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## Just Accepted

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# with Aryl Boronic Acids

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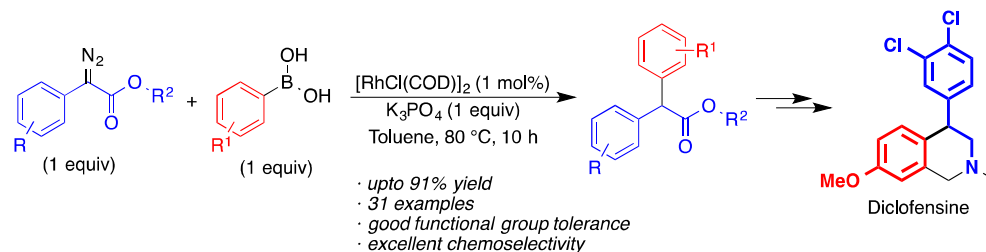
**Abstract:** A general and efficient synthesis of diarylacetate, a diarylmethine derivatives were accomplished through rhodium catalyzed direct arylation of diazo compounds with arylboronic acids. The reaction tolerates various boronic acid derivatives and functional groups. Notably, chemoselective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

## Introduction

Diarylmethines are ubiquitous subunits found in 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 inhibitor of serotonin dopamine uptake.[2] Due to these potential, the synthesis of diarylmethine derivatives, particularly, (di)arylacetic acid derivatives, the most obvious synthetic equivalent, is the

topic of interest to many synthetic chemist over the past few decades.[3]
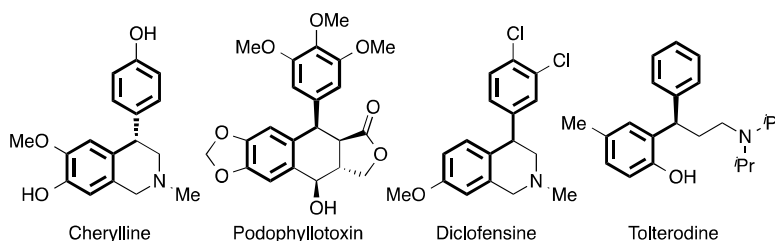


Figure 1: Representative examples of diarylmethine containing therapeutically important molecules.

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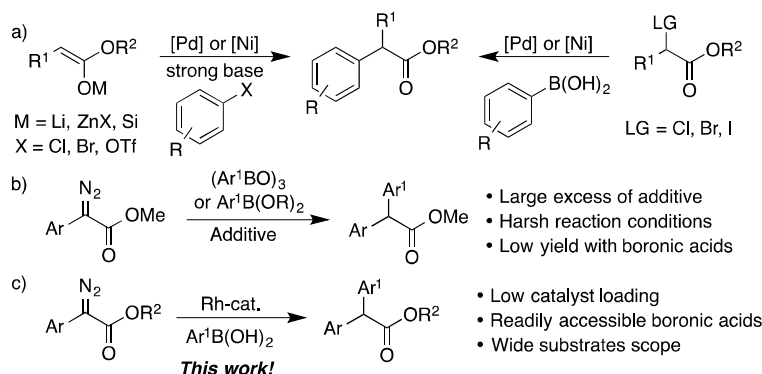


Scheme 1: Synthesis of diarylacetic acid derivatives.

Most recently, an alternative synthesis of diarylacetates was accomplished from diazo carbonyl compounds and ester of arylboronic acids employing strong base[6] or expensive $CF_3TMS$[7] as an additive (Scheme 1b). Instead of protonation as termination step, tandem alkylation was also achieved with benzyl halide and $KO^tBu$ to afford the $\alpha,\alpha$-diaryl carboxylic esters.[8] Thus, development of 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 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, solution of **1a** was introduced slowly through syringe pump over the period of 30 min;

to our delight we observed the formation of expected product **3aa**. Screening of various metal catalysts,

such as palladium and rhodium, revealed that rhodium based catalyst is superior than the palladium

based catalyst and afforded the product in 31% yield (Table 1, entry 1 and see Supporting information).

