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Regioselective Direct C-3 Arylation of Imidazo[1,2-*a*]pyridines with Aryl Tosylates and Mesylates Promoted by Palladium−Phosphine Complexes

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Supporting Information

ABSTRACT: Direct C-3 arylation of imidazo[1,2-*a*]pyridines with aryl tosylates and mesylates has been accomplished by employing palladium(II) acetate associated with SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) or **L1** (2-(2-(diisopropylphosphino)-phenyl)-1-methyl-1*H*-indole). This catalyst system can be applied to a wide range of aryl sulfonates and shows excellent C-3 regioselectivity of imidazo[1,2-*a*]pyridine. These results represent the first examples of using tosylate- and mesylate-functionalized arenes as the electrophile partners for this regioselective direct arylation.

INTRODUCTION

Imidazo[1,2-*a*]pyridine scaffold is exemplified as one of the most significant structural subunits in materials,[1] agrochemical,[2] and especially pharmaceutical products.[3] They possess important activities in antiviral, antimicrobial, herbicidal, antitumor, and immunosuppressive agents.[4] In particular, 3-aryl-imidazo[1,2-*a*]pyridines are often found as the core structures of various bioactive compounds, such as liver X receptor (LXR) agonists,[5] GABAAα2/α3 agonists,[6] γ-secretase modulators (GSMs),[7] positive allosteric modulators (PAMs) of metabotropic glutamate 2 receptor,[8] TP-003,[9] and kinase inhibitors (Figure 1).[10]

Having the increased interest of this class of compound, we envisage that the development of a direct and convergent synthetic method for preparing such versatile 3-aryl-imidazo-[1,2-*a*]pyridines would be valuable for drug development. There have been scanty literature reports to-date for the synthesis of 3-aryl-imidazo[1,2-*a*]pyridine derivatives. Relevant organic transformations for accessing these compounds are the condensation of 2-aminopyridine derivatives with α-halogen ketones,[11] aldehydes,[2,12] alkynes,[13] nitroolefins,[14] or other functional species (Figure 2).[15] In 2012, Lei showed the silver-mediated C−H/N-H oxidative cyclization for preparing arylimidazo[1,2-*a*]pyridines.[16] Jiang and co-workers recently reported a rapid transformation of pyridine to 3-arylimidazo-[1,2-*a*]pyridine derivatives via a copper-catalyzed aerobic dehydrogenative cyclization with ketone oxime esters (Figure 2).[17] Recent advances of palladium-catalyzed cross-coupling, for instance Suzuki reaction[6,18] and decarboxylative coupling, offer convergent approaches to synthesize a number of these diversified analogues (Figure 2).[19] However, they usually need the preactivation of organometallic nucleophiles or

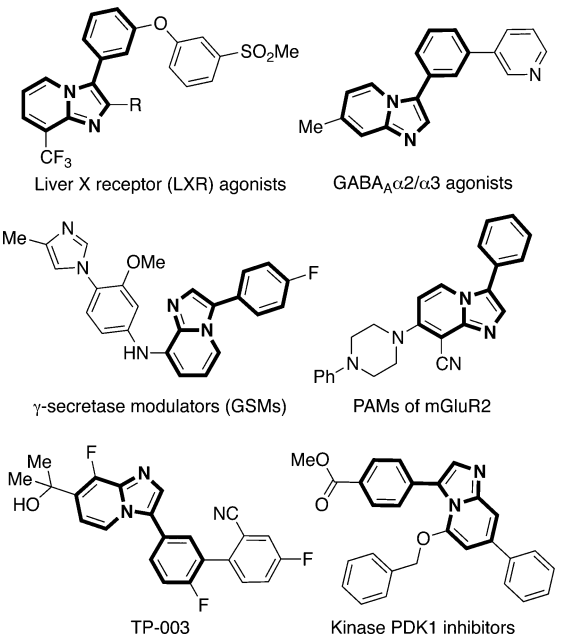

Figure 1. Examples of useful 3-aryl-imidazo[1,2-*a*]pyridine-containing molecules.

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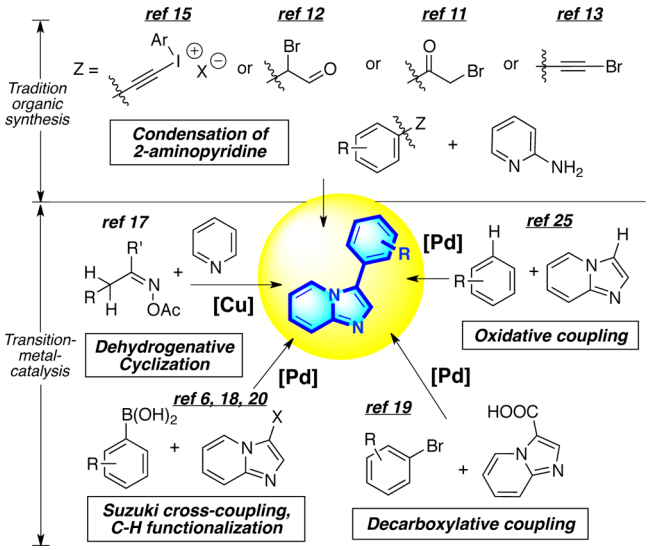


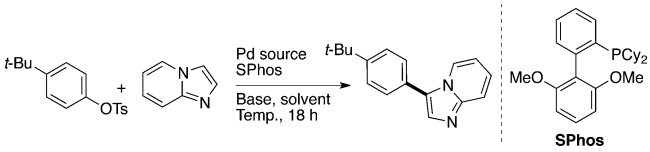
Figure 2. Selected synthetic methods for preparation of 3-arylimidazo[1,2-*a*]pyridines.

