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Palladium-Catalyzed Direct C−H Arylation of Cyclic Enaminones with Aryl Iodides

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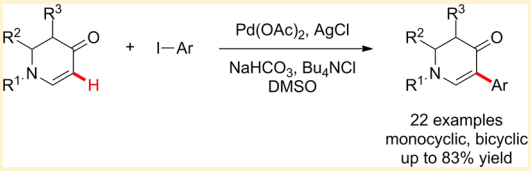
Supporting Information

ABSTRACT: A ligand-free method for the Pd-catalyzed direct arylation of cyclic enaminones using aryl iodides was developed. This method can be applied to a wide range of cyclic enaminones and aryl iodides with excellent C5-regioselectivity. Using widely available aryl iodides, the generality of this transformation provides easy access to a variety of 3-arylpiperidine structural motifs.

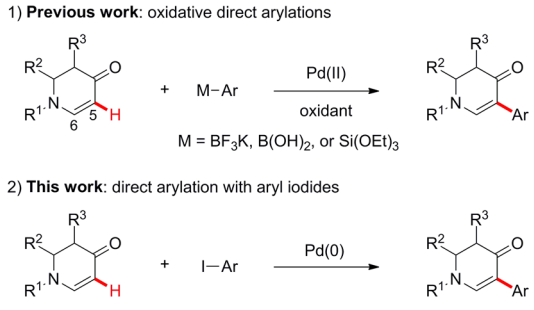


INTRODUCTION

Cyclic enaminones, also known as 2,3-dihydropyrid-4(1*H*)-ones, have displayed a distinctive reactivity profile, including notably a strong innate nucleophilicity.[1] As piperidine surrogates, these nonaromatic substrates have been exploited as versatile synthetic intermediates in the syntheses of various heterocycles and heterocyclic natural products.[2] As our laboratory continues to investigate the pharmaceutical applications of phenanthropiperidine alkaloids, the syntheses of these natural products and analogs entail a regioselective C5-arylation of cyclic enaminones as a key step.[3] Our strategy has been employing direct C−H arylation reactions because of their convenience and efficiency.

Direct C−H arylation chemistry has been extensively studied over the years due to the ubiquity of heterocycle−aryl linkages in pharmaceuticals.[4] Our previous syntheses have demonstrated that the regioselective C5-arylation of cyclic enaminones can be achieved through convenient and high-yielding C−H arylation protocols via oxidative Pd catalysis (Scheme 1, route 1).[5] In these protocols, aryl metal precursors were used (i.e., aryl boronic acids,[5a] silanes,[5b] and trifluoroborates[5c]). Issues of limited commercial availability or high cost led us to explore the widely available aryl iodides as alternative reagents (Scheme 1, route 2).[6]

Scheme 1. Direct Arylation of Cyclic Enaminones



Among the possible C−H activation mechanisms,[7] our past study suggested that an electrophilic palladation pathway was more likely involved in reactions with the nucleophilic enaminones (Figure 1, top).[1a] However, a carbopalladation process is also feasible and would lead to C6-arylation as the double bond in the *nonaromatic* enaminone scaffold could be a Heck donor (Figure 1, bottom).[7c,d] Therefore, the regioselectivity of the coupling reaction presented another challenge. Herein, we disclose the development of a C5 regioselective direct C−H arylation of cyclic enaminones using aryl iodides.

RESULTS AND DISCUSSION

We initiated our study by examining a collection of C−H arylation conditions (catalysts, additives, reagent stoichiometry, and reaction time)[8] and then proceeded with the Jeffery conditions (a combination of a Pd^{II} catalyst, a tetraalkylammonium salt, and an inorganic base)[9] for the optimization studies shown in Table 1. As anticipated, in addition to the desired C5-arylated **3a**, C6-arylated **4a** was observed as well. A survey of seven solvents (entries 1−7) revealed that DMSO favored the formation of **3a** via the presumed electrophilic palladation pathway (e.g., 50% in DMSO, entry 7 vs 10% in dioxane, entry 2), whereas toluene (entry 1) significantly increased the formation of **4a**. Indeed, DMSO provided the highest yield and the best regioselectivity (entry 7). The choice of the base was also proven imperative (entries 8−15). $NaHCO_3$ (entry 7) and Na_2CO_3 (entry 9) were more effective in facilitating the deprotonation process than NaOAc (entry 8). Addition of pivalic acid (PivOH) with Na_2CO_3 did not improve the yield (entry 10). The selection of base cations also showed that the sodium cation had beneficial effects on direct arylation (entries 11−13). Unsurprisingly, strong bases such as NaOH (entry 14) or NaO-*t*-Bu (entry 15) decomposed the enaminones. Thus, the originally chosen $NaHCO_3$ provided the best outcome (50%, entry 7). Next, the reaction temperature was tuned from

