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Carboxylic acid as a traceless directing group for palladium-catalyzed proaromatic C(alkenyl)–H arylation

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Dedicated to Prof. Tien-Yau Luh on the occasion of his 76th anniversary

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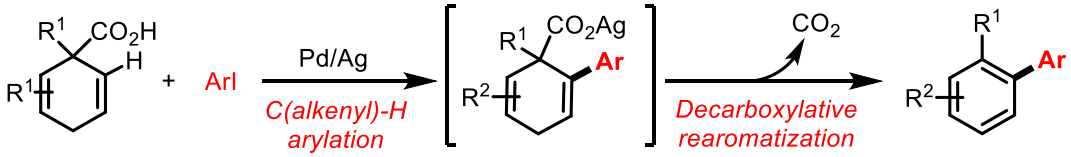
Abstract

A Pd-catalyzed tandem decarboxylative C–H arylation/rearomatization of proaromatic acids with aryl iodides is reported. This method using carboxylic acid as a traceless directing group for proaromatic C(alkenyl)–H arylation followed by a decarboxylative rearomatization in the presence of Pd/Ag bimetallic system, allowing preparation of 2-alkylated biaryls. Additionally, experimental results suggest that the carboxylic acid functional group is crucial for the reaction outcome.

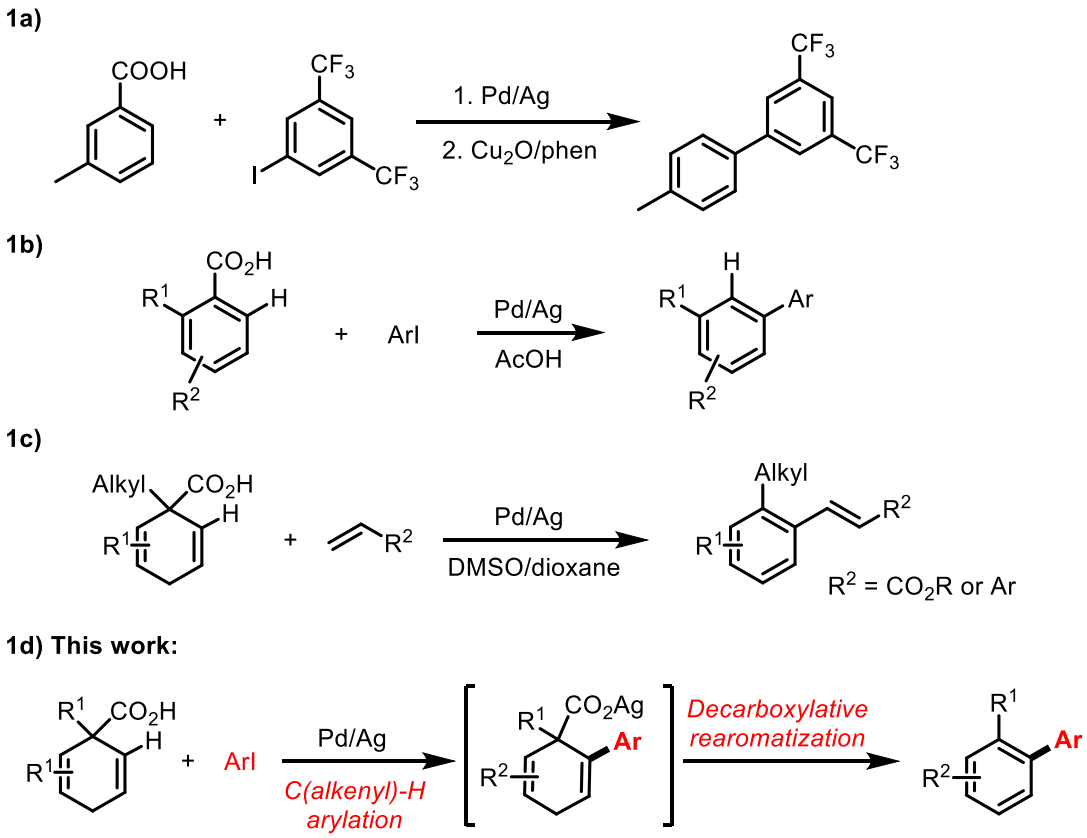


Keywords: Carboxylic acid, traceless directing group, C(alkenyl)–H arylation, palladium-catalyzed

Introduction

Carbon–hydrogen bond is the most abundant and chemically inert covalent bond which is ubiquitous in all organic compounds. Therefore, how to effectively and selectively activate a specific C–H bond for further functionalization to expand molecular complexity and diversity has attracted much attention in organic chemistry.[1-3] Over the past decades, direct C–H activation has become one of the promising strategy for site-selective C−H functionalizations.[4-6] In general, site-selective C−H activation can be realized by conducting with an exogenous directing group which can guide the metal to the selected position allowing formation of an energetically favored metallocycle intermediate. Using directing group strategy, these reactions can deliver site-selective C−H functionalization products in a predictable fashion. Many directing groups have been used for direct C−H functionalization with remarkable results.[7] However, certain directing groups needed several steps in prefabrication and remove it after functionalization.

