JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

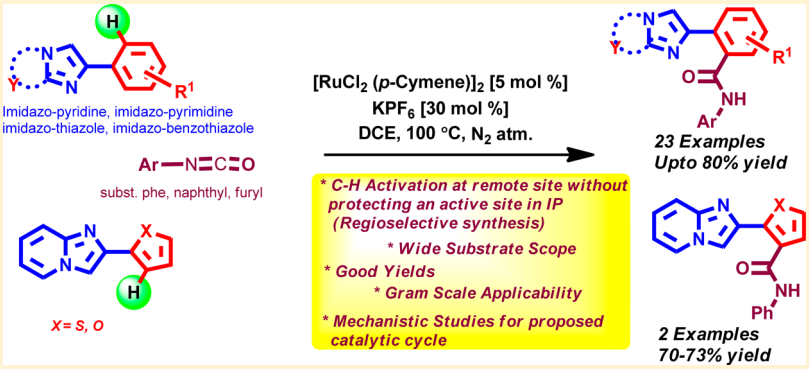
Ruthenium(II)-Catalyzed Regioselective Ortho Amidation of Imidazo Heterocycles with Isocyanates

S. M. Abdul Shakoor,[†] Santosh Kumari,[†] Sadhika Khullar,[‡] Sanjay K. Mandal,[‡] Anil Kumar,[†] and Rajeev Sakhuja*[,†]

[†]Department of Chemistry, Birla Institute of Technology & Science, Pilani, Rajasthan 333031, India

[‡]Department of Chemical Sciences, Indian Institute of Science Education and Research Mohali, Sector 81, S.A.S. Nagar, Manuali P.O., Punjab 140306, India

Supporting Information



ABSTRACT: Direct ortho amidation at the phenyl ring of 2-phenylimidazo heterocycles with aryl isocyanates has been achieved via a chelation-assisted cationic ruthenium(II) complex catalyzed mechanism. The methodology provides a straightforward, high-yielding regioselective approach toward the synthesis of an array of ortho-amidated phenylimidazo heterocycles without prior activation of C(sp^2)−H. This also reports the first method for coupling of aryl isocyanates with the imidazo[1,2-*a*]pyridine system via a pentacyclometalated intermediate. The methodology is found to be easily scalable and could be applied toward the selective ortho amidation of 2-heteroarylimidazo[1,2-*a*]pyridine frameworks.

INTRODUCTION

Transition-metal-catalyzed direct C−H activation of non-activated C−H bonds with various coupling partners via chelation-assisted activation has streamlined chemical synthesis by ceasing tedious and expensive substrate preactivation steps. Within the same domain, immense progress has been recently documented toward the development of pivotal C−C bonds.[1] Chelation-assisted direct C−H bond activation via directing groups was initially showcased by Pd or Rh catalysts;[2] however, at present the use of a large variety of other metal catalysts, including the environmentally benign Ru catalysts, has been well exemplified.[3] A multitude of functionalities, including amides, amines, ketones, esters, alcohols, and azo groups, have acted as directing groups in C−H functionalization via metal chelation−activation strategy.[4] In 1993, Murai's group utilized a Ru(0) catalyst precursor for chelation-assisted ortho alkylation of aromatic ketones with alkenes via C−H bond activation.[5] Ever since this work, chelation-assisted Ru(II)-catalyzed addition to C−C π bonds via a cyclometalation−migratory insertion mechanism has witnessed enormous progress in comparison to Rh or Re catalysis.[6] However, such reactions have not been extended to systems incorporating polar C−N bonds and only proceed in the presence of strongly coordinating arylpyridines or arylpyrazoles.[7]

Along this line, the direct insertion of activated or nonactivated C−H bonds into the polar C−N π bond of isocyanates is a highly auspicious methodology for providing synthetically and biologically important amides. Pioneering efforts have been made by Ackermann, Kuninobu and Takai, Bergman and Ellman, Cheng, and Li toward introducing amide functionalities[7,8] on various biologically important heterocyclic scaffolds, by virtue of versatile directing groups. In most strategies, the directing group (DG) is introduced in the parent moiety to accomplish its ortho amidation,[7b,8a−d,f] while in very few substrate-directed motifs, the ortho amidation proceeds through an inbuilt coordinating site[7,8g] (Figure 1).

Imidazo[1,2-*a*]pyridine (IP) is an example of a privileged heterocyclic motif that has been immensely highlighted in recent literature due to its versatile biological profile, including antiviral, antimicrobial, antitumor, anti-inflammatory, antiparasitic, and hypnotic activities.[9] In addition, numerous commercially available drugs such as alpidem, zolpidem, olprinone, mino-

Received: September 16, 2016
Published: November 18, 2016

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

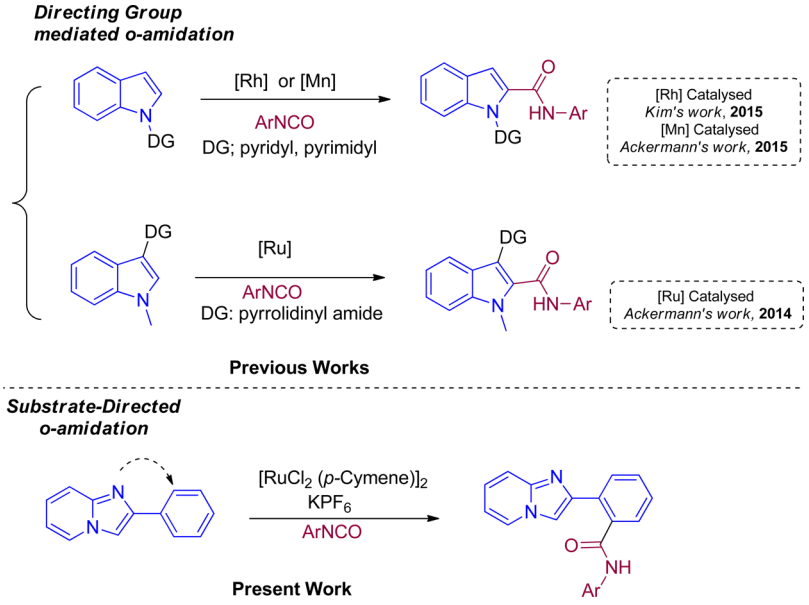


Figure 1. Examples of chelation-assisted ortho amidation of heterocycles (previous and present work).

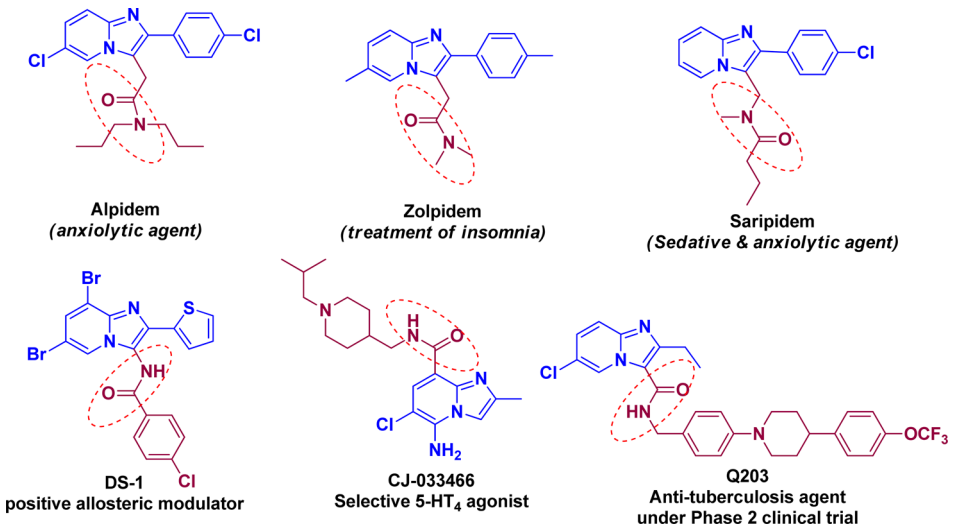


Figure 2. Some examples of biologically active amido-functionalized imidazo[1,2-*a*]pyridines.

dronic acid, zolimidine, nicopidem, and optically active GSK812397 candidates are IP-functionalized derivatives. In particular, the amido-functionalized imidazo[1,2-*a*]pyridine scaffold constitutes the core skeleton of numerous marketed drugs such as alpidem, zolpidem, saripidem, and others (DS-1, CJ-033466, Q203) that are under clinical trials (Figure 2).[9,10] This spurred our interest toward the synthesis of new amido-functionalized IPs as potential drug pharmacophores.