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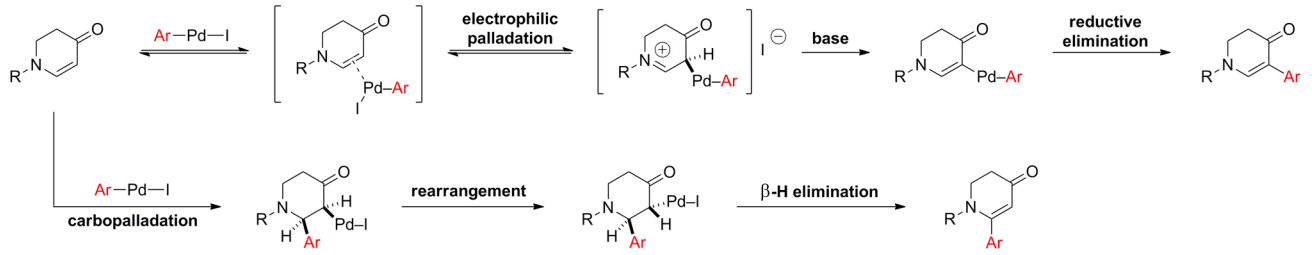
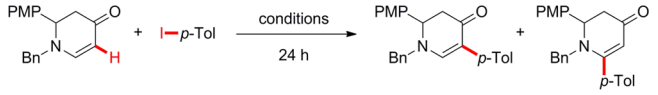


Figure 1. Postulated competing pathways for direct C−H arylation.

Table 1. Initial Optimization of the Direct C−H Arylation of Cyclic Enaminones[a]



1a **2a** **3a** **4a**

entry	ligand	additive	base	temp (°C)	solvent	**3a**[b] (%)	**4a**[b] (%)
1		Bu_4NBr	$NaHCO_3$	80	toluene	14	18
2		Bu_4NBr	$NaHCO_3$	80	dioxane	10	12
3		Bu_4NBr	$NaHCO_3$	80	*t*-BuOH	8	12
4		Bu_4NBr	$NaHCO_3$	80	NMP	15	7
5		Bu_4NBr	$NaHCO_3$	80	DMF	29	7
6		Bu_4NBr	$NaHCO_3$	80	DMA	22	8
7		Bu_4NBr	$NaHCO_3$	80	DMSO	50	6
8		Bu_4NBr	NaOAc	80	DMSO	36	5
9		Bu_4NBr	Na_2CO_3	80	DMSO	49	8
10[c]		Bu_4NBr	Na_2CO_3	80	DMSO	51	8
11		Bu_4NBr	Li_2CO_3	80	DMSO	29	3
12		Bu_4NBr	K_2CO_3	80	DMSO	16	0
13		Bu_4NBr	Cs_2CO_3	80	DMSO	0	0
14		Bu_4NBr	NaOH	80	DMSO	0	0
15		Bu_4NBr	NaO*t*Bu	80	DMSO	0	0
16		Bu_4NBr	$NaHCO_3$	20	DMSO	8	2
17		Bu_4NBr	$NaHCO_3$	50	DMSO	31	3
18		Bu_4NBr	$NaHCO_3$	110	DMSO	46	9
19		Bu_4NBr	$NaHCO_3$	140	DMSO	35	7
20			$NaHCO_3$	80	DMSO	40	12
21		Bu_4NCl	$NaHCO_3$	80	DMSO	**49**	**3**
22		Bu_4NI	$NaHCO_3$	80	DMSO	35	16
23	PPh_3	Bu_4NCl	$NaHCO_3$	80	DMSO	0	0
24	$P(OPh)_3$	Bu_4NCl	$NaHCO_3$	80	DMSO	0	0
25	$P(C_6F_5)_3$	Bu_4NCl	$NaHCO_3$	80	DMSO	0	0
26[d]	Boc-Ala-OH	Bu_4NCl	$NaHCO_3$	80	DMSO	52	6
27[d]	Boc-Phe-OH	Bu_4NCl	$NaHCO_3$	80	DMSO	45	4

[a] **1a** (0.2 M), **2a** (1.5 equiv), $Pd(OAc)_2$ (20 mol %), ligand (40 mol %), additive (1.0 equiv), base (3.0 equiv) in DMSO (1 mL). *p*-Tol = *p*-tolyl. [b] NMR yields with Ph_3SiMe (1.0 equiv) as the internal standard. [c] With PivOH (40 mol %). [d] **2a** (3.0 equiv), Bu_4NCl (0.5 equiv), and $NaHCO_3$ (1.0 equiv).

20 to 140 °C in 30-degree intervals (entries 16−19). We found that 80 °C was the optimal temperature to activate the transformation without decomposing the heat-sensitive enaminones. Moreover, several tetraalkylammonium salts were assessed as phase-transfer agents in order to enhance yields and selectivities (entries 20−22).[9] The absence of Bu_4NBr indeed resulted in a lower yield of **3a** and a reduced regioselectivity (entry 20). Interestingly, Bu_4NCl (entry 21) provided a better regioselectivity than Bu_4NI (entry 22) or Bu_4NBr (entry 7). Lastly, the ligand effect was investigated. Phosphine ligands (i.e., PPh_3, $P(OPh)_3$, and $P(C_6F_5)_3$), regardless of their electronic properties, were detrimental to catalysis (entries 23−25). Amino acids (i.e., Boc-L-alanine and Boc-L-phenylalanine), supposedly coordinating to the Pd center through weak ligation,[10] showed no improvement in either yields or regioselectivity (entries 26 and 27).

