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Rhodium Catalyzed Arylation of Diazo Compounds with Aryl Boronic Acids

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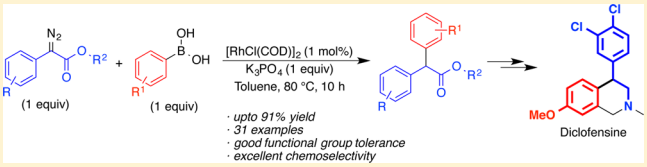
Supporting Information

ABSTRACT: A general and efficient synthesis of diarylacetate, a diarylmethine derivative, was accomplished through rhodium catalyzed direct arylation of diazo compounds with arylboronic acids. The reaction tolerates various boronic acid derivatives and functional groups. Notably, chemoselective arylation of diazo compounds over other electrophiles were demonstrated. The efficacy of the developed methodology is shown by the expeditious synthesis of the core structure of diclofensine.



INTRODUCTION

Diarylmethines are ubiquitous subunits found in a wide range of natural products and therapeutically important molecules, such as cherylline and diclofensine (Figure 1).[1] These molecules were shown to have potent bioactivity such as antiviral, antirheumatic, antitumor, and central nervous system activity as well as be an inhibitor of serotonin dopamine uptake.[2] Due to these potential benefits, the synthesis of diarylmethine derivatives, particularly, (di)arylacetic acid derivatives, the most obvious synthetic equivalent, is the topic of interest to many synthetic chemists over the past few decades.[3]

Typical syntheses of arylacetic acid derivatives from simple aromatic compounds suffer from the use of toxic reagents, harsh reaction conditions, and a multistep sequence.[4] These traditional methods were subsequently replaced by a transition metal (Pd or Ni) catalyzed direct arylation of either acetic acid derivatives or α-halo acetic acid derivatives (Scheme 1a).[5] However, these transformations suffer from limited functional group tolerance and a substrate scope due to the need for a strong base; additionally, most of these strategies are mainly focused on the synthesis of arylacetic acid derivatives.

Most recently, an alternative synthesis of diarylacetates was accomplished from diazo carbonyl compounds and an ester of arylboronic acids employing strong base[6] or expensive CF_3TMS[7] as an additive (Scheme 1b). Instead of protonation as a termination step, tandem alkylation was also achieved with benzyl halide and KO^{t}Bu to afford the α,α-diaryl carboxylic esters.[8] Thus, development of an alternative and general strategy for the synthesis of diarylacetic acid derivatives employing simple arylboronic acid is highly warranted.[9] Inspired by the recent development in the transition metal catalyzed cross-coupling of diazo compounds[10] with organoboron reagents[11] and our interest in the functionalization of diazo compounds,[12] we herein disclose the rhodium-catalyzed synthesis of diarylacetic acid derivatives through direct arylation of diazocarbonyl compounds with readily accessible arylboronic acids under mild conditions (Scheme 1c).

RESULTS AND DISCUSSION

To test our hypothesis, we chose the direct arylation of diazo compound **1a** with phenylboronic acid **2a** as model reaction. Initial study on the reaction of **1a** (1 equiv) and **2a** (1 equiv) in the presence of metal catalysts (in toluene at 80 °C) led to the rapid decomposition of diazo compound **1a**. To avoid the decomposition, a solution of **1a** was introduced slowly through a syringe pump over the period of 30 min; to our delight we observed the formation of expected product **3aa**. A screening of various metal catalysts, such as palladium and rhodium, revealed that a rhodium based catalyst is superior to the palladium based catalyst and afforded the product in 31% yield (Table 1, entry 1 and see Supporting Information).

Interestingly, introduction of 1 equiv of additive, K_3PO_4, to promote the transmetalation gave the product **3aa** in 91% isolated yield (Table 1, entry 3). In the absence of a rhodium catalyst (with or without additive) the expected reaction did not occur, which proves that the present reaction is indeed catalyzed by a rhodium catalyst (Table 1, entries 2 and 4). Next, we examined the other critical parameters such as the additive, solvent, and temperature. A noticeable decrease in the yield of the isolated product **3aa** was observed, when the reaction temperature was reduced to 70 °C as well as with 0.5 equiv of additive (Table 1, entries 5 and 8). Furthermore, changing the additive, solvent, or metal catalyst did not afford the expected product in comparable yield (Table 1, entries 6−12). From these studies, we chose the following optimized conditions for investigating the generality of the methodology: Diazo compound (1 equiv), arylboronic acid (1 equiv), $[RhCl(COD)]_2$ (1 mol %), K_3PO_4 (1 equiv), toluene, 80 °C, 10 h.

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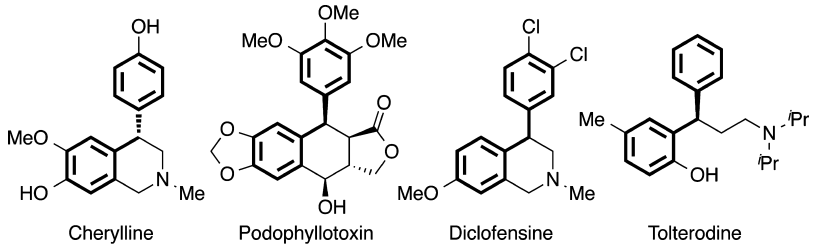


Figure 1. Representative examples of diarylmethine containing therapeutically important molecules.

