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Transition-Metal-Free C–H Arylation of Unactivated Arenes with 8-Hydroxyquinoline as a Promoter

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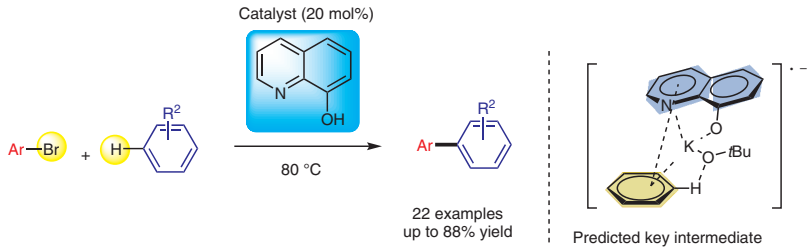

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Abstract A method for the transition-metal-free direct C–H arylation of unactivated arenes is developed with aryl bromides as substrates and 8-hydroxyquinoline as an efficient promoter. A variety of biaryl compounds with structural diversity are obtained in moderate to high yields. Mechanistic studies reveal that the reaction proceeds via a homolytic aromatic substitution pathway.

Key words C–H arylation, metal-free, 8-hydroxyquinoline, biaryl compounds, homolytic aromatic substitution

The biaryl motif is one of the most common scaffolds present in pharmaceuticals and natural products.[1] Developing efficient synthetic methods to construct biaryl motifs is of great importance for drug discovery. An efficient method should firstly be tolerant of different functional groups, providing biaryl compounds with structural diversity for exploring structure–activity relationships to identify lead compounds. The method should also be easy and economic, reducing the synthetic efforts and cost to a meaningful extent. In current drug synthesis, transition-metal-catalyzed aromatic carbon–carbon bond-forming reactions such as the Suzuki reaction have been widely applied.[2] However, the starting materials, organohalides (Ar–X) and organometallic reagents (Ar′–M), for these reactions can sometimes be difficult to obtain, especially in the cases of particular organometallic reagents. Research on using more common unactivated arenes instead of organometallic reagents has achieved remarkable advances. However, high catalyst loading or specially designed and sophisticated ligands are usually required, making such procedures costly.[3] Furthermore, the active pharmaceutical ingredients and drug candidates have very strict demands for the absence of transition-metal impurities. Tedious procedures are needed to verify and remove the transition-metal impurity once a transition metal is involved in a synthesis. Thus, the development of green and economic metal-free conditions for the synthesis of biaryls is highly desirable.

In 2008, Itami and co-workers disclosed the first transition-metal-free catalyzed biaryl coupling of electron-deficient nitrogen heterocycles and iodoarenes.[4] With the assistance of the inorganic base potassium *tert*-butoxide (KO*t*Bu), a number of biaryl compounds were obtained in moderate to high yields. In 2010, the application of this methodology for non-activated arenes was reported by Lei and Kwong with DMEDA,[5] and independently by Hayashi and Shirakawa[6] and Shi[7] with phenanthroline derivatives as promoters. Mechanistic studies revealed that this type of reaction proceeds through a homolytic aromatic substitution (HAS) pathway. A single electron transfer (SET) from KO*t*Bu occurs firstly to form the aryl radical, which is regarded as the key intermediate in the procedure. Besides KO*t*Bu, promoters such as DMEDA and phenanthroline derivatives also facilitate the generation of aryl radicals. Thus, an efficient promoter may allow this procedure to occur under mild conditions and afford products in high yields. Since these pioneering studies, phenyl hydrazine, proline, imidazolium salts and others have proved to be able to facilitate the direct C–H arylation of non-activated arenes (Figure 1).[8] However, most of these reactions are limited to the use of iodoarenes as substrates and high temperatures are sometimes required. Hence, the development of a simple and inexpensive promoter to catalyze intramolecular C–H arylations with bromoarenes under mild conditions is still in demand.