We also examined eight silver salts as additives (Table 2). Silver salts are often used to irreversibly abstract halide anions from Pd complexes, thus rendering them more electrophilic and preventing the formation of mostly inactive PdI_2.[11] Indeed, the regioselectivity was greatly enhanced in the presence of a silver salt (entries 1−8). We found that AgCl not only increased the yield of **3a**, but also promoted exclusive reaction at the C5-position (entry 6). Additional extensive fine-tuning[8] of reagent stoichiometry and reaction time furnished the desired C5-arylated **3a** in 72% with Bu_4NCl (0.5 equiv) and $NaHCO_3$ (1.0 equiv) in DMSO (0.5 mL) (entry 9).

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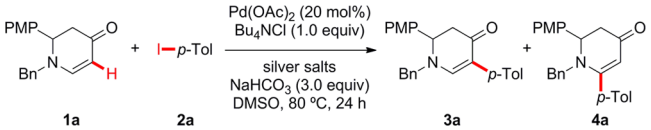
Table 2. Silver Effect on the Regioselectivity of the Direct C−H Arylation of Cyclic Enaminones[a]



1a 2a 3a 4a

entry	Ag salt	3a[b] (%)	4a[b] (%)
1	AgTFA	33	<1
2	AgF_2	14	0
3	$AgNO_3$	32	0
4	AgOAc	30	<1
5	Ag_2CO_3	30	<1
6	AgCl	65	0
7[c]	Ag_2O + benzoic acid	30	0
8[c,d]	Ag_2O + PivOH	49	3
9[e]	AgCl	**75** (72[f])	**<1**

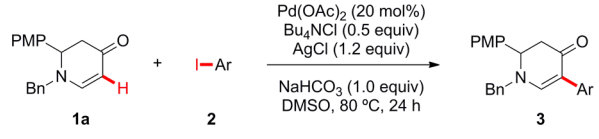
[a] **1a** (0.2 M), **2a** (3.0 equiv), $Pd(OAc)_2$ (20 mol %), Bu_4NCl (1.0 equiv), $NaHCO_3$ (3.0 equiv), silver salt (1.2 equiv) in DMSO (1 mL). *p*-Tol = *p*-tolyl. [b] NMR yields with Ph_3SiMe (1.0 equiv) as the internal standard. [c] Ag_2O (0.75 equiv), acid (1.5 equiv), no $NaHCO_3$. [d] No Bu_4NCl. [e] AgCl (1.2 equiv), Bu_4NCl (0.5 equiv), $NaHCO_3$ (1.0 equiv) in DMSO (0.5 mL). (See Table S2 in the Supporting Information for more details.) [f] Isolated yield.

Next, we explored the scope of aryl iodides in this reaction using the optimized conditions (Table 3) and found that the electronic properties of the aryl iodides affected reaction yields significantly. Good yields were generally obtained with electron-rich aryl iodides (**3a−l**). Electron-poor aryl iodides afforded slightly lowered yields (**3m−p**). Reactions of aryl iodides with strongly electron-withdrawing substituents, e.g., NO_2 (**3o**) and CF_3 (**3p**), resulted in low yields. Steric hindrance, as expected, impeded the effectiveness of the cross coupling. For instance, compared to the 4-tolyl derivative (**3a**), 2-tolyl iodide afforded a lower yield (**3b**) with 14% recovered **1a**. In addition, arylation of bifunctional 4-chlorophenyliodide (**2n**) proceeded exclusively at the iodine terminus with the chlorine terminus intact, which may be subjected to sequential cross-coupling reactions.[12] It is worth mentioning that phenyl bromide was tested under the optimized conditions and afforded an inferior yield (21% with 32% recovered **1a**) compared to phenyl iodide, which afforded **3d** in 68%. Neither 4-chlorotoluene nor phenyl triflate functioned as arylating reagents to afford the desired product.