In contrast, employing free carboxylic acid as a directing group is a straightforward method to facilitate C–H functionalization in a step-economical manner.[8-12] In addition, carboxylic acid groups can also serve as traceless directing groups.[13] In 2007, Daugulis disclosed the first case of using carboxylic acid as a traceless directing group for C−H functionalizations.[14] Later on, Gooßen's group further demonstrated this traceless directing group strategy by two step reaction sequences of palladium-catalysed *ortho* C−H bond arylation of benzoic acids followed by copper-catalysed protodecarboxylation for preparation of biaryls (Scheme 1a).[15] A protocol for the one-pot C−H arylation/decarboxylation of benzoic acids was reported by Larrosa and co-workers in which *ortho*-substituted benzoic acids reacted with aryl iodides in the presence of a Pd/Ag bimetallic catalytic system in acetic acid solvent (Scheme 1b).[16] Previously, we have reported a carboxylate-directed Pd-catalyzed C(alkenyl)−H olefination of proaromatic acids with alkenes followed by tandem decarboxylative rearomatization, resulting in generation of *ortho*-alkylated vinylarenes (Scheme 1c).[9] We envisioned that the aformentioned approach could be extented to arylation. Herein, we report a method using carboxylic acid as a traceless directing group for proaromatic C(alkenyl)–H arylation with aryl iodides followed by a decarboxylative rearomatization in the presence of Pd/Ag bimetallic system, allowing the synthesis of 2-alkylated biaryls. (Scheme 1d).



Scheme 1. Palladium-catalyzed C−H functionalizations using carboxylic acids as traceless directing groups.

Results and Discussion

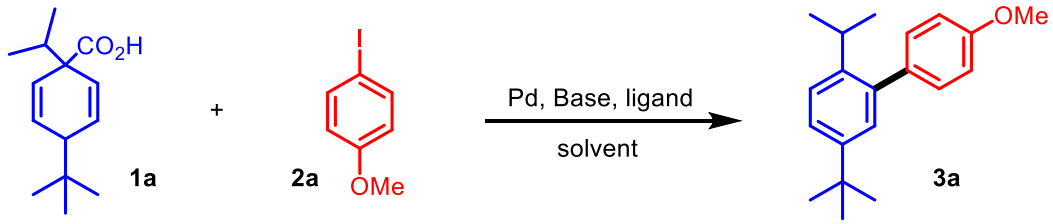
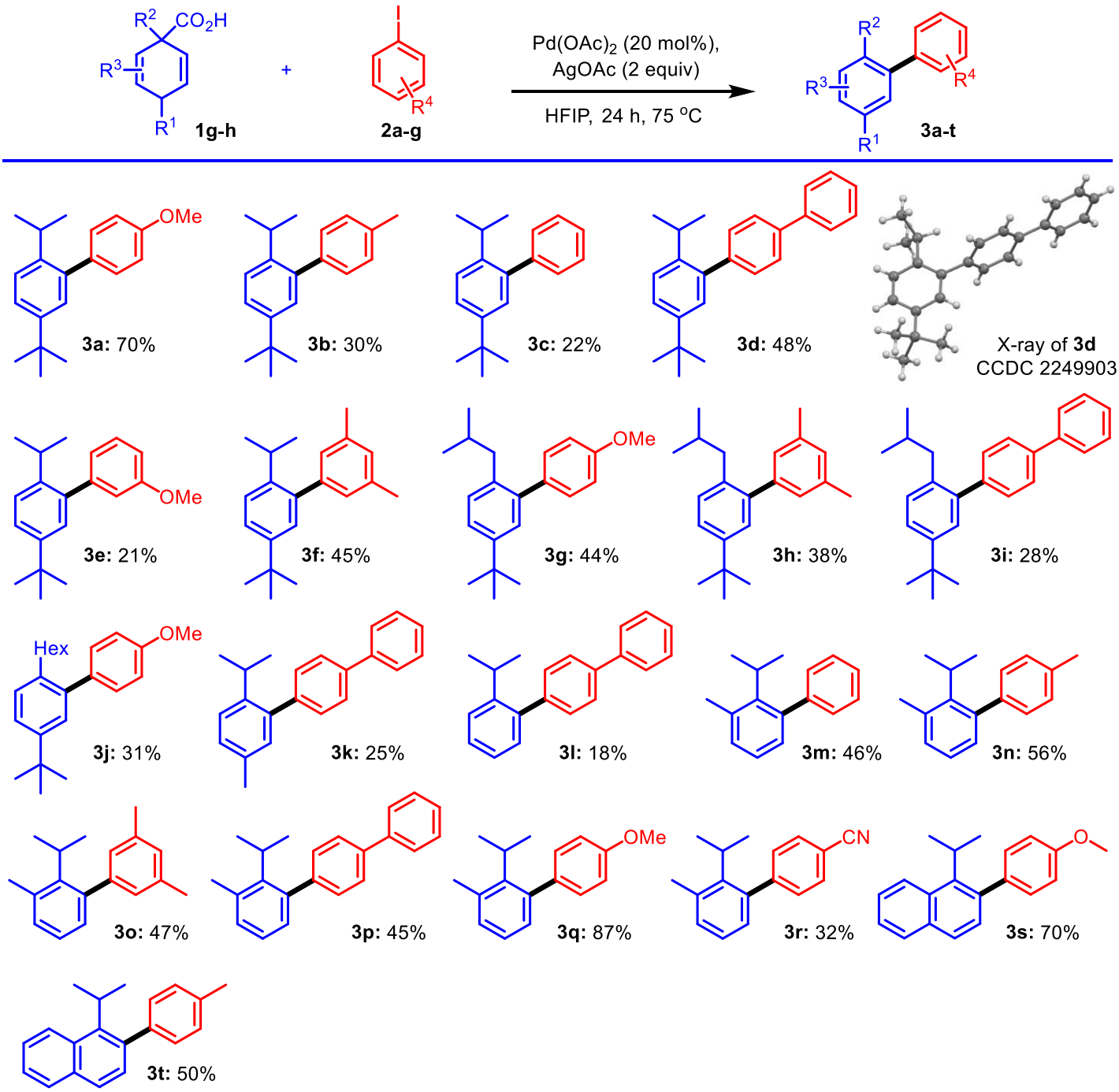