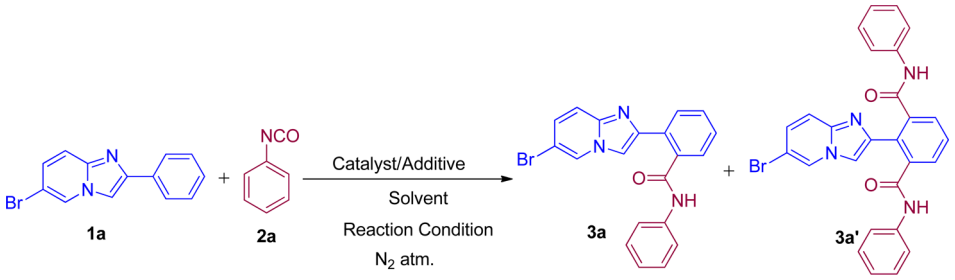
To the best of our knowledge, there is no report for the direct ortho amidation of 2-arylimidazo[1,2-*a*]pyridines with isocyanate under any metal-catalyzed conditions. Within our program for synthesizing functionalized imidazo[1,2-*a*]pyridines[11] and hypothesizing it to be a self-directing motif, we developed a convergent regioselective Ru(II)-catalyzed approach toward direct ortho amidation of 2-arylimidazo[1,2-*a*]pyridine with aryl isocyanates.

RESULTS AND DISCUSSION

Our initial investigation commenced with the identification of a suitable catalyst and appropriate reaction conditions that would allow selective ortho amidation on the phenyl ring of 6-bromo-2-phenylimidazo[1,2-*a*]pyridine (**1a**) using phenyl isocyanate (**2a**). To identify an efficient catalyst for developing the above strategy, we initially employed 5 mol % of $[RuCl_2(p\text{-cymene})]_2$ in a variety of solvents such as dichloromethane, toluene, xylene, 1,2-dichloroethane, etc. under reflux conditions (entry 1). However, the reaction failed to furnish the expected product (**3a**) under any of these conditions, in the absence or presence of a variety of additives such as NaOAc, KOAc, and CsOAc (Table 1, entries 1−4). Delightfully, the use of $AgSbF_6$ (30 mol %) with $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) gave 56% of the expected mono-ortho-amidated product (**3a**) along with 25% of bis-ortho-amidated product (**3a′**) using DCE at 100 °C in 18 h (Table 1, entry 5). Replacing $AgSbF_6$ with $Cu(OAc)_2$ also resulted in similar yields of **3a** and **3a′** (Table 1, entry 6). Interestingly, the use of comparatively cheaper and stable KPF_6 (30 mol %)

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

Table 1. Selected Optimization[a] of Reaction Conditions for Synthesis of 3a



entry	catalyst	additive	solvent	yield (%) 3a	yield (%) 3a′
1	$[RuCl_2(p\text{-cymene})]_2$		DCE/DCM/xylene/toluene, reflux, 24 h	NR	
2	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	DCE/xylene, 100 °C, 24 h	NR	
3	$[RuCl_2(p\text{-cymene})]_2$	KOAc	DCE/xylene, 100 °C, 24 h	NR	
4[a]	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	DCE/xylene, 100 °C, 24 h	NR	
5	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	DCE, 100 °C, 18 h	56	25
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$	DCE, 100 °C, 18 h	55	22
7	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE, 100 °C, 18 h	62	20
8	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE, 100 °C, 14 h	72	trace
9[b]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE, 100 °C, 14 h	73	trace
10[c]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE, 100 °C, 14 h	70	trace
11[d]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCE, 100 °C, 14 h	62	trace
12[e]	**$[RuCl_2(p\text{-cymene})]_2$**	**KPF_6**	**DCE, 100 °C, 14 h**	**75**	**trace**
13[e]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	toluene, 100 °C, 14 h	54	trace
14[e]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	benzene, 80 °C, 14 h	46	trace
15[e]	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	DCM, 40 °C, 14 h	48	15
16[e]	$RuCl_2(PPh_3)_3$	KPF_6	DCE, 100 °C, 14 h	NR	
17[e]	$RuCl_3{\cdot}xH_2O$	KPF_6	DCE, 100 °C, 14 h	NR	
18[e]	$Rh(OAc)_2$	KPF_6	DCE, 100 °C, 14 h	NR	
19[e]	$Pd(OAc)_2$	KPF_6	DCE, 100 °C, 14 h	NR	

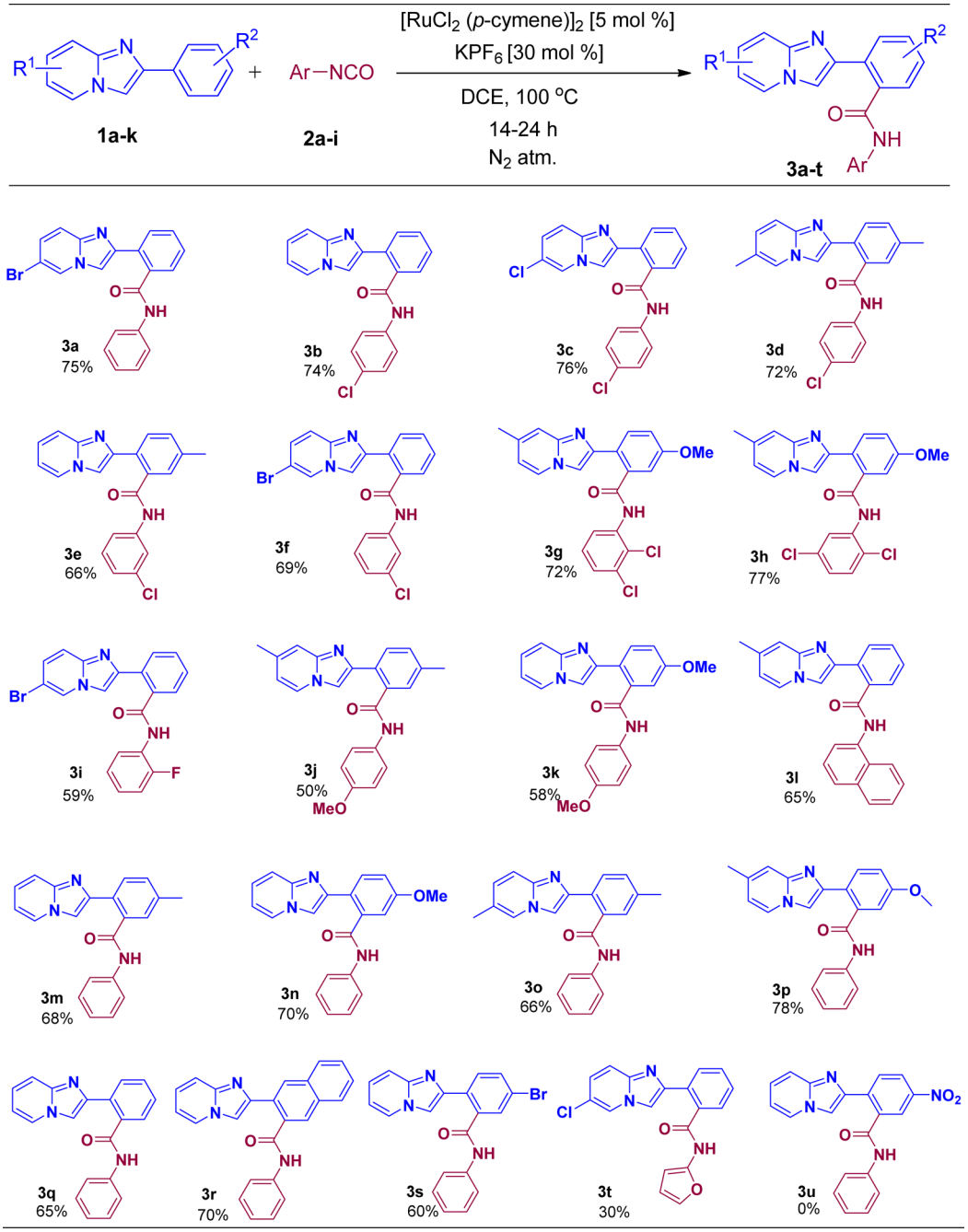
[a]Reaction conditions unless specified otherwise: **1a** (0.25 mmol), **2a** (0.25 mmol), catalyst (5 mol %), additive (30 mol %), solvent (4 mL). The reactions were performed as per the conditions mentioned. [b]10 mol % of $[RuCl_2(p\text{-cymene})]_2$. [c]50 mol % of KPF_6. [d]20 mol % of KPF_6. [e]**2a** (0.37 mmol). NR = no reaction