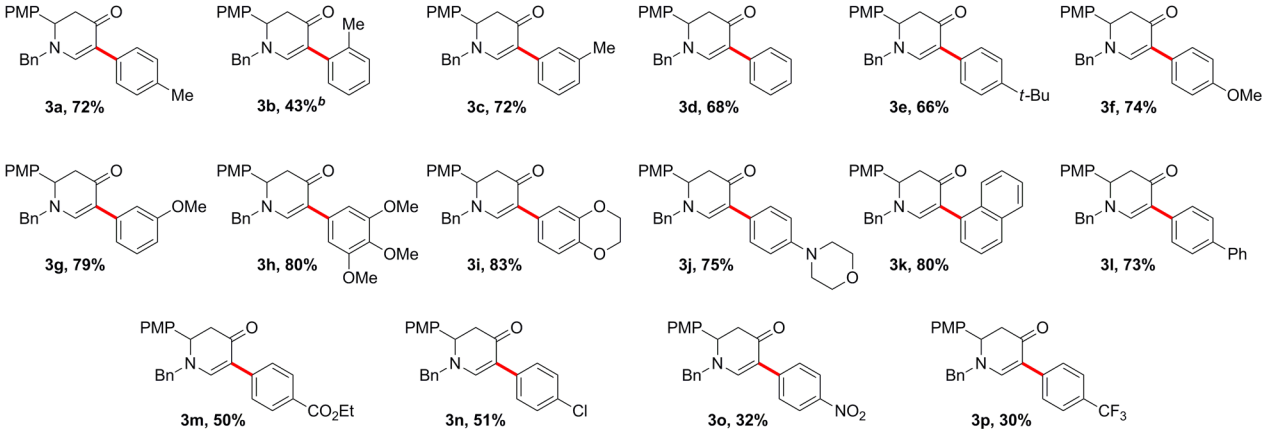
Given the high coupling efficiency of electron-rich aryl iodides, a series of cyclic enaminones was subjected to the optimized conditions with 4-iodoanisole (**2f**, Table 4). Consistent with our previous results,[1a,5] electron-rich, monocyclic, and bicyclic enaminones were all compatible with the optimized conditions (**3q−v**). Compared to *N*-benzylenaminone **3q**, *N*-phenylenaminone **3r** was formed in a decreased yield probably due to its attenuated nucleophilicity. Notably, these mildly basic conditions did not compromise the stereochemical integrity of the epimerizable enaminone **3v**. In contrast, no reaction took place on either the *N*-unprotected enaminone **1w** or the *E*-enaminone **1x** to form products **3w** or **3x**.[1a,5] Electron-deficient enaminones also failed to furnish desired 5-arylated products **3y** or **3z**.

Mechanistically, the aforementioned electrophilic palladation pathway (Figure 1) for direct arylation can account for the observed C5-regioselectivity, the silver salt effect, the solvent dependency, and the substituent effects. Presumably, AgCl abstracts the iodide from the Pd oxidative adduct (i.e., Ar−Pd−I) to generate a cationic $[Ar−Pd]^+$ complex, whose electrophilicity matches the innate C5-nucleophilicity of enaminones to yield C5-arylated enaminones. This unique C5-regioselectivity is enhanced by DMSO because the cationic $[Ar−Pd]^+$ species should be stabilized by this highly polar and coordinating solvent. In addition, the $[Ar−Pd]^+$ species should also be stabilized by electron-donating substituents, which would lead to less catalyst degradation and subsequently higher yields (e.g., 80% of **3h** vs 32% of **3o**). It is worth noting that a concerted metalation−deprotonation (CMD) mechanism cannot be excluded at this time. However, the lack of reactivity

Table 3. Scope of Aryl Iodides for the Direct C−H Arylation[a]



1a 2 3



[a] **1a** (0.2 M), **2** (3.0 equiv), $Pd(OAc)_2$ (20 mol %), Bu_4NCl (0.5 equiv), $NaHCO_3$ (1.0 equiv), AgCl (1.2 equiv) in DMSO (0.5 mL), 24 h. Isolated yields with full consumption of **1a**, unless otherwise noted. [b] 14% recovered **1a**.

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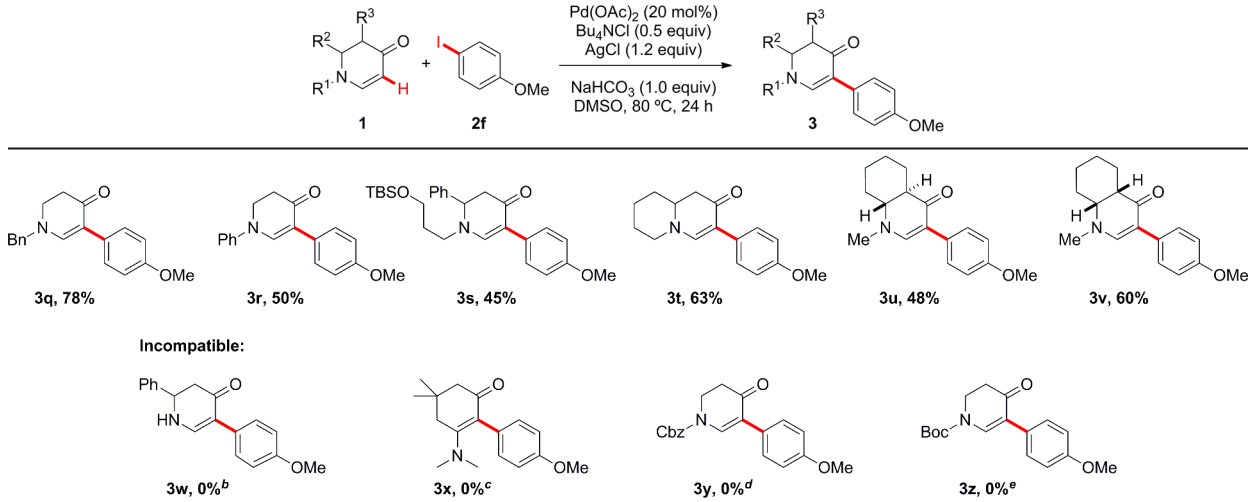
Table 4. Scope of Cyclic Enaminones for the Direct C−H Arylation[a]