require specific carboxylate substrates. A more streamlined and attractive strategy is thus established in which the reaction can proceed via C−H functionalization/arylation pathway.[20] Although direct arylation of heterocycles has been successful, direct C3-arylation of free imidazo[1,2-*a*]pyridines still has room for further development.[21] In 2006, Berteina-Raboin employed 5 mol % of $Pd(OAc)_2$ associated with 10 mol % of PPh_3 for the C3-arylation of imidazo[1,2-*a*]pyridines (Figure 2).[22] Only aryl bromides were found applicable, and long reaction times (~48 h) were required to generate sufficient yield. Bazin and Marchand reported coupling between 3-haloimidazo[1,2-*a*]pyridines and arylboronic acids in the presence of 4−8 mol % $Pd(OAc)_2$ and $PCy_3{\cdot}HBF_4$ salt (Figure 2).[23] Recently, Doucet and co-workers disclosed a phosphine-free Pd-catalyzed direct C-3 arylation of imidazo[1,2-*a*]-pyridines with aryl bromides at low catalyst loading.[24] Nevertheless, aryl bromides were the only suitable electrophiles. In 2014, Zhan and Liu reported a facile synthesis of arylimidazo[1,2-*a*]pyridines through oxidative coupling.[25] In fact, previous literature reports were mainly focused on aryl halide electrophiles, as well as the 2-substituted imidazo[1,2-*a*]pyridines. Thus, a catalyst system which allows general aryl sulfonates and free imidazo[1,2-*a*]pyridines to serve as the coupling partners is still in demand. In continuing our former works on transition metal-catalyzed direct arylation[26] and C−H functionalization of heteroarenes,[27] herein we report our investigation of using aryl sulfonates as the electrophilic partners for direct C−H arylation of imidazo[1,2-*a*]pyridines.

RESULTS AND DISCUSSION

We initially started our investigation by employing commercially available imidazo[1,2-*a*]pyridine and 4-*tert*-butylphenyl tosylate as the model substrates (Table 1). A series of well-recognized and commercially available phosphines, as well as our previously developed ligands, were initially screened (Scheme 1). Poor conversion of aryl tosylate was observed with BrettPhos, whereas CataCXium PCy did not promote this direct arylation. A combination of $Pd(OAc)_2$ with SPhos was found to be the best catalyst of choice for this tosylate coupling. **L1** and XPhos showed comparable results while CM-phos gave slightly lower yield.

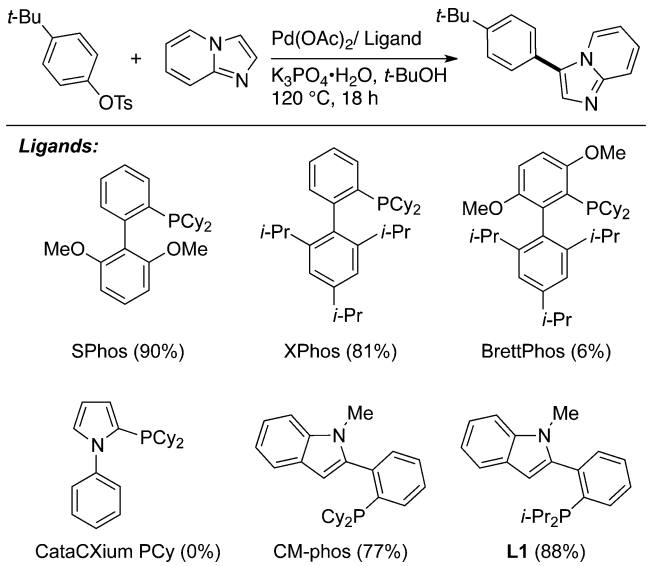
Table 1. Initial Screening of the Palladium-Catalyzed Direct Arylation of Imidazo[1,2-*a*]pyridine with ArOTs[a]



entry	catalyst	solvent	base	% yield[b]
1	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	90 (88)
2	$PdCl_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	32
3	$Pd_2(dba)_3$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	44
4	$Pd(TFA)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	80
5	$Pd(OAc)_2$	*t*-BuOH	K_2CO_3	61
6	$Pd(OAc)_2$	*t*-BuOH	K_3PO_4	88
7	$Pd(OAc)_2$	*t*-BuOH	Cs_2CO_3	79
8	$Pd(OAc)_2$	*t*-BuOH	KOAc	10
9	$Pd(OAc)_2$	toluene	$K_3PO_4{\cdot}H_2O$	NR
10	$Pd(OAc)_2$	dioxane	$K_3PO_4{\cdot}H_2O$	NR
11[c]	$Pd(OAc)_2$	CH_3CN	$K_3PO_4{\cdot}H_2O$	NR
12	$Pd(OAc)_2$	DMF	$K_3PO_4{\cdot}H_2O$	20
13[d]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	NR
14[e]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	NR
15[f]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	67
16[g]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	24
17[h]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	70
18[c]	$Pd(OAc)_2$	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	9

[a]Reaction conditions: ArOTs (0.5 mmol), imidazo[1,2-*a*]pyridine (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol, 2 mol %), SPhos (0.04 mmol, 8 mol %; Pd/L 1:4), base (1.5 mmol), and solvent (1 mL) were stirred at 120 °C under nitrogen for 18 h. [b]Calibrated GC yields are reported, using dodecane as the internal standard. [c]The reaction was performed at 80 °C. [d]Pd/Ligand = 1:1. [e]Pd/Ligand = 1:2. [f]Pd/Ligand = 1:3. [g]1.0 mol % of $Pd(OAc)_2$ was used. [h]1.5 mol % of $Pd(OAc)_2$ was used.

Scheme 1. Ligand Screening for the Palladium-Catalyzed Direct Arylation of Imidazo[1,2-*a*]pyridine[a]



[a]Reaction conditions: 4-*tert*-butylphenyl tosylate (0.5 mmol), imidazo[1,2-*a*]pyridine (1.0 mmol), $Pd(OAc)_2$ (2.0 mol %), L (8.0 mol %; Pd/L 1:4), $K_3PO_4{\cdot}H_2O$ (1.5 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C for 18 h. Yields were determined by GC analysis with dodecane as the internal standard.

