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Suzuki–Miyaura Coupling of Aryl Sulfonates with Arylboronic Acids Using a Morpholine–$Pd(OAc)_2$ Catalyst System

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We report a new catalyst system, a morpholine–$Pd(OAc)_2$ complex, for Suzuki–Miyaura coupling of aryl tosylates or mesylates with arylboronic acids to give biaryl compounds. The morpholine–$Pd(OAc)_2$ catalyst system is proposed to be a precursor of the catalytically active species in the coupling reaction. Aryl chlorides and aryl triflates can also be used in this coupling reaction. Altogether, 22 biaryl compounds were obtained using this catalyst system.

Introduction

The Suzuki–Miyaura coupling reaction is an extremely reliable method for the formation of C–C bonds on scales from laboratory synthesis to industrial manufacturing. Numerous procedures have been reported, and most large-scale applications use aryl halides together with boronic acid derivatives.[1] From the points of view of cost and handling, tosylates and mesylates are promising candidates for coupling partners, because they can be obtained from inexpensive phenol derivatives and TsCl or MsCl. In addition, since almost all aryl tosylates and mesylates are crystalline, they are easy to purify and stable in storage.[2] In fact, there are many reports of Suzuki–Miyaura coupling reactions using aryl or alkenyl tosylates and aryl mesylates catalysed by Ni,[3,4] Ru,[5] and Pd.[2,6–9] However, the reported palladium-catalysed Suzuki–Miyaura coupling reactions of aryl sulfonates use expensive phosphine ligands (e.g., **1**,[6a] **2**,[6c] and **3**[6d]). In addition, harsh conditions above the solvent's boiling point, and 2 equiv. of boronic acid are normally required.[6a,6c,6d] On the other hand, nitrogen-based ligands such as amines,[10] N-heterocyclic carbenes (NHC),[11] oximes,[12] hydrazones,[13] and others[14] have been used in Suzuki–Miyaura coupling reactions with aryl or alkenyl halides. Only one report exists, though, of the use of nitrogen-based ligands with aryl tosylates or mesylates: NHC-Pd^{II}-Im (**4**) was used by Shao (Figure 1).[15] However, this procedure needs an expensive carbene-type catalyst, morpholine as a solvent, and heating to 110–130 °C for 24 h. On the other hand, amine ligands are easy to prepare, and their use is cost effective. DAPCy (**5**)[10c] and diamine palladium complex **6**[10e] have been used for the Suzuki–Miyaura coupling of aryl halides (Figure 2). In this paper, we report the application of a new morpholine-

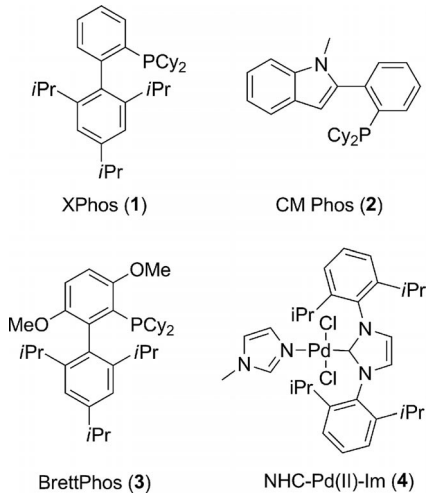

Figure 1. Ligands for Suzuki–Miyaura coupling reactions of aryl tosylates.

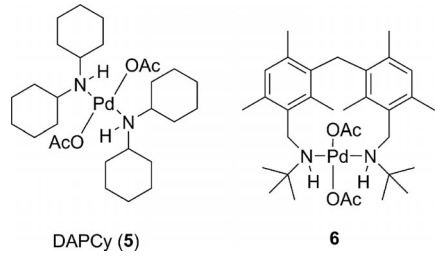

Figure 2. Palladium complexes with amine ligands for Suzuki–Miyaura coupling reactions.

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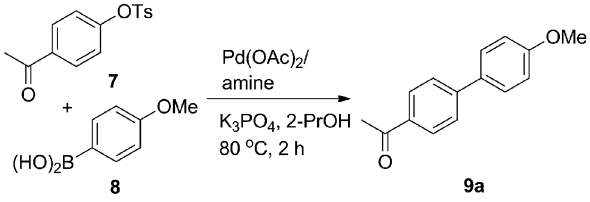
$Pd(OAc)_2$ complex for the formation of biaryl compounds using aryl tosylates or mesylates togther with arylboronic acids at 80 °C.

Results and Discussion

First, we screened secondary amines using the coupling reaction between 4-acetylphenyl tosylate (**7**) and 4-methoxyphenylboronic acid (**8**). When morpholine was used, the desired biaryl compound (i.e., **9**) was obtained in a 92% yield (Table 1, entry 1). We also attempted a lower equivalence (250 mol-%) of morpholine, and other solvents (*tert*-butyl alcohol and acetonitrile) for the reaction, but these experiments only gave moderate yields (Table 1, entries 2–4). Cyclic amines containing a second heteroatom gave good yields (Table 1, entries 5–10), but the yield decreased when piperidine or pyrrolidine was used (Table 1, entries 11 and 12). Aliphatic amines gave poor yields (Table 1, entries 13 and 14). Finally, we tested dicyclohexylamine for this reaction, which has been shown to be catalysed by DAPCy (**5**).[10c] This gave a coupled compound in 19% yield (Table 1, entry 15), which suggests that morpholine might generate a highly reactive amine–palladium complex for Suzuki–Miyaura coupling.