Table 1. Decarboxylative C−H arylation/Rearomatization **1a** with **2a**

Entry[a]	Ligand	Base	Pd cat.	Solvent	T [°C]	Yield of **3a**[b]
1	--	KOAc	$Pd(OAc)_2$	HFIP	75	0
2	--	K_2CO_3	$Pd(OAc)_2$	HFIP	75	0
3	--	*t*-BuOK	$Pd(OAc)_2$	HFIP	75	0
4	--	Cs_2CO_3	$Pd(OAc)_2$	HFIP	75	0
5	--	AgOAc	$Pd(OAc)_2$	HFIP	75	71
6	--	Ag_2CO_3	$Pd(OAc)_2$	HFIP	75	0[c]
7	--	AgTFA	$Pd(OAc)_2$	HFIP	75	8[c]
8	--	$AgNO_3$	$Pd(OAc)_2$	HFIP	75	0[c]
9	--	$AgClO_4$	$Pd(OAc)_2$	HFIP	75	0[c]
10	--	AgOAc	$Pd(OAc)_2$	DMSO	130	0[c]
11	--	AgOAc	$Pd(OAc)_2$	DMF	130	0[c]
12	--	AgOAc	$Pd(OAc)_2$	Dioxane	80	0[c]
13	--	AgOAc	$Pd(OAc)_2$	Toluene	110	0[c]
14		AgOAc	$Pd(dba)_2$	HFIP	75	10
15		AgOAc	$Pd(TFA)_2$	HFIP	75	9
16	XantPhos	AgOAc	$Pd(OAc)_2$	HFIP	75	>5[d]
17	Xphos	AgOAc	$Pd(OAc)_2$	HFIP	75	>5[e]
18	PPh_3	AgOAc	$Pd(OAc)_2$	HFIP	75	>5[f]

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.2 mmol), Pd cat.(20 mol %), base (0.4 mmol) solvent (1.0 mL) under an argon atmosphere for 24 h. [b]Yield of isolated product. [c]Decarboxylative aromatization of **3a** was the major product. [d]XantPhos (0.04 mmol). [e]XPhos (0.08 mmol). [f]PPh_3 (0.08 mmol)

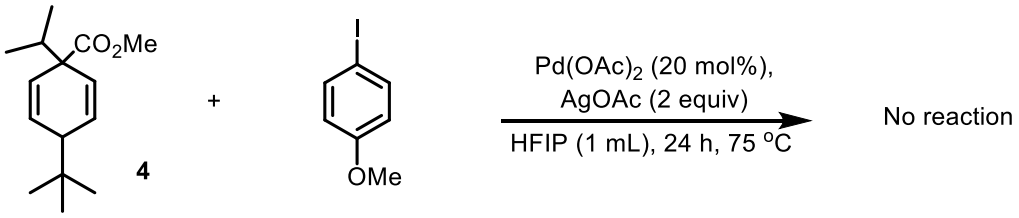
Initially, we began our investigation by treating 4-(*tert*-butyl)-1-isopropylcyclohexa-2,5-diene-1-carboxylic acid (**1a**) with 4-iodoanisole (**2a**) using 20 mol % $Pd(OAc)_2$ as a catalyst and screening the reaction with a variety of bases such as KOAc, K_2CO_3, and *t*-BuOK, Cs_2CO_3 in hexafluoroisopropanol (HFIP) at 75 °C for 24 h, but no reaction occurred (Table 1, entries 1-4). We then switched the base to AgOAc and glad to find that the tandem decarboxylative C−H arylation/rearomatization product can be isolated in 71% yield (entry 5). Other silver additive sources (entries 6-9) and solvent systems (entries 10-13) were also test but gave negative results. Further testing of Pd sources and the presence of exogenous phosphine ligands but ended up with unsatisfied results (entries 14-18). Therefore, ligand-free with 20 mol % $Pd(OAc)_2$ and 2.0 equiv AgOAc in HFIP at 75 °C for 24 h was found to be an optimum reaction condition for this tandem decarboxylative C−H arylation/ rearomatization.