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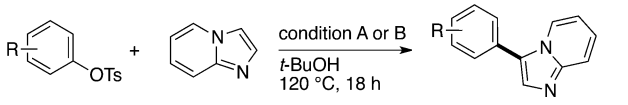
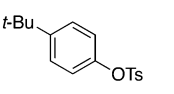
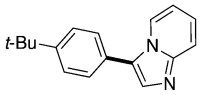
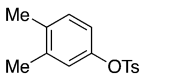
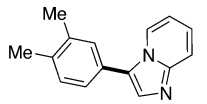
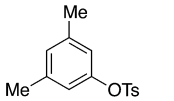
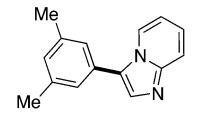
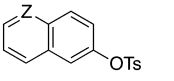
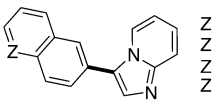
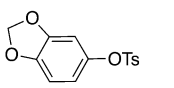
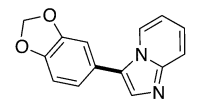
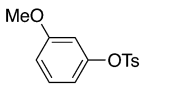
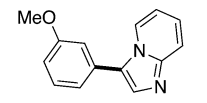
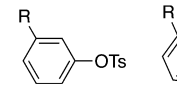
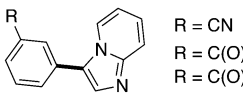
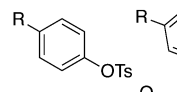
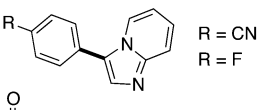
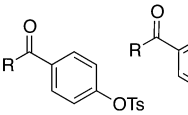
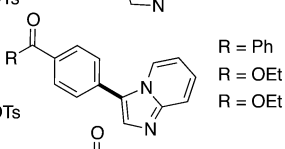
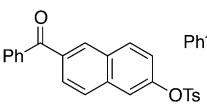
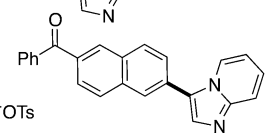
We carried out a series of investigations to optimize the reaction conditions (Table 1). $Pd(OAc)_2$ showed superior performance, and palladium(II) trifluoroacetate ($Pd(TFA)_2$) gave slightly lower conversion among other palladium sources examined (Table 1, entries 1−4). A screening of commonly used inorganic bases indicated that K_3PO_4 and $K_3PO_4·H_2O$ were both suitable bases for this coupling process (Table 1, entry 1 vs entries 5−8). The use of solvents, such as dioxane, toluene, CH_3CN, and DMF, in place of *t*-BuOH proved much less effective (Table 1, entry 1 vs entries 9−12). The Pd/L ratio of 1:4 afforded the best product yield whereas the ratio of 1:3 provided lower substrate conversions (Table 1, entry 1 vs entries 13−15). The Pd/L ratio of 1:4 gave good yield possibly because some of the ligands are required to serve as the reductant to reduce Pd(II) to Pd(0) at the initial stage of the catalysis. The ratio of Pd/L = 1:3 showed insufficient amount of reductant, and thus the effective Pd(0) complex. A 2.0 mol % amount of $Pd(OAc)_2$ was sufficient to catalyze the arylation (Table 1, entry 1 vs entries 16−17). Lowering the reaction temperature to 80 °C led to poor substrate conversion (Table 1, entry 1 vs entry 18).

With the preliminary optimized reaction conditions in hand, we next tested the generality of this catalyst system for the direct arylation of imidazo[1,2-*a*]pyridine with aryl tosylates (Table 2). A variety of aryl tosylates underwent the arylation smoothly. To the best of our knowledge, there has been no successful example of aryl tosylates reported to-date in the direct arylation of imidazo[1,2-*a*]pyridines. Slightly lower yield was afforded when this direct arylation of imidazo[1,2-*a*]pyridine was performed under air (entry 1). In the presence of SPhos, various electronically neutral aryl tosylates could be efficiently coupled to give the corresponding products in good-to-excellent yields (entries 1, 3, 5, and 7). Although functional groups such as methoxy (entry 13), fluoro (entry 19), keto (entry 20), and ester (entries 16 and 21) were compatible under the catalyst system of $Pd(OAc)_2$ and SPhos, moderate-to-good product yields were obtained. It should be noted that no desired product was observed when 3-cyanophenyl or 4-cyanophenyl tosylate was used as coupling substrate. Upon replacing the ligand SPhos with **L1** (condition B), coupling of 3-cyanophenyl or 4-cyanophenyl tosylate with imidazo[1,2-*a*]pyridine proceeded smoothly (entries 15 and 18). In fact, the substrate scope of direct arylation with **L1** was found comparable to SPhos (entries 2, 4, 6, and 8) while functional groups ester (entries 17 and 22), keto (entry 23), and even cyano groups (entries 15 and 18) could be tolerated to afford the product in improved yields. Yet, heterocyclic quinolyl tosylate gave better yield when SPhos was employed (entries 9 and 10). We also examined the multiheteroatom-containing aryl sulfonates, such as benzo[*d*]thiazol-6-yl 4-methylbenzenesulfonate and benzo[*d*]thiazol-6-yl methanesulfonate. However, they were found not successful as coupling partners in this reaction. Only monoheteroatom-containing aryl tosylate was found suitable to afford the desirable product. When naphthalen-1-yl tosylate was applied as coupling partner, 12% yield was obtained. For bromo-group compatibility, we additionally tested 3-bromophenyl tosylate. A 4:1 ratio of the products 2-[3-(4-tolylsulfonyloxy)]imidazo[1,2-*a*]pyridine and 2-(3-bromophenyl)imidazo[1,2-*a*]pyridine, respectively, were observed from GC-MS analysis.

No examples of direct arylation of imidazo[1,2-*a*]pyridines with aryl mesylates were reported. To expand the substrate scope further, we next probed the possibility of using mesylate-functionalized arenes as the electrophilic coupling partners (Table 3). Essentially no coupling products were observed when the use of Pd−SPhos complex was initially attempted. Further detailed screening revealed that XPhos, SPhos, and BrettPhos did not promote the reaction. Only **L1** was found capable to facilitate this coupling process, and the desired product was afforded in satisfactory yield under the same reaction conditions as in Table 2, entry 2. With this effective ligand **L1** in hand, various aryl mesylates were then evaluated.

