JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

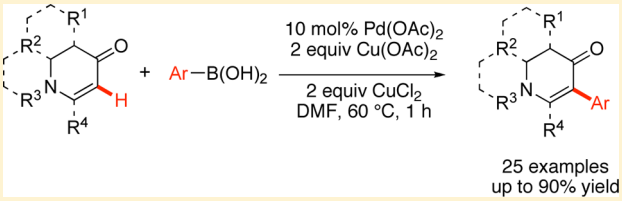
Copper-Assisted Palladium(II)-Catalyzed Direct Arylation of Cyclic Enaminones with Arylboronic Acids

Yong Wook Kim, Micah J. Niphakis, and Gunda I. Georg*

Department of Chemistry, Department of Medicinal Chemistry, and the Institute for Therapeutics Discovery and Development, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414, United States

Supporting Information

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 toward 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 laboratory 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 tylocrebrine.[4c]

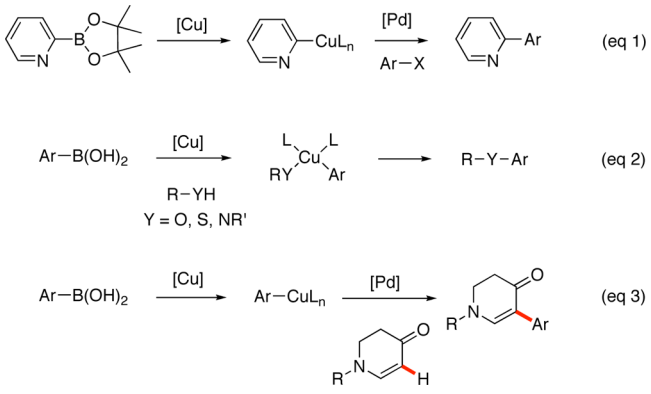
To date, we have demonstrated that cyclic enaminones undergo direct arylation with aryltrifluoroborates[3a] and arylsilanes.[3b] Although these methods provide a short and convenient route to arylated enaminones, several shortcomings limit their utility and inspired us to expand the scope and efficiency 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 substitutent effects on the aryl donor, a significant improvement over previous reports that 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 transmetalation 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 Stille[9] and Suzuki[10] reactions and are used in Sonogashira[11] reactions. It has been postulated that Cu(I) transmetalates 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., who showed that 2-pyridyl boronates, which are notoriously poor coupling partners, undergo high-yielding Suzuki reactions in the presence of copper but not in the absence of copper (Scheme 1, eq 1).[12b] It is also well-known that arylboronic acids undergo facile transmetalation 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 transmetalation 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 transmetalation (Scheme 1, eq 3).

Received: August 30, 2012
Published: October 22, 2012

dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496−9503

Scheme 1. Copper-Mediated Reactions with Organoborons

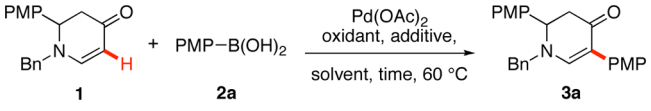


RESULTS AND DISCUSSION

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 transmetalation. As such, $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2$ (2 equiv) were initially chosen on the basis of 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) center[16] 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

Table 1. Screening of Solvents and Oxidants[a]

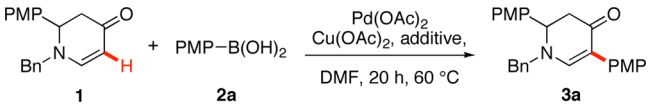


1 2a 3a

entry	solvent	reoxidant	**3a** (%)
1	*t*-BuOH	$Cu(OAc)_2$	6
2	*t*-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_2O = 9/1	$Cu(OAc)_2$	15
14	MeCN	$Cu(OAc)_2$	9
15	DMF	$Cu(OTf)_2$	11
16	DMF	duroquinone	<3
17	DMF	$PhCO_3t$-Bu[b]	<3
18	DMF	Ag_2O	<3
19	DMF	AgOAc	15
20	DMF	O_2[c]	0
21	DMSO	O_2[c]	0
22	DMF	$Cu(OAc)_2$[b] + Ag_2O[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 N_2 at 60 °C for 20 h. The yield was determined by ^{1}H NMR analysis of the crude product using Ph_3SiMe (1 equiv) as the internal standard. PMP = *p*-methoxyphenyl. [b]1 equiv. [c]Balloon pressure.