resulted in the formation of **3a** and **3a′** in 62% and 20% yields, respectively, after 18 h (Table 1, entry 7). Gratifyingly, conducting the above reaction for a shorter time period (14 h) yielded 72% of **3a** as a major product (Table 1, entry 8). An increment in the catalyst loading from 5 to 10 mol % or additive loading to 50 mol % did not show any noticeable amelioration in the yield of **3a** (Table 1, entries 9 and 10). On the other hand, reduction in the yield of **3a** was observed when 20 mol % of KPF_6 was used with 5 mol % of the ruthenium catalyst (Table 1, entry 11). Further, an enhancement in the yield of **3a** up to 75% was observed by using 1.5 equiv of phenyl isocyanate, possibly due to the unstable behavior of isocyanate (Table 1, entry 12). However, a change of solvent to toluene, benzene, and dichloromethane was less effective for the catalytic reaction, giving **3a** in 54, 46, and 48% yields, respectively (Table 1, entries 13−15). The use of other ruthenium catalysts such as $RuCl_2(PPh_3)_3$ and $RuCl_3{\cdot}xH_2O$ and other available transition-metal catalysts including $Rh(OAc)_2$ and $Pd(OAc)_2$ were found to be completely inactive for the above transformation (Table 1, entries 16−19).

With the optimized conditions in hand, the scope of the developed transformation was applied to a variety of aryl isocyanates and a wide range of 2-arylimidazo[1,2-*a*]pyridines (Scheme 1). Among the isocyanates used, chloro-substituted phenyl isocyanates (**2b−e**) showed fairly good reactivity with the substituted and unsubstituted imidazo[1,2-*a*]pyridines. For example, 4-chlorophenyl isocyanate (**2b**) resulted in the formation of the corresponding imidazo[1,2-*a*]pyridin-2-yl benzamides **3b−d** in 74%, 76%, and 72% isolated yields, respectively. However, 3-chlorophenyl isocyanate (**2c**) showed slightly lower reactivity, affording **3e,f** in 66% and 69% isolated yields with **1e,a**, respectively. The use of 2,5-dichlorophenyl isocyanate (**2d**) gave a comparatively better yield of the desired ortho-amidated product **3h** (77%) in comparison to 2,3-dichlorophenyl isocyanate (**2e**). A reduction in the yield of amidated product **3i** (59%) was noticed when 2-fluorophenyl isocyanate (**2f**) was allowed to react with **1a** in comparison to phenyl isocyanate (**2a**). 4-Methoxyphenyl isocyanate (**2g**) showed comparative reluctance to react with **1g,h** under the optimized reaction conditions, giving **3j,k** in 50% and 58% yields, respectively. 1-Naphthyl isocyanate (**2h**) also reacted well with **1i** to give the corresponding product **3l** in 65% isolated yield. The presence of electron-donating groups such as methyl and methoxy on the aryl ring of 2-arylimidazo[1,2-*a*]pyridines resulted in ortho amidation, affording **3m−p** in fairly good yields. 2-Naphthylimidazo[1,2-*a*]pyridine (**1j**) also showed similar affinity toward the formation of the desired product **3r** in 70% isolated yield. Imidazo[1,2-*a*]pyridine (**1k**) having bromo substitution on the aryl ring showcased retardation in its reactivity, resulting in 60% of **3s**. However, **3t** was isolated in poor yield when 2-furyl isocyanate (synthesized in situ) was used under similar conditions. Unfortunately, nitro-substituted

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

Scheme 1. Substrate Scope of Imidazo[1,2-*a*]pyridines and Isocyanates



imidazo[1,2-*a*]pyridine (**1l**) failed to yield the desired amidated product (**3u**) under our optimized conditions.

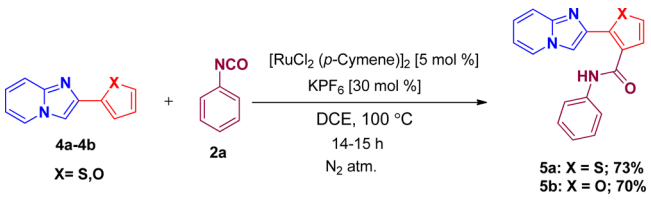
All of the synthesized compounds were isolated by column chromatography and characterized by detailed spectroscopic analysis. The ^{1}H NMR spectrum of **3a** showed three characteristic singlets, for one proton each at δ 10.28, 8.39, and 7.92 for the amidic (*N*–*H*), C-5 *H*, and C-3 *H*, respectively, with other expected signals evidencing the presence of an amidic group at the 2-phenyl ring suggesting the correct structure of the desired compound **3a**. As a representative example, single crystals of **3d** were grown in ethyl acetate/hexanes for X-ray diffraction studies.[12] **3d** crystallizes in the monoclinic $P2_1/c$ space group. An ORTEP diagram of **3d** (CCDC No. 1501223) is shown in (Figure 2S in the Supporting Information).

The scope of the reaction was further explored toward the selective ortho amidation of 2-thiophenylimidazo[1,2-*a*]pyridine (**4a**) and 2-furylimidazo[1,2-*a*]pyridine (**4b**) to afford the corresponding ortho-amidated products **5a**,**b** in 73% and 70% yields, respectively (Scheme 2).

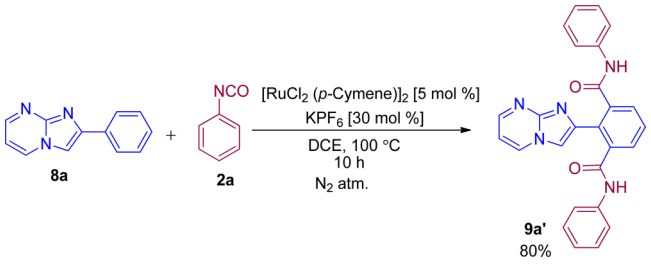
To extend the scope of our methodology, a few other imidazo heterocycles such as imidazo[2,1-*b*]thiazole (**6a**) and benzo[*d*]-imidazo[2,1-*b*]thiazole (**6b**) were reacted with phenyl isocyanate (**2a**) under optimized experimental conditions to give their corresponding amidated products **7a**,**b** in 67% and 70% yields, respectively (Scheme 3). In addition, it was observed that imidazo[2,1-*b*]thiazole (**6a**) showed excellent reactivity, and heating for 14 h resulted in the isolation of bis-ortho-amidated product **7a′** in 18% yield along with **7a**.

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340–12349

Scheme 2. Ortho Amidation of 2-Heteroaryl Imidazo[1,2-*a*]pyridines with Isocyanate



Scheme 4. Ortho Amidation of 2-Phenylimidazo[1,2-*a*]pyrimidine with Isocyanate



It is noteworthy that attempts to carry out ortho amidation of 2-arylimidazo[1,2-*a*]pyrimidine (**8a**) with phenyl isocyanate under similar experimental conditions resulted in predominant formation of bis-ortho-amidated product **9a′** in 80% yield even in 10 h. This could possibly be due to the presence of an extra nitrogen in the chelating vicinity that enhances its reactivity and restrains the reaction to stop after mono ortho amidation (Scheme 4).

To assess the scalability of this Ru(II)-catalyzed C−H bond amidation process, a gram-scale reaction was performed between **1f** and **2a** under optimized conditions to yield the desired ortho-amidated product **3p** in 70% (1.05 g) yield, which was similar to that obtained on a smaller scale (Scheme 5).