Table 1. Optimization of the amine component for the amine–palladium-catalysed Suzuki–Miyaura coupling of aryl tosylates.[a]

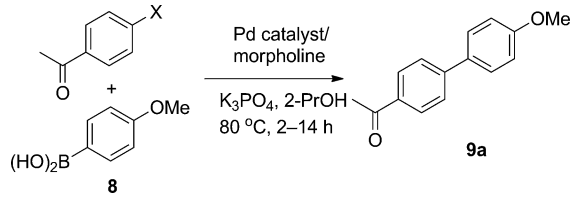


Entry	Amine	Yield of **9a** [%][b]
1	morpholine	92
2	morpholine	60[c]
3	morpholine	66[d]
4	morpholine	57[e]
5	thiomorpholine	53
6	*N*-methylpiperazine	80
7	*N*-methylpiperazine	69[d]
8	*N*-methylpiperazine	66[e]
9	*N*-ethylpiperazine	73
10	*N*-phenylpiperazine	72
11	piperidine	62
12	pyrrolidine	58
13	di-*n*-propylamine	39
14	methylbenzylamine	27
15	dicyclohexylamine	19

[a] Reaction conditions: 4-acetylphenyl tosylate (**7**; 0.5 mmol), (4-methoxyphenyl)boronic acid (**8**; 0.6 mmol), $Pd(OAc)_2$ (2.5 mol-%), amine (2.5 mmol), K_3PO_4 (1.5 mmol), 2-propanol (1.5 mL), N_2, 80 °C, 2 h. [b] Yield from NMR spectroscopy with piperonal as internal standard. [c] 250 mol-% of morpholine was used. [d] *tert*-butyl alcohol was used as a solvent. [e] MeCN was used as a solvent.

We also optimized the base and the palladium source. When Na_3PO_4 was used as a base, the yield decreased (Table 2, entry 2), and a reaction using K_2CO_3 gave a 67% yield (Table 2, entry 3). When 1 mol-% of $Pd(OAc)_2$ was used, the yield decreased to 55%, and when the reaction was run under air the yield dropped to 38%. Other palladium sources also gave good yields. $PdCl_2$ in particular gave almost the same yield as $Pd(OAc)_2$ (Table 2, entries 6–8). However, $Pd_2(dba)_3$ was not effective for this coupling reaction (Table 2, entry 9). No amination products were observed in any of these reactions.

Table 2. Study of the palladium catalyst for the morpholine–palladium-catalysed Suzuki–Miyaura coupling of aryl tosylates (acac = acetylacetone; tfa = trifluoroacetate; dba = dibenzylideneacetone).[a]



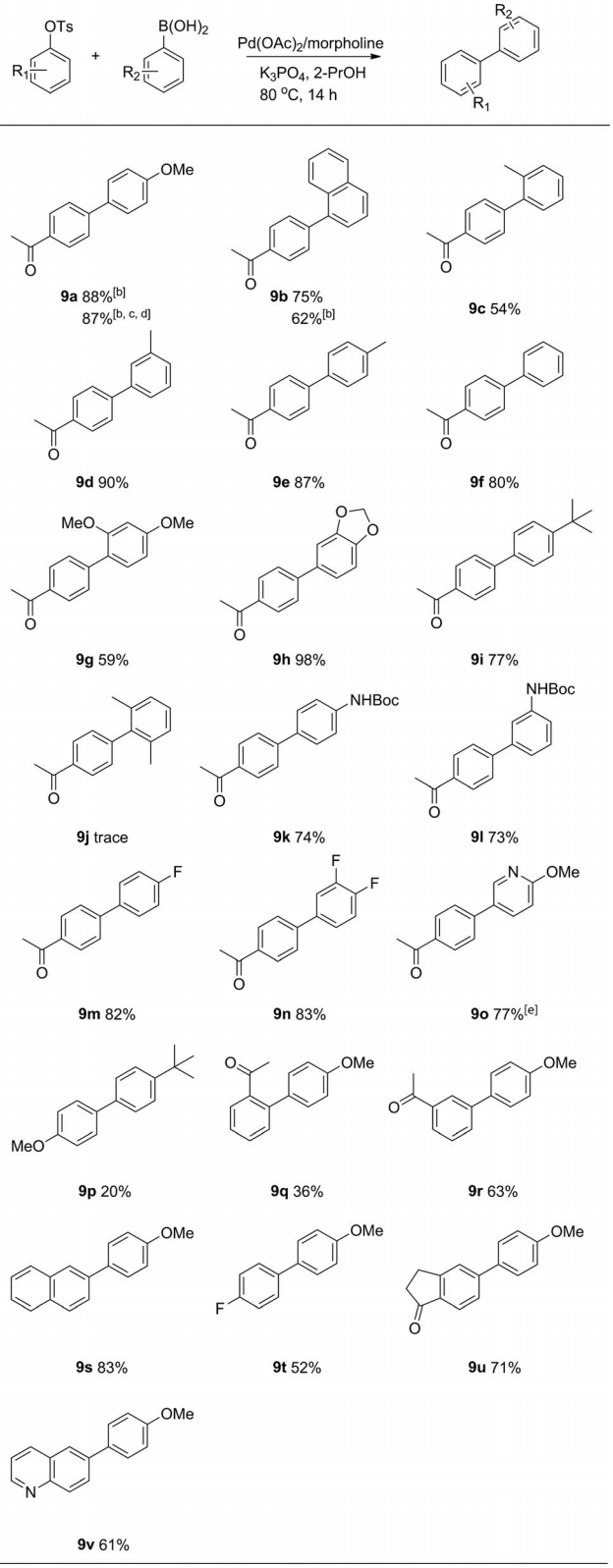
Entry	Pd catalyst	Yield of **9a** [%][b]
1	$Pd(OAc)_2$	92
2	$Pd(OAc)_2$	26[c]
3	$Pd(OAc)_2$	67[d]
4	$Pd(OAc)_2$	55[e]
5	$Pd(OAc)_2$	38[f]
6	$PdCl_2$	89
7	$Pd(acac)_2$	80
8	$Pd(tfa)_2$	71
9	$Pd_2(dba)_3$	1

[a] Reaction conditions: 4-acetylphenyl tosylate (**7**; 0.5 mmol), 4-methoxyphenylboronic acid (**8**; 0.6 mmol), Pd catalyst (2.5 mol-%), morpholine (2.5 mmol), K_3PO_4 (1.5 mmol), 2-propanol (1.5 mL), N_2, 80 °C, 2 h. [b] Yield from NMR spectroscopy with piperonal as internal standard. [c] Na_3PO_4 was used as a base. [d] K_2CO_3 was used as a base. [e] 1.0 mol-% of $Pd(OAc)_2$ was used. [f] Reaction was carried out in air for 14 h.