Table 2. Palladium-Catalyzed Direct Arylation of Imidazo[1,2-*a*]pyridine with ArOTs[a]



entry	ArOTs	product	condition	% yield[b]
1			A	88[c], 67[d]
2			B	80
3			A	79
4			B	71
5			A	81
6			B	73
7			Z = C A	52
8			Z = C B	87
9			Z = N A	79[e]
10			Z = N B	38
11			A	61[e]
12			B	57
13			A	79[e]
14			B	52[e]
15			R = CN B	64[e]
16			R = C(O)OEt A	49[e]
17			R = C(O)OEt B	71[e,f]
18			R = CN B	74[e]
19			R = F A	58[e]
20			R = Ph A	46[e]
21			R = OEt A	58[e]
22			R = OEt B	68[e,f]
23			B	82[e,f]

[a]Reaction conditions: ArOTs (0.5 mmol), imidazo[1,2-*a*]pyridines (1.0 mmol), Condition A: $Pd(OAc)_2$ (0.01 mmol, 2.0 mol %), SPhos (0.04 mmol, 8.0 mol %; Pd/L 1:4), K_3PO_4 (1.5 mmol) and *t*-BuOH (1.0 mL) were stirred at 120 °C under nitrogen for 18 h. Condition B: $Pd(OAc)_2$ (0.01 mmol, 2.0 mol %), **L1** (0.04 mmol, 8.0 mol %; Pd/L 1:4), $K_3PO_4·H_2O$ (1.5 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. [b]Isolated yields are reported. [c]$K_3PO_4·H_2O$ was used as base. [d]The reaction was performed under air. [e]K_2CO_3 was used as base. [f]ArOTs (1.0 mmol) and imidazo[1,2-*a*]pyridines (0.5 mmol) were used.

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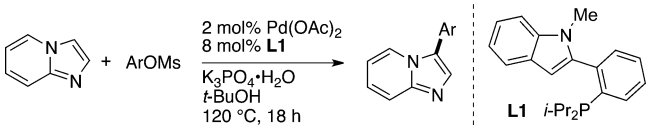
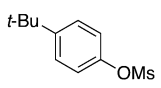
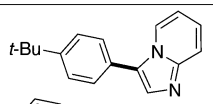
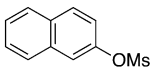
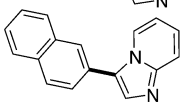
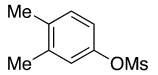
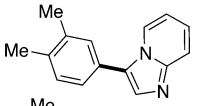
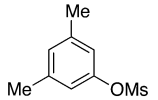
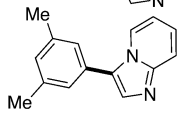
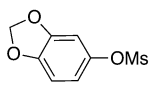
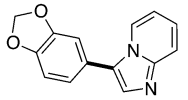
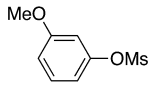
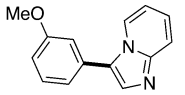
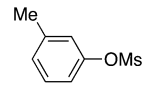
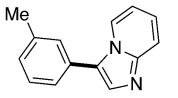
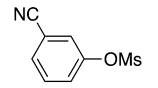
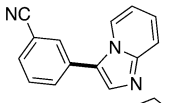
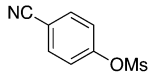
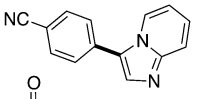
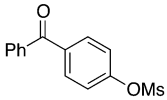
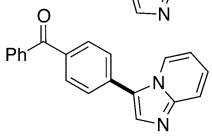
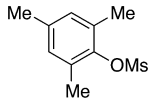
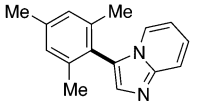
Table 3. Palladium-Catalyzed Direct Arylation of Imidazo[1,2-*a*]pyridines with ArOMs[a]



entry	ArOMs	product	% yield[b]
1			60
2			73
3			72
4			72
5			62[c,d]
6			50[c]
7			71
8			43[c,d]
9			52[c,d]
10			47[c,d]
11			NR

[a]Reaction conditions: ArOMs (0.5 mmol), imidazo[1,2-*a*]pyridines (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.0 mol %), **L1** (0.04 mmol, 8.0 mol %; Pd/L 1:4), $K_3PO_4·H_2O$ (1.5 mmol) and *t*-BuOH (1 mL) were stirred at 120 °C under nitrogen for 18 h. [b]Isolated yields are reported. [c]K_2CO_3 was used as base. [d]ArOMs (1.0 mmol) and imidazo[1,2-*a*]pyridines (0.5 mmol) were used.

Good product yields were afforded for electronically neutral aryl mesylates (entries 1–4). Functionalized aryl mesylates containing nitrile (entries 8 and 9), keto (entry 10), and benzodioxolyl groups (entry 5) were shown tolerable under this system. When highly sterically hindered 2,4,6-trimethylphenyl mesylates were tested, only hydrolyzed phenolic side product was observed and no desired coupling product was afforded.

CONCLUSION

We have reported the first general palladium-catalyzed direct arylation of imidazo[1,2-*a*]pyridines with aryl tosylates and mesylates. The Pd–SPhos catalyst system is effective for the coupling of a range of tosylate-functionalized substrates. Particularly noteworthy is that we also showed the first successful examples of aryl mesylate coupling when the Pd–**L1** catalyst system was employed. Having the Pd–SPhos and new Pd–**L1** systems, the coupling of both functionalized aryl tosylates and a range of aryl mesylates can be accomplished, respectively.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All the reactions were performed in Rotaflo (England) resealable screw-cap tubes (approximately 10 mL volume) in the presence of a Teflon-coated magnetic stirrer bar (4 mm × 10 mm). Dioxane and toluene were freshly distilled over sodium under nitrogen.[28] *t*-BuOH was first distilled over sodium and stored with calcium hydride under nitrogen. Thin layer chromatography was performed on precoated silica gel 60 F_{254} plates. Silica gel (230–400 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), or with TMS (δ 0.00 ppm) as the internal standard. Chemical shifts (δ) are reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer, and the spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak). Coupling constants (J) are reported in hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a mass spectrometer. High-resolution mass spectra (HRMS) were obtained on a ESIMS mass spectrometer. GC-MS analysis was conducted on a GCD system. GC yields are according to the authentic samples/dodecane calibration standard from the GC-FID system.