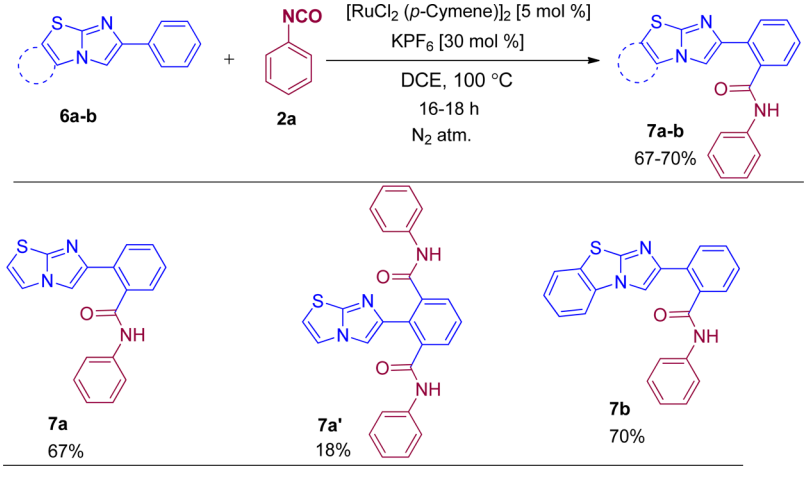
To gain some insights into the mechanism, a few control experiments were performed. A stoichiometric reaction between 6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**1d**) with phenyl isocyanate (**2a**) under catalyst-free conditions failed to yield either C-3-amidated or ortho-amidated product, thereby suggesting the vital role of catalyst and additive (Scheme 6i). The inability of imidazo[1,2-*a*]pyridine (**1m**) to give any amidated product with **2a** under the optimized conditions further affirmed the nonreactivity of the C-3 center under ruthenium-catalyzed conditions (Scheme 6ii). Reaction of **1d** with $[RuCl_2(p\text{-cymene})]_2$ in the presence of KPF_6 (3 equiv) in 1,2-dichloroethane resulted in the formation of the cyclometalated complex $\mathbf{C_3}$ (Scheme 6iii). The formation of $\mathbf{C_3}$ was confirmed by ESI-MS analysis (Figure 1S in the Supporting Information); however, it was only partially purified by repeated diethyl ether washes. Attempts to purify $\mathbf{C_3}$ by undertaking column chromatography (using silica gel or neutral alumina as adsorbents) were unsuccessful, probably due to the instability of the complex. The proposed structure of $\mathbf{C_3}$ is in accordance with the literature reports.[8a] Employing catalytic amounts of the complex $\mathbf{C_3}$ for a coupling reaction between **1d** and **2a** in the presence of KPF_6 under optimized conditions gave the desired product **3o** in comparable yields (Scheme 6iv). Finally attempting a stoichiometric reaction between $\mathbf{C_3}$ and **1d** also resulted in the formation of **3o** in 40% yield (Scheme 6v), thereby suggesting $\mathbf{C_3}$ to be an intermediate and a reservoir of active species $\mathbf{C_2}$ in the catalytic process.

From the control experiments and literature reports[8a,13] it is proposed that the plausible catalytic process is initiated by the dissociation of the $[RuCl_2(p\text{-cymene})]_2$ dimer ($\mathbf{C_1}$) into cationic ruthenium monomeric species $\mathbf{C_2}$ (active catalyst), most likely by substitution of the Cl^- ligand by PF_6. Thereafter, reversible C−H ruthenation at the ortho position of the phenyl ring on 2-phenylimidazo[1,2-*a*]pyridine leads to formation of the cationic intermediate complex $\mathbf{C_3}$. Coordination of isocyanate **2a** to $\mathbf{C_3}$ followed by migratory insertion provides $\mathbf{C_5}$ via $\mathbf{C_4}$, which on protodemetalation affords ortho-amidated product, along with the regeneration of the cationic ruthenium species $\mathbf{C_2}$ that continues the catalytic process (Scheme 7).

CONCLUSIONS

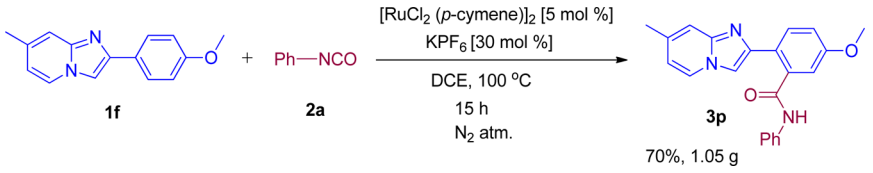
In summary, we have described a convergent and straightforward method for the regioselective synthesis of ortho-amidated imidazo heterocycles via $C(sp^2)$−H bond functionalization with aryl isocyanates employing $[RuCl_2(p\text{-cymene})]_2$ and KPF_6 in catalytic amounts. An array of ortho-amidated phenylimidazo[1,2-*a*]pyridine derivatives with broad functionalities were synthesized in moderate to good yields. The developed protocol was also applicable to the selective ortho amidation of other imidazo-fused heterocycles such as imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]thiazole, and imidazo-

Scheme 3. Ortho Amidation of 2-Phenylimidazolyl Thiazoles with Isocyanate

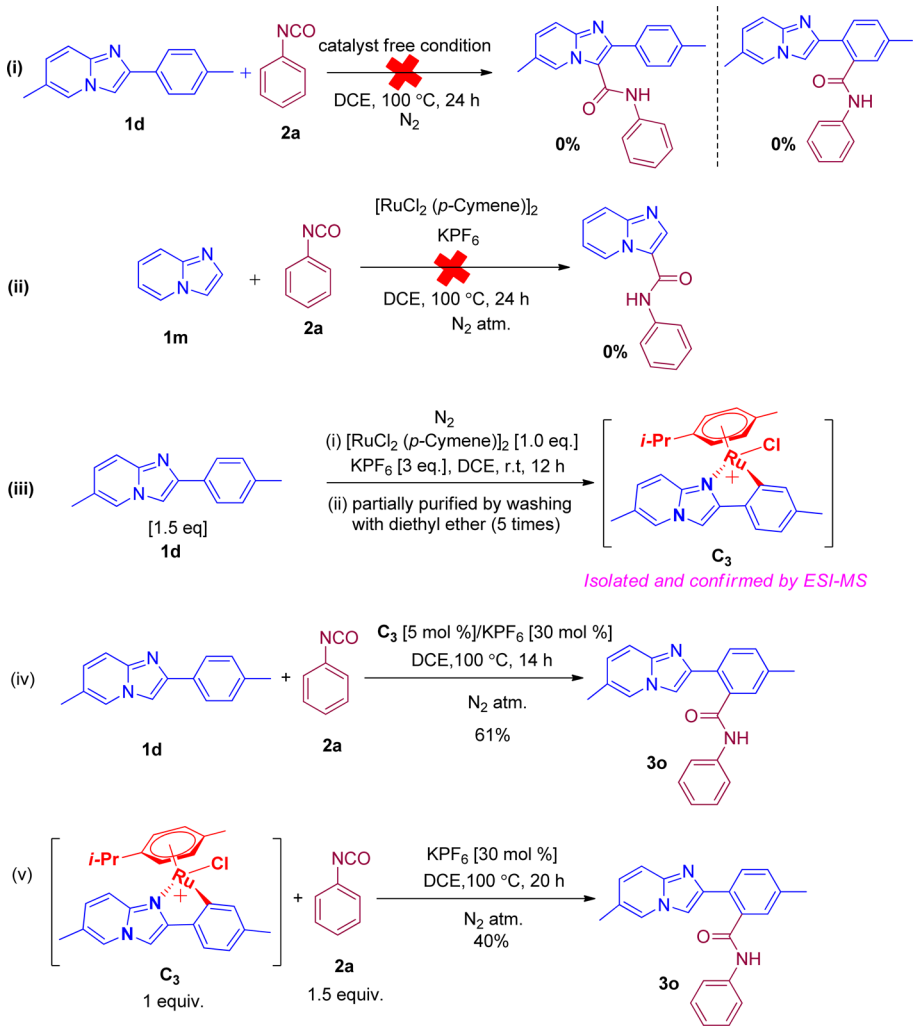


DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

Scheme 5. Gram-Scale Synthesis of 3p



Scheme 6. Control Experiments



[1,2-*a*]pyrimidine. This is the first report of direct ortho amidation on the imidazo[1,2-*a*]pyridine scaffold using aryl isocyanates.