Having optimized our reaction conditions, we explored the scope of the morpholine–$Pd(OAc)_2$ catalyst system for the Suzuki–Miyaura coupling of arylboronic acids with aryl tosylates.

The reaction was carried out using $Pd(OAc)_2$ (2.5 mol-%), morpholine (5.0 equiv.), and arylboronic acid (1.2 equiv.). First, we clarified that using less arylboronic acid (1.03 equiv.) gave **9a** in almost the same yield as when 1.2 equiv. of arylboronic acid was used. The coupling reactions proceeded in good yields with electron-rich or electron-withdrawing arylboronic acids to give **9b**–**9n**. However, the only examples of coupled products obtained from *ortho*-substituted arylboronic acids were **9c**, **9g**, and **9j**. A heteroarylboronic acid also coupled with 4-acetylphenyl tosylate to give **9o** in good yield. When electron-rich 4-methoxyphenyl tosylate was tested, the yield of **9p** decreased to 20%. As had been seen with the regioisomeric arylboronic acids, *ortho*- or *meta*-substituted aryl tosylates gave couping products **9q** and **9r** in moderate yields. 2-Naphthyl tosylate and 4-fluorophenyl tosylate gave the desired biaryl compounds (i.e., **9s** and **9t**). 5-(*p*-Tolylsulfonoxy)-1-indanone also coupled in good yield to give **9u**. Biphenyl indanone is an intermediate for the synthesis of pharmacologically

Table 3. Scope and limitations of the morpholine–$Pd(OAc)_2$ catalyst system for the Suzuki–Miyaura coupling of aryl tosylates.[a]

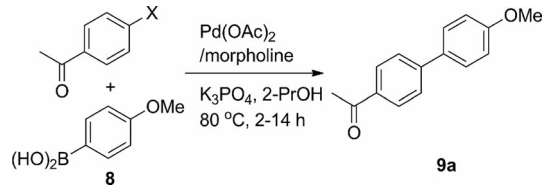


[a] Reaction conditions: aryl tosylate (0.5 mmol), arylboronic acid (0.6 mmol), $Pd(OAc)_2$ (2.5 mol-%), morpholine (2.5 mmol), K_3PO_4 (1.5 mmol), 2-propanol (1.5 mL), N_2, 80 °C, 14 h. [b] Reaction time was 2 h. [c] 1.03 equiv. of arylboronic acid was used. [d] Yield from NMR spectroscopy (piperonal was used as standard). [e] *tert*-Butyl alcohol was used as a solvent.

active compounds, and this coupling method simplifies the preparation of this intermediate.[16] In addition, a heteroaryl tosylate compound was tested in the reaction, and coupled compound **9v** was obtained in moderate yield (Table 3).

Next, we studied the coupling partners of the arylboronic acid. 4-acetylphenyl mesylate was tested, and it reacted to give the product in 56% yield using 5 mol-% of $Pd(OAc)_2$ and *tert*-butyl alcohol as a solvent − 2-propanol gave a poor yield (Table 4, entry 2). The triflate also reacted in to give the product in good yield (Table 4, entry 3). The chloride was also tested, and it gave the product in high yield (Table 4, entry 4). Thus, it is possible to use this new method for the Suzuki–Miyaura coupling reactions of aryl halides.

Table 4. Study of coupling partners for the morpholine–palladium-catalysed Suzuki–Miyaura coupling of arylboronic acids.[a]



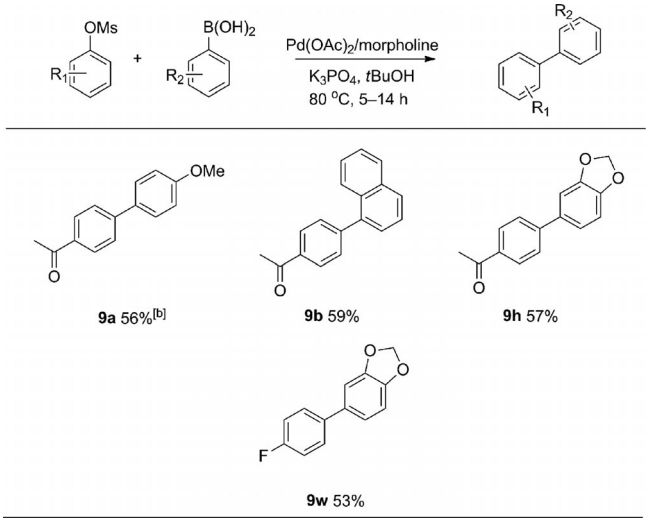
Entry	X	Yield of **9a** [%][b]
1	OTs	92
2	OMs	56[c–e]
3	OTf	80[d,e]
4	Cl	93

[a] Reaction conditions: aryl coupling partner (0.5 mmol), (4-methoxyphenyl)boronic acid (**8**; 0.6 mmol), $Pd(OAc)_2$ (2.5 mol-%), morpholine (2.5 mmol), K_3PO_4 (1.5 mmol), 2-propanol (1.5 mL), N_2, 80 °C, 2 h. [b] Yield from NMR spectroscopy (piperonal was used as standard). [c] *tert*-butyl alcohol was used as a solvent. [d] 5 mol-% of $Pd(OAc)_2$ was used for the reaction. [e] Reaction was carried out for 14 h.