Table 1. Rhodium catalyzed arylation of diazo compounds: Optimization[a]
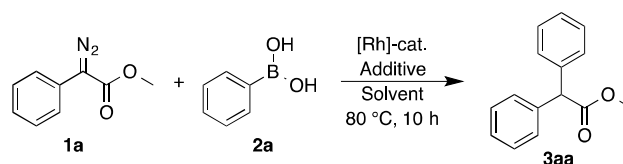


| Entry | [Rh]-cat. | Additive | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | [RhCl(COD)]$_2$ | - | Toluene | 31 |
| 2 | - | - | Toluene | 0 |
| 3 | [RhCl(COD)]$_2$ | K$_3$PO$_4$ | Toluene | 91 |
| 4 | - | K$_3$PO$_4$ | Toluene | 0 |
| 5[c] | [RhCl(COD)]$_2$ | K$_3$PO$_4$ | Toluene | 60 |
| 6 | Rh$_2$(OAc)$_4$ | K$_3$PO$_4$ | Toluene | 18 |
| 7 | [Cp*RhCl$_2$]$_2$ | K$_3$PO$_4$ | Toluene | 33 |
| 8[d] | [RhCl(COD)]$_2$ | K$_3$PO$_4$ | Toluene | 55 |
| 9 | [RhCl(COD)]$_2$ | K$_2$CO$_3$ | Toluene | 38 |
| 10[e] | [RhCl(COD)]$_2$ | CsF | Toluene | 29 |
| 11 | [RhCl(COD)]$_2$ | K$_3$PO$_4$ | 1,4-Dioxane | 14 |
| 12 | [RhCl(COD)]$_2$ | K$_3$PO$_4$ | 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$_3$PO$_4$ is used; [e] 7 h.

Interestingly, introduction of one equivalent 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 rhodium catalyst (with or without additive) the expected reaction didn't occur, which proves that the present reaction is indeed catalyzed by rhodium catalyst (Table 1, entries 2 and 4). Next, we examined the other critical parameters like additive, solvent and temperature. 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 equivalents of additive (Table 1, entries 5 and 8). Furthermore, changing 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.

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 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 equivalents of **5**. Although, all the boron reagents examined gave the product **3aa** in good to moderate yield, arylboronic acid was found to be superior.
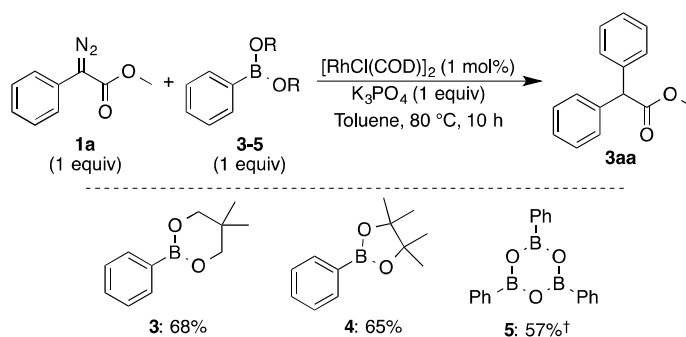


Scheme 2: Rhodium catalyzed arylation of **1a** with various phenylboron reagents (**3-5**). [†]0.66 equiv of

triphenylboroxin.