EXPERIMENTAL SECTION

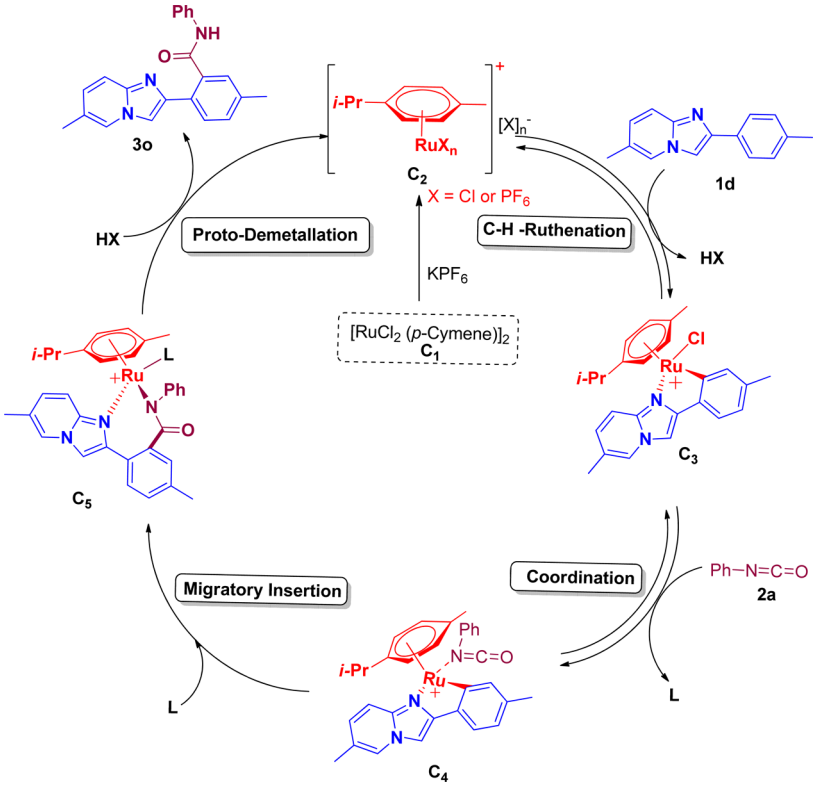
General Considerations. Commercially available reagents were used without purification. Commercially available solvents were dried by standard procedures prior to use. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer, and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, and m = multiplet. Coupling constants J are reported in Hz. The ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.0 ppm) or [d_6]DMSO (39.5 ppm). Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. High-resolution mass spectra were recorded with a TOF analyzer spectrometer by using electrospray mode.

General Procedure for Ortho Amidation of Imidazo Heterocycles. A mixture of imidazo heterocycles (**1a**−**k**, **4a**−**b**, **6a**,**b**, and **8a**; 0.37 mmol), aryl isocyanates (**2a**−**h**; 0.56 mmol), [$RuCl_2$(*p*-cymene)]$_2$, (0.02 mmol), and KPF_6 (0.11 mmol) in dichloroethane (10 mL) were heated at 100 °C under a nitrogen atmosphere for 14−20 h. On completion of the reaction as indicated by TLC, the reaction mixture was filtered, evaporated, and directly subjected to silica gel column chromatography (SiO_2 (100−200 mesh), hexane/EtOAc 8/2) to yield the ortho-amidated products (**3a**−**s**, **5a**,**b**, **7a**,**b**). In a few cases, the bis-ortho-amidated products (**3a′**, **7a′**, **9a′**) were also isolated.

*2-(6-Bromoimidazo[1,2-a]pyridin-2-yl)-N-phenylbenzamide (**3a**):* white solid; yield 109 mg (75%); mp 198−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.39 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.92 (s, 1H), 7.67−7.63 (m, 2H), 7.52−7.44 (m, 2H), 7.41−7.35 (m, 2H), 7.23 (t, J = 7.9 Hz, 2H), 7.15 (dd, J = 9.5, 1.8 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 148.6, 147.9, 144.3, 141.7, 135.9, 134.4, 134.2, 133.5, 132.9, 132.7, 132.6, 131.9, 128.6, 125.1, 122.6, 116.3,

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

Scheme 7. Plausible Catalytic Pathway for Ortho Amidation of 2-Phenylimidazo[1,2-*a*]pyridine with Isocyanate



111.2; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{20}H_{15}BrN_3O^+$ 392.0398, found 392.0405 $[M + H]^+$.

N-(4-Chlorophenyl)-2-(imidazo[1,2-a]pyridin-2-yl)benzamide (***3b***)*:* white solid; yield 95 mg (74%); mp 225−227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.56 (dd, J = 6.8, 1.0 Hz, 1H), 8.09 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.9 Hz, 2H), 7.61−7.56 (m, 1H), 7.54−7.50 (m, 2H), 7.48−7.45 (m, 1H), 7.39 (d, J = 8.9 Hz, 2H), 7.25−7.19 (m,1H), 6.88−6.84 (m,1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 144.7, 143.0, 138.7, 136.7, 131.7, 129.8, 129.4, 128.9, 128.0, 127.8, 127.4, 125.3, 121.8, 120.2, 117.0, 112.6, 111.0; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{20}H_{15}ClN_3O^+$ 348.0903, found 348.0910 $[M + H]^+$.

2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-N-(4-chlorophenyl)-benzamide (***3c***)*:* white solid; yield 107 mg (76%); mp 165−166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.90 (dd, J = 2.0, 0.8 Hz, 1H), 8.11 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.74−7.69 (m, 2H), 7.61−7.55 (m, 2H), 7.53−7.47 (m, 2H), 7.41−7.37 (m, 2H), 7.28 (dd, J = 9.6, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 144.1, 143.1, 136.7, 131.2, 130.1, 129.4, 129.0, 128.3, 128.2, 127.6, 126.4, 125.4, 121.9, 120.3, 119.5, 117.9, 111.7; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{20}H_{14}Cl_2N_3O^+$ 382.0513, found 382.0521 $[M + H]^+$.

N-(4-Chlorophenyl)-5-methyl-2-(6-methylimidazo[1,2-a]pyridin-2-yl)benzamide (***3d***)*:* white solid; yield 100 mg (72%); mp 230−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.88 (s, 1H), 7.67 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H), 7.50 (t, J = 8.3 Hz, 2H), 7.28−7.26 (m, 2H), 7.25−7.22 (m, 1H), 7.10 (dd, J = 9.2, 1.4 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.2, 143.4, 138.3, 137.6, 135.4, 131.0, 130.6, 130.4, 128.9, 128.8, 128.7,128.1, 123.5, 122.7, 121.0, 116.1, 110.9, 21.1, 18.1; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{22}H_{19}ClN_3O^+$ 376.1216, found 376.1235 $[M + H]^+$.

N-(3-Chlorophenyl)-2-(imidazo[1,2-a]pyridin-2-yl)-5-methylbenzamide (***3e***)*:* white solid; yield 88 mg (66%); mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.56 (d, J = 6.7 Hz, 1H), 8.07 (s, 1H), 7.98−7.90 (m, 2H), 7.58−7.46 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 2H), 7.24−7.18 (m, 1H), 7.14 (d, J = 7.86 Hz, 1H), 6.84 (t, J = 6.6 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 144.6, 143.1, 141.3, 137.5, 136.4, 133.4, 130.8, 130.7, 129.4, 128.9, 128.5, 127.5, 125.4, 123.6, 119.7, 118.6, 116.9, 112.6, 110.7, 21.0 ; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{21}H_{17}ClN_3O^+$ 362.1060, found 362.1079 $[M + H]^+$.

2-(6-Bromoimidazo[1,2-a]pyridin-2-yl)-N-(3-chlorophenyl)-benzamide (***3f***)*:* white solid; yield 108 mg (69%); mp 217−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.98 (d, J = 1.0 Hz, 1H), 8.12 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.93 (s, 1H), 7.65−7.56 (m, 1H), 7.56−7.45 (m, 4H), 7.35 (dd, J = 9.3, 7.1 Hz, 2H), 7.15 (dd, J = 7.9, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 143.8, 143.2, 141.1, 136.6, 133.5, 131.2 130.8, 130.1, 129.4, 128.4, 128.3, 128.2, 127.6, 123.7, 119.8, 118.7, 118.1, 111.5, 106.4; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{20}H_{14}BrClN_3O^+$ 426.0008, found 426.0023 $[M + H]^+$.

N-(2,3-Dichlorophenyl)-5-methoxy-2-(7-methylimidazo[1,2-a]-pyridin-2-yl)benzamide (***3g***)*:* white solid; yield 113 mg (72%); mp 238−240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, J = 7.1 Hz, 1H), 8.50 (dd, J = 8.2, 1.5 Hz, 1H), 8.28 (s, 1H), 7.72−7.61 (m, 2H), 7.50 (s, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.90 (dd, J = 7.2, 1.6 Hz, 1H), 3.90 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) 160.7, 159.5, 149.1, 146.7, 139.4, 137.0, 132.3, 131.4, 128.6, 127.1, 126.1, 126.1, 121.9, 116.9, 115.7, 114.8, 113.9, 55.8, 21.3; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{22}H_{18}Cl_2N_3O_2^+$: 426.0776 , found 426.0793 $[M + H]^+$.