Scheme 1. Synthesis of Diarylacetic Acid Derivatives

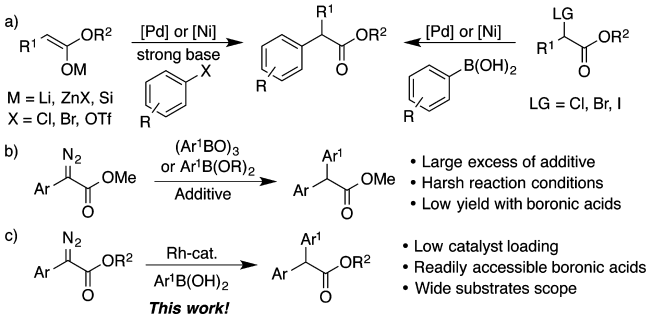
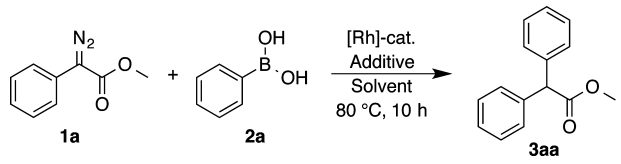


Table 1. Rhodium Catalyzed Arylation of Diazo Compounds: Optimization[a]

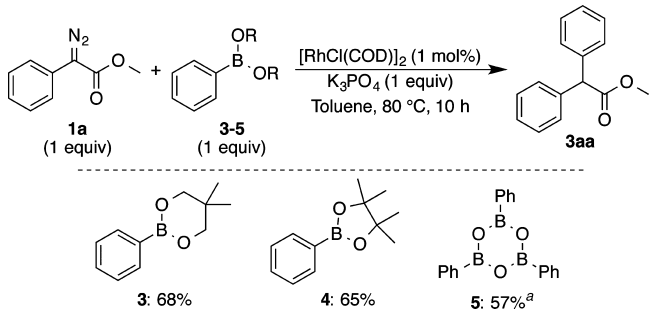


entry	[Rh]-cat.	additive	solvent	yield (%)[b]
1	$[RhCl(COD)]_2$	–	toluene	31
2	–	–	toluene	0
3	$[RhCl(COD)]_2$	K_3PO_4	toluene	91
4	–	K_3PO_4	toluene	0
5[c]	$[RhCl(COD)]_2$	K_3PO_4	toluene	60
6	$Rh_2(OAc)_4$	K_3PO_4	toluene	18
7	$[Cp^*RhCl_2]_2$	K_3PO_4	toluene	33
8[d]	$[RhCl(COD)]_2$	K_3PO_4	toluene	55
9	$[RhCl(COD)]_2$	K_2CO_3	toluene	38
10[e]	$[RhCl(COD)]_2$	CsF	toluene	29
11	$[RhCl(COD)]_2$	K_3PO_4	1,4-dioxane	14
12	$[RhCl(COD)]_2$	K_3PO_4	DCE	37

[a]Reaction conditions: Diazo compound **1a** (0.28 mmol, 1 equiv), phenylboronic acid **2a** (0.28 mmol, 1 equiv), Rh-cat. (1 mol %), additive (0.28 mmol, 1 equiv), 80 °C, 10 h. [b]All are isolated yield. [c]70 °C. [d]0.14 mmol of K_3PO_4 is used. [e]7 h.

After identifying the best reaction conditions for direct arylation of diazo compounds with phenylboronic acid, we subjected other phenylboron reagents under the optimized conditions to demonstrate the generality of the present method. As can be seen in Scheme 2, reaction of diazo compound **1a** with neopentylglycol and pinacol ester of phenylboronic acid (**3** and **4**) in the presence of a rhodium catalyst afforded the expected arylated product **3aa** in 68% and 65% yield, respectively. Interestingly, use of triphenylboroxin **5** also furnished the product **3aa** in comparable yield, with only 0.66 equiv of **5**. Although all the boron reagents examined gave

Scheme 2. Rhodium Catalyzed Arylation of 1a with Various Phenylboron Reagents (3−5)

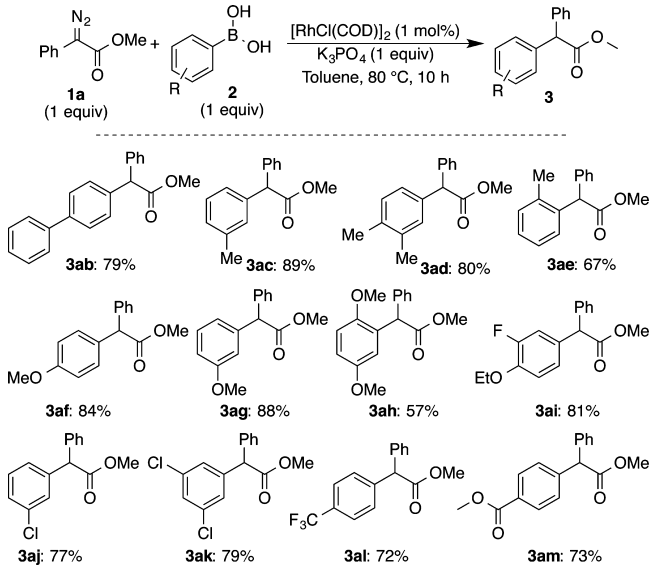


[a]0.66 equiv of triphenylboroxin.

the product **3aa** in good to moderate yield, arylboronic acid was found to be superior.