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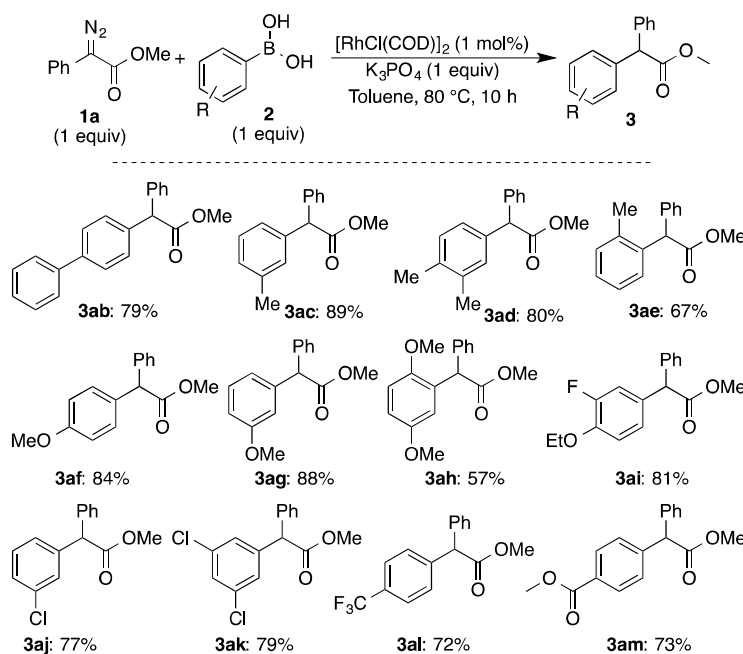


Scheme 3. Rhodium catalyzed synthesis of diarylacetic acid derivatives **3**: Scope and limitation of arylboronic acids.

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, 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.
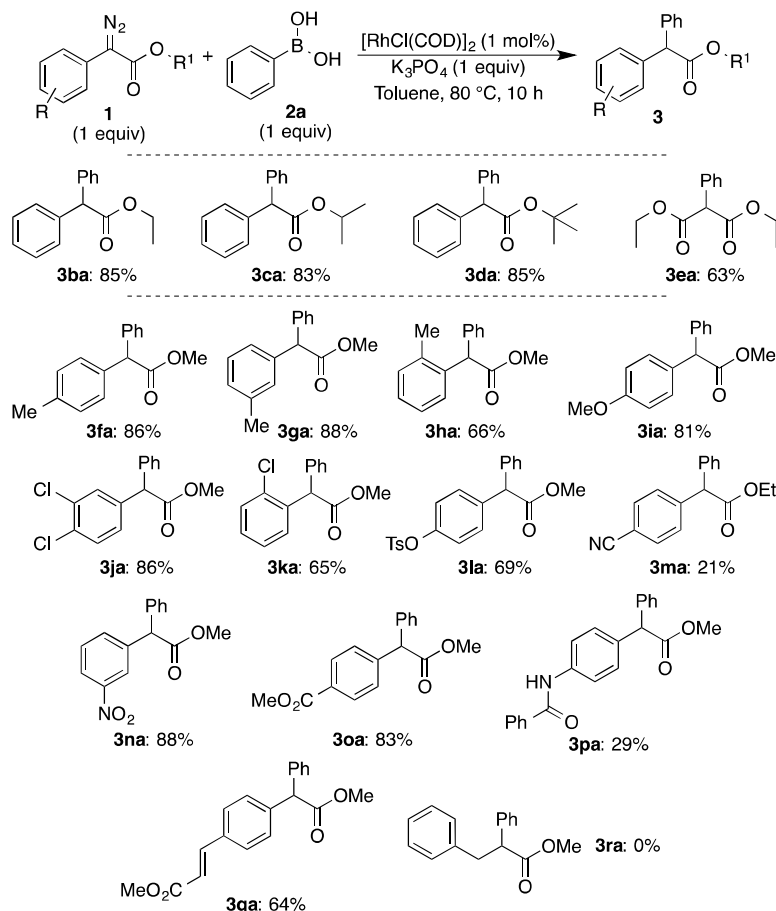


Scheme 4: Rhodium catalyzed synthesis of diarylacetic acid derivatives **3**: Scope and limitation of diazo compounds.