[a]**1** (0.2 M), **2f** (3.0 equiv), $Pd(OAc)_2$ (20 mol %), Bu_4NCl (0.5 equiv), $NaHCO_3$ (1.0 equiv), AgCl (1.2 equiv) in DMSO (0.5 mL), 24 h. Isolated yields with full consumption of **1**, unless otherwise noted. [b]60% recovered **1w**. [c]65% recovered **1x**. [d]15% recovered **1y**. [e]27% recovered **1z**.

of the electron-deficient enaminones **1y** and **1z** indicates a low possibility for this process, which often works well on electron-deficient substrates.[13] In addition, a Pd^{II}/Pd^{IV} catalytic cycle, albeit not ruled out, is also less likely because (1) more than one catalytic turnover was observed in the absence of silver salts (e.g., Table 1, entry 7, TON = 2.5), suggesting that silver salts did not serve to regenerate the Pd catalyst;[14] (2) our initial optimization demonstrated that other Pd^0 catalysts (e.g., $Pd(dba)_2$ or $Pd_2(dba)_3$) would catalyze C5-arylation as well, albeit in low yields (8−11%).[8] Presumably, the ligands in these Pd^0 conditions tempered the electrophilicity of the Pd^{II} center after oxidative addition, hence resulting in the observed low yields.

CONCLUSION

We have developed a straightforward method for the regioselective C−H arylation of cyclic enaminones with aryl iodides. In spite of showing reduced but nevertheless good yields compared to our earlier arylation protocols, the new method reported herein utilizes aryl iodides with broader commercial availability. This transformation tolerates a wide range of substrates and presents an alternative approach to synthesize 3-arylpiperidine derivatives.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in clear 1-dram vials under air. Vials were used without drying. Palladium(II) acetate, aryl iodides, all other chemicals and solvents were purchased and were directly used without further purification. Cyclic enaminones (**1a**,[1a] **1q**,**r**,[3d,15] **1s**,[5b] and **1t**−**w**[3d,15]) were prepared according to the reported procedures, and enaminone **1x** is commercially available. Flash column chromatography was carried out on silica gel (230−400 mesh). TLC was conducted on 250 μm, F_{254} silica gel plates. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz with complete proton decoupling. Chemical shifts are reported as ppm relative to chloroform ($CHCl_3$: 7.26 ppm for ^1H, 77.16 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. IR spectra of solids were obtained by dissolving the sample in CH_2Cl_2 and letting the solvent evaporate on a NaCl plate. High-resolution mass spectrometry was performed on an ESI-TOF instrument. Melting points are uncorrected.

Representative Procedure for Direct C−H Arylation of Cyclic Enaminones with Aryl Iodides. In a clear 1-dram vial, the cyclic enaminone (0.1 mmol), aryl iodide (0.3 mmol, 3.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 20 mol %), Bu_4NCl (13.9 mg, 0.05 mmol, 0.5 equiv), $NaHCO_3$ (8.4 mg, 0.1 mmol, 1.0 equiv), and AgCl (17.2 mg, 0.12 mmol, 1.2 equiv) were mixed in DMSO (0.5 mL). The reaction vessel was then capped and stirred at 80 °C for 24 h and then cooled to room temperature. The mixture was filtered through a pad of Celite (washed with EtOAc). The filtrate was concentrated under reduced pressure and purified by flash column chromatography.

1-Benzyl-2-(4-methoxyphenyl)-5-*p*-tolyl-2,3-dihydropyridin-4(1*H*)-one (3a). Compound **3a** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 27.3 mg (72%) as an orange wax. Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-2-(4-methoxyphenyl)-6-*p*-tolyl-2,3-dihydropyridin-4(1*H*)-one (4a). Compound **4a** was a side product during the optimization study and purified by flash column chromatography (25% EtOAc in hexanes) on silica gel as a yellow wax: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 9H overlapping with $CHCl_3$), 7.15 (d, J = 6.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.17 (s, 1H), 4.76 (d, J = 15.7 Hz, 1H), 4.61 (dd, J = 7.3, 4.0 Hz, 1H), 3.99 (d, J = 15.7 Hz, 1H), 3.81 (s, 3H), 2.97 (dd, J = 16.5, 7.4 Hz, 1H), 2.61 (dd, J = 16.7, 3.9 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 164.9, 159.4, 140.0, 137.8, 133.6, 131.3, 129.6, 129.0, 128.0, 128.0, 127.8, 127.2, 114.4, 102.8, 59.4, 55.5, 53.9, 42.6, 21.5; FTIR (NaCl, cm^{-1}) 3054, 2987, 1639, 1598, 1513, 1442, 1179, 1032, 896; HRMS (ESI+) m/e calcd for $[M + H]^+$ $C_{26}H_{26}NO_2$ 384.1963, found 384.1969.

