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A Copper-Assisted Palladium(II)-catalyzed Direct Arylation of Cyclic Enaminones with Arylboronic Acids

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Abstract

Described herein is a palladium(II)-catalyzed direct arylation of cyclic enaminones with arylboronic acids. The versatility of this method is that both electron-rich and electron-poor boronic acids can be coupled in high yields. A mixture of two Cu(II) additives was crucial for efficient cross-coupling. The role of each Cu(II) reagent appears to be distinct and complementary serving to assist catalyst reoxidation and transmetalation through a putative arylcopper intermediate.

Introduction

The direct conversion of C–H to C–C bonds via transition metal catalysis has streamlined the syntheses of many useful molecules.^{1,2} Palladium-catalysis has proven to be remarkably versatile in this respect and has added a host of valuable tools to the organic chemist's toolbox.² In the course of our studies towards the synthesis and functionalization of the cyclic enaminones (2,3-dihydropyridin-4(1*H*)-ones),^{3,4} we discovered that these multifunctional scaffolds could serve as viable C–H donors in Pd(II)-catalyzed direct arylation^{3a,b} and olefination^{3a,c} reactions. Key to the success of these reactions was that the enaminone substrates were sufficiently nucleophilic to undergo electrophilic palladation. Moreover, relative to many nonaromatic enamine/enamide systems,^{5,6} 6-membered cyclic enaminones are considerably more stable, making them ideal substrates for these reactions which require elevated temperatures and an acidic reaction medium. Furthermore, cyclic enaminones have great potential in various synthetic transformations, considering the multiple functional groups including alkene, enamine and enone that are embedded within this substrate.⁷ The synthetic utility of cyclic enaminones is particularly attractive when considering the ubiquity of piperidine-containing molecules. Our lab has taken interest in indolizidine and quinolizidine alkaloids,⁸ many of which are known to have important biological activities. In our efforts toward the synthesis of these natural products, cyclic enaminones have served as invaluable synthetic intermediates, expediting the synthesis of several members of this class including boehmeriasin A^{4a}, ipalbidine^{4b} and tylocrine.^{4c}

To date, we have demonstrated that cyclic enaminones undergo direct arylation with aryltrifluoroborates^{3a} and arylsilanes.^{3b} Although these methods provide a short and convenient route to arylated enaminones, several shortcomings limit their utility and

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Supporting information

Optimization studies of reaction temperature and time, and copies of ¹H/¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

inspired us to expand the scope and efficiency of this reaction. In this regard, we have developed a new arylation protocol that accommodates boronic acids, which are more readily available than either aryltrifluoroborates or arylsilanes. Furthermore, the yield and conversion of each reaction are seemingly independent of the electronic substituent effects on the aryl donor—a significant improvement over previous reports which exhibited a significant preference for electron-rich arenes.^{3a} We believe that the success of this reaction can be attributed to a unique mixture of Cu(II) additives, assisting transmetallation to the palladated enaminone through an intermediate arylcopper species. Herein we report the discovery of this copper-assisted Pd(II)-catalyzed C–H arylation reaction.

Copper(I) halide additives have been shown to improve Stille⁹, Suzuki¹⁰ and are used in Sonogashira¹¹ reactions. It has been postulated that Cu(I) transmetallates with organometals to generate a more reactive organocopper intermediate which assists the delivery of the aryl group to the palladium center.¹² This was recently exemplified by Deng *et al.* showing that 2-pyridyl boronates, which are notoriously poor coupling partners, undergo high-yielding Suzuki reactions in the presence of copper but not without (Scheme 1, eq 1).¹² It is also well known that arylboronic acids undergo facile transmetallation to arylcopper species in the presence of copper(II) salts (Scheme 1, eq 2).¹³ In our previously developed method,^{3a} the limited scope of coupling partners implicated either the transmetallation step or the preceding hydrolysis of the trifluoroborates to their respective boronic acids as the primary cause of poor conversions.¹⁴ Thus, we hypothesized that conditions which were amenable to an *in situ* formation of an arylcopper species could remedy this substrate bias by increasing the efficiency of the transmetallation (Scheme 1, eq 3).

Results and Discussion

We undertook an intensive screening process (Table 1) using enaminone **1** and *p*-methoxyphenylboronic acid (**2a**) as model substrates. Since the reaction conditions require an oxidant to regenerate the Pd(II) catalyst, we hypothesized that our copper source could serve a dual role as an oxidant and to assist transmetallation. As such, Pd(OAc)₂ (10 mol%) and Cu(OAc)₂ (2 equiv) were initially chosen based on previously optimized conditions for enaminone coupling reactions.³ Amide solvents (DMF, NMP and DMA) were superior to other solvents, however, the yields were quite low. It is worth noting that the use of a cosolvent to promote the oxidation of Pd(0)¹⁵ or increase the electrophilicity of the Pd(II) center¹⁶ did not improve yields (entries 10 and 11). We next screened various oxidants, finding no improvement in yield over Cu(OAc)₂. We noted that in most reactions the majority of enaminone **1** remained unreacted and the major product was 4,4'-dimethoxy-1,1'-biphenyl, suggesting that the low yields resulted from consumption of the boronic acid and the reoxidant through a competing homodimerization pathway.

Next we turned to screening various additives to improve our low reaction yields (Table 2). We were pleased to find that many organic and inorganic additives improved yields. Most notably, the addition of potassium salts (entries 3 and 9), acetate salts (entries 8–10) or chloride salts (entries 16–24) seemed to have beneficial effects. The advantageous effects of CuCl₂ (entry 24) led us to examine alternative sources of copper and optimal quantities of these additives (entries 24–29). As seen in entries 26 and 27, the highest yields (81%) were obtained when using at least two equivalents of CuCl₂. Interestingly, CuCl only moderately improved yields and CuI completely suppressed product formation. We also investigated the time that it takes to complete the reaction (see SI and Table 3) and found that reaction for 1 h at 60 °C provided the same yield of **3a** (81%) as obtained from a 20 h reaction time (Table 2).