Interestingly, the present methodology also tolerates various functional groups, like 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 diazocompound derived from malonic acid diester, which led the formation of arylated product **3ea** in 63% yield. However, replacing aryl moiety in diazo compounds with 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 diazo compound containing $\alpha,\beta$-unsaturated ester group[13] that are 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 to other electrophiles,[14] like aldehyde, ketone and nitrile (Scheme 5). Reaction of equimolar mixture of diazo 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 equimolar mixture of **1a** and ketone **8** (or aldehyde **6**) with **2a** furnished the mixture of arylated product **3aa** and **9** (or **7**) with 2.1:1 (or 1:1) ratio favoring the arylation of diazo compound (Scheme 5b and 5a). Thus, the present rhodium catalyzed arylation condition is highly selective towards the diazo compounds compared to $\alpha,\beta$-unsaturated ester, nitriles and ketones.
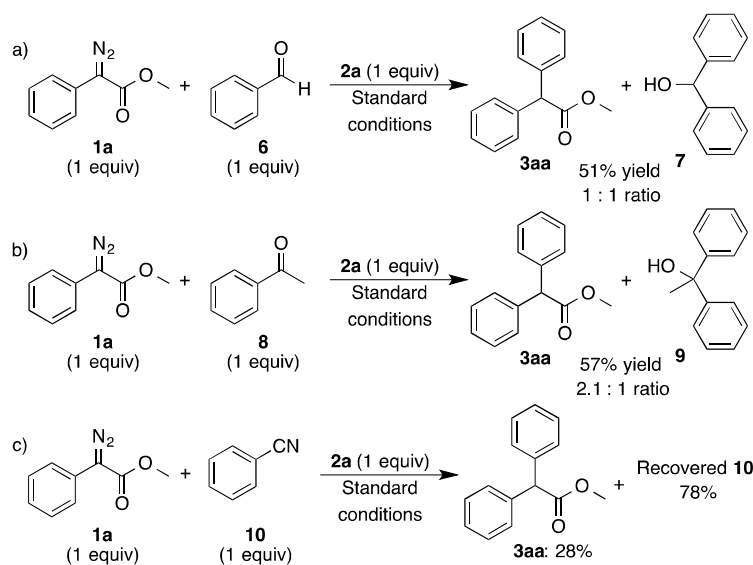


Scheme 5: Chemoselectivity in rhodium catalyzed arylation of **1a** with **2a**.

Subsequently, effect of substituents on the phenyl ring of diazo compounds and arylboronic acids was

also examined. Arylation of equimolar mixture of methoxy- and methoxycarbonyl-substituted diazo

compounds, **1i** and **1o**, respectively, with phenylboronic acid gave the mixture of **3ia** and **3oa** in 1:1.5

ratio (Scheme 6a). In contrast, arylated products **3af** and **3am** were isolated in 1.4:1 ratio from the

rhodium catalyzed reaction of methoxy and methoxycarbonyl substituted arylboronic acids, **2f** and **2m**,

respectively, with diazo compound **1a** (Scheme 6b). The ratio of the product revealed that the presence

of electron withdrawing group (methoxycarbonyl) in the diazo compounds **1** and electron-donating

group in the arylboronic acid **2** slightly favors the arylation over the corresponding counter part. Thus,

the present methodology complements the base mediated arylation reaction (Scheme 1b), where the

electron-withdrawing arylboronic acids gave moderately high reactivity.
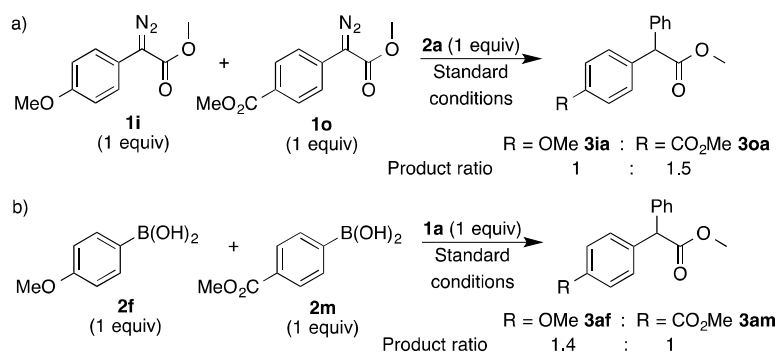


Scheme 6: Rhodium catalyzed direct arylation: Effect of the substituents.