8-Hydroxyquinolines are privileged structures for drug candidates having biological effects such as neuroprotection, anticancer, antibacterial and antifungal.[9] 8-Hydroxyquinolines can form a stable radical via a two-center, three-

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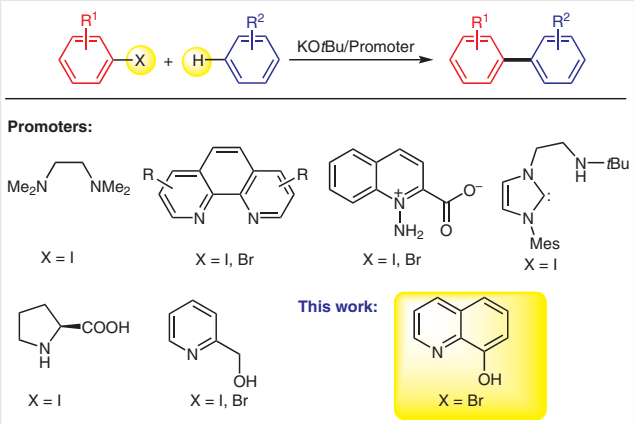
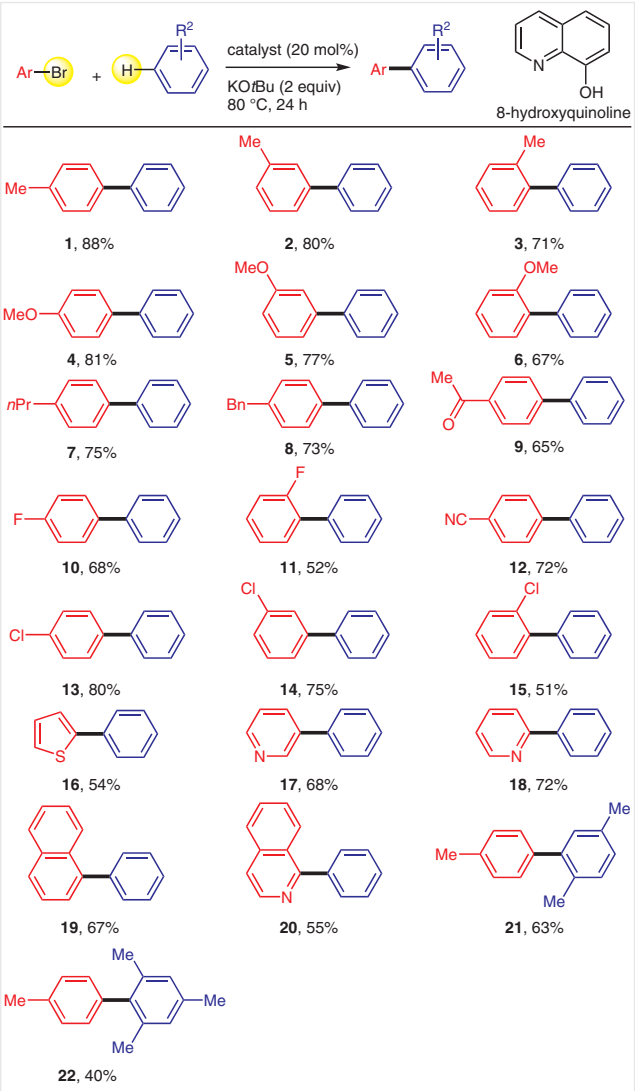


Figure 1 Transition-metal-free arylations of unactivated arenes



Scheme 1 Transition-metal-free direct arylation of unactivated arenes with aryl bromides

electron bond configuration, and thus exhibit moderate metal-binding affinity.[10] In continuation of our earlier work on the C–H arylation of arenes catalyzed by 2-pyridyl carbinol[11] and intramolecular C–H arylations mediated by ethylene glycol,[12] herein, we chose to explore the application of 8-hydroxyquinoline as a simple and cheap promoter for the C–H arylation of aryl bromides.

We initially investigated the 8-hydroxyquinoline-catalyzed C–H bond cross-coupling of benzene with different 4-halotoluenes as substrates (Table 1). 8-Hydroxyquinoline (40 mol%) was first applied in the reaction at 120 °C in the presence of KO*t*Bu (2.5 equiv). An excellent product yield was obtained with 4-iodotoluene or 4-bromotoluene as the substrate, whereas the reaction with 4-chlorotoluene only afforded a trace of product (entries 1–3). The reaction with K_2CO_3 instead of KO*t*Bu as the base gave no product, even when using iodotoluene as the substrate (entries 4 and 5). No reaction occurred in the absence of KO*t*Bu or 8-hydroxyquinoline (entries 6 and 7). A series of screening experiments was carried out to optimize the reaction parameters. Lowering the catalyst loading from 40% to 10% led to decreased product yields (entries 8–10). The yield was 88% when lowering the reaction temperature to 80 °C, but decreased dramatically when the reactions were run at 60 °C and 40 °C (entries 11–13). Increasing the reaction time to 48 hours at 60 °C did not improve the yield (entry 14). However, the amount of KO*t*Bu could be decreased to 2.0 equivalents without decreasing the yield (entry 15).