Subsequently, we investigated the scope and limitation of substituted arylboronic acid (Scheme 3). Simple aryl and alkyl

Scheme 3. Rhodium Catalyzed Synthesis of Diarylacetic Acid Derivatives 3: Scope and Limitation of Arylboronic Acids



substituted diarylacetic acid derivatives (**3ab**, **3ac**, and **3ad**) were achieved in excellent yield from corresponding arylboronic acids. It is important to note that both electron-donating and -withdrawing substitution containing arylboronic acids gave the corresponding diarylacetic acid derivatives (**3af**, **3ag**, and **3am**) in very good yield. Sterically hindered *ortho* substituted arylboronic acids (*o*-methyl and *o*-methoxy arylboronic acids) gave the corresponding arylated products (**3ae** and **3ah**) in

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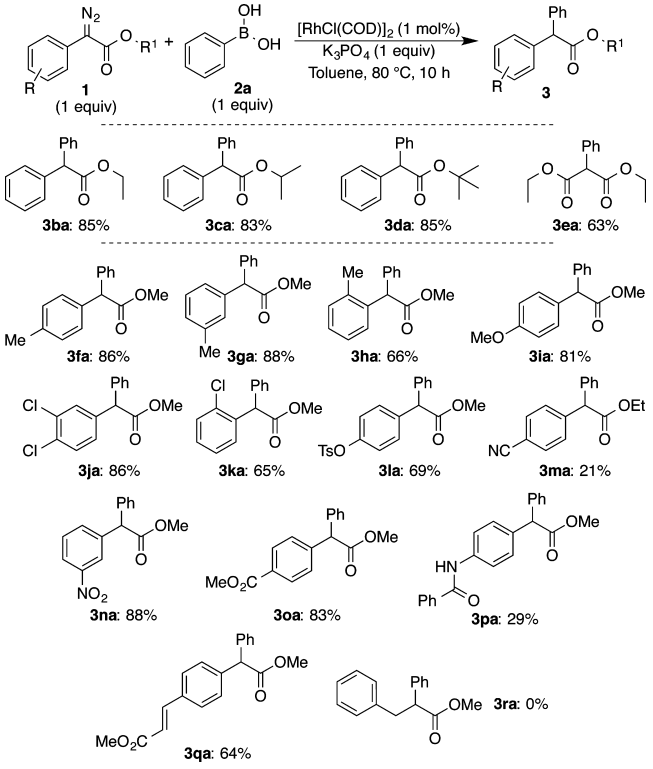
moderate yield. Arylation using the chlorinated arylboronic acids afforded the synthetically useful and readily modifiable chlorinated diarylacetic acid derivatives **3aj** and **3ak** in 77% and 79% yield, respectively. Furthermore, medicinally important fluorinated and trifluoromethylated diarylacetic acid derivatives (**3ai** and **3al**) were readily accessible under the present methodology.

Having demonstrated the generality of substituted arylboronic acids; next, we moved on to study the scope and limitation of substituted diazo compounds (Scheme 4). Gratifyingly,

Scheme 4. Rhodium Catalyzed Synthesis of Diarylacetic Acid Derivatives 3: Scope and Limitation of Diazo Compounds

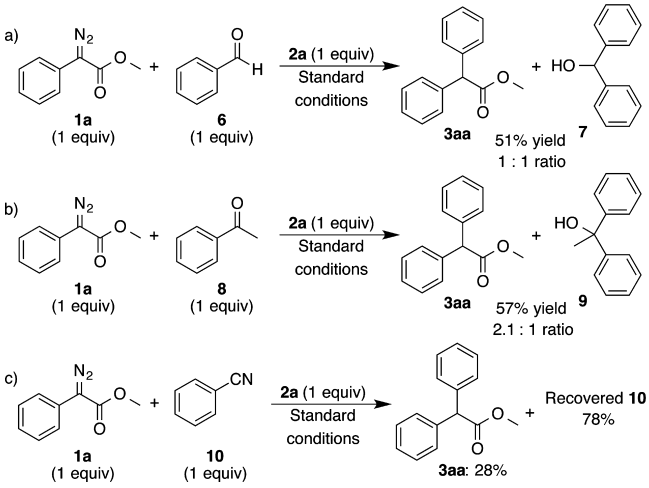


changing the bulkiness of the ester group from methyl to ethyl, isopropyl, and *tert*-butyl were tolerated in the present conditions and furnished the corresponding diarylacetic acid derivatives (**3ba**, **3ca**, and **3da**) in excellent yield. Next, arylation of simple alkyl, chloro, and electron-donating methoxy group substituted diazo compounds also furnished the corresponding arylated product in comparable yield. Sterically demanding aryl-containing diazo compounds gave the arylated products **3ha** and **3ka** in only moderate yield.

Interestingly, the present methodology also tolerates various functional groups, such as tosyloxy, nitro, and ester, and led to the formation of corresponding products (**3la**, **3na**, and **3oa**) in 69%, 88%, and 83% yield, respectively. Reaction of strongly chelating cyano and secondary amide substituted diazo compounds afforded the arylated products (**3ma** and **3pa**) in low yield. In addition to the arylation of diazo compounds derived from arylacetic acids, we also examined the rhodium-catalyzed arylation of the diazo compound derived from malonic acid diester, which led the formation of arylated product **3ea** in 63% yield. However, replacing the aryl moiety in diazo compounds with a benzyl group ($PhCH_2$), derived from methyl phenylpropionate, did not afford the expected product **3ra**. Furthermore, to understand the chemoselectivity of the present reaction, we examine the arylation of a diazo compound containing an α,β-unsaturated ester group[13] that is reactive under the present conditions. Remarkably, exclusive formation of diazo carbon arylated product **3qa** was observed in 64% yield (Scheme 4).