Using our optimized reaction conditions for aryl tosylates, we then tested the reactivity of aryl mesylates. Several coupling reactions using electron-withdrawing aryl mesylates and electron-rich arylboronic acids were conducted. These reactions gave almost the same yields for all examples (Table 5).

To clarify the reaction mechanism, $Pd(OAc)_2$ was treated with morpholine in 2-propanol at 80 °C (Figure 3), and the resulting crystalline **10** was analysed by single-crystal X-ray analysis. We confirmed that the palladium centre was *trans*-coordinated by two acetates and two nitrogen atoms of morpholine to form a morpholine–$Pd(OAc)_2$ catalyst system (Figure 4).[17] We assume that a similar catalyst system (morpholine–$PdCl_2$) was generated when $PdCl_2$ was used in the optimization (Table 2, entry 6).[18] However, when **10** was used instead of $Pd(OAc)_2$ and morpholine, a poor yield was obtained (Table 6, entry 1). The addition of morpholine allows the reaction to proceed (Table 6, entry 2), and no significant difference was observed between this reaction with **10** and a reaction using $Pd(OAc)_2$ (Table 6, entry 3). We assume that the coupling reaction is initiated by the generation of the morpholine–$Pd(OAc)_2$ species (i.e., **10**).

Table 5. Scope and limitations of the morpholine–$Pd(OAc)_2$ catalyst system for the Suzuki–Miyaura coupling of aryl mesylates.[a]



[a] Reaction conditions: aryl mesylate (0.5 mmol), arylboronic acid (0.6 mmol), $Pd(OAc)_2$ (5 mol-%), morpholine (2.5 mmol), K_3PO_4 (1.5 mmol), *tert*-butyl alcohol (1.5 mL), N_2, 80 °C, 14 h. [b] Yield from NMR spectroscopy (piperonal was used as standard).

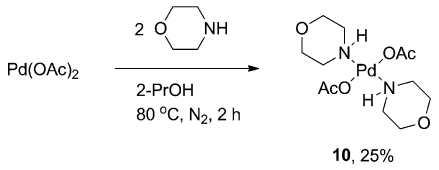


Figure 3. Synthesis of morpholine–$Pd(OAc)_2$ complex **10**.

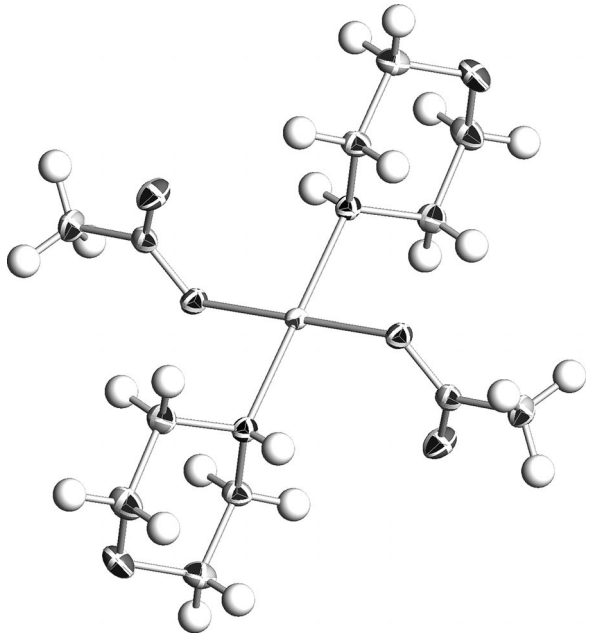
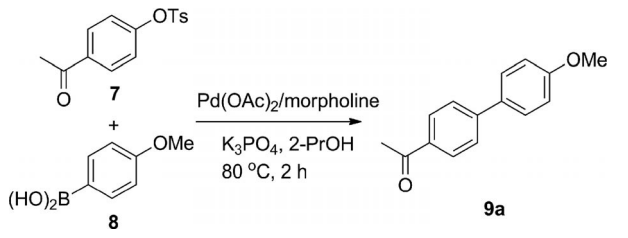


Figure 4. ORTEP drawing of morpholine–$Pd(OAc)_2$ complex **10** [solvent molecules (H_2O) are omitted for clarity.].

Then **10** is transformed into **12** (Figure 5), which acts as the active species. The generation of **11** under the reaction conditions was also considered,[11a] but this was rejected based on the result obtained in the absence of morpholine (Table 6, entry 1). Further studies are needed to clarify the reaction mechanism of the morpholine–$Pd(OAc)_2$ catalyst system.[19]

Table 6. Study of the active species in the morpholine–$Pd(OAc)_2$ catalyst system.[a]



Entry	Catalyst	Morpholine [mol-%]	Yield of **9a** [%][b]
1	**10**	0	7
2	**10**	250	82
3	$Pd(OAc)_2$	250	60

[a] Reaction conditions: 4-acetylphenyl tosylate (**7**; 0.5 mmol), 4-methoxyphenylboronic acid (**8**; 0.6 mmol), Pd catalyst (2.5 mol-%), K_3PO_4 (1.5 mmol), 2-propanol (1.5 mL), N_2, 80 °C, 2 h. [b] Yield from NMR spectroscopy (piperonal was used as standard).