N-(2,5-Dichlorophenyl)-5-methoxy-2-(7-methylimidazo[1,2-a]-pyridin-2-yl)benzamide (***3h***)*:* white solid; yield 121 mg (77%); mp 217−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, J = 7.1 Hz, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.18 (s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.50 (s, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.97 (dd, J = 8.5, 2.4 Hz, 1H), 6.94−6.86 (m, 1H), 3.89 (s, 3H), 2.51 (s, 3H). ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.1, 150.2, 147.4, 139.6, 135.8, 133.3, 131.4, 129.6, 127.6, 125.6, 123.9, 120.8, 120.2, 116.7, 115.9, 114.9, 113.7, 55.5, 21.5; HRMS (ESI-TOF) (*m*/*z*) calculated $C_{22}H_{18}Cl_2N_3O_2^+$ 426.0776, found 426.0798 $[M + H]^+$.

2-(6-Bromoimidazo[1,2-a]pyridin-2-yl)-N-(2-fluorophenyl)-benzamide (***3i***)*:* white solid; yield 89 mg (59%); mp 225−227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 9.00 (d, J = 1.1 Hz, 1H), 8.17 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.84 (dd, J = 9.0, 6.5 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.57−7.53 (m, 2H), 7.48 (t, J = 7.0 Hz, 1H), 7.37 (dd, J = 9.5, 1.9 Hz, 1H), 7.24 (dd, J = 8.0, 5.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 156.6, 154.2, 143.9, 143.1, 136.5, 131.3,

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

130.0, 129.4, 128.4, 128.2, 127.5, 126.8, 126.7, 126.3, 124.7, 118.1, 116.2, 111.7, 106.4; HRMS (ESI-TOF) (m/z) calculated $C_{20}H_{14}BrFN_3O^+$ 410.0304, found 410.0327 $[M + H]^+$.

*N-(4-Methoxyphenyl)-5-methyl-2-(7-methylimidazo[1,2-a]pyridin-2-yl)benzamide (**3j**):* white solid; yield 68 mg (50%); mp 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.96 (d, J = 6.9 Hz, 1H), 7.65 (s, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 9.0 Hz, 2H), 7.36 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 6.9 Hz, 1H), 3.81 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.1, 144.9, 144.0, 138.2, 136.5, 135.8, 132.1, 130.8, 130.4, 130.0, 128.1, 125.0, 121.5, 115.4, 115.3, 114.1, 110.5, 55.5, 21.5, 21.1;HRMS (ESI-TOF) (m/z) calculated $C_{23}H_{22}N_3O_2^+$ 372.1712, found 372.1730 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-5-methoxy-N-(4-methoxyphenyl)-benzamide (**3k**):* white solid; yield 80 mg (58%); mp 198−201 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.34 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 10.4 Hz, 2H), 7.53 (d, J = 9.2 Hz, 1H), 7.51−7.45 (m, 2H), 7.30 (dd, J = 6.8, 2.2 Hz, 1H), 7.20−7.11 (m, 2H), 6.89 (dd, J = 7.1, 2.0 Hz, 2H), 6.86 (dd, J = 4.7, 2.2 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz MeOH-d_4) δ 169.3, 159.5, 156.8, 144.9, 142.6, 137.5, 131.3, 130.8, 126.4, 125.6, 121.9, 121.4, 115.6, 115.2, 113.7, 113.6, 112.7, 110.2, 54.7, 54.4; HRMS (ESI-TOF) (m/z) calculated $C_{22}H_{20}N_3O_3^+$ 374.1504, found 374.1523 $[M + H]^+$.

*2-(7-Methylimidazo[1,2-a]pyridin-2-yl)-N-(naphthalen-1-yl)-benzamide (**3l**):* white solid; yield 90 mg (65%); mp 199−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.43 (d, J = 6.7 Hz, 1H), 8.09 (s, 1H), 8.01−7.75 (m, 5H), 7.68 (d, J = 7.1 Hz, 1H), 7.62−7.47 (m, 4H), 7.36 (s, 1H), 7.30 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 6.6 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 145.2, 143.3, 137.3, 135.9, 134.1, 132.1, 129.8, 129.6, 129.2, 128.3, 127.9, 127.1, 126.8, 126.8, 126.0, 126.0, 123.7, 123.5, 115.2, 110.7, 21.3; HRMS (ESI-TOF) (m/z) calculated $C_{25}H_{20}N_3O^+$ 378.1606, found 378.1614 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-5-methyl-N-phenylbenzamide (**3m**):* white solid; yield 82 mg (68%); mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.10 (d, J = 6.8 Hz, 1H), 7.75 (s, 1H), 7.71 (s, 1H), 7.68−7.61 (m, 4H), 7.33 (d, J = 7.7 Hz, 3H), 7.26−7.21 (m, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 6.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 144.6, 138.7, 138.4, 135.8, 131.0, 130.5, 130.0, 129.0, 128.1, 125.9, 125.4, 124.2, 123.2, 120.0, 119.9, 117.0, 112.8, 21.1; HRMS (ESI-TOF) (m/z) calculated $C_{21}H_{18}N_3O^+$ 328.1449, found 328.1455 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-5-methoxy-N-phenylbenzamide (**3n**):* white solid; yield 89 mg (70%); mp 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 7.71 (s, 1H), 7.63 (d, J = 7.3 Hz, 3H), 7.46 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 7.22−7.16 (m, 1H), 7.11−7.03 (m, 2H), 6.85 (t, J = 6.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 159.6, 144.4, 138.7, 137.1, 132.3, 128.9, 128.8, 125.9, 125.6, 124.1, 119.8, 119.6, 116.9, 116.8, 114.2, 112.9, 111.0, 55.5; HRMS (ESI-TOF) (m/z) calculated $C_{21}H_{18}N_3O_2^+$ 344.1399, found 344.1406 $[M + H]^+$.

*5-Methyl-2-(6-methylimidazo[1,2-a]pyridin-2-yl)-N-phenylbenzamide (**3o**):* white solid; yield 75 mg (66%); mp 174−176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.96 (s, 1H), 7.88 (dd, J = 7.9, 2.1 Hz, 1H), 7.79 (dd, J = 8.4, 2.4 Hz, 1H), 7.65 (d, J = 7.1 Hz, 2H), 7.36 (d, J = 9.1 Hz, 1H), 7.30 (s, 1H), 7.28−7.17 (m, 3H), 7.04−6.93 (m, 2H), 2.36 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 143.7, 142.9, 139.4, 137.2, 136.4, 130.3, 129.4, 128.8, 128.6, 128.5, 128.2, 124.0, 123.8, 121.9, 120.1, 116.2, 110.3, 21.1, 18.0; HRMS (ESI-TOF) (m/z) calculated $C_{22}H_{20}N_3O^+$ 342.1606, found 342.1612 $[M + H]^+$.

*5-Methoxy-2-(7-methylimidazo[1,2-a]pyridin-2-yl)-N-phenylbenzamide (**3p**):* white solid; yield 102 mg (78%); mp 189−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.40 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.89 (s, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.28 (s, 1H), 7.13 (dd, J = 8.7, 2.6 Hz, 1H), 7.10−7.01 (m, 2H), 6.66 (d, J = 6.9 Hz, 1H), 3.84 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.6, 149.6, 147.5, 144.5, 142.6, 140.4, 135.6, 133.9, 131.3, 129.0, 128.8, 125.1, 120.4, 119.9, 119.7, 117.9, 114.4, 60.7, 26.0; HRMS (ESI-TOF) (m/z) calculated $C_{22}H_{20}N_3O_2^+$ 358.1555, found 358.1560 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-N-phenylbenzamide (**3q**):* white solid; yield 75 mg (65%); mp 184−186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.58 (d, J = 6.1 Hz, 1H), 8.11 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.53 (m, 4H), 7.33 (t, J = 7.1 Hz, 2H), 7.28−7.23 (m, 1H), 7.08 (t, J = 6.8 Hz, 1H), 6.87 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 144.5, 142.9, 139.7, 137.0, 131.4, 129.9, 129.4, 129.1, 128.1, 128.0, 127.9, 125.8, 124.0, 120.3, 117.0, 112.8, 111.1; HRMS (ESI-TOF) (m/z) calculated $C_{20}H_{16}N_3O^+$ 314.1293, found 314.1303 $[M + H]^+$.