Having established a high-yielding protocol for cross-coupling, we applied our optimized conditions to a collection of electronically diverse arylboronic acids (Table 3). In contrast to our previously reported method using trifluoroborates,^{3a} both electron-rich and electron-poor arylboronic acids coupled smoothly and in high yields. As exemplified by the lower yields of *o*-methoxy substituted arenes (Table 3, **3c**) compared with those of *p*- and *m*-methoxy substituted arenes (Table 3, **3a** and **3b**), steric factors clearly reduced cross-coupling efficiency, albeit to a lesser extent than we had previously noted in reactions with trifluoroborates.^{3a}

In general, this method was found to have excellent functional group compatibility. A phenol (Table 3, **3f**), an aryl bromide (Table 3, **3i**), a 1° amide (Table 3, **3k**), a ketone (Table 3, **3l**) and an aldehyde (Table 3, **3o**) were all well tolerated. However, thienylboronic acid coupled in low yield (Table 3, **3q**) and furanylboronic acid did not afford any product (Table 3, **3r**).

Next we varied the enaminone component **4**, and used *p*-methoxyphenylboronic acid (**2a**) as a model boronic acid (Table 4). As we observed previously,^{3a} mono- and bicyclic enaminones with *N*-alkyl substituents were all suitable substrates in this transformation (Table 4, **5a–5e**). Notably, *N*-phenyl enaminone **5b** was also formed in comparable yields to *N*-benzyl (Table 4, **5a**) or *N*-methyl (Table 4, **5c**) analogs despite its tempered nucleophilicity. In contrast, the arylation of *N*-carbamylated enaminone **5h** was not observed. A methyl group in the C6 position was surprisingly well-tolerated, furnishing tetrasubstituted olefinic compound **5j**. However, substrates with more sterically demanding groups at C6, such as *tert*-butyl or phenyl, did not react.

The expanded substrate scope and lack of dependency on the electronic nature of boronic acids led us to speculate that this reaction was proceeding through a mechanism which was distinct from our previously reported method using trifluoroborates.^{3a} To shed light on the mechanism and respective roles of each reagent, we investigated the optimized reaction conditions in further detail (Tables 5 and 6). We first noted that subjecting boronic acid **2a** to the cross-coupling conditions in the absence of an enaminone coupling partner resulted in high yields of the homocoupled by-product (Table 5 entry 1).¹⁷ Similar results were obtained in the absence of CuCl₂ (entry 2), but yields were considerably lower in the absence of Cu(OAc)₂ or Pd(OAc)₂ (entries 3–6). Notably, under palladium-free condition (entry 4), we observed rapid and near complete (> 95%) consumption of the boronic acid in under 15 min.¹⁸ In the presence of the enaminone coupling partner, cross-coupling was only observed in the presence of palladium (Table 6). Thus, in contrast to boronic acid homocoupling, cyclic enaminone cross-coupling is an exclusively Pd-mediated process. Indeed, the reaction proceeds, albeit in modest yield, in the absence of any copper source when using 100 mol% of Pd(OAc)₂ (entry 9). Nevertheless, under these stoichiometric conditions, which presumably minimizes the necessity of a reoxidant, product formation was improved upon the addition of Cu(OAc)₂, CuCl₂ or both (entries 10–12). Interestingly, the beneficial effects of the mixed Cu(OAc)₂/CuCl₂ system was enhanced when Pd(OAc)₂ was employed catalytically (entry 5). Neither Cu(OAc)₂ or CuCl₂ alone provided high yields of arylated enaminone **3a**. Additionally, doubling the quantity of Cu(OAc)₂ (entry 8) did not significantly improve the coupling reaction, thereby indicating that the effects of the Cu(OAc)₂ and CuCl₂ system are cooperative and not merely additive.

We propose a mechanism that could explain these observations. We envision that electrophilic palladation initially furnishes an enaminone-palladium complex, which has previously been shown to occur within minutes at room temperature.^{3c} Once this palladium-enaminone complex has formed, the aryl group is delivered to the palladium center via transmetallation, which could transpire directly from the boronic acid or from a putative

arylcopper intermediate. Although the former cannot be completely ruled out, we believe that the latter mechanism is plausible considering: (1) boronic acids are known to readily transmetallate with $\text{Cu}(\text{OAc})_2$ to form organocopper species;¹³ (2) the arylboronic acid is rapidly consumed upon exposure to the $\text{Cu}(\text{OAc})_2/\text{CuCl}_2$ mixture in the absence of palladium; (3) in contrast to our previously developed trifluoroborate cross-coupling method,^{3a} the rate of reaction is extremely fast;¹⁹ and (4) the reaction efficiency is seemingly independent of the electronic nature of the boronic acid. Collectively, these data suggest that $\text{Cu}(\text{OAc})_2$ and CuCl_2 have mutual roles on improving the efficiency of cross-coupling, presumably through facilitating the delivery of the aryl moiety to the Pd-center via an aryl-copper intermediate. However, the precise roles of each reagent in this process remain elusive.

Conclusion

In summary, we have developed a new method for the C–H arylation of cyclic enaminones using boronic acids as aryl donors. In large part, the success of this reaction is due to a mixture of $\text{Cu}(\text{OAc})_2$ and CuCl_2 that appear to be cooperative and allows for efficient cross-coupling with a diverse set of arylboronic acids without the previously observed preference for electron-rich coupling partners.^{3a} Although the exact role of each copper additive is not clear, we believe that these reagents not only serve as Pd-reoxidants, but also assist aryl delivery to the palladated enaminone through a putative arylcopper intermediate. As such, this reaction represents a significant advancement over previously developed methods for enaminone arylation and leads us to speculate that this copper additive mixture could be of more general utility in boronic acid cross-coupling reactions where transmetallation is disfavored.

Experimental Section

General Procedure for Enaminone Arylation

The cyclic enaminone (0.20 mmol), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), $\text{Cu}(\text{OAc})_2$ (73 mg, 0.40 mmol) and CuCl_2 (54 mg, 0.40 mmol) were combined in DMF (1.0 mL) under N_2 and stirred for 5 min (Note: Solvents were used without purification or degassing). The resulting solution was heated to 60 °C and the arylboronic acid (0.40 mmol) was added in one portion. After stirring for 1 h the reaction mixture was cooled to room temperature and diluted with EtOAc (5 mL). The precipitate was filtered through Celite using EtOAc as the eluent. The filtrate was concentrated and purified by flash column chromatography on silica gel using hexanes and an increasing proportion of EtOAc as eluent.

1-Benzyl-2,5-bis(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3a)—

Compound **3a** was prepared by the general procedure described above and 65 mg (81%) was isolated as light yellow oil. R_f 0.48 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.46 (s, 1H), 7.39–7.31 (m, 5H), 7.22–7.14 (m, 4H), 6.92–6.85 (m, 4H), 4.51 (dd, J = 8.6, 6.8 Hz, 1H), 4.38 (d, J = 15.1 Hz, 1H), 4.18 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.92 (dd, J = 16.2, 6.7 Hz, 1H), 2.82 (dd, J = 16.2, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.2, 159.6, 157.9, 152.7, 136.1, 130.6, 129.0, 128.9, 128.6, 128.4, 128.2, 127.7, 114.3, 113.7, 111.1, 60.4, 57.2, 55.3, 44.5; FTIR (KBr, cm^{-1}) 3030, 2932, 2835, 1634, 1594, 1440, 1357, 1302, 1246, 1177, 1124, 1033, 837, 735, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{26}\text{NO}_3$: 400.1913, found 400.1902.

1-Benzyl-5-(3-methoxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3b)—Compound **3b** was prepared by the general procedure described above and 64 mg (81%) was isolated as light yellow oil. R_f 0.50 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.55 (s, 1H), 7.40–7.30 (m, 3H), 7.26–7.13 (m, 5H), 7.09–7.06 (m, 1H),

7.01 (d, $J = 7.7$ Hz, 1H), 6.90–6.83 (m, 2H), 6.78–6.71 (m, 1H), 4.51 (dd, $J = 7.9, 7.1$ Hz, 1H), 4.40 (d, $J = 15.1$ Hz, 1H), 4.20 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.94 (dd, $J = 16.2, 6.8$ Hz, 1H), 2.81 (dd, $J = 16.2, 8.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.7, 159.6, 159.4, 153.2, 137.5, 135.8, 130.3, 129.0, 128.9, 128.3, 128.2, 127.7, 119.8, 114.4, 113.3, 111.3, 110.8, 60.2, 57.4, 55.3, 55.2, 44.5; FTIR (KBr, cm^{-1}) 3030, 2957, 2835, 1635, 1594, 1511, 1453, 1357, 1253, 1178, 1121, 1036, 833, 734, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{26}\text{NO}_3$: 400.1913, found 400.1901.

1-Benzyl-5-(2-methoxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3c)—Compound **3c** was prepared by the general procedure described above and 41

mg (51%) was isolated as a light yellow solid (mp 102–105 °C). R_f 0.31 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.52 (s, 1H), 7.38–7.30 (m, 4H), 7.26–7.17 (m, 5H), 6.99–6.85 (m, 4H), 4.53 (dd, $J = 9.0, 6.8$ Hz, 1H), 4.34 (d, $J = 15.1$ Hz, 1H), 4.14 (d, $J = 15.1$ Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.91 (dd, $J = 16.2, 6.8$ Hz, 1H), 2.84 (dd, $J = 16.1, 9.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.8, 159.6, 157.1, 155.2, 136.1, 132.0, 130.8, 128.8, 128.6, 128.1, 127.8, 127.6, 124.9, 120.6, 114.3, 111.4, 107.4, 60.6, 57.2, 55.7, 55.3, 44.5; FTIR (KBr, cm^{-1}) 3030, 2932, 2835, 1634, 1593, 1512, 1455, 1376, 1306, 1250, 1178, 1129, 1029, 836, 753, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{26}\text{NO}_3$: 400.1913, found 400.1898.

1-Benzyl-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridin-4(1H)-one (3d)—

Compound **3d** was prepared by the general procedure described above and 59 mg (80%) was isolated as light yellow oil. R_f 0.60 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 1H), 7.46–7.42 (m, 2H), 7.39–7.29 (m, 5H), 7.23–7.14 (m, 5H), 6.90–6.85 (m, 2H), 4.52 (dd, $J = 8.2, 6.9$ Hz, 1H), 4.40 (d, $J = 15.1$ Hz, 1H), 4.20 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 2.95 (dd, $J = 16.2, 6.8$ Hz, 1H), 2.82 (dd, $J = 16.2, 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.9, 159.6, 153.1, 136.1, 135.9, 130.5, 129.0, 128.4, 128.3, 128.2, 127.7, 127.7, 125.8, 114.4, 111.3, 60.4, 57.4, 55.3, 44.5; FTIR (KBr, cm^{-1}) 3030, 2918, 2836, 1635, 1595, 1512, 1452, 1375, 1358, 1304, 1251, 1178, 1124, 1030, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{25}\text{H}_{24}\text{NO}_2$: 370.1807, found 370.1810.

1-Benzyl-2-(4-methoxyphenyl)-5-(*p*-tolyl)-2,3-dihydropyridin-4(1H)-one (3e)—

Compound **3e** was prepared by the general procedure described above and 58 mg (75%) was isolated as a light yellow solid (mp 88–90 °C). R_f 0.45 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 1H), 7.38–7.29 (m, 5H), 7.22–7.12 (m, 6H), 6.90–6.84 (m, 2H), 4.51 (dd, $J = 8.5, 6.8$ Hz, 1H), 4.39 (d, $J = 15.1$ Hz, 1H), 4.18 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 2.93 (dd, $J = 16.2, 6.7$ Hz, 1H), 2.82 (dd, $J = 16.2, 8.6$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.0, 159.6, 152.9, 136.0, 135.4, 133.1, 130.6, 129.0, 128.9, 128.4, 128.2, 127.7, 127.6, 114.4, 111.4, 60.5, 57.3, 55.3, 44.6, 21.1; FTIR (KBr, cm^{-1}) 3028, 2919, 1637, 1595, 1512, 1440, 1357, 1303, 1252, 1178, 1122, 1032, 836, 810, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{26}\text{NO}_2$: 384.1964, found 384.1964.

1-Benzyl-5-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3f)—Compound **3f** was prepared by the general procedure described above and 48 mg

(62%) was isolated as colorless oil. R_f 0.21 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.46 (s, 1H), 7.39–7.29 (m, 3H), 7.28–7.26 (m, 1H), 7.25 (d, $J = 2.9$ Hz, 1H), 7.22–7.13 (m, 4H), 6.93–6.85 (m, 2H), 6.80–6.74 (m, 2H), 5.39 (s, 1H), 4.51 (dd, $J = 8.6, 6.8$ Hz, 1H), 4.38 (d, $J = 15.1$ Hz, 1H), 4.18 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 2.93 (dd, $J = 16.3, 6.8$ Hz, 1H), 2.82 (dd, $J = 16.3, 8.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.4, 159.6, 154.2, 153.1, 136.0, 130.4, 129.2, 129.0, 128.4, 128.3, 128.2, 127.7, 115.3, 114.4, 111.3, 60.4, 57.3, 55.4, 44.4; FTIR (KBr, cm^{-1}) 3326, 1606, 1566, 1511, 1370, 1294, 1248,

1129, 1031, 957, 823, 731, 695, 612, 585; HRMS (ESI, TOF) m/e calculated for $[M+H]^+$ $C_{26}H_{24}NO_3$: 398.1756, found 398.1747.

1-Benzyl-5-(4-fluorophenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3g)—Compound **3g** was prepared by the general procedure described above and 66 mg

(85%) was isolated as a yellow solid (mp 131–134 °C). R_f 0.45 (hexanes/EtOAc, 1:1). 1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.43–7.30 (m, 5H), 7.22–7.13 (m, 4H), 7.06–6.97 (m, 2H), 6.91–6.85 (m, 2H), 4.52 (dd, J = 8.2, 6.9 Hz, 1H), 4.40 (d, J = 15.1 Hz, 1H), 4.20 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.94 (dd, J = 16.3, 6.8 Hz, 1H), 2.81 (dd, J = 16.3, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 161.2 (d, J = 244.3 Hz), 159.7, 152.9, 135.9, 132.0 (d, J = 3.2 Hz), 130.3, 129.2 (d, J = 7.7 Hz), 128.7 (d, J = 63.5 Hz), 128.4, 127.7, 115.1, 114.9, 114.4, 110.4, 60.4, 57.4, 55.3, 44.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.3; FTIR (KBr, cm^{-1}) 3031, 2931, 2837, 1634, 1595, 1509, 1441, 1357, 1295, 1252, 1178, 1123, 1032, 840, 735, 699; HRMS (ESI, TOF) m/e calculated for $[M+H]^+$ $C_{25}H_{23}FNO_2$: 388.1713, found 388.1704.

1-Benzyl-5-(4-chlorophenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3h)—Compound **3h** was prepared by the general procedure described above and 63 mg

(78%) was isolated as a yellow solid (mp 129–132 °C). R_f 0.55 (hexanes/EtOAc, 1:1). 1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.41–7.33 (m, 5H), 7.31–7.24 (m, 2H), 7.21–7.13 (m, 4H), 6.93–6.82 (m, 2H), 4.52 (t, J = 7.4 Hz, 1H), 4.41 (d, J = 15.1 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.94 (dd, J = 16.3, 6.8 Hz, 1H), 2.81 (dd, J = 16.3, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 159.7, 152.9, 135.8, 134.6, 131.3, 130.2, 129.0, 128.8, 128.4, 128.3, 127.7, 114.5, 110.0, 60.3, 57.5, 55.3, 44.3; FTIR (KBr, cm^{-1}) 3030, 2928, 2836, 1634, 1598, 1511, 1440, 1372, 1294, 1251, 1178, 1124, 1032, 837, 735, 698; HRMS (ESI, TOF) m/e calculated for $[M+H]^+$ $C_{25}H_{23}ClNO_2$: 404.1417, found 404.1411.

1-Benzyl-5-(4-bromophenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (3i)—Compound **3i** was prepared by the general procedure described above and 77 mg

(86%) was isolated as yellow oil. R_f 0.60 (hexanes/EtOAc, 1:1). 1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.47 (m, 1H), 7.45–7.38 (m, 2H), 7.37–7.29 (m, 5H), 7.20–7.11 (m, 4H), 6.89–6.82 (m, 2H), 4.50 (t, J = 7.5 Hz, 1H), 4.40 (d, J = 15.1 Hz, 1H), 4.20 (d, J = 15.1 Hz, 1H), 3.79 (s, 3H), 2.92 (dd, J = 16.3, 6.9 Hz, 1H), 2.78 (dd, J = 16.3, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 159.7, 152.9, 135.7, 135.0, 131.2, 130.2, 129.1, 129.0, 128.3, 127.7, 119.3, 114.5, 110.0, 60.3, 57.5, 55.3, 44.3; FTIR (KBr, cm^{-1}) 3030, 2932, 2835, 1634, 1596, 1511, 1440, 1356, 1294, 1252, 1178, 1123, 1032, 836, 811, 735, 698; HRMS (ESI, TOF) m/e calculated for $[M+H]^+$ $C_{25}H_{23}BrNO_2$: 448.0912, found 448.0898.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)-2,3-dihydropyridin-4(1H)-one (3j)—Compound **3j** was prepared by the general procedure

described above and 70 mg (80%) was isolated as yellow oil. R_f 0.55 (hexanes/EtOAc, 1:1). 1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.59–7.53 (m, 4H), 7.43–7.30 (m, 3H), 7.21–7.14 (m, 4H), 6.92–6.85 (m, 2H), 4.55 (t, J = 7.4 Hz, 1H), 4.45 (d, J = 15.1 Hz, 1H), 4.25 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.97 (dd, J = 16.3, 6.9 Hz, 1H), 2.82 (dd, J = 16.3, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 159.8, 153.3, 139.8, 135.6, 130.1, 129.1, 128.5, 128.3, 127.7, 127.4 (q, J = 32.2 Hz), 127.3, 125.1 (q, J = 3.8 Hz), 124.5 (q, J = 27.2 Hz), 114.5, 109.6, 60.2, 57.7, 55.3, 44.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ 62.8; FTIR (KBr, cm^{-1}) 3032, 2934, 2838, 1639, 1596, 1512, 1443, 1374, 1325, 1253, 1161, 1112, 1067, 847, 736, 699; HRMS (ESI, TOF) m/e calculated for $[M+H]^+$ $C_{26}H_{23}F_3NO_2$: 438.1681, found 438.1692.

4-(1-Benzyl-6-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydropyridin-3-yl)benzamide (3k)—Compound **3k** was prepared by the general procedure described above and 61 mg (74%) was isolated as a light yellow solid (mp 194–197 °C). R_f 0.47 (EtOAc). ^1H NMR (400 MHz, DMSO) δ 8.24 (s, 1H), 7.85 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.42–7.35 (m, 2H), 7.35–7.29 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 7.21 (s, 1H), 6.92 (d, J = 8.7 Hz, 2H), 4.86 (d, J = 15.2 Hz, 1H), 4.64 (dd, J = 7.0, 4.9 Hz, 1H), 4.23 (d, J = 15.2 Hz, 1H), 3.73 (s, 3H), 2.96 (dd, J = 16.0, 7.3 Hz, 1H), 2.54 (dd, J = 16.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 186.1, 167.8, 158.8, 154.3, 139.7, 136.9, 130.0, 129.9, 128.7, 127.8, 127.6, 127.1, 125.7, 114.2, 107.3, 58.4, 56.8, 55.1, 43.9; FTIR (KBr, cm^{-1}) 3346, 3194, 2925, 1669, 1594, 1511, 1378, 1250, 1027, 820, 774, 734, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_3$: 413.1865, found 413.1860.

4-(1-Benzyl-6-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydropyridin-3-yl)benzamide (3l)—Compound **3l** was prepared by the general procedure described above and 67 mg (82%) was isolated as yellow oil. R_f 0.41 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.95–7.87 (m, 2H), 7.68 (s, 1H), 7.61–7.56 (m, 2H), 7.41–7.32 (m, 3H), 7.22–7.12 (m, 4H), 6.91–6.84 (m, 2H), 4.55 (t, J = 7.3 Hz, 1H), 4.48 (d, J = 15.1 Hz, 1H), 4.26 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.98 (dd, J = 16.2, 7.0 Hz, 1H), 2.81 (dd, J = 16.2, 7.6 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.7, 187.5, 159.7, 153.5, 141.3, 135.5, 134.1, 130.0, 129.1, 128.5, 128.4, 128.3, 127.7, 126.8, 114.5, 109.6, 60.1, 57.8, 55.3, 44.3, 26.5; FTIR (KBr, cm^{-1}) 3032, 3003, 2961, 2837, 1673, 1634, 1591, 1512, 1442, 1358, 1269, 1180, 1124, 1032, 957, 844, 734, 700; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{27}\text{H}_{26}\text{NO}_3$: 412.1913, found 412.1913.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2,3-dihydropyridin-4(1H)-one (3m)—Compound **3m** was prepared by the general procedure described above and 75 mg (90%) was isolated as a brown solid (mp 98–101 °C). R_f 0.45 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 8.15–8.11 (m, 2H), 7.75 (s, 1H), 7.67–7.63 (m, 2H), 7.42–7.34 (m, 3H), 7.21–7.15 (m, 4H), 6.90–6.86 (m, 2H), 4.58 (t, J = 7.1 Hz, 1H), 4.52 (d, J = 15.1 Hz, 1H), 4.30 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 3.00 (dd, J = 16.3, 7.1 Hz, 1H), 2.81 (dd, J = 16.3, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.3, 159.8, 153.8, 144.9, 143.4, 135.2, 129.7, 129.2, 128.6, 128.2, 127.7, 126.8, 123.6, 114.6, 108.4, 60.0, 58.0, 55.3, 44.1; FTIR (KBr, cm^{-1}) 3031, 2914, 2837, 1638, 1578, 1510, 1443, 1329, 1251, 1179, 1107, 1031, 854, 735, 698; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_4$: 415.1658, found 415.1651.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2,3-dihydropyridin-4(1H)-one (3n)—Compound **3n** was prepared by the general procedure described above and 62 mg (78%) was isolated as yellow oil. R_f 0.43 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.65 (s, 1H), 7.62–7.54 (m, 4H), 7.42–7.32 (m, 3H), 7.19–7.15 (m, 4H), 6.92–6.85 (m, 2H), 4.56 (t, J = 7.2 Hz, 1H), 4.48 (d, J = 15.1 Hz, 1H), 4.28 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.98 (dd, J = 16.3, 7.0 Hz, 1H), 2.81 (dd, J = 16.3, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.3, 159.8, 153.4, 141.1, 135.3, 132.0, 129.8, 129.2, 128.6, 128.2, 127.7, 127.2, 119.6, 114.6, 108.9, 108.3, 60.1, 57.9, 55.4, 44.2; FTIR (KBr, cm^{-1}) 3032, 2932, 2837, 2221, 1634, 1575, 1512, 1443, 1353, 1253, 1179, 1123, 1032, 962, 844, 735, 700; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_2$: 395.1760, found 395.1751.

4-(1-Benzyl-6-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydropyridin-3-yl)benzaldehyde (3o)—Compound **3o** was prepared by the general procedure described above and 66 mg (83%) was isolated as yellow oil. R_f 0.36 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 9.94 (s, 1H), 7.85–7.76 (m, 2H), 7.71 (s, 1H), 7.68–7.65 (m, 2H),

7.42–7.32 (m, 3H), 7.22–7.13 (m, 4H), 6.92–6.85 (m, 2H), 4.56 (t, $J = 7.2$ Hz, 1H), 4.49 (d, $J = 15.1$ Hz, 1H), 4.28 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 2.99 (dd, $J = 16.2, 7.0$ Hz, 1H), 2.82 (dd, $J = 16.2, 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.9, 187.4, 159.8, 153.6, 142.9, 135.4, 133.5, 129.9, 129.1, 128.5, 128.3, 127.7, 127.1, 114.5, 109.4, 60.1, 57.9, 55.3, 44.3; FTIR (KBr, cm^{-1}) 3031, 2933, 2837, 1693, 1590, 1512, 1443, 1353, 1305, 1251, 1176, 1123, 1031, 833, 735, 700; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{24}\text{NO}_3$: 398.1756, found 398.1747.

1-Benzyl-2-(4-methoxyphenyl)-5-(naphthalen-2-yl)-2,3-dihydropyridin-4(1H)-one (3p)—Compound **3p** was prepared by the general procedure described above and 70 mg (83%) was isolated as brown oil. R_f 0.43 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.79 (dd, $J = 8.3, 5.8$ Hz, 3H), 7.68–7.59 (m, 2H), 7.46–7.29 (m, 5H), 7.26–7.13 (m, 4H), 6.93–6.85 (m, 2H), 4.53 (t, $J = 7.5$ Hz, 1H), 4.43 (d, $J = 15.2$ Hz, 1H), 4.21 (d, $J = 15.1$ Hz, 1H), 3.80 (s, 3H), 2.98 (dd, $J = 16.2, 6.8$ Hz, 1H), 2.84 (dd, $J = 16.2, 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.0, 159.6, 153.4, 135.9, 133.8, 133.7, 131.9, 130.4, 129.0, 128.4, 128.3, 127.7, 127.7, 127.5, 127.5, 126.7, 125.7, 125.3, 125.0, 114.4, 111.0, 60.3, 57.5, 55.3, 44.5; FTIR (KBr, cm^{-1}) 3054, 2960, 2836, 1635, 1592, 1511, 1441, 1360, 1303, 1251, 1178, 1107, 1032, 818, 734, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{29}\text{H}_{26}\text{NO}_2$: 420.1964, found 420.1953.

1-Benzyl-2-(4-methoxyphenyl)-5-(thiophen-3-yl)-2,3-dihydropyridin-4(1H)-one (3q)—Compound **3q** was prepared by the general procedure described above and 18 mg (24%) was isolated as yellow oil. R_f 0.50 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.69 (s, 1H), 7.60 (dd, $J = 3.0, 1.1$ Hz, 1H), 7.39–7.31 (m, 3H), 7.27 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.22 (dd, $J = 5.0, 1.1$ Hz, 1H), 7.20–7.14 (m, 4H), 6.90–6.84 (m, 2H), 4.50 (t, $J = 7.5$ Hz, 1H), 4.42 (d, $J = 15.1$ Hz, 1H), 4.21 (d, $J = 15.1$ Hz, 1H), 3.81 (s, 3H), 2.94 (dd, $J = 16.3, 6.9$ Hz, 1H), 2.80 (dd, $J = 16.3, 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.8, 159.6, 152.3, 135.9, 130.3, 129.0, 128.4, 128.3, 127.7, 125.6, 124.5, 118.9, 114.4, 106.9, 60.2, 57.5, 55.3, 44.3; FTIR (KBr, cm^{-1}) 3030, 2925, 2853, 1598, 1511, 1440, 1296, 1252, 1178, 1112, 1031, 838, 783, 734, 699; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{23}\text{H}_{22}\text{NO}_2\text{S}$: 376.1371, found 376.1370.

1-Benzyl-5-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (5a)—Compound **5a** was prepared by the general procedure described above and 41 mg (70%) was isolated as yellow oil. Spectral data of the title compound was identical to that in our previous report.^{3a}

5-(4-Methoxyphenyl)-1-phenyl-2,3-dihydropyridin-4(1H)-one (5b)—Compound **5b** was prepared by the general procedure described above and 34 mg (60%) was isolated as a brown solid (mp 129–132 °C). R_f 0.26 (hexanes/EtOAc, 1:1). ^1H NMR (400 MHz, CDCl_3) δ 7.59 (s, 1H), 7.42–7.31 (m, 4H), 7.18–7.10 (m, 3H), 6.91–6.85 (m, 2H), 4.06 (t, $J = 7.6$ Hz, 2H), 3.79 (s, 3H), 2.79 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.7, 158.3, 147.7, 145.2, 129.7, 129.3, 128.2, 124.2, 118.0, 114.4, 113.7, 55.3, 47.6, 36.6; FTIR (KBr, cm^{-1}) 3052, 2952, 2835, 1645, 1583, 1510, 1386, 1302, 1243, 1178, 1130, 1029, 831, 760, 698; HRMS (ESI, TOF) m/e calculated for $[\text{M}+\text{H}]^+ \text{C}_{18}\text{H}_{18}\text{NO}_2$: 280.1338, found 280.1339.

5-(4-Methoxyphenyl)-1-methyl-2,3-dihydropyridin-4(1H)-one (5c)—Compound **5c** was prepared by the general procedure described above and 28 mg (65%) was isolated as yellow oil. Spectral data of the title compound was identical to that in our previous report.³

3-(4-Methoxyphenyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (5d)—Compound **5d** was prepared by the general procedure described above and 42 mg (82%)

was isolated as a pale yellow solid. Spectral data of the title compound was identical to that in our previous report.^{3a}

6-(4-Methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one (5e)—Compound **5e** was prepared by the general procedure described above and 27 mg (56%) was isolated as a pale yellow solid. Spectral data of the title compound was identical to that in our previous report.^{3a}

(cis)-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1H)-one (5f)—Compound **5f** was prepared by the general procedure described above and 41 mg (76%) was isolated as colorless oil. Spectral data of the title compound was identical to that in our previous report.^{3a}

(trans)-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1H)-one (5g)—Compound **5g** was prepared by the general procedure described above and 45 mg (83%) was isolated as a pale yellow solid. Spectral data of the title compound was identical to that in our previous report.^{3a}

1-Benzyl-5-(4-methoxyphenyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (5j)—Compound **5j** was prepared by the general procedure described above and 38 mg (61%) was isolated as a yellow solid (mp 92–95 °C). *R_f* 0.32 (hexanes/acetone, 1:1). ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.36 (m, 2H), δ 7.34–7.30 (m, 1H), 7.27–7.22 (m, 2H), 7.09–7.04 (m, 2H), 6.90–6.85 (m, 2H), 4.58 (s, 2H), 3.79 (s, 3H), 3.56 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 189.2, 159.9, 158.0, 137.0, 132.7, 129.8, 129.0, 127.8, 126.4, 113.6, 113.4, 55.3, 55.2, 48.8, 36.1, 18.6; FTIR (KBr, cm⁻¹) 3030, 2959, 2834, 1621, 1538, 1469, 1297, 1240, 1160, 1098, 1028, 835, 732, 698; HRMS (ESI, TOF) *m/e* calculated for [M+H]⁺ C₂₀H₂₂NO₂: 308.1610, found 308.1630.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. The reaction was monitored by ^1H NMR using the crude reaction mixture in deuterated DMF. A new compound was observed as a major product in the NMR spectrum of the crude mixture; however it was not isolable because the product decomposed. The formation of the homodimer was also observed but only as a minor product.
19. See Supporting Information

SCHEME 1.
Copper Mediated Reactions with Organoborons

TABLE 1

Screening of Solvents and Oxidants^a

entry	solvent	reoxidant	3a (%)
1	<i>t</i> -BuOH	Cu(OAc) ₂	6
2	<i>t</i> -AmOH	Cu(OAc) ₂	< 3
3	toluene	Cu(OAc) ₂	< 3
4	DMSO	Cu(OAc) ₂	11
5	AcOH	Cu(OAc) ₂	4
6	DMF	Cu(OAc) ₂	18
7	DMA	Cu(OAc) ₂	18
8	NMP	Cu(OAc) ₂	14
9	dioxane	Cu(OAc) ₂	< 3
10	DMF/DMSO = 20/1	Cu(OAc) ₂	9
11	DMF/AcOH = 4/1	Cu(OAc) ₂	< 3
12	DMF/AcOH/DMSO = 20/5/1	Cu(OAc) ₂	15
13	DMF/H ₂ O = 9/1	Cu(OAc) ₂	15
14	MeCN	Cu(OAc) ₂	9
15	DMF	Cu(OTf) ₂	11
16	DMF	duroquinone	< 3
17	DMF	PhCO ₃ <i>t</i> -Bu ^b	< 3
18	DMF	Ag ₂ O	< 3
19	DMF	AgOAc	15
20	DMF	O ₂ ^c	0
21	DMSO	O ₂ ^c	0
22	DMF	Cu(OAc) ₂ ^b + Ag ₂ O ^b	16
23	DMF	Cu(OAc) ₂ ^b + air	8
24	DMF	Cu(OAc) ₂ ^b + O ₂ ^c	8
25	DMF	CuCl ₂	18
26	DMF	CuCl ₂ ^b + O ₂ ^c	15

^a Reaction conditions unless otherwise specified: **1** (0.2 M), **2a** (2 equiv), Pd(OAc)₂ (10 mol%), reoxidant (2 equiv) under N₂ at 60 °C for 20 h, the yield was determined by ¹H NMR analysis of the crude product using Ph₃SiMe (1 equiv) as the internal standard. (PMP = *p*-methoxyphenyl)

^b 1 equiv.

^c balloon pressure.

TABLE 2

Screening of Additives^a

+ PMP-B(OH) ₂
		$\xrightarrow[\text{DMF, 20 h, 60 } ^\circ\text{C}]{\text{Pd(OAc)}_2, \text{Cu(OAc)}_2, \text{additive}}$					
1		2a		3a		3a (%)	
entry	additive (equiv)	3a (%)	entry	additive (equiv)	3a (%)	entry	3a (%)
1	none	18	16	HCl ^c (1)	22		
2	NaF (2)	16	17	LiCl (1)	55		
3	KF (2)	41	18	NaCl (1)	18		
4	CsF (2)	28	19	KCl (1)	16		
5	TBAF ^b (2)	11	20	CsCl (1)	34		
6	KTFA (1)	33	21	MgCl ₂ (1)	51		
7	LiBF ₄ (1)	17	22	CaCl ₂ (1)	25		
8	NaOAc (1)	29	23	BiCl ₃ (1)	61		
9	KOAc (1)	47	24	CuCl ₂ (0.5)	60		
10	CsOAc (1)	28	25	CuCl ₂ (1)	73		
11	K ₂ CO ₃ (1)	34	26	CuCl₂ (2)	81		
12	Cs ₂ CO ₃ (1)	17	27	CuCl ₂ (3)	81		
13	K ₃ PO ₄ (1)	31	28	CuCl (2)	31		
14	Me ₃ CCO ₂ H (1)	16	29	CuI (2)	0		
15	TFA (0.1)	31					

^aReaction conditions: **1** (1 equiv), **2a** (2 equiv), Pd(OAc)₂ (10 mol%), Cu(OAc)₂ (2 equiv), DMF (0.2 M) under N₂ for 20 h at 60 °C; the yield was determined by ¹H NMR analysis of the crude product using Ph₃SiMe (1 equiv) as the internal standard.

^b1.0 M in THF.

^c12.1 M.

TABLE 3

Scope of Arylboronic Acids

CC1=C(C(=O)N)C(=O)N(C1)c2ccccc2 + CC1=C(C(=O)N)C(=O)N(C1)c2ccccc2
 $\xrightarrow[\text{DMF, 60 } ^\circ\text{C, 1 h}]{\text{Pd(OAc)}_2 \text{ (10 mol\%)}, \text{Cu(OAc)}_2 \text{ (2 equiv)}, \text{CuCl}_2 \text{ (2 equiv)}}$
CC1=C(C(=O)N)C(=O)N(C1)c2ccccc2

1 **2a** **3a**

3a (81%)	3b (80%)	3c (51%)	3d (80%)
3e (75%)	3f (62%)	3g (85%)	3h (78%)
3i (86%)	3j (80%)	3k (74%)	3l (82%)
3m (90%)	3n (78%)	3o (83%)	3p (83%)
	3q (24%)	3r (not observed)	

^a Conditions: **1** (0.2 M), **2** (2 equiv), Pd(OAc)₂ (10 mol%), Cu(OAc)₂ (2 equiv), CuCl₂ (2 equiv) in DMF under N₂ at 60 °C for 1 h.

TABLE 4

Scope of Cyclic Enaminones^a

TABLE 5

Homocoupling of Arylboronic Acids^a

$2 \text{ MeO-C}_6\text{H}_4\text{-B(OH)}_2 \xrightarrow[\text{DMF, 60 } ^\circ\text{C, 1 h}]{\text{conditions}} \text{MeO-C}_6\text{H}_4\text{-C}_6\text{H}_4\text{-OMe}$ <div style="display: flex; justify-content: space-around; width: 100%;"> 2a 6 </div>				
entry	Pd(OAc) ₂	Cu(OAc) ₂	CuCl ₂	6 (%)
1	10 mol%	2 equiv	2 equiv	70
2	10 mol%	2 equiv	none	82
3	10 mol%	none	2 equiv	9
4	none	2 equiv	2 equiv	14
5	none	2 equiv	none	25
6	none	none	2 equiv	6

^aReaction conditions: **2a** (0.4 M) in DMF under N₂ at 60 °C for 1 h.

TABLE 6

Cross Coupling of Cyclic Enaminone and Arylboronic Acid^a

entry	Pd(OAc) ₂	Cu(OAc) ₂	CuCl ₂	3a (%)
1	none	2 equiv	2 equiv	0
2	none	2 equiv	none	0
3	none	none	2 equiv	0
4	10 mol%	none	none	< 5
5	10 mol%	2 equiv	2 equiv	81
6	10 mol%	2 equiv	none	18
7	10 mol%	none	2 equiv	18
8	10 mol%	4 equiv	none	25
9	100 mol%	none	none	30
10	100 mol%	2 equiv	2 equiv	66
11	100 mol%	2 equiv	none	49
12	100 mol%	none	2 equiv	60

^aReaction conditions: **1** (1 equiv), **2a** (2 equiv), DMF (0.2 M) under N₂ at 60 °C for 1 h, the yield was determined by ¹H NMR analysis of the crude product using Ph₃SiMe (1 equiv) as the internal standard.