Next, we were interested in extending the methodology to other electrophiles,[14] such as aldehyde, ketone, and nitrile (Scheme 5). Reaction of an equimolar mixture of diazo

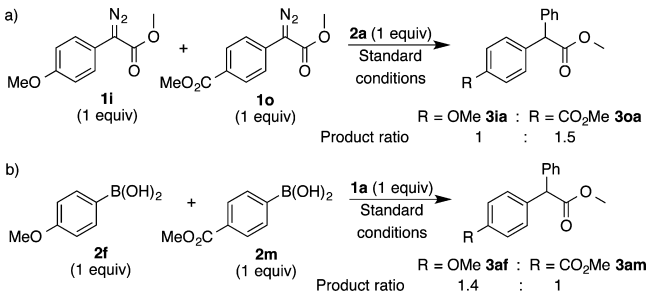
Scheme 5. Chemoselectivity in Rhodium Catalyzed Arylation of 1a with 2a



compound **1a** and nitrile **10** with phenylboronic acid **2a** afforded the exclusive formation of arylated product **3aa** along with the 78% recovery of nitrile **10** (Scheme 5c). However, the reaction of an equimolar mixture of **1a** and ketone **8** (or aldehyde **6**) with **2a** furnished the mixture of arylated product **3aa** and **9** (or **7**) with a 2.1:1 (or 1:1) ratio favoring the arylation of diazo compound (Scheme 5b and 5a). Thus, the present rhodium catalyzed arylation conditions are highly selective toward the diazo compounds compared to an α,β-unsaturated ester, nitrile, and ketone.

Subsequently, effect of substituents on the phenyl ring of diazo compounds and arylboronic acids was also examined. Arylation of an equimolar mixture of methoxy- and methoxycarbonyl-substituted diazo compounds, **1i** and **1o**, respectively, with phenylboronic acid gave the mixture of **3ia** and **3oa** in a 1:1.5 ratio (Scheme 6a). In contrast, arylated products **3af** and **3am** were isolated in a 1.4:1 ratio from the rhodium catalyzed reaction of methoxy and methoxycarbonyl

Scheme 6. Rhodium Catalyzed Direct Arylation: Effect of the Substituents



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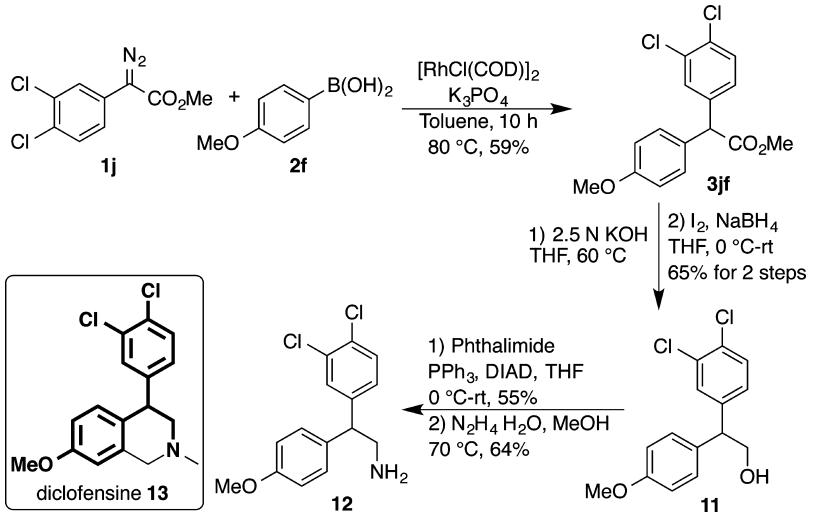
Scheme 7. Synthesis of Core Structure of Diclofensine 13

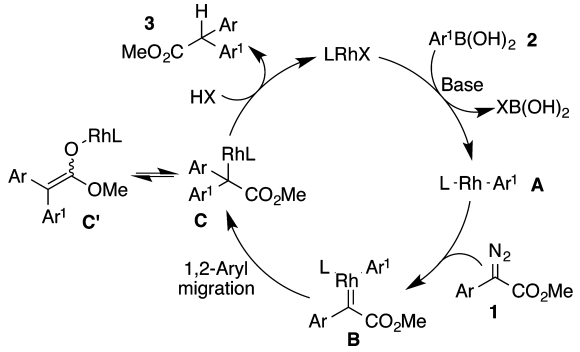


substituted arylboronic acids, **2f** and **2m**, respectively, with diazo compound **1a** (Scheme 6b). The ratio of the product revealed that the presence of an electron-withdrawing group (methoxycarbonyl) in the diazo compounds **1** and an electron-donating group in the arylboronic acid **2** slightly favors the arylation over the corresponding counterpart. Thus, the present methodology complements the base mediated arylation reaction (Scheme 1b), where the electron-withdrawing arylboronic acids gave moderately high reactivity.

Next, we envisaged the synthesis of amine **12**, the core structure present in the diclofensine **13**, to demonstrate the efficiency and applicability of the present methodology in organic synthesis (Scheme 7). Diclofensine is a stimulant drug having a 4-aryltetrahydroisoquinoline framework and shown to have both antidepressant and monoamine reuptake inhibitor activity.[15] Synthesis began with the rhodium-catalyzed arylation of diazo compound **1j** with *p*-anisylboronic acid **2f** under the optimized conditions to lead to the formation of **3jf** in 59% yield (Scheme 7). Hydrolysis of the ester followed by reduction with the combination of sodium borohydride and iodine gave the alcohol **11** in 65% yield in two steps. Finally, the key intermediate amine **12** was achieved from alcohol **11** through a Mitsunobu reaction with phthalimide followed by hydrolysis with hydrazine hydrate. Thus, the present method could be readily integrated in the synthesis of various diarylmethine containing natural products.

On the basis of a previous report on the rhodium-catalyzed arylation of various electrophiles[14,16] and from the present studies, we postulate the following mechanism for the rhodium-catalyzed arylation of diazo compounds (Scheme 8). The catalytic reaction began with the generation of reactive arylrhodium(I) species **A** from a rhodium precursor and **2**, through base assisted transmetalation of the aryl group. Reaction of **A** with diazo compounds **1** furnished the rhodium species **B** with extrusion of nitrogen. 1,2-Aryl migration in rhodium species **B** could result in rhodium complex **C**, which might exist in equilibrium with its tautomer **C′**. Finally, proto-demetalation of rhodium species **C** could afford the arylated product **3** along with the active rhodium species to complete the catalytic cycle.