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 4-aryltetrahydroisoquinoline framework and shown to have

both antidepressant and monoamines reuptake inhibitor activity.[15] Synthesis began with the rhodium-

catalyzed arylation of diazo compound **1j** with *p*-anisylboronic acid **2f** under the optimized condition to

lead to the formation of **3jf** in 59% yield (Scheme 7). Hydrolysis of ester followed by reduction with the

combination of sodium borohydride and iodine gave the alcohol **11** in 65% for two steps. Finally, the

key intermediate amine **12** was achieved from alcohol **11** through 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.
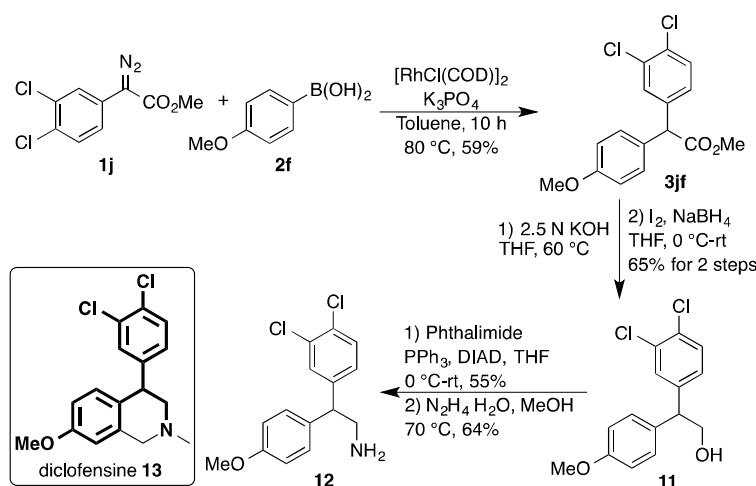


Scheme 7: Synthesis of core structure of diclofensine **13**.

On the basis of 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 rhodium precursor and **2**, through base assisted transmetallation of 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 to a rhodium complex **C**, which might exist in equilibrium with its tautomer **C'**. Finally, proto-demetallation of rhodium species **C** could afford the arylated product **3** along with the active rhodium species to complete the catalytic cycle.
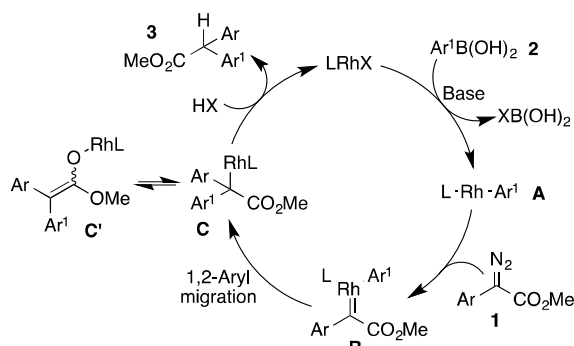


Scheme 8: Plausible mechanism.

## 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 yield under operationally simple and mild reaction conditions. Importantly, the optimized condition tolerates various functional groups like nitro, amide, ester, nitrile, trifluoromethyl and etc. In addition, the excellent chemoselectivity was observed for arylation of diazo compounds over $\alpha,\beta$-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 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 nitrogen atmosphere and the reaction tube was sealed with septa 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 half an hour and stirred at same temperature till the time mentioned in the table below. The reaction mixture was cooled to room temperature and dissolved in 15 mL 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 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 ($v_{max}$, cm$^{-1}$): 2961, 2933, 1739, 1443, 1381, 1273, 912, 658; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 7.31-7.24 (m, 10H), 5.03 (s, 1H), 3.74 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($v_{max}$, cm$^{-1}$): 3028, 1729, 2487, 1434, 1200, 1163, 1011, 760, 698; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz CDCl$_3$, , 24 °C): $\delta$ 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$_2$Na, 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 ($v_{max}$, cm$^{-1}$): 3026, 2947, 1732, 1442, 1445, 1156, 1014, 700; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 7.34-7.07 (m, 9H), 5.00 (s, 1H), 3.74 (s, 3H), 2.32 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($v_{max}$, cm$^{-1}$): 2948, 2084, 1955, 1889, 1737, 1604, 1498, 1447, 1315, 1156, 1013, 727; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_2$Na, 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 ($v_{max}$, cm$^{-1}$): 3029, 2952, 2104, 1736, 1603, 1494, 1454, 1434, 1245, 1153, 1007, 735; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 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): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2947, 1735, 1602, 1511, 1249, 1158, 1022, 815, 703; $^1H$ NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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): $\delta$ 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$_3$Na, 279.0997, found 279.0994.