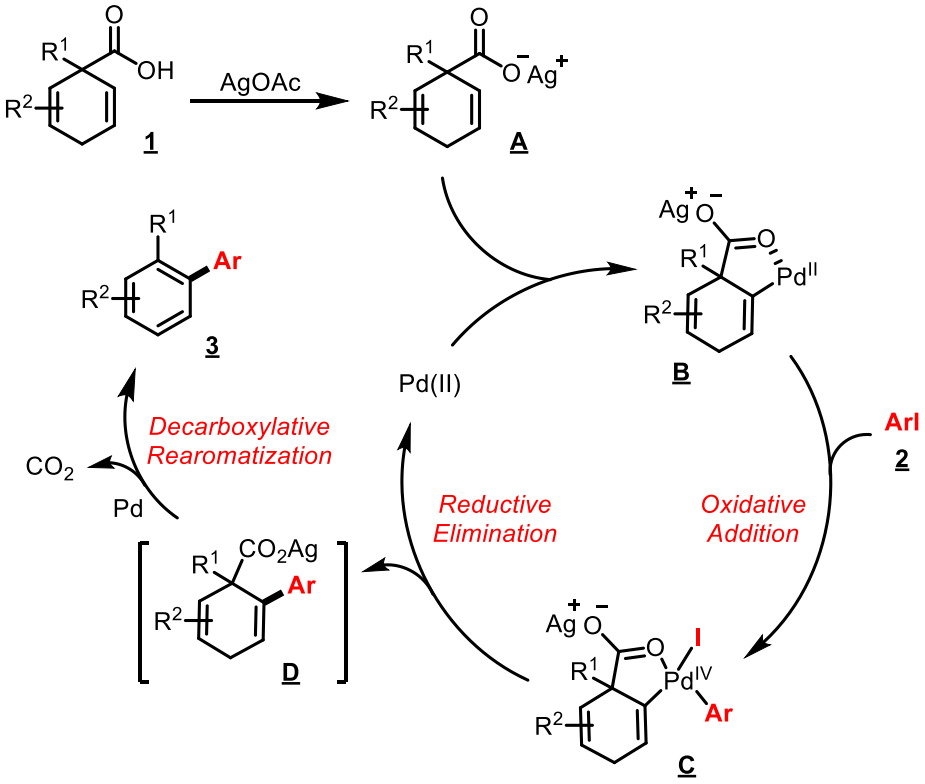
Scheme 2. Substrate scope of Pd-catalyzed tandem decarboxylative C–H arylation/rearomatization of proaromatic acids with aryl iodides.

With the optimized conditions in hand, we next investigated the scope of proaromatic acids **1** with various aryl iodides **2** (Scheme 2). 1-Isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid **1a** reacted well with 4-substituted phenyl iodides bearing methoxy, methyl, hydrogen, and biphenyl affording **3a**–**3d** in 22–70% yields. The relative structure of the **3d** was determined unambiguously by X-ray analysis as shown in Scheme 2. With 3-methoxy and 3,5-dimethyl phenyl iodides provided **3e** and **3f** in 21% and 45% yields, respectively. Sec-butyl, *n*-hexyl, and isopropyl substituents at the 1-position of the 4-*tert*-butyl or 4-methyl cyclohexa-2,5-dienyl carboxylic acids coupled with aryl iodides were compatible with this procedure, leading to the

corresponding 2-alkylated biaryls **3g**–**3k** in 28–44% yields. We previously found that the efficiency of the interior methylene proaromatic acid was limited in C(alkenyl)–H olefination due to the rapid decarboxylative aromatization. To our delight, 1-isopropyl or 2-methyl-1-isopropyl cyclohexa-2,5-dienyl carboxylic acids reacted well with aryl iodides to afford decarboxylative C–H arylation/rearomatization products **3l**–**3r** in 18–87% yields. In the case of substituted 1,4-dihydro-1-naohthoic acids also gave satisfying results (**3s** and **3t**). In order to gain insight into the reaction mechanism, we therefore performed a control experiment. The reaction of methyl ester (**4**) with 4-iodoanisole failed to produce the desired product, suggesting that carboxylic acid directing group is necessary for reaction outcome (Scheme 3).



Scheme 3. Control experiment.



Scheme 4. Proposed mechanism for the Pd-catalyzed proaromatic C(alkenyl)–H arylation using carboxylic acid as a traceless directing group.