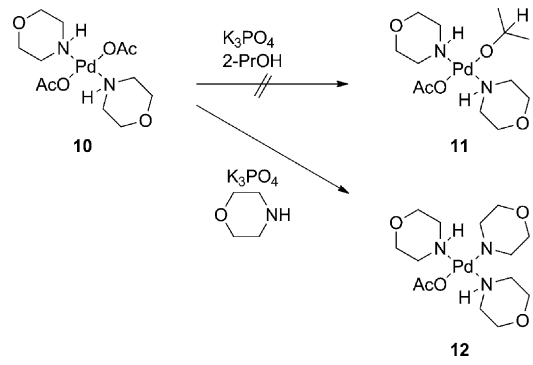


Figure 5. Plausible active species in the morpholine–$Pd(OAc)_2$ catalyst system.

Conclusions

In summary, we have found a new Suzuki–Miyaura coupling procedure using a morpholine–$Pd(OAc)_2$ catalyst system to generate biaryl compounds from aryl tosylates or mesylates. This is the first application of the *trans*-type amine-coordinated palladium catalyst. This easy procedure is useful for large-scale reactions in the laboratory, and it uses only inexpensive reagents. We also successfully achieved coupling reactions using other sulfonates and chloride as coupling partners.

Experimental Section

General Methods: Melting points were recorded with a melting-point apparatus. ^1H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra were recorded at 75, 100, or 150 MHz,

and the solvent peak was used as an internal reference. Electronic impact (EI) mass spectra were recorded with a GC–MS instrument. High-resolution mass spectra (HRMS) were recorded using the electrospray ionization (ESI) method.

General Procedure to Prepare Aryl Tosylates: Acetone (10 mL) was added to a mixture of phenol (1.0 mmol), *p*-toluenesulfonyl chloride (1.05 mmol), and K_2CO_3 (1.1 mmol), and the mixture was stirred at room temperature. After 5–24 h, the reaction mixture was diluted with ethyl acetate and HCl (2 N aq.). The organic layer was separated and washed with brine, then dried with $MgSO_4$, and concentrated under reduced pressure. Hexane was added to the residue, and the resulting suspension was stirred in an ice bath to give the pure solid.

5-(*p*-Tolylsulfonyloxy)-1-indanone (9u): Acetone (7.5 mL) was added to a mixture of 5-hydroxy-1-indanone (10 mmol), K_2CO_3 (11 mmol), and *p*-toluenesulfonylchloride (10.5 mmol), and the mixture was stirred at room temperature for 24 h. The mixture was diluted with ethyl acetate and HCl (2 N aq.). The organic layer was washed with $NaHCO_3$ (aq.) and brine, then dried with $MgSO_4$. The resulting solution was concentrated under reduced pressure to give 5-*p*-toluenesulfonoxy-1-indanone (2.88 g, 9.53 mmol, 95%) as a white solid, m.p. (ethyl acetate): 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.8 Hz, 2 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.34 (d, J = 7.9 Hz, 2 H), 7.25 (s, 1 H), 6.91–6.88 (m, 1 H), 3.12 (t, J = 5.4 Hz, 2 H), 2.73–2.69 (m, 2 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2, 156.9, 154.3, 145.8, 135.6, 132.1, 129.9, 128.4, 125.1, 121.7, 120.6, 36.3, 25.7, 21.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}O_4S$ [M + H]$^+$ 303.0686; found 303.0675.

General Procedure for the Palladium–Morpholine-Catalysed Suzuki Coupling of Aryl Tosylates with Arylboronic Acids: 2-Propanol (1.5 mL) and morpholine (2.5 mmol) were added to a mixture of Aryl tosylate (0.5 mmol), K_3PO_4 (1.5 mmol), $Pd(OAc)_2$ (12.5 μmol), and arylboronic acid (0.6 mmol). The mixture was stirred at 80 °C under a nitrogen atmosphere. After 2–14 h, the mixture was diluted with ethyl acetate and HCl (2 N aq.; H_2O was used for compounds **9k**, **9l**, **9o**, and **9v**). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate. The combined organic extracts were washed with brine, then dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate).

1-(4′-Methoxylbiphenyl-4-yl)ethanone (9a):[20] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 2 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 25:1) gave compound **9a** (99.6 mg, 0.440 mmol, 88%) as a white solid, m.p. (hexane/ethyl acetate): 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 3.87 (s, 3 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 159.9, 145.3, 135.2, 132.2, 128.9, 128.3, 126.5, 114.3, 55.3, 26.6 ppm. MS (EI): m/z = 226 [M]$^+$.

2-(4′-Ethanoylphenyl)naphthalene (9b):[21] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (1-naphthyl)boronic acid (0.60 mmol), after 2 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9b** (92.4 mg, 0.375 mmol, 75%) as a white solid, m.p. (hexane/ethyl acetate): 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.3 Hz, 2 H), 7.96–7.89 (m, 2 H), 7.86 (d, J = 9.0 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 2 H), 7.58–7.50 (m, 2 H), 7.50–7.42 (m, 2 H), 2.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 145.8, 139.0, 136.0, 133.8, 131.2, 130.3, 128.4, 128.34, 128.32, 126.9, 126.4, 126.0, 125.5, 125.3, 26.7 ppm. MS (EI): m/z = 246 [M]$^+$.

1-(2′-Methylbiphenyl-4-yl)ethanone (9c):[22] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (2-methylphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9c** (57.2 mg, 0.272 mmol, 54%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.2 Hz, 2 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.30–7.19 (m, 4 H), 2.63 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 146.9, 140.7, 135.5, 135.1, 130.5, 129.44, 129.41, 128.2, 127.9, 125.9, 26.6, 20.4 ppm. MS (EI): m/z = 210 [M]$^+$.