**3ag:**[18] 63 mg, 88% yield; colorless liquid; $R_f$ = 0.37 in 1:9 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2947, 2835, 1742, 1585, 1491, 1431, 1265, 1155, 1051, 772; $^1H$ NMR (CDCl$_3$, 500 MHz, 24 °C): $\delta$ 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): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2948, 2834, 1742, 1591, 1499, 1430, 1228, 1054, 805, 703; $^1H$ NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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): $\delta$ 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$_4$Na, 309.1103, found 309.1110.

**3ai:** 65 mg, 81% yield; colorless liquid; $R_f$ =0.37 in1:9 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 3654, 3454, 2979, 2940, 1959, 1736, 1591, 1511, 1277, 1130, 916, 721, 647; $^1H$ NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 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): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2923, 2851, 1740, 1594, 1433, 1198, 1154, 1013, 755, 702; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 7.36-7.18 (m, 9H), 4.99 (s, 1H), 3.75 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 3460, 3073, 2949, 1957, 1739, 1575, 1435, 1160, 1013, 856, 702; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 7.37-7.25 (m, 6H), 7.20 (d, $J$ = 1.8 Hz, 2H), 4.94 (s, 1H), 3.75 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 3052, 2953, 2480, 2426, 2308, 1738, 1601, 1504, 1442, 1011, 733; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 7.34-7.15 (m, 9H), 5.03 (s, 1H), 3.75 (s, 3H); $^{13}$C{$^1$H} 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 ($\nu_{max}$, cm$^{-1}$): 2952, 1732, 1433, 1286, 1198, 1152, 1104, 1017, 964, 813; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 1729, 1490,

1451, 1367, 1346, 1309, 1277, 1189, 1153, 1020, 743, 705, 628; ^{1}H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 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{^{1}H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2982, 1725, 1603, 1497, 1451, 1374, 1308, 1266, 1192, 1164, 1106, 971, 743, 700; ^{1}H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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, 2C**H**$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 1729 1490, 1448, 1364, 1206, 1144, 758, 746, 701; ^{1}H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 7.32-7.23 (m, 10H), 4.92 (s, 1H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_2$Na, 291.1361, found 291.1370.

**3ea:**[23] 42 mg, 63% yield; colorless liquid; $R_f$ = 0.38 in 1:4 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2982, 2306, 1735, 1602, 1498, 1453, 1368, 1307, 1266, 1221, 1152, 1031, 729, 607, 582, 491, 468; ^{1}H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{^{1}H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2952, 1735, 1600, 1517, 1496, 1456, 1436, 1308, 1011, 808, 732, 701; ^{1}H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{^{1}H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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.

**3ja:** 71 mg, 86% yield; colorless liquid; $R_f$ = 0.40 in 1:9 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 1735, 1630, 1469, 1266, 1199, 1153, 1030, 132, 700; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_2$O$_2$Na, 317.0112, found 317.0101.

**3ka:** 47 mg, 65% yield; colorless liquid; $R_f$ = 0.44 in 1:9 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2093, 1735, 1630, 1469, 1433, 1266, 1199, 1030, 893, 816; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 7.37-7.19 (m, 9H), 5.49 (s, 1H), 3.76 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_2$Cl, 261.0682, found 261.0677.