With the preliminary optimized reaction conditions in hand, we next examined the generality of the catalyst system for the direct arylation of unactivated arenes with various aryl bromides (Scheme 1). Aiming at developing mild conditions for the synthesis of biaryl compounds, we chose 20 mol% of 8-hydroxyquinoline as the catalyst and a temperature of 80 °C to perform the reaction. Bromoarenes substituted with a methyl or a methoxy group reacted with benzene to afford good yields of the coupled products **1**–**6**. The position of the substituent did not affect the yield dramatically. Sterically hindered *ortho*-substituted aryl bromides reacted with benzene to give the desired products in moderate yields (compounds **3**, **6** and **11**). Acetyl, fluoro and cyano groups were tolerated under these reaction conditions, although the product yields decreased a little compared with methyl groups (compounds **9**–**12**). Notably, a chloro group remained unreactive in this reaction, offering further structural fine-tuning using other reaction conditions. Heteroaryl bromides such as thienyl, pyridyl, and isoquinolinyl bromides along with 1-bromonaphthalene were feasible coupling partners for this reaction, giving the corresponding products in moderate to good yields (compounds **16**–**20**). Besides benzene, other unactivated arenes including *p*-xylene and mesitylene were also used for the direct arylation with 4-bromotoluene, affording the substituted biaryl products **21** and **22** in moderate yields.

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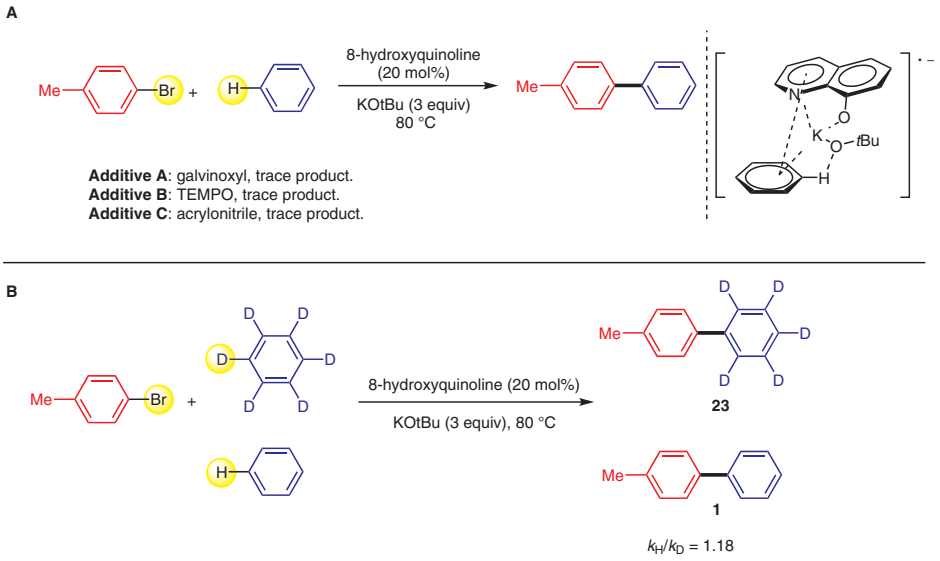
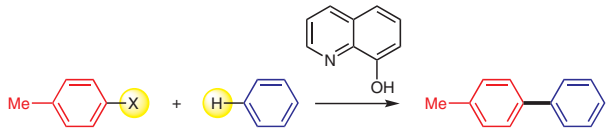


Scheme 2 Mechanistic and kinetic isotope effect studies

Table 1 Optimization of the Reaction Conditions[a]