1-Benzyl-2-(4-methoxyphenyl)-5-*o*-tolyl-2,3-dihydropyridin-4(1*H*)-one (3b). Compound **3b** was prepared by the general procedure described above and purified by flash column chromatography (25% EtOAc in hexanes) on silica gel to provide 16.9 mg (43%) as a yellow solid (mp 139−142 °C): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (m, 4H overlapping with $CHCl_3$), 7.18−7.03 (m, 8H), 6.83 (d, J = 8.6 Hz, 2H), 4.48 (t, J = 7.6 Hz, 1H), 4.27 (d, J = 15.1 Hz, 1H), 4.10 (d, J = 15.1 Hz, 1H), 3.75 (s, 3H), 2.85 (dd, J = 16.3, 6.7 Hz, 1H), 2.76 (dd, J = 16.3, 8.7 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 159.7, 154.0, 138.2, 136.2, 136.0, 130.6, 130.2, 129.1, 128.6, 128.5, 128.3, 127.9, 127.2, 125.8, 114.5, 112.6, 60.7, 57.3, 55.5, 44.4, 20.7; FTIR (NaCl, cm^{-1}) 3054, 2987, 1638, 1596, 1551, 1422, 1157, 1029, 896; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{26}H_{25}NO_2Na$ 406.1783, found 406.1779.

1-Benzyl-2-(4-methoxyphenyl)-5-*m*-tolyl-2,3-dihydropyridin-4(1*H*)-one (3c). Compound **3c** was prepared by the general procedure described above and purified by flash column chromatog-

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raphy (30% EtOAc in hexanes) on silica gel to provide 27.2 mg (72%) as a yellow wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.34 (td, J = 18.5, 15.9, 9.5 Hz, 4H), 7.25−7.14 (m, 6H), 7.07−6.99 (m, 1H), 6.89 (d, J = 8.5 Hz, 2H), 4.52 (t, J = 7.5 Hz, 1H), 4.41 (d, J = 15.1 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.82 (s, 3H), 2.95 (dd, J = 16.2, 6.8 Hz, 1H), 2.82 (dd, J = 16.2, 8.3 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 159.7, 153.3, 137.8, 136.1, 130.6, 129.1, 128.6, 128.6, 128.5, 128.3, 128.3, 127.8, 126.7, 124.8, 114.5, 111.4, 60.4, 57.5, 55.5, 44.6, 21.7; FTIR (NaCl, cm^{-1}) 3054, 2987, 1639, 1598, 1513, 1422, 1179, 1035, 896; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{26}H_{25}NO_2Na$ 406.1783, found 406.1779.

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 purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 24.8 mg (68%) as a yellow oil. Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-5-(4-*tert*-butylphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3e). Compound **3e** was prepared by the general procedure described above and purified by flash column chromatography (25% EtOAc in hexanes) on silica gel to provide 27.9 mg (66%) as a yellow wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43−7.29 (m, 7H), 7.24−7.14 (m, 4H), 6.88 (d, J = 8.7 Hz, 2H), 4.52 (t, J = 7.5 Hz, 1H), 4.40 (d, J = 15.1 Hz, 1H), 4.20 (d, J = 15.1 Hz, 1H), 3.82 (s, 3H), 2.96 (dd, J = 16.2, 6.8 Hz, 1H), 2.83 (dd, J = 16.2, 8.4 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 159.7, 153.1, 148.7, 136.1, 133.2, 130.7, 129.1, 128.5, 128.3, 127.9, 127.4, 125.3, 114.5, 111.3, 60.5, 57.5, 55.5, 44.6, 34.5, 31.5; FTIR (NaCl, cm^{-1}) 3054, 2986, 1637, 1598, 1513, 1422, 1376, 1358, 1306, 1179, 1130, 1034, 896, 837; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{29}H_{31}NO_2Na$ 448.2252, found 448.2259.

1-Benzyl-2,5-bis(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3f). Compound **3f** was prepared by the general procedure described above and purified by flash column chromatography (50% EtOAc in hexanes) on silica gel to provide 29.2 mg (74%) as a yellow oil. Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-5-(3-methoxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3g). Compound **3g** was prepared by the general procedure described above and purified by flash column chromatography (35% EtOAc in hexanes) on silica gel to provide 31.2 mg (79%) as a red oil. Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-2-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3h). Compound **3h** was prepared by the general procedure described above and purified by flash column chromatography (50% EtOAc in hexanes) on silica gel to provide 36.5 mg (80%) as a yellow solid (mp 125−128 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.39−7.31 (m, 3H), 7.23−7.14 (m, 4H), 6.89 (d, J = 8.6 Hz, 2H), 6.67 (s, 2H), 4.52 (t, J = 7.5 Hz, 1H), 4.42 (d, J = 15.1 Hz, 1H), 4.22 (d, J = 15.1 Hz, 1H), 3.87 (s, 6H), 3.83 (s, 3H), 3.81 (s, 3H), 2.95 (dd, J = 16.2, 6.8 Hz, 1H), 2.81 (dd, J = 16.2, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 159.8, 153.1, 136.5, 136.0, 131.9, 130.5, 129.1, 128.5, 128.5, 128.4, 127.9, 114.6, 111.0, 105.2, 61.0, 60.4, 57.5, 56.3, 55.5, 44.6; FTIR (NaCl, cm^{-1}) 3054, 2987, 2840, 1639, 1598, 1583, 1512, 1422, 1357, 1327, 1129, 1034, 1005, 896; HRMS (ESI+) m/e calcd for $[M + H]^+$ $C_{28}H_{30}NO_5$ 460.2118, found 460.2126.