General Procedures for Reaction Condition Screenings. Palladium source (2.0 mol %), ligand (8.0 mol %), aryl tosylates (0.5 mmol), and base (1.5 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Imidazo[1,2-*a*]pyridines (1.0 mmol, 101 μL) and the solvent (1.0 mL) were then added with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath (120 °C or indicated in Table 1) and stirred for 18 h. After completion of reaction, the reaction tube was allowed to cool to room temperature. Ethyl acetate (~10 mL), dodecane (114 μL, internal standard), and water (~3 mL) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated with the authentic sample/dodecane calibration curve.

General Procedures for Direct C–H Bond Arylation: Palladium-Catalyzed Direct Arylation of Imidazo[1,2-*a*]-pyridines. Condition A: $Pd(OAc)_2$ (2.0 mol %, 0.0022 g), SPhos (8.0 mol %, 0.0164 g), aryl tosylates (0.5 mmol), and base (1.5 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Imidazo[1,2-*a*]pyridines (1.0 mmol, 101 μL) and the solvent *t*-BuOH (1.0 mL) were then added with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath (120 °C) and stirred for 18 h. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and ethyl acetate then added for dilution. The organic layer was separated, and the aqueous layer was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product.

Condition B: $Pd(OAc)_2$ (2.0 mol %, 0.0022 g) and **L1** (8.0 mol %, 0.0129 g) were loaded into a Schlenk tube equipped with a Teflon-

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coated magnetic stir bar. The tubes were evacuated and backfilled with nitrogen (three cycles). Precomplexation was applied by adding freshly distilled dichloromethane (1.0 mL) and Et_3N (0.05 mL) into the tube. The palladium complex stock solution was stirred and warmed using a hair drier for 1 to 2 min until the solvent started boiling. The solvent was then evaporated under high vacuum. Aryl mesylates/tosylates (0.5 mmol) and base (1.5 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. Imidazo[1,2-*a*]pyridines (1.0 mmol, 101 μL) and the solvent *t*-BuOH (1.0 mL) were then added with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath (120 °C) and stirred for 18 h. After completion of reaction, the reaction tube was allowed to cool to room temperature, quenched with water, and diluted with ethyl acetate. The organic layer was separated, and the aqueous layer was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230−400 mesh) to afford the desired product.

3-(4-(tert-Butyl)phenyl)imidazo[1,2-a]pyridine (Table 2, entries 1 and 2; Table 3, entry 1).[24a] EA:hexane = 1:2, R_f = 0.4, Table 2: 88% (110 mg), Table 3: 60% (75 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 6.77 (t, J = 6.8 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.47−7.55 (m, 4H), 7.65 (s, 1H), 7.67 (s, 1H), 8.32 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 31.3, 34.7, 112.4, 118.1, 123.4, 124.1, 125.7, 126.1, 126.3, 127.7, 132.1, 145.9, 151.3.

3-(3,4-Dimethylphenyl)imidazo[1,2-a]pyridine (Table 2, entries 3 and 4; Table 3, entry 3).[25] EA:hexane = 1:2, R_f = 0.4, Table 2: 79% (88 mg), Table 3: 72% (80 mg); 1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 6.77 (t, J = 6.8 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.26 (s, 2H), 7.30 (s, 1H), 7.64 (s, 1H), 7.67 (s, 1H), 8.29 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 19.8, 112.4, 118.0, 123.4, 124.1, 125.4, 125.8, 126.5, 129.2, 130.4, 131.8, 136.9, 137.5, 145.7.

3-(3,5-Dimethylphenyl)imidazo[1,2-a]pyridine (Table 2, entries 5 and 6; Table 3, entry 4).[25] EA:hexane = 1:2, R_f = 0.4, Table 2: 81% (90 mg), Table 3: 72% (80 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 6.74 (t, J = 6.8 Hz, 1H), 7.02 (s, 1H), 7.11−7.14 (m, 3H), 7.62 (s, 1H), 7.64 (s, 1H), 8.29 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 112.3, 118.1, 123.5, 124.0, 125.7, 125.9, 129.0, 129.8, 132.3, 138.8, 145.9.

3-(Naphthalen-2-yl)imidazo[1,2-a]pyridine (Table 2, entries 7 and 8; Table 3, entry 2).[24a] EA:hexane = 1:2, R_f = 0.3, Table 2: 87% (106 mg), Table 3: 73% (89 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.54 (s, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 7.88 (s, 2H), 7.95 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 8.42 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.5, 118.1, 123.2, 124.2, 125.6, 126.4 (overlapped), 126.5, 126.6, 127.7, 127.8, 128.9, 132.7, 133.4, 146.1.

6-(Imidazo[1,2-a]pyridin-3-yl)quinoline (Table 2, entries 9 and 10). EA, R_f = 0.2, pale yellow viscous oil, 79% (97 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (t, J = 6.8 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.38−7.41 (q, J = 4.0 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.76 (s, 1H), 7.82−7.84 (dd, J = 7.2, 1.6 Hz, 1H), 7.90 (s, 1H), 8.12, (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.35 (d, J = 7.2 Hz, 1H), 8.88−8.90 (dd, J = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.9, 118.3, 121.8, 123.2, 124.6, 124.9, 126.1, 127.4, 128.5, 129.1, 130.5, 133.3, 135.9, 146.4, 147.6, 150.8; HRMS: calcd for $C_{16}H_{12}N_3^+$: 246.1026, found 246.1025.