On the basis of our experiment results, a plausible mechanism for this Pd-catalyzed proaromatic C(alkenyl)–H arylation using carboxylic acid as a traceless directing group was proposed and is illustrated in Scheme 4. First, proaromatic acid **1** is deprotonated with silver acetate to generate Ag–carboxylate species **A** followed by a C(alkenyl)–H bond activation with Pd(II), leading to formation of a five-membered palladacycle

B. Subsequently, palladacycle **B** undergoes oxidative addition with aryl iodide **2** affords a Pd(IV) species **C**, which is followed by a reductive elimination to give the arylated Ag−carboxylate **D** and regenerating the Pd(II)−species to complete the catalytic cycle. Meanwhile, arylated Ag−carboxylate **D** readily undergoes decarboxylative rearomatization in the presence of a Pd catalyst, therefore eventually delivering the desired 2-alkylated biaryls.

Conclusions

In conclusion, we have developed a Pd-catalyzed tandem decarboxylative C–H arylation/rearomatization of proaromatic acids with aryl iodides. This method using carboxylic acid as a traceless directing group for proaromatic C(alkenyl)–H arylation followed by a decarboxylative rearomatization in the presence of Pd/Ag bimetallic system, allowing the synthesis of 2-alkylated biaryls. The reaction mechanism most likely proceeds through a Pd(II)/Pd(IV) catalytic cycle. In addition, the control experiment suggests that the carboxylic acid functional group is essential for controlling the reaction outcome.

Experimental Section

General. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian-Mercury-300 (300 MHz) spectrometer. Chemical shifts for protons are reported in parts per million (ppm) downfield from TMS and are referenced to residual proton in the solvent ($CDCl_3$ δ = 7.26). Chemical shifts for carbon are reported in ppm and are referenced to the carbon signal ($CDCl_3$ δ = 77.0 ppm). NMR data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz (Hz). TLC was examined by using Merck silica gel 60 F-254 plates, and detection of compounds with UV light or dipping into a solution of $KMnO_4$ followed by heating. Flash column chromatography was performed by using Merck silica gel 60 (40-63 µm). Melting point were performed by using Fargo MP-2D. In relative rate experiments the ratio of the products were determined through NMR by using 1,3,5-trimethoxybenzene as internal standard. The single crystal X-ray diffraction data were obtained using a Bruker APEX DUO. The electron impact (EI) mass spectral data were obtained using a SHIMADZU QP2020 and JEOL AccuTOF GCx-plus. Proaromatic acids **1a**-**1h** were prepared in accord to the earlier reported method.[9, 10, 17]

General procedure for Pd(II)-catalyzed tandem decarboxylative C–H arylation/rearomatization. To a screw cap Schlenk tube, AgOAc (0.4 mmol), aryl iodide (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1,4-alkylated cyclohexa-2,5-dienyl carboxylic acid were added. The resulting mixture was stirred under Argon atmosphere at 75 °C for 24 h. The crude mixture was extracted with ethyl acetate (75 mL), and the organic phases were then dried over $MgSO_4$ for 10 min. The crude mixture was purified by flash column chromatography (SiO_2) to afford desired product of **3a**-**3t**.

5-(*tert*-Butyl)-2-isopropyl-4'-methoxy-1,1'-biphenyl (3a). After the reaction based on general procedure: AgOAc (0.4 mmol), 4-iodoanisole (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3a** in 70% (39 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.29 (m, 2H), 7.25 – 7.17 (m, 3H), 6.99 – 6.94 (m, 2H), 3.87 (s, 3H), 3.11 – 3.03 (m, 1H), 1.33 (s, 9H), 1.16 (d, *J* =

6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 147.8, 143.4, 140.1, 135.0, 130.4, 127.1, 125.0, 124.4, 113.3, 55.3, 31.4, 29.3, 28.9, 24.3. HRMS (EI) calculated for $C_{20}H_{26}O$ ([M]$^+$): 282.1984, Found: 282.1979.

5-(*tert*-Butyl)-2-isopropyl-4'-methyl-1,1'-biphenyl (3b). The reaction based on general procedure: AgOAc (0.4 mmol), 4-iodotoluene (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0. 04 mmol), HFIP (1 mL), and 1-isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using hexane, and obtained **3b** in 30% (16 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 3H), 7.22 (m, 3H), 7.17 (d, *J* = 2.1 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.42 (s, 3H), 1.32 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 143.3, 140.5, 139.7, 136.1, 129.3, 128.6, 127.0, 125.0, 124.4, 34.3, 31.4, 29.0, 24.3, 21.2. HRMS (EI) calculated for $C_{20}H_{26}$ ([M]$^+$): 266.2035, Found:266.2028.

5-(*tert*-Butyl)-2-isopropyl-1,1'-biphenyl (3c). After the reaction based on general procedure: AgOAc (0.4 mmol), iodobenezene (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using hexane, and obtained **3c** in 22% (11 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 7H), 7.18 (d, *J* = 2.1 Hz, 1H), 3.07 – 2.98 (m, 1H), 1.33 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 143.2, 142.6, 140.5, 129.4, 127.9, 126.9, 126.5, 125.0, 124.6, 34.4, 31.4, 29.0, 24.3. HRMS (EI) calculated for $C_{19}H_{24}$ ([M]$^+$): 252.1878, Found: 252.1873.