1-(3′-Methylbiphenyl-4-yl)ethanone (9d):[23] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (3-methylphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9d** (95.0 mg, 0.452 mmol, 90%) as a white solid, m.p. (hexane/ethyl acetate): 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.3 Hz, 2 H), 7.69 (d, J = 8.5 Hz, 2 H), 7.44 (d, J = 8.5 Hz, 2 H), 7.38 (t, J = 7.8 Hz, 1 H), 7.24 (d, J = 7.6 Hz, 1 H), 2.65 (s, 3 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 145.9, 139.8, 138.5, 135.7, 128.9, 128.8 (×2), 128.0, 127.2, 124.3, 26.6, 21.5. MS (EI): m/z = 210 [M]$^+$.

1-(4′-Methylbiphenyl-4-yl)ethanone (9e):[24] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (4-methylphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9e** (91.7 mg, 0.436 mmol, 87%) as a white solid, m.p. (hexane/ethyl acetate): 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.9 Hz, 2 H), 7.68 (d, J = 9.3 Hz, 2 H), 7.55 (d, J = 7.1 Hz, 2 H), 7.29 (d, J = 7.7 Hz, 2 H), 2.64 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 145.6, 138.2, 136.9, 135.5, 129.6, 128.8, 127.0, 126.9, 26.6, 21.1 ppm. MS (EI): m/z = 210 [M]$^+$.

1-(Biphenyl-4-yl)ethanone (9f):[25] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and phenylboronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9f** (78.7 mg, 0.401 mmol, 80%) as a white solid, m.p. (hexane/ethyl acetate): 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.3 Hz, 2 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.64 (d, J = 7.1 Hz, 2 H), 7.49 (t, J = 7.3 Hz, 2 H), 7.40 (t, J = 7.1 Hz, 1 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 145.8, 139.9, 135.8, 128.92, 128.88, 128.2, 127.24, 127.19, 26.6 ppm. MS (EI): m/z = 196 [M]$^+$.

1-(2′,4′-Dimethoxylbiphenyl-4-yl)ethanone (9g): Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and 2,4-methoxyphenylboronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9g** (75.4 mg, 0.294 mmol, 59%) as a white solid, m.p. (hexane/ethyl acetate): 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.5 Hz, 2 H), 7.62 (d, J = 8.5 Hz, 2 H), 7.28 (d, J = 8.3 Hz, 1 H), 6.62–6.57 (m, 2 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 160.9, 157.5, 143.4, 134.9, 131.2, 129.4, 128.0, 122.1, 104.8, 98.9, 55.4, 55.3, 26.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}O_3Na$ [M + Na]$^+$ 279.0992; found 279.0987.

1-[3′,4′-(Methylenedioxy)biphenyl-4-yl]ethanone (9h):[26] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (3,4-methylendioxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9h** (118.2 mg, 0.492 mmol, 98%) as a white solid, m.p. (hexane/ethyl acetate): 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 8.01 (d, J = 8.3 Hz, 2 H), 7.62 (d, J = 8.5 Hz, 2 H), 7.15–7.11 (m, 2 H), 6.92 (d, J = 7.6 Hz, 1 H), 6.04 (s, 2 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 148.3, 147.9, 145.4, 135.4, 134.0, 128.9, 126.8, 121.0, 108.7, 107.5, 101.3, 26.6 ppm. MS (EI): m/z = 240 $[M]^+$.

1-(4′-*tert*-Butylbiphenyl-4-yl)ethanone (Table 3, **9i**)**:** Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (4-*tert*-butylphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9i** (96.5 mg, 0.382 mmol, 77%) as as a white solid, m.p. (hexane/ethyl acetate): 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.1 Hz, 2 H), 7.71 (d, J = 8.1 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.52 (d, J = 7.6 Hz, 2 H), 2.65 (s, 3 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 151.4, 145.5, 136.8, 135.5, 128.9, 126.92, 126.86, 125.9, 34.6, 31.3, 26.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}O$ $[M + H]^+$ 253.1587; found 253.1580.

1-[4′-(*N*-*tert*-Butylcarbamate)biphenyl-4-yl]ethanone (9k): Following the general procedure, using the 4-acetylphenyl tosylate (0.50 mmol) and [4-(*N*-*tert*-butylcarbamate)phenyl]boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 5:1) gave compound **9k** (115.4 mg, 0.371 mmol, 74%) as a white solid, m.p. (hexane/ethyl acetate): 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.8 Hz, 2 H), 7.66 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.5 Hz, 2 H), 7.47 (d, J = 8.3 Hz, 2 H), 6.63 (br. s, 1 H), 2.64 (s, 3 H), 1.55 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.8, 152.6, 145.2, 138.6, 135.5, 134.3, 128.9, 127.8, 126.7, 118.8, 80.8, 28.3, 26.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}O_3NNa$ $[M + Na]^+$ 334.1414; found 334.1407.

1-[3′-(*N*-*tert*-Butylcarbamate)biphenyl-4-yl]ethanone (9l): Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and [3-(*N*-*tert*-butylcarbamate)phenyl]boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9l** (113.2 mg, 0.364 mmol, 73%) as a white solid, m.p. (hexane/ethyl acetate): 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.9 Hz, 2 H), 7.75 (s, 1 H), 7.69 (d, J = 8.3 Hz, 2 H), 7.39 (t, J = 7.1 Hz, 1 H), 7.36–7.28 (m, 2 H), 6.63 (br. s, 1 H), 2.65 (s, 3 H), 1.54 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.9, 152.8, 145.5, 140.8, 139.1, 136.0, 129.5, 128.9, 127.3, 121.9, 118.3, 117.3, 80.7, 28.4, 26.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}O_3NNa$ $[M + Na]^+$ 334.1414; found 334.1404.