Table 2. Screening of Additives[a]



1 2a 3a

entry	additive (equiv)	**3a** (%)	entry	additive (equiv)	**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_2CO_3 (1)	34	**26**	**$CuCl_2$ (2)**	**81**
12	Cs_2CO_3 (1)	17	27	$CuCl_2$ (3)	81
13	K_3PO_4 (1)	31	28	CuCl (2)	31
14	Me_3CCO_2H (1)	16	29	CuI (2)	0
15	TFA (0.1)	31			

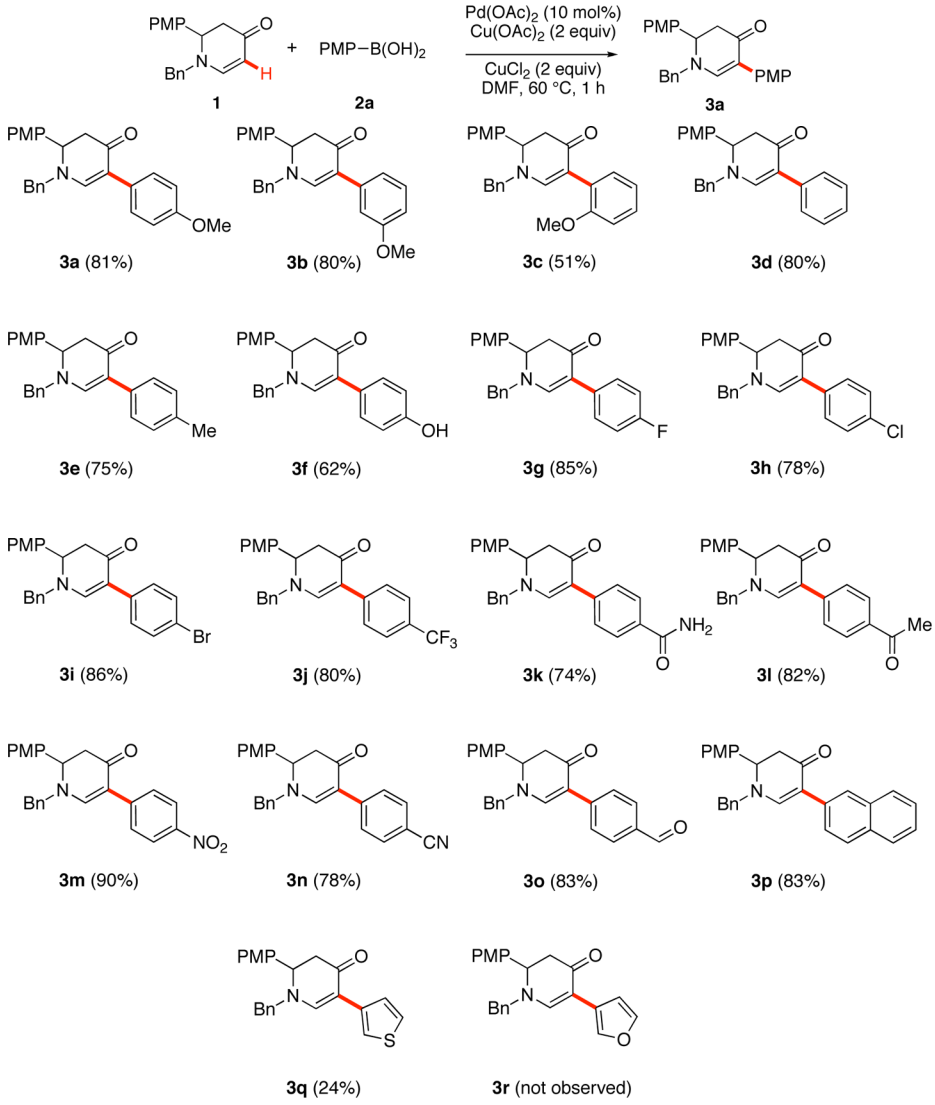
[a]Reaction conditions: **1** (1 equiv), **2a** (2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), DMF (0.2 M) under N_2 for 20 h at 60 °C. The yield was determined by ^{1}H NMR analysis of the crude product using Ph_3SiMe (1 equiv) as the internal standard. [b]1.0 M in THF. [c]12.1 M.