Scheme 8. Plausible Mechanism



CONCLUSION

We accomplished a general and direct rhodium catalyzed arylation of diazo carbonyl compounds with arylboronic acids. The present strategy allows the synthesis of various diarylacetic acid derivatives in good to excellent yields under operationally simple and mild reaction conditions. Importantly, the optimized conditions tolerate various functional groups such as nitro, amide, ester, nitrile, trifluoromethyl, etc. In addition, excellent chemoselectivity was observed for arylation of diazo compounds over an α,β-unsaturated ester, nitrile, and ketone. Study on the effect of substitution disclosed the better reactivity of electron-rich arylboronic acids and electron-deficient diazo compounds, which is complementary to the base mediated arylation of diazo compound. Furthermore, the potential of the developed methodology was demonstrated by the synthesis of the core structure of an antidepressant agent, diclofensine.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Substituted Diarylacetic Acid 3 from Diazo Compounds 1 and Arylboronic Acids 2. In a dry reaction tube, arylboronic acid **2** (0.28 mmol, 1 equiv), K_3PO_4 (59 mg, 0.28 mmol, 1 equiv), Rh catalyst (1.38 mg, 1 mol %), and dry toluene (0.5 mL) were added under a nitrogen atmosphere, and the reaction tube was sealed with a septum and kept in a preheated oil bath at 80 °C. Diazo compound **1a** (50 mg, 0.28 mmol, 1 equiv) was dissolved in 0.5 mL of dry toluene and slowly added to the reaction mixture over a period of 0.5 h and stirred at the same temperature for 10 h. The reaction mixture was cooled to room temperature and dissolved in 15 mL of DCM. The DCM layer was

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washed with water (10 mL × 2) and brine (10 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to get the crude product. The crude product was purified by column chromatography to afford the arylated product **3**.

3aa:[6] 58 mg, 91% yield; colorless liquid; R_f = 0.55 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2961, 2933, 1739, 1443, 1381, 1273, 912, 658; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.31−7.24 (m, 10H), 5.03 (s, 1H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 173.1, 138.7, 128.7, 128.7, 127.4, 57.1, 52.4; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}O_2$, 227.1072, found 227.1066.

3ab:[17] 68 mg, 81% yield; white solid; R_f = 0.33 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3028, 1729, 2487, 1434, 1200, 1163, 1011, 760, 698; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.58−7.55 (m, 4H), 7.45−7.39 (m, 4H), 7.37−7.29 (m, 6H), 5.09 (s, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz $CDCl_3$, 24 °C): δ 173.0, 140.8, 140.3, 138.7, 137.8, 129.1, 128.8, 128.8, 128.8, 128.7, 127.4, 127.4, 127.2, 56.8, 52.5; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{18}O_2Na$, 325.1204, found 325.1190.

3ac (3ga):[18] 60 mg, 89% yield (59 mg, 88% yield); colorless liquid; R_f = 0.37 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3026, 2947, 1732, 1442, 1445, 1156, 1014, 700; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.34−7.07 (m, 9H), 5.00 (s, 1H), 3.74 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 173.2, 138.8, 138.6, 136.4, 129.4, 128.7, 128.6, 128.2, 127.3, 125.7, 57.1, 52.4, 21.6; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1233.

3ad: 59 mg, 83% yield; colorless liquid; R_f = 0.44 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2948, 2084, 1955, 1889, 1737, 1604, 1498, 1447, 1315, 1156, 1013, 727; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.32−7.28 (m, 4H), 7.27−7.23 (m, 1H), 7.10−7.03 (m, 3H), 4.97 (s, 1H), 3.74 (s, 3H), 2.23 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 173.3, 139.0, 136.9, 136.1, 135.8, 130.0, 129.9, 128.6, 127.2, 126.0, 56.8, 52.3, 19.9, 19.4; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{18}O_2Na$, 277.1204, found 277.1205.

3ae (3ha):[19] 45 mg, 67% yield (44 mg, 66% yield); pale yellow liquid; R_f = 0.40 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3029, 2952, 2104, 1736, 1603, 1494, 1454, 1434, 1245, 1153, 1007, 735; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.33−7.31 (m, 2H), 7.28−7.23 (m, 4H), 7.20−7.18 (m, 3H), 5.22 (s, 1H), 3.75(s, 3H), 2.29(s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 173.3, 137.9, 137.0, 136.5, 130.8, 129.0, 128.6, 127.5, 127.3, 126.3, 53.8, 52.4, 19.9; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1236.

3af (3ia):[6] 60 mg, 84% yield (58 mg, 81% yield); colorless liquid; R_f = 0.28 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2947, 1735, 1602, 1511, 1249, 1158, 1022, 815, 703; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.34−7.24 (m, 7H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.99 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 24 °C): δ 173.3, 158.9, 139.0, 130.8, 129.7, 128.7, 128.5, 127.3, 114.1, 56.3, 55.3, 52.4; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{16}O_3Na$, 279.0997, found 279.0994.

3ag:[18] 63 mg, 88% yield; colorless liquid; R_f = 0.37 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2947, 2835, 1742, 1585, 1491, 1431, 1265, 1155, 1051, 772; ^1H NMR ($CDCl_3$, 500 MHz, 24 °C): δ 7.32−7.22 (m, 6H), 6.91−6.79 (m, 3H), 5.00 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, 24 °C): δ 172.9, 159.8, 140.1, 138.5, 129.7, 128.7, 128.7, 127.4, 121.1, 114.7, 112.6, 57.0, 55.3, 52.4; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}O_3$, 257.1178, found 257.1166.