3-(Benzo[d][1,3]dioxol-5-yl)imidazo[1,2-a]pyridine (Table 2, entries 11 and 12; Table 3, entry 5). EA:hexane = 1:2, R_f = 0.35, colorless oil, Table 2: 61% (73 mg), Table 3: 62% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 2H), 6.76−6.80 (td, J = 6.8, 0.8 Hz, 1H), 6.93−7.01 (m, 3H), 7.14−7.19 (m, 1H), 7.61 (s, 1H), 7.63 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3, 108.5, 108.9, 112.3, 118.0, 121.9, 122.7, 123.9, 125.3, 132.0, 145.7, 147.6, 148.2. HRMS: calcd for $C_{14}H_{11}N_2O_2^+$: 239.0821, found 239.0820.

3-(3-Methoxyphenyl)imidazo[1,2-a]pyridine (Table 2, entries 13 and 14; Table 3, entry 6).[19] EA:hexane = 1:2, R_f = 0.35, Table 2: 79% (88 mg), Table 3: 50% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.80 (t, J = 6.8 Hz, 1H), 6.94−6.97 (dd, J = 8.0 Hz, 1H), 7.09 (s, 1H), 7.14−7.21 (m, 2H), 7.43 (t, J = 8.0 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.70 (s, 1H), 8.35 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 112.4, 113.4, 113.6, 118.1, 120.1, 123.4, 124.1, 125.4, 130.1, 130.4, 132.4, 146.0, 160.0.

3-(Imidazo[1,2-a]pyridin-3-yl)benzonitrile (Table 2, entries 15; Table 3, entry 8).[24a] EA:hexane = 1:2, R_f = 0.30, Table 2: 64% (70 mg), Table 3: 43% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (t, J = 6.8 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.60−7.82 (m, 6H), 8.27 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.1, 113.4, 118.0, 118.3, 122.7, 123.2, 124.8, 130.0, 130.6, 130.7, 131.1, 131.7, 133.3, 146.4.

Ethyl 3-(imidazo[1,2-a]pyridin-3-yl)benzoate (Table 2, entries 16 and 17). EA:hexane = 1:2, R_f = 0.30, yellow viscous oil, 71% (94 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 4.32 (d, J = 5.6 Hz, 2H), 6.75 (s, 1H), 7.13 (s, 1H), 7.50−7.66 (m, 4H), 8.00 (s, 1H), 8.16 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 61.3, 112.8, 118.3, 123.1, 124.5, 124.7 (overlapped), 129.0, 129.3, 131.5, 132.1, 132.9, 146.3, 166.0; HRMS: calcd for $C_{16}H_{15}N_2O_2^+$: 267.1134, found 267.1131.

4-(Imidazo[1,2-a]pyridin-3-yl)benzonitrile (Table 2, entry 18; Table 3, entry 9).[24a] EA:hexane = 1:2, R_f = 0.30, Table 2: 74% (80 mg), Table 3: 52% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (td, J = 6.8 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.71−7.74 (m, 3H), 7.81−7.83 (m, 3H), 8.38 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.2, 113.4, 118.5, 118.7, 123.1, 125.2, 127.6, 133.1, 134.0, 134.2.

3-(4-Fluorophenyl)imidazo[1,2-a]pyridine (Table 2, entry 19).[24a] EA:hexane = 1:2, R_f = 0.20, 58% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (t, J = 6.0 Hz, 1H), 7.18−7.24 (m, 3H), 7.50−7.54 (m, 2H), 7.66 (s, 1H), 7.68 (s, 1H), 8.23 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 116.3 (d, J = 21 Hz), 118.3, 123.0, 124.2, 124.6, 125.3 (d, J_{CF} = 3 Hz), 130.0 (d, J_{CF} = 8 Hz), 132.5, 146.0, 162.5 (d, J_{CF} = 247); ^{19}F NMR (400 MHz, $CDCl_3$) δ −112.7.

(4-(Imidazo[1,2-a]pyridin-3-yl)phenyl)(phenyl)methanone (Table 2, entry 20; Table 3, entry 10). EA:hexane = 1:2, R_f = 0.25, pale yellow oil, Table 2: 46% (69 mg), Table 3: 47% (70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (t, J = 6.4 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.68−7.71 (m, 3H), 7.81 (s, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 8.43 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.1, 118.4, 123.4, 124.7, 124.9, 127.1, 128.4, 130.0, 131.1, 132.6, 133.3, 133.6, 136.7, 137.4, 146.8, 195.8; HRMS: calcd for $C_{20}H_{15}N_2O^+$: 299.1184, found 299.1181.

Ethyl 4-(Imidazo[1,2-a]pyridin-3-yl)benzoate (Table 2, entries 21 and 22). EA:hexane = 1:2, R_f = 0.3, colorless oil, 68% (90 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 6.8 Hz, 2H), 6.82 (t, J = 6.8 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.59−7.66 (m, 3H), 7.73 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H), 8.34 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 60.9, 112.8, 118.2, 123.1, 124.6, 126.9, 129.5, 130.3, 133.3, 133.4, 146.5, 165.8; HRMS: calcd for $C_{16}H_{15}N_2O_2^+$: 267.1134, found 267.1136.

(7-(Imidazo[1,2-a]pyridin-3-yl)naphthalen-2-yl)(phenyl)-methanone (Table 2, entry 23). EA:hexane = 1:2, R_f = 0.25, pale yellow viscous oil, 82% (143 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (t, J = 6.8 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.70−7.73 (m, 2H), 7.84−7.87 (m, 3H), 7.95−8.07 (m, 4H), 8.29 (s, 1H), 8.48 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 118.2, 123.2, 124.6, 125.1, 125.7, 126.3, 126.6, 128.1, 129.0, 129.9, 130.4, 131.4 (overlapped), 132.3, 133.3, 135.0, 135.3, 137.5, 146.4, 196.2; HRMS: calcd for $C_{24}H_{17}N_2O^+$: 349.1341, found 349.1330.