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 $CuCl_2$ (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 2 equiv of $CuCl_2$. 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 the Supporting Information 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

dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496−9503

Table 3. Scope of Arylboronic Acids[a]



[a]Conditions: **1** (0.2 M), **2** (2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), $CuCl_2$ (2 equiv) in DMF under N_2 at 60 °C for 1 h.

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]

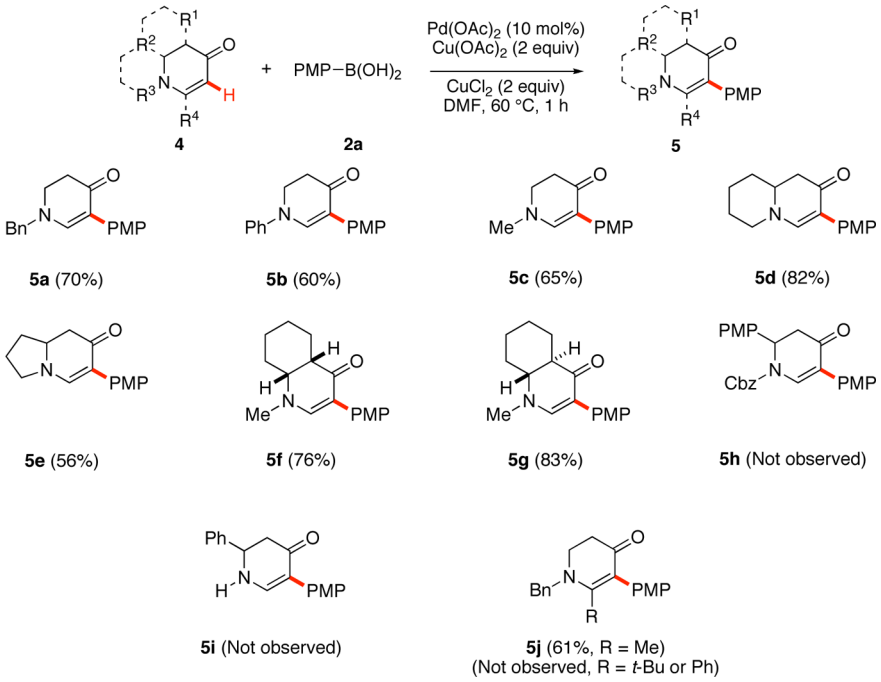
In general, this method was found to have excellent functional group compatibility. A phenol (Table 3, **3f**), an aryl bromide (Table 3, **3i**), a primary amide (Table 3, **3k**), a ketone (Table 3, **3l**), and an aldehyde (Table 3, **3o**) were all well tolerated. However, thienylboronic acid coupled 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**−**e**). Notably, *N*-phenylenaminone **5b** was also formed in comparable yields to *N*-benzyl (Table 4, **5a**) or *N*-methyl (Table 4, **5c**) analogues 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 byproduct (Table 5 entry 1).[17] Similar results were obtained in the absence of $CuCl_2$ (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 conditions (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,

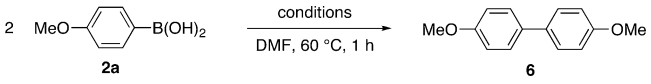
dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496−9503

Table 4. Scope of Cyclic Enaminones[a]



[a]Conditions: **1** (0.2 M), **2** (2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), $CuCl_2$ (2 equiv) in DMF under N_2 at 60 °C for 1 h.