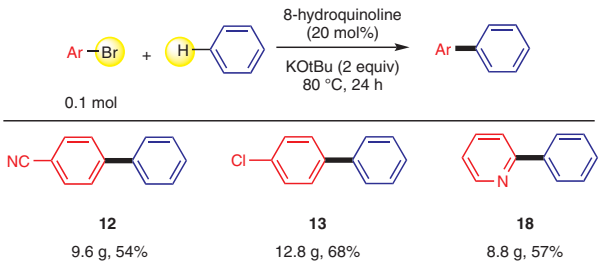


Entry	X	Cat. (mol%)	Temp (°C)	Conv. (%)[b]
1	I	40	120	99
2	Br	40	120	93
3	Cl	40	120	2
4[c]	Br	40	120	trace
5[c]	I	40	120	trace
6[d]	Br	40	120	trace
7[e]	Br	40	120	trace
8	Br	30	120	94
9	Br	20	120	89
10	Br	10	120	65
11	Br	20	80	88
12	Br	20	60	45
13	Br	20	40	21
14[f]	Br	20	60	47
15[g]	Br	20	80	88

[a] Reaction conditions: 4-halotoluene (1.0 mmol), benzene (8 mL), 8-hydroxyquinoline, KO*t*Bu (2.5 mmol), 18 h, N_2 atm.
[b] GC-FID conversion.
[c] With K_2CO_3 (2.5 equiv) as the base.
[d] Without 8-hydroxyquinoline.
[e] Without KO*t*Bu.
[f] Reaction time: 48 h.
[g] The amount of KO*t*Bu was decreased to 2 equiv.

Control experiments were performed with radical scavengers such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), galvinoxyl, or acrylonitrile added to the reaction of 4-bromotoluene and benzene (Scheme 2, A). Under the same conditions, no product was detected after the radical scavengers had been added, confirming that the generation of the aryl radical from the bromoarene was a key step in the reaction. We speculated that 8-hydroxyquinoline and KO*t*-Bu interacted with the arene by π-stacking, forming the key intermediate to facilitate the reaction. A kinetic isotope effect (KIE) experiment was performed and consistent KIE values were observed with 1-bromo-4-methylbenzene (k_H/k_D = 1.18) (Scheme 2, B). This result is in accordance with coupling reactions using other promoters such as DMEDA and 2-pyridyl carbinol, indicating that the C–H bond cleavage step might not be the rate-determining step of this transformation.[11]

We also performed the synthesis of compounds **12**, **13** and **18** on gram scale (Scheme 3). With 20 mol% of 8-hydroxyquinoline as the promoter, these reactions gave slightly decreased yields at 80 °C on 0.1 mol scale compared



Scheme 3 Arylation of substituted aryl bromides on gram scale

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to those run on 1 mmol scale. The procedure is simple and easy to handle, suggesting that this method can be applied efficiently in drug synthesis.

In summary, we have disclosed that 8-hydroxyquinoline can be used as an efficient promoter in the transition-metal-free C–H arylation of unactivated arenes. A wide range of aryl/heteroaryl bromides was coupled efficiently with unactivated arenes under mild reaction conditions. Particularly noteworthy is that a chloro group was inactive in the reaction, providing a reaction site for further modification. This simple and inexpensive protocol can be expanded to gram-scale reactions without significantly decreasing the yield. Further investigations applying this method in drug synthesis are currently underway.

Unless otherwise noted, all reagents were purchased from commercial suppliers and were used without purification. All the reactions were performed in Rotaflo® (UK) resealable screw-cap Schlenk flasks (ca. 20 mL volume) in the presence of a Teflon-coated magnetic stir bar (4 mm × 10 mm). Benzene and toluene were distilled from sodium under nitrogen. Thin-layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 70–230 and 230–400 mesh) was used for column chromatography. Melting points were obtained using an SRS-Opti Melt automated melting point instrument. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker (400 MHz) spectrometer. ^{1}H NMR spectra are referenced internally to the residual proton resonance of $CDCl_3$ (δ 7.26) or with tetramethylsilane (TMS) (δ 0.00) as the internal standard. Chemical shifts (δ) are reported as parts per million (ppm) downfield from TMS. ^{13}C NMR spectra are referenced to $CDCl_3$ (δ 77.0, the central signal). Coupling constants (*J*) are reported in Hertz (Hz). Low-resolution mass spectra (EI) were recorded using a MAT-95 spectrometer. The GC yields were referenced to authentic samples/dodecane calibration standards using a HP 6890 GC-FID (gas chromatography-flame ionization detection) system.