3-(p-Tolyl)imidazo[1,2-a]pyridine (Table 3, entry 7).[22] EA:hexane = 1:2, R_f = 0.20, 71% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.79 (t, J = 6.0 Hz, 1H), 7.16−7.21 (m, 2H), 7.35−7.41 (m, 3H), 7.65 (d, J = 8.0 Hz, 2H), 8.32 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 112.3, 118.0, 123.3, 124.0, 124.9, 125.7, 128.5, 128.8, 128.9, 129.0, 132.1, 138.9, 145.9.

3-(Naphthalen-1-yl)imidazo[1,2-a]pyridine.[24a] EA:hexane = 1:1, R_f = 0.20, colorless oil, 12% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (t, J = 7.6 Hz, 1H), 7.21−7.25 (m, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.51−7.62 (m, 4H), 7.73 (t, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7,95−8.00

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(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.2, 118.0, 124.1, 124.2, 125.2, 125.6, 126.4, 126.9, 128.7, 129.1, 129.6, 132.0, 133.9, 145.9.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra. 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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■ REFERENCES

(1) Bae, J. S.; Lee, D. W.; Lee, D. H.; Jeong, D. S. PCT Int. Appl. WO2007011163A1, 2007.

(2) Egner, U.; Gerbling, K. P.; Hoyer, G.-A.; Krüger, G.; Wegner, P. *Pestic. Sci.* **1996**, *47*, 145−158.

(3) (a) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347−350. (b) Moraski, G. C.; Markley, L. D.; Hipskind, P. A.; Boshoff, H.; Cho, S.; Franzblau, S. G.; Miller, M. J. *ACS Med. Chem. Lett.* **2011**, *2*, 466−470.

(4) (a) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61−72. (b) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13−18. (c) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170−1176. (d) Kaminsky, J. J.; Doweyko, a. M. *J. Med. Chem.* **1997**, *40*, 427−436. (e) Katritzky, A. R.; Xu, Y. J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935−4937. (f) Jain, A. N. *J. Med. Chem.* **2004**, *47*, 947−961. (g) Harrison, T. S.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65−89. (h) Puerstinger, G.; Paeshuyse, J.; Declercq, E.; Neyts, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 390−393. (i) Gueiffier, E. C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888−899. (j) Hanson, S. M.; Morlock, E. V.; Satyshur, K. A.; Czajkowski, C. *J. Med. Chem.* **2008**, *51*, 7243−7252. (k) Li, A.-R.; Johnson, M. G.; Liu, J.; Chen, X.; Du, X.; Mihalic, J. T.; Deignan, J.; Gustin, D. J.; Duquette, J.; Fu, Z.; Zhu, L.; Marcus, A. P.; Bergeron, P.; McGee, L. R.; Danao, J.; Lemon, B.; Carabeo, T.; Sullivan, T.; Ma, J.; Tang, L.; Tonn, G.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 688−693. (l) Hsua, N.; Jha, S. K.; Coleman, T.; Frank, M. G. *Behav. Brain Res.* **2009**, *201*, 233−236.

(5) Singhaus, R. R.; Bernotas, R. C.; Steffan, R.; Matelan, E.; Quinet, E.; Nambi, P.; Feingold, I.; Huselton, C.; Wilhelmsson, A.; Goos-Nilsson, A.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 521−525.

(6) Goodacre, S. C.; Street, L. J.; Hallett, D. J.; Crawforth, J. M.; Kelly, S.; Owens, A. P.; Blackaby, W. P.; Lewis, R. T.; Stanley, J.; Smith, A. J.; Ferris, P.; Sohal, B.; Cook, S. M.; Pike, A.; Brown, N.; Wafford, K. A.; Marshall, G.; Castro, J. L.; Atack, J. R. *J. Med. Chem.* **2006**, *49*, 35−38.

(7) Bischoff, F.; Berthelot, D.; De Cleyn, M.; Macdonald, G.; Minne, G.; Oehlrich, D.; Pieters, S.; Surkyn, M.; Trabanco, A. A.; Tresadern, G.; Brandt, S. V.; Velter, I.; Zaja, M.; Borghys, H.; Masungi, C.; Mercken, M.; Gijsen, H. J. M. *J. Med. Chem.* **2012**, *55*, 9089−9106.

(8) Tresadern, G.; Cid, J. M.; Macdonald, G. J.; Vega, J. A.; de Lucas, A. I.; García, A.; Matesanz, E.; Linares, M. L.; Oehlrich, D.; Lavreysen, H.; Biesmans, I.; Trabanco, A. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 175−179.

(9) Fradley, R. L.; Guscott, M. R.; Bull, S.; Hallett, D. J.; Goodacre, S. C.; Wafford, K. A.; Garrett, E. M.; Newman, R. J.; O'Meara, G. F.; Whiting, P. J.; Rosahl, T. W.; Dawson, G. R.; Reynolds, D. S.; Atack, J. R. *J. Psychopharmacol.* **2007**, *21*, 384−391.

(10) (a) Follot, S.; Debouzy, J.-C.; Crouzier, D.; Enguehard-Gueiffier, C.; Gueiffier, A.; Nachon, F.; Lefebvre, B.; Fauvelle, F. *Eur. J. Med. Chem.* **2009**, *44*, 3509−3518. (b) Colletti, S. L.; Frie, J. L.; Dixon, E. C.; Singh, S. B.; Choi, B. K.; Scapin, G.; Fitzgerald, C. E.; Kumar, S.; Nichols, E. A.; O'Keefe, S. J.; O'Neill, E. A.; Porter, G.; Samuel, K.; Schmatz, D. M.; Schwartz, C. D.; Shoop, W. L.; Thompson, C. M.; Thompson, J. E.; Wang, R.; Woods, A.; Zaller, D. M.; Doherty, J. B. *J. Med. Chem.* **2003**, *46*, 349−352. (c) Katz, J.; Jewell, J.; Jung, J.; Kattar, S.; Hou, Y.; Maccoss, R.; Ito, S. PCT Int. Appl. WO 2010017047 A1, 2010.