*3-(Imidazo[1,2-a]pyridin-2-yl)-N-phenyl-2-naphthamide (**3r**):* white solid; yield 94 mg (70%); mp 190−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.12 (d, J = 7.4 Hz, 2H), 8.04 (s, 1H), 7.84 (s, 1H), 7.81−7.74 (m, 1H), 7.67 (d, J = 7.6 Hz, 3H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (dd, J = 5.9, 2.8 Hz, 2H), 7.38−7.29 (m, 3H), 7.12 (t, J = 7.3 Hz, 1H), 6.87 (t, J = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 206.9, 139.0, 135.7, 133.3, 131.8, 128.76, 128.7, 128.7, 128.2, 127.9, 127.4, 126.9, 126.1, 125.6, 124.2, 123.9, 119.9, 117.6, 116.6, 112.7, 111.2, 111.2; HRMS (ESI-TOF) (m/z) calculated $C_{24}H_{18}N_3O^+$ 364.1449, found 364.1454 $[M + H]^+$.

*5-Bromo-2-(imidazo[1,2-a]pyridin-2-yl)-N-phenylbenzamide (**3s**):* white solid; yield 87 mg (60%); mp 200−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.08 (d, J = 6.8 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.78 (s, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 8.4 Hz, 2H), 7.47 (dd, J = 8.3, 2.1 Hz, 1H), 7.36 (t, J = 7.9 Hz, 2H), 7.28−7.23 (m, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 144.6, 142.9, 138.6, 137.4, 132.9, 132.1, 131.6, 129.1, 125.9, 125.9, 124.4, 122.2, 119.9, 117.0, 113.2, 111.3; HRMS (ESI-TOF) (m/z) calculated $C_{20}H_{15}BrN_3O^+$ 392.0398, found 392.0403 $[M + H]^+$.

Procedure for the Ortho Amidation of 1c with Furyl Isocyanate (2i). Furyl isocyanate was synthesized in situ by heating furan-2-carbonyl azide[14] (0.150 g) in 1,2-dichloroethane at 100 °C for about 45 min under a nitrogen atmosphere via a Curtius rearrangement. Furyl isocyanate (assuming 100% conversion) was directly used for the ortho amidation of **1c** (0.100 g, 0.43 mmol) following the procedure described earlier to yield **3t**.

*2-(6-Chloroimidazo[1,2-a]pyridin-2-yl)-N-(furan-2-yl)benzamide (**3t**):* yellow solid; yield 66 mg (30%); mp 200−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 7.60 (d, J = 9.5 Hz, 1H), 7.47−7.40 (m, 3H), 7.36 (dd, J = 7.3, 5.3 Hz, 2H), 7.27−7.24 (m, 1H), 7.23−7.19 (m, 1H), 6.69 (dd, J = 3.4, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 146.5, 145.5, 129.8, 128.8, 128.5, 127.3, 125.2, 121.3, 120.3, 120.3, 117.8, 117.2, 112.9; HRMS (ESI-TOF) (m/z) calculated $C_{18}H_{13}ClN_3O_2^+$ 338.0696, found 338.0675 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-N-phenylthiophene-3-carboxamide (**5a**):* white solid; yield 86 mg (73%); mp 221−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.65−8.60 (m, 1H), 8.43 (s, 1H), 7.80 (d, J = 7.7 Hz, 2H), 7.68 (dd, J = 9.1, 0.7 Hz, 1H), 7.63 (d, J = 5.3 Hz, 1H), 7.51 (d, J = 5.3 Hz, 1H), 7.42−7.30 (m, 3H), 7.14−7.08 (m, 1H), 6.96 (td, J = 6.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 144.3, 139.7, 138.3, 137.9, 133.6, 130.6, 129.3, 127.7, 126.7, 125.7, 124.1, 120.3, 116.7, 113.4, 111.9; HRMS (ESI-TOF) (m/z) calculated $C_{18}H_{14}N_3OS^+$ 320.0857, found 320.0885 $[M + H]^+$.

*2-(Imidazo[1,2-a]pyridin-2-yl)-N-phenylfuran-3-carboxamide (**5b**):* white solid; yield 75 mg (67%); mp 180−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.77 (s, 1H), 8.69 (m, 1H), 8.53 (d, J = 0.5 Hz, 1H), 7.94−7.86 (m, 4H), 7.50 (m, 1H), 7.46−7.40 (m, 2H), 7.16−7.09 (m, 2H), 7.05 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 151.4, 148.9, 147.8, 147.7, 144.9, 140.3, 134.3, 132.6, 128.5, 124.9, 124.4, 121.5, 119.1, 118.9, 117.2; HRMS (ESI-TOF) (m/z) calculated $C_{18}H_{14}N_3O_2^+$ 304.1086, found 304.1092 $[M + H]^+$.

*2-(Imidazo[2,1-b]thiazol-6-yl)-N-phenylbenzamide (**7a**):* yellow solid; yield 80 mg (67%); mp 195−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.96 (t, J = 6.7 Hz, 2H), 7.92 (s, 1H), 7.70 (d, J = 7.7 Hz, 2H), 7.56−7.50 (m, 1H), 7.46 (d, J = 6.5 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.9 Hz, 2H), 7.24 (d, J = 4.4 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 149.2, 144.7, 139.8, 136.2, 131.7, 129.8, 129.1, 128.7, 128.0, 127.4, 124.0, 120.6, 120.2, 113.6, 111.4; HRMS (ESI-TOF) (m/z) calculated $C_{18}H_{14}N_3OS^+$ 320.0857, found 320.0864 $[M + H]^+$.

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

*2-(Benzo[d]imidazo[2,1-b]thiazol-2-yl)-N-phenylbenzamide (**7b**):* white solid; yield 95 mg (70%); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.92 (s, 1H), 7.80−7.72 (m, 2H), 7.66 (dd, J = 7.3, 4.7 Hz, 3H), 7.55 (d, J = 7.9 Hz, 1H), 7.48−7.41 (m, 2H), 7.36 (m, 4H), 7.13 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 147.5, 145.4, 138.5, 135.6, 132.0, 131.0, 130.2, 130.1, 129.8, 129.0, 128.9, 128.9, 128.0, 126.4, 125.2, 124.3, 120.0, 113.0, 110.2; HRMS (ESI-TOF) (m/z) calculated $C_{22}H_{16}N_3OS^+$ 370.1014, found 370.1022 [M + H]$^+$.

*2-(6-Bromoimidazo[1,2-a]pyridin-2-yl)-N^1,N^3-diphenylisophthalamide (**3a′**):* white solid; yield[(Table 1, entry 5)]: 25%; mp 240−242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 2H), 8.97 (d, J = 1.1 Hz, 1H), 8.03 (s, 1H), 7.70−7.67 (m, 2H), 7.63−7.59 (m, 1H), 7.54 (d, J = 7.7 Hz, 4H), 7.39 (d, J = 9.6 Hz, 1H), 7.29−7.24 (m, 5H), 7.04 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 142.7, 142.6, 139.5, 139.3, 129.8, 129.0, 128.9, 128.3, 127.9, 127.3, 123.9, 120.3, 118.1, 112.8, 106.3; HRMS (ESI-TOF) (m/z) calculated $C_{27}H_{20}BrN_4O_2^+$ 511.0769, found 511.0778 [M + H]$^+$.

*2-(Imidazo[2,1-b]thiazol-6-yl)-N^1,N^3-diphenylisophthalamide (**7a′**):* yellow solid; yield 0.024 mg (18%); mp 224−225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 2H), 7.92 (d, J = 4.5 Hz, 1H), 7.83 (d, J = 3.8 Hz, 1H), 7.64−7.60 (m, 2H), 7.60−7.52 (m, 5H), 7.28 (t, J = 7.9 Hz, 4H), 7.16 (d, J = 4.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 148.5, 142.8, 139.6, 139.0, 130.0, 128.9, 128.7, 127.6, 123.8, 120.3, 120.2, 113.2, 112.6; HRMS (ESI-TOF) (m/z) calculated $C_{25}H_{19}N_4O_2S^+$ 439.1228, found 439.1236 [M + H]$^+$.