Arylation of Substituted Aryl Bromides; General Procedure

The substituted aryl bromide (1.0 mmol), 8-hydroxyquinoline (20 mol%) and KO*t*Bu (2.0 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The unactivated arene (8.0 mL or 80 equiv) was then added and the mixture was stirred at r.t. for 3–5 min. The Schlenk tube was placed in a preheated oil bath at 80 °C and the mixture was stirred for 18 h. After completion of the reaction as judged by GC analysis, the Schlenk tube was allowed to cool to r.t. and the contents quenched with H_2O and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the desired biaryl product.

4-Methyl-1,1′-biphenyl (1)

The spectroscopic data are in accordance with those reported.[7]

White solid; yield: 147 mg (88%); mp 46–48 °C; R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.9 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 7.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.16, 138.36, 136.97, 129.45, 128.68, 126.97, 126.94, 21.05.

MS (EI): *m*/*z* = 168 [M$^+$].

3-Methyl-1,1′-biphenyl (2)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 134 mg (80%); R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.7 Hz, 2 H), 7.37 (t, *J* = 7.8 Hz, 4 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.11 (d, *J* = 7.4 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.34, 141.21, 138.22, 128.64, 128.62, 127.96, 127.92, 127.12, 127.10, 124.24, 21.46.

MS (EI): *m*/*z* = 168 [M$^+$].

2-Methyl-1,1′-biphenyl (3)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 119 mg (71%); R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.1 Hz, 2 H), 7.32 (d, *J* = 7.0 Hz, 3 H), 7.29–7.21 (m, 4 H), 2.27 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.99, 135.38, 130.34, 129.84, 129.23, 128.10, 127.28, 127.21, 126.80, 125.80, 20.51.

MS (EI): *m*/*z* = 168 [M$^+$].

4-Methoxy-1,1′-biphenyl (4)

The spectroscopic data are in accordance with those reported.[7]

White solid; yield: 149 mg (81%); mp 87–88 °C; R_f = 0.2 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 8.4 Hz, 4 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 1 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 3.86 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.18, 140.86, 133.82, 128.72, 128.16, 126.75, 126.66, 114.23, 55.35.

MS (EI): *m*/*z* = 184 [M$^+$].

3-Methoxy-1,1′-biphenyl (5)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 142 mg (77%); R_f = 0.2 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.34–7.25 (m, 2 H), 7.15 (d, *J* = 7.7 Hz, 1 H), 7.11 (s, 1 H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1 H), 3.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.93, 142.70, 141.04, 129.68, 128.66, 127.38, 127.11, 119.60, 112.86, 112.62, 55.14.

MS (EI): *m*/*z* = 184 [M$^+$].

2-Methoxy-1,1′-biphenyl (6)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 123 mg (67%); R_f = 0.2 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.23 (dt, *J* = 16.6, 8.1 Hz, 3 H), 6.94 (t, *J* = 7.4 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 3.63 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.34, 138.46, 130.70, 130.58, 129.41, 128.46, 127.85, 127.81, 126.72, 120.70, 111.15, 55.22.

MS (EI): *m*/*z* = 184 [M$^+$].

4-Propyl-1,1′-biphenyl (7)

The spectroscopic data are in accordance with those reported.[13]

Colorless oil; yield: 147 mg (75%); R_f = 0.55 (hexane).

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^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.7 Hz, 2 H), 7.50 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 2 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 1.67 (dd, *J* = 14.8, 7.4 Hz, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.87, 141.26, 138.65, 128.92, 128.73, 127.03, 127.01, 126.99, 37.75, 24.57, 13.91.

MS (EI): *m*/*z* = 196 [M$^+$].

4-Benzyl-1,1′-biphenyl (8)

The spectroscopic data are in accordance with those reported.[7]

Yellow solid; yield: 178 mg (73%); mp 86–88 °C; R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 8.3, 0.9 Hz, 2 H), 7.53–7.48 (m, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.34–7.25 (m, 4 H), 7.25–7.19 (m, 4 H), 4.01 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.04, 140.28, 139.09, 129.35, 128.99, 128.74, 128.54, 127.28, 127.24, 127.10, 127.03, 126.17, 41.63.

MS (EI): *m*/*z* = 244 [M$^+$].