(11) (a) Djerassi, C.; Pett, G. R. *J. Am. Chem. Soc.* **1954**, *76*, 4470−4472. (b) Elliott, A. J.; Guzik, H.; Soler, J. R. *J. Heterocycl. Chem.* **1982**, *19*, 1437−1440. (c) Stasyuk, A. J.; Banasiewicz, M.; Cyrański, M. K.; Gryko, D. T. *J. Org. Chem.* **2012**, *77*, 5552−5558. (d) Bangade, V. M.; Reddy, B. C.; Thakur, P. B.; Babu, B. M.; Meshram, H. M. *Tetrahedron Lett.* **2013**, *54*, 4767−4771.

(12) (a) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013−1016. (b) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191−3194. (c) Yan, H.; Wang, Y.; Pan, C.; Zhang, H.; Yang, S.; Ren, X.; Li, J.; Huang, G. *Eur. J. Org. Chem.* **2014**, 2754−2763.

(13) (a) Wu, Z.; Pan, Y.; Zhou, X. *Synthesis* **2011**, 2255−2260. (b) Dixon, L. I.; Carroll, M. A.; Gregson, T. J.; Ellames, G. J.; Harrington, R. W.; Clegg, W. *Org. Biomol. Chem.* **2013**, *11*, 5877−5884.

(14) (a) Yan, H.; Yang, S.; Gao, X.; Zhou, K.; Ma, C.; Yan, R.; Huang, G. *Synlett* **2012**, *23*, 2961−2964. (b) Nair, D. K.; Mobin, S. M.; Namboothiri, N. N. *Org. Lett.* **2012**, *14*, 4580−4583.

(15) (a) Collins, M. R.; Huang, Q.; Ornelas, M. A.; Scales, S. A. *Tetrahedron Lett.* **2010**, 3528−3530. (b) Marhadour, S.; Marchand, P.; Pagniez, F.; Bazin, M.-A.; Picot, C.; Lozach, O.; Ruchaud, S.; Antoine, M.; Meijer, L.; Rachidi, N.; Pape, P. L. *Eur. J. Med. Chem.* **2012**, 543−556. (c) Liu, G.; Cong, X.; He, J.; Luo, S.; Wu, D.; Lan, J. *J. Chem. Res.* **2012**, *36*, 687−690.

(16) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073−11075.

(17) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. *Org. Lett.* **2013**, *15*, 6254−6257.

(18) (a) Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572−6575. (b) Crawforth, J. M.; Goodacre, S. C.; Hallett, D. J.; Harrison, T.; Owens, A. P.; Rowley, M.; Teall, M. R. PCT Int. Appl. WO 2001038326 A2, 2001. (c) Bilodeau, M. T.; Fraley, M. E.; Wu, Z. PCT Int. Appl. WO 2003092595 A2, 2003. (d) Masuda, N.; Miyamoto, S.; Kikuchi, S.; Samizu, K.; Sato, F.; Shiina, Y.; Hamaguchi, W.; Seo, R.; Mihara, T. PCT Int. Appl. WO 2012133607 A1, 2012.

(19) Nandi, D.; Jhou, Y.-M.; Lee, J.-Y.; Kuo, B.-C.; Liu, C.-Y.; Huang, P.-W.; Lee, H. M. *J. Org. Chem.* **2012**, *77*, 9384−9390.

(20) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009.

(21) Selected examples for using palladium-catalysis, see: (a) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979−1982. (b) Kumar, P. V.; Lin, W.-S.; Shen, J.-S.; Nandi, D.; Lee, H. M. *Organometallics* **2011**, *30*, 5160−5169. (c) Ke, C.-H.; Kuo, B.-C.; Nandi, D.; Lee, H. M. *Organometallics* **2013**, *32*, 4775−4784. (d) Lee, J.; Chung, J.; Byun, S. M.; Kim, B. M.; Lee, C. *Tetrahedron* **2013**, *69*, 5660−5664. Selected examples for using other transition-metal-catalysis, see: (e) Yang, H.; Yang, L.; Li, Y.; Zhang, F.; Liu, H.; Yi, B. *Catal. Commun.* **2012**, *26*, 11−14. (f) Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.* **2012**, *14*, 1688−1691. (g) Liu, Y.; He, L.; Yin, G.; Wu, G.; Cui, Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 2340−2342. (h) Liu, B.; Huang, Y.; Lan, J.; Song, F.; You, J. *Chem. Sci.* **2013**, *4*, 2163−2167.

DOI: 10.1021/jo502386w
J. Org. Chem. XXXX, XXX, XXX−XXX

(22) Koubachi, J.; Kazzouli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synlett* **2006**, 3237−3242.
(23) Marhadour, S.; Bazin, M.-A.; Marchand, P. *Tetrahedron Lett.* **2012**, 297−300.
(24) (a) Fu, H. Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473−4478. (b) Laroche, J.; Beydoun, K.; Guerchais, V.; Doucet, H. *Catal. Sci. Technol.* **2013**, *3*, 2072−2080.
(25) Wang, S.; Liu, W.; Cen, J.; Liao, J.; Huang, J.; Zhan, H. *Tetrahedron Lett.* **2014**, 1589−1592.
(26) (a) So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.—Eur. J.* **2011**, *17*, 761−765. (b) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912−2915. (c) Lee, D. S.; Choy, P. Y.; So, C. M.; Wang, J.; Lau, C. P.; Kwong, F. Y. *RSC Adv.* **2012**, *2*, 9179−9182. (d) Yuen, O. Y.; So, C. M.; Wong, W. T.; Kwong, F. Y. *Synlett* **2012**, *23*, 2714−2718.
(27) (a) Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80−84. (b) Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 3258−3261. (c) Wu, Y.; Choy, P. Y.; Mao, F.; Kwong, F. Y. *Chem. Commun.* **2013**, *49*, 689−691. (d) Yuen, O. Y.; Choy, P. Y.; Chow, W. K.; Wong, W. T.; Kwong, F. Y. *J. Org. Chem.* **2013**, *78*, 3374−3378. (e) Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y. *Chem.—Asian J.* **2014**, *9*, 26−47.
(28) Armarego, W. L. F.; Perrin, D. D. In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, 1996.

DOI: 10.1021/jo502386w
J. Org. Chem. XXXX, XXX, XXX−XXX