5-(*tert*-Butyl)-2-isopropyl-1,1':4',1''-terphenyl (3d). After the reaction based on general procedure: AgOAc (0.45 mmol), 4-iodo-1,1'-biphenyl (0.33 mmol), $Pd(OAc)_2$ (20 mol %, 0.045 mmol), HFIP (1.5 mL), and 4-(*tert*-butyl)-1-isopropylcyclohexa-2,5-diene-1-carboxylic acid (0.22 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3d** in 48% (36 mg) as white solid. Melting Point: 160 - 168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.51 – 7.44 (m, 2H), 7.42 – 7.32 (m, 5H), 7.24 (d, *J* = 1.7 Hz, 1H), 3.11 (hept, *J* = 6.9 Hz, 1H), 1.35 (s, 9H), 1.20 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.99, 143.30, 141.70, 140.91, 140.16, 139.43, 129.85, 128.80, 127.24, 127.10, 126.94, 126.68, 125.19, 124.72, 117.53, 34.41, 31.45, 29.05, 24.42. HRMS (EI) calculated for $C_{25}H_{28}$ ([M]$^+$): 328.2184, Found: 328.2185.

5-(*tert*-Butyl)-2-isopropyl-3'-methoxy-1,1'-biphenyl (3e). After the reaction based on general procedure: AgOAc (0.4 mmol), 3-iodoanisole (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3e** in 21% (12 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 3H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.92 – 6.86 (m, 3H), 3.85 (s, 3H), 3.09 – 3.00 (m, 1H), 1.33 (s, 9H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 147.9, 144.1, 143.1, 140.4, 128.8, 126.7, 125.1, 124.7, 121.9, 115.1, 112.0, 55.2, 34.4, 31.4, 29.0, 24.4. HRMS (EI) calculated for $C_{20}H_{26}O$ ([M]$^+$): 282.1984, Found: 282.1986.

5-(*tert*-Butyl)-2-isopropyl-3',5'-dimethyl-1,1'-biphenyl (3f). The reaction based on general procedure: AgOAc (0.4 mmol), 1-iodo-3,5-dimethylbenzene (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-isopropyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using hexane, and obtained **3f** in 45% (25 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.22 – 7.20 (m, 2H), 7.13 – 7.07 (m, 2H), 3.13 – 3.04 (m, 1H), 2.35 (s, 6H), 1.35 (s, 9H), 1.18 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 143.2, 140.6, 140.3, 136.0, 134.8, 130.7, 129.1, 127.0, 126.8, 125.0, 124.3, 34.3, 31.4, 29.0, 24.4, 19.9, 19.5. HRMS (EI) calculated for $C_{21}H_{28}$ ([M]$^+$): 280.2191, Found: 280.2183.

5-(*tert*-Butyl)-2-isobutyl-4'-methoxy-1,1'-biphenyl (3g). After the reaction based on general procedure: AgOAc (0.4 mmol), 4-iodoanisole (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-*sec*-butyl -4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3g** in 44% (26 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 1H), 7.25 – 7.16 (m, 4H), 6.97 – 6.94 (m, 2H), 3.87 (s, 3H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.73 – 1.64 (m, 1H), 1.33 (s, 9H), 0.77 – 0.74 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 148.2, 141.3, 136.2, 135.2, 130.4, 129.5,

127.2, 123.8, 113.2, 55.2, 41.7, 34.3, 31.4, 29.6, 22.5. HRMS (EI) calculated for $C_{21}H_{28}O$ ([M]$^+$): 296.2140, Found: 296.2149.

5-(*tert*-Butyl)-2-isobutyl-3',5'-dimethyl-1,1'-biphenyl (3h). After the reaction based on general procedure: AgOAc (0.42 mmol), 1-iodo-3,5-dimethylbenzene (0.31 mmol), $Pd(OAc)_2$ (20 mol %, 0.042 mmol), HFIP (1 mL), and 4-(*tert*-butyl)-1-isobutylcyclohexa-2,5-diene-1-carboxylic acid (0.21 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3h** in 38% (24 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 1H), 7.24 – 7.16 (m, 3H), 7.12 – 7.04 (m, 2H), 2.47 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 6H), 1.80 – 1.65 (m, 1H), 1.34 (s, 9H), 0.78 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.12, 141.78, 140.39, 136.06, 135.94, 134.66, 130.72, 129.37, 129.12, 127.16, 126.85, 123.75, 41.63, 34.37, 31.45, 29.62, 22.55, 19.87, 19.50. HRMS (EI) calculated for $C_{22}H_{30}$ ([M]$^+$): 294.2345, Found: 294.2342.

5-(*tert*-Butyl)-2-isobutyl-1,1':4',1''-terphenyl (3i). After the reaction based on general procedure: AgOAc (0.42 mmol), 4-iodo-1,1'-biphenyl (0.31 mmol), $Pd(OAc)_2$ (20 mol %, 0.042 mmol), HFIP (1 mL), and 4-(*tert*-butyl)-1-isobutylcyclohexa-2,5-diene-1-carboxylic acid (0.21 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3i** in 28% (20 mg) as colorless gummy. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 4H), 7.52 – 7.45 (m, 2H), 7.43 – 7.32 (m, 4H), 7.27 – 7.20 (m, 2H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.78 – 1.68 (m, 1H), 1.36 (s, 9H), 0.78 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ148.33, 141.88, 141.33, 140.89, 139.26, 136.12, 129.92, 129.58, 128.79, 127.22, 127.06, 126.59, 124.11, 41.68, 31.46, 29.69, 22.53. HRMS (EI) calculated for $C_{26}H_{30}$ ([M]$^+$): 342.2339, Found: 342.2342.