1-([1,1′-Biphenyl]-4-yl)ethanone (9)

The spectroscopic data are in accordance with those reported.[14]

Colorless oil; yield: 127 mg (65%); mp 153–155 °C; R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.65–7.61 (m, 2 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 2.64 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.70, 145.79, 139.89, 135.90, 128.95, 128.90, 128.22, 127.26, 127.22, 26.63.

MS (EI): *m*/*z* = 196 [M$^+$].

4-Fluoro-1,1′-biphenyl (10)

The spectroscopic data are in accordance with those reported.[7]

White solid; yield: 117 mg (68%); mp 76–78 °C; R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.1 Hz, 4 H), 7.45 (t, *J* = 7.4 Hz, 2 H), 7.37 (d, *J* = 7.1 Hz, 1 H), 7.14 (t, *J* = 8.3 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.72, 161.27, 140.28, 137.37 (d, *J* = 3.1 Hz), 128.82, 128.69 (d, *J* = 8.1 Hz, 1 H), 127.26, 127.03, 115.61 (d, *J* = 21.4 Hz, 1 H).

MS (EI): *m*/*z* = 172 [M$^+$].

2-Fluoro-1,1′-biphenyl (11)

The spectroscopic data are in accordance with those reported.[15]

White solid; yield: 89 mg (52%); mp 71–73 °C; R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 7.5 Hz, 3 H), 7.37 (d, *J* = 7.3 Hz, 1 H), 7.30 (d, *J* = 6.9 Hz, 1 H), 7.20 (dd, *J* = 13.6, 6.1 Hz, 1 H), 7.17–7.10 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.03, 158.57, 135.85, 130.79 (d, *J* = 3.4 Hz), 129.01 (dd, *J* = 9.7, 5.5 Hz), 128.44, 127.66, 124.34 (d, *J* = 3.7 Hz), 116.21, 115.99.

MS (EI): *m*/*z* = 172 [M$^+$].

4-Cyano-1,1′-biphenyl (12)

The spectroscopic data are in accordance with those reported.[7]

White solid; yield: 129 mg (72%); mp 90–92 °C; R_f = 0.3 (EtOAc/hexane, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (q, *J* = 8.2 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 2 H), 7.44 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.67, 139.18, 132.59, 129.12, 128.67, 127.73, 127.23, 118.92, 110.94.

MS (EI): *m*/*z* = 179 [M$^+$].

4-Chloro-1,1′-biphenyl (13)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 150 mg (80%); R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.7 Hz, 2 H), 7.52 (d, *J* = 8.1 Hz, 2 H), 7.43 (dd, *J* = 18.1, 7.9 Hz, 4 H), 7.37 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.01, 139.68, 133.39, 128.92, 128.90, 128.41, 127.61, 127.01.

MS (EI): *m*/*z* = 188 [M$^+$].

3-Chloro-1,1′-biphenyl (14)

The spectroscopic data are in accordance with those reported.[15]

White solid; yield: 141 mg (75%); mp 86–88 °C; R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.55 (m, 3 H), 7.47 (ddd, *J* = 9.8, 6.8, 5.1 Hz, 3 H), 7.42–7.31 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.12, 139.85, 134.69, 129.99, 128.91, 127.88, 127.33, 127.28, 127.13, 125.31.

MS (EI): *m*/*z* = 188 [M$^+$].

2-Chloro-1,1′-biphenyl (15)

The spectroscopic data are in accordance with those reported.[16]

Colorless oil; yield: 196 mg (51%); R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 4.1 Hz, 4 H), 7.40 (dd, *J* = 5.8, 2.7 Hz, 1 H), 7.37–7.34 (m, 1 H), 7.34–7.28 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.99, 140.55, 139.44, 132.53, 131.42, 129.97, 129.48, 128.57, 128.08, 127.64, 126.86.

MS (EI): *m*/*z* = 188 [M$^+$].

2-Phenylthiophene (16)

The spectroscopic data are in accordance with those reported.[17]

Colorless oil; yield: 86 mg (54%); R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.7 Hz, 2 H), 7.37 (t, *J* = 7.2 Hz, 2 H), 7.34–7.23 (m, 3 H), 7.13–7.06 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.42, 134.43, 128.88, 128.00, 127.46, 125.97, 124.80, 123.08.

MS (EI): *m*/*z* = 160 [M$^+$].