**3la:** 79 mg, 71% yield; white solid; $R_f$ = 0.32 in 1:4 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2365, 2344, 2090, 1739, 1648, 1375, 1154, 1110, 863; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_5$SNa, 419.0929, found 419.0927.

**3ma:** 15 mg, 21% yield; pale yellow solid; $R_f$ = 0.34 in 1:9 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2225, 1735, 1603, 1506, 1371, 1338, 1241, 1164, 1038, 551; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 1734, 1525, 1346, 1206, 1164, 705; $^1$H NMR (500 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (125 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 2952, 1732, 1433, 1286, 1198, 1152, 1104, 1017, 964, 813; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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 ($\nu_{max}$, cm$^{-1}$): 1729, 1655, 1596, 1522, 1420, 1318, 1257, 1164, 712; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_3$N, 346.1443, found 346.1436.

**3qa:** 62 mg, 71% yield; white solid; $R_f$ = 0.32 in 1:4 EtOAc/Hexane; IR ($\nu_{max}$, cm$^{-1}$): 2365, 2344, 2090, 1648, 1375, 1154, 1110, 863; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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$_3$PO$_4$ (140 mg, 0.66 mmol, 1 equiv), Rh catalyst (3.2 mg, 1 mol%), and dry toluene (1.5 mL) were added under nitrogen atmosphere and the reaction tube was sealed with septa 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 half an hour and stirred at same temperature till the time mentioned in the table below. The reaction mixture was cooled to room temperature and dissolved in 15 mL 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 get 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; $^1H$ NMR (400 MHz, $CDCl_3$, 24 °C): $\delta$ 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): $\delta$ 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 pre-heated 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 drop wise addition of 1N HCl. The aqueous layer was extracted with ethyl acetate (15 mL × 3). Combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the corresponding acid, which was directly subjected to next step without further purification. 84% yield; $R_f$ = 0.24 in 2:3 EtOAc/Hexane; $^1H$ NMR (400 MHz, $CDCl_3$, 24 °C): $\delta$ 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): $\delta$ 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, 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 portion wise with the interval of 1 min. Subsequently, solution of

elemental iodine (485 mg, 1.92 mmol, 1 equiv) in dry THF (1.0 mL) was introduced to the reaction

mixture drop wise over the period of 10 mins at 0 °C. The reaction mixture was warmed to room

temperature and stirred at room temperature for 24 hours. After completion of the reaction (monitored

by TLC), the reaction mixture was cooled to 0 °C and quenched by addition of 1N 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 sulphate. 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 ($v_{max}$, cm$^{-1}$): 3443, 3201, 3054, 1734, 1374, 1298, 1046,

713; $^1$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^1$H} NMR (100 MHz,

CDCl$_3$, 24 °C): $\delta$ 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$_2$Cl$_2$, 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 gm, 3.87 mmol) and phthalimide (568 mg, 3.87 mmol)

were added and flask was purged with argon. Dry THF (10 mL) was added at room temperature and the

flask was cooled to 0 °C using ice bath. After 10 mins, DIAD (0.8 mL, 3.87 mmol) was added to the

reaction mixture over the period of 10 minutes. The reaction mixture was warmed to room temperature

and stirred for 6 hours. After completion of the reaction monitored by (TLC), water (25 mL) was added

and extracted with diethyl ether (10 mL × 3). Combined organic layer was washed with brine (10 mL)

and dried over anhydrous sodium sulphate. 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 above 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 hours. After completion the reaction (monitored by TLC), the compound was extracted with ethyl acetate (10 mL × 3) and dried over anhydrous sodium sulphate. 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 ($\nu_{max}$, cm$^{-1}$): 3379, 2933, 2840, 1630, 1252, 1084, 1027, 803; $^{1}$H NMR (400 MHz, CDCl$_3$, 24 °C): $\delta$ 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{$^{1}$H} NMR (100 MHz, CDCl$_3$, 24 °C): $\delta$ 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.

**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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