3ah: 46 mg, 57% yield; pale yellow liquid; R_f = 0.24 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2948, 2834, 1742, 1591, 1499, 1430, 1228, 1054, 805, 703; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.36−7.26 (m, 5H), 6.82−6.74 (m, 2H), 6.64 (d, *J* = 4.0 Hz, 1H), 5.29 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 173.4, 153.6, 151.3, 137.6, 129.1, 129.0, 128.7, 127.4, 116.2, 112.3, 111.5, 56.2, 55.7, 52.3, 51.0; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{18}O_4Na$, 309.1103, found 309.1110.

3ai: 65 mg, 81% yield; colorless liquid; R_f = 0.37 in1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3654, 3454, 2979, 2940, 1959, 1736, 1591, 1511, 1277, 1130, 916, 721, 647; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.35−6.84 (m, 8H), 4.95 (s, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.8, 152.6 (d, *J* = 246.0 Hz), 146.2 (d, *J* = 10.7 Hz), 138.5, 131.6 (d, *J* = 5.7 Hz), 128.8, 128.5, 127.5, 124.4 (d, *J* = 3.4 Hz), 116.7 (d, *J* = 19.5 Hz), 114.8, 65.1, 56.1, 52.5, 14.9; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{17}O_3NaF$, 311.1059, found 311.1072.

3aj: 58 mg, 80% yield; colorless liquid; R_f = 0.53 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2923, 2851, 1740, 1594, 1433, 1198, 1154, 1013, 755, 702; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.36−7.18 (m, 9H), 4.99 (s, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.5, 140.6, 138.0, 134.5, 129.9, 128.9, 128.6, 127.7, 127.6, 126.9, 56.7, 52.5; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}O_2Cl$, 261.0682, found 261.0685.

3ak: 66 mg, 80% yield; colorless liquid; R_f = 0.44 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3460, 3073, 2949, 1957, 1739, 1575, 1435, 1160, 1013, 856, 702; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.37−7.25 (m, 6H), 7.20 (d, *J* = 1.8 Hz, 2H), 4.94 (s, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 171.9, 141.9, 137.3, 135.2, 129.1, 128.5, 128.0, 127.7, 127.3, 56.4, 52.7; HRMS: *m/z*: $[M + Na]+$ Calcd for $C_{15}H_{12}O_2NaCl_2$, 317.0112, found 317.0101.

3al: 62 mg, 75% yield; colorless liquid; R_f = 0.44 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3052, 2953, 2480, 2426, 2308, 1738, 1601, 1504, 1442, 1011, 733; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.34−7.15 (m, 9H), 5.03 (s, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): 172.7, 148.5, 138.2, 137.4, 130.1, 128.9, 128.5, 127.7, 121.1, 120.5 (q, *J* = 257 Hz, CF_3), 56.4, 52.6; HRMS: *m/z*: $[M+K]^+$ Calcd for $C_{16}H_{13}O_2F_3K$, 333.0505, found 333.0512.

3am: 58 mg, 73% yield; white solid; R_f = 0.45 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2952, 1732, 1433, 1286, 1198, 1152, 1104, 1017, 964, 813; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.33−7.23 (m, 5H), 5.05 (s, 1H), 3.87 (s, 3H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.4, 166.9, 143.7, 138.0, 130.0, 129.3, 128.9, 128.8, 128.6, 127.7, 57.0, 52.6, 52.2; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}O_4$, 285.1127, found 285.1122.

3ba:[20] 57 mg, 85% yield; colorless liquid; R_f = 0.37 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 1729, 1490, 1451, 1367, 1346, 1309, 1277, 1189, 1153, 1020, 743, 705, 628; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.34−7.25 (m, 10H), 5.03 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.6, 138.9, 128.7, 128.6, 127.3, 61.3, 57.2, 14.2; HRMS: *m/z*: $[M + H]+$ Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1237.

3ca:[21] 59 mg, 83% yield; colorless liquid; R_f = 0.39 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2982, 1725, 1603, 1497, 1451, 1374, 1308, 1266, 1192, 1164, 1106, 971, 743, 700; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.31−7.21 (m, 10H), 5.07 (sep, *J* = 6.2 Hz, 1H), 4.96 (s, 1H), 1.21 (d, *J* = 6.2 Hz, 6H, $2CH_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.0, 139.0, 128.7, 128.6, 127.2, 68.7, 57.4, 21.8; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}O_2$, 255.1385, found 255.1380.

3da:[22] 64 mg, 85% yield; colorless liquid; R_f = 0.38 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 1729, 1490, 1448, 1364, 1206, 1144, 758, 746, 701; ^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.32−7.23 (m, 10H), 4.92 (s, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 171.8, 139.3, 128.7, 128.6, 127.1, 81.4, 58.2, 28.1; HRMS: *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{20}O_2Na$, 291.1361, found 291.1370.

3ea:[23] 42 mg, 63% yield; colorless liquid; R_f = 0.38 in 1:4 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2982, 2306, 1735, 1602, 1498, 1453, 1368, 1307, 1266, 1221, 1152, 1031, 729, 607, 582, 491, 468; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.41−7.30 (m, 5H), 4.60 (s, 1H), 4.27−4.15 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 168.3, 132.9, 129.4, 128.7, 128.3, 61.9, 58.1, 14.1; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{17}O_4$, 237.1127, found 237.1127.