*2-(Imidazo[1,2-a]pyrimidin-2-yl)-N^1,N^3-diphenylisophthalamide (**9a′**):* yellow solid; yield 127 mg (80%); mp 273−275 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 2H), 9.04−8.98 (m, 1H), 8.42 (d, J = 1.9 Hz, 1H), 8.00 (s, 1H), 7.70 (d, J = 7.4 Hz, 2H), 7.66−7.61 (m, 1H), 7.57 (d, J = 7.9 Hz, 4H), 7.27 (t, J = 7.7 Hz, 4H), 7.04 (t, J = 7.3 Hz, 2H), 6.98 (dd, J = 6.5, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 150.5, 147.4, 143.0, 139.6, 139.4, 135.4, 130.0, 129.0, 128.9, 128.4, 124.0, 120.3, 110.7, 109.3; HRMS (ESI-TOF) (m/z) calculated $C_{26}H_{20}N_5O_2^+$ 434.1617, found 434.1625 [M + H]$^+$.

Procedure for Synthesis of Complex C$_3$. A mixture of 6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**1d**; 0.17 mmol, 0.040 g), $[RuCl_2(p\text{-cymene})]_2$, (0.11 mmol, 0.070 g), and KPF_6 (3 equiv) in dichloroethane (5 mL) under a nitrogen atmosphere was stirred for 12 h. After filtration through Celite, the solvent was concentrated under reduced pressure and the residue was washed with Et_2O (15 mL × 5) to afford partially purified complex **C$_3$**: ESI-MS (m/z) calculated $C_{25}H_{27}N_2Ru^+$ 457.1217, found 457.1382 [M − Cl]$^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02282.

NMR data, ESI-MS of C_3, single-crystal X-ray analysis data for **3d**, and an ORTEP diagram of **3d** (PDF)

Crystallographic data for **3d** (which is also deposited with the Cambridge Crystallographic Data Centre; CCDC No. 1501223) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*R.S.: fax, 91-1596-244183; tel, 91-5196-5155663; e-mail, sakhuja.rajeev@gmail.com.

ORCID

Anil Kumar: 0000-0003-4699-3178

Rajeev Sakhuja: 0000-0002-9284-9137

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the Department of Science & Technology (DST), New Delhi, India, for providing a research grant (SB/FT/CS-033/2012) for this work. We also thank BITS Pilani for providing a research grant (BITS additional research grant) for this work. S.M.A.S. and S.K. thank BITS Pilani and UGC, New Delhi, India, respectively, for providing Senior Research Fellowships. The use of the X-ray facility at IISER Mohali is gratefully acknowledged.

■ REFERENCES

(1) (a) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308. (b) Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 11481. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (d) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, *356*, 17. (e) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (f) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.

(2) (a) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, *2006*, 3382. (d) Li, S.-S.; Qin, L.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 4554. (e) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(3) (a) Liu, P. M.; Frost, C. G. *Org. Lett.* **2013**, *15*, 5862. (b) Park, Y.; Jeon, I.; Shin, S.; Min, J.; Lee, P. H. *J. Org. Chem.* **2013**, *78*, 10209. (c) Banerjee, A.; Santra, S. K.; Mohanta, P. R.; Patel, B. K. *Org. Lett.* **2015**, *17*, 5678. (d) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332. (e) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154. (f) Reddy, M. C.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 10738. (g) Ziriakus, J.; Pöthig, A.; Drees, M.; Haslinger, S.; Jantke, D.; Kühn, F. E. *Adv. Synth. Catal.* **2013**, *355*, 2845. (h) Reddy, M. C.; Jeganmohan, M. *Eur. J. Org. Chem.* **2013**, *2013*, 1150.

(4) (a) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843. (b) Wang, W.; Liang, L.; Xu, F.; Huang, W.; Niu, Y.; Sun, Q.; Xu, P. *Eur. J. Org. Chem.* **2014**, *2014*, 6863. (c) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (d) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107.

(5) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(6) (a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem.* **2011**, *123*, 6503. (c) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293. (d) Nan, J.; Zuo, Z.; Luo, L.; Bai, L.; Zheng, H.; Yuan, Y.; Liu, J.; Luan, X.; Wang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 17306. (e) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744. (f) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886. (g) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem.* **2010**, *122*, 6779. (h) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem.* **2006**, *118*, 2681.

(7) (a) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 4262. (b) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430.

(8) (a) De Sarkar, S.; Ackermann, L. *Chem. - Eur. J.* **2014**, *20*, 13932. (b) Shi, X. Y.; Liu, K. Y.; Fan, J.; Dong, X. F.; Wei, J. F.; Li, C. J. *Chem. - Eur. J.* **2015**, *21*, 1900. (c) Shi, X. Y.; Renzetti, A.; Kundu, S.; Li, C. J. *Adv. Synth. Catal.* **2014**, *356*, 723. (d) Geng, X.; Wang, C. *Org. Biomol. Chem.* **2015**, *13*, 7619. (e) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (f) Liu, W.; Bang, J.; Zhang, Y.; Ackermann, L. *Angew. Chem.* **2015**, *127*, 14343. (g) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400. (h) Han, S.; Mishra, N. K.;

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349

Sharma, S.; Park, J.; Choi, M.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 8026.
(9) (a) Bode, M. L.; Gravestock, D.; Moleele, S. S.; van der Westhuyzen, C. W.; Pelly, S. C.; Steenkamp, P. A.; Hoppe, H. C.; Khan, T.; Nkabinde, L. A. *Bioorg. Med. Chem.* **2011**, *19*, 4227. (b) Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.* **2007**, *9*, 5175. (c) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E. V.; Sagar, M. V. P.; Pushpavalli, S.; Ray, P.; Pal-Bhadra, M. *MedChemComm* **2010**, *1*, 355. (d) Kim, O.; Jeong, Y.; Lee, H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2011**, *54*, 2455. (e) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13. (f) Rival, Y.; GRASSY, G.; MICHEL, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170.
(10) (a) Swainston Harrison, T.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65. (b) Jain, A. N. *J. Med. Chem.* **2004**, *47*, 947. (c) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Aramori, I.; Hatori, C.; Sawai, H. *J. Med. Chem.* **1998**, *41*, 4587. (d) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305. (e) Wafford, K.; Van Niel, M.; Ma, Q.; Horridge, E.; Herd, M.; Peden, D.; Belelli, D.; Lambert, J. *Neuropharmacology* **2009**, *56*, 182. (f) Mikami, T.; Ochi, Y.; Suzuki, K.; Saito, T.; Sugie, Y.; Sakakibara, M. *J. Pharmacol. Exp. Ther.* **2008**, *325*, 190. (g) Toga, T.; Kohmura, Y.; Kawatsu, R. *J. Pharmacol. Sci.* **2007**, *105*, 207. (h) Pethe, K.; Bifani, P.; Jang, J.; Kang, S.; Park, S.; Ahn, S.; Jiricek, J.; Jung, J.; Jeon, H. K.; Cechetto, J. *Nat. Med.* **2013**, *19*, 1157.
(11) (a) Sakhuja, R.; Shakoor, S.; Kumari, S.; Kumar, A. *J. Heterocyclic Chem.* **2015**, *52*, 773. (b) Shakoor, S. A.; Agarwal, D. S.; Kumar, A.; Sakhuja, R. *Tetrahedron* **2016**, *72*, 645.
(12) Crystal data for **3d**: $C_{22}H_{18}ClN_3O$, M_r = 375.84, monoclinic, space group $P2_1/c$, a = 10.8372(10) Å, b = 10.5719(5) Å, c = 16.5469(8) Å, α = 90°, β = 90.413(1)°, γ = 90°, V = 1895.7(2) Å^3, Z = 4, D_c = 1.317 Mg/cm^3, μ(Mo Kα) = 0.218 mm^{-1}, T = 296(2) K, 48825 reflections collected. Refinement of 2619 reflections (246 parameters) with $I > 2\sigma(I)$ converged at a final R1 = 0.046, wR2 = 0.1098, and GOF = 1.057.
(13) (a) Chinnagolla, R. K.; Vijeta, A.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 12992. (b) Sawant, D.; Singh, I.; Tulsyan, G.; Abbagani, K.; Pardasani, R. T. *Synlett* **2015**, *26*, 1671. (c) Manikandan, R.; Madasamy, P.; Jeganmohan, M. *ACS Catal.* **2016**, *6*, 230.
(14) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609.

DOI: 10.1021/acs.joc.6b02282
J. Org. Chem. 2016, 81, 12340−12349