3-Phenylpyridine (17)

The spectroscopic data are in accordance with those reported.[18]

Colorless oil; yield: 105 mg (68%); R_f = 0.55 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 8.59 (d, *J* = 3.6 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.58 (d, *J* = 7.0 Hz, 2 H), 7.47 (t, *J* = 7.1 Hz, 2 H), 7.41 (d, *J* = 6.8 Hz, 1 H), 7.38–7.33 (m, 1 H).

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^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.40, 148.26, 137.75, 136.56, 134.27, 129.00, 128.02, 127.07, 123.47.

MS (EI): *m*/*z* = 155 [M$^+$].

2-Phenylpyridine (18)

The spectroscopic data are in accordance with those reported.[14]

Colorless oil; yield: 112 mg (72%); R_f = 0.45 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 8.53 (d, *J* = 4.3 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.46 (s, 1 H), 7.44 (s, 1 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.18 (dd, *J* = 7.5, 5.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.67, 147.47, 136.93, 135.65, 133.30, 128.26, 127.27, 126.27, 122.71.

MS (EI): *m*/*z* = 155 [M$^+$].

1-Phenylnaphthalene (19)

The spectroscopic data are in accordance with those reported.[7]

Colorless oil; yield: 137 mg (67%); R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.3 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 4.4 Hz, 1 H), 7.37 (s, 1 H), 7.35–7.28 (m, 5 H), 7.25 (dd, *J* = 8.3, 3.7 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.69, 140.17, 133.78, 131.60, 129.96, 129.94, 128.19, 128.15, 127.55, 127.10, 126.85, 125.94, 125.65, 125.27.

MS (EI): *m*/*z* = 204 [M$^+$].

4-Phenylisoquinoline (20)

The spectroscopic data are in accordance with those reported.[19]

Colorless oil; yield: 113 mg (55%); R_f = 0.55 (EtOAc/hexane, 1:100).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 5.6 Hz, 1 H), 8.11 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 1 H), 7.77–7.61 (m, 4 H), 7.58–7.46 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.68, 142.16, 139.53, 136.78, 129.92, 129.85, 128.50, 128.27, 127.50, 127.09, 126.91, 126.64, 119.84.

MS (EI): *m*/*z* = 205 [M$^+$].

2,4′,5-Trimethyl-1,1′-biphenyl (21)

The spectroscopic data are in accordance with those reported.[20]

Colorless oil; yield: 123 mg (63%); R_f = 0.35 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 4 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 7.08 (d, *J* = 7.1 Hz, 2 H), 2.42 (s, 3 H), 2.36 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.71, 139.18, 136.30, 135.17, 132.24, 130.63, 130.25, 129.08, 128.76, 127.78, 21.20, 20.95, 20.03.

MS (EI): *m*/*z* = 196 [M$^+$].

2,4,4′,6-Tetramethylbiphenyl (22)

The spectroscopic data are in accordance with those reported.[21]

Colorless oil; yield: 84 mg (40%); R_f = 0.45 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 7.9 Hz, 2 H), 7.02 (d, *J* = 7.9 Hz, 2 H), 6.93 (s, 2 H), 2.40 (s, 3 H), 2.32 (s, 3 H), 2.00 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.98, 137.95, 136.38, 136.12, 135.93, 129.12, 129.04, 127.98, 21.22, 20.99, 20.77.

MS (EI): *m*/*z* = 210 [M$^+$].

Kinetic Isotope Effect Experiment

4-Bromotoluene (1.0 mmol), 8-hydroxyquinoline (20 mol%) and KO*t*-Bu (2.0 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. Benzene-H_6 (4.0 mL) and Benzene-D_6 (4.0 mL) were then added and the mixture was stirred at r.t. for 3–5 min. The Schlenk tube was placed in a preheated oil bath at 80 °C and the mixture was stirred for 18 h. After completion of the reaction as judged by GC analysis, the Schlenk tube was allowed to cool to r.t. and the contents quenched with H_2O and diluted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel. The product distribution was analyzed by ^{1}H NMR spectroscopy.

4′-Methyl-1,1′-biphenyl-2,3,4,5,6-*d*$_5$ (23)

The spectroscopic data are in accordance with those reported.[22]

Colorless oil; yield: 40 mg (63%); R_f = 0.55 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.9 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.04, 138.36, 137.07, 129.56, 127.05, 21.17.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591874.

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