1-(4′-Fluorobiphenyl-4-yl)ethanone (9m):[27] Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (3-fluorophenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane, then *n*-hexane/ethyl acetate, 20:1, then 10:1) gave compound **9m** (88.0 mg, 0.411 mmol, 82%) as a white solid, m.p. (hexane/ethyl acetate): 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.1 Hz, 2 H), 7.58–7.67 (m, 4 H), 7.17 (t, J = 8.1 Hz, 2 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 162.9 (d, $J_{C,F}$ = 248.0 Hz), 144.6, 135.9 (d, $J_{C,F}$ = 4.1 Hz), 135.8, 128.91, 128.86 (d, $J_{C,F}$ = 8.3 Hz), 127.0, 115.8 (d, $J_{C,F}$ = 21.6 Hz), 26.6 ppm. MS (EI): m/z = 214 $[M]^+$.

1-(3′,4′-Difluorobiphenyl-4-yl)ethanone (9n): Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol) and (3,4-fluorophenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 20:1, then 10:1) gave compound **9n** (96.3 mg, 0.415 mmol, 83%) as a white solid, m.p. (hexane/ethyl acetate): 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 6.3 Hz, 2 H), 7.60 (d, J = 6.8 Hz, 2 H), 7.45–7.37 (m, 1 H), 7.37–7.30 (m, 1 H), 7.30–7.19 (m, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.6, 151.4 (dd, $J_{C,F}$ = 13.5, 18.8 Hz), 149.7 (dd, $J_{C,F}$ = 13.5, and 19.5 Hz), 143.6, 137.0 (dd, $J_{C,F}$ = 4.5 and 6.8 Hz), 136.3, 129.1, 127.1, 123.3 (dd, $J_{C,F}$ = 3.0 and 6.0 Hz), 117.8 (d, $J_{C,F}$ = 16.5 Hz), 116.3 (d, $J_{C,F}$ = 16.5 Hz), 26.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}OF_2$ $[M + H]^+$ 233.0772; found 233.0775.

5-(4-Acetylphenyl)-2-methoxypyridine (9o): Following the general procedure, using 4-acetylphenyl tosylate (0.50 mmol), 2-methoxy-5-pyridineboronic acid (0.60 mmol), and *tert*-butyl alcohol as a solvent, after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 7.5:1) gave compound **9o** (87.0 mg, 0.383 mmol, 77%) as a white solid, m.p. (hexane/ethyl acetate): 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, J = 2.0 Hz, 1 H), 8.04 (d, J = 8.8 Hz, 2 H), 7.83 (dd, J = 2.6, 8.7 Hz, 1 H), 7.63 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.1 Hz, 1 H), 4.00 (s, 3 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 164.2, 145.3, 142.5, 137.3, 135.8, 129.1, 128.7, 126.6, 111.1, 53.7, 26.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}NO_2$ $[M + H]^+$ 228.1019; found 228.1017.

1-Methoxy(4′-*tert*-butylphenyl-4-yl)benzene (9p):[20] Following the general procedure, using 4-methoxyphenyl tosylate (0.50 mmol) and (4-*tert*-butylphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 25:1, then 10:1) gave compound **9p** (24.3 mg, 0.101 mmol, 20%) as a white solid, m.p. (hexane/ethyl acetate): 136–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.50 (m, 4 H), 7.50–7.45 (m, 2 H), 7.00 (d, J = 9.0 Hz, 2 H), 3.87 (s, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 149.6, 137.9, 133.6, 128.0, 126.4, 125.6, 114.1, 55.3, 34.5, 31.4 ppm. MS (EI): m/z = 240 $[M]^+$.

1-(4′-Methoxybiphenyl-2-yl)ethanone (9q):[28] Following the general procedure, using 2-acetylphenyl tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9q** (61.1 mg, 0.270 mmol, 54%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 1 H), 7.49–7.46 (m, 1 H), 7.39–7.36 (m, 2 H), 7.26 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2, 159.5, 140.9, 140.1, 133.0, 130.6, 130.1, 129.9, 127.7, 127.0, 114.1, 55.3, 30.4 ppm. MS (EI): m/z = 226 $[M]^+$.

1-(4′-Methoxybiphenyl-3-yl)ethanone (9r):[29] Following the general procedure, using 3-acetylphenyl tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9r** (66.6 mg, 0.294 mmol, 59%) as a white solid, m.p. (hexane/ethyl acetate): 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.75 (d, J = 7.3 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.01 (d, J = 8.5 Hz, 2 H), 3.88 (s, 3 H), 2.67 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 159.5, 141.2, 137.6, 132.6, 131.2, 128.9, 128.2, 126.5, 126.4, 114.3, 55.3, 26.7 ppm. MS (EI): m/z = 226 $[M]^+$.

2-(4′-Methoxyphenyl)naphthalene (9s):[30] Following the general procedure, using 2-naphthyl tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 15:1) gave compound **9s** (97.6 mg, 0.417 mmol, 83%) as a white solid, m.p. (hexane/ethyl acetate): 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.96–7.88 (m, 3 H), 7.77 (d, J = 8.5 Hz, 1 H), 7.71 (d, J = 8.8 Hz, 2 H), 7.57–7.48 (m, 2 H), 7.07 (d, J = 9.0 Hz, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 138.1, 133.7, 133.6, 132.3, 128.4, 128.3, 128.0, 127.6, 126.2, 125.6, 125.4, 125.0, 114.3, 55.3 ppm. MS (EI): m/z = 234 $[M]^+$.