3fa:[24] 58 mg, 86% yield; colorless liquid; R_f = 0.41 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2952, 1735, 1600, 1517, 1496, 1456, 1436, 1308, 1011, 808, 732, 701; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.32−7.31 (m, 4H), 7.27−7.24 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.01 (s, 1H), 3.74 (s, 3H) 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 173.2, 139.0, 137.1, 135.8, 129.4, 128.6, 128.6, 127.3, 56.8, 52.3, 21.1; HRMS: *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1217.

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3ja: 71 mg, 86% yield; colorless liquid; R_f = 0.40 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 1735, 1630, 1469, 1266, 1199, 1153, 1030, 132, 700; ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.41−7.26 (m, 7H), 7.15 (dd, J = 8.3, 2.2 Hz, 1H), 4.96 (s, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.2, 138.8, 137.6, 132.7, 131.6, 130.7, 130.6, 129.0, 128.5, 128.1, 127.8, 56.1, 52.7; HRMS: m/z: [M + Na]$^+$ Calcd for $C_{15}H_{12}Cl_2O_2Na$, 317.0112, found 317.0101.

3ka: 47 mg, 65% yield; colorless liquid; R_f = 0.44 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2093, 1735, 1630, 1469, 1433, 1266, 1199, 1030, 893, 816; ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ 7.37−7.19 (m, 9H), 5.49 (s, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.5, 137.2, 136.7, 134.3, 130.2, 129.7, 129.0, 128.9, 128.7, 127.6, 127.0, 53.8, 52.6; HRMS: m/z: [M + H]$^+$ Calcd for $C_{15}H_{14}O_2Cl$, 261.0682, found 261.0677.

3la: 79 mg, 71% yield; white solid; R_f = 0.32 in 1:4 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2365, 2344, 2090, 1739, 1648, 1375, 1154, 1110, 863; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.72 (d, J = 8.0 Hz, 2H), 7.36−7.23 (m, 9H), 6.95 (d, J = 8.0 Hz, 2H), 4.99 (s, 1H), 3.75 (s, 3H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.6, 148.8, 145.4, 138.2, 137.6, 132.6, 130.0, 129.9, 128.8, 128.6, 127.6, 122.5, 56.3, 52.5, 21.8; HRMS: m/z: [M + Na]$^+$ Calcd for $C_{22}H_{20}O_5SNa$, 419.0929, found 419.0927.

3ma: 15 mg, 21% yield; pale yellow solid; R_f = 0.34 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2225, 1735, 1603, 1506, 1371, 1338, 1241, 1164, 1038, 551; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.64 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.40−7.29 (m, 5H), 5.07 (s, 1H), 4.26 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 171.5, 144.2, 137.5, 132.4, 129.6, 129.0, 128.6, 127.9, 118.7, 61.7, 57.1, 14.2; HRMS: m/z: [M + Na]$^+$ Calcd for $C_{17}H_{15}NNaO_2$, 288.1000, found 288.0995.

3na:[25] 67 mg, 88% yield; white solid; R_f = 0.51 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 1734, 1525, 1346, 1206, 1164, 705; ^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ 8.10 (t, J = 2 Hz, 1H), 8.13 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 7.67−7.65 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.38−7.29 (m, 4H), 5.12 (s, 1H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 24 °C): δ 172.1, 148.4, 140.8, 137.4, 134.9, 129.6, 129.1, 128.5, 128.0, 123.8, 122.5, 56.5, 52.8; HRMS: m/z: [M + Na]$^+$ Calcd for $C_{15}H_{13}NNaO_4$, 294.0742, found 294.0737.

3oa: 66 mg, 83% yield; white solid; R_f = 0.45 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2952, 1732, 1433, 1286, 1198, 1152, 1104, 1017, 964, 813; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.97 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.33−7.23 (m, 5H), 5.05 (s, 1H), 3.87 (s, 3H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.4, 166.9, 143.7, 138.0, 130.0, 129.3, 128.9, 128.8, 128.6, 127.7, 57.0, 52.6, 52.2; HRMS: m/z: [M + H]$^+$ Calcd for $C_{17}H_{17}O_4$, 285.1127, found 285.1122.

3pa:[17] 28 mg, 29% yield; white solid; R_f = 0.40 in 1:9 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 1729, 1655, 1596, 1522, 1420, 1318, 1257, 1164, 712; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.88−7.83 (m, 3H), 7.61−7.58 (m, 2H), 7.54−7.52 (m, 1H), 7.48−7.45 (m, 2H), 7.34−7.31 (m, 6H), 5.02 (s, 2H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 173.0, 165.8, 138.7, 137.2, 135.0, 134.9, 132.0, 129.4, 128.9, 128.7, 128.6, 127.4, 127.1, 120.4, 56.6, 52.5; HRMS: m/z: [M + H]+ Calcd for $C_{22}H_{20}O_3N$, 346.1443, found 346.1436.

3qa: 62 mg, 71% yield; white solid; R_f = 0.32 in 1:4 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 2365, 2344, 2090, 1648, 1375, 1154, 1110, 863; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.66 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.35−7.33 (m, 2H), 7.32−7.27 (m, 4H), 7.22−7.14 (m, 1H), 6.41 (d, J = 16.0 Hz, 1H), 5.04 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.6, 167.5, 144.4, 141.1, 138.3, 133.6, 129.3, 128.9, 128.6, 128.4, 127.6, 118.1, 57.0, 52.5, 51.8; HRMS: m/z: [M + H]$^+$ Calcd for $C_{19}H_{19}O_4$, 311.1283, found 311.1276.