1-Benzyl-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3i). Compound **3i** was prepared by the general procedure described above and purified by flash column chromatography (40% EtOAc in hexanes) on silica gel to provide 35.4 mg (83%) as an orange wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.39−7.30 (m, 3H), 7.20−7.14 (m, 4H), 6.98−6.81 (m, 5H), 4.50 (dd, J = 8.4, 6.8 Hz, 1H), 4.37 (d, J = 15.1 Hz, 1H), 4.24 (s, 4H), 4.17 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.92 (dd, J = 16.2, 6.7 Hz, 1H), 2.80 (dd, J = 16.2, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 159.7, 152.9, 143.3, 142.0, 136.1, 130.6, 129.7, 129.1, 128.5, 128.3, 127.8, 121.1, 117.0, 116.7, 114.5, 111.0, 108.8, 64.5, 60.5, 57.4, 55.5, 44.6; FTIR (NaCl, cm^{-1}) 3155, 2935, 1635, 1597, 1583, 1511, 1459, 1442, 1377, 1357, 1315, 1298, 1282, 1250, 1178, 1127, 1071, 1036, 834; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{27}H_{25}NO_4Na$ 450.1681, found 450.1684.

1-Benzyl-2-(4-methoxyphenyl)-5-(4-morpholinophenyl)-2,3-dihydropyridin-4(1*H*)-one (3j). Compound **3j** was prepared by the general procedure described above and purified by flash column chromatography (70% EtOAc in hexanes) on silica gel to provide 33.9 mg (75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.38−7.30 (m, 5H), 7.23−7.12 (m, 4H), 6.92−6.86 (m, 4H), 4.51 (t, J = 7.6 Hz, 1H), 4.38 (d, J = 15.1 Hz, 1H), 4.18 (d, J = 15.1 Hz, 1H), 3.86 (t, J = 4.6 Hz, 4H), 3.81 (s, 3H), 3.14 (t, J = 4.0 Hz, 4H), 2.93 (dd, J = 16.3, 6.6 Hz, 1H), 2.82 (dd, J = 16.2, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 159.7, 152.7, 149.6, 136.2, 130.7, 129.1, 128.6, 128.6, 128.3, 127.8, 116.0, 114.5, 114.5, 111.3, 67.1, 60.6, 57.4, 55.4, 49.8, 44.7; FTIR (NaCl, cm^{-1}) 3155, 2967, 2901, 2839, 1794, 1634, 1595, 1514, 1452, 1380, 1307, 1231, 1177, 1121, 1035, 907; HRMS (ESI+) m/e calcd for $[M + H]^+$ $C_{29}H_{31}N_2O_3$ 455.2329, found 455.2324.

1-Benzyl-2-(4-methoxyphenyl)-5-(naphthalen-1-yl)-2,3-dihydropyridin-4(1*H*)-one (3k). Compound **3k** was prepared by the general procedure described above and purified by flash column chromatography (40% EtOAc in hexanes) on silica gel to provide 33.3 mg (80%) as a red wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.75 (m, 3H), 7.50−7.28 (m, 10H), 7.19 (d, J = 6.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 4.66 (t, J = 7.7 Hz, 1H), 4.38 (d, J = 15.1 Hz, 1H), 4.23 (d, J = 15.1 Hz, 1H), 3.86 (s, 3H), 3.06 (dd, J = 16.3, 6.5 Hz, 1H), 2.97 (dd, J = 16.2, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 159.8, 154.8, 136.1, 134.3, 134.0, 133.2, 130.5, 129.1, 128.6, 128.6, 128.4, 128.0, 128.0, 127.9, 127.7, 126.3, 125.7, 125.7, 114.6, 111.1, 60.7, 57.4, 55.6, 44.5; FTIR (NaCl, cm^{-1}) 3155, 3035, 2936, 2840, 1794, 1637, 1599, 1513, 1464, 1442, 1388, 1376, 1359, 1306, 1253, 1178, 1137, 1096, 1035, 834, 796; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{29}H_{25}NO_2Na$ 442.1783, found 442.1783.

5-([1,1′-Biphenyl]-4-yl)-1-benzyl-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3l). Compound **3l** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 32.2 mg (73%) as a yellow wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.51 (m, 7H), 7.46−7.31 (m, 6H), 7.23−7.18 (m, 4H), 6.90 (d, J = 8.6 Hz, 2H), 4.55 (t, J = 7.5 Hz, 1H), 4.44 (d, J = 15.1 Hz, 1H), 4.23 (d, J = 15.1 Hz, 1H), 3.82 (s, 3H), 2.99 (dd, J = 16.2, 6.8 Hz, 1H), 2.86 (dd, J = 16.2, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 159.8, 153.1, 141.3, 138.6, 136.0, 135.3, 130.5, 129.1, 128.8, 128.5, 128.5, 128.4, 128.0, 127.9, 127.1, 127.1, 114.6, 110.9, 60.5, 57.6, 55.5, 44.6; FTIR (NaCl, cm^{-1}) 3054, 2087, 1638, 1597, 1513, 1488, 1421, 1357, 1179, 1126, 1035, 896; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{31}H_{27}NO_2Na$ 468.1939, found 468.1937.

