y. Wang, Y. He, L. Liu, Q. Zhu, *Org. Lett.* **2012**, *14*, 1078–1081; d) J. Zhao, Q. Zhang, L. Liu, Y. He, J. Li, J. Li, Q. Zhu, *Org. Lett.* **2012**, *14*, 5362–5365.

[6] a) D. D. Hennings, S. Iwasa, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 2–3; b) Y. Kawamura, T. Satoh, M. Miura, M. Nomura, *Chem. Lett.* **1997**, 961–962.

[7] a) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114; *Angew. Chem.* **2003**, *115*, 116; b) S. Oi, S. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665–8668; c) R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. Lewis-Alleyne, P. D. Long, D. Polo-Cerón, S. Prashar, *Chem. Commun.* **2008**, 990–992; d) R. B. Bedford, M. F. Haddow, R. L. Webster, C. J. Mitchell, *Org. Biomol. Chem.* **2009**, *7*, 3119–3127.

[8] a) R. B. Bedford, R. L. Webster, C. J. Mitchell, *Org. Biomol. Chem.* **2009**, *7*, 4853–4857; b) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 468–469; c) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837–5844.

[9] a) T. Moriuchi, K. Kikushima, T. Kajikawa, T. Hirao, *Tetrahedron Lett.* **2009**, *50*, 7385–7387; b) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209–213; c) Y. Izawa, C. Zheng, S. S. Stahl, *Angew. Chem. Int. Ed.* **2013**, *52*, 3672–3675; *Angew. Chem.* **2013**, *125*, 3760; d) K. Kikushima, Y. Nishina, *RSC Adv.* **2013**, *3*, 20150–20156; e) D. Pun, T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8213–8221; f) For review, see; M. T. Kesler, M. H. G. Prechtl, *ChemCatChem* **2012**, *4*, 326–327.

[10] a) M.-O. Simon, S. A. Girard, C.-J. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 7537–7540; *Angew. Chem.* **2012**, *124*, 7655; b) A. Hajra, Y. Wei, N. Yoshikai, *Org. Lett.* **2012**, *14*, 5488–5491; c) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng, C.-J. Li, *Org. Lett.* **2012**, *14*, 5606–5609; d) W. P. Hong, A. V. Iosub, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 13664–13667.

[11] Dehydrogenative aromatization of cyclohexenones to phenol by using recyclable catalyst was also reported. See: K. Manna, T. Zhang, W. Lin, *J. Am. Chem. Soc.* **2014**, *136*, 6566–6569.

[12] When the reaction was carried out under molecular oxygen, the corresponding coupling product was reported to be the sole product, see: F.-X. Felpin, *J. Org. Chem.* **2005**, *70*, 8575–8578.

[13] a) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569; b) T. Diao, D. Pun, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8205–8212.

[14] Synthesis of *meta*-substituted phenols through oxidative Heck/dehydrogenation reaction was reported by Stahl group, see ref.[9c]

[15] a) M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263–1266; b) R. Benhida, P. Blanchard, J.-L. Fourrey, *Tetrahedron Lett.* **1998**, *39*, 6849–6852.

[16] Excess amounts of 48% HBr aq. was added to acidify the basic reaction mixture, and 1,4-dioxane was added to reduce the ratio of H_2O in the mixed solvent.

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