1-Fluoro(4′-methoxyphenyl-4-yl)benzene (9t):[31] Following the general procedure, using 4-fluorophenyl tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 20:1) gave compound **9t**

(53.0 mg, 0.262 mmol, 52%) as a white solid, m.p. (hexane/ethyl acetate): 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 4 H), 7.16–7.09 (m, 2 H), 7.02–6.97 (m, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1 (d, $J_{C,F}$ = 245.5 Hz), 159.1, 136.9 (d, $J_{C,F}$ = 3.3 Hz), 132.8, 128.2 (d, $J_{C,F}$ = 8.3 Hz), 128.0, 115.5 (d, $J_{C,F}$ = 20.7 Hz), 114.2, 55.3 ppm. MS (EI): *m*/*z* = 202 $[M]^+$.

5-(4-Methoxyphenyl)-2,3-dihydroindene-1-one (9u):[16a] Following the general procedure, using 5-(*p*-tolylsulfonoxy)-1-indanone (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 10:1) gave compound **9u** (84.6 mg, 0.355 mmol, 71%) as a white solid, m.p. (hexane/ethyl acetate): 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 1 H), 7.63 (s, 1 H), 7.62–7.53 (m, 3 H), 7.01 (d, *J* = 7.9 Hz, 2 H), 3.87 (s, 3 H), 3.18 (t, *J* = 6.3 Hz, 2 H), 2.76–2.70 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.5, 160.0, 155.9, 147.2, 135.4, 132.5, 128.6, 126.2, 124.4, 124.0, 114.4, 55.4, 36.5, 25.8 ppm. MS (EI): *m*/*z* = 238 $[M]^+$.

6-(4-Methoxyphenyl)quinoline (9v):[32] Following the general procedure, using 6-quinoline tosylate (0.50 mmol) and (4-methoxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane/ethyl acetate, 5:1, then *n*-hexane/ethyl acetate, 3:1) gave compound **9v** (72.2 mg, 0.307 mmol, 61%) as a white solid, m.p. (hexane/ethyl acetate): 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (dd, *J* = 1.7, 4.1 Hz, 1 H), 8.24–8.15 (m, 2 H), 7.99–7.91 (m, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.43–7.37 (m, 1 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 149.8, 147.1, 138.9, 136.3, 132.6, 129.5, 129.1, 128.5, 128.4, 124.5, 121.3, 114.4, 55.3 ppm. MS (EI): *m*/*z* = 235 $[M]^+$.

General Procedure for the Study of Coupling Partners for Morpholine–Palladium-Catalysed Suzuki–Miyaura Coupling of Arylboronic Acids: 2-Propanol (1.5 mL) and morpholine (2.5 mmol) were added to a mixture of aryl coupling partner (0.5 mmol), K_3PO_4 (1.5 mmol), $Pd(OAc)_2$ (12.5 μmol), and arylboronic acid (0.6 mmol). The mixture was stirred at 80 °C under a nitrogen atmosphere. After 2 h, the mixture was diluted with ethyl acetate and HCl (2 N aq.). The organic layer was separated, and aqueous layer was re-extracted with ethyl acetate. The combined organic extracts were washed with brine, then dried with $MgSO_4$, and concentrated under reduced pressure. The yield was calculated from the NMR spectrum using piperonal as an internal standard.

General Procedure for Palladium–Morpholine-Catalysed Suzuki Coupling of Aryl Mesylates with Arylboronic Acids: *tert*-Butyl alcohol (1.5 mL) and morpholine (2.5 mmol) were added to a mixture of aryl mesylate (0.5 mmol), K_3PO_4 (1.5 mmol), $Pd(OAc)_2$ (25.0 μmol), and arylboronic acid (0.6 mmol). The mixture was stirred at 80 °C under a nitrogen atmosphere. After 14 h, the mixture was diluted with ethyl acetate and HCl (2 N aq.). The organic layer was separated, and aqueous layer was re-extracted with ethyl acetate. The combined organic extracts were washed with brine, then dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate).

1-Fluoro-[3′,4′-(methylenedioxy)phenyl-4-yl]benzene (9w):[33] Following the general procedure, using 4-fluorophenyl mesylate (0.50 mmol) and (3,4-methylendioxyphenyl)boronic acid (0.60 mmol), after 14 h at 80 °C, flash chromatography (*n*-hexane, then *n*-hexane/ethyl acetate, 10:1) gave compound **9w** (57.5 mg, 0.266 mmol, 53%) as a white solid, m.p. (hexane/ethyl acetate): 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 2 H), 7.13–7.08 (m, 2 H), 7.02–7.00 (m, 2 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 6.01 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (d, $J_{C,F}$ = 245.5 Hz), 148.1, 147.0, 137.1 (d, $J_{C,F}$ = 3.3 Hz), 134.6, 128.4 (d, $J_{C,F}$ = 8.3 Hz), 120.5, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 108.6, 107.6, 101.2 ppm. MS (EI): *m*/*z* = 216 $[M]^+$.

Synthesis of Morpholine-$Pd(OAc)_2$ Complex 10:[17] 2-Propanol (10 mL) was added to a mixture of $Pd(OAc)_2$ (1.0 mmol) and morpholine (2.0 mmol), and the mixture was heated to 80 °C for 2 h under a nitrogen atmosphere. Then the reaction mixture was allowed to stand for 13 d, and the resulting crystalline solid was collected by filtration to give compound **10** (107.0 mg, 0.246 mmol, 25%) as yellow crystals, m.p. (2-propanol): 140–142 °C (decomposed). ^{1}H NMR (300 MHz, DMSO): δ = 5.60–5.53 (m, 2 H), 3.58–3.38 (m, 8 H), 2.79–2.64 (m, 8 H), 1.82 (s, 6 H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 177.7, 65.9, 48.6, 24.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{25}O_6N_2Pd$ $[M + H]^+$ 399.0742; found 399.0734.

Supporting Information (see footnote on the first page of this article): Characterization data and copies of the NMR spectra of the products.

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