Synthesis of 3jf. In a dry reaction tube, *p*-methoxyphenylboronic acid (**2f**) (100 mg, 0.66 mmol, 1 equiv), K_3PO_4 (140 mg, 0.66 mmol, 1 equiv), Rh catalyst (3.2 mg, 1 mol %), and dry toluene (1.5 mL) were added under a nitrogen atmosphere, and the reaction tube was sealed with a septum and kept in a preheated oil bath at 80 °C. Diazo compound **1j** (161 mg, 0.66 mmol, 1 equiv) was dissolved in 1.0 mL of dry toluene and slowly added to the reaction mixture over a period of 0.5 h and stirred at the same temperature for 10 h. The reaction mixture was cooled to room temperature and dissolved in 15 mL of DCM. The DCM layer was washed with water (10 mL × 2) and brine (10 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product. The crude product was purified by column chromatography to afford the arylated product **3jf**. 130 mg, 61% yield; R_f = 0.54 in 1:4 EtOAc/Hexane; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.38−7.36 (m, 2H), 7.21−7.17 (m, 2H), 7.13 (dd, J = 8.3, 2.1 Hz, 1H), 6.89−6.85 (m, 2H), 4.91 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 172.5, 159.2, 139.3, 132.7, 131.5, 130.6, 130.5, 129.7, 129.6, 128.0, 114.4, 55.4, 55.3, 52.6; HRMS: m/z: [M + Na]$^+$ Calcd for $C_{16}H_{14}Cl_2NaO_3$, 347.0217, found 347.0208.

Synthesis of 11. In an oven-dried round bottomed flask equipped with a magnetic stir bar, compound **3jf** (744 mg, 2.29 mmol) was taken and 2.5 M aq. KOH (2.0 mL) and THF (5 mL) were added. The round-bottom flask was kept in a preheated oil bath at 60 °C. After completion of the reaction (monitored by TLC), the reaction mixture was washed DCM (15 mL × 2) and made acidic by dropwise addition of 1 N HCl. The aqueous layer was extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the corresponding acid, which was directly subjected to the next step without further purification. 84% yield; R_f = 0.24 in 2:3 EtOAc/Hexane; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.41−7.37 (m, 2H), 7.24−7.20 (m, 2H), 7.15 (dd, J = 8.41, 1.94 Hz, 1H), 6.90−6.86 (m, 2H), 4.93 (s, 1H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 177.7, 159.4, 138.5, 132.8, 131.8, 130.7, 130.6, 129.7, 129.0, 128.1, 114.4, 55.4, 55.3.

In an oven-dried round-bottom flask equipped with a magnetic stir bar, the acid (597 mg, 1.92 mmol) obtained above was dissolved in dry THF (5 mL) and cooled to 0 °C. Sodium borohydride (290 mg, 7.66 mmol, 4 equiv) was added portionwise in intervals of 1 min. Subsequently, a solution of elemental iodine (485 mg, 1.92 mmol, 1 equiv) in dry THF (1.0 mL) was introduced to the reaction mixture dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched by addition of 1 N HCl. The aqueous layer was extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated by evaporation of the solvent and purified by column chromatography to yield the corresponding alcohol **11**. 462 mg, 81% yield; R_f = 0.33 in 3:7 EtOAc/Hexane; IR (ν_{max}, cm^{-1}): 3443, 3201, 3054, 1734, 1374, 1298, 1046, 713; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.37−7.34 (m, 2H), 7.12 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 2H), 4.10−4.07 (m, 3H), 3.78 (s, 3H), 1.95 (br, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 158.7, 142.5, 134.3, 132.5, 130.6, 130.5, 130.2, 129.2, 127.7, 114.3, 65.7, 55.3, 51.8; HRMS: m/z: [M + H]$^+$ Calcd for $C_{15}H_{15}O_2Cl_2$, 297.0449, found 297.0440.

Synthesis of 12. In an oven-dried round-bottom flask equipped with a magnetic stir bar, compound **11** (462 mg, 1.55 mmol), triphenylphosphine (1.01 g, 3.87 mmol), and phthalimide (568 mg, 3.87 mmol) were added and the flask was purged with argon. Dry THF (10 mL) was added at room temperature, and the flask was cooled to 0 °C using an ice bath. After 10 min, DIAD (0.8 mL, 3.87 mmol) was added to the reaction mixture over a period of 10 min. The reaction mixture was warmed to room temperature and stirred for 6 h. After completion of the reaction (monitored by TLC), water (25 mL) was added and extracted with diethyl ether (10 mL × 3). The combined organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification using column chromatography afforded the imide.

In an oven-dried round bottomed flask, imide (362 mg, 0.85 mmol) obtained previously was added and dissolved in methanol (8 mL). Aqueous solution of hydrazine (0.31 mL, 25% in water) was added to the reaction mixture and heated at 70 °C for 2 h. After completion of the reaction (monitored by TLC), the compound was extracted with ethyl acetate (10 mL × 3) and dried over anhydrous sodium sulfate.

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After evaporation of the solvent, the crude product was purified by column chromatography to yield the primary amine **12**. 160 mg, 35% yield for two steps; R_f = 0.2 in EtOAc; IR (ν_{max}, cm^{-1}): 3379, 2933, 2840, 1630, 1252, 1084, 1027, 803; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.34 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.1 (d, J = 8.6 Hz, 2H), 7.08 (dd, J = 8.3, 2.1 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 3.88 (t, J = 7.6 Hz, 1H), 3.77 (s, 3H), 3.24 (d, J = 6.8 Hz, 2H), 1.70 (brs, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 158.6, 143.7, 133.5, 132.6, 130.5, 130.5, 130.0, 129.0, 127.5, 114.3, 55.3, 53.2, 46.8; HRMS: m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}NOCl_2$, 296.0609, found 296.0620.

■ ASSOCIATED CONTENT

Supporting Information

General experimental, reaction optimization data, and spectral copies of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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