5-(*tert*-Butyl)-2-hexyl-4'-methoxy-1,1'-biphenyl (3j). After the reaction based on general procedure: AgOAc (0.4 mmol), 4-iodoanisole (0.2 mmol), $Pd(OAc)_2$ (20 mol %, 0.04 mmol), HFIP (1 mL), and 1-hexyl-4-*tert*-butyl cyclohexa-2,5-dienyl carboxylic acid (0.25 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3j** in 31% (20 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.23 – 7.19 (m, 3H), 6.97 – 6.94 (m, 2H), 3.86 (s, 3H), 2.56 – 2.51 (m, 2H), 1.49 – 1.44 (m, 2H), 1.33 (s, 9H), 1.26 – 1.18 (m, 6H), 0.86 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 148.2, 140.9, 137.5, 135.0, 130.3, 128.7, 127.2, 124.0, 113.3, 55.3, 34.3, 32.6, 31.5, 31.4, 31.3,29.3, 22.5, 14.1. HRMS (EI) calculated for $C_{23}H_{32}O$ ([M]$^+$): 324.2453, Found: 324.2445.

2-Isopropyl-5-methyl-1,1':4',1''-terphenyl (3k). After the reaction based on general procedure: AgOAc (0.55 mmol), 4-iodo-1,1'-biphenyl (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-4-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3k** in 25% (20 mg) as white solid. Melting Point: 88 - 94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 3H), 7.51 – 7.35 (m, 4H), 7.27 – 7.14 (m, 5H), 2.93 (hept, *J* = 6.9 Hz, 1H), 2.30 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.42, 141.29, 141.25, 140.88, 139.51, 132.68, 130.35, 129.66, 128.78, 127.98, 127.23, 127.08, 126.76, 125.37, 33.73, 24.10, 20.10. HRMS (EI) calculated for $C_{22}H_{22}$ ([M]$^+$): 286.1714, Found: 286.1716.

2-Isopropyl-1,1':4',1''-terphenyl (3l). After the reaction based on general procedure: AgOAc (0.6 mmol), 4-iodo-1,1'-biphenyl (0.45 mmol), $Pd(OAc)_2$ (20 mol %, 0.06 mmol), HFIP (1.5 mL), and 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid (0.3 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3l** in 18% (15 mg) as white solid. Melting Point: 88 - 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.64 (m, 6H), 7.54 – 7.44 (m, 4H), 7.43 – 7.34 (m, 2H), 7.27 – 7.23 (m, 1H), 3.01 (hept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.42, 140.76, 140.50, 139.99, 128.81, 127.59, 127.45, 127.31, 127.06, 125.50, 125.35, 124.62, 34.29, 24.09. HRMS (EI) calculated for $C_{21}H_{20}$ ([M]$^+$): 272.1560, Found: 272.1559.

2-Isopropyl-3-methyl-1,1'-biphenyl (3m). After the reaction based on general procedure: AgOAc (0.55 mmol), iodobenzene (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using

hexane solvent and obtained **3m** in 46% (27 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 2H), 7.50 – 7.42 (m, 3H), 7.39 – 7.31 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.18, 141.69, 139.21, 134.23, 130.65, 128.68, 127.09, 126.90, 124.29, 123.71, 29.41, 23.29, 19.03. HRMS (EI) calculated for $C_{16}H_{18}$ ([M]$^+$): 210.1404, Found: 210.1403.

2-Isopropyl-3,4'-dimethyl-1,1'-biphenyl (3n). After the reaction based on general procedure: AgOAc (0.55 mmol), 1-iodo-4-methylbenzene (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3o** in 56% (35 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 3H), 7.36 – 7.20 (m, 4H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.42 (d, *J* = 6.1 Hz, 6H), 1.32 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.11, 139.14, 138.82, 136.61, 133.92, 130.61, 129.40, 126.93, 124.13, 123.54, 29.41, 23.30, 21.12, 19.01. HRMS (EI) calculated for $C_{17}H_{20}$ ([M]$^+$): 224.1562, Found: 224.1559.

2-Isopropyl-3,3',5'-trimethyl-1,1'-biphenyl (3o). After the reaction based on general procedure: AgOAc (0.55 mmol), 1-iodo-3,5-dimethylbenzene (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3o** in 47% (31 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 – 7.29 (m, 3H), 7.24 – 7.15 (m, 2H), 3.20 (hept, *J* = 6.8 Hz, 1H), 2.42 – 2.31 (m, 9H), 1.30 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.05, 139.36, 139.27, 136.80, 135.30, 133.82, 130.55, 129.98, 128.36, 124.47, 124.15, 123.57, 29.40, 23.30, 19.97, 19.45, 19.01. HRMS (EI) calculated for $C_{18}H_{22}$ ([M]$^+$): 238.1719, Found: 238.1716.