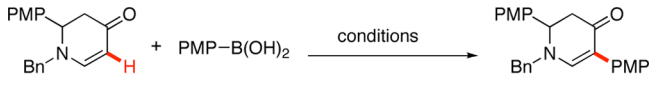
Table 5. Homocoupling of Arylboronic Acids[a]



entry	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (equiv)	$CuCl_2$ (equiv)	**6** (%)
1	10	2	2	70
2	10	2	none	82
3	10	none	2	9
4	none	2	2	14
5	none	2	none	25
6	none	none	2	6

[a]Reaction conditions: **2a** (0.4 M) in DMF under N_2 at 60 °C for 1 h.

Table 6. Cross-Coupling of Cyclic Enaminone and Arylboronic Acid[a]



entry	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (equiv)	$CuCl_2$ (equiv)	**3a** (%)
1	none	2	2	0
2	none	2	none	0
3	none	none	2	0
4	10	none	none	<5
5	10	2	2	81
6	10	2	none	18
7	10	none	2	18
8	10	4	none	25
9	100	none	none	30
10	100	2	2	66
11	100	2	none	49
12	100	none	2	60

[a]Reaction conditions: **1** (1 equiv), **2a** (2 equiv), DMF (0.2 M) under N_2 at 60 °C for 1 h, the yield was determined by ^1H NMR analysis of the crude product using Ph_3SiMe (1 equiv) as the internal standard.

in the absence of any copper source when using 100 mol % of $Pd(OAc)_2$ (entry 9). Nevertheless, under these stoichiometric conditions, which presumably minimize the necessity of a reoxidant, product formation was improved upon the addition of $Cu(OAc)_2$, $CuCl_2$, or both (entries 10–12). Interestingly, the beneficial effects of the mixed $Cu(OAc)_2/CuCl_2$ system were enhanced when $Pd(OAc)_2$ was employed catalytically (entry 5). Neither $Cu(OAc)_2$ nor $CuCl_2$ 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 $CuCl_2$ 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 transmetalation, 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 $Cu(OAc)_2$ to form organocopper species;[13] (2) the arylboronic acid is rapidly consumed upon exposure to the $Cu(OAc)_2/CuCl_2$ 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 $Cu(OAc)_2$ 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 arylcopper

dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496–9503

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 $Cu(OAc)_2$ 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 transmetalation is disfavored.

EXPERIMENTAL SECTION

General Procedure for Enaminone Arylation. The cyclic enaminone (0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (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 being stirred 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(1*H*)-one (3a). Compound **3a** was prepared by the general procedure described above, and 65 mg (81%) was isolated as a light yellow oil: R_f 0.48 (hexanes/EtOAc, 1:1). ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{26}NO_3$ 400.1913, found 400.1902.

1-Benzyl-5-(3-methoxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{26}NO_3$ 400.1913, found 400.1901.

1-Benzyl-5-(2-methoxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{26}NO_3$ 400.1913, found 400.1898.

1-Benzyl-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridin-4(1*H*)-one (3d). Compound **3d** was prepared by the general procedure described above, and 59 mg (80%) was isolated as a light yellow oil: R_f 0.60 (hexanes/EtOAc, 1:1); ^{1}H 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 calcd for $[M + H]^+$ $C_{25}H_{24}NO_2$ 370.1807, found 370.1810.

1-Benzyl-2-(4-methoxyphenyl)-5-(*p*-tolyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{26}NO_2$ 384.1964, found 384.1964.

1-Benzyl-5-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd 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(1*H*)-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); ^{1}H 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 calcd 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(1*H*)-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); ^{1}H 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,

dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496−9503

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 calcd 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(1*H*)-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); ^{1}H 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 calcd 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(1*H*)-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); ^{1}H 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 = 272 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 calcd 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); ^{1}H 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, 127.8, 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 calcd for $[M + H]^+$ $C_{26}H_{25}N_2O_3$ 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); ^{1}H 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 calcd for $[M + H]^+$ $C_{27}H_{26}NO_3$ 412.1913, found 412.1913.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{25}H_{23}N_2O_4$ 415.1658, found 415.1651.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{23}N_2O_2$ 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); ^{1}H 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 calcd for $[M + H]^+$ $C_{26}H_{24}NO_3$ 398.1756, found 398.1747.

1-Benzyl-2-(4-methoxyphenyl)-5-(naphthalen-2-yl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{29}H_{26}NO_2$ 420.1964, found 420.1953.