1-Benzyl-5-(4-(ethoxycarbonyl)phenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3m). Compound **3m** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 21.9 mg (50%) as a yellow wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.37 (q, J = 6.1 Hz, 3H), 7.22−7.14 (m, 4H), 6.88 (d, J = 8.6 Hz, 2H), 4.55 (t, J = 7.3 Hz, 1H), 4.46 (d, J = 15.1 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.25 (d, J = 15.1 Hz, 1H), 3.81 (s, 3H), 2.98 (dd, J = 16.2, 6.9 Hz, 1H), 2.82 (dd, J = 16.2, 7.8 Hz, 1H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C 187.7, 166.9, 159.9, 153.5, 141.1, 135.7, 130.2, 129.7, 129.2, 128.6, 128.4, 127.89, 127.4, 126.9, 114.6, 110.0, 60.8, 60.3, 57.8, 55.4, 44.5, 14.5; FTIR (NaCl, cm^{-1}) 3054, 2987, 1707, 1642, 1597, 1513, 1422, 1368, 1180, 1127, 1107, 1034, 896; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{28}H_{27}NO_4Na$ 464.1838, found 464.1832.

1-Benzyl-5-(4-chlorophenyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3n). Compound **3n** was prepared by the general procedure described above and purified by flash column chromatography (25% EtOAc in hexanes) on silica gel to provide 20.3 mg (51%) as a yellow wax. Analytical data are consistent with those from our previous report.[5a]

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1-Benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-2,3-dihydropyridin-4(1*H*)-one (3o). Compound **3o** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 13.0 mg (32%) as a bright yellow solid (mp 98−100 °C). Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-2-(4-methoxyphenyl)-5-(4-(trifluoromethyl)-phenyl)-2,3-dihydropyridin-4(1*H*)-one (3p). Compound **3p** was prepared by the general procedure described above and purified by flash column chromatography (25% EtOAc in hexanes) on silica gel to provide 12.8 mg (30%) as a yellow wax. Analytical data are consistent with those from our previous report.[5a]

1-Benzyl-5-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3q). Compound **3q** was prepared by the general procedure described above and purified by flash column chromatography (70% EtOAc in hexanes) on silica gel to provide 22.6 mg (78%) as a yellow oil. Analytical data are consistent with those from our previous report.[5a]

5-(4-Methoxyphenyl)-1-phenyl-2,3-dihydropyridin-4(1*H*)-one (3r). Compound **3r** was prepared by the general procedure described above and purified by flash column chromatography (50% EtOAc in hexanes) on silica gel to provide 14.1 mg (50%) as an orange solid (mp 129−132 °C). Analytical data are consistent with those from our previous report.[5a]

1-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-(4-methoxyphenyl)-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (3s). Compound **3s** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 20.3 mg (45%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.39−7.28 (m, 7H), 6.87 (d, J = 8.7 Hz, 2H), 4.67 (t, J = 7.4 Hz, 1H), 3.80 (s, 3H), 3.64 (t, J = 5.6 Hz, 2H), 3.37 (dt, J = 14.6, 7.4 Hz, 1H), 3.23 (dt, J = 13.6, 6.4 Hz, 1H), 3.01 (dd, J = 16.2, 6.7 Hz, 1H), 2.82 (dd, J = 16.2, 8.0 Hz, 1H), 1.72 (p, J = 6.3 Hz, 2H), 0.85 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 157.9, 153.3, 138.9, 129.2, 128.9, 128.9, 128.4, 127.0, 113.8, 110.8, 61.4, 59.4, 55.5, 50.5, 44.6, 31.7, 26.0, 18.3, −5.3; FTIR (NaCl, cm^{-1}) 3054, 2987, 2930, 2857, 1635, 1596, 1512, 1422, 1178, 1156, 1101, 1036, 896, 836; HRMS (ESI+) m/e calcd for $[M + Na]^+$ $C_{27}H_{37}NO_3SiNa$ 474.2440, found 474.2440.

3-(4-Methoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (3t). Compound **3t** was prepared by the general procedure described above and purified by flash column chromatography (50% EtOAc in hexanes) on silica gel to provide 16.0 mg (63%) as a yellow oil. Analytical data are consistent with those from our previous report.[5a]

(4a*R*,8a*R*)-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (3u). Compound **3u** was prepared by the general procedure described above and purified by flash column chromatography (30% EtOAc in hexanes) on silica gel to provide 12.9 mg (48%) as a yellow wax. Analytical data are consistent with those from our previous report.[5a]

(4a*S*,8a*R*)-3-(4-Methoxyphenyl)-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (3v). Compound **3v** was prepared by the general procedure described above and purified by flash column chromatography (50% EtOAc in hexanes) on silica gel to provide 16.3 mg (60%) as a yellow wax. Analytical data are consistent with those from our previous report.[5a]

■ ASSOCIATED CONTENT

Supporting Information

Optimization data of the catalytic condition screen and stoichiometric study and ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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