2-Isopropyl-3-methyl-1,1':4',1''-terphenyl (3p). After the reaction based on general procedure: AgOAc (0.55 mmol), 4-iodo-1,1'-biphenyl (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3p** in 45% (36 mg) as white solid. Melting Point: 98 - 105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 6H), 7.54 (d, *J* = 1.6 Hz, 1H) 7.52 – 7.45 (m, 2H), 7.42 – 7.35 (m, 2H), 7.27 – 7.23 (m, 1H), 3.23 (hept, *J* = 4.2 Hz, 1H), 2.41 (s, 3H), 1.32 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.27, 140.85, 140.62, 139.78, 138.67, 134.39, 130.74, 128.82, 127.45, 127.43, 127.07, 124.21, 123.60, 29.44, 23.32, 19.07. HRMS (EI) calculated for $C_{22}H_{22}$ ([M]$^+$): 286.1717, Found: 286.1716.

2-Isopropyl-4'-methoxy-3-methyl-1,1'-biphenyl (3q). After the reaction based on general procedure: AgOAc (0.55 mmol), 1-iodo-4-methoxybenzene (0.41 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3q** in 87% (58 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 2H), 7.45 – 7.38 (m, 1H), 7.30 – 7.26 (m, 1H), 7.21 – 7.16 (m, 1H), 7.01 – 6.94 (m, 2H), 3.86 (s, 3H), 3.19 (hept, *J* = 6.9 Hz, 1H), 2.37 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.85, 147.11, 138.79, 134.28, 133.59, 130.60, 128.05, 123.90, 123.28, 114.11, 55.35, 29.39, 23.28, 18.97. HRMS (EI) calculated for $C_{17}H_{20}O$ ([M]$^+$): 240.1510, Found: 240.1508.

2'-Isopropyl-3'-methyl-[1,1'-biphenyl]-4-carbonitrile (3r). After the reaction based on general procedure: AgOAc (0.55 mmol), 4-iodobenzonitrile (0.22 mmol), $Pd(OAc)_2$ (20 mol %, 0.055 mmol), HFIP (1.5 mL), and 1-isopropyl-2-methylcyclohexa-2,5-diene-1-carboxylic acid (0.27 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3r** in 32% (17 mg) as white solid. Melting Point: 80 - 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 4H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 3.21 (hept, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.69, 146.09, 137.08, 135.96, 132.51, 131.00, 127.54, 124.31, 123.65, 119.12, 110.39, 29.39, 23.22, 19.10. HRMS (EI) calculated for $C_{17}H_{17}N$ ([M]$^+$): 235.1358, Found: 235.1355.

1-Isopropyl-2-(4-methoxyphenyl)naphthalene (3s). After the reaction based on general procedure: AgOAc (0.46 mmol), 1-iodo-4-methoxybenzene (0.34 mmol), $Pd(OAc)_2$ (20 mol %, 0.046 mmol), HFIP (1.5 mL), and 1-isopropyl-1,4-dihydronaphthalene-1-carboxylic acid (0.23 mmol). The crude mixture was purified by FC (SiO_2) using EtOAc/hexane solvent and obtained **3s** in 70% (45 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 1H), 7.93 – 7.84 (m, 2H), 7.72 – 7.63 (m, 3H), 7.55 – 7.46 (m, 2H), 7.07 – 7.00 (m, 2H), 3.88 (s, 3H), 3.83 – 3.76 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.20, 145.15, 137.82, 134.33, 134.15, 130.31, 129.10, 128.49, 128.21, 125.69, 125.50, 123.54, 123.23, 121.50, 114.29, 55.41, 28.70, 23.65. HRMS (EI) calculated for $C_{20}H_{20}O$ ($[M]^+$): 276.1508, Found: 276.1508.

1-Isopropyl-2-(*p*-tolyl)naphthalene (3t). After the reaction based on general procedure: AgOAc (0.46 mmol), 1-iodo-4-methylbenzene (0.34 mmol), $Pd(OAc)_2$ (20 mol %, 0.046 mmol), HFIP (1.5 mL), and 1-isopropyl-1,4-dihydronaphthalene-1-carboxylic acid (0.23 mmol). The crude mixture was purified by FC (SiO_2) using hexane solvent and obtained **3t** in 50% (30 mg) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.7 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.73 – 7.63 (m, 3H), 7.57 – 7.49 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 2H), 3.84 (hept, *J* = 6.9 Hz, 1H), 2.47 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.15, 138.75, 138.16, 137.07, 134.29, 130.49, 129.56, 129.19, 127.34, 125.68, 125.62, 123.91, 123.24, 121.64, 28.71, 23.65, 21.19. HRMS (EI) calculated for $C_{20}H_{20}$ ($[M]^+$): 260.1556, Found: 260.1559.

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Supplementary Material

For NMR spectra see the Supplementary Material. CCDC-2249903 (**3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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