1-Benzyl-2-(4-methoxyphenyl)-5-(thiophen-3-yl)-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{23}H_{22}NO_2S$ 376.1371, found 376.1370.

1-Benzyl-5-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-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 were identical to those in our previous report.[3a]

dx.doi.org/10.1021/jo301531k | J. Org. Chem. 2012, 77, 9496−9503

5-(4-Methoxyphenyl)-1-phenyl-2,3-dihydropyridin-4(1*H*)-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); ^{1}H 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 calcd for $[M + H]^+$ $C_{18}H_{18}NO_2$ 280.1338, found 280.1339.

5-(4-Methoxyphenyl)-1-methyl-2,3-dihydropyridin-4(1*H*)-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 were identical to those in our previous report.[3]

3-(4-Methoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-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 were identical to those 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 were identical to those in our previous report.[3a]

(*cis*)-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-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 were identical to those in our previous report.[3a]

***trans*-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-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 were identical to those in our previous report.[3a]

1-Benzyl-5-(4-methoxyphenyl)-6-methyl-2,3-dihydropyridin-4(1*H*)-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); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $[M + H]^+$ $C_{20}H_{22}NO_2$ 308.1610, found 308.1630.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: georg@umn.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NIH (GM081267) and the University of Minnesota through the Vince and McKnight Endowed Chairs (to G.I.G) and an ACS Division of Medicinal Chemistry Predoctoral Fellowship (to M.J.N).

■ REFERENCES

(1) For review, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082−1146. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463. (f) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991. (g) Hirano, K.; Miura, M. *Synlett* **2011**, 294−307. (h) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013−3039. (i) Kulkarni, A.; Daugulis, O. *Synthesis* **2009**, 4087−4109. (j) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013−1025.

(2) For review, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (d) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949−957. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169.

(3) (a) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708−3709. (b) Bi, L.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5413−5415. (c) Yu, Y.-Y.; Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5932−5935.

(4) (a) Leighty, M. W.; Georg, G. I. *ACS Med. Chem. Lett.* **2011**, *2*, 313−315. (b) Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019−6022. (c) Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 196−199. (d) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793−6805. (e) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512−15513. (f) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702−8073. (g) Wang, X.; Turunen, B. J.; Leighty, M. W.; Georg, G. I. *Tetrahedron Lett.* **2007**, *48*, 8811−8814.

(5) For Pd-catalyzed direct arylation of enamine/enamide systems, see: (a) Pelletier, G.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 4791−4794. (b) Sørensen, U.; Pombo-Villar, E. *Helv. Chim. Acta* **2004**, *87*, 82−89. (c) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230−7233. (d) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472−3474. (e) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355−5357.

(6) For α-arylation of enone systems, see: (a) Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350−5351. (b) Koech, P. K.; Krische, M. J. *Tetrahedron* **2006**, *62*, 10594−10602.

(7) (a) Negri, G.; Kascheres, C.; Kascheres, A, J. *J. Heterocycl. Chem.* **2004**, *41*, 461−491. (b) Elassar, A, A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463−8480. (c) Comins, D, L. *J. Heterocycl. Chem.* **1999**, *36*, 1491−1500.

(8) For review, see: (a) Michael, J. P. In *The Alkaloids: Chemistry and Biology*; Academic Press: New York, 2001; Vol. *55*, pp 91−258. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191−222. (d) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603−626. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625−649.

(9) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605. (c) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132−1136.

(10) (a) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149−2152. (b) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858−11859. (c) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053−2057.

(11) For a review, see: Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *50*, 5084−5121.

(12) (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662−664. (b) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345−347.

(13) Qiao, J.; Lam, P. *Synthesis* **2010**, 829−856.

(14) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286.

(15) (a) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766−767. (c) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302−2303.
(16) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252−7263.
(17) For copper-mediated homocoupling of arylboronic acids, see: (a) Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183−2186. (b) Demir, A. S.; Reis, O.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 10130−10134. (c) Cheng, G.; Luo, M. *Eur. J. Org. Chem.* **2011**, *13*, 2519−2523.
(18) The reaction was monitored by ^{1}H